Lewis Acid-Catalysed σ and π Activation Triggered Cascade Annulation Reactions of Alkynyl Alcohols to Construct Heterocyclic Compounds

By

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Under the supervision of

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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, *"Lewis Acid-Catalysed σ and π Activation Triggered Cascade Annulation Reactions of Alkynyl Alcohols to Construct Heterocyclic Compounds"* submitted by *Ms. Nakate Ashwini Kadaji* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc*., used in the thesis from other source(s), have also been duly cited and acknowledged.

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Research Supervisor
Date: 06/01/2023

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I Ms. Nakate Ashwini Kadaji, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC16A26003 hereby undertake that, the thesis entitled "Lewis Acid-Catalysed σ and π Activation Triggered Cascade Annulation Reactions of Alkynyl Alcohols to Construct Heterocyclic Compounds" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)"*.

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Name: Dr. Ravindar Kontham
Date: 06/01/2023
Place: Pune

This Research is lovingly dedicated to

My beloved Parents and lovely sister and brothers

My better half -Prashant

My lovely daughter-Anaya

And my whole family and teachers

Whose constant love, trust, and

support helped me to reach this stage of

my life

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Section B:

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Suksha *(mother) for giving birth to me at the first place and endless love, support they have given me throughout my life. Also want to thank my lovely sister* ***Gokarna****, I wish to express my special thanks to the* ***Dr. Hemant Chavan*** *(Brother-in-law) for their support in critical situations. I extend heartiest thanks to my Brothers* ***Jagadish*** *(Pocket money) and* ***Sudarshan*** *for continuous encouragement and support have been a source of inspiration in completion of this task. I also big thanks to my Vahini (****Madhuri****). I am forever indebted to my family. Words fail me to express my appreciation to my husband* ***Prashant*** *for his unconditional love and persistent confidence in me, has taken the load off my shoulder and also lovely thanks to my cute and beautiful daughter,* ***Anaya (Shona)****, who is such an amazing girl- I am blessed to be her Aai. I will like to also thank my Mother-in-law (****Anita****), Father-in-law (****Subhash****) for their support. Lovely thanks to my source of happiness* ***Ayush****,* ***Advik****, and* ***Arav*** *(bacha party).*

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With many thanks,

Ashwini Kadaji Nakate

the good and bad times.

Units	
°C	Degree centigrade
g	Gram
mg	Milligram
h	Hour (s)
Hz	Hertz
µg	Microgram
µM	Micromolar
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
nM	Nanometre
ppm	Parts per million
ɗ	Delta
m/z	Mass to charge ratio
cm	Centimetre
Chemical Notations	
AcOH	Acetic acid
$AlCl_3$	Aluminum Trichloride
AgOTf	Silver trifluoromethanesulfonate
n-Bu_2BOTf	Dibutylboryl trifluoromethanesulfonate
LAH	Lithium Aluminium Hydride
n-BuLi	*n*-Butyl lithium
BH_3	Borane
t-BuOH	*tert*-Butyl alcohol
$BiCl_3$	Bismuth trichloride
$BF_3.OEt_2$	Boron trifluoride etherate
$Bi(OTf)_3$	Bismuth(**III**) trifluoromethanesulfonate

CD_3OD	Deuterated Methanol
$CHCl_3$	Chloroform
CrO_3	Chromium (VI) trioxide
COSY	Correlation Spectroscopy
CH_2Cl_2	Dichloromethane
$CDCl_3$	Deuterated Chloroform
CD	Circular dichroism
PhF	Flourobenzene
$CeCl_3.7H_2O$	Cerium(III) chloride heptahydrate
$(CH_2O)_n$	Paraformaldehyde
$CaCO_3$	Calcium carbonate
$CuCl_2$	Copper(II) chloride
CuO	Copper oxide
CAN	ceric ammonium nitrate
$Cu(OAc)_2$	Copper acetate
$(CH_2)_2Cl_2$ (DCE)	Dichloroethane
CO	Carbon monoxide
Conc.	Concentrated
DA	Diels Alder
DABCO	1,4-diazabicyclo[2.2. 2]octane
2D	Two Dimensional
3D	Three Dimensional
DMAP	4-Dimethylaminopyridine
DCC	N,N′-Dicyclohexylcarbodiimide
DMF	N, N'-Dimethylformamide
DIBAL-H	Diisobutylaluminium hydride
DMP	Dess–Martin periodinane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
EtOH	Ethanol
EtOAc	Ethyl Acetate

ESI	Electrospray ionization Mass spectrometry
EC_{50}	Half maximal effective concentration
eq.	Equation
FDA	Food and Drug Administration
HBV	Hepatitis B virus
HSQC	Heteronuclear Single Quantum Coherence
HMBC	Heteronuclear Multiple Bond Coherence
HRMS	High Resolution Mass Spectrometry
HCl	Hydrochloric acid
H_2O	Water
H_2O_2	Hydrogen peroxide
IED-DA	Inverse Electron Demand Diels-Alder
$HgCl_2$	Mercuric chloride.
$Hg(OTf)_2$	Mercury(II) trifluoromethanesulfonate
IC_{50}	Inhibitory Concentration required for 50% inhibition
IR	Infra-Red
IBX	2-Iodoxybenzoic acid
I_2	Iodine
$In(OTf)_3$	Indium(III) trifluoromethanesulfonate
J	Coupling constant (in NMR)
$KMnO_4$	Potassium permanganate
K_2CO_3	Potassium carbonate
KOAc	Potassium acetate
LiHMDS	Lithium bis(trimethylsilyl)amide
TM/LA	Transition Metal/Lewis Acid
LDA	Lithium diisopropylamide
MPA	Methoxyphenylacetic acid

GC-MS	Gas Chromatography Mass
Tf	Triflate
Mg	Magnesium
MnO_2	Manganese dioxide
MeONHMe.HCl	N,O-Dimethylhydroxylamine hydrochloride
Me_3Al	Trimethyl aluminium
MeI	Methyl Iodide
MeCN/ACN	Acetonitrile
$Mn(OAc)_3$	Manganese(III) acetate
$NaClO_2$	Sodium chlorite
AgI	Silver Iodide
NMR	Nuclear magnetic Resonance
$NaIO_4$	Sodium metaperiodate
NOESY	Nuclear Overhausser Effect Spectroscopy
Na_2SO_4	Sodium sulphate
NH_4Cl	Ammonium chloride
$NaHCO_3$	Sodium bicarbonate
$Na_2S_2O_3$	Sodium thiosulphate
NO	Nitric oxide
$NaBH_4$	Sodium borohydride
NMO	N-Methylmorpholine-N-Oxide
NIS	N-Iodosuccinimide
NaOH	Sodium hydroxide
OsO_4	Osmium tetroxide
ORTEP	Oak Ridge Thermal Ellipsoid Plot
IR	Infra-red spectroscopy
PPh_3AuCl	Chloro(triphenylphosphine)gold(I)
PhF	Fluorobenzene
Pd/C	Palladium on charcoal

PPTS	Pyridinium p-toluenesulfonate
PIFA	phenyliodine(III) bis(trifluoracetate)
$Pd(OAc)_2$	Palladium acetate
HPLC	High performance Liquid Chromatography
i-Pr_2NEt	N,N-Diisopropylethylamine
rt	Room temperature
R_f	Retention factor
SiO_2	Silica
DFT	Density functional Theory
$Sc(OTf)_3$	Scandium triflate
TEA (Et_3N)	Triethylamine
$TiCl_4$	Titanium tetrachloride
TMEDA	Tetramethylethylenediamine
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride
TS	Transition state
TLC	Thin Layer Chromatography
TMS	Trimethyl silyl
TBS	tert-butyldimethylsilyl
p-TSA	*p*-Toluenesulfonic acid
tert	Tertiary
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TFA	Trifluoro acetic acid
TfOH	Triflic acid
XRD	X-Ray Diffraction
$ZnBr_2$	Zinc Bromide
Zn	Zinc

- Independent compound and reference numbering have been used for each chapter as well as for sections of the chapters.
- All reagents and solvents were purchased from commercial suppliers and used as such without any further purification. Starting materials were obtained from commercial suppliers or prepared using known procedures.
- All the known compounds reported in literature were characterized by their NMR spectra.
- Solvents were distilled and dried following standard procedures. Petroleum ether used for column chromatography was of 60-80 °C boiling range.
- Column chromatographic separations were carried out on silica gel (100-200 or 230-400 mesh size).
- All reactions were monitored by TLC with 0.25 mm pre-coated E-Merck silica gel plates (60 F254) and TLC spots were made visible by exposing to UV light, Iodine adsorbed on silica gel or by immersion into an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, ninhydrin or KMnO4 followed by heating with a heat gun for ~15sec.
- NMR spectra were recorded on Bruker AV200 (200.13 MHz for ^{1}H NMR and 50.03 MHz for ^{13}C NMR), AV 400 (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR), Jeol-400 (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR), DRX 500 (500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR) and AV 700 (700 MHz for ^{1}H NMR and 176 MHz for ^{13}C NMR) spectrometers.
- Chemical shifts (δ) have been expressed in ppm units relative to tetramethylsilane (TMS) as an internal standard and coupling constants (J) were measured in Hertz.
- The following abbreviations were used for ^{1}H NMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet and ddd = doublet of doublet of doublet.
- Optical rotations were recorded on a JASCO P-1020 polarimeter at 589 nm (sodium D-line). Specific rotations [α]D are reported in deg/dm, and the concentration (c) is given in g/100 mL in the specific solvent.
- Structures and IUPAC nomenclature were generated using ChemBioDraw Ultra 14.0 software.
- High-resolution mass spectra (HRMS) (ESI) were recorded on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer.

AcSIR	**Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for the award of the degree of Doctor of Philosophy in Chemical Science**
Name of the Candidate	Ms. Nakate Ashwini Kadaji
Enrollment No. and Date	Ph.D. in Chemical Sciences (10CC16A26003); August 2016
Title of the Thesis	"Lewis acid-catalysed σ and π activation triggered cascade annulation reactions of alkynyl alcohols to construct heterocyclic compounds"
Research Supervisor	Dr. Ravindar Kontham

1. <u>Introduction:</u> Alkynes are essential functional groups widely found in numerous organic small molecules. Their inactivity towards multiple reagents and catalytic systems attracted the chemists to use them as building blocks and intermediates in multistep organic synthesis. Due to the available robust process technologies involving acetylene (gas) as a precursor, a plethora of alkyne-derived fine chemicals and reagents entered the commercial market at affordable costs.[1] These positive aspects of alkynes triggered the interest of the academic and industrial organic synthesis community to develop novel and sustainable synthetic methodologies, which can be employed in the production of active pharmaceutical ingredients, bioactive natural products, and organic functional materials. Aiming at developing sustainable catalytic systems to activate alkynes (through π-activation), and their subsequent annulation reactions with arenes and carbonyl compounds (through σ-activation) to access diverse heterocyclic molecules, we have devised novel synthetic methodologies for the facile construction of simple to complex tetrahydrofurans, tetrahydropyrans, chromanes, tetrahydro benzoisothiazolo-pyrans and furans, and the outcome of these investigations embodied in the form of this thesis, which is categorized into four chapters.

Chapter 1 provides a general introduction to the chemistry of alkynes. It details the origin of alkynes, and various synthetic methods reported to access alkynes, which facilitate the expansion of the alkyne-based synthetic transformations. It also collates a literature review focusing on recent advancements in chemistry involving various alkynyl alcohols and carbonyl compounds *via* dual activation (σ and π-activation).

Chapter 2 has been divided into two sections. *Section-A* provides an introduction to the importance of α-aryl tetrahydrofurans/pyrans-containing natural products and previous reports on the synthesis of α-aryl tetrahydrofurans/pyrans. *Section B* deals with the bismuth(III)-catalyzed cycloisomerization and (hetero)arylation of alkynols: simple access to 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans (Present work).

Chapter 3 is divided further into two sections. *Section A* details the introduction to previous synthetic approaches disclosed for chromanes, and chromane-derived bioactive natural products. *Section B* deals with the silver-catalyzed [3 + 3]-annulation cascade of alkynyl alcohols and α,β-unsaturated ketones for the regioselective assembly of chromanes (Present work),

Chapter 4 also has been divided into two sections. *Section A* provides an introduction to sulphonamide-containing natural products and drugs, and previous methods to synthesize benzoisothiazolo-pyranopyridine dioxides. *Section B* describes the $Bi(OTf)_3$-catalyzed intramolecular hydroalkoxylation and inverse-electron-demand hetero-Diels Alder reaction cascade of alkynols and *α-β*-unsaturated sulfonyl ketimines (Present work).

2. <u>Statement of the problem</u>: As per the recent statistical data, more than 75% of low-molecular weight-containing marketed drugs have N, O, or S-based heterocycles. Incorporation of a heteroatom into the drug molecule provides a valuable tool for altering its physicochemical properties like solubility, lipophilicity, polarity, and H-bonding capability, which in turn control the ADME and toxicology profile. After nitrogen-based heterocycles, oxygen-heterocycles are the second most common category that present as a structural unit of FDA-approved drugs as of 2017, 27% of unique approved small molecules and 15% of all approved drugs belong to oxygen heterocycles.[2] Among diverse heterocycles present in the chemical space of bioactive molecules, cyclic ethers (tetrahydrofurans and tetrahydrofurans and their structurally close analogs) have been employed as bioisostere of the amide bond in the drug discovery to address the degradation of amide groups by proteases.[3] In general, these oxygen-heterocycles are prepared from hydroxy or carbonyl functionalized building blocks utilizing various catalytic and non-catalytic methodologies. These methods have several limitations, such as multiple steps, non-selective product formation, and usage of strongly acidic, or basic conditions. In recent times, due to the ready accessibility (from acetylene precursors), affordability, inherent low reactivity, and acyl

equivalency (which can be regarded as masked carbonyls), alkyne-containing scaffolds emerged as key starting materials in the construction of various O-heterocycles. So far, various Au(I), Au(III), Pt(II), Pd(II), Ir(I), and Rh(I)-derived catalytic systems have been used for the alkyne-activation (π-activation) induced intramolecular and intermolecular cycloisomerization and annulation reactions.[4] These transition metal salts are highly expensive and unsustainable, and many are unstable toward oxygen, moisture, and light, and special care is needed while performing respective chemical reactions. Further, possess several issues like low yields, long reaction times, poor regioselectivities, elevated temperatures, and the need for the additional Brønsted acid catalyst (σ-activation of carbonyls) in intermolecular transformations. Hence, there is still a great need to develop a novel, sustainable and efficient catalytic system to address the above issues. Having these key objectives in mind, novel synthetic methodologies are designed as a part of this thesis work, involving Lewis acid [particularly Bi(III), Ag(I) as dual activating catalysts]-catalyzed σ and π-activation triggered cascade annulation of alkynyl alcohols (4-pentyn-1ols and 5-hexyn-1-ols) with (hetero)arenes and carbonyl compounds to give diverse simple to complex O, N, and S-heterocycles.

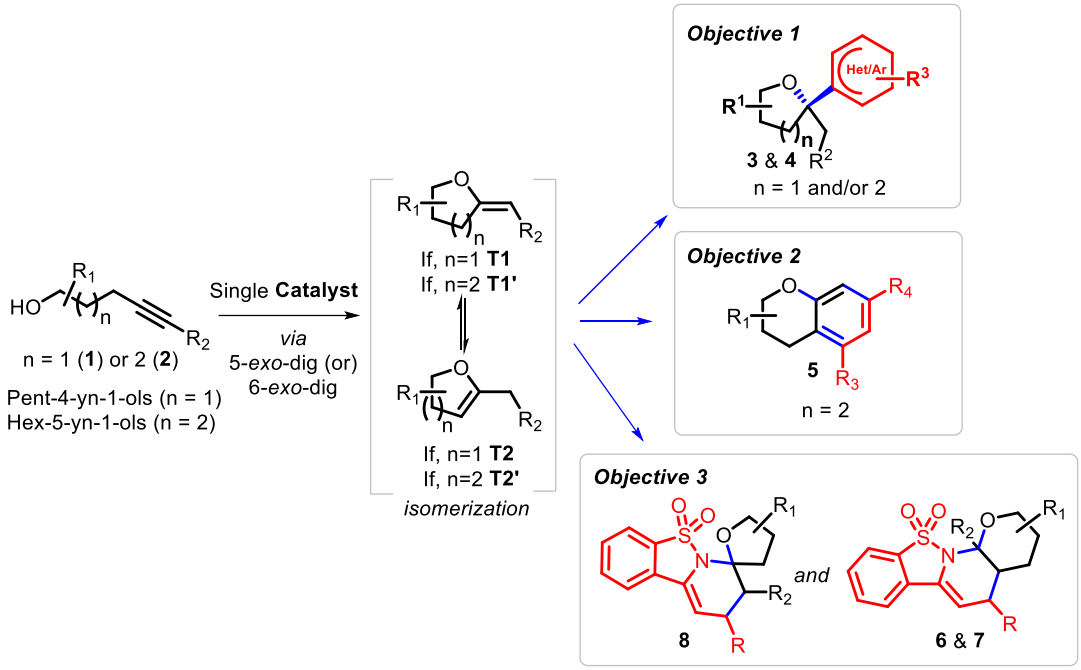
3. <u>Objectives:</u> Inspired by the exciting reaction profile of alkynes, alkynyl alcohols, and the biological relevance of various oxygen-heterocycles (tetrahydrofuran, tetrahydropyran, piperidine, and thiazole-derived), and to address the difficulties associated with the know-how transition metal-catalyzed transformations involving σ and π-activation,[1-4] we have postulated four objectives comprising the construction of diverse heterocycles via σ and π-activation-triggered cascade annulation of alkynols with (hetero)arenes, and carbonyl compounds with a unique single catalytic system. Accordingly, we set out three objectives as follows.

The initial aspect of this thesis was focused on the extensive literature survey on the structure and reactivity of alkynes and various transformations reported in the literature using alkynes.

The *First Objective* was aimed at developing a novel and sustainable catalytic system (containing a single metal salt) for the construction of 2-(hetero)aryl furans and pyrans from 4-pentyn-1-ols and 5-hexyn-1-ols respectively *via* π-activation-induced cycloisomerization of alkynols as a key step (Scheme 1).

The *Second Objective* was formulated to construct biologically relevant simple to complex chromanes in a single step starting from readily accessible alkynyl alcohols and enones using a single catalytic system (Scheme 1).

The *Third Objective* was to construct biologically relevant polycyclic benzoisothiazolo furo-pyridines and pyrano-pyridines through σ and π-activation-induced cascade annulation of alkynyl alcohols (alkynols) and *α*-*β*-unsaturated sulfonyl ketimines employing a single catalytic system (Scheme 1).



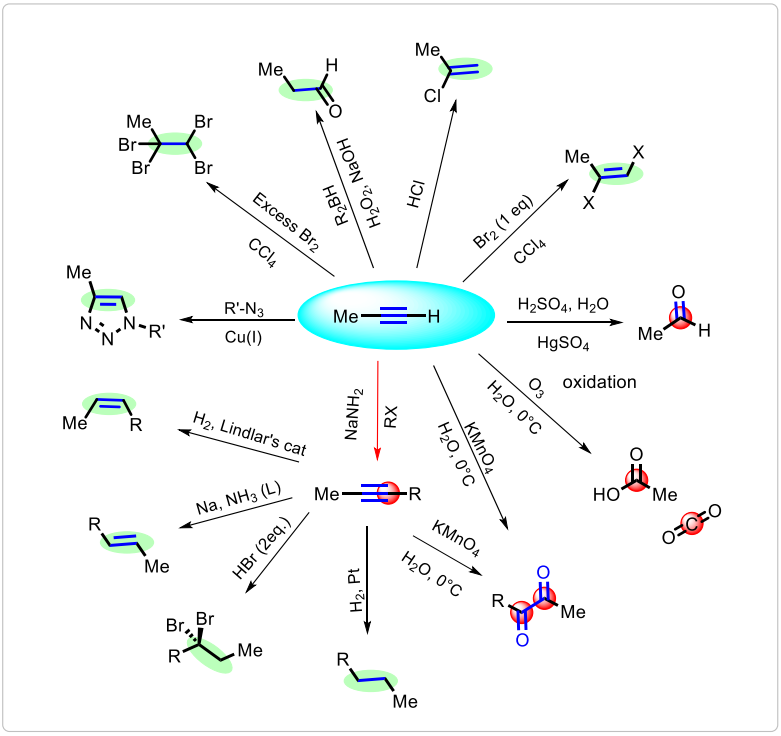
Scheme 1 | Schematic presentation of Objectives of the Thesis.

4. Methodology:

Chapter 1: Introduction to alkyne chemistry

Synthesis and reactivity of isolated alkynes: The simplest alkyne is acetylene which was discovered in 1836 by Edmund Davy through heating potassium carbonate with carbon at a very high temperature, who also identified it as a "new carburet of hydrogen." Subsequently, it was produced from the reactions of CaO with carbon, CaC_2 with water, and methane combustion. Several synthetic methodologies were recently disclosed to access various simple to complex alkynes. Corey-Fuch's reaction, Ohira-Bestmann's reaction, dehalogenation of 1,2-dibromides, and $PhNTF_2$-mediated rearrangement of ketones are notable examples. Alkynes are very important unsaturated hydrocarbons used in organic

synthesis as synthons and are electron-rich molecules with a high density of π-electrons (due to the carbon-carbon triple bond).

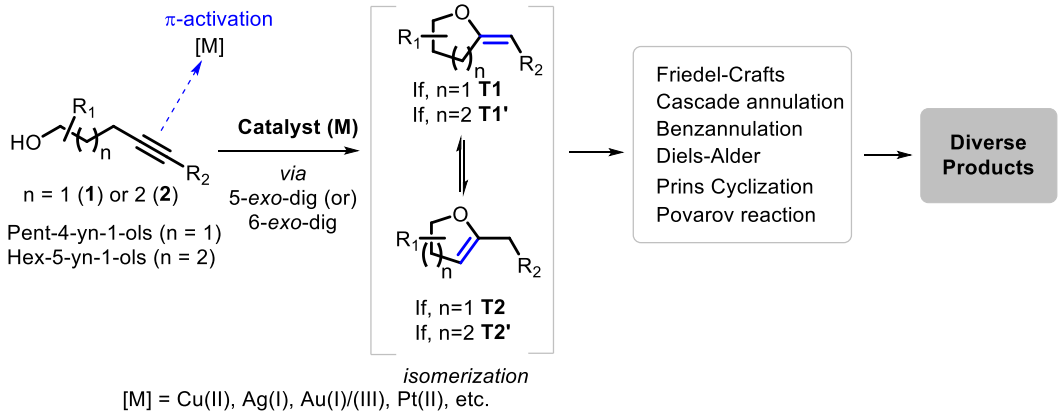


Scheme 2 | Synthetic applications of alkynes.

Similar to alkenes, alkynes undergo various addition reactions *via* breaking the C-C π-bonds. For instance, partial or complete hydrogenation reactions deliver corresponding alkenes and alkanes and participate in diverse electrophilic reactions (with the aid of an array of π-activating catalysts: Brønsted acids, transition metal salts, and Lewis acids) of halogenation, hydrohalogenation, hydroamination, hydrometallation, hydration, oxidation, ozonolysis, dissolved metal reductions, vinylation (hydroalkoxylation), dipolar cycloadditions ("Click" chemistry) and many others, which would produce important synthons like alcohols, aldehydes, ketones, amines, enamines, organo halides, dihalides and many other functional groups utilized in the synthetic organic chemistry. Whereas, terminal alkynes undergo nucleophilic addition reactions with the aid of terminal acidic C-H bond, and are also used as coupling partners in transition metal-catalyzed coupling reactions (Sonogashira) (Scheme 2).[5]

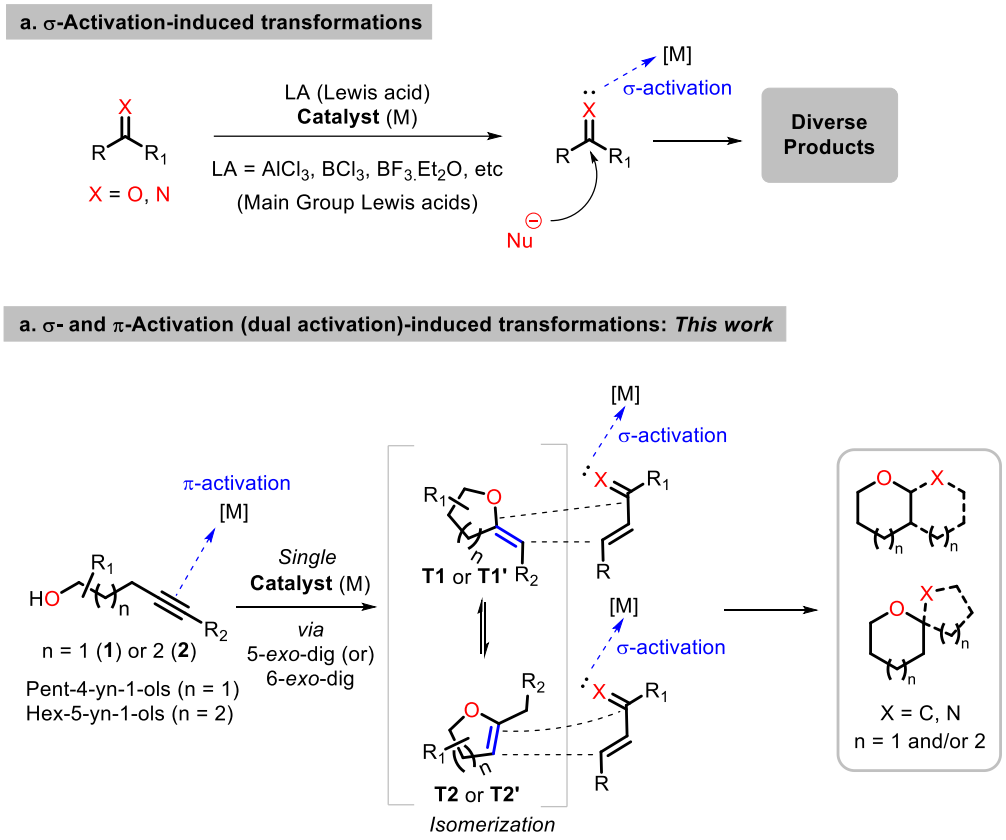
Reactivity of alkynyl alcohols: Alkynyl alcohols (alkynols) are one of the important classes of building blocks disclosed in the literature. These include prop-2-yn-1-ols (propargylic

alcohols), but-3-yn-1-ols (homopropargylic alcohols), pent-4-yn-1-ols and hex-5-yn-1-ols. These last two categories of alkynols (pent-4-yn-1-ols (**1**) and hex-5-yn-1-ols (**2**)) readily undergo intramolecular hydroalkoxylation (via 5-*exo*-dig and/or 6-*endo*-dig mode of ring closure) with the aid of suitable π-activating catalysts and generate the corresponding oxacarbenium species followed by enol-ethers (**T1**/**T1'**, **T2**/**T2'**) which participate in diverse intra- and intermolecular annulation reactions and deliver corresponding 5- and/or 6-membered oxygen-heterocycles through Friedel-Craft reaction,[11d] cascade annulation,[11c] benzannulation, Diels-Alder,[6] Prins-type reaction,[7] Povarov reaction[8] pathways. This phenomenon was earlier studied using Cu(II), Au(I), Au(III), Pt(II), Pd(II), Ir(I), and Rh(I)-derived π-activating catalysts and utilized in the construction of various spiroketals and applied in the field of total synthesis of bioactive natural products (Scheme 3).



Scheme 3 | Catalytic synthetic applications of alkynols *via* cyclic enol-ether intermediates.

In a similar way, carbonyl compounds and imines undergo σ-activation with the aid of various Lewis acids ($AlCl_3$, BCl_3, $BF_3.Et_2O$ and others, and Brønsted acids) and participate in diverse 1,2-addition reactions and deliver corresponding products. Since the formation of cyclic enol ethers (acyl anion equivalents; **T1**/**T1'**, **T2**/**T2'**) from alkynols like pent-4-yn-1-ols (**1**) and hex-5-yn-1-ols (**2**) is well established using the above-mentioned π-activating (carbophilic) catalysts, we would like to develop unique intermolecular cascade annulation reactions of alkynols with arenes and carbonyl compounds employing a cost-effective, environmentally benign and sustainable catalytic system (single catalyst), which can work through σ and π-activation (dual activation) and furnish simple to complex tetrahydrofuran/pyran-tethered and N, S-heterocycles related to biologically potent natural products (Scheme 4).[9]



Scheme 4 | Cascade annulation of alkynols and carbonyl compound-derivatives involving single catalyst-mediated dual activation (σ- and π-activation).

Chapter 2: Bismuth(III)-catalyzed cycloisomerization and (hetero)arylation of alkynols: a simple access to 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans

Introduction and previous approaches: Saturated oxygen heterocycles, such as tetrahydropyrans and tetrahydrofurans are ubiquitous structural units found in an array of chemotherapeutic agents and bioactive natural products. In view of the drug discovery research, still, there is ample scope for the expansion of the chemical space derived from medium-sized oxygen-heterocyclic compounds. Historically, more than 10000 furan and pyran-containing natural products are present in the chemical space of Nature.[10] Recently, many natural products possessing α-aryl substituents were isolated and known to possess interesting biological activities. For instance, (–)-centrolobine (antibacterial, anti-

inflammatory, and anti-leishmanial), (–)-hedycoropyran B, and aflatoxin B1(AFB1) (anti-cancer) are notable examples of this category (Figure 1).[2]

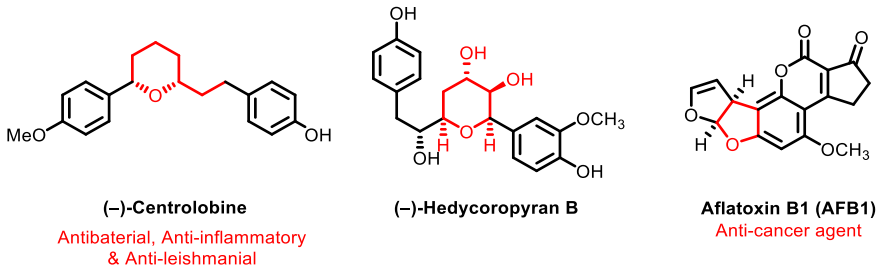


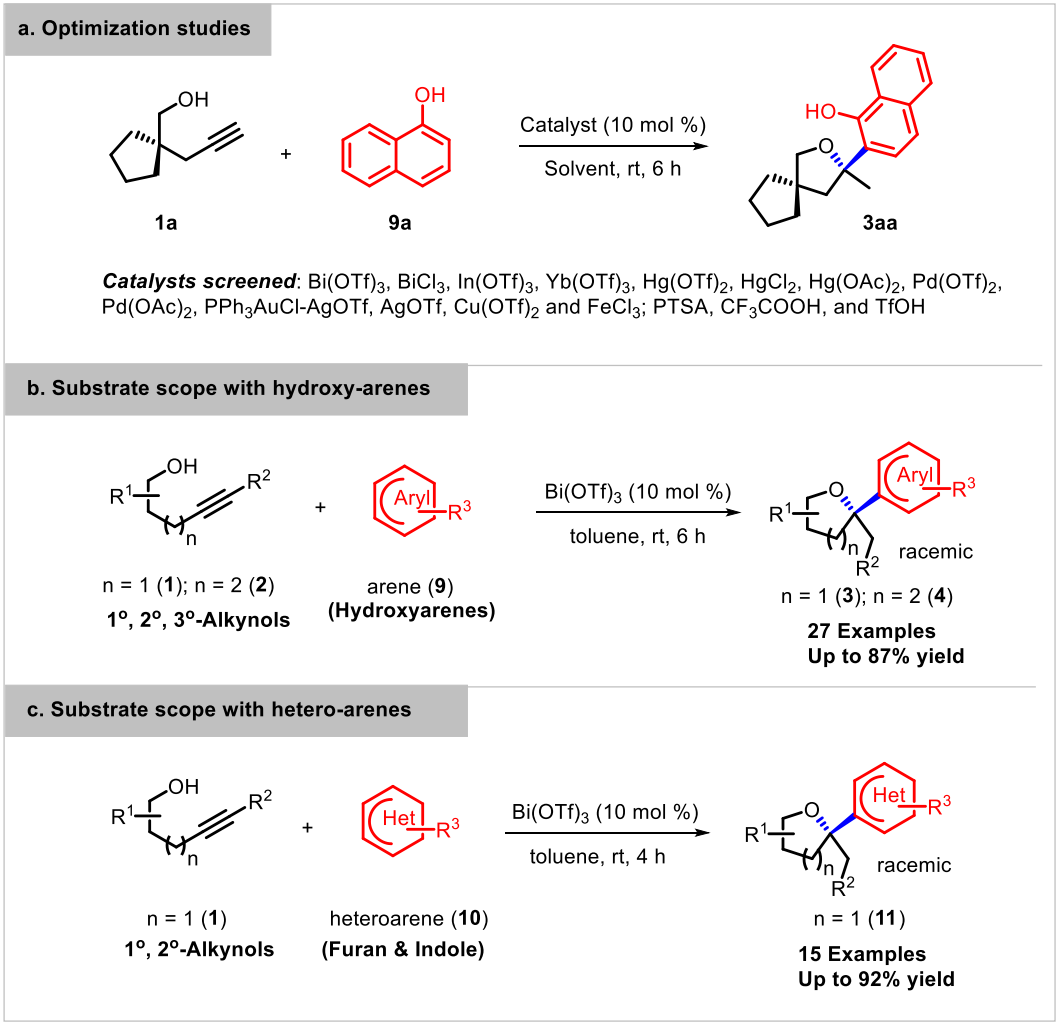
Figure 1 | Selected examples of natural products containing tetrahydrofuran and tetrahydropyran scaffolds.

In this context, it's noteworthy to mention that the Gordan et al., report of $GaCl_3$ induced hydroalkoxylation followed by Friedel-Crafts type addition using alkynol and anisole, however, it is limited to a single example.[10c] Some other miscellaneous reports also present in the literature have constraints such as the use of prefunctionalized starting materials and multiple steps. As part of our interest in the development of novel synthetic methodologies involving cycloisomerization (intramolecular hydroalkoxylation) of alkynyl alcohols, and inspired by the interesting biological profile of α-aryl substituted tetrahydrofurans and pyrans, we intended to develop a novel protocol for the construction of 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans using $Bi(OTf)_3$-as unique π-activating catalysts for the first time.

Based on our earlier investigations,[11a] we hypothesized that $Bi(OTf)_3$-catalyzed hydroalkoxylation (cycloisomerization) of pent-4-yn-1-ols (**1**) and hex-5-yn-1-ols (**2**) (*via* 5- or 6-*exo*-dig cyclization respectively) through activation of the triple bond lead to the formation of oxocarbenium ions, which subsequently participates in (hetero)hydroarylation with electron-rich arenes, and could deliver corresponding α-substituted tetrahydrofurans and/or pyrans (*vide infra*).

Results and discussion (**Present work**): To verify our hypothesis, a mixture of known 4-pentyn-1ol (**1a**) and α-naphthol (**9a**) were used as standard building blocks, and performed reaction optimization studies. Initially, several π-activating metal catalysts (alkynophilic) $Bi(OTf)_3$, $BiCl_3$, $In(OTf)_3$, $Yb(OTf)_3$, $Hg(OTf)_2$, $HgCl_2$, $Hg(OAc)_2$, $Pd(OTf)_2$, $Pd(OAc)_2$, PPh_3AuCl-AgOTf, AgOTf, $Cu(OTf)_2$ and $FeCl_3$ were tested varying solvents and reaction times. Next, we screened Brønsted acids PTSA, CF_3COOH, and TfOH using various solvents. Among all these catalysts tested, $Bi(OTf)_3$ (10 mol%) turned out to be the

preeminent choice. A brief solvent screen prompted us to use toluene as an optimal solvent (87% yield) (entry a, Scheme 5).



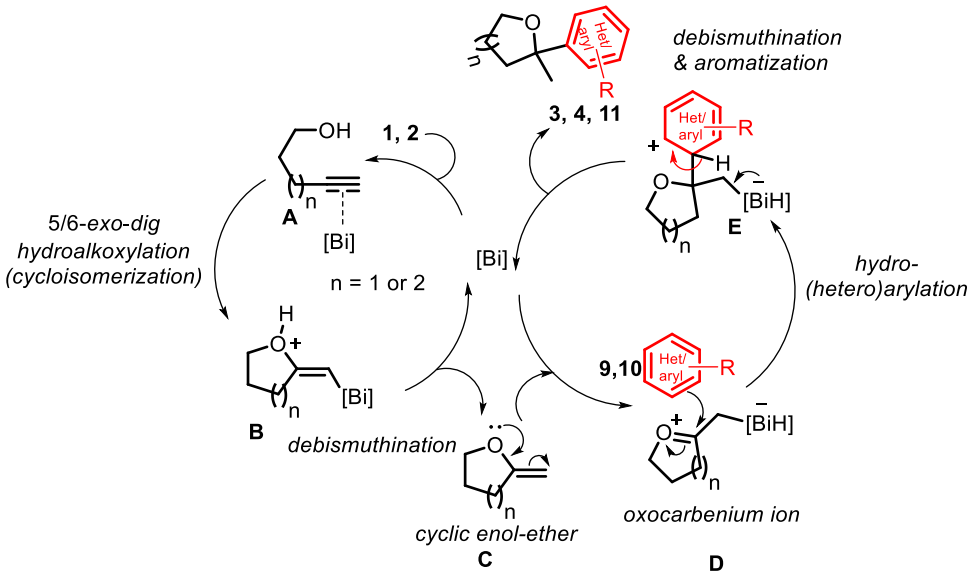
Scheme 5 | Synthesis of 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans from alkynols.

Having the optimal reaction conditions in hand, we investigated the reactivity profiles of alkynols (**1**, 4-pentyn-1-ols) varying diverse substituents, containing primary, secondary, and tertiary hydroxyl groups with diverse arenes (**9**) (α- and β-naphthols, phenol). Next, tested the reactivity of 5-hexyn-1-ols (**2**) with α-naphthol (**9**). All these reactions worked well under optimal reaction conditions and delivered corresponding a-aryl tetrahydrofurans (**3**) and pyrans (**4**) (a total number of 27 examples) in good to excellent yields (up to 87%) (entry b, Scheme 5).

Subsequently, the reactivity of various hetero-arenes (**10**) (furan, thiophene, pyrrole, pyridine, benzoxazole, and benzothiazole) was tested. Among all of these heteroarenes,

furan, indole, and 1-methylindole were found to be good substrates and delivered corresponding monomeric and/or dimeric (formed *via* bis hydro-heteroarylation) heteroaryl-substituted tetrahydrofurans (15 examples) in good to excellent yields (up to 92% yield) (entry c, Scheme 5).

As observed in our previous investigations, the reactivity of unsubstituted 4-pentyn-1-ols is slightly slower than that of substituted analogs (Thorpe–Ingold effect)[12] and 5-hexyn- 1-ols are less reactive compared to 4-pentyn-1-ols, which is in agreement with Baldwin rules.[13] All products synthesized in this work were well-established using extensive analytical data (^{1}H, ^{13}C NMR, ESI-MS), and the diastereomer ratios were calculated using ^{1}H NMR analyses.



Scheme 6 | Plausible reaction mechanism.

A plausible mechanism of this transformation based on our (and others) earlier mechanistic investigations[11a-b] and the results obtained in this work is shown in Scheme 6. The reaction is initiated by the π-coordination of $Bi(OTf)_3$ to the C-C triple bond of alkynol **1**, **2** to form intermediate **A**, which triggers the hydroalkoxylation (cycloisomerization) *via* 5 or 6-*exo*-dig mode of addition on to the alkyne triple bond, which leads to the intermediate **B**. Proto-debismuthination of **B** affords the *exo*cyclic enol ether **C**, further activation of enol ether **C** to generate the oxocarbenium ion **D**, which undergo hydro-(hetero)arylation with arenes **9** or heteroarenes **10** to give **E**. Concomitant second proto-debismuthination step in **E** leads to desired products **3**, **4**, **11** (Scheme 6).

In summary, hydroalkoxylation (cycloisomerization) and hydro-(hetero)arylation cascade reaction of alkynols with arenes and hetero-arenes mediated by main group element derived borderline metal catalyst $Bi(OTf)_3$ is identified. Reactions employing diverse alkynols and electron-rich arenes/heteroarenes proceeded cleanly under ambient reaction conditions and furnished a series of novel 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans in good to excellent yields in an atom and step economic way.

Chapter 3: Silver-catalyzed [3+3]-annulation cascade of alkynyl alcohols and *α-β*,-unsaturated ketones for the regioselective assembly of chromanes

Introduction and previous approaches: Chromanes are ubiquitous in biologically potent natural products and pharmaceuticals; hence the synthetic strategies for constructing these scaffolds are particularly important. For instance, α-tocopherol (vitamin E family), catechins (antitumor and antioxidant agents), troglitazone (antidiabetic and anti-inflammatory drug), nebivolol (antihypertensive drug), LL-D253α (antibiotic), γ-rubromycin (antioxidant), chromanol 293B (IKs blocker), caesalpinflavans (cytotoxic), virgatolides (cytotoxic), cebulactam (antioxidant) and many others.[14] Further, chromanes constitute the core structure of versatile flavonoids, cannabinoids, and related bioactive molecules. Consequently, the past few decades have earned enormous attention from synthetic organic chemists to construct these scaffolds (Figure 2).

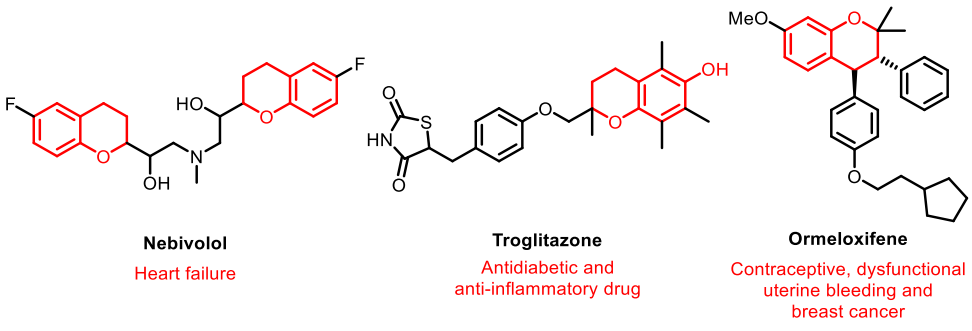
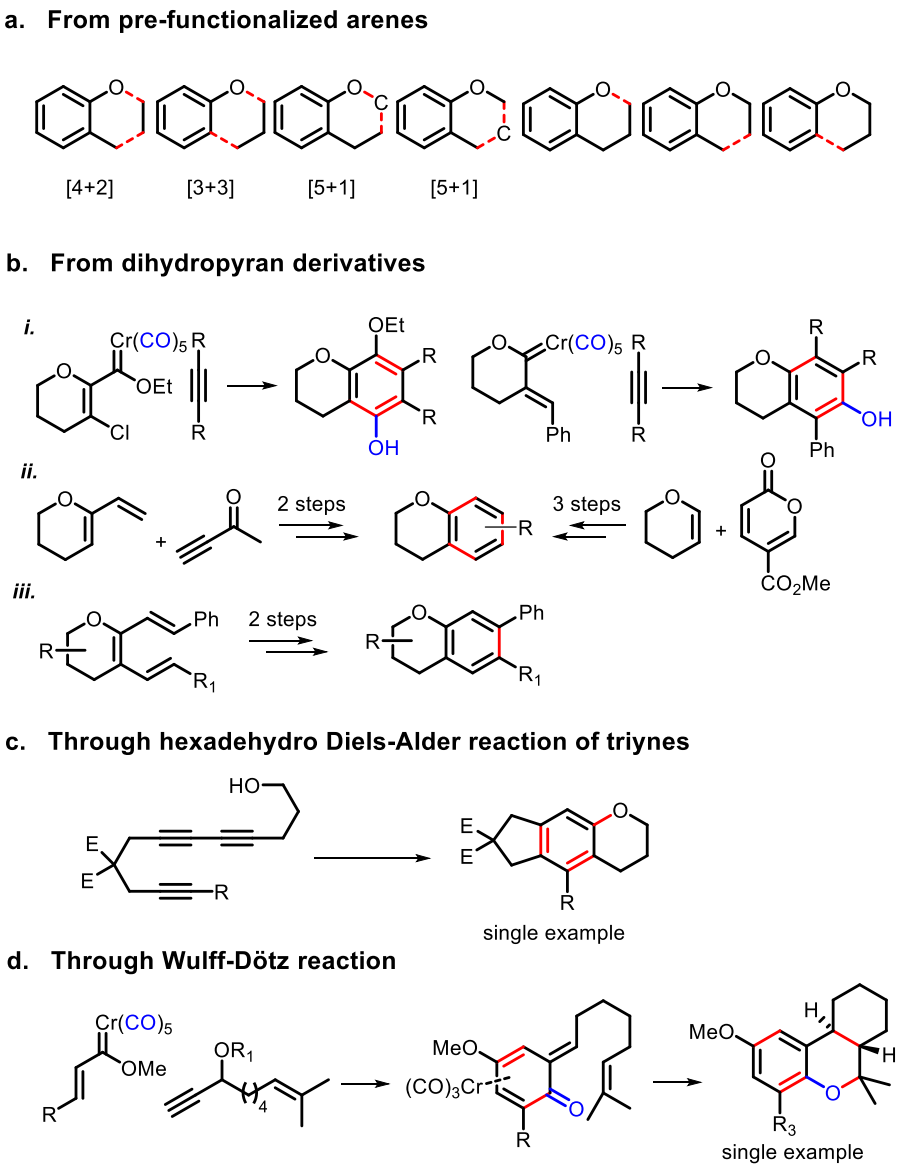


Figure 2 | Selected examples of chromane-containing natural products.

Nearly, the majority of the reported protocols rely on the closure of the pyran ring of substrates with pre-functionalized arene appendage *via* [4+2]-, [3+3]-, [5+1]-annulations, and intramolecular [6]-ring closures (Scheme 7, entry a). In a few instances, dihydropyran

derivatives were used as precursors to construct chromane skeleton through arene ring formation. For example, the reaction of pyran-derived Fisher chromium carbene complexes and alkynes with complete regio-selection (Scheme 71, entry b. i), a recent report from Kirschning's group comprising [4+2]-cycloaddition of dihydropyran derived diene or dienophiles with ynones or pyranones (Scheme 7, entry b. ii), and a multi-step involving 6-π-electrocyclization of pyran-tethered triene followed by aromatization (Scheme 7, entry b. iii).

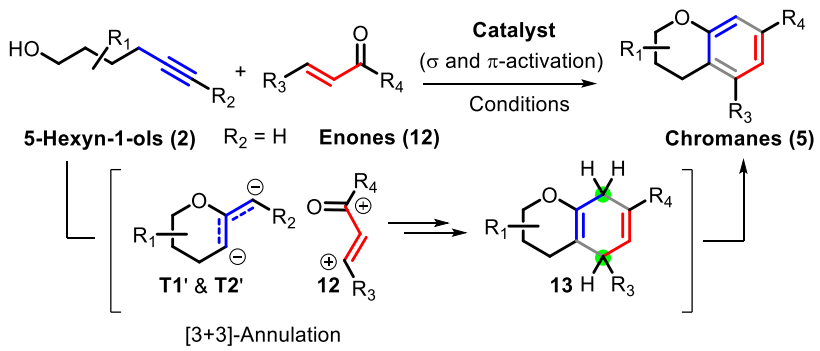


Scheme 7 | Known synthetic strategies for chromanes.

The next possible way is *via* the installation of both rings simultaneously from acyclic building blocks in intra or inter-molecular pathways, in this context, Hoye's

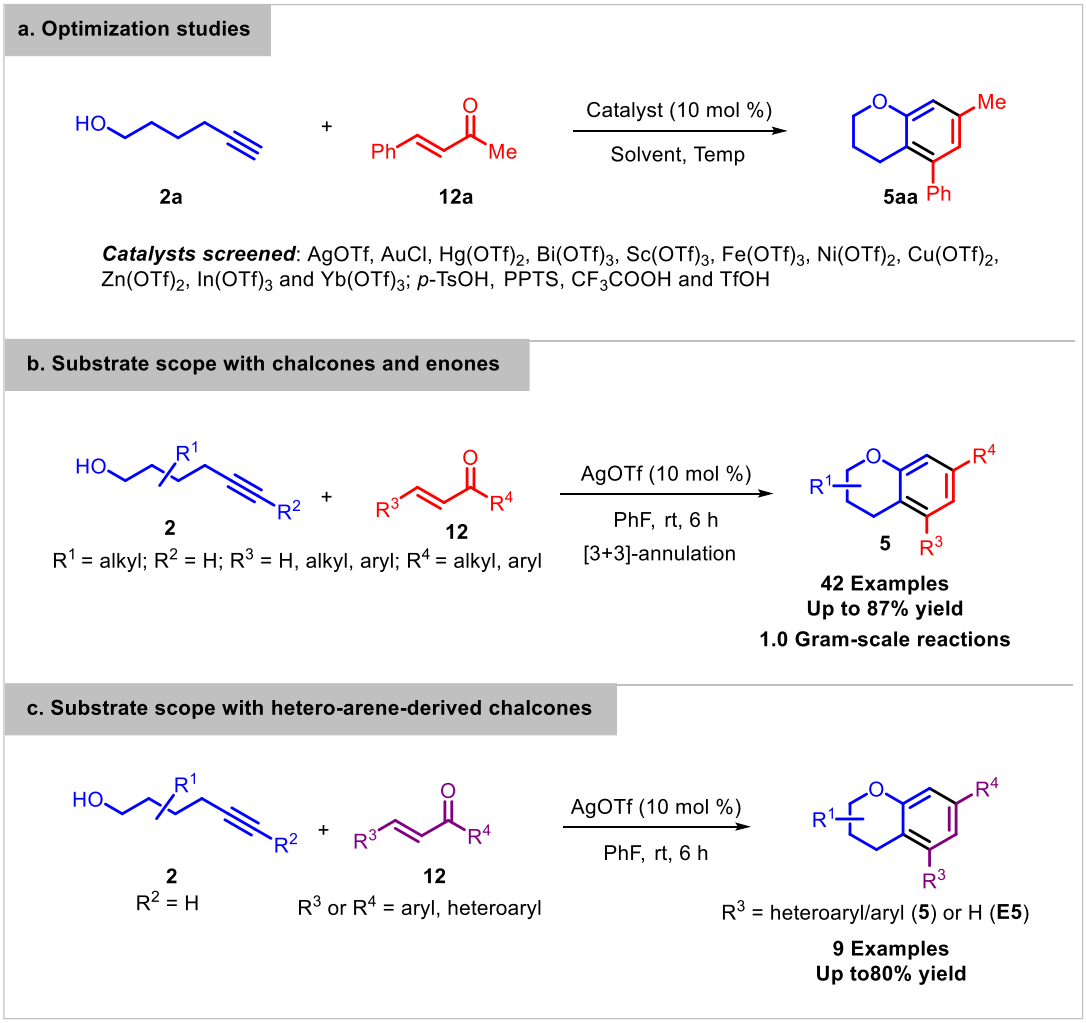
intramolecular hexa-dehydro Diels-Alder reaction (HDDA) of triyne-tethered alkynol to give tricyclic chromane is a notable example (however, this report is limited to a single example and simple chromanes can't be accessed) (Scheme 7, entry c). It's teworthy to mention the intermolecular strategy of Wulff-Dötz reaction involving α,β-unsaturated Fischer-carbene complex of chromium with alkenyl-propargylic ethers involving 6-π-electrocyclization or [4+2]-cycloaddition of *in situ* formed ortho-quinone methide to give tricyclic chromenes or chromanes (extra reduction step is required in the former case and it is limited to a single example in the latter case) (Scheme 7, entry d).[15]

Of all the methods of the myriad, to the best of our knowledge, there is no report on the construction of both rings of chromanes (bicyclic) using an intermolecular cascade transformation. In light of this exciting landscape of chromanes, we aimed to develop a novel and facile strategy in which the complete skeleton of chromanes **5** is generated from readily available alkynols **2** and α,β-unsaturated ketones **12** employing a dual activating (σ and π-activation) catalyst *via* [3+3]-annulation of cyclic enol ether (**T1'** & **T2'** acts as a bis nucleophile) generates from alkynyl alcohol **2** (5-hexyn-1ol) and enone (Scheme 8).



Scheme 8 | Our hypothesis for the synthesis of chromanes from alkynols and enones.

Results and discussion (**Present work**): The feasibility of our projected hypothesis was tested using 5-hexyne-1-ol **2a** and α,β-unsaturated ketones **12a** as starting materials, various σ and π-activating Lewis acids AgOTf, AuCl, $Hg(OTf)_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, $Fe(OTf)_3$, $Ni(OTf)_2$, $Cu(OTf)_2$, $Zn(OTf)_2$, $In(OTf)_3$, $Yb(OTf)_3$; and Brønsted acids (*p*-TsOH, PPTS, CF_3COOH, TfOH) as catalysts in different solvents. To our delight, 10 mol% of AgOTf in PhF at room temperature delivered the desired chromane **5aa** exclusively in the best yield compared to other Lewis acids tested.[11a,b,d] Whereas, other silver salts (AgCl, AgBr, AgI, $AgNO_3$ and AgO) were failed to facilitate this annulation (entry a, Scheme 9).



Scheme 9 | Optimization and scope of [3+3]-annulation reaction concerning alkynols (5-hexyn-1-ols) and various enones.

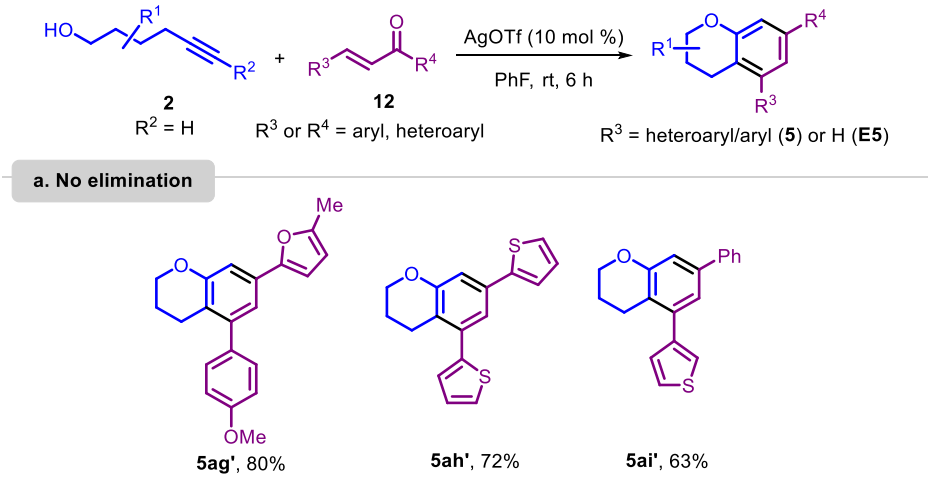
Having established optimal reaction conditions, we sought to explore the generality of this annulation reaction. As illustrated in Scheme 9, we methodically investigated the substrate scope of 5-hexyn-1-ols **2** and enones **12**. Diverse alkynols (possessing primary, secondary, tertiary hydroxyl functionalities, alkyl/cycloalkyl, and lactone substituents) were well reacted with an array of enones (chalcones, aryl/alkyl-ketone-derived enones moieties) substituted with electron-donating, electron-withdrawing, protected-phenolic and halide groups and delivered the corresponding simple to complex chromanes (42 examples) in good to excellent yields (45-87% isolated yield) (entry b, Scheme 9). Setting a limitation, the reaction of 5-hexyn-1ol (**2a**) with cinnamaldehyde and alkyl-derived enones, and internal 5-hexyn-1ols with chalcones/enones did not proceed. The reaction of analogous 4-pentyn-1-

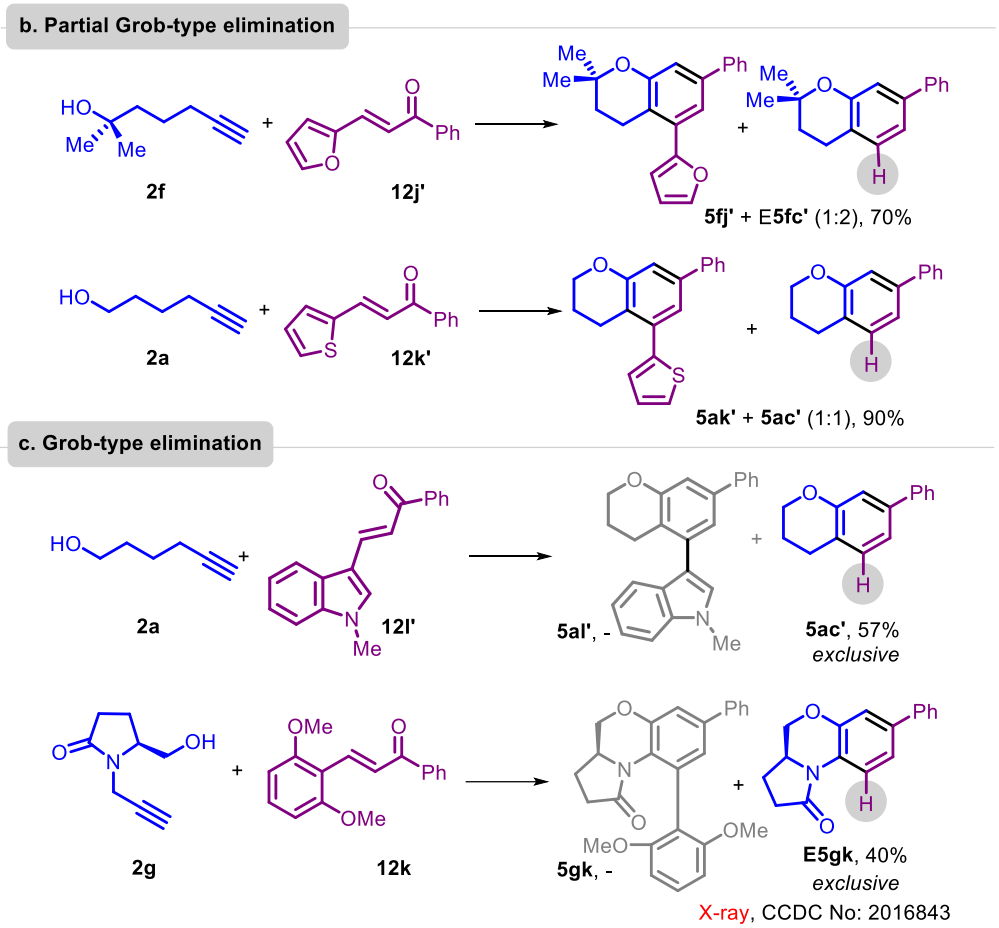
ol with chalcone ((2*E*)-1,3-diphenylprop-2-en-1-one) failed to deliver the anticipated 2,3-dihydro-benzofuran.

To extrapolate the generality further, we investigated the scope of enones with hetero arene appendage **12**. Among several enones (possessing furan, thiophene, pyrrole, indole, pyridine benzoxazole, and benzothiazole) tested, furan thiophene and indole-tethered enones were found to be reliable substrates and led to some interesting results as delineated in entry c, Scheme 9.

The reaction of alkynol **2a** with (*E*)-3-(4-methoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**12g'**), (E)-1,3-di(thiophen-2-yl)prop-2-en-1-one (1**2h'**) and (*E*)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one (**12i'**) delivered corresponding chromanes **12ag'**, **12ah'** and **12ai'** respectively in good yields (Scheme 10, entry a). To our surprise, (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**12j'**) and (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (**12k'**) in reaction with alkynols **2f** and **2a** gave an inseparable mixture of chromanes and heteroarene eliminated products (**5fj'** and **E5fc'**; **5ak'** and **5ac'**; established by ^{1}H and ^{13}C NMR analyses) under optimal reaction conditions (Scheme 10, entry b).

Interestingly, *N*-methyl indole derived chalcone **12l'** in reaction with **2a** at 85 °C delivered the eliminated product **5ac'** exclusively in 57% yield. Similarly, alkynol **2g** (obtained from (*S*)-pyroglutamic acid) in reaction with sterically hindered chalcone **12k** furnished tricyclic lactam fused N,O-heterocycle **E5gk** (confirmed by X-ray analyses) in 40% yield (Scheme 3, entry c), this unusual formation of heteroarene/arene eliminated products could be due to stereoelectronic effects-driven competitive Grob-type elimination pathway[16], instead of classical oxidative aromatization (*vide infra*) (Scheme 10, entry c).



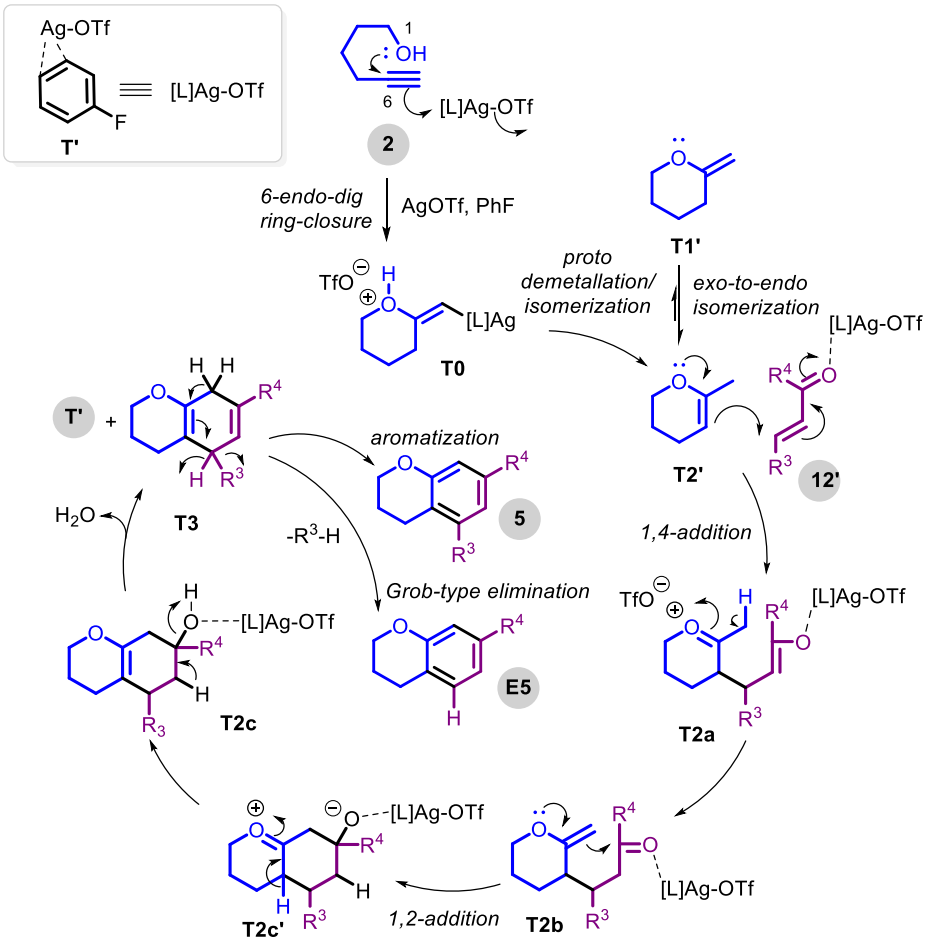


Scheme 10 | Scope of [3+3]- annulation reaction using heteroarenes-derived chalcones.

After successfully constructing various chromanes, we performed a series of supporting experiments to gain insight into the reaction mechanism. The real-time GC-MS analyses confirmed the initial cycloisomerization-induced formation of cyclic-enol ether intermediates (**T1'** & **T2')**, and also the formation of 1,4-cyclohexadiene intermediate (**T3**). Enhancement of the yield and shortening of the reaction time under an oxygen atmosphere suggested the probable involvement of aerobic aromatization steps. To better understand the enhanced efficiency using fluorobenzene (PhF) as a solvent, selective participation of endocyclic enol ether (**T2'**) over exocyclic enol ether (**T0**'), and other key steps involved in the cascade annulation, we carried out full quantum chemical calculations (thermodynamic calculations) using density functional theory at PBE/TZVP level of theory (*vide infra*).

Based on experimental results obtained in this work, DFT calculations, and earlier observations by our group and others,[11a-b,d] we have drawn a more authenticated reaction mechanism for this Ag(I)-catalyzed [3+3]-annulation reaction (Scheme 11). The initial AgOTf (η^2 coordinated with PhF; observed herein for the first time, **T1'**) mediated π-

activation of alkynol **2** triggers the 6-exo-dig cyclization (hydroalkoxylation), which leads to the formation of the exocyclic enol ether **T1'** via **T0**, which then converts into thermodynamically more favored endocyclic enol ether **T2'**. Enol ether **T2'** reacts with the activated enone **12'** in a 1,4-addition pathway to give the oxocarbenium species **T2a**, which would then be transformed into exocyclic enol ether **T2b** through deprotonation. Then **T2b** undergoes intramolecular 1,2-addition and produces the bicyclic dihydropyran **T2c** *via* oxacarbenium species **T2c'**. Subsequent catalyst-induced dehydration of **T2c** delivers pyran-tethered 1,4-cyclohexadiene species **T3** (trapped and established by GC-MS and X-ray diffraction analyses). In the final step of the cascade, cyclohexadiene intermediate **T3** either delivers chromane **5** through oxidative (aerobic) aromatization step or arene/heteroarene eliminated product **E5** *via* Grob-type elimination (Scheme 11).



Scheme 11 | Plausible reaction mechanism for [3+3]-annulation reaction.

In summary, in this Chapter, we have established a facile protocol for the regioselective construction of simple to complex chromanes by employing an Ag(I)-

catalyzed cascade [3+3]-annulation of 5-hexyn-1-ols and α,β-unsaturated ketones *via* unravelling the bis-nucleophilic nature of cyclic enol-ether reaction intermediates for the first time. More importantly, theoretical calculations elucidated the role of the fluorobenzene (solvent) in fine-tuning the Ag-catalysis by stabilizing respective complexes, thermodynamically favoured endocyclic enol ether formation, and its selective participation in an intermolecular 1,4-addition reaction which led to exclusive regioselectivity. Operationally simple reaction parameters, scalability, good to excellent yields (up to 90%), and broad substrate scope are salient features of this strategy. This protocol may find applications in the total synthesis of relevant biologically active natural products and diversity-oriented synthesis of medicinal chemistry.

Chapter 4: $Bi(OTf)_3$-catalyzed inverse-electron-demand aza-Diels-Alder (IED-ADA) reaction of alkynols and α-β-unsaturated ketimines

Introduction and previous approaches: The [4+2]-cycloaddition (Diels-Alder reactions) is one of the most universal synthetic methods used for the construction of six-membered carbon and heterocyclic structures.[17] In contrast to normal electron demand Diels-Alder reaction (where an electron-rich diene moiety reacts with an electron-deficient dienophile), in an inverse–electron–demand Diels-Alder reaction (IEDDA) an electron-rich dienophile reacts with an electron-poor diene. Both these reactions provide complex cyclic molecules with high stereoselectivity, atom, and step economy. Particularly, IEDDA reactions are versatile and aid the constructions of O-, N-, and S-containing heterocycles related to bioactive natural products and drugs (for instance piperidines, dihydropyrans, sulphonamides, and many others).[2]

In the field of drug discovery, sulphonamide and/or cyclic sulphonamides (1,2-thiazole dioxides) are considered privileged scaffolds, and these derivatives are known to exert excellent biological activities. In addition to cyclic-sulphonamides, N-sulphonyl imidazole, benzothiazole-dioxides, and benzoisothiazolo-furo-piperidines (associated with our present work) are well precedent in the literature and known to possess interesting biological activities. These piperidine scaffolds are found in a total of 72 currently marketed molecules that are approved by the FDA (Figure 3).[18]

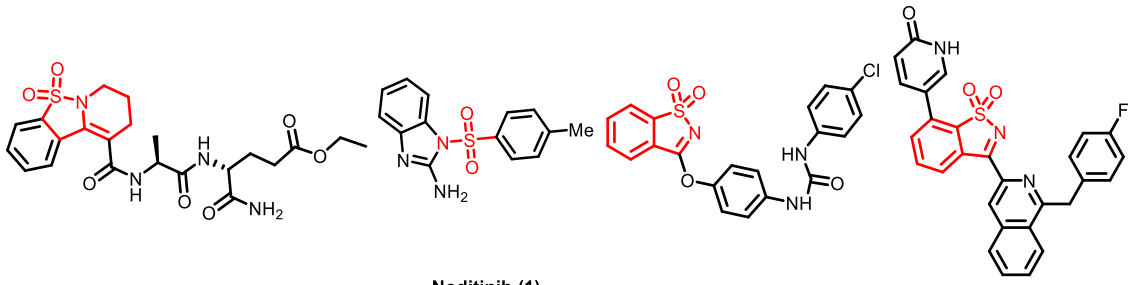
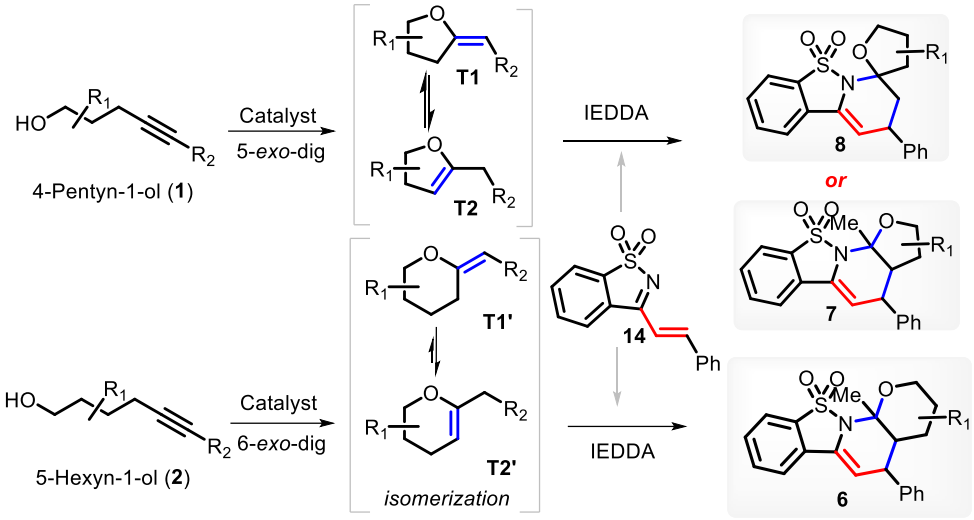


Figure 3 | Selected examples of natural products (sulfonamide) benzoisothiazolo pyranopyridine scaffolds.

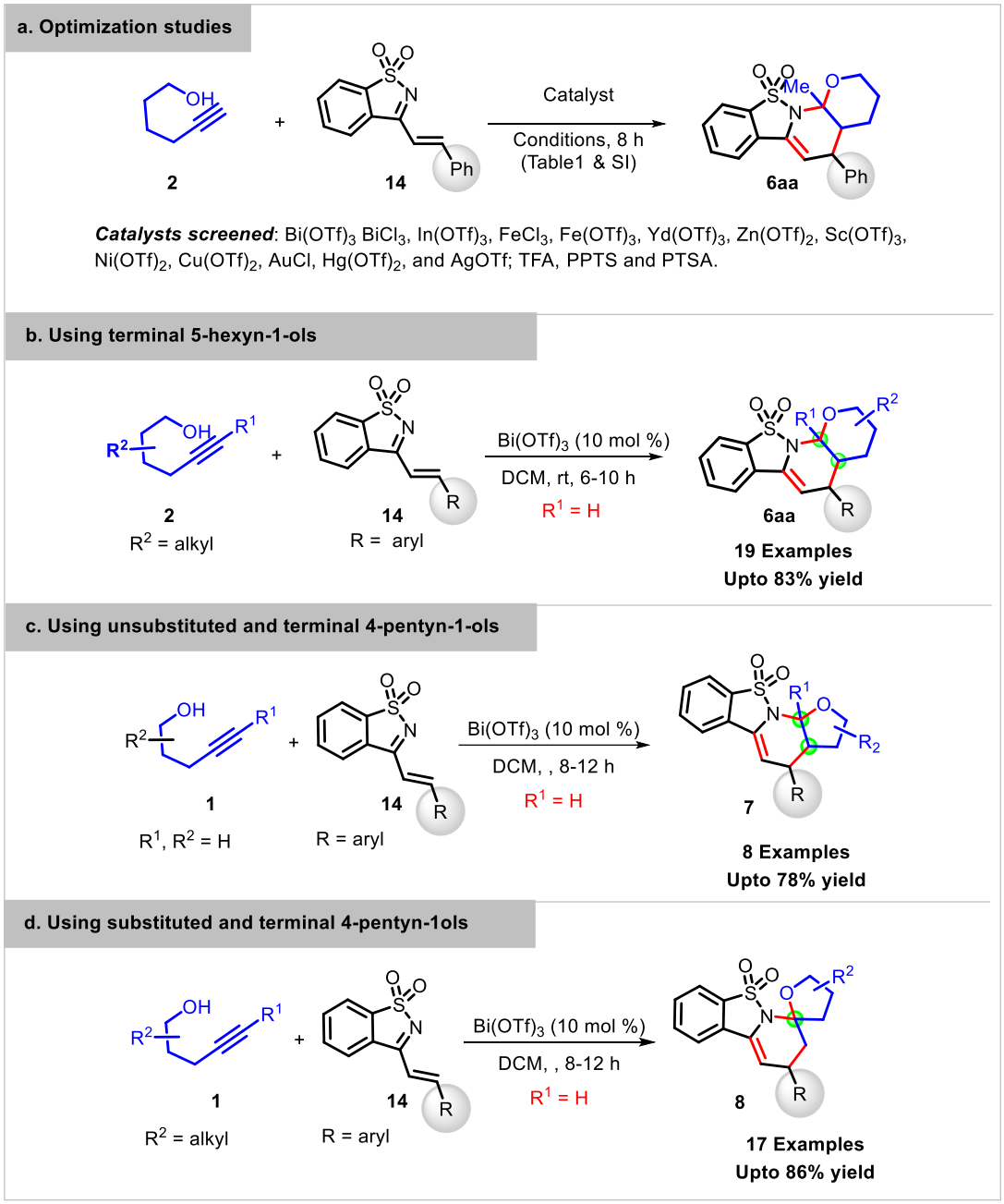
Inspired by the interesting biological profile and structural features of sulphonamide and/or cyclic sulphonamides (1,2-thiazole dioxides), oxygen heterocycles, and continuing our interest in the development of novel synthetic methodologies involving alkynyl alcohols, herein we aimed to verify the reactivity of alkenyl-tethered cyclic sulphonamides (acts as electron-deficient diene system) and alkynyl alcohols (which would generate cyclic enol ethers and are act as electron-rich dienophiles) using a single (σ and π dual-activating) catalytic system.

Based on our earlier investigations[13] (described in Chapter 2 and 3), we envisioned that alkynyl alcohols (4-pentyn-1-ols **1** and 5-hexyn-1-ols **2**) undergo initial catalytic π-activation-induced cycloisomerization to give respective cyclic enol ethers (**T1**, **T2**/ **T1'**, **T2'**), which further react with activated α,β-unsaturated ketimines **14** (sulphonamide-derived) *via* inverse-electron demand Diels-Alder reaction (IEDDA) and give corresponding spirocyclic or fused N,O-ketals in a stereoselective manner. To the best of our knowledge, there is no report on this IEDDA reaction involving alkenyl- cyclic sulphonamides and enol-ethers (Scheme 12).



Scheme 12 | Our hypothesis for the inverse-electron demand Diels-Alder reaction (IEDDA).

Results and discussion (**Present work**): To test our hypothesis, an initial scouting reaction was performed with known 5-hexyne-ol **2a** (possessing terminal alkyne) and α,β-unsaturated ketimines **14a**, under our in-house developed cycloisomerization conditions using $Bi(OTf)_3$ (10 mol%) in CH_2Cl_2 at rt, which delivered benzoisothiazolo pyranopyridine dioxide **6aa** in 82% yield with dr 1:0.2. Subsequent experiment altering the solvent and temperature (DCE, 80 ºC) did not lead to any improvement in the outcome of **6aa**. Next, a series of known π-electrophilic catalysts ($BiCl_3$, $In(OTf)_3$, $FeCl_3$, $Fe(OTf)_3$, $Yd(OTf)_3$, $Zn(OTf)_2$, $Sc(OTf)_3$, $Ni(OTf)_2$, $Cu(OTf)_2$, AuCl, $Hg(OTf)_2$, and AgOTf) were examined,[13] and found that many of them could catalyze this reaction albeit delivered products in low to moderate yields (70-79%) and moderate diastereoselectivity. Brønsted acids TFA, PPTS, PTSA were found to be inactive towards this transformation. Taking into consideration the low cost, environmentally benign nature of bismuth, initially identified conditions using $Bi(OTf)_3$ (10 mol%) in CH_2Cl_2 at rt were chosen as optimal for this methodolgy (entry a, Scheme 13).



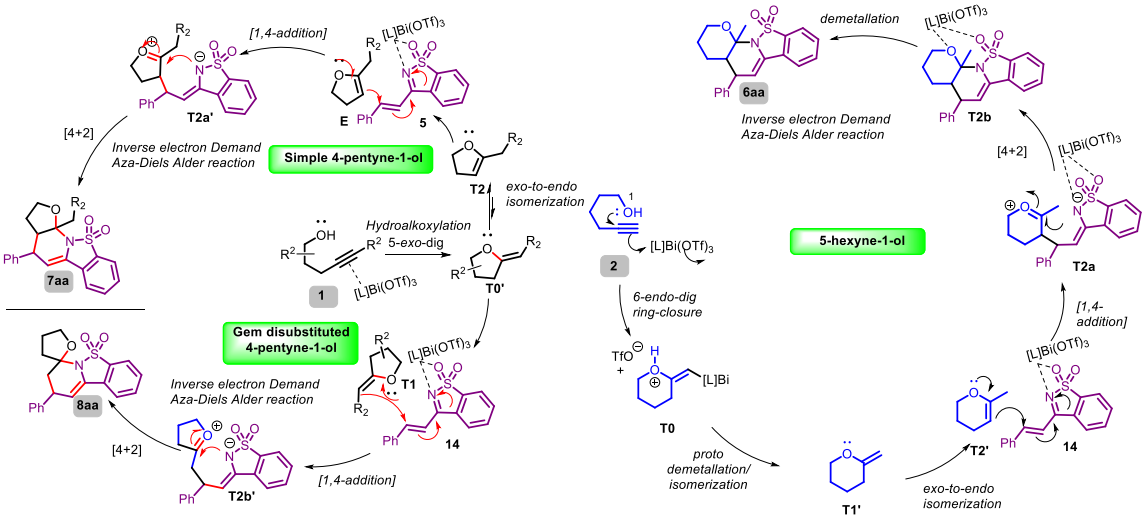
Scheme 13 | Optimization and scope of [4+2]-annulation (IEDDA) reaction.

With optimal reaction conditions in hand, initially, we have investigated the scope of this process with respect to 5-hexyne-1-ols **2a** (possessing terminal alkyne functionality) and α,β-unsaturated ketimines **14a**. All the tested reactions delivered corresponding benzoisothiazolo-pyranopyridine-dioxides (having fused 5/6/6 ring system; synthesized 19 examples) in good to excellent yields (up to 83% yield) and diastereoselectivity (dr 1 :0.2 to exclusive). In this work, alkynols possessing 1°, 2° and 3° hydroxyl functionality, and

sulphonamides containing diverse aryl substitueents were found to be good substrates (entry b, Scheme 13).

To extrapolate the generality further, we began investigating the scope of terminal alkyne-containing and unsubstituted 4-pentyn-1-ols alkynols (**1**) with α,β-unsaturated ketimine (**14**). To our surprise, a strikingly different reaction pattern was observed by providing fused benzoisothiazolo furopyridine dioxides (instead of anticipated spiro benzoisothiazolo furopyridine dioxide). This could be due to the initial formation of exo-cyclic enol ether followed by its isomerization into its eno-cyclic enol ether and participation in the annulation reaction. All reactions were worked well and able to deliver desired products in good yields and exclusive diastereoselectivity (entry c, Scheme 13).

We continued further to verify the scope of the reaction with germinal substituted 4-pentyn-1-ols (having a primary hydroxyl group).[13] To our surprise, spirocyclic benzoisothiazolo pyridinyl-furan 5,5-dioxide **8** were obtained instead of fused benzoisothiazolo furopyridine dioxides (**7**). This annulation reaction was found to be general, diastereoselective and delivered products in good to excellent yield at ambient temperature in 8-12 h (entry d, Scheme 13).



Scheme 14: Plausible reaction mechanism.

Plausible mechanistic pathways based on the above experimental results (Scheme 13) and earlier reports[11] is described in Scheme 14 for products **6**, **7**, and **8**. In the case of product 6 formation (fused N,O-heterocycle), the reaction is initiated by the π-coordination of $Bi(OTf)_3$ to the C-C triple bond of alkynol **2**, which triggers the 6-*exo*-dig cyclization

(hydroalkoxylation) and gives, exocyclic enol ether **T1'** *via* **T0**. Then **T0** converts into favored endocyclic enol ether **T2'**. Enol ether **T2'** reacts with the activated α,β-unsaturated ketimine **14** in [4+2]-cycloaddition (IEDDA) mode or step-wise Michael addition mode and delivers corresponding product **6**. In a similar, way unsubstituted 4-pentyn-aols (**1**) undergo initial exo-dig cycloisomerization and form **T0'**, which subsequently undergo *exo*-endo isomerization and participated in annulation reaction to give fused 6/5-N, O-heterocycle **7**. In contrast to this outcome, 4-pentyn-1ols containing geminal substituents undergo *exo*-dig mode of cycloisomerization and lead to exocyclic enol ether selectively, which undergoes annulation reaction and delivers spirocyclic 6/5 N,O-heterocycle **8**.

In conclusion, we have accomplished a novel $Bi(OTf)_3$-catalyzed inverse electron demand aza Diels-Alder [4+2] reaction for the construction of isothiazolo-pyridinyl-furan dioxide and pyranopyridine dioxide through regioselective 1,4-addition of bis-nucleophilic cyclic enol ether intermediates for the first time. It was disclosed from readily accessible 4-pentyn-1-ols or 5-hexyn-1-ols and α,β-unsaturated ketimine. The additional supporting experimental study supports our proposed [4+2] reaction pathway. Products obtained in this work were established by single-crystal X-ray diffraction analyses and analogy. Usage of readily available starting materials, operational simplicity, ambient temperature, wider substrate scope, and good to excellent yields, scalability, and step and atom economy are salient features of this strategy.

5. <u>Summary</u>: In Chapter 1 provided a general introduction to the chemistry of alkynes. It details the origin of alkynes, and various synthetic methods reported to access alkynes, which facilitate the expansion of the alkyne-based synthetic transformations. It also collates a literature review focusing on recent advancements in chemistry involving various alkynyl alcohols and carbonyl compounds *via* dual activation (σ and π-activation). In Chapter 2, we have disclosed an unprecedented hydroalkoxylation (cycloisomerization) and hydro-(hetero)arylation cascade reaction of alkynols with arenes and hetero-arenes $Bi(OTf)_3$. Reactions employing diverse alkynols and electron-rich arenes/heteroarenes proceeded smoothly under facile reaction conditions and furnished a library of novel 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans in good to excellent yields in an atom and step economic way. In Chapter 3, we have established a protocol for the facile construction of complex chromanes *via* Ag(I)-catalyzed cascade [3+3]-annulation of 5-hexyn-1-ols and α,β-

unsaturated ketones. Theoretical calculations elucidated the role of the fluorobenzene (solvent) in fine-tuning the Ag-catalysis by stabilizing respective complexes for the first time, thermodynamically favored endocyclic enol ether formation and its selective participation in an intermolecular 1,4-addition reaction which led to exclusive regioselectivity. Operationally simplicity, scalability, and broad substrate scope are salient features of this strategy. Chapter 4 describes our investigations involving $Bi(OTf)_3$-catalyzed inverse electron demand aza Diels-Alder [4+2] reaction for the construction of isothiazolo-pyridinyl-furan dioxide and pyranopyridine dioxide through regioselective 1,4-addition of bis-nucleophilic cyclic enol ether intermediates for the first time. Herein, we used readily accessible 4-pentyn-1-ols or 5-hexyn-1-ols and α,β-unsaturated ketimine as building blocks for the construction of medicinally relevant sulphonamide-derived scaffolds. The additional supporting experimental study supports our proposed [4+2] reaction pathway. Products obtained in this work were established by single-crystal X-ray diffraction analyses and analogy.

6. <u>Future directions:</u> As part of this thesis work, several heterocyclic compounds (O, N, and S-containing) related to bioactive natural products and drugs were synthesized via developing unprecedented cascade annulation reactions of diverse alkynols with hydroxy arenes, enones, and sulphonamides. Several new chemical entities (NCEs) like a-(hetero)aryl-furans/pyrans (Chapter 2), simple to complex chromanes (Chapter 3), and cyclic sulphonamide-derived N, o-heterocycles (fused and spirocyclic) (Chapter 4) were synthesized in good quantities and good to excellent isolated yields. All of these NCEs may be tested for their biological activity profile, which leads to the identification of lead structures for drug discovery. In addition, these developed protocols may be utilized in the stereoselective total synthesis of related bioactive natural products, and their congeners.

7. <u>Publications:</u>

1. **Ashwini, K. N.;** Madhukar, S. P.; Kontham, R. Bismuth(III)-catalyzed cycloisomerization and (hetero)arylation of alkynols: simple access to 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans. *Org. Biomol. Chem*., **2018**, *16,* 3229–3240.
2. **Ashwini, K. N,;** Thorat, S. S.; Jain, S.; Gamidi, R. K.; Vanka, K.; Kontham, R. Silver-Catalyzed [3+3]-Annulation Cascade of Alkynyl Alcohols and α,β-Unsaturated Ketones for the Regioselective Assembly of Chromanes. *Org. Chem. Fornt*. **2022**, *9*, 802-809.
3. **Ashwini, K. N**.; Kataria, P.; Gamidi, R. K.; Ravindar, K. $Bi(OTf)_3$-catalyzed Inverse-Electron-Demand Aza-Diels-Alder reaction of alkynols and *α-β* -unsaturated ketimines (*Manuscript under preparation*).
4. Vinodkumar, R.; **Ashwini, K. N.;** Gamidi, R. K.; Kontham, R. Bronsted acid (MsOH)-mediated dimerisation cascade of α,β-Unsaturated γ- ketoesters: Diastereoselective synthesis of pyrano-ketal lactones (*Manuscript under preparation*).
5. Pooja, I. S.; **Ashwini, K. N.;** Gamidi, R. K.; Kontham, R. Fe(III)-Catalyzed Diastereoselective Friedel-Crafts Alkylation-Hemiketalization-Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol-Lactones (*Manuscript under preparation*).
6. **Ashwini, K. N.;** Pooja, I. S.; Digambar, A. K.; Kontham, R. Stereoselective Total Synthesis of Polyketide Natural Product Opaliferin. *Manuscript under preparation.*
7. Vinodkumar, R.; **Ashwini, K. N.;** Gamidi, R. K.; Kontham, R. Synthesis of of (5-6-5)- bis-spiroketals *via* silver- catalyzed cascade annulation of 4-pentyn-1-ols and aldehydes. *Manuscript under preparation.*
8. Vinodkumar, R.; **Ashwini, K. N.;** Gamidi, R. K.; Kontham, R. Synthesis of dipyrano pyrans *via* silver-catalyzed cascade annulation of 5-hexyn-1-ols and aldehydes. *Manuscript under preparation.*

8. References:

1. (a) Jampilek, J.; *Molecules*, **2019**, *24*, 3839; (b) Martins, P.; Jesus, J.; Santos, S.; Raposo, L. R.; Roma-Rodrigues, C.; Baptista, P. V.; Fernandes, A. R. *Molecules*, **2015**, *20*, 16852–16891.
2. Delost, M. D.; Smith, D. T.; Anderson, B. J.; Njardarson, J. T. *J. Med. Chem*., **2018**, *61*, 10996–11020.
3. Singh P. K.; Silakari, O. *Chem. Med. Chem*, **2018**, *13*, 1071–1087.
4. Heinz, G.; Wolfgang, K.; Hans-Martin, W.;Wolfgang, R.; Guido, S.; Herbert, D.; Horst, B.; Kurt-Kieczka. S. *Ullmann's Encyclopedia of Industrial Chemistry. Weinheim*: Wiley-VCH. doi:10.1002/14356007.a04_455.
5. Krstenansky, J. L.; Del Rosario-Chow, M.; Currie, B. L. *J. Heterocycl. Chem*., **1992**, *29*, 707–711.
6. Wang, X.; yao, Z.; Dong, S.; Wei, F.; wang, H.; Xu, Z. *Org. Lett*., **2013**, *9*, 2234-2237.
7. Li, D. Y.; Jiang, L. L.; Chen, S.; Huang, Z. L.; Dang, L.; Wu, X. Y.; Liu, P. N.; *Org. Lett*. **2016**, *18*, (19), 5134-5137.
8. (a) Wang, L.; Liu, L.; Chang, W.; Li, J. *J. Org. Chem.*, **2018**, *83*, 7799–7813. (b) He, C.; Cai, J.; Zheng, Y.; Pei, C.; Qiu, L.; Xu, X. *ACS Omega*, **2019**, *4*, 15754 – 15763.
9. Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817-7831.
10. (a) Liu, Z.; Breit, B. *Angew. Chem. Int. Ed.*, **2016**, *55*, 8440−8443; (b). Zhdanko, A.; Maier, M. E. *ACS Catal.*, **2015**, *5*, 5994-6004; (c). Masatoshi, S.; Fujita, S.; Masanori, A.; Yamamoto, Y. *ACS Catal.*, **2017**, *7*, 2848−2852; (c) Li, H-J.; Guillot, R.; Gandon, V. *J. Org. Chem*., **2010**, *75*, 8435–8449.
11. (a) Kambale, D. A.; Thorat, S. S.; Pratapure, M. S.; Gonnade, R. G.; Kontham, R. *Chem. Commun.*, **2017**, *53*, 6641-6644; (b) Thorat, S. S.; Kataria, P.; Kontham, R.; *Org. Lett*., **2018**, *20*, 872–875; (c) Ashwini K. N.; Thorat, S. S.; Jain, S.; Gamidi R. K.; Vanka, K.; Kontham, R. *Org. Chem. Fornt*. **2022**, *9*, 802-809. (d) Nakate, A. K.; Pratapure, M. S.; Kontham, R. *Org. Biomol. Chem.*, **2018**, *16*, 3229–3240.
12. Bessley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans* **1915**, *107*, 1081−1092.
13. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun*., **1976**, *18*, 734−736; (b) Gilmore, K.; Alabugin, I. V. *Chem. Rev*., **2011**, *111*, 6513–6556.

14. (a) Celebioglu, A.; Uyar, T.; *Agric. J. Food Chem*. **2017**, *65*, 5404−5412; b) Ding, J.; Yao, J.; Xue, J.; Li, R.; Bao, B.; Jiang, L.; Zhu, J.; He, Z. *ACS Appl. Mater. Interfaces* **2015**, *7*, 18145−18155; (c) Allen, K. M.; Coughlan, K. A.; Mahmood, F. N.; Valentine, R. J.; Ruderman, N. B.; Saha, A. K. *Arch. Biochem. Biophys*. **2017**, *623−624*, 49−57; (d) Coats, A.; Jain, S.; *J. Hum.Hypertens*. **2017**, *31*, 376−381;
15. (a) Dalpozzo, R.; Mancuso, R. *Symmetry* **2019**, *11*, 1510-1540; (b) Hallett, M. R.; Painter, J. E.; Quayle, P.; Ricketts, D.; Patel, P. *Tetrahedron Lett.* **1998**, *39*, 2851–2852; (c) Maikhuri, V. K.; Khatri, V.; Kumar, A.; Singh, B.; Prasad, A. K. *J. Org. Chem.* **2020**, *85*, 7068–7076.
16. Grob C. A.; Baumann, W.; *Helv. Chim. Acta*, **1955**, *38*, 594-610.
17. (a) Liang, L.; Li, E.-Q.; Huang, Y. *Org. Lett.*, **2015**, *17*, 4914-4917; (b) Tharra, P.; Baire, B. *Chem. Commun*., **2016**, *52*, 14290–14293:c); (c) Lin, H.; Dong, L. *Org. Lett*., **2016**, *18*, 5524–5527; (d) Li, Y.-Y.; Zhu, C.-Z.; Zhang, J. L. *Eur. J. Org. Chem*., **2017**, 6609–6613.
18. (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem*. **2014**, *57*, 10257–10274; (b) Gunatilaka, A. A. L. *J. Nat. Prod*. **2006**, *69*, 509. (c) Li, M.; Tang, C.; Yang, J.; Gu, Y. *Chem. Commun*. **2011**, *47*, 4529.

Chapter-1: Introduction to alkyne chemistry

1.1 Introduction

Alkynes are essential functional groups widely found in numerous organic small molecules. Their inactivity towards multiple reagents and catalytic systems attracted the chemists to use them as building blocks and intermediates in multistep organic synthesis. Due to the available robust process technologies involving acetylene (gas) as a precursor, many alkyne-derived fine chemicals and reagents entered the commercial market at affordable costs.[1] The C-C triple bond introduces two degrees of unsaturation and alkynes have the suffix "yne" (Figure 1.1).

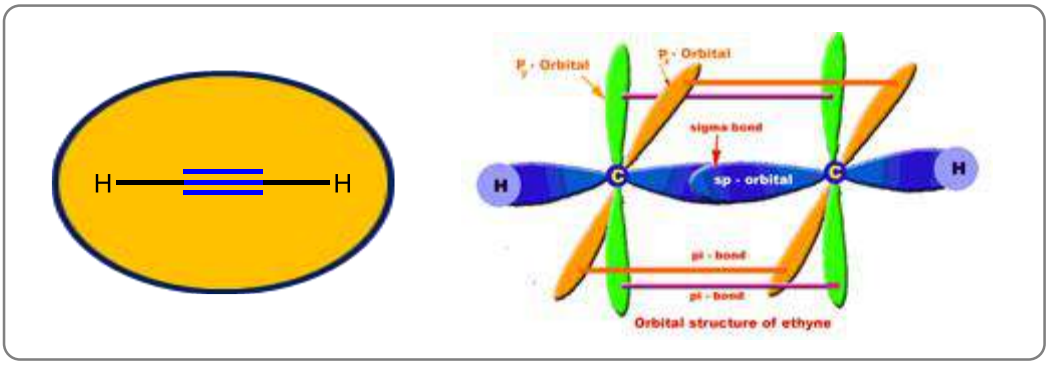


Figure 1.1 | Electronic structure of the alkyne (acetylene).

The physical properties of alkynes are determined by molecular size and the number of triple bonds present. The alkyne size increases the state of molecules from gas (C1-C3) to liquid (C4-C8) to solid (>C8). The number of triple bonds increases, the boiling point of alkyne increases due to higher bond energy than alkene and alkane, and the melting point and density decrease due to kinks in their shape, causing poor packing, and these are non-polar in nature and insoluble in water. Generally, most reactions work fast on alkynes compared to alkenes and alkanes. The other hydrocarbons are less acidic than terminal alkynes. Alkynes are the hybrid orbital concept for unsaturated hydrocarbons containing C-C triple bonds, such as nitrile and alkyne. Their empirical formula is $C_nH_{2n-2.}$ The alkyne molecules are linear; all four atoms are in a straight line. The triple bond length is 1.20 A^o, significantly shorter than alkenes and alkanes. Its bond energy is 839 kJ/mol. Alkyne carbon and hydrogen atoms are sp-hybridized. The sp-hybridization forms from the 2s orbital combined with the 2p orbital and gives two sp hybrids whose oriented angle is 180^o to each other. The

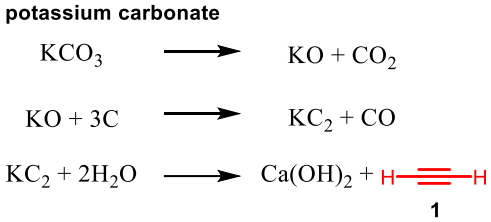
sigma bond of the C-C bond is formed by the overlapping of each carbon sp orbital, and the overlap of the 1s orbital of the hydrogen atom and the sp orbital of each carbon atom forms the C-H sigma bond. The π (pi) bond is formed from 2p and 2p orbitals of carbon, which remain non-hybridized, and are oriented along the *z* and *y* axes, respectively. However, π (pi) -bonds are highly reactive and give many transformations due to their being weaker than sigma bonds (Figure 1.1).[2]

1.2 Methods for the synthesis of alkynes precursor

As discussed in the above section, alkynes are well-known as unsaturated hydrocarbons possessing C-C triple bonds. Herein, we provide a brief history and literature survey on known synthetic methods for alkynes, facilitating access to various synthetic organic chemistry transformations.

I. Synthesis of acetylene from potassium carbonate and carbon

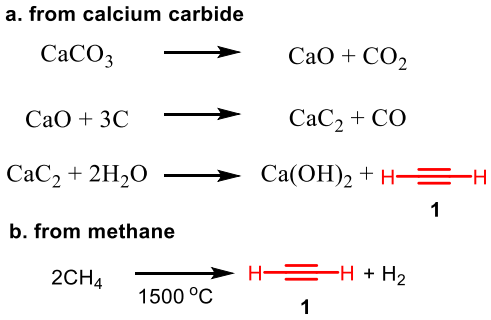
The simplest alkyne is acetylene which was discovered in 1836 by Edmund Davy by heating potassium carbonate with carbon at a very high temperature, and he named it the "new carburet of hydrogen" (Scheme 1.1)



Scheme 1.1. Edmund Davy's first synthesis of acetylene.

II. Synthesis of acetylene from calcium carbide:

Another exciting and well-developed process for producing acetylene was disclosed using calcium carbide in the presence of water.

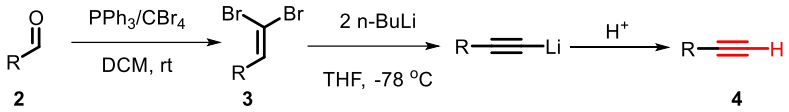


Scheme 1.2

This method is beneficial at the industrial level (entry a, Scheme 1.2). Nowadays, this method is replaced by pyrolysis of methane; the methane is heated at a high temperature of 1500 ^{o}C in an airless chamber (entry b, Scheme 1.2).

III. Synthesis of alkynes through Corey-Fuchs reaction

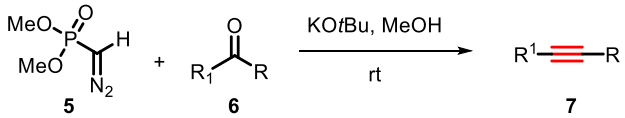
Corey and Fuch, in 1972, developed a two-step synthetic route for alkynes. In this route, aldehydes (**2**) are used as precursors, which are initially converted into vinyl gem-dibromides (**3**) using PPh_3/CBr_4. The second step using 2 equivalents of *n*-BuLi furnish corresponding alkynes via dehydro-bromination and the exchange of alkynyl bromide with lithium (Scheme 1.3).[3]



Scheme 1.3

IV. Synthesis of internal alkynes by Seyferth-Gilbert reagent

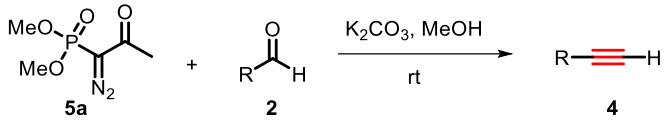
Seyferth-Gilbert reported a fascinating method for the synthesis of alkyne from the reaction of aldehydes or ketones with dimethyl (diazomethyl)phosphonate (**5**) and potassium *tert*-butoxide. The mechanism of the reaction follows Horner-Wadsworth-Emmons olefination followed by Fritsch-Buttemberg-Wiechell rearrangement of the *in situ* generated alkylidene carbene (Scheme 1.4).[4]



Scheme 1.4

V. Ohira-Bestmann reaction for the synthesis of terminal alkynes

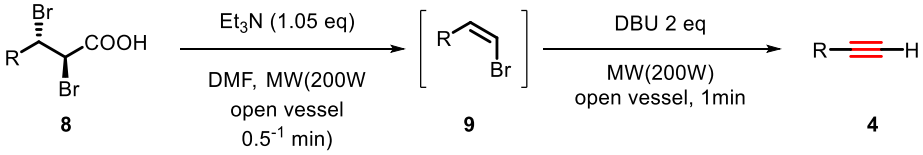
The Bestmann-Ohira reagent (dialkyl (1-diazo-2-oxopropyl)phosphonate (**5a**) is a versatile reagent in synthetic organic chemistry, which is widely used for the construction of terminal alkynes through homologation of aldehydes. The discovery of this reagent initially began in the 1970s and was inspired by the Seferth-Gilbert reagent (**5**) (Scheme 1.5). [5,6]



Scheme 1.5

VI. Through microwave-assisted decarboxylative debromination

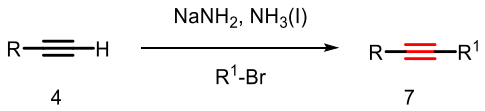
Tokuda developed an expeditious Microwave-assisted one-pot synthesis of terminal alkynes and enynes from *anti*-2,3-dibromoalkanoic acid *via*, (*Z*)-1-broo-1-alkenes. This protocol delivered diverse alkynes in excellent yields (Scheme 1.6) [7]



Scheme 1.6

VII. Synthesis of unsymmetrical alkynes from sodium acetylides

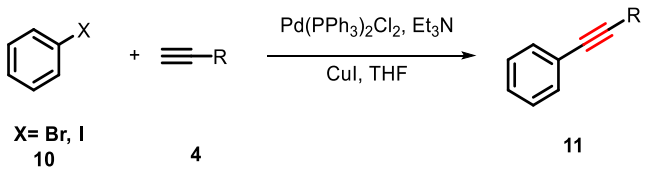
Shepherd and co-workers, in 2006, developed a widely used methodology for synthesizing unsymmetrical or internal alkynes from terminal alkynes through the initial generation of sodium acetylides followed by alkylation using the alkyl halides *via* SN^2 type reaction (Scheme 1.7).[8]



Scheme 1.7

VIII. Synthesis of aryl alkynes through Sonogashira coupling

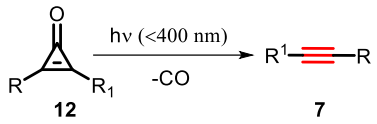
Synthesis of conjugated alkynes and aryl alkynes (**11**) was reported by Sonogashira in 2002 using palladium-catalyzed cross-coupling (sp2-sp) between aryl/alkenyl halide/triflate (**10**) and terminal alkynes (**4**), in the presence of CuI as a cocatalyst and Et_3N as a base (Scheme 1.8). [9]



Scheme 1.8

IX. Through photo-triggered decarbonylation of cyclopropenones

In 2019, Kunishima and co-workers reported a novel method for the synthesis of alkyne (**7**) by photo catalyst-induced decarbonylation of cyclopropenones (**12**) (Scheme 1.9).[10]

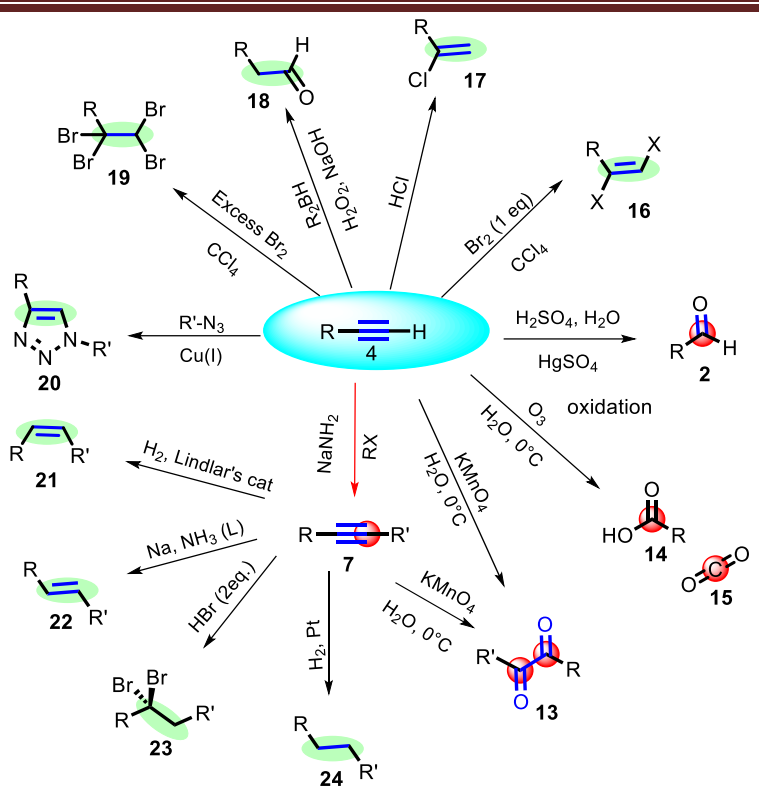


Scheme 1.9

With the availability of the above robust synthetic tools to access diverse alkynes (terminal and internal), and their inherent selectivity toward many catalysts and reaction conditions, a plethora of synthetic organic transformations involving alkynes was developed in recent times, which were widely employed in the fields of medicinal chemistry, material chemistry, and natural products synthesis. In this context, a brief literature survey is provided on the general reactivity of alkynes and our present thesis's hypothesis generation.

1.3 General reactivity of alkynes

Like alkenes, alkynes undergo various addition reactions *via* breaking the C-C π-bonds. For instance, partial or complete hydrogenation reactions deliver corresponding alkenes and alkanes and participate in diverse electrophilic reactions (with the aid of an array of π-activating catalysts: Brønsted acids, transition metal salts, and Lewis acids) of halogenation, hydrohalogenation, hydroamination, hydrometallation, hydration, oxidation, ozonolysis, dissolved metal reductions, vinylation (hydroalkoxylation), dipolar cycloadditions (Nobel prize-winning "Click" chemistry) and many others, which would produce important synthons like alcohols, aldehydes, ketones, amines, enamines, organo halides, dihalides and many other functional groups utilized in the synthetic organic chemistry. Whereas terminal alkynes undergo nucleophilic addition reactions with the aid of terminal acidic C-H bond and are also used as coupling partners in transition metal-catalyzed coupling reactions (Sonogashira) (Scheme 1.10).



Scheme 1.10 Synthetic applications of alkynes.

1.4 Reactions involving alkynes: Literature survey

Organic chemists have paid much attention to developing flexible synthetic methodologies involving alkyne-containing building blocks in the presence of suitable catalytic systems (via π-activation). Recent years have seen much work put into developing the transition metal-catalyzed reactions that are used to access complex scaffolds in a more straightforward way.

The triple bond tends to fold back away once the π bond of the alkyne chelate to the metal center, making the carbon-metal bond distance slightly shorter than that of the comparable alkene complexes. Similar to how alkenes coordinate with metals, alkynes do as well. Alkynes can function as either a 4- or a 2-electron donor, depending on the metal. Alkyne-containing scaffolds emerged as key starting materials in the construction of various O- and N-heterocycles. So far, various Au(I), Au(III), Pt(II), Pd(II), Ir(I), Bi(III), Ag(I), Hg(II), Co(II), Cu(III), and Rh(I)-derived catalytic systems have been used for the alkyne-activation (π-activation) induced intramolecular and intermolecular cycloisomerization and annulation reactions. (Figure 1.2).

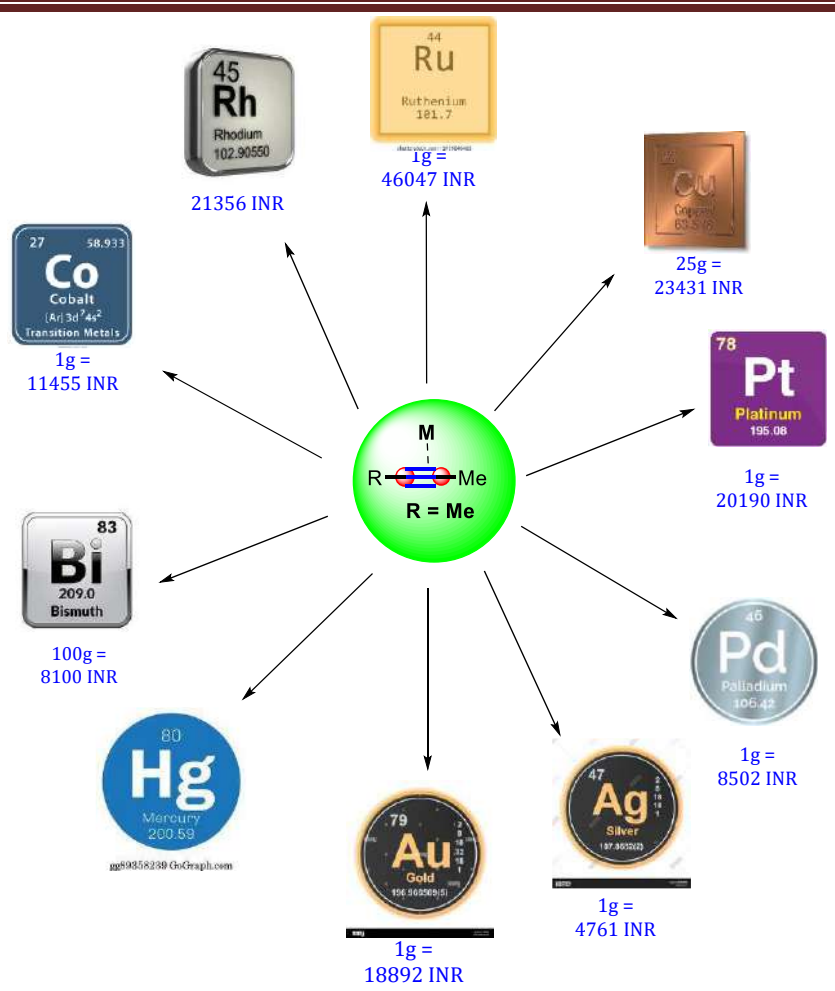
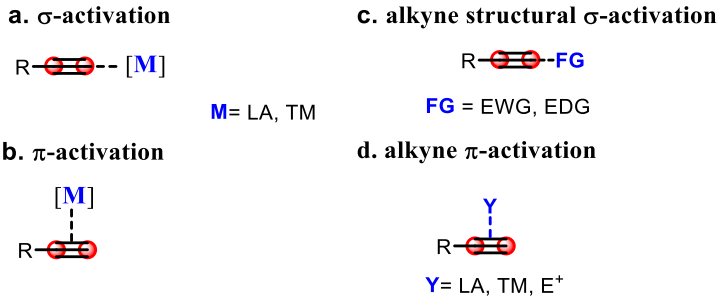


Figure 1.2 Selected list of metal catalysts used for alkyne activation (π - activation).

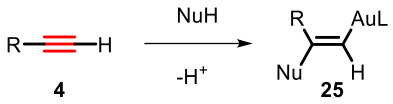
Gold complexes function as gentle and effective Lewis's acids and π -bond activating catalysts, and are one of the numerous metal catalysts used to activate C-C triple bonds,[11] which can be attributed to the relativistic effects displayed by gold-based catalysts.[12] In 1998, Telesin reported the first instance of activating alkynes using gold(I)-catalyst, which sparked the development of numerous adaptable synthetic techniques.

In general, the alkynes activations are two types, σ-activation of terminal alkynes is possible in the metathesis reaction, whereas π-activations are possible in the terminal and internal alkyne.[13] The drawback σ-activations of the alkyne is the necessity of the stoichiometric amount of coordinating moiety (entries a and b, Scheme 1.11).



Scheme 1.11 Rout of functionalization of C-C multiple bonds.

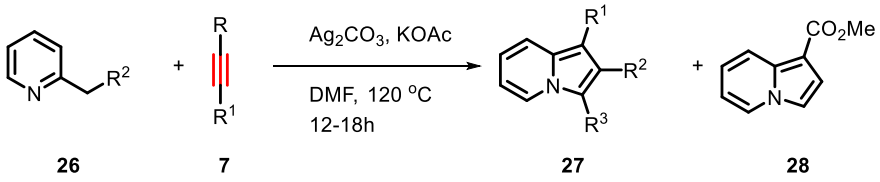
Generally, nucleophilic addition reaction on C-C triple bonds works via Markovnikov's rule by η^2 activated alkynes **4** and forms a *trans* alkene metal complex (**25**) (Scheme 1.12).



Scheme 1.12 Anti-nucleophilic attack on the metal-activated alkyne.

1.4.1 Annulation of pyridines with alkynes:

Liang and Pan developed a method for the synthesis of indolizines **27** and **28** *via* silver-mediated oxidative C-H functionalization induced by and 5-*endo*-dig mode of cyclization of 2 -alkylazaarenes **26** with internal alkyne **7**. The Ag_2CO_3 was recycled and reused, and 19 different types of indolizine derivatives were prepared by following this strategy in good yields. This reaction works via the alkyne radical and ionic pathways.[14] Similar work was reported by Agrawal et al. in 2014 with the same reaction conditions, focusing on only terminal alkynes with 15 different derivatives (Scheme 1.13).[15]

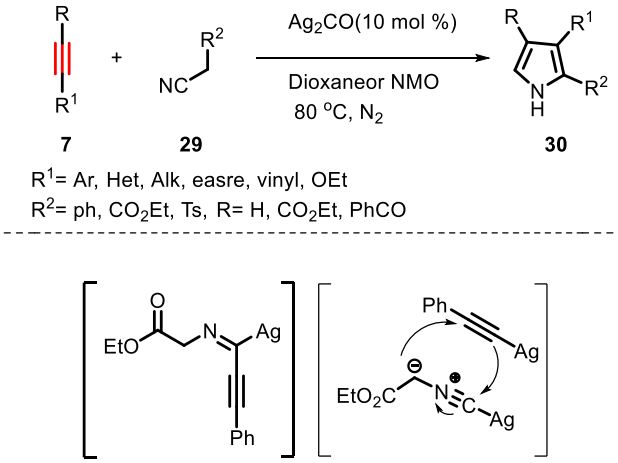


Scheme 1.13 Synthesis of indolizines from alkyl pyridines and alkynes.

1.4.2 [3+2]-Cycloaddition reaction involving alkynes and methylene-isonitriles:

The initial report for the synthesis of pyrroles from isocyanides and alkynes via [3+2] cycloaddition reaction was reported in 1997.[16] After a long time in 2005, Yamamoto and Meijer developed a method using copper-catalysed conditions, which

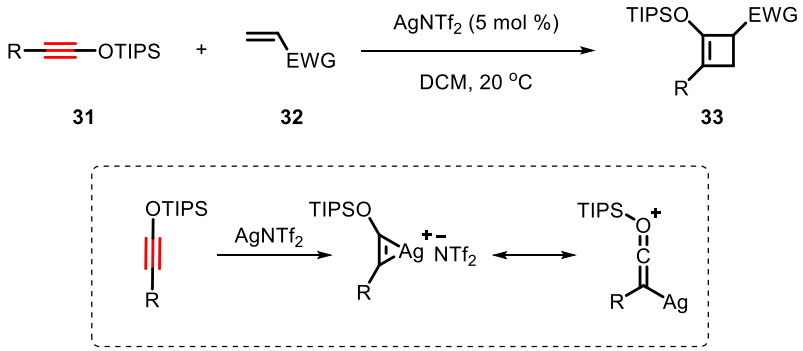
isn't applicable for substrates possessing non-activated alkynes.[17] In 2013, Lei and co-workers discovered novel reaction conditions for the synthesis of pyrroles **30** using Ag_2CO_3 as a unique and robust catalyst via [3+2] cycloaddition reaction of isocyanides **29** and alkynes **7** (Scheme 1.14).[18]



Scheme 1.14 Synthesis of pyrroles.

1.4.3 [2+2]-Cycloaddition reaction:

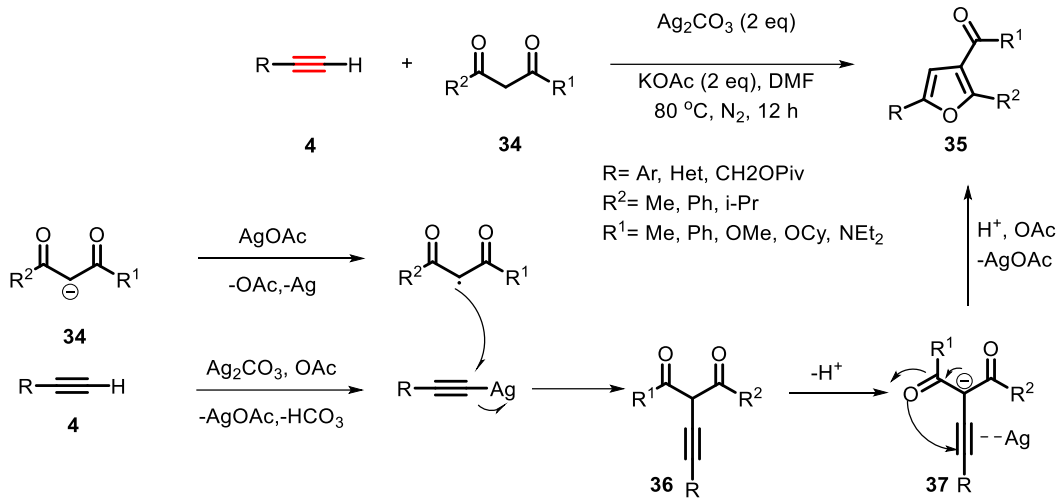
Kozmin and colleagues in 2004, reported on the [2+2]-cycloaddition reaction by using siloxy-alkyne **31** and, α,β-unsaturated ketone/esters/and nitriles **32** that produced cyclobutanes **33**. Here authors were able to identify electron-rich silyloxy alkynes **31** are activated by the $AgNTf_2$ catalyst to produce the corresponding Ag complex, which then participates in cycloaddition to produce the desired product, cyclobutenes (Scheme 1.15).[19]



Scheme 1.15 Synthesis of cyclobutenes through [2+2]-cycloaddition reaction.

1.4.4 Oxidative C-H/C-H functionalization:

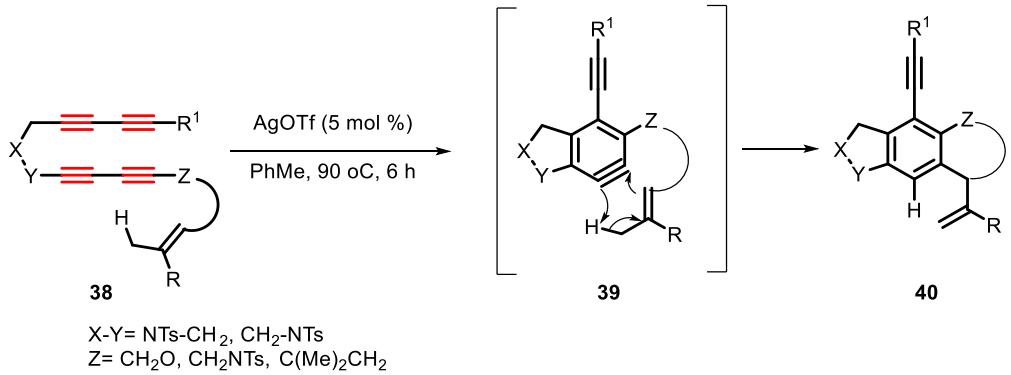
By employing readily available alkyne **4** and 1,3-dicarbonyl compounds **34** as starting materials terminal, Lei's group devised a protocol for the oxidative C-H/C-H functionalization in 2013, which led to the synthesis of diverse furan derivatives **35** (Scheme 1.16).[20]



Scheme 1.16 Synthesis of furan derivatives.

1.4.5 Hexa-Dehydro Diels-Alder Reaction (HDDA):

Lee and co-workers in 2013, developed a very interesting methodology for the construction of complex benzenoids **40** from bis-1,3-diynes **38** (tethered with an alkene functionality) in the presence of AgOTf (5 mol, %) as a catalyst. This reaction proceeds through intramolecular tandem hexa-dehydro Diels-Alder reaction (HDDA), followed by the Alder-ene reaction of aryne intermediate **39** (Scheme 1.17).[21]



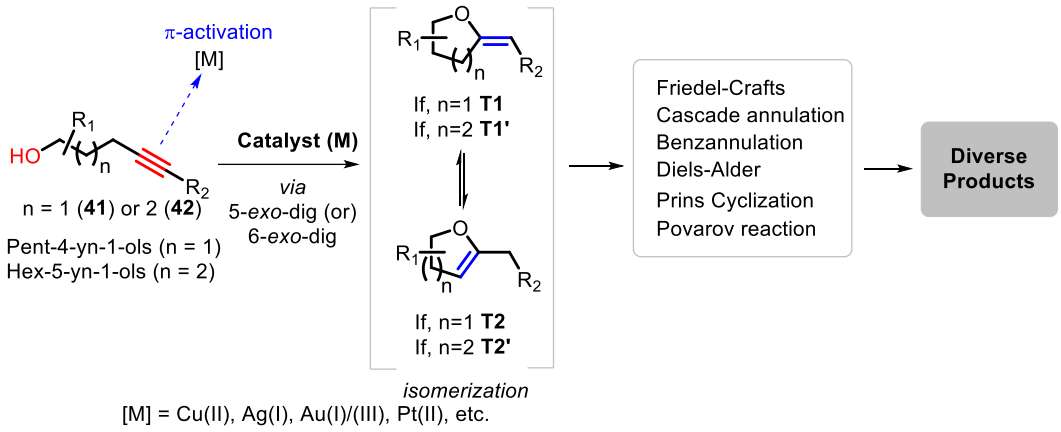
Scheme 1.17 Synthesis alkene and allyl substituted complex benzenoids.

1.5 Reactivity of alkynyl alcohols

Alkynyl alcohols (alkynols) are one of the important classes of building blocks disclosed in the literature. These include prop-2-yn-1-ols (propargylic alcohols), but-

3-yn-1-ols (homopropargylic alcohols), pent-4-yn-1-ols and hex-5-yn-1-ols. These last two categories of alkynols (pent-4-yn-1-ols (**41**) and hex-5-yn-1-ols (**42**)) readily undergo intramolecular hydroalkoxylation (via 5-*exo*-dig and/or 6-*endo*-dig mode of ring closure) with the aid of suitable π-activating catalysts and generate the corresponding oxacarbenium species followed by enol-ethers (**T1**/**T1'**, **T2**/**T2'**) which participate in diverse intra- and intermolecular annulation reactions and deliver corresponding 5- and/or 6-membered oxygen- and/or nitrogen heterocycles (for instance chromanes, furopyrans, spiro acetals, spiroquinolines and corresponding 5- or 6-membered aromatic heterocycles) through Friedel-Craft reaction,[22] cascade annulation,[23] benzannulation,[24] Diels-Alder,[25] Prins-type reaction,[26] Povarov reaction[27] pathways.

This phenomenon was earlier studied using Cu(II), Au(I), Au(III), Pt(II), Pd(II), Ir(I), and Rh(I)-derived π-activating catalysts and utilized in the construction of various spiroketals and applied in the field of total synthesis of bioactive natural products, medicinal chemistry and pheromone technology (Scheme1.18).[28]



Scheme 1.18 Catalytic transformations involving alkynols (*via* cyclic enol-ether intermediates).

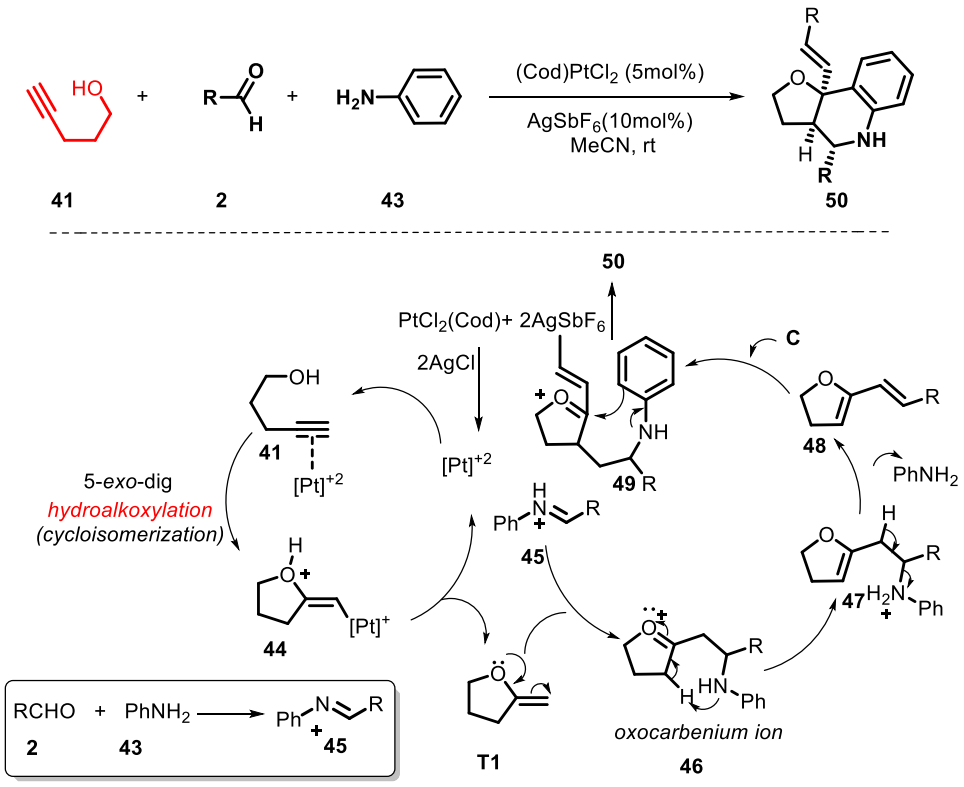
1.6 Reactions involving 4-pentyn-1ols

As discussed in the previous section, 4-pentyn-1ols readily undergo intramolecular hydroalkoxylation and generate corresponding cyclic enol ethers possessing *exo*- or *endo*-cyclic-olefinic functionality (**T1** and **T2**, respectively) with the aid of transition metal-based catalysts, simple Lewis's acids or Brønsted acid catalysts (Scheme 1.18). These cyclic enol-ethers can

participate as nucleophiles or electrophiles in subsequent inter- or intramolecular annulation reactions and deliver corresponding oxygen heterocycles related to bioactive natural and unnatural products. These annulation reactions are highly straightforward and produce complex molecules in an atom- and step-economic way. Herein, furnished a selected list of important synthetic transformations involving 4-pentyn-1ols (**41**).

1.6.1 Pt-Catalyzed cascade reactions of 4-pentyn-1-ols with aldehydes and amines:

In 2008, Fañanás and co-workers reported an expedient one-pot-multicomponent cascade protocol encompassing Pt(II)-catalyzed construction of furuquinolones from readily available alkynols **41**/**42**, aldehydes **2** and anilines **43**.

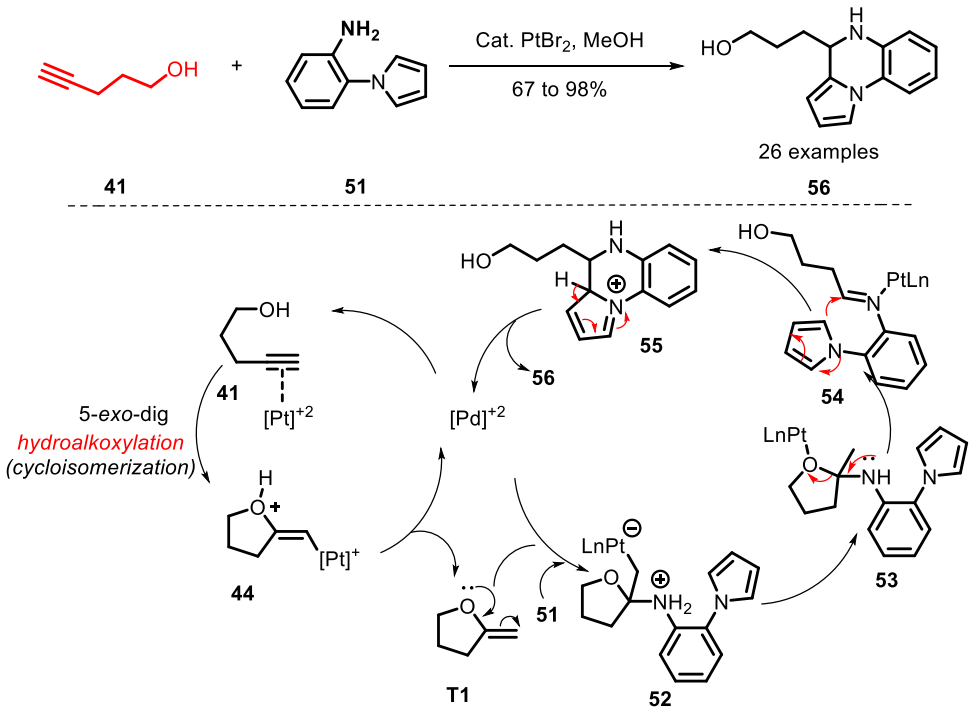


Scheme 1.19. Three-component synthesis of furuquinolones.

Mechanistically, this reaction proceeds through the Pt(II) and $AgSbF_6$(10 mol%)-catalyzed formation of cyclic enol ether intermediate **T1** (via triple bond activation and intramolecular hydroalkoxylation of alkynols steps), which would subsequently react

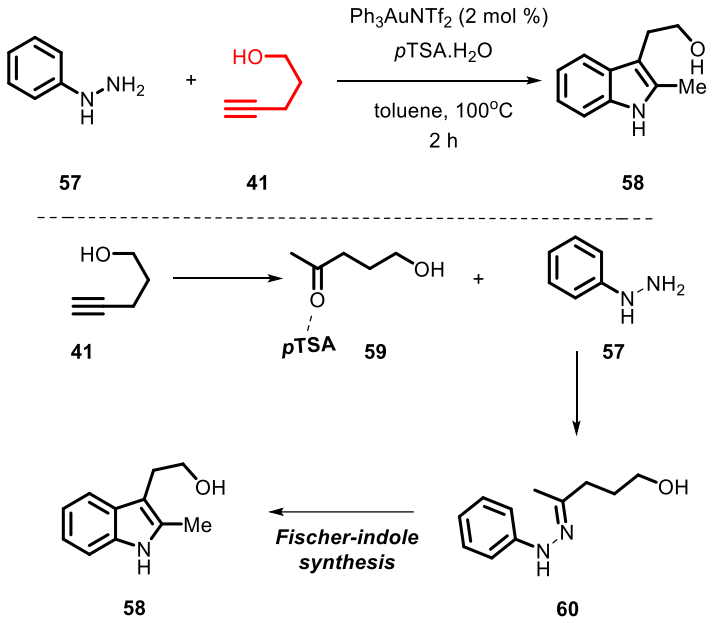
with imines **45** (formed through Mannich type reaction of amine and aldehyde; nitrogen coordinate with Pt-complex) to give oxocarbenium ion **46** followed by amine derivative **47**. Next, the elimination of amines would give the diene intermediate **48** which further reacts with imines **45** to deliver the final product furuquinolones (**44**). Broad substrate scope, functional group tolerability, and scalability are salient features of this work (Scheme 1.19).[23]

Patil's research group developed an efficient methodology for the synthesis of quinoxalines and indolo-quinolines from alkynols using Pt(II) catalysis. Through Markownikov's hydroamination-hydroarylation of cyclic enol ethers as key transformations.[29] The treatment of alkynol **41** with amino group-containing aromatics **51** using $PtBr_2$ as a catalyst in MeOH as a solvent produced substituted pyrrolo[1,2-a] quinoxalines and indolo[3,2-c] quinolines **56** with excellent yields. This reaction first gives an oxocarbenium ion from enol ether **T1** through Pt(II)-catalyzed intramolecular hydroalkoxylation of alkynol **41**, then it reacts with amines **51**, the opening of tetrahydrofuran ring **53** to produce the final substituted pyrrolo[1,2-a] quinoxalines and indolo[3,2-c] quinolines **56** (Scheme 1.20).



Scheme 1.20. Synthesis of substituted pyrrolo[1,2-a] quinoxalines and indolo[3,2-c] quinolines.

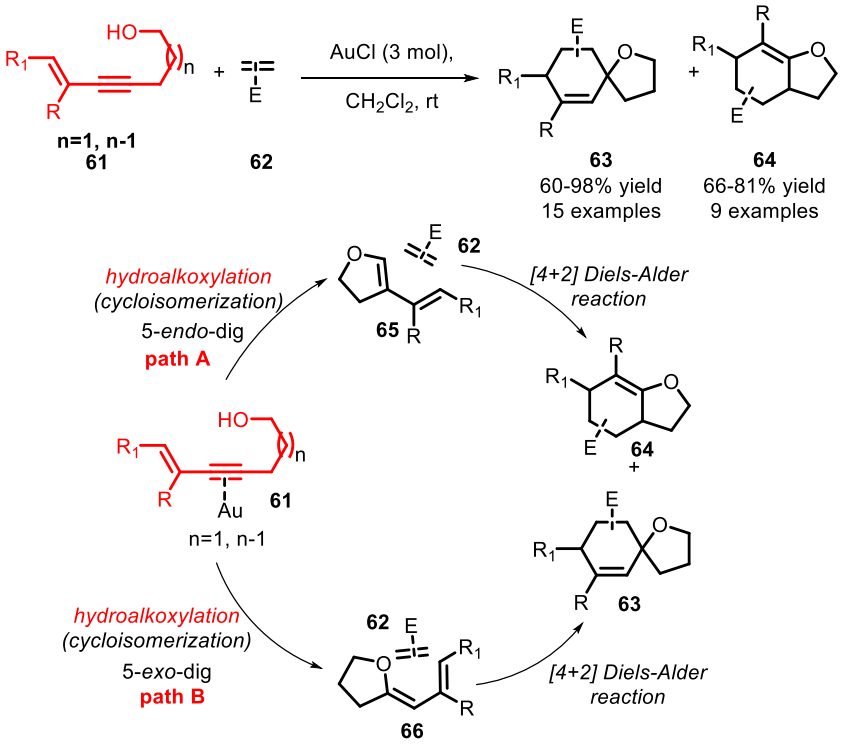
In another report, Patil's group disclosed a novel protocol for the synthesis of 2,3-disubstituted indoles via hydroamination of alkynols **41** using arylhydrazines **57**. The Ph_3AuNTf_2 (2 mol%)/pTSA-H_2O binary catalytic system was used in this technique. The initial p-TSA-mediated hydration of alkynols **41** would lead to the formation of hydroxyl-ketone **59**, this subsequently undergoes a reaction with arylhydrazine **57** to produce arylhydrazone **60**, which then converts to indole **58** following the Fischer-indolization mechanism (Scheme 1.21).[30]



Scheme 1.21. Synthesis of 2,3-substituted indole mimicking the Fisher indolization.

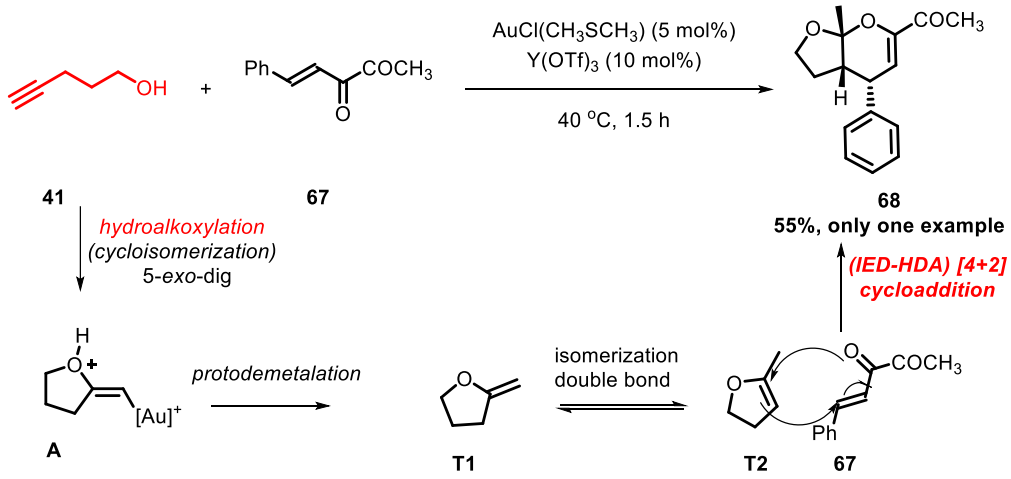
1.6.2 [4+2]-Cycloaddition reactions involving alkynols

Fañanás research group in 2010 developed a Diels-Alder cascade reaction involving enyne-ols and olefins.[25e] This cascade [4+2]-cycloaddition uses alkynols as modular building blocks for diverse heterocycles. This reaction is triggered by the π-activation of alkynols to give corresponding enol-derived diene and subsequently participates in cycloaddition reaction. Alkynol **61** treated with olefin **62** in the presence of AuCl in dichloroethane at rt, which is delivered two products spiro-bicycle **63** and fused bicycle **64** in good yields. Intramolecular hydroalkoxylation **61** (alkynols) generates endocyclic enol ether **65** and exocyclic enol ether **66**, these act as dienes and participate in Diels-Alder [4+2]-cycloaddition with suitable dienophiles to afford the spiro-bicycles and fused bicycles (Scheme 1.22).



Scheme 1.22. Synthesis of spiro and fused bicycles.

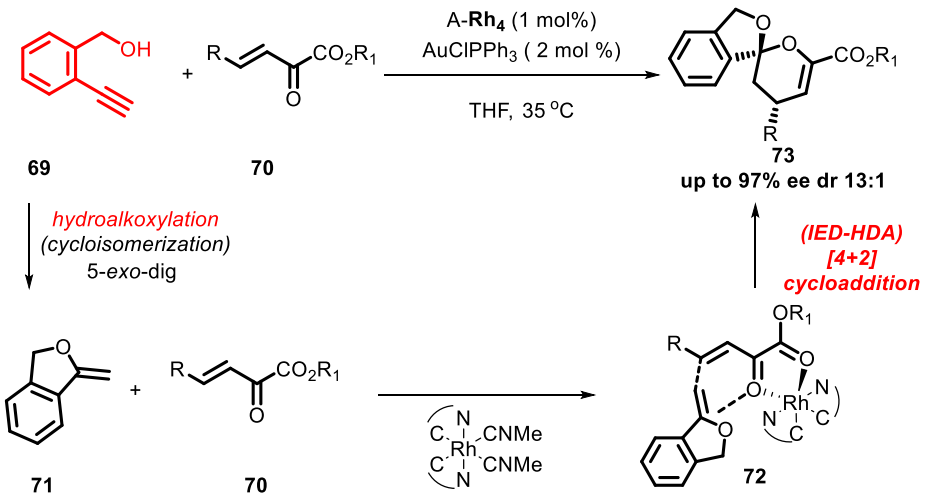
In 1013, Xu and co-workers disclosed the synthesis of bicyclo[4.3.0] ketals **68** under mild reaction conditions.[25c] The alkynol **41** was treated with β-γ-unsaturated α-ketoesters **67** in the presence of a gold catalyst (5 mol%) and $Y(OTf)_3$ (10 mol %) in dichloromethane as a solvent at 40 °C for 1.5 h.



Scheme 1.23. Synthesis of bicyclo[4.3.0] ketals.

The alkynol converted into endocyclic-enol ether **T2** via exocyclic enol ether **T1,** which participates as dienophiles in inverse-electron demand hetero-Diels-Alder (IED-HAD) reaction with β-γ-unsaturated α-ketoesters **67** to deliver the final product ketal **68**, this investigation is limited to only one example (Scheme 1.23).

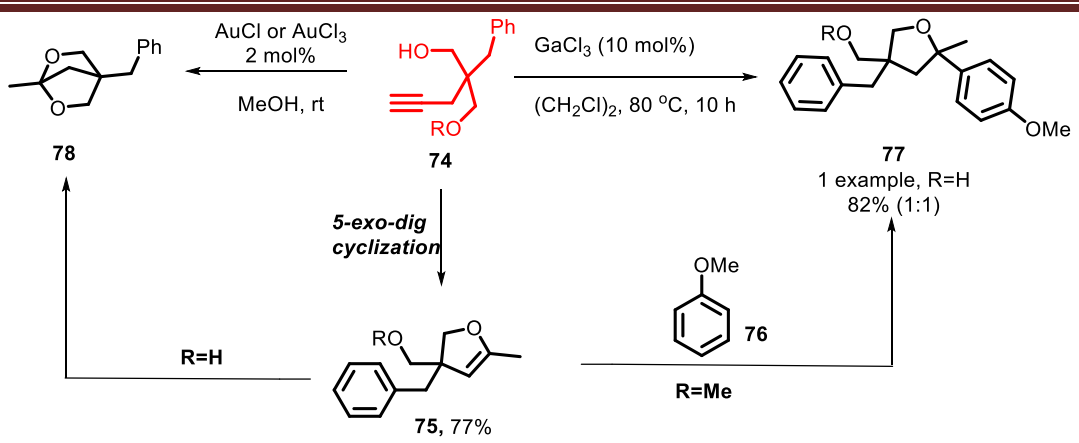
Kang's research group in 2018 developed a protocol for the asymmetric synthesis of spiroketals.[25f] The asymmetric cascade annulation of alkynyl alcohol **69** with keto ester **70** was catalyzed by the combination with bimetallic achiral gold (II) and Rh (III) Lewis acids (as asymmetric relay catalyst) to deliver the corresponding spiroketals **73** in good yields and diastereoselectivity (20:1) and with excellent enantioselectivity (98%). This reaction proceeds through the [4+2]-cycloaddition reaction of exocyclic enol ether **71** (formed from alkynol via a 5-*exo*-dig mode of ring-closure) with keto-ester **70** via **72** (Scheme 1.24).



Scheme 1.24. Asymmetric synthesis of spiroketals.

1.6.3 Friedel-Crafts type reaction involving alkynols

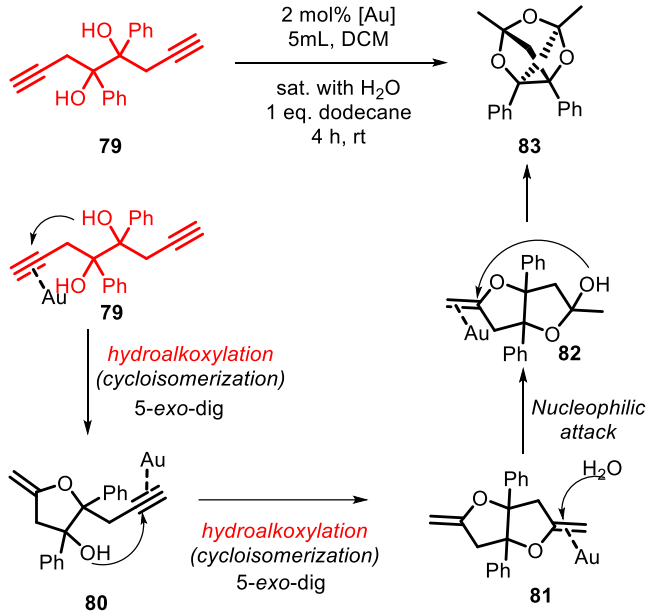
In 2010, Gandon and co-workers developed a method for the construction of tetrahydrofurans and bicyclic ketals via Friedel-Crafts type reaction.[22] The alkyne diol **74** was treated with $GaCl_3$ as a catalyst in dichloromethane solvent at 80 °C for 10 h which delivered tetrahydrofuran **77** through the initial formation of endocyclic enol ether **75** followed by the coupling with electron-rich arene **76** (via Friedel-crafts type addition), this investigation was limited to only one example. In contrast, the same substrate **74** delivered bicyclic ketal **78** under Au-catalysis (Scheme 1.25).



Scheme 1.25. Divergent synthesis of tetrahydrofurans and bicyclic ketals.

1.6.4 Cascade domino reaction

Hashmi and co-workers developed an interesting methodology for the synthesis of the tricyclic cage-like structures **83** via a gold-catalyzed tandem reaction of alkyne diol **79** and water as an external nucleophile.[23b] The two terminal homopropargylic alcohol groups undergo iterative intramolecular hydroalkoxylation reactions to give bis cyclic-enol ether **81** (via intermediates **79** and **80**).

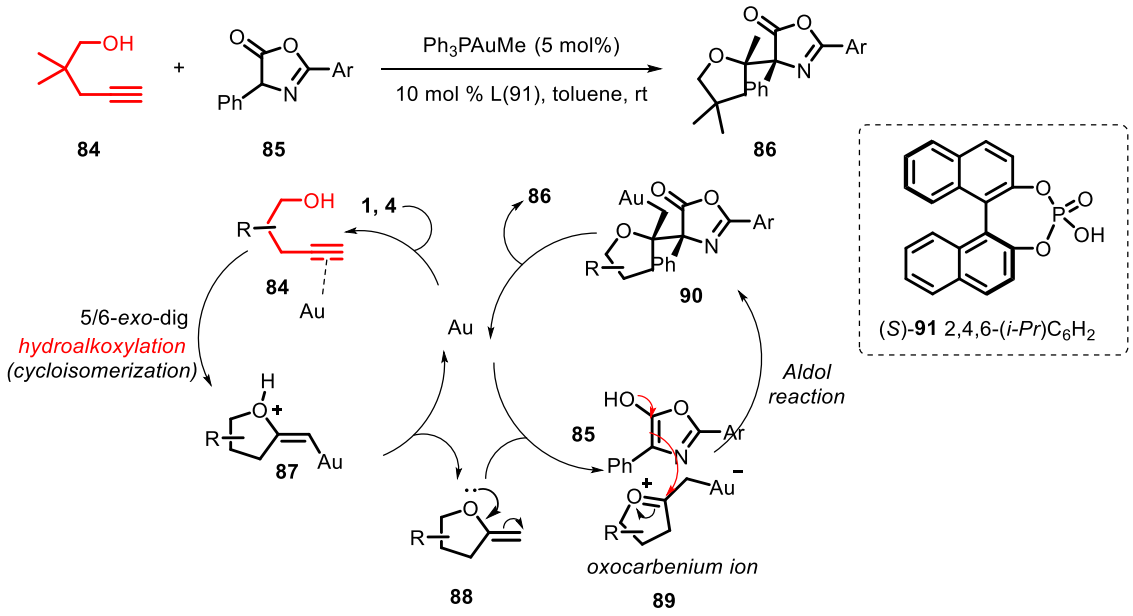


Scheme 1.26. Synthesis of tricyclic cage-like structures.

Subsequent addition of water on to the enol ether followed by intramolecular ketalization delivers the subjected product **83**. The intermediate **81** was confirmed as a *syn* diastereomer, which is isolated and characterised by X-ray analysis. Formation

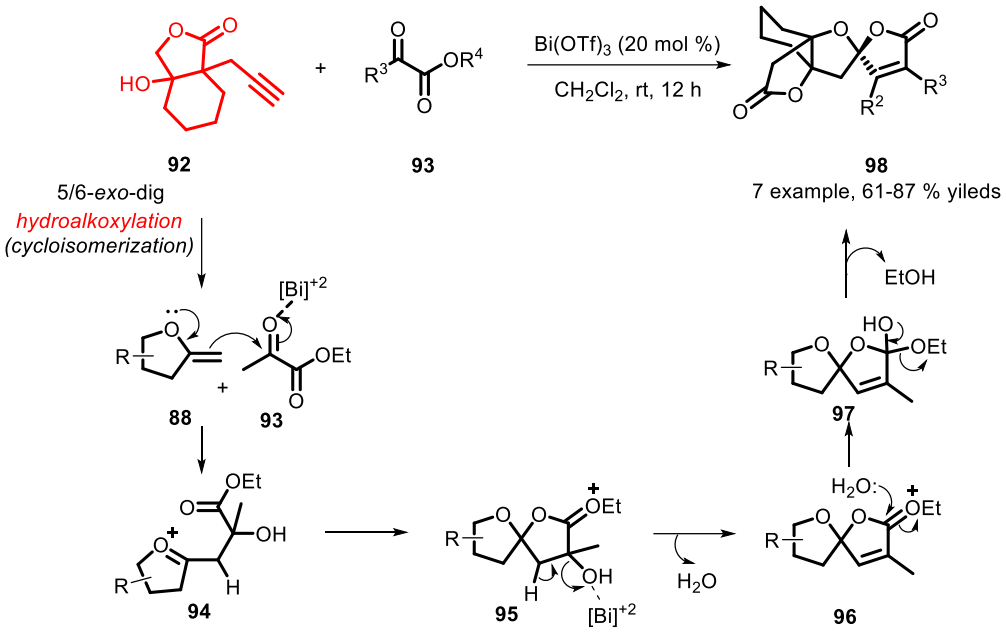
of eight new bonds through a unimolecular cascade, highly stereoselective hydroalkoxylation of **82** followed by an external nucleophilic attack, and excellent yields are key features of this protocol (Scheme 1.26).

Han's and co-workers in 2011 reported an efficient method for the construction of quaternary stereogenic centers containing azlactone-tethered furans from alkynol **84** and azlactones **85** by using a combination Ph_3AuMe/chiral gold and phosphoric acid **91** catalysis (Scheme 1.27).[23c] This reaction works *via* intramolecular hydroalkoxylation of alkynols to give *exo*-cyclic enol ether **88** (via **87**), followed by the nucleophilic addition of azlactone onto the oxocarbenium ion **89** (generates from **88**) (Scheme 1.27).



Scheme 1.27. Synthesis of azlactone-tethered furans.

Recently, in 2020, Piva group developed a facile protocol for the synthesis of oxaspiro[n,3,3]propellanes **98** comprising a Lewis acid-catalyzed ($Bi(OTf)_3$) cascade annulation of bicyclic lactones alkynols **92** with α-ketoesters **93** *via* a dual activation process.[23d] This reaction was expected to proceed through the initial formation of exocyclic enol-ether **88** (5-*exo* dig cyclization) followed by annulation with pre-activated α-ketoesters **93** to give **95** via aldol-type addition and cyclization through oxocarbenium species **94**. Dehydration of intermediate **95** and intramolecular transesterification steps (via **96** and **97**) furnish oxaspirolactones **98** (Scheme1.28).

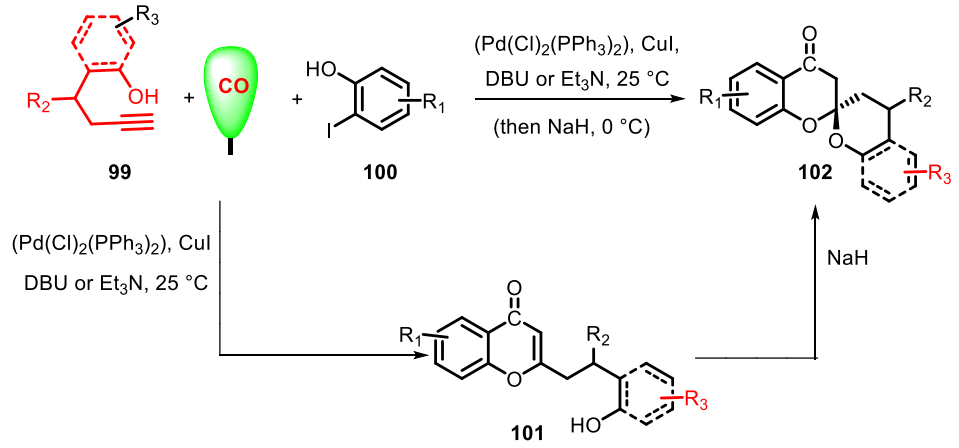


Scheme 1.28. Synthesis of oxaspiro[n,3,3]propellanes.

1.7 Reactions involving 5-hexyne-1-ols

1.7.1 Sonogashira coupling followed by a cascade reaction

Recently Li's group devised an efficient one-pot protocol for the synthesis of benzannulated [6,6]-spiroketals **102** from o-iodophenol **100** and terminal alkynols **99** or alkynyl phenols using Pd catalysis.[31]



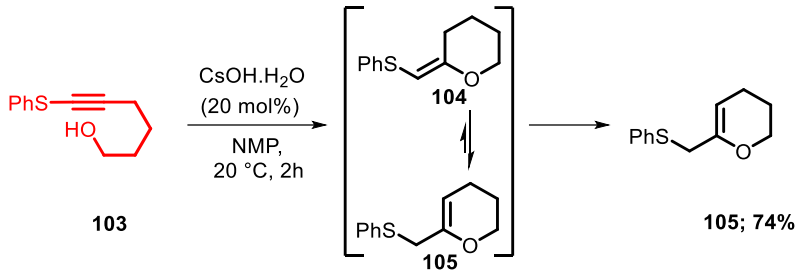
Scheme 1.29. Synthesis of benzannulated [6,6]-spiroketals using cascade reaction.

This transformation proceeds through Pd-catalyzed carbonylative Sonogashira coupling followed by a spiroketalization cascade to furnish benzannulated [6,6]-

spiroketals **102** via pyranone intermediate **101**. This method features the high diastereoselectivity, good functional group tolerance and employs a simple balloon pressure of CO at room temperature (Scheme 1.29).

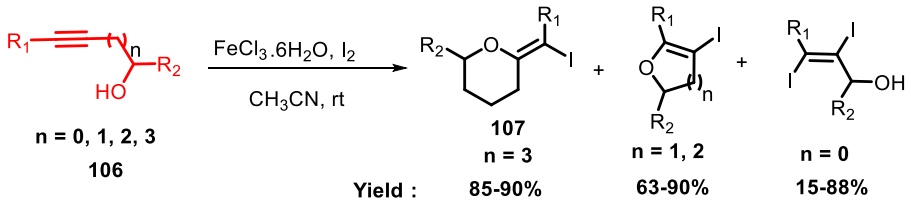
1.7.2 Synthesis of functionalized dihydropyrans

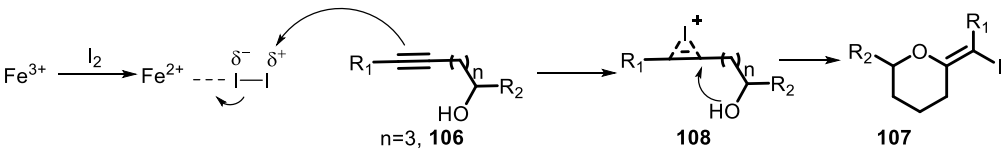
In 1999, Paul Knochel and co-workers developed caesium hydroxide ($CsOH.H_2O$)-catalyzed cycloisomerization of thiopehenyl-tethered alkynyl alcohols to access corresponding cyclic enol ethers.[32] In this approach, they observed that methanol gives best yields. Diverse internal alkynols (**103**) subjected to this intramolecular hydroalkoxylation, which proceeds via 6-*exo*-dig cyclisation to furnish initially exocyclic enol ether **104**, which would undergo inward isomerisation and deliver dihydropyran **105** (Scheme 1.30).



Scheme 1.30. Synthesis of functionalized dihydropyrans.

Similarly, Su *et al.* reported a robust method for the synthesis of vinyl iodide **107** starting from 5-hexynols **106**.[33]



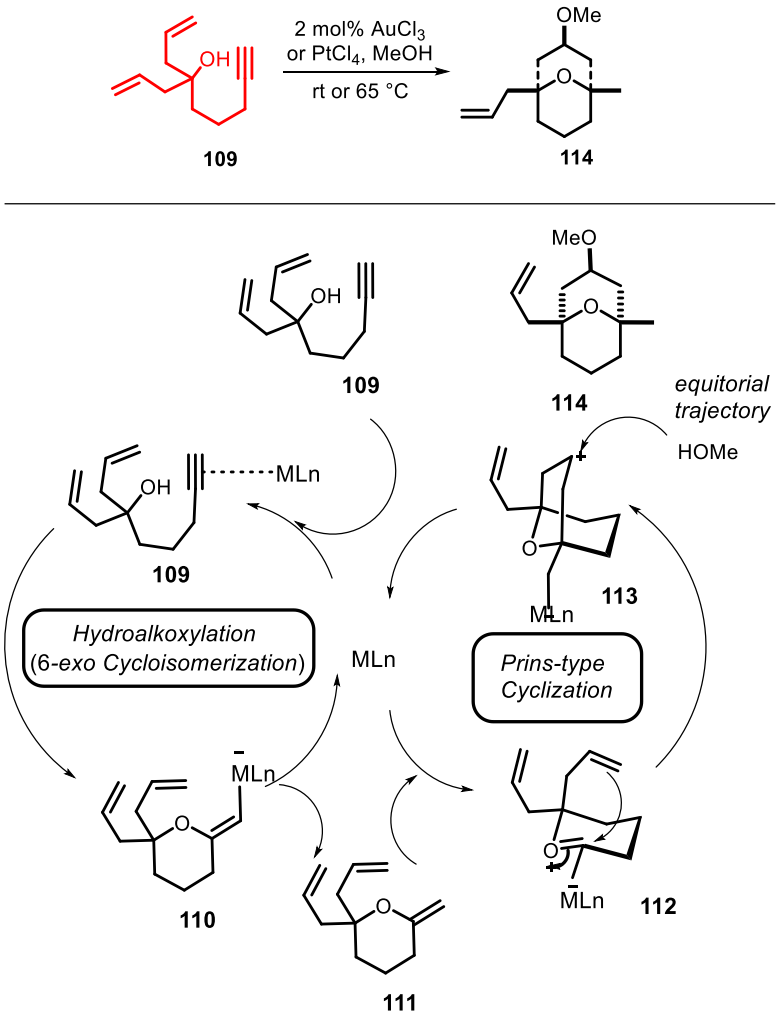


Scheme 1.31. Synthesis vinyl iodides from alkynols.

$FeCl_3$ catalyzed π-activation of triple bond of 5-hexynol induced intramolecular hydroalkoxylation gives the *exo* enol ether which will be trapped by iodine to deliver the desired vinyl iodides. They have screened various alkynophilic catalysts and found $FeCl_3.6H_2O$ found to be the best catalytic system for this transformation. Further, they have also studied the reactivity of propargylic alcohols under same condition and found 1,2-diiodides are as products (Scheme 1.31).

1.7.3 Prins-type reaction

In 2009, Fananas and co-workers devised a gold or platinum-catalyzed cascade annulation reaction for the synthesis of [3,3,1] bicyclic ethers **114** by using homoallyl-tethered alkynols **109** via Prins-type cyclization.[26b]

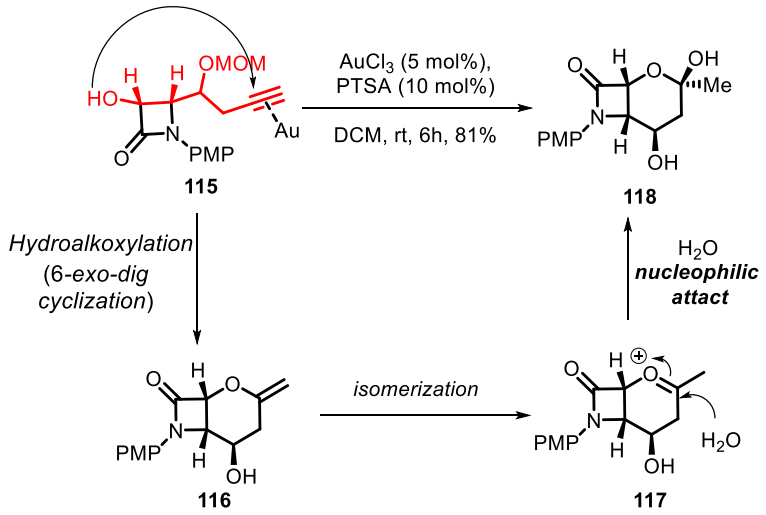


Scheme 1.32. Synthesis of bicyclic ether *via* Prins-type reactions.

This method involves initial C-C triple bond activation followed by intramolecular hydroalkoxylation of alcohol steps to give **111**, which subsequently undergoes Prins-type cyclization. They have performed several reactions using various alkynols and hetero atom-containing nucleophiles. In addition, used halogen as a nucleophile, and the elimination phenomenon was also studied. By employing this method, synthesized enantiomerically pure [3,3,1] bicyclic ethers as well as employing a chiral pool approach (Scheme 1.32).

1.7.4 Synthesis of pyrano-β-lactams

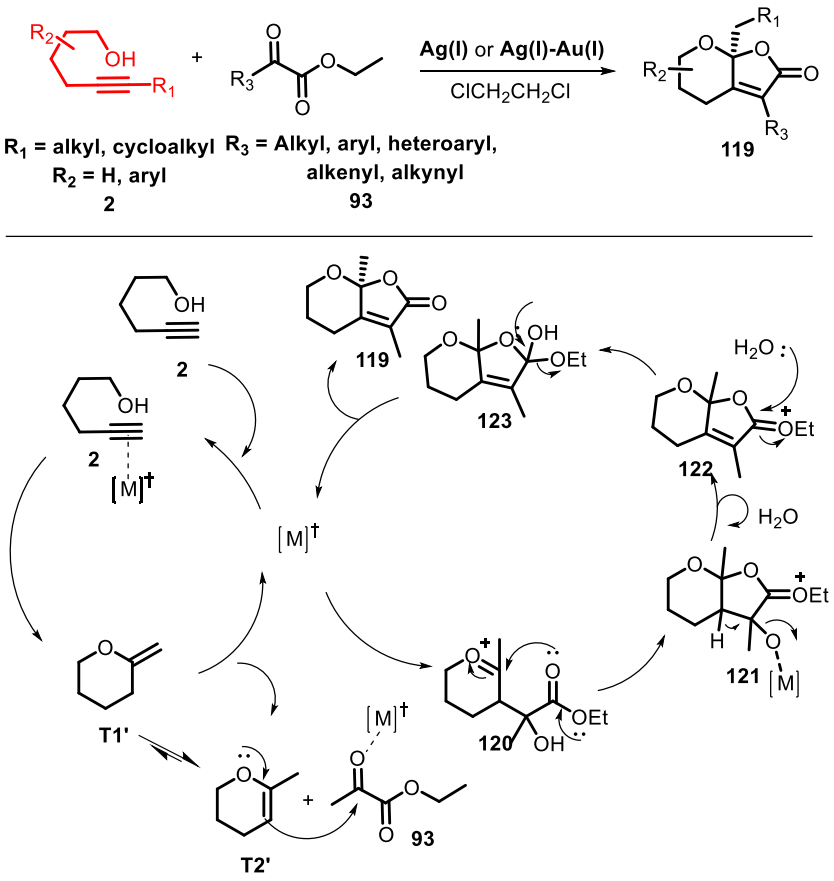
In 2010, Carrascosa and co-workers developed an expedient methodology for the synthesis of tetrahydropyran-fused β-lactam **118** using gold-catalysis. Gold catalyzed regioselective intramolecular hydroalkoxylation (6-exo-dig cyclization) of β-lactam-tethered alkynols gives corresponding pyran possessing exocyclic olefin **116**, which subsequently undergo hydration (*via* oxocarbenium species **117**) to give the lactol-derived β-lactams **118** (Scheme 1.33). [34]



Scheme 1.33. Synthesis of tetrahydropyran fused β-lactams.

In 2018, Kontham's (our) group developed a cascade annulation of alkynols (5-hexyn-1-ols) **2** with α-ketoesters **93** by using Ag(I) or Ag(I)-Au(I) as a dual activation (π and σ) catalytic system to access furo-pyranones **119** related to bioactive natural products.[23e] In this process, the initial π-activation of alkynols leads to the intramolecular hydroalkoxylation (*via* the 6-*exo*-dig mode of cyclization) to give the exocyclic enol ether **T1'** (via **2**), which undergoes inward isomerization to provide

thermodynamically stable endocyclic enol ether **T2'**. Subsequent addition of **T2'** onto the σ-activated α-ketoester to give **120**, intramolecular ester attack onto the oxocarbenium ion to give **121**, followed by the addition of H_2O and EtOH expulsion deliver furopyranone **119** in a cascade manner (Scheme 1.34).

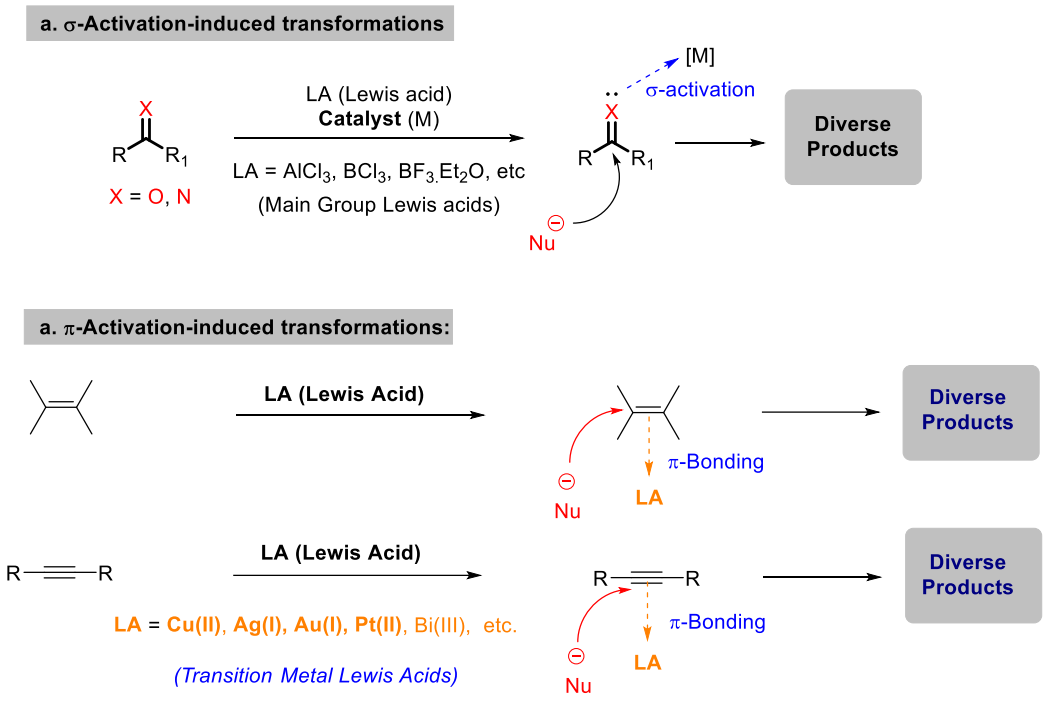


Scheme 1.34. Synthesis of furo-pyranones from hexyn-1-ols and α-ketoesters.

1.8 Lewis acid-catalyzed σ and π (dual) activation-induced cascade annulations (our hypothesis)

Carbonyl compounds (aldehydes, ketones, esters, α,β-unsaturated carbonyl compounds) and imines, undergo σ-activation with the aid of various Lewis acids ($AlCl_3$, BCl_3, $BF_3.Et_2O$ and others, and Brønsted acids) and participate in diverse 1,2-addition or 1,4-addition reactions and deliver corresponding addition products. Whereas, alkenes and alkynes undergo π-activation with the aid of π-activating (carbophilic) catalysts (Cu(I), Cu(II), Ag(I), Gold(I) and Pt(II), Bi(III), etc.) and

participate in diverse nucleophilic addition reactions and deliver diverse products (Scheme 1.35).



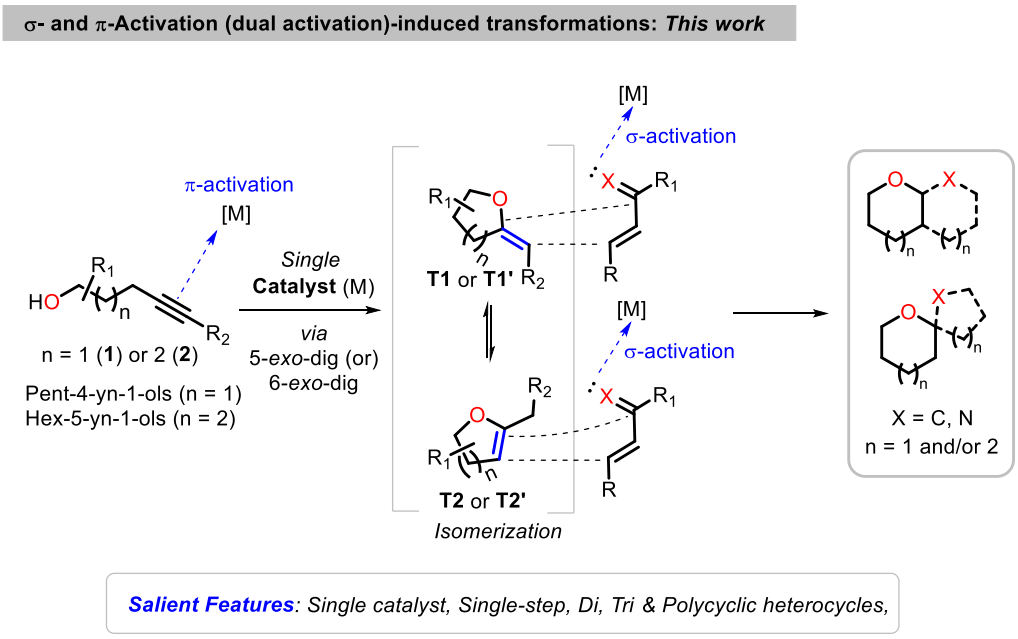
Scheme 1.35 | Lewis acid-catalyzed σ- and π-activation strategies.

Similarly, pent-4-yn-1-ols (**1**) and hex-5-yn-1-ols (**2**) undergo C-C multiple bond activation (π-activation) and form corresponding *exo*- or *endo*-cyclic enol ethers (**T1**/**T1'**, **T2**/**T2'**) based on their thermodynamic stability (following Baldwin rules), which participate as acyl anion equivalents in subsequent annulation reactions with diverse carbonyl compounds (through σ activation) and deliver diverse oxygen heterocycles related drugs and bioactive natural products. In this context, we aimed to find a single affordable and sustainable catalytic system that can solely perform σ and π-activation (dual activation) and deliver oxygen heterocycles from alkynols and carbonyl compound derivatives in a cascade manner (Scheme 1.35).[35]

As part of the research work incorporated in this thesis, we unveiled the σ- and π-activation (dual activation) potential of Bi(III) and Ag(I)-salts as reliable catalysts. Extensive investigations led to the identification of bismuth(III)-salts as excellent dual activating catalysts and able to perform diverse annulation reactions. Bismuth is belonging to the main group metals, non-transition metals and relatively it is less toxic

than mercury, thallium, silver, and lead.[36] Bismuth is having high hydro-compatibility than transition metals. Besides, bismuth is used in medicines pigments and cosmetics, etc. Inspired by these interesting features of bismuth salts as catalysts, in recent times, a plethora of synthetic methodologies were disclosed in the literature.[37]

In this thesis, we have disclosed the results obtained from our investigations, which were directed toward the development of unique intermolecular cascade annulation reactions of alkynols with arenes and carbonyl compounds employing a cost-effective, environmentally benign, and sustainable catalytic system (single catalyst), which can work through σ- and π-activation (dual activation) and furnish simple to complex tetrahydrofuran/pyran-tethered and N, S-heterocycles related to biologically potent natural products (Scheme 1.36).



Scheme 1.36 | Cascade annulation strategies involving alkynols and carbonyl compounds as substrates and a single catalyst-mediated dual activation (σ- and π-activation).

1.9 Conclusion

In conclusion, this chapter provided a general introduction to the chemistry of alkynes (including 4-pentyn-1-ols and 5-hexyn-1-ols). It details the origin of alkynes, and various synthetic methods reported to access alkynes, which facilitate the

expansion of the alkyne-based synthetic transformations. It also collates a literature review focusing on recent advancements in chemistry involving various alkynyl alcohols and carbonyl compounds *via* dual activation (σ- and π-activation) that led to the generation of our hypotheses (objectives of this thesis).

1.10 References

1. (a) Jampilek, J.; *Molecules*, **2019**, *24*, 3839; (b) Martins, P.; Jesus, J.; Santos, S.; Raposo, L. R.; Roma-Rodrigues, C.; Baptista, P. V.; Fernandes, A. R. *Molecules*, **2015**, *20*, 16852–16891.
2. (a) Chao, J. Li.; Trost, B. M. / doi.org/10.1002/9783527677894.ch1 (b) Alabugin, I.V.; Gold B. J. *Org.Chem*. **2013**,*78,* 7777–7784. (c) Mahrwald, R. *Wiley-VCH Verlag GmbH and Co. KGaA*, **2004**, *1* (2), 1218–23.
3. Corey, E. J., Fuchs, P. L.; *Tetrahedron Lett.* **1972**, 13, 36, 3769.
4. (a) Seyferth, D.; Marmor, R. S.; Hilbert, P.; *J. Org. Chem.*, **1971**, *36*, 10, 1379. (b) Gilbert, J. C.; Weerasooriya, U.; *J. Org. Chem.* **1982**, *47*, 1837. (c) Hauske, J. R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J.; *Tetrahedron Lett.*, **1992**, *33*, 3715.
5. Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett*, **1996**, 521.
6. Ohira, S.; *Synth. Commun.;* **1989**, 19, 561.
7. Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Tetrahedron*, **2005**, *61*, 4043-4052.
8. Shepherd, J. N.; Stenzel, J. R.; *Journal of Chemical Education*., **2006,** *83,* 425-428.
9. Sonogashira, K. J. *Organomet. Chem*. **2002**, *653*, 46–49.
10. Mishiro, K.; Kimura, T.; Furuyama, T.; Kunishima. M. *Org. Lett.* **2019**, *21*, 4101–4105.
11. (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed*. **1998**, *37*, 1415–1418; (b) Goodwin, J. A.; Aponick, A. *Chem. Commun*. **2015**, *51*, 8730–8741.
12. (a) Pyykkö, P. *Angew. Chem., Int. Ed*. **2002**, *41*, 3573–3578. (b) Pyykkö, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4412–4456. (c) Schwartz, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4442–4454. (d) Gorin, D. J.; Toste, F. D. *Nature*. **2007**, *446*, 395–403. (e) Leyva-Perez, A.; Corma, A.´ *Angew. Chem., Int. Ed.* **2012**, *51*, 614–635.
13. (a) Zhang, C.; Zhang, H.; Zhang, L.; Wen, T. B.; He, X.; Xia, H. *Organometallics,* **2013**, *32*, 3738; (b) Kumara, R. K.; Bi, X. *Chem. Commun.*, **2016**, *52*, 853-868.
14. Tan, X.-C.; Liang, Y.; Bao, F.-P.; Wang, H.-S.; Pan, Y.-M. *Tetrahedron*, **2014**, *70*, 6717–6722.
15. Pandya, A. N.; Fletcher, J. T.; Villa, E. M.; Agrawal, D. K. *Tetrahedron Lett.*, **2014**, *55*, 6922–6924.
16. Saikachi, H.; Kitagawa, T.; Sasaki, H. *Chem. Pharm. Bull.*,**1979**, *27*, 2857–2861.

17. (a) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc*., **2005**, *127*, 9260–9266; (b) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed*., **2005**, *44,* 5664–5667.
18. Gao, M.; He, C.; Chen, H.-Y.; Bai, R.-P.; Cheng, B.; Lei, A.-W. *Angew. Chem., Int. Ed.,* **2013**, *52*, 6958–6961.
19. Sun, J.-W.; Keller, V. A.; Meyer, S. T.; Kozmin, S. A. *Adv. Synth. Catal*., **2010**, *352*, 839–842.
20. He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.-Y. Lei, A.-W. *J. Am. Chem. Soc*., **2012**, *134*, 5766–5769.
21. Karmakar, P.; Mamidipalli, S.; Yun, Y.; Lee, D. *Org. Lett*., **2013**, *15*, 1938-1941.
22. (a) Li, H-J.; Guillot, R.; Gandon, V. *J. Org. Chem*., 2010, **75**, 8435-8449; (b) Barluenga, J.; Fernandez, A.; Dieguez, A.; Rodriguez, F.; Fananas, F. J. *Chem. Eur. J*. **2009**, *15*, 11660 - 11667.
23. (a) Barluenga, J.; Mendoza, A.; Rodrguez, F,; Fañanás, J. F. *Chem. Eur. J*. **2008**, 14, 10892 – 10895; (b) Hashmi, A. S.; Bhrle, M.; Michael, W.; Rodolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *chem. Eur. J.,* **2010**, 16, 9846-9854; (c) Han, Z. Y.; Guo, R.; Wang, Pu-S.; Chen, Dian-F.; Xiao, H.; Gong, Liu-Z. *Tetrahedron,* **2011**, **52,** 5963-5967; (d) Nassar, Y.; Piva, O. *Org. Biomol. Chem.,* **2020,***18*, 5811-5815; (e) Thorat, S. S.; Kataria, P.; Kontham, R. *Org. Lett*. **2018**, *20*, 872–875.
24. Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H. Woods, B. P. *Nature*, **2012**, *490*, 208–212.
25. (a) Li, J.; Lin, L.; Hu, B.; Lian, X.; Wang, G.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed*., **2016**, *55*, 6075–6078; (b) Wang, X.; Dong, S.; Yao, Z.; Feng, L.; Daka, P.; Wang, H.; Xu, Z. *Org. Lett*., **2014**, *16*, 22–25; (c) Wang, X.; Yao, Z.; Dong, S.; Wei, F.; Wang, H.; Xu, Z. *Org. Lett*., **2013**, *15*, 2234–2237; (d) Hu, B.; Li, J.; Cao, W.; Lin, Q.; Yang, J.; Lin, L.; Liu, X.; Feng, X. *Adv. Synth. Catal*., **2018**, *360*, 2831–2835; (e) Barluenga, J.; Calleja, J.; Mendoza, A.; Rodrguez, F.; Fañanás, J. F. *Chem. Eur. J*. **2010**, 16, 7110 – 7112; (f) Gong, J.; Wan, Q.; Kang, Q. *Adv. Synth. Catal.,* **2018**, 360, 4031-4036.
26. Barluenga, A. Fernández, A. Diéguez, F. Rodríguez and F. J. Fañanás, *Chem. Eur. J*., **2009**, *15*, 11660–11667.
27. Barluenga, J.; Mendoza, A.; Rodríguez, F. Fañanás, F. J. *Angew. Chem., Int. Ed.,* **2008**, *47*, 7044–7047.
28. Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett*., **2005**, 7, 5437.

29. Patil, N. T.; Kavthe, R. D.; Raut, V. S.; Reddy, V. N. *J. Org. Chem,* **2009**, 74, 6315-6318.
30. Patil, N. T.; Konala, A. Eur. J. *Org.* **2010,** 6831-6839**.**
31. Xiang, K.; Tong, P.; Yan, B.; Long, L.; Zhao, C.; Zhang, Y.; Li, Y. *Org. Lett.* **2019***, 21*, 412–416.
32. Tzalis, D.; Christopher Koradin, C.; Knochel, P. *Tetrahedron Letters*, **1990**, *40,* 6193-6195.
33. Su, L.; Lei, C. Y.; Fan, W. Y.; Liu, L. X. *Synthetic Communications*, 41:8, 1200-1207, 2011.
34. Alcaide, B.; Almendros, P.; Mart´ınez del Campo, T.; Carrascosa, R. *Eur. J. Org. Chem.*, **2010**, 4912–4919.
35. (a) Perron, F.; Albizati, K.F. *Chem. Rev*. **1989**, *89,* 1617–1661. (b) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem*. **2003**, *7*, 227–256. (c) Jacobs, M. F.; Kitching, W. B. *Curr. Org. Chem*. **1998**, *2*, 395–436. (d) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev*. **2005**, *105*,4406−4440. (e) Palmes J. A.; Aponick, A. *Synthesis* **2012**, *44*, 3699–3721. (f) Chorley, D.F.; Furkert, D. P.; Brimble, M. A. *Eur. J. Org. Chem.* **2016**, *2*, 314–319. (g) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817-7831.
36. Xiao, Y.; Zhang, L. *Org. Lett.* **2012**, *14*, 17, 4662–4665.

CHAPTER-2

Section-A

Introduction and previous approaches to tetrahydrofurans and pyrans

Chapter-2, Section-A: Introduction and previous approaches

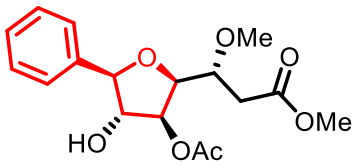
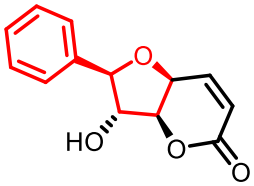
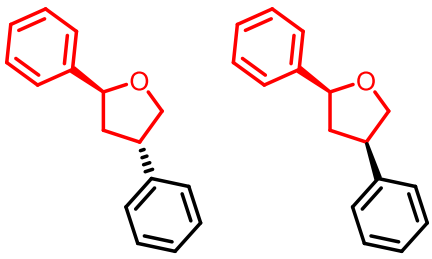
2.1 Introduction

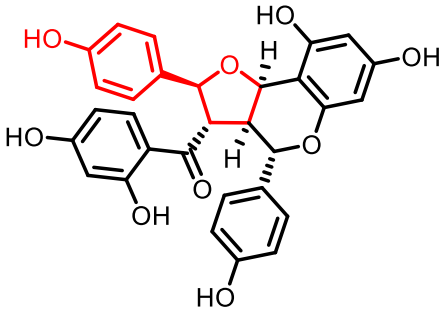
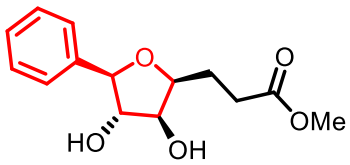
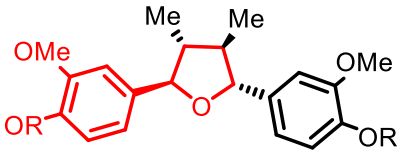
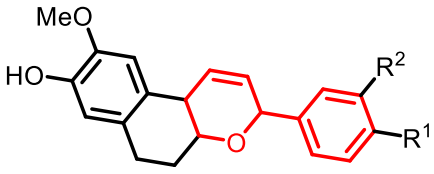
Saturated oxygen heterocycles, such as tetrahydrofurans and tetrahydropyrans are ubiquitous core structures of bioactive natural products and pharmaceutical drugs.[1] From the perspective of drug discovery research, still, there is a much scope for the development of chemical space derived from medium-sized heterocyclic frameworks. As per the recent statistical data, more than 75% of low-molecular weight-containing marketed drugs have N, O-based heterocycles. Incorporation of a heteroatom into the drug molecule provides a valuable tool for altering its physicochemical properties like solubility, lipophilicity, polarity, and H-bonding capability, which in turn control the ADME and toxicology profile (Figure 2.1).

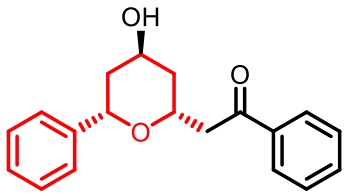
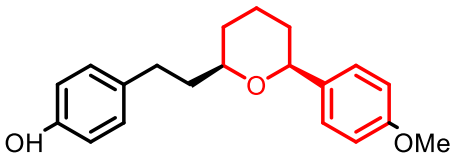
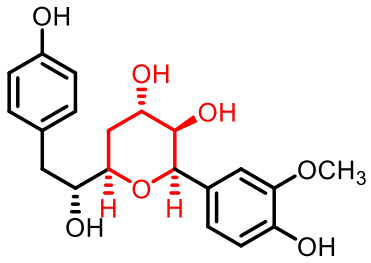
Figure 2.1 | Structures of tetrahydrofurans and tetrahydropyrans

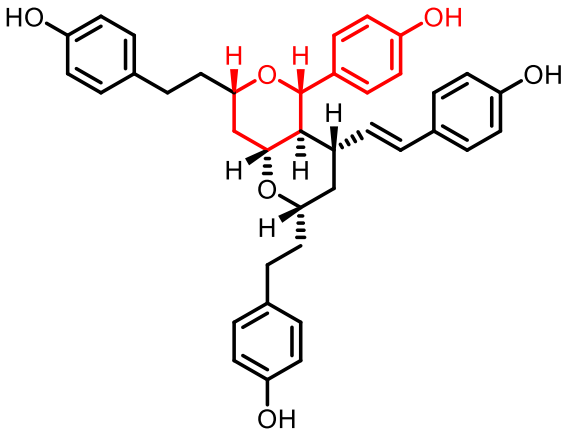
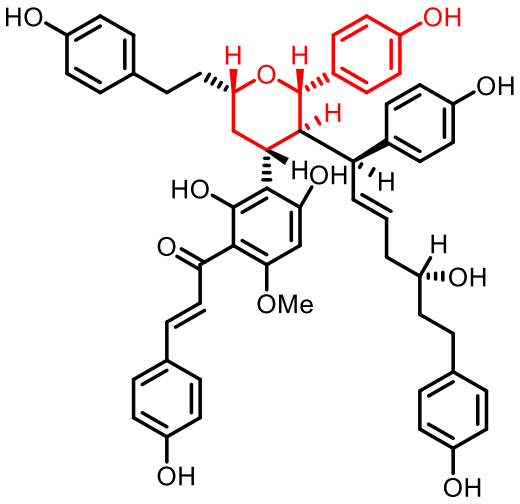
After nitrogen-based heterocycles, oxygen-heterocycles are the second most common category that presents as a structural unit of FDA-approved drugs, as of 2017, 27% of unique approved small molecules and 15% of all approved drugs belong to oxygen heterocycles.[2] Among diverse heterocycles present in the chemical space of bioactive molecules, cyclic ethers (tetrahydrofurans and tetrahydrofurans and their structurally close analogs) have been employed as bioisostere of the amide bond in the drug discovery to address the degradation of amide groups by proteases.[3] Historically, more than 10000 furan and pyran-containing natural products are present in the chemical space of Nature.[4] Involving vitamins, hormones, sugars, antibiotics, and others. Herein, a brief survey of bioactive natural products/drugs containing α-arylated tetrahydrofurans and tetrahydrofurans as core structures, and synthetic methodologies to construct these scaffolds are presented (Table 1.1).

Table 2.1 | Representative examples of 2-aryl tetrahydrofuran and tetrahydropyran-containing biologically active natural products.

S. No.	Structure	Isolation and Activity
1.	 (+)- Goniothalesacetate	Sabitha and co-workers, in 2015, synthesized (+)-Goniothalesacetate, which is isolated from the stems of a southern Taiwan tree *Goniothalamus amuyon*. It shows an excellent cytotoxicity profile.[5]
2.	 (+)- Altholactone	(+)-Altholactone is a cytotoxic styryl lactone containing tetrahydrofuro[3,2-b]pyran-5-one skeleton, was first isolated in 1977 from a *Polyalthia species* (Annonaceae) by Loder and co-workers[6a] and later, in 1985 from the bark of *Goniothalamus giganteus* by El-Zayat et al.[6b]
3.	 Caloxylane A Caloxylane B	Calyxolane A and B were isolated from the *Caribbean marine sponge Calyx podatypa* in Puerto Rico.[7]

4.	 **Cordigol**	Cordigol was first isolated by Hostettmann et al. from the stem bark of the *Cordia goetzei Guerke* (Boraginaceae) in 1988, and it displays fungicidal activity against *Cladosporium cucumerinium*.[8]
5.	 **(+)- Goniothalesdiol**	Goniothalesdiol, was isolated from the bark of the *Malaysian tree Goniothalamus borneensis.* which exhibit potent antitumor activity against P388 mouse leukemia cells.[9]
6.	 **R=H, Fragransin A** **R=Me, Galbelgin**	Barker and co-workers synthesized Fragrasin and Galbegin in 2015, It is a lignan-type natural product it belongs to the family of secondary metabolites, and is present in human food sources.[10]
7.	 **Musellarin A: R_1= OH, R_2=H** **Musellarin B: R_1= OH, R_2=OMe** **Musellarin C: R_1= OMe, R_2=OH**	Musellarin A was isolated by Zhao and co-workers from the monotypic plant *Musella lasiocarpa* in Yunan, China, with 0.0006% yield (18 mg from 3 kg of dry plant materials). Musellarin A significantly induced quinone reductase activity against Hepa1c1c7 cells,2 and musellarin B has shown moderate cytotoxicity against several cancer

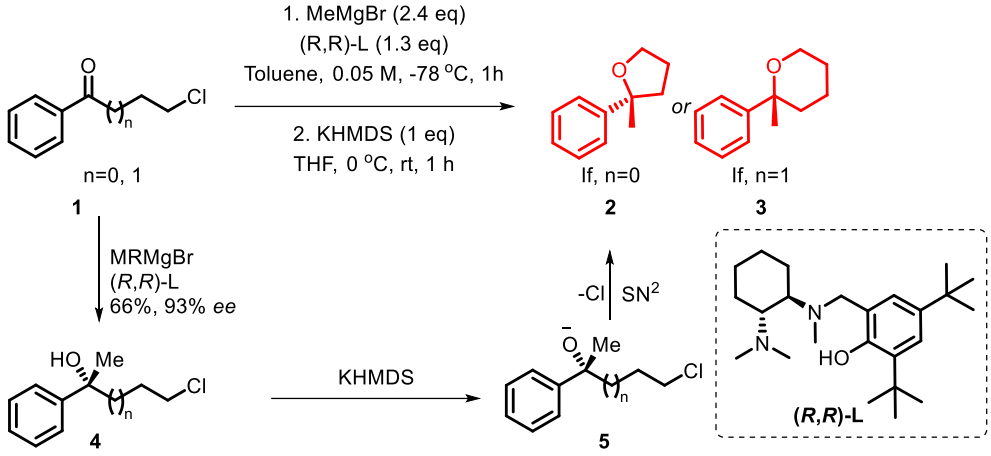
		cell lines, including HL-60 (IC_{50} 21.3 mM), SMMC-7721 (IC_{50} 26.7 mM) and A-549 (IC_{50} 25.1 mM).[11]
8.	 **(-)- Diospogin B**	(–)-Diospongin B was isolated in 2003 by Kadota and co-workers from the rhizomes of *Dioscorea spongiosa* and was reported to have anti-osteoporotic activity.[12]
9.	 **(+) - Centrolobine**	(–)-Centrolobine was isolated in 1964 by Gazz and co-workers from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile* in the Amazon rain forest, which exhibits anti-inflammatory, antibacterial and antileishmania1 activity.[13]
10.	 **(–)-Hedycoropyran B**	Lee and co-workers, in 2015, isolated two new dihydropyrans, hedycoropyrans A and B, from the rhizome of *Hedychium coronarium*, which is *ent*-rhoiptelol B.[14]

11.	 **Blepharocalyxin D**  **Blepharocalyxin E**	Kadota and co-workers, in 2000, isolated three novel diarylheptanoids, Blepharocalyxins C-E, from seeds of *Alpinia blepharocalyx*, Blepharocalyxins D and E exhibited potent antiproliferative activity against murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells, with ED50 values of 3.61 and 9.02 mM, respectively.[15]

2.1.1 Methods for the synthesis of 2-aryl tetrahydrofurans scaffold

I. Through the Grignard addition to acyl-halides

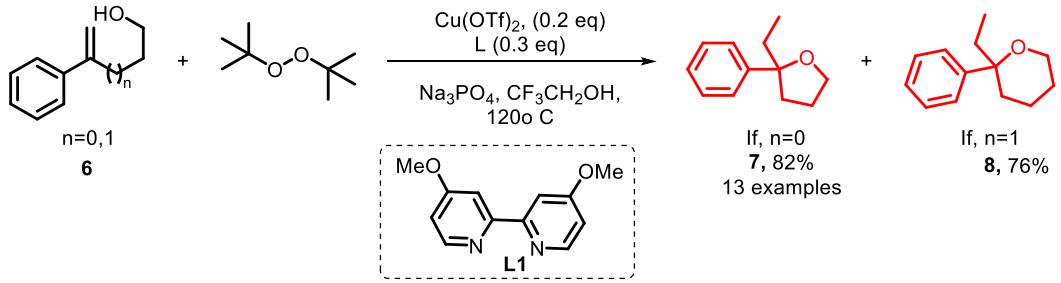
The asymmetric synthesis of 2-aryl tetrahydrofurans (THFs) and tetrahydropyrans (THPs) in two steps were reported by Gilheany and group in 2019.[16] Mechanistically, the first step involves the asymmetric addition of Grignard addition onto the acyl-halide **1** to form chiral tertiary alcohols **4**. The second step involved the ring-closing of the tertiary alcohol-tethered primary halides to the THPs **3** and THFs **2** in the presence of a base. This technique is the first to be reported for an asymmetric Grignard addition, and it is highly enantioselective (**93ee**) (Scheme 2.1).



Scheme 2.1. Asymmetric synthesis of 2-aryl tetrahydrofurans and tetrahydropyrans.

II. Copper-catalyzed synthesis of 2-aryl tetrahydrofuran and tetrahydropyrans

In 2018, Zhu and o-worker discovered a method for the metal-catalyzed synthesis of 2-aryl tetrahydrofuran **7** and tetrahydropyrans **8** by employing 4-phenylpent-4-en-1-ol **6** as a substrate in the presence of Cu(II) catalyst and DTBP was utilized as a methyl source, 4,4'-dimethoxy-2,2'-dipyridine (**L1**, 0.3 equiv), Na_3PO_4 (0.2 equiv) at 120 °C.[17] They have successfully synthesized 13 different 2-aryl tetrahydrofurans **7** with good yield under optimal conditions. The reaction is tolerable with both electron-withdrawing groups (OMe, Ph, and Me) and electron-donating groups (F, Cl, and CN). They have synthesized 2-aryl tetrahydropyran **8** with 76% yield under these identical reaction conditions, with only one example (Scheme 2.2).

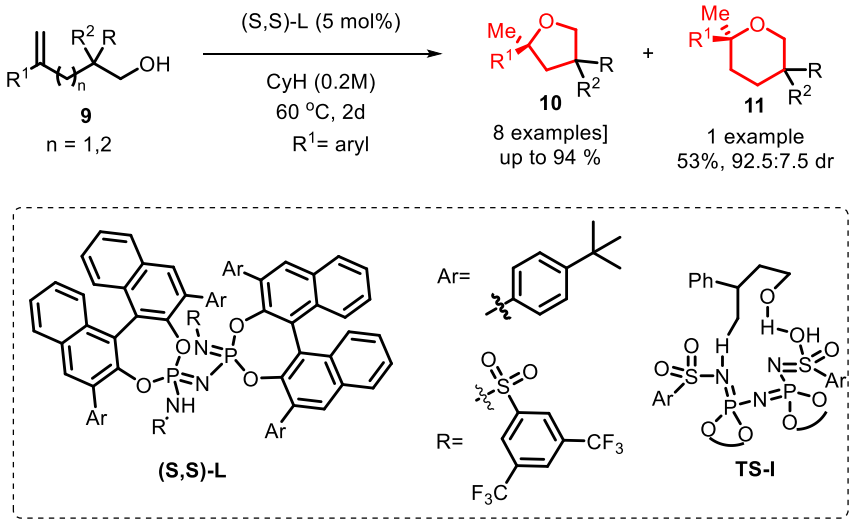


Scheme 2.2. Copper-catalyzed synthesis of THFs and THPs.

III. Enantioselective synthesis of tetrahydrofurans and tetrahydropyrans

In 2018, List and co-workers developed a methodology for the asymmetric activation of electronically and sterically hindered alkenes **9** in the presence of acidic

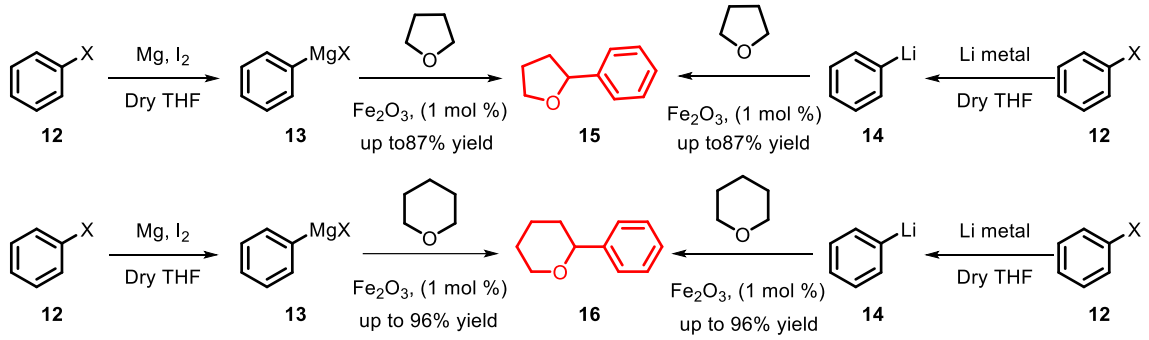
organocatalyst to obtain chiral tetrahydrofurans **10** and tetrahydropyrans **11.**[18] The reaction works *via* the catalytic asymmetric intramolecular hydroalkoxylation of olefins **9** (is made possible by chiral Bronsted acids to generate carbocation). The high stereochemical outcome of this reaction was attributed to the intermediacy of well-defined chair- or boat-like transition states (Scheme 2.3).



Scheme 2.3. Enantioselective synthesis of tetrahydrofurans and tetrahydropyrans.

IV. Using sp2-sp3 cross-coupling reaction

The Iron oxide-catalyzed cross-coupling reaction for activation of α-C (SP^3)-H was disclosed by Viswakarma et al. in 2012 for the construction of 2-aryl tetrahydrofurans and tetrahydropyrans from aryl magnesium halides or organo lithium species and α-hydrogen bearing cyclic unbranched and branched aliphatic ethers.[19]

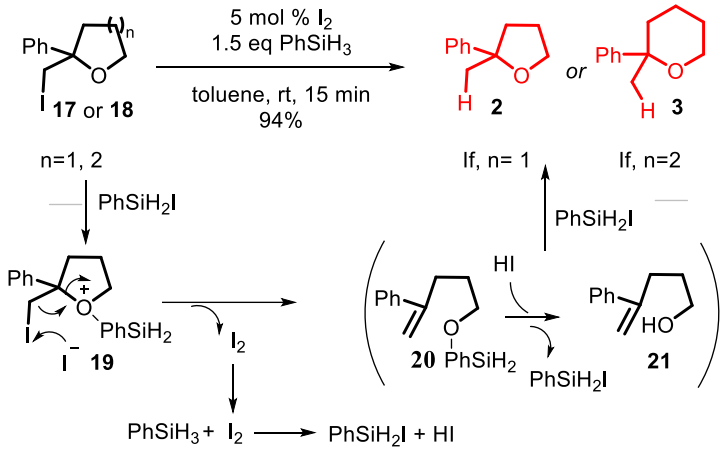


Scheme 2.4. Synthesis of 2-aryl tetrahydrofurans and tetrahydropyrans by using cross-coupling reaction.

This cross-coupling process is catalyzed by Fe_2O_3, and is extremely selective for cyclic ethers. This catalyst doesn't require harmful or pricey ligands (Scheme 2.4).

V. Through reductive deiodination

In 2016, Yamamoto and group disclosed the synthesis of α-aryl tetrahydrofurans **2** and tetrahydropyrans **3** through a cascade transformation of 2-(iodomethyl)-2-phenyltetrahydrofuran and tetrahydropyrans by using cat. I_2 and $PhSiH_3$.[20]



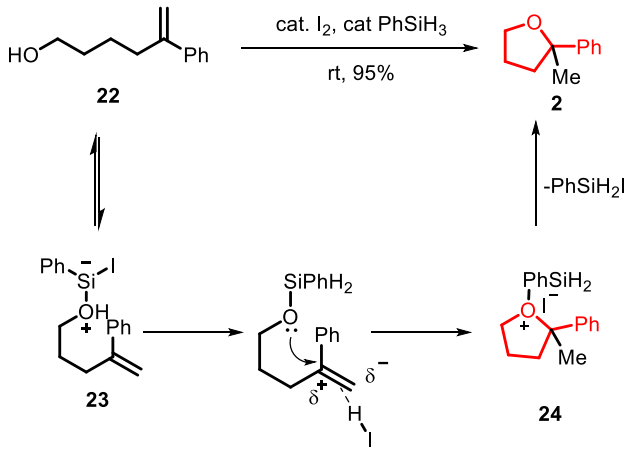
Scheme 2.5. Synthesis of 2-aryl tetrahydrofurans and tetrahydropyrans by reductive deiodination.

This reaction works *via* deiodination of iodoether **17** or **18**. Iodine-mediated ring opening of **17** or **18** (activated by $PhSiH_3$) gives styryl intermediates **20** and **21**, which would undergo subsequent hydroalkoxylation reaction to deliver THFs or THPs (**2** and **3** respectively) (Scheme 2.5).

VI. Synthesis of 2-aryl tetrahydrofurans from unactivated hydroxy alkyl-tethered alkenes

Yamamoto's group, in 2015, reported that treatment of unactivated alkenes **22** (tethered with hydroxy alkyl groups) with catalytic system I_2 and $PhSiH_3$ deliver corresponding a-aryl tetrahydrofurans **2**. This reaction proceeds through HI (in situ generated) mediated activation of alkene, which leads to cycloisomerization/hydroalkoxylation and delivers corresponding cyclized products.[21] NMR analysis supports the *in situ* generation of $PhSiH_2I$, which acts as an alkene activator and gives intermediate **23,** followed by intramolecular

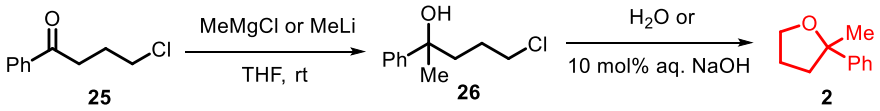
hydroalkoxylation to get intermediate **24**. Subsequent elimination of $PhSiH_2I$ delivers the final product tetrahydrofurans **2**. An additional mechanistic experiment established that HI involves activating C-C double bonds and speeding up the rate of reaction. This work was limited to just two examples (Scheme 2.6).



Scheme 2.6. Synthesis of 2-aryl tetrahydrofurans from alkenes.

VII. Synthesis of tetrahydrofurans by using a heterogeneous solvent system

In 2016, Capriati and co-workers published the first report for the synthesis of tetrahydrofurans **2** in good yield by using nucleophilic addition of both organolithium and Grignard reagents to carbonyl compounds **25**, under air at room temperature as well as batch conditions.[22] Subsequent intramolecular ring-closure of hydroxy-halide intermediate **26** was carryout in aqueous conditions to get the desired tetrahydrofuran **2** (Scheme 2.7).

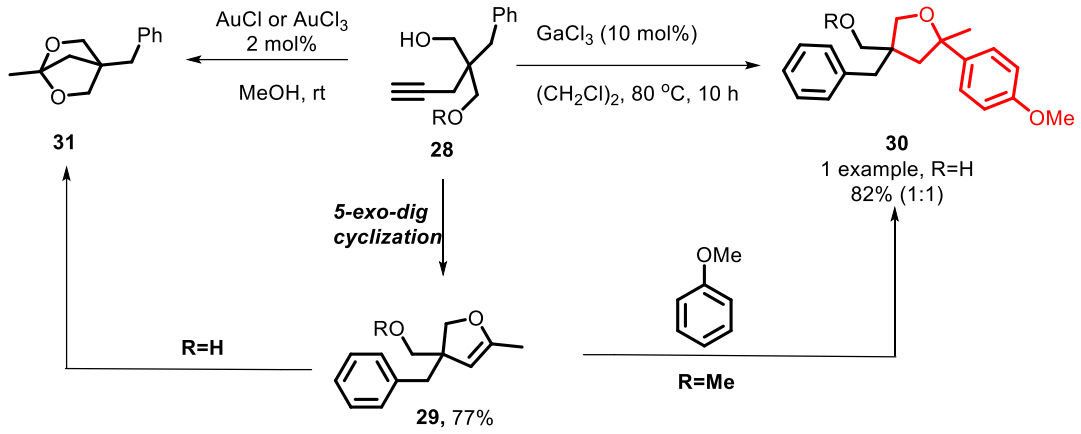


Scheme 2.7. Synthesis of tetrahydrofurans by using a heterogeneous solvent.

VIII. Using Friedel-Crafts type reaction

In 2010, Gandon and co-workers developed an interesting methodology for the synthesis of α-arylated tetrahydrofuran **30** and bicyclic ketals **31** from suitably functionalized alkynols and electron-rich arene and divergent catalysis.[23] This reaction proceeds through $GaCl_3$-catalyzed hydroalkoxylation of alkyne diol **28** to

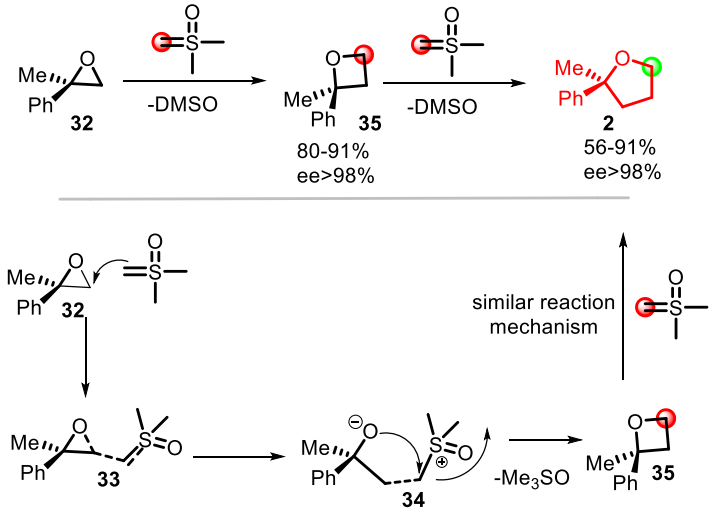
give cyclic enol ether, which subsequently undergoes Friedel-Crafts type C-C bond forming reaction with arene and delivers α-arylated tetrahydrofuran **30**. In contrast, AuCl or $AuCl_3$ produced bicyclic ketals 31 from the same anticipated cyclic enol ether intermediate **29** (Scheme 2.8).



Scheme 2.8. Synthesis of a-arylated tetrahydrofurans and bicyclic ketals.

IX. Synthesis of α-arylated tetrahydrofurans via epoxide ring expansions

The method for stereospecific successive epoxide ring expansion using dimethylsulfoxonium methylide in the presence of DMSO was revealed by Butova *et al*. in 2010.[24] Additionally, they have investigated the solvent effect utilizing the second-order Moller-Plesset (MP2) levels theory by using the polarizable continuum model (PCM) and density functional theory (DFT).

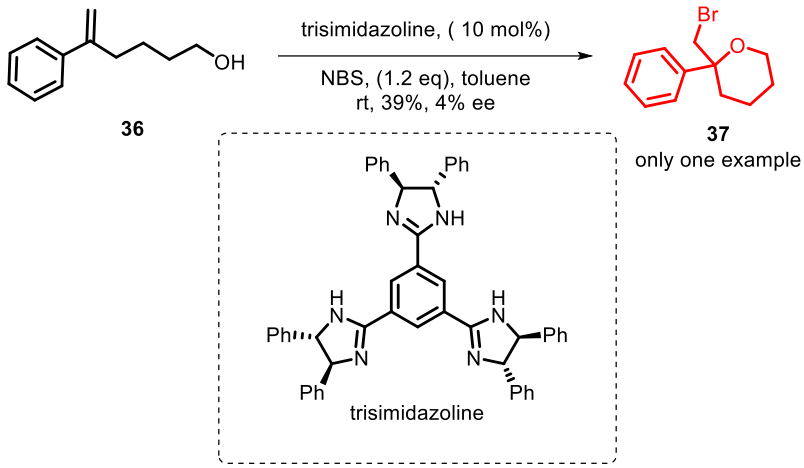


Scheme 2.9. Synthesis of tetrahydrofurans via epoxide ring expansions.

Here, they synthesized chiral tetrahydrofurans **2** through epoxide ring expansion via four-membered cyclic ethers **35**. This reaction works through the strain-induced opening of epoxide with sulphoxide reagent to give **34**, followed by an intramolecular SN^2 -type reaction of **34** to give **35**, and elimination of DMSO (Scheme 2.9).

X. Synthesis of α-arylated tetrahydropyrans via intramolecular bromo-hydroxylation

Murai *et al*. in 2010, reported a method for synthesis of α-arylated tetrahydropyrans **37** in 39% and 4% ee by treating 5-phenyl-5-hexyn-1-ol **36** with trisimidazoline and NBS in the presence of toluene as a solvent at room temperature (Scheme 2.10).[25]



Scheme 2.10. Synthesis of tetrahydrofuran via bromocyclization.

In recent years, the catalytic hydroalkoxylation/cycloisomerization of alkynols has emerged as a powerful tool, which represents a direct mean for the synthesis of enol-ethers and diverse oxygen-containing heterocycles *via* inter or intramolecular reaction modes.[26] These cascade/tandem processes offer great potential from the synthetic point of view, because, reactions of this type can be performed with step and atom efficiency, with negligible waste generation, which fulfills green chemistry requirements. In the last three decades, inter and intramolecular bis(hydroalkoxylation),[27] bis(arylation),[28] hydroalkoxylation-alkylation[29] of suitably functionalized alkynes using π-acidic transition metal (especially noble metals) derived catalysts are well studied.[30] In contrast, studies on tandem intramolecular

hydroalkoxylation (cycloisomerization) followed by intermolecular hydro-(hetero)arylation of alkynols, which gives 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans is very limited.

Hence, the development of efficient synthetic methodologies using readily available starting materials, and environmentally benign and affordable main group element-derived catalysts is of considerable interest in the field of diversity-oriented synthesis, and in turn, in drug discovery research. We planned to develop an efficient and novel protocol for the synthesis of 2-aryl tetrahydrofurans and tetrahydropyrans using readily accessible building blocks of suitably functionalized alkynols and electron-rich arenes and heteroarenes and environmentally benign and non-toxic bismuth-salts as catalysts.

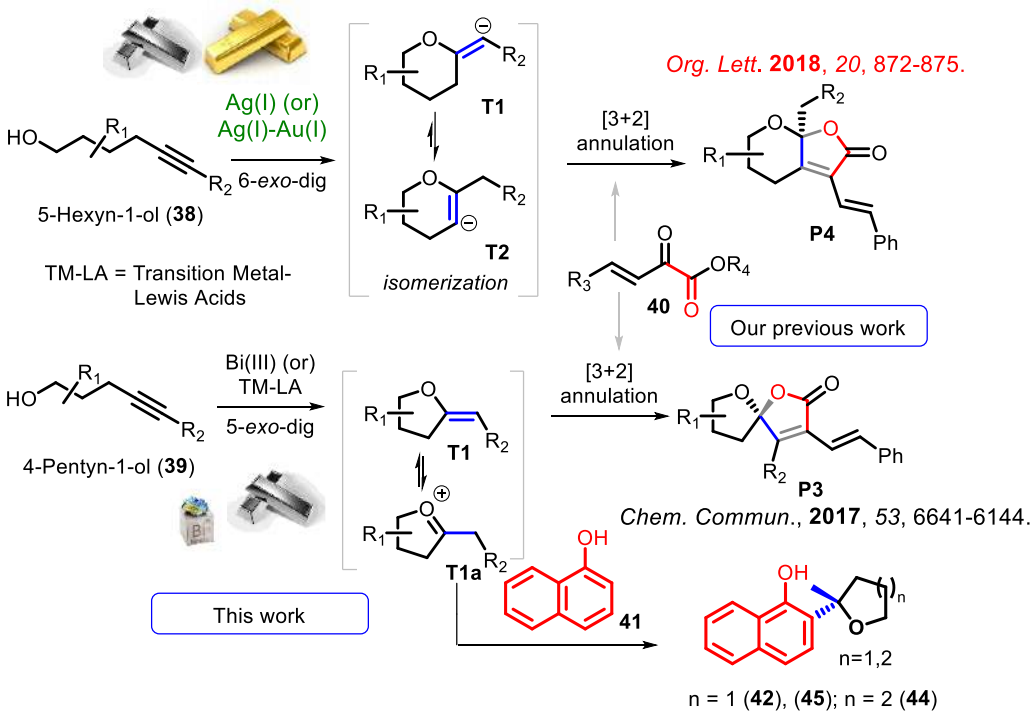
CHAPTER-2

Section-B

Bismuth-(III)-catalysed hydroalkoxylation hydro(hetero)arylation cascade: simple access to 2- (hetero)aryl tetrahydrofurans and tetrahydropyrans from alkynols

2.2. Hypothesis

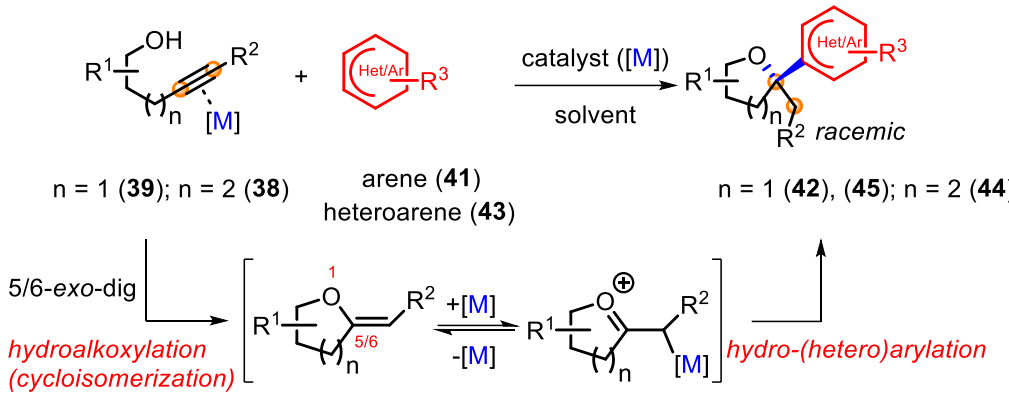
In light of the emerging importance of cascade and domino reactions, and as a part of our interest in the development of new synthetic methodologies involving cycloisomerization of alkynyl alcohols,[31,32] we have recently the reported the synthesis of oxa-spirolactones **P3** *via* an intermolecular cascade annulation of alkynols (4-pentyn-1-ols) with α-ketoesters using $Bi(OTf)_3$ as a dual activating (σ and π) catalyst, which proceeds through an oxocarbenium ion intermediate (formed through 5-*exo*-dig hydroalkoxylation of alkynol) and subsequent cascade annulation process. In another investigation, disclosed Ag(I) or Au(I)-Ag(I)-catalyzed [2+3]-annulation cascade reaction of 5-hexyn-1-ols with α-ketoesters and/or β-γ-unsaturated α-ketoesters to give furo-pyranones **P4** *via* cyclic enol-ether **T2** (formed from alkynol *via* **T1**) (Scheme 2.2.1).[33]



Scheme 2.2.1 | Concept of the cascade annulation of alkynols and arenes using a π- and σ-acidic catalyst.

Inspired by our earlier investigations,[31-33] we hypothesized that, an oxocarbenium ion **T1a** could be generated from **T1** or **T2**, that would undergo Friedel-Crafts-type addition hydro-(hetero)arylation under identical reaction

conditions to give 2-(-(hetero)aryl-tetrahydrofurans and pyrans from suitably functionalized alkynols and (hetero)arenes (Scheme 2.2.1 and Scheme 2.2.2).



Scheme 2.2.2 | Strategy for synthesis of 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans from alkynols.

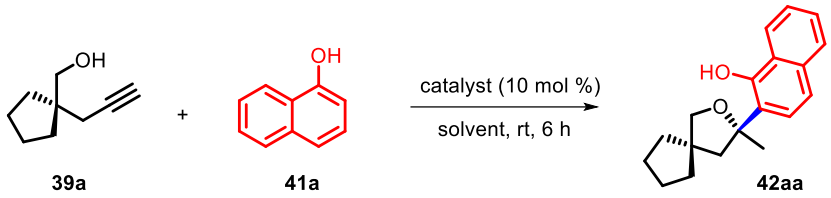
2.2.2 Result and discussions

To investigate the feasibility of this hypothesis, known alkynol **39a** (0.36 mmol) and α-naphthol (**41a**) (0.36 mmol) were treated with $Bi(OTf)_3$ (10 mol %, 0.036 mmol), in anhydrous CH_2Cl_2 under argon atmosphere. This reaction proceeded smoothly and gave the desired 2-naphthyl tetrahydrofuran **42aa** in the good yield of 80% in 6 h at room temperature (Scheme 2.2.2).

2.2.3 Optimization of reaction conditions

Encouraged by these results, we continued to identify effective catalyst and reaction conditions. Several Lewis acids (entries 4-15) and Brønsted acids (entries 16-20) were screened, in which some were found to be moderately active. Among all, $Bi(OTf)_3$ turned out to be the preeminent catalyst. A brief solvent screen (entries 1-3) prompts us to replace the chlorinated solvent (CH_2Cl_2) with relatively benign toluene (entry 2, 87% yield). Further tuning of the reaction parameters, like the molar ratios of the substrates, and catalyst loading, did not lead to any noticeable improvement in the outcome of the reaction. Control experiments verified that the reaction did not proceed in the absence of $Bi(OTf)_3$ (entry 21), and minimal conversion was observed with TfOH (a usual contaminant in $Bi(OTf)_3$ catalyst) (entry 20) (Table 1).

Table 2.2 | Optimization of reaction conditions.[a]



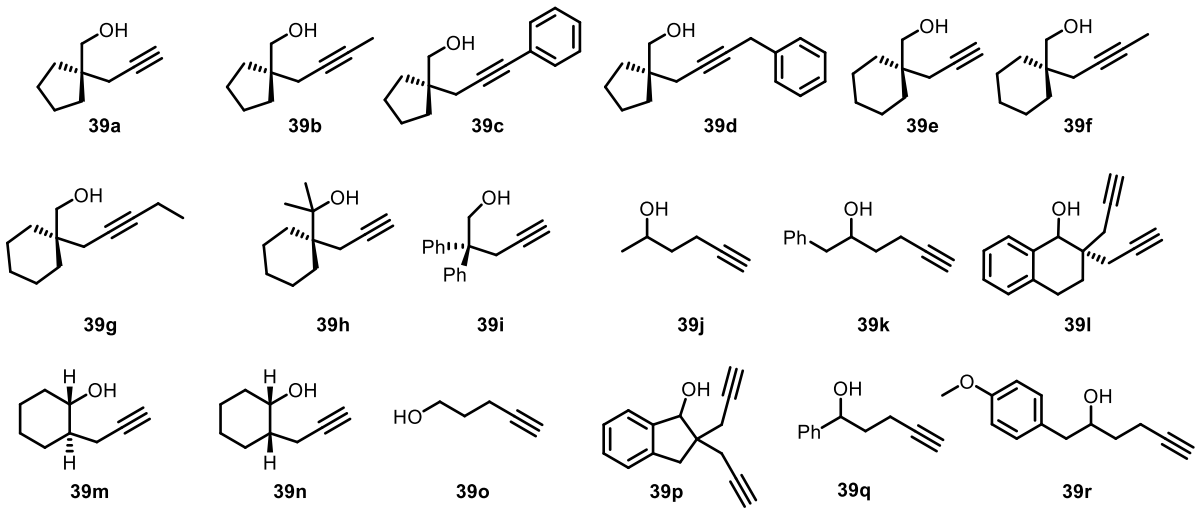
39a + 41a → 42aa

Entry	Catalyst	Solvent	Yield (%)[b]
1	$Bi(OTf)_3$	CH_2Cl_2	80
2	$Bi(OTf)_3$	toluene	87
3	$Bi(OTf)_3$[c]	toluene	65
4	$BiCl_3$	toluene	60
5	$In(OTf)_3$	CH_2Cl_2	58
6	$Yb(OTf)_3$	CH_2Cl_2	62
7	$Hg(OTf)_2$	toluene	80
8	$HgCl_2$	toluene	55
9	$Hg(OAc)_2$	toluene	60
10	$Pd(OTf)_2$	toluene	62
11	$Pd(OAc)_2$	toluene	40
12	Ph_3PAuCl, AgOTf	CH_2Cl_2	45
13	AgOTf	CH_2Cl_2	42
14	$Cu(OTf)_2$	CH_2Cl_2	50
15	$FeCl_3$	CH_3CN	10
16	PTSA	$(CH_2)_2Cl_2$	10
17	PTSA	toluene	20
18	CF_3COOH	CH_2Cl_2	25
19[d]	TfOH	CH_2Cl_2	10
20[d]	TfOH	toluene	15
21[d]	no catalyst	toluene	-

[a]All reactions were carried out with 0.36 mmol of **39a** and 0.36 mmol of **41a** in 2 mL of the solvent unless otherwise specified. [b]Isolated yield of **42aa**. [c]5 mol %. [d]Control experiments. rt = room temperature, Tf = triflate (CF_3SO_2).

2.2.4 Synthesis of alkynol building blocks:

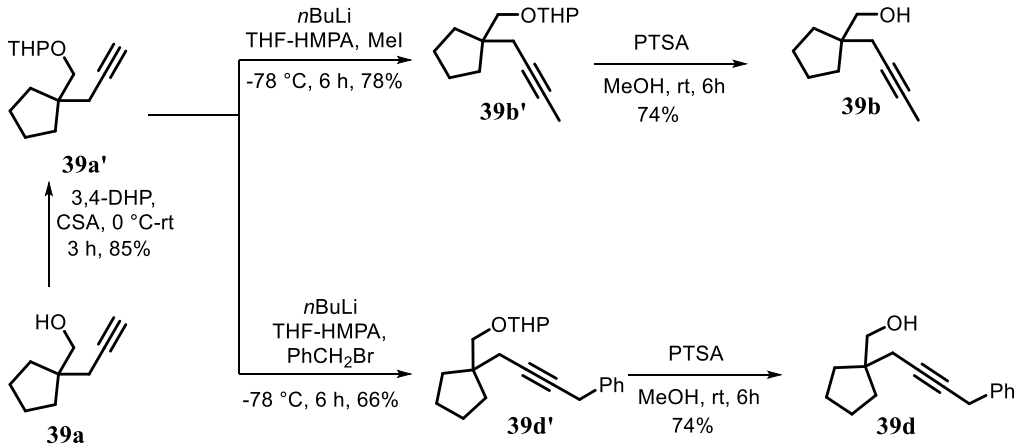
In order to investigate the generality of this methodology, we have prepared diverse alkynols (4-pentyne -1-ols and 5-hexyn-1-ols), and arenes using the following strategies.



Scheme 2.2.3 | Preparation of alkynols.

Compound **39a-j, 39l** & **39q** were prepared using known literature procedures.[33] **39k** and **39r** was prepared using the reported procedure.[34] **39o** was purchased from commercial sources.

Synthesis of alkynols 39b and 39d:

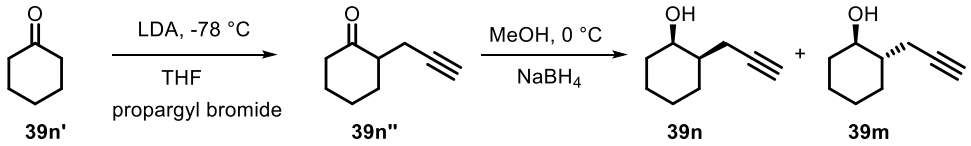


Scheme 2.2.4 Preparation of alkynols.

The internal alkynol **39b** and **39d** prepared from known alkynol **39a** *via* THP protection of primary alcohol to give **39a'**, which on subsequent alkylation of triple bond by using *n*BuLi, HMPA and suitable alkyl halide at –78 °C in THF furnished desired alkylated products **39b** & **39d** (Scheme 2.2.4).

Synthesis of alkynols 39n and 39m:

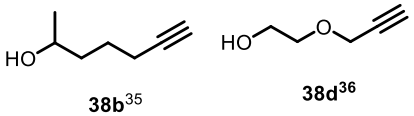
The alkynol **39n and 39m** was prepared by a two-step reaction sequence involving α-propragylation of cyclohexanone with propargyl bromide to give **39n''**. The ketone **39n''** undergoes reduction by using sodium borohydride in MeOH to furnish the alkynol **39n** and **39m** as separable *cis*- and *trans* isomers(Scheme 2.2.5).



Scheme 2.2.5`

Preparation of alkynols 38b, 38d:

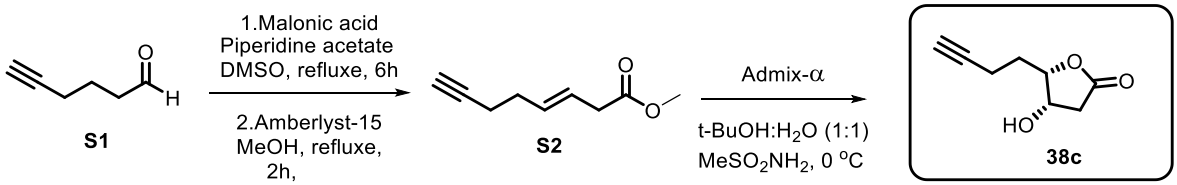
The alkynols **38b** and **38d** were prepared by using known literature procedures.[35,36]



Scheme 2.2.6

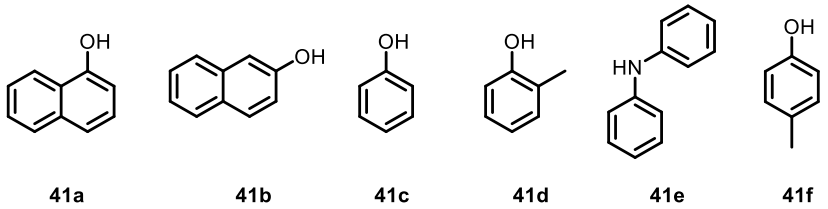
Synthesis of alkynol 38c:

The alkynol **38c** was synthesized by using hex-5-ynal **(S1)** & piperidine acetate in DMSO reflux, followed by Amberlist-15 to deliver the (*E*)-oct-3-en-7-ynoic acid, which on treated with AD mix-α for lactonization at 0°C in t-BuOH: H2O gave lactone fused alkynol **38c** (Scheme 2.2.7).

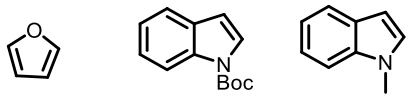


Scheme 2.2.7

Synthesis of *arenes & heteroarenes*:



41a, 41b, 41c, 41d, 41e and **41f** were purchased from commercial sources.



43a 43b 43c

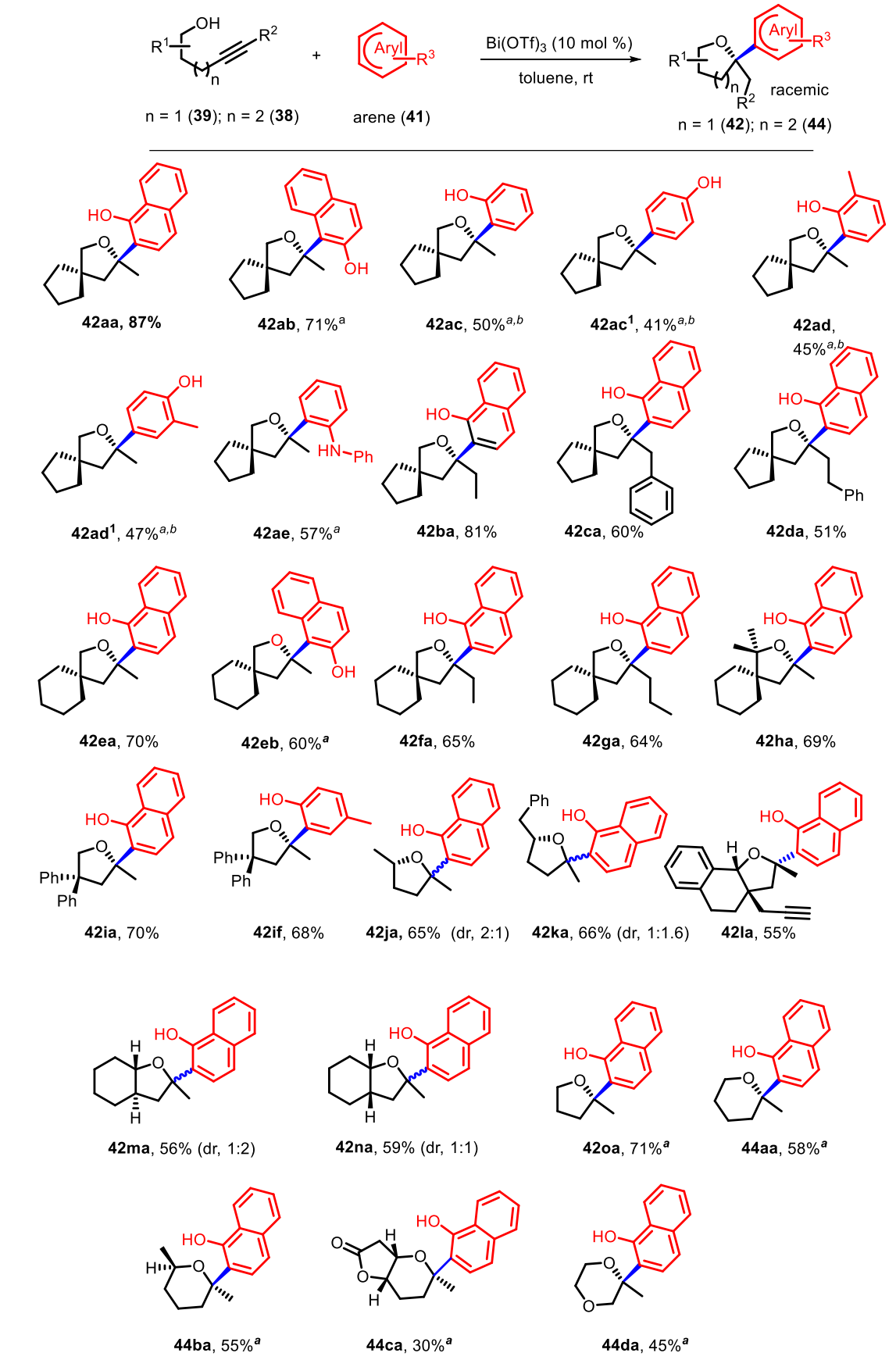
Scheme 2.2.8

Compounds **43a** and **43c** are purchased from commercial sources. Compound **43b** was prepared using a known procedure. [37]

2.2.5 Scope and Generality of Reaction:

With the optimal conditions at hand, we then investigated the substrate scope of this tandem process (Scheme 2.2.2). Firstly, the reaction of diverse terminal/internal-alkynols and arenes was tested. The known cyclopentane fused 4-pentyn-1-ol worked well with α/β-naphthols, phenol, *o*-cresol, and diphenylamine to afford corresponding adducts **42aa**-**ae** in excellent yields (41-87%). Cyclopentane fused internal alkynols (having methyl, phenyl, and benzyl substituents on alkyne termini) were well condensed with α-naphthol and furnished corresponding tetrahydrofurans **42ba**, **42ca,** and **42da,** respectively. Condensation of cyclohexane fused terminal/internal alkynols with α and β -naphthols gave **42ea**, **42eb**, **42fa,** and **42ga** in good yields. Tertiary alkynol was also well tolerated and gave **42ha** in 69% yield. The reaction of 2,2-Diphenyl substituted primary alkynol with α-naphthol, and *p*-cresol provided **42ia** and **42if** in good yield. Secondary alkynols with α-naphthol furnished **42ja** and **42ka**. Conformationally confined tetralin-derived alkynol with α-naphthol delivered **42la** as a single diastereomer. Cyclohexane-derived secondary alkynols (having *trans*/*cis* fusion) with α-naphthol provided **42ma** and **42na** in good yield (Scheme 2.29).

The reaction of 4-pentyn-1-ol with α-naphthol gave **42oa** (71%) in a little longer reaction time (10 h). To our delight, 5-hexyn-1-ol also reacted well with α-naphthol and furnished the expected tetrahydropyran **44aa** (via the 5-*exo*-dig mode of cyclization) in the good yield of 58% in 10 h.



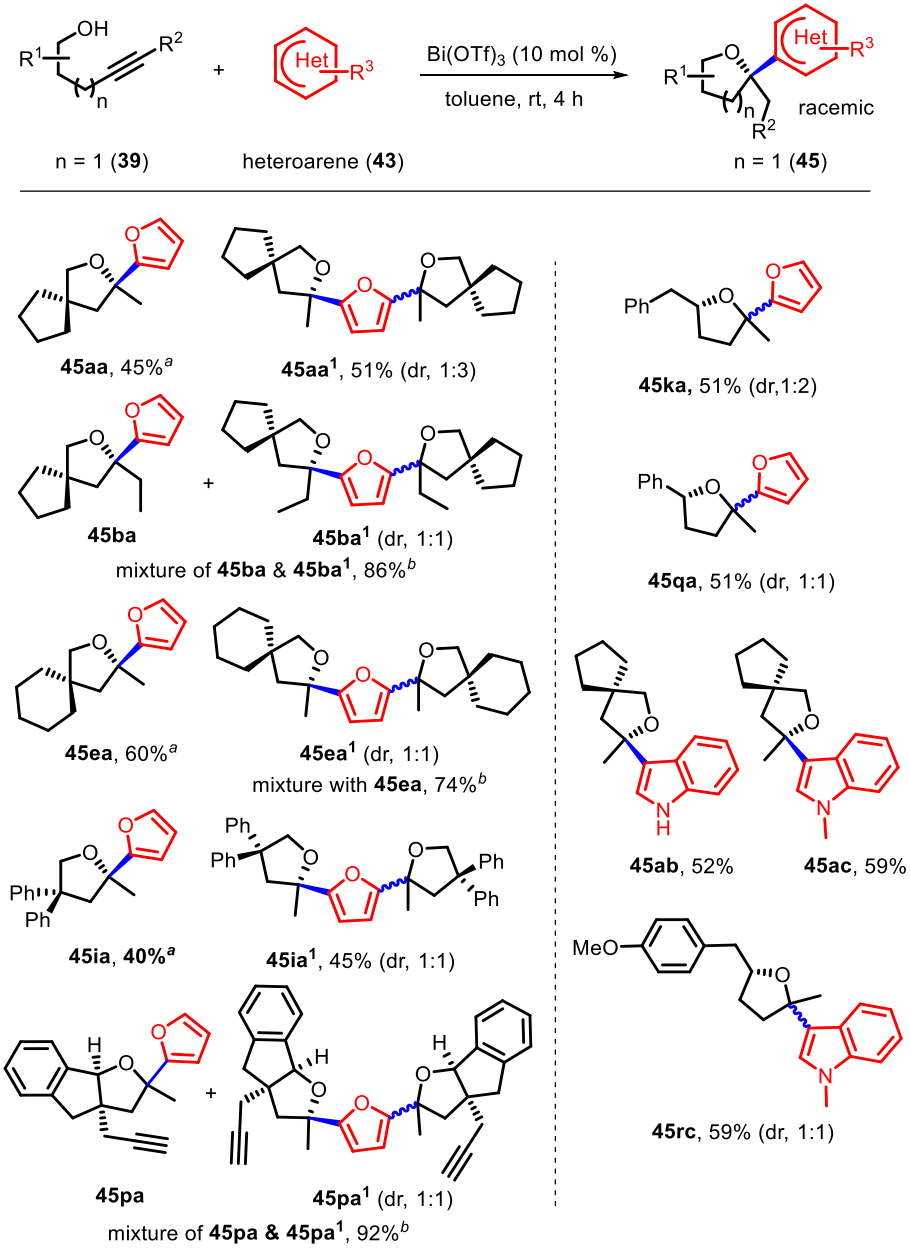
Scheme 2.2.9. Substrate scope concerning alkynols and arenes.

Hexyn-1-ol-derived secondary alcohol was well tolerated, and gave **44ba** as a single diastereomer. Lactone-fused alkynol also found a good substrate and furnished the corresponding pyran **44ca** in a moderate yield of 30%. Propargyl ether-derived alkynol proceeded smoothly and delivered the product **44da** in good yield. Exclusive alpha-substituted products in the case of α and β-naphthols are attributed to the probable chelation of the catalyst with the free hydroxyl functionality of arenes and the oxocarbenium ion in the probable transition state.[38] Relative stereochemistry of **42la**, **42ba** and **42ca** was confirmed by NOE analysis (Scheme 2.2.9).

Next, we were curious to verify the reactivity of alkynols with heteroarenes in this tandem process, which provides access to 2-heteroaryl tetrahydrofurans, and the results are summarized in Scheme 2.2.10. Among several heterocycles (furan, thiophene, pyrrole, pyridine, bezoxazole, and benzothiazole) tested for this reaction, furan, indole, and 1-methylindole were found to be suitable substrates. Interestingly, the reaction of cyclopentane fused alkynol with furan afforded mono-arylation and double-arylation products **45aa** and **45aa¹** (dr, 1:3, confirmed by HPLC analysis) in 45% and 51% yield, respectively. Internal alkynol with furan gave an inseparable mixture of **45ba** and **45ba¹** (dr, 1:1) in 60% yield. Cyclohexane fused alkynol and furan in 1:2 molar ratio furnished **45ea** exclusively, whereas with 1:1 molar ratio afforded **45ea** and **45ea¹** (dr, 1:1) as an inseparable mixture. Diphenyl substituted alkynol provided mono and double arylated adducts **45ia** and **45ia¹** (dr, 1:1, confirmed by ^{1}H NMR and HPLC analysis). The reaction of indane derived alkynol with furan furnished **45pa** and **45pa¹**. In contrast, the benzyl group extended alkynol and secondary (benzylic) alkynols furnished corresponding mono-furylated products **45ka** and **45qa** as a mixture of diastereomers (confirmed by ^{1}H NMR analysis). Moreover, indole and 1-methylindole also reacted well with primary and secondary alkynols to give **45ab**, **45ac**, and **45rc** in good yields (Scheme 2.2.9).

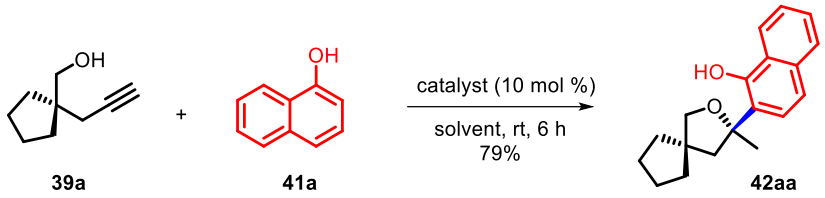
Electron-deficient arenes (nitroarenes, aryl carboxylates, cyanoarenes, haloarenes, and pseudo-haloarenes) and anisoles did not participate in the

reaction, which could be due to the unfavorable hydroarylation (Friedel-Crafts) step of the tandem process (Scheme 2.2.9 and 2.2.10).



Scheme 2.2.10. Substrate scope concerning alkynols and hetero-arenes.

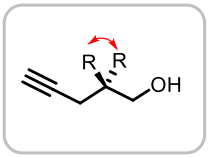
To exemplify the practical applicability of this protocol, a 1 g scale reaction under the standard conditions was conducted to obtain **42aa** in 79% yield with similar efficacy (Scheme 2.2.11). The known cyclopentane fused 4-pentyn-1-ol with α-naphthols condensed well and delivered tetrahydrofuran.



Scheme 2.2.11 | Example for the practical applicability of this methodology.

As observed in our previous studies,[33] the reactivity of unsubstituted 4-pentyn-1-ols is slightly slower compared to geminal disubstituted analogs (this could be attributed to the Thorpe-Ingold effect).

Thorpe–Ingold effect: This effect was disclosed by Beesly, Thorpe, and Ingold in 1915 as part of their investigations on the feasibility of diverse cyclization reactions. This effect is also called the gem-dimethyl effect or angle compression, in which ring closures or intramolecular transformations are favored by steric hindrance.[39]



In this work, substrates possessing geminal substituents (which lead to the angle compression at the tetrahedral carbon chain and facilitate the ring-closure/hydroalkoxylation) showed superior reactivity compared to unsubstituted analogs.

In addition, we observed that 5-hexyn-1-ols reacted slowly compared to 4-pentyn-1-ols, which could be due to the favored ring closure in the latter case, and agrees with Baldwin's rules.[40]

Baldwin's rules: In 1976, Jack Baldwin proposed this rule, which is applicable in ring-closing reactions of synthetic organic chemistry and provides insight into the feasibility of these processes based on below structural features of the acyclic molecules.

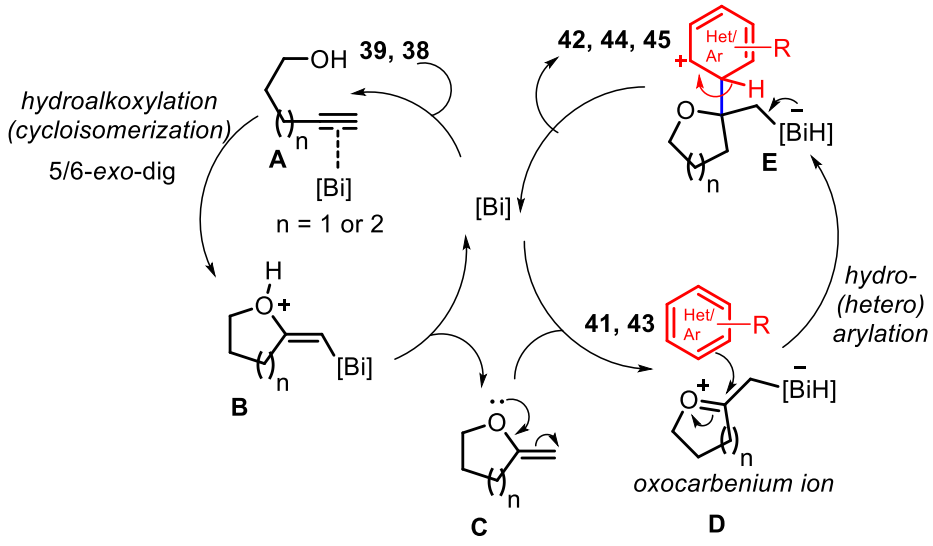
1. How many numbers of atoms are present in a newly formed ring?

2. Ring-closing through *exo* or *endo* modes (outside or inside, respectively).

3.Ring closures involving sp3 hybridized atoms are called *trig*-cyclizations, sp2 atoms called *dig*-cyclizations, and sp atoms called *trig*-cyclizations.

