Gold-Catalysed Cycloisomerization of Alkynols: Studies Toward the Total Synthesis of Mersicarpine and C35–C53 Fragment of Symbiospirols A/B/C

by

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10CC16A26017

A thesis submitted to the
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DOCTOR OF PHILOSOPHY

in

SCIENCE

Under the supervision of

Dr. C. V. Ramana

CSIR- National Chemical Laboratory, Pune

Academy of Scientific and Innovative Research
AcSIR Headquarters, CSIR-HRDC campus
Sector 19, Kamla Nehru Nagar,
Ghaziabad, U.P. – 201 002, India

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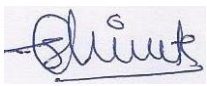
Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled "*Gold-Catalysed Cycloisomerization of Alkynols: Studies Toward the Total Synthesis of Mersicarpine and C35–C53 Fragment of Symbiospirols A/B/C*" submitted by *Mr. Mahesh Harishchandra Shinde* 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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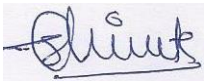
Dr. C. V. Ramana
Research Supervisor
Date: 25/01/2022

STATEMENTS OF ACADEMIC INTEGRITY

I, Mr. Mahesh Harishchandra Shinde, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC16A26017 hereby undertake that, the thesis entitled "Gold-Catalysed Cycloisomerization of Alkynols: Studies Toward the Total Synthesis of Mersicarpine and C35–C53 Fragment of Symbiospirols A/B/C" 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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Place :

Signature of the Supervisor

Name : Dr. C. V. Ramana

Date : 25/01/2022

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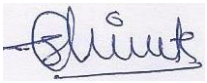
DECLARATION

The research work embodied in this thesis has been carried out at CSIR–National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR–National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.



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Dedicated to

My Beloved Family

With Lots of Love

Acknowledgement

I would like to name a few people from the infinite personalities associated in the path of my research career and who have contributed enormously directly or indirectly for the success of the thesis.

It's a great privilege to convey my gratitude to my supervisor ***Dr. C. V. Ramana*** *for his guidance and encouragement throughout my PhD tenure. I believe this thesis would never be a success in the absence of his blessings and support. I would like to thank him for being the huge source of inspiration in all the highs and lows of work as well as life. I always feel that, he is a true teacher and good human being who trained me to keep going sincerely.*

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Acknowledgement

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I am also thankful to CSIR for the financial assistance in the form of a fellowship. Finally, my acknowledgement would not be complete without thanking the Almighty, for the strength and determination to put my chin up when faced with hardships in life.

Mahesh

ABRIVATION

Ac	– Acetyl
TBS	– *tert*-Butyldimethylsilyl ether
Boc	– *tert*-Butyl oxy carbonyl
Ms	– Methanesulphonyl chloride
Ts	– Toluenesulphonyl chloride
Bn	–Benzyl
THP	–Tetrahydropyran
TMS	–Trimethylsilyl
TBSOTf	– *tert*-butyldimethylsilyl trifluoromethanesulfonate
Ac_2O	– Acetic anhydride
DCM	– Dichloromethane
DMP	– 2,2'-Dimethoxypropane
DMF	– *N*,*N*-Dimethylformamide
DMAP	– *N,N'*-Dimethylaminopyridine
DMSO	– Dimethyl sulfoxide
CH_3CN	–Acetonitrile
Py	– Pyridine
THF	– Tetrahydrofuran
p-TSA	– *para*-Toluenesulfonic acid
TBAF	– Tetra-*n*-butylammonium fluoride
Et_3N	–Triethylamine
Me	– Methyl
Ph	– Phenyl
n-BuLi	–*n*-butyl lithium
$BF_3.OEt_2$	–Boron trifluoride etherate
Bu_3SnH	– Tributyltin hydride
Bu_2SnO	– Dibutyltin oxide
AIBN	– Azobisisobutyronitrile
GDA	–D-Glucose diacetonide
Cat.	– Catalytic/catalyst
rt	– Room Temperature
Sat.	– Saturated

Conc.	– Concentrated
Liq.	– Liquid
NMR	– Nuclear Magnetic Resonance
HRMS	– High Resolution Mass Spectroscopy
ORTEP	–Oak Ridge Thermal Ellipsoid Plot
$AgSbF_6$	– Silver hexafluoroantimonate
$AgNTf_2$	– Silver(I) Bis(trifluoromethanesulfonyl)imide
AgOAc	– Silver acetate
$AuCl_3$	– Gold(III) chloride
$AuPPh_3Cl$	– Chloro(triphenylphosphine)gold(I)
*I*PrAuCl	– Chloro[1,3-bis(2,6-diisopropylphenyl) midazole-2-ylidene]gold(I)
JohnPhosAuCl	– Chloro[(1,1′-biphenyl-2-yl)di-tert-butylphosphine]gold(I)
$Pd(PPh_3)_2Cl_2$	– Bis(triphenylphosphine)palladium(II) chloride
$PtCl_2$	– Platinum(II) chloride

Abbreviations used for NMR spectral information:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet
ddd	doublet of doublet of doublets		
ddt	doublet of doublet of triplets		
tt	triplet of triplets		

General Remarks

- ✓ All the moisture and air sensitive reactions have been carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. The anhydrous solvents were distilled prior to use: CH_2Cl_2, DCE and DMF from CaH_2; methanol from Mg cake; THF on Na/benzophenone; triethylamine and pyridine over KOH; acetic anhydride from sodium acetate.

- ✓ ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL- 400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

- ✓ ^{13}C NMR spectra were recorded on AV–100 MHz, JEOL AL- 100 (100 MHz) and DRX–125 MHz spectrometer.

- ✓ High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.

- ✓ Infrared spectra were scanned on FT-IR Bruker Alpha II spectrometer as solution of chloroform and measured in cm^{-1}.

- ✓ All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I2, and anisaldehyde in ethanol as developing agents.

- ✓ All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C unless otherwise specified.

- ✓ Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENT

Synopsis Report

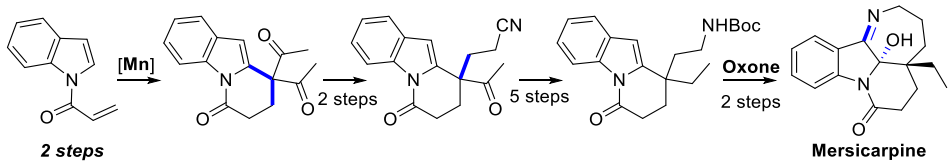
AcSIR	**Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Sciences/ Engineering**
Name of the Candidate	Shinde Mahesh Harishchandra
Degree Enrollment No. & Date	10CC16A26017 & 01/07/2016
Laboratory	CSIR-National Chemical Laboratory
Title of the Thesis	Gold-Catalysed Cycloisomerization of Alkynols: Studies Toward the Total Synthesis of Mersicarpine and C35–C53 Fragment of Symbiospirols A/B/C
Research Supervisor/ Co-supervisor	Dr. C. V. Ramana

The proposed thesis comprises of two chapters. The first chapter deals with our efforts towards the total synthesis of Mersicarpine employing intramolecular gold catalysed cycloisomerization of indole templated alkynols as the key step. The addition of nucleophiles (allyl/methallylsilane, Et_3SiH, $TMSN_3$, indole) to the C3 of indoles *via* umpolung reactivity and the synthesis of the proposed spiro intermediate with its analogues is described. The second chapter describes the studies toward the synthesis of the C35–C53 fragment of Symbiospirols A/B/C employing gold catalysed spiroketalization an alkynediol as the key step.

Introduction

Nature is a source of bioactive small molecules and also of complex natural products possessing diverse molecular skeletons. Nature has conferred us with more than 2000 monoterpene indole alkaloids with a broad spectrum of biological activities and drug candidates like vinblastine, vincristine, yohimbine, ajmalicine, ajmaline, quinine, camptothecin etc[1]. In 2004, Kam and co-workers[2] reported the isolation of Mersicarpine from the bark of *K. fruticosa* as well as *K. arborea*. Mesicarpine is characterized with an unprecedented 6/5/6/7 fused ring system, bearing a seven-membered cyclic amine, a quaternary carbon and an oxidized indole moiety. Its unique structure has attracted the attention of several synthetic groups, which has culminated in several total syntheses and formal synthesis.[3] In 2008, the Kerr's group reported the first total synthesis

of Mesicarpine that comprises of [Mn]-catalysed *β*-dicarbonyl radical cyclisation and oxone mediated indole oxidation as the key steps.



Scheme 1. First Total Synthesis by M. Kerr

Similarly, the spiroketal natural products like Reveromycin (mitogenic EGF inhiibitor), Tautomycin (protein phosphatase inhibitor), Integramycin (HIV-1 integrase inhibitor), spongistatin family natural products (inhibitory effect against tumour cells), Cephalosporolide, Aculetin, Akaspiradiol, Spirolaxine, Symbiospirol A/B/C etc (Figure 1) are privileged scaffolds in drug discovery. Symbiospirols A/B/C comprises of a linear chain of 67 carbons with a ketone moiety, 8 –OH groups, 1-(THP) tetrahydropyran ring, and 2-dioxaspiro[4,4]nonane rings.[4] The Symbiospirol A has shown inhibitory effect against L-phosphatidylserine-induced PKC activation.

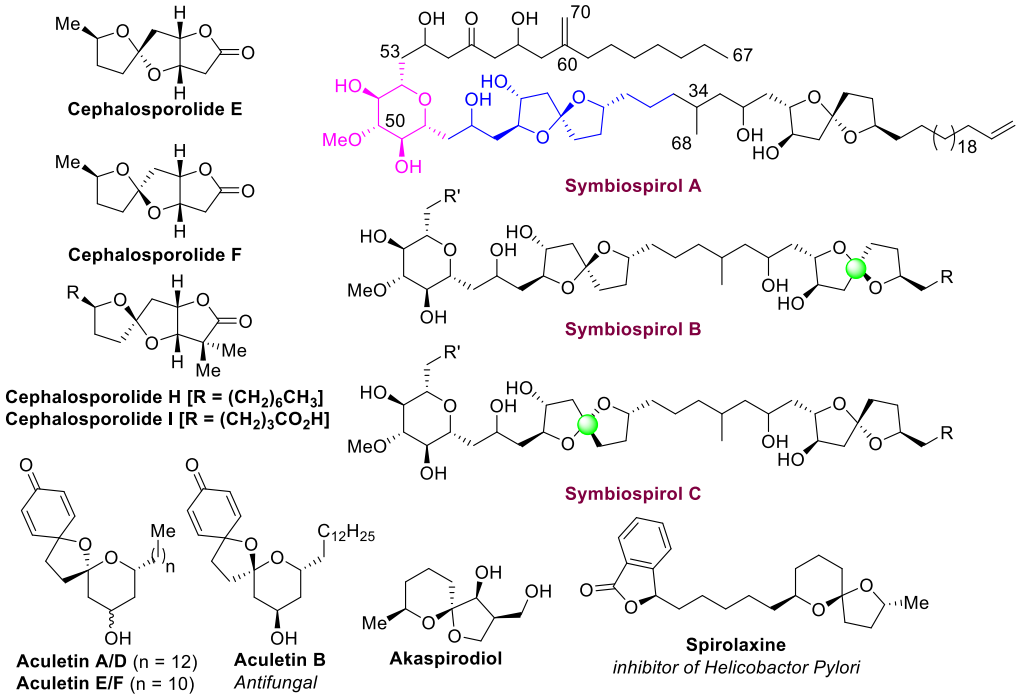


Figure 1. Spiroketal Natural Products

Statement of the problem

Recently, the organic synthetic chemists have been attracted more towards transition metal catalysed cascade reactions to construct complex natural products. The gold catalysed hydroarylation/spiroketalization of alkynols has evolved rapidly and has become a significant tool in the context of natural products synthesis. The significant advantages associated with gold catalysis are environmentally friendly catalysts, requiring mild reaction conditions, atom economic conversions and great functional group tolerance, to name a few. Our group has been involved in solving the puzzles of natural products and related scaffolds synthesis by employing transition metal catalysed cascade reactions as the key skeletal transform.[5] In continuation, the total synthesis of Mersicarpine and related monoterpene indole alkaloids has been aimed at by proposing a gold catalysed hydroarylation (intermediates A and B) and a gold catalysed spiroketalization to construction the central spiroketal fragment of Symbiospirol A/B/C (Figure 2). Till date, there are no reports on the total synthesis of Symbiospirol A/B/C.

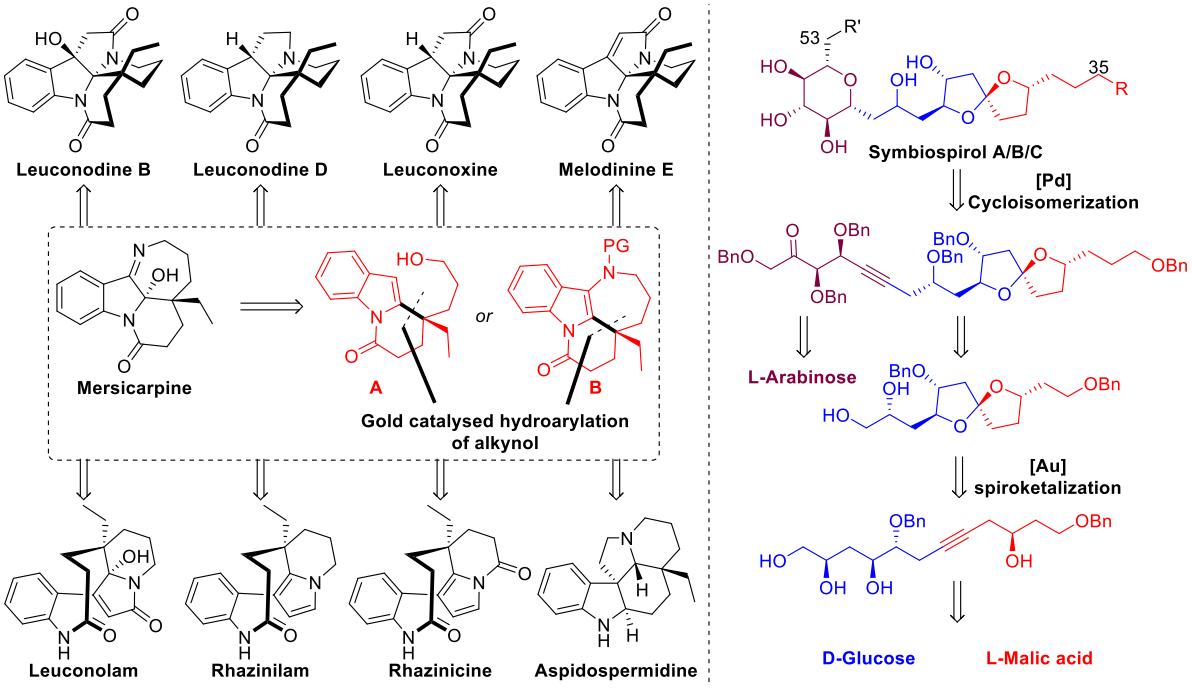


Figure 2. Proposed Gold Catalysed Hydroarylation/Spiroketalization in Natural Products Synthesis

Methodology

The careful observation of literature reports has encouraged us to hypothesise gold catalysed functionalization/hydroarylation of alkyne embedded in a *bis*-nucleophile (internal/external) atmosphere. Accordingly, Alkynols (S2.3, Scheme 2 and S3.6 Scheme 3) with suitably located indole as internal nucleophile was planned in the context of Mersicarpine and we speculated on the formation of different products depending upon the mode of cyclisation (5-*endo*-dig/6-*exo*-dig) or the reactivity difference in the presence of external nucleophile. Similarly, the carbohydrate based tetrol was planned to build the spiro-*bis*-THF unit *via* [Au] catalysed spiroketalization, whereas the [Pd] catalysed alkynone cycloisomerization was employed to construct pyran core of Symbiospirol A/B/C (Figure 2).

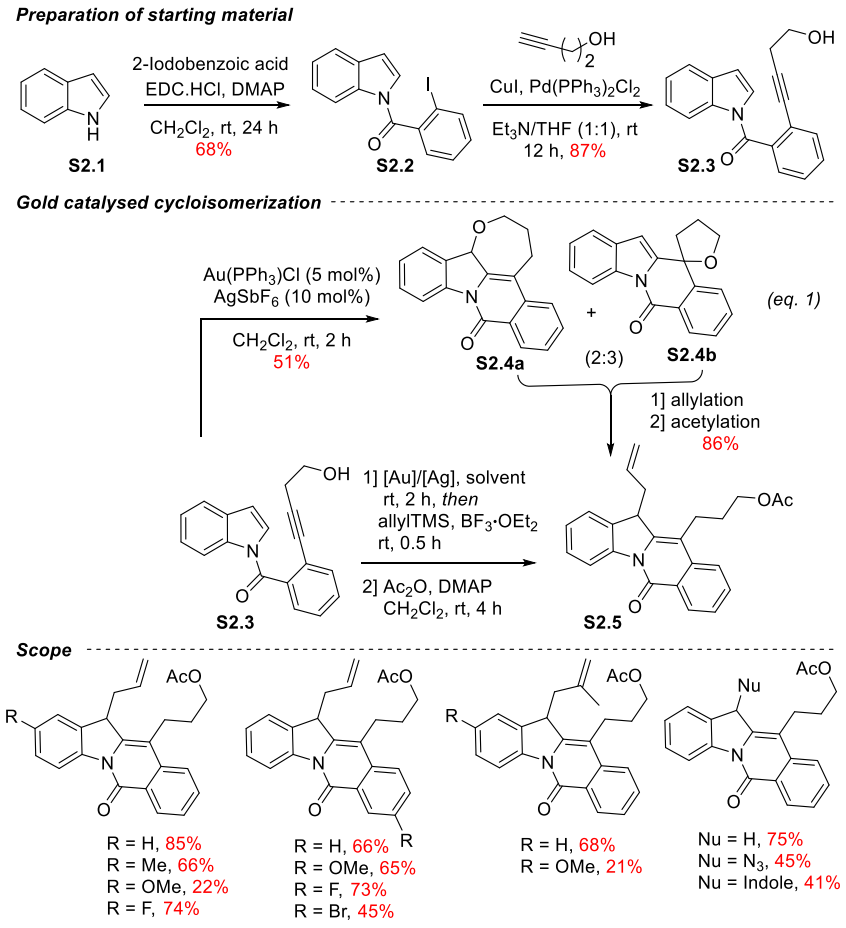
<u>Chapter I</u>- Gold Catalysed Cycloisomerization of Alkynols: Studies Toward the Total Synthesis of Mersicarpine

Results and discussion

Although several syntheses of Mersicarpine are already reported, they require lengthy sequences, and extra protection/deprotection steps to install the indole skeleton or pendant alkyl chain for the construction of azepine. This, taken together with the promising biological activity of this class of compounds, led us to develop concise and flexible approaches to construct the central core of Mersicarpine aiming at the total synthesis of Mersicarpine and its derivatives.

Considering the possibility of differential selectivity/reactivity, the model substrate was synthesised by the sequential EDC coupling of indole with 2-iodobenzoic acid followed by Sonogashira cross coupling with 3-butyn-1-ol (Scheme 2)[6]. The alkynol **S2.3** was subjected for the cyclisation in the presence of 5 mol% $Au(PPh_3)Cl$ as catalyst and 10 mol% $AgSbF_6$ additive in dichloromethane at room temperature, where the formation of two new products was noticed (Scheme 2, eq. 1). The observed interconversion of these compounds in $CDCl_3$ revealed that the cleavage of the C–O bond in both **S2.4a** and **S2.4b** is facile, indicating that the formation of an intermediate allyl cation is facile. This prompted us to examine the allylation of purified and/or mixture of **S2.4a** and/or **S2.4b** with excess trimethylallylsilane in the presence of $BF_3{\cdot}OEt_2$, which resulted in compound **S2.5 of** up to 86% yield exclusively over two steps. With this

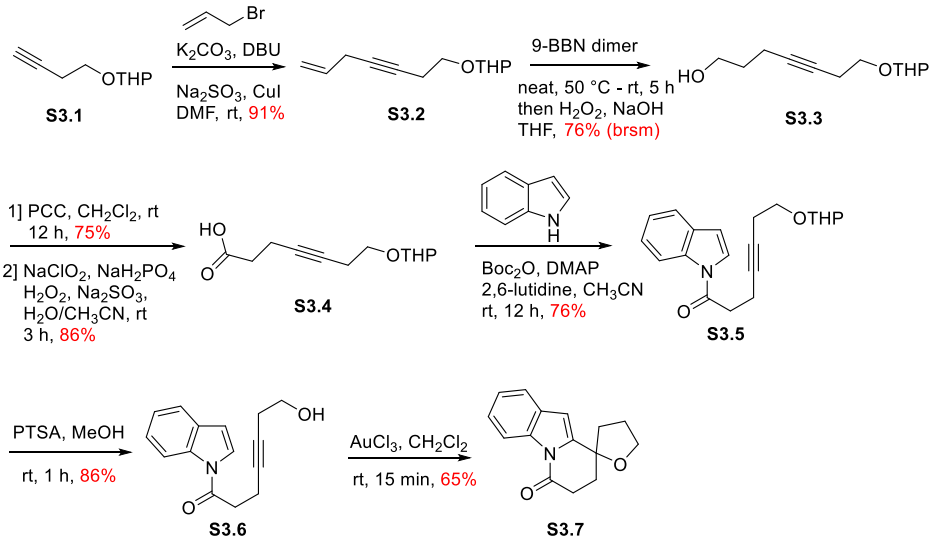
encouraging result, we next examined combining both cyclisation with $Au(PPh_3)Cl/AgSbF_6$ and subsequent allylation in one pot. The one pot reaction was optimised and the scope of the reaction was studied using alkynols possessing different electron donating/withdrawing groups, and nucleophiles such as allyltrimethylsilane, methallyltrimethylsilane, Et_3SiH, $TMSN_3$, indole etc. The detailed mechanistic pathway was proposed by performing the control experiments.



Scheme 2. Synthesis of Starting Material and Gold Catalysed Cycloisomerization

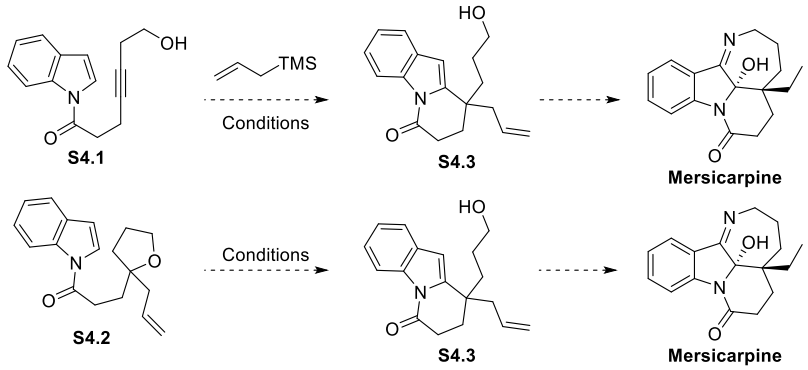
The modified substrate was presumed for the total synthesis of mersicarpine. Accordingly, the substrate was synthesised in 6 steps (Scheme 3). The synthesised alkynol was employed for the gold catalysed spirocyclisation to deliver the compound **S3.7** in 65% yield. The generality of the reaction was studied by employing alkynols with different electron donating/electron withdrawing groups to synthesise substituted spiro indole derivatives (15 examples). Eventually, the intermediate **S4.1** was selected in order to add the nucleophiles at the benzylic spiro center

and **S4.2** for the Friedel crafts type cyclisation *via* C2 of indole (Scheme 4). After the enormous screening of reagents/conditions and different nucleophile sources,[7] we concluded that it is challenging to add the nucleophile to the required center.



Scheme 3. Synthesis of Starting Alkynol and Gold Catalysed Spirocyclisation

The disappointment in the proposed nucleophile addition at the spiro-center prompted us to develop alternative routes for the construction of the tetracyclic core of Mersicarpine. Work in this direction is currently in progress.



Scheme 4. Towards the Total Synthesis of Mersicarpine

<u>Chapter II</u>- Gold Catalysed Alkynediol Spiroketalization: Studies Toward the Synthesis of the C35–C53 Fragment of Symbiospirols A/B/C

In 2009, Uemura's group reported the isolation of Symbiospirols A/B/C from the cultured marine dinoflagellate *Symbiodinium sp.*[4] Its partial structure was elucidated by 1D/2D NMR spectroscopy and chemical degradations studies. It consists of a linear chain of 67 carbons with the ketone moiety, 8 –OH groups, one tetrahydropyran (THP) ring and two dioxaspiro[4,4]nonane (spiroketal) rings. The Sybmiospirols B and C were reported as diastereomers of Symbiospirol A at the C27 center and the C41 center (Figure 3). Symbiospirol A showed the inhibitory effect against L-phosphatidylserine-induced PKC activation.

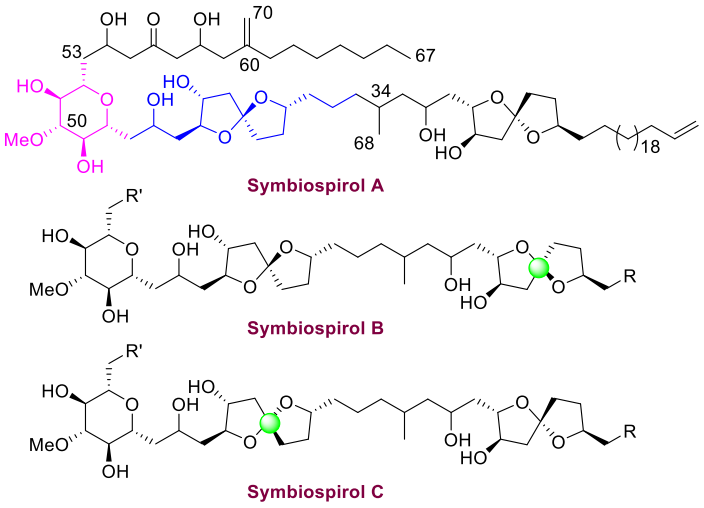
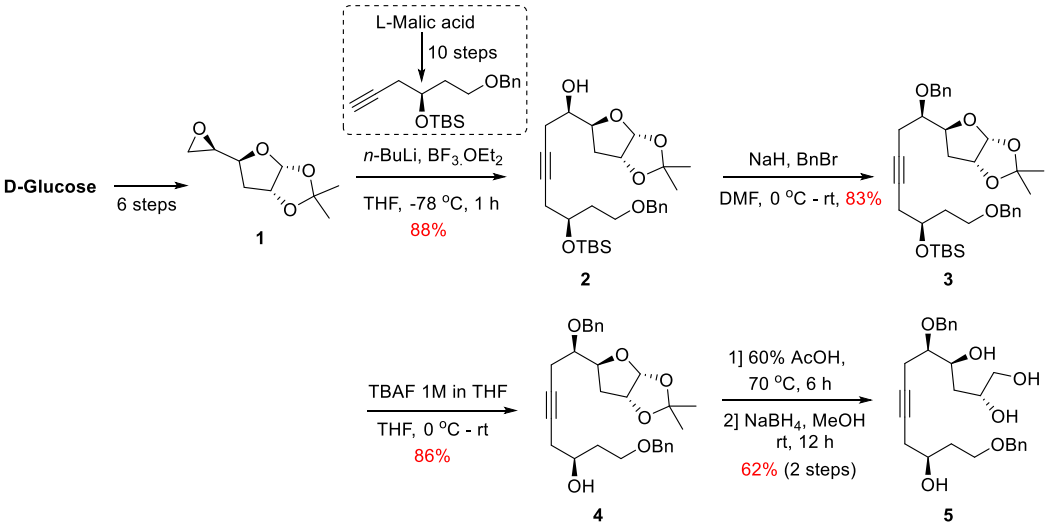


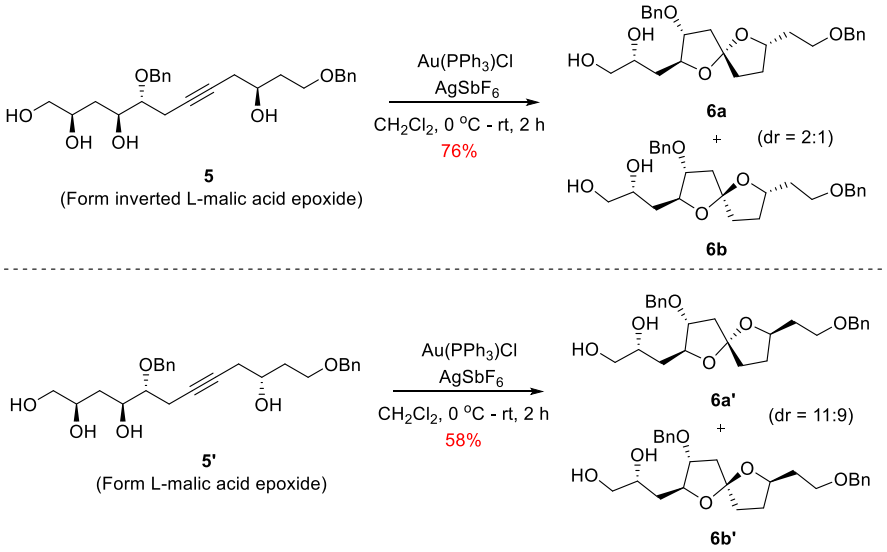
Figure 3. Structure of Symbiospirol A/B/C

Results and Discussion



Scheme 5. Synthesis of Tetrol **5**

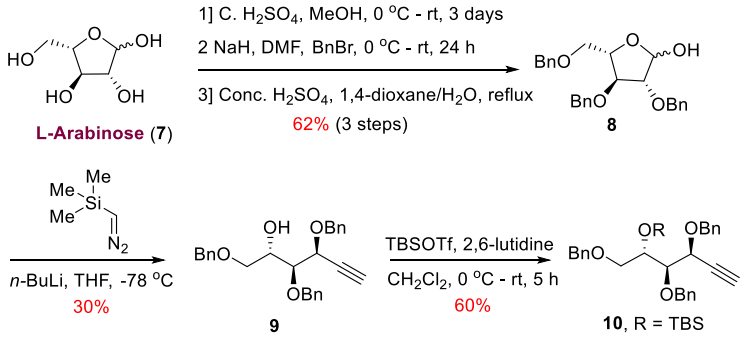
As shown in Scheme 5, the [Au]-catalysed alkynediol spiroketalization has been selected for the construction of spiro-*bis*-THF unit and for the [Pd]-mediated alkynone were planned from D-glucose diacetonide (GDA), and L-malic acid. The malic acid derived alkyne and known epoxide **6** were reacted in the presence of *n*-BuLi and $BF_3.OEt_2$, resulting in the alcohol **2** in 88% yield, which was then converted to tetrol **5** *via* protection/deprotection and reduction steps. Similarly, the diasteromeric tetrol **5'** was also synthesised in order to assign/confirm the stereochemistry at the spirocenter after gold catalysed spiroketalization. The tetrols **5** and **5'** were subjected for gold catalysed spiroketalization to afford a mixture of respective diastereomers, which were separated by column chromatography or HPLC. The stereochemistry at the spirocenter was assigned with the help of extensive 2D NMR spectral data analysis.



Scheme 6. Synthesis of Spiro Diastereomers

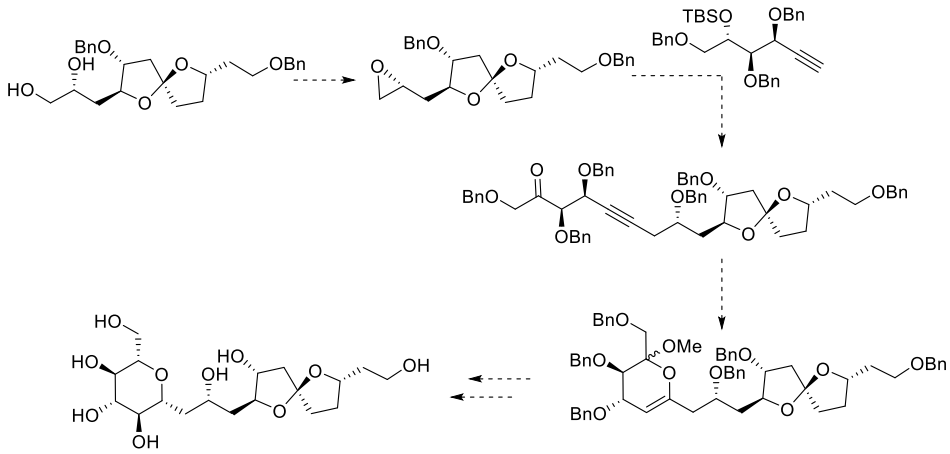
Next, the L-arabinose was glycosylated in the presence of conc. H_2SO_4 in methanol followed by per benzylation and subsequent hydrolysis of methyl glycoside to afford the lactols **8** in 62% overall yield.[8] The lactols **8** failed to give the requisite alkyne under Ohira Bestman and Corey Fuchs conditions. The successful conversion was accomplished in the presence of trimethylsilyl diazomethane/LDA at -78 ^oC to afford the required alkynol **9** in 30% yield. The

resultant alkynol **9** was protected as TBS in the presence of TBSOTf and 2,6-lutidine to provide compound **10** in 60% yields.



Scheme 7. Synthesis of Arabinose Alkyne

Subsequent work (Scheme 8) is ongoing in our laboratory and we will shortly be able to complete the synthesis of the proposed fragment of Symbiospirols A/B/C.



Scheme 8. Work in progress

Conclusions

The intramolecular [Au]-catalysed cycloisomerization of indole templated alkynols and $BF_3.OEt_2$ mediated addition of nucleophiles (allyl/methallylsilane, Et_3SiH, $TMSN_3$, indole) to the C3 of indoles *via* umpolung reactivity has successfully been demonstrated. The intended total synthesis of mersicarpine *via* extension of the developed protocol of adding nucleophile to the proposed spiro intermediate failed; however, we successfully synthesised the analogues of spiro-

indolopyridone. Next, [Au]-catalysed spiroketalization of alkynediol was successfully applied for the construction of the spiro-*bis*-THF unit of Symbiospirols A/B/C. The stereochemistry at the spirocenter has been assigned with the help of 2D NMR spectrum studies and supported by comparing the ^{13}C chemical shifts.

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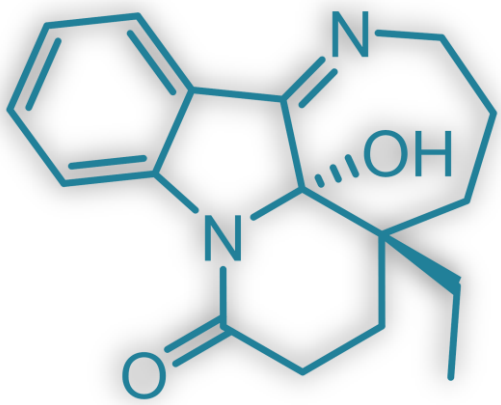
1. An Apparent Umpolung Reactivity of Indole through [Au]-Catalysed Cyclisation and Lewis-Acid-Mediated Allylation, Mahesh H. Shinde, Chepuri V. Ramana, *Chem. Eur. J.*, **2020**, *26*, 17171–17175.
2. Ru-catalyzed asymmetric transfer hydrogenation of a-acyl butyrolactone via dynamic kinetic resolution: Asymmetric synthesis of bis-THF alcohol intermediate of darunavir, Ganesh V. More, Pushpa V. Malekar, Rupali G. Kalshetti, Mahesh H. Shinde, Chepuri V. Ramana, *Tetrahedron Lett.*, **2021**, *66*, 152831–152835.
3. Facile synthesis of the spiro-pyridoindolone scaffold via a gold-catalysed intramolecular alkynol cyclisation/hydroindolylation, Mahesh H. Shinde, Chepuri V. Ramana, *Org. Biomol. Chem*., **2022**, *20*, 2086–2095.

Chapter I

Gold Catalysed Cycloisomerization of Alkynols: Studies Toward the Total Synthesis of Mersicarpine



1.1 Introduction to Drug Discovery and Natural Products:

The motivation for understanding the association of life processes at the molecular level demands the design of small organic molecules and is the basis of drug discovery. The goal of drug discovery is to discover safer medicines for all diseases. The drug development process is the most irreplaceable science that plays the most crucial role in maintaining the healthcare of the world. It is one of the most composite and expensive activities within the framework of the pharmaceutical industry. Thus chemistry serves as the strength to outline drug discovery and boost the growth of the pharmaceutical industry. Each successful drug has to go through a discovery phase, a preclinical phase, early-stage development, mid-stage development and late-stage development. It costs an average between $800 m to $1 bn investment to develop each successful drug.[1]

One of the important approaches, in this context, adopted by medicinal chemists, involves identification and modification of natural products. Natural products have served as an invaluable source and inspiration for many of the existing drugs. It is believed that about half of all the new drugs approved structurally resemble in their origins to natural products.[2]

The drug discovery field has emerged over the past few years with the development of various approaches for the rapid construction of small molecular libraries such as combinatorial chemistry (combichem), diversity oriented synthesis, biology oriented synthesis, and function oriented synthesis, for their advancement and efficiency.[3] These advances in small molecule synthesis and biological evaluation processes has accelerated the

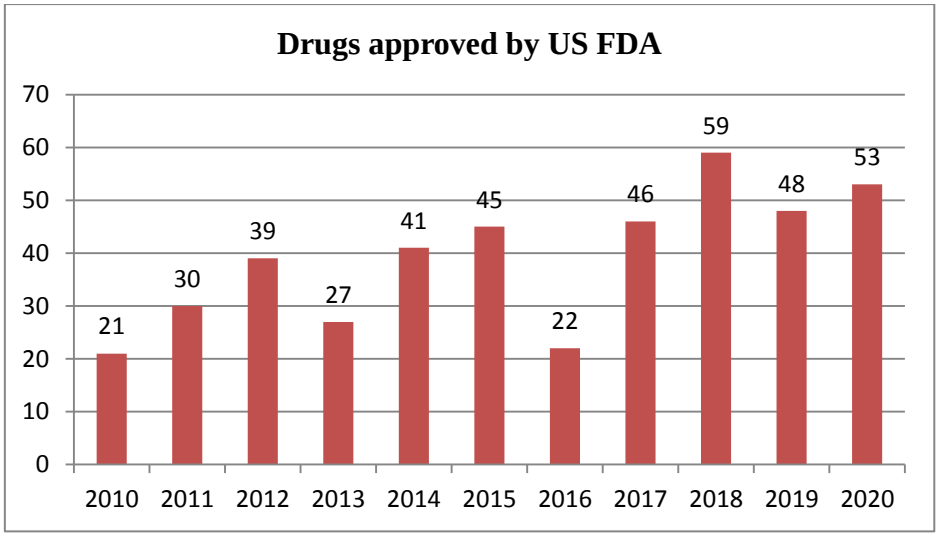


Figure 1. Drug Molecules Approved by US FDA from 2010–2020

drug discovery process. However, the unseen challenges before the pharmaceutical industry are responsible for the smaller number of drugs approved by US FDA every year. The foremost are insufficient revenues from drugs those are becoming generic, reduced funding for early stage start-ups, and the lack of communication between universities/academic institutes and industry. The chart above shows the number of drugs approved by US FDA per year from 2010 to 2020 (Figure 1). The minimum number of drugs were approved in 2010 and 2016 (21 & 22 respectively), whereas a maximum of 59 new drugs were approved in the year 2018.[4]

The heterocyclic scaffolds such as pyrrole, imidazole, pyrrazole, triazole, thiazole, oxazole, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, quinoline, isoquinoline, indole, and benzofuran are some of the important scaffolds that are commonly present in a majority of the approved drugs or new chemical entities. In particular, the indole structural unit has been termed as a privileged scaffold because many of the natural products and approved drugs and NCEs associated with a wide range of pharmacological activities, such as antiasthmatic, antiviral, antipsychotic, anti-inflammatory, anticancer, antimigraine, antihypertensive, antibacterial, antitubercular, anticonvulsant, antimalarial, and antidiabetic possess the indole skeleton.[5] Hence, it has received increasing attention from the beginning of drug development. The precise structural and biological features of the skeleton attracted the research community to design, synthesise and investigate the therapeutics related to it. Over this period, this field has seen tremendous growth and plenty of methods for the synthesis of indole ring and related complex scaffolds have been reported.

Coming to the indole class of natural products, nature has conferred us with more than 2000 monoterpene indole alkaloids with a broad spectrum of biological activities and drug candidates like vinblastine, vincristine, yohimbine, ajmalicine, ajmaline, quinine, and camptothecin.[6] Some of the examples provided in Figure 2, to below demonstrate the structural complexity and diversity of this indole class of natural products. This, taken together with their promising biological activities, has made the indole class of natural products promising targets for total synthesis. The synthesis of these polycyclic indole alkaloids and related complex molecules possessing multiple stereogenic centers has indeed inspired the synthetic chemists to develop a plethora of novel methods that include metal-/ organocatalysed, metal free C-X (X = C, N, S, O, F) bond forming reactions, cyclisation, cycloisomerization, photochemical, and electrochemical reactions for forging complex scaffolds.[7] One of the important approaches in this context is the design of cascade processes

to address the structural complexity in the shortest possible way. Among these, the transition metal catalysed hydroarylation reactions of alkynes have been intensely explored.[8]

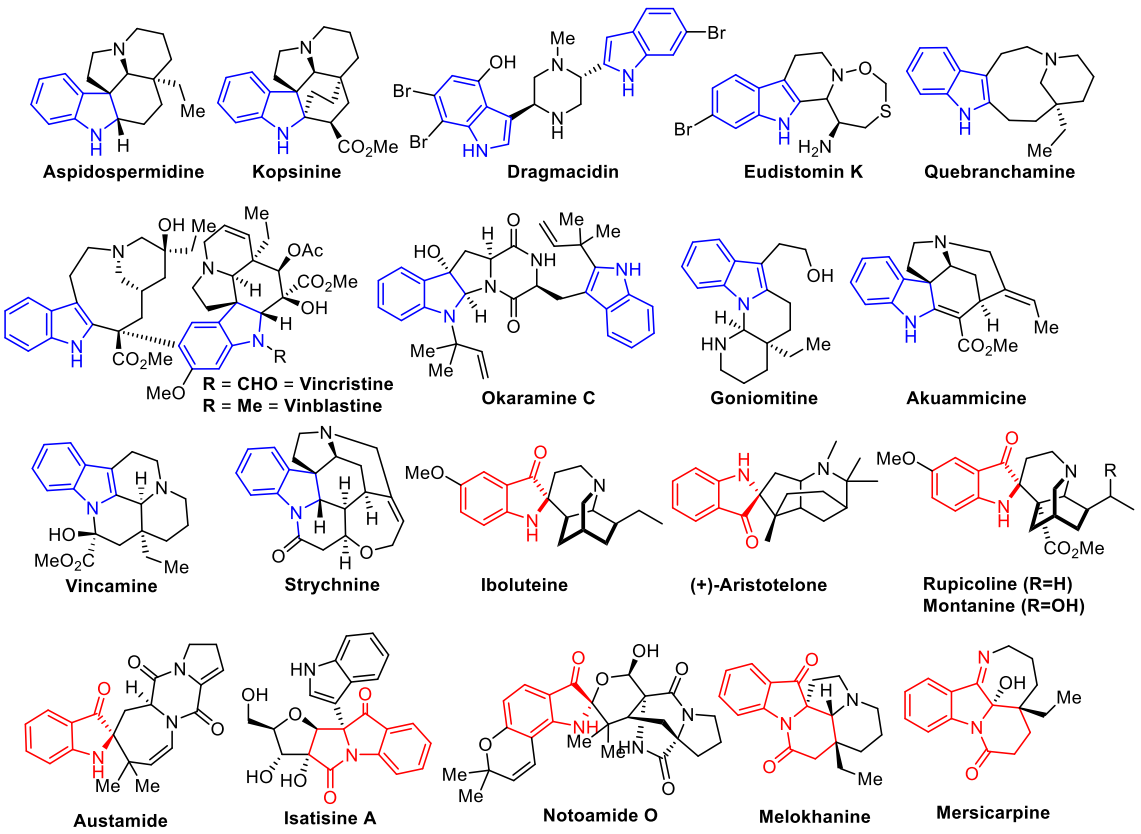
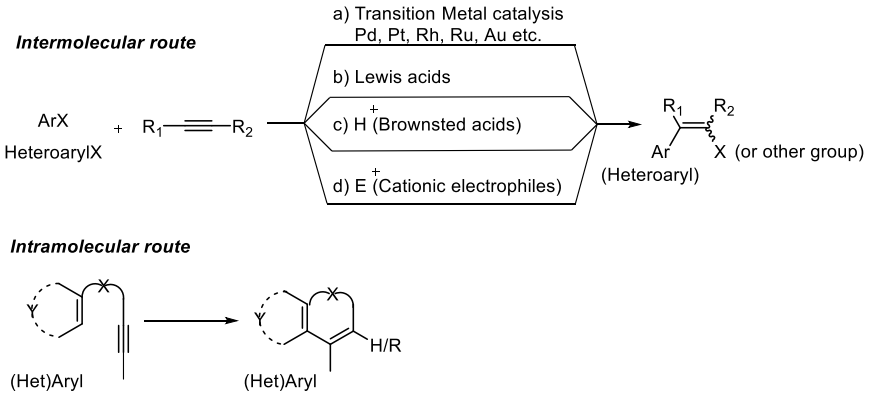


Figure 2. Indole and Pseudoindoxyl Natural Products

1.2.1 Transition Metal Catalysed Hydroarylation of Alkynes:

"Alkyne" is a unique functional group in organic synthesis that allows the introduction of a wide range of carbon and/or hetero atom centered functional groups that can be easily transformed into carbo-/heterocycles of varying ring sizes.[9] The alkyne unit possess interesting structural and electronic features because of two orthogonal π bonds, irreversible and highly favourable thermodynamic conversions, and the ability to provide flexibility in designing effective cascade transformations. It is thus is a synthon of choice for organic chemists. Furthermore, it has atom economy, carbon rich building blocks, super stabilized 1,2-dicarbenes are complementary features associated with it. The important organic transformation of arenes and heteroarenes, namely hydro(hetero)arylation/alkenylation (vinylation), uses alkynes as a reacting partner. The hydroarylation of alkynes has been considered as an important alternative to the classical Negishi, Heck-Mizoroki, Stille, and Suzuki-Miyaura reactions.



Scheme 1. Strategies for the Introduction of the Alkenyl Group

The four main strategies of hydroarylation of arenes are as follows

a) transition metal Pd, Pt, Rh, Ru catalysed reactions
b) Lewis acid Al(III), Fe(III), Ga(III), In(III), Sc(III), Zn(IV), Au(I or III), Hf(IV), Hg(II) promoted transformations
c) Brønsted acid catalysed reactions
d) Cationic electrophiles I+, Br+, RS+, RSe+

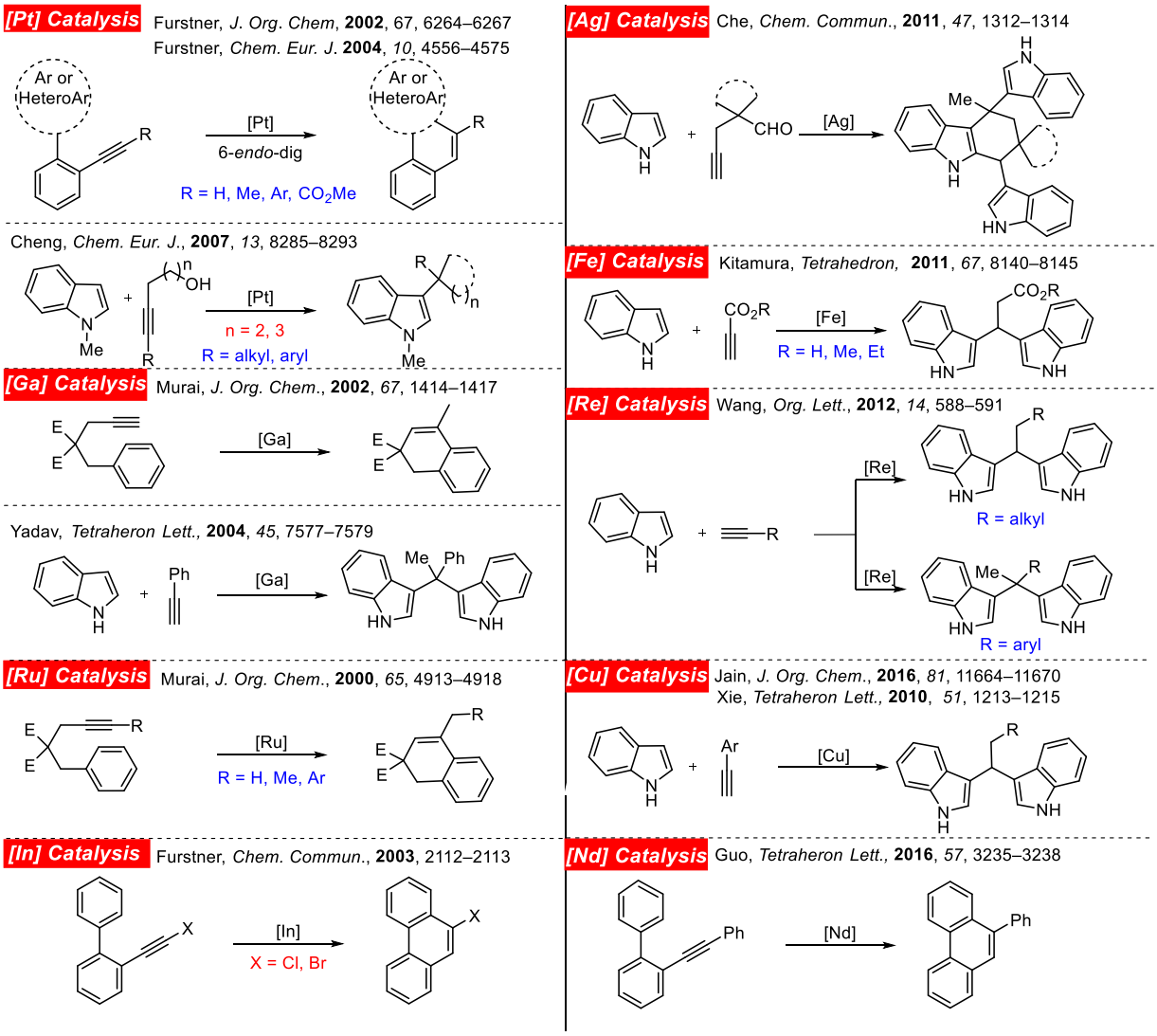
In general, the catalytic hydroarylation of alkynes employing the complexes of Pd, Pt, Rh, and Ru follow analogous paths. The Lewis acid mediated reaction involves activation of alkynes and increases the reactivity of alkynes. A Bronsted acid involves protonation of alkynes that results in the generation of a transient vinyl cation, which is subsequently trapped by arenes or heteroarenes. In a similar fashion, the addition of carbon centered-cationic species to the alkynes also ends up in the formation of a vinyl cation and in the subsequent trapping with the arenes or heteroarenes.[10]

1.2.2 Collection of Transition Metal Catalysts for Hydroarylations of Alkynes:

The alkyne functional group has been regarded as an atom-economical and carbon-rich building block for the synthesis of poly(hetero)cyclic compounds. An extensive range of transition metal catalysts that include Pt, Ga, Ru, In, Ag, Fe, Re, Cu, and Nd complexes have been widely employed for the inter and/or intramolecular alkyne hydroarylation reactions. As shown below (Scheme 2), a wide range of arenes and heteroarenes have been employed for the hydroarylation of diverse symmetrical/unsymmetrical and terminal alkynes, possessing electron withdrawing and donating groups. Despite the wide range of transition metal

catalysts accessible for the hydroarylation of alkynes, the drawbacks associated with these complexes restrict their use in organic transformations. Some of these drawbacks include:

1. The toxicity allied with some of the metal complexes.
2. The air/moisture sensitivity or stability to air, which makes them difficult to handle.
3. They sometimes need high catalyst loading and harsh conditions.
4. Difficulty in understanding the mechanistic cycle or pathways.
5. The higher cost of some of the metal complexes.

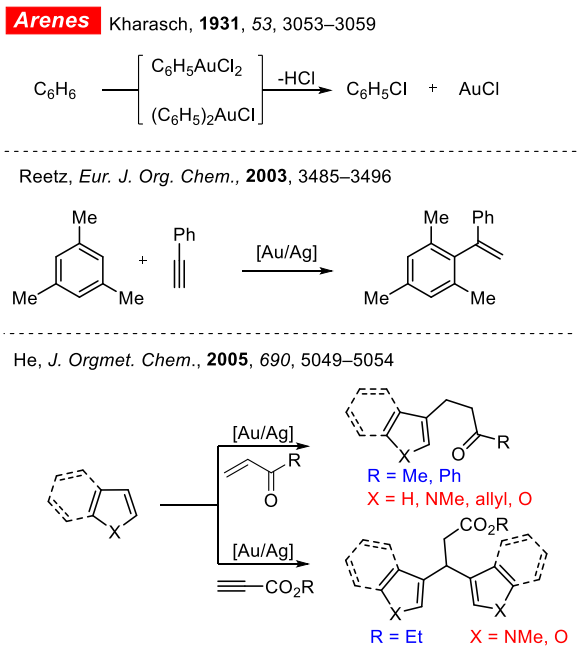


Scheme 2. Collection of Metal Catalysts for the Hydroarylation of Alkynes

1.2.3 Gold Catalysed Hydroarylations of Alkynes:

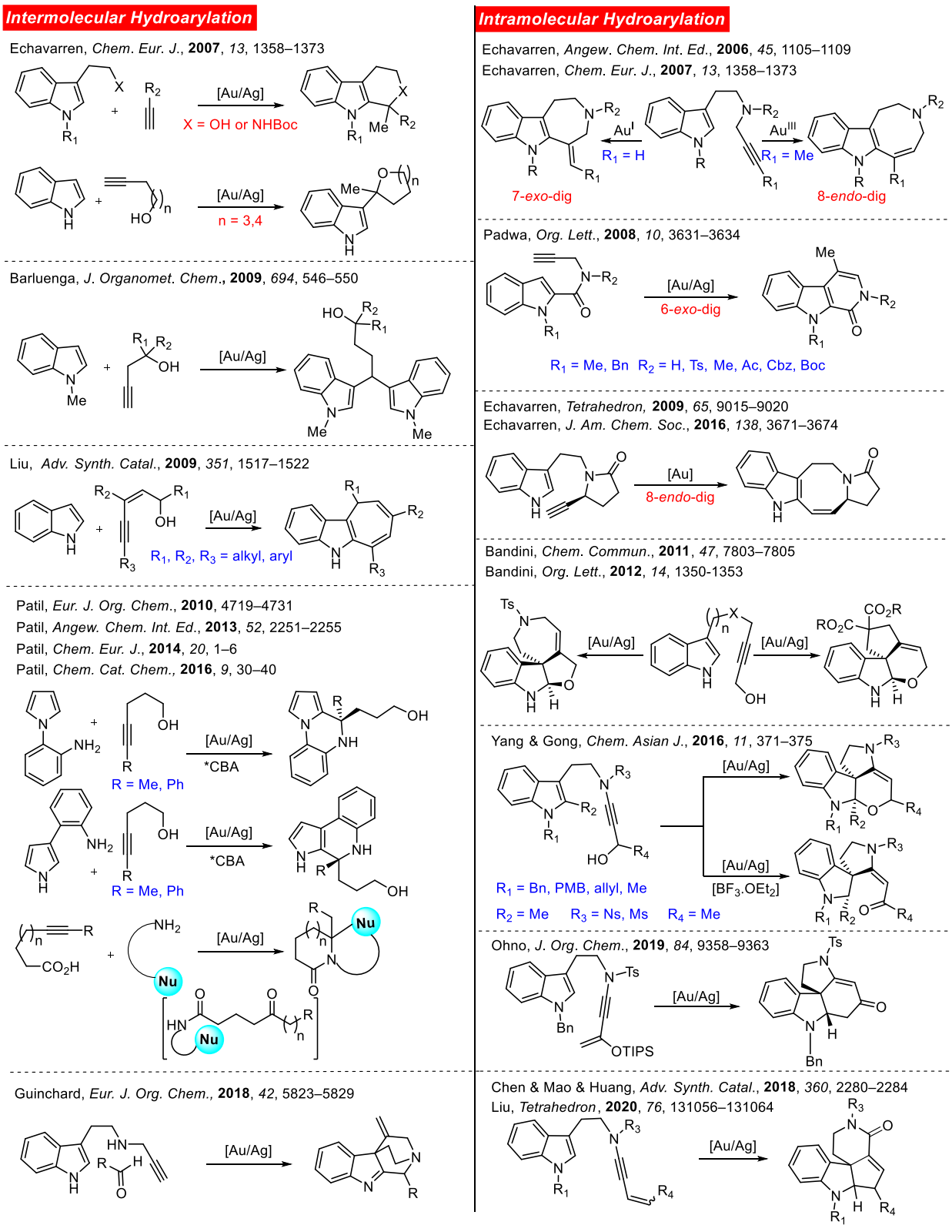
In the last two-decades, homogeneous gold-catalysis has seen much popularity amongst the organic synthetic community because of their proven alkynophilicity and Lewis acidic character.[11] In addition, due to the large nuclear charge of the metal (Z = 79), the

resulting carbocation is further stabilized because of expanded 5d orbitals that back donate the electrons into the empty p-type orbital. This renders significant carbene character to these cations, a propensity that has been widely explored for cyclopropanation and C-H insertion reactions.



Scheme 3. Gold Catalysed Hydroarylation of Alkenes/Alkynes

The Kharasch and Isbell group first started the use of Grignard's reagent for the preparation of organogold compounds.[12] The limitation of the Grignard reagent and the unsuitability of other secondary methods for the preparation of organogold compounds inspired them to check the direct reaction of gold chloride and aromatic compounds. In 1931, the Kharasch group successfully synthesised the aromatic gold compounds and also studied the effect of substituents (on the aromatic rings) on reactivity. The first gold catalysed hydroarylation of alkynes was reported in 2003 by the Reetz group.[13] The hydroarylation of mesitylene and phenylacetylene has been carried out in the presence of $AuCl_3$ as the catalyst and nitromethane as the solvent. The reaction provided exclusively styrene with a branched regioselectivity. Subsequently, the gold-catalysed hydroarylation reactions have been explored by many other research groups employing a wide range of arenes/heteroarenes and terminal or symmetrical/unsymmetrical internal alkynes. The inter and intramolecular hydroarylation reactions have been employed to synthesize a wide range of compounds such as styrenes, stilbenes, chalcones, cinnamic acids, and various fused carbo- and heterocycles.[14]



Scheme 4. Gold Catalysed Inter-/Intramolecular Hydroarylation of Alkynes

In this context, the gold-catalysed π-activation of unsaturated systems and the trapping of the electrophilic species obtained in inter- or intramolecular fashion with multiple nucleophilic centers led to the development of an elegant domino process to synthesize

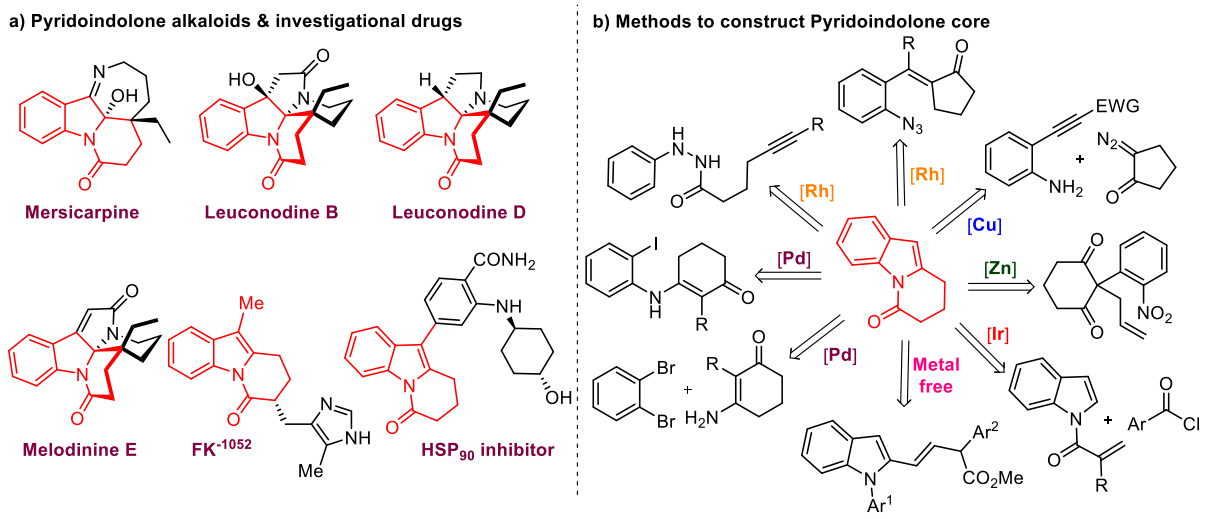
(hetero)cyclic scaffolds in a simple fashion.[15] As mentioned previously, due to their prominence and the diverse biological activities exhibited, the indole class of alkaloids occupied a special place in organic synthesis. In addition, due to the presence of multiple nucleophilic N- and C-centers on the indole ring, in gold-catalysis, the hydroarylation of alkynes employing indole nucleus has seen a wide increase in popularity. The most typical hydroarylation with indoles take place at the C3 position. As the indole class of alkaloids are characterized with the complex fused polycyclic frameworks, methods for the annulation around the indole nucleus has been explored in parallel to the synthesis of the indole framework. The domino processes that combine the gold catalysed π-activation of alkynes and subsequent indole functionalization have been established as a promising approach for the synthesis of complex polycyclic indole derivatives and also for the synthesis of indole based natural products.[16] The synthesis of the tetracyclic indole skeleton *via* intramolecular cyclisation of indole tethered alkynols/ynamides and the trapping of the resultant electrophilic intermediate with the oxygen centred nucleophile in the presence of a π-activated gold complex has been pioneered by the groups of Bandini and Gong-Yang respectively.[17] Likewise, the addition of carbon centred nucleophiles to the C2 of indole was explored by the Ohno, Huang, and Liu groups.[18] Scheme 4 saliently describes some of the important gold catalysed hydroarylation reactions of alkynes with indoles (*via* the participation of the C3 and C2 of indole), delivering a diverse range of carbo-/heterocycles.

1.3 Methods for the Synthesis of Pyridoindolones:

The pyridoindolone skeleton is a privileged structural unit present in several of the indole class of alkaloids and investigational drugs (Scheme 5a) such as the orally active serotonin receptor antagonist FK-1052, which is an attractive anticancer agent.[19] Given the importance, numerous transition metals catalysed or metal free approaches to construct the pyridoindolone core have been reported over the past few decades.[20]

As shown in Scheme 5b, the Edmondson and the Liu group separately documented the [Pd]-catalysed inter/intramolecular cross (Heck) coupling reaction, which involves sequential C–N and C–C bond formation, to afford the pyridoindolone skeleton.[21] Li and co-workers reported the synthesis of the pyridoindolone scaffold *via* the [Rh]-catalysed redox neutral annulation of tethered alkynes, and the Driver's group reported a [Rh]-catalysed acyl migration reaction of styryl azide in this regard.[22] Similarly, the N–H insertion into [Cu]-carbenoid,[23] [Zn]-catalysed tandem sequential reduction/condensation/fragmentation/

cyclisation,[24] visible light induced cascade radical cyclisation,[25] and metal free syntheses of pyridoindolone have been reported.[26]



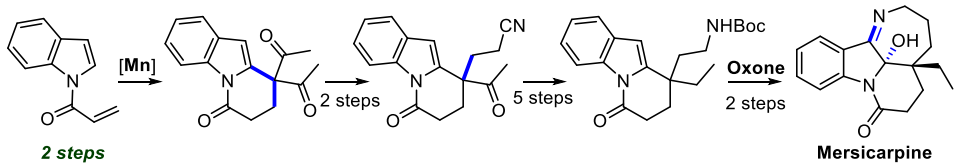
Scheme 5. Metal Catalysed/Metal Free Methods for the Synthesis of Pyridoindolones

Though there are several methods reported for the synthesis of the pyridoindolone scaffold, the gold catalysed hydroarylation of alkynes has not been documented yet. This has been planned in the context of developing simple methods for the synthesis of a pyridoindolone skeleton, which is a privileged structural unit present in numerous alkaloids and investigational drugs.

1.4 Isolation & Total/Formal Syntheses of Mersicarpine:

The isolation of novel monoterpene indole alkaloids such as Mersicarpine, Leuconodines, Leuconoxine, Melodinine E, Leuconolam, Rhazinilam, Rhazinal, Rhazincine and Meloscine has been reported over the past 3-4 decades.[27] The synthesis of leuconolam−leuconoxine−mersicarpine triad alkaloids was a challenging task before the organic synthetic community because of their daunting complex polycyclic architecture. In 2004, Kam and co-workers reported the isolation of mersicarpine as a colourless oil from the bark of *K. fruticosa* as well as *K. arborea* (0.3 mg/kg, $[\alpha]_D$ -18 (*c* 0.28, $CHCl_3$).[28] The structure of mersicarpine was characterized with an unprecedented 6/5/6/7 fused ring system, bearing a seven-membered cyclic amine, a quaternary carbon and complexly oxidized indole moiety. Several total/formal syntheses of Mersicarpine have been reported and in the following pages, some of the salient features of these total syntheses will be discussed.[29]

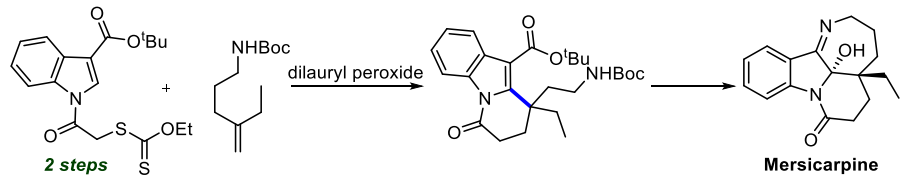
The first total synthesis of mersicarpine was documented in 2008 by Kerr and co-workers. The salient features of this synthesis include a [Mn]-catalysed *β*-dicarbonyl radical cyclisation and an oxone-mediated indole oxidation as the key steps. The synthesis was accomplished in 14 linear steps and also comprised of studying the variation of ^{1}H NMR chemical shifts with respect to varying equivalent amounts of TFA present in the solution.



Scheme 6. The 1st Total Synthesis by M. Kerr

(*Org. Lett*., **2008**, *10*, 1437)

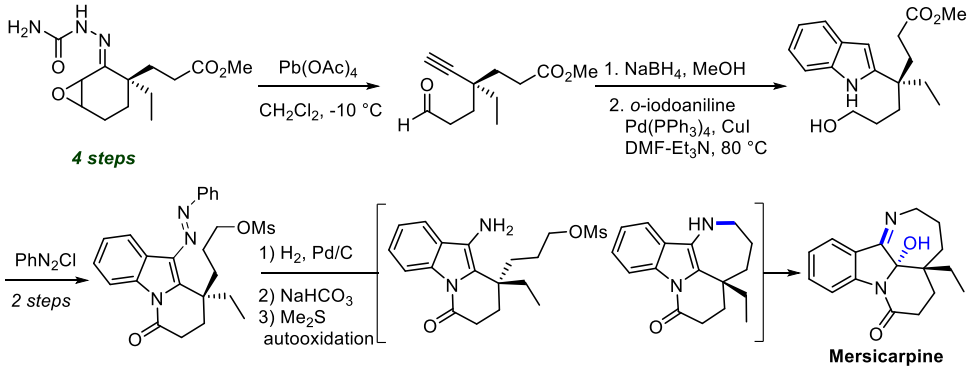
Immediately after this synthesis, Zard's group documented the formal synthesis of mersicarpine in 2009. The intermolecular radical addition-radical cyclisation cascade was employed for the construction of the key intermediate reported by Kerr's group. The intermediate was synthesised in 12 steps.



Scheme 7. Formal Synthesis by S. Zard

(*Org. Lett*., **2009**, *11*, 2800)

In the next year, Fukuyama and co-workers documented the total synthesis of

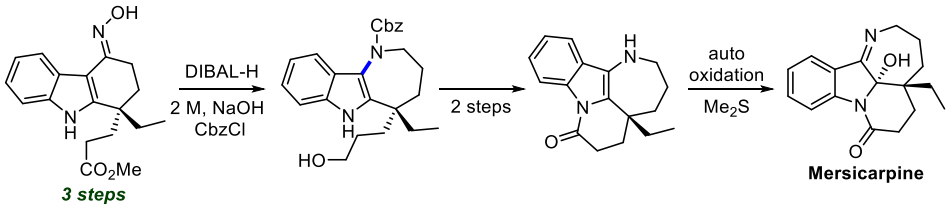


Scheme 8. Formal Synthesis by T. Fukuyama

(*J. Am. Chem. Soc*, **2010**, *132*, 1236)

Mersicarpine employing Eschenmoser-Tanabe type fragmentation to synthesize the alkyne unit, which was subjected to a one-pot Sonogashira coupling and gold (III) catalysed cyclisation to construct the indole skeleton. Addition of diazobenzene to the indole and subsequent hydrogenation followed by intramolecular displacement and the final oxidation completed the total synthesis of mersicarpine in 13 steps.

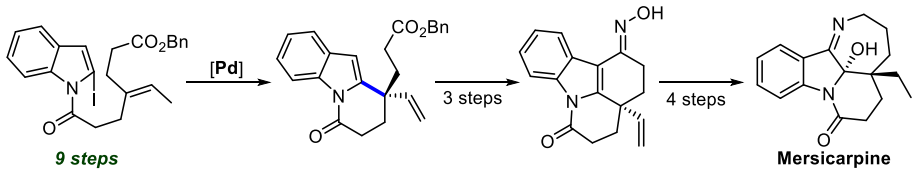
In 2012, Tokuyama and co-workers documented a concise total synthesis, which involved a DIBAL-H mediated reductive ring expansion of oxime to construct the azepinoindole core. The cyclic ketoxime was prepared by Fischer indole synthesis and the total synthesis was accomplished in 9 steps starting from known keto-ester.



Scheme 9. Total Synthesis by H. Tokuyama

(*Org. Lett.*, **2012**, *14*, 2320)

In the same year, a second generation total synthesis of mersicarpine has been documented from the group of Tokuyama. A [Pd]-catalysed enantioselective intramolecular Mizoroki-Heck reaction has been used as the key reaction for the construction of the indolopyridone core. However, including the synthesis of the starting material, the total synthesis comprised of a 16 steps linear sequence.

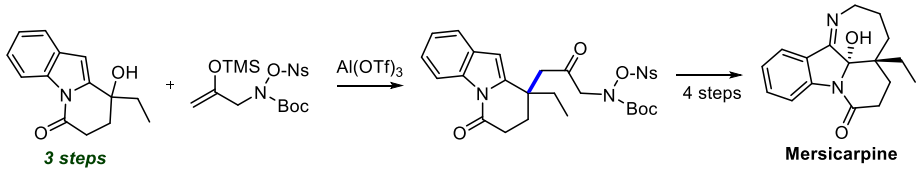


Scheme 10. Total Synthesis by H. Tokuyama

(*Chem. Eur. J.*, **2013**, *19*, 9325)

In parallel, Han and co-workers documented the formal synthesis of mersicarpine in 2012 and also a total synthesis in 2015 employing the Friedel Craft's reaction of indole and succinic anhydride. Subsequently, $Al(OTf)_3$-catalysed catalysed addition of vinyl silyl ether to the tertiary alcohol present next to the indole C2 employing a modified Wolf-Kishner

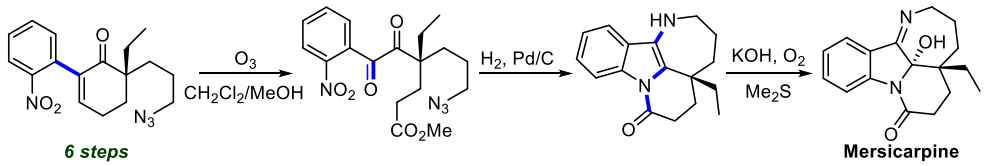
reduction followed by a simple synthetic maneuverer, the Kerr's intermediate was obtained in 6 steps, whereas the total synthesis was accomplished in 8 linear steps.



Scheme 11. Total Synthesis by F. Han

(*Chem. Eur. J*., **2012**, *18*, 9784 and *Tetrahedron*, **2015**, *71*, 3734)

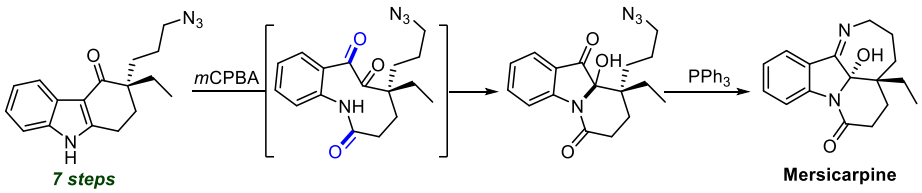
An elegant approach in this context has been developed by Zhu and co-workers addressing a unified, concise enantioselective total synthesis of Mersicarpine and the related monoterpene indole class of alkaloids. The Suzuki−Miyaura reaction and an unprecedented oxidation/reduction/cyclization sequence has been established as the key reactions to construct the complete tetracyclic core and the total synthesis was completed in 9 steps.



Scheme 12. Total Synthesis by J. Zhu

(*J. Am. Chem. Soc*., **2013**, *135*, 19127 and *J. Am. Chem. Soc*., **2015**, *137*, 6712)

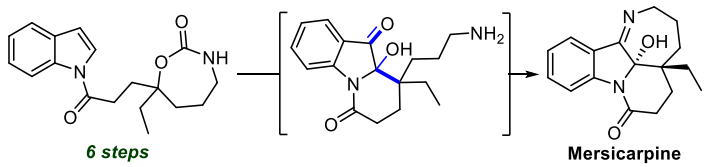
In the meantime, Dai and co-workers reported a biosynthetically inspired divergent approach for the synthesis of Mersicarpine and its family members. The key steps involve a Witkop−Winterfeldt oxidative indole cleavage followed by transannular cyclisation and a Staudinger aza-Wittig reaction. The synthesis was completed in 9 steps.



Scheme 13. Total Synthesis by M. Dai

(*Org. Lett*., **2014**, *16*, 6216)

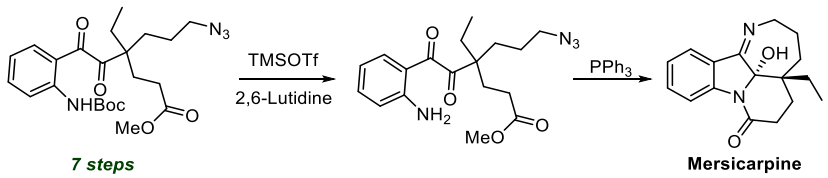
In 2014, Liang's group documented a concise total synthesis of Mersicarpine, which involves, the $AlCl_3$-mediated intramolecular Friedel−Crafts alkylation of the cyclic carbamate derived tertiary carbocation, followed by a subsequent oxidation-cyclisation cascade.



Scheme 14. Total Synthesis by G. Liang

(*Org. Lett.*, **2014**, *16*, 1653)

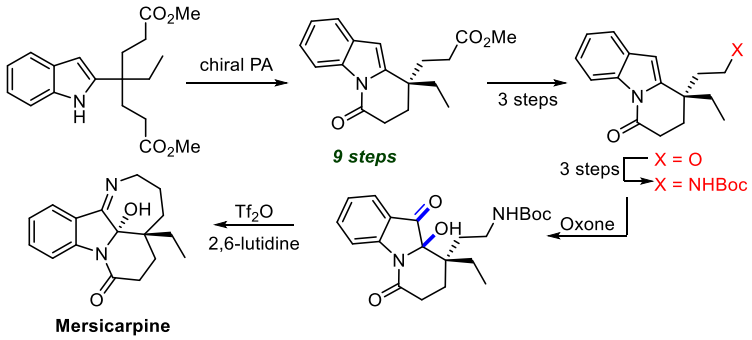
Immediately, the same group reported the collective total synthesis of Leuconolam, Leuconoxine and Mersicarpine employing a common intermediate that has been earlier reported by Zhu's group in his total synthesis of monoterpene indole alkaloids.



Scheme 15. Total Synthesis by G. Liang

(*Org. Chem. Front.*, **2015**, *2*, 236)

In 2015, Kawasaki and co-workers documented the asymmetric total synthesis of mersicarpine *via* a chiral phosphoric acid catalysed desymmetrization of prochiral diester. The synthesis was accomplished in 22 steps.

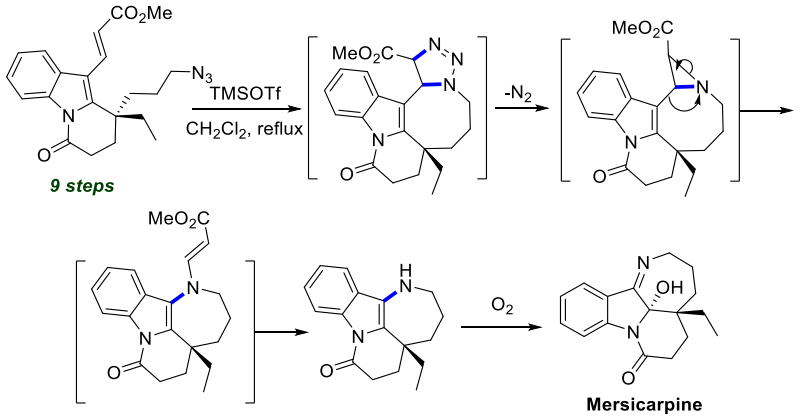


Scheme 16. Total Synthesis by T. Kawasaki

(*Org. Lett.*, **2015**, *17*, 154)

Later, in 2017, Luo's group described an unexpected cycloaddition/nitrogen extrusion/rearrangement/oxidation tandem reaction for the total synthesis of Mersicarpine. The key tandem process comprised of refluxing the advanced azide intermediate in dichloromethane in the presence of 3 equivalents of TMSOTf which gave the penultimate intermediate of several mersicarpine total synthesis *via* the intramolecular [3+2]

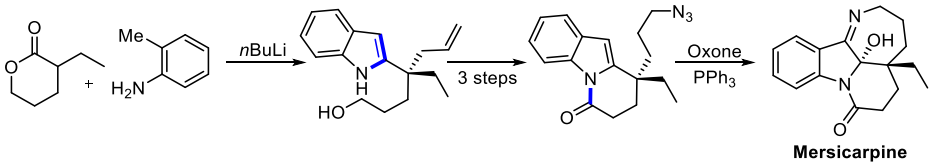
cycloaddition between an alkyl azide and a pendant conjugated ester, followed by nitrogen extrusion, resulting in aziridine and subsequent rearrangement (with C–C bond cleavage) and hydrolysis of the resulting β-aminoacrylate intermediate. The synthesis was accomplished in 4 steps with 35% overall yield.



Scheme 17. Total Synthesis by T. Luo

(*Tetrahedron*, **2017**, *73*, 4201)

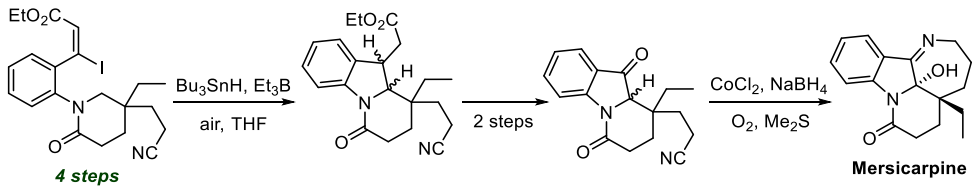
Recently, Wang and co-workers have documented a unified enantioselective total synthesis of Mersicarpine and related alkaloids. The C2 alkylated indole with a quaternary stereogenic center was synthesised by the Smith-modified Madelung indole synthesis. It involves the base mediated reaction of *o*-toluidine with a chiral lactone. The total synthesis was completed in 8 steps.



Scheme 18. Total Synthesis by H. Wang

(*Chem. Comm*., **2019**, *55*, 3544)

Very recently, Beaudry's group reported the collective synthesis of Leuconoxine, Melodinine E and Mersicarpine by employing a radical translocation-cyclisation cascade to synthesise a highly functionalized indolopiperidinone intermediate that served as the common intermediate in these total syntheses. The key step involves a 1,5-HAT–5-*exo*-trig radical cascade reaction.



Scheme 19. Total Synthesis by C. M. Beaudry

(*Chem. Comm*., **2019**, *55*, 3544)

As described above, the total synthesis of Mersicarpine has been well explored, employing established transformations, as well as designing novel cascade processes that assembled the central indolopyrrolidinone core elegantly. However, the promising biological activity of this class of compounds warrants more concise and divergent approaches, which could provide a focussed collection of related small molecules, and has not been explored. In this context, as a part of our ongoing project that deals with the synthesis of natural product like small molecule libraries, the total synthesis of Mersicarpine has been considered.

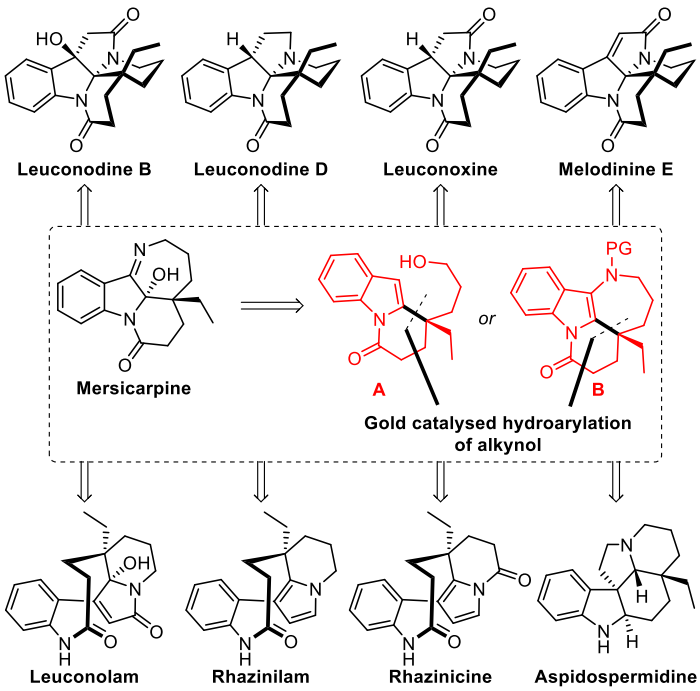


Figure 3. Intermediates Involved in the Synthesis of Monoterpene Indole Alkaloids

Also, in some of our recent work dealing with the total synthesis of indole/oxyindole natural products especially employing the gold catalysed one pot cascade reactions, the pyridoindolone core of Mersicarpine was identified as a potential scaffold to forge in a one-pot cascade process.[30] In this context, the intermediate **A** (Figure 3) has been identified as a potential common precursor to address the synthesis of Mersicarpine and related

monoterpene indole alkaloids, the synthesis of which, in turn, was inspired from the gold catalysed hydroindolylation of alkynes.