3.2.6 Plausible reaction Mechanism

A plausible mechanism of this transformation based on our (and other's) earlier mechanistic investigations and the results obtained in this work is shown in Scheme 2.2.11.[4c,34,33] The reaction is initiated by the π-coordination of $Bi(OTf)_3$ to the C-C triple bond of alkynol **39**, **38** to form intermediate **A**, which triggers the hydroalkoxylation (cycloisomerization) *via* 5- or 6-*exo*-dig mode of addition on to the alkyne triple bond, which leads to the intermediate **B**. Protodebismuthination of **B** affords the *exo*-cyclic enol ether **C**, further activation of enol ether **C** to generate the oxocarbenium ion **D**, which undergo hydro-(hetero)arylation with arenes **41** or heteroarenes **43** to give **E**. Concomitant second protodebismuthination step in **E** leads to the desired products **42**, **44**, **45** (Scheme 2.2.12).



Scheme 2.2.12 | Plausible reaction mechanism.

3.2.7 Conclusion

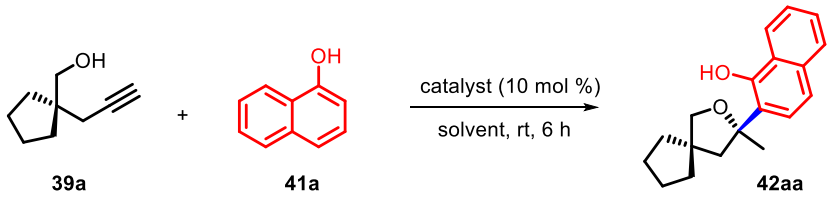
In summary, hydroalkoxylation (cycloisomerization) and hydro-(hetero)arylation cascade reaction of alkynols with (hetero)arenes mediated by main group element derived borderline metal catalyst $Bi(OTf)_3$ is identified.

Diverse alkynols and electron-rich arenes/heteroarenes, which proceeded cleanly under ambient reaction conditions and furnished a series of novel 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans in good to excellent yields in an atom and step economic way. A further expansion of this work in building libraries related to pharmacologically active molecules and their biochemical evaluation is in progress and will be communicated in due course.

2.2.8 Experimental Procedures and Data:

All reactions were performed under an argon atmosphere with an oven (80 ºC) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under an argon atmosphere immediately before use. Dichloromethane and acetonitrile were freshly distilled over calcium hydride under an argon atmosphere. 30 °C corresponded to the room temperature (rt) of the laboratory when the experiments were carried out. Reaction temperatures are the reported as the bath temperature surrounding the reaction vessel.

***General Procedure* for the Synthesis of 2-(Hetero)aryl Tetrahydrofurans and Tetrahydropyrans from Alkynols**

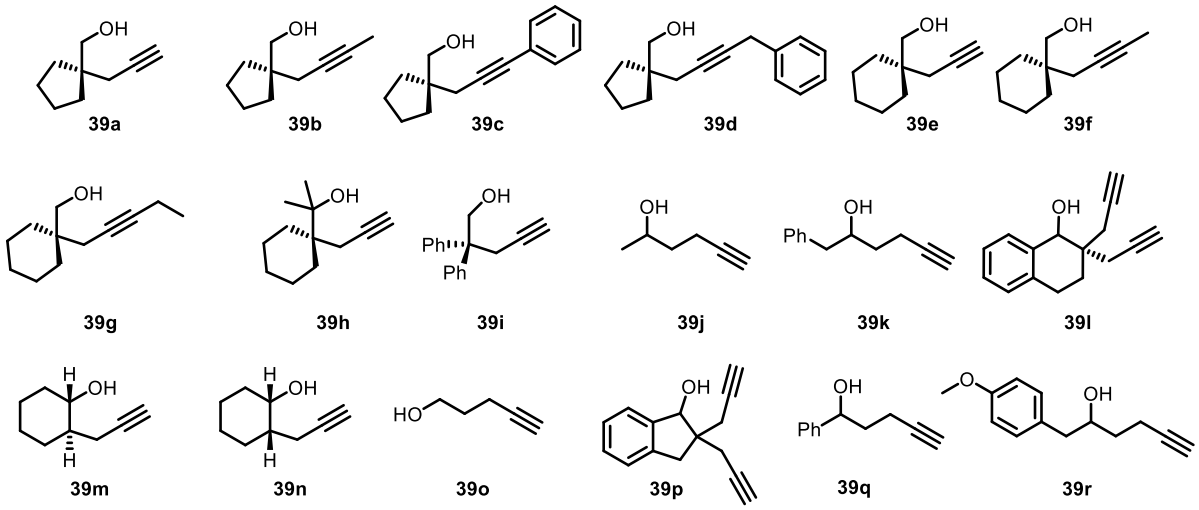


Alkynol **39** (0.36 mmol) and arens or heteroarenes **41** (0.36 mmol) were taken into a single neck 10 mL round bottom flask equipped with positive argon flow, then dissolved in 2 mL of anhydrous toluene. $Bi(OTf)_3$ (0.036mmol) was added under an argon atmosphere at room temperature (rt). The resulting reaction mixture was stirred at rt for 6 h. After completion of the reaction (monitored by TLC, visualized using UV, anisaldehyde, and $KMnO_4$ staining solutions), quenched with saturated aqueous $NaHCO_3$solution, then extracted with CH_2Cl_2 (2x5 mL) and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and filtered through sintered glass funnel. The filtrate was concentrated

under reduced pressure and purified using silica-gel column chromatography (100-200 mesh) to afford the corresponding tetrahydrofuran **42, 44 & 45**.

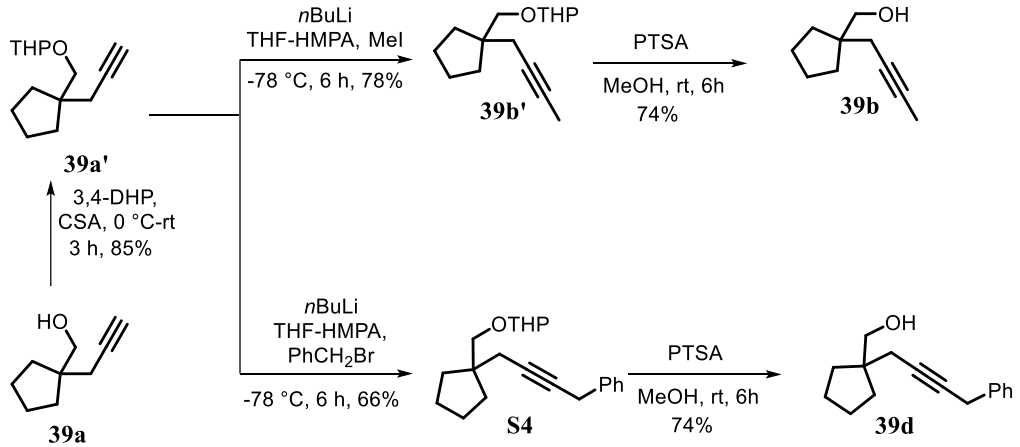
2.2.8.1 Experimental Procedure & Spectroscopic Data of Synthesised Products:

Synthesis of alkynols:



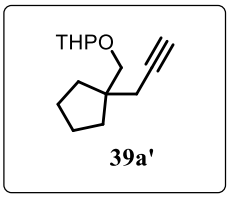
Compounds **39a-j, 39l** & **39q** were prepared using known literature procedures.[33] **39k** and **39r** were prepared using the reportedprocedure.[34] **39o** was purchased from commercial sources.

Synthesis of (1-(But-2-yn-1-yl) cyclopentyl) methanol (39b) & 2-((1-(but-2-yn-1-yl)cyclopentyl)methoxy)tetrahydro-2H-pyran (39d):



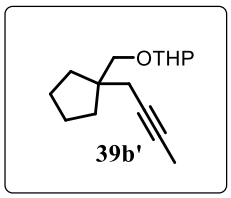
((1-(Prop-2-yn-1-yl) cyclopentyl) methoxy) tetrahydro-2H-pyran (39a'):

((1-(Prop-2-yn-1-yl) cyclopentyl) methoxy) tetrahydro-2H-pyran (**39a'**) colorless oil was prepared using the reported procedure.[33]



^{1}H NMR ($CDCl_3$, 200MHz): δ 4.61 (m, 1H) 3.97-3.79 (m, 1H), 3.62 (d, *J* = 9.35 Hz, 1H), 3.57-3.35 (m, 1H), 3.19 (d, *J*=9.35 Hz, 1H), 2.31 (t, *J* = 2.40 Hz, 2H), 1.91 (t, *J* = 2.65 Hz, 1H), 1.67-1.56 (m, 14H).

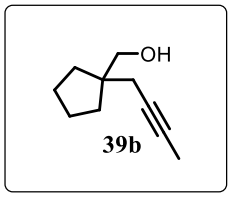
2-((1-(But-2-yn-1-yl) cyclopentyl) methoxy) tetrahydro-2H-pyran (39b'):



2-((1-(But-2-yn-1-yl)cyclopentyl) methoxy) tetrahydro-2H-pyran (**39b'**) colorless oil was prepared using the reported procedure.[33]

^{1}H NMR ($CDCl_3$, 200MHz): δ 4.66-4.55 (m, 1 H), 3.97-3.79 (m, 1 H), 3.61 (d, *J*=9.09 Hz, 1 H), 3.56-3.44 (m, 1 H), 3.17 (d, *J* = 9.09 Hz, 1 H), 2.23 (q, *J*=2.15 Hz, 2 H), 1.78 (t, *J* = 2.53 Hz, 3 H), 1.67-1.42 (m, 14 H).

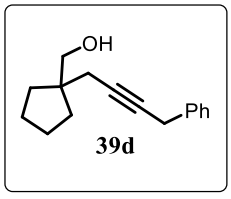
(1-(But-2-yn-1-yl) cyclopentyl) methanol (39b):



(1-(But-2-yn-1-yl) cyclopentyl) methanol (**39b**) colorless oil was prepared using the reportedprocedure.[33]

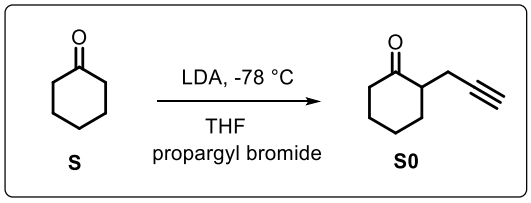
^{1}H NMR ($CDCl_3$, 200MHz); δ 3.50 (s, 2H), 2.18-2.12 (m, 2H), 2.08 (m, 1H), 1.78 (t, *J* = 2.59 Hz, 3H), 1.68-1.53 (m, 4H), 1.53-1.40 (m, 4H).

(1-(4-phenylbut-2-yn-1-yl)cyclopentyl)methanol (39d):



(1-(4-phenylbut-2-yn-1-yl)cyclopentyl)methanol (**39d**) colorless oil was prepared using the reported procedure[33], by using crude(39d'). **^{1}H NMR ($CDCl_3$, 200MHz)**: δ 7.39-7.15 (m, 5 H), 3.61-3.55 (m, 2 H), 3.53-3.50 (m, 2 H), 2.37-2.23 (m, 2 H), 1.95 (d, *J* = 2.65 Hz, 1 H), 1.66-1.57 (m, 4 H), 1.54-1.46 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50MHz) δ 131.6, 128.2, 127.6, 123.8, 87.6, 82.8, 68.7, 38.2, 32.0, 26.2, 26.1, 21.6, 14.2.

2-(prop-2-yn-1-yl)cyclohexan-1-one (S0):

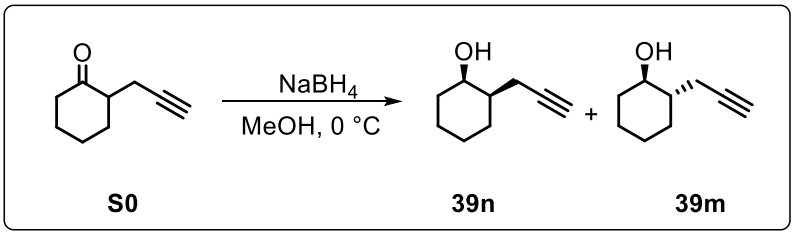


To a flame dried (100 mL) two-neck round bottom flask, anhydrous THF (30 mL) was added under argon atmosphere and cooled it to -78 °C, to this diisopropylamine (4.35 mL, 3.05 mmol) followed by *n*-butyllithium (1.6 M in hexanes, 19 mL,) was added

dropwise at -78 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution was added cyclohexanone (**S**) (3.75 mL,3.05 mmol) in THF (20 mL) and stirred the reaction mixture at -78 °C for 30 min, then warmed to 0 °C and stirred for another 30 min. The reaction mixture was cooled back to -78 °C and propargyl bromide (80% in toluene, 2.31 mL, 3.05 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h and warmed to 25 °C and stirred for overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3x25 mL), combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford2-(prop-2-yn-1-yl) cyclohexan-1-one (**S0)** crude which was subjected to the next step without further purification. (1.5 g).

TLC: R_f= 0.6.

2-(Prop-2-yn-1-yl)cyclohexan-1-ol (39n) & 2-(prop-2-yn-1-yl)cyclohexan-1-ol (39m);



To a solution of 2-(prop-2-yn-1-yl)cyclohexan-1-one (**S0**) (1.5 g 11.01 mmol) in methanol (10 mL), sodium borohydride (0.25 g, 6.61 mmol) was slowly added at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then for 2.5 h at room temperature, after which the solvent was evaporated under reduced pressure. Aqueous NH_4Cl solution (10 mL) was added to the resulting suspension, and then extracted with EtOAc (3×5 mL). Organic phases were combined and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 2% EtOAc/hexanes) to afford a mixture of alcohols **39n** (1,2-*cis*) (614 mg, 50%) colorless oil and **39m**, (1,2-*trans* fused) (594 mg, 39%) colorless oil.

For 39n (cis) TLC: R_f= 0.4 (SiO_2, 2% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.07 (s, 1H), 2.31 (ddd, *J* = 16.98, 7.82, 2.67 Hz, 1H), 2.18 (ddd, *J* = 16.78, 6.87, 2.67 Hz, 1H), 2.00 (t, *J* = 2.67 Hz, 1H), 1.86-1.77 (m, 1H), 1.71-1.59 (m, 3H), 1.59-1.40 (m, 5H), 1.34-1.23 (m, 1H).

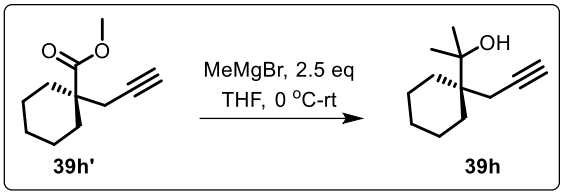
^{13}C NMR ($CDCl_3$, 126 MHz): ^{13}C NMR ($CDCl_3$, 126 MHz): δ 83.5, 69.2, 68.3, 40.8, 32.9, 26.2, 25.1, 21.5, 20.1.

For 39m (trans) TLC: R_f = 0.1 (SiO_2, 2% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.39-3.37 (m, 1H), 2.49-2.43 (m, 1H), 2.32 (ddd, *J* = 16.78, 6.87, 2.67 Hz, 1H), 2.02-1.95 (m, 3H), 1.84-1.89 (m, 1H), 1.79-1.73 (m, 1H),1.71-1.65 (m, 2H) , 1.49-1.40 (m, 1H), 1.31-1.15 (m, 4H).

^{13}C NMR ($CDCl_3$, 126 MHz): ^{13}C NMR ($CDCl_3$, 126 MHz): δ82.9, 73.5, 69.7, 43.9, 35.5, 30.2, 25.4, 24.8, 21.7.

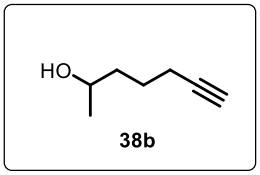
2-(1-(Prop-2-yn-1-yl)cyclohexyl)propan-2-ol (39h)



To a flame dried (100 mL) two neck round bottom flask, methyl 1-(prop-2-yn-1-yl)cyclohexane-1-carboxylate **(39h')** (2 g,1.10 mmol)in anhydrous THF (30 mL) and cooled it to 0 °C followed by methyl magnesium bromide(1.0 M THF) (22 ml, 2.77 mmol) was added dropwise under argon atmosphere after completion of addition gradually increased temperature to rt. Reaction monitored by TLC, after completion of reaction quenched with Aqueous NH_4Cl solution (10 mL), extracted with EtOAc (3×5 mL). Organic phases were combined and dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 4% EtOAc/hexanes) to afford an alcohol **39h** (2-(1-(prop-2-yn-1-yl)cyclohexyl)propan-2-ol) (1.43 g, 71%) colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.43 (d, *J* = 2.78, 2H), 2.33 (br. s, 1H), 2.8 (t, *J* = 2.78, 1H), 1.71-1.32 (m, 10H), 1.25 (s, 6H).

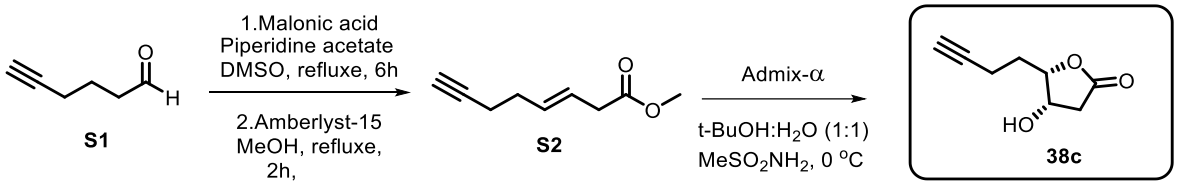
Hept-6-yn-2-ol (38b):



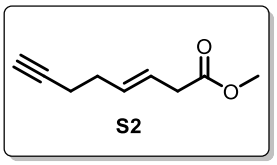
Hept-6-yn-2-ol (**38b**) colorless oil was prepared using thereported procedure. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 3.87-3.78 (m, 1H), 2.24-2.19 (m, 2H), 1.96 (t, *J* = 2.3 Hz, 1H), 1.62-1.52 (m, 4H), 1.20 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 84.4, 68.5, 67.6, 38.2, 24.7, 23.6, 18.4.

5-(But-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (38c):



Methyl-(*E*)-oct-3-en-7-ynoate (S2):



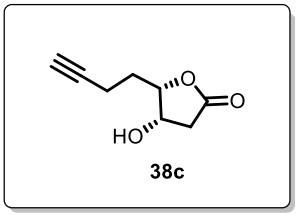
A freshly prepared solution of piperidinium acetate (by mixing piperidine (35 μL, 0.41 mmol) and acetic acid (20 mL, 0.37 mmol)) in DMSO (1 mL) was injected in to a stirred solution of the readily available hex-5-ynal (**S1**) (1.5 g, 15.61 mmol) and malonic acid (3.24 g, 31.2 mmol), in DMSO (40 mL), the resulting reaction mixture was stirred for 6 h at 160°C. Then it was quenched by adding water and extracted with diethyl ether (3x50 mL) and dried over anhydrous sodium sulphate, concentrated under reduced pressure toafford crude (*E*)-oct-3-en-7-ynoic acid, which was subjected to the next step without further purification. The (*E*)-oct-3-en-7-ynoic acid (0.9 g, 6.51 mmol) was dissolved in methanol (5 mL), then amberlyst-15 (2.05 g, 6.5 mmol) was added to the reaction mixture and refluxed for 1 h. The reaction mixture was cooled to room temperature and filtered through sintered funnel and washed with diethyl ether (20 mL) and dried over anhydrous sodium sulphate. Then, filtered using a sintered funnel and concentrated under reduced pressure. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded the pure methyl-(*E*)-oct-3-en-7-ynoate (**S2**) (1.6 g, 78%) as a yellow oil.

TLC: R_f = 0.8 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.69-5.59 (m, 2H), 3.69 (s, 3H), 3.11-3.03 (m, 2H), 2.34-2.21 (m, 4H), 1.97 (s, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.3, 132.3, 123.1, 83.7, 68.7, 51.7, 37.7, 31.4, 18.5.

5-(But-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (38c):



To a solution of methyl (*E*)-oct-3-en-7-ynoate **(S2)** (0.1g, 0.66mmol) in 2 mL of t-BuOH:H_2O (1:1) in a single neck round bottom flask, was added AD-mix-α (0.92 g, 0.66

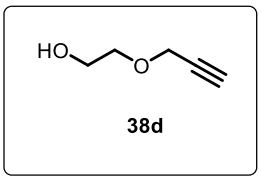
mmol)and methane sulfonamide (0.062 g, 0.66) at 0 °C. The resulting reaction mixture was stirred for 36 h at 0 °C under an argon atmosphere. Then it was quenched with a saturated aqueous solution of sodium sulphite (Na_2SO_3), then extracted with *t*-BuOMe (2x10 mL), dried over anhydrous sodium sulphate. Filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (SiO_2, 40% EtOAc/hexanes) to afford5-(but-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (**38c**) as a colourless oil.

TLC: R_f = 0.12 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.61-4.5 (m, 2H), 2.83 (dd, *J* = 17.7, 4.88 Hz, 1H), 2.56 (d, *J* = 18.31 Hz, 1H), 2.50-2.32 (m, 2H), 2.14-2.06 (m, 1H), 2.08 - 2.06 (m, 1H), 2.06-1.92 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.1, 83.7, 83.1, 69.6, 68.6, 39.3, 27.1, 14.7.

2-(Prop-2-yn-1-yloxy)ethan-1-ol (38d):



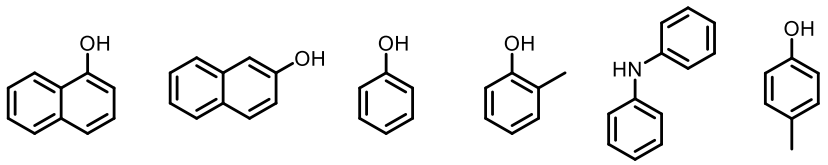
38d

2-(Prop-2-yn-1-yloxy)ethan-1-ol (**38d**) colorless oil was prepared using the reported procedure.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.22-4.15 (m, 2H), 3.80-3.68 (m, 2H), 3.67-3.57 (m, 2H), 2.64 (br s, 1H), 2.45 (t, *J* = 2.4 Hz, 1H).

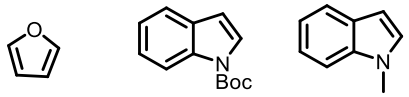
^{13}C NMR ($CDCl_3$, 50 MHz): δ 79.5, 74.8, 71.3, 61.6, 58.4.

Synthesis of Arenes and Heteroarenes:



41a 41b 41c 41d 41e 41f

41a, 41b, 41c, 41d, 41e and **41f** were purchased from commercial sources.



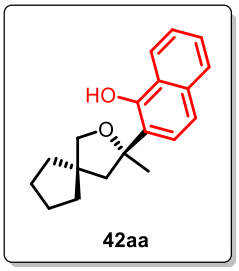
43a 43b 43c

Compounds **43a** and **43c** are purchased from commercial sources.

Compound **43b** was prepared using a known procedure.[37]

Synthesis and Characterization of 2-Aryl Tetrahydrofurans from 4-Pentyn-1-ols and Arenes

-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (42aa):



Following the *General Procedure*, to the mixture of(1-(prop-2-yn-1-yl)cyclopentyl) methanol (**39a**) (0.050 g, 0.36 mmol) and naphthalen-1-ol (**41a**) (0.052 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded2-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (**42aa**) (0.089 g, 87%) yellow oil. Selective ortho substitution of **3aa** was confirmed by ^1H NMR, 2D NMR (HMBC, HSQC, COSY & NOESY) analysis (please see below **Figure 1** and Spectral Section for details.).

TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^1H NMR ($CDCl_3$, 500 MHz): δ 10.57 (s, 1H), 8.36-8.21 (m, 1H), 7.78-7.66 (m, 1H), 7.52-7.40 (m, 2H), 7.30 (d, *J* = 8.72 Hz, 1H), 7.03 (d, *J* = 8.59 Hz, 1H), 3.84 (d, *J* = 8.21 Hz, 1H), 3.74 (d, *J* = 8.21 Hz, 1H), 2.57 (d, *J* = 12.51 Hz, 1H), 2.19 (d, *J* = 12.51 Hz, 1H), 1.65 (s, 3H), 1.63-1.38 (m, 8H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.2, 133.5, 127.1, 126.1, 125.6, 125.1, 124.9, 122.9, 122.5, 118.6, 89.2, 78.7, 52.7, 51.08, 37.75, 36.8, 30.9, 24.8, 24.7.

HRMS (ESI): m/z calcd for $C_{19}H_{23}O_2$ $[M+H]^+$ 283.1693**,** found 283.1690.

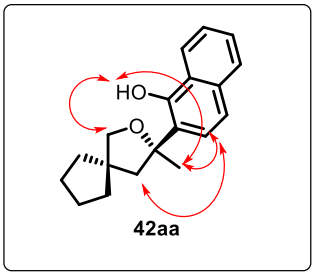
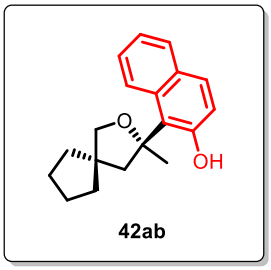


Figure 1. Key NOE interactions in compound **42aa**.

1-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-2-ol (42ab):

Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.050 g, 0.36 mmol) and naphthalen-2-ol (**41b**)) (0.052 g, 0.36



42ab

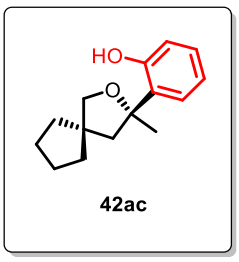
mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 1-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-2-ol (**42ab**) (0.073 g, 71%) yellow oil.. **TLC**: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 11.20 (s, 1H), 7.78-7.65 (m, 2H), 7.61 (d, *J*= 8.84 Hz, 1H), 7.39 (ddd, *J* = 8.62, 6.92, 1.52 Hz, 1H), 7.29-7.19 (m, 1H), 7.04 (d, *J* = 8.84 Hz, 1H), 3.81 (d, *J* = 8.08 Hz, 1H), 3.67 (d, *J* = 8.08 Hz, 1H), 2.72 (d, *J*= 12.51 Hz, 1H), 2.55 (d, *J*=12.51 Hz, 1H), 1.88 (s, 3H), 1.67-1.48 (m, 8H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.2, 131.2, 129.6, 129.4, 129.2, 125.6, 124.3, 122.1, 120.9, 120.5, 89.9, 54.8, 51.2, 37.8, 35.7, 29.8, 25, 24.6.

HRMS (ESI): m/z calcd for $C_{19}H_{23}O_2$ $[M+H]^+$ 283.1693, found 283.1689.

2-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (42ac):



42ac

Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.050 g, 0.36 mmol) and phenol (**41c**) (0.033 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexane) afforded 2-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (**42ac**) (0.042g, 50%) colurless oil.

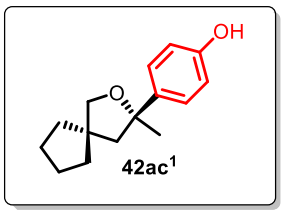
TLC: R_f= 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.72 (s, 1H), 7.02 (m, 1H), 6.93-6.85 (m, 1H), 6.74 (m, 2H), 3.72 (d, *J* = 8.01 Hz, 1H), 3.61 (d, *J* = 8.39 Hz, 1H), 2.46 (d, *J* = 12.59 Hz, 1H), 2.08 (d, *J*= 12.59 Hz, 1H), 1.61-1.46 (m, 11H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.2, 130.6, 128.3, 126.8, 119.2, 117.4, 88.6, 78.6, 52.4, 51.0, 37.9, 36.9, 30.8, 24.7, 24.6.

HRMS (ESI): m/z calcd for $C_{15}H_{21}O_2$ $[M+H]^+$ 233.1536, found 233.1536.

4-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (42ac^1):



Following the *General Procedure*, to the mixture of(1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.050 g, 0.36 mmol) and phenol (**41c**) (0.033 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2%EtOAc/hexanes) afforded 4-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (**42ac^1**) (0.035 g, 41%) colurless oil.

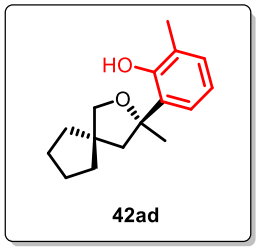
TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.26(d, *J* = 8.59 Hz, 2H), 6.78 (d, *J* = 8.59 Hz, 2H), 5.65 (br. s., 1H), 3.78 (d, *J* = 8.3 Hz, 1H), 3.64 (d, *J* = 8.3 Hz, 1H), 2.26 (d, *J* = 12.38 Hz, 1H), 2.08 (d, *J* = 12.38 Hz, 1H), 1.85-1.28 (m, 11H).

^{13}C NMR ($CDCl_3$, 50 MHz): 154.2, 141.2, 125.9, 114.9, 84.7, 78.5, 53.2, 51.7, 38.4, 37.2, 31.4, 24.7.

HRMS (ESI;) m/z calcd for $C_{15}H_{21}O_2$ $[M+H]^+$ 233.1536, found 233.1535.

2-Methyl-6-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (42ad):



Following the *General Procedure*, to the mixture of(1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.050 g, 0.036 mmol) and o-cresol (**41d**) (0.039 g, 0.036 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-methyl-6-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (**42ad**) (0.040 g, 45%) colurless oil.

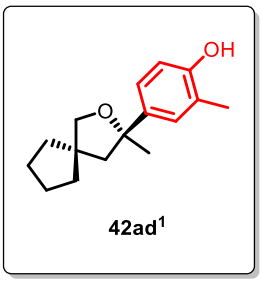
TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.92 (s, 1H), 7.12-6.63 (m, 3H), 3.70 (d, *J* = 8.21 Hz, 1H), 3.72 (d, *J* = 8.21 Hz, 1H), 2.56 (d, *J* = 12.63 Hz 1H), 2.37-2.09 (m, 4H), 1.92-1.34 (m, 11H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.2, 130.6, 128.3, 126.8, 119.3, 117.4, 88.6, 78.6, 52.4, 51.0, 37.9, 36.9, 30.8, 24.7, 24.6.

HRMS (ESI): m/z calcd for $C_{16}H_{23}O_2$ $[M+H]^+$ 247.1693, found 247.1685.

3-Methyl-4-(3-methyl-oxaspiro[4.4]nona3-yl)phenol (42ad[1]):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.050 g, 0.36 mmol) and o-cresol (**41d**) (0.039 g, 0.36 mmol) in anhydrous toluene(2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 3-methyl-4-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (**42ad[1]**) (0.042 g, 47%) colurless oil.

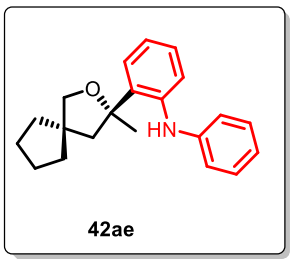
TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.15 (s, 1H), 7.10 (d, *J* = 7.94 Hz, 1H), 6.74 (d, *J* = 8.54 Hz, 1H), 6.16 (br. s., 1H), 3.80 (d, *J* = 7.93 Hz, 1H), 3.67 (d, *J* = 7.93 Hz, 1H), 2.23 - 2.33 (m, 4H), 2.10 (d, *J* = 12.2 Hz, 1H), 1.71-1.47(m, 8H), 1.45-1.26 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.5, 140.8, 127.3, 123.6, 123.0, 114.5, 84.8, 78.4, 53.2, 51.6, 38.4, 37.2, 31.5, 24.7, 24.7, 16.1.

HRMS (ESI): m/z calcd for $C_{16}H_{23}O_2$ $[M+H]^+$ 247.1693, found 247.1689.

2-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)-N-phenylaniline (42ae):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclopentyl) methanol (**39a**) (0.050 g, 0.36 mmol) and diphenylamine (**41e**) (0.061 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 2-(3-methyl-2-oxaspiro[4.4] nonan-3-yl)-*N*-phenylamine (**42ae**) (0.063 g, 57%) yellow oil.

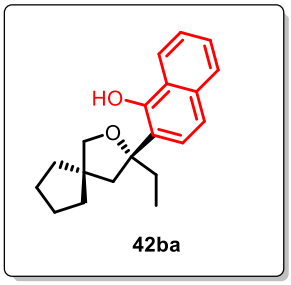
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33-7.21 (m, 4H), 7.12-6.97 (m, 4H), 6.96–6.83 (m, 1H), 5.67 (s, 1H), 3.77 (d, *J* = 8.21 Hz, 1H), 3.64 (d, *J* = 8.21 Hz, 1H), 2.27 (d, *J* = 12.38 Hz, 1H), 2.08 (d, *J* = 12.38 Hz, 1H), 1.82-1.56 (m, 6H), 1.52 (s, 3H), 1.44-1.35 (m, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 143.5, 142.2, 141.1, 129.3, 125.6, 120.6, 117.8, 117.4, 84.4, 78.5, 53.1, 51.8, 38.4, 37.2, 31.4, 24.7.

HRMS (ESI): m/z calcd for $C_{21}H_{26}NO$ $[M+H]^+$ 308.2009, found 308.2006.

2-(3-Ethyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (42ba):



42ba

Following the *General Procedure*, to the mixture of (1-(but-2-yn-1-yl) cyclopentyl) methanol (**39b**) (0.050 g, 0.32 mmol) and naphthalen-1-ol (**41a**)) (0.047 g, 0.32 mmol)in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.021 g, 0.032 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(3-ethyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (**42ba**) (0.079 g, 81%) yellow oil.

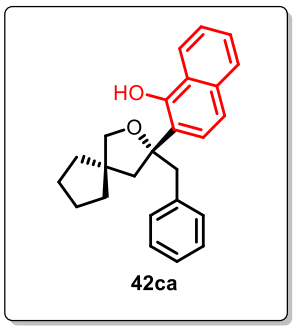
TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.68 (s, 1H), 8.29 (d, *J* = 8.55 Hz, 1H), 7.75 (d, *J* = 7.32 Hz, 1H), 7.54-7.43 (m, 2H), 7.30 (d, *J* = 8.55 Hz, 1H), 7.01 (d, *J* = 8.54 Hz, 1H), 3.86-3.78 (m, 2H), 2.54 (d, *J* = 12.82 Hz, 1H), 2.24 (d, *J* = 12.21 Hz, 1H),2.06-1.86 (m, 2H), 1.74-1.47 (m, 8H), 0.88 (t, *J* = 7.32 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 151.4, 133.4, 127.0, 126.1, 125.4, 125.3, 125.0, 122.4, 120.6, 118.4, 92.5, 78.6, 51.8, 50.7, 37.4, 37.0, 36.6, 24.7, 24.6, 8.6.

HRMS (ESI): m/z calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1849, found 297.1848.

2-(3-Benzyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (42ca):



42ca

Following the *General Procedure*, to the mixture of (1-(3-phenylprop-2-yn-1-yl) cyclopentyl) methanol (**39c**) (0.050 g, 0.23 mmol) andnaphthalen-1-ol (**41a**)) (0.033 g, 0.23 mmol)in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.015 g, 0.023 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(3-benyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (**42ca**) (0.050 g, 60%) yellow oil.

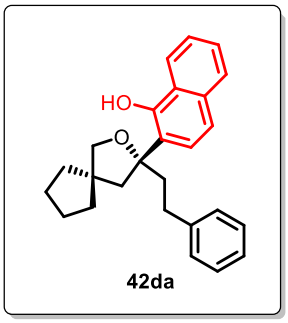
TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.30 (s, 1H), 8.26-8.11 (m, 1H), 7.80-7.63 (m, 1H), 7.48-7.38 (m, 2H), 7.30-7.22 (m, 2H), 7.18-7.08 (m, 3H), 7.02-6.86 (m, 2H), 3.79-3.64 (m, 2H), 3.79-3.64 (m, 2H), 2.51 (d, *J* = 12.63 Hz, 1H), 2.32 (d, *J* = 12.63 Hz, 1H), 1.69 - 1.44 (m, 8H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 151.3, 137.5, 136.5, 133.6, 130.8, 130.3, 127.7, 127.0, 126.5, 126.2, 125.6, 125.4, 124.9, 122.5, 120.8, 118.2, 91.8, 78.8, 50.8, 50.1, 49.0, 37.3, 37.1, 29.7, 24.7, 24.6.

HRMS (ESI): m/z calcd for $C_{25}H_{27}O_2$ $[M+H]^+$ 359.2006, found 359.2003.

2-(3-Phenethyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (42da):



42da

Following the *General Procedure*, to the mixture of (1-(4-phenylbut-2-yn-1-yl) cyclopentyl) methanol (**39d**) (0.050 g, 0.021 mmol) and naphthalen-1-ol (**41a**)) (0.031 g, 0.021 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.013 g, 0.0021 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 8h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(3-phenethyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (**42da**) (0.045 g, 51%) yellow oil.

TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

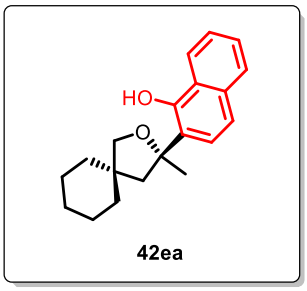
^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.58 (s, 1H), 8.30 (d, *J*=7.9 Hz, 1H), 7.76 (d, *J* = 9.16 Hz 1H), 7.55-7.42 (m, 2H), 7.39-7.17 (m, 4H), 7.17-6.96 (m, 3H), 3.91-3.15 (m, 2H), 2.68-2.54 (m, 1H), 2.27-2.22 (m, 1H), 1.71-1.44 (m, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): 150.1, 142.1, 133.5 128.3, 127.0, 126.1, 125.1, 124.9, 122.4, 118.7, 118.6, 91.9, 89.2, 78.7, 52.7, 51.1, 50.07, 46.1, 37.7, 37.3,36.9, 36.8, 30.9, 30.6, 24.7.

HRMS (ESI): m/z calcd for $C_{26}H_{29}O_2$ $[M+H]^+$ 373.2162, found 373.2155.

2-(3-Methyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (42ea):

Following the *General Procedure*, to the mixture of(1-(prop-2-yn-1-yl) cyclohextyl) methanol (**39e**) (0.050 g, 0.032 mmol) and naphthalen-1-ol (**41a**)) (0.049 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.020 g, 0.0032 mmol)



42ea

under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(3-methyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (**42ea**) (0.068 g, 70%) yellow oil.

TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

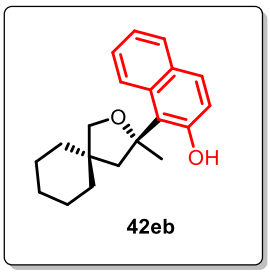
^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.37 (s, 1H), 8.27-8.14 (m, 1H), 7.71-7.57 (m, 1H), 7.44-7.30 (m, 2H), 7.22 (d, *J* = 8.59 Hz, 1H), 6.98 (d, *J* = 8.59 Hz, 1H), 3.79 (d, *J* = 8.59 Hz, 1H), 3.63 (d, *J* = 8.59 Hz, 1H), 2.43 (d, *J* = 12.88 Hz, 1H), 1.93 (d, *J* = 12.76 Hz, 1H), 1.56 (s, 3H), 1.50-1.11 (m, 10H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.0, 133.5, 127.1, 126.1, 125.5, 125.1, 124.9, 122.6, 122.4, 118.7, 88.9, 77.8, 51.7, 44.3, 36.9, 35.9, 31.1, 25.8, 23.8, 23.7.

HRMS (ESI): m/z calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1849, found 297.1847.

1-(3-Methyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-2-ol (42eb):

Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclohextyl) methanol (**39ea**) (0.050 g, 0.32 mmol) and naphthalen-2-ol (**41b**)) (0.049 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.020 g, 0.032 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 8h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 1-(3-methyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-2-ol (**42eb**) (0.065 g, 60%) yellow oil.



42eb

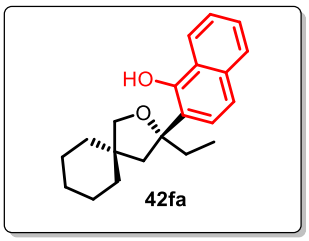
TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.1 (s, 1H), 7.75-7.74 (m, 1H), 7.64 (d, *J* = 9.16 Hz,1H), 7.48-7.40 (m,2H), 7.30-7.27 (m, 1H), 7.06 (d, *J* = 8.54 Hz, 1H), 3.91 (d, *J* = 8.54 Hz 1H), 3.72 (d, *J* = 8.54 Hz, 1H), 2.58 (d, *J* = 12.82 Hz, 1H), 2.46 (d, *J* = 12.82 Hz, 1H) 1.90 (s, 3H), 1.73-1.59 (m, 10H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.9, 131.2, 129.6, 129.3, 129.1, 125.5, 124.4, 122, 120.9, 120.4, 89. 63, 77.34, 54.08, 44.4, 35.9, 35.5, 30.3, 29.7, 25.9, 23.8, 23.5.

HRMS (ESI): m/z calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1849, found 297.1846.

2-(3-Ethyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (42fa):



Following the *General Procedure*, to the mixture of (1-(but-2-yn-1-yl) cyclohextyl) methanol (**39f**) (0.050 g, 0.30 mmol) and naphthalen-1-ol (**41a**)) (0.043 g, 0.30 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.019 g, 0.030 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(3-ethyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (**42fa**) (0.047 g, 49.88%) yellow oil.

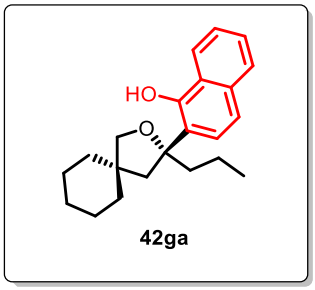
TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.56 (s, 1H), 8.35 - 8.26 (m, 1H), 7.79-7.71 (m, 1H), 7.51-7.42 (m, 2H), 7.34 (d, *J* = 8.77 Hz, 1H), 7.06 (d, *J* = 8.77 Hz, 1H), 3.84 (d, *J* = 8.77 Hz, 1H), 3.79 (d, *J* = 8.77 Hz, 1H), 2.48 (d, *J* = 12.59 Hz, 1H), 2.01 (d, *J* = 12.97 Hz, 1H), 2.0-1.83 (m, 2H), 1.62-1.45 (m, 5H), 1.43-1.26 (m, 5H), 0.88 (t, *J* = 7.44 Hz, 3H)**.**

^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.18, 133.5, 127.05, 126.1, 125.4, 125.0, 122.4, 120.6, 118.4, 92.1, 77.7, 50.8, 43.9, 36.8, 36.7, 35.9, 29.7, 25.8, 23.9, 23.6, 8.7.

HRMS (ESI): m/z calcd for $C_{21}H_{27}O_2$ $[M+H]^+$ 311.2006, found 311.2003.

2-(3-Propyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (42ga):



Following the *General Procedure*, to the mixture of 2-(1-(pent-2-yn-1-yl)cyclohexyl)ethan-1-ol (**39g**) (0.050 g, 0.27 mmol) and naphthalen-1-ol (**41a**) (0.039 g, 0.27 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.018 g, 0.027 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 2-(3-propyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (**42ga**) (0.058 g, 64%) yellow oil.

TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

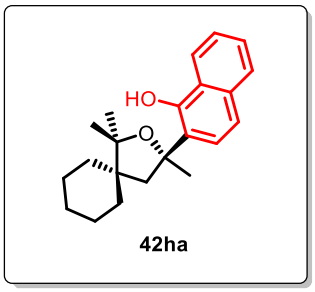
^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.57 (s, 1H), 8.38-8.26 (m, 1H), 7.82-7.74 (m, 1H), 7.54-7.44 (m, 2H), 7.33 (d, *J* = 8.77 Hz, 1H), 7.06 (d, *J* = 8.77 Hz, 1H), 3.86 (d, *J* = 8.39 Hz, 1H), 3.79 (d, *J* = 8.39 Hz, 1H), 2.51 (d, *J* = 12.97 Hz, 1H), 2.05 (d, *J* = 12.59 Hz, 1H),

1.91-1.98 (m, 1H), 1.85 (td, *J* = 12.78, 4.58 Hz, 1H), 1.45-1.60 (m, 6H), 1.40 (m, 2H), 1.29-1.34 (m, 4H), 0.85 (t, *J* = 7.25 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.9, 133.4, 127.05, 126.1, 125.4, 125.04, 122.4, 120.9, 118.4, 91.7, 77.7, 51.2, 46.5, 43.9, 36.8, 35.9, 29.7, 25.8, 23.9, 23.6, 17.6, 14.3.

HRMS (ESI): m/z calcd for $C_{22}H_{29}O_2$ $[M+H]^+$ 325.2162, found 325.1908.

2-(1,1,3-Trimethyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (42ha):



Following the *General Procedure*, to the mixture of2-methyl-1-(1-(prop-2-yn-1-yl)cyclohexyl)propan-2-ol (**39h**) (0.050 g, 0.39 mmol) and naphthalen-1-ol (**41a**) (0.039 g, 0.39 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.018 g, 0.039 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(1,1,3-trimethyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol **(42ha):** (0.062 g, 69%) yellow oil.

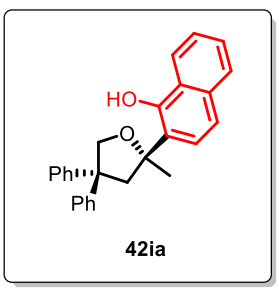
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.79 (s, 1H), 8.43-8.28 (m, 1H), 7.77 (m, 1H), 7.57-7.44 (m, 2H), 7.35 (d, *J* = 8.55 Hz, 1H), 7.15 (d, *J* = 8.54 Hz, 1H), 2.76 (d, *J* = 13.43 Hz, 1H), 2.45 (d, *J* = 12.82 Hz, 1H), 1.81-1.69 (m, 4H), 1.66 (s, 3H), 1.58-1.40 (m, 4H), 1.33 (s, 3H), 1.21 (s, 3H), 1.18-1.11 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.2, 133.3, 127.1, 125.9, 125.6, 125.4, 124.9, 124.3, 122.5, 118.5, 87.9, 85.4, 77.4, 47.7, 46.8, 33.3, 32.05, 31.9, 26.2, 24.4, 23.3, 23.28, 23.1.

HRMS (ESI): m/z calcd for $C_{22}H_{29}O_2$ $[M+H]^+$ 325.2162, found 325.2161.

2-(2-Methyl-4,4-diphenyltetrahydrofuran-2-yl)naphthalen-1-ol (42ia):



Following the *General Procedure*, to the mixture of 2,2diphenylpent-4-yn-1-ol (**39i**) (0.050 g, 0.21 mmol) and naphthalen-1-ol (**41a**) (0.031 g, 0.21 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.013 g, 0.021 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 8h at rt. Purification of the crude

product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 2-(2-methyl-4,4-diphenyltetrahydrofuran-2-yl) naphthene-1-ol (**42ia**) (0.057 g, 70%) yellow oil.

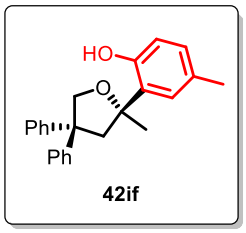
TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes)

^{1}H NMR ($CDCl_3$, 200 MHz): d 10.19 (s, 1H), 8.37-8.17 (m, 1H), 7.76-7.61 (m, 1H), 7.49-7.03 (m, 14H), 5.02-4.86 (d, *J* = 9.09 Hz, 1H), 4.30 (d, *J* = 9.09 Hz, 1H), 3.43 (d, *J* = 12.76 Hz, 1H), 3.18-3.03 (d, *J* = 12.76 Hz, 1H), 1.47 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 149.5, 145.8, 145.03, 133.4, 128.6, 128.4, 127.1, 127.07, 126.9, 126.5, 126.2, 125,5, 125.23, 124.7, 122.5, 119.1, 89.4, 76.1, 55.7, 52.3, 30.7.

HRMS (ESI): m/z calcd for $C_{27}H_{25}O_2$ $[M+H]^+$ 381.1849, found 381.1846.

5-Methyl-2-(2-methyl-4,4-diphenyltetrahydrofuran-2-yl)phenol (42if):



42if

Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39i**) (0.050 g, 0.21 mmol) and *p*-cresol (**41f**) (0.022 g, 0.21 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.013 g, 0.021 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 5-methyl-2-(2-methyl-4,4-diphenyltetrahydrofuran-2-yl)phenol (**42if**) (0.050 g, 68%) yellow oil.

TLC: R_f = 0.66 (SiO_2, 20% EtOAc/hexanes).

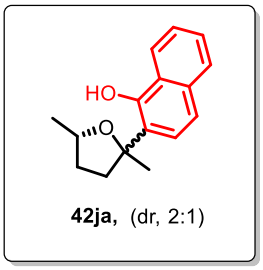
^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.13 (s, 1H), 7.43-7.27 (m, 4H), 7.22-7.09 (m, 6H), 6.92-6.83 (m, 1H), 6.80-6.73 (m, 1H), 6.73-6.65 (d, *J* = 8.21 Hz, 1H), 4.88 (d, *J* = 9.2 Hz, 1H), 4.23 (d, *J* = 9.09 Hz, 1H), 3.36 (d, *J* = 12.63 Hz, 1H), 3.06 (d, *J* = 11.62 Hz, 1H), 2.23 (s, 3H), 1.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.2, 145.8, 145.2, 130.9, 128.9, 128.5, 128.4, 127.1, 126.9, 126.5, 117.1, 88.7, 75.9, 55.7, 52.0, 30.7, 20.6.

HRMS (ESI): m/z calcd for $C_{24}H_{24}O_2$ $[M]^+$ 344.1771, found 344.2276.

2-(2,5-Dimethyltetrahydrofuran-2-yl)naphthalen-1-ol (42ja):

Following the *General Procedure*, to the mixture of hex-5-yn-2-ol (**39j**) (0.050 g, 0.50 mmol) and naphthalen-1-ol (**41a**) (0.073 g, 0.50 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.032 g, 0.050 mmol) under argon atmosphere at room



42ja, (dr, 2:1)

temperature and reaction mixture was stirred for 6hat rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(2,5-dimethyltetrahydrofuran-2-yl) naphthalen-1-ol (**42ja**, dr. 2:1) as a mixture of two diastereomers (0.080 g, 65%) colorless oil.

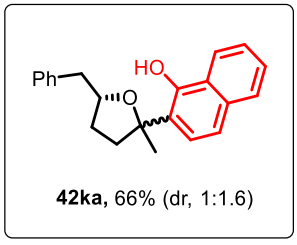
TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): d 10.64 (s, 1H, major isomer), 10.49 (s, 1H, minor isomer), 8.18-8.34 (m, 2H), 7.66-7.79 (m, 2H, major & minor isomers), 7.39-7.51 (m, 4H, major & minor isomers), 7.30 (d, *J* = 8.72 Hz, 2H, major & minor isomers), 7.01-7.13 (m, 2 H, major & minor isomers), 4.49–4.36 (m, 1H, minor isomer), 4.31-4.11 (m, 1H, major isomer), 2.6-1.9 (m, 6H, major & minor isomers), 1.61 (s, 3H, major isomer), 1.6 (s, 3H, minor isomer), 1.38 (d, *J* = 6.06 Hz, 3H, major isomer), 1.34 (d, *J* = 6.1 Hz, 3H, minor isomer).

^{13}C NMR ($CDCl_3$, 50 MHz): δ (two diastereomers) 150.84, 150.51, 133.57, 127.09, 126.12, 125.71, 125.52, 125.12, 125.07, 124.88, 124.40, 124.15, 122.67, 122.49, 122.40, 118.79, 118.62, 88.64, 88.42, 76.43, 39.66, 39.30, 32.84, 32.78, 30.53, 29.74, 29.52, 21.53, 21.13.

HRMS (ESI); m/z calcd for $C_{16}H_{19}O_2$ $[M+H]^+$ 243.1380**,** found 243.1377.

2-(5-Benzyl-2-methyltetrahydrofuran-2-yl)naphthalen-1-ol (42ka):



42ka, 66% (dr, 1:1.6)

Following the *General Procedure*, to the mixture of 2-phenylpent-4-yn-1-ol (**39k**) (0.100 g, 0.062mmol) and 1-Napthol (**41a**) (0.089 g, 0.062mmol) in anhydrous toluene (5 mL) was added $Bi(OTf)_3$ (0.04 g, 0.0062mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 2h. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 2-(5-benzyl-2-methyltetrahydrofuran-2-yl)naphthalen-1-ol (**42ka**, dr, 1:1.6)as a mixture of two diastereomers (0.120 g, 66%) colorless oil.

TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes)**.**

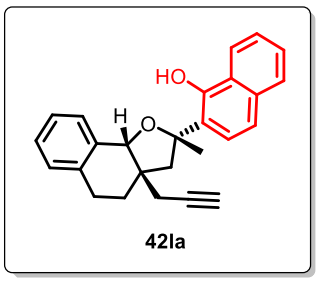
^{1}H NMR ($CDCl_3$, 400 MHz): δ (two diastereomers)10.34 and 10.18 (s, 1H), 8.4-8.34 and 8.33-28 (m, 1H), 7.82-7.71 (m, 1H), 7.5-7.4 (m, 2H), 7.39-7.24 (m, 5H), 7.17-7.03

(m, 1H), 4.67-4.51 and 4.45-4.25 (m, 1H),3.1-3.05 (m, 1H), 3.02-2.93 and 2.86-2.79 (m, 1H), 2.61-2.41 (m, 1H), 2.30-1.92 (m, 2H), 1.89-1.75 (m, 1H), 1.63 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (two diastereomers) 150.8, 150.5, 138.1, 137.9, 133.5, 129.5, 129.1, 128.5, 128.4, 127.1, 126.5, 126.5, 126.1, 125.5, 125.1, 124.4, 122.2, 118.8, 88.8, 88.5, 81.4, 80.8, 42.2, 42.01, 38.9, 38.8, 30.6, 30.4, 30.2, 29.3.

HRMS (ESI): m/z calcd for $C_{22}H_{23}O_2$ $[M+H]^+$ 319.1693, found 319.1688.

2-(2-Methyl-3a-(prop-2-yn-1-yl)-2,3,3a,4,5,9b-hexahydronaphtho[1,2-b]furan-2-yl)naphthalen-1-ol (42la):



42la

Following the *General Procedure*, to the mixture of 2,2-di(prop-2-yn-1-yl)-1,2,3,4-tetrahydronaphthalen-1-ol **(39l)** (0.050 g, 0.22 mmol) and naphthalen-1-ol (**41a**) (0.032 g, 0.22 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.014 g, 0.022 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(2-methyl-3a-(prop-2-yn-1-yl)-2,3,3a,4,5,9b-hexahydronaphtho[1,2-b]furan-2-yl)naphthalen-1-ol (**42la**) as a single diastereomer (0.045 g, 55%) yellow oil. Diastereo-selectivity was confirmed by 2D NMR analysis (COSY, HMBC, HSQC and NOE)

TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.46 (s, 1H), 8.43-8.31 (m, 1H), 7.81-7.71 (m, 1H), 7.53-7.34 (m, 4H), 7.29 (m, 2H), 7.25-7.15 (m, 2H), 4.59 (s, 1H), 3.07 (d, J = 13.26 Hz, 1H), 2.83 (m, 1H), 2.37–1.91 (m, 5H), 1.67 (s, 3H), 1.46-1.21 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.3, 137.5, 133.7, 132.4, 131.2, 128.78, 128.76, 127.2, 126.7, 126.3, 125.5, 125.2, 124.8, 122.6, 121.9, 119.1, 87.1, 81.9, 80.9, 70.4, 51.04, 44.1, 31.4, 30.7, 25.9, 25.8.

HRMS (ESI): m/z calcd for $C_{26}H_{25}O_2$ $[M+H]^+$ 369.1849, found 369.1847.

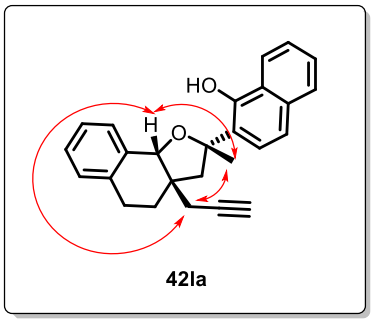
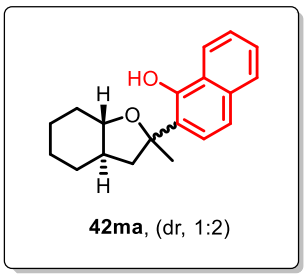


Figure 2. Key NOE interactions in compound **42la**.

2-(2-Methyloctahydrobenzofuran-2-yl)naphthalen-1-ol (42ma):



Following the *General Procedure*, to the mixture of 2-(prop-2-yn-1-yl)cyclohexan-1-ol (**39m,** 1,2-trans substituted) (0.050 g, 0.36 mmol) and naphthalen-1-ol **(41a)** (0.062 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.0036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 8h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(2-methyloctahydrobenzofuran-2-yl)naphthene-l-ol (**42ma**) (0.059 g, 56%) colorless oil as a mixture of two diastereomers (dr, 1:2).

TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

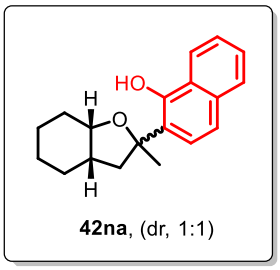
^{1}H NMR ($CDCl_3$, 400 MHz): δ (two diastereomers) 10.95 and 10.78 (s, 1H), 8.34-8.22 (m, 1 H), 7.76-7.64 (m, 1H), 7.52-7.31 (m, 2H), 7.34-7.23 (m, 1 H), 7.08-6.99 (m, 1H), 3.52-3.23 (m, 1H), 2.61-2.30 (m, 2H), 2.28-2.10 (m, 1H), 2.02-1.78 (m, 2H), 1.75 and 1.60 (s, 2H), 1.54-1.01 (m, 6H).

^{13}CNMR ($CDCl_3$, 101 MHz): δ (two diastereomers)151.3, 149.7, 133.4, 129.1, 128.3, 127.1,127.03, 126.2, 126.1, 125.8, 125.5, 125.3, 125.2, 125.1, 125.1, 124.7, 124.1, 122.5, 122.3, 118.9, 118.4, 89.2, 87.6, 84.1, 83.9, 47.4, 46.3, 45.1, 44.1. 31.4, 31.3, 31.01, 30.08, 30.26, 28.8, 28.6, 25.5, 25.4, 24.3, 24.1, 21.5.

HRMS (ESI): m/z calcd for $C_{19}H_{23}O_2$ $[M+H]^+$ 283.1693, found 283.1691.

2-(2-Methyloctahydrobenzofuran-2-yl)naphthalen-1-ol (42na):

Following the *General Procedure*, to the mixture of 2-(prop-2-yn-1-yl)cyclohexan-1-ol **(39n)** (0.050 g, 0.36 mmol) and naphthalen-1-ol **(41a)** (0.062 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon



42na, (dr, 1:1)

atmosphere at room temperature and reaction mixture was stirred for 8h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 2-(2-methyloctahydrobenzofuran-2-yl)naphthene-l-ol (**42na**) (0.062 g, 59%) colorless oil. as mixture of two diastereomers (dr, 1:1).

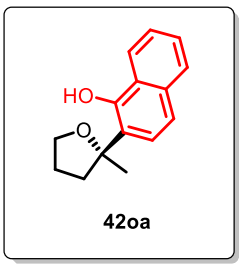
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ (two diastereomers) 10.85 (s, 1H), 10.67 (s, 1H), 8.37 & 8.22 (m, 2H), 7.75 & 7.65 (m, 2H), 7.46-7.40 (m, 4H), 7.29 (d, *J* = 8.59 Hz, 2H), 7.04 (dd, *J* = 8.53, 4.61 Hz, 2H), 4.25 (d, *J* = 4.93 Hz, 1H), 4.07 (d, *J* = 4.04 Hz, 1H), 2.64 (dd, *J* = 11.62, 6.32 Hz, 1H), 2.43 & 2.24 (m, 5H), 1.91 & 2.16 (m, 5H), 1.71 & 1.58 (s, 3H) & (s, 3H), 1.24 - 1.50 (m, 12H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ (two diastereomers) 150.3, 149.8,149.7, 133.4, 133.3, 127, 126.1, 126, 125.7, 125.5, 125.2, 125.1, 125, 124.9, 124.5, 123.9, 123.6, 122.6, 122.4, 118.9, 118.7,118.5, 87.8, 87.6, 86.3, 81.1, 80.5, 78.6, 77.8, 77.4, 77.1,76.7, 70.4, 52.4, 45.9, 45.8, 43.2, 37.9, 37.9, 32.1, 32.1, 31.9, 31.6, 30.2, 28.5, 28.1, 28.0, 26.6, 25.9, 24.9, 23.8, 22.6, 21.6, 21.5, 20.9, 20.

HRMS (ESI): m/z calcd for $C_{19}H_{23}O_2$ $[M+H]^+$ 283.1693, found 283.1690.

2-(2-Methyltetrahydrofuran-2-yl)naphthalen-1-ol (42oa)



42oa

Following the *General Procedure*, to the mixture of pent-4-yn-1-ol **(39o)** (0.050 g, 0.59 mmol) and naphthalen-1-ol **(41a)** (0.085 g, 0.59 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.038 g, 0.059 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 8h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(2-methyltetrahydrofuran-2-yl)naphthalen-1-ol (**42oa**) (0.096 g, 71%) colorless oil.

TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.44 (s, 1H), 8.39-8.26 (m, 1H), 7.83-7.71 (m, 1H), 7.56-7.44 (m, 2H), 7.35 (d, *J* = 8.55 Hz, 1H), 7.13 (d, *J* = 8.55 Hz, 1H), 4.21-4.11 (m,

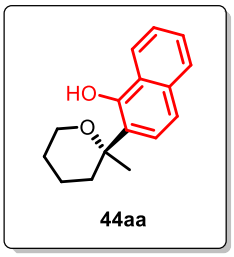
1H), 4.04-3.97 (m, 1H), 2.59-2.46 (m, 1H), 2.24-2.16 (m, 1H), 2.15-2.06 (m, 1H), 2.04-1.94 (m, 1H), 1.66 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.7, 133.6, 127, 126.1, 125.5, 125.1, 124.3, 122.4, 121.9, 118.8, 88.5, 68.6, 38.8, 29.1, 25.3

HRMS (ESI): m/z calcd for $C_{15}H_{17}O_2$ $[M+H]^+$ 229.1223, found 229.1222.

***Synthesis and Characterization* of 2-Aryl Tetrahydropyrans from 5-Hexyn-1-ols and Arenes**

2-(2-Methyltetrahydro-2H-pyran-2-yl)naphthalen-1-ol (44aa):



44aa

Following the *General Procedure*, to the mixture of hex-5-yn-1-ol **(38a)** (0.050 g, 0.50 mmol)and naphthalen-1-ol **(41a)** (0.073 g, 0.50 mmol)in anhydrous Toluene (2 mL) was added $Bi(OTf)_3$ (0.033 g, 0.0050mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 10h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(2-methyltetrahydro-2H-pyran-2-yl) naphthalen-1-ol**(44aa)** (0.072 g, 58%) colrless oil.

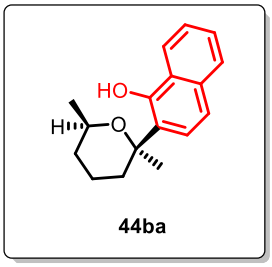
TLC: R_f = 0.70 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.68 (s, 1H), 8.29 (dd, *J* = 6.19, 3.41 Hz, 1H), 7.75 (dd, *J* = 5.81, 3.03 Hz, 1H), 7.46 (dd, *J*= 6.19, 3.28 Hz, 1H), 7.36 (d, *J* = 8.46 Hz, 1H), 7.17 (d, *J* = 8.72 Hz, 1H), 4.01–3.82 (m, 1H), 3.67-3.46 (m, 1H), 2.49 (d, *J* = 11.37 Hz, 1H), 1.86-1.78 (m, 1H), 1.77-1.64 (m, 4H), 1.56 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.1, 133.9, 127, 126.3, 125.4, 125, 124.5, 122.3, 119.4, 118.9, 80.1, 63.6, 34.7, 29.3, 25.4, 19.6.

HRMS (ESI): m/z calcd for $C_{16}H_{19}O_2$ $[M+H]^+$ 243.1380, found 243.1378.

2-(2,6-Dimethyltetrahydro-2H-pyran-2-yl)naphthalen-1-ol (44ba):



44ba

Following the General Procedure, to the mixture of hept-6-yn-2-ol **(38b)** (0.050 g, 0.40 mmol) and naphthalen-1-ol **(41a)** (0.058 g, 0.40 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.026 g, 0.0040 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 10h at

rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 2-(2,6-dimethyltetrahydro-2H-pyran-2-yl)naphthalen-1-ol (**44ba**)(0.063 g, 55%) colorless oil.

TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.79 (s, 1H), 8.38-8.33 (m, 1H), 7.79 (dd, *J* = 5.91, 3.62 Hz, 1H), 7.53-7.47 (m, 2H), 7.39 (d, *J* = 8.77 Hz, 1H), 7.20 (d, *J* = 8.39 Hz, 1H), 3.62 (ddd, *J*=12.21, 6.10, 2.29 Hz, 1H), 2.60-2.54 (m, 1H), 1.81-1.67 (m, 4H), 1.60 (s, 3H), 1.43-1.33 (m, 2H), 1.29 (d, *J* = 6.49 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.4, 133.9, 127.1, 126.2, 125.4, 124.9, 124.5, 122.4, 119.5, 118.8, 80.5, 69.4, 33.9, 32.6, 30.5, 22.5, 20.06, 19.7.

HRMS (ESI): m/z calcd for $C_{17}H_{21}O_2$ $[M+H]^+$257.1536, found 257.1532.

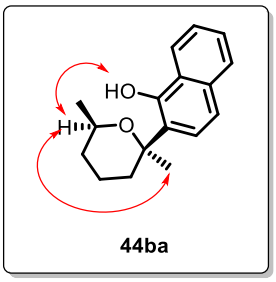
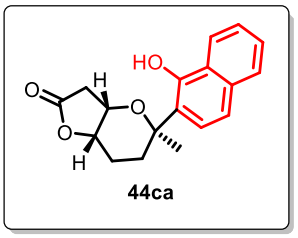


Figure 3. Key NOE interactions in compound **44ba**.

5-(1-Hydroxynaphthalen-2-yl)-5-methylhexahydro-2H-furo[3,2-b]pyran-2-one (44ca):



Following the General Procedure, to the mixture of5-(but-3-yn-1-yl)-4-hydroxydihydrofuran-2(3H)-one (**38c**) (0.050 g, 0.32 mmol) andnaphthalen-1-ol (**41a**) (0.047 g, 0.32 mmol)in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.021 g, 0.0032 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 10h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 5-(1-hydroxynaphthalen-2-yl)-5-methylhexahydro-2H-furo[3,2-b]pyran-2-one (**44ca**) (0.029 g, 30%) as an colorless oil, as a single diastereomer.

TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.88 (s, 1H), 8.34-8.24 (m, 1H), 7.84-7.77 (m, 1H), 7.59-7.49 (m, 2H), 7.43 (d, *J* = 8.77 Hz, 1H), 7.15 (d, *J* = 8.39 Hz, 1H), 4.28 (d, *J* = 3.05 Hz, 2H), 2.79 (dd, *J* = 17.17, 3.81 Hz, 1H), 2.69 (d, *J* = 17.17 Hz, 1H) , 2.40 (m, 1H), 2.34-2.26 (m, 1H), 2.01- 2.07 (m, 2H), 1.62 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.3, 151.8, 134.1, 127.1, 126.8, 125.5, 125.3, 123.7, 122.2, 119.8, 116.9, 79.6, 75.6, 69.9, 38.9, 29.8, 27.1, 21.6

HRMS (ESI): m/z calcd for $C_{18}H_{19}O_4$ $[M+H]^+$ 299.1278, found 299.1276.

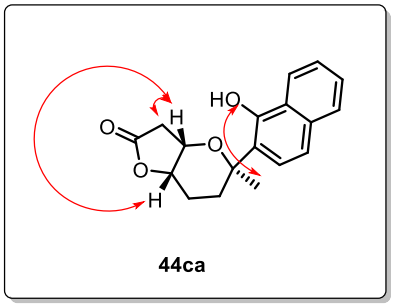
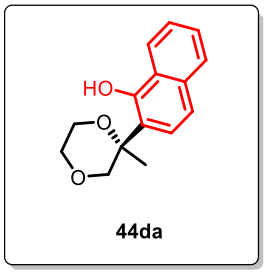


Figure 4. Key NOE interactions in compound **44ca**.

2-(2-Methyl-1, 4-dioxan-2-yl)naphthalen-1-ol (44da):

Following the General Procedure, to the mixture of 2-(prop-2-yn-1-yloxy)ethan-1-ol (**38d**) (0.050 g, 0.49 mmol)and naphthalen-1-ol (**41a**) (0.072 g, 0.49 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.032 g, 0.0049 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 10h at rt.



Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded2-(2-methyl-1,4-dioxan-2-yl)naphthalen-1-ol (**44da**) (0.055 g, 45%) as an colorless oil.

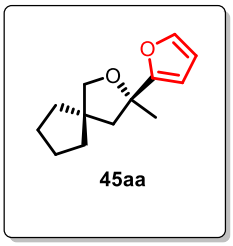
TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.20 (s, 1H), 8.37-8.24 (m, 1H), 7.76 (dd, *J* = 5.87, 3.47 Hz, 1H), 7.55-7.45 (m, 2H), 7.42-7.35 (m, 1H), 7.27-7.19 (m, 1H), 4.41 (d, *J* = 12.38 Hz, 1H), 3.86-3.66 (m, 5H), 1.56 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 151.9, 134.1, 127.1, 126.5, 125.5, 125.1, 124.3, 122.3, 119.3, 118.1 78.6, 72.6, 66.5, 62, 23.6.

HRMS (ESI): m/z calcd for $C_{15}H_{17}O_3$ $[M+H]^+$ 245.1172,found 245.1169.

Synthesis and Characterization of 2-Heteroaryl Tetrahydrofurans from 4-Pentyn-1-ols and Heteroarenes



3-(Furan-2-yl)-3-methyl-2-oxaspiro[4.4]nonane(45aa):

Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.50 g, 0.36 mmol) and furan (**43a**) (0.024 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 4h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 3-(furan-2-yl)-3-methyl-2-oxaspiro[4.4]nonane (**45aa**) (0.033 g, 45%) as an colorless oil.

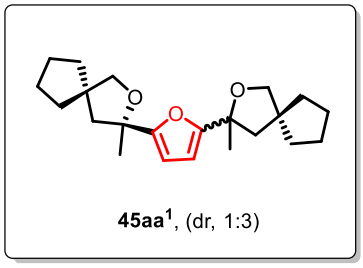
TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35 (s, 1H), 6.63 (s, 1H), 6.20 (d, *J* = 3.05 Hz, 1H); 3.69 (m, 2H), 2.40 (d, *J* = 12.82 Hz, 1H), 1.90 (d, *J* = 12.21 Hz, 1H), 1.68-1.52 (m, 11H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.5, 141.5, 109.8, 104.3, 80.3, 78.6, 51.6, 50.2, 38.5, 36.9, 27.2, 24.7, 24.6.

HRMS (ESI): m/z calcd for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1380, found 207.1166.

2,5-Bis(3-methyl-2-oxaspiro[4.4]nonan-3-yl)furan (45aa^1):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.50 g, 0.36 mmol) and furan (**43a**) (0.024 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 4hat rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 2,5-bis(3-methyl-2-oxaspiro[4.4]nonan-3-yl)furan (**45aa^1**) (0.064 g, 51%) as an colorless oil, as a mixture of two diastereomers (dr, 1:3, confirmed by HPLC analysis).

TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

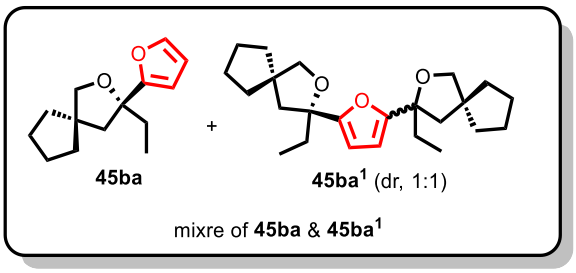
^{1}H NMR ($CDCl_3$, 400 MHz): δ (two diastereomers) 6.10 (s, 2H), 3.69 (d, *J* = 1.4 Hz, 4H), 2.42 (d, *J* = 12.8 Hz, 2H), 1.88 (d, *J* = 12.8 Hz, 2H), 1.58 (s, 22H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (two diastereomers) 158.3, 158.3, 104.7, 104.7, 80.2, 80.1, 78.53, 51.6, 50.1, 38.4, 36.8, 36.8, 27.0, 26.9, 24.7, 24.7, 24.5.

HRMS (ESI): m/z calcd for $C_{22}H_{33}O_3$ $[M+H]^+$ 345.2424**,** found 345.2423.

3-Ethyl-3-(furan-2-yl)-2-oxaspiro[4.4]nonane(45ba)

2,5-Bis(3-ethyl-2-oxaspiro[4.4]nonan-3-yl)furan (45ba[1]):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39b**) (0.50 g, 0.32 mmol) and furan (**43a**) (0.022 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.021 g, 0.032 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 4h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded the mixture of **45ba** & **45ba[1]** (0.085 g, 86%) as an colorless oil..

TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes).

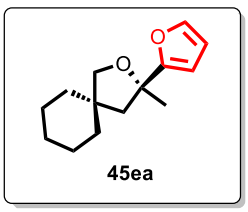
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40 - 7.31 (m, 1 H), 6.34 - 6.24 (m, 1 H), 6.20 (d, *J* = 3.16 Hz, 1 H), 6.12 (s, 2H), 3.82 - 3.44 (m, 5H), 2.31 (d, *J* = 12.76 Hz, 3H), 1.97-1.37 (m, 34H), (td, *J* = 7.45, 1.77 Hz, 9H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.1, 156.8, 141.4, 109.7, 106.36, 105.9, 105.6, 84.2, 78.3, 72.4, 71.1, 51.2, 48.4, 48.2, 41.5, 38.5, 38.4, 37.3, 37.3, 37.2, 36.3, 34.5, 33.3, 33., 31.7, 29.6, 28.8, 24.9, 24.6, 24.5, 24.4, 8.9.

HRMS (ESI): m/z calcd for (**45ba**) $C_{14}H_{21}O_2$, $[M+H]^+$ 221.1536, found 221.1534.

HRMS (ESI): m/z calcd for (**45ba[1]**) $C_{24}H_{37}O_3$, $[M+H]^+$ 373.2737, found 373.2735.

3-(Furan-2-yl)-3-methyl-2-oxaspiro[4.5]decane (45ea):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl) cyclohexyl) methanol (**39e**) (0.050 g, 0.32 mmol) and furan (**43a**) (0.042 g, 0.64 mmol) in anhydrous Toluene (2 mL) was added $Bi(OTf)_3$ (0.020 g, 0.032 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 4h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 3-(furan-2-yl)-3-methyl-2-oxaspiro[4.5]decane (**45ea**) (0.043 g, 60%) as an colorless oil..

TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes).

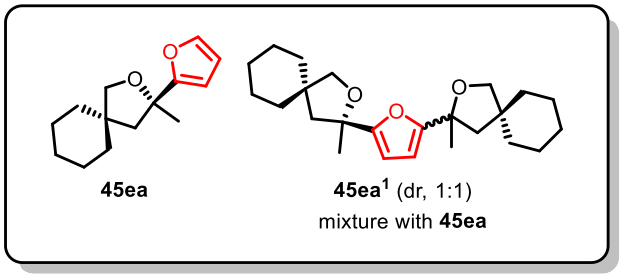
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39-7.31 (m, 1H), 6.33-6.25 (m, 1H), 6.18 (d, *J* = 2.65 Hz, 1H), 3.73 (d, *J* = 8.72 Hz, 1H), 3.62 (d, *J* = 8.72 Hz, 1H), 2.26 (d, *J* = 12.88 Hz, 1H), 1.76 (d, *J* = 13.0 Hz, 1H), 1.59 (s, 3H), 1.56-1.36 (m, 10H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.4, 141.5, 109.8, 104.4, 80.1, 49.3, 44.7, 37.2, 36, 27.6, 25.9, 23.9, 23.7.

HRMS (ESI): m/z calcd for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1536, found 221.1534.

3-(Furan-2-yl)-3-methyl-2-oxaspiro[4.5]decane (45ea)

2,5-Bis(3-methyl-2-oxaspiro[4.5]decan-3-yl)furan (45ea^1)



Following the *General Procedure*, to the mixture of and (1-(prop-2-yn-1-yl)cyclopentyl) methanol (**39e**) (0.050 g, 0.32 mmol) and furan (**43a**) (0.021 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.22 g, 0.032 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 4h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded the inseparable mixture of **45ea** & **45ea^1** (0.070 g, 74%) as an colorless oil..

TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes).

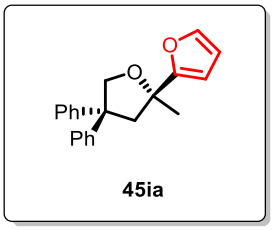
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.36 - 7.30 (m, 1H), 6.28 (dd, *J* = 3.28, 1.89 Hz, 1H), 6.18 (d, *J* = 3.28 Hz, 1H), 6.07 (d, *J* = 0.88 Hz, 2H), 3.76-3.58 (m, 6H), 2.33-2.22 (m, 3H), 1.80-1.68 (m, 3H), 1.56 (d, *J* = 2.02 Hz, 8H), 1.52-1.36 (m, 30H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.4, 158.3, 158.2, 141.6, 109.8, 104.8, 104.4, 80.1, 80, 77.8, 49.2, 44.6, 37.2, 36, 29.7, 27.6, 27.5, 27.4, 25.9, 23.9, 23.7.

HRMS (ESI): m/z calcd for (**45ea**) $C_{14}H_{21}O_2$, $[M+H]^+$ 221.1536, found 221.1533.

HRMS (ESI): m/z calcd for (**45ea^1**) $C_{24}H_{37}O_3$ $[M+H]^+$ 373.2737, found 373.2733.

2-(2-Methyl-4,4-diphenyltetrahydrofuran-2-yl)furan (45ia):



45ia

Following the *General Procedure*, to the mixture of 2,2diphenylpent-4-yn-1-ol (**3f**) (0.050 g, 0.21 mmol) and furan (**43a**) (0.014 g, 0.21 mmol) in anhyd9rous toluene (2 mL) was added $Bi(OTf)_3$ (0.13 g, 0.021mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 4h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 2-(2-methyl-4,4-diphenyltetrahydrofuran-2-yl)furan (**45ia**) (0.028g, 40%) as an colorless oil..

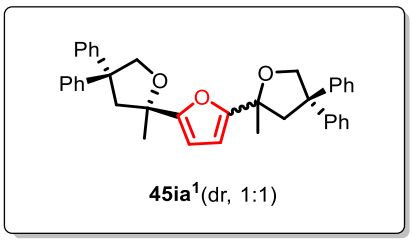
TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.42-7.09 (m, 11H), 6.29-6.16 (m, 1H), 6.07 (d, *J* = 3.03 Hz, 1H), 4.76 (d, *J* = 9.22 Hz, 1H), 4.31 (d, *J* = 9.35 Hz, 1H), 3.30 (d, *J* = 12.88 Hz, 1H), 2.73 (d, *J* = 12.88 Hz, 1H), 1.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.1, 147, 145.9, 141.7, 128.4, 127.2, 126.2, 126.1, 109.9, 104.6, 80.6, 56.5, 49.6, 26.6.

HRMS (ESI): m/z calcd for $C_{21}H_{20}O_2$ $[M+Na]^+$ 327.1356, found 327.1352.

2-(2-Methyl-4,4-diphenyltetrahydrofuran-2-yl)-5-(2-methyl-4,4-diphenyltetrahydrofuran-2-yl)furan (45ia^1):



45ia^1(dr, 1:1)

Following the *General Procedure*, to the mixture of 2,2diphenylpent-4-yn-1-ol (**39f**) (0.050 g, 0.21 mmol)and furan (**43a**) (0.014 g, 0.21 mmol) in anhydrous Toluene (2 mL) was added $Bi(OTf)_3$ (0.013 g, 0.021mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 4h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded (**45ia^1**) (0.067g, 59%) as an yellow oil, as a mixture of two inseparable diastereomers (confirmed by ^{1}H NMR and HPLC analysis).

TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

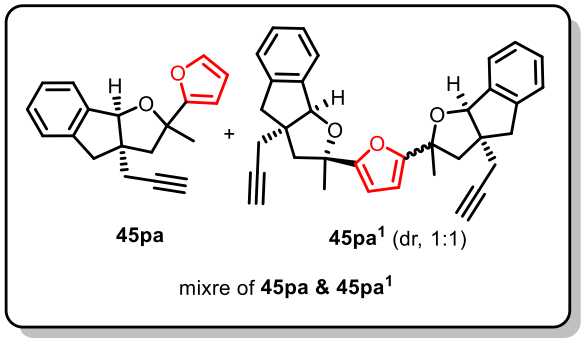
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.36-7.09 (m, 20H), 6.03–5.84 (d, *J* = 0.63 Hz, 2H), 4.68 (dd, *J* = 8.84, 4.80 Hz, 2H), 4.26 (dd, *J* = 9.35, 1.01 Hz, 2H), 3.22 (dd, *J* = 13.01, 7.33 Hz, 2H), 2.64 (d, *J* = 13.01 Hz, 2H), 1.38 (d, *J* = 2.53 Hz, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.1, 158, 147.3, 145.9, 128.3, 127.2, 126.2, 126.1, 105, 105, 80.6, 80.6, 76.5, 76.5, 56.5, 56.5, 49.7, 26.6, 26.4.

HRMS (ESI): m/z calcd for $C_{38}H_{37}O_3$ $[M+H]^+$ 541.2737, found 541.2737.

2-(Furan-2-yl)-2-methyl-3a-(prop-2-yn-1-yl)-3,3a,4,8b-tetrahydro-2H-indeno[1,2-*b*]furan (45pa)

2-(2-Methyl-3a-(prop-2-yn-1-yl)-3,3a,4,8b-tetrahydro-2H-indeno[1,2-*b*]furan-2-yl)-5-(2-methyl-3a-(prop-2-yn-1-yl)-3,3a,4,8b-tetrahydro-2H-indeno[1,2-*b*]furan-2-yl)furan (45pa^1)



Following the General Procedure, to the mixture of 2,2-di(prop-2-yn-1-yl)-2,3-dihydro-1H-inden-1-ol **(39p)** (0.050 g, 0.23 mmol) and furan **(43a)** (0.016 g, 0.23 mmol) in anhydrous Tolune (2 mL) was added $Bi(OTf)_3$ (0.015 g, 0.023 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 4h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded mixture of **45pa** & **(45pa^1)** (0.085 g, 92%) yellow oil.

TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes).

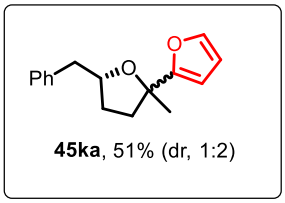
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.44 (d, *J* = 2.53 Hz, 1H), 7.40-7.37 (m, 2H), 7.28-7.20 (m, 10H), 6.32-6.31 (m, 2H), 6.00 (dd, *J* = 3.22, 1.83 Hz, 1H), 5.64-5.60 (m, 1H), 5.31-5.26 (m, 3H), 3.13 (d, *J* = 6.06 Hz, 4H), 2.92 (d, *J* = 2.53 Hz, 2H), 2.79 (d, *J* = 13.39 Hz, 3H), 2.53-2.48 (m, 3H), 2.41 (dd, *J* = 4.93, 2.65 Hz, 4H), 2.33 (t, *J* = 4.23 Hz, 2H), 2.07-1.96 (m, 4H), 1.92 (t, *J* = 2.59 Hz, 2H), 1.64 (s, 3H), 1.43 (s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 159, 142.7, 141.7, 141.5, 141, 128.7, 127.1, 125.8, 125.7, 125.2, 124.7, 110.1, 109.8, 104.6, 91.7, 91.6, 82.8, 82.4, 82.2,69.8, 69.5, 54.7, 54.5, 49.4, 48.8, 43.7, 43.5, 29.7, 28.8, 28.5, 28.3, 27.5.

HRMS (ESI): m/z calcd for (**45pa**) $C_{19}H_{19}O_2$, $[M+H]^+$ 279.1380, found 279.1375.

HRMS (ESI): m/z calcd for (**45pa^1**) $C_{34}H_{33}O_3$, $[M+H]^+$ 489.2424, found 489.2418.

2-(5-Benzyl-2-methyltetrahydrofuran-2-yl)furan (45ka)



45ka, 51% (dr, 1:2)

Following the *General Procedure*, to the mixture of 2-phenylpent-4-yn-1-ol (**39k**) (0.100 g, 0.062mmol) and Furan (**43a**) (0.042 g, 0.062mmol) in anhydrous toluene (5 mL) was added $Bi(OTf)_3$ (0.04 g, 0.006mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 2h. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded two inseparable mixture of diastereomers of **45ka** (dr, 1:2) as a colourless liquid (0.072 g, 51%) colorless oil.

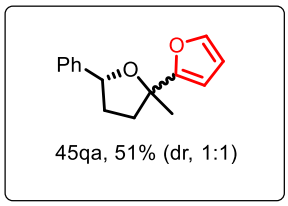
TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes)**.**

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.4-7.1 (m, 6H), 6.37-6.28 (m, 1H), 6.26-6.17 (m, 1H), 4.39-4.30 (m, 1H), 3.15-3.01 (m, 1H), 2.83-2.70 (m, 1H), 2.05-1.96 (m, 1H), 1.9-1.7 (m, 2H), 1.60 and 1.59 (s, 1:2, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.6, 159.3, 141.6, 141.4, 138.8, 138.5, 129.5, 129.3, 128.3, 128.2, 126.2, 109.9, 109.8, 104.5, 104.4, 80.7, 80.4, 80.3, 80.2, 42.5, 42.2, 37.6, 36.7, 31.6, 30.8, 26.9, 26.5.

HRMS (ESI): m/z calcd for $C_{16}H_{19}O_2$ $[M+H]^+$ 243.1380, found 243.1376.

2-(2-Methyl-5-phenyltetrahydrofuran-2-yl)furan (45qa):



45qa, 51% (dr, 1:1)

Following the *General Procedure*, to the mixture of 1-phenylpent-4-yn-1-ol (**39q**) (0.1 g, 0.062 mmol) and Furan (**43a**) (0.042 g, 0.062mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.040 g, 0.006mmol), under argon atmosphere at room temperature and reaction mixture was stirred for 2h. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded inseparable mixture of diastereomers of **45qa** (dr, 1:1) as a colourless liquid (0.078 g, 51%) colorless oil.

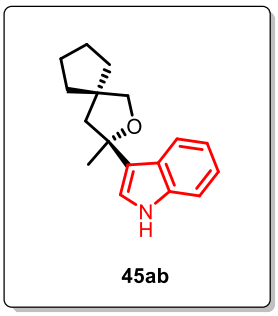
TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes)**.**

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.46-7.02 (m, 6H), 6.38-6.29 (m, 1H), 6.28-6.20 (m, 1H), 4.41-4.22 (m, 1H), 4.01-3.82 (m, 1H), 3.75-3.49 (m, 1H), 2.85-2.69, (m, 1H), 2.66-2.30 (m, 1H) 2.05 (dd, *J* = 10.74, 10.61 Hz, 1H), 1.69 and 1.66 (two s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.8, 142, 141.7, 140.5, 128.6, 127.5, 127.3, 126.7, 126.6, 110, 104.8, 104.7, 81.2, 80.4, 74.5, 74.4, 46.1, 45.3, 44.8, 26.6.

HRMS (ESI): m/z calcd for $C_{15}H_{17}O_2$ $[M+H]^+$ 229.1223, found 229.1585.

3-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)-1H-indole (45ab):



45ab

Following the *General Procedure*, to the mixture of(1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.050 g, 0.36 mmol) and 1H-indole-1-carboxylic pivalic anhydride (**43b**) (0.078 g, 0.36 mmol) in anhydrous toluene(2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 3-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)-1H-indol (**45ab**) (in this case -BOC deprotected in situ) (0.048 g, 52%) colorless oil.

TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes).

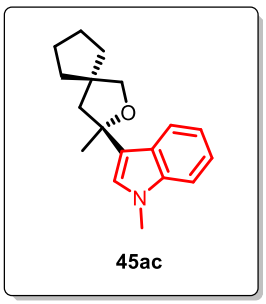
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (br. s, 1H), 7.72 (m, 1H), 7.37 (m, 1H), 7.22-7.18 (m, 3H), 3.85 (d, *J* = 8.34 Hz, 1H), 3.77 (d, *J* = 8.21 Hz, 1H), 2.46 (d, *J* = 12.25 Hz, 1 H), 2.15 (d, *J* = 12.25 Hz, 1H), 1.75 (s, 3H) , 1.71–1.49 (m, 8H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.1, 125.1, 124.3, 121.7, 120.2, 119.9, 119.2, 111.2, 82.2, 78.2, 52.1, 51.8, 38.6, 37.3, 30, 24.7, 24.7.

HRMS (ESI): m/z calcd for $C_{17}H_{22}NO$ $[M+H]^+$ 256.1696, found 256.1694.

1-Methyl-3-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)-1H-indole (45ac):

Following the *General Procedure*, to the mixture of(1-(prop-2-yn-1-yl) cyclopentyl) methanol (**39a**) (0.050 g, 0.36 mmol) and 1-methyl-1H-indole (**43c**) (0.047 g, 0.36 mmol)in anhydrous toluene(2 mL) was added $Bi(OTf)_3$ (0.037 g, 0.036 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded 1-methyl-3-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)-1H-indol (**45ac**) (0.057 g, 59%) colrless oil.



45ac

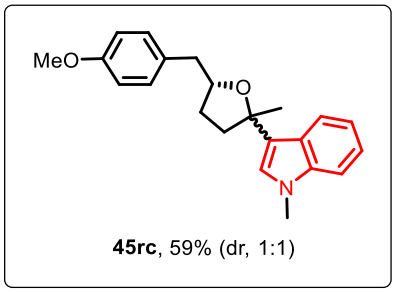
TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$,400 MHz): δ 7.65 (d, *J* = 7.83 Hz, 1H), 7.34-7.18 (m, 2H), 7.18-7.02 (m, 1H), 6.97 (s, 1H), 3.81-3.29 (m, 5H), 2.45 (d, *J* = 12.38 Hz, 1H), 2.14 (d, *J* = 12.25 Hz, 1H), 1.68 (s, 3H), 1.67-1.36 (m, 8H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.7, 125.5, 124.7, 123, 121.3, 120.3, 118.7, 109.3, 82.2, 78.1, 52.3, 51.9, 38.6, 37.3, 32.6, 30.3, 24.7, 24.7.

HRMS (ESI): m/z calcd for $C_{18}H_{24}NO$ $[M+H]^+$ 270.1852, found 270.1851.

3-(5-(4-Methoxybenzyl)-2-methyltetrahydrofuran-2-yl)-1-methyl-1H-indole (45rc):



45rc, 59% (dr, 1:1)

Following the *General Procedure*, to the mixture of 2-(4-methoxybenzyl)pent-4-yn-1-ol (**39r**) (0.100 g, 0.048mmol) and1-methyl-1H-indole (**43c**) (0.064 g, 0.048mmol) in anhydrous toluene (5 mL) was added $Bi(OTf)_3$ (0.031 g, 0.004mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 2h. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 1:1 diastereomers 3-(5-(4-methoxybenzyl)-2-methyltetrahydrofuran-2-yl)-1-methyl-1H-indole **(45rc)** as a colourless liquid (0.081 g, 59%).

TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes)**.**

^{1}H NMR ($CDCl_3$, 500 MHz): d 7.67 (d, *J* = 8.01 Hz 1H), 7.15-6.98 (m, 3H), 7.15-7.01 (m, 3H), 6.82 (t, *J* = 8.77 Hz, 2H), 4.11 (dt, *J* = 8.01, 7.63 Hz, 1H), 3.83-3.66 (m, 6H), 2.73-2.52 (m, 3H), 2.37-2.07 (m, 1H), 1.75 and 1.66 (two singlet, 3H)

^{13}C ($CDCl_3$, 126 MHz): d 157.9, 137.7, 133.0, 129.5, 125.4, 124.6, 121.4, 121.3, 120.5, 120.3, 118.8, 118.8, 113.8, 109.3, 82.6, 82.1, 72.7, 72.4, 55.2, 45.6, 45.3, 42.1, 41.6, 38.8, 38.3, 32.6, 29.6, 29.3.

HRMS (ESI): m/z calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$ 336.1958, found 336.1954.

3.2.10 References

1. (a) Cossy, J. Synthesis of Saturated Oxygenated Heterocycles I: 5-and 6-Membered Rings; Springer: Paris, **2014**; (b) Elliot, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303–2340; (c) Elliot, M. C. *J. Chem. Soc., Perkin Trans.1* **2000**, 1291–1318; (d) Boivin, T. L. B. *Tetrahedron,* **1987**, *43*, 3309–3362.
2. Delost, M. D.; Smith, D. T.; Anderson, B. J.; Njardarson, J. T. *J. Med. Chem*., **2018**, *61*, 10996–11020.
3. Singh P. K.; Silakari, O. *Chem. Med. Chem*, **2018**, *13*, 1071–1087.
4. (a) Liu, Z.; Breit, B. *Angew. Chem. Int. Ed.,* **2016**, *55*, 8440–8443; (b). Zhdanko, A.; Maier, M. E. *ACS Catal.,* **2015**, *5*, 5994-6004; (c). Masatoshi, S.; Fujita, S.; Masanori, A.; Yamamoto, Y. *ACS Catal.,* **2017**, *7*, 2848–2852; (d) Li, H-J.; Guillot, R.; Gandon, V. *J. Org. Chem*., **2010**, *75*, 8435–8449.
5. Reddy, S. A.; Reddy, P. A.; Sabitha, G. *Org. Biomol. Chem*., **2015**, *13*, 10487–10495.
6. (a) J. W. Loder and R. H. Nearn, Altholactone, a Novel from a Polyalthia Species (Annonaceae), *Heterocycles*, **1977**, *7*, 113–118; (b) A. E. El-Zayat, N. R. Ferrigni, T. G. McCloud, A. T. McKenzie, S. R. Byrn, J. M. Cassady, C. J. Chang and J. L. McLaughlin, *Tetrahedron Lett*., **1985**, *26*, 955–956.
7. Rodríguez, A.D.; Cóbar, O.M.; Padilla, O.L. The calyxolanes: New 1,3-diphenylbutanoid metabolites isolated from the Caribbean marine sponge. Calyx Podatypa. *J. Nat. Prod*. **1997**, *60*, 915–917.
8. (a) Spivey, A. C.; Laraia, L.; Bayly,A. R.; Rzepa, H. S.; White. A. J. P. *Org. Lett*.,**2010** *12*, (5) 900-903; (b) Marston, A.; Zagorski, M. G.; Hostettmann, K. *HelV. Chim. Acta* **1988**, *71*, 1210.
9. Gholap, S. L.; Prasad, K. R. *J. Org. Chem*. **2006***, 71*, 3643-3645.
10. Jung, E-K.; Dittrich, N.; Pilkington, L. I.; Rye, C. E.; Leung, E.; Barker, D. *Tetrahedron,* **2015**, *71*, 9439-9456.
11. Dong, L-B.; HE, J.; Li, X-Y.; Wu, X-D.; Deng, X.; XU, G.; Peng, L-Y.; Zhao, Y.; LI, Y.; Gong, X.; Qin-Shi Zhao, Q-S. *Nat. Prod. Bioprospect*. **2011**, *1*, 41–47.
12. (a) Yin, J.; Kouda, K.; Tezuka, Y.; Tran, Q. L.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med*. **2004**, *70*, 54–58; S. (b) Chandrasekhar.; Shyamsunder, T.; Jaya

Prakash, S.; a Prabhakarb.; B. Jagadeesh, B. *Tetrahedron Letters*, **2006,** 47 (1) 47-49.

13. (a) Marini Bettolo, G. B. Gazz. *Chim. Ital.* **1964**, 287. (b) Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. Gazz. *Chim. Ital*. **1965,** 95. (c) Arango Craveiro, A.; da Costa Prado, A.; Gottlieb, O. R.; Welerson de Albuquerque, P. C. *Phytochemistry* **1970**, *9*, 1869. (d) Jurd, L.; Wong, R. Y. *Aust. J. Chem*. **1984**, *37*, 1127. (e) de C. Alcantara, A. F.; Souza, M. R.; Pilo-Veloso, D.´ Fitoterapia **2000**, *71*, 613.
14. Lin, Y.-S.; Lin, J.-H.; Chang, C.-H.; Lee, S.-S. *J. Nat. Prod*., **2015**, *78*, 181–187.
15. Tezuka, Y.; Ali, M. S.; Banskota, A. H.; Kadota, S. *Tetrahedron Letters*, 2**000**, *41,* 5903-5907.
16. Monasterolo, C.; Helge M-B.; Gilheany, D. G. *Chem. Sci*., **2019**, *10*, 6531–6538.
17. Bao, X.; Yokoe, T.; Ha, T. M.; Wang, Q.; Zhu, J. *NATURE COMMUNICATIONS.* **2018,** *9,* 3725.
18. Tsuji, N.; Kennemur, J. L.; Buyck, T.; Lee, S.; Prevost, S.; Kaibi, P. S. J.; Bykov, D.; Fares, C.; List, B. *Science*, **2018**, *359*, 1501-1505.
19. Singh, P. P.; Gudup, S.; Aruri, H.; Singh, U.; Ambala, S.; Yadav, M.; Sawant, S. D.; Viswakarma, R. A. *Org. Biomol. Chem*., **2012**, *10*, 1587–1597.
20. Shibuya, M.; Abe, M.; Fujita, S.; Yamamoto, Y. *Org. Biomol. Chem.*, **2016**, *14*, 5322–5328.
21. Fujita, S.; Abe, M.; Shibuya, M.; Yamamoto, Y. *Org. Lett*. **2015**, *17*, 3822−3825.
22. Cicco, L.; Sblendorio, S.; Mansueto, R.; Perna, F. M.; Salomone, A.; Florio, S.; Capriati, V. *Chem. Sci*., **2016**, *7*,1192–1199.
23. Barluenga, J.; Fernandez, A.; Dieguez, A.; Rodriguez, F.; Fananas, F. J. *Chem. Eur. J*. **2009**, *15*, 11660 - 11667.
24. Butova, D.; Barabash, A. V.; Petrova, A. A.; Kleiner, C. M.; Schreiner, P. R.; Fokin, A. A. *J. Org. Chem*., **2010**, *75*, 6229–6235.
25. Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. Angew. *Chem. Int. Ed*. **2010**, *49*, 9174 –9177.
26. (a) Liu Z.; Breit, B. *Angew. Chem. Int. Ed.,* **2016**, *55*, 8440–8443; (b) Zhdanko, A.; Maier, M. E*. ACS Catal.,* **2015**, *5*, 5994-6004; (c) Masatoshi, S.; Fujita, S.; Masanori, A.; Yamamoto, Y. *ACS Catal.,* **2017**, *7*, 2848−2852; (d) Pouy, M. J.; Delp, A. S.; Uddin, J.; Ramdeen, V. M.; Cochrane, N. A.; Fortman, G. C.; Gunnoe,

T. B.; Cundari, T. R.; Sabat, M.; Myers, W. H. *ACS Catalysis*., **2012**, *2*, 2182–2193; (e) Wipf, P.; Graham, T. H. *J. Org. Chem.,* **2003**, *68*, 8798–8807; (f) Sheng, Y.; Musaev, D. G.; Reddy, K. S.; McDonald, F. E.; Morokuma, K. *J. Am. Chem. Soc.,* **2002**, *124*, 4149–4157; (g) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.,* **2002**, *124*, 2528–2533; (h) Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett,* **2001**, *42*, 6207–6210; (i) Pale, P.; Chuche, J.; *Eur. J. Org. Chem.,* **2000**, 1019–1025; (j) Elgafi, S.; Field, L. D.; Messerle, B. A. *J. Organomet. Chem.,* **2000**, *607*, 97–104; (k) McDonald, F. E.; Reddy, K. S.; Dı´az, Y. *J. Am. Chem. Soc.,* **2000**, *122*, 4304–4309; (l) McDonald, F. E. *Chem. Eur. J.,* **1999**, *5*, 3103–3106; (m) Tzalis, D.; Koradin, C.; Knochel, P.; *Tetrahedron Lett,* **1999**, *40*, 6193–6195; (n) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.,* **1993**, *58*, 6952–6953.

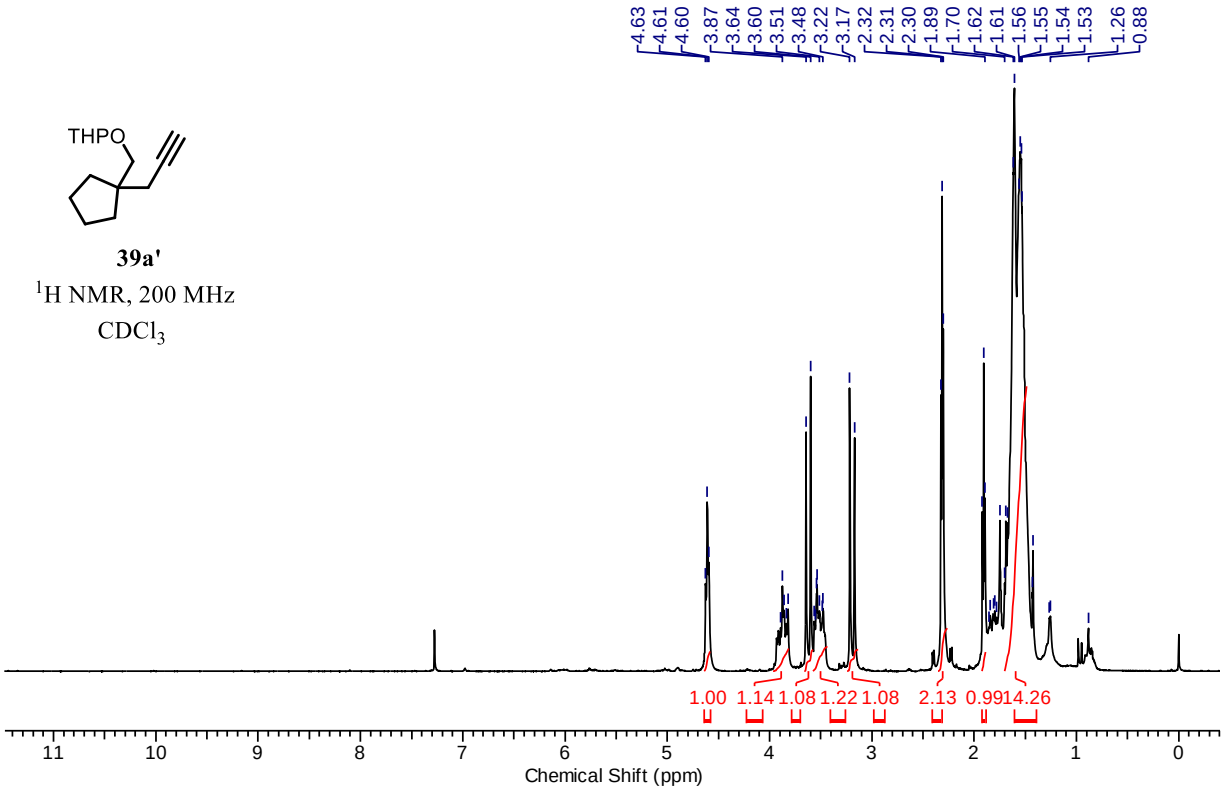
27. (a) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc*., **2009**, *131*, 15061–15074; (b) Aponick, A.; Li, C. Y.; Palmes, J. A. *Org. Lett*., **2009**, *11*, 121–124; (c) Selvaratnam, S.; Ho, J. H. H.; Huleatt, P. B.; Messerle, B.; Chai, C. L. L. *Tetrahedron Lett*, **2009**, *50*, 1125–1127; (d) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem*., **2009**, *74*, 2842–2845; (e) Trost, B. M.; O'Blyle, B. M. *J. Am. Chem. Soc*., **2008**, *130*, 16190–16192; (f) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed*., **2007**, *46*, 279–282; (g) Liu, B.; Brabander, J. K. D. *Org. Lett*., **2006**, *8*, 4907–4910; (h) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J. P. *J. Am. Chem. Soc*., **2005**, *127*, 9976–9977; (i) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett*., **2005**, *7*, 5437–5440; (j) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.,* **1998**, *37*,1415–1418; (k) Kataoka, Y.; Matsumoto, O.; Tani, K. *Chem. Lett.,* **1996**, *25*, 727–728; (l) Fukuda, Y.; Utimoto, K. *J. Org. Chem*., **1991**, *56*, 3729–3731.

28. (a) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J*., **2007,** *13,* 1358–1373; (b) Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem*., **2006**, 4340–4342; (c) Li, Z.; Shi, Z.; He, C.; *J. Organomet. Chem*., **2005**, *690*, 5049–5054; (d) Yadav, J. S.; Reddy, B. V. S.; Padmavani, B.; Gupta, M. K. *Tetrahedron Lett*, **2004,** *45*, 7577–7579; (e) Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun*., **2003**, 2454–2455.

29. Barluenga, J.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem. Int. Ed*., **2005,** *44*, 126–128; and references cited therein
30. (a) Pflasterer, D.; Hashmi, A. S. K. *Chem. Soc. Rev*., **2016**, *45*, 1331–1367; (b) Dorel, R.; Echavarren, A. M. *Chem. Rev*., **2015**, *115*, 9028–9072; (c) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev*., **2012**, *41*, 2448–2462; (d) Krause, N.; Winter, C. *Chem. Rev*., **2011**, *111*, 1994–2009; (e) Fürstner, A. *Chem. Soc. Rev*., **2009**, *38,* 3208–3221.
31. (a) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett*., **2011**, *13*, 3178–3181; (b) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *J. Org. Chem*., **2011**, *76*, 1269–1284; (c) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett*., **2010,** *12*, 4420–4423.
32. (a) Zhou, Q.-L. *Angew. Chem., Int. Ed*., **2016**, *55*, 5352–5353; (b) Ollevier, T. *Org. Biomol. Chem*., **2013**, *11*, 2740–2755; (c) Bothwell, J. M.; Krabbe, S. W.; Mohan, R. S. *Chem. Soc. Rev*., **2011**, *40*, 4649–4707; and references cited therein; (d) Yamamoto, Y. *J. Org. Chem*., **2007**, *72*, 7817–7831.
33. (a) Kambale, D. A.; Thorat, S. S.; Pratapure, M. S.; Gonnade, R. G.; Kontham, R. *Chem. Commun*, **2017**, *53*, 6641-6644. (b) Thorat, S. S.; Kataria, P.; Kontham, R.; *Org. Lett*., **2018**, *20*, 872–875.
34. Fananas, F. J.; Fernandez, A.; Cevic, D.; Rodrıguez, F. *J. Org. Chem*. **2009**, *74*, 932-934.
35. Shibata, N.; Tsuchiya, T.; Hashimoto, Y.; Morita, N.; Ban, S.; Tamura, O. *Org. Biomol. Chem.,* **2017**, *15*, 3025–3034.
36. Harada, T.; Muramatsu, K.; Mizunashi, K.; Kitano, C.; Imaoka, D.; Fujiwara, T.; Kataoka, H. *J. Org. Chem.*, **2008**, *73*, 249–258.
37. Jeanese, C. B.; Jason, A. J.; Gordon, W. G.; *Tetrahedron Letters*, **2013**, *54*, 2759–2762.
38. (a) Zhou, Y.; Liu, S.; Chen, H.; Chen, J.; Sun, W.; Li, S.; Yang, Q.; Fan, B. *Chin. J. Chem.,* **2015**, *33*, 1115–1118; (b) Chen, J.; Liu, S.; Zhou, Y.; Li, S.; Lin, C.; Bian, Z.; Fan, B. *Organometallics.,* **2015**, *34*, 4318–4322.
39. (a) Bachrach, S. M. *J. Org. Chem*., **2008**, *73*, 2466-2468; (b) Bessley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.*, **1915**, *107*, 1080–1106.

40. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.*, **1976**, *18*, 734–736; (b) Gilmore, K.; Alabugin, I. V. *Chem. Rev*., **2011**, *111*, 6513–6556.

^{1}H NMR spectrum of compound 39a'

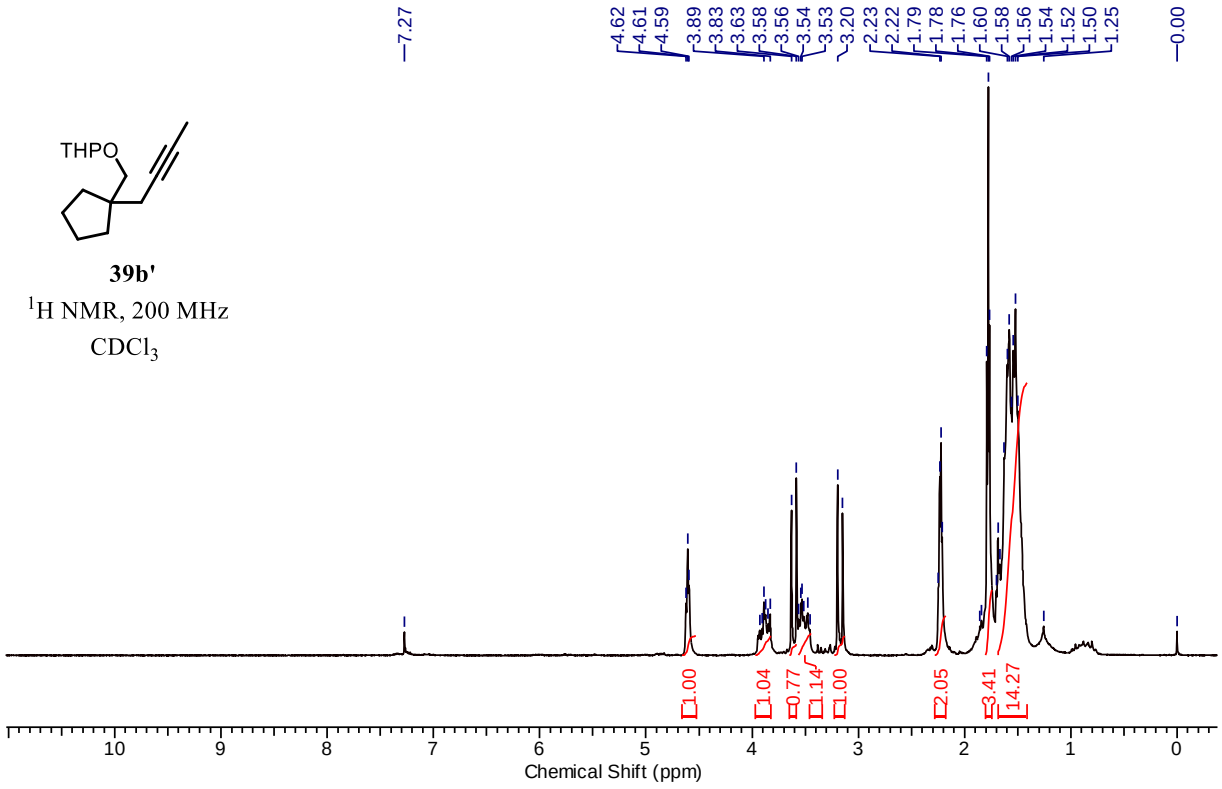


39a'

^{1}H NMR, 200 MHz

$CDCl_3$

^{1}H NMR spectrum of compound 39b'

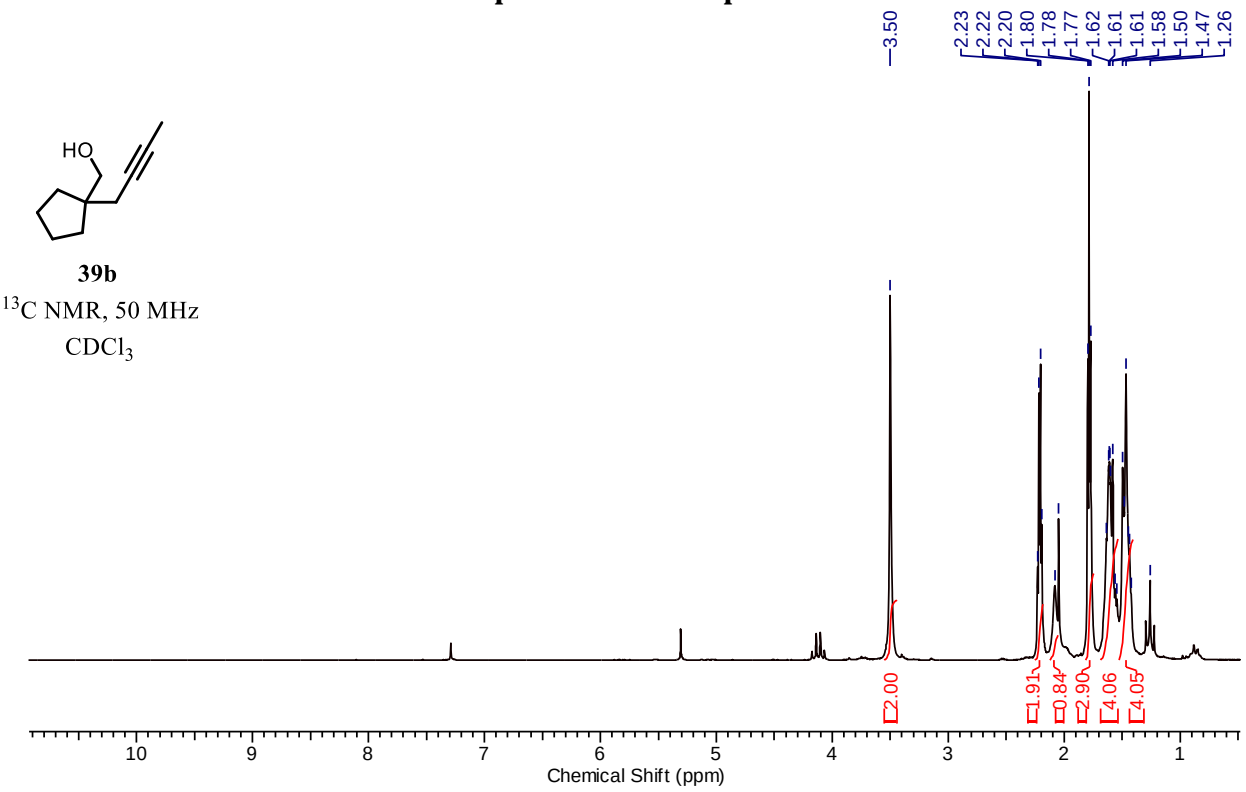


39b'

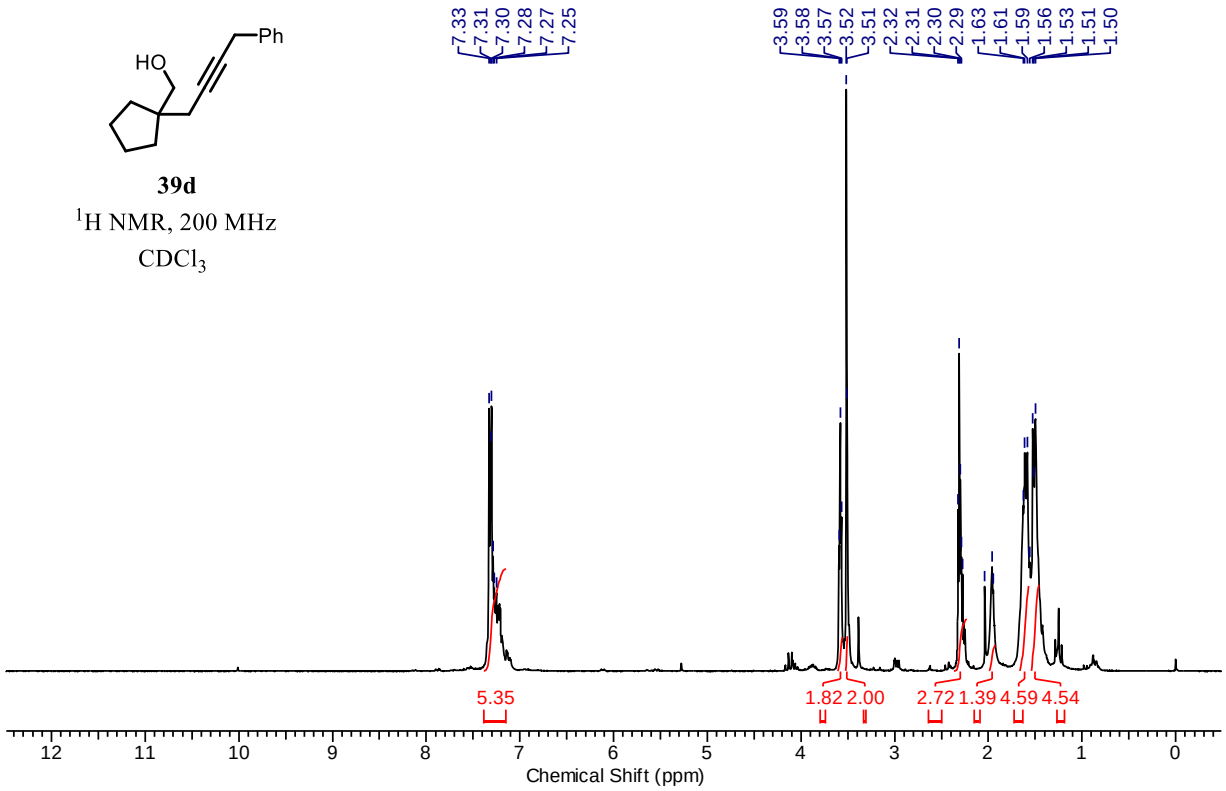
^{1}H NMR, 200 MHz

$CDCl_3$

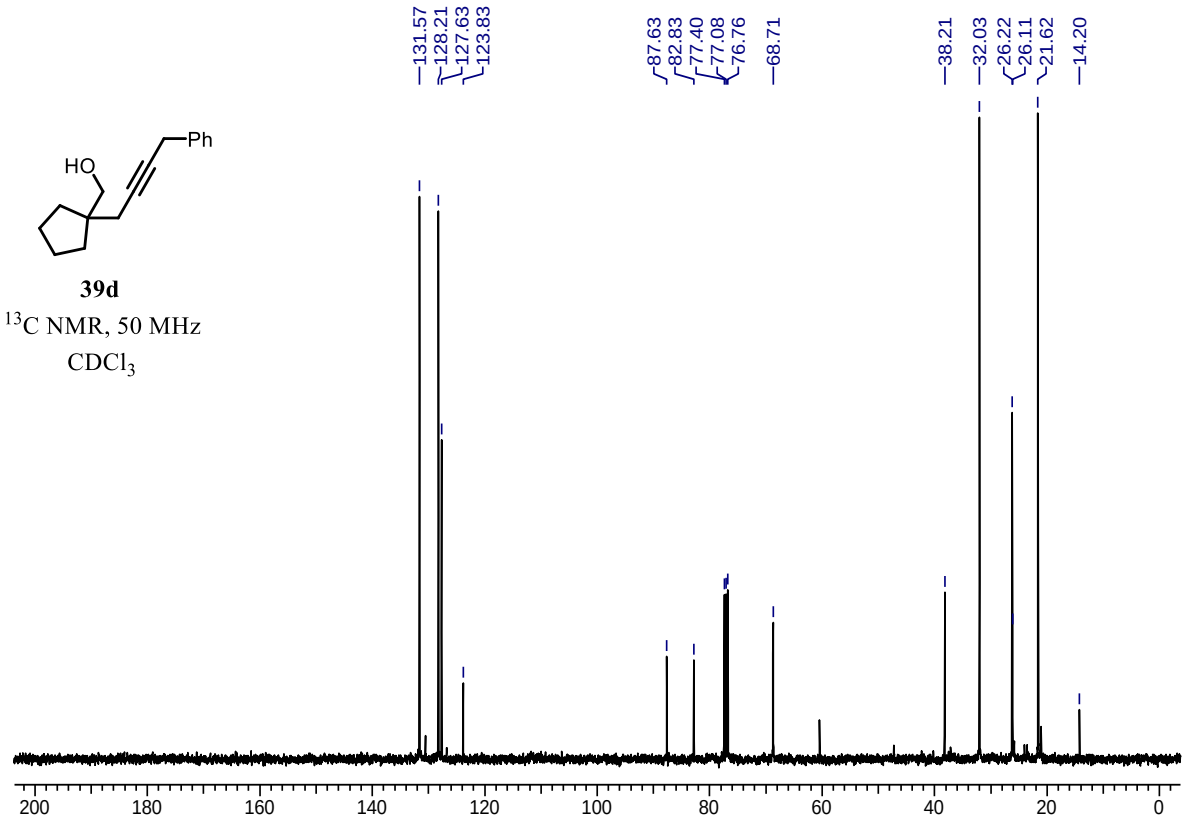
^{1}H NMR spectrum of compound 39b



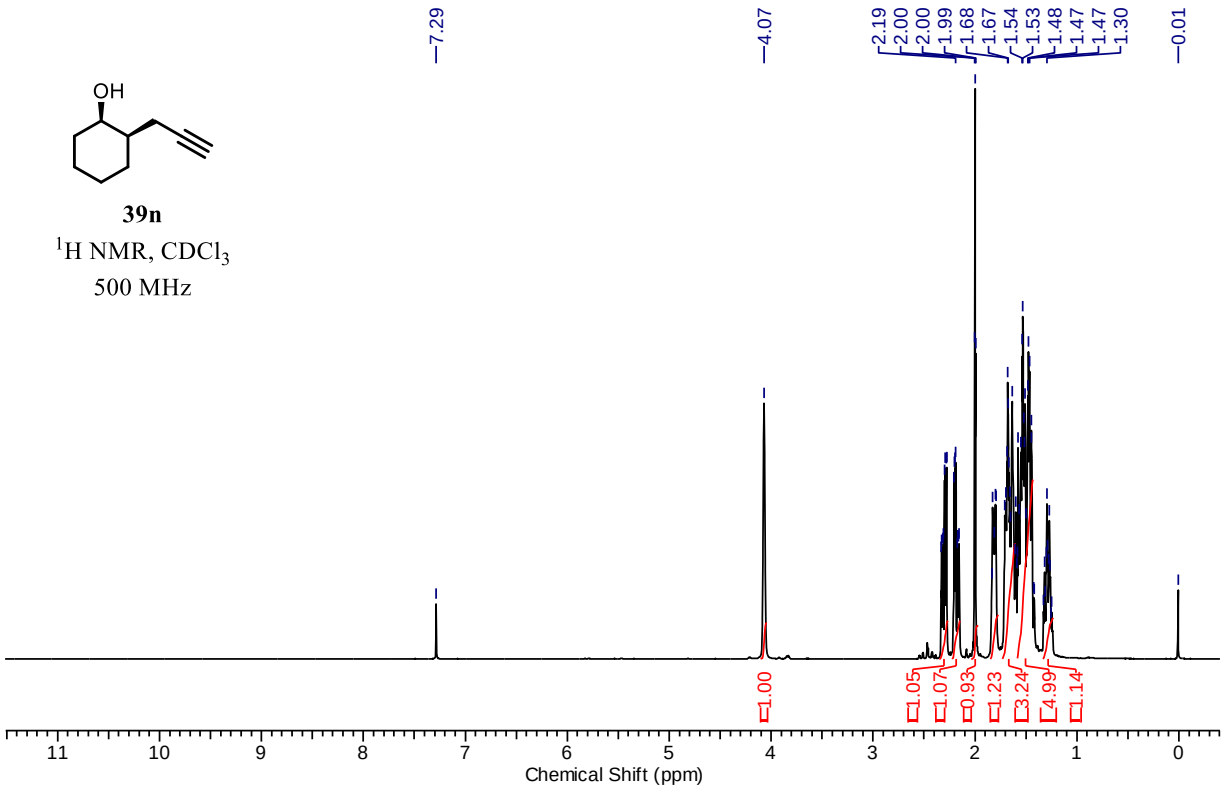
^{1}H NMR spectrum of compound 39d



^{13}C NMR spectrum of compound 39d



^{1}H NMR spectrum of compound 39n



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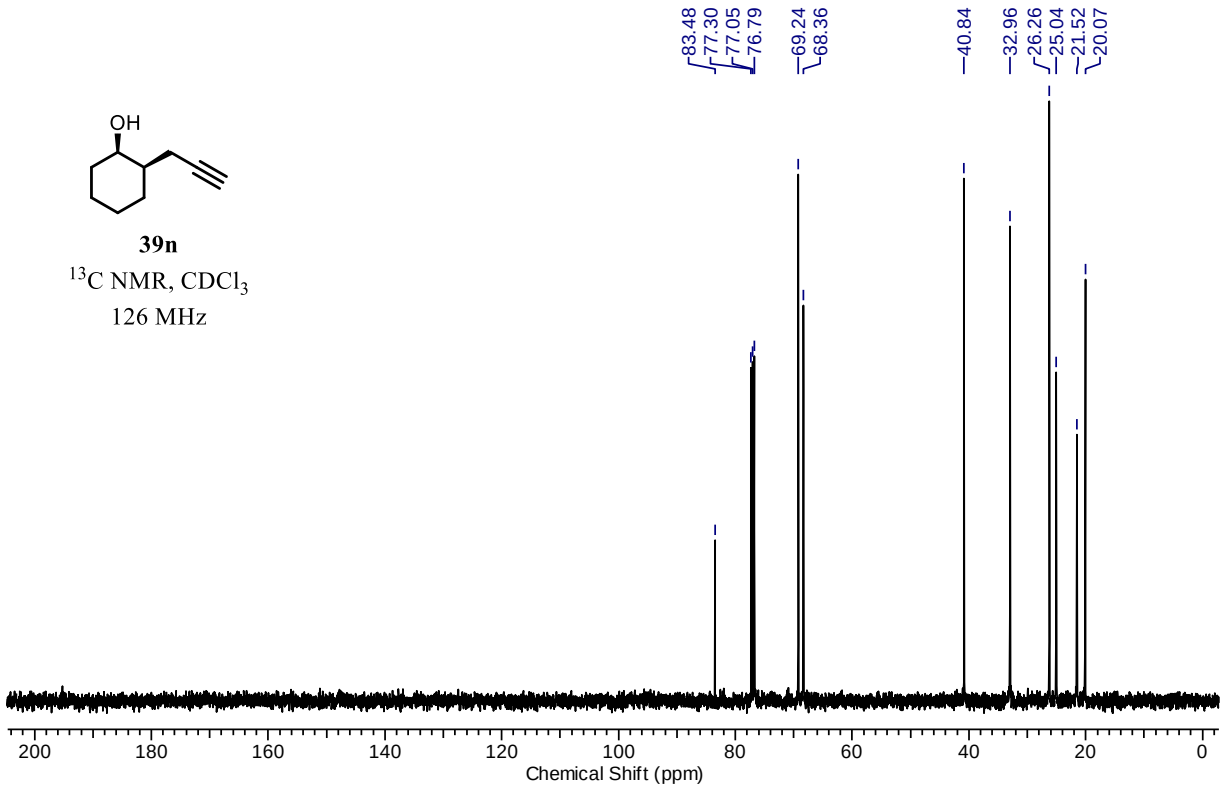
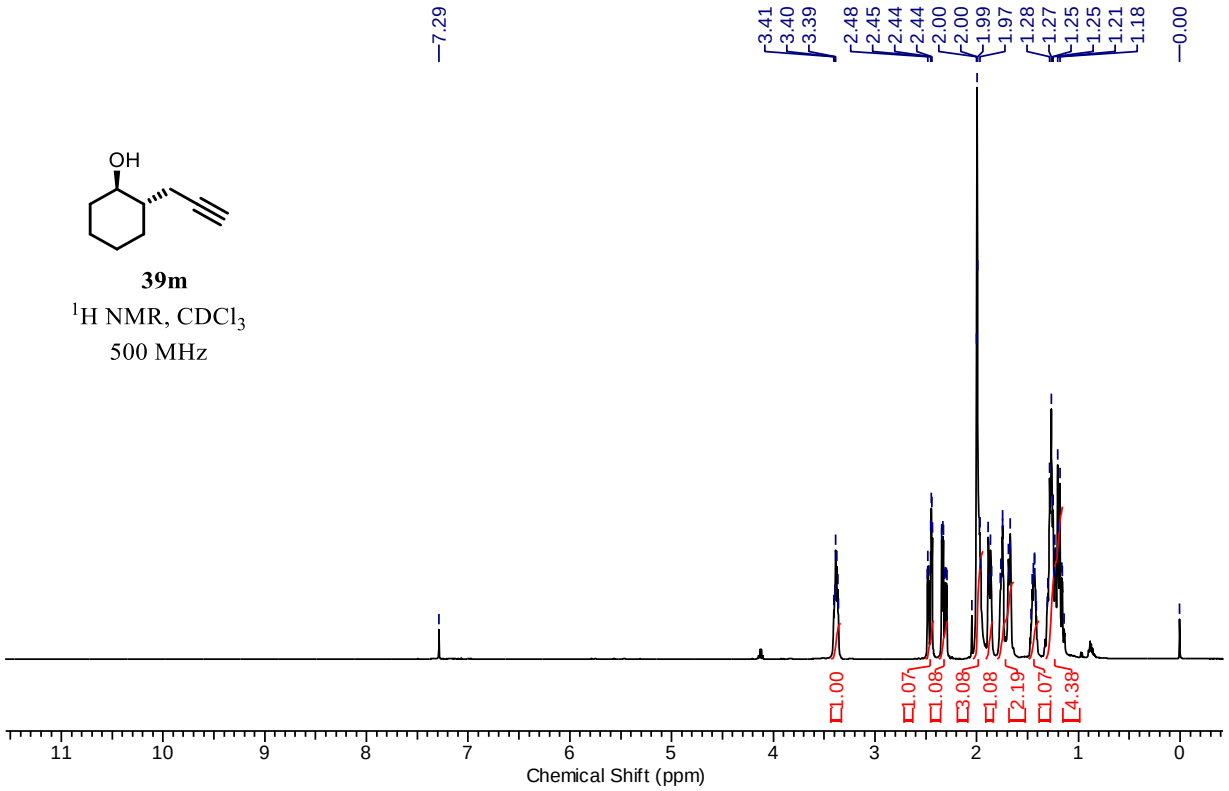


^{1}H NMR spectrum of compound 39m



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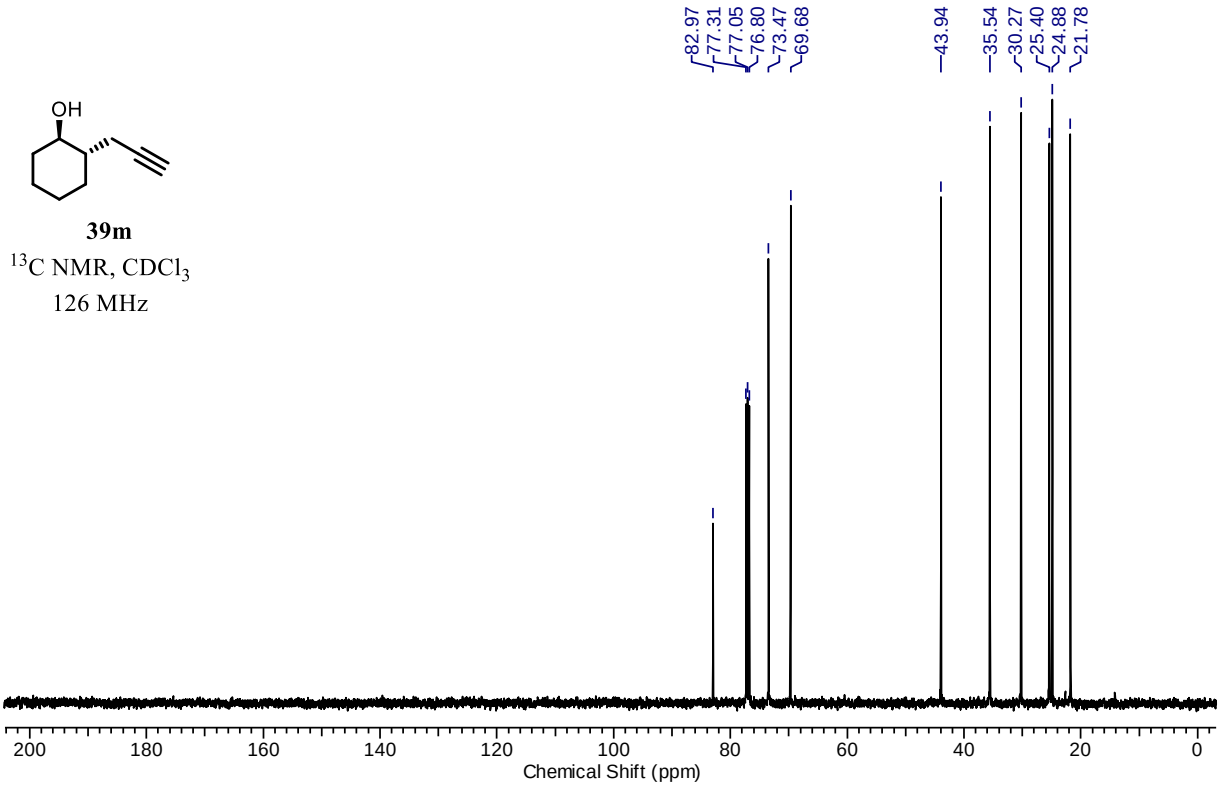
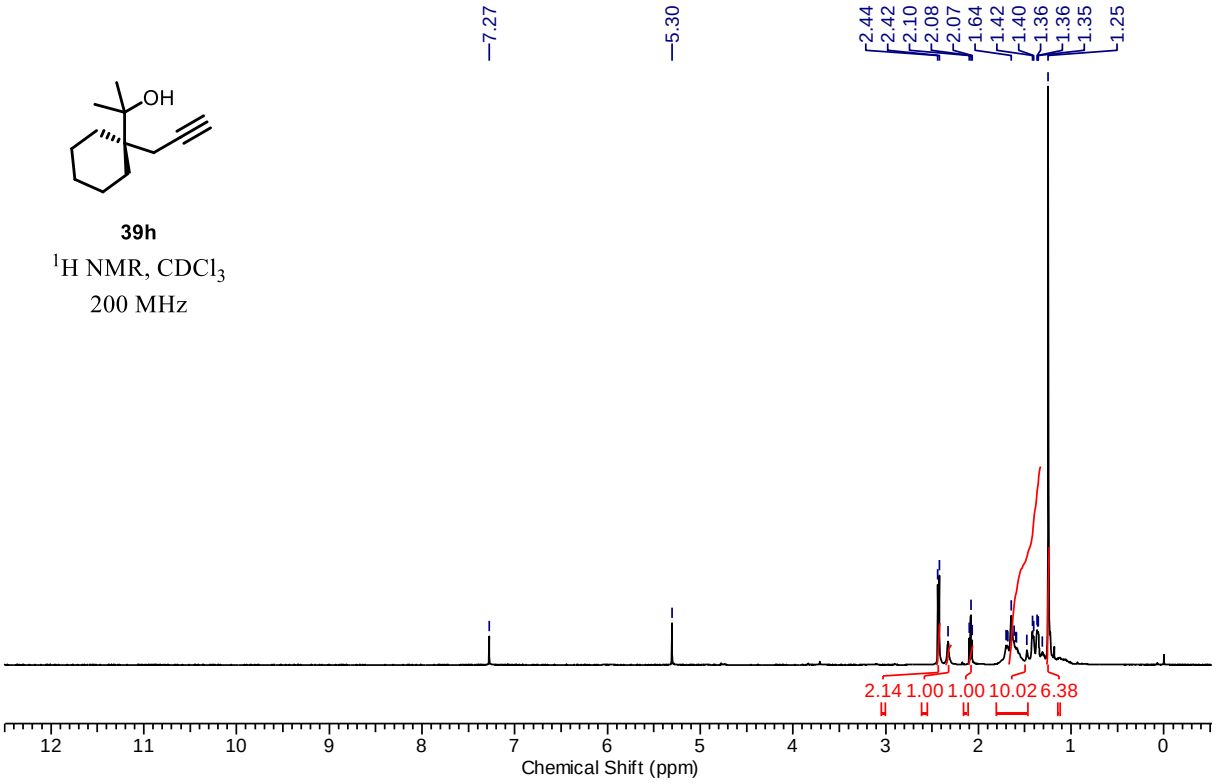
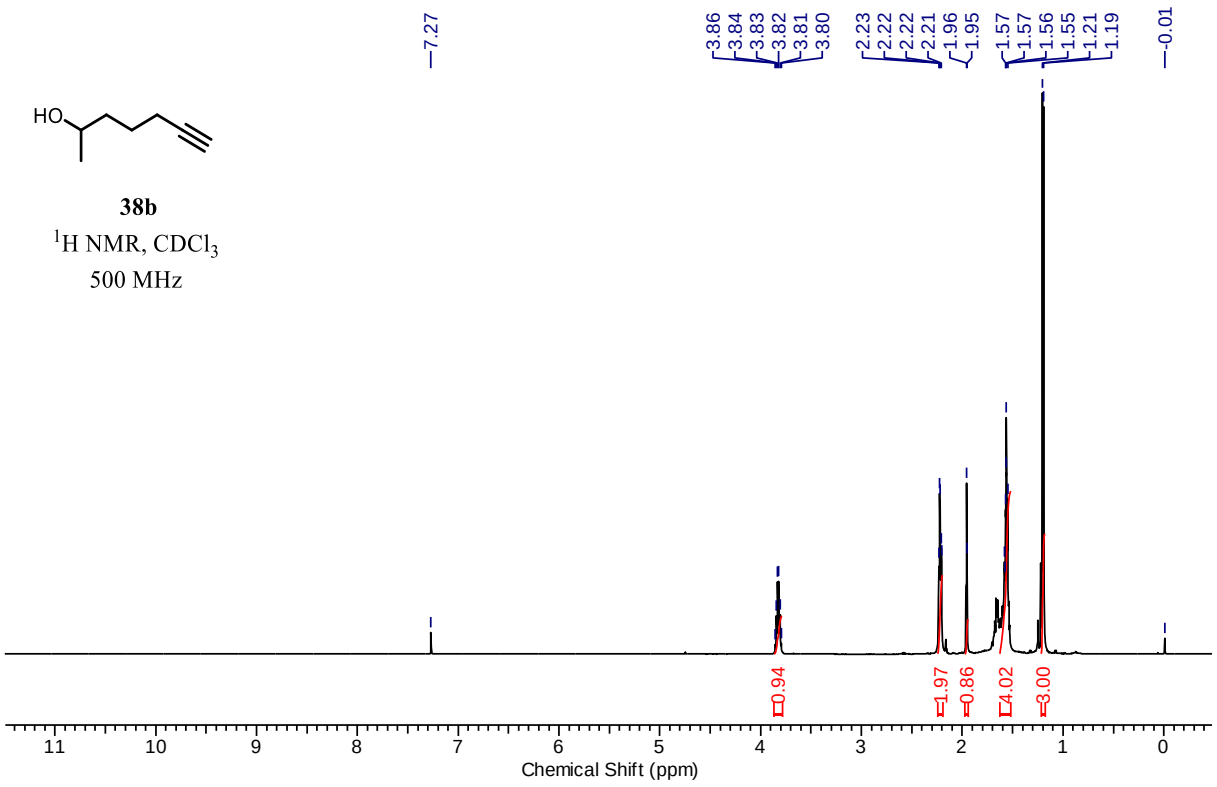


^{1}H NMR spectrum of compound 39h



^{1}H NMR spectrum of compound 38b



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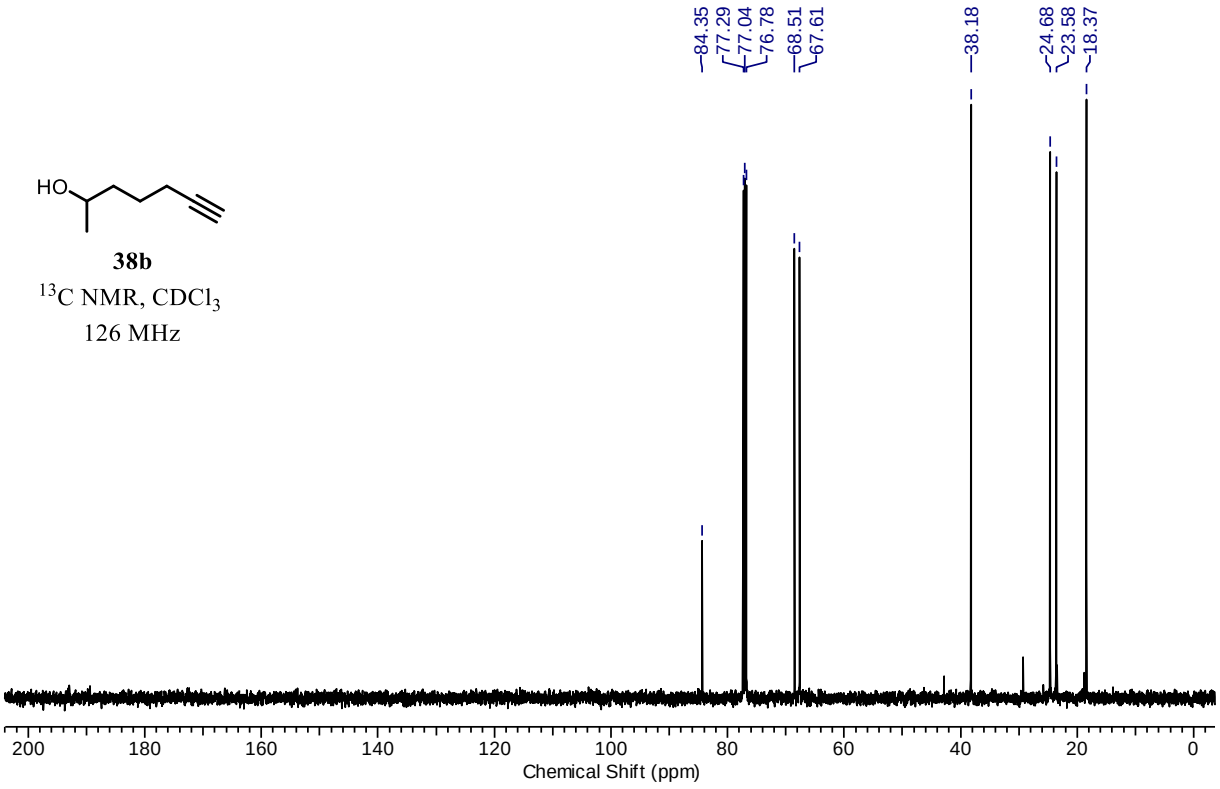
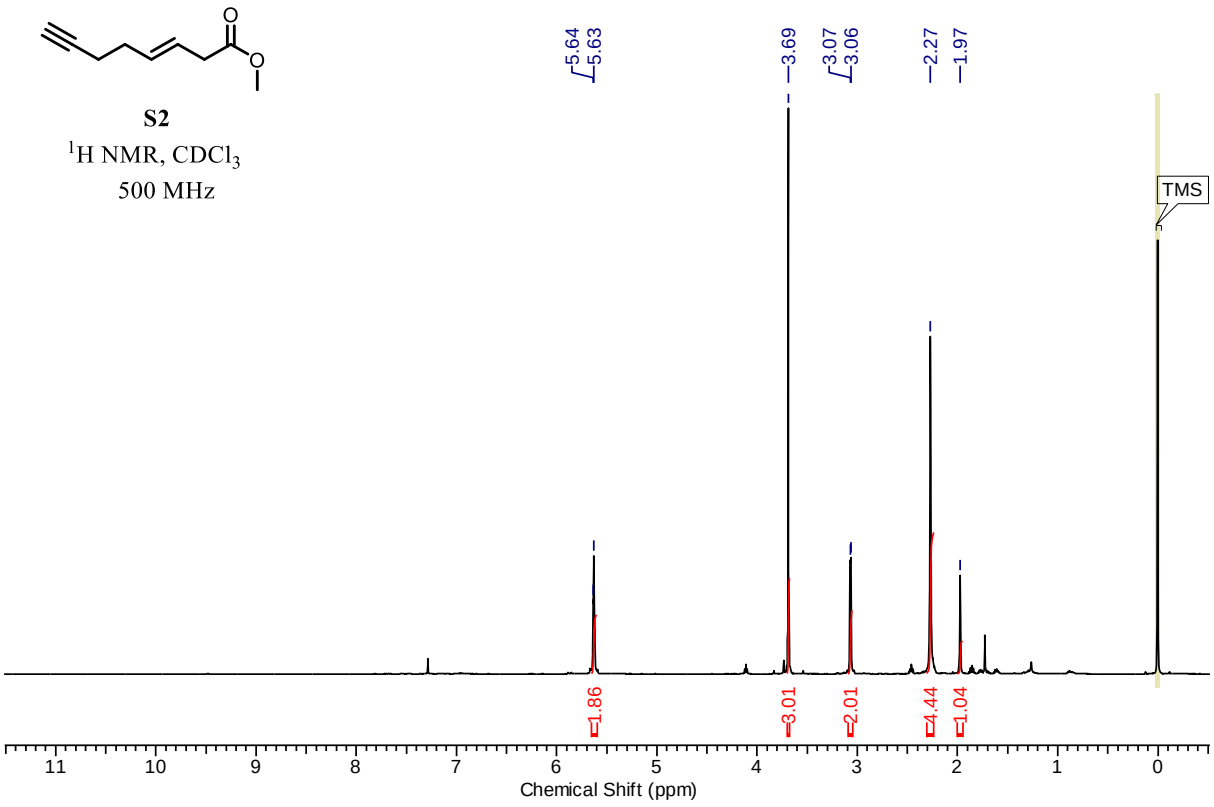
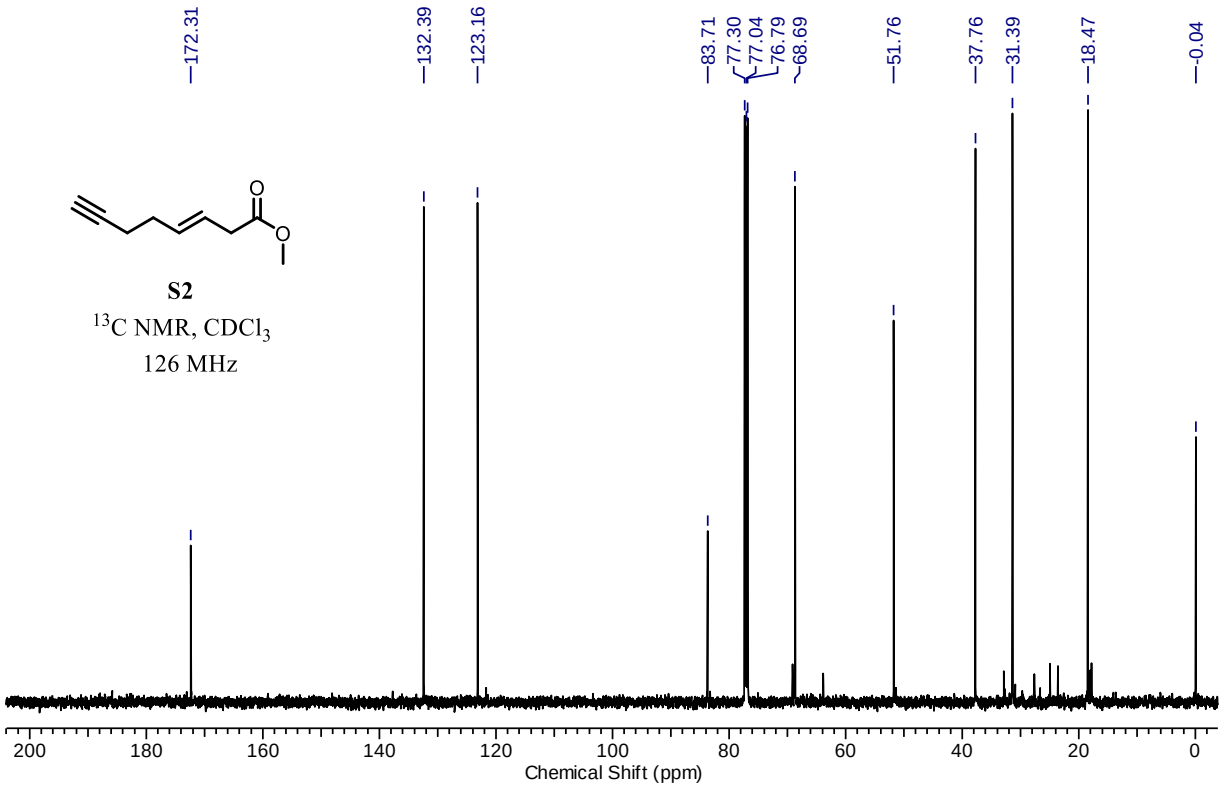


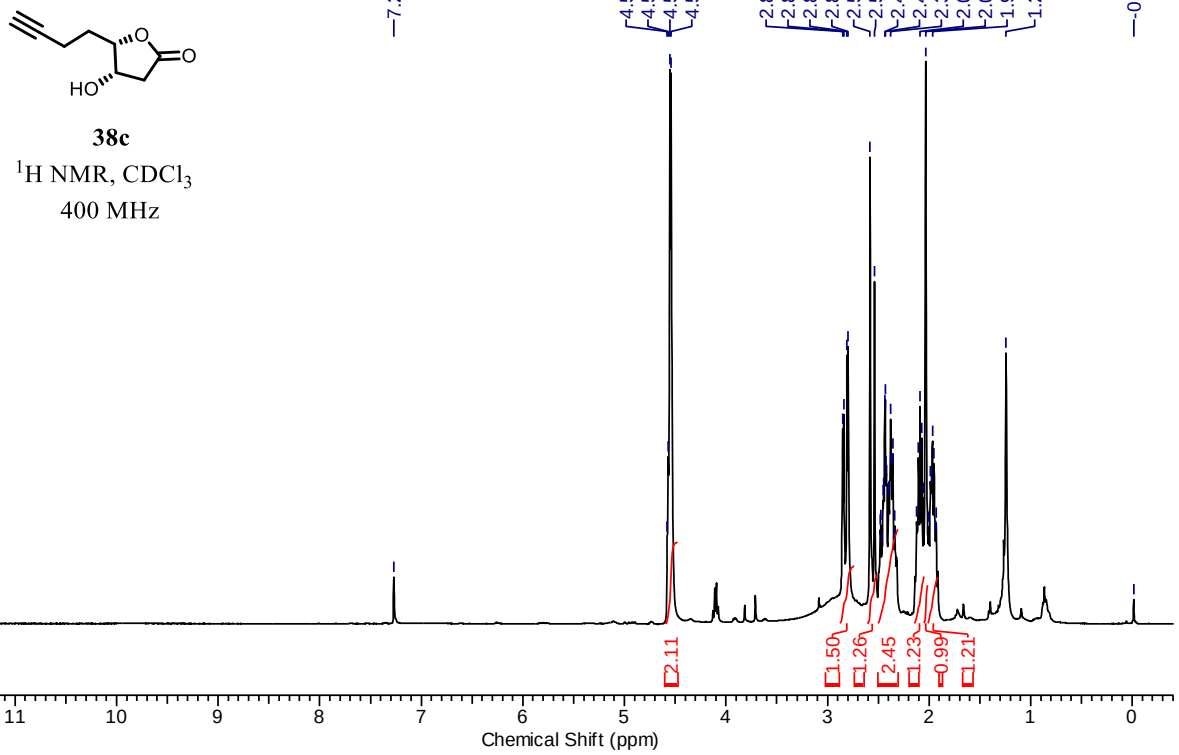
^{1}H NMR spectrum of compound S2



^{13}C NMR spectrum of compound S2

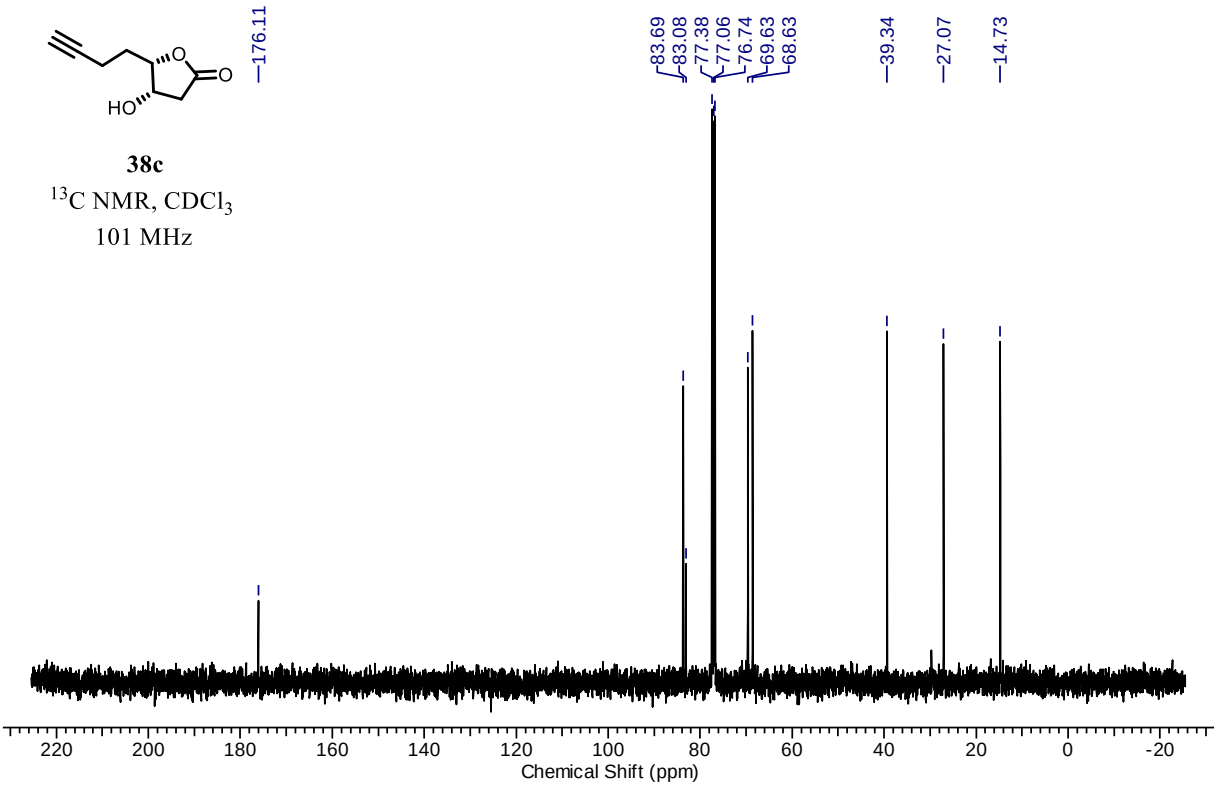


^{1}H NMR spectrum of compound 38c



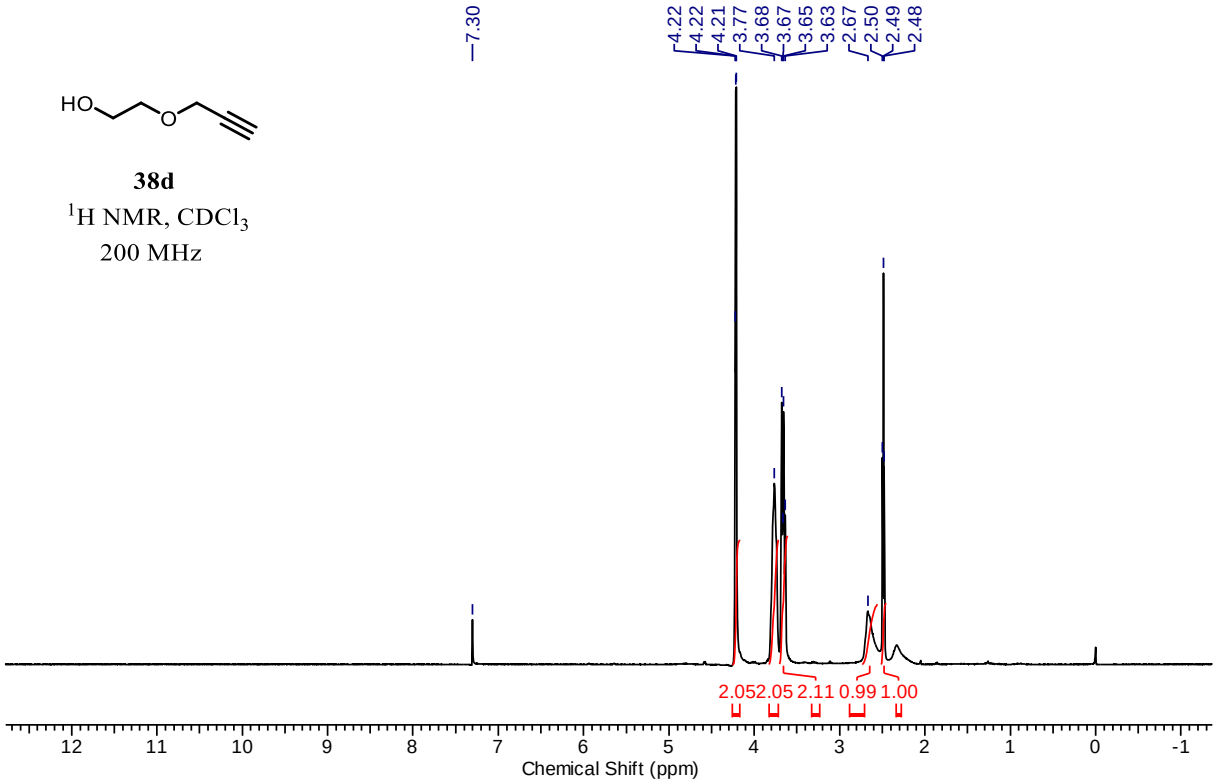
38c
^{1}H NMR, $CDCl_3$
400 MHz

^{13}C NMR spectrum of compound 38c

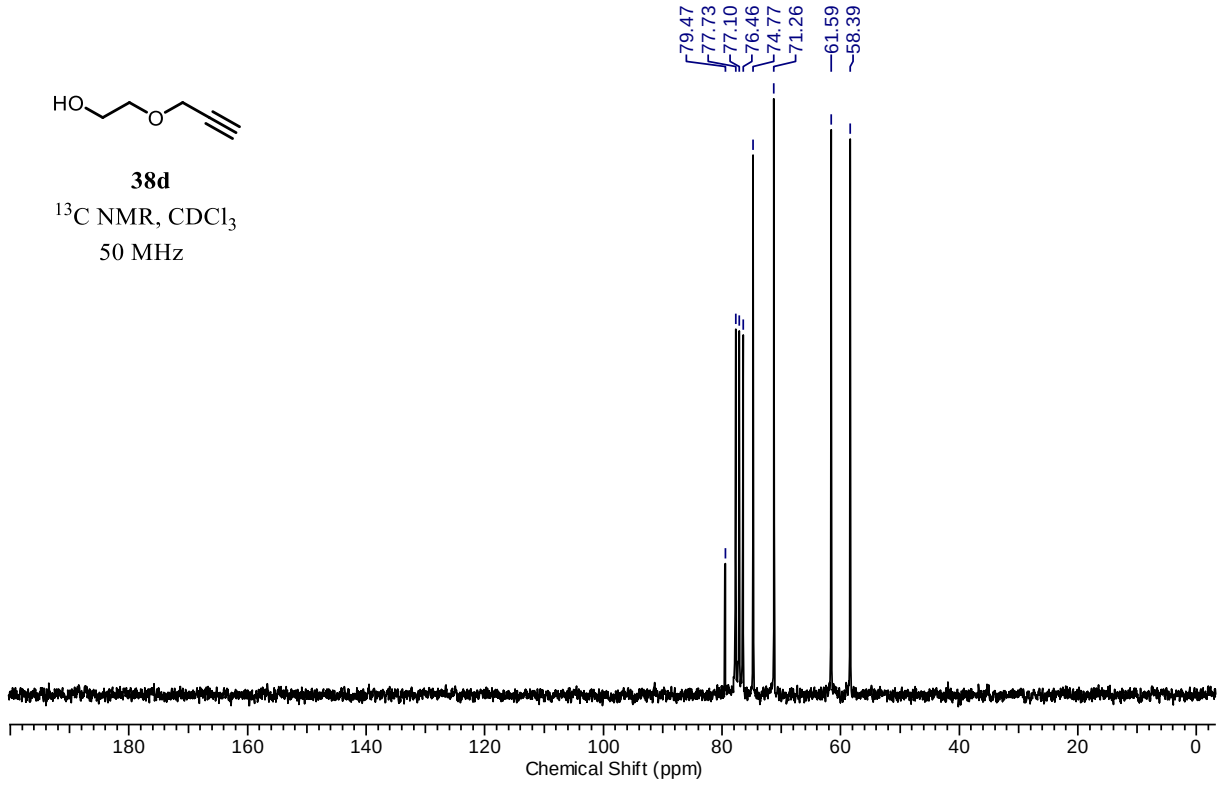


38c
^{13}C NMR, $CDCl_3$
101 MHz

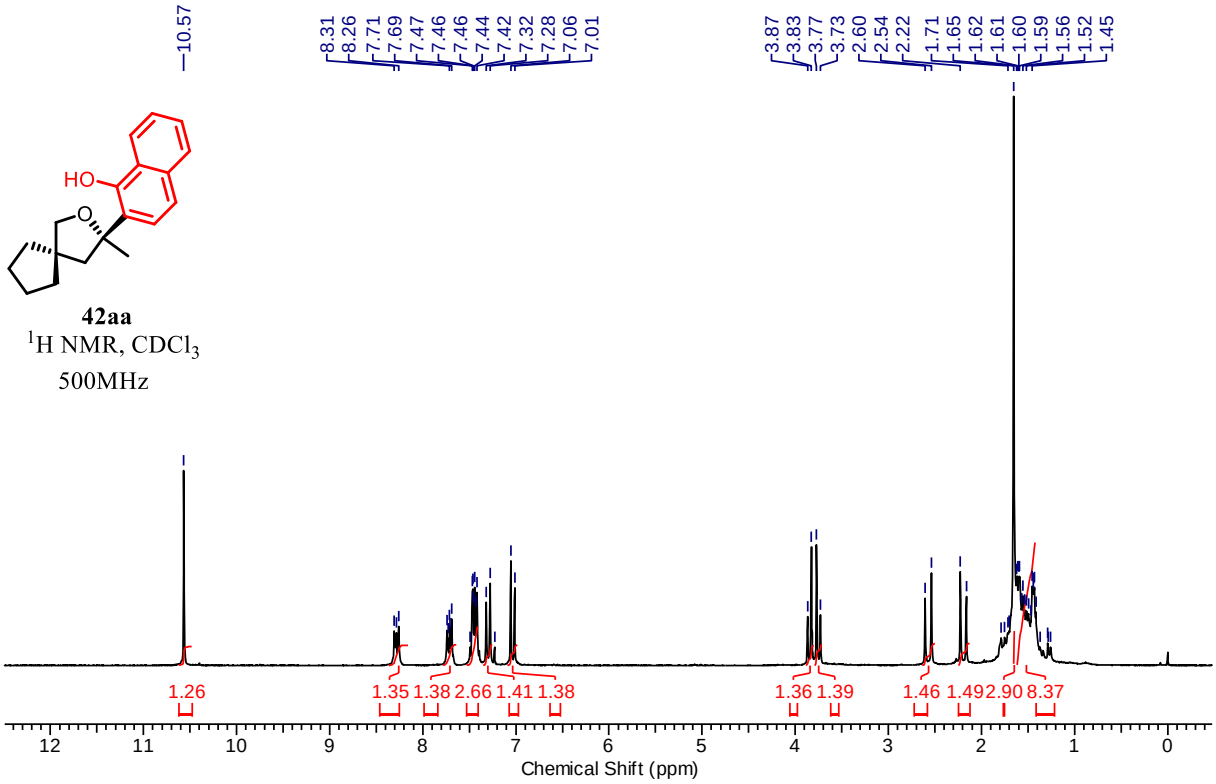
^{1}H NMR spectrum of compound 38d



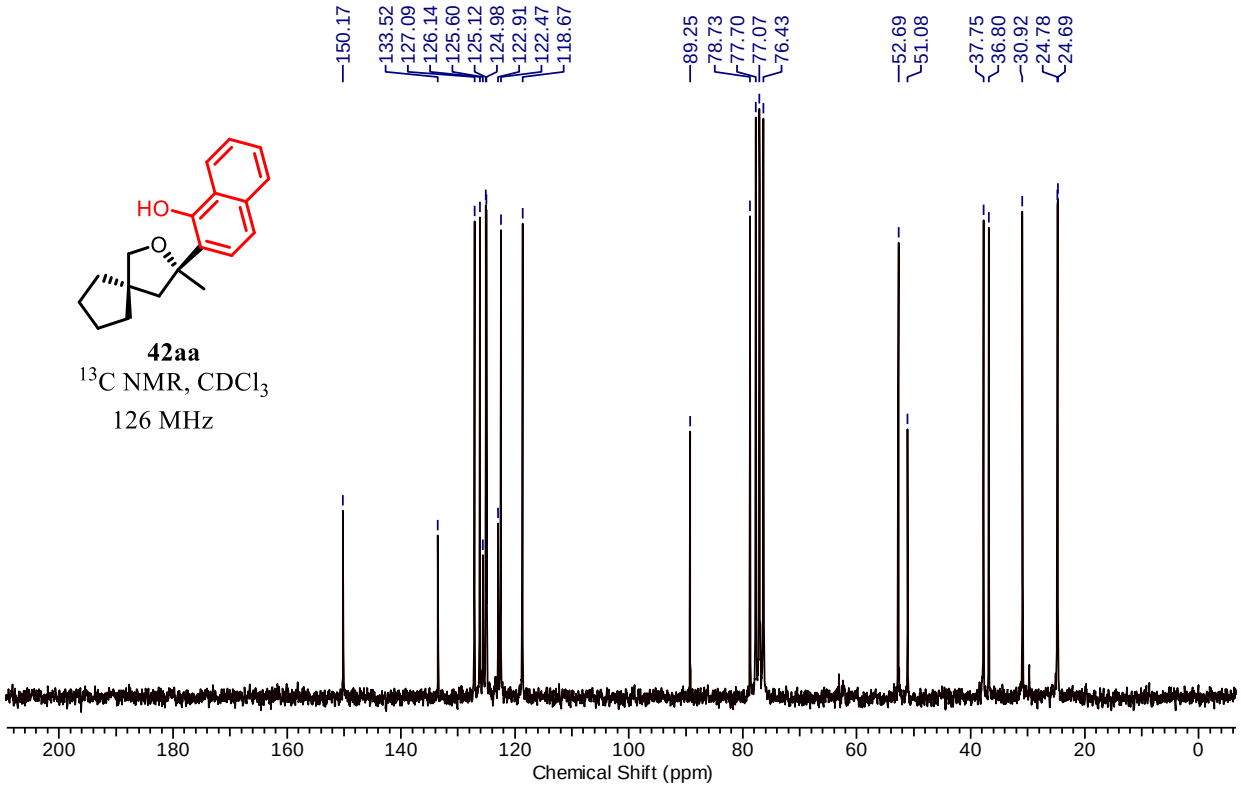
^{13}C NMR spectrum of compound 38d



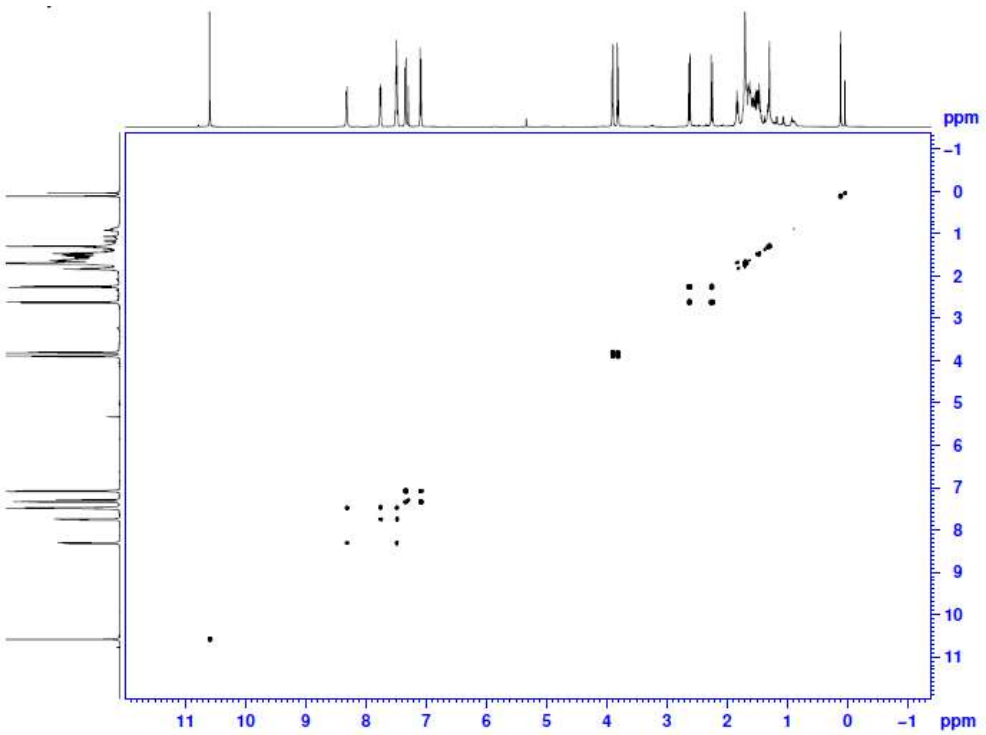
^{1}H NMR spectrum of compound 42aa



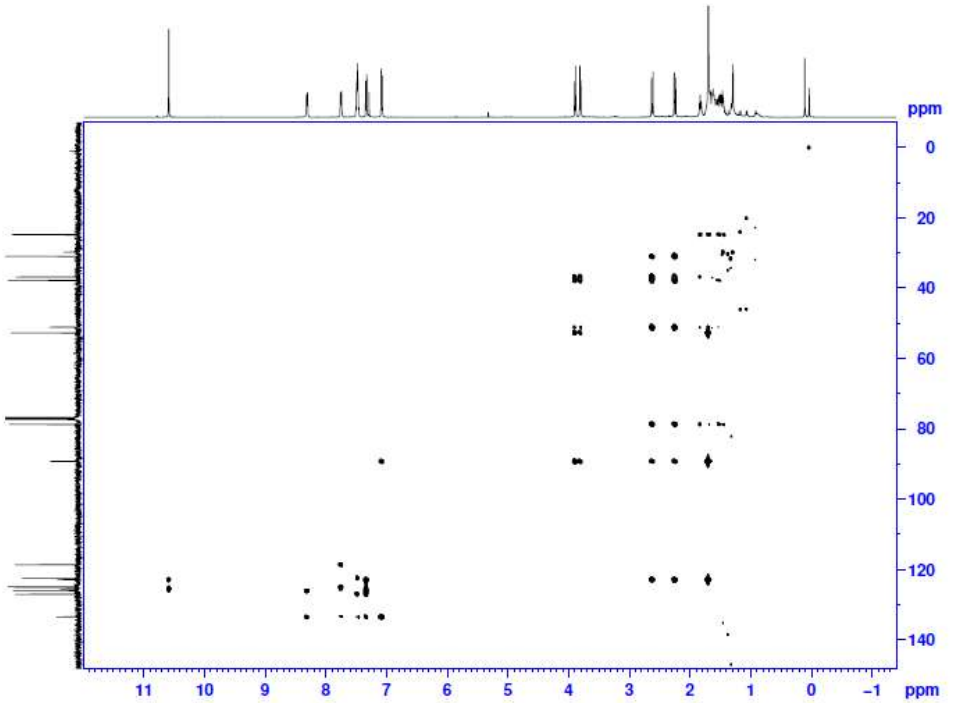
^{13}C NMR spectrum of compound 42aa



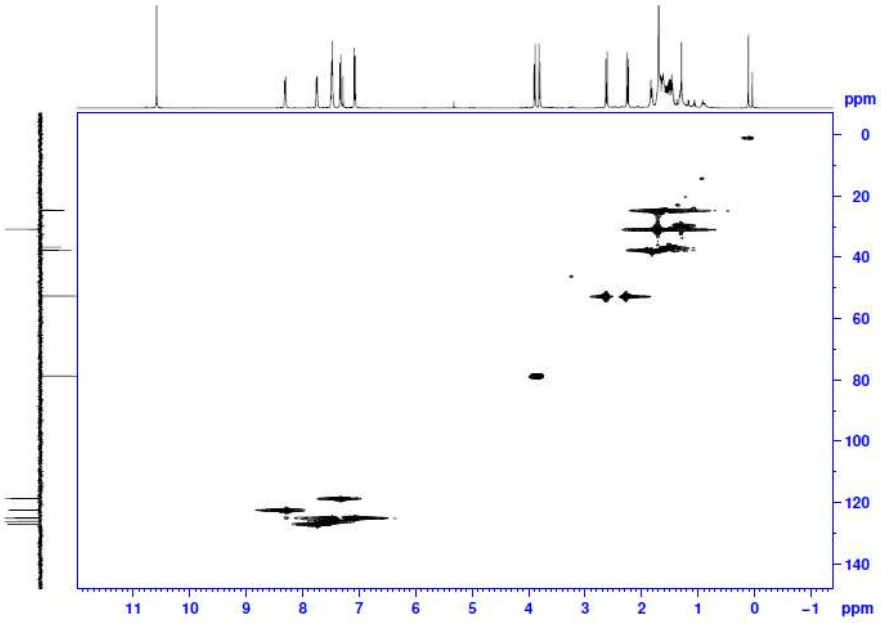
COSY **(42aa):**



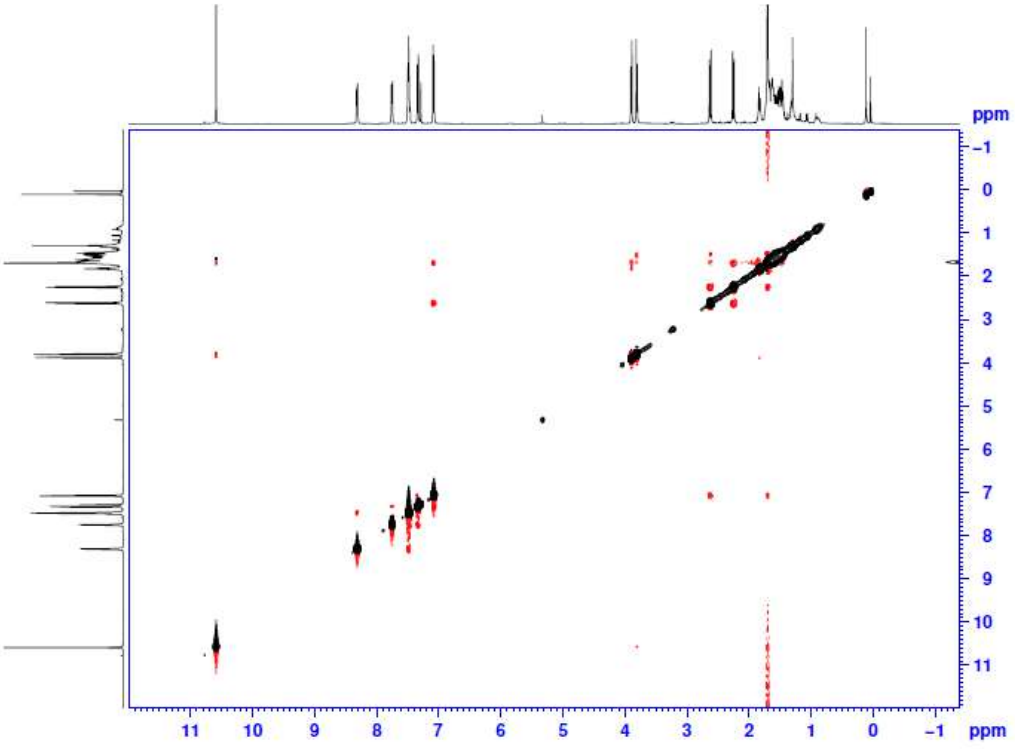
HMBC **(42aa):**



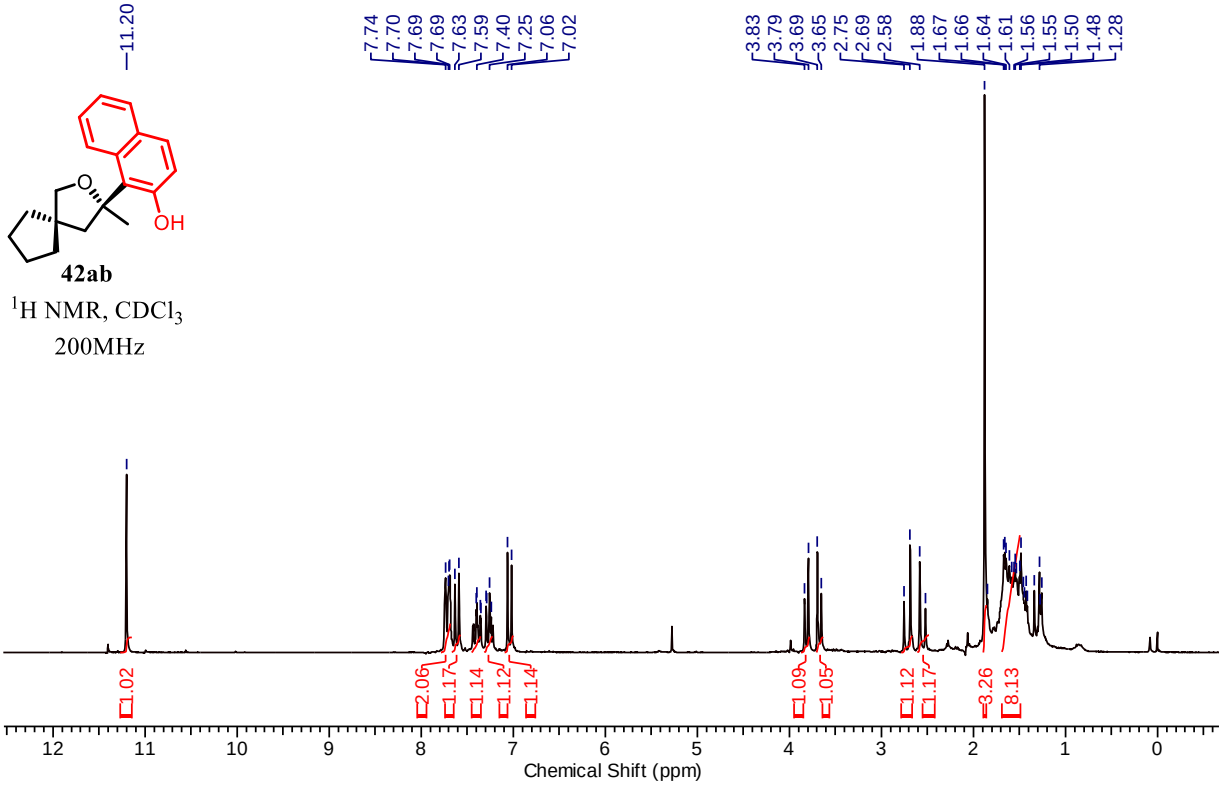
HSQC **(42aa):**



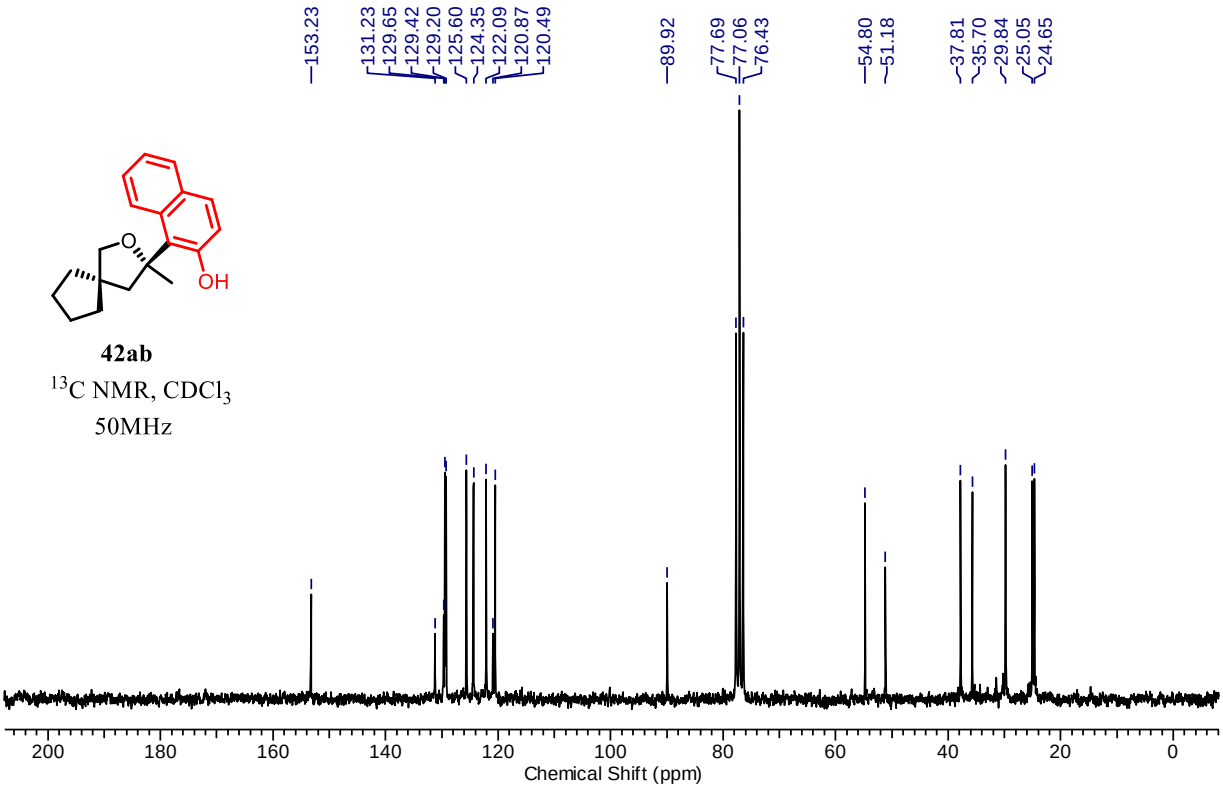
NOESY **(42aa):**



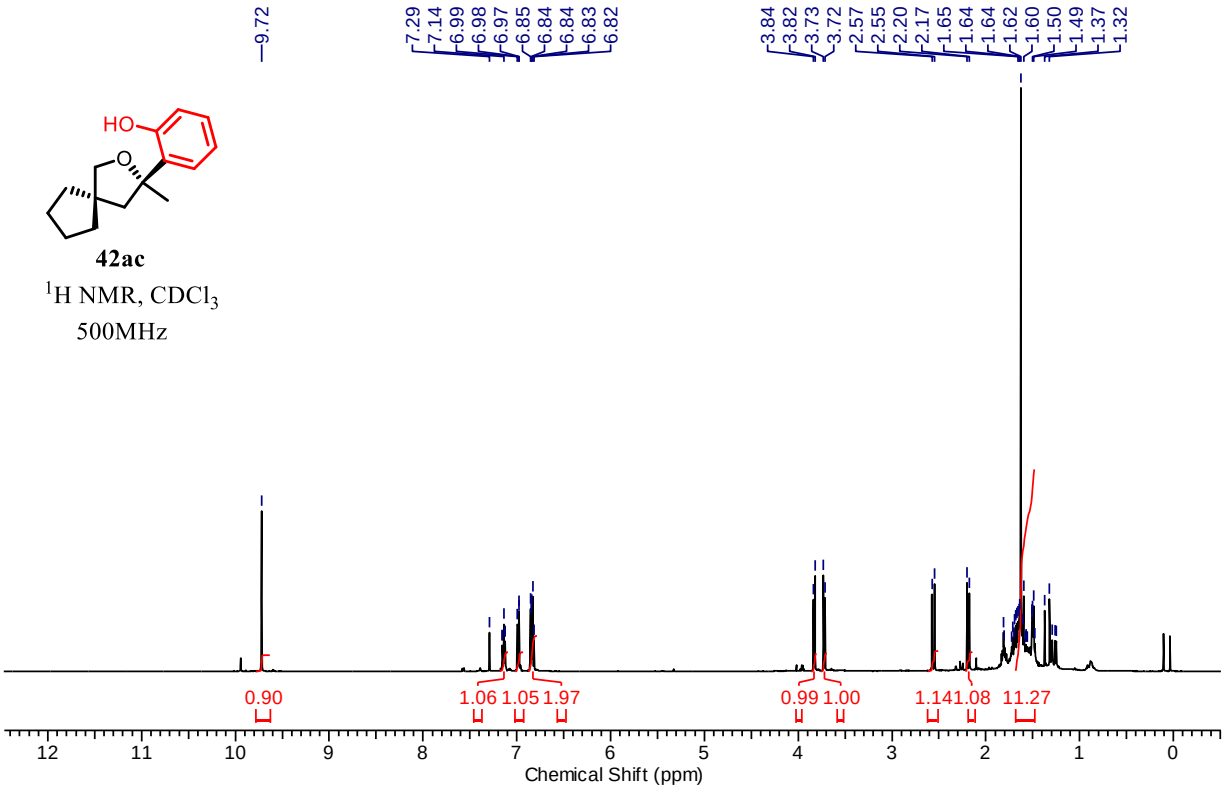
^{1}H NMR spectrum of compound 42ab



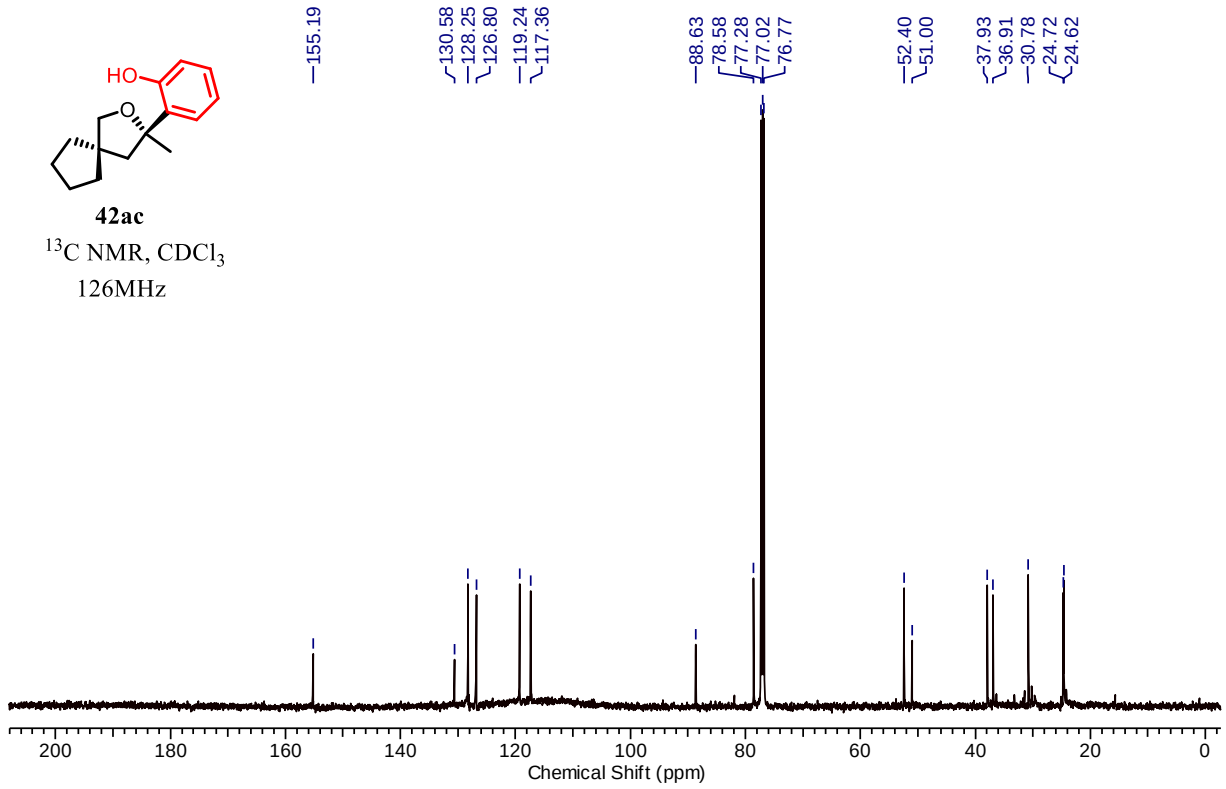
^{13}C NMR spectrum of compound 42ab



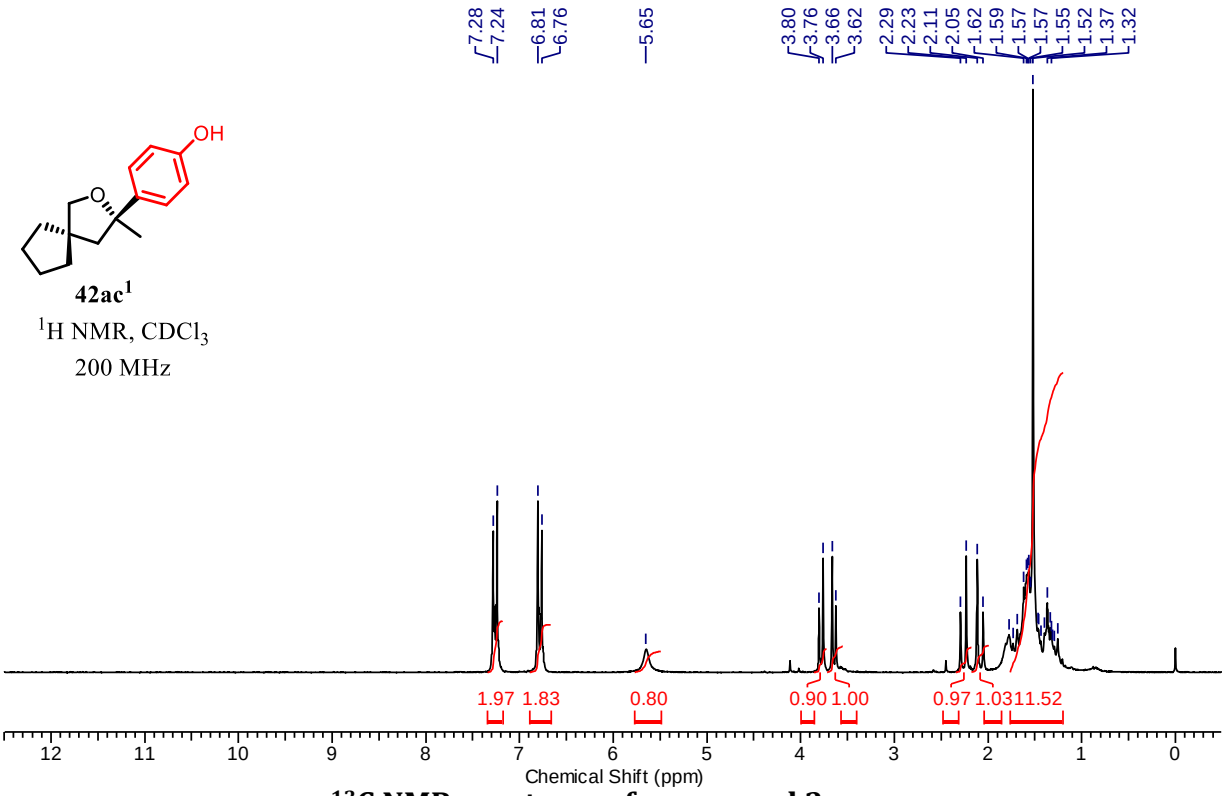
^{1}H NMR spectrum of compound 42ac



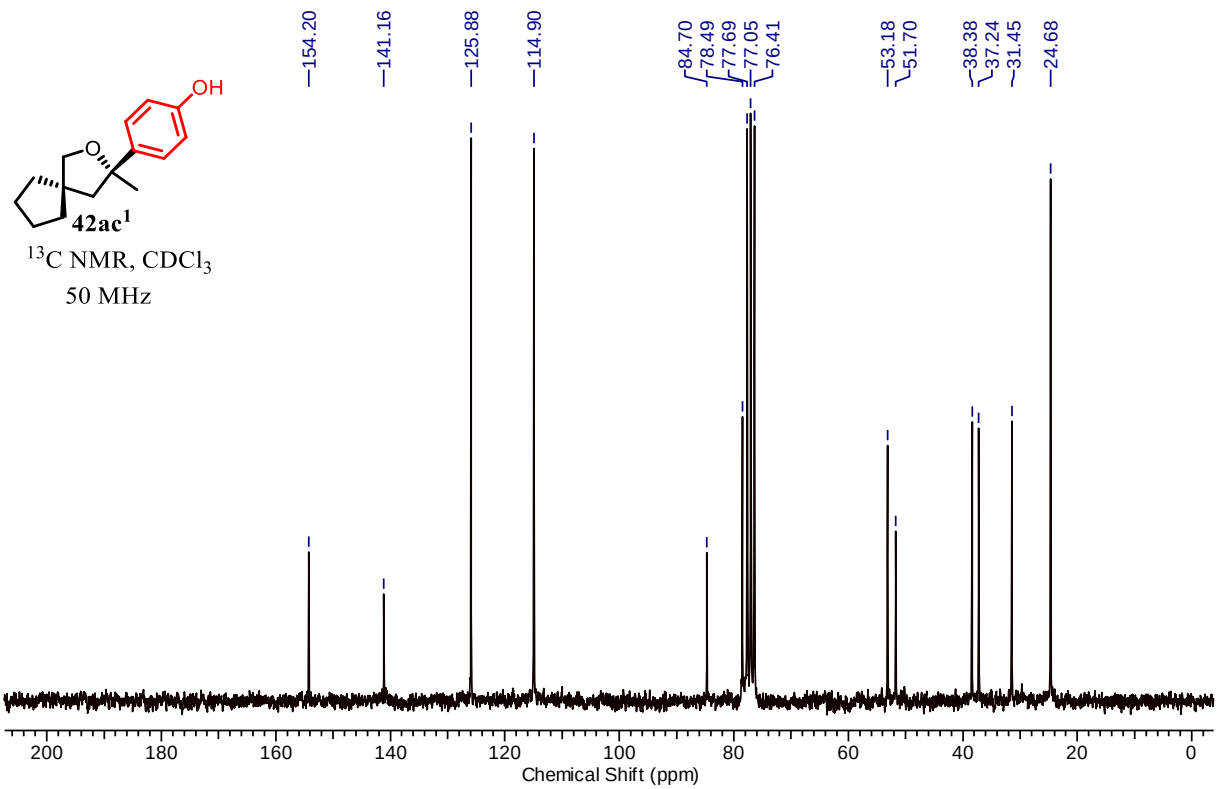
^{13}C NMR spectrum of compound 42ac



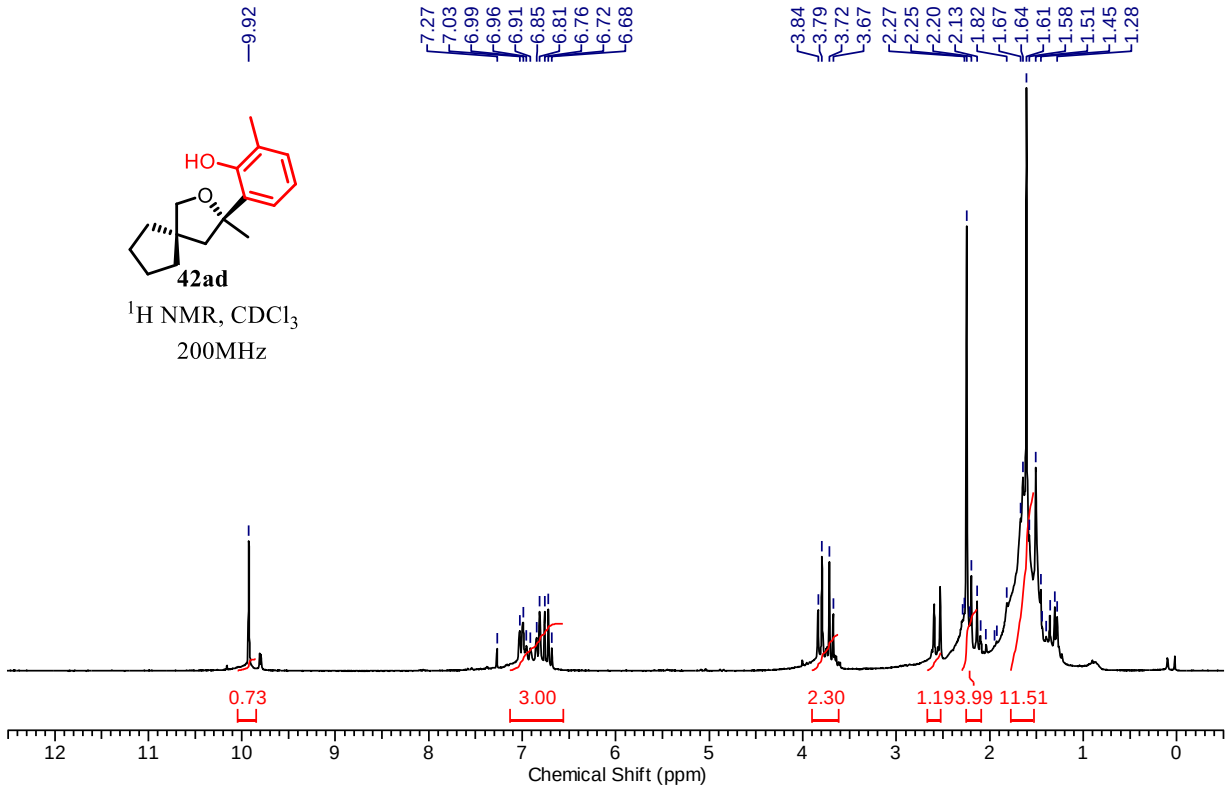
^{1}H NMR spectrum of compound 42ac'



^{13}C NMR spectrum of compound 3ac

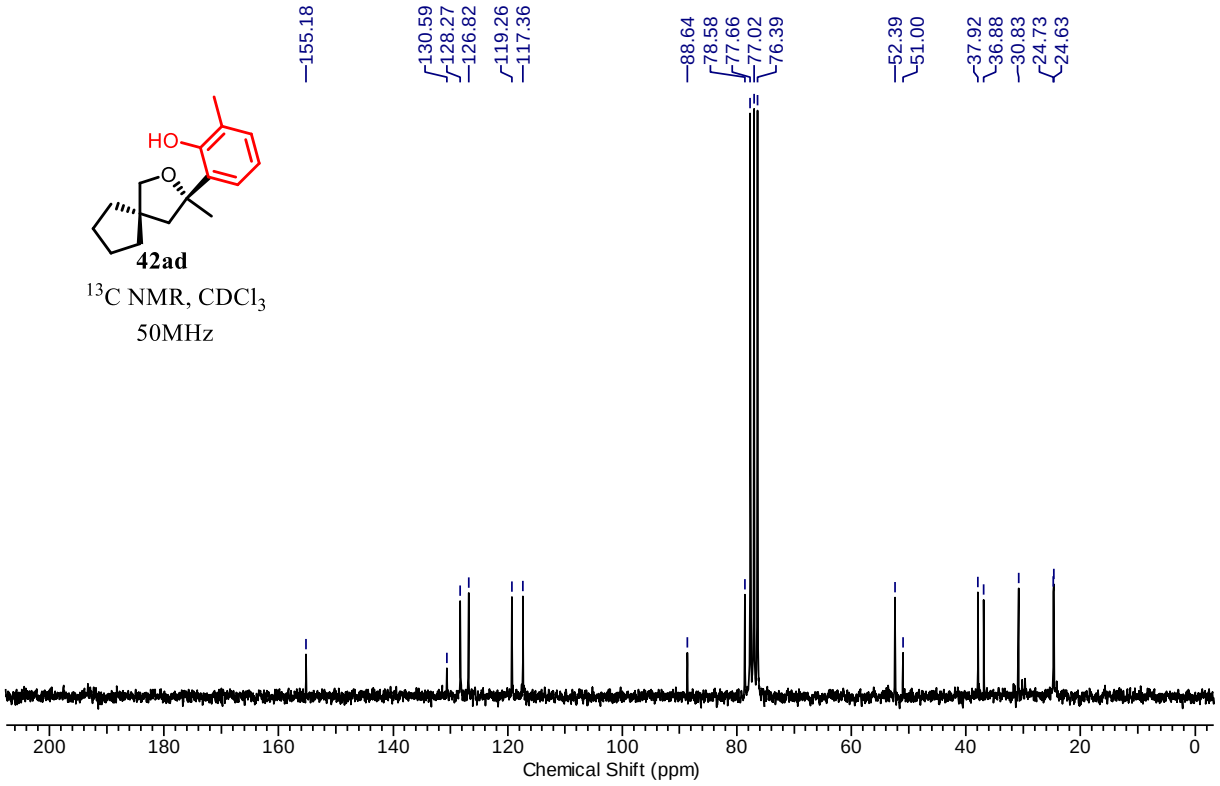


^{1}H NMR spectrum of compound 42ad



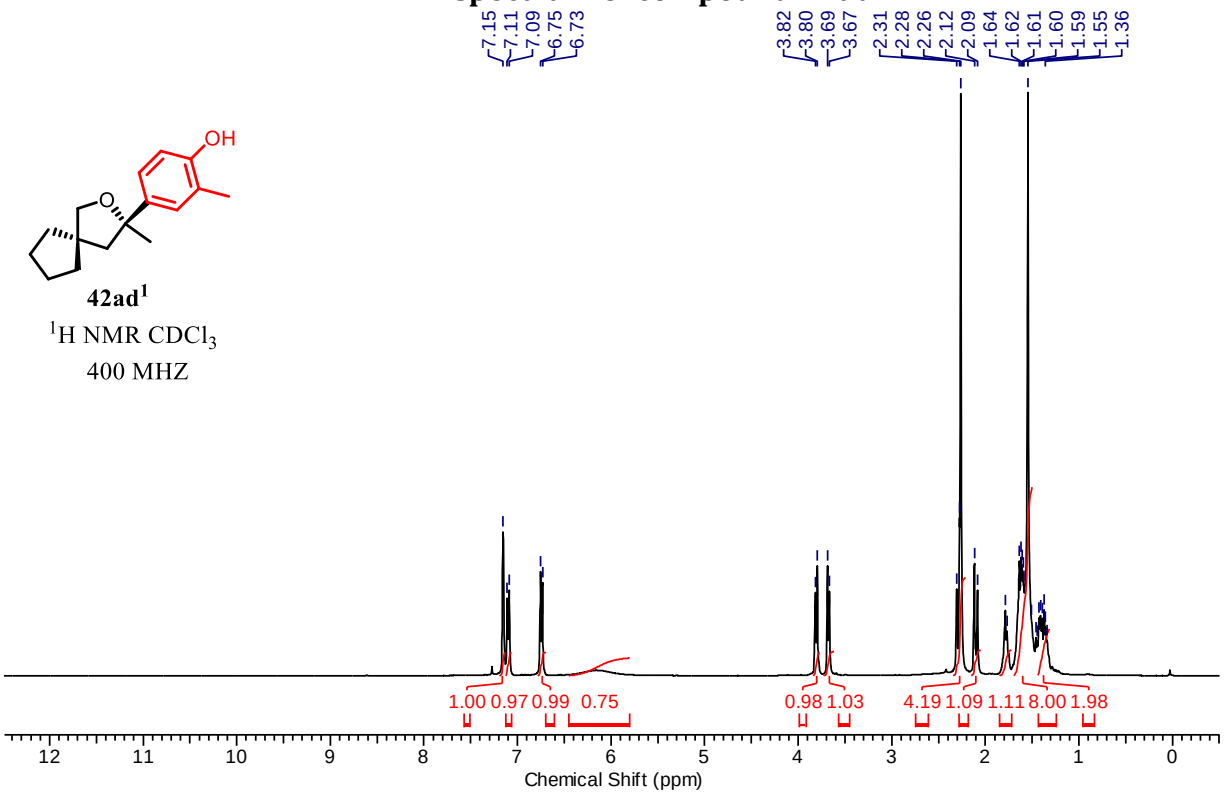
^{1}H NMR, $CDCl_3$
200MHz

^{13}C NMR spectrum of compound 42ad

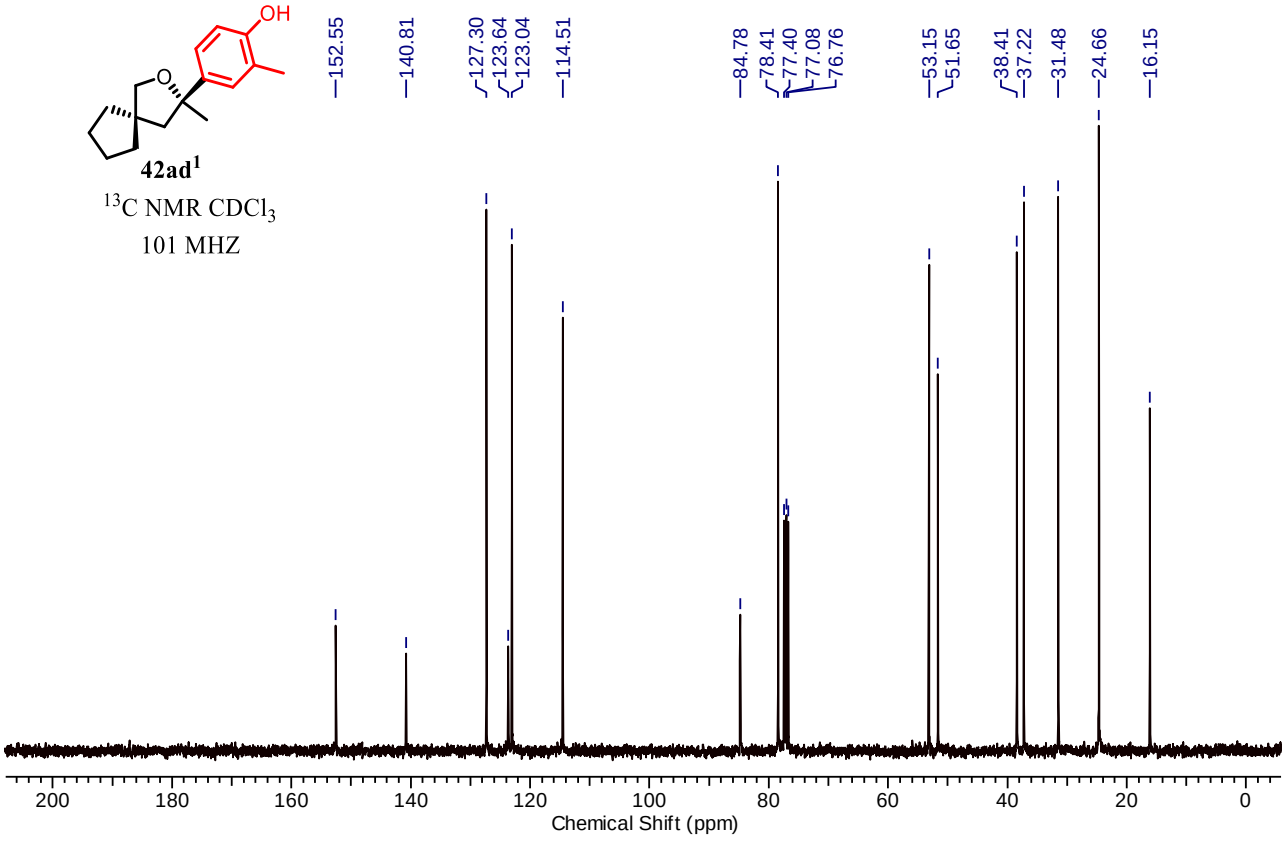


^{13}C NMR, $CDCl_3$
50MHz

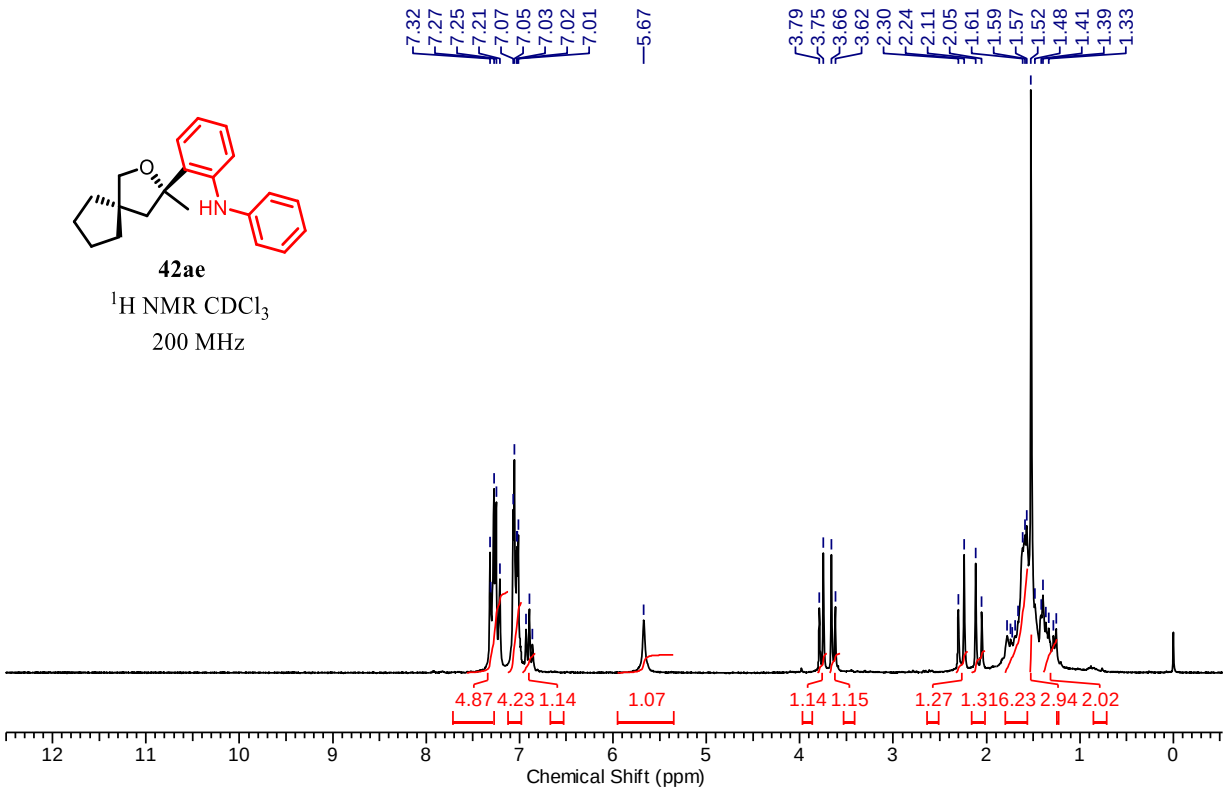
^{1}H NMR spectrum of compound 42ad'



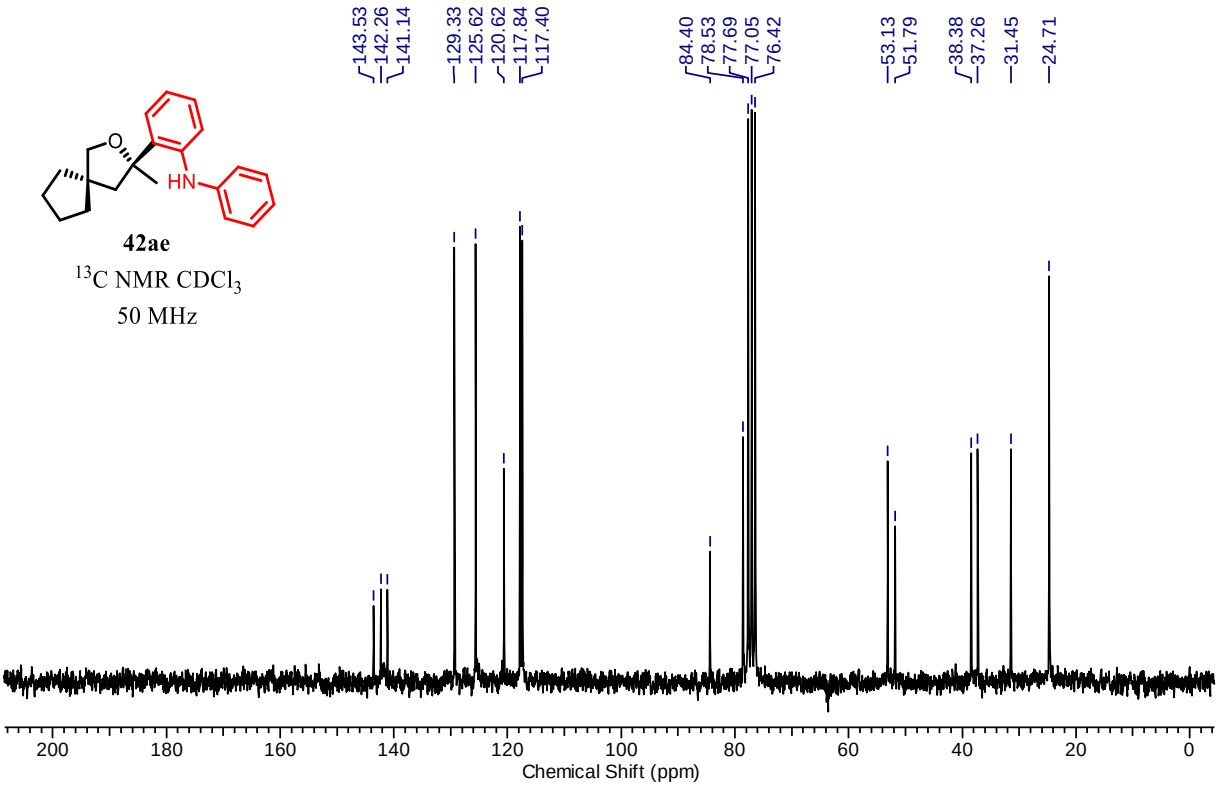
^{13}C NMR spectrum of compound 42ad'



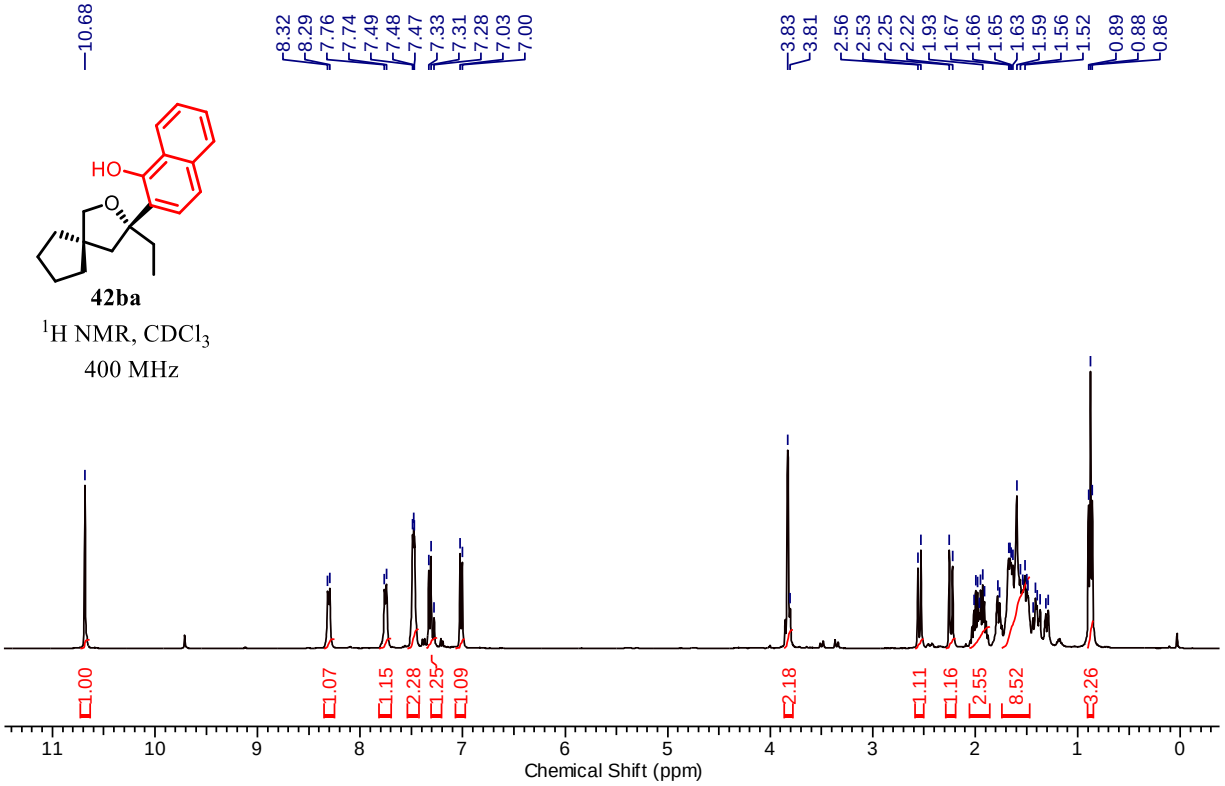
^{1}H NMR spectrum of compound 42ae



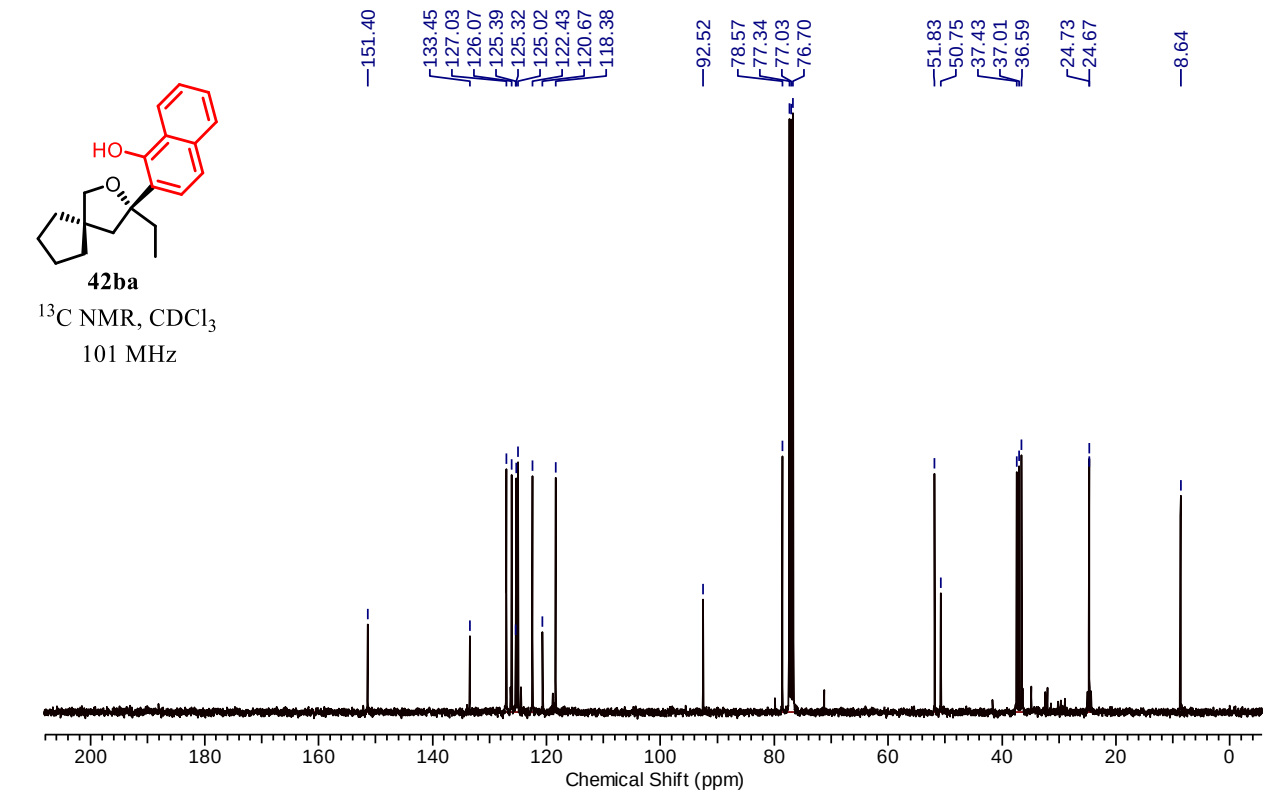
^{13}C NMR spectrum of compound 42ae



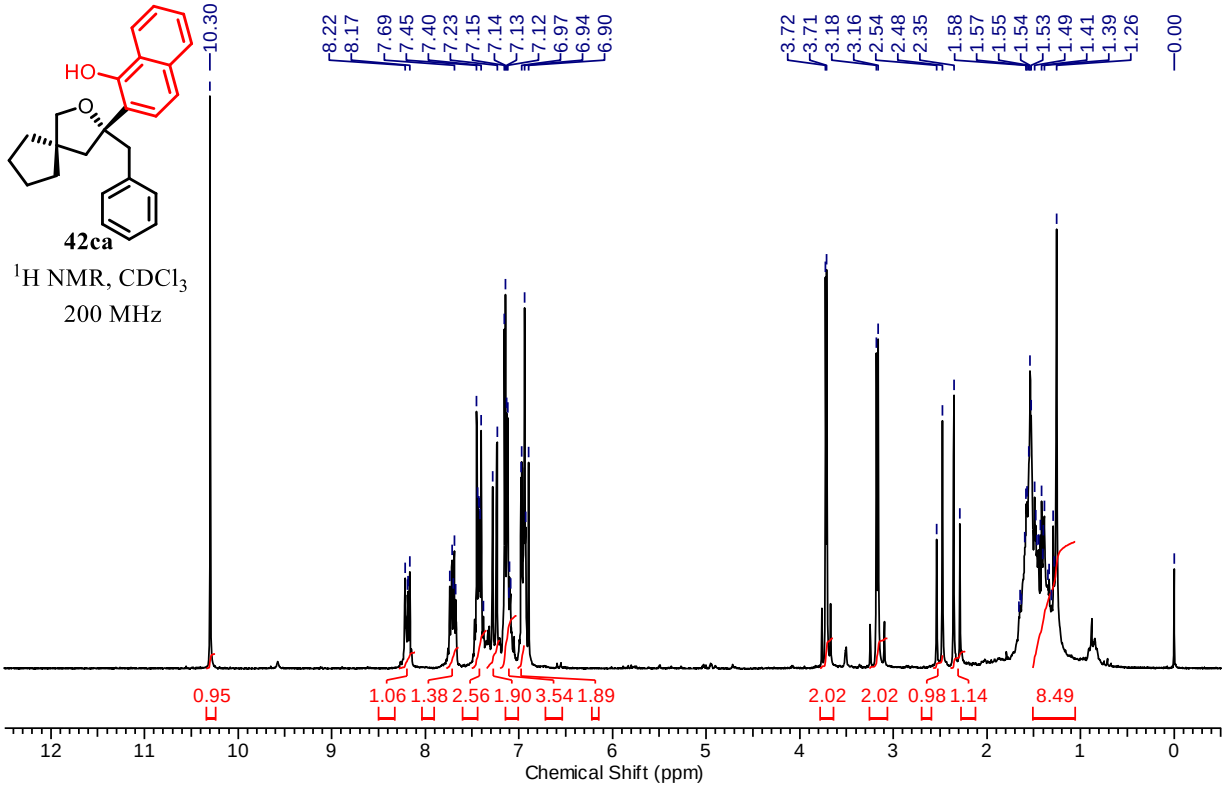
^{1}H NMR spectrum of compound 42ba



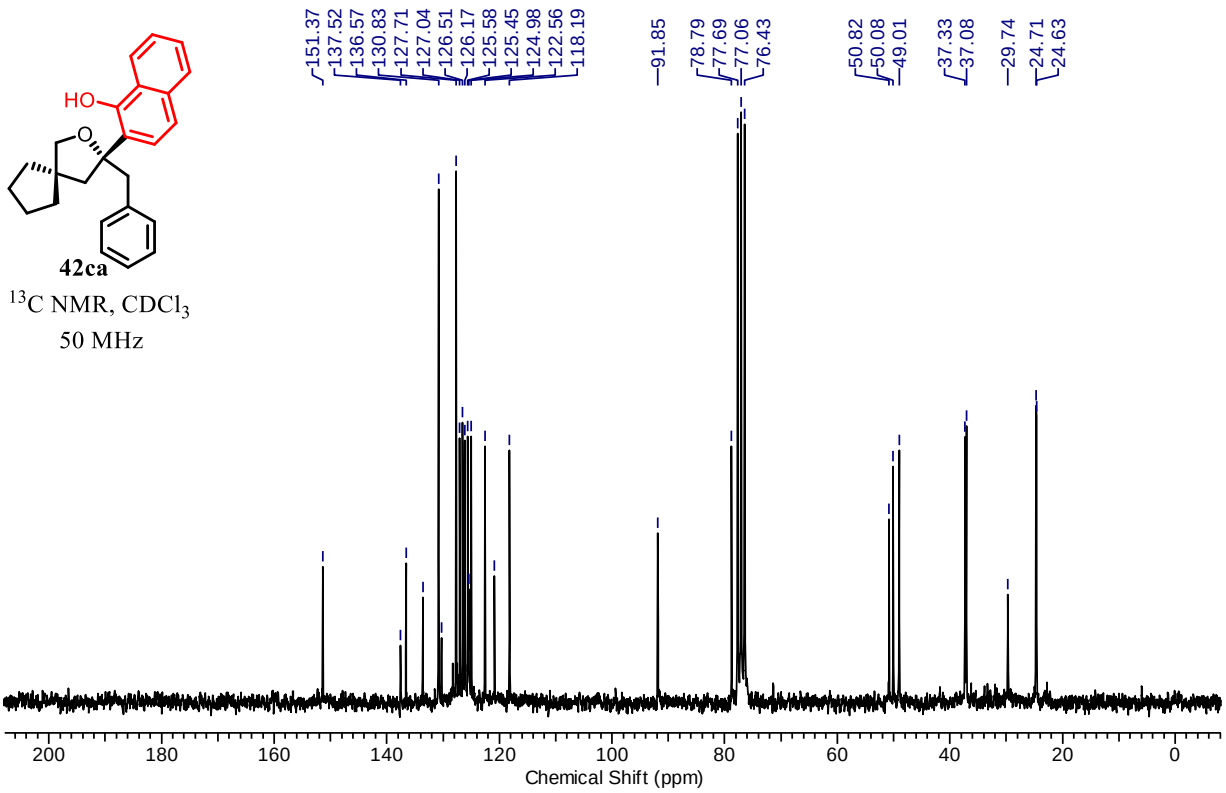
^{13}C NMR spectrum of compound 42ba



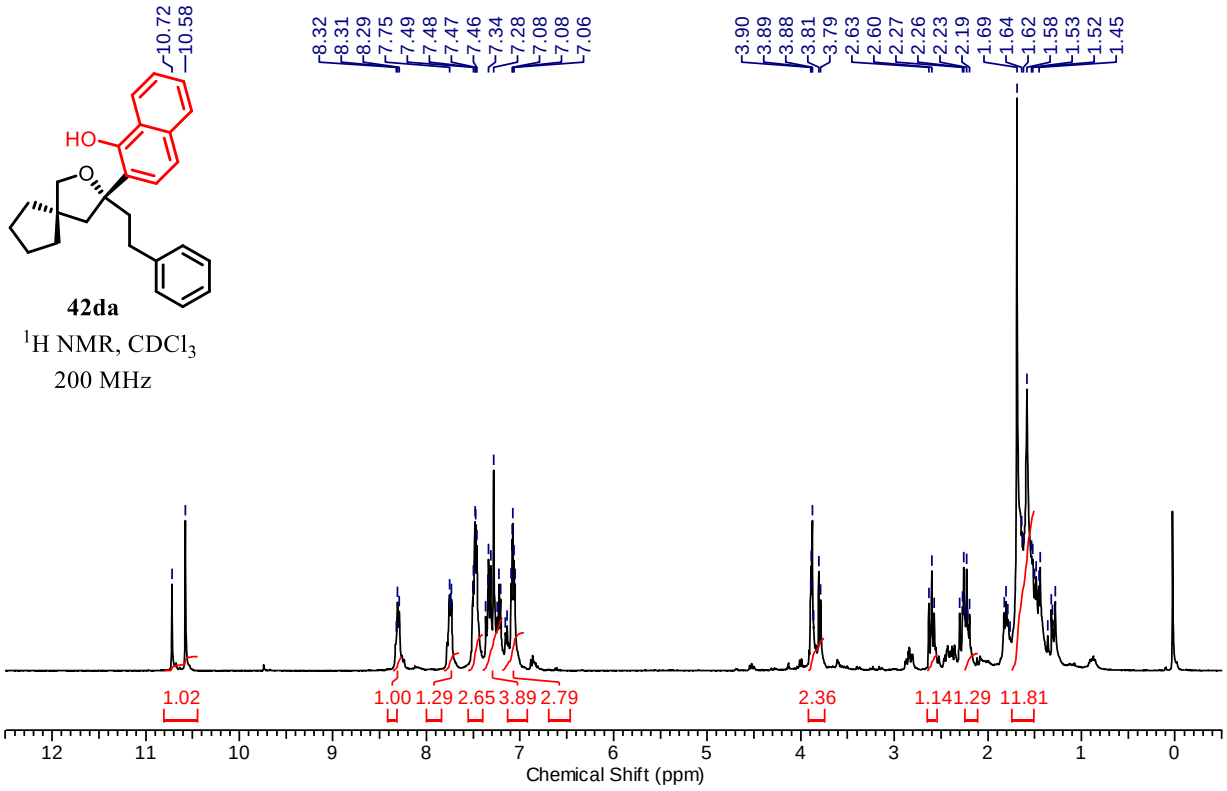
^{1}H NMR spectrum of compound 42ca



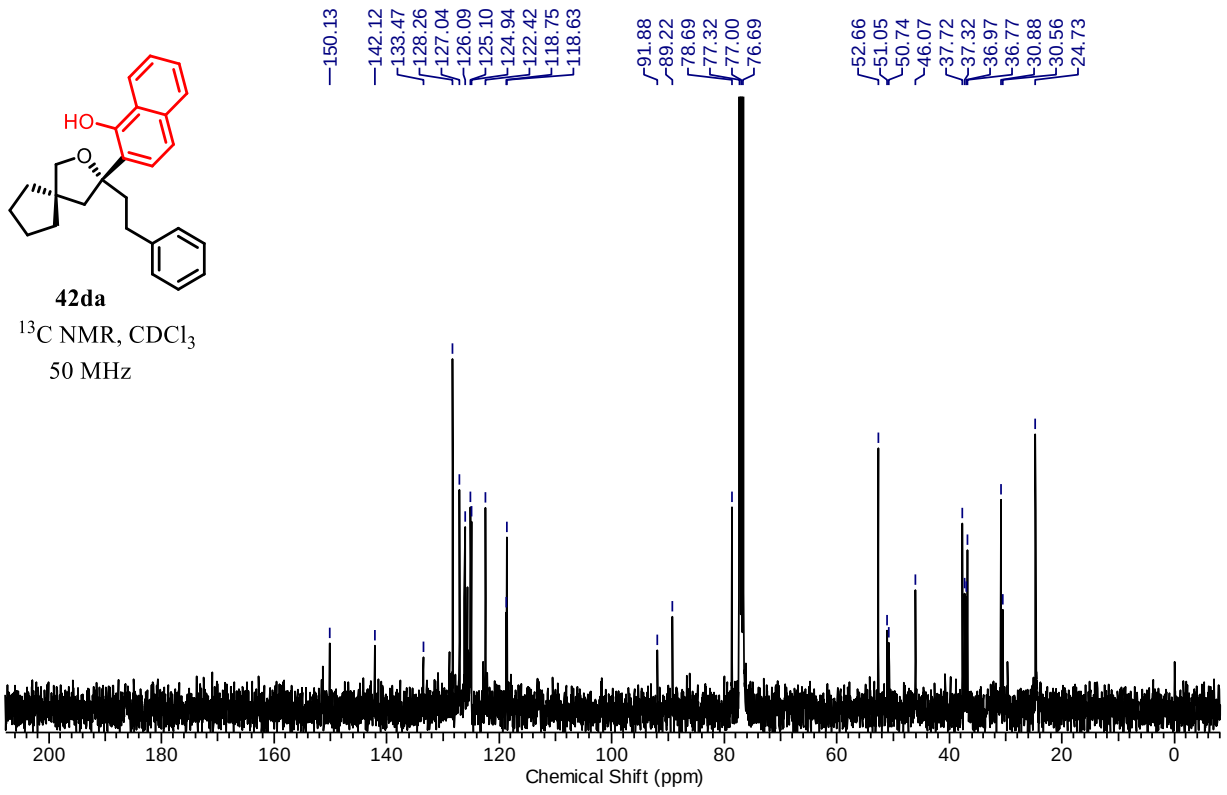
^{13}C NMR spectrum of compound 42ca



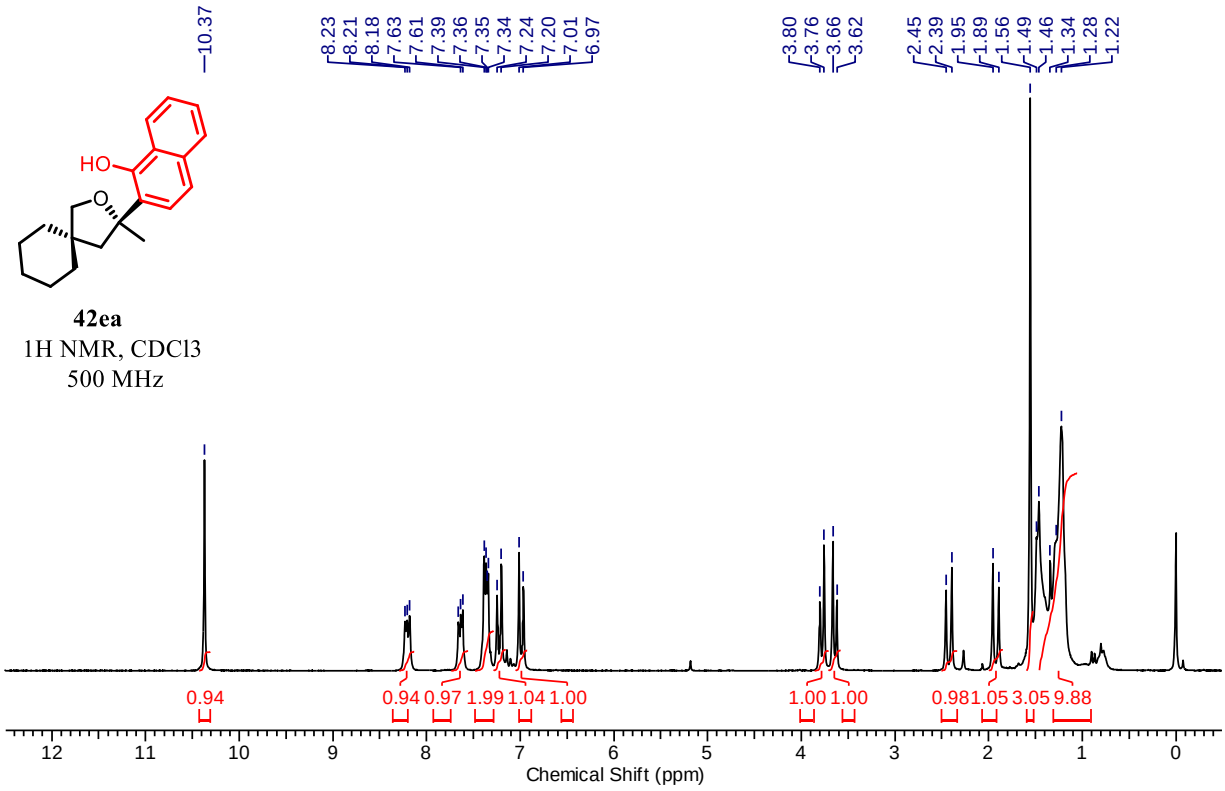
^{1}H NMR spectrum of compound 42da



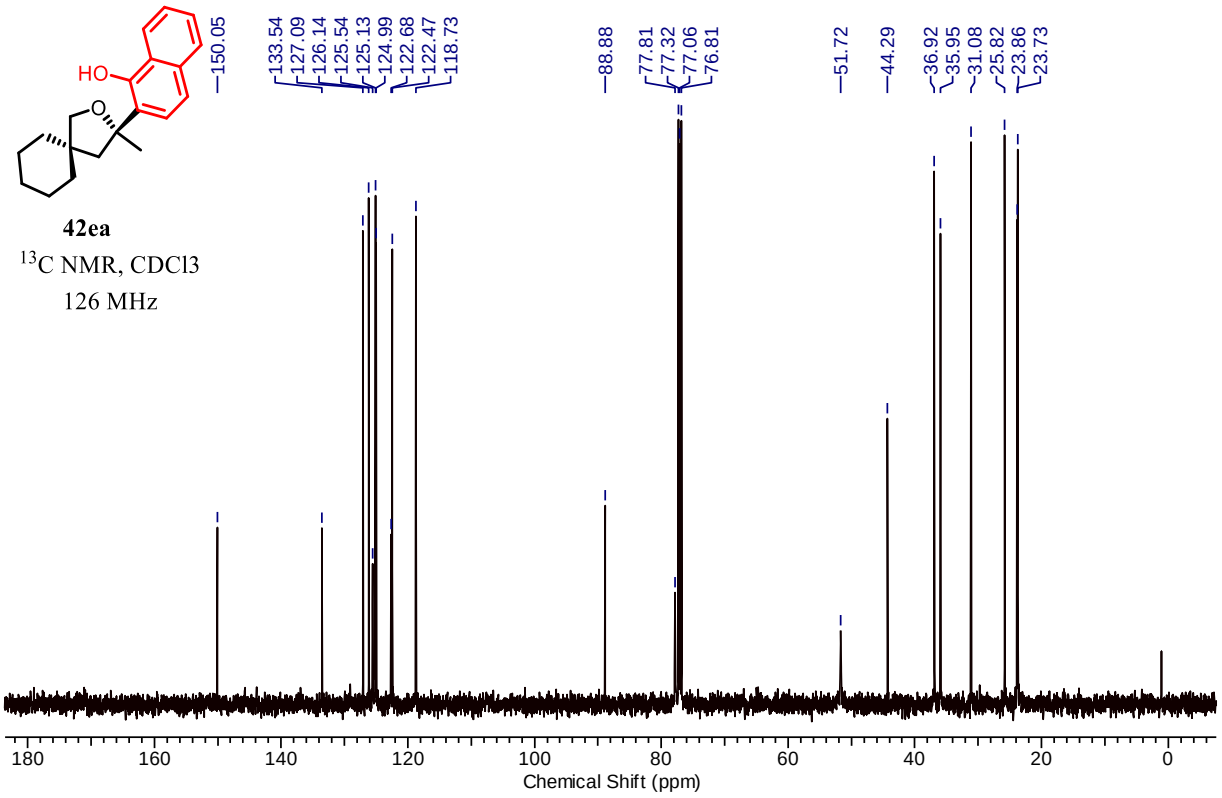
^{13}C NMR spectrum of compound 42da



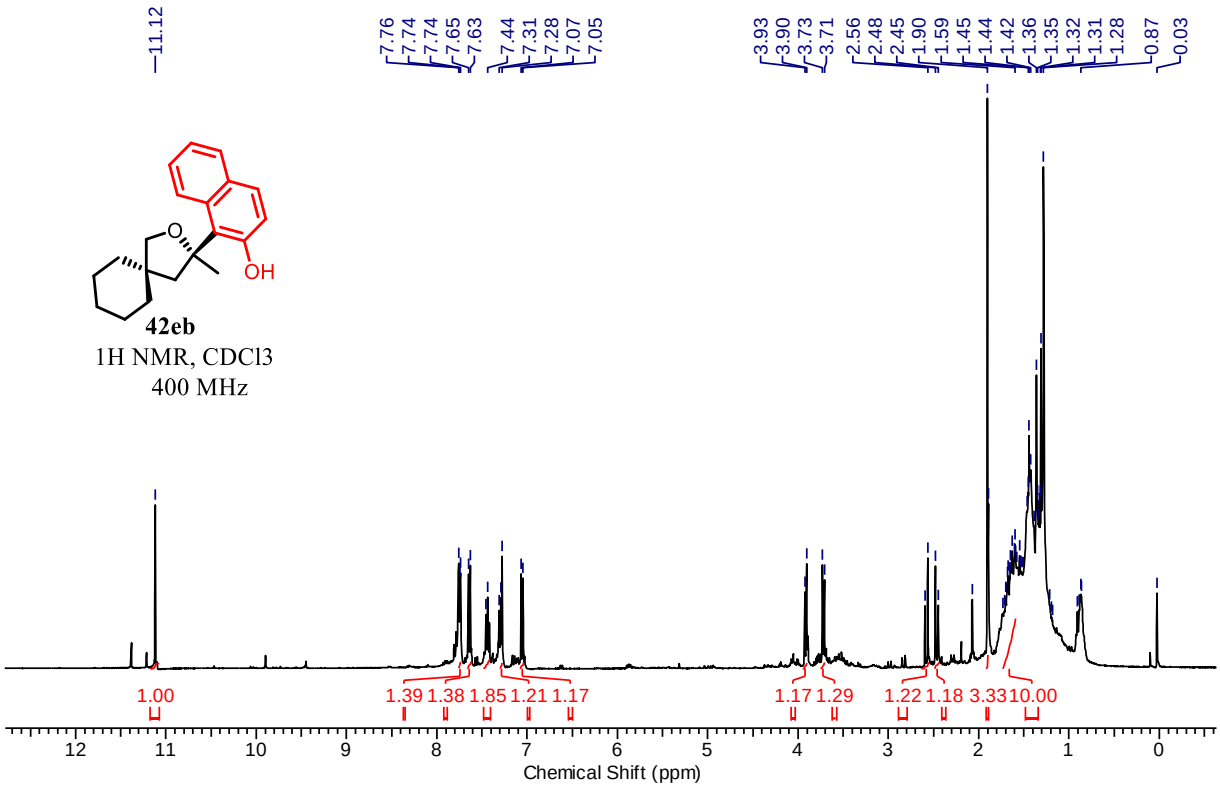
^{1}H NMR spectrum of compound 42ea



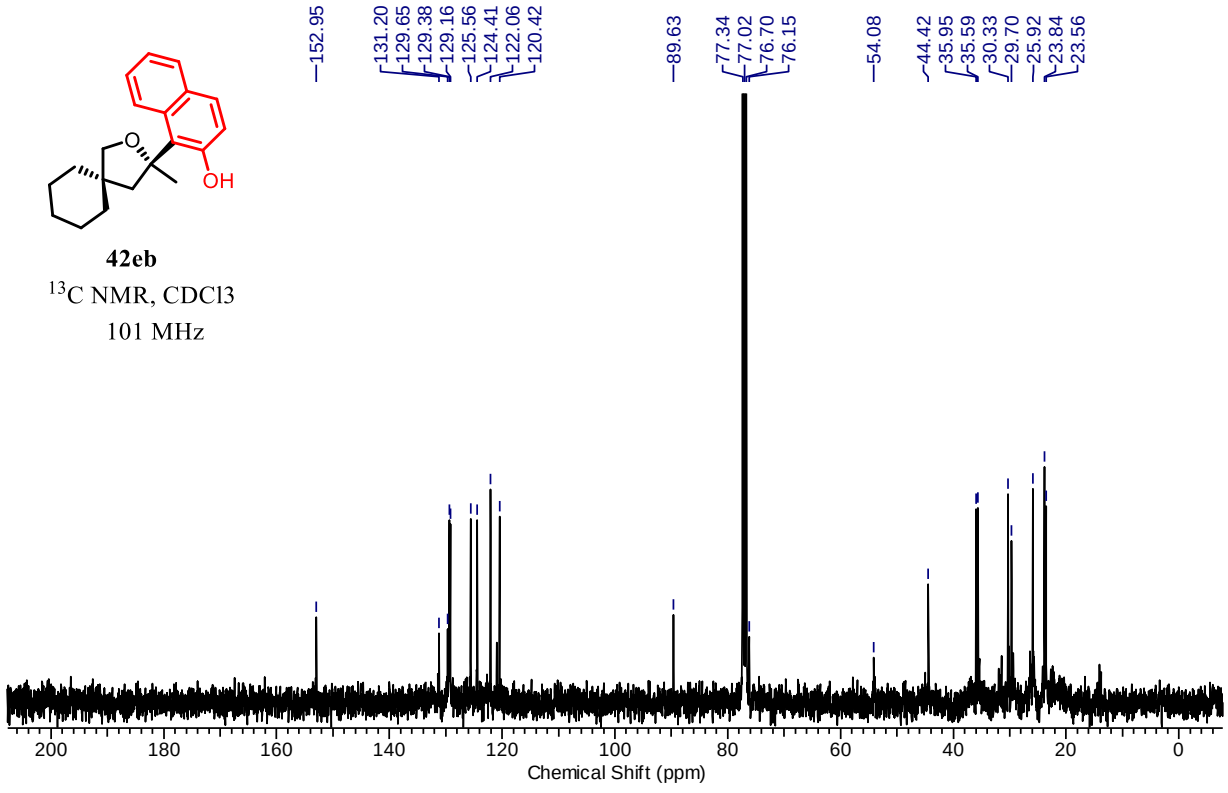
^{13}C NMR spectrum of compound 42ea



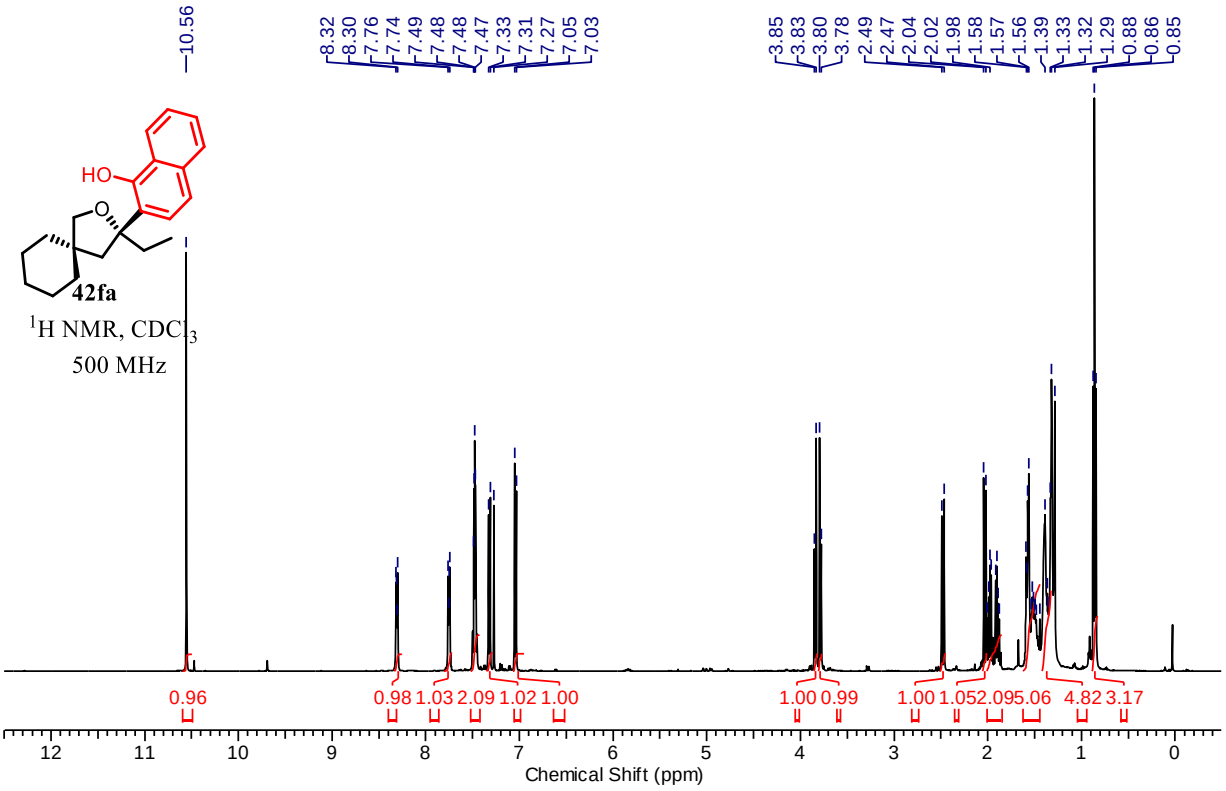
^{1}H NMR spectr um of compound 42eb



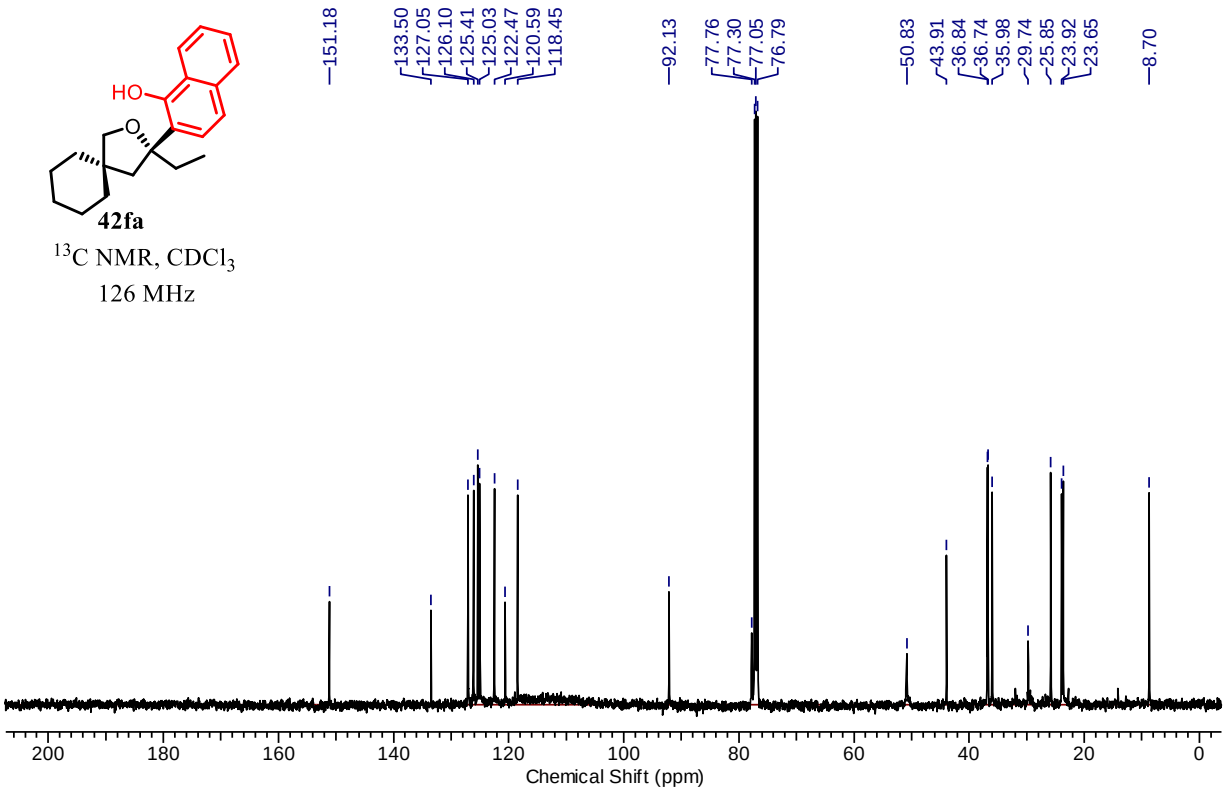
^{13}C NMR spectrum of compound 42eb



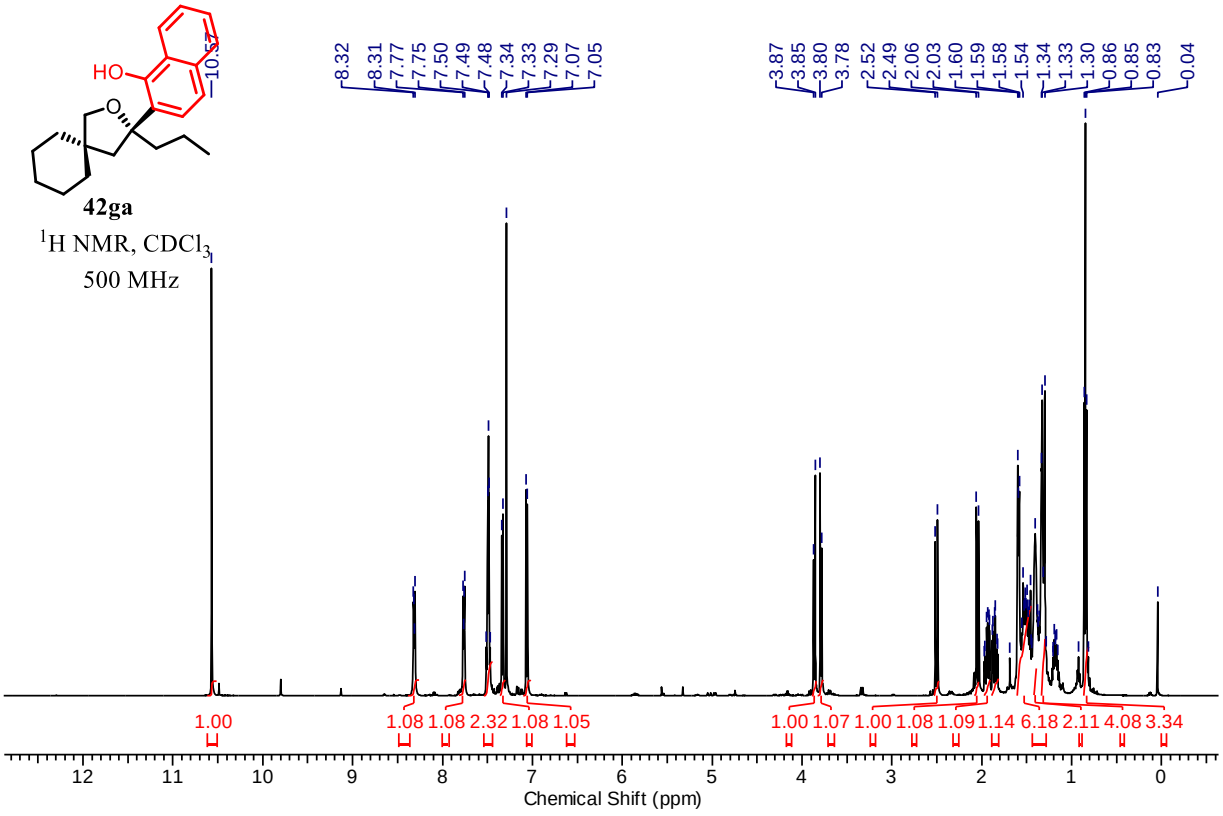
^{1}H NMR spectrum of compound 42fa



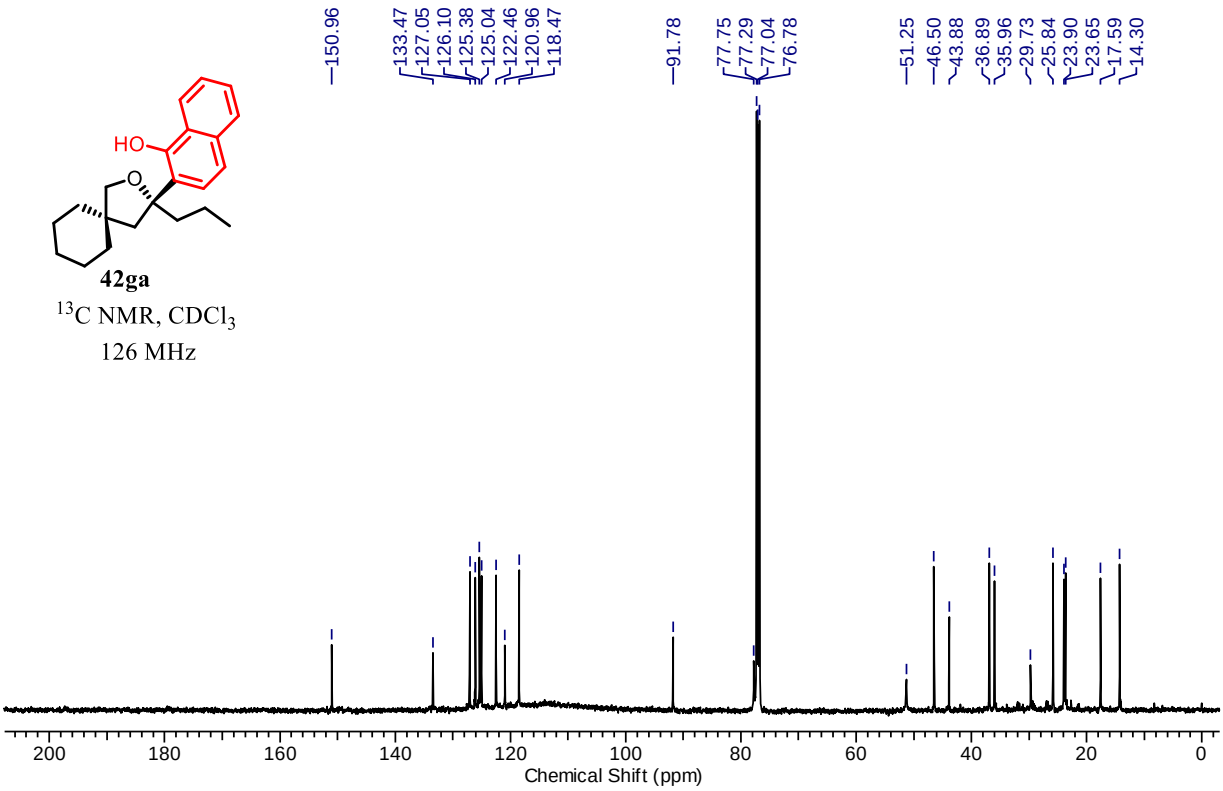
^{13}C NMR spectrum of compound 42fa



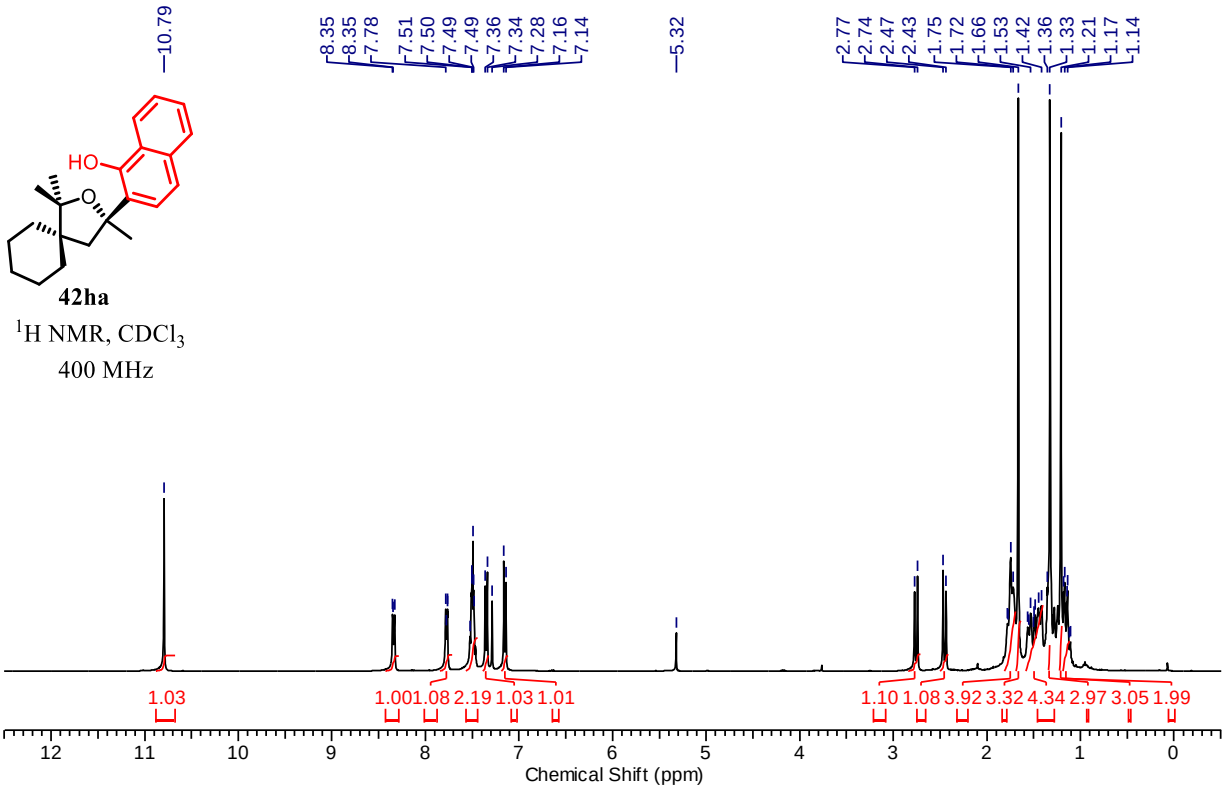
^{1}H NMR spectrum of compound 42ga



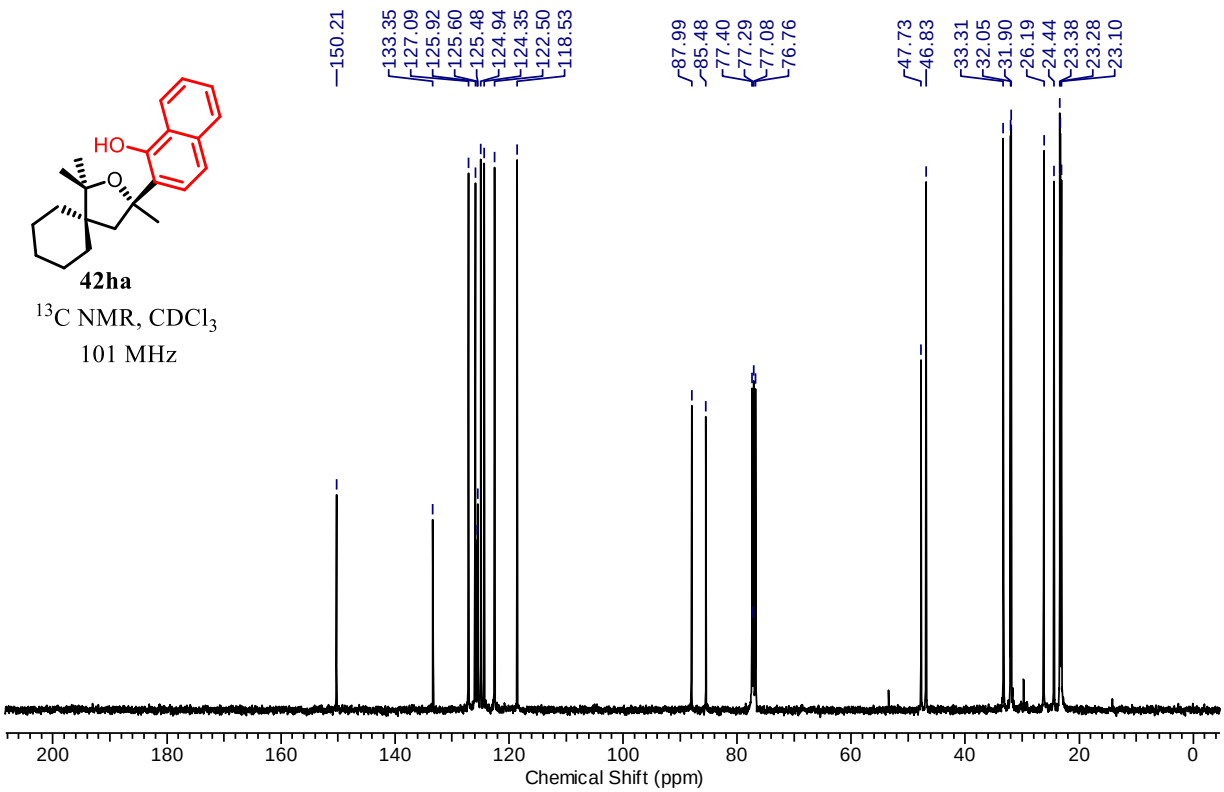
^{13}C NMR spectrum of compound 42ga



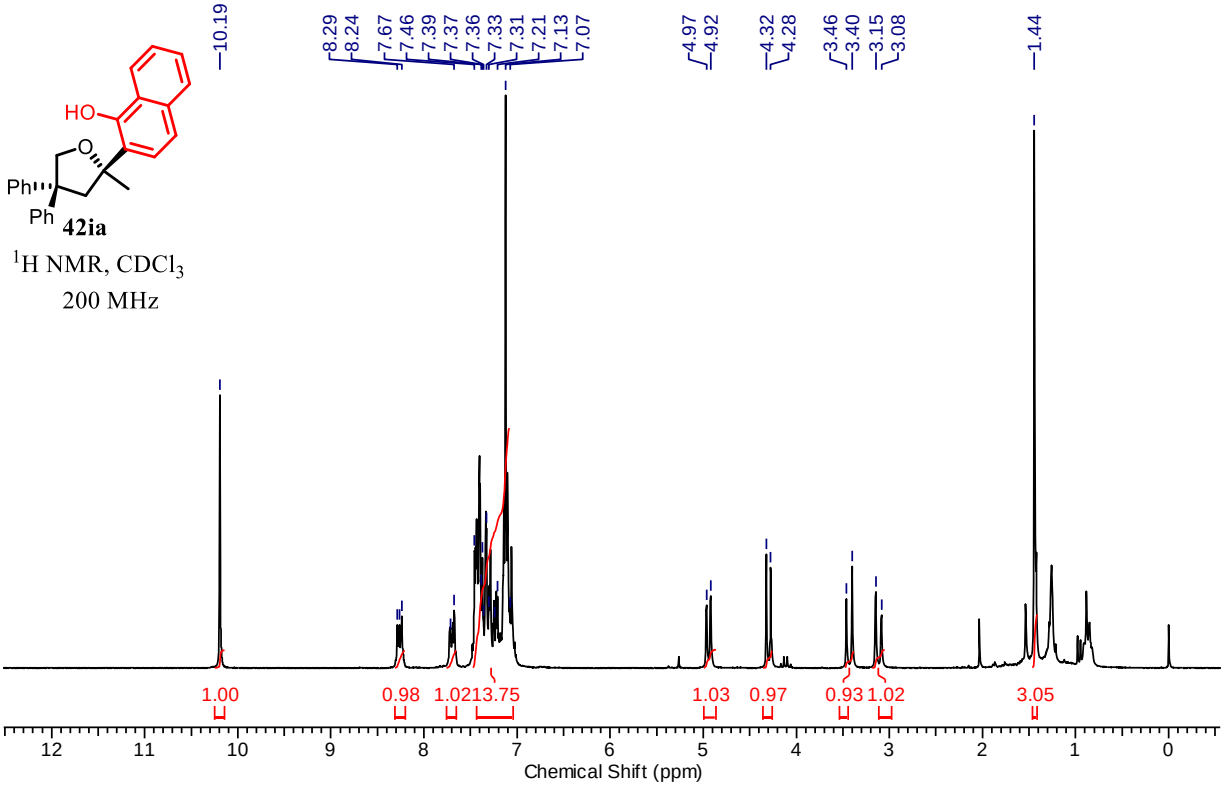
^{1}H NMR spectrum of compound 42ha



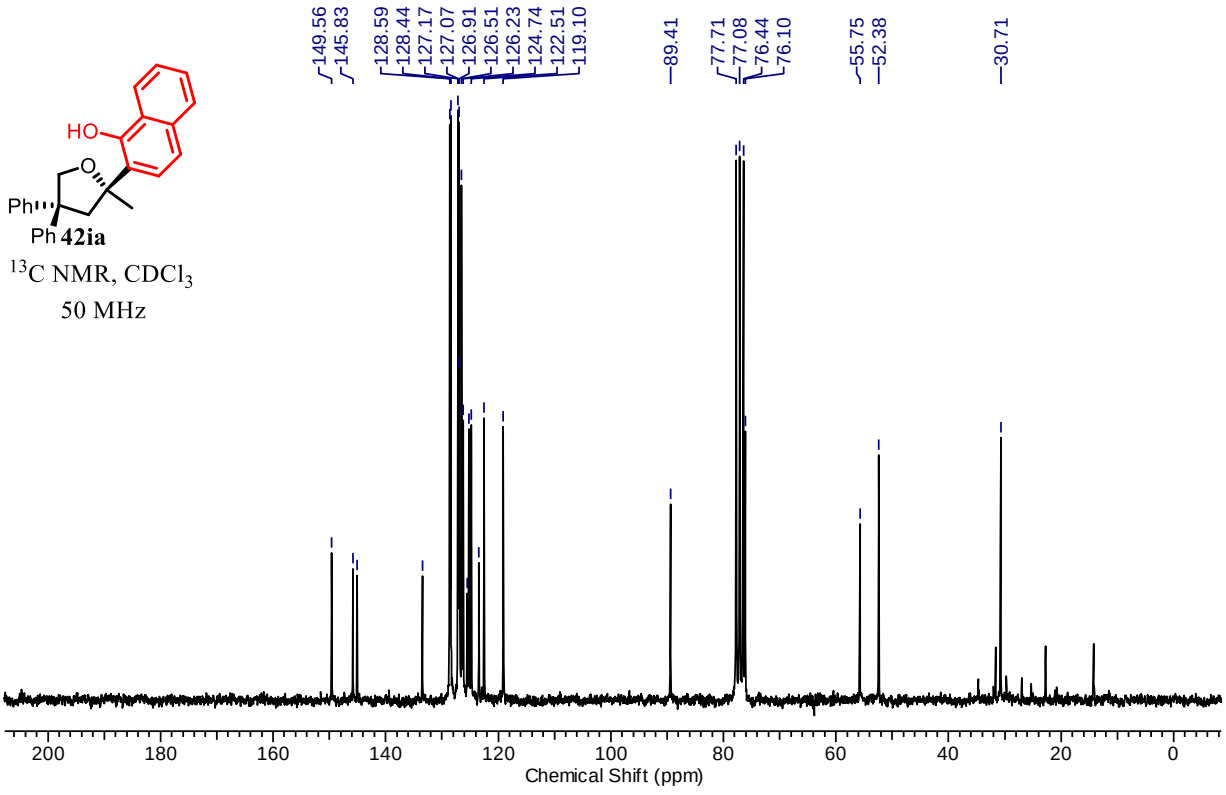
^{13}C NMR spectrum of compound 42ha



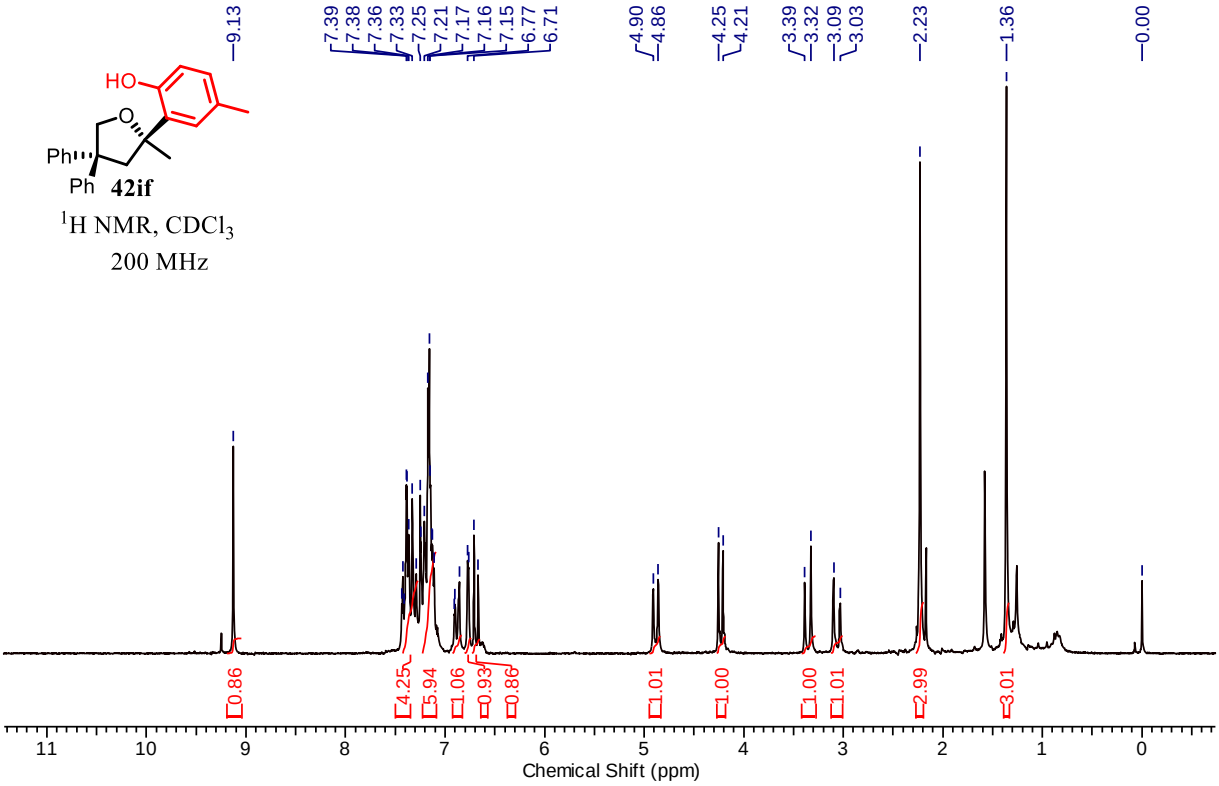
^{1}H NMR spectrum of compound 42ia



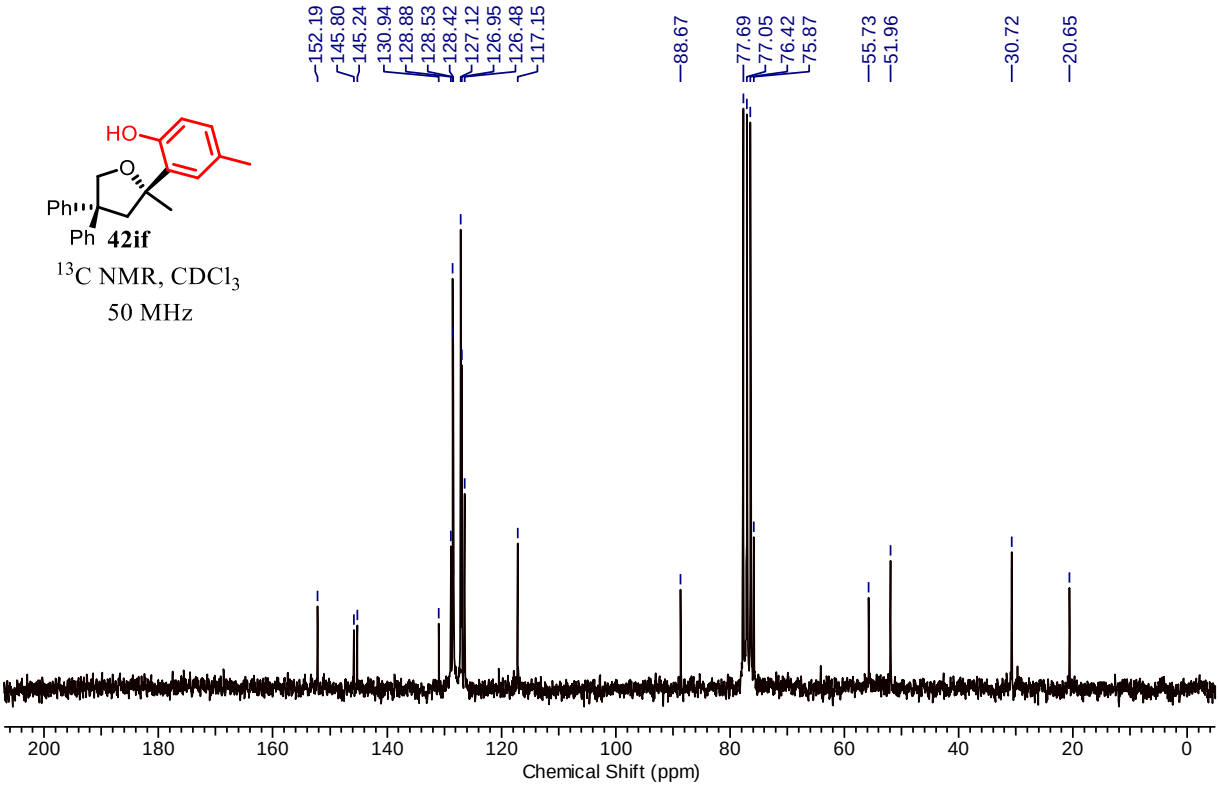
^{13}C NMR spectrum of compound 42ia



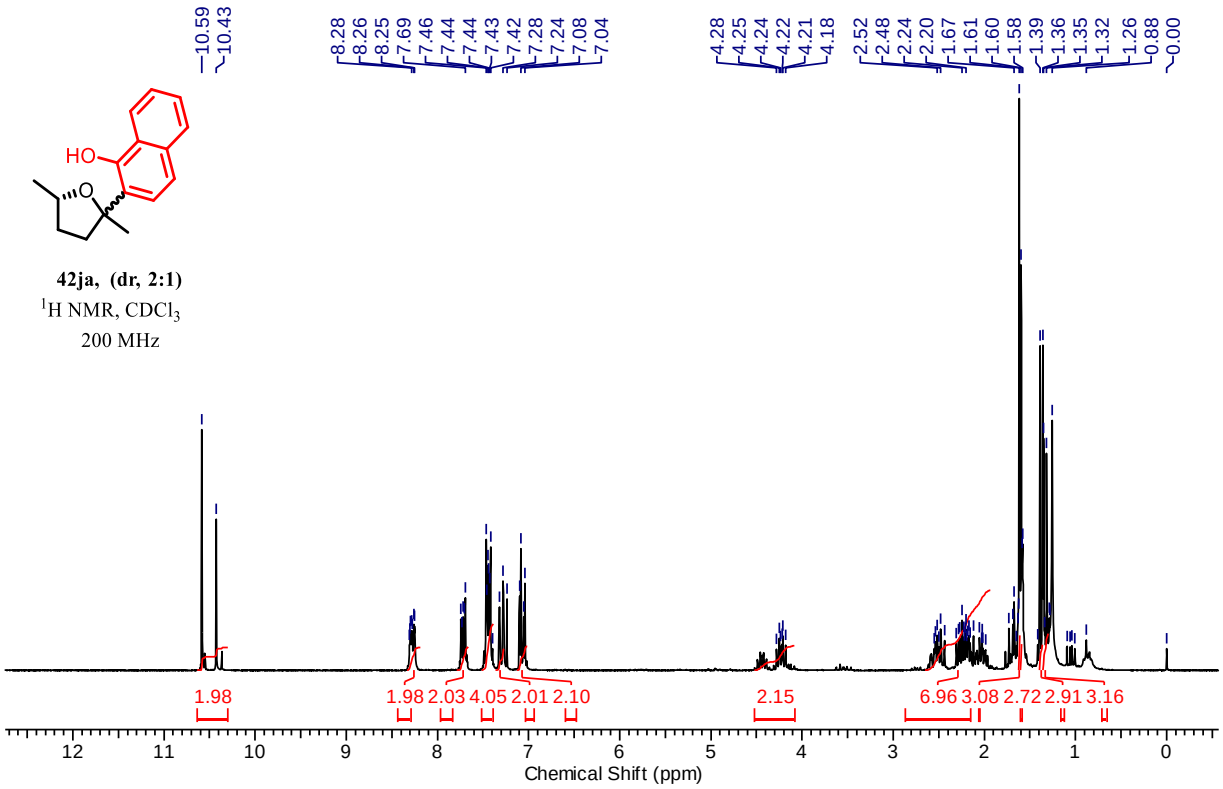
^{1}H NMR spectrum of compound 42if



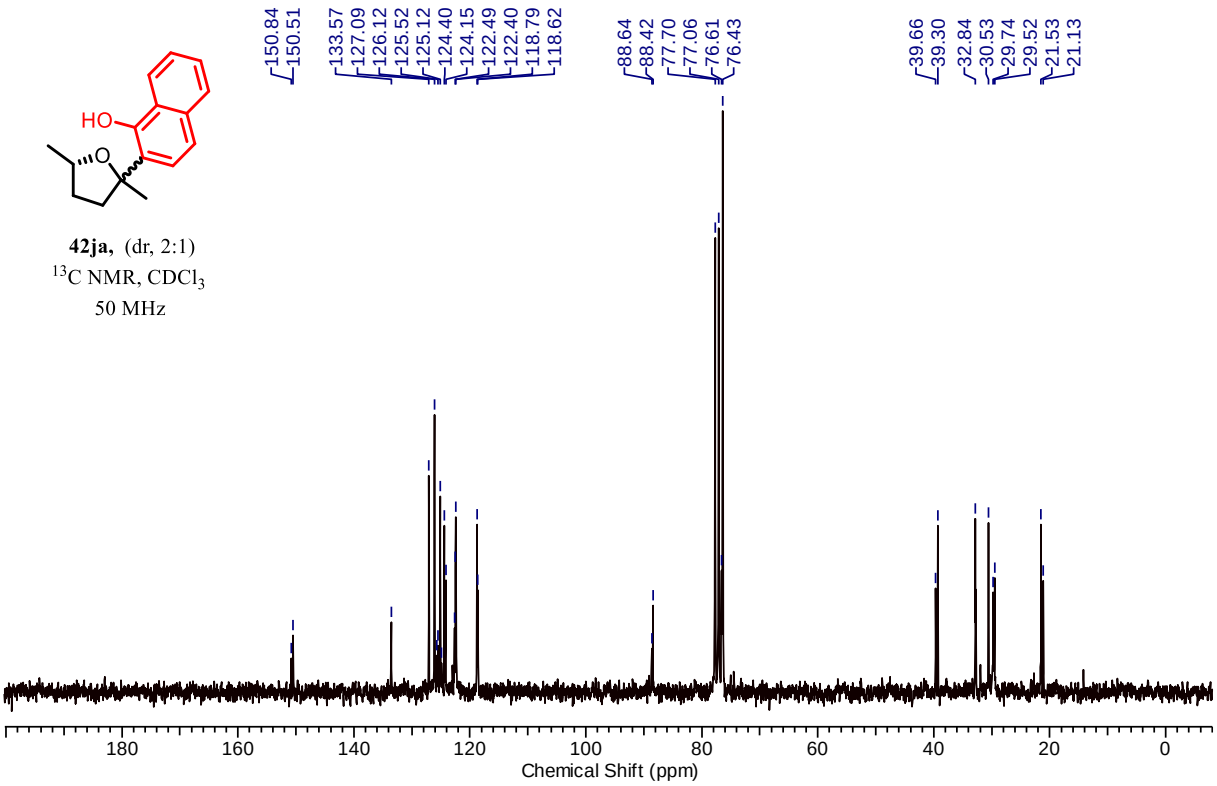
^{13}C NMR spectrum of compound 42if



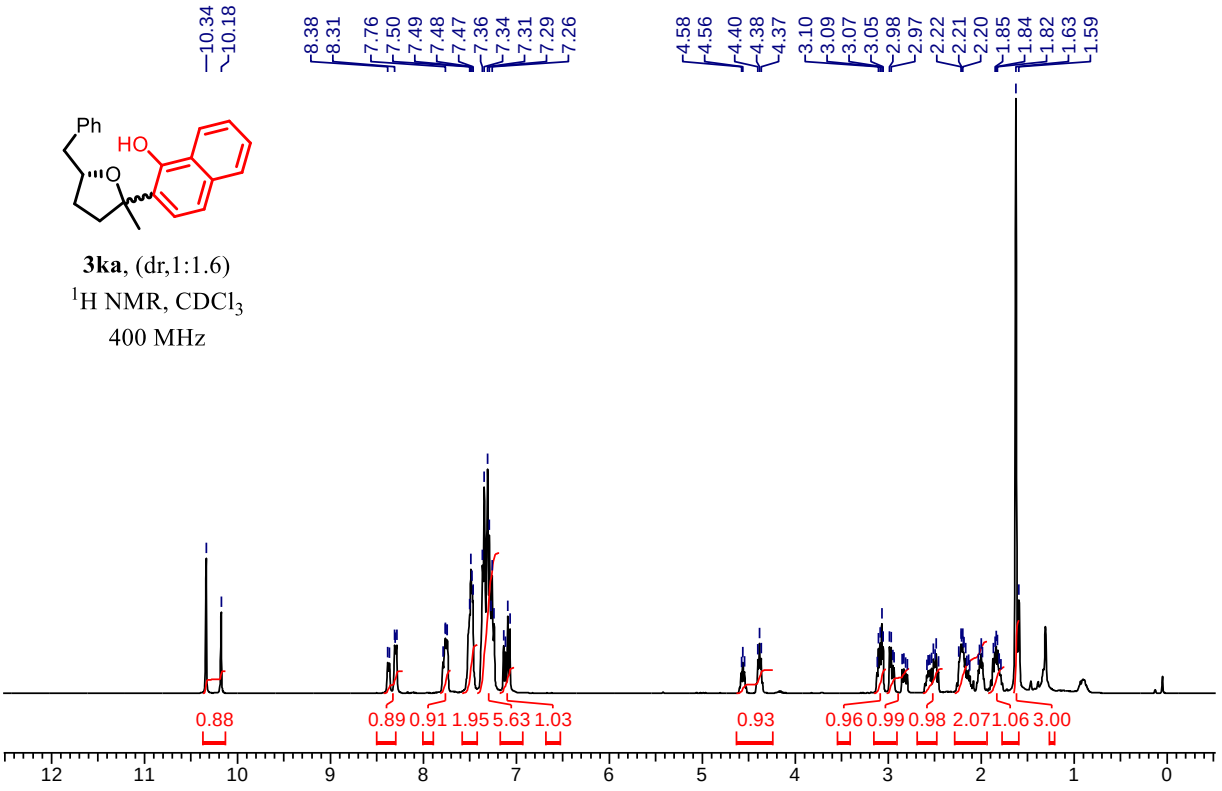
^{1}H NMR spectrum of compound 42ja



^{13}C NMR spectrum of compound 42ja

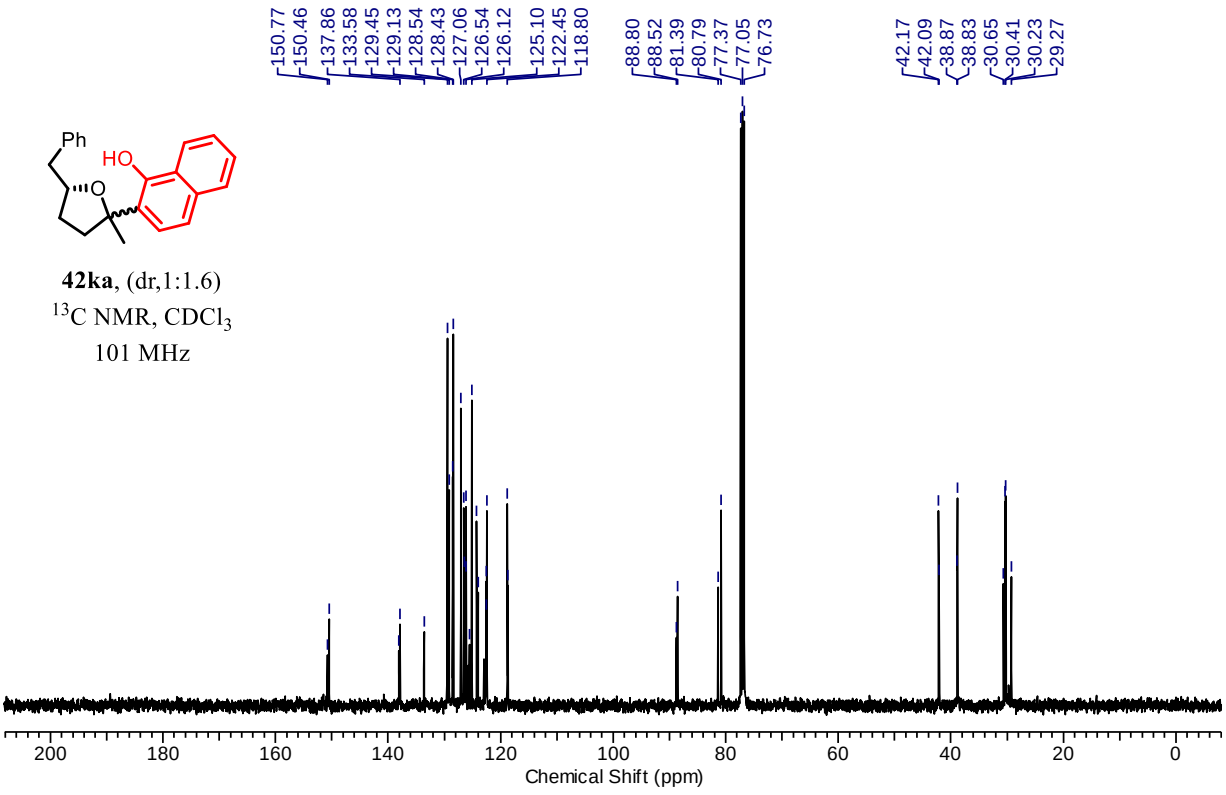


^{1}H NMR spectrum of compound 42ka



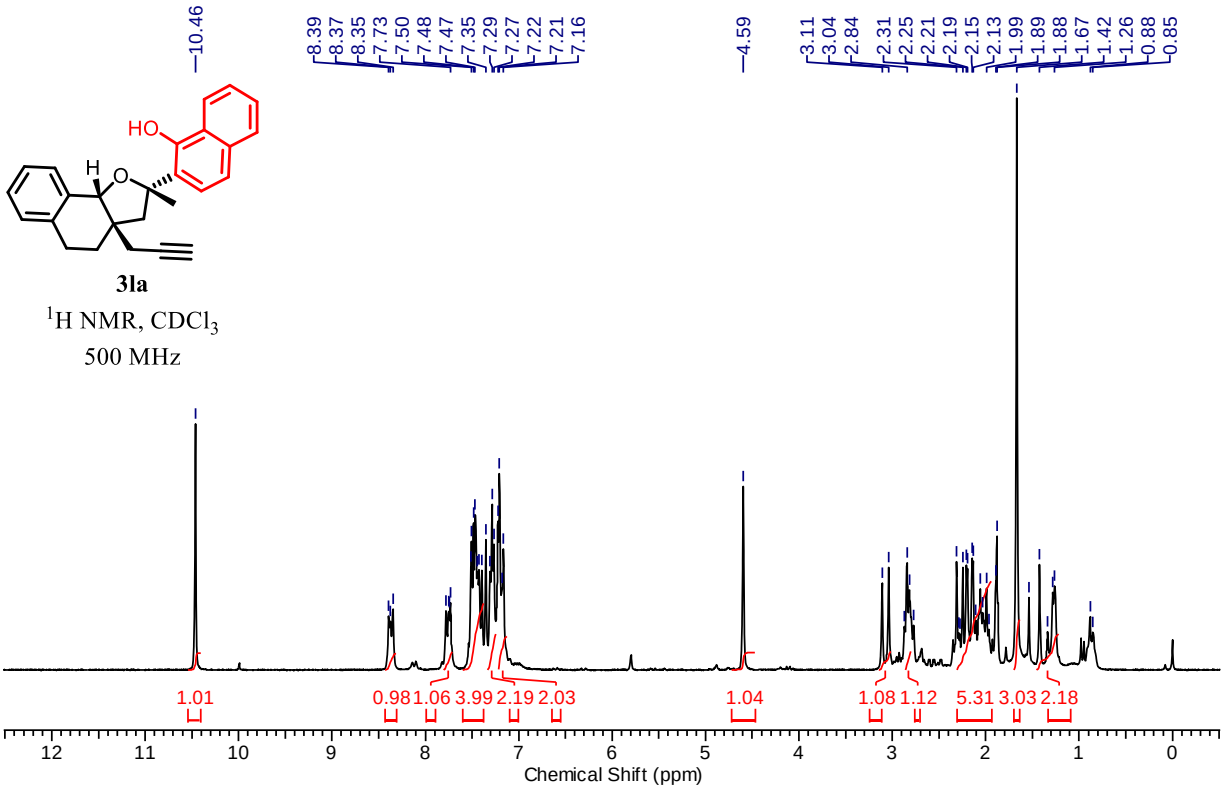
3ka, (dr,1:1.6)
^{1}H NMR, $CDCl_3$
400 MHz

^{13}C NMR spectrum of compound 42ka



42ka, (dr,1:1.6)
^{13}C NMR, $CDCl_3$
101 MHz

^{1}H NMR spectrum of compound 42la

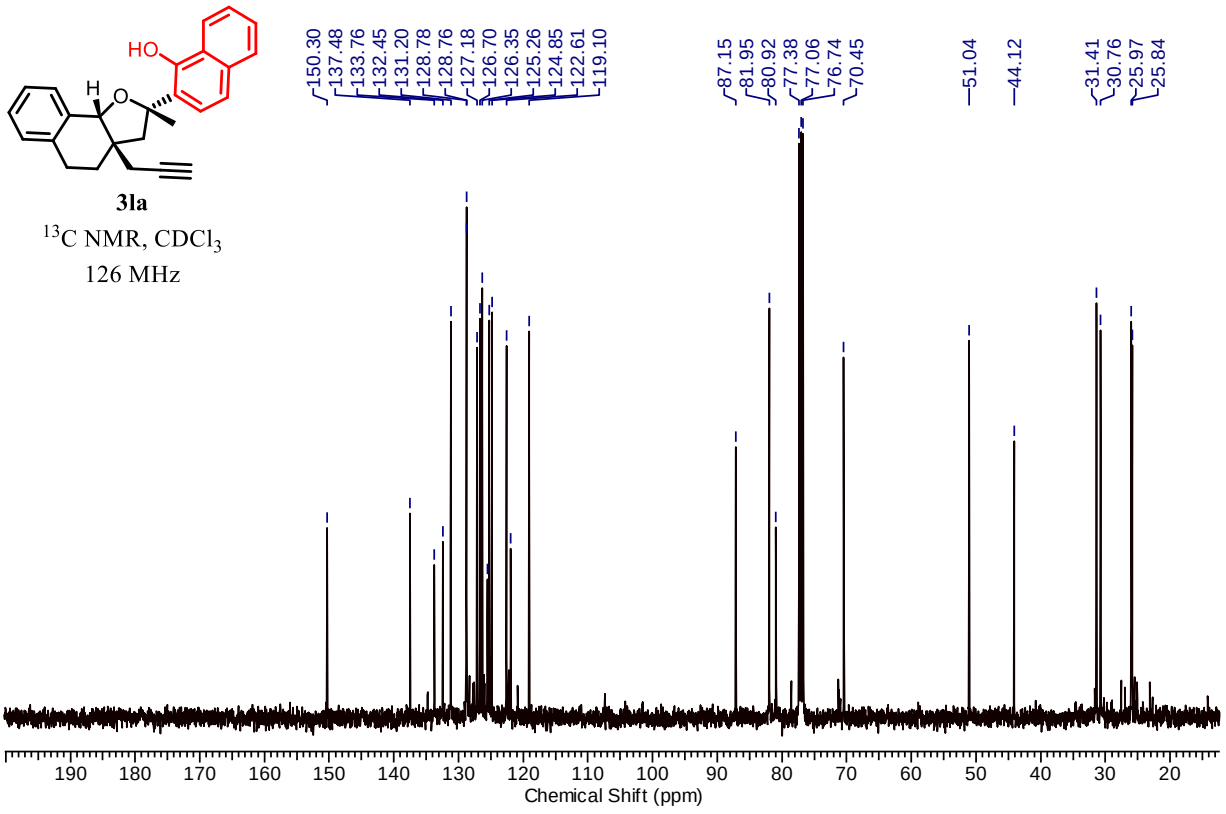


3la

^{1}H NMR, $CDCl_3$

500 MHz

^{13}C NMR spectrum of compound 42la

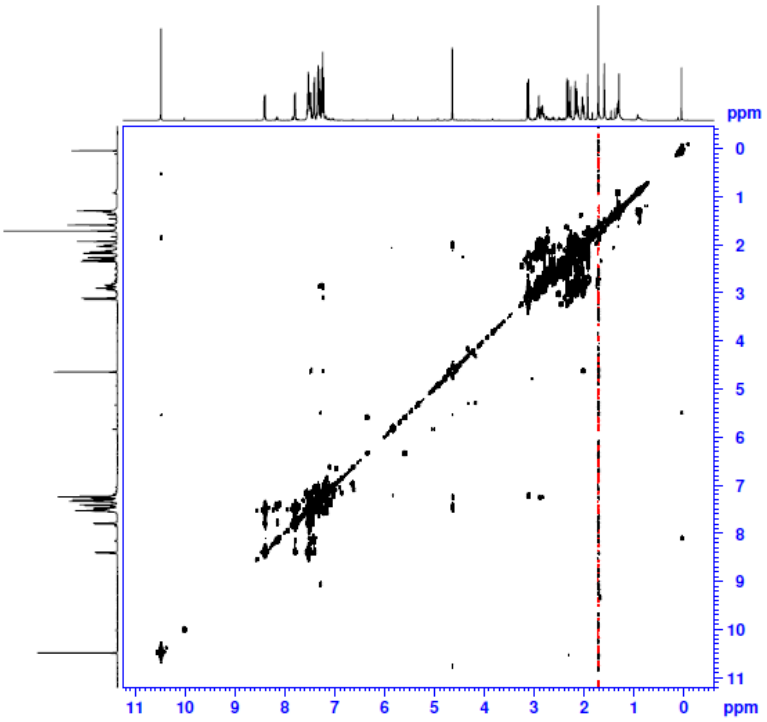


3la

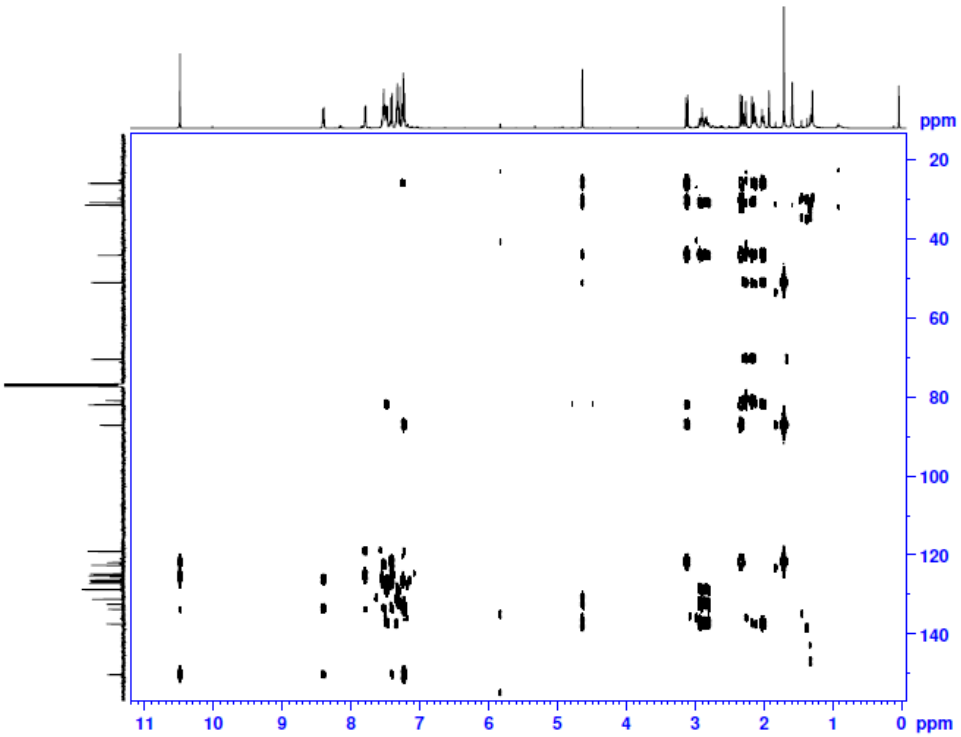
^{13}C NMR, $CDCl_3$

126 MHz

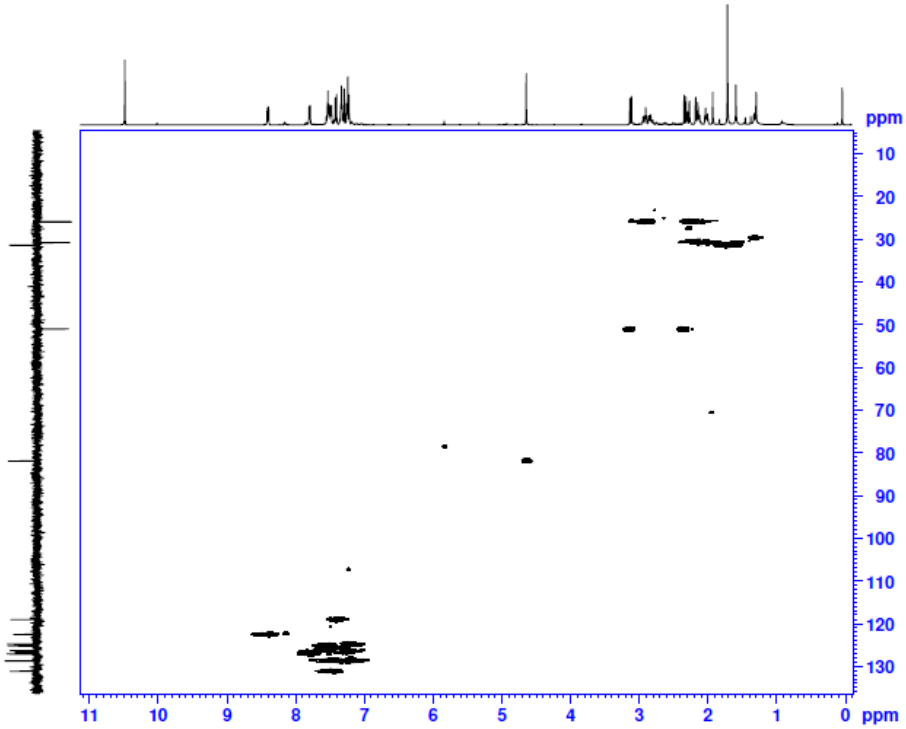
COSY **(42la):**



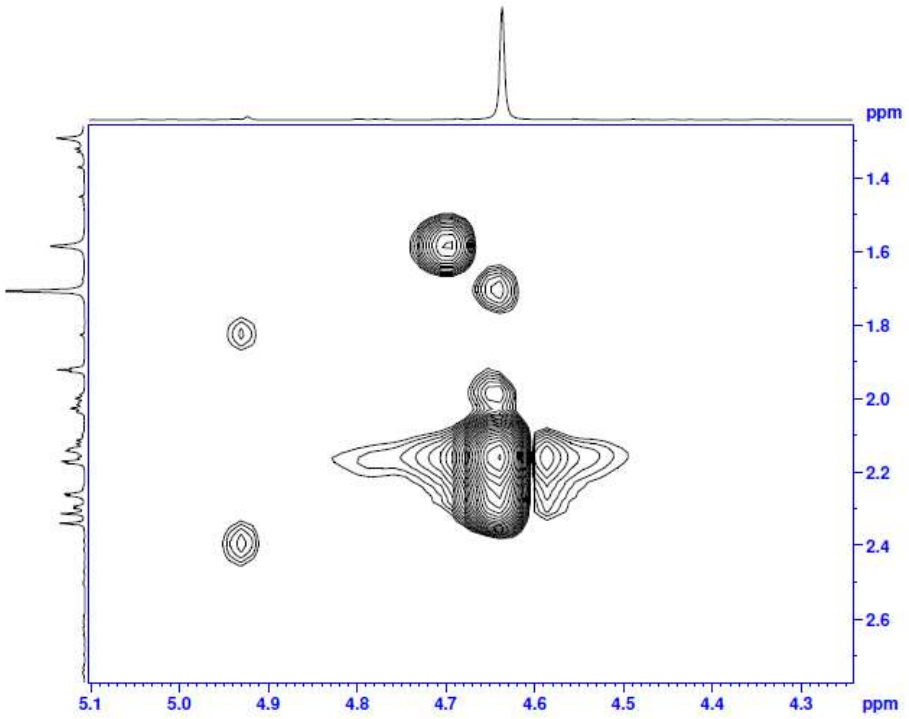
HMBC **(42la):**



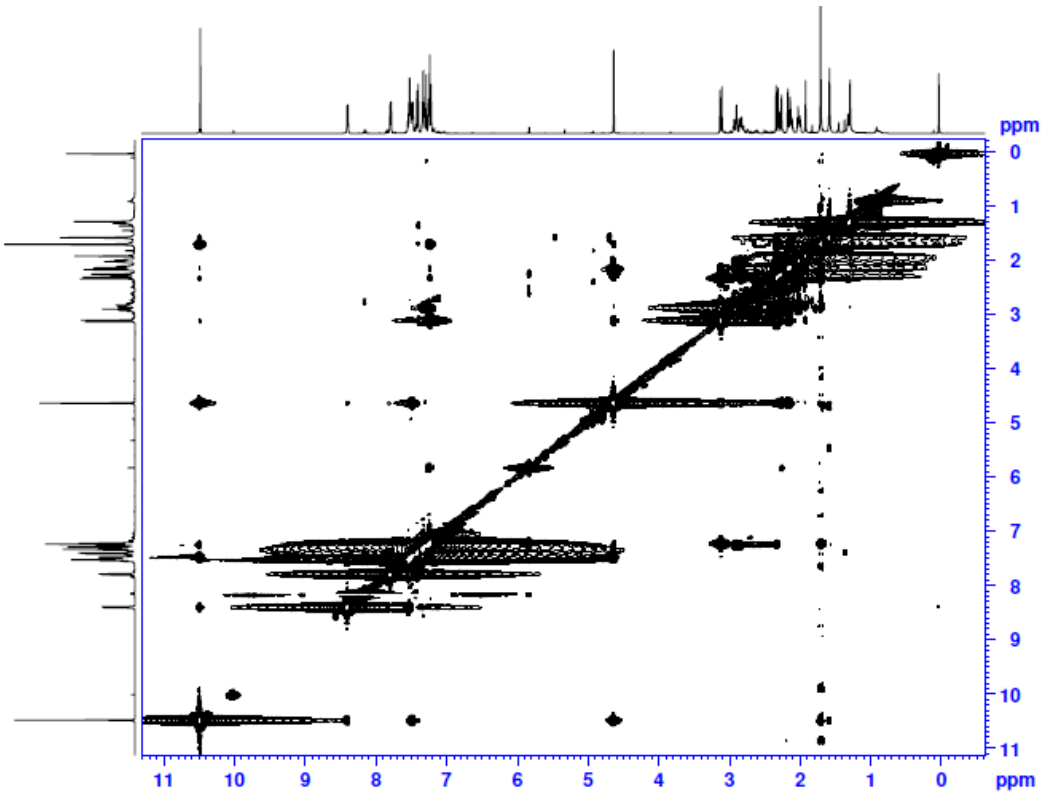
HSQC **(42la):**



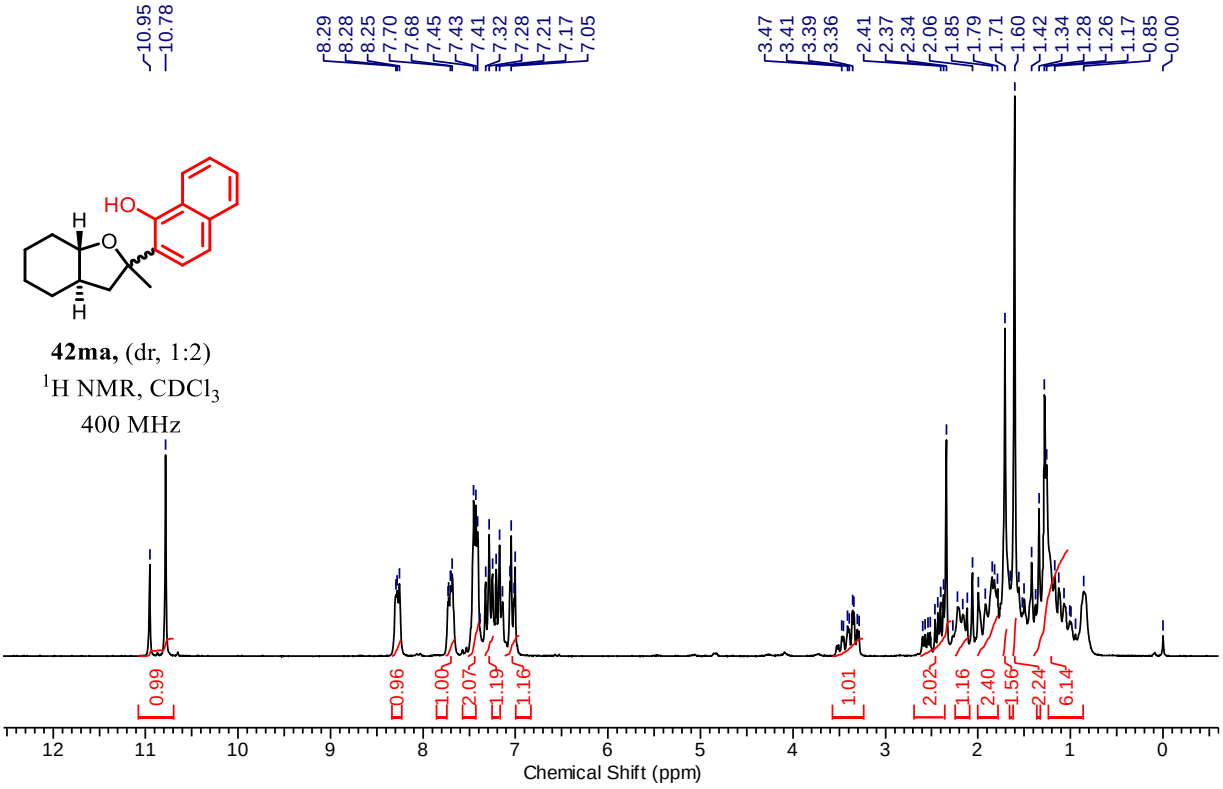
Expanded NOESY **(42la):**



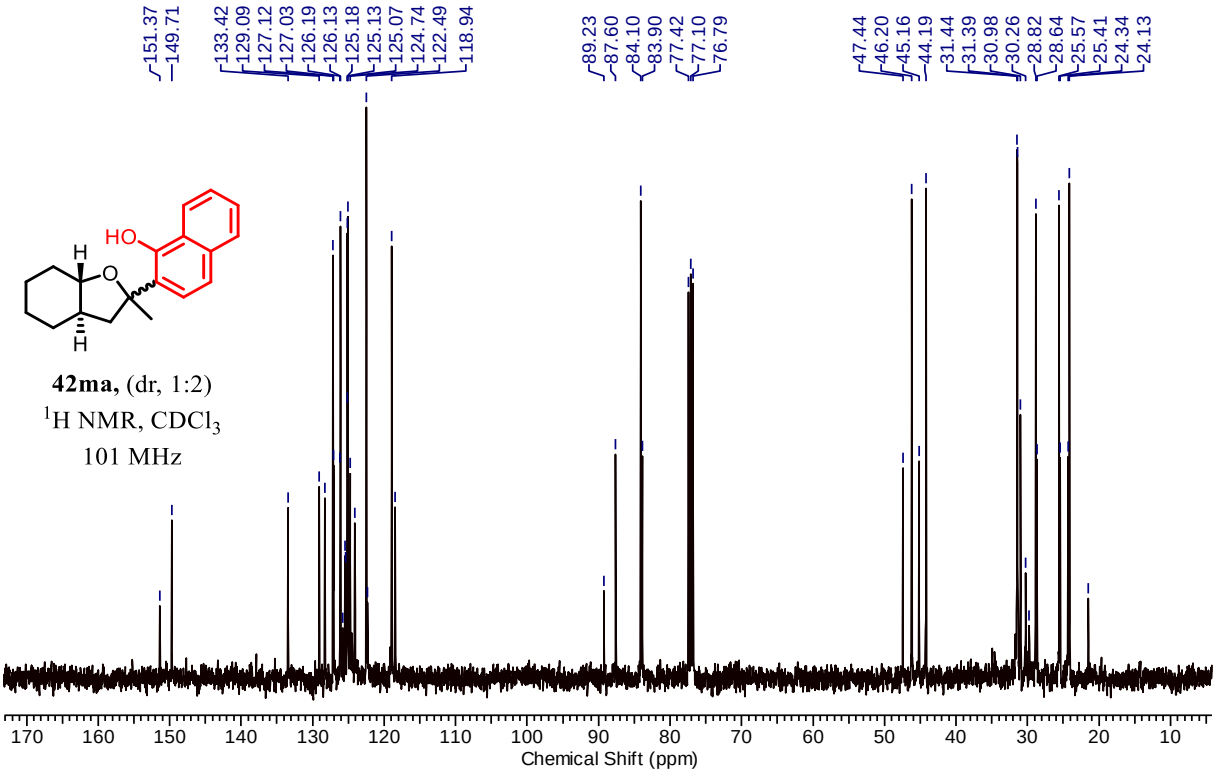
NOESY **(42la):**



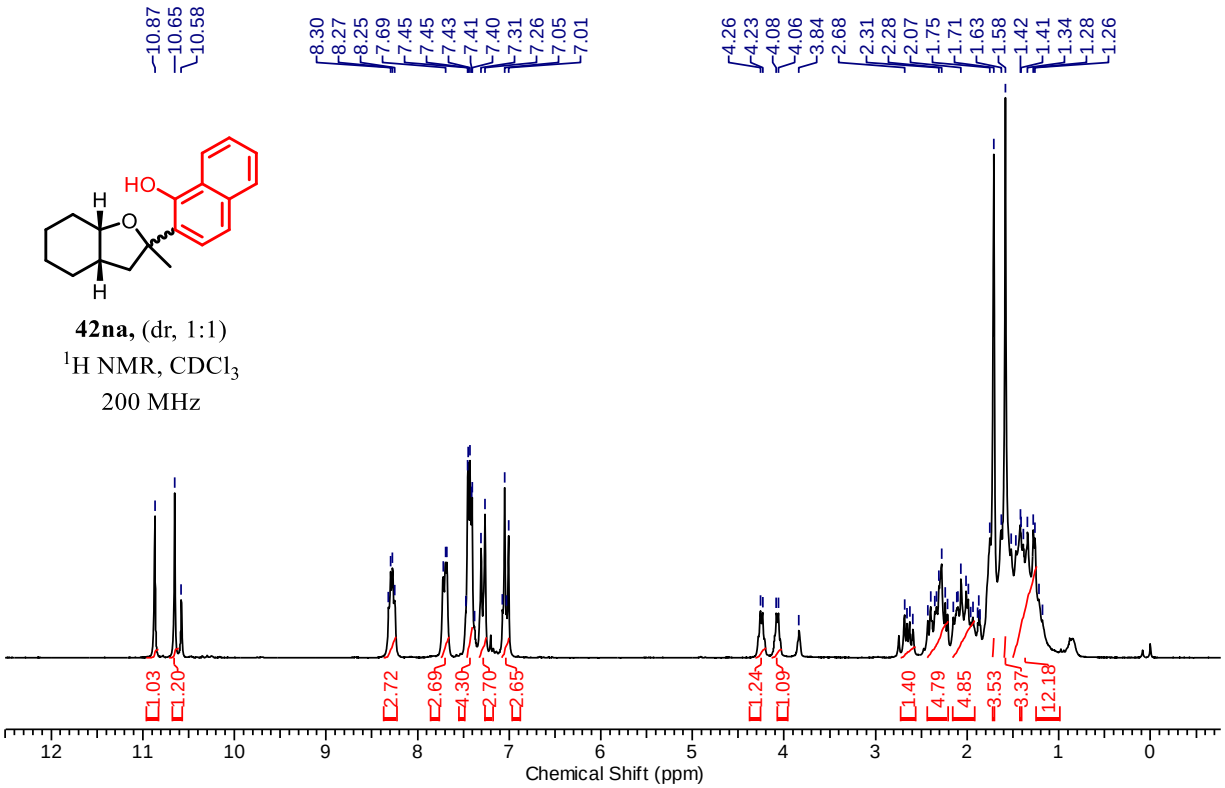
^{1}H NMR spectrum of compound 42ma



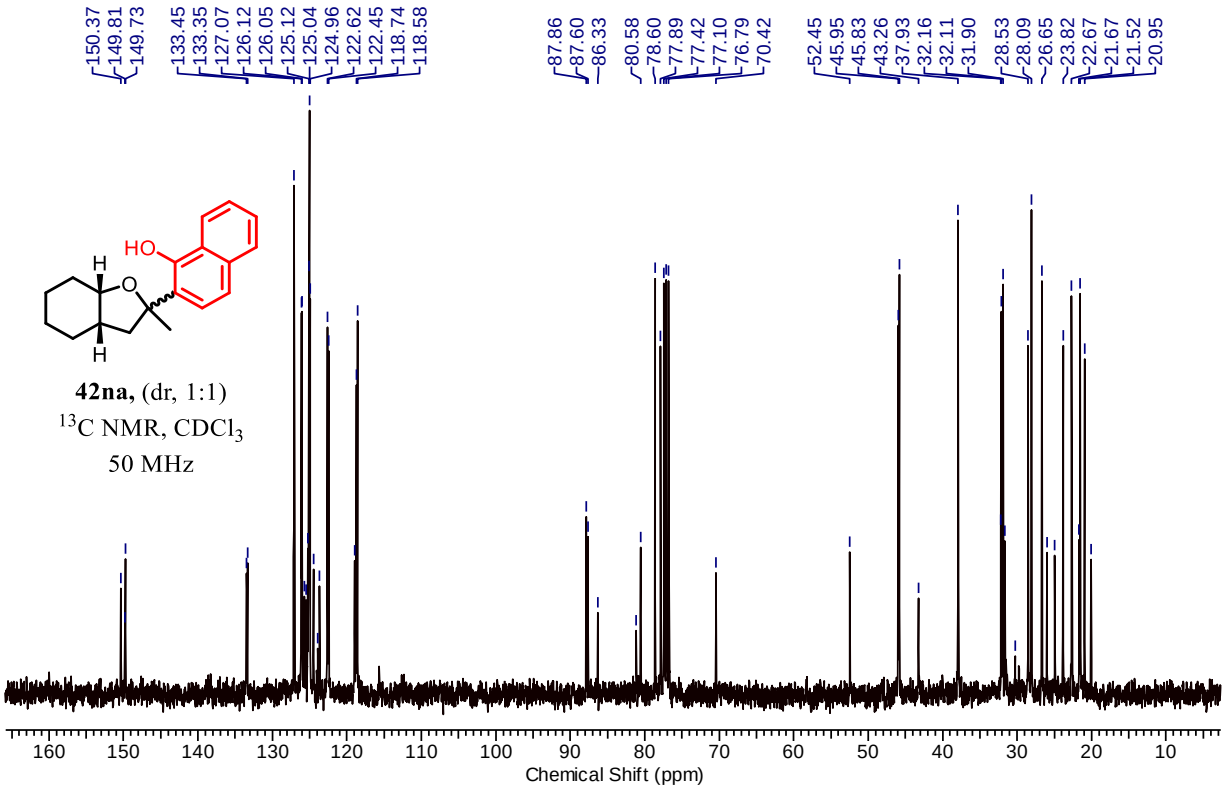
^{13}C NMR spectrum of compound 42ma



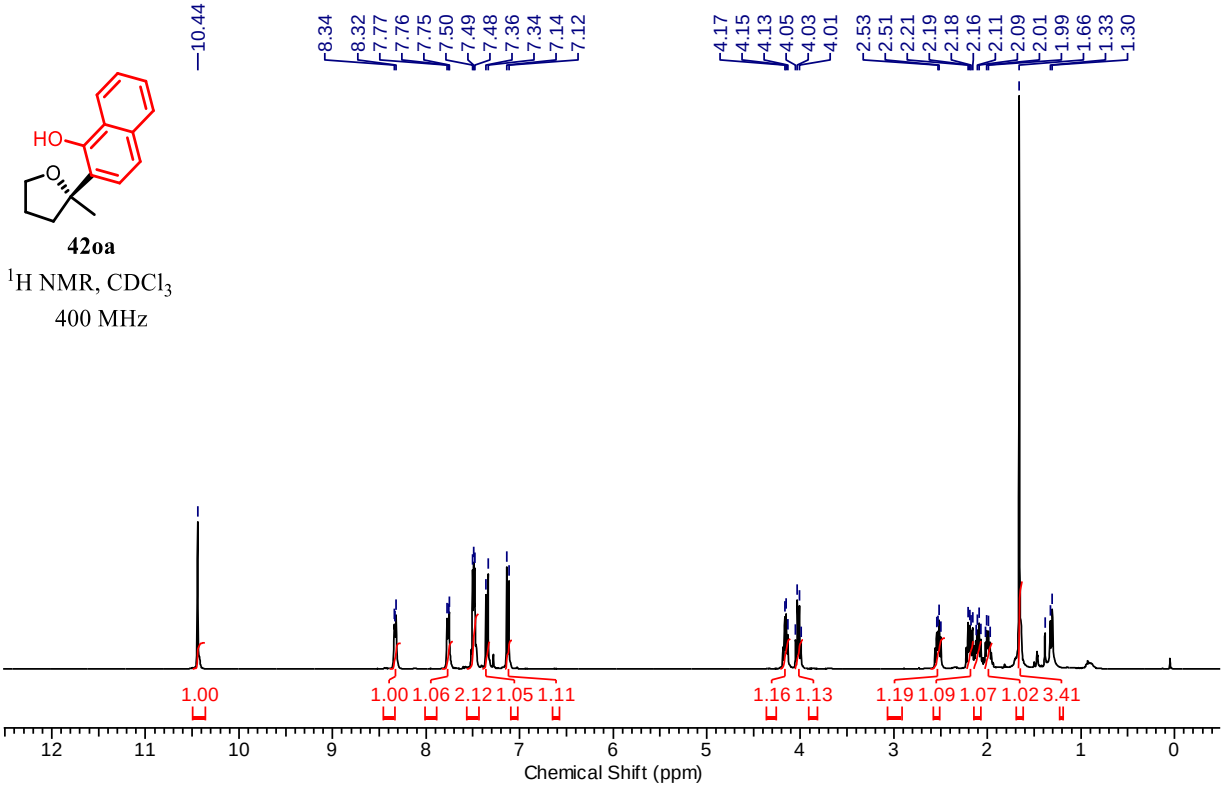
^{1}H NMR spectrum of compound 42na



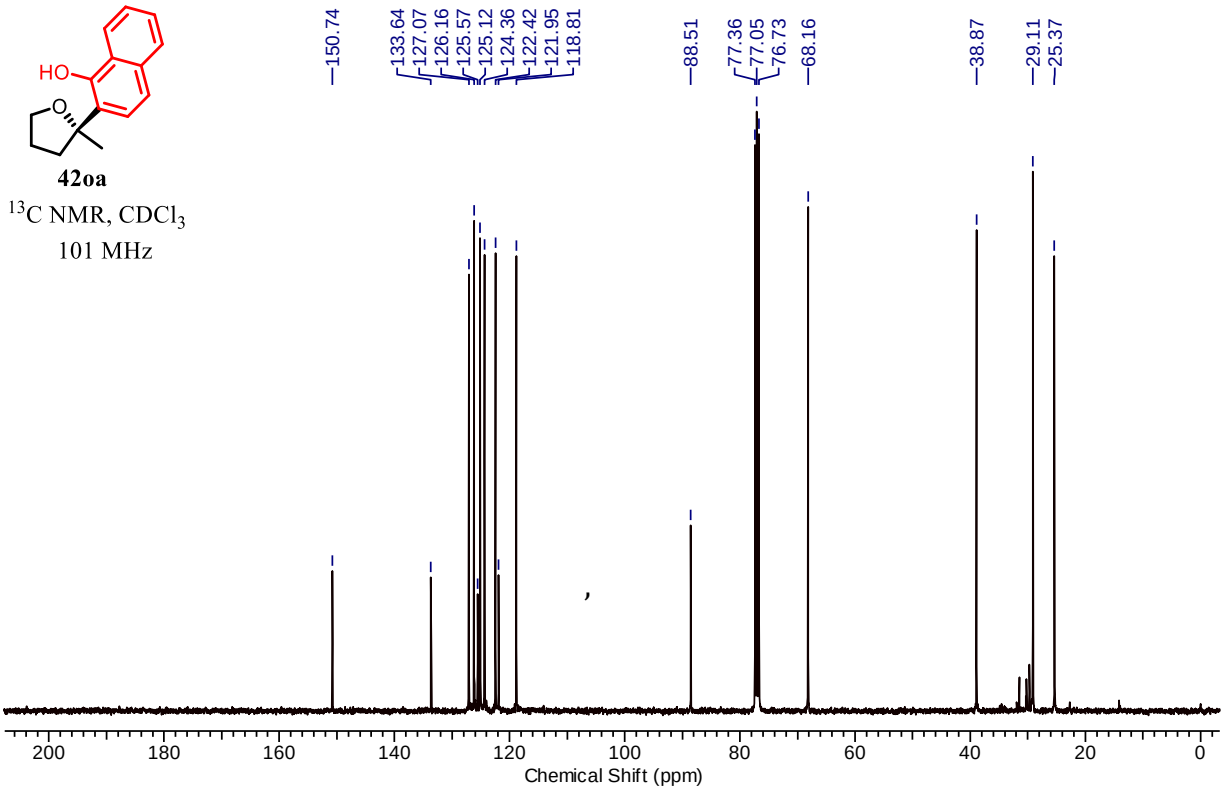
^{13}C NMR spectrum of compound 42na



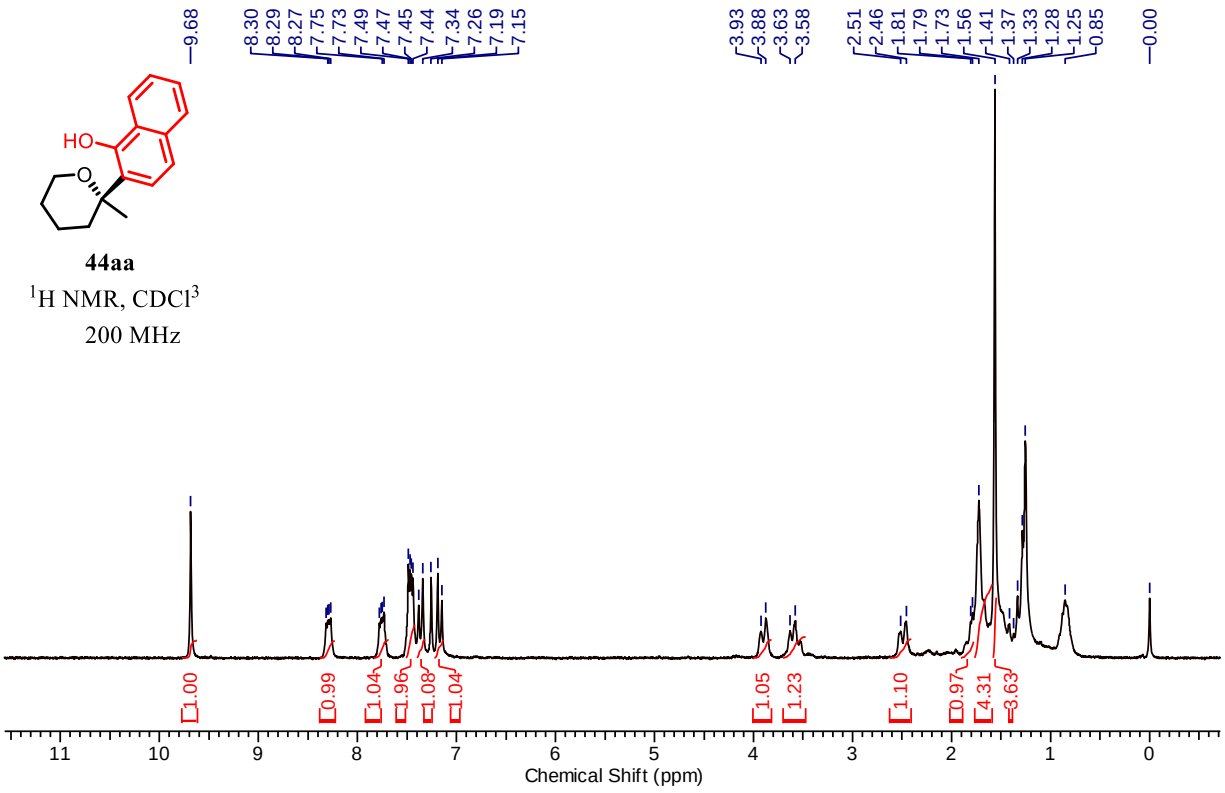
^{1}H NMR spectrum of compound 43oa



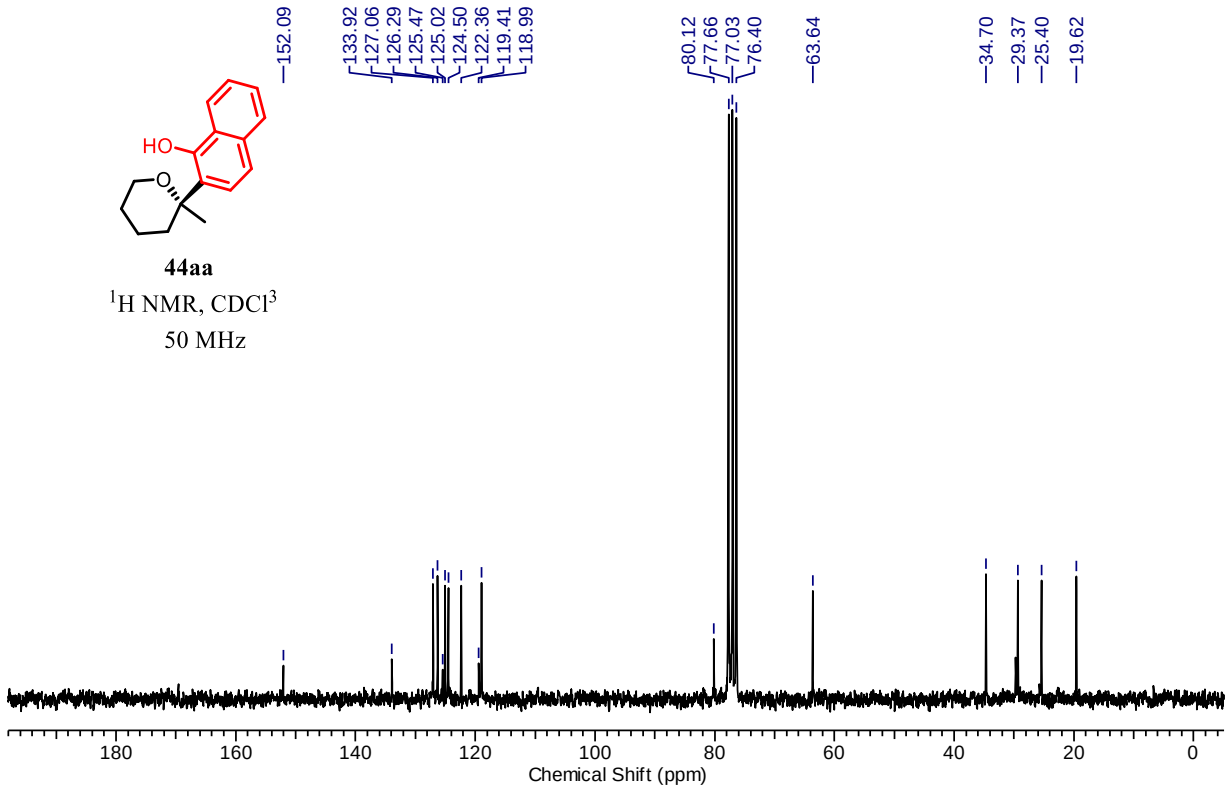
^{13}C NMR spectrum of compound 42oa



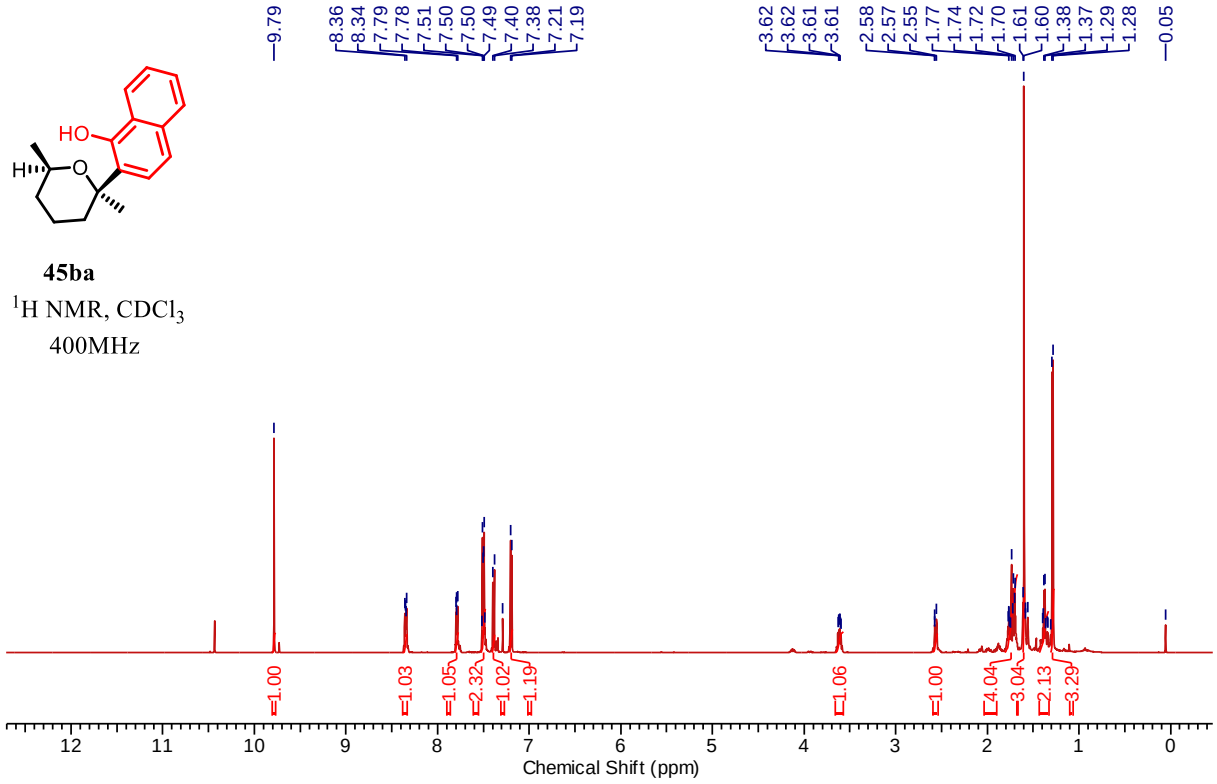
^{1}H NMR spectrum of compound 44aa



^{13}C NMR spectrum of compound 44aa



^{1}H NMR spectrum of compound 44ba

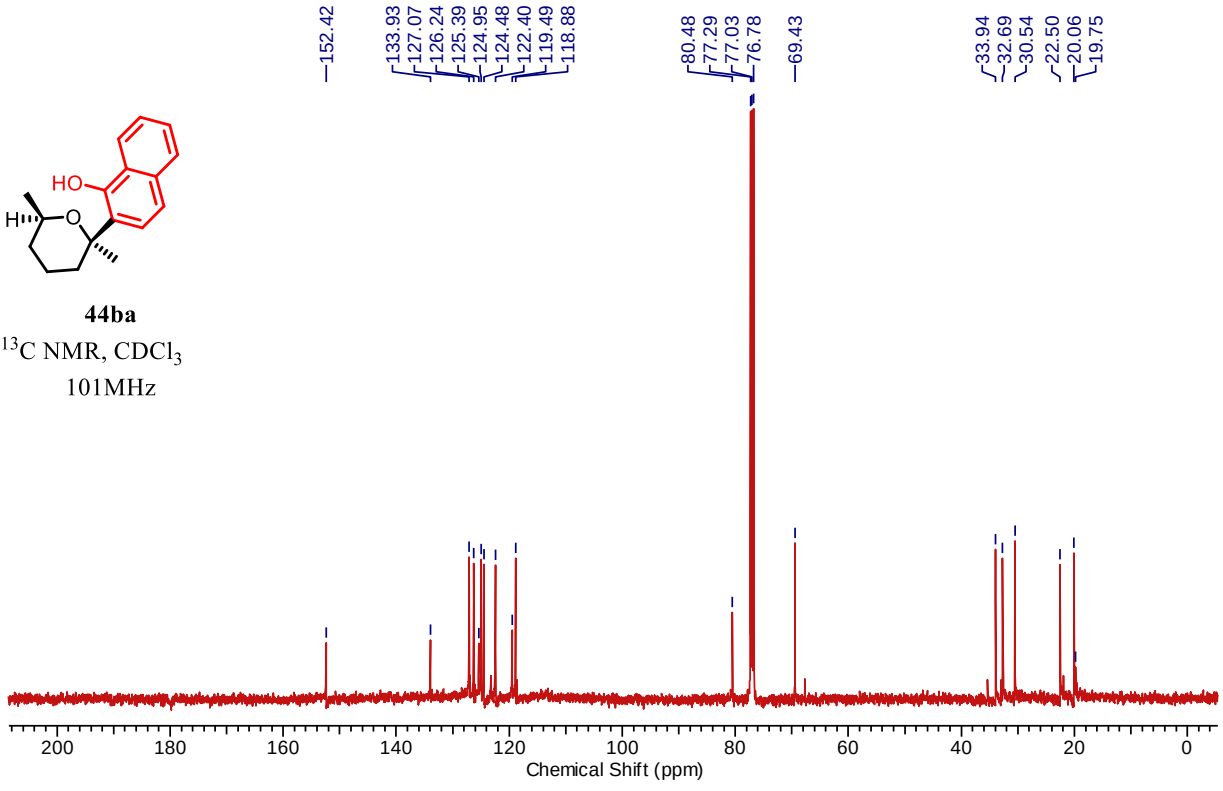


45ba

^{1}H NMR, $CDCl_3$

400MHz

^{13}C NMR spectrum of compound 44ba

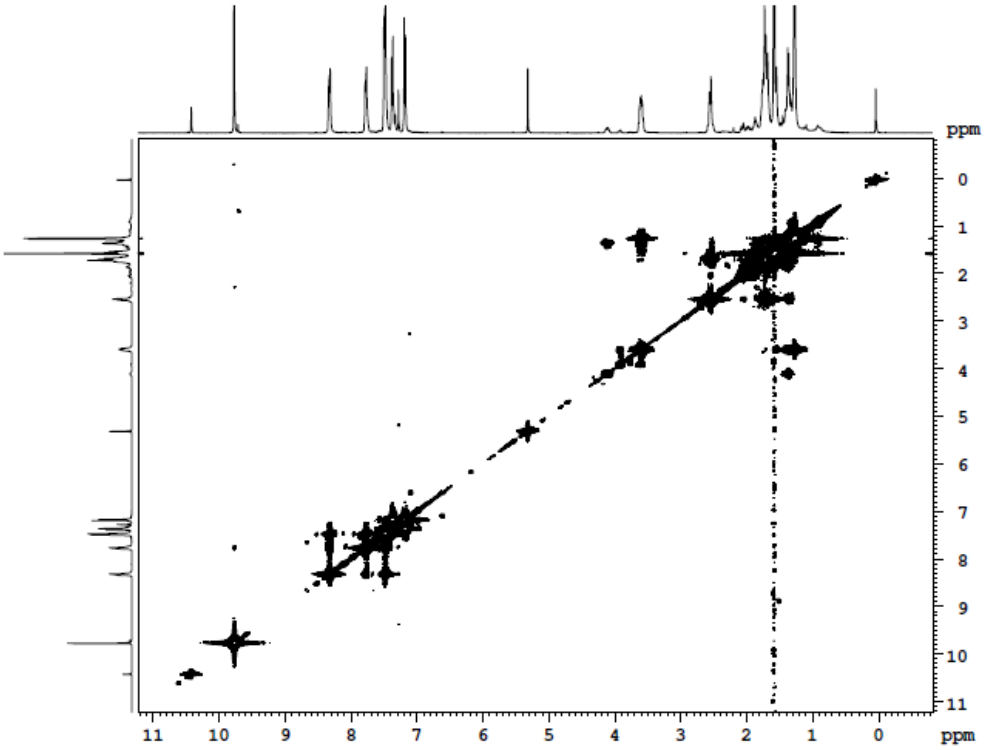


44ba

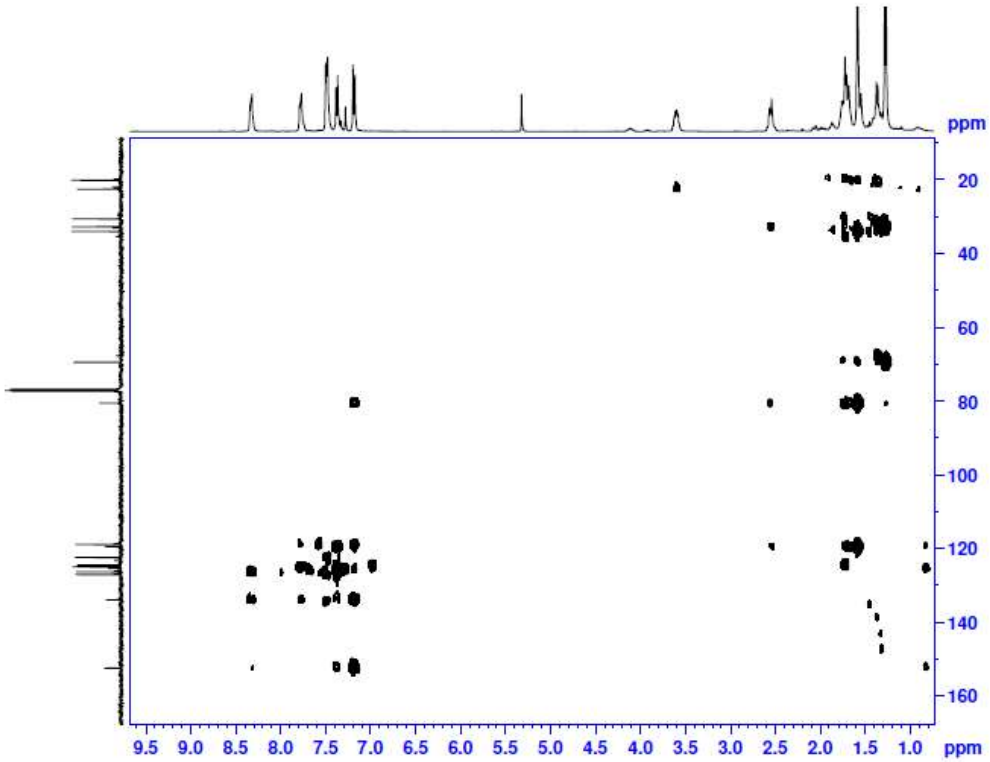
^{13}C NMR, $CDCl_3$

101MHz

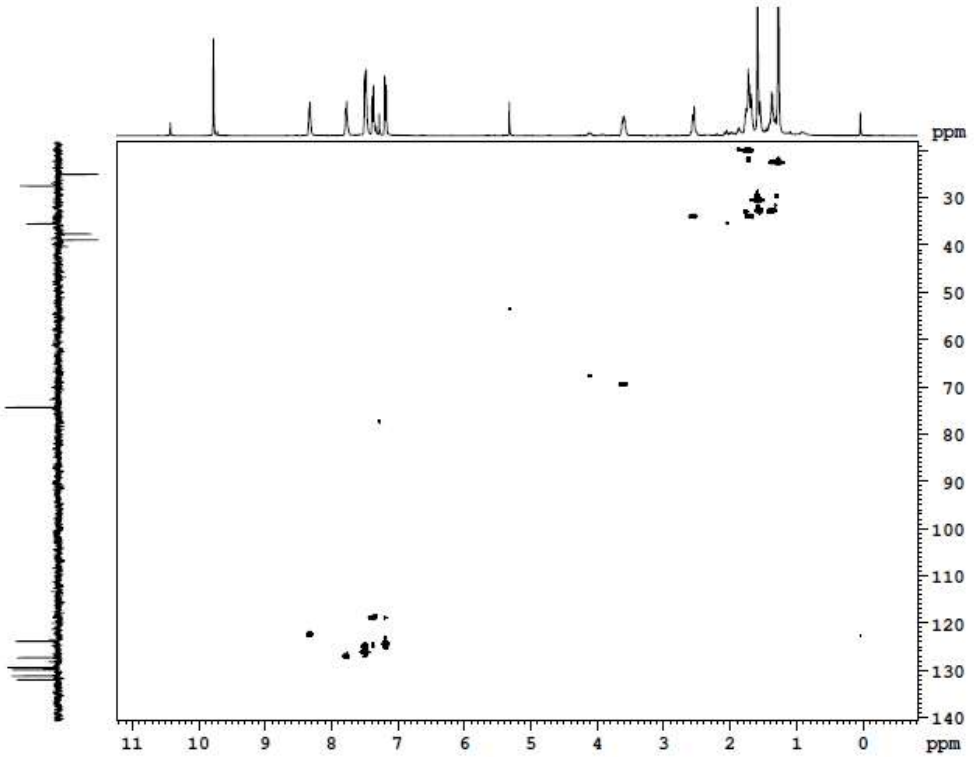
COSY **(44ba):**



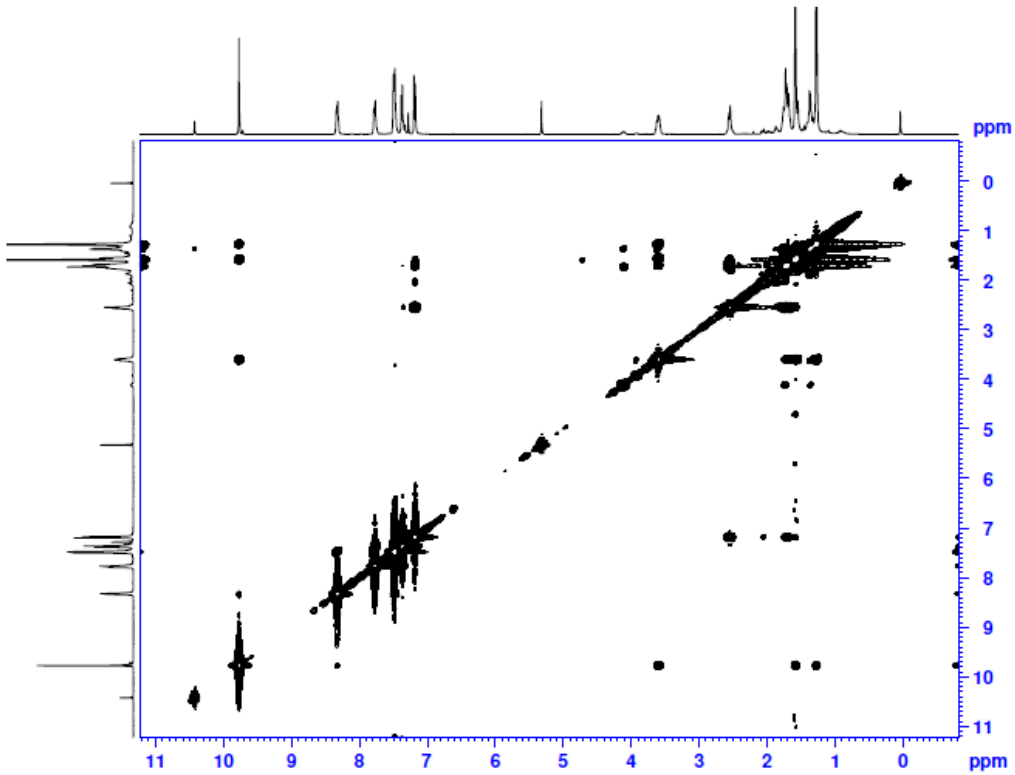
HMBC **(44ba):**



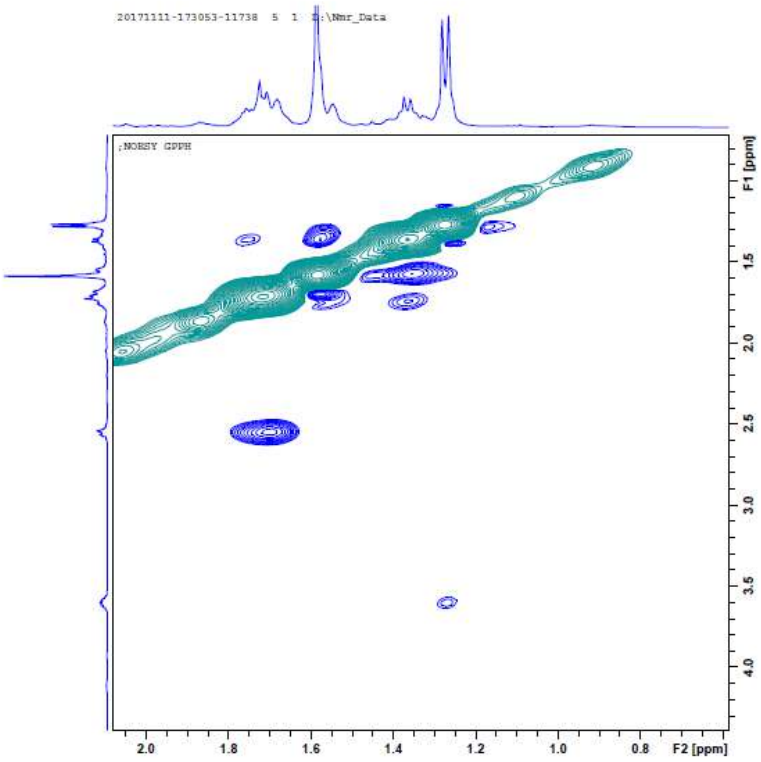
HSQC **(44ba):**



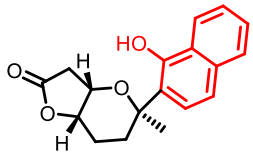
NOESY **(44ba):**



Expanded NOESY **(44ba):**



^{1}H NMR spectrum of compound 44ca

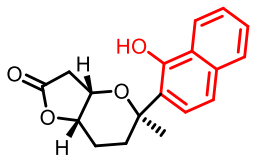


44ca

^{1}H NMR, $CDCl_3$

500 MHz

^{13}C NMR spectrum of compound 44ca

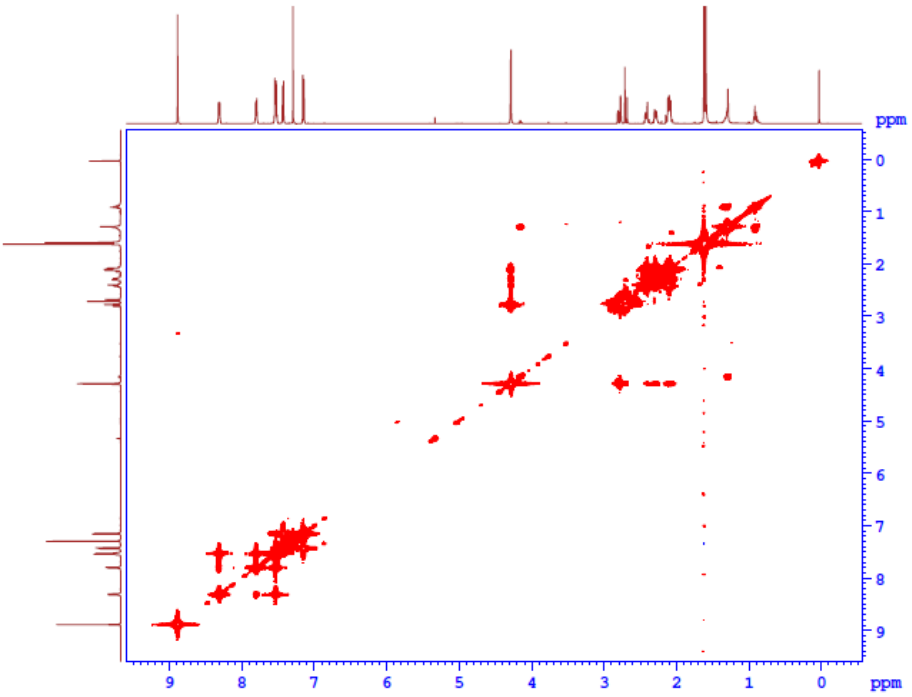


44ca

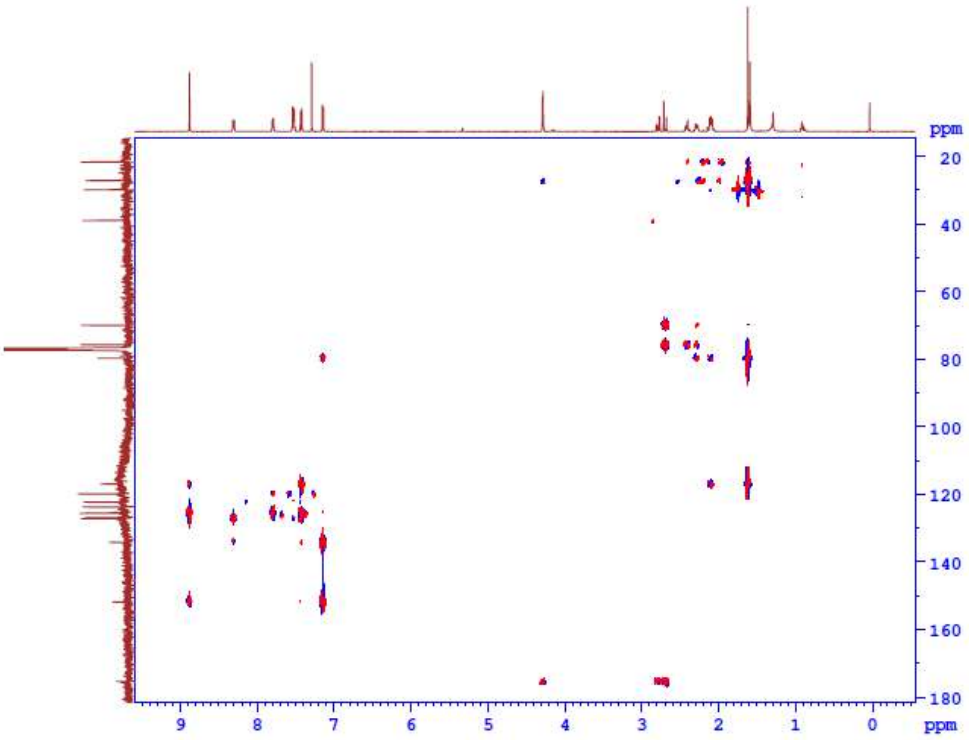
^{13}C NMR, $CDCl_3$

126 MHz

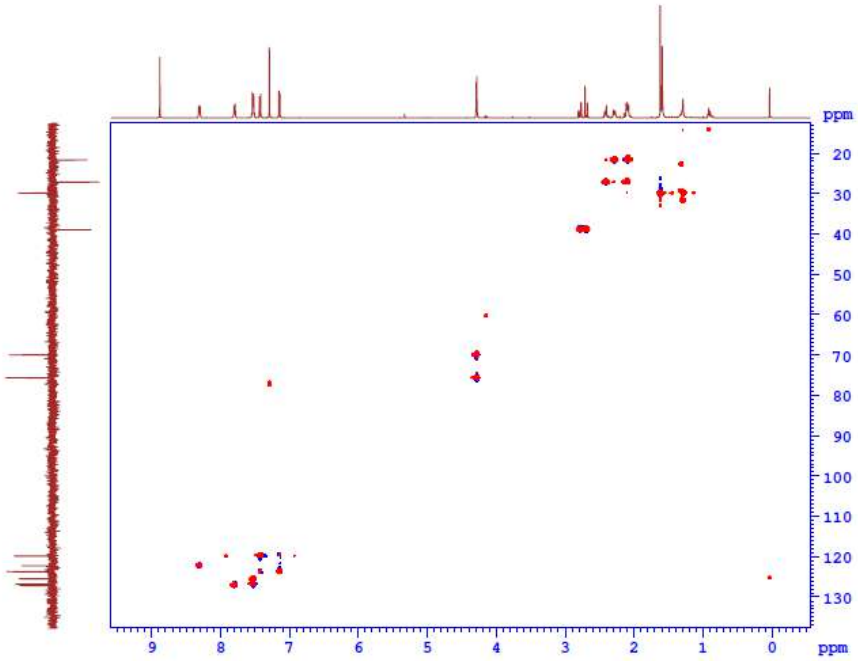
COSY **(44ca):**



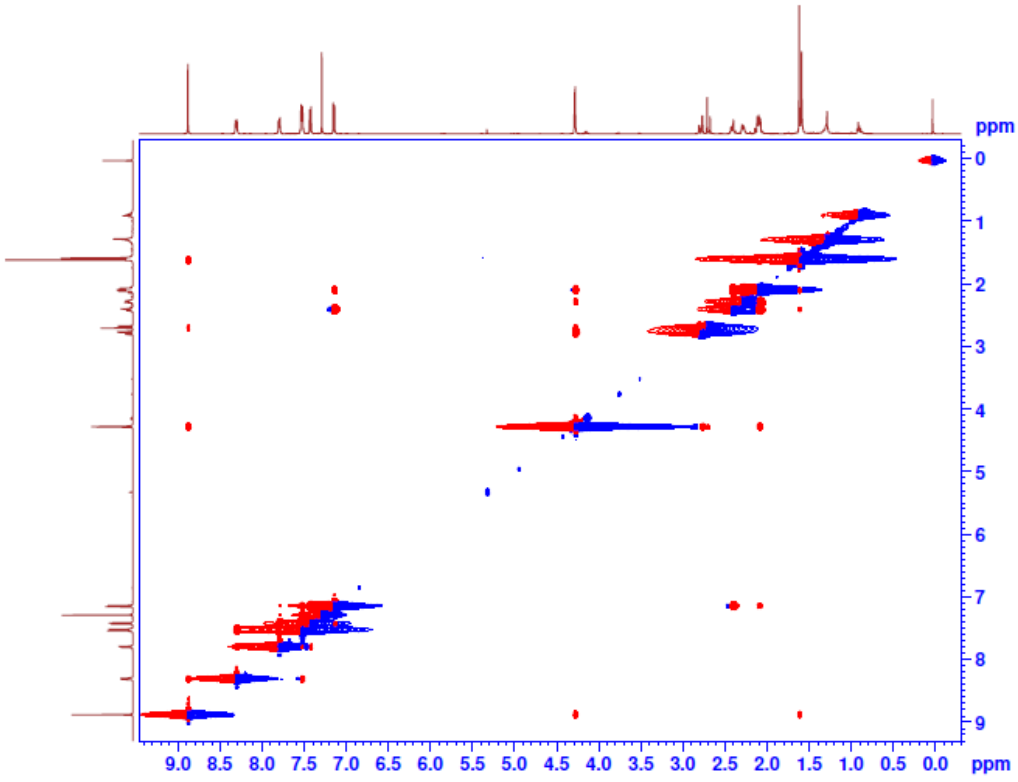
HMBC **(44ca):**



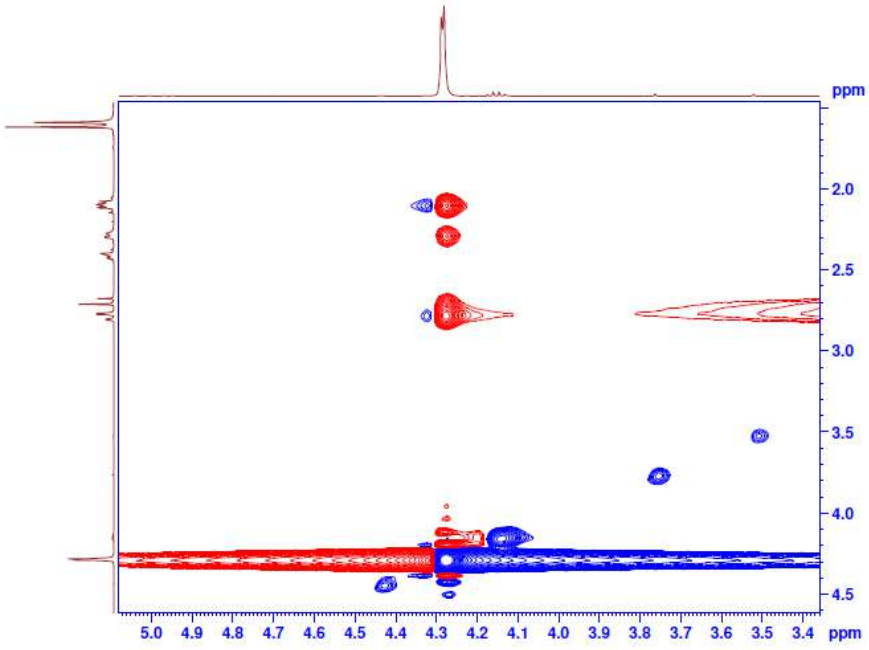
HSQC **(44ca):**



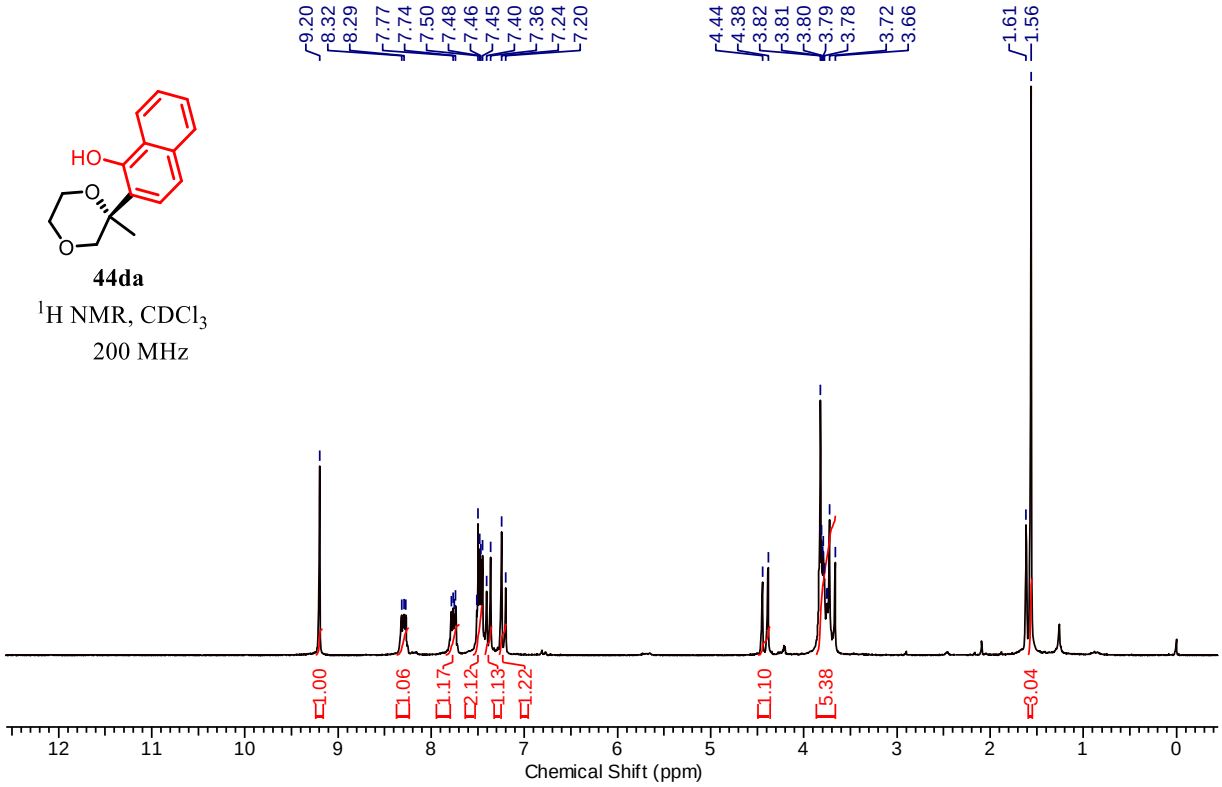
NOESY **(44ca):**



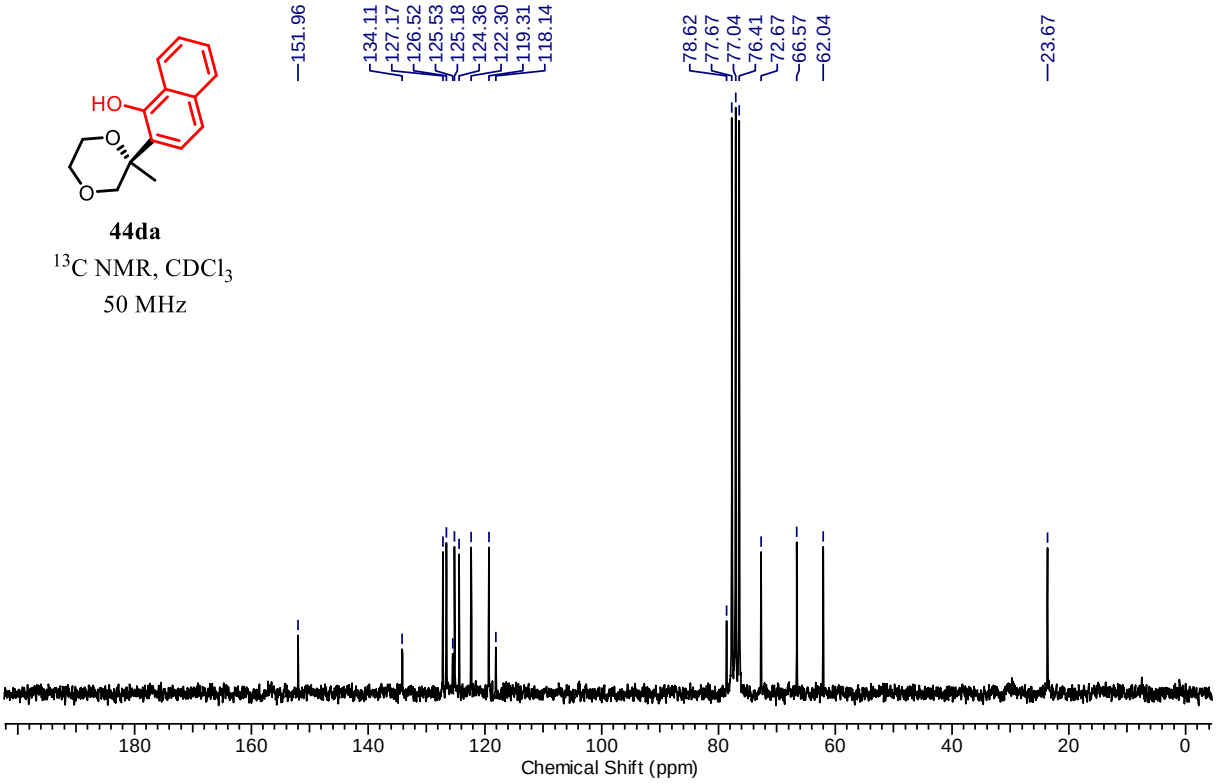
NOESY **(44ca):**


ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 ppm

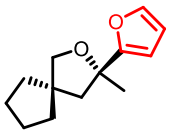
^{1}H NMR spectrum of compound 44da



^{13}C NMR spectrum of compound 44da



^{1}H NMR spectrum of compound 45aa

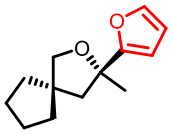


45aa

^{1}H NMR, $CDCl_3$

200 MHz

^{13}C NMR spectrum of compound 45aa

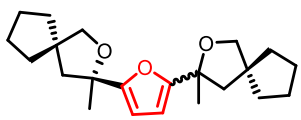


45aa

^{13}C NMR, $CDCl_3$

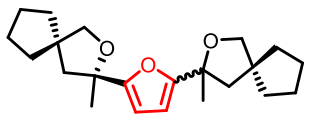
50 MHz

^{1}H NMR spectrum of compound 45aa'



45aa[1], (dr, 1:3)
^{1}H NMR, $CDCl_3$
200 MHz

^{13}C NMR spectrum of compound 45aa'



45aa[1], (dr, 1:3)
^{13}C NMR, $CDCl_3$
50 MHz

HPLC Analysis Report (45aa[1])

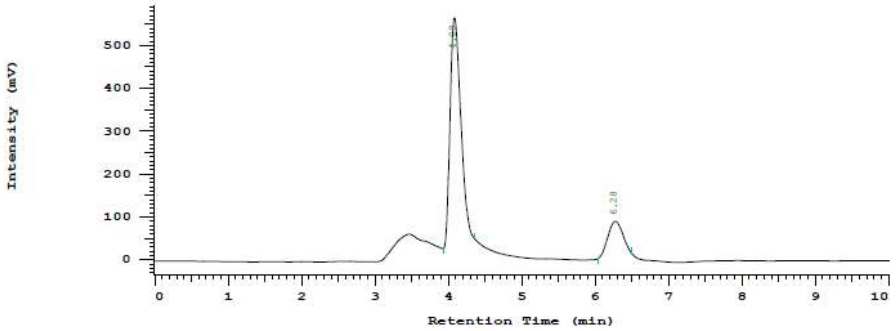
D-7000 HPLC System Manager Report

Analyzed: 11/06/17 04:35 PM
Reported: 11/06/17 05:00 PM
Processed: 11/06/17 04:59 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9916\
Processing Method: cal

System(acquisition): Sys 1
Series:9916
Application: HPLC
Volume: 10.0 ul
Sample Name: AN-03
Injection from this vial: 1 of 1
Sample Description: IPA:PE(01:99)

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	4.08	5338034	82.837	BB
2	6.28	1105998	17.163	BB
		6444032	100.000	

Peak rejection level: 0

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Project Leader: Dr.RAVINDAR kONTHAM
Column     :Chiralcel OJ-H(250 mm x 4.6mm)
Mobile Ph  : IPA:PE(01:99)
Wavelength : 220nm
Flow       : 1 ml/min.
Inject vol: 2ul
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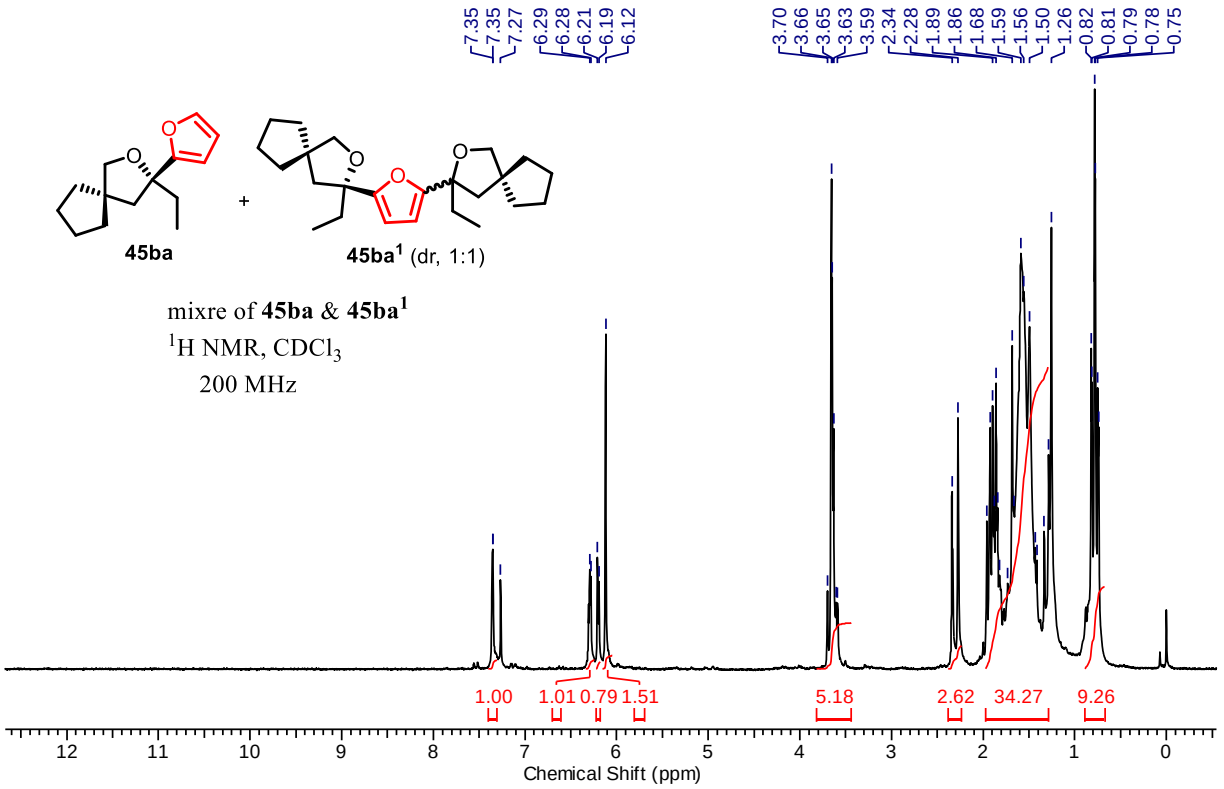
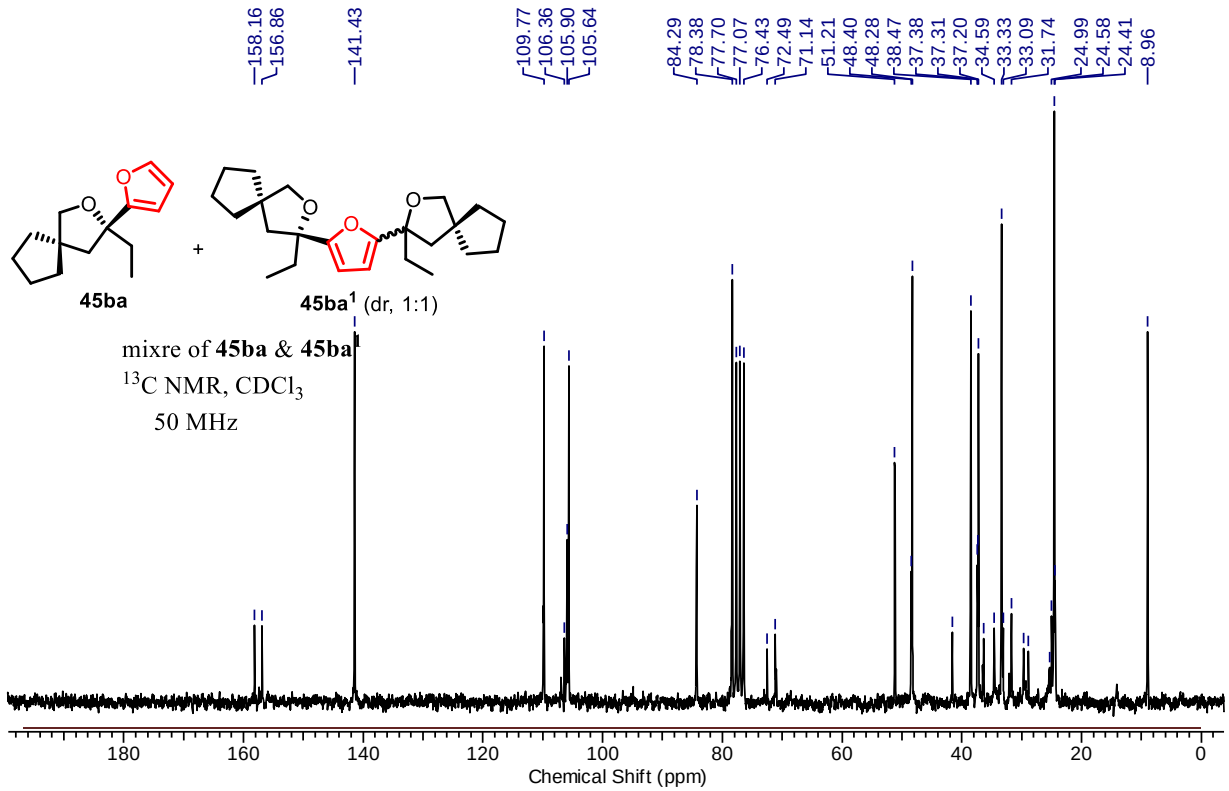
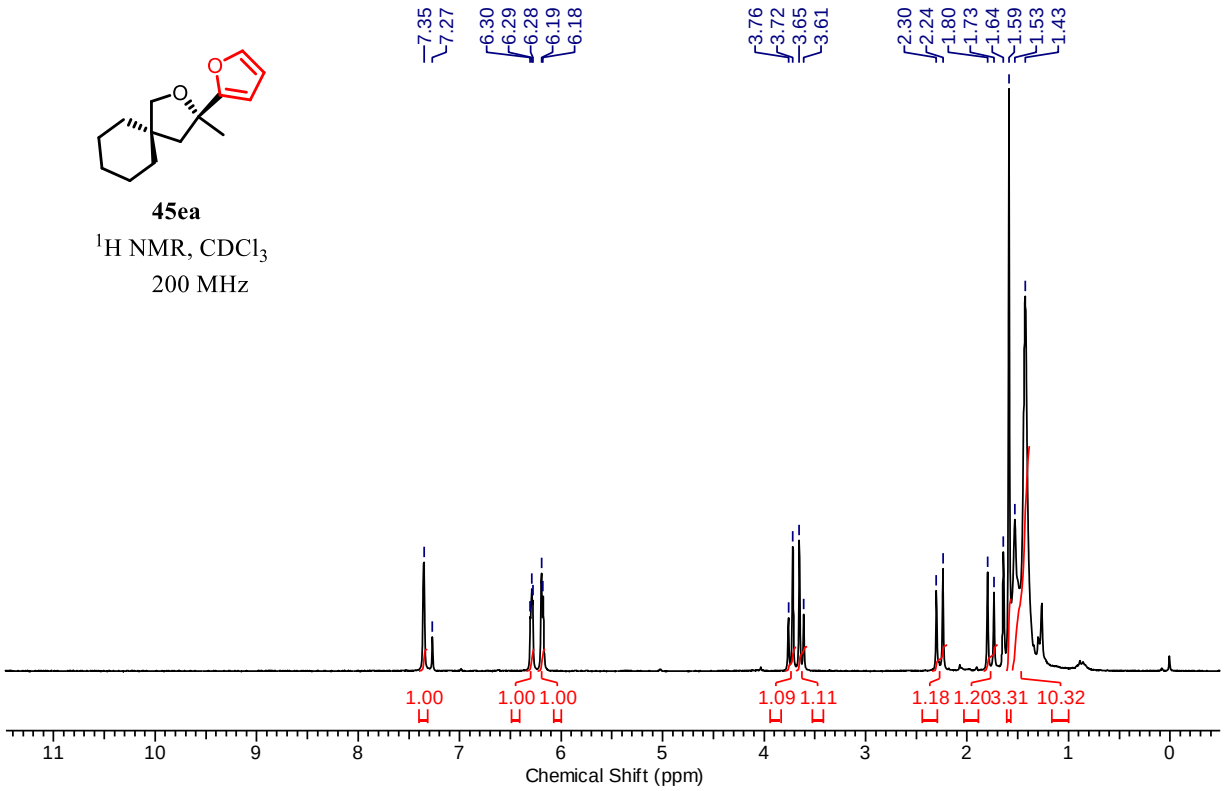
^{1}H NMR spectrum of compound 45ba &45ba'



^{13}C NMR spectrum of compound 45ba' & 45ba'



^{1}H NMR spectrum of compound 45ea

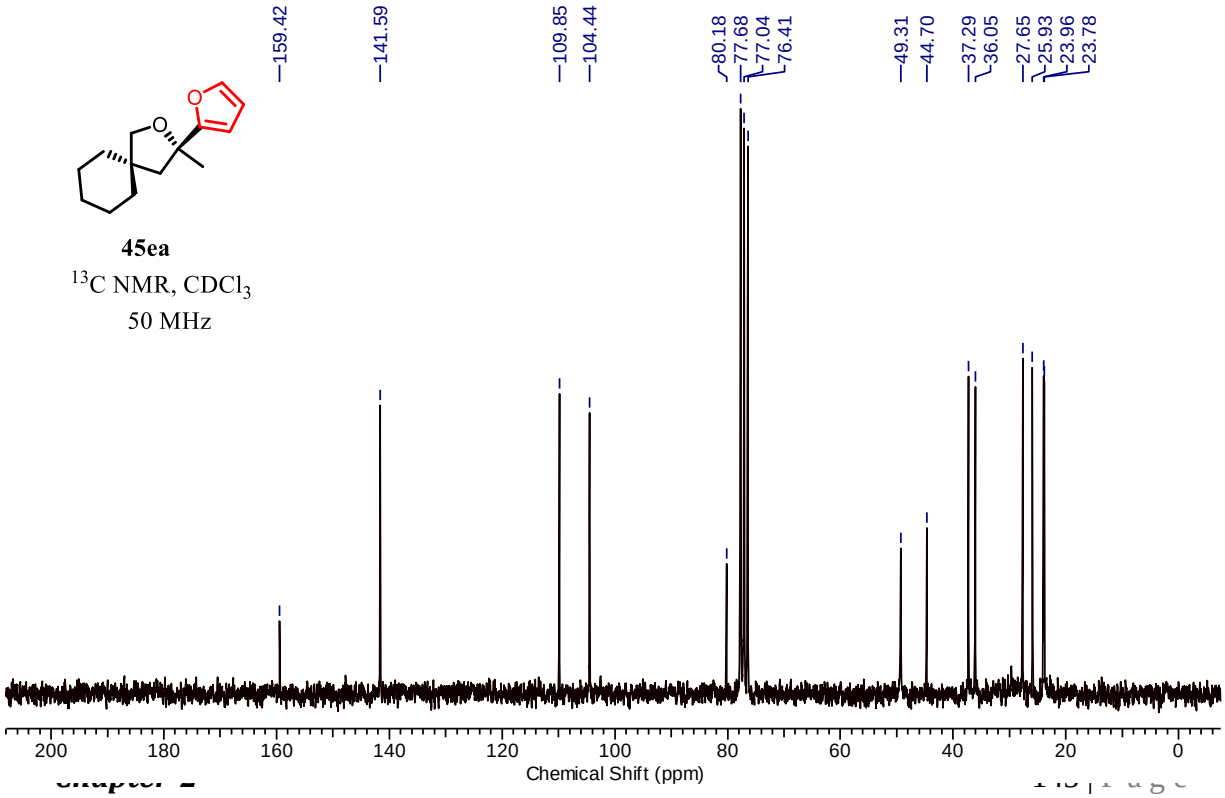


45ea

^{1}H NMR, $CDCl_3$

200 MHz

^{13}C NMR spectrum of compound 45ea

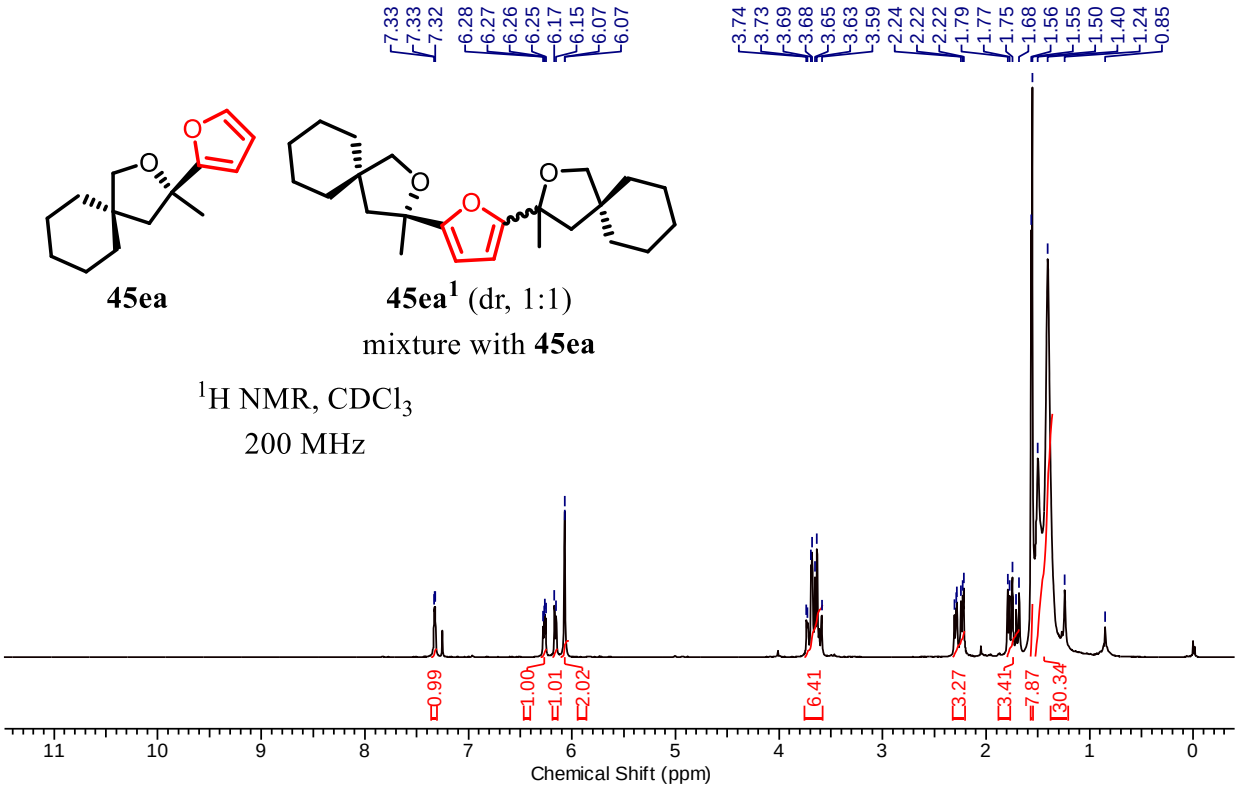


45ea

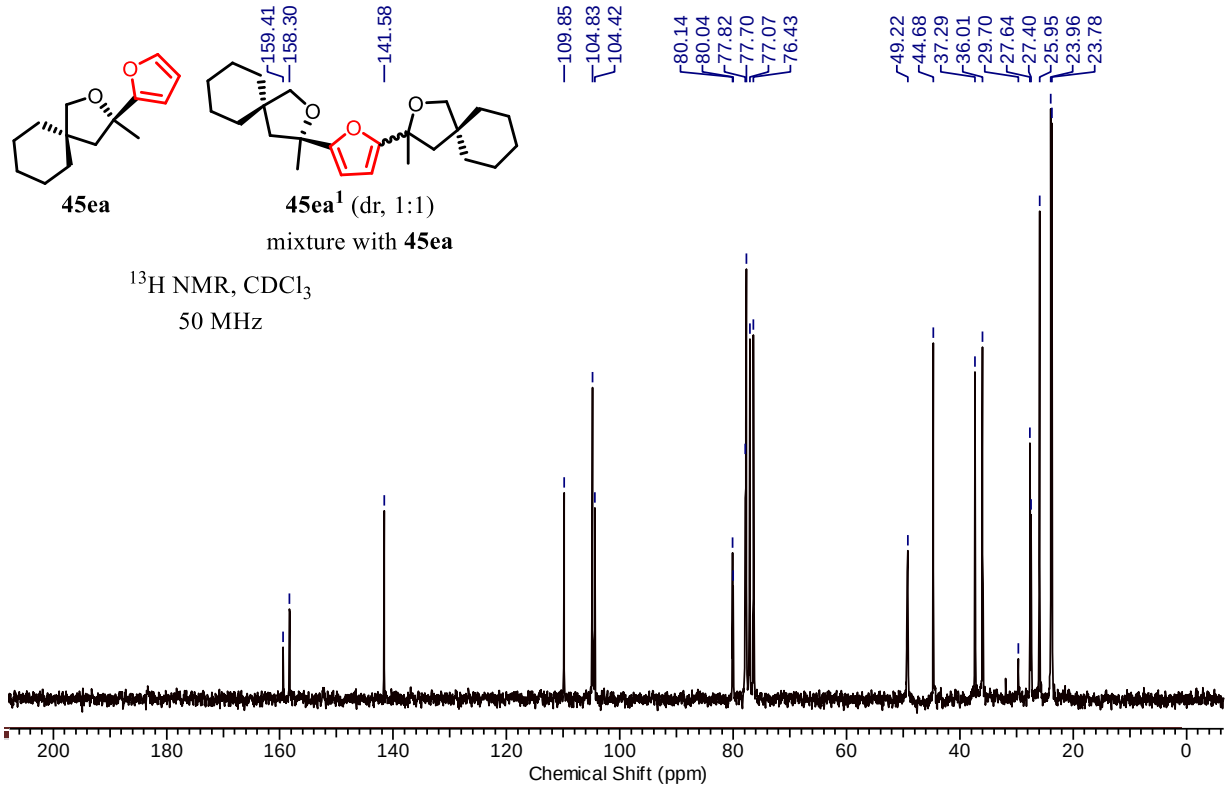
^{13}C NMR, $CDCl_3$

50 MHz

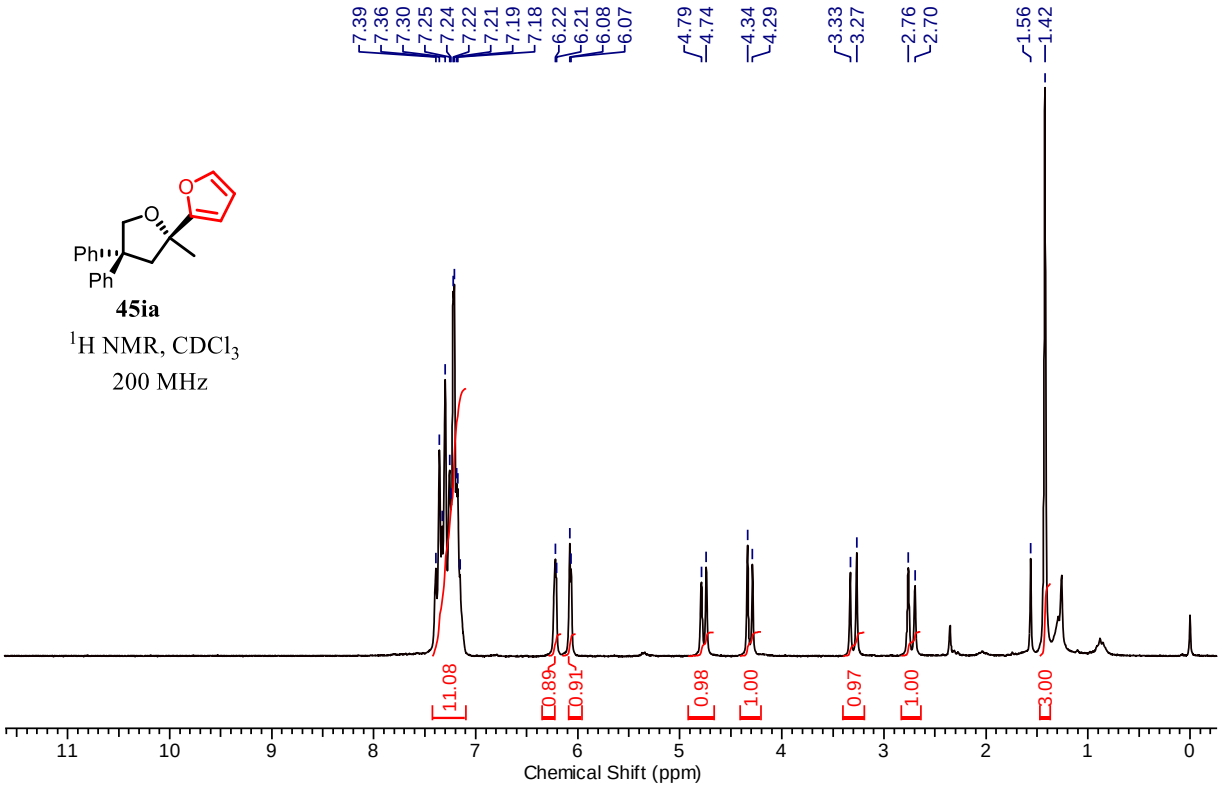
^{1}H NMR spectrum of compound 45ea & 45ea'



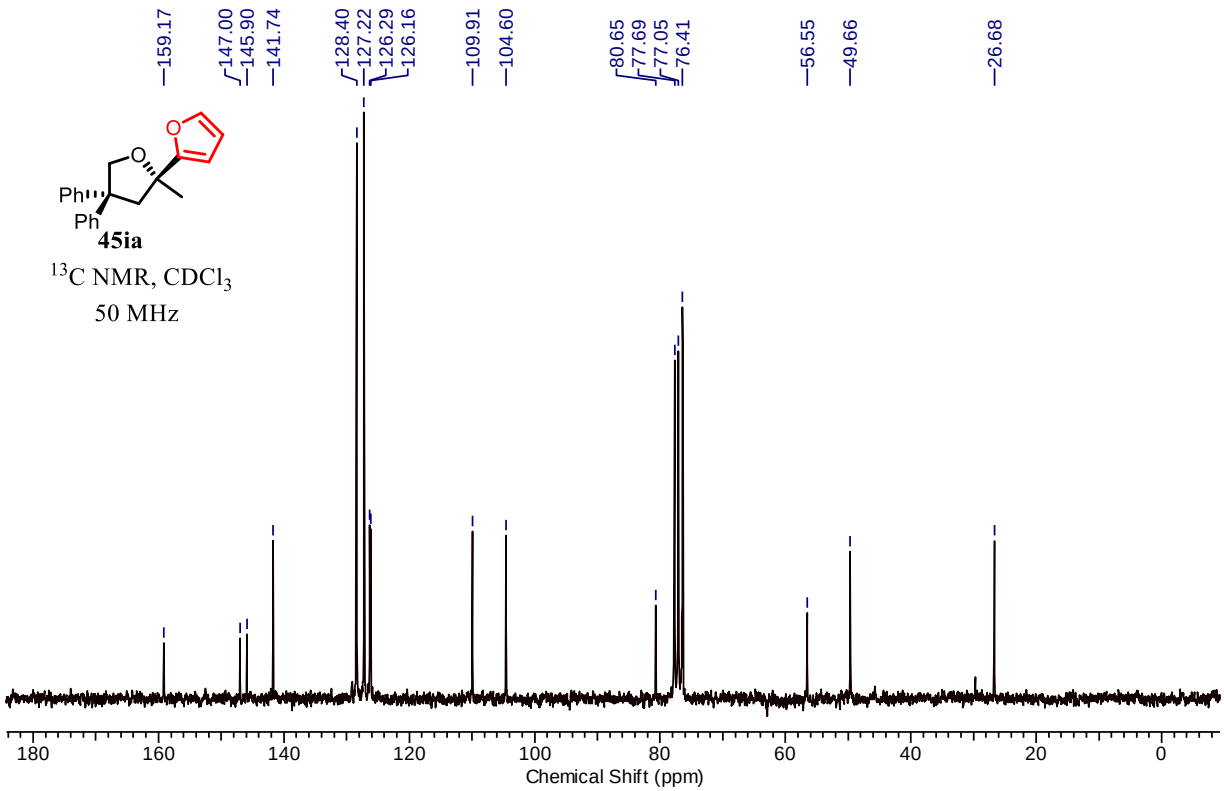
^{13}C NMR spectrum of compound 45ea & 45ea'



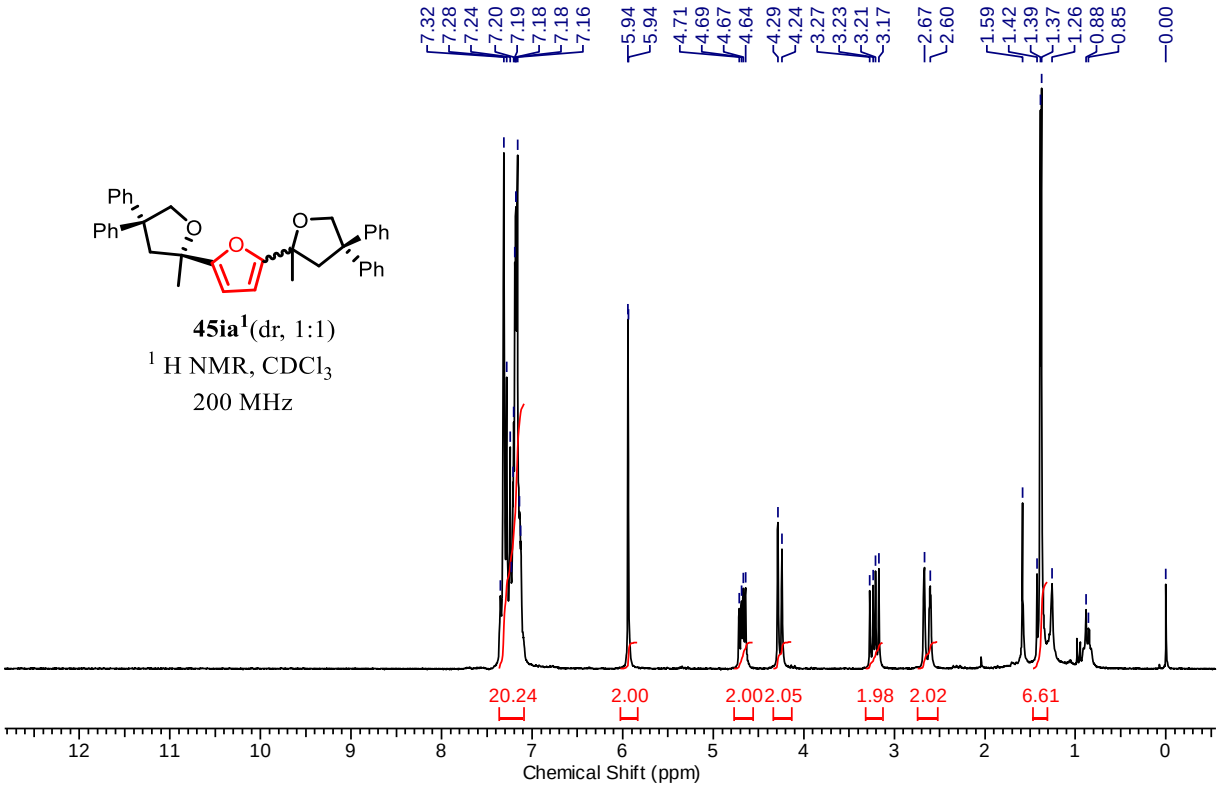
^{1}H NMR spectrum of compound 45ia



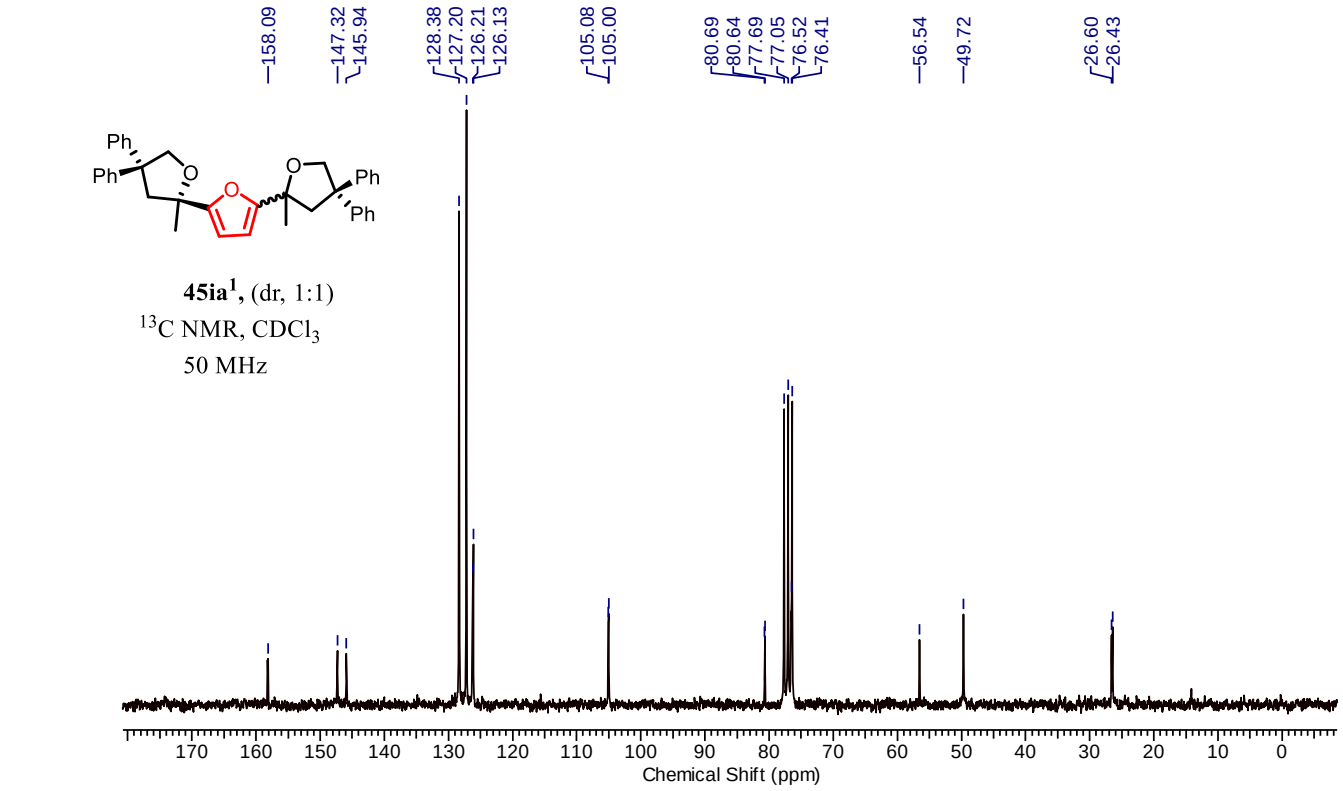
^{13}C NMR spectrum of compound 45ia



^{1}H NMR spectrum of compound 45ia'



^{13}C NMR spectrum of compound 45ia



HPLC Analysis Report (45ia[1])

D-7000 HPLC System Manager Report

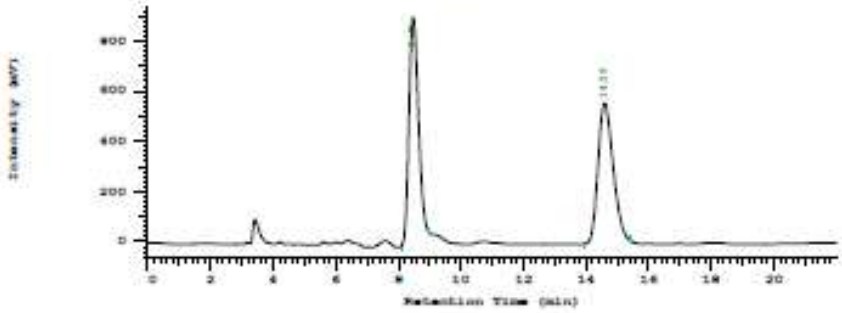
Analyzed: 11/06/17 02:37 PM
Reported: 11/06/17 03:04 PM
Processed: 11/06/17 03:03 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9910\
Processing Method: cal

System(acquisition): Sys 1
Application: HPLC
Sample Name: AN=04
Injection from this vial: 1 of 1
Sample Description: IPA:PE(02:98)

Series:9910
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



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		37293860	100.000	

Peak rejection level: 0

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Project Leader: Dr.RAVINDAR kONTHAM
Column      :Kromasil 5-cellucoat(250 mm x 4.6mm)
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Wavelength  : 220nm
Flow        : 1 ml/min.
Inject vol: 5ul
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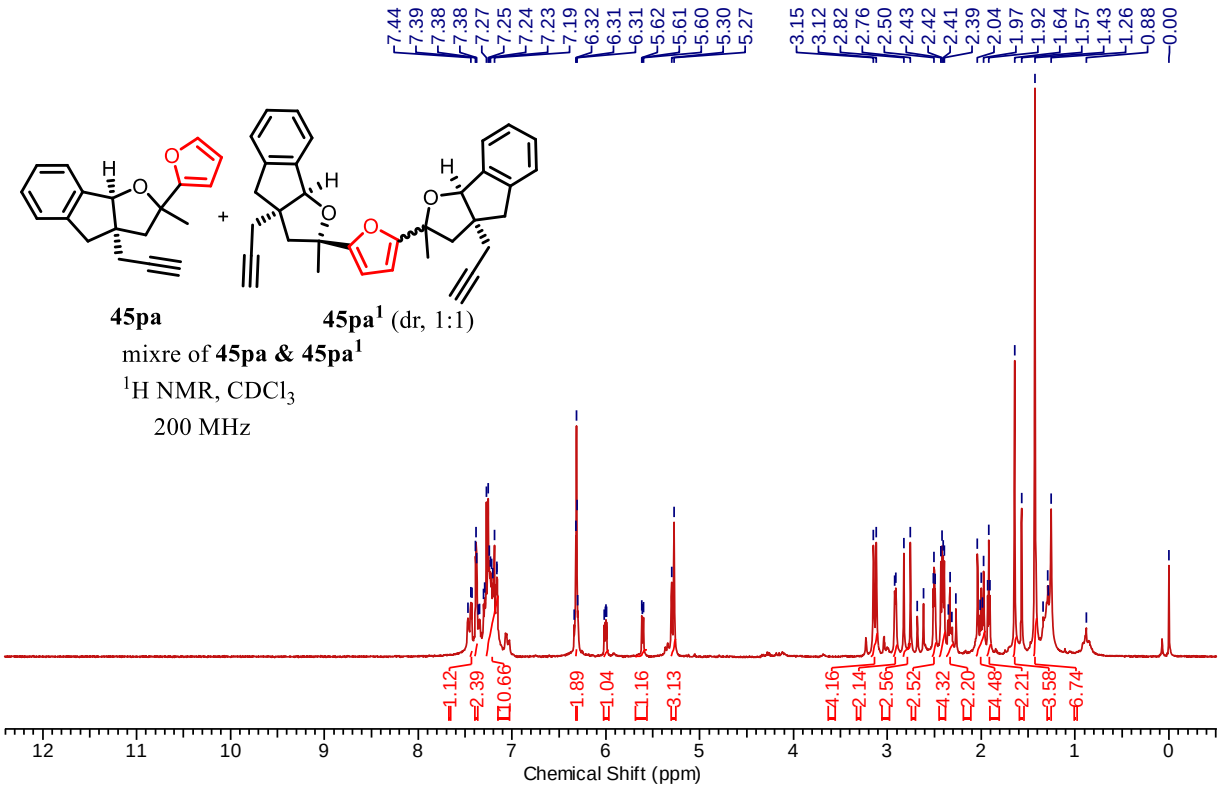
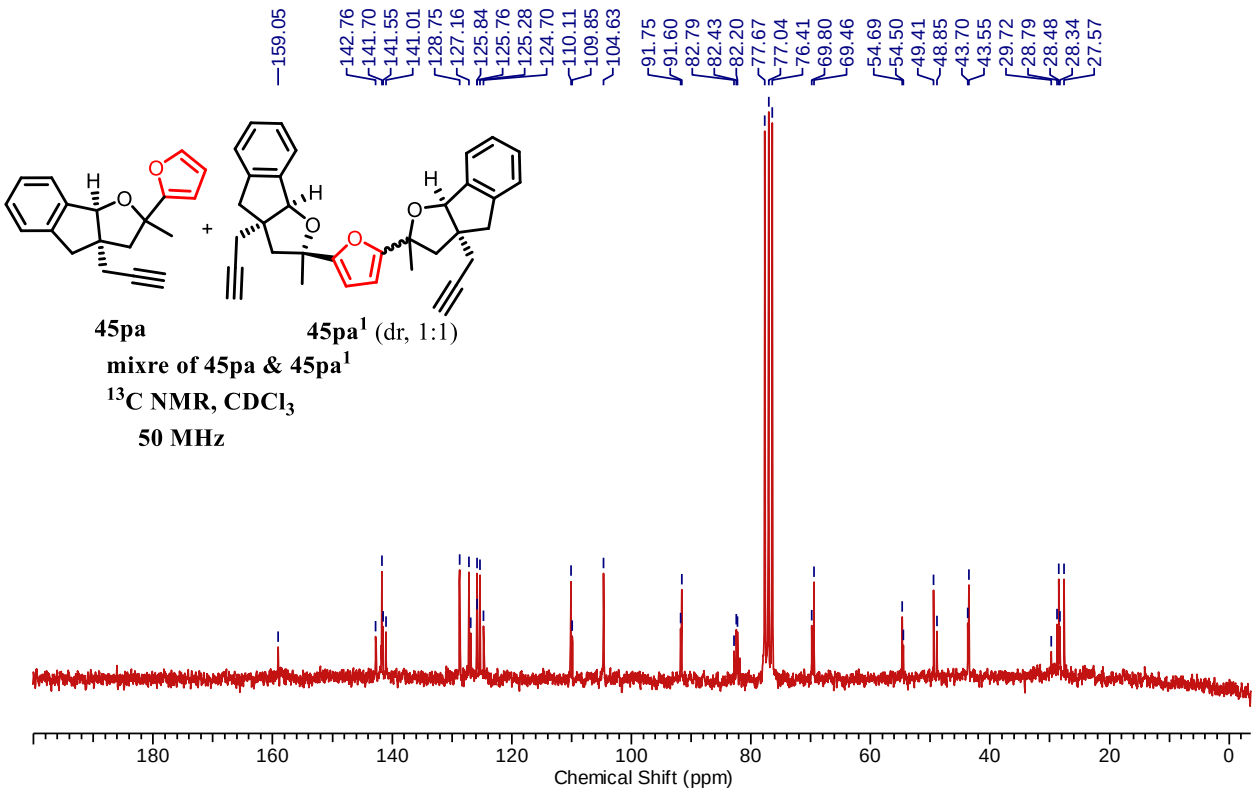
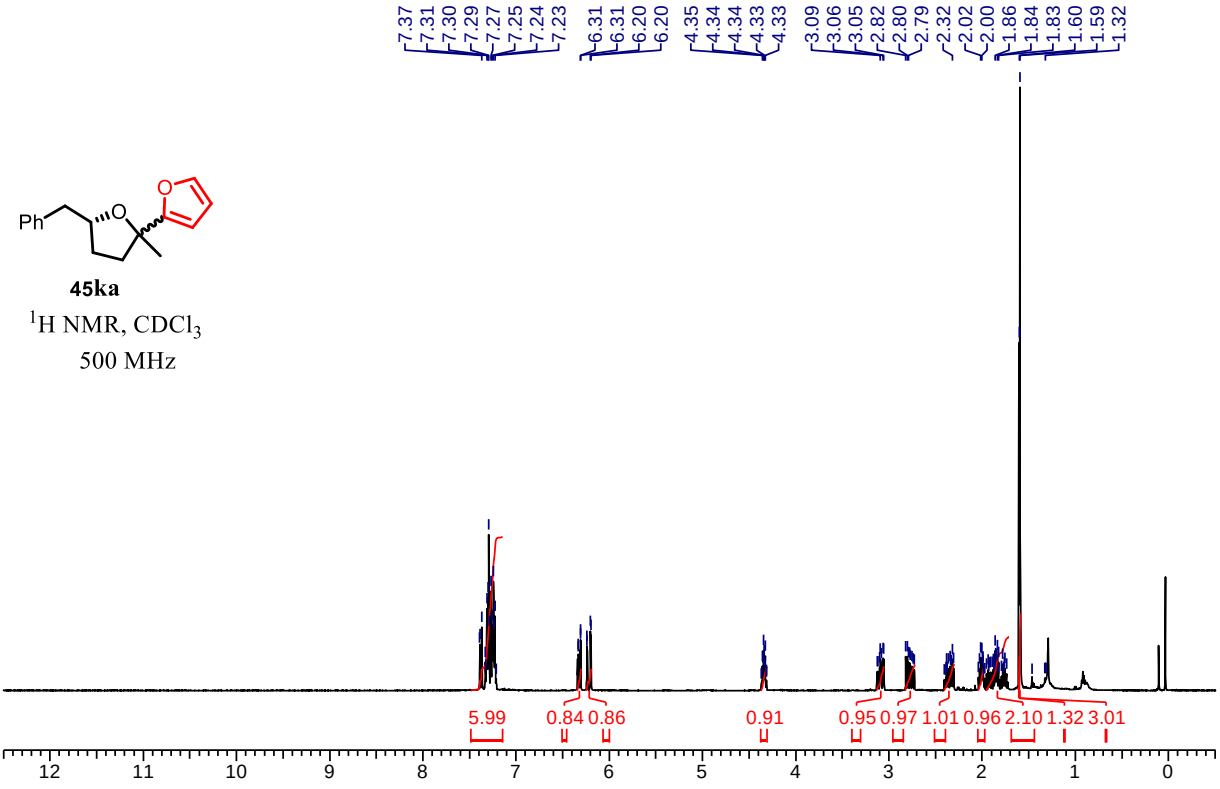
^{1}H NMR spectrum of compound 45pa & 45pa'



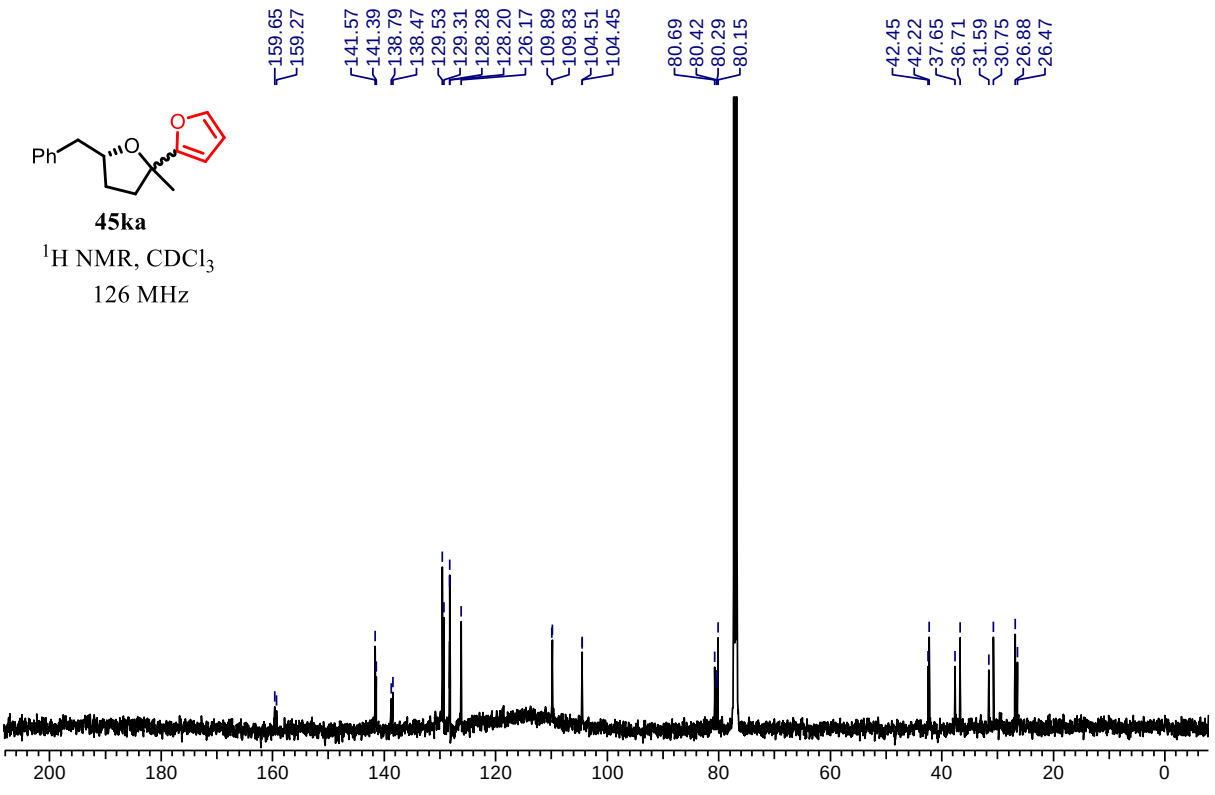
^{13}C NMR spectrum of compound 45pa & 45pa'



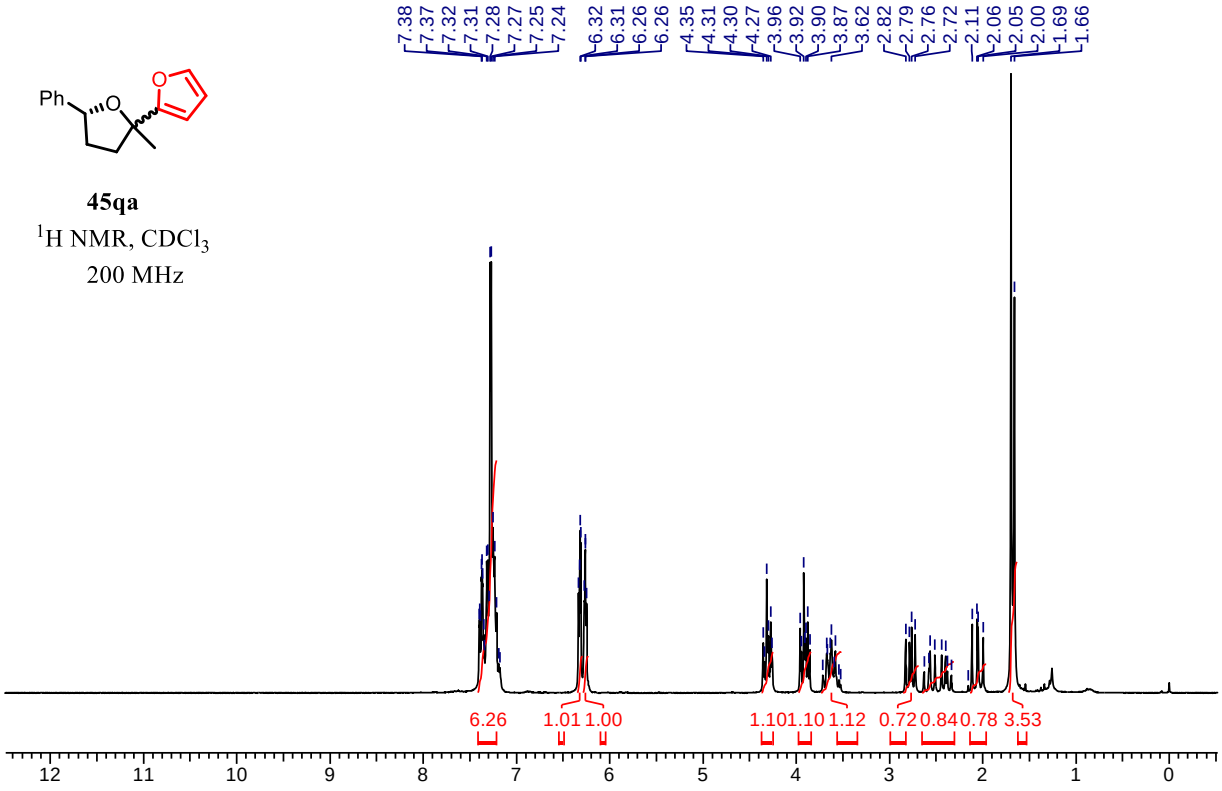
^{1}H NMR spectrum of compound 45ka



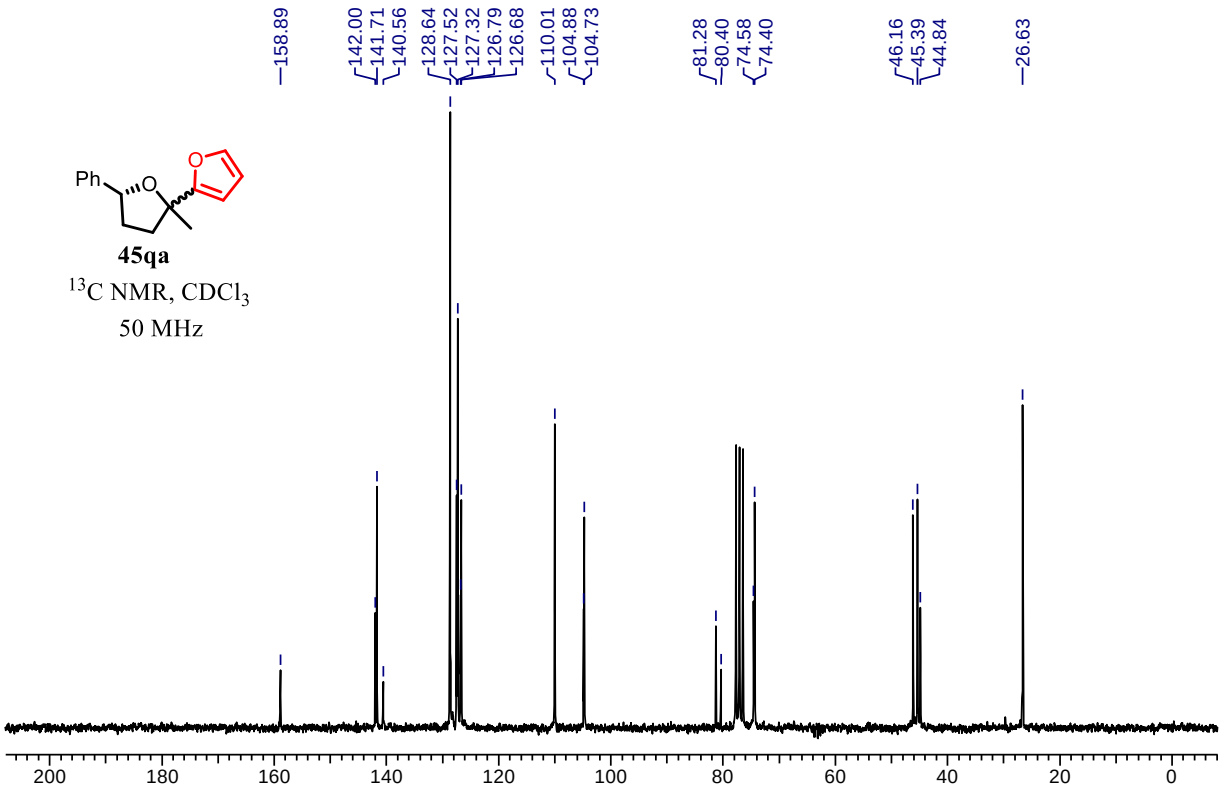
^{13}C NMR spectrum of compound 45ka



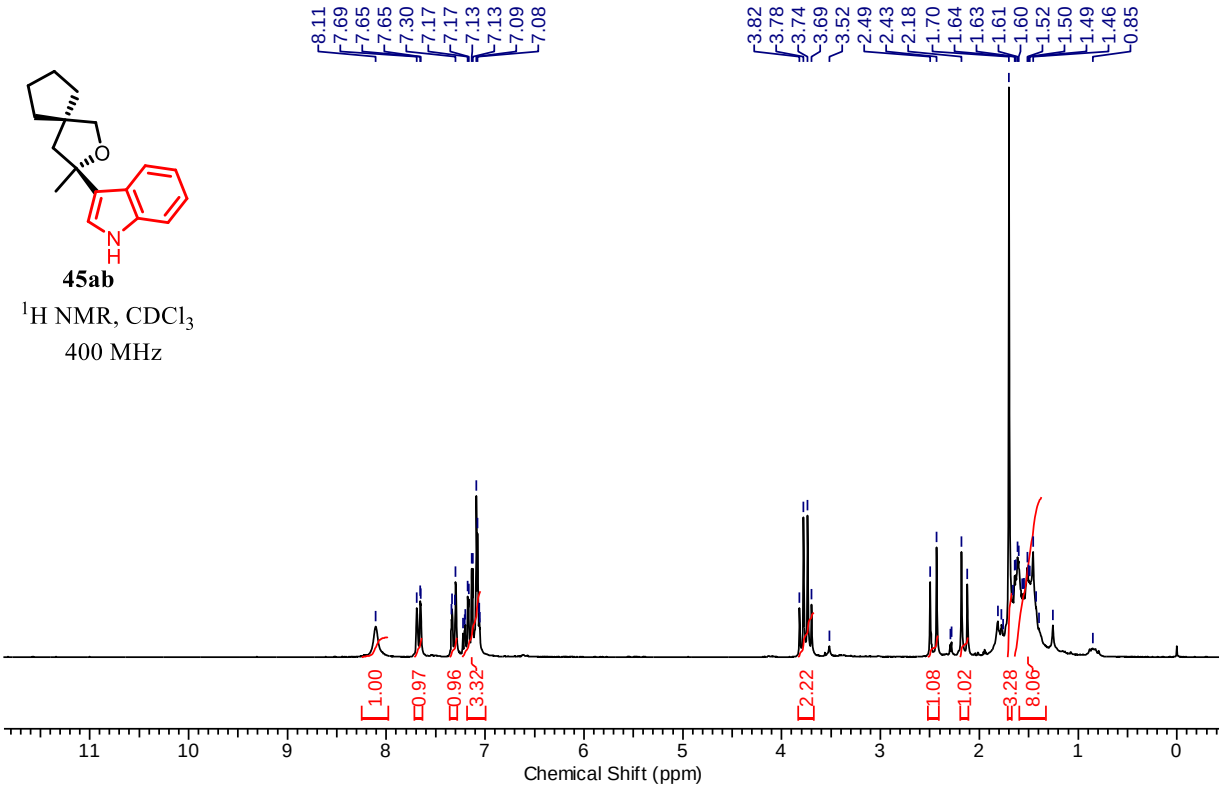
^{1}H NMR spectrum of compound 45qa



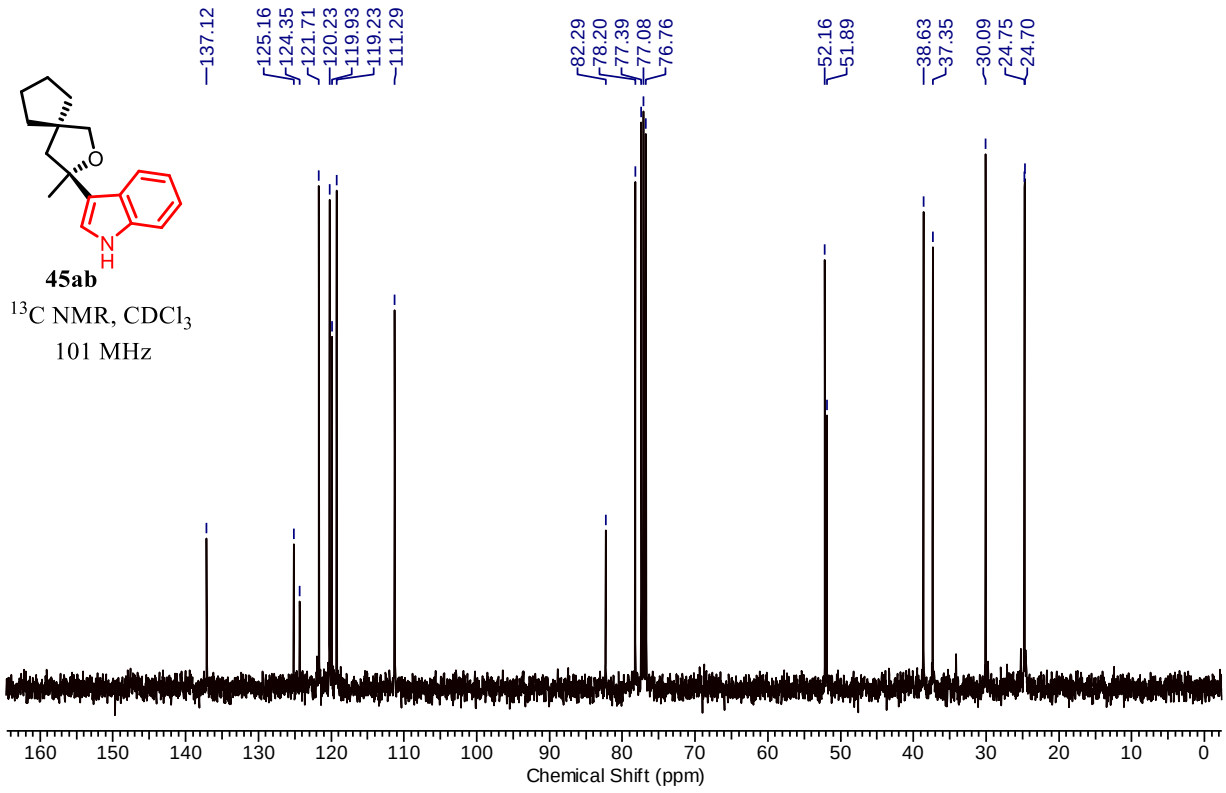
^{13}C NMR spectrum of compound 45qa



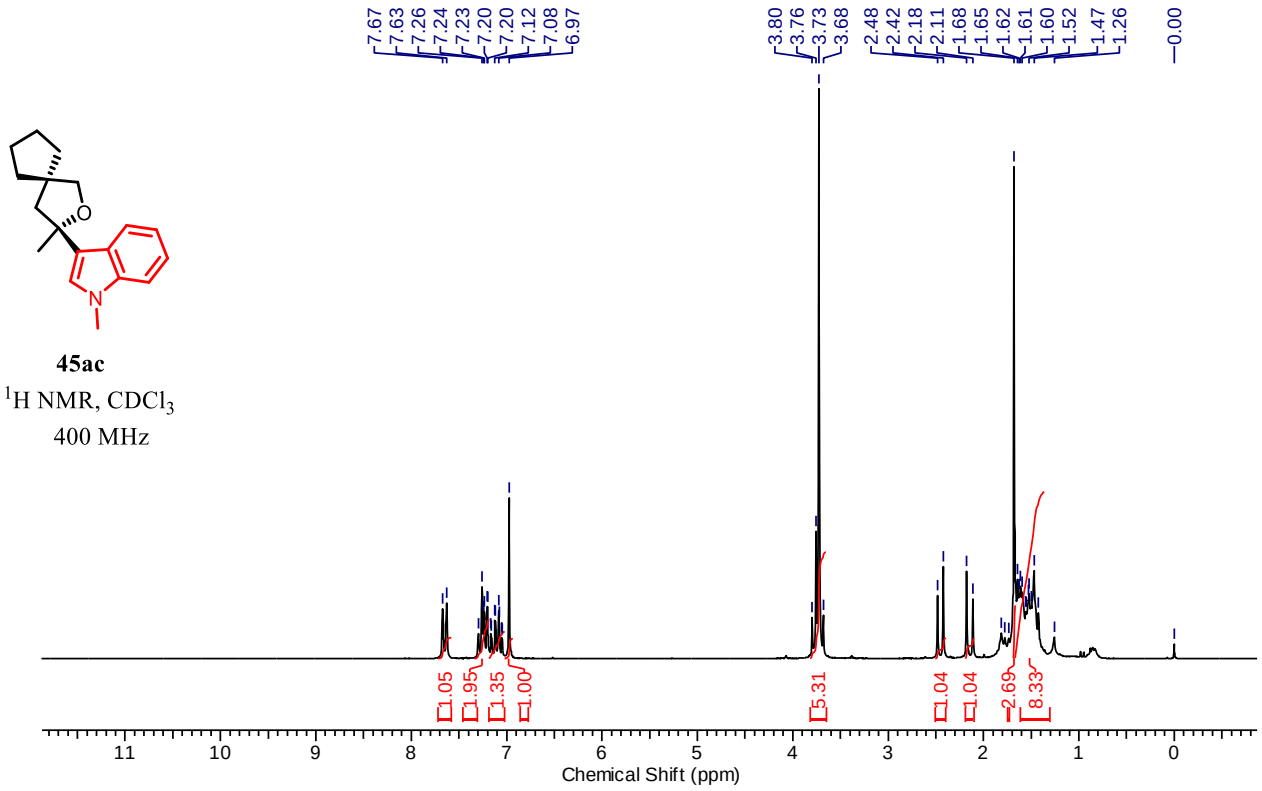
^{1}H NMR spectrum of compound 45ab



^{13}C NMR spectrum of compound 45ab



^{1}H NMR spectrum of compound 45ac

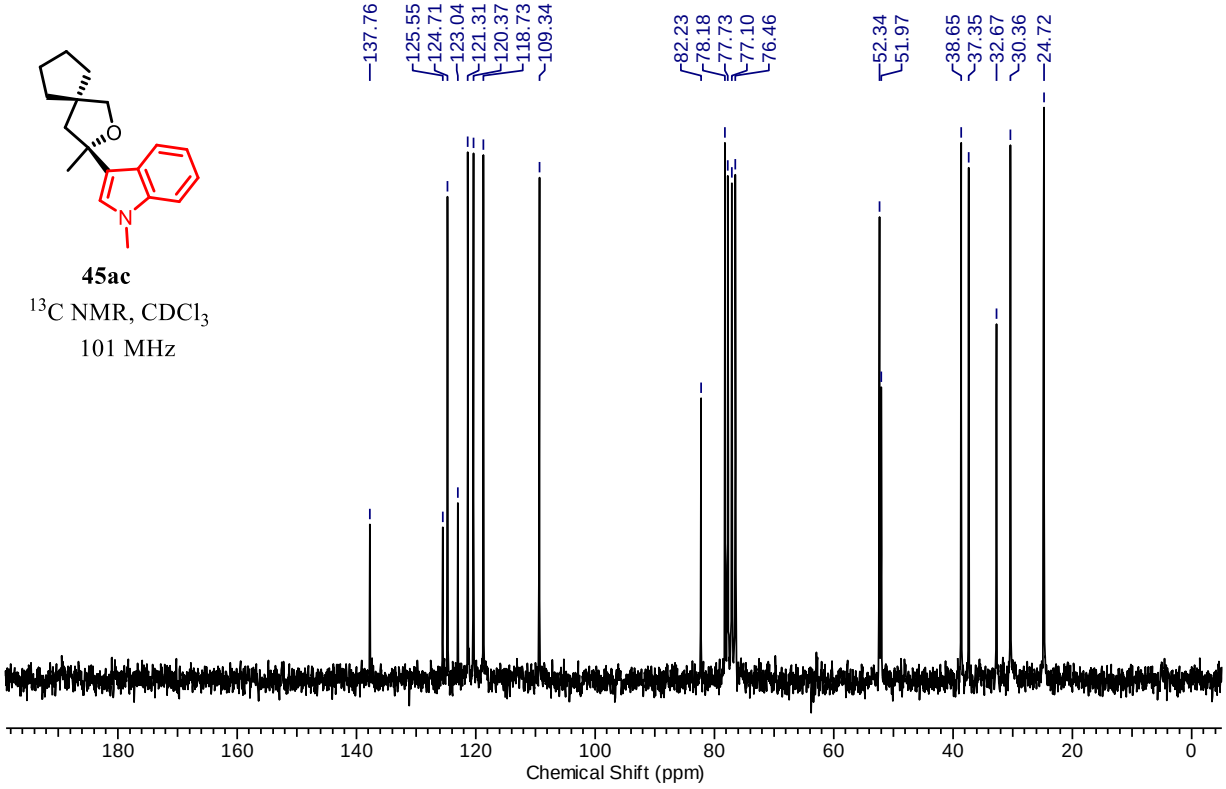


45ac

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 45ac

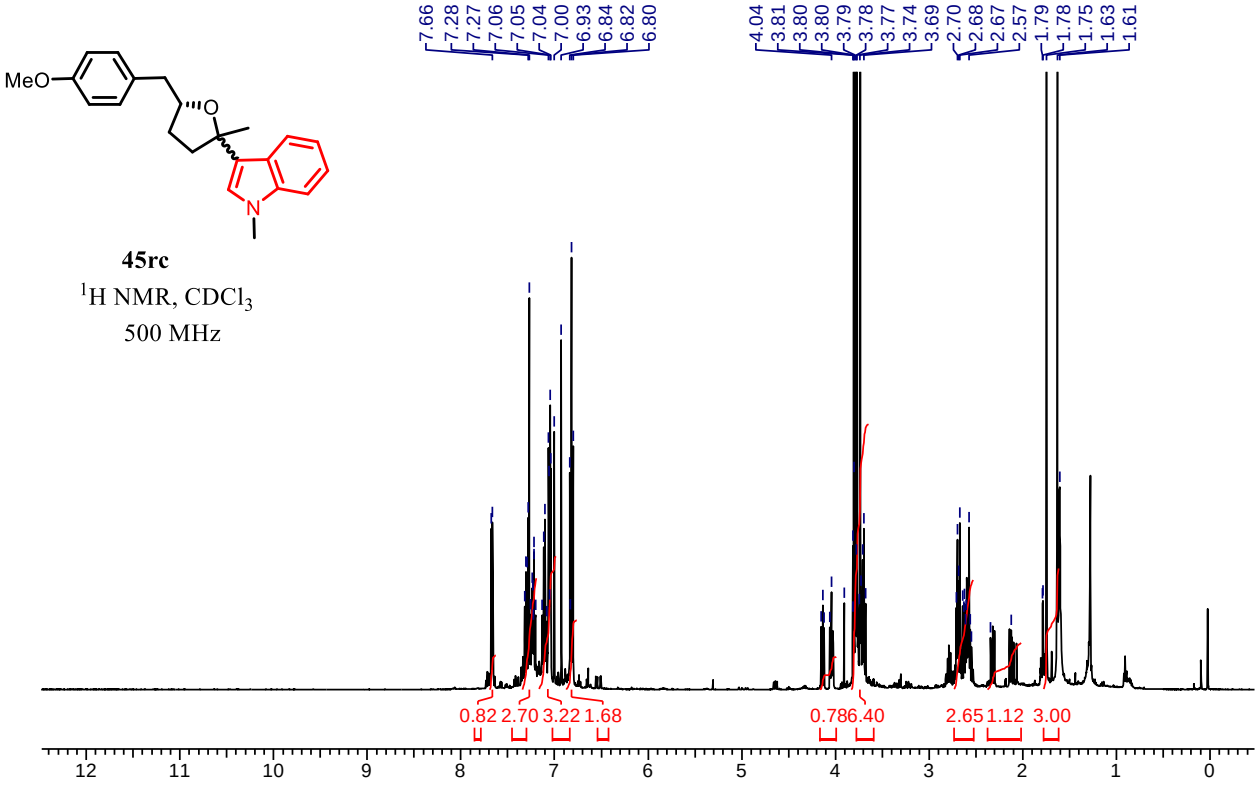


45ac

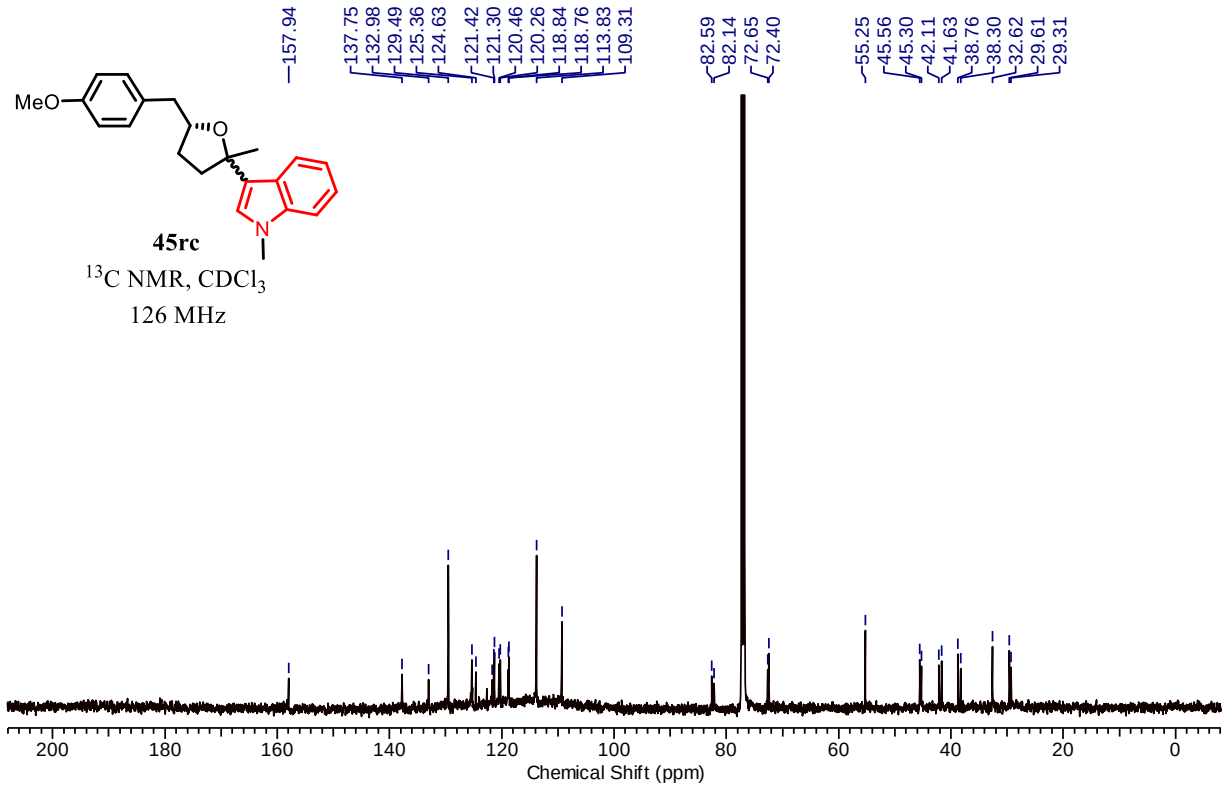
^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 45rc



^{13}C NMR spectrum of compound 45rc



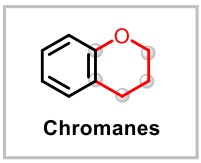
CHAPTER-3

Section-A

Introduction and previous approaches to chromanes

Chapter-3, Section-A: Introduction and previous approaches

3.1 Introduction



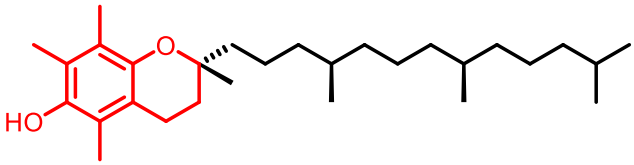
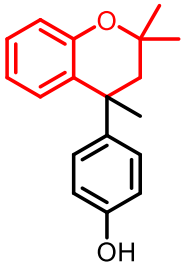
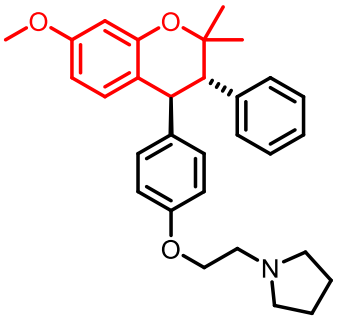
Heterocycles are widespread structural motifs found in various bioactive natural and unnatural compounds and are used as chemotherapeutic agents (mainly as antibiotic, antifungal, anti-inflammatory, anticancer, and cardiovascular agents). Particularly cyclic ether (tetrahydrofuran, tetrahydro-2H-pyran) containing small molecules has been successfully used in drug design as bioisosteres of amide (peptide) bonds in the discovery and development of potent protease inhibitors to help combat drug-resistant viral strains, among the many readily available O-heterocycles in the chemical world. By increasing the drug's affinity for binding to the receptors of the relevant enzymes, the oxygen atom of these cyclic ethers can generate H-bonds (like peptides). Additionally, replacing an amide bond with cyclic ether in the drug candidate makes the molecule more bioavailable and vulnerable to protease degradation.[1]

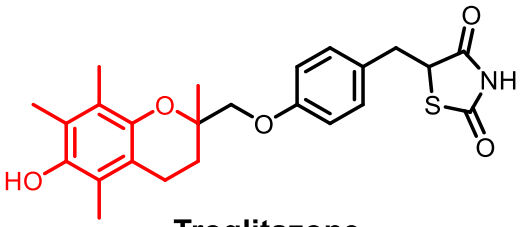
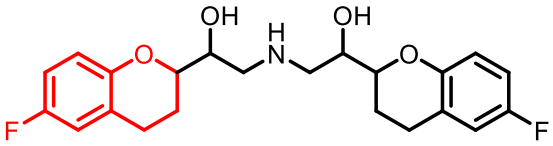
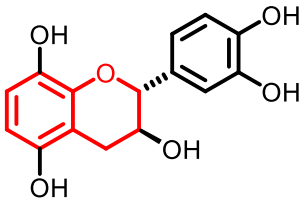
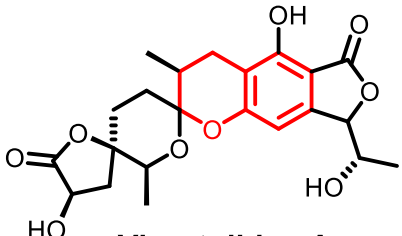
Chromane is a heterocyclic compound with a skeleton containing dihydropyran and benzene rings (fused bicycle). Generally, chromanes are omnipresent in biologically potent natural products and pharmaceuticals such as antiviral, antitumor, antimicrobial, sex pheromone, and those of central nervous system activity (Ellis and Lockhart, 2007; Horton et al., 2003).[2,3] Generally, all chromones derivatives are characterized by good membrane permeability properties and low cellular toxicity, and some derivatives inhibit mycobacterial growth as well as possessing antitumoral activity.[4]

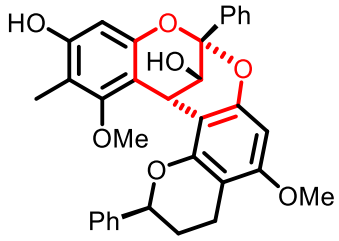
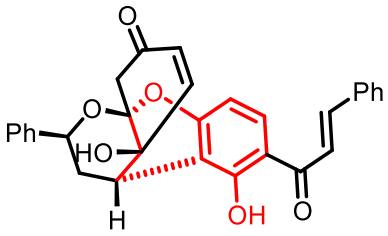
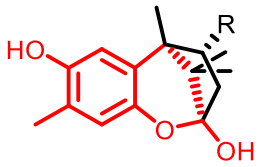
Inspired by the interesting structural features and biological activity profile of chromanes, and in continuation of our interest in developing novel synthetic methodologies for the construction of oxygen heterocycles involving alkynyl alcohols and carbonyl compounds as building blocks, we embarked on the development of a facile synthetic approach for simple to complex chromanes.

Herein, we furnish a brief literature survey of chromane-derived biologically active natural products (Table 3.1).

Table 3.1 | Representative chromane-containing natural products.

Sr. No.	Structure	Isolation and Activity
1.	 ***alpha*-Tocopherol** **&** ***beta/gamma/delta*-Tocopherols**	Alpha-tocopherol is known to display antioxidant properties and is used as a drug. It's an active form of Vitamin E.[5] The higher biological activity of alpha-tocopherol could be due to its higher water solubility.
2.	 **Dianin's Compound**	In 1914, Alexander disclosed the first total synthesis of dianin. Later, in 2005, Barbour demonstrated the host-guest chemistry of dianin's compound and studied the format of clathrates with suitably flexible guest molecules. [6]
3.	 **Ormeloxifene**	In 2013, Gara et al. disclosed the identification and biological profile of ormeloxifene. It is also known as centchroman (one of the selective estrogen receptor modulators). It has been used for birth control medication since the early 1990s in India. It was marketed there under the trade name Saheli.[7]

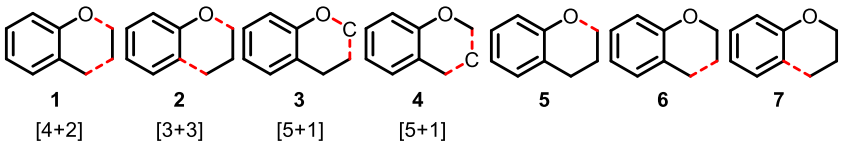
4.	 **Troglitazone**	Troglitazone is an anti-diabetic medication investigated in 2017 by Saha and co-workers. It has been found to impact HepG2 cells and AMP-activated protein kinase.[8]
5.	 **Nebivolol**	Jain and co-workers, in 2017, worked on the development of nebivolol. It is a third-generation β-blocker used to treat hypertensive patients with decreased blood pressure.[9]
6.	 **Catechins**	Kopustinskiene and the group worked on the chemistry and biology of catechins. These are polyphenolic flavans and are known to display potent antioxidant properties.[10]
7.	 **Virgatolides A**	Che et al. (in 2011) reported the isolation of virgatolides A–C from *Pestalotiopsis virgatula*, an endophytic fungus. These natural products exhibited mild cytotoxicity toward HeLa cells with IC_{50} values of 19.0, 22.5, and 20.6 M, respectively.[11]

8.	 **Dracoflavan B**	In 2015, Zhi *et al.* isolated dracoflavan B from the dragon's blood resin from *Daemonorops draco*, this natural product showed pancreatic α-amylase inhibitory activity with IC_{50} 23 μM and K_i= 11.7 μM.[12]
9.	 **(+)-Caesalpinnone A**	In 2017, Wang and co-workers isolated caesalpinflavans A–C (hybrids of flavone and chalcone) from the twigs and leaves of *Caesalpinnea enneaphylla*, and these natural products displayed excellent cytotoxic activity against several cancer cell lines.[13]
10.	 **Enokipodin A (R = H)** **Enokipodin C (R = OH)**	In 2000, Ishikawa and co-workers isolated enokipodin A and B from the culture broth of an *edible mushroom.* These showed antimicrobial activity against fungus and gram-positive bacteria.[14]

3.1.1 Previous approaches for the synthesis of chromanes

I. Synthesis of chromanes from pre-functionalized arenes.

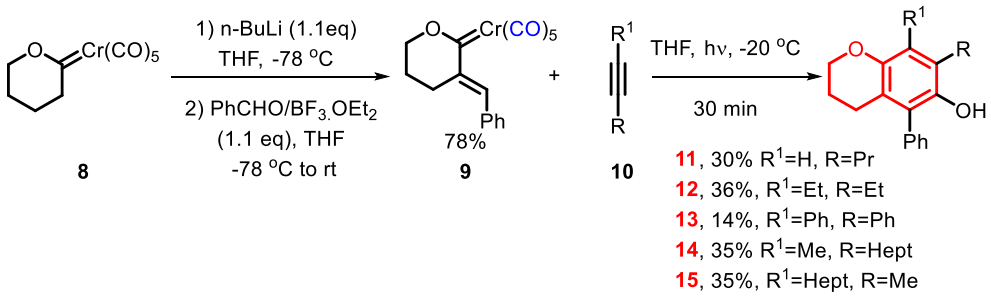
A general strategy that was extensively studied for constructing chromanes using pyran ring closure from pre-functionalized arenes. This strategy mainly involves intramolecular [6]-ring closures, [4+2], [3+3], and [5+1] annulations, as well as enantioselective cyclization (relies on the Diels-Alder approach) (Scheme 3.1.1).[15]



Scheme 3.1.1

II. Synthesis of chromanes from pre-functionalized dihydropyran-mediated carbene benzannulation

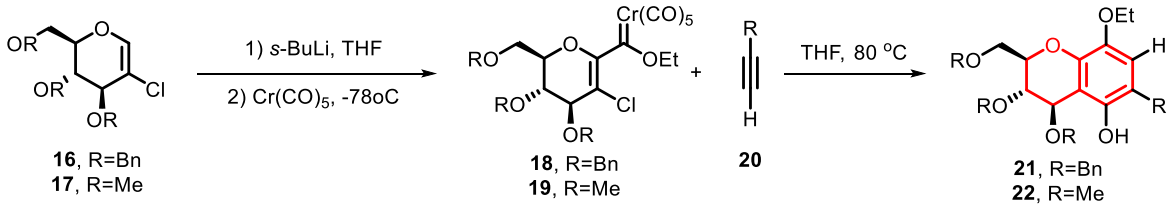
In 1998, Dötz and co-workers showed the photochemical benzannulation reaction of thermostable chromium carbene complex.[16] The tetrahydropyran **8** was treated with n-BuLi in THF, followed by benzaldehyde in the presence of $BF_3.OEt_2$ to give corresponding Fisher chromium carbene complexes **9**, which is irradiated at -20 ^oC for 30 min in the presence of 5 equivalents of alkynes **10** to get the corresponding 5,7,8-trisubstituted 2,3-dihydro-6-benzopyranols *via* cycloaddition reaction. In this transformation, they were able to isolate tricarbonyl chromium complexes (Scheme 3.1.2).



Scheme 3.1.2

III. Synthesis of carbohydrate-derived chromanes through annulation of Fisher chromium carbene complexes with alkynes.

In 1998, Ricketts and Quayle, developed an exciting protocol for the construction of carbohydrate-derived chromanes through the annulation of carbohydrate-derived chromium carbene complexes with alkynes. Carbohydrate derived dihydropyrans (**16**/**17**) were converted into corresponding carbohydrate-derived chromium carbene complexes **18**, **19** *via* the initial lithiation using s-BuLi, followed by the exchange with chromium. Subsequent annulation reaction of these chromium carbenes with alkynes delivered corresponding chromanes in good to excellent yields (Scheme 3.1.3).[17]

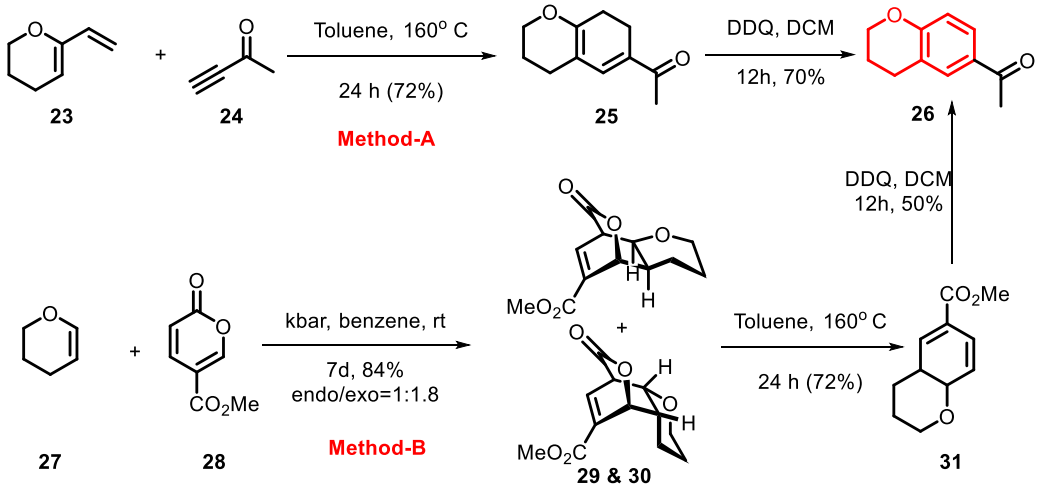


Scheme 3.1.3

IV. Synthesis of chromanes via Diels-Alder reaction of pre-constructed pyrans as dienes or dienophiles.

In 1019, Kirschning and co-workers reported an exciting methodology for the construction of chromanes via [4+2]-cycloaddition of dihydropyran-derived diene or dienophiles with ynones or pyranones, which provide access to the formation of the benzene ring.[18] In method-A, dihydropyran-derived diene **23** undergoes [4+2]-cycloaddition reaction with ynones dienophile **24** to deliver the corresponding cyclized product **25** with **72%,** which was subsequently subjected to DDQ-mediated oxidative aromatization to get the acyl-substituted chromane **26**.

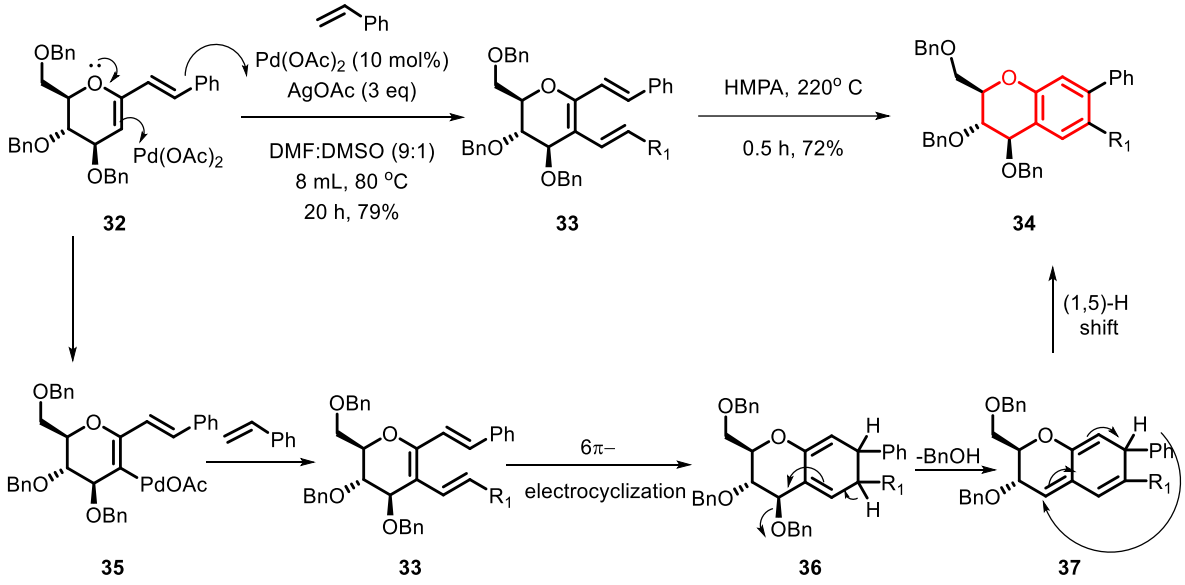
In an alternative route (method-B), the same acyl-substituted chromane **26** was synthesized from dihydropyran **27** (used as a dienophile) and pyranones **28** (used as a diene). This reaction proceeds through the inverse-electron demand Diels-Aldrer pathway. It delivers an *endo*/*exo* mixture of adducts **29** and **30** in 84% yield, subsequent thermal decomposition of adducts to give bicyclic pyran-tethered diene **31** followed by DDQ-mediated oxidative aromatization delivered the desired product 26 (Scheme 3.1.4).



Scheme 3.1.4

V. Synthesis of chromanes through 6-π-electrocyclization of pyran-derived triene.

Recently, in 2020 Maikhuri *et al*. developed an interesting synthetic strategy from carbohydrate-derived chromanes using multi-step involving 6-π-electrocyclization of pyran tethered triene in HMPA followed by in situ aromatization.[19] Synthetic sequence involves the palladium-catalyzed Fujiwara–Moritani reaction of tetrahydropyran **32** to give its organo-palladium species **35**, which would undergo Heck coupling reaction with styrene to deliver the triene intermediate **33**. This intermediate undergoes further thermal 6-π-electrocyclization to furnish chromane 34 with simultaneous elimination of BnOH and (1,5)-H shift (Scheme 3.1.5).

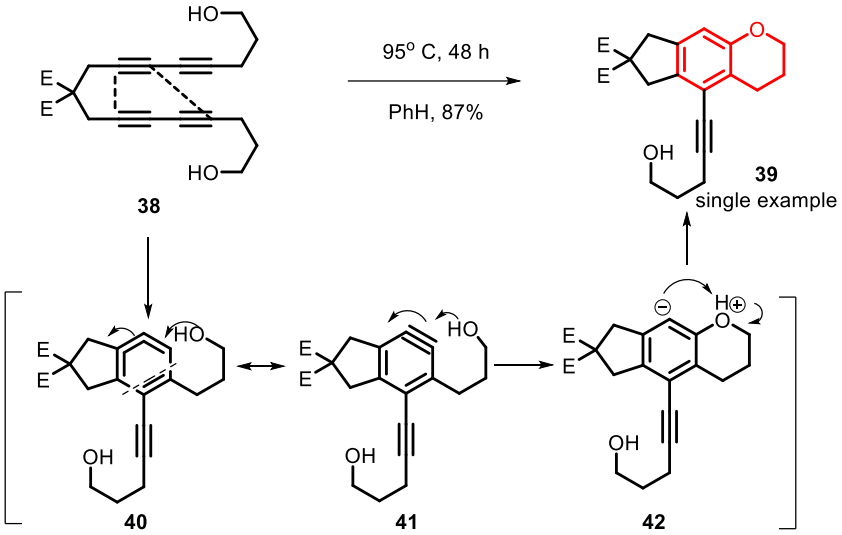


Scheme 3.1.5

VI. Through hexa-dehydro Diels-Alder reaction (HDDA) reaction involving triyne-alkynol

In 2012, Wood and co-workers disclosed an expeditious methodology for synthesizing chromanes **39** via metal-free intramolecular hexa-dehydro Diels-Alder reaction (HDDA) of triyne-tethered alkynol **38** to install both rings from acyclic building blocks simultaneously.[20]

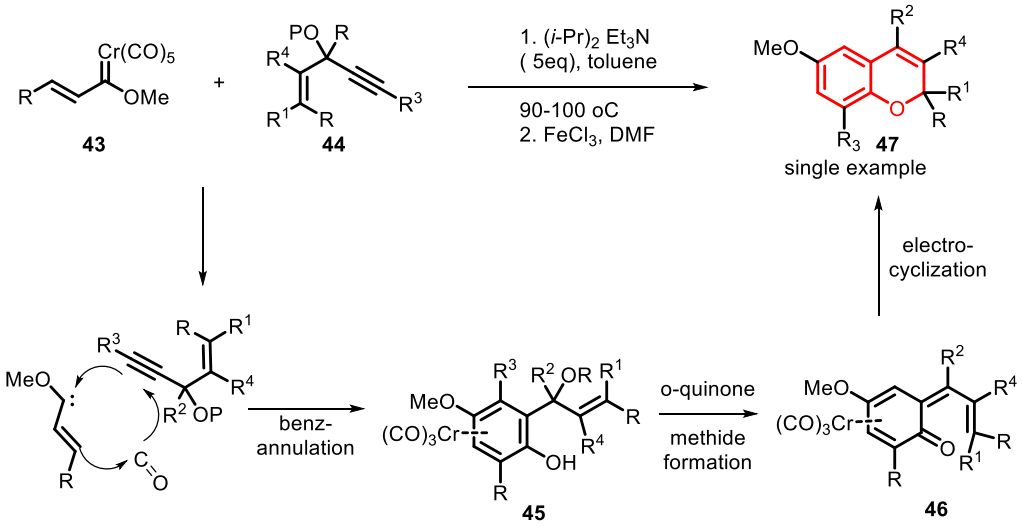
Mechanistic steps include a straightforward thermal HDDA reaction of triyne building block 38, which generates an aryne intermediate 41 via 40. It undergoes an intramolecular hydroalkoxylation to give **39** via **42** (Scheme 3.1.6).



Scheme 3.1.6

VII. 6-π-electrocyclization or [4+2]-cycloaddition reaction of α,β-unsaturated Fischer-carbene complex of chromium with alkenyl-propargylic ethers

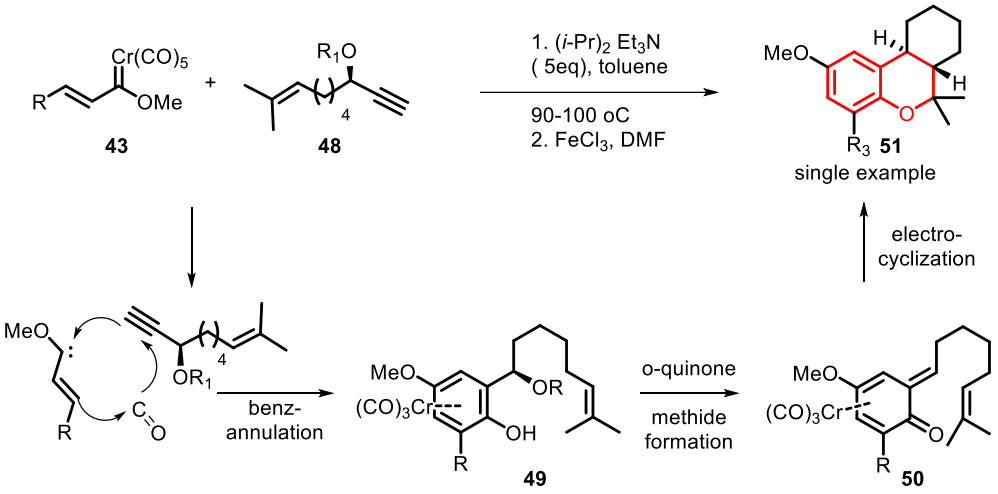
In 2012, Wulff's research groups reported an elegant method to access chromanes via α,β-unsaturated Fischer-carbene complex of chromium with alkenyl-propargylic ethers via 6-π-electrocyclization or [4+2]-cycloaddition of in situ formed *o*-quinone methide.[21] They demonstrated that the reaction mechanism involves cascade transformations by following the first benzannulation step to give phenol **45** followed by the formation of o-quinone methide. Which undergoes subsequent electrocyclization reaction to form chromane **47** via **46** (Scheme 3.1.7).



Scheme 3.1.7

VII. Stereoselective [4+2]-cycloaddition reaction of α,β-unsaturated Fischer-carbene complex of chromium with alkenyl-propargylic ethers

Like the previously discussed approach, Wulff's research group reported an interesting methodology for the construction of tricyclic hexhydrodibenzopyrans **51** starting from chiral propargylic ethers **43** and α,β,-unsaturated Fischer-carbene complex of chromium **48** via 6-electron cyclization or [4+2]-cycloaddition of in situ formed o-quinone methide (Scheme 3.1.8).[22]



Scheme 3.1.8

Above discussed methods have significant shortcomings, including selectivity, a narrow range of substrates, the need for stoichiometric amounts of catalysts, unfavorable reaction conditions, additional stages to obtain the raw materials, etc. Therefore, it is necessary to discover practical and valuable synthetic methods to build these crucial chromanes scaffolds. To the best of our knowledge, there is no report on the construction of both rings of chromanes (particularly bicyclic) through an intermolecular cascade reaction.

3.1.2 σ, π and dual activation process (our hypothesis)

As discussed in previous Sections of the thesis, carbonyl compounds undergo σ-activation in the presence of diverse Lewis acids and Brønsted acid catalysts and deliver various 1,2-addition/1,4-addition products. Similarly, unsaturated molecules like alkynes/alkenes undergo π-activation with Lewis acids and Brønsted acid catalysts and participate in nucleophilic addition reactions ad deliver various products. Cascade annulation reactions of these functional groups (carbonyl compounds with alkynes/alkene) are well-reported in the literature using two

catalyst-mediated one-pot transformations (particularly involving transition-metal catalyzed σ- and π-activation) (Scheme 3.1.9).

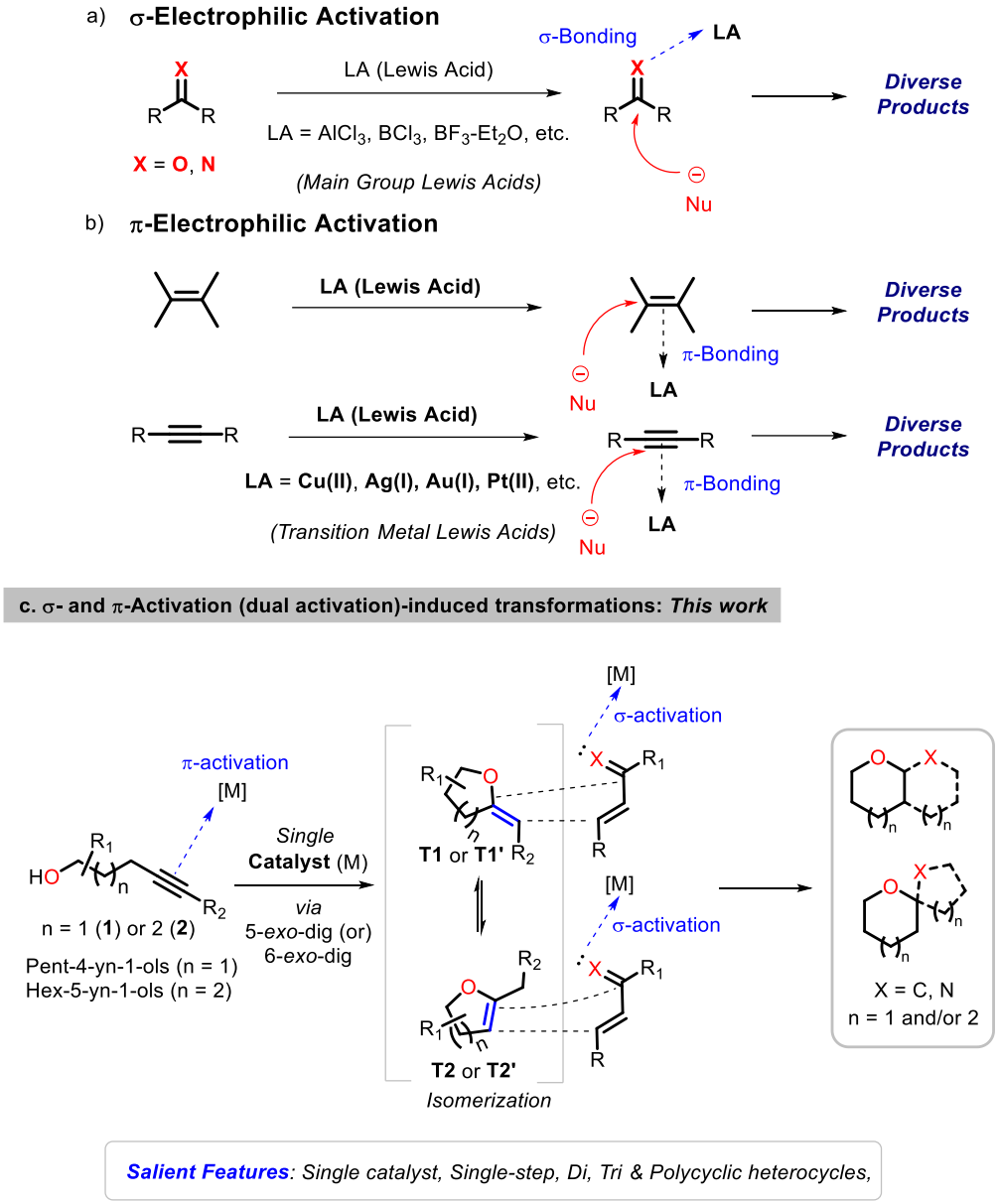


Figure 3.1.9 | σ, π, and dual activation process.

Inspired by the interesting structural and bioactivity profile of chromanes, and in continuation of our interest in developing single catalyst-mediated cascade annulation reactions of alkynols and carbonyl compounds, herein, we devised a novel hypothesis to access chromanes from readily accessible 5-hexyn-1ols, and α,β-unsaturated carbonyl compounds utilizing a single catalytic system in a cascade manner.

CHAPTER-3

Section-B

Silver-catalyzed [3+3]-annulation cascade of alkynyl alcohols and α-β,-unsaturated ketones for the regioselective assembly of chromanes

3.2. Hypothesis

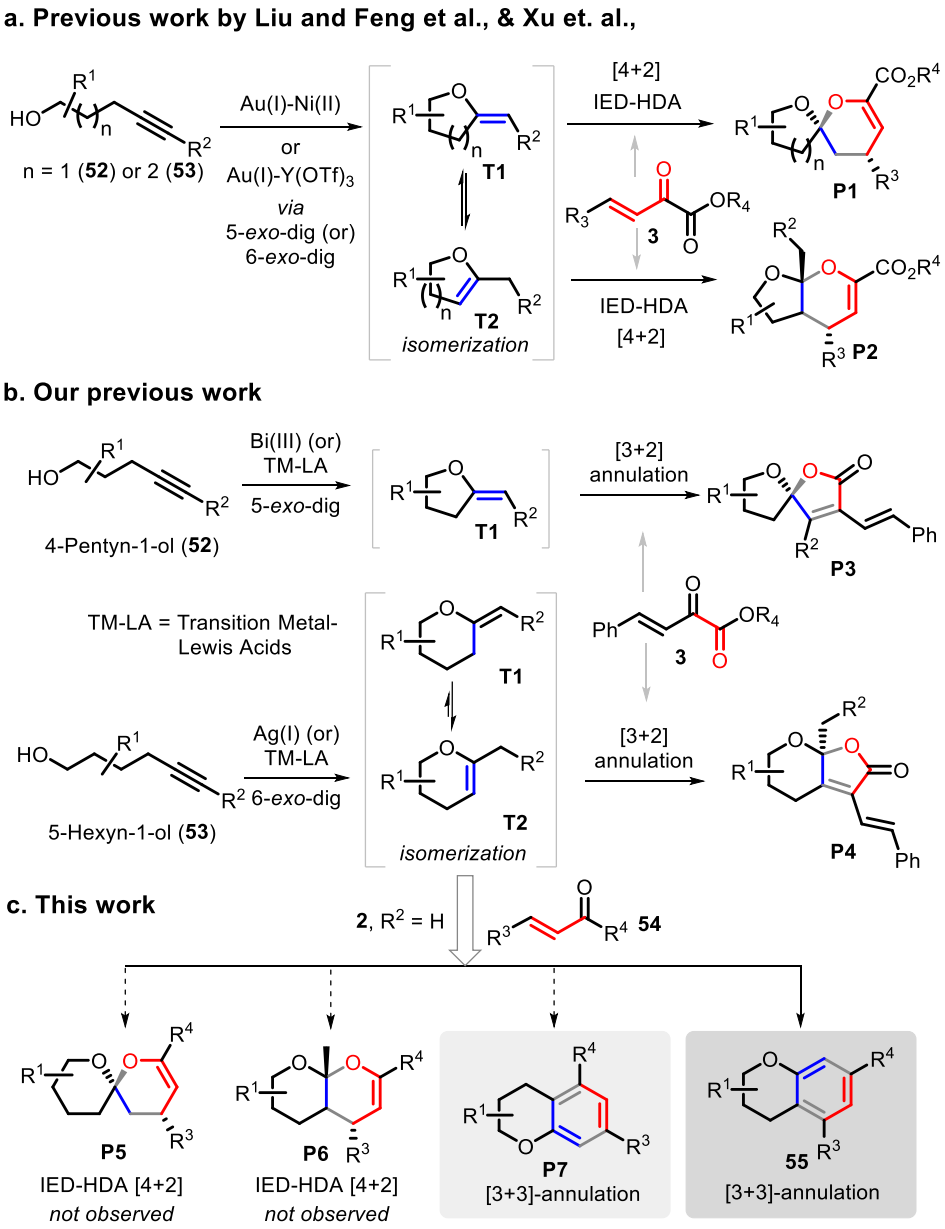
Inspired by the emerging importance of cascade/domino reactions as part of our interest in developing new synthetic methodologies involving cycloisomerization of internal alkynols (**52** or **53**and others) as building blocks are emerging as versatile tools for constructing diverse heterocycles. Generally, these reactions proceed through the initial π-electrophilic catalyst-promoted cycloisomerization alkynols via *exo*-dig or *endo*-dig mode of cyclization to give respective cyclic enol ethers (**T1** or **T2**), and their subsequent participation in transformations of Povarov reaction,[23] Prins-type cyclization,[24] acetal or spiroacetal formation through the intermediacy of an oxocarbenium species,[25] [4+2]-cycloaddition and others (Scheme 1).[26]

Recently, Liu and Feng's, and Xu's research groups disclosed participation of cyclic enol ethers (**T1** and **T2**) as dienophiles in inverse-electron demand hetero-Diels-Alder (IED-HDA) reaction with β-γ-unsaturated α-ketoesters **3** to give spiroketals **P1** or fused acetals **P2** under catalyst dependent conditions (Scheme 1, entry a).[27] In contrast to these findings, we previously reported that 4-pentyn-1-ols **52** would react with *α*-ketoesters or β-γ-unsaturated α-ketoesters **3** to deliver [5,5]-oxaspirolactones **P3**,[28] and 5-hexyn-1-ols **53** would undergo [3+2] annulation with **3** to give furopyranones[29] **P4** instead of IED-HDA adducts (**P1**, **P2**) under Bi(III) and Ag(I) or Au(I)-Ag(I)-catalysis respectively. These distinct results could be attributed to the act of cyclic enol ethers (**T1** and **T2**) as enolizable carbonyl equivalents under specific catalytic conditions. Their participation in the initial 1,2-addition reaction with the carbonyl functionality of α-ketoesters **3** and subsequent annulation (Scheme 1, entry b).

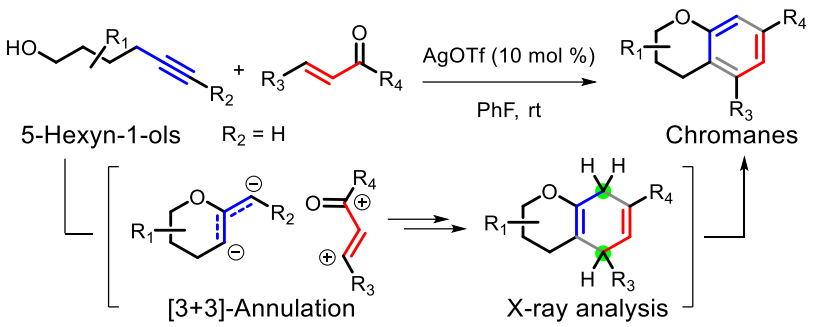
In continuation to this work, we were curious to explore the reactivity of alkynyl alcohols **53** with readily accessible α,β-unsaturated ketones **54** employing our previously identified σ and π-dual activating[30] catalytic systems,[28, 29, 31] that may deliver either ketals (spiro/fused) **P5**, **P6** through [4+2]-cycloaddition (IED-HDA), or regio-isomeric chromanes **P7** or **55** via [3+3]-annulation pathways (Scheme 1, entry c).

3.2.2 Result and discussions

To investigate the feasibility of this hypothesis, known alkynol **53a** (1.0 mmol) and (*E*)-4-phenylbut-3-en-2-one **54a** (2.0 mmol) were treated with AgOTf (10 mol %, 0.10 mmol), in anhydrous PhF under argon atmosphere. The reaction proceeded smoothly and gave the desired chromane **55aa** in a good yield of 87% in 6 h at room temperature (Scheme 3.2.2)



Scheme 3.2.1 | Intermolecular cascade annulation reactions of alkynols with α,β-unsaturated carbonyl compounds using bimetallic catalysis, and our previous and current investigation.



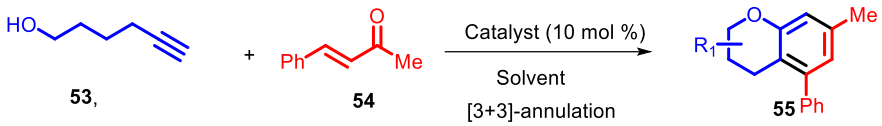
Scheme 3.2.2 | Strategy for synthesis of chromanes from alkynols.

3.2.3 Optimization of reaction conditions

We initiated our studies by probing representative reaction conditions between commercially available 5-hexyn-1-ol **53a** and (*E*)-4-phenylbut-3-en-2-one **54a** (Table 3.2.3). Delightfully, the initial experiment using AgOTf (10 mol %) in $(CH_2)_2Cl_2$ and equimolar **53a** and **54a** at room temperature (rt, 27 °C) furnished chromane **55aa** with exclusive regioselectivity in a good yield of 62% in 6 h, no trace amounts of IED-HDA adduct **P5** or **P6**, and isomeric chromane **P7** were observed (Scheme 3.2.1, entry c; Table 3.2.3, entry 1). This formation of chromane **55aa** could be ascribed to the bis-nucleophilic character of enol-ether intermediates **T1** or **T2** (Scheme 3.2.1, entries b and c) formed from alkynol **53**, and their subsequent reaction with bis-electrophilic enone **54**. Fascinated by this result, we continued further to ascertain optimal reaction conditions to improve the overall efficiency of this [3+3]-annulation through altering solvent, temperature, and ratio of substrates under AgOTf catalysis (Table 3.2.3, entries 1-7), which led to discerning the best outcome of 87% yield of **55aa** in PhF (reaction found to be clean and faster in PhF compared to other solvents tested) at rt using alkynol **53a** and enone **54a** in 2:1 molar ratio and 10 mol % of AgOTf (Table 3.2.3, entry 4 and 5). Whereas other silver salts (AgCl, AgBr, AgI, $AgNO_3$ and AgO) failed to facilitate this annulation reaction (Table 3.2.3, entries 8-12). Next, a series of known π-electrophilic catalysts were examined, and it found that AuCl, $Hg(OTf)_2$, $Bi(OTf)_3$ could catalyze this reaction but with compromised yields (53-70%) and longer reaction time (Table 3.2.3 entries 13-16). Among several

other metal triflate-based catalysts tested, $Sc(OTf)_3$, $Fe(OTf)_3$, $Cu(OTf)_2$, and $In(OTf)_3$ delivered **55aa** in low to moderate yields (15-52%) (Table 3.2.3, entries 17-24). Whereas $Ni(OTf)_2$, $Zn(OTf)_2$ and $Yb(OTf)_3$ failed to facilitate the task. Brønsted acids *p*-TsOH, PPTS, and TFA were found to be futile catalysts (Table 3.2.3, entries 25-27). Control experiments using TfOH as a catalyst (a usual impurity of metal-triflates) and without using a catalyst validated the function of AgOTf in this annulation reaction (Table 3.2.3, entries 28 and 29).

Table 3.2.3 | Optimization of reaction conditions[a]



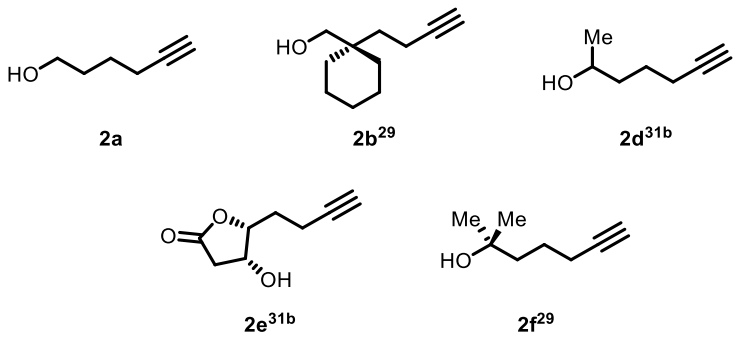
Entry	Catalyst	Solvent, temp.	Time	Yield (%)
1	AgOTf	CH_2Cl_2, rt	6 h	62[c]
2	AgOTf	$(CH_2)_2Cl_2$, rt	6 h	70
3	AgOTf	Toluene, 85 °C	6 h	57
4	**AgOTf**	**PhF,** rt	**2 h**	**75**
5	**AgOTf**	**PhF,** rt	**6 h**	**87**
6	AgOTf (5 mol %)	PhF, rt	12 h	60
7	AgOTf (2 mol %)	PhF, rt	12 h	45
8	AgCl	PhF, rt	12 h	-[c]
9	AgBr	PhF, rt	12 h	-[c]
10	AgI	PhF, rt	12 h	-[c]
11	$AgNO_3$	PhF, rt	12 h	-[c]
12	Ag_2O	PhF, rt	12 h	-[c]
13	AuCl	CH_2Cl_2, rt	12 h	70
14	$Hg(OTf)_2$	CH_2Cl_2, rt	12 h	68
15	$Bi(OTf)_3$	CH_2Cl_2, rt	12 h	53
16	$Bi(OTf)_3$	PhF, 85 °C	12 h	65
17	$Sc(OTf)_3$	CH_2Cl_2, rt	12 h	15
18	$Fe(OTf)_3$	CH_2Cl_2, rt	12 h	15
19	$Fe(OTf)_3$	PhF, 85 °C	12 h	42
20	$Ni(OTf)_2$	CH_2Cl_2, rt	12 h	-[c]

21	$Cu(OTf)_2$	CH_2Cl_2, rt	12 h	43
22	$Zn(OTf)_2$	CH_2Cl_2, rt	12 h	-[c]
23	$In(OTf)_3$	CH_2Cl_2, rt	12 h	52
24	$Yb(OTf)_3$	CH_2Cl_2, rt	12 h	-[c]
25	*p*-TsOH	$(CH_2)_2Cl_2$	6 h	-[d]
26	PPTS	$(CH_2)_2Cl_2$	6 h	-[d]
27	CF_3COOH	$(CH_2)_2Cl_2$	6 h	-[d]
28	TfOH	$(CH_2)_2Cl_2$	6 h	-[d,e]
29 [d]	no catalyst	PhF	6 h	-[d,e]

[a]Unless otherwise noted all reactions were carried out with **54a** (1.0 mmol), **53a** (2 mmol) and catalyst (10 mol %) at rt. [b]Isolated yields of **55aa**. [c]**54a** (1 mmol) and **53a** (1 mmol) used. [d]No reaction was observed. [e]Control experiments Tf = triflate (CF_3SO_2).