As shown in Figure 4, we hypothesised that the gold catalysed cyclisation of alkynol **F4.1** with a suitably positioned indole as an internal nucleophile should provide **F4.2** *via* a 5-*endo*-dig alkynol cyclisation and subsequent hydroindololylation. Considering the work of Han and co-workers, we reasoned that the opening of the benzylic spirocylic furan with a carbon-centered nucleophile such as ethyl will provide the alcohol **F4.3**, which can be transformed to the known advanced intermediate **F4.4** employed in the Mersicarpine

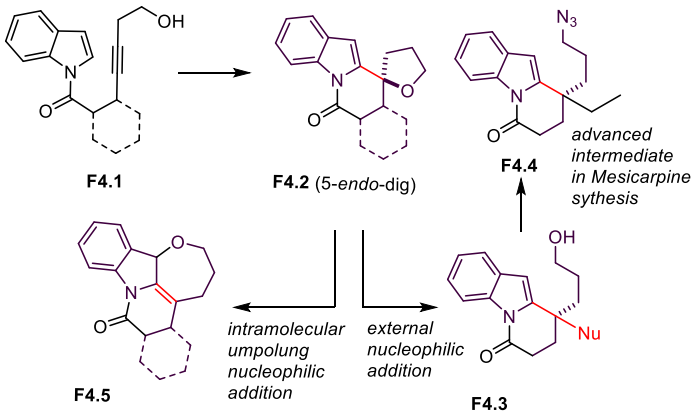


Figure 4. Substrate Design and Possible Hydroarylation Products

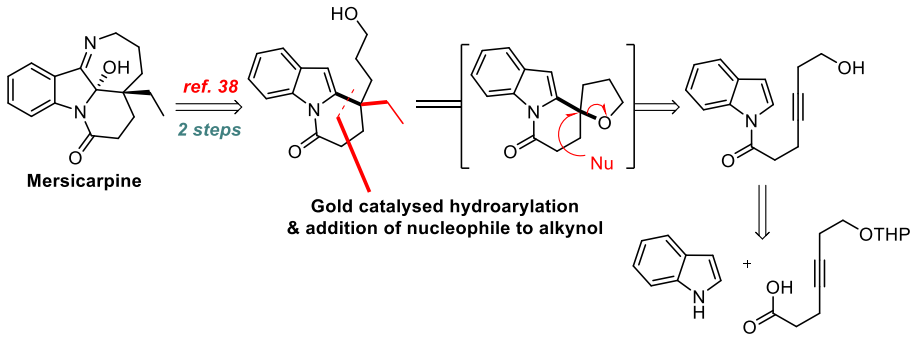
synthesis, by a simple synthetic transformation. The late stage addition of the ethyl group offers the possible alterations at this position. However, competing intramolecular participation of the –OH resulting from the tetrahydrofuran ring at the C3-position of indole is expected to provide a fused tetracyclic derivative **F4.5.** In the following section, some of our endeavours in this direction will be described.

1.5 Result and discussion:

As mentioned in the introduction section, (–)-Mersicarpine possesses an unprecedented 6/5/6/7 fused ring system, bearing a seven-membered cyclic imine, a quaternary carbon center and a complexly oxidized indole moiety. There are several total/formal synthesis of Mersicarpine that have been reported. However, the gold catalysed hydroarylation approach has not yet been attempted in the context of mersicarpine total synthesis. As shown in Scheme 20, we hypothesized that a substrate where the alkyne is embedded by oxygen and carbon centred bis nucleophiles should undergo cycloisomerization upon gold catalysed π-activation and subsequent hydroarylation followed by addition of nucleophile to the corresponding spiro-pyridoindolone. The desired alkynol was assumed by the coupling of indole with the corresponding acid.

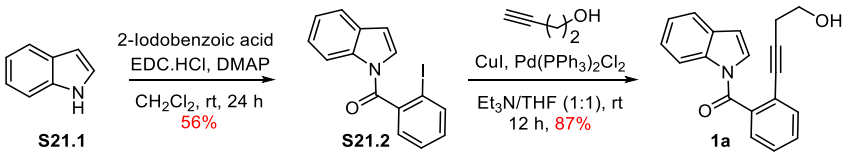
The complements of our strategy are

- The alkynol is of appropriate length to from the spiro intermediate and can be further used in the construction of the azepine ring without protection/deprotection.
- The installation of indole at the early stage reduces the number of steps in the total synthesis (needs extra steps or protection/deprotection sequences when the indole ring is constructed in later stages of the synthesis).



Scheme 20. Retrosynthetic Strategy

One of first concerns in this regard was the outcome of the gold catalysed cycloisomerization/spirocyclisation of alkynol, because of the possibility of differential modes of cyclisations. Accordingly, considering the ease of access, the alkynol compound **1a** has been selected as a model substrate to execute our hypothesis. Here, the difference is that there is a benzene ring fused between the alkyne and the acid groups. The sequential EDC coupling of indole with 2-iodobenzoic acid followed by Sonogashira cross coupling with 3-butyn-1-ol afforded the desire alkynol **1a** in 87% yield (Scheme 21).[31]

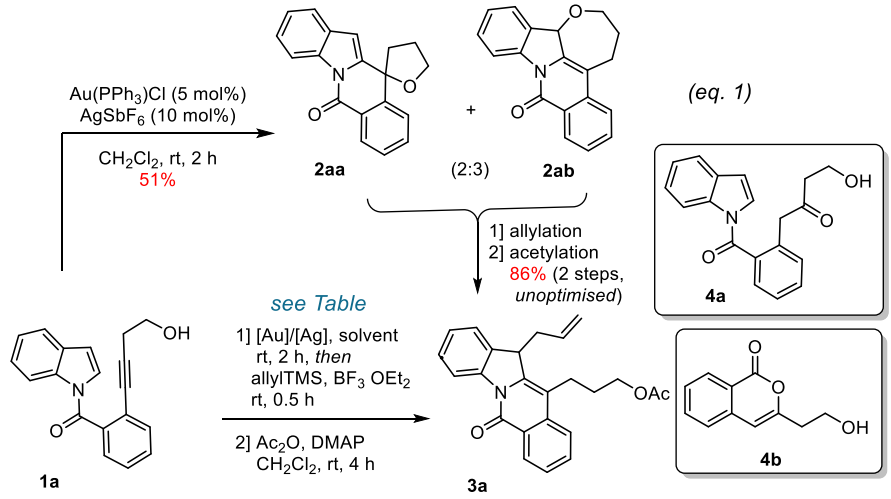


Scheme 21. Synthesis of Starting Material **1a**

The structure of alkynol **1a** was characterised with the help of spectral and analytical data. In the ^{1}H NMR spectrum of alkynol **1a**, the methylene protons of 3-butynol appeared as two triplets at δ 2.40 (t, *J* = 6.1 Hz, 2H) and 3.36 (t, *J* = 5.8 Hz, 2H) respectively, whereas the characteristic C3 proton of the indole appeared as a doublet at δ 6.61 (d, *J* = 3.7 Hz, 1H). In the ^{13}C NMR spectrum, the singlet at δ 168.1 corresponds to the amide carbonyl and the alkyne carbons appeared as singlets at δ 79.0 (s), 92.7 (s) respectively. The constitution of the compound **1a** was further supported by ESI-MS (HRMS) where the base peak was found at 312.0994.

After successful synthesis of the alkynol **1a** the stage was set to check the gold catalysed cycloisomerization/spirocyclisation. Accordingly, **1a** was subjected for the reaction, in the presence of the 5 mol% $Au(PPh_3)Cl$ as catalyst and 10 mol% $AgSbF_6$ additive in dichloromethane at room temperature.[32] The starting compound **1a** disappeared completely within 2 h with the formation of two new products, as evidenced by the TLC (Table 1, eq. 1). The separation of these two compounds was found to be tedious, because of their sensitivity towards silica and also these compounds found to be interconverting in $CDCl_3$ within a couple of hours. With great difficulty, the clean spectral data of these compounds could be obtained to establish the proposed structures. One of the compounds **2aa** was found to be the proposed spirocyclic derivative, as indicated by the spectral and analytical data. The ^{1}H NMR spectrum of compound **2aa** shows three multiplets at δ 2.1–2.3 (m, 2H), 2.3–2.4 (m, 2H), 4.5–4.6 (m, 1H) and a doublet of triplet at δ 4.4 (dt, *J* = 6.1, 8.2, Hz, 1H) corresponding to the methylene groups of the spiro-THF ring. In the ^{13}C NMR spectrum, the amide carbonyl peak appeared as singlet at δ 160.9 and the carbon at the spirocenter appeared as singlet at δ 80.2 ppm. The disappearance of alkyne carbons in the ^{13}C NMR spectrum and the appearance of an extra methylene peak for two protons in the ^{1}H NMR spectrum confirm the formation of **2aa**. The structure was further supported by ESI-MS (HRMS) where the base peak was found at 312.0998.

Table. **1** Optimization of reaction[a]



entry	[Au] 5 mol%	[Ag] 10 mol%	solvent	Time[b]	% yield **3a**
1	$Au(PPh_3)Cl$	$AgSbF_6$	CH_2Cl_2	2 h	51
2	$AuCl_3$	$AgSbF_6$	CH_2Cl_2	12 h	trace
3	$AuBr_3$	$AgSbF_6$	CH_2Cl_2	12 h	trace
4	*i*PrAuCl	$AgSbF_6$	CH_2Cl_2	12 h	hydration
5	$PtCl_4$	-	CH_2Cl_2	2 h	41
6	$Au(PPh_3)Cl$	$AgSbF_6$	$(CH_2)_2Cl_2$	2 h	52
7	$Au(PPh_3)Cl$	$AgSbF_6$	1,4-dioxane	2 h	58
8	$Au(PPh_3)Cl$	$AgSbF_6$	CH_3CN	2 h	--
9	$Au(PPh_3)Cl$	AgTFA	CH_2Cl_2	4 h	--
10	$Au(PPh_3)Cl$	Ag_2CO_3	CH_2Cl_2	4 h	--
11	$Au(PPh_3)Cl$	AgOTf	CH_2Cl_2	2 h	79
12	$Au(PPh_3)Cl$	$AgNTf_2$	CH_2Cl_2	4 h	54

[a]Reaction conditions: alkynol (1 equiv) in CH_2Cl_2 (3 mL) under Argon, $Au(PPh_3)Cl$ (5 mol%), Ag-salt (10 mol%) at rt for 2 h, trimethylallylsilane (10 equiv), $BF_3{\cdot}OEt_2$ (10 equiv), Ac_2O (1 equiv), DMAP (1 equiv), CH_2Cl_2 (5 mL). [b]time for the [Au]-catalysed cyclisation

The structure of the other compound formed in the reaction was confirmed as a pentacyclic fused oxepane **2ab**. The ^1H NMR spectrum shows several multiplets in the aliphatic region (δ 1.5–4.5 ppm) corresponding to the oxepine methylene chain and the characteristic peak of benzylic proton appeared as singlet at δ 5.8 (s, 1H) ppm. The distinguishing peak in the ^{13}C NMR spectrum was appeared as a doublet at δ 79.7 (d) corresponding to the benzylic carbon. However, the amide carbonyl appeared as a singlet at δ 159.9 (s). The ESI-MS (HRMS) analysis shows a base peak at 290.1174. The structure of

compound **2ab** was further confirmed by its single crystal *X*-ray diffraction studies (Figure 5).

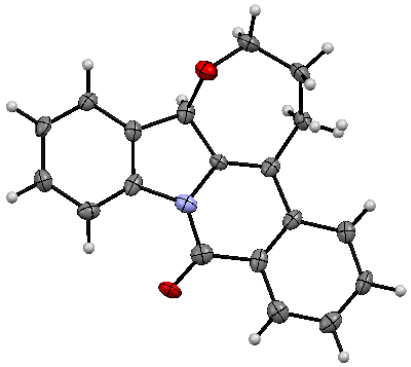


Figure 5. ORTEP Diagram of Compound **2ab** (CCDC No. 2005834)

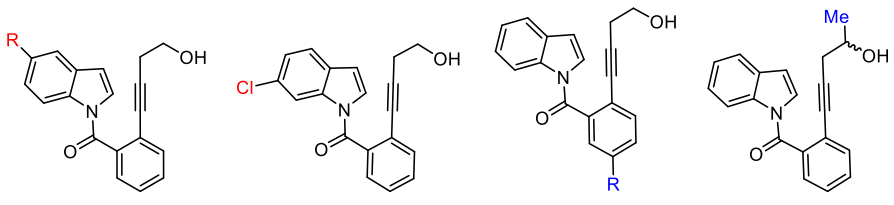
Next, the observed interconversion of these compounds in $CDCl_3$ revealed that the cleavage of the C–O bond in both **2aa** and **2ab** is facile, indicating that the formation of an intermediate allyl cation is facile. This prompted us to examine the allylation of purified and/or mixture of **2aa** and/or **2ab** with excess trimethylallylsilane in the presence of $BF_3{\cdot}OEt_2$. Initially, we tried to isolate the allylation product, but it was found to be unstable on silica gel. To overcome this, the crude alcohol, subsequently isolated after the work up, was subjected for acetylation to obtain exclusively compound **3a** up to 86% over two steps. The ^{1}H NMR spectrum shows characteristic peaks of allyl group as multiplet at δ 4.90–4.97 (m, 2H) corresponding to terminal olefin protons, and the internal proton being resonated at δ 5.42–5.52 (m, 1H) ppm. The benzylic proton/the proton of the stereogenic center (C3 of indoline) appeared as a doublet of doublet at δ 4.47 (dd, J = 3.8, 6.8 Hz, 1H) indicating that the proton at this stereogenic center is coupling with the adjacent methylene group. In the ^{13}C NMR spectrum of compound **3a**, the amide carbonyl appeared as singlet at δ 160.6 and the ester carbonyl as a singlet at δ 171.0 ppm. The disappearance (C2 and C3 of indole) of two protons in the aromatic region revealed the dearomatization of the indole nucleus (cyclisation occurring *via* indole C2) and the formation of isoquinolin-1-one core was supported by the increased number of quaternary carbons (two) in the aromatic region of the ^{13}C NMR spectrum. In ESI-MS (HRMS) analysis, the base peak was obtained at 374.1761.

With this encouraging result, next we examined combining both cyclisation with $Au(PPh_3)Cl/AgSbF_6$ and subsequent allylation in one-pot. After exploring a couple of conditions, the addition of 10 equiv of each allyl silane and $BF_3{\cdot}OEt_2$ led to the complete consumption of the intermediates **2aa**/**2ab** that resulted after the initial cyclisation. The

resulting crude alcohol isolated after the work up, was subjected for acetylation to obtain the acetate **3a** in 51% overall yield (Table 1). Subsequent experiments in dealing with the optimization lead to the identification of the (in)compatible [Au]-complexes/additives for the initial cyclisation. As shown in Table 1, when $AuCl_3$ or $AuBr_3$ were employed as catalysts, the initial cyclisation itself was not facile. In case of $^{i}PrAuCl/AgSbF_6$, the cyclisation resulted in the formation of an inseparable 2:1 mixture of a ketone **4a** (resulting from the alkyne hydration beta to the phenyl ring) and the known 3-(2-hydroxyethyl)-1*H*-isochromen-1-one **4b**[33] (resulting from either a 6-*endo*-dig cyclisation with the amide carbonyl with a concomitant amide bond cleavage, or the intramolecular lactonization of the enol ether of the hydration product). With $PtCl_4$ as well, the reaction was facile; however, the final product was isolated in poor yields. Also, the reaction seemed to be facile in 1,2-dichloroethane and 1,4-dioxane, providing average yields (52 & 58%). However, there was no reaction in acetonitrile. Using the same [Au]-complex, when other silver additives were screened, it was observed that there was no reaction with AgTFA or Ag_2CO_3. With AgOTf, the product **3a** was isolated in 79% yield, whereas $AgNTf_2$ gave the final product **3a** in 54% yield. The possibility of affecting the initial cyclisation with $BF_3{\cdot}OEt_2$, as well as with other Lewis acids such as $Sc(OTf)_3$, $Cu(OTf)_2$, $In(OTf)_3$, $InCl_3$, $Hg(OTf)_2$ and $Bi(OTf)_3$ revealed that they were not suitable for the current transformation.

1.5.1 Scope of Umpolung Reaction:

Having realized the possibility of the simultaneous functionalization of indole C2 and C3, we next proceeded to generalize the scope of this reaction by employing alkynol substrates **1a**–**1l** (prepared by EDC coupling followed by a Sonogashira cross coupling protocol) having different substituents on indole and benzoic acid rings (Scheme 22). All the synthesised alkynols were employed for the gold catalysed cycloisomerization and



1a, R = H, 87%
1b, R = Me, 76%
1c, R = F, 78%
1d, R = Br, 67%
1e, R = NO_2, 88%
1f, R = OMe, 68%

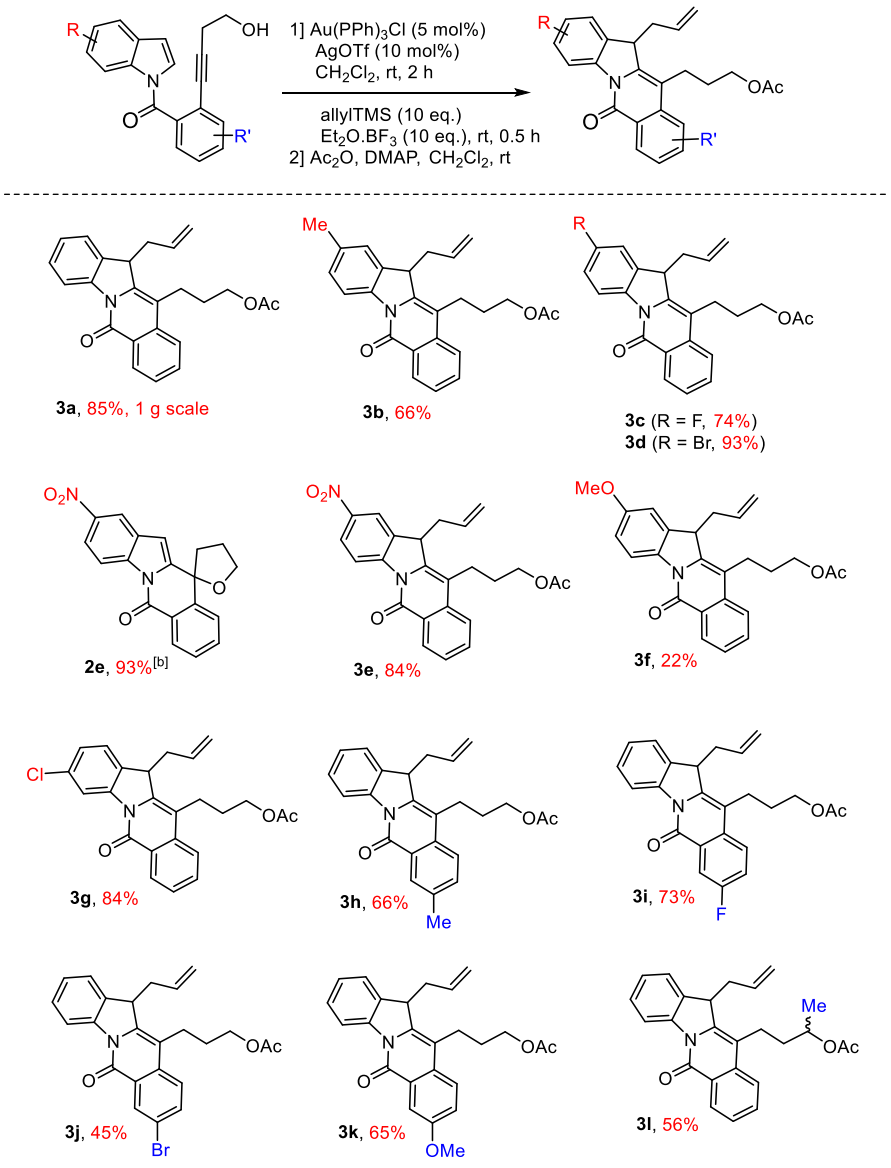
1g, 74%

1h, R = H, 89%
1i, R = F, 68%
1j, R = Br, 52%
1k, R = OMe, 64%

1l, 39%

Scheme 22. Starting Materials Prepared for the Gold Catalysed Cycloisomerization

allylation protocol to gain insight into the influence of the substituents, especially on the indole ring. As shown in Scheme 23, the substrates **1c**–**1e** having electron withdrawing groups at the C5 of the indole ring gave better results (74%–93%) when compared to the corresponding methyl and methoxy substituted derivatives **1b** (66%) and **1f** (22%). The structure of product **3d** was further confirmed by its single crystal *X*-ray diffraction studies (Figure 6). Even with the substrate **1g** having a C6-Cl, the yield was excellent. Interestingly, with the C5-nitro substrate **1e**, the initial cyclisation gave exclusively the spiro derivative **2e** and was found to be stable. In case of the substrates **3h**–**3k** having different substituents on the benzoyl ring placed *para* to the alkyne group; the yields were very good, with both electrons withdrawing and donating groups.



Scheme 23. Substrate Scope of the Umpolung Reaction

The starting material possessing a secondary alcohol was reacted under standard conditions to yield an inseparable mixture of diastereomers **3l** in 56% yield.

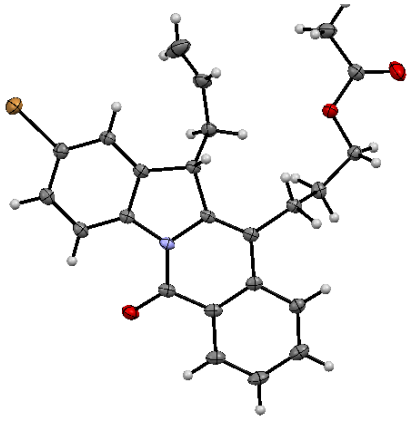
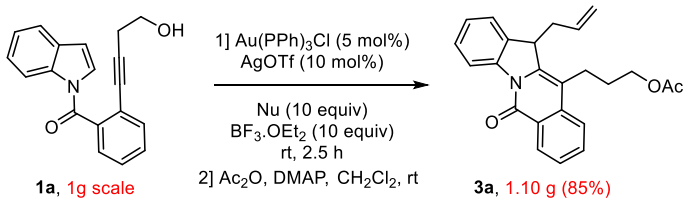


Figure 6. ORTEP Diagram of Compound **3d** (CCDC No. 2005836)

1.5.2 Gram Scale Synthesis:

In order to show gram scale utility of the current methodology, the cyclisation/allylation of substrate **1a** was performed on a 1 g scale. The reaction proceeded smoothly and the yield of the product **3a** was improved further from 79% to 85%.

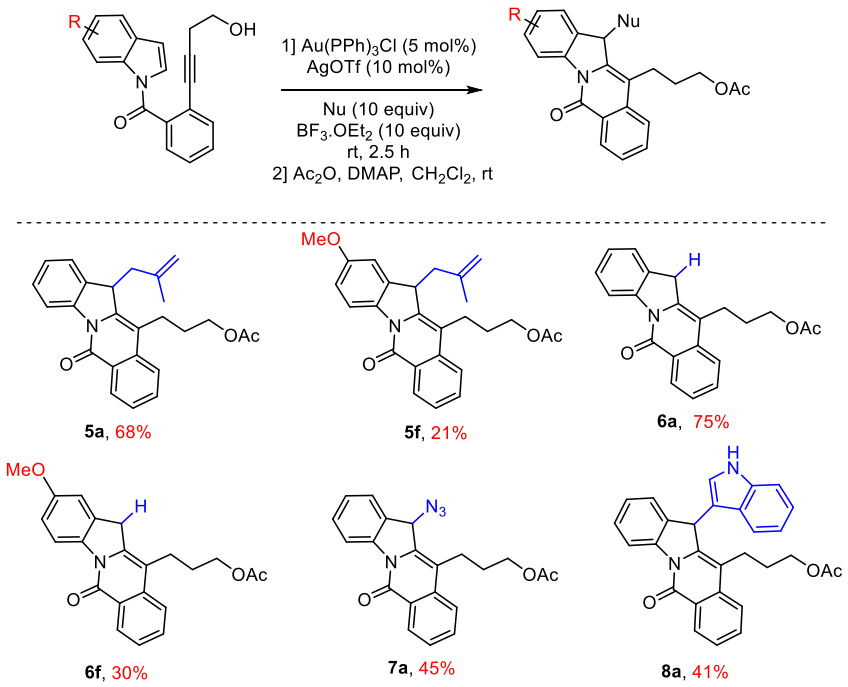


Scheme 24. Gram Scale Reaction

1.5.3 Scope of the Nucleophile:

The current methodology showcasing the umpolung reactivity of indole nucleus has the potential to be a significant tool in the total synthesis of indole alkaloids, provided that a wide range of nucleophiles could be added to the C3 of indole. For the given purpose, the compatibility of other nucleophiles such as methallylTMS, Et_3SiH, $TMSN_3$ and indole in the current sequence, employing the alkynols **1a** and **1f** was investigated. As shown in Scheme 25, when the gold catalysed cycloisomerization of unsubstituted alkynol **1a** and 5-methoxy indole containing alkynol **1f** was carried in the presence of $BF_3.OEt_2$ and methallyltrimethyl silane nucleophile, the expected products **5a** and **5f** were obtained in 68 and 21% yield respectively. The ^1H NMR spectrum of compound **5a** showed a peak at δ 2.12 (s, 3H) as

singlet, corresponding to the acetyl group, whereas the singlet at δ 1.82 (s, 3H) corresponded to the methyl of the methyallyl side chain. Also, the characteristic benzylic proton appeared as doublet of doublet at δ 4.46 (dd, J = 3.1, 9.9 Hz, 1H) ppm. In the ^{13}C NMR spectrum of compound **5a**, the singlets corresponding to the amide and ester carbonyl respectively were seen at δ 160.6 (s) and 171.0 (s). The base peak in ESI-MS was obtained at 388.1911. Similarly, the compound **5f** was also characterised and displayed analogous spectral and analytical data.



Scheme 25. Scope for the Nucleophile

The same (**1a**/**1f**) starting materials, when employed for the gold catalysed cycloisomerization in the presence of $BF_3.OEt_2$ and triethylsilane nucleophile, led to the respective products **6a** and **6f** being obtained in 75% and 30% yields. The ^{1}H NMR spectrum compound **6a** revealed four methylene multiplets 1.93–2.00 (m, 2H), 2.78–2.85 (m, 2H), 4.12 (s, 2H), 4.18 (t, J = 6.5 Hz, 2H) in the aliphatic region and a singlet at δ 2.11 (s, 3H) ppm corresponding to the acetyl group. The ^{13}C NMR spectrum showed an amide carbonyl appearing as a singlet at δ 160.6 (s) and the ester carbonyl as singlet at δ 171.0 (s) ppm. The four triplets corresponding to methylene groups appeared at δ 24.2 (t), 27.7 (t), 33.2 (t), 63.8 (t) and a quartet at δ 21.0 (q) ppm belonged to the acetyl group. The ESI-MS (HRMS) showed a base peak at 334.1453. In a similar fashion, the structure of the compound **6f** was also established with the help of spectral and analytical data.

Interestingly, employing azide and indole as nucleophiles in the reaction mixture afforded the desired products **7a** and **8a** in 45% & 41% yields respectively. The ^{1}H and ^{13}C NMR spectrum of azide **7a** indicated the presence of three methylene groups in the aliphatic region however the distinguishing benzylic proton appeared as a singlet at δ 5.56 (s, 1H). The ^{13}C NMR spectrum also showed the peaks that relate to the amide carbonyl at δ 160.0 (s) and ester carbonyl at δ 171.1 (s) ppm. The ESI-MS (HRMS) displayed a base peak at 375.1455. The structure of compound **7a** was further confirmed with the help of its single crystal *X*-ray diffraction studies (Figure 7). The compound **8a** possessing indole nucleophile was also characterized with the help of spectral and analytical data. For example, in the ^{1}H NMR spectrum of compound **8a**, a singlet at δ 5.96 (s, 1H) specified the benzylic proton, whereas other methylene protons were observed in the aliphatic region. The presence of an external nucleophile indole was indicated by the peak at δ 11.13 (d, J = 2.3 Hz, 1H) ppm, which also confirms the selective acetylation of alcohol. In the ^{13}C NMR spectrum of compound **8a**, amide carbonyl appeared as a singlet at δ 159.7 and the ester carbonyl appeared at δ 170.3 as a singlet. The existence of base peak at 449.1862 in ESI-MS (HRMS) also supported the formation of compound **8a**.

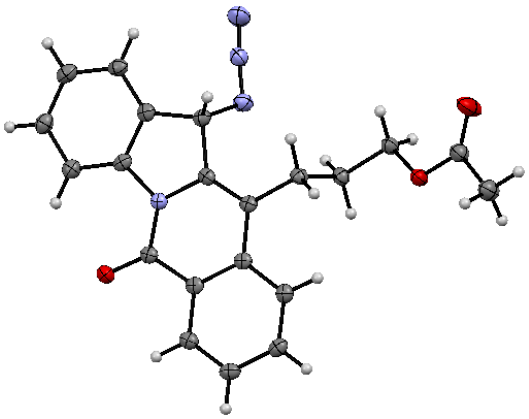


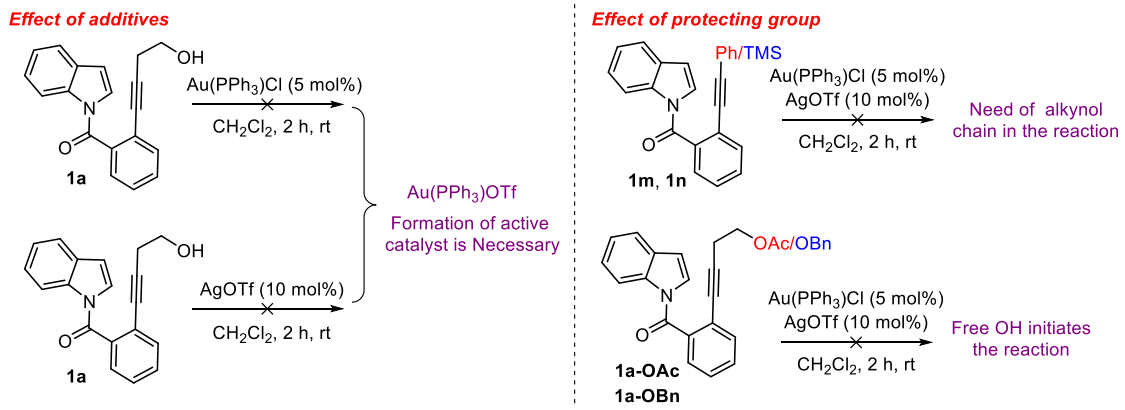
Figure 7. ORTEP Diagram of Compound **7a** (CCDC No. 2005835)

In general, the reactions with all these four nucleophiles were facile and provided the corresponding isoquinolin-1-ones in moderate to good yields. However, with the methoxy bearing substrate **1f**, the reactions were sluggish and resulted in an intractable mixture when $TMSN_3$ and indole were employed as the nucleophiles.

1.5.4 Control Experiments to Understand the Mechanistic Details:

The successful synthesis of isoqinolin-1-one derivatives from alkynols *via* established umpolung protocol inspired us to investigate the mechanistic pathway of the reaction. As a

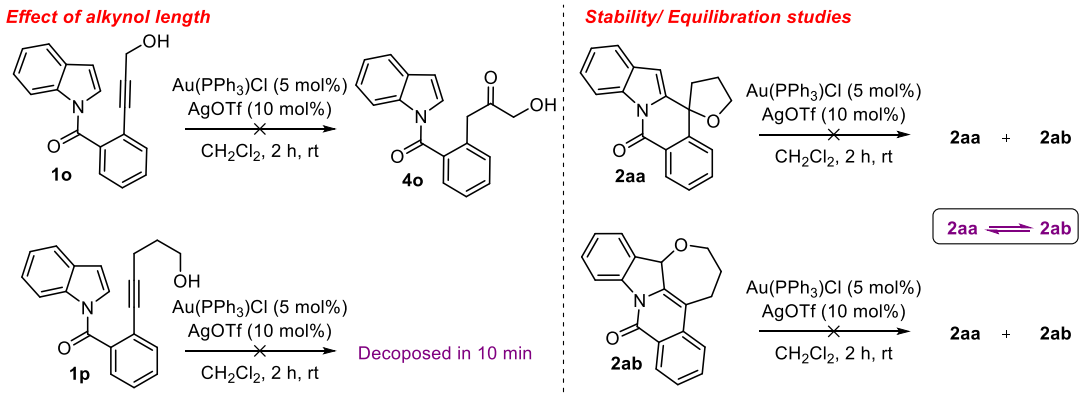
control and to understand the compatibility/course of the reaction, substrates having different substituents on the alkyne terminus were synthesized and their [Au]-catalysed intramolecular hydroarylation reaction under the current conditions was examined. As shown in Scheme 26, the alkynol **1a** was exposed separately to the 5 mol% of [Au] catalyst and 10 mol% of [Ag] additive. The recovery of starting material in both the reactions suggests that the combination of the [Au] catalyst and [Ag] additive is essential to form the active complex [Au(PPh_3)OTf], which initiates the reaction. Similar experiments were carried out with the phenyl and TMS-substituted alkynes **1m** and **1n** respectively, where the starting materials were found to be intact under the current conditions. This clearly revealed that the presence of an –OH group is essential for a successful cycloisomerization/indoloylation and importantly, the current domino process seems to be initiated by an alkynol cyclisation. This was further supported by the experiment with acetate and benzyl protected alkynols **1a-Ac** and **1a-Bn**, which were found to be intact under these conditions.



Scheme 26. Controlled Experiments and Their Conclusions

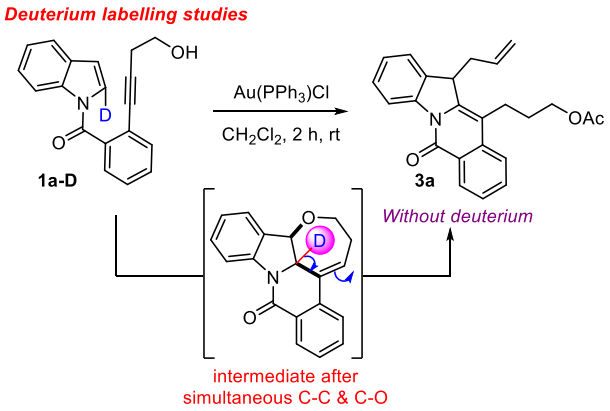
Interestingly, when the one carbon truncated **1o** and homologated **1p** alkynols were employed as substrates (Scheme 27), the hydration at the carbon next to the hydroxymethyl was the major event, with alkyne **1o** providing compound **4o** and the formation of a complex mixture was observed in case of the homologated alkyne **1p**. The experiments indicate that, only the 3-butynol chain length is suitable in order to have good conversion and the possibility of 5-*endo*-dig mode of alkynol cyclisation, resulting in the reactive oxocarbenium ion. In order to study the stability between pentacyclic intermediates **2aa** and **2ab**, they were further subjected for the gold catalysed cycloisomerization, expecting that either of these should be the single product. Surprisingly, we observed the formation of an equimolar mixture of **2aa** and **2ab**, suggesting that the pentacyclic intermediates are in equilibrium

under mild acidic conditions. The unstable behaviour of pentacycles towards silica and $CDCl_3$ was supported by this experiment.



Scheme 27. Controlled Experiments and Their Conclusions

Remarkably, when the C2-deuterated analogue of **1a** was employed, the product **3a** (without any labelled deuterium) was obtained exclusively, revealing that there was no hydride migration event[17e] and, hence, the possibility of simultaneous C–C and C–O bond formation was ruled out (scheme 28).

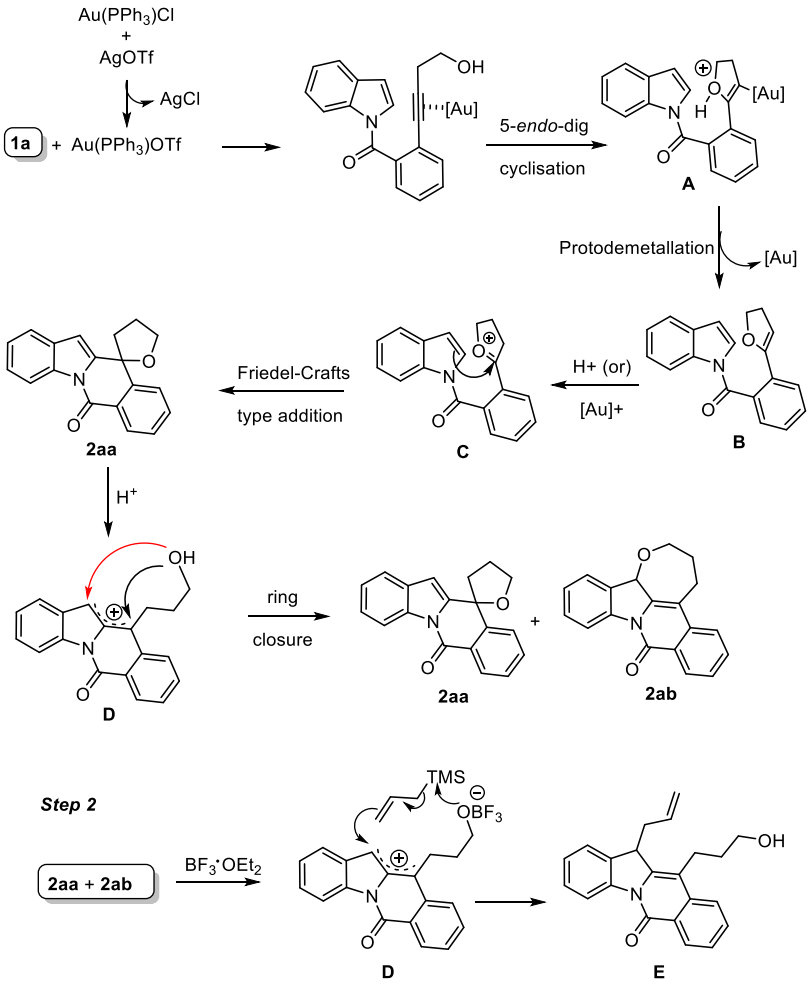


Scheme 28. The Deuterium Labelling Experiment

1.5.5 Possible Mechanistic Pathway:

Coming to the mechanism, with the information available from the control experiments and considering the previous reports,[34] we propose the following tentative mechanism (Scheme 29). The catalytic cycle starts with the formation of the active catalyst [$Au(PPh_3)OTf$] and subsequent 5-*endo*-dig alkynol cycloisomerization, followed by protodemetallation, leading to the intermediate dihydrofuran **B**.[35] The protonation of the intermediate dihydrofuran (either with the [Au]-complex or with the triflic acid generated *in*

situ) results in the oxocarbenium cation **C**, which, upon Friedel-Crafts type addition of the C2 of indole, leads to the spiro-tetrahydrofuran **2aa**.[36] As indicated by the control experiments, the spiro-compound **2aa** seems to be susceptible and is in equilibration with the corresponding oxepin derivative **2ab**. The isolation of the stable spirocycle **2e** with the 5-nitroindole derivative **1e** supports this argument, as the formation of a C3-cation is not favored in this case under normal conditions. Next, exposure of the resulting compounds **2aa** and **2ab** to $BF_3.OEt_2$ should lead to the allyl cationic species **D**, which undergoes allylation in S_N2' fashion with trimethylallylsilane to afford product **E**.[37]

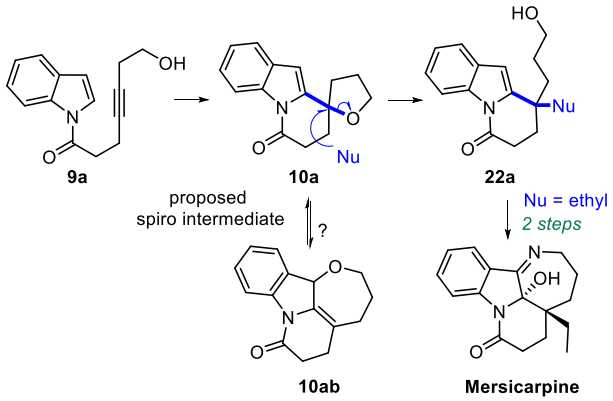


Scheme 29. Possible Mechanistic Pathway

1.6.1 Substrate Modification for Mersicarpine Synthesis:

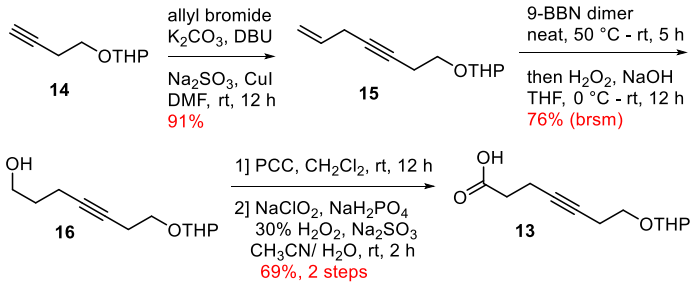
After having established, a novel cascade process for the construction of indoloisoquinolone derivatives, next we focussed our attention on the synthesis of the originally targeted pyridoindolone core of mersicarpine. As shown in Scheme 30, for the gold

catalysed cyclisation of compound **9a**, from the previous results, one could now expect the formation of both spiro derivative **10a** and/or a fused oxepine **10ab**. However, considering the electronic nature of the spiro center (which is flanked between the aryl and heteroaryl units in the previous case), we assumed the exclusive formation of spiropyridoindolone **10a**. As indicated previously, further nucleophilic addition at the spiro carbon of **10a** could be modulated to arrive at the advanced intermediates documented in the total synthesis of this class of natural products.[38] For example, a simple addition of the ethyl anion at this spiro-center should deliver the known key intermediate **22a**, employed in the mersicarpine synthesis and, importantly, takes place in a short and convergent fashion.



Scheme 30. Planned synthesis of Mersicarpine

Our journey in this direction started with the synthesis of the key acid **13**. The synthesis began with allylation of the –OTHP protected 3-butyn-1-ol in the presence of allyl bromide, potassium carbonate as a base, and copper iodide as catalyst in DMF solvent to obtain the expected enyne **15** in 91% yield.[39] The structure of the resulting product was confirmed with the help of NMR and HRMS analysis. For example, in the ^{1}H NMR spectrum of compound **15**, the characteristic olefinic protons appeared at δ 5.05 (dq, *J* = 10.0, 1.6 Hz, 1H), 5.32 (dq, *J* = 10.0, 1.6 Hz, 1H), 5.81 (ddt, *J* = 10.0, 5.0, 1.6 Hz, 1H) and a peak at 4.65 (t, *J* = 3.0 Hz, 1H) represents (C1) hemiacetal proton and indicates the presence of the tetrahydropyran ring. In the ^{13}C NMR spectrum of compound **15**, the alkyne carbons were seen to resonate at 77.7 (s), and 79.4 (s), while a triplet and a doublet at δ 115.7 (t), 133.1 (d) were assigned to the olefin carbons. The ESI-MS (HRMS) shows base a peak at 217.1197 supports the formation of compound **15**. The selective hydroboration oxidation of alkene in the presence of internal alkyne was achieved employing the 9-BBN dimer when heated to 50 °C in neat conditions for 10 min. and later allowed to stir at rt for 5 h.[40] After the complete conversion of the starting material to the borate complex, it was decomposed in the presence



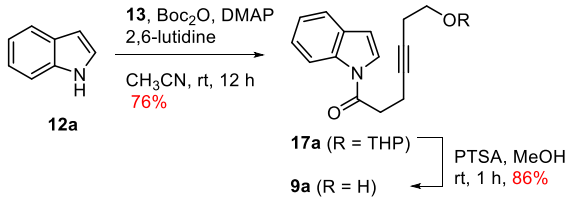
Scheme 31. Preparation of Starting Acid **13**

of excess hydrogen peroxide and sodium hydroxide to obtain the corresponding alcohol **16** in 76% yield. In the ^{1}H NMR spectrum of compound **16**, the disappearance of olefinic protons and the existence of two extra protons in the region of δ 3.5–4.0 ppm indicated the formation of alcohol. The ^{13}C NMR spectra displayed characteristic alkyne carbons at δ 77.7 (s), and 80.4 (s) and the (C1) hemiacetal carbon appeared as a doublet at δ 98.8 (d) specifying the presence of a tetrahydropyran ring. The ESI-MS (HRMS) confirmed formation of alcohol, showing a base peak at 235.1299.

Next, the alcohol **16** was subjected for the sequential PCC and Pinnick oxidation conditions to afford the desired acid **13** in 69% yield over 2 steps.[41] The disappearance of a characteristic CH_2 signal at δ 3.5–4.0 ppm present in **16** and the presence of a new peak at δ 2.5 ppm indicated the oxidation of alcohol to form the corresponding carboxylic acid **13**. The ^{1}H NMR spectrum also showed a peak at δ 2.43–2.49 ppm corresponding to four methylene protons next to an internal alkyne, and a (C1) hemiacetal proton at δ 4.65 ppm indicated the presence of tetrahydropyran ring. The characteristic alkyne carbons resonated at δ 78.0 (s), and 78.9 (s) whereas the presence of an acid carbonyl was confirmed from the peak at δ 177.4 ppm. The ESI-MS (HRMS) supported the formation of acid by showing a base peak at 249.1091.

The next assignment was the coupling of indole **12a** with acid **13** and subsequent –OTHP deprotection to reach the desired alkynol **9a**. Consequently, the previously used condition (EDC.HCl/DMAP in CH_2Cl_2 solvent) for the coupling of indole and acid was attempted. However, the results were disappointing. The starting material indole was found to be intact in the given conditions. The detailed investigation of literature reports guided us to conclude that the difference in the reactivity of the currently employed aliphatic carboxylic acid and previously used benzoic acid is responsible for halting the conversion. Also, we came across a report which stated that a *tert*-butylpyrocarbonate (BOC-anhydride)/4-dimethylaminopyridine (DMAP) could be employed, especially for the coupling of a less

reactive acid and non-nucleophilic heterocycles.[42] Inspired from the report, we carried out the coupling of indole **12a** and acid **13** in the presence of BOC-anhydride/DMAP, which resulted in the satisfying and expected compound **17a** in 76% yield.

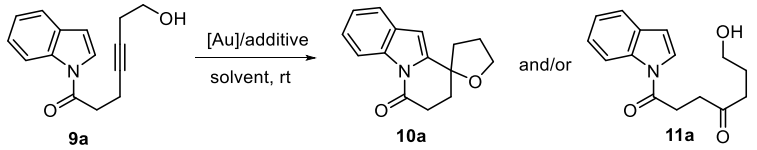


Scheme 32. Synthesis of the Key Alkynol Substrate **9a**

The ^{1}H NMR spectrum of the product displayed a distinguishing C3 proton of indole at δ 6.66 (dd, *J* = 3.8, 0.4 Hz, 1H) and a (C1) hemiacetal proton at δ 4.62 (t, *J* = 3.0 Hz, 1H) represents the tetrahydropyran ring present in the acid coupling partner. Overall, the remaining aliphatic and aromatic protons were matched appropriately to the product. The symbolic amide peak appeared at δ 169.7 (s) in the ^{13}C NMR spectrum. The typical alkyne carbons resonated at δ 79.0 (s), and 98.8 (d) and confirm the presence of the acid coupling partner in the product. The base peak in ESI-MS (HRMS) was observed at 348.1560 and confirms the presence of compound **17a**. The –OTHP deprotection of alcohol was carried out with the help of cat. PTSA methanol at rt to afford the desired alkynol **9a** in 86% yield. The disappearance of the illustrative (C1) hemiacetal proton at δ 4.62 (t, *J* = 3.0 Hz, 1H) and other protons corresponding to the tetrahydropyran ring indicates deprotection of the –OTHP group. Also, the presence of four triplets from δ 2.4–3.8 ppm and a doublet at δ 6.68 (d, *J* = 3.7 Hz, 1H) of C3 indole confirm the formation of the product. The ^{13}C NMR spectrum showed four triplets at 14.4 (t), 23.12 (t), 35.3 (t), and 61.2 (t) corresponding to methylene groups, and the alkyne carbons appeared at δ 78.1 (s), and 80.3 (s), whereas the symbolic amide carbonyl peak at 169.7 (s) confirmed the formation of the product. The ESI-MS (HRMS) base peak at 242.1173 supports formation of compound **9a**.

Now, the stage was all set, and we were excited to check the outcome of the alkynol **9a** cycloisomerization reaction under gold catalysed conditions. Next, the alkynol **9a** was subjected for the proposed gold catalysed hydroarylation-spirocyclisation in the presence of the $AuPPh_3Cl$ catalyst and the commonly employed $AgSbF_6$/AgOTf as additive in CH_2Cl_2 solvent (entries 1 & 2, Table 2). The expected spirocyclic pyridoindolone **10a** was obtained in 42% and 36% yields respectively, along with a trace amount of the hydrated compound

Table 2. Optimization of Gold Catalysed Hydroarylation-Spirocyclisation[a].



Sr. No	[Au]	Additive	Solvent	Temperature /time	% Yield[b]	
					10a	**11a**
1.	$Au(PPh_3)Cl$	$AgSbF_6$	CH_2Cl_2	rt/15 min	42	15
2.	$Au(PPh_3)Cl$	AgOTf	CH_2Cl_2	rt/15 min	36	22
3.	(JohnPhos)AuCl	$AgSbF_6$	CH_2Cl_2	rt/15 min	36	13
4.	AuCl	-	CH_2Cl_2	rt/15 min	60	5
5.	$AuCl_3$	-	CH_2Cl_2	rt/15 min	65	12
6.	$AuCl_3$	-	THF	rt/15 min	26	30
7.	$AuCl_3$	-	PhMe	rt/15 min	66	5
8.	$AuCl_3$	-	CH_3CN	rt/15 min	86	--
9.	$AuCl_3$	-	$(CH_2Cl)_2$	rt/15 min	93	--

[a] In general, the reactions were carried out with **9a** (124.03 µmol), Au (5 mol%), and additive (10 mol%) in 3 ml dry solvent for 15 min. [b]Isolated yields.

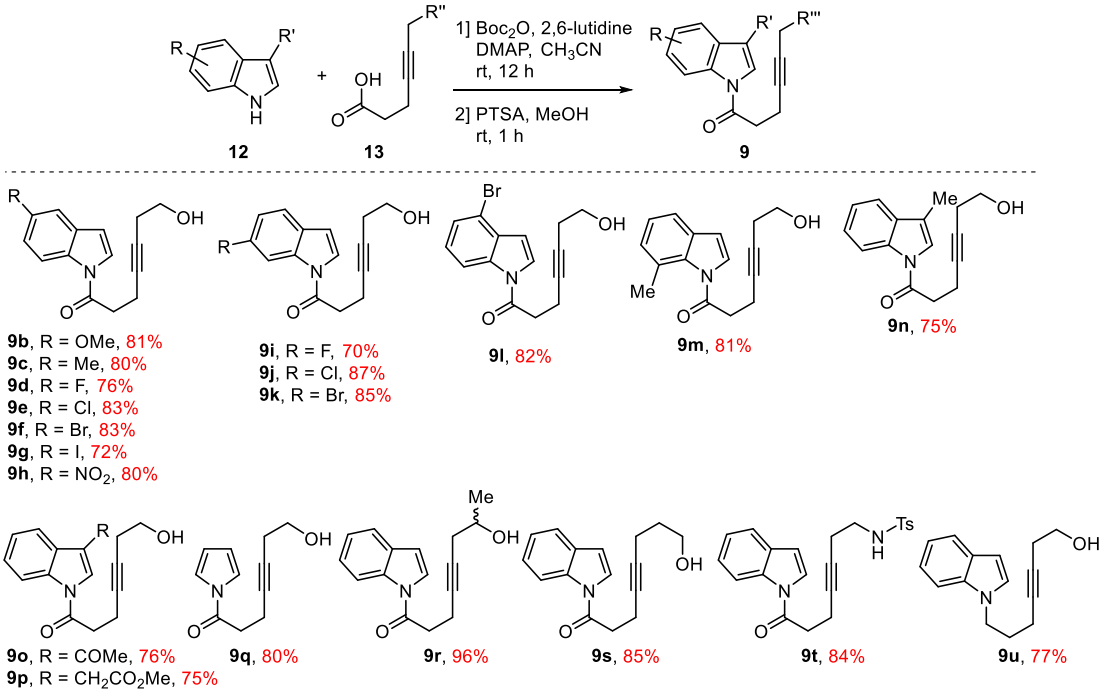
11a. The ^{1}H NMR spectrum of compound **10a** showed the disappearance of an aromatic proton (C2 Indole) at δ 7.59 (d, *J* = 7.6 Hz, 1H) and the arrival of two extra protons in the aliphatic region (δ 2–4 ppm) supports the formation of the expected pyridoindolone. The ^{13}C NMR spectrum of compound **10a** showed the vanishing of alkyne carbons at δ 78.1 (s), and 80.3 (s) and the arrival of an extra triplet in the aliphatic region along with two quaternary carbons at δ 77.7 (s) & 141.5 (s) supports the formation of the product. Further, this was supported by ESI-MS (HRMS) which showed a base peak at 242.1174. The formation of a hydration compound **11a** was established from the NMR spectroscopy and HRMS. The ^{1}H NMR spectra displayed the appearance of an extra quintet for two protons at δ 1.92 (quin, *J* = 6.5 Hz, 2H). The ^{13}C NMR spectrum showed a peak at δ 209.4 (s) corresponding to the ketone carbonyl, and the ESI-MS (HRMS) specified a base peak at 282.1106 confirming the formation of compound **11a**. The successful isolation and characterisation of spiro-pyridoindolone prompts us to screen various gold complexes and solvents in order to improve the yield of the current reaction. When the same reaction was carried out in the presence of (JohnPhos)AuCl/$AgSbF_6$, the reaction yield was 36%, whereas the reaction with AuCl

resulted in the isolation of compound **10a** in 60% yield (entries 3 & 4). Interestingly, the $AuCl_3$ catalyst without the [Ag] additive in CH_2Cl_2 solvent gave promising results (65% yield of spirocyclic compound **10a**, entry 5). This result prompted us to screen the $AuCl_3$ catalyst in different solvent systems. Accordingly, the reactions were carried out by employing THF, toluene, acetonitrile and 1,2-DCE to obtain **10a** in 26–93% yields (entries 6–9), where 1,2-DCE, was found to be the solvent of choice.

1.6.2 Scope of Hydroarylation-Spirocyclisation Reaction:

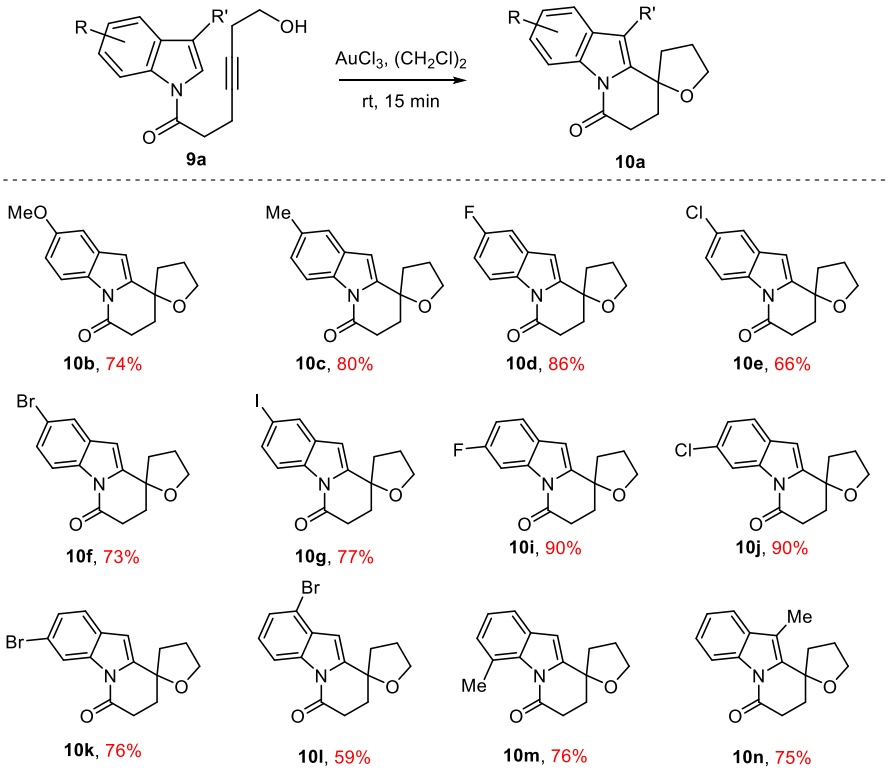
After having the optimized conditions in hand, in order to extend the scope of the reaction various indole templated alkynols **9b**–**9n** (70–87%) having different electron donating/withdrawing groups on the indole ring were synthesized (Scheme 33) by following the established two-step sequence. In addition, pyrrolyl flanked alkynol **9q** (80%), alkynol **9r** (96%) with a 2°-OH group, and also the alkyne substrates **9s**–**9u** (77–85%) (where the flanking group around the alkyne was varied) have been synthesised to test the limitations of the current methodology.[43]

Next, the scope of the current methodology has been explored by employing the differently substituted alkynols **9b**–**9u** under the optimized conditions. In general, the reactions proceeded smoothly with the substrates **9b** and **9c** having strong (-OMe) or



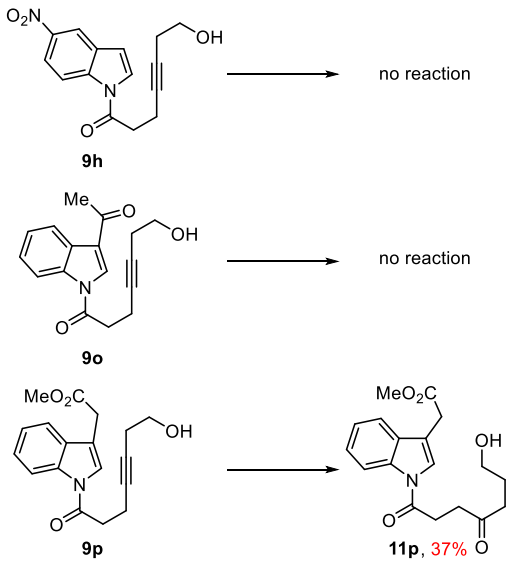
Scheme 33. Alkynols Synthesized to Study the Scope of Reaction

moderate (-Me) electron donating groups at the C5 of indole respectively, and provided the corresponding cyclised products **10b** (74%) and **10c** (80%) in good to excellent yields (Scheme 34). Similarly, the alkynols with C7 and C3 methyl indoles gave the spiropyridoindolone compounds **10m** and **10n** (76% & 75%). However, the substrates with strong electron withdrawing groups, such as C5 nitro **9h** or C3 acetyl **9o**, blocked the conversion (Scheme 35). Along similar lines, when the alkynol flanked with indole-3-acetic acid **9p** was employed under optimised conditions, the hydration of alkyne was the major event to yield 37% of compound **11p**. The existence of an extra quintet was observed at δ 1.92 (quin, J = 6.2 Hz, 2H) in the ^{1}H NMR spectrum and the appearance of a corresponding ketone carbonyl peak at δ 209.3 (s) in ^{13}C NMR spectrum and ESI-MS (HRMS) base peak at 354.1307 confirmed the hydration product **11p**.



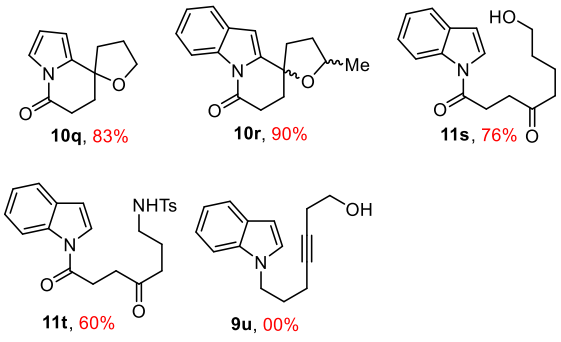
Scheme 34. Scope for the Gold Catalysed Hydroarylation-Spirocyclisation

Next, the halogenated substrates **9d**–**9g** having respectively an F, Cl, Br or I groups at the C5 position of indole afforded the corresponding spiro compounds **10d**–**10g** in good to excellent yields (66–86%). Likewise, the position of deactivators at the C4 and C6 of indole did not affect the outcome of the reaction, and afforded the desired spiro products (**10i**–**10l**) in moderate to excellent yields (59–90%).



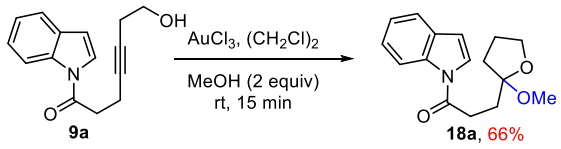
Scheme 35. Incompatible Substrates

Next, the scope of this transformation has been examined by selected indole templated alkynes **9q**–**9t**. The reaction of the pyrrole containing alkynol **9q** gave the corresponding spiro compound **10q** in 83% yield, revealing the suitability of this reaction to synthesize the spiro-pyrrolopyridone scaffolds. Similarly, with the substrate **9r** having the secondary alkynol, the reaction proceeded smoothly and provided the corresponding spiro compound **10r** in 90% yield as a mixture of inseparable diastereomers (1:0.3 dr from ^{1}H NMR). In case of the tosyl protected alkynyl amine **9t** (was prepared by the Mitsunobu reaction of alkynol **9a** with *tert*-butyl tosylcarbamate followed by deprotection of the –Boc group in the presence of oxalyl chloride in methanol), where the participating –OH was replaced with an –NHTs, the hydration of the alkyne seemed to be facile under the current conditions. A similar observation was noticed with the homologated alkynol **9s**. When the alkynol **9u** (without amide carbonyl) was treated under the optimized conditions, surprisingly, the starting material was intact (Scheme 36).



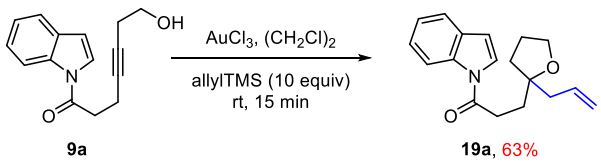
Scheme 36. Scope of the Reaction with Differently Substituted Alkynes.

Next, the effect of external nucleophiles in the current gold catalysed hydroarylation-spirocyclisation reaction and the possibility of adding an external nucleophile to the reactive spiro center was attempted. Accordingly, the alkynol **9a** was subjected to gold catalysed cycloisomerization in the presence of different O *or* C centred nucleophiles. When the MeOH (2 equiv) was employed as nucleophile, the cyclised intermediate dihydrofuran product **18a** was obtained in 66% yield (Scheme 37). The ^{1}H NMR spectrum of compound **18a** displayed six aromatic protons, indicating that the arylation had not occurred and the appearance of two extra protons in the aliphatic region along with a singlet at δ 3.15 (s, 3H) supported the addition of methanol to the intermediate dihydrofuran derivative. ^{13}C NMR revealed the presence of four triplets form δ 24–35 ppm, corresponding to the methylene and a quartet at δ 48.5 represented the methanol carbon. The presence of a singlet at δ 108.7 (s) revealed the presence of hemiketal and hence gave the proof for 5-*endo*-dig cycloisomerization followed by addition f methanol to form the intermediate tetrahydrofuran **18a**, which displayed a ESI-MS (HRMS) base peak at 296.1252.



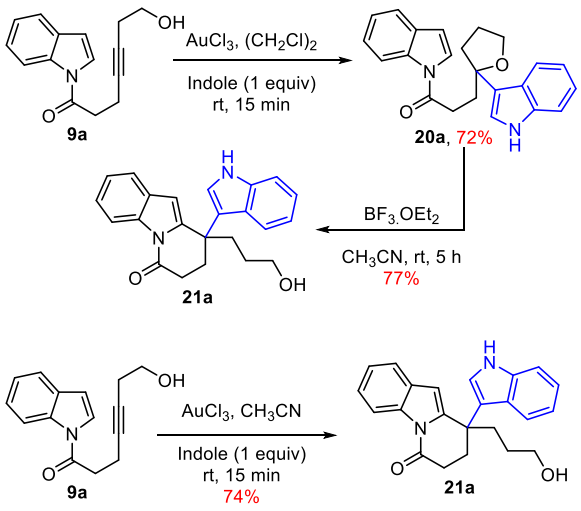
Scheme 37. Cyclisation of Alkynol **9a** in the Presence of MeOH

Similarly, when the cyclization of alkynol **9a** was carried out under standard conditions and in the presence of trimethylallyl silane (10 equiv.) as nucleophile, compound **19a** was obtained in 63% yield (Scheme 38). In this case also, the ^{1}H NMR of compound **19a** displayed six aromatic protons (δ 6.5–8.5 ppm), which clearly indicated the interruption of the hydroarylation-spirocyclisation reaction. The existence of three olefin protons at δ 5.08–5.19 m, 2H) and 5.83 (ddt, *J* = 17.1, 10.1, 7.2 Hz, 1H) indicated the addition of the allyl group. (Along the similar lines of the previous observation, ^{13}C NMR evidenced the 5-*endo*-dig cycloisomerization to form the intermediate tetrahydrofuran **19a** which was further supported by a ESI-MS (HRMS) base peak at 306.1472.



Scheme 38. Cyclisation of Alkynol **9a** in the Presence of Excess Trimethylallylsilane

Likewise, with the addition 1 equiv of Indole as external nucleophile under the optimized conditions, the intermediate tetrahydrofuran product **20a** was obtained in 72% yield (Scheme 39).

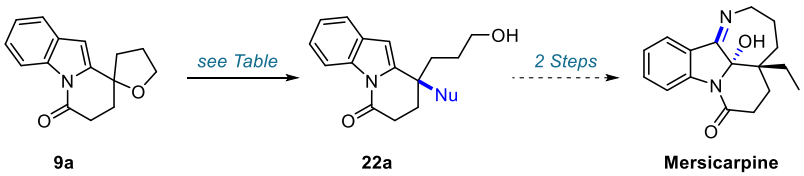


Scheme 39. Cyclisation of Alkynol **9a** in the Presence of indole

These experiments clearly support the proposed mechanism that the reaction proceeded *via* initial alkynol cyclisation followed by intramolecular addition of the indolyl C2 to the intermediate oxocarbeneium cation. The possibility of carrying out the intramolecular cyclisation of the resulting products **18a**–**20a** was checked with the addition of external Lewis acids. However, only in case of **20a**, was the cyclisation seen to be facile in the presence of borontrifluoride etherate in acetonitrile and provided the corresponding indole substituted pyridoindolone **21a** in good yields (77%). The ^{1}H NMR spectra of this compound showed a peak for ten protons in the aliphatic region (1.5– 3.5 ppm), corresponding to five methylene in the product. However, the existence of ten aromatic protons and an indole N-H proton at δ 10.92 (s, 1H) indicated the presence of a bis-indole unit in the product. The ^{13}C NMR spectrum showed a benzylic quaternary carbon at δ 39.6 and an amide carbonyl at δ 169.2 (s), along with ten C–H and six quaternary carbons in the aromatic region, thereby providing evidence of the formation of compound **21a** which was supported by the ESI-MS (HRMS) base peak at 381.1583. Alternatively, the same product **21a** was obtained in excellent yields (74%) when the cyclisation of alkynol **9a** in the presence of indole was conducted under the optimized conditions, with the change of the solvent from 1,2-DCE to acetonitrile (Scheme 39).

Eventually, the addition of the ethyl nucleophile to spiro-pyridoindolone was attempted in order to complete the total synthesis of Mersicarpine. We speculated that, the addition of an external nucleophile to spiro-pyridoindolone **9a** in the presence of $BF_3.OEt_2$ at the reactive benzylic spiro centre reacts regioselectively, unlike the previously observed C3 allylation of indole. Consequently, the spiro-pyridoindolone was treated with diethyl zinc (Et_2Zn) and allyltrimethyl silane as nucleophiles and the $BF_3.OEt_2$ Lewis acid in THF solvent at -78 °C to rt (entry 1 & 2, Table 3). In these cases, the results were disappointing and the starting material was recovered with the Et_2Zn nucleophile. However, in the case of the reaction with allyltrimethyl silane, the compound underwent decomposition. Next, we screened several transition metal catalysts/Lewis acids in the presence of a variety of nucleophiles at a range of temperatures -78 °C to 100 °C. Nonetheless, we failed to get the expected conversion (entries 3–16, Table 3).[44]

Table 3. Screening of Lewis acid/Catalyst for Nucleophiles Addition at Spiro-Pyridoindolone



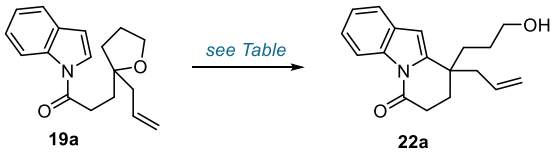
9a **22a** **Mersicarpine**

Sr. No	Lewis acid/Catalyst	Nucleophile	solvent	Temp/time	Yield
1.	$BF_3.OEt_2$	Et_2Zn	THF	-78 °C – rt/12 h	NR
2.	$BF_3.OEt_2$	Allyl-TMS	CH_2Cl_2	0 °C/30 min	decomposed
3.	$BF_3.OEt_2$	$(EtO)_3SiEt$	CH_2Cl_2	0 °C – rt/30 min	NR
4.	TMSOTf	Allyl-TMS	CH_2Cl_2	0 °C/30 min	decomposed
5.	BBr_3	–	CH_2Cl_2	0 °C/30 min	decomposed
6.	Amberlyst	Allyl-TMS	Toluene	60 °C/4 h	NR
7.	$Ni(acac)_2$/xanthphos	Et_2Zn	Toluene	rt/24 h	NR
8.	$Ni(cod)_2$/*rac*-BINAP	Et_2Zn	Toluene	rt/12 h	NR
9.	$Sc(OTf)_3/PdCl_2$	Allyl-TMS	CH_3CN	100 °C/6 h	NR
10.	$Sc(OTf)_3/PdCl_2$	TMSCN	CH_3CN	rt/12 h	NR
11.	$Bi(OTf)_3$	Allyl-TMS	$(CH_2Cl)_2$	rt – 60 °C/24 h	NR

12.	$Al(OTf)_3$	Allyl-TMS	CH_3CN	rt/24 h	decomposed
13.	$Al(OTf)_3$	VinylMgBr	THF	0 °C/6 h	decomposed
14.	$Al(OTf)_3$	TMSCN	CH_3CN	rt/12 h	decomposed
15.	$Cu(OTf)_2/PdCl_2$	TMS-acetylene	CH_3CN	100 °C/6 h	NR
16.	$AuCl_3$	TMS-ethanol	CH_2Cl_2	rt/15 min	decomposed

Subsequently, we explored the possibility of subjecting compound **19a** for the intramolecular Friedel-Crafts reaction in this regard. In this case, the allyl group is already installed and the task left is the dearomative cyclisation of indole with THF in the presence of Lewis acid/metal catalyst. Keeping this in mind, the Lewis acids like $BF_3.OEt_2$ and TMSOTf were tested. Unfortunately, the starting material was decomposed in both the reactions (entryes 1 & 2, Table 4). When compound **19a** was employed in the presence of a metal catalyst like $ZnCl_2$, $AuCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$ etc., the starting material was recovered in all reactions (entries 3–6, Table 4).

Table 4. Screening of Lewis acids/Catalyst for Dearomative Cyclisation of indole with THF

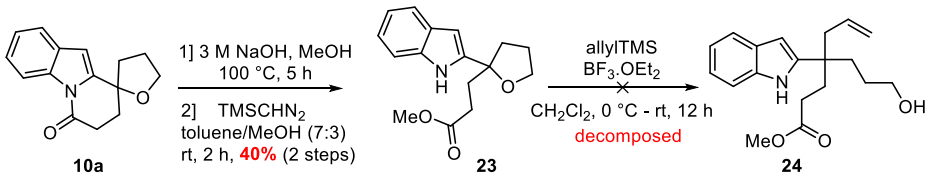


Sr. No	Lewis acid/ Catalyst	solvent	Temp/time	Yield
1.	$BF_3.OEt_2$	CH_2Cl_2	0 °C/2 h	decomposed
2.	TMSOTf	CH_2Cl_2	0 °C/2 h	decomposed
3.	$ZnCl_2$	CH_2Cl_2	40 °C/4 h	NR
4.	$AuCl_3$	CH_2Cl_2	µW 100 °C/10 min	NR
5.	$Yb(OTf)_3$	THF	µW 100 °C/10 min	NR
6.	$Sc(OTf)_3/PdCl_2$	CH_3CN	100 °C/20 h	NR

Microwave details = Anton Parr, Monowave 300, Power = 25 W

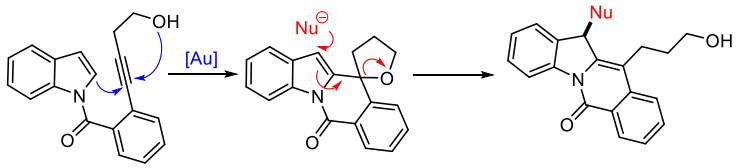
Considering the previous difficulties in the addition of nucleophiles to the spiro-pyridoindolone, we believed that the pyridone ring could be responsible for blocking the path of nucleophiles. With this belief, we aimed for the opening of the pyridone ring by cleaving the amide bond in the presence of 3M NaOH in methanol at 100 °C, followed by

esterification in the presence of TMS-diazoethane to afford compound **23** in 40% yield over 2 steps.[38c] The ^{1}H NMR spectra of showed a singlet at δ 3.51 (s, 3H) corresponding to methyl ester and also the ^{13}C NMR spectrum displayed an ester carbonyl at δ 174.0 which confirmed the formation of ester **23**. When the ester **23** was employed for the allylation in the presence of allyltrimethylsilane/$BF_3.OEt_2$, unluckily, the starting material was decomposed in this reaction as well (Scheme 40). At this stage, we concluded, with unlimited disappointment, that the desired addition of nucleophiles to the spiro-pyridoindolone is a tricky reaction. We realized the need to search for alternatives to complete the total synthesis of Mersicarpine.

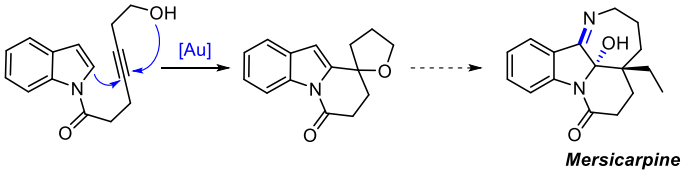


Scheme 40. Attempted Pyridoindolone Opening Followed by Allylation

Conclusion: To conclude, the possibility of adding electrophilic and nucleophilic centers respectively at indole C2 and C3 with a net reactivity umpolung was executed successfully. To this end, a simple protocol for the synthesis of tetracyclic indoloisoquinolinones with a pendant allylic group at C3 of indole has been developed. This protocol comprises of a gold-catalyzed 5-*endo*-dig alkynol cycloisomerization followed by intramolecular addition of C2-of indole and subsequent regioselective C3 allylation/azidation/reduction/indolylation. The utility of the developed protocol towards the total synthesis of Mersicarpine was examined. The modified alkynol underwent the expected gold-catalysed 5-*endo*-dig mode of alkynol cyclisation followed by Friedel Crafts type addition of C2 indole to afford the proposed spiro-pyridoindolone intermediate in the context of Mersicarpine synthesis. Initial studies on the addition of an external nucleophile to the resulting spiro-THF carbon were seen to have only limited success. Eventually, a simple catalytic method for the construction of a pyridoindolone core present in the indole class of alkaloids has been established. Further exploration in this direction and its utility in Mersicarpine synthesis are underway in our laboratory.



- 18 Examples
- up to 93% yield
- Nu = allyl, methallyl, Et_3SiH, $TMSN_3$, indole

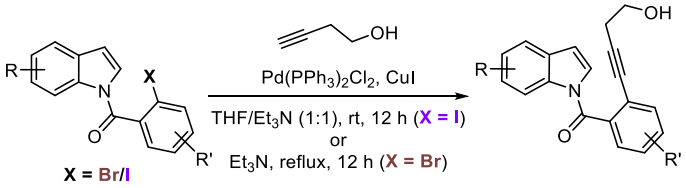


Mersicarpine

- 15 Examples
- mild conditions
- up to 97% yield

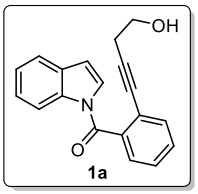
Synthesis of substrates 1a–1p, 1a-Ac, 1a-Bn and 1a-D

Genera procedure for Sonogashira coupling of *N*-(2-iodo)aroylindole with but-3-yn-1-ol: All starting *N*-(2-halo)aroylindole derivatives were prepared according to well–known literature procedures. In general, the Sonogashira coupling reactions were carried out employing 500 mg of corresponding indole derivative. A representative procedure is given below.

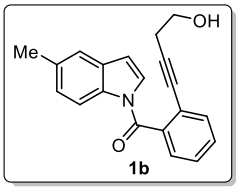


At rt, a solution of aryl halide (1.0 equiv) and alkynol (1.2 equiv) in THF/Et_3N (1:1) was degassed with argon (3 times) and treated with $Pd(PPh_3)_2Cl_2$ (0.1 equiv) followed by CuI (0.2 equiv). The reaction mixture was degassed once again with argon gas and stirred under argon atmosphere at room temperature for 12 h. When a 2-bromoaroyl derivative was employed as a substrate, the reaction was performed in neat Et_3N at reflux. After completion (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude compound was purified by using silica gel column chromatography employing ethyl acetate/petroleum ether solvent system as eluent to afford the corresponding N-(2-(4-hydroxybut-1-yn-1-yl))aroylindole derivative **1**.

(2-(4-Hydroxybut-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (1a): brown liquid; yield: 362 mg (87%); R_f = 0.3 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.87 (br.s, 1H), 2.40 (t, *J* = 6.1 Hz, 2H), 3.36 (t, *J* = 5.8 Hz, 2H), 6.61 (d, *J* = 3.7 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.37–7.62 (m, 6H), 8.23–8.52 (d, *J* = 5.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.7 (t), 60.7 (t), 79.0 (s), 92.7 (s), 109.0 (d), 116.3 (d), 120.9 (d), 122.0 (s), 124.2 (d), 125.2 (d), 127.3 (d), 127.7 (d), 128.0 (d), 130.5 (d), 130.8 (s), 132.4 (d), 135.4 (s), 137.6 (s), 168.1 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{15}NO_2Na$: 312.0995 $[M+Na]^+$; found 312.0994.

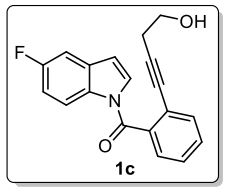


(2-(4-Hydroxybut-1-yn-1-yl)phenyl)(5-methyl-1*H*-indol-1-yl)methanone (1b): yellow liquid; yield: 320 mg (76%); R_f = 0.4 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz,

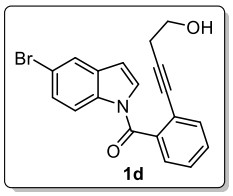


$CDCl_3$): δ 2.41 (t, J = 5.9 Hz, 2H), 2.47 (s, 3H), 3.39 (t, J = 5.9 Hz, 2H), 6.53 (d, J = 3.4 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.45 (t, J = 7.63 Hz, 1H), 7.47–7.57 (m, 3H), 8.25 (br.s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.4 (q), 23.8 (t), 60.8 (t), 79.2 (s), 92.7 (s), 108.8 (d), 115.9 (d), 120.9 (d), 122.0 (s), 126.5 (d), 127.3 (d), 127.7 (d), 128.0 (d), 130.4 (d), 131.1 (s), 132.3 (d), 133.7 (s), 133.9 (s), 137.8 (s), 167.9 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{17}NO_2Na$: 326.1152 $[M + Na]^+$; found 326.1149.

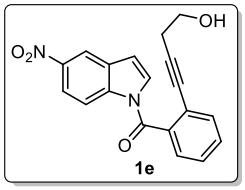
(5-Fluoro-1*H*-indol-1-yl)(2-(4-hydroxybut-1-yn-1-yl)phenyl)methanone (**1c**)**:** brown liquid; yield: 332 mg (78%); R_f = 0.3 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.38 (t, J = 6.1 Hz, 2H), 3.34 (t, J = 6.1 Hz, 2H), 6.65 (d, J = 3.8 Hz, 1H), 7.08 (d, J = 3.4 Hz, 1H), 7.22 (dt, J = 2.7, 8.4 Hz, 1H), 7.27 (dd, J = 2.7, 8.4 Hz, 1H), 7.35 (dt, J = 1.1, 7.6 Hz, 1H), 7.40–7.44 (m, 1H), 7.55 (dd, J = 5.1, 8.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 8.41 (br.s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.6 (t), 60.6 (t), 77.9 (s), 92.4 (s), 109.5 (d), 115.1 (dd, $^2J_{C\text{-}F}$ = 23.8 Hz), 116.2 (d), 118.0 (dd = $^2J_{C\text{-}F}$ = 21.9 Hz), 118.2 (dd, $^4J_{C\text{-}F}$ = 3.8 Hz), 121.0 (d), 124.4 (d), 125.3 (d), 127.0 (d), 130.8 (s), 134.4 (dd, $^3J_{C\text{-}F}$ = 7.6 Hz), 135.3 (s), 139.4 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 161.5 (dd, $^1J_{C\text{-}F}$ = 252.7 Hz), 166.5 (s) ppm; **^{19}F NMR** (376 MHz) δ -118.3 ppm; **HRMS** (ESI) calcd for $C_{19}H_{14}FNO_2Na$: 330.0901 $[M + Na]^+$; found 330.0895.



(**5-Bromo-1*H*-indol-1-yl**)(**2-(4-hydroxybut-1-yn-1-yl)phenyl)methanone** (**1d**)**:** colourless solid; yield: 290 mg (67%); mp: 101–102 °C; R_f = 0.3 (ethyl acetate/hexane, 4:6); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.72 (s, 1H), 2.37 (t, J = 6.1 Hz, 2H), 3.33 (q, J = 6.1 Hz, 2H), 6.64 (d, J = 3.8 Hz, 1H), 7.05 (d, J = 3.1 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.38–7.44 (m, 2H), 7.58–7.65 (m, 2H), 7.68 (s, 1H), 8.40 (br.s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.7 (t), 60.7 (t), 79.0 (s), 92.9 (s), 108.1 (d), 117.5 (s), 117.7 (d), 122.1 (s), 123.6 (d), 127.8 (d), 128.0 (d), 128.1 (d), 128.5 (d), 130.8 (s), 132.5 (d), 134.2 (s), 132.6 (s), 137.1 (s), 167.9 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{14}BrNO_2Na$: 390.0100 $[M + Na]^+$; found 390.0099.

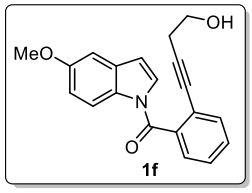


(2-(4-Hydroxybut-1-yn-1-yl)phenyl)(5-nitro-1*H*-indol-1-yl)methanone (**1e**)**:** colourless solid; yield: 377 mg (88%); mp: 101–102 °C; R_f = 0.2 (40% ethyl acetate in petroleum ether); **^{1}H NMR**

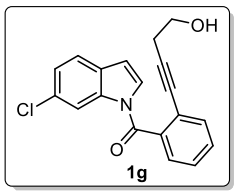


(500 MHz, $CDCl_3$): δ 2.37 (t, J = 6.1 Hz, 2H), 3.38 (t, J = 6.1 Hz, 2H), 6.73 (d, J = 3.8 Hz, 1H), 7.26 (d, J = 3.4 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.51–7.60 (m, 3H), 8.23 (dd, J = 1.9, 9.2 Hz, 1H), 8.40–8.54 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.6 (t), 60.5 (t), 78.7 (s), 93.1 (s), 109.0 (d), 116.3 (d), 117.0 (d), 120.2 (d), 122.1 (s), 128.0 (d), 128.1 (d), 130.2 (d), 130.8 (s), 131.2 (d), 132.7 (d), 136.3 (s), 138.4 (s), 144.5 (s), 168.0 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{14}N_2O_4Na$: 357.0846 $[M + Na]^+$; found 357.0843.

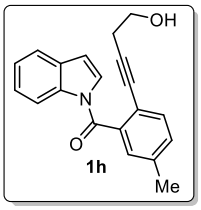
(2-(4-Hydroxybut-1-yn-1-yl)phenyl)(5-methoxy-1*H*-indol-1-yl)methanone (**1f):** yellow liquid; yield: 290 mg (68%); R_f = 0.2 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.40 (t, J = 6.1 Hz, 2H), 3.39 (t, J = 6.1 Hz, 2H), 3.87 (s, 3H), 6.53 (d, J = 3.8 Hz, 1H), 6.99 (d, J = 9.1 Hz, 1H), 7.03–7.05 (m, 2H), 7.41–7.54 (m, 4H), 8.3 (br.s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.7 (t), 55.6 (q), 60.7 (t), 79.0 (s), 92.7 (s), 103.7 (d), 108.9 (d), 113.4 (d), 117.0 (d), 122.0 (s), 127.7 (d), 127.9 (d), 128.0 (s), 130.1 (s), 130.4 (d), 131.8 (s), 132.3 (d), 137.6 (s), 156.8 (s), 167.7 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{17}NO_3Na$: 342.1101 $[M + Na]^+$; found 342.1096.



(6-Chloro-1*H*-indol-1-yl)(2-(4-hydroxybut-1-yn-1-yl)phenyl)methanone (**1g):** yellow liquid; yield: 312 mg (74%); R_f = 0.3 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.81 (br.s, 1H), 2.41 (t, J = 6.1 Hz, 2H), 3.40 (t, J = 6.0 Hz, 2H), 6.57 (d, J = 3.8 Hz, 1H), 7.06 (d, J = 3.6 Hz, 1H), 7.31 (dt, J = 0.9, 8.4 Hz, 1H), 7.42 –7.58 (m, 5H), 8.48 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.7 (t), 60.6 (t), 78.8 (s), 92.8 (s), 108.5 (d), 116.5 (d), 121.5 (d), 121.9 (s), 124.7 (d), 127.8 (d), 127.9 (d), 128.0 (d), 129.2 (s), 130.7 (d), 131.0 (s), 132.5 (d), 135.7 (s), 137.0 (s) 168.0 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{14}ClNO_2Na$: 346.0605 $[M + Na]^+$; found 346.0600.

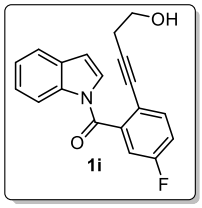


(2-(4-Hydroxybut-1-yn-1-yl)-4-methylphenyl)(1*H*-indol-1-yl)methanone (**1h):** yellow liquid; yield: 375 mg (89%); R_f = 0.4 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.34–2.38 (m, 2H), 2.39 (s, 3H), 3.35 (t, J = 5.7 Hz, 2H), 6.56 (d, J = 3.8 Hz, 1H), 7.09 (d, J = 3.8 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.28–7.32 (m, 1H), 7.32–7.38 (m, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3 (q), 23.8 (t), 60.8 (t),

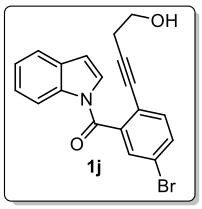


79.3 (s), 92.2 (s), 108.7 (d), 116.3 (d), 120.8 (d), 122.1 (s), 124.1 (d), 125.1 (d), 127.5 (d), 128.0 (d), 128.8 (d), 130.8 (s), 132.9 (d), 134.7 (s), 135.5 (s), 141.0 (s), 168.3 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{17}NO_2Na$: 326.1152 $[M + Na]^+$; found 326.1147.

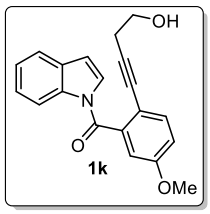
(5-Fluoro-2-(4-hydroxybut-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (**1i):** yellow liquid; yield: 328 mg (68%); R_f = 0.3 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.66 (s, 1H), 2.38 (t, J = 5.9 Hz, 2H), 3.34 (q, J = 6.0 Hz, 2H), 6.64 (d, J = 3.8 Hz, 1H), 7.06 (d, J = 3.6 Hz, 1H), 7.22 (dt, J = 2.6, 8.3 Hz, 1H), 7.25–7.28 (m, 1H), 7.32–7.45 (m, 2H), 7.54 (dd, J = 5.2, 8.6 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 5.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.6 (t), 60.6 (t), 77.9 (s), 92.4 (s), 109.5 (d), 115.1 (d, $^2J_{C\text{-}F}$ = 23.8 Hz), 116.2 (d), 117.9 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 118.1 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 120.9 (d), 124.4 (d), 125.3 (d), 126.9 (d), 130.8 (s), 134.4 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 135.3 (s), 139.4 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 160.5 (s), 161.5 (d, $^1J_{C\text{-}F}$ = 252.7 Hz); **^{19}F NMR** (376 MHz) δ -109.6 ppm; **HRMS** (ESI) calcd for $C_{19}H_{14}FNO_2Na$: 330.0901 $[M + Na]^+$; found 330.0894.



(5-Bromo-2-(4-hydroxybut-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (**1j):** yellow liquid; yield: 225 mg (52%); R_f = 0.3 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.72 (s, 1H), 2.37 (t, J = 6.1 Hz, 2H), 3.33 (q, J = 6.1 Hz, 2H), 6.64 (d, J = 3.8 Hz, 1H), 7.05 (d, J = 3.1 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.38–7.44 (m, 2H), 7.58–7.65 (m, 2H), 7.68 (s, 1H), 8.40 (br.s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.7 (t), 60.5 (t), 78.0 (s), 94.0 (s), 109.5 (d), 116.2 (d), 120.8 (s), 120.9 (d), 122.0 (s), 124.4 (d), 125.3 (d), 126.9 (d), 130.6 (d), 130.7 (s), 133.6 (d), 133.7 (d), 135.3 (s), 139.1 (s), 166.3 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{14}BrNO_2Na$: 390.0100 $[M + Na]^+$; found 390.0099.

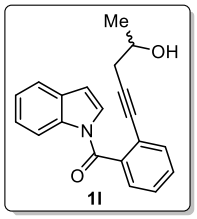


(2-(4-Hydroxybut-1-yn-1-yl)-5-methoxyphenyl)(1*H*-indol-1-yl)methanone (**1k):** yellow liquid; yield: 310 mg (64%); R_f = 0.3 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.36 (t, J = 6.0 Hz, 2H), 3.31 (t, J = 6.0 Hz, 2H), 3.85 (s, 3H), 6.62 (d, J = 3.8 Hz, 1H), 7.01–7.05 (m, 2H), 7.12 (d, J = 3.7 Hz, 1H), 7.31–7.35 (m, 1H), 7.40 (dd, J = 1.3, 8.3 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 8.40 (br.s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.7 (t), 55.6 (q), 60.8 (t), 78.7 (s), 90.6 (s), 109.0 (d), 112.9 (d), 114.0 (s), 116.2 (d), 116.7 (d), 120.9 (d), 124.2

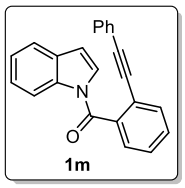


(d), 125.2 (d), 127.3 (d), 130.8 (s), 133.7 (d), 135.4 (s), 138.9 (s), 159.1 (s), 167.8 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{17}NO_3Na$: 342.1101 $[M + Na]^+$; found 342.1095.

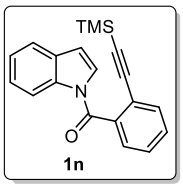
(2-(4-Hydroxypent-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (1l): The starting pent-4-yn-2-ol was prepared by following Barbier reaction condition. yellow liquid; yield: 170 mg (39%); R_f = 0.4 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86 (d, J = 6.3 Hz, 3H), 1.95 (br.s, 1H), 2.14–2.30 (m, 2H), 3.51 (q, J = 5.7 Hz, 1H), 6.50 (dd, J = 0.5, 3.8 Hz, 1H), 6.97 (d, J = 3.8 Hz, 1H), 7.22 (dt, J = 1.2, 7.5 Hz, 1H), 7.25–7.32 (m, 1H), 7.34 (dd, J = 7.4, 1.4 Hz, 1H), 7.36–7.43 (m, 2H), 7.43–7.51 (m, 2H), 8.30 (d, J = 7.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.9 (q), 29.8 (t), 66.1 (d), 79.5 (s), 92.3 (s), 109.0 (d), 116.3 (d), 120.8 (d), 122.0 (s), 124.2 (d), 125.1 (d), 127.2 (d), 127.6 (d), 127.9 (d), 130.4 (d), 130.8 (s), 132.4 (d), 135.5 (s), 137.5 (s), 168.0 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{18}NO_2$: 388.1907 $[M + H]^+$; found 388.1905.



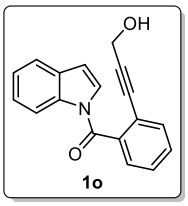
(1*H*-Indol-1-yl)(2-(phenylethynyl)phenyl)methanone (1m): yellow solid; yield: 412 mg (89%); R_f = 0.5 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.62 (d, J = 3.8 Hz, 1H), 6.97 (d, J = 6.9 Hz, 2H), 7.09–7.25 (m, 4H), 7.36 (t, J = 7.6 Hz, 1H), 7.43 (dd, J = 7.6, 15.2 Hz, 1H), 7.49–7.58 (m, 2H), 7.60–7.72 (m, 3H), 8.54 (d, J = 6.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 85.8 (s), 94.6 (s), 109.0 (d), 116.3 (d), 120.7 (d), 121.6 (s), 122.0 (s), 124.0 (d), 125.0 (d), 127.4 (s), 127.9 (d), 128.0 (d, 2C), 128.4 (d), 128.4 (d), 130.5 (d), 130.9 (s), 131.4 (d, 2C), 132.1 (d), 135.4 (s), 137.6 (s), 167.8 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{16}NO$: 322.1232 $[M + H]^+$; found 322.1231.



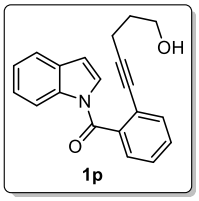
(1*H*-Indol-1-yl)(2-((trimethylsilyl)ethynyl)phenyl)methanone (1n): pale brown solid; yield: 378 mg (83%); R_f = 0.5 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ –0.18 (s, 9H), 6.57 (d, J = 3.8 Hz, 1H), 7.02 (d, J = 3.8 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H), 7.45–7.50 (m, 2H), 7.53–7.60 (m, 3H), 8.45 (br.s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ –0.9 (q, 3C), 100.4 (s), 100.7 (s), 108.8 (s), 116.2 (d), 120.6 (d), 121.4 (s), 123.9 (d), 124.8 (d), 127.3 (d), 127.7 (d), 128.7 (d), 130.3 (d), 130.9 (s), 132.1 (d), 135.4 (s), 138.4 (s), 167.8 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{20}NOSi$: 318.1314 $[M + H]^+$; found 318.1314.



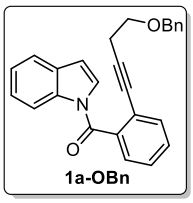
(2-(3-Hydroxyprop-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (**1o**)**:** yellow liquid; yield: 280 mg (70%); R_f = 0.3 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.31 (br.s, 1H), 4.16 (d, *J* = 4.9 Hz, 2H), 6.61 (d, *J* = 3.7 Hz, 1H), 7.08 (d, *J* = 3.7 Hz, 1H), 7.30–7.43 (m, 2H), 7.46–7.65 (m, 5H), 8.38 (d, *J* = 6.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 51.2 (t), 82.1 (s), 92.4 (s), 109.0 (d), 116.3 (d), 120.9 (d), 121.1 (s), 124.2 (d), 125.1 (d), 127.3 (d), 127.9 (d), 128.7 (d), 130.6 (d), 130.8 (s), 132.6 (d), 135.5 (s), 137.7 (s), 167.7 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{14}NO_2$: 276.1024 $[M + H]^+$; found 276.1030.



(2-(5-Hydroxypent-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (**1p**)**:** yellow liquid; yield: 345 mg (79%); R_f = 0.4 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 6.5 Hz, 2H), 2.23 (d, *J* = 13.7 Hz, 2H), 3.28 (t, *J* = 6.1 Hz, 2H), 6.59 (d, *J* = 3.8 Hz, 1H), 7.05 (d, *J* = 3.1 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.37–7.56 (m, 5H), 7.60 (d, *J* = 7.6 Hz, 1H), 8.43 (d, *J* = 5.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.6 (t), 30.5 (t), 60.9 (t), 77.6 (s), 95.2 (s), 108.8 (d), 116.3 (d), 120.8 (d), 122.1 (s), 124.1 (d), 125.0 (d), 127.5 (d, 2C), 127.9 (d), 130.4 (d), 130.9 (s), 132.2 (d), 135.4 (s), 137.8 (s), 168.2 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{18}NO_2$: 304.1337 $[M + H]^+$; found 304.1341.

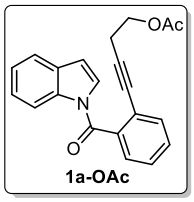


(2-(4-(Benzyloxy)but-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (**1a-OBn**)**:** yellow liquid; yield: 402 mg (73%); R_f = 0.5 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.40 (t, *J* = 7.2 Hz, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 4.22 (s, 2H), 6.54 (d, *J* = 3.8 Hz, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 7.18–7.23 (m, 2H), 7.24–7.34 (m, 4H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.40–7.46 (m, 1H), 7.48 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.50–7.55 (m, 2H), 7.56 (d, *J* = 7.6 Hz, 1H), 8.42 (d, *J* = 6.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.6 (t), 67.9 (t), 72.7 (t), 78.1 (s), 92.5 (s), 108.8 (d), 116.4 (d), 120.7 (d), 121.9 (s), 124.0 (d), 124.9 (d), 127.4 (d), 127.5 (d), 127.6 (d, 2C), 127.7 (d), 128.0 (d), 128.3 (d, 2C), 130.3 (d), 130.9 (s), 132.3 (d), 135.5 (s), 137.9 (s), 138.0 (s), 168.0 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{22}NO_2$: 380.1650 $[M + H]^+$; found 380.1649.

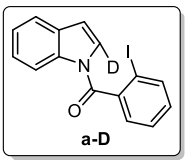


4-(2-(1*H*-Indole-1-carbonyl)phenyl)but-3-yn-1-yl acetate (**1a-OAc**)**:** A solution of **1a** (150 mg, 0.52 mmol) and acetic anhydride (53 mg, 0.52 mmol), DMAP (63 mg, 0.52 mmol) in

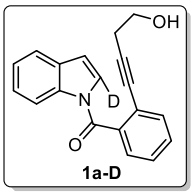
dichloromethane (5 mL) was stirred at rt for 4 h. After completion, the reaction mixture was concentrated and purified by column chromatogrphy (30% ethyl acetate in petroleum ether) to afford the acetate **1a-Ac** as pale brown liquid; yield: 146 mg (85%); R_f = 0.4 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.43 (t, *J* = 6.9 Hz, 2H), 3.78 (t, *J* = 6.9 Hz, 2H), 6.56 (d, *J* = 3.8 Hz, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 7.30 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.35 (dt, *J* = 1.5, 8.3 Hz, 1H), 7.39–7.47 (m, 2H), 7.47–7.50 (m, 1H), 7.50–7.53 (m, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 8.26–8.42 (d, *J* = 6.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.6 (t), 20.5 (q), 61.6 (t), 78.4 (s), 91.1 (s), 108.8 (d), 116.2 (d), 120.7 (d), 121.5 (s), 123.9 (d), 124.9 (d), 127.2 (d), 127.6 (d), 128.1 (d), 130.3 (d), 130.8 (s), 132.4 (d), 135.4 (s), 137.7 (s,), 167.7 (s), 170.4 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{18}NO_3$: 332.1286 $[M + H]^+$; found 332.1279.



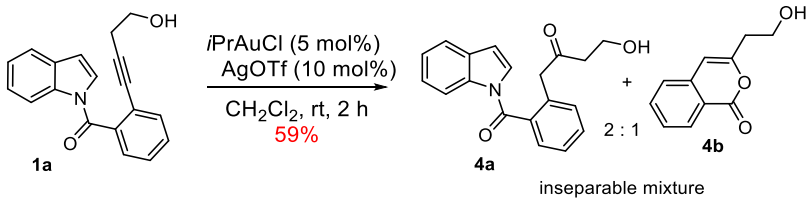
(1*H*-Indol-1-yl-2-d)(2-iodophenyl)methanone (**a-D**)**:** C2-D Indole has been prepared following the known procedures and subjected for the N-bezoylation according to the general procedure. yellow liquid; yield: 1.34 g (45%); R_f = 0.6 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.53 (s, 1H), 7.23 (dt, *J* = 1.5, 7.6 Hz, 1H), 7.33 (t, *J* = 6.8 Hz, 1H), 7.37–7.46 (m, 2H), 7.5 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 8.30 (br.s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 92.5 (s), 109.6 (d), 116.5 (s), 121.0 (d), 124.3 (d), 125.2 (d), 128.3 (d, 2C), 128.3 (d), 131.1 (s), 131.6 (d), 135.4 (s), 139.5 (d), 141.0 (s), 168.0 (s)ppm; **HRMS** (ESI) calcd for $C_{15}H_{10}DNOI$: 348.9943 $[M + H]^+$; found 348.9940.



(2-(4-Hydroxybut-1-yn-1-yl)phenyl)(1*H*-indol-1-yl-2-d)methanone (1a-D): yellow liquid; yield: 342 mg (82%); R_f = 0.3 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.64 (s, 1H), 2.41 (t, *J* = 6.1 Hz, 2H), 3.37 (q, *J* = 6.1 Hz, 2H), 6.61 (s, 1H), 7.33 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.38–7.43 (m, 1H), 7.46 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.50 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.52–7.57 (m, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 8.40 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.8 (t), 60.8 (t), 79.1 (s), 92.7 (s), 108.8 (d), 116.3 (d), 120.9 (d), 122.1 (d), 124.3 (d), 125.2 (d), 127.8 (d), 128.0 (d), 130.6 (d), 130.8 (s), 132.4 (d), 135.4 (s), 137.6 (s), 168.1 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{15}DNO_2$: 291.1238 $[M + H]^+$; found 291.1231.



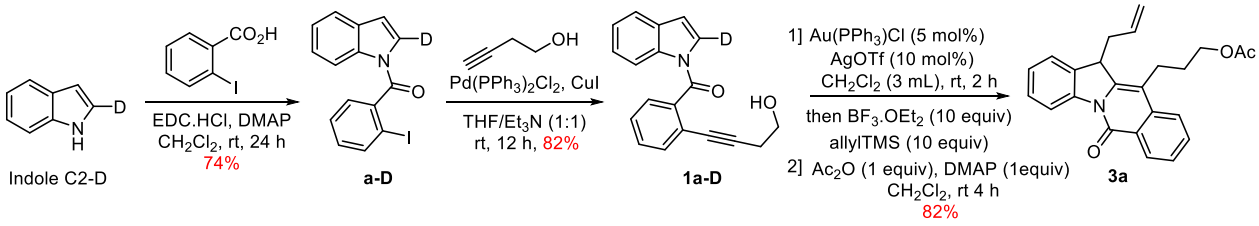
Scheme S1. The *i*PrAuCl/$AgSbF_6$ Catalysed Cyclisation of Alkynol 1a



4a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (t, J = 5.3 Hz, 2H), 3.78 (t, J = 5.3 Hz, 2H), 3.97 (s, 2H), 6.61 (d, J = 3.7 Hz, 1H), 7.19 (d, J = 3.7 Hz, 1H), 7.32 (br. dt, J = 1.4, 7.6 Hz, 1H), 7.36 (br. dt, J = 0.5, 8.1 Hz, 1H), 7.37–7.39 (dd, J = 1.3, 7.2 Hz, 1H), 7.42 (dd, J = 1.1, 7.5 Hz, 1H), 7.47 (br. dd, J = 1.5, 7.5 Hz, 1H), 7.54 (dt, J = 1.5, 7.5 Hz, 1H), 7.60–7.62 (m, 1H), 8.34 (d, J = 8.0 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 44.5 (t), 47.6 (t), 58.0 (t), 108.9 (d), 116.4 (d), 121.0 (d), 124.1 (d), 125.0 (d), 127.0 (d), 127.5 (d), 128.8 (d), 130.9 (s), 131.1 (d), 131.9 (d), 133.4 (s), 135.8 (s), 168.8 (s), 207.8 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{18}NO_3$: 308.1281 $[M + H]^+$; found 308.1278.

4b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80 (t, J = 6.1 Hz, 2H), 4.0 (t, J = 6.1 Hz, 2H), 6.39 (s, 1H), 7.37–7.39 (m, 1 H), 7.48 (br. dt, J = 1.1, 7.6 Hz, 1H), 7.69 (dt, J = 1.5, 7.8 Hz, 1H), 8.26 (dt, J = 0.5, 7.8 Hz, 1H), ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 36.8 (t), 59.6 (t), 104.8 (d), 120.3 (s), 125.2 (d), 127.9 (d), 129.5 (d), 134.8 (d), 137.2 (s), 154.8 (s), 162.9 (s).

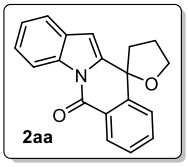
Scheme S2. Deuterium Labelling Studies



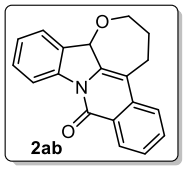
Au(PPh$_3$)Cl/$AgSbF_6$ catalysed cyclisation of alkynol 1a: At room temperature, a solution of alkynol **1a** (150 mg, 0.518 mmol) in anhydrous dichloromethane (3mL) was treated with Au(PPh$_3$)Cl (12.8 mg, 0.025 mmol, 5 mol%) and $AgSbF_6$ (17.8 mg, 0.051 mmol, 10 mol%) and the contents stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting crude was purified by column chromatography (20 – 30%

ethyl acetate in petroleum ether) to afford **2aa** (30 mg, 20% yield) as a colourless liquid and **2ab** (47 mg, 31%) as a colourless solid.

(2-(4-Hydroxybut-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (**2aa**)**:** coloureless liquid, R_f = 0.7 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.1–2.3 (m, 2H), 2.3–2.4 (m, 2H), 4.4 (dt, *J* = 6.1, 8.2, Hz, 1H), 4.5–4.6 (m, 1H), 6.7 (d, *J* = 0.75 Hz, 1H), 7.31 (dt, *J* = 1.1, 7.6 Hz, 1H), 7.38 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.49–7.53 (m, 1H), 7.6 (ddd, *J* = 0.7 , 1.3, 7.7 Hz, 1H), 7.7–7.7 (m, 2H), 8.3 (dt, *J* = 1.0, 7.8, Hz 1H), 8.6–8.7 (dd, *J* = 1.0, 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.5 (t), 45.4 (t), 71.1 (t), 80.2 (s), 105.7 (d), 116.5 (d), 120.5 (d), 124.2 (d), 124.3 (d), 124.7 (d), 126.6 (s), 128.1 (d), 128.7 (d), 129.5 (s), 133.8 (d), 135.9 (s), 142.9 (s), 145.2 (s), 160.9 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{15}NNaO_2$: 312.0995 $[M + Na]^+$; found 312.0998.



(2-(4-Hydroxybut-1-yn-1-yl)phenyl)(1*H*-indol-1-yl)methanone (**2ab**)**:** mp: 177 °C; R_f = 0.5 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.9–2.1 (m, 2H), 2.8–3.0 (m, 1H), 3.4 (dd, *J* = 5.1, 15.8 Hz, 1H), 4.2 (dt, *J* = 2.0, 12.2 Hz, 1H), 4.5 (dt, *J* = 3.4, 11.8 Hz, 1H), 5.8 (s, 1H), 7.3 (t, *J* = 7.4 Hz, 1H), 7.5 (t, *J* = 7.8 Hz, 1H), 7.5–7.6 (m, 2H), 7.71 (dt, *J* = 1.1, 8.3 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 8.59 (dd, *J* = 0.75, 8.0 Hz, 1H), 8.7 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 25.6 (t), 29.8 (t), 75.4 (t), 79.7 (d), 116.4 (s), 117.6 (d), 122.7 (d), 125.4 (d), 125.8 (d), 126.7 (d), 127.0 (s), 128.5 (d), 129.4 (s), 130.4 (d), 132.4 (d), 135.7 (s), 141.6 (s), 141.6 (s), 159.9 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{16}NO_2$: 290.1176 $[M + H]^+$; found 290.1174.



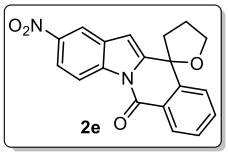
$BF_3.OEt_2$ Mediated Allylation of 2aa and 2ab

At rt, a solution **2aa** and/or **2ab** (25 mg, 0.086 mmol, 1equiv) in dichloromethane (2 ml) was treated with $BF_3.OEt_2$ (10 to 15 equiv) and trimethylallylsilane (15 equiv) and stirred for 30 min. After complete conversion (checked by TLC), the reaction mixture was cooled and quenched with aq. $NaHCO_3$, extracted with dichloromethane (2 x 15 mL). The combined organic layer was washed with brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude was dissolved dichloromethane 5 ml, and treated with acetic anhydride (1.5 equiv) and *N*,*N*-dimethylpyridin-4-amine (DMAP, 1 equiv). The contents were stirred at room temperature under argon atmosphere. After the complete conversion as indicated by TLC, the reaction mixture was

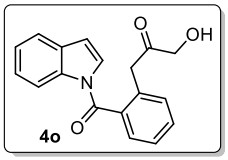
concentrated under reduced vacuum and purified with by column chromatography to afford the product **3a** (21 to 25 mg, 62–77% yield) as yellow solid.

Au(PPh$_3$)Cl/AgOTf catalysed cyclisation of alkynol 1e: At room temperature, a solution of alkynol **1e** (150 mg, 0.448 mmol) in anhydrous dichloromethane (3mL) was treated with Au(PPh$_3$)Cl (11.1 mg, 0.0224 mmol, 5 mol%) and AgOTf (11.5 mg, 0.0448 mmol, 10 mol%) and the contents stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting crude was purified by column chromatography (20 – 30% ethyl acetate in petroleum ether) to afford **2e** (140 mg, 93% yield) as a yellow liquid.

2'-Nitro-4,5-dihydro-3*H*,6'*H*-spiro[furan-2,11'-indolo[1,2-*b*]isoquinolin]-6'-one (2e): R_f = 0.6 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.12–2.30 (m, 2H), 2.30–2.42 (m, 2H), 4.40 (dd, J = 6.1, 8.4 Hz, 1H), 4.53 (ddd, J = 3.8, 7.6, 8.4 Hz, 1H), 6.61 (s, 1H), 7.46 (dd, J = 2.0, 8.4 Hz, 1H), 7.51 (ddd, J = 2.3 5.9, 7.8 Hz, 1H), 7.65–7.71 (m, 3H), 8.30 (d, J = 7.6 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.5 (t), 45.6 (t), 71.2 (t), 80.0 (s), 104.7 (d), 117.4 (s), 117.8 (d), 123.2 (d), 124.4 (d), 126.1 (s), 127.5 (d), 128.2 (d), 128.8 (d), 131.2 (s), 134.1 (d), 134.5 (s), 144.3 (s), 145.2 (s), 160.7 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{14}N_2NaO_4$: 357.0846 $[M + Na]^+$; found 357.843.



1-(2-(1*H*-indole-1-carbonyl)phenyl)-3-hydroxypropan-2-one (4o): The Au(PPh$_3$)Cl/AgOTf catalysed cycloisomerization of alkynol **4o** (150 mg) following the above procedure on pale yellow liquid gave the ketone yield: 132 mg (82%); R_f = 0.3 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.92 (t, J = 4.9 Hz, 1H), 3.93 (s, 2H), 4.31 (d, J = 4.6 Hz, 2H), 6.62 (dd, J = 0.7, 3.8 Hz, 1H), 7.18 (d, J = 3.8 Hz, 1H), 7.29–7.42 (m, 3H), 7.45 (dd, J = 7.4, 1.2 Hz, 1H), 7.50 (dd, J = 1.5, 7.6 Hz, 1H), 7.56 (dt, J = 1.5, 7.3 Hz, 1H) 7.59–7.64 (m, 1H), 8.34 (d, J = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 42.8 (t), 68.0 (t), 109.0 (d), 116.4 (d), 121.0 (d), 124.2 (d), 125.0 (d), 127.3 (d), 127.4 (d), 129.0 (d), 130.9 (s), 131.3 (d), 131.9 (9), 132.6 (s), 134.4 (s), 135.8 (s), 168.5 (s), 206.4 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{15}NNaO_3$: 316.0944 $[M + Na]^+$; found 316.0944.

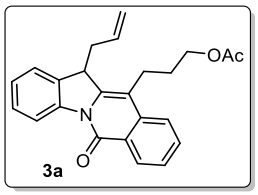


General Procedure for Cycloisomerization and Allylation Followed by Acetylation

In general, all reactions were carried out employing 150 mg of respective alkynol substrate **1** and the product yield's provided are with respect to this substrate.

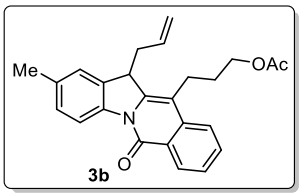
Step 1. At room temperature, a solution of alkynol (150 mg) in anhydrous dichloromethane (3mL) was treated with 5 mol% $Au(PPh_3)Cl$ and 10 mol% AgOTf and the contents stirred at room temperature for 2 h. After complete conversion of starting alkynol as indicated by TLC, 10 equiv of boron trifluoride etherate and 10 equiv of allyl trimethylsilane were added sequentially and the stirring was continued for additional 30 minutes. The reaction mixture was cooled and quenched with sat. $NaHCO_3$ solution (15 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layer was washed with brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure.

Step 2. The resulting crude was dissolved in dichloromethane (5 mL) and treated with acetic anhydride (1 equiv) and *N*,*N*-dimethylpyridin-4-amine (DMAP) (1 equiv) in dichloromethane (10 mL) and the contents were stirred at room temperature under argon atmosphere. After the complete conversion as indicated by TLC, the reaction mixture was concentrated under reduced vacuum and purified with by column chromatography to afford the product **3**.

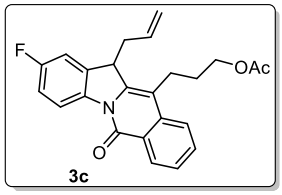


3-(12-Allyl-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3a): Yellow gum; yield: 154 mg (79%); MP: 118 °C; R_f = 0.6 (20% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.97–2.11 (m, 2H), 2.14 (s, 3H), 2.72 (dt, *J* = 7.6, 14.5 Hz, 1H), 2.83–2.90 (m, 1H), 2.93–3.03 (m, 2H), 4.18–4.24 (m, 1H), 4.26–4.32 (m, 1H), 4.47 (dd, *J* = 3.8, 6.8 Hz, 1H), 4.90–4.97 (m, 2H), 5.42–5.52 (m, 1H), 7.23–7.28 (m, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.52 (dt, *J* = 1.5, 7.6 Hz, 1H), 7.67–7.75 (m, 2H), 8.59 (d, *J* = 7.6 Hz, 1H), 8.76 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.9 (q), 24.0 (t), 28.8 (t), 38.9 (t), 44.2 (d), 64.0 (t), 111.9 (s), 117.6 (d), 118.8 (t), 122.5 (d), 123.8 (d), 125.4 (d), 126.3 (d), 126.6 (s), 128.4 (d, 2C), 132.3 (d), 132.5 (d), 132.7 (s), 135.8 (s), 141.8 (s) 142.2 (s), 160.7 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{24}NO_3$: 374.1756 $[M + H]^+$; found: 374.1761.

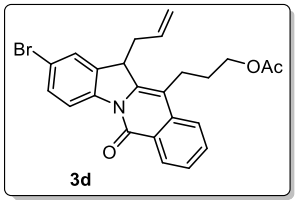
3-(12-Allyl-2-methyl-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3b): Yellow gum; yield: 128 mg (66%); R_f = 0.8 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.96–2.12 (m, 2H), 2.14 (s, 3H), 2.42 (s, 3H), 2.73 (dt, *J* = 7.2, 14.3 Hz, 1H), 2.80–2.89 (m, 1H), 2.97 (td, *J* = 5.9, 9.9 Hz, 2H), 4.21 (ddd, *J* = 5.5, 7.3, 11.0 Hz, 1H), 4.28 (dd, *J* = 5.6, 11.5 Hz, 1H), 4.43 (dd, *J* = 3.5, 6.5 Hz, 1H), 4.88–5.01 (m, 2H), 5.39–5.54 (m, 1H), 7.19–7.25 (m, 2H), 7.53 (ddd, *J* = 1.7, 6.4, 8.0 Hz, 1H), 7.67–7.76 (m, 2H), 8.61 (t, *J* = 9.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (q), 21.3 (q), 24.0 (t), 28.8 (t), 38.8 (t), 44.1 (d), 64.0 (t), 111.8 (s), 117.2 (d), 118.6 (t), 122.4 (d), 124.3 (d), 126.2 (d), 126.5 (s), 128.3 (d), 128.9 (d), 132.2 (d), 132.6 (d), 132.8 (s), 135.2 (s), 135.8 (s), 140.0 (s), 142.0 (s), 160.4 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{26}NO_3$: 388.1912 $[M + H]^+$; found: 388.1913.



3-(12-Allyl-2-fluoro-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3c): Yellow solid; yield: 142 mg (74%); MP: 150 °C; R_f = 0.8 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.90–2.10 (m, 2H), 2.12–2.16 (m, 3H), 2.65–2.75 (m, 1H), 2.79–2.88 (m, 1H), 2.88–3.03 (m, 2H), 4.16–4.25 (m, 1H), 4.25–4.34 (m, 1H), 4.43 (dd, *J* = 3.8, 6.9 Hz, 1H), 4.94 (s, 1H), 4.97 (d, *J* = 3.8 Hz, 1H), 5.39–5.53 (m, 1H), 7.02–7.15 (m, 2H), 7.52 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1H), 7.63–7.76 (m, 2H), 8.51–8.61 (m, 1H), 8.67–8.75 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (q), 24.0 (t), 28.8 (t), 38.7 (t), 44.1 (d), 63.9 (t), 111.2 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 112.2 (s, 2C), 114.8 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 118.7 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 119.2 (t), 122.5 (d), 126.4 (d), 128.3 (d), 132.0 (d), 132.4 (d), 134.8 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 135.7 (s), 138.2 (s), 141.5 (s), 160.3 (s), 160.3 (d, $^1J_{C\text{-}F}$ = 244.4 Hz), 171.0 (s) ppm; **^{19}F NMR** (376 MHz) δ -116.2 ppm; **HRMS** (ESI) calcd for $C_{24}H_{23}FNO_3$: 392.1662 $[M + H]^+$; found: 392.1669.

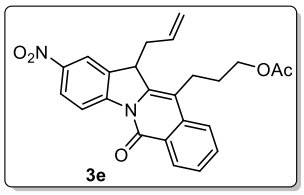


3-(12-Allyl-2-bromo-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3d): Yellow solid; yield: 172 mg (93%); MP: 159 °C; R_f = 0.8 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.90–2.02 (m, 1H), 2.03–2.12 (m, 1H), 2.13 (s, 3H), 2.63–2.77 (m, 1H), 2.77–2.87 (m, 1H), 2.87–3.00 (m, 2H), 4.12–4.23 (m, 1H), 4.23–4.32 (m, 1H), 4.40 (dd, *J* = 3.4, 6.4 Hz, 1H), 4.93 (s, 1H), 4.96 (d, *J* = 5.5 Hz, 1H), 5.43 (dd, *J* = 10.1, 16.8 Hz, 1H), 7.46–7.54 (m, 3H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.71 (t, *J* = 7.3 Hz, 1H), 8.53 (d, *J* = 7.9 Hz, 1H), 8.59 (d,

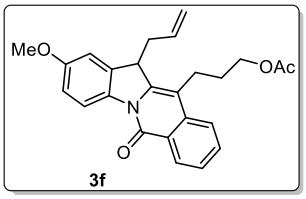


J = 9.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.9 (q), 24.0 (t), 28.7 (t), 38.7 (t), 43.9 (d), 63.9 (t), 112.2 (s), 118.3 (s), 118.8 (d), 119.3 (t), 122.5 (d), 126.3 (s), 126.4 (d), 126.9 (d), 128.3 (d), 131.2 (d), 131.9 (d), 132.5 (d), 134.9 (s), 135.7 (s), 141.0 (s), 141.1 (s), 160.4 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{23}BrNO_3$: 452.0861 $[M + H]^+$; found: 452.0862.

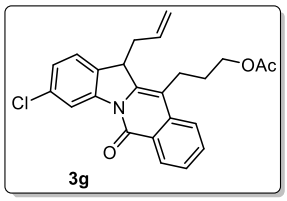
2'-Nitro-4,5-dihydro-3*H*,6'*H*-spiro[furan-2,11'-indolo[1,2-*b*]isoquinolin]-6'-one (3e): Yellow solid; yield: 158 mg (84%); MP: 145 °C; R_f = 0.8 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.97–2.14 (m, 2H), 2.15 (s, 3H), 2.72–2.84 (m, 1H), 2.86–2.93 (m, 1H), 2.93–3.08 (m, 2H), 4.12–4.27 (m, 1H), 4.27– 4.35 (m, 1H), 4.56 (dd, *J* = 3.5,7.0 Hz, 1H), 4.93–5.04 (m, 2H), 5.41–5.55 (m, 1H), 7.59 (ddd, *J* = 1.2, 7.0, 8.0 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.79 (ddd, *J* = 1.4, 7.0, 8.2 Hz, 1H), 8.25–8.31 (m, 1H), 8.33–8.38 (m, 1H), 8.59 (dd, *J* = 1.0, 8.0 Hz, 1H), 8.89 (d, *J* = 8.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.5 (t), 45.6 (t), 71.2 (t), 79.9 (s), 104.7 (d), 117.5 (s), 117.8 (d), 123.2 (d), 124.4 (d), 126.1 (s), 127.5 (d), 128.2 (d), 128.8 (d), 131.2 (s), 134.1 (d), 134.5 (s), 144.3 (s), 145.2 (s), 160.7 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{23}N_2NaO_5$: 419.1606 $[M + H]^+$; found: 419.1607.



3-(12-Allyl-2-methoxy-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3f): Pale brown solid; yield: 42 mg (22%); MP: 134 °C; R_f = 0.8 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.94–2.12 (m, 2H), 2.14 (s, 3H), 2.73 (dd, *J* = 7.2, 14.5 Hz, 1H), 2.81–2.89 (m, 1H), 2.91–3.06 (m, 2H), 3.87 (s, 3H), 4.15–4.25 (m, 1H), 4.29 (dd, *J* = 5.8, 11.1 Hz, 1H), 4.44 (dd, *J* = 3.5, 6.9 Hz, 1H), 4.90–5.01 (m, 2H), 5.41–5.55 (m, 1H), 6.95 (dt, *J* = 2.5, 14.1 Hz, 2H), 7.53 (ddd, *J* = 1.8, 6.3, 8.1 Hz, 1H), 7.68–7.75 (m, 2H), 8.56–8.62 (dd, *J* = 0.8, 8.7 Hz, 1H), 8.68 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (q), 24.0 (t), 28.8 (t), 38.8 (t), 44.2 (d), 55.6 (q), 64.0 (t), 110.3 (d), 111.9 (s), 112.6 (d), 118.3 (d), 118.8 (t), 122.4 (d), 126.2 (d), 126.5 (s), 128.2 (d), 132.1 (d), 132.5 (d), 134.4 (s), 135.7 (s), 135.9 (s), 141.9 (s), 157.6 (s), 160.1 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{26}NO_4$: 404.1856 $[M + H]^+$; found: 404.1854.

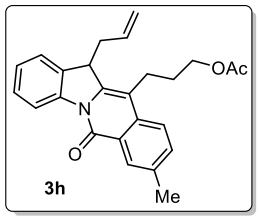


3-(12-Allyl-3-chloro-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3g): Brown gum; yield: 159 mg (84%); R_f = 0.8 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.93–2.13 (m, 2H), 2.14 (s, 3H), 2.60 (quin, *J* = 7.2 Hz, 1H), 2.79–2.89 (m, 1H), 2.89–

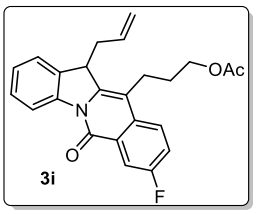


3.02 (m, 2H), 4.17–4.25 (m, 1H), 4.25–4.34 (m, 1H), 4.44 (dd, *J* = 3.4, 6.9 Hz, 1H), 4.91–5.00 (m, 2H), 5.41–5.54 (m, 1H), 7.23 (dd, *J* = 1.9, 8.1 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H) 7.55 (dt, *J* = 1.0, 7.8 Hz, 1H), 7.66–7.78 (m, 2H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.81 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 21.0 (q), 24.0 (t), 28.8 (t), 38.8 (t), 43.8 (d), 64.0 (t), 112.3 (s), 117.9 (d), 119.2 (t), 122.5 (d), 124.5 (d), 125.3 (d), 126.3 (s), 126.5 (d), 128.4 (d), 131.1 (s), 132.1 (d), 132.6 (d), 133.9 (s), 135.7 (s), 141.5 (s), 142.9 (s), 160.5 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{23}ClNO_3$: 408.1361 $[M + H]^+$; found: 408.1362.

3-(12-Allyl-8-methyl-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3h): Yellow solid; yield: 127 mg (66%); MP: 104 °C; R_f = 0.8 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.94–2.11 (m, 2H), 2.13 (s, 3H), 2.52 (s, 3H), 2.65–2.76 (m, 1H), 2.77–2.87 (m, 1H), 2.87–3.00 (m, 2H), 4.14–4.23 (m, 1H), 4.23–4.32 (m, 1H), 4.42 (dd, *J* = 3.1, 6.9 Hz, 1H), 4.85–4.97 (m, 2H), 5.44 (ddt, *J* = 7.0, 10.2, 17.1 Hz, 1H), 7.20–7.25 (m, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.35–7.40 (m, 2H), 7.43 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.72 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 21.0 (q), 22.2 (q), 23.9 (t), 28.7 (t), 38.9 (t), 44.2 (d), 64.0 (t), 111.7 (s), 117.5 (t), 118.7 (t), 122.4 (t), 123.8 (t), 124.3 (s), 125.2 (t), 127.8 (t), 128.3 (t, 2C), 132.5 (t), 132.7 (s), 135.9 (s), 141.8 (s), 142.3 (s), 142.9 (s), 160.7 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{26}NO_3$: 388.1907 $[M + H]^+$; found: 388.1911.

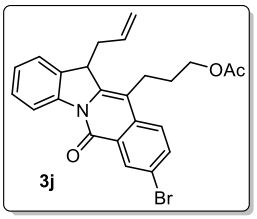


3-(12-Allyl-8-fluoro-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3i): Yellow gum; yield: 140 mg (73%); MP: 145 °C; R_f = 0.6 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.97– 2.12 (m, 2H), 2.14 (s, 3H), 2.72 (dt, *J* = 14.4, 7.3 Hz, 1H), 2.81– 2.91 (m, 1H), 2.91–3.04 (m, 2H), 4.17– 4.26 (m, 1H), 4.29 (dt, *J* = 5.8, 11.1 Hz, 1H), 4.47 (dd, *J* = 6.8, 3.4 Hz, 1H), 4.90– 4.99 (m, 2H), 5.39– 5.54 (m, 1H), 7.25– 7.31 (m, 2H), 7.39– 7.44 (m, 2H), 7.47 (dd, *J* = 2.8, 8.0 Hz, 1H), 7.70 (dd, *J* = 8.9, 4.9 Hz, 1H), 8.24 (dd, *J* = 9.3, 2.8 Hz, 1H), 8.68 - 8.74 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 20.9 (q), 24.2 (t), 28.8 (t), 38.9 (t), 44.1 (d), 63.9 (t), 111.6 (s), 113.5 (d, $^2J_{C\text{-}F}$ = 23.1 Hz), 117.7 (d), 118.9 (t), 120.9 (d, $^2J_{C\text{-}F}$ = 23.1 Hz), 123.9 (d), 124.8 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, 2C), 125.7 (d), 128.4 (d,), 132.4 (d, 2C), 132.8 (s), 141.1

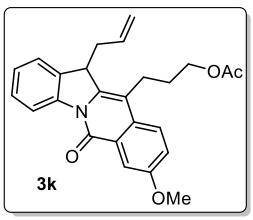


(s), 142.0 (s), 159.7 (s), 161.1 (d, $^{1}J_{C\text{-}F}$ = 248 Hz), 171.0 (s) ppm; **^{19}F NMR** (376 MHz) δ -114.1 ppm; **HRMS** (ESI) calcd for $C_{24}H_{23}NFO_3$: 392.1656 $[M + H]^+$; found: 392.1657.

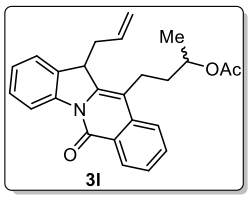
33-(12-Allyl-8-bromo-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3j): Yellow solid; yield: 84 mg (45%); MP: 169 °C; R_f = 0.6 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.93–2.05 (m, 2H), 2.12 (s, 3H), 2.64–2.74 (m, 1H), 2.80–2.87 (m, 1H), 2.88–2.96 (m, 2H), 4.14–4.22 (m, 1H), 4.22–4.30 (m, 1H), 4.42 (dd, *J* = 3.4, 6.5 Hz, 1H), 4.89 (s, 1H), 4.92 (d, *J* = 5.3 Hz, 1H), 5.35–5.49 (m, 1H), 7.21–7.29 (m, 1H), 7.40 (t, *J* = 6.1 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.72–7.79 (m, 1H), 8.66–8.72 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (q), 24.0 (t), 28.7 (t), 38.8 (t), 44.3 (d), 63.9 (t), 111.5 (s), 117.6 (d), 119.0 (t), 120.3 (s), 123.9 (d), 124.3 (d), 125.7 (d), 128.0 (s), 128.4 (d), 131.0 (d), 132.3 (d), 132.6 (s), 134.5 (s), 135.4 (d), 141.9 (s), 142.4 (s), 159.3 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{23}NBrO_3$: 452.0856 $[M + H]^+$; found: 452.0862.



3-(12-Allyl-8-methoxy-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (3k): Yellow gum; yield: 124 mg (65%); R_f = 0.8 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.96–2.12 (m, 2H), 2.12 (s, 3H), 2.67–2.77 (m, 1H), 2.81–2.90 (m, 1H), 2.90–3.04 (m, 2H), 3.97 (s, 3H), 4.16–4.24 (m, 1H), 4.24–4.32 (m, 1H), 4.46 (dd, *J* = 3.4, 6.5 Hz, 1H), 4.86–4.99 (m, 2H), 5.40–5.55 (m, 1H), 7.27 (d, *J* = 15.3 Hz, 1H), 7.34 (dd, *J* = 3.1, 9.2 Hz, 1H), 7.40–7.45 (m, 2H), 7.63 (d, *J* = 9.2 Hz, 1H), 8.02 (d, *J* = 2.3 Hz, 1H), 8.77 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (q), 24.1 (t), 28.9 (t), 39.0 (t), 44.0 (d), 55.7 (q), 64.0 (t), 108.3 (d), 111.9 (s), 117.7 (d), 118.7 (t), 122.7 (d), 123.9 (d), 124.1 (d), 125.4 (d), 127.8 (s), 128.4 (d), 129.8 (s), 132.6 (d), 133.0 (s), 139.4 (s), 142.3 (s), 158.3 (s), 160.3 (s), 171.1 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{26}NO_4$: 404.1856 $[M + H]^+$; found: 404.1857.

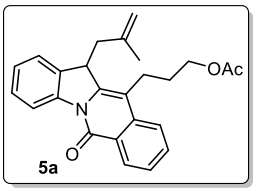


4-(12-Allyl-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)butan-2-yl acetate (3l): Yellow gum; yield: 43 mg (56%); R_f = 0.7 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 1.34 (dd, *J* = 8.0, 6.5 Hz, 3H), 1.81–2.07 (m, 2H), 2.10–2.15 (m, 3H), 2.68–2.97 (m, 4H), 4.44 (dt, *J* = 7.6, 3.8 Hz, 1H), 4.87–4.96 (m, 2H), 5.11 (dt, *J* = 12.6, 6.1 Hz, 1H), 5.38–5.51 (m, 1H), 6.80

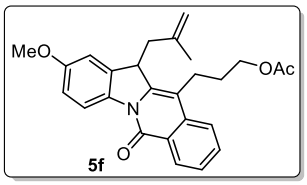


(d, J = 9.1 Hz, 0.6H), 7.11 (d, *J* = 7.6 Hz, 0.6H), 7.22–7.28 (m, 1H), 7.37–7.44 (m, 2H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.65–7.76 (m, 2H), 8.55–8.61 (m, 1H), 8.74 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.0 (q), 20.1 (q), 21.4 (q), 21.4 (q), 23.5 (t), 23.6 (t), 35.9 (t), 36.0 (t), 38.8 (t), 38.9 (t), 44.2 (d), 44.23 (d), 70.9 (d), 71.0 (d), 112.1 (s), 112.2 (s), 113.9 (s), 117.6 (d), 118.7 (t), 118.8 (t), 122.5 (d), 123.8 (d), 125.4 (d), 126.3 (s), 128.4 (d), 132.4 (d), 132.5 (d), 132.6 (d), 132.7 (d), 135.9 (s), 141.5 (s), 141.6 (s), 142.3 (s), 160.7 (s), 170.8 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{26}NO_3$: 388.1907 $[M + H]^+$; found: 388.1905.

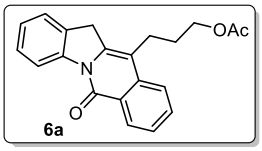
3-(12-(2-Methylallyl)-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (5a): Yellow solid; yield: 137 mg (68%); MP: 170 °C; R_f = 0.6 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.00–2.09 (m, 2H), 2.12 (s, 3H), 2.33 (dd, *J* = 9.9, 13.7 Hz, 1H), 2.78–2.86 (m, 1H), 2.93–3.02 (m, 2H), 4.14–4.22 (m, 1H), 4.24–4.32 (m, 1H), 4.46 (dd, *J* = 3.1, 9.9 Hz, 1H), 4.64 (s, 1H), 4.89 (s, 1H), 7.18–7.24 (m, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.38–7.43 (m, 1H), 7.49–7.54 (m, 1H), 7.66–7.70 (m, 2H), 8.54–8.63 (m, 1H), 8.77 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (q), 22.5 (q), 24.0 (t), 28.8 (t), 42.4 (d), 43.6 (t), 64.0 (t), 111.5 (s), 114.7 (t), 117.6 (d), 122.4 (d), 124.3 (d), 125.0 (d), 126.2 (d), 126.5 (s), 128.3 (d), 128.4 (d), 132.3 (d), 133.0 (s), 135.8 (s), 140.7 (s), 141.8 (s), 142.8 (s), 160.6 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{26}NO_3$: 388.1907 $[M + H]^+$; found: 388.1911.



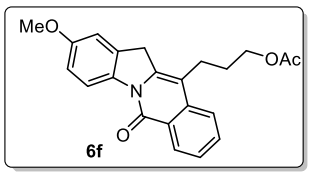
3-(2-Methoxy-12-(2-methylallyl)-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (5f): Yellow solid; yield: 42 mg (21%); MP: 160 °C; R_f = 0.6 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.83 (s, 3H), 2.00–2.11 (m, 2H), 2.12 (s, 3H), 2.35 (dd, *J* = 9.8, 14.3 Hz, 1H), 2.83 (dd, *J* = 2.0, 14.0 Hz, 1H), 2.99 (ddd, *J* = 2.8, 6.7, 9.3 Hz, 2H), 3.84 (s, 3H), 4.13–4.22 (m, 1H), 4.24–4.32 (m, 1H), 4.44 (dd, *J* = 3.1, 9.7 Hz, 1H), 4.69 (s, 1H), 4.92 (s, 1H), 6.90–6.96 (m, 2H), 7.53 (ddd, *J* = 1.7, 6.5, 8.1 Hz, 1H), 7.66–7.75 (m, 2H), 8.60 (dd, *J* = 0.7, 8.1 Hz, 1H), 8.66–8.72 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (q), 22.6 (q), 24.0 (t), 28.9 (t), 42.4 (d), 43.5 (t), 55.6 (q), 64.0 (t), 111.0 (d), 111.5 (s), 112.5 (d), 114.7 (t), 118.3 (d), 122.4 (d), 126.2 (d), 128.3 (d), 132.1 (d), 134.8 (s), 135.5 (s), 135.7 (s), 140.8 (s), 143.0 (s), 157.3 (s), 160.2 (s), 171.0 (s) ppm; *HRMS* (ESI) calcd for $C_{25}H_{28}NO_4$: 404.1856 $[M + H]^+$; found: 404.1854.



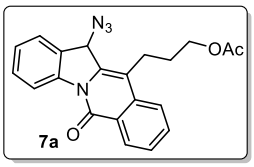
3-(6-Oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (6a): Yellow solid; yield: 130 mg (75%); MP: 137 °C; R_f = 0.6 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.93–2.00 (m, 2H), 2.11 (s, 3H), 2.78–2.85 (m, 2H), 4.12 (s, 2H), 4.18 (t, *J* = 6.5 Hz, 2H), 7.18–7.26 (m, 1H), 7.34–7.42 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.65–7.72 (m, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 8.73 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (q), 24.2 (t), 27.7 (t), 33.2 (t), 63.8 (t), 111.0 (s), 117.8 (d), 122.0 (d), 124.2 (d), 125.4 (d), 125.9 (d), 126.2 (s), 128.0 (d), 128.3 (d), 128.5 (s), 132.3 (d), 135.6 (s), 138.5 (s), 143.0 (s), 160.6 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{20}NO_3$: 334.1443 $[M + H]^+$; found: 334.1453.



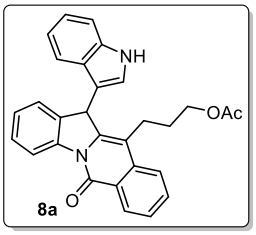
3-(2-Bromo-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (6f): Brown gum; yield: 52 mg (30%); R_f = 0.6 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.91–2.00 (m, 2H), 2.10 (s, 3H), 2.73–2.85 (m, 2H), 3.79 (d, *J* = 3.1 Hz, 3H), 4.04–4.09 (m, 2H), 4.17 (t, *J* = 5.7 Hz, 2H), 6.82–6.92 (m, 2H), 7.42–7.49 (m, 1H), 7.56–7.61 (m, 1H), 7.62–7.68 (m, 1H), 8.50–8.56 (m, 1H), 8.60 (dd, *J* = 3.8, 9.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.9 (q), 24.2 (t), 27.7 (t), 33.3 (t), 55.5 (q), 63.9 (t), 110.4 (d), 111.1 (s), 112.5 (d), 118.4 (d), 122.0 (d), 125.8 (d), 126.1 (s), 128.1 (d), 130.2 (s), 132.0 (d), 135.4 (s), 136.6 (s), 138.6 (s), 157.6 (s), 160.0 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{22}NO_4$: 364.1543 $[M + H]^+$; found: 364.1545.



3-(12-Azido-6-oxo-6,11-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (7a): Brown solid; yield: 88 mg (45%); MP: 136 °C; R_f = 0.6 (40% ethyl acetate/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.04–2.11 (m, 2H), 2.14 (s, 3H), 2.87–2.97 (m, 1H), 3.06–3.15 (m, 1H), 4.19–4.26 (m, 1H), 4.28–4.36 (m, 1H), 5.56 (s, 1H), 7.33–7.39 (m, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.57–7.60 (m, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.72–7.79 (m, 2H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.74 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.0 (q), 24.1 (t), 28.9 (t), 61.2 (d), 64.0 (t), 116.6 (s), 118.0 (d), 123.2 (d), 125.0 (d), 126.1 (d), 126.7 (s), 127.6 (s), 127.7 (d), 128.7 (d), 131.2 (d), 132.9 (d), 135.3 (s), 136.1 (s), 142.0 (s), 160.0 (s), 171.1 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{19}N_4O_3$: 375.1457 $[M + H]^+$; found: 375.1455.



3-(12-(1*H*-Indol-3-yl)-6-oxo-6,12-dihydroindolo[1,2-*b*]isoquinolin-11-yl)propyl acetate (8a): (Indole nucleophile was used 2 equiv) Brown solid; yield: 97 mg (41%); MP: 217 °C; R_f = 0.6 (40% ethyl acetate/hexane); **^{1}H NMR** (400 MHz, DMSO-*d*6): δ 1.98 (s, 3H), 2.65–2.78 (m, 2H), 3.38 (s, 2H), 3.74–3.84 (m, 2H), 5.96 (s, 1H), 6.65–6.76 (m, 2H), 6.96 (t, *J* = 8.4 Hz, 1H), 7.16–7.23 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.37–7.42 (m, 1H), 7.55–7.61 (m, 2H), 7.67–7.71 (m, 1H), 7.73–7.78 (m, 1H), 8.45–8.50 (m, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 11.13 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-*d*6): δ 20.7, 22.8, 27.2, 42.6, 63.5, 111.8, 112.4, 113.0, 116.7, 117.6, 118.8, 121.2, 122.8, 124.2, 124.7, 125.1, 125.7, 125.8, 126.3, 127.6, 127.9, 132.7, 134.7, 136.0, 136.5, 140.9, 142.0, 159.7, 170.3 ppm; **HRMS** (ESI) calcd for $C_{29}H_{25}N_2O_3$: 449.1860 $[M + H]^+$; found: 449.1862.



Synthesis of Acid 13, 13a, 13b

2-(Hept-6-en-3-yn-1-yloxy)tetrahydro-2*H*-pyran (15): At rt, a solution of THP-protected but-3-ynol **14** (8.0 g, 51.9 mmol) in DMF (60 ml) was treated with allyl bromide (8.97 mL, 103.8 mmol), K_2CO_3 (10.75 g, 77.8 mmol), Na_2SO_3 (3.27 g, 25.9 mmol), CuI (988 mg, 5.2 mmol), and cat. DBU sequentially and the reaction mixture was stirred for 12 h at rt. The reaction mixture was filtered through celite pad (washed with EtOAc), diluted with EtOAc (200 mL X 2), washed with water (2 x 100 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford alkene **15** (9.2 g, 91% yield) as a colourless liquid. R_f = 0.8 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.49–1.65 (m, 4H), 1.71 (tt, *J* = 13.1, 3.5 Hz, 1H), 1.80–1.88 (m, 1H), 2.50 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.89–2.98 (m, 2H), 3.45–3.60 (m, 2H), 3.77–3.94 (m, 2H), 4.65 (t, *J* = 3.0 Hz, 1H), 5.05 (dq, *J* = 10.0, 1.6 Hz, 1H), 5.32 (dq, *J* = 10.0, 1.6 Hz, 1H), 5.81 (ddt, *J* = 10.0, 5.0, 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.4 (t), 20.2 (t), 23.1 (t), 25.4 (t), 30.6 (t), 62.2 (t), 66.1 (t), 77.7 (s), 79.4 (s), 98.7 (d), 115.7 (t), 133.1 (d) ppm; **HRMS** (ESI) calcd for $C_{12}H_{18}NaO_2$: 217.1199 $[M + Na]^+$; found 217.1197.

7-((Tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-ol (16): A mixture of alkene **15** (9.2 g, 47.36 mmol) and 9-BBN dimer (5.78 g, 23.7 mmol) was heated at 50 °C for 10 min. The contents were cooled to 0 °C, diluted with THF (100 mL) and stirred at rt for 5 h. The reaction mixture was

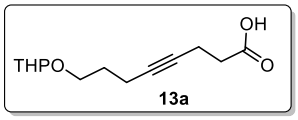
treated with 30% H_2O_2 (37.0 mL, 473.6 mmol) and 3M NaOH (157.8 mL, 473.6 mmol) and stirring was continued at rt for 12 h. The reaction mixture was diluted with cold water (200 mL) and was extracted with EtOAc (200 mL X 2). The combined organic layer was washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting crude by column chromatography gave the alcohol **16** (4.94 g, 76% yield brsm) as colourless liquid along with the starting olefin **15** (3.3 g). R_f = 0.4 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.49–1.64 (m, 4H), 1.69–1.77 (m, 4H), 1.80–1.88 (m, 1H), 2.28 (tt, *J* = 6.8, 2.3 Hz, 2H), 2.46 (tt, *J* = 6.8, 2.4 Hz, 2H), 3.53 (dt, *J* = 9.6, 7.1 Hz, 2H), 3.74–3.83 (m, 3H), 3.89 (tt, *J* = 8.3, 3.0 Hz, 1H), 4.64 (t, *J* = 4.6 Hz, 1Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.5 (t), 19.4 (t), 20.2 (t), 25.4 (t), 30.6 (t), 31.4 (t), 62.0 (t), 62.3 (t), 66.1 (t), 77.7 (s), 80.4 (s), 98.8 (d) ppm; **HRMS** (ESI) calcd for $C_{12}H_{20}NNaO_3$: 235.1305 $[M + Na]^+$; found 235.1299.

16

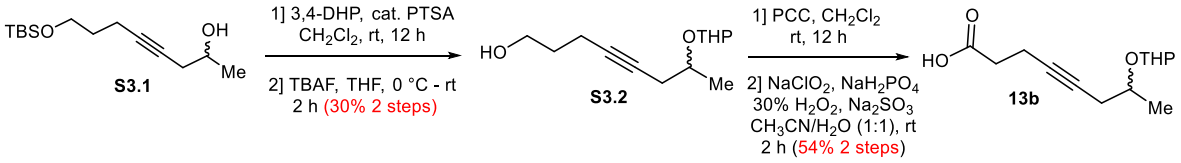
7-((Tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-ynoic acid (**13**)**:** A solution of alcohol **16** (4.9 g, 23.1 mmol) in CH_2Cl_2 (100 mL) was treated with PCC (9.95 g, 46.2 mmol) and stirred for 12 h at rt. The reaction mixture was filtered through silica bed using CH_2Cl_2 as eluent to obtain the crude aldehyde as colourless liquid which was used directly for the next step. The above crude aldehyde was dissolved in a 1:1 CH_3CN/H_2O (50 mL) and treated with $NaClO_2$ (1.88 g, 20.8 mmol), NaH_2PO_4 (2.5 g, 20.8 mmol) and 30% H_2O_2 (1.63 mL, 20.8 mmol) and the contents were stirred at rt for 2 h. The reaction mixture was quenched by adding Na_2SO_3 (2.63 g, 20.8 mmol) and then extracted with EtOAc (100 X 2 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford acid **13** as colourless liquid (3.62 g, 69% yield, 2 steps). R_f = 0.3 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.47–1.65 (m, 4H), 1.72 (tt, *J* = 13.0, 3.1 Hz, 1H), 1.79–1.88 (m, 1H), 2.43–2.49 (m, 4H), 2.56 (td, *J* = 8.2, 7.5 Hz, 2H), 3.49–3.55 (m, 2H), 3.78 (dt, *J* = 9.7, 7.1 Hz, 1H), 3.89 (tt, *J* = 8.2, 3.0 Hz, 1H), 4.65 (t, *J* = 3.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5 (t), 19.4 (t), 20.2 (t), 25.4 (t), 30.5 (t), 33.7 (t), 62.2 (t), 66.0 (t), 78.0 (s), 78.9 (s), 98.7 (d), 177.4 (s) ppm; **HRMS** (ESI) calcd for $C_{12}H_{18}NaO_4$: 249.1097 $[M + Na]^+$; found 249.1091

13

8-((Tetrahydro-2*H*-pyran-2-yl)oxy)oct-4-ynoic acid (13a): prepared by employing OTHP-pent-4-ynol (2.0 g, 10.97 mmol) following 4 steps. Acid **13a** (720 mg, 61% yield, 2 steps) was obtained as a colourless liquid; R_f = 0.3 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.47–1.62 (m, 4H), 1.67–1.85 (m, 4H), 2.25 (tt, J = 6.9, 2.2 Hz, 2H), 2.42–2.50 (m, 2H), 2.50–2.58 (m, 2H), 3.46 (dt, J = 9.7, 6.2 Hz, 1H), 3.50–3.55 (m, 1H), 3.80 (dt, J = 9.7, 6.3 Hz, 1H), 3.84–3.90 (m, 1H), 4.62 (t, J = 3.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5 (t), 15.5 (t), 19.3 (t), 25.4 (t), 28.9 (t), 30.6 (t), 33.8 (t), 62.0 (t), 66.0 (t), 78.2 (s), 80.5 (s), 98.7 (d), 177.3 (s) ppm; **HRMS** (ESI) calcd for $C_{13}H_{20}NaO_4$: 241.1434 $[M + Na]^+$; found 241.1428.

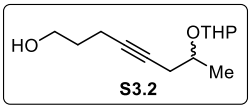


Scheme S3. Synthesis of Acid 13b



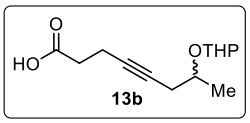
A solution of alcohol **S3.1** (1.5 g, 5.85 mmol), 3,4-dihydropyran (0.64 mL, 7.02 mmol) and pTSA (100 mg, 0.58 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 12 h. After completion of the reaction (indicated by TLC), the reaction mixture was neutralised with the addition of Et_3N. The volatiles were removed under reduced pressure. The resulting crude was dissolved in THF (50 mL) and cooled to 0 °C. To this, tetra-*n*-butyl ammonium fluoride (TBAF 1.38 g, 5.29 mmol) was added at stirred at rt for 2 h. After completion of reaction (indicated by TLC), the reaction was diluted with water (20 mL) and extracted with EtOAc (50 mL X 2), dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by column chromatography to afford alkynol **S3.2** (400 mg, 30% yield, 2 steps) as colourless liquid.

7-((Tetrahydro-2*H*-pyran-2-yl)oxy)oct-4-yn-1-ol (S3.2): Colourless liquid (400 mg, 40%); R_f = 0.2 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.21 (d, J = 6.1 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.47–1.59 (m, 8H), 1.66–1.76 (m, 6H), 1.78–1.86 (m, 2H), 1.96 (br. s. 2H), 2.23–2.31 (m, 5.6H), 2.32–2.39 (m, 1.6H), 2.45–2.53 (m, 1H), 3.45–3.53 (m, 2H), 3.69–3.77 (m, 4H), 3.83–3.96 (m, 4H), 4.69 (s, 1H), 4.74 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 15.4 (t), 15.4 (t), 18.9 (q), 19.6 (t), 19.7 (t), 21.0 (q), 25.4 (t), 25.4 (t), 26.0 (t), 27.4 (t), 30.9 (t), 31.0 (t), 31.4 (t), 31.5 (t), 61.8

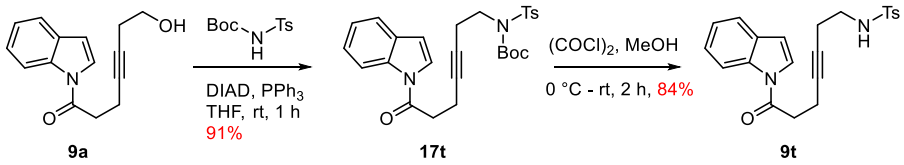


(t), 62.4 (t), 62.6 (t), 71.0 (d), 71.3 (d), 77.4 (s), 77.8 (s), 80.9 (s), 80.9 (s), 96.7 (d), 97.7 (d) ppm; **HRMS** (ESI) calcd for $C_{13}H_{22}NaO_3$: 249.1461 $[M + Na]^+$; found 249.1459.

7-((Tetrahydro-2*H*-pyran-2-yl)oxy)oct-4-ynoic acid (13b): The alcohol **S3.2** was oxidised to corresponding acid **13b** by following the established procedure (54% yield, 2 steps). Colourless liquid; R_f = 0.2 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.22 (d, J = 6.1 Hz, 2.37H), 1.29 (d, J = 6.1 Hz, 3H), 1.48–1.61 (m, 7.5H), 1.69–1.75 (m, 2H), 1.80–1.87 (m, 2H), 2.20–2.39 (m, 3H), 2.44–2.52 (m, 4H), 2.53–2.60 (m, 4H), 3.47–3.54 (m, 2H), 3.85–3.98 (m, 3.71H), 4.72 (t, J = 4.2 Hz, 1H), 4.76 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.5 (t), 19.0 (q), 19.5 (t), 19.8 (t), 21.1 (q), 25.4 (t), 26.1 (t), 27.4 (t), 30.9 (t), 31.0 (t), 33.6 (t), 62.4 (t), 62.7 (t), 71.1 (d), 71.5 (d), 78.0 (s), 78.3 (s), 79.4 (s, 2C), 96.7 (d), 97.8 (d), 176.7 (s) ppm; **HRMS** (ESI) calcd for $C_{13}H_{20}NaO_4$: 263.1254 $[M + Na]^+$; found 263.1246.

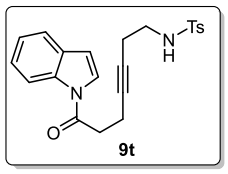


Scheme S4. Synthesis of Alkynylamine 9t



***tert*-Butyl (7-(1*H*-indol-1-yl)-7-oxohept-3-yn-1-yl)(tosyl)carbamate (9t):** At 0 °C, a solution of alcohol **9a** (100 mg, 0.42 mmol), TsNHBoc (146 mg, 0.54 mmol), PPh_3 (141 mg, 0.54 mmol) in THF (10 mL) was treated with DIAD (106 µL, 0.54 mmol) and stirring was continued at rt for 1 h. The reaction mixture was and purified by column chromatography to afford alkynylamine **17t** (188 mg, 91% yield) as a colourless syrup colourless sticky liquid (188 mg, 91%); R_f = 0.7 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.43 (s, 3H), 2.62 (tt, J = 7.3, 2.2 Hz, 2H), 2.69 (tt, J = 7.8, 2.1 Hz, 2H), 3.16 (dd, J = 8.4, 6.5 Hz, 2H), 3.93–3.98 (m, 2H), 6.66 (d, J = 3.3 Hz, 1H), 7.26–7.32 (m, 3H), 7.36 (td, J = 8.3, 1.1 Hz, 1H), 7.49 (d, J = 3.7 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 8.46 (d, J = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2 (t), 20.2 (t), 21.6 (q), 27.8 (q, 3C), 35.2 (t), 45.6 (t), 77.5 (s), 80.4 (s), 84.4 (s), 109.3 (d), 116.5 (d), 120.8 (d), 123.7 (d), 124.5 (d), 125.1 (d), 127.8 (d, 2C), 129.2 (d, 2C), 130.3 (s), 135.5 (s), 137.3 (s), 144.2 (s), 150.7 (s), 169.8 (s) ppm; HRMS (ESI) calcd for $C_{27}H_{30}N_2O_5SNa$: 517.1768 $[M + Na]^+$; found 517.1758.

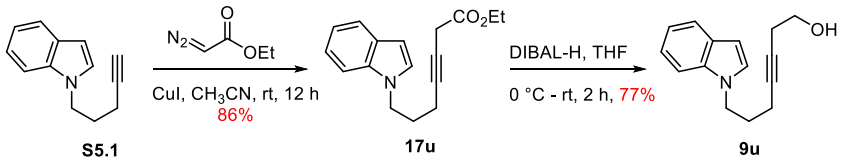
N-(7-(1*H*-indol-1-yl)-7-oxohept-3-yn-1-yl)-4-methylbenzenesulfonamide (9t): At 0 °C, a solution of amine **17t** (80 mg, 0.16 mmol) in MeOH (5 mL) was treated with oxalyl chloride (42 µL, 0.5 mmol) and stirring was continued at rt for 2 h. After completion of the reaction (indicated by TLC), the reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography to afford alkynyl amine **9t** (54 mg, 84% yield) as a colourless syrup. R_f = 0.4 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.29 (tt, J = 8.6, 2.2 Hz, 2H), 2.40 (s, 3H), 2.65 (tt, J = 9.5, 2.2 Hz, 2H), 3.01–3.14 (m, 4H), 5.15 (t, J = 6.2 Hz, 1H), 6.66 (d, J = 3.7 Hz, 1H), 7.23–7.32 (m, 3H), 7.36 (td, J = 7.7, 1.2 Hz, 1H), 7.45 (d, J = 3.7 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 8.47 (d, J = 8.2 Hz, 1H);



9t

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 20.0 (t), 21.5 (q), 35.1 (t), 42.0 (t), 77.5 (s), 80.9 (s), 109.5 (d), 116.6 (d), 120.9 (d), 123.8 (d), 124.3 (d), 125.3 (d), 127.0 (d, 2C), 129.7 (d, 2C), 130.3 (s), 135.5 (s), 137.1 (s), 143.4 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{22}N_2O_3Na$: 417.1243 $[M + Na]^+$; found 417.1249.

Scheme S5. Synthesis of Alkynol 9u

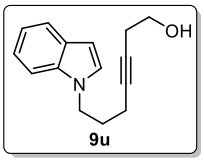


S5.1 **17u** **9u**

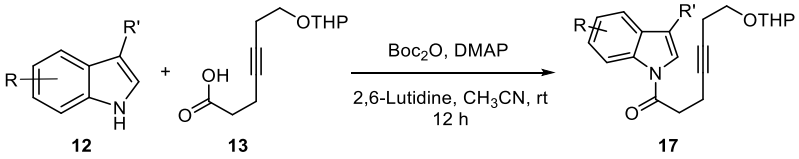
Ethyl 7-(1*H*-indol-1-yl)hept-3-ynoate (9u): A solution of alkyne **S5.1** (1 g, 5.46 mmol), ethyl diazoacetate (3.11 g, 27.28 mmol) and CuI (519 mg, 2.73 mmol) in CH_3CN (30 mL) was stirred at rt for 12 h. After completion of reaction (indicated by TLC), the reaction mixture was filtered through celite and washed with EtOAc (30 mL X 2). The combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by column chromatography to afford alkyne **17u** (1.27 g, 86% yield) as a colourless liquid. R_f = 0.5 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.1 Hz, 3H), 1.92 (quin, J = 6.6 Hz, 2H), 2.02–2.09 (m, 2H), 3.19 (t, J = 2.3 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 6.39 (d, J = 3.0 Hz, 1H), 7.0 (t, J = 7.7 Hz, 1H), 7.05–7.14 (m, 2H), 7.29 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 16.0 (t), 26.0 (t), 28.7 (t), 44.6 (t), 61.4 (t), 73.1 (s), 82.1 (s), 100.9 (d), 109.3

(d), 119.2 (d), 120.8 (d), 121.3 (d), 128.1 (d), 128.6 (s), 135.8 (s), 168.7 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{20}N_2O_2$: 270.1489 $[M + H]^+$; found 270.1484.

7-(1*H*-indol-1-yl)hept-3-yn-1-ol (9u): At 0 °C, a solution of alkyne **17u** (800 mg, 2.97 mmol) in dry THF (20 mL) was treated drop wise with 1N DIBAL-H in THF (3.56 mL, 3.56 mmol) and the stirring was continued for additional 2 h at the same temperature. After completion of the reaction as indicated by TLC), the reaction mixture was quenched with aq. sodium potassium tartarate (Rochelle's salt), diluted with EtOAc (50 mL), washed with water (20 mL X 2), brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting crude by column chromatography afforded the alkynol **9u** (522 mg, 77% yield) as a pale yellow liquid in. R_f = 0.5 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.91 (quin, J = 6.6 Hz, 2H), 2.02–2.10 (m, 2H), 2.37 (tt, J = 6.2, 2.3 Hz, 2H), 3.61 (t, J = 6.2 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 66.41 (dd, J = 3.1, 0.5 Hz, 1H), 6.98–7.06 (m, 2H), 7.10–7.16 (m, 1H), 7.25–7.31 (m, 1H), 7.55 (d, J = 7.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.1 (t), 23.0 (t), 29.1 (t), 44.8 (t), 61.3(t), 77.8 (s), 80.8 (s), 101.1 (d), 109.3 (d), 119.2 (d), 120.9 (d), 121.4 (d), 127.9 (d), 128.6 (s), 135.9 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{17}NONa$: 250.1202 $[M + Na]^+$; found 250.1209.

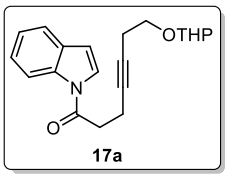


General Procedure for Coupling of Indoles and Acid 13



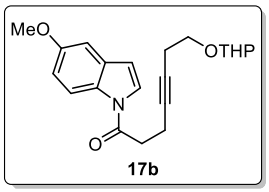
The coupling reactions are carried out employing the acid 0.5 (200 mg, 0.88 mmol) and used the corresponding indole in excess (2.21 mmol, 2.5 equiv). A representative coupling procedure as follows. To a solution of acid **13** (1 equiv) and indole **12** (2.5 equiv) in CH_3CN (5 mL) were added Boc_2O (2.5 equiv), DMAP (0.15 equiv), and 2,6-lutidine (0.5 equiv) sequentially at rt and the stirring was continued for additional12 h. After completion of reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography to afford THP protected alkynol **17**.

1-(1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17a): Following the general procedure, the coupling of indole **12a** (258 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17a** (219 mg, 76%) as a colourless solid. R_f = 0.2 (10% ethyl acetate in petroleum ether); mp: 88–90 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.46–1.61 (m, 4H), 1.63–1.71 (m, 1H), 1.81 (dt, *J* = 13.0, 3.8 Hz, 1H), 2.47 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.71 (tt, *J* = 7.2, 2.3 Hz, 2H), 3.14 (dd, *J* = 8.1, 6.9 Hz, 2H), 3.44–3.56 (dt, *J* = 9.6, 7.1 Hz, 2H), 3.79 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.87 (td, *J* = 8.2, 3.0 Hz, 1H), 4.62 (t, *J* = 3.0 Hz, 1H), 6.66 (dd, *J* = 3.8, 0.4 Hz, 1H), 7.28 (td, *J* = 7.4, 1.0 Hz, 1H), 7.36 (td, *J* = 7.7, 1.2 Hz, 1H), 7.47 (d, *J* = 3.7 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 19.4 (t), 20.2 (t), 25.4 (t), 30.5 (t), 35.4 (t), 62.2 (t), 65.9 (t), 78.2 (s), 79.0 (s), 98.8 (d), 109.3 (d), 116.6 (d), 120.8 (d), 123.7 (d), 124.4 (d), 125.2 (d), 130.3 (s), 135.6 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{23}NNaO_3$: 348.1570 $[M + Na]^+$; found 348.1560.



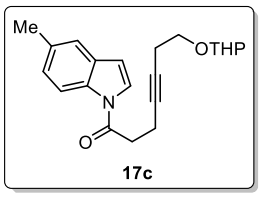
17a

1-(5-Methoxy-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17b): Following the procedure, the coupling of indole **12b** (325 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17b** (213 mg, 67%) as a pale yellow solid. R_f = 0.2 (30% ethyl acetate in petroleum ether); mp: 64–66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44–1.58 (m, 4H), 1.71 (tt, *J* = 13.0, 3.6 Hz, 1H), 1.78–1.87 (m, 1H), 2.46 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.69 (tt, *J* = 7.6, 2.3 Hz, 2H), 3.11 (dd, *J* = 8.1, 6.6 Hz, 2H), 3.46–3.55 (m, 2H), 3.79 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.84–3.91 (m, 4H), 4.62 (dd, *J* = 4.0, 3.0 Hz, 1H), 6.59 (dd, *J* = 3.7, 0.6 Hz, 1H), 6.96 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 3.7 Hz, 1H), 8.35 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 19.4 (t), 20.2 (t), 25.4 (t), 30.6 (t), 35.1 (t), 55.6 (q), 62.3 (t), 65.9 (t), 78.2 (s), 79.1 (s), 98.8 (d), 103.6 (d), 109.2 (d), 113.5 (d), 117.3 (d), 125.0 (d), 130.3 (s), 131.3 (s), 156.5 (s), 169.33 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{25}NNaO_4$: 378.1676 $[M + Na]^+$; found 378.1660.



17b

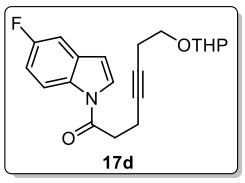
1-(5-Methyl-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17c): Following the general procedure, the coupling of indole **12c** (289 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17c** (199 mg, 66%) as a colourless liquid. R_f = 0.3 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45–1.59 (m, 4H), 1.66–



17c

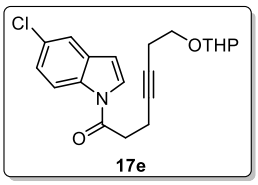
1.75 (tt, *J* = 13.0, 3.1 Hz, 1H), 1.82 (dd, *J* = 9.2, 3.6 Hz, 1H), 2.45 (s, 3H), 2.46–2.49 (m, 2H), 2.70 (tt, *J* = 7.8, 2.2 Hz, 2H), 3.12 (dd, *J* = 8.1, 6.6 Hz, 2H) 3.52 (dt, *J* = 9.6, 7.1 Hz, 2H), 3.79 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.85–3.90 (m, 1H), 4.62 (t, *J* = 3.1 Hz, 1H), 6.59 (d, *J* = 3.7 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.36 (s, 1H), 7.44 (d, *J* = 3.7 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.3 (t), 19.5 (t), 20.2 (t), 21.3 (q), 25.4 (t), 30.5 (t), 35.3 (t), 62.3 (t), 66.0 (t), 78.2 (s), 79.1 (s), 98.8 (d), 109.1 (d), 116.2 (d), 120.8 (d), 124.4 (d), 126.5 (d), 130.6 (s), 133.3 (s), 133.8 (s), 169.5 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{25}NNaO_3$: 362.1727 $[M + Na]^+$; found 362.1715.

1-(5-Fluoro-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17d): Following the general procedure, the coupling of indole **12d** (298 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded **17d** (203 mg, 67%) as a colourless solid. R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 68–70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.48–1.56 (m, 4H), 1.70 (tt, *J* = 12.8, 3.1 Hz, 1H), 1.78–1.84 (m, 1H), 2.46 (tt, *J* = 7.2, 2.2 Hz, 1H), 2.70 (tt, *J* = 7.8, 2.2 Hz, 2H), 3.13 (dd, *J* = 7.0, 1.5 Hz, 2H), 3.47–3.54 (m, 2H), 3.71–3.82 (m, 2H), 3.87 (ddd, *J* = 11.1, 8.1, 3.2 Hz, 1H), 4.62 (t, *J* = 3.0 Hz, 1H), 6.63 (d, *J* = 3.7 Hz, 1H), 7.08 (td, *J* = 9.1, 2.6 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.52 (d, *J* = 3.7 Hz, 1H), 8.43 (dd, *J* = 9.0, 4.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.3 (t), 19.5 (t), 20.2 (t), 25.4 (t), 30.6 (t), 35.1 (t), 62.3 (t), 65.9 (t), 78.4 (s), 78.9 (s), 98.8 (d), 106.3 (dd, $J_{C\text{-}F}$ = 24.4 Hz), 109.5 (dd, $J_{C\text{-}F}$ = 3.8 Hz), 112.9 (dd, $J_{C\text{-}F}$ = 25.1 Hz), 117.6 (dd, $J_{C\text{-}F}$ = 9.1 Hz), 125.9 (d), 131.3 (sd, $J_{C\text{-}F}$ = 9.9 Hz), 132.0 (s), 159.7 (sd, $J_{C\text{-}F}$ = 240.3 Hz), 169.5 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* –119.25 ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NFNaO_3$: 366.1476 $[M + Na]^+$; found 366.1462.



17d

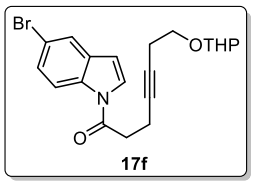
1-(5-Chloro-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17e): Following the general procedure, the coupling of indole **12e** (335 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17e** (253 mg, 83%) as a colourless liquid. R_f = 0.5 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.48–1.60 (m, 4H), 1.69 (tt, *J* = 13.0, 3.1 Hz, 1H) 1.78–1.83 (m, 1H), 2.46 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.70 (tt, *J* = 7.6, 2.3 Hz, 2H), 3.12 (dd, *J* = 8.0, 6.6 Hz, 2H), 3.46–3.55 (m, 2H), 3.78 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.83–3.91 (m,



17e

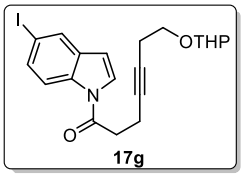
1H), 4.62 (dd, *J* = 2.8, 1.0 Hz, 1H), 6.60 (dd, *J* = 3.8, 0.6 Hz, 1H), 7.31 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.49 (d, *J* = 3.7 Hz, 1H), 7.54 (d, *J* = 1.7 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 19.5 (t), 20.2 (t), 25.4 (t), 30.5 (t), 35.2 (t), 62.3 (t), 65.9 (t), 78.4 (s), 78.9 (s), 98.8 (d), 108.6 (d), 117.6 (d), 120.5 (d), 125.3 (d), 125.6 (d), 129.3 (s), 131.5 (s), 133.9 (s), 169.6 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NClNaO_3$: 382.1180 $[M + Na]^+$; found 382.1169.