2.2.4 Preparation of alkynol building blocks:

To investigate the generality of this methodology, we have prepared diverse 5-hexyn-1-ols and *α,β*-unsaturated ketones using the following strategies.



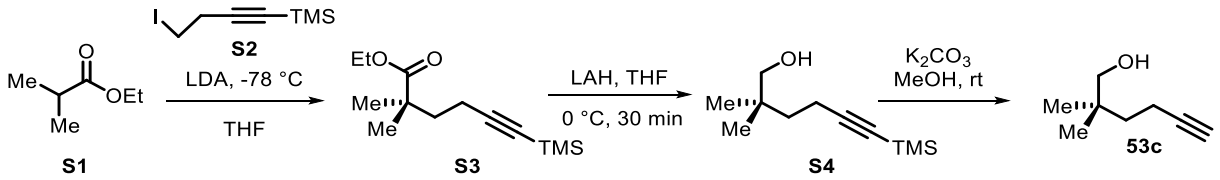
Scheme 3.2.3 | Preparation of alkynols.

Compound **53a, 53b, 53d, 53e, 53d, 53f** were prepared using known literature procedures.[29,31b]

Synthesis of alkynol 53c:

The alkynol **53c** were prepared from known carboxylic acid esters **S1.** LDA mediated *α*-alkylation of ester **S1** with iodo fragment **S2** at -78 °C in THF furnished the

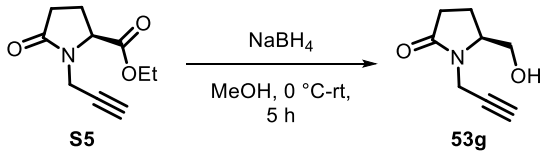
desired alkylated intermediate **S3**, which on subsequent reduction of ester functionality by using lithium aluminium hydride ($LiAlH_4$) in THF at 0°C gave **S4**. The K_2CO_3 mediated deprotection of the C-TMS group in MeOH gave the desired alkynol coupling partner **53c** (Scheme 3.2.4).



Scheme 3.2.2

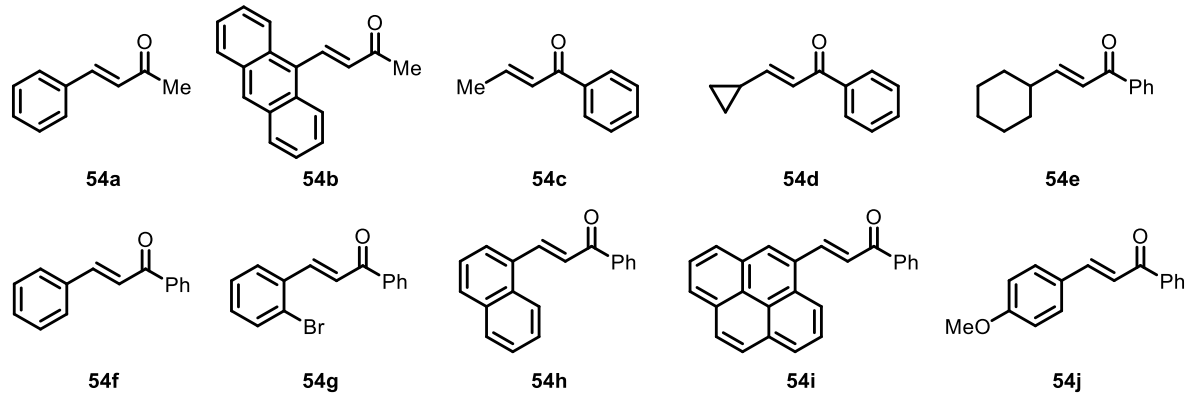
Synthesis of alkynol (53g):

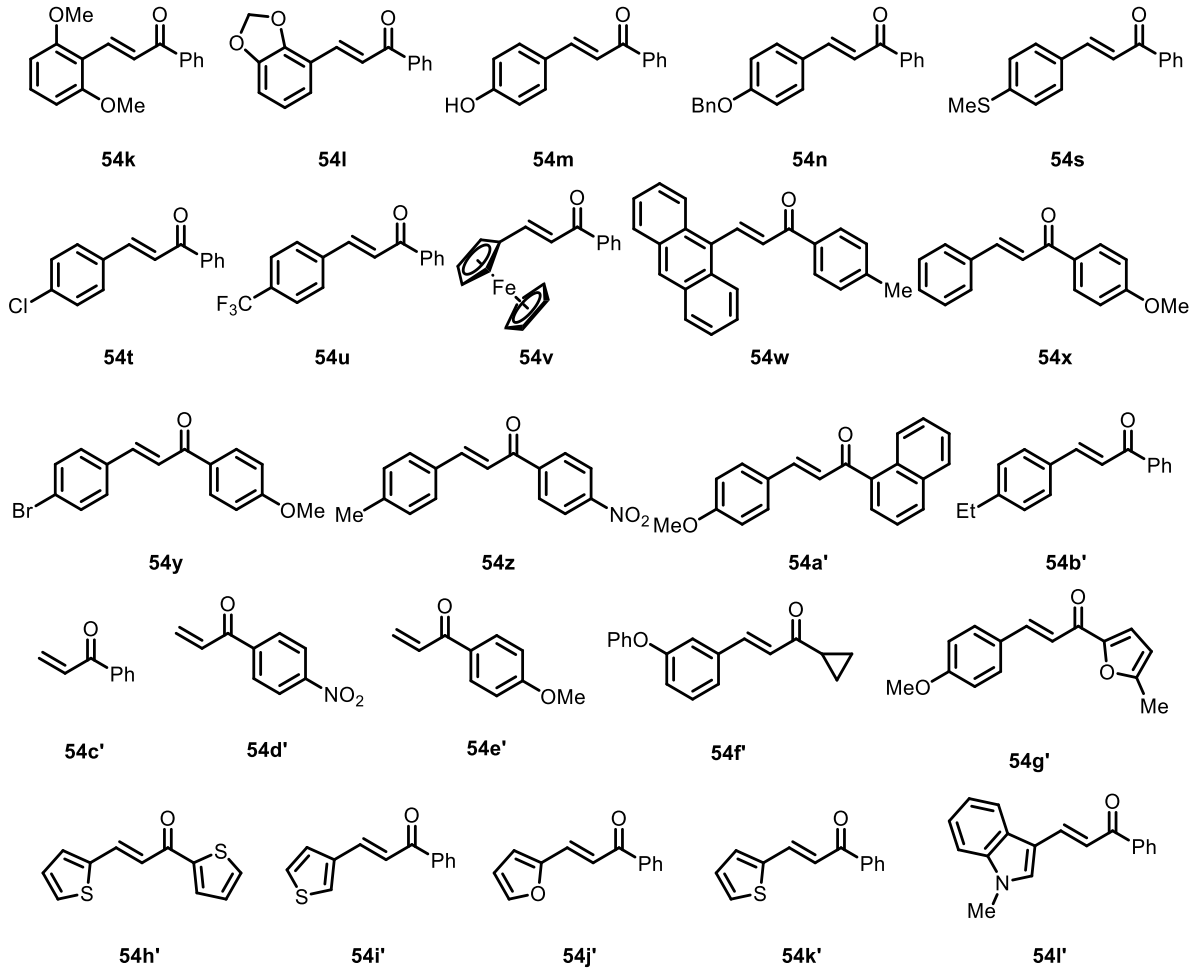
The alkynol **53g** was prepared by reduction of ester functionality by using sodium borohydride ($NaBH_4$) in MeOH at 0°C gave **53g** (Scheme 3.2.5).



Scheme 3.2.5`

Synthesis of α,β-unsaturated ketones (54):

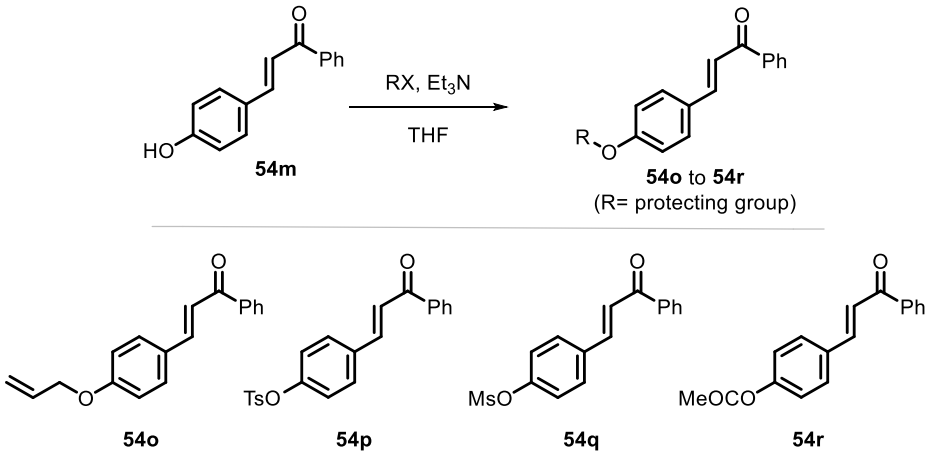




Scheme 3.2.6

Compound **54** was prepared using a known procedure (scheme 3.2.6).[32]

Synthesis of α,β-unsaturated ketones (chalcone) (54):



Scheme 3.2.7

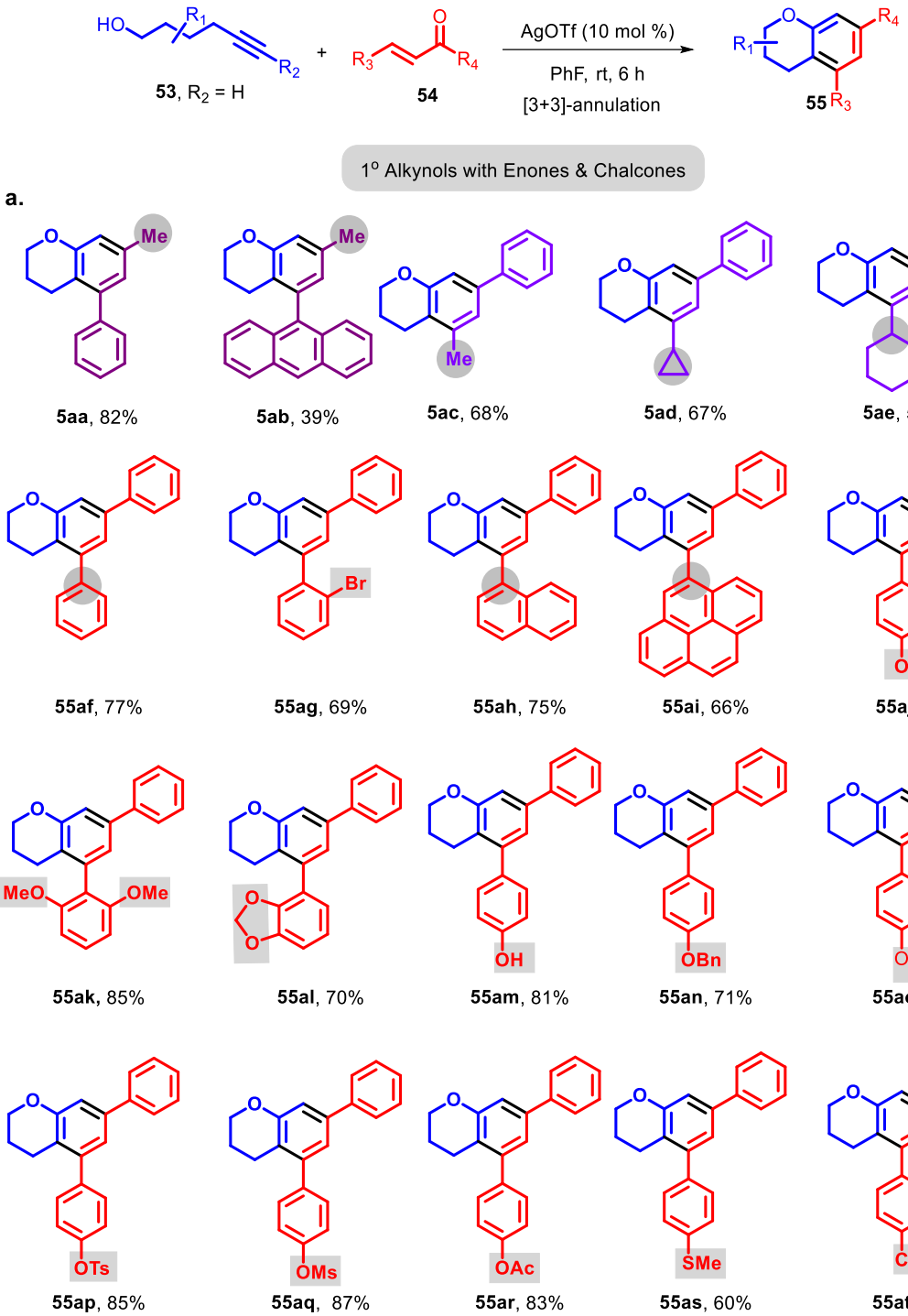
The chalcones **54o, 54p, 54q** and **54r** were prepared by the protection of 4-hydroxychalcone (**54m**) with organo-halide in the presence of triethylamine in THF to get required chalcones.

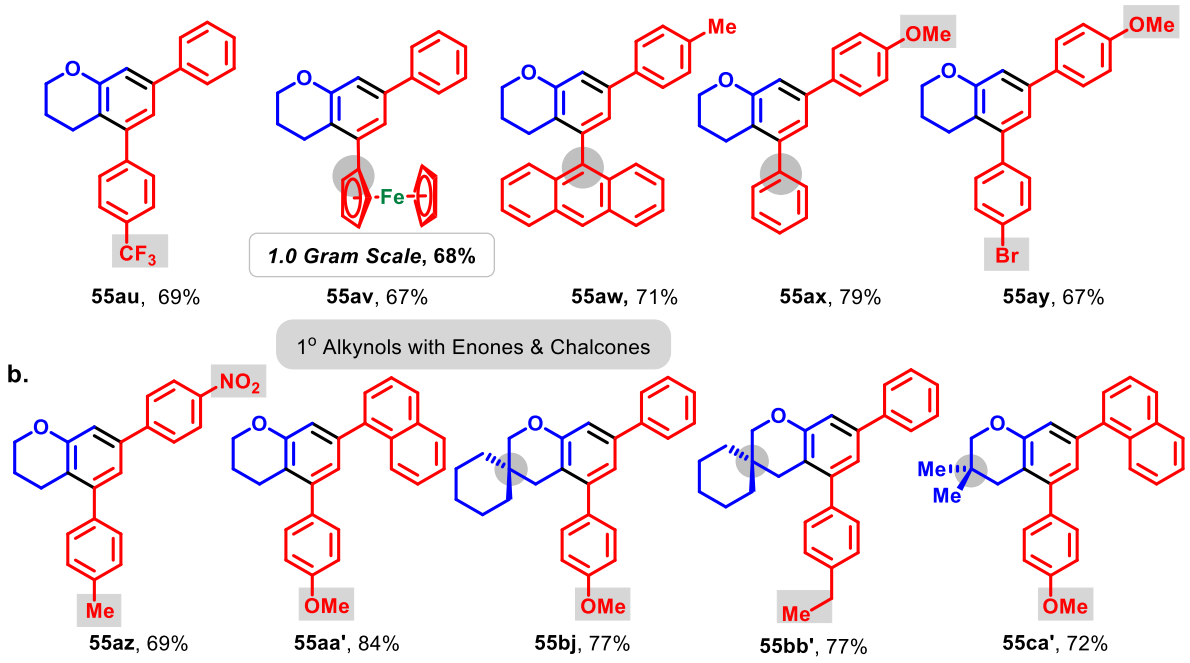
2.2.5 Scope and Generality of Reaction:

Having established optimal reaction conditions, we sought to explore the generality of this annulation reaction. As illustrated in Scheme 2, we methodically investigated the substrate scope of 5-hexyn-1-ols **53** and enones **54**.[3] Initially, diverse α,β-unsaturated ketones **4** were tested in combination with 5-hexyn-1-ols possessing primary hydroxyl group. Arylidene acetones bearing anthracenyl groups were treated with 5-hexyn-1-ol (**53a**) to access corresponding chromane **55ab** and 1,4-cyclohexadiene reaction intermediate **T3ab** (*vide infra*) in 39% and 34% yield, respectively. Methyl, cyclopropyl, and cyclohexyl substituted phenyl ketones successfully delivered corresponding chromanes **55ac-55ae** (56-68%) (Scheme 3.2.8, entry a).

Next, the reactivity profile of various chalcones possessing electronically and sterically divergent aryl constituents was verified using alkynol **53a** as a cascade partner (Scheme 3.2.8, entry b). Thus, performed reactions with chalcones containing phenyl, bromophenyl, naphthyl, pyrenyl, anisyl, 2,5-dimethoxyphenyl, and methylenedioxy-phenyl groups and prepared diverse chromanes (**55af-55al**) in good to excellent yields. The *p*-hydroxyphenyl derived chalcone was also well-tolerated and delivered chromane **55am** in 81% yield. Annulation of protected (with methyl, benzyl, allyl, tosyl, mesyl, and acetyl groups) phenol-derived chalcones with alkynol **53a** afforded chromanes **55aj-55ar** in 71-87% yields. Chalcones with *p*-SMe, *p*-Cl, *p*-CF_3-phenyl, and *p*-ferrocenyl groups were also found to be good annulation partners by delivering adducts **55as-55au** and **55av**. Alteration in aryl ketone part of chalcones (with *p*-Me, *p*-OMe, *p*-NO_2 and naphthyl) led to the formation of respective chromanes **55aw**, **55ax**, **55ay**, **55az** and **55aa'** in 67-84% yields. The cyclohexyl derived alkynol **53b** and *gem*-dimethyl substituted alkynol **53c** smoothly delivered corresponding chromanes

55bj, **55bb'** and **55ca'** (Scheme 3.2.8, entry b). Interestingly, acrylophenones (with phenyl, *p*-nitrophenyl, and *p*-anisyl groups) were also ascertained to be good substrates and delivered corresponding chromanes **55ac'**-**55ae'** in 54-85% yield (Scheme 3.2.8, entry a).

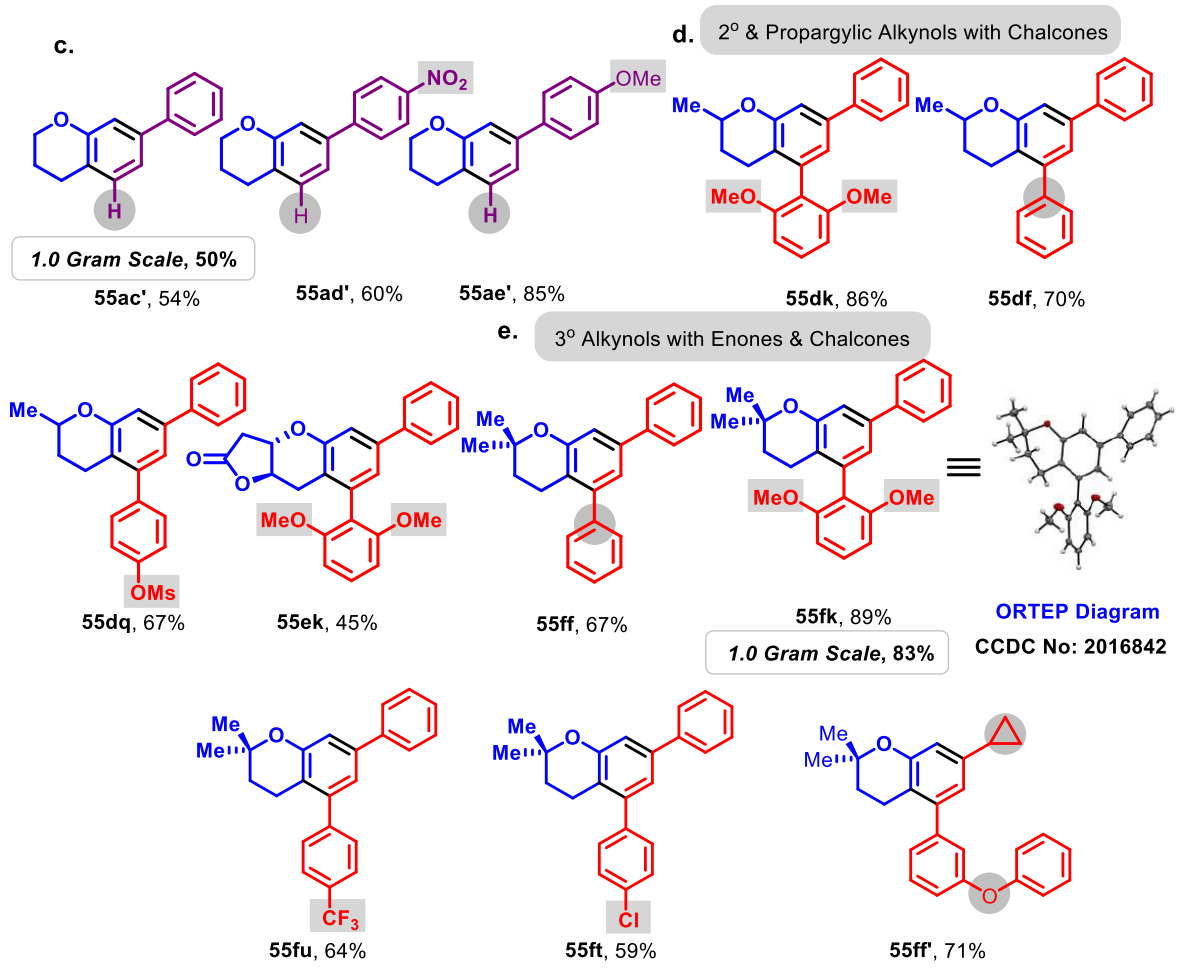




Scheme 3.2.8: Scope of [3+3]-annulation reaction concerning alkynols and enones. Reactions were performed on a 1.0 mmol scale, yield after column chromatography.

Secondary alkynols also well participated in this reaction and delivered corresponding chromanes **55dk**, **55df**, and **55dq** with equal ease that compared to primary alkynols. Known optically pure secondary alkynol possessing *trans*-butanolide skeleton was well reacted with chalcone **54k** and delivered pentacyclic complex chromane **55ek** in 45% isolated yield (Scheme 3.2.9, entry d).

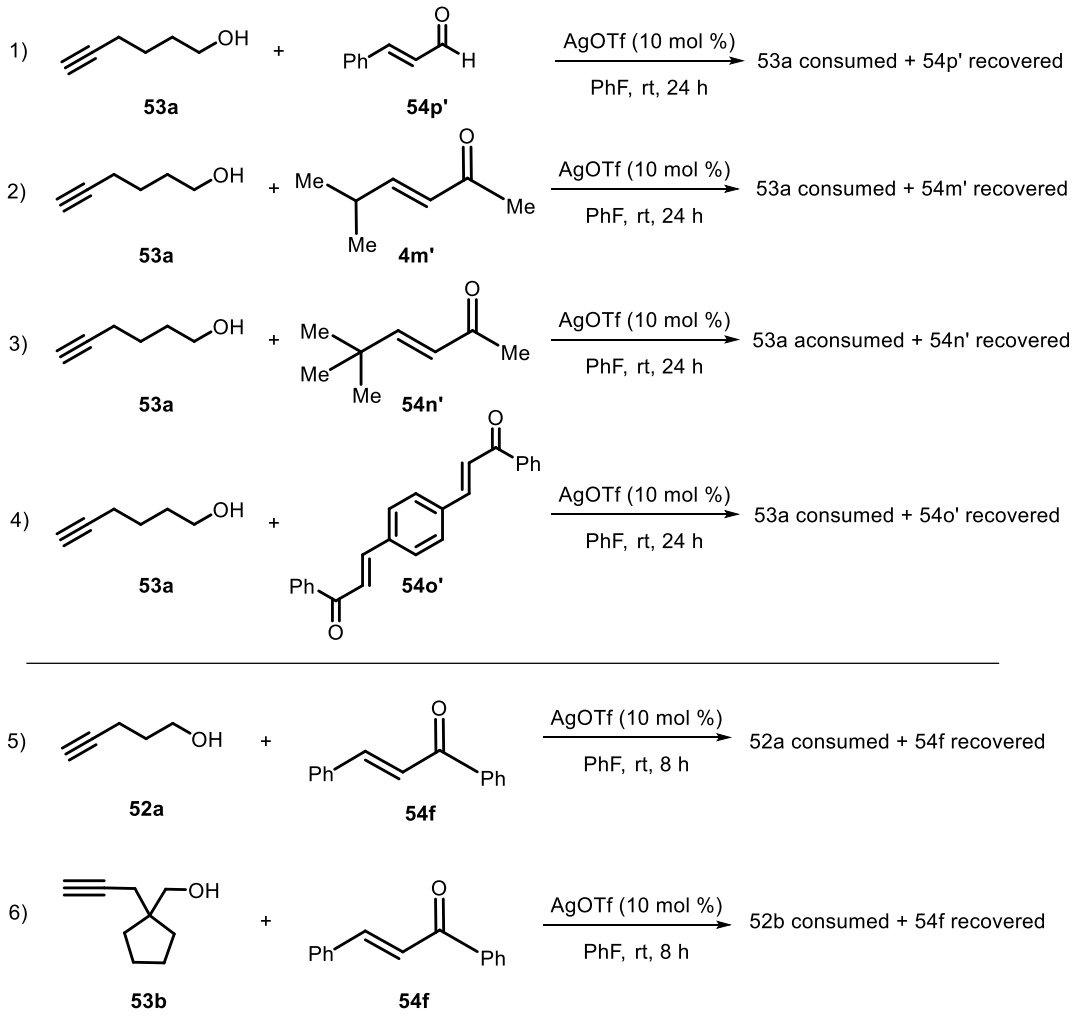
Alkynols possessing tertiary alcohol are also well-tolerated under optimal conditions and delivered a series of chromanes (**55ff**, **55fk**, **55fu**, **55ft**, and **55ff'**) in good yields (Scheme 3.2.9, entry c). Next, the practicality and scalability of this protocol were demonstrated by performing reactions on a 1.0-gram scale of enone, which delivered **55av**, **55ac'**, and **55fk** (Scheme 3.2.9) in good yields without loss of efficiency. Based on isolated yields, it is clear that electron-releasing substituents and small arene ring-size of chalcone and *geminal* substituents on alkynols would favor the outcome of the reaction. The structure and the regio-selectivity of all products were unequivocally determined by X-ray crystallographic analysis (of **55fk**) and analogy (Scheme 3.2.9, entry c).



Scheme 3.2.9: Scope of [3+3]-annulation reaction concerning alkynols and enones. Reactions were performed on a 1.0 mmol scale, yield after column chromatography.

Setting a limitation, the reaction of 5-hexyn-1ol (**53a**) with cinnamaldehyde and alkyl-derived enones, and internal 5-hexyn-1ols with chalcones/enones did not proceed. The reaction of analogous 4-pentyn-1-ol with chalcone ((2*E*)-1,3-diphenylprop-2-en-1-one) failed to deliver the anticipated 2,3-dihydro-benzofuran (entries 1-6, Scheme 3.2.10).

Unsuccessful examples:

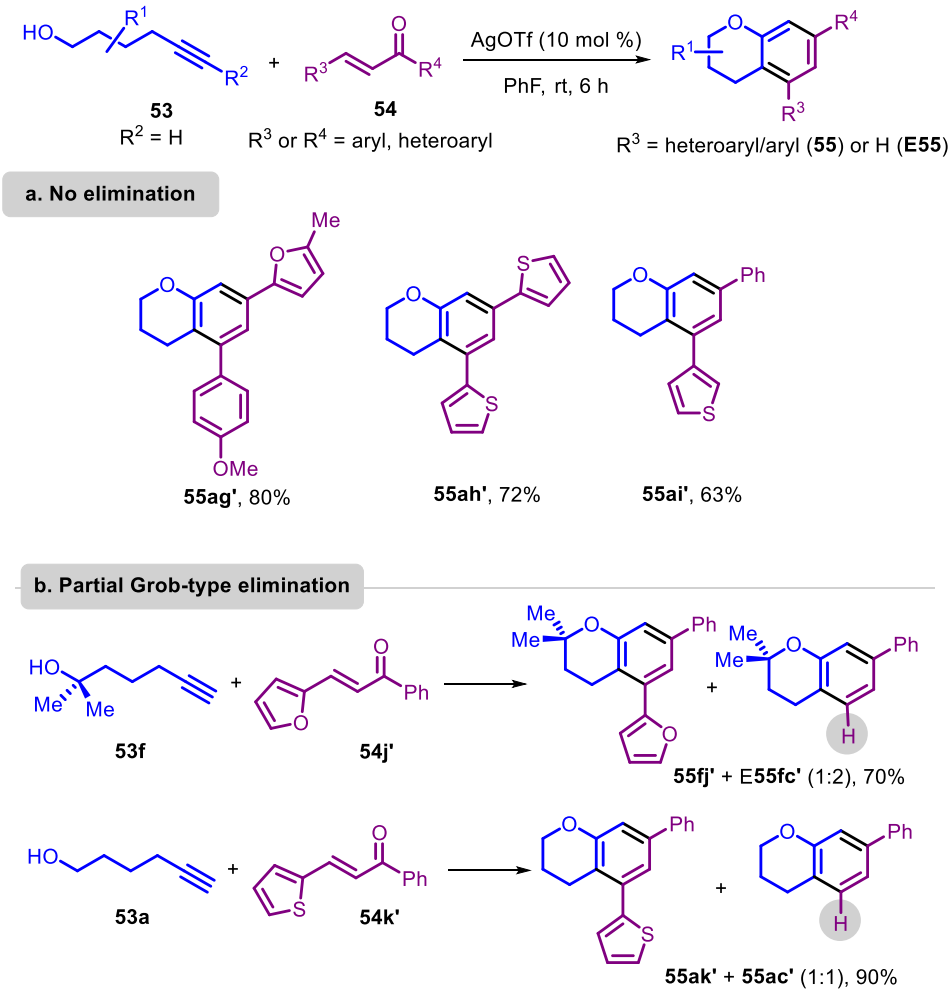


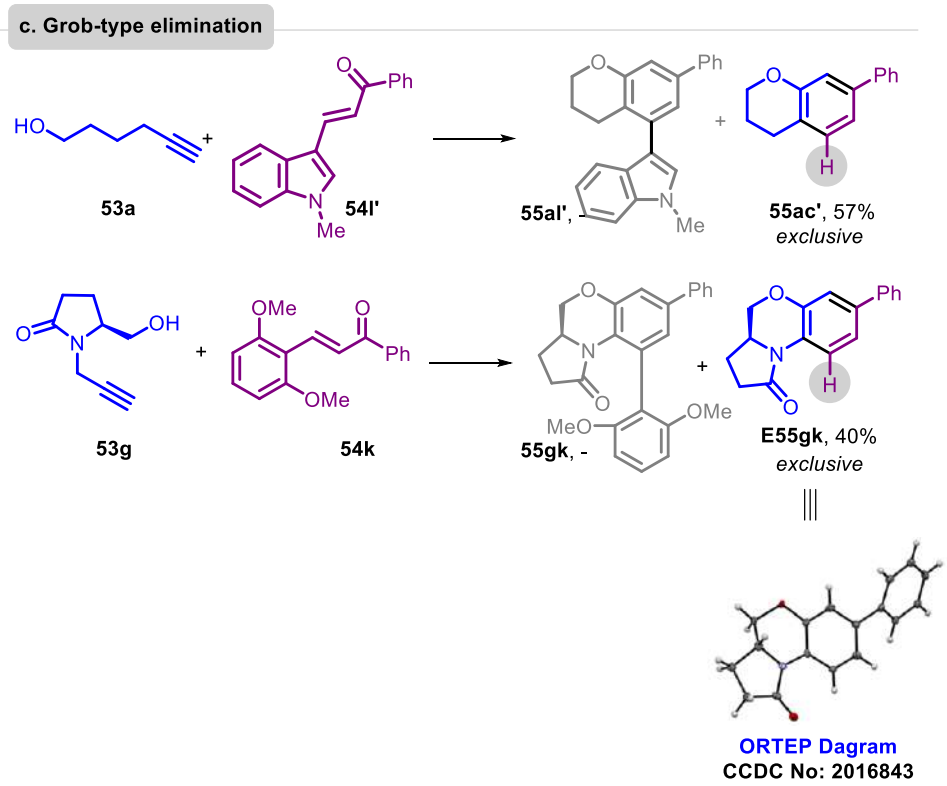
Scheme 3.2.10: Unsuccessful [3+3]-annulation experiments

To extrapolate the generality further, we began investigating the scope of enones with hetero arene appendage **54**. Among several enones (possessing furan, thiophene, pyrrole, indole, pyridine benzoxazole and benzothiazole) tested, furan thiophene and indole tethered enones were found to be reliable substrates and led to some interesting results as delineated in Scheme 3.2.11. The reaction of alkynol **53a** with (*E*)-3-(4-methoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**54g'**), (*E*)-1,3-di(thiophen-2-yl)prop-2-en-1-one (**54h'**) and (*E*)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one (**54i'**) delivered corresponding chromanes **55ag'**, **55ah'** and **55ai'** respectively in good yields (Scheme 3.2.11, entry a). To our surprise, (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**54j'**) and (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (**54k'**) in reaction with

alkynols **53f** and **53a** gave an inseparable mixture of chromanes and heteroarene eliminated products (**55fj'** and **E55fc'**; **55ak'** and **55ac'**; established by ^{1}H and ^{13}C NMR analyses) under optimal reaction conditions (Scheme 3.2.11, entry b). Interestingly, N-methyl indole derived chalcone **54l'** in reaction with **53a** at 85 ^{o}C delivered the eliminated product **33ac'** exclusively in 57% yield.

Similarly, alkynol **53g** (obtained from (*S*)-pyroglutamic acid) in reaction with sterically hindered chalcone **54k** furnished tricyclic lactam fused N,O-heterocycle **E44gk** (confirmed by X-ray analyses) in 40% yield (Scheme 3, entry c), this unusual formation of heteroarene/arene eliminated products could be due to stereoelectronic effects-driven competitive Grob-type elimination pathway[18, 33] instead of classical oxidative aromatization (*vide infra*) (Scheme 3.2.11, entry c).





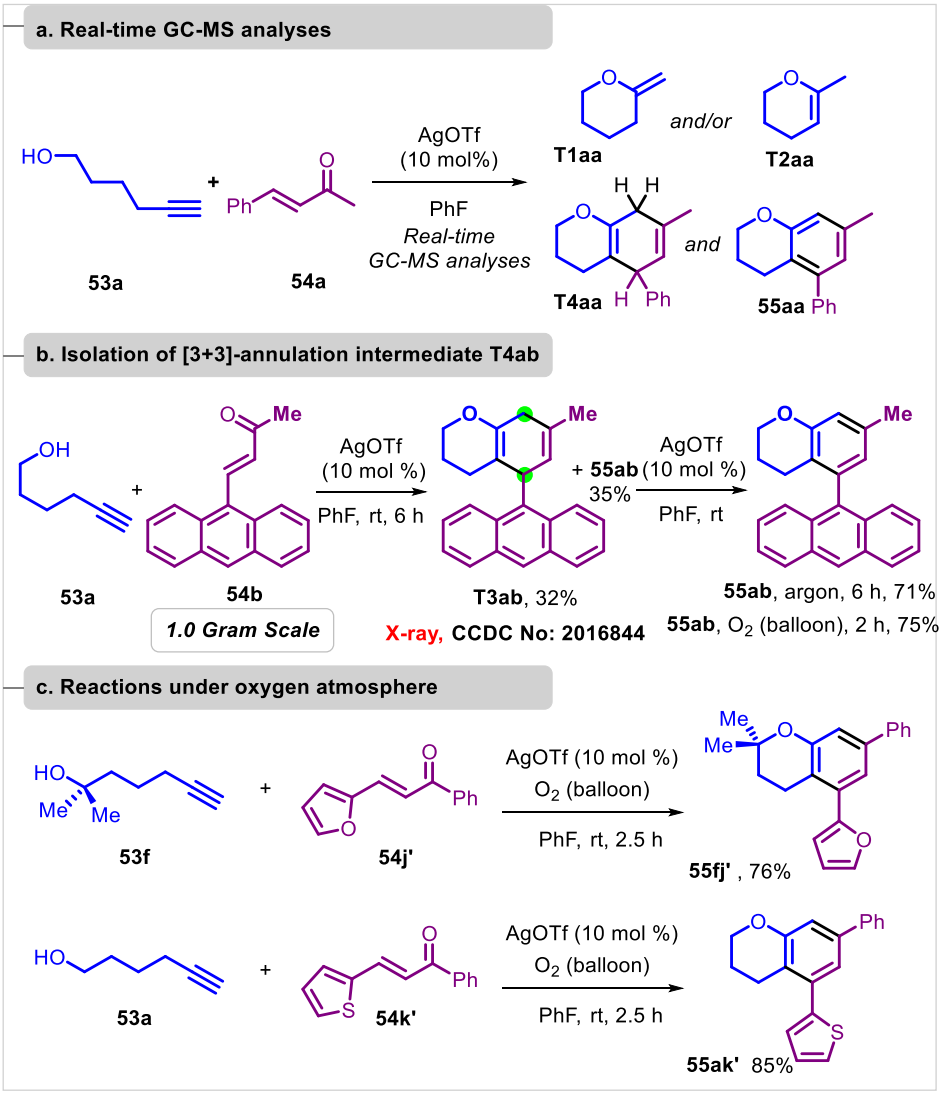
Scheme 3.2.11: Scope of [3+3]-annulation reaction using heteroarene derived chalcones.

Next, we performed a series of supporting experiments to gain insight into the reaction mechanism. The reaction of **53a** and **54a** was real-time monitored with the aid of GC-MS, which showed *m/z* signals related to cyclic enol ethers (**T1aa** or **T2aa**) and cyclohexadiene (**T4aa**) reaction intermediates, suggesting intermediacy of these species (Scheme 3.2.12, entry a).

The scale-up experiment of **53a** with **54b** enabled us to isolate a crystalline pyran-tethered cyclohexadiene **T3ab** and confirms this as one of the reaction intermediates, which is quite stable under open-air conditions and was further converted into chromane **55ab** under optimal reaction conditions as well as under O_2 atmosphere (Scheme 3.2.12, entry b).

To our delight, the annulation of **53f/53a** with **54j'/54k'** under oxygen atmosphere (balloon pressure) delivered corresponding annulation products **55fj'/55ak'** exclusively (no partial Grob-type elimination product was observed,

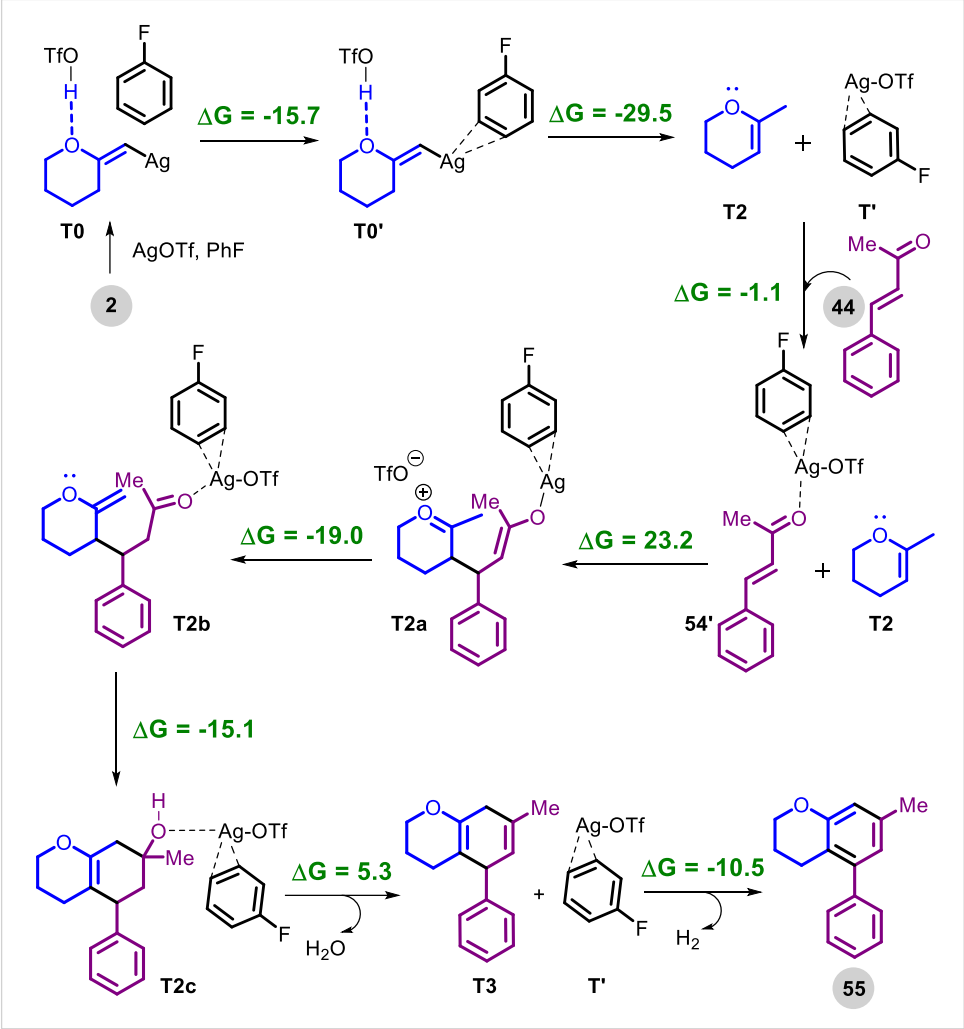
which is in contrast to our observations in Scheme 3, entry b). This outcome indicates the probable role of the aerobic oxidative aromatization step in this annulation (Scheme 3.2.12, entry c). Additionally, we have performed DFT calculations to complement the experimental findings on this cascade annulation reaction's mechanistic sequence (Scheme 3.2.12).



Scheme 3.2.12: Supporting experiments for the reaction mechanism.

To better understand the enhanced efficiency using fluorobenzene (PhF) as a solvent, selective participation of endocyclic enol ether (**T2**) over exocyclic enol ether (**T0'**), and other key steps involved in the cascade annulation, we carried out full quantum chemical calculations using density functional theory at

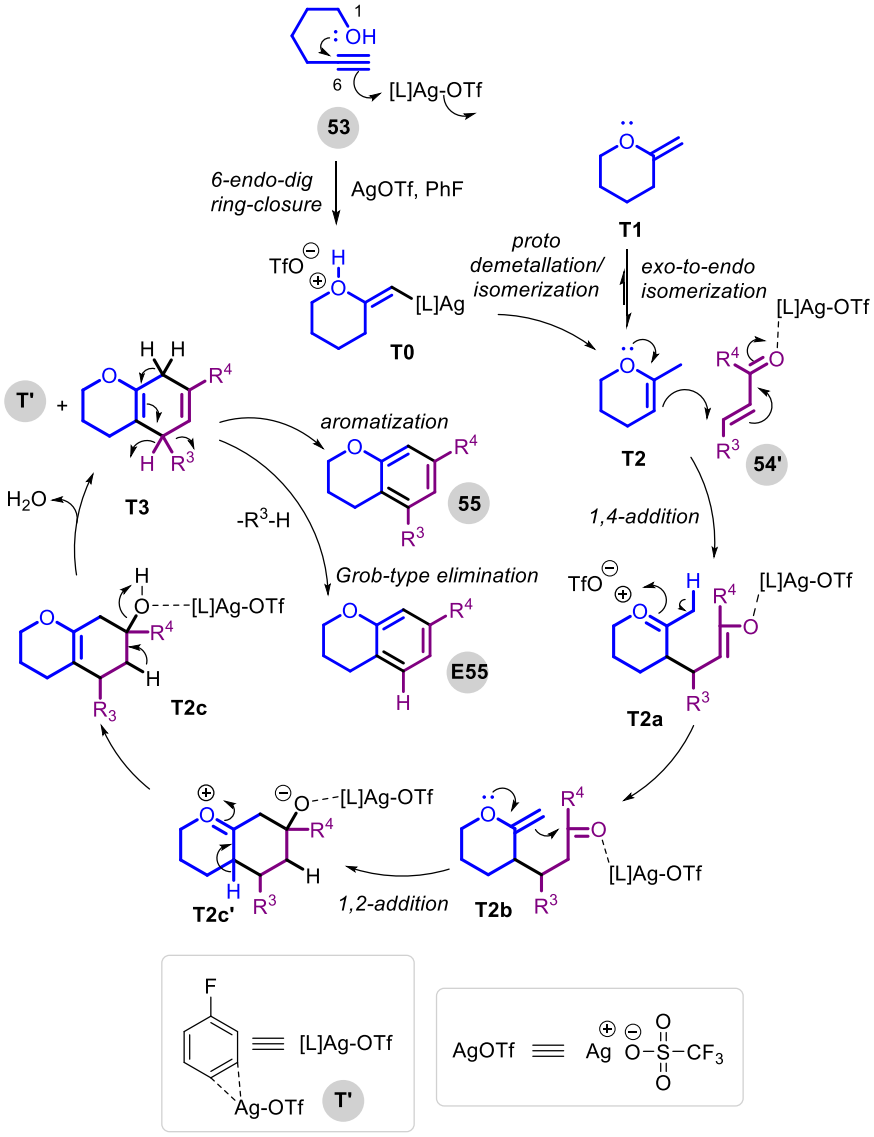
PBE/TZVP level of theory. Our thermodynamic calculations indicate that PhF reacts with Ag of the substrate **T0**, leading to the formation of compound **T0'**, which is a 1,2 coordinated structure, where PhF is coordinated to Ag in a η^2 fashion at the *meta-para* positions. Next, **T0'** generates exocyclic enol ether **T2** and silver-PhF complex **T'**, a process that is exergonic by 29.5 kcal/mol.



Scheme 3.2.13: Thermodyanamic calculations for the formation of chromanes **55** by AgOTf-catalyzed annulation of 5-hexyn-1ol **53** with enone **54**. Free energy values are provided in kcal/mol.

Subsequently, enone **54** reacts with silver-PhF complex **T'**, leading to the formation of **54'** *via* the coordination of Ag with the carbonyl oxygen. In the next step, the formation of **T2a** species occurs from the reaction of **T2** and **54'** *via* the

1,4-addition pathway. The formation of intermediate **T2a** is endergonic by 23.2 kcal/mol. Subsequently, the intermediate **T2b** is formed (ΔG = -19.0 kcal/mol). Furthermore, intramolecular 1,2-addition (cyclization) of **T2b** leads to the formation of species **T2c** (ΔG = -15.1 kcal/mol. After this, the formation of pyran-tethered 1,4-cyclohexadiene **T3** takes place from **T2c** with the elimination of **T'** and a water molecule. In the final step of the reaction, the cyclohexadiene intermediate **T3** delivers chromane **55** through aromatization (Scheme 3.2.13).



Scheme 3.2.14: Plausible reaction mechanism.

Based on the above experimental results, DFT calculations, and earlier observations by our group[28,29] and others,[23-27,30] we have drawn a more

authenticated reaction mechanism for this Ag(I)-catalyzed [3+3]-annulation reaction (Scheme 4). The initial AgOTf (η2 coordinated with PhF; observed herein for the first time) mediated π-activation of alkynol **53** triggers the 6-*exo*-dig cyclization (hydroalkoxylation), which leads to the formation of the exocyclic enol ether **T1** via **T0**, which then converts into thermodynamically more favored endocyclic enol ether **T2**.[23] Enol ether **T2** reacts with the activated enone **54'** in a 1,4-addition pathway to give the oxocarbenium species **T2a**, which would then be transformed into exocyclic enol ether **T2b** thorough deprotonation. Then **T2b** undergoes intramolecular 1,2-addition and produces the bicyclic dihydropyran **T2c** via oxacarbenium species **T2c'**. Subsequent catalyst-induced dehydration of **T2c** delivers pyran-tethered 1,4-cyclohexadiene species **T3**. In the final step of the cascade, cyclohexadiene intermediate **T3** either delivers chromane **55** through oxidative (aerobic) aromatization step or arene/heteroarene eliminated product **E55** via Grob-type elimination (Scheme 3.2.14).

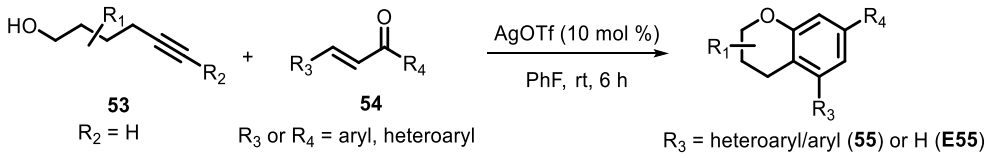
3.2.6 Conclusion

In summary, we have established a facile protocol for the regioselective construction of simple to complex chromanes by employing an Ag(I)-catalyzed cascade [3+3]-annulation of 5-hexyn-1-ols and α,β-unsaturated ketones via unravelling the bis-nucleophilic nature of cyclic enol-ether intermediates for the first time. More importantly, theoretical calculations elucidated the role of the fluorobenzene (solvent) in fine-tuning the Ag-catalysis by stabilizing respective complexes, thermodynamically favored endocyclic enol ether formation and its selective participation in an intermolecular 1,4-addition reaction which led to exclusive regioselectivity. Operationally simple reaction parameters, scalability, good to excellent yields (up to 90%), and broad substrate scope are salient features of this strategy. This protocol may find applications in the total synthesis of relevant biologically active natural products and diversity-oriented synthesis of medicinal chemistry.

3.2.7 Experimental Procedures and Data:

All reactions were performed under an argon atmosphere with an oven (80 ºC) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under an argon atmosphere immediately before use. Dichloromethane and acetonitrile were freshly distilled over calcium hydride under an argon atmosphere. 30 °C corresponded to the room temperature (rt) of the laboratory when the experiments were carried out. Reaction temperatures are reported as the bath temperature surrounding the reaction vessel.

***General Procedure* for the synthesis of chromanes (55 or E55) from alkynols (53) and *α,β*-unsaturated ketones (54):**

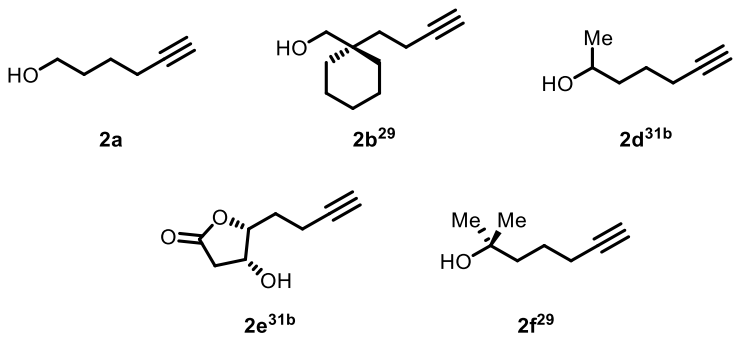


Alkynol **53** (1.01 mmol) and α,β-unsaturated ketone **54** (0.505mmol) were taken into a single neck 10 mL round bottom flask equipped with positive argon flow, then dissolved in 2 mL of anhydrous PhF. Catalyst (AgOTf, 0.101mmol) was added under an argon atmosphere at room temperature. The resulting reaction mixture was stirred at rt for six h. After completion of the reaction (monitored by TLC, visualized using UV, anisaldehyde, and $KMnO_4$ staining solutions), quenched with saturated aqueous $NaHCO_3$solution, then extracted with CH_2Cl_2 (2x5 mL), then washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified using silica-gel column chromatography (SiO_2, 100-200 mesh) to afford the correspondingchromanes **55** or **E55**.

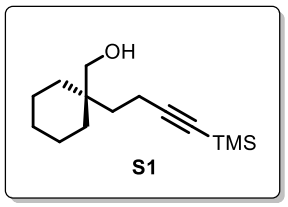
2.2.8.1 Experimental Procedure & Spectroscopic Data of Synthesised Products:

Synthesis of alkynols:

53a commercially available **53b, 53d, 53e, and 53f:** Prepared using reported procedures. [29, 31b]



(1-(4-(Trimethylsilyl)but-3-yn-1-yl)cyclohexyl)methanol (S1):



1-(4-(Trimethylsilyl)but-3-yn-1-yl)cyclohexyl)methanol (**S1**) colourless liquid.

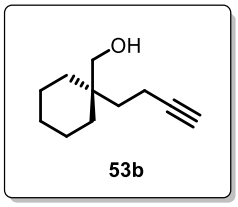
TLC: R_f= 0.8 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.44 (s, 2H), 2.2 (t, *J* = 7.3 Hz, 2H), 2.0 (br s, 1H), 1.61 (t, *J* = 7.3 Hz, 2H), 1.5-1.35 (m, 6H), 1.3-1.2 (m, 4H), 0.14 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 108.6, 84.1, 67.7, 37.0, 33.8, 32.5, 26.4, 21.4, 14.0, 0.05.

(1-(But-3-yn-1-yl)cyclohexyl)methanol (53b):

1-(But-3-yn-1-yl)cyclohexyl)methanol (**53b**) colorless oil.



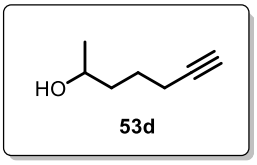
TLC: R_f= 0.8 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.45 (s, 2H), 2.22-2.13 (m, 2H), 1.97 (br s, 1H), 1.65 (t, *J* = 7.9 Hz, 2H), 1.50-1.39 (m, 6H), 1.34-1.27 (m, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 85.6, 67.9, 37.0, 33.8, 32.9, 32.4, 26.3, 21.4, 12.7.

HRMS (ESI): *m/z* calcd for $C_{11}H_{19}O$ $[M+H]^+$ 167.1431, found 167.1430.

Hept-6-yn-2-ol (53d):

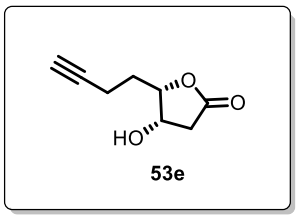


Hept-6-yn-2-ol colorless oil (**53d**) was prepared using reported procedure.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87-3.78 (m, 1H), 2.24-2.19 (m, 2H), 1.96 (t, *J* = 2.3 Hz, 1H), 1.62-1.52 (m, 4H), 1.20 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 84.4, 68.5, 67.6, 38.2, 24.7, 23.6, 18.4.

-(But-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (53e):



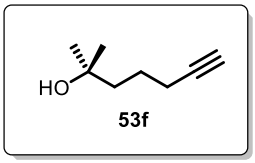
5-(but-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (**53e**) as a colourless oil.

TLC: R_f = 0.12 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.61-4.5 (m, 2H), 2.83 (dd, *J* = 17.7, 4.88 Hz, 1H), 2.56 (d, *J* = 18.31 Hz, 1H), 2.50-2.32 (m, 2H), 2.14-2.06 (m, 1H), 2.08 - 2.06 (m, 1H), 2.06-1.92 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.1, 83.7, 83.1, 69.6, 68.6, 39.3, 27.1, 14.7.

2-Methylhept-6-yn-2-ol (53f):

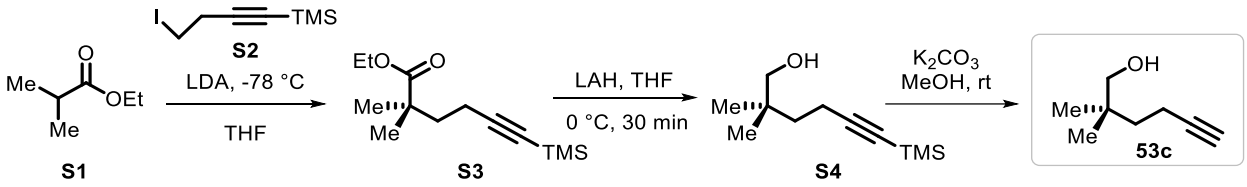


2-Methylhept-6-yn-2-ol (**53f**) as a colorless liquid.

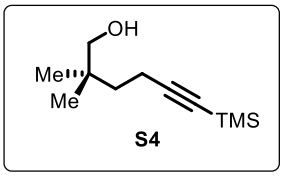
TLC: R_f = 0.3 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.20 (td, *J* = 6.8, 2.7 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.63-1.53 (m, 4H), 1.50 (br s, 1H), 1.21(s, 6H).

Synthesis of alkynol 53c:



2,2-Dimethyl-6-(trimethylsilyl)hex-5-yn-1-ol (S4):



To a flame dried (100 mL) two neck round bottom flask, anhydrous THF (20 mL) was added under argon atmosphere and cooled to 0 °C, to this diisopropylamine (1.18 g, 11.74mmol) followed by *n*-butyllithium (1.6 M in hexanes, 7.95 mL, 12.7 mmol) was added dropwise at 0 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution, was added ethyl isobutyrate (**S1**) (1 g, 9.79 mmol) in THF (3 mL) and stirred the reaction mixture at -78 °C for 30 min, then warmed to 0 °C and stirred for

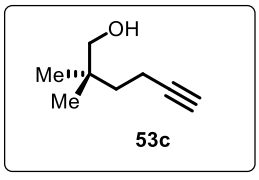
another 30 min. The reaction mixture was cooled back to -78 °C and (4-iodobut-1-yn-1-yl) trimethylsilane (**S2**) (3.69 g, 14.68 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h and warmed to rt and stirred overnight. Then, the reaction wasquenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc (3x20 mL), combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford ethyl 2,2-dimethyl-6-(trimethylsilyl) hex-5-ynoate (**S3**) TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes), this crude product was subjected to the next step without further purification.

Lithium aluminium hydride (0.74 g, 19.58 mmol) was dissolved in a 20 mL of anhydrous THF in a 100 mL two neck round bottom flask under argon atmosphere, then ethyl 2,2-dimethyl-6-(trimethylsilyl) hex-5-ynoate (**S3**) in (5 mL) THF was added drop by drop at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature, after completion of the reaction monitored by TLC quenched with a saturated aqueous solution of sodium sulphate (very carefully). After quenching the reaction,the mixture diluted with 50 mL EtOAc and stirred for 1h to obtain the white powder, which was filtered through Celite. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford 2,2-dimethyl-6-(trimethylsilyl) hex-5-yn-1-ol (**S4**) (0.726 g, 43% for two steps) as a colorless liquid. TLC: R_f= 0.8 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.35 (s, 2H), 2.23 (t, *J* = 7.32 Hz, 2H), 1.55 (t, *J* = 7.32 Hz, 2H), 0.88 (s, 6H), 0.15 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 108.3, 84.2, 70.9, 37.3, 35.2, 23.9, 14.9, 0.04.

2,2-Dimethylhex-5-yn-1-ol (53c):



53c

To a stirred solution of 2,2-dimethyl-6-(trimethylsilyl)hex-5-yn-1-ol (**S4**) (0.8 g, 4.03 mmol) in MeOH (20 mL) was added K_2CO_3 (1.2 g, 8.68 mmol) at room temperature. The reaction mixture was stirred for 6 h. After quenched with H_2O, the mixture was extracted twice with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica

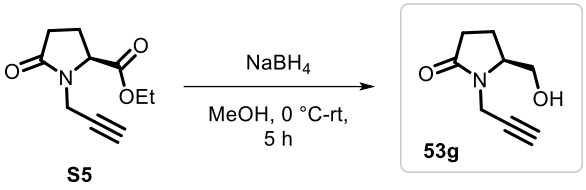
gel column chromatography (SiO_2, 5% EtOAc /hexanes) to give 2,2-dimethylhex-5-yn-1-ol (**53c**) (0.402 g, 79%) as a colourless oil.

TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.35 (s, 2H), 2.19 (td, *J* = 7.63, 3.05 Hz, 2H), 1.97-1.95 (m, 1H), 1.60-1.54 (m,2H), 0.89 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 85.4, 71.1, 67.9, 37.3, 35.1, 23.7, 13.5.

(*S*)-5-(Hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one(53g):



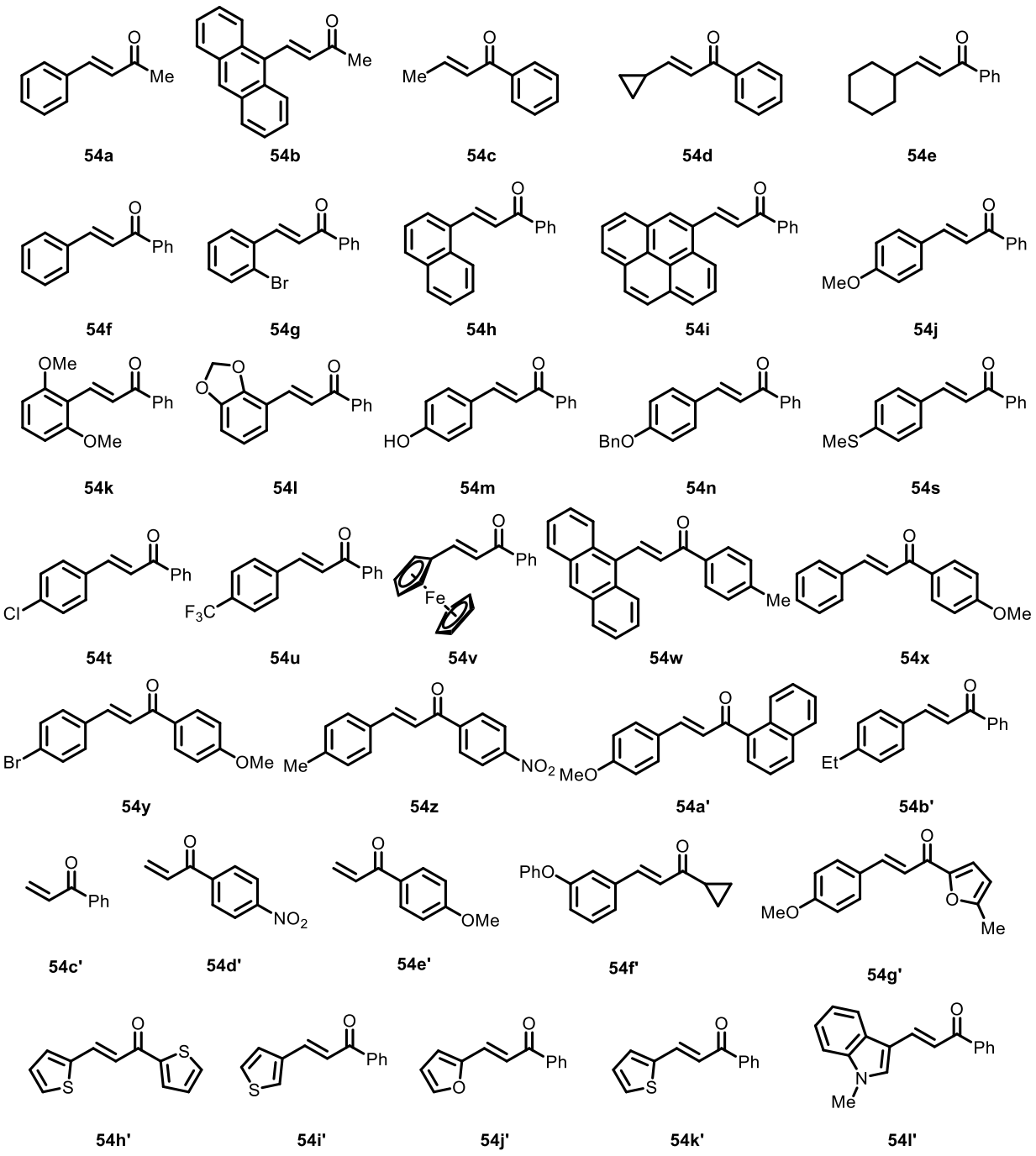
To a solution of ethyl (*S*)-5-oxo-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (**S5**)[15] (0.4 g, 2.05 mmol) in methanol (10 mL), sodium borohydride (0.155 g,4.1 mmol) was added batch wise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. and then at rt for 5 h after which the solvent was evaporated under reduced pressure. Aqueous NH_4Cl solution (5 mL) was added to the resulting suspension, and then extracted with EtOAc (3×5 mL). Organic phases were combined and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (SiO_2, 10% MeOH/CH_2Cl_2) to afford (*S*)-5-(hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (**53g**) (0.302 g, 96%) as a colourless liquid.

TLC: R_f = 0.1 (SiO_2, 70% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.32 (d, *J* = 17.70 Hz, 1H) , 4.02-3.82 (m, 3H), 3.69-3.56 (m, 1H), 2.86 (br.s., 1H), 2.53-2.43 (m, 1H), 2.37-2.29 (m, 1H), 2.18-2.07 (m, 1H), 2.04-1.95 (m, 1H).

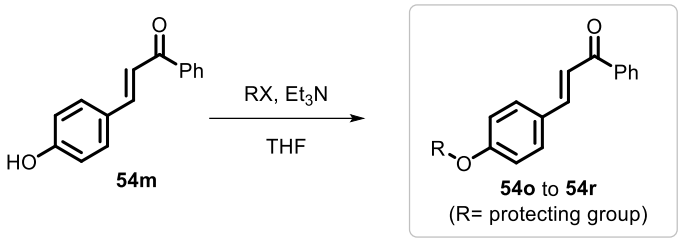
^{13}C NMR ($CDCl_3$, 101 MHz): δ175.5, 78.3, 71.9, 62.5, 59.2, 30.5, 30.3, 20.7.

Synthesis of *α,β*-unsaturated ketones (54):



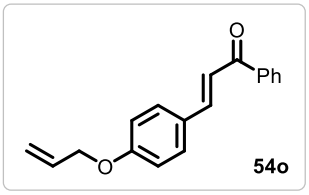
4a-4l prepared using reported procedures (see below details of chemical structures with related referenes.[32]

7. *General procedure* for the synthesis of protected chalcones (54o-54r):



To a solution of 4-hydroxychalcone (**54m**) (10.0 mmol) and triethylamine (12.0 mmol) in anhydrous THF (20 ml) was added drop wise organo-halide (12.0 mmol) and the mixture was stirred at ambient temperature. After a certain reaction time the volatile was concentrated under reduced pressure. The residue was extracted with ethyl acetate (20 ml) and water (20 ml). The organic layer was washed with saturated aqueous solution of sodium hydrogen carbonate (20 mL), 10% aqueous solution of sodium hydrogen sulfonate (20 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The solid was purified by recrystallization.

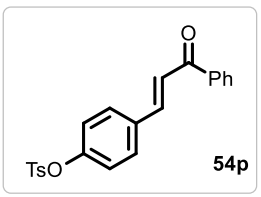
(*E*)-3-(4-(Allyloxy)phenyl)-1-phenylprop-2-en-1-one (54o):



(*E*)-3-(4-(Allyloxy)phenyl)-1-phenylprop-2-en-1-one (**54o**) was prepared by using general procedureas a yellow crystalline solid in 57% yield.

^{1}H NMR ($CDCl_3$,200 MHz): δ 8.20-7.97 (m, 2H),7.78 (d, *J*=15.66 Hz, 1H),7.69-7.43 (m, 6H),7.10-6.86 (m, 2H),6.21-5.91 (m, 1H),5.59-5.20 (m, 2H),4.53 (d, *J*=5.18 Hz, 2H).

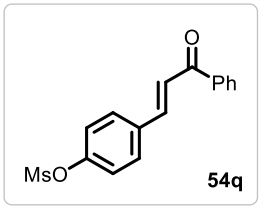
(*E*)-4-(3-Oxo-3-phenylprop-1-en-1-yl)phenyl 4-methylbenzenesulfonate (54p):



(*E*)-4-(3-Oxo-3-phenylprop-1-en-1-yl)phenyl 4-methylbenzenesulfonate (**54p**) was prepared by using general procedureas a yellow crystalline solid in 68% yield.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.00 (d, *J* = 7.17 Hz, 2H), 7.85-7.66 (m, 3H), 7.66-7.41 (m, 6H), 7.31 (d, *J* = 8.38 Hz, 2H), 7.03 (d, *J* = 8.60 Hz, 2H), 2.44 (s, 3H).

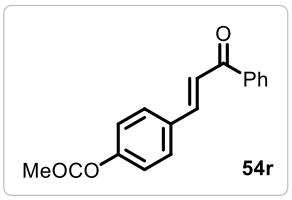
(*E*)-4-(3-Oxo-3-phenylprop-1-en-1-yl)phenylmethanesulfonate (54q):



(*E*)-4-(3-Oxo-3-phenylprop-1-en-1-yl)phenylmethanesulfonate (**54q**) was prepared by using general procedureas a yellow crystalline solid in 80% yield.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.14-7.94 (m, 2H), 7.81-7.47 (m, 7H), 7.33 (d, *J*=8.71 Hz, 2H), 3.18 (s, 3H).

(*E*)-4-(3-Oxo-3-phenylprop-1-en-1-yl)phenyl acetate (54r):

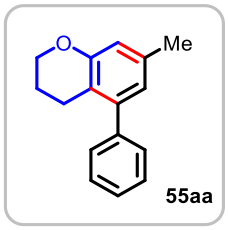


(*E*)-4-(3-Oxo-3-phenylprop-1-en-1-yl)phenyl acetate (**54r**) was prepared by using general procedureas a light yellow solid in 77% yield.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.16-7.97 (m, 2H), 7.86-7.43 (m, 7H), 7.14 (d, *J*=8.49 Hz, 2H),2.30 (s, 3H).

Synthesis and characterization of chromanes (55) from alkynols (53) and α,β-unsaturated ketones (54)

7-Methyl-5-phenylchromane (55aa):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-4-phenylbut-3-en-2-one (**54a**) (0.073 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-methyl-5-phenylchromane (**55aa**) (0.086 g, 87%)colorless oil .

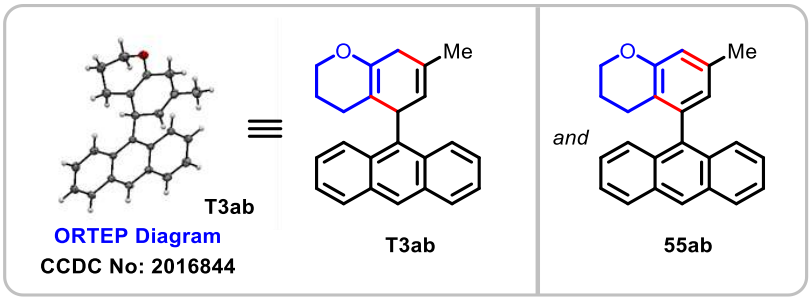
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.38(m, 2H), 7.37-7.31 (m, 3H),6.67 (d, *J* = 4.96 Hz, 2H), 4.22-4.18 (m,2H), 2.62-2.58 (m, 2H), 2.32 (s, 3H), 1.94-1.88 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 154.8, 142.8, 141.3, 136.7, 129.1, 127.9, 126.8, 122.7, 116.9, 116.3, 66.2, 23.9, 22.6, 21.0.

HRMS (ESI): *m/z* calcdfor $C_{16}H_{17}O$ $[M+H]^+$ 225.1274, found 225.1273.

5-(Anthracen-9-yl)-7-methyl-3,4,5,8-tetrahydro-2*H*-chromene (T3ab) and 5-(Anthracen-9-yl)-7-methylchromane (55ab):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g,1.01 mmol) and (*E*)-4-(anthracen-9-yl)but-3-en-2-one (**54b**) (0.124 g,0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded a mixture of two product5-(anthracen-9-yl)-7-methyl-3,4,5,8-tetrahydro-2H-chromene (**T3ab**) (0.056 g, 34%) as a yellow crystalsand 5-(anthracen-9-yl)-7-methylchromane (**55ab**) as a yellow powder (0.063 g, 39%).

TLC: R_f = 0.9(SiO_2, 10% EtOAc/hexanes).

T3ab: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.56-8.52 (m, 1H), 8.46 (d, *J* = 9.14 Hz, 1H), 8.38 (s, 1H), 8.04-7.97 (m, 2H), 7.53-7.41 (m, 3H), 7.39-7.34 (m, 1H), 5.63-5.57 (m, 1H), 5.54-5.51 (m, 1H), 4.06-3.99 (m, 1H), 3.91-3.85 (m, 1H), 2.93 (d, *J* = 8.20 Hz, 2H), 1.78 (s, 3H), 1.77-1.59 (m, 4H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.3, 134.6, 131.8, 131.6, 130.9, 130.6, 129.5, 129.3, 129.0, 127.0, 125.8, 125.2, 124.8, 124.5, 124.2, 123.6, 106.8, 65.7, 41.7, 33.6, 22.9, 22.7, 22.4.

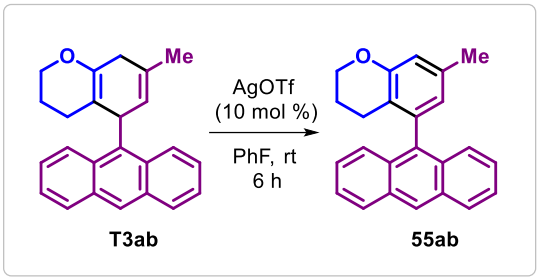
HRMS (ESI): *m/z* calcd for $C_{24}H_{23}O$ $[M+H]^+$ 327.1743, found 327.1745.

55ab: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H), 8.06 (d, *J* = 8.39 Hz, 2H), 7.62 (d, *J* = 9.16 Hz, 2H), 7.51-7.44 (m, 2H), 7.41-7.35 (m, 2H), 6.84 (s, 1H), 6.70 (s, 1H),4.17 (t, *J* = 5.34 Hz, 2H), 2.37 (s, 3H), 2.08-2.03 (m, 2H), 1.84-1.73 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.5, 139.8, 139.4, 137.6, 137.0, 131.4, 129.9, 129.4, 128.5, 126.7, 126.5,125.6, 125.2, 121.8, 121.3, 114.3, 66.4, 22.5, 22.3, 21.1; IR (KBr, cm^{-1}): υ 2929, 2860, 1612, 1575, 1454, 1215, 1138, 908, 733, 642.

HRMS (ESI): *m/z* calcd for $C_{24}H_{21}O$ $[M+H]^+$ 325.1587, found 325.1586.

5-(Anthracen-9-yl)-7-methylchromane (55ab) (prepared from **T3ab**):

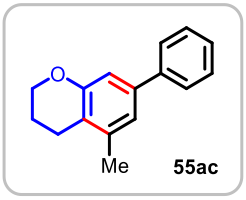


Following the *General Procedure*, to the mixture of 5-(anthracen-9-yl)-7-methyl-3,4,5,8-tetrahydro-2H-chromene (**T3ab**) (0.050 g, 0.15 mmol) in anhydrous PhF (2.0 mL) was added AgOTf (0.003 g, 0.015 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(anthracen-9-yl)-7-methylchromane (**55ab**) (0.035 g, 71%) yellow powder.

TLC: R_f = 0.9 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.49 (s, 1H), 8.06 (d, *J*= 7.94 Hz, 2H), 7.62 (d, *J*= 9.16 Hz, 2H), 7.54-7.32 (m, 4H), 7.41-7.35 (m, 2H), 6.84 (s, 1H), 6.70 (s, 1H), 4.18 (t, *J*= 5.07 Hz, 2H), 2.37 (s, 3H), 2.06 (t, *J*=6.39 Hz, 2H), 1.88-1.72 (m, 2H).

5-Methyl-7-phenylchromane (55ac):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-1-phenylbut-2-en-1-one (**54c**) (0.073 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and the reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-methyl-5-phenylchromane (**55ac**) (0.73 g, 68%) colorless oil.

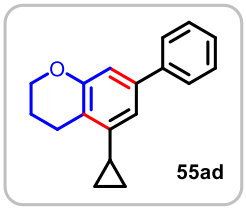
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.55 (m, 2H), 7.46-7.40 (m, 2H), 7.36-7.30 (m, 1H), 7.03-6.94 (m, 2H), 4.23-4.17 (m, 2H), 2.70 (t, *J* = 6.63 Hz, 2H), 2.30 (s, 3H), 2.13-2.05 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.3, 141.0, 139.8, 138.0, 128.6, 127.0, 126.9, 120.6, 120.2, 113.1, 66.0, 22.5, 22.4, 19.3.

HRMS (ESI): *m/z* calcd for $C_{16}H_{17}O$ $[M+H]^+$ 225.1274, found 225.1276.

5-Cyclopropyl-7-phenylchromane (55ad):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-cyclopropyl-1-phenylprop-2-en-1-one (**54d**) (0.086 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded5-cyclopropyl-7-phenylchromane (**55ad**) (0.085 g, 67%) colorless oil. **TLC:** R_f = 0.9 (SiO_2, 10% EtOAc/hexanes).

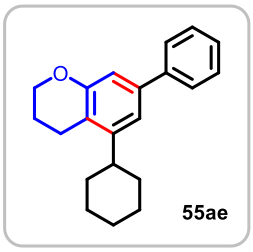
^{1}H NMR ($CDCl_3$,400 MHz): δ 7.59-7.53 (m, 2H), 7.46-7.39 (m, 2H), 7.37-7.30 (m, 1H), 6.93 (d, *J* = 1.88 Hz, 1H), 6.83 (d, *J* = 1.50 Hz, 1H), 4.21 (t, *J* = 5.13 Hz, 2H), 2.93 (t, *J* = 6.63 Hz, 2H), 2.15-2.07 (m, 2H), 1.90-1.83 (m, 1H), 0.99-0.92 (m, 2H) 0.77-0.65 (m, 2H);

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.1, 142.7, 141.2, 139.8, 128.6, 127.1, 126.9, 121.4, 116.7, 113.3, 66.0, 22.5, 22.2, 13.1, 6.8.

IR (KBr, cm^{-1}): υ 3019, 2955, 2927, 2855, 1663, 1612, 1600, 1583, 1565, 1518, 1502, 1410, 1172, 962, 850, 771, 699, 625.

HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O$ $[M+H]^+$ 251.1430 found 251.1432.

5-Cyclohexyl-7-phenylchromane (55ae):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-cyclohexyl-1-phenylprop-2-en-1-one (**54e**) (0.108 g, 0.505 mmol) in anhydrous PhF (2 mL) was add AgOTf (0.012 g, 0.05 mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 8h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-cyclohexyl-7-phenylchromane (**55ae**) (0.083 g, 56%) colorless oil.

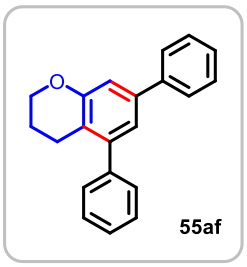
TLC: R_f = 0.9 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60-7.56 (m, 2H), 7.45-7.39 (m, 2H), 7.35-7.30 (m, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 4.23-4.18 (m, 2H), 2.84-2.78 (m, 2H), 2.73-2.65 (m, 1H), 2.11-2.04 (m, 2H), 1.92-1.76 (m, 5H), 1.55-1.33 (m, 5H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.2, 147.5, 141.4, 140.0, 128.6, 127.0, 118.8, 116.6, 113.0, 65.8, 39.5, 33.8, 27.2, 26.3, 22.6, 21.8.

HRMS (ESI): *m/z* calcd for $C_{21}H_{25}O$ $[M+H]^+$ 293.1900, found 293.1897.

5,7-Diphenylchromane (55af):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-chalcone (**54f**) (0.105 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5,7-diphenylchromane (**55af**) (0.111 g, 77%) colorless oil.

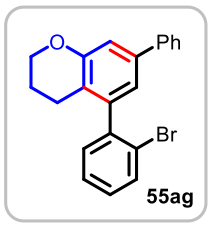
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.62 (d, *J* = 7.63 Hz, 2H), 7.48-7.32 (m, 8H), 7.10 (d, *J* = 4.20 Hz, 2H), 4.33-4.20 (m, 2H), 2.68 (t, *J* = 6.10 Hz, 2H), 2.03-1.90 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.2, 143.3, 141.1, 140.6, 140.0, 129.1, 128.7, 128.1, 127.2, 127.1, 127.0, 120.6, 119.2, 114.3, 66.3, 24.0, 22.5.

HRMS (ESI): *m/z* calcd for $C_{21}H_{19}O$ $[M+H]^+$ 287.1430 found 287.1430.

5-(2-Bromophenyl)-7-phenylchromane (55ag):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(2-bromophenyl)-1-phenylprop-2-en-1-one (**54g**) (0.144 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf(0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(2-bromophenyl)-7-phenylchromane (**55ag**) (0.126 g, 69%) white solid.

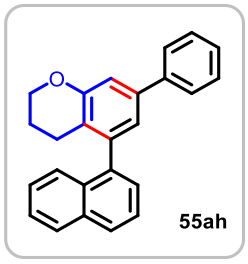
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.66-7.60 (m, 2H), 7.46-7.21 (m, 6H), 7.14 (d, *J* = 1.88 Hz, 1H), 6.99 (d, *J* = 1.88 Hz, 1H), 4.26-4.23(m, 2H), 2.60-2.52 (m, 1H), 2.43-2.36 (m, 1H), 2.02-1.97 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.1, 142.3, 141.8, 140.5, 139.7, 132.6, 130.8, 128.9, 128.7, 127.2 (2C), 126.9, 123.6, 120.0, 119.8, 114.7, 66.3, 23.0, 22.3.

IR (KBr, cm^{-1}): υ 3018, 2952, 2880, 1612, 1603, 1583, 1566, 1479, 1216, 1177, 1053, 1009, 772, 669.

5-(Naphthalen-1-yl)-7-phenylchromane (55ah):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one (**54h**) (0.130 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012g, 0.05 mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(naphthalen-1-yl)-7-phenylchromane (**55ah**) (0.127 g, 75%) yellow solid.

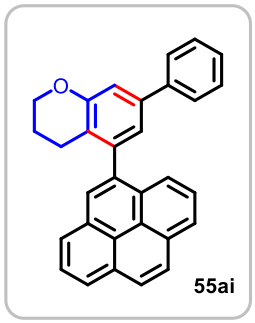
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.83 (m, 2H), 7.60 (d, *J* = 7.25 Hz, 3H), 7.54-7.44 (m, 2H), 7.42-7.35 (m, 4H), 7.32-7.28 (m, 1H), 7.23 (s, 1H), 7.13 (dd, *J* = 1.75, 22.3 Hz, 2H) 4.24-4.18 (m, 2H), 2.44-2.34 (m, 1H), 2.32-2.22 (m, 1H), 1.91-1.82 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.2, 141.5, 140.6, 139.7, 138.8, 133.5, 131.9, 128.7, 128.2, 127.6, 127.2, 126.9, 126.5, 126.1, 126.0, 125.8, 125.4, 121.2, 120.6, 114.4, 66.4, 23.1, 22.3.

HRMS (ESI): ***m/z*** calcd for $C_{25}H_{21}O$ $[M+H]^+$ 337.1587 found 337.1587.

7-Phenyl-5-(pyren-4-yl)chromane(55ai):



Following the *General Procedure,*to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-1-phenyl-3-(pyren-4-yl)prop-2-en-1-one (**54i**) (0.167 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-Phenyl-5-(pyren-4-yl)chromane (**55ai**) (0.136 g, 66%) white solide.

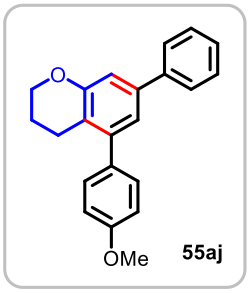
TLC: R_f = 0.9 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28-8.16 (m, 4H), 8.13 (d, *J* = 0.9 Hz, 2H), 8.07-8.00 (m, 3H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 9.3 Hz, 1H), 7.71-7.65 (m, 2H), 7.47-7.40 (m, 2H), 7.35-7.28 (m, 1H), 4.26-4.22 (m, 2H), 2.41-2.36 (m, 2H), 1.93-1.87 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.3, 142.0, 140.6, 139.8, 136.3, 131.4, 131.0, 130.6, 128.9, 128.7, 128.3, 127.6, 127.4, 127.3, 127.2, 127.0, 126.0, 125.8, 125.3, 125.2, 125.1, 125.0, 124.8, 124.7, 124.5, 121.5, 120.8, 114.5, 66.4, 23.4, 22.3.

HRMS (ESI): *m/z* calcd for $C_{31}H_{23}O$ $[M+H]^+$ 411. 1743, found 411.1741.

5-(4-Methoxyphenyl)-7-phenylchromane (55aj):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**)(0.1 g, 1.01 mmol) and (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (**54j**) (0.120 g, 0.505 mmol)in anhydrous PhF (2 mL) was addedAgOTf(0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded5-(4-methoxyphenyl)-7-phenylchromane(**55aj**)(0.116 g, 73%) colourless solid.

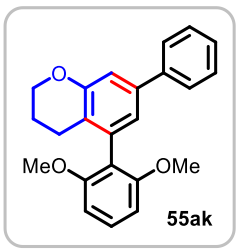
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.60 (m, 2H), 7.45-7.40 (m, 2H), 7.36-7.30 (m, 3H), 7.08 (s, 2H), 7.01-6.96 (m, 2H), 4.27-4.23 (m, 2H), 3.87 (s, 3H), 2.71-2.65 (m, 2H), 2.01-1.93 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.7, 155.2, 143.0, 140.7, 139.9, 133.5, 130.2, 128.7, 127.2, 127.0, 120.7, 119.3, 114.1, 113.5, 66.3, 55.3, 24.1, 22.5.

HRMS (ESI): *m/z* calcd for $C_{22}H_{21}O_2$ $[M+H]^+$ 317.1536, found 317.1530.

5-(2,6-Dimethoxyphenyl)-7-phenylchromane (55ak):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(2,6-dimethoxyphenyl)-1-phenylprop-2-en-1-one (**54k**) (0.135 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol)under argon

atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(2,6-dimethoxyphenyl)-7-phenylchromane (**55ak**) (0.149 g, 85%) colurless solid.

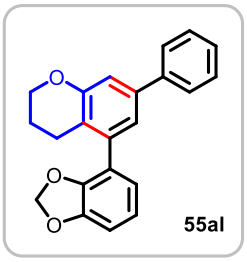
TLC: R_f = 0.70 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63-7.60 (m, 2H), 7.42-7.37 (m, 2H), 7.34-7.29 (m, 2H), 7.08 (d, *J* = 1.53 Hz, 1H), 7.00 (d, *J* = 1.91 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 4.26-4.19 (m, 2H), 3.75 (s, 6H), 2.46 (t, *J* = 6.49 Hz, 2H), 2.01-1.93 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 157.8, 155.0, 141.1, 139.2, 135.5, 128.8, 128.5, 127.0, 126.8, 121.7, 121.3, 118.0, 114.3, 104.0, 66.3, 55.9, 22.6, 22.4.

HRMS (ESI): *m/z* calcd for $C_{23}H_{23}O_3$ $[M+H]^+$347.1642, found 347.1645.

5-(Benzo[d][1,3]dioxol-4-yl)-7-phenylchromane (55al):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(benzo[d][1,3]dioxol-4-yl)-1-phenylprop-2-en-1-one (**54l**) (0.127 g, 0.505 mmol)in anhydrous PhF (2 mL) was addedAgOTf(0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded5-(benzo[d][1,3]dioxol-4-yl)-7-phenylchromane (**55al**) (0.117 g, 70%) colorless oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

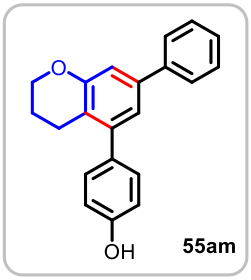
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.56 (m, 2H), 7.47-7.40 (m, 2H), 7.35-7.32 (m, 1H), 7.10-7.03 (m, 2H), 6.90-6.86 (m, 2H), 6.85-6.81 (m, 1H), 6.02 (s, 2H), 4.24 (t, *J* = 5.04 Hz, 2H), 2.68 (t, *J* = 6.41 Hz, 2H), 2.02-1.91 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.3, 147.3, 146.7, 142.9, 140.6, 139.9, 134.9, 128.7, 127.2, 127.0, 122.5, 120.6, 119.3, 114.3, 109.7, 108.1, 101.1, 66.3, 24.1, 22.5.

HRMS (ESI): *m/z* calcd for $C_{22}H_{19}O_3$ $[M+H]^+$ 331.1329, found 331.1337.

4-(7-Phenylchroman-5-yl)phenol (55am):

Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**)(0.1 g, 1.01 mmol)



and (*E*)-3-(4-(hydroxy)phenyl)-1-phenylprop-2-en-1-one (**54m**) (0.113 g, 0.505 mmol)in anhydrous PhF (2 mL) was addedAgOTf(0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded4-(7-Phenylchroman-5-yl)phenol (**55am**) (0.124 g, 81%) white solid.

TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes).

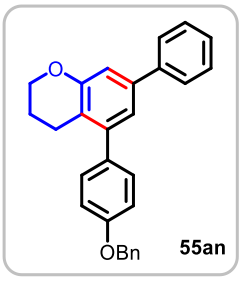
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63-7.58 (m, 2H), 7.45-7.39 (m, 2H), 7.36-7.31 (m, 1H), 7.28-7.23 (m, 2H), 7.08 (dd, *J* = 8.4, 1.9 Hz, 2H), 6.92-6.88 (m, 2H), 5.36 (br. s, 1H), 4.25 (t, *J* = 5.0 Hz, 2H), 2.73-2.67 (m, 2H), 1.99-1.93 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.1, 154.7, 142.9, 140.6, 139.9, 133.5, 130.4, 128.7, 127.2, 126.9, 120.7, 119.3, 115.0, 114.0, 66.3, 24.1, 22.5.

IR (KBr, cm^{-1}): υ 3019, 2953, 2881, 1611, 1563, 1515, 1424, 1347, 1321, 1257, 1215, 1173, 1048, 1009, 869, 835, 760, 699, 669.

HRMS (ESI): *m/z* calcd for $C_{21}H_{19}O_2$ $[M+H]^+$ 303.1380, found 303.1379.

5-(4-(Benzyloxy)phenyl)-7-phenylchromane(55an):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-(benzyloxy)phenyl)-1-phenylprop-2-en-1-one (**54n**) (0.158 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 5-(4-(benzyloxy)phenyl)-7-phenylchromane (**55an**) (0.140 g, 70%) white solid.

TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes).

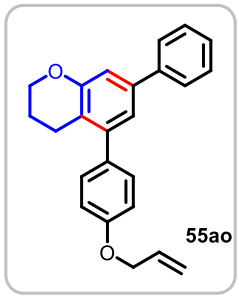
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.59 (m, 2H), 7.50-7.46 (m, 2H), 7.45-7.39 (m, 4H), 7.38-7.30 (m, 4H), 7.08-7.03 (m, 4H), 5.13 (s, 2H), 4.27-4.23 (m,2H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.00-1.93 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.0, 155.2, 142.9, 140.7, 139.9, 137.0, 133.7, 130.2, 128.7, 128.6, 128.0, 127.5, 127.2, 127.0, 120.7, 119.3, 114.4, 114.1, 70.1, 66.3, 24.1, 22.5.

IR (KBr, cm^{-1}): υ 3019, 2935, 1608, 1563, 1512, 1401, 1347, 1287, 1218, 1176, 1141, 1076, 1018, 929, 903, 868, 772, 697, 669.

HRMS (ESI): *m/z* calcd for $C_{28}H_{25}O_2$ $[M+H]^+$ 393.1849, found 393.1850.

5-(4-(Allyloxy)phenyl)-7-phenylchromane (55ao):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-allyloxyphenyl)-1-phenylprop-2-en-1-one (**54o**) (0.133 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded5-(4-(allyloxy)phenyl)-7-phenylchromane (**55ao**) (0.131 g, 76%) white solid.

TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes).

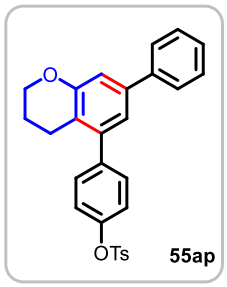
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66-7.61 (m, 2H), 7.48-7.41 (m, 2H), 7.38-7.30 (m, 3H), 7.13-7.09 (m, 2H), 7.04-6.98 (m, 2H), 6.19-6.08 (m, 1H), 5.53-5.46 (m, 1 H), 5.38-5.33 (m, 1H), 4.64-4.60 (m, 2H), 4.27 (t, *J* = 5.0 Hz, 2H), 2.70 (t, *J* = 6.4 Hz, 2H), 2.02-1.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.7, 155.2, 142.9, 140.7, 139.9, 133.6, 133.2, 130.1, 128.6, 127.2, 126.9, 120.6, 119.2, 117.7, 114.3, 114.0, 68.8, 66.2, 24.1, 22.5.

IR (KBr, cm^{-1}): υ 3019, 1609, 1563, 1512, 1466, 1424, 1347, 1321, 1286, 1215, 1177, 1076, 929, 834, 760, 669.

HRMS (ESI): *m/z* calcd for $C_{24}H_{23}O_2$ $[M+H]^+$ 343.1693, found 343.1689.

4-(7-Phenylchroman-5-yl)phenyl 4-methylbenzenesulfonate (55ap):



Following the *General Procedure,* to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-4-(3-oxo-3-phenylprop-1-en-1-yl)phenyl 4-methylbenzenesulfonate (**54p**) (0.191 g, 0.505 mmol) in anhydrous PhF (2 mL) was add AgOTf(0.012 g, 0.05 mmol) under

argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 4-(7-phenylchroman-5-yl)phenyl 4-methylbenzenesulfonate (**55ap**) (0.195 g, 85%) white solid.

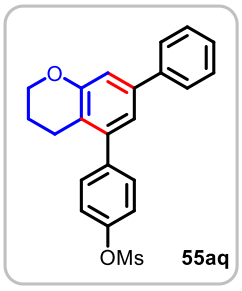
TLC: R_f = 0.60 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.76 (m, 2H), 7.60-7.56 (m, 2H), 7.45-7.39 (m, 2H), 7.37-7.33 (m, 3H), 7.32-7.28 (m, 2H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.07-7.03 (m, 2H), 7.01 (d, *J* = 1.8 Hz, 1H), 4.24 (t, *J* = 5.0 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 2.47 (s, 3H), 1.99-1.92 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.3, 148.7, 145.4, 141.9, 140.4, 140.1, 140.0, 132.5, 130.3, 129.8, 128.7, 128.5, 127.4, 126.9, 122.1, 120.4, 119.0, 114.7, 66.3, 24.0, 22.4, 21.7.

HRMS (ESI): *m/z* calcd for $C_{28}H_{25}O_4S$ $[M+H]^+$ 457.1468, found 457.1467.

4-(7-Phenylchroman-5-yl)phenylmethanesulfonate (55aq):



Following the *General Procedure,* to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-4-(3-oxo-3-phenylprop-1-en-1-yl)phenyl methanesulfonate (**54q**) (0.152 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf(0.012 g, 0.05 mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 4-(7-phenylchroman-5-yl)phenyl methanesulfonate (**55aq**) (0.167 g, 87%) white solid.

TLC: R_f = 0.60 (SiO_2, 20% EtOAc/hexanes).

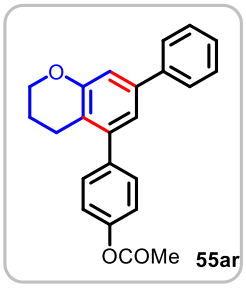
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.59 (m, 2H), 7.46-7.41 (m, 4H), 7.38-7.34 (m, 3H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.05 (d, *J* = 1.5 Hz, 1H), 4.28-4.24 (m, 2H), 3.21 (s, 3H), 2.68-2.63 (m, 2H), 2.08-1.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.3, 148.2, 141.7, 140.4, 140.3, 140.1, 130.7, 128.7, 127.4, 126.9, 121.7, 120.4, 119.0, 114.7, 66.3, 37.4, 24.0, 22.3.

IR (KBr, cm^{-1}): υ 3019, 2939, 2877, 1723, 1601, 1583, 1565, 1467, 1412, 1372, 1351, 1321, 1287, 1215, 1149, 1101, 1048, 1011, 969, 929, 903, 871, 849, 758, 669.

HRMS (ESI): calcd for $C_{22}H_{21}O_4S$ $[M+H]^+$ 381.1155, found 381.1149.

4-(7-Phenylchroman-5-yl)phenyl acetate (55ar):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-4-(3-oxo-3-phenylprop-1-en-1-yl)phenyl acetate (**54r**) (0.134 g, 0.505 mmol) in anhydrous PhF (2 mL) was add AgOTf (0.012 g, 0.05mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded4-(7-phenylchroman-5-yl)phenyl acetate (**55ar**) (0.145 g, 83%) colorless oil.

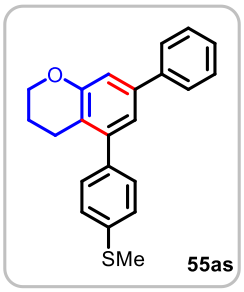
TLC: R_f = 0.70 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.65-7.57 (m, 2H), 7.46-7.38 (m, 4H), 7.37-7.31 (m, 1H), 7.18-7.14 (m, 2H), 7.10 (d, *J*= 1.88 Hz, 1H), 7.08 (d, *J*= 1.88 Hz, 1H), 4.28-4.23 (m, 2H), 2.68 (t, *J*=6.38 Hz, 2H), 2.35 (s, 3H), 2.01-1.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.6, 155.3, 149.8, 142.4, 140.5, 140.0, 138.6, 130.1, 128.7, 127.3, 126.9, 121.2, 120.6, 119.2, 114.5, 66.3, 24.0, 22.3, 21.2.

HRMS (ESI): *m/z* calcd for $C_{23}H_{21}O_3$ $[M+H]^+$ 345.1485, found 345.1476.

5-(4-(Methylthio)phenyl)-7-phenylchromane(55as):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**)(0.1 g, 1.01 mmol) and (*E*)-3-(4-(methylthio)phenyl)-1-phenylprop-2-en-1-one (**54s**) (0.128 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(4-(methylthio)phenyl)-7-phenylchromane (**55as**) (0.100 g, 60%) colorless oil.

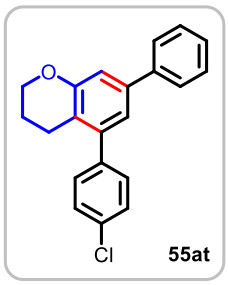
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.59 (m, 2H), 7.46-7.39 (m, 2H), 7.37-7.30 (m, 5H), 7.08 (d, *J* = 1.83 Hz, 1H), 7.06 (d, *J* = 1.83 Hz, 1H), 4.27-4.23 (m, 2H), 2.68 (t, *J* = 6.41 Hz, 2H), 2.54 (s, 3H), 2.03-1.89 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.3, 142.7, 140.6, 140.1, 137.9, 137.3, 129.6, 128.7, 127.3, 126.9, 126.2, 120.5, 119.2, 114.4, 66.3, 24.1, 22.5, 15.8.

HRMS (ESI): *m/z* calcd for $C_{22}H_{21}OS$ $[M+H]^+$ 333.1308 found 333.1306.

5-(4-Chlorophenyl)-7-phenylchromane (55at):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**)(0.1 g, 1.01 mmol) and (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**54t**) (0.122 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded5-(4-chlorophenyl)-7-phenylchromane (**55at**) (0.094 g, 58%) colorless oil.

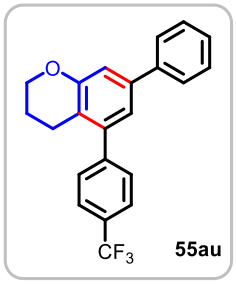
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.58 (m, 2H), 7.45-7.39 (m, 4H), 7.36-7.30 (m, 3H), 7.10 (d, *J* = 1.9 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 4.25 (t, *J* = 5.13 Hz, 2H), 2.67-2.62 (m, 2H), 2.01-1.93 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.3, 142.1, 140.5, 140.1, 139.5, 133.1, 130.4, 128.7, 128.3, 127.3, 126.9, 120.4, 119.0, 114.6, 66.3, 24.0, 22.4.

HRMS (ESI): *m/z* calcd for $C_{21}H_{18}OCl$ $[M+H]^+$ 321.1041, found 321.1039.

7-Phenyl-5-(4-(trifluoromethyl)phenyl)chromane (55au):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**54u**) (0.139 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf(0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-phenyl-5-(4-(trifluoromethyl)phenyl)chromane (**55au**) (0.178 g, 69%) colorless oil.

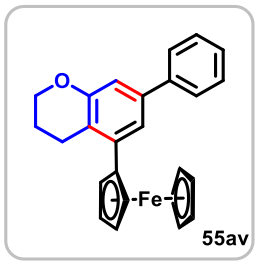
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.63-7.58 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.47-7.40 (m, 2H), 7.38-7.32 (m, 1H), 7.13 (d, *J* = 1.75 Hz, 1H), 7.05 (d, *J* = 1.9 Hz, 1H), 4.30-4.24 (m, 2H), 2.64 (t, *J* = 6.5 Hz, 2H), 2.02-1.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.4, 144.8, 141.9, 140.4, 140.3, 129.5, 128.8, 127.4, 126.9, 125.2, 125.1 (2C), 125.0 120.3, 118.9, 115.0, 66.3, 23.9, 22.3.

HRMS (ESI): *m/z* calcd for $C_{22}H_{18}OF_3$ $[M+H]^+$ 355.1304, found 355.1304.

7-Phenyl-5-(ferrocenyl)chromane (55av):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**)(0.1 g, 1.01 mmol) and (*E*)-3-(ferrocene)-1-phenylprop-2-en-1-one (**54v**) (0.156 g, 0.505 mmol)in anhydrous PhF (2 mL) was addedAgOTf(0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded7-phenyl-5-(ferrocenyl)chromane (**55av**) (0.134 g, 67%) blackesh yellow oil.

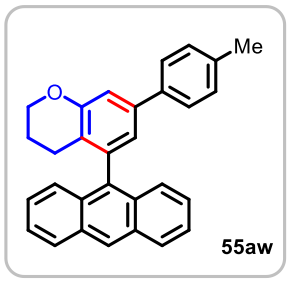
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66-7.63 (m, 2H), 7.61 (d, *J* = 2.3 Hz, 1H), 7.50-7.45 (m, 2H), 7.40-7.34 (m, 1H), 6.97 (d, *J* = 1.5 Hz, 1H), 4.49-4.48 (m, 2H), 4.32-4.30 (m, 2H), 4.24-4.21 (m, 2H), 4.19 (s, 5H), 2.83-2.78 (m, 2H), 2.00-1.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.0, 141.0, 139.5, 139.1, 128.8, 127.2, 126.9, 121.7, 119.9, 113.5, 87.1, 70.2, 69.6, 67.8, 66.1, 24.4, 22.6.

HRMS (ESI): *m/z* calcd for $C_{25}H_{23}OFe$ $[M+H]^+$ 395.1093, found 395.1066.

5-(Anthracen-9-yl)-7-(*p*-tolyl)chromane(55aw):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(anthracen-9-yl)-1-(*p*-tolyl)prop-2-en-1-one (**54w**) (0.162 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf(0.012 g, 0.05 mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the

crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(anthracen-9-yl)-7-(*p*-tolyl)chromane (**55aw**) (0.142 g, 71%) yellow solid.

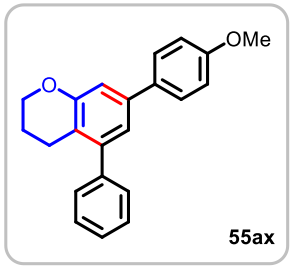
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.52 (s, 1H), 8.08 (d, *J* = 8.39 Hz, 2H), 7.69 (d, *J* = 8.39 Hz, 2H), 7.55 (d, *J* = 8.39 Hz, 2H), 7.51-7.46 (m, 2H), 7.42-7.34 (m, 2H), 7.28-7.27 (m, 1H), 7.21 (d, *J* = 8.39 Hz, 2H), 7.15 (d, *J* = 1.53 Hz, 1H),4.24 (t, *J* = 5.34 Hz, 2H), 2.37 (s, 3H), 2.16-2.11 (m, 2H), 1.88-1.80 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.5, 139.8, 139.4, 137.6, 137.0, 135.5, 131.4, 129.9, 129.4, 128.5, 126.7, 126.5, 125.6, 125.2, 121.8, 121.3, 114.3, 66.4, 22.5, 22.3, 21.1.

HRMS (ESI): *m/z* calcd for $C_{30}H_{25}O$ $[M+H]^+$ 401.1900 found 401.1899.

7-(4-Methoxyphenyl)-5-phenylchromane (55ax):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (**54x**) (0.120 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-(4-methoxyphenyl)-5-phenylchromane (**55ax**) (0.126 g, 79%) colorless oil.

TLC: R_f = 0.80 (SiO_2, 10% EtOAc/hexanes).

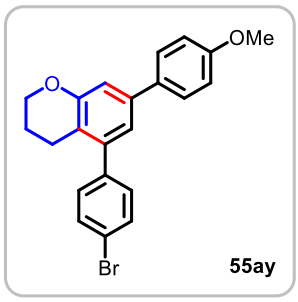
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60-7.51 (m, 2H), 7.48-7.33 (m, 5H), 7.06-7.04 (m, 2H), 6.99-6.91 (m, 2H), 4.25 (t, *J* = 5.34 Hz, 2H), 3.85 (s, 3H) 2.69-2.64 (m, 2H), 2.01-1.92 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.1, 155.2, 143.3, 141.2, 139.6, 133.2, 129.1, 128.1, 127.9, 127.0, 120.2, 118.5, 114.1, 113.8, 66.3, 55.3, 24.0, 22.5.

HRMS (ESI): *m/z* calcd for $C_{22}H_{21}O_2$ $[M+H]^+$317.1536, found 317.1531.

5-(4-Bromophenyl)-7-(4-methoxyphenyl)chromane (55ay):

Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**)(0.1 g, 1.01 mmol) and (*E*)-3-(4-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**54y**) (0.160 g,



0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(4-bromophenyl)-7-(4-methoxyphenyl)chromane (**55ay**) (0.135 g, 67%) white solid.

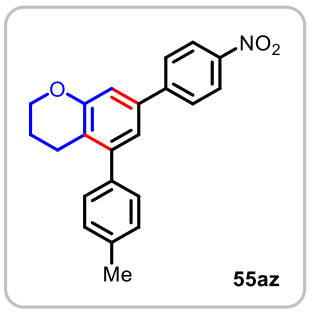
TLC: R_f = 0.80 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.73 (m, 1H), 7.54-7.50 (m, 1H), 7.47-7.43 (m, 1H), 7.32-7.25 (m, 3H), 7.03-7.00 (m, 2H), 6.99-6.95 (m, 2H), 4.25 (t, *J* = 5.13 Hz, 2H), 3.87 (s, 3H), 2.68 (t, *J* = 6.50 Hz, 2H), 2.00-1,92 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.8, 155.4, 143.2, 142.9, 138.3, 133.2, 130.2 (2C), 130.1, 130.0, 125.5, 122.8, 120.5, 120.,0 114.0, 113.6, 66.3, 55.3, 24.1, 22.4.

HRMS (ESI): *m/z* calcd for $C_{22}H_{20}O_2Br$ $[M+H]^+$ 395.0641, found 395.0645.

7-(4-Nitrophenyl)-5-(*p*-tolyl)chromane (55az):



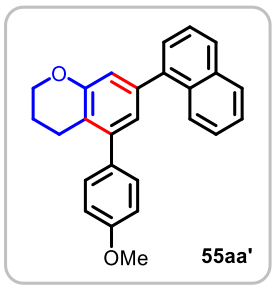
Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**)(0.1 g, 1.01 mmol) and (*E*)-1-(4-nitrophenyl)-3-(*p*-tolyl)prop-2-en-1-one (**54z**) (0.134 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 7-(4-nitrophenyl)-5-(*p*-tolyl)chromane (**55az**) (0.120 g, 69%) colorless oil.

TLC: R_f = 0.70 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.47 (m, 2H), 7.36-7.30 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.15-7.08 (m, 2H), 7.05 (dd, *J* = 19.4, 1.9 2H), 4.24 (t, *J* = 5.1 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.39 (s, 3H), 2.00-1.92 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.3, 160.8, (unidentified aromatic impurity) 155.3, 142.2, 140.0, 137.6, 137.1, 137.0, 130.7, 130.6, 129.4, 126.8, 120.4, 118.9, 115.1, 114.9, 114.2, 66.3, 29.7 (grease), 24.0, 22.5, 21.1.

5-(4-Methoxyphenyl)-7-(naphthalen-1-yl)chromane(55aa'):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-methoxyphenyl)-1-(naphthalen-1-yl)prop-2-en-1-one (**54a'**) (0.145 g, 0.505 mmol) in anhydrous PhF (2 mL) was addedAgOTf(0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded5-(4-methoxyphenyl)-7-(naphthalen-1-yl)chromane (**55aa'**) (0.155 g, 84%) colorless oil.

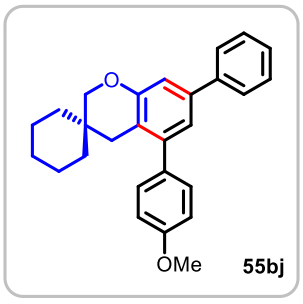
TLC: R_f = 0.80 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11-8.09 (m, 1H), 7.93-7.88 (m, 1H), 7.85 (d, *J* = 7.79 Hz, 1H), 7.54-7.43 (m, 4H), 7.37-7.32 (m, 2H), 7.02-6.93 (m, 4H), 4.31-4.27 (m, 2H), 3.86 (s, 3H), 2.76 (t, *J* = 6.41 Hz, 2H), 2.08-1.96 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.7, 154.8, 142.4, 139.8, 139.4, 133.8, 133.3, 131.5, 130.3, 128.2, 127.5, 126.8, 126.2, 125.9, 125.7, 125.4, 123.7, 119.1, 117.1, 113.5, 66.3, 55.3, 24.3, 22.6.

HRMS (ESI): *m/z* calcd for $C_{26}H_{23}O_2$ $[M+H]^+$367.1693, found 367.1696.

5-(4-Methoxyphenyl)-7-phenylspiro[chromane-3,1'-cyclohexane] (55bj):



Following the *General Procedure*, to the mixture of (1-(but-3-yn-1-yl)cyclohexyl)methanol (**53b**) (0.1 g, 0.60 mmol) and (*E*)3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (**54j**) (0.071 g, 0.30 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.007 g, 0.03mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(4-methoxyphenyl)-7-phenylspiro[chromane-3,1'-cyclohexane] (**55bj**) (0.088 g, 77%) colorless oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

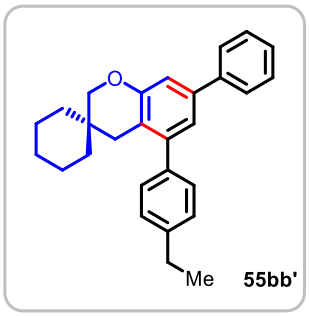
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.62 (m, 1H), 7.61-7.59 (m, 1H), 7.46-7.39 (m, 2H), 7.36-7.29 (m, 3H), 7.10-7.06 (m, 2H), 7.01-6.99 (m, 1H), 6.99-6.98 (m, 1H), 3.94 (s, 2H), 3.89 (s, 3H), 2.50 (s, 2H), 1.49-1.34 (m, 10H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.6, 154.4, 143.2, 140.7, 133.5, 130.2, 128.7, 127.2, 126.9, 121.0, 118.2, 113.5 (2C), 73.3, 55.3, 33.2, 31.2, 26.4, 21.5.

IR (KBr, cm^{-1}): υ 3019, 2932, 2855, 1609, 1563, 1514, 1466, 1341, 1215, 1150, 929, 869, 767, 669.

HRMS (ESI): *m/z* calcd for $C_{27}H_{29}O_2$ $[M+H]^+$ 385.2162, found 385.2168.

5-(4-Ethylphenyl)-7-phenylspiro[chromane-3,1'-cyclohexane] (55bb'):



Following the *General Procedure*, to the mixture of (1-(but-3-yn-1-yl)cyclohexyl)methanol (**53b**)(0.1 g, 0.60 mmol) and (*E*)-3-(4-ethylphenyl)-1-phenylprop-2-en-1-one (**54b'**) (0.070 g, 0.30 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.007 g, 0.030 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(4-ethylphenyl)-7-phenylspiro[chromane-3,1'-cyclohexane] (**54bb'**) (0.075 g, 66%) colorless oil.

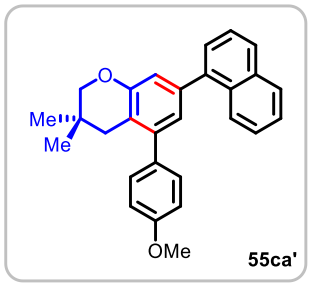
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.57 (m, 2H), 7.42-7.36 (m, 2H), 7.33-7.25 (m, 5H), 7.08-7.05 (m, 2H), 3.93 (s, 2H), 2.72 (q, *J* = 7.63 Hz, 15.26 Hz, 2H), 2.48 (s, 2H), 1.51-1.34 (m, 9H), 1.33-1.28 (m, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 154.4, 143.6, 142.9, 140.7, 139.6, 138.4, 129.0, 128.6, 127.6, 127.1, 126.9, 121.0, 118.1, 113.6, 73.5, 35.9, 33.2, 31.2, 28.6, 26.4, 21.5, 15.4.

HRMS (ESI): *m/z* calcd for $C_{28}H_{31}O$ $[M+H]^+$ 383.2369, found 383.2374.

5-(4-Methoxyphenyl)-3,3-dimethyl-7-(naphthalen-1-yl)chromane (55ca'):



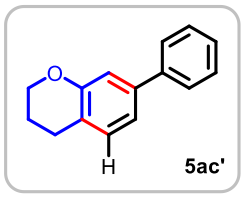
Following the *General Procedure*, to the mixture of 2,2-dimethylhex-5-yn-1-ol (**53c**) (0.1 g, 0.79 mmol) and (*E*)-3-(4-methoxyphenyl)-1-(naphthalen-1-yl)prop-2-en-1-one (**54a'**) (0.112 g, 0.39 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.010 g, 0.039mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(4-methoxyphenyl)-3,3-dimethyl-7-(naphthalen-1-yl)chromane (**55ca'**) (0.110 g, 72%) colorless oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, *J* = 8.39 Hz, 1H), 7.93-7.84 (m, 2H), 7.54-7.46 (m, 4H), 7.37-7.33 (m, 2H), 7.06-6.94 (m, 4H), 3.87 (s, 5H), 2.55 (s, 2H), 1.06 (s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.7, 153.6, 142.6, 139.8, 139.3, 133.8, 133.4, 131.5, 130.3, 129.0, 128.2, 127.5, 126.9, 126.2, 125.9, 125.7, 125.4, 124.1, 118.3, 116.8, 113.9, 113.5, 75.4, 55.3, 38.2, 28.8, 24.9.

7-Phenylchromane(55ac'):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and1-phenylprop-2-en-1-one (**54c'**) (0.066 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded7 -phenylchromane (**55ac'**)(0.057 g, 54%) colorless oil.

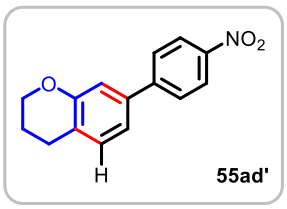
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.57 (m, 2H), 7.48-7.41 (m, 2H), 7.38-7.32 (m, 1H), 7.16-7.10 (m, 2H), 7.09-7.06 (m, 1H), 4.25 (t, *J* = 5.13 Hz, 2H), 2.85 (t, *J* = 6.5 Hz, 2H), 2.11-2.02 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.1, 140.9, 140.5, 130.1, 128.7, 127.1, 126.9, 121.3, 119.0, 115.2, 66.5, 24.6, 22.4.

HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O$ $[M+H]^+$ 211.1117, found 211.1110.

7-(4-Nitrophenyl)chromane (55ad'):



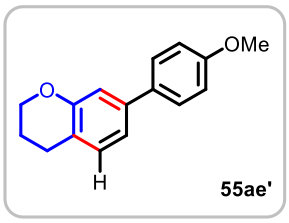
Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and 1-(4-nitrophenyl)prop-2-en-1-one (**54d'**) (0.089 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-(4-nitrophenyl)chromane (**55ad'**) (0.078 g, 60%) colorless oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33-8.22 (m, 2H), 7.75-7.65 (m, 2H), 7.18-7.05 (m, 3H), 4.31-4.21 (m, 2H), 2.85 (t, *J* = 6.50 Hz, 2H), 2.13-1.99 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.4, 147.3, 146.9, 137.8, 130.6, 127.5, 124.0, 123.3, 119.0. 115.5, 66.6, 24.7, 22.2.

7-(4-Methoxyphenyl)chromane (55ae'):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and1-(4-methoxyphenyl)prop-2-en-1-one (**54e'**) (0.081 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-(4-methoxyphenyl)chromane (**55ae'**) (0.071 g, 59%) colorless oil.

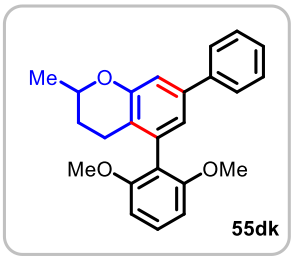
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58-7.42 (m, 2H), 7.11-7.03 (m, 2H), 7.02-6.94 (m, 3H), 4.23 (t, *J* = 5.13 Hz, 2H), 3.85 (s, 3H), 2.86-2.80 (m, 2H), 2.13-2.00 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.0, 155.1, 140.1, 133.5, 130.1, 127.9, 120.7, 118.6, 114.7, 114.1, 66.5, 55.3, 24.6, 22.4.

5-(2,6-Dimethoxyphenyl)-2-methyl-7-phenylchromane (55dk):

Following the *General Procedure*, to the mixture of hept-6-yn-2-ol (**53d**) (0.1 g, 0.8 mmol) and (*E*)-3-(2,6-dimethoxyphenyl)-1-phenylprop-2-en-1-one (**54k**) (0.119 g, 0.4 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.011 g, 0.04mmol)under argon



atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(2,6-dimethoxyphenyl)-2-methyl-7-phenylchromane (**55dk**) (0.138 g, 86%) white solid.

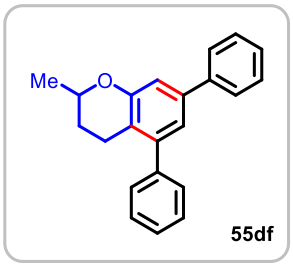
TLC: R_f = 0.70 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J*=7.63 Hz, 2H), 7.41 (t, *J* = 7.63 Hz, 2H), 7.37-7.28 (m, 2H), 7.12 (d, *J* = 1.53 Hz, 1H), 7.03 (d, *J* = 1.53 Hz, 1H), 6.69 (d, *J* = 8.39 Hz, 2H), 4.25-4.21 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.59-2.53 (m, 1H), 2.46-2.38 (m, 1H), 1.99-1.81 (m, 1H), 1.81-1.67 (m, 1H), 1.45 (d, *J* = 6.10 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.9, 157.6, 155.1, 141.1, 139.2, 135.3, 128.8, 128.5, 127.0, 126.8, 121.5, 120.9, 118.1, 114.2, 104.0, 103.9, 71.9,55.9, 55.8, 29.3, 22.6, 21.6.

HRMS (ESI): *m/z* calcd for $C_{24}H_{25}O_3$ $[M+H]^+$ 361.1798 found, 361.1800.

2-Methyl-5,7-diphenylchromane (55df):



Following the *General Procedure*, to the mixture of hept-6-yn-2-ol (**53d**) (0.1 g, 0.8 mmol) and (*E*)-chalcone (**54f**) (0.092 g, 0.4mmol) in anhydrous PhF (2 mL) was added AgOTf (0.011 g, 0.04 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded2-methyl-5,7-diphenylchromane (**55df**) (0.093 g, 70%) colorless oil.

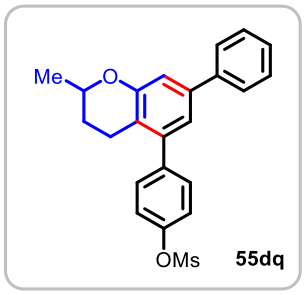
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.59 (m, 2H), 7.47-7.30 (m, 8H), 7.13-7.07 (m, 2H), 4.28-4.19 (m, 1H), 2.84-2.73 (m, 1H), 2.63-2.54 (m, 1H), 2.02-1.94 (m, 1H), 1.72-1.60 (m, 1H), 1.43 (d, *J* = 6.25 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.5, 143.1, 141.3, 140.7, 139.9, 129.1, 128.7, 128.1, 127.2, 127.0, 126.9, 120.4, 118.8, 114.3, 72.1, 29.4, 24.0, 21.4.

HRMS (ESI): *m/z* calcd for $C_{22}H_{21}O$ $[M+H]^+$ 301.1587, found 301.1587.

4-(2-Methyl-7-phenylchroman-5-yl)phenylmethanesulfonate (55dq):



Following the *General Procedure*, to the mixture of hept-6-yn-2-ol (**53d**) (0.1 g, 0.8 mmol) and(*E*)-4-(3-oxo-3-phenylprop-1-en-1-yl)phenyl methanesulfonate (**54q**) (0.134 g, 0.4 mmol) in anhydrous PhF (2 mL) was addedAgOTf(0.011 g, 0.04mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 4-(2-methyl-7-phenylchroman-5-yl)phenyl methanesulfonate (**55dq**) (0.116 g, 67%) colorless oil.

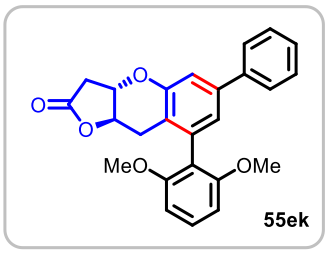
TLC: R_f = 0.70 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.58 (m, 2H), 7.46-7.39 (m, 4H), 7.37-7.31 (m, 3H), 7.14-7.11 (m, 1H), 7.05-7.03 (m, 1H), 4.34-4.12 (m, 1H), 3.21 (s, 3H), 2.80-2.71 (m, 1H), 2.65-2.52 (m, 1H), 2.06-1.95 (m, 1H), 1.73-1.60 (m, 1H), 1.45 (d, *J* = 6.25 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.6, 148.2, 141.6, 140.6, 140.4, 140.1, 130.7, 128.7, 127.4, 126.9, 121.7, 120.4, 118.7, 115.3, 114.8, 72.1, 37.5, 26.9, 24.0, 21.4.

HRMS (ESI): *m/z* calcd for $C_{23}H_{23}O_4S$ $[M+H]^+$ 395.1312, found 395.1305.

(*3aS,9aR*)-8-(2,6-Dimethoxyphenyl)-6-phenyl-3,3a,9,9a-tetrahydro-2*H*-furo[3,2-b]chromen-2-one (55ek):



Following the *General Procedure*, to the mixture of (*4S,5R*)-5-(but-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (**53e**)(0.1 g, 0.64 mmol) and (*E*)-3-(2,6-dimethoxyphenyl)-1-phenylprop-2-en-1-one (**54k**) (0.085 g, 0.32 mmol)in anhydrous PhF (2 mL) was addedAgOTf(0.008 g, 0.032mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded (*3aS,9aR*)-8-(2,6-dimethoxyphenyl)-6-phenyl-3,3a,9,9a-tetrahydro-2*H*-furo[3,2-*b*]chromen-2-one (**55ek**)(0.058 g, 45%) white solid.

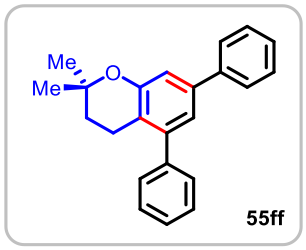
TLC: R_f = 0.70 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.58 (m, 2H), 7.44-7.38 (m, 2H), 7.37-7.29 (m, 2H), 7.17-7.15 (m, 2H), 6.68 (dd, *J* = 8.4, 1.63 Hz, 2H), 4.92-4.87 (m, 1H), 4.83-4.80 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.98-2.81 (m, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.8, 157.9, 157.6, 153.6, 140.6, 140.1, 135.2, 129.3, 128.6, 127.2, 127.1, 124.3, 119.4, 116.5, 114.8, 104.2, 103.8, 78.3, 73.1, 55.9, 55.8 37.4, 25.7.

HRMS (ESI): *m/z* calcd for $C_{25}H_{23}O_5$ $[M+H]^+$403.1540, found 403.1536.

2,2-Dimethyl-5,7-diphenylchromane (55ff):



Following the *General Procedure*, to the mixture of 2-methylhept-6-yn-2-ol (**53f**) (0.1 g, 0.79 mmol) and (*E*)-chalcone (**54f**) (0.081 g, 0.39 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.010 g, 0.039mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 2,2-dimethyl-5,7-diphenylchromane (**55ff**) (0.082 g, 67%) colorless oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

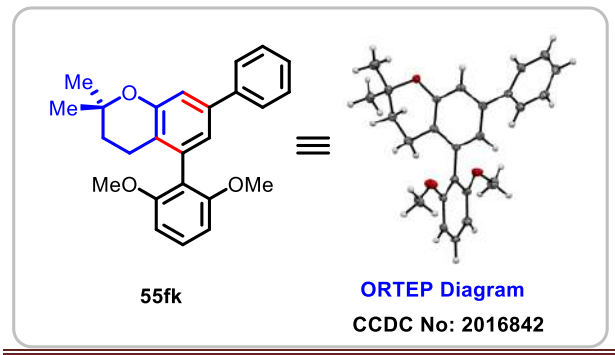
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.66 (m, 2H), 7.51-7.43 (m, 6H), 7.41-7.34 (m, 2H), 7.20-7.14 (m, 2H), 2.75-2.69 (m, 2H), 1.84-1.79 (m, 2H), 1.47 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 154.4, 143.0, 141.3, 140.7, 140.0, 129.1, 128.6, 128.1, 127.1, 127.0, 126.9, 120.1, 117.9, 114.8, 73.9, 32.9, 26.9, 21.5.

IR (KBr, cm^{-1}): υ 3019, 2978, 1600, 1563, 1526, 1468, 1440, 1402, 1332, 1217, 1164, 1029, 967, 929, 772, 702, 669.

HRMS (ESI): *m/z* calcd for $C_{23}H_{23}O$ $[M+H]^+$ 315.1743, found 315.1740.

5-(2,6-Dimethoxyphenyl)-2,2-dimethyl-7-phenylchromane (55fk):



Following the *General Procedure*, to the mixture of 2-methylhept-6-yn-2-ol (**53f**) (0.1 g, 0.79 mmol) and (*E*)-3-(2,6-dimethoxyphenyl)-1-phenylprop-2-en-1-one (**54k**) (0.105 g, 0.39 mmol) in

anhydrous PhF (2 mL) was added AgOTf (0.010 g, 0.039mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(2,6-dimethoxyphenyl)-2,2-dimethyl-7-phenylchromane (**55fk**) as a white crystal (0.130 g, 89%) white crystal.

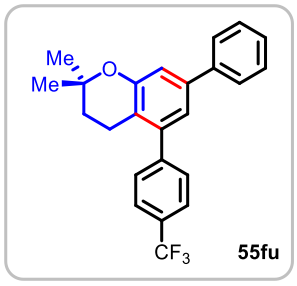
TLC: R_f = 0.60 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 7.33 Hz, 2H), 7.43-7.38 (m, 2H), 7.37-7.28 (m, 2H), 7.11 (d, *J* = 1.37 Hz, 1H), 7.03 (d, *J* = 1.37 Hz, 1H), 6.73-6.65 (m, 2H), 3.76 (s, 6H), 2.49-2.44 (m, 2H), 1.79 (t, *J* = 6.87 Hz, 2H), 1.40 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.8, 154.1, 141.1, 139.2, 135.2, 128.8, 128.4, 127.0, 126.7, 121.1, 120.2, 118.2, 114.6, 104.0, 73.9, 55.8, 32.8, 26.8, 20.3.

HRMS (ESI): *m/z* calcd for $C_{25}H_{27}O_3$ $[M+H]^+$ 375.1955, found 375.1956.

2,2-Dimethyl-7-phenyl-5-(4-(trifluoromethyl)phenyl)chromane (55fu):



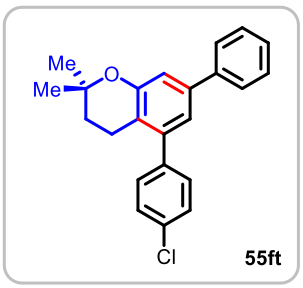
Following the *General Procedure*, to the mixture of 2-methylhept-6-yn-2-ol (**53f**)(0.1 g, 0.79 mmol) and (*E*)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**54u**) (0.109 g, 0.39 mmol) in anhydrous PhF (2 mL) was added Ag OTf (0.010 g, 0.039 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 2,2-dimethyl-7-phenyl-5-(4-(trifluoromethyl)phenyl)chromane (**55fu**) (0.097 g, 64%) white solid.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 8.00 Hz, 2H), 7.63-7.58 (m, 2H), 7.51 (d, *J* = 8.00 Hz, 2H), 7.44-7.40 (m, 2H), 7.36-7.32 (m, 1H), 7.13 (d, *J* = 1.88 Hz, 1H), 7.04 (d, *J* = 2.00 Hz, 1H), 2.65-2.59 (m, 2H), 1.80-1.75 (m, 2H), 1.41 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 154.6, 145.1, 145.0, 141.6, 140.4, 140.3, 129.5, 128.7, 127.4, 126.9, 125.1 (2C), 119.9, 117.7, 115.5, 74.1, 32.8, 26.9, 21.4.

5-(4-Chlorophenyl)-2,2-dimethyl-7-phenylchromane (55ft):



Following the *General Procedure*, to the mixture of 2-methylhept-6-yn-2-ol (**53f**) (0.1 g, 0.79 mmol) and (*E*)-1-phenyl-3-(4-(chloro)phenyl)prop-2-en-1-one (**54t**) (0.095 g, 0.39mmol)in anhydrous PhF (2 mL) was added AgOTf (0.010 g, 0.039 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(4-chlorophenyl)-2,2-dimethyl-7-phenylchromane (**55ft**) (0.081 g, 59%) white solid.

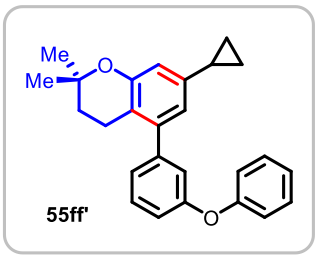
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.59 (m, 2H), 7.43-7.39 (m, 4H), 7.35-7.31 (m, 3H), 7.10 (d, *J* = 1.88 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 2.63 (t, *J* = 6.75 Hz, 2H), 1.79-1.75 (m, 2H), 1.40 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 154.6, 141.8, 140.5, 140.2, 139.8, 133.1, 130.5, 128.7, 128.3, 127.6, 127.3, 126.9, 120.0, 117.8, 115.2, 74.0, 32.9, 26.9, 21.5.

HRMS (ESI): *m/z* calcd for $C_{23}H_{22}OCl$ $[M+H]^+$ 349.1554, found 349.1353.

7-Cyclopropyl-2,2-dimethyl-5-(3-phenoxyphenyl)chromane (55ff'):



Following the *General Procedure*, to the mixture of 2-methylhept-6-yn-2-ol (**53f**) (0.1 g, 0.79 mmol) and(*E*)-1-cyclopropyl-3-(3-phenoxyphenyl)prop-2-en-1-one (**54f'**) (0.103 g, 0.39 mmol) in anhydrous PhF (2 mL) was add AgOTf (0.010 g, 0.039 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-cyclopropyl-2,2-dimethyl-5-(3-phenoxyphenyl)chromane (**55ff'**) (0.086 g, 71%) colorless oil.

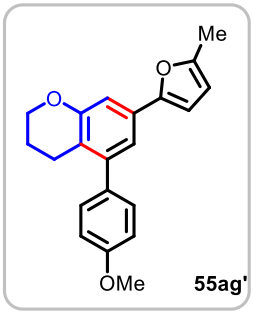
TLC: R_f = 0.80 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.34 (m, 3H), 7.11-7.15 (m, 1H), 7.11-7.07 (m, 3H), 7.02-6.98 (m, 2H), 6.59 (d, *J* = 1.91 Hz, 1H), 6.51 (d, *J* = 1.91 Hz, 1H), 2.59-2.55 (m, 2H), 1.89-1.81 (m, 1H), 1.73-1.68 (m, 2H), 1.36 (s, 6H), 0.96-0.91 (m, 2H), 0.74-0.69 (m, 2H)

^{13}C NMR ($CDCl_3$,126 MHz): δ 157.1, 156.9, 154.2, 143.3, 143.1, 141.8, 129.8, 129.3, 124.0, 123.3, 119.6, 119.1, 118.9, 117.1, 115.7, 113.0, 73.8, 33.0, 26.9, 21.3, 15.0, 9.13.

Synthesis and characterization of heterocyclic chromanes (55 or E55) fromalkynols (53) and α,β-unsaturated ketone (54)

5-(4-Methoxyphenyl)-7-(5-methylfuran-2-yl)chromane (55ag'):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-methoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**54g'**) (0.122 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(4-methoxyphenyl)-7-(5-methylfuran-2-yl)chromane (**55ag'**) (0.130 g, 80%) colorless oil.

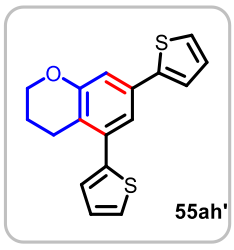
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30-7.23 (m, 2H), 7.09-7.01 (m, 2H), 6.99-6.82 (m, 2H), 6.45 (d, *J* = 3.09 Hz, 1H), 6.07-5.90 (m, 1H), 4.23-4.15 (m, 2H), 3.84 (s, 3H), 2.59 (t, *J* = 6.39 Hz, 2H), 2.32 (s, 3H), 2.01-1.81 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.7, 155.1, 152.0, 151.7, 142.8, 133.4, 130.1, 129.9, 118.9, 117.1, 113.5, 110.3, 107.5, 105.7,66.2, 55.3, 24.2, 22.5, 13.7.

HRMS (ESI): *m/z* calcd for $C_{21}H_{21}O_3$ $[M+H]^+$ 321.1485, found 321.1485.

5,7-Di(thiophen-2-yl)chromane (55ah'):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**)(0.1 g, 1.01 mmol) and (*E*)-1,3-di(thiophen-2-yl)prop-2-en-1-one (**54h'**) (0.111 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded5,7-di(thiophen-2-yl)chromane (**55ah'**) (0.108 g, 72%) yellow oil.

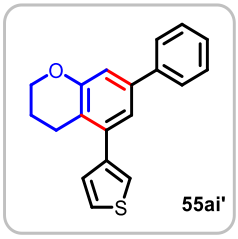
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.37(m, 1H), 7.31-7.29 (m, 1H), 7.27-7.24 (m, 2H), 7.16-7.04 (m, 4H), 4.30-4.20 (m, 2H), 2.82 (t, *J* = 6.49 Hz, 2H), 2.03-1.95 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.4, 143.7, 141.8, 135.6, 133.2, 127.9, 127.1,126.8, 125.5, 124.8, 123.2, 120.3, 120.1, 113.8, 66.2, 24.3, 22.4.

HRMS (ESI): *m/z* calcd for $C_{17}H_{15}OS_2$ $[M+H]^+$ 299.0559 found 299.0558.

7-Phenyl-5-(thiophen-3-yl)chromane (55ai'):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one (**54i'**) (0.108 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05 mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-phenyl-5-(thiophen-3-yl)chromane (**55ai'**) (0.093 g, 63%) yellow oil.

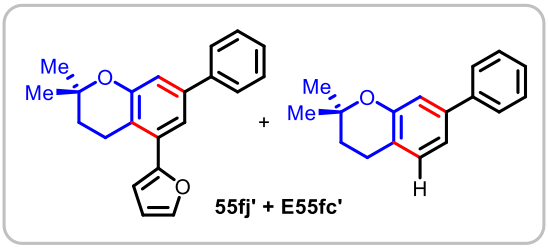
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.58 (m, 2H), 7.46-7.37 (m, 3H), 7.36-7.31 (m, 1H), 7.28 (s, 1H), 7.21-7.18 (m, 1H), 7.15 (d, *J* = 1.5 Hz, 1H), 7.07 (d, *J* = 1.5 Hz, 1H), 4.28-2.23 (m, 2H), 2.78-2.73 (m, 2H), 2.03-1.96 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.3, 141.3, 140.6, 140.0, 138.0, 128.8, 128.7, 127.3, 127.0, 125.0, 122.9, 120.6, 119.4, 114.5, 66.3, 24.1, 22.4.

IR (KBr, cm^{-1}): υ 3019, 2929, 1600, 1566, 1528, 1474, 1310, 1216, 1017, 772, 669.

5-(furan-2-yl)-2,2-dimethyl-7-phenylchromane (55fj') and 2,2-Dimethyl-7-phenylchromane (E55fc'):



Following the *General Procedure*, to the mixture of 2-methylhept-6-yn-2-ol (**53f**) (0.1 g, 0.79 mmol) and (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**54j'**) (0.077 g, 0.39 mmol) in anhydrous PhF (2 mL) was add AgOTf(0.010 g, 0.039 mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 5-(furan-2-yl)-2,2-dimethyl-7-

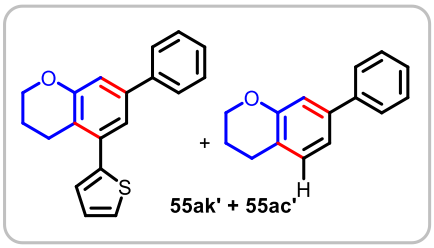
phenylchromane (**55fj'**) and 2,2-dimethyl-7-phenylchromane (**E55fc'**) (0.089 g, 70%) colorless oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66-7.56 (m, 3H), 7.47-7.39 (m, 4H), 7.37-7.30 (m, 2H), 7.16-7.01 (m, 4H), 2.98-2.92 (m, 1H), 2.83 (t, *J* = 6.75 Hz, 2H), 1.89-1.83 (m, 3H), 1.41 (s, 3H), 1.38 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 154.2, 141.0, 140.5, 129.8, 128.7, 128.6, 127.2, 127.0 (3C), 126.9, 120.0, 118.5, 117.4, 115.7, 115.0, 74.3, 73.6, 32.8, 27.0, 22.2.

7-Phenyl-5-(thiophen-2-yl)chromane (55ak') and 7-phenylchromane (55ac'):



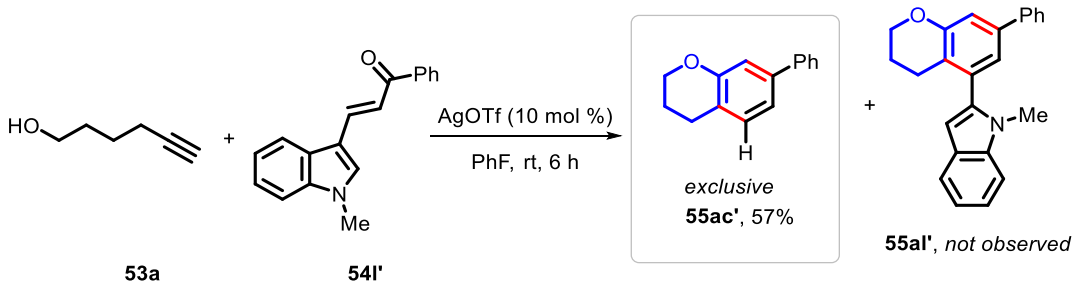
Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (**54k'**) (0.108 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.010 g, 0.05 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded a mixture of 7-phenyl-5-(thiophen-2-yl)chromane (**55ak'**) and 7-phenylchromane (**55ac'**) (0.079 g, 90%) yellow oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59-7.51(m, 4H), 7.42-7.35 (m, 4H), 7.34-7.26 (m, 3H), 7.23-7.20 (m, 1H), 7.11-6.99 (m, 6H), 4.27-4.13 (m, 4H), 2.84-2.78 (m, 4H), 2.06-1.92 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.5, 155.1, 142.1, 140.9, 140.5,140.4, 140.0, 135.5, 130.1, 128.7, 128.7, 127.4, 127.1, 127.0, 126.9, 126.6, 125.3, 121.4, 121.3, 119.7, 118.9, 115.2, 115.1, 66.5, 66.1, 24.6, 24.3, 22.4.

7-Phenylchromane (5ac'):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-3-(1-methyl-1H-indol-2-yl)-1-phenylprop-2-en-1-one (**54l'**) (0.131 g, 0.505 mmol)in anhydrous PhF (2 mL) was added AgOTf (0.012 g, 0.05mmol)under argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded 7-phenylchromane (**55ac'**) (0.060g, 57%) colorless oil.

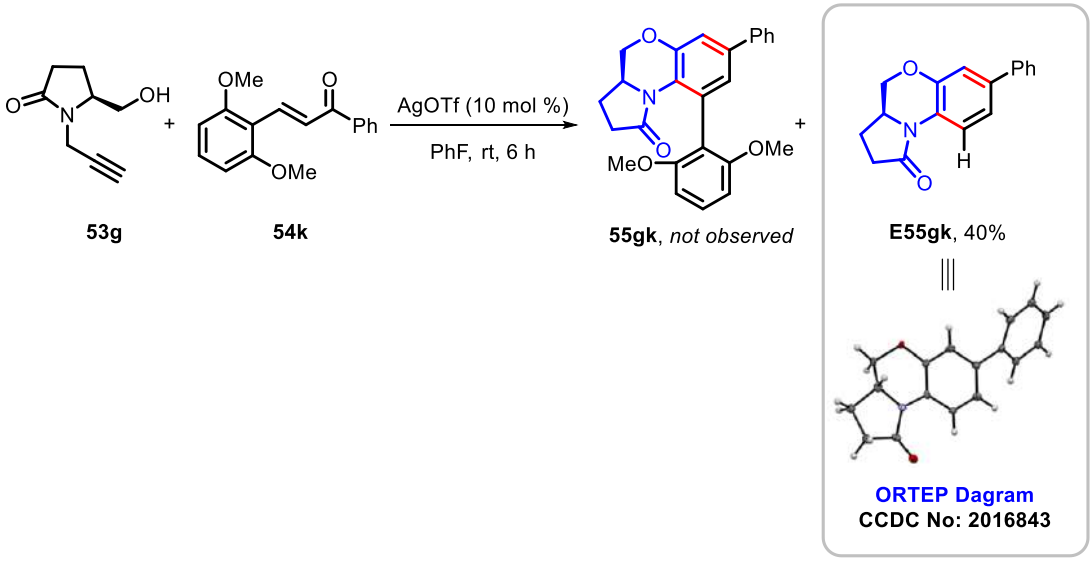
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.56-7.44 (m, 2H), 7.39-7.27 (m, 2H), 7.25-7.17 (m, 1H), 7.06-6.92 (m, 3H), 4.20-4.12 (m, 2H), 2.81-2.71 (m, 2H), 2.05-1.82 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.1, 140.9, 140.5, 130.1, 128.7, 127.1, 126.9, 121.3, 119.0, 115.2, 66.5, 24.7, 22.4.

HRMS (ESI); *m/z* calcd for $C_{15}H_{15}O$ $[M+H]^+$ 211.1117, found 211.1116.

(*S*)-7-Phenyl-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (E55gk):



Following the *General Procedure*, to the mixture of (*S*)-5-(hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (**53g**) (0.1 g, 0.63 mmol) and (*E*)-3-(2,6-dimethoxyphenyl)-1-phenylprop-2-en-1-one (**54k**) (0.084 g, 0.31mmol)in anhydrous PhF (2 mL) was added AgOTf (0.008 g, 0.031 mmol) under argon atmosphere at room temperature and reaction mixture was stirred for 6h at 85 °C. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes)afforded(*S*)-7-phenyl-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**E55gk**) as a white crystal (0.034 g, 40%) white crystal.

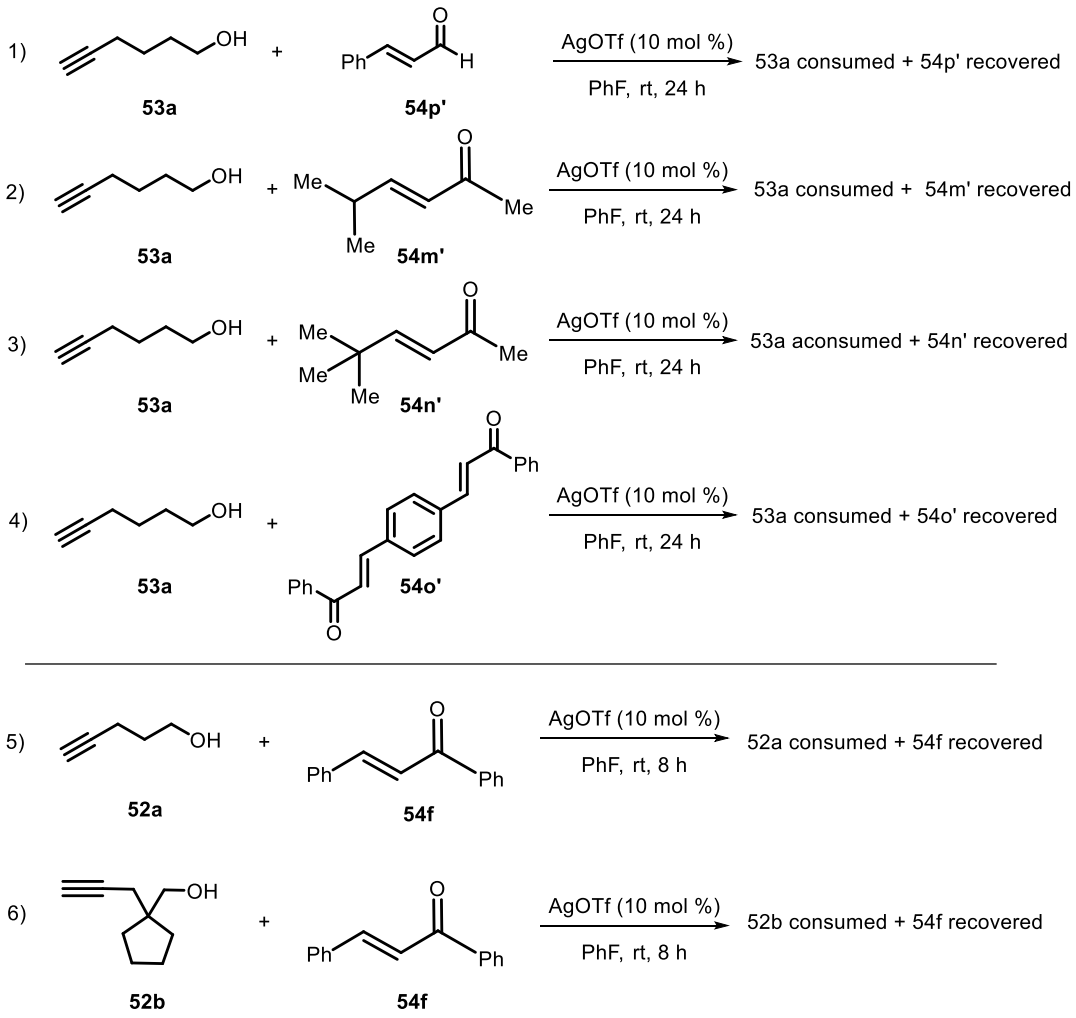
TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.59 (d, *J* = 8.60 Hz, 1H), 7.61-7.57 (m, 1H), 7.55-7.33 (m, 3H), 7.33-7.17 (m, 3H), 4.54 (dd, *J* = 10.58, 2.98 Hz, 1H), 4.20-4.02 (m, 1H), 3.90-3.74 (m, 1H), 2.82-2.47 (m, 2H), 2.45-2.27 (m, 1H), 1.85-1.66 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.5, 144.7, 140.2, 137.7, 128.8, 127.3, 126.8, 124.21 120.2, 119.5, 115.2, 69.6, 54.0, 31.1, 21.0.

HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_2N$ $[M+H]^+$ 266.1176, found 266.1173.

3.2.8 Unsuccessful [3+3]-annulation experiments:



3.2.9 X-ray crystallography data: The single crystal X-ray diffraction measurements were performed for **55fk**, **E55gk** and **T3ab** at 100 K using APEX3 (Bruker, 2016; Bruker D8 VENTURE Kappa Duo PHOTON II CPAD) diffractometer having graphite-monochromatized (Mo = 0.71073 Å). The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of unit cell parameters and an orientation matrix were calculated from a total of 36 frames, and the cell refinement was performed by SAINT-Plus (Bruker, 2016). An optimized strategy used for data collection consisted of different sets of φ and ω scans with 0.5^{0} steps φ/ω. The data were collected with a time frame of 10 Sec for all the three components by setting the sample to detector distance fixed at 40 cm. All the data points were corrected for Lorentzian, polarization, and absorption effects using SAINT-Plus and SADABS programs (Bruker, 2016). SHELXS-97 (Sheldrick,

2008) was used for structure solution and full-matrix least-squares refinement on F^2. The molecular graphics of ORTEP diagrams of all three components were performed by Mercury software. The crystal symmetry of all the three components of single crystals are cross-checked by running the cif files through PLATON (Spek, 2020) software, and notified that there is no additional symmetry was observed. The Encifer software was used to correct the cif files (Figures 1, 2 and 3).

All the three compounds 55fk, E55gk and T3ab have been crystallized in Monoclinic space group $P2_1/c$, $P2_1$ and $P2_1/c$ respectively from the 1% EtOAc/pet.ether solvent by the slow evaporation method. The asymmetric unit contains one molecule in compound 55fk and T3ab, while two molecules are present in E5gk component (Tables 1 and 2).

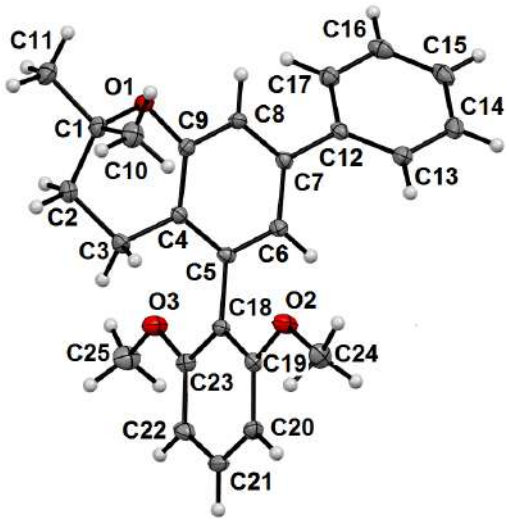


Figure S1. ORTEP diagram of **55fk**, herein, the thermal ellipsoids are drawn with 50% of probability. Moreover, the asymmetric unit contains a single molecule.

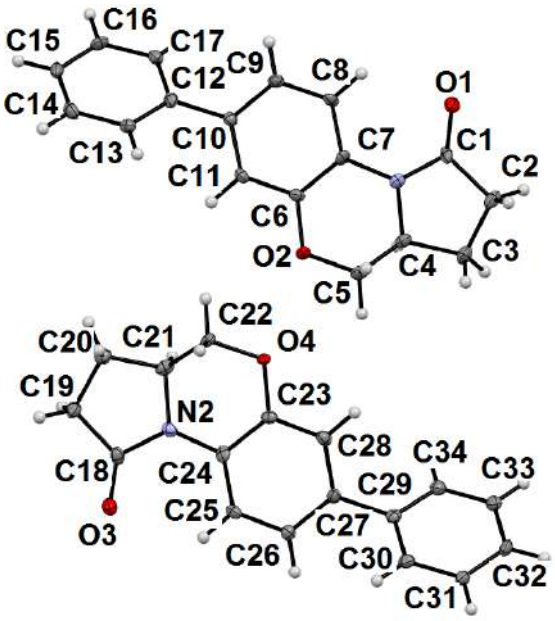


Figure S2. ORTEP diagram of **E55gk**, herein, the thermal ellipsoids are drawn with 50% of probability. Moreover, the asymmetric unit contains two molecules.

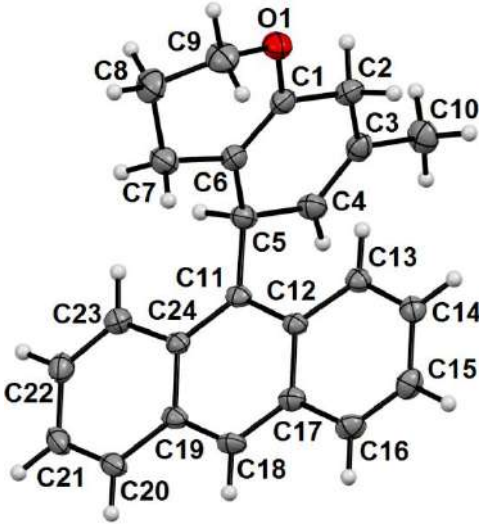


Figure S3. ORTEP diagram of **T3ab**, herein, the thermal ellipsoids are drawn with 50% of probability. Moreover, the asymmetric unit contains a single molecule.

Table S2. Crystallographic information details about the compound **55fk**, **E55gk** and **T3ab**.

Crystal data	Compound **55fk**	Compound **E55gk**	Compound **T3ab**
Chemical formula	$C_{25}H_{26}O_3$	$C_{17}H_{15}NO_2$	$C_{24}H_{22}O$
Formula weight (M_r)	374.46	265.30	326.42
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1$	$P2_1/c$
Temperature T (K)	100 (2)	100 (2)	100 (2)
a (Å)	14.6475(7)	7.2766(18)	9.9695(5)
b (Å)	10.4651(5)	14.676(4)	7.7193(4)
c (Å)	13.6161(6)	12.381(4)	22.7874(10)
α (°)	90	90	90
β (°)	103.479(2)	101.962(13)	101.538(2)
γ (°)	90	90	90
Z	4	4	4
Volume (Å^3)	2029.69(16)	1293.5(6)	1718.22(15)
Source of radiation	MoKα	MoKα	MoKα
D_{calc} (g cm^{-3})	1.225	1.362	1.262
Crystal size (mm)	0.5x0.19x0.16	0.56x0.24x0.22	0.42Xx0.2x0.12
μ (mm^{-1})	0.079	0.090	0.075
Data collection			
Diffractometer	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD
Absorption correction	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)
T_{min}, T_{max}	0.3929, 0.7455	0.6561, 0.7451	0.4158, 0.7455
No. of measured, independent and observed [I > 2σ(I)] reflections	63797, 4351, 3979	46945, 5615, 5525	32959, 3351, 3027
Theta range (°)	2.41-27.11	2.78-27.16	2.48-27.11
R_{int}	0.0596	0.0790	0.0765
Refinement			
R[F^2> 2σ (F^2)], wR(F^2)	0.0551	0.0782	0.0721

GOF on F^2	1.216	1.129	1.056
No. of independent reflections	4351	5615	3351
No. of parameters	258	362	227
No. of restraints	0	1	0
H-atom treatment	constr	constr	constr
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $A^{\circ -3}$)	0.570, -0.564	0.665, -0.373	0.709, -0.328
CCDC number	**2016842**	**2016843**	**2016844**

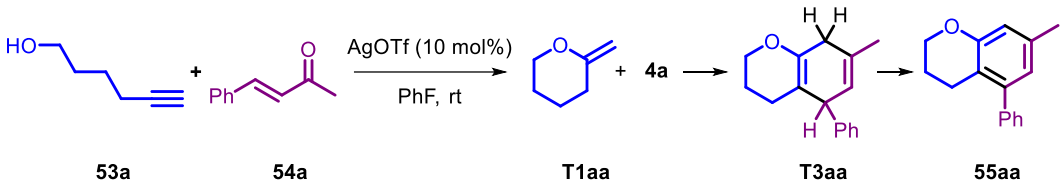
Table S3. Hydrogen-bond geometry (A˚, °) of compound **55fk**, **E55gk** and **T3ab**.

Name of the compound	*D*–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
Compound **55fk**	C21–H21···O2	0.95	2.57	3.2738(15)	131
Compound **E55gk**	C4–H4···O3	1.00	2.59	3.317(8)	130
	C8–H8···O1	0.95	2.44	2.995(8)	117
	C25–H25···O3	0.95	2.33	2.946(8)	122
Compound **T3ab**	There is no prominent hydrogen bond				

3.2.10 Supporting experiments for the postulated reaction mechanism:

a. Real-time GC-MS analyses: To gain insight into the probabale reaction pathway, the following experiment was carried out under optimized reaction conditions using alkynol **53a** (hex-5-yn-1-ol) and enone **44a** ((*E*)-4-phenylbut-3-en-2-one) in PhF solvent at room temperature, which was monitored through GC-MS analyses at 1 h, 3 h and 5 h reaction times. To our delight we were able to find cyclic eno-lether intermediate (**T1aa**) as a major product at t_1 = 1 h with *m/z* value of 99.1 (Figure 4), 1,3-cyclohexadiene intermediate (**T3aa**) at t_2 = 2 h with *m/z* value of 226.2 (Figure 5) and also the final desired product **54aa**at t_3 = 2 h 37 min h with *m/z* value of 224.2

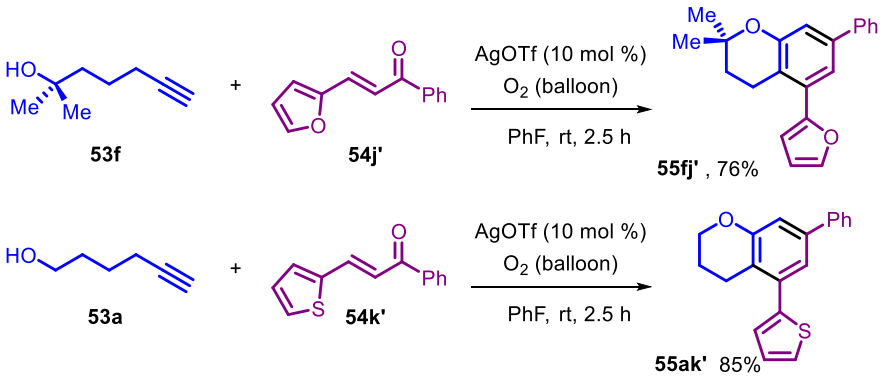
(Figure 6). This investigation results were in accordance with the proposed mechanistic sequence.



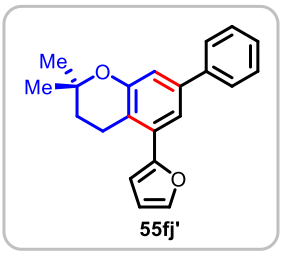
GC-MS*Method Details:*

1. Instrument name: Agilent 7890N 5977MSD
2. Column: HP-5MS column
3. Diameter: 30 m X 0.25 micro meter X 0.25 mm
4. temperature: 80 °C (1 min.) $\xrightarrow{\text{20 min.}}$ 280 °C (10 min.)
5. Injected temp: 250 °C
6. Detector temp: 280 °C
7. Solvent: MeOH

b. Reactions under oxygen atmosphere:



5-(Furan-2-yl)-2,2-dimethyl-7-phenylchromane(55fj'):



Following the *General Procedure*, to the mixture of 2-methylhept-6-yn-2-ol (**53f**) (0.1 g, 0.79 mmol) and (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**54j'**) (0.077 g, 0.39 mmol)in anhydrous PhF (2 mL) was add AgOTf (0.010 g, 0.039 mmol) under oxygen

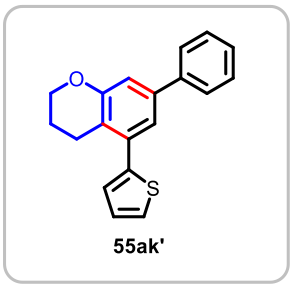
atmosphere (O_2 balloon pressure) at room temperature and reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded **55fj'** (0.147 g, 76%) colorless oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.62 (m, 2H), 7.55-7.49 (m, 2H), 7.46-7.41 (m, 2H), 7.36-7.31 (m, 1H), 7.06 (d, *J* = 1.88Hz, 1H), 6.58 (dd, *J* = 3.38, 0.63 Hz, 1H), 6.53 (dd, *J* = 3.38, 1.88 Hz, 1H), 2.98-2.90 (m, 2H), 1.89-1.85 (m, 2H), 1.41 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 154.7, 153.4,141.8, 140.6, 140.1, 131.2, 129.8, 128.7, 128.6, 127.2, 127.0, 126.9, 120.9, 117.9, 117.3, 115.5, 111.2, 73.7, 32.8, 26.9, 26.8, 21.9.

7-Phenyl-5-(thiophen-2-yl)chromane(55ak'):



55ak'

Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**53a**) (0.1 g, 1.01 mmol) and (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (**54k'**) (0.108 g, 0.505 mmol) in anhydrous PhF (2 mL) was added AgOTf (0.010 g, 0.05 mmol) under oxygen atmosphere (O_2 balloon pressure) at room temperature and reaction mixture was stirred for 2.5 h at rt (both starting materials were completely consumed as per the TLC visualization). Purification of the crude product by column chromatography (SiO_2, 1% EtOAc/hexanes) afforded **55ak'** (0.125 g, 85%) yellow oil.

TLC: R_f = 0.90 (SiO_2, 10% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66-7.57 (m, 2H), 7.48-7.42 (m, 2H), 7.40-7.33 (m, 2H), 7.26 (d, *J* = 1.9 Hz, 1H), 7.16-7.05 (m, 3H), 4.26 (t, *J* = 5.1 Hz, 2H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.06-1.98 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.5, 142.1, 140.4, 140.0, 135.5, 128.7, 127.4, 127.0 (2C), 126.6, 125.3, 121.4, 119.7, 115.1, 66.2, 24.3, 22.4.

3.2.11 Quantum chemical calculations:

The quantum chemical calculations have been performed using density functional theory (DFT), as a tool with the aid of the Turbomole 7.2 suite of programs.[34a] The PBE functional,[34b] and the TZVP[34c] basis set has been employed. The resolution of identity

(RI),[34d] along with the multipole accelerated resolution of identity (marij)[34e] approximations have been used for an accurate and efficient treatment of the electronic Coulomb term in the DFT calculations. Solvent effects were introduced by using the COSMO model[34f] with the dielectric constant ε = 2.38 for toluene.The option "disp" provided in the Turbomole package (DFT-D3) was employed for dispersion-corrected DFT calculations.[34g] The values reported are ΔG values, with zero point energy corrections, internal energy and entropic contributions included through frequency calculations on the optimized minima with the temperature taken to be 298.15 K. Harmonic frequency calculations were performed for all stationary points to confirm them as local minima.

XYZ coordinates for optimized geometries of all the compounds at PBE/TZVP level of theory.

T0

38

O	-0.416898	-2.717829	-1.487655
C	-0.115974	-1.316846	-1.430287
C	-0.141249	-0.689150	-2.794112
C	0.749653	-1.450979	-3.791797
C	0.381110	-2.937227	-3.796693
C	0.444169	-3.498971	-2.389911
C	0.088052	-0.759365	-0.232504
Ag	0.370742	1.248730	0.094947
O	-1.282382	-3.725228	0.626926
S	-1.024130	-5.291000	0.806155
O	-0.888204	-5.974358	-0.502987

O	-1.929896	-5.799091	1.854795
C	0.739013	-5.269378	1.566820
F	1.594616	-4.720754	0.682815
F	1.118032	-6.527529	1.832576
F	0.746990	-4.548067	2.696055
F	-0.786397	6.797410	-0.753288
C	-0.446439	7.899397	-0.017903
C	0.207753	7.713759	1.196023
C	0.551486	8.846495	1.941833
C	0.241778	10.127194	1.469982
C	-0.416737	10.279274	0.244482
C	-0.769251	9.158266	-0.515232
H	-1.182654	-0.699815	-3.163769
H	0.168214	0.361013	-2.706371
H	1.469995	-3.465354	-1.985857
H	0.062087	-4.524573	-2.322854
H	1.068514	-3.516613	-4.432383
H	-0.635409	-3.077864	-4.199715
H	1.806802	-1.333032	-3.499383
H	0.639550	-1.019242	-4.797482
H	0.065567	-1.398926	0.655993
H	-0.882490	-3.338217	-0.294646
H	0.438723	6.705956	1.543371
H	-0.661006	11.275833	-0.127817
H	1.064301	8.722569	2.897336

H	0.512984	11.005819	2.057418
H	-1.283026	9.251287	-1.472889

T0'

38

H	-19.275972	-5.203827	-10.754047
C	-18.602067	-5.821057	-10.132325
H	-17.969005	-6.408271	-10.811584
C	-17.721670	-4.909782	-9.325908
O	-18.507593	-4.168831	-8.360057
C	-19.290049	-5.005425	-7.434785
H	-18.578479	-5.592851	-6.830320
H	-19.820343	-4.294844	-6.789090
C	-20.232352	-5.902041	-8.214977
H	-20.770821	-6.543726	-7.500067
H	-20.983838	-5.278768	-8.726632
C	-19.454778	-6.738640	-9.235661
H	-18.793782	-7.446357	-8.707186
H	-20.143588	-7.333343	-9.853682
C	-16.407854	-4.679350	-9.415634
H	-15.991755	-3.962816	-8.696794
H	-17.918033	-3.076843	-7.831422
F	-16.138166	-9.131578	-13.680262
C	-15.355238	-8.074149	-13.342115
C	-14.476176	-8.210486	-12.276647

H -14.416463 -9.150644 -11.728324

C -15.473211 -6.896478 -14.085663

C -14.666029 -5.812657 -13.748718

H -14.732380 -4.887881 -14.323008

C -13.744113 -5.909530 -12.680814

H -12.893899 -7.233584 -11.172398

C -13.657253 -7.114347 -11.943264

H -13.026322 -5.105279 -12.506050

Ag -15.143501 -5.494034 -10.826869

O -17.393353 -2.160685 -7.478954

F -15.774350 -2.210386 -4.895013

C -17.091875 -2.445426 -4.806497

F -17.315534 -3.768401 -4.940410

O -19.460705 -1.874759 -6.024237

F -17.539309 -2.039440 -3.608476

S -18.032927 -1.499742 -6.186486

O -17.596906 -0.090812 -6.092659

H -16.185729 -6.843234 -14.909339

T2

17

C 0.096050 1.173950 -4.879263

C 0.020407 1.084053 -3.377988

C 0.189619 -0.068478 -2.698969

O 0.527179 -1.265594 -3.300902

C	0.978100	-1.150847	-4.673018
C	0.080557	-0.232662	-5.490588
C	0.033040	-0.240774	-1.221065
H	-0.221228	1.980917	-2.804533
H	2.014173	-0.766325	-4.663856
H	0.987206	-2.178482	-5.059003
H	0.424689	-0.221931	-6.535703
H	-0.943630	-0.639276	-5.483971
H	1.005787	1.717099	-5.194682
H	-0.752325	1.764334	-5.263692
H	-0.725692	-1.008877	-1.002028
H	0.977121	-0.575960	-0.763191
H	-0.275626	0.700696	-0.749985

T'

21

F	-13.945875	-5.547477	-9.139749
C	-14.800869	-4.545765	-8.821436
C	-15.318347	-3.761682	-9.843057
H	-15.045766	-3.954384	-10.880746
C	-15.123732	-4.351391	-7.473771
C	-16.007459	-3.331694	-7.135736
H	-16.280128	-3.172824	-6.091978
C	-16.578700	-2.513958	-8.141877
H	-16.749652	-2.199543	-10.299262
C	-16.225152	-2.733436	-9.503978

H -17.387253 -1.824249 -7.889778

Ag -14.900018 -1.018523 -8.631149

O -13.405966 0.504582 -8.362987

F -14.254106 0.322043 -5.497586

C -13.022253 0.838605 -5.716883

F -13.123121 2.176565 -5.800209

O -11.033358 0.844520 -7.578197

F -12.230430 0.520713 -4.677658

S -12.303747 0.111904 -7.340424

O -12.257098 -1.364216 -7.098107

H -14.678864 -4.994268 -6.713867

4

21

C -16.746530 -17.710864 4.079011

C -15.725709 -16.992157 4.739729

C -14.969026 -17.659221 5.727228

C -15.217828 -18.995315 6.043235

C -16.231707 -19.692577 5.378324

C -16.994079 -19.044074 4.395919

C -15.415286 -15.595731 4.449527

C -16.008417 -14.796885 3.529473

C -15.646273 -13.392188 3.284615

C -14.548490 -12.741620 4.102987

O -16.247387 -12.750905 2.411313

H -14.620176 -19.493743 6.808645

H -16.429630 -20.737962 5.622906

H -17.786402 -19.585442 3.875437

H -17.350822 -17.222257 3.312743

H -14.176629 -17.115120 6.247124

H -14.607009 -15.175789 5.057984

H -16.817629 -15.163553 2.891306

H -13.603008 -13.297164 4.012128

H -14.400666 -11.714055 3.752450

H -14.816919 -12.724708 5.170445

4'

42

C -16.722440 -17.716602 4.053633

C -15.699825 -17.002181 4.722203

C -14.937603 -17.654644 5.731823

C -15.199879 -19.003208 6.057306

C -16.213053 -19.656271 5.374919

C -16.979089 -19.045122 4.374360

Ag -16.566465 -16.308055 6.800808

O -17.242763 -18.686954 8.866115

S -16.091822 -17.968647 9.507038

O -14.780549 -18.685475 9.530810

F -16.476228 -20.953225 5.678483

O -18.221917 -14.790619 6.953063

C -19.162096 -14.751040 7.789906

C -19.420825 -15.904194 8.716021

C	-19.954609	-13.533615	7.843096
C	-20.957733	-13.309432	8.732948
C	-21.753215	-12.099276	8.870975
C	-22.722030	-12.047035	9.898403
C	-23.509204	-10.911336	10.083440
C	-23.346301	-9.805219	9.241933
C	-22.391567	-9.842360	8.215732
C	-21.601906	-10.973294	8.030425
C	-16.581530	-17.814054	11.353440
F	-16.719269	-19.039869	11.898194
O	-16.004074	-16.499761	9.086629
F	-17.755467	-17.155205	11.482408
F	-15.634792	-17.140983	12.036936
H	-14.634903	-19.515416	6.834908
H	-14.057747	-17.167809	6.157517
H	-15.398348	-16.017903	4.358418
H	-17.297849	-17.225618	3.268029
H	-17.759165	-19.613802	3.867847
H	-24.250897	-10.887552	10.883681
H	-23.962001	-8.914990	9.383439
H	-22.265183	-8.979966	7.558108
H	-20.863688	-10.983710	7.227084
H	-22.847830	-12.911069	10.554715
H	-21.208487	-14.101746	9.445490
H	-19.657398	-12.772060	7.117819

H -20.489007 -16.054224 8.916623

H -18.989855 -16.827818 8.309363

H -18.921234 -15.709012 9.678416

T2a

59

C -11.904320 -4.072698 -3.808188

C -10.803185 -4.485261 -4.562759

C -10.822692 -5.607951 -5.379350

C -12.001848 -6.376282 -5.431301

C -13.137328 -5.993437 -4.669491

C -13.072602 -4.829377 -3.865698

F -9.664383 -3.742863 -4.501823

Ag -13.645570 -5.161493 -6.741383

O -15.776116 -6.839881 -6.691579

S -15.406287 -8.254273 -7.098420

C -15.718390 -8.230617 -8.990626

F -15.565493 -9.459121 -9.523151

O -14.160971 -4.276064 -8.570985

C -14.742462 -3.100549 -8.746716

C -15.775421 -2.952962 -9.635802

C -16.263534 -4.132587 -10.442730

C -15.790094 -4.019222 -11.887581

C -14.848929 -4.928219 -12.392184

C -14.378090 -4.819508 -13.705264

C -14.848317 -3.799825 -14.537696

C	-15.789120	-2.886726	-14.045150
C	-16.251390	-2.994533	-12.731490
C	-14.227172	-1.936027	-7.934930
C	-17.794762	-4.377387	-10.390276
C	-18.259114	-5.499417	-11.380703
C	-19.666744	-6.022444	-11.059467
C	-20.416675	-5.032389	-10.189658
O	-19.645225	-4.850163	-8.939801
C	-18.373063	-4.615227	-9.041155
C	-17.636650	-4.561023	-7.793758
O	-13.939791	-8.555272	-6.988951
O	-16.342946	-9.307818	-6.596728
F	-16.986649	-7.809444	-9.257136
F	-14.864649	-7.386356	-9.610153
H	-21.391424	-5.387992	-9.843633
H	-20.524346	-4.042300	-10.657119
H	-19.615660	-6.979119	-10.518560
H	-20.250682	-6.196166	-11.973959
H	-18.211553	-5.074899	-12.390002
H	-17.524624	-6.314235	-11.335168
H	-18.320677	-3.450004	-10.711155
H	-17.005288	-3.647217	-7.825802
H	-18.288283	-4.622985	-6.916945
H	-16.185565	-1.961349	-9.841689
H	-16.975493	-2.264760	-12.357590

H	-16.159751	-2.084563	-14.687318
H	-14.483904	-3.714425	-15.563370
H	-13.642950	-5.536369	-14.077753
H	-14.478780	-5.726476	-11.743994
H	-16.887526	-5.382194	-7.760058
H	-15.775131	-5.022804	-10.015688
H	-9.938603	-5.888885	-5.952523
H	-12.022252	-7.314510	-5.989226
H	-13.992322	-6.667590	-4.590861
H	-13.937721	-4.538079	-3.269174
H	-11.832899	-3.176915	-3.190855
H	-14.743903	-0.996431	-8.174881
H	-14.357836	-2.144870	-6.85840
H	-13.147147	-1.804476	-8.106730

T2b

59

C	-3.972005	-1.818608	1.445549
C	-4.279875	-0.412341	0.978700
C	-5.265738	-0.509410	-0.216448
C	-6.288310	-1.645046	0.003679
C	-6.361708	-2.018605	1.476494
O	-5.071840	-2.505825	1.932446
C	-3.034559	0.444368	0.653740
C	-3.400019	1.717451	-0.090433

C	-2.981075	1.902207	-1.416008
C	-3.309814	3.067252	-2.117227
C	-4.071869	4.064298	-1.502688
C	-4.501787	3.888304	-0.181656
C	-4.165518	2.726928	0.517042
C	-2.786633	-2.450488	1.423958
C	-2.240883	0.752757	1.970082
C	-0.781927	0.961131	1.666799
C	-0.334099	2.282848	1.132383
O	0.001042	0.008500	1.833527
Ag	1.995802	-0.343482	0.827639
O	1.490837	0.605164	-1.235259
S	0.440488	-0.097073	-2.099873
O	-0.110103	0.771799	-3.180990
C	4.978344	-0.059296	0.204323
C	5.388536	0.808931	1.202828
C	5.047706	0.638876	2.550631
C	4.253673	-0.444838	2.908423
C	3.804750	-1.360907	1.927282
C	4.172462	-1.162730	0.566288
F	6.163342	1.873155	0.866863
C	1.492367	-1.412290	-3.015656
F	0.726593	-2.126434	-3.862115
F	2.048372	-2.265367	-2.118755
F	2.485089	-0.826188	-3.714480

O	-0.536172	-0.910570	-1.305606
H	-7.057899	-2.846882	1.661376
H	-6.678256	-1.160618	2.096600
H	-5.990593	-2.543814	-0.558736
H	-7.287533	-1.356268	-0.353985
H	-5.772323	0.458795	-0.333327
H	-4.691946	-0.685858	-1.138937
H	-4.816441	0.084789	1.809035
H	-2.715377	-3.489832	1.746102
H	-2.665355	1.645339	2.450532
H	-4.509577	2.606182	1.548057
H	-5.099954	4.661101	0.306151
H	-4.328685	4.975386	-2.047022
H	-2.963213	3.193733	-3.145057
H	-2.380920	1.131214	-1.903990
H	-1.877757	-1.948335	1.100545
H	-2.390466	-0.149965	-0.013208
H	5.278949	0.104959	-0.830406
H	3.962015	-1.934349	-0.177337
H	3.315555	-2.288188	2.232675
H	3.989449	-0.602865	3.954716
H	5.407556	1.352682	3.292218
H	-2.324233	-0.101390	2.653540
H	-0.647086	3.085893	1.816908
H	0.750592	2.311722	0.975122

H -0.847153 2.480172 0.175961

T2C

59

C -16.492364 -4.223584 -8.427505

C -15.268176 -3.375653 -8.786891

C -15.361894 -2.961771 -10.257381

C -15.440449 -4.158709 -11.230455

C -16.259626 -5.314443 -10.690800

C -16.749463 -5.305539 -9.433237

O -17.510547 -6.313609 -8.881676

C -18.010012 -7.283145 -9.833390

C -16.920443 -7.729232 -10.794948

C -16.406843 -6.521858 -11.582918

O -14.039679 -4.158965 -8.579765

Ag -13.775263 -5.236954 -6.601630

C -15.486679 -6.885121 -4.951125

C -16.758253 -6.328299 -5.052307

C -16.921865 -4.970736 -4.760025

C -15.868257 -4.144401 -4.396177

C -14.579692 -4.703739 -4.309085

C -14.377694 -6.086088 -4.571978

F -18.166932 -4.436544 -4.854677

C -15.133962 -2.169395 -7.868404

C -15.953592 -3.676093 -12.583126

C	-15.080189	-3.494202	-13.663444
C	-15.550794	-3.018938	-14.893581
C	-16.906741	-2.721172	-15.058269
C	-17.788837	-2.902549	-13.985293
C	-17.313792	-3.375507	-12.760290
O	-13.334065	-6.498579	-9.847855
S	-12.474706	-7.349297	-8.945304
O	-12.201977	-6.706870	-7.589671
C	-13.627825	-8.806526	-8.477101
F	-13.022180	-9.621789	-7.590485
F	-13.952912	-9.522619	-9.571105
F	-14.766913	-8.336217	-7.915931
O	-11.287494	-7.991210	-9.574116
H	-18.395526	-8.110504	-9.223662
H	-18.850819	-6.824560	-10.385590
H	-16.100222	-8.177106	-10.216630
H	-17.316967	-8.506427	-11.465404
H	-17.077305	-6.293614	-12.429941
H	-15.422489	-6.750358	-12.027342
H	-13.987351	-4.922724	-9.215994
H	-17.376590	-3.573049	-8.316045
H	-14.505746	-2.323219	-10.522421
H	-18.005554	-3.529982	-11.927341
H	-18.851002	-2.677742	-14.106595
H	-17.277058	-2.354316	-16.017758

H -14.856094 -2.885536 -15.725726

H -14.019984 -3.731573 -13.540188

H -16.334879 -4.693684 -7.439603

H -14.414198 -4.537101 -11.402765

H -16.043873 -3.090685 -4.178832

H -13.755429 -4.093927 -3.934769

H -13.424340 -6.559790 -4.324587

H -15.341937 -7.947085 -5.151811

H -17.619450 -6.924892 -5.353093

H -14.228435 -1.598656 -8.115726

H -16.007281 -1.512027 -7.972131

H -15.070574 -2.490602 -6.816832

H -16.269627 -2.347736 -10.363346

T3

35

C -15.900242 -4.278734 -8.426346

C -15.463608 -4.424599 -9.859640

C -16.322108 -4.817730 -10.813223

C -17.778008 -5.131774 -10.581934

C -18.168051 -5.142627 -9.119925

C -17.310588 -4.713731 -8.172888

O -17.614422 -4.632475 -6.826818

C -19.025715 -4.725253 -6.518710

C -19.685616 -5.874169 -7.264905

C -19.547103 -5.645781 -8.773478

C	-14.027474	-4.087760	-10.147160
C	-18.659700	-4.158841	-11.374109
C	-19.497289	-4.604959	-12.403807
C	-20.304233	-3.704561	-13.111398
C	-20.280262	-2.343568	-12.794227
C	-19.443942	-1.888048	-11.766268
C	-18.642015	-2.789662	-11.064799
H	-19.074608	-4.850511	-5.429214
H	-19.502649	-3.765647	-6.789598
H	-19.193642	-6.816080	-6.972989
H	-20.742332	-5.947744	-6.966322
H	-20.311937	-4.931801	-9.128607
H	-19.738991	-6.585267	-9.321262
H	-15.775941	-3.226413	-8.103893
H	-15.976113	-4.896502	-11.849298
H	-17.993084	-2.436240	-10.259413
H	-19.418190	-0.825885	-11.512422
H	-20.910104	-1.639689	-13.342393
H	-20.953986	-4.069245	-13.910279
H	-19.520440	-5.669734	-12.652728
H	-15.224631	-4.853631	-7.764166
H	-17.983322	-6.138367	-10.998223
H	-13.345522	-4.722405	-9.556484
H	-13.786497	-4.216133	-11.211329
H	-13.805029	-3.044360	-9.865533

5

33

C	-16.553635	-4.642184	-8.223386
C	-15.731527	-4.413359	-9.338638
C	-16.240577	-4.687202	-10.619626
C	-17.537502	-5.183169	-10.780916
C	-18.345527	-5.415335	-9.662266
C	-17.850658	-5.140875	-8.383225
C	-14.348640	-3.878113	-9.160500
C	-14.181472	-2.518598	-8.865096
C	-12.904010	-1.961895	-8.692410
C	-11.795997	-2.805598	-8.796360
C	-11.955929	-4.171228	-9.071345
C	-13.231758	-4.734905	-9.276112
O	-10.790189	-4.901366	-9.139187
C	-10.933920	-6.341414	-9.116366
C	-12.040136	-6.805651	-10.047085
C	-13.373243	-6.209875	-9.588684
C	-12.731208	-0.487686	-8.425154
H	-9.949424	-6.727465	-9.409851
H	-11.142531	-6.657532	-8.078002
H	-11.805902	-6.480468	-11.073591
H	-12.080988	-7.905017	-10.049606
H	-13.730195	-6.743723	-8.690131

H -14.147130 -6.361497 -10.354534

H -10.783439 -2.421149 -8.652467

H -15.066530 -1.883354 -8.778612

H -16.167571 -4.430772 -7.223605

H -18.475803 -5.315404 -7.504857

H -19.357544 -5.805927 -9.787320

H -17.919383 -5.386280 -11.783781

H -15.613674 -4.501430 -11.495085

H -11.806147 -0.285928 -7.866781

H -12.675813 0.077819 -9.369676

H -13.577494 -0.083441 -7.851688

H_2

2

H 0.000000 0.000000 -0.001151

H 0.000000 0.000000 0.751151

H_2O

3

O -0.027895 0.000000 -0.019709

H 0.019953 0.000000 0.951352

H 0.903612 0.000000 -0.298306

3.2.12 References

1. Singh, P. K.; Silakari, O. *Chem. Med. Chem,* **2018**, *13*, 1071–1087.
2. a) Ellis G. P.; Lockhart, I. M. *New York, Wiley–VCH* **2007**. 1-119; b) Horton D. A., Boume G. T., Smythe M. L. *Chem. Rev.* **2003,** *103*, 893—930.
3. Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.,* **2000**, *122*, 9939-9953.
4. (a) Tanaka, N.; Takaish, Y.; Shikishima Y.; Nakanishi Y.; Bastow K.; Lee K. H.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.,* **2004**, *67,* 1870-1875; (b) Zou, Y. S.; Hou, A.J.; Zhu, G. F. *Chem. Biodivers.* **2005**, *2*, 131-138.
5. Celebioglu, A.; Uyar, T. J. Agric. Food Chem. 2017, 65, 5404−5412.
6. (a) *Dianin, A. P. J. Russ. Phys. Chem. Soc.**1914**, 36, 1310–1319; (b) Lloyd, G. O.; Bredenkamp, M W.; Barbour, Leonard J. Chemical Communications. **2005,** 32, 4053–4055.*
7. Gara, R. K.; Sundram, V.; Chauhan, S. C.; Jaggi, M. *Curr Med Chem.* **2013**, *20* (33), 4177–4184.
8. Allen, K. M.; Coughlan, K. A.; Mahmood, N. M.; Valentine, R. J.; Ruderman, N. B.; Asish K. Saha, A. K.; *Archives of Bio.and Biophysics*, **2017**, *623-624*, 49-57.
9. Coats, A S.; Jain, S. *Journal of Human Hypertension,* **2017,** *31*, 376–381.
10. Bernatoniene, J.; Kopustinskiene, D. M. *Molecules,* **2018** *23* (4) 965.
11. Hume, P. A.; Furkert, D. P.; Margaret A. Brimble, M. A.; *Org. Lett.*, **2013**, 15 (17), 4588-4591.
12. Toh, Z. S.; Wang, H.; Yib, Y. M.; Lu, Y.; Lim, B. J. A.; Z.; D.; Huang, D. *Bio., ang Med. Chem*., **2015**, *23*(24), 7641-7649.
13. (a) Zhang, L.-J.; Bi, D.-W.; Hu, J.; Mu, W.-H.; Li, Y.-P.; Xia, G.-H.; Yang, L.; Liang, X.-S.; Wang, L.-Q. *Org. Lett.* **2017**, *19*, 4315−4318. (b) Timmerman, J. C.; Sims, N. J.; Wood, J. L. *J. Am. Chem. Soc.* **2019**, *141,* 10082−10090.
14. Ishikawa, N. K.; Yamaji, K.; Tahara, S.; Fukushi, Y.; Takahashi, K.; *Phytochemistry,* **2000**, *54*, 777–782.

15. (a) Dalpozzo, R.; Mancuso, R. Nuclei, *Symmetry,* **2019**, *11*, 1510-1540; (b) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev*. **2018**, *118*, 2080–2248; (c) Vetica, F.; Chauhan, P.; Dochain, S.; Enders, D. *Chem. Soc. Rev*. **2017**, *46*, 1661–1674; (d) Li, P.; Zhao, G.; Zhu, S. *Chin. J. Chem.,* **2011**, *29*, 2749-2758.
16. Weyershausen, B.; Dötz, K. H. *Synlett,* **1999**, 231–233.
17. Hallett, M. R.; Painter, J. E.; Quayle, P.; Ricketts, D.; Patel, P. *Tetrahedron Lett.* **1998**, *39*, 2851–2852.
18. Geist, E.; Berneaud-Kötz, H.; Baikstis, T.; Dräger, G.; Kirschning, A. *Org. Lett*. **2019**, *21*, 8930–8933.
19. Maikhuri, V. K.; Khatri, V.; Kumar, A.; Singh, B.; Prasad, A. K. *J. Org. Chem.* **2020**, *85*, 7068–7076.
20. Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature,* **2012**, *490*, 208–212.
21. Majumdar, N.; Korthals, K. A.; Wulff, W. D. *J. Am. Chem. Soc*. **2012**, *134*, 1357–1362.
22. Korthals, K. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 2898–2899.
23. Barluenga, J.; Mendoza, V.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7044–7047.
24. Barluenga, J.; Fernández, A.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Chem. Eur. J*. **2009**, *15*, 11660–11667.
25. (a) Thorat, S. S.; Kontham, R. *Org. Biomol. Chem*. **2019**, *17*, 7270–7292; (b) Xiang, K.; Tong, P.; Yan, B.; Long, L.; Zhao, C.; Zhang, Y.; Li, Y. *Org. Lett*. **2019**, *21*, 412–416; (c) Lenci, E.; Menchi, G.; Saldívar-Gonzalez, F. I.; Medina-Franco, J. L.; Trabocchi, A. *Org. Biomol. Chem*. **2019**, *17*, 1037–1052; (d) Zhang, F. M.; Zhang, S. Y.; Tu, Y. Q. *Nat. Prod. Rep*. **2018**, *35*, 75–104; (e) Paioti, P. H. S.; Ketcham, J. M.; Aponick, A. *Org. Lett*. **2014**, *16*, 5320–5323; (f) Zeng, X. *Chem. Rev*. **2013**, *113*, 6864–6900; (g) Wu, H.; He, Y.- P.; Gong, L. Z. *Org. Lett*. **2013**, *15*, 460–463; (h) Cala, L.; Mendoza, A.; Fañanás, F. J.; Rodríguez, F. *Chem. Commun*. **2013**, *49*, 2715–2717; (i) Ravindar, K.; Sridhar Reddy, M.; Deslongchamps, P. *Org. Lett*. **2011**, *13*, 3178–3181; (j) Hashmi, A. S. K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem.*

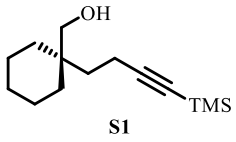
Eur. J. **2010**, *16*, 9846–9854; (k) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 1644–1647; (l) Aponick, A.; Li, C. Y.; Palmes, J. A. *Org. Lett*. **2009**, *11*, 121–124; (m) Aho, J. E.; Pihko, P. M.; Rissa, T. K.; *Chem. Rev*, **2005**, *105*, 4406–4440; (n) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4949–4953; (o) Jacobs, M. F.; Kitching, W. B. *Curr. Org. Chem*, **1998**, *2*, 395–436; (p) Perron, F.; Albizati, K. F. *Chem. Rev*, **1989**, *89*, 1617–1661.

26. (a) Liang, M.; Zhang, S.; Jia, J.; Tung, C. H.; Wang, J.; Xu, Z. *Org. Lett.* **2017**, *19*, 2526–2529; (b) Li, X.; Xue, J.; Huang, C.; Li, Y. *Chem. - An Asian J.* **2012**, *7*, 903–906; (c) Fañanás, F. J.; Mendoza, A.; Arto, T.; Temelli, B.; Rodríguez, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4930–4933; (d) Barluenga, J.; Calleja, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Chem. - A Eur. J.* **2010**, *16*, 7110–7112.
27. (a) Li, J.; Lin, L.; Hu, B.; Lian, X.; Wang, G.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.,* **2016**, *55*, 6075–6078; (b) Wang, X.; Dong, S.; Yao, Z.; Feng, L.; Daka, P.; Wang, H.; Xu, Z. *Org. Lett*. **2014**, *16*, 22–25; (c) Wang, X.; Yao, Z.; Dong, S.; Wei, F.; H. Wang, H.; Xu, Z. *Org. Lett*. **2013**, *15*, 2234–2237; (d) Hu, B.; Li, J.; Cao, W.; Lin, Q.; Yang, J.; Lin, L.; Liu, X.; Feng, X. *Adv. Synth. Catal*. **2018**, *360*, 2831–2835.
28. Kambale, D. A.; Thorat, S. S.; Pratapure, M. S.; Gonnade, R. G.; Kontham, R. *Chem. Commun*. **2017**, *53*, 6641–6644.
29. Thorat, S. S.; Kataria, P. Kontham, R. *Org. Lett*. **2018**, *20*, 872–875.
30. Yamamoto, Y. *J. Org. Chem*. **2007**, ***72***, 7817–7831.
31. (a) Borade, B. R.; Nomula, R.; Gonnade, R. G.; Kontham, R. *Org. Lett*. **2019**, *21*, 2629–2633; (b) Nakate, A. K.; Pratapure, M. S.; Kontham, R. *Org. Biomol. Chem.* **2018**, *16*, 3229–3240.
32. (a) Amit, B.; Subhash, C. G.; Amit, K. D.; Valerio, B. *Org. Biomol. Chem.,* **2005**, *3*, 4050-4052; (b) Ajay, H. B.; Gurunath, S. *ACS Omega,* **2019**, *4*, 9636-9644; (c)Titu, D.; Chadha, A. *Tetrahedron,* **2008**, *19*, 1698-1701; (d)Wang, Y.; Franzen, R. *Synlett,* **2012**,*6*, 925-929; (e)Gopinath, V. K.; Swarup, H. A.; Mantelingu, K.; Rangappa, K. S. *Synlett,* **2019**, *30*, 12-20; (f)Robinson, T. P.; Hubbard, R. B.; IV, Ehlers, T. J.; Arbiser, J. L.; Goldsmith, D. J.; Bowen, J. P.

Bioorg. Med. Chem., **2005**, *13*, 4007-4013; (g)Hassan, S. Y. *J. Braz. Chem. Soc.,* **2011**, *22*, 1286-1298; (h) D'Aleo, A.; Karapetyan, A.; Heresanu, V.; Giorgi, M.; Fages, F. *Tetrahedron*, **2015**, *71*, 2255-2259. (i)Singh, G.; Arora, A.; Kalra, P.; Maurya, I. K.; Ruizc, C. E.; Estebanc, A. M.; Sinha, S.; Goyal, K. Sehgal, R. *Bioorg. Med. Chem*., **2019**, *27*, 188-195. (j) Astekar, K. D.; Staples, R. J.; Borhan, B. *Org. Lett*., **2011**, *13*, 5732-5735; (k) Rajasekar, S.; Anbarasan, P. *Org. Lett*., **2019**, *21*, 3067-3071; (l) Liu, S.; Cui, P.; Wang, J.; Zhou, H.; Liu, Q.; Ly. J. *Org. Biomol. Chem.,* **2019,** *17*, 264-267; (m) Basnet, A.; Thapa, P. Karki, R.; Na, Y.; Jahng, Y.; Jeong, B. S.; Jeong, T. C. Lee, C. S.; Lee, E. S. *Bioorg. Med. Chem.,* **2007**, *15*, 4351-4359; (n) Cheng, S.; Yu, S. *Org. Biomol. Chem*., **2014**, *12*, 8607-8610; (o) Thomson, C. J.; Barber, D. M.; Dixon, D. J. *Angew. Chem. Int. Edi.,* **2019**, *58*, 8, 2469-2473; (q) Salfeena, C. T.; Basavaraja, Ashitha, K. T.; Kumar, V. P.; Varughese, S.; Cherumuttathu, H. S.; Sasidhar, B. S. *Chem. Commun*., **2018**, *54*, 12463-12466; (r) Wang, D.; Li, L.; Feng, H.; Sun, H.; Almedida-Velodo, F.; Charavin, M.; Yu, P.; Désaubry, L. *Green Chemistry*, **2018**, 20, 2775-2780.

33. Grob, C. A.; Baumann, W. *Helv. Chim. Acta*, **1955**, ***38***, 594-610.
34. (a) TURBOMOLE V **7.0** 2015, a development of University of Karlsruhe and for schungszentrum Karlsruhe GmbH, 1989-2007, TURBOMOLE GmbH, since 2007; available from http://www.turbomole.com.; (b) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett*. **1996**, *77*, 3865. (c) Ansgar, S.; Christian, H.; Reinhart, A. *J. Chem. Phys*. **1994**, *100*, 5829. (d) Eichkorn, K.; Treutler, O.; hm, H. Ö.; Haser, M.; Ahlrichs, R. *Chem. Phys. Lett*. **1995**, *240*, 283. (e) Sierka, M.; Hogekamp, A.; Ahlrichs, R. *J. Chem. Phys*. **2003**, *118*, 9136. (f) Klamt, A.; Schuurmann, G. *J. Chem. Soc. Perkin Trans.,* **1993**, *2,* 799-805. (g) Grimme, S. *J. Comput. Chem*. **2004**, *25*, 1463.

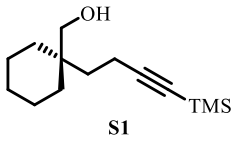
^{1}H NMR spectrum of compound S1



S1

^{1}H NMR -400 MHz
$CDCl_3$

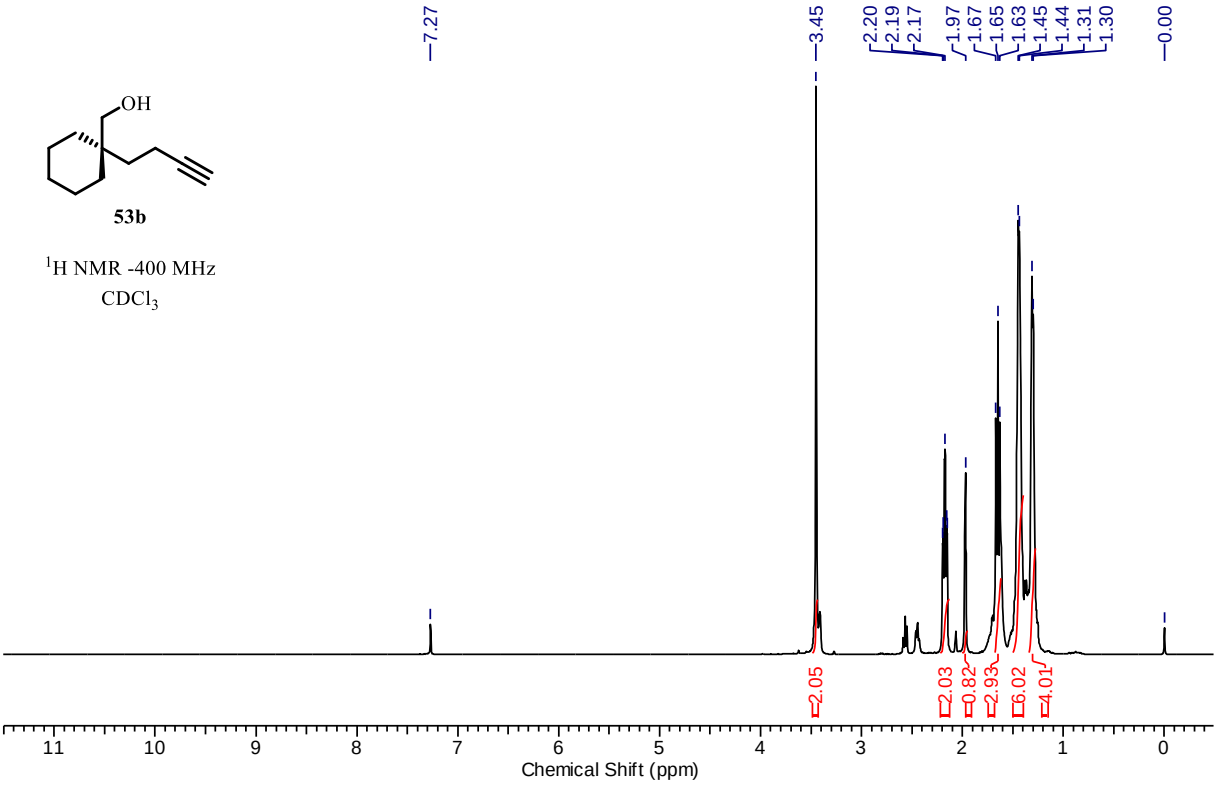
^{13}C NMR spectrum of compound S1



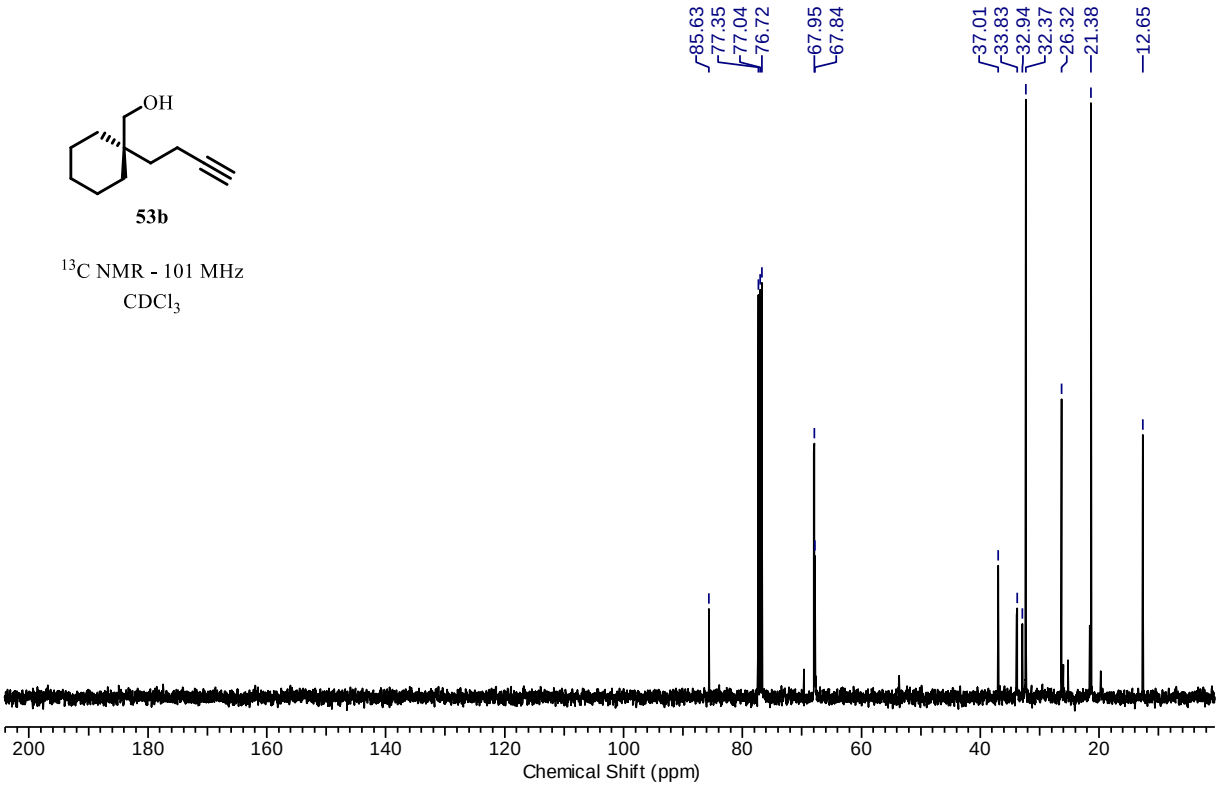
S1

^{13}C NMR - 101 MHz
$CDCl_3$

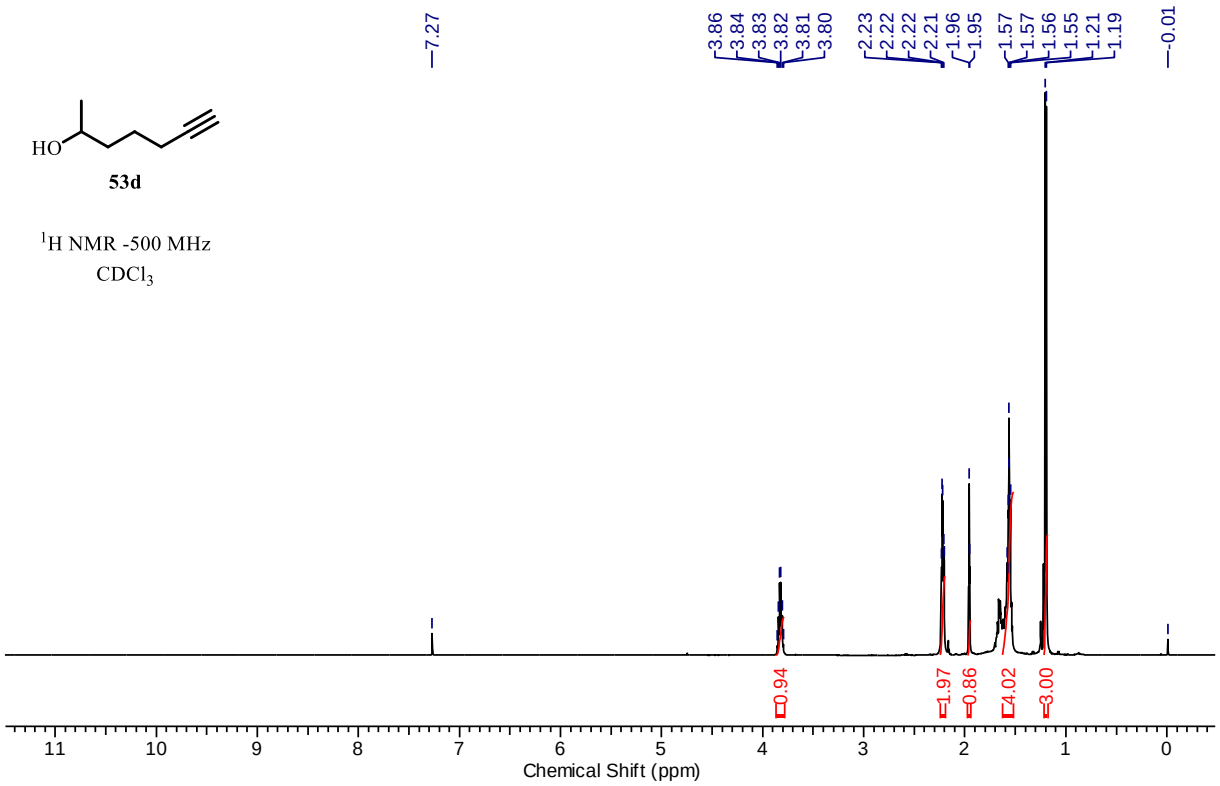
^{1}H NMR spectrum of compound 53b



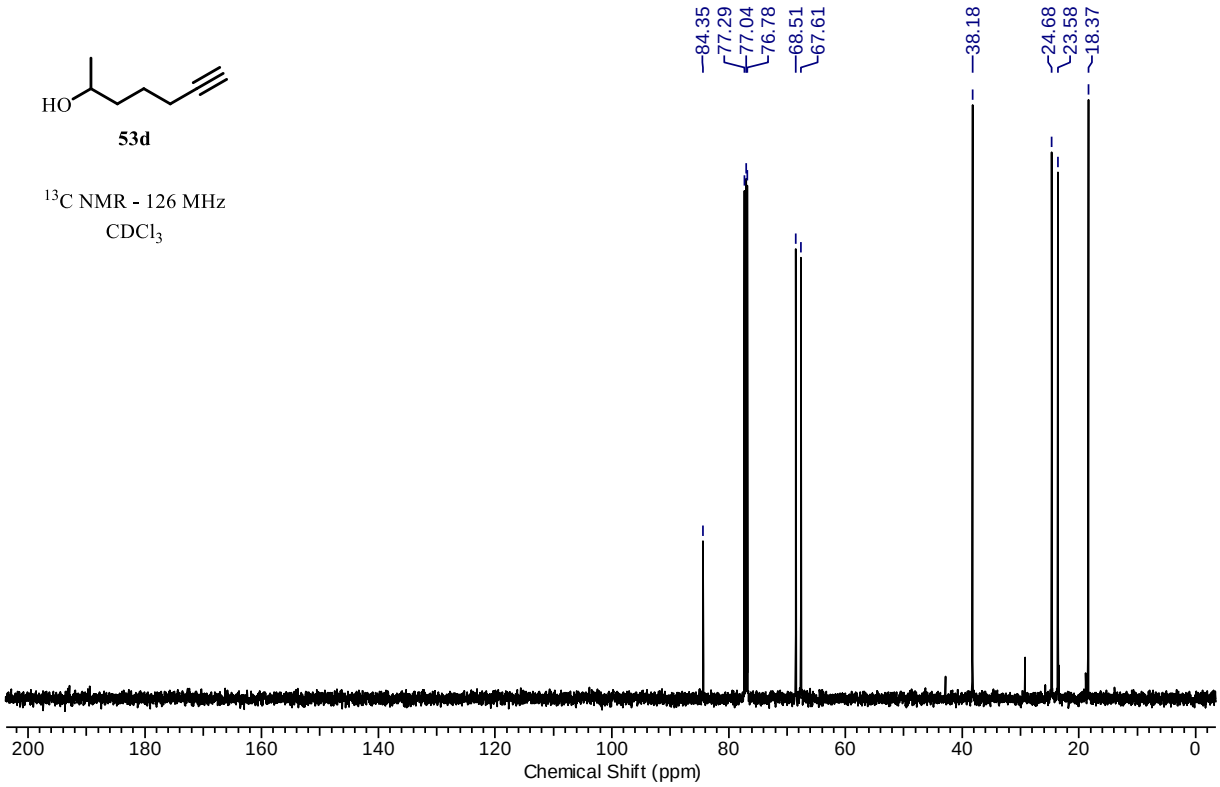
^{13}C NMR spectrum of compound 53b



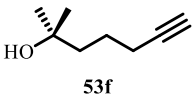
^{1}H NMR spectrum of compound 53d



^{13}C NMR spectrum of compound 53d



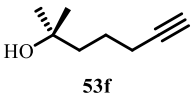
^{1}H NMR spectrum of compound 53f



53f

^{1}H NMR -500 MHz
$CDCl_3$

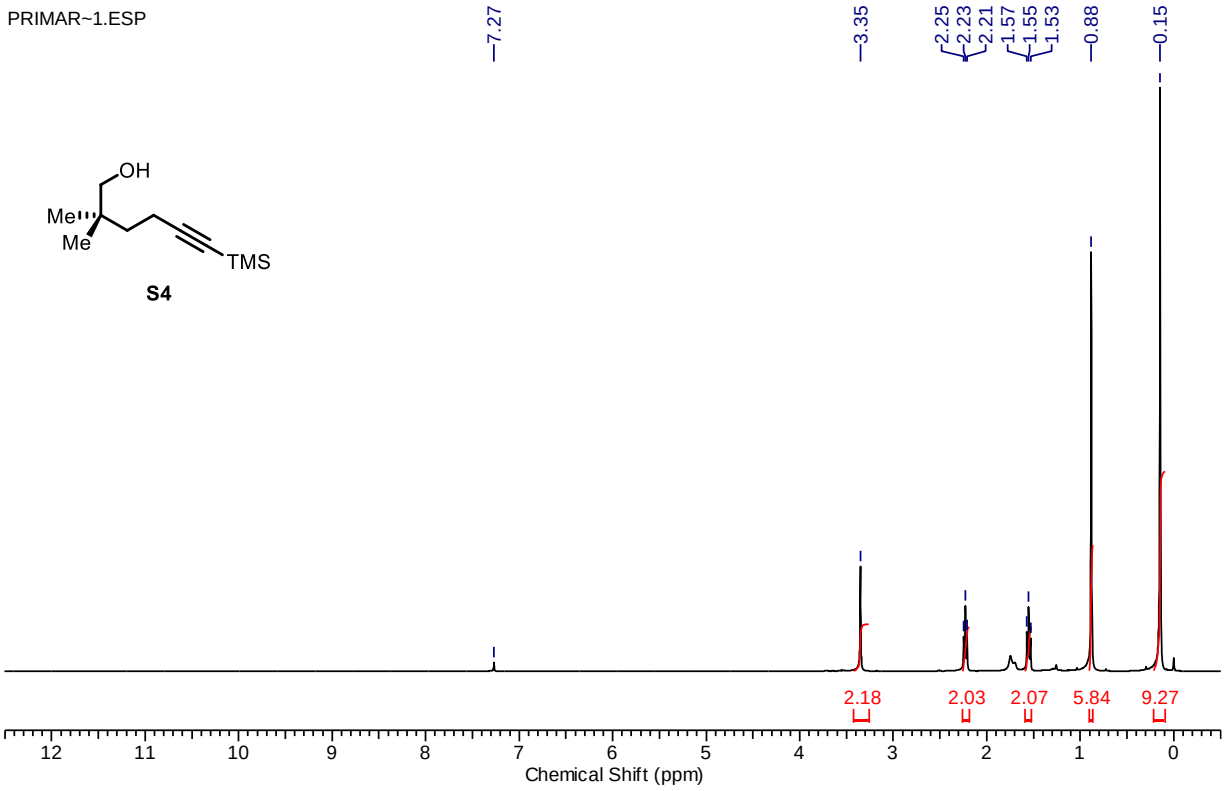
^{13}C NMR spectrum of compound 53f



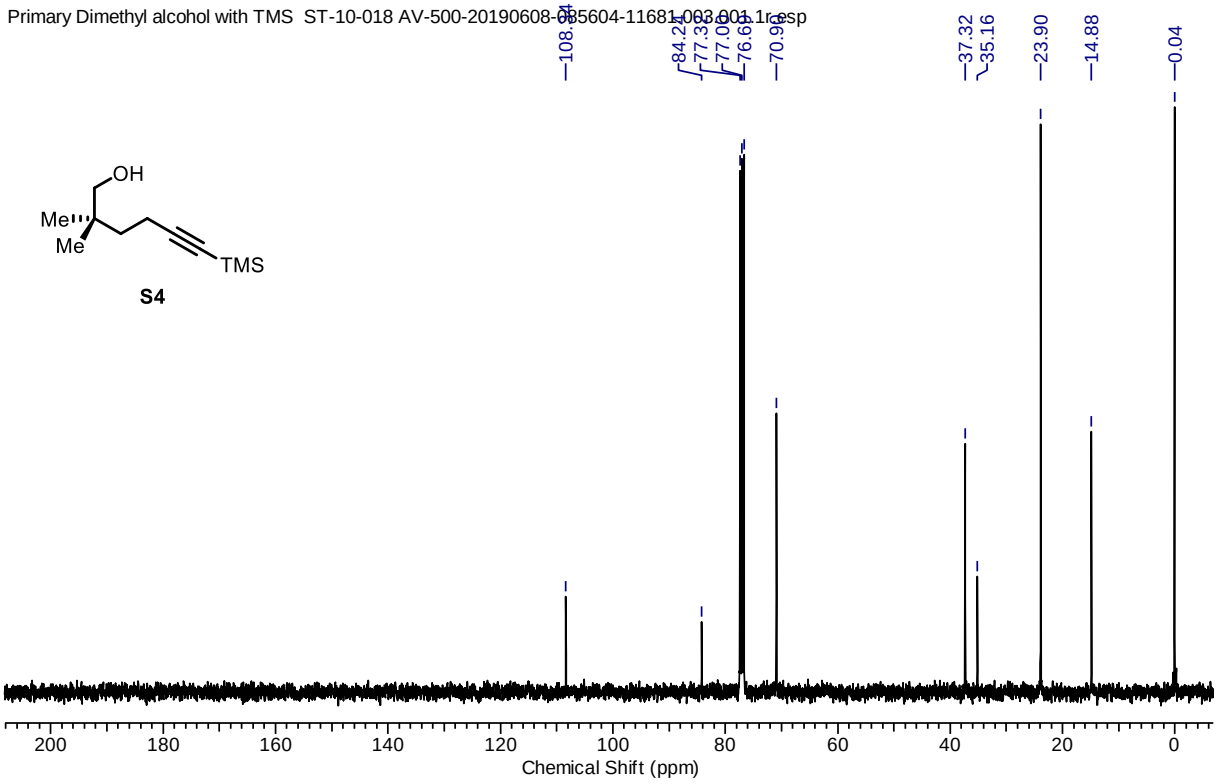
53f

^{13}C NMR - 126 MHz
$CDCl_3$

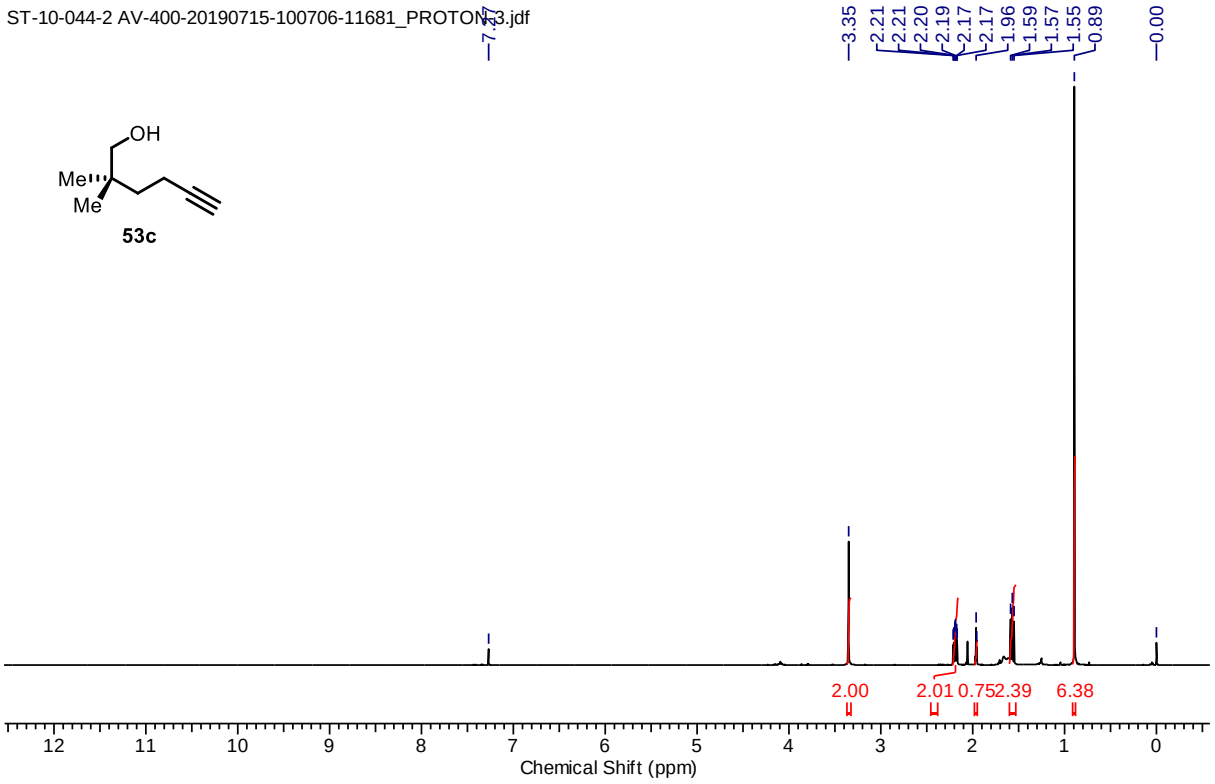
^{1}H NMR spectrum of compound S4



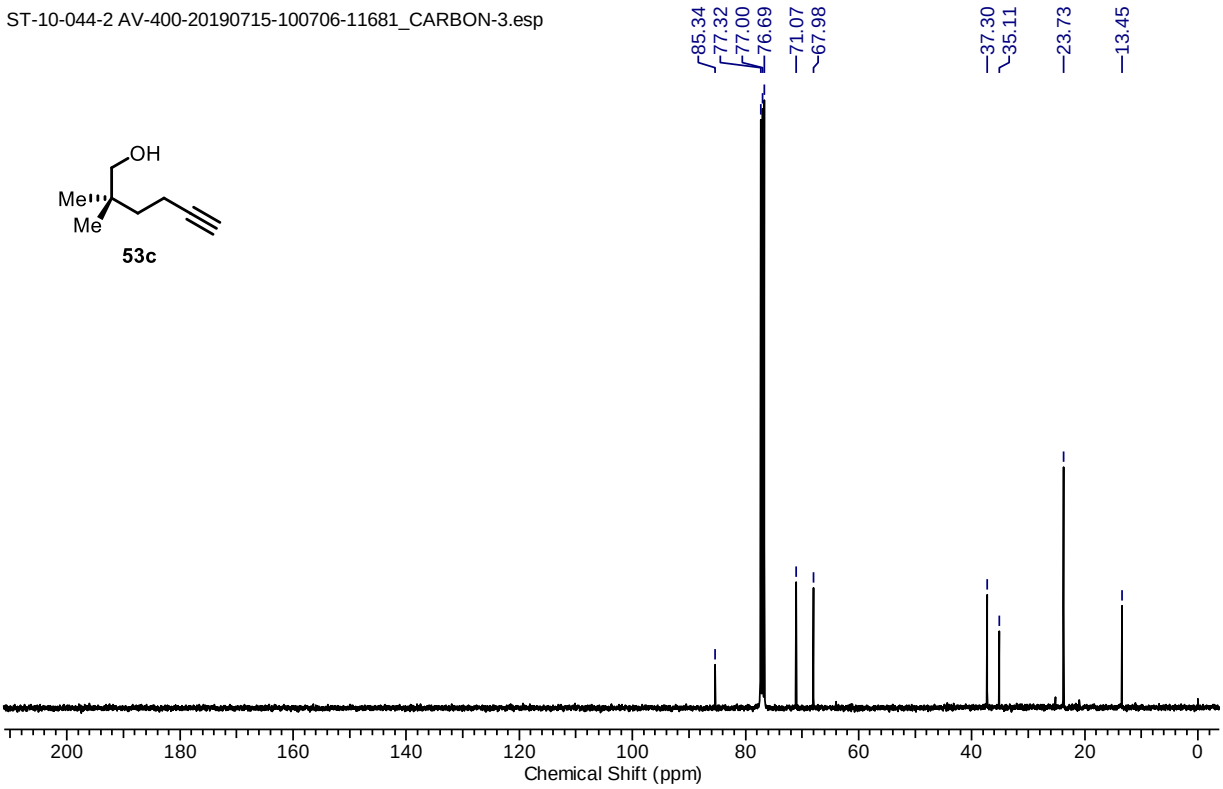
^{13}C NMR spectrum of compound S4



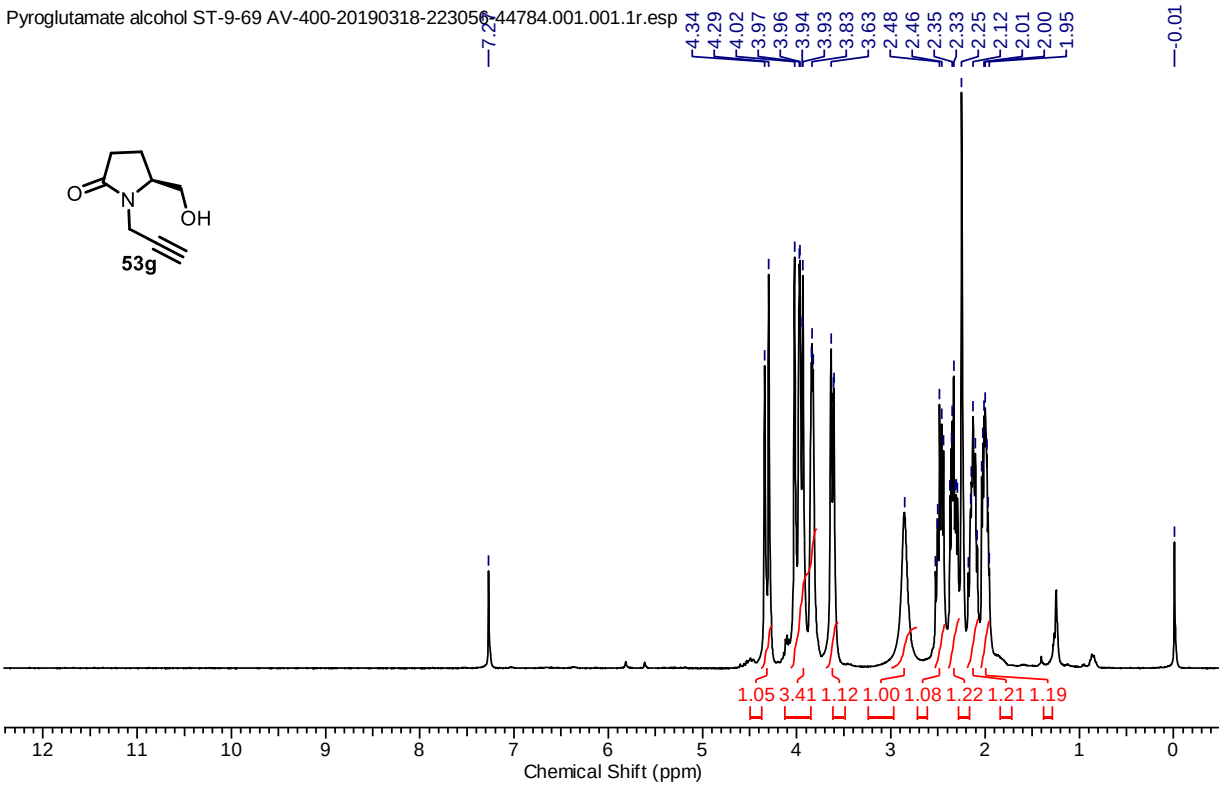
^{1}H NMR spectrum of compound 53c



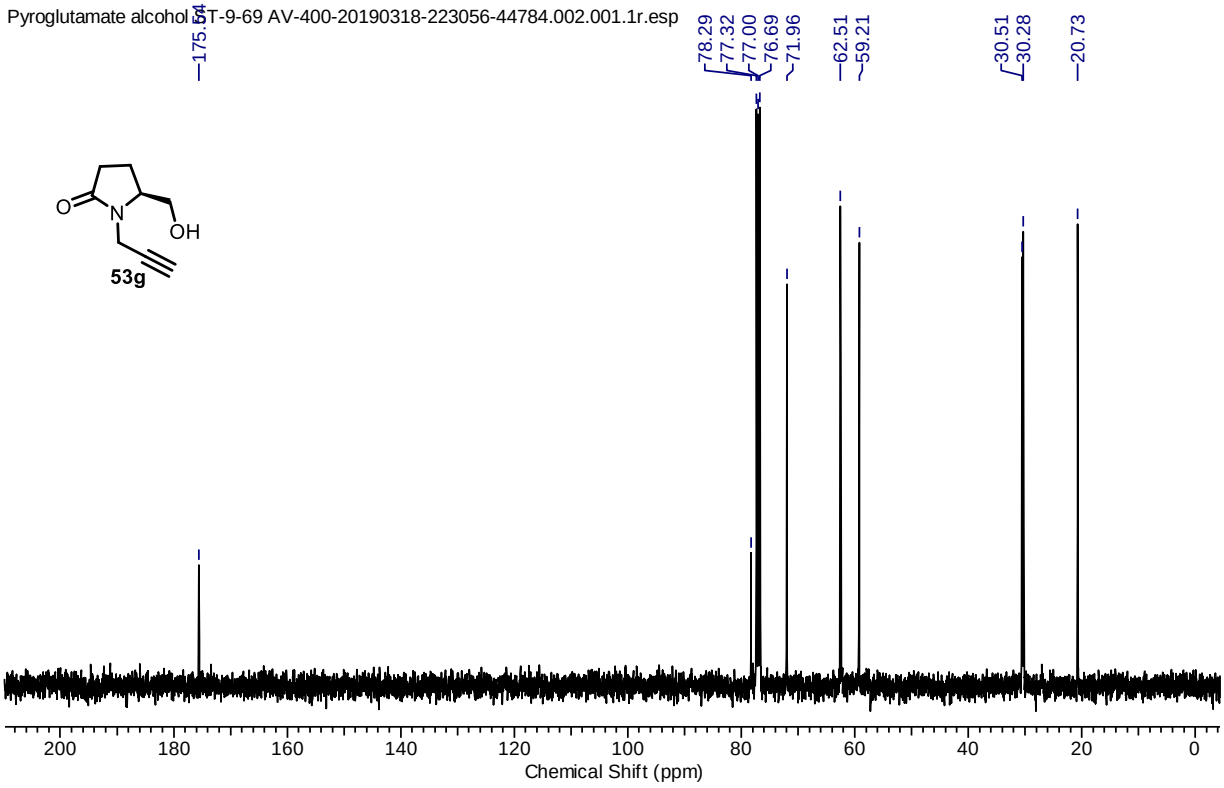
^{13}C NMR spectrum of compound 53c



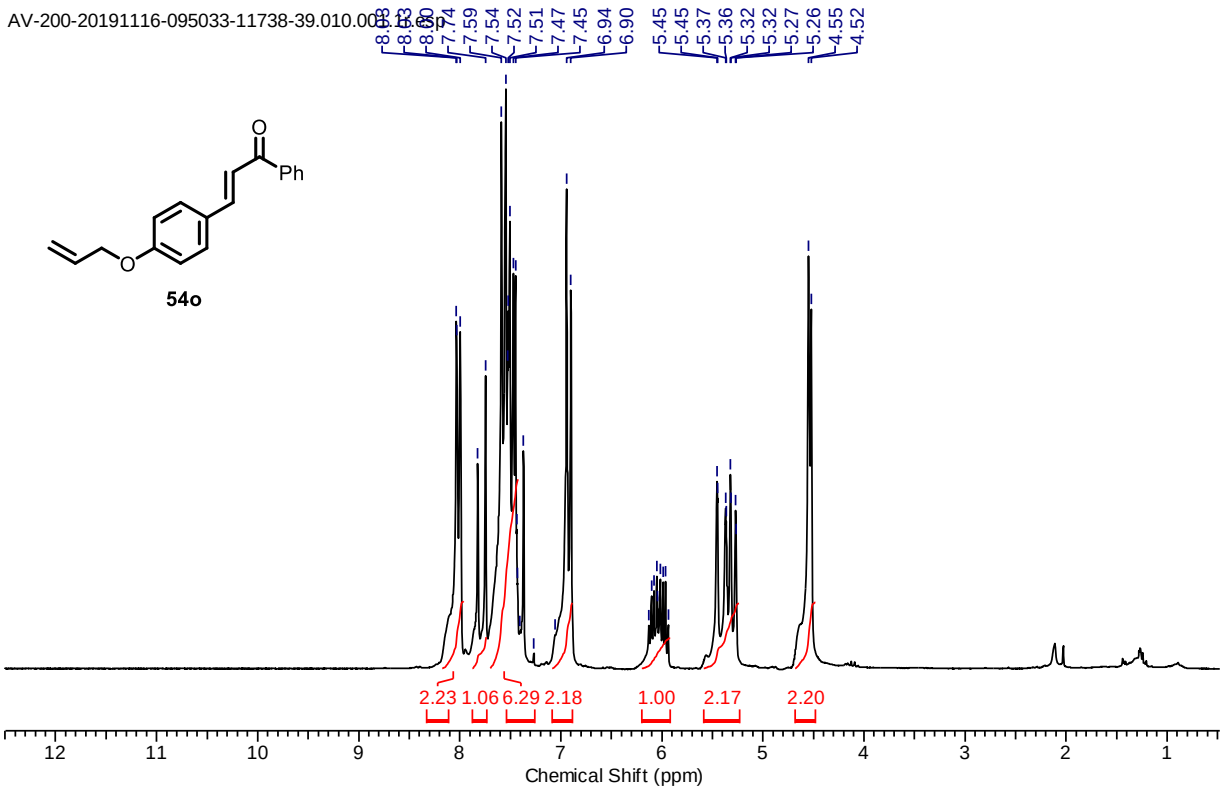
^{1}H NMR spectrum of compound 53g



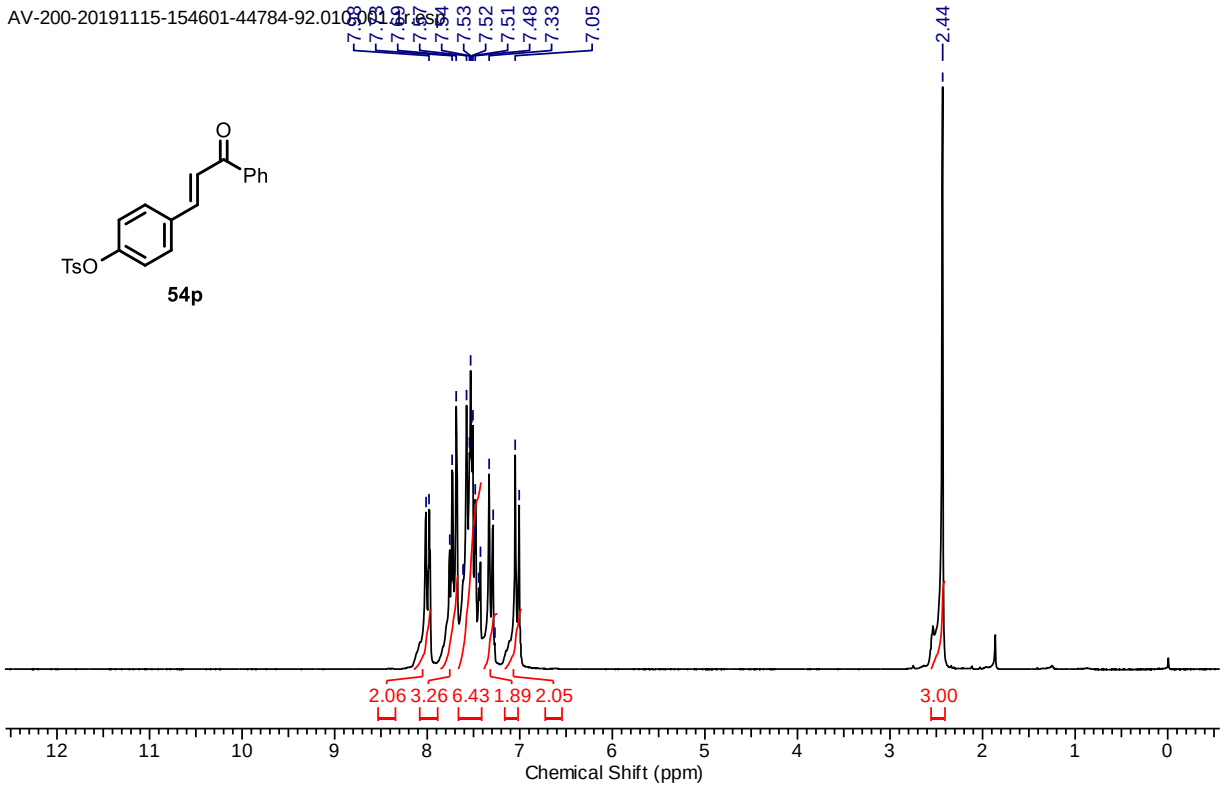
^{13}C NMR spectrum of compound 53g



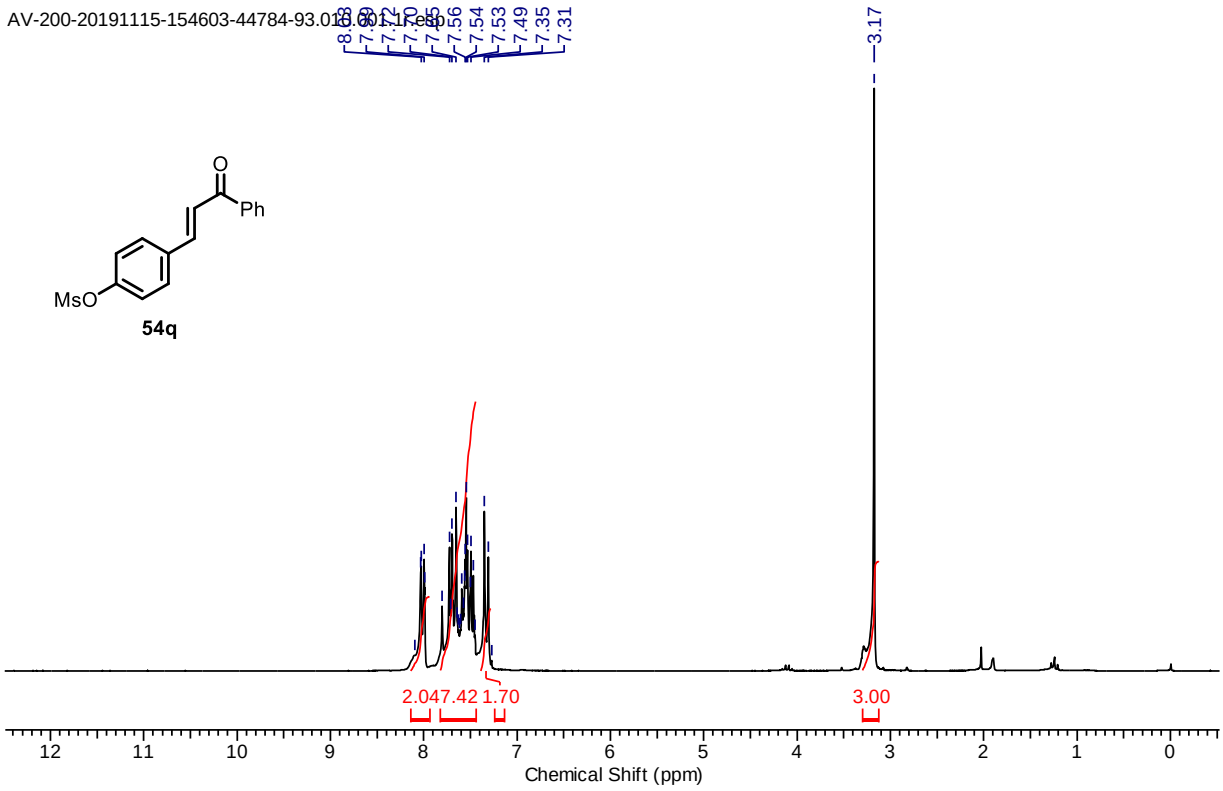
^{1}H NMR spectrum of compound 54o



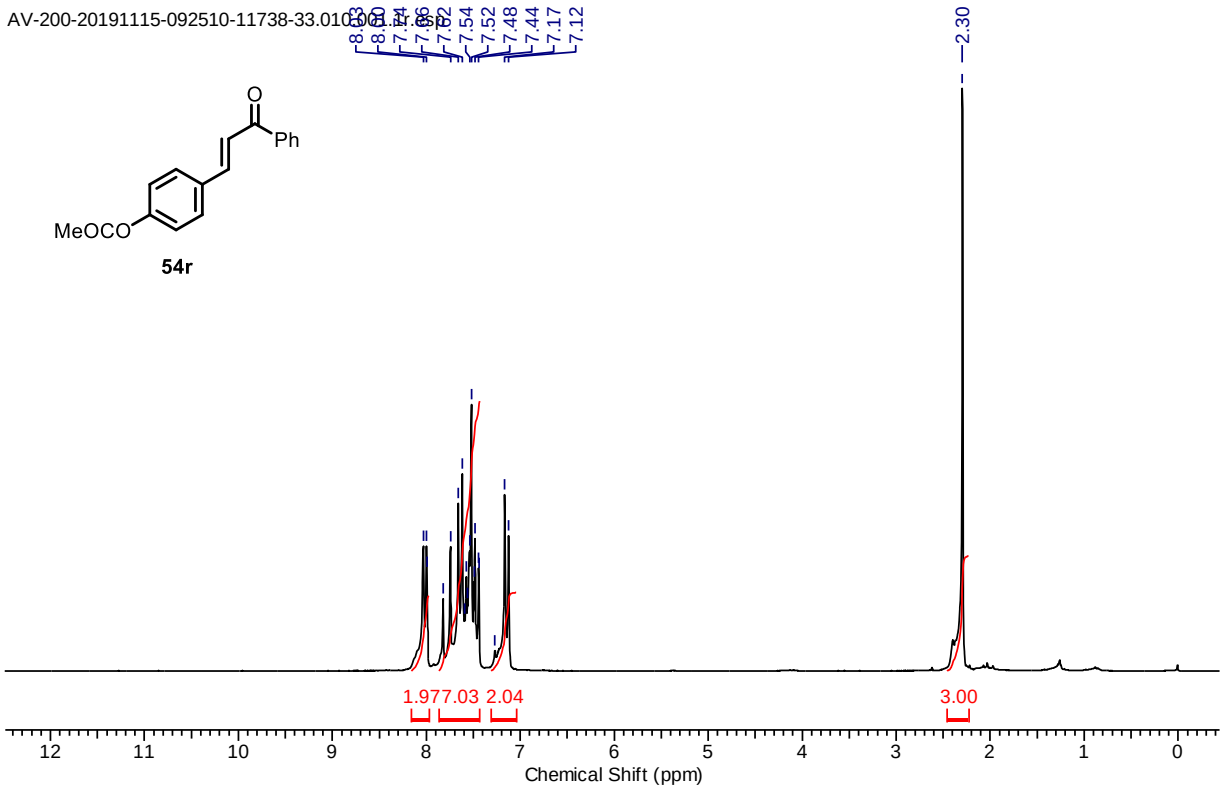
^{1}H NMR spectrum of compound 54p



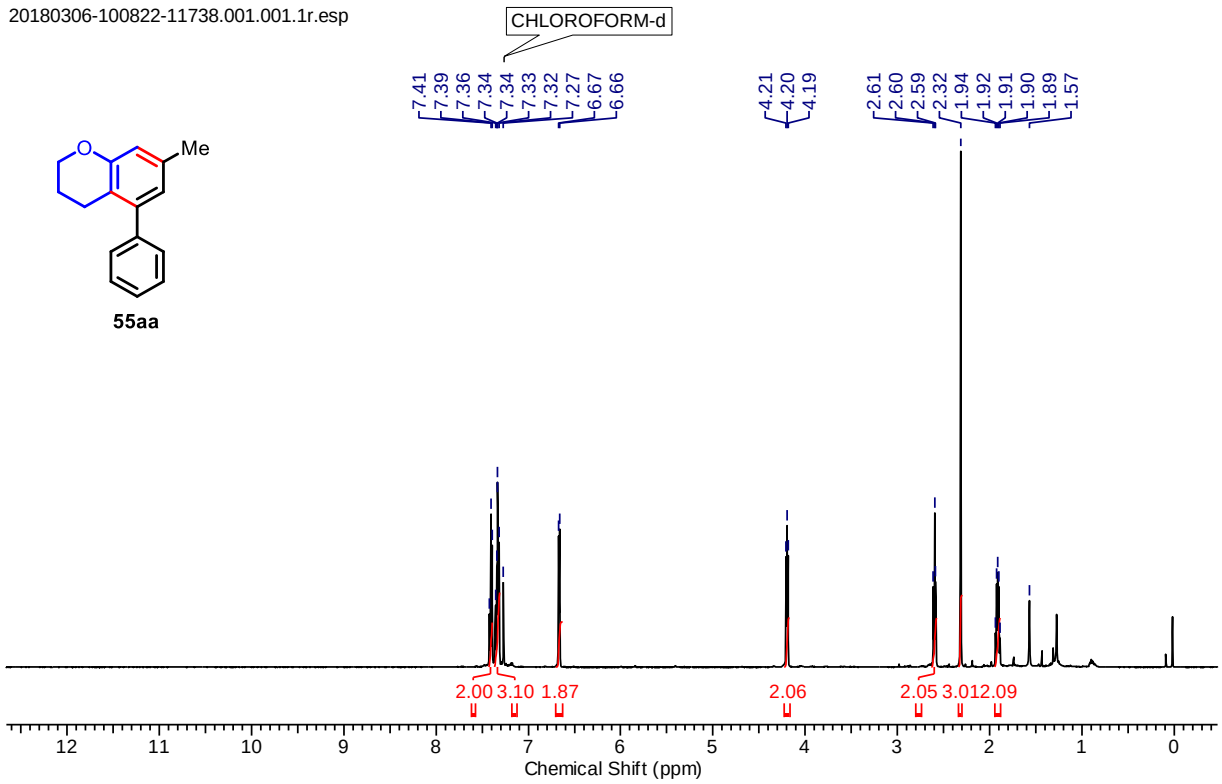
^{1}H NMR spectrum of compound 54q



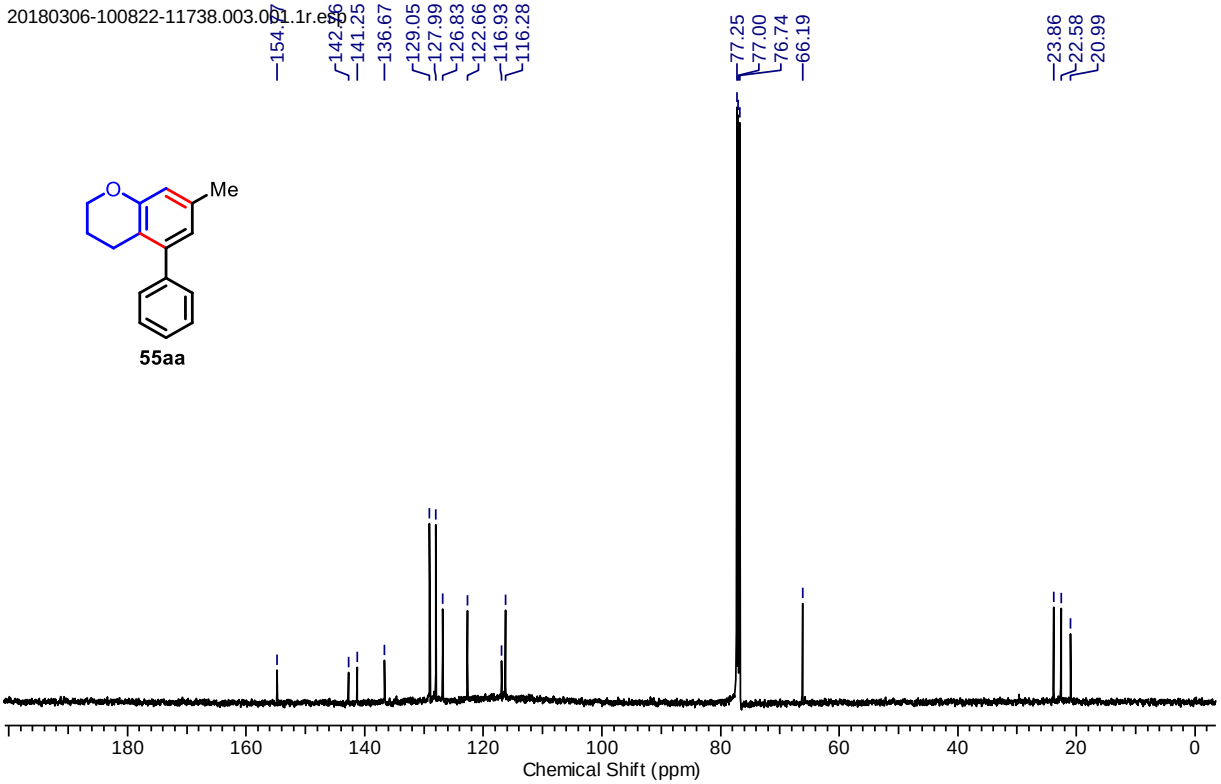
^{1}H NMR spectrum of compound 54r



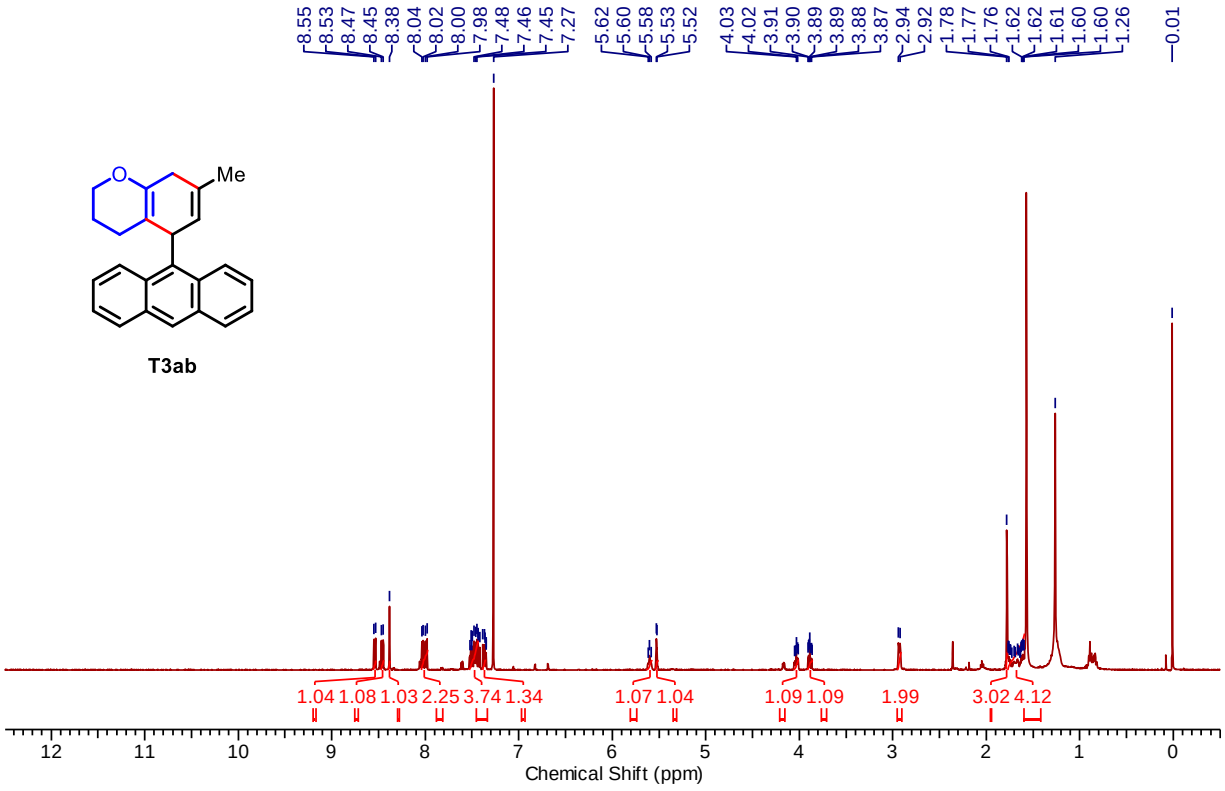
^{1}H NMR spectrum of compound 55aa



^{13}C NMR spectrum of compound 55aa



^{1}H NMR spectrum of compound T3ab



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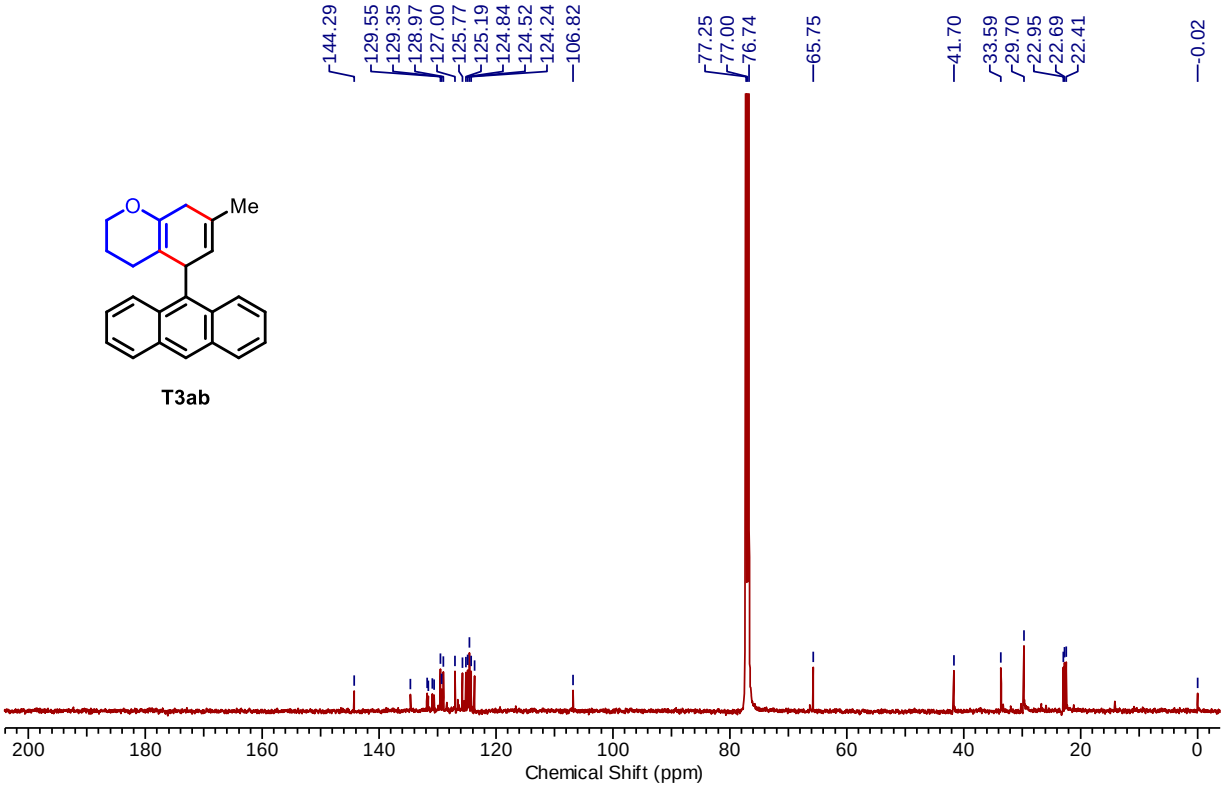