1-(5-Bromo-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17f): Following the general procedure, the coupling indole **12f** (433 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17f** (306 mg, 85%) as a colourless solid. R_f = 0.5 (30% ethyl acetate in petroleum ether); mp: 78–80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.48–1.60 (m, 4H), 1.70 (tt, *J* = 13.0, 3.1 Hz, 1H), 1.77–1.88 (m, 1H), 2.46 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.65–2.75 (m, 2H), 3.12 (dd, *J* = 8.1, 6.6 Hz, 2H), 3.46–3.55 (m, 2H), 3.78 (dt, *J* = 9.7, 7.1 Hz, 1H), 3.83–3.92 (m, 1H), 4.61 (dd, *J* = 2.8, 1.3 Hz, 1H), 6.60 (dd, *J* = 3.8, 0.6 Hz, 1H), 7.45 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.48 (d, *J* = 3.7 Hz, 1H), 7.70 (d, *J* = 1.7 Hz, 1H), 8.35 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 19.5 (t), 20.2 (t), 25.4 (t), 30.5 (t), 35.2 (t), 62.3 (t), 65.9 (t), 78.4 (s), 78.8 (s), 98.8 (d), 108.4 (d), 117.0 (s), 118.0 (d), 123.5 (d), 125.5 (d), 128.0 (d), 132.0 (s), 134.3 (s), 169.6 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NBrNaO_3$: 426.0675 $[M + Na]^+$; found 426.0667.



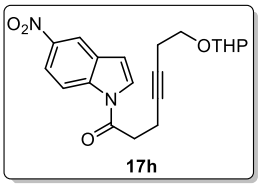
17f

1-(5-Iodo-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17g): Following the general procedure, the coupling of indole **12g** (537 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) provided compound **17g** (245 mg, 61%) as a pale yellow liquid. R_f = 0.3 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.48–1.57 (m, 4H), 1.66–1.74 (m, 1H), 1.77–1.85 (m, 1H), 2.46 (tt, *J* = 7.1, 2.2 Hz, 2H), 2.67–2.73 (m, 2H), 3.12 (t, *J* = 7.3 Hz, 2H), 3.46–3.55 (m, 2H), 3.77 (td, *J* = 9.6, 2.5 Hz, 1H), 3.82–3.91 (m, 1H), 4.61 (t, *J* = 3.0 Hz 1H), 6.59 (d, *J* = 3.7 Hz, 1H), 7.45 (d, *J* = 3.7 Hz, 1H), 7.63 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.92 (d, *J* = 1.6 Hz, 1H), 8.24 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 19.5 (t), 20.2 (t), 25.4 (t), 30.5 (t), 35.3 (t), 62.3 (t), 65.9 (t), 78.4 (s), 78.8 (s), 87.9 (s), 98.8 (d), 108.2 (d), 118.4 (d), 125.1 (d), 129.7 (d), 132.6 (s), 133.7 (d), 134.9 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NINaO_3$: 474.0537 $[M + Na]^+$; found 474.0521.



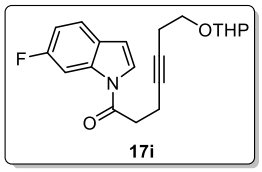
17g

1-(5-Nitro-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17h): Following the general procedure, the coupling of indole **12h** (358 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) gave compound **17h** (197 mg, 60%) as an yellow solid. R_f = 0.3 (40% ethyl acetate in petroleum ether); mp: 80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.46–1.59 (m, 4H), 1.70 (tt, *J* = 12.88, 3.50 Hz, 1H), 1.76–1.87 (m, 1H), 2.46 (tt, *J* = 7.13, 2.38 Hz, 2H), 2.73 (tt, *J* = 7.63, 2.38 Hz, 2H), 3.18 (dd, *J* = 7.88, 6.63 Hz, 2H), 3.51 (dt, *J* = 9.76, 7.13 Hz, 2H), 3.78 (dt, *J* = 9.69, 7.16 Hz, 1H), 3.87 (ddd, *J* = 11.29, 8.10, 3.25 Hz, 1H), 4.62 (dd, *J* = 2.88, 1.21 Hz, 1H), 6.82 (dd, *J* = 3.88, 0.63 Hz, 1H), 7.65 (d, *J* = 3.88 Hz, 1H), 8.25 (dd, *J* = 9.19, 2.31 Hz, 1H), 8.50 (d, *J* = 2.13 Hz, 1H), 8.60 (d, *J* = 9.13 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2 (t), 19.5 (t), 20.16 (t), 25.4 (t), 30.5 (t), 35.4 (t), 62.3 (t), 65.9 (t), 78.5 (s), 78.7 (s), 98.8 (d), 109.7 (d), 116.8 (d), 117.1 (d), 120.5 (d), 127.2 (d), 130.2 (s), 138.6 (s), 144.3 (s), 169.9 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}N_2NaO_5$: 393.1421 $[M + Na]^+$; found 393.1411.



17h

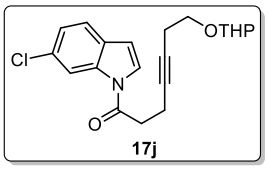
1-(6-Fluoro-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17i): Following the general procedure, the coupling of indole **12i** (298 mg, 2.21) and acid **13** (200 mg, 0.88 mmol) provided compound **17i** (167 mg, 55%) as a colourless syrup. R_f = 0.2 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.48–1.60 (m, 4H), 1.71 (tt, *J* = 13.0, 3.2 Hz, 1H), 1.77–1.85 (m, 1H), 2.46 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.70 (ddt, *J* = 8.3, 6.3, 2.3 Hz, 2H), 3.12 (dd, *J* = 8.1, 6.6 Hz, 2H), 3.47–3.54 (m, 2H), 3.79 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.87 (ddd, *J* = 11.1, 8.0, 3.1 Hz, 1H), 4.62 (t, *J* = 3.0 Hz, 1H), 6.62 (d, *J* = 3.8 Hz, 1H), 7.03 (td, *J* = 8.8, 2.3 Hz, 1H), 7.44–7.50 (m, 2H), 8.22 (dd, *J* = 10.3, 2.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2 (t), 19.5 (t), 20.2 (t), 25.4 (t), 30.5 (t), 35.2 (t), 62.3 (t), 65.9 (t), 78.4 (s), 78.9 (s), 98.8 (d), 104.0 (dd, $J_{C\text{-}F}$ = 28.9 Hz), 109.0 (d), 111.9 (dd, $J_{C\text{-}F}$ = 24.4 Hz), 121.3 (dd, $J_{C\text{-}F}$ = 9.9 Hz), 124.6 (dd, $J_{C\text{-}F}$ = 3.8 Hz), 126.5 (s), 135.7 (sd, $J_{C\text{-}F}$ = 12.9 Hz),161.3 (sd, $J_{C\text{-}F}$ = 241.0 Hz), 169.8 (s); ^{19}F NMR (376 MHz, $CDCl_3$): δ –116.35 ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NFNaO_3$: 366.1476 $[M + Na]^+$; found 366.1467.



17i

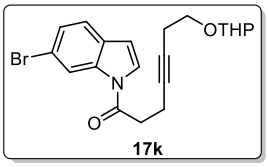
1-(6-Chloro-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17j): Following the general procedure, the coupling of indole **12j** (335 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) gave compound **17j** (217 mg, 68%) as a pale yellow liquid. R_f = 0.4 (10%

ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45–1.62 (m, 4H), 1.63–1.74 (m, 1H), 1.76–1.87 (m, 1H), 2.46 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.70 (tt, *J* = 7.7, 2.2 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 3.52 (dt, *J* = 9.7, 7.1 Hz, 2H), 3.78 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.87 (ddd, *J* = 11.1, 8.0, 3.2 Hz, 1H), 4.58–4.65 (m, 1H), 6.62 (d, *J* = 3.8 Hz, 1H), 7.22–7.30 (m, 1H), 7.42–7.50 (m, 2H), 8.53 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 19.4 (t), 20.2 (t), 25.4 (t), 30.5 (t), 35.3 (t), 62.3 (t), 65.9 (t), 78.4 (s), 78.8 (s), 98.8 (d), 109.0 (d), 116.9 (d), 121.4 (d), 124.3 (d), 124.9 (d), 128.7 (s), 131.1 (s), 135.9 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NClNaO_3$: 382.1180 $[M + Na]^+$; found 382.1185.



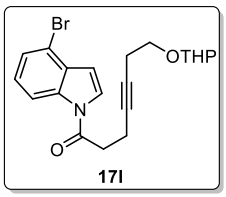
17j

1-(6-Bromo-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17k): Following the procedure, the coupling of indole **12k** (433 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) gave compound **17k** (201 mg, 56%) as a colourless syrup. R_f = 0.2 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.48–1.60 (m, 4H), 1.740 (tt, *J* = 12.8, 3.2 Hz, 1H), 1.768–1.86 (m, 1H), 2.46 (tt, *J* = 7.1, 2.2 Hz, 2H), 2.69 (tt, *J* = 7.3, 2.3 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 3.44–3.56 (m, 2H), 3.78 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.87 (ddd, *J* = 11.1, 8.0, 3.1 Hz, 1H), 4.62 (t, *J* = 3.0 Hz, 1H), 6.62 (d, *J* = 3.8 Hz, 1H), 7.36–7.42 (m, 2H), 7.43 (d, *J* = 3.7 Hz, 1H), 8.70 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2 (t), 19.4 (t), 20.2 (t), 25.4 (t), 30.5 (t), 35.2 (t), 62.3 (t), 65.9 (t), 78.4 (s), 78.8 (s), 98.8 (d), 109.0 (d), 118.9 (s), 119.7 (d), 121.8 (d), 124.8 (d), 127.0 (d), 129.1 (s), 136.2 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NBrNaO_3$: 426.0675 $[M + Na]^+$; found 426.0663.



17k

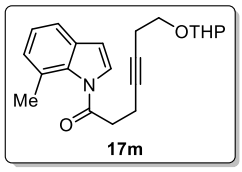
1-(4-Bromo-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17l): Prepared by following procedure of coupling indole **12l** (433 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17l** as colourless sticky liquid (210 mg, 58%); R_f = 0.2 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.48–1.55 (m, 4H), 1.71 (tt, *J* = 12.8, 3.2 Hz, 1H), 1.83 (dd, *J* = 9.8, 3.1 Hz, 1H), 2.47 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.72 (ddt, *J* = 8.3, 6.3, 2.3 Hz, 2H), 3.15 (dd, *J* = 8.0, 6.6 Hz, 2H), 3.46–3.56 (m, 2H), 3.80 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.84–3.94 (m, 1H), 4.62 (dd, *J* = 4.0, 3.0 Hz, 1H), 6.73 (d, *J* = 3.8 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.45 (dd, *J* = 7.7, 0.5 Hz, 1H), 7.54 (d, *J* = 3.7 Hz, 1H), 8.44 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (100



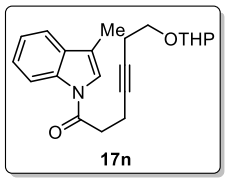
17l

MHz, $CDCl_3$): δ 14.3 (t), 19.5 (t), 20.2 (t), 25.4 (t), 30.5 (t), 35.4 (t), 62.3 (t), 65.9 (t), 78.4 (s), 78.8 (s), 98.8 (d), 109.1 (d), 114.6 (s), 115.6 (d), 124.9 (d), 126.2 (d), 126.7 (d), 131.0 (s), 135.9 (s), 169.8 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}NBrNaO_3$: 426.0675 $[M + Na]^+$; found 426.0666.

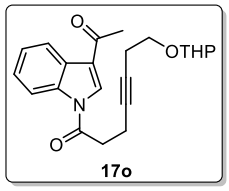
1-(7-Methyl-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17m): Following the general procedure, the coupling of indole **12m** (290 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17m** (107 mg, 35%) as a colourless oil; R_f = 0.3 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.49–1.57 (m, 4H), 1.70 (tt, *J* = 9.8, 3.1 Hz, 1H), 1.81 (dd, *J* = 9.1, 3.5 Hz, 1H), 2.46 (tt, *J* = 7.2, 2.3 Hz, 2H), 2.56 (s, 3H), 2.71 (tt, *J* = 7.9, 2.3 Hz, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 3.4–3.54 (m, 2H), 3.78 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.86 (ddd, *J* = 11.1, 7.8, 3.1 Hz, 1H), 4.6 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.65 (d, *J* = 3.8 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.44 (d, *J* = 3.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.1 (t), 19.4 (t), 20.15 (t), 22.6 (q), 25.4 (t), 30.5 (t), 36.1 (t), 62.3 (t), 65.9 (t), 78.4 (s), 79.0 (s), 98.8 (d), 109.2 (d), 118.5 (d), 124.1 (d), 125.7 (d), 126.7 (s), 128.2 (d), 131.9 (s), 135.1 (s), 169.2 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{25}NNaO_3$: 362.1727 $[M + Na]^+$; found 362.1717.



1-(3-Methyl-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17n): Following the general procedure, coupling of indole **12n** (290 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17n** (183 mg, 61%) as a colourless syrup. R_f = 0.8 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.48–1.52 (m, 4H), 1.70 (tt, *J* = 12.8, 3.2 Hz, 1H), 1.78–1.87 (m, 1H), 2.29 (d, *J* = 1.2 Hz, 3H), 2.47 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.69 (tt, *J* = 7.4, 2.3 Hz, 2H), 3.09 (dd, *J* = 8.3, 6.6 Hz, 2H), 3.46–3.56 (m, 2H), 3.80 (ddd, *J* = 9.6, 7.2, 2.3 Hz, 1H), 3.88 (ddd, *J* = 11.1, 8.0, 3.1 Hz, 1H), 4.62 (t, *J* = 3.1 Hz, 1H), 7.23 (s, 1H), 7.30 (td, *J* = 7.4, 1.1 Hz, 1H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.50 (dd, *J* = 7.6, 0.6 Hz, 1H), 8.44 (d, *J* = 7.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 9.7 (q), 14.3 (d), 19.4 (d), 20.2 (d), 25.4 (d), 30.5 (d), 35.4 (d), 62.2 (d), 65.9 (d), 78.1 (s), 79.2 (s), 98.7 (d), 116.6 (d), 118.6 (s), 118.8 (d), 121.3 (d), 123.4 (d), 125.2 (d), 131.3 (s), 135.8 (s), 169.3 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{25}NNaO_3$: 362.1737 $[M + Na]^+$; found 362.1718.

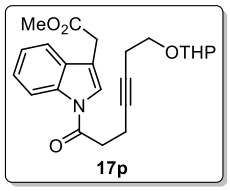


1-(3-Acetyl-1*H*-indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17o): Following the general procedure, the coupling of indole **12o** (351 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) gave the compound **17o** (179 mg, 55%) as a pale yellow oil. R_f = 0.6 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.46–1.60 (m, 4H), 1.69 (dt, *J* = 8.7, 3.3 Hz, 1H), 1.75–1.85 (m, 1H), 2.46 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.58 (s, 3H), 2.73 (tt, *J* = 7.6, 2.3 Hz, 2H), 3.19 (dd, *J* = 8.0, 6.6 Hz, 2H), 3.50 (dt, *J* = 9.6, 7.1 Hz, 2H), 3.79 (dt, *J* = 9.7, 7.1 Hz, 1H), 3.86 (ddd, *J* = 11.2, 8.0, 3.2 Hz, 1H), 4.56–4.64 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.36–7.46 (m, 2H), 8.07 (s, 1H), 8.34 (ddd, *J* = 6.3, 2.6, 0.6 Hz, 1H), 8.39 (ddd, *J* = 7.0, 2.6, 0.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2 (t), 19.4 (t), 20.14 (t), 25.3 (t), 27.9 (q), 30.5 (t), 35.4 (t), 62.3 (t), 65.9 (t), 78.6 (s), 78.7 (s), 98.8 (d), 116.1 (d), 121.9 (s), 122.5 (d), 125.2 (d), 126.3 (d), 127.1 (s), 130.4 (d), 136.0 (s), 169.9 (s), 193.6 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{25}NNaO_4$: 390.1676 [M + Na]$^+$; found 390.1663.



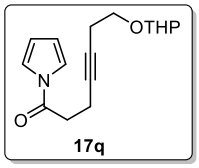
17o

Methyl 2-(1-(7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-ynoyl)-1*H*-indol-3-yl)acetate (17p): Following the procedure, the coupling of indole **12p** (418 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) afforded compound **17p** (162 mg, 46%) as a colourless syrup. R_f = 0.3 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45–1.62 (m, 5H), 1.67–1.69 (m, 1H), 1.69–1.74 (m, 1H), 1.77–1.86 (m, 1H), 2.46 (tt, *J* = 7.1, 2.3 Hz, 2H), 2.66–2.73 (m, 2H), 3.13 (dd, *J* = 8.2, 6.6 Hz, 2H), 3.47–3.55 (m, 2H), 3.74 (s, 3H), 3.78 (dt, *J* = 9.7, 7.2 Hz, 1H), 3.87 (ddd, *J* = 11.2, 8.0, 3.2 Hz, 1H), 4.62 (t, *J* = 2.8 Hz, 1H), 7.31 (td, *J* = 7.4, 1.0 Hz, 1H), 7.38 (td, *J* = 7.7, 1.3 Hz, 1H), 7.49–7.55 (m, 2H), 8.45 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2 (t), 19.4 (t), 20.2 (t), 25.4 (t), 30.5 (t), 30.7 (t), 35.3 (t), 52.2 (q), 62.2 (t), 65.9 (t), 78.2 (s), 79.0 (s), 98.7 (d), 115.1 (s), 116.7 (d), 118.8 (d), 122.9 (d), 123.7 (d), 125.5 (d), 129.9 (s), 135.7 (s), 169.5 (s), 171.2 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{27}NNaO_5$: 420.1781 [M + Na]$^+$; found 420.1778.



17p

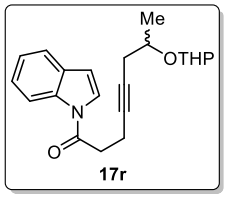
1-(1*H*-Pyrrol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-4-yn-1-one (17q): Following the procedure, the coupling of pyrrole **12q** (148 mg, 2.21 mmol) and acid **13** (200 mg, 0.88 mmol) gave compound **17q** (80 mg, 33%) as a colourless syrup. R_f = 0.6 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45–1.65 (m, 4H), 1.65–1.75 (m, 1H), 1.76–1.89 (m, 1H), 2.45 (tt, *J* = 7.1, 2.3



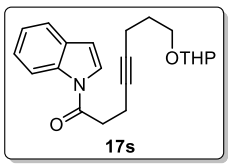
17q

Hz, 2H), 2.64 (ddt, *J* = 8.4, 6.4, 2.3 Hz, 2H), 3.04 (dd, *J* = 8.1, 6.6 Hz, 2H), 3.45–3.57 (m, 2H), 3.78 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.87 (tt, *J* = 8.3, 3.0 Hz, 1H), 4.60–4.65 (m, 1H), 6.30 (t, *J* = 2.3 Hz, 2H), 7.32 (br. s., 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (t), 19.4 (t), 20.1 (t), 25.4 (t), 30.5 (t), 34.2 (t), 62.2 (t), 65.9 (t), 78.2 (s), 78.8 (s), 98.7 (d), 113.2 (d, 2C), 118.9 (d, 2C), 168.9 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{21}N\,Na\,O_3$: 298.1414 $[M + Na]^+$; found 298.1406.

1-(1*H*-Indol-1-yl)-7-((tetrahydro-2*H*-pyran-2-yl)oxy)oct-4-yn-1-one (17r): Following the procedure, the coupling of indole **12a** (244 mg, 2.08 mmol) and acid **13b** (200 mg, 0.83 mmol) gave compound **17r** (198 mg, 70%) as a colourless oil; R_f = 0.5 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.1 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 2.85H), 1.47–1.61 (m, 8H), 1.68–1.76 (m, 3H), 1.78–1.89 (m, 2H), 2.26–2.33 (m, 1.5H), 2.35–2.45 (m, 1.5H), 2.53–2.57 (m, 1H), 2.73 (tt, *J* = 8.6, 2.5 Hz, 3.8H), 3.16 (td, *J* = 7.3, 3.6 Hz, 3.7H), 3.46–3.55 (m, 1.95H), 3.85–4.00 (m, 3.79H), 4.71–4.76 (m, 1.87H), 6.68 (d, *J* = 3.8 Hz, 1.79H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.38 (7.6 Hz, 1.82H), 7.49 (m, 1.76H), 7.59 (d, *J* = 7.6 Hz, 1.77H), 8.48 (d, *J* = 8.3 Hz, 1.75H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.3 (t), 14.4 (t), 19.0 (q), 19.5 (t), 19.8 (t), 21.1 (q), 25.4 (t), 25.5 (t), 26.1 (t), 27.5 (t), 30.9 (t), 31.0 (t), 35.4 (t), 62.4 (t), 62.7 (t), 71.0 (d), 71.4 (d), 78.2 (s), 78.5 (s), 79.5 (s) 96.7 (d), 97.8 (d), 109.3 (d), 116.6 (d), 120.8 (d), 123.7 (d), 124.4 (d), 125.2 (d), 130.3 (s), 135.6 (s), 169.7 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{25}N\,Na\,O_3$: 362.1727 $[M + Na]^+$; found 362.1720.

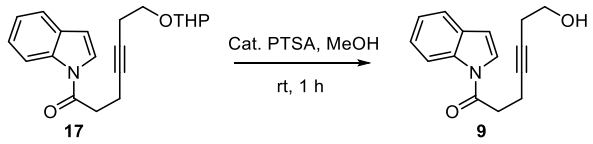


1-(1*H*-Indol-1-yl)-8-((tetrahydro-2*H*-pyran-2-yl)oxy)oct-4-yn-1-one (17s): Following the procedure, the coupling of indole **12a** (244 mg, 2.08 mmol) and acid **13a** (200 mg, 0.83 mmol) gave compound **17s** (117 mg, 41%) as a colourless oil. R_f = 0.5 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45–1.61 (m, 4H), 1.66–1.85 (m, 4H), 2.22–2.31 (m, 2H), 2.70 (tt, *J* = 7.8, 2.3 Hz, 2H), 3.14 (dd, *J* = 8.2, 6.6 Hz, 2H), 3.41–3.53 (m, 2H), 3.79 (dt, *J* = 9.7, 3.3 Hz, 1H), 3.6 (tt, *J* = 11.2, 3.2 Hz, 1H), 4.57 (t, *J* = 3.4 Hz, 1H), 6.66 (d, *J* = 3.7 Hz, 1H), 7.24–7.32 (m, 1H), 7.33–7.40 (m, 1H), 7.48 (d, *J* = 3.8 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 15.6 (t), 19.5 (t), 25.4 (t), 29.0 (t), 30.7 (t), 35.5 (t), 62.2 (t), 66.0 (t), 78.2 (s), 80.9 (s), 98.8 (d), 109.3 (d), 116.6 (d), 120.8 (d), 123.7 (d), 124.4



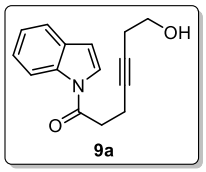
(d), 125.2 (d), 130.3 (s), 135.6 (s), 169.8 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{25}N$ Na O_3: 362.1727 $[M + Na]^+$; found 362.1717.

General Procedure for the Deprotection of –OTHP Group

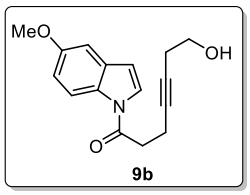


A solution of alkyne **17** and *p*TSA (0.1 equiv) in MeOH (5 mL) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography to afford alkynol **9**.

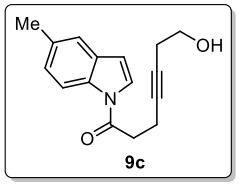
7-Hydroxy-1-(1*H*-indol-1-yl)hept-4-yn-1-one (**9a**)**:** Prepared from alkyne **17a** (100 mg, 0.30 mmol). Colourless solid (64 mg, 86%); R_f = 0.4 (40% ethyl acetate in petroleum ether); mp: 84–86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.04 (br. s., 1H), 2.44 (dt, *J* = 6.1, 2.0 Hz, 2H), 2.70–2.79 (dt, *J* = 7.1, 2.0 Hz, 2H), 3.17 (t, *J* = 7.1 Hz, 2H), 3.70 (t, *J* = 6.0 Hz, 2H), 6.68 (d, *J* = 3.7 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.48 (d, *J* = 3.7 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 8.48 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4 (t), 23.12 (t), 35.3 (t), 61.2 (t), 78.1 (s), 80.3 (s), 109.5 (d), 116.6 (d), 120.9 (d), 123.8 (d), 124.3 (d), 125.3 (d), 130.3 (s), 135.6 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{16}NO_2$: 242.1176 $[M + H]^+$; found 242.1173.



7-Hydroxy-1-(5-methoxy-1*H*-indol-1-yl)hept-4-yn-1-one (**9b**)**:** Prepared from alkyne **17b** (100 mg, 0.28 mmol). Colourless solid (62 mg, 81%); R_f = 0.3 (40% ethyl acetate in petroleum ether); mp: 114–116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.91 (br. s., 1H), 2.43 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.72 (tt, *J* = 7.2, 2.3 Hz, 2H), 3.13 (t, *J* = 7.2 Hz, 2H) 3.68 (dd, *J* = 4.2, 1.0 Hz, 2H), 3.87 (s, 3H), 6.59 (dd, *J* = 3.7, 0.6 Hz, 1H), 6.97 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 3.7 Hz, 1H), 8.36 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5 (t), 23.2 (t), 35.0 (t), 55.7 (q), 61.2 (t), 78.1 (s), 80.4 (s), 103.7 (d), 109.3 (d), 113.6 (d), 117.3 (d), 124.9 (d), 130.3 (s), 131.3 (s), 156.5 (s), 169.3 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}N$ Na O_3: 294.1101 $[M + Na]^+$; found 294.1106.

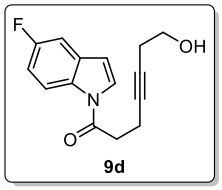


7-Hydroxy-1-(5-methyl-1*H*-indol-1-yl)hept-4-yn-1-one (**9c**)**:** Prepared form alkyne **17c** (98 mg, 0.27 mmol). Colourless solid (60 mg, 80%); R_f = 0.3 (40% ethyl acetate in petroleum ether); mp: 94–96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.94 (br. s., 1H), 2.42 (tt, *J* = 6.1, 2.38 Hz, 2H), 2.45 (s, 3H), 2.72 (tt, *J* = 7.5, 2.3 Hz, 2H), 3.14 (t, *J* = 7.3 Hz, 2H), 3.69 (dd, *J* = 11.3, 6.0 Hz, 2H), 6.55–6.62 (dd, *J* = 3.8, 0.6 Hz, 1H), 7.18 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.36 (t, *J* = 0.7 Hz, 1H) 7.43 (d, *J* = 3.7 Hz, 1H) 8.32 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4 (t), 21.3 (q), 23.2 (t), 35.2 (t), 61.2 (t), 78.1 (s), 80.4 (s), 109.3 (d), 116.2 (d), 120.8 (d), 124.4 (d), 126.6 (d), 130.6 (s), 133.4 (s), 133.8 (s), 169.5 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}N\,Na\,O_2$: 278.1152 $[M + Na]^+$; found 278.1159.



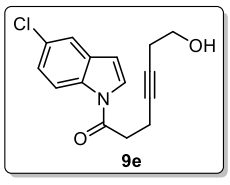
9c

1-(5-Fluoro-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (**9d**)**:** Prepared from alkyne **17d** (100 mg, 0.29 mmol). Colourless solid (58 mg, 76%); R_f = 0.2 (40% ethyl acetate in petroleum ether); mp: 94–96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.91 (t, *J* = 5.8 Hz, 1H), 2.43 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.73 (tt, *J* = 7.3, 2.3 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 3.64–3.73 (m, 2H), 6.63 (dd, *J* = 3.7, 0.6 Hz, 1H), 7.09 (td, *J* = 9.1, 2.6 Hz, 1H), 7.22 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.50 (d, *J* = 3.8 Hz, 1H), 8.43 (dd, *J* = 9.1, 4.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4 (t), 23.1 (t), 35.1 (t), 61.2 (t), 78.2 (s), 80.2 (s), 106.4 (dd, $J_{C\text{-}F}$ = 24.4 Hz), 109.1 (dd, $J_{C\text{-}F}$ = 3.8 Hz), 112.0 (dd, $J_{C\text{-}F}$ = 24.4 Hz), 117.6 (dd, $J_{C\text{-}F}$ = 9.1 Hz), 125.8 (s), 131.2 (sd, $J_{C\text{-}F}$ = 7.6 Hz), 132.0 (s), 159.7 (sd, $J_{C\text{-}F}$ = 240.3 Hz), 169.5 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ –119.12 ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NFNaO_2$: 282.0901 $[M + Na]^+$; found 282.0908.



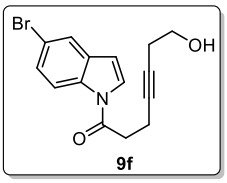
9d

1-(5-Chloro-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (**9e**)**:** Prepared from alkyne **17e** (100 mg, 0.27 mmol). Pale yellow solid (64 mg, 83%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 106–108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.93 (br. s., 1H), 2.42 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.72 (tt, *J* = 7.1, 2.3 Hz, 2H), 3.14 (t, *J* = 7.1 Hz, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 6.61 (d, *J* = 3.7 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.49 (d, *J* = 3.7 Hz, 1H), 7.54 (t, *J* = 2.1 Hz, 1H), 8.40 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.1 (t), 61.2 (t), 78.3 (s), 80.1 (s), 108.7 (d), 117.6 (d), 120.5 (d), 125.4 (d), 125.5 (d), 129.4 (s), 131.5 (s), 133.9 (s), 169.6 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NClNaO_2$: 298.0605 $[M + Na]^+$; found 298.0614.

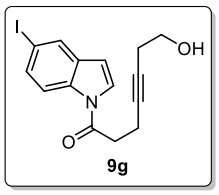


9e

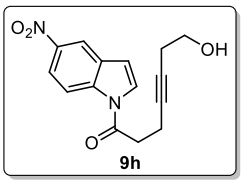
1-(5-Bromo-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (**9f**)**:** Prepared from alkyne **17f** (100 mg, 0.24 mmol). Pale brown solid (66 mg, 83%); R_f = 0.2 (40% ethyl acetate in petroleum ether); mp: 108–110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.93 (br. s., 1H), 2.42 (tt, *J* = 6.0, 2.3 Hz, 2H), 2.72 (tt, *J* = 7.1, 2.3 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 6.60 (d, *J* = 3.8 Hz, 1H), 7.41–7.50 (m, 2H), 7.70 (d, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.2 (t), 61.2 (t), 78.3 (s), 80.1 (s), 108.6 (d), 117.1 (s), 118.0 (d), 123.5 (d), 125.4 (d), 128.1 (d), 132.0 (s), 134.3 (s), 169.6 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NBrNaO_2$: 342.0100 $[M + Na]^+$; found 342.0112.



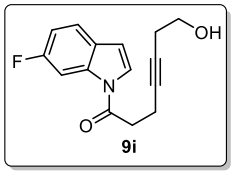
7-Hydroxy-1-(5-iodo-1*H*-indol-1-yl)hept-4-yn-1-one (**9g**)**:** Preapred from alkyne **17g** (100 mg, 0.22 mmol). Pale brown solid (59 mg, 72%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 112–114 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.86 (br. s., 1H), 2.43 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.72 (tt, *J* = 7.5, 2.3 Hz, 2H), 3.14 (t, *J* = 7.1 Hz, 2H), 3.69 (dd, *J* = 11.0, 4.8 Hz, 2H), 6.59 (dd, *J* = 3.8, 0.5 Hz, 1H), 7.44 (d, *J* = 3.8 Hz, 1H), 7.64 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.92 (d, *J* = 1.5 Hz, 1H), 8.24 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.2 (t), 61.12 (t), 80.1 (s), 88.0 (s), 108.4 (d), 118.4 (d), 125.1 (d), 129.8 (d), 132.6 (s), 133.8 (d, 2C), 134.9 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NINaO_2$: 389.9961 $[M + Na]^+$; found 389.9974.



7-Hydroxy-1-(5-nitro-1*H*-indol-1-yl)hept-4-yn-1-one (**9h**)**:** Prepared from alkyne **17h** (100 mg, 0.27 mmol). Pale yellow solid (62 mg, 80%); R_f = 0.1 (40% ethyl acetate in petroleum ether); mp: 118–120 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.43 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.74 (tt, *J* = 7.2, 2.3 Hz, 2H), 3.19 (t, *J* = 7.1 Hz, 2H), 3.69 (t, *J* = 6.1 Hz, 2H), 6.82 (d, *J* = 3.8 Hz, 1H), 7.64 (d, *J* = 3.8 Hz, 1H), 8.25 (dd, *J* = 9.1, 2.3 Hz, 1H), 8.49 (d, *J* = 2.2 Hz, 1H), 8.59 (d, *J* = 9.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2 (t), 23.1 (t), 35.3 (t), 61.1 (t), 78.5 (s), 79.8 (s), 109.8 (d), 116.8 (d), 117.1 (d), 120.5 (d), 127.2 (d), 130.2 (s), 138.5 (s), 144.3 (s), 169.9 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}N_2NaO_4$: 309.0846 $[M + Na]^+$; found 309.0853.



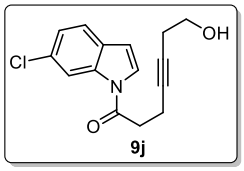
1-(6-Fluoro-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (**9i**)**:** Prepared from alkyne **17i** (100 mg, 0.29 mmol). Pale yellow solid (53 mg, 70%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 96–98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.43 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.67–2.76



9i

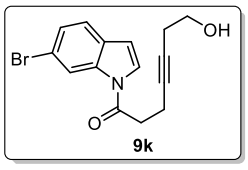
(m, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 3.69 (t, *J* = 6.1 Hz, 2H), 6.63 (dd, *J* = 3.7, 0.6 Hz, 1H), 7.04 (td, *J* = 8.8, 2.5 Hz, 1H), 7.44 (d, *J* = 3.8 Hz, 1H), 7.48 (dd, *J* = 8.6, 5.3 Hz, 1H), 8.22 (dd, *J* = 10.3, 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.1 (t), 61.1 (t), 78.2 (s), 80.1 (s), 104.1(dd, , $J_{C\text{-}F}$ = 28.9 Hz), 109.2 (d), 111.9 (dd, , $J_{C\text{-}F}$ = 24.4 Hz), 121.3 (dd, , $J_{C\text{-}F}$ = 9.9 Hz), 124.5 (dd, , $J_{C\text{-}F}$ = 3.8 Hz), 126.4 (s), 135.6 (dd, , $J_{C\text{-}F}$ = 12.9 Hz), 161.3 (dd, , $J_{C\text{-}F}$ = 241.0 Hz), 169.8 (s) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –116.19 ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}FNNaO_2$: 282.0901 $[M + Na]^+$; found 282.0892.

1-(6-Chloro-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (**9j**)**:** Prepared from alkyne **17j** (100 mg, 0.27 mmol). Colourless solid (65 mg, 84%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 102–104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.96 (br. s., 1H), 2.44 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.69–2.77 (m, 2H), 3.14 (t, *J* = 7.1 Hz, 2H), 3.66–3.75 (m, 2H), 6.64 (d, *J* = 3.8 Hz, 1H), 7.28 (dd, *J* = 1.7, 8.2 Hz, 1H), 7.44–7.50 (m, 2H), 8.54 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3(t), 23.1 (t), 35.2 (t), 61.2 (t), 78.2 (s), 80.1 (s), 109.1 (d), 116.9 (d), 121.5 (d), 124.4 (d), 124.8 (d), 128.7 (s), 131.2 (s), 135.8 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NClNaO_2$: 298.0605 $[M + Na]^+$; found 298.0611.



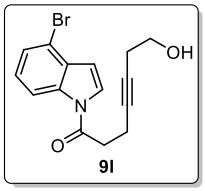
9j

1-(6-Bromo-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (**9k**)**:** Preapred from alkyne **17k** (100 mg, 0.24 mmol). Colourless solid (68 mg, 85%); R_f = 0.6 (40% ethyl acetate in petroleum ether); mp: 116–118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.43 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.71 (ddt, *J* = 7.7, 6.7, 2.3 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 3.69 (t, *J* = 6.1 Hz, 2H), 6.63 (dd, *J* = 3.8, 0.6 Hz, 1H), 7.37–7.45 (m, 3H), 8.69 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.1 (t), 61.2 (t), 78.2 (s), 80.1 (s), 109.2 (d), 119.0 (s), 119.7 (d), 121.9 (d), 124.7 (d), 127.1 (d), 129.0 (s), 136.1 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NBrNaO_2$: 342.0100 $[M + Na]^+$; found 342.0090.



9k

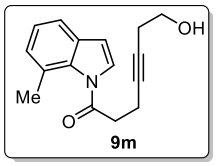
1-(4-Bromo-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (**9l**)**:** Prepared from alkyne **17l** (100 mg, 0.24 mmol). Colourless solid (65 mg, 82%); R_f = 0.3 (40% ethyl acetate in petroleum ether); mp: 90–92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.96 (br. s., 1H), 2.44 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.74 (tt, *J* = 7.1, 2.3 Hz, 2H), 3.17 (t, *J* = 7.2 Hz, 2H), 3.65–3.72 (m, 2H), 6.75 (dd, *J* = 3.3, 0.5 Hz, 1H), 7.24 (t, *J* = 8.0 Hz,



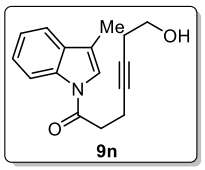
9l

1H) 7.47 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.53 (d, *J* = 3.7 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.3 (t), 23.1 (t), 35.3 (t), 61.2 (t), 78.3 (s), 80.1 (s), 109.2 (d), 114.6 (s), 115.6 (d), 124.8 (d), 126.3 (d), 126.7 (d), 131.0 (s), 135.9 (s), 169.8 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{15}NBrO_2$: 320.0281 $[M + H]^+$; found 320.0288.

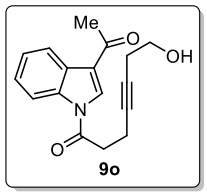
7-Hydroxy-1-(7-methyl-1*H*-indol-1-yl)hept-4-yn-1-one (**9m**)**:** Prepared from alkyne **17m** (100 mg, 0.29 mmol). Colourless solid (61 mg, 81%); R_f = 0.4 (40% ethyl acetate in petroleum ether); mp: 92–94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.34 (tt, *J* = 6.2, 2.2 Hz, 2H), 2.49 (s, 3H), 2.65 (tt, *J* = 7.1, 2.3 Hz, 2H), 3.08 (t, *J* = 7.0 Hz, 2H), 3.60 (t, *J* = 6.1 Hz, 2H), 6.57 (d, *J* = 3.8 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H) 7.33 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 3.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 15.1 (t), 22.6 (q), 23.1 (t), 36.0 (t), 61.2 (t), 78.2 (s), 80.2 (s), 109.3 (d), 118.5 (d), 124.2 (d), 125.7 (d), 126.7 (s), 128.3 (d), 131.9 (s), 135.1 (s), 169.1 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1142.



7-Hydroxy-1-(3-methyl-1*H*-indol-1-yl)hept-4-yn-1-one (**9n**)**:** Prepared from alkyne **17n** (100 mg, 0.29 mmol). Colourless solid (57 mg, 75%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 177 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.96 (t, *J* = 6.0 Hz, 1H), 2.30 (d, *J* = 1.3 Hz, 3H), 2.43 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.71 (tt, *J* = 7.5, 2.3 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 3.70 (dd, *J* = 11.8, 5.8 Hz, 2H), 7.23 (s, 1H), 7.31 (td, *J* = 7.4, 1.1 Hz, 1H), 7.37 (td, *J* = 7.7, 1.4 Hz, 1H), 7.51 (dq, *J* = 7.6, 0.7 Hz, 1H), 8.44 (d, *J* = 7.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 9.71 (q), 14.41 (t), 23.16 (t), 35.31 (t), 61.20 (t), 78.05 (s), 80.49 (s), 116.61 (d), 118.77 (s), 118.84 (d), 121.25 (d), 123.53 (d), 125.31 (d), 131.33 (s), 135.87 (s), 169.31 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1158.

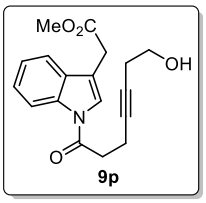


1-(3-Acetyl-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (**9o**)**:** Preapred from alkyne **17o** (100 mg, 0.27 mmol). Pale brown solid (59 mg, 76%); R_f = 0.2 (50% ethyl acetate in petroleum ether); mp: 116–118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.44 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.61 (s, 3H), 2.77 (tt, *J* = 7.5, 2.3 Hz, 2H), 3.24 (dd, *J* = 6.8, 1.0 Hz, 2H), 3.70 (t, *J* = 6.1 Hz, 2H), 7.37–7.47 (m, 2H), 8.11 (s, 1H), 8.33–8.37 (m, 1H), 8.39–8.44 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.3 (t), 23.1 (t), 28.0 (q), 35.4 (t), 61.1 (t), 78.5 (s), 79.8 (s), 116.2 (d), 122.1 (s), 122.5 (d), 125.3 (d), 126.4 (d), 127.2 (s),

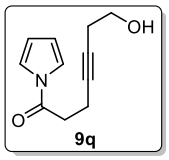


130.3 (d), 136.1 (s), 169.9 (s), 193.7 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{18}NO_2$: 290.1176 $[M + H]^+$; found 290.1174.

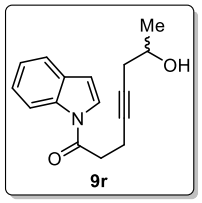
Methyl 2-(1-(7-hydroxyhept-4-ynoyl)-1*H*-indol-3-yl)acetate (9p): Prepared from alkyne **17p** (100 mg, 0.25 mmol). Colourless solid (59 mg, 75%); R_f = 0.1 (40% ethyl acetate in petroleum ether); mp: 82–84 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.05 (br. s., 1H), 2.42 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.71 (tt, *J* = 7.1, 2.3 Hz, 2H), 3.14 (t, *J* = 7.1 Hz, 2H), 3.68 (d, *J* = 4.2 Hz, 2H), 3.75 (s, 5H), 7.31 (td, *J* = 7.6, 1.0 Hz, 1H), 7.39 (td, *J* = 8.3, 1.2 Hz, 1H), 7.50–7.55 (m, 2H), 8.46 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4 (t), 23.1 (t), 30.7 (t), 35.3 (t), 52.2 (q), 61.2 (t), 78.2 (s), 80.3 (s), 115.2 (s), 116.7 (d), 118.8 (d), 122.9 (d), 123.8 (d), 125.6 (d), 129.9 (s), 135.7 (s), 169.6 (s), 171.3 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{19}NNaO_4$: 336.1206 $[M + Na]^+$; found 336.1193.



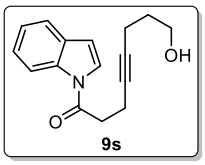
7-Hydroxy-1-(1*H*-pyrrol-1-yl)hept-4-yn-1-one (9q): Prepared from alkyne **17q** (94 mg, 0.34 mmol). Pale brown solid (56 mg, 80%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 62–64 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.85 (br. s., 1H), 2.42 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.66 (tt, *J* = 7.5, 2.3 Hz, 2H), 3.06 (dd, *J* = 7.0, 1.3 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 6.32 (t, *J* = 2.3 Hz, 2H), 7.33 (br. s., 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 34.1 (t), 61.2 (t), 78.1 (s), 80.10 (s), 113.3 (d, 2C), 119.0 (d, 2C), 168.9 (s) ppm; **HRMS** (ESI) calcd for $C_{11}H_{13}NNaO_2$: 214.0838 $[M + Na]^+$; found 214.0846.



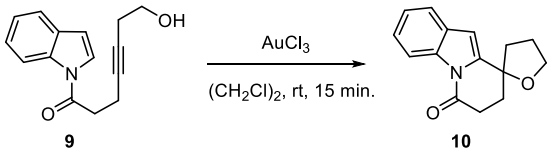
7-Hydroxy-1-(1*H*-indol-1-yl)oct-4-yn-1-one (9r): Prepared from alkyne **17r** (100 mg, 0.29 mmol). Colourless solid (72 mg, 96%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 104–106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.1 Hz, 2H), 2.11 (br. s., 1H), 2.24–2.31 (m, 1H), 2.33–2.40 (m, 1H), 2.73 (tt, *J* = 7.2, 2.4 Hz, 2H), 3.16 (t, *J* = 7.0 Hz, 2H), 3.91 (sext, *J* = 6.1 Hz, 1H), 6.67 (d, *J* = 3.4 Hz, 1H), 7.26–7.32 (m, 1H), 7.37 (td, *J* = 8.3, 1.1 Hz, 1H), 7.47 (d, *J* = 3.4 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 8.47 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4 (t), 22.2 (q), 29.4 (t), 35.3 (t), 66.4 (d), 77.9 (s), 80.8 (s), 109.5 (d), 116.6 (d), 120.9 (d), 123.8 (d), 124.3 (d), 125.3 (d), 130.3 (s), 135.6 (s), 169.7 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 [$M + Na]^+$; found 278.1141.



8-hydroxy-1-(1*H*-indol-1-yl)oct-4-yn-1-one (**9s**)**:** Prepared from alkyne **17s** (100 mg, 0.29 mmol). Pale yellow solid (64 mg, 85%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 84–86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65 (br. s., 1H), 1.74 (quin, *J* = 6.5 Hz, 2H), 2.29 (tt, *J* = 6.9, 2.3 Hz, 2H), 2.72 (tt, *J* = 7.3, 2.3 Hz, 2H), 3.15 (t, *J* = 7.0 Hz, 2H), 3.74 (t, *J* = 6.1 Hz, 2H), 6.68 (d, *J* = 3.7 Hz, 1H), 7.27–7.34 (m, 1H), 7.38 (td, *J* = 8.3, 1.2 Hz, 1H), 7.49 (d, *J* = 3.8 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 8.49 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4 (t), 15.3 (t), 31.3 (t), 35.4 (t), 61.8 (t), 78.7 (s), 80.7 (s), 109.4 (d), 116.6 (d), 120.9 (d), 123.8 (d), 124.4 (d), 125.2 (d), 130.3 (s), 135.6 (s), 169.8 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1143.

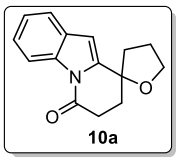


General Procedure for the Gold-Catalysed Spirocyclisation-Hydroarylation

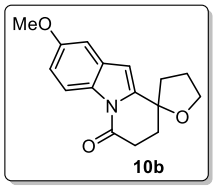


At rt, a solution of alkynol **9** (30 mg) in $(CH_2Cl)_2$ (3 mL) was stirred for 15 min. in presence of $AuCl_3$ (5 mol%). After completion of the reaction, it was concentrated under reduced pressure, purified by column chromatography to afford spiro-indolopyridones **10**.

4,5,7',8'-Tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (**10a**)**:** Colourless solid (28 mg, 93%); R_f = 0.6 (40% ethyl acetate in petroleum ether); mp: 92–94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.06 (tt, *J* = 8.8, 3.1 Hz, 1H), 2.11–2.20 (m, 1H), 2.20–2.31 (m, 3H), 2.47 (ddd, *J* = 12.1, 8.2, 5.5 Hz, 1H), 2.79 (dt, *J* = 17.6, 5.1 Hz, 1H), 3.17 (ddd, *J* = 17.6, 9.9, 5.7 Hz, 1H), 3.99 (td, *J* = 6.8, 1.0 Hz, 2H), 6.51 (d, *J* = 0.5 Hz, 1H), 7.24–7.30 (m, 1H), 7.34 (td, *J* = 7.2, 1.3 Hz, 1H), 7.53 (ddd, *J* = 7.6, 1.3, 0.8 Hz, 1H), 8.49 (dd, *J* = 8.2, 1.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.9 (t), 31.4 (t), 33.8 (t), 36.1 (t), 67.4 (t), 77.66 (s), 104.8(d), 116.6 (d), 120.4 (d), 124.0 (d), 125.0 (d), 129.0 (s), 135.2 (s), 141.5 (s), 169.1 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{16}NNaO_2$: 242.1176 $[M + H]^+$; found 242.1174.

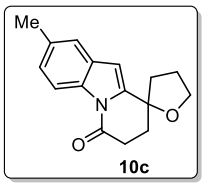


2'-Methoxy-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (**10b**)**:** Colourless solid (22.3 mg, 74%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 82–84 °C;

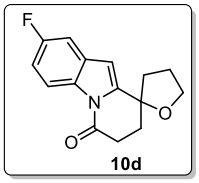


^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.09 (m, 1H), 2.09–2.20 (m, 2H), 2.20–2.27 (m, 2H), 2.44 (ddd, *J* = 12.1, 8.2, 5.6 Hz, 1H), 2.77 (dt, *J* = 17.6, 5.1 Hz, 1H), 3.13 (ddd, *J* = 17.5, 9.8, 5.7 Hz, 1H), 3.85 (s, 3H), 3.98 (t, *J* = 6.6 Hz, 2H), 6.44 (d, *J* = 0.6 Hz, 1H), 6.93 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 8.36 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.9 (t), 31.2 (t), 33.9 (t), 36.1 (t), 55.6 (q), 67.4 (t), 77.7 (s), 103.5 (d), 104.6 (d), 113.1 (d), 117.3 (d), 129.9 (s), 130.1 (s), 142.2 (s), 156.7 (s), 168.7 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}NNaO_3$: 294.1101 $[M + Na]^+$; found 294.1108.

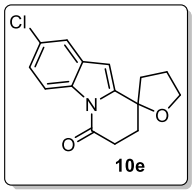
2'-Methyl-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10c): Colourless syrup (24 mg, 80%); R_f = 0.5 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.04 (ddd, *J* = 12.0, 6.5, 2.1 Hz, 1H), 2.09–2.17 (m, 1H), 2.17–2.27 (m, 3H), 2.40–2.49 (m, 4H), 2.77 (dt, *J* = 17.6, 5.2 Hz, 1H), 3.14 (ddd, *J* = 17.5, 9.9, 5.7 Hz, 1H), 3.98 (td, *J* = 6.8, 0.7 Hz, 2H), 6.4 (d, *J* = 0.6 Hz, 1H), 7.15 (ddd, *J* = 8.3, 1.7, 0.5 Hz, 1H), 7.30 (dd, *J* = 1.5, 0.7 Hz, 1H), 8.34 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4 (q), 25.9 (t), 31.3 (t), 33.8 (t), 36.1 (t), 67.4 (t), 77.7 (s), 104.6 (d), 116.1 (d), 120.4 (d), 126.3 (d), 129.2 (s), 133.4 (s), 133.5 (s), 141.5 (s), 168.9 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1158.



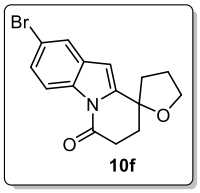
2'-Fluoro-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10d): Colourless solid (25.9 mg, 86%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 68–70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.10 (ddd, *J* = 11.5, 5.0, 1.6 Hz, 1H), 2.12–2.19 (m, 1H), 2.19–2.29 (m, 3H), 2.45 (ddd, *J* = 11.8, 5.3, 1.7 Hz, 1H), 2.79 (dt, *J* = 17.7, 5.2 Hz, 1H), 3.15 (ddd, *J* = 17.6, 9.9, 5.6 Hz, 1H), 3.95 (td, *J* = 6.8, 1.6 Hz, 2H), 6.47 (d, *J* = 0.6 Hz, 1H), 7.05 (td, *J* = 9.1, 2.6 Hz, 1H), 7.17 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.43 (dd, *J* = 9.0, 4.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.9 (t), 31.23 (t), 33.8 (t), 36.1 (t), 67.5 (t), 77.6 (s), 104.4 (dd, $J_{C\text{-}F}$ = 3.81 Hz), 106.0 (dd, $J_{C\text{-}F}$ = 23.65 Hz), 112.5 (dd, $J_{C\text{-}F}$ = 24.41 Hz), 117.5 (dd, $J_{C\text{-}F}$ = 9.16 Hz), 130.1 (sd, $J_{C\text{-}F}$ = 9.92 Hz), 131.6 (s), 143.2 (s), 159.9 (dd, $J_{C\text{-}F}$ = 239.56 Hz), 168.8 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ –118.85 ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NFNaO_2$: 282.0901 $[M + Na]^+$; found 282.0907.



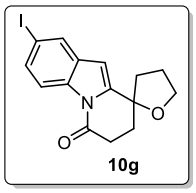
2'-Chloro-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10e): Colourless solid (20 mg, 66%); R_f = 0.6 (40% ethyl acetate in petroleum ether); mp: 90–92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.04–2.12 (m, 1H), 2.12–2.18 (m, 1H), 2.19–2.30 (m, 3H), 2.39–2.49 (m, 1H), 2.79 (dt, *J* = 17.7, 5.1 Hz, 1H), 3.16 (ddd, *J* = 17.6, 9.9, 5.6 Hz, 1H), 3.93–4.03 (m, 2H), 6.45 (s, 1H), 7.27–7.32 (m, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.9 (t), 31.3 (t), 33.8 (t), 36.1 (t), 67.5 (t), 77.6 (s), 103.9 (d), 117.5 (d), 120.1 (d), 125.1 (d), 129.5 (s), 130.3 (s), 133.6 (s), 143.0 (s), 168.9 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NClNaO_2$: 298.0605 $[M + Na]^+$; found 298.0615.



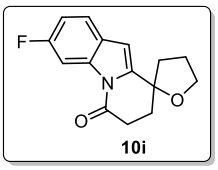
2'-Bromo-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10f): Colourless solid (22 mg, 73%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 92–94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.02–2.11 (m, 1H), 2.11–2.19 (m, 1H), 2.19–2.29 (m, 3H), 2.39–2.48 (m, 1H), 2.79 (dt, *J* = 17.7, 5.2 Hz, 1H), 3.15 (ddd, *J* = 17.7, 9.8, 5.6 Hz, 1H), 3.92–4.03 (m, 2H), 6.44 (s, 1H), 7.42 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.9 (t), 31.3 (t), 33.7 (t), 36.1 (t), 67.5 (t), 77.5 (s), 103.8 (d), 117.2 (s), 117.9 (d), 123.1 (d), 127.8 (d), 130.8 (s), 133.9 (s), 142.8 (s), 169.0 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NBrNaO_2$: 342.0100 $[M + Na]^+$; found 342.0110.



2'-Iodo-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10g): Colourless syrup (23.3 mg, 77%); R_f = 0.4 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.03–2.11 (m, 1H), 2.11–2.18 (m, 1H), 2.18–2.27 (m, 3H), 2.44 (ddd, *J* = 12.4, 8.2, 5.7 Hz, 1H), 2.78 (dt, *J* = 17.6, 5.2 Hz, 1H), 3.15 (ddd, *J* = 17.6, 10.0, 5.5 Hz, 1H), 3.93–4.02 (m, 2H), 6.42 (s, 1H), 7.60 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.86 (d, *J* = 1.5 Hz, 1H), 8.24 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 25.9 (t), 31.3 (t), 33.7 (t), 36.1 (t), 67.5 (t), 77.5 (s), 88.1 (s), 103.6 (d), 118.3 (d), 129.3 (d), 131.3 (s), 133.5 (d), 134.5 (s), 142.5 (s), 169.0 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{15}NIO_2$: 368.0142 $[M + H]^+$; found 368.0155.

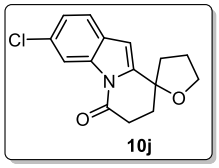


3'-Fluoro-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10i): Colourless syrup (27 mg, 90%); R_f = 0.5 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.01–2.10 (m, 1H), 2.10–2.18 (m, 1H), 2.18–2.27 (m, 3H), 2.45 (ddd, *J* = 12.2,

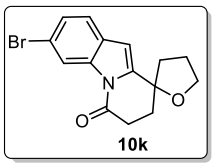


8.2, 5.8 Hz, 1H), 2.78 (dt, *J* = 17.6, 5.0 Hz, 1H), 3.16 (ddd, *J* = 17.5, 10.0, 6.0 Hz, 1H), 3.92–4.03 (m, 2H), 6.48 (s, 1H), 7.02 (td, *J* = 8.9, 2.4 Hz, 1H), 7.43 (dd, *J* = 8.5, 5.3 Hz, 1H), 8.22 (dd, *J* = 10.1, 2.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 25.9 (t), 31.2 (t), 33.7 (t), 36.0 (t), 67.4 (t), 77.5 (s), 104.0 (dd, $J_{C\text{-}F}$ = 28.2 Hz), 104.3 (d), 112.1 (dd, $J_{C\text{-}F}$ = 24.4 Hz), 120.9 (dd, $J_{C\text{-}F}$ = 9.9 Hz), 125.2 (sd, $J_{C\text{-}F}$ = 1.5 Hz), 135.2 (sd, $J_{C\text{-}F}$ = 12.9 Hz), 141.8 (sd, $J_{C\text{-}F}$ = 3.8 Hz), 161.1 (sd, $J_{C\text{-}F}$ = 240.3 Hz), 169.14 (s) ppm; **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* –116.47 ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NFNaO_2$: 282.0901 $[M + Na]^+$; found 282.0890.

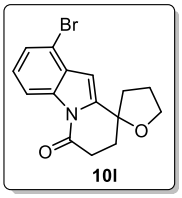
3'-Chloro-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10j): Colourless oil (27 mg, 90%); ; R_f = 0.6 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 2.06 (dt, *J* = 8.7, 2.2 Hz, 1H), 2.10–2.18 (m, 1H), 2.18–2.27 (m, 3H), 2.45 (ddd, *J* = 12.4, 8.2, 5.7 Hz, 1H), 2.79 (dt, *J* = 17.6, 5.1 Hz, 1H), 3.15 (ddd, *J* = 17.6, 10.2, 5.7 Hz, 1H), 3.93–4.02 (m, 2H), 6.47 (s, 1H), 7.24 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 8.52 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 25.9 (t), 31.2 (t), 33.7 (t), 36.0 (t), 67.5 (t), 77.5 (s), 104.3 (d), 116.7 (d), 121.1 (d), 124.5 (d), 127.5 (s), 130.8 (s), 135.4 (s), 142.2 (s), 169.0 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NClNaO_2$: 298.0605 $[M + Na]^+$; found 298.0609.



3'-Bromo-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10k): Pale yellow solid (23 mg, 76%); R_f = 0.6 (40% ethyl acetate in petroleum ether); mp: 74–76 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.02–2.11 (m, 1H), 2.12–2.18 (m, 1H), 2.18–2.28 (m, 3H), 2.45 (dd, *J* = 6.6, 2.5 Hz, 1H), 2.79 (dt, *J* = 17.6, 5.1 Hz, 1H), 3.16 (ddd, *J* = 17.6, 10.0, 5.8 Hz, 1H), 3.93–4.02 (m, 2H), 6.47 (s, 1H), 7.34–7.42 (m, 2H), 8.68 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 25.9 (t), 31.3 (t), 33.7 (t), 36.1 (t), 67.5 (t), 77.5 (s), 104.4 (d), 118.5 (s), 119.6 (d), 121.5 (d), 127.2 (d), 127.9 (s), 135.8 (s), 142.1 (s), 169.0 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{15}BrNO_2$: 320.0281 $[M + H]^+$; found 320.0278.

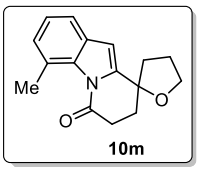


1'-Bromo-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10l): Colourless oil (17.8 mg, 59%); R_f = 0.6 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.04–2.20 (m, 2H), 2.20–2.31

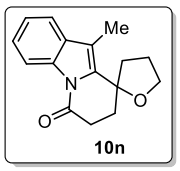


(m, 3H), 2.50 (ddd, *J* = 12.3, 5.8, 1.7 Hz, 1H), 2.80 (dt, *J* = 17.7, 5.1 Hz, 1H), 3.12–3.23 (m, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 6.58 (s, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.3 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 26.0 (t), 31.3 (t), 33.8 (t), 36.1 (t), 67.6 (t), 77.5 (s), 104.5 (t), 114.4 (s), 115.6 (d), 126.1 (d), 126.9 (d), 129.7 (s), 135.5 (s), 142.3 (s), 169.2 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}NBrNaO_2$: 342.0100 $[M + Na]^+$; found 342.0110.

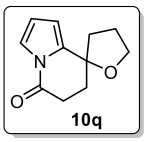
4'-Methyl-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10m): Colourless oil (23 mg, 76%); R_f = 0.6 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.01–2.17 (m, 2H), 2.17–2.30 (m, 3H), 2.40–2.50 (m, 1H), 2.63 (s, 3H), 2.81 (dt, *J* = 16.8, 5.5 Hz, 1H), 3.16 (ddd, *J* = 16.8, 9.8, 5.6 Hz, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 6.51 (s, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 23.0 (q), 25.8 (t), 32.2 (t), 34.3 (t), 36.2 (t), 67.5 (t), 78.4 (s), 105.7 (d), 118.1 (d), 124.5 (d), 127.1 (s), 128.3 (d), 130.8 (s), 135.3 (s), 143.2 (s), 168.6 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1141.



10'-Methyl-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-*a*]indol]-6'-one (10n): Pink syrup (22.5 mg, 75%); R_f = 0.5 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.08 (dt, *J* = 13.0, 4.85 Hz, 1H), 2.13–2.23 (m, 3H), 2.23–2.33 (m, 2H), 2.36 (s, 3H), 2.76 (ddd, *J* = 17.5, 12.1, 5.0 Hz, 1H), 2.94 (dt, *J* = 17.6, 4.7 Hz, 1H), 4.04 (ddd, *J* = 6.8, 5.6, 1.3 Hz, 1H), 4.15–4.23 (m, 1H), 7.34 (ddd, *J* = 7.2, 2.6, 1.3 Hz, 2H), 7.48 (ddd, *J* = 2.6, 1.5, 0.6 Hz, 1H), 8.48 (ddd, *J* = 2.3, 1.7, 0.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 8.9 (q), 26.3 (t), 31.8 (t), 34.0 (t), 36.8 (t), 68.0 (t), 80.3 (s), 113.8 (s), 116.4 (d), 118.2 (d), 123.8 (d), 125.0 (d), 131.4 (s), 134.3 (s), 136.1 (s), 168.5 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{17}NNaO_3$: 278.1152 $[M + Na]^+$; found 278.1159.

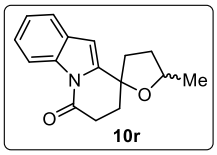


4,5,6',7'-Tetrahydro-3*H*,5'*H*-spiro[furan-2,8'-indolizin]-5'-one (10q): Colourless syrup (25.2 mg, 83%); R_f = 0.5 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.97 (ddd, *J* = 12.2, 6.0, 2.7 Hz, 1H), 2.03–2.13 (m, 1H), 2.13–2.21 (m, 3H), 2.39 (ddd, *J* = 12.3, 8.3, 6.5 Hz, 1H), 2.70 (dt, *J* = 17.6, 4.3 Hz, 1H), 3.10 (ddd, *J* = 9.8, 7.6, 1.7 Hz, 1H), 3.83–3.98 (m, 2H), 6.18 (dd, *J* = 3.3, 1.5 Hz, 1H), 6.24 (t, *J* = 3.3 Hz, 1H), 7.39 (dd, *J* = 3.3, 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 25.9 (t), 30.4 (t), 34.2

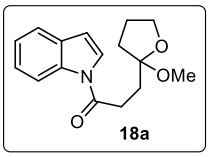


(t), 35.9 (t), 67.0 (t), 76.8 (s), 109.1 (d), 112.2 (d), 117.2 (d), 136.3 (s), 168.2 (s), ppm; **HRMS** (ESI) calcd for $C_{11}H_{13}NNaO_2$: 214.0838 $[M + Na]^+$; found 214.0846.

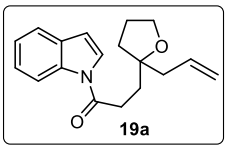
5-Methyl-4,5,7',8'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-a]indol]-6'-one (**10r**)**:** Colourless syrup (dr 1:0.3, 27 mg, 90%); R_f = 0.5 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.30 (d, *J* = 6.1 Hz, 3H), 1.39 (d, *J* = 6.1 Hz, 1H), 1.73 (ddd, *J* = 3.4, 9.1, 12.5 Hz, 1H), 1.83–1.91 (m, 0.3H), 2.09–2.19 (m, 1.77H), 2.20–2.27 (m, 2.5H), 2.27–2.34 (m, 1.45H), 2.44–2.56 (m, 1.4H), 2.80 (dt, *J* = 17.4, 4.8 Hz, 1.4H), 3.12 (ddd, *J* = 4.9, 8.0, 12.9 Hz, 0.3H), 3.23 (ddd, *J* = 17.4, 9.4, 7.0 Hz, 1H), 4.19–4.31 (m, 1.33H), 6.53 (s, 1H), 6.56 (s, 0.3H), 7.26–7.31 (m, 1.67H), 7.32–7.38 (m, 1.38H), 7.54 (d, *J* = 7.6 Hz, 1.3H), 8.47–8.53 (m, 1.3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.0 (q), 21.2 (q), 31.3 (t), 31.5 (t), 33.2 (t), 33.6 (t), 34.1 (t), 35.0 (t), 36.1 (t), 37.7 (t), 74.8 (d), 75.9 (d), 77.4 (s), 78.3 (s), 104.5 (d), 104.8 (d), 116.5 (d), 116.6 (d), 120.4 (d, 2C), 123.9 (d), 124.0 (d), 124.8 (d), 125.0 (d), 129.0 (s), 129.2 (s), 135.3 (s), 141.8 (s), 168.9 (s), 169.3 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{18}NO_2$: 256.1332 $[M + H]^+$; found 256.1326.



1-(1*H*-Indol-1-yl)-3-(2-methoxytetrahydrofuran-2-yl)propan-1-one (**18a**): Cyclization of alkynol **9a** (30 mg, 0.12 mmol) in the presence of methanol (10 μL, 0.24 mmol) provided compound **18a** (22.5 mg, 66%) as a colourless syrup. R_f = 0.5 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.68–1.73 (m, 1H), 1.81–1.91 (m, 1H), 1.92–2.02 (m, 2H), 2.11 (ddd, *J* = 6.7, 14.3, 9.0 Hz, 1H), 2.32 (ddd, *J* = 14.5, 8.9, 7.0 Hz, 1H), 2.92–2.96 (m, 2H), 3.15 (s, 3H), 3.81–3.90 (m, 2H), 6.56 (dd, *J* = 3.9, 0.5 Hz, 1H), 7.20 (td, *J* = 7.5, 1.1 Hz, 1H), 7.28 (td, *J* = 7.7, 1.3 Hz, 1H), 7.44 (d, *J* = 3.8 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.5 (t), 29.8 (t), 31.2 (t), 35.0 (t), 48.4 (q), 67.9 (t), 108.7 (s), 109.1 (d), 116.6 (d), 120.8 (d), 123.6 (d), 124.7 (d), 125.1 (d), 130.3 (s), 135.6 (s), 171.2 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{19}NNaO_3$: 296.1257 $[M + Na]^+$; found 296.1252.

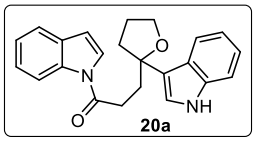


3-(2-Allyltetrahydrofuran-2-yl)-1-(1*H*-indol-1-yl)propan-1-one (**19a**): Cyclization of alkynol **1a** (30 mg, 0.12 mmol) in the presence of trimethylallyl silane (0.2 mL, 1.2 mmol) gave compound **19a** (22.2 mg, 63%)as a colourless liquid. R_f = 0.8 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.73 (dt, *J* = 12.5, 6.6 Hz, 1H), 1.84–1.92 (m, 1H), 1.92–2.00 (m, 2H), 2.05 (t, *J* = 8.0 Hz, 2H), 2.30–2.41 (m, 2H), 3.02 (dt, *J* = 13.3, 7.8 Hz, 2H), 3.87 (t,

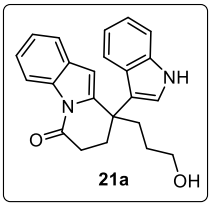


J = 6.6 Hz, 2H), 5.08–5.19 (m, 2H), 5.83 (ddt, *J* = 17.1, 10.1, 7.2 Hz, 1H), 6.65 (dd, *J* = 3.7, 0.6 Hz, 1H), 7.24–7.31 (m, 1H), 7.36 (td, *J* = 7.7, 1.3 Hz, 1H), 7.49–7.60 (m, 2H), 8.47 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.4 (t), 31.1 (t), 33.6 (t), 35.1 (t), 43.7 (t), 68.1 (t), 83.8 (s), 109.4 (d), 116.9 (d), 118.4 (t), 121.1 (d), 123.9 (d), 125.1 (d), 125.4 (d), 130.7 (s), 134.5 (d), 135.9 (s), 172.1 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{21}NNaO_2$: 306.1465 $[M + Na]^+$; found 306.1472.

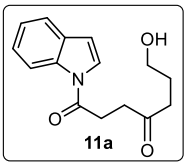
3-(2-(1*H*-Indol-3-yl)tetrahydrofuran-2-yl)-1-(1*H*-indol-1-yl)propan-1-one (**20a**): Cyclization of alkynol **1a** (30 mg, 0.12 mmol) in the presence of indole **4a** (15 mg, 0.13 mmol) gave compound **20a** as colourless syrup (32.1 mg, 72%); R_f = 0.7 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.89–2.00 (m, 1H), 2.00–2.11 (m, 1H), 2.22 (dt, *J* = 12.0, 7.8 Hz, 1H), 2.39–2.48 (m, 2H), 2.59–2.74 (m, 2H), 3.10 (tt, *J* = 12.0, 5.0 Hz, 1H), 3.97–4.06 (m, 2H), 6.51 (dd, *J* = 3.7, 0.5 Hz, 1H), 7.11–7.16 (m, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.19–7.26 (m, 2H), 7.27–7.33 (m, 2H), 7.35–7.40 (m, 1H), 7.48–7.54 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 8.07 (br. s., 1H), 8.38 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.9 (t), 31.9 (t), 35.6 (t), 38.3 (t), 67.5 (t), 83.7 (s), 108.6 (d), 111.3 (d), 116.5 (d), 119.7 (d), 120.0 (d), 120.6 (d), 120.7 (s), 121.5 (d), 122.1 (d), 123.4 (d), 124.8 (s), 124.9 (d), 124.9 (s), 130.3 (s), 135.5 (s), 137.1 (s), 172.0 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{22}N_2NaO_2$: 381.1573 $[M + Na]^+$; found 381.12585.



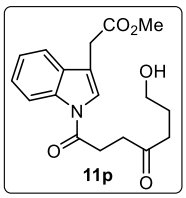
9-(3-Hydroxypropyl)-9-(1*H*-indol-3-yl)-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (**21a**): Cyclization of alkynol **1a** (30 mg, 0.12 mmol) in the presence of indole **4a** (15 mg, 0.13 mmol) in CH_3CN solvent gave compound **21a** as pale brown gum (33 mg, 74%); R_f = 0.2 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.47 –1.64 (m, 2H), 2.13 –2.31 (m, 2H), 2.34–2.49 (m, 2H), 2.69 (dt, *J* = 13.2, 4.9 Hz, 1H), 2.80 (dt, *J* = 17.7, 5.0 Hz, 1H), 3.42 (q, *J* = 6.0 Hz, 2H), 4.45 (t, *J* = 5.0 Hz, 1H), 6.56 (s, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.88–6.95 (m, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.25–7.31 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.56–7.61 (m, 1H), 8.35 (dd, *J* = 6.3, 2.0 Hz, 1H), 10.92 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 28.1 (s), 30.3 (s), 31.0 (s), 35.2 (s), 39.6 (s), 61.1 (s), 105.0 (d), 112.0 (d), 115.7 (d), 117.9 (s), 118.5 (d), 119.9 (d), 120.3 (d), 120.9 (d), 123.7 (d), 123.9 (d), 124.9 (s), 129.2 (s), 134.4 (s), 137.2 (s), 144.7 (s), 169.2 (s), ppm; **HRMS** (ESI) calcd for $C_{23}H_{22}N_2NaO_2$: 381.1573 $[M + Na]^+$; found 381.1583.



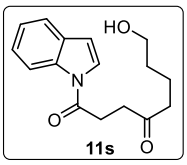
7-Hydroxy-1-(1*H*-indol-1-yl)heptane-1,4-dione (11a): Colourless syrup (5 mg, 15%); R_f = 0.2 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.82 (br. s., 1H), 1.92 (quin, *J* = 6.5 Hz, 2H), 2.73 (t, *J* = 6.9 Hz, 2H), 2.97 (t, *J* = 6.2 Hz, 2H), 3.26 (t, *J* = 6.2 Hz, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 6.66 (d, *J* = 3.7 Hz, 1H), 7.23–7.29 (m, 1H) 7.31–7.37 (m, 1H), 7.53 (d, *J* = 3.7 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 8.40 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.5 (t), 29.7 (t), 36.5 (t), 39.5 (t), 62.1 (t), 109.4 (d), 116.5 (d), 120.9 (d), 123.7 (d), 124.4 (d), 125.1 (d), 130.3 (s), 135.6 (s), 170.3 (s), 209.4 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{17}NNaO_3$: 282.1101 $[M + Na]^+$; found 282.1106.



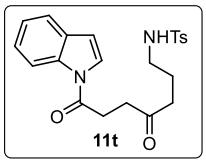
Methyl 2-(1-(7-hydroxy-4-oxoheptanoyl)-1*H*-indol-3-yl)acetate (11p): Colourless liquid (12 mg, 37%); R_f = 0.1 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.83–1.96 (m, 2H), 2.73 (t, *J* = 6.9 Hz, 2H), 2.96 (t, *J* = 6.1 Hz, 2H), 3.25 (t, *J* = 6.2 Hz, 2H), 3.67–3.71 (m, 2H), 3.71–3.76 (m, 5H), 7.28–7.33 (m, 1H), 7.33–7.39 (m, 1H), 7.49–7.57 (m, 2H), 8.39 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.5 (t), 29.7 (t), 30.8 (t), 36.5 (t), 39.5 (t), 52.2 (q), 62.1 (t), 115.2 (s), 116.6 (d), 118.8 (d), 123.1 (d), 123.7 (d), 125.5 (d), 130.0 (s), 135.8 (s), 170.1 (s), 171.3 (s), 209.3 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{21}NNaO_5$: 354.1312 $[M + Na]^+$; found 354.1307.



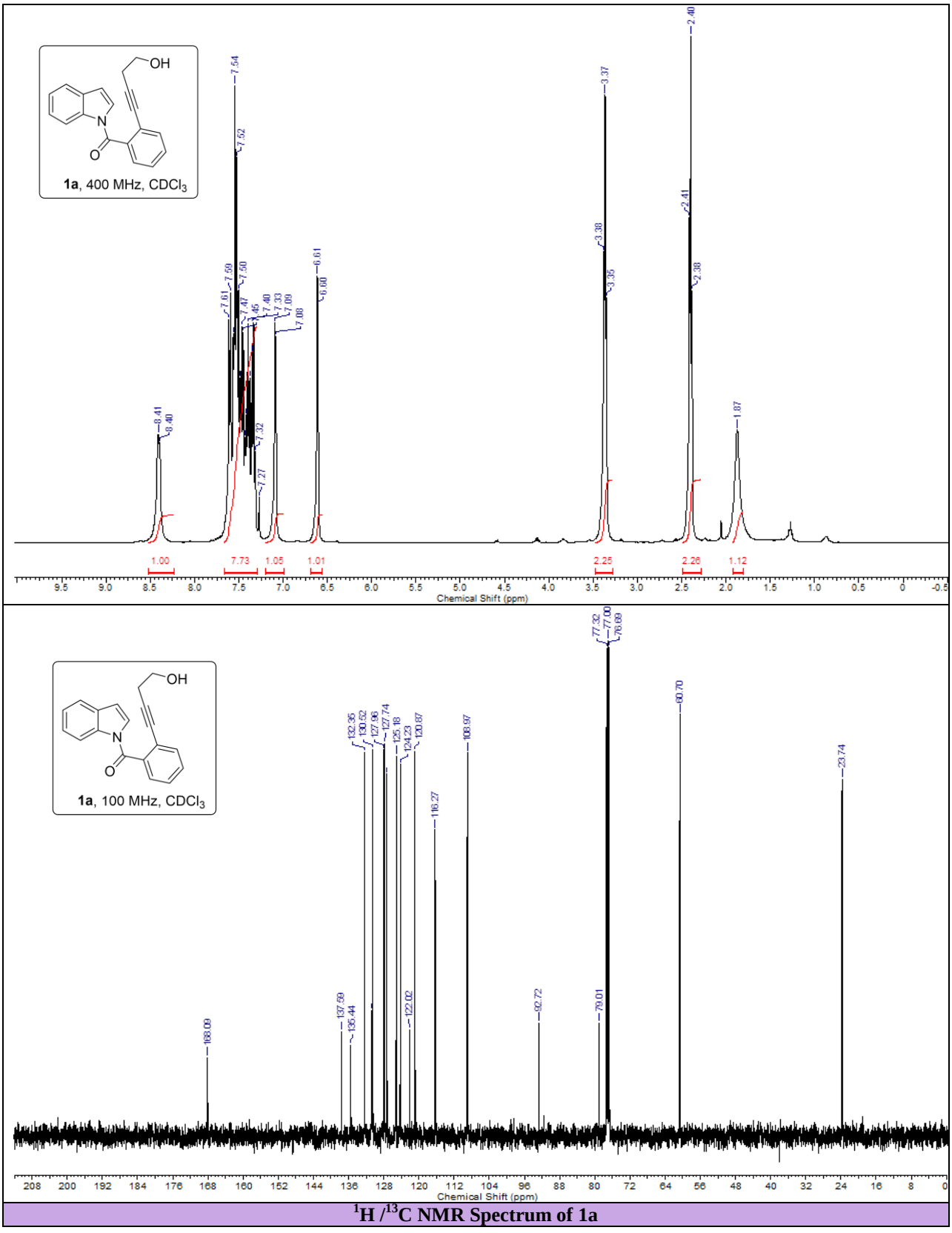
8-Hydroxy-1-(1*H*-indol-1-yl)octane-1,4-dione (11s): Colourless oil (24.5 mg, 76%); R_f = 0.2 (40% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.63 (br. s., 1H), 1.82–1.91 (m, 2H), 2.13 (quin, *J* = 6.9 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.98 (t, *J* = 7.0 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 6.65 (d, *J* = 3.7 Hz, 1H), 7.28 (td, *J* = 1.0, 7.4 Hz, 1H), 7.34–7.39 (m, 1H), 7.51 (d, *J* = 3.8 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 8.46 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.6 (t), 26.5 (t), 34.7 (t), 39.6 (t), 41.3 (t), 62.2 (t), 109.3 (d), 116.5 (d), 120.8 (d), 123.7 (d), 124.7 (d), 125.1 (d), 130.4 (s), 135.6 (s), 171.1 (s), 210.8 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{19}NNaO_3$: 296.1257 $[M + Na]^+$; found 296.1252.



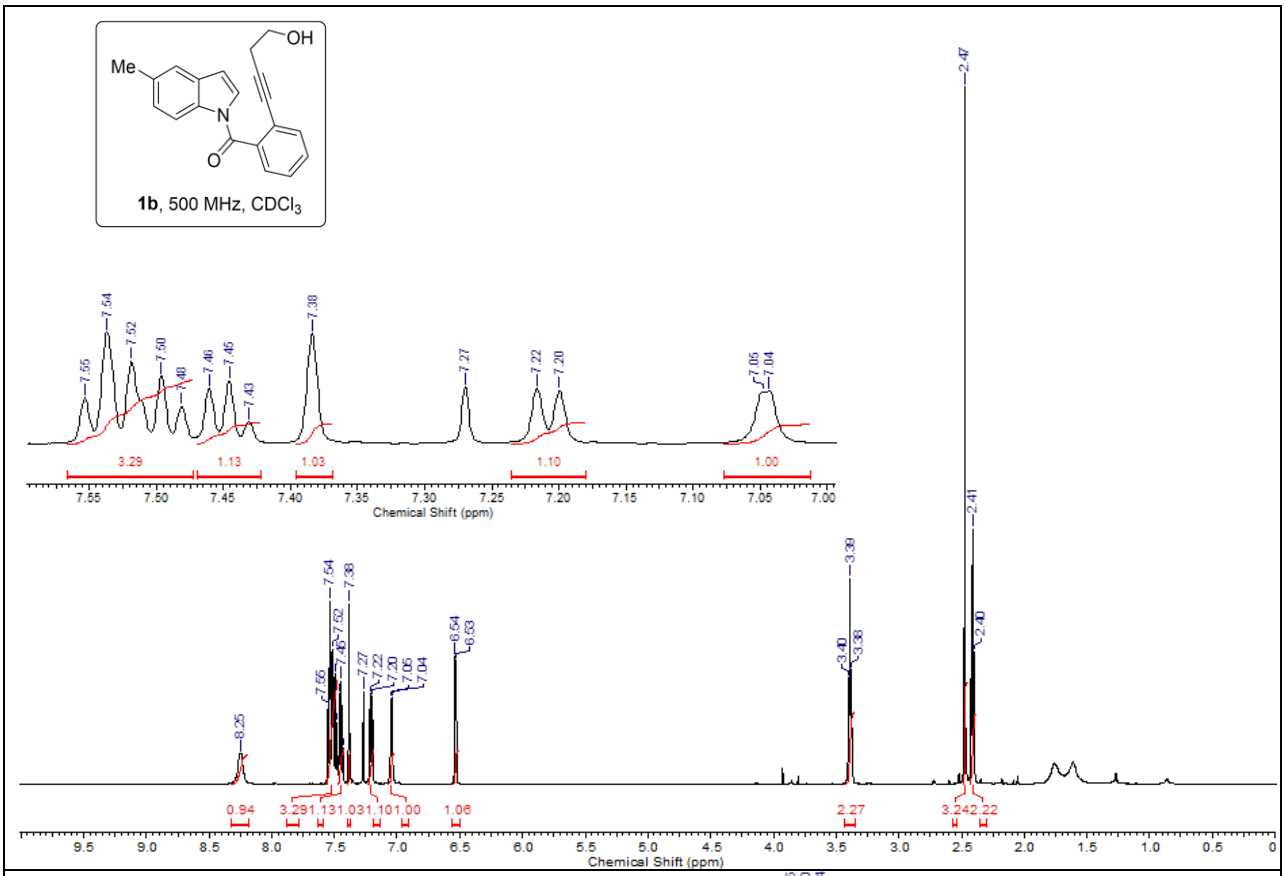
N-(7-(1*H*-indol-1-yl)-4,7-dioxoheptyl)-4-methylbenzenesulfonamide (11t): Prepared from alkynylamine **1t** (50 mg, 0.12 mmol). Pale brown solid (31 mg, 60%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 94–96 °C; **^{1}H NMR** (400 MHz,

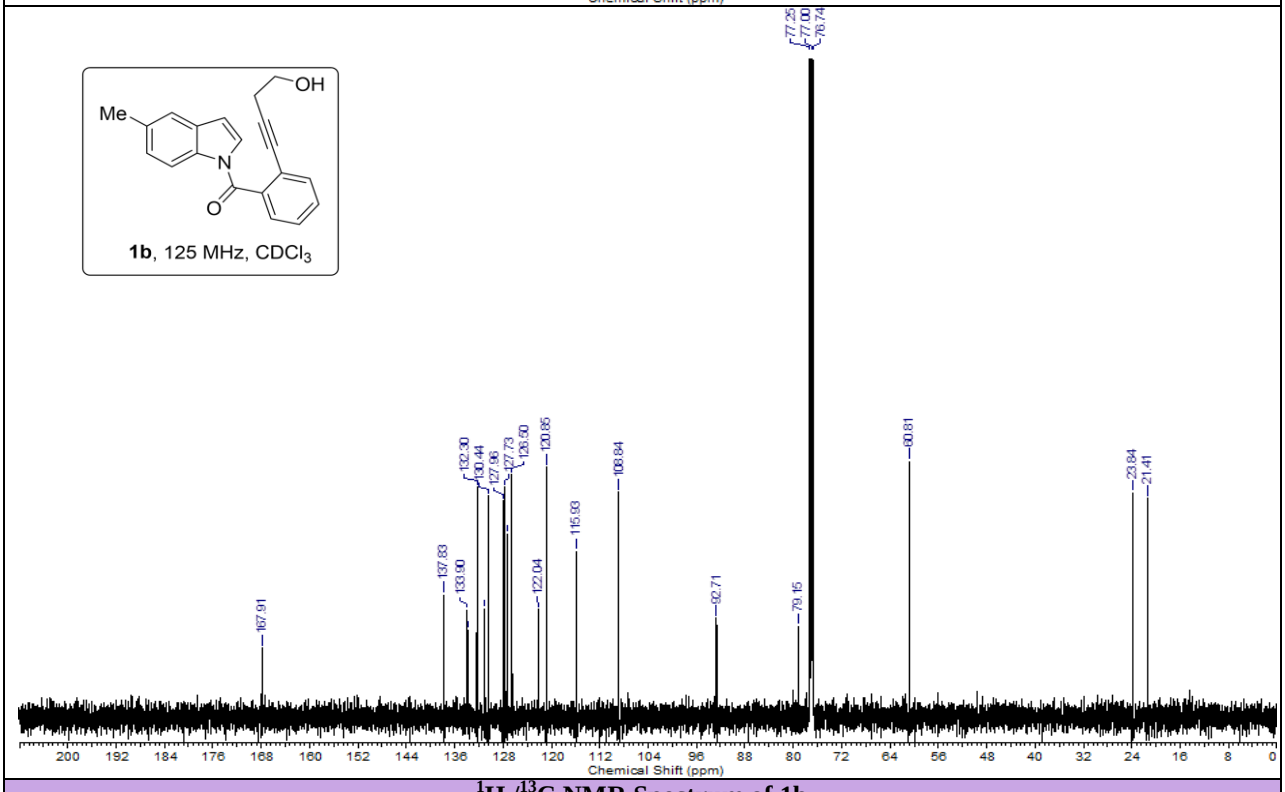


$CDCl_3$): δ 1.83 (quin, J = 6.6 Hz, 1H), 2.41 (s, 3H), 2.69 (t, J = 6.6 Hz, 2H), 2.91 (dd, J = 6.7, 5.8 Hz, 2H), 2.99 (q, J = 6.4 Hz, 2H) 3.19–3.30 (m, 2H), 4.72 (t, J = 6.3 Hz, 1H), 6.67 (d, J = 3.7 Hz, 1H), 7.28–7.32 (m, 3H), 7.32–7.37 (m, 1H), 7.50–7.60 (m, 2H), 7.74 (d, J = 8.2 Hz, 2H), 8.38 (d, J = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.5 (q), 23.3 (t), 29.8 (t), 36.5 (t), 39.4 (t), 42.4 (t), 109.5 (d), 116.5 (d), 120.9 (d), 123.7 (d), 124.5 (d), 125.1 (d), 127.0 (d, 2C), 129.7 (d, 2C), 130.3 (s), 135.6 (s), 137.0 (s), 143.4 (s), 170.3 (s), 208.7 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{24}N_2SNaO_4$: 435.1349 $[M + Na]^+$; found 435.1360.