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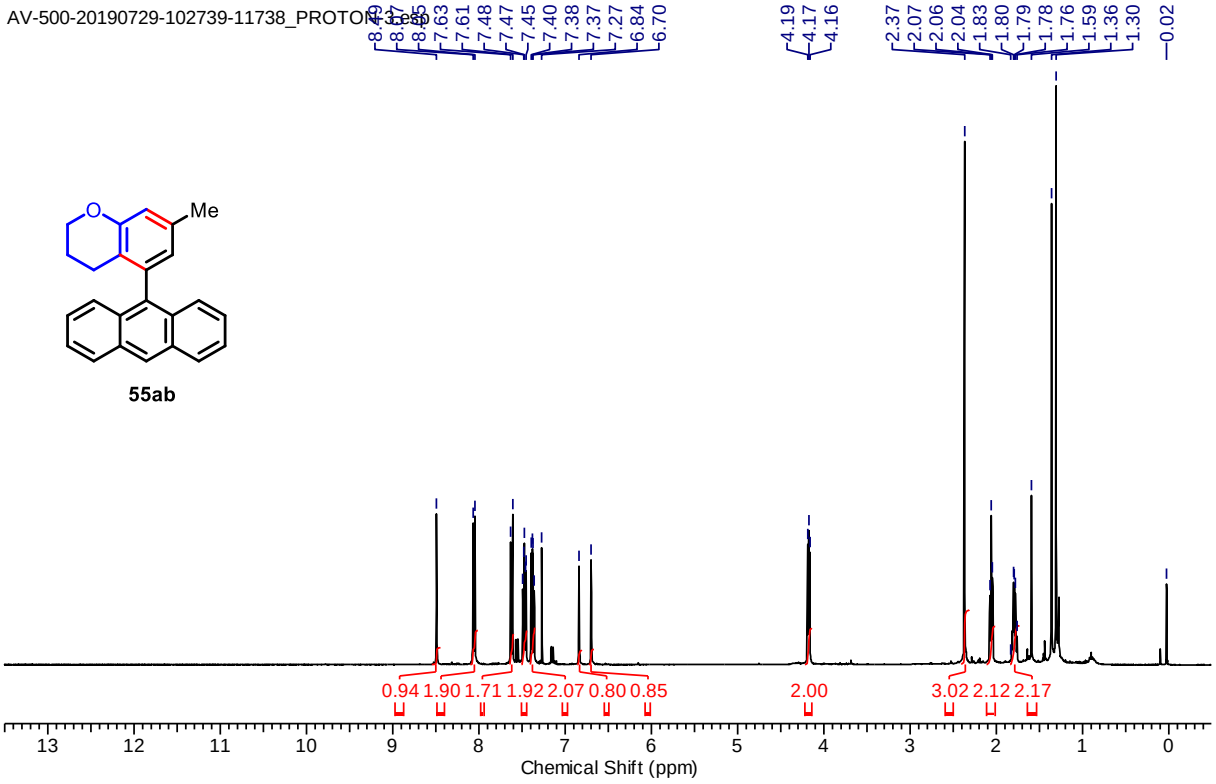
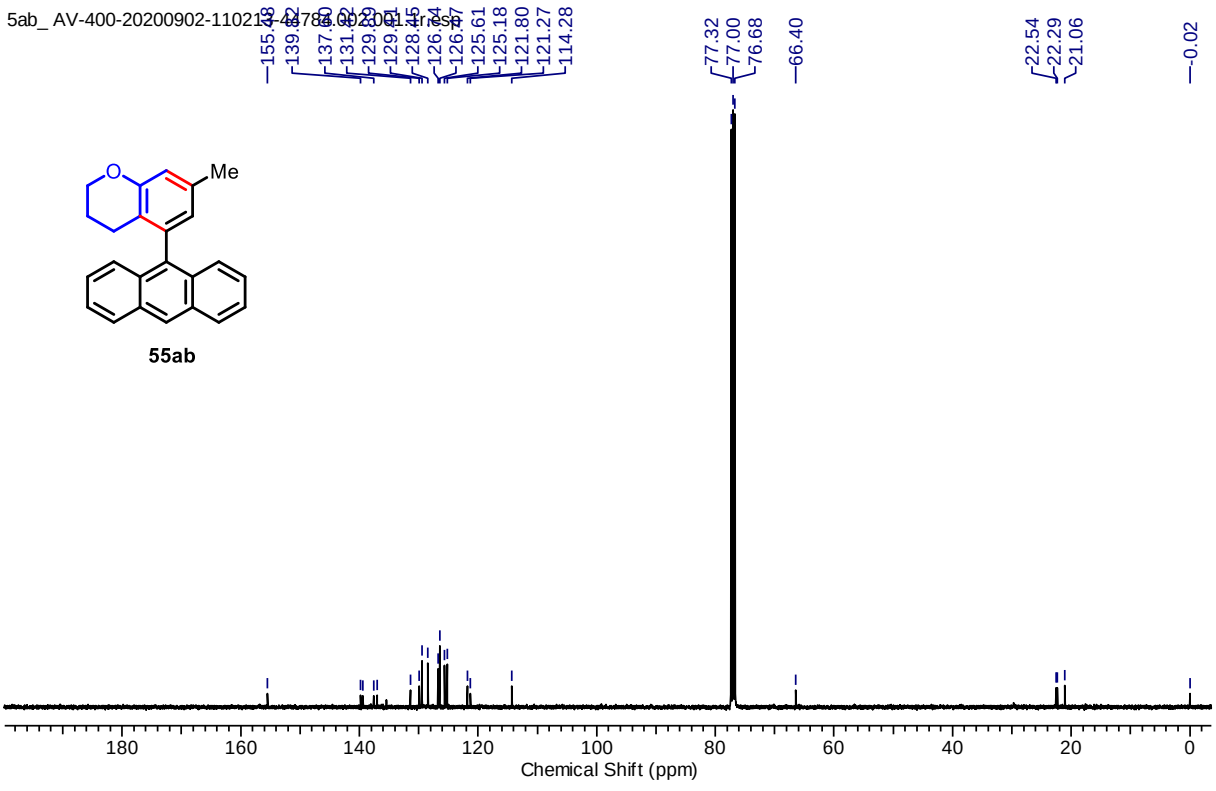
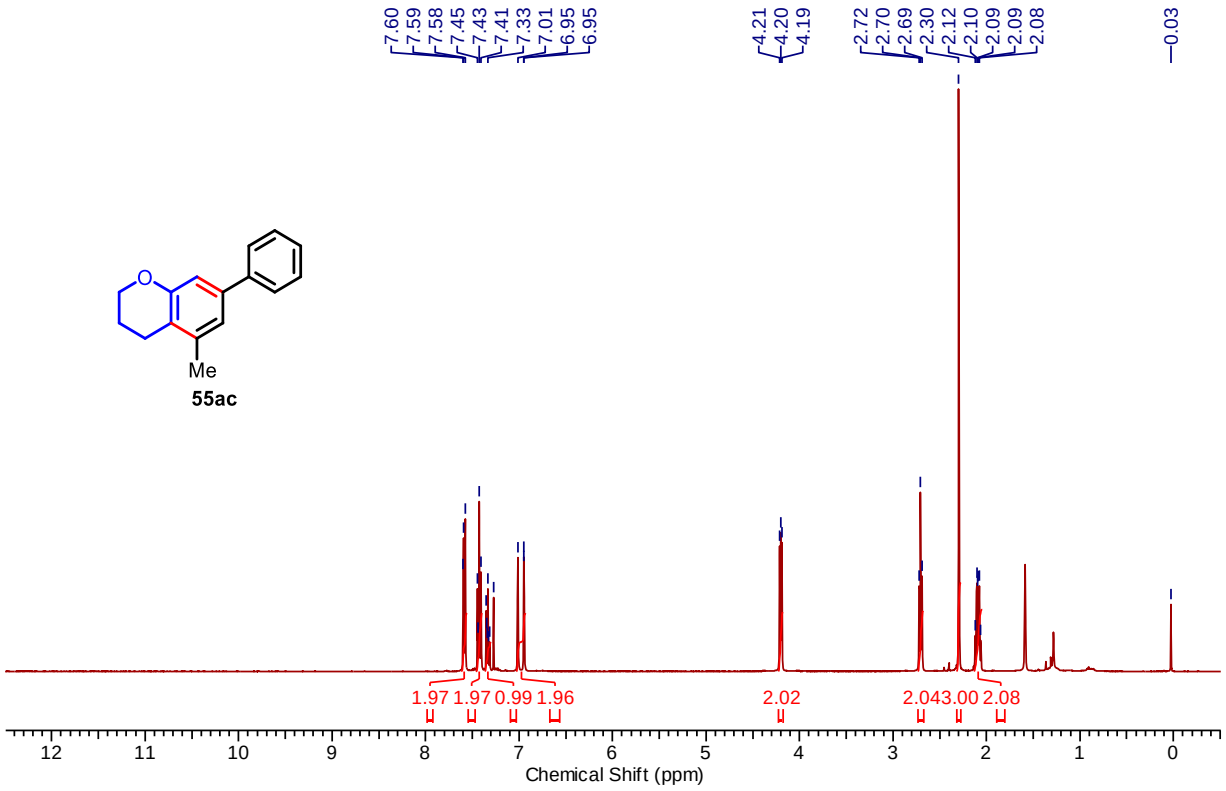


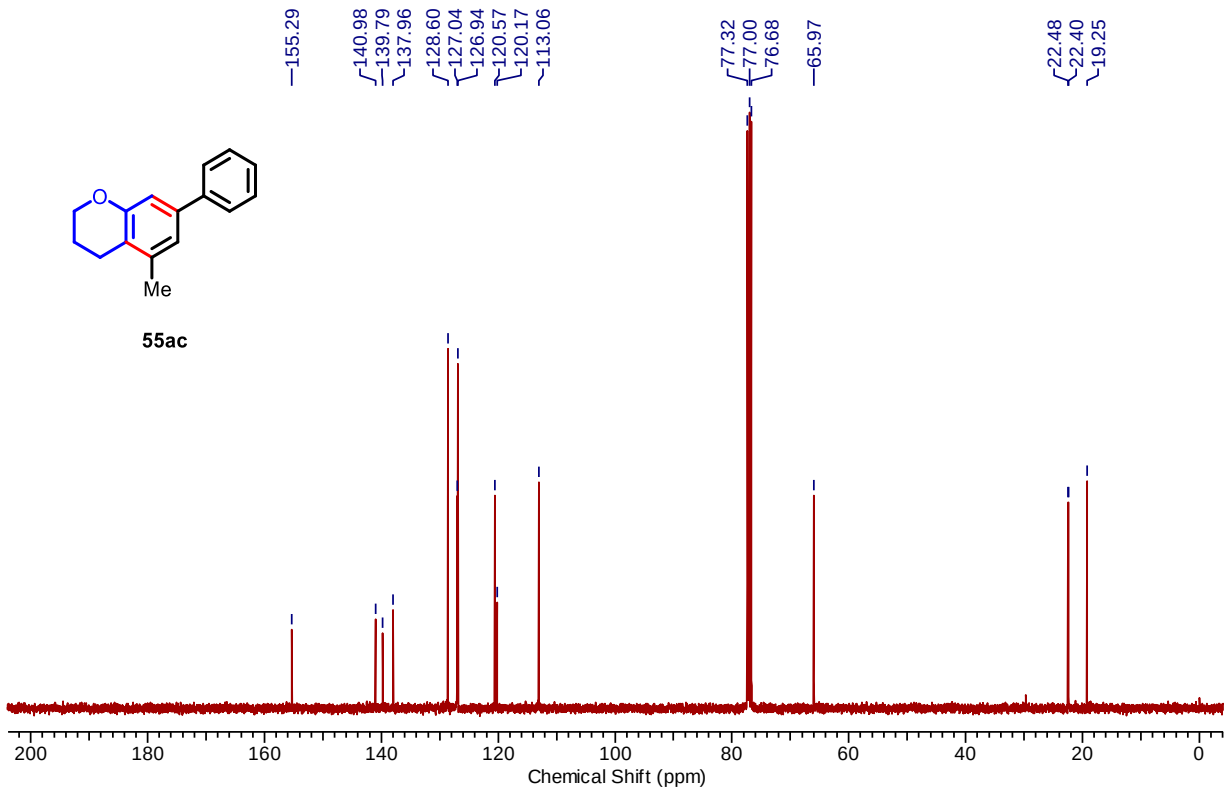
^{13}C NMR spectrum of compound 55ab



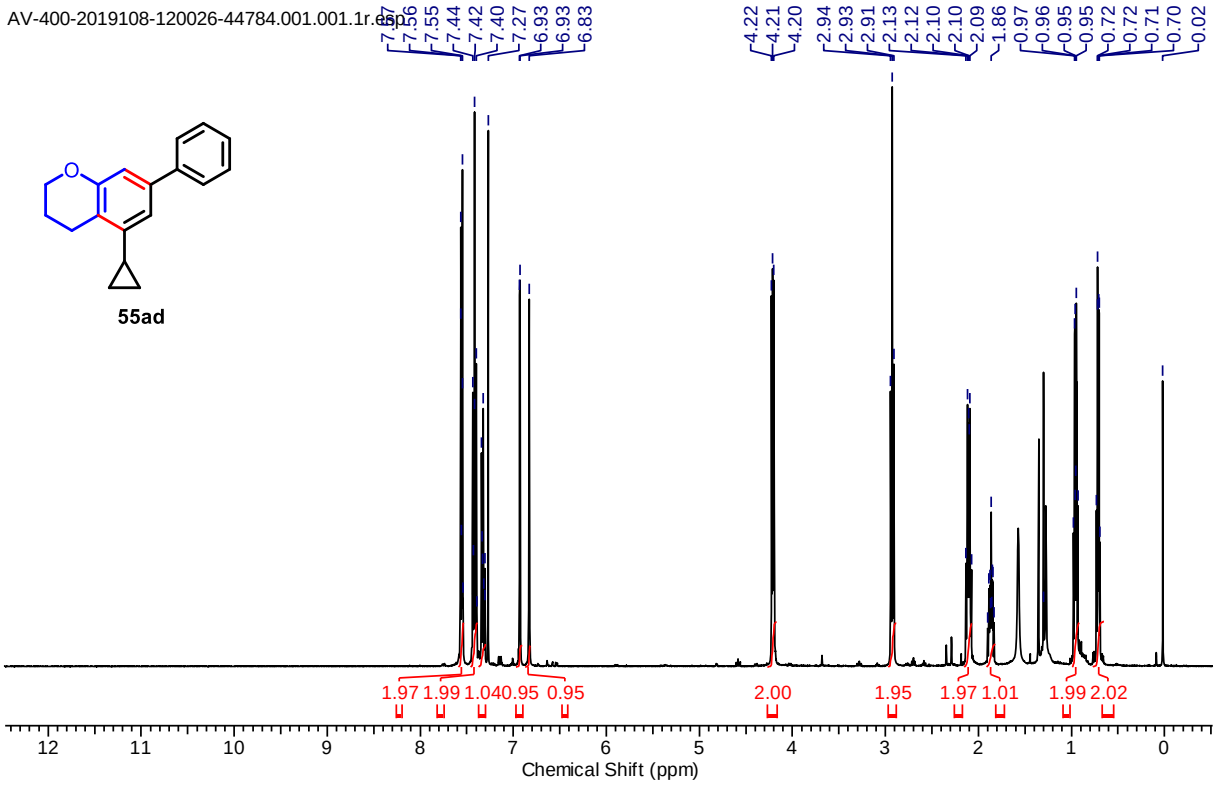
^{1}H NMR spectrum of compound 55ac



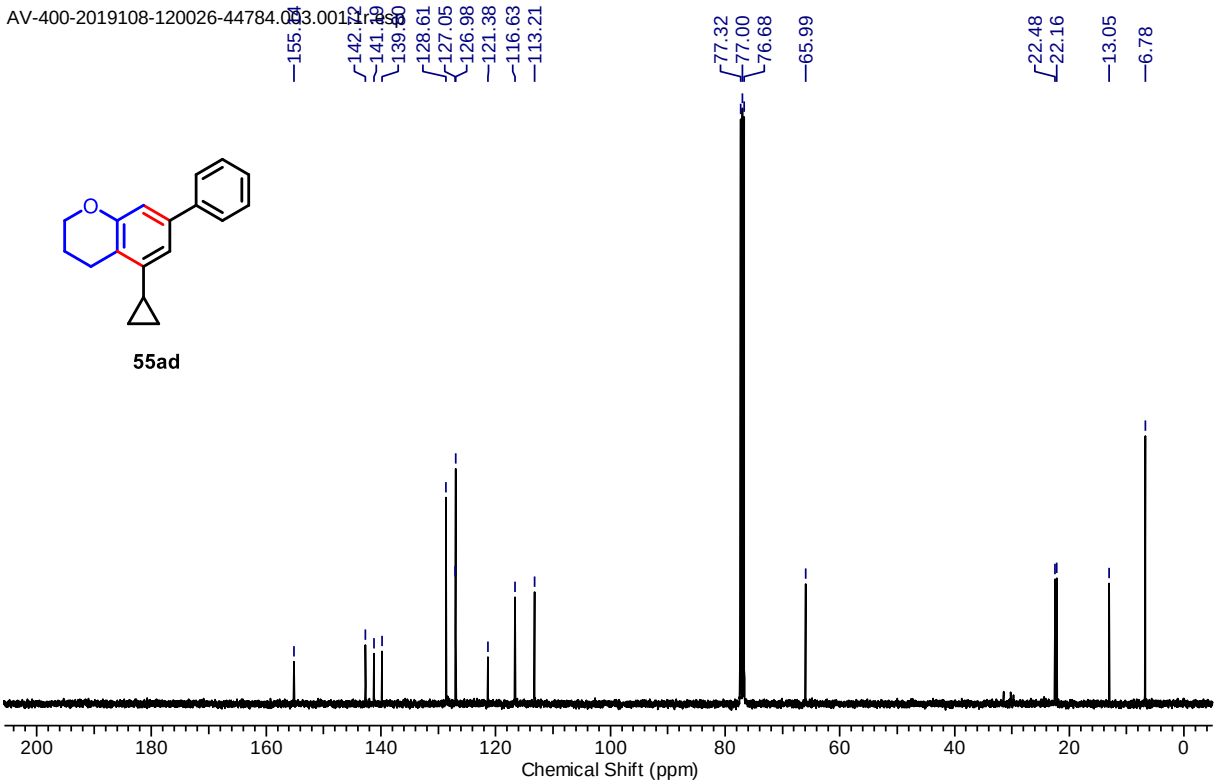
^{13}C NMR spectrum of compound 55ac



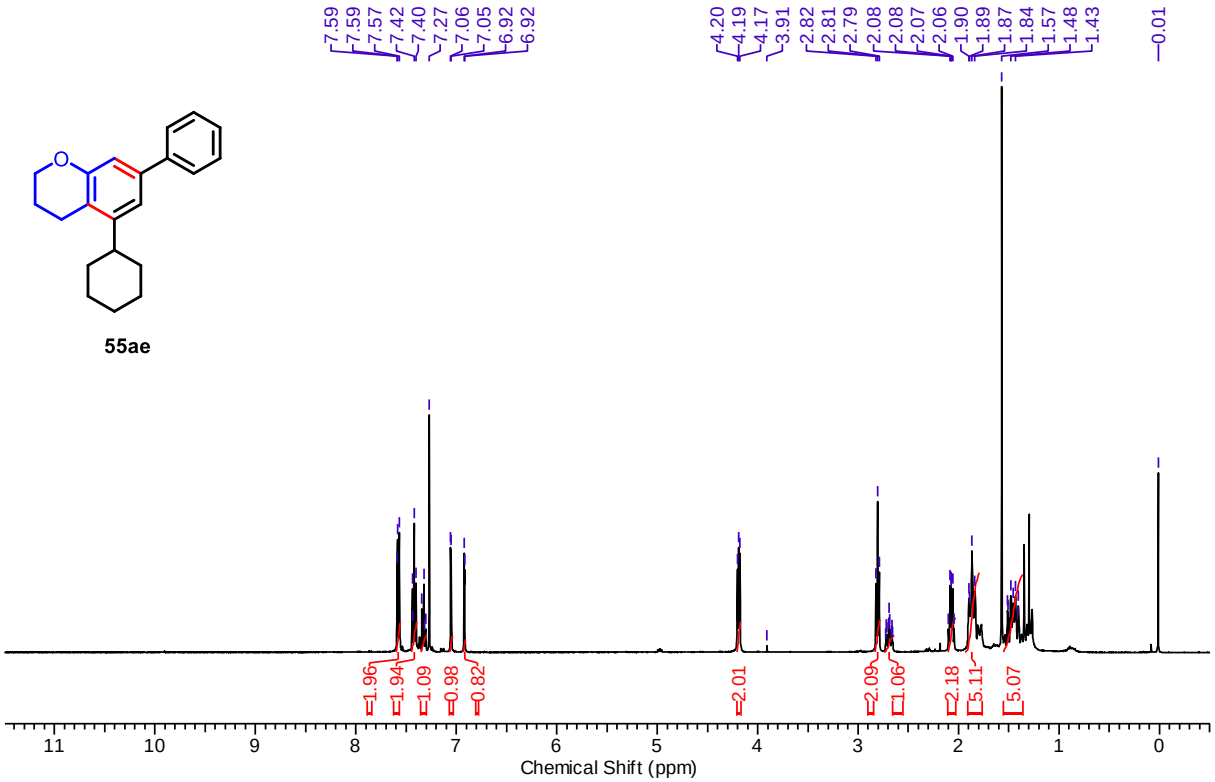
^{1}H NMR spectrum of compound 55ad



^{13}C NMR spectrum of compound 55ad

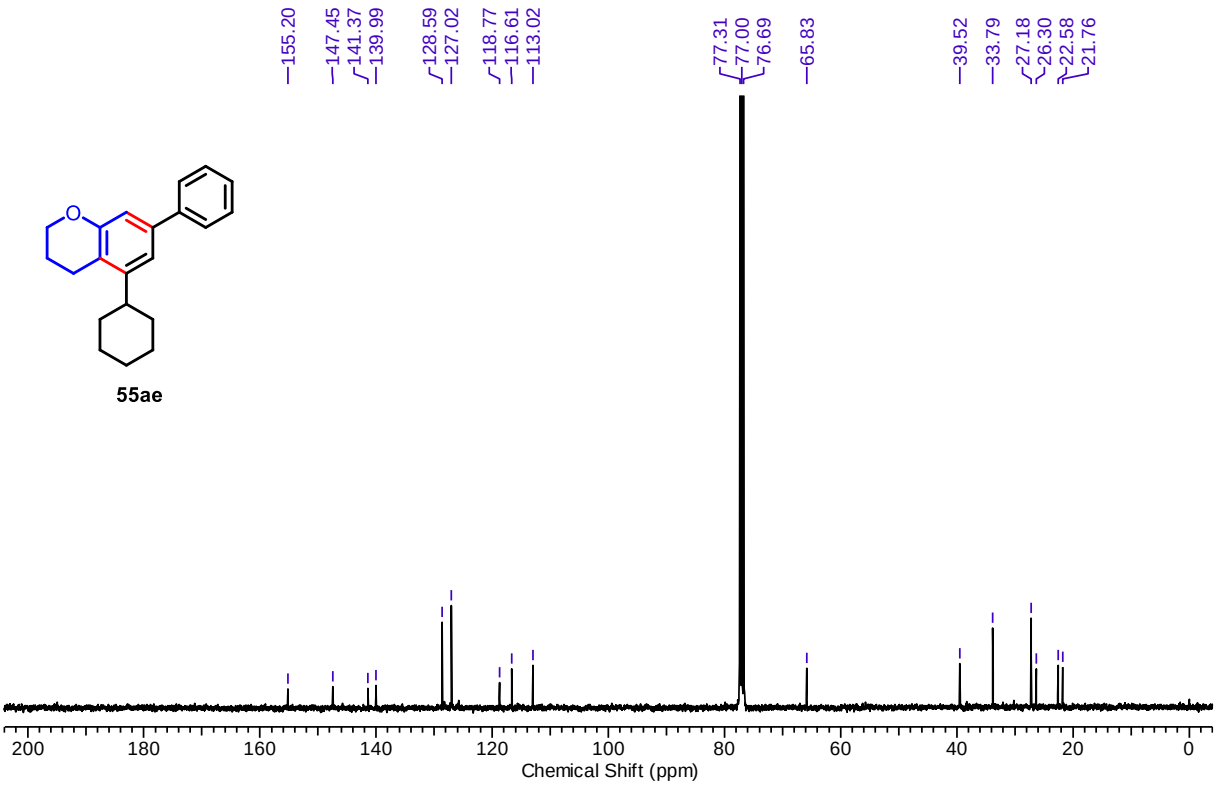


^{1}H NMR spectrum of compound 55ae



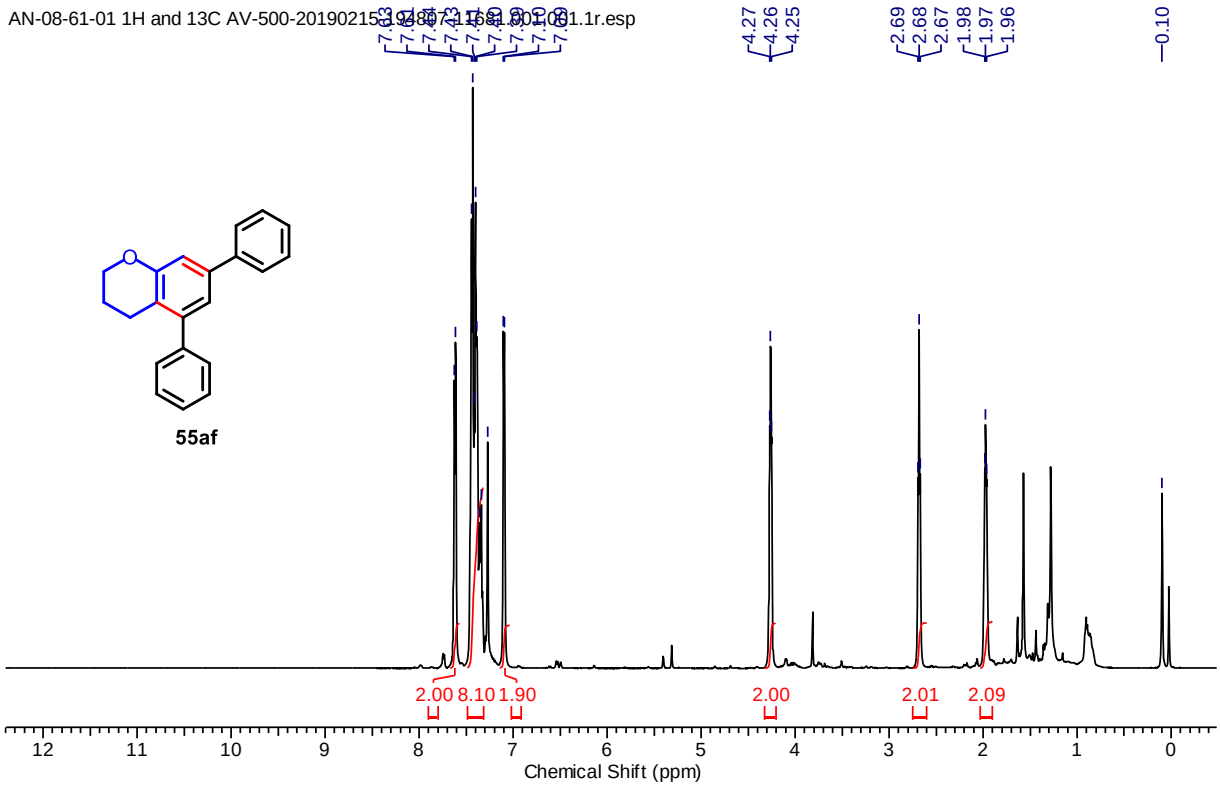
55ae

^{13}C NMR spectrum of compound 55ae



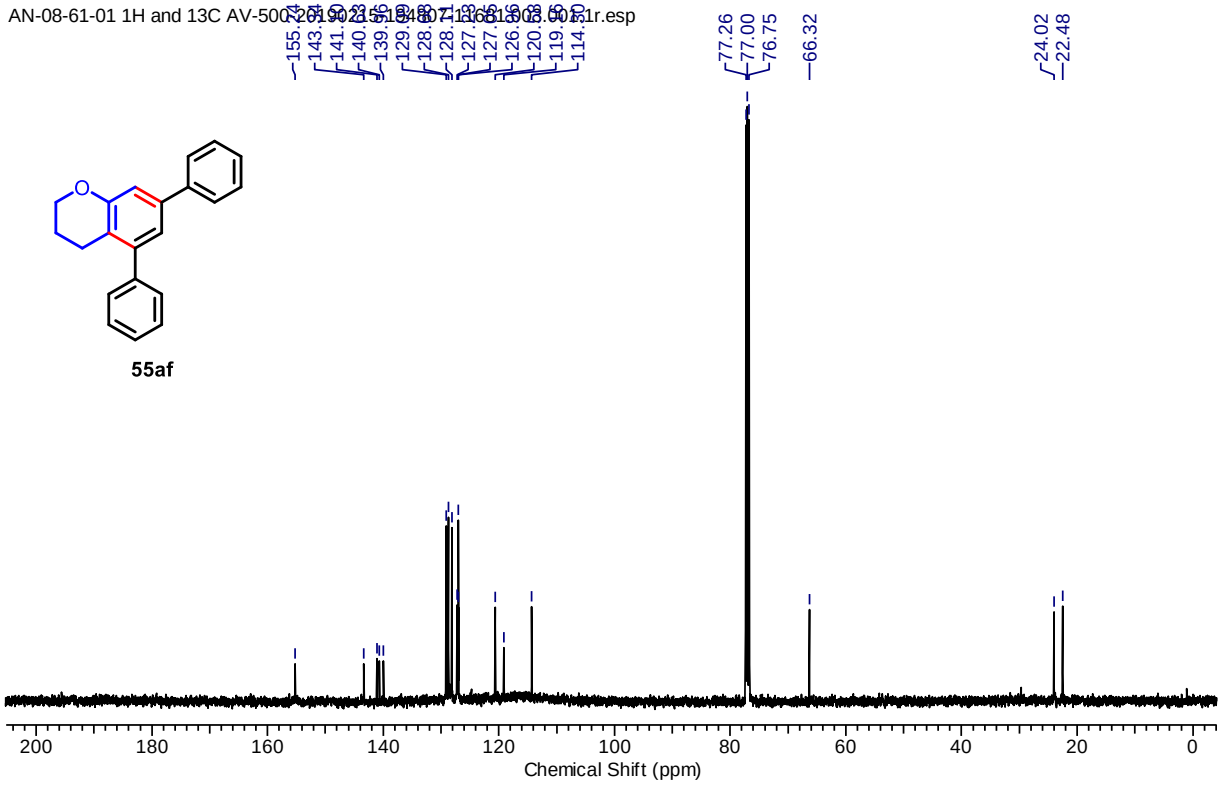
55ae

^{1}H NMR spectrum of compound 55af



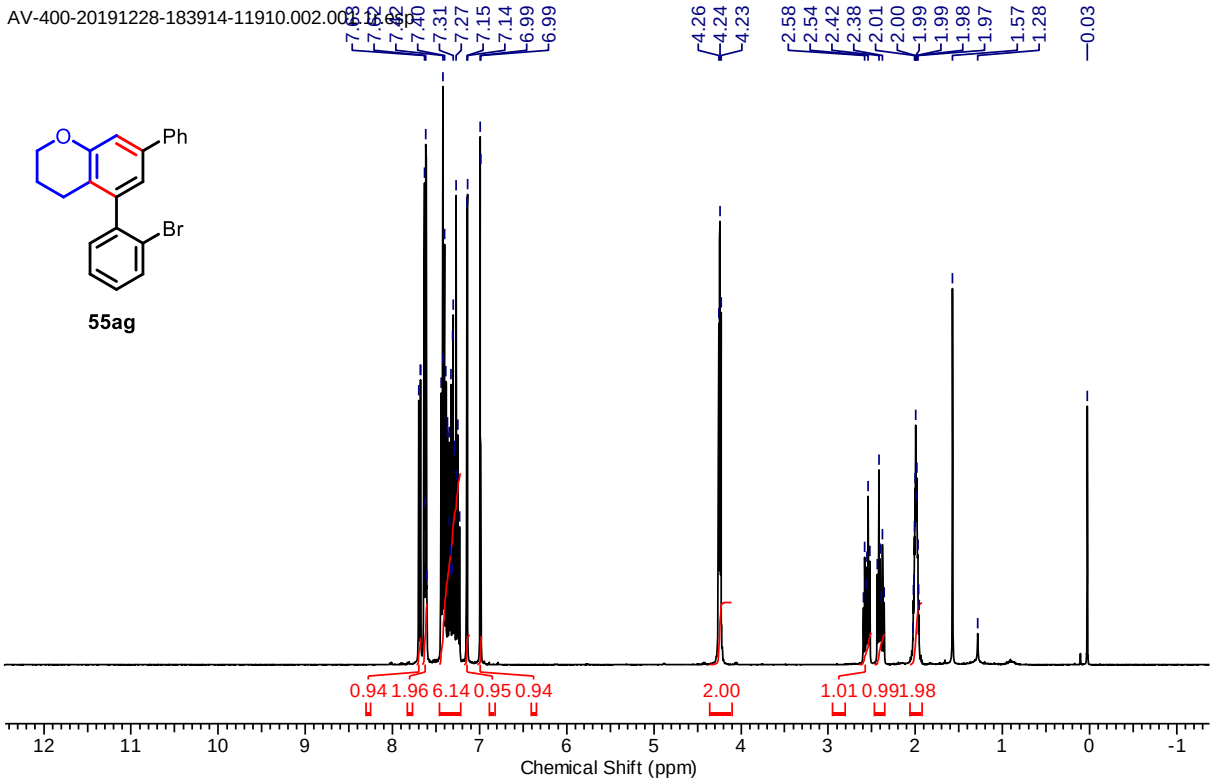
55af

^{13}C NMR spectrum of compound 55af

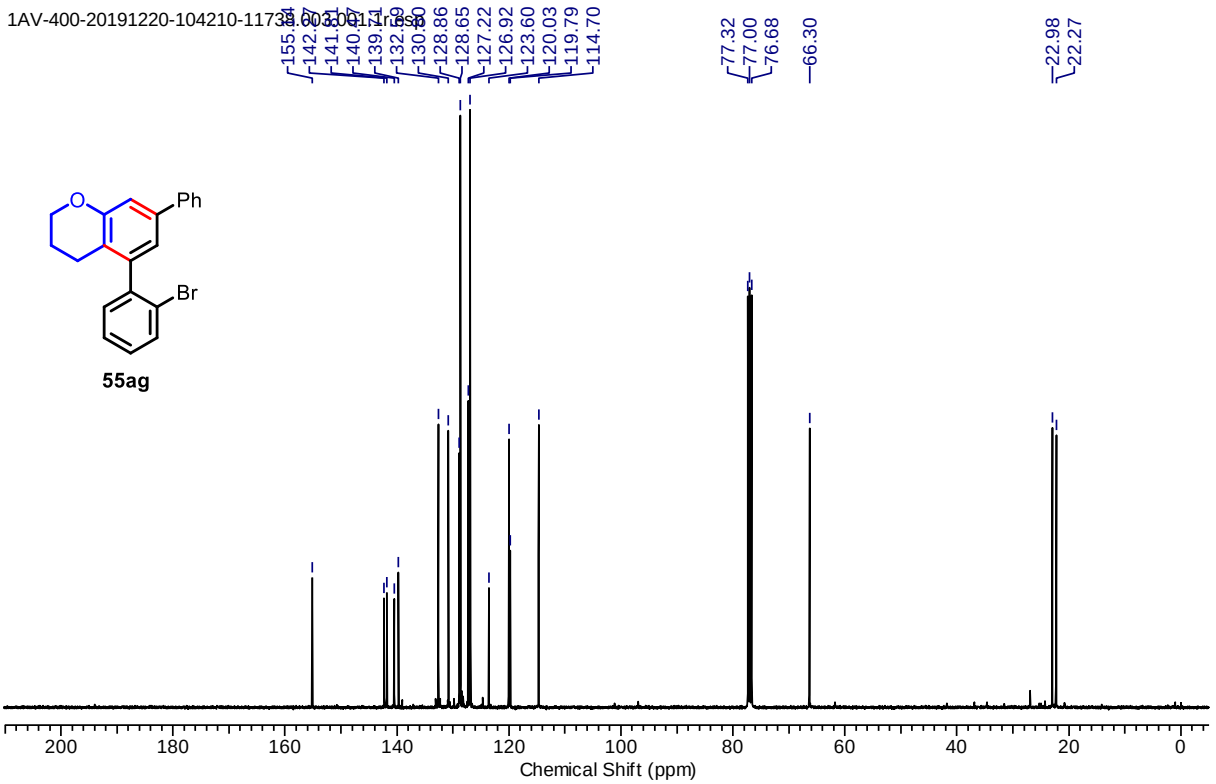


55af

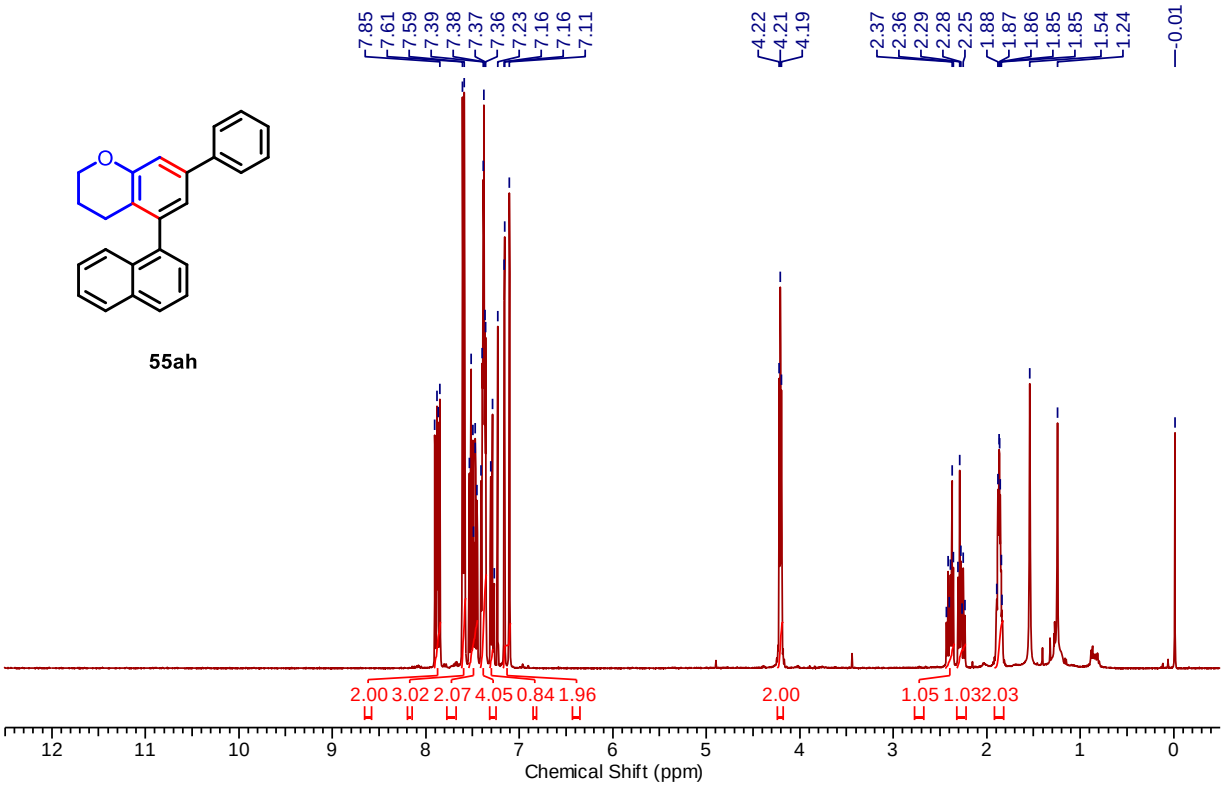
^{1}H NMR spectrum of compound 55ag



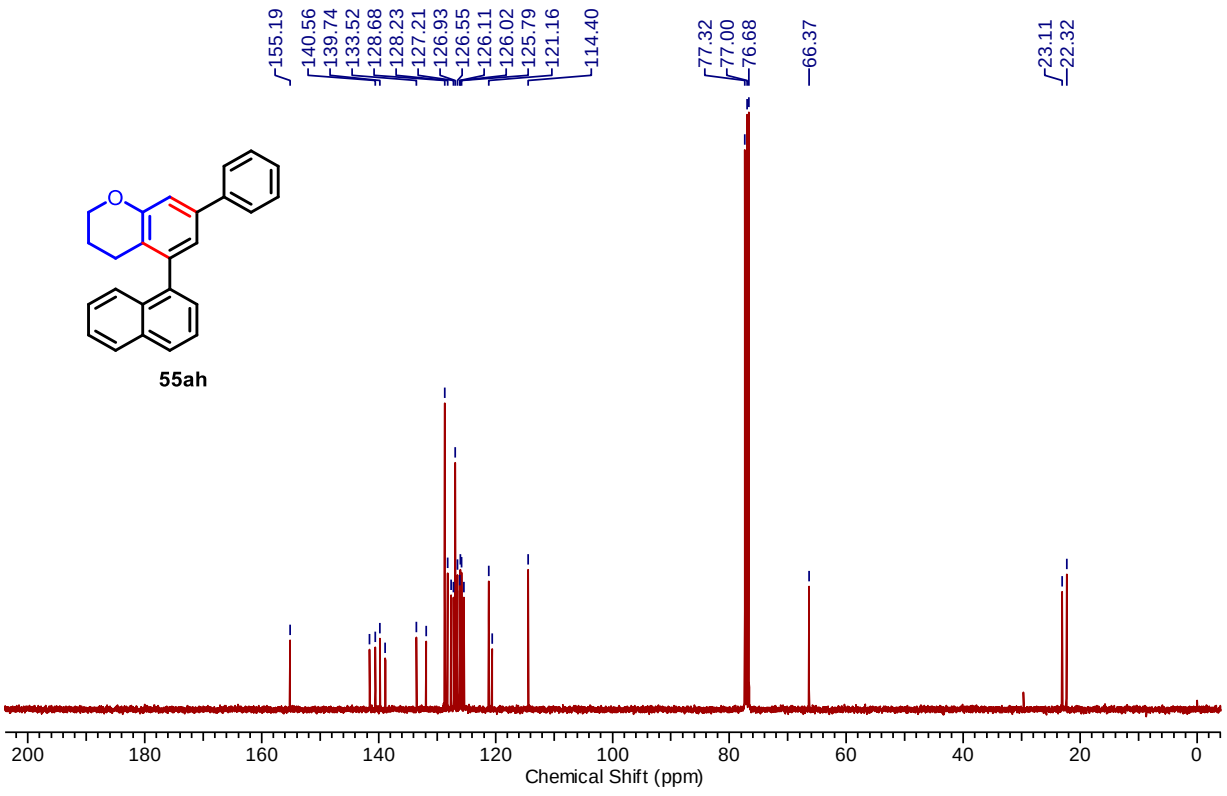
^{13}C NMR spectrum of compound 55ag



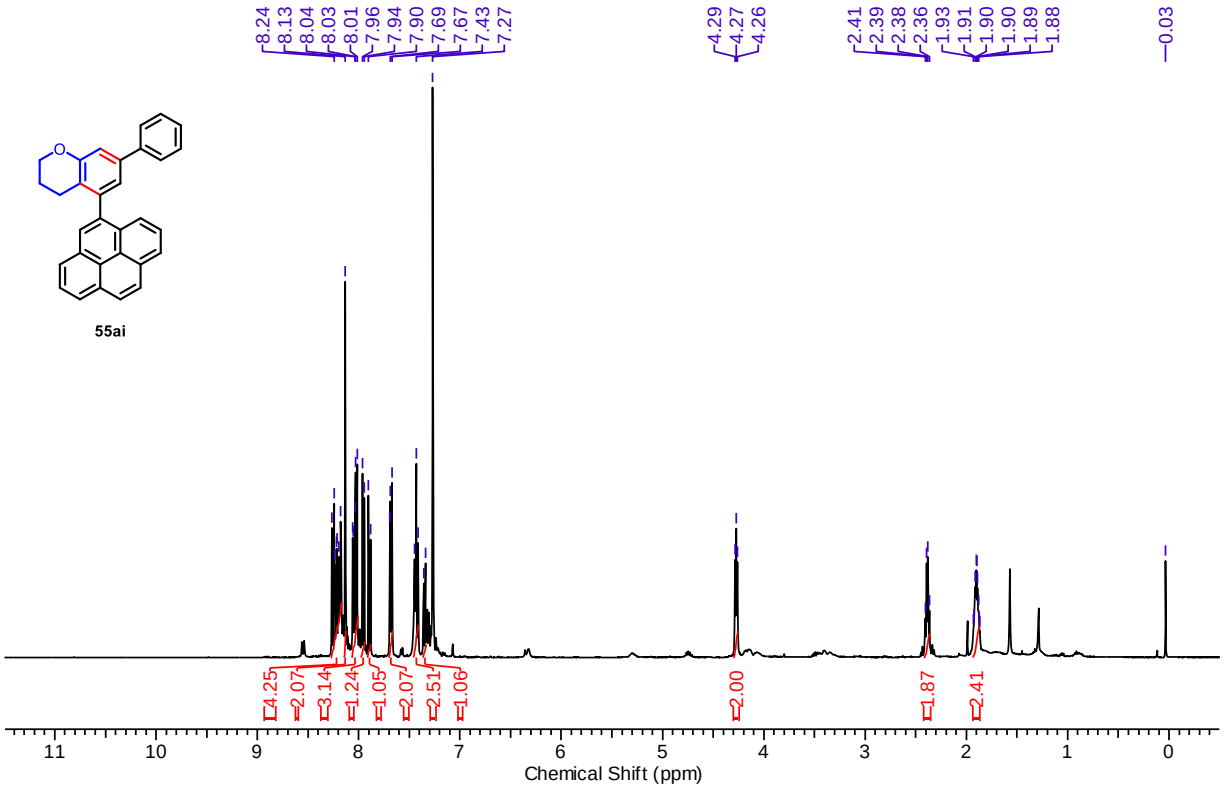
^{1}H NMR spectrum of compound 55ah



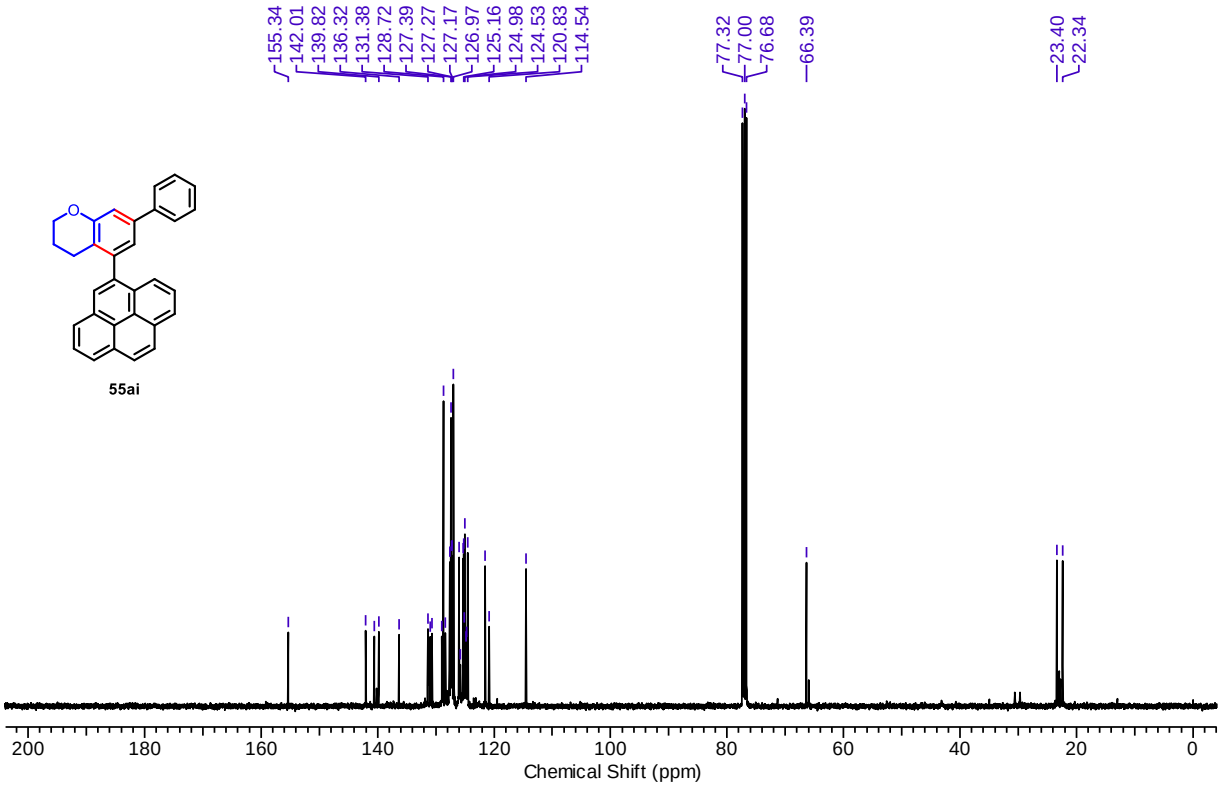
^{13}C NMR spectrum of compound 55ah



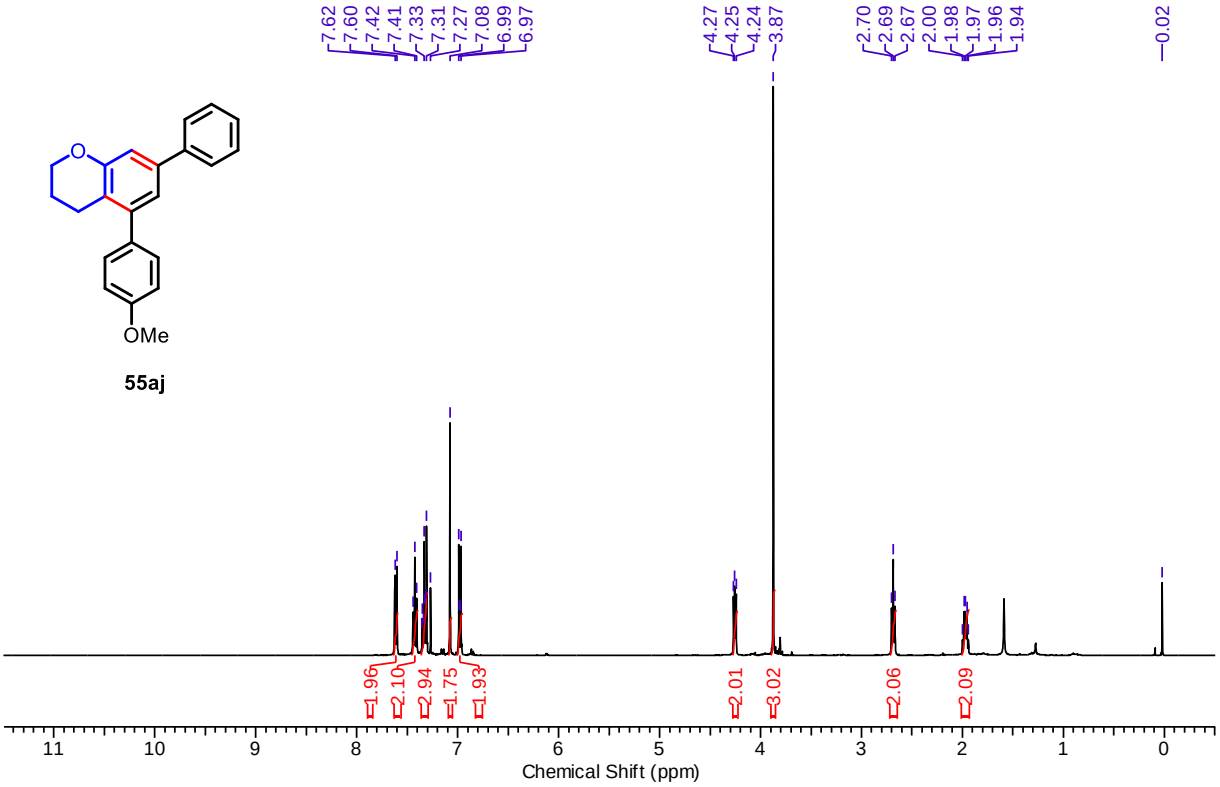
^{1}H NMR spectrum of compound 55ai



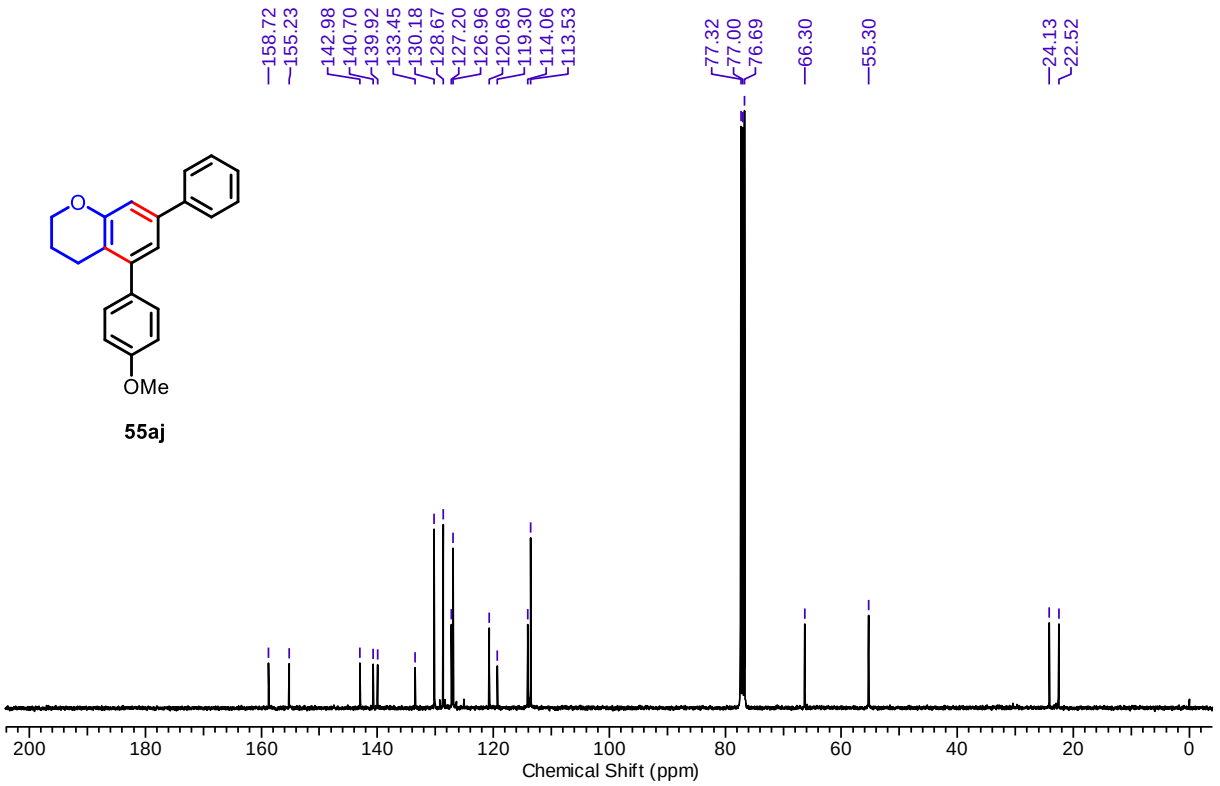
^{13}C NMR spectrum of compound 55ai



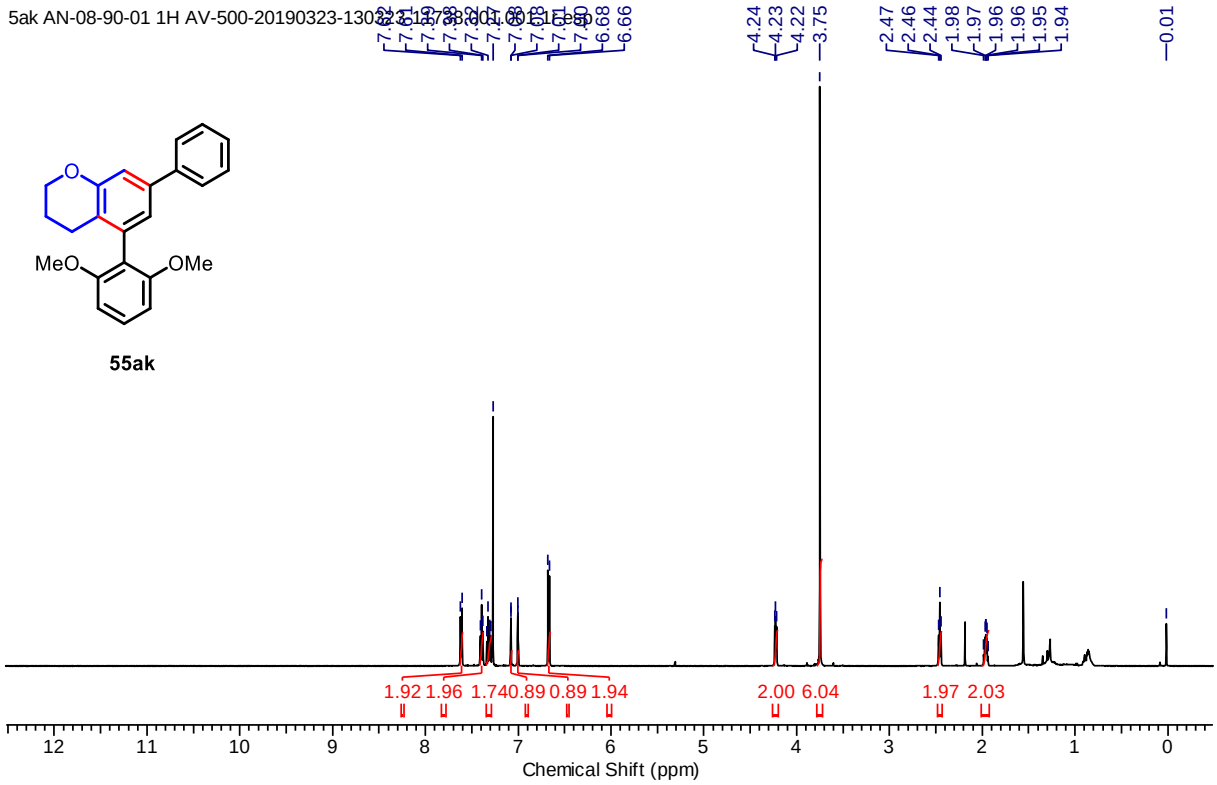
^{1}H NMR spectrum of compound 55aj



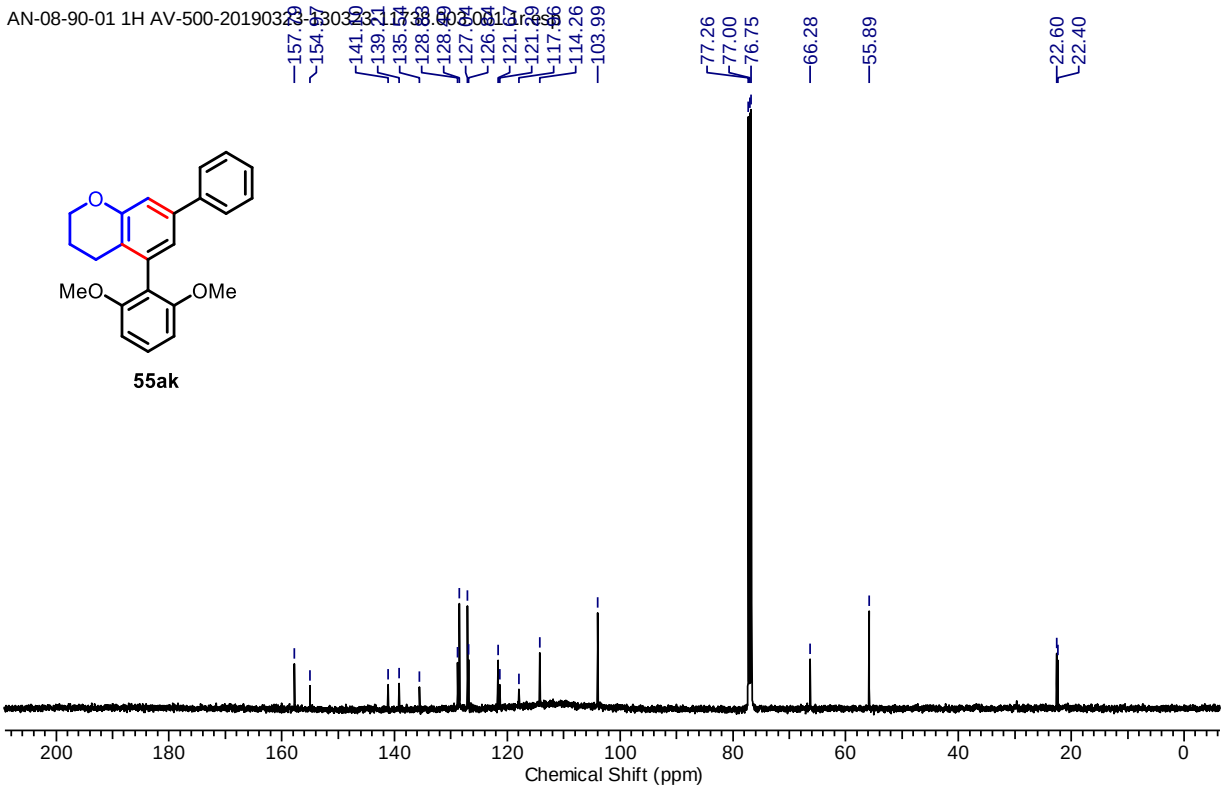
^{13}C NMR spectrum of compound 55aj



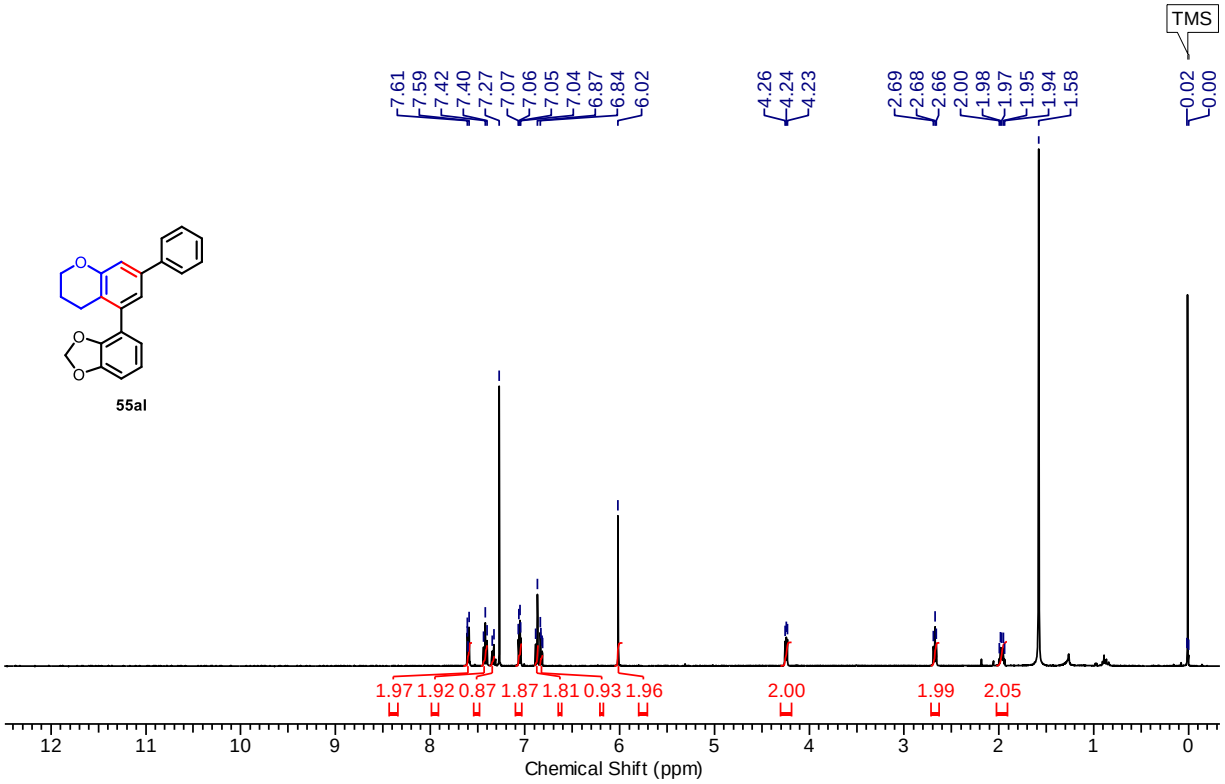
^{1}H NMR spectrum of compound 55ak



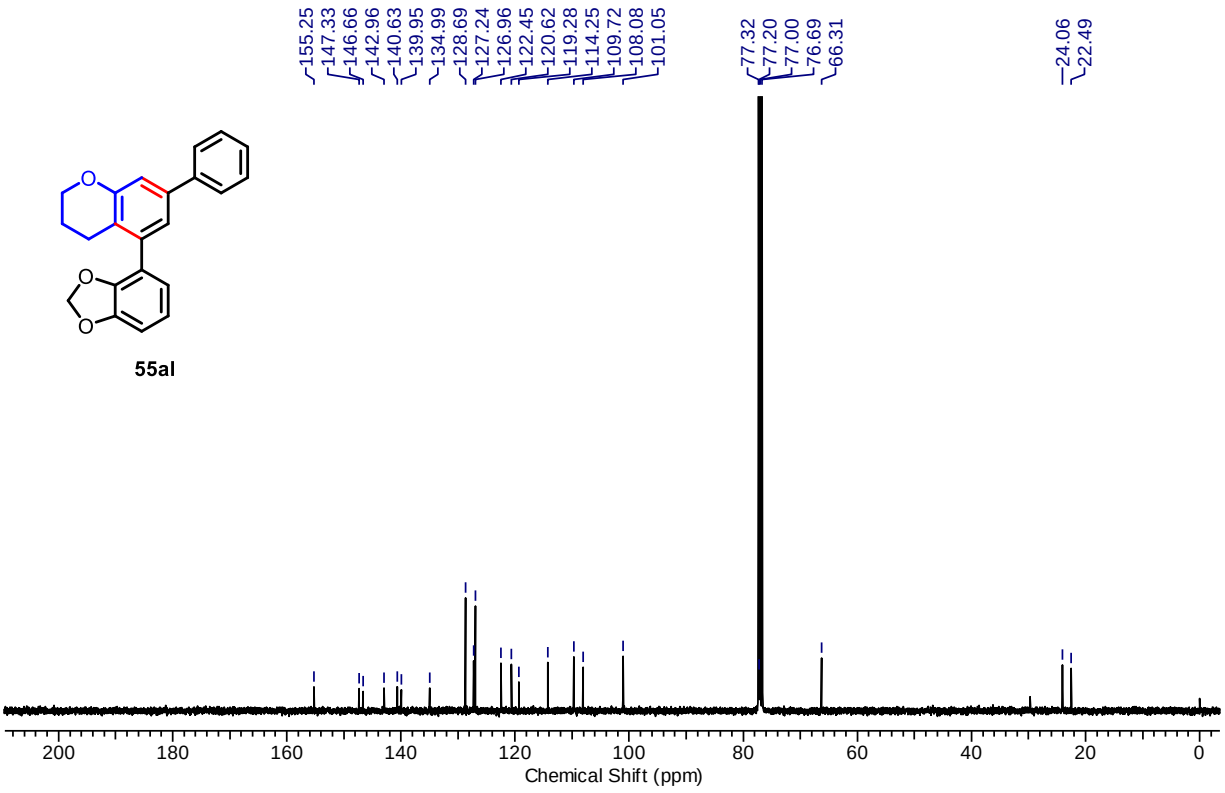
^{13}C NMR spectrum of compound 55ak



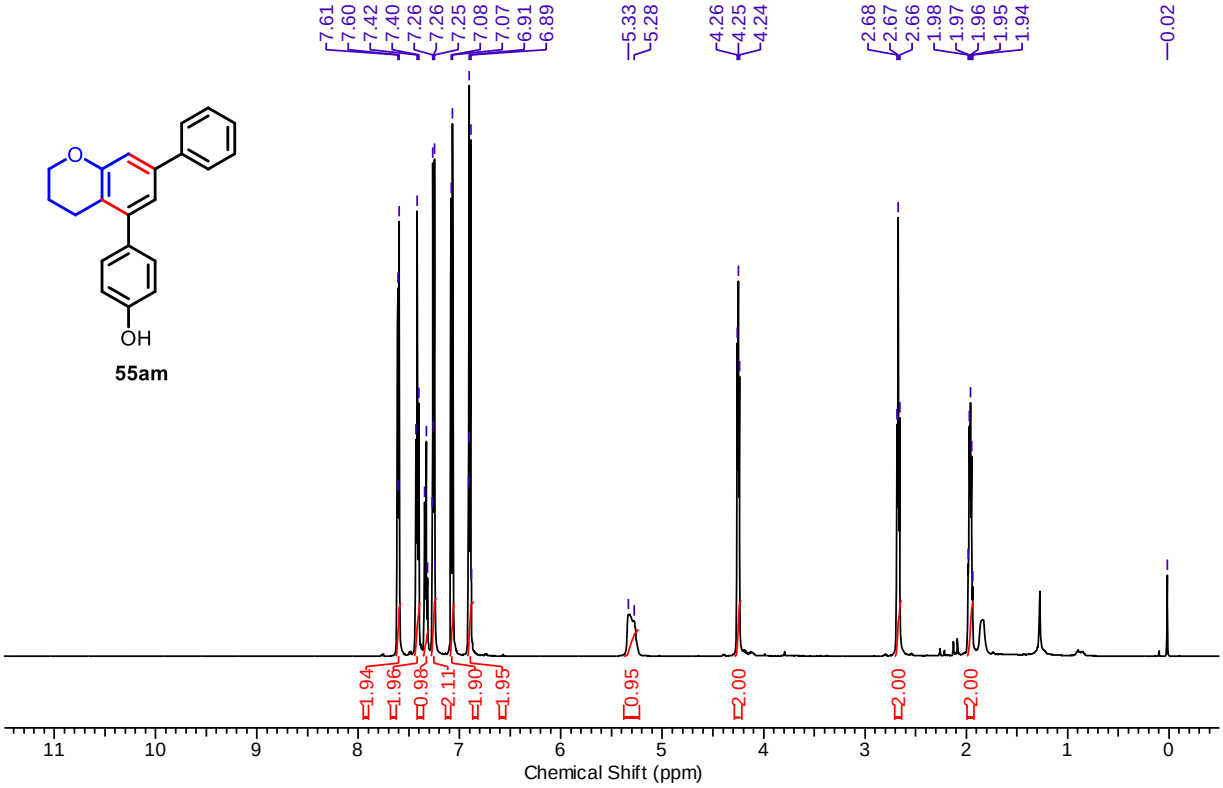
^{1}H NMR spectrum of compound 55al



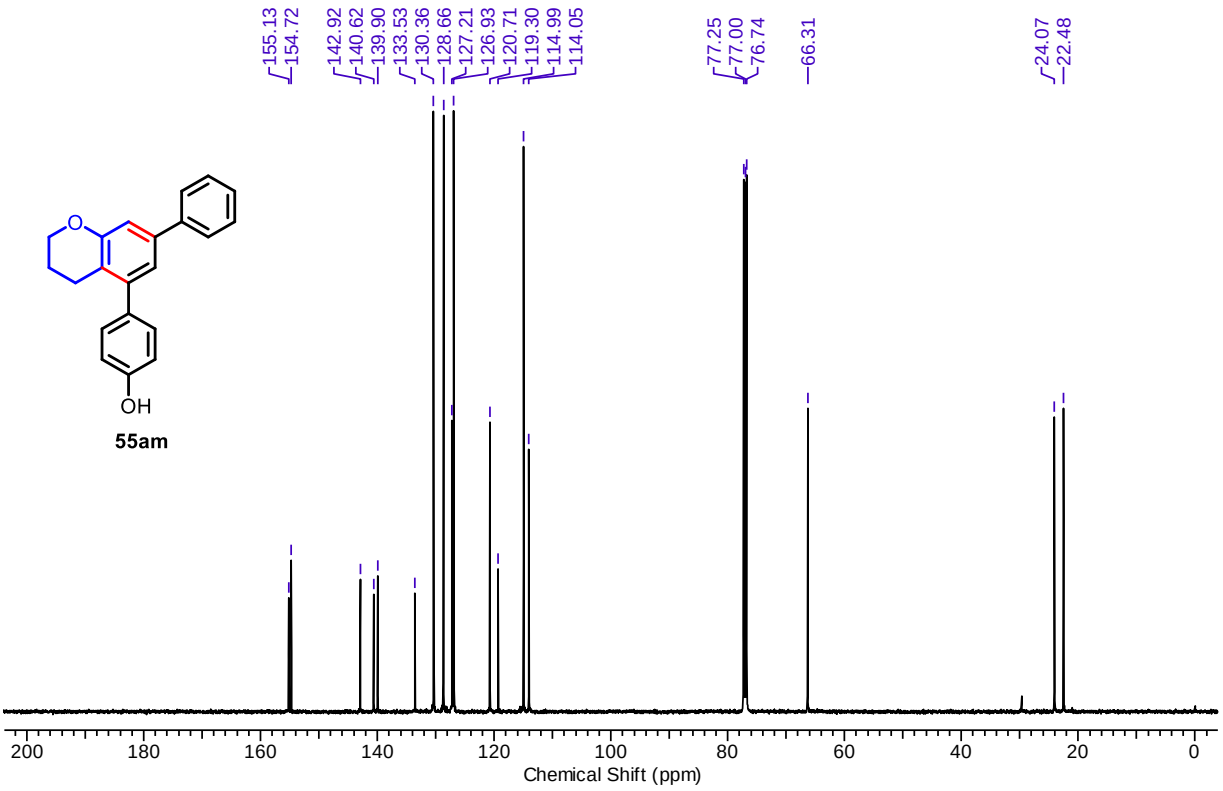
^{13}C NMR spectrum of compound 55al



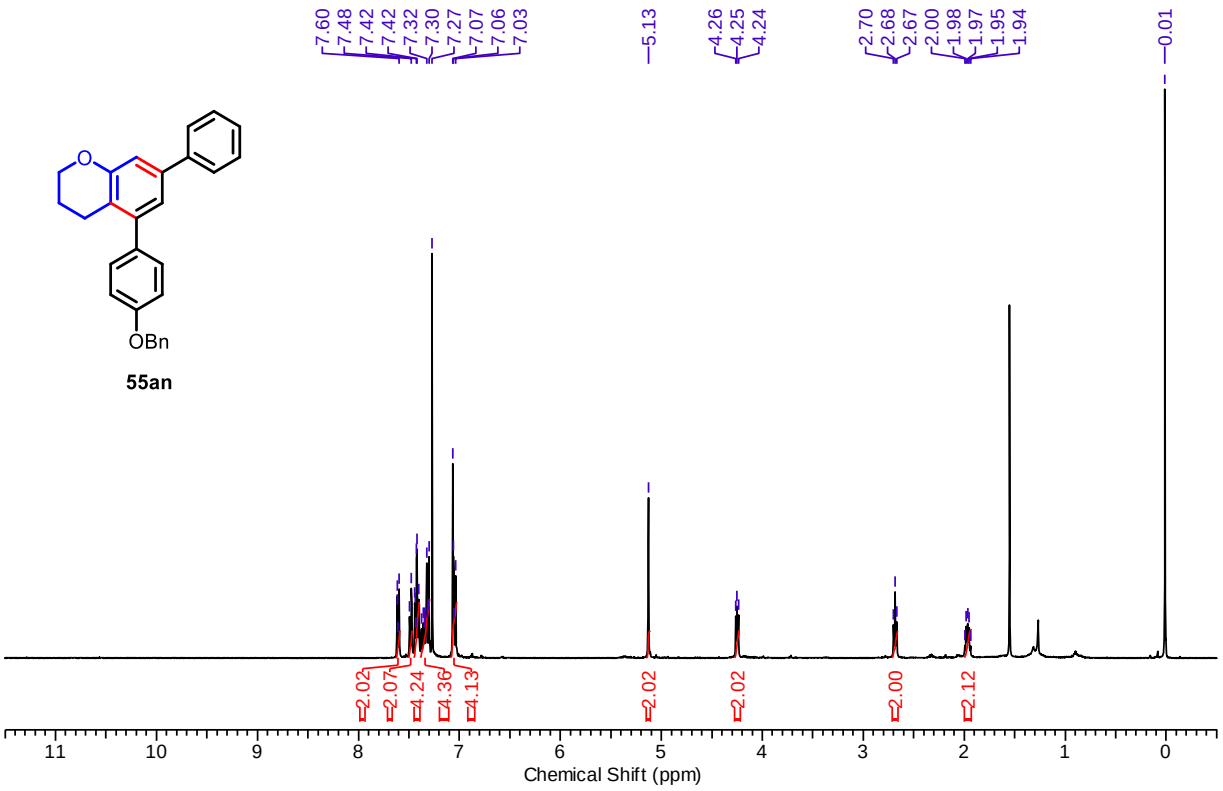
^{1}H NMR spectrum of compound 55am



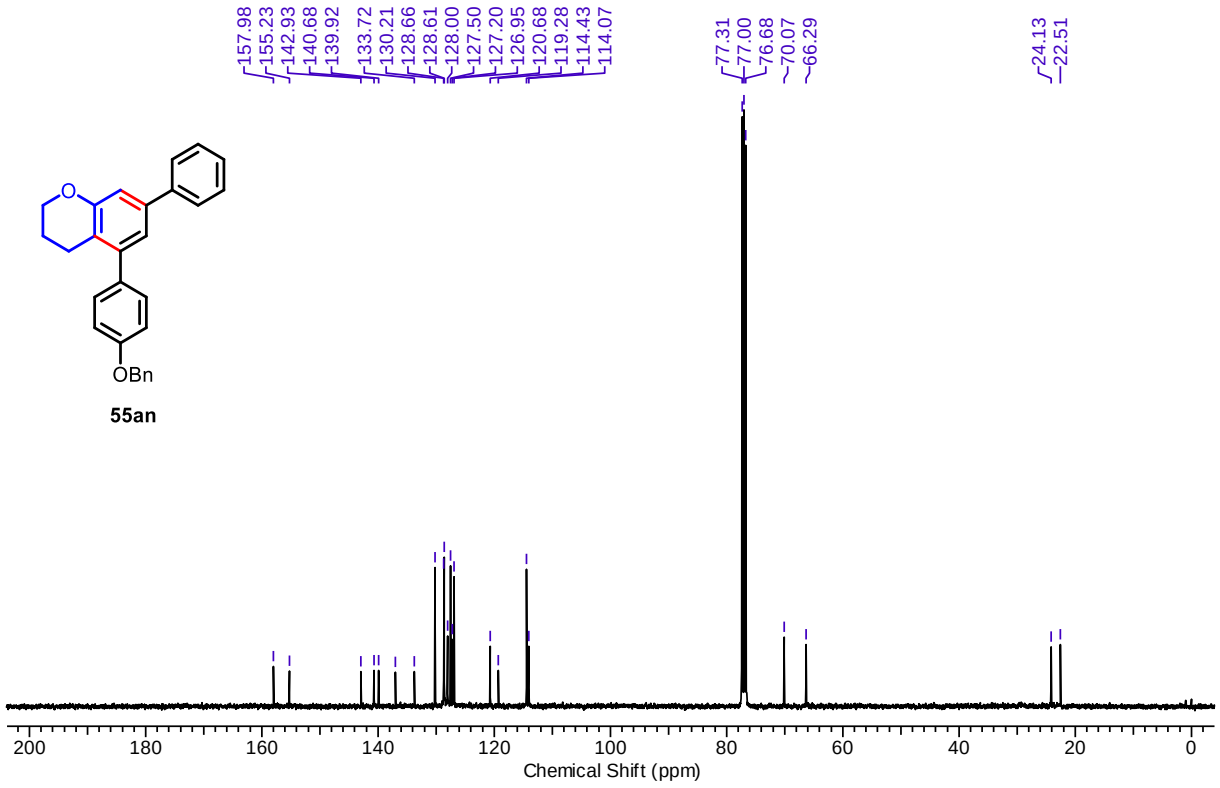
^{13}C NMR spectrum of compound 55am



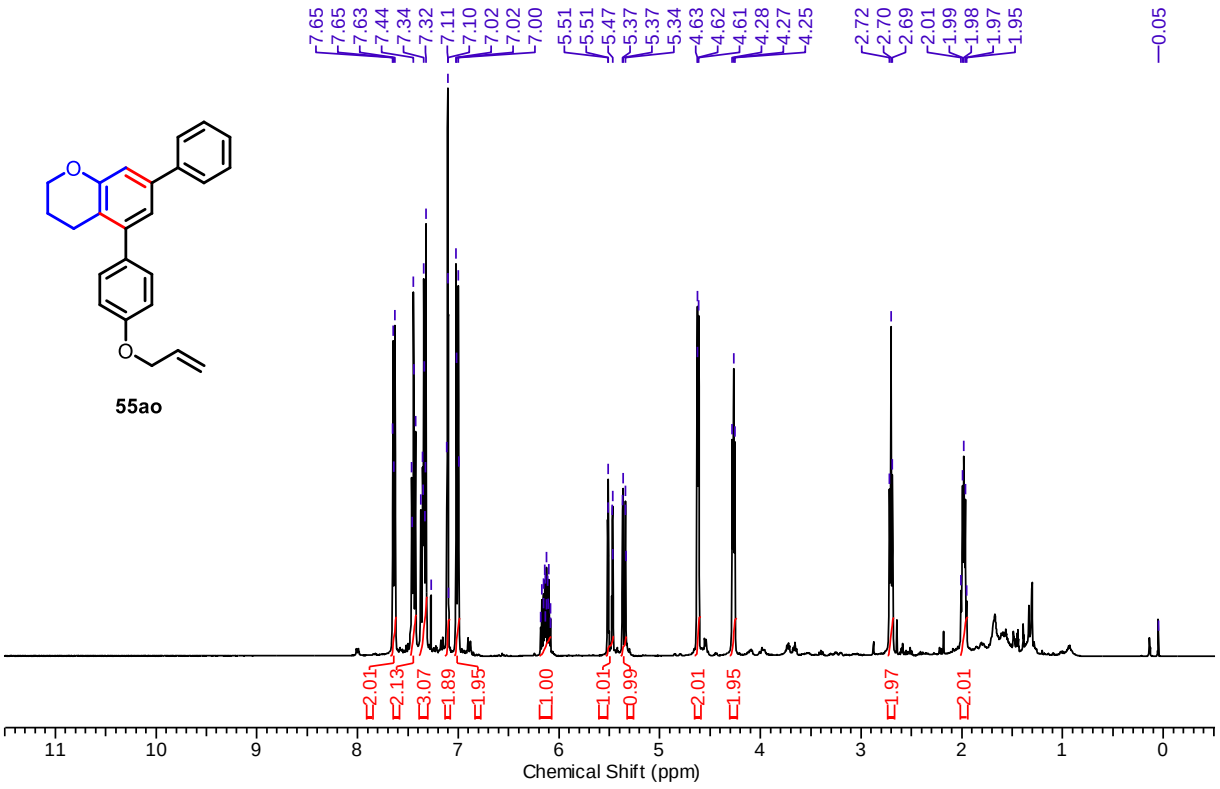
^{1}H NMR spectrum of compound 55an



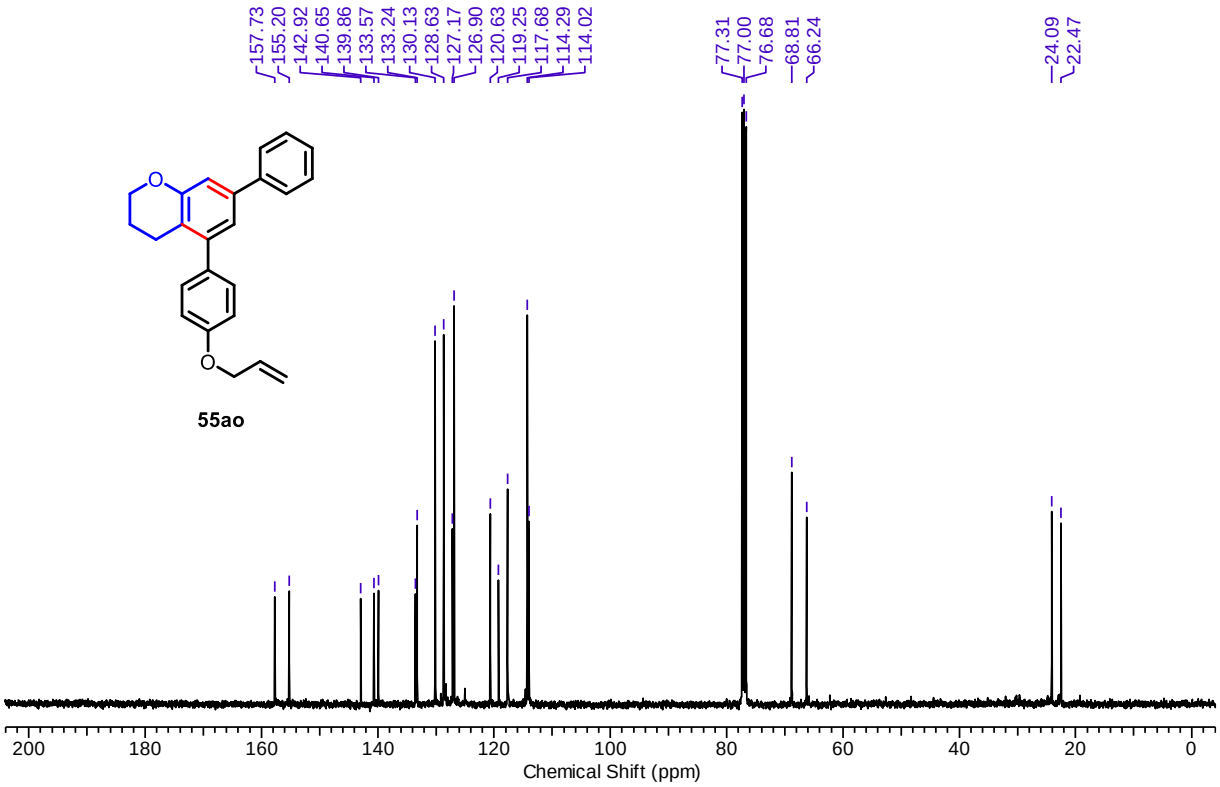
^{13}C NMR spectrum of compound 55an



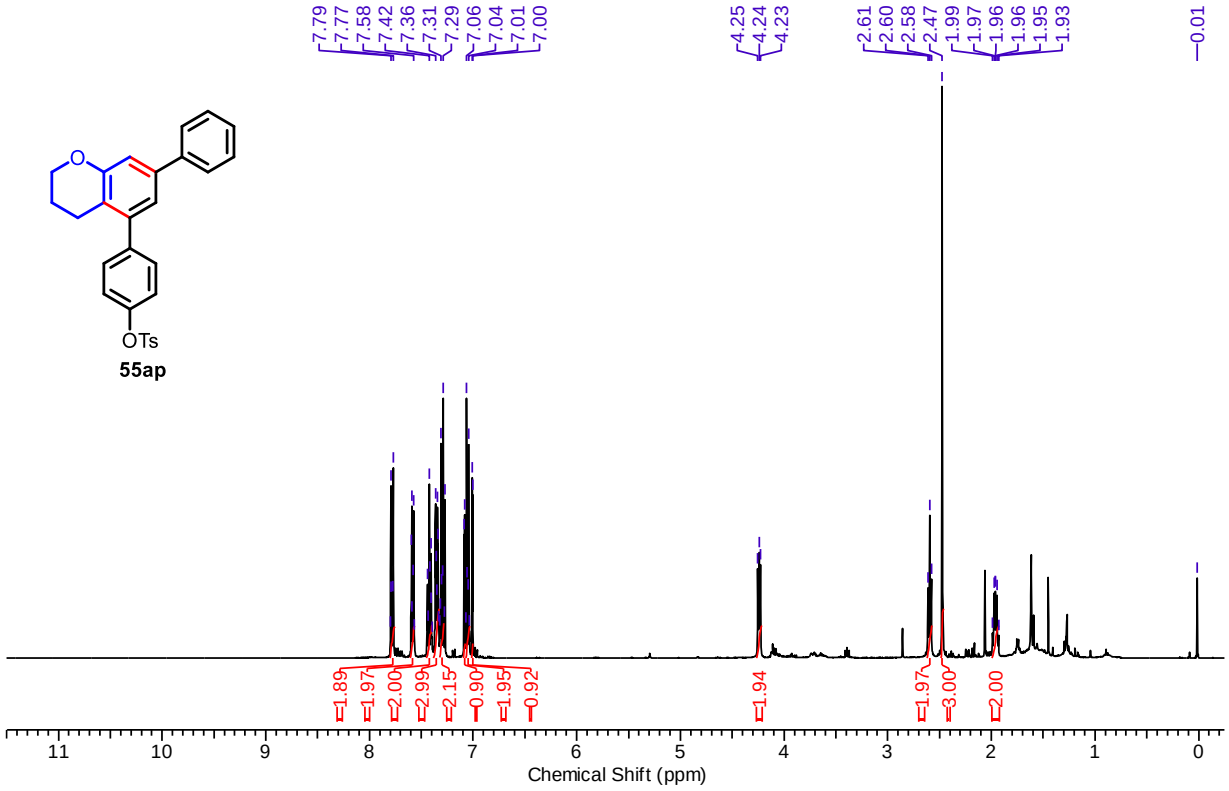
^{1}H NMR spectrum of compound 55ao



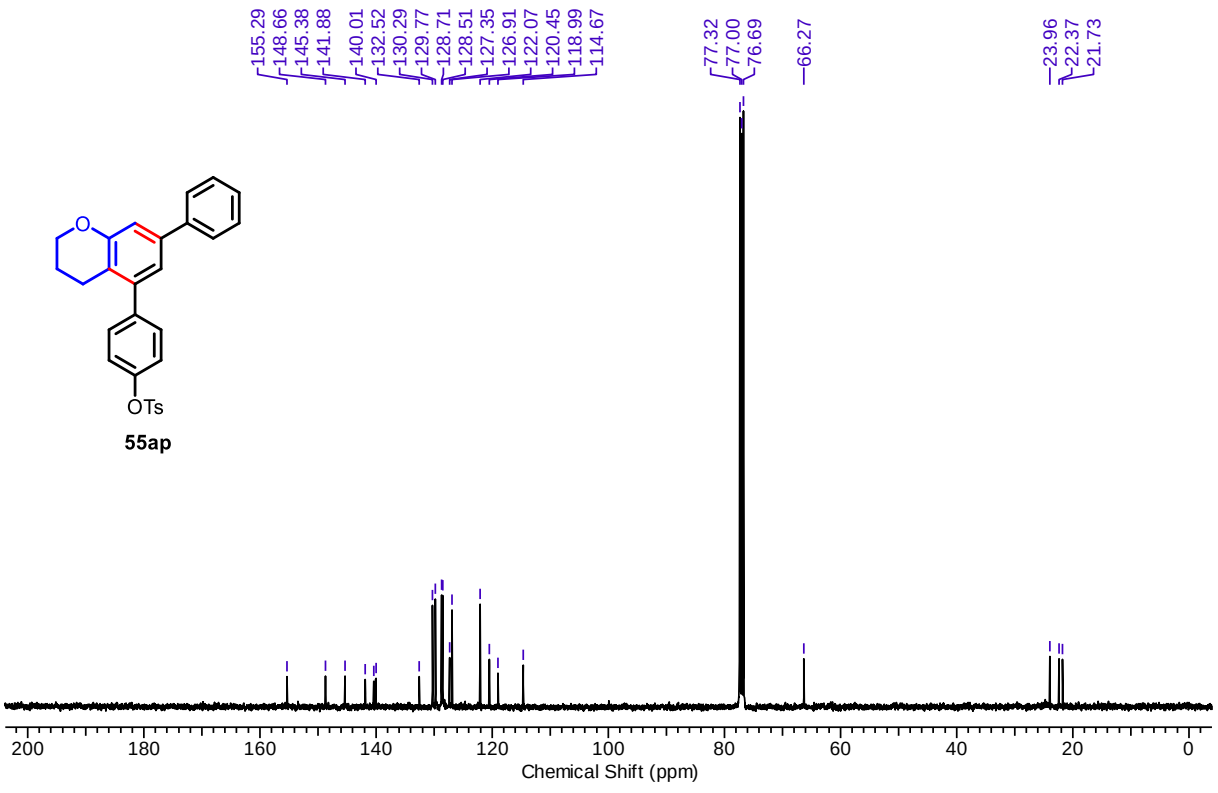
^{13}C NMR spectrum of compound 55ao



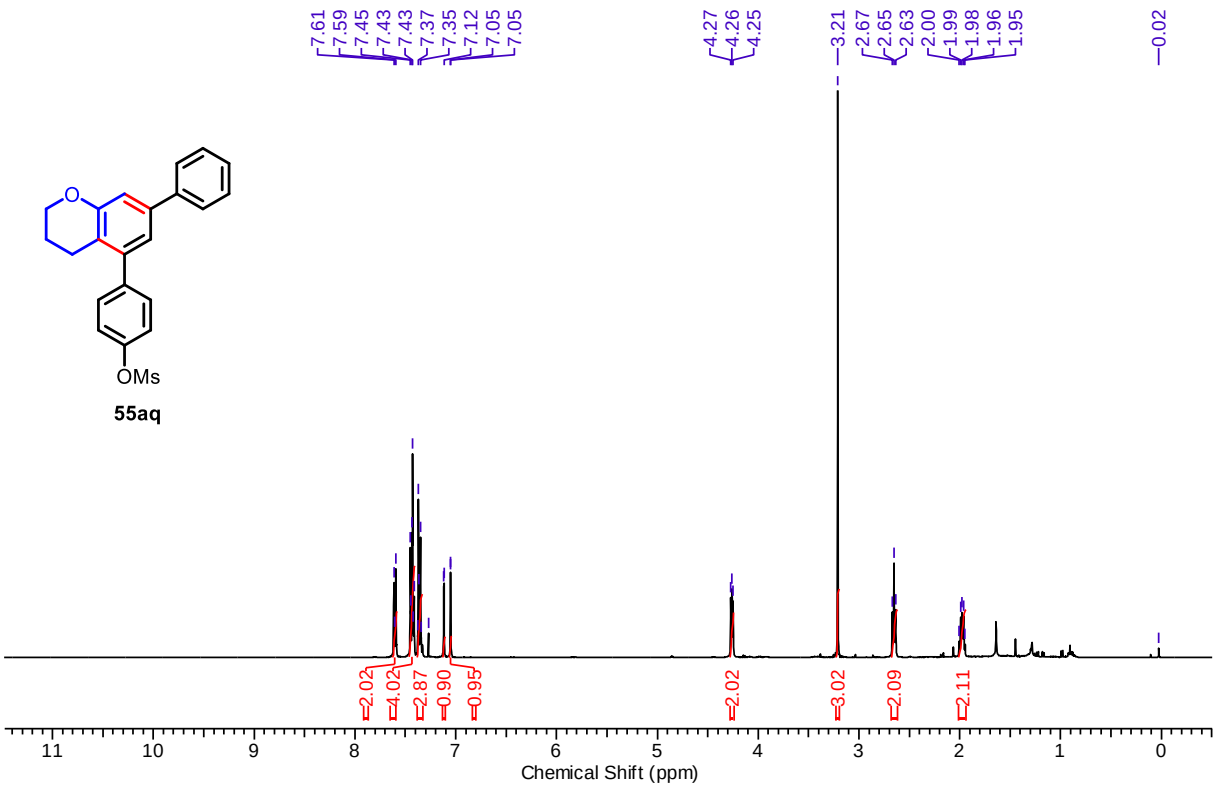
^{1}H NMR spectrum of compound 55ap



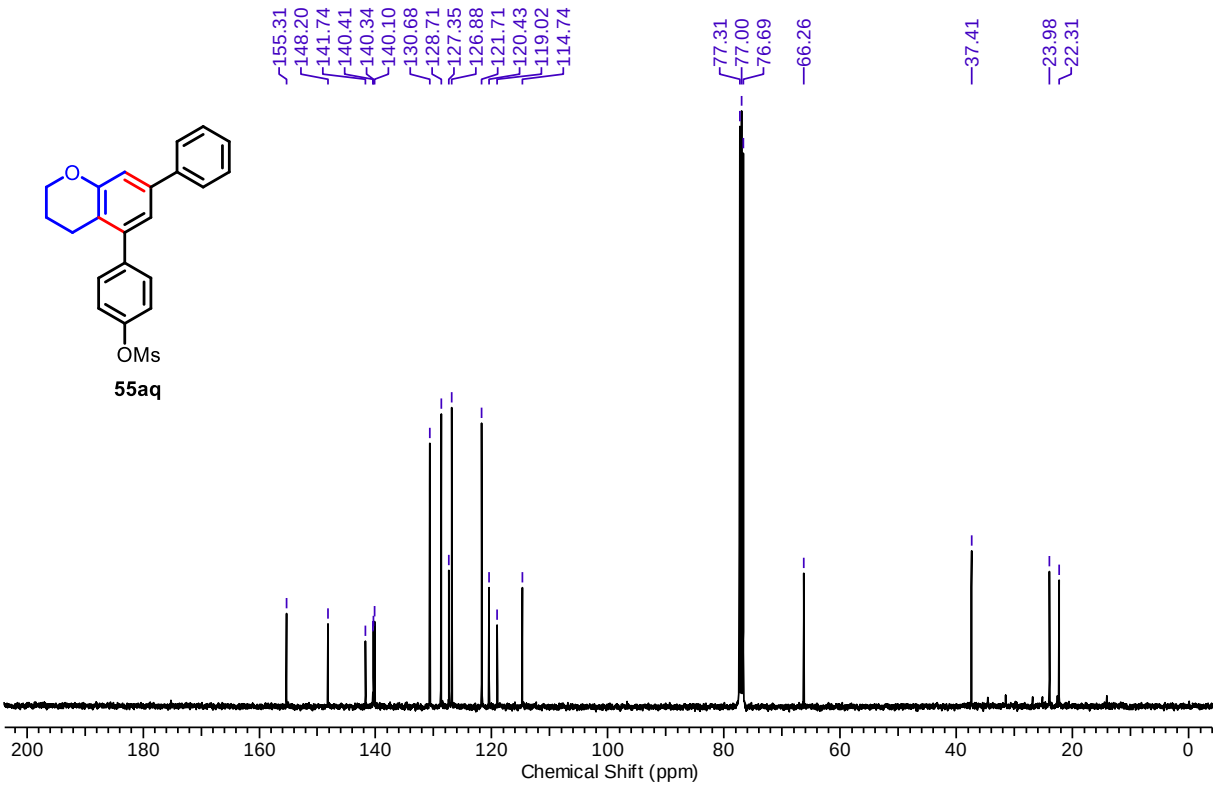
^{13}C NMR spectrum of compound 55ap



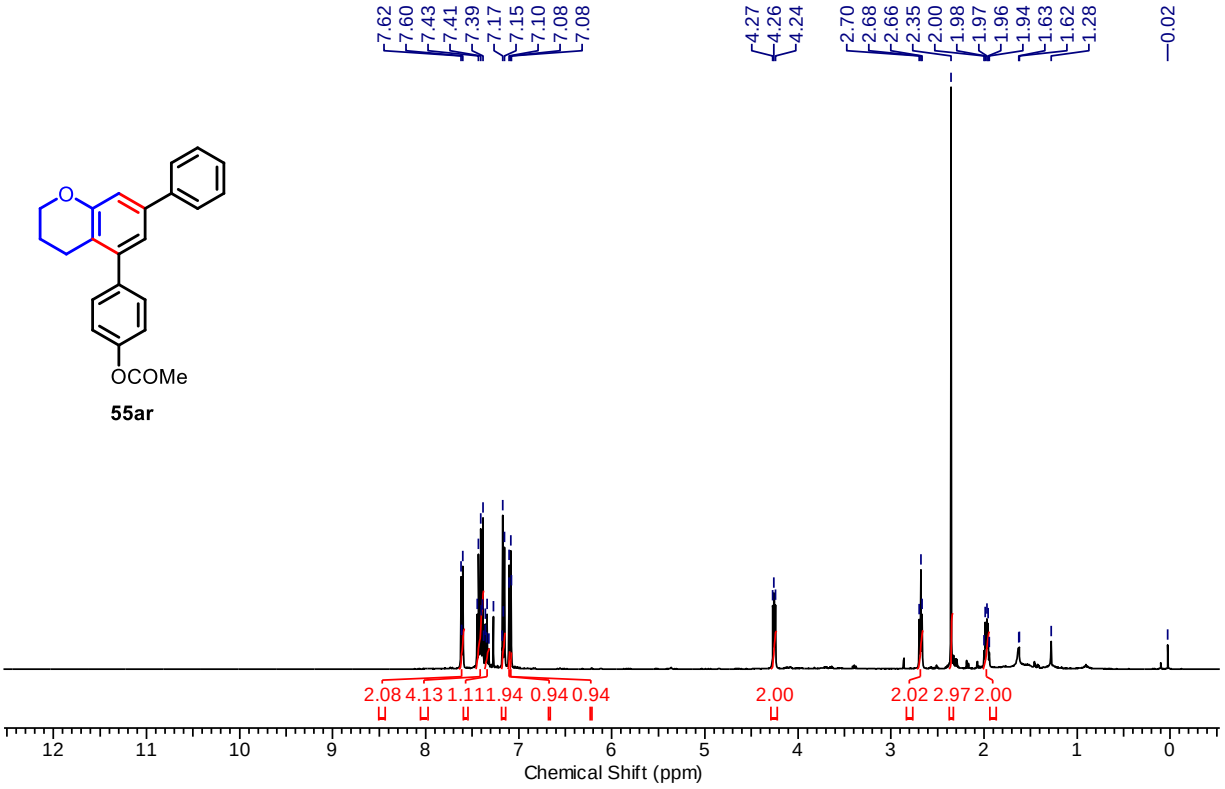
^{1}H NMR spectrum of compound 55aq



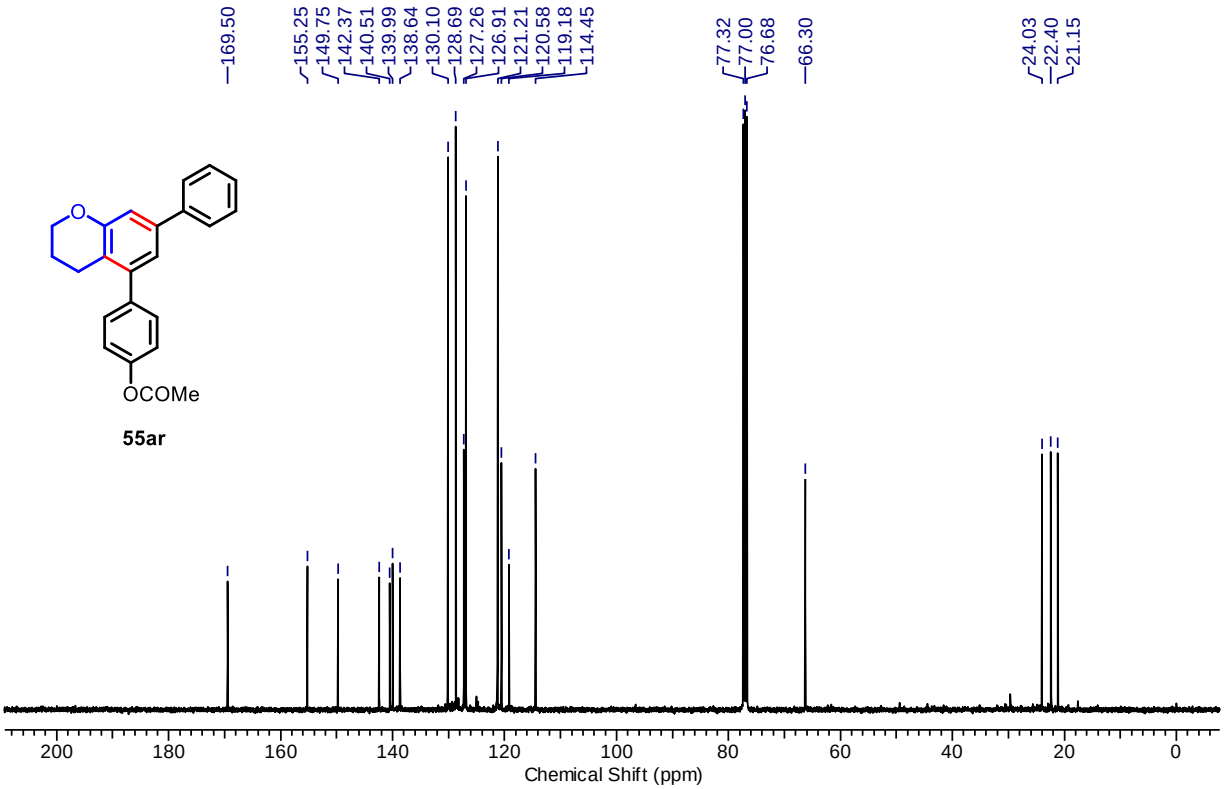
^{13}C NMR spectrum of compound 55aq



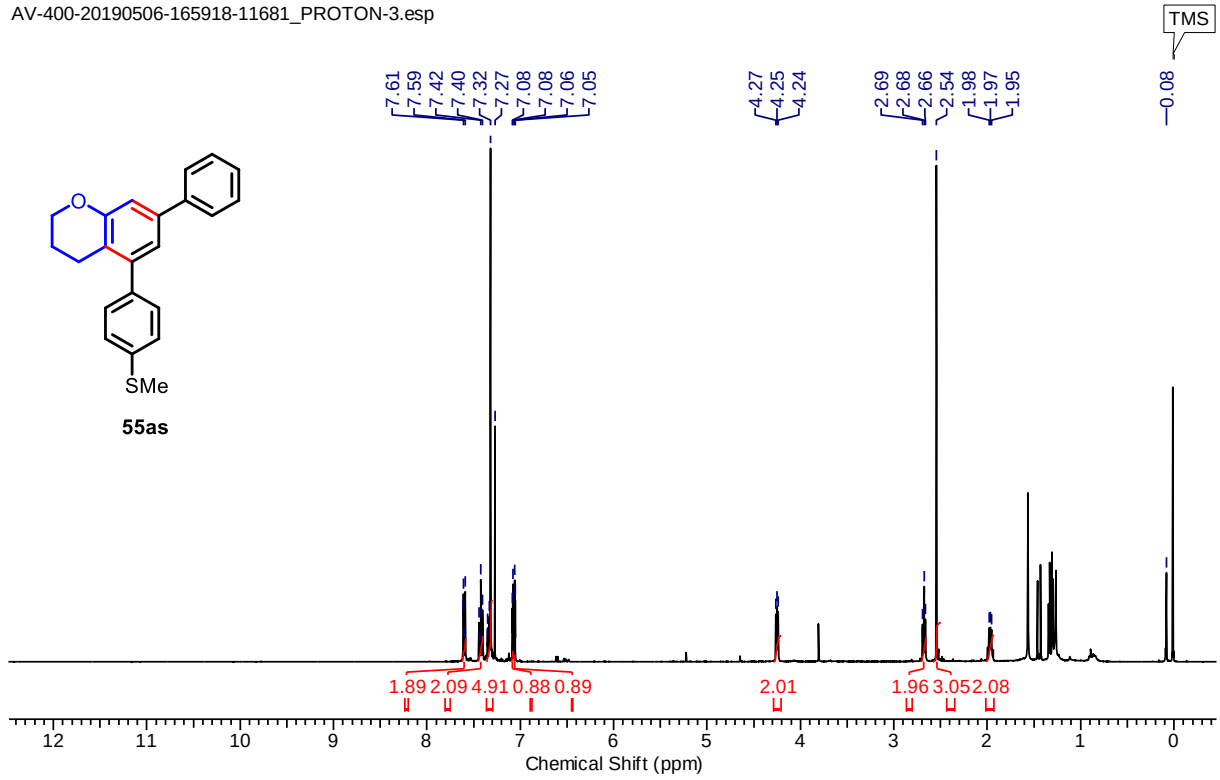
^{1}H NMR spectrum of compound 55ar



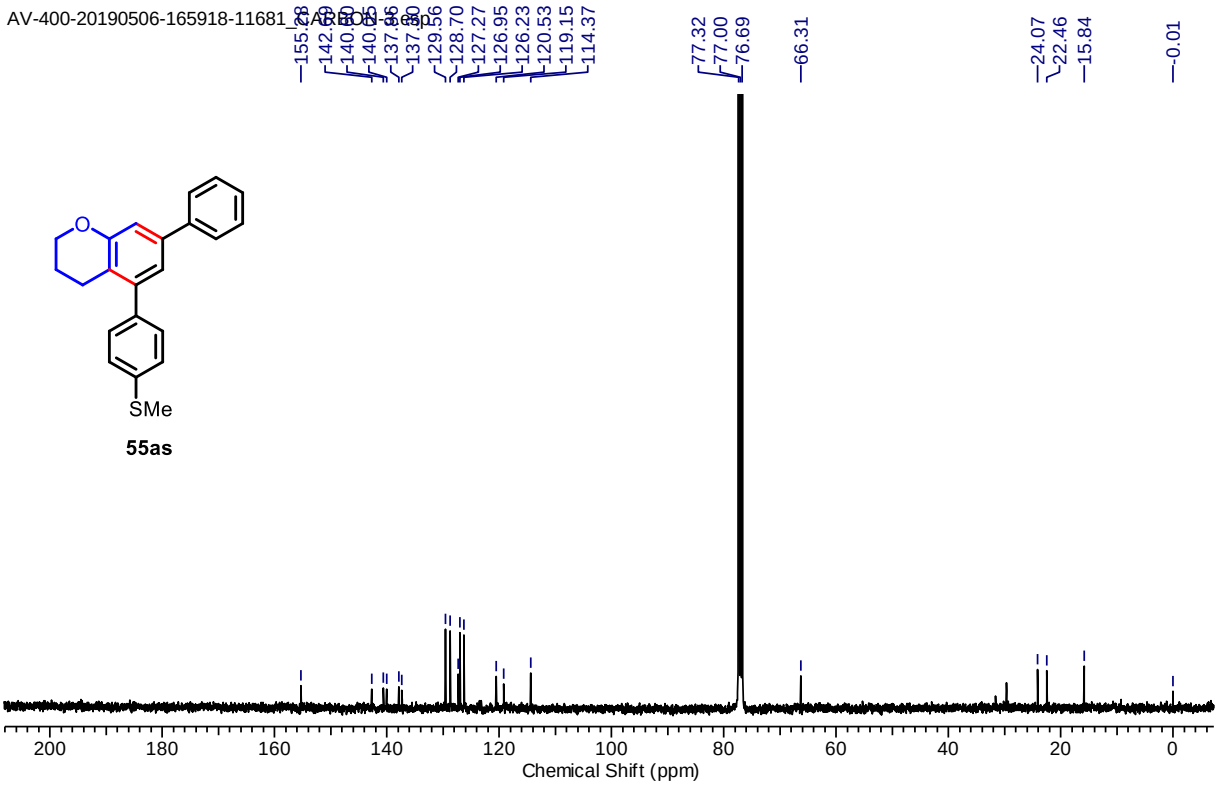
^{13}C NMR spectrum of compound 55ar



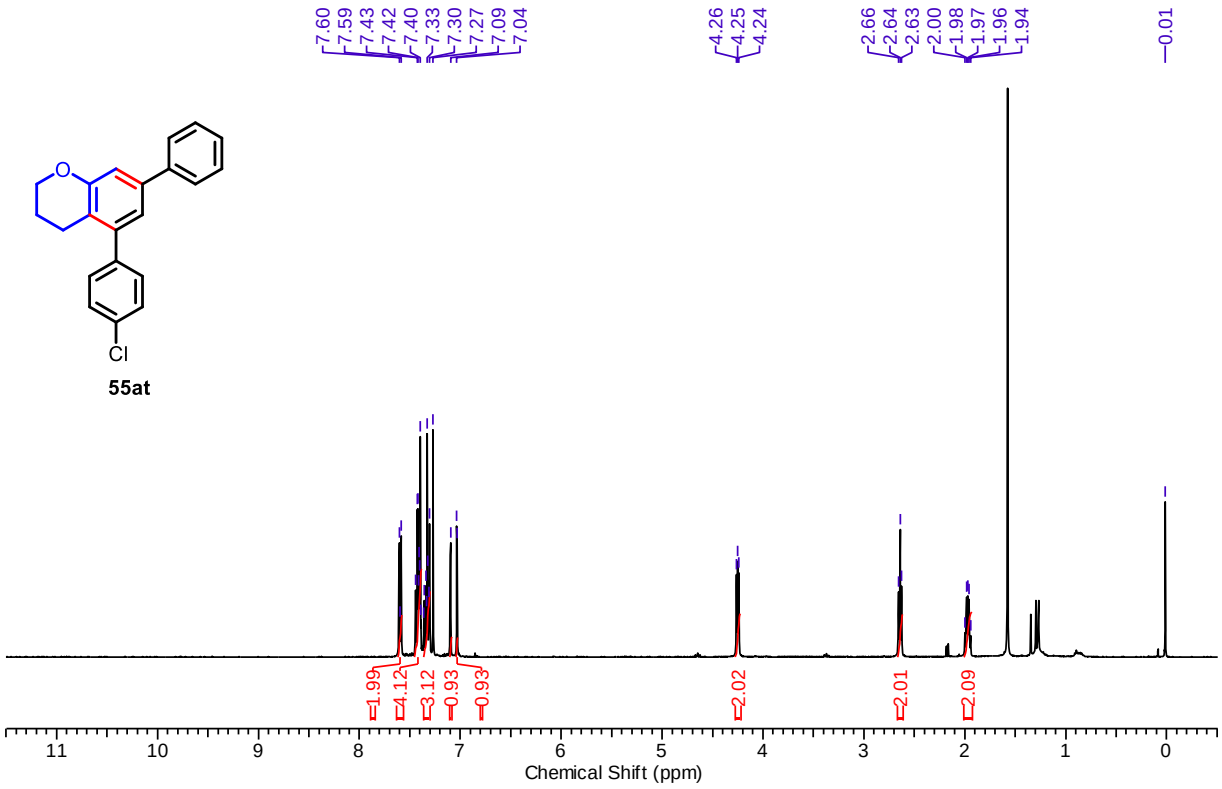
^{1}H NMR spectrum of compound 55as



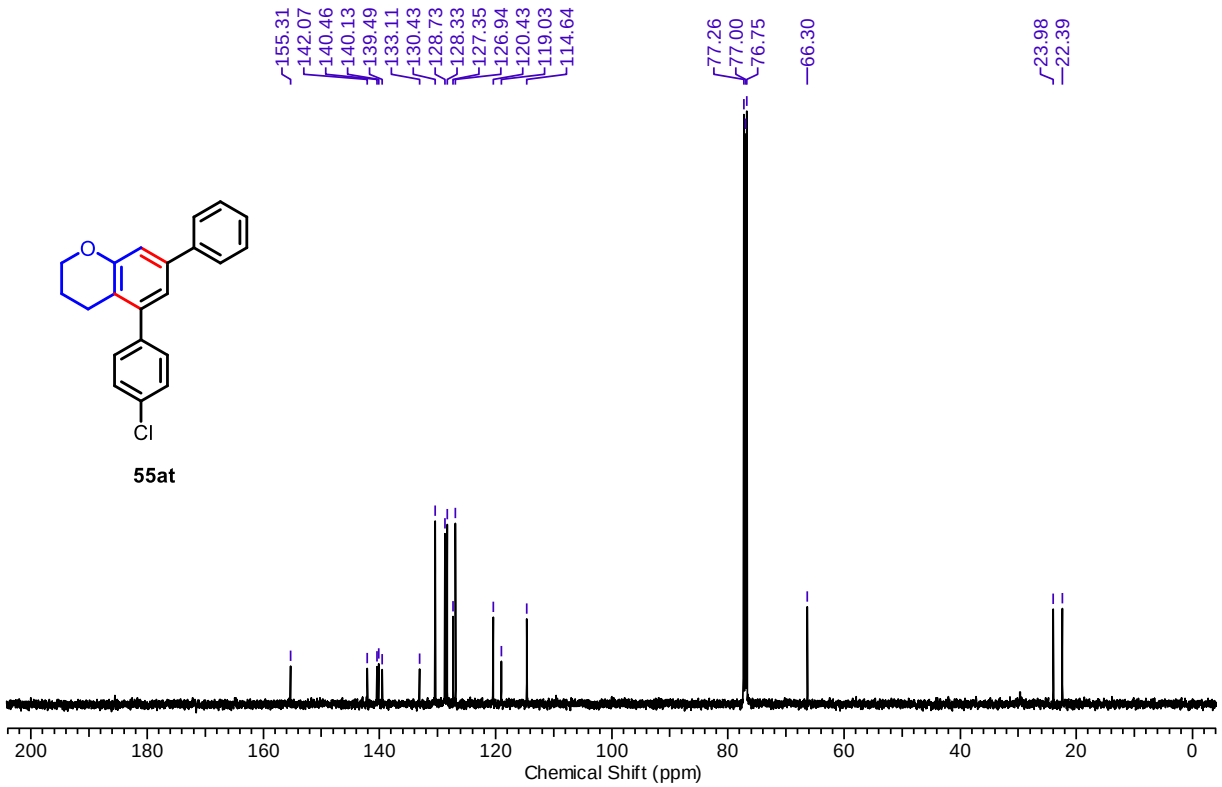
^{13}C NMR spectrum of compound 55as



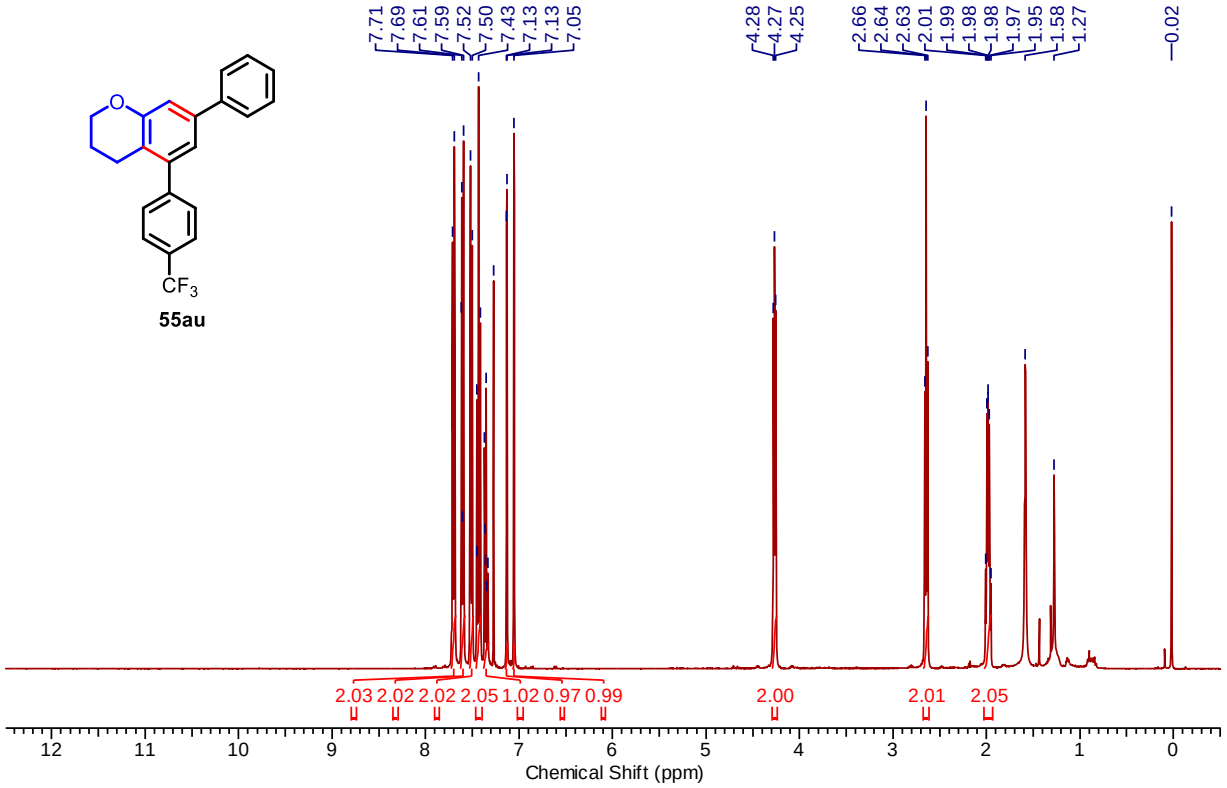
^{1}H NMR spectrum of compound 55at



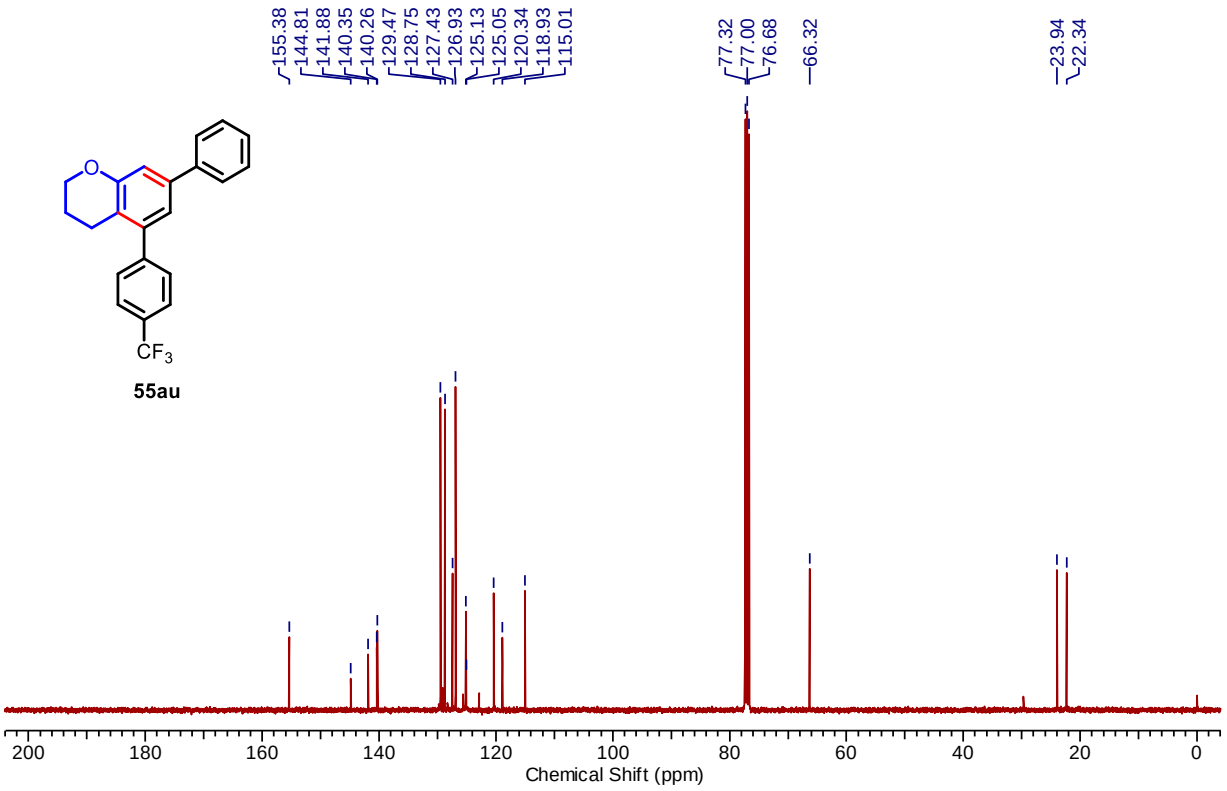
^{13}C NMR spectrum of compound 55at



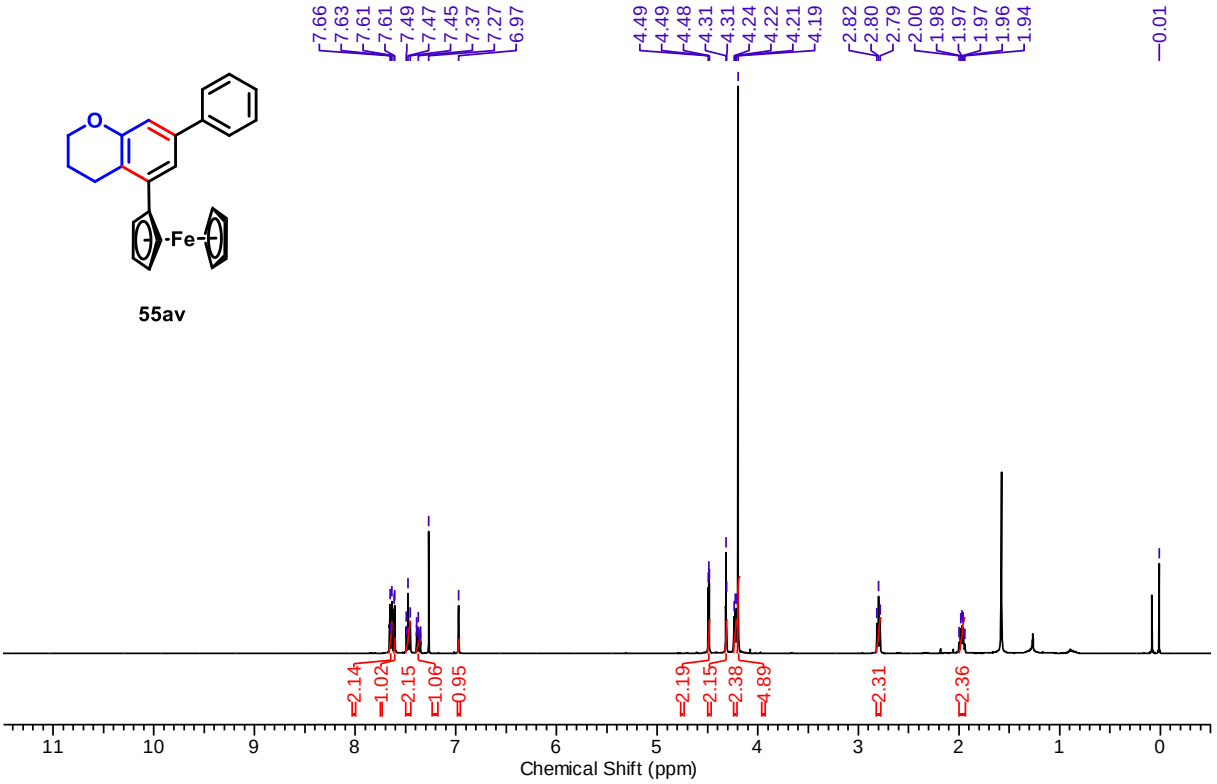
^{1}H NMR spectrum of compound 55au



^{1}H NMR spectrum of compound 55au

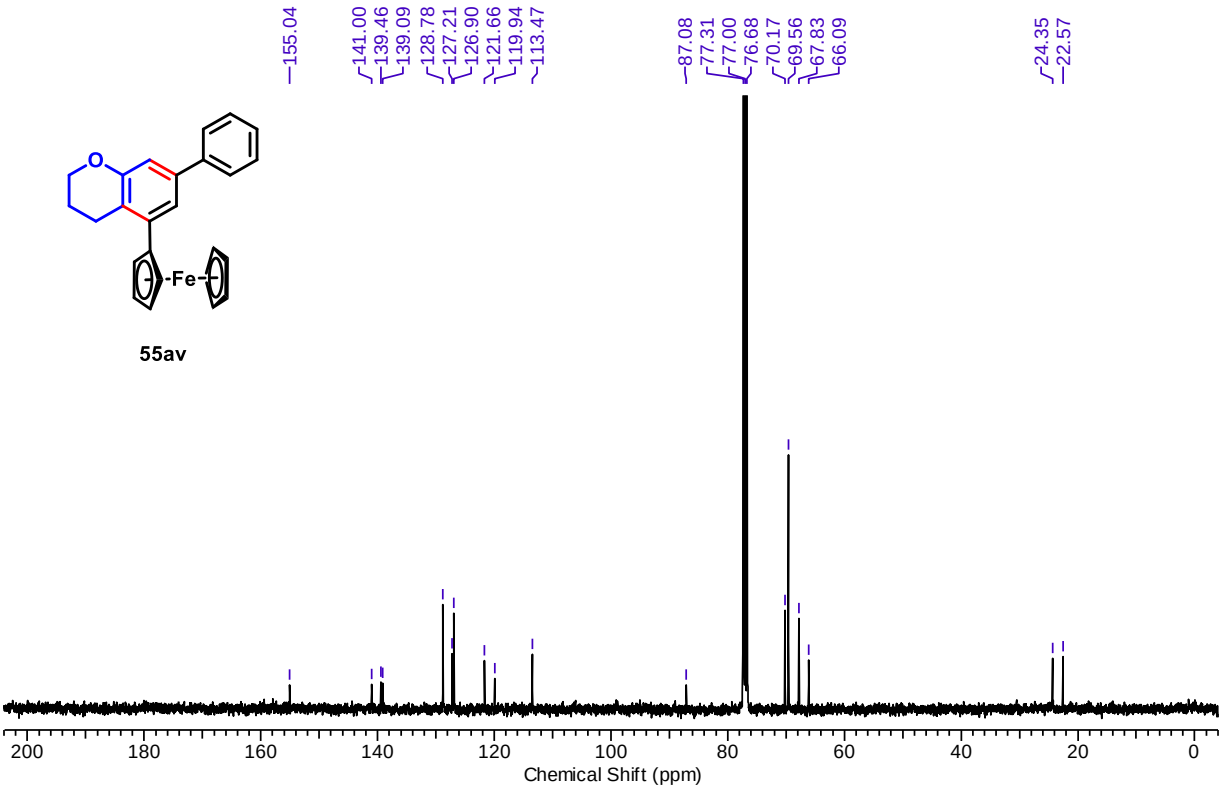


^{1}H NMR spectrum of compound 55av



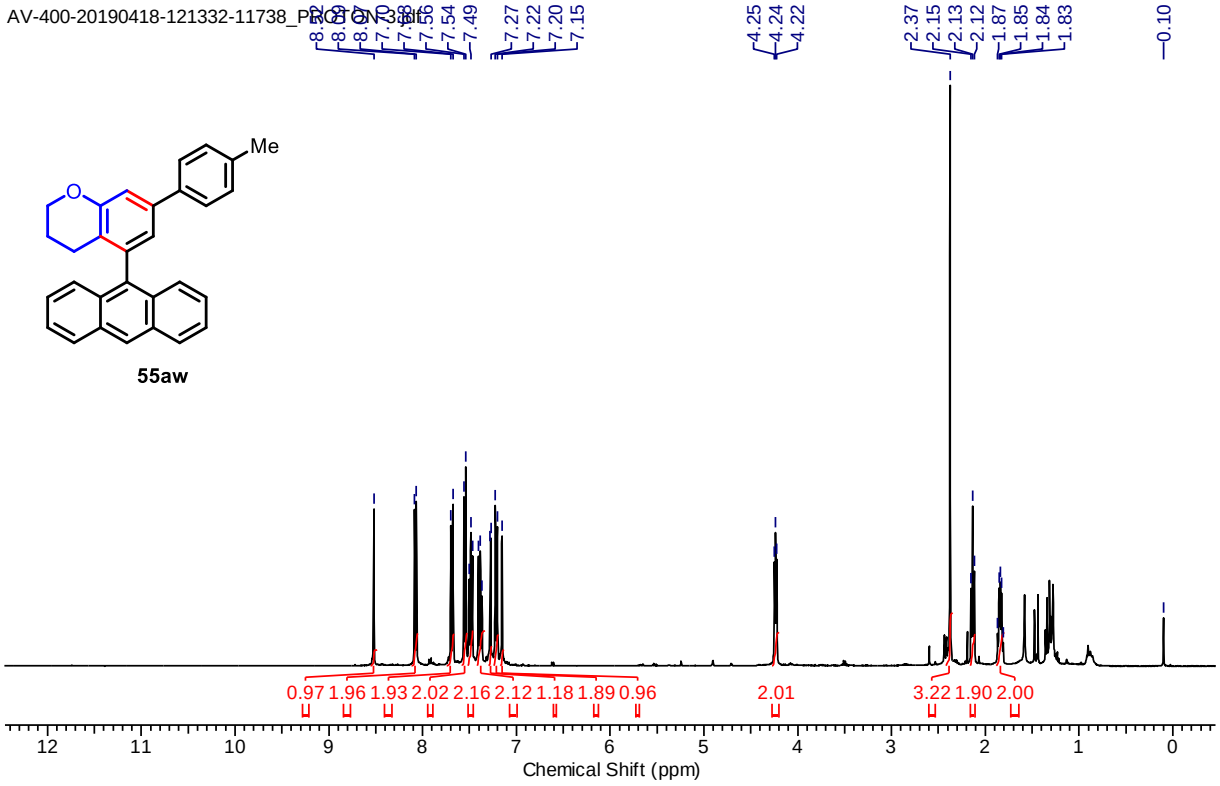
55av

^{1}H NMR spectrum of compound 55av

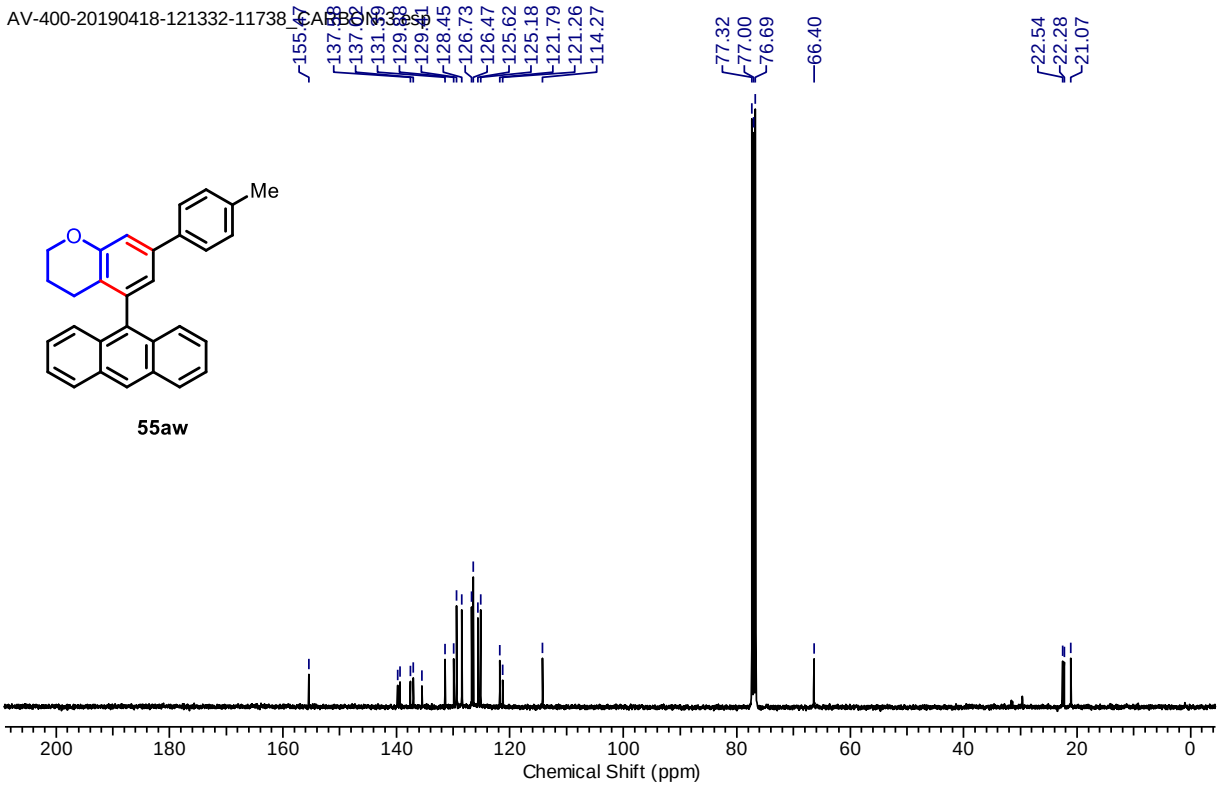


55av

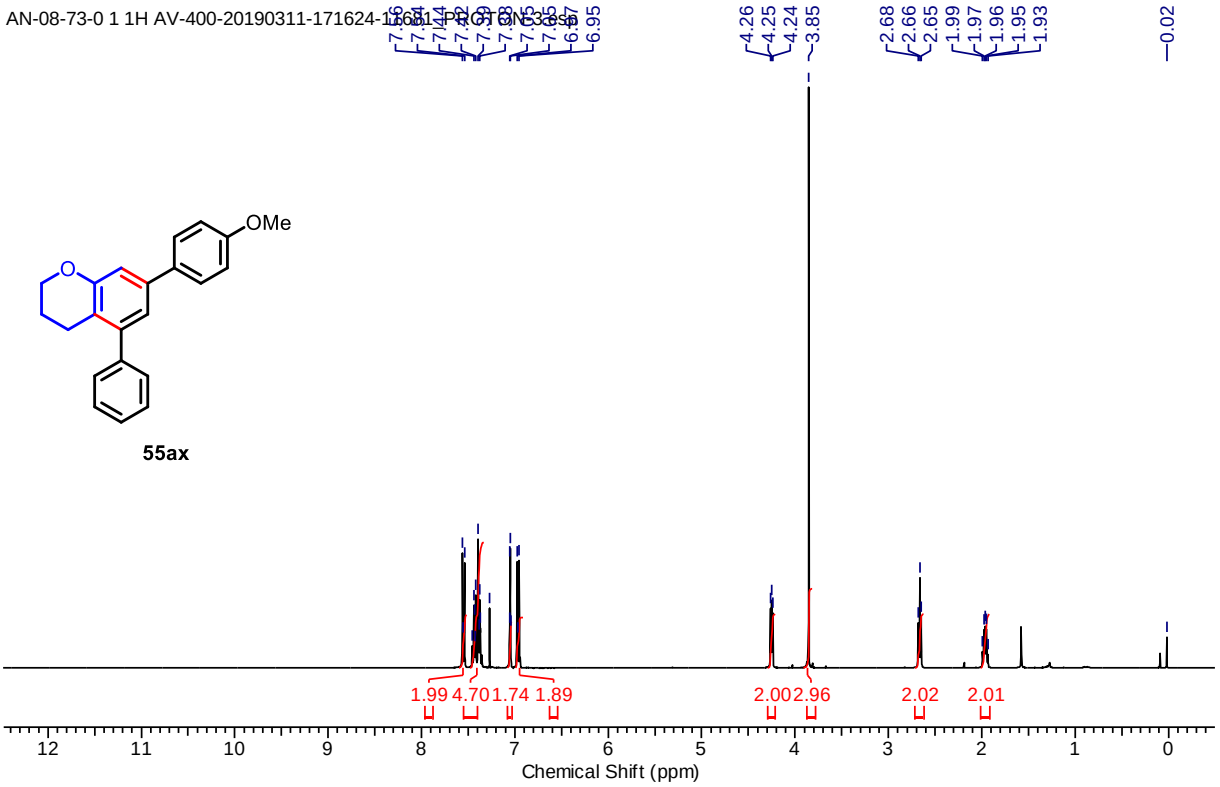
^{1}H NMR spectrum of compound 55aw



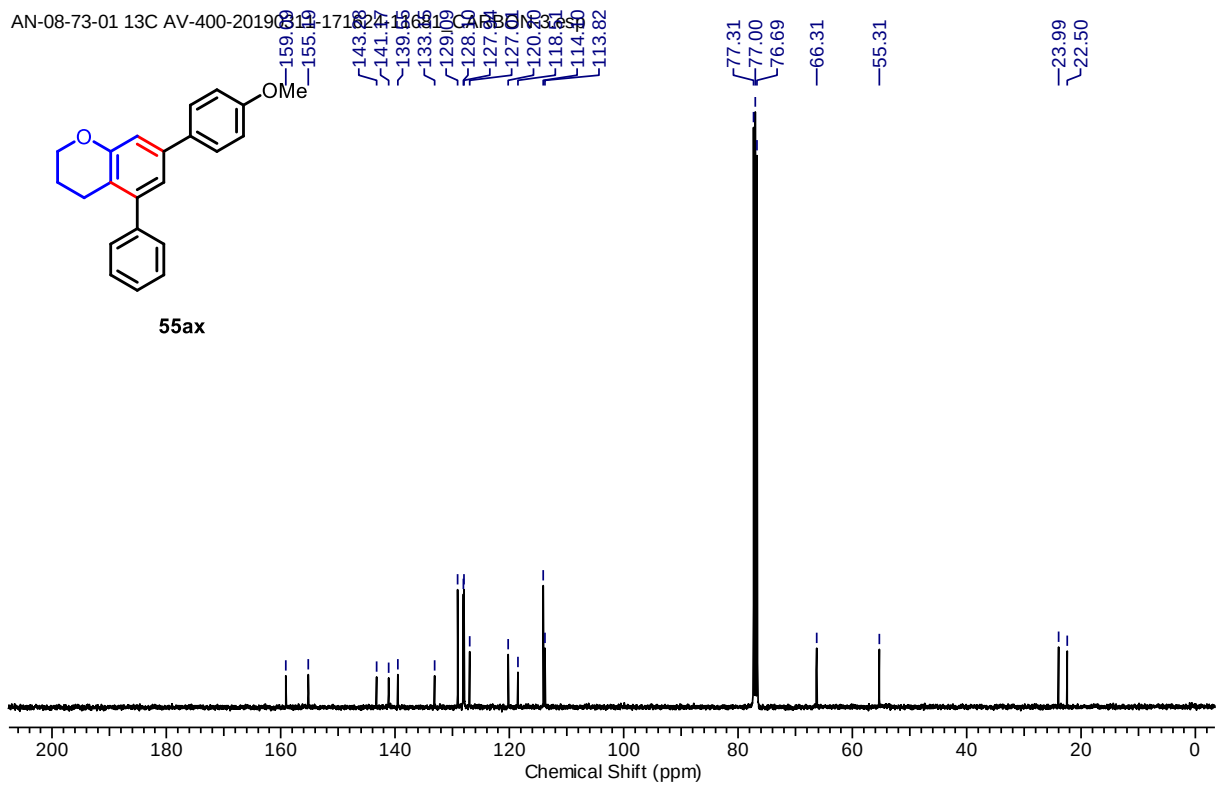
^{13}C NMR spectrum of compound 55aw



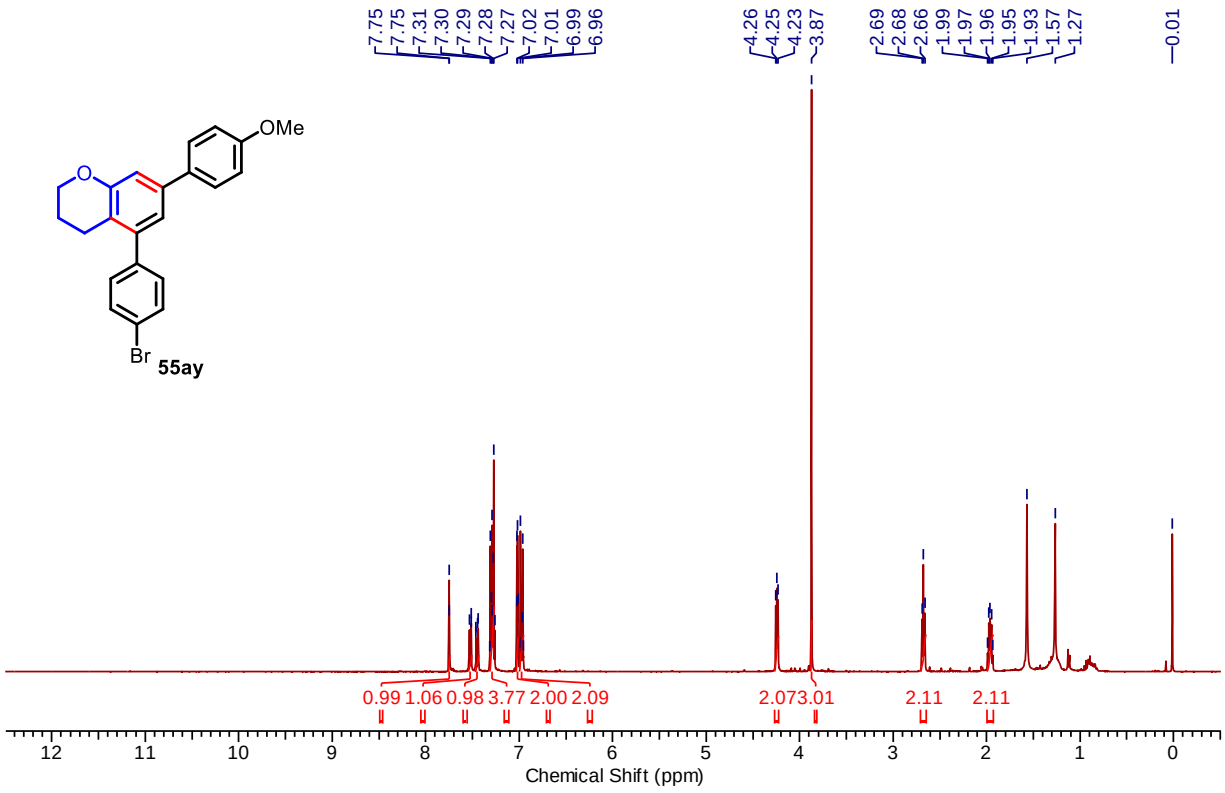
^{1}H NMR spectrum of compound 55ax



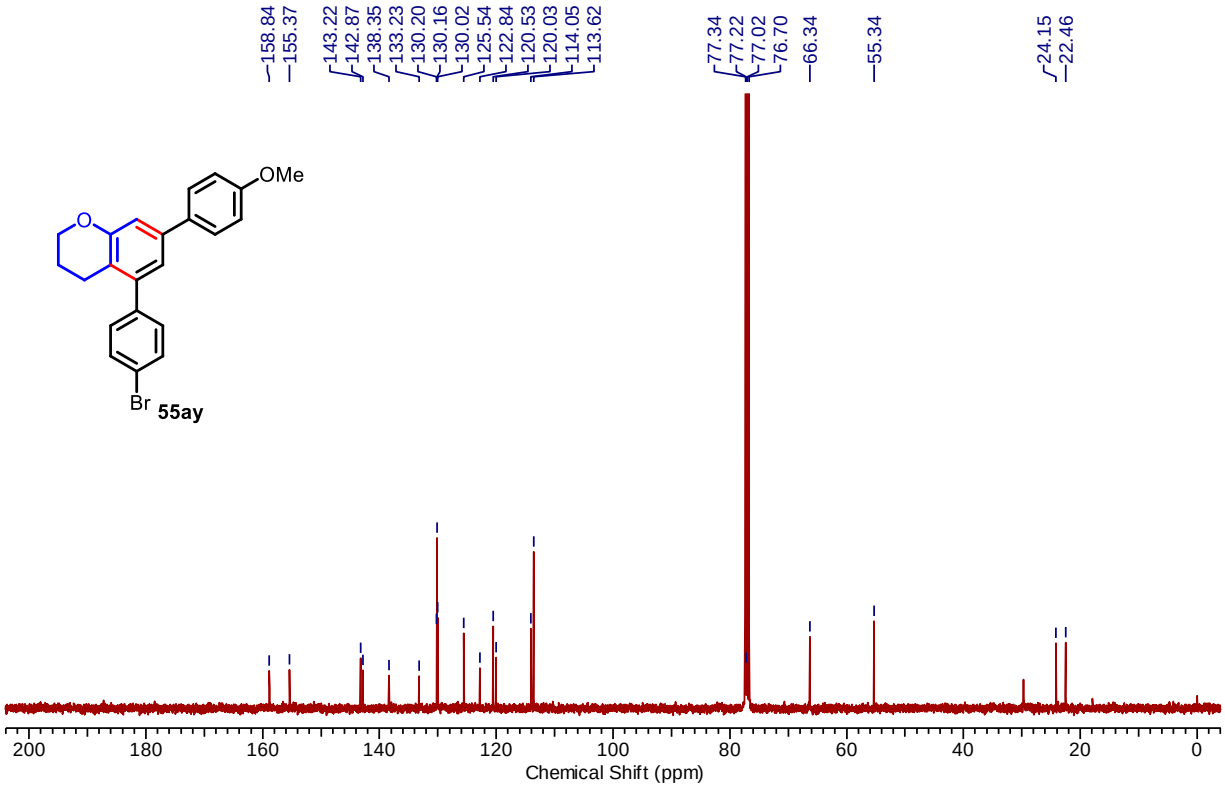
^{13}C NMR spectrum of compound 55ax



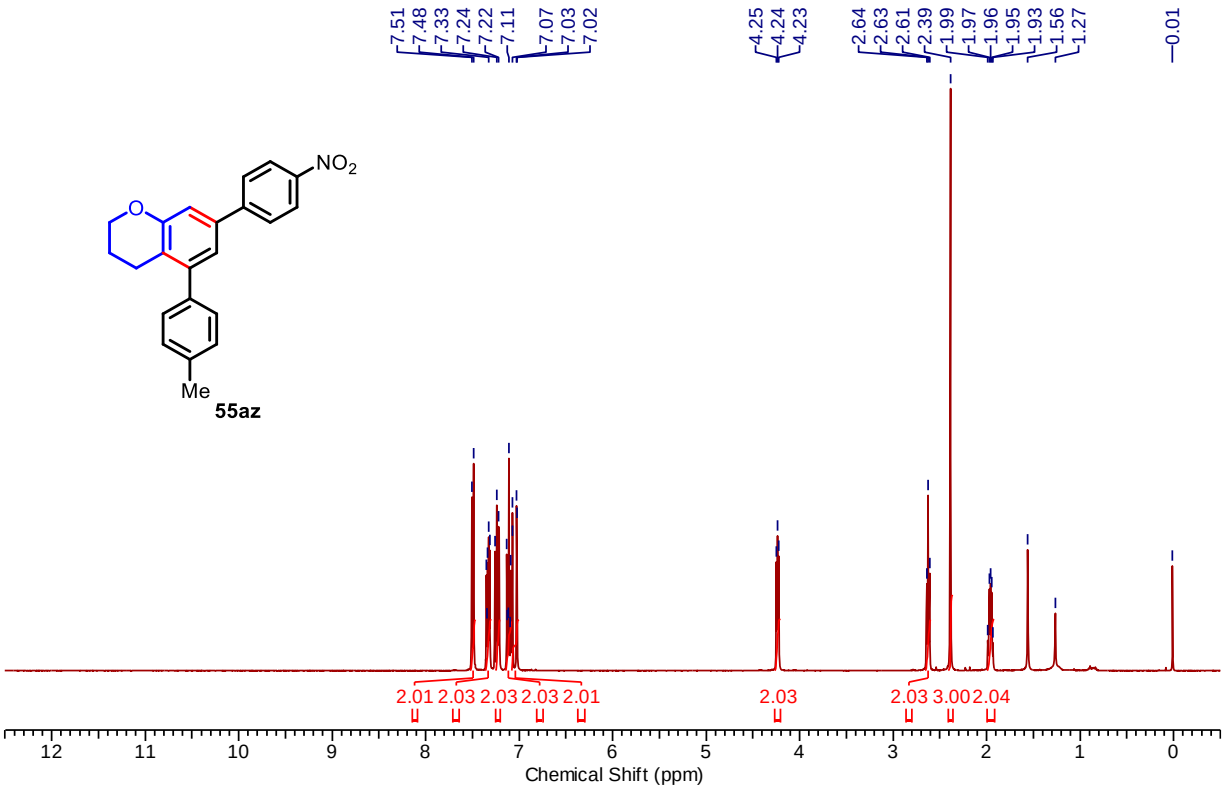
^{1}H NMR spectrum of compound 55ay



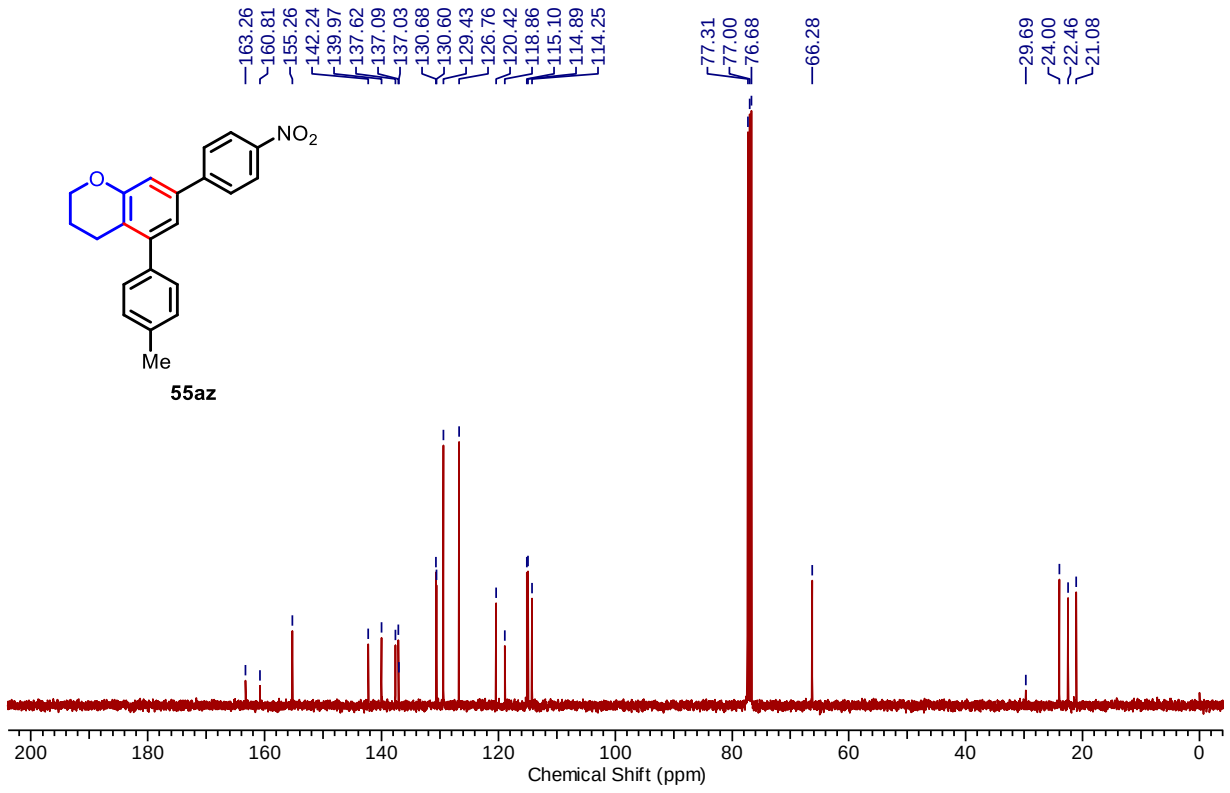
^{13}C NMR spectrum of compound 55ay

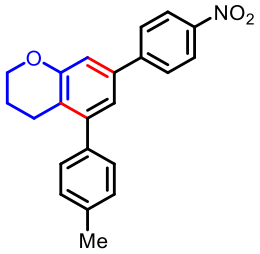


^{1}H NMR spectrum of compound 55az



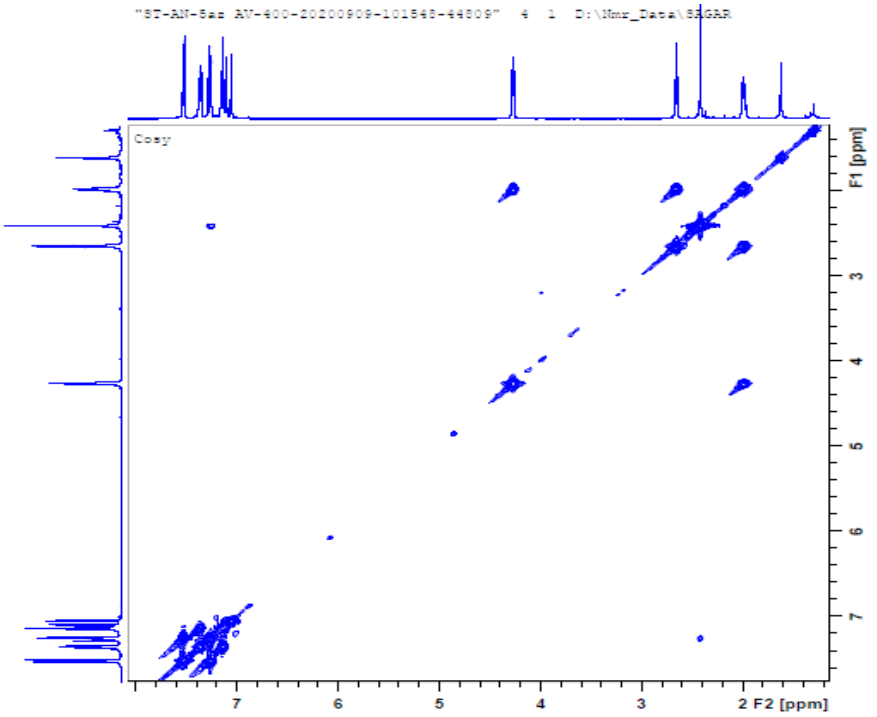
^{13}C NMR spectrum of compound 55az



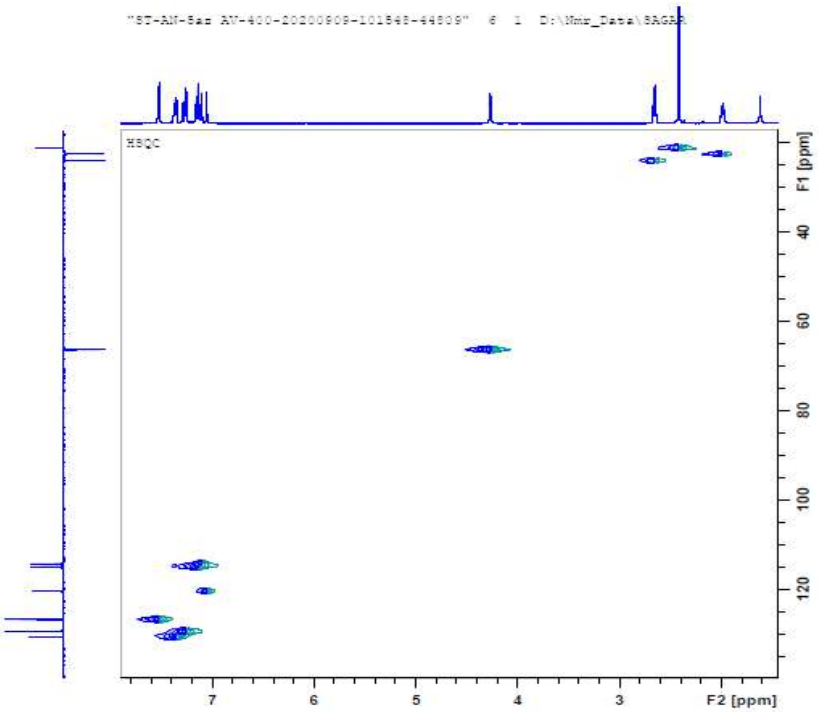


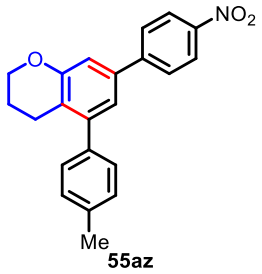
55az

COSY spectrum of compound 55az



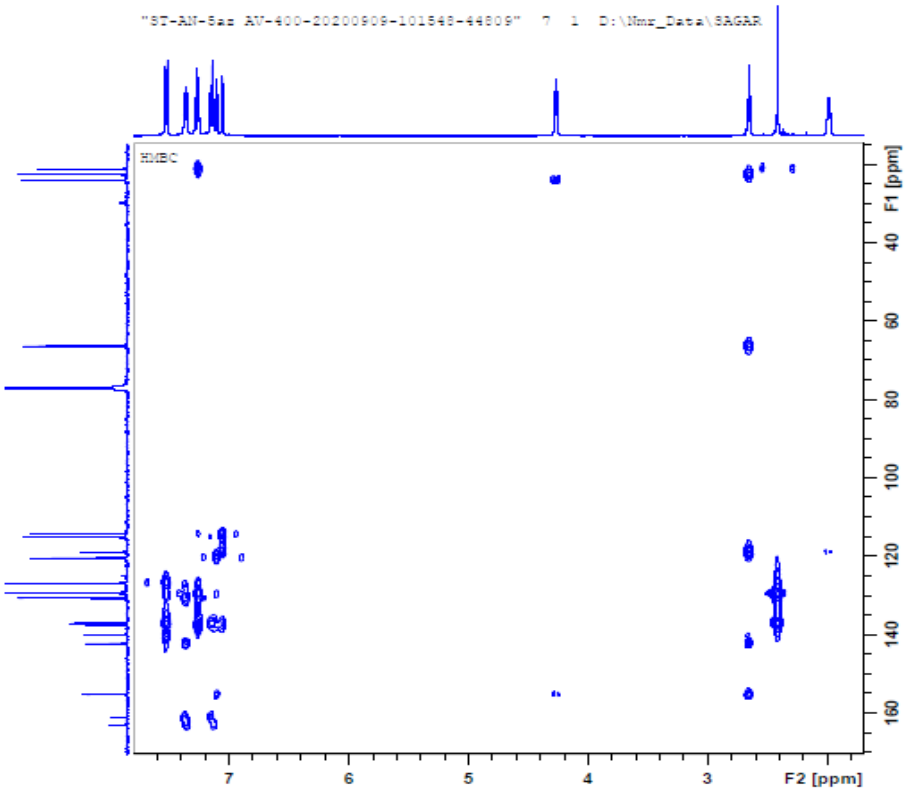
HSQC spectrum of compound 5az



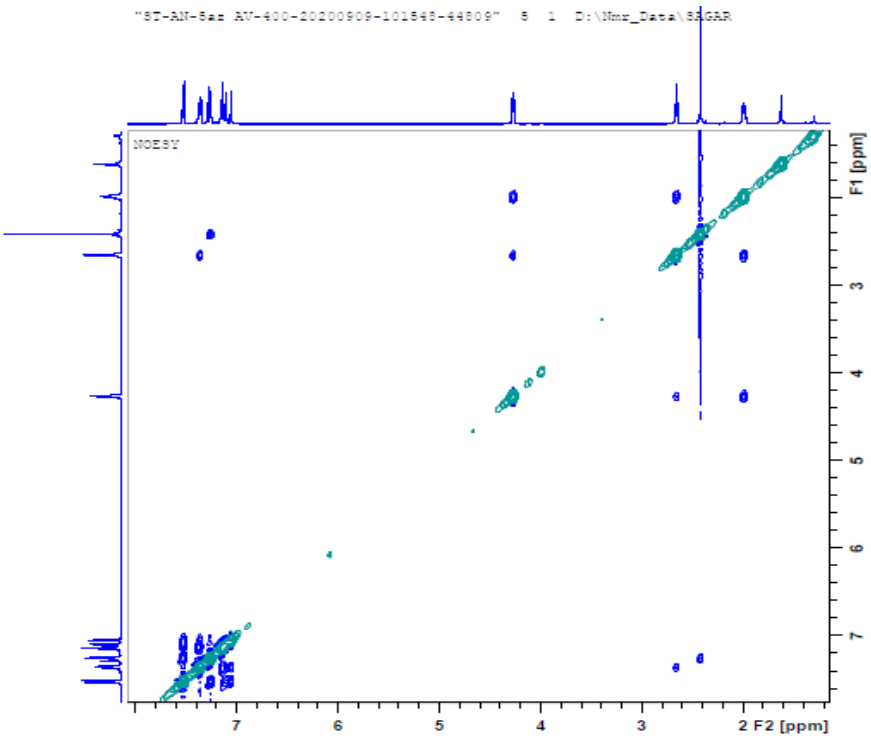


55az

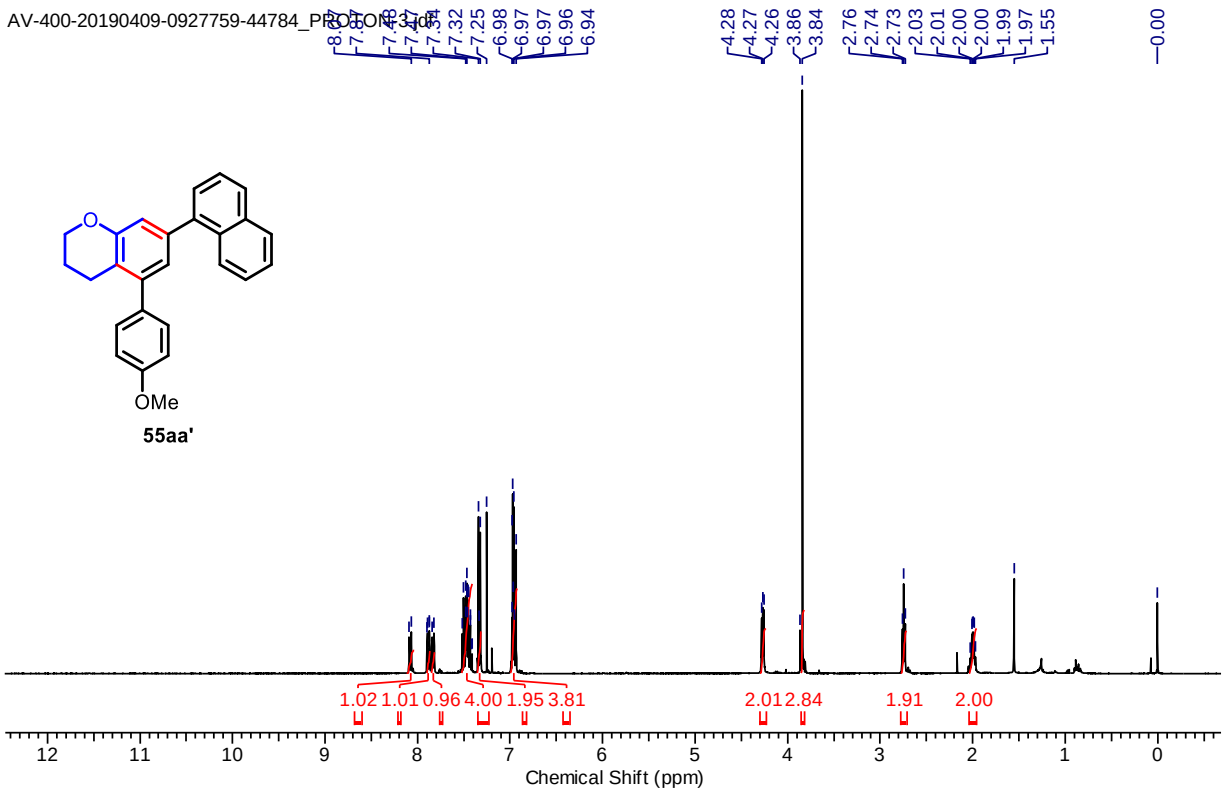
HMBC spectrum of compound 55az



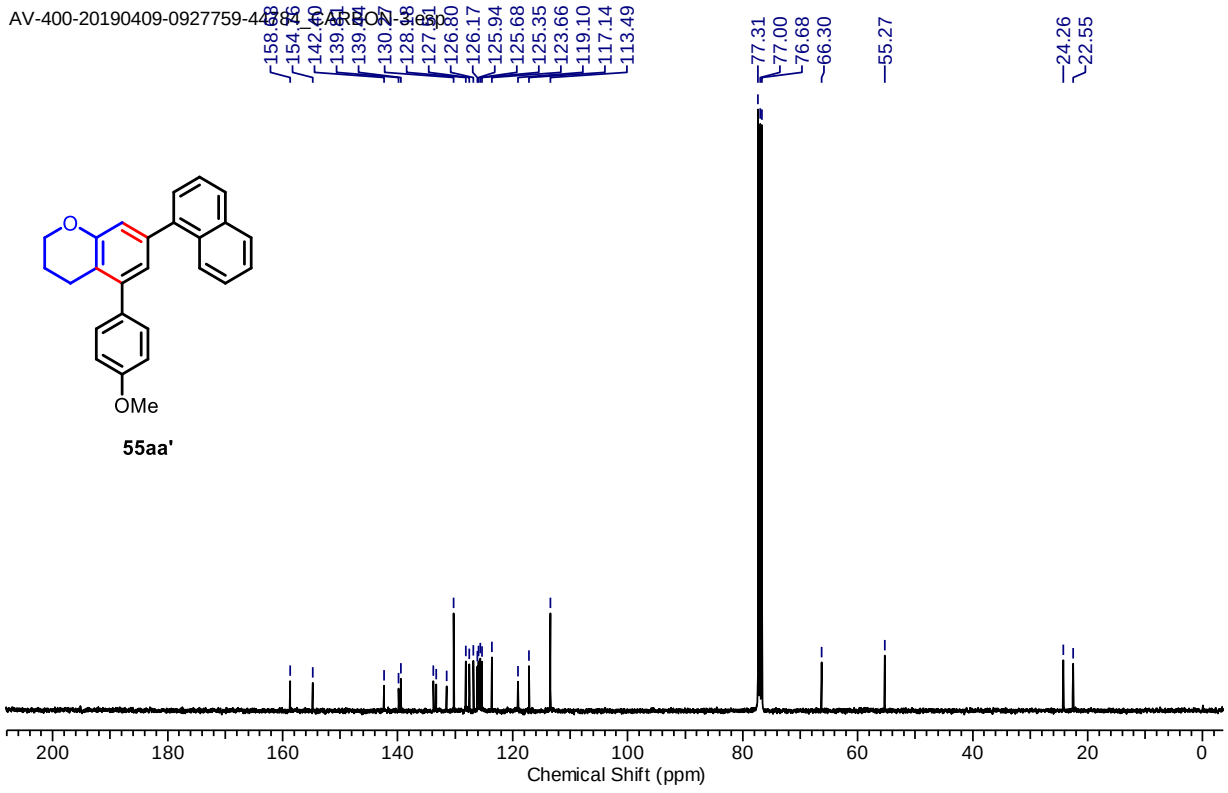
NOESY spectrum of compound 5az



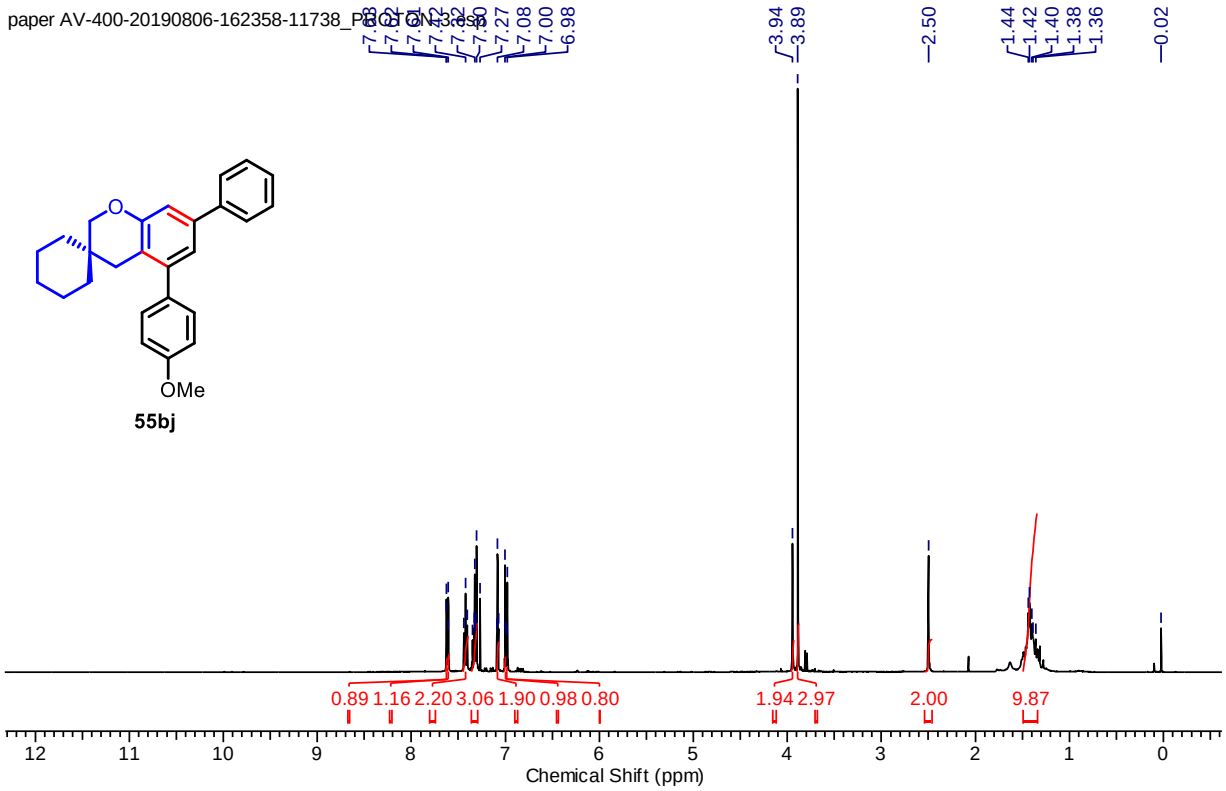
^{1}H NMR spectrum of compound 55aa'



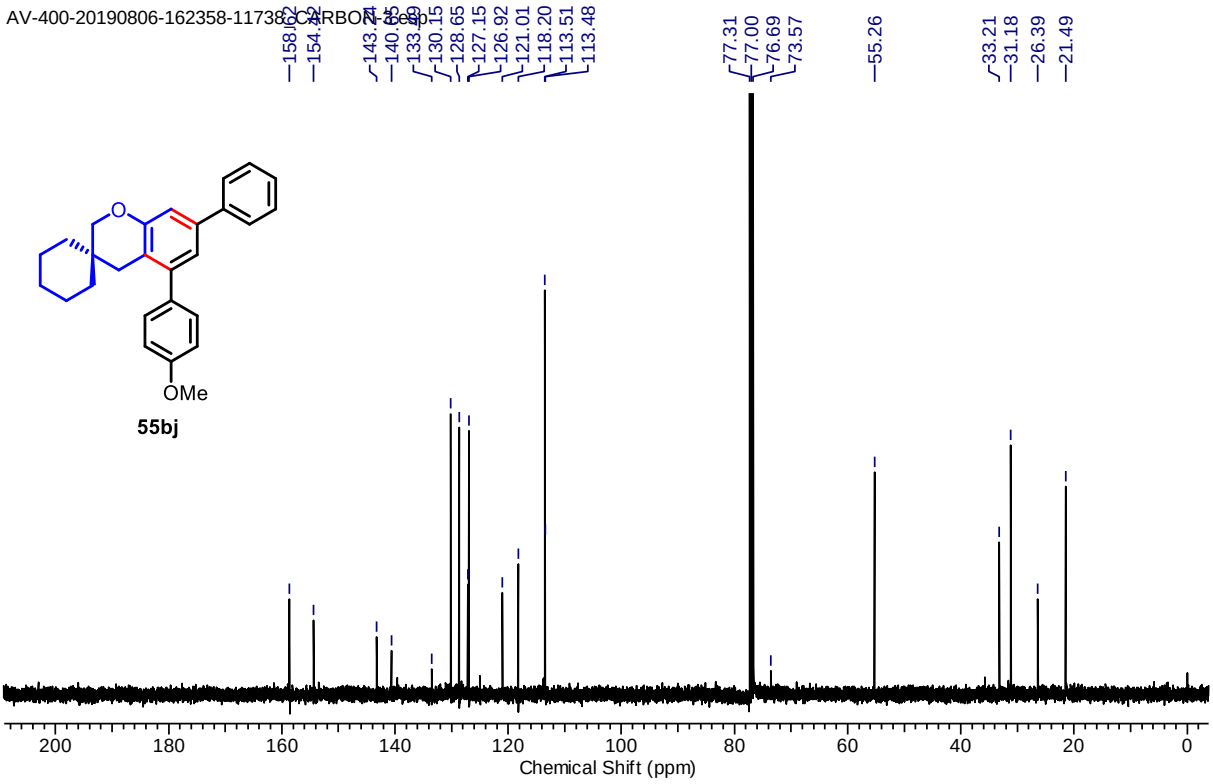
^{13}C NMR spectrum of compound 55aa'



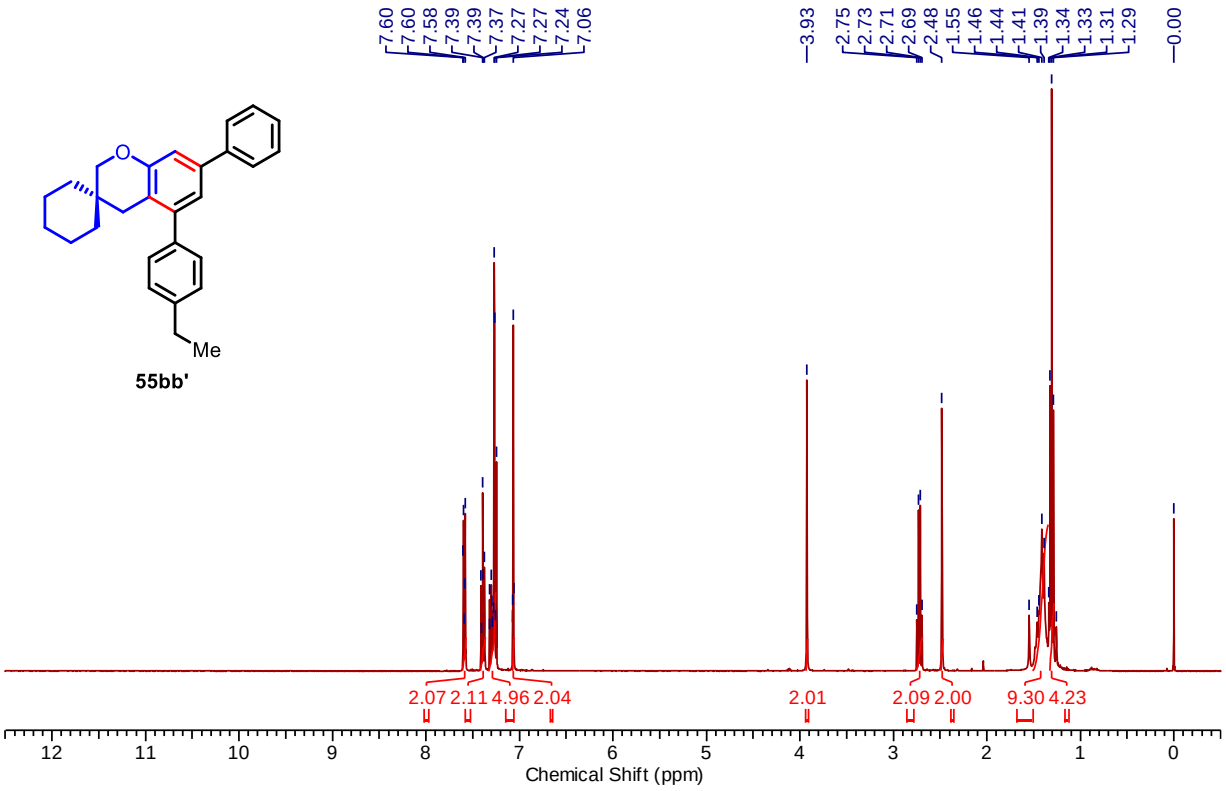
^{1}H NMR spectrum of compound 55bj



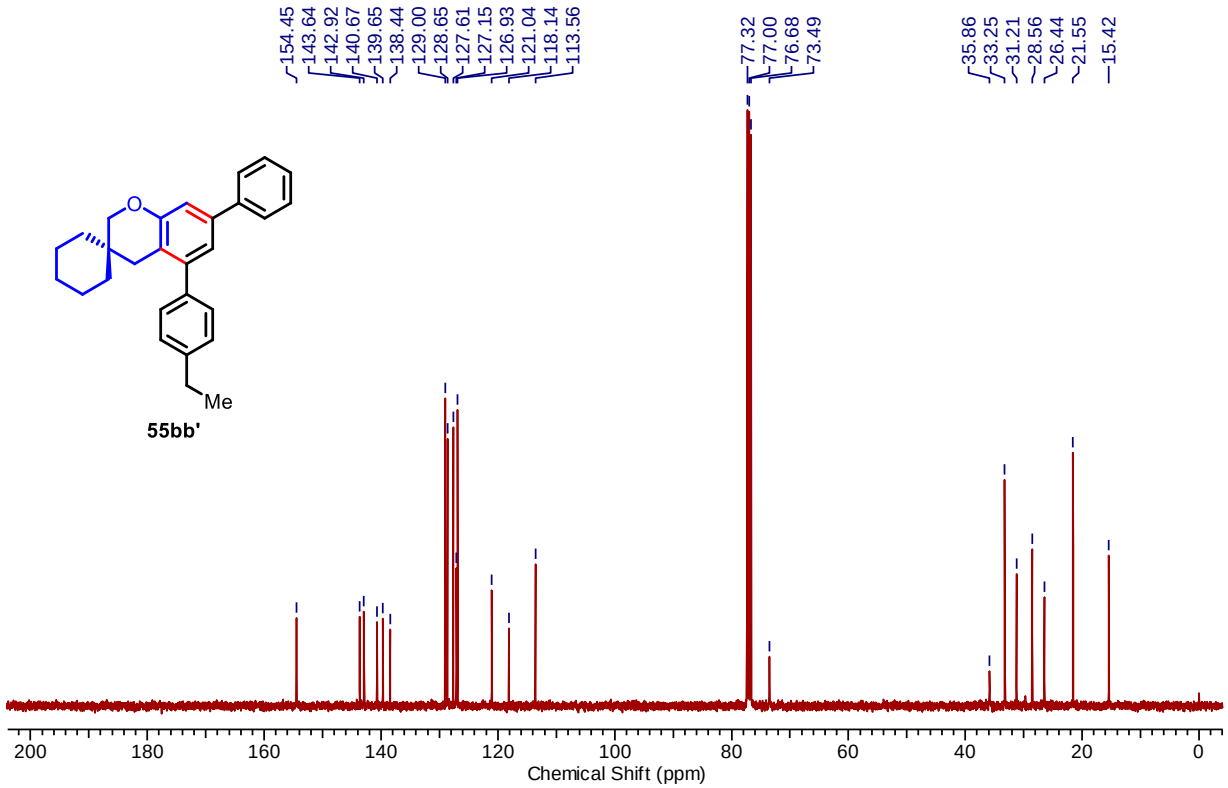
^{13}C NMR spectrum of compound 55bj



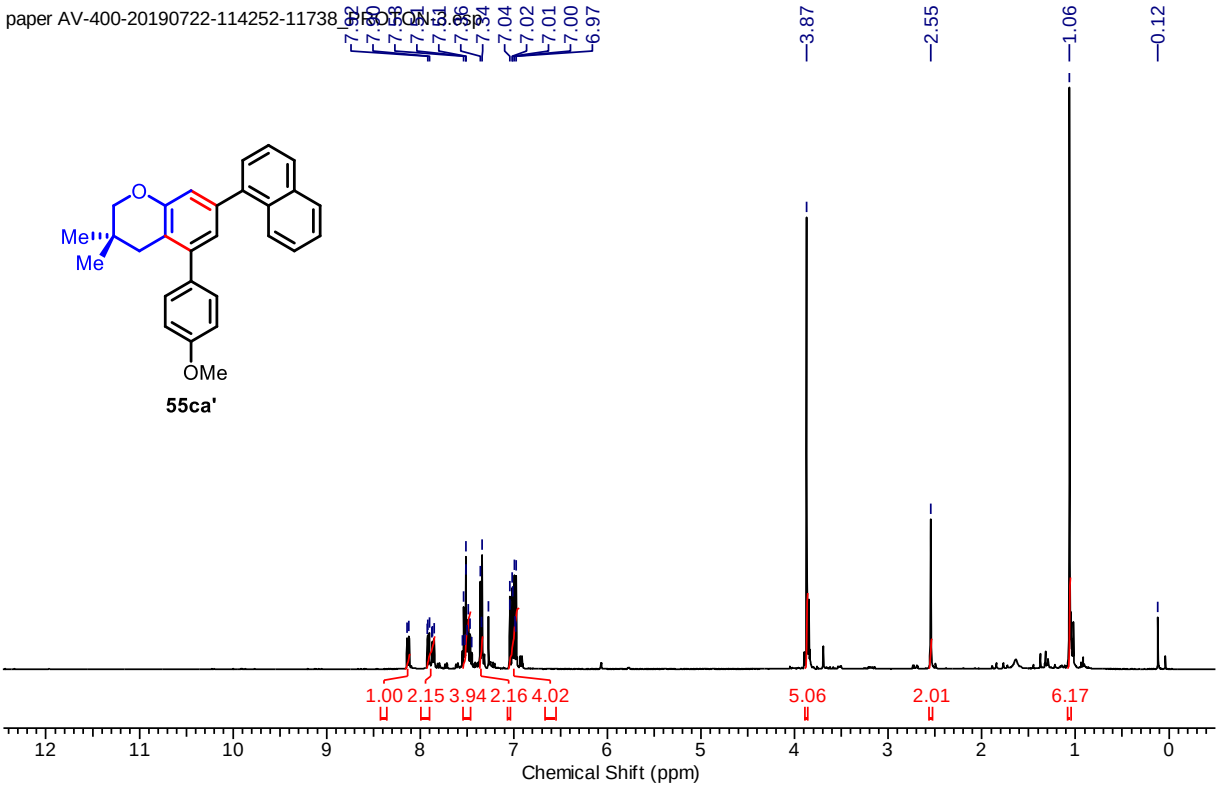
^{1}H NMR spectrum of compound 55bb'



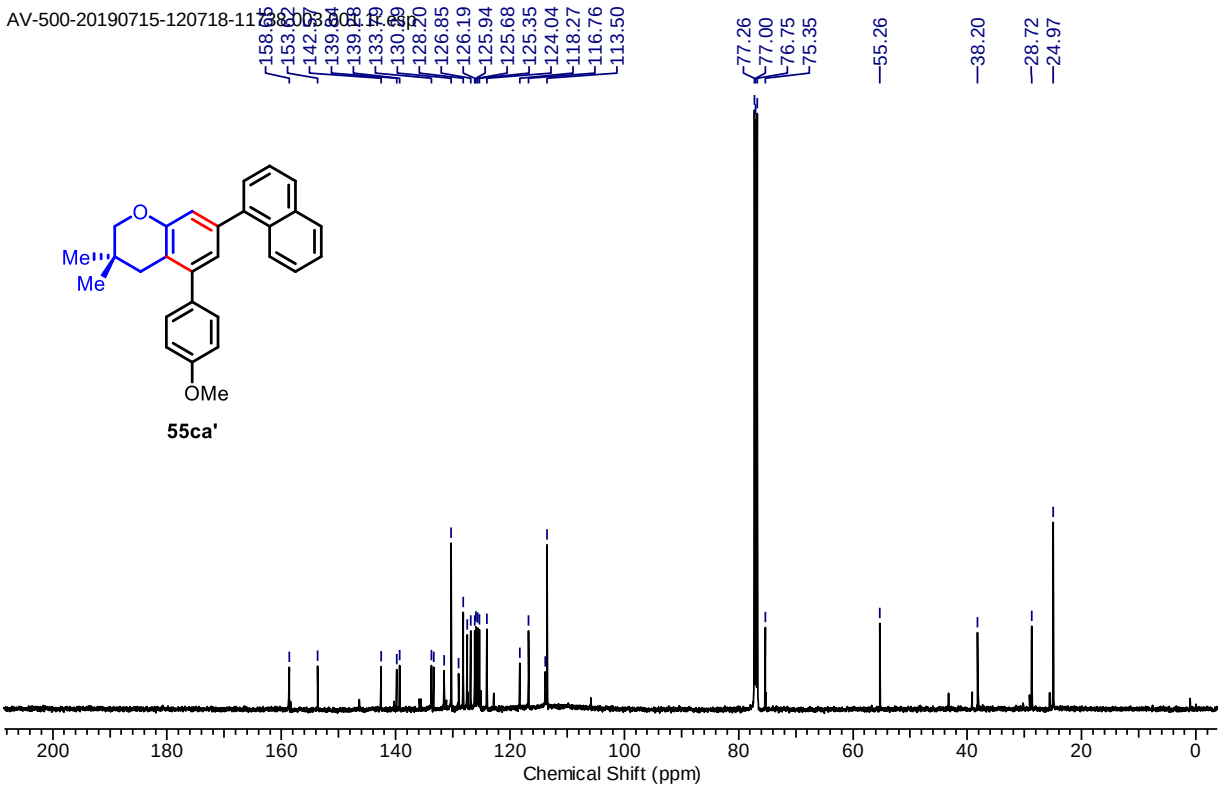
^{13}C NMR spectrum of compound 55bb'



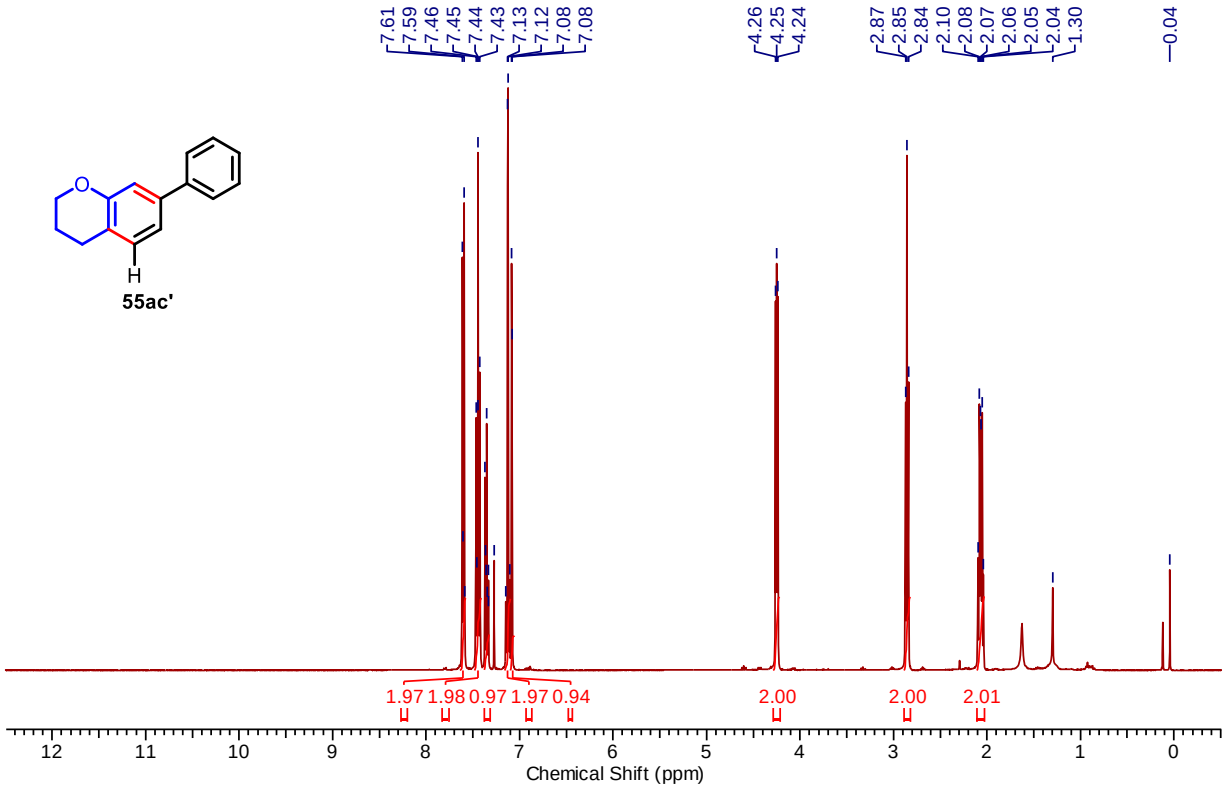
^{1}H NMR spectrum of compound 55ca'



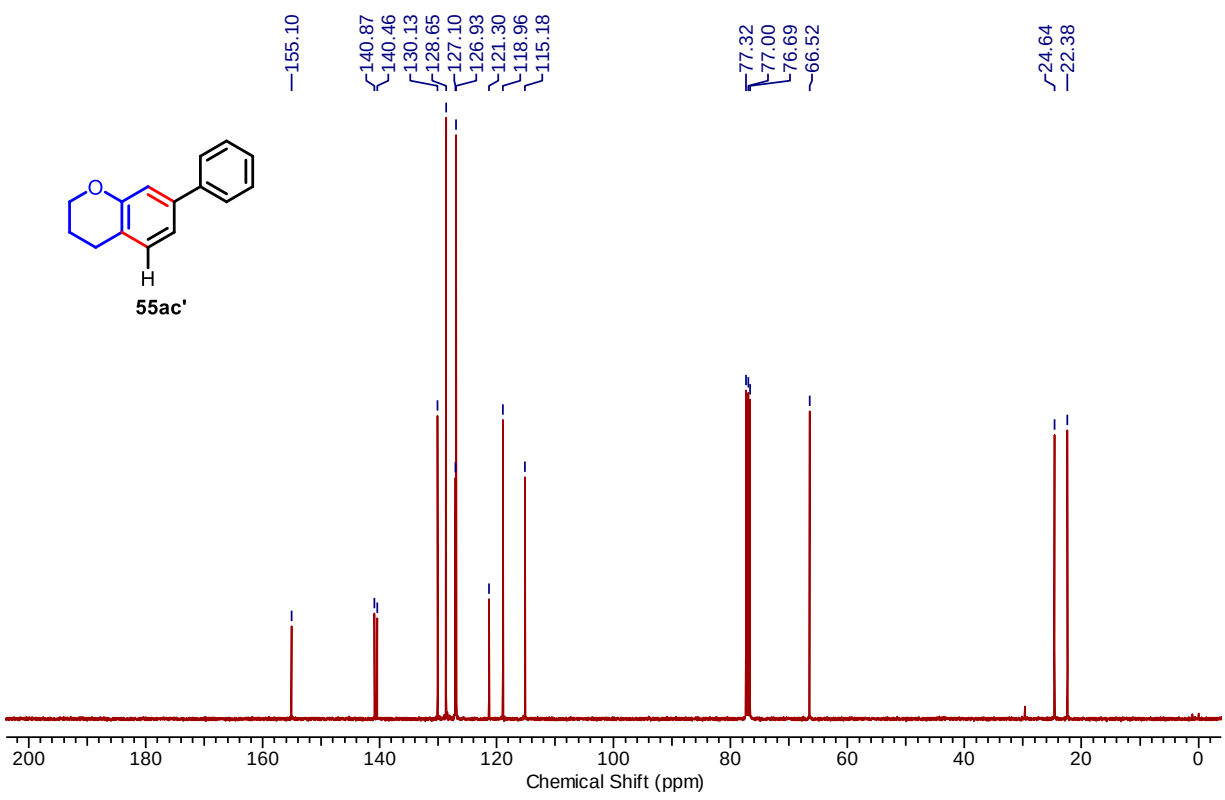
^{13}C NMR spectrum of compound 55ca'



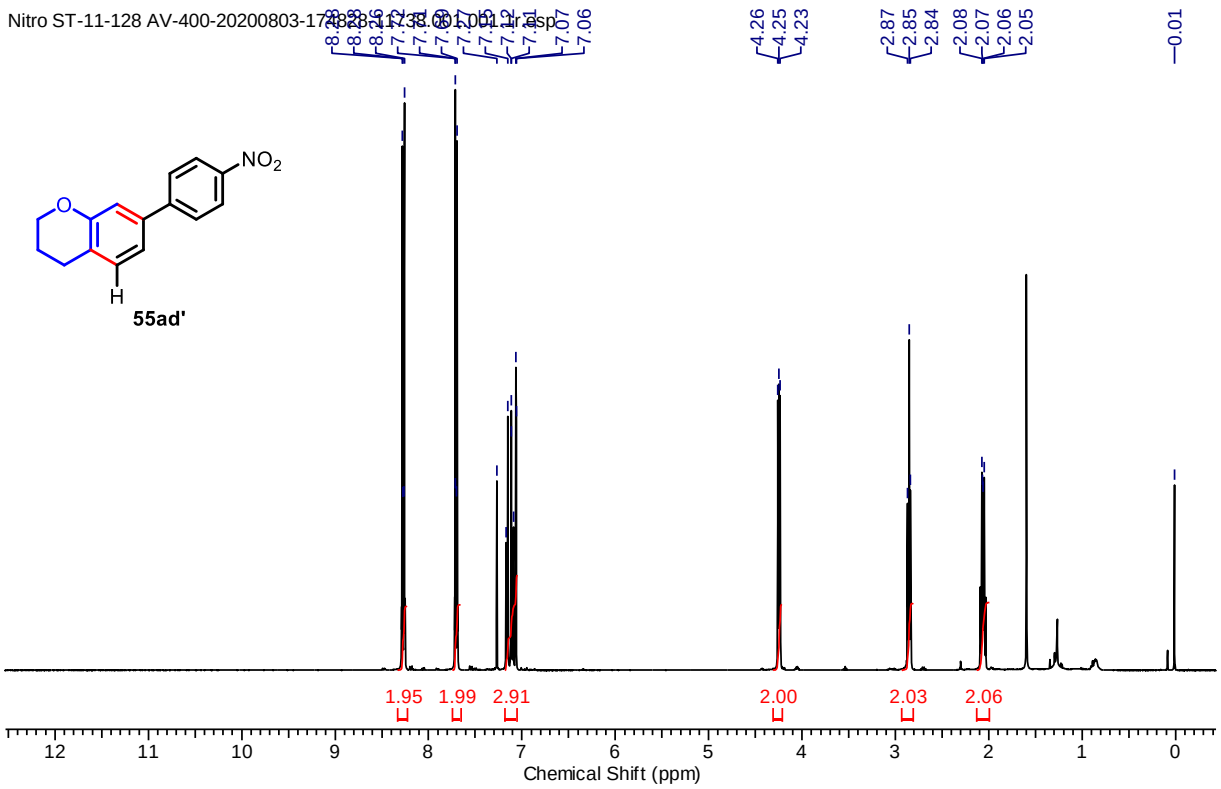
^{1}H NMR spectrum of compound 55ac'



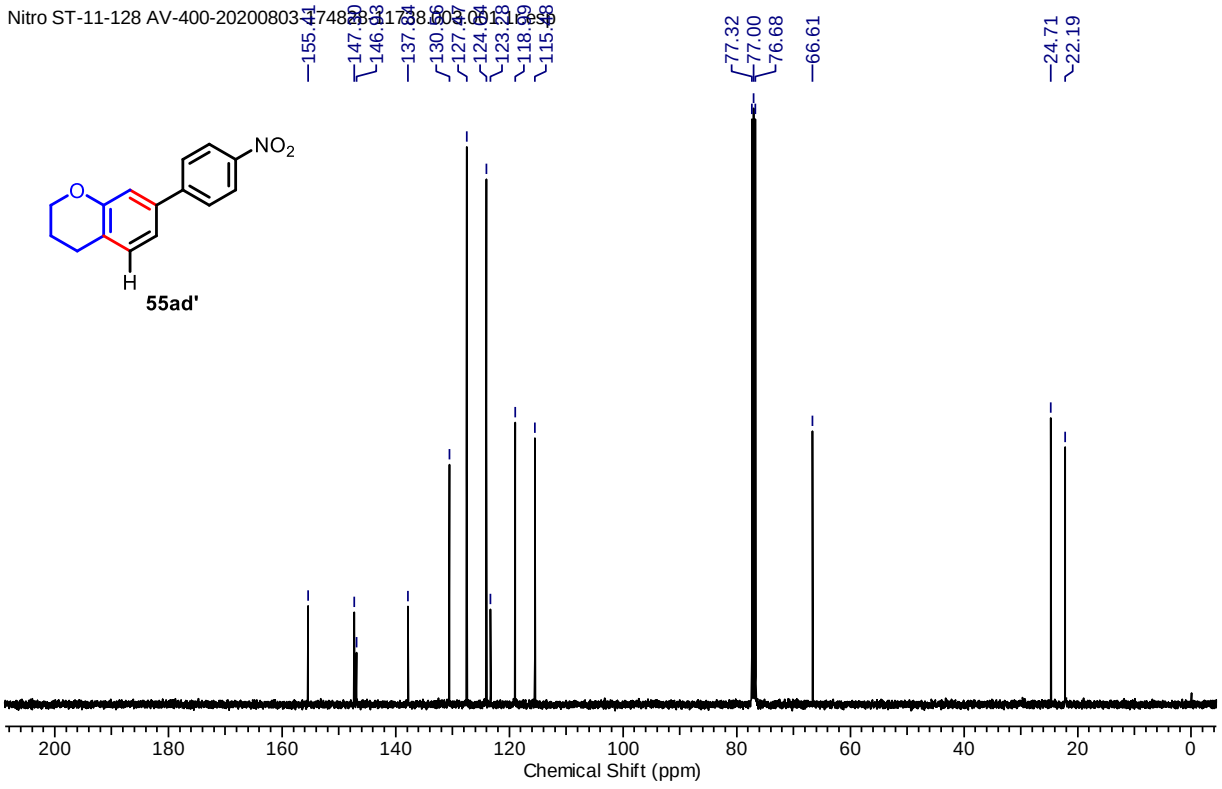
^{13}C NMR spectrum of compound 55ca'



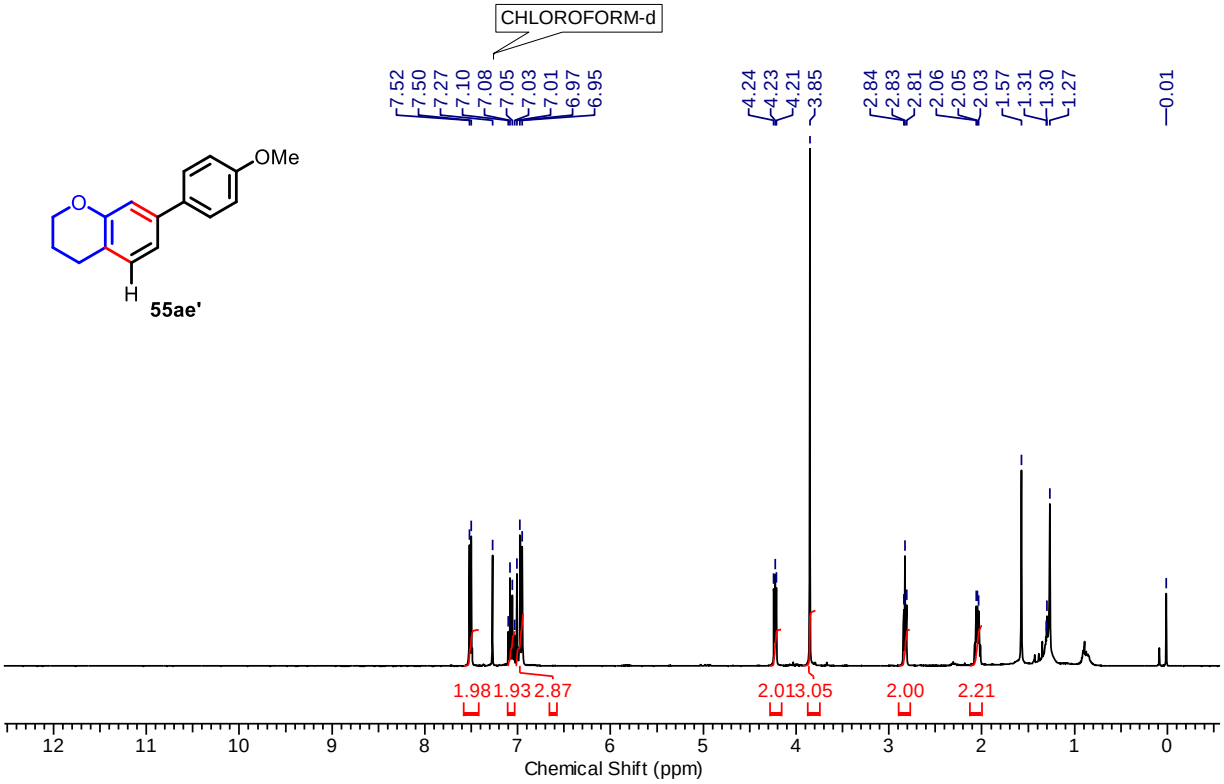
^{1}H NMR spectrum of compound 55ad'



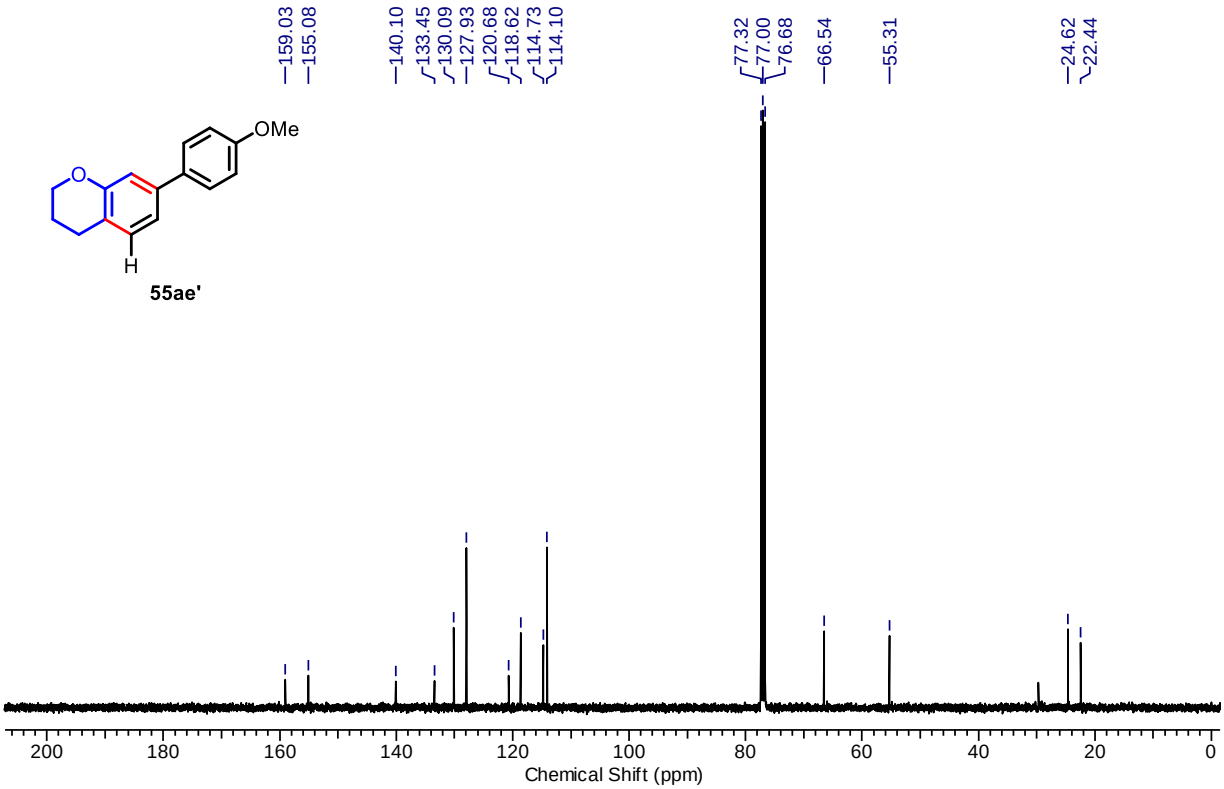
^{13}C NMR spectrum of compound 55ad'



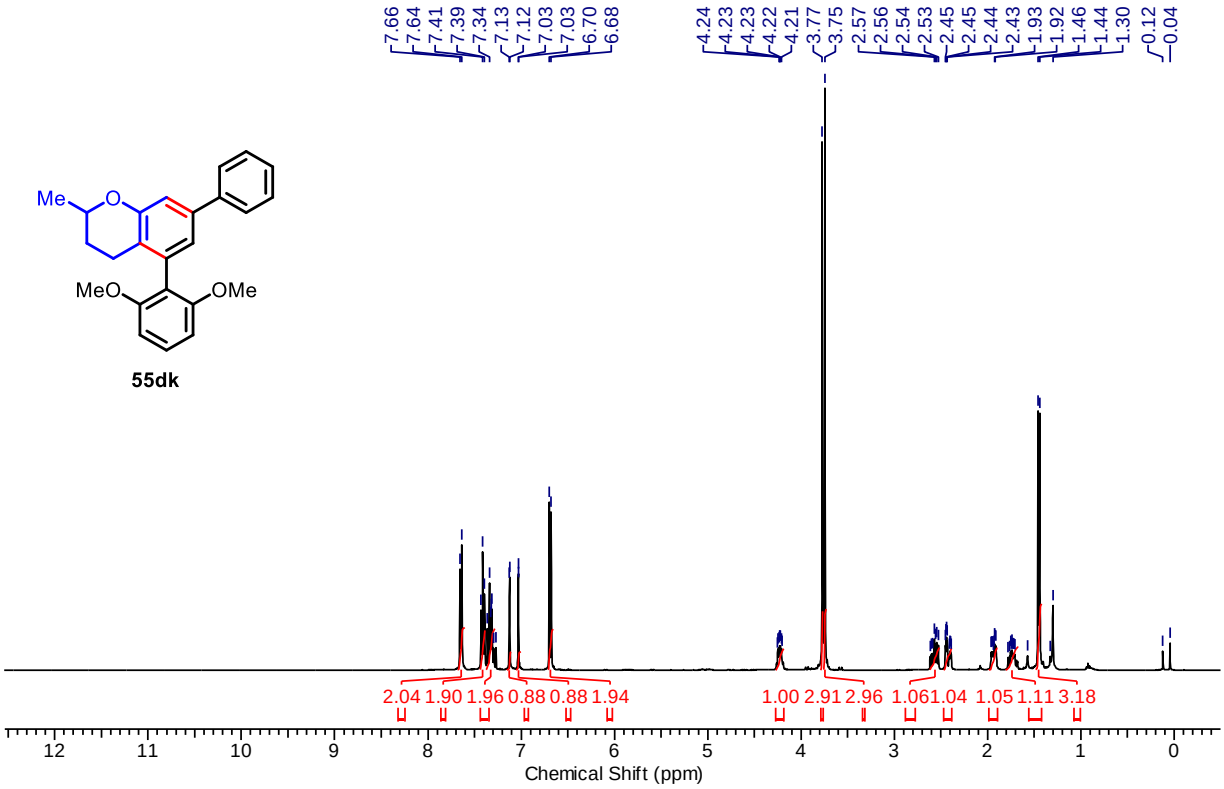
^{1}H NMR spectrum of compound 55ae'



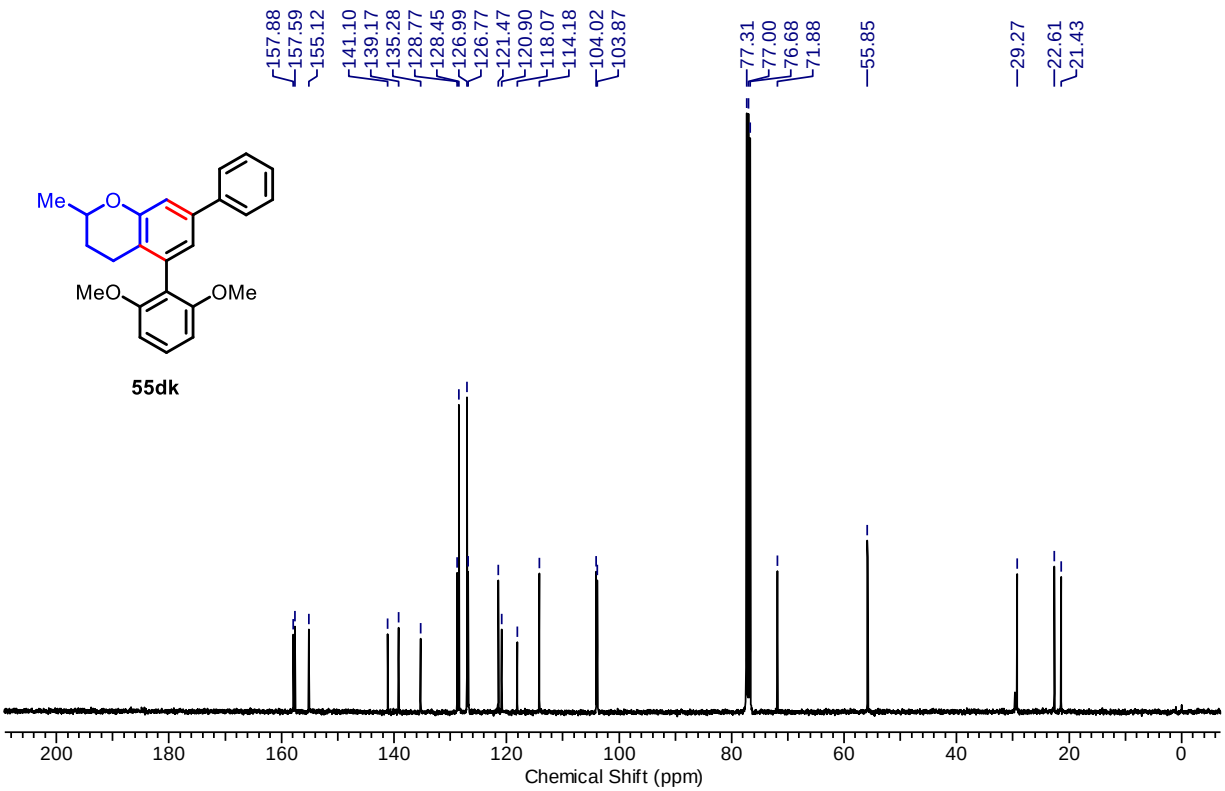
^{13}C NMR spectrum of compound 55ae'