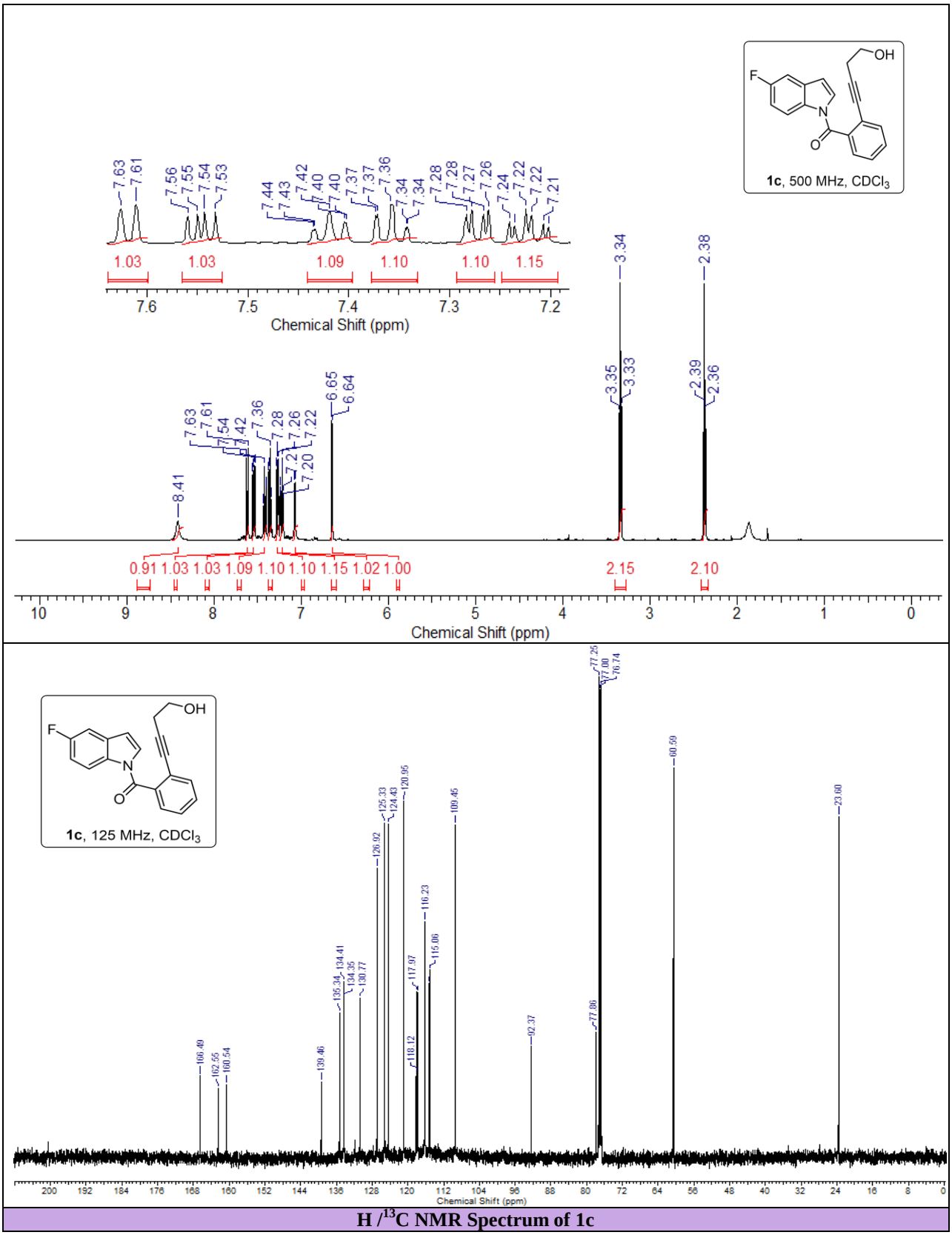


^{1}H /^{13}C NMR Spectrum of 1a

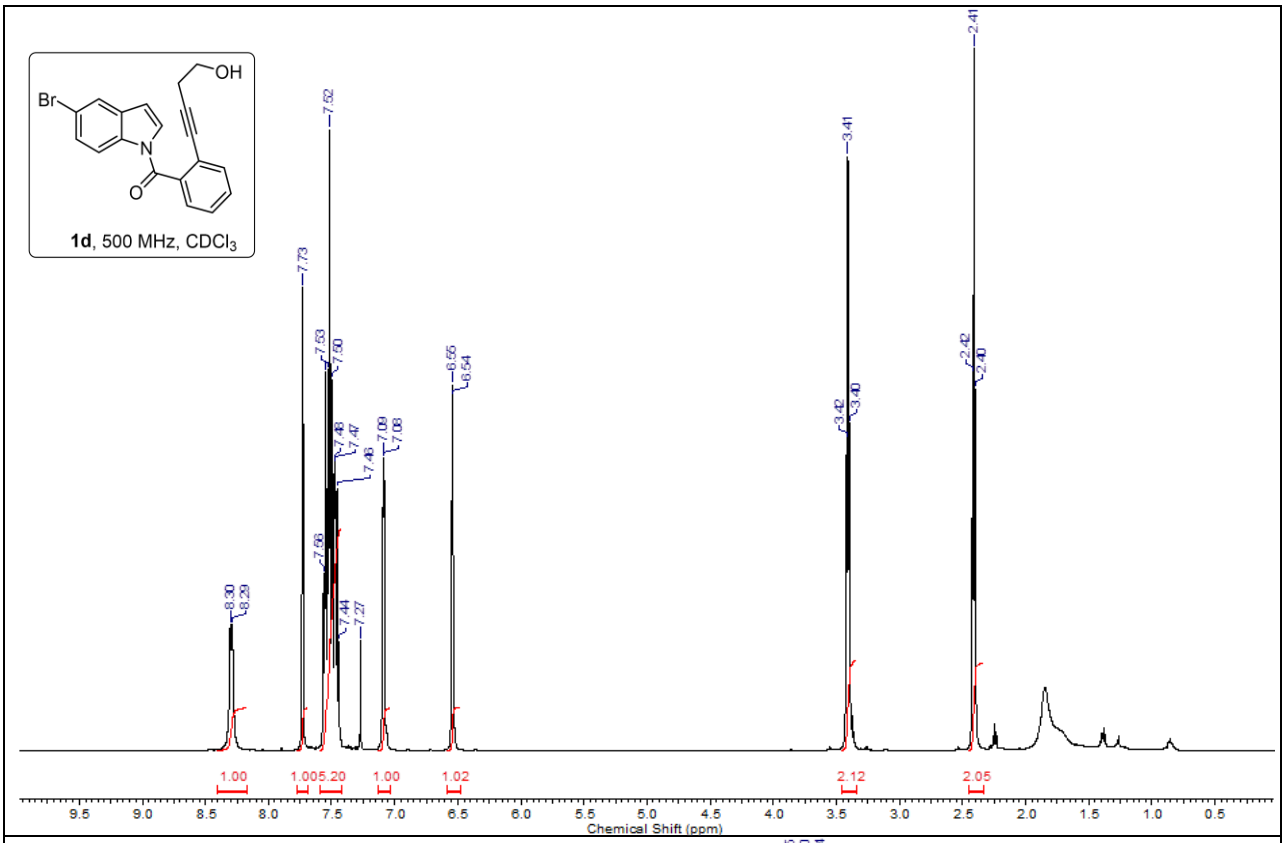


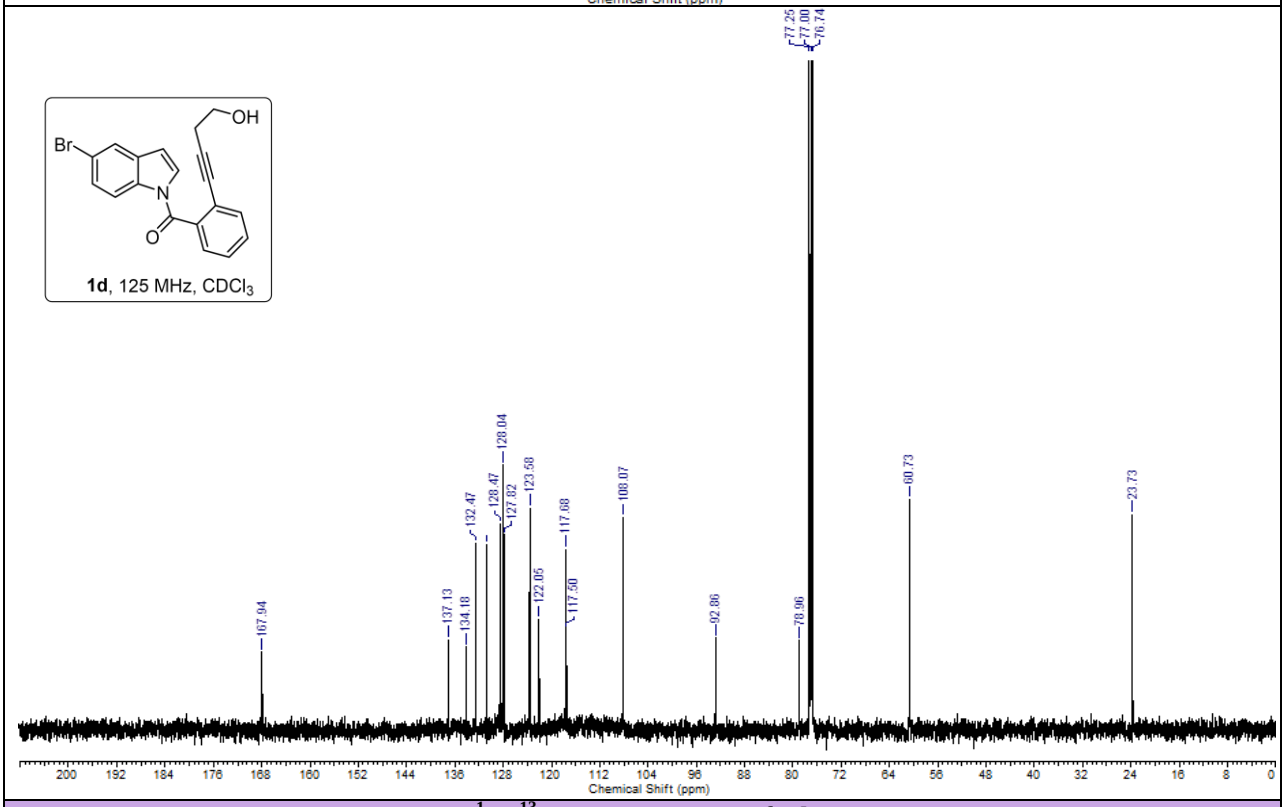


^{1}H /^{13}C NMR Spectrum of 1b

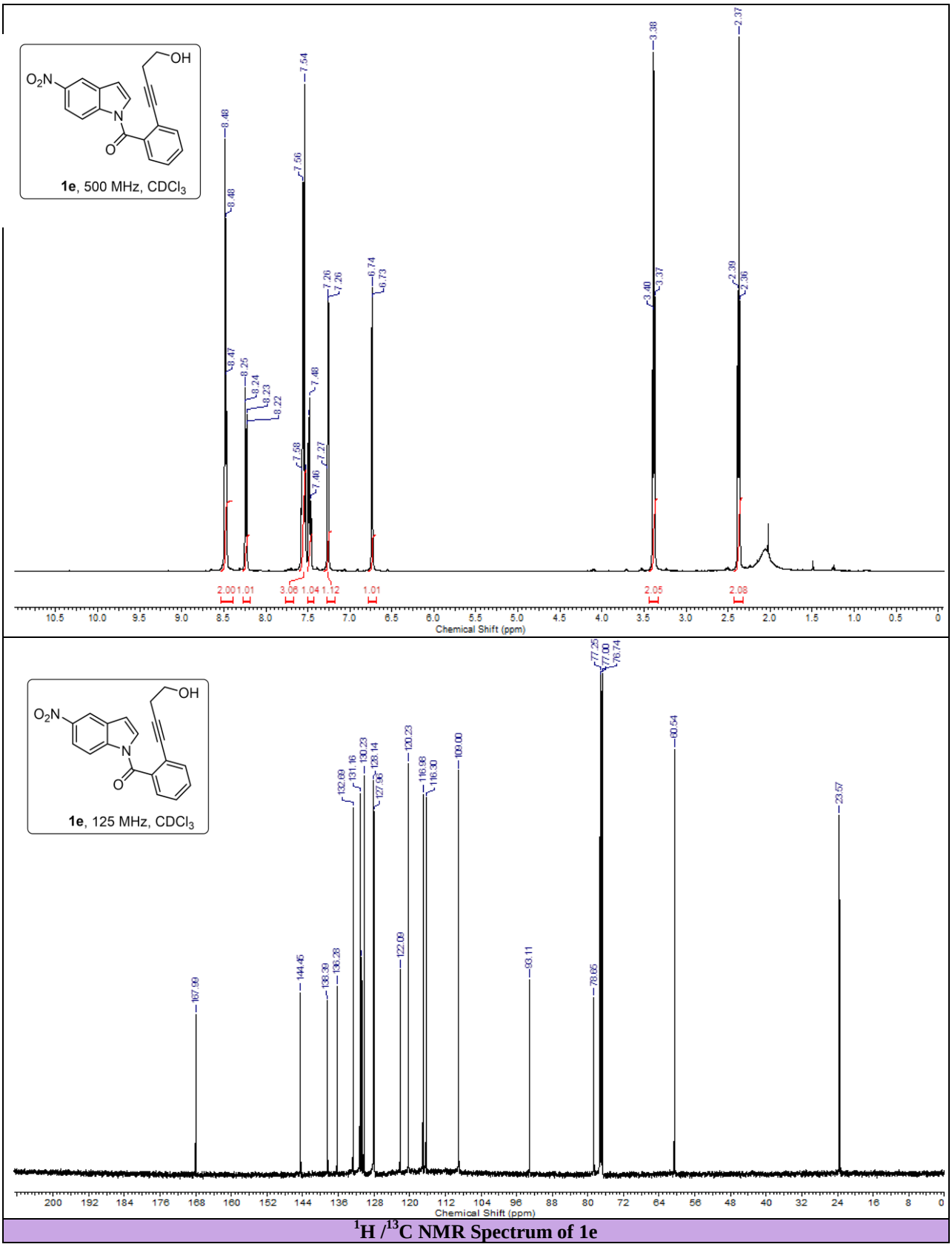


H /^{13}C NMR Spectrum of 1c

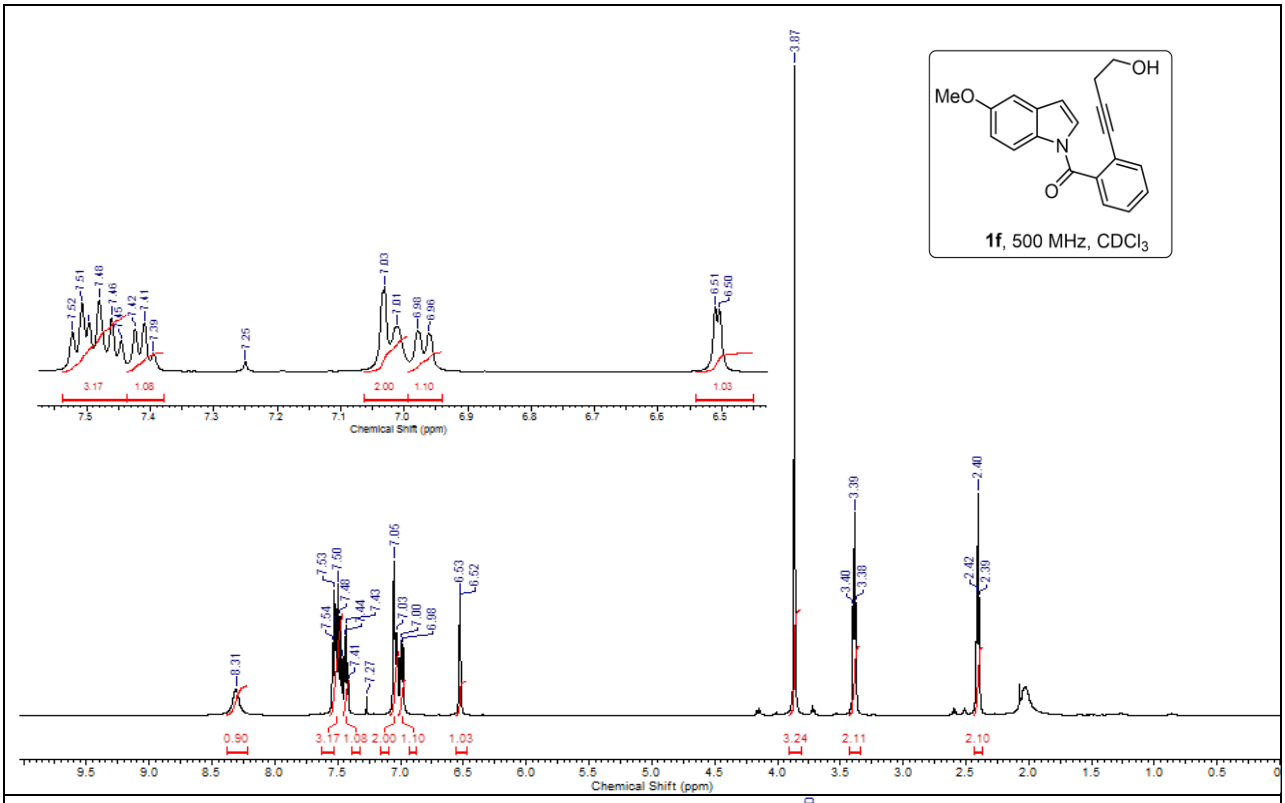


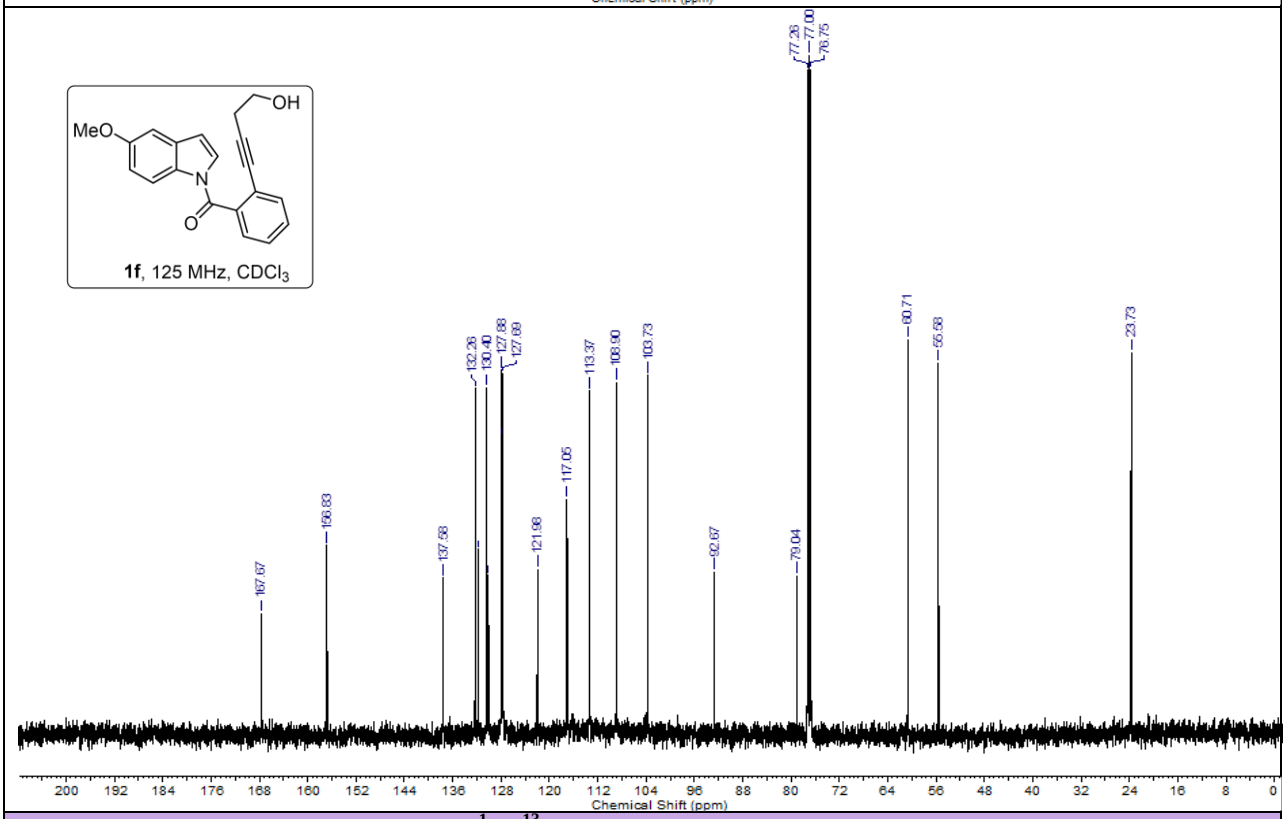


^{1}H /^{13}C NMR Spectrum of 1d

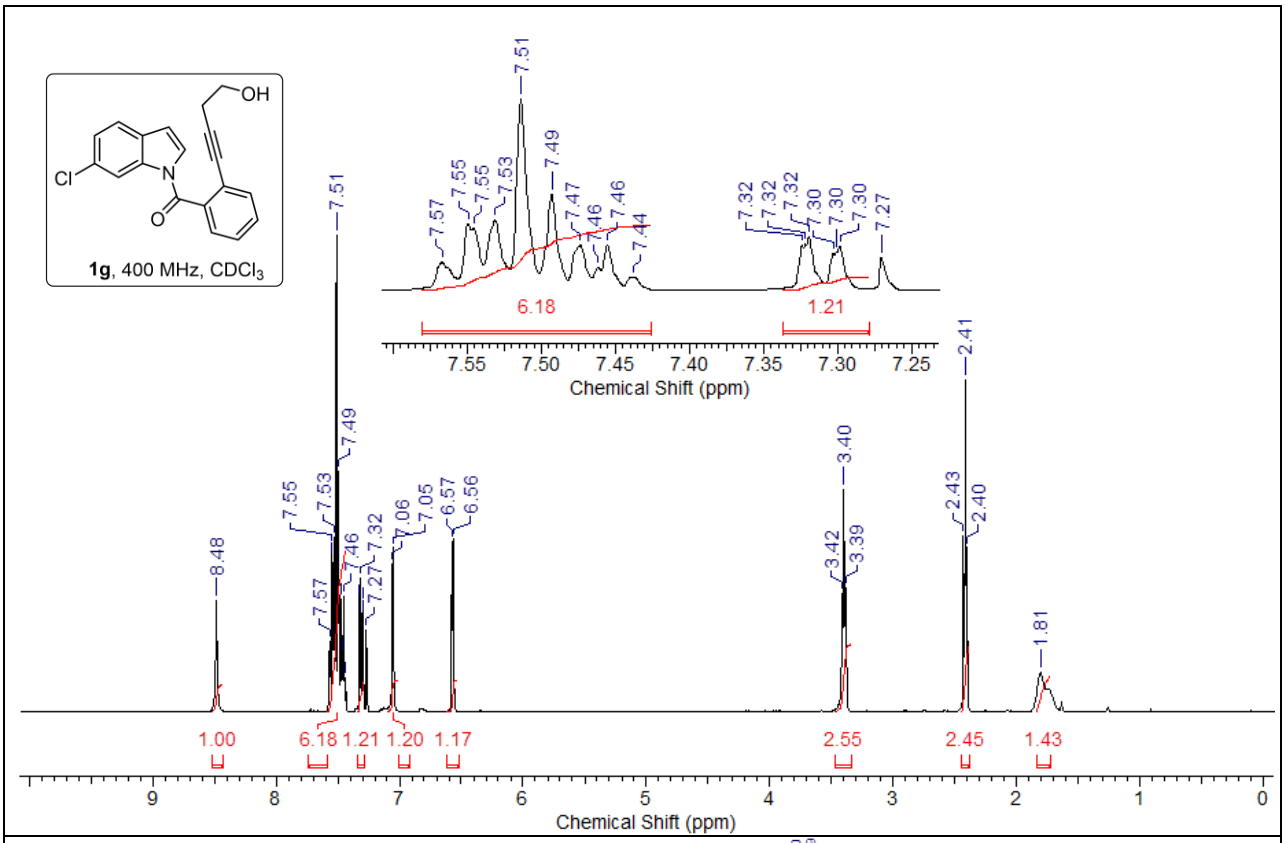


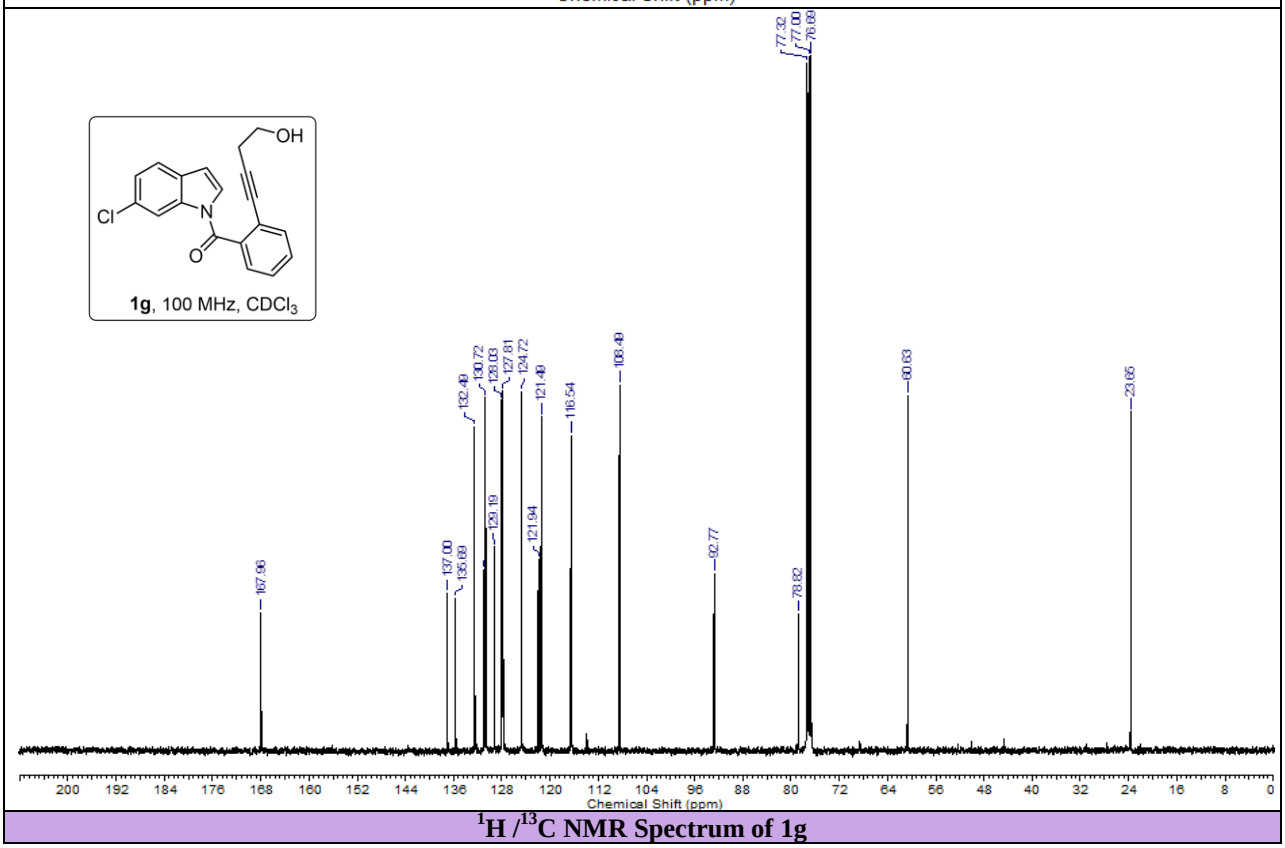
^{1}H /^{13}C NMR Spectrum of 1e



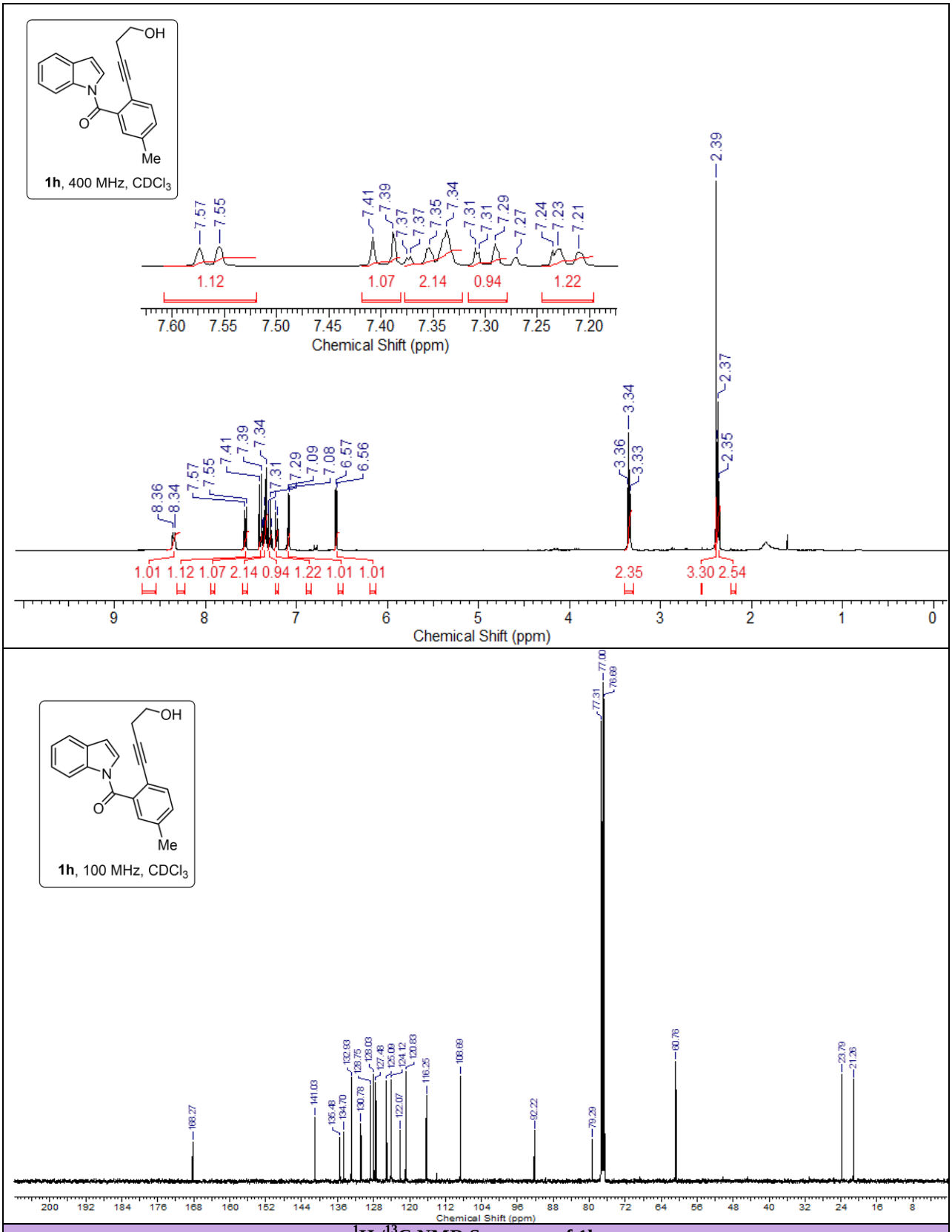


^{1}H /^{13}C NMR Spectrum of 1f

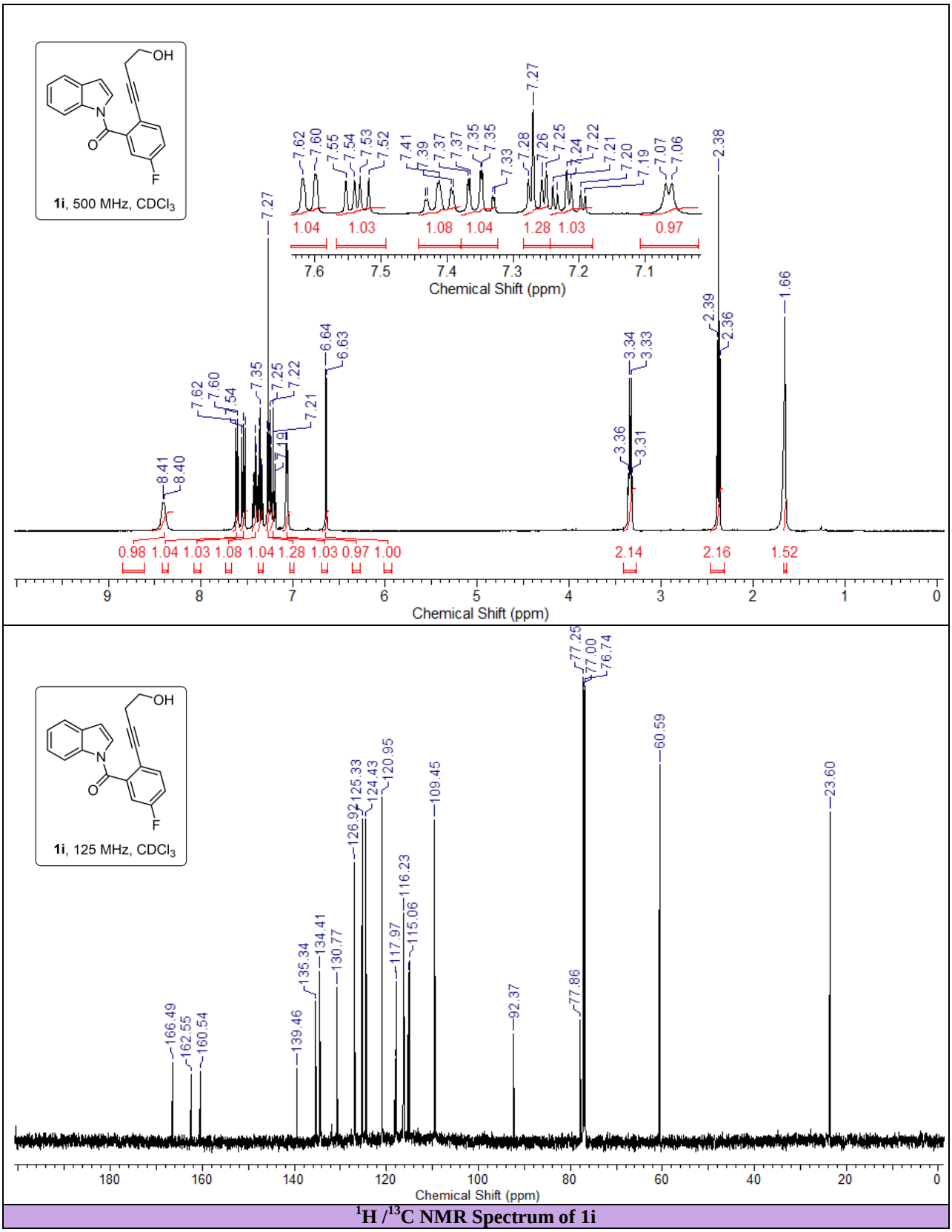




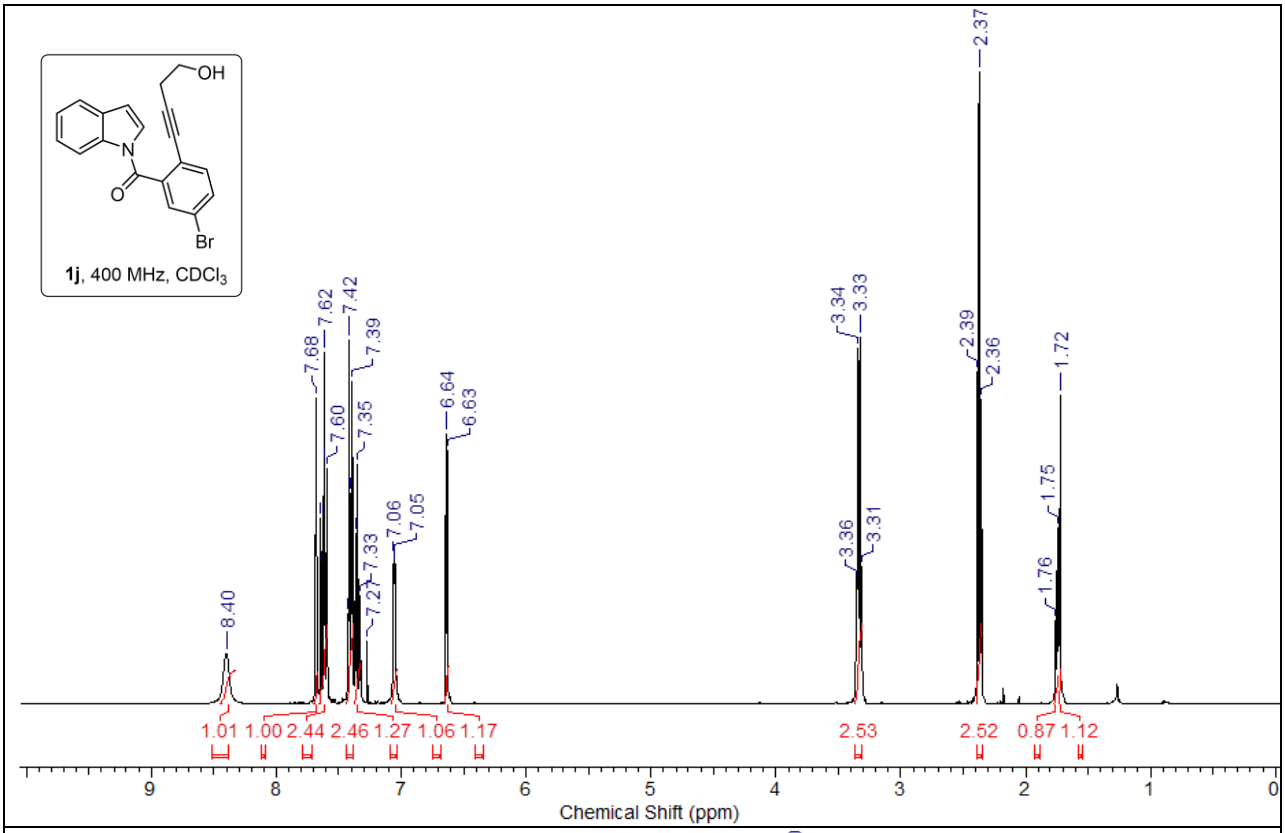
^{1}H /^{13}C NMR Spectrum of 1g

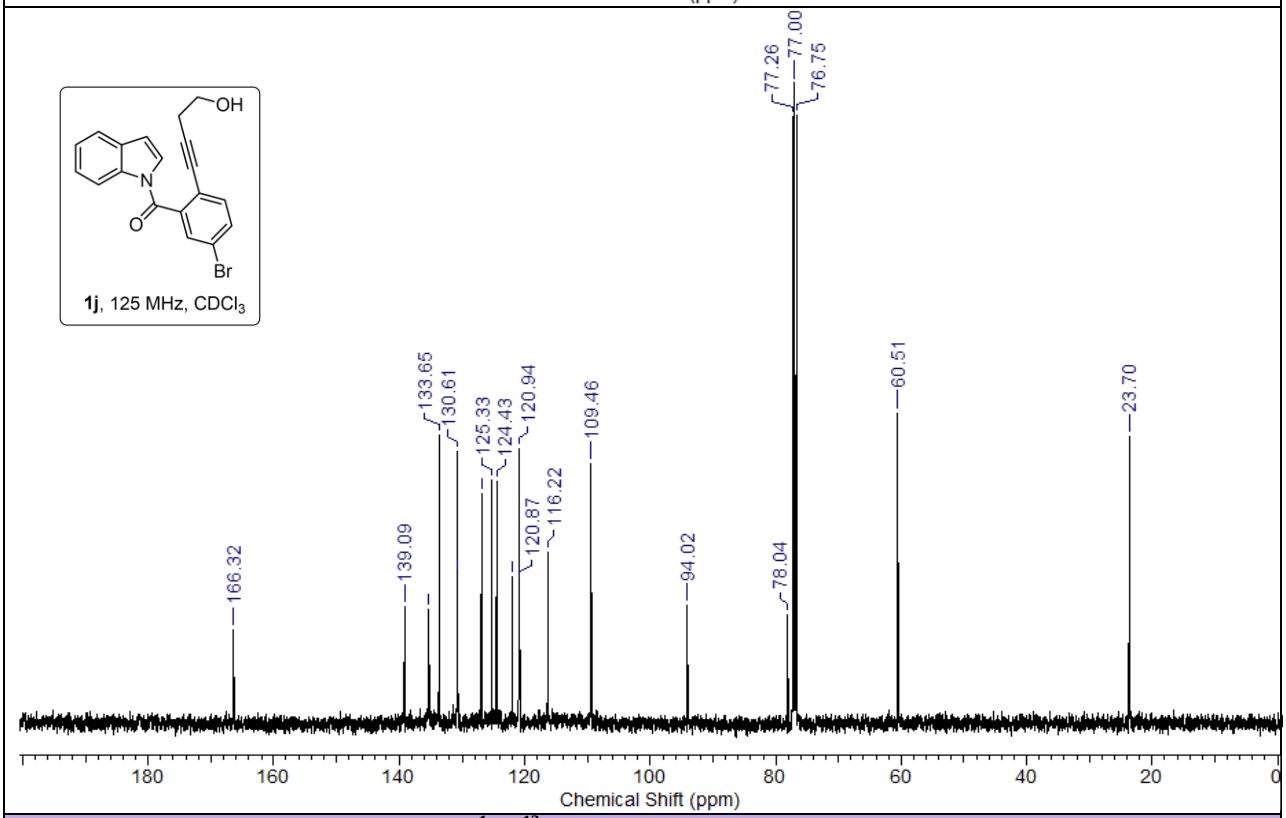


^{1}H /^{13}C NMR Spectrum of 1h

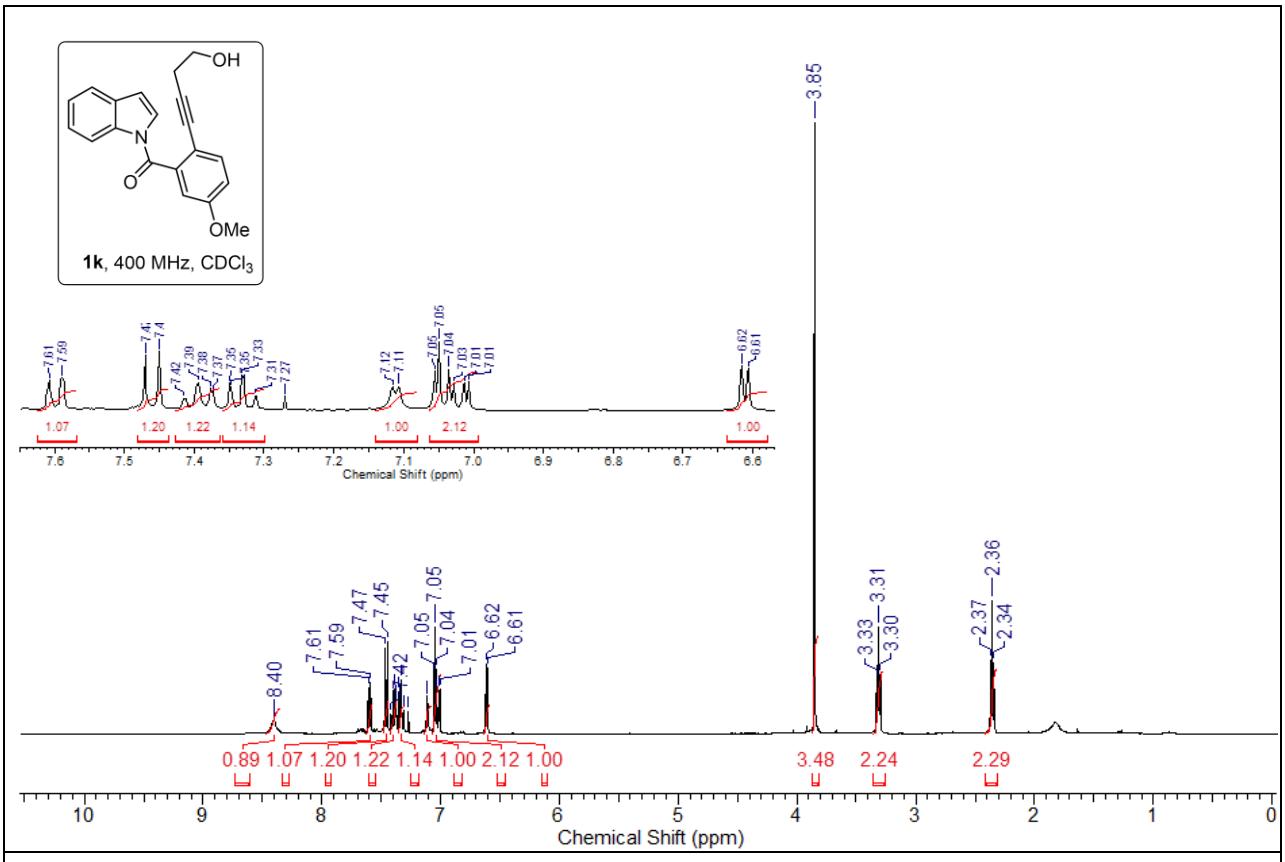


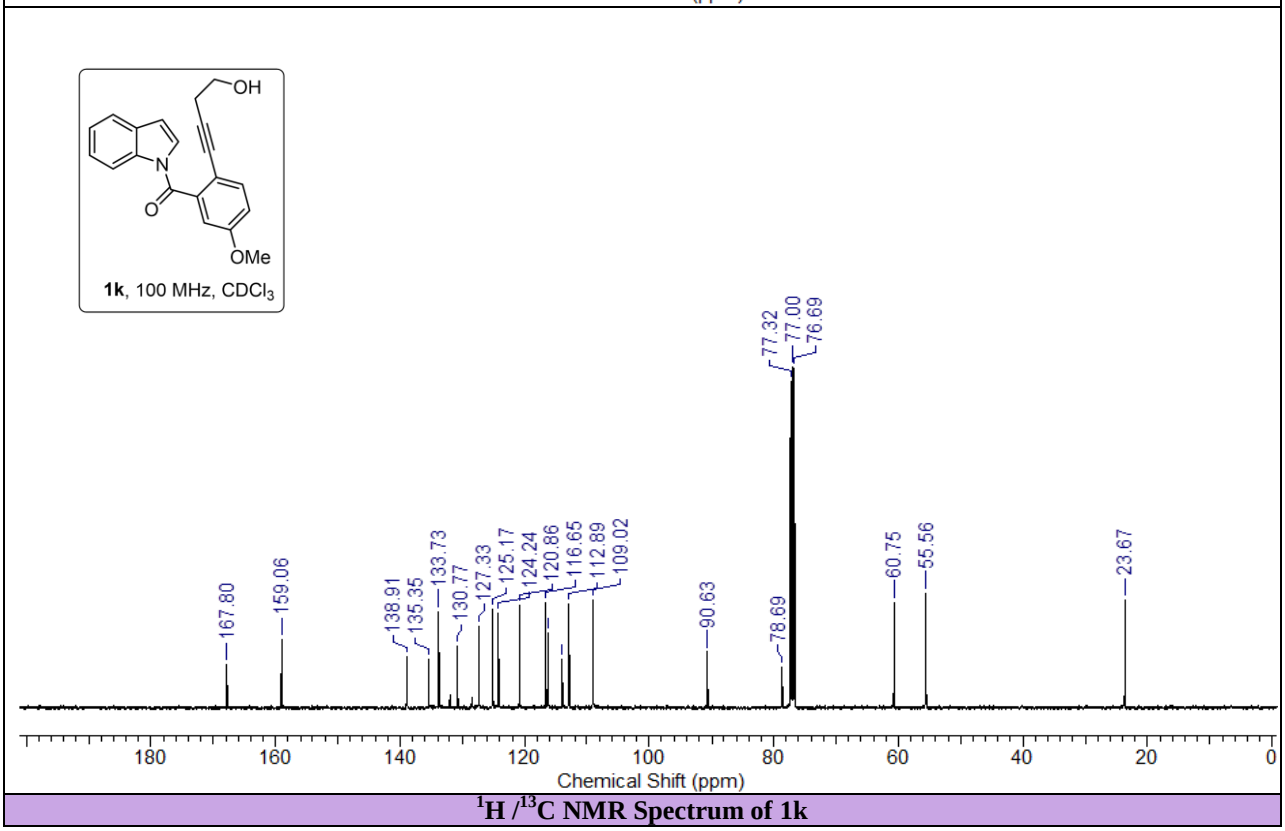
^{1}H /^{13}C NMR Spectrum of 1i



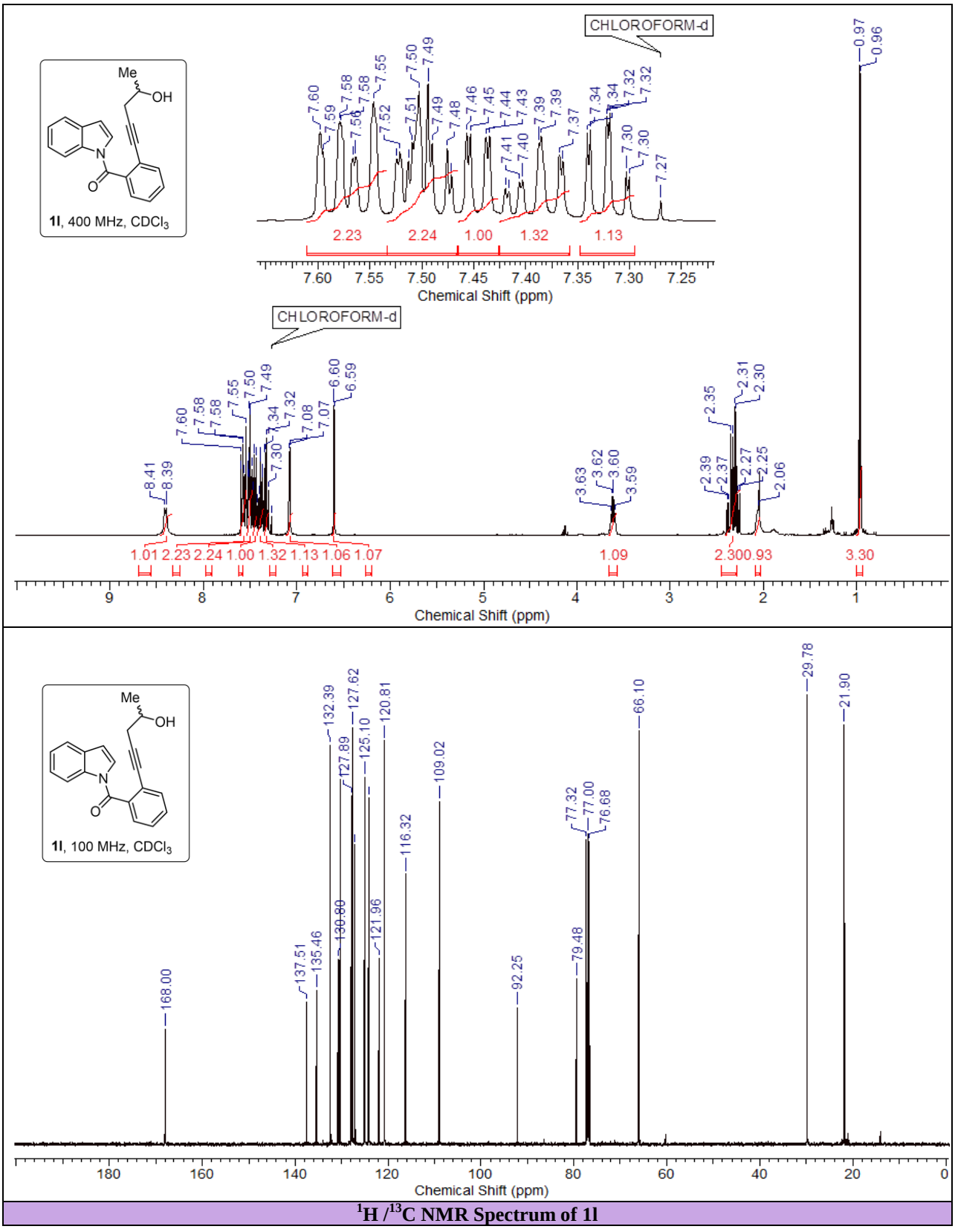


^{1}H /^{13}C NMR Spectrum of 1j

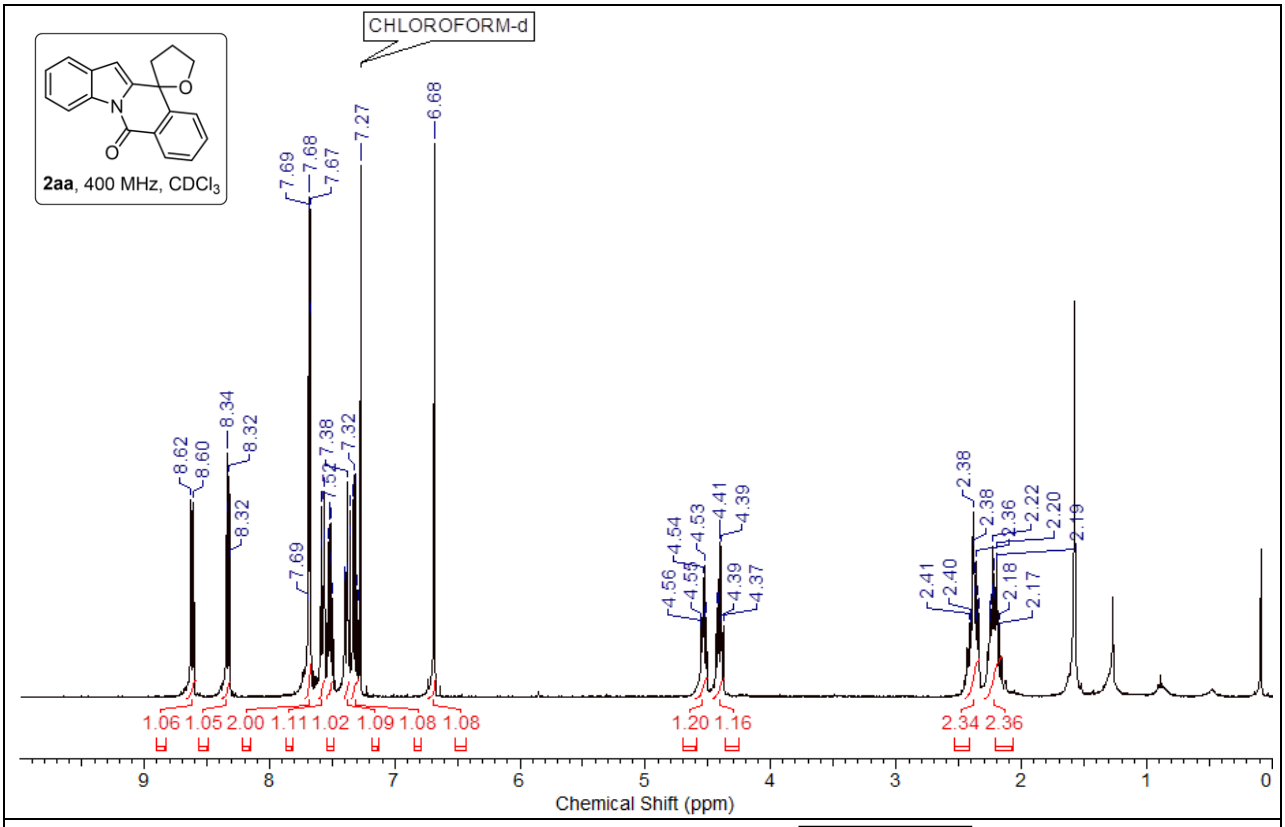


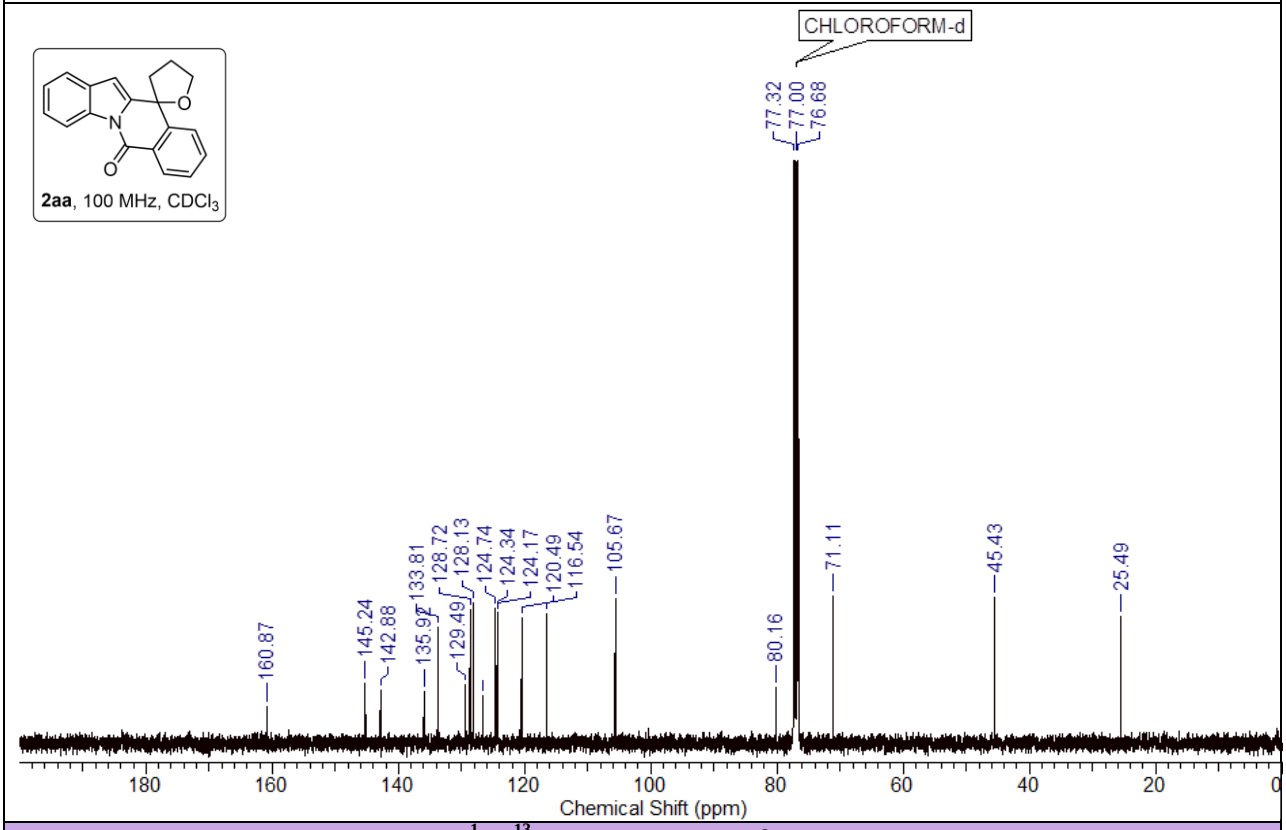


^{1}H /^{13}C NMR Spectrum of 1k

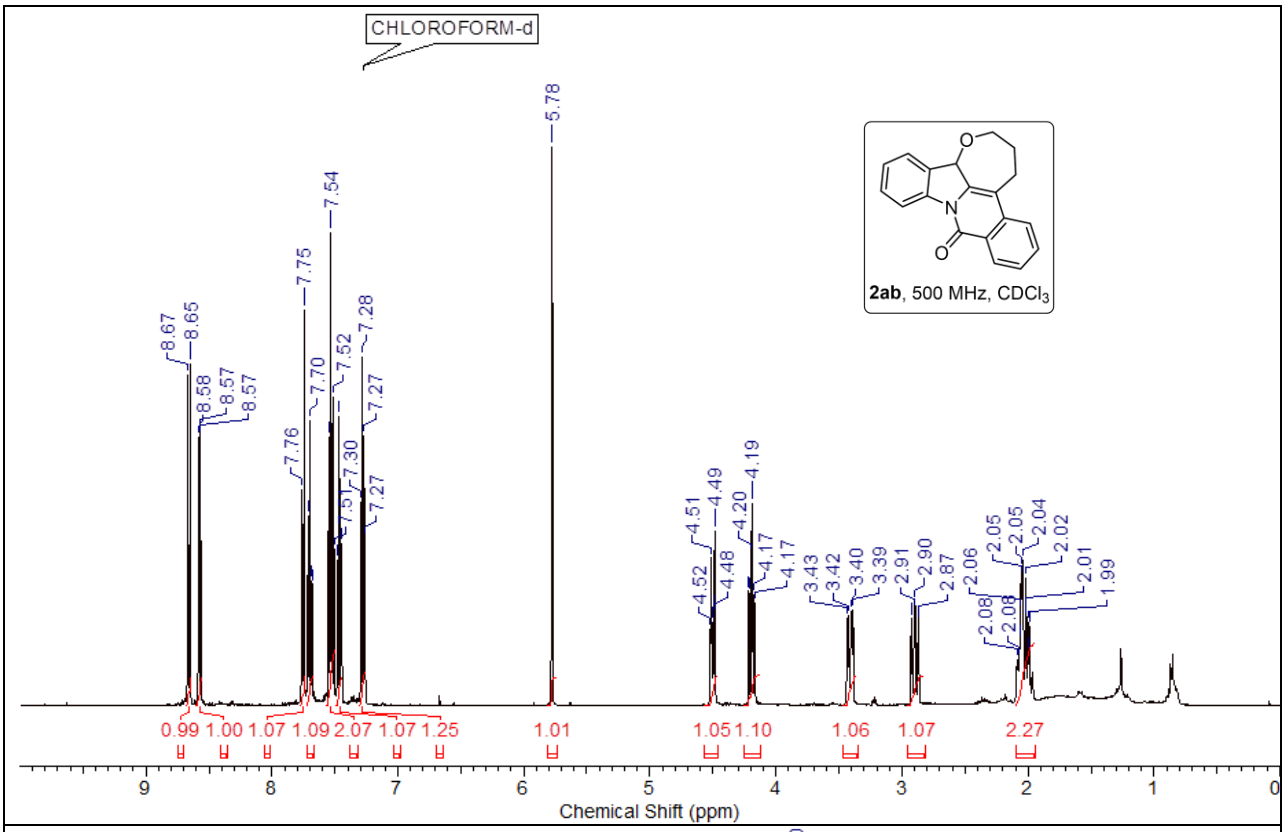


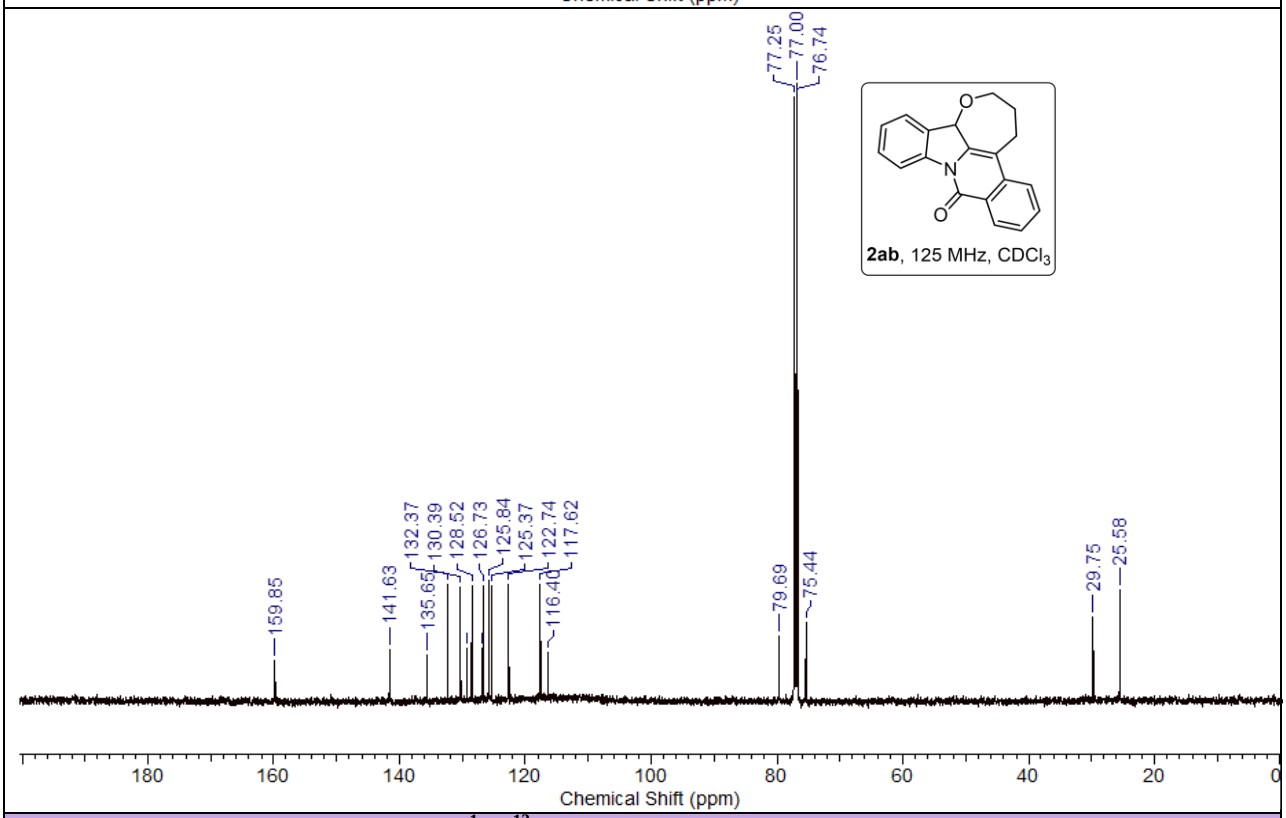
^{1}H /^{13}C NMR Spectrum of 1l



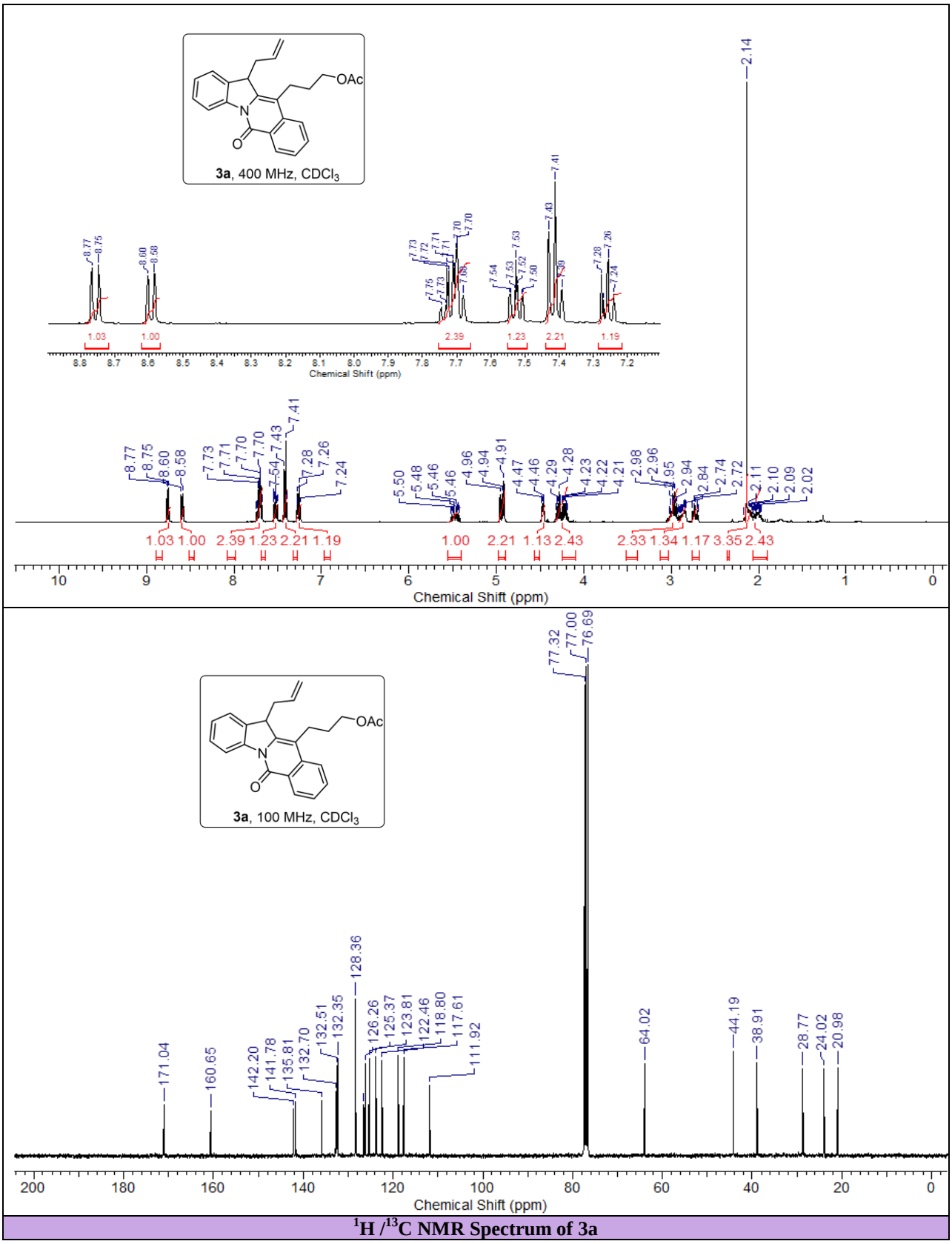


^{1}H /^{13}C NMR Spectrum of 2aa

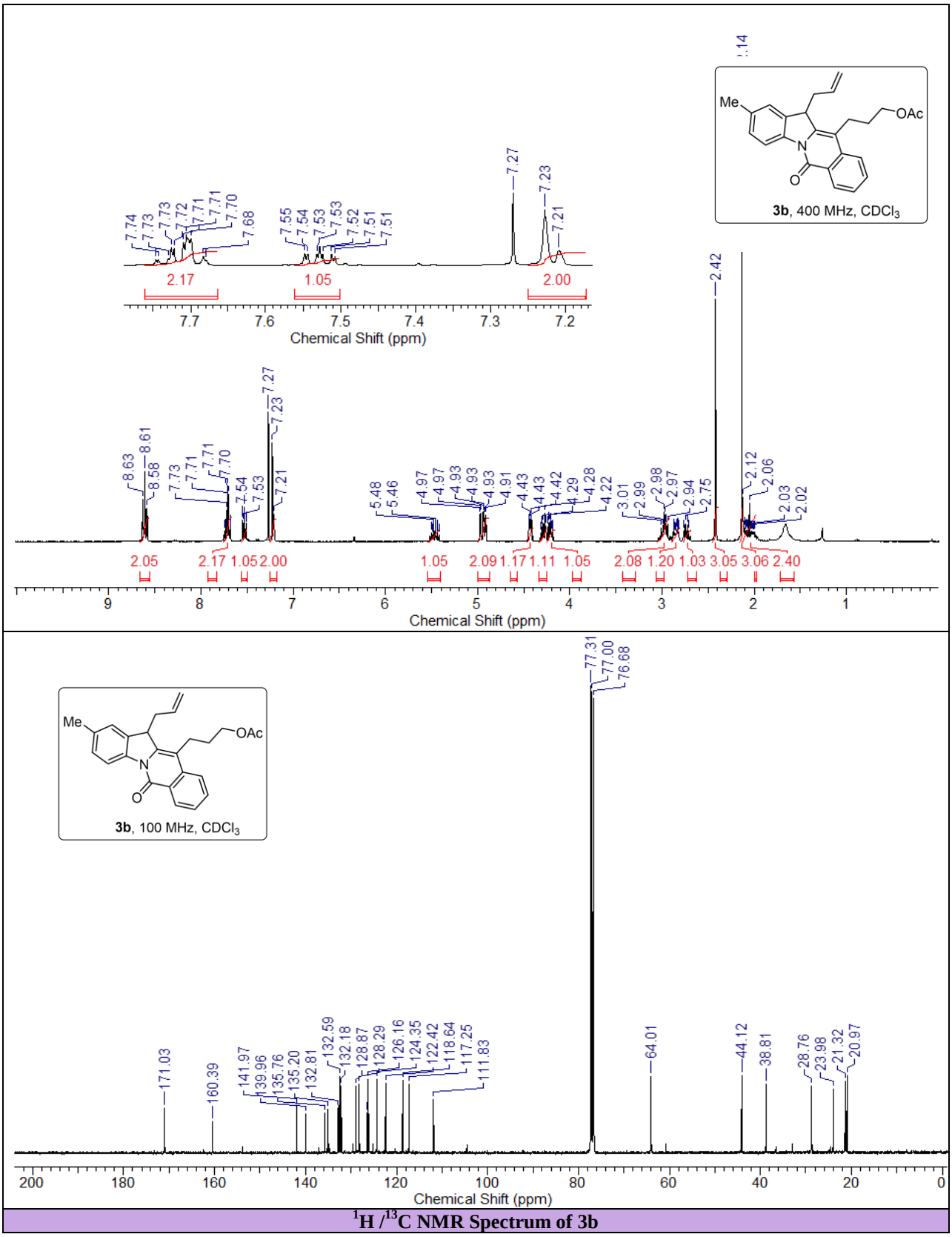




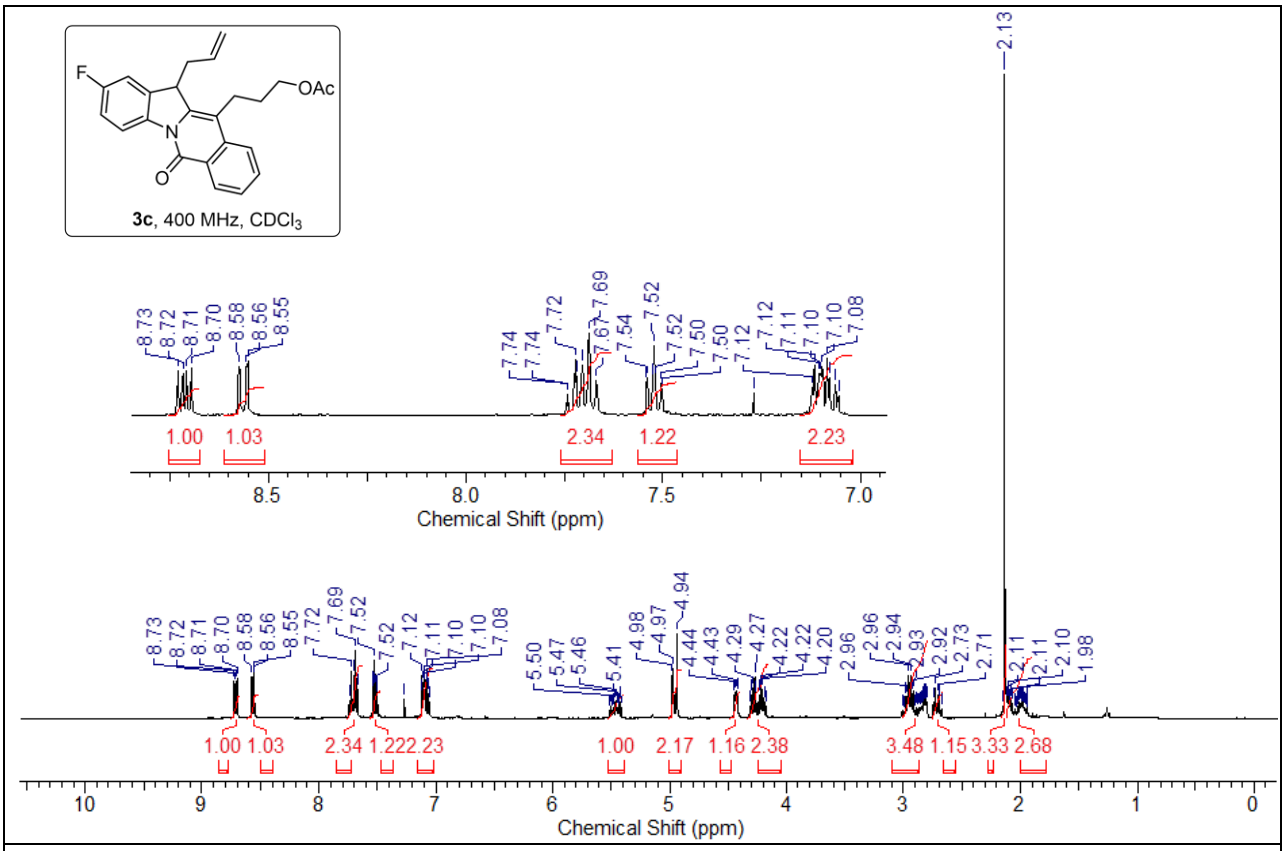
^{1}H /^{13}C NMR Spectrum of 2ab

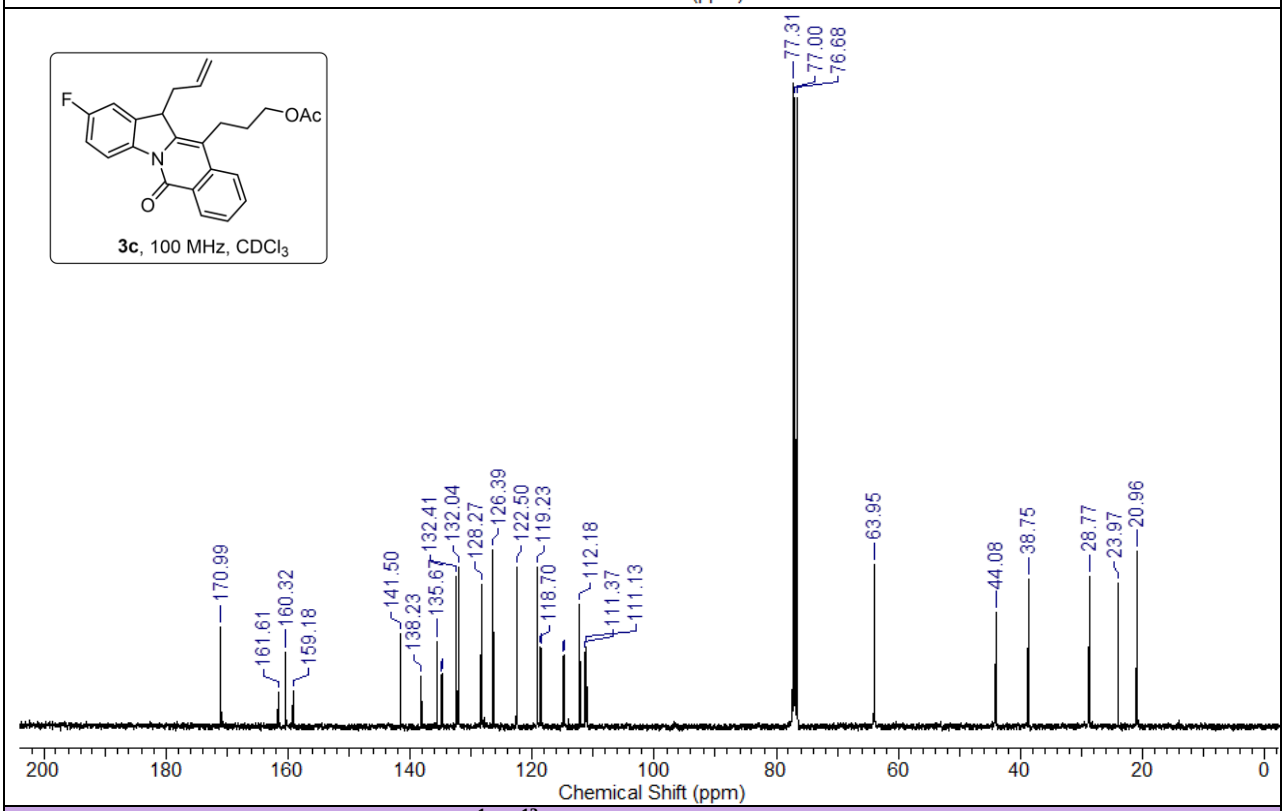


^{1}H /^{13}C NMR Spectrum of 3a

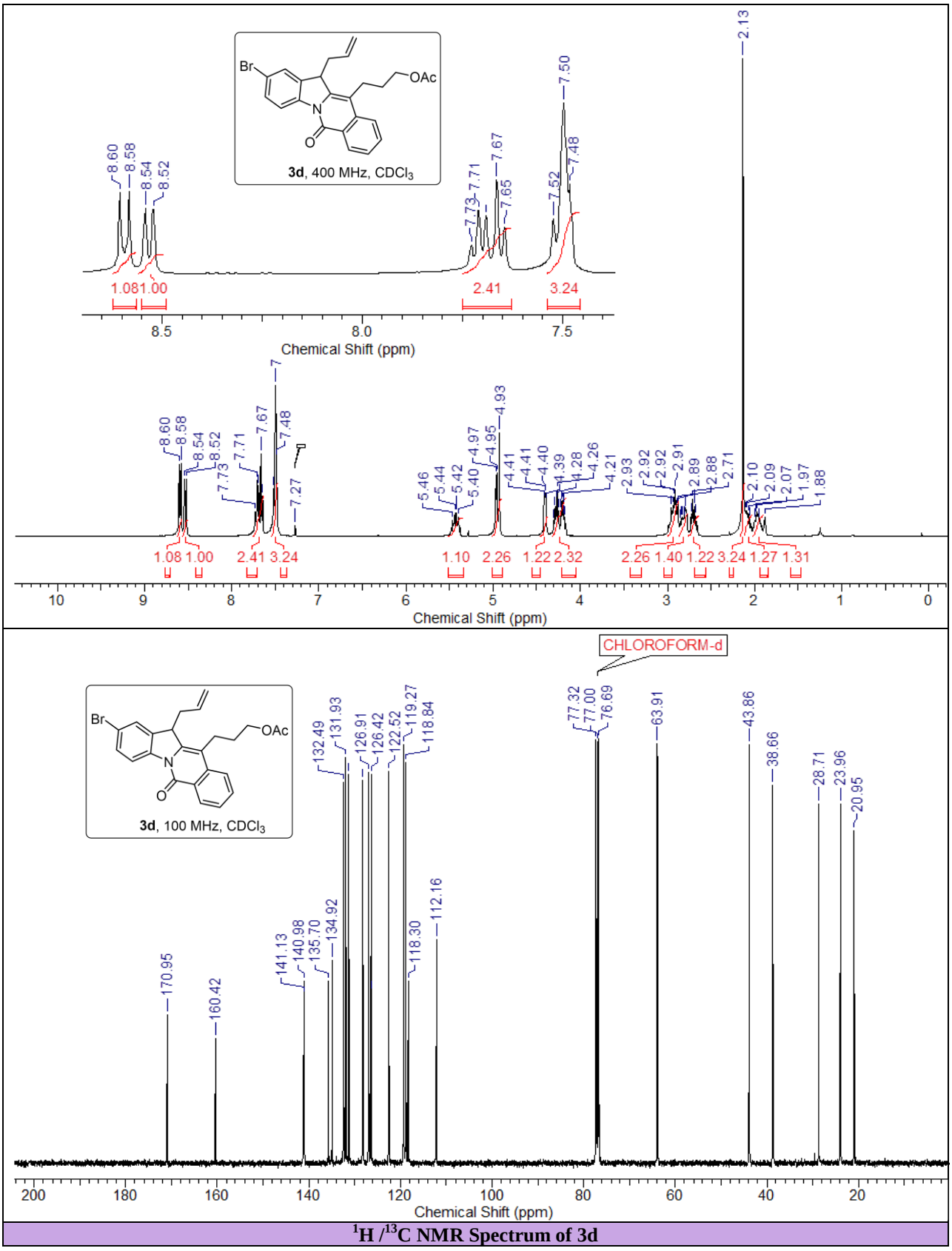


^{1}H /^{13}C NMR Spectrum of 3b

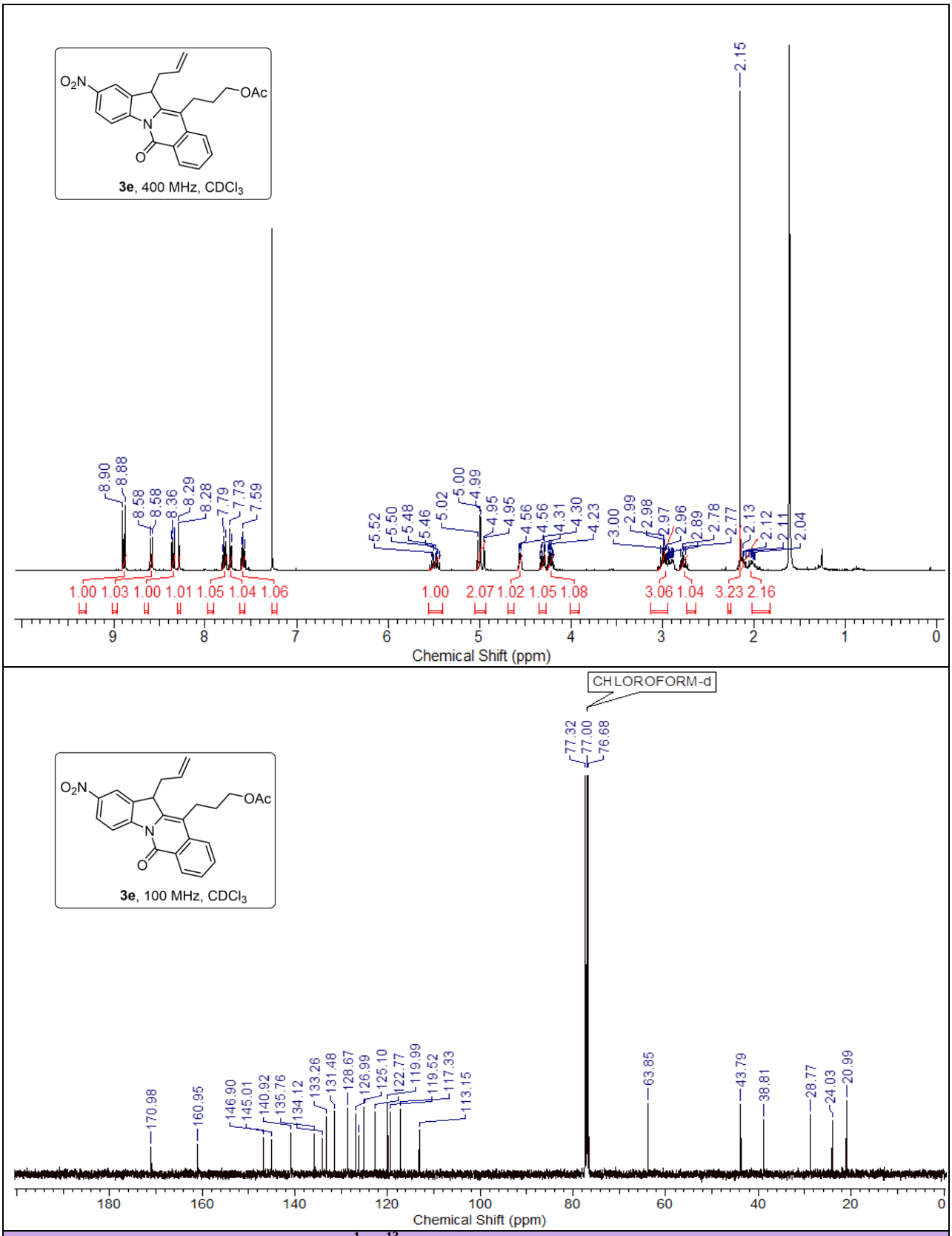




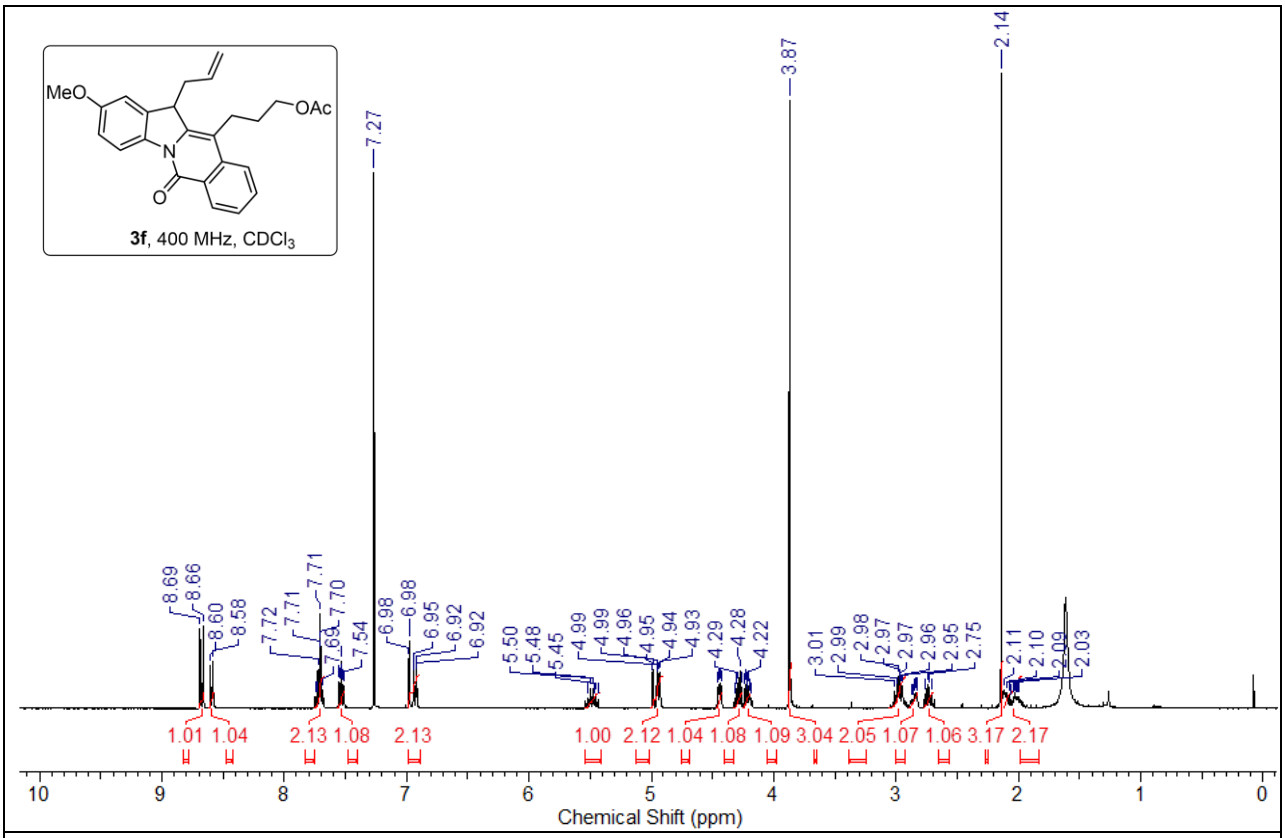
^{1}H /^{13}C NMR Spectrum of 3c

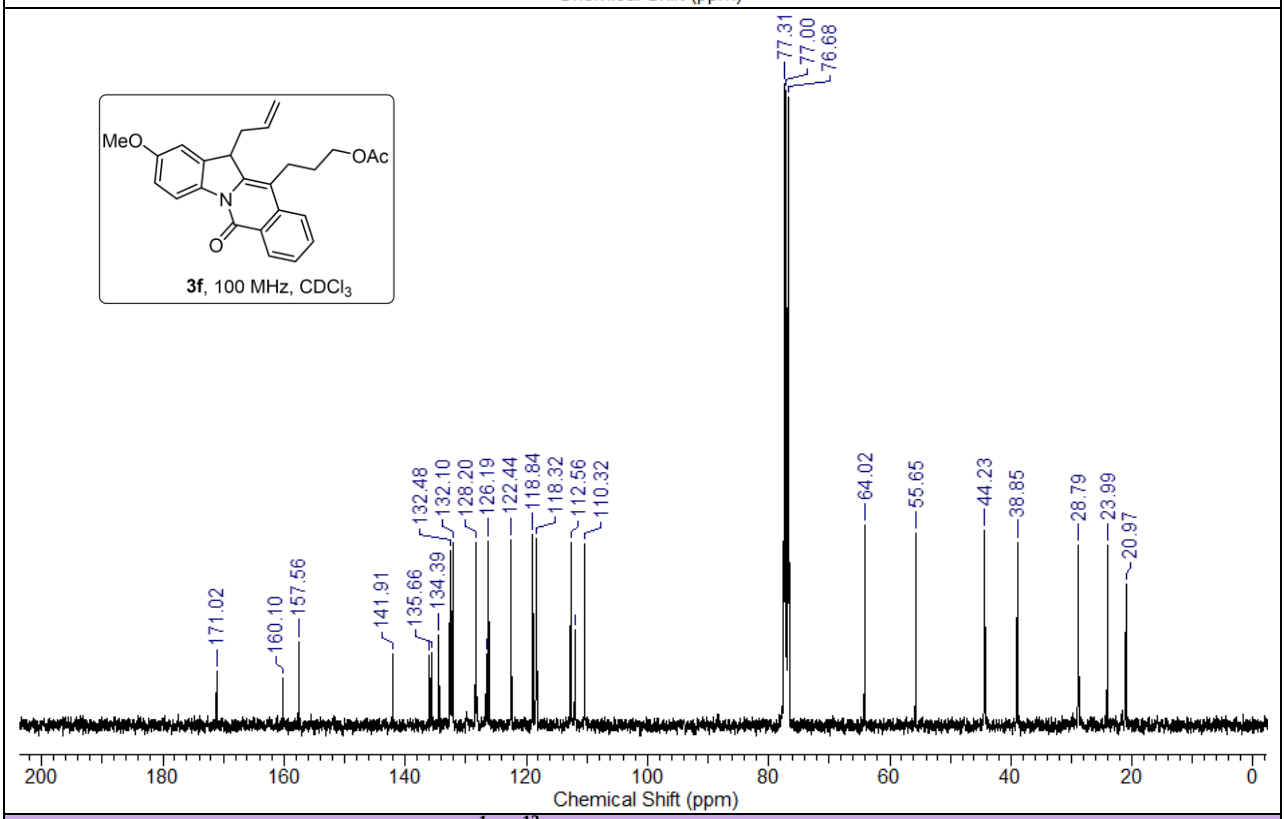


^{1}H /^{13}C NMR Spectrum of 3d

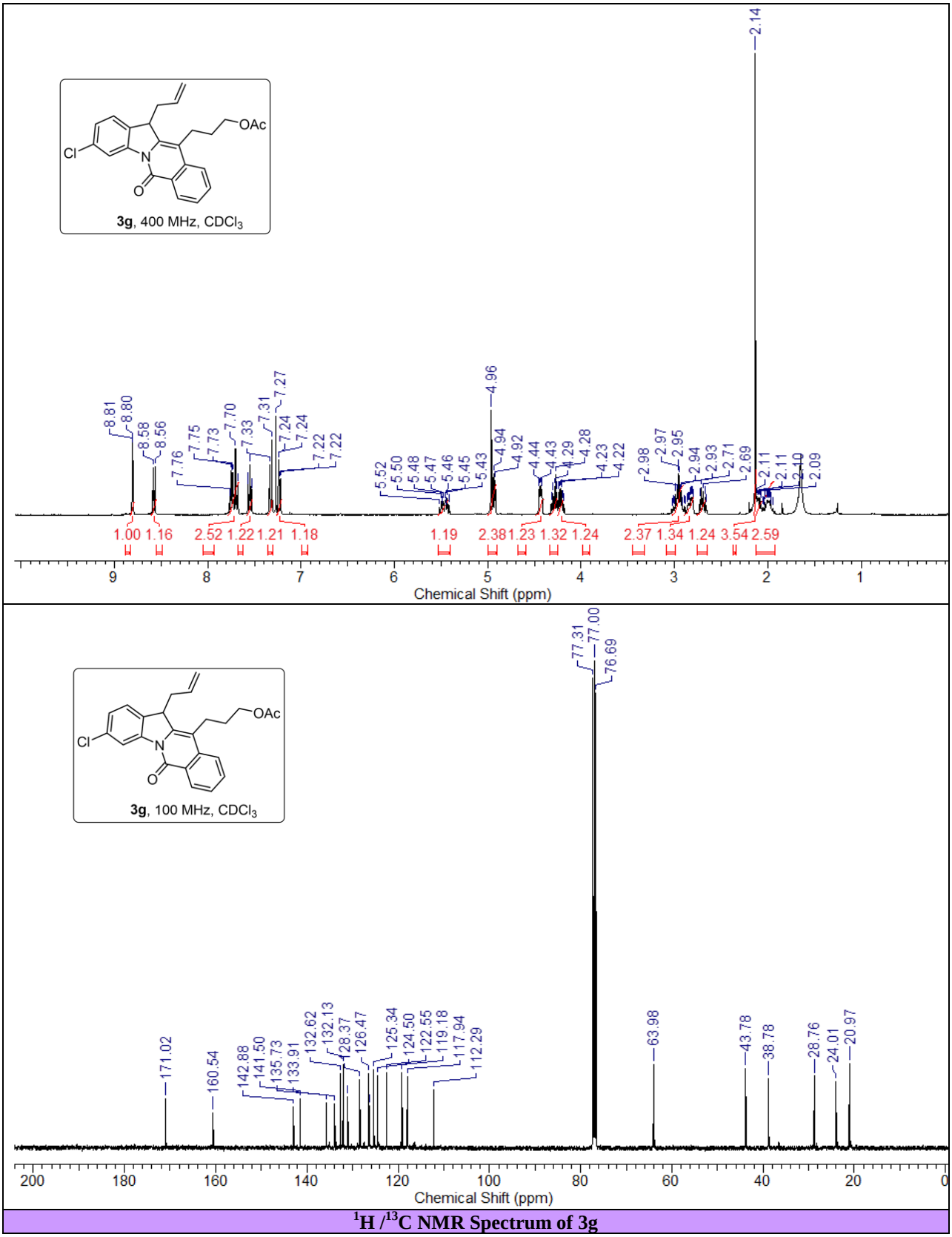


^{1}H /^{13}C NMR Spectrum of 3e

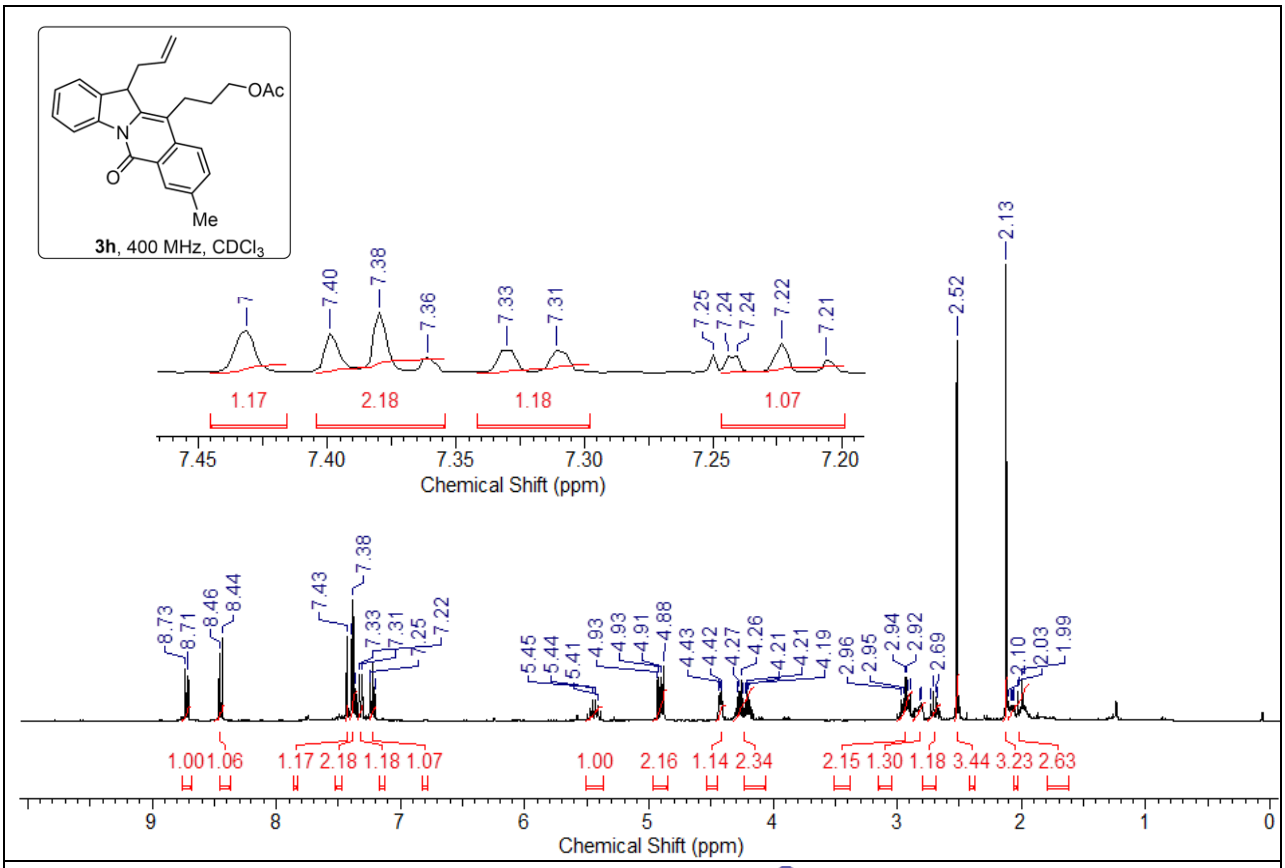




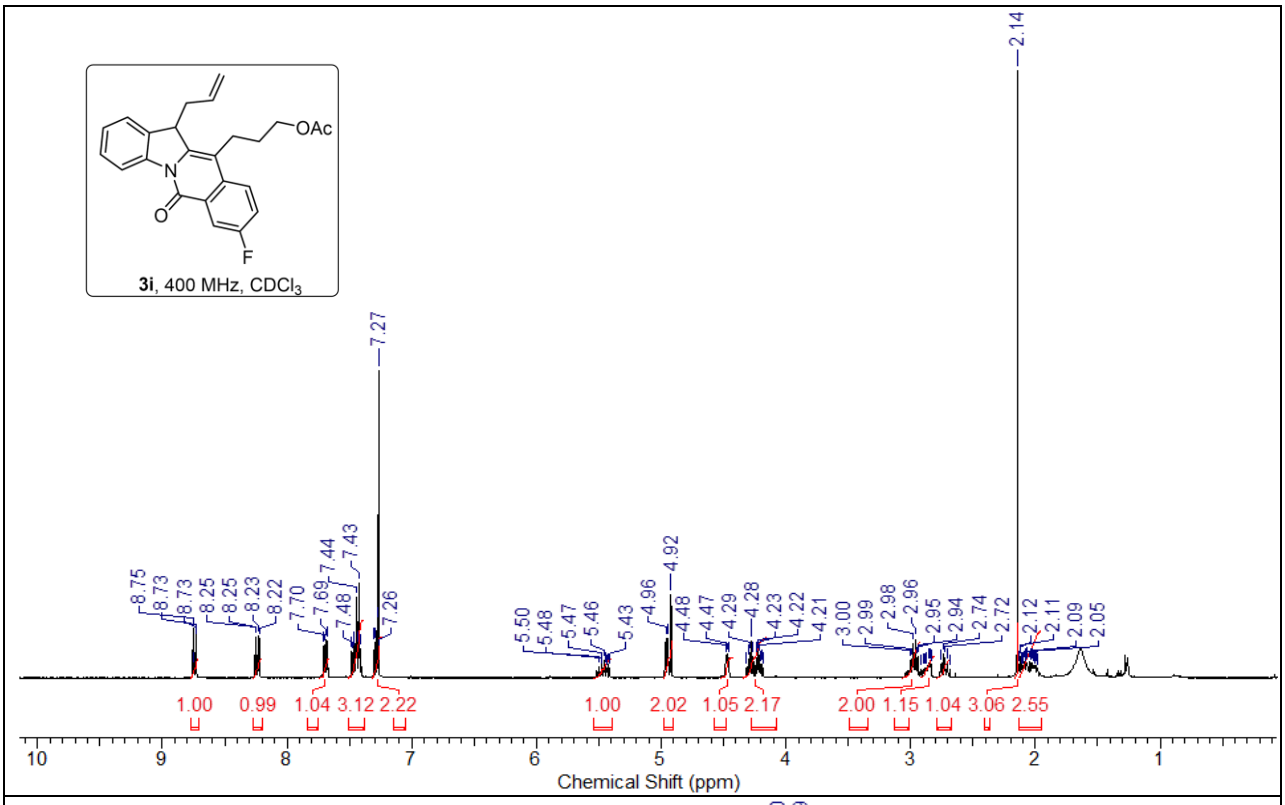
^{1}H /^{13}C NMR Spectrum of 3f

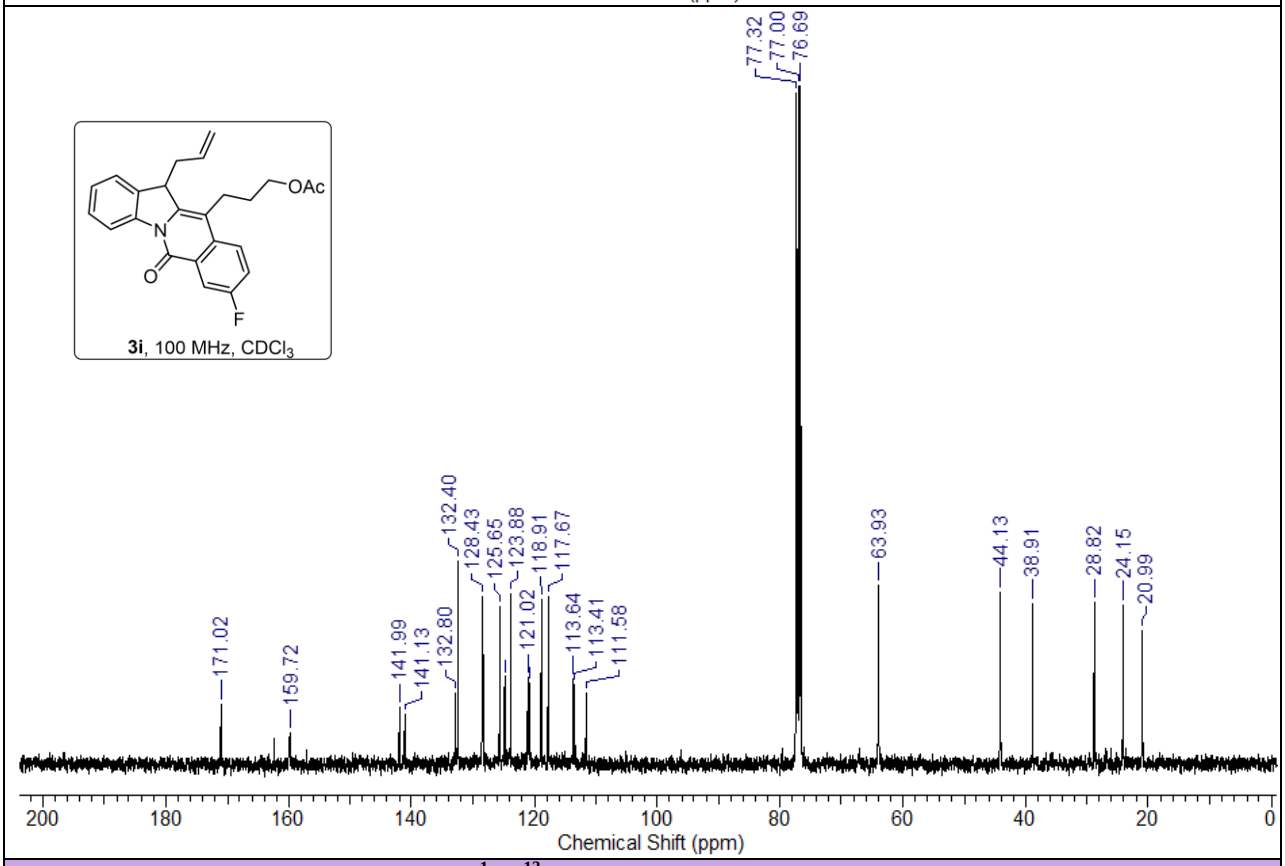


^{1}H /^{13}C NMR Spectrum of 3g

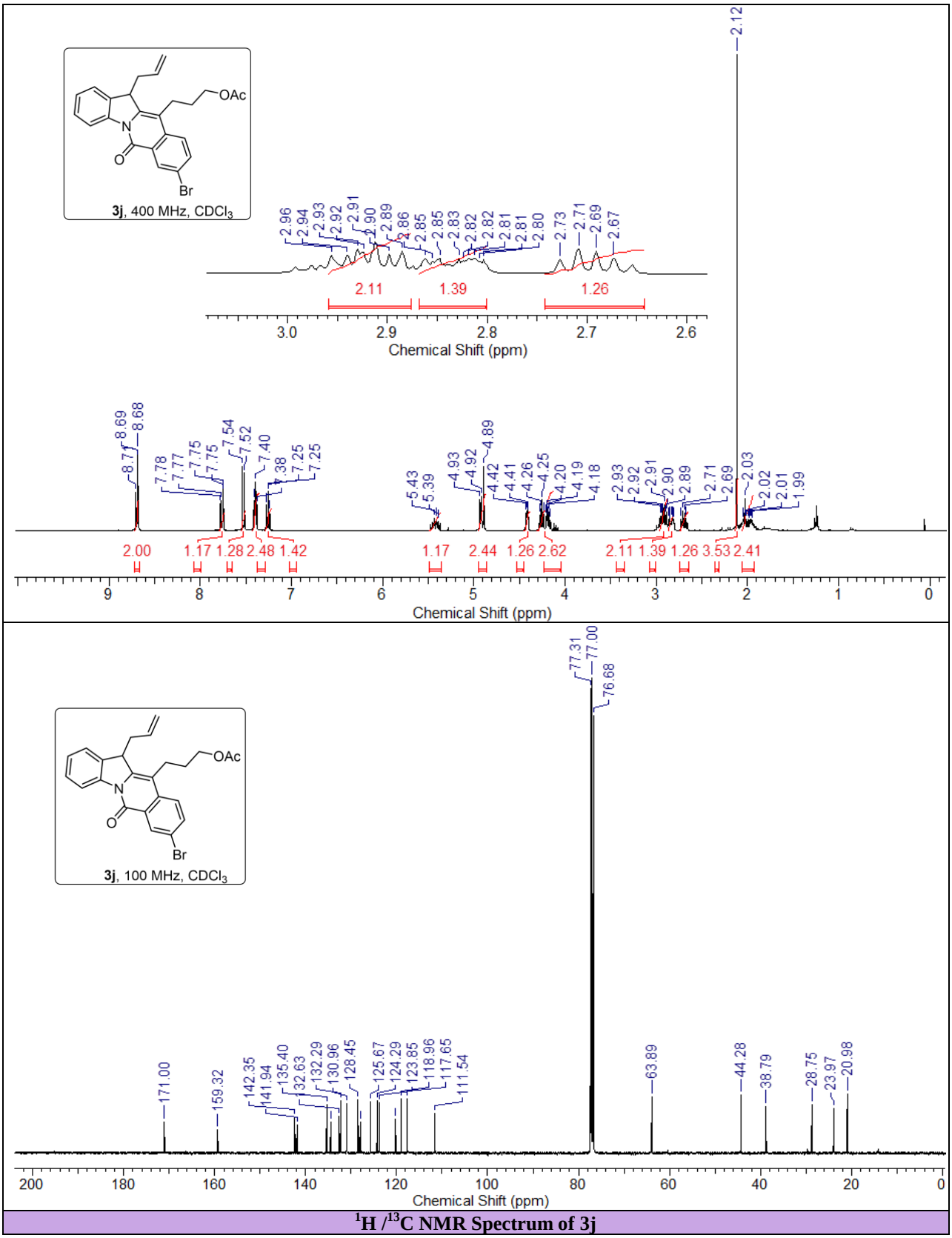