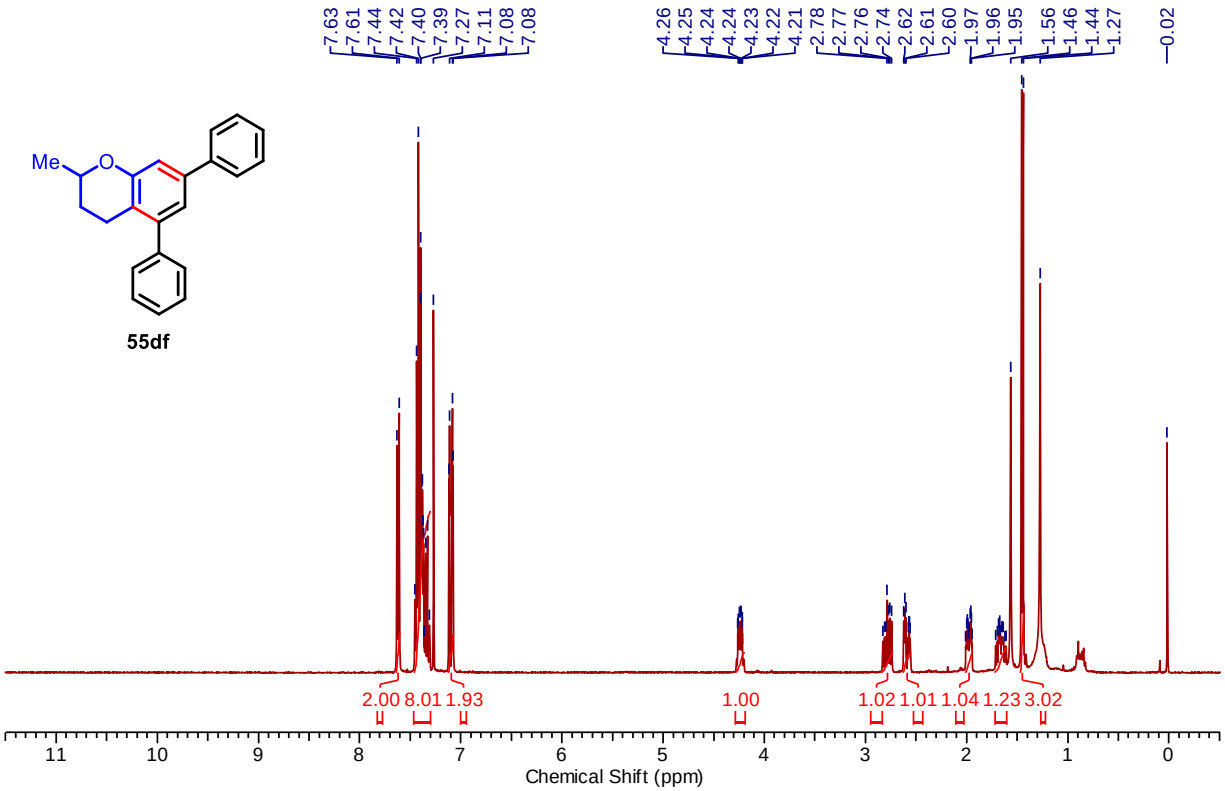
^{1}H NMR spectrum of compound 55dk



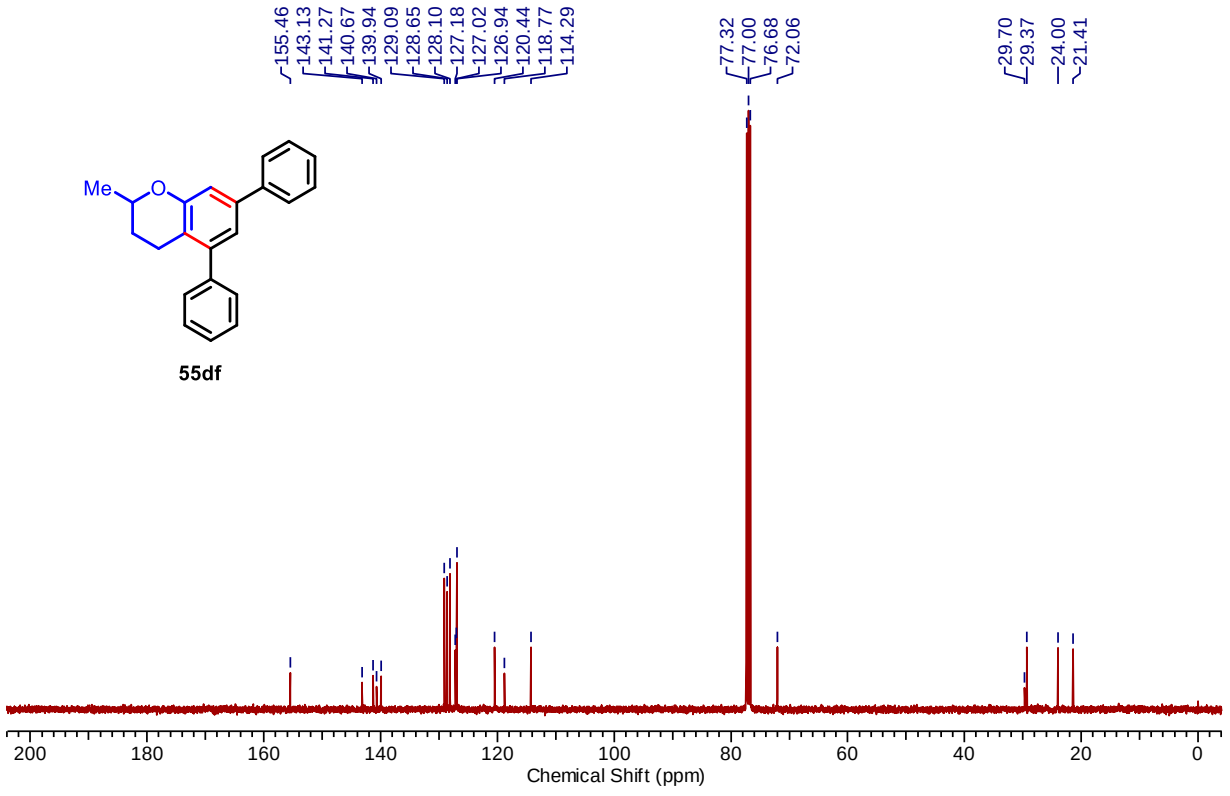
^{13}C NMR spectrum of compound 55dk



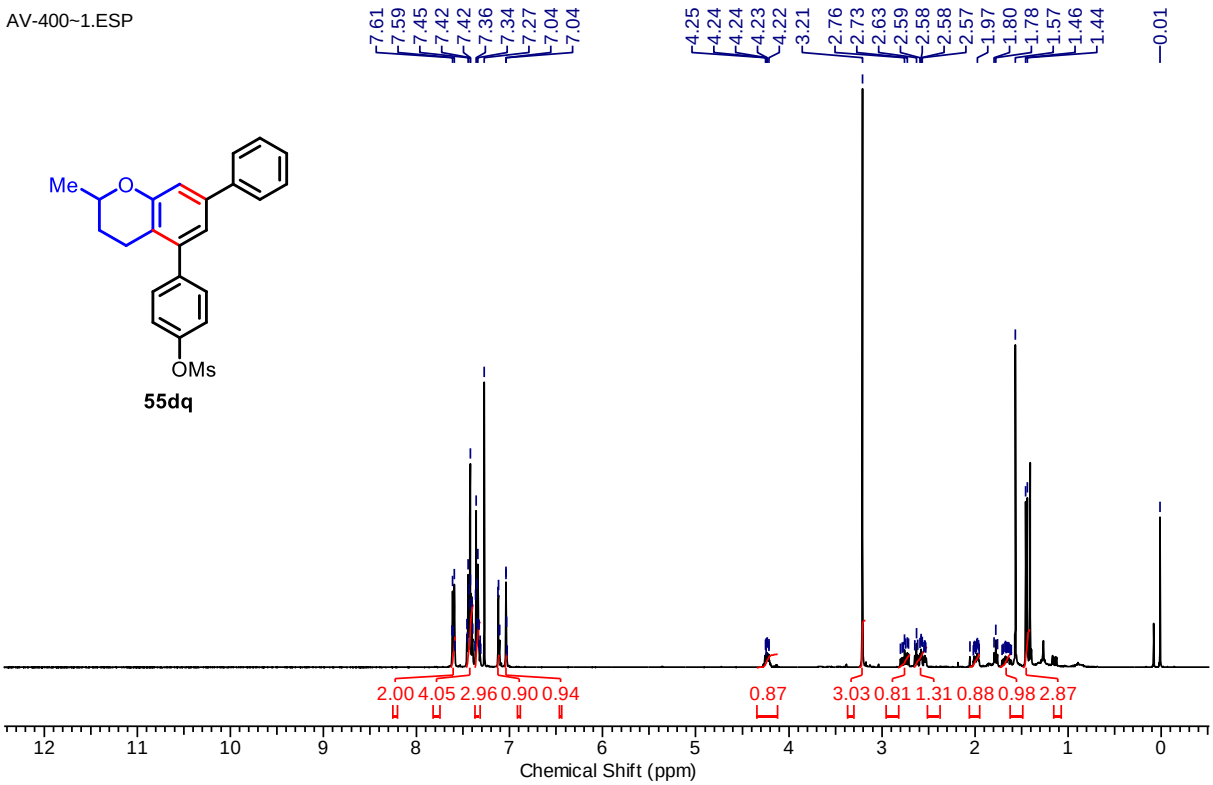
^{1}H NMR spectrum of compound 55df



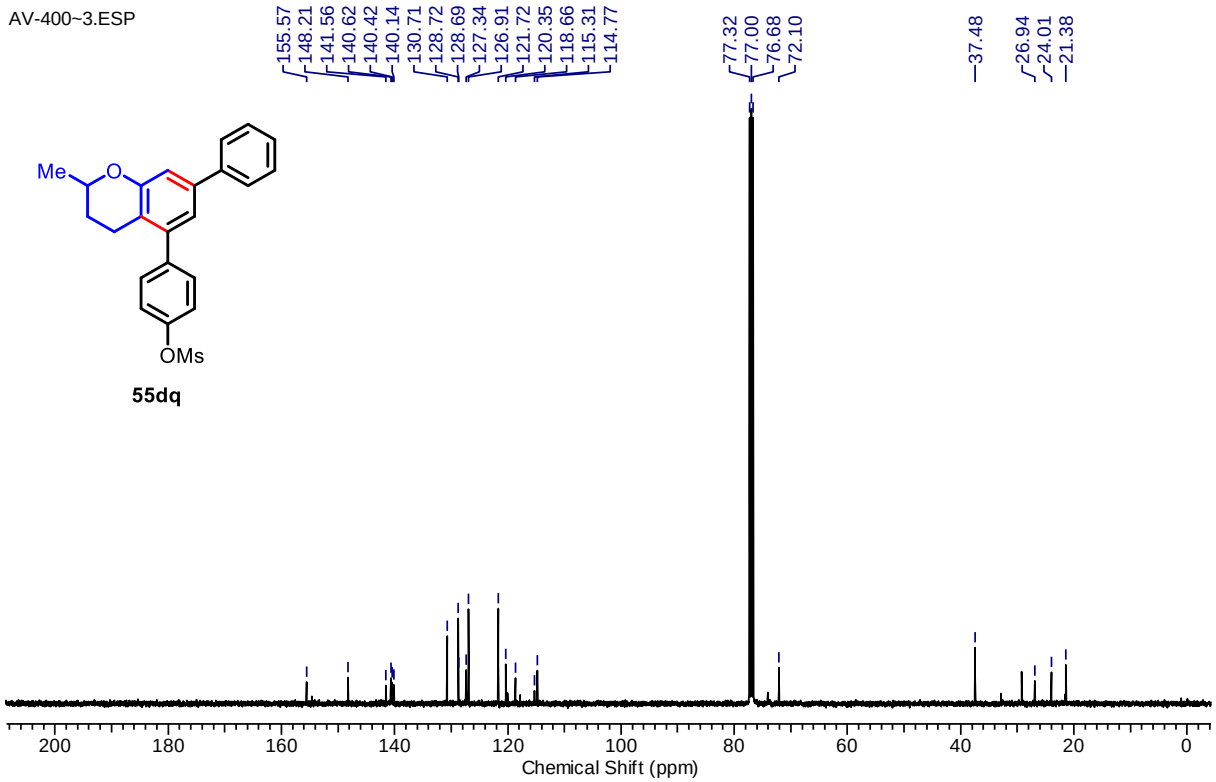
^{13}C NMR spectrum of compound 55df



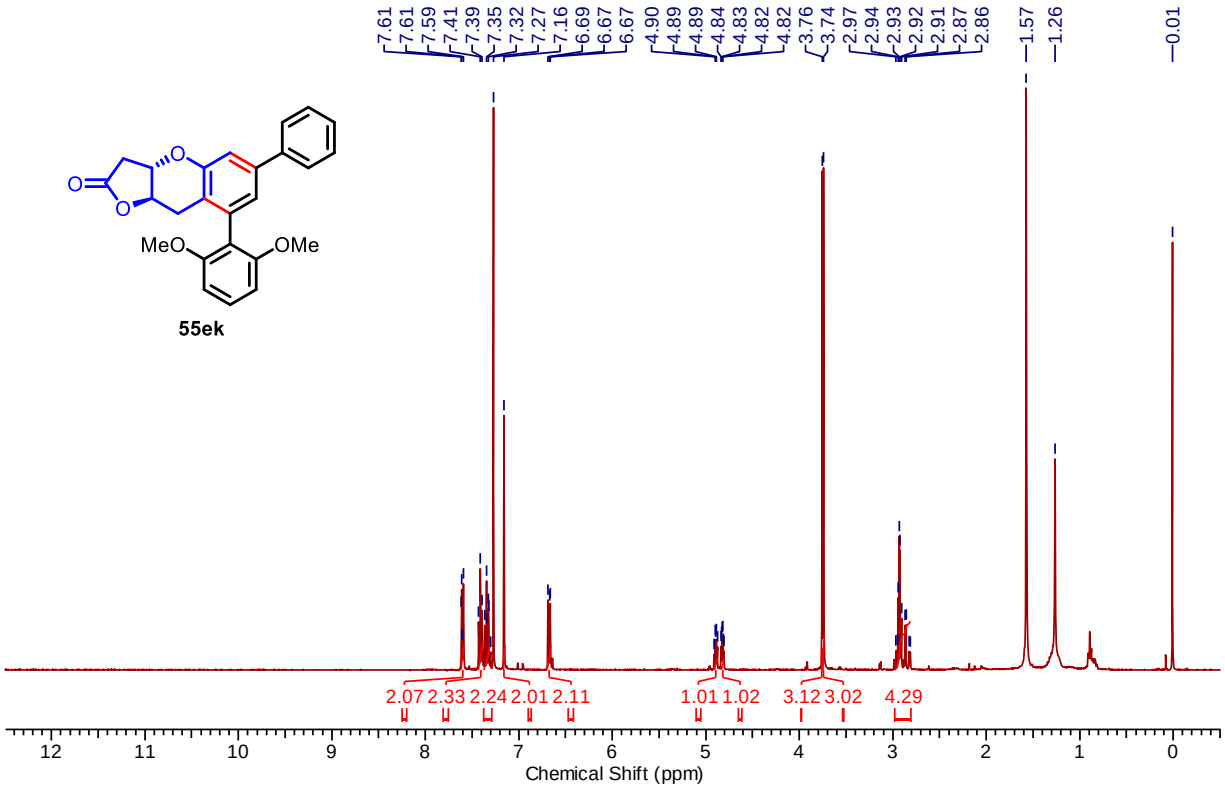
^{1}H NMR spectrum of compound 55dq



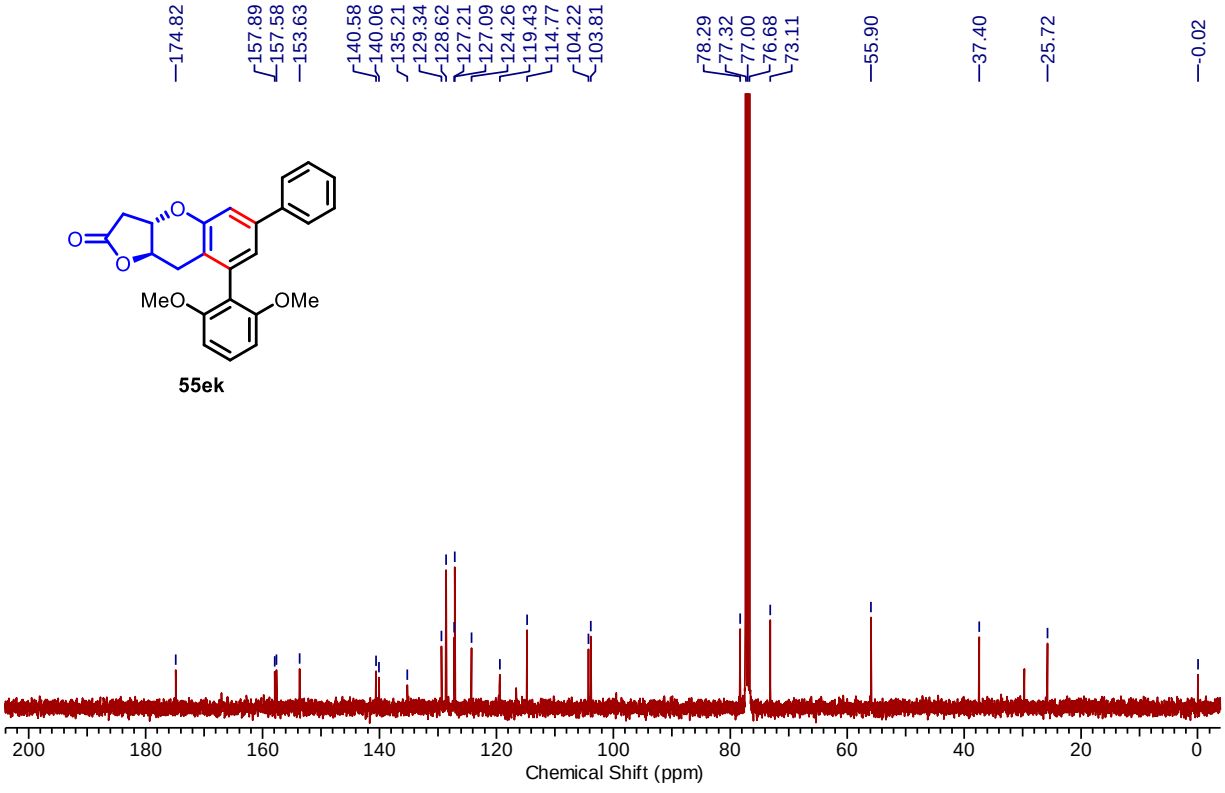
^{13}C NMR spectrum of compound 55dq



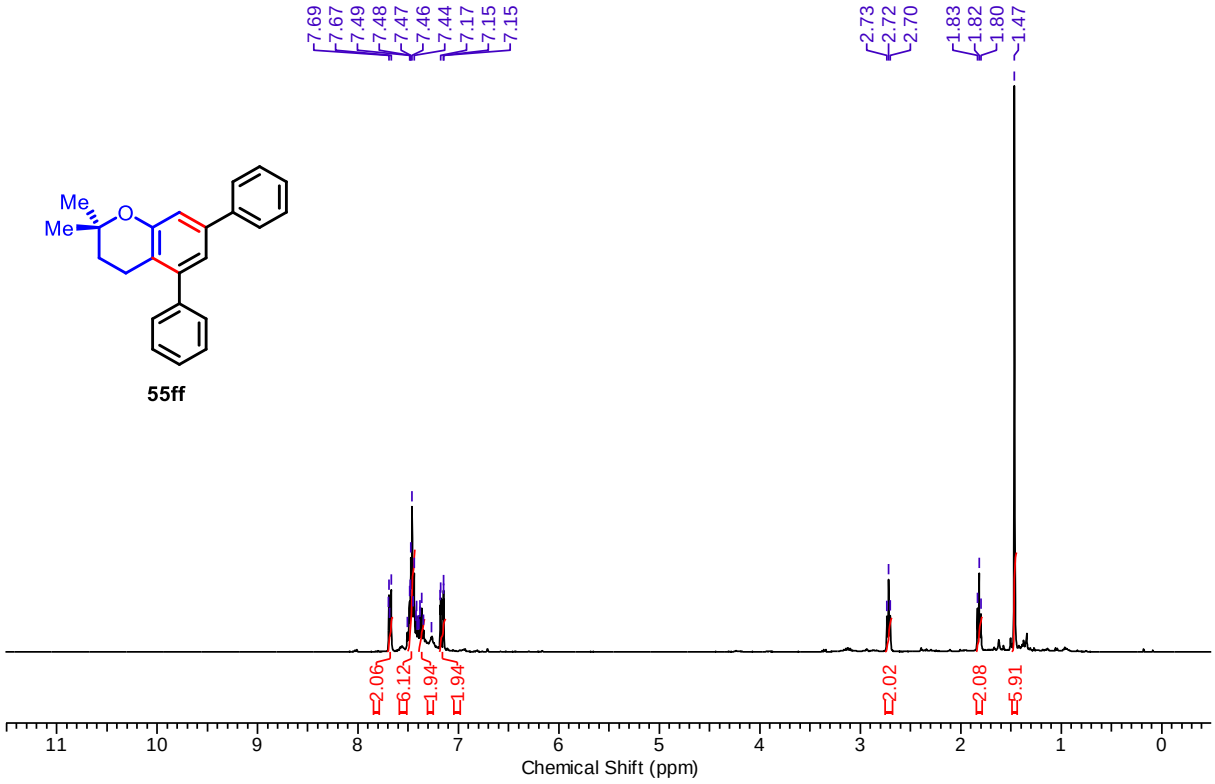
^{1}H NMR spectrum of compound 55ek



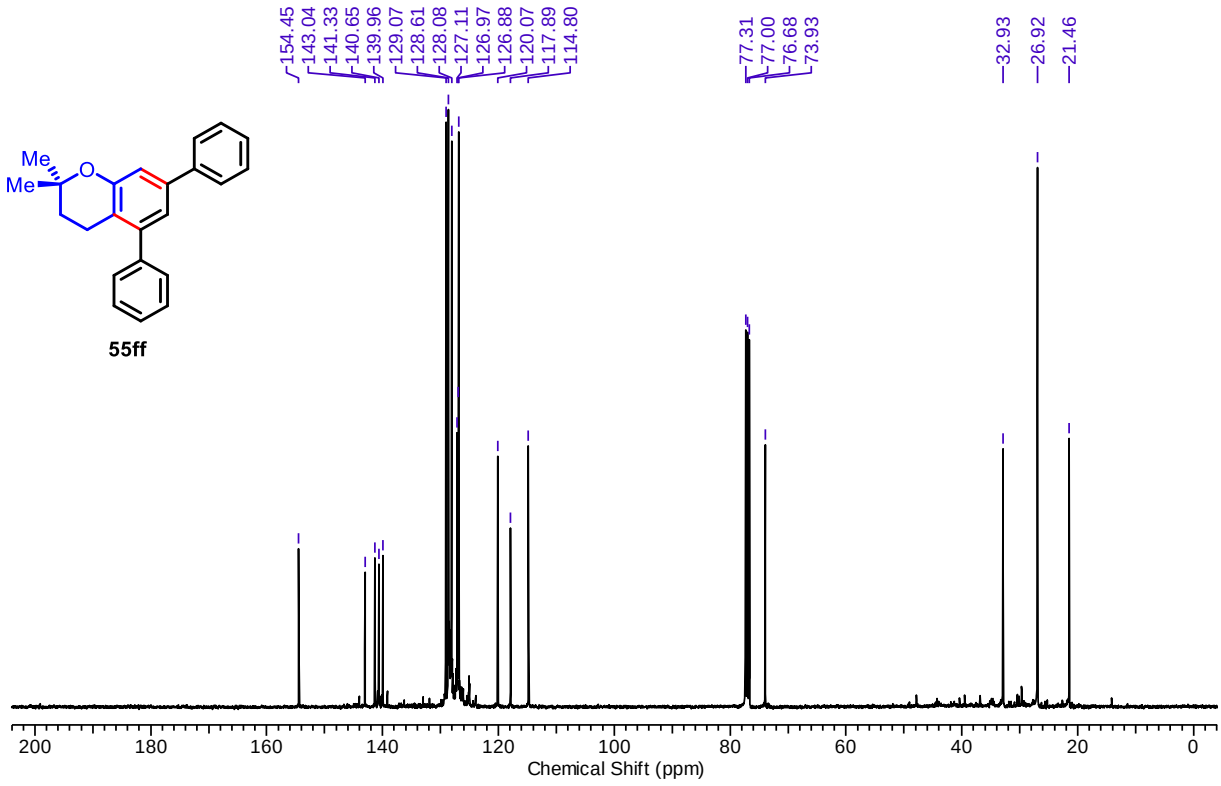
^{13}C NMR spectrum of compound 55ek



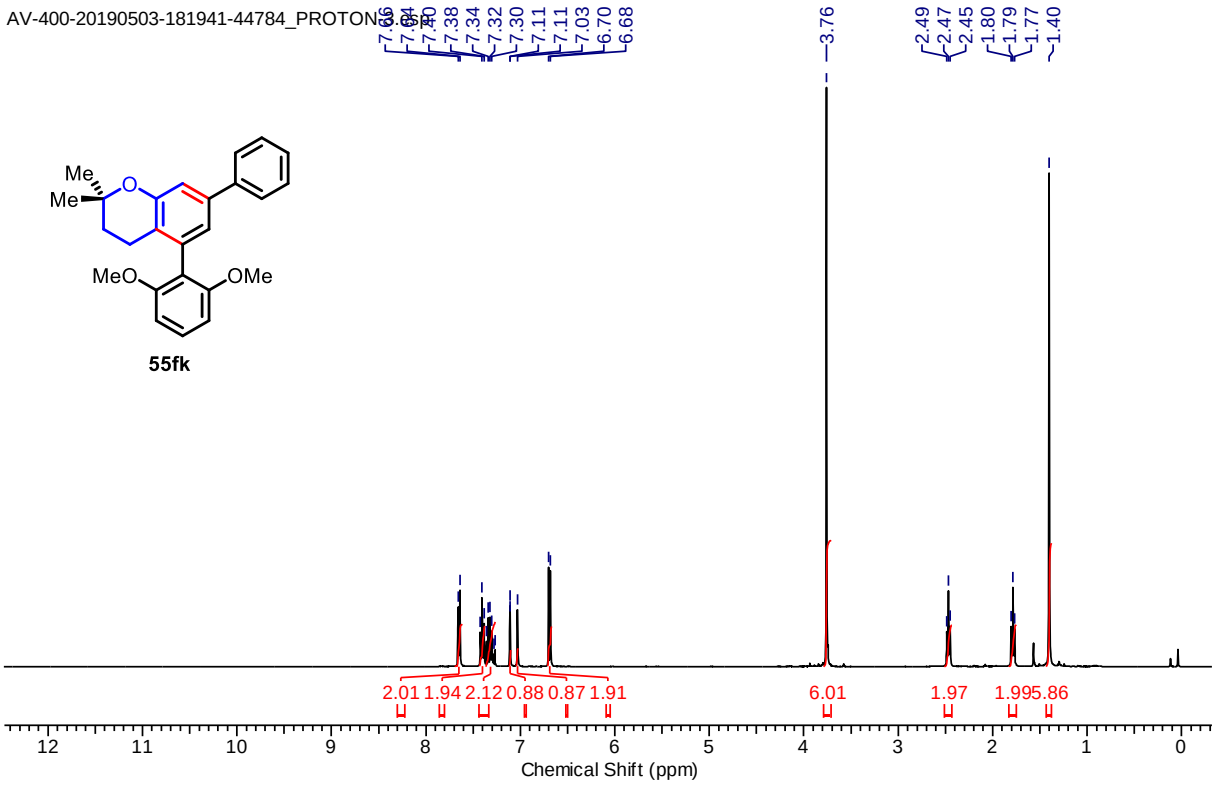
^{1}H NMR spectrum of compound 55ff



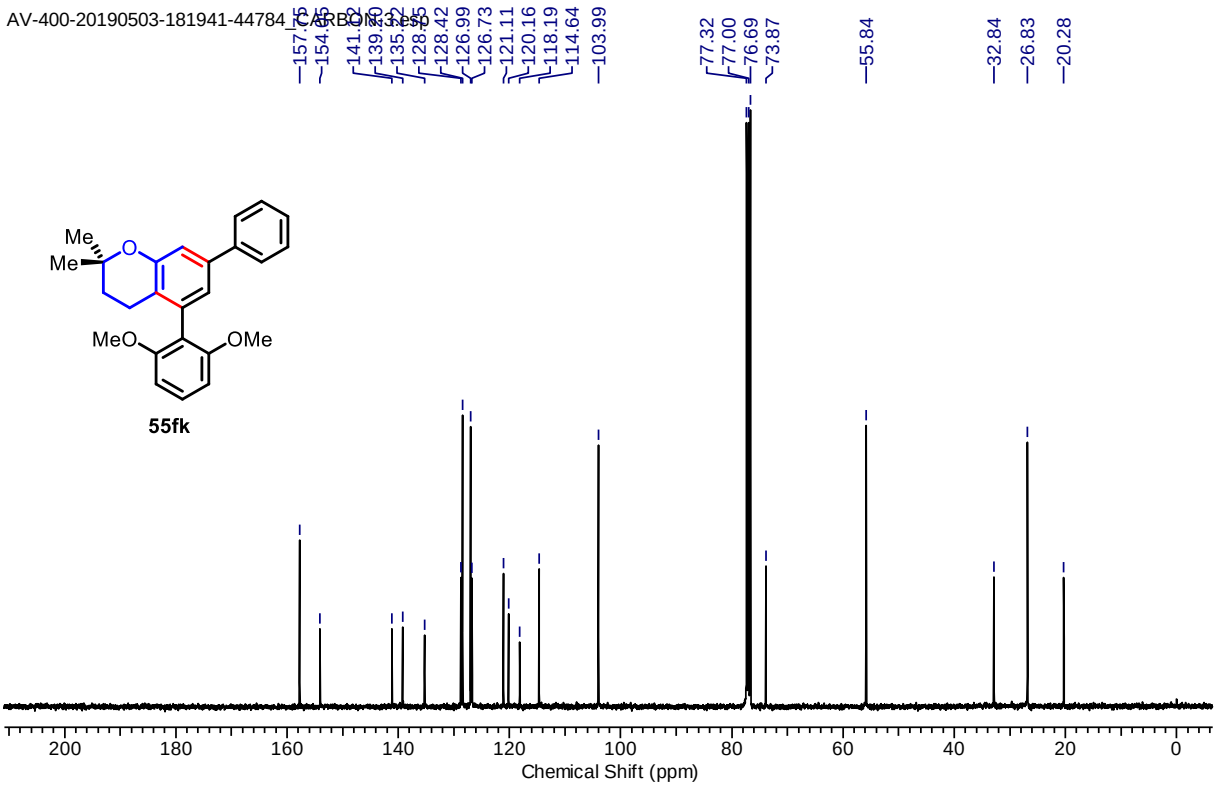
^{13}C NMR spectrum of compound 55ff



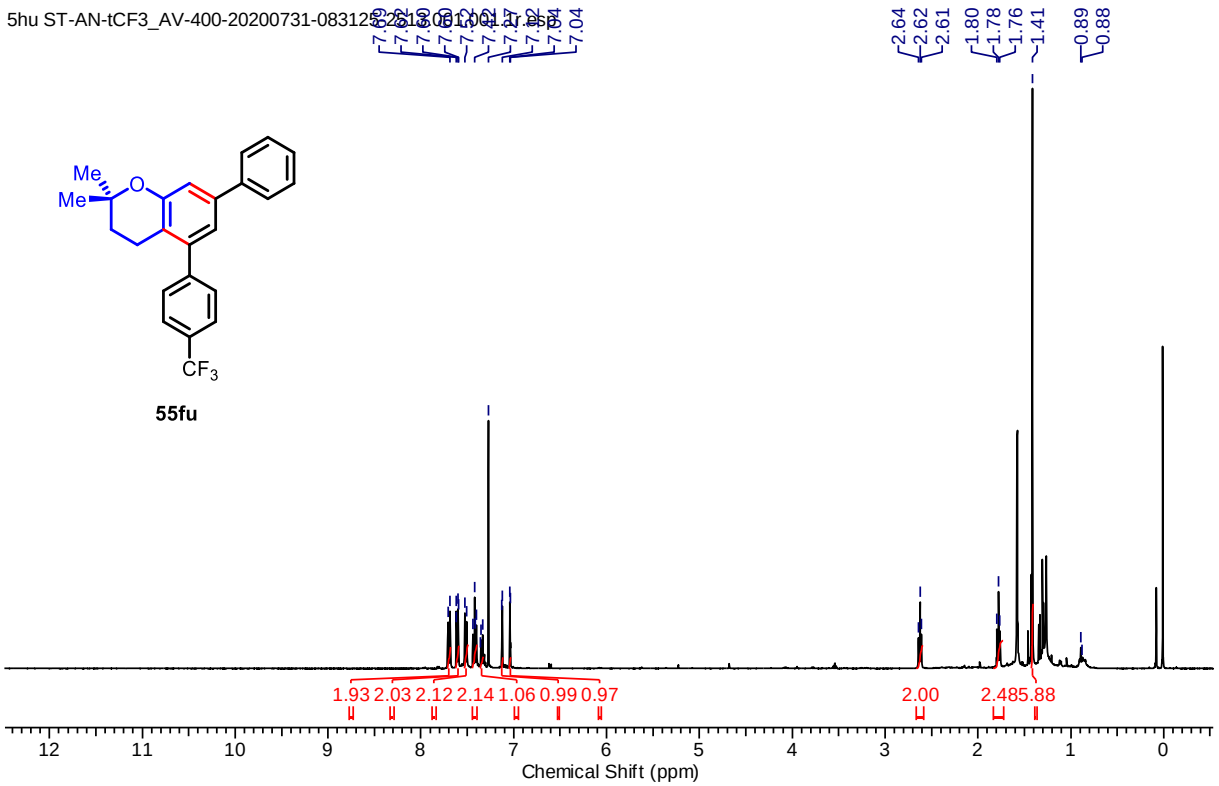
^{1}H NMR spectrum of compound 55fk



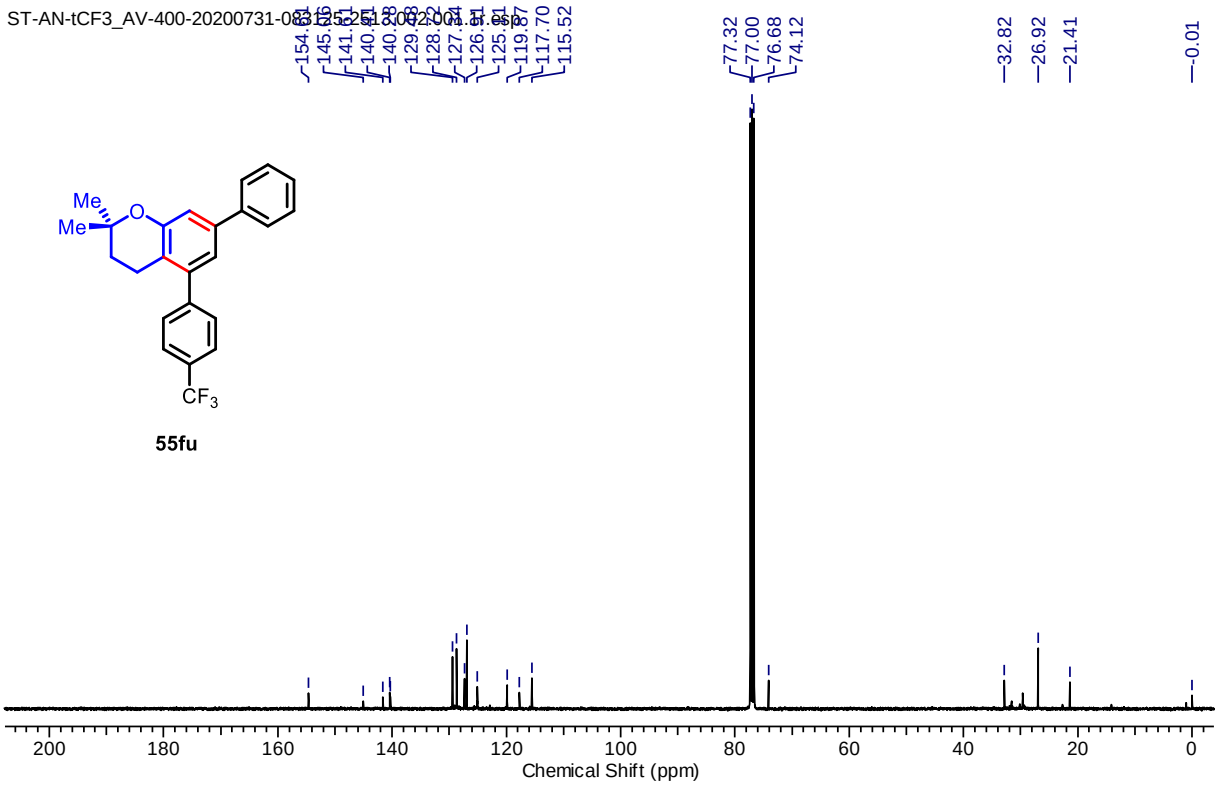
^{13}C NMR spectrum of compound 55fk



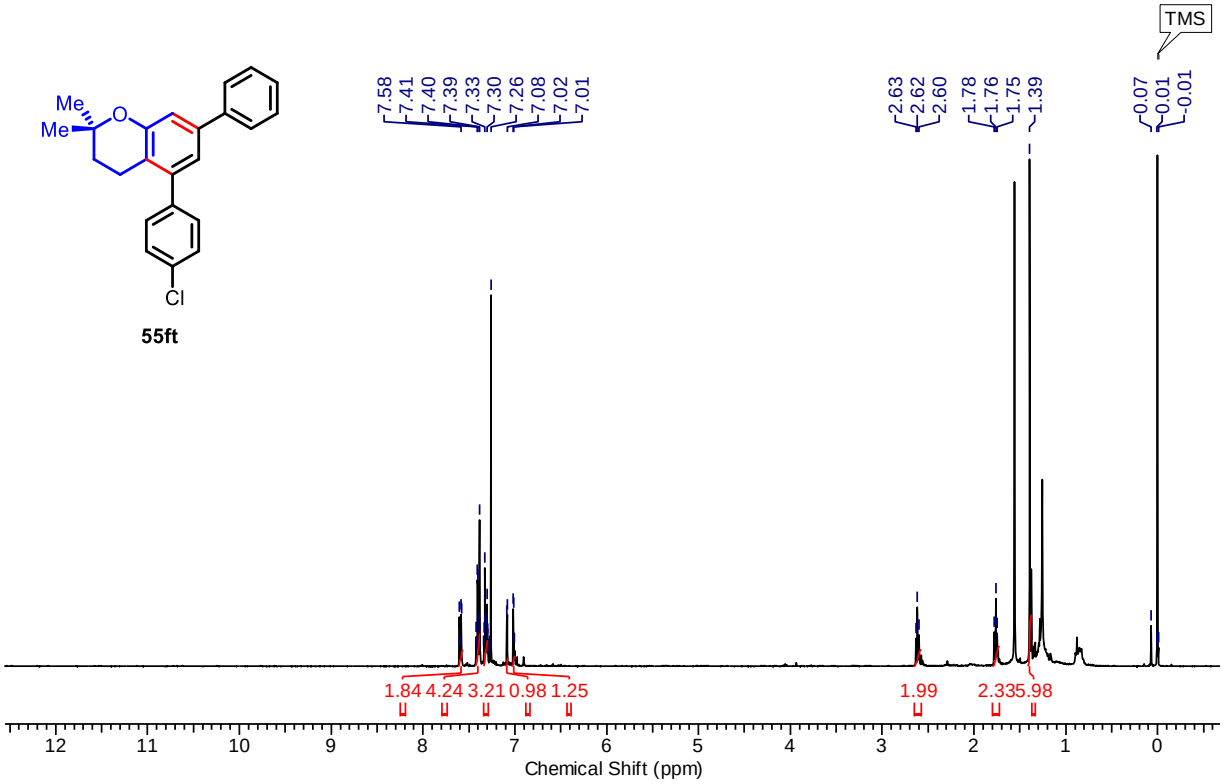
^{1}H NMR spectrum of compound 55fu



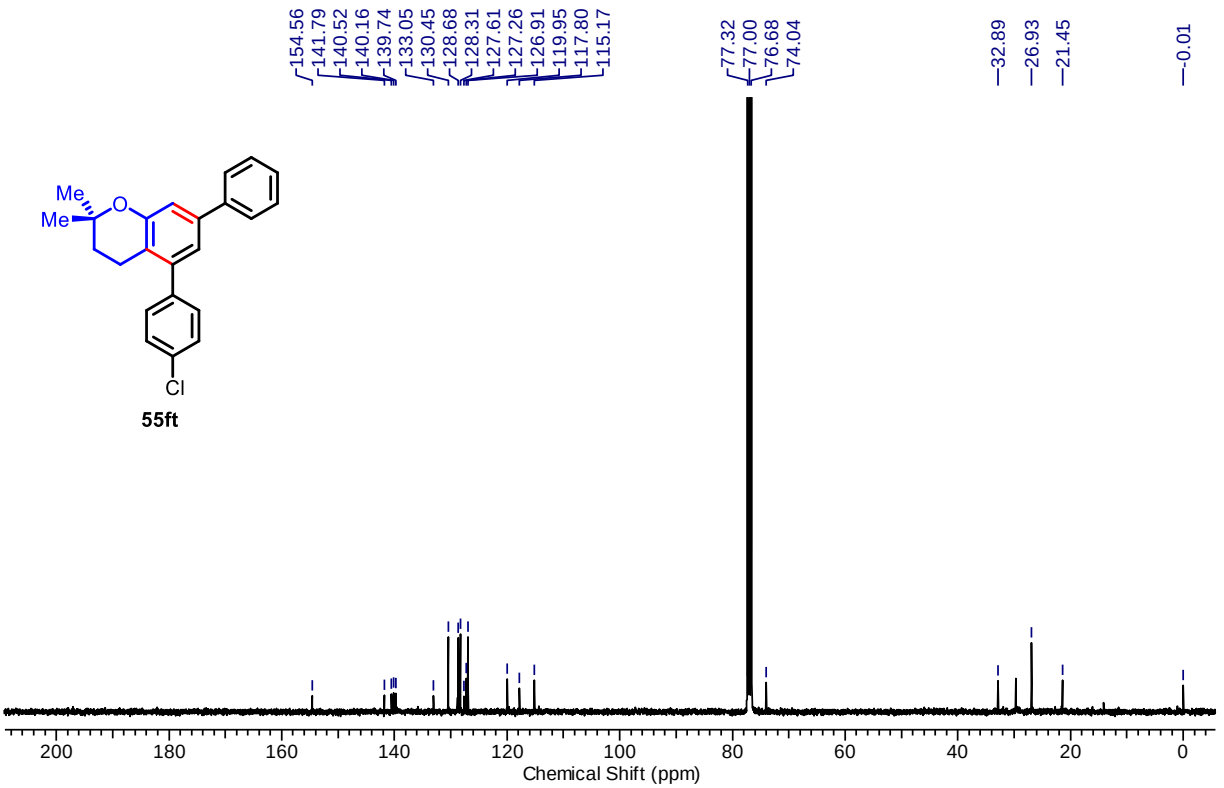
^{13}C NMR spectrum of compound 55fu



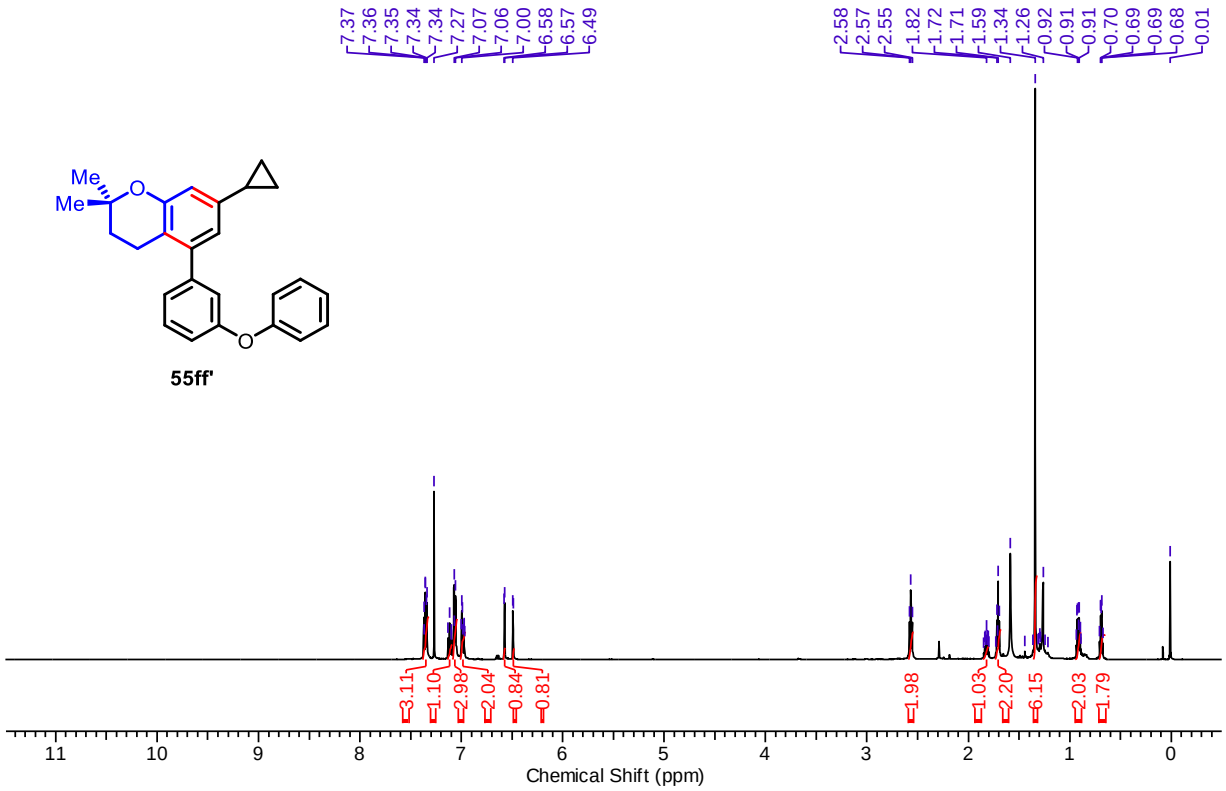
^{1}H NMR spectrum of compound 55ft



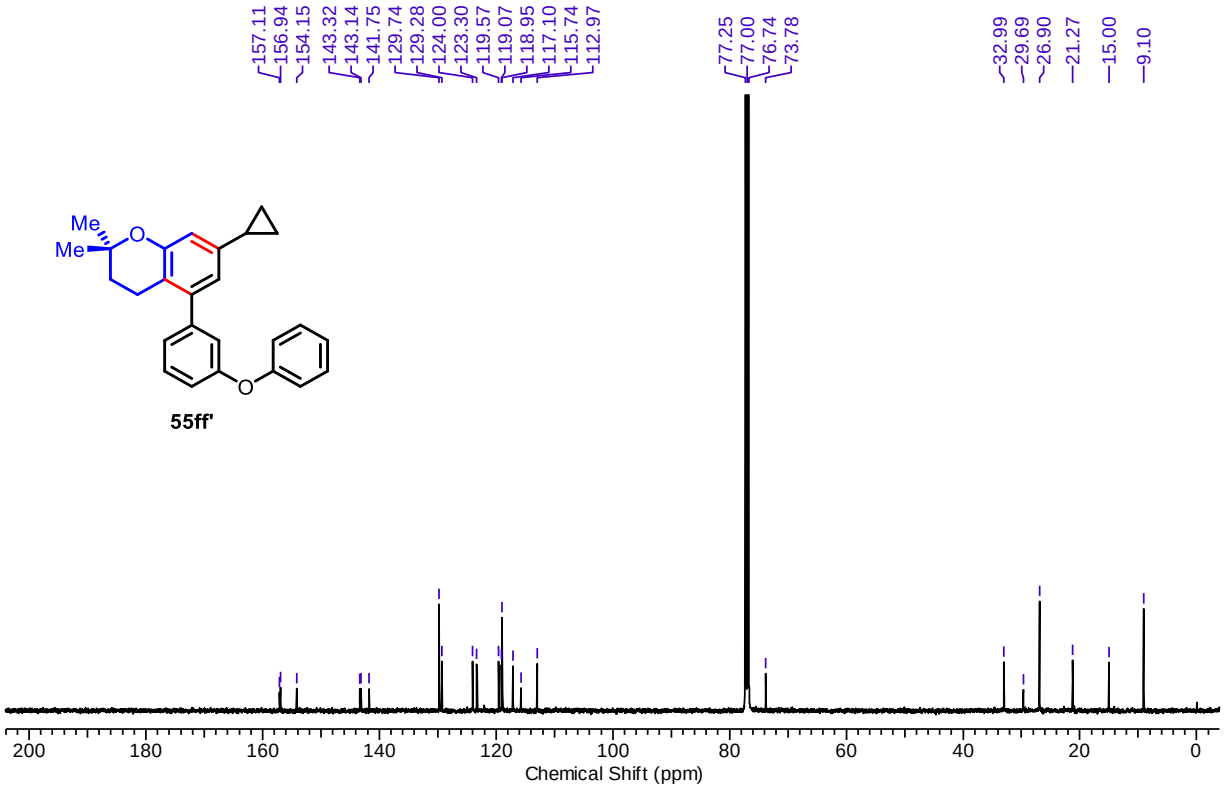
^{13}C NMR spectrum of compound 55ft



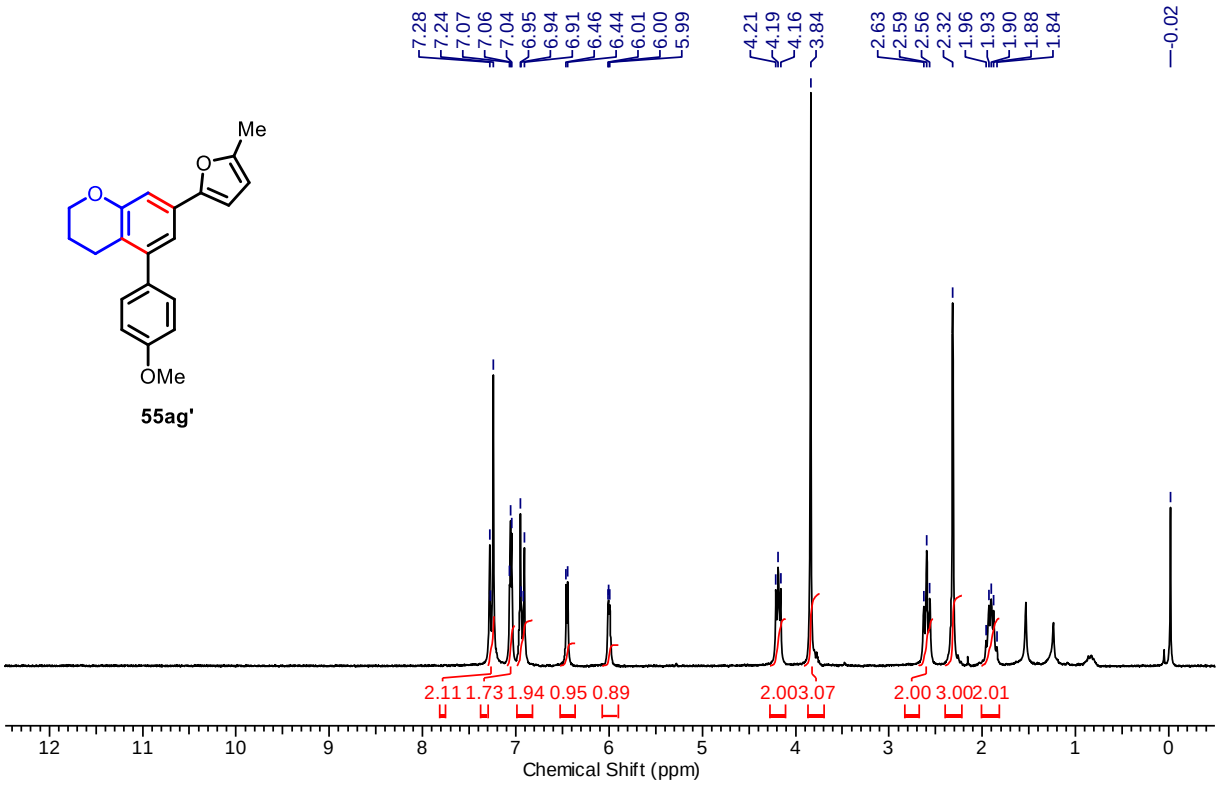
^{1}H NMR spectrum of compound 55ff'



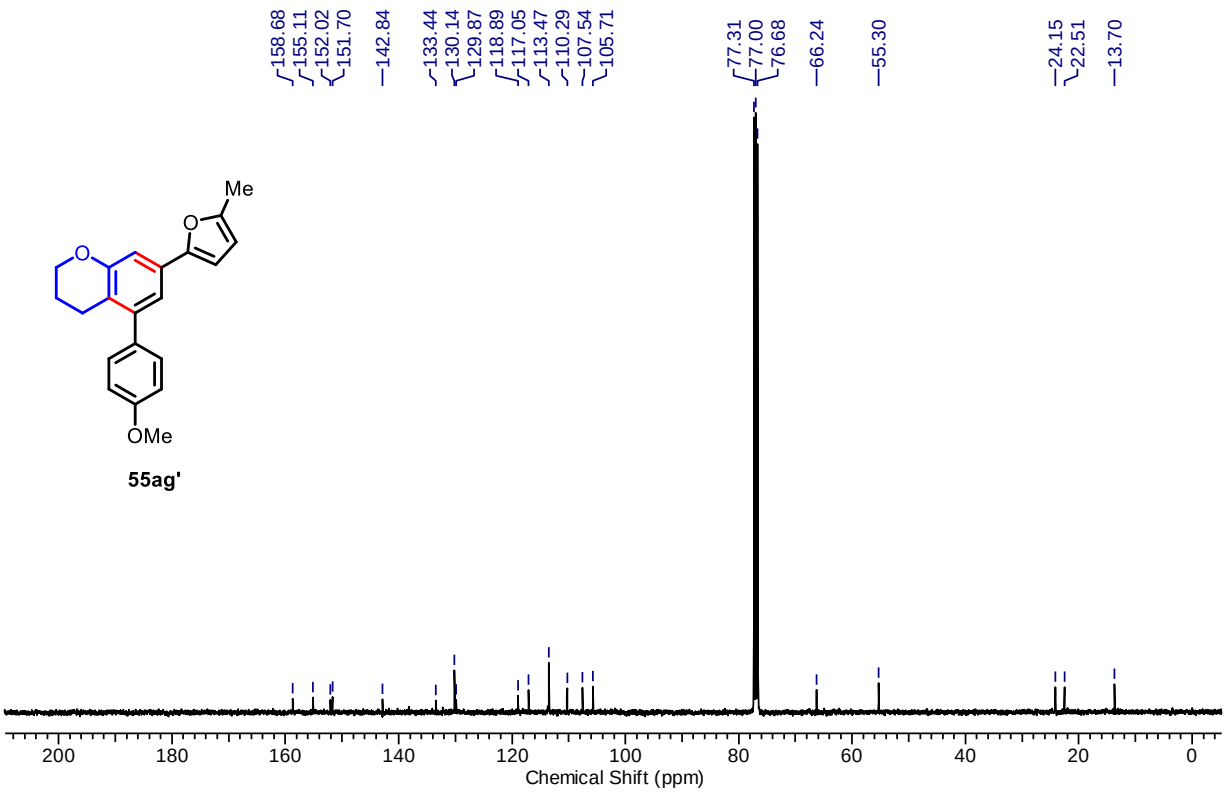
^{13}C NMR spectrum of compound 55ff'



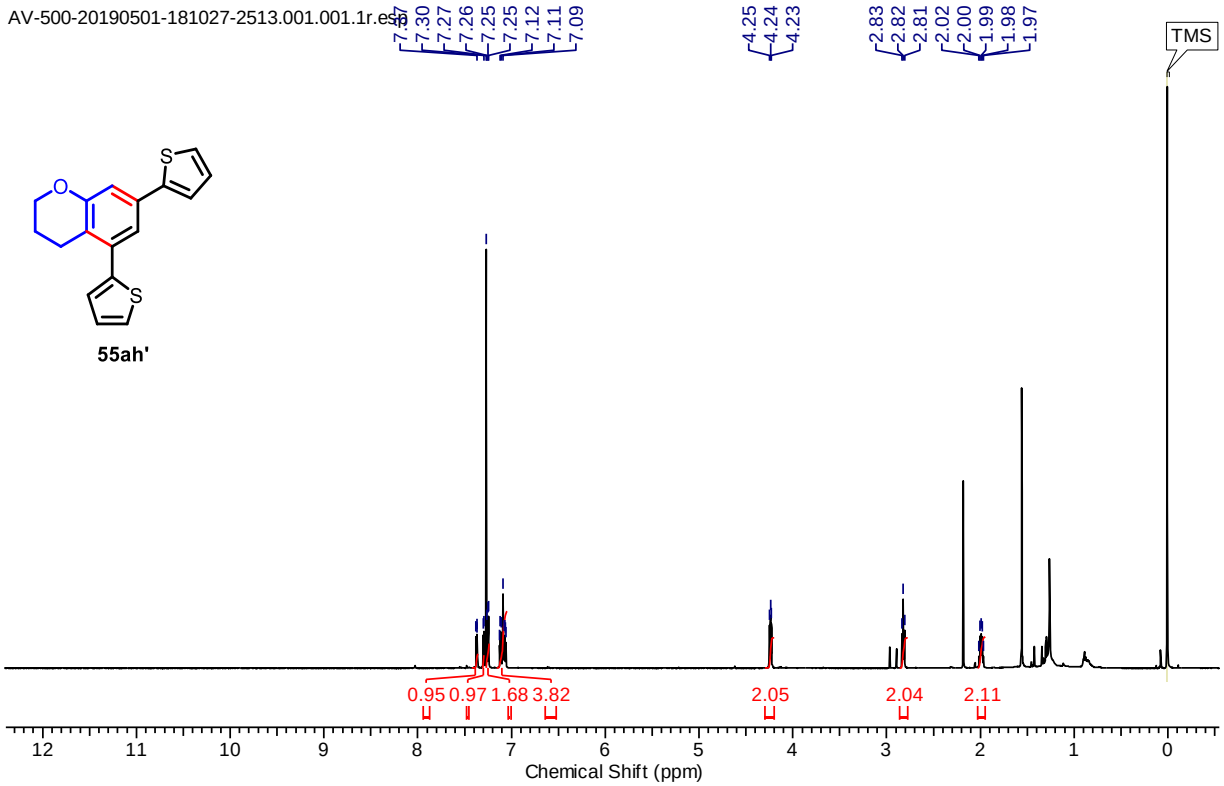
^{1}H NMR spectrum of compound 55ag'



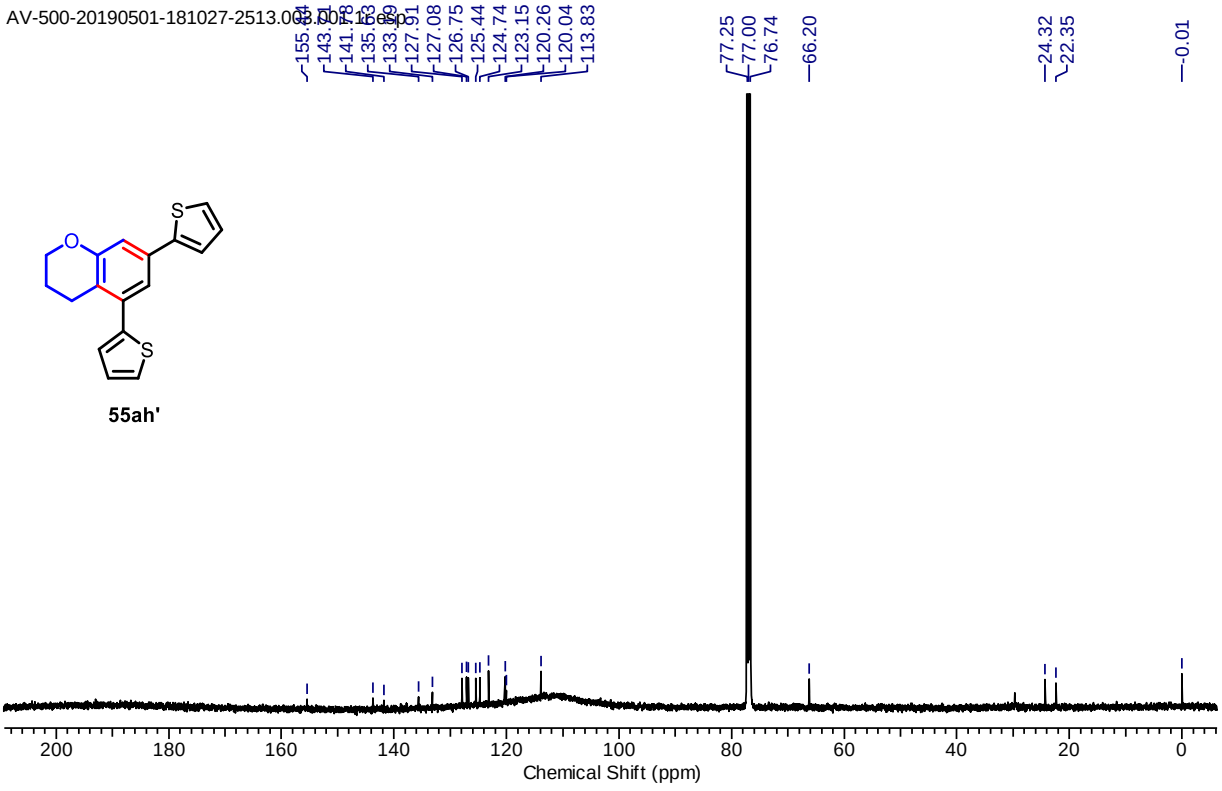
^{13}C NMR spectrum of compound 55ag'



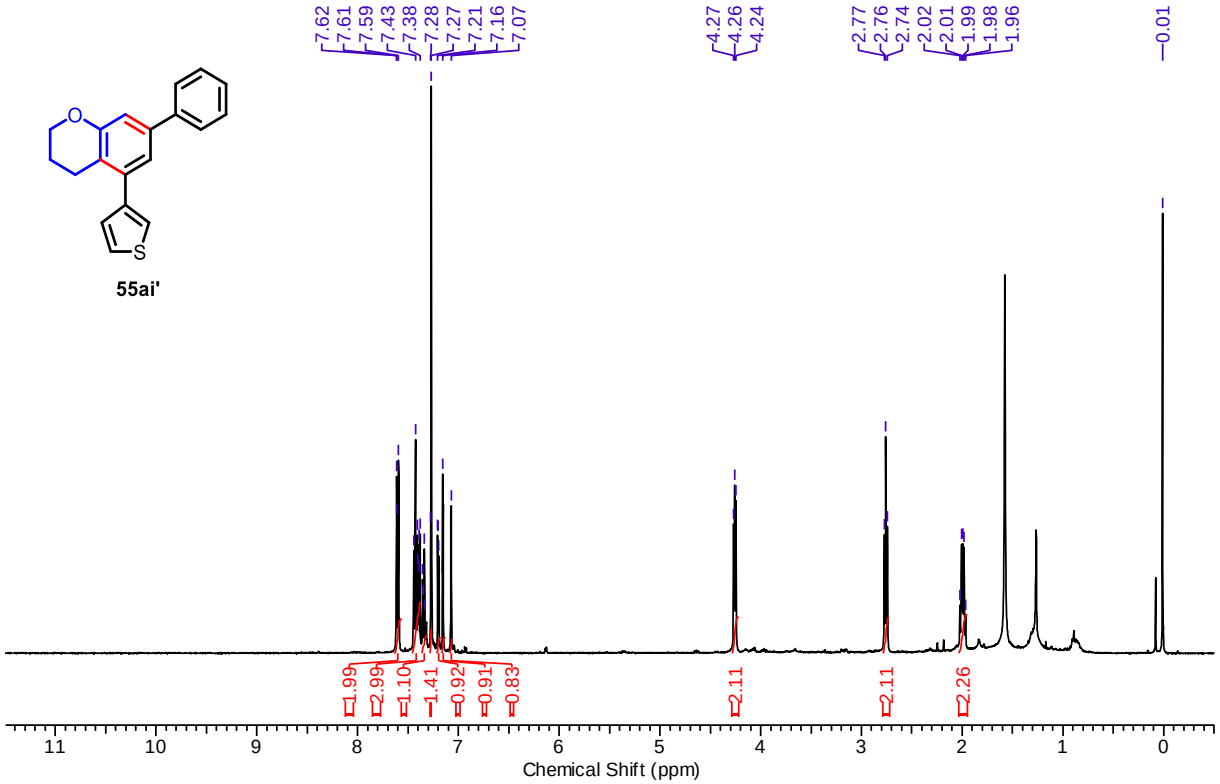
^{1}H NMR spectrum of compound 55ah'



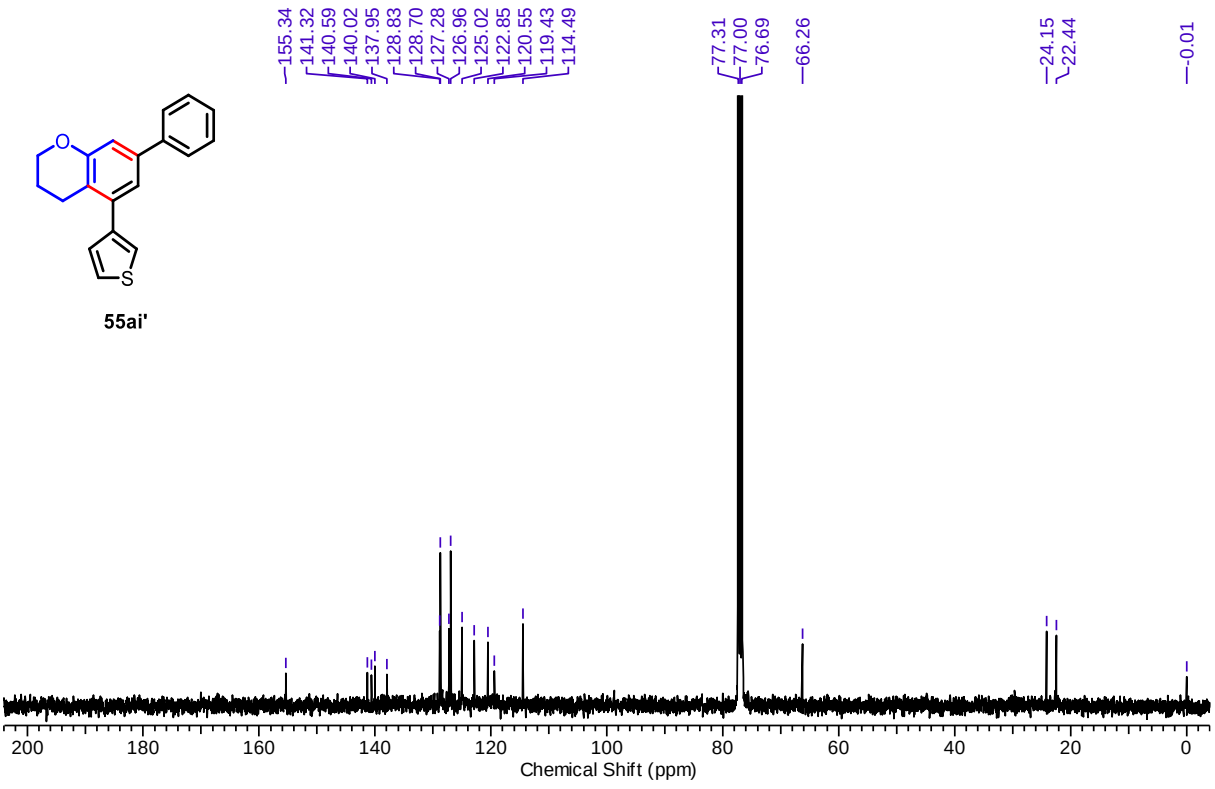
^{1}H NMR spectrum of compound 55ah'



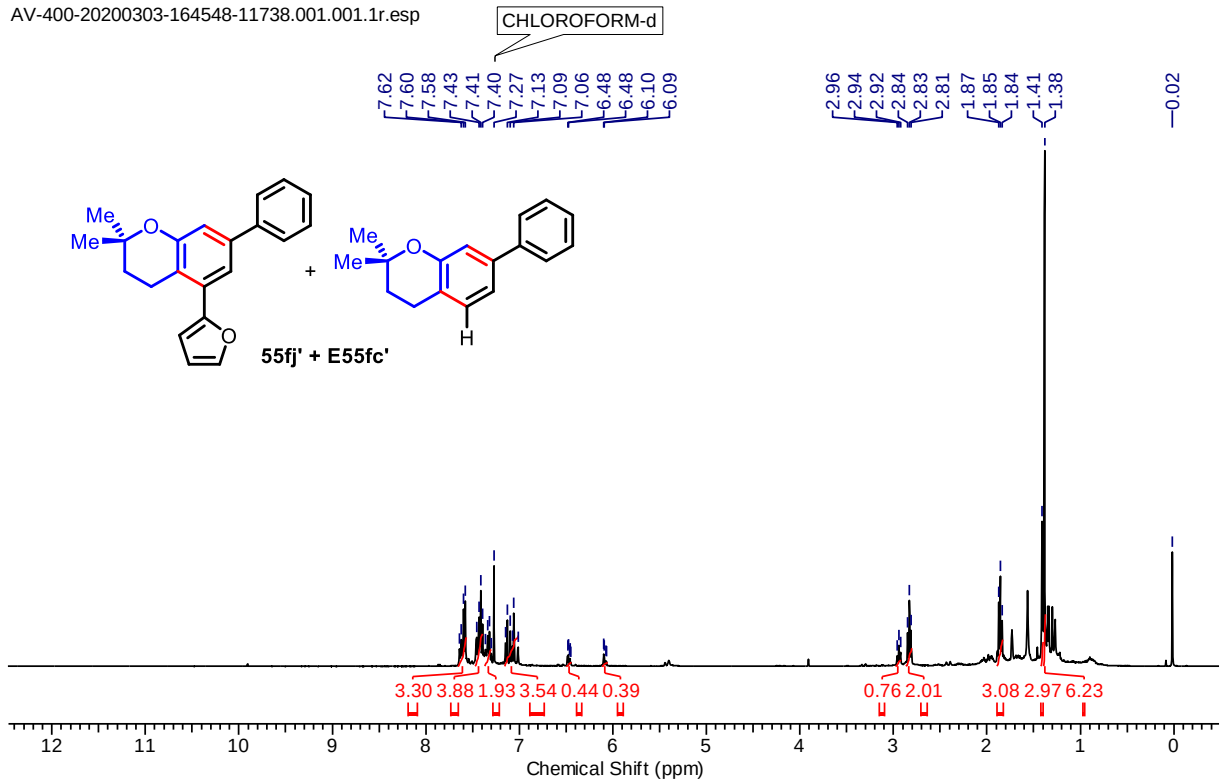
^{1}H NMR spectrum of compound 55ai'



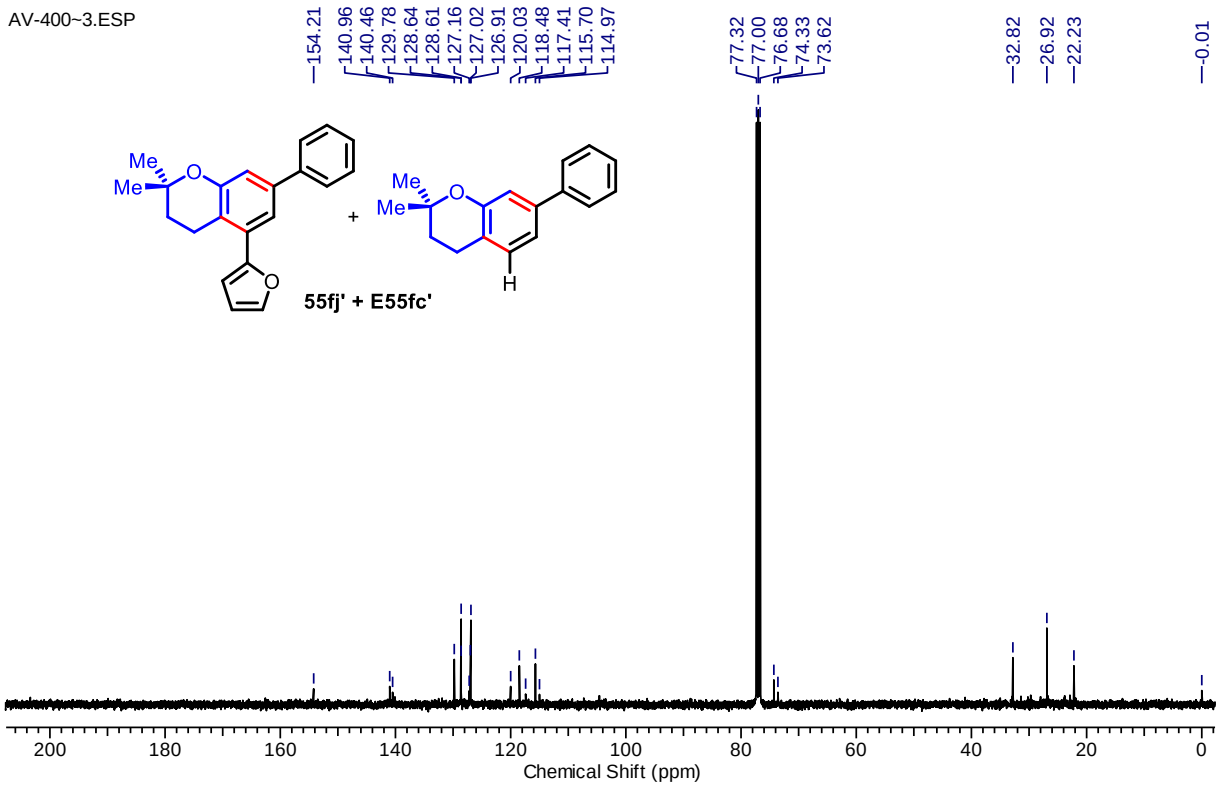
^{13}C NMR spectrum of compound 55ai'



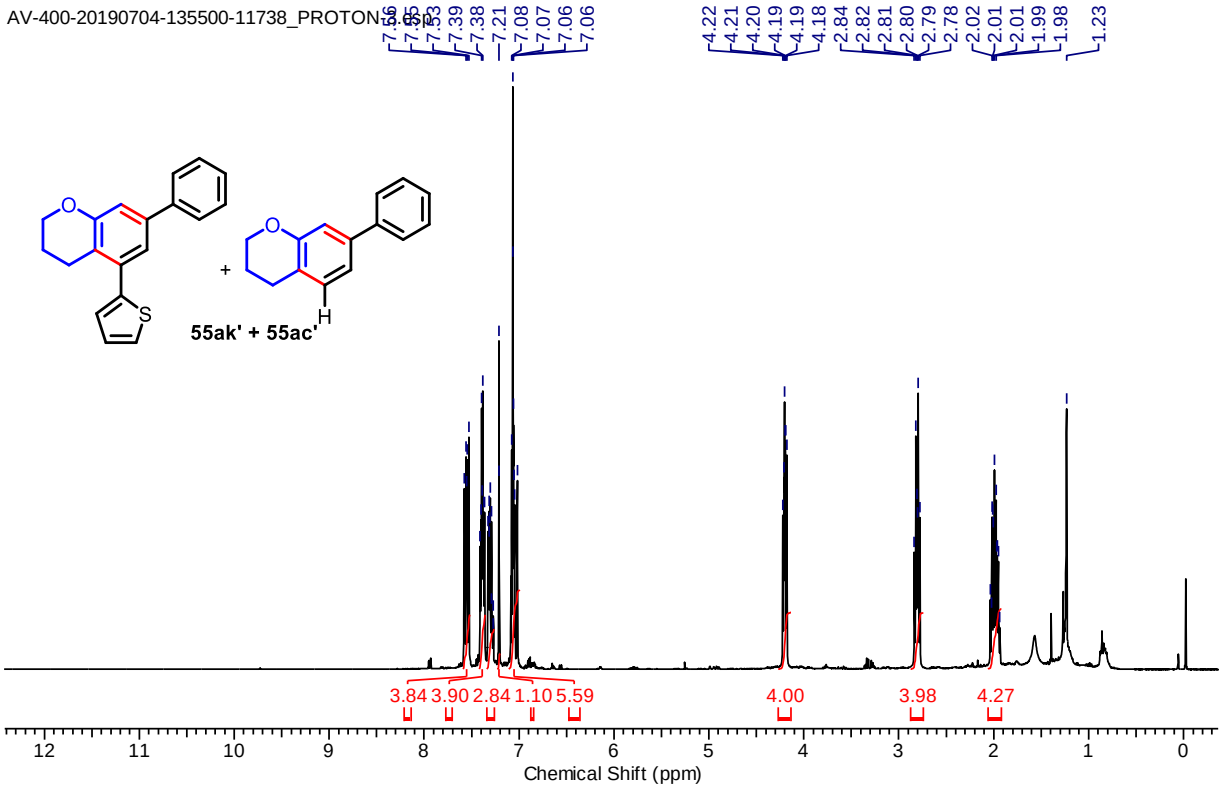
^{1}H NMR spectrum of compound 55fj'+E55fc'



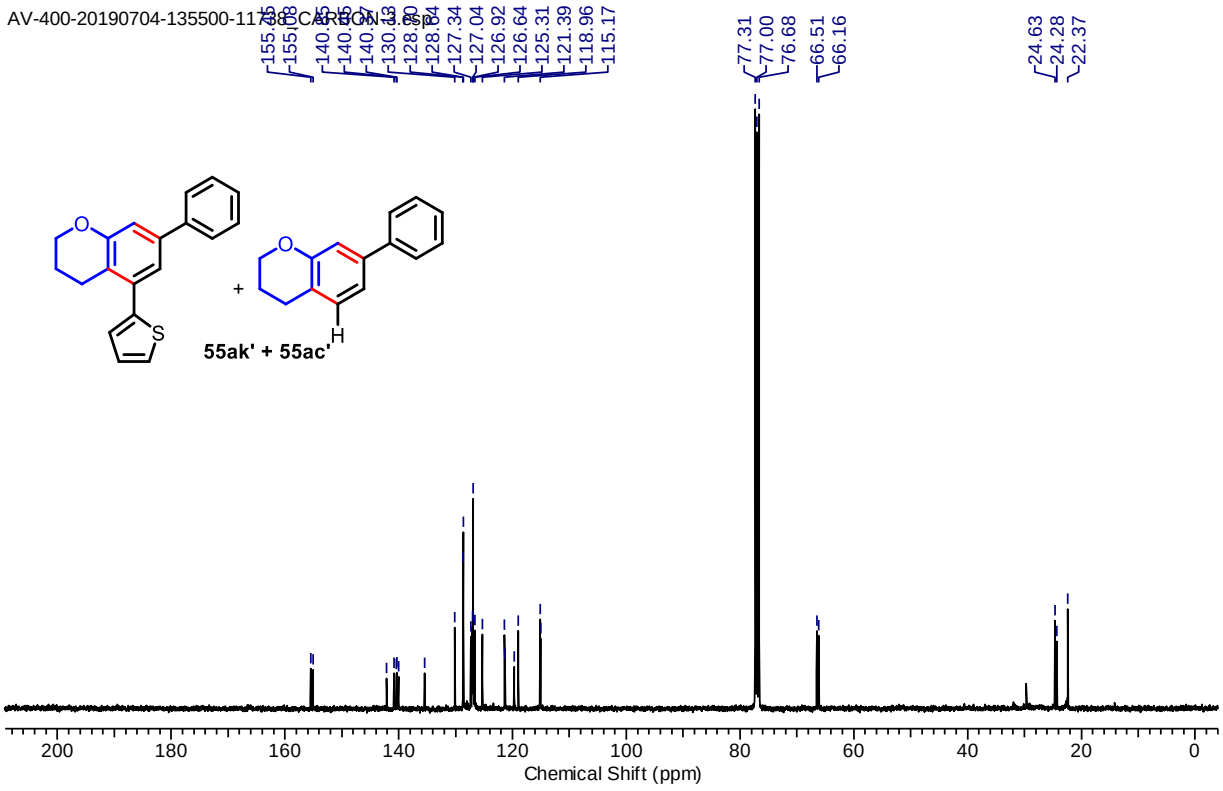
^{13}C NMR spectrum of compound 55fj'+E55fc'



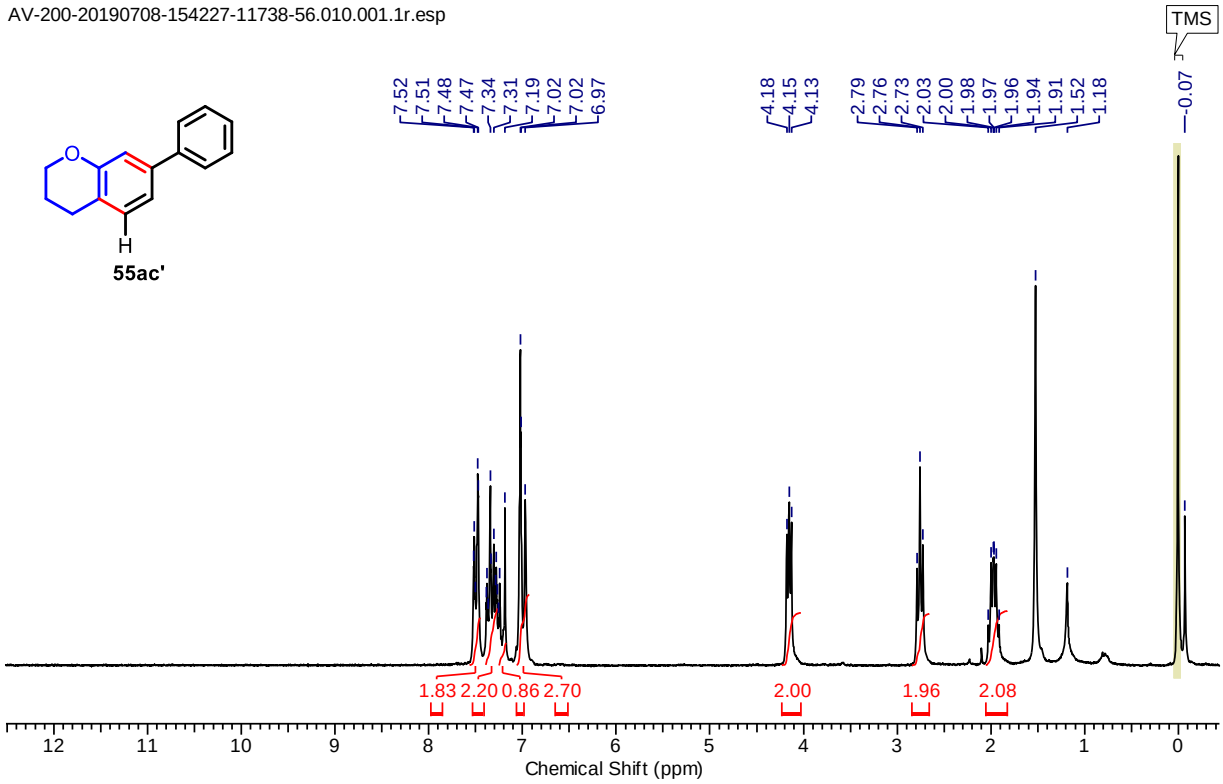
^{1}H NMR spectrum of compound 55ak' +55ac'



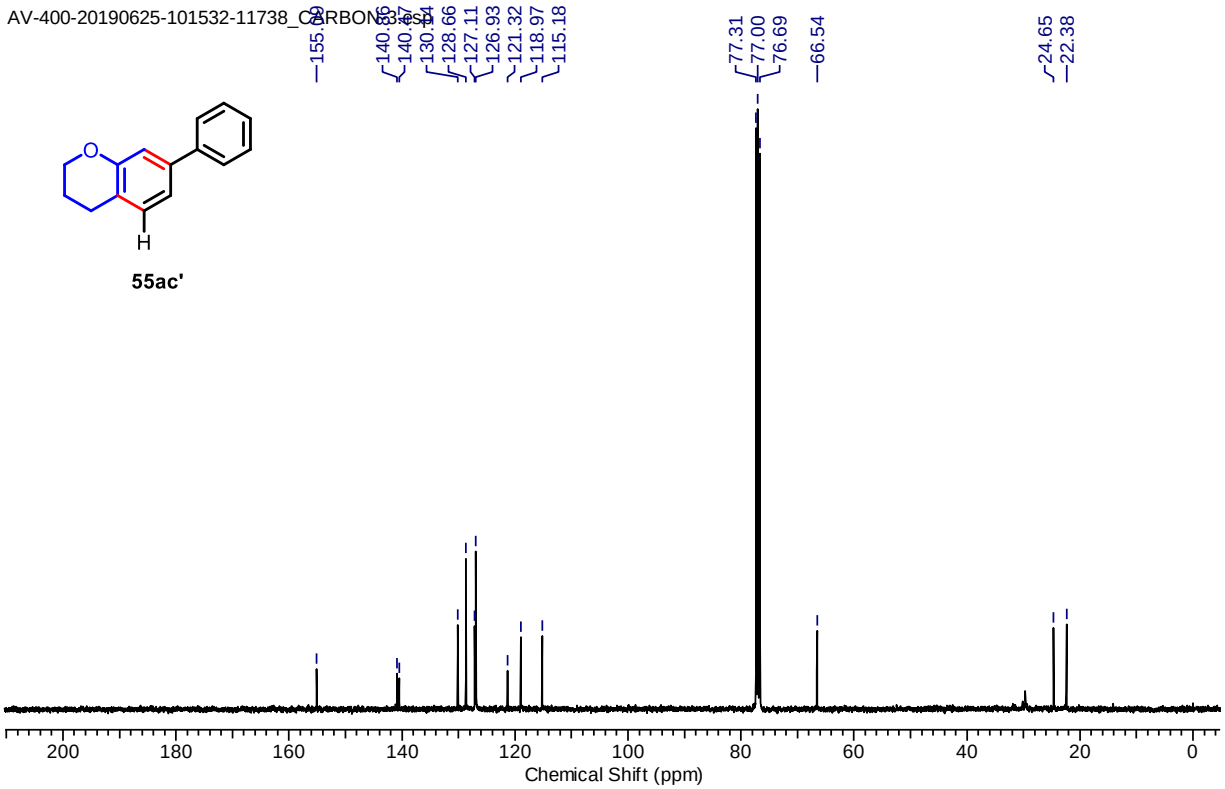
^{13}C NMR spectrum of compound 55ak' +55ac'



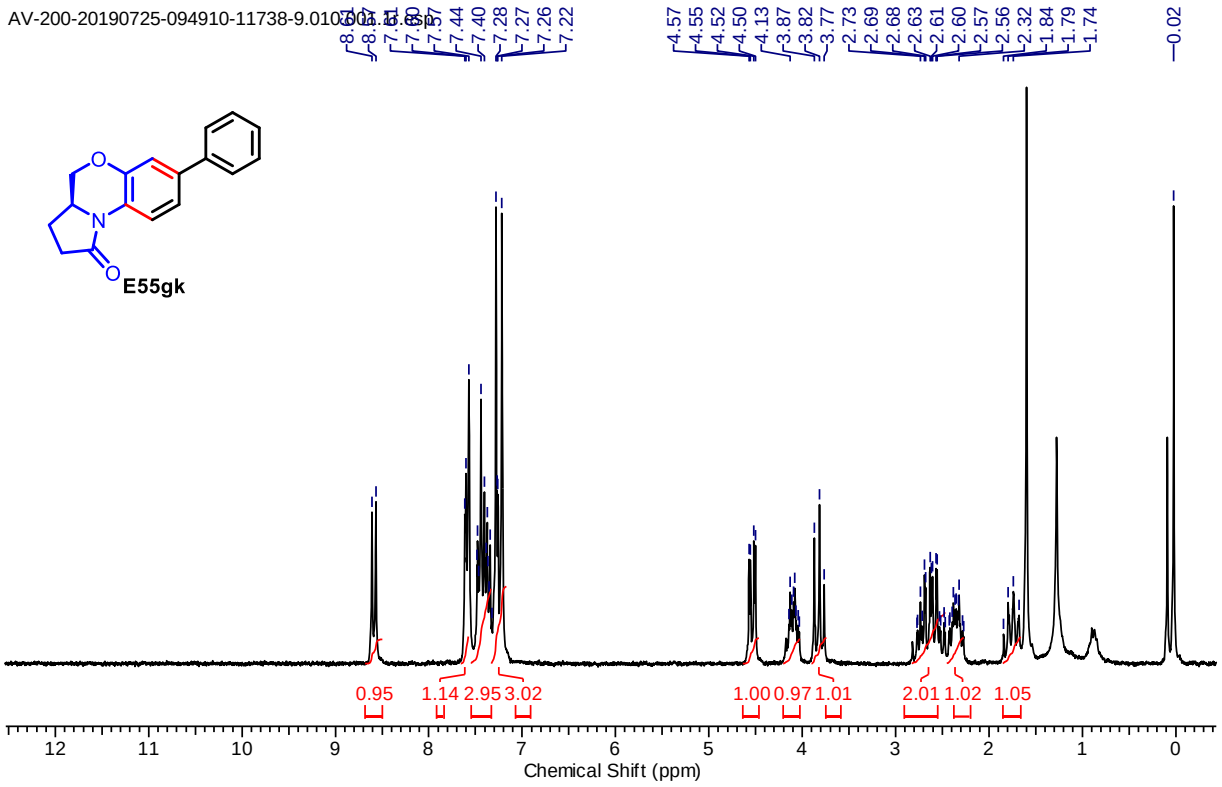
^{1}H NMR spectrum of compound 55ac' (prepared from 53a and 54l')



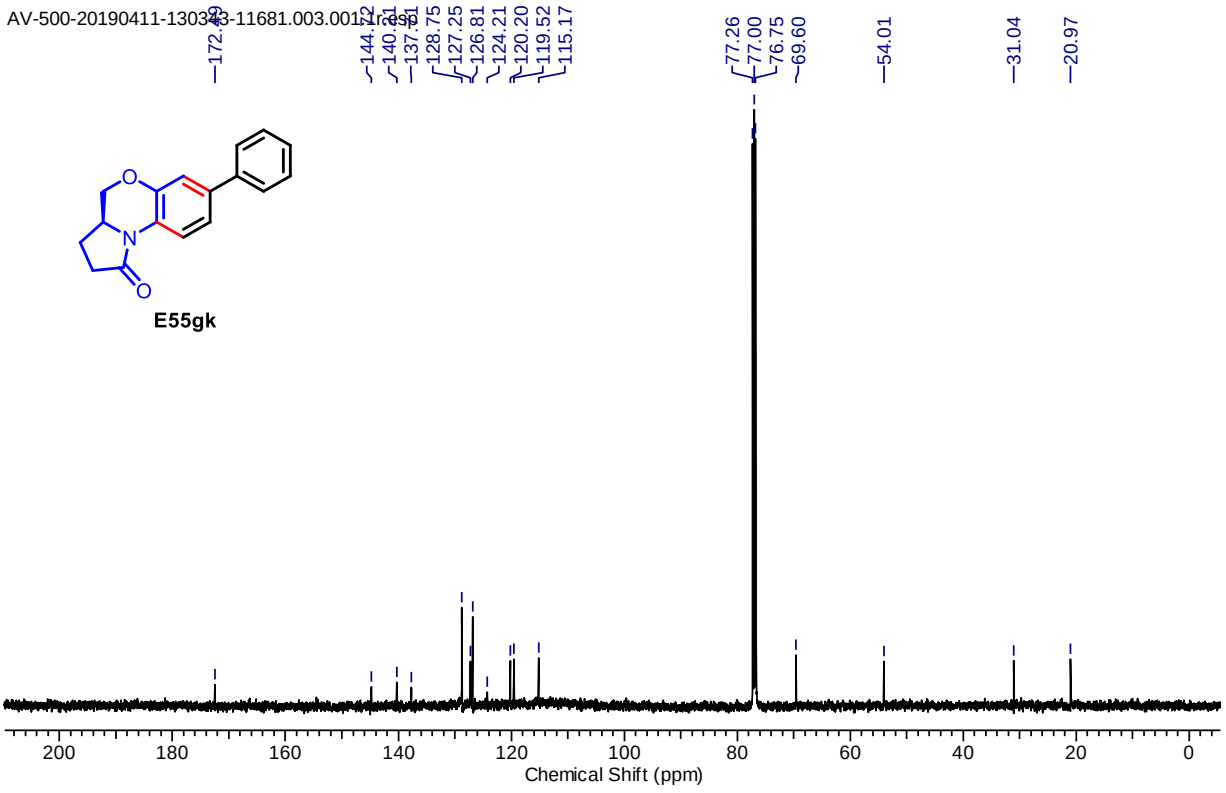
^{13}C NMR spectrum of compound 55ac'(prepared from 53a and 54l')



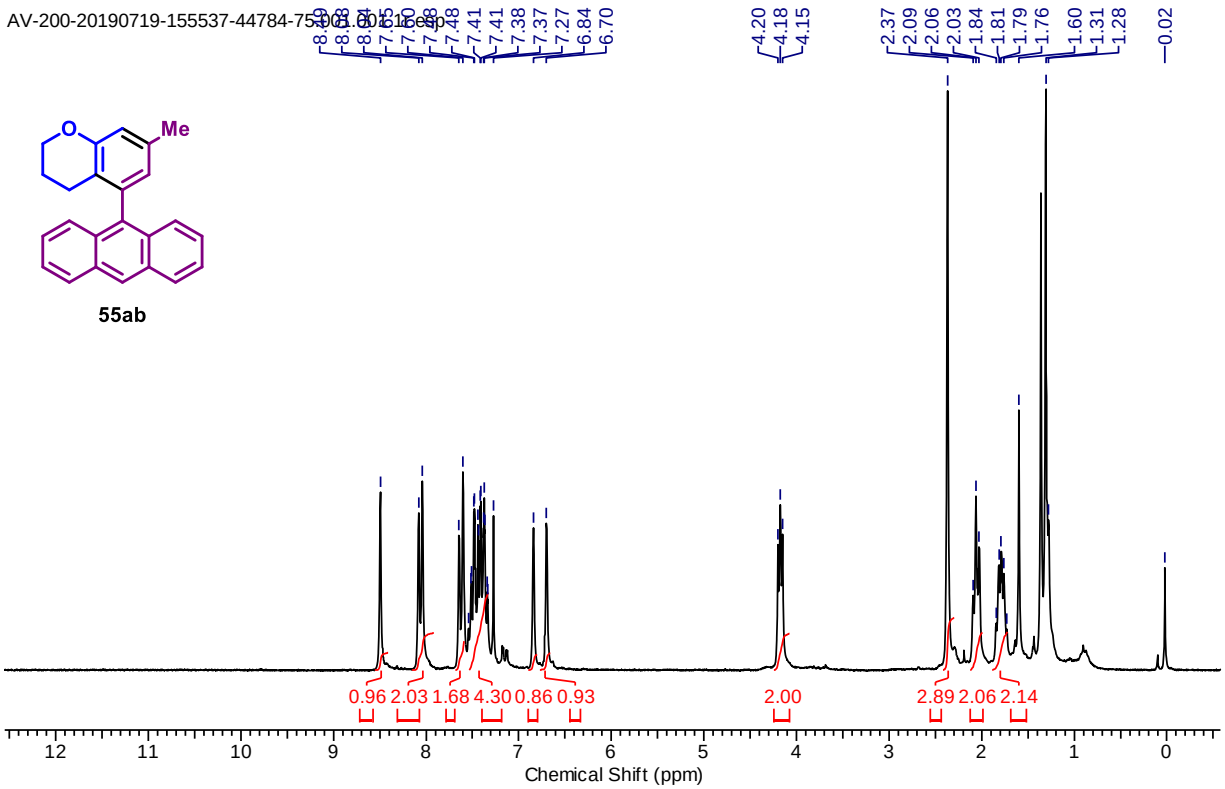
^{1}H NMR spectrum of compound E55gk (prepared from 53g and 54k)



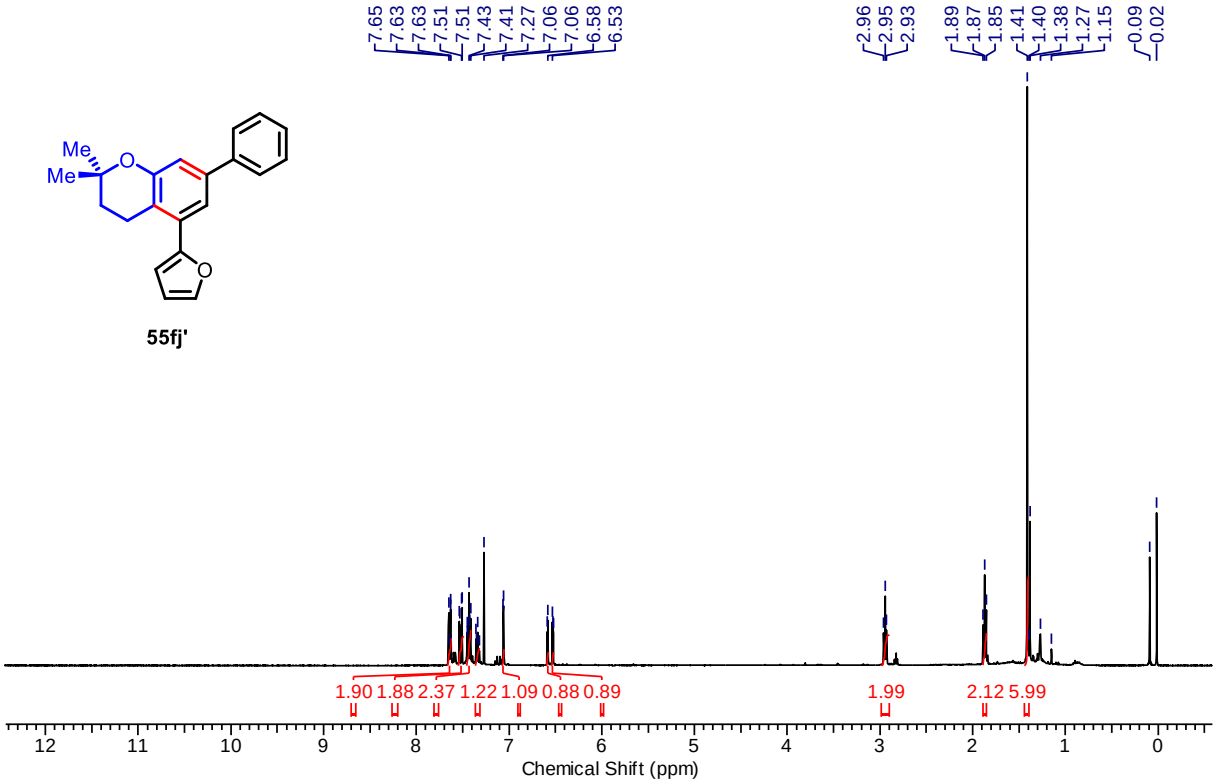
^{13}C NMR spectrum of compound E55gk (prepared from 53g and 54k)



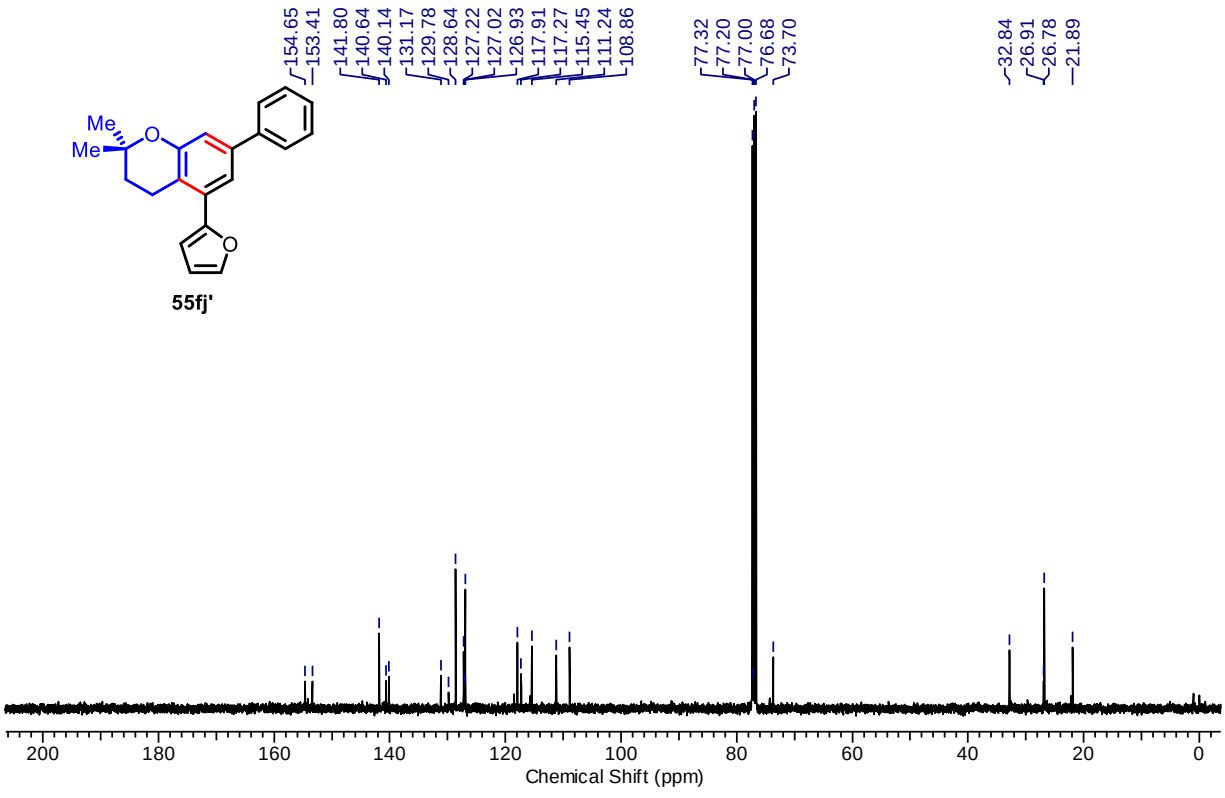
^{1}H NMR spectrum of compound 55ab (prepared from T3ab):



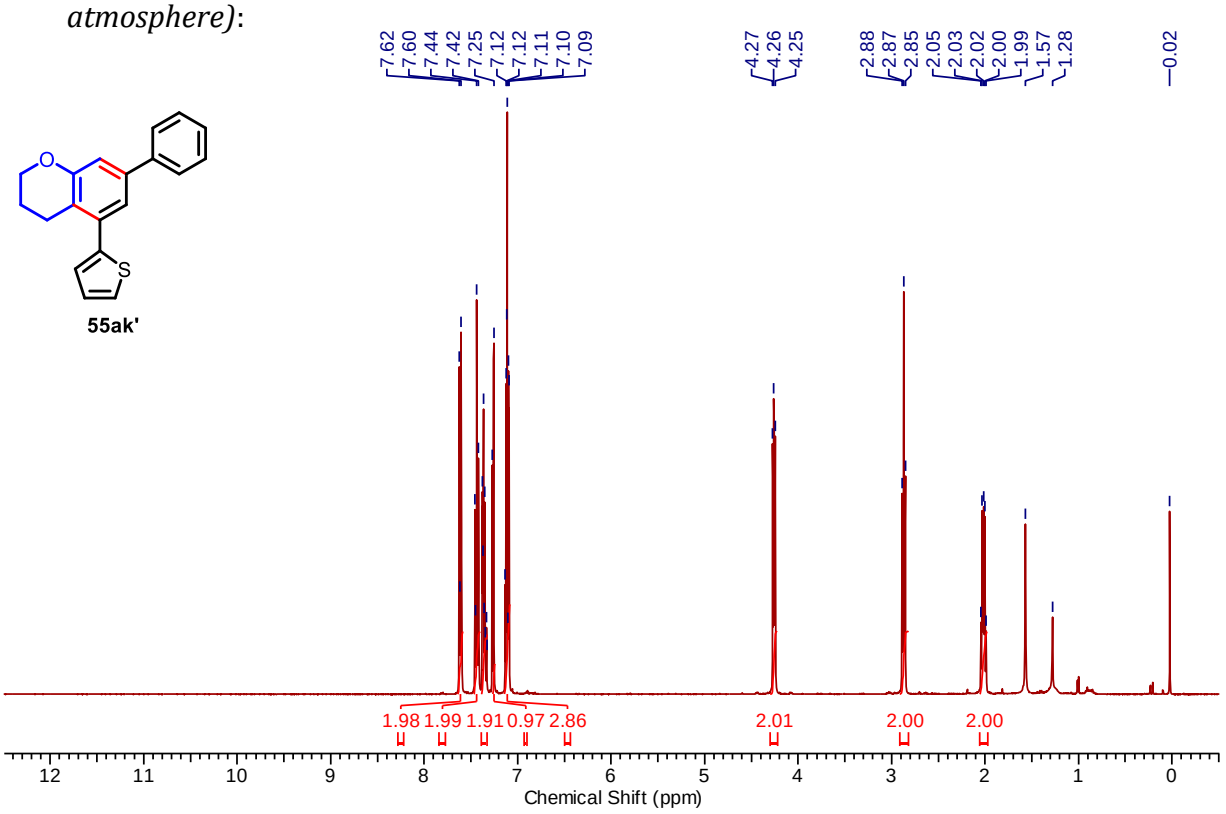
^{1}H NMR spectrum of compound 55fj' *(obtained from the reaction under oxygen atmosphere)*:



^{13}C NMR spectrum of compound 55fj':

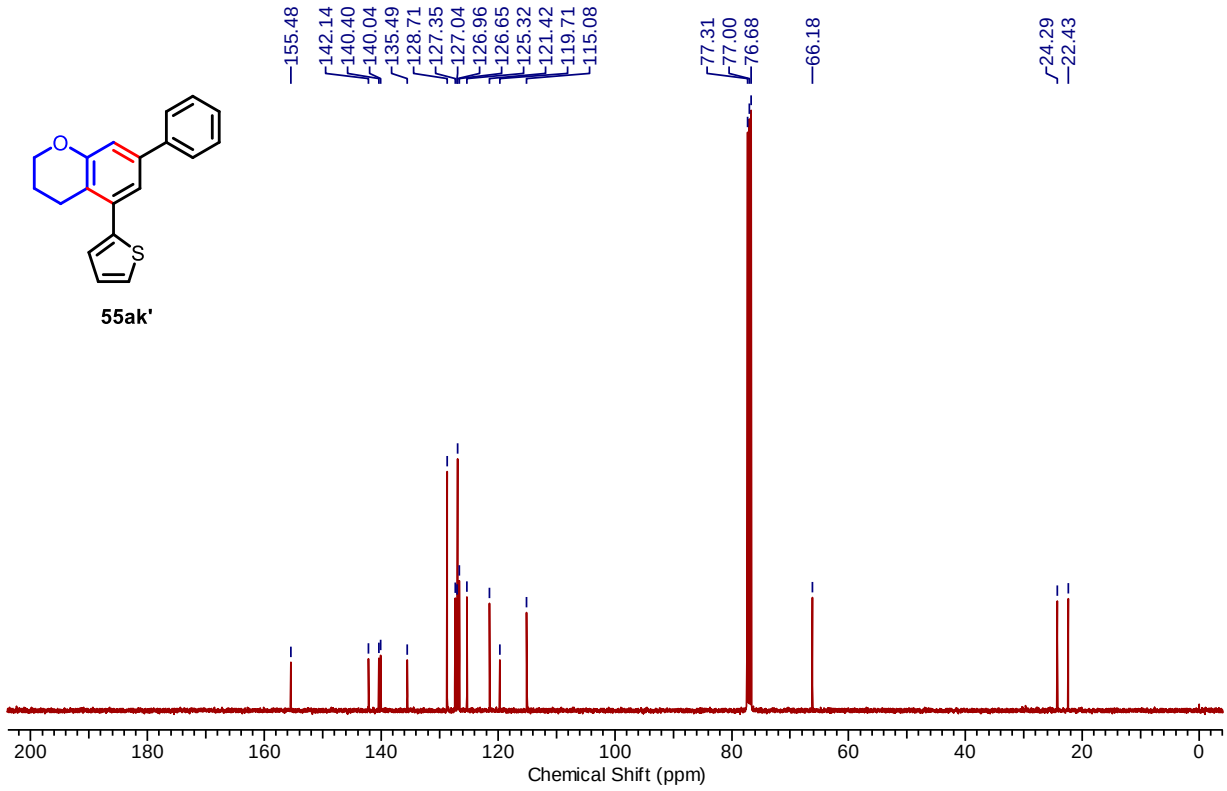


^{13}C NMR spectrum of compound 55ak' *(obtained from the reaction under oxygen atmosphere)*:



55ak'

^{13}C NMR spectrum of compound 55ak':



55ak'

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Instrument :     GCMS
Sample Name: F
Misc Info  :
Vial Number: 3
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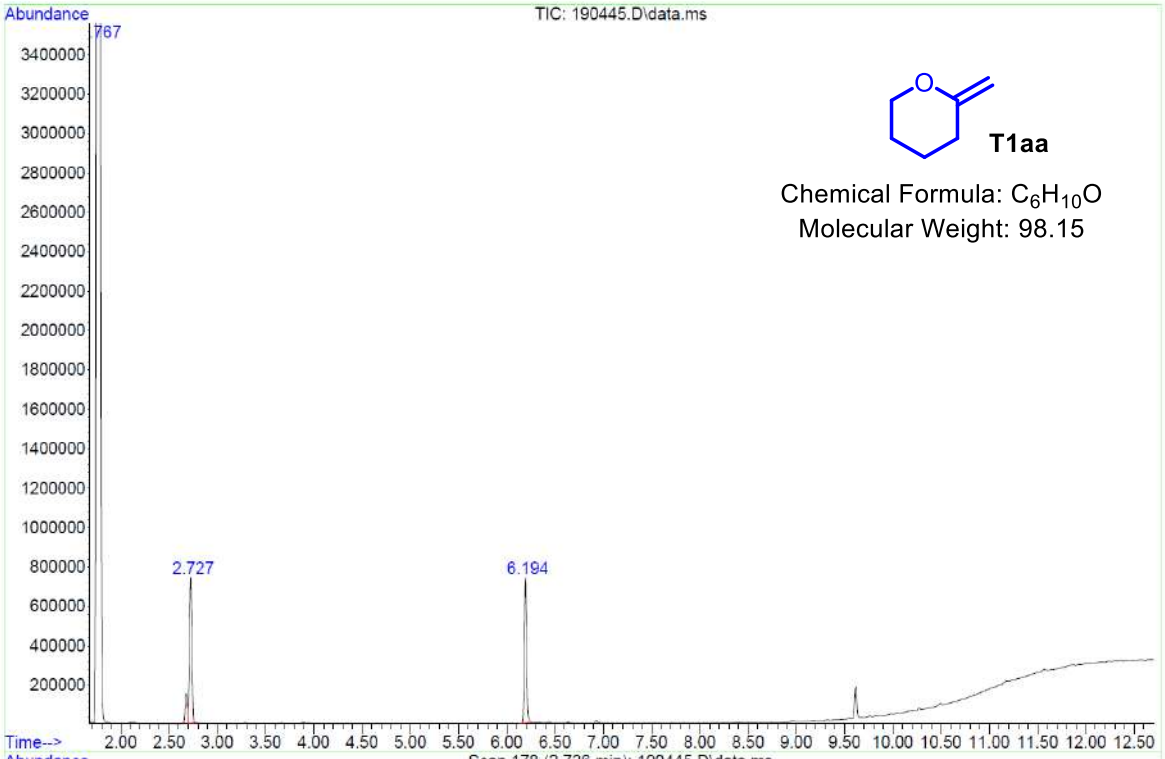

T1aa

Chemical Formula: $C_6H_{10}O$
Molecular Weight: 98.15

Figure S4. GC-MS chromatogram at t_1 = 1h of the reaction mixture of **53a** and **54a**.

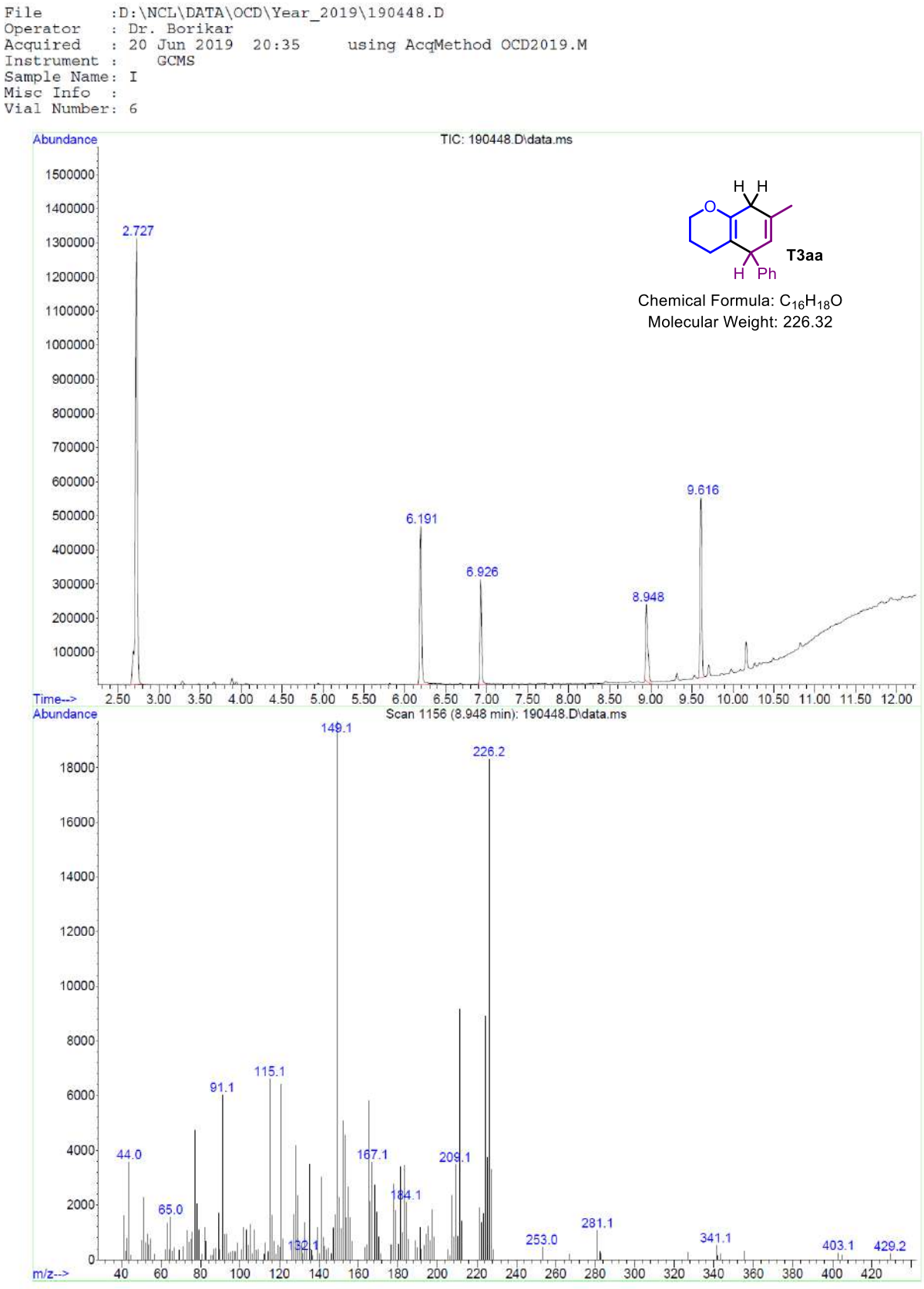

Figure S5. GC-MS chromatogram at t_2 = 2h of the reaction mixture of **53a** and **54a**.

```
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Acquired   : 20 Jun 2019  21:12     using AcqMethod OCD2019.M
Instrument :    GCMS
Sample Name: K
Misc Info  :
Vial Number: 8
```
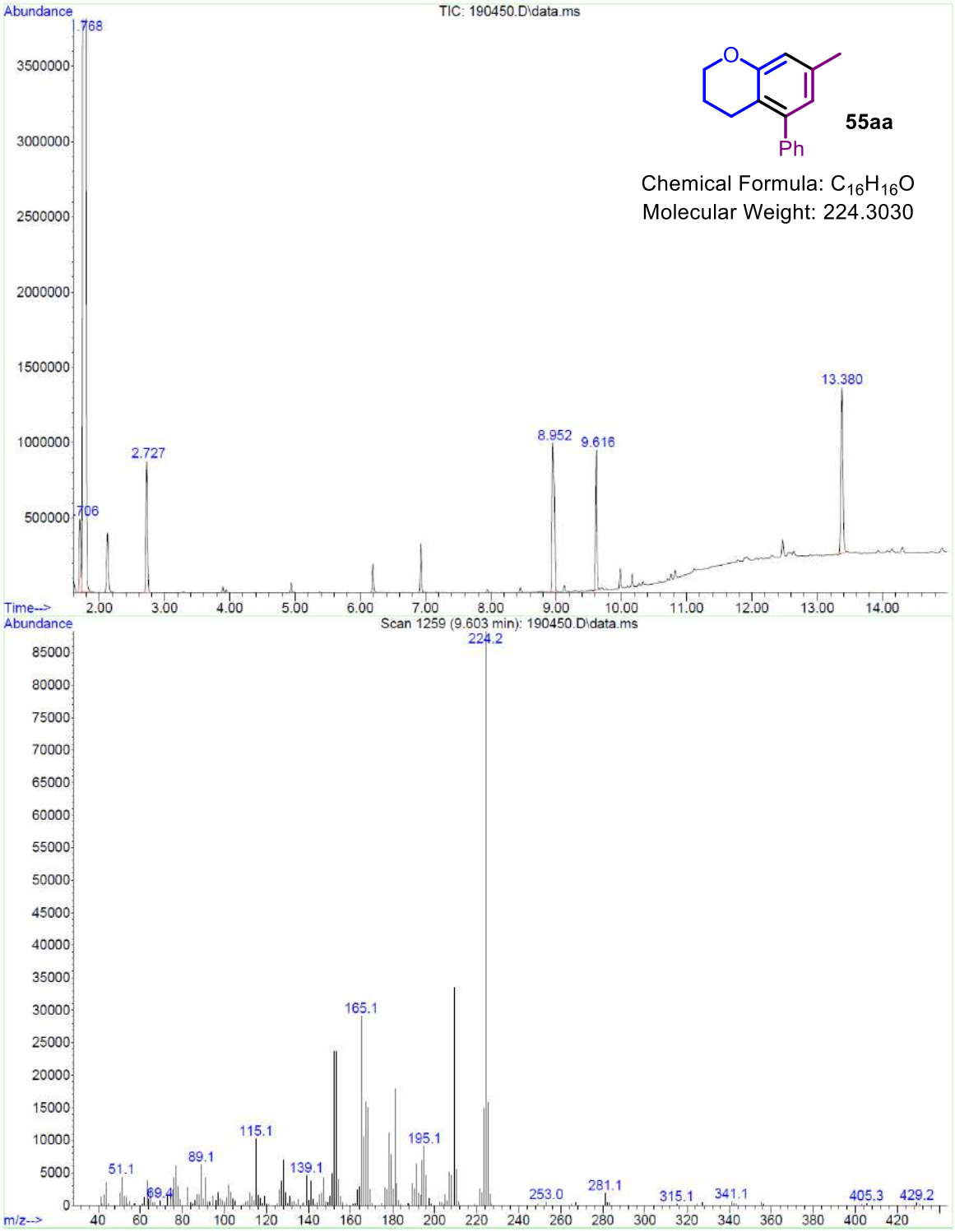



55aa

Chemical Formula: $C_{16}H_{16}O$
Molecular Weight: 224.3030

Figure S6. GC-MS chromatogram at t_3 = 2h37 min of the reaction mixture of **53a** and **54a**.

CHAPTER-4

Section-A

Introduction and previous approaches to (sulfonamides) benzoisothiazolo furo- and pyrano-pyridines

4.1 Introduction

The [4+2]-cycloaddition (Diels-Alder reactions) is one of the universal synthetic methods used to construct six-membered carbocyclic and heterocyclic structures.[1] In contrast to the normal electron-demand Diels-Alder reaction (where an electron-rich diene moiety reacts with an electron-deficient dienophile), in an inverse–electron–demand Diels-Alder reaction (IEDDA), an electron-rich dienophile reacts with an electron-poor diene. These both reactions provide complex cyclic molecules with high stereoselectivity, atom, and step economy. Mainly, IEDDA reactions are versatile and aid the constructions of O-, N-, and S-containing heterocycles related to bioactive natural products and drugs (for instance, piperidines, dihydropyrans, sulphonamides, and many others).[2]

In the field of drug discovery, sulphonamide and/or cyclic sulphonamides (1,2-thiazole dioxides) are considered privileged scaffolds, and these derivatives are known to exert excellent biological activities. In addition to cyclic-sulphonamides, N-sulphonyl imidazole, benzothiazole-dioxides, and benzoisothiazolo-furo-piperidines (associated with our present work) are well precedent in the literature and known to possess excellent biological activities. These piperidine scaffolds are found in 72 currently marketed drugs approved by the FDA (Food and Drug Administration) (Figure 4.1).[3]

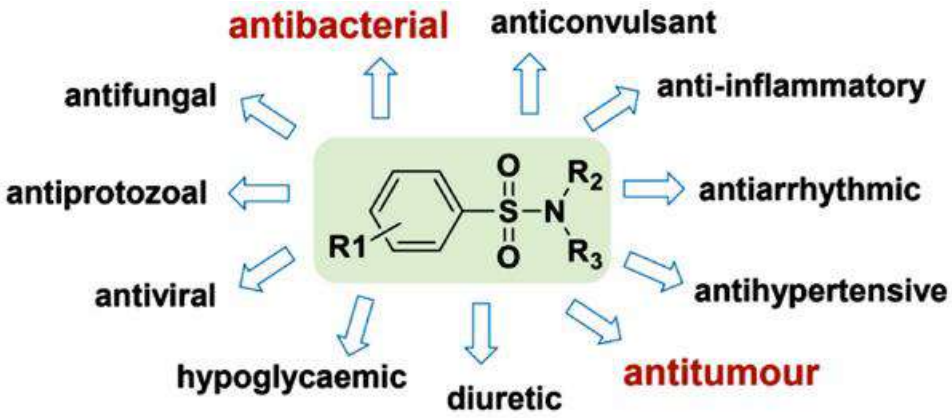


Figure 4.1: Therapeutic applications of sulfonamide scaffolds.

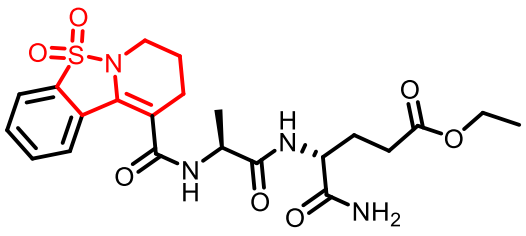
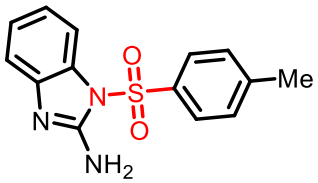
Sulphonamides are used extensively as antibacterial medicines (according to Seydel 1968 and the Supuran 2003 data source) to treat bacterial infections in humans and animals.[4] Sulphonamide medicines are known to cause allergic reactions

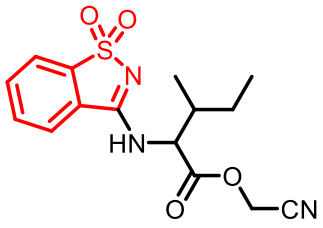
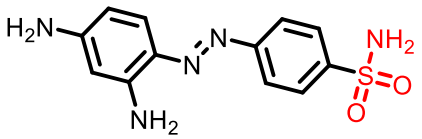
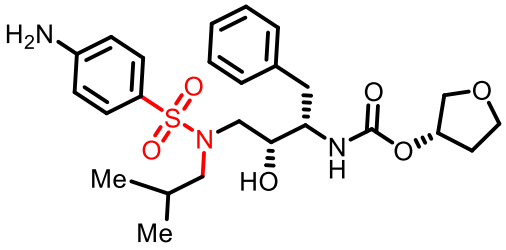
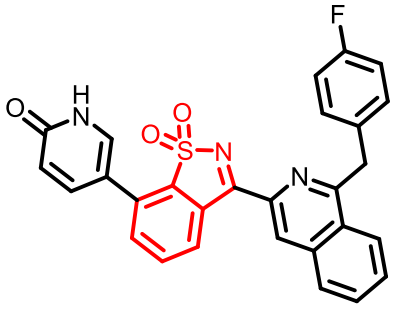
in high doses, similar to the 3% of adverse drug reactions to penicillin.[5] Typically, the folate synthesis enzyme dihydropteroate synthase (DHPS) is competitively inhibited by antimicrobial sulfonamide.[6]

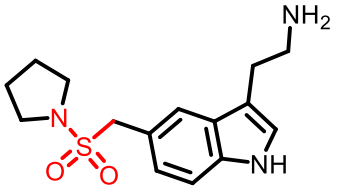
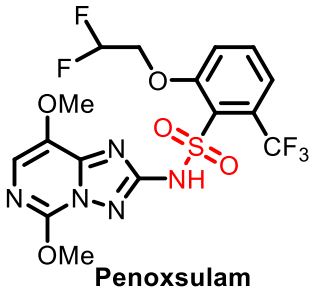
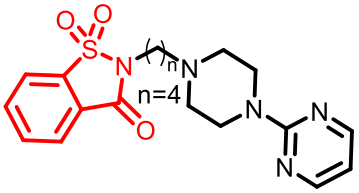
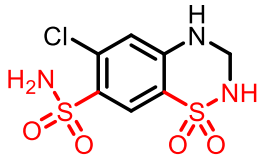
This chapter describes our effort directed towards developing a novel, practical, and efficient synthetic methodology for arene-tethered tricyclic sulphonamides (having benzoisothiazolo pyranopyridine and furopyridine dioxides) using readily accessible alkynols and isothiazole 1,1-dioxide as building blocks and involving σ- and π-activation (dual activation) induced cascade annulation reactions (an inverse–electron–demand Diels-Alder reaction (IEDDA)).

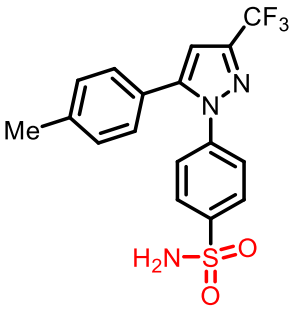
Herein provided a brief literature survey on sulfonamide-derived bioactive molecules and earlier synthetic approaches for these scaffolds (Table 4.1).

Table 4.1 | Representative examples of sulfonamide-containing natural products.

Sr. No.	Structure	Isolation and Activity
1.	 **Desmuramyldipeptide analogs**	In 2012, Dolencand's research group disclosed the synthesis of desmuramyldipeptide analogs and found that these compounds increase the production of proinflammatory cytokines such as TNF-a, IL-6, IL-1b, and IL-8.[7]
2.	 **Noditinib-1**	In 2011, Correa et al. discovered noditinib-1 as a selective NOD1 inhibior. Noditinib-1 is a selective and potent inhibitor of NOD1-induced NF-kB activation. Mutations associated with NOD proteins cause various inflammatory diseases, noditinib-1 showed promise as a potential

		therapeutic agent.[8]
3.	 Saccharine derivative	In 2015, Lui et al. synthesized diverse saccharine derivatives and evaluated them for their biological profile. Many of them showed significant human leukocyte elastase inhibitory activity.[9]
4.	 Prontosil (1932)	In 1932, Bayer and his co-worker discovered prontosil as an antibacterial medication.[10] It is effective against gram-positive *cocci* *but* isn't active against enterobacteria.
5.	 Amprenavir	Amprenavir was discovered in 1992 while researching and developing renin inhibitors as potent antihypertensive agents. Amprenavir is a potent inhibitor used to treat HIV patents. It was approved by the FDA in 1999.[11]
6.	 Saccharine derivative	Zhao's research group synthesized diverse saccharine derivatives, which showed potent HCV NS5b inhibitor properties.. [12]
7.		Almotriptan medicine was patented in 1992 and was approved for

	 **Almotriptan**	medical use in 2000. It is used to treat the acute headache phase of migraine attacks that either have or do not have an aura.[13]
8.	 **Penoxsulam**	Penoxsulam is a herbicide. In 2009, it was registered by the EPA for aquatic usage. It is a liquid (Galleon SCTM) used to regulate vast amounts of submerged, emergent, and floating-leaf vegetation.[14]
9.	 **Saccharine derivative**	Kulanga *et al.,* in 2021, studied the synthesis and medicinal properties of diverse saccharine derivatives containing long-chain aryl piperazine appendage. These molecules are known to work as HT1AR ligands and showed strong antidepressant effects (high affinity for the 5-HT1AR with Ki < 20 nM).[15]
10.	 **Hydrochlorothiazide**	The FDA approved Hydrochlorothiazide in 2020 to treat excessive blood pressure and edema. It is generally prescribed to people who have low blood potassium levels. [16]

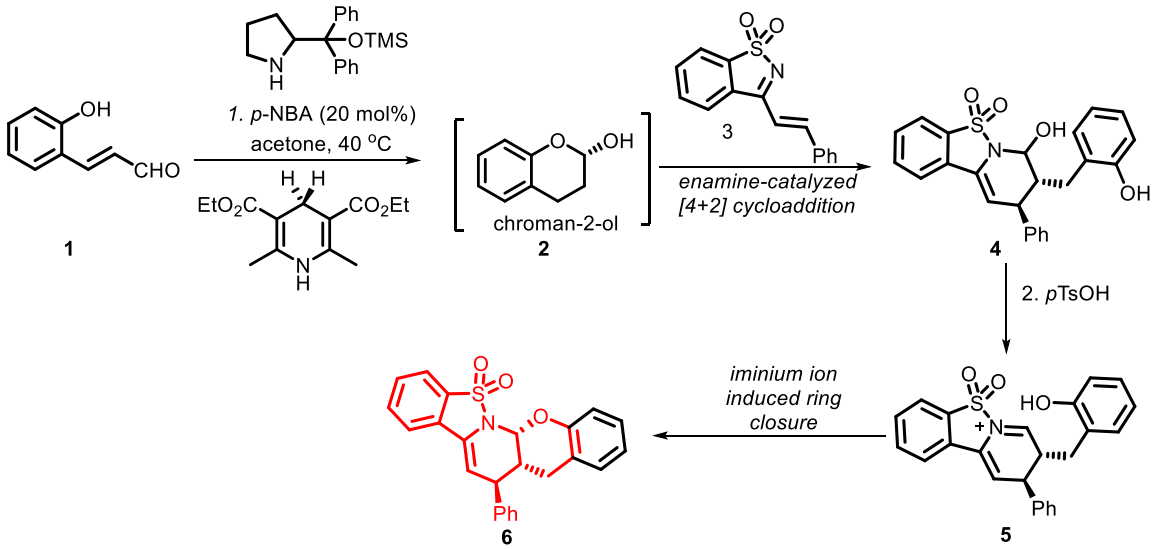
11.	 Celecoxib	Celecoxib is a non-steroidal anti-inflammatory drug that is used to treat osteoarthritis-related pain, soreness, stiffness, and swelling. The outcome is seen within one hour of administration.[17]

4.1.1 Previous approaches for the synthesis of benzoisothiazolo-pyranopyridines and furopyridine dioxides

I. Synthesis of benzoisothiazolo-pyranopyridine dioxides by an organocatalytic cascade reaction.

In 2018, the Li and Lui research group established a method for the diversified synthesis of polyheterocyclic compounds by organocatalytic cascade reaction of *α,β*-unsaturated ketimines, and 2-hydroxy cinnamaldehyde.[18]

The electron-deficient *α,β*-unsaturated ketimines **3** reacts with 2-hydroxy cinnamaldehydes **1** via one-pot [4+2]-cycloaddition (in the presence of the Hayashi catalyst and Hantzsch ester) to generate chiral iminium ion intermediate **5**. This would participate in a *p*-TsoH-mediated oxycyclization to deliver product **6** (up to 79% yield and 99% ee)(Scheme 4.1.1).

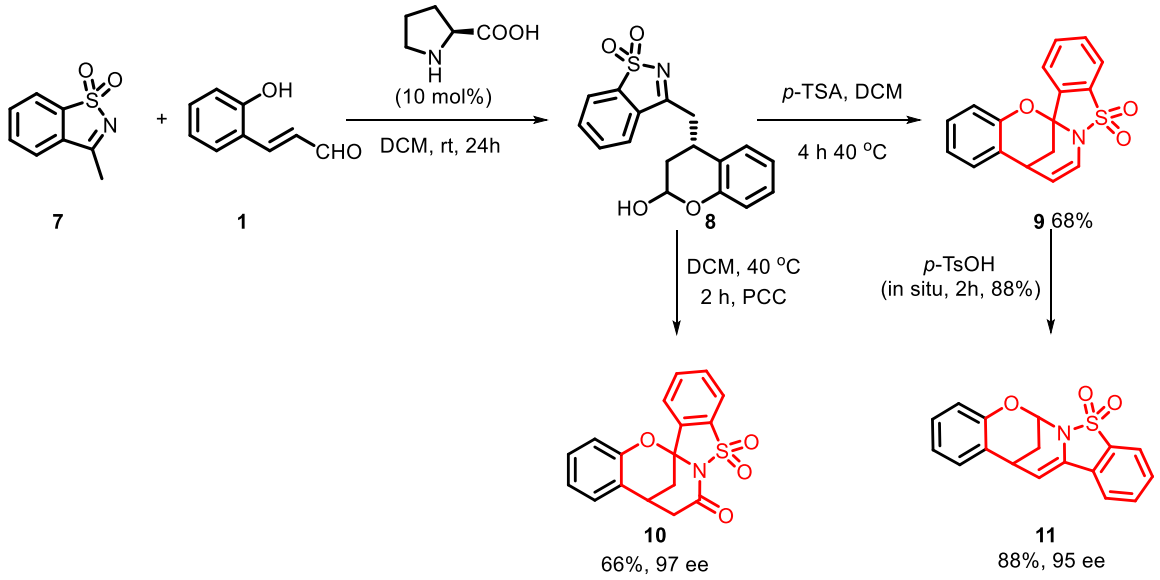


Scheme 4.1.1

II. Synthesis of benzoisothiazolo pyranopyridine dioxides by organocatalytic cascade reactions.

In 2019, Lui and co-workers demonstrated that asymmetric organocatalysis triggered the reaction of 2-Hydroxy cinnamaldehydes **1** with cyclic N-sulfonyl ketimines **7** to access enantioselective synthesis of structurally diverse chiral bridged **11** 88% yield and 95% ee, and spiro-bridged benzofused aminal derivative **9.**[19]

Mechanistically, the initial conjugate addition step involving **7** and **1** followed by hemiacetal formation, lead to the intermediate **8** (as an inseparable and equilibrating mixture of isomers). Next, PCC oxidation of **8** afforded the oxidized product (spiro benzofused aminal **10**), whereas *p*-TsOH mediated reaction delivered fused product **11** via dehydrative amino-cylization step (in 66% yield and 97% ee) (Scheme 4.1.2).

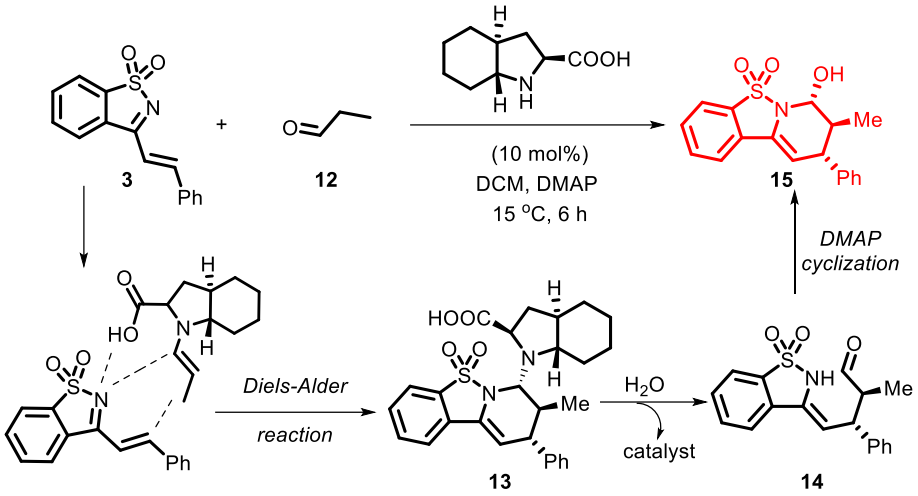


Scheme 4.1.2

III. Synthesis of benzoisothiazolo pyranopyridine dioxides by [4+2]-cycloaddition reaction

In 1998, Lui and Zangh developed an interesting protocol of *trans*-perhydroindolic acid-catalyzed synthesis of benzoisothiazolo pyranopyridine **15** (up to 98% yield and 99% ee) through asymmetric aza-Diels–Alder reaction of *α,β*-unsaturated ketimines **3** with propanal **12.**[20] A plausible reaction mechanism involves acid-catalysed [4+2]-cycloaddition reaction to get 3-methyl-4-aryldehydropiperidine intermediate **13** followed by hydrolytic cleavage of the

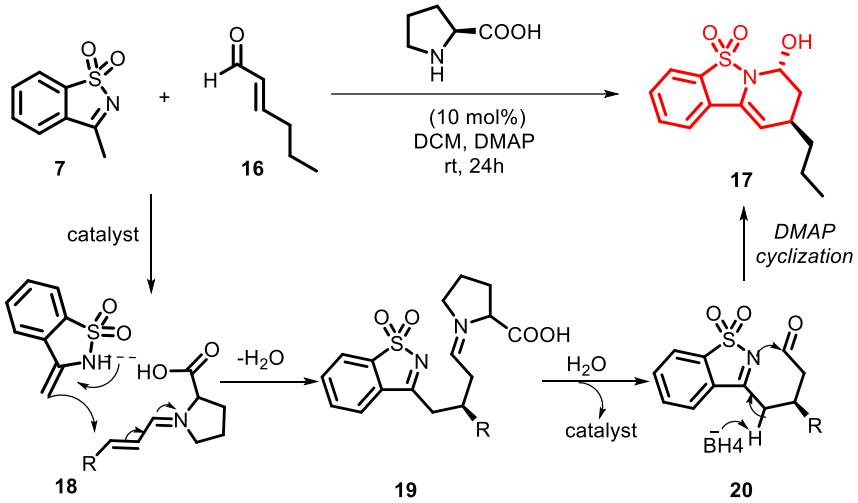
catalyst to get aldehyde **14**, subsequent DMAP-mediated cyclization delivers the product **15** with good yield and stereoselectivity (Scheme 4.1.3).



Scheme 4.1.3

IV. Synthesis of benzoisothiazolo pyranopyridine dioxides by Diels-Alder reaction

In 2015, Lui and Zangh reported a method for constructing piperidine derivatives **17** via organocatalyzed asymmetric domino reaction of saccharine **7** and a,β-unsaturated aldehydes **16**. The facile construction of a piperidine ring in an enantioselective manner is the key feature of this strategy (Scheme 4.1.4).[21]



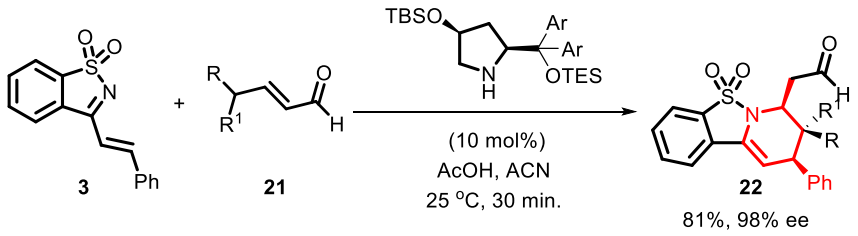
Scheme 4.1.4

The possible reaction mechanism involves the proline-catalyzed formation of enamine from 7 and its subsequent conjugate addition to the proline-derived

conjugated imine electrophile **18** to give the dimine intermediate **19**. Next, the hydrolytic release of the catalyst from **19** delivers the corresponding aldehyde, followed by DMAP-mediated ring-closure, which furnishes the desired cyclic N,O-acetal **17** (up to 93% and diastereoselective with up to 420:1 and enantioselective with up to 99.7% ee) (Scheme 4.1.4).

V. Synthesis of benzoisothiazolo piperidine dioxides by Diels-Alder reaction

Chen's research group published their study in 2014 on the production of enantioenriched fused piperidine derivatives employing a dienamine catalyst via stereoselective inverse-electron-demand aza-Diels-Alder cycloaddition process of α,β -unsaturated ketimines and, α,β -unsaturated aldehydes.[22] Diverse piperidine derivatives were accessed in up to 81% yield and 98% ee (Scheme 4.1.5).

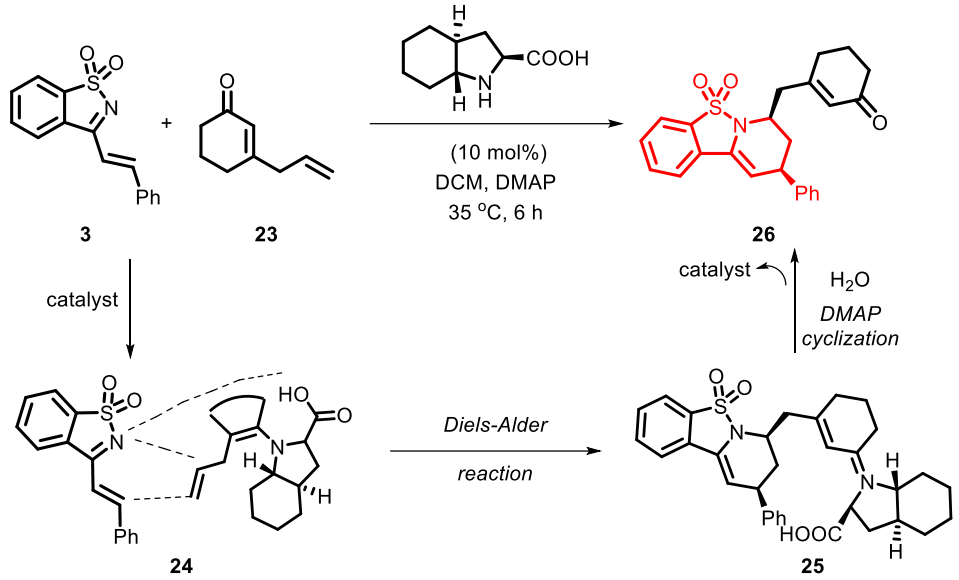


Scheme 4.1.5

VI. Asymmetric Inverse-Electron-Demand Aza-Diels–Alder Reaction

In 2013, Li and Chen disclosed an exciting protocol for synthesizing piperidine derivatives **24** via asymmetric inverse-electron-demand aza-Diels–Alder reaction of cyclic 2,5-dienones **23** and electron-deficient *α,β*-unsaturated ketimines **3** in the presence of chiral amine-derived catalyst.[23]

Mechanistic steps include a straightforward and simple, organocatalyzed [4+2]-cycloaddition reaction of interrupted cyclic 2,5-dienones **23** and *α,β*-unsaturated ketimines **3** to get piperidine intermediate **25** (via **24**), which will be followed by hydrolytic regeneration of the catalyst to deliver the final product **26** (up to 83% yield and 99% ee) (Scheme 4.1.6).



Scheme 4.1.6

4.1.2 σ, π and dual activation process (our hypothesis)

Inspired by interesting biological profile and structural features of sulphonamide and/or cyclic sulphonamides (1,2-thiazole dioxides), oxygen heterocycles, and continuing our interest in the development of novel synthetic methodologies involving alkynyl alcohols and carbonyl compounds (employing our inhouse developed σ and π-dual activain strategies), herein, we hypothesized to use 5- and/or 6-membered cyclic enol ethers (reaction intermediates of 4-pentyn-1-ols and 5-hexyn-1-ols) as inverse electron-demand dienophiles and saccharine derivatives as dienes to construct benzoisothiazolo pyrano-/furano-pyridines.

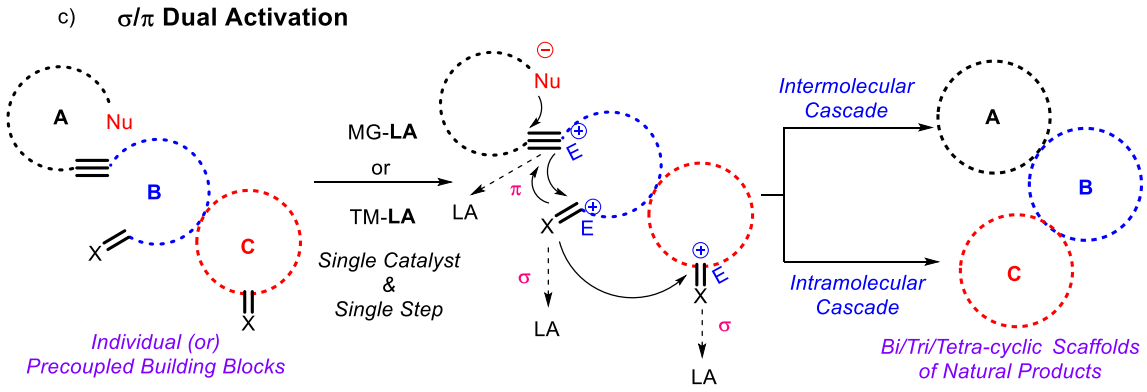


Figure 4.2 | Modify the Scheme with presynopsis Scheme.

CHAPTER-4

Section-B

$Bi(OTf)_3$-catalyzed inverse-electron-demand aza-Diels-Alder (IED-ADA) reaction of alkynols and α-β-unsaturated ketimines

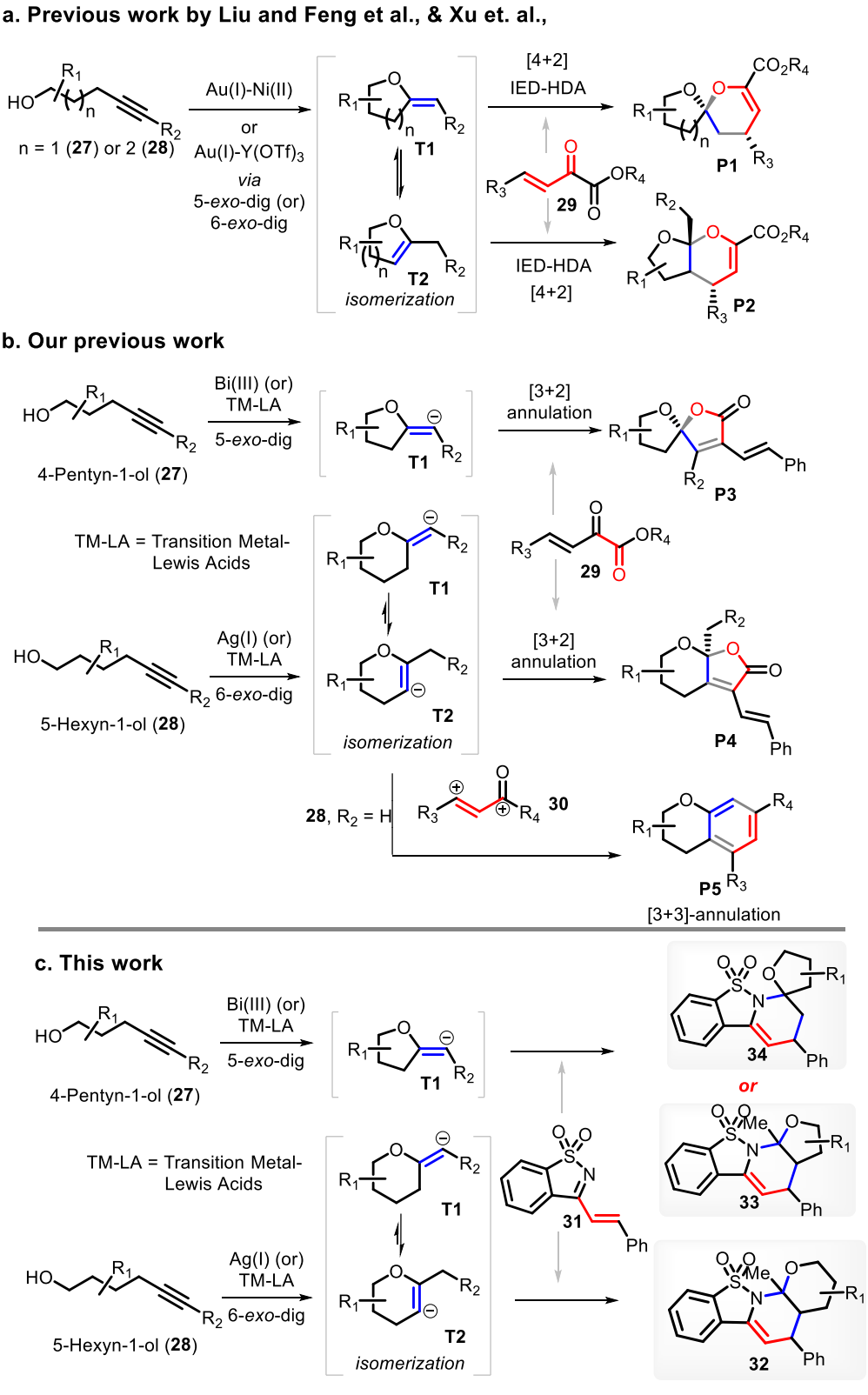
4.2. Hypothesis

Inspired by the emerging importance of cascade/domino reactions, we aimed at developing new synthetic methodologies involving dual activation (σ and π)-enabled cascade annulation reactions of alkynyl alcohols and diverse carbonyl compounds to construct biologically relevant oxygen-heterocycles.

Recently, Liu and Feng, and Xu research groups reported that cyclic enol ethers (**T1** and **T2**) could be served as multifaceted dienophiles in inverse-electron demand aza-Diels-Alder (IED-HDA) reaction with β-γ-unsaturated α-ketoesters **3** to furnish spiroketals **P1** or fused acetals **P2** under catalyst dependent reaction conditions (entry a, Scheme 4.2.1).[24]

In contrast to these reports,[25,26] we have recently reported Bi(III)-catalyzed [2+3]-annulation cascade reaction of 4-pentyn-1-ols with α-ketoesters and/or β-γ-unsaturated α-ketoesters to give diverse oxaspirolactones **P3** via cyclic enol-ether **T1**.[27] Ag(I) or Au(I)-Ag(I)-Catalyzed [2+3]-annulation cascade reaction of 5-hexyn-1-ols with α-ketoesters and/or β-γ-unsaturated α-ketoesters delivered diverse furo-pyranones **P4** via cyclic enol-ether **T2** (formed from alkynol via **T1**).[28] In another investigation, Ag(I)-catalyzed [3+3]-annulation of alkynyl alcohols (5-hexyn-1-ols) and α,β-unsaturated ketones furnished simple to complex chromanes **P5** via cyclic enol-ether **T2** (formed from alkynol via **T1**) (entry b, Scheme 4.2.1).[29]

Inspired by this success, we envisioned that the same alkynols (4-pentyn-1-ols or 5-hexyn-1-ols) would undergo initial catalytic π-activation-induced cycloisomerization to give respective cyclic enol ethers, which subsequently participate in annulation reactions with activated *α,β*-unsaturated ketimines (sulfonamide-deived) and deliver benzoisothiazolo furano-pyridine dioxies (spiro or fused) and benzoisothiazolo pyrano-pyridine dioxide (entry c, Scheme 4.2.1).



Scheme 4.2.1 | Previous approaches for cascade annulation reactions involving alkynols and current hypothesis.

4.2.2 Result and discussions

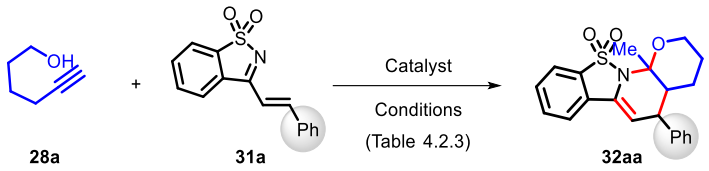
4.2.3 Optimization of reaction conditions

To test our hypothesis, we initiated our studies by probing representative reaction using commercially available 5-hexyn-1-ol **28a** and known *α,β*-unsaturated ketimines **31a** (Table 4.2.3), under our in-house developed cascade annulation reaction conditions using $Bi(OTf)_3$ in CH_2Cl_2 at rt, which delivered desired benzoisothiazolo pyrano-pyridine dioxide **32aa** in 82% yield with dr (diastereomeric ratio) 1:0.2. Subsequent experiments altering the solvent and temperature (DCE, PhF 80 ^oC) did not lead to any improvement in the outcome of **32aa** as well as different polar solvents in the presence of $Bi(OTf)_3$, which delivered the product in moderate yields. (entries 2-6, Table 4.2.3). Furthermore catalyst loading which did not significantly improvement in yields (entries 7-9, Table 4.2.3). Further, screened the reaction employing other bismuth salts ($BiCl_3$, $BiBr_3$, $Bi(NO_3)_3.5H_2O$) as promoters, which failed to deliver the anticipated product (entries 10-12, Table 4.2.3).

Next, a series of known π and σ-electrophilic catalysts were examined and found that AgOTf, $Hg(OTf)_2$, and AuCl could also catalyze this reaction albeit in moderate yields (68-80%), with compromised stereoselectivity (dr) (Table 4.2.3, entries 13-16). Next, the screening of other π- and σ-activating catalysts like $Sc(OTf)_3$, $FeCl_3$, $Fe(OTf)_3$, $Cu(OTf)_2$, and $In(OTf)_3$ delivered **32aa** in 15-78% yield, with dr. ratio 1:0.4 to 1:0.6. Whereas, $Zn(OTf)_2$, $Ni(OTf)_2$, $Zn(OTf)_2$ and $Yb(OTf)_3$ failed to deliver the desired product (entries 17-24 Table 4.2.3).

Further, we verified the effect of Brønsted acid catalysts such as *p*-TsOH, PPTS, CF_3COOH, and TfOH in DCE at rt, which did not lead to annulation reactions; both starting materials were fully recovered (entries 25-28 Table 4.2.3). Ultimately, conditions involving $Bi(OTf)_3$ (10 mol%) in DCM at rt were found to be optimal for this annulation. Further alteration of reaction parameters like molar ratios of **28a** and **31a**, catalyst loading, and reaction temperatures did not significantly improve (Table 4.2.3).

Table 4.2.3 Optimization of reaction conditions[a]



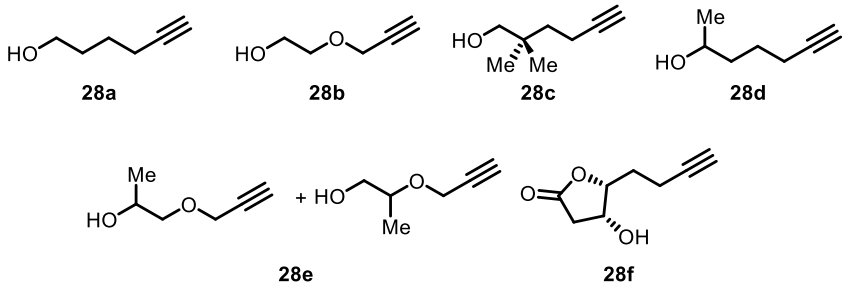
28a 31a 32aa

Entry	Catalyst	Solvent, temp.	Time	dr. ratio	Yield (%)[b]
1	$Bi(OTf)_3$ (10 mol%)	CH_2Cl_2, rt	8 h	1:0.2	82
2	$Bi(OTf)_3$	DCE, 80 °C	8 h	1:0.5	80
3	$Bi(OTf)_3$	ACN, rt	8 h	1:0.4	79
4	$Bi(OTf)_3$	THF, rt	8 h	-	10
5	$Bi(OTf)_3$	MeOH	8 h	3:1	65
6	$Bi(OTf)_3$	PhF, 85 °C	8 h	1:0.6	78
7	$Bi(OTf)_3$ (5 mol %)	CH_2Cl_2, rt	8 h	1:0.2	60
8	$Bi(OTf)_3$ (2 mol %)	CH_2Cl_2, rt	8 h	1:0.2	45
9	$Bi(OTf)_3$ (20 mol %)	CH_2Cl_2, rt	8 h	1:0.3	80
10	$Bi(NO_3)_3.5H_2O$	CH_2Cl_2, rt	8 h	-	-[c]
11	$BiCl_3$	CH_2Cl_2, rt	8 h	-	-[c]
12	$BiBr_3$	CH_2Cl_2, rt	8 h	-	-[c]
13	AgOTf	PhF, 85 °C	8 h	1:0.4	80
14	AgOTf	CH_2Cl_2, rt	8 h	2:1	79
15	$Hg(OTf)_2$	CH_2Cl_2, rt	8 h	1:0.3	68
16	AuCl	CH_2Cl_2, rt	8 h	1:1	70
17	$Sc(OTf)_3$	CH_2Cl_2, rt	8 h	-	15
18	$Fe(OTf)_3$	CH_2Cl_2, rt	8 h	1:0.4	77
19	$Fe(OTf)_3$	PhF, 85 °C	8 h	1:0.6	78
20[c]	$Ni(OTf)_2$	CH_2Cl_2, rt	8 h	-	-
21	$Cu(OTf)_2$	CH_2Cl_2, rt	12 h	-	43
22[c]	$Zn(OTf)_2$	CH_2Cl_2, rt	8 h	-	-
23	$In(OTf)_3$	CH_2Cl_2, rt	8 h	-	34
24[c]	$Yb(OTf)_3$	CH_2Cl_2, rt	8 h	-	-
25[c]	*p*-TsOH	$(CH_2)_2Cl_2$	8h	-	-
26[c]	PPTS	$(CH_2)_2Cl_2$	8 h	-	-
27[c]	CF_3COOH	$(CH_2)_2Cl_2$	8 h	-	-
28[c]	TfOH	$(CH_2)_2Cl_2$	8 h	-	-
29[d]	no catalyst	PhF	8 h	-	-

[a]Reaction conditions unless otherwise specified: **28a** (1.01 mmol), **31a** (1.01 mmol), catalyst (10 mol %) in the indicated solvent (anhydrous, 2 mL) in 8 h. [b]Isolated % yields of **32aa**. [c]No conversion was observed. [d]Control experiments Tf = triflate (CF_3SO_2).

4.2.4 Preparation of alkynols building blocks:

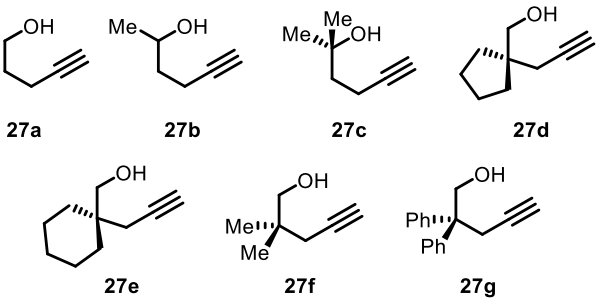
We have synthesized a variety of 5-hexyn-1-ols (28) to investigate the generality of this methodology by using the following procedures.



Scheme 4.2.3 | Synthesis of 5-hexyn-1-ols (**28a-f**).

Alkynols **28a, 28b, 28c, 28d,** and **28f** were obtained using known literature procedures as discussed in Chapters 2 and 3. Compound **28e** (a mixture of regioisomers) was prepared using a known literature procedure.[31]

After the successful synthesis of 5-hexyn-1-ols (**28a-f**), we focused on the synthesis of diverse 4-pentyne-1-ols (to verify the applicability of this methodology employing 4-pentyn-1ols as substrates).



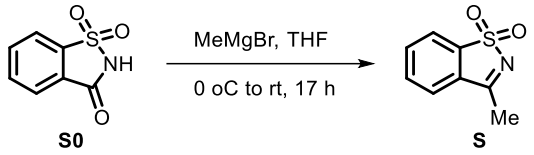
Scheme 4.2.4 | Preparation of 4-pentyne-1-ols (**27b-g**).

Compound **27a** was purchased from commercial sources, and **27b, 27c, 27d, 27e, 27f** and **27g** were prepared using known literature procedures (as described in Chapters 2 and 3).

4.2.5 Preparation of α,β-unsaturated ketimine building blocks:

Methylbenzo[d]isothiazole 1,1-dioxide (S):

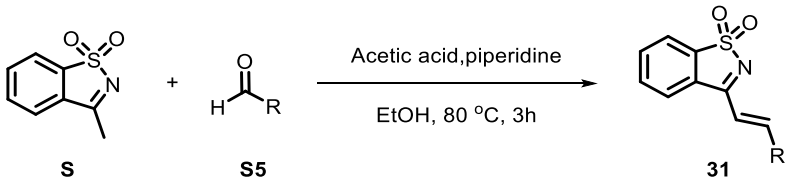
Methylbenzo[d]isothiazole 1,1-dioxide (**S**, a common precursor for the construction of α,β-unsaturated ketamine **31** substrates of this methodology) was prepared using the following general procedure in a single step. This reaction involves the addition of Methyl magnesium bromide in saccharin in THF solvent at 0 °C to furnish the Methylbenzo[d]isothiazole 1,1-dioxide (**S**) (Scheme 4.2.5).[32]

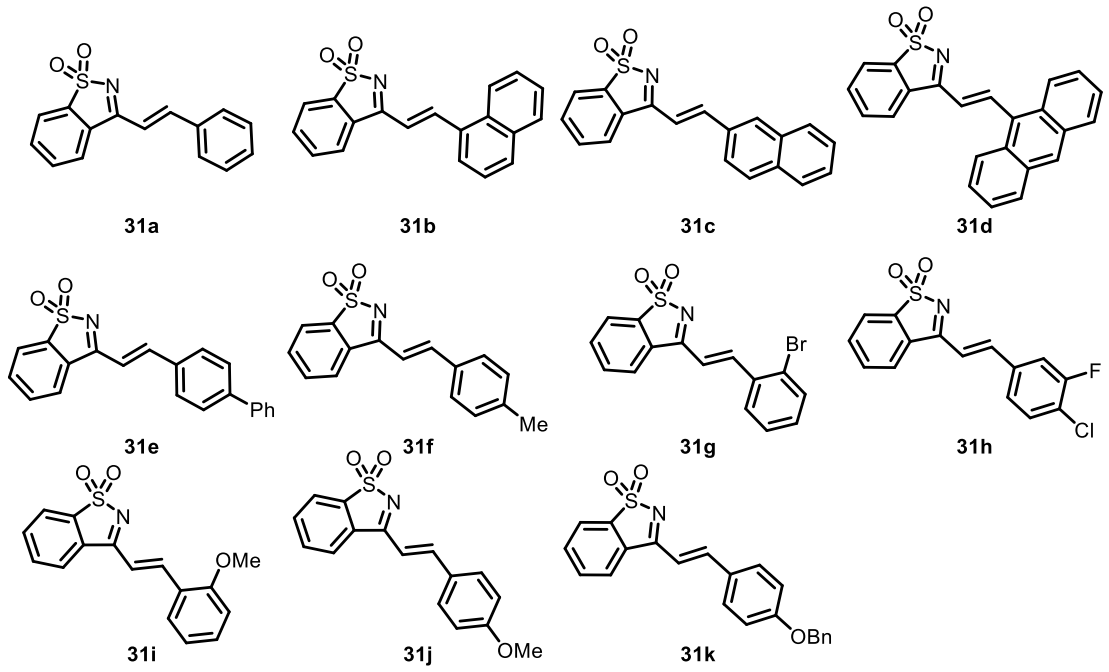


Scheme 4.2.5 | Synthesis of methylbenzo[d]isothiazole 1,1-dioxide (**S**).

Synthesis of α,β-unsaturated ketimines (31):

Following a literature procedure [32], compound **S** (1 eq) and aldehyde derivatives **S5** (1 eq) were dissolved in ethanol (10 mL), then added acetic acid (0.1 eq) and piperidine (0.1 eq), then the reaction mixture was stirred at 80 °C for 3 h. After completion of the reaction, it was cooled to 0 °C and filtered. The filtered cake was washed with cold ethanol and subjected to the next step without further purification. Following this general procedure, all α,β-unsaturated ketimines (**31a-31k**) were synthesized (Scheme 4.2.6).



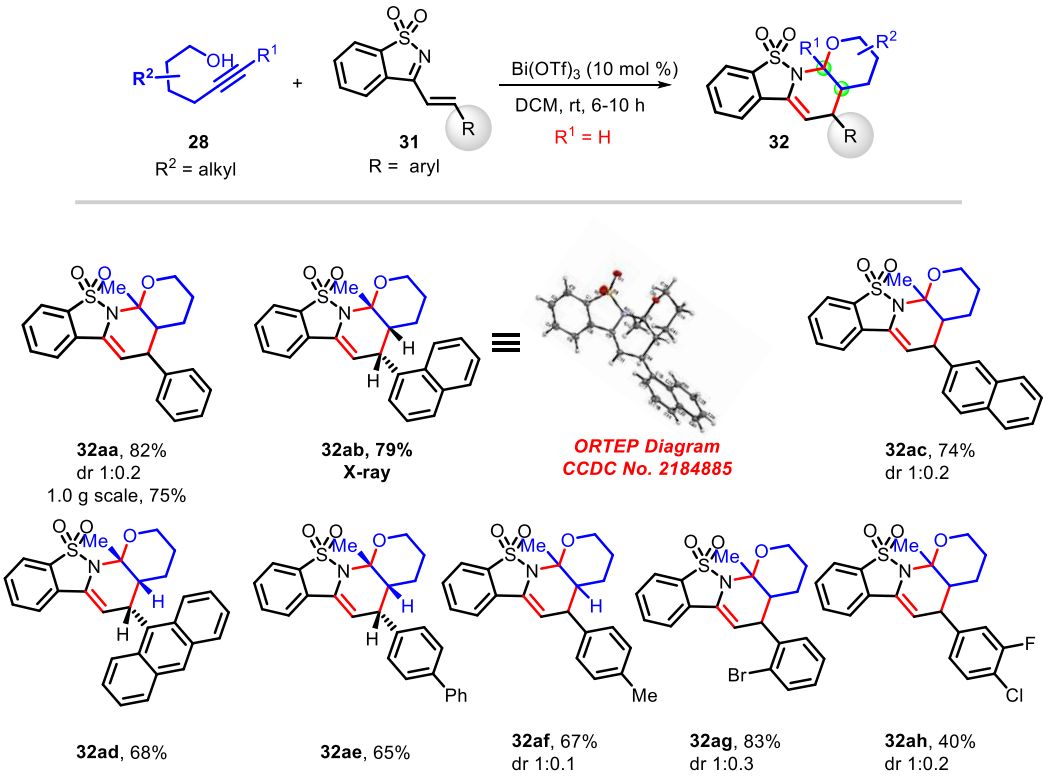


Scheme 4.2.6 | Synthesis of α,β-unsaturated ketimines (**31a-k**).

4.26 Substrate scope and generality of the reaction:

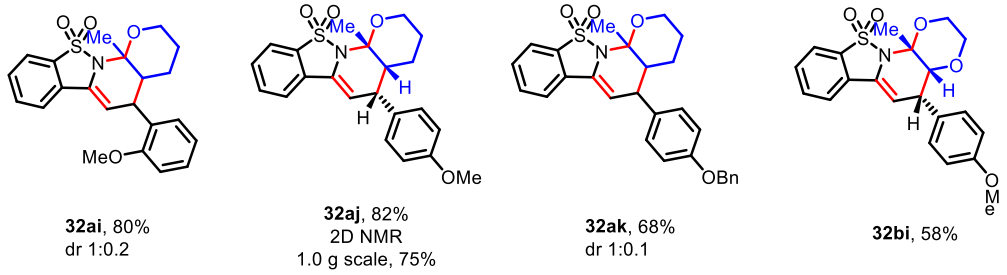
With optimal reaction conditions in hand, investigated the scope of this protocol employing 5-hexyne-1-ols **28** and *α,β*-unsaturated ketimines **31** as reaction partners. The reactions of commercially available 5-hexyne-1-ol (**27a**) with several *α,β*-unsaturated ketimines possessing phenyl, *α*-naphthyl, *β*-naphthyl, and 9-anthracenyl substituents, cleanly furnished corresponding benzoisothiazolo pyrano-pyridine dioxide **32aa**-**32ad** in good yields (68-82%) and diastereoselectivity. To our delight, **32ab** was obtained as a single diastereomer and was established by single-crystal X-ray analyses.

Similarly, annulation of 5-hexyne-1-ol (**27a**) with diverse ketimines possessing *p*-methyl, *p*-phenyl, *o*-Bromo, *m*-flouro-*p*-chloro-phenyl substituents were found to be a good substrate and delivered coresponding benzoisothiazolo pyrano-pyridine dioxides **32ae**-**32ah** in good yields (40-83%) and with good dr (1.01-1.03) (Scheme 4.2.7).



Scheme 4.2.7 | Substrate scope.

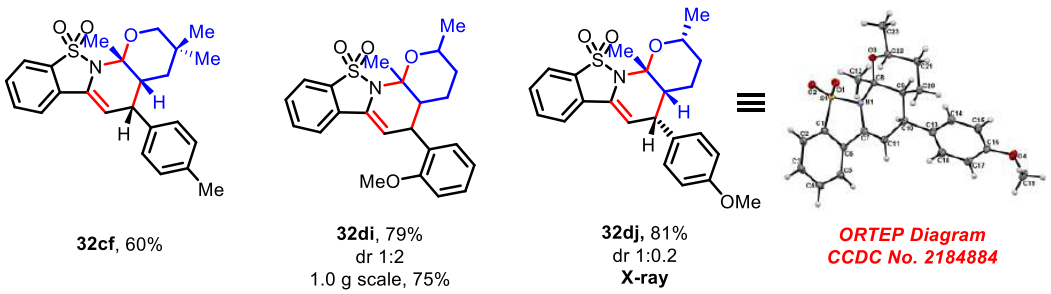
Ketimines containing methoxy and benzyloxy-phenyl substituents delivered corresponding adducts **32ai-32ak** in good yields. Next, we examined the reactivity of oxygen inserted 5-hexyne-1-ol **28b** (derived from propargyl alcohol) with *p*-OMe substituted *α,β*-unsaturated ketimines **31i**, which delivered corresponding product **32bi** in a good yield 58% as asingle diastereomer (Scheme 4.2.8).



Scheme 4.2.8 | Substrate scope.

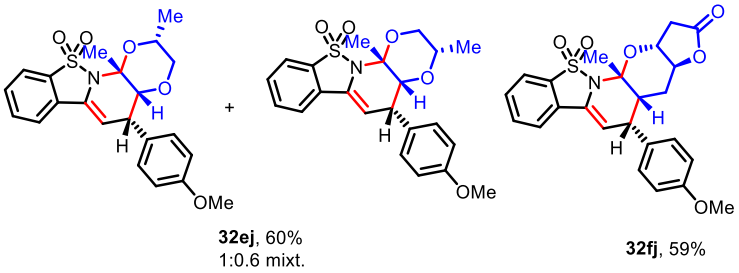
Next, we focused on verifying the reactivity profile of substituted 5-hexyn-1-ols. The reactions of geminal dimethyl substituted alkynol **28c** (possessing primary hydroxyl functionality) treated with the ketamine **31f**, which delivered **32cf** in 60%

isolated yield and with exclusive diastereoselectivity. Then, we examined this annulation reaction using 5-hexyn-1-ols having secondary hydroxyl functionality (**28d**) and synthesized corresponding adducts **32di** and **32dj** (confirmed by single-crystal X-ray analyses) in good yields and dr of 1:2 and 1:0.2, respectively (Scheme 4.2.9).



Scheme 4.2.9 | Substrate scope.

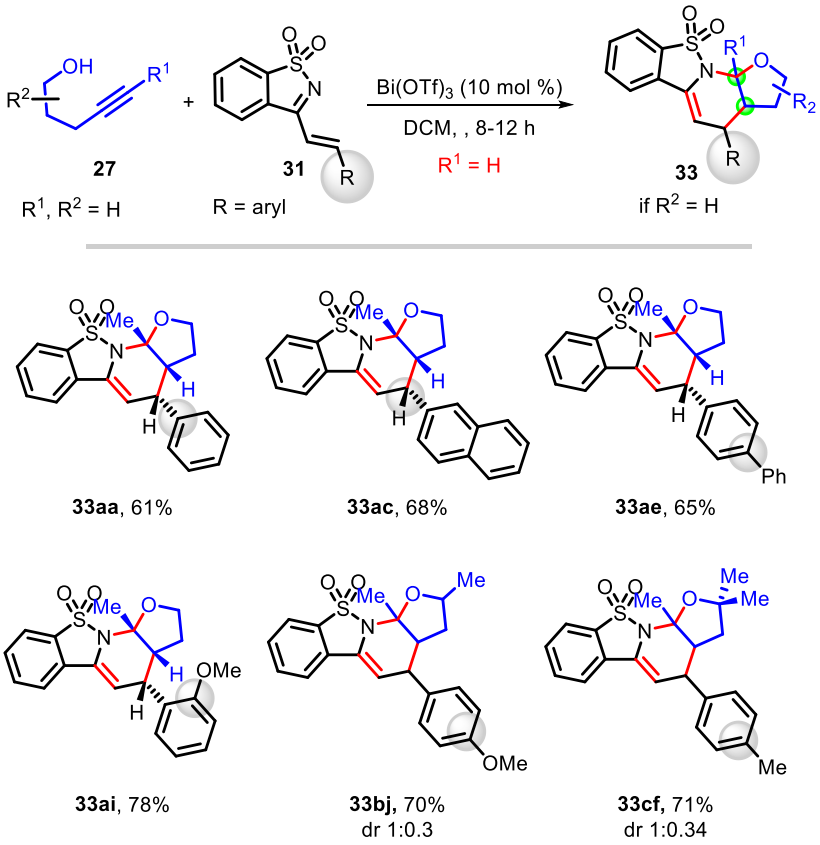
Interestingly, oxygen-inserted secondary and primary alkynol (**28e**, mixture of regioisomers) was also ascertained to be a suitable substrate and delivered the corresponding product **32ej** as an inseparable mixture in 60% yield. Known[16] optically pure secondary alkynol **28f** possessing the *trans*-butanolide skeleton was well reacted with *p*-OMe substituted *α,β*-unsaturated ketimine **31i** and delivered hexacyclic complex benzoisothiazolo pyrano-pyridine dioxide **32fj** in 59% isolated yield as a single diasteromermer (Scheme 4.2.10).



Scheme 4.2.10 | Substrate scope.

Further, the practicality of this protocol was demonstrated by performing a gram scale reaction, which delivered the adduct **32di** in 75% yield with similar ease and outcome.

Electron-donating substituents (*o*-OMe, *p*-OMe) containing *α,β*-unsaturated ketimine delivered adducts in good yield yields compared to *p*-tolyl and *p*-phenyl substituents containing substrates. Setting a limitation, ketimines tethered with electron-withdrawing groups (CN, nitro, and CO_2Me) containing aryl, cyclohexyl, isopropyl, *t*-butyl groups, and heterocycles (furan, thiophene, pyrrole, indole, pyridine benzoxazole, benzothiazole) were failed to deliver corresponding products (Scheme 4.2.11).

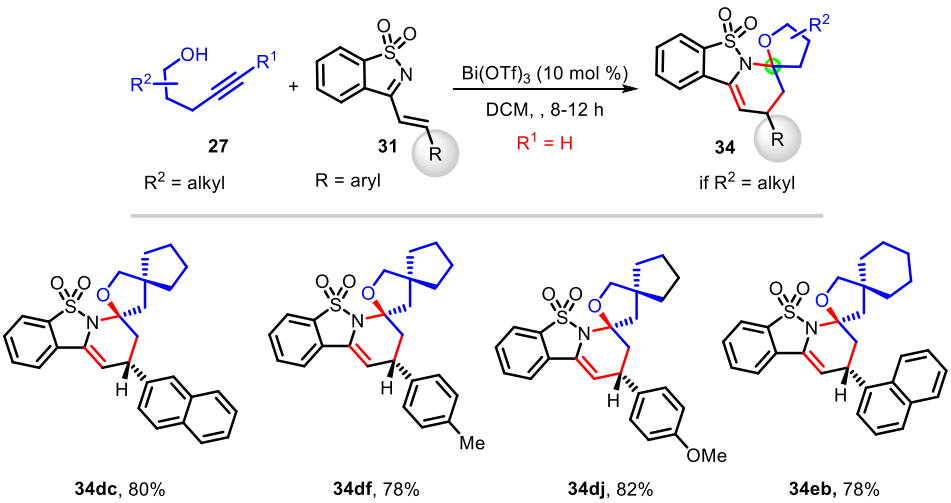


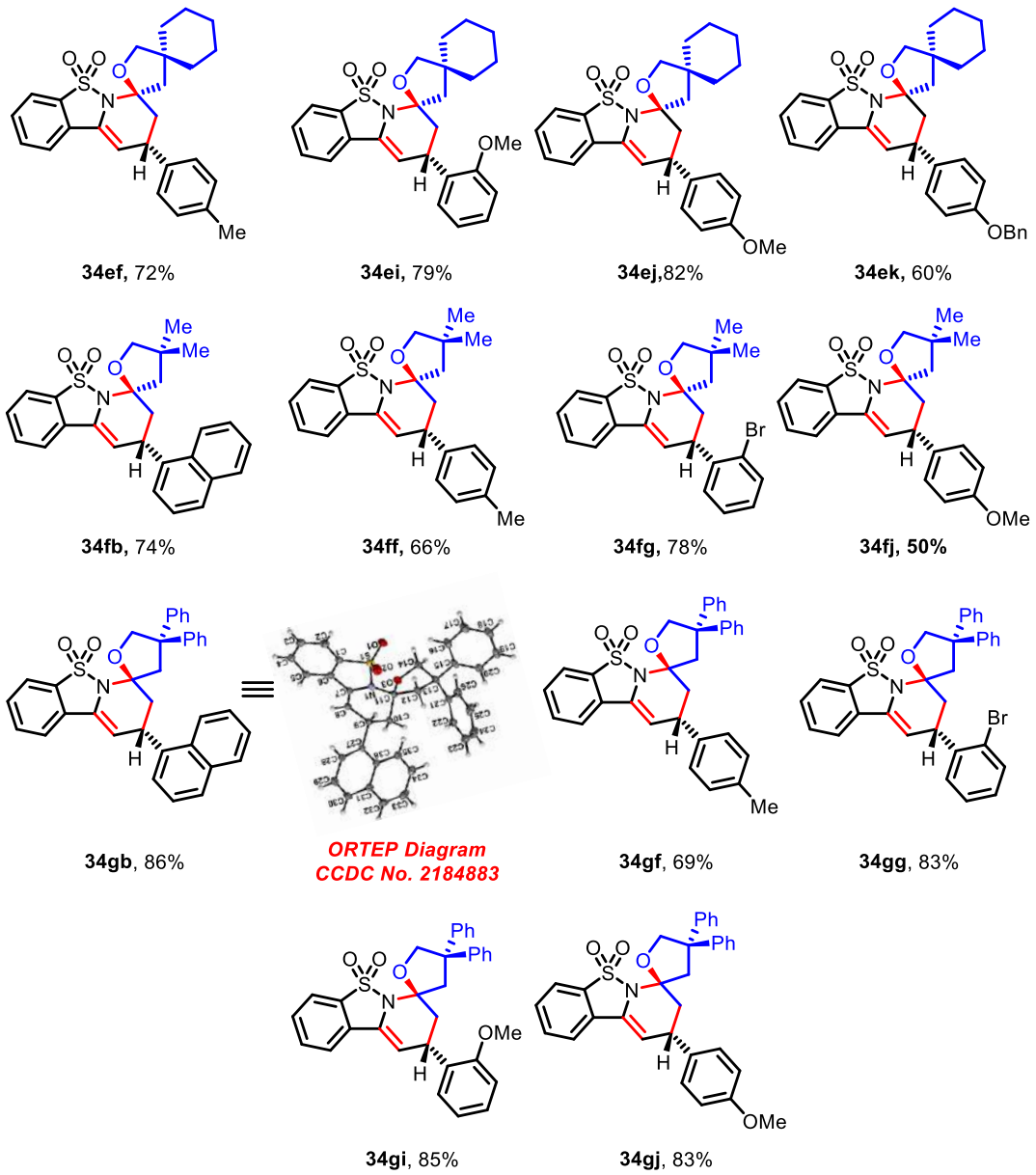
Scheme 4.2.11 Scope of [4+2]-annulation reaction concerning alkynols **27** and *α,β*-unsaturated ketimine **31**. Reaction conditions unless otherwise specified: **28**(1.01 mmol), **31** (1.01 mmol), and 10 mol% catalyst used.

To extrapolate the generality of this protocol. we began investigating the reaction using various 4-pentyn-1-ols **27** with *α,β*-unsaturated ketimines **31**. The annulation reaction involving commercially available 4-pentyn-1-ol (possessing terminal alkyne functionality) **27a** and phenyl-derived ketamine **31a** under the optimized reaction

conditions furnished corresponding benzoisothiazolo furo-pyridine dioxide **33aa** (fused) in 61% yield and exclusive diastereoselectivity. Then, altered ketamine substrates (**31c**, **31e,** and **31i**) in the reaction with **27a**, which cleanly furnished corresponding adducts (**33ac**, **33ae,** and **33ai**) in good yields and diastereoselectivity. Alkynols containing secondary and tertiary hydroxyl functionality were also found to be suitable substrates in reaction with *α,β*-unsaturated ketimines, and delivered corresponding benzoisothiazolo furo-pyridine dioxide **33bj** and **33cf** in good yields and diasteroselectivity.

To our surprise, cyclopentane (geminal) substituted 4-pentyn-1-ol (**27d**) delivered spiro-benzoisothiazolo furo-pyridine dioxides **34dc**, **34df** and **34dj** instead of fused adducts (as observed in the above Scheme) under optimized reaction conditions. Similarly, cyclohexane (germinal) substituted 4-pentyn-1-ol (**27e**) also furnished corresponding spiro adduct **34eb** exclusively in 78% yield and complete diastereoselectivity. This phenomenon could be attributed to the Thorpe-Ingold effect (angle compression effect, which facilitates the ring-closure step of the process)[33] induced selective *exo*-enolether formation and its participation in anuulation with ketamine (*vide infra*) (Scheme 4.2.12) .



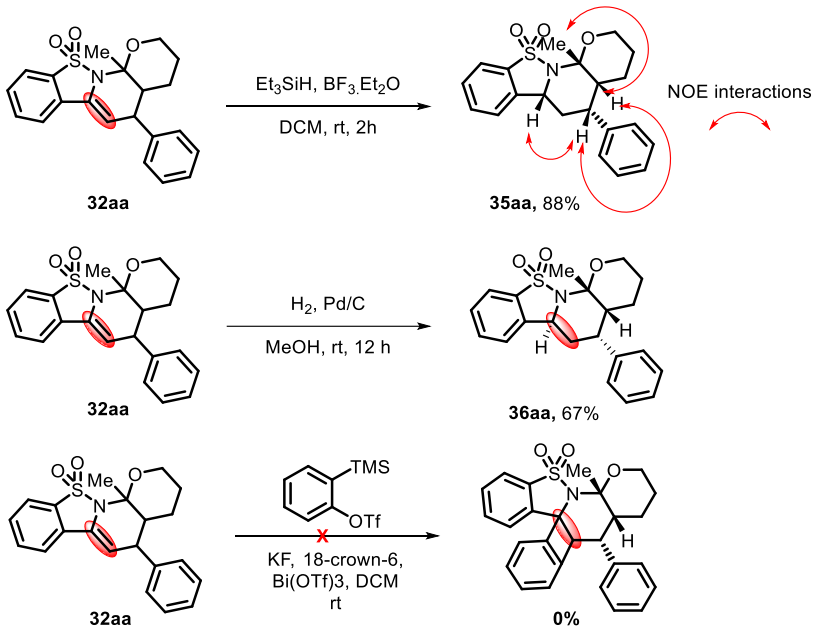


Scheme 4.2.12: Scope of [4+2]-annulation reaction concerning alkynols **27** and *α,β*-unsaturated ketimine **31**. Reaction conditions unless otherwise specified: **28** (1.01 mmol), **31** (1.01 mmol) and 10 mol% catalyst used.

Encouraged by these results, substrate scope was studied using cyclohexane substituted alkynol **27e** and diverse ketimines **31b, 31f, 31i, 31j, and 31k** to access corresponding spiro-benzoisothiazolo furo-pyridine dioxides **34ef, 34ei, 34ej and 34ek** respectively in good yields. The geminal dimethyl substituted alkynol **27f** with *β*-naphthyl, *p*-tolyl, *o*-Br and *p*-OMe substituted-aryl containing *α,β*-unsaturated ketimine was also well-tolerated and gave the corresponding spiro-benzoisothiazolo furo-

pyridine dioxides **34fb, 34ff, 34fg, 34fh** in good yields. Similarrly, diphenyl substituted alkynol **27g** treated with *α*-naphthyl, p-tolyl, o-Br o-OMe and p-OMe-henyl substituted *α,β*-unsaturated ketimine to furnish corresponding adducts **34gb, 34gf, 34gg, 34gi** and **34gj**. Product **34gb** was rigorously established by single-crystal X-ray analyses, and remaining products were confirmed by analogy (^{1}H and ^{13}C-NMR, and MS analyses). Diatereomeric ratios were calculated using ^{1}H NMR analyses (Scheme 4.2.12).

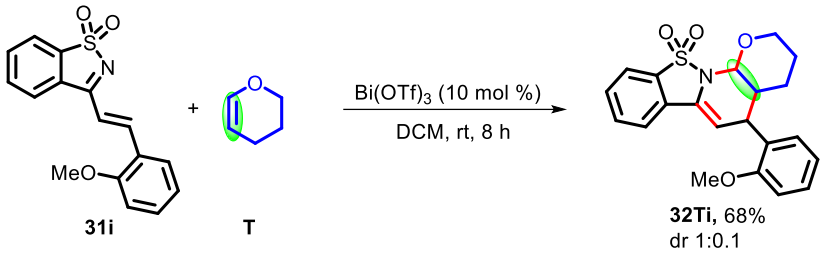
Furthermore, the synthetic utility of this methodology was examined by a couple of very interesting transformations.[34] The benzoisothiazolo pyrano-pyridine dioxide **32aa** was subjected to $Et_3SiH/BF_3{\cdot}Et_2O$ reduction, which delivered corresponding tetrahydropyridine analog **35aa** in 88% yield and exclusive diastereoselectivity (stereochemistry established by NOE analyses). In contrst to this outcome, Pd/C-catalyzed hydrogenation delivered diasteromer of **35aa** (**36aa**, epimeric at benzylic position) in 67% yield. The anticipated [2+2]-annulation reaction of **32aa** with benzynes (in situ generated from o-trimethylsilyl phenyltriflate using known protocol) in the presence of KF and 18-crown-6 was found to be unsuccessful (Scheme 4.2.13).



Scheme 4.2.13: Synthetic utility.

Next, we performed a supporting experiment to gain insight into the reaction mechanism involving the proposed initial formation of cyclic enol ethers from alkynols

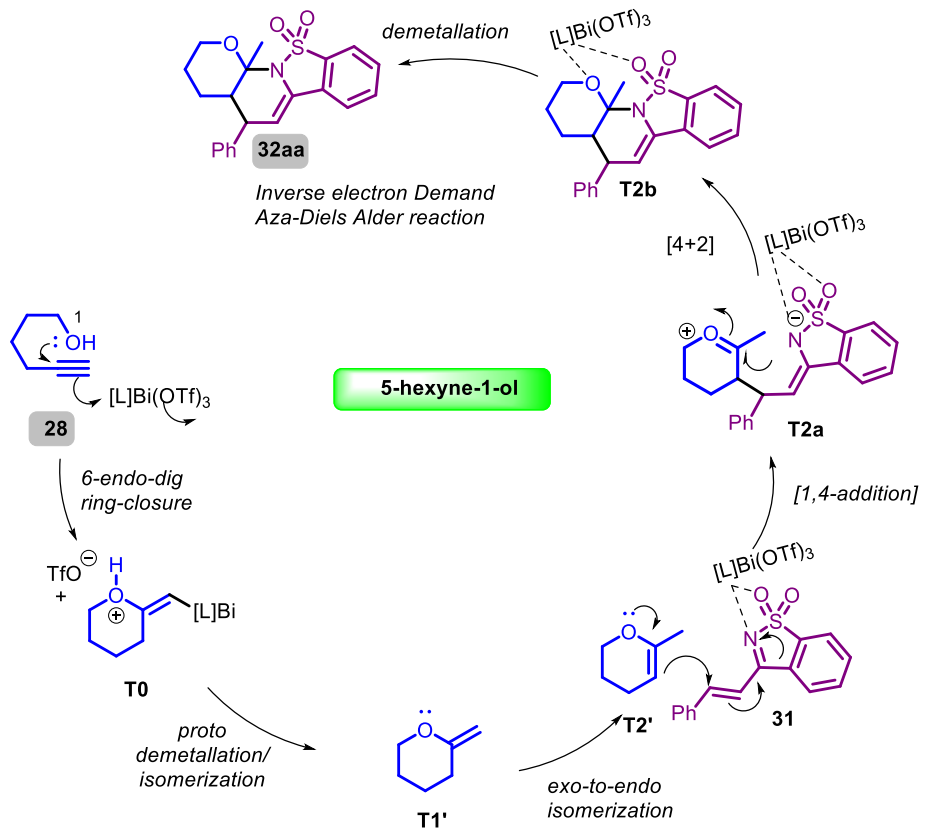
and their participation in annulation.[35] The [4+2]-annulation of reaction of ketamine **31i** (diene equivalent) and commercially available 3,4-dihydro tetrahydropyrans (**T**, 3,4-DHP, dienophile equivalent) under optimal reaction conditions delivered the corresponding annulation product **32Ti** in 68% yield and with 1:0.1 dr. This outcome clearly indicates that the formation of cyclic enol ether and inverse electron demand [4+2]-cycloaddition step involves in this cascade annulation reactions mechanistic sequence (Scheme 4.2.14).



Scheme 4.2.14: Supporting Experiments for the mechanism.

Plausible mechanistic pathways based on the above experimental results (Scheme 4.2.10, 11, 12, 14), control experiment is described in Scheme 4.2.14.

Formation of the adduct 32: In this annulation, 5-hexyn-1-ol (**28**) undergoes intramolecular hydroalkoxylation with the aid bismuth(III) triflate to geneate exocyclic enolether **T1'** (via **T0**, through π-activation). Inward isomerization of **T1'** gives more thermodynamically stable **T2'** (endocycic enol ether). Subsequent inverse electron demand [4+2] annulation of **T2'** with activated conjugated ketamine (**31**, σ-activation), or following the step-wise mechanism involving Michael addition to give oxocarbenium ion **T2a**, and intramolecular amination delivers fused benzoisothiazolo pyrano-pyridine dioxides **32** (Scheme 4.2.15).

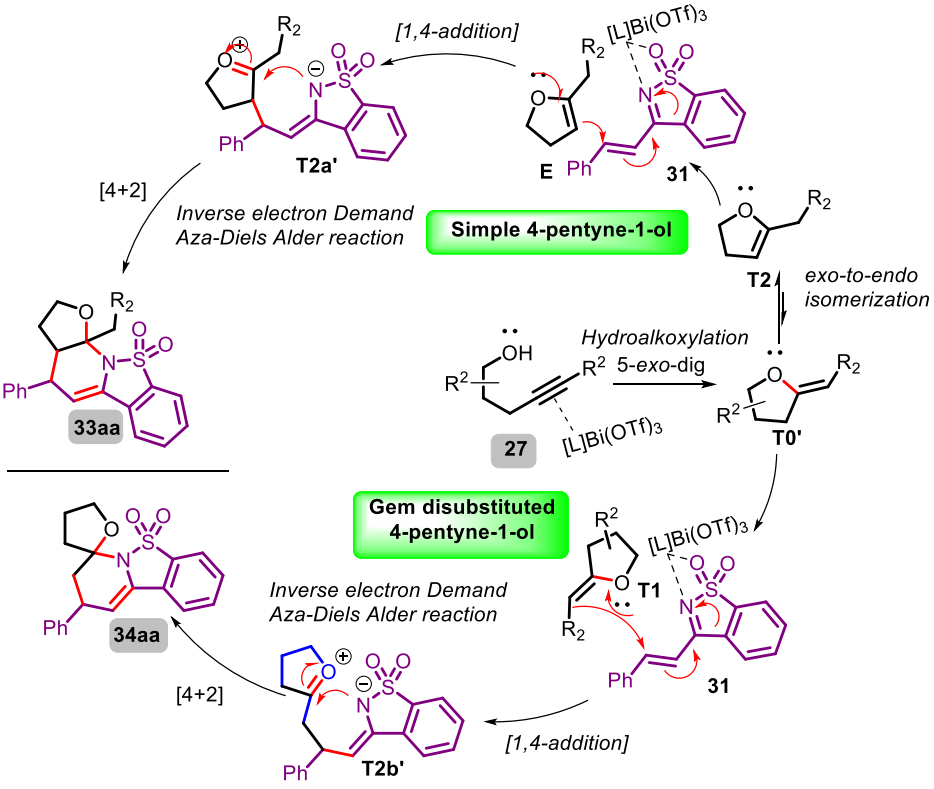


Scheme 4.2.15: Plausible reaction mechanism for the formation of **32**.

Formation of the adduct 33: In this transformation, 4-pentyn-1-ol (**27**) undergoes intramolecular hydroalkoxylation with the aid bismuth(III) triflate catalyst to geneate exocyclic enolether **T0'** (through π-activation). Inward isomerization of **T0'** gives endocyclic enol ether **T2**. Subsequent inverse electron demand [4+2] annulation of **T2** with activated conjugated ketamine (**31**, σ-activation), or following the step-wise mechanism involving Michael addition to give oxocarbenium ion **T2a'**, and intramolecular amination delivers fused benzoisothiazolo furano-pyridine dioxide **33**.

Formation of the adduct 34: In this transformation, 4-pentyn-1-ol (**27**) undergoes intramolecular hydroalkoxylation with the aid bismuth(III) triflate catalyst to geneate exocyclic enolether **T0'** (through π-activation). Instead of inward isomerization, **T0'** directly participates in subsequent inverse electron demand [4+2] annulation with activated conjugated ketamine (**31**, σ-activation), or following the step-wise mechanism

involving Michael addition to give oxocarbenium ion **T2b'**, and intramolecular amination delivers spiro-benzoisothiazolo furano-pyridine dioxide **34** (Scheme 4.2.16).



Scheme 4.2.16: Plausible reaction mechanism for the formation of **32**.

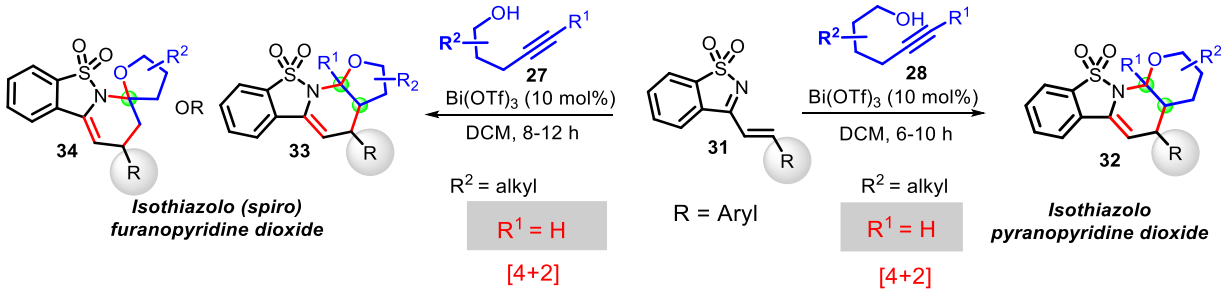
3.2.7 Conclusion

In conclusion, we have developed a novel $Bi(OTf)_3$-catalyzed inverse electron demand aza Diels-Alder [4+2] reaction for the construction of fused-benzoisothiazolo pyrano-pyridine dioxides (**32**), fused-benzoisothiazolo furano-pyridine dioxides (**33**), and spiro-benzoisothiazolo furano-pyridine dioxides (**34**) from readily accessible 5-hexyn-1-ols (**28**)/4-pentyn-1-ols (**27**) and cyclic sulphonamide-derived ketimines (**31**). Products were confirmed by extensive NMR analyses (1D and 2D NMR), single-crystal X-ray analyses and analogy. Broad substrate scope, facile reaction conditions, good yields and diastereoselectivities are salient features of this study.

4.2.8 Experimental Procedures and Data:

All reactions were performed under an argon atmosphere with an oven (80 °C) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under an argon atmosphere immediately before use. Dichloromethane and acetonitrile were freshly distilled over calcium hydride under an argon atmosphere. 30 °C corresponded to the laboratory's room temperature (rt) when the experiments were carried out. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel.

***General Procedure* for the synthesis of tetrahydro benzoisothiazolo pyrano (32) or furano pyridine(33) and tetrahydro spiro-benzoisothiazolo pyridine furan(34) from alkynols and *α,β*-unsaturated ketimines:**

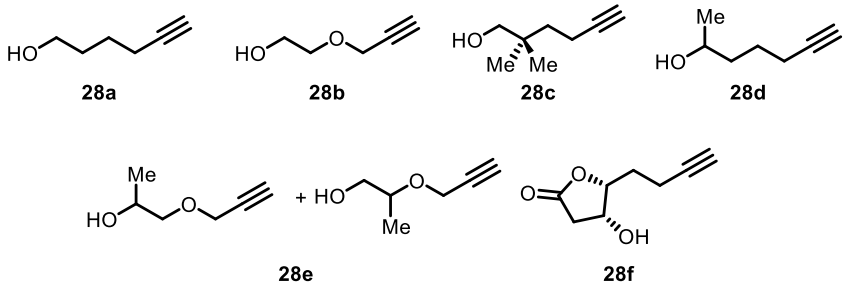


Alkynol **27 or 28** (1.01 mmol), *α,β*-unsaturated ketimines **31** (1.01 mmol) were taken into a single neck 10 mL round bottom flask equipped with positive an argon flow, then dissolved in 2 mL of anhydrous CH_2Cl_2. $Bi(OTf)_3$ (0.101 mmol) was added ed under an argon atmosphere at room temperature (rt, 40°C). The resulting reaction mixture was stirred at rt for 6 h. After completion of the reaction (monitored by TLC, visualized using UV, anisaldehyde, and $KMnO_4$ staining solutions), quenched with saturated aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2 (2x5 mL) and washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and filtered through sintered glass funnel. The filtrate was concentrated under reduced pressure and purified using silica-gel column chromatography (100-200 mesh) to afford the corresponding tetrahydro benzoisothiazolo pyrano/ or furo pyridine/ and tetrahydro spiro benzoisothiazolo pyridine furans **32, 33,** and **34** respectively.

4.2.8.1 Experimental Procedure & Spectroscopic Data of Synthesised Products:

Synthesis of 5-hexyn-1-ols:

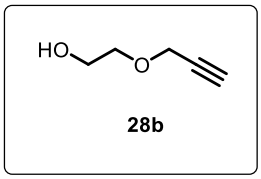
We have synthesized a variety of 5-hexyn-1-ols (28) to investigate the generality of this methodology by using the following procedures.



Scheme 4.2.3 | Synthesis of 5-hexyn-1-ols (**28a-f**).

Alkynols **28a, 28b, 28c, 28d,** and **28f** were obtained using known literature procedures as discussed in Chapters 2 and 3. Compound **28e** (a mixture of regioisomers) was prepared using a known literature procedure.[31]

2-(Prop-2-yn-1-yloxy)ethan-1-ol (28b):

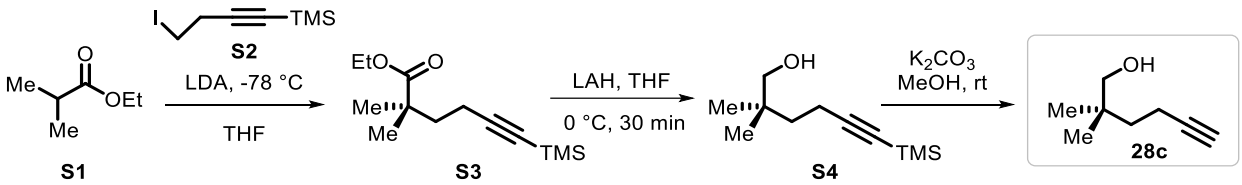


2-(Prop-2-yn-1-yloxy)ethan-1-ol colorless liquid (**28b**) was prepared using the reported procedure.

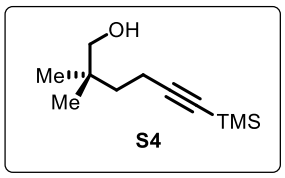
^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.22-4.15 (m, 2H), 3.80-3.68 (m, 2H), 3.67-3.57 (m, 2H), 2.64 (br s, 1H), 2.45 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 79.5, 74.8, 71.3, 61.6, 58.4.

Synthesis of alkynol 28c:



2,2-Dimethyl-6-(trimethylsilyl)hex-5-yn-1-ol (S4):



S4

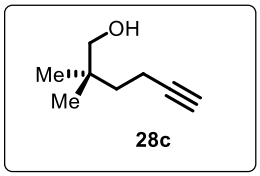
To a flame dried (100 mL) two-neck round bottom flask, anhydrous THF (20 mL) was added ed under an argon atmosphere and cooled to 0 °C, to this diisopropylamine (1.18 g, 11.74mmol) followed by *n*-butyllithium (1.6 M in hexanes, 7.95 mL, 12.7 mmol) was added ed dropwise at 0 °C and stirred for 45 min at 0 °C to generate LDA solution. To this LDA solution, added ethyl isobutyrate (**S1**) (1 g, 9.79 mmol) in THF (3 mL) and stirred the reaction mixture at -78 °C for 30 min, then warmed to 0 °C and stirred for another 30 min. The reaction mixture was cooled back to -78 °C, and (4-iodobut-1-yn-1-yl) trimethylsilane (**S2**) (3.69 g, 14.68 mmol) was added ed dropwise. The resulting mixture was stirred at -78 °C for 1 h and warmed to rt and stirred overnight. Then, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3x20 mL). Combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford ethyl 2,2-dimethyl-6-(trimethylsilyl) hex-5-ynoate (**S3**) TLC: R_f = 0.7 (SiO_2, 10% EtOAc/hexanes), this crude product was subjected to the next step without further purification.

Lithium aluminium hydride (0.74 g, 19.58 mmol) was dissolved in 20 mL of anhydrous THF in a 100 mL two-neck round bottom flask under an argon atmosphere, then ethyl 2,2-dimethyl-6-(trimethylsilyl) hex-5-ynoate (**S3**) in (5 mL) THF was added ed drop by drop at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature, after completion of the reaction monitored by TLC quenched with a saturated aqueous solution of sodium sulphate (very carefully). After quenching the reaction,the mixture diluted with 50 mL EtOAc and stirred for 1h to obtain the white powder, which was filtered through Celite. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (SiO_2, 8% EtOAc/hexanes) to afford 2,2-dimethyl-6-(trimethylsilyl) hex-5-yn-1-ol (**S4**) (0.726 g, 43% for two steps) as a colorless liquid. TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.35 (s, 2H), 2.23 (t, *J* = 7.32 Hz, 2H), 1.55 (t, *J* = 7.32 Hz, 2H), 0.88 (s, 6H), 0.15 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 108.3, 84.2, 70.9, 37.3, 35.2, 23.9, 14.9, 0.04.

2,2-Dimethylhex-5-yn-1-ol (28c):



28c

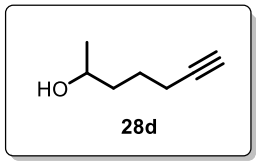
To a stirred solution of 2,2-dimethyl-6-(trimethylsilyl)hex-5-yn-1-ol (**S4**) (0.8 g, 4.03 mmol) in MeOH (20 mL) was added ed K_2CO_3 (1.2 g, 8.68 mmol) at room temperature. The reaction mixture was stirred for 6 h. After quenched with H_2O, the mixture was extracted twice with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 5% EtOAc /hexanes) to give 2,2-dimethylhex-5-yn-1-ol (**28c**) (0.402 g, 79%) as a colourless oil.

TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.35 (s, 2H), 2.19 (td, *J* = 7.63, 3.05 Hz, 2H), 1.97-1.95 (m, 1H), 1.60-1.54 (m,2H), 0.89 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 85.4, 71.1, 67.9, 37.3, 35.1, 23.7, 13.5

Hept-6-yn-2-ol (28d):



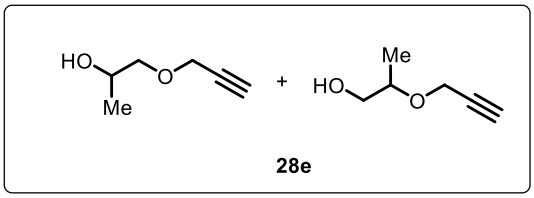
28d

Hept-6-yn-2-ol colourless oil (**28d**) was prepared using reported procedure.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87-3.78 (m, 1H), 2.24-2.19 (m, 2H), 1.96 (t, *J* = 2.3 Hz, 1H), 1.62-1.52 (m, 4H), 1.20 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 84.4, 68.5, 67.6, 38.2, 24.7, 23.6, 18.4.

1-(prop-2-yn-1-yloxy)propan-2-ol and 2-(prop-2-yn-1-yloxy)propan-1-ol (28e):



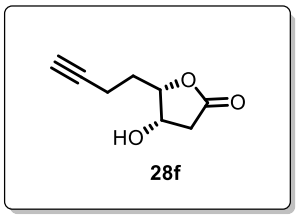
28e

1-(prop-2-yn-1-yloxy)propan-2-ol and 2-(prop-2-yn-1-yloxy)propan-1-ol (**28e**) colourless oil was prepared using reported procedure.[31]

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.25-4.15 (m,2 H), 4.07-3.92 (m, 1H), 3.61-3.49 (m, 1H), 3.42-3.27 (m, 1H), 2.56 (br. s., 1H), 2.51-2.41 (m, 1H), 1.23-1.07 (m, 3H).

5-(But-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (28f):

5-(but-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (**28f**) as a colourless oil.



28f

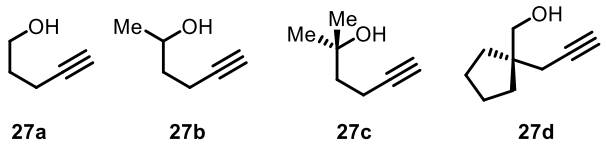
TLC: R_f = 0.12 (SiO_2, 40% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.61-4.5 (m, 2H), 2.83 (dd, *J* = 17.7, 4.88 Hz, 1H), 2.56 (d, *J* = 18.31 Hz, 1H), 2.50-2.32 (m, 2H), 2.14-2.06 (m, 1H), 2.08 - 2.06 (m, 1H), 2.06-1.92 (m, 1H).

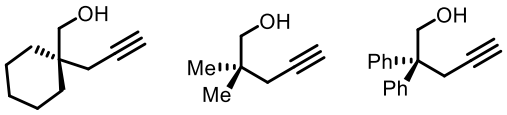
^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.1, 83.7, 83.1, 69.6, 68.6, 39.3, 27.1, 14.7.

4.2.8.2 Experimental Procedure & Spectroscopic Data of Synthesised Products:

Synthesis of 4-pentyne-1-ols:



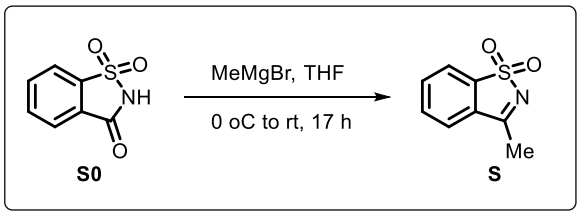
27a **27b** **27c** **27d**



27e **27f** **27g**

Compound **27a** was purchased from commercial sources. **27b, 27c, 27d, 27e, 27f,** and **27g** were prepared using known literature procedures.

Methylbenzo[d]isothiazole 1,1-dioxide (S):



S0 **S**

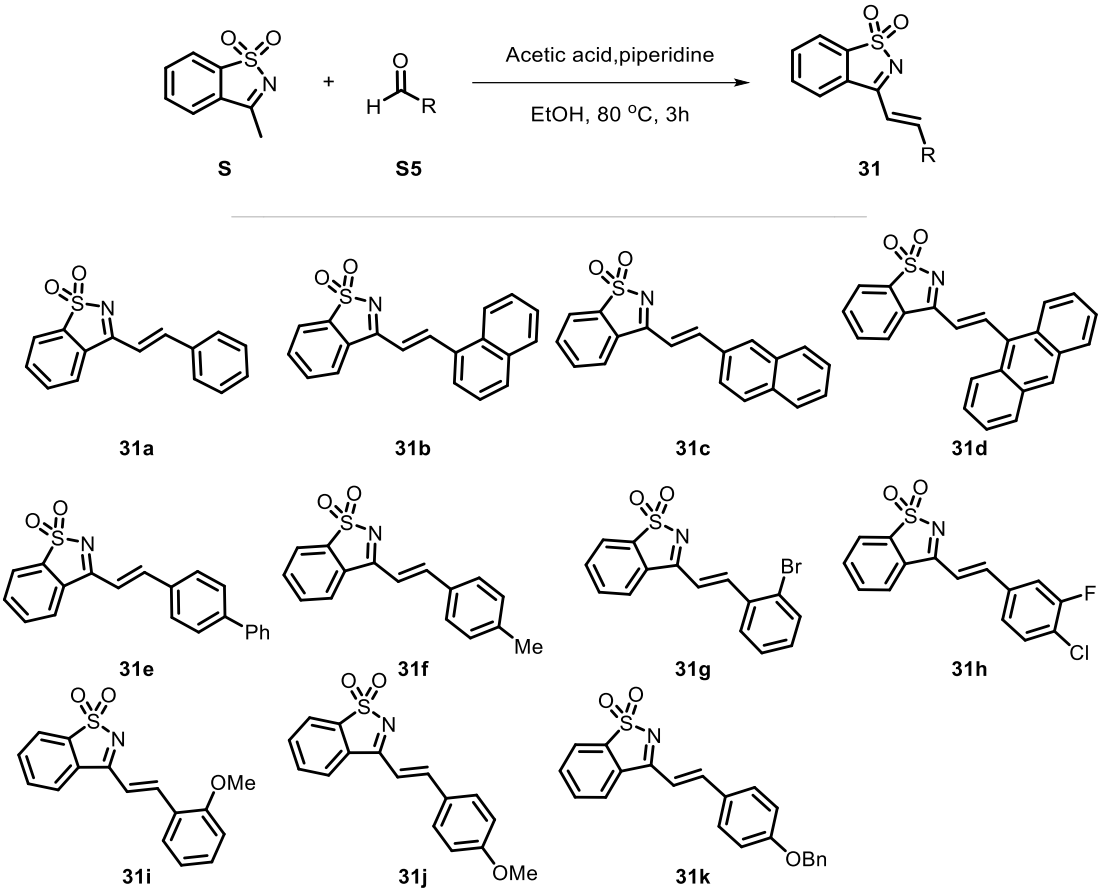
The Methylbenzo[d]isothiazole 1,1-dioxide (**S**) was prepared by following a known procedure. [32] Following a literature procedure, in two necked round bottom flasks, saccharin (10 g, 54.5 mmol, 1.0 eq.) was dissolved in anhydrous THF (100 ml) and cooled to 0 ^{o}C. Methyl magnesium bromide (0.3 M in ether, 36 mL, 109 mmol, 2.0 eq.) was added ed over 10 minutes. The reaction mixture moved to room temperature for 17 h. After completion of the reaction, it was quenched by sat. aq. solution of NH_4Cl (50mL) was added ed, and the layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3X50 mL). The combined organic layer was filtered through $MgSO_4$ and concentrated to dryness under reduced pressure, washed with CH_2Cl_2 (20 mL) to give

Methylbenzo[d]isothiazole 1,1-dioxide (**S**) as an off-white solid (5.34 g, 29.5 mmol, 54%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.99-7.87 (m, 1H), 7.80-7.70 (m, 3H), 2.67 (s, 3H).

Synthesis of α,β-unsaturated ketimines (31):

Following a literature procedure [32], compound **S** (1 eq) and aldehyde derivatives **S5** (1 eq) was dissolved in ethanol (10 mL) followed by added acetic acid (0.1 eq) and piperidine (0.1 eq), and the reaction mixture was stirred at 80 °C for 3 h then cooled to 0 °C and filtered. The filter cake was washed with cold ethanol and subjected to the next step without further purification. Following all α,β-unsaturated ketimines (**31a-31k**) were synthesized by following the above procedure and subjected to the next step further without purification.

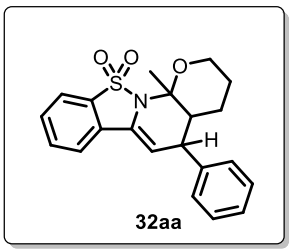


4a-4l prepared using reported procedures (see below details of chemical structures with related references.[32]

7. *General procedure* for the synthesis of protected chalcones (54o-54r):

Synthesis and characterization of tetrahydro benzoisothiazolo pyrano pyridine (32) from 5-Hexyn-1-ols (28) and α,β-unsaturated ketimines (31)

12a-Methyl-5-phenyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32aa):



32aa

Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-styrylbenzo[*d*]isothiazole 1,1-dioxide (**31a**) (0.272 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added ed $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 12a-methyl-5-phenyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32aa)** (0.086 g, 82%), as an white solid a mixture of two diastereomers (dr, 1:0.2, confirmed by NMR analysis).

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

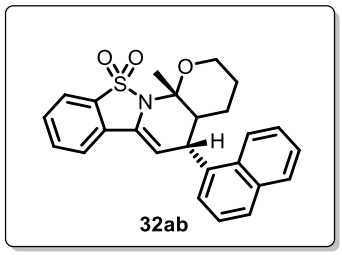
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.81 (d, *J* = 7.75 Hz, 1H), 7.74-7.71 (m, 1H), 7.66-7.61 (m, 1H), 7.59-7.54 (m, 1H), 7.41-7.35 (m, 2H), 7.33-7.28 (m, 2H), 7.25-7.22 (m, 2H), 5.79 (dd, *J* = 4.88, 0.88 Hz, 0.24H), 5.67 (dd, *J* = 2.38, 1.13 Hz, 1H), 4.40-4.29 (m, 1H), 4.21 (dd, *J* = 5.88, 2.38 Hz, 1H), 3.84-3.93 (m, 1H), 1.93-1.87 (m, 4H), 1.61-1.52 (m, 2H), 1.38-1.24 (m, 1H), 1.04-0.92 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 143.7, 140.6, 133.6, 133, 132.9, 132.4, 130.2, 130.2, 129.1, 128.7, 128.6, 127.8, 127.1, 126.8, 121.1, 121, 100.6, 99.3, 91.6, 89.6, 63.9, 63.5, 49.2, 46.6, 45.5, 43.1, 26.2, 25.9, 25.6, 25.5, 20.9; IR (KBr, cm^{-1}): υ 3153, 3072, 2934, 1717, 1461, 1305, 1177, 1071, 1010, 758, 699; MP: 202.5 ^oC.

M.P.: 201-203^oC

HRMS (ESI): *m/z* calcd for $C_{21}H_{21}O_3NS$ $[M+H]^+$ 368.1315 found 368.1306.

12a-Methyl-5-(naphthalen-1-yl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32ab):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(2-(naphthalen-1-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31b**) (0.322 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added ed $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 12a-methyl-5-(naphthalen-1-yl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ab)** (0.075 g, 79%) as an white solid. **32ab** was confirmed by ^{1}H NMR, ^{13}C NMR, DEPT, HRMS, and XRD analysis (please see below **Figure 1** and Spectral Section for details).

TLC: R_f = 0.50 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 8.38 Hz, 1H), 7.92 (dd, *J* = 7.88, 1.13 Hz, 1H), 7.86-7.74 (m, 3H), 7.68-7.63 (m, 1H), 7.61-7.52 (m, 3H), 7.50-7.45 (m, 1H), 7.40 (dd, *J* = 7.07, 1.06 Hz, 1H), 5.76 (d, *J* = 1.25 Hz, 1H), 5.02 (dd, *J* = 5.63, 2.25 Hz, 1H), 4.35 (td, *J* = 11.76, 3.63 Hz, 1H), 3.86 (td, *J* = 11.76, 2.63 Hz, 1H), 2.33-2.20 (m, 1H), 2.08 (s, 3H) 1.51-1.29 (m, 3H), 0.80-0.71 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 136.2, 134.1, 133.6, 133, 132.5, 131.4, 130.2, 129.4, 129.2, 127.9, 126.7, 126.4, 126.1, 125.3, 122.5, 121.1, 101.6, 91.6, 63.8, 44.5, 25.8, 25.5, 21.5.

IR (KBr, cm^{-1}): υ 3142, 3064, 2930, 1705, 1459, 1311, 1177, 1069, 1027, 794, 698.

HRMS (ESI): *m/z* calcd for $C_{25}H_{23}O_3NS$ $[M+H]^+$ 418.1471 found 418.1466.

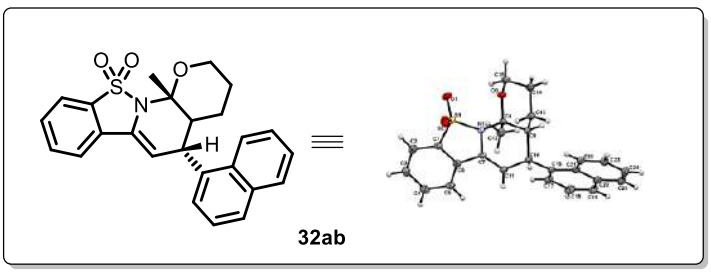
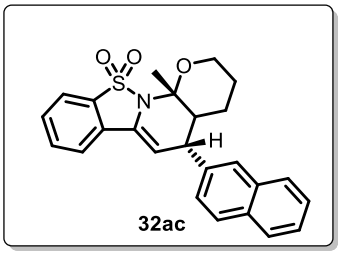


Figure 1. ORTEP diagram of **32ab**.

12a-Methyl-5-(naphthalen-2-yl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32ac):



32ac

Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(2-(naphthalen-2-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31c**) (0.322 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 12a-methyl-5-(naphthalen-2-yl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ac)** (0.076 g, 74%) as an white solid, mixture of two diastereomers (dr, 1:0.2, confirmed by NMR analysis).

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88-7.81 (m, 5H), 7.79 (d, *J* = 7.88 Hz, 1H), 7.71-7.63 (m, 2H), 7.61-7.55 (m, 1H), 7.54-7.40 (m, 3H), 7.36 (dd, *J* = 8.50, 1.75 Hz, 1H), 5.91 (dd, *J* = 4.88, 0.88 Hz, 0.2H), 5.79 (dd, *J* = 2.38, 1.13 Hz, 1H), 4.41-4.33 (m, 2H), 3.96-3.84 (m, 1H), 2.08-1.99 (m, 1H), 1.96 (s, 3H), 1.64-1.50 (4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 138.2, 133.7, 133.5, 133, 132.6, 132.6, 130.3, 129.2, 128.4, 127.8, 127.8, 127, 126.9, 126.5, 126, 121.1, 121.1, 100.5, 91.6, 63.9, 46.6, 43.2, 25.9, 25.5, 21.1.

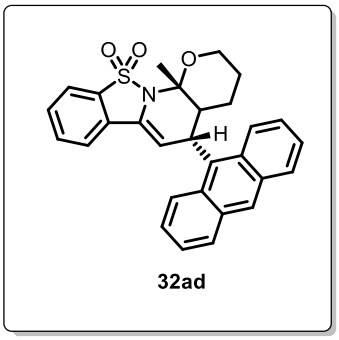
IR (KBr, cm^{-1}): υ 3143, 3004, 2929, 1702, 1599, 1464, 1308, 1178, 1069, 1011, 746;

M.P.: 177.2-179 ^{0}C.

HRMS (ESI): *m/z* calcd for $C_{25}H_{23}O_3NS$ $[M+H]^+$ 418.1471 found 418.1464.

5-(Anthracen-9-yl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32ad):

Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(2-(anthracen-9-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31d**) (0.073 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for



32ad

6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(anthracen-9-yl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ad)** (0.066 g, 68%) as an white solid.

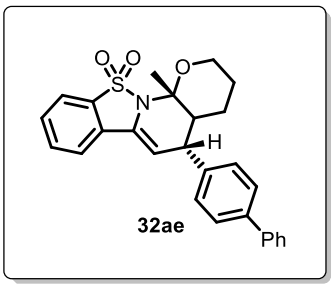
TLC: R_f = 0.50 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 9.01 Hz, 1H), 8.46 (s, 1H), 8.28 (d, *J* = 9.01 Hz, 1H), 8.08 (d, *J* = 8.25 Hz, 1H), 8.03 (d, *J* = 8.26 Hz, 1H), 7.89 (d, *J* = 7.50 Hz, 1H), 7.73-7.58 (m, 4H), 7.58-7.50 (m, 1H), 7.50-7.34 (m, 2H), 6.09 (m, 1H), 5.69-5.66 (m, 1H), 4.46 (dt, *J* = 3.63, 11.88 Hz, 1H), 3.96-3.90 (m, 1H), 2.53-2.45 (m, 1H), 2.18 (s, 3H), 2.12-1.82 (m, 2H), 1.60 (br. s., 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 133.6, 133.1, 132.1, 131.7, 131.6, 131.3, 130.7, 130.1, 130.0, 129.7, 129.6, 129.5, 128.4, 127.0, 126.7, 125.2, 125.1, 124.8, 122.9, 121.2, 120.9, 105.3, 91.4, 64.3, 46.9, 39.5, 26.0, 26.0, 22.8.

HRMS (ESI): *m/z* calcd for $C_{29}H_{26}O_3NS$ $[M+H]^+$ 468.1628, found 468.1622.

5-([1,1'-Biphenyl]-4-yl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32ae):



32ae

Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(2-([1,1'-biphenyl]-4-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31e**) (0.073 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-([1,1'-biphenyl]-4-yl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ae)** (0.066 g, 65%) as an white solid.

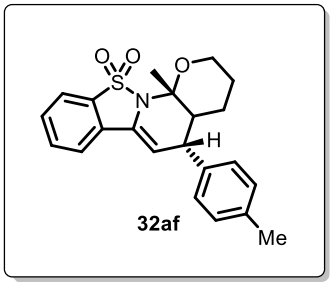
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.80 (m, 1H), 7.74 (d, *J* = 7.75 Hz, 1H), 7.67-7.53 (m, 6H), 7.48-7.43 (m, 2H), 7.37 (td, *J* = 1.13, 7.25 Hz, 1H), 7.31(d, *J* = 8.13 Hz, 2H), 5.70 (dd, *J* = 1.13, 2.50 Hz, 1H), 4.40-4.29 (m, 1H), 4.25 (dd, *J* = 2.38, 5.88 Hz, 1H), 3.95-3.84 (m, 1H), 1.99-1.94 (m, 1H), 1.93 (s, 3H), 1.65-1.55 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.7, 140.1, 139.7, 133.6, 133.0, 132.5, 130.2, 129.1, 129.0, 129.0, 127.5, 127.3, 127.1, 121.0, 121.0, 100.5, 91.6, 63.9, 46.6, 42.8, 25.9, 25.6, 21.0.

HRMS (ESI): *m/z* calcd for $C_{27}H_{26}O_3NS$ $[M+H]^+$ 444.1628, found 444.1621.

12a-methyl-5-(p-tolyl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32af):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-methylstyryl)benzo[d]isothiazole 1,1-dioxide (**31f**) (0.286 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 12a-methyl-5-(p-tolyl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32af)** (0.070 g, 67%) as an white solid mixture of two diastereomers (dr, 1:0.1, confirmed by NMR analysis).

TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

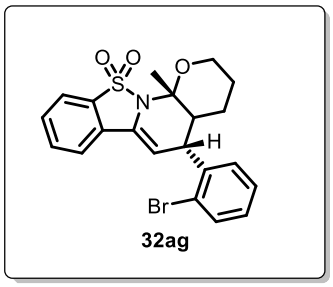
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, *J* = 7.63 Hz, 1H), 7.71(d, *J* = 7.75 Hz, 1H), 7.63 (t, *J* = 7.63 Hz, 1H), 7.55 (t, *J* = 7.50 Hz, 1H), 7.18 (d, *J* = 7.50 Hz, 2H), 7.12 (d, *J* = 7.38 Hz, 2H), 5.78 (d, *J* = 4.50 Hz, 0.1H), 5.65 (s, 1H), 4.40-4.27(m 1H), 4.17 (d, *J* = 5.00 Hz, 1H), 3.87 (d, *J* = 10.38 Hz, 1H), 2.36 (s, 3H), 2.16 (d, *J* = 14.88 Hz, 1H), 1.90 (s, 3H), 1.57-1.52 (m, 2H), 1.35-1.23 (m, 2H).

^{13}CNMR ($CDCl_3$, 101 MHz): δ 137.5, 136.8, 133.6, 132.9, 132.3, 130.1, 129.3, 129.2, 128.5, 121, 101, 91.6, 63.9, 46.6, 42.7, 25.6, 25.6, 21.2, 20.9.

IR (KBr, cm^{-1}): υ 3133, 3071, 2940, 1667, 1511, 1463, 1308, 1176, 1069, 1008, 932, 748.

HRMS (ESI): *m/z* calcd for $C_{22}H_{23}O_3NS$ $[M+H]^+$ 382.1471 found 382.1469.

5-(2-Bromophenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32ag):



32ag

Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(2-bromostyryl)benzo[d]isothiazole 1,1-dioxide (**31g**) (0.351 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(2-bromophenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ag)** (0.080 g, 8%) mixture of two diastereomers (dr, 1:0.35, confirmed by NMR analysis) as an white solid.

TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 - 7.79 (m, 1H), 7.77 - 7.70 (m, 1H), 6.68-7.52 (m, 4H), 7.36-7.29 (m, 1H), 7.26-7.06 (m, 3H), 5.60-5.53 (m, 1H), 5.65 (d, *J* = 488 Hz, 0.34H), 4.62 (dd, *J* = 2.4, 5.7 Hz, 1H), 4.38-4.24(m, 1H), 3.89 (td, *J* = 2.2, 11.4 Hz, 1H), 2.34-2.19 (m, 1H), 1.94 (s, 3H), 159-1,56 (m, 2H), 139-1.30 (m, 1H), 0.94-0.86 (m 1H).

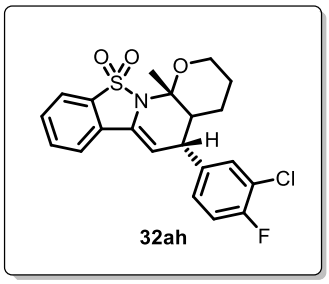
^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.9, 139.5, 133.7, 133.6, 133.3, 133.1, 133, 132.6, 130.7, 130.6, 130.4, 130.3, 129, 128.8, 128.7, 127.4, 127.3, 124.7, 121.1, 121.1, 121, 100.5, 98.7, 91.7, 90.2, 63.9, 63.7, 47.1, 46.1, 42.9, 42.4, 27.9, 27.2, 25.8, 25.5, 25.5, 21.3.

IR (KBr, cm^{-1}): υ 3191, 3144, 3069, 2928, 2859, 1699, 1666, 1462, 1391, 1311, 1184, 1012, 933, 750, 693.

M.P.: 197-199 ^{0}C.

HRMS (ESI): *m/z* calcd for $C_{21}H_{20}O_3NBrS$ $[M+H]^+$ 446.0420 found 446.0411.

5-(3-Chloro-4-fluorophenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32ah):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-chloro-3-fluorostyryl)benzo[*d*]isothiazole 1,1-dioxide (**31h**) (0.073 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(3-chloro-4-fluorophenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ah)** (0.050 g, 40%) mixture of two diastereomers (dr, 1:0.2, confirmed by NMR analysis) as an white solid.

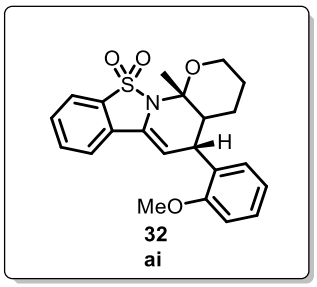
TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.54 (m, 4H), 7.25-7.00 (m, 3H), 5.62-5.50 (m, 1H), 4.47 (dd, *J* = 2.38, 5.63 Hz, 1H), 4.37-4.15 (m, 1H), 3.94-3.82 (m, 1H), 2.11-1.98 (m, 1H), 1.89 (s, 3H), 1.77-1.70 (m, 1H), 1.70-1.64 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8, 159.3, 133.8, 133.7, 133.6, 133.5, 133.1, 133.0, 133.0, 132.9, 131.0, 130.9, 130.5, 130.4, 130.3, 130.2, 128.8, 128.8, 126.5, 126.4, 124.5, 124.5, 124.4, 124.3, 121.1, 121.0, 116.6, 116.3, 98.7, 97.0, 91.4, 89.9, 63.8, 43.9, 36.3, 36.3, 25.7, 25.6, 25.4, 21.3.

HRMS (ESI): *m/z* calcd for $C_{21}H_{20}O_3NClFS$ $[M+H]^+$ 420.0831, found 420.0825.

5-(2-Methoxyphenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32ai):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(2-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31i**) (0.302 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30%

EtOAc/hexanes) afforded 5-(2-methoxyphenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ai)** (0.086 g, 87%) mixture of two diastereomers (dr, 1:0.2, confirmed by NMR analysis) as an white solid.

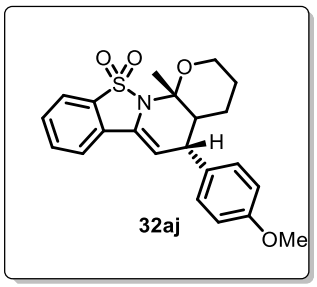
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.79 (m, 1H), 7.76-7.70 (m, 1H), 7.62 (td, *J* = 7.25, 1.06 Hz, 1H), 7.58-7.52 (m, 1H), 7.30-7.27(m, 1H), 7.23-7.16 (m, 1H), 6.98-6.85 (m, 2.46H), 5.68 (dd, *J* = 4.88, 1.06 Hz, 0.23H), 5.63 (dd, *J* = 2.56, 1.06 Hz, 1H), 4.59 (dd, *J* = 5.63, 2.50 Hz, 1H), 4.40-4.23 (m, 1H), 3.90-3.88 (m, 1H), 3.86 (m, 3H), 2.22-2.12 (m, 1H), 1.92 (s, 3H), 1.60-1.53(m, 2H), 1.35-1.22 (m, 1H), 0.99-0.88(m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.1, 133.5, 132.9, 132.9, 132.2, 130.1, 130, 129.5, 129.3, 128.8, 128.2, 128, 121.1, 120.9, 120.3, 120.3, 110.4, 101.7, 99.9, 91.8, 90.6, 63.8,, 63.6, 55.5, 55.5, 47.2, 43, 41.1, 36.8, 26.6, 256, 25.7, 25.7, 21.4

HRMS (ESI)*: m/z* calcd for $C_{22}H_{23}O_4NS$ $[M+H]^+$ 398.1421 found 398.1413.

5-(4-Methoxyphenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32aj):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31j**) (0.302 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(4-methoxyphenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32aj)** (0.084 g, 82%), as an white solid. **32aj** was confirmed by ^{1}H NMR, ^{13}C NMR, DEPT, HRMS and 2D analysis (please see below **Figure 2** and Spectral Section for details).

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (d, *J* = 7.78 Hz, 1H), 7.70 (d, *J* = 7.78 Hz, 1H), 7.65-7.60 (m, 1H), 7.58-7.53 (m, 1H), 7.16-7.12 (m, 2H), 6.93-6.88 (m, 2H), 5.63 (dd, *J* = 2.40

Hz, 1.03 1H), 4.39-4.28 (m, 1H), 4.16 (dd, *J* = 5.72, 2.29 Hz, 1H), 3.87 (dt, *J* = 11.27, 1.92 Hz, 1H), 3.82 (s, 3H), 1.92-1.83 (m, 4H), 1.57-1.54 (m, 2H), 1.34-1.27 (m, 1H), 1.07-0.97 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.8, 133.6, 132.9, 132.5, 132.3, 130.2, 129.6, 129.2, 121.1, 114.1, 101.1, 91.7, 63.9, 55.5, 46.7, 42.3, 25.9, 25.6, 20.6.

HRMS (ESI)*: m/z* calcd for $C_{22}H_{23}O_4NS$ $[M+H]^+$ 398.1421 found 398.1416.

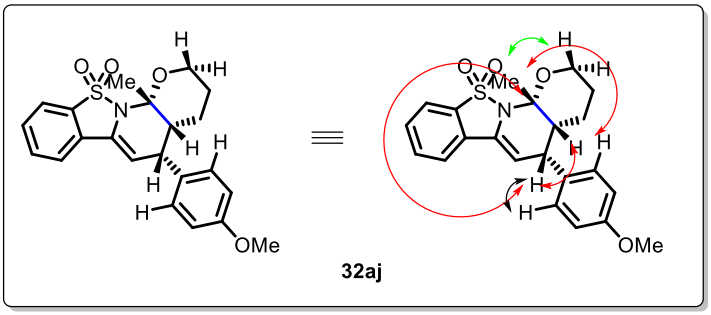
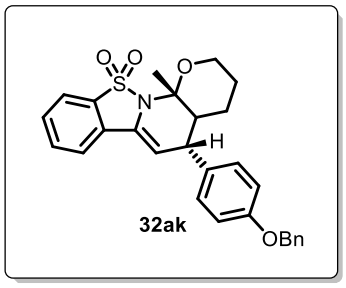


Figure 2. NOESY analyses of **32aj**.

5-(4-(Benzyloxy)phenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32ak):



Following the *General Procedure*, to the mixture of 5-hexyn-1-ol (**28a**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-(benzyloxy)styryl)benzo[*d*]isothiazole 1,1-dioxide (**31k**) (0.380 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(4-(benzyloxy)phenyl)-12a-methyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ak)** (0.069 g, 68%). as an white solid, mixture of two diastereomers (dr, 1:0.1, confirmed by NMR analysis).

TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

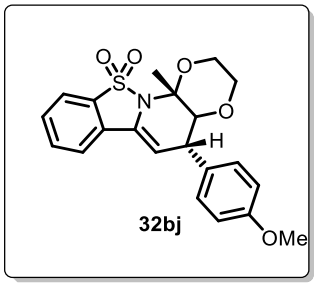
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, *J* = 7.75 Hz, 1H), 7.70 (d, *J* = 7.75 Hz, 1H), 7.63 (td, *J* = 7.50, 1.13 Hz, 1H), 7.59-7.53 (m, 1H), 7.48-7.43 (m, 2H), 7.40 (d, *J* = 7.32 Hz, 2H), 7.35

(d, *J* = 7.13 Hz, 1H), 7.20 (d, *J* = 8.63 Hz, 0.2H), 7.14 (d, *J* = 8.50 Hz, 2H), 6.98 (d, *J* = 8.63 Hz, 2H), 6.92 (d, *J* = 8.63 Hz, 0.2H), 5.76 (d, *J* = 4.48 Hz, 0.1H), 5.63 (d, *J* = 1.25 Hz, 1H), 5.08 (s, 2H), 5.04 (s, 0.2H), 4.40-4.30 (m, 1H), 4.16 (dd, *J* = 5.75, 2.13 Hz, 1H), 3.95-3.81 (m, 1H), 1.95-1.85 (m, 4H), 1.36-1.25 (m, 2H), 1.08-0.98 (m, 1H), 0.90-0.83 (m, 1H).

^{13}CNMR ($CDCl_3$, 101 MHz): δ 158. 137.1, 133.6, 132.9, 132.8, 132.3, 130.2, 129.6, 129.2, 128.8, 128.2, 127.6, 121, 121, 115, 101.1, 91.6, 70.3, 63.9, 46.7, 42.3, 25.9, 25.6, 21; IR (KBr, cm^{-1}): υ 3747, 3401, 3363, 3293, 2934, 1510, 1452, 1307, 1244, 1179, 1057, 934, 815, 697.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}O_4NS$ $[M+H]^+$ 474.1734 found 474.1731.

5-(4-Methoxyphenyl)-12a-methyl-2,3,4a,12a-tetrahydro-5H-benzo[4,5]isothiazolo[2,3-*a*][1,4]dioxino[2,3-*e*]pyridine 11,11-dioxide (32bj):



Following the *General Procedure*, to the mixture of 2-(prop-2-yn-1-yloxy)ethan-1-ol (**28b**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31j**) (0.299 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(4-methoxyphenyl)-12a-methyl-2,3,4a,12a-tetrahydro-5H-benzo[4,5]isothiazolo[2,3-*a*][1,4]dioxino[2,3-*e*]pyridine 11,11-dioxide **(32bj)** (0.059 g, 58%) as an white solid.

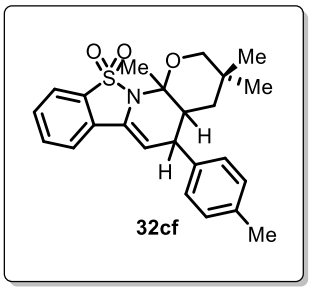
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, *J* = 7.93 Hz, 1H), 7.69 (d, *J* = 7.63 Hz, 1H), 7.62 (td, *J* = 7.32, 1.22 Hz, 1H), 7.59-7.55 (m, 1H), 7.25-7.23 (m, 2H), 6.95-6.88(m, 2H), 5.57 (dd, *J* = 2.44, 1.22 Hz, 1H), 4.61 (d, *J* = 3.36 Hz, 1H), 4.03-3.97 (m, 1H), 3.82 (s, 3H), 3.81-3.78 (m, 1H), 3.69-3.62 (m, 2H), 3.54 (dd, *J* = 4.27, 1.22 Hz, 1H), 1.80 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 133.5, 133, 131.6, 131.1, 130.4, 130.2, 129, 121.2, 121, 113.8, 100.2, 88.2, 79.4, 67.5,61.9, 55.4, 42.9, 23.5.

HRMS (ESI)*: m/z* calcd for $C_{21}H_{22}O_5NS$ $[M+H]^+$ 400.1213 found 400.1205.

3,3,12a-Trimethyl-5-(*p*-tolyl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32cf):



Following the *General Procedure*, to the mixture of 3,3-dimethylhex-5-yn-1-ol (**28c**) (0.1 g, 0.792 mmol) and (*E*)-3-(4-methylstyryl)benzo[*d*]isothiazole 1,1-dioxide (**31f**) (0.223 g, 0.792 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.051 g, 0.079 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 3,3,12a-trimethyl-5-(*p*-tolyl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32cf)** dr. 1:0.1 (0.059 g, 60%) as an white solid.

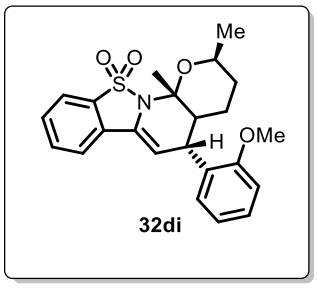
TLC: R_f = 0.70 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, *J* = 7.75 Hz, 1H), 7.71(d, *J* = 7.88 Hz, 1H), 7.63 (td, *J* = 7.25, 1.13 Hz, 1H), 7.58-7.53 (m, 1H), 7.19-7.16 (m, 2H), 7.13-7.08 (m, 2H), 5.65 (dd, *J* = 2.38, 1.00 Hz, 1H), 4.18 (dd, *J* = 5.88, 2.38 Hz, 1H), 4.06 (d, *J* = 11.88 Hz, 1H), 3.36 (dd, *J* = 11.63, 2.63 Hz, 1H), 2.37 (s, 3H), 2.18-2.08 (m, 1H), 1.94 (s, 3H), 1.14 (d, *J* = 13.3 Hz, 1H), 0.91 (s, 3H), 0.73 (s, 3H), 0.68-0.64 (m, 1H).

^{13}CNMR ($CDCl_3$, 101 MHz): δ 137.4, 136.7, 133.6, 132.9, 132.3, 130.1, 129.4, 129.2, 128.4, 121, 101, 91.1, 73.1, 42.7, 42.2, 34.2, 30.5, 27.4, 25.7, 23.7, 21.2.

HRMS (ESI)*: m/z* calcd for $C_{24}H_{27}O_3NS$ $[M+H]^+$ 410.1784 found 410.1779.

5-(2-Methoxyphenyl)-2,12a-dimethyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32di):



Following the *General Procedure*, to the mixture of hept-6-yn-2-ol (**28d**) (0.1 g, 0.892 mmol) and (*E*)-3-(2-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31i**) (0.266 g, 0.892 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.058 g, 0.089 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(2-

methoxyphenyl)-2,12a-dimethyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32di)** (0.080 g, 79%) mixture of two diastereomers (dr, 1:2 confirmed by NMR analysis) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

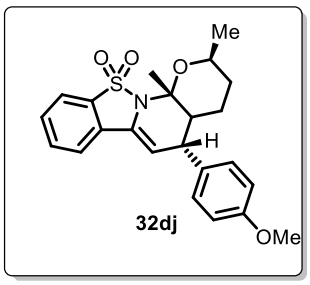
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.69 (m, 3H), 7.66-7.58 (m, 1.43H), 7.53 (q, *J* = 7.84 Hz, 1.46H), 7.31-7.26 (m, 1H), 7.24-7.16 (m, 2H), 6.99-6.83 (m, 3H), 5.66 (d, *J* = 4.48 Hz, 0.5H); 5.61 (s, 1H), 4.63-4.55 (m, 1H), 4.47-4.31 (m, 1H), 3.89 (s, 1H), 3.86 (s, 3H), 2.17-2.05 (m, 2H), 1.92 (s, 3H), 1.72 (d, *J* = 11.13, Hz, 1H), 1.60-1.54 (m, 1H), 1.32 (dd, *J* = 12.88, 2.63 Hz, 1H),1.25-1.21 (m, 4H), 0.91 (dd, *J* = 13.13, 3.25 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.1, 156.9, 133.6, 133.4, 132.8, 132.7, 132.1, 131.5, 130, 129.9, 129.4, 129.1, 128.9, 128.7, 128, 127.9, 121, 120.9, 120.7, 120.2, 120.1, 110.2, 101.4, 99.5, 91.8, 90.7, 69.1, 68.9, 55.4, 55.4, 46.8, 42.5, 40.9, 36.5, 33.3, 32.8, 28.9, 27, 25.9, 22, 21.4, 21.3; IR (KBr, cm^{-1}): υ 3175, 3145, 3077, 2933, 1705, 1661, 1593, 1532, 1458, 1307, 1241, 1169, 1075, 1023, 916, 833, 752, 647.

M.P.:196-198^{0}C.

HRMS (ESI): *m/z* calcd for $C_{23}H_{25}O_4NS$ $[M+H]^+$ 412.1577 found 412.1571.

5-(4-Methoxyphenyl)-2,12a-dimethyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32dj):



32dj

Following the *General Procedure*, to the mixture of hept-6-yn-2-ol (**28d**) (0.1 g, 0.892 mmol) and (*E*)-3-(4-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31j**) (0.266 g, 0.892 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.058 g, 0.089 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(4-methoxyphenyl)-2,12a-dimethyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32dj)** (0.080 g, 81%) as an white crystal. **32dj** was confirmed by ^{1}H NMR, ^{13}C NMR, DEPT, HRMS and XRD analysis (please see below **Figure 3** and Spectral Section for details).

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 - 7.52 (m, 6H), 7.23 - 7.11 (m, 3H),6.95-6.81 (m, 3H), 5.62 (dd, *J* = 2.38, 1.13 Hz, 1 H), 4.49-4.36 (m, 1H), 4.16 (dd, *J* = 5.82, 2.31 Hz, 1 H), 3.85-3.81 (m, 3H), 3.79 (s, 3H), 1.90 (s, 4H), 1.86-1.80 (m, 2H), 1.65-1.53 (m, 3H), 1.26-1.21 (m, 4H), 1.04-0.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.7, 133.6, 132.8, 132.8, 132.2, 130.1, 129.5, 129.1, 121.0, 120.9, 114.0, 113.9, 100.9, 99.1, 91.8, 90.3, 69.3, 55.4, 49.4, 46.4, 45.0, 42.1, 32.8, 27.1, 26.1, 21.6, 21.4.

IR (KBr, cm^{-1}): υ 3146, 3074, 2952, 1722, 1603, 1458, 1373, 1260, 1174, 1127, 1038, 978, 831, 698.

HRMS (ESI)*: m/z* calcd for $C_{23}H_{25}O_4NS$ $[M+H]^+$ 412.1577 found 412.1574.

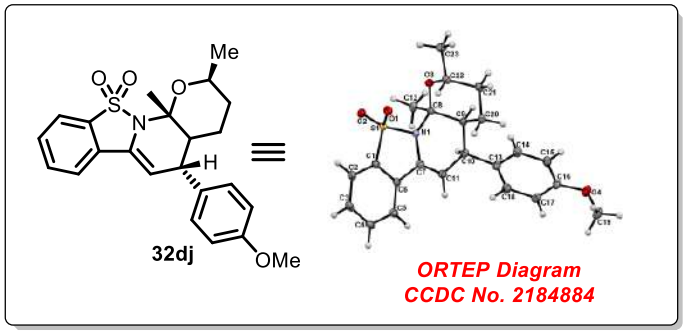
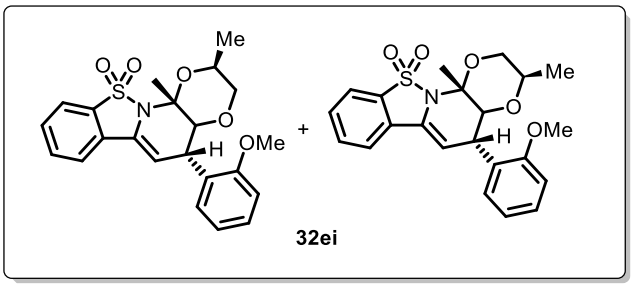


Figure 3. ORTEP diagram of **32dj**.

5-(2-Methoxyphenyl)-2,12a-dimethyl-2,3,4a,12a-tetrahydro-5H-benzo[4,5]isothiazolo[2,3-*a*][1,4]dioxino[2,3-*e*]pyridine 11,11-dioxide (32ei):



Following the *General Procedure*, to the mixture of 1-(prop-2-yn-1-yloxy)propan-2-ol (**28e**) (0.1 g, 0.876 mmol) and (*E*)-3-(2-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31i**) (0.262 g, 0.876 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.057 g, 0.087 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(2-methoxyphenyl)-2,12a-dimethyl-3,4,4a,12a-tetrahydro-

2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32ei)** (0.061 g, 60%) as an white solid, mixture of two diastereomers (dr, 1:0.6, confirmed by NMR analysis).

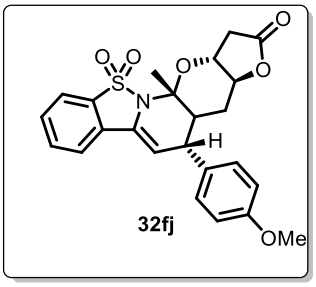
TLC: R_f = 0.80 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.83-7.77 (m, 1.56H), 7.73-7.67 (m, 1.65H), 7.61(t, *J* = 7.44 Hz, 1.58H), 7.57-7.52 (m, 1.55H), 7.32-7.27 (m, 3H), 7.00-6.94 (m, 1H), 6.94-6.90 (m, 1.6H), 5.58 (dd, *J* = 2.29, 1.14 Hz, 1H), 5.56-5.54 (m, 0.5H), 4.65 (ddd, *J* = 10.68, 6.48, 3.05, Hz, 1H), 4.60-4.54 (m, 1.54H), 4.18-4.12 (m, 1H), 3.91-3.86 (m, 5H), 3.72-3.69 (m, 2H), 3.66-3.61 (m, 1H), 3.20 (t, *J* = 11.44 Hz, 1H), 1.86-1.77 (m, 5H), 1.13 (d, *J* = 6.10 Hz, 3H); 0.94 (d, *J* = 6.10 Hz, 1.69H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.8, 133.4, 132.9, 131.9, 131.4, 130.8, 130, 129.9, 129.1, 128.4, 128.1, 127.3, 121.1, 120.9, 120.5, 120.3, 110.1, 110, 100.9, 100.1, 88.6, 87.4, 76.4, 73, 72.2, 67.3, 66.7, 55.6, 36.5, 36.3, 23.5, 23.1, 16.7, 16.3.

HRMS (ESI)*: m/z* calcd for $C_{22}H_{23}O_5NS$ $[M+H]^+$ 414.1370 found 414.1367.

5-(4-Methoxyphenyl)-12a-methyl-1,3a,4,4a,12a,13a-hexahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]furo[2',3':5,6]pyrano[3,2-*e*]pyridin-2-one 11,11-dioxide (32fj):



Following the *General Procedure*, to the mixture of (4*R*,5*S*)-5-(but-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (**28f**) (0.1 g, 0.648 mmol) and (*E*)-3-(4-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31j**) (0.073 g, 0.648 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.042 g, 0.064 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(4-methoxyphenyl)-12a-methyl-1,3a,4,4a,12a,13a-hexahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]furo[2',3':5,6]pyrano[3,2-*e*]pyridin-2-one 11,11-dioxide **(32fj)** (0.060 g, 59%) as an white solid.

TLC: R_f = 0.40 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 7.63 Hz, 1H), 7.76-7.72 (m, 1H), 7.67 (td, *J* = 7.57, 1.25 Hz, 1H), 7.62-7.57 (m, 1H), 7.18-7.09 (m, 2H), 6.95-6.87 (m, 2H), 5.72 (d, *J* =

2.44, 1.19 Hz, 1H), 5.17 (q, *J* = 2.50, Hz, 1H), 4.42 (q, *J* = 3.00, Hz, 1H), 4.22 (dd, *J* = 5.75, 2.38 Hz, 1H), 3.83 (s, 3H), 2.74 (d, *J* = 2.50 Hz, 2H), 2.27-2.16 (m, 1H), 1.87 (s, 3H), 1.59-1.57 (m, 1H), 1.55-1.51 (m, 1H).

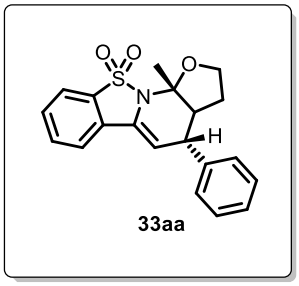
^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.1, 159, 133.3, 132.4, 131.1, 130.5, 129.4, 129, 121.2, 121.1, 114.3, 101.4, 90.3, 77.5, 69.9, 55.5, 41.3, 39, 38.7, 25.1, 22.6.

IR (KBr, cm^{-1}): υ 3144, 3037, 2924, 1781, 1702, 1653, 1510, 1464, 1307, 1248, 1180, 1105, 1047, 935, 832, 698.

HRMS (ESI): *m/z* calcd for $C_{24}H_{23}O_6NS$ $[M+H]^+$ 454.1319 found 454.1314.

Synthesis and Characterization of tetrahydro benzoisothiazolo furo pyridine from 4-pentyn-1-ols and *α,β*-unsaturated ketimines

11a-Methyl-4-phenyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide (33aa):



33aa

Following the *General Procedure*, to the mixture of 4-pentyn-1-ol (**27a**) (0.1 g, 1.18 mmol) and (*E*)-3-styrylbenzo[*d*]isothiazole 1,1-dioxide (**31a**) (0.317 g, 1.18 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.077 g, 0.118 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 4-([1,1'-biphenyl]-4-yl)-11a-methyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide **(33aa)** (0.060 g, 61%) as an white solid.

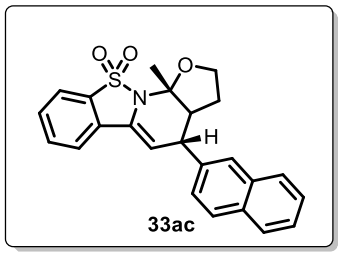
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (d, *J* = 7.63 Hz, 1H), 7.70 (d, *J* = 7.63 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.58-7.54 (m, 1H), 7.38-7.34 (m, 2H), 7.31-7.27 (m, 3H), 5.61 (d, *J* = 1.53 Hz, 1H), 4.39-4.31 (m, 1H), 4.15 (dd, *J* = 6.10, 2.29 Hz, 1H), 3.95 (q, *J* = 8.52 Hz, 1H), 2.49-2.40 (m, 1H), 2.01-1.93 (m, 1H), 1.92 (s, 3H), 1.45-1.38 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 141.7, 134.1, 132.7, 130.7, 130.2, 128.9, 128.7, 127.9, 127.3, 121.1, 120.9, 98.5, 95.2, 67.3, 52, 40.3, 26.6, 22.9.

HRMS (ESI): *m/z* calcd for $C_{20}H_{19}O_3NS$ $[M+H]^+$ 354.1158 found 354.1155.

11a-Methyl-4-(naphthalen-2-yl)-2,3,3a,11a-tetrahydro-4H benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide (33ac):



Following the *General Procedure*, to the mixture of 4-pentyn-1-ol (**27a**) (0.1 g, 1.18 mmol) and (*E*)-3-(2-(naphthalen-2-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31c**) (0.379 g, 1.18 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.077 g, 0.118 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 11a-methyl-4-(naphthalen-2-yl)-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide **(33ac)** (0.067 g, 68%) as an white solid.

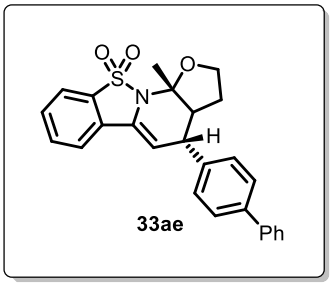
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.80 (m, 4H), 7.76 (d, *J* = 7.75 Hz, 1H), 7.73 (s, 1H), 7.64 (dt, *J* = 1.13, 7.50 Hz, 1H), 7.60-7.54 (m, 1H), 7.51-7.47 (m, 2H), 7.41 (dd, *J* = 1.75, 8.50 Hz, 1H), 5.73 (dd, *J* = 1.00, 2.50 Hz, 1H), 4.42-4.28 (m, 2H), 3.94 (q, *J* = 8.38 Hz, 1H), 2.60-2.51 (m, 1H), 2.08-1.98 (m, 1H), 1.96 (s, 3H), 1.62 (s, 2H), 1.44-1.34(m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.2, 134.1, 133.6, 132.8, 132.7, 130.9, 130.3, 128.7, 128.6, 127.8, 127.8, 126.5, 126.3, 126.2, 126.0, 121.2, 120.9, 98.5, 95.3, 67.3, 51.9, 40.4, 26.7, 22.9.

HRMS (ESI): *m/z* calcd for $C_{24}H_{22}O_3NS$ $[M+H]^+$ 404.1315, found 404.1313.

4-([1,1'-Biphenyl]-4-yl)-11a-methyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide (33ae):



Following the *General Procedure*, to the mixture of 4-pentyn-1-ol (**27a**) (0.1 g, 1.18 mmol) and (*E*)-3-(2-([1,1'-biphenyl]-4-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31e**) (0.450 g, 1.18 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.077 g, 0.118 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 4-([1,1'-biphenyl]-4-yl)-11a-methyl-2,3,3a,11a-tetrahydro-

4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide **(33ae)** (0.066 g, 65%) as an white solid.

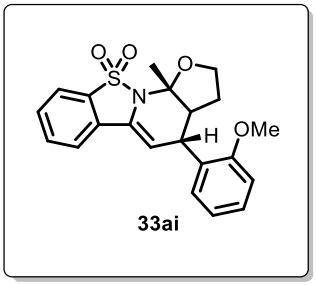
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 7.63 Hz, 1H), 7.72 (d, *J* = 7.63 Hz, 1H), 7.65 - 7.55 (m, 6H), 7.49-7.42 (m, 2H), 7.39-7.33 (m, 3H), 5.64 (d, *J* = 1.75 Hz, 1H), 4.44-4.34 (m, 1H), 4.20 (dd, *J* = 6.19, 2.31 Hz, 1H), 3.98 (q, *J* = 8.46 Hz, 1H), 2.55-2.47 (m, 1H), 2.06-1.94 (m, 1H), 1.94 (s, 3H), 0.88-0.84 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 140.8, 140.7, 140.3, 134.1, 132.7, 130.8, 130.3, 129, 128.7, 128.3, 127.6, 127. 2, 121.2, 120.9, 98.5, 95.3, 67.4, 51.9, 40.1, 26.6, 22.9

HRMS (ESI): *m/z* calcd for $C_{26}H_{23}O_3NS$ $[M+H]^+$ 430.1471 found 430.1470.

4-(2-methoxyphenyl)-11a-methyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide (33ai):



33ai

Following the *General Procedure*, to the mixture of 4-pentyn-1-ol (**27a**) (0.1 g, 1.18 mmol) and (*E*)-3-(2-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31i**) (0.355 g, 1.18 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.077 g, 0.118 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 4-(2-methoxyphenyl)-11a-methyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide **(33ai)** (0.077 g, 78%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, *J* = 7.75 Hz, 1H), 7.70 (d, *J* = 7.75 Hz, 1H), 7.65 - 7.52 (m, 2H), 7.29 (s, 1H), 7.21 (d, *J* = 7.50 Hz, 1H), 6.97-6.88 (m, 2H), 5.57 (d, *J* = 2.25 Hz, 1H), 4.55 (dd, *J* = 6.13, 2.50 Hz, 1H), 4.37-4.30 (m, 1H), 3.95 (q, *J* = 8.59 Hz, 1H), 3.88 (s, 3H), 2.78-2.66 (m, 1H), 1.92 (s, 3H), 0.87-0.84 (m, 2H).

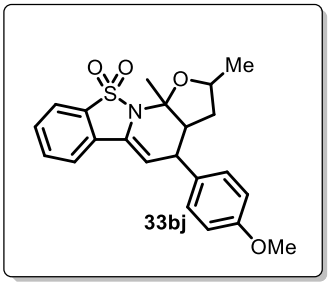
^{13}C NMR ($CDCl_3$, 101 MHz): δ 156.9, 134 132.6, 130.5, 130.3, 128.3, 128.3, 121.1, 120.9, 120.7, 110.3, 99.5, 95.3, 67.4, 55.6, 48.5, 26.9, 22.8.

IR (KBr, cm^{-1}): υ 3200, 3143, 2927, 1705, 1651, 1605, 1465, 1304, 1242, 1174, 1025, 962, 896, 752, 695.

HRMS (ESI): *m/z* calcd for $C_{21}H_{21}O_4NS$ $[M+H]^+$ 384.1264 found 384.1257.

4-(4-Methoxyphenyl)-2,11a-dimethyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide (33bj):

Following the *General Procedure*, to the mixture of hex-5-yn-2-ol (**27b**) (0.1 g, 1.01 mmol) and (*E*)-3-(4-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**431j**) (0.304 g, 1.01 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.066 g, 0.101 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 4-(4-methoxyphenyl)-2,11a-dimethyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide **(33bj),** (0.069 g, 70%) as an white solid mixture of two diastereomers (dr, 1:0.3, confirmed by NMR analysis).



TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

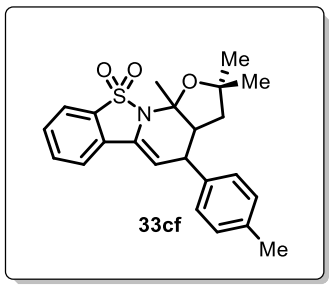
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.51 (m, 6H), 7.23-7.12 (m, 3H), 6.93-6.86 (m, 3H), 5.70-5.63 (m, 0.3H), 5.56 (d, *J* = 1.63 Hz, 1H), 4.71-4.63 (m,1H), 4.08 (dd, *J* = 6.13, 2.38 Hz, 1H), 3.82 (s, 3H), 2.54-2.44 (m, 1H), 2.14-1.97 (m, 1H), 1.91-1.87 (m, 3H), 1.19(d, *J* = 6.38 Hz, 4H), 1.10-1.00(m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.8, 134.1, 133.8, 132.7, 132.7, 130.8, 130.2, 130.2, 129.2, 129.1, 128.9, 128.9, 128.8, 121.1, 120.9, 114.3, 114.2, 114.1, 98.9, 95.8, 74.6, 55.5, 50.9, 39.4, 33.3, 23.3, 22.6.

IR (KBr, cm^{-1}): υ 3267, 3194, 3143, 3076, 2931, 1728, 1655, 1607, 1513, 1460, 1305, 1246, 1175, 1115, 1031, 957, 896, 753.

HRMS (ESI): *m/z* calcd for $C_{22}H_{23}O_4NS$ $[M+H]^+$ 398.1421 found 398.1417.

4-(4-Methoxyphenyl)-2,2,11a-trimethyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide (33cf):



Following the *General Procedure*, to the mixture of 2-methylhex-5-yn-2-ol (**27c**) (0.1 g, 0.892 mmol) and (*E*)-3-(4-methylstyryl)benzo[*d*]isothiazole 1,1-dioxide (**31f**) (0.252 g, 0.892 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.058 g, 0.089 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 4-(4-methoxyphenyl)-2,2,11a-trimethyl-2,3,3a,11a-tetrahydro-4H-benzo[4,5]isothiazolo[2,3-*a*]furo[3,2-*e*]pyridine 10,10-dioxide **(33cf)** (0.069 g, 71%) as an white solid mixture of two diastereomers (dr, 1:0.6, confirmed by NMR analysis).

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

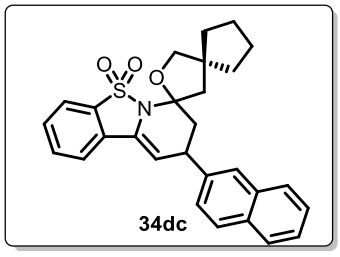
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 - 7.78 (m, 1H), 7.70 - 7.66 (m, 1H), 7.64-7.51 (m, 3H), 7.20-7.12 (m 5H), 5.61 (d, *J* = 2.25 Hz, 1H), 5.70 (d, *J* = 4.63 Hz, 0.3H), 4.10 (dd, *J* = 6.63, 2.63 Hz, 1H), 2.70-2.59 (m, 1H), 2.39-2.32 (m, 4H), 2.17-210 (m, 1H), 1.94-1.90 (m, 3H), 1.25 (s, 6H), 1.19 (s, 4H), 0.92-0.79 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 138.8, 136.9, 134.1, 132.8, 132.7, 130.9, 130.2, 129.5, 128.8, 127.9, 121.1, 120.9, 99.6, 95.6, 83.5, 51.7, 39.9, 39.8, 29.7, 29.4, 24.7, 21.2.

HRMS (ESI): *m/z* calcd for $C_{23}H_{26}O_3NS$ $[M+H]^+$ 396.1628 found 396.1619.

***Synthesis and Characterization* of tetrahydro spiro benzoisothiazolo pyridine furan from 4-pentyn-1-ols and *α,β*-unsaturated ketimines**

9-(Naphthalen-2-yl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclopentane] 5,5-dioxide (34dc):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**27d**) (0.1 g, 0.724 mmol) and (*E*)-3-(2-(naphthalen-2-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31c**) (0.230 g, 0.724 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.047 g, 0.072 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30%

EtOAc/hexanes) afforded 9-(naphthalen-2-yl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclopentane] 5,5-dioxide **(34dc)** (0.079 g, 80%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

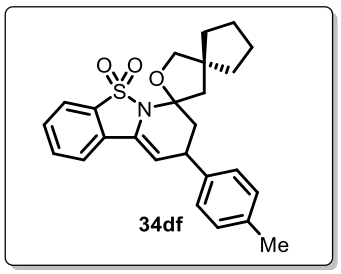
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.79 (m, 4H), 7.77 (s, 1H), 7.70 - 7.66 (m, 1H), 7.64-7.53 (m, 2H), 7.51-7.41 (m, 3H), 5.87 (m, 1H), 4.27-4.16 (m, 2H), 3.92 (d, *J* = 8.50, Hz, 1H), 3.45 (d, *J* = 6.38 Hz, 1H), 3.25 (d, *J* = 14.76 Hz, 1H), 2.31 (d, *J* = 12.51 Hz, 1H), 2.14 (d, *J* = 14.88 Hz, 1H), 1.80-1.67 (m, 4H), 1.57-1.50 (m, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.9, 133.6, 132.9, 132.6, 132.4, 131.5, 130, 129.2, 128.6, 127.7, 127.6, 126.3, 126.2, 126.1, 125.8, 120.9, 104.9, 94.1, 68.8, 46.7, 44.1, 37.4, 36.8, 35. 25.9, 25.8, 24.4, 23.1.

IR (KBr, cm^{-1}): υ 3065, 2924, 1699, 1632, 1536, 1455, 1455, 1301, 1238, 1170, 1020, 748.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}O_3NS$ $[M+H]^+$ 458.1784 found 458.1770.

9-(*p*-Tolyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclopentane] 5,5-dioxide (34df):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**27d**) (0.1 g, 0.724 mmol) and (*E*)-3-(4-methylstyryl)benzo[*d*]isothiazole 1,1-dioxide (**31f**) (0.194 g, 0.724 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.047 g, 0.072 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(*p*-tolyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclopentane] 5,5-dioxide **(34df)** (0.076 g, 78%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 7.63, Hz, 1H), 7.67-7.49 (m, 3H), 7.22-7.13 (m, 4H), 5.76 (m, 1H), 4.16 (d, *J* = 8.50, Hz, 1H), 4.00 (ddd, *J* = 12.35, 5.66, 2.25 Hz, 1H), 3.87

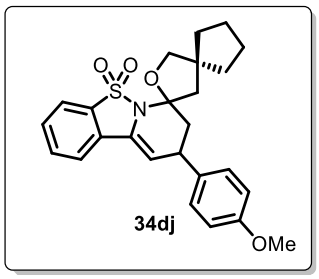
(d, *J* = 8.50, Hz, 1H), 3.21 (d, *J* = 14.76, Hz, 1H), 2.35 (s, 3H), 2.31-2.23 (m, 1H) 2.20-2.07 (m, 2H), 1.69-1.60 (m, 2H), 1.54-1.42 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.6, 136.8, 133, 132.5, 131.4, 130, 129.6, 129.4, 127.7, 121, 120.9, 105.5, 94.3, 78.3, 46.9, 44.2, 37, 36.8, 35.1, 26.1, 24.5, 23.2, 21.2.

IR (KBr, cm^{-1}): υ 3065, 2924, 1699, 1632, 1536, 1455, 1455, 1301, 1238, 1170, 1020, 748.

HRMS (ESI): *m/z* calcd for $C_{25}H_{27}O_3NS$ $[M+H]^+$ 422.1784 found 422.1778.

9-(4-Methoxyphenyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclopentane] 5,5-dioxide (34dj):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**27d**) (0.1 g, 0.724 mmol) and (*E*)-3-(4-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31j**) (0.215 g, 0.724 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.047 g, 0.072 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(4-methoxyphenyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclopentane] 5,5-dioxide **(34dj)** (0.081 g, 82%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

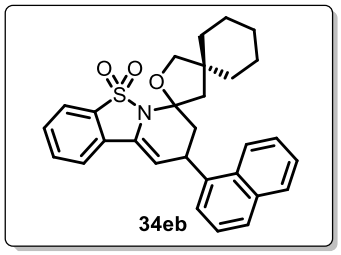
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (td, *J* = 1.0, 7.7 Hz, 1 H), 7.66 - 7.46 (m, 4 H), 7.25 - 7.19 (m, 2 H), 6.93 - 6.84 (m, 2 H), 5.76 (dt, *J* = 1.4, 3.0 Hz, 1 H), 4.27 - 4.14 (m, 1 H), 4.00 (ddd, *J* = 2.5, 5.7, 12.3 Hz, 1 H), 3.84 - 3.81 (m, 3 H), 3.81 - 3.74 (m, 1 H), 3.55 - 3.42 (m, 1 H), 2.38 - 2.24 (m, 1 H), 2.18 - 2.08 (m, 2 H), 1.89 - 1.79 (m, 2 H), 1.78 - 1.58 (m, 6 H), 1.57 - 1.42 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.6, 135.6, 135.5, 132.9, 132.9, 132.3, 131.3, 129.9, 129.3, 129.3, 128.7, 120.9, 120.8, 120.8, 114.2, 105.6, 105.4, 94.2, 94.2, 78.9, 55.4, 50.8, 46.9, 46.2, 46.0, 44.0, 39.6, 36.7, 36.5, 36.3, 35.0, 34.8, 29.6, 25.9, 25.9, 24.9, 24.4, 24.2, 23.1

IR (KBr, cm^{-1}): υ 3068, 2935, 1725, 1653, 1603, 1511, 1456, 1456, 1303, 1245, 1171, 1029, 832, 746.

HRMS (ESI): *m/z* calcd for $C_{25}H_{27}O_4NS$ $[M+H]^+$ 438.1734 found 438.1719.

9-(Naphthalen-1-yl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide (34eb):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclohexyl)methanol (**27e**) (0.1 g, 0.657 mmol) and (*E*)-3-(2-(naphthalen-1-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31b**) (0.207 g, 0.657 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.042 g, 0.065 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(naphthalen-2-yl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclopentane] 5,5-dioxide **(34eb)** (0.077 g, 78%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.79 (m, 4H), 7.76 (s, 1H), 7.71 - 7.65 (m, 1H), 7.64-7.58 (m, 1H), 7.58-7.51 (m, 1H), 7.50-7.46 (m, 2H), 7.42 (dd, *J* = 8.50, 1.63 Hz, 1H), 5.87 (s, 1H), 4.29-4.18 (m, 2H), 3.80 (d, *J* = 8.13, Hz, 1H), 3.52 (d, *J* = 14.51 Hz, 1H), 2.46-2.37 (m, 1H), 2.31-2.21 (m, 1H), 2.13 (d, *J* = 14.51 Hz, 1H), 1.76-1.60 (m, 8H), 1.57-1.48 (m, 2H).

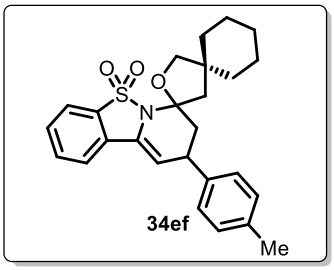
^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.1, 133.7, 133.1, 132.7, 132.5, 131.7, 130.1, 129.4, 128.7, 127.8, 127.7, 126.4, 126.3, 126.2, 125.9, 121.1, 121, 105.2, 94.3, 79.1, 51, 46.3, 45.9, 39.7, 37.4, 35, 25, 24.4.

IR (KBr, cm^{-1}): υ 3066, 2942, 2867, 1697, 1665, 1599, 1464, 1305, 1243, 1172, 1005, 815, 746.

HRMS (ESI): *m/z* calcd for $C_{29}H_{29}O_3NS$ $[M+H]^+$ 472.1941 found 472.1928.

9-(*p*-Tolyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide (34ef):

Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclohexyl)methanol (**27e**) (0.1 g, 0.657 mmol) and (*E*)-3-(4-methylstyryl)benzo[*d*]isothiazole 1,1-dioxide (**31f**) (0.186 g, 0.657 mmol) in anhydrous



CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.042 g, 0.065 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(*p*-tolyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide **(34ef)** (0.070 g, 72%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

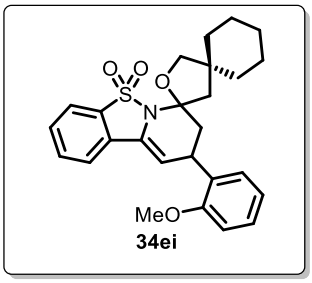
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 7.63, Hz, 1H), 7.67-7.49 (m, 3H), 7.22-7.13 (m, 4H), 5.76 (m, 1H), 4.16 (d, *J* = 8.50, Hz, 1H), 4.00 (ddd, *J* = 12.35, 5.66, 2.25 Hz, 1H), 3.87 (d, *J* = 8.50, Hz, 1H), 3.21 (d, *J* = 14.76, Hz, 1H), 2.35 (s, 3H), 2.31-2.23 (m, 1H) 2.20-2.07 (m, 2H), 1.80-1.60 (m, 4H), 1.54-1.42 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.6, 136.8, 133, 132.5, 131.4, 130, 129.6, 129.4, 127.7, 121, 120.9, 105.5, 94.3, 78.3, 46.9, 44.2, 37, 36.8, 35.1, 26.1, 24.5, 23.2, 21.2.

IR (KBr, cm^{-1}): υ 3065, 2924, 1699, 1632, 1536, 1455, 1455, 1301, 1238, 1170, 1020, 748.

HRMS (ESI)*: m/z* calcd for $C_{26}H_{30}O_3NS$ $[M+H]^+$ 436.1941 found 436.1934.

9-(2-Methoxyphenyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide (34ei):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclohexyl)methanol (**27e**) (0.1 g, 0.657 mmol) and (*E*)-3-(2-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31i**) (0.194 g, 0.657 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.042 g, 0.065 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(2-methoxyphenyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide **(34ei)** (0.078 g, 79%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

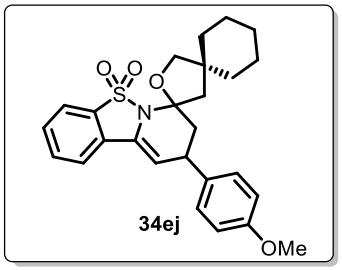
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 8.00 Hz, 1H), 7.64-7.50 (m, 3H), 7.46 (d, *J* = 7.75 Hz, 1H), 7.24-7.18 (m, 1H), 7.12 (dd, *J* = 7.50, 1.25 Hz, 1H), 6.95-6.82 (m, 3H), 4.70 (s, 1H), 4.08 (d, *J* = 8.50 Hz, 1H), 3.92 (d, *J* = 8.51 Hz, 1H), 3.87 (s, 3H), 3.69-3.57 (m, 1H), 2.54 (d, *J* = 5.38 Hz, 1H), 2.46-2.37 (m, 1H), 2.26-2.16 (m, 2H), 1.91-1.84 (m, 1H), 1.64 (d, *J* = 7.63 Hz, 1H), 1.54-1.49 (m, 1H), 1.43 (dd, *J* = 9.88, 7.63 Hz, 2H), 1.07 (dd, *J* = 11.01, 8.50 Hz, 1H), 0.91-0.80 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.7, 157.2, 143.7, 135.8, 132.9, 131.3, 129.6, 127.9, 126.4, 125.4, 121.6, 120.7, 110.7, 108.9, 83.7, 65.2, 55.5, 55.1, 47.2, 36.6, 36.4, 32, 29.9, 23.6, 22.5.

IR (KBr, cm^{-1}): υ 3011, 2944, 2355, 1673, 1600, 1454, 1345, 1289, 1241, 1163, 1036, 938, 750.

HRMS (ESI): *m/z* calcd for $C_{26}H_{29}O_4NS$ $[M+H]^+$ 452.1890 found 452.1874.

9-(4-Methoxyphenyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide (34ej):



Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclohexyl)methanol (**27e**) (0.1 g, 0.657 mmol) and (*E*)-3-(4-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31j**) (0.194 g, 0.657 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.042 g, 0.065 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(4-methoxyphenyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide **(34ej)** (0.081g, 82%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

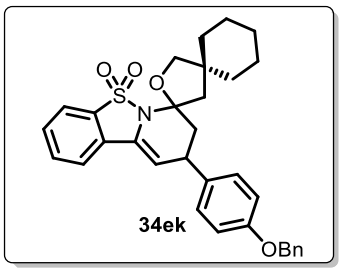
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 7.5 Hz, 1 H), 7.67 - 7.48 (m, 4 H), 7.24 - 7.14 (m, 2 H), 6.93 - 6.86 (m, 2 H), 5.75 (br. s., 1 H), 4.25 - 4.12 (m, 1 H), 3.98 (dt, *J* = 3.0, 6.1 Hz, 1 H), 3.87 (d, *J* = 8.5 Hz, 1 H), 3.81 (s, 3 H), 3.79 - 3.74 (m, 1 H), 3.52 - 3.42 (m, 1 H), 3.21 (d, *J* = 14.9 Hz, 1 H), 2.35 - 2.23 (m, 1 H), 2.20 - 2.07 (m, 2 H), 1.87 - 1.57 (m, 9 H), 1.57 - 1.42 (m, 6 H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.6, 135.6, 135.5, 132.9, 132.8, 132.3, 131.3, 131.2, 129.9, 129.3, 129.3, 128.7, 120.9, 120.8, 120.8, 114.2, 105.6, 105.4, 94.2, 94.1, 78.9, 68.8, 55.4, 50.8, 46.9, 46.2, 46.0, 44.0, 40.5, 39.6, 36.7, 36.5, 36.3, 35.0, 34.8, 29.7, 29.6, 26.6, 25.9, 25.8, 24.9, 24.4, 24.2, 23.1

IR (KBr, cm^{-1}): υ 3019, 2938, 1706, 1664, 1607, 1514, 1449, 1305, 1242, 1172, 1023, 833, 743.

HRMS (ESI): *m/z* calcd for $C_{26}H_{29}O_4NS$ $[M+H]^+$ 452.1890 found 452.1876.

9-(4-(Benzyloxy)phenyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide (34ek):



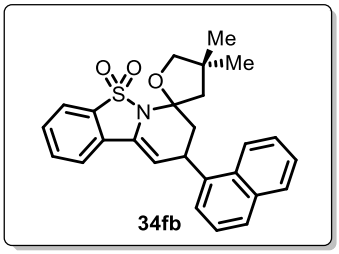
Following the *General Procedure*, to the mixture of (1-(prop-2-yn-1-yl)cyclohexyl)methanol (**27e**) (0.1 g, 0.657 mmol) and (*E*)-3-(4-(benzyloxy)styryl)benzo[*d*]isothiazole 1,1-dioxide (**31k**) (0.244 g, 0.657 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.042 g, 0.065 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(4-(benzyloxy)phenyl)-8,9-dihydro-3'H,5'H-dispiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan-4',1''-cyclohexane] 5,5-dioxide **(34ek)** (0.059g, 60%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 7.75, Hz, 1H), 7.65-7.50 (m, 3H), 7.46-7.33 (m, 5H), 7.21(d, *J* = 8.50, Hz, 2H), 6.96 (d, *J* = 8.63, Hz, 2H), 5.76 (s, 2H), 4.21 (d, *J* = 8.38, Hz, 1H), 3.99 (d, *J* = 12.88, Hz, 1H), 3.76 (d, *J* = 8.25, Hz, 1H), 3.48 (d, *J* = 14.38, Hz, 1H), 2.37-2.31 (m, 1H), 2.16-2.08 (m, 2H), 1.70-1.64 (m, 4H), 1.49 (d, *J* = 6.38, Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158, 136.0, 133.0, 130.1, 128.9, 128.8, 128.1, 127.6, 121.1, 120.9, 115.3, 105.7, 94.4, 79.1, 70.3, 51.0, 46.1, 39.7, 36.4, 35, 25, 24.4.

4',4'-Dimethyl-9-(naphthalen-1-yl)-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxidedioxide (34f



Following the *General Procedure*, to the mixture of 2,2-dimethylpent-4-yn-1-ol (**27f**) (0.1 g, 0.891 mmol) and (*E*)-3-(2-(naphthalen-1-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31b**) (0.284 g, 0.891 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.038 g, 0.89 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 4',4'-dimethyl-9-(naphthalen-1-yl)-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxidedioxide **(34fb)** (0.073g, 74%) as an white solid.

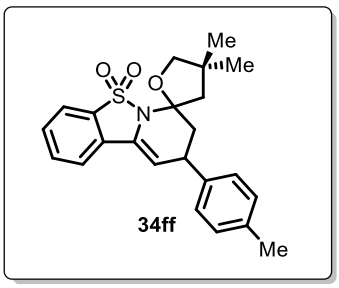
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, *J* = 8.38 Hz, 1 H), 7.95-7.89 (m, 1 H), 7.83 - 7.76 (m, 2 H), 7.70-7.63 (m, 1 H), 7.62-7.50 (m, 4 H), 7.48-7.43 (m, 2 H), 5.96 (s, 1 H), 4.94 (s, 1 H), 4.31 (d, *J* = 8.25, Hz, 1 H), 3.77 (d, *J* = 8.13, Hz, 1 H), 3.37 (d, *J* = 14.76 Hz, 1 H), 2.57 (dd, *J* = 12.69, 4.57 Hz, 1 H), 2.36-2.20 (m, 1 H), 2.01 (d, *J* = 14.63 Hz, 1 H), 1.31 (s, 3 H), 1.24 (s, 3 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 139.4, 134.2, 133.1, 132.5, 131.5, 131.1, 130.1, 129.4, 129.3, 129, 127.7, 126.6, 125.9, 125.9, 123, 121.1, 121, 105.5, 95, 80.4, 61.8, 47.8, 45.3, 40.1, 28.9, 25.

HRMS (ESI): *m/z* calcd for $C_{26}H_{26}O_3NS$ $[M+H]^+$ 432.1628 found 432.1626.

4',4'-Dimethyl-9-(*p*-tolyl)-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide (34ff):



Following the *General Procedure*, to the mixture of 2,2-dimethylpent-4-yn-1-ol (**27f**) (0.1 g, 0.891 mmol) and (*E*)-3-(4-methylstyryl)benzo[*d*]isothiazole 1,1-dioxide (**31f**) (0.252 g, 0.891 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.058 g, 0.089 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the

crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 4',4'-dimethyl-9-(*p*-tolyl)-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide **(34ff)** (0.065g, 66%) as an white solid.

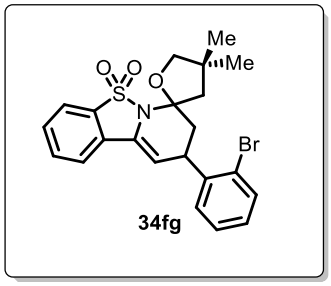
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.76 (m, 1H), 7.65-7.56 (m, 2H), 7.55-7.50 (m, 1H),7.22-7.14 (m, 4H), 5.80-5.74 (m, 1H), 4.22 (d, *J* = 8.25 Hz, 1H), 4.02 (ddd, *J* = 12.48, 5.72, 2.44 Hz, 1H), 3.67 (d, *J* = 8.25 Hz, 1H), 3.32 (d, *J* = 14.76 Hz, 1H), 2.40-2.29 (m, 4H), 2.22-2.12 (m, 1H), 2.07-1.95(m, 1H), 1.28 (s, 3H), 1.22 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.6, 136.9, 133, 132.5, 131.4, 130, 129.6, 127.7, 121, 120.9, 105.5, 94.9, 80.4, 47.8, 46.6, 40.1, 37, 29, 25, 21.2.

HRMS (ESI): *m/z* calcd for $C_{23}H_{26}O_3NS$ $[M+H]^+$ 396.1628 found 396.1619.

9-(2-Bromophenyl)-4',4'-dimethyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide (34fg):



34fg

Following the *General Procedure*, to the mixture of 2,2-dimethylpent-4-yn-1-ol (**27f**) (0.1 g, 0.891 mmol) and (*E*)-3-(2-bromostyryl)benzo[*d*]isothiazole 1,1-dioxide (**31g**) (0.310 g, 0.891 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.058 g, 0.089 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(2-bromophenyl)-4',4'-dimethyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide **(34fg)** (0.076g, 78%) as an white solid.

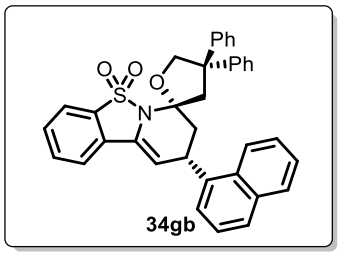
TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, *J* = 7.75 Hz, 1H), 7.71-7.66 (m, 1H), 7.64-7.51 (m, 3H), 7.31 (d, *J* = 7.75 Hz, 2H), 7.17-7.10 (m, 1H), 5.78 (s, 1H), 4.58 (ddd, *J* = 12.29, 5.41, 2.31 Hz, 1H), 4.20 (d, *J* = 8.25 , Hz, 1H), 3.70 (d, *J* = 8.13 , Hz, 1H), 3.30 (d, *J* = 14.63, Hz, 1H), 2.54 (dd, *J* = 12.95, 4.57 Hz, 1H), 2.04-1.94 (m, 2H), 1.25 (s, 3H), 1.28 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 142.6, 133.2, 133.1, 132.5, 132.3, 130.2, 129.3, 128.9, 128.6, 128.2, 124.5, 121.1, 120.9, 104.1, 94.7, 80.4, 47.8, 44.2, 40.1, 36.8, 28.8, 25.1.

HRMS (ESI): *m/z* calcd for $C_{22}H_{23}O_3NBrS$ $[M+H]^+$ 460.0577 found 460.0571.

(7*S*,9*S*)-9-(Naphthalen-1-yl)-4',4'-diphenyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide (34gb):



Following the *General Procedure*, to the mixture of 2,2-diphenylpent-4-yn-1-ol (**27g**) (0.1 g, 0.423 mmol) and (*E*)-3-(2-(naphthalen-1-yl)vinyl)benzo[*d*]isothiazole 1,1-dioxide (**31b**) (0.135 g, 0.423 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.027 g, 0.042 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded (7*S*,9*S*)-9-(naphthalen-1-yl)-4',4'-diphenyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide **(34gb)** (0.086 g, 86%) as an white crystal. **34gb** was confirmed by ^1H NMR, ^{13}C NMR, DEPT, HRMS and XRD analysis (please see below **Figure 4** and Spectral Section for details).

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.80 (m, 3H), 7.73 (t, *J* = 7.00 Hz, 2H), 7.64 (td, *J* = 7.60, 1.19 Hz, 1H), 7.59-7.43 (m, 5H), 7.42-7.28 (m 8H), 7.24-7.20 (m 1H), 7.11-7.06 (m, 1H), 6.01-5.94 (m, 1H), 5.11-5.03 (m, 1H), 4.83-4.71(m, 2H), 4.44 (d, *J* = 14.13 Hz, 1H), 2.86 (dd, *J* = 14.20, 1.31 Hz, 1H), 2.09-1.96 (m, 1H), 1.88(d, *J* = 12.26 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.9, 143.9, 139.5, 133.9, 133.2, 132.3, 131.3, 130.2, 129.4, 129, 128.8, 128.7, 127.6, 128.5, 127.6, 127.4, 127.3, 126.8, 126.7, 126.4, 125.9, 123.1, 121.1, 121.1, 105.6, 94.9, 76.2, 56.1, 46.1, 43.8.

IR (KBr, cm^{-1}): υ 3067, 3031, 2926, 1595, 1539, 1492, 1451, 1306, 1249, 1174, 1039, 813, 751, 696.

HRMS (ESI): *m/z* calcd for $C_{36}H_{29}O_3NS$ $[M+H]^+$ 556.1941 found 556.1931.

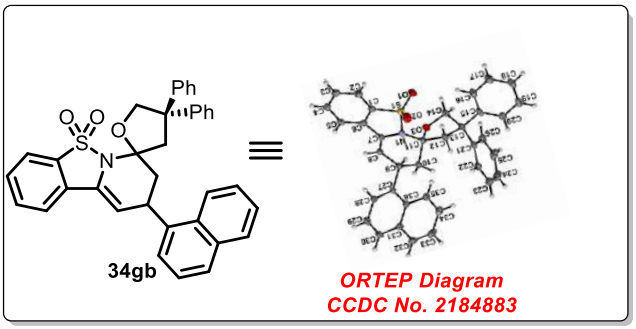
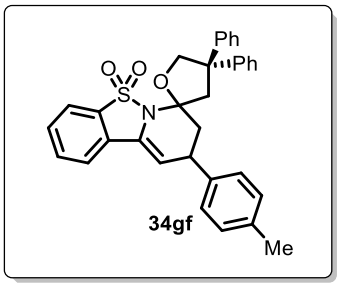


Figure 4. ORTEP diagram of **34gb**.

4',4'-Diphenyl-9-(*p*-tolyl)-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide (34gf):



Following the *General Procedure*, to the mixture of 2,2-diphenylpent-4-yn-1-ol (**27g**) (0.1 g, 0.423 mmol) and (*E*)-3-(4-methylstyryl)benzo[*d*]isothiazole 1,1-dioxide (**31f**) (0.119 g, 0.423 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.027 g, 0.042 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 4',4'-diphenyl-9-(*p*-tolyl)-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide **(34gf)** (0.067 g, 69%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

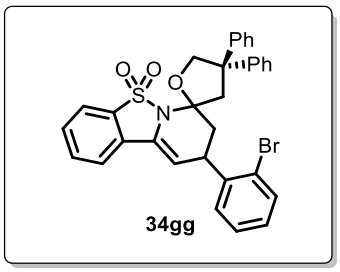
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 7.88 Hz, 1H), 7.67-7.58 (m, 2H), 7.56-7.51 (m, 1H), 7.42 (d, *J* = 7.75 Hz, 2H), 7.33-7.29 (m, 5H), 7.25-7.16 (m, 3H), 7.10 (d, *J* = 8.00 Hz, 2H), 7.03 (m, *J* = 7.88 Hz, 2H) 5.79 (s, 1H), 4.97 (d, *J* = 9.38 Hz, 1H), 4.67 (d, *J* = 9.26 Hz, 1H), 4.42 (d, *J* = 14.01 Hz, 1H), 3.95-3.83 (m, 1H), 2.85 (d, *J* = 14.13 Hz, 1H), 2.31 (s, 3H), 1.87-1.76 (m, 1H), 1.74-1.65 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.1, 144.1, 140.5, 136.6, 133.1, 130.1, 129.5, 129.4, 128.7, 128.6, 127.5, 127.5, 127.3, 126.8, 126.7, 121.1, 120.9, 105.7, 94.8, 76.3, 56, 46.1, 44.9. 36.2, 21.1.

IR (KBr, cm^{-1}): υ 3062, 3014, 2927, 1659, 1596, 1491, 1449, 1304, 1174, 1037, 751, 695.

HRMS (ESI): *m/z* calcd for $C_{33}H_{29}O_3NS$ $[M+H]^+$ 520.1941 found 520.1927.

9-(2-Bromophenyl)-4',4'-diphenyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide (34gg):



34gg

Following the *General Procedure*, to the mixture of 2,2-diphenylpent-4-yn-1-ol (**27g**) (0.1 g, 0.423 mmol) and (*E*)-3-(2-bromostyryl)benzo[*d*]isothiazole 1,1-dioxide (**31g**) (0.147 g, 0.423 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.027 g, 0.042 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(2-bromophenyl)-4',4'-diphenyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide **(34gg)** (0.082 g, 83%) as an white solid.

TLC: R_f = 0. (SiO_2, 15% EtOAc/hexanes).

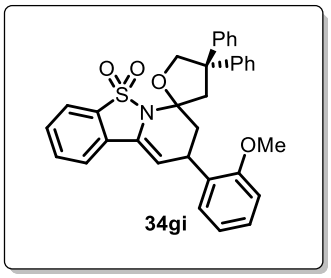
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, *J* = 7.63 Hz, 1H), 7.71-7.67 (m, 1H), 7.66-7.60 (m, 1H), 7.56 (d, *J* = 7.75 Hz, 1H), 7.49 (d, *J* = 7.75 Hz, 1H), 7.42 (d, *J* = 7.38 Hz, 2H), 7.35-7.29 (m, 6H), 7.25-7.20 (m, 4H), 7.09-7.04 (m, 1H), 5.77 (s, 1H), 4.99 (d, *J* = 9.51 Hz, 1H), 4.67 (d, *J* = 9.26 Hz, 1H), 4.52-4.40 (m, 2H), 2.82 (d, *J* = 14.01 Hz, 1H), 2.00-1.90 (m, 1H), 1.65(t, *J* = 12.44 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ146.2, 144.2, 142.6, 133.2, 133.1, 132.4, 130.3, 129.2, 129, 128.9, 128.7, 128.5, 128.5, 128.1, 128, 127.6, 127.4, 126.8, 126.6, 124.5, 121.2, 121, 104.5, 94.9, 76.5, 56.1, 46.1, 43, 36.4.

IR (KBr, cm^{-1}): υ 3745, 3073, 3040, 2997, 2924, 2336, 1699, 1656, 1590, 1468, 1306, 1245, 1174, 1024, 868, 755, 697.

HRMS (ESI): *m/z* calcd for $C_{32}H_{27}O_3NSBr$ $[M+H]^+$ 584.0890 found 584.0886.

9-(2-Methoxyphenyl)-4',4'-diphenyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide (34gi):



Following the *General Procedure*, to the mixture of 2,2-diphenylpent-4-yn-1-ol (**27g**) (0.1 g, 0.423 mmol) and (*E*)-3-(2-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31i**) (0.126 g, 0.423 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.027 g, 0.042 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(2-methoxyphenyl)-4',4'-diphenyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide **(34gi)** (0.084 g, 85%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

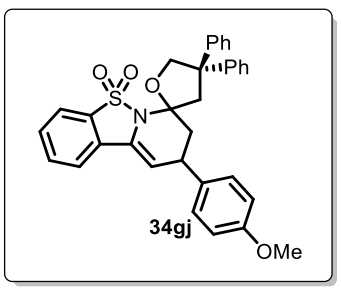
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 7.50 Hz, 1H), 7.71-7.66 (m, 1H), 7.60 (td, *J* = 7.25, 1.13 Hz, 1H), 7.56- 7.5 (m, 1H), 7.44-7.37 (m, 2H), 7.31-7.27 (m, 5H), 7.23-7.16 (m, 4H), 7.12 (dd, *J* = 7.63, 1.75 Hz, 1H), 6.88 (td, *J* = 7.50, 1.13 Hz, 1H), 6.81 (dd, *J* = 8.25, 0.88 Hz, 1H), 5.80 (dd, *J* = 2.25, 1.25 Hz, 1H), 4.97 (dd, *J* = 8.00, 1.25 Hz, 1H), 4.68 (d, *J* = 9.26 Hz, 1H), 4.43-4.32 (m, 2H), 3.76 (s, 3H), 2.84 (dd, *J* = 14.13, 1.38 Hz, 1H), 1.86 (qd, *J* = 12.88, 5.75, 1.38 Hz, 1H), 1.72 (t, *J* = 11.66 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.1, 146.3, 133.1, 132.3, 131.9, 131.6, 129.9, 129.6, 128.7, 128.5, 128, 127.9, 127.6, 127.4, 126.8, 126.4, 121.1, 120.9, 120.8, 110.5, 105.7, 95.1, 76.4, 56.1, 55.4, 46.2, 42.6, 30.1.

IR (KBr, cm^{-1}): υ 3062, 3008, 2886, 1702, 1665, 1598, 1491, 1443, 1378, 1292, 1221, 1044, 747, 696.

HRMS (ESI): *m/z* calcd for $C_{33}H_{29}O4NS$ $[M+H]^+$ 536.1890 found 536.1880.

9-(4-Methoxyphenyl)-4',4'-diphenyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide (34gj):



Following the *General Procedure*, to the mixture of 2,2-diphenylpent-4-yn-1-ol (**27g**) (0.1 g, 0.423 mmol) and (*E*)-3-(4-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31j**) (0.126 g, 0.423mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.027 g, 0.042 mmol) under an argon atmosphere

at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 9-(4-methoxyphenyl)-4',4'-diphenyl-4',5',8,9-tetrahydro-3'H-spiro[benzo[4,5]isothiazolo[2,3-*a*]pyridine-7,2'-furan] 5,5-dioxide **(34gj)** (0.081 g, 83%) as an white solid.

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

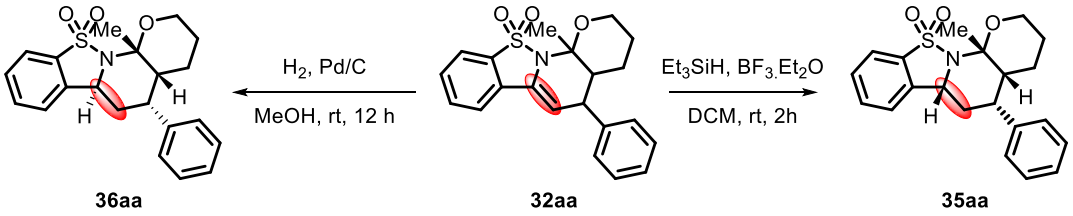
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.76 (m, 1H), 7.69-7.49 (m, 3H), 7.47-7.38 (m, 2H), 7.34-7.27 (m, 6H), 7.25-7.15 (m, 2H), 7.08-7.01 (m, 2H), 6.85-6.80 (m, 2H), 5.78 (dd, *J* = 2.38, 1.50 Hz, 1H), 5.01-4.94 (m, 1H), 4.68 (d, *J* = 9.26 Hz, 1H), 4.42 (d, *J* = 14.13 Hz, 1H), 3.89 (ddd, *J* = 12.10, 5.63, 2.38 Hz, 1H), 3.81-3.73 (m, 3H), 2.85 (dd, *J* = 14.07, 1.3 Hz, 1H), 1.81 (t, *J* = 12.57 Hz, H), 1.64-1.72(m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.6, 146.1, 144.1, 135.5, 133.1, 132.3, 131.5, 130.1, 129.4, 128.7, 128.6, 128.6, 127.5, 127.3, 126.8, 126.7, 121.1, 120.9, 114.3, 105.8, 94.8, 76.3, 56, 55.4, 46.1, 45, 35.8.

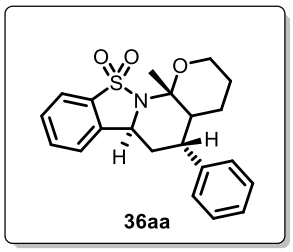
IR (KBr, cm^{-1}): υ 3064, 3011, 2886, 1745, 1703, 1664, 1604, 1508, 1459, 1305, 1243, 1170, 1028, 831, 746.

HRMS (ESI): *m/z* calcd for $C_{33}H_{29}O4NS$ $[M+H]^+$ 536.1890 found 536.1882.

Synthetic utility



12a-Methyl-5-phenyl-3,4,4a,6,6a,12a-hexahydro-2H,5H-benzo[4,5]isothiazolo[2,3-a]pyrano[3,2-e]pyridine 11,11-dioxide (36aa)



Synthesis of **35aa**: The 10 mL round bottom flask charged with 5-(5*R*,12a*R*)-12a-methyl-5-phenyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32aa)** (0.1 g, 1.01 mmol), in anhydrous MeOH (2 mL) followed by 10% Pd/C (5.7 mg, 0.2 mmol) under an

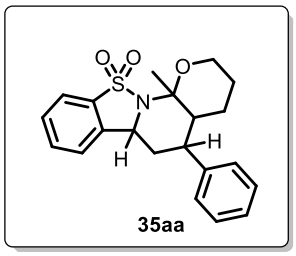
argon atmosphere. The resulting suspension was hydrogenated for 12 h at room temperature under the H_2 balloon pressure (1 atm). Then the mixture was filtered through a Celite pad, and the filtrate was concentrated to give the crude product which was purified by silica-gel chromatography (SiO_2, 20% EtOAc/hexanes) afforded 12a-methyl-5-phenyl-3,4,4a,6,6a,12a-hexahydro-2H,5H-benzo[4,5]isothiazolo[2,3-a]pyrano[3,2-e]pyridine 11,11-dioxide (**36aa**) as a white solid (0.087 g, 88%) as an white solid.

TLC: R_f = 0.40 (SiO_2, 30% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, *J* = 7.5 Hz, 1 H), 7.64-7.59 (m, 1 H), 7.57-7.52 (m, 1 H), 7.40 (d, *J* = 7.5 Hz, 1 H), 7.38-7.34 (m, 2 H), 7.29 (s, 1 H), 7.18 (d, *J* = 7.4 Hz, 2 H), 4.63 (dd, *J* = 2.6, 11.8 Hz, 1 H), 4.35-4.24 (m, 1 H), 3.91-3.77 (m, 1 H), 3.56-3.42 (m, 1 H), 2.46-2.34 (m, 1 H), 2.24-2.09 (m, 1 H), 2.00 (s, 3 H), 1.91-1.83 (m, 1 H), 1.53 (br. s., 3 H), 1.11-1.02 (m, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.4, 137.2, 136.8, 132.6, 129.4, 128.7, 127.6, 126.9, 122.4, 121.0, 90.8, 63.9, 58.3, 48.1, 42.6, 28.0, 25.3, 23.9, 19.2.

12a-Methyl-5-phenyl-3,4,4a,6,6a,12a-hexahydro-2H,5H-benzo[4,5]isothiazolo[2,3-a]pyrano[3,2-e]pyridine 11,11-dioxide (35aa):



35aa

To a solution of 5-(5*R*,12a*R*)-12a-methyl-5-phenyl-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32aa)** (0.1 g, 1.01 mmol), in anhydrous DCM (2 mL) was added ed Et_3SiH (0.62 g, 2.01 mmol) and $BF_3.Et_2O$ (0.42 g, 2.01 mmol) dropwise under an argon atmosphere at room temperature and reaction mixture was stirred for 2h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded (5*R*,6a*R*,12a*R*)-12a-methyl-5-phenyl-3,4,4a,6,6a,12a-hexahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (**35aa**) (0.066 g, 67%) as an white solid.

TLC: R_f = 0.80 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, *J* = 7.6 Hz, 1 H), 7.58-7.49 (m, 2 H), 7.35-7.32 (m, 2 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 7.24-7.21 (m, 2 H), 4.30 (dd, *J* = 2.4, 11.9 Hz, 1 H), 3.52-3.33 (m, 3 H), 2.78 (dt, *J* = 3.5, 11.8 Hz, 1 H), 2.44 (td, *J* = 3.2, 12.9 Hz, 1 H), 1.93-1.86 (m, 1 H), 1.80 (d, *J* = 6.4 Hz, 3 H), 1.54-1.46 (m, 2 H), 1.38-1.32 (m, 1 H), 0.90-0.84 (m, 1 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 143.5, 137.4, 136.2, 132.8, 129.3, 129.0, 127.7, 127.2, 122.6, 121.3, 63.0, 60.7, 56.5, 47.0, 46.3, 38.4, 28.2, 24.3, 16.3.

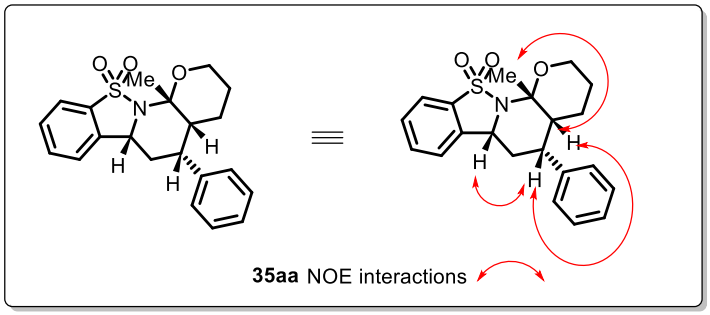
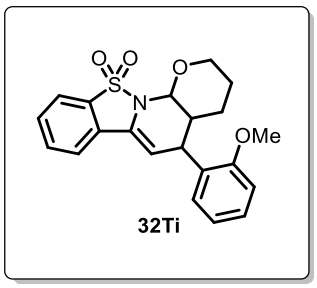


Figure 5. NOESY analyses of **35aa**.

***7.* Mechanism Study:**

5-(2-Methoxyphenyl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide (32Ti):



Following the *General Procedure*, to the mixture of 3,4-dihydro-2H-pyran (**T**) (0.1 g, 1.18 mmol) and (*E*)-3-(2-methoxystyryl)benzo[*d*]isothiazole 1,1-dioxide (**31i**) (0.355 g, 1.18 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $Bi(OTf)_3$ (0.077 g, 0.118 mmol) under an argon atmosphere at room temperature and reaction mixture was stirred for 6h at rt. Purification of the crude product by column chromatography (SiO_2, 30% EtOAc/hexanes) afforded 5-(2-methoxyphenyl)-3,4,4a,12a-tetrahydro-2H,5H-benzo[4,5]isothiazolo[2,3-*a*]pyrano[3,2-*e*]pyridine 11,11-dioxide **(32Ti)** (0.067 g, 68%), as an white solid mixture of two diastereomers (dr, 1:0.1, confirmed by NMR analysis).

TLC: R_f = 0.60 (SiO_2, 15% EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, *J* = 7.63 Hz, 1H), 7.67-7.60 (m, 2H), 7.58-7.53 (m, 1H), 7.26-7.22 (m, 1H), 7.25-7.21 (m, 1H), 6.96-6.90 (m, 2H), 5.61(d, *J* = 3.50 Hz, 1H),

5.40 (d, *J* = 3.00 Hz, 1H), 4.33-4.17 (m, 2H), 3.87 (s, 3H), 3.84-3.76 (m, 1H), 2.16-2.09 (m, 1H), 2.0-1.90 (m, 1H), 1.78-1.68 (m, 2H), 0.93-0.82 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.2, 133.1, 132.8, 131.4, 130, 129.6, 129.1, 128.2, 121.4, 121.2, 120.9 110.7, 103.8, 79.3, 55.6, 39.6, 28.8, 25.5.

IR (KBr, cm^{-1}): υ 3200, 3144, 3065, 3030, 2929, 2853, 1737, 1661, 1594, 1527, 1457, 1311, 1244, 1166, 1094, 1025, 847, 753, 696.

HRMS (ESI): *m/z* calcd for $C_{21}H_{21}O_4NS$ $[M+H]^+$ 384.1264 found 384.1261.

X-ray write-up

SC-XRD: The single crystal X-ray diffraction measurements were performed to determine the crystal structure of compounds 6ab, 6dj and 8gb at 100 K using APEX3 (Bruker, 2016; Bruker D8 VENTURE Kappa Duo PHOTON II CPAD) diffractometer having graphite-monochromatized (MoKα = 0.71073 Å). The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of unit cell parameters and an orientation matrix were calculated from 36 frames, and the cell refinement was performed by SAINT-Plus (Bruker, 2016). An optimized strategy used for data collection consisted of different sets of φ and ω scans with 0.5^{θ} steps φ/ω. The data were collected with a time frame of 10 sec for both the components by setting the sample to a detector distance fixed at 40 cm. All the data points were corrected for Lorentzian, polarization, and absorption effects using SAINT-Plus and SADABS programs (Bruker, 2016). The structure was refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-2013,[36] constrained and fixed isotropic thermal parameters for aliphatic C−H hydrogen atoms following the riding model, localization of N−H hydrogen atoms from the difference Fourier map and free refinement of their positions with fixed isotropic thermal parameters.[36] The molecular graphics of ORTEP diagrams were performed by Mercury software. The crystal symmetry of the components was cross-checked by running the cif files through PLATON (Spek, 2020) software and notified that no additional symmetry was observed. The Encifer software was used to correct the cif files.

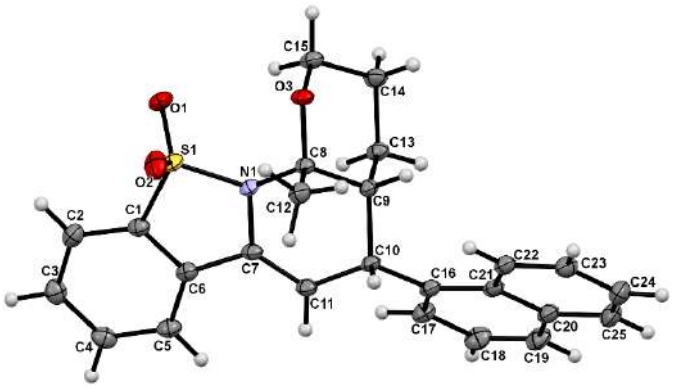


Figure 1. ORTEP diagram of compound **32ab**, the asymmetric unit, contains a single molecule. Herein, the ellipsoids are drawn with a 50% probability.

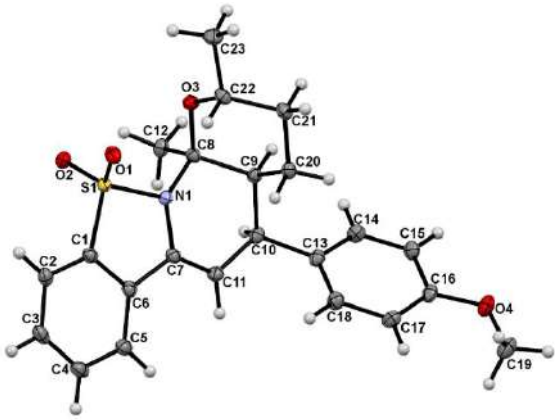


Figure 2. ORTEP diagram of compound **32dj,** the asymmetric unit, contains a single molecule. Herein, the ellipsoids are drawn with a 50% probability.

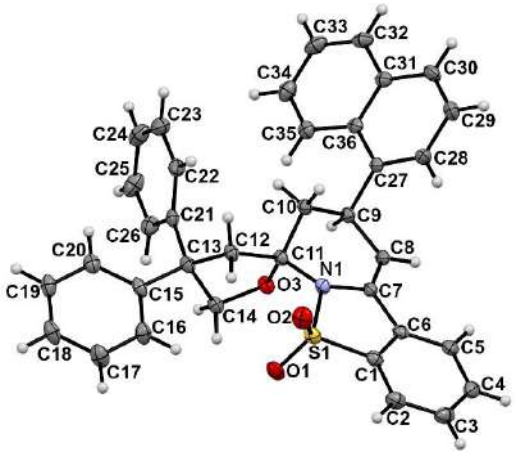


Figure 3. ORTEP diagram of compound **34gb**, the asymmetric unit contains a single molecule. Herein, the ellipsoids are drawn with a 50% probability.

Table 1. Crystallographic information details of compounds 6ab, 6dj and 8gb.

Crystal data	32ab	32dj	34gb
Chemical formula	$C_{25}H_{23}NO_3S$	$C_{23}H_{25}NO_4S$	$C_{36}H_{29}NO_3S$
Formula weight (M_r)	417.50	411.50	555.66
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/c$
Temperature T (K)	100	100	100
a (Å)	10.9271 (10)	10.2361 (15)	18.5043 (18)
b (Å)	16.5749 (17)	18.336 (3)	8.0564 (8)
c (Å)	10.9904 (10)	10.7234 (18)	18.6190 (19)
α (°)	90	90	90
β (°)	93.352 (3)	98.878 (7)	103.185 (4)
γ (°)	90	90	90
Z	4	4	4
Volume (Å^3)	1987.1 (3)	1988.6 (6)	2702.5 (5)
Source of radiation	MoKα	MoKα	MoKα
D_{calc} (Mg m^{-3})	1.396	1.375	1.366
Crystal size (mm)	0.16 × 0.12 × 0.1	0.16 × 0.09 × 0.08	0.23 × 0.12 × 0.09
μ (mm^{-1})	0.19	0.19	0.16
Data collection			
Diffractometer	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD
Absorption correction	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)
T_{min}, T_{max}	0.711, 0.746	0.705, 0.746	0.694, 0.739
No. of measured, independent and observed [I > 2σ(I)] reflections	95965, 4321, 4113	107127, 4308, 4173	132550, 5900, 5062
Theta range (°)	2.46–27.49	2.30-27.49	2.26- 28.49
R_{int}	0.055	0.043	0.097
Refinement			

R[$F^2 > 2\sigma(F^2)$], wR(F^2)	0.046, 0.130	0.034, 0.109	0.043, 0.105
GOF on F^2	1.18	1.19	1.06
No. of independent reflections	4321	4308	5900
No. of parameters	273	266	371
F_000	880	872	1168
No. of restraints	0	0	0
H-atom treatment	Constr	Constr	Constr
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $A^{\circ-3}$)	0.63, −0.57	0.51, −0.39	0.49, −0.40
CCDC number	2184885	2184884	2184883

Table 2. Hydrogen-bond geometry (A˚, °) of 32ab, 32dj and 34gb components are given below.

Name of the compound	*D*–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
32ab	C5–H5···O3	0.9500	2.5400	3.252(2)	132
	C11–H11···O1	0.9500	2.4500	3.382(2)	168
	C12–H12C···O2	0.9800	2.4900	3.061(2)	117
	C15–H15B···O1	0.9900	2.4700	3.202(2)	131
32dj	C10–H10····O2	1.0000	2.4800	3.3882(17)	151
	C12–H12A···O2	0.9800	2.4400	3.1143(17)	125
	C12–H12C···O1	0.9800	2.4900	3.3736(17)	150
	C22–H22···O1	1.0000	2.3800	3.1239(16)	130
	C23–H23B···O2	0.9800	2.5700	3.4433(18)	149
34gb	C2–H2···O1	0.9500	2.3500	3.210(2)	150

	C12–H12B···O2	0.9900	2.5800	3.341(2)	134
	C14–H14A···O1	0.9900	2.4500	3.184(2)	130

4.2.12 References

1. (a) Liang, L.; Li, E.-Q.; Huang, Y. *Org. Lett.,* **2015**, *17*, 4914-4917;(b) Tharra, P.; Baire, B. *Chem. Commun*., **2016**, *52*, 14290–14293;(c) Lin, H.; Dong, L. *Org. Lett*., **2016**, *18*, 5524–5527; (d)Li, Y.-Y.; Zhu, C.-Z.; Zhang, J. L. *Eur. J. Org. Chem*., **2017**, 6609–6613; (e) Zhang, J-T.; Jiang, H.-F. Zhu, S.-F. *Adv. Synth. Catal*., **2017**, *359*, 2924–2930; (f) Shin, J. W.; Lee, J. Y.; Yoo, *E. J. Org. Lett*., **2017**, *19*, 2901–2904; (g) Hegmann, N.; Prusko, L.; Heinrich, M. R. *Org. Lett*., **2017**, *19*, 2222–2225; (h) Yan, R.-J.; Xiao, B.-X.; Du, W.; Chen, Y.-C. *Org. Lett*., **2018**, *20*, 8000–8003; (i) Guo, S.-S.; Dong, P.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed*., **2018**, *57*, 16852–16856; (j) Xiao, W.; Zhou, Z.; Du, W.; Chen, Y.-C. *Adv. Synth. Catal*., **2018**, *360*, 3526–3533;(k) Wang, W.-B.; Bai, X.-G.; Jin, S.-J.; Bu, Z.-W. *Org. Lett*., **2018**, *20*, 3451–3453; (l) Artigas, A.; Vila, J.; Roglans, A. *Org. Lett*., **2019**, *21*, 6608–6613; (m) Feinandez, P.; Valdes, C.; Rodriguez, F. *J. Org. Chem*., **2019**, *84*, 3184–3191; (n) Li, X.-H.; Wang, S.-M.; Liu, L.-Y.; Chang, W.-X.; Li, J. *J. Org. Chem*., **2019**, *84*, 1288–1298; (o) Ge, S.-L.; Kang, T.-F.; Liu, X.-H.; Feng, X.-M. Angew. *Chem., Int. Ed*., **2019**, *58*, 4017–4021; (p) Hu, H.-P.; Xu, J.-X.; Wang, F.; Liu, X.-H.; Feng, X.-M. *Org. Lett*., **2020**, *22*, 93–97.
2. (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev*. **1986**, *86*, 781. (c) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (d) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259. (e) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (f) Pellissier, H. *Tetrahedron* **2009**, *65*, 2839. (g) Jiang, X.; Wang, R. *Chem. Rev*. **2013**, *113*, 5515.
3. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem*. **2014**, *57*, 10257–10274.
4. (a) Seydel JK (1968) Sulfonamides, structure-activity relationship, and mode of action. J Pharm Sci 57:1455–1478; (b) Supuran CT, Casini A, Scozzafava A (2003) Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents. Med Res Rev 23(5):535–558. https://doi.org/10.1002/med. 10047.
5. "Sulfa Drugs Allergy -- Sulfa Bactrim Drug Allergies". *allergies.about.com. Retrieved 17* January *2014.*

6. M. Madigan, J. Martinko, D. Stahl, D. Clark, *Brock Biology of Microorganisms (13th ed.)*, Pearson Education, 2012, p. 797.
7. Ž. Jakopin, E. Corsini, M. Gobec, I. Mlinarič-Raščan and M. S. Dolenc, *J. Med. Chem*. **2012**, *55*, 6478−6488.
8. Correa, R. C.; Khan, P. M.; Askari, N.; Zhai, D.; Gerlic, M.; Brown, B.; Magnuson, G.; Spreafico, R.; Albani, S.; Sergienko, E.; Diaz, P. W.; 1 Roth, G. P.; Reed, J. C. *Chem. & Biology*, **2011**, *18*, 825–832.
9. Li, X.; Dong, Y.; Qu, F.; Liu, G. *J. Org. Chem.* **2015**, *80*, 790-798.
10. *Oxford Handbook of Infectious Diseases and Microbiology*. OUP Oxford. 2009. p. 56. ISBN 9780191039621.
11. Fischer J, Ganellin CR (2006). *Analogue-based Drug Discovery*. John Wiley & Sons. p. 509. ISBN 9783527607495.
12. Chang, Li.; Zhu, G-Z.; Yang, T.; Xiao-Li Zhao, X-L.; Shia, M.; Zhao, M-X. Org. *Biomol. Chem.*,**202**1, *19*, 3687–3697.
13. Fischer J, Ganellin CR (2006). *Analogue-based Drug Discovery*. John Wiley & Sons. p. 531. ISBN 9783527607495.DNR PUB-WT-977 2012
14. Penoxsulam Chemical Fact Sheet, DNR PUB-WT-977 2012.
15. Kułaga, D.; Ja´skowska, J.; Satała, G. *Bio. & Med. Chem.Let.,* **2021***, 42, 128028.*
16. " "Dyazide: FDA-Approved Drugs". *U.S. Food and Drug Administration (FDA)*. Retrieved 20 August 2020.
17. *"Celecoxib (Celebrex) Use During Pregnancy". Drugs.com. 4 May 2020. Archived from the original on 25 January 2021. Retrieved 5 May 2020.*
18. Chen, Y-H.; De-Hai Li, D-H.; Liu, Y-K. *ACS Omega* **2018**, *3*, 16615−16625.
19. Chen, Y-H.; Lv, X-J,; You, Z-H.; Liu, Y-K. *Org. Lett*. **2019**, *21*, 5556−5561.
20. An, Q.; Shen, J.; Butt, N.; Liu, D.; Liu, Y.; Zhang, W. *Adv. Synth. Catal*. **2015**, *357*, 3627 – 3638.
21. An, Q.; Shen, J.; Butt, N.; Liu, D.; Liu, Y.; Zhang, W. *Chem. Commun*., **2015**, *51*, 885-888.
22. Gu, J.; Ma, C.; Li, Q-Z.; Du, W.; Chen, Y-C. *Org. Lett.* **2014**, *16*, 3986−3989.
23. Feng, X.; Zhou, Z.; Ma, C.; Yin, X.; Li, X.; Dong, L.; Chen, Y-C. *Angew. Chem. Int. Ed***. 2013***, 52*, 14173 –14176.

24. (a) Li, J.; Lin, L.; Hu, B.; Lian, X.; Wang, G.; Liu, X.; Feng, X. *Angew. Chemie - Int. Ed.* **2016**, *55*, 6075–6078; (b) Wang, X.; Dong, S.; Yao, Z.; Feng, L.; Daka, P.; H. Wang, H.; Xu, Z. *Org. Lett.* **2014**, *16*, 22–25.

25. (a) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett*., **2011**, *13*, 3178–3181; (b) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *J. Org. Chem.*, **2011**, *76*, 1269–1284; (c) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett*., **2010**, *12*, 4420–4423.

26. (a) Zhou, Q.-L.; Angew. *Chem., Int. Ed*., **2016**, *55*, 5352–5353; (b) Ollevier, T.; *Org. Biomol. Chem*., **2013**, *11*, 2740–2755; (c) Bothwell, J. M.; Krabbe, S. W.; Mohan, R. *S. Chem. Soc. Rev*., **2011**, *40*, 4649–4707; and references cited therein; (d) Yamamoto, Y. *J. Org. Chem*., **2007**, *72*, 7817–7831.

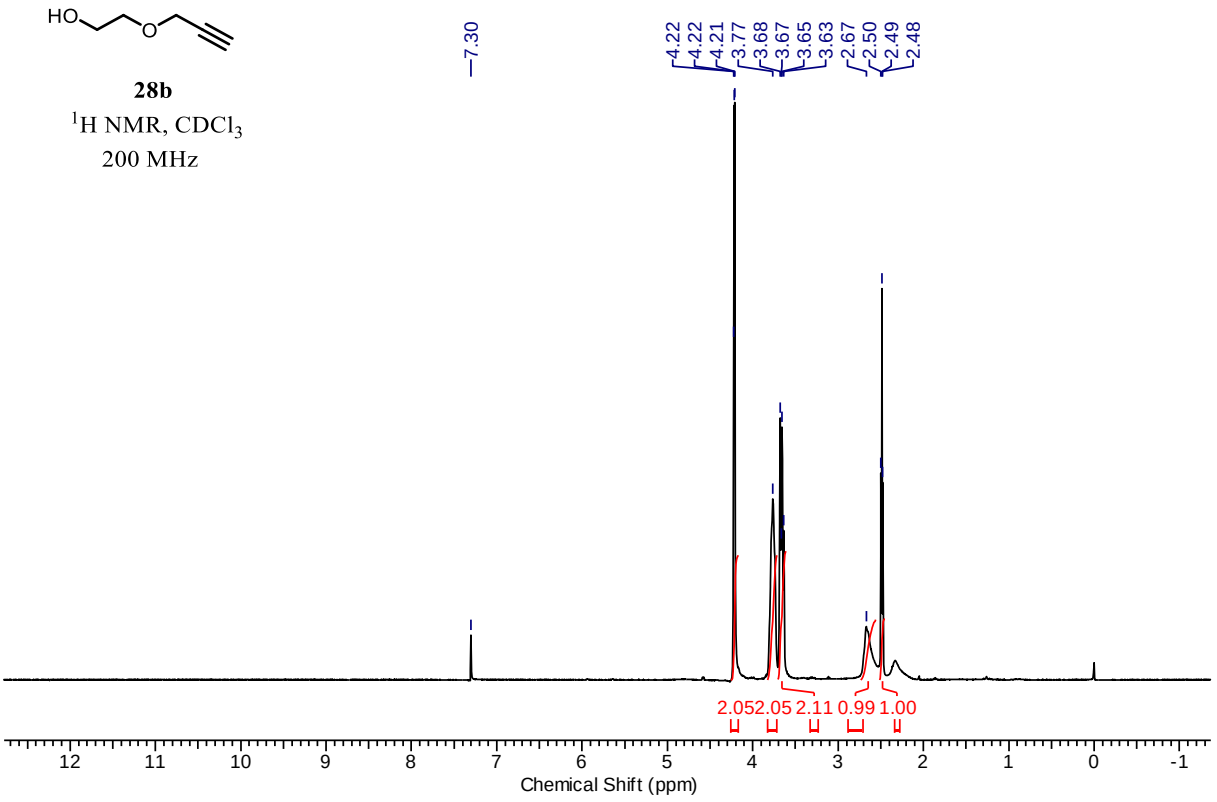
27. (a) Kambale, D. A.; Thorat, S. S.; Pratapure, M. S.; Gonnade, R. G.; Kontham, R. *Chem. Commun*., **2017**, *53*, 6641–6644. (b) Ashwini K. N.; Madhukar S. P.; Ravindar K. *Org. Biomol. Chem*., **2018**, *16*, 3229-3240. (c) Fañanás, F. J.; Fernández, A.; Çevic, D.; Rodríguez, F. *J. Org. Chem*., **2009**, *74*, 932–934; (d) Barluenga, J.; Fernández, A.; Satrústegui, A.; Diéguez, A.; Rodríguez, F.; Fañanás, F. *J. Chem. Eur. J*., **2008**, *14*, 4153–4156.

28. Thorat, S. S.; Kataria, P.; Kontham, R.; *Org. Lett*., **2018**, *20*, 872–875.

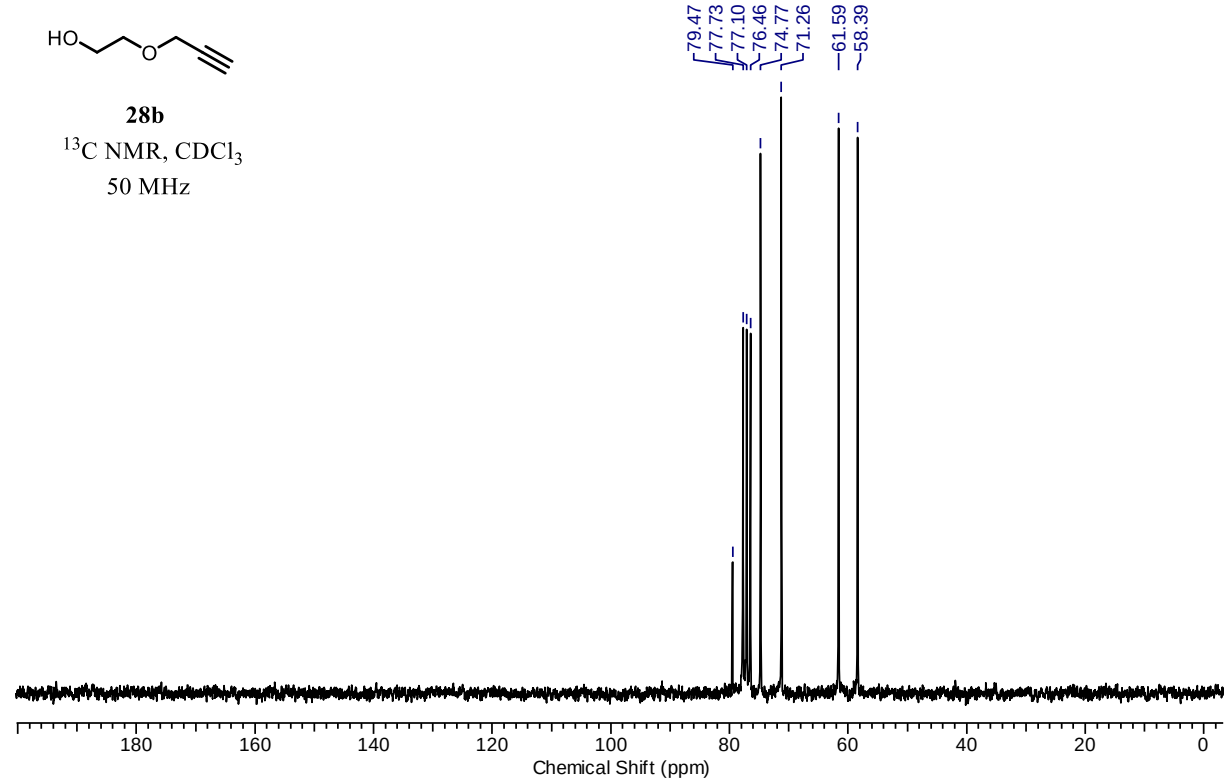
29. Ashwini K. N.; Sagar S. T.; Shailja J.; Gamidi R. K.; Kumar V.; Ravindar K. *Org. Chem. Front*., **2022**, *9*, 802–809.

30. Yamamoto, Y. J. Org. Chem., 2007, 72, 7817–7831.
31. Harada, T.; Muramatsu, K.; Mizunashi, K.; Kitano, C.; Imaoka, D.; Fujiwara, T.; Kataoka, H. *J. Org. Chem.*, **2008**, *73*, 249–258.
32. Stark, D. G.; Young, C. M.; O'Riordan, T. J. C.; Slawin, M. Z.; Smith, A. D. *Org. Biomol. Chem.,* **2016**, 14, 8068–8073.
33. Bessley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans* **1915**, *107*, 1081–1092.
34. (a) An, Q.; Shen, J.; X Butt, B.; X Liu, D.; Liu, Y.; Zhang, W. *Adv. Synth. Catal*. **2015**, *357*, 3627 – 3638 (b) Wang, Z.; Xu, H.; Su, Q.; Hu, P.; Shao, P-L.; He, Y.; Lu, Y. *Org. Lett.* **2017**, *19*, 3111–3114.
35. Chen, Y-H.; De-Hai Li, D-H.; Liu, Y-K. *ACS Omega* **2018**, *3*, 16615–16625.
36. Gruene, T., Hahn, H. W., Luebben, A. V., Meilleur, F. & Sheldrick, G. M. (2014). *J. Appl. Cryst*. 47, 462-466.