^{1}H /^{13}C NMR Spectrum of 3h

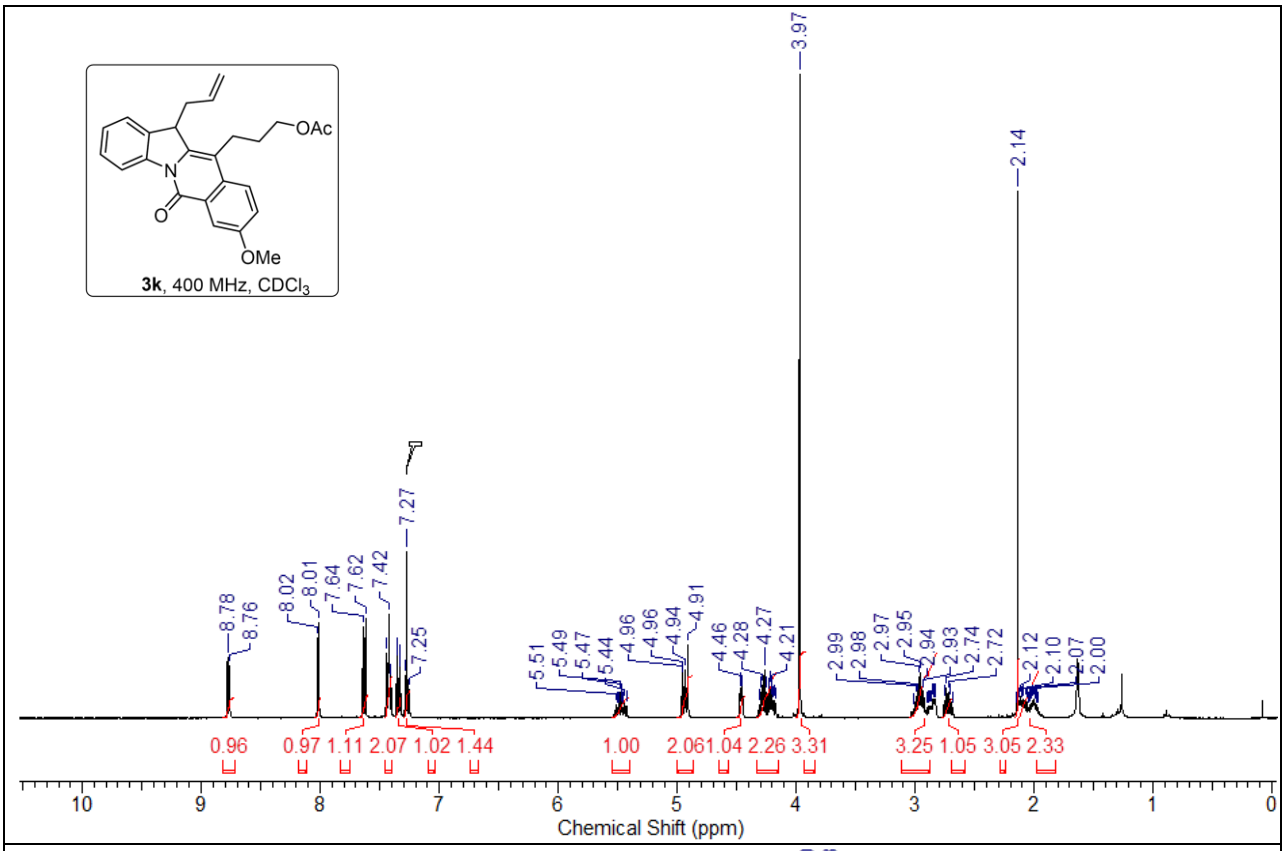


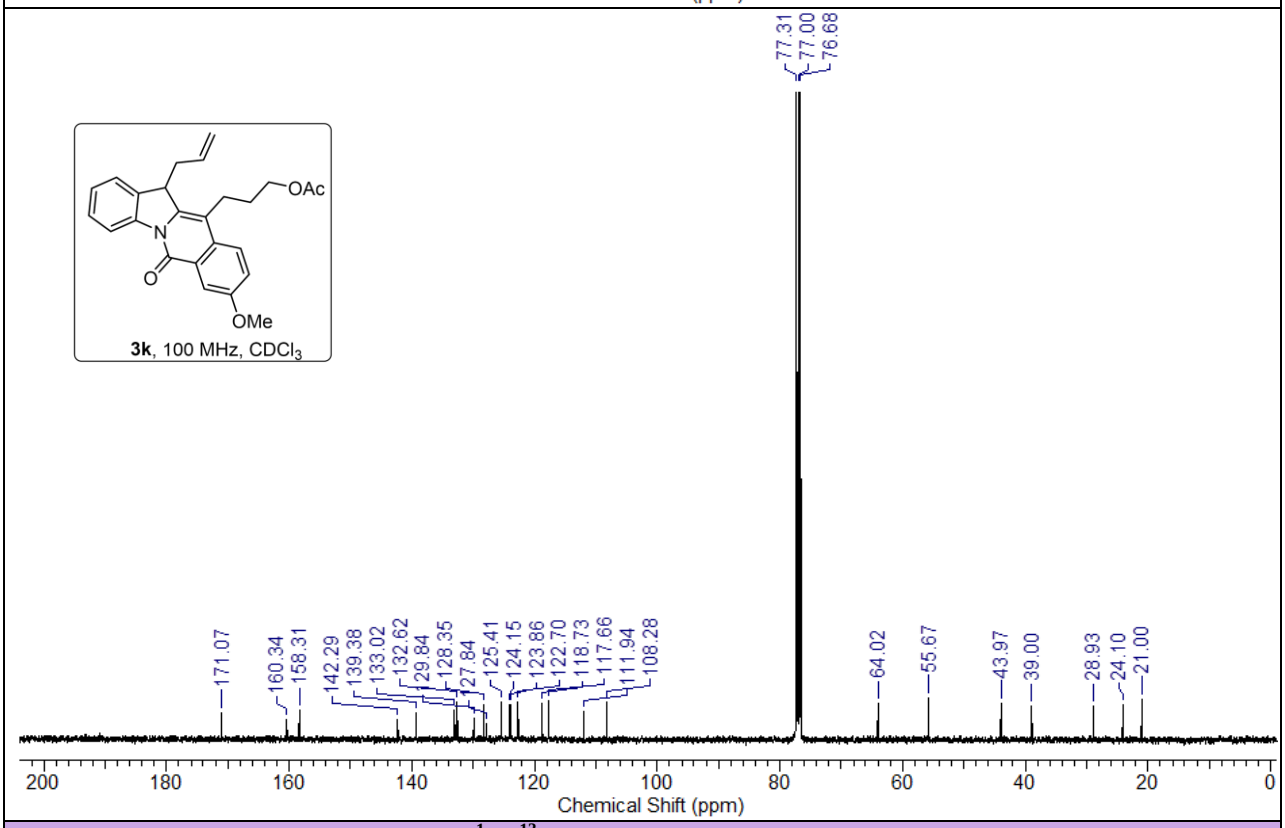


^{1}H /^{13}C NMR Spectrum of 3i

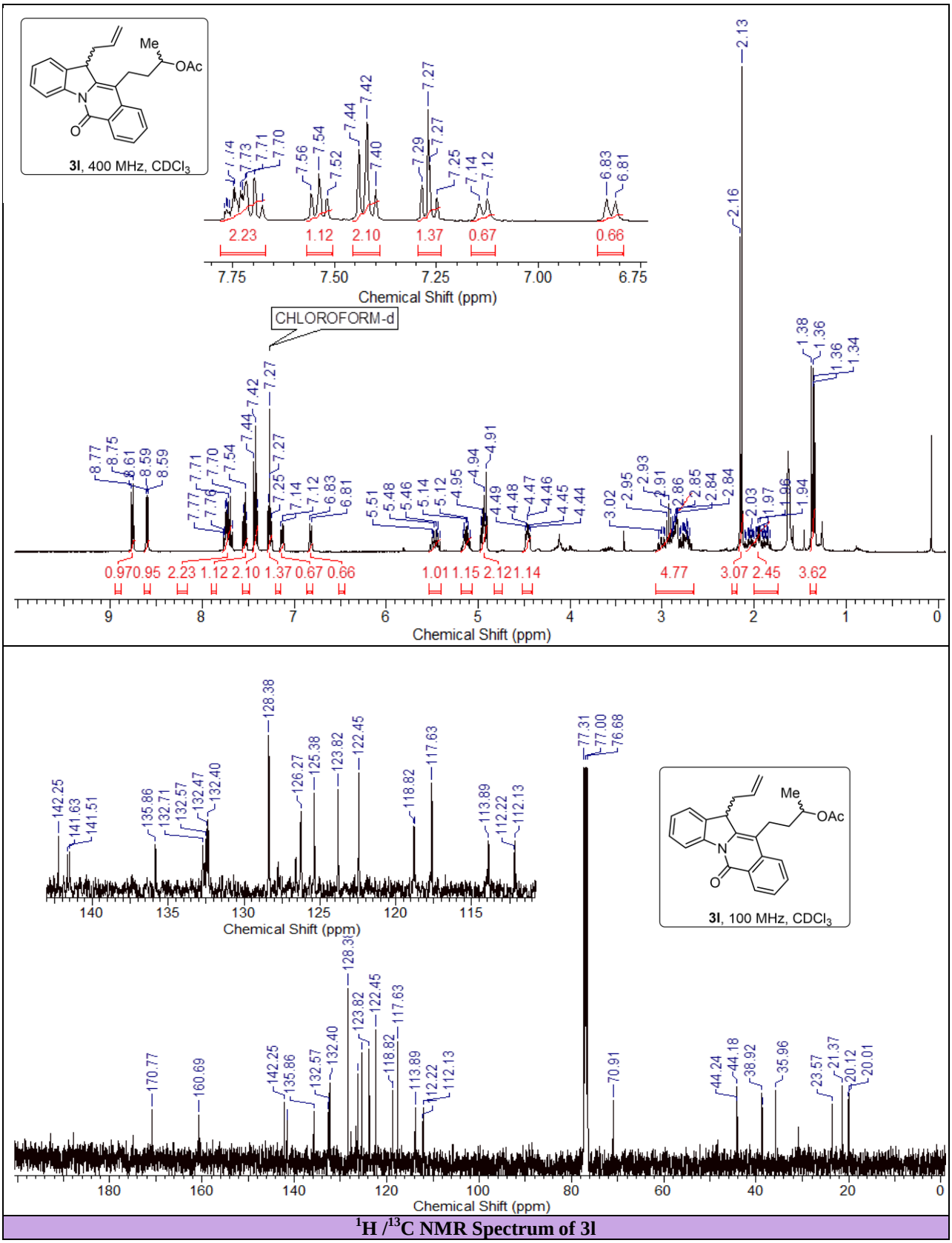


^{1}H /^{13}C NMR Spectrum of 3j

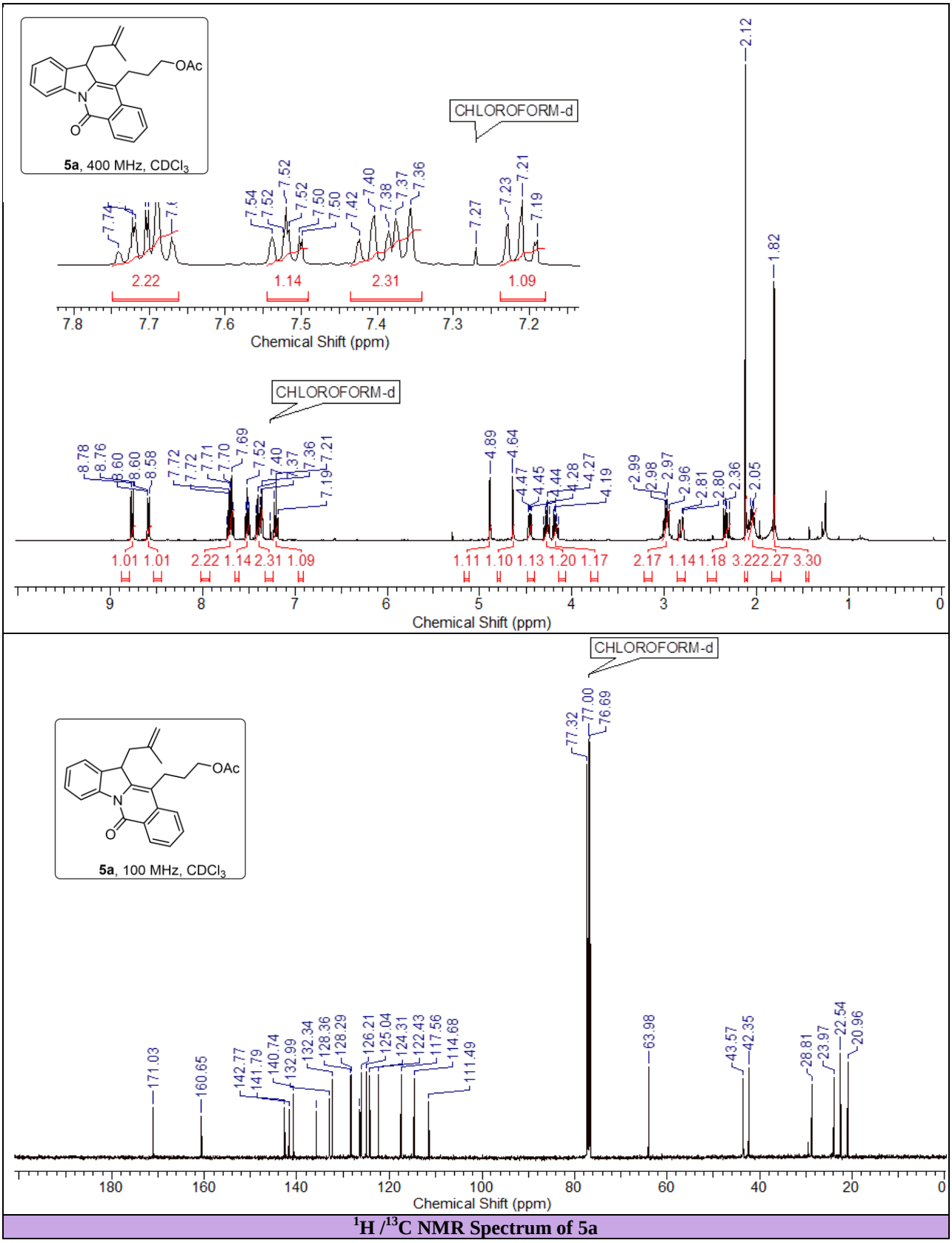




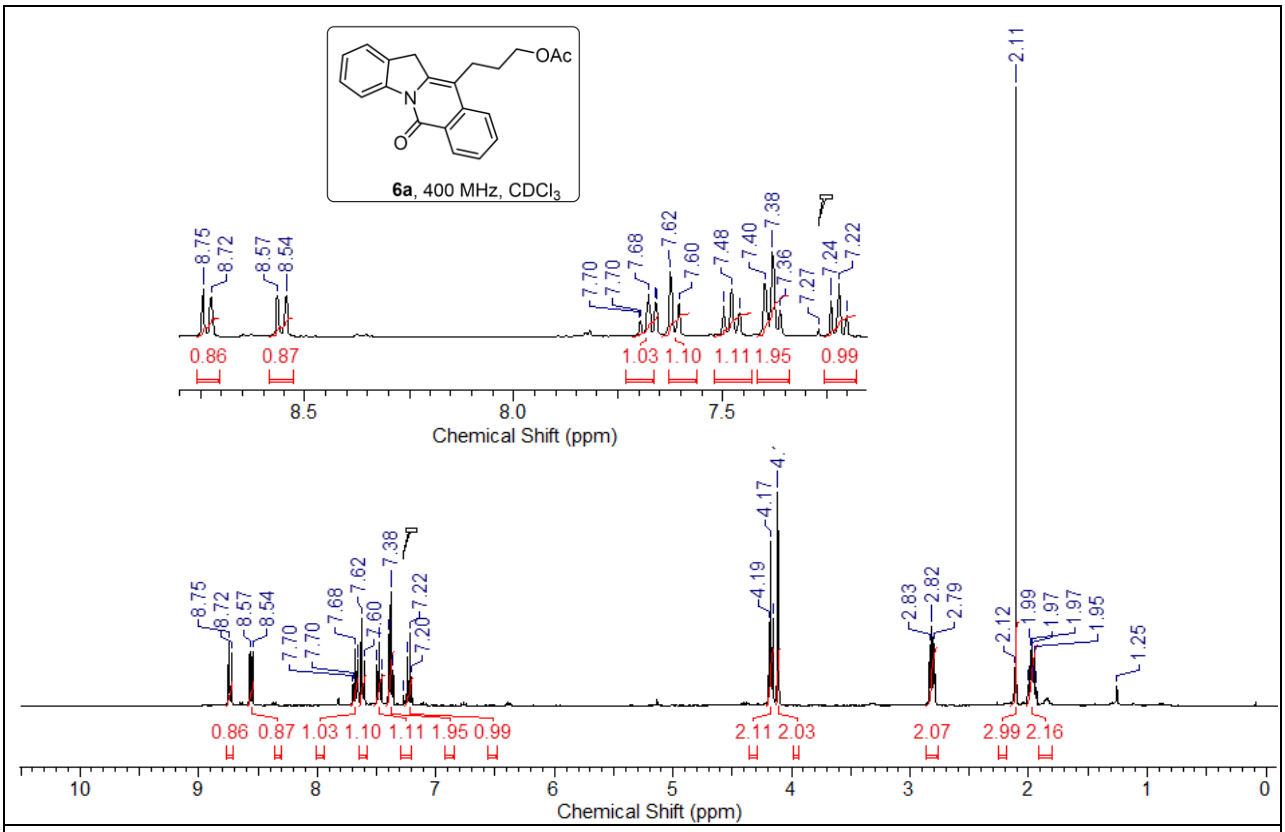
^{1}H /^{13}C NMR Spectrum of 3k

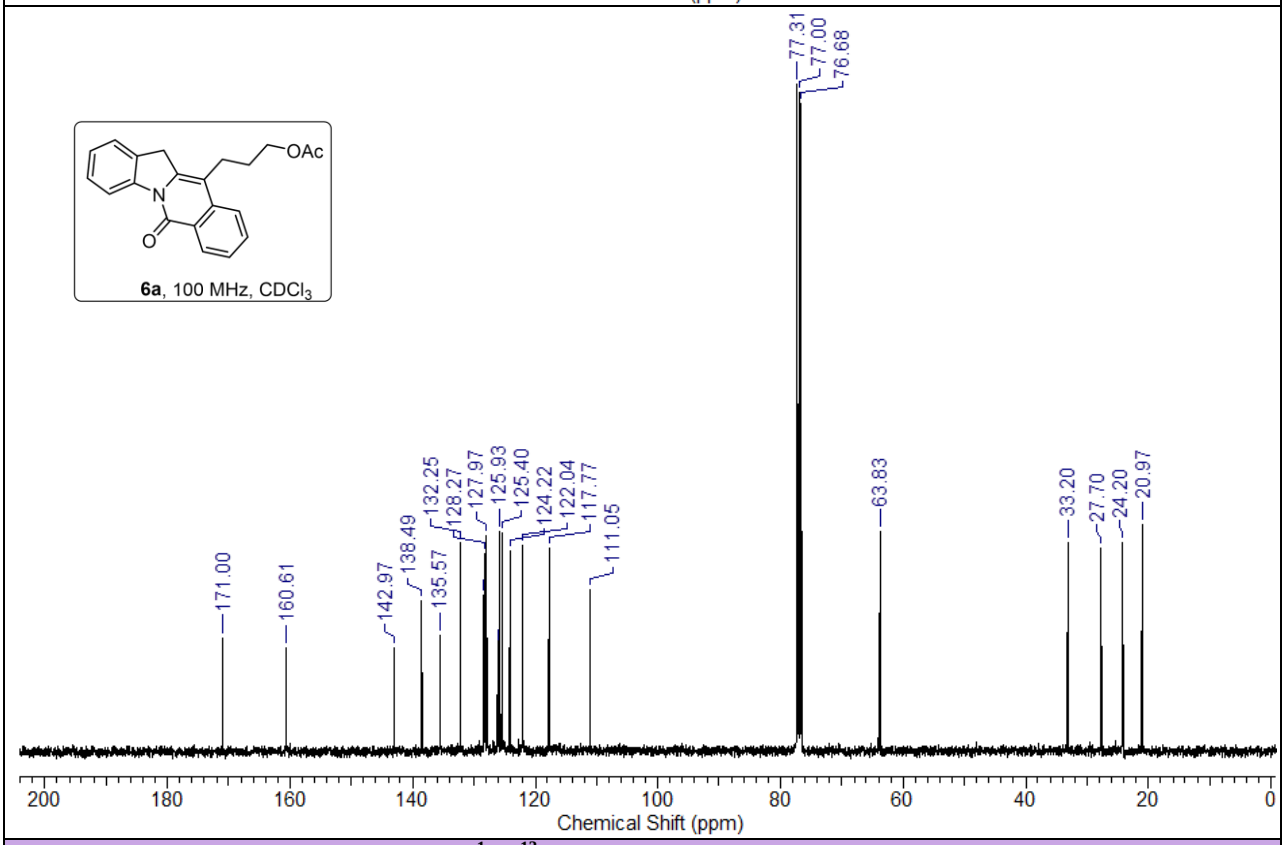


^{1}H /^{13}C NMR Spectrum of 3l

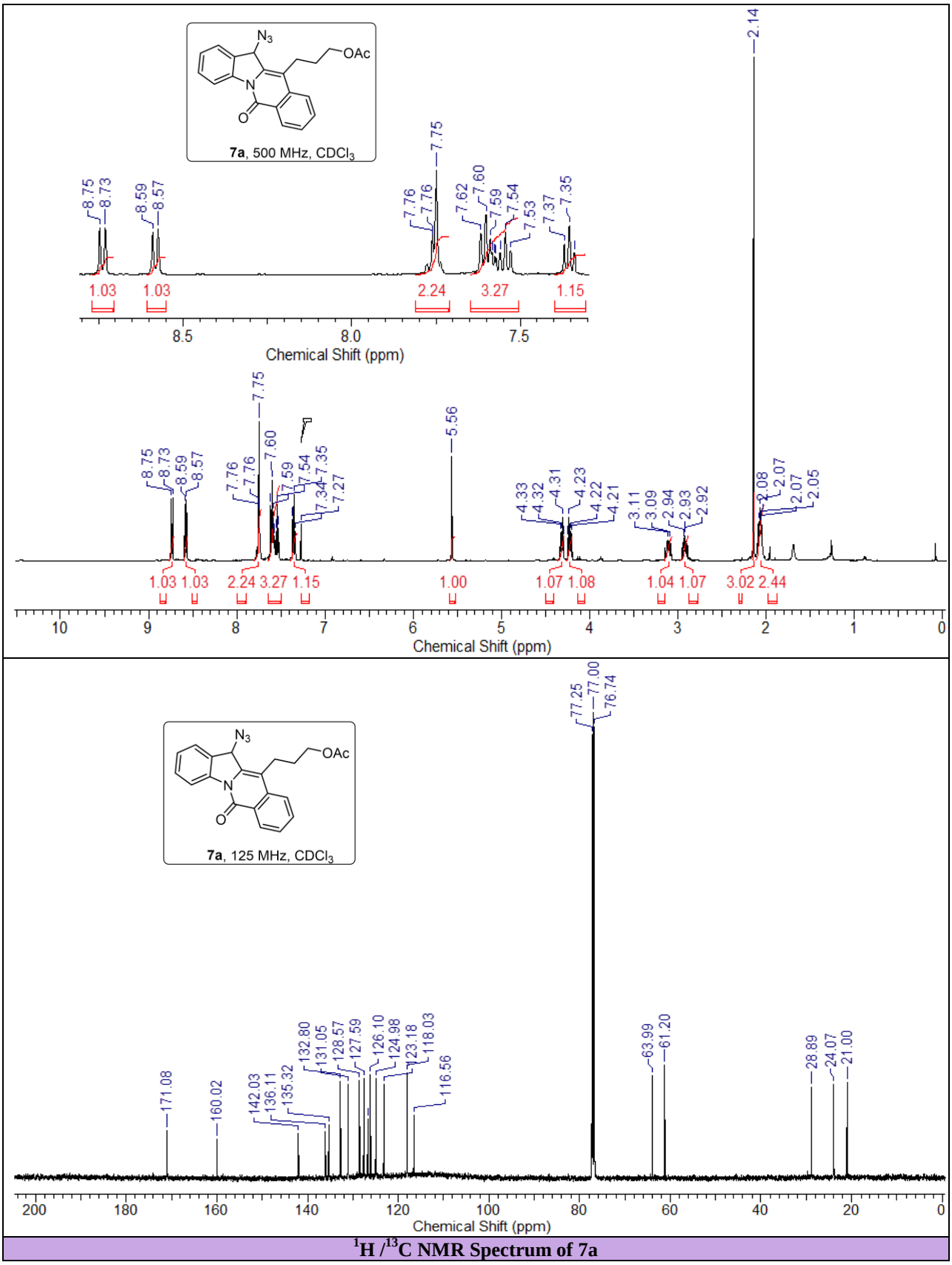


^{1}H /^{13}C NMR Spectrum of 5a

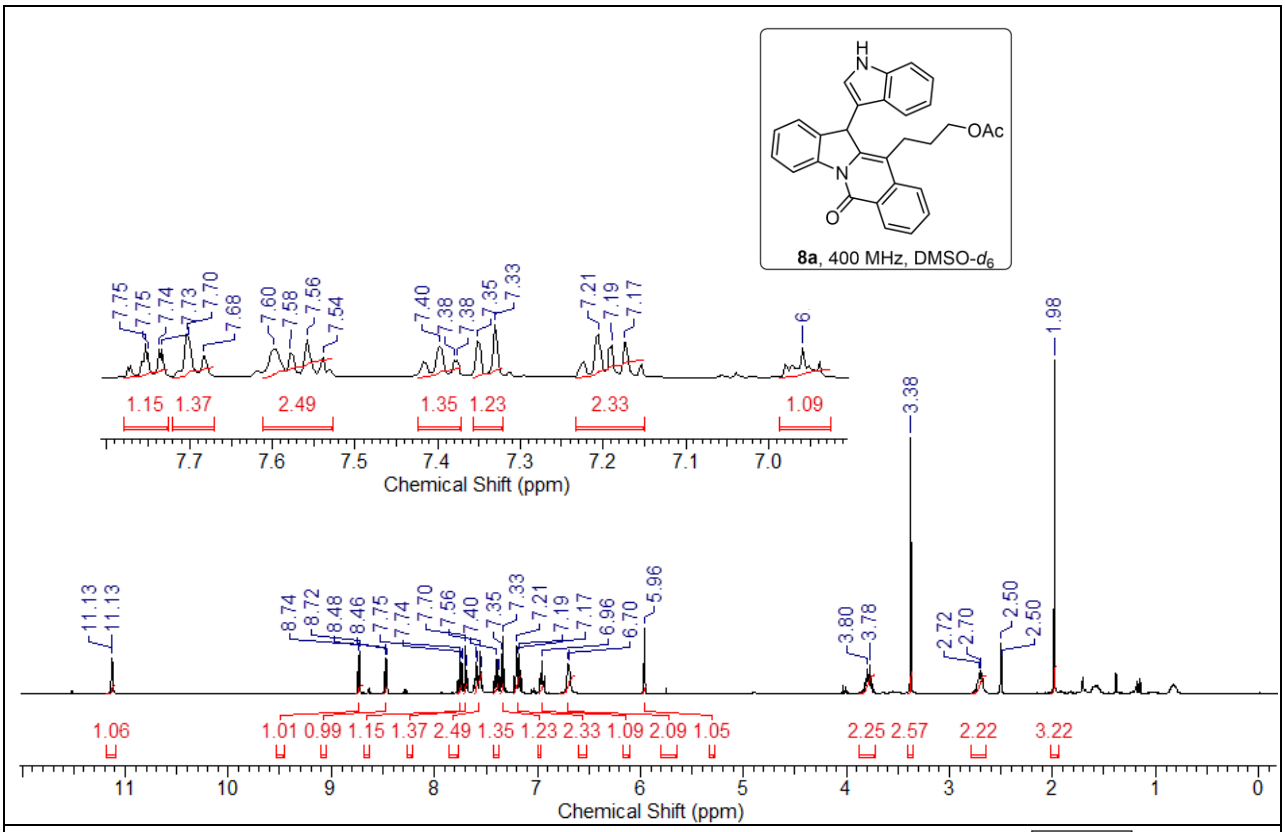


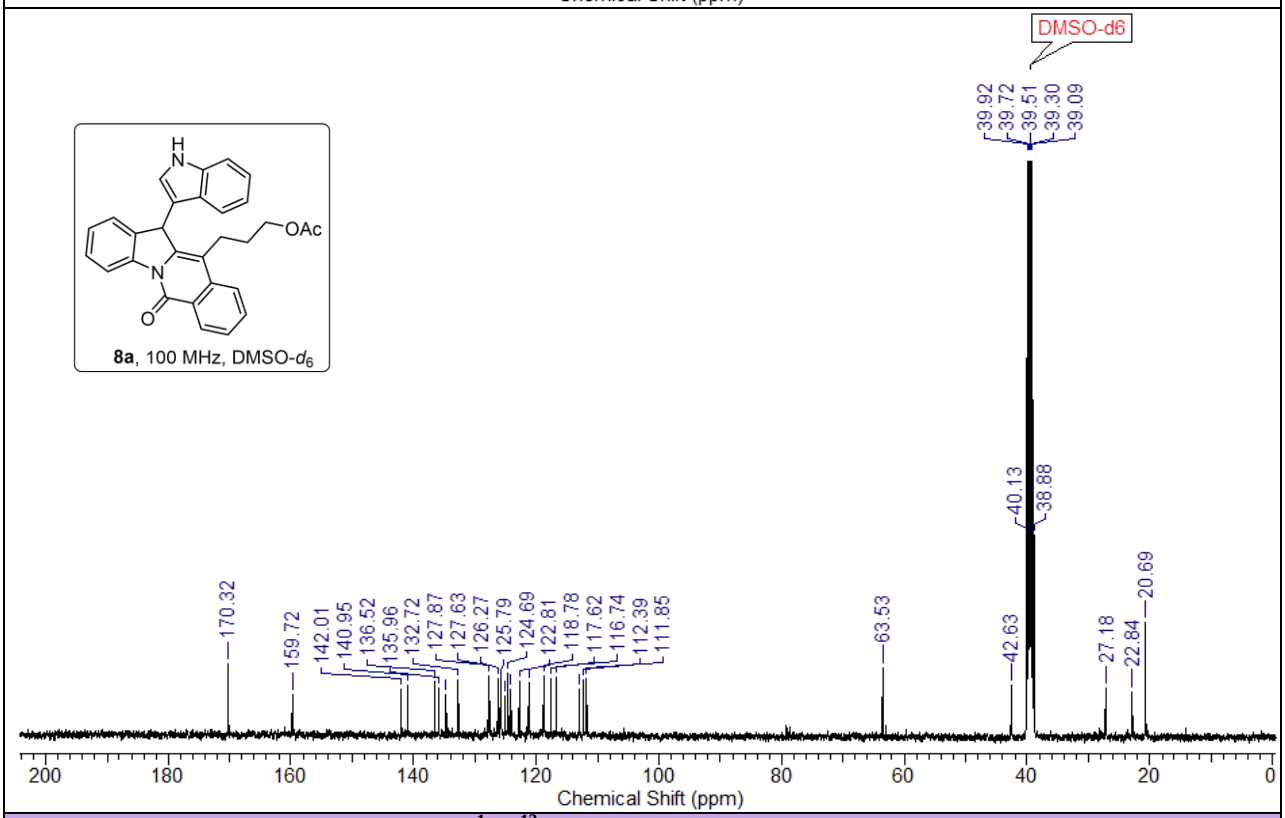


^{1}H /^{13}C NMR Spectrum of 6a

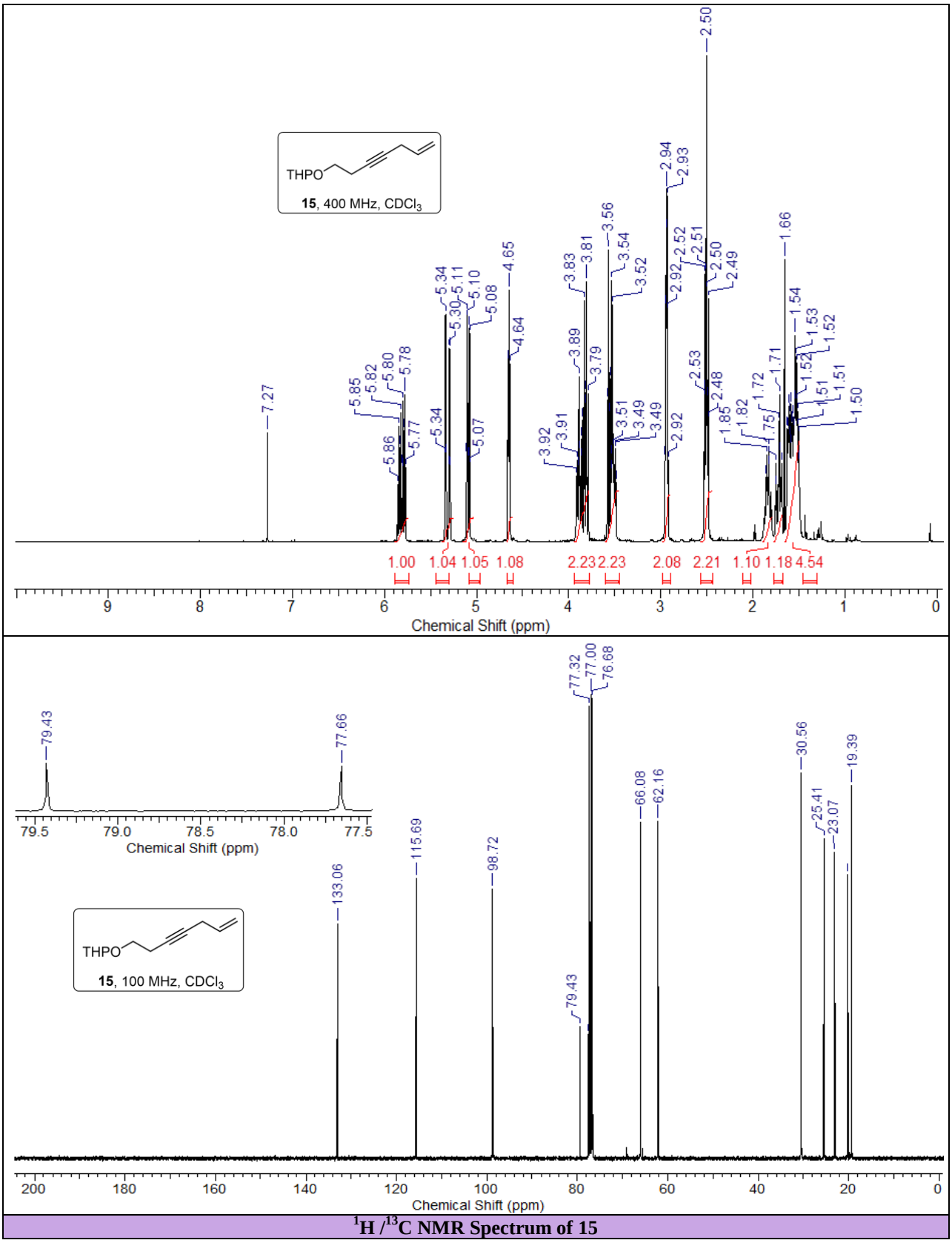


^{1}H /^{13}C NMR Spectrum of 7a

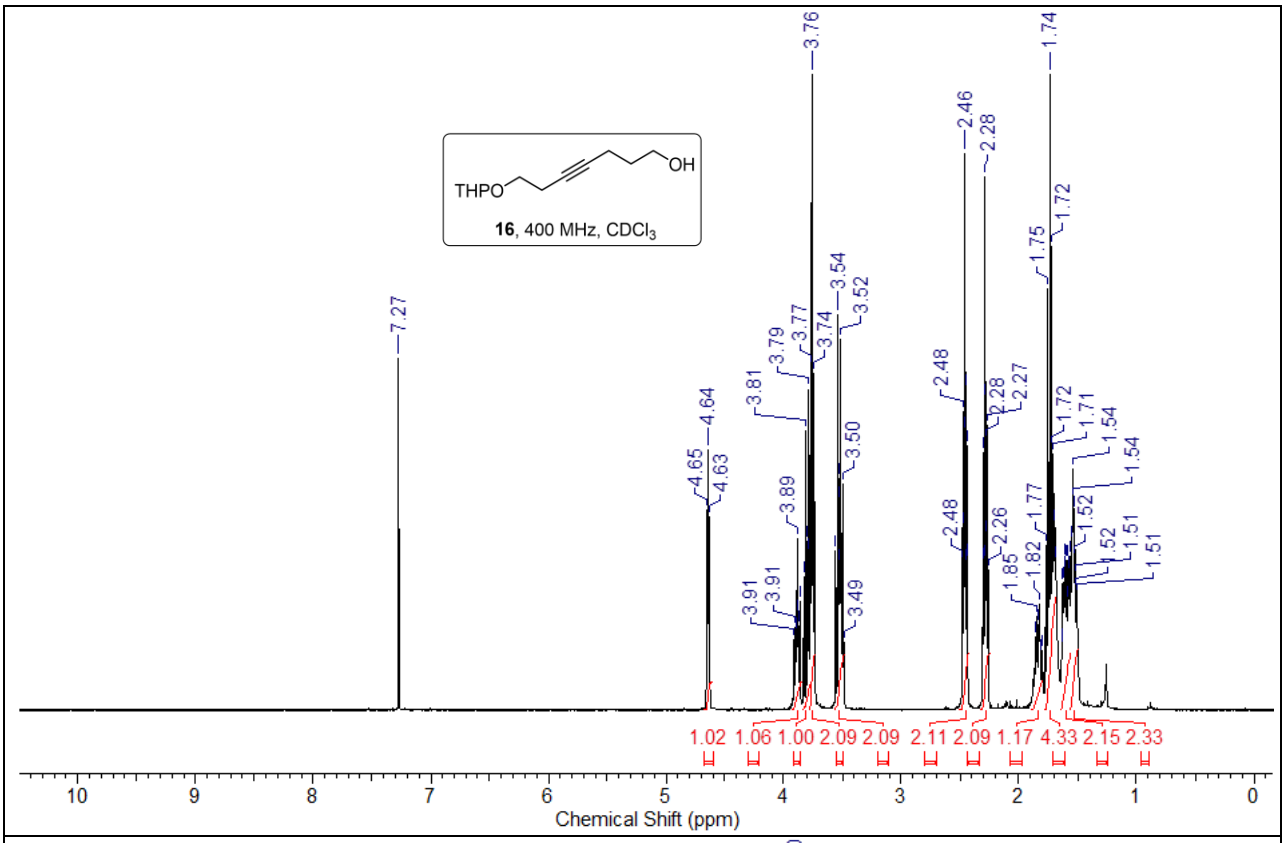


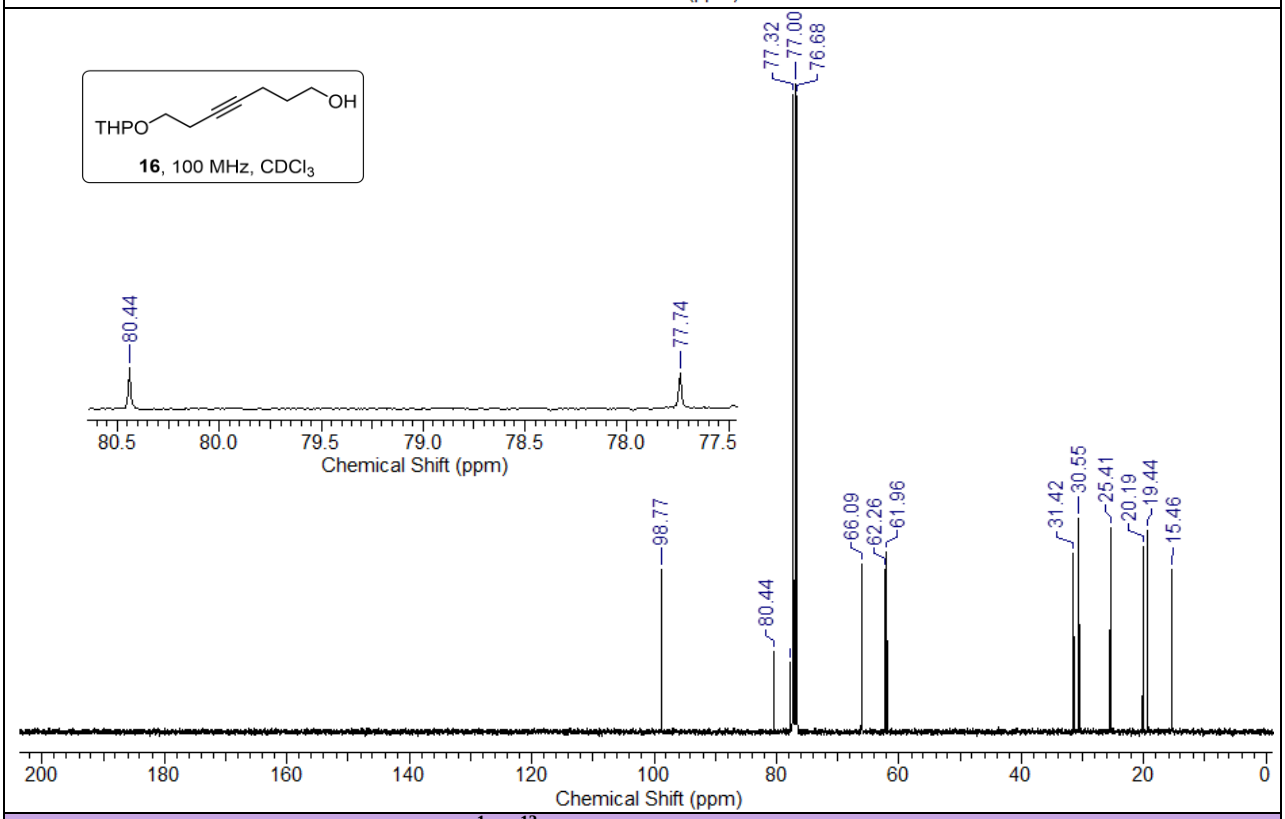


^{1}H /^{13}C NMR Spectrum of 8a

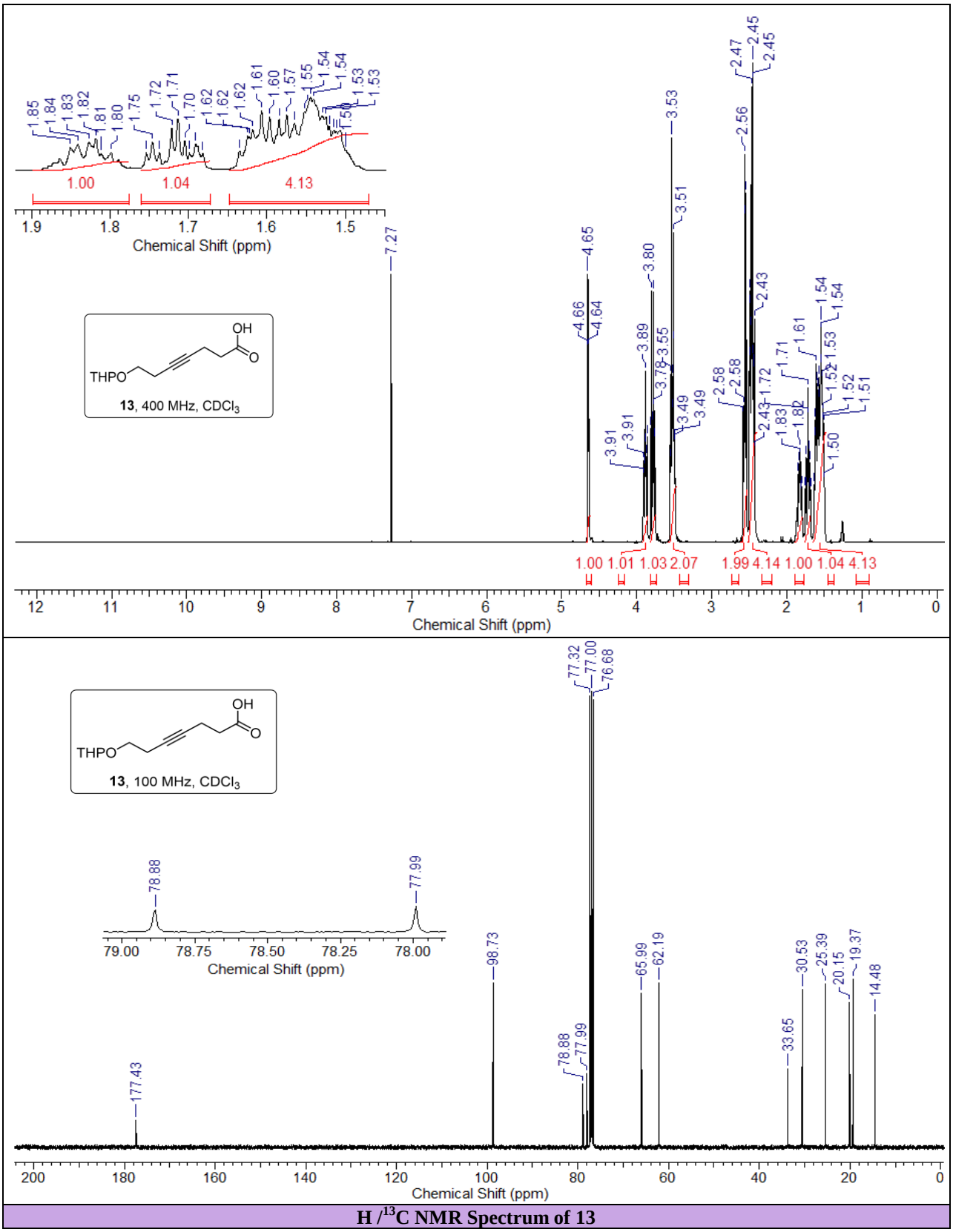


^{1}H /^{13}C NMR Spectrum of 15

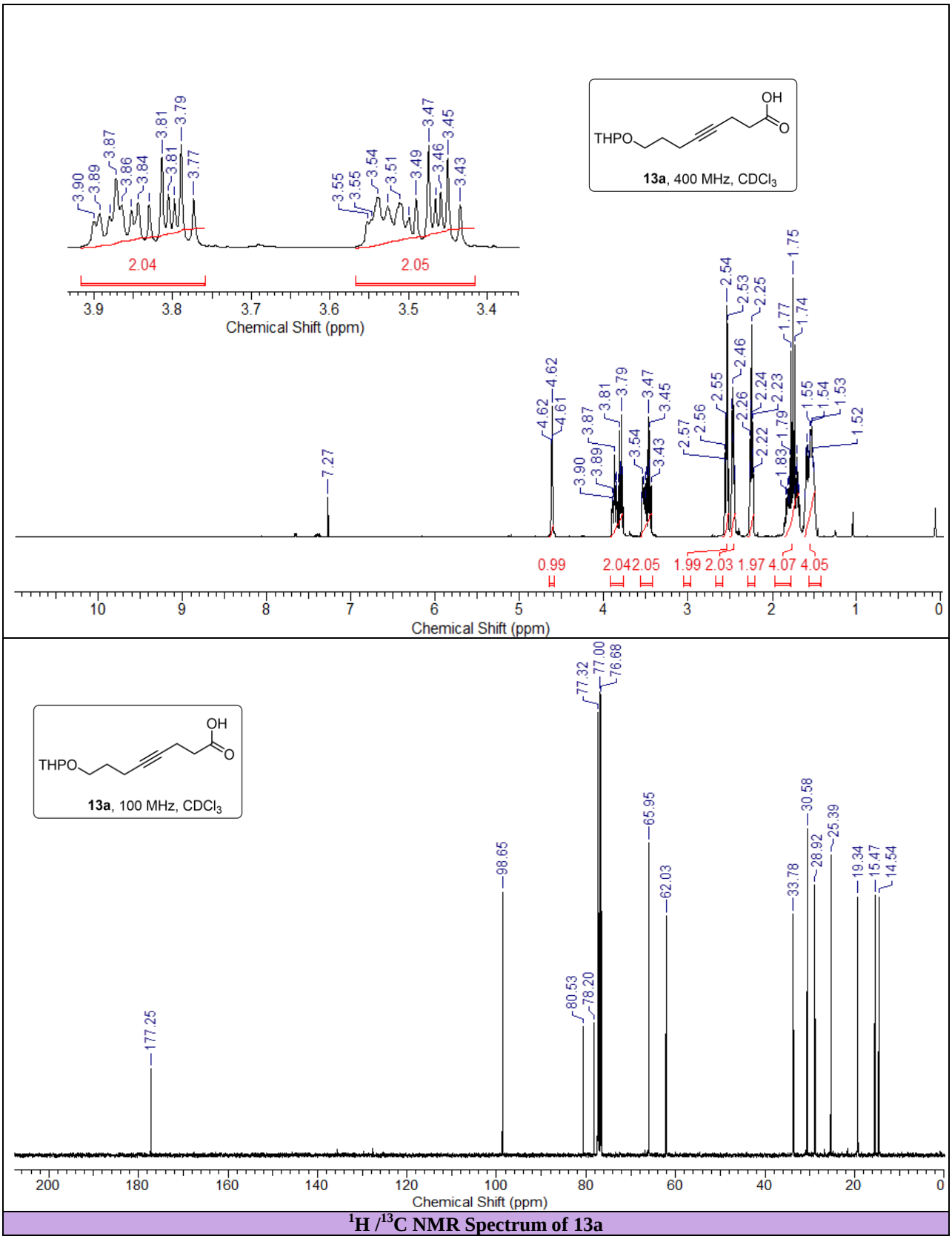




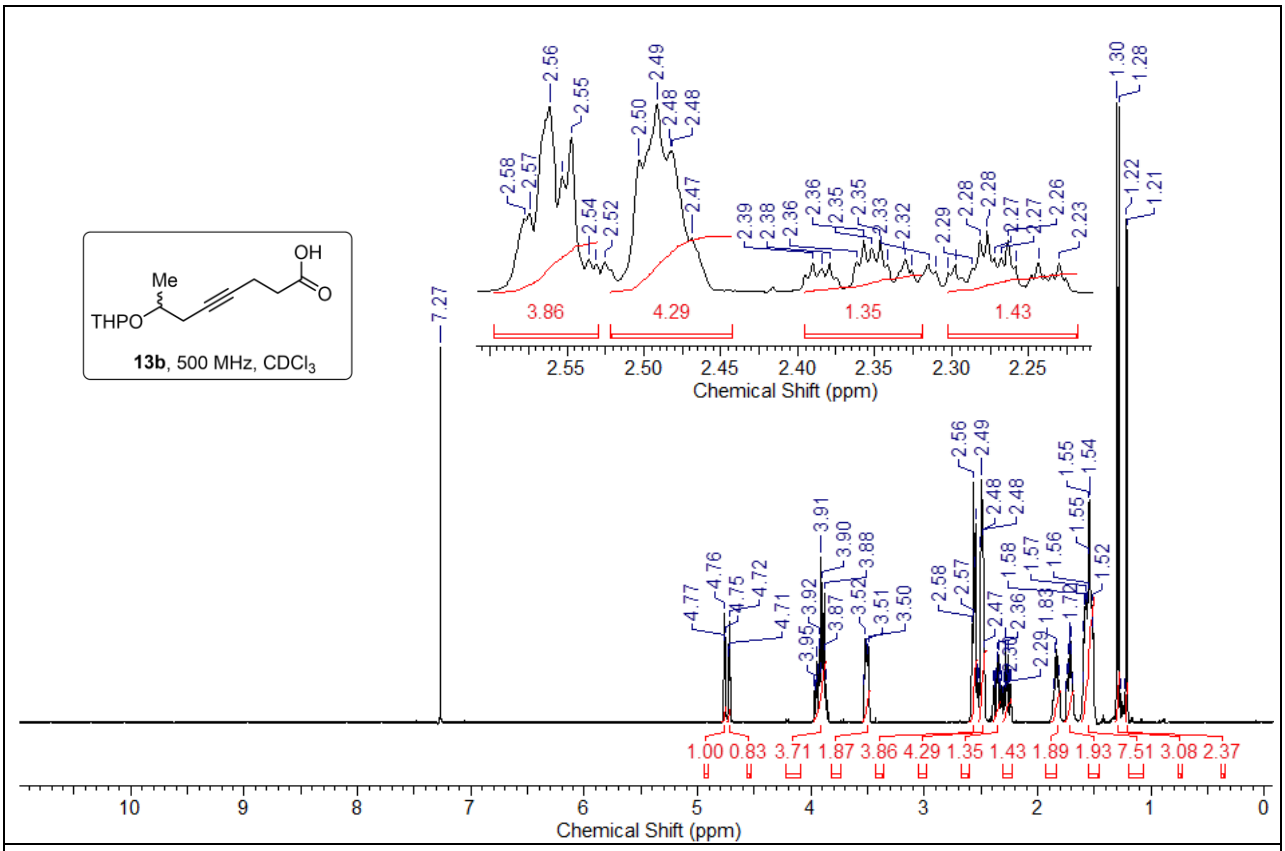
^{1}H /^{13}C NMR Spectrum of 16

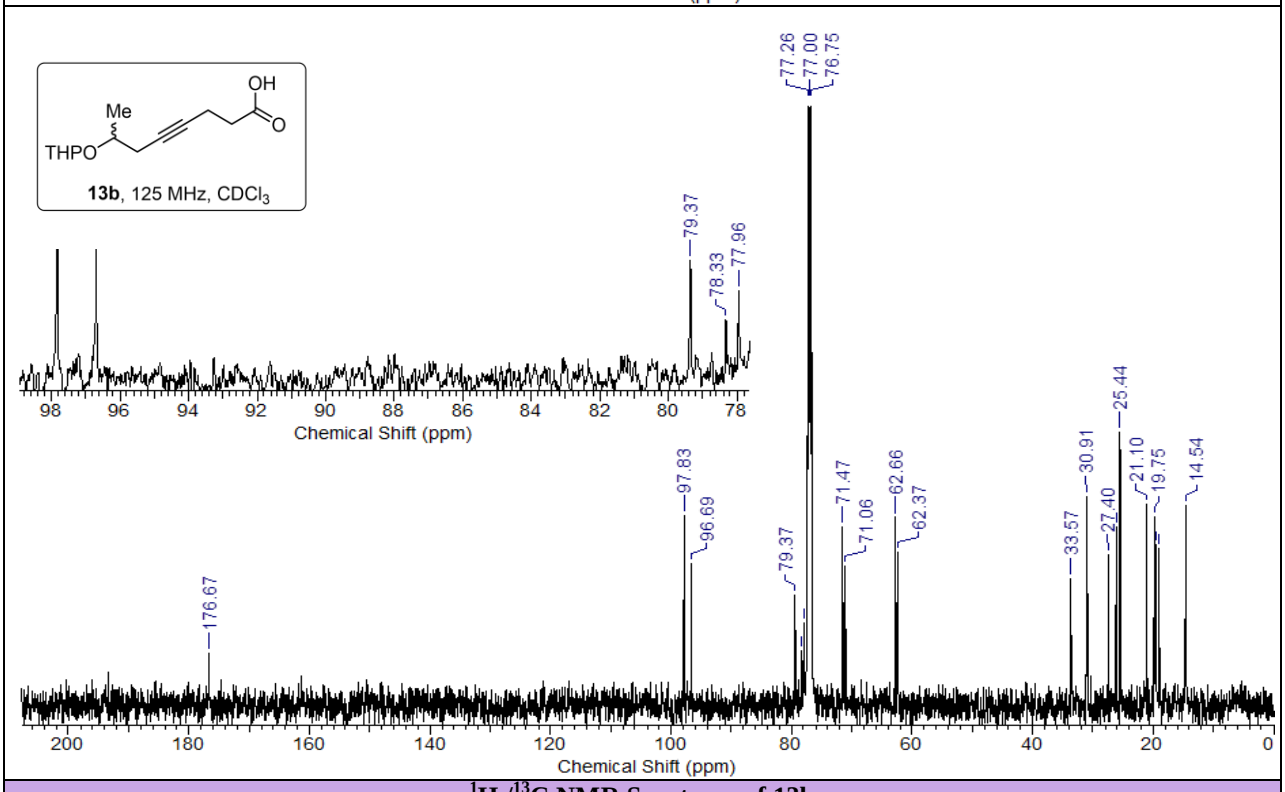


H /^{13}C NMR Spectrum of 13

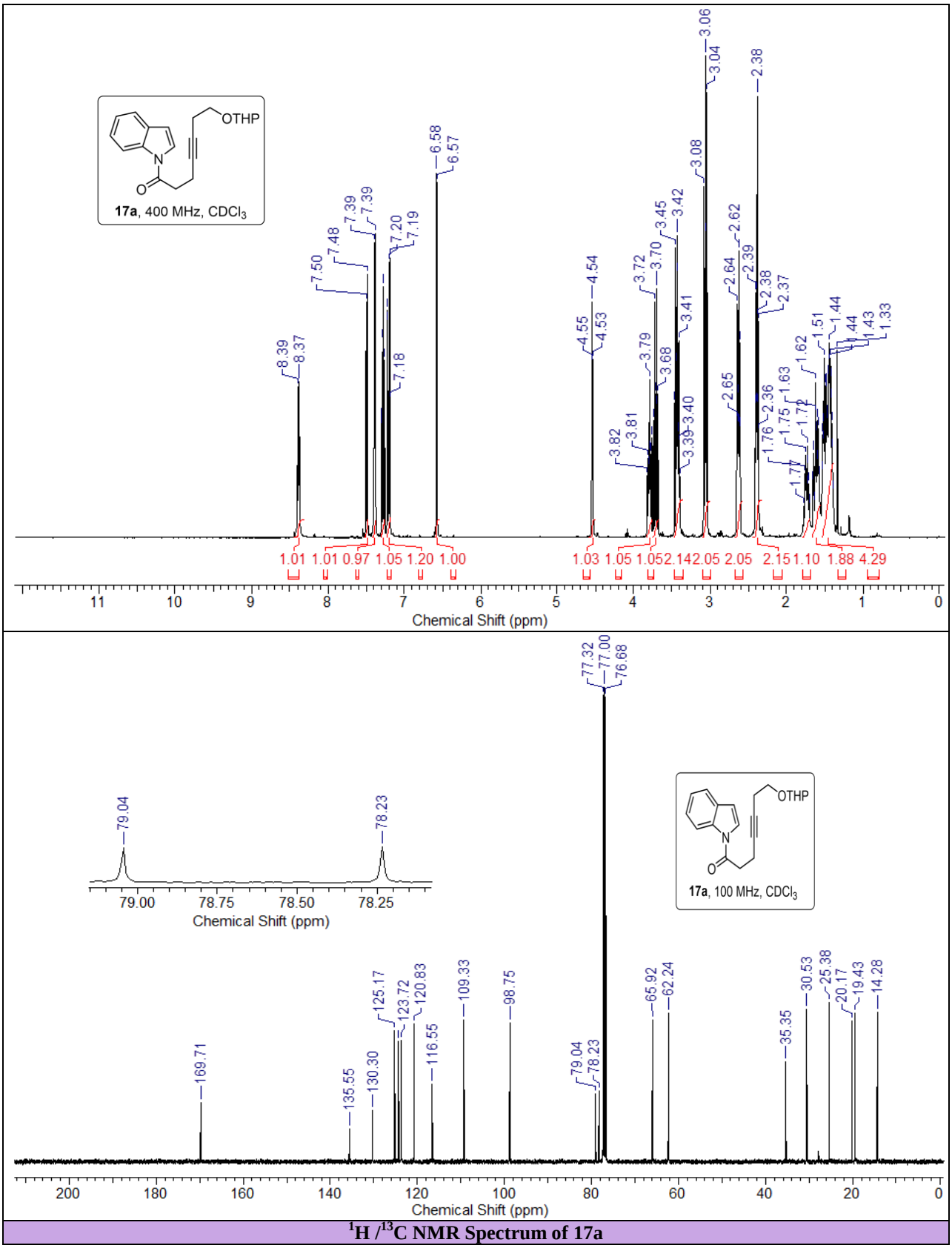


^{1}H /^{13}C NMR Spectrum of 13a

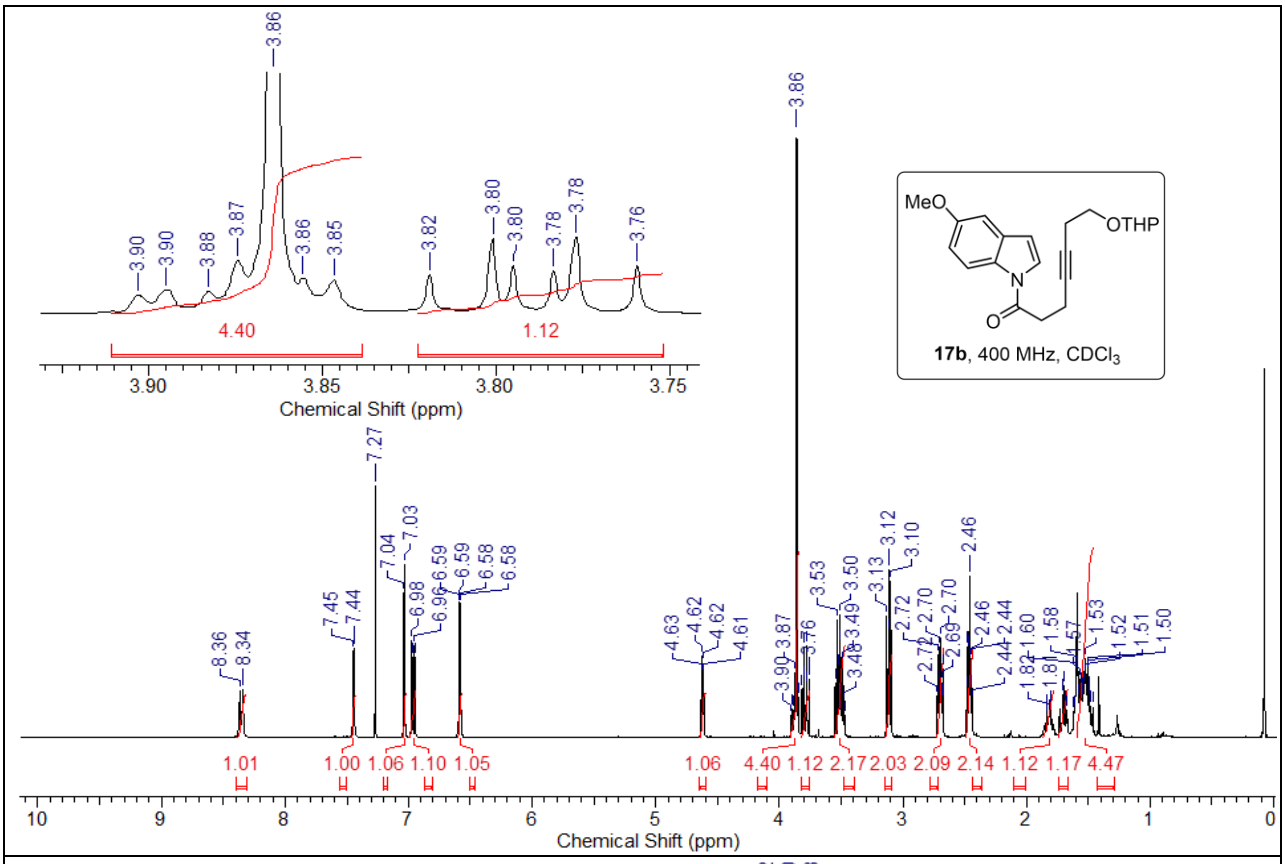




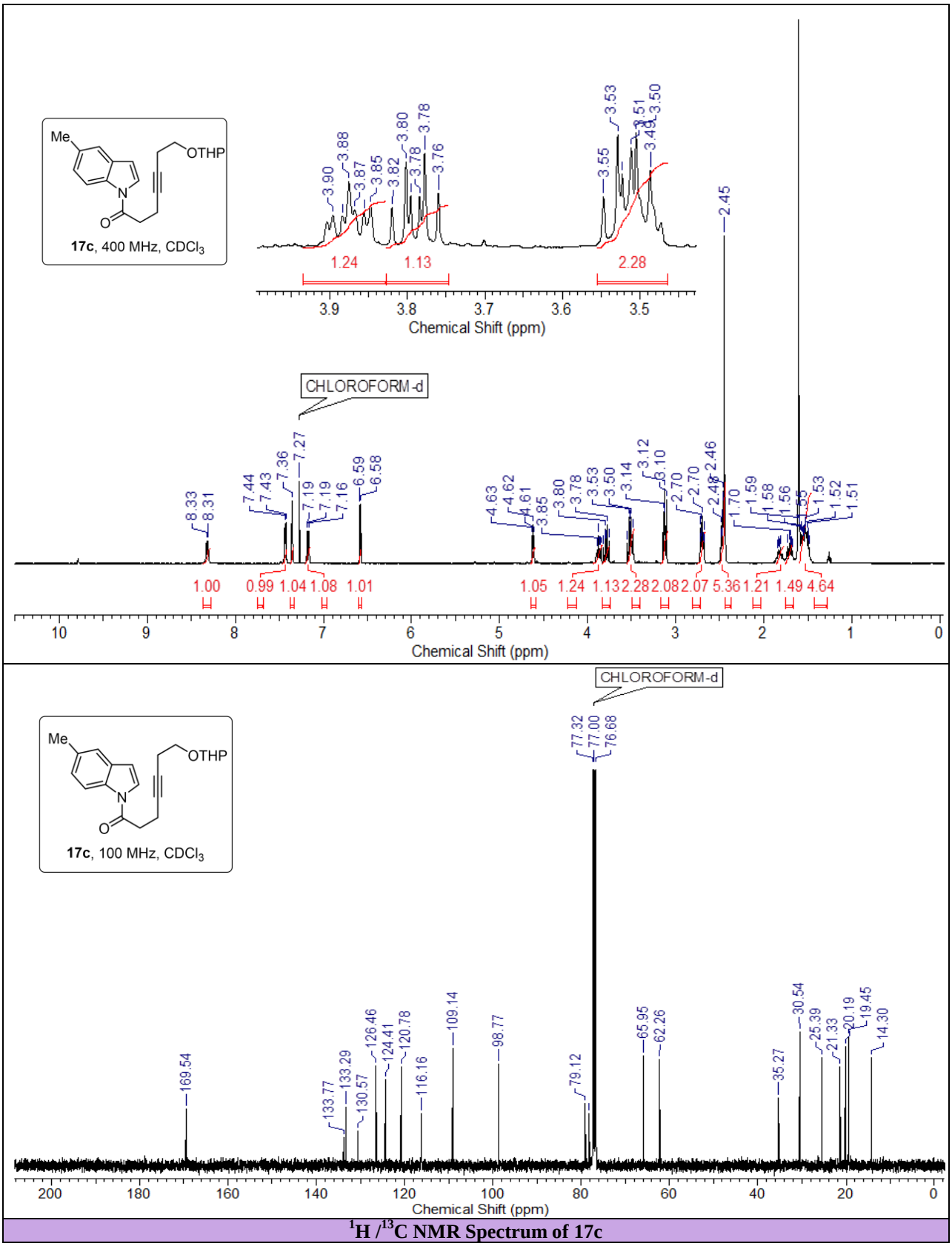
^{1}H /^{13}C NMR Spectrum of 13b



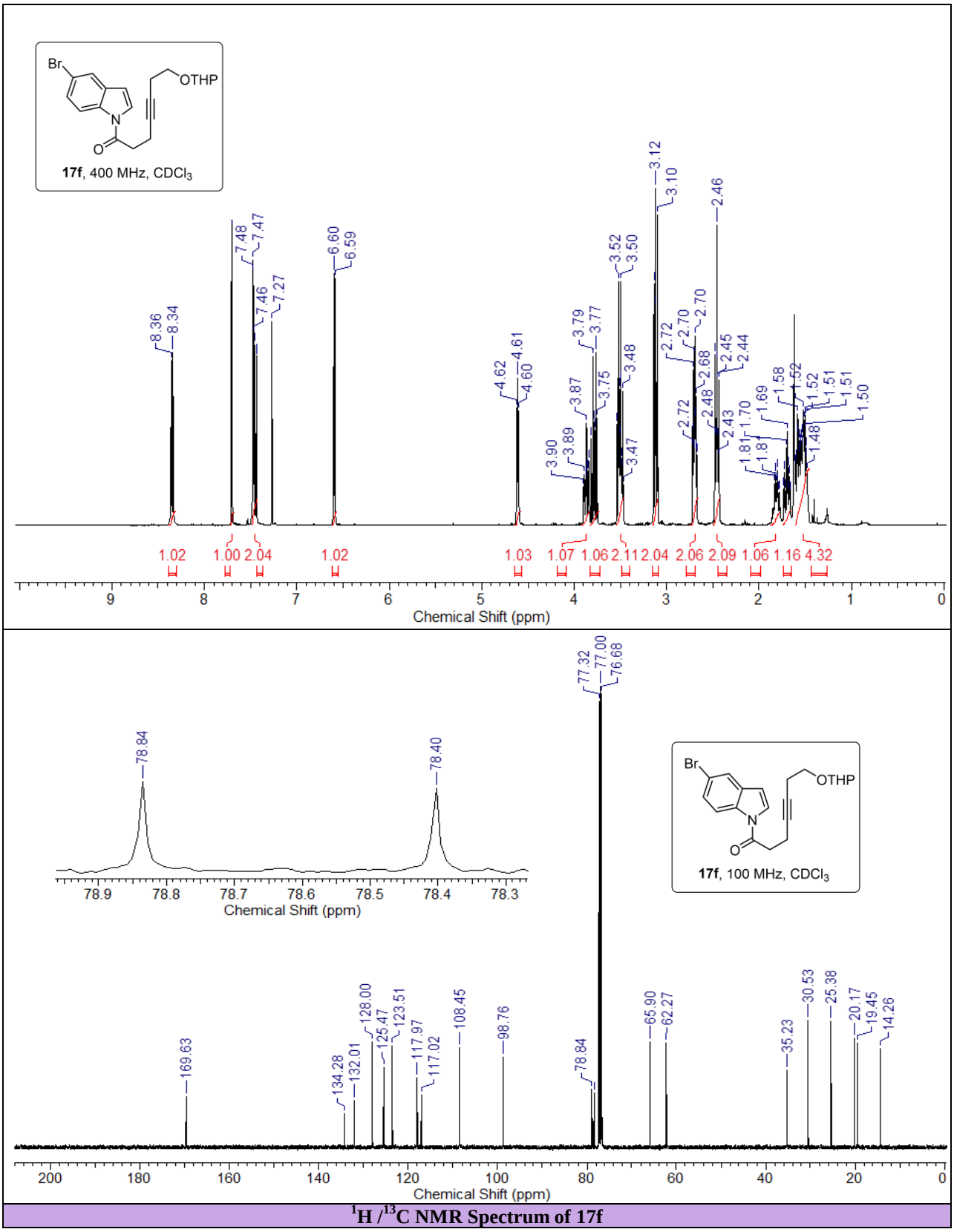
^{1}H /^{13}C NMR Spectrum of 17a



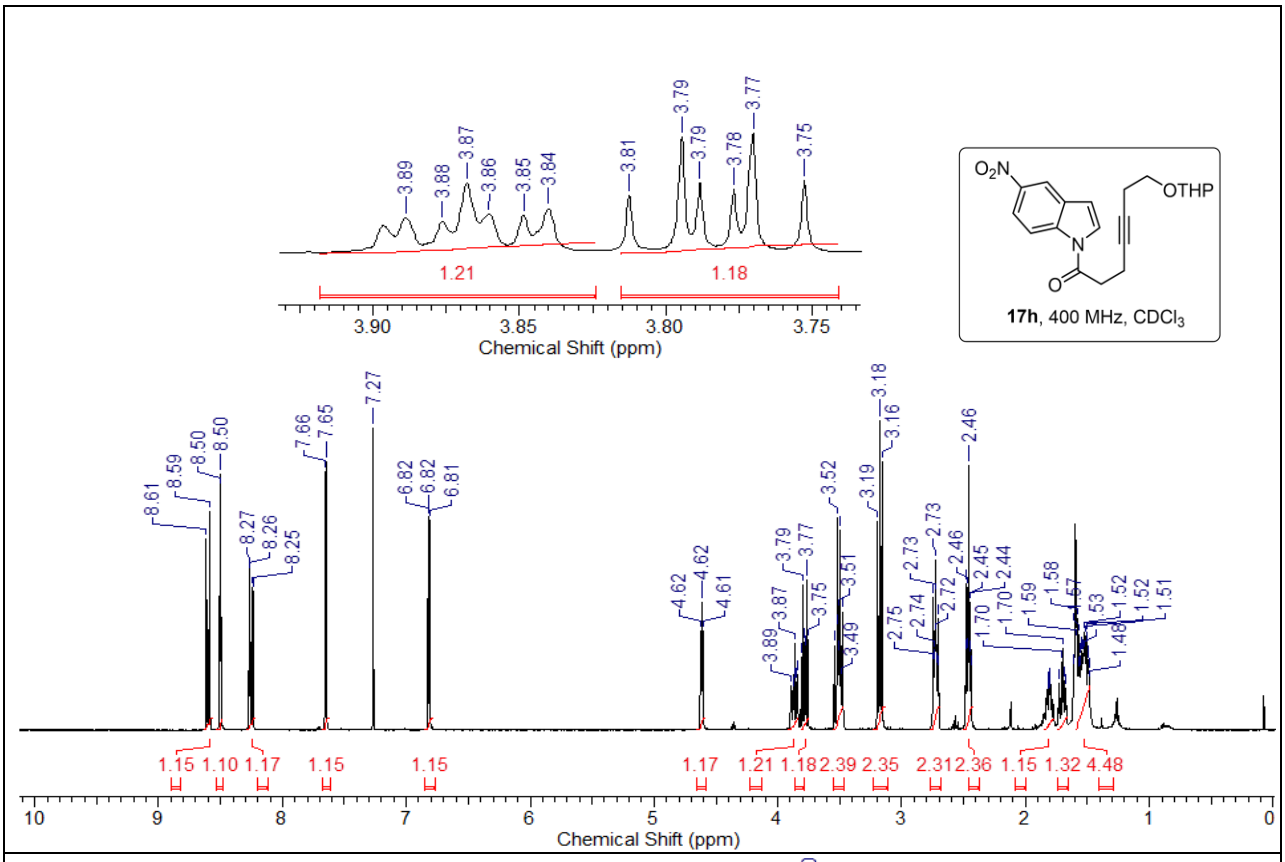
^{1}H /^{13}C NMR Spectrum of 17b



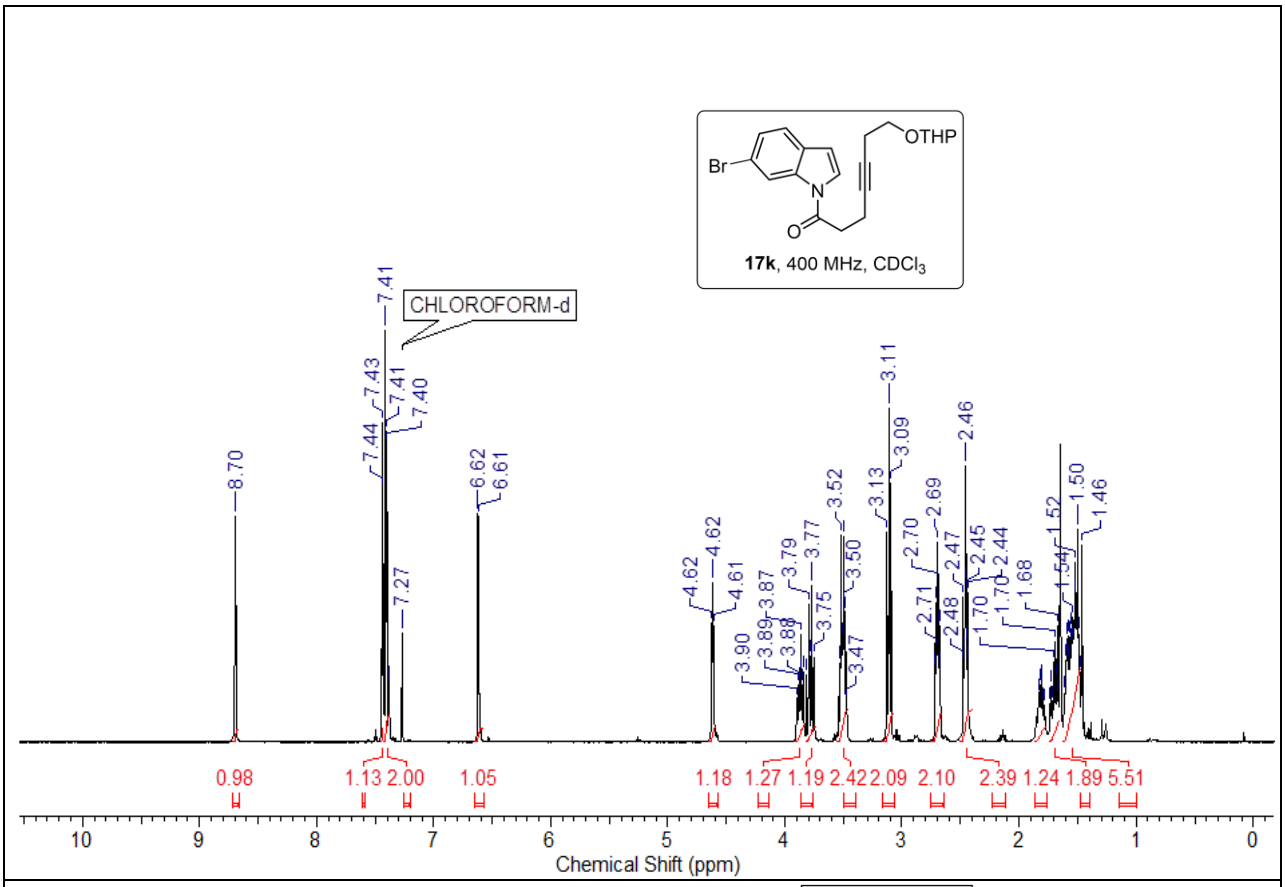
^{1}H /^{13}C NMR Spectrum of 17c



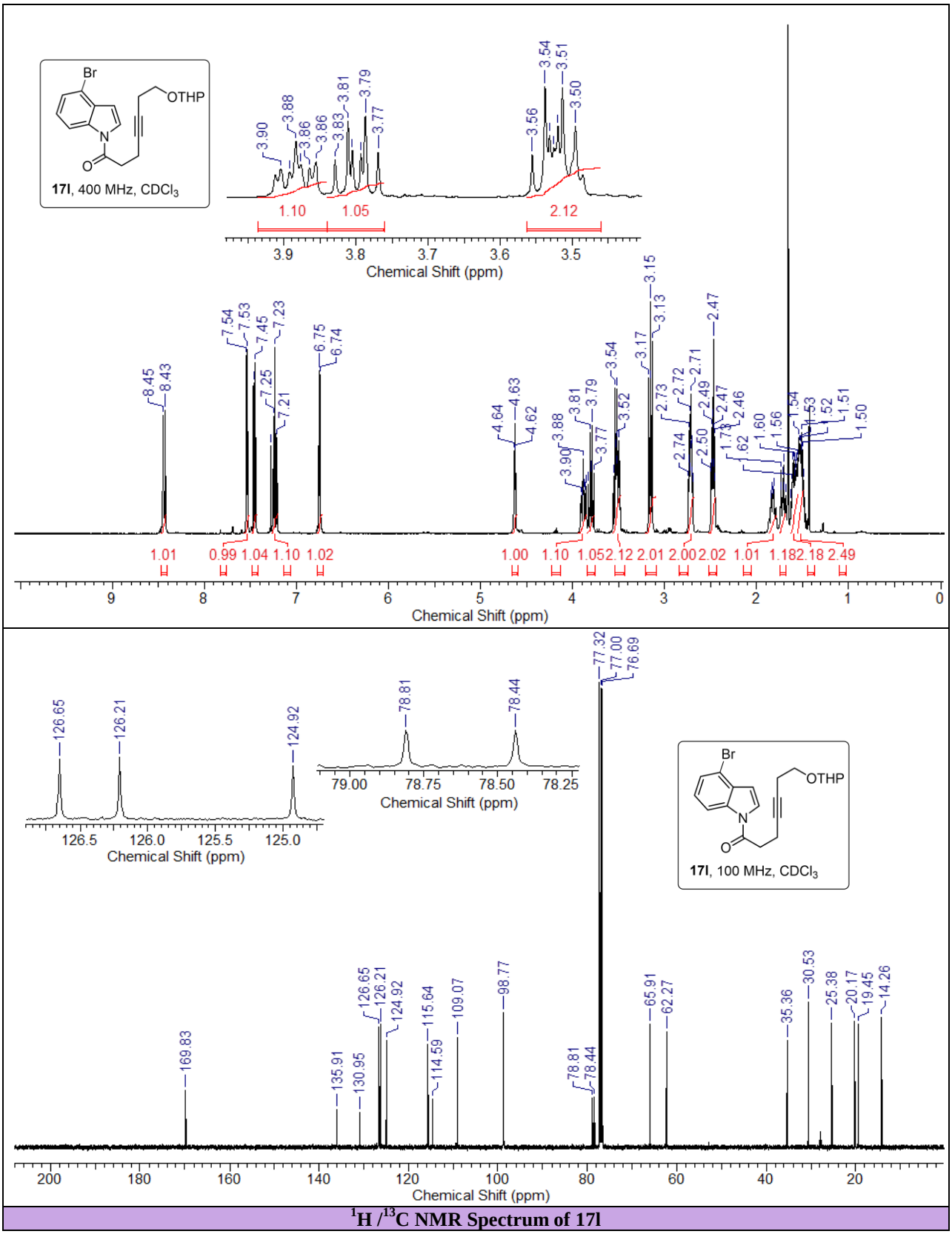
^{1}H /^{13}C NMR Spectrum of 17f



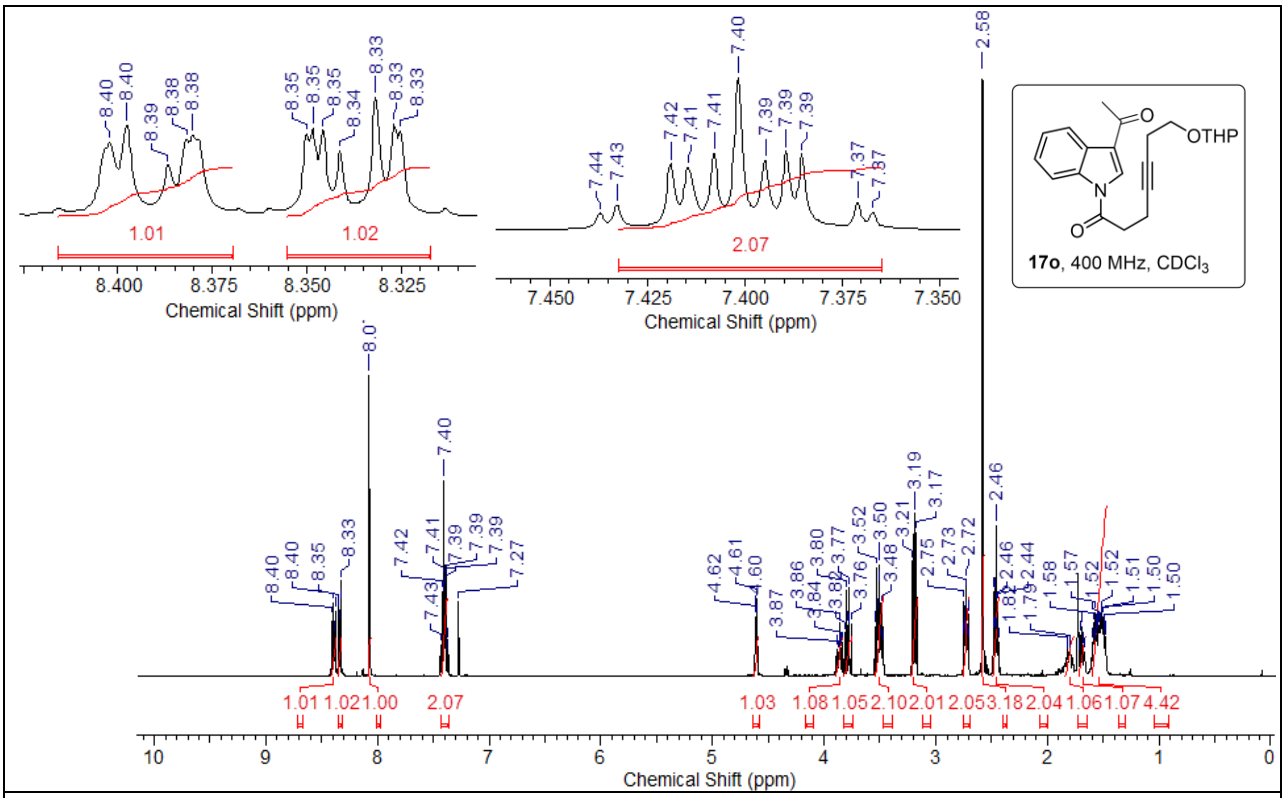
^{1}H /^{13}C NMR Spectrum of 17h

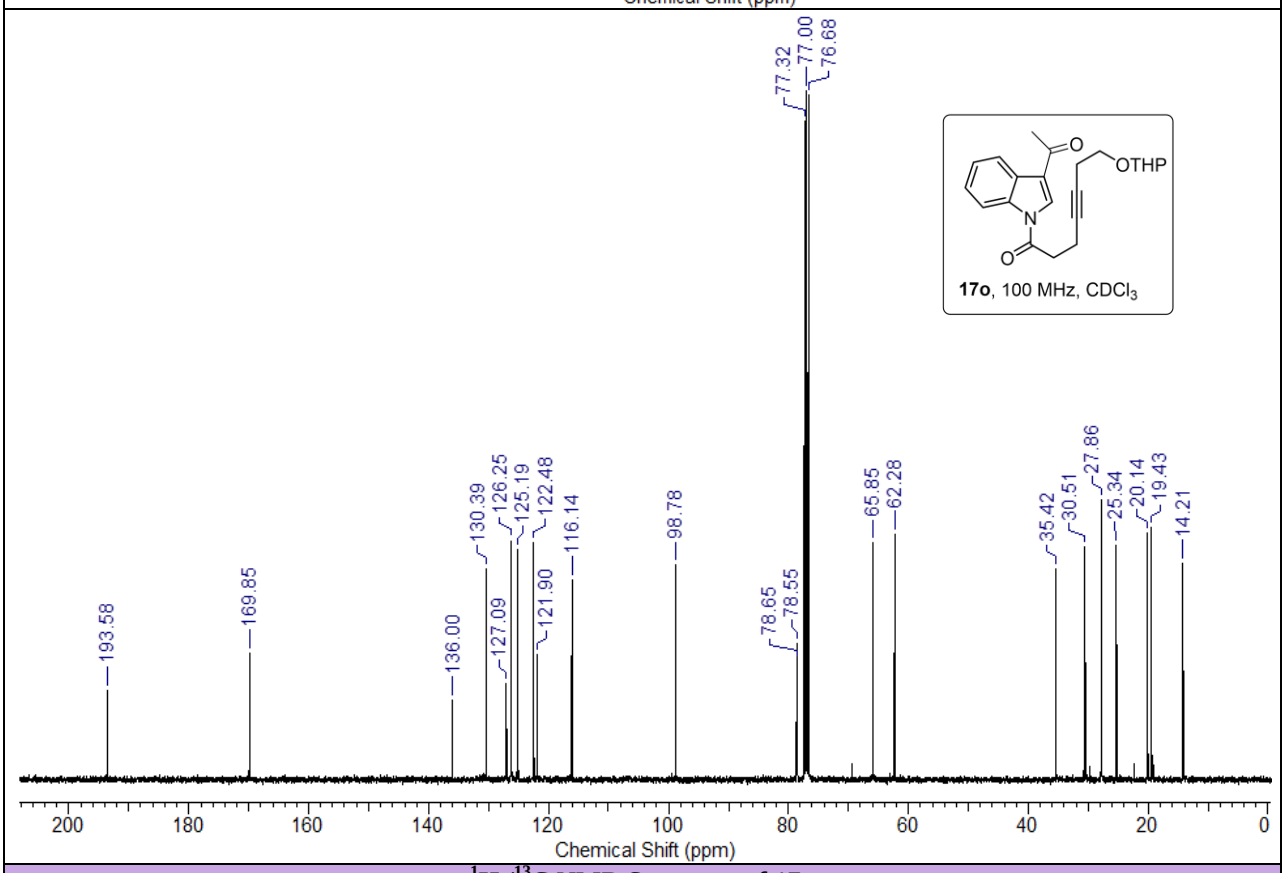


^{1}H /^{13}C NMR Spectrum of 17k

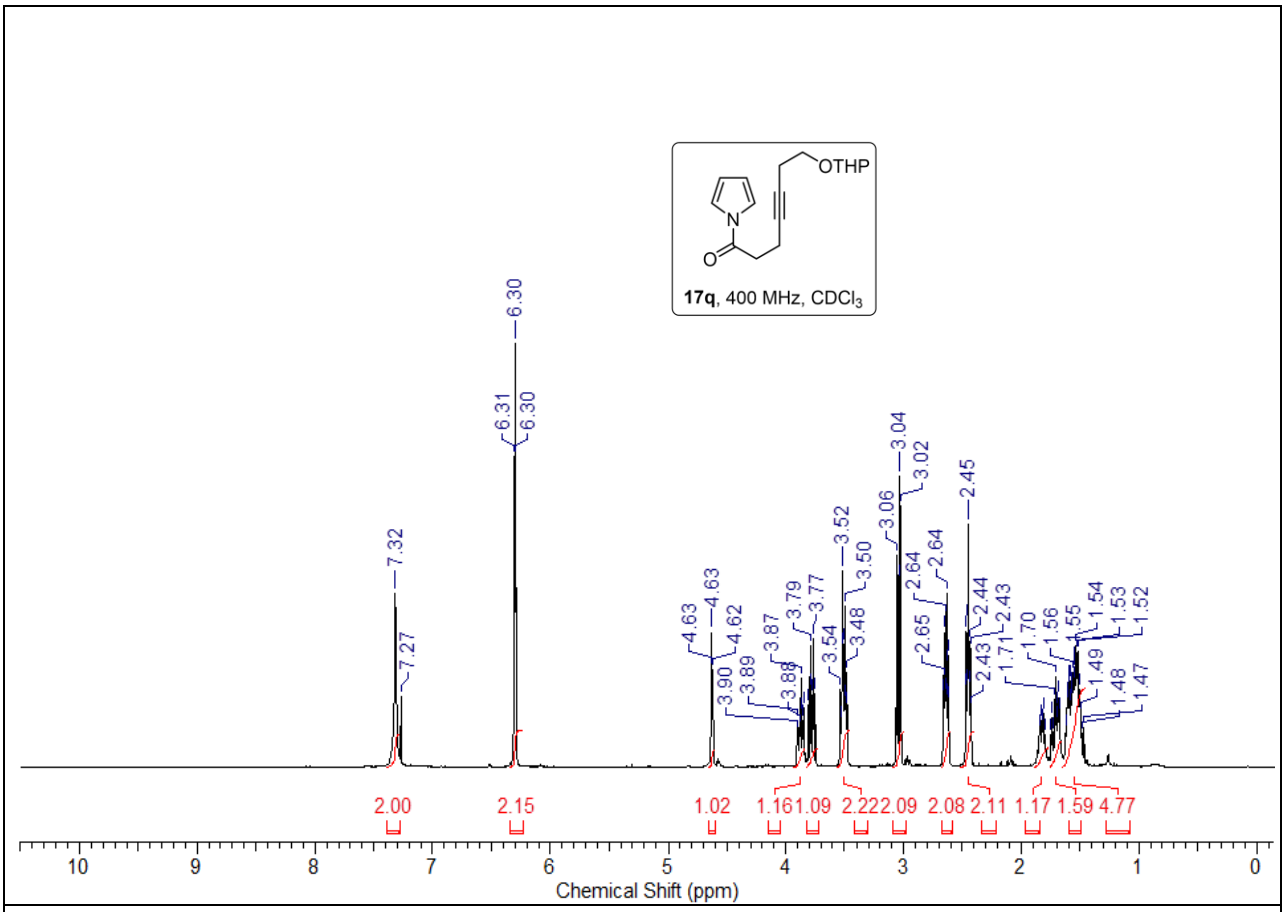


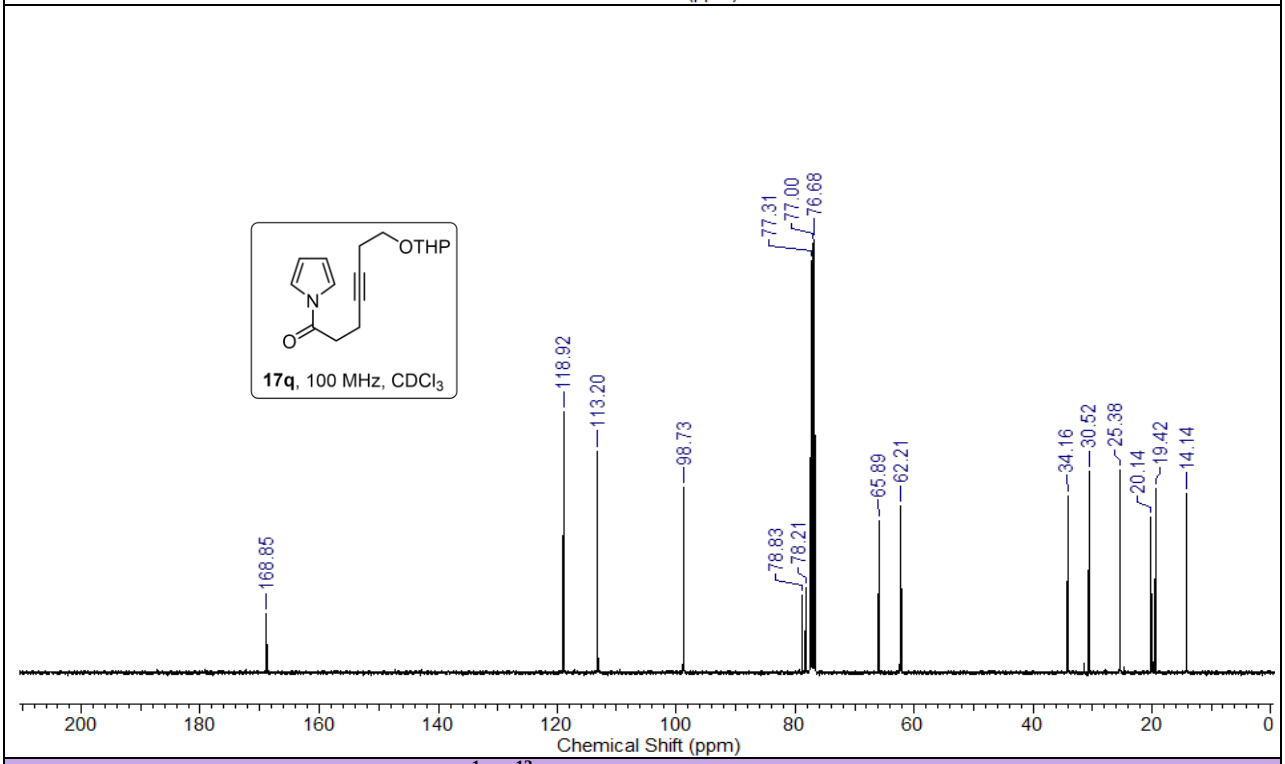
^{1}H /^{13}C NMR Spectrum of 17l



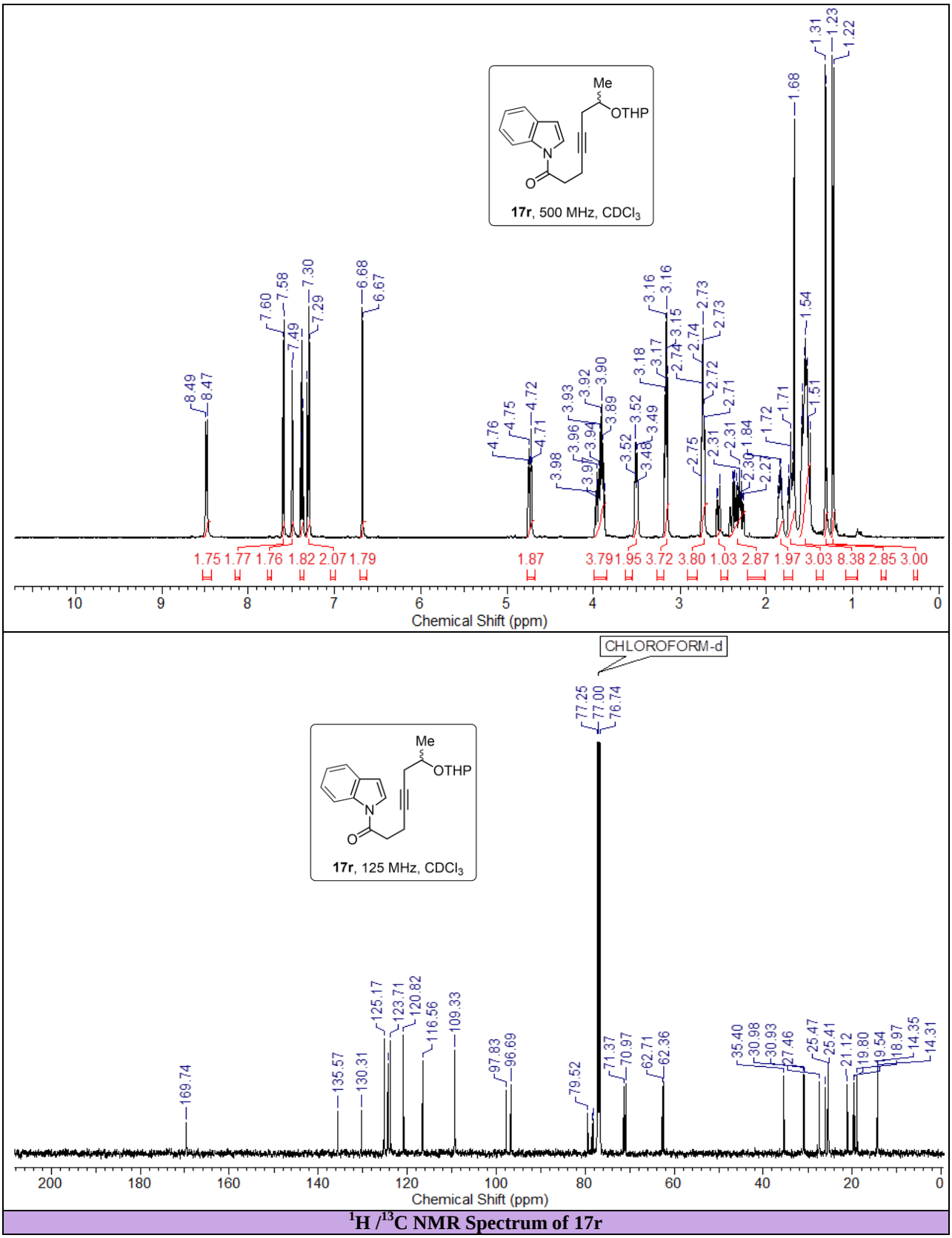


^{1}H /^{13}C NMR Spectrum of 17o

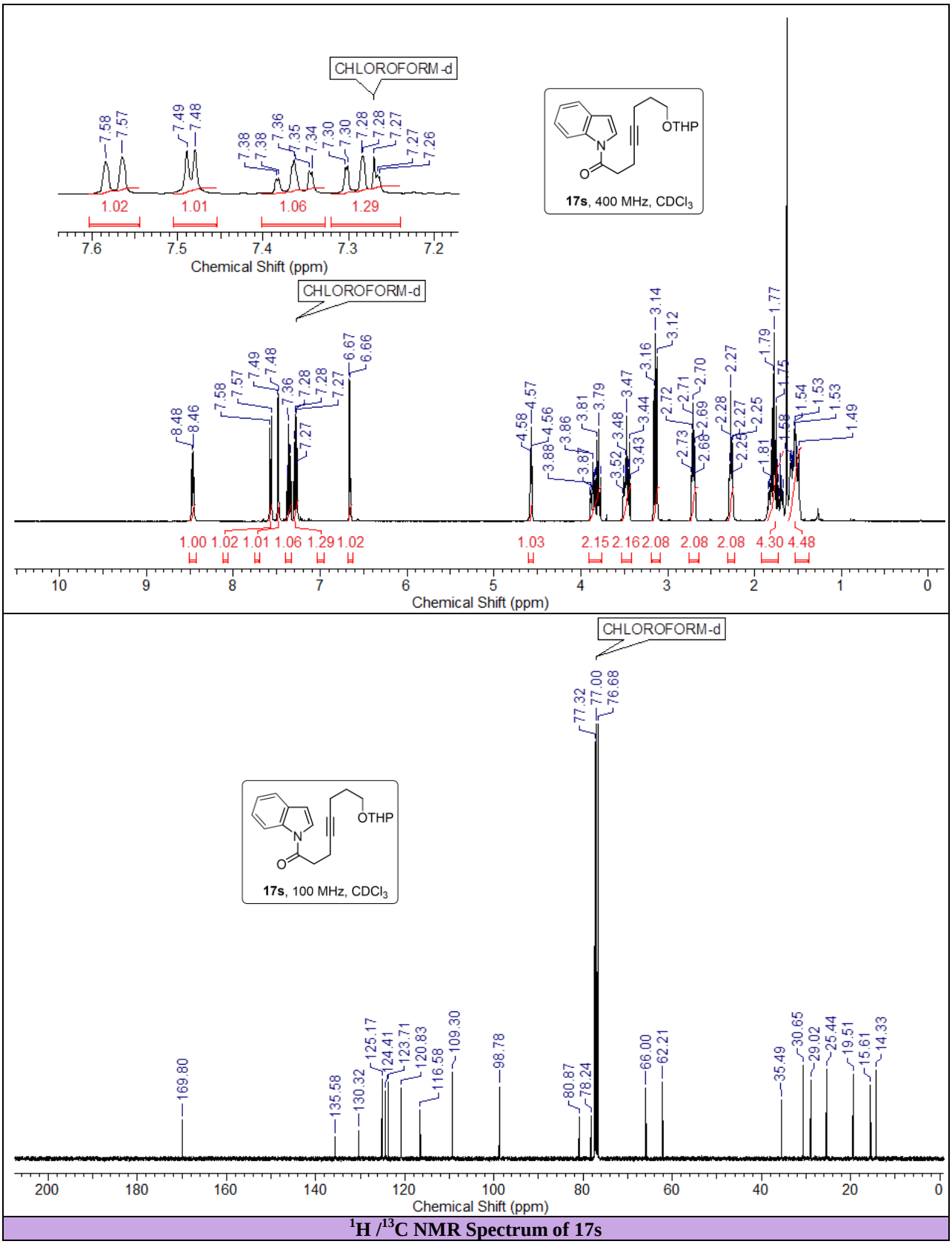




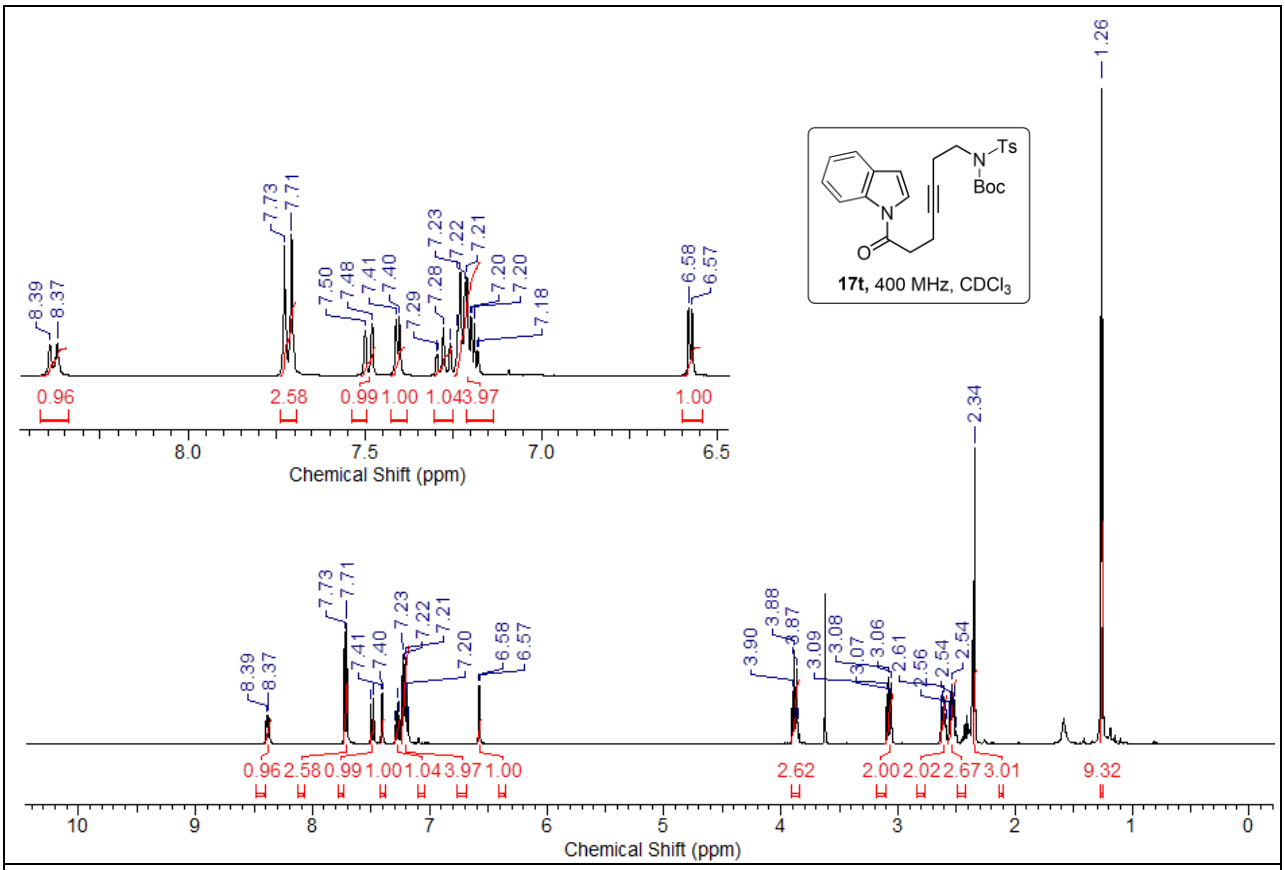
^{1}H /^{13}C NMR Spectrum of 17q

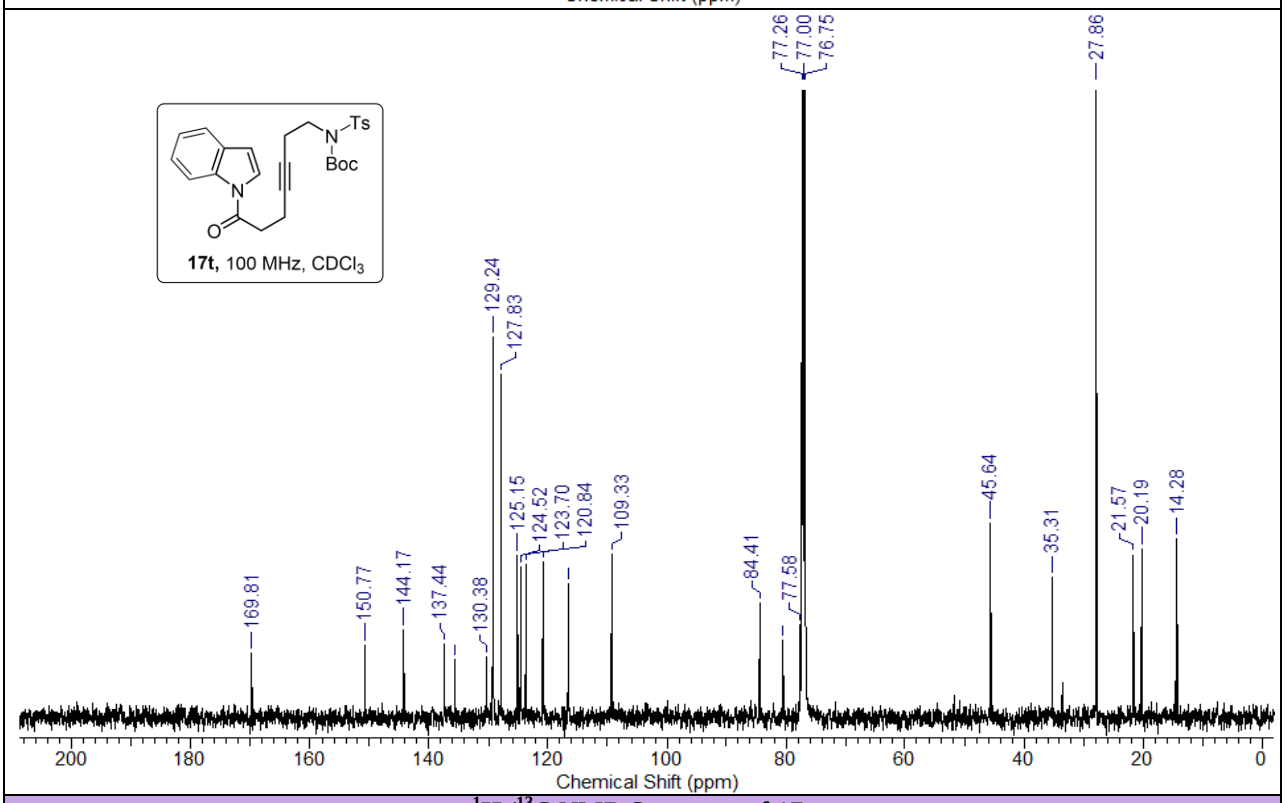


^{1}H /^{13}C NMR Spectrum of 17r

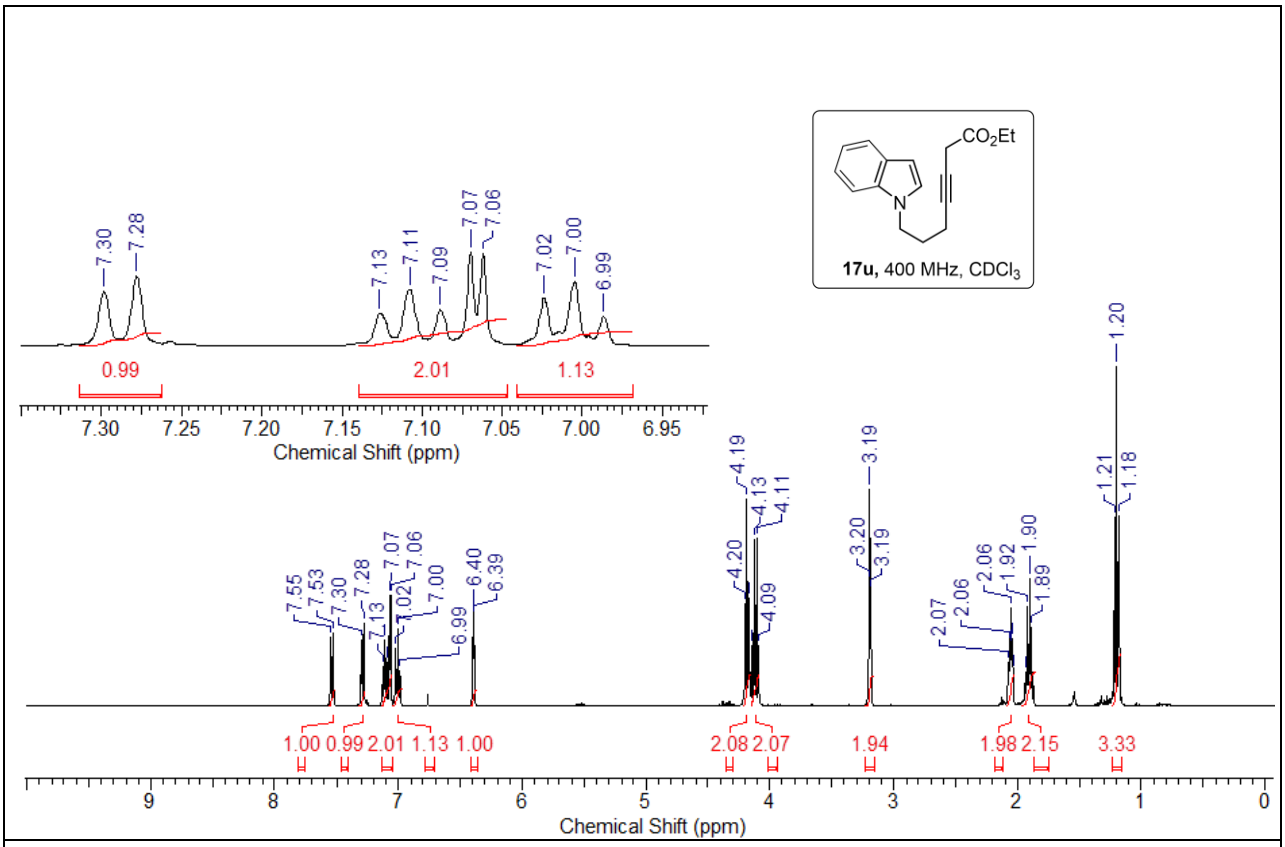


^{1}H /^{13}C NMR Spectrum of 17s

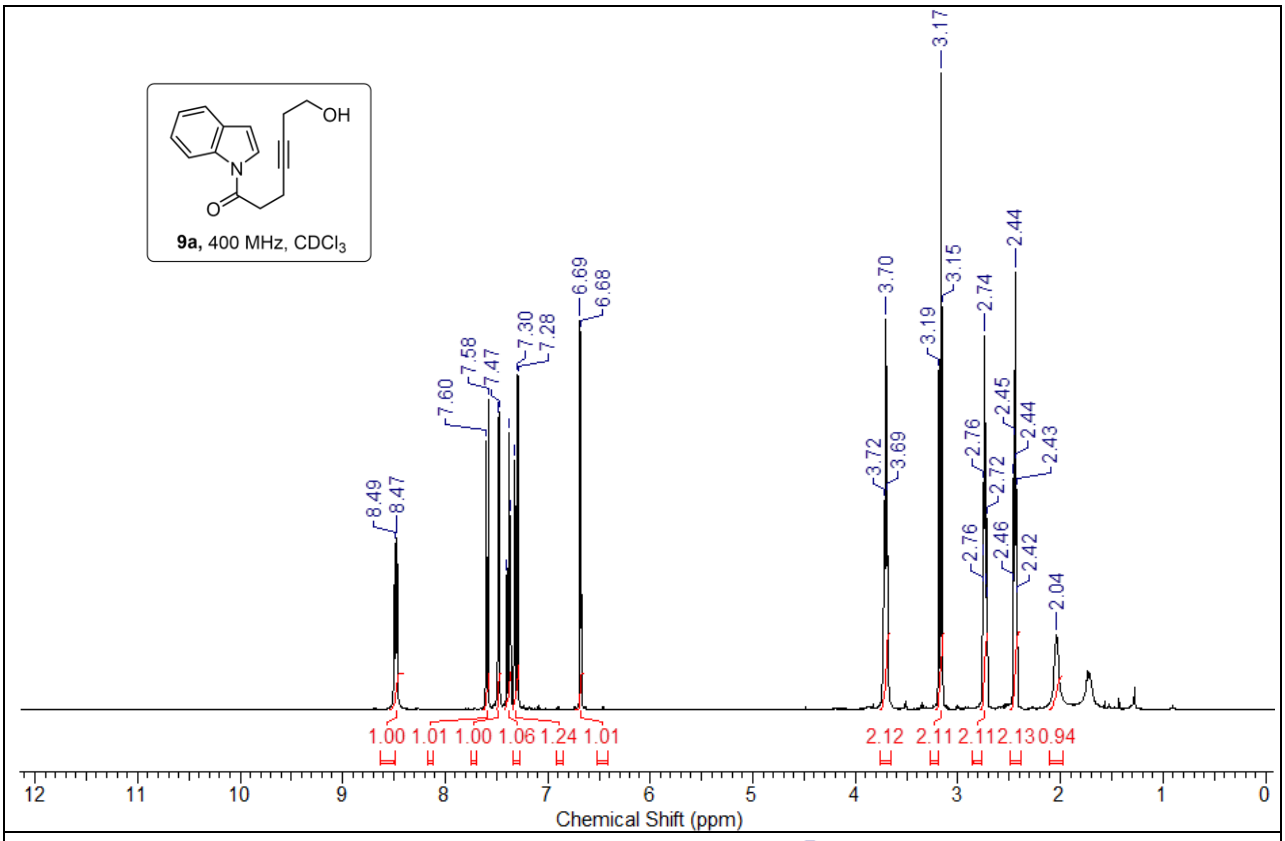


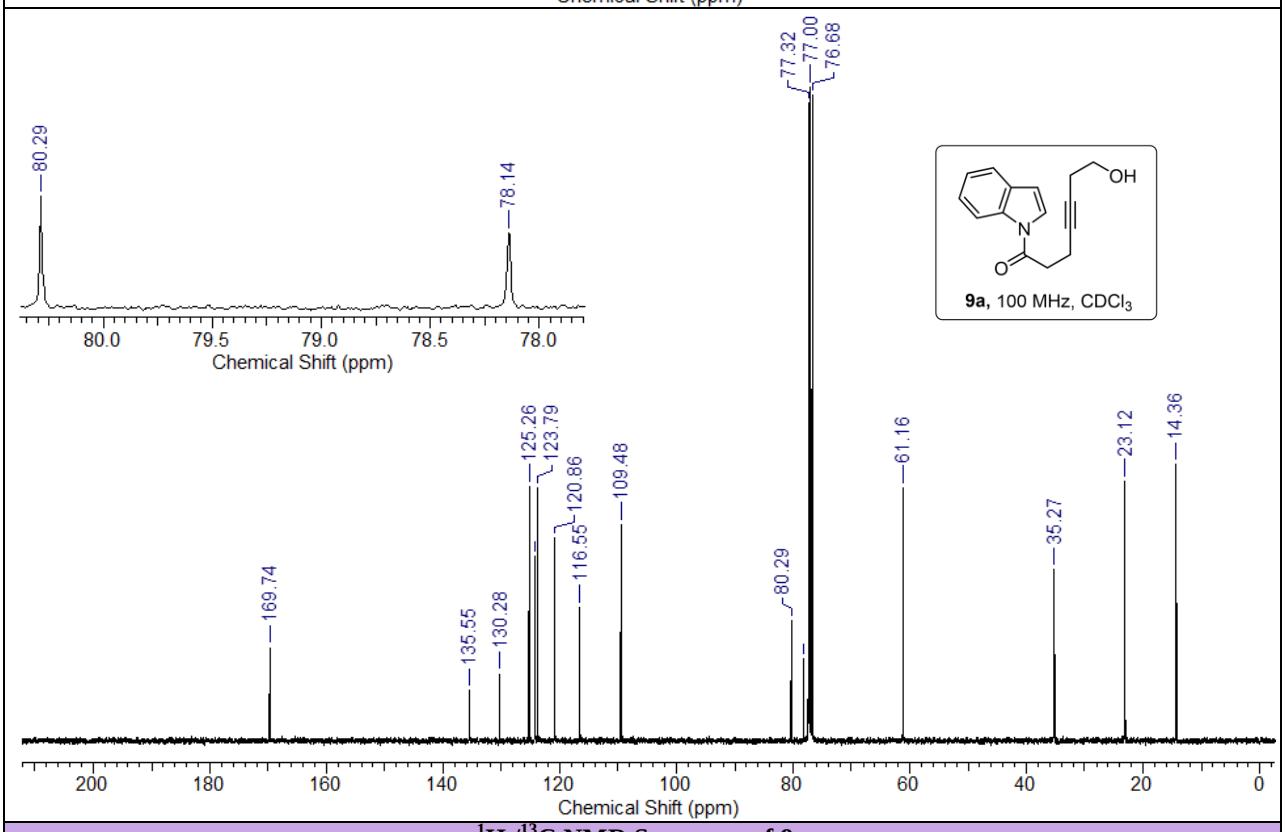


^{1}H /^{13}C NMR Spectrum of 17t

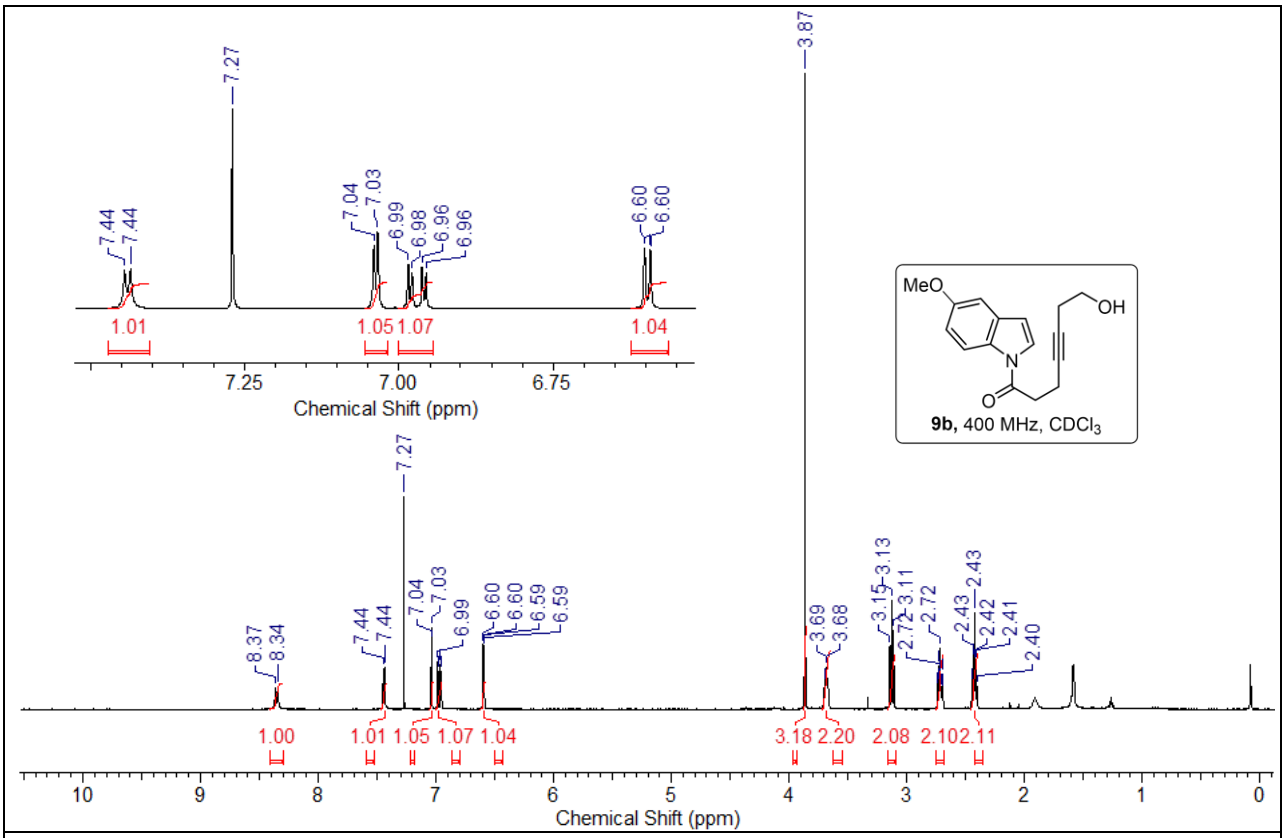


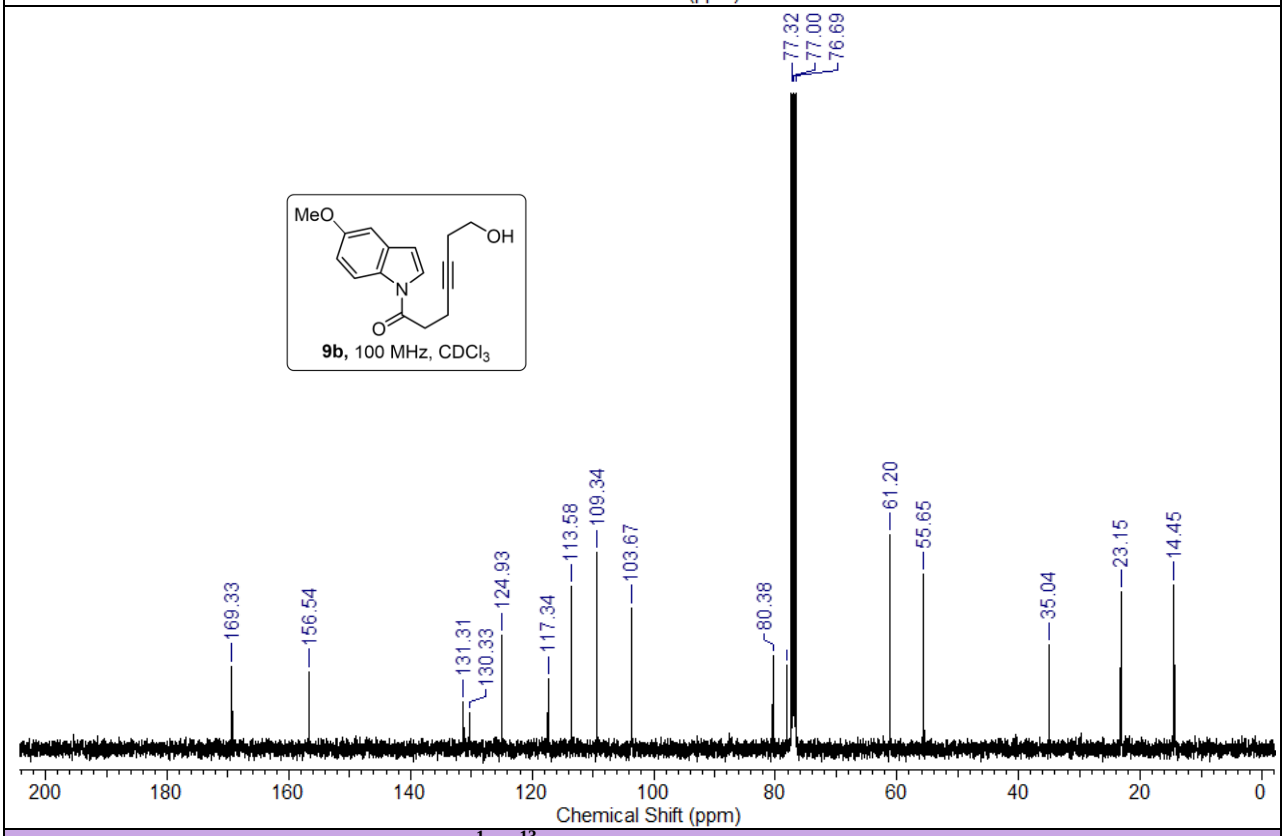
^{1}H /^{13}C NMR Spectrum of 17u



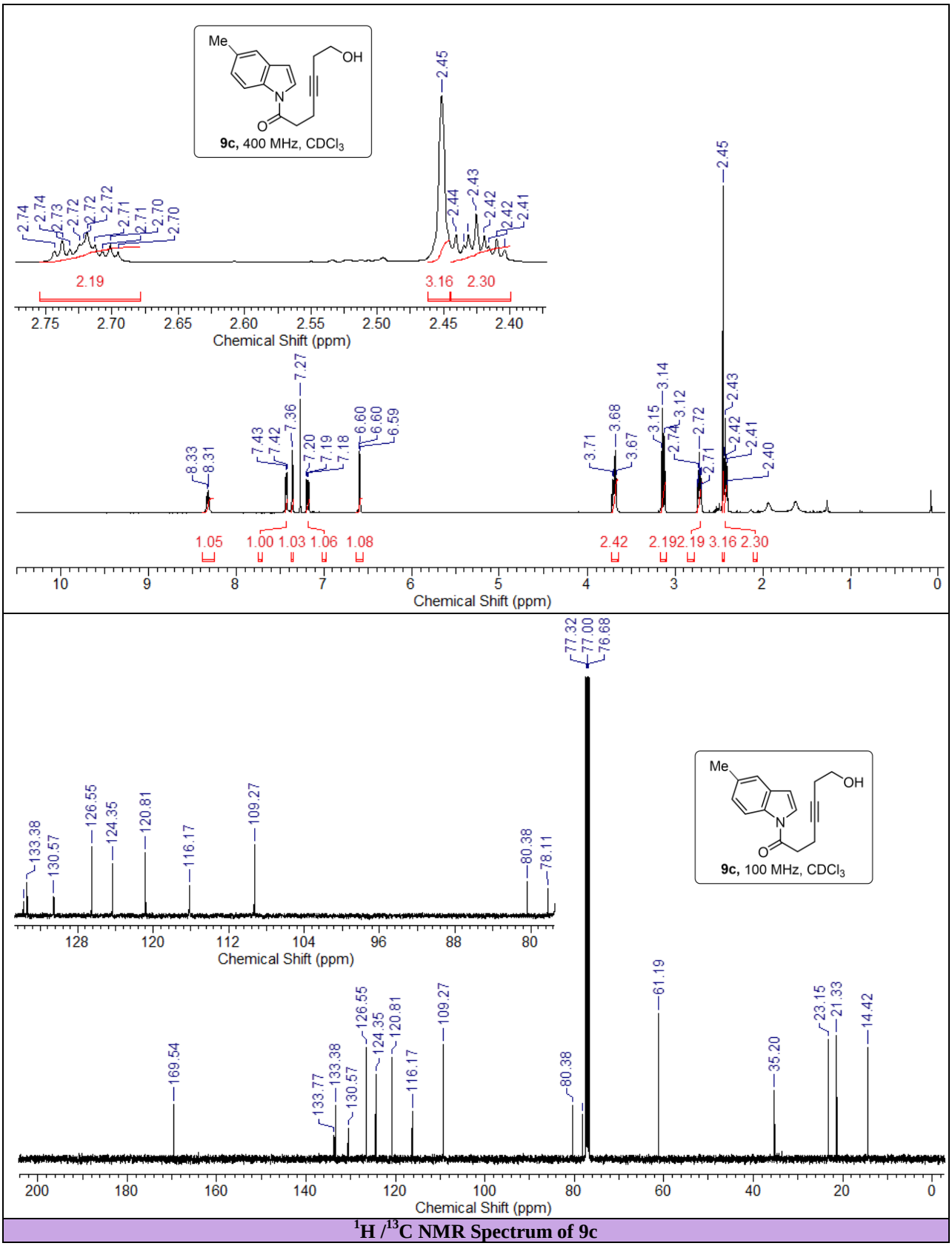


^{1}H /^{13}C NMR Spectrum of 9a

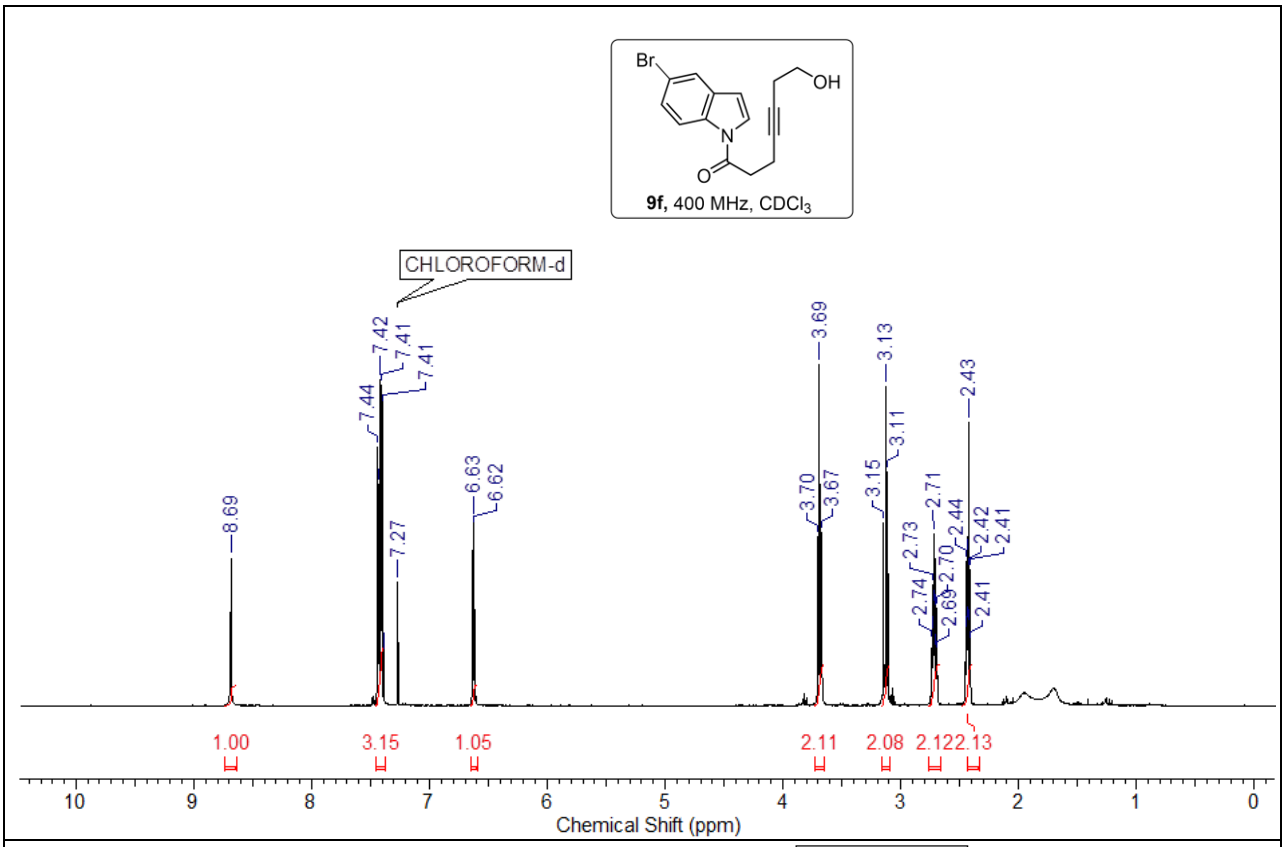


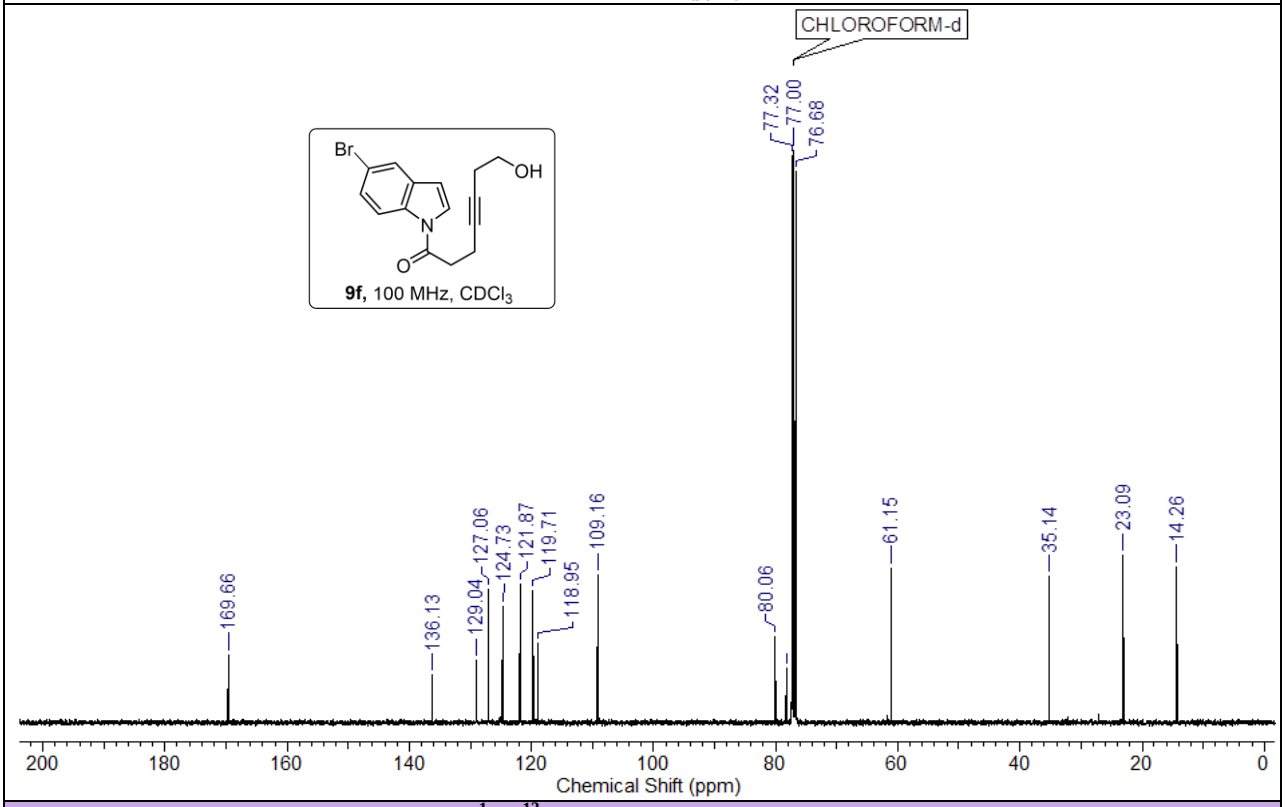


^{1}H /^{13}C NMR Spectrum of 9b

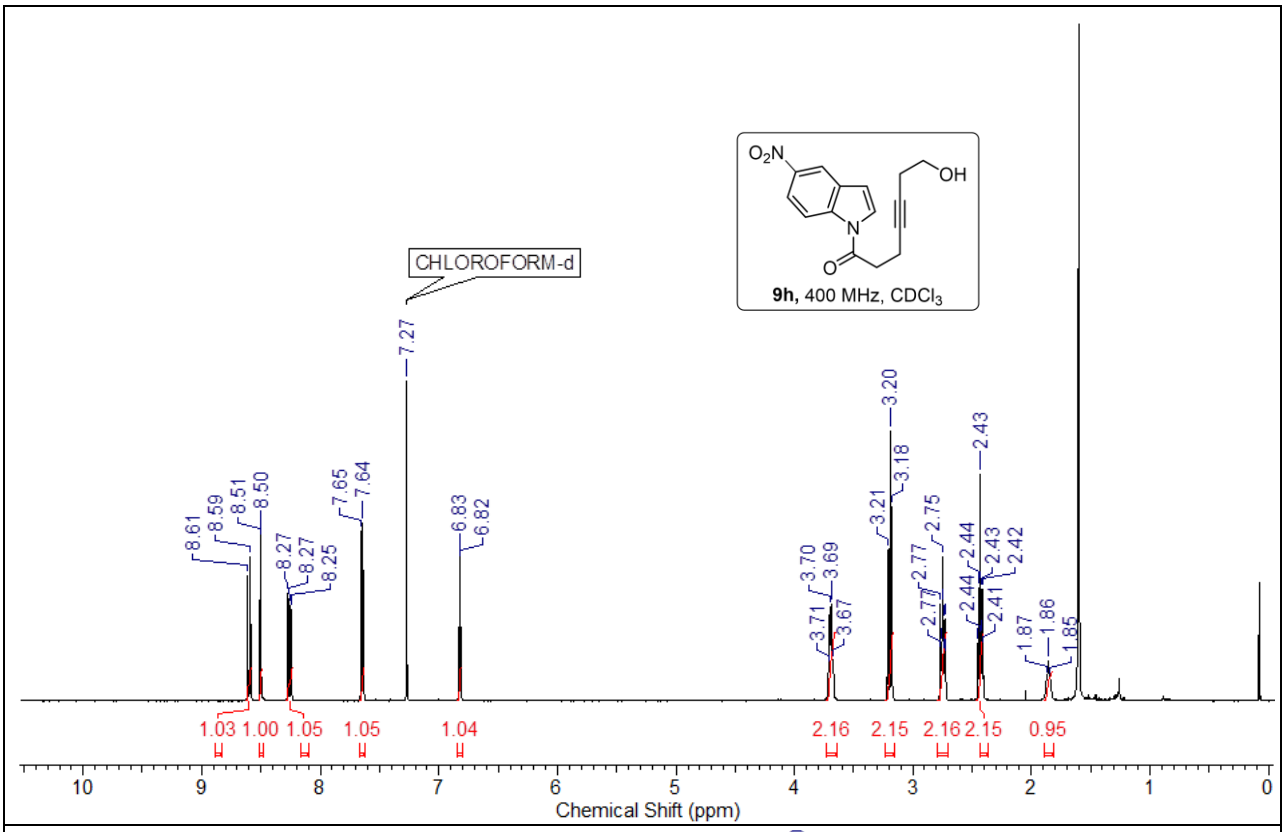


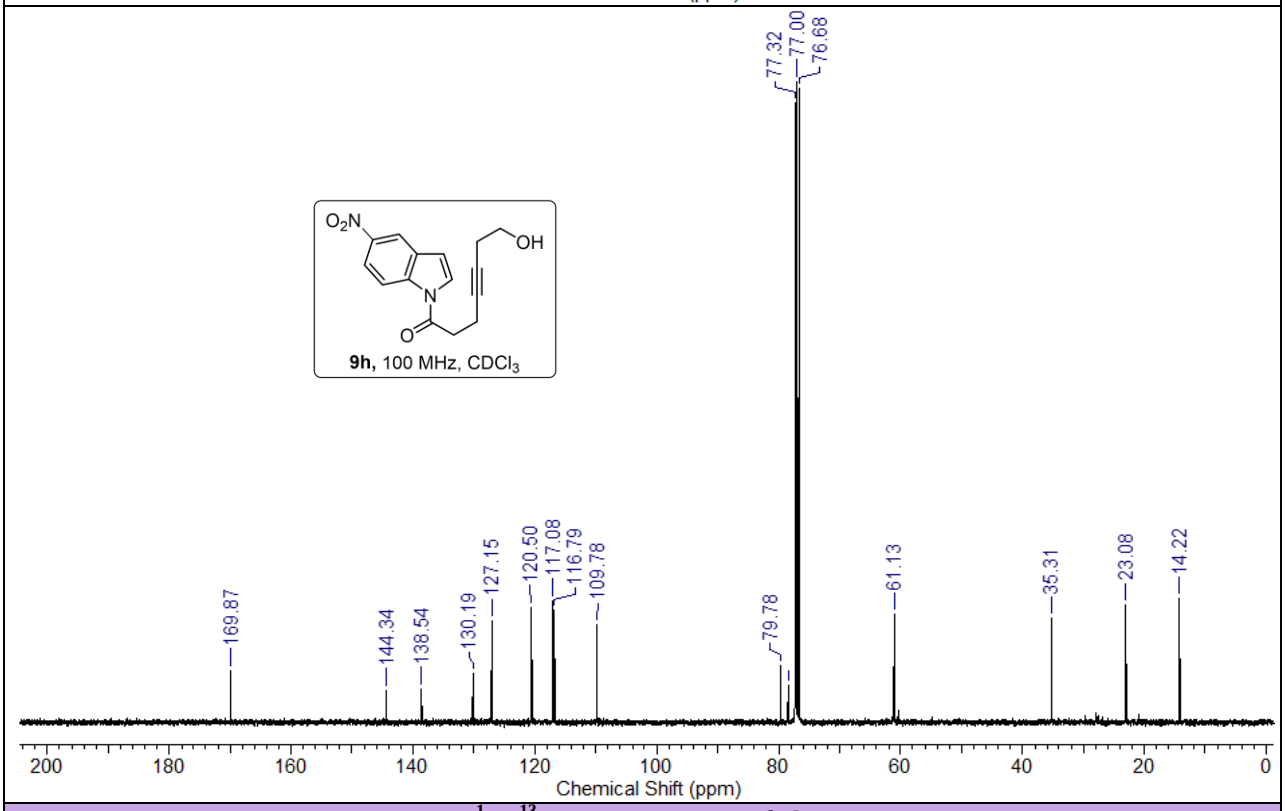
^{1}H /^{13}C NMR Spectrum of 9c



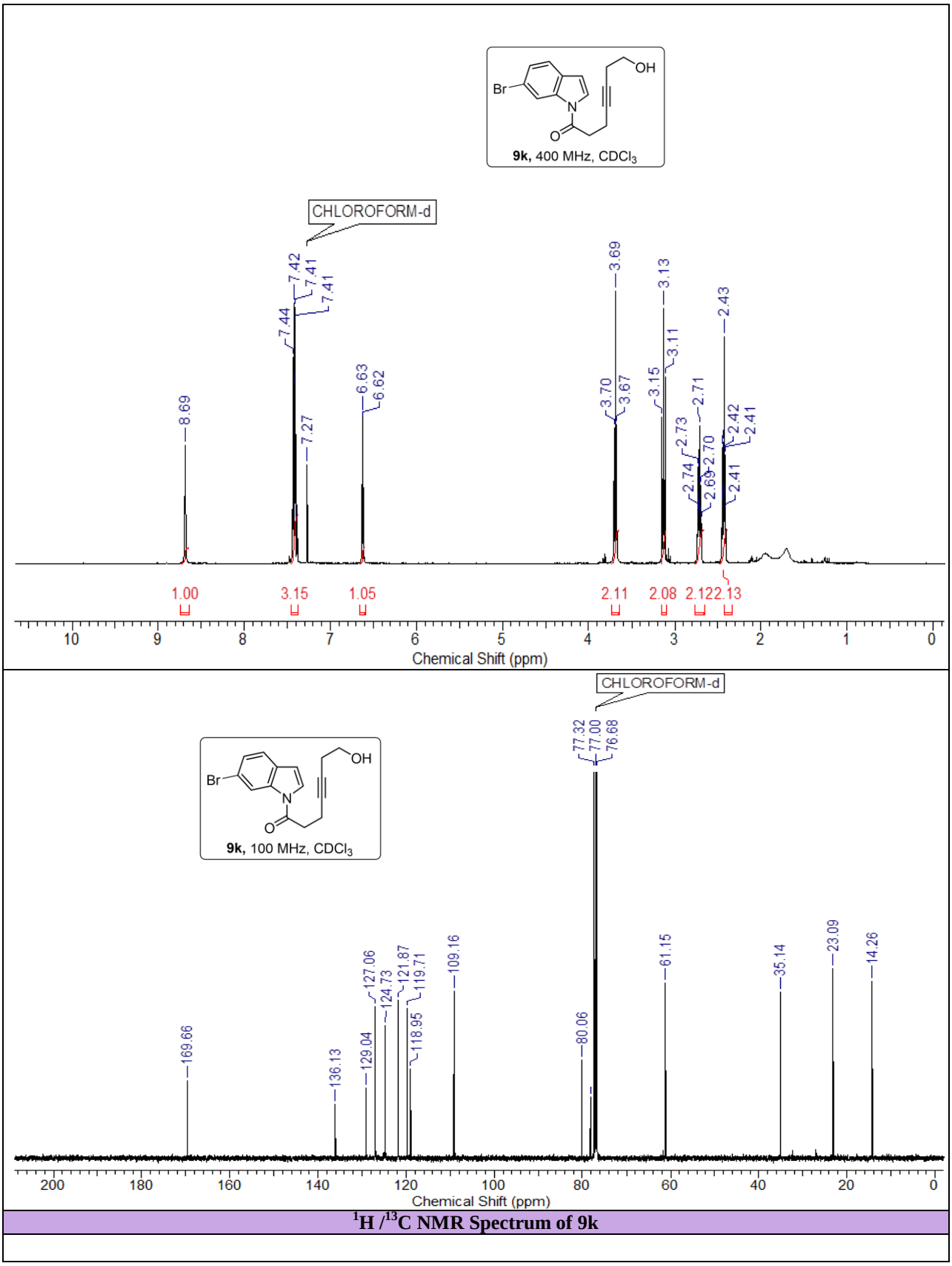


^{1}H /^{13}C NMR Spectrum of 9f

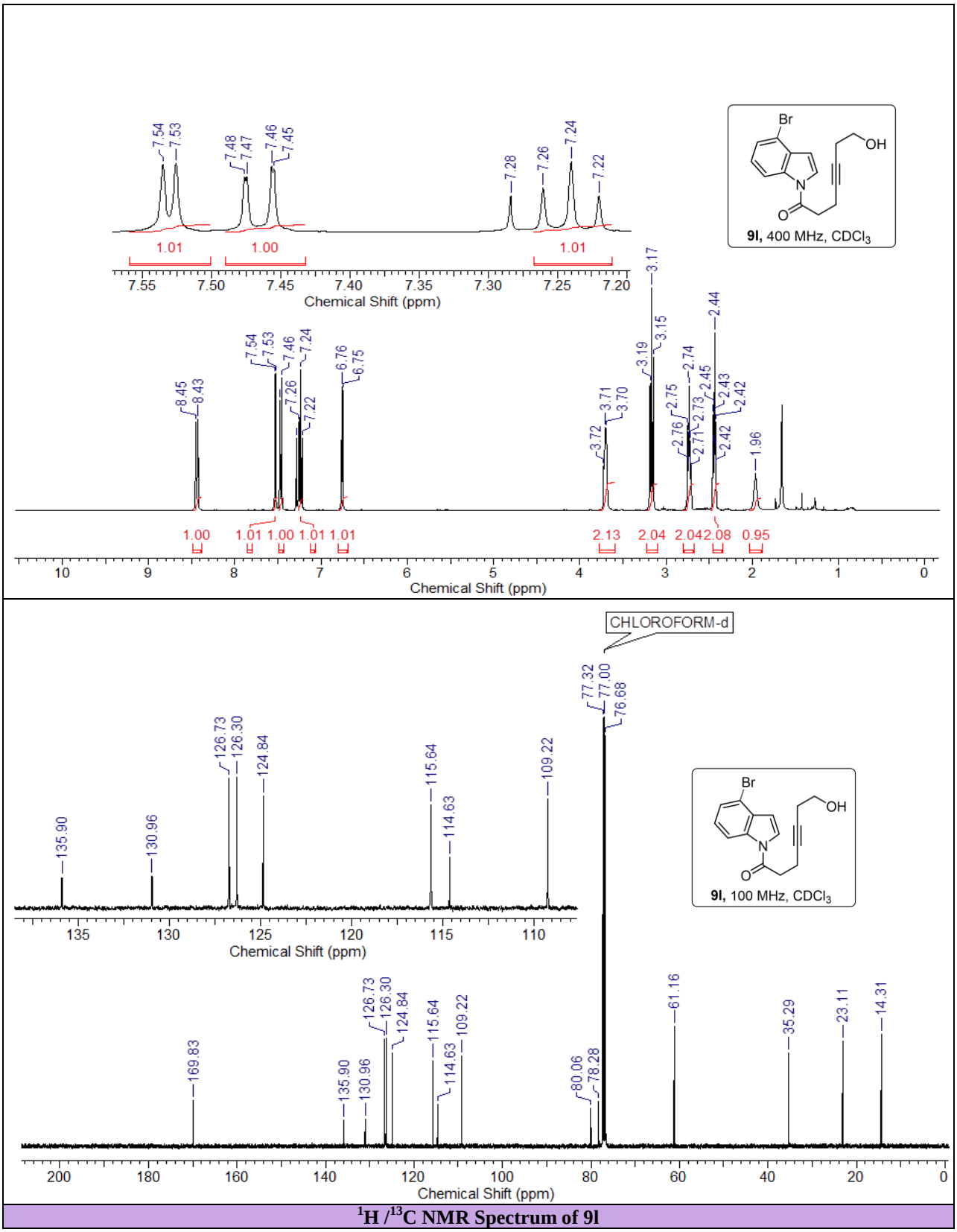




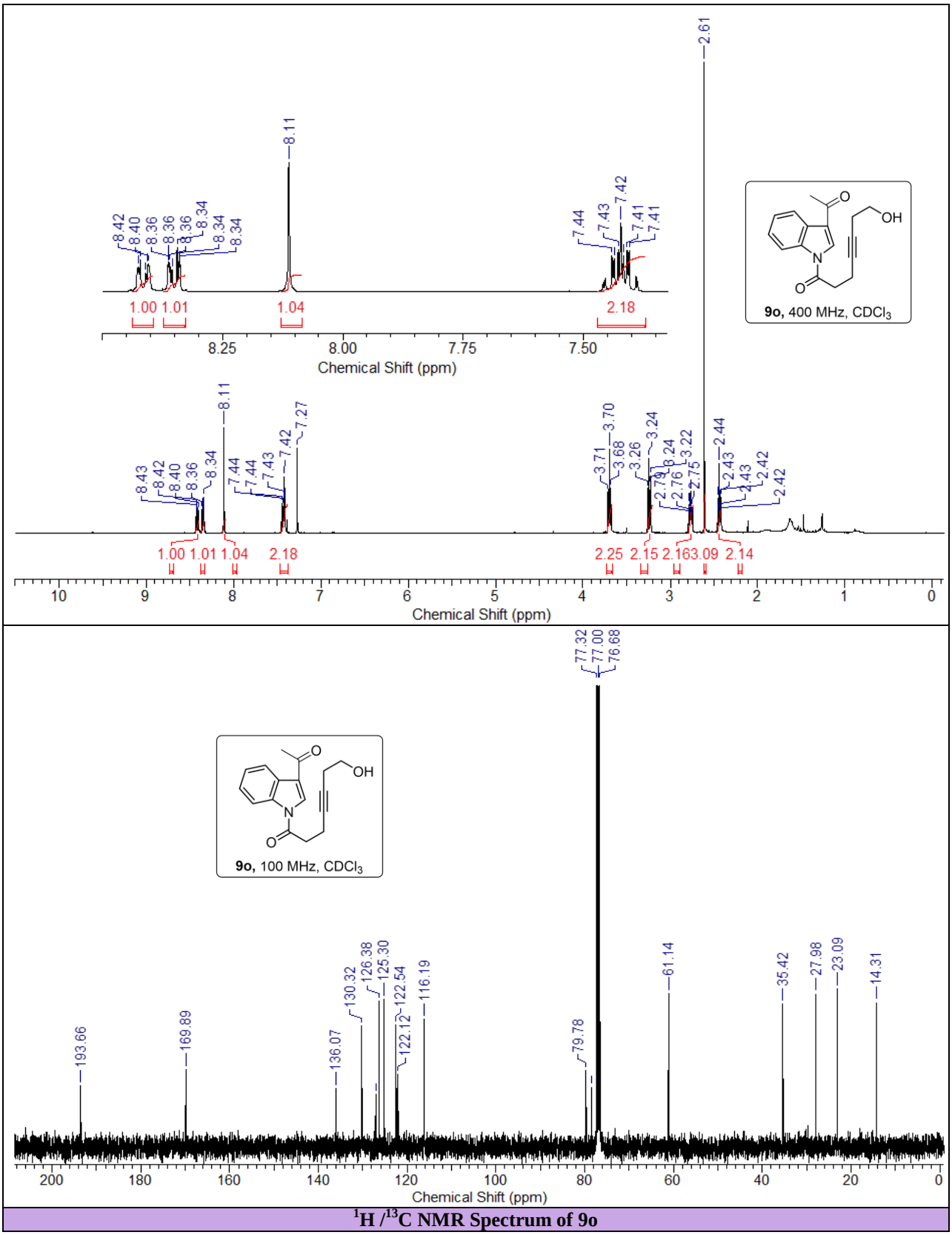
^{1}H /^{13}C NMR Spectrum of 9h



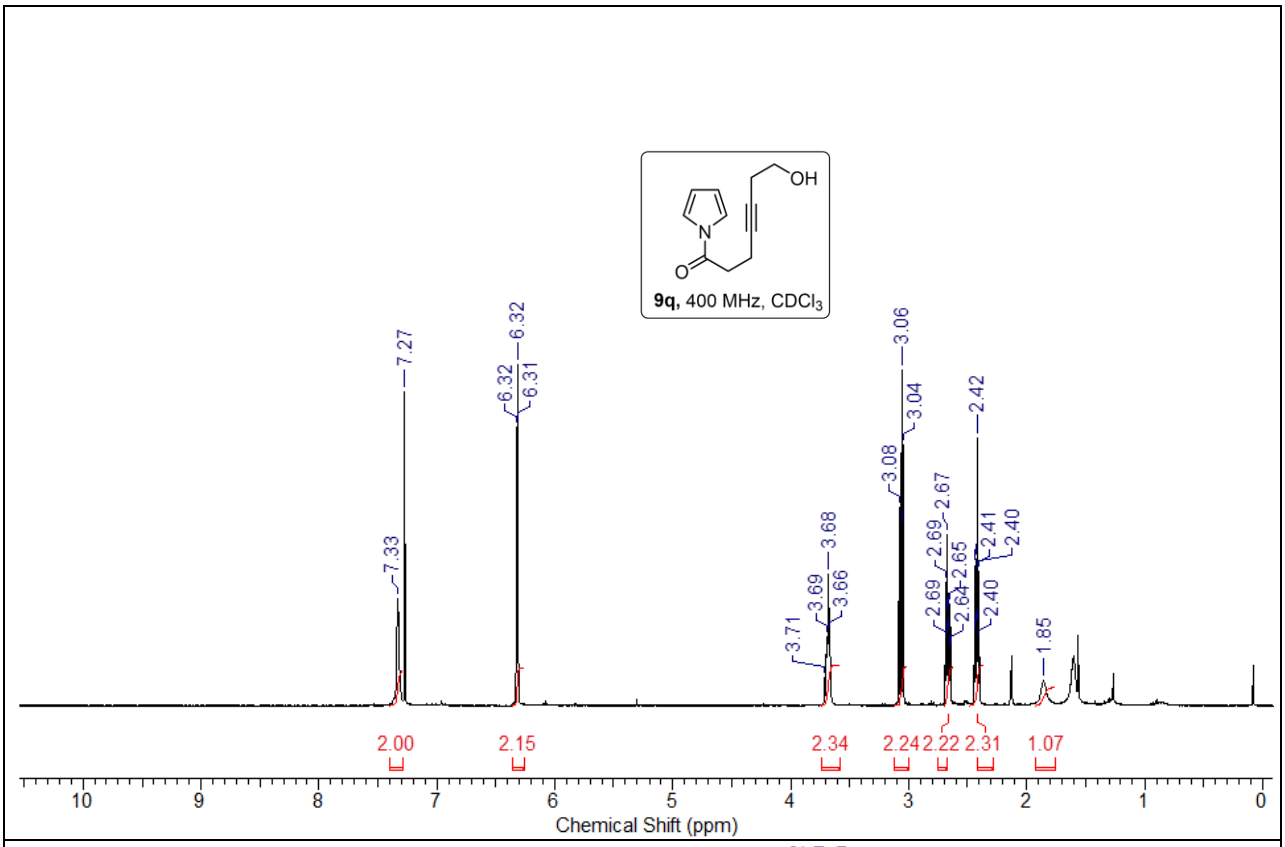
^{1}H /^{13}C NMR Spectrum of 9k

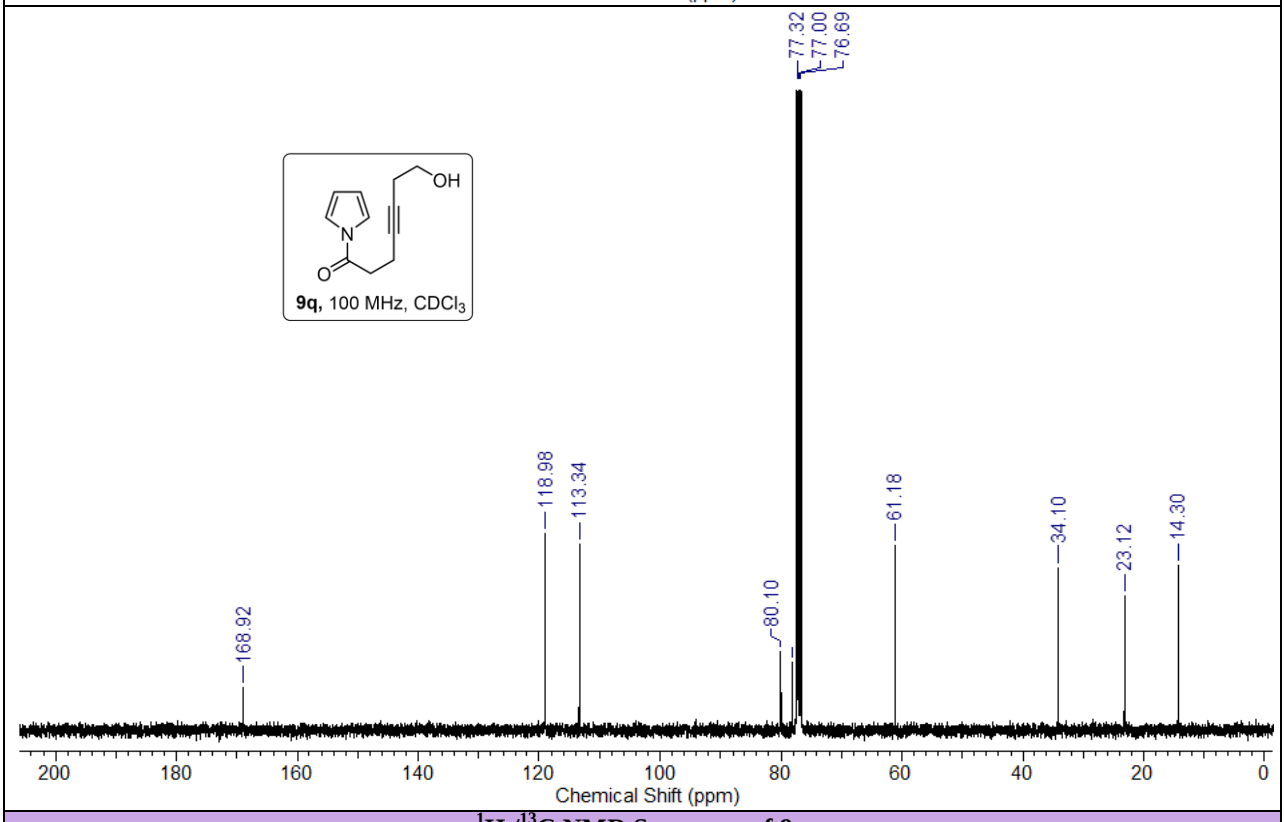


^{1}H /^{13}C NMR Spectrum of 9l

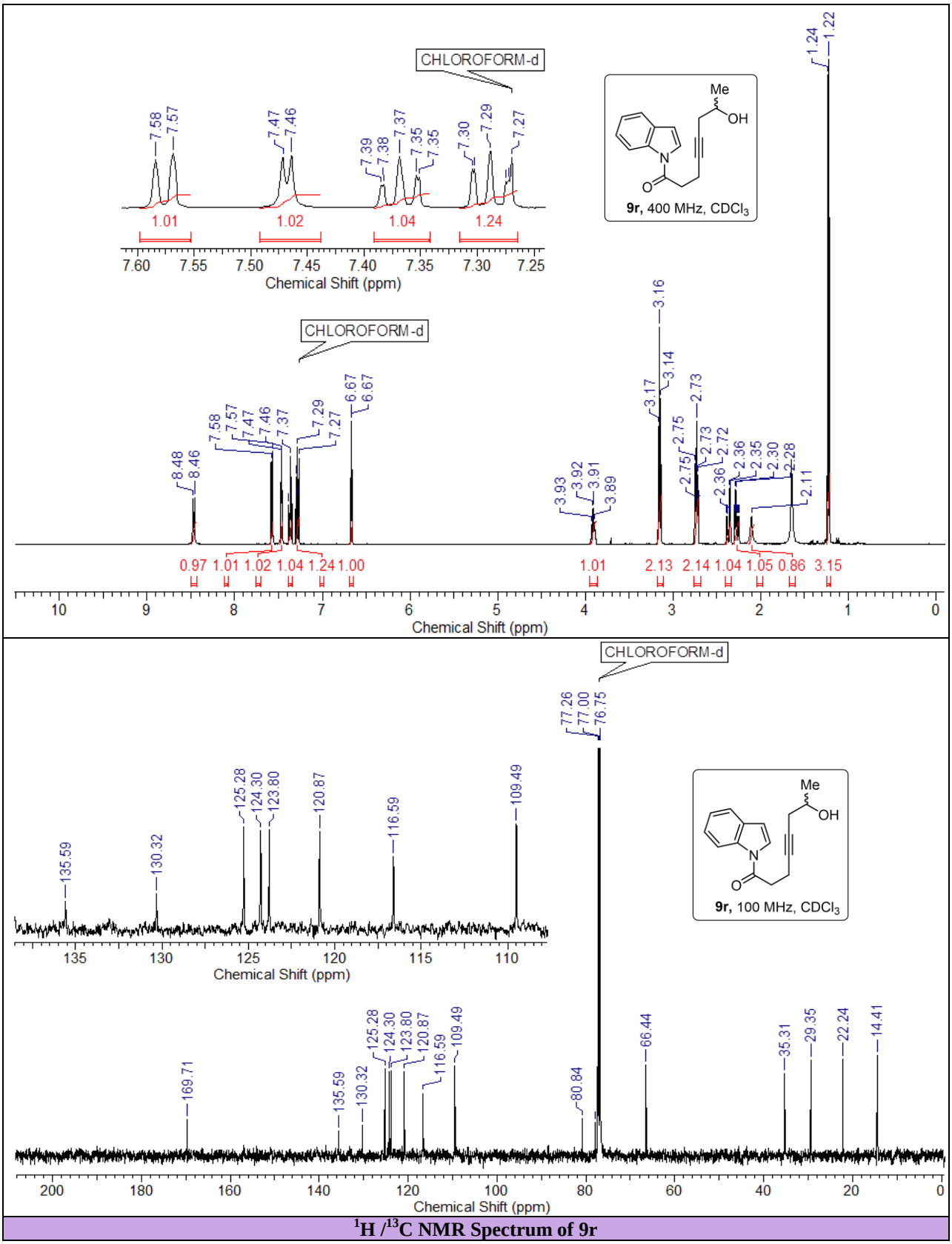


^{1}H /^{13}C NMR Spectrum of 9o

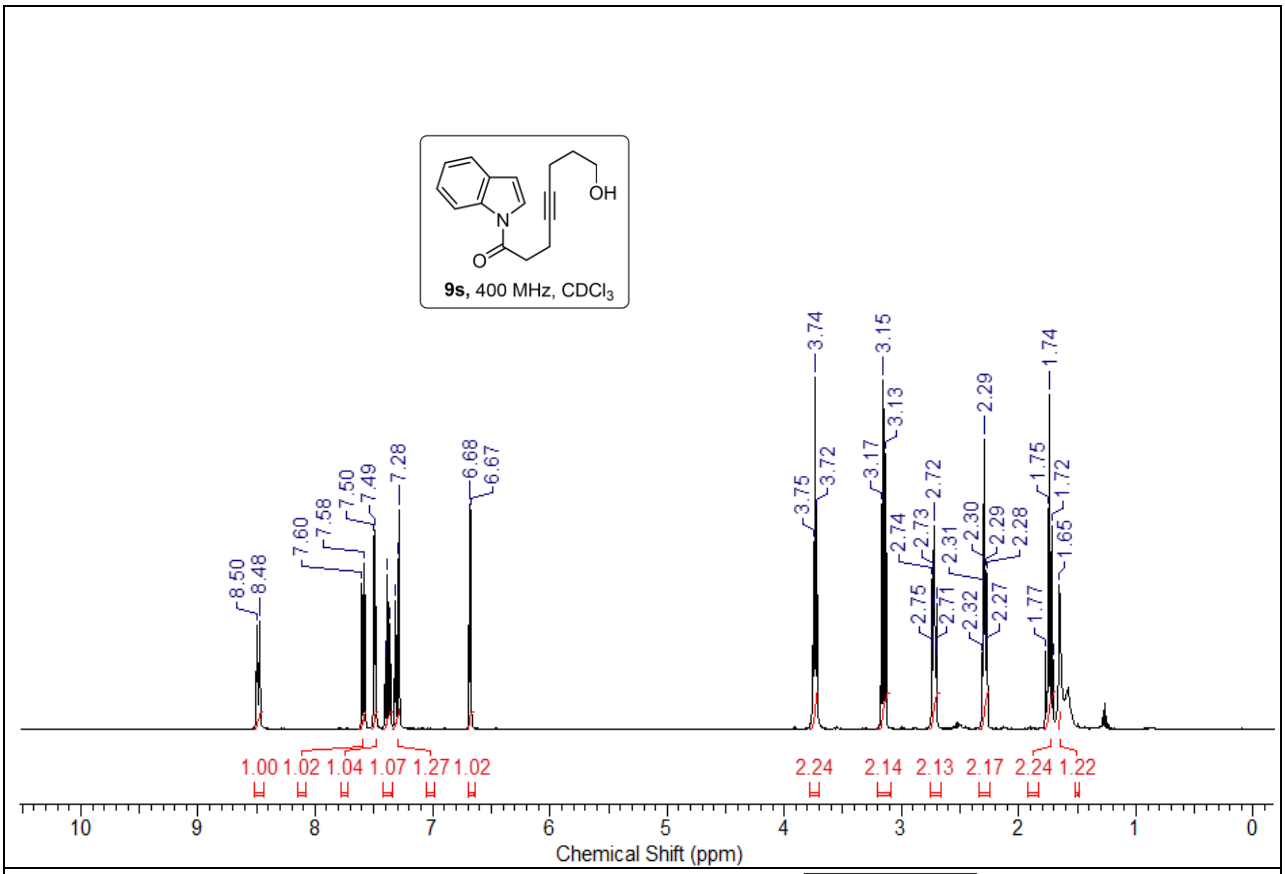


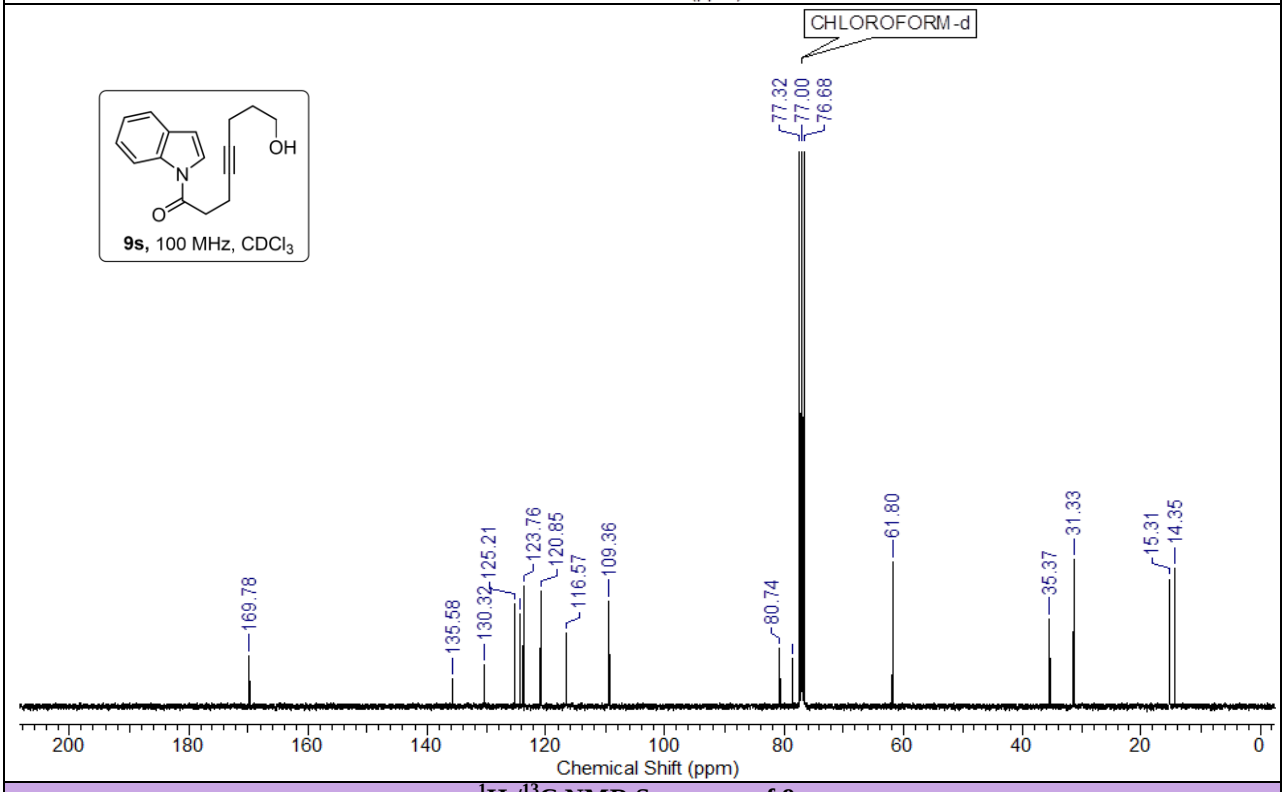


^{1}H /^{13}C NMR Spectrum of 9q

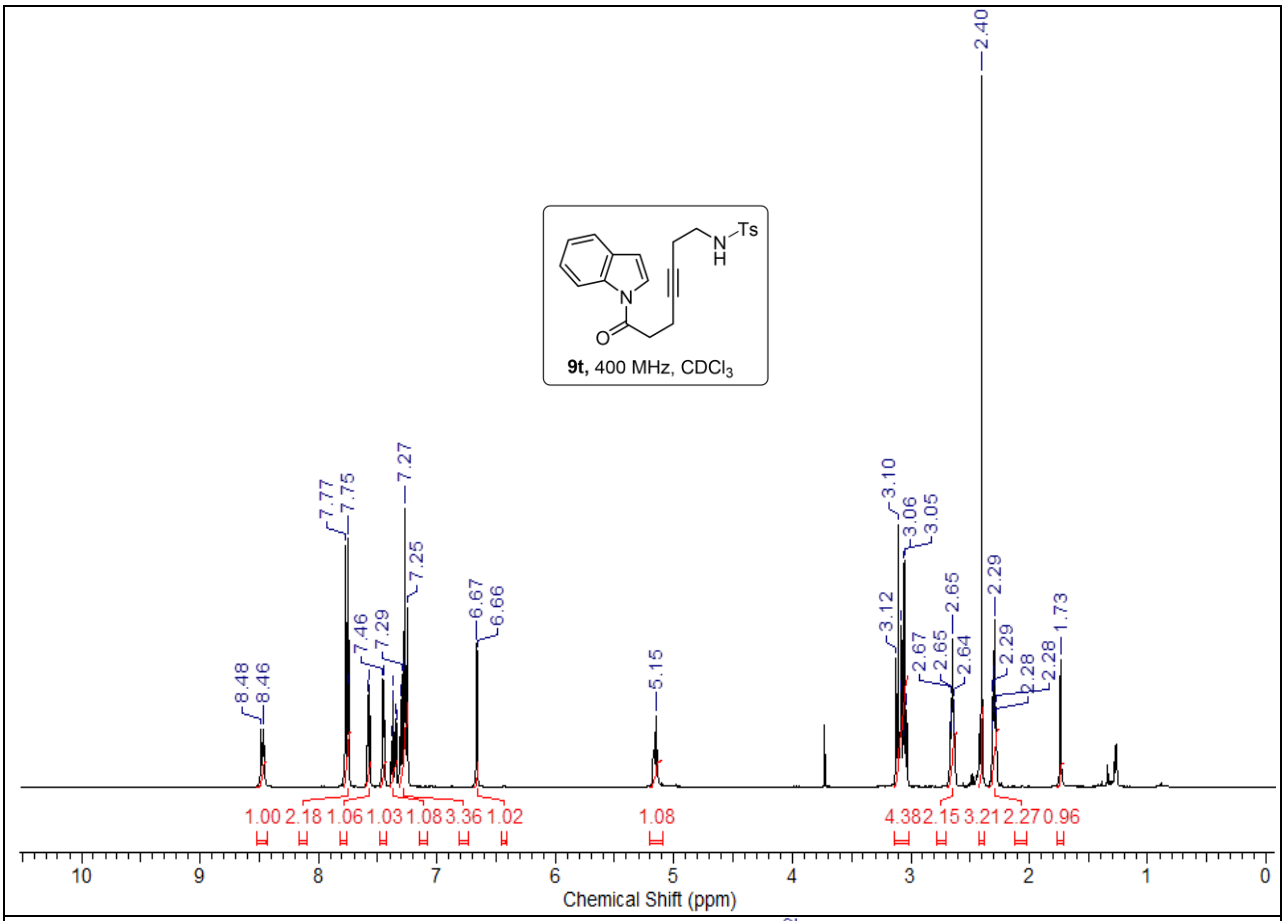


^{1}H /^{13}C NMR Spectrum of 9r

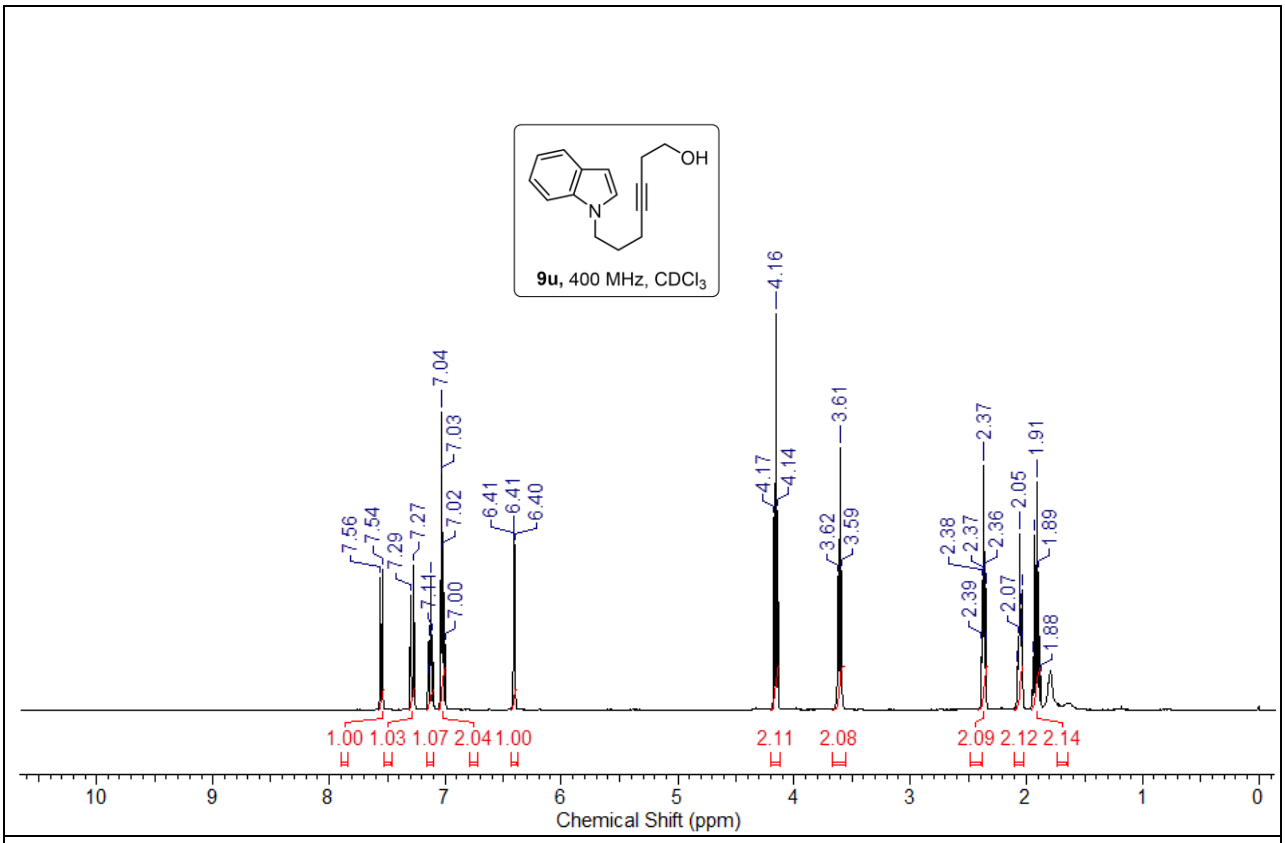


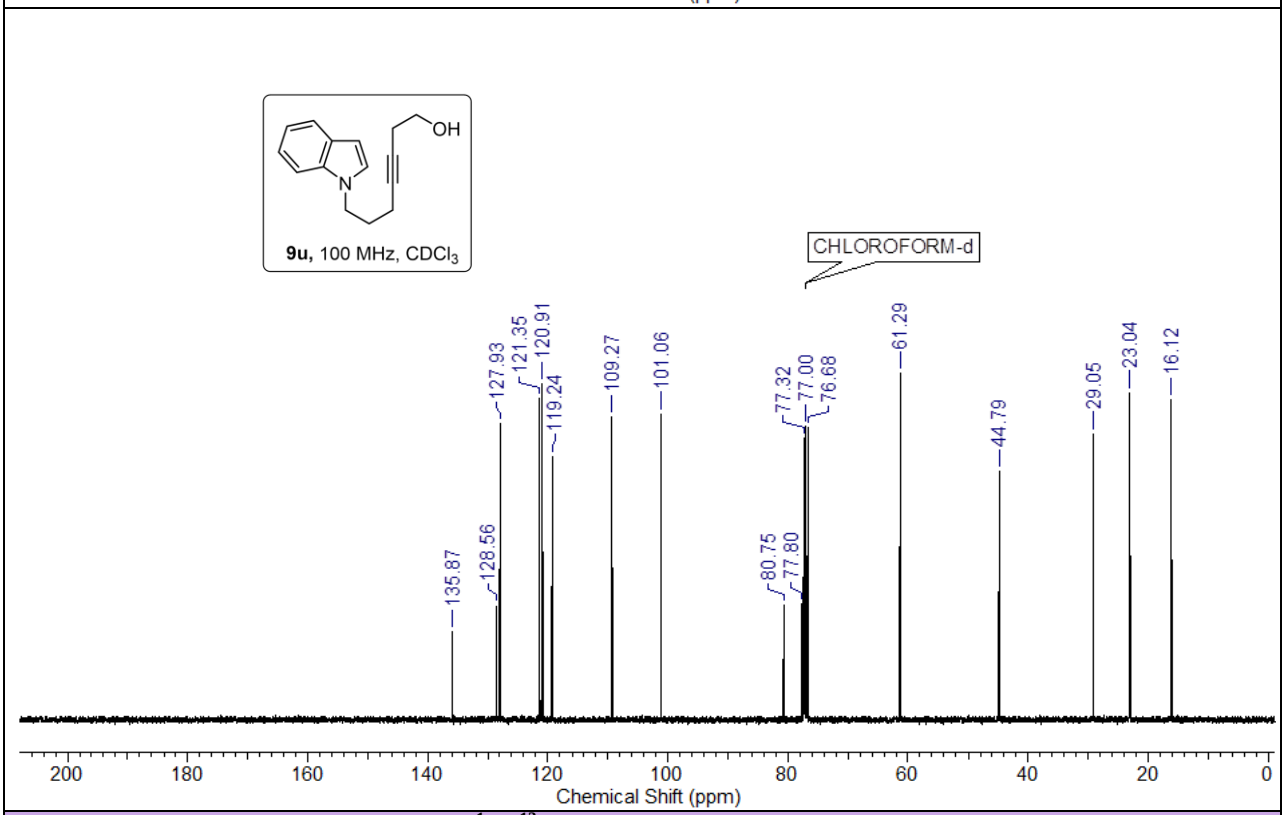


^{1}H /^{13}C NMR Spectrum of 9s

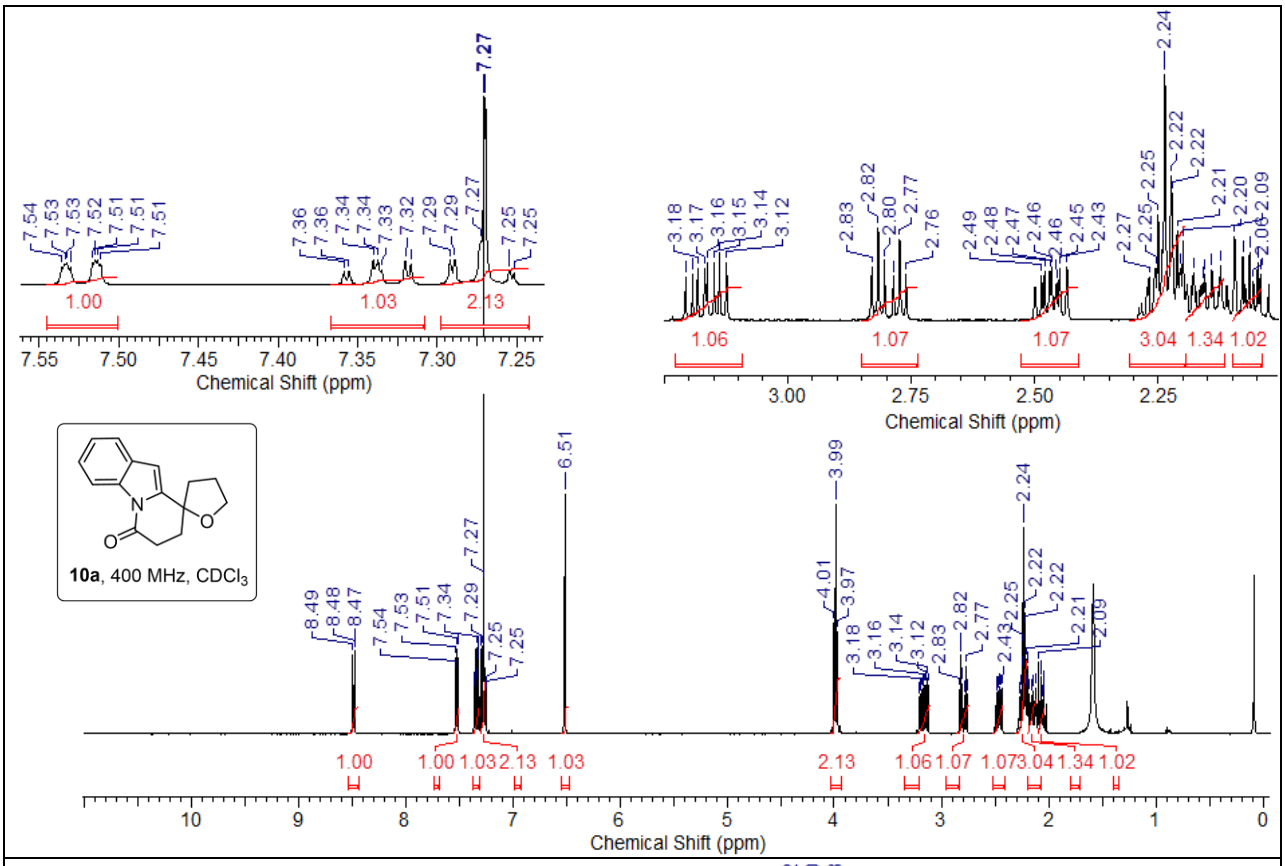


^{1}H /^{13}C NMR Spectrum of 9t

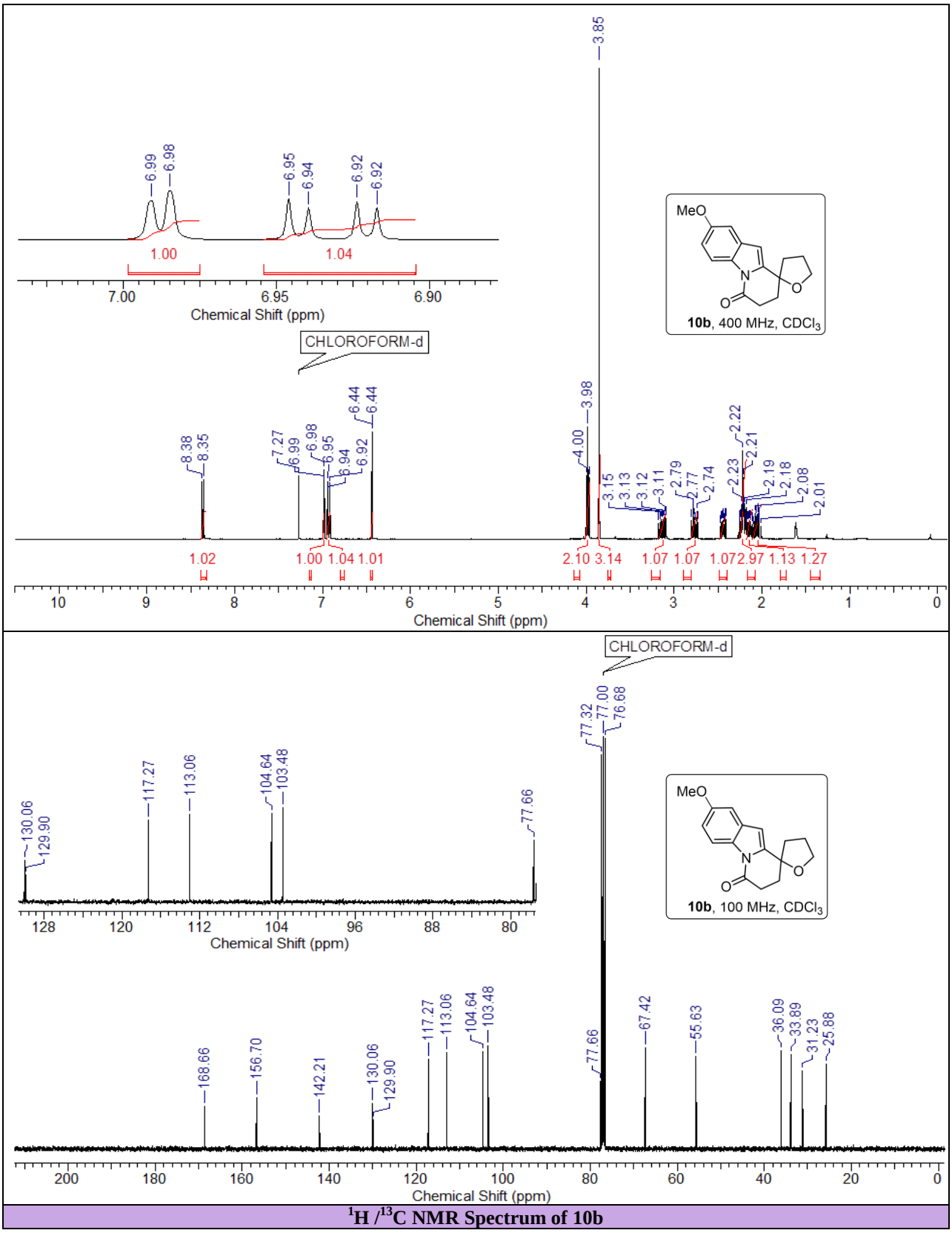




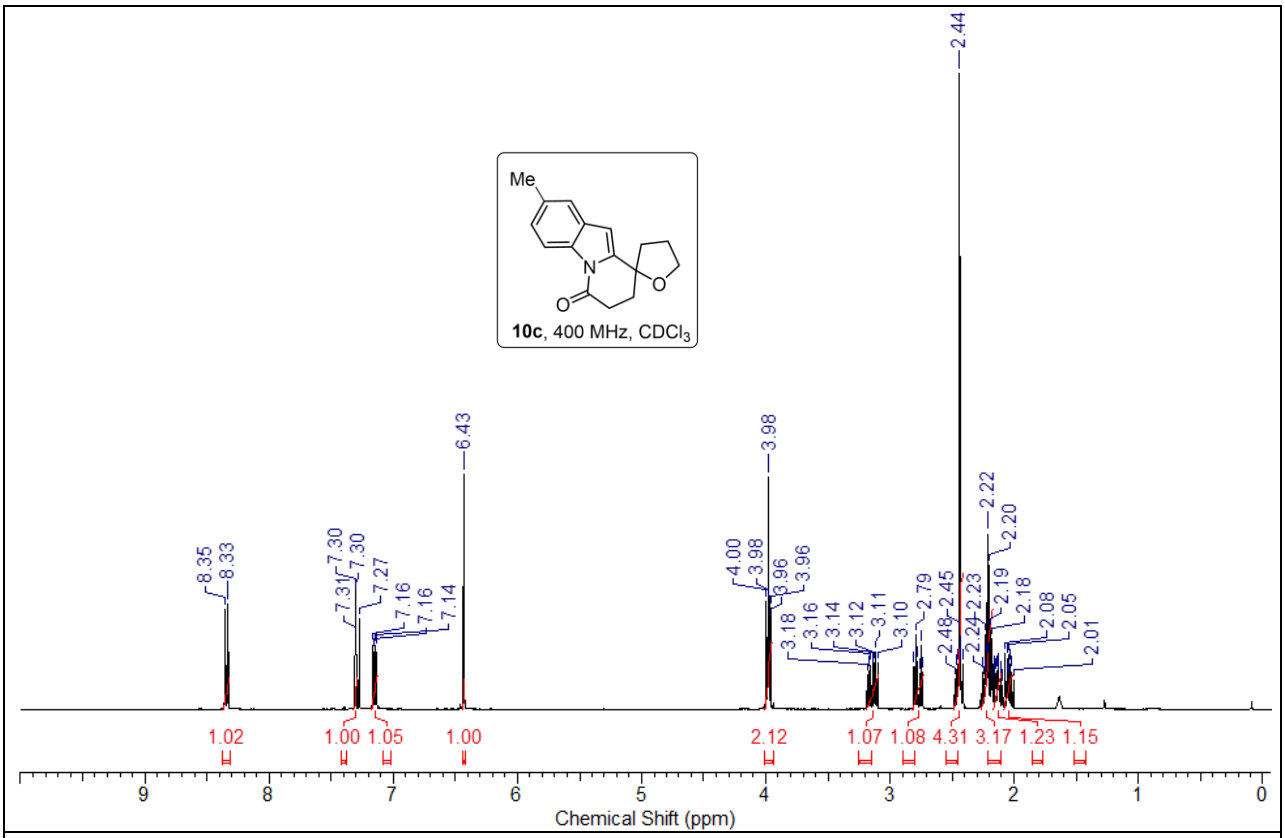
^{1}H /^{13}C NMR Spectrum of 9u

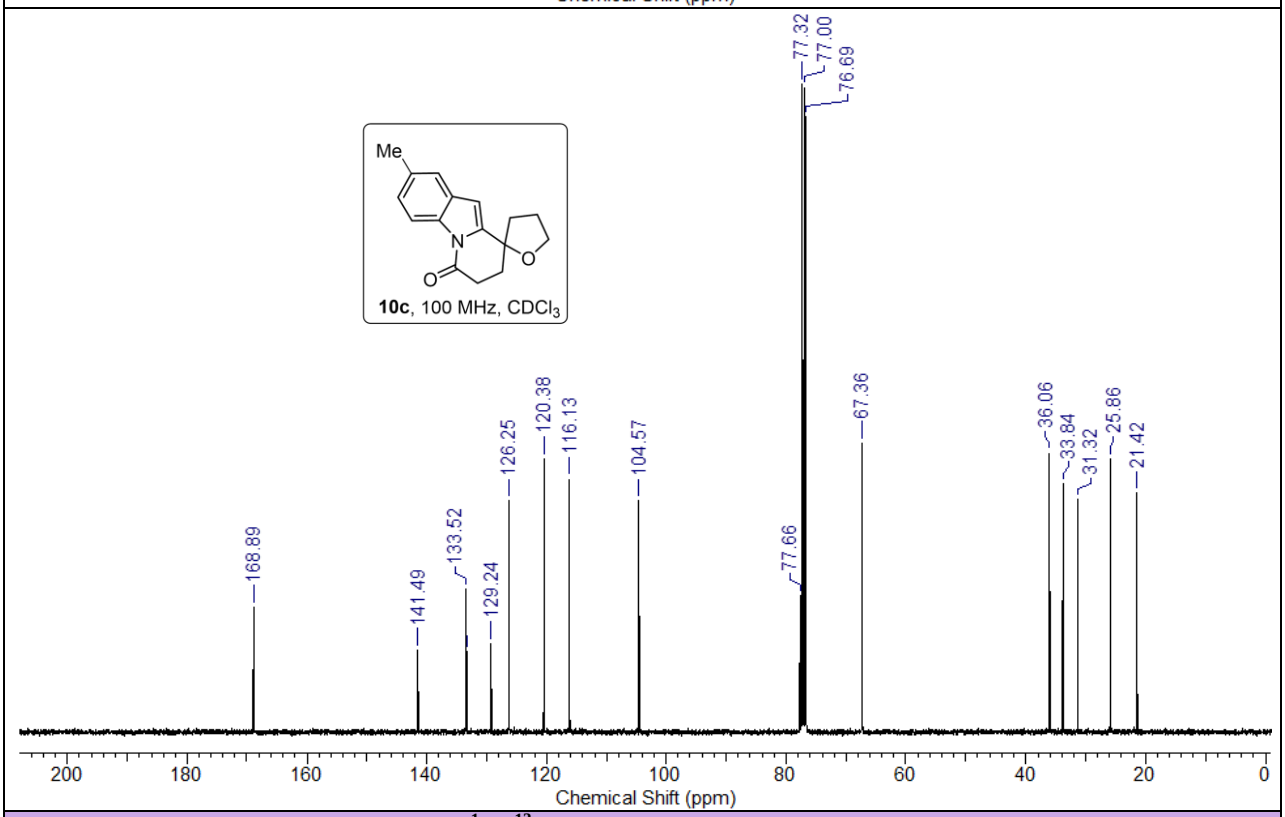


^{1}H /^{13}C NMR Spectrum of 10a

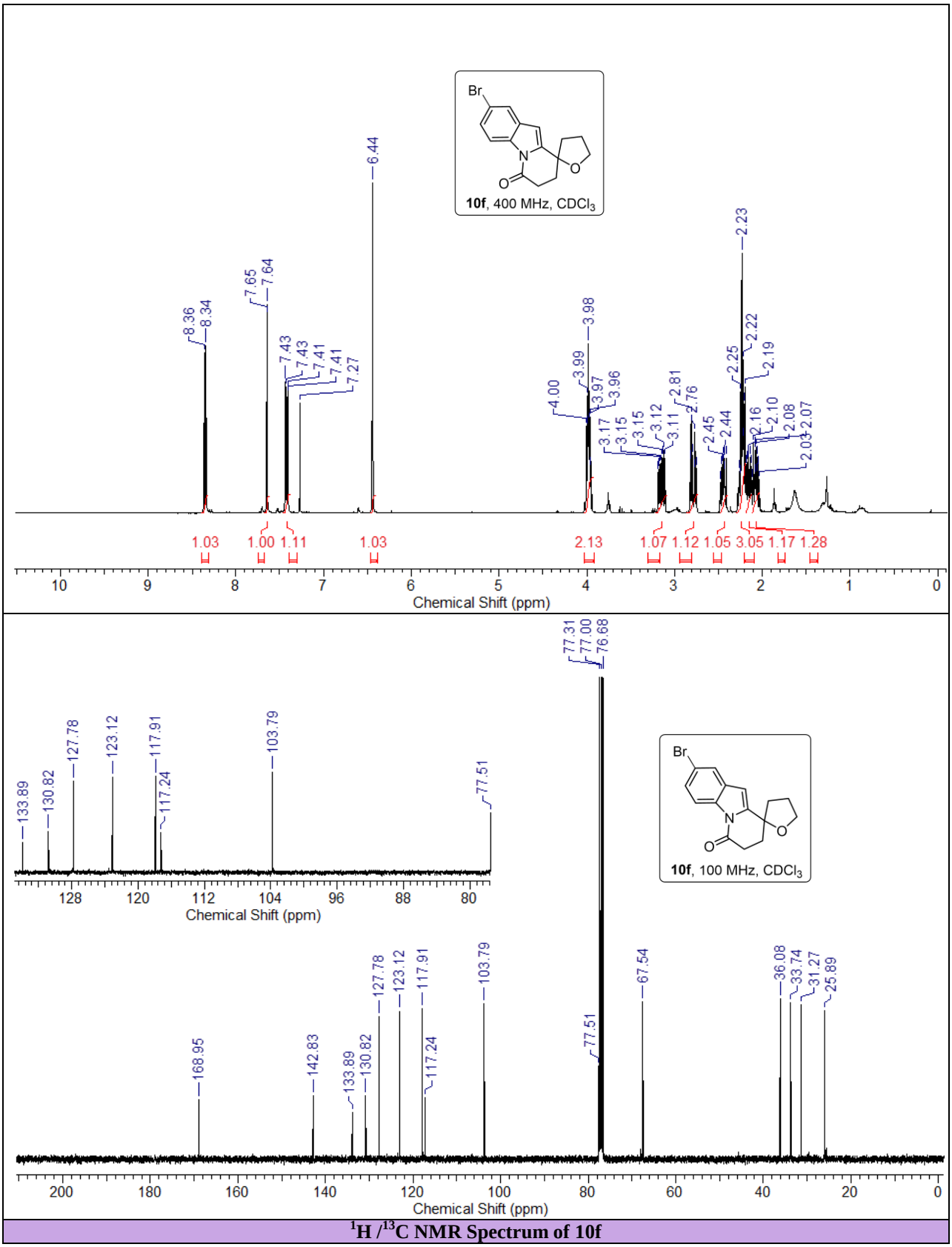


^{1}H /^{13}C NMR Spectrum of 10b

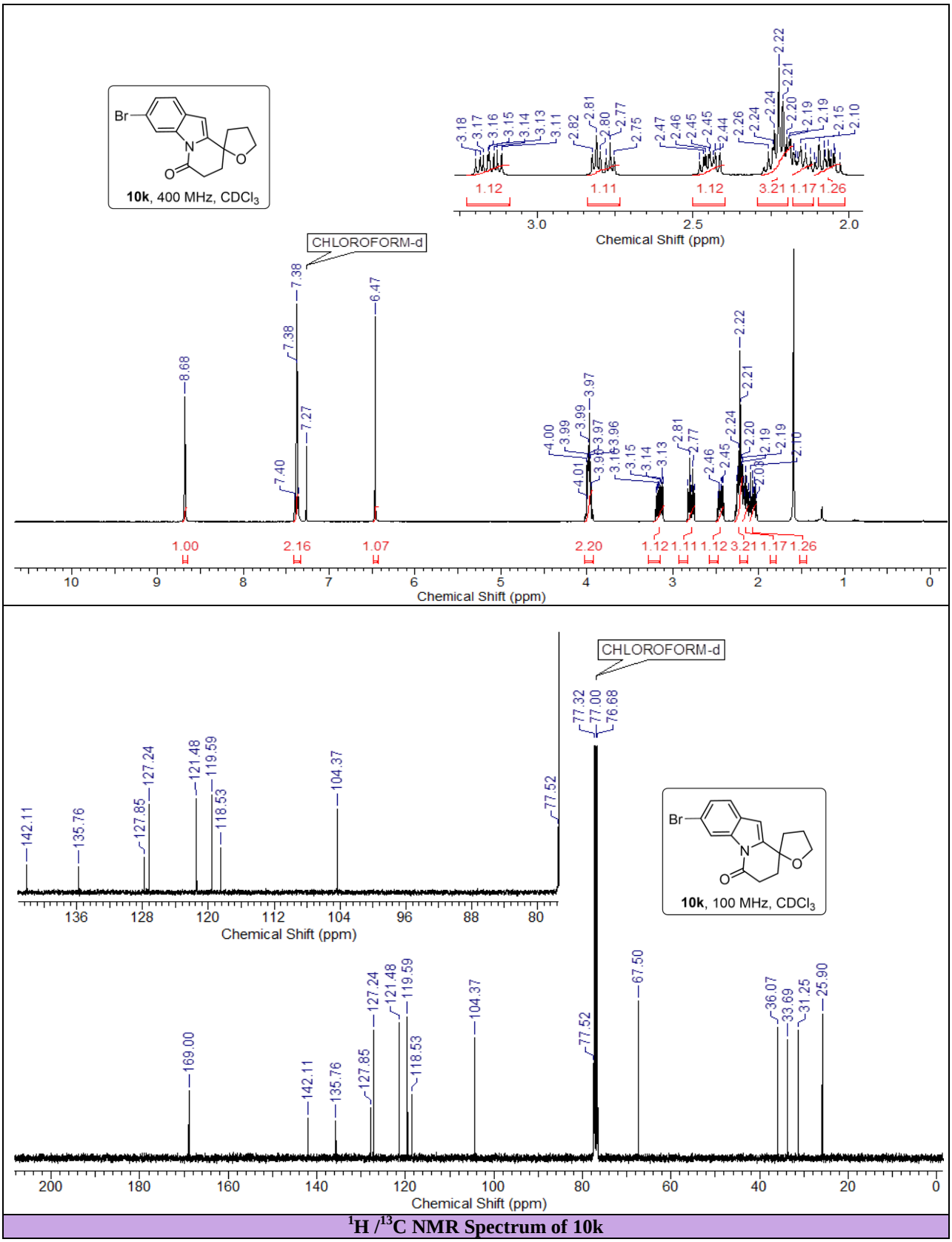




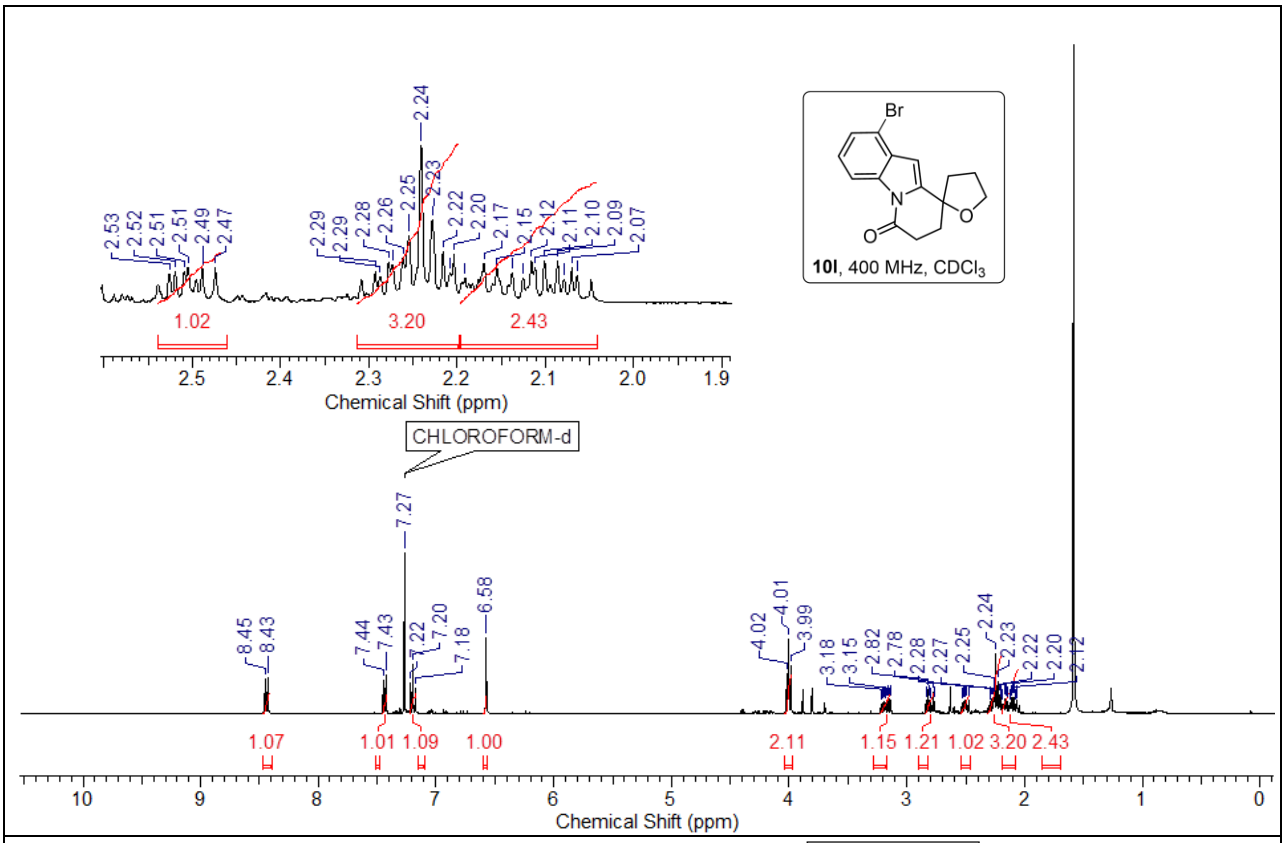
^{1}H /^{13}C NMR Spectrum of 10c



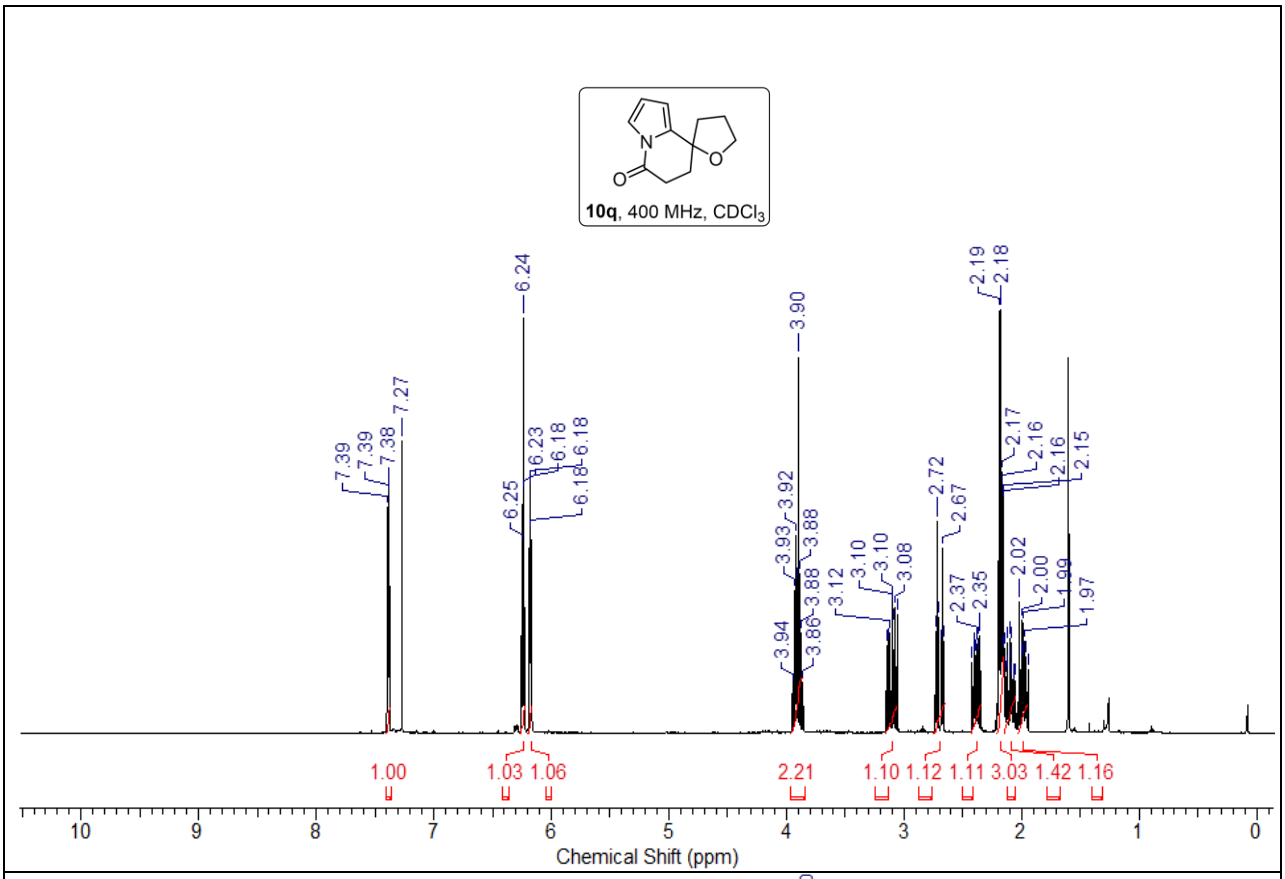
^{1}H /^{13}C NMR Spectrum of 10f

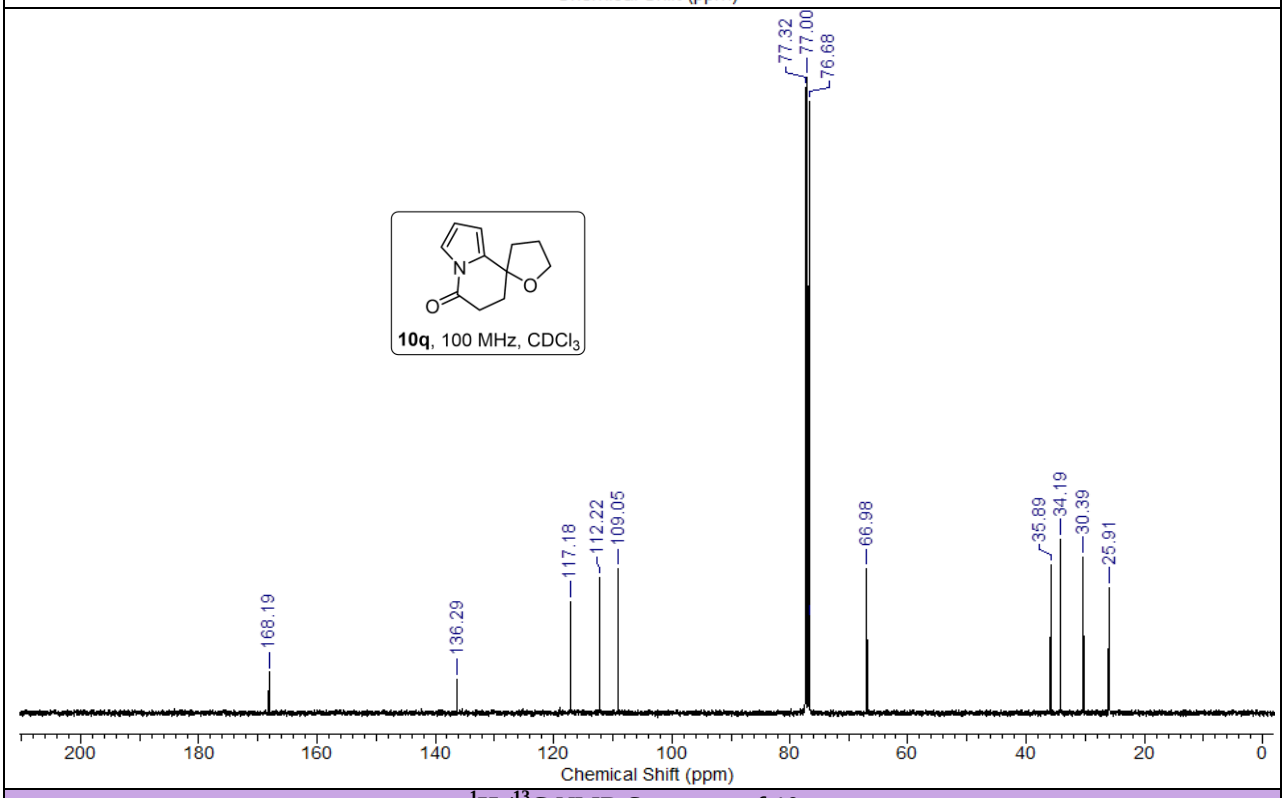


^{1}H /^{13}C NMR Spectrum of 10k

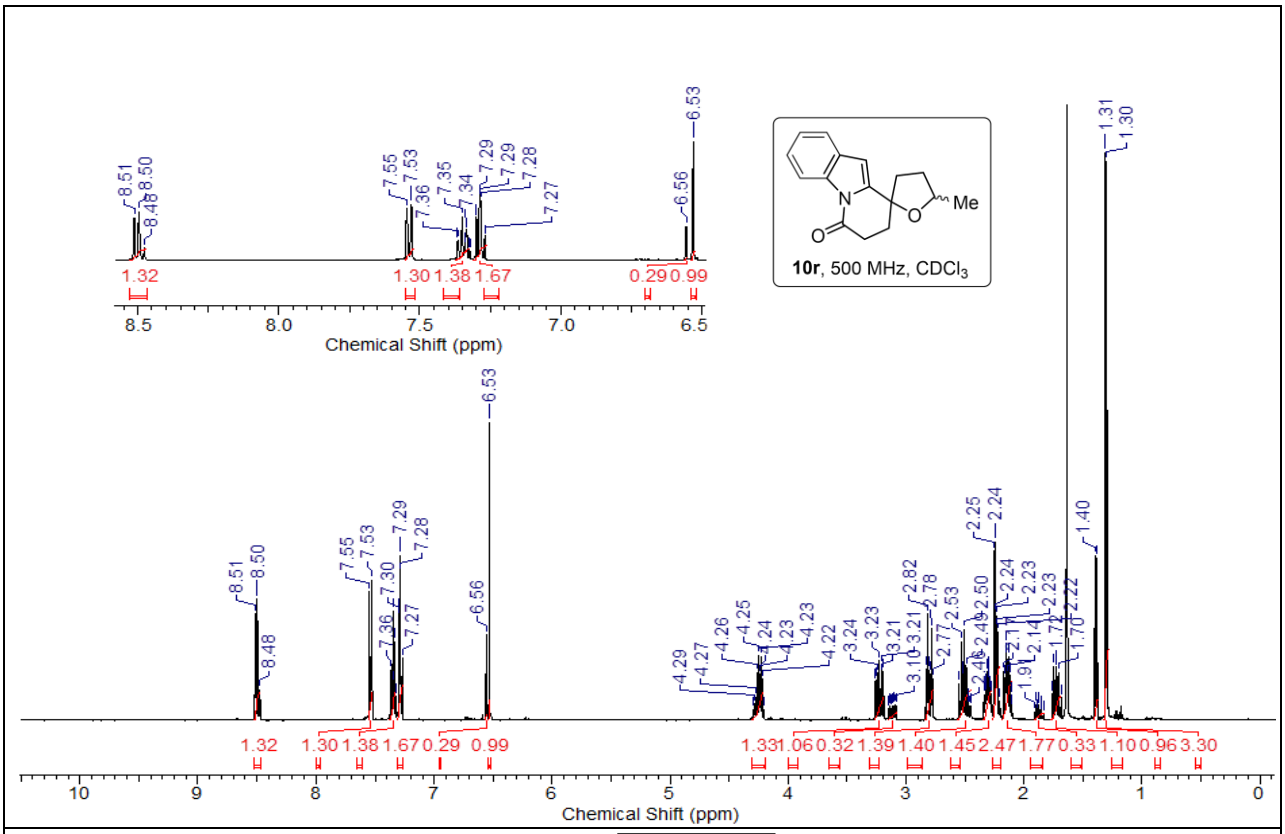