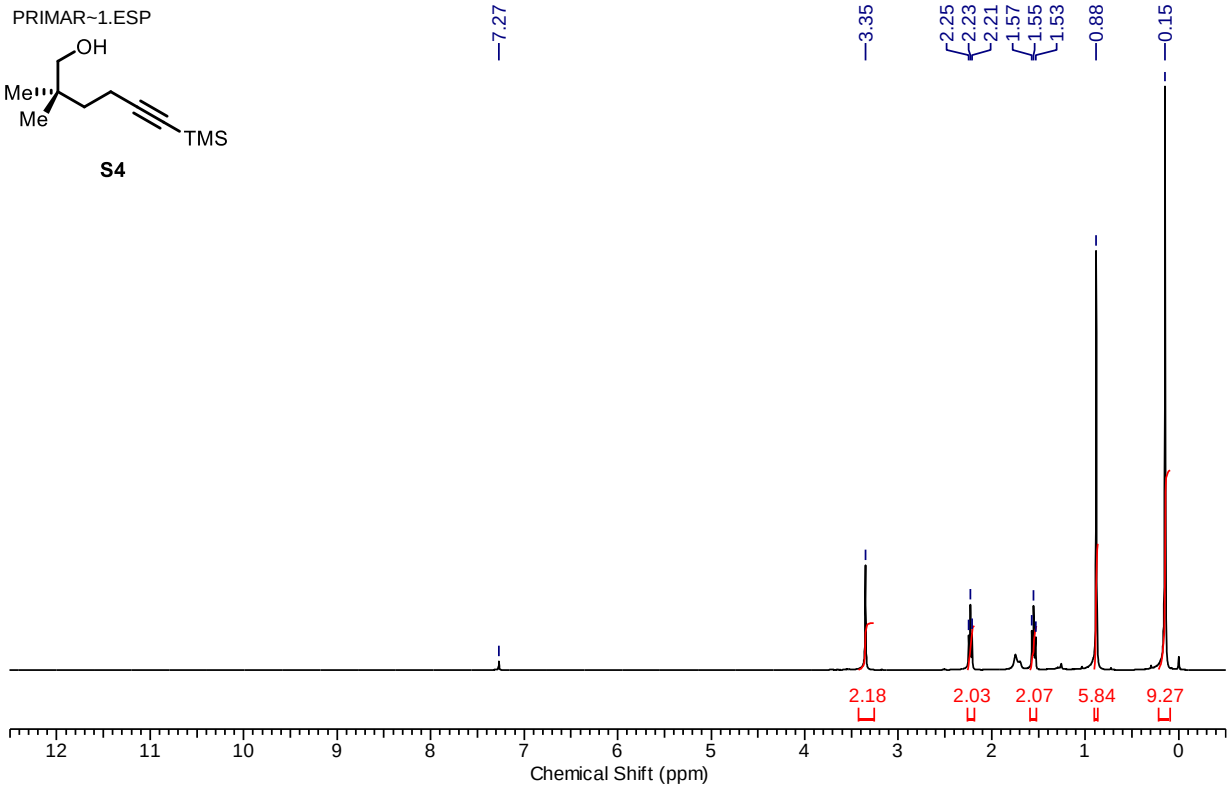
^{1}H NMR spectrum of compound 28b



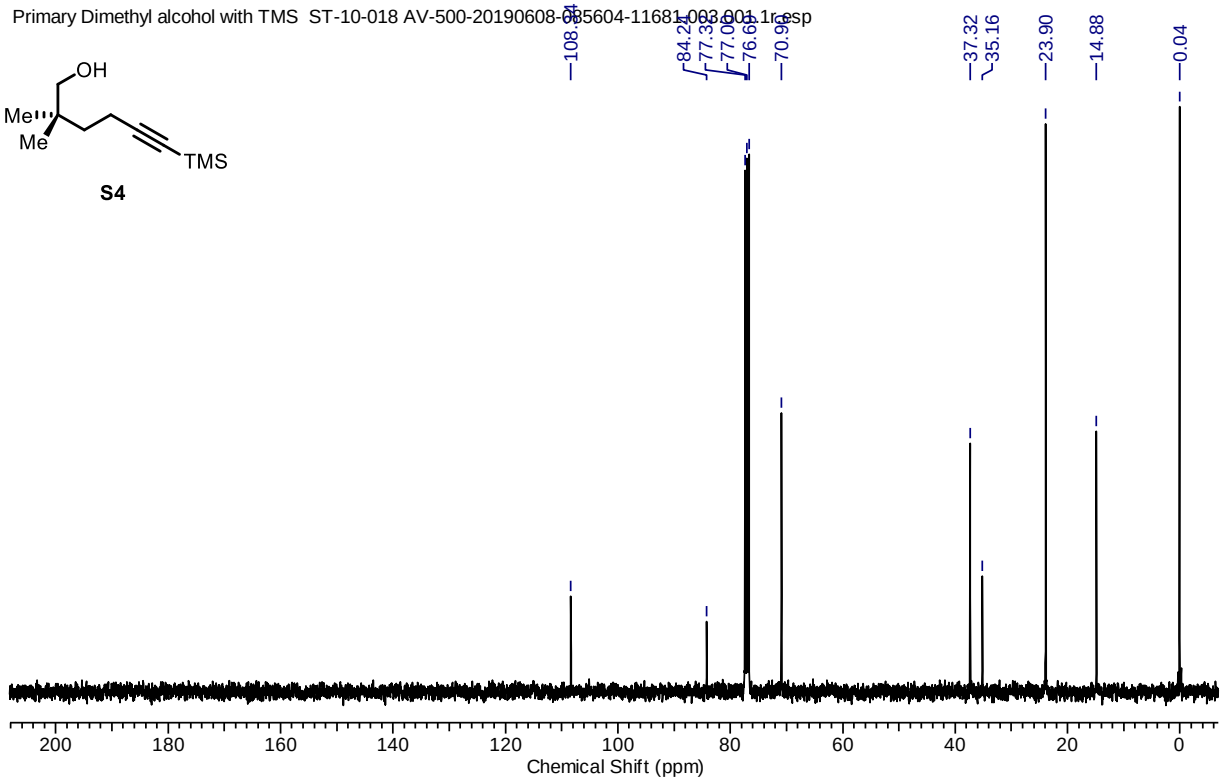
^{13}C NMR spectrum of compound 28b



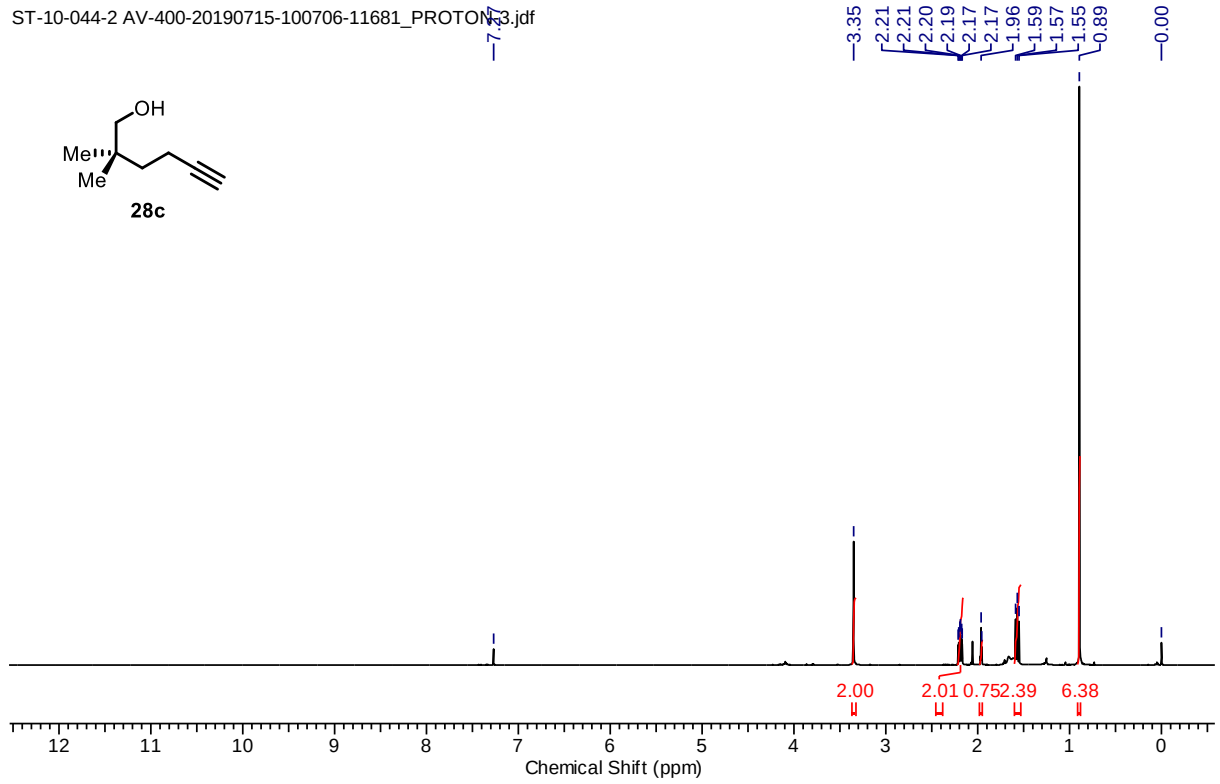
^{1}H NMR spectrum of compound S4



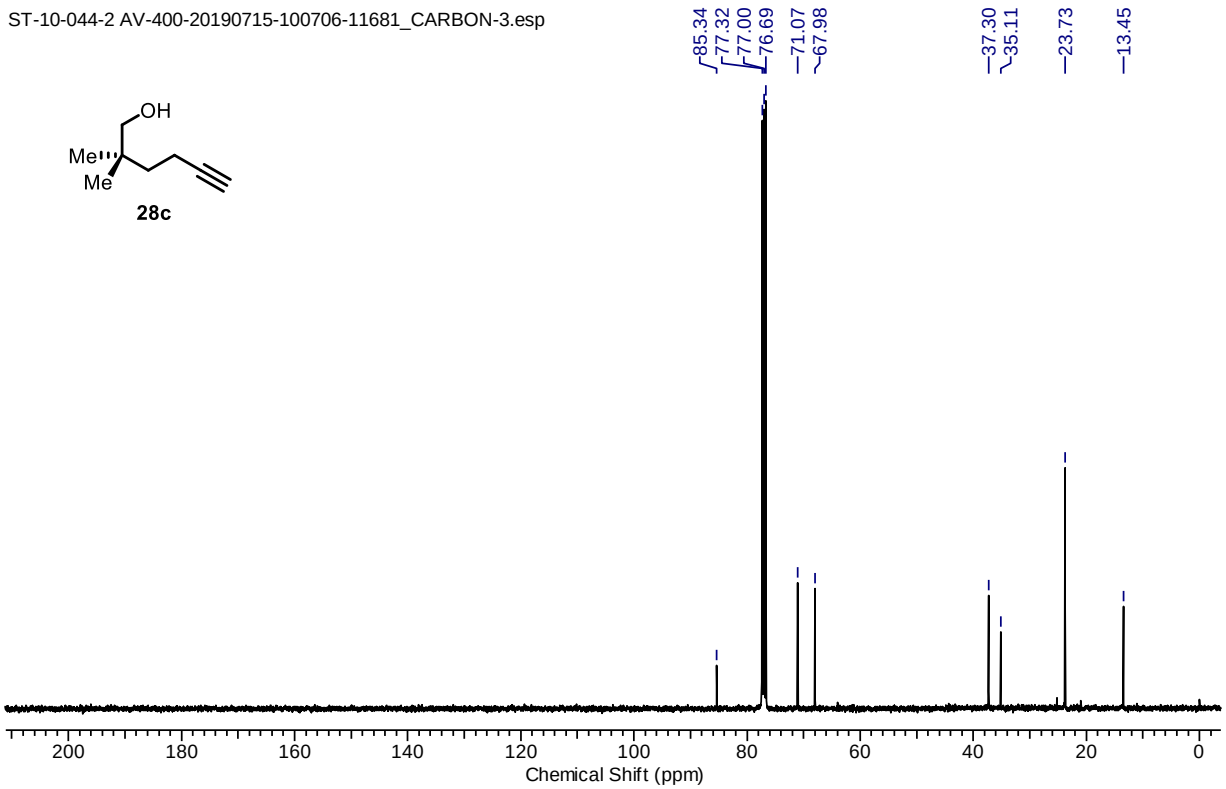
^{13}C NMR spectrum of compound S4



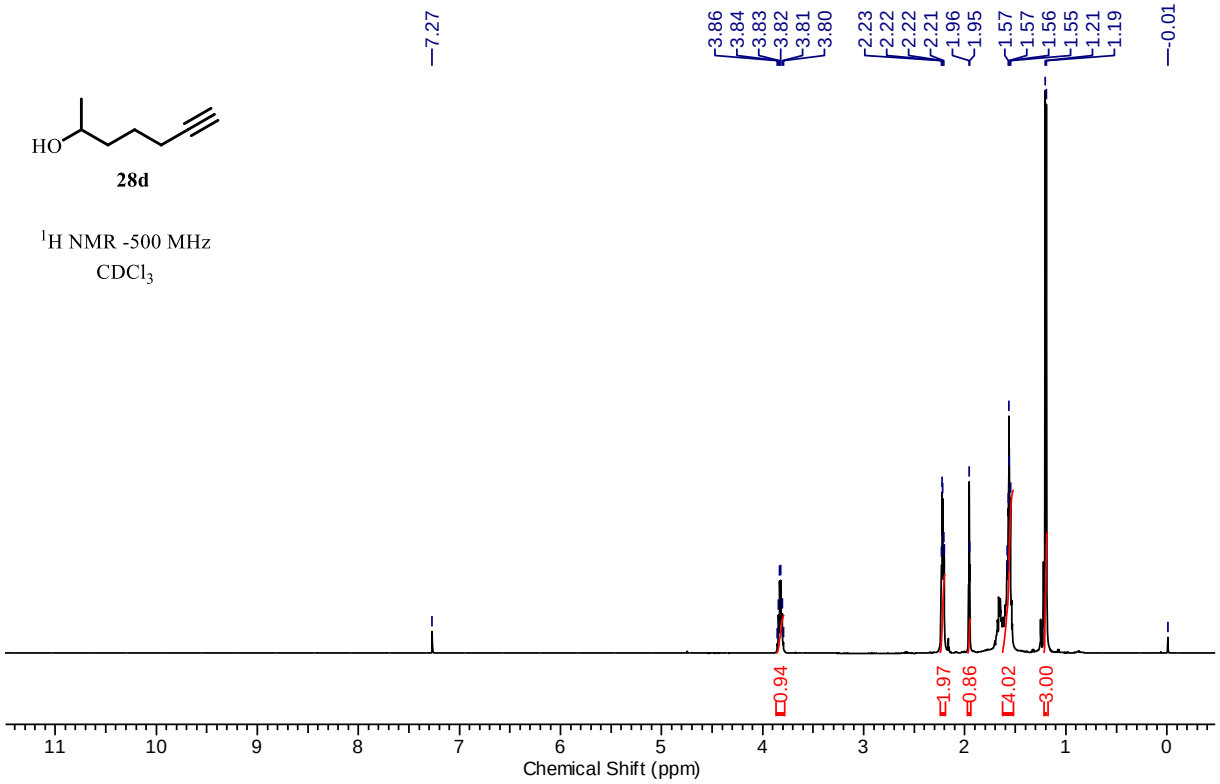
^{1}H NMR spectrum of compound 28c



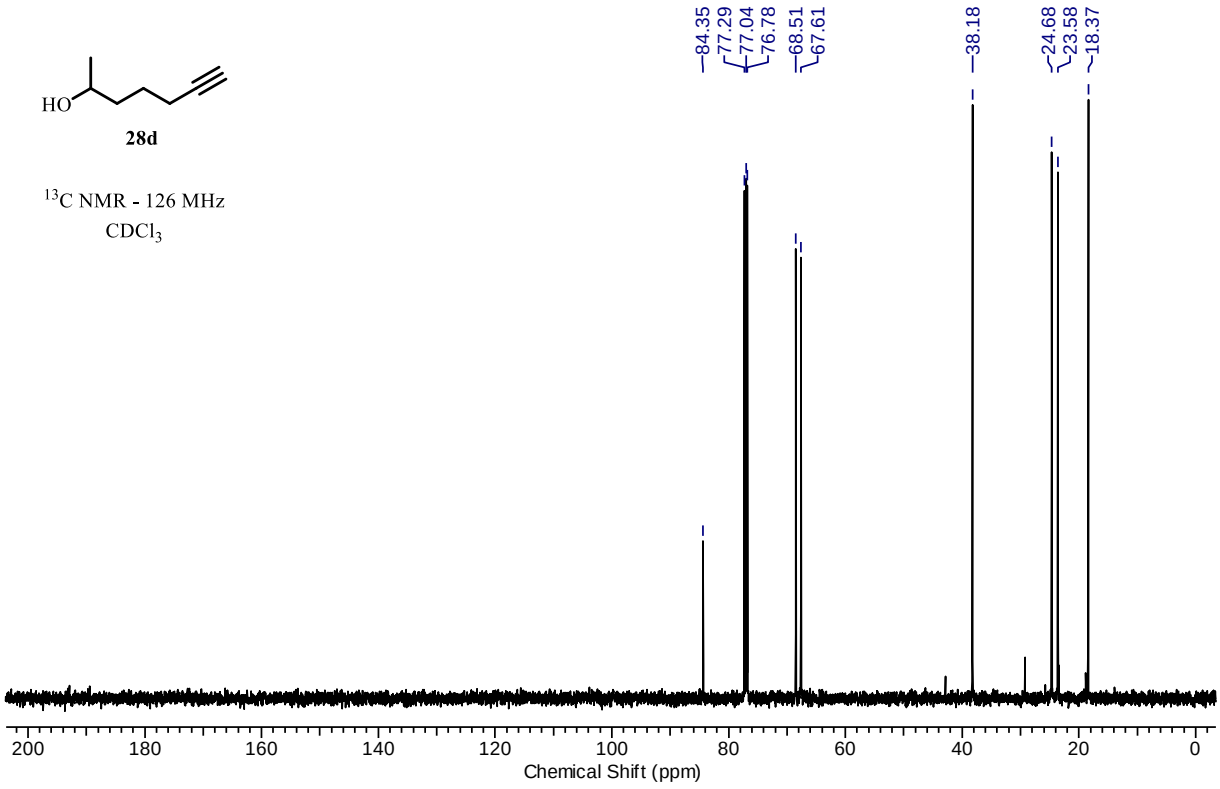
^{13}C NMR spectrum of compound 53c



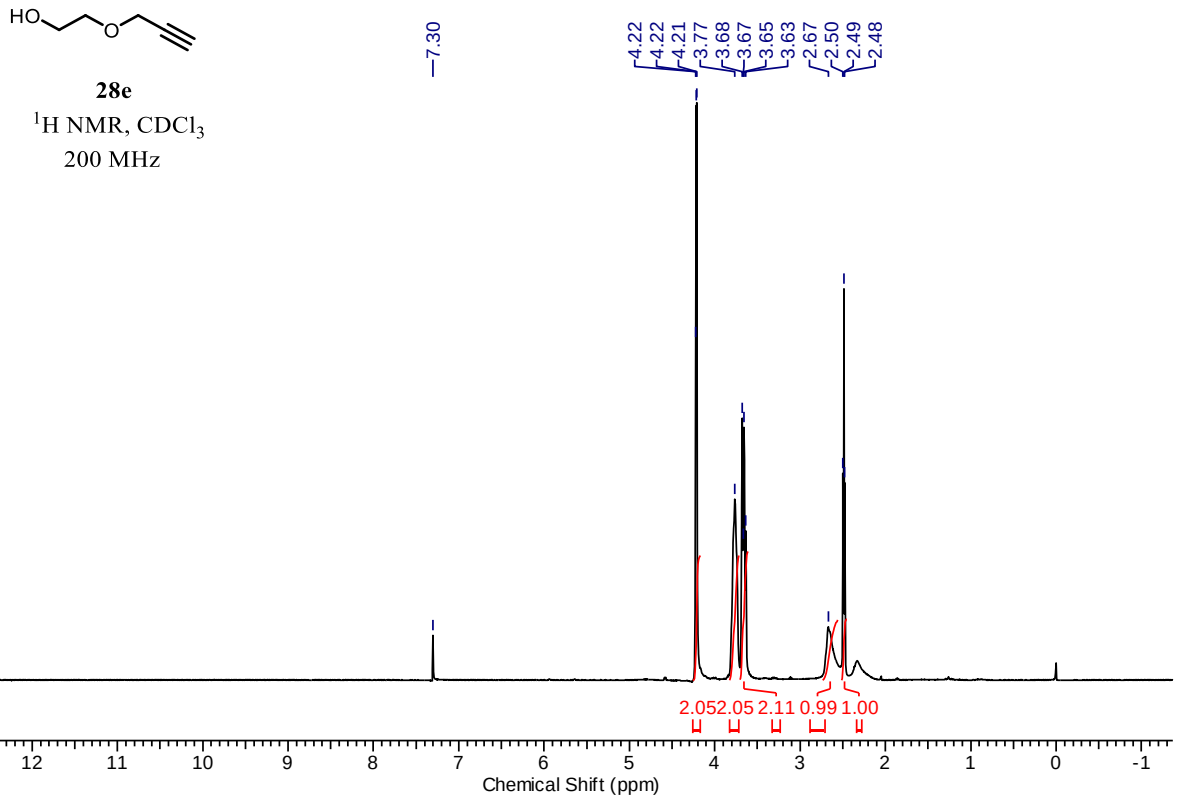
^{1}H NMR spectrum of compound 28d



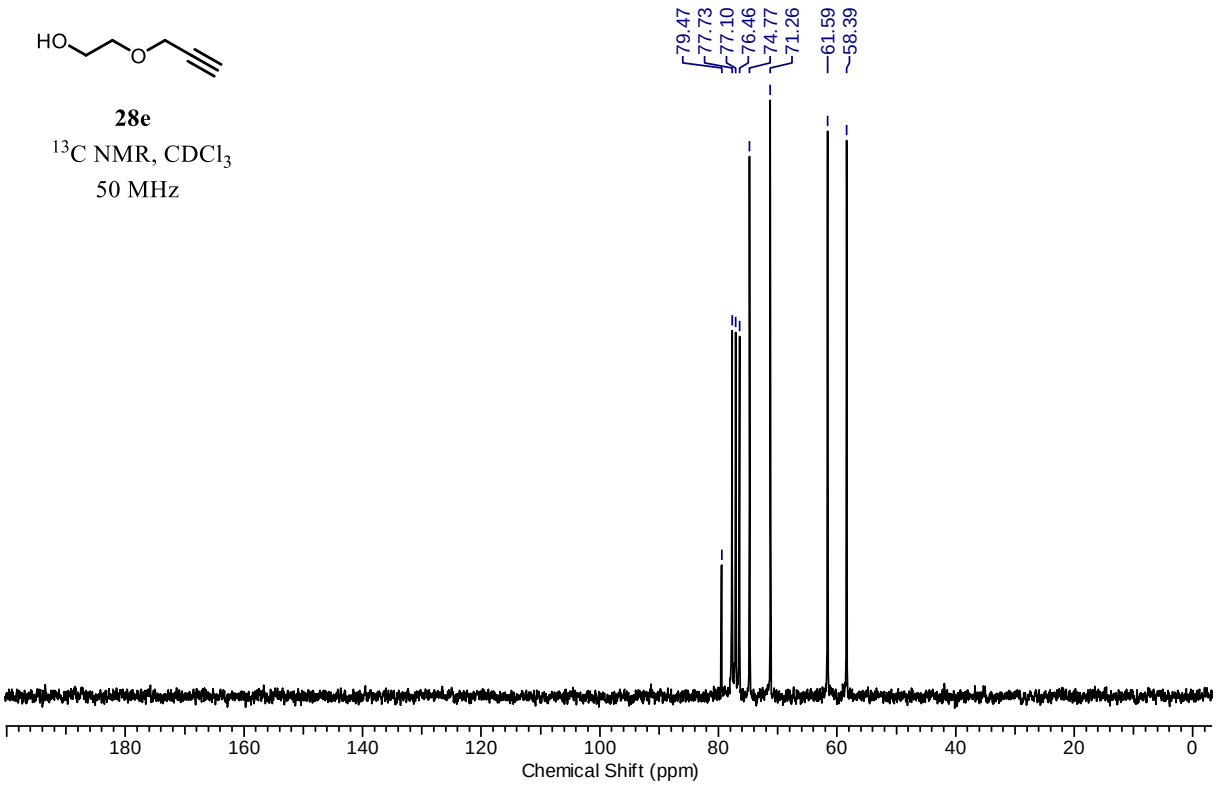
^{13}C NMR spectrum of compound 28d



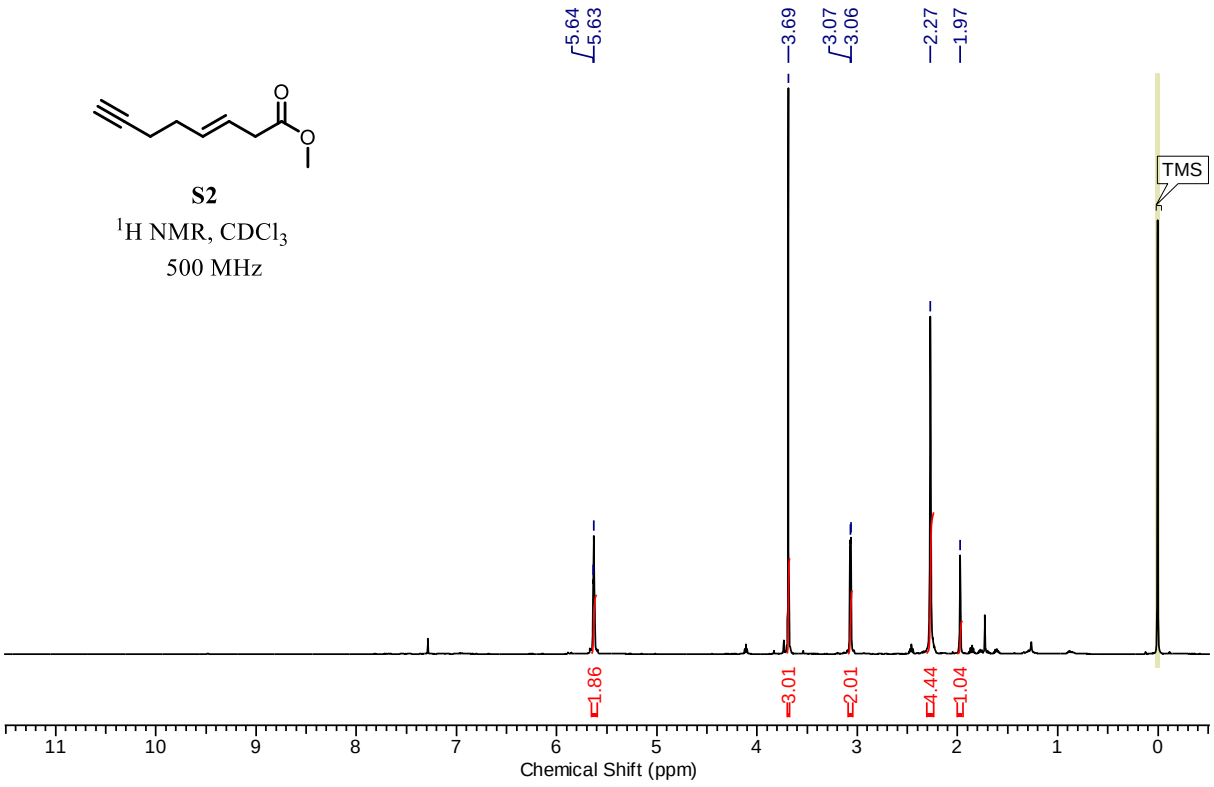
^{1}H NMR spectrum of compound 28e



^{13}C NMR spectrum of compound 28b



^{1}H NMR spectrum of compound S2

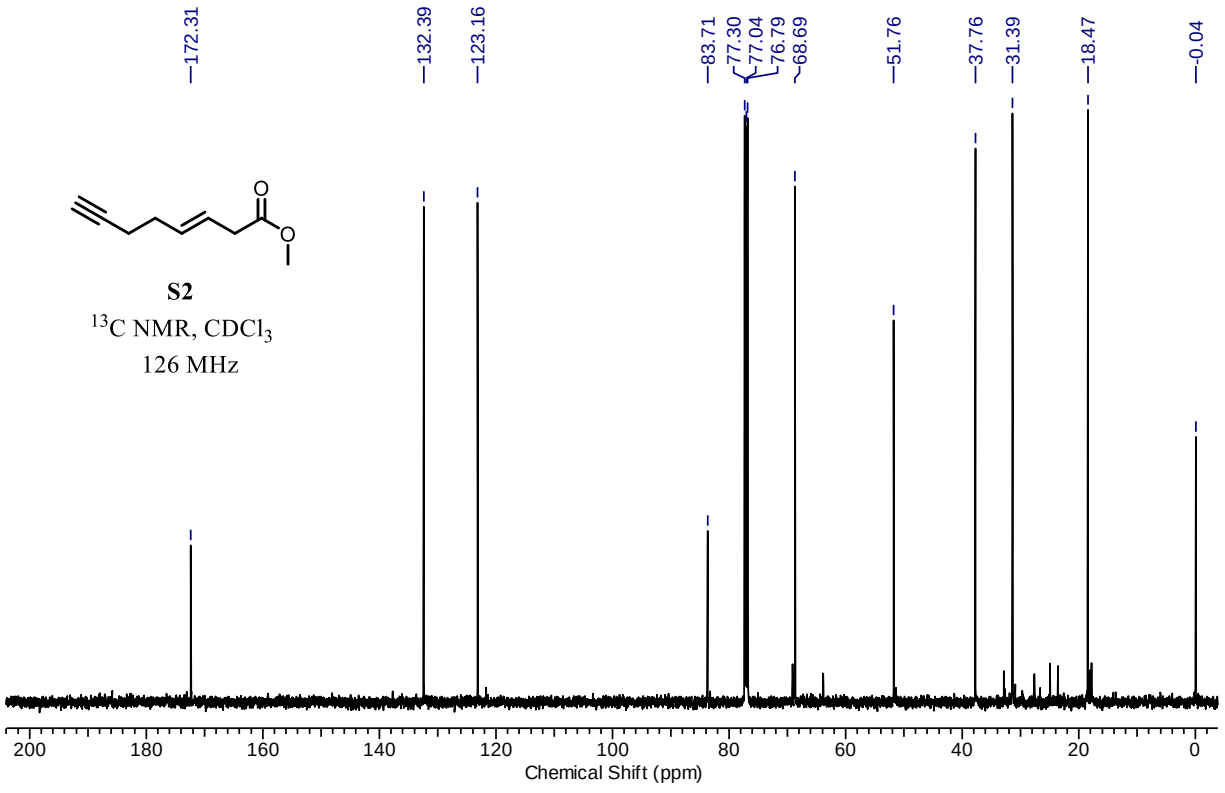


S2

^{1}H NMR, $CDCl_3$

500 MHz

^{13}C NMR spectrum of compound S2

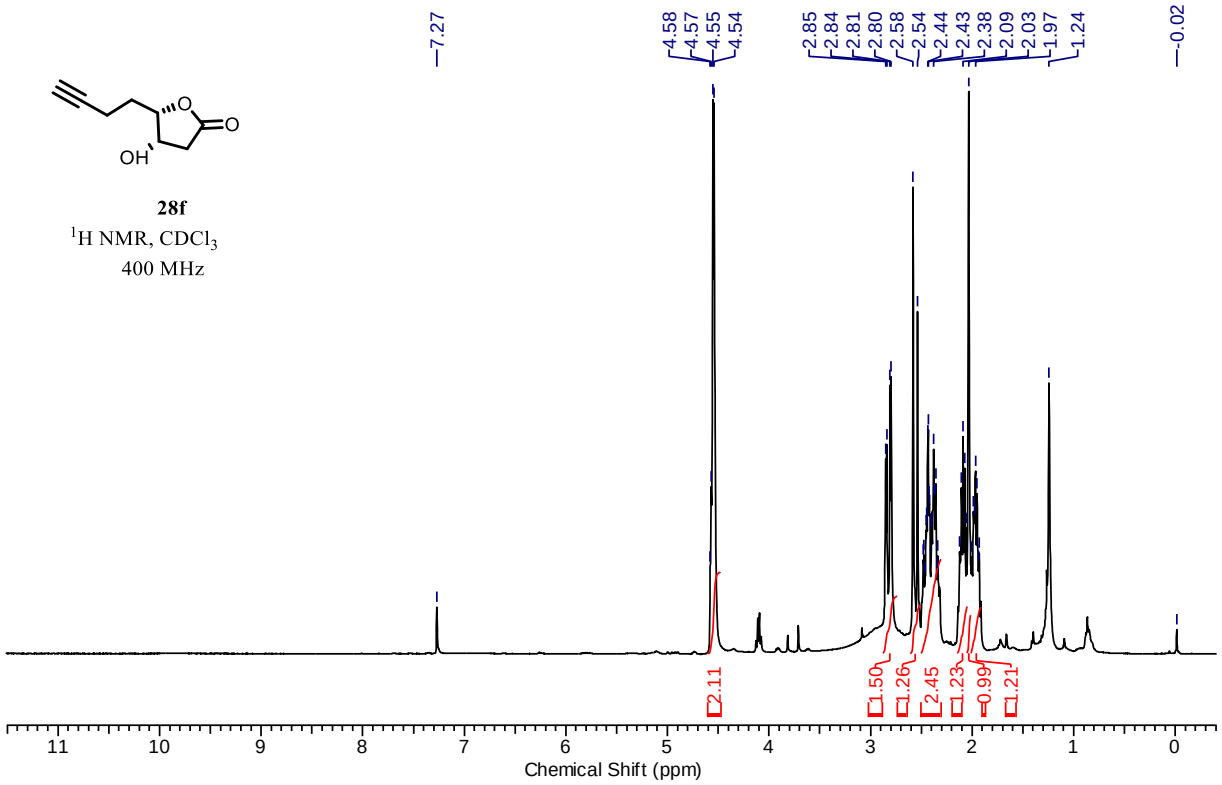


S2

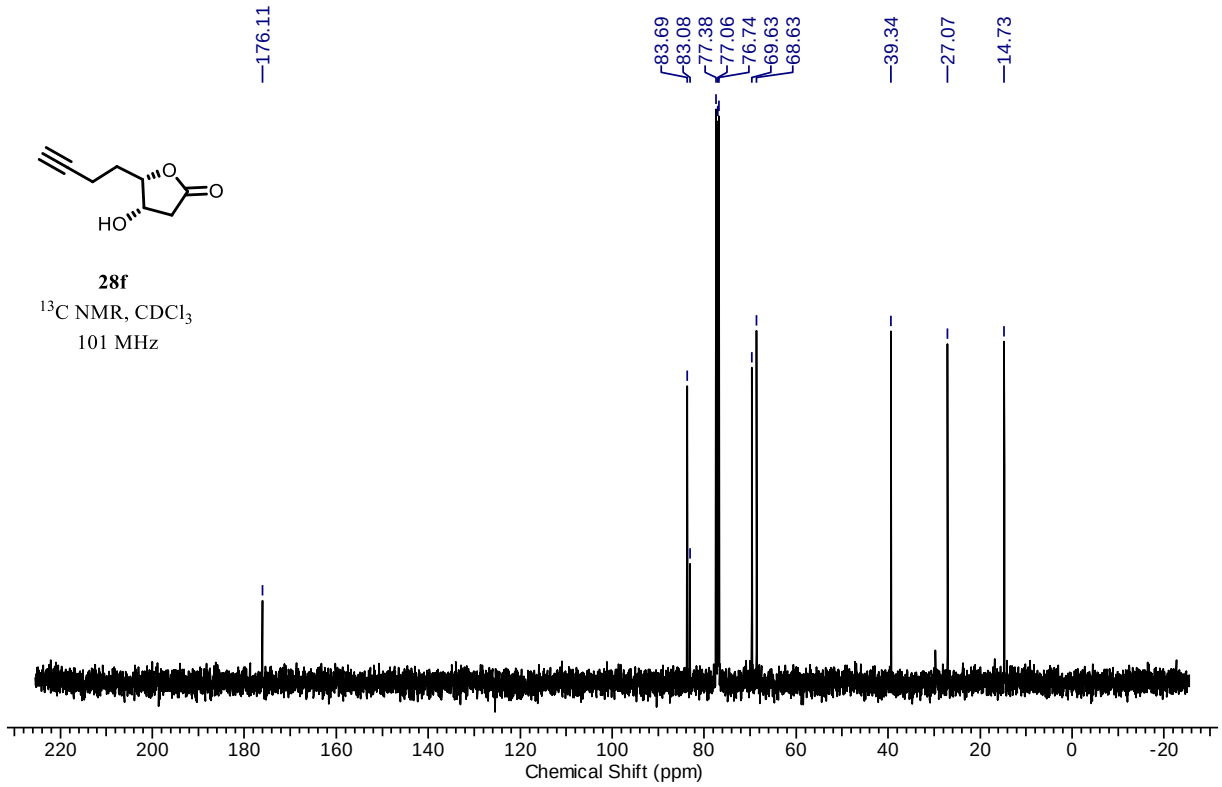
^{13}C NMR, $CDCl_3$

126 MHz

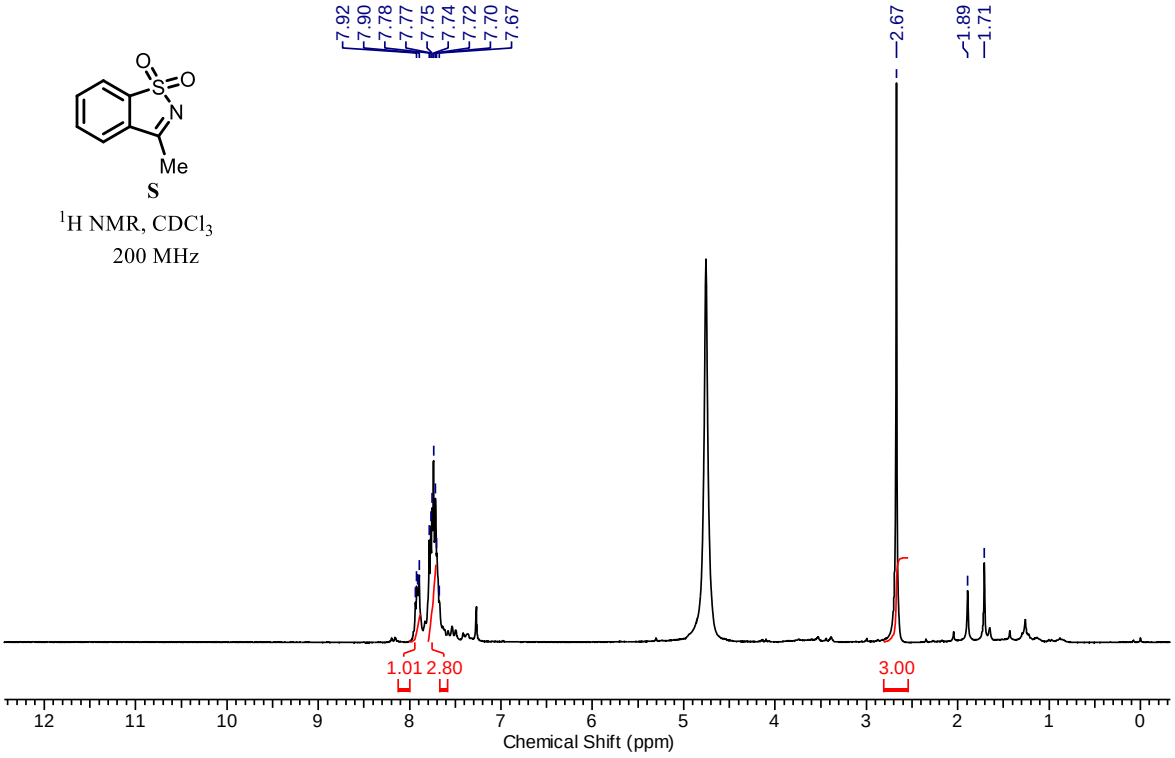
^{1}H NMR spectrum of compound 28f



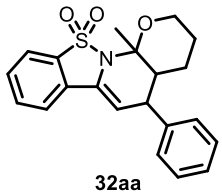
^{13}C NMR spectrum of compound 28f



^{1}H NMR spectrum of compound S



^{1}H NMR spectrum of compound 32aa

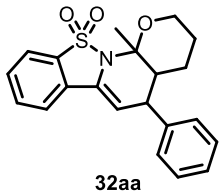


32aa

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound32aa

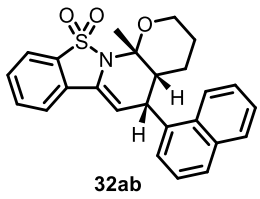


32aa

^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 32ab

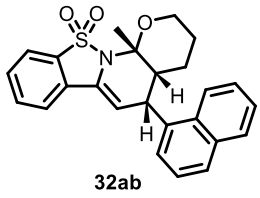


32ab

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 32ab

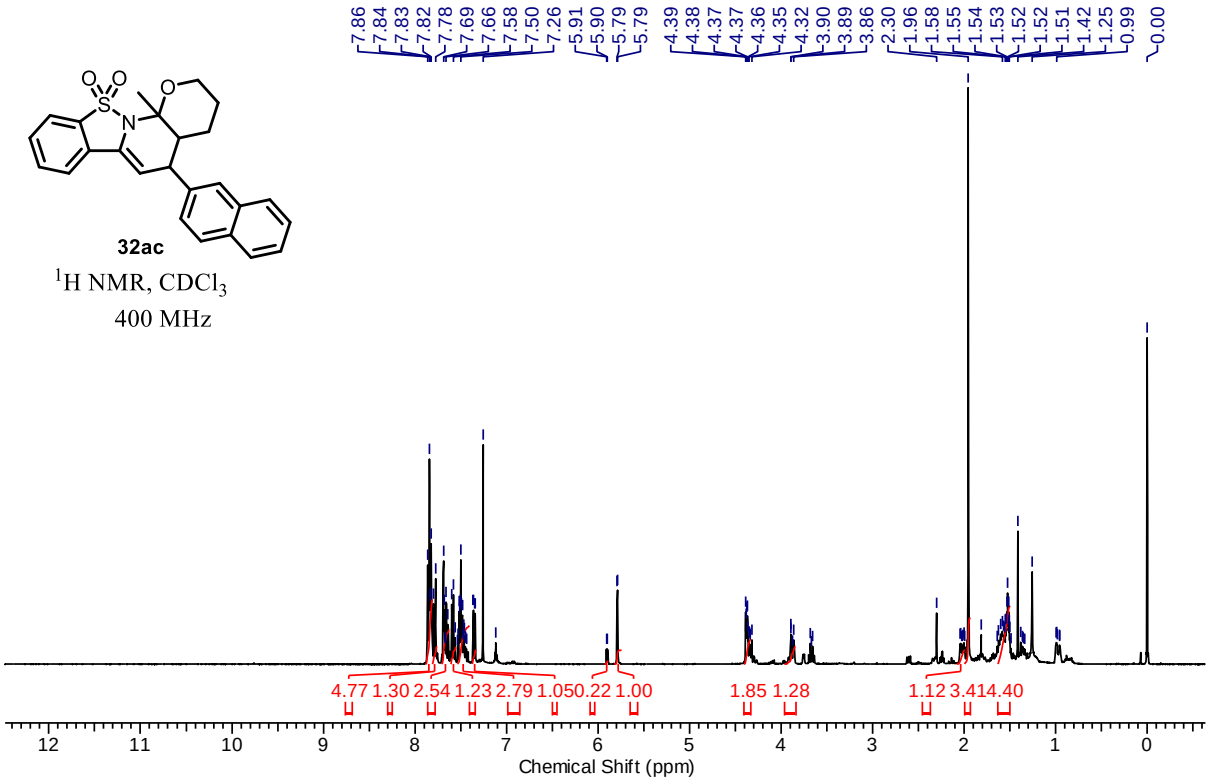


32ab

^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 32ac

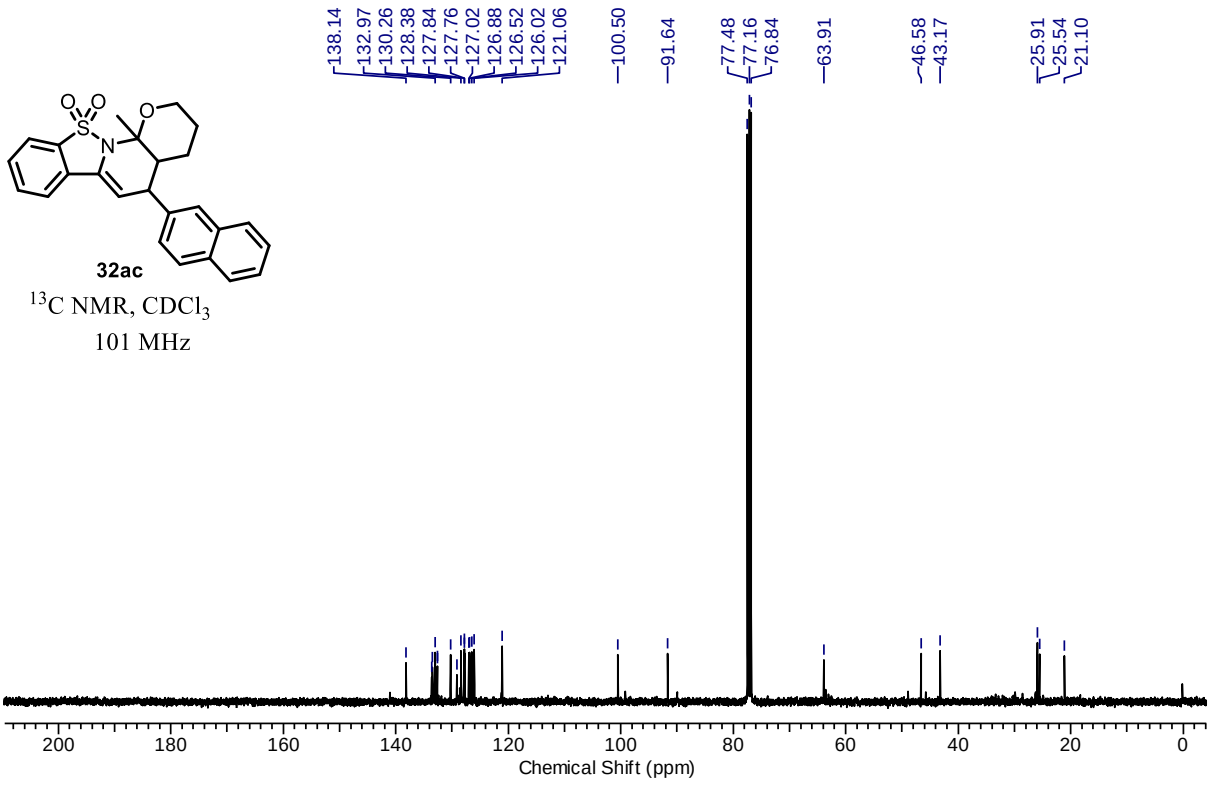


32ac

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 32ac

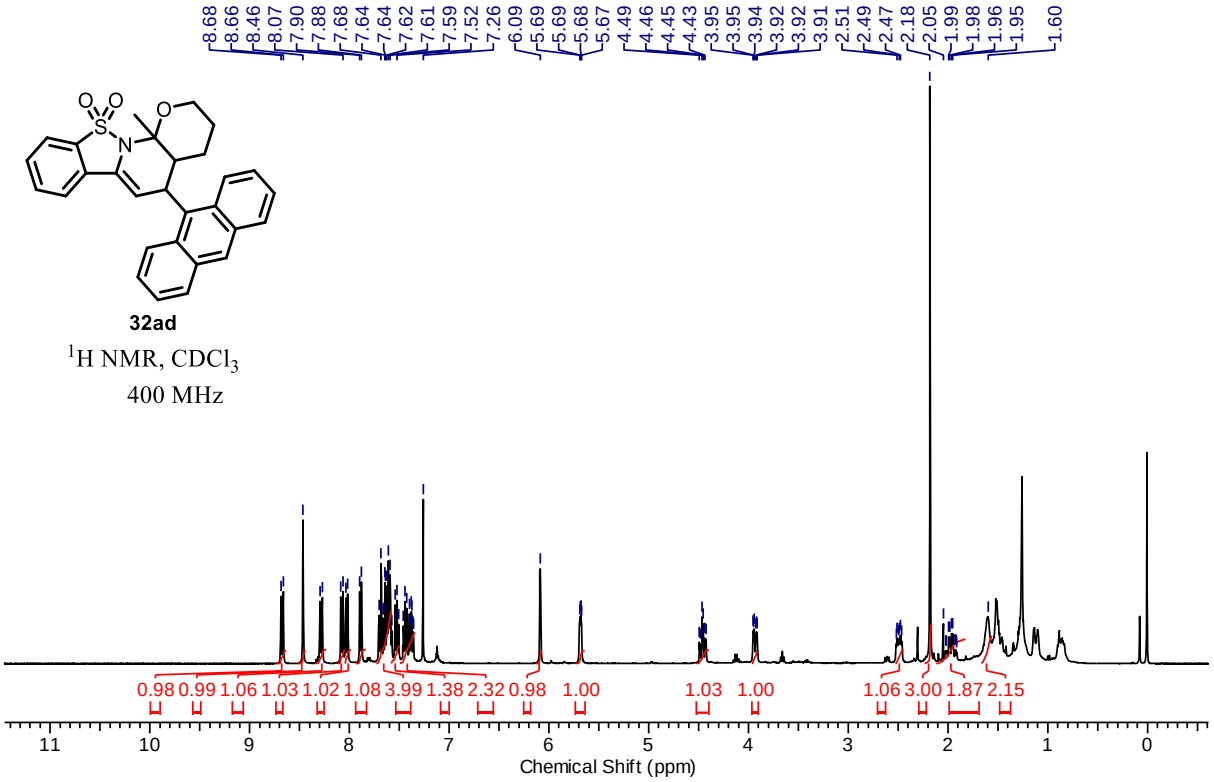


32ac

^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound32ad

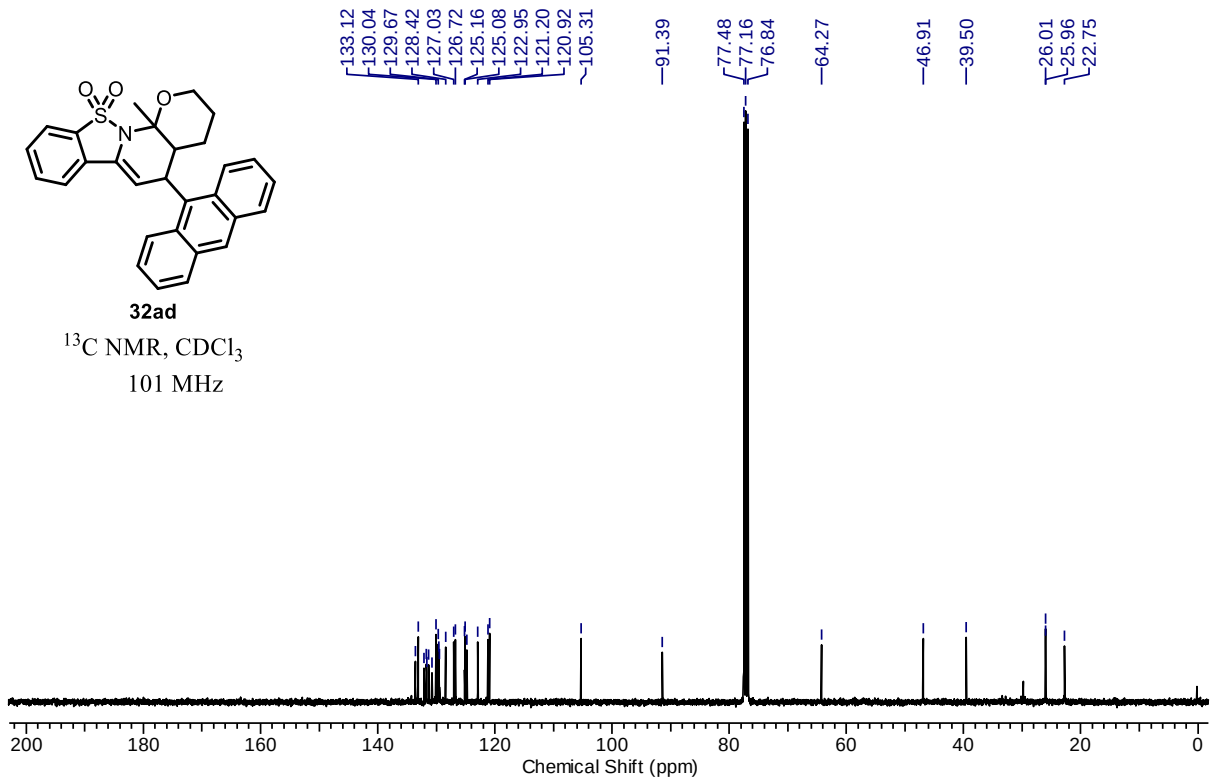


32ad

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 32ad

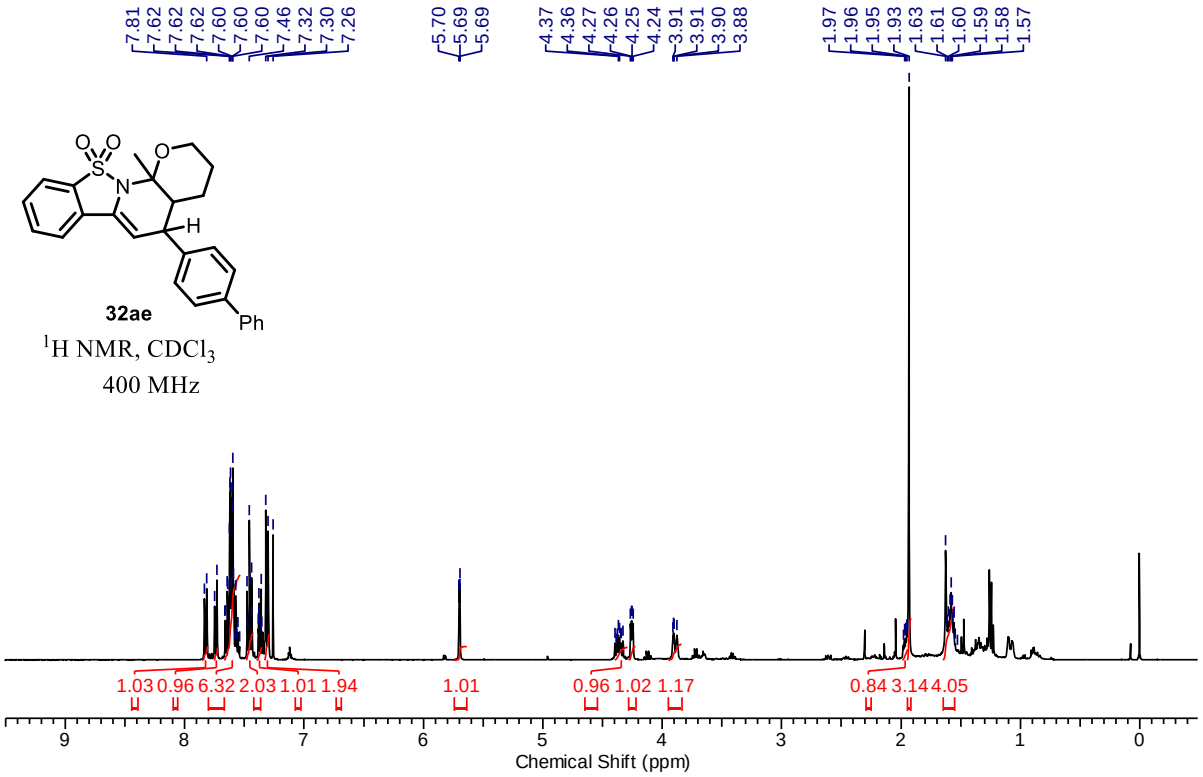


32ad

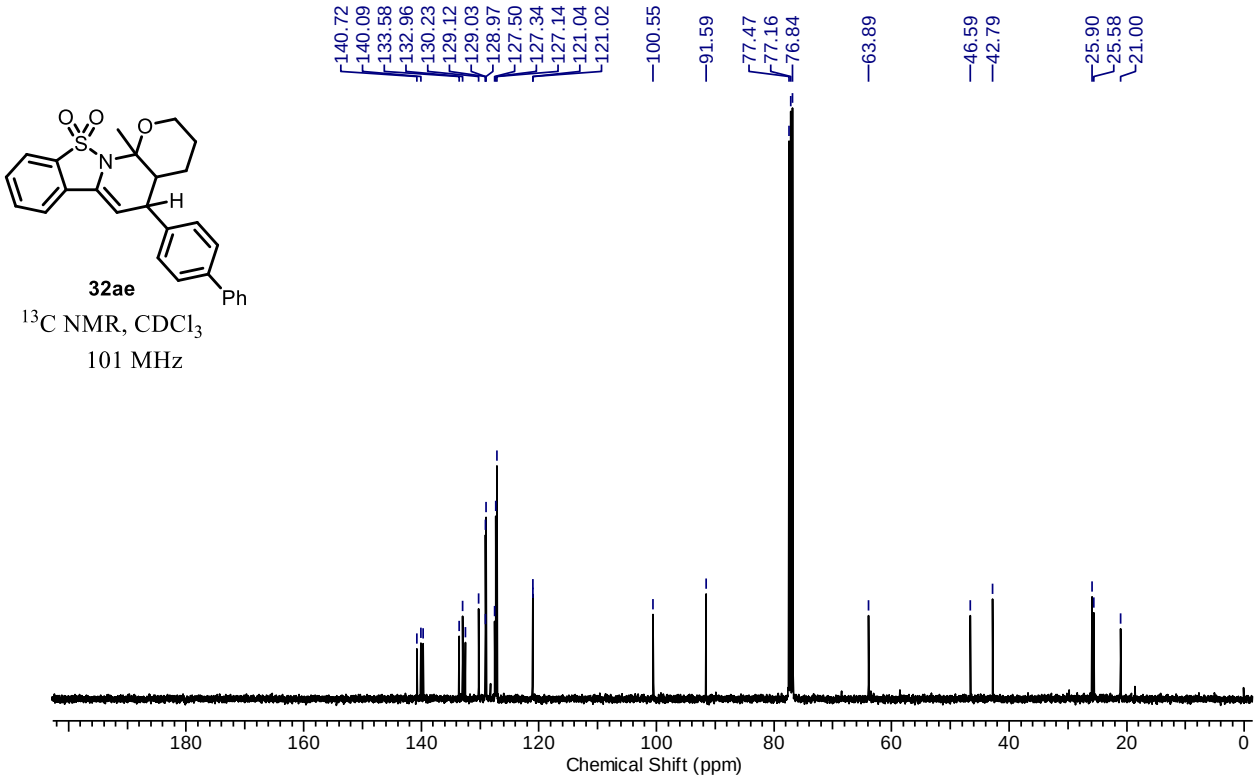
^{13}C NMR, $CDCl_3$

101 MHz

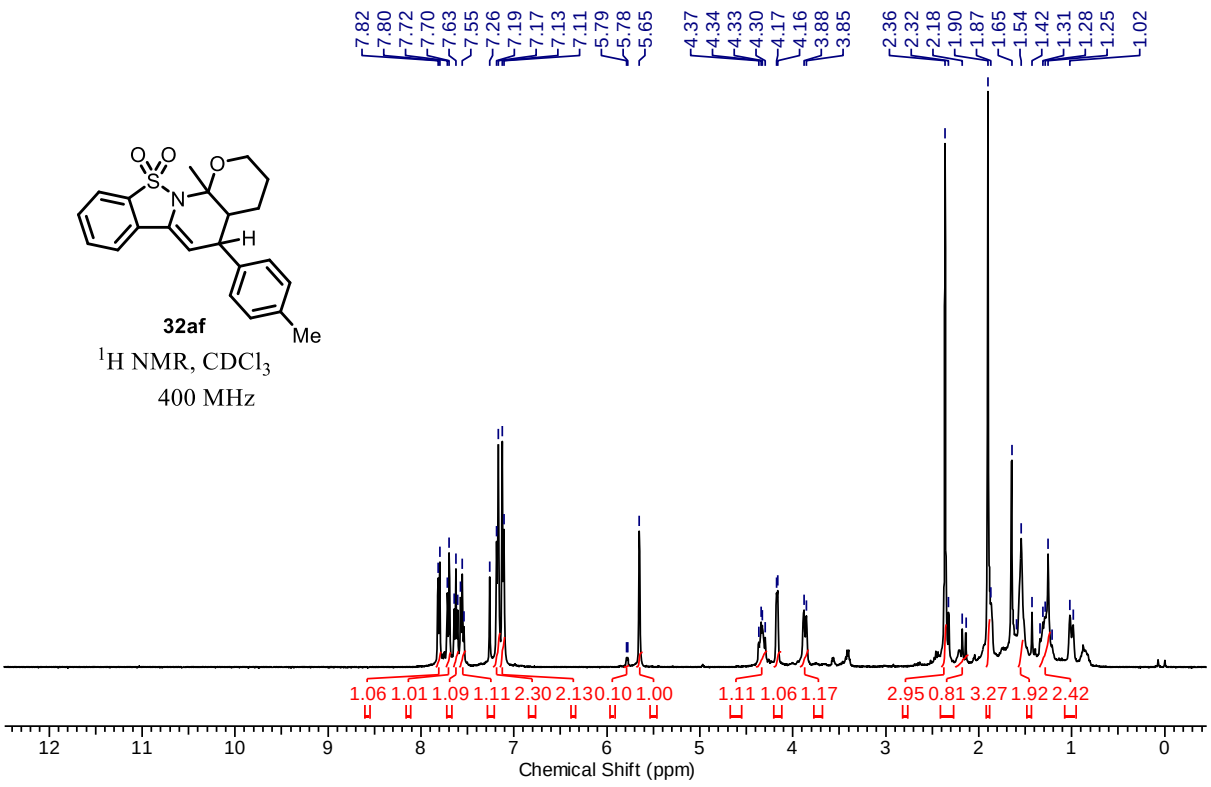
^{1}H NMR spectrum of compound 32ae



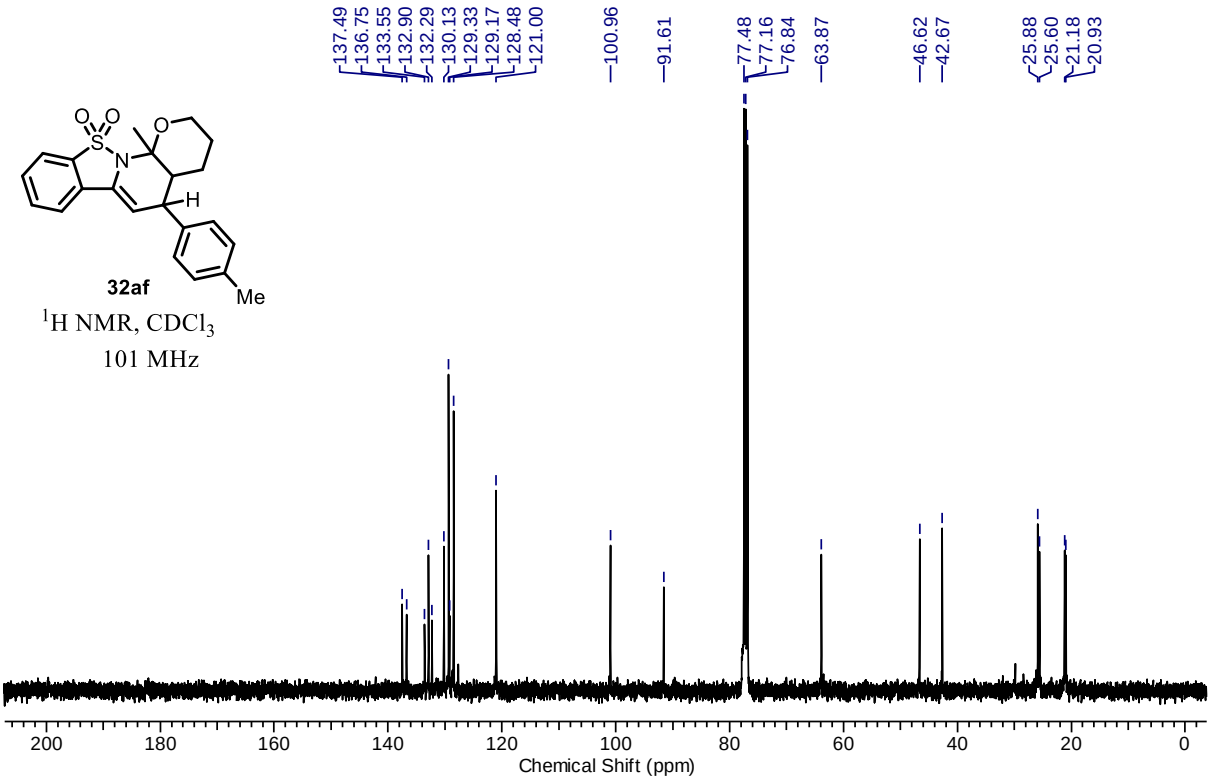
^{13}C NMR spectrum of compound 32ae



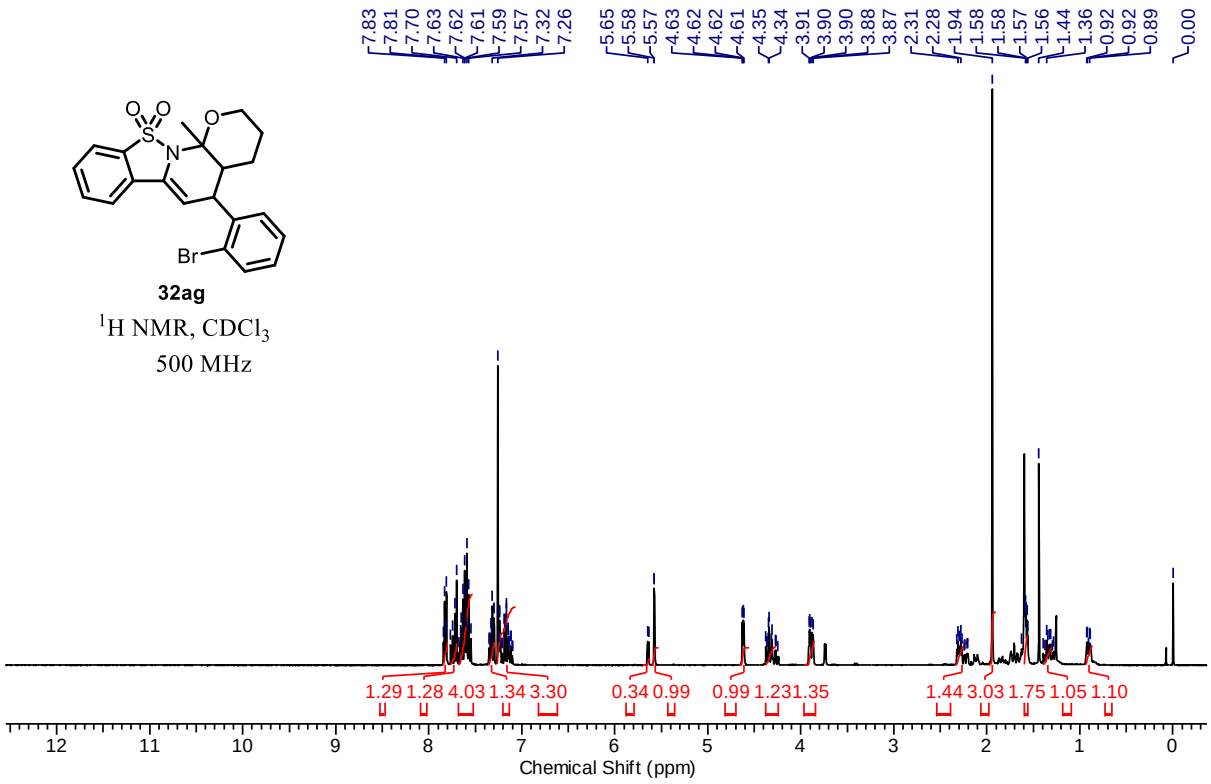
^{1}H NMR spectrum of compound 32af



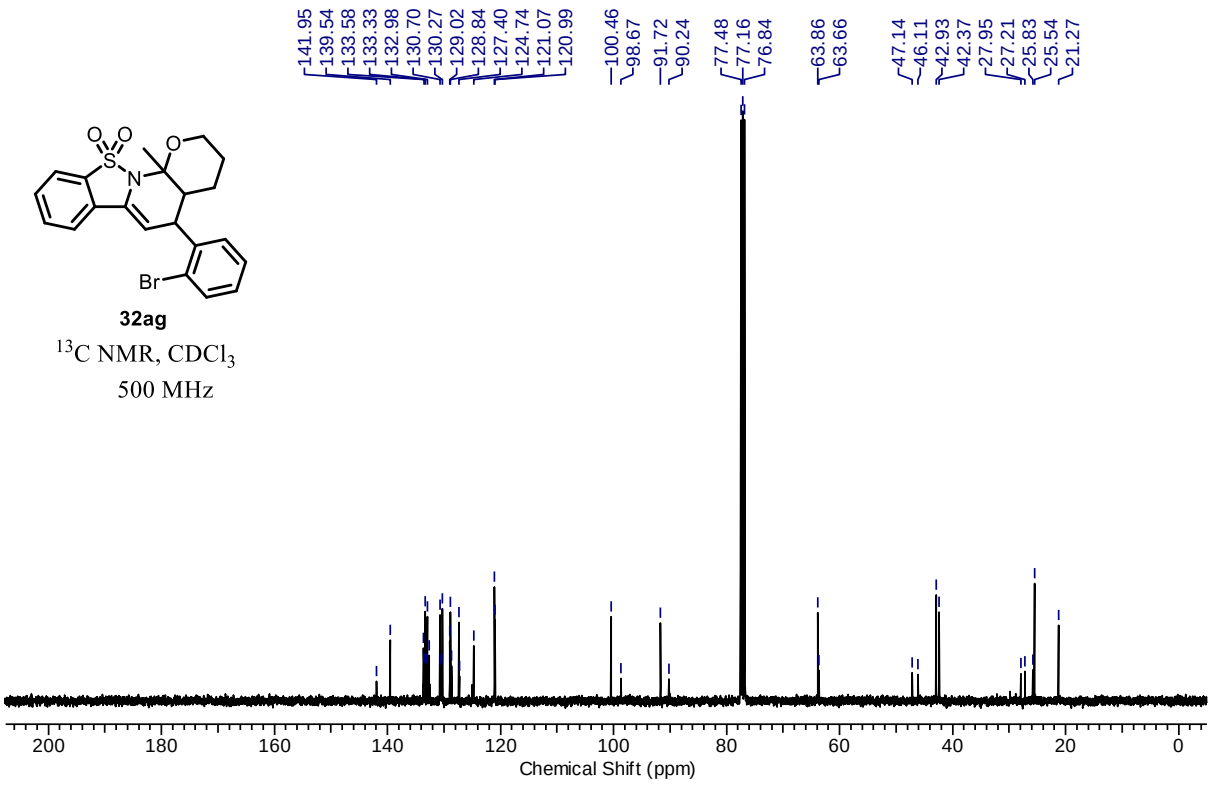
^{13}C NMR spectrum of compound 32af



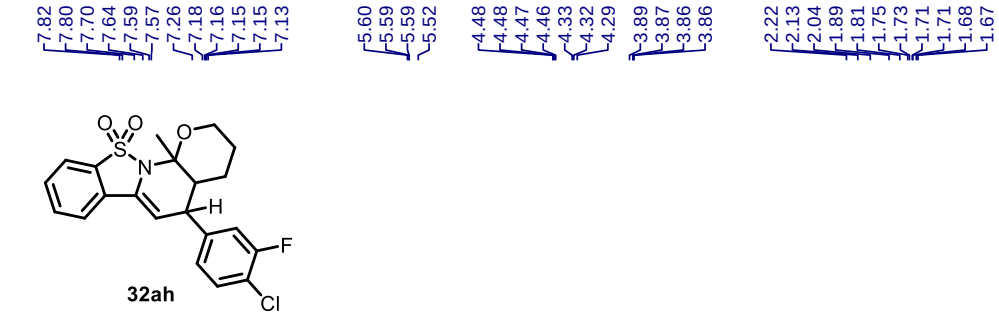
^{1}H NMR spectrum of compound 32ag



^{13}C NMR spectrum of compound 55aa



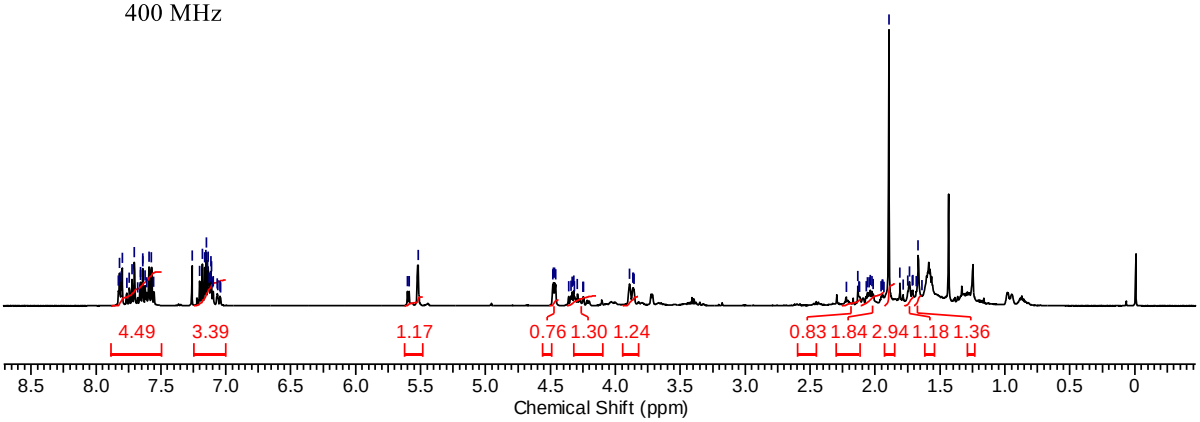
^{1}H NMR spectrum of compound 32ah



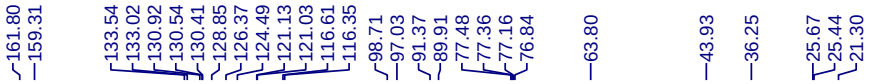
32ah

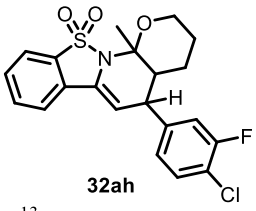
^{1}H NMR, $CDCl_3$

400 MHz



^{13}C NMR spectrum of compound 32ah



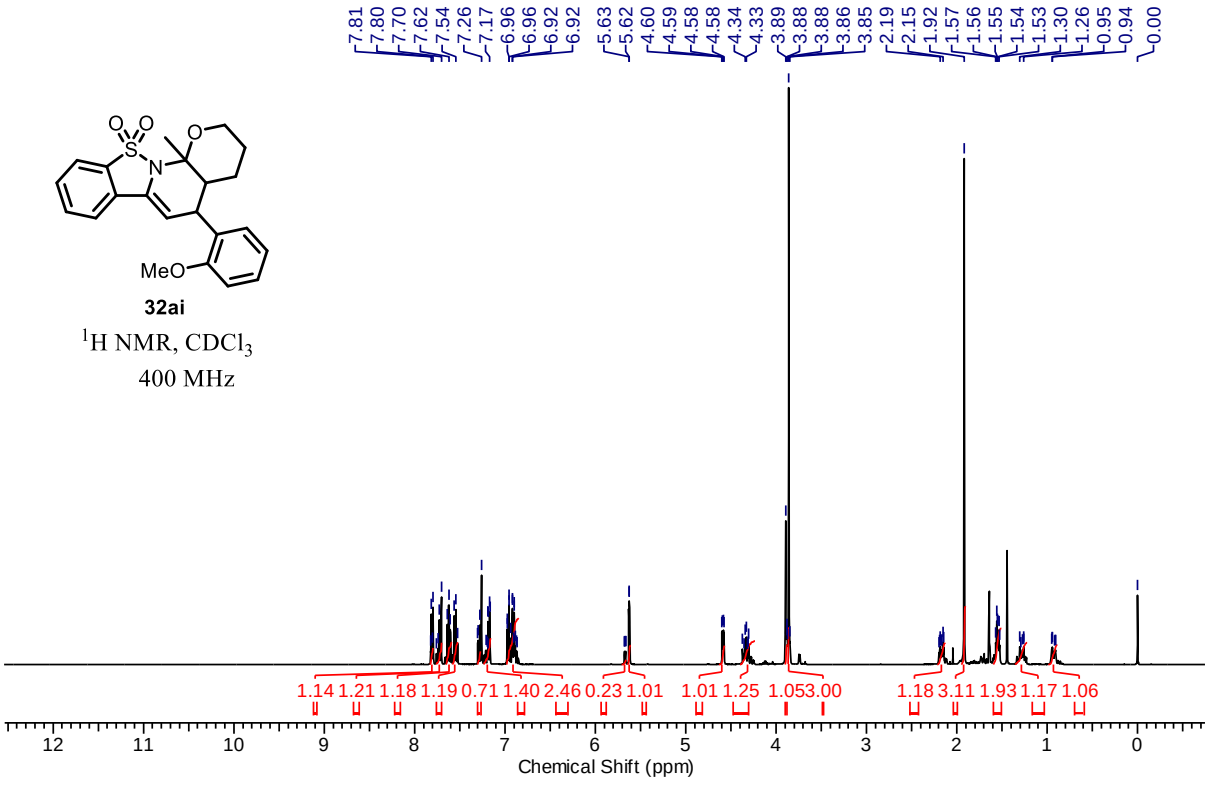


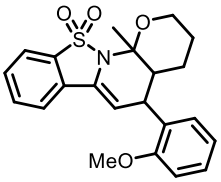
32ah

^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 32ai





32ai

^{1}H NMR, $CDCl_3$

400 MHz

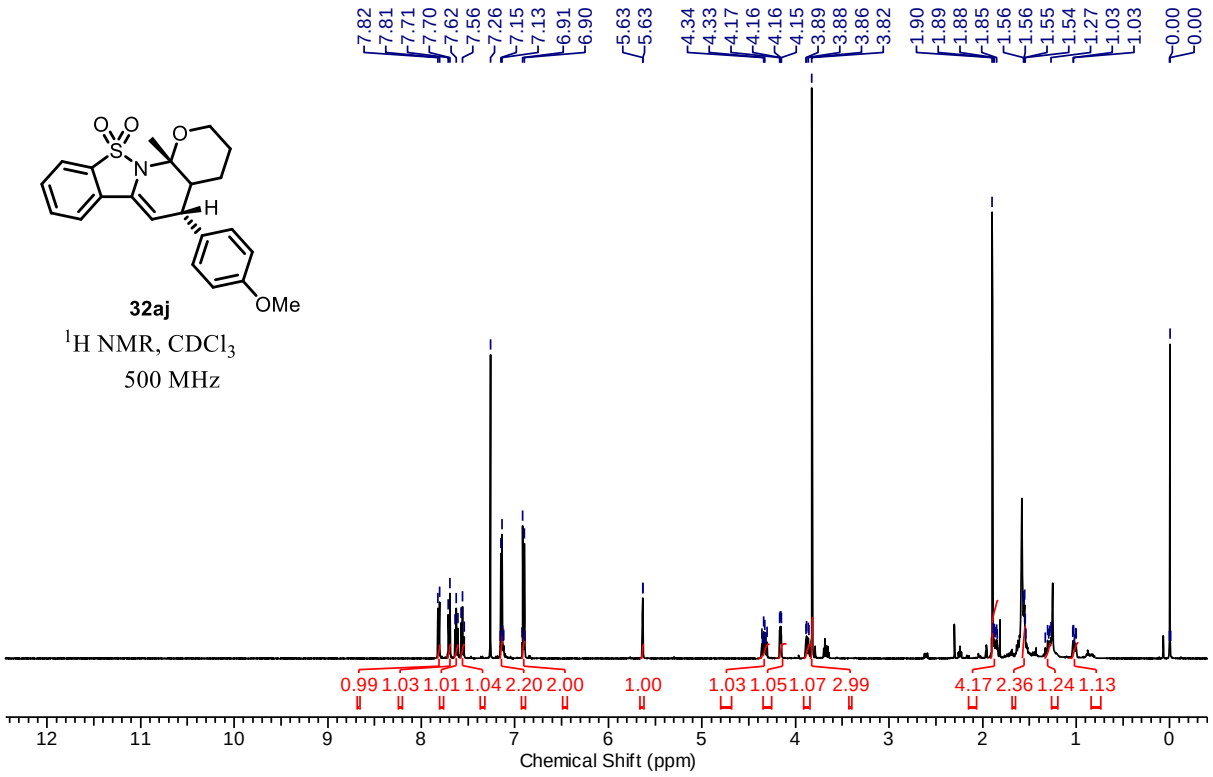
^{13}C NMR spectrum of compound 32ai

32ai

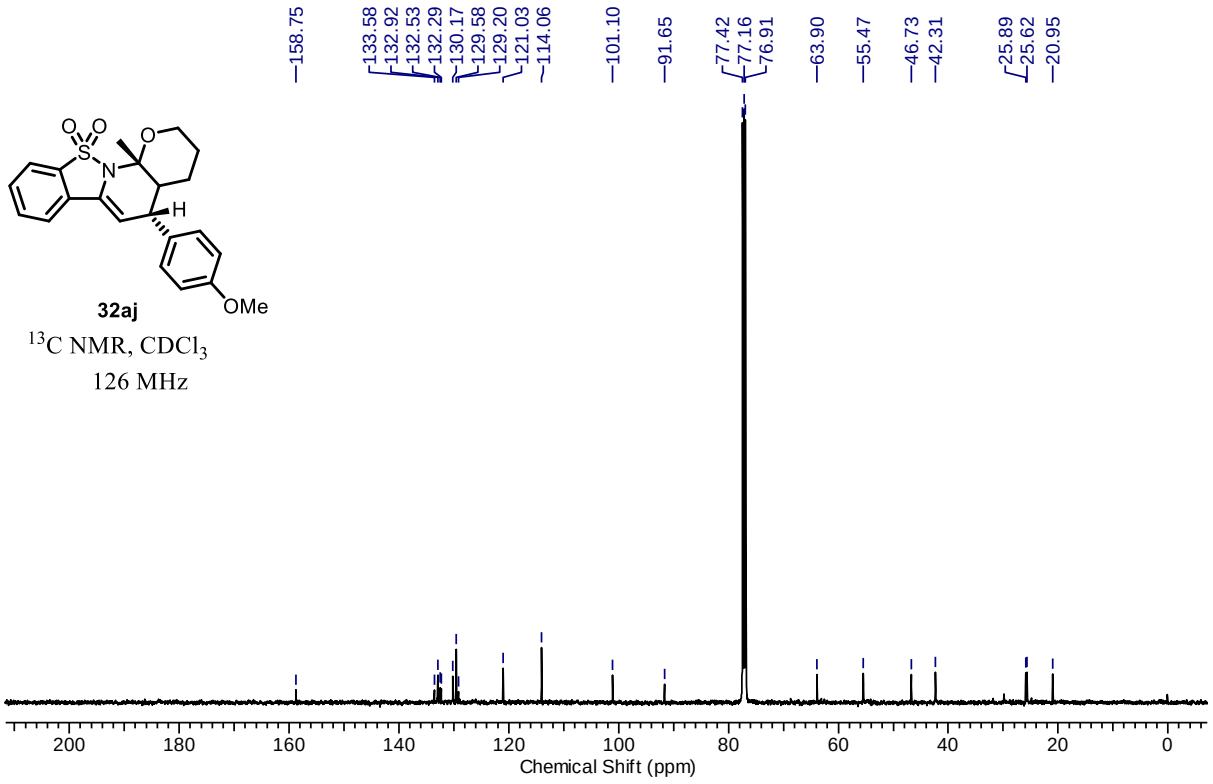
^{13}C NMR, $CDCl_3$

101 MHz

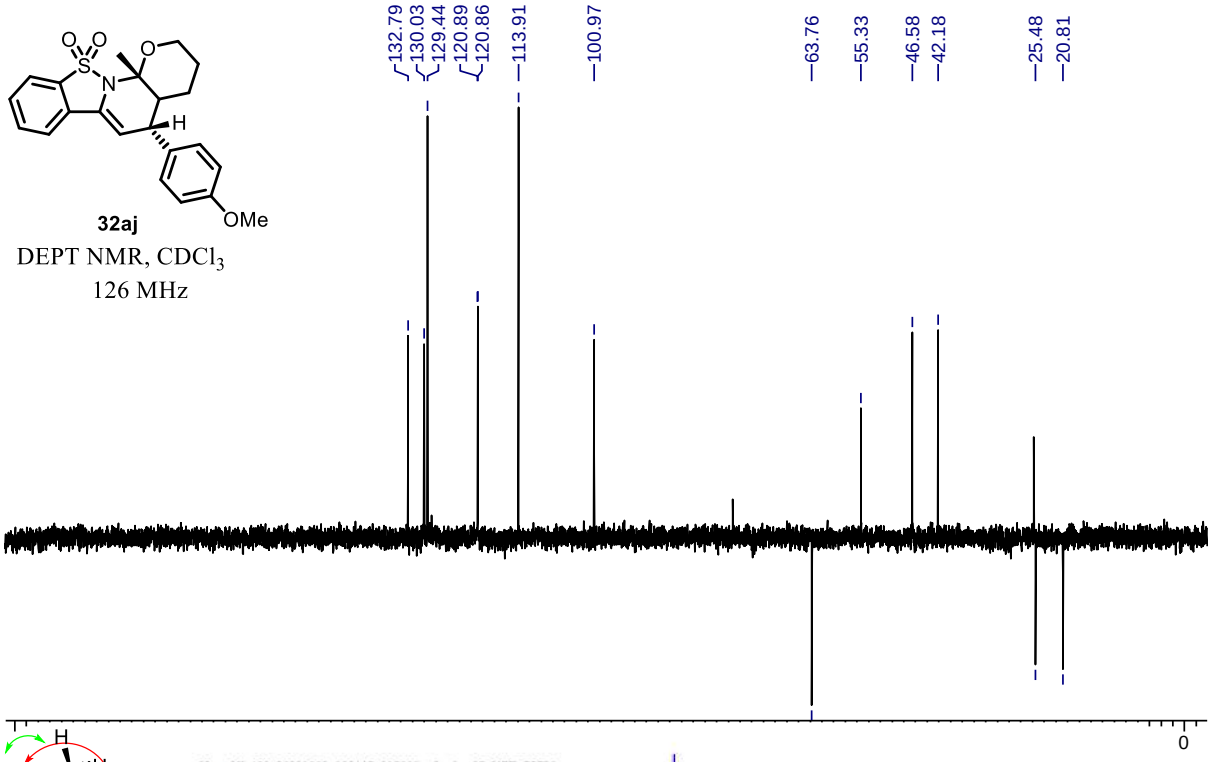
^{1}H NMR spectrum of compound 32aj



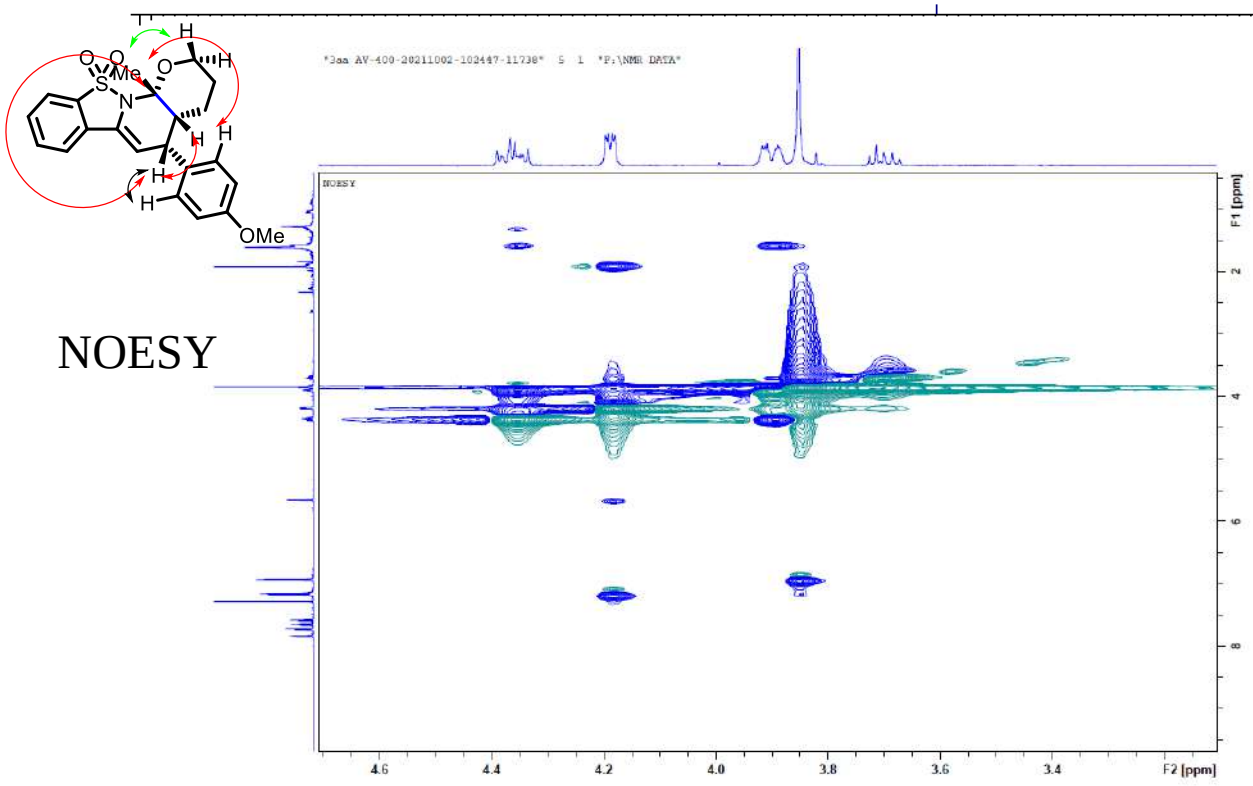
^{13}C NMR spectrum of compound 32aj



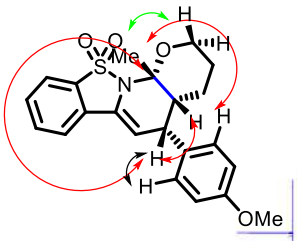
^{1}H NMR spectrum of compound 32aj



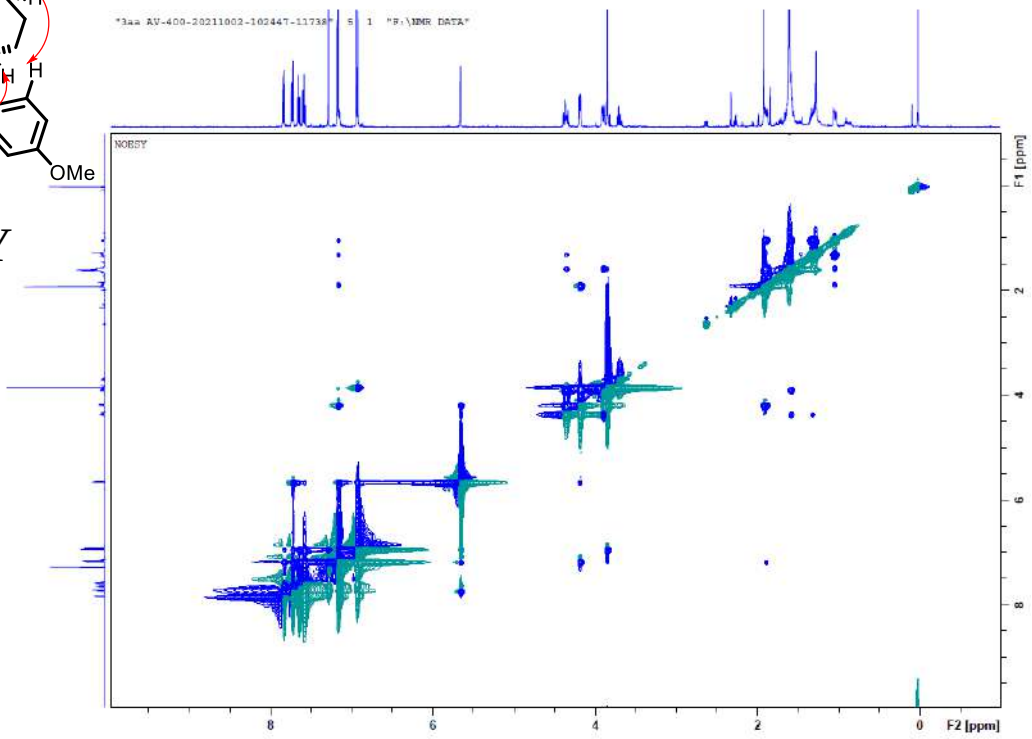
NOESY

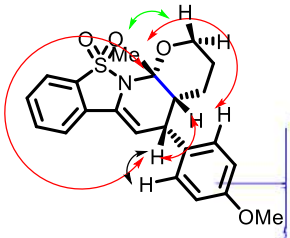


^{1}H NMR spectrum of compound 32aj

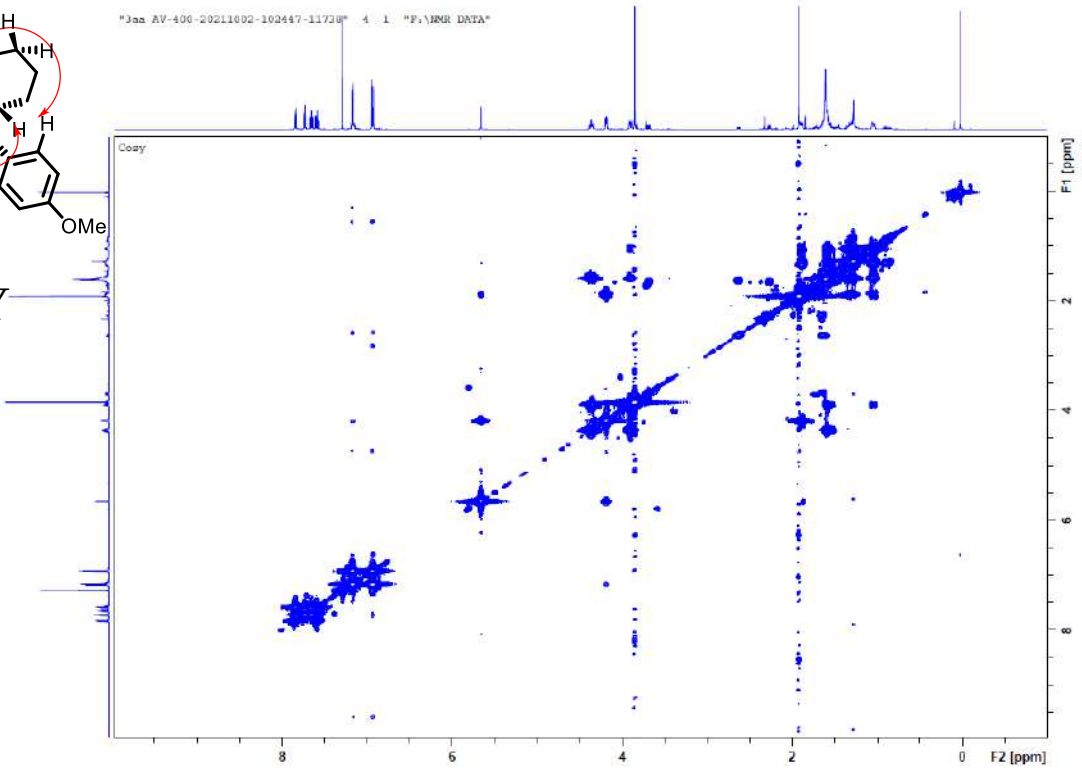


NOESY



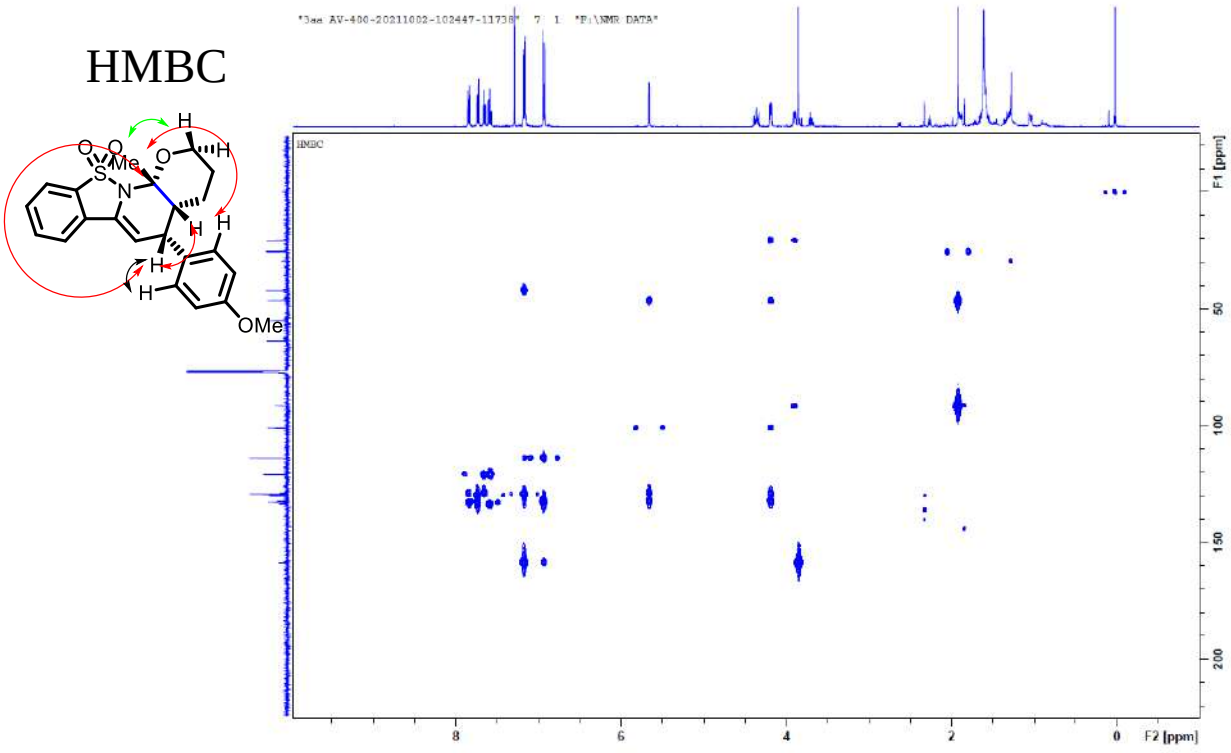


COESY

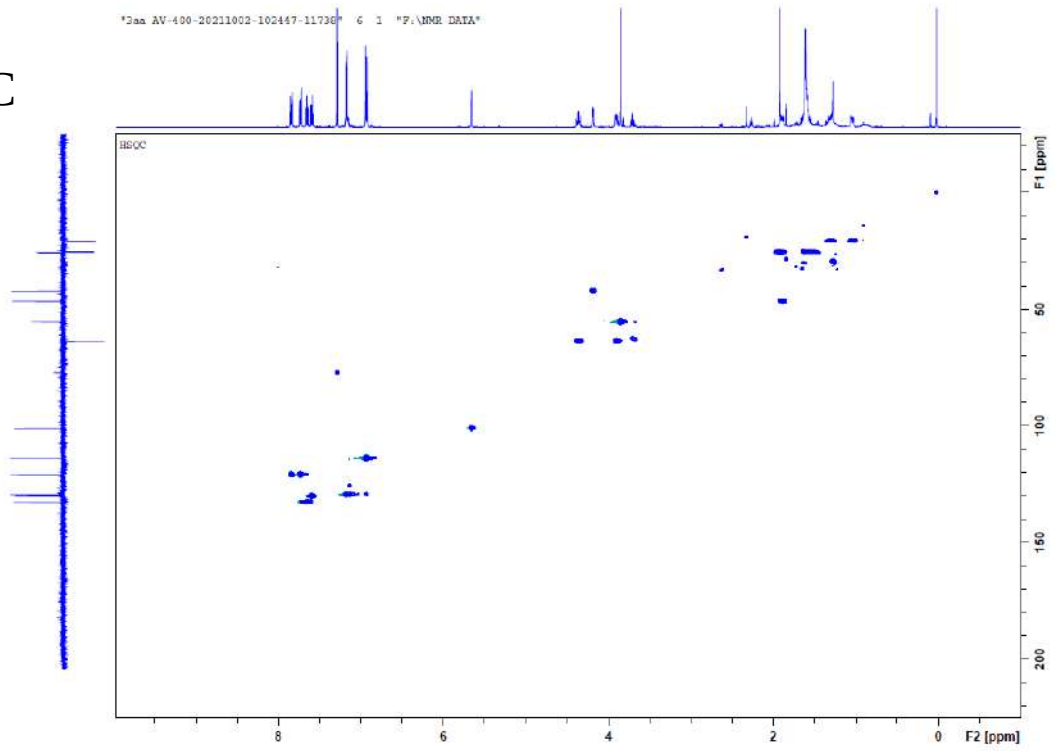


^{1}H NMR spectrum of compound 32aj

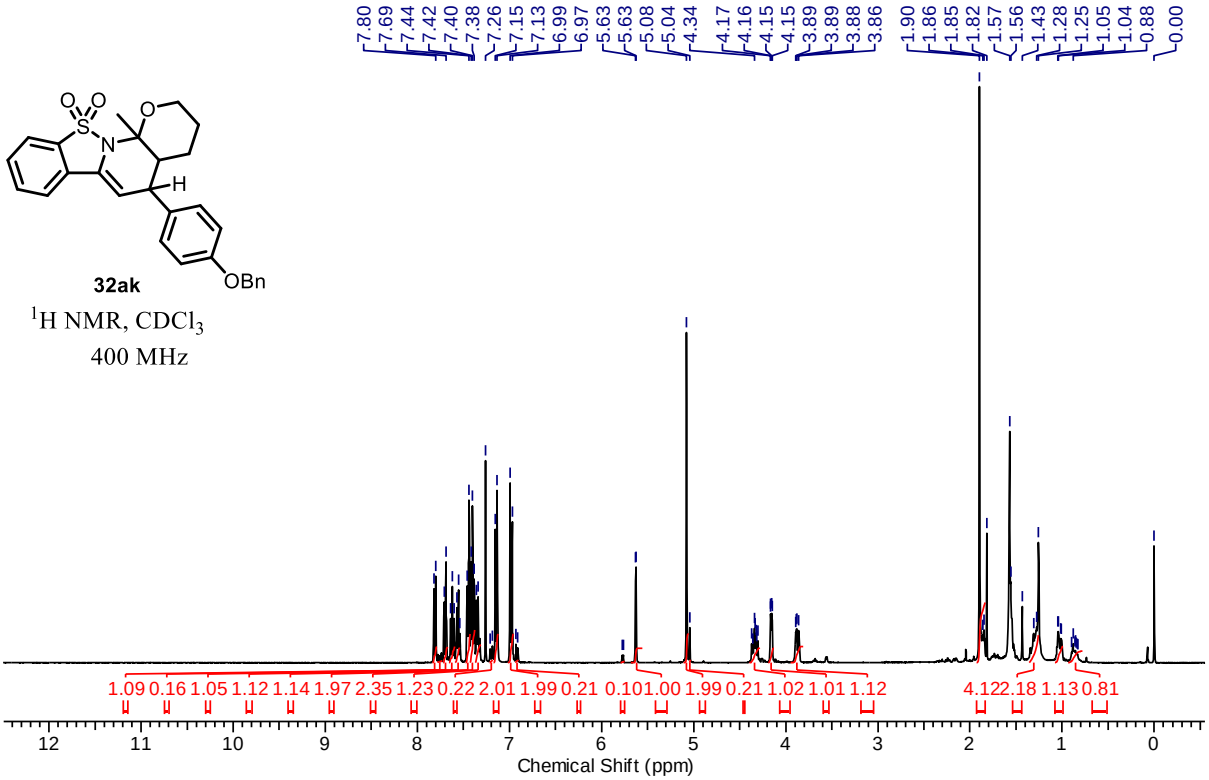
HMBC



HSQC



^{1}H NMR spectrum of compound 32ak

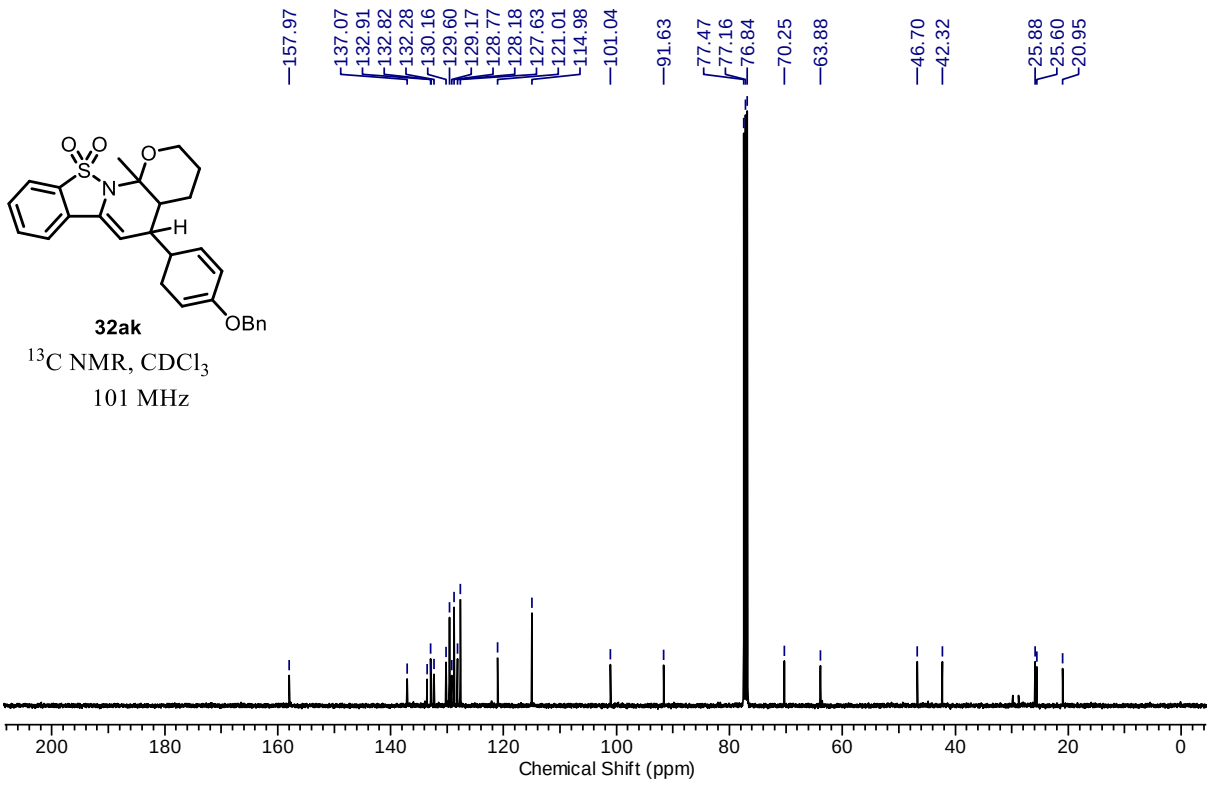


32ak

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 32ak

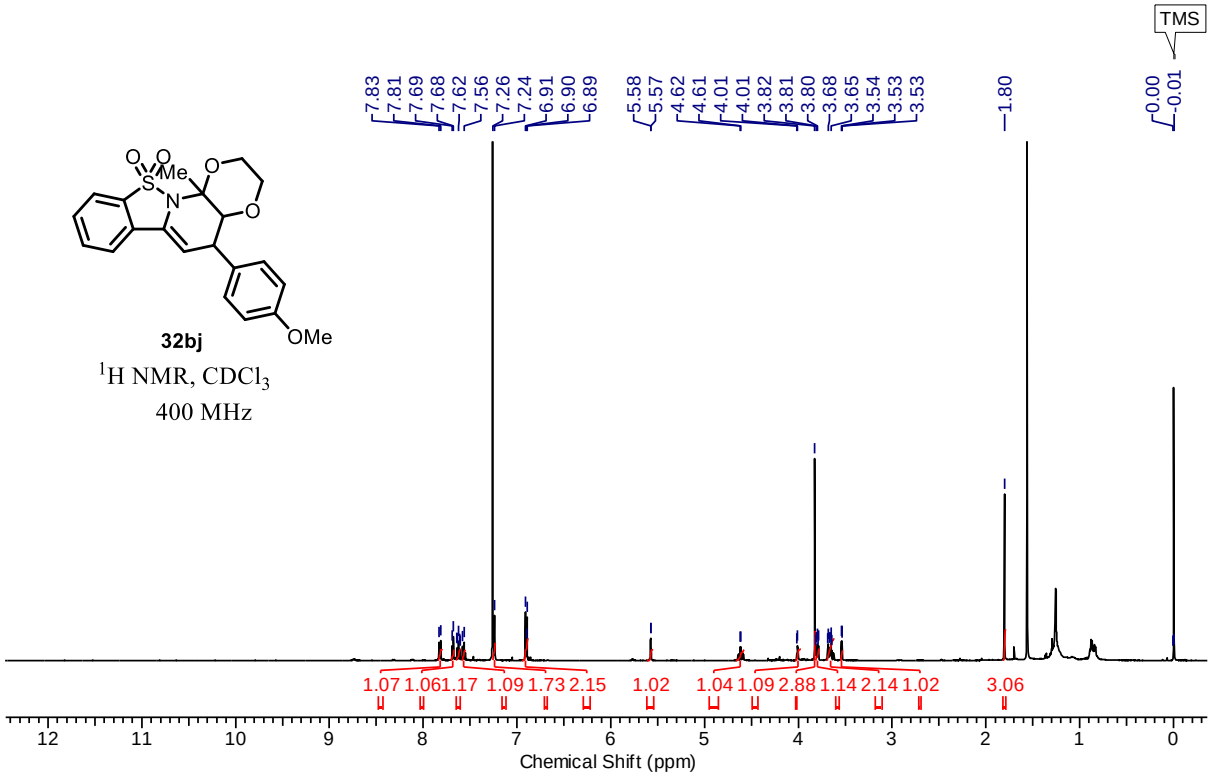


32ak

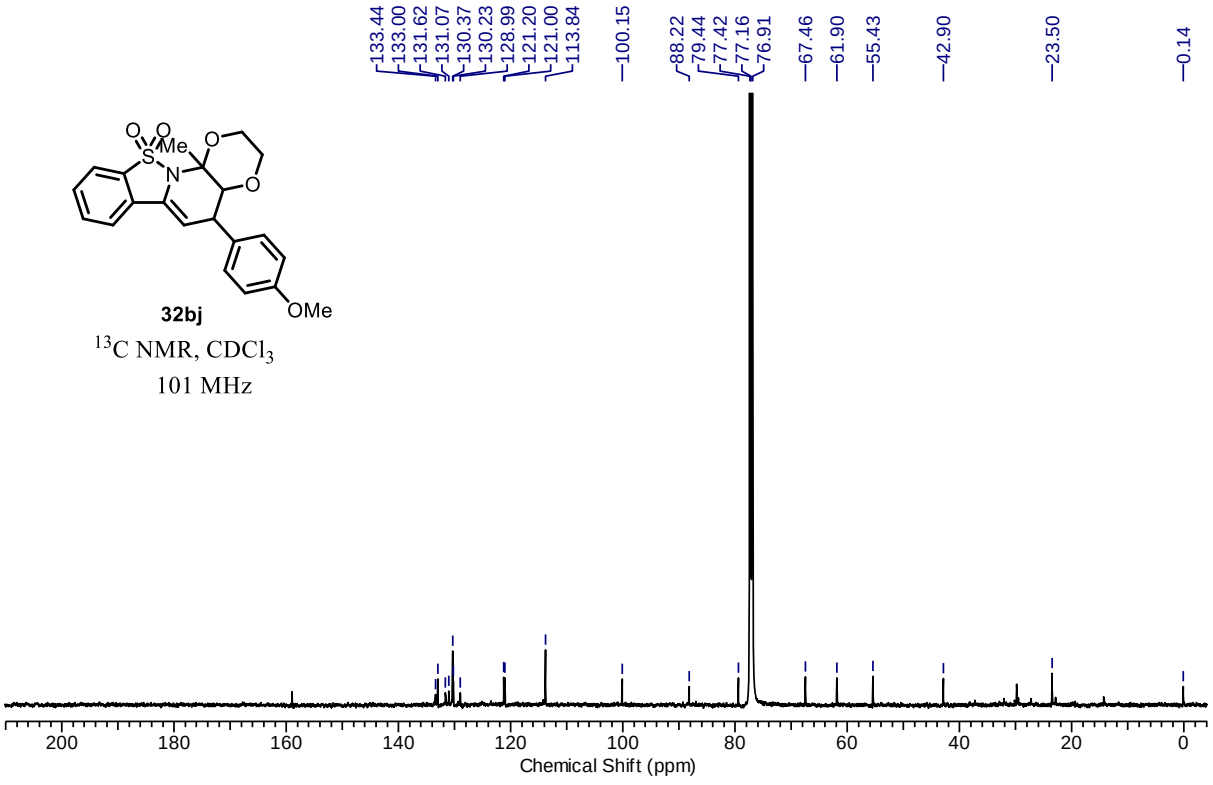
^{13}C NMR, $CDCl_3$

101 MHz

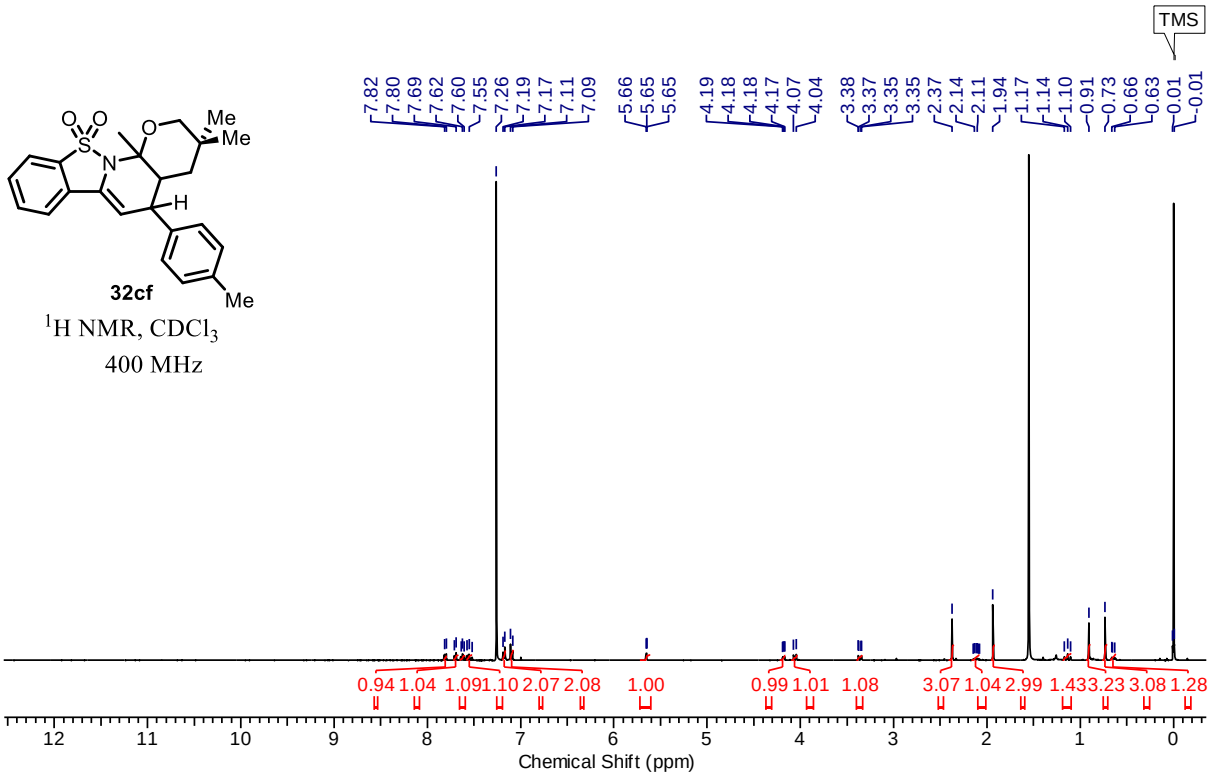
^{1}H NMR spectrum of compound 32bj



^{13}C NMR spectrum of compound 32bj

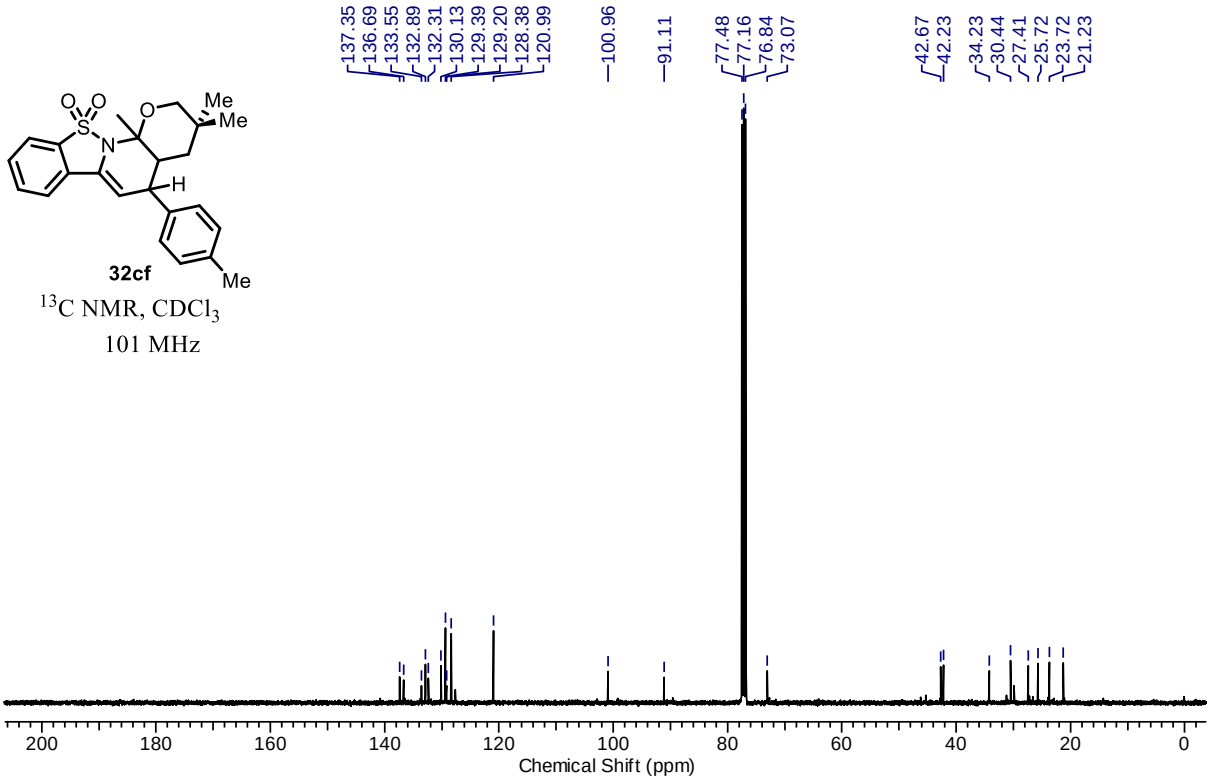


^{1}H NMR spectrum of compound 32cf



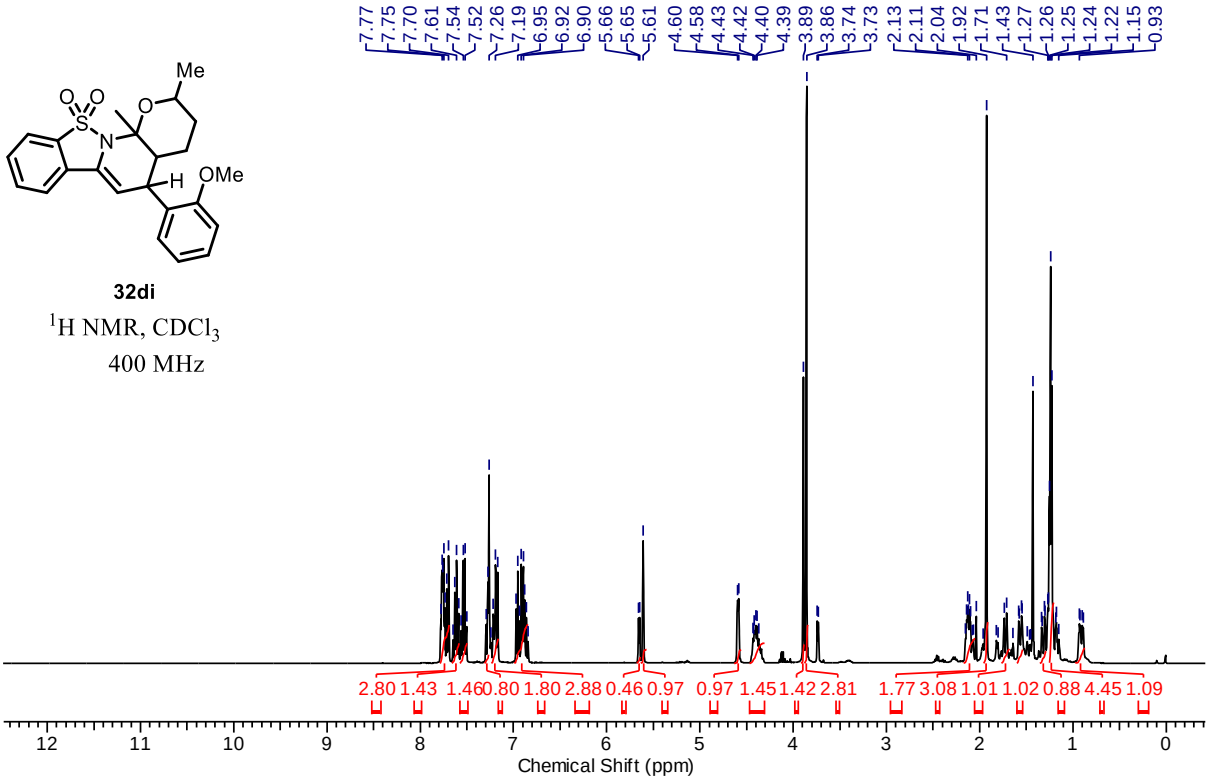
^{1}H NMR, $CDCl_3$
400 MHz

^{13}C NMR spectrum of compound 32cf

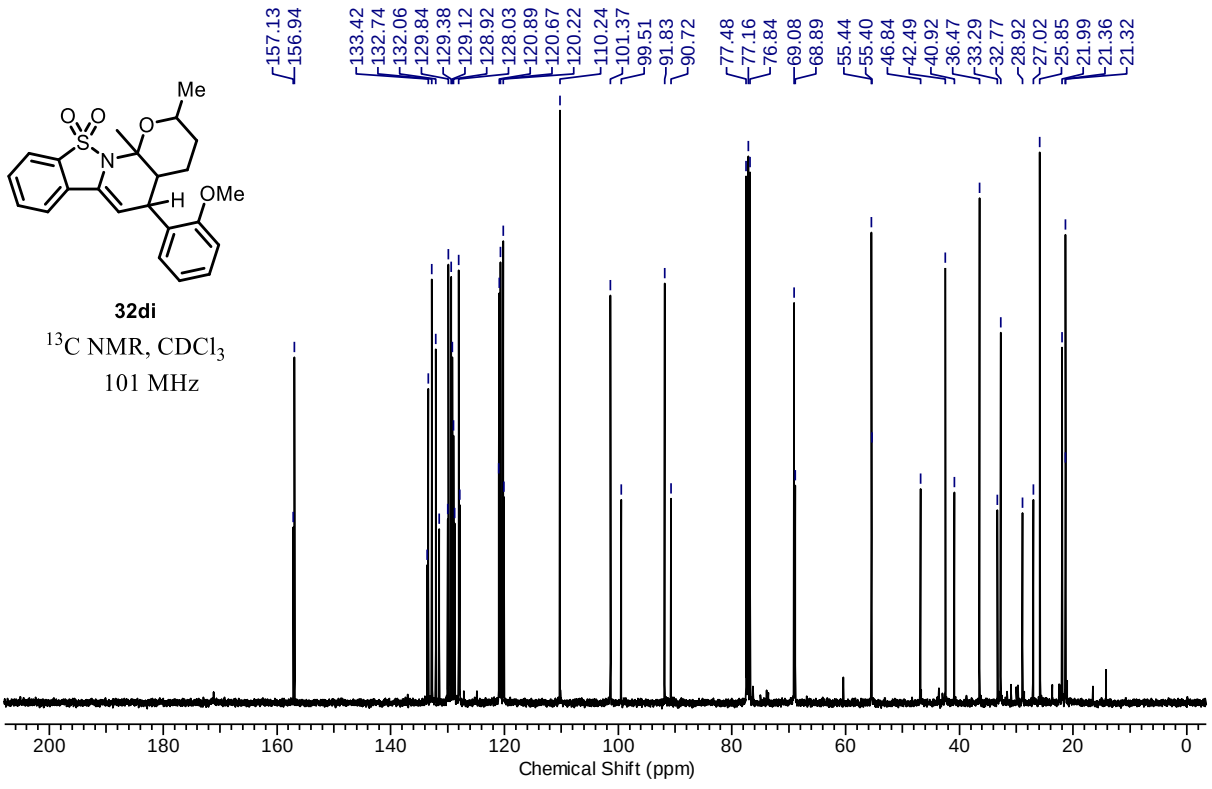


^{13}C NMR, $CDCl_3$
101 MHz

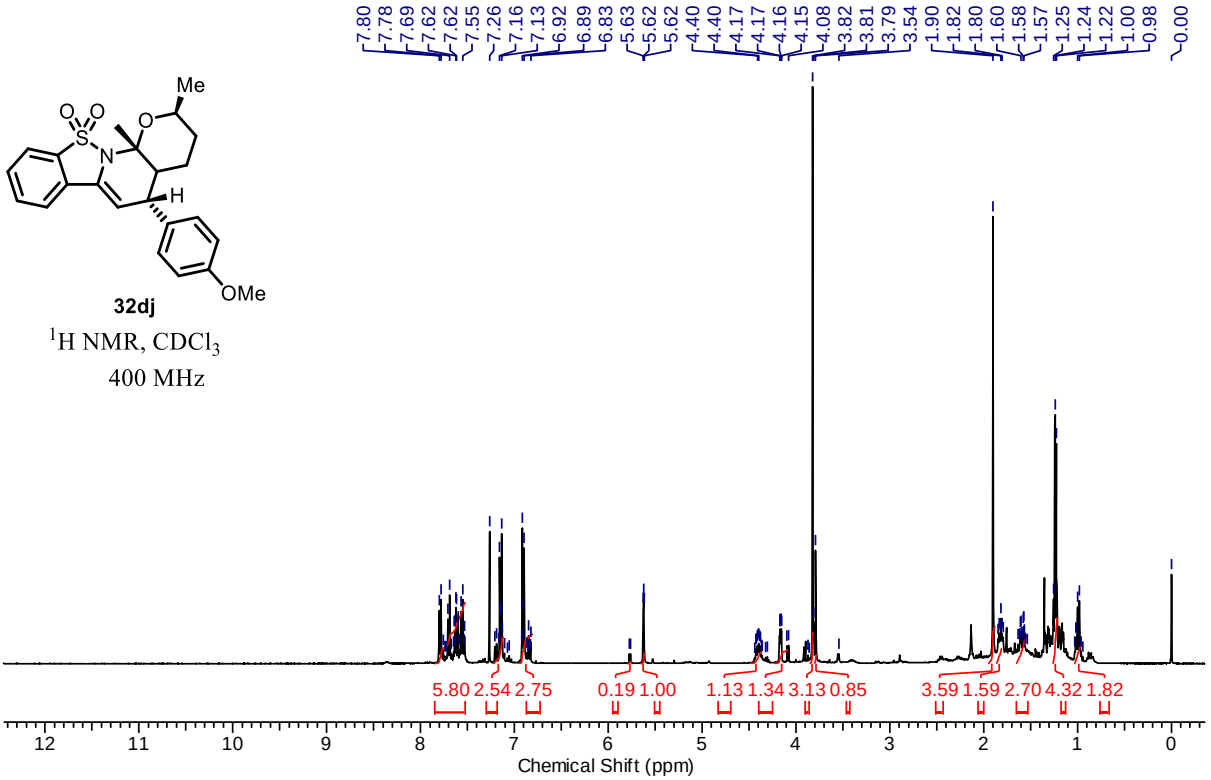
^{1}H NMR spectrum of compound 32di



^{13}C NMR spectrum of compound 32di



^{1}H NMR spectrum of compound 32dj

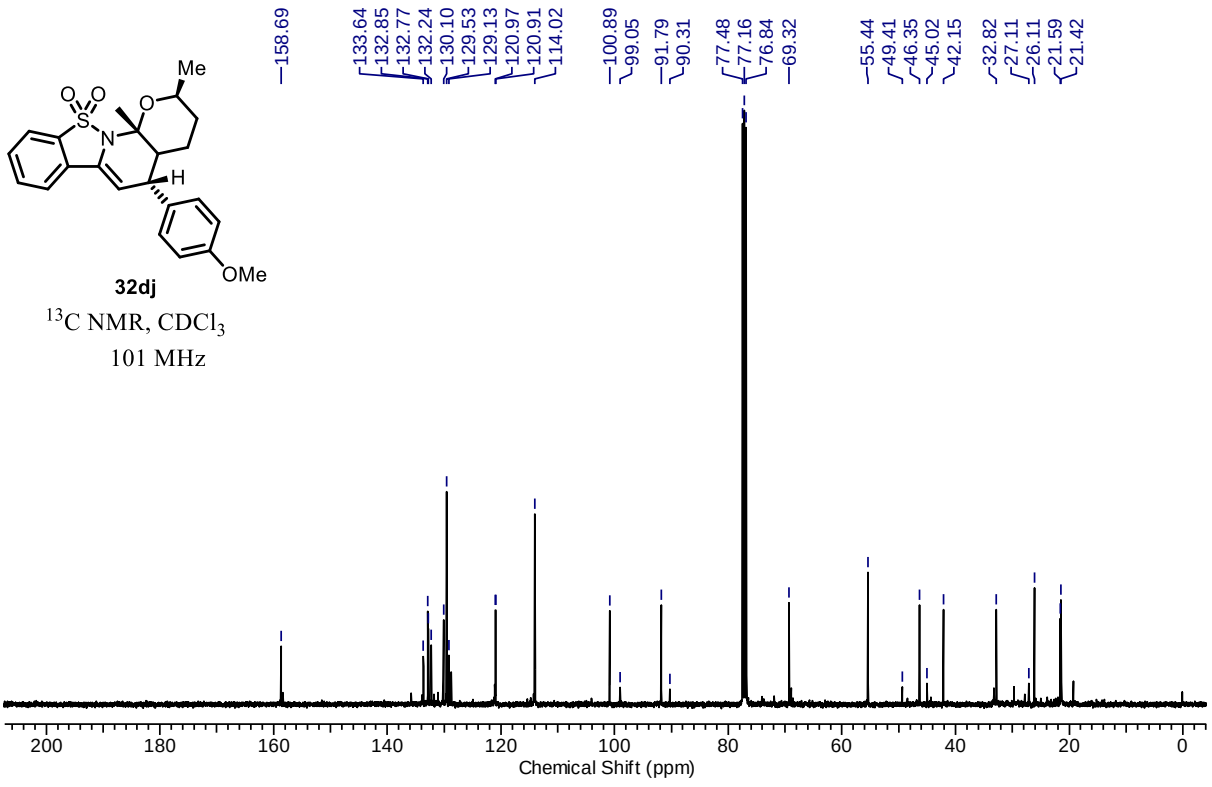


32dj

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 32dj

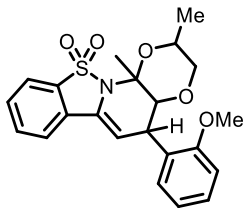


32dj

^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 32ai

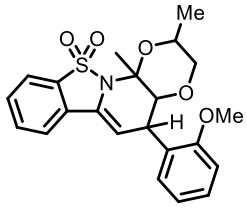


32ei

^{1}H NMR, $CDCl_3$

500 MHz

^{13}C NMR spectrum of compound 32ai

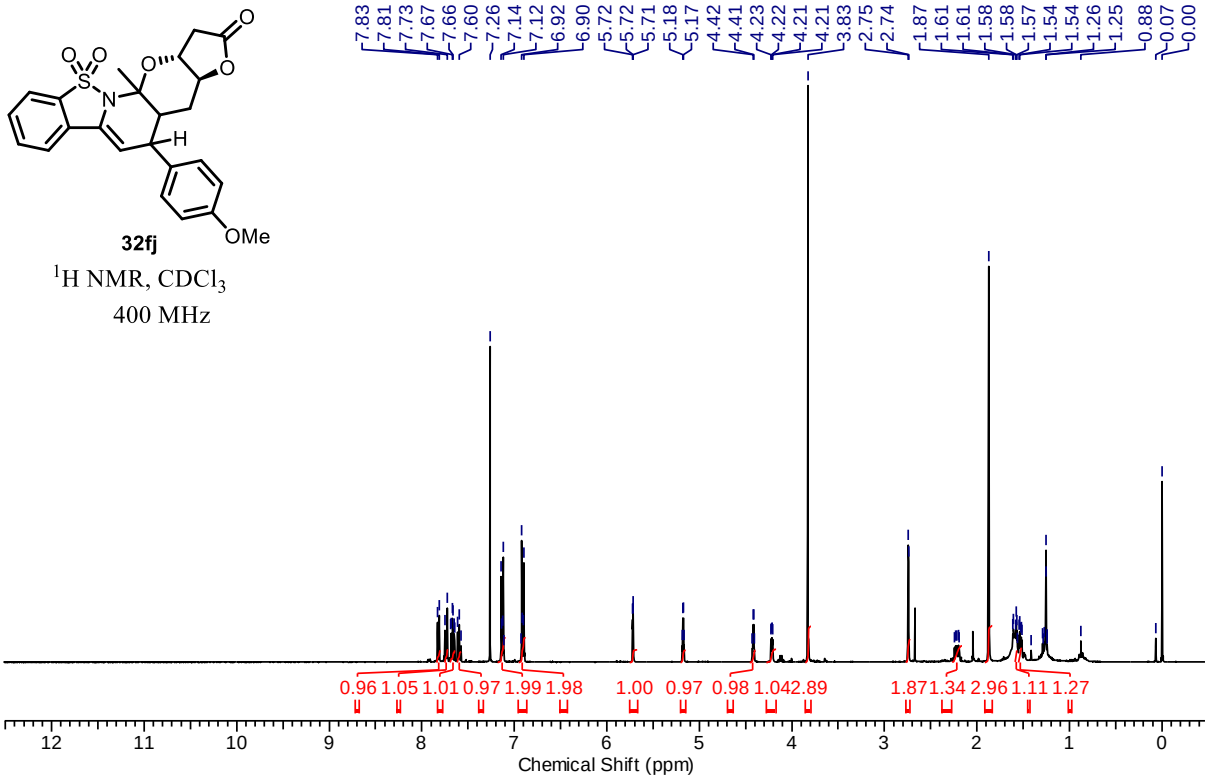


32ei

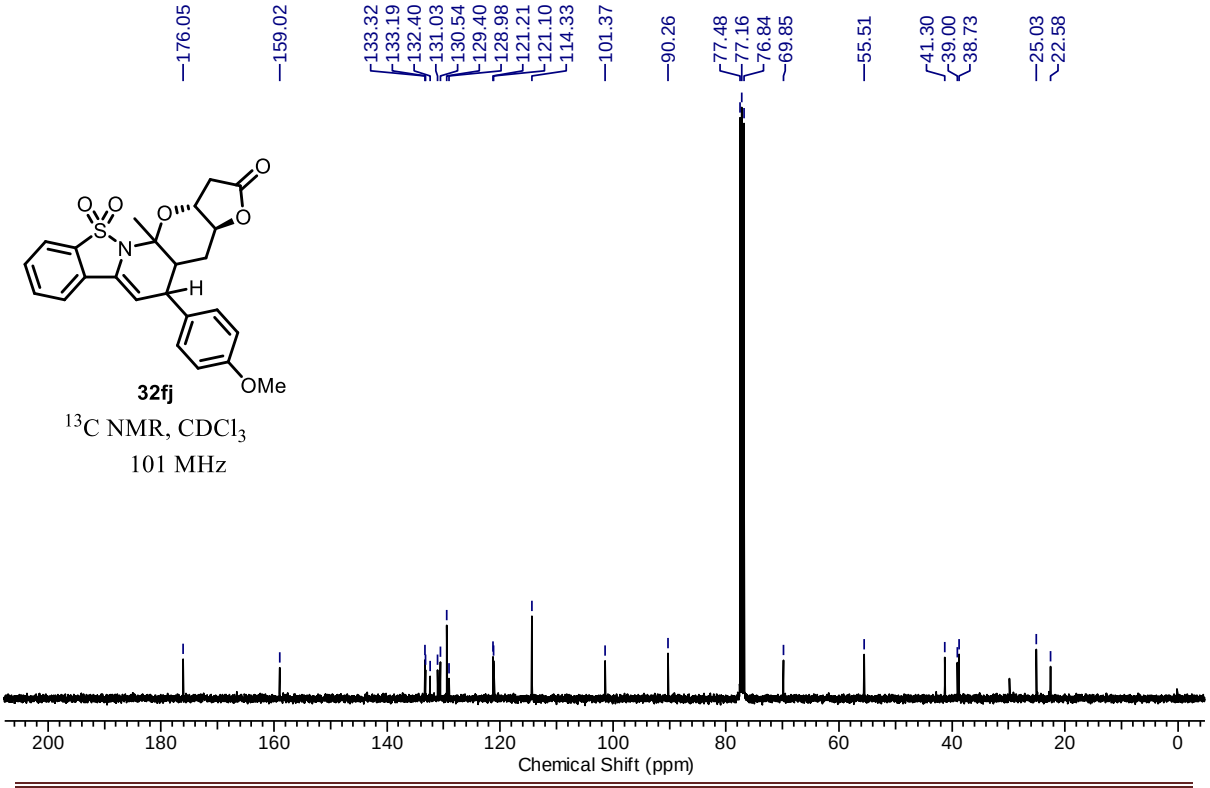
^{13}C NMR, $CDCl_3$

126 MHz

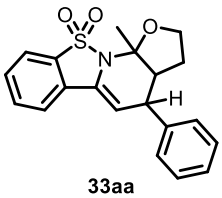
^{1}H NMR spectrum of compound32fj



^{13}C NMR spectrum of compound 32fj



^{1}H NMR spectrum of compound 33aa

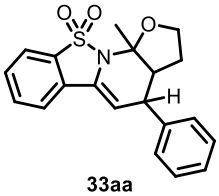


33aa

^{1}H NMR, $CDCl_3$

500 MHz

^{13}C NMR spectrum of compound 33aa

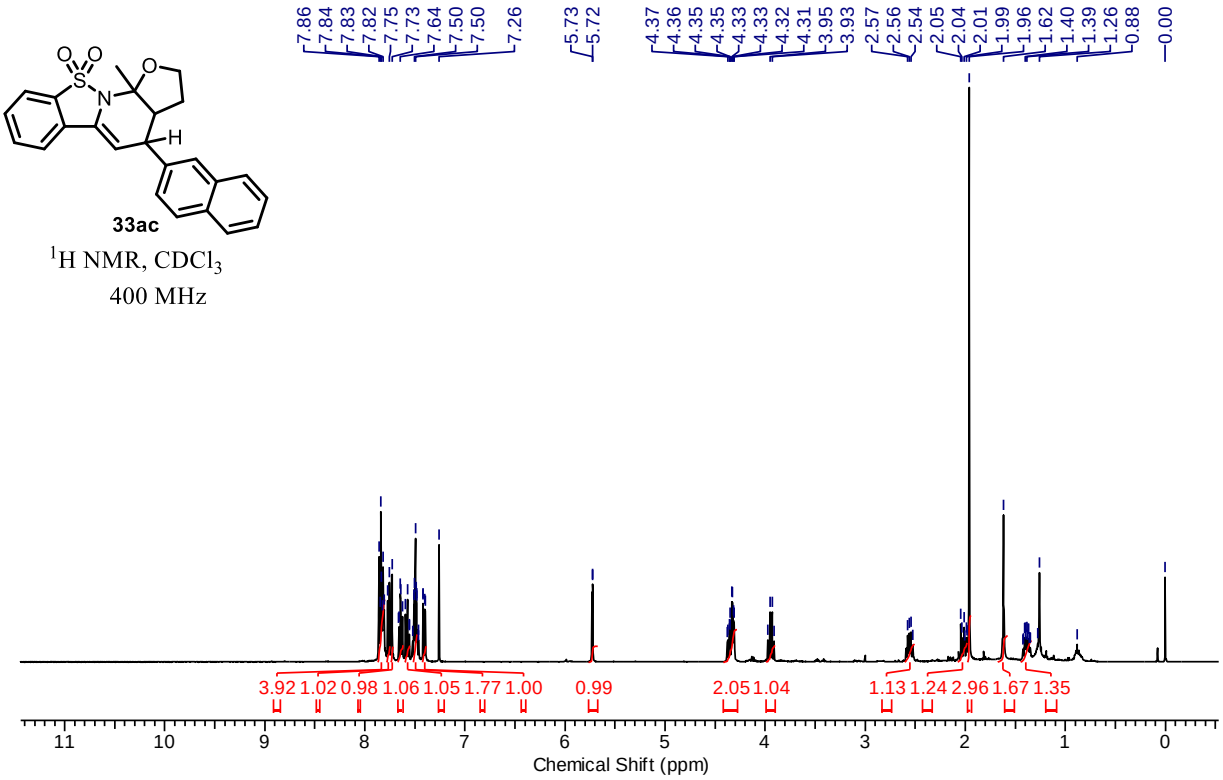


33aa

^{13}C NMR, $CDCl_3$

126 MHz

^{1}H NMR spectrum of compound 32ac

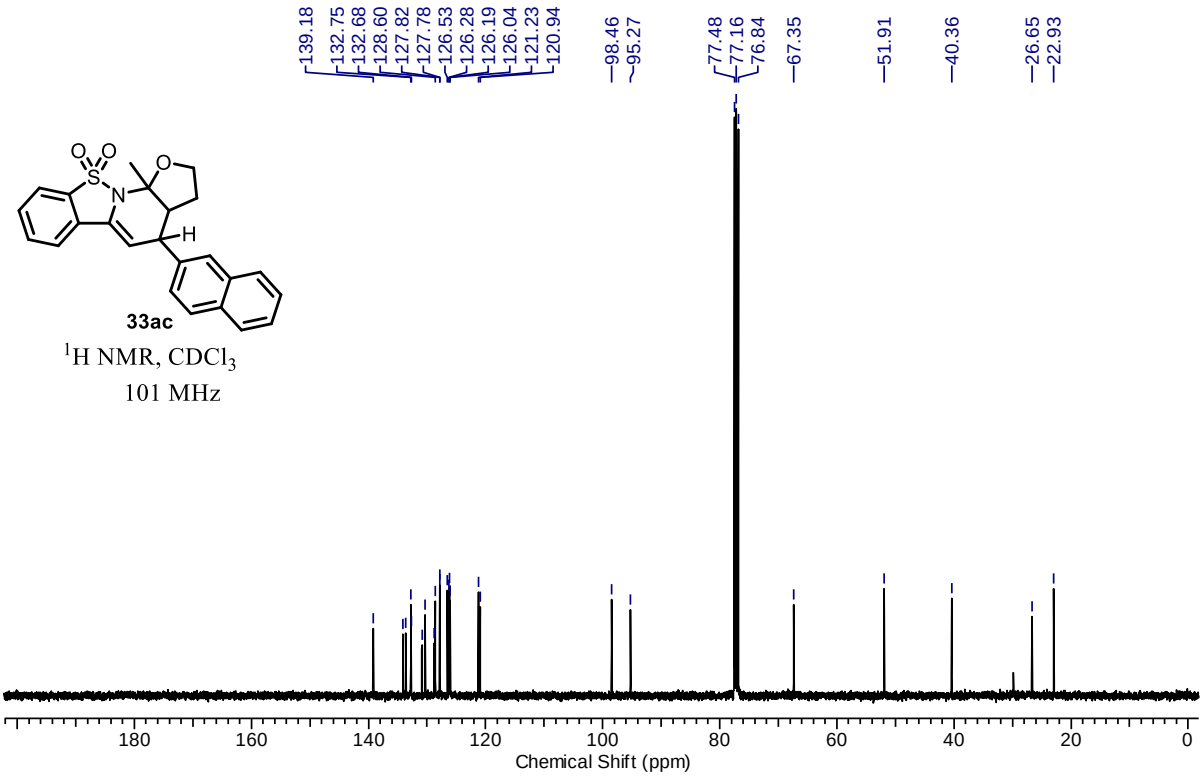


33ac

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 33ac

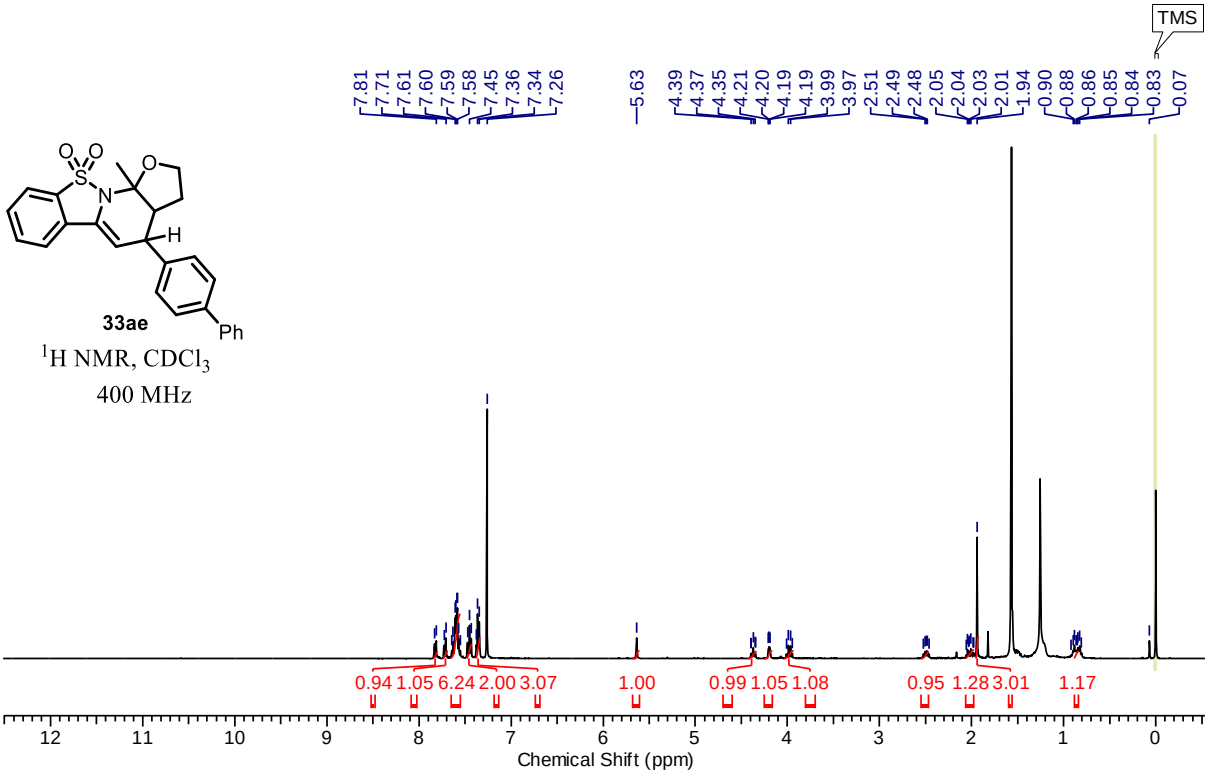


33ac

^{1}H NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 33ae

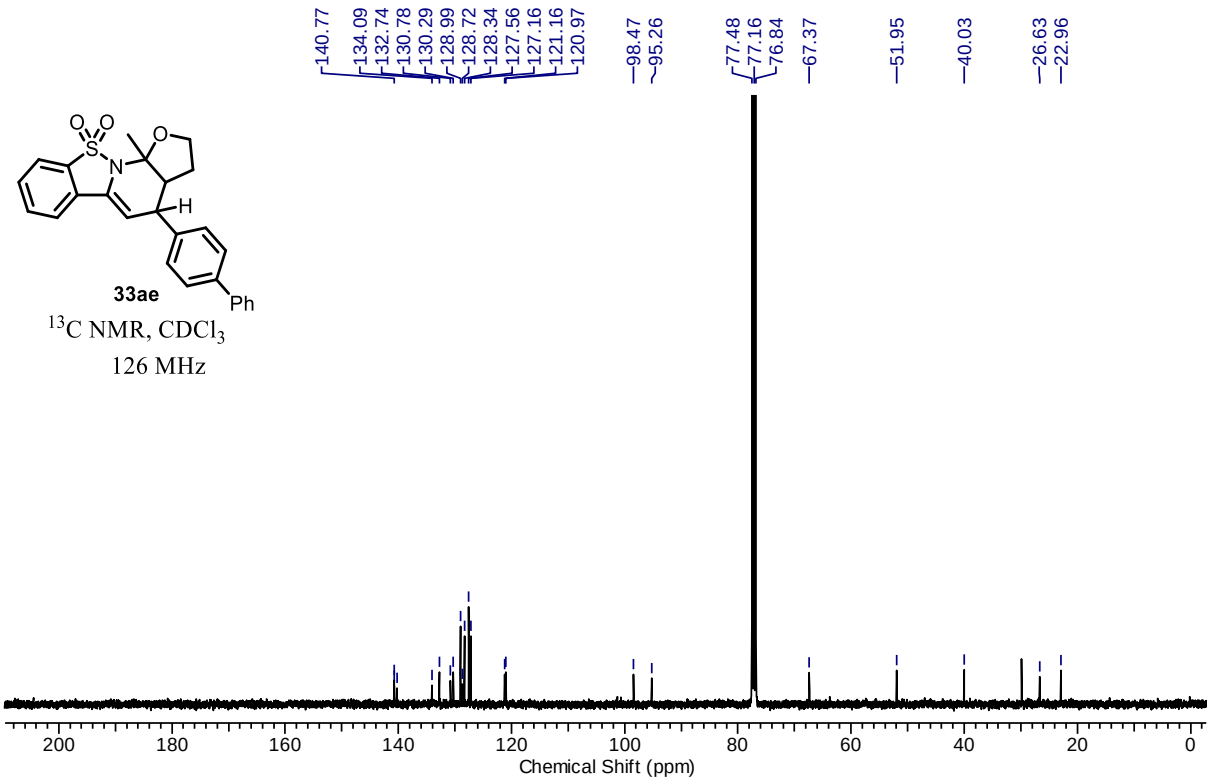


33ae

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 33ae

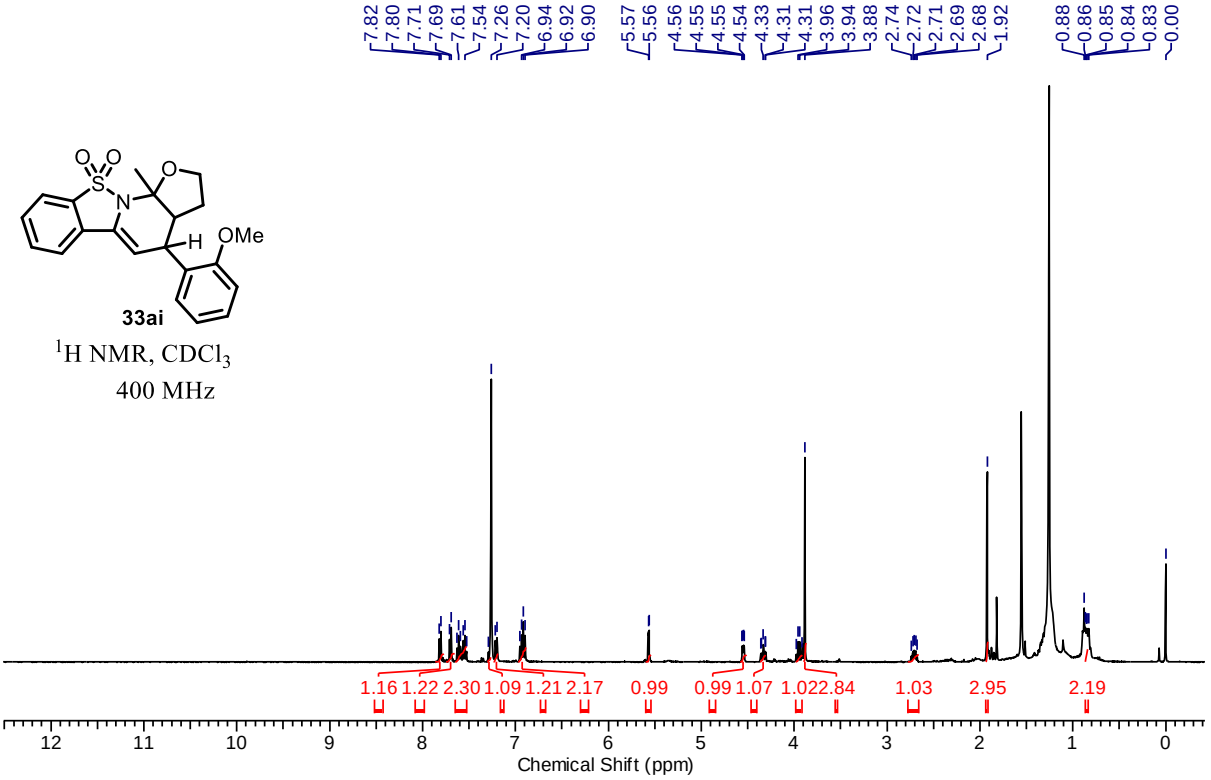


33ae

^{13}C NMR, $CDCl_3$

126 MHz

^{1}H NMR spectrum of compound 33ai

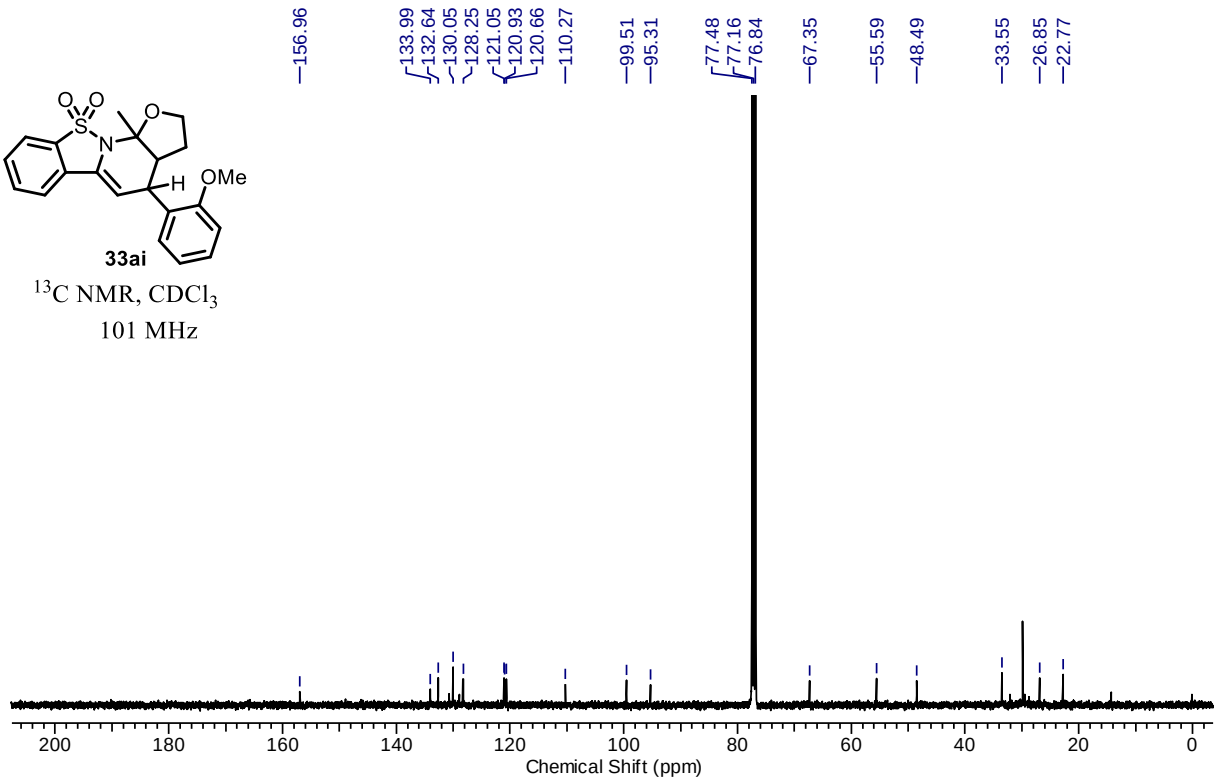


33ai

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 33ai

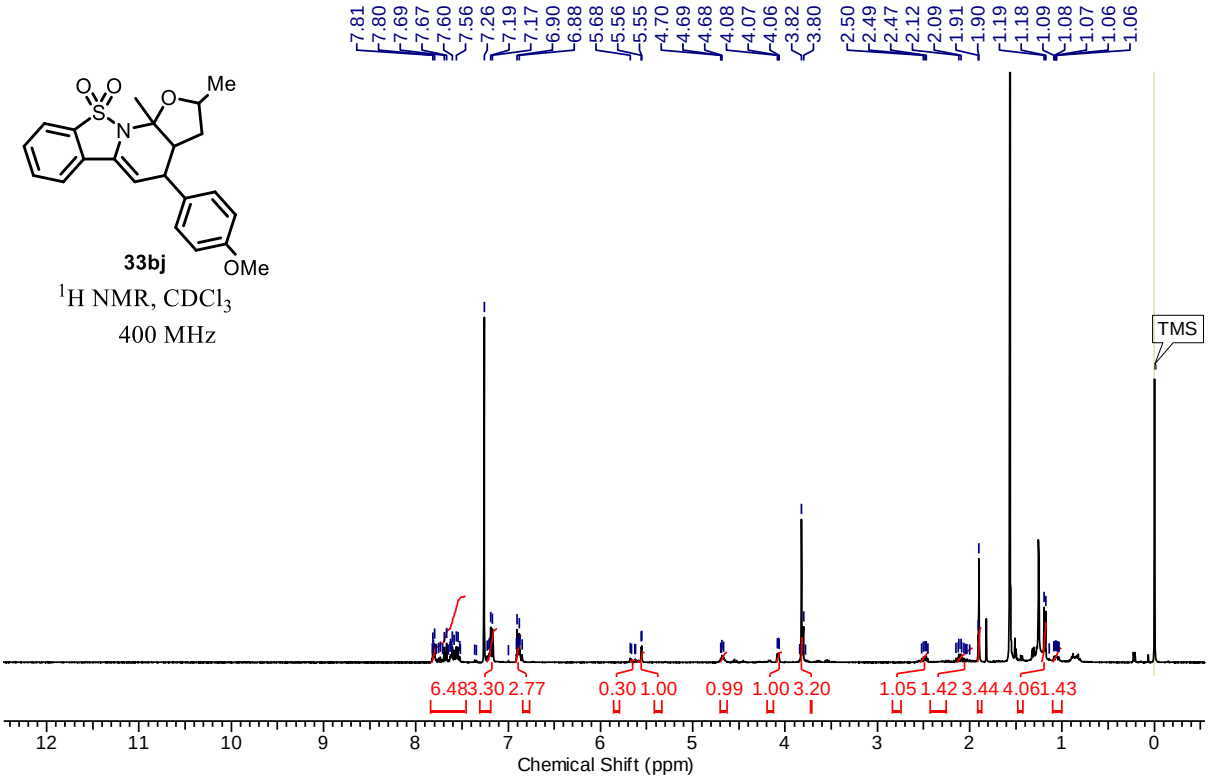


33ai

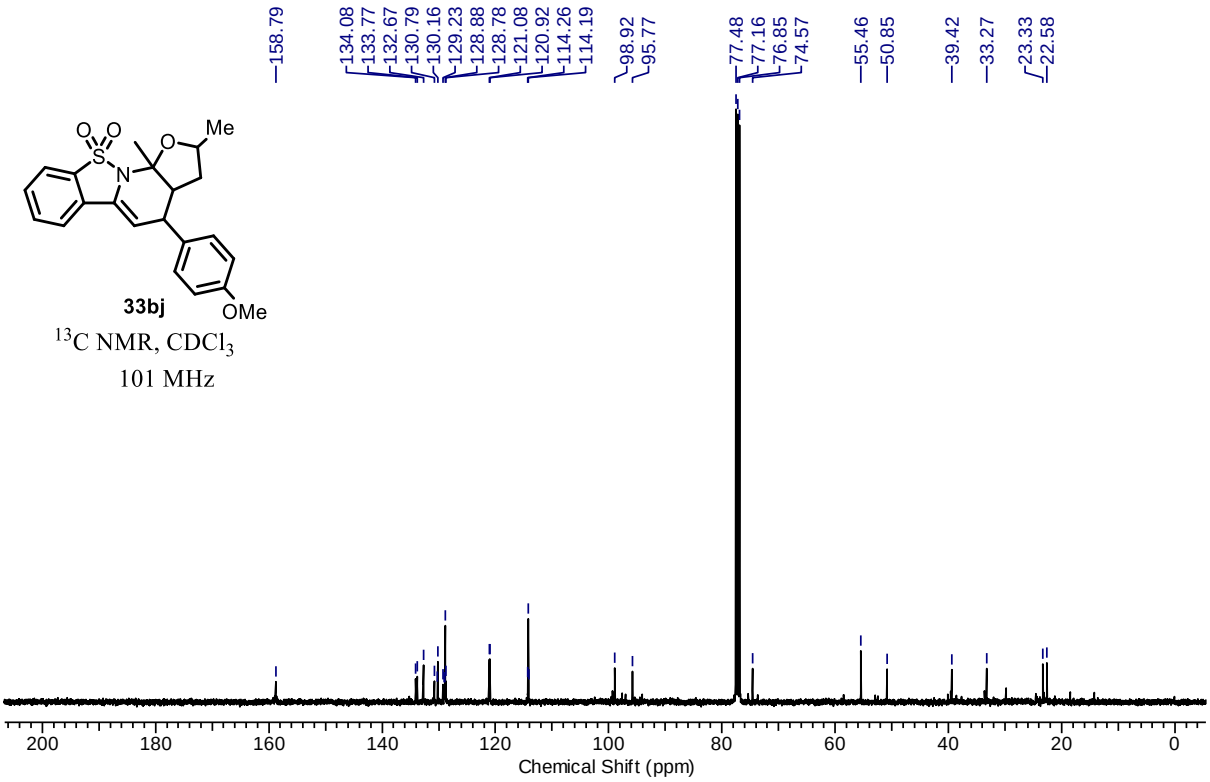
^{13}C NMR, $CDCl_3$

101 MHz

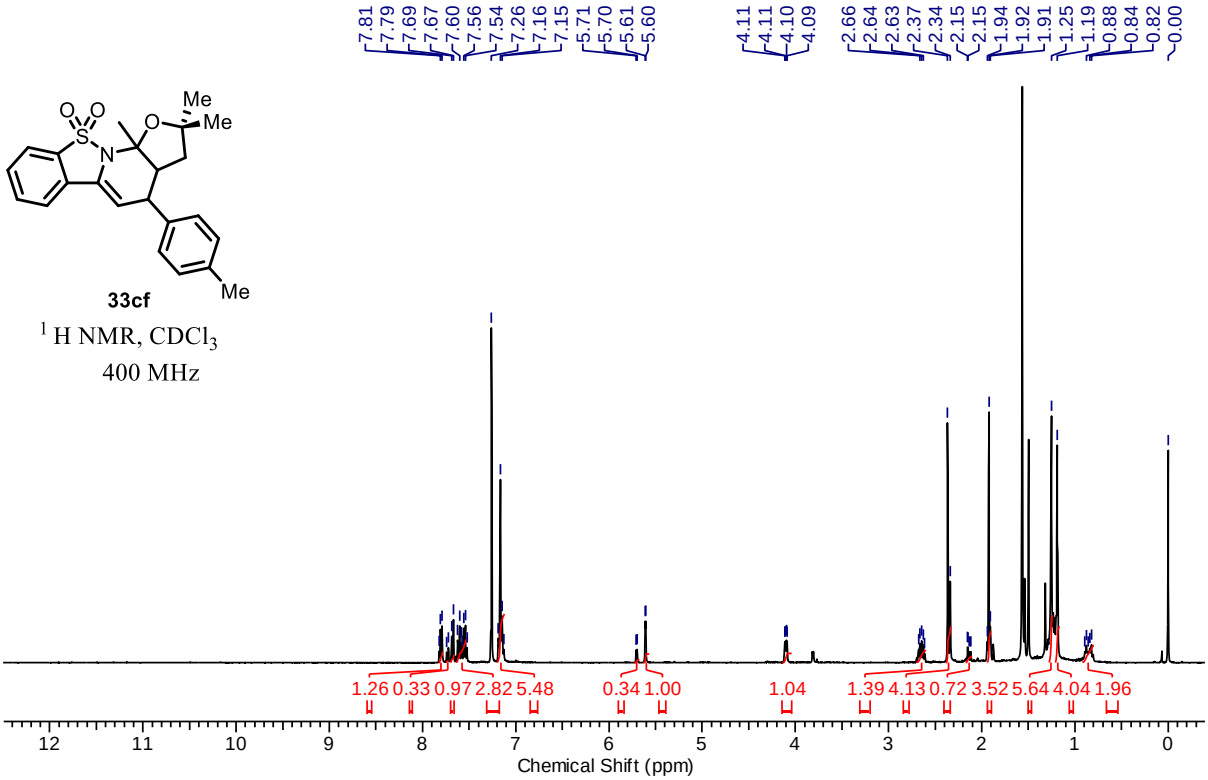
^{1}H NMR spectrum of compound 33bj



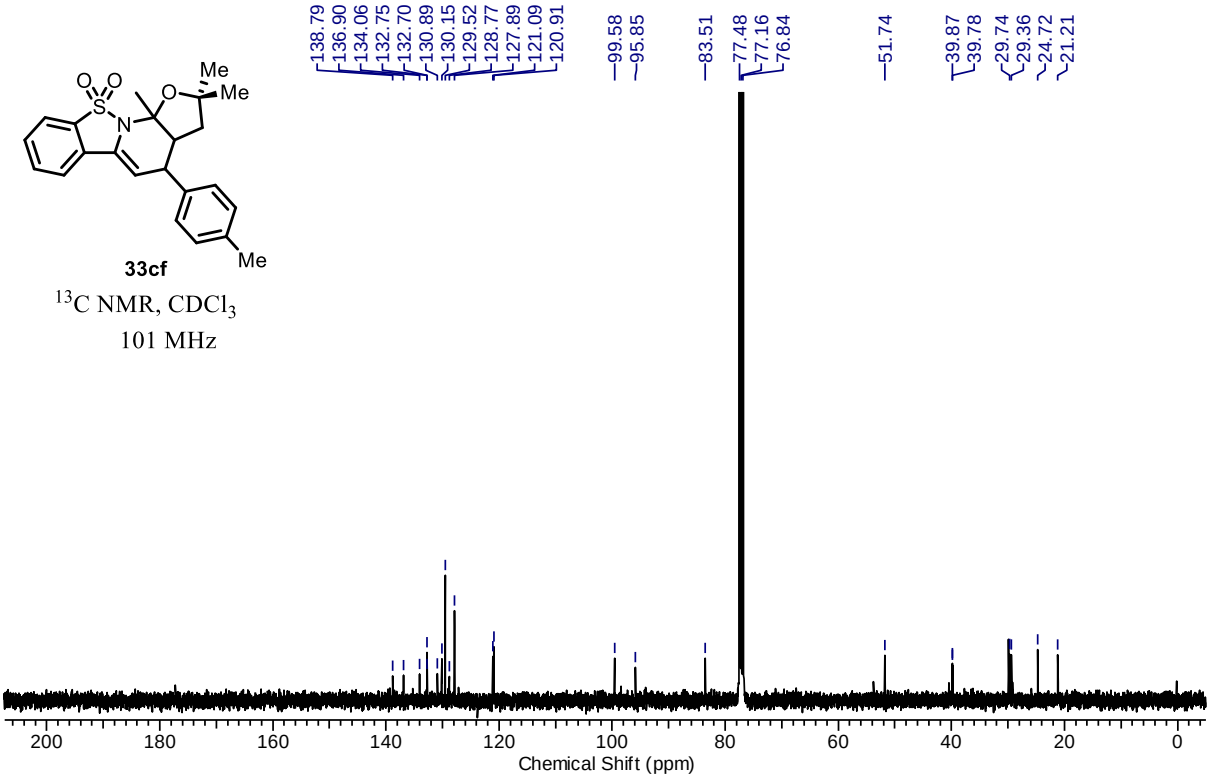
^{13}C NMR spectrum of compound 33bj



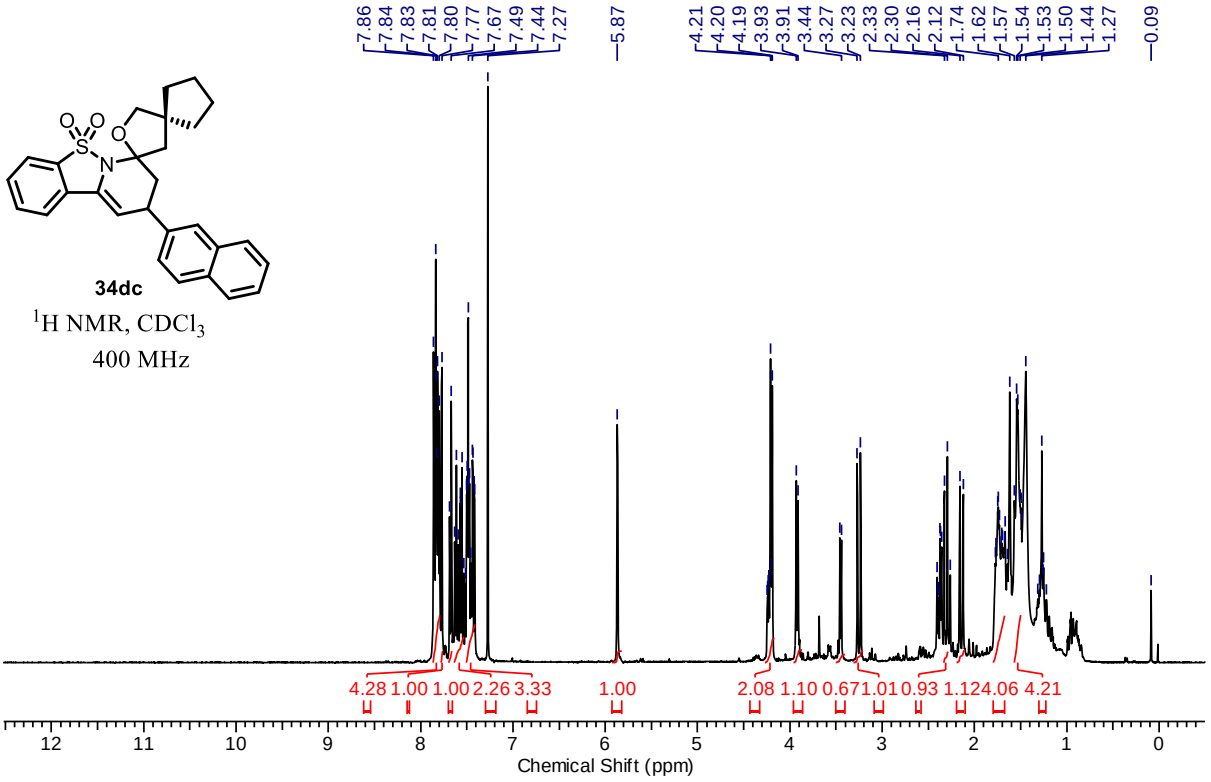
^{1}H NMR spectrum of compound 33cf



^{13}C NMR spectrum of compound 33cf



^{1}H NMR spectrum of compound 34dc

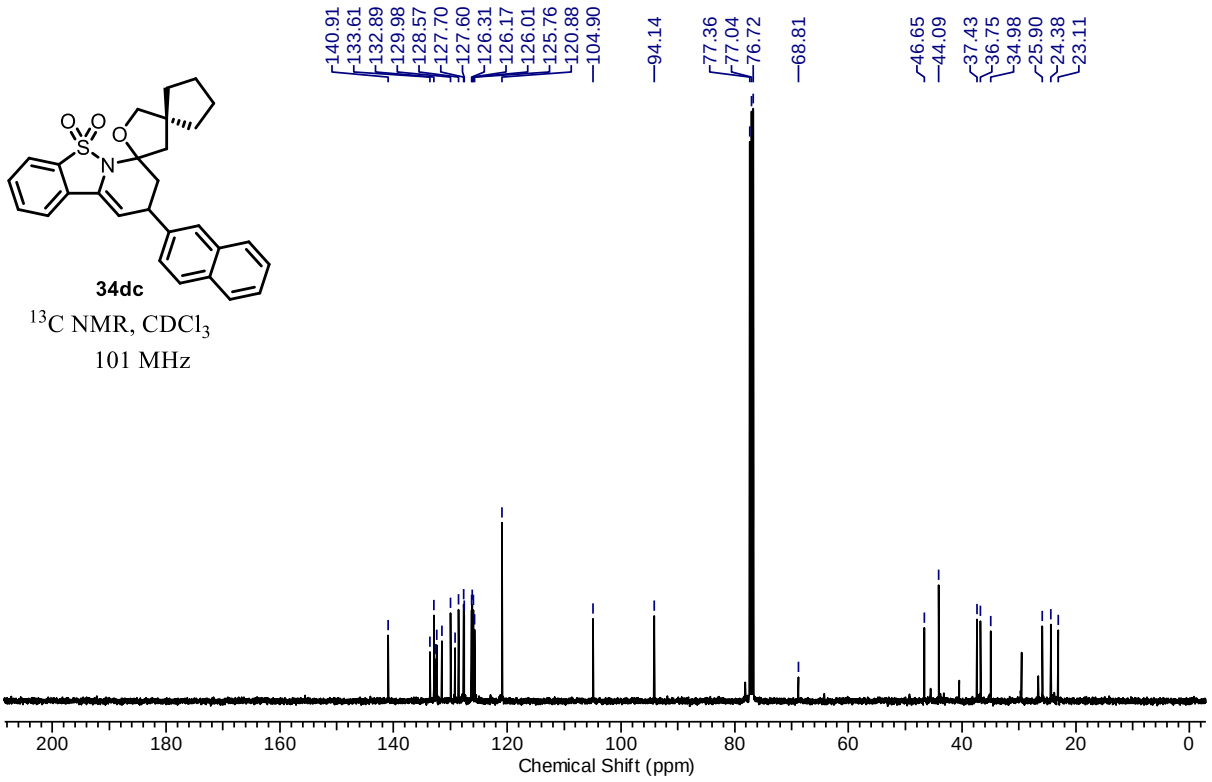


34dc

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 43dc

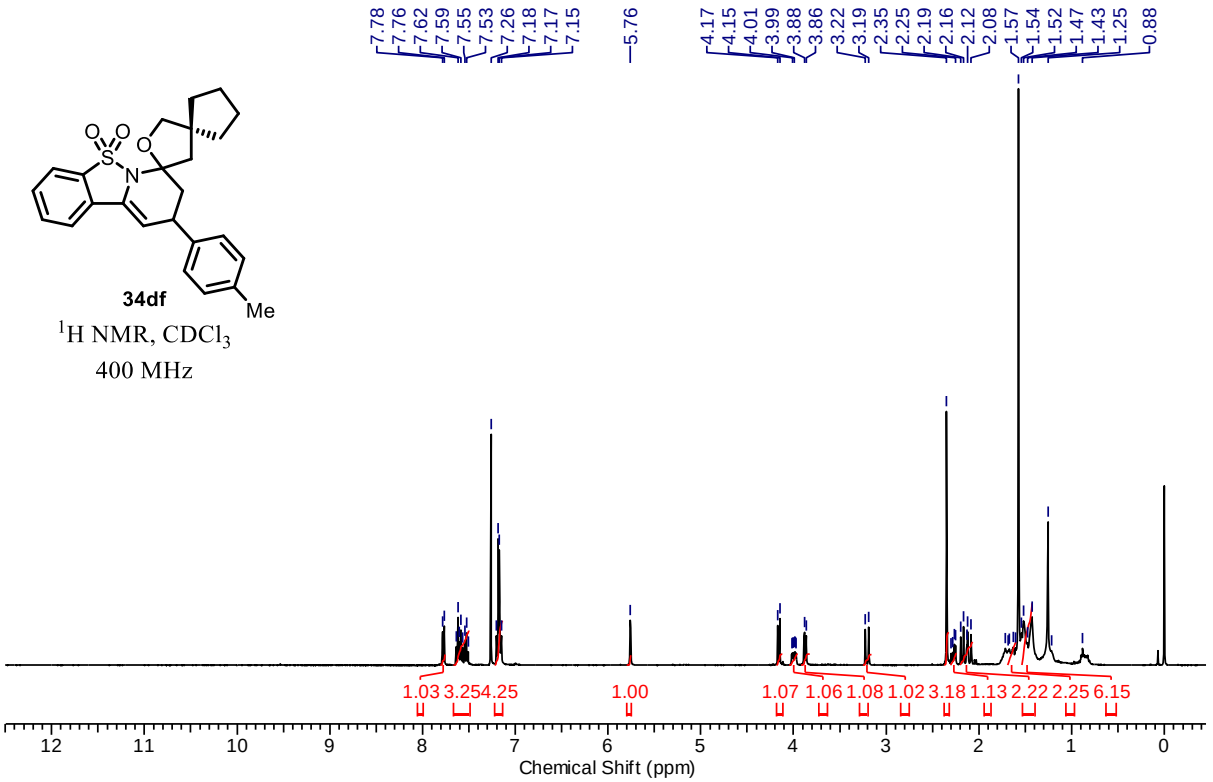


34dc

^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 34df



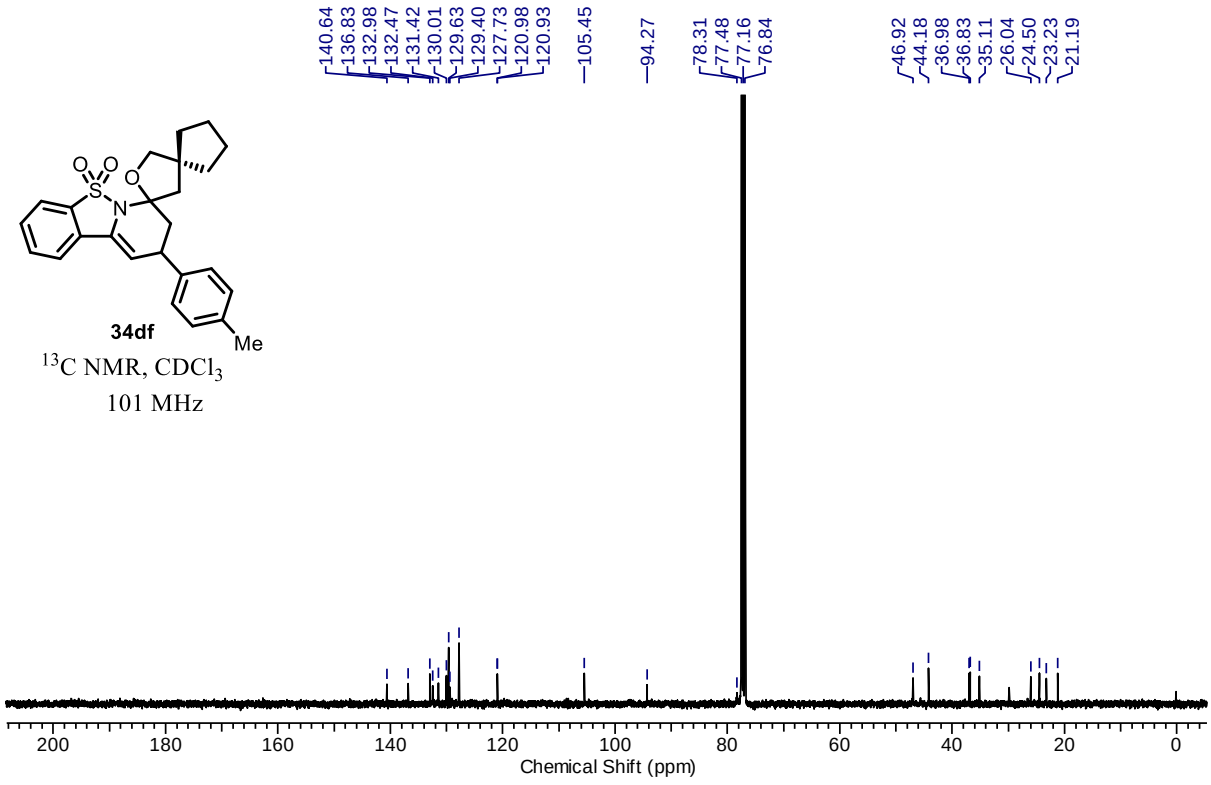
34df

Me

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 34df



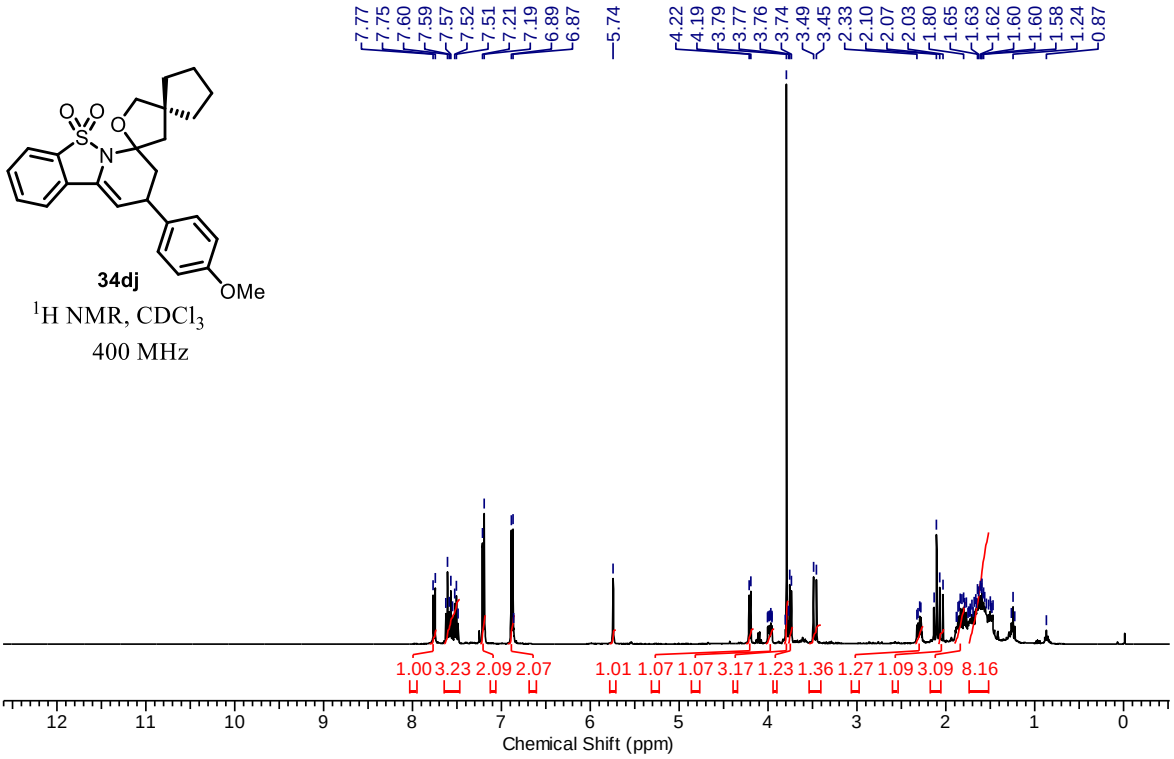
34df

Me

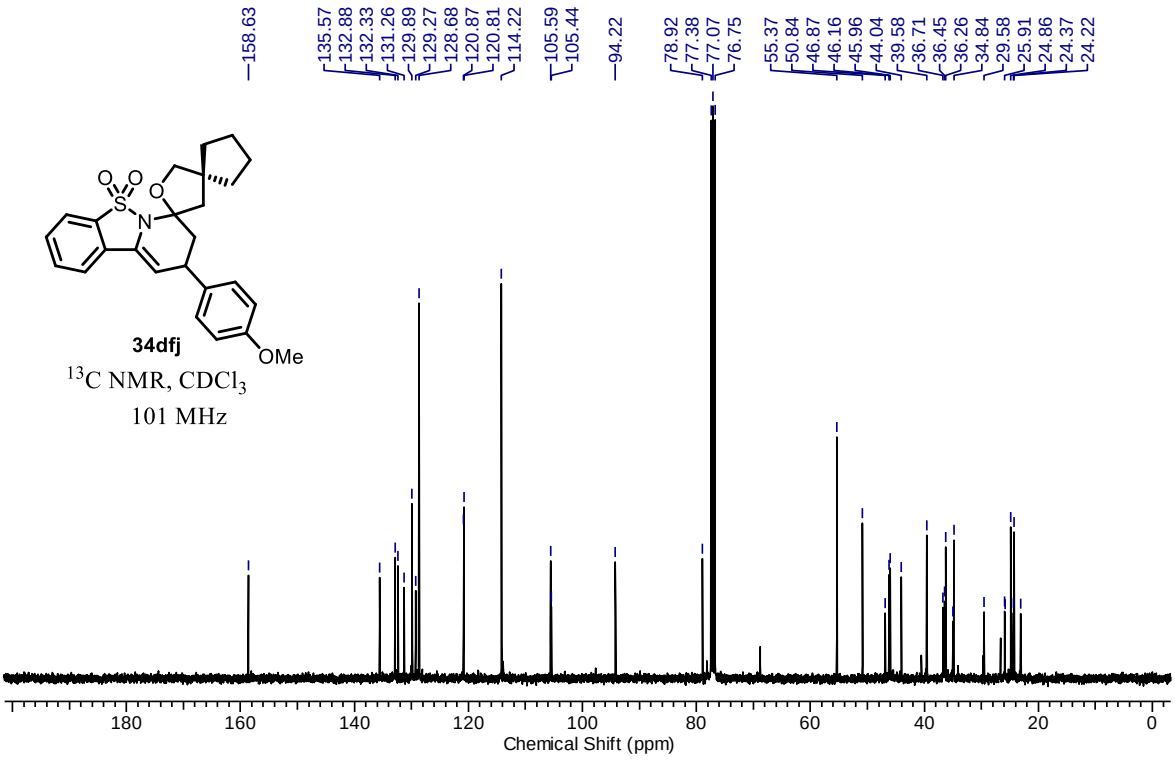
^{13}C NMR, $CDCl_3$

101 MHz

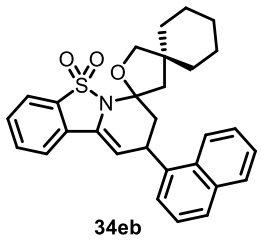
^{1}H NMR spectrum of compound 34dj



^{13}C NMR spectrum of compound 34dj



^{1}H NMR spectrum of compound 34eb

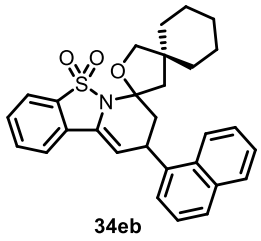


34eb

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 34eb

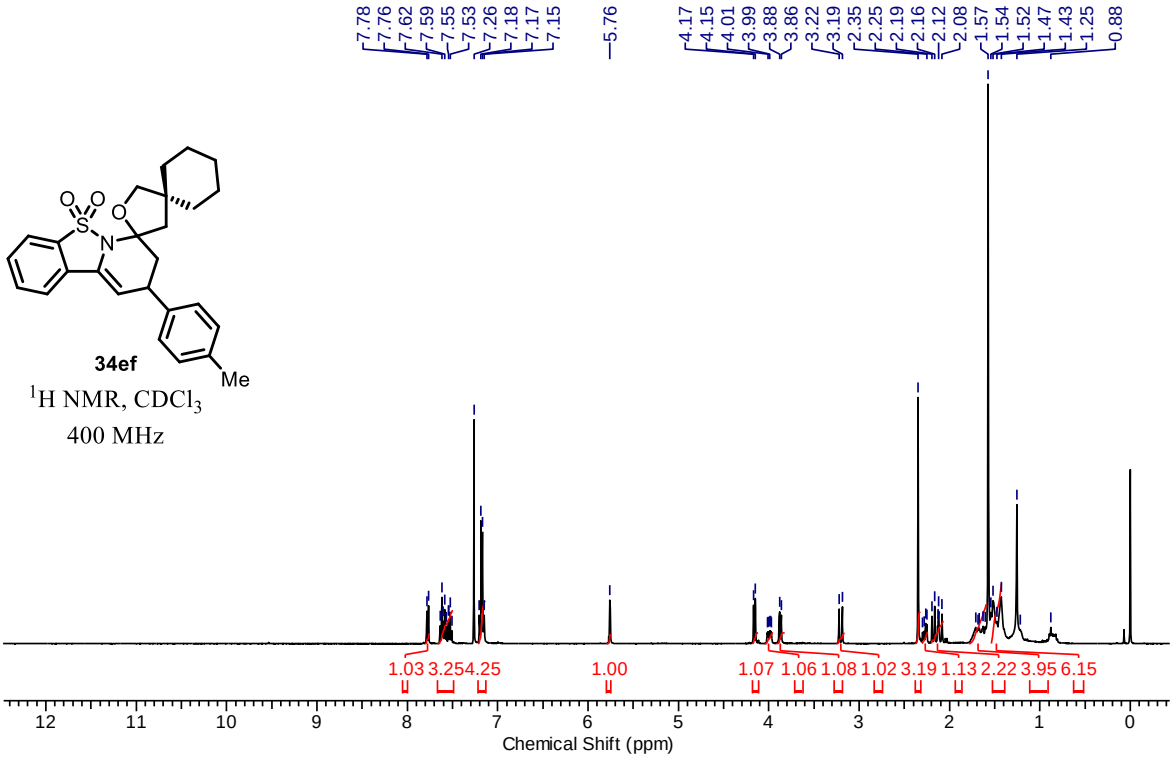


34eb

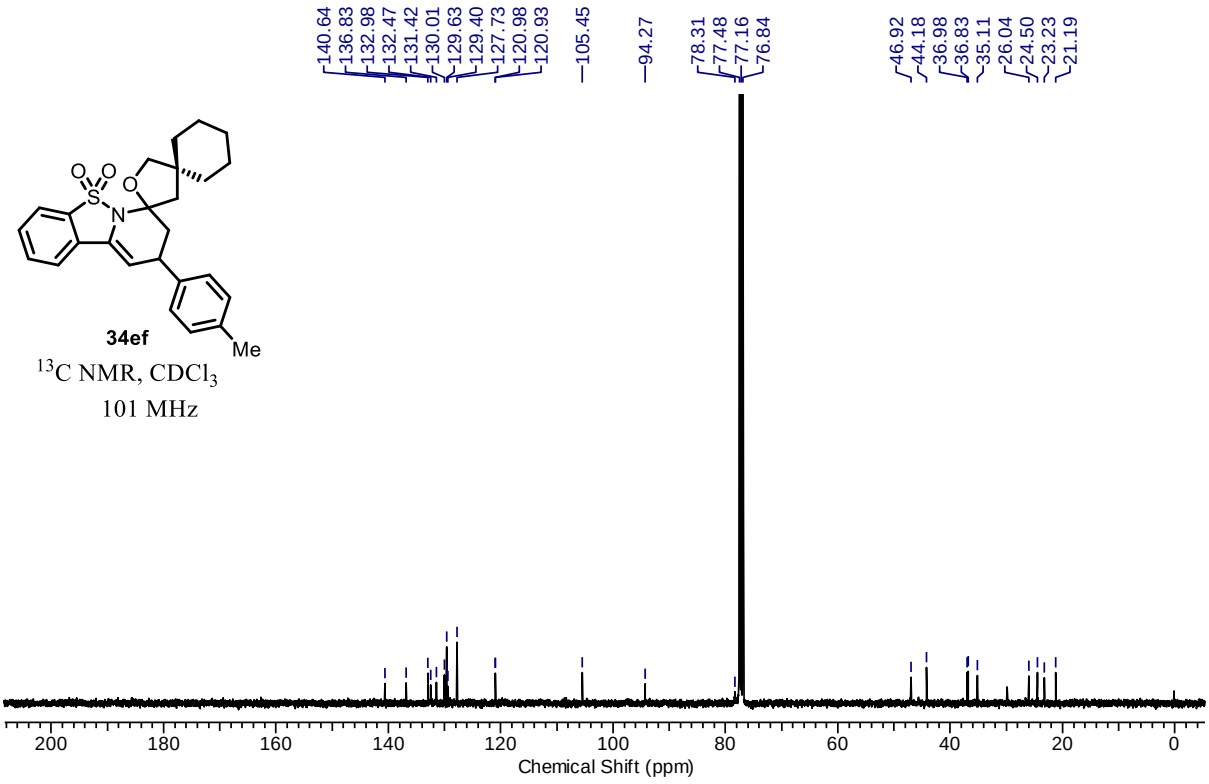
^{13}C NMR, $CDCl_3$

101 MHz

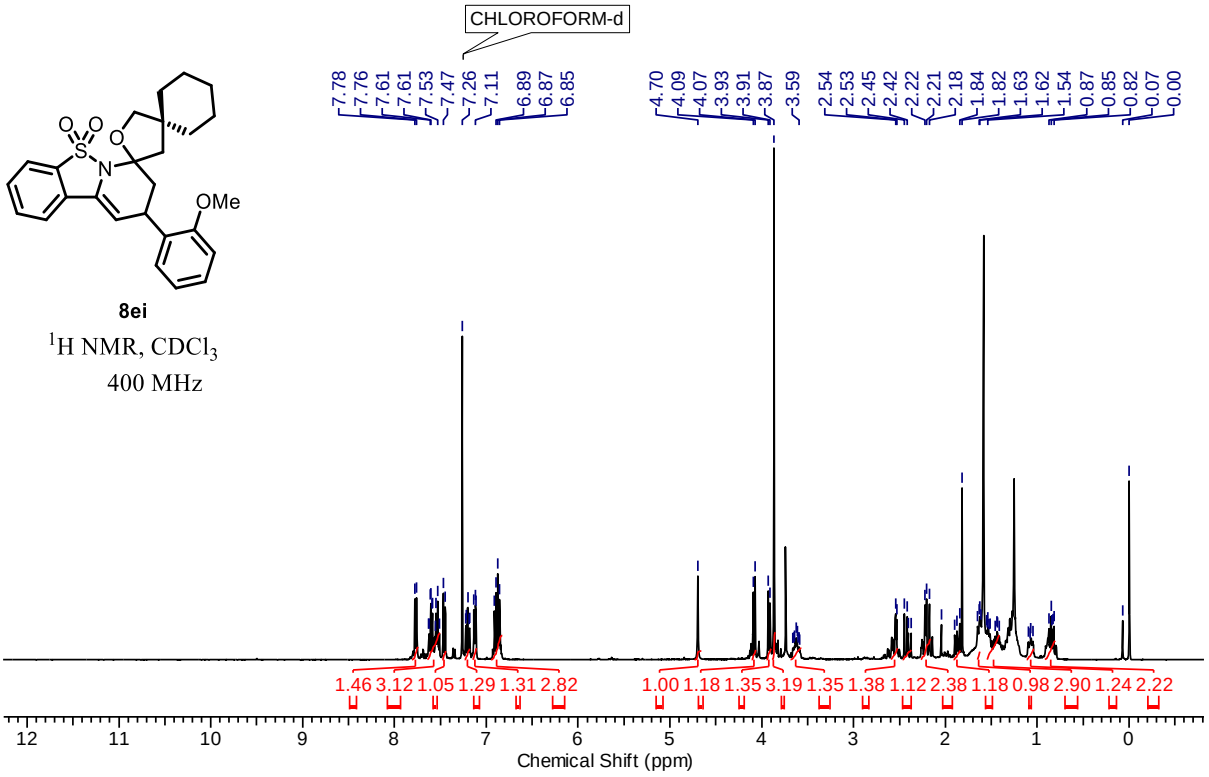
^{1}H NMR spectrum of compound 34ef



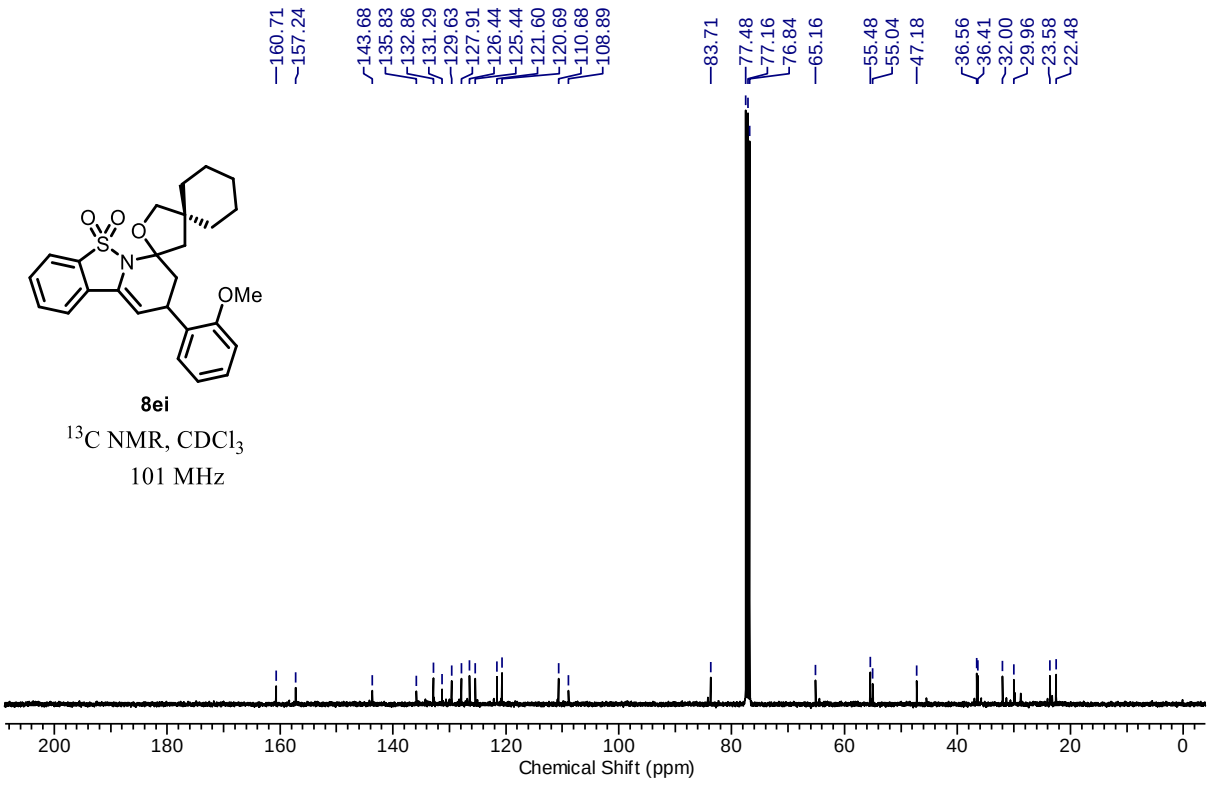
^{13}C NMR spectrum of compound 34df



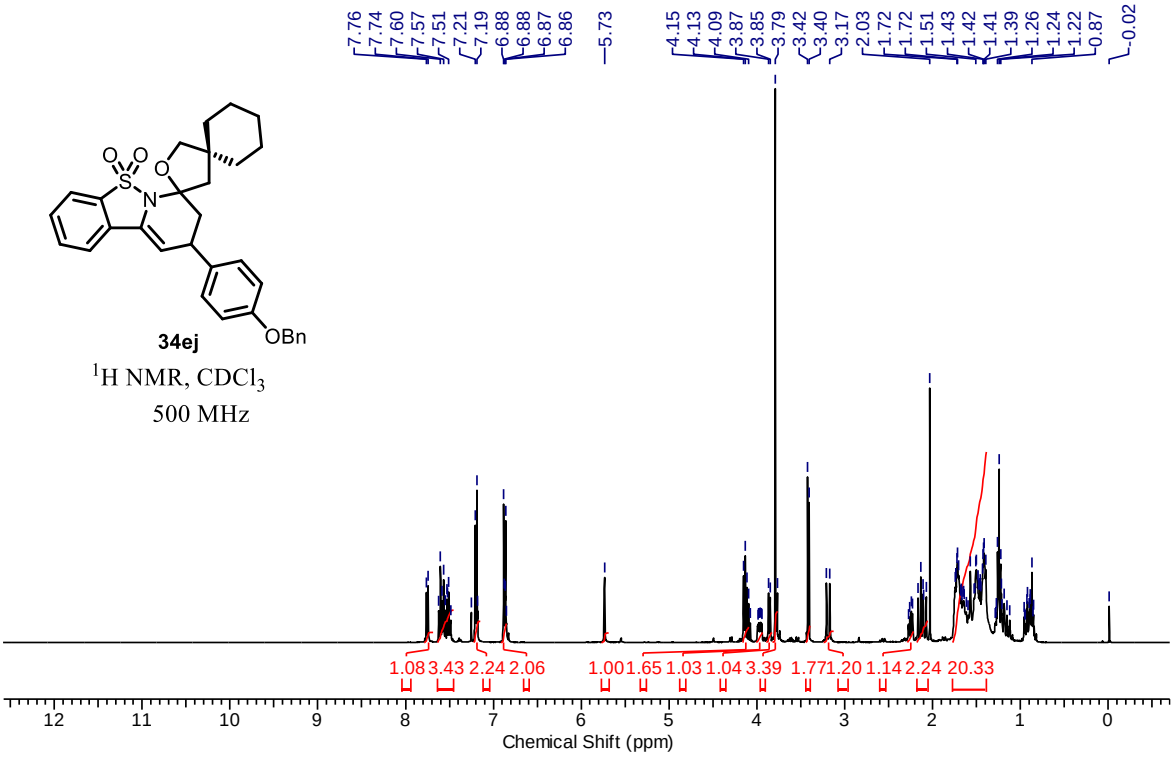
^{1}H NMR spectrum of compound 34ei



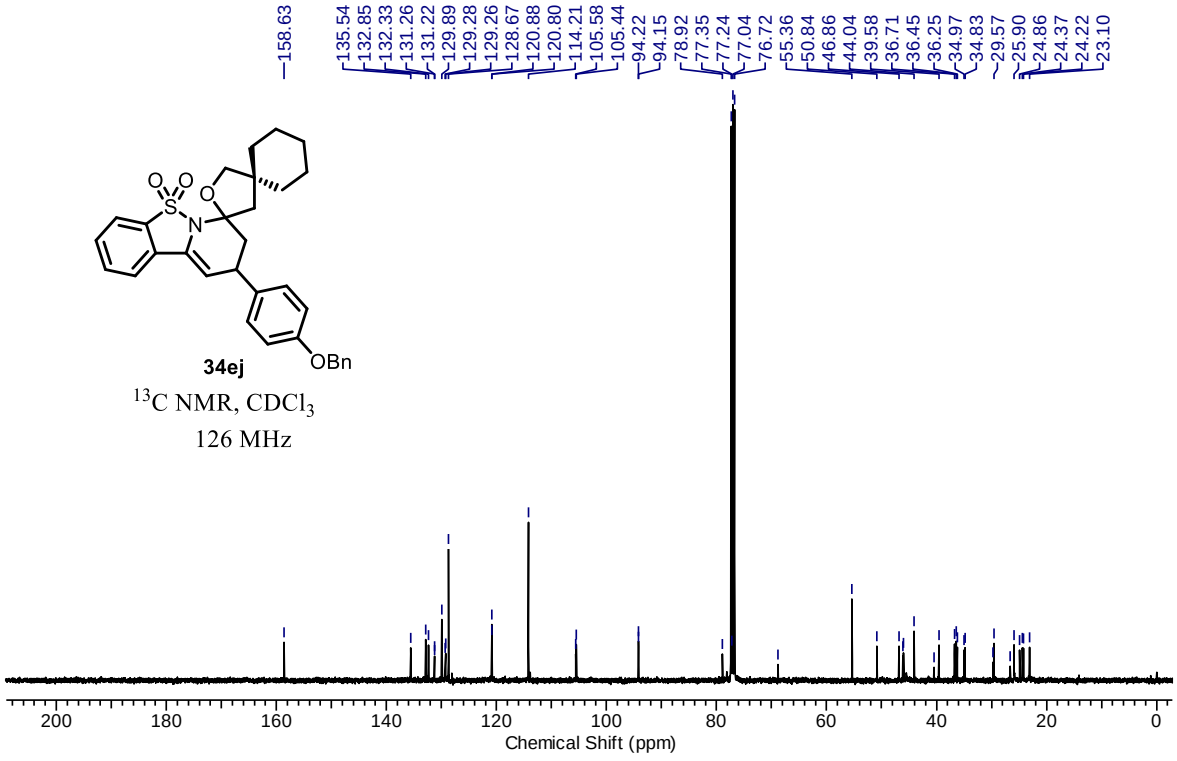
^{13}C NMR spectrum of compound 55aa



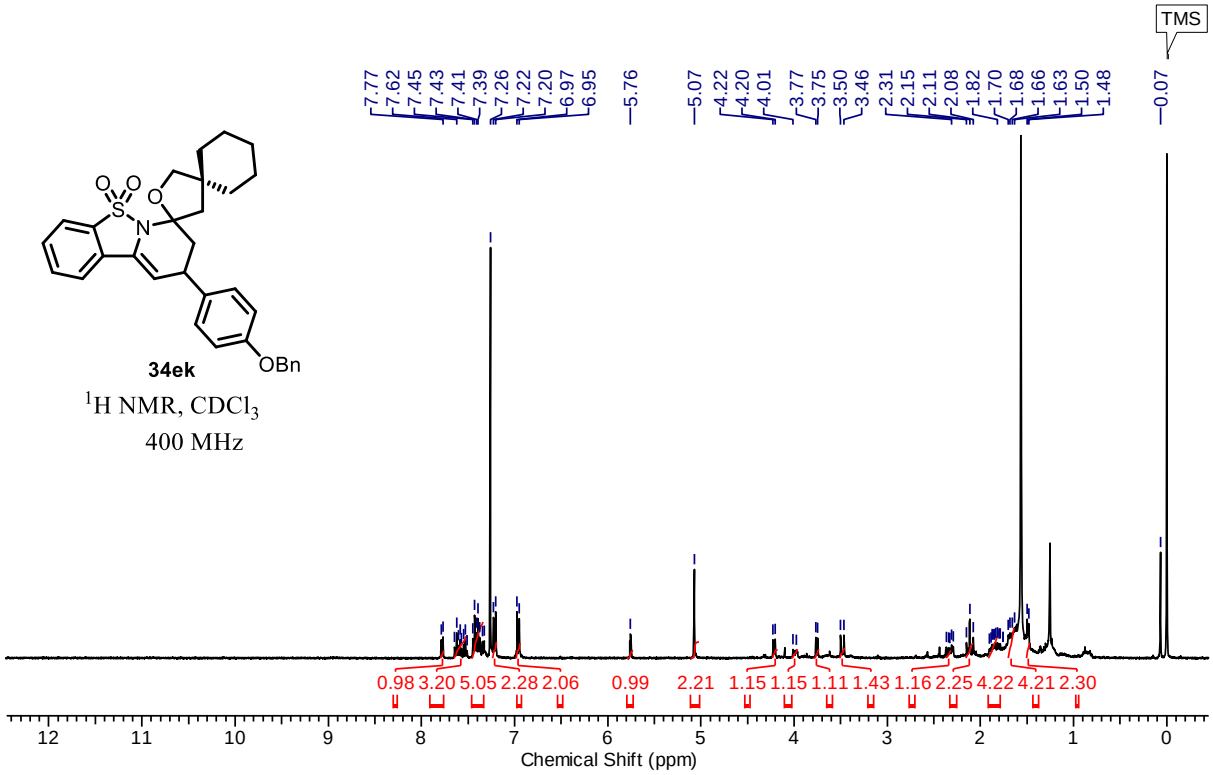
^{1}H NMR spectrum of compound 34ej



^{13}C NMR spectrum of compound 34ej



^{1}H NMR spectrum of compound 43ek

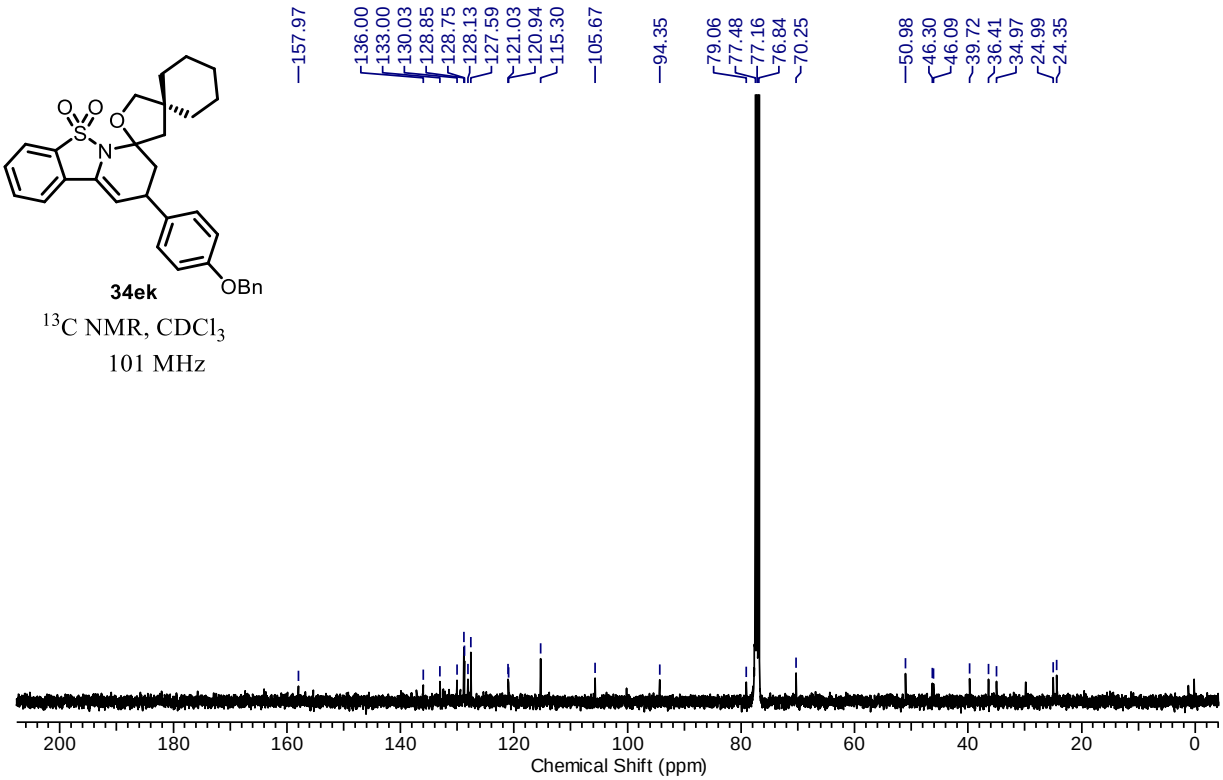


34ek

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 34ek

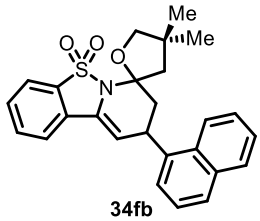


34ek

^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 34fb

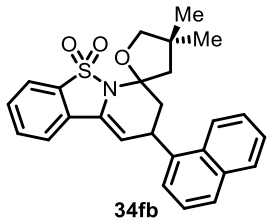


34fb

^{1}H NMR, CDCl3

400 MHz

^{13}C NMR spectrum of compound 34fb

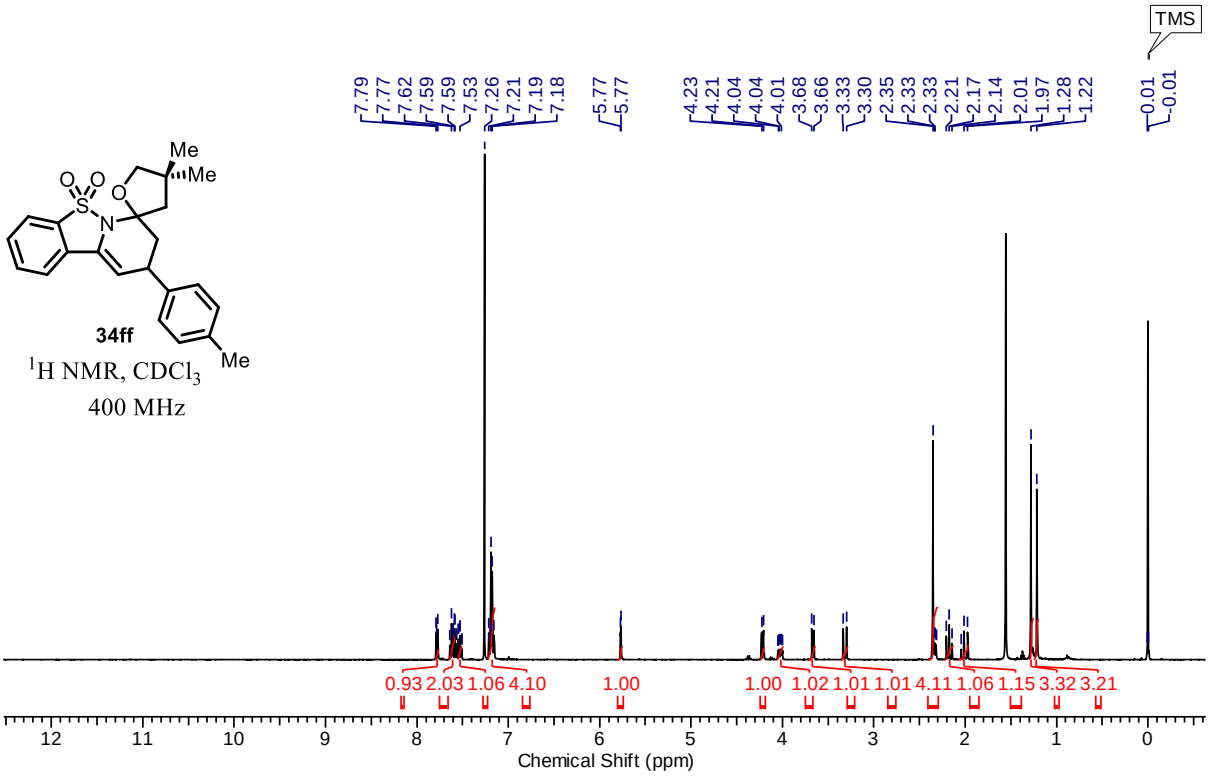


34fb

^{13}C NMR, CDCl3

126 MHz

^{1}H NMR spectrum of compound 34ff

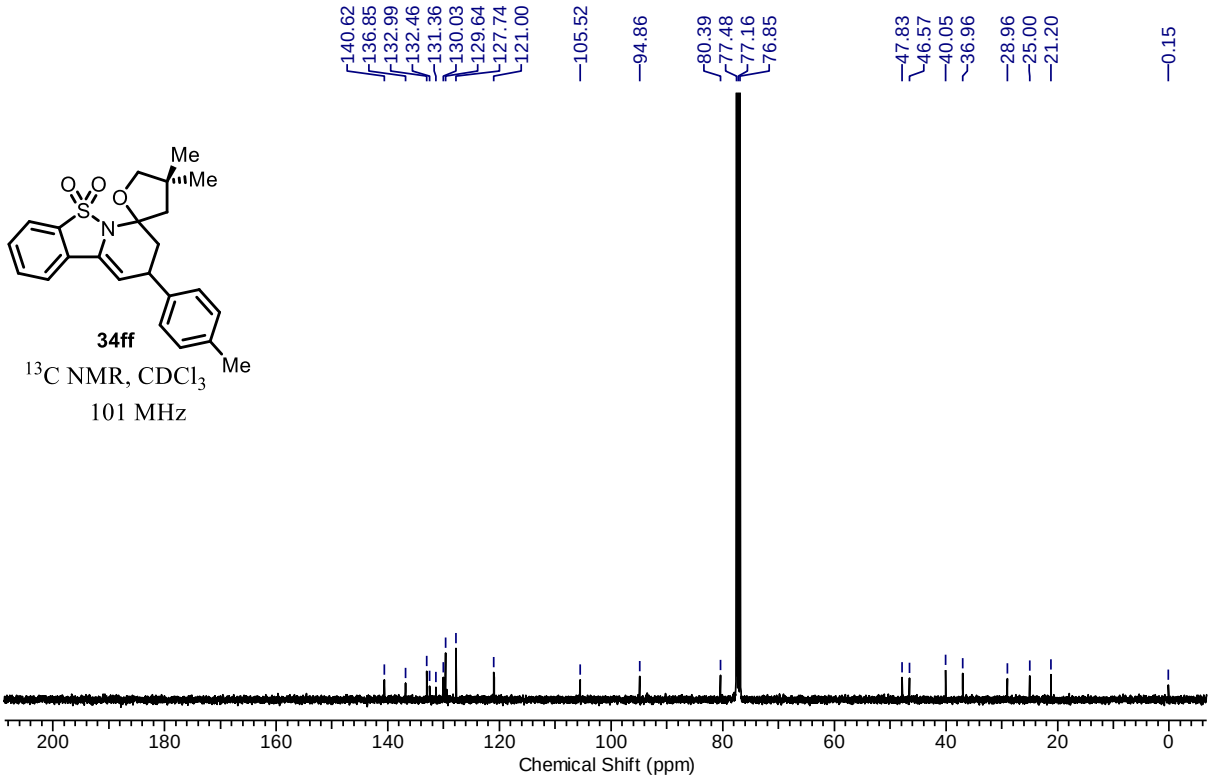


34ff

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 34ff

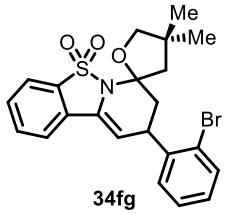


34ff

^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 34fg

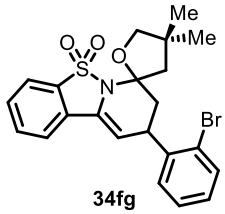


34fg

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 34fg

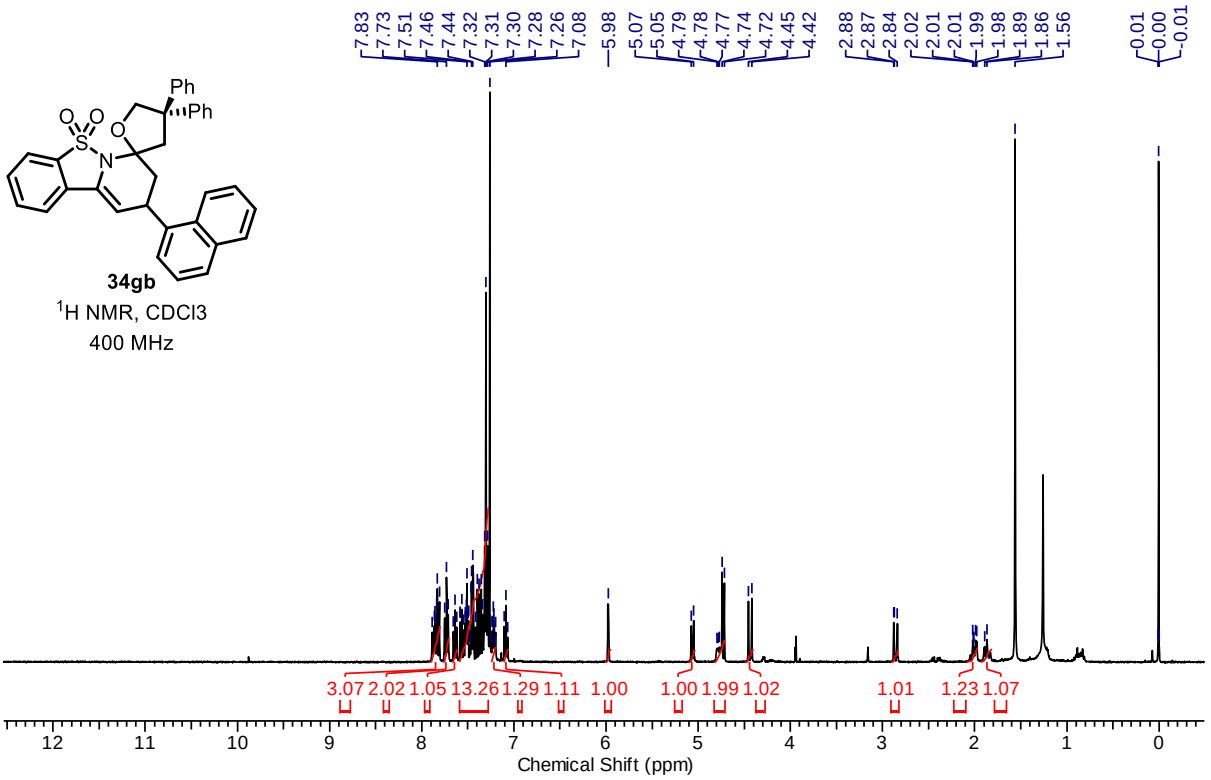


34fg

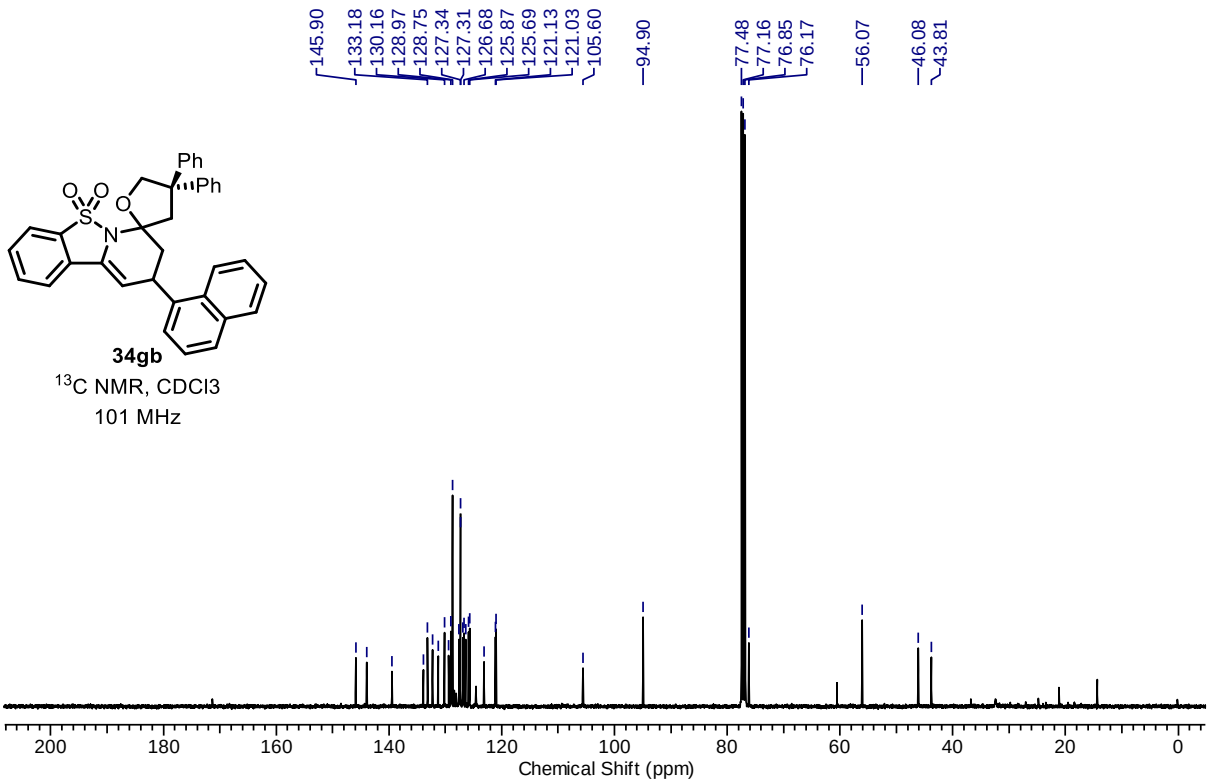
^{13}C NMR, $CDCl_3$

101 MHz

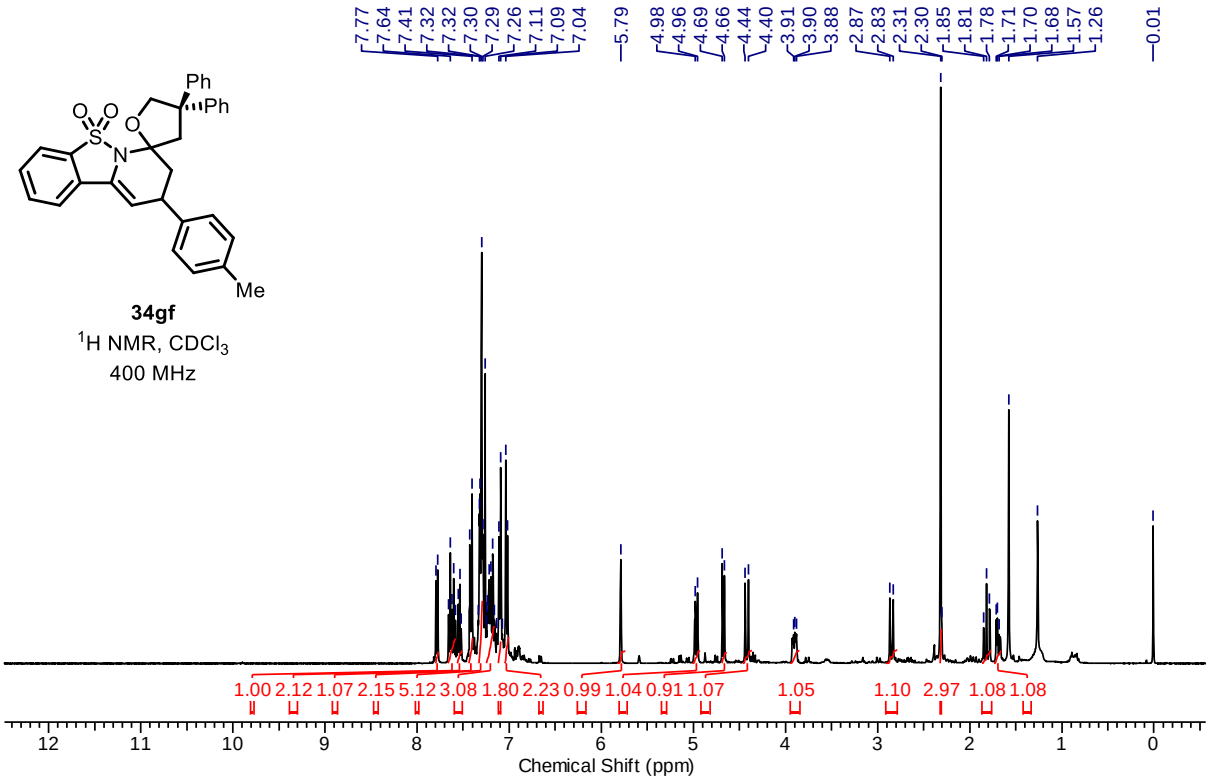
^{1}H NMR spectrum of compound 34gb



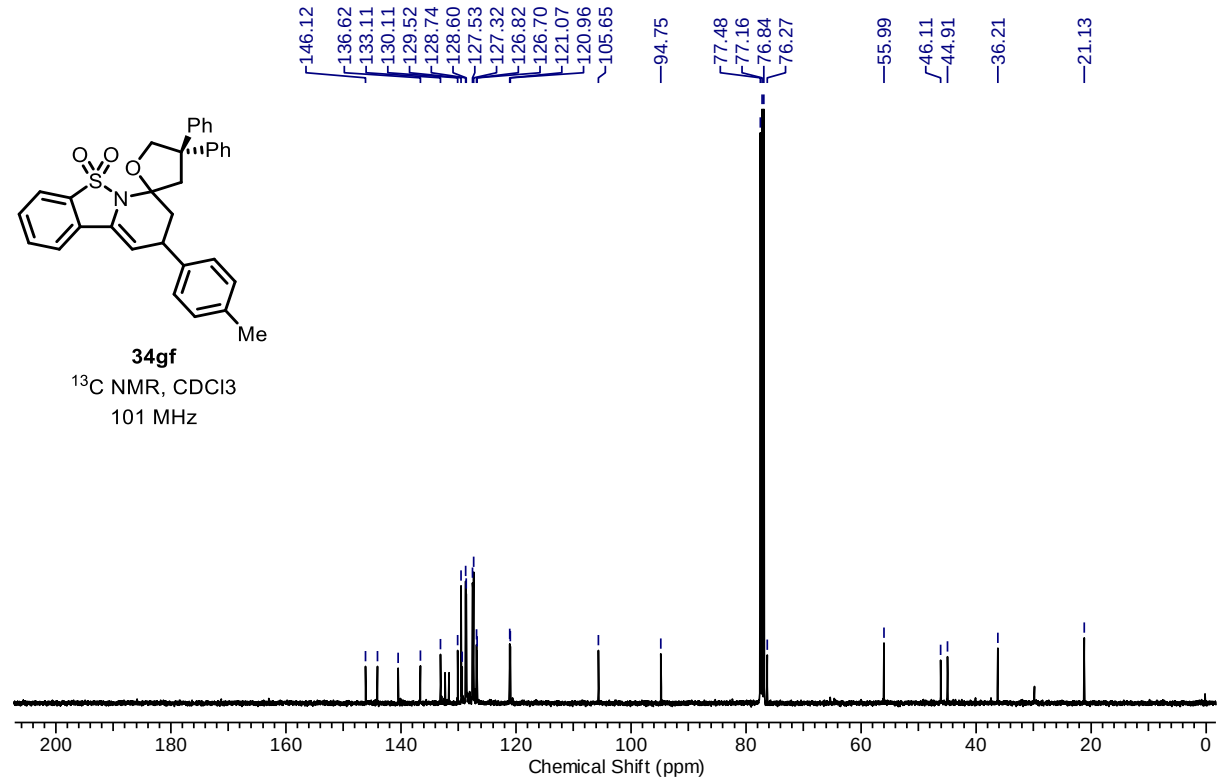
^{13}C NMR spectrum of compound 34gb



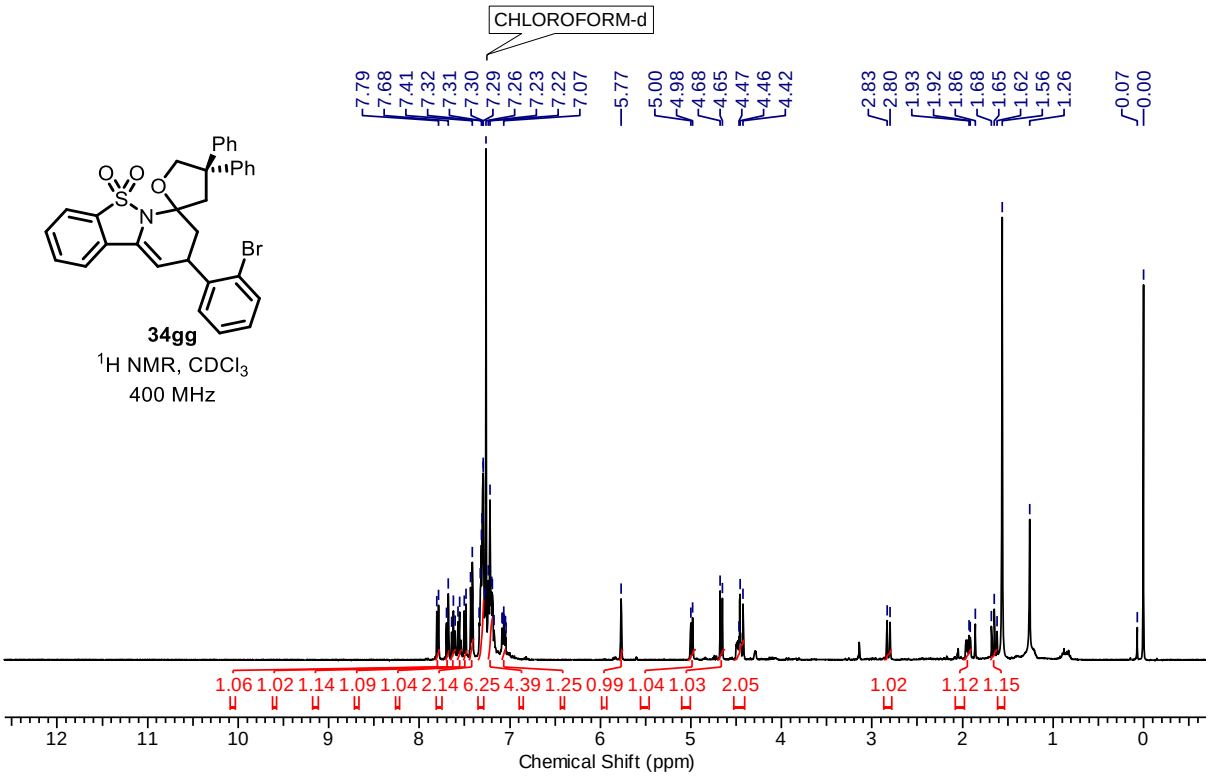
^{1}H NMR spectrum of compound 34gf



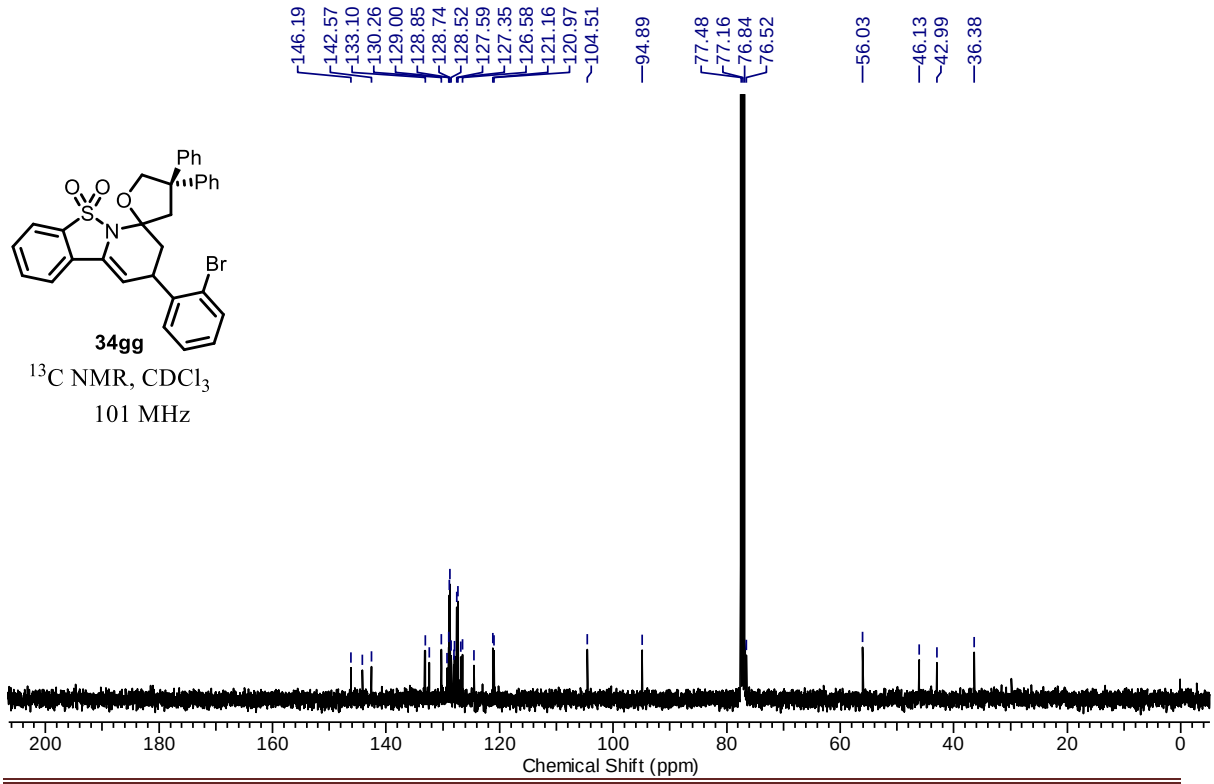
^{13}C NMR spectrum of compound 34gf



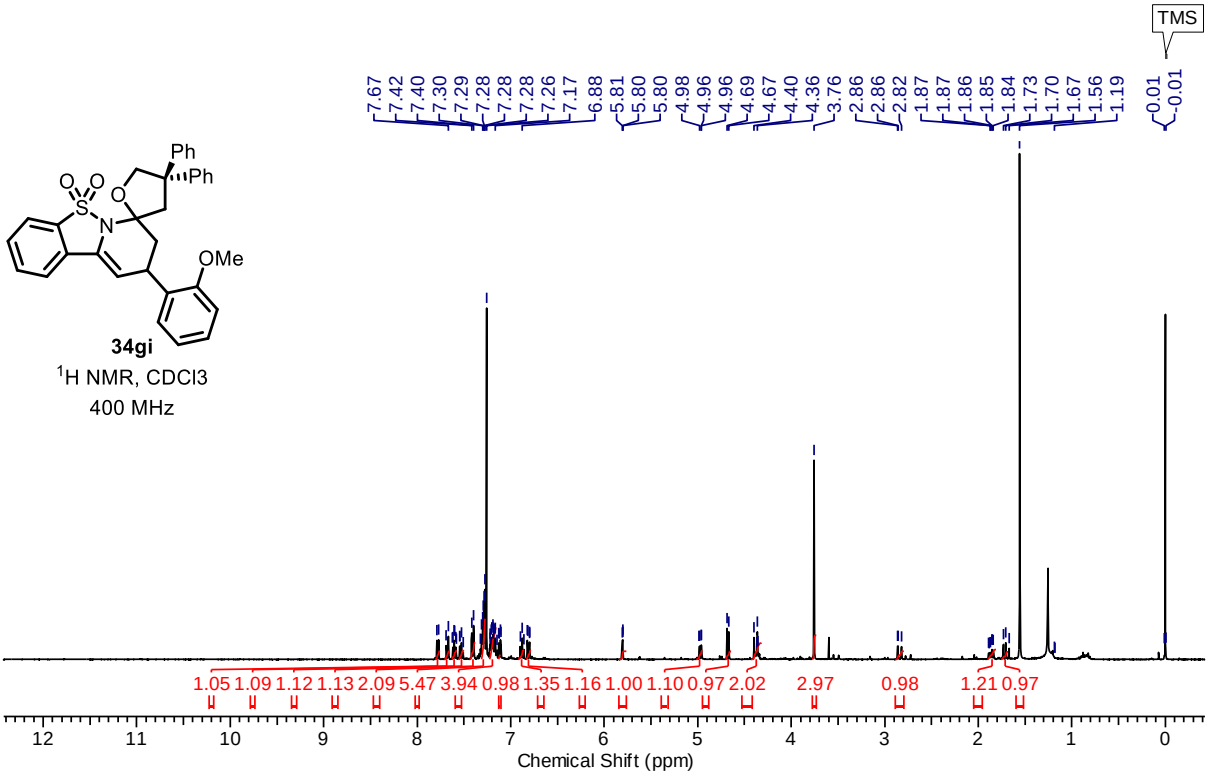
^{1}H NMR spectrum of compound 34gg



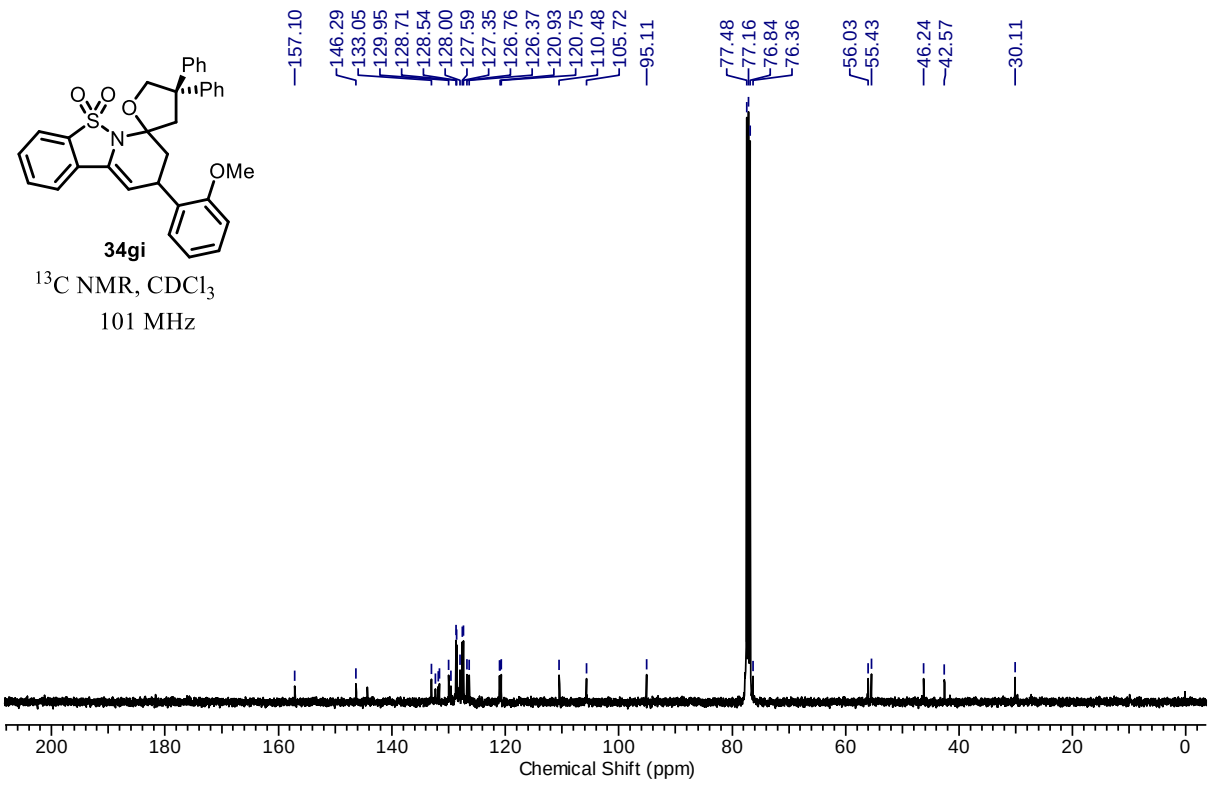
^{13}C NMR spectrum of compound 34gg



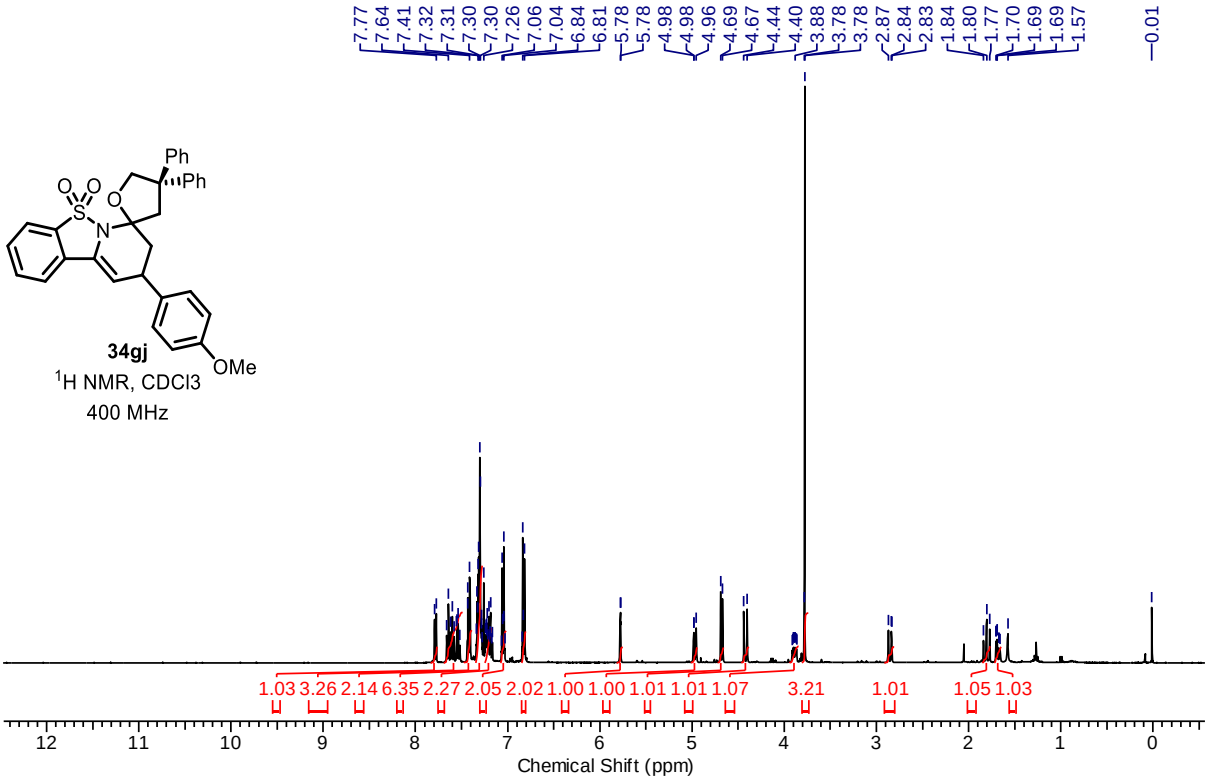
^{1}H NMR spectrum of compound 34gi



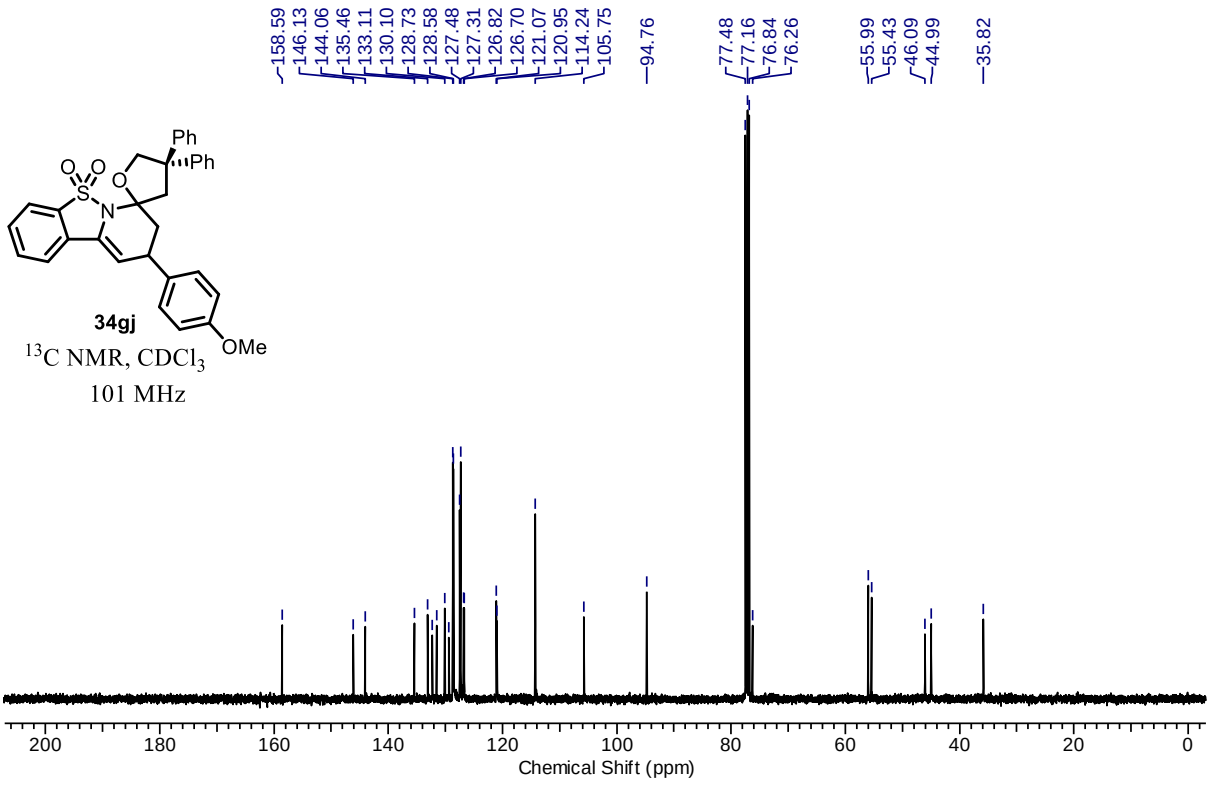
^{13}C NMR spectrum of compound 34gi



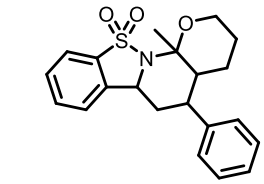
^{1}H NMR spectrum of compound 34gj



^{13}C NMR spectrum of compound 34gj



^{1}H NMR spectrum of compound 35aa

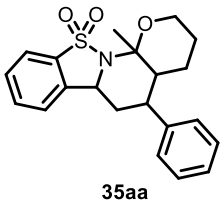


35aa

^{1}H NMR, $CDCl_3$

500 MHz

^{13}C NMR spectrum of compound 35aa

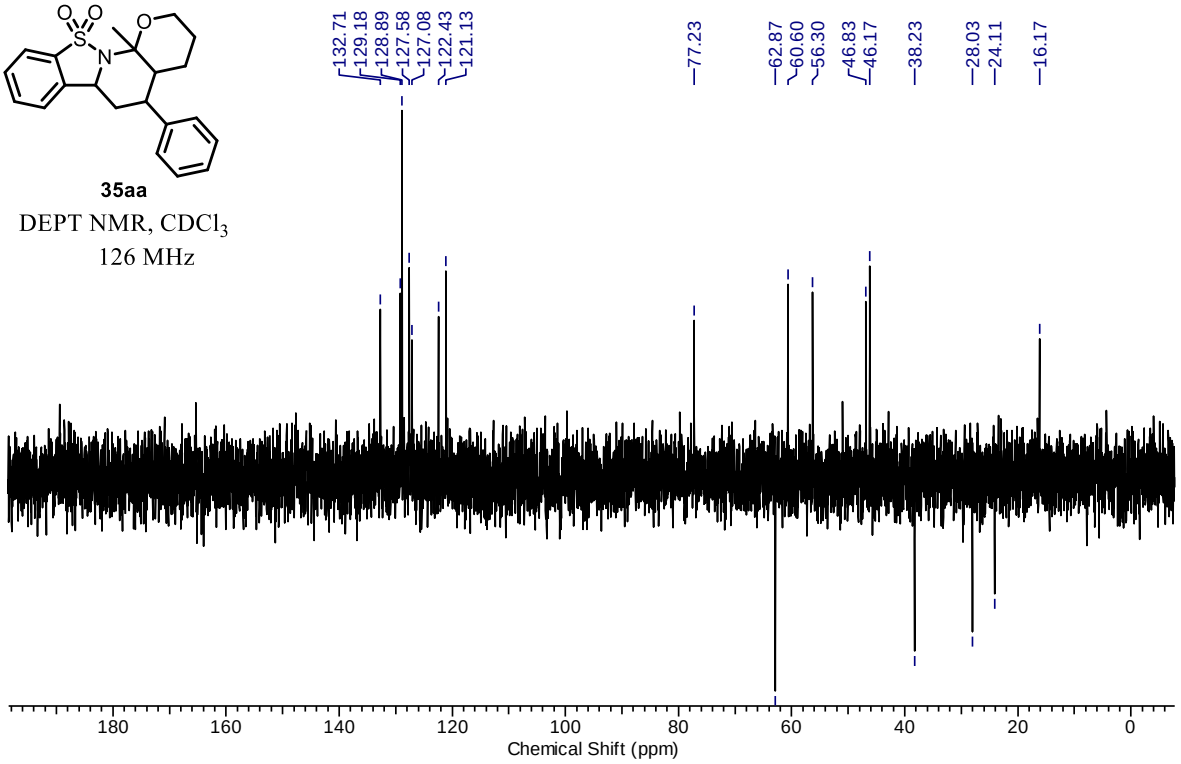


35aa

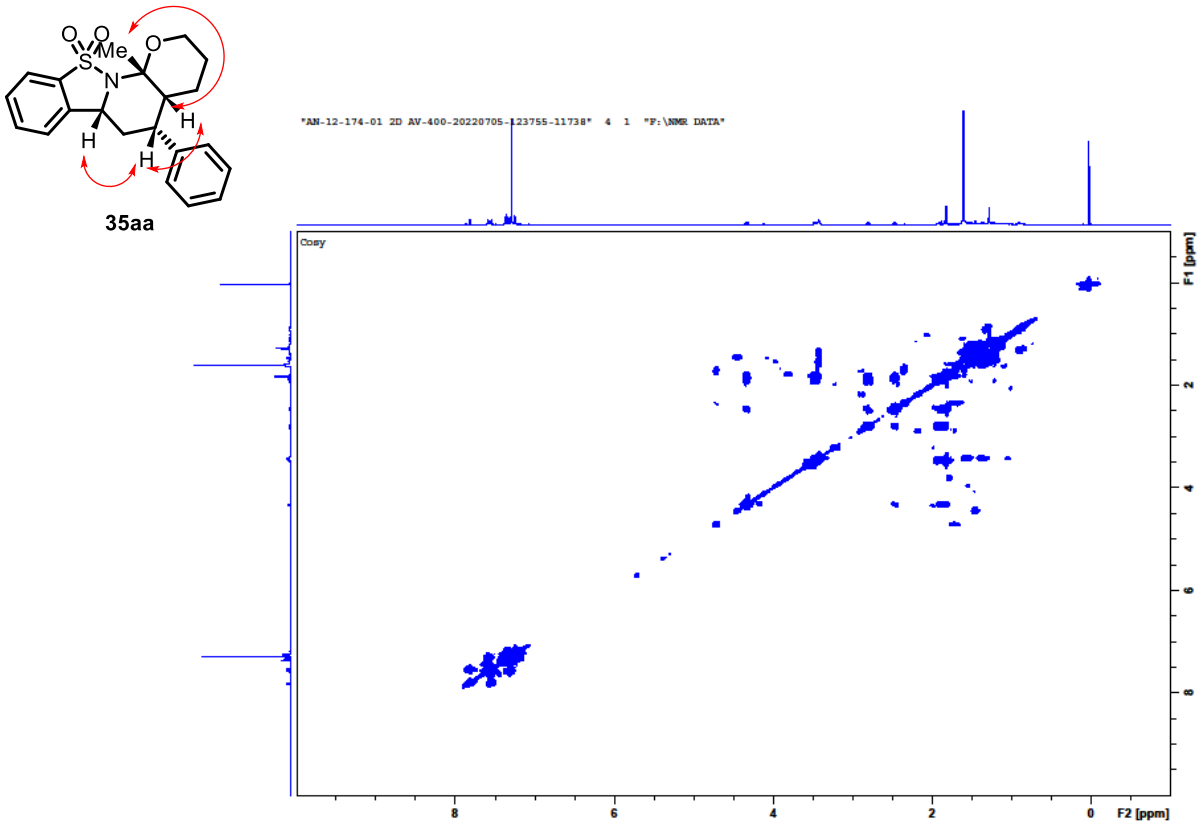
^{13}C NMR, $CDCl_3$

126 MHz

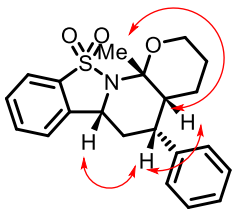
DEPT NMR spectrum of compound 35aa



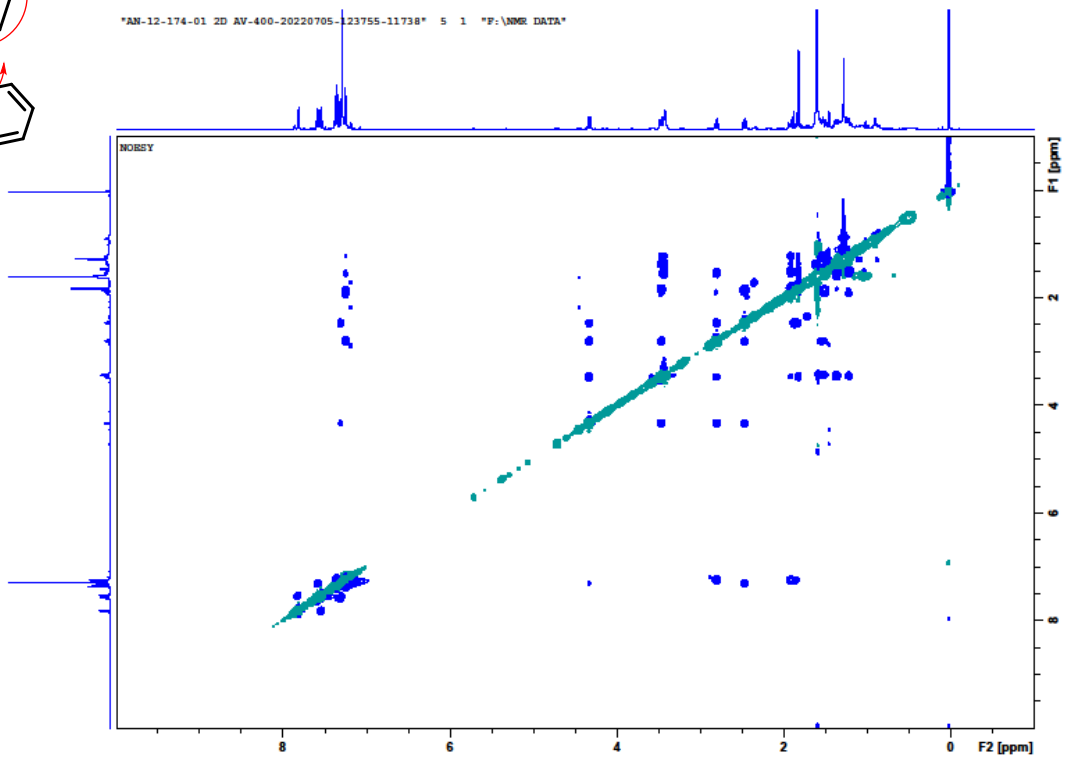
COSY NMR spectrum of compound 35aa



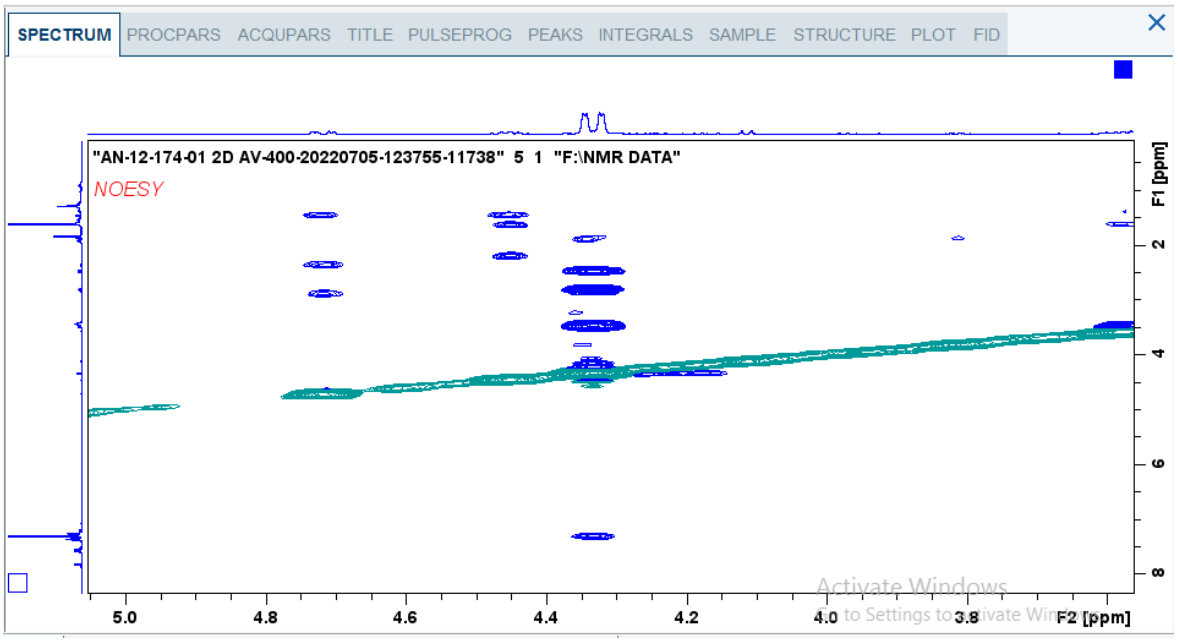
NOESY NMR spectrum of compound 35aa



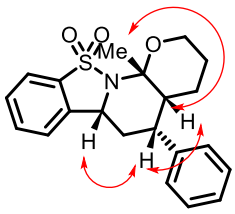
35aa



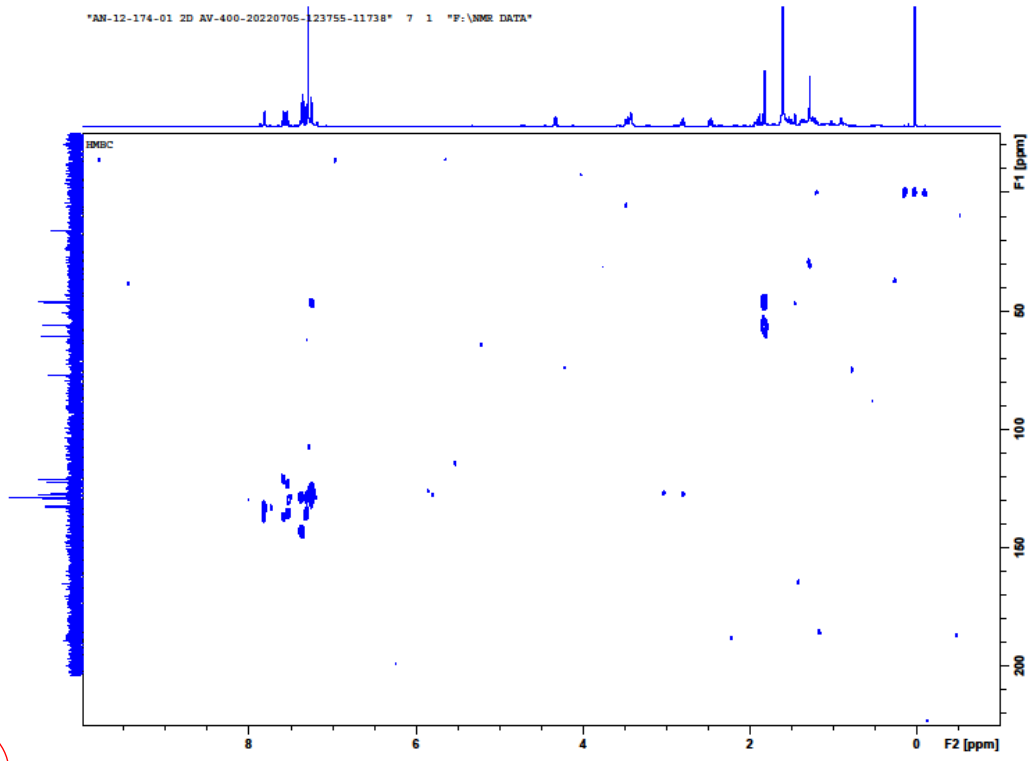
ZOOM NOESY NMR spectrum of compound 35aa



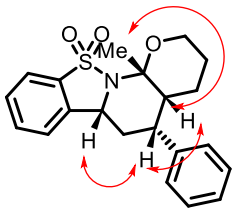
HMBC NMR spectrum of compound 35aa



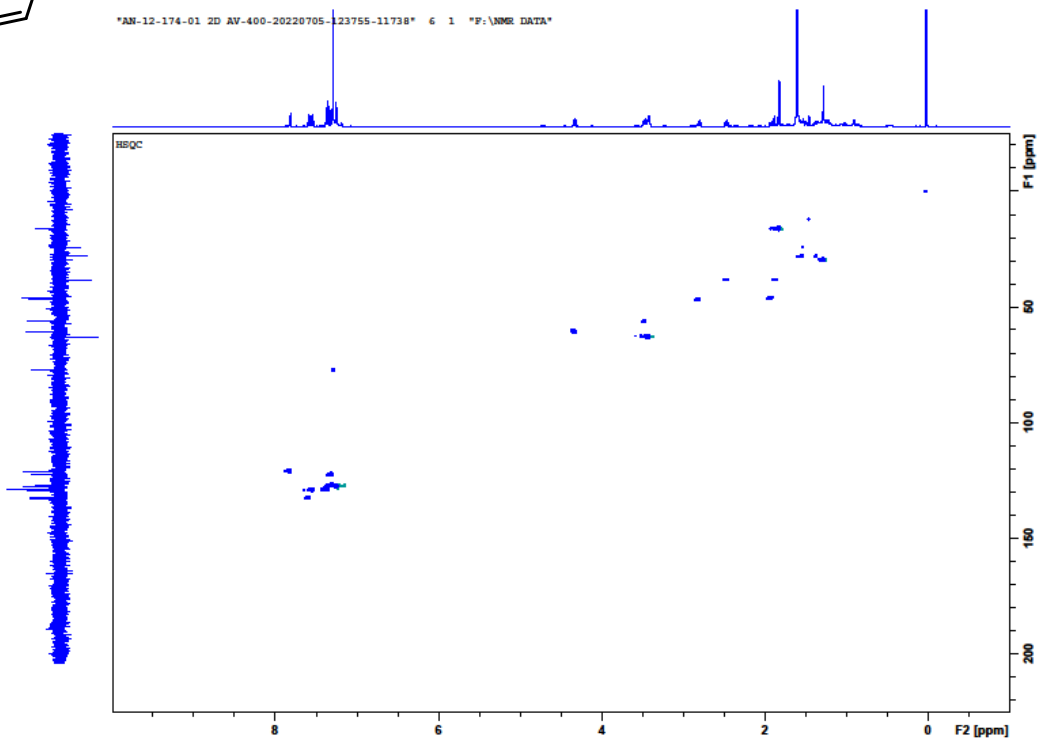
35aa



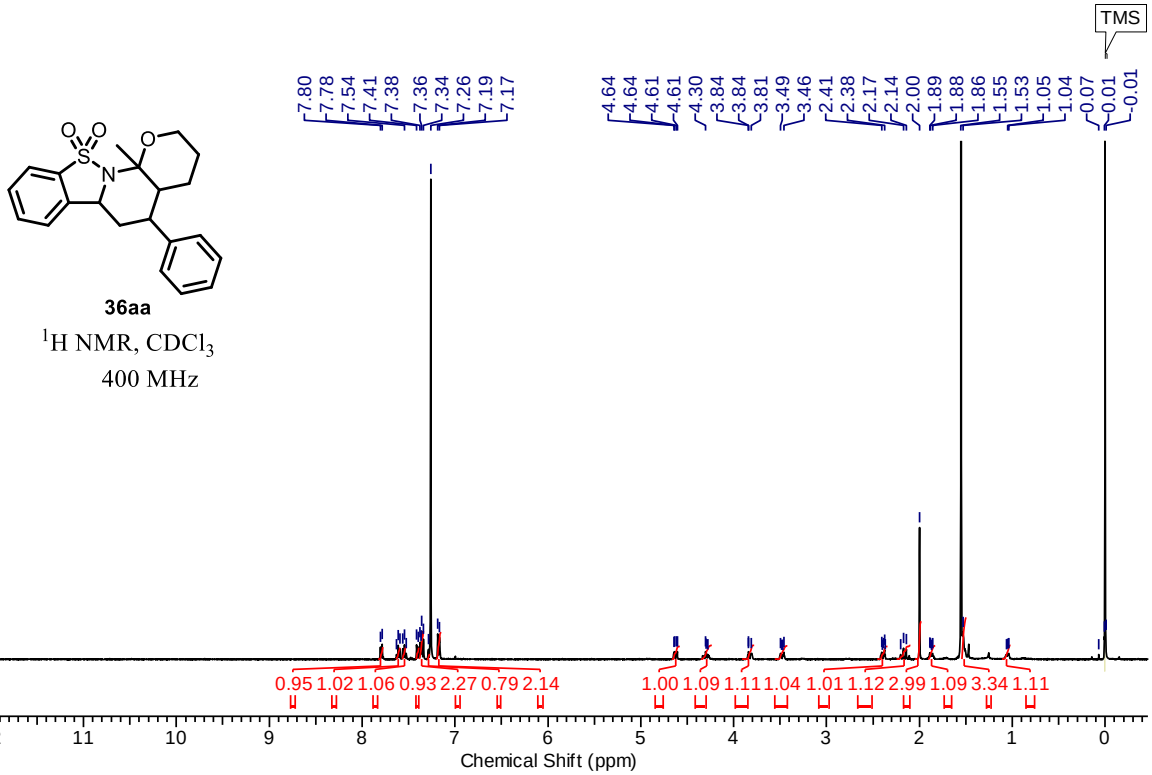
HSQC NMR spectrum of compound 35aa



35aa



^{1}H NMR spectrum of compound 36aa

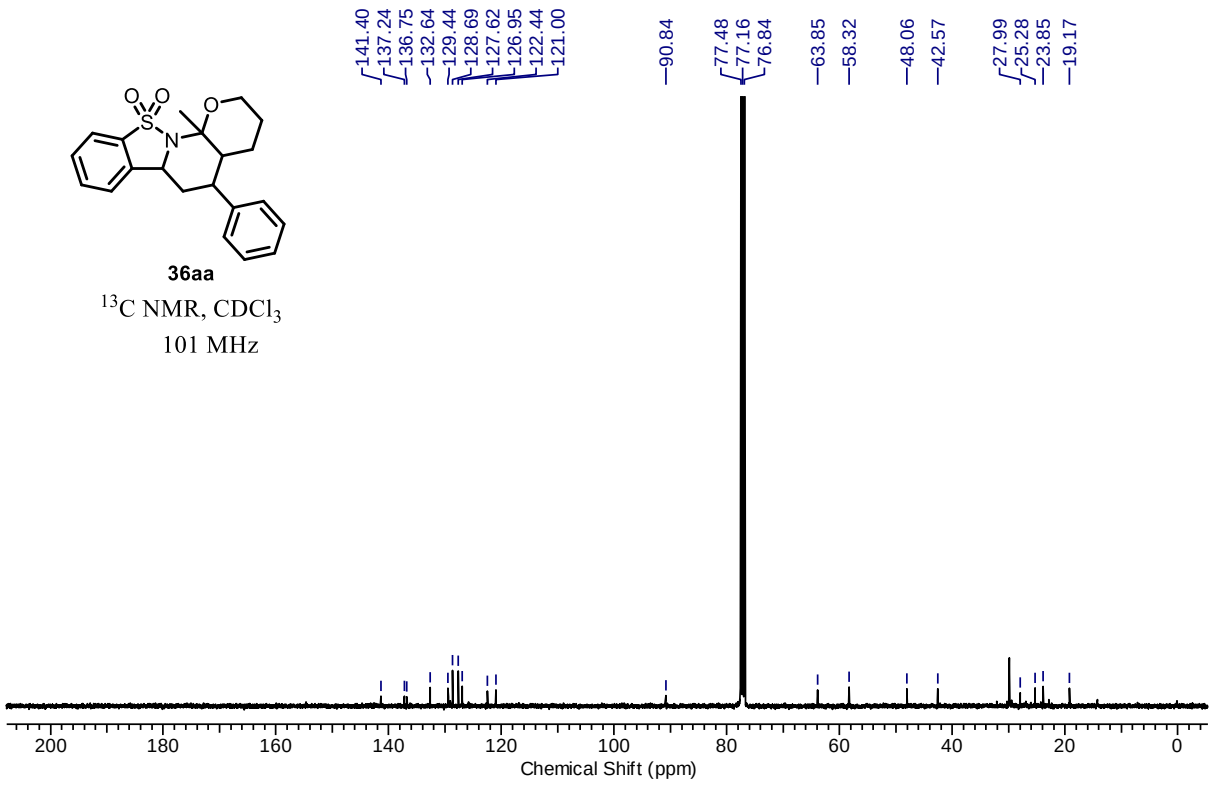


36aa

^{1}H NMR, $CDCl_3$

400 MHz

^{13}C NMR spectrum of compound 36aa

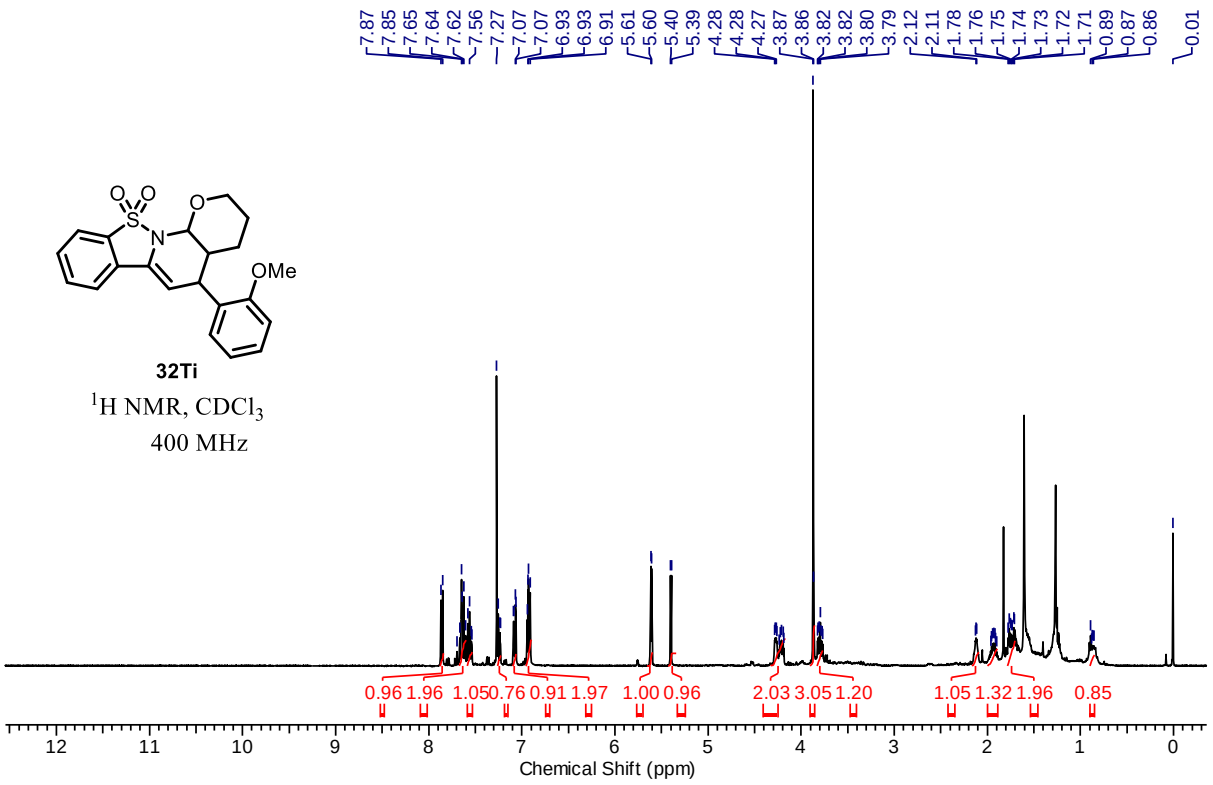


36aa

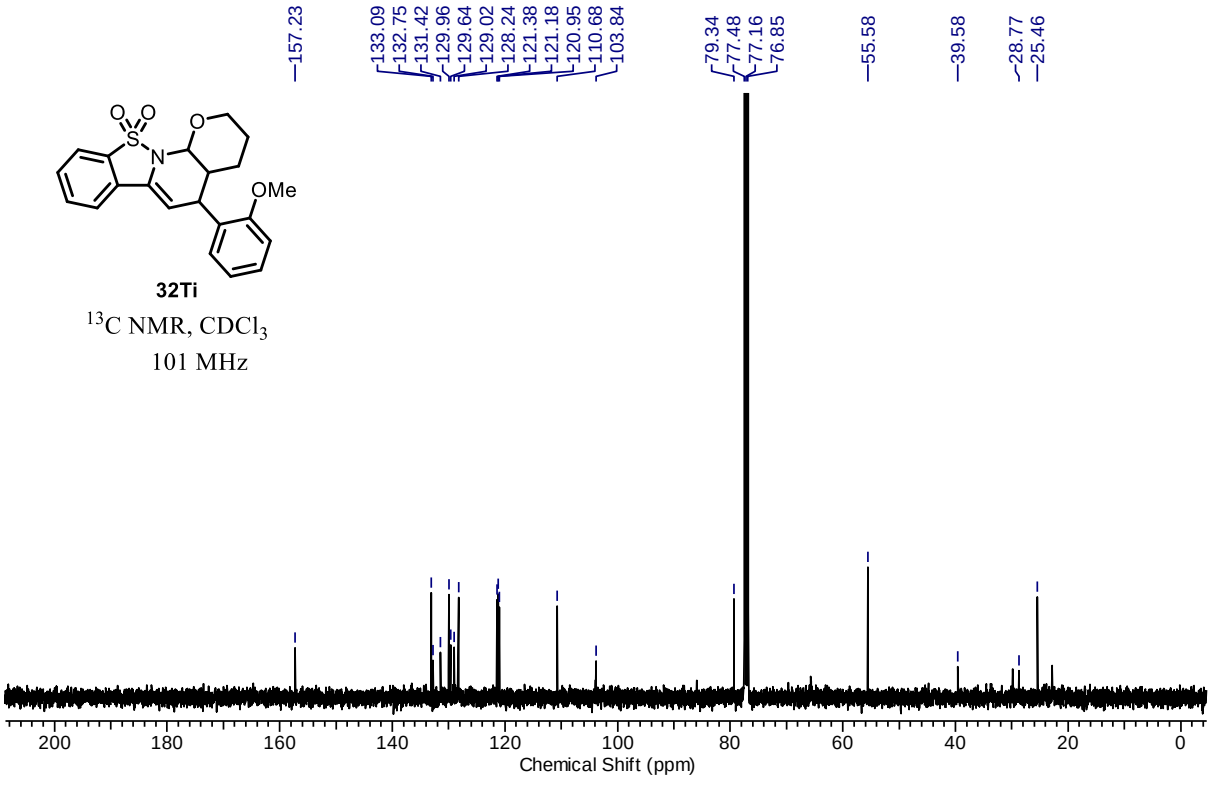
^{13}C NMR, $CDCl_3$

101 MHz

^{1}H NMR spectrum of compound 32Ti



^{13}C NMR spectrum of compound 32Ti



ABSTRACT

Name of the Student: Nakate Ashwini Kadaji **Registration No.:**10CC16A26003

Faculty of Study: Chemical Science **Year of Submission:**2023

AcSIR academic centre/CSIR Lab: **Name of the Supervisor:**Dr. RavindarKontham

CSIR-National Chemical Laboratory, Pune

Title of the thesis:"Lewis Acid-Catalysed σ and π Activation Triggered Cascade Annulation Reactions of Alkynyl Alcohols to Construct Heterocyclic Compounds"

Alkynes are essential functional groups widely found in numerous organic small molecules. Due to the available robust process technologies involving acetylene (gas) as a precursor, a plethora of alkyne-derived fine chemicals and reagents entered the commercial market at affordable costs. These positive aspects of alkynes triggered the interest of the academic and industrial organic synthesis community to develop novel and sustainable synthetic methodologies, which can be employed in the production of active pharmaceutical ingredients, bioactive natural products, and organic functional materials. Aiming at developing sustainable catalytic systems to activate alkynes (through π-activation), and their subsequent annulation reactions with arenes and carbonyl compounds (through σ-activation) to access diverse heterocyclic molecules, we have devised novel synthetic methodologies for the facile construction of simple to complex tetrahydrofurans, tetrahydropyrans, chromanes, tetrahydro benzoisothiazolo-pyrans and furans, and the outcome of these investigations embodied in the form of this thesis, which is categorized into four chapters. The initial aspect of this thesis was focused on the extensive literature survey on the structure and reactivity of alkynes and various transformations reported in the literature using alkynes. The *First chapter* was aimed at developing a novel and sustainable catalytic system (containing a single metal salt) for the construction of 2-(hetero)aryl furans and pyrans from 4-pentyn-1-ols and 5-hexyn-1-ols respectively *via* π-activation-induced cycloisomerization of alkynols as a key step. The *Second chapter* was formulated to construct biologically relevant simple to complex chromanes in a single step starting from readily accessible alkynyl alcohols and enones using a single catalytic system. The *Third chapter* was to construct biologically relevant polycyclic benzoisothiazolo furo-pyridines and pyrano-pyridines through σ and π-activation-induced cascade annulation of alkynyl alcohols (alkynols) and *α-β*-unsaturated sulfonyl ketimines employing a single catalytic system.

List of Publications Emanating from the Thesis Work

1. **Ashwini, K. N.;** Madhukar, S. P.; Kontham, R. Bismuth(III)-catalyzed cycloisomerization and (hetero)arylation of alkynols: simple access to 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans. *Org. Biomol. Chem*., 2018, *16*, 3229–3240.
2. **Ashwini, K. N.;** Thorat, S. S.; Jain, S.; Gamidi, R. K.; Vanka, K.; Kontham, R. Silver-Catalyzed [3+3]-Annulation Cascade of Alkynyl Alcohols and α,β-Unsaturated Ketones for the Regioselective Assembly of Chromanes. *Org. Chem. Fornt*. **2022**, *9*, 802-809.
3. **Ashwini, K. N.;** Kataria, P.; Gamidi, R. K.; Ravindar, K. $Bi(OTf)_3$-catalyzed Inverse-Electron-Demand Aza-Diels-Alder reaction of alkynols and *α-β* -unsaturated ketimines.(*Manuscript under preparation*).

List of Publications Non-Emanating from the Thesis Work

1. Vinodkumar, R.; **Ashwini, K. N.;** Gamidi, R. K.; Kontham, R. Bronsted acid (MsOH)-mediated dimerisation cascade of α,β-Unsaturated γ- ketoesters: Diastereoselective synthesis of pyrano-ketal lactones. (*Manuscript under preparation*).
2. Pooja, I. S.; **Ashwini, K. N.;** Gamidi, R. K.; Kontham, R. Fe(III)-Catalyzed Diastereoselective Friedel-Crafts Alkylation-Hemiketalization-Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol-Lactones. (*Manuscript under preparation*).
3. **Ashwini, K. N.;** Pooja, I. S.; Digambar, A. K.; Kontham, R. Stereoselective Total Synthesis of Polyketide Natural Product Opaliferin. *Manuscript under preparation.*
4. Vinodkumar, R.; **Ashwini, K. N.;** Gamidi, R. K.; Kontham, R. Synthesis of of (5-6-5)-bis-spiroketals *via* silver- catalyzed cascade annulation of 4-pentyn-1-ols and aldehydes. *Manuscript under preparation.*
5. Vinodkumar, R.; **Ashwini, K. N.;** Gamidi, R. K.; Kontham, R. Synthesis of dipyrano pyrans *via* silver-catalyzed cascade annulation of 5-hexyn-1-ols and aldehydes. *Manuscript under preparation.*
6. Intermolecular Cascade Transformations of alkynols and their Application in Total Synthesis of Natural Products, (review) *Manuscript under preparation.*

List of Posters Presented with Details

1. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2018**)

   Title: Bismuth(III)-catalyzed hydroalkoxylation-hydro(hetero)arylation cascade: simple access to 2-(Hetero)aryl tetrahydrofurans and tetrahydropyrans from alkynols

   Abstract: 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans were successfully synthesized using Bi(OTf)3-catalyzed hydroalkoxylation (cycloisomerization) of alkynols (via 5 or 6 exo-dig cyclization) and intermolecular (hetero)arylation. This reaction involves a highly efficient cascade process, where initially the alkynol undergoes a cycloisomerization step via activation of the triple bond and generates the oxocarbenium ion, which subsequently participates in (hetero)hydroarylation step with electron-rich arenes. Simple to complex suitably functionalized alkynols (4-pentyn-1-ols and 5-hexyn-1ols) and electron-rich aromatic compounds were found to be reliable substrates in this cascade transformation and furnished a wide range of oxygen heterocycles. This practical tandem process provides a means to build libraries related to pharmacologically active molecules and natural product like scaffolds.

2. DST review meeting Poster Presentation at Pillai Collage of Engineering Panvel Mumbai on DST review meeting (August 02-08, **2019**)

   Title: Bismuth(III)-catalyzed hydroalkoxylation-hydro(hetero)arylation cascade: simple access to 2-(Hetero)aryl tetrahydrofurans and tetrahydropyrans from alkynols

   Abstract: 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans were successfully synthesized using Bi(OTf)3-catalyzed hydroalkoxylation (cycloisomerization) of alkynols (via 5 or 6 exo-dig cyclization) and intermolecular (hetero)arylation. This reaction involves a highly efficient cascade process, where initially the alkynol undergoes a cycloisomerization step via activation of the triple bond and generates the oxocarbenium ion, which subsequently participates in (hetero)hydroarylation step with electron-rich arenes. Simple to complex suitably functionalized alkynols (4-pentyn-1-ols and 5-hexyn-1ols) and electron-rich aromatic compounds were found to be reliable substrates in this cascade transformation and furnished a wide range of oxygen

heterocycles. This practical tandem process provides a means to build libraries related to pharmacologically active molecules and natural product like scaffolds.

3. National Science Day Poster Presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2020**)

   Title: Silver-catalyzed [3+3]-annulation cascade of alkynyl alcohols and *α-β*,-unsaturated ketones for the regioselective assembly of chromanes

   Abstract: An unprecedented Ag(I)-catalyzed [3+3]-annulation of alkynyl alcohols (5-hexyn-1-ols) and α,β -unsaturated ketones is reported to construct simple to complex chromanes. This transformation begins with hydroalkoxylation of alkynol through C-C triple bond activation to give cyclic-enol ether, followed by intermolecular 1,4-addition and intramolecular 1,2-addition of enol ethers onto the enone and oxidative aromatization or Grob-type elimination steps. Facile reaction conditions, broad substrate scope, good to excellent yields, and atom economy are salient features of this protocol. Isolation of active pyran-tethered cyclohexadiene reaction intermediate, additional supporting experiments, and DFT calculations strongly support the experimental findings and corroborate our proposed mechanism.

4. National Chemical Laboratory Research Foundation Day Oral Presentation at CSIR-National Chemical Laboratory, Pune (November 29-30, **2022**)

   Title: $Bi(OTf)_3$-catalyzed inverse-electron-demand aza-Diels-Alder reaction of alkynols and *α-β* -unsaturated ketimines

   Abstract: We disclosed that the Bi(III)-catalyzed IED [4 + 2]-cascade cycloaddition reaction has been established for the diversified synthesis of Benzoisothiazolo pyridinefuran dioxide and Benzoisothiazolo pyranopyridine dioxide compounds from readily accessible alkynols and *α,β*-unsaturated ketimines. This transformation begins with hydroalkoxylation of alkynol through C-C triple bond activation to generate endo or Exo cyclic-enol ether, followed by regioselective 1,4-addition and then the inverse electron demand aza Diels-Alder reaction, to provide a wide variety of Benzoisothiazolo pyridinefuran or Benzoisothiazolo pyranopyridine dioxide related to many natural products. Following this simple and facile protocol, a broad range of products was

prepared with good to excellent yields. The additional supporting experiments strongly support to our proposed reaction mechanism.

List of Conference Attended with Details

International Conference on Nature Inspired Initiatives in Chemical Trends Organic synthesis (**2016**).

1. Poster presentation on National science day at NCL on 28th Feb, 2018.
2. poster presented at Pillai collage of Engineering Panvel Mumbai on DST review meeting 2019.
3. Poster presentation on National Science Day at NCL on 28th Feb, 2020.
4. Oral presentation on National Chemical Laboratory Research Foundation Day.

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PAPER

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Cite this: *Org. Biomol. Chem.*, 2018, **16**, 3229

Bismuth(III)-catalyzed cycloisomerization and (hetero)arylation of alkynols: simple access to 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans†

Ashwini K. Nakate, [a,b] Madhukar S. Pratapure [a,b] and Ravindar Kontham *[a,b]

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2-(Hetero)aryl tetrahydrofurans and tetrahydropyrans were successfully synthesized using $Bi(OTf)_3$-catalyzed hydroalkoxylation (cycloisomerization) of alkynols (*via* 5 or 6 *exo*-dig cyclization) and intermolecular (hetero)arylation. This reaction involves a highly efficient cascade process, where initially the alkynol undergoes a cycloisomerization step *via* activation of the triple bond and generates the oxocarbenium ion, which subsequently participates in the (hetero)hydroarylation step with electron-rich arenes. Simple to complex suitably functionalized alkynols (4-pentyn-1-ols and 5-hexyn-1-ols) and electron-rich aromatic compounds were found to be reliable substrates in this cascade transformation and furnished a wide range of oxygen heterocycles. This practical tandem process provides a means to build libraries related to pharmacologically active molecules and natural product like scaffolds.

Introduction

Saturated oxygen heterocycles, such as tetrahydrofurans and tetrahydropyrans, are ubiquitous core structures of bioactive natural products and pharmaceutical drugs.[1] From the perspective of drug discovery research, still, there is much scope for the development of chemical space derived from medium-sized heterocyclic frameworks. In this context, the limitations of conventional heterocycle synthetic protocols have fueled considerable interest in developing new and efficient catalytic methods. In recent years, the catalytic hydroalkoxylation/cycloisomerization of alkynols has emerged as a powerful tool, which represents a direct means for the synthesis of enol-ethers and diverse oxygen-containing heterocycles *via* inter- or intra-molecular reaction modes.[2] These cascade/tandem processes offer great potential from the synthetic point of view because reactions of these types can be performed with step and atom efficiency, with negligible waste generation, which fulfills green chemistry requirements.

In the last three decades, inter- and intra-molecular bis(hydroalkoxylation),[3] bis(arylation),[4] and hydroalkoxylation–alkylation[5] of suitably functionalized alkynes using π-acidic transition metal (especially noble metals) derived catalysts have been well studied.[6] In contrast, studies on tandem intramolecular hydroalkoxylation (cycloisomerization) followed by the intermolecular hydro-(hetero)arylation of alkynols, which gives 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans, are very limited. Recently, Fañanás *et al.* reported an elegant approach to construct benzo-fused cyclic ethers *via* the gold or platinum catalyzed intramolecular hydroalkoxylation–hydroarylation of alkynols.[7]

It's noteworthy to mention the Gandon *et al.*'s report of $GaCl_3$ induced hydroalkoxylation followed by Friedel–Crafts type addition using alkynol and anisole; however, it is limited to a single example.[8] Some other miscellaneous reports having constraints such as the use of prefunctionalized starting materials and multiple steps are also present in the literature.[9] Hence, the development of an efficient synthetic method using readily available starting materials, and environmentally benign and affordable main group element derived catalysts is of considerable interest in the field of diversity-oriented synthesis and in turn in drug discovery research.

As part of our interest in the development of new synthetic methodologies involving the cycloisomerization of internal alkynols,[10,11] we have recently reported the synthesis of oxa-spirolactones *via* an intermolecular cascade annulation of alkynols with α-ketoesters using $Bi(OTf)_3$ as a dual activating (σ and π) catalyst, which proceeds through an oxocarbenium ion intermediate (*via* the 5-*exo*-dig hydroalkoxylation of alkynols) and a subsequent cascade annulation process.[12] In light of these observations, we envisioned that the same oxocarbenium ion species would undergo Friedel–Crafts type addition (hydro-

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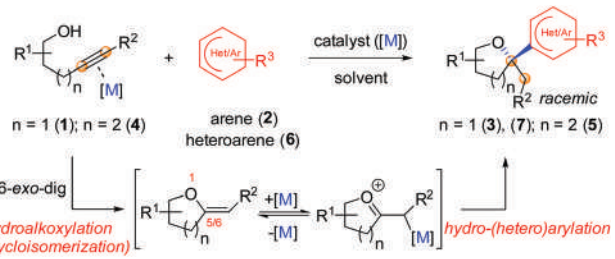
[b]*Academy of Scientific and Innovative Research (AcSIR), New Delhi, India*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ob00368h



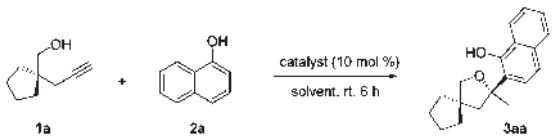
Scheme 1 Strategy for the synthesis of 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans from alkynols.

(hetero)arylation) under identical reaction conditions to give 2-(hetero)aryl tetrahydrofurans and pyrans from suitably functionalized alkynols and (hetero)arenes (Scheme 1).

Results and discussion

To investigate the feasibility of this hypothesis, known alkynol **1a** (0.36 mmol) and α-naphthol (**2a**) (0.36 mmol) were treated with $Bi(OTf)_3$ (10 mol%, 0.036 mmol), in anhydrous CH_2Cl_2 under an argon atmosphere. The reaction proceeded smoothly and gave the desired 2-naphthyl tetrahydrofuran **3aa** in a good yield of 80% in 6 h at room temperature (entry 1) (Table 1). To identify the effective catalyst and reaction conditions, several

Table 1 Optimization studies[a]

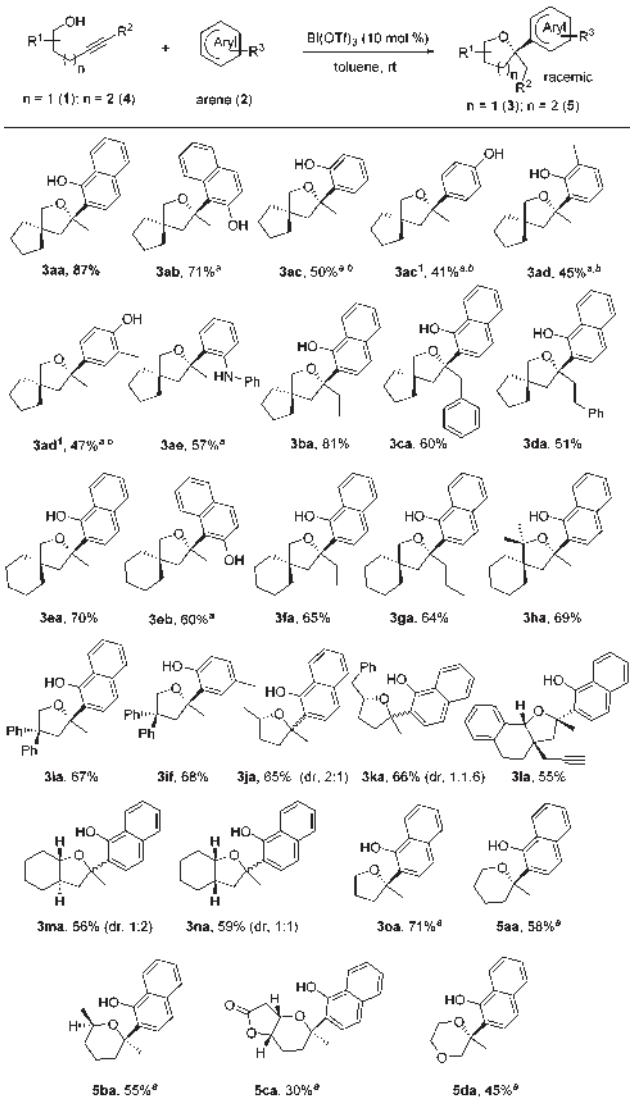


Entry	Catalyst	Solvent	Yield[b] (%)
1	$Bi(OTf)_3$	CH_2Cl_2	80
2	$Bi(OTf)_3$	Toluene	87
3	$Bi(OTf)_3$[c]	Toluene	65
4	$BiCl_3$	Toluene	60
5	$In(OTf)_3$	CH_2Cl_2	58
6	$Yb(OTf)_3$	CH_2Cl_2	62
7	$Hg(OTf)_2$	Toluene	80
8	$HgCl_2$	Toluene	55
9	$Hg(OAc)_2$	Toluene	60
10	$Pd(OTf)_2$	Toluene	62
11	$Pd(OAc)_2$	Toluene	40
12	Ph_3PAuCl, AgOTf	CH_2Cl_2	45
13	AgOTf	CH_2Cl_2	42
14	$Cu(OTf)_2$	CH_2Cl_2	50
15	$FeCl_3$	CH_3CN	10
16	PTSA	$(CH_2)_2Cl_2$	10
17	PTSA	Toluene	20
18	CF_3COOH	CH_2Cl_2	25
19[d]	TfOH	CH_2Cl_2	10
20[d]	TfOH	Toluene	15
21[d]	No catalyst	Toluene	—

[a] All reactions were carried out with 0.36 mmol of **1a** and 0.36 mmol of **2a** in 2 mL of the solvent unless otherwise specified. [b] Isolated yield of **3aa**. [c] 5 mol%. [d] Control experiments. rt = room temperature, Tf = triflate (CF_3SO_2).

Lewis acids (entries 4–15) and Brønsted acids (entries 16–20) were screened, in which some were found to be moderately active. Among all, $Bi(OTf)_3$ turned out to be the pre-eminent catalyst. A brief solvent screening (entries 1–3) prompted us to replace the chlorinated solvent (CH_2Cl_2) with relatively benign toluene (entry 2, 87% yield). Further tuning of the reaction parameters like molar ratios of the substrates and catalyst loading did not lead to any noticeable improvement in the outcome of the reaction. Control experiments verified that the reaction did not proceed in the absence of $Bi(OTf)_3$ (entry 21) and very little conversion was observed with TfOH (a usual contaminant in the $Bi(OTf)_3$ catalyst) (entry 20) (Table 1).[13]

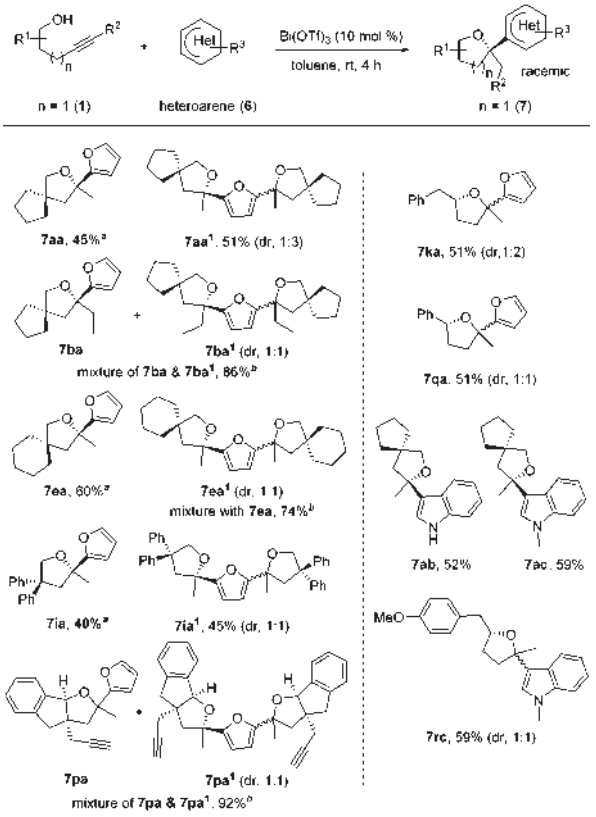
With the optimal conditions in hand, we then investigated the substrate scope of this tandem process (Scheme 2). Firstly, the reactions of diverse terminal/internal-alkynols and arenes



Scheme 2 Synthesis of 2-aryl tetrahydrofurans/pyrans from 4-pentyn-1-ols, 5-hexyn-1-ols and arenes; reaction time is 6 h, unless otherwise specified, [a] 10 h, [b] *ortho*/*para* isomers obtained from the same reaction. All yields mentioned above are isolated yields.

were tested. The known cyclopentane-fused 4-pentyn-1-ol worked well with α/β-naphthols, phenol, *o*-cresol and diphenylamine to afford the corresponding adducts **3aa–ae** in excellent yields (50–92%). Cyclopentane-fused internal alkynols (having methyl, phenyl and benzyl substituents on alkyne termini) were also well condensed with α-naphthol and furnished the corresponding tetrahydrofurans **3ba**, **3ca** and **3da**, respectively. The condensation of cyclohexane-fused terminal/internal alkynols with α and β-naphthols gave **3ea**, **3eb**, **3fa** and **3ga** in good yields. Tertiary alkynol was also well tolerated and gave **3ha** in 69% yield. The reaction of 2,2-diphenyl substituted primary alkynol with α-naphthol and *p*-cresol provided **3ia** and **3if** in good yields. Secondary alkynols with α-naphthol furnished **3ja** and **3ka**. Conformationally confined tetralin derived alkynol with α-naphthol furnished **3la** as a single diastereomer.[13] Cyclohexane derived secondary alkynols (having the *trans*/*cis* fusion) with α-naphthol provided **3ma** and **3na** in good yields. The reaction of 4-pentyn-1-ol with α-naphthol gave **3oa** (71% yield) in a little longer reaction time (10 h). To our delight, 5-hexyn-1-ol also reacted well with α-naphthol and furnished the expected tetrahydropyran **5aa** (*via* the 5-*exo*-dig mode of cyclization) in a good yield of 58% in 10 h. Hexyn-1-ol derived secondary alcohol was also well tolerated and gave **5ba** as a single diastereomer. Lactone-fused alkynol was also found to be a good substrate and furnished the corresponding pyran **5ca** in a moderate yield of 30%. Propargyl ether derived alkynol proceeded smoothly, and delivered the product **5da** in good yield. Exclusive alpha-substituted products in the case of α and β-naphthols are attributed to the probable chelation of the catalyst with the free hydroxyl functionality of arenes and the oxocarbenium ion in the probable transition state.[9,14] Relative stereochemistry of **3la**, **5ba** and **5ca** was confirmed by NOE analysis (Scheme 2).[13]

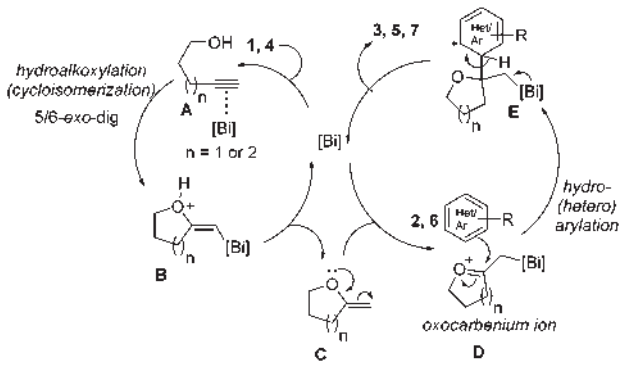
Next, we were curious to verify the reactivity of alkynols with heteroarenes in this tandem process, which provides access to 2-heteroaryl tetrahydrofurans and the results are summarized in Scheme 3. Among several heterocycles (furan, thiophene, pyrrole, pyridine, benzoxazole, and benzothiazole) tested for this reaction, furan, indole and 1-methylindole were found to be good substrates. Interestingly, the reaction of cyclopentane-fused alkynol with furan afforded mono-arylation and double-arylation products **7aa** and **7aa^1** (dr, 1 : 3, confirmed by HPLC analysis)[13] in 45% and 51% yields, respectively. An internal alkynol with furan gave an inseparable mixture of **7ba** and **7ba^1** (dr, 1 : 1) in 86% yield. Cyclohexane-fused alkynol and furan in a 1 : 2 molar ratio furnished **7ea** exclusively, whereas in a 1 : 1 molar ratio they afforded **7ea** and **7ea^1** (dr, 1 : 1) as an inseparable mixture. Diphenyl substituted alkynol provided mono- and double-arylated adducts **7ia** and **7ia^1** (dr, 1 : 1, confirmed by ^{1}H NMR and HPLC analyses).[13] The reaction of indanone derived alkynol with furan furnished **7pa** and **7pa^1**. In contrast, benzyl group extended alkynol and secondary (benzylic) alkynols furnished the corresponding mono-furylated products **7ka** and **7qa** as a mixture of diastereomers (confirmed by ^{1}H NMR analysis). To our surprise, the reaction of 2-methylfuran with 4-pentyn-1-ol failed to deliver the mono-substituted product. Moreover, indole and 1-methylindole also reacted well with primary and secondary alkynols to give **7ab**, **7ac** and **7rc** in good yields (Scheme 3).



Scheme 3 Synthesis of 2-heteroaryl tetrahydrofurans from 4-pentyn-1-ols and heteroarenes; [a] separated and characterized, [b] inseparable mixture, NMR yields provided. All yields mentioned above are isolated yields unless otherwise specified.

As observed in our previous studies,[12] the reactivity of unsubstituted 4-pentyn-1-ols is slightly slower compared to that of substituted analogs (Thorpe–Ingold effect)[15] and 5-hexyn-1-ols are less reactive compared to 4-pentyn-1-ols, which is in agreement with Baldwin rules.[16] Electron-deficient arenes (nitroarenes, aryl carboxylates, cyanoarenes, haloarenes and pseudo-haloarenes) and anisoles did not participate in the reaction, which could be due to the unfavorable hydroarylation (Friedel–Crafts) step of the tandem process (Schemes 2 and 3).

A plausible mechanism of this transformation based on our (and others) earlier mechanistic investigations and the results obtained in this work is shown in Scheme 4.[7,8,12] The reaction is initiated by the π-coordination of $Bi(OTf)_3$ to the C–C triple bond of alkynol **1** or **4** to form intermediate **A**, which triggers the hydroalkoxylation (cycloisomerization) *via* 5 or 6-*exo*-dig mode of addition on to the alkyne triple bond, which leads to the formation of the intermediate **B**. The protodebismuthination of **B** affords the *exo*-cyclic enol ether **C** and further activation of enol ether **C** affords the oxocarbenium ion **D**, which undergoes hydro-(hetero)arylation with arenes **2** or heteroarenes **6** to give **E**. The concomitant second protodebismuthina-



Scheme 4 Plausible reaction mechanism.

tion step in **E** leads to the formation of the desired products **3**, **5** and **7** (Scheme 4).

Conclusions

In summary, the hydroalkoxylation (cycloisomerization) and hydro-(hetero)arylation cascade reaction of alkynols with (hetero)arenes mediated by the main group element derived borderline metal catalyst $Bi(OTf)_3$ is identified. Diverse alkynols and electron rich arenes/heteroarenes proceeded cleanly under ambient reaction conditions and furnished a series of novel 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans in good to excellent yields in an atom and step economic way. A further expansion of this work in building libraries related to pharmacologically active molecules and their biochemical evaluation is in progress and will be communicated in due course.

Experimental

All reactions were performed under an argon atmosphere with oven (80 °C) or flame-dried glassware with a septum seal. Tetrahydrofuran (THF) was distilled from sodium-benzophenone under an argon atmosphere immediately prior to use. Dichloromethane and acetonitrile were freshly distilled over calcium hydride under an argon atmosphere. 30 °C corresponds to the room temperature (rt) of the laboratory when the experiments were carried out. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. Analytical thin layer chromatography (TLC) was performed on TLC Silica gel 60 F254. Visualization was accomplished with shortwave UV light, anisaldehyde or $KMnO_4$ staining solutions followed by heating. Chromatography was performed on silica gel (100–200 mesh) by standard techniques eluting with solvents as indicated. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 200, 400 and 500 spectrometers in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm). The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; AB q, AB quartet; dd, doublet of doublet; td, triplet doublet; and br, broad. IR spectra were recorded on an FT-IR instrument (Bruker Alpha Model) at normal temperature with a KBr pellet (IR grade). HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Experimental procedures for all new compounds and known compounds without published experimental procedures are described below. Compounds that are not presented in the main text (manuscript) are numbered starting from S1.†

General procedure for the synthesis of 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans

Alkynol **1a** (0.36 mmol) and α-naphthol **2a** (0.36 mmol) was taken into a single neck 10 mL round bottom flask under argon atmosphere, then added 2 mL of anhydrous toluene. $Bi(OTf)_3$ (0.036 mmol) was added under an argon atmosphere at room temperature (rt). The resulting reaction mixture was stirred at rt for 6 h. After completion of the reaction (monitored by TLC and visualized using UV, anisaldehyde, and $KMnO_4$ staining solutions), the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 5 mL) and then washed with brine solution (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified using silica-gel column chromatography (100–200 mesh) to afford the corresponding tetrahydrofuran **3aa**.

2-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (3aa). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.36 mmol) and naphthalen-1-ol (**2a**) (0.052 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3aa** as a brown liquid (0.089 g, 87%). The *ortho*-substitution of **3aa** was confirmed by ^1H NMR and 2D NMR (HMBC, HSQC, COSY and NOESY) analyses.[13] TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz): δ 10.57 (s, 1H), 8.36–8.21 (m, 1H), 7.78–7.66 (m, 1H), 7.52–7.40 (m, 2H), 7.30 (d, J = 8.72 Hz, 1H), 7.03 (d, J = 8.59 Hz, 1H), 3.84 (d, J = 8.21 Hz, 1H), 3.74 (d, J = 8.21 Hz, 1H), 2.57 (d, J = 12.51 Hz, 1H), 2.19 (d, J = 12.51 Hz, 1H), 1.65 (s, 3H), 1.63–1.38 (m, 8H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.2, 133.5, 127.1, 126.1, 125.6, 125.1, 124.9, 122.9, 122.5, 118.6, 89.2, 78.7, 52.7, 51.08, 37.75, 36.8, 30.9, 24.8, 24.7; IR (KBr, cm^{-1}): ν 3209, 3061, 3016, 2963, 2865, 1733, 1633, 1503, 1380, 1024, 801, 762; HRMS (ESI) m/z calcd for $C_{19}H_{23}O_2$ $[M + H]^+$ 283.1693, found 283.1690.

1-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-2-ol (3ab). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.36 mmol) and naphthalen-2-ol (**2b**) (0.052 g, 0.36 mmol) in anhydrous

toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ab** as a brown liquid (0.073 g, 71%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 11.20 (s, 1H), 7.78–7.65 (m, 2H), 7.61 (d, J = 8.84 Hz, 1H), 7.39 (ddd, J = 8.62, 6.92, 1.52 Hz, 1H), 7.29–7.19 (m, 1H), 7.04 (d, J = 8.84 Hz, 1H), 3.81 (d, J = 8.08 Hz, 1H), 3.67 (d, J = 8.08 Hz, 1H), 2.72 (d, J = 12.51 Hz, 1H), 2.55 (d, J = 12.51 Hz, 1H), 1.88 (s, 3H), 1.67–1.48 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.2, 131.2, 129.6, 129.4, 129.2, 125.6, 124.3, 122.1, 120.9, 120.5, 89.9, 54.8, 51.2, 37.8, 35.7, 29.8, 25, 24.6; HRMS (ESI) m/z calcd for $C_{19}H_{23}O_2$ $[M + H]^+$ 283.1693, found 283.1689.

2-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (3ac). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.36 mmol) and phenol (**2c**) (0.033 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexane) afforded **3ac** as a brown liquid (0.042 g, 50%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.72 (s, 1H), 7.02 (m, 1H), 6.93–6.85 (m, 1H), 6.74 (m, 2H), 3.72 (d, J = 8.01 Hz, 1H), 3.61 (d, J = 8.39 Hz, 1H), 2.46 (d, J = 12.59 Hz, 1H), 2.08 (d, J = 12.59 Hz, 1H), 1.61–1.46 (m, 11H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.2, 130.6, 128.3, 126.8, 119.2, 117.4, 88.6, 78.6, 52.4, 51.0, 37.9, 36.9, 30.8, 24.7, 24.6; HRMS (ESI) m/z calcd for $C_{15}H_{21}O_2$ $[M + H]^+$ 233.1536, found 233.1536.

4-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (3ac^1). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.36 mmol) and phenol (**2c**) (0.033 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ac^1** as a brown liquid (0.035 g, 41%). TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.26 (d, J = 8.59 Hz, 2H), 6.78 (d, J = 8.59 Hz, 2H), 5.65 (br. s., 1H), 3.78 (d, J = 8.3 Hz, 1H), 3.64 (d, J = 8.3 Hz, 1H), 2.26 (d, J = 12.38 Hz, 1H), 2.08 (d, J = 12.38 Hz, 1H), 1.85–1.28 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz): 154.2, 141.2, 125.9, 114.9, 84.7, 78.5, 53.2, 51.7, 38.4, 37.2, 31.4, 24.7; HRMS (ESI) m/z calcd for $C_{15}H_{21}O_2$ $[M + H]^+$ 233.1536, found 233.1535.

2-Methyl-6-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)phenol (3ad). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.036 mmol) and *o*-cresol (**2d**) (0.039 g, 0.036 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ad** as a brown liquid (0.040 g, 45%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.92 (s, 1H), 7.12–6.63 (m, 3H), 3.70 (d, J = 8.21 Hz, 1H), 3.72 (d, J = 8.21 Hz, 1H), 2.56 (d, J = 12.63 Hz 1H), 2.37–2.09 (m, 4H), 1.92–1.34 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.2, 130.6, 128.3, 126.8, 119.3, 117.4, 88.6, 78.6, 52.4, 51.0, 37.9, 36.9, 30.8, 24.7, 24.6; HRMS (ESI) m/z calcd for $C_{16}H_{23}O_2$ $[M + H]^+$ 247.1693, found 247.1685.

3-Methyl-4-(3-methyl-oxaspiro[4.4]nona3-yl)phenol (3ad^1). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.36 mmol) and *o*-cresol (**2d**) (0.039 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ad^1** as a brown liquid (0.042 g, 47%). TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 (s, 1H), 7.10 (d, J = 7.94 Hz, 1H), 6.74 (d, J = 8.54 Hz, 1H), 6.16 (br. s., 1H), 3.80 (d, J = 7.93 Hz, 1H), 3.67 (d, J = 7.93 Hz, 1H), 2.23–2.33 (m, 4H), 2.10 (d, J = 12.2 Hz, 1H), 1.71–1.47 (m, 8H), 1.45–1.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.5, 140.8, 127.3, 123.6, 123.0, 114.5, 84.8, 78.4, 53.2, 51.6, 38.4, 37.2, 31.5, 24.7, 24.7, 16.1; HRMS (ESI) m/z calcd for $C_{16}H_{23}O_2$ $[M + H]^+$ 247.1693, found 247.1689.

2-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)-*N*-phenylaniline (3ae). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.36 mmol) and diphenylamine (**2e**) (0.061 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ae** as a brown liquid (0.063 g, 57%). TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33–7.21 (m, 4H), 7.12–6.97 (m, 4H), 6.96–6.83 (m, 1H), 5.67 (s, 1H), 3.77 (d, J = 8.21 Hz, 1H), 3.64 (d, J = 8.21 Hz, 1H), 2.27 (d, J = 12.38 Hz, 1H), 2.08 (d, J = 12.38 Hz, 1H), 1.82–1.56 (m, 6H), 1.52 (s, 3H), 1.44–1.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 143.5, 142.2, 141.1, 129.3, 125.6, 120.6, 117.8, 117.4, 84.4, 78.5, 53.1, 51.8, 38.4, 37.2, 31.4, 24.7; HRMS (ESI) m/z calcd for $C_{21}H_{26}NO$ $[M + H]^+$ 308.2009, found 308.2006.

2-(3-Ethyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (3ba). Following the general procedure, to a mixture of (1-(but-2-yn-1-yl)cyclopentyl)methanol (**1b**) (0.050 g, 0.32 mmol) and naphthalen-1-ol (**2a**) (0.047 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.021 g, 0.032 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ba** as a brown liquid (0.079 g, 81%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.68 (s, 1H), 8.29 (d, J = 8.55 Hz, 1H), 7.75 (d, J = 7.32 Hz, 1H), 7.54–7.43 (m, 2H), 7.30 (d, J = 8.55 Hz, 1H), 7.01 (d, J = 8.54 Hz, 1H), 3.86–3.78 (m, 2H), 2.54 (d, J = 12.82 Hz, 1H), 2.24 (d, J = 12.21 Hz, 1H), 2.06–1.86 (m, 2H), 1.74–1.47 (m, 8H), 0.88 (t, J = 7.32 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 151.4,

133.4, 127.0, 126.1, 125.4, 125.3, 125.0, 122.4, 120.6, 118.4, 92.5, 78.6, 51.8, 50.7, 37.4, 37.0, 36.6, 24.7, 24.6, 8.6; IR (KBr, cm^{-1}): ν 3200, 2061, 2955, 2866, 1634, 1502, 1382, 807, 758, 671; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{25}O_2$ $[M + H]^+$ 297.1849, found 297.1848.

2-(3-Benzyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (3ca). Following the general procedure, to a mixture of (1-(3-phenylprop-2-yn-1-yl)cyclopentyl)methanol (**1c**) (0.050 g, 0.23 mmol) and naphthalen-1-ol (**2a**) (0.033 g, 0.23 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.015 g, 0.023 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ca** as a brown liquid (0.050 g, 60%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 200 MHz): δ 10.30 (s, 1H), 8.26–8.11 (m, 1H), 7.80–7.63 (m, 1H), 7.48–7.38 (m, 2H), 7.30–7.22 (m, 2H), 7.18–7.08 (m, 3H), 7.02–6.86 (m, 2H), 3.79–3.64 (m, 2H), 3.79–3.64 (m, 2H), 2.51 (d, J = 12.63 Hz, 1H), 2.32 (d, J = 12.63 Hz, 1H), 1.69–1.44 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 151.3, 137.5, 136.5, 133.6, 130.8, 130.3, 127.7, 127.0, 126.5, 126.2, 125.6, 125.4, 124.9, 122.5, 120.8, 118.2, 91.8, 78.8, 50.8, 50.1, 49.0, 37.3, 37.1, 29.7, 24.7, 24.6; IR (KBr, cm^{-1}): ν 3229, 3060, 2948, 2863, 1632, 1499, 1382, 805, 754, 702; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{27}O_2$ $[M + H]^+$ 359.2006, found 359.2003.

2-(3-Phenethyl-2-oxaspiro[4.4]nonan-3-yl)naphthalen-1-ol (3da). Following the general procedure, to a mixture of (1-(4-phenylbut-2-yn-1-yl)cyclopentyl)methanol (**1d**) (0.050 g, 0.021 mmol) and naphthalen-1-ol (**2a**) (0.031 g, 0.021 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.013 g, 0.0021 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3da** as a brown liquid (0.045 g, 51%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz): δ 10.58 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 9.16 Hz 1H), 7.55–7.42 (m, 2H), 7.39–7.17 (m, 4H), 7.17–6.96 (m, 3H), 3.91–3.15 (m, 2H), 2.68–2.54 (m, 1H), 2.27–2.22 (m, 1H), 1.71–1.44 (m, 12H); ^{13}C NMR ($CDCl_3$, 101 MHz): 150.1, 142.1, 133.5, 128.3, 127.0, 126.1, 125.1, 124.9, 122.4, 118.7, 118.6, 91.9, 89.2, 78.7, 52.7, 51.1, 50.07, 46.1, 37.7, 37.3, 36.9, 36.8, 30.9, 30.6, 24.7; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{29}O_2$ $[M + H]^+$ 373.2162, found 373.2155.

2-(3-Methyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (3ea). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclohexyl)methanol (**1e**) (0.050 g, 0.032 mmol) and naphthalen-1-ol (**2a**) (0.049 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.020 g, 0.0032 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ea** as a brown liquid (0.068 g, 70%). TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz): δ 10.37 (s, 1H), 8.27–8.14 (m, 1H), 7.71–7.57 (m, 1H), 7.44–7.30 (m, 2H), 7.22 (d, J = 8.59 Hz, 1H), 6.98 (d, J = 8.59 Hz, 1H), 3.79 (d, J = 8.59 Hz, 1H), 3.63 (d, J = 8.59 Hz, 1H), 2.43 (d, J = 12.88 Hz, 1H), 1.93 (d, J = 12.76 Hz, 1H), 1.56 (s, 3H), 1.50–1.11 (m, 10H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.0, 133.5, 127.1, 126.1, 125.5, 125.1, 124.9, 122.6, 122.4, 118.7, 88.9, 77.8, 51.7, 44.3, 36.9, 35.9, 31.1, 25.8, 23.8, 23.7; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{25}O_2$ $[M + H]^+$ 297.1849, found 297.1847.

1-(3-Methyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-2-ol (3eb). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclohexyl)methanol (**1ea**) (0.050 g, 0.32 mmol) and naphthalen-2-ol (**2b**) (0.049 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.020 g, 0.032 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3eb** as a brown liquid (0.065 g, 60%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz): δ 11.1 (s, 1H), 7.75–7.74 (m, 1H), 7.64 (d, J = 9.16 Hz, 1H), 7.48–7.40 (m, 2H), 7.30–7.27 (m, 1H), 7.06 (d, J = 8.54 Hz, 1H), 3.91 (d, J = 8.54 Hz 1H), 3.72 (d, J = 8.54 Hz, 1H), 2.58 (d, J = 12.82 Hz, 1H), 2.46 (d, J = 12.82 Hz, 1H), 1.90 (s, 3H), 1.73–1.59 (m, 10H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.9, 131.2, 129.6, 129.3, 129.1, 125.5, 124.4, 122, 120.9, 120.4, 89.63, 77.34, 54.08, 44.4, 35.9, 35.5, 30.3, 29.7, 25.9, 23.8, 23.5; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{25}O_2$ $[M + H]^+$ 297.1849, found 297.1846.

2-(3-Ethyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (3fa). Following the general procedure, to a mixture of (1-(but-2-yn-1-yl)cyclohexyl)methanol (**1f**) (0.050 g, 0.30 mmol) and naphthalen-1-ol (**2a**) (0.043 g, 0.30 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.019 g, 0.030 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc /hexanes) afforded **3fa** as a brown viscous liquid (0.047 g, 49.88%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz): δ 10.56 (s, 1H), 8.35–8.26 (m, 1H), 7.79–7.71 (m, 1H), 7.51–7.42 (m, 2H), 7.34 (d, J = 8.77 Hz, 1H), 7.06 (d, J = 8.77 Hz, 1H), 3.84 (d, J = 8.77 Hz, 1H), 3.79 (d, J = 8.77 Hz, 1H), 2.48 (d, J = 12.59 Hz, 1H), 2.01 (d, J = 12.97 Hz, 1H), 2.0–1.83 (m, 2H), 1.62–1.45 (m, 5H), 1.43–1.26 (m, 5H), 0.88 (t, J = 7.44 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.18, 133.5, 127.05, 126.1, 125.4, 125.0, 122.4, 120.6, 118.4, 92.1, 77.7, 50.8, 43.9, 36.8, 36.7, 35.9, 29.7, 25.8, 23.9, 23.6, 8.7; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{27}O_2$ $[M + H]^+$ 311.2006, found 311.2003.

2-(3-Propyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (3ga). Following the general procedure, to a mixture of 2-(1-(pent-2-yn-1-yl)cyclohexyl)ethan-1-ol (**1g**) (0.050 g, 0.27 mmol) and naphthalen-1-ol (**2a**) (0.039 g, 0.27 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.018 g, 0.027 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ga** as a brown viscous liquid (0.058 g, 64%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz): δ 10.57 (s, 1H), 8.38–8.26 (m, 1H), 7.82–7.74 (m, 1H), 7.54–7.44 (m, 2H), 7.33 (d, J = 8.77 Hz, 1H), 7.06 (d, J = 8.77 Hz, 1H), 3.86 (d, J = 8.39 Hz, 1H), 3.79 (d, J = 8.39 Hz, 1H),

2.51 (d, J = 12.97 Hz, 1H), 2.05 (d, J = 12.59 Hz, 1H), 1.91–1.98 (m, 1H), 1.85 (td, J = 12.78, 4.58 Hz, 1H), 1.45–1.60 (m, 6H), 1.40 (m, 2H), 1.29–1.34 (m, 4H), 0.85 (t, J = 7.25 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.9, 133.4, 127.05, 126.1, 125.4, 125.04, 122.4, 120.9, 118.4, 91.7, 77.7, 51.2, 46.5, 43.9, 36.8, 35.9, 29.7, 25.8, 23.9, 23.6, 17.6, 14.3; HRMS (ESI) m/z calcd for $C_{22}H_{29}O_2$ $[M + H]^+$ 325.2162, found 325.1908.

2-(1,1,3-Trimethyl-2-oxaspiro[4.5]decan-3-yl)naphthalen-1-ol (3ha). Following the general procedure, to a mixture of 2-methyl-1-(1-(prop-2-yn-1-yl)cyclohexyl)propan-2-ol (**1h**) (0.050 g, 0.39 mmol) and naphthalen-1-ol (**2a**) (0.039 g, 0.39 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.018 g, 0.039 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ha** as a brown liquid (0.062 g, 69%). TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.79 (s, 1H), 8.43–8.28 (m, 1H), 7.77 (m, 1H), 7.57–7.44 (m, 2H), 7.35 (d, J = 8.55 Hz, 1H), 7.15 (d, J = 8.54 Hz, 1H), 2.76 (d, J = 13.43 Hz, 1H), 2.45 (d, J = 12.82 Hz, 1H), 1.81–1.69 (m, 4H), 1.66 (s, 3H), 1.58–1.40 (m, 4H), 1.33 (s, 3H), 1.21 (s, 3H), 1.18–1.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.2, 133.3, 127.1, 125.9, 125.6, 125.4, 124.9, 124.3, 122.5, 118.5, 87.9, 85.4, 77.4, 47.7, 46.8, 33.3, 32.05, 31.9, 26.2, 24.4, 23.3, 23.28, 23.1; IR (KBr, cm^{-1}): ν 3218, 3019, 2933, 1597, 1381, 1216, 760, 666; HRMS (ESI) m/z calcd for $C_{22}H_{29}O_2$ $[M + H]^+$ 325.2162, found 325.2161.

2-(2-Methyl-4,4-diphenyltetrahydrofuran-2-yl)naphthalen-1-ol (3ia). Following the general procedure, to a mixture of 2,2-diphenylpent-4-yn-1-ol (**1i**) (0.050 g, 0.21 mmol) and naphthalen-1-ol (**2a**) (0.031 g, 0.21 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.013 g, 0.021 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ia** as a brown liquid (0.054 g, 67%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.25 (s, 1H), 8.31–8.17 (m, 1H), 7.7–7.61 (m, 1H), 7.53–7.47 (m, 4H), 7.43–7.34 (m, 3H), 7.28 (d, J = 8.77 MHz, 1H), 7.23–7.16 (m, 4H), 7.14–7.10 (m, 2H), 5.02–4.86 (d, J = 9.16 Hz, 1H), 4.3 (d, J = 9.16 Hz, 1H), 3.43 (d, J = 12.59 Hz, 1H), 3.18–3.03 (d, J = 12.59 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.5, 145.8, 145.03, 133.4, 128.6, 128.4, 127.1, 127.07, 126.9, 126.5, 126.2, 125.5, 125.23, 124.7, 123.44, 122.5, 119.1, 89.4, 76.1, 55.7, 52.3, 30.7; HRMS (ESI) m/z calcd for $C_{27}H_{25}O_2$ $[M + H]^+$ 381.1849, found 381.1846.

5-Methyl-2-(2-methyl-4,4-diphenyltetrahydrofuran-2-yl)phenol (3if). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1i**) (0.050 g, 0.21 mmol) and p-cresol (**2f**) (0.022 g, 0.21 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.013 g, 0.021 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3if** as a brown liquid (0.050 g, 68%). TLC: R_f = 0.66 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.13 (s, 1H), 7.43–7.27 (m, 4H), 7.22–7.09 (m, 6H), 6.92–6.83 (m, 1H), 6.80–6.73 (m, 1H), 6.73–6.65 (d, J = 8.21 Hz, 1H), 4.88 (d, J = 9.2 Hz, 1H), 4.23 (d, J = 9.09 Hz, 1H), 3.36 (d, J = 12.63 Hz, 1H), 3.06 (d, J = 11.62 Hz, 1H), 2.23 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.2, 145.8, 145.2, 130.9, 128.9, 128.5, 128.4, 127.1, 126.9, 126.5, 117.1, 88.7, 75.9, 55.7, 52.0, 30.7, 20.6; HRMS (ESI) m/z calcd for $C_{24}H_{24}O_2$ $[M]^+$ 344.1771, found 344.2276.

2-(2,5-Dimethyltetrahydrofuran-2-yl)naphthalen-1-ol (3ja). Following the general procedure, to a mixture of hex-5-yn-2-ol (**1j**) (0.050 g, 0.50 mmol) and naphthalen-1-ol (**2a**) (0.073 g, 0.50 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.032 g, 0.050 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ja** (dr. 2 : 1) as a mixture of two diastereomers (0.080 g, 65%) as a brown liquid. TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.64 (s, 1H, major isomer), 10.49 (s, 1H, minor isomer), 8.18–8.34 (m, 2H), 7.66–7.79 (m, 2H, major and minor isomers), 7.39–7.51 (m, 4H, major and minor isomers), 7.30 (d, J = 8.72 Hz, 2H, major and minor isomers), 7.01–7.13 (m, 2 H, major and minor isomers), 4.49–4.36 (m, 1H, minor isomer), 4.31–4.11 (m, 1H, major isomer), 2.6–1.9 (m, 6H, major and minor isomers), 1.61 (s, 3H, major isomer), 1.6 (s, 3H, minor isomer), 1.38 (d, J = 6.06 Hz, 3H, major isomer), 1.34 (d, J = 6.1 Hz, 3H, minor isomer); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (two diastereomers) 150.84, 150.51, 133.57, 127.09, 126.12, 125.71, 125.52, 125.12, 125.07, 124.88, 124.40, 124.15, 122.67, 122.49, 122.40, 118.79, 118.62, 88.64, 88.42, 76.43, 39.66, 39.30, 32.84, 32.78, 30.53, 29.74, 29.52, 21.53, 21.13; HRMS (ESI) m/z calcd for $C_{16}H_{19}O_2$ $[M + H]^+$ 243.1380, found 243.1377.

2-(5-Benzyl-2-methyltetrahydrofuran-2-yl)naphthalen-1-ol (3ka). Following the general procedure, to a mixture of 2-phenylpent-4-yn-1-ol (**1k**) (0.100 g, 0.062 mmol) and 1-napthol (**1a**) (0.089 g, 0.062 mmol) in anhydrous toluene (5 mL) was added $Bi(OTf)_3$ (0.04 g, 0.0062 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 2 h. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ka** (dr, 1 : 1.6) as a mixture of two diastereomers (0.120 g, 66%) as a brown liquid. TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (two diastereomers) 10.34 and 10.18 (s, 1H), 8.4–8.34 and 8.33–28 (m, 1H), 7.82–7.71 (m, 1H), 7.5–7.4 (m, 2H), 7.39–7.24 (m, 5H), 7.17–7.03 (m, 1H), 4.67–4.51 and 4.45–4.25 (m, 1H), 3.1–3.05 (m, 1H), 3.02–2.93 and 2.86–2.79 (m, 1H), 2.61–2.41 (m, 1H), 2.30–1.92 (m, 2H), 1.89–1.75 (m, 1H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ (two diastereomers) 150.8, 150.5, 138.1, 137.9, 133.5, 129.5, 129.1, 128.5, 128.4, 127.1, 126.5, 126.5, 126.1, 125.5, 125.1, 124.4, 122.2, 118.8, 88.8, 88.5, 81.4, 80.8, 42.2, 42.01, 38.9, 38.8, 30.6, 30.4, 30.2, 29.3; HRMS (ESI) m/z calcd for $C_{22}H_{23}O_2$ $[M + H]^+$ 319.1693, found 319.1688.

2-(2-Methyl-3a-(prop-2-yn-1-yl)-2,3,3a,4,5,9b-hexahydronaphtho[1,2-*b*]furan-2-yl)naphthalen-1-ol (3la). Following the general

procedure, to a mixture of 2,2-di(prop-2-yn-1-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (**1l**) (0.050 g, 0.22 mmol) and naphthalen-1-ol (**2a**) (0.032 g, 0.22 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.014 g, 0.022 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3la** as a single diastereomer (0.045 g, 55%) as a brown liquid. Diastereoselectivity was confirmed by 2D NMR analysis (COSY, HMBC, HSQC and NOE).[13] TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.46 (s, 1H), 8.43–8.31 (m, 1H), 7.81–7.71 (m, 1H), 7.53–7.34 (m, 4H), 7.29 (m, 2H), 7.25–7.15 (m, 2H), 4.59 (s, 1H), 3.07 (d, J = 13.26 Hz, 1H), 2.83 (m, 1H), 2.37–1.91 (m, 5H), 1.67 (s, 3H), 1.46–1.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.3, 137.5, 133.7, 132.4, 131.2, 128.78, 128.76, 127.2, 126.7, 126.3, 125.5, 125.2, 124.8, 122.6, 121.9, 119.1, 87.1, 81.9, 80.9, 70.4, 51.04, 44.1, 31.4, 30.7, 25.9, 25.8; HRMS (ESI) m/z calcd for $C_{26}H_{25}O_2$ $[M + H]^+$ 369.1849, found 369.1847.

2-(2-Methyloctahydrobenzofuran-2-yl)naphthalen-1-ol (3ma). Following the general procedure, to a mixture of 2-(prop-2-yn-1-yl)cyclohexan-1-ol (**1m**, 1,2-trans substituted) (0.050 g, 0.36 mmol) and naphthalen-1-ol (**2a**) (0.062 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.0036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3ma** (0.059 g, 56%) as a mixture of two diastereomers (dr, 1 : 2) as a brown liquid. TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (two diastereomers) 10.95 and 10.78 (s, 1H), 8.34–8.22 (m, 1 H), 7.76–7.64 (m, 1H), 7.52–7.31 (m, 2H), 7.34–7.23 (m, 1 H), 7.08–6.99 (m, 1H), 3.52–3.23 (m, 1H), 2.61–2.30 (m, 2H), 2.28–2.10 (m, 1H), 2.02–1.78 (m, 2H), 1.75 and 1.60 (s, 2H), 1.54–1.01 (m, 6H); ^{13}CNMR ($CDCl_3$, 101 MHz): δ (two diastereomers) 151.3, 149.7, 133.4, 129.1, 128.3, 127.1, 127.03, 126.2, 126.1, 125.8, 125.5, 125.3, 125.2, 125.1, 125.1, 124.7, 124.1, 122.5, 122.3, 118.9, 118.4, 89.2, 87.6, 84.1, 83.9, 47.4, 46.3, 45.1, 44.1, 31.4, 31.3, 31.01, 30.08, 30.26, 28.8, 28.6, 25.5, 25.4, 24.3, 24.1, 21.5; HRMS (ESI) m/z calcd for $C_{19}H_{23}O_2$ $[M + H]^+$ 283.1693, found 283.1691.

2-(2-Methyloctahydrobenzofuran-2-yl)naphthalen-1-ol (3na). Following the general procedure, to a mixture of 2-(prop-2-yn-1-yl)cyclohexan-1-ol (**1n**) (0.050 g, 0.36 mmol) and naphthalen-1-ol (**2a**) (0.062 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3na** (0.062 g, 59%) as a mixture of two diastereomers (dr, 1 : 1) and as a brown liquid. TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ (two diastereomers) 10.85 (s, 1H), 10.67 (s, 1H), 8.37 and 8.22 (m, 2H), 7.75 and 7.65 (m, 2H), 7.46–7.40 (m, 4H), 7.29 (d, J = 8.59 Hz, 2H), 7.04 (dd, J = 8.53, 4.61 Hz, 2H), 4.25 (d, J = 4.93 Hz, 1H), 4.07 (d, J = 4.04 Hz, 1H), 2.64 (dd, J = 11.62, 6.32 Hz, 1H), 2.43 and 2.24 (m, 5H), 1.91 and 2.16 (m, 5H), 1.71 and 1.58 (s, 3H) and (s, 3H), 1.24–1.50 (m, 12H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (two diastereomers) 150.3, 149.8, 149.7, 133.4, 133.3, 127, 126.1, 126, 125.7, 125.5, 125.2, 125.1, 125, 124.9, 124.5, 123.9, 123.6, 122.6, 122.4, 118.9, 118.7, 118.5, 87.8, 87.6, 86.3, 81.1, 80.5, 78.6, 77.8, 77.4, 77.1, 76.7, 70.4, 52.4, 45.9, 45.8, 43.2, 37.9, 37.9, 32.1, 32.1, 31.9, 31.6, 30.2, 28.5, 28.1, 28.0, 26.6, 25.9, 24.9, 23.8, 22.6, 21.6, 21.5, 20.9, 20; HRMS (ESI) m/z calcd for $C_{19}H_{23}O_2$ $[M + H]^+$ 283.1693, found 283.1690.

2-(2-Methyltetrahydrofuran-2-yl)naphthalen-1-ol (3oa). Following the general procedure, to a mixture of pent-4-yn-1-ol (**1o**) (0.050 g, 0.59 mmol) and naphthalen-1-ol (**2a**) (0.085 g, 0.59 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.038 g, 0.059 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 8 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **3oa** as a brown liquid (0.096 g, 71%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.44 (s, 1H), 8.39–8.26 (m, 1H), 7.83–7.71 (m, 1H), 7.56–7.44 (m, 2H), 7.35 (d, J = 8.55 Hz, 1H), 7.13 (d, J = 8.55 Hz, 1H), 4.21–4.11 (m, 1H), 4.04–3.97 (m, 1H), 2.59–2.46 (m, 1H), 2.24–2.16 (m, 1H), 2.15–2.06 (m, 1H), 2.04–1.94 (m, 1H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.7, 133.6, 127, 126.1, 125.5, 125.1, 124.3, 122.4, 121.9, 118.8, 88.5, 68.6, 38.8, 29.1, 25.3; IR (KBr, cm^{-1}): ν 3205, 2973, 1501, 1455, 1304, 1216, 1030, 804, 757; HRMS (ESI) m/z calcd for $C_{15}H_{17}O_2$ $[M + H]^+$ 229.1223, found 229.1222.

2-(2-Methyltetrahydro-2*H*-pyran-2-yl)naphthalen-1-ol (5aa). Following the general procedure, to a mixture of hex-5-yn-1-ol (**4a**) (0.050 g, 0.50 mmol) and naphthalen-1-ol (**2a**) (0.073 g, 0.50 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.033 g, 0.0050 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 10 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **5aa** as a brown liquid (0.072 g, 58%). TLC: R_f = 0.70 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.68 (s, 1H), 8.29 (dd, J = 6.19, 3.41 Hz, 1H), 7.75 (dd, J = 5.81, 3.03 Hz, 1H), 7.46 (dd, J = 6.19, 3.28 Hz, 1H), 7.36 (d, J = 8.46 Hz, 1H), 7.17 (d, J = 8.72 Hz, 1H), 4.01–3.82 (m, 1H), 3.67–3.46 (m, 1H), 2.49 (d, J = 11.37 Hz, 1H), 1.86–1.78 (m, 1H), 1.77–1.64 (m, 4H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.1, 133.9, 127, 126.3, 125.4, 125, 124.5, 122.3, 119.4, 118.9, 80.1, 63.6, 34.7, 29.3, 25.4, 19.6; IR (KBr, cm^{-1}): ν 3239, 3019, 2935, 1577, 1379, 1275, 760, 669; HRMS (ESI) m/z calcd for $C_{16}H_{19}O_2$ $[M + H]^+$ 243.1380, found 243.1378.

2-(2,6-Dimethyltetrahydro-2*H*-pyran-2-yl)naphthalen-1-ol (5ba). Following the general procedure, to a mixture of hept-6-yn-2-ol (**4b**) (0.050 g, 0.40 mmol) and naphthalen-1-ol (**2a**) (0.058 g, 0.40 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.026 g, 0.0040 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 10 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **5ba** as a brown liquid (0.063 g, 55%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.79 (s, 1H), 8.38–8.33 (m, 1H),

7.79 (dd, J = 5.91, 3.62 Hz, 1H), 7.53–7.47 (m, 2H), 7.39 (d, J = 8.77 Hz, 1H), 7.20 (d, J = 8.39 Hz, 1H), 3.62 (ddd, J = 12.21, 6.10, 2.29 Hz, 1H), 2.60–2.54 (m, 1H), 1.81–1.67 (m, 4H), 1.60 (s, 3H), 1.43–1.33 (m, 2H), 1.29 (d, J = 6.49 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.4, 133.9, 127.1, 126.2, 125.4, 124.9, 124.5, 122.4, 119.5, 118.8, 80.5, 69.4, 33.9, 32.6, 30.5, 22.5, 20.06, 19.7; HRMS (ESI) m/z calcd for $C_{17}H_{21}O_2$ $[M + H]^+$257.1536, found 257.1532.

5-(1-Hydroxynaphthalen-2-yl)-5-methylhexahydro-2*H*-furo[3,2-*b*]pyran-2-one (5ca). Following the general procedure, to a mixture of 5-(but-3-yn-1-yl)-4-hydroxydihydrofuran-2(3*H*)-one (**4c**) (0.050 g, 0.32 mmol) and naphthalen-1-ol (**2a**) (0.047 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.021 g, 0.0032 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 10 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **5ca** as a colourless liquid (0.029 g, 30%) as a single diastereomer. TLC: R_f = 0.4 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.88 (s, 1H), 8.34–8.24 (m, 1H), 7.84–7.77 (m, 1H), 7.59–7.49 (m, 2H), 7.43 (d, J = 8.77 Hz, 1H), 7.15 (d, J = 8.39 Hz, 1H), 4.28 (d, J = 3.05 Hz, 2H), 2.79 (dd, J = 17.17, 3.81 Hz, 1H), 2.69 (d, J = 17.17 Hz, 1H), 2.40 (m, 1H), 2.34–2.26 (m, 1H), 2.01–2.07 (m, 2H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.3, 151.8, 134.1, 127.1, 126.8, 125.5, 125.3, 123.7, 122.2, 119.8, 116.9, 79.6, 75.6, 69.9, 38.9, 29.8, 27.1, 21.6; IR (KBr, cm^{-1}): ν 3685, 3345, 3022, 2931, 1784, 1580, 1379, 1215, 763, 672; HRMS (ESI) m/z calcd for $C_{18}H_{19}O_4$ $[M + H]^+$ 299.1278, found 299.1276.

2-(2-Methyl-1,4-dioxan-2-yl)naphthalen-1-ol (5da). Following the general procedure, to a mixture of 2-(prop-2-yn-1-yloxy) ethan-1-ol (**4d**) (0.050 g, 0.49 mmol) and naphthalen-1-ol (**2a**) (0.072 g, 0.49 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.032 g, 0.0049 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 10 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **5da** as a brown liquid (0.055 g, 45%). TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.20 (s, 1H), 8.37–8.24 (m, 1H), 7.76 (dd, J = 5.87, 3.47 Hz, 1H), 7.55–7.45 (m, 2H), 7.42–7.35 (m, 1H), 7.27–7.19 (m, 1H), 4.41 (d, J = 12.38 Hz, 1H), 3.86–3.66 (m, 5H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 151.9, 134.1, 127.1, 126.5, 125.5, 125.1, 124.3, 122.3, 119.3, 118.1, 78.6, 72.6, 66.5, 62, 23.6; IR (KBr, cm^{-1}): ν 3259, 3016, 2965, 2858, 1631, 1578, 1458, 1110, 803, 757; HRMS (ESI) m/z calcd for $C_{15}H_{17}O_3$ $[M + H]^+$ 245.1172, found 245.1169.

3-(Furan-2-yl)-3-methyl-2-oxaspiro[4.4]nonane (7aa). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.50 g, 0.36 mmol) and furan (**6a**) (0.024 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 4 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **7aa** as a brown liquid (0.033 g, 45%). TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35 (s, 1H), 6.63 (s, 1H), 6.20 (d, J = 3.05 Hz, 1H); 3.69 (m, 2H), 2.40 (d, J = 12.82 Hz, 1H), 1.90 (d, J = 12.21 Hz, 1H), 1.68–1.52 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.5, 141.5, 109.8, 104.3, 80.3, 78.6, 51.6, 50.2, 38.5, 36.9, 27.2, 24.7, 24.6; HRMS (ESI) m/z calcd for $C_{13}H_{19}O_2$ $[M + H]^+$ 207.1380, found 207.1166.

2,5-Bis(3-methyl-2-oxaspiro[4.4]nonan-3-yl)furan (7aa[1]). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.50 g, 0.36 mmol) and furan (**6a**) (0.024 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 4h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **7aa[1]** as a brown liquid (0.064 g, 51%) as a mixture of two diastereomers (dr, 1 : 3, confirmed by HPLC analysis).[13] TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (two diastereomers) 6.10 (s, 2H), 3.69 (d, J = 1.4 Hz, 4H), 2.42 (d, J = 12.8 Hz, 2H), 1.88 (d, J = 12.8 Hz, 2H), 1.58 (s, 22H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ (two diastereomers) 158.3, 158.3, 104.7, 104.7, 80.2, 80.1, 78.53, 51.6, 50.1, 38.4, 36.8, 36.8, 27.0, 26.9, 24.7, 24.7, 24.5; HRMS (ESI) m/z calcd for $C_{22}H_{33}O_3$ $[M + H]^+$ 345.2424, found 345.2423.

3-Ethyl-3-(furan-2-yl)-2-oxaspiro[4.4]nonane (7ba) and 2,5-bis(3-ethyl-2-oxaspiro[4.4]nonan-3-yl)furan (7ba[1]). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**7b**) (0.50 g, 0.32 mmol) and furan (**6a**) (0.022 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.021 g, 0.032 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 4 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded a mixture of **7ba** and **7ba[1]** as a brown liquid (0.085 g, 86%). TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40–7.31 (m, 1 H), 6.34–6.24 (m, 1 H), 6.20 (d, J = 3.16 Hz, 1 H), 6.12 (s, 2H), 3.82–3.44 (m, 5H), 2.31 (d, J = 12.76 Hz, 3H), 1.97–1.37 (m, 34H) (td, J = 7.45, 1.77 Hz, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.1, 156.8, 141.4, 109.7, 106.36, 105.9, 105.6, 84.2, 78.3, 72.4, 71.1, 51.2, 48.4, 48.2, 41.5, 38.5, 38.4, 37.3, 37.3, 37.2, 36.3, 34.5, 33.3, 33.1, 31.7, 29.6, 28.8, 24.9, 24.6, 24.5, 24.4, 8.9; HRMS (ESI) m/z calcd for (**7ba**) $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1536, found 221.1534; HRMS (ESI) m/z calcd for (**7ba[1]**) $C_{24}H_{37}O_3$, $[M + H]^+$ 373.2737, found 373.2735.

3-(Furan-2-yl)-3-methyl-2-oxaspiro[4.5]decane (7ea). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclohexyl)methanol (**1e**) (0.050 g, 0.32 mmol) and furan (**6a**) (0.042 g, 0.64 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.020 g, 0.032 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 4 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **7ea** as a brown liquid (0.043 g, 60%). TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39–7.31 (m, 1H), 6.33–6.25 (m, 1H), 6.18 (d, J = 2.65 Hz, 1H), 3.73 (d, J = 8.72 Hz, 1H), 3.62 (d, J = 8.72 Hz, 1H), 2.26 (d, J = 12.88 Hz, 1H), 1.76 (d, J = 13.0 Hz, 1H), 1.59 (s, 3H), 1.56–1.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.4, 141.5, 109.8, 104.4, 80.1, 49.3, 44.7, 37.2, 36,

27.6, 25.9, 23.9, 23.7; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1536, found 221.1534.

3-(Furan-2-yl)-3-methyl-2-oxaspiro[4.5]decane (7ea) and 2,5-bis(3-methyl-2-oxaspiro[4.5]decan-3-yl)furan (7ea[1]). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1e**) (0.050 g, 0.32 mmol) and furan (**6a**) (0.021 g, 0.32 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.22 g, 0.032 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 4 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded an inseparable mixture of **7ea** and **7ea[1]** as a brown viscous liquid (0.070 g, 74%). TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.36–7.30 (m, 1H), 6.28 (dd, J = 3.28, 1.89 Hz, 1H), 6.18 (d, J = 3.28 Hz, 1H), 6.07 (d, J = 0.88 Hz, 2H), 3.76–3.58 (m, 6H), 2.33–2.22 (m, 3H), 1.80–1.68 (m, 3H), 1.56 (d, J = 2.02 Hz, 8H), 1.52–1.36 (m, 30H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.4, 158.3, 158.2, 141.6, 109.8, 104.8, 104.4, 80.1, 80, 77.8, 49.2, 44.6, 37.2, 36, 29.7, 27.6, 27.5, 27.4, 25.9, 23.9, 23.7; HRMS (ESI) *m*/*z* calcd for (**7ea**) $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1536, found 221.1533; HRMS (ESI) *m*/*z* calcd for (**7ea[1]**) $C_{24}H_{37}O_3$ $[M + H]^+$ 373.2737, found 373.2733.

2-(2-Methyl-4,4-diphenyltetrahydrofuran-2-yl)furan (7ia). Following the general procedure, to a mixture of 2,2-diphenylpent-4-yn-1-ol (**1f**) (0.050 g, 0.21 mmol) and furan (**6a**) (0.014 g, 0.21 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.13 g, 0.021 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 4 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **7ia** as a viscous yellow liquid (0.028 g, 40%). TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.42–7.09 (m, 11H), 6.29–6.16 (m, 1H), 6.07 (d, J = 3.03 Hz, 1H), 4.76 (d, J = 9.22 Hz, 1H), 4.31 (d, J = 9.35 Hz, 1H), 3.30 (d, J = 12.88 Hz, 1H), 2.73 (d, J = 12.88 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.1, 147, 145.9, 141.7, 128.4, 127.2, 126.2, 126.1, 109.9, 104.6, 80.6, 56.5, 49.6, 26.6; IR (KBr, cm^{-1}): ν 3057, 2975, 2862, 1596, 1493, 1448, 1292, 1155, 1057, 755, 698; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{20}O_2$ $[M + Na]^+$ 327.1356, found 327.1352.

2-(2-Methyl-4,4-diphenyltetrahydrofuran-2-yl)-5-(2-methyl-4,4-diphenyltetrahydrofuran-2-yl)furan (7ia[1]). Following the general procedure, to a mixture of 2,2-diphenylpent-4-yn-1-ol (**1f**) (0.050 g, 0.21 mmol) and furan (**6a**) (0.014 g, 0.21 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.013 g, 0.021 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 4 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **7ia[1]** as a viscous yellow liquid (0.067 g, 59%), as a mixture of two inseparable diastereomers (confirmed by ^{1}H NMR and HPLC analysis). TLC: R_f = 0.8 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.36–7.09 (m, 20H), 6.03–5.84 (d, J = 0.63 Hz, 2H), 4.68 (dd, J = 8.84, 4.80 Hz, 2H), 4.26 (dd, J = 9.35, 1.01 Hz, 2H), 3.22 (dd, J = 13.01, 7.33 Hz, 2H), 2.64 (d, J = 13.01 Hz, 2H), 1.38 (d, J = 2.53 Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.1, 158, 147.3, 145.9, 128.3, 127.2, 126.2, 126.1, 105, 105, 80.6, 80.6, 76.5, 76.5, 56.5, 56.5, 49.7, 26.6, 26.4; IR (KBr, cm^{-1}): ν 3376, 3016, 1599, 1444, 1216, 760, 702; HRMS (ESI) *m*/*z* calcd for $C_{38}H_{37}O_3$ $[M + H]^+$ 541.2737, found 541.2737.

2-(Furan-2-yl)-2-methyl-3a-(prop-2-yn-1-yl)-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan (7pa) and 2-(2-methyl-3a-(prop-2-yn-1-yl)-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-yl)-5-(2-methyl-3a-(prop-2-yn-1-yl)-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-yl) furan (7pa[1]). Following the general procedure, to a mixture of 2,2-di(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-ol (**1p**) (0.050 g, 0.23 mmol) and furan (**6a**) (0.016 g, 0.23 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.015 g, 0.023 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 4 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded a mixture of **7pa** and **7pa[1]** as a viscous brown liquid (0.085 g, 92%). TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.44 (d, J = 2.53 Hz, 1H), 7.40–7.37 (m, 2H), 7.28–7.20 (m, 10H), 6.32–6.31 (m, 2H), 6.00 (dd, J = 3.22, 1.83 Hz, 1H), 5.64–5.60 (m, 1H), 5.31–5.26 (m, 3H), 3.13 (d, J = 6.06 Hz, 4H), 2.92 (d, J = 2.53 Hz, 2H), 2.79 (d, J = 13.39 Hz, 3H), 2.53–2.48 (m, 3H), 2.41 (dd, J = 4.93, 2.65 Hz, 4H), 2.33 (t, J = 4.23 Hz, 2H), 2.07–1.96 (m, 4H), 1.92 (t, J = 2.59 Hz, 2H), 1.64 (s, 3H), 1.43 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159, 142.7, 141.7, 141.5, 141, 128.7, 127.1, 125.8, 125.7, 125.2, 124.7, 110.1, 109.8, 104.6, 91.7, 91.6, 82.8, 82.4, 82.2, 69.8, 69.5, 54.7, 54.5, 49.4, 48.8, 43.7, 43.5, 29.7, 28.8, 28.5, 28.3, 27.5; HRMS (ESI) *m*/*z* calcd for (**7pa**) $C_{19}H_{19}O_2$, $[M + H]^+$ 279.1380, found 279.1375; HRMS (ESI) *m*/*z* calcd for (**7pa[1]**) $C_{34}H_{33}O_3$ $[M + H]^+$ 489.2424, found 489.2418.

2-(5-Benzyl-2-methyltetrahydrofuran-2-yl)furan (7ka). Following the general procedure, to a mixture of 2-phenylpent-4-yn-1-ol (**1k**) (0.100 g, 0.062 mmol) and furan (**6a**) (0.042 g, 0.062 mmol) in anhydrous toluene (5 mL) was added $Bi(OTf)_3$ (0.04 g, 0.006 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 2 h. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded two inseparable mixtures of diastereomers of **7ka** (dr, 1 : 2) as a viscous and colourless liquid (0.072 g, 51%). TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.4–7.1 (m, 6H), 6.37–6.28 (m, 1H), 6.26–6.17 (m, 1H), 4.39–4.30 (m, 1H), 3.15–3.01 (m, 1H), 2.83–2.70 (m, 1H), 2.05–1.96 (m, 1H), 1.9–1.7 (m, 2H), 1.60 and 1.59 (s, 1 : 2, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.6, 159.3, 141.6, 141.4, 138.8, 138.5, 129.5, 129.3, 128.3, 128.2, 126.2, 109.9, 109.8, 104.5, 104.4, 80.7, 80.4, 80.3, 80.2, 42.5, 42.2, 37.6, 36.7, 31.6, 30.8, 26.9, 26.5. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{19}O_2$ $[M + H]^+$ 243.1380, found 243.1376.

2-(2-Methyl-5-phenyltetrahydrofuran-2-yl)furan (7qa). Following the general procedure, to a mixture of 1-phenylpent-4-yn-1-ol (**1q**) (0.1 g, 0.062 mmol) and furan (**6a**) (0.042 g, 0.062 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.040 g, 0.006 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 2 h. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/

hexanes) afforded an inseparable mixture of diastereomers of **7qa** (dr, 1 : 1) as a viscous colourless liquid (0.078 g, 51%). TLC: R_f = 0.9 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.46–7.02 (m, 6H), 6.38–6.29 (m, 1H), 6.28–6.20 (m, 1H), 4.41–4.22 (m, 1H), 4.01–3.82 (m, 1H), 3.75–3.49 (m, 1H), 2.85–2.69 (m, 1H), 2.66–2.30 (m, 1H), 2.05 (dd, J = 10.74, 10.61 Hz, 1H), 1.69 and 1.66 (two s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.8, 142, 141.7, 140.5, 128.6, 127.5, 127.3, 126.7, 126.6, 110, 104.8, 104.7, 81.2, 80.4, 74.5, 74.4, 46.1, 45.3, 44.8, 26.6. HRMS (ESI) m/z calcd for $C_{15}H_{17}O_2$ $[M + H]^+$ 229.1223, found 229.1585.

3-(3-Methyl-2-oxaspiro[4.4]nonan-3-yl)-1*H*-indole (7ab). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.36 mmol) and 1*H*-indole-1-carboxylic pivalic anhydride (**6b**) (0.078 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.023 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **7ab** as a viscous brown liquid (in this case –BOC deprotected *in situ*) (0.048 g, 52%). TLC: R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (br. s, 1H), 7.72 (m, 1H), 7.37 (m, 1H), 7.22–7.18 (m, 3H), 3.85 (d, J = 8.34 Hz, 1H), 3.77 (d, J = 8.21 Hz, 1H), 2.46 (d, J = 12.25 Hz, 1 H), 2.15 (d, J = 12.25 Hz, 1H), 1.75 (s, 3H), 1.71–1.49 (m, 8H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.1, 125.1, 124.3, 121.7, 120.2, 119.9, 119.2, 111.2, 82.2, 78.2, 52.1, 51.8, 38.6, 37.3, 30, 24.7, 24.7; IR (KBr, cm^{-1}): ν 3618, 3475, 3416, 3011, 2957, 2863, 1544, 1340, 1216, 1040, 764; HRMS (ESI) m/z calcd for $C_{17}H_{22}NO$ $[M + H]^+$ 256.1696, found 256.1694.

1-Methyl-3-(3-methyl-2-oxaspiro[4.4]nonan-3-yl)-1*H*-indole (7ac). Following the general procedure, to a mixture of (1-(prop-2-yn-1-yl)cyclopentyl)methanol (**1a**) (0.050 g, 0.36 mmol) and 1-methyl-1*H*-indole (**6c**) (0.047 g, 0.36 mmol) in anhydrous toluene (2 mL) was added $Bi(OTf)_3$ (0.037 g, 0.036 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 6 h at rt. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded **7ac** as a viscous brown liquid (0.057 g, 59%). TLC: R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, J = 7.83 Hz, 1H), 7.34–7.18 (m, 2H), 7.18–7.02 (m, 1H), 6.97 (s, 1H), 3.81–3.29 (m, 5H), 2.45 (d, J = 12.38 Hz, 1H), 2.14 (d, J = 12.25 Hz, 1H), 1.68 (s, 3H), 1.67–1.36 (m, 8H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.7, 125.5, 124.7, 123, 121.3, 120.3, 118.7, 109.3, 82.2, 78.1, 52.3, 51.9, 38.6, 37.3, 32.6, 30.3, 24.7, 24.7; HRMS (ESI) m/z calcd for $C_{18}H_{24}NO$ $[M + H]^+$ 270.1852, found 270.1851.

3-(5-(4-Methoxybenzyl)-2-methyltetrahydrofuran-2-yl)-1-methyl-1*H*-indole (7rc). Following the general procedure, to a mixture of 2-(4-methoxybenzyl)pent-4-yn-1-ol (**1r**) (0.100 g, 0.048 mmol) and 1-methyl-1*H*-indole (**6c**) (0.064 g, 0.048 mmol) in anhydrous toluene (5 mL) was added $Bi(OTf)_3$ (0.031 g, 0.004 mmol) under an argon atmosphere at room temperature and the reaction mixture was stirred for 2 h. Purification of the crude product by column chromatography (SiO_2, 2% EtOAc/hexanes) afforded 1 : 1 diastereomers **7rc** as a viscous colourless liquid (0.081 g, 59%). TLC: R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, J = 8.01 Hz 1H), 7.15–6.98 (m, 3H), 7.15–7.01 (m, 3H), 6.82 (t, J = 8.77 Hz, 2H), 4.11 (dt, J = 8.01, 7.63 Hz, 1H), 3.83–3.66 (m, 6H), 2.73–2.52 (m, 3H), 2.37–2.07 (m, 1H), 1.75 and 1.66 (two singlets, 3H); ($CDCl_3$, 126 MHz): δ 157.9, 137.7, 133.0, 129.5, 125.4, 124.6, 121.4, 121.3, 120.5, 120.3, 118.8, 118.8, 113.8, 109.3, 82.6, 82.1, 72.7, 72.4, 55.2, 45.6, 45.3, 42.1, 41.6, 38.8, 38.3, 32.6, 29.6, 29.3. HRMS (ESI) m/z calcd for $C_{22}H_{26}NO_2$ $[M + H]^+$ 336.1958, found 336.1954.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) J. Cossy, *Synthesis of Saturated Oxygenated Heterocycles I: 5-and 6-Membered Rings*, Springer, Paris, 2014; (*b*) M. C. Elliot and E. Williams, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2303–2340; (*c*) M. C. Elliot, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1291–1318; (*d*) T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309–3362.

2 For examples of alkyne hydroalkoxylation, see: (*a*) Z. Liu and B. Breit, *Angew. Chem., Int. Ed.*, 2016, **55**, 8440–8443; (*b*) A. Zhdanko and M. E. Maier, *ACS Catal.*, 2015, **5**, 5994–6004; (*c*) S. Masatoshi, S. Fujita, A. Masanori and Y. Yamamoto, *ACS Catal.*, 2017, **7**, 2848–2852; (*d*) M. J. Pouy, A. S. Delp, J. Uddin, V. M. Ramdeen, N. A. Cochrane, G. C. Fortman, T. B. Gunnoe, T. R. Cundari, M. Sabat and W. H. Myers, *ACS Catal.*, 2012, **2**, 2182–2193; (*e*) P. Wipf and T. H. Graham, *J. Org. Chem.*, 2003, **68**, 8798–8807; (*f*) Y. Sheng, D. G. Musaev, K. S. Reddy, F. E. McDonald and K. Morokuma, *J. Am. Chem. Soc.*, 2002, **124**, 4149–4157; (*g*) B. M. Trost and Y. H. Rhee, *J. Am. Chem. Soc.*, 2002, **124**, 2528–2533; (*h*) I. Kadota, L. M. Lutete, A. Shibuya and Y. Yamamoto, *Tetrahedron Lett.*, 2001, **42**, 6207–6210; (*i*) P. Pale and J. Chuche, *Eur. J. Org. Chem.*, 2000, 1019–1025; (*j*) S. Elgafi, L. D. Field and B. A. Messerle, *J. Organomet. Chem.*, 2000, **607**, 97–104; (*k*) F. E. McDonald, K. S. Reddy and Y. Díaz, *J. Am. Chem. Soc.*, 2000, **122**, 4304–4309; (*l*) F. E. McDonald, *Chem. – Eur. J.*, 1999, **5**, 3103–3106; (*m*) D. Tzalis, C. Koradin and P. Knochel, *Tetrahedron Lett.*, 1999, **40**,

6193–6195; (*n*) F. E. McDonald, C. B. Connolly, M. M. Gleason, T. B. Towne and K. D. Treiber, *J. Org. Chem.*, 1993, **58**, 6952–6953.

3 (*a*) B. M. Trost, B. M. O'Boyle and D. Hund, *J. Am. Chem. Soc.*, 2009, **131**, 15061–15074; (*b*) A. Aponick, C. Y. Li and J. A. Palmes, *Org. Lett.*, 2009, **11**, 121–124; (*c*) S. Selvaratnam, J. H. H. Ho, P. B. Huleatt, B. Messerle and C. L. L. Chai, *Tetrahedron Lett.*, 2009, **50**, 1125–1127; (*d*) C. V. Ramana, S. B. Suryawanshi and R. G. Gonnade, *J. Org. Chem.*, 2009, **74**, 2842–2845; (*e*) B. M. Trost and B. M. O'Blyle, *J. Am. Chem. Soc.*, 2008, **130**, 16190–16192; (*f*) Y. Li, F. Zhou and C. J. Forsyth, *Angew. Chem., Int. Ed.*, 2007, **46**, 279–282; (*g*) B. Liu and J. K. D. Brabander, *Org. Lett.*, 2006, **8**, 4907–4910; (*h*) S. Antoniotti, E. Genin, V. Michelet and J. P. Genet, *J. Am. Chem. Soc.*, 2005, **127**, 9976–9977; (*i*) X. Li, A. R. Chianese, T. Vogel and R. H. Crabtree, *Org. Lett.*, 2005, **7**, 5437–5440; (*j*) J. H. Teles, S. Brode and M. Chabanas, *Angew. Chem., Int. Ed.*, 1998, **37**, 1415–1418; (*k*) Y. Kataoka, O. Matsumoto and K. Tani, *Chem. Lett.*, 1996, **25**, 727–728; (*l*) Y. Fukuda and K. Utimoto, *J. Org. Chem.*, 1991, **56**, 3729–3731.

4 (*a*) C. Ferrer, C. H. M. Amijs and A. M. Echavarren, *Chem. – Eur. J.*, 2007, **13**, 1358–1373; (*b*) A. S. K. Hashmi and M. C. Blanco, *Eur. J. Org. Chem.*, 2006, 4340–4342; (*c*) Z. Li, Z. Shi and C. He, *J. Organomet. Chem.*, 2005, **690**, 5049–5054; (*d*) J. S. Yadav, B. V. S. Reddy, B. Padmavani and M. K. Gupta, *Tetrahedron Lett.*, 2004, **45**, 7577–7579; (*e*) T. Tsuchimoto, K. Hatanaka, E. Shirakawa and Y. Kawakami, *Chem. Commun.*, 2003, 2454–2455.

5 J. Barluenga, A. Diéguez, F. Rodríguez and F. J. Fañanás, *Angew. Chem., Int. Ed.*, 2005, **44**, 126–128; and references cited therein.

6 For a collection of recent reviews, see: (*a*) D. Pflasterer and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2016, **45**, 1331–1367; (*b*) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028–9072; (*c*) M. Rudolph and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2012, **41**, 2448–2462; (*d*) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994–2009; (*e*) A. Fürstner, *Chem. Soc. Rev.*, 2009, **38**, 3208–3221.

7 (*a*) F. J. Fañanás, A. Fernández, D. Çevic and F. Rodríguez, *J. Org. Chem.*, 2009, **74**, 932–934; (*b*) J. Barluenga, A. Fernández, A. Satrústegui, A. Diéguez, F. Rodríguez and F. J. Fañanás, *Chem. – Eur. J.*, 2008, **14**, 4153–4156.

8 H.-J. Li, R. Guillot and V. Gandon, *J. Org. Chem.*, 2010, **75**, 8435–8449.

9 (*a*) L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salomone, S. Florio and V. Capriati, *Chem. Sci.*, 2016, **7**, 1192–1199; (*b*) M. Shibuya, M. Abe, S. Fujita and Y. Yamamoto, *Org. Biomol. Chem.*, 2016, **14**, 5322–5328; (*c*) S. Fujita, M. Abe, M. Shibuya and Y. Yamamoto, *Org. Lett.*, 2015, **17**, 3822–3825; (*d*) P. P. Singh, S. Gudup, H. Aruri, U. Singh, S. Ambala, M. Yadav, S. D. Sawant and R. A. Viswakarma, *Org. Biomol. Chem.*, 2012, **10**, 1587–1597; (*e*) E. D. Butova, A. V. Barabash, A. A. Petrova, C. M. Kleiner, P. R. Schreiner and A. A. Fokin, *J. Org. Chem.*, 2010, **75**, 6229–6235.

10 (*a*) K. Ravindar, M. S. Reddy and P. Deslongchamps, *Org. Lett.*, 2011, **13**, 3178–3181; (*b*) K. Ravindar, M. S. Reddy, L. Lindqvist, J. Pelletier and P. Deslongchamps, *J. Org. Chem.*, 2011, **76**, 1269–1284; (*c*) K. Ravindar, M. S. Reddy, L. Lindqvist, J. Pelletier and P. Deslongchamps, *Org. Lett.*, 2010, **12**, 4420–4423.

11 (*a*) Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2016, **55**, 5352–5353; (*b*) T. Ollevier, *Org. Biomol. Chem.*, 2013, **11**, 2740–2755; (*c*) J. M. Bothwell, S. W. Krabbe and R. S. Mohan, *Chem. Soc. Rev.*, 2011, **40**, 4649–4707; and references cited therein; (*d*) Y. Yamamoto, *J. Org. Chem.*, 2007, **72**, 7817–7831.

12 (*a*) D. A. Kambale, S. S. Thorat, M. S. Pratapure, R. G. Gonnade and R. Kontham, *Chem. Commun.*, 2017, **53**, 6641–6644; (*b*) S. S. Thorat, P. Kataria and R. Kontham, *Org. Lett.*, 2018, **20**, 872–875.

13 See the ESI† for details.

14 (*a*) Y. Zhou, S. Liu, H. Chen, J. Chen, W. Sun, S. Li, Q. Yang and B. Fan, *Chin. J. Chem.*, 2015, **33**, 1115–1118; (*b*) J. Chen, S. Liu, Y. Zhou, S. Li, C. Lin, Z. Bian and B. Fan, *Organometallics*, 2015, **34**, 4318–4322.

15 (*a*) S. M. Bachrach, *J. Org. Chem.*, 2008, **73**, 2466–2468; (*b*) R. M. Bessley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc., Trans.*, 1915, **107**, 1080–1106.

16 (*a*) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, **18**, 734–736; (*b*) K. Gilmore and I. V. Alabugin, *Chem. Rev.*, 2011, **111**, 6513–6556.

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A silver-catalyzed [3 + 3]-annulation cascade of alkynyl alcohols and α,β-unsaturated ketones for the regioselective assembly of chromanes†

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An unprecedented Ag(I)-catalyzed [3 + 3]-annulation of alkynyl alcohols (5-hexyn-1-ols) and α,β-unsaturated ketones is reported to construct simple to complex chromanes. This transformation begins with hydroalkoxylation of alkynol through C–C triple bond activation to give cyclic-enol ether, followed by intermolecular 1,4-addition and intramolecular 1,2-addition of enol ethers onto the enone and oxidative aromatization or Grob-type elimination steps. Facile reaction conditions, broad substrate scope, good to excellent yields, and atom economy are the salient features of this protocol. Isolation of the active pyran-tethered cyclohexadiene reaction intermediate, additional supporting experiments, and DFT calculations strongly support the experimental findings and corroborate our proposed mechanism.

Introduction

Chromanes are omnipresent in biologically potent natural products and pharmaceuticals; hence synthetic strategies towards constructing these scaffolds are particularly important. Examples include α-tocopherol (vitamin E family),[1a] catechins (antitumor and antioxidant agents),[1b] troglitazone (antidiabetic and anti-inflammatory drug),[1c] nebivolol (antihypertensive drug),[1d] LL-D253α (antibiotic),[1e] γ-rubromycin (antioxidant),[1f] chromanol 293B (IKs blocker),[1g] caesalpinflavans (cytotoxic),[1h] virgatolides (cytotoxic),[1i] cebulactam (antioxidant)[1j] and many others.[1k] Furthermore, chromanes constitute the core structure of versatile flavonoids, cannabinoids, and related bio-active molecules. Consequently, in the past few decades, the construction of these scaffolds has earned enormous attention from synthetic organic chemists.[2]

Nearly, the majority of existing protocols rely on the pyran ring-closure of substrates containing pre-functionalized arene appendage *via* [4 + 2], [3 + 3], [5 + 1] annulations, and intramolecular [6]-ring closures (Scheme S1,†[3] entry a).[2] In a few instances, dihydropyran derivatives were also used as precursors to construct the chromane skeleton through arene ring construction. For example, the reaction of pyran-derived Fisher chromium carbene complexes with alkynes (Scheme S1,† entry b. i),[4] Kirschning's [4 + 2]-cycloaddition of dihydropyran derived dienes or dienophiles with ynones or pyranones (Scheme S1,† entry b. ii),[5] and a multi-step reaction involving 6-π-electrocyclization of pyran tethered trienes followed by aromatization (Scheme S1,† entry b. iii).[6]

The next possible way is to install both rings simultaneously from acyclic building blocks in intra- or intermolecular pathways. Hoye's intramolecular hexa-dehydro Diels–Alder reaction (HDDA) of triyne-tethered alkynols (Scheme S1,† entry c),[7] and the intermolecular strategy of the Wulff–Dötz reaction involving the α,β-unsaturated Fischer-carbene complex of chromium with alkenyl-propargylic ethers *via* 6-π-electrocyclization or [4 + 2]-cycloaddition of *in situ* formed *o*-quinone methide are notable examples of this category. However, an extra reduction step is required in the former case and the latter case is limited to a single example (Scheme S1,† entry d).[3,8]

Of all the methods, to the best of our knowledge, there is no report on the construction of both rings of chromanes (particularly bicyclic) through an intermolecular cascade reaction. In light of this exciting landscape of chromanes, herein, we disclose a conceptually novel protocol using 5-hexyn-1-ols and α,β-unsaturated ketones as building blocks through the Ag(I)-catalyzed [3 + 3]-annulation reaction.

In recent times, cascade/domino reactions involving alkynols (**1** or **2** and others) as building blocks have emerged as versatile tools for constructing diverse heterocycles. Generally, these reactions proceed through the initial π-electrophilic cata-

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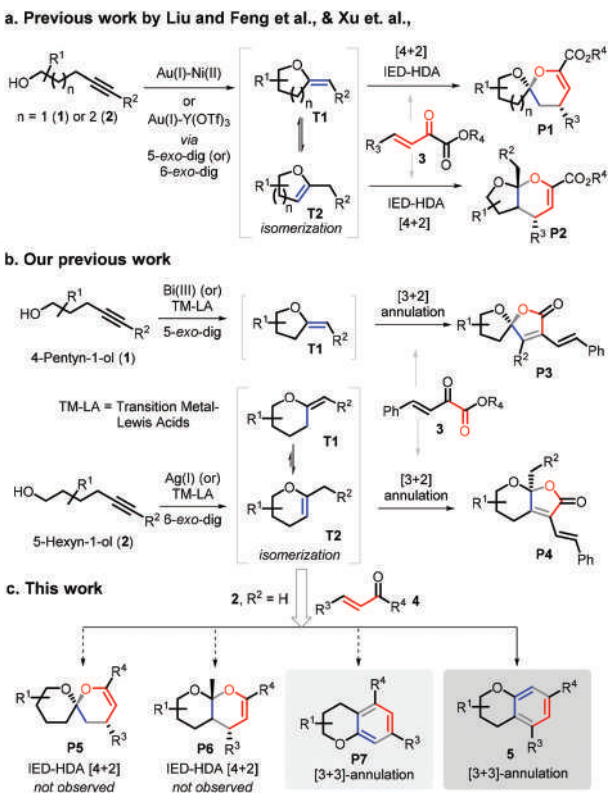
lyst promoted cycloisomerization of alkynols *via exo-dig* or *endo-dig* mode of cyclization to give the respective cyclic enol ethers (**T1** or **T2**), and their subsequent participation in transformations of the Povarov reaction,[9] Prins-type cyclization,[10] acetal or spiroacetal formation through the intermediacy of an oxocarbenium species,[11] [4 + 2]-cycloaddition and others (Scheme 1).[12]

Recently, Liu and Feng's, and Xu's research groups disclosed the participation of cyclic enol ethers (**T1** and **T2**) as dienophiles in the inverse-electron demand hetero-Diels–Alder (IED-HDA) reaction with β-γ-unsaturated α-ketoesters **3** to give spiroketals **P1** or fused acetals **P2** under catalyst dependent conditions (Scheme 1, entry a).[13] In contrast to these findings, we previously reported that 4-pentyn-1-ols **1** would react with α-ketoesters or β-γ-unsaturated α-ketoesters **3** to deliver [5,5]-oxaspirolactones **P3**,[14] and 5-hexyn-1-ols **2** would undergo [3 + 2] annulation with **3** to give furopyranones[15] **P4** instead of IED-HDA adducts (**P1**, **P2**) under Bi(III) and Ag(I) or Au(I)-Ag(I)-catalysis respectively. These distinct results could be attributed to the act of cyclic enol ethers (**T1** and **T2**) as enolizable carbonyl equivalents under specific catalytic conditions. They participated in the initial 1,2-addition reaction with the carbonyl functionality of α-ketoesters **3** and subsequent annulation (Scheme 1, entry b). In continuation of this work, we were curious to explore the reactivity of alkynyl alcohols **2** with readily accessible α,β-unsaturated ketones **4** employing our previously identified σ and π-dual activating[16] catalytic systems,[14,15,17] which may deliver either ketals (spiro/fused) **P5** and **P6** through [4 + 2]-cycloaddition (IED-HDA), or regio-isomeric chromanes **P7** or **5** *via* [3 + 3]-annulation pathways (Scheme 1, entry c).

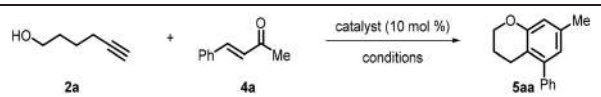


Scheme 1 Intermolecular cascade annulation reactions of alkynols with α,β-unsaturated carbonyl compounds using bimetallic catalysis, and our previous and current investigations.

Results and discussion

We initiated our studies by probing the representative reaction conditions between commercially available 5-hexyn-1-ol **2a** and (*E*)-4-phenylbut-3-en-2-one **4a** (Table 1). Delightfully, the initial experiment using AgOTf (10 mol%) in CH_2Cl_2 and equimolar **2a** and **4a** at room temperature (rt, 27 °C) furnished chromane **5aa** with exclusive regioselectivity in a good yield of 62% in 6 h and no trace amounts of IED-HDA adduct **P5** or **P6**, and isomeric chromane **P7** were observed (Scheme 1, entry c; Table 1, entry 1). This formation of chromane **5aa** could be ascribed to the bis-nucleophilic character of enol-ether intermediates **T1** or **T2** (Scheme 1, entries b and c) formed from alkynol **2** and their subsequent reaction with bis-electrophilic enone **4**. Fascinated by this result, we continued further to ascertain optimal reaction conditions to improve the overall efficiency of this [3 + 3]-annulation through altering the solvent, temperature, and the ratio of substrates under AgOTf catalysis (Table 1, entries 1–7), which led to discerning the best outcome of 87% yield of **5aa** in PhF (the reaction was found to be clean and faster in PhF compared to other solvents tested) at rt using alkynol **2a** and enone **4a** in 2 : 1 molar ratio and 10 mol% AgOTf (Table 1, entries 4 and 5), whereas other silver salts (AgCl, AgBr, AgI, $AgNO_3$ and AgO) failed to facilitate this annulation reaction (Table S1,† entries 1–5). Brønsted acids *p*-TsOH, PPTS and TFA were found to be futile catalysts (Table 1, entries 8–10). Control experiments using TfOH as a

Table 1 Optimization studies[a]



Entry	Catalyst	Solvent	Time	Yield[b] (%)
1	AgOTf	CH_2Cl_2	6 h	62[c]
2	AgOTf	$(CH_2)_2Cl_2$	6 h	70
3	AgOTf	Toluene, 85 °C	6 h	57
4	**AgOTf**	**PhF**	**2 h**	**75**
5	**AgOTf**	**PhF**	**6 h**	**87**
6	AgOTf (5 mol%)	PhF	12 h	60
7	AgOTf (2 mol%)	PhF	12 h	45
8	*p*-TsOH	$(CH_2)_2Cl_2$	6 h	—[d]
9	PPTS	$(CH_2)_2Cl_2$	6 h	—[d]
10	CF_3COOH	$(CH_2)_2Cl_2$	6 h	—[d]
11	TfOH	$(CH_2)_2Cl_2$	6 h	—[d,e]
12	No catalyst	PhF	6 h	—[d,e]

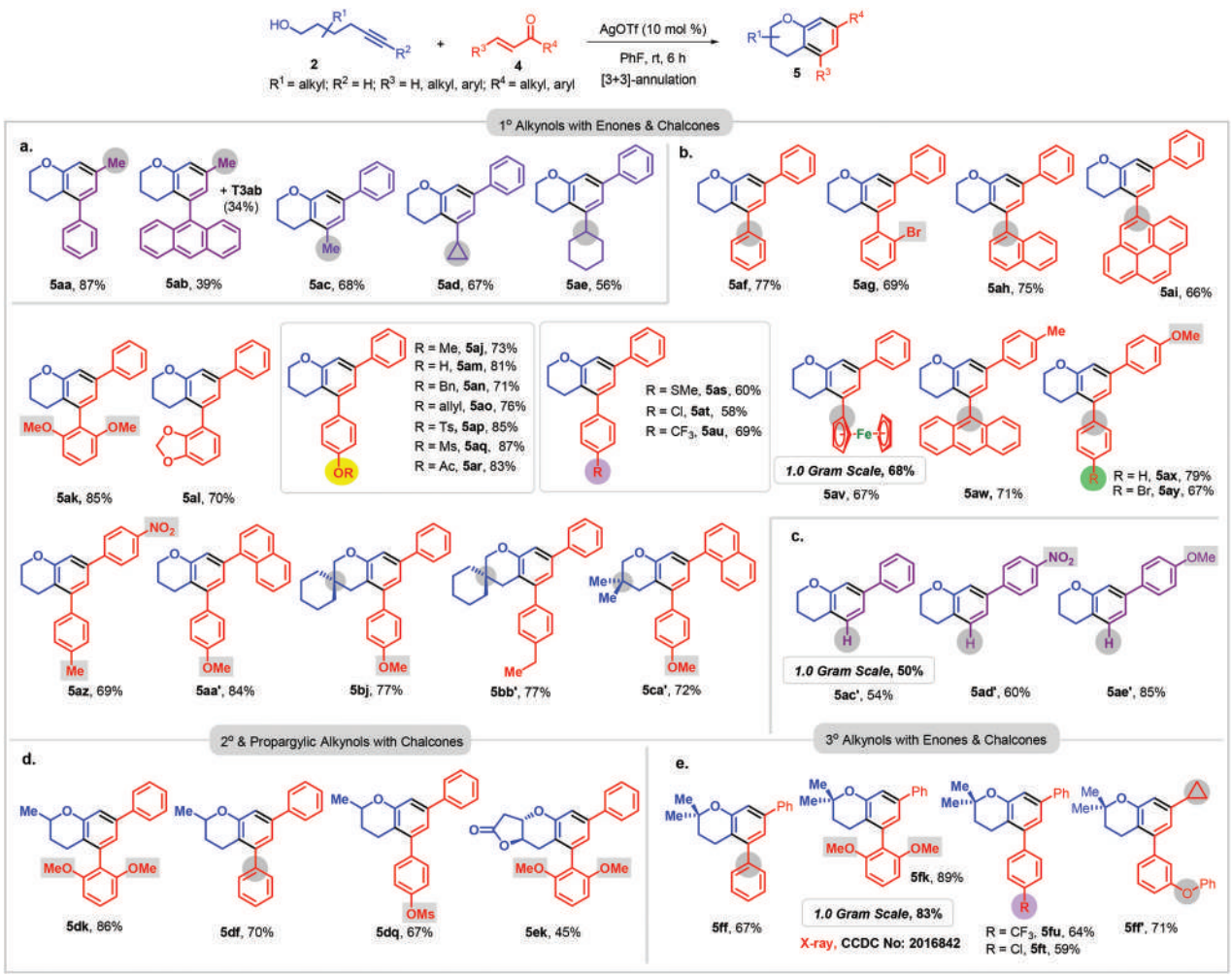
[a] Unless otherwise noted all reactions were carried out with **4a** (1.0 mmol), **2a** (2 mmol) and catalyst (10 mol%) at rt. [b] Isolated yields of **5aa**. [c] **4a** (1 mmol) and **2a** (1 mmol) were used. [d] No reaction was observed. [e] Control experiments Tf = triflate (CF_3SO_2).

catalyst (the usual impurity of metal-triflates) and without using a catalyst validated the function of AgOTf in this annulation reaction (Table 1, entries 11 and 12).

Next, a series of known π-electrophilic catalysts were examined, and we found that AuCl, $Hg(OTf)_2$, and $Bi(OTf)_3$ could catalyze this reaction but with compromised yields (53–70%) and a longer reaction time (Table S1,†[3a,b] entries 6–9). Among several other metal triflate-based catalysts tested, $Sc(OTf)_3$, $Fe(OTf)_3$, $Cu(OTf)_2$ and $In(OTf)_3$ delivered **5aa** in low to moderate yields (15–52%) (Table S1,† entries 10–17), whereas $Ni(OTf)_2$, $Zn(OTf)_2$ and $Yb(OTf)_3$ failed to facilitate the task (see the ESI for details. Table S1†).[3]

Having established the optimal reaction conditions, we sought to explore the generality of this annulation reaction. As shown in Scheme 2, we methodically investigated the substrate scope of 5-hexyn-1-ols **2** and enones **4**.[3] Initially, diverse α,β-unsaturated ketones **4** were tested in combination with 5-hexyn-1-ols possessing a primary hydroxyl group. Arylidene acetones bearing anthracenyl groups were treated with 5-hexyn-1-ols (**2a**) to access the corresponding chromane **5ab** and 1,4-cyclohexadiene reaction intermediate **T3ab** (*vide infra*) in 39% and 34% yield respectively. Methyl, cyclopropyl and cyclohexyl substituted phenyl ketones successfully delivered the corresponding chromanes **5ac–5ae** (56–68%) (Scheme 2, entry a).

Next, the reactivity profile of various chalcones possessing electronically and sterically divergent aryl constituents was verified using alkynol **2a** as a cascade partner (Scheme 2, entry b). Thus, reactions performed with chalcones containing phenyl, bromophenyl, naphthyl, pyrenyl, anisyl, 2,5-dimethoxyphenyl, and methylenedioxy-phenyl groups gave diverse chromanes (**5af–5al**) in good to excellent yields. The *p*-hydroxyphenyl derived chalcone was also well-tolerated and delivered chromane **5am** in 81% yield. Annulation of protected (with methyl, benzyl, allyl, tosyl, mesyl, and acetyl groups) phenol-derived chalcones with alkynol **2a** afforded chromanes **5aj–5ar** in 71–87% yields. Chalcones with *p*-SMe, *p*-Cl, *p*-CF_3-phenyl, and *p*-ferrocenyl groups were also found to be good annulation partners by delivering adducts **5as–5au** and **5av**. Alteration in the aryl ketone part of chalcones (with *p*-Me, *p*-OMe, *p*-NO_2



Scheme 2 Scope of the [3 + 3]-annulation reaction concerning alkynols and enones. Reactions were performed on a 1.0 mmol scale, yield after column chromatography.

and naphthyl) led to the formation of the respective chromanes **5aw**, **5ax**, **5ay**, **5az** and **5aa′** in 67–84% yields. The cyclohexyl derived alkynol **2b** and *gem*-dimethyl substituted alkynol **2c** smoothly delivered the corresponding chromanes **5bj**, **5bb′** and **5ca′** (Scheme 2, entry b).

Interestingly, acrylophenones (with phenyl, *p*-nitrophenyl, and *p*-anisyl groups) were also ascertained to be good substrates and delivered the corresponding chromanes **5ac′**–**5ae′** in 54–85% yields (Scheme 2, entry c).[3]

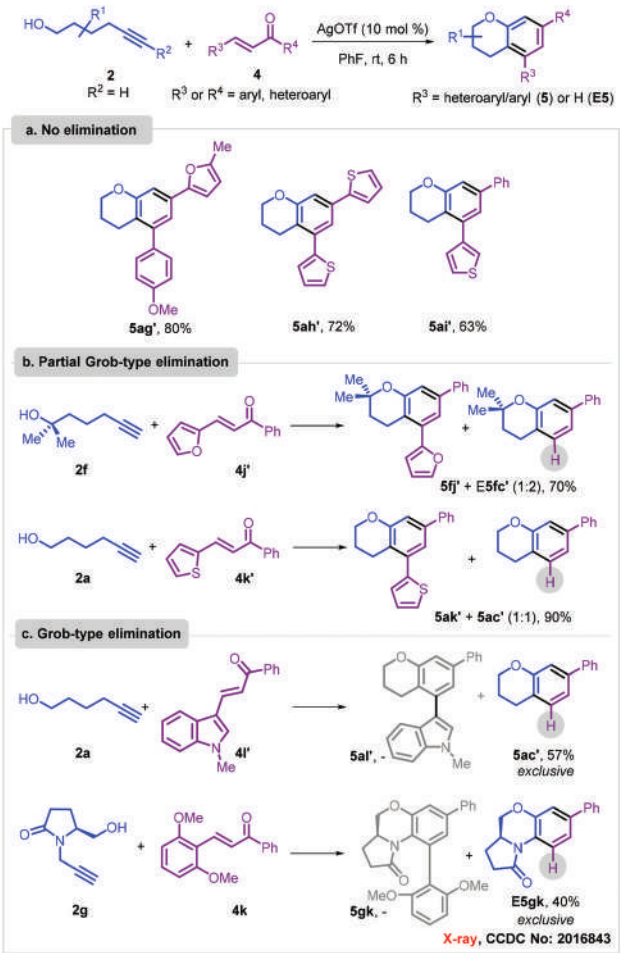
Secondary alkynols also participated well in this reaction and delivered the corresponding chromanes **5dk**, **5df**, and **5dq** with equal ease compared to primary alkynols. A known[3] optically pure secondary alkynol possessing the *trans*-butanolide skeleton was well reacted with chalcone **4k** and delivered pentacyclic complex chromane **5ek** in 45% isolated yield (Scheme 2, entry d).

Alkynols possessing a tertiary alcohol were also well-tolerated under the optimal conditions and delivered a series of chromanes (**5ff**, **5fk**, **5fu**, **5ft** and **5ff′**) in good yields (Scheme 2, entry e). Next, the practicality and scalability of this protocol were demonstrated by performing reactions on a 1.0-gram scale of enone, which delivered **5av**, **5ac′** and **5fk** (Scheme 2) in good yields without loss of efficiency. Based on the isolated yields, it is clear that the electron-releasing substituents and small arene ring-size of chalcone and *geminal* substituents on alkynols would favor the outcome of the reaction. The structure and the regio-selectivity of all products were unequivocally determined by X-ray crystallographic analysis (of **5fk**) and analogy (Scheme 2).[3]

Setting a limitation, the reaction of 5-hexyn-1ol (**2a**) with cinnamaldehyde and alkyl-derived enones, and internal 5-hexyn-1ols with chalcones/enones did not proceed. The reaction of analogous 4-pentyn-1-ols with chalcone ((2*E*)-1,3-diphenylprop-2-en-1-one) failed to deliver the anticipated 2,3-dihydro-benzofuran (entries 1–6, Scheme S1†).[3]

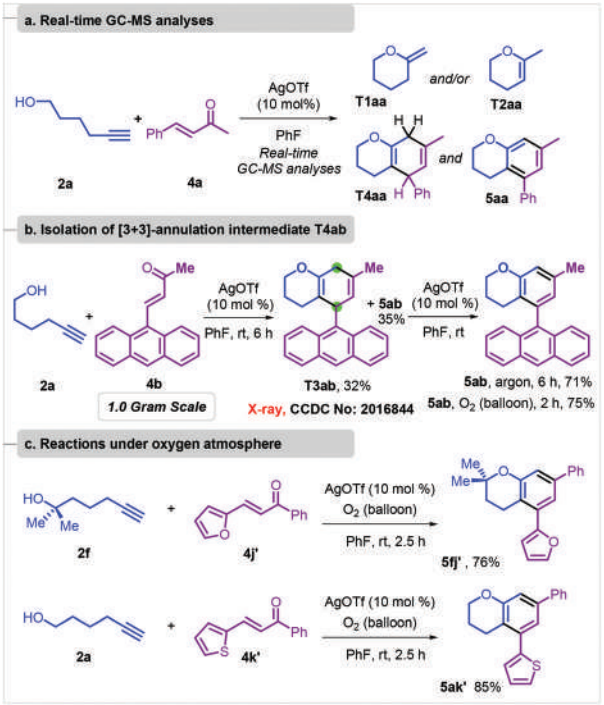
To extrapolate the generality further, we began investigating the scope of enones with hetero arene appendage **4**. Among several enones (possessing furan, thiophene, pyrrole, indole, pyridine benzoxazole and benzothiazole) tested, furan thiophene and indole tethered enones were found to be reliable substrates and this led to some interesting results as shown in Scheme 3.[3] The reaction of alkynol **2a** with (*E*)-3-(4-methoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one (**4g′**), (*E*)-1,3-di(thiophen-2-yl)prop-2-en-1-one (**4h′**) and (*E*)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one (**4i′**) delivered the corresponding chromanes **5ag′**, **5ah′** and **5ai′** respectively in good yields (Scheme 3, entry a).

To our surprise, (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**4j′**) and (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (**4k′**) in reaction with alkynols **2f** and **2a** gave an inseparable mixture of chromanes and heteroarene eliminated products (**5fj′** and **E5fc′**; **5ak′** and **5ac′**; established by ^{1}H and ^{13}C NMR analyses) under the optimal reaction conditions (Scheme 3, entry b). Interestingly, *N*-methyl indole derived chalcone **4l′** in reaction with **2a** at 85 °C delivered the eliminated product **5ac′** exclusively in 57% yield. Similarly, alkynol **2g** (obtained from (*S*)-pyroglutamic acid)[3] in reaction with sterically hindered chalcone **4k** furnished tricyclic lactam fused N, O-heterocycle **E5gk** (confirmed by X-ray analyses) in 40% yield (Scheme 3, entry c); this unusual formation of heteroarene/arene eliminated products could be due to the stereoelectronic effect-driven competitive Grob-type elimination pathway[5,18] instead of classical oxidative aromatization (*vide infra*) (Scheme 3, entry c).

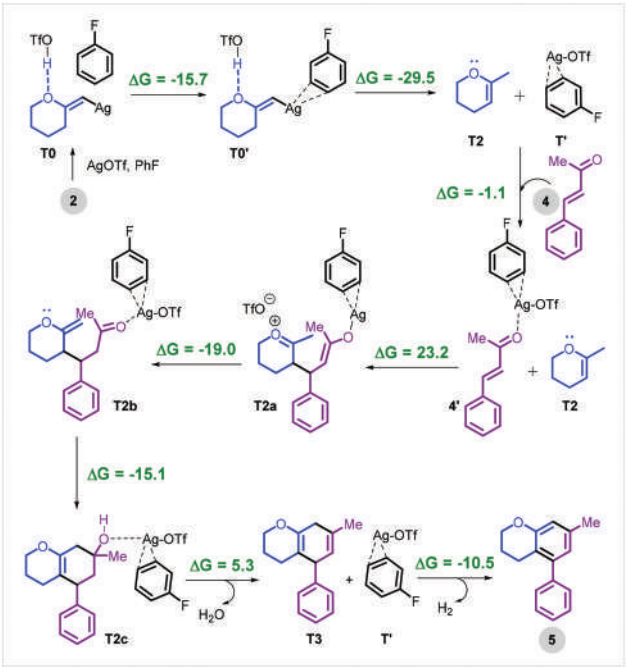


Scheme 3 Scope of the [3 + 3]-annulation reaction using heteroarene derived chalcones.

Next, we performed a series of supporting experiments to gain insight into the reaction mechanism. The reaction of **2a** and **4a** was real-time monitored with the aid of GC-MS which showed *m*/*z* signals related to cyclic enol ethers (**T1aa** or **T2aa**) and cyclohexadiene (**T4aa**) reaction intermediates, suggesting the intermediacy of these species (Scheme 4, entry a). The scale-up experiment of **2a** with **4b** enabled us to isolate a crystalline pyran-tethered cyclohexadiene **T3ab** and confirms this as one of the reaction intermediates, which is quite stable under open-air conditions and was further converted into chromane **5ab** under the optimal reaction conditions as well as under an O_2 atmosphere (Scheme 4, entry b). To our delight, the annulation of **2f**/**2a** with **4j′**/**4k′** under an oxygen atmosphere (balloon pressure) delivered the corresponding



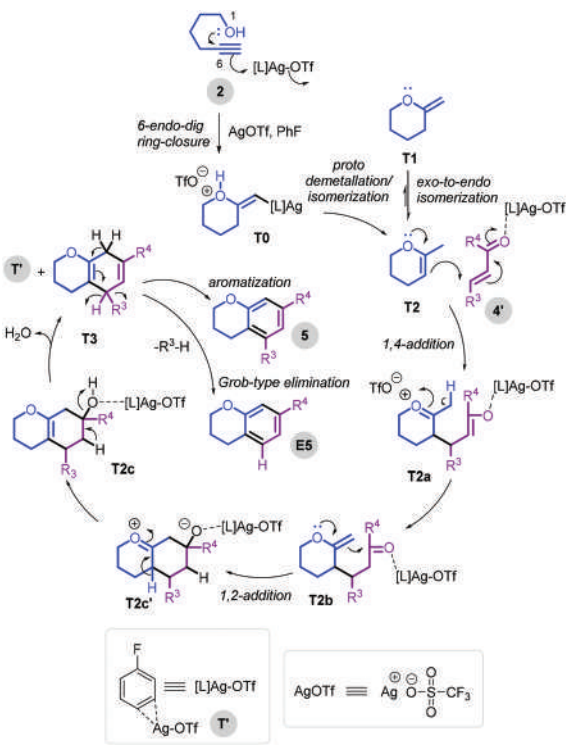
Scheme 4 Supporting experiments for the reaction mechanism.



Scheme 5 Thermodynamic calculations for the formation of chromanes **5** by AgOTf-catalyzed annulation of 5-hexyn-1-ol **2** with enone **4**. Free energy values are provided in kcal mol^{-1}.

annulation products **5fj′**/**5ak′** exclusively (no partial Grob-type elimination product was observed, which is in contrast to our observations in Scheme 3, entry b). This outcome indicates the probable role of the aerobic oxidative aromatization step in this annulation (Scheme 4, entry c). Additionally, we have performed DFT calculations to complement the experimental findings on this cascade annulation reaction's mechanistic sequence (Scheme 4).

To better understand the enhanced efficiency using fluorobenzene (PhF) as a solvent, selective participation of endocyclic enol ether (**T2**) over exocyclic enol ether (**T0′**), and other key steps involved in the cascade annulation, we carried out full quantum chemical calculations using density functional theory at PBE/TZVP level of theory. Our thermodynamic calculations indicate that PhF reacts with Ag of the substrate **T0**, leading to the formation of compound **T0′**, which is a 1,2 coordinated structure, where PhF is coordinated to Ag in a η2 fashion at the *meta–para* positions. Next, **T0′** generates exocyclic enol ether **T2** and silver-PhF complex **T′**, a process that is exergonic by 29.5 kcal mol^{-1}. Subsequently, enone **4** reacts with silver-PhF complex **T′**, leading to the formation of **4′** *via* the coordination of Ag with the carbonyl oxygen. In the next step, the formation of **T2a** species occurs from the reaction of **T2** and **4′** *via* the 1,4-addition pathway. The formation of intermediate **T2a** is endergonic by 23.2 kcal mol^{-1}. Subsequently, the intermediate **T2b** is formed (ΔG = −19.0 kcal mol^{-1}). Furthermore, intramolecular 1,2-addition (cyclization) of **T2b** leads to the formation of species **T2c** (ΔG = −15.1 kcal mol^{-1}. After this, the formation of pyran-tethered 1,4-cyclohexadiene **T3** takes place from **T2c** with the elimination of **T′** and a water molecule. In the final step of the reaction, the cyclohexadiene intermediate **T3** delivers chromane **5** through aromatization (Scheme 5).



Scheme 6 Plausible reaction mechanism.

Based on the above experimental results, DFT calculations, and earlier observations by our group[14,15] and others,[9–13,16] we have drawn a more authenticated reaction mechanism for this Ag(I)-catalyzed [3 + 3]-annulation reaction (Scheme 4). The initial AgOTf (η2 coordinated with PhF; observed herein for the first time) mediated π-activation of alkynol **2** triggers the 6-*exo-dig* cyclization (hydroalkoxylation), which leads to the formation of the exocyclic enol ether **T1** *via* **T0**, which then converts into thermodynamically more favored endocyclic enol ether **T2**.[15] Enol ether **T2** reacts with the activated enone **4′** in a 1,4-addition pathway to give the oxocarbenium species **T2a**, which would then be transformed into exocyclic enol ether **T2b** through deprotonation. Then **T2b** undergoes intramolecular 1,2-addition and produces the bicyclic dihydropyran **T2c** *via* oxocarbenium species **T2c′**. Subsequent catalyst-induced dehydration of **T2c** delivers pyran-tethered 1,4-cyclohexadiene species **T3**. In the final step of the cascade, cyclohexadiene intermediate **T3** either delivers chromane **5** through the oxidative (aerobic) aromatization step or arene/heteroarene eliminated product **E5** *via* Grob-type elimination (Scheme 6).[3]

Conclusions

In summary, we have established a facile protocol for the regioselective construction of simple to complex chromanes by employing an Ag(I)-catalyzed cascade [3 + 3]-annulation of 5-hexyn-1-ols and α,β-unsaturated ketones by unravelling the bis-nucleophilic nature of cyclic enol-ether intermediates for the first time. More importantly, theoretical calculations elucidated the role of the fluorobenzene (solvent) in fine-tuning the Ag-catalysis by stabilizing the respective complexes, thermodynamically favored endocyclic enol ether formation and its selective participation in an intermolecular 1,4-addition reaction which led to exclusive regioselectivity. Operationally simple reaction parameters, scalability, good to excellent yields (up to 90%), and broad substrate scope are the salient features of this strategy. This protocol may find applications in the total synthesis of relevant biologically active natural products and diversity-oriented synthesis in medicinal chemistry.

Data availability

All experimental data and detailed procedures are available in the ESI.†

Author contributions

R. K. conceived the project and directed the research work. A. K. N. and S. S. T. carried out the synthetic experiments and analyzed data. S. J. and K. V. carried out the computations, data analysis and wrote the data. G. R. K. carried out X-ray crystallography data acquisition and analyses. All authors commented on the manuscript and the ESI.†

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) A. Celebioglu and T. Uyar, Antioxidant Vitamin E/Cyclodextrin Inclusion Complex Electrospun Nanofibers: Enhanced Water Solubility, Prolonged Shelf Life, and Photostability of Vitamin E, *J. Agric. Food Chem.*, 2017, **65**, 5404–5412; (*b*) J. Ding, J. Yao, J. Xue, R. Li, B. Bao, L. Jiang, J. Zhu and Z. He, Tumor-Homing Cell-Penetrating Peptide Linked to Colloidal Mesoporous Silica Encapsulated (-)-Epigallocatechin-3-gallate as Drug Delivery System for Breast Cancer Therapy in Vivo, *ACS Appl. Mater. Interfaces*, 2015, **7**, 18145–18155; (*c*) K. M. Allen, K. A. Coughlan, F. N. Mahmood, R. J. Valentine, N. B. Ruderman and A. K. Saha, The effects of troglitazone on AMPK in HepG2 cells, *Arch. Biochem. Biophys.*, 2017, **623–624**, 49–57; (*d*) A. Coats and S. Jain, Protective effects of nebivolol from oxidative stress to prevent hypertension-related target organ damage, *J. Hum. Hypertens.*, 2017, **31**, 376–381; (*e*) I. M. Chandler, C. R. McIntyre and T. J. Simpson, Biosynthesis of LL-D253, a polyketide chromanone metabolite of, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2285–2293; (*f*) D. J. Atkinson and M. A. Brimble, Isolation, biological activity, biosynthesis and synthetic studies towards the rubromycin family of natural products, *Nat. Prod. Rep.*, 2015, **32**, 811–840; (*g*) R. F. Bosch, R. Gaspo, A. E. Busch, H. J. Lang, G. R. Li and S. Nattel, Effects of the chromanol 293B, a selective blocker of the slow, component of the delayed rectifier K+ current, on repolarization in human and guinea pig ventricular myocytes, *Cardiovasc. Res.*, 1998, **38**, 441–450; (*h*) J. C. Timmerman, N. J. Sims and J. L. Wood, Total Synthesis of Caesalpinnone A and Caesalpinflavan B: Evolution of a Concise Strategy, *J. Am. Chem. Soc.*, 2019, **141**, 10082–10090; (*i*) P. A. Hume, D. P. Furkert and M. A. Brimble, Total Synthesis of Virgatolide B, *Org. Lett.*, 2013, **15**, 4588–4591; (*j*) S. M. Pimentel-Elardo, T. A. M. Gulder, U. Hentschel and G. Bringmann, Cebulactams A1 and A2, new macrolactams isolated from Saccharopolyspora cebuensis, the first obligate marine strain of the genus Saccharopolyspora, *Tetrahedron Lett.*, 2008, **49**, 6889–6892; (*k*) B. M. Trost, H. C. Shen, L. Dong, J.-P. Surivet and C. Sylvain, Synthesis

of Chiral Chromans by the Pd-Catalyzed Asymmetric Allylic Alkylation (AAA): Scope, Mechanism, and Applications, *J. Am. Chem. Soc.*, 2004, **126**, 11966–11983.

2 (*a*) R. Dalpozzo and R. Mancuso, Recent Advances in Organocatalyzed Asymmetric Synthesis of Benzopyran and Benzodihydropyran (Chromane) Nuclei, *Symmetry*, 2019, **11**, 1510–1540; (*b*) G. Desimoni, G. Faita and P. Quadrelli, Forty Years after "Heterodiene Syntheses with α,β-Unsaturated Carbonyl Compounds": Enantioselective Syntheses of 3,4-Dihydropyran Derivatives, *Chem. Rev.*, 2018, **118**, 2080–2248; (*c*) F. Vetica, P. Chauhan, S. Dochain and D. Enders, Asymmetric organocatalytic methods for the synthesis of tetrahydropyrans and their application in total synthesis, *Chem. Soc. Rev.*, 2017, **46**, 1661–1674; (*d*) P. Li, G. Zhao and S. Zhu, Highly Enantioselective Synthesis of α-Trifluoromethyldihydropyrans Using a Chiral Trifluoroethyl-substituted Thiourea Catalyst Derived from Amino Acid, *Chin. J. Chem.*, 2011, **29**, 2749–2758.

3 (*a*) See the ESI for details;†; (*b*) See the ESI for Scheme S1, S2, and Table S1.†

4 (*a*) M. R. Hallett, J. E. Painter, P. Quayle, D. Ricketts and P. Patel, Second generation benzannulation reactions: Sugar-derived Fischer chlorocarbene complexes in organic synthesis, *Tetrahedron Lett.*, 1998, **39**, 2851–2852; (*b*) B. Weyershausen and K. H. Dötz, Novel Approach to 6-Chromanols via Photochemical Benzannulation of α-exo-Benzylidene-2-oxacyclohexylidene Chromium Complexes, *Synlett*, 1999, 231–233.

5 E. Geist, H. Berneaud-Kötz, T. Baikstis, G. Dräger and A. Kirschning, Toward Chromanes by de Novo Construction of the Benzene Ring, *Org. Lett.*, 2019, **21**, 8930–8933.

6 V. K. Maikhuri, V. Khatri, A. Kumar, B. Singh and A. K. Prasad, Synthesis of Sugar Diene and Its Pd-Catalyzed Transformation into Chromanes, *J. Org. Chem.*, 2020, **85**, 7068–7076.

7 T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby and B. P. Woods, The hexadehydro-Diels–Alder reaction, *Nature*, 2012, **490**, 208–212.

8 (*a*) N. Majumdar, K. A. Korthals and W. D. Wulff, Simultaneous Synthesis of Both Rings of Chromenes via a Benzannulation/o-Quinone Methide Formation/Electrocyclization Cascade, *J. Am. Chem. Soc.*, 2012, **134**, 1357–1362; (*b*) K. A. Korthals and W. D. Wulff, Traceless Stereoinduction in the One-Pot Assembly of All Three Rings of Hexahydrodibenzopyrans, *J. Am. Chem. Soc.*, 2008, **130**, 2898–2899; (*c*) K. H. Dötz and J. S. Jr, Fischer Carbene Complexes in Organic Synthesis: Metal-Assisted and Metal-Templated Reactions, *Chem. Rev.*, 2009, **109**, 3227–3274.

9 J. Barluenga, A. Mendoza, F. Rodríguez and F. J. Fañanás, Synthesis of Spiroquinolines through a One-Pot Multicatalytic and Multicomponent Cascade Reaction, *Angew. Chem., Int. Ed.*, 2008, **47**, 7044–7047.

10 J. Barluenga, A. Fernández, A. Diéguez, F. Rodríguez and F. J. Fañanás, Gold- or Platinum-Catalyzed Cascade Processes of Alkynol Derivatives Involving Hydroalkoxylation Reactions Followed by Prins-Type Cyclizations, *Chem. – Eur. J.*, 2009, **15**, 11660–11667.

11 (*a*) S. S. Thorat and R. Kontham, Recent advances in the synthesis of oxaspirolactones and their application in the total synthesis of related natural products, *Org. Biomol. Chem.*, 2019, **17**, 7270–7292; (*b*) K. Xiang, P. Tong, B. Yan, L. Long, C. Zhao, Y. Zhang and Y. Li, Synthesis of Benzannulated [6,6]-Spiroketals by a One-Pot Carbonylative Sonogashira Coupling/Double Annulation Reaction, *Org. Lett.*, 2019, **21**, 412–416; (*c*) E. Lenci, G. Menchi, F. I. Saldívar-Gonzalez, J. L. Medina-Franco and A. Trabocchi, Bicyclic acetals: biological relevance, scaffold analysis, and applications in diversity-oriented synthesis, *Org. Biomol. Chem.*, 2019, **17**, 1037–1052; (*d*) F. M. Zhang, S. Y. Zhang and Y. Q. Tu, Recent progress in the isolation, bioactivity, biosynthesis, and total synthesis of natural spiroketals, *Nat. Prod. Rep.*, 2018, **35**, 75–104; (*e*) P. H. S. Paioti, J. M. Ketcham and A. Aponick, Controlling Regiochemistry in the Gold-Catalyzed Synthesis of Unsaturated Spiroketals, *Org. Lett.*, 2014, **16**, 5320–5323; (*f*) X. Zeng, Recent Advances in Catalytic Sequential Reactions Involving Hydroelement Addition to Carbon–Carbon Multiple Bonds, *Chem. Rev.*, 2013, **113**, 6864–6900; (*g*) H. Wu, Y.-.P. He and L. Z. Gong, Direct Access to Enantioenriched Spiroacetals through Asymmetric Relay Catalytic Three-Component Reaction, *Org. Lett.*, 2013, **15**, 460–463; (*h*) L. Cala, A. Mendoza, F. J. Fañanás and F. Rodríguez, A catalytic multicomponent coupling reaction for the enantioselective synthesis of spiroacetals, *Chem. Commun.*, 2013, **49**, 2715–2717; (*i*) K. Ravindar, M. Sridhar Reddy and P. Deslongchamps, A Highly Efficient Access to Spiroketals, Mono-unsaturated Spiroketals, and Furans: Hg(II)-Catalyzed Cyclization of Alkyne Diols and Triols, *Org. Lett.*, 2011, **13**, 3178–3181; (*j*) A. S. K. Hashmi, M. Bührle, M. Wölfle, M. Rudolph, M. Wieteck, F. Rominger and W. Frey, Gold Catalysis: Tandem Reactions of Diyne–Diols and External Nucleophiles as an Easy Access to Tricyclic Cage-Like Structures, *Chem. – Eur. J.*, 2010, **16**, 9846–9854; (*k*) J. Barluenga, A. Mendoza, F. Rodríguez and F. J. Fañanás, A Palladium(II)-Catalyzed Synthesis of Spiroacetals through a One-Pot Multicomponent Cascade Reaction, *Angew. Chem., Int. Ed.*, 2009, **48**, 1644–1647; (*l*) A. Aponick, C. Y. Li and J. A. Palmes, Au-Catalyzed Cyclization of Monopropargylic Triols: An Expedient Synthesis of Monounsaturated Spiroketals, *Org. Lett.*, 2009, **11**, 121–124; (*m*) J. E. Aho, P. M. Pihko and T. K. Rissa, Nonanomeric Spiroketals in Natural Products: Structures, Sources, and Synthetic Strategies, *Chem. Rev.*, 2005, **105**, 4406–4440; (*n*) E. Genin, S. Antoniotti, V. Michelet and J. P. Genêt, An Ir^{I}-Catalyzed exo-Selective Tandem Cycloisomerization/Hydroalkoxylation of Bis-Homopropargylic Alcohols at Room Temperature, *Angew. Chem., Int. Ed.*, 2005, **44**, 4949–4953; (*o*) M. F. Jacobs and W. B. Kitching, Spiroacetals of Marine Origin, *Curr. Org. Chem.*, 1998, **2**, 395–436; (*p*) F. Perron and K. F. Albizati, Chemistry of spiroketals, *Chem. Rev.*, 1989, **89**, 1617–1661.

12 (*a*) M. Liang, S. Zhang, J. Jia, C. H. Tung, J. Wang and Z. Xu, Synthesis of Spiroketals by Synergistic Gold and Scandium Catalysis, *Org. Lett.*, 2017, **19**, 2526–2529; (*b*) X. Li, J. Xue, C. Huang and Y. Li, Copper(I)-Catalyzed Hydroalkoxylation/Hydrogen-Bonding-Induced Asymmetric Hetero-Diels–Alder Cycloaddition Cascade: An Approach to Aromatic Spiroketals, *Chem. – Asian J.*, 2012, **7**, 903–906; (*c*) F. J. Fañanás, A. Mendoza, T. Arto, B. Temelli and F. Rodríguez, Scalable Total Synthesis of (−)-Berkelic Acid by Using a Protecting-Group-Free Strategy, *Angew. Chem., Int. Ed.*, 2012, **51**, 4930–4933; (*d*) J. Barluenga, J. Calleja, A. Mendoza, F. Rodríguez and F. J. Fañanás, Synthesis of Polycyclic Compounds by a Cascade Cycloisomerisation/Diels–Alder Reaction, *Chem. – Eur. J.*, 2010, **16**, 7110–7112.

13 (*a*) J. Li, L. Lin, B. Hu, X. Lian, G. Wang, X. Liu and X. Feng, Bimetallic Gold(I)/Chiral N,N′-Dioxide Nickel(II) Asymmetric Relay Catalysis: Chemo- and Enantioselective Synthesis of Spiroketals and Spiroaminals, *Angew. Chem., Int. Ed.*, 2016, **55**, 6075–6078; (*b*) X. Wang, S. Dong, Z. Yao, L. Feng, P. Daka, H. Wang and Z. Xu, Synthesis of Spiroaminals and Spiroketals with Bimetallic Relay Catalysis, *Org. Lett.*, 2014, **16**, 22–25; (*c*) X. Wang, Z. Yao, S. Dong, F. Wei, H. Wang and Z. Xu, Synthesis of Fused Bicyclic Aminals through Sequential Gold/Lewis Acid Catalysis, *Org. Lett.*, 2013, **15**, 2234–2237; (*d*) B. Hu, J. Li, W. Cao, Q. Lin, J. Yang, L. Lin, X. Liu and X. Feng, Asymmetric Synthesis of Fused Bicyclic N,O- and O,O-Acetals via Cascade Reaction by Gold(I)/N,N′-Dioxide-Nickel(II) Bimetallic Relay Catalysis, *Adv. Synth. Catal.*, 2018, **360**, 2831–2835.

14 D. A. Kambale, S. S. Thorat, M. S. Pratapure, R. G. Gonnade and R. Kontham, Lewis acid catalyzed cascade annulation of alkynols with α-ketoesters: a facile access to γ-spiroketal-γ-lactones, *Chem. Commun.*, 2017, **53**, 6641–6644.

15 S. S. Thorat, P. Kataria and R. Kontham, Synthesis of Furo[2,3-*b*]pyran-2-ones through Ag(I)- or Ag(I)–Au(I)-Catalyzed Cascade Annulation of Alkynols and α-Ketoesters, *Org. Lett.*, 2018, **20**, 872–875.

16 Y. Yamamoto, From σ- to π-Electrophilic Lewis Acids. Application to Selective Organic Transformations, *J. Org. Chem.*, 2007, **72**, 7817–7831.

17 (*a*) B. R. Borade, R. Nomula, R. G. Gonnade and R. Kontham, Fe(III)-Catalyzed Diastereoselective Friedel–Crafts Alkylation–Hemiketalization–Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol Lactones, *Org. Lett.*, 2019, **21**, 2629–2633; (*b*) A. K. Nakate, M. S. Pratapure and R. Kontham, Bismuth(III)-catalyzed cycloisomerization and (hetero)arylation of alkynols: simple access to 2-(hetero)aryl tetrahydrofurans and tetrahydropyrans, *Org. Biomol. Chem.*, 2018, **16**, 3229–3240.

18 C. A. Grob and W. Baumann, Die 1,4-Eliminierung unter Fragmentierung, *Helv. Chim. Acta*, 1955, **38**, 594–610.

Erratum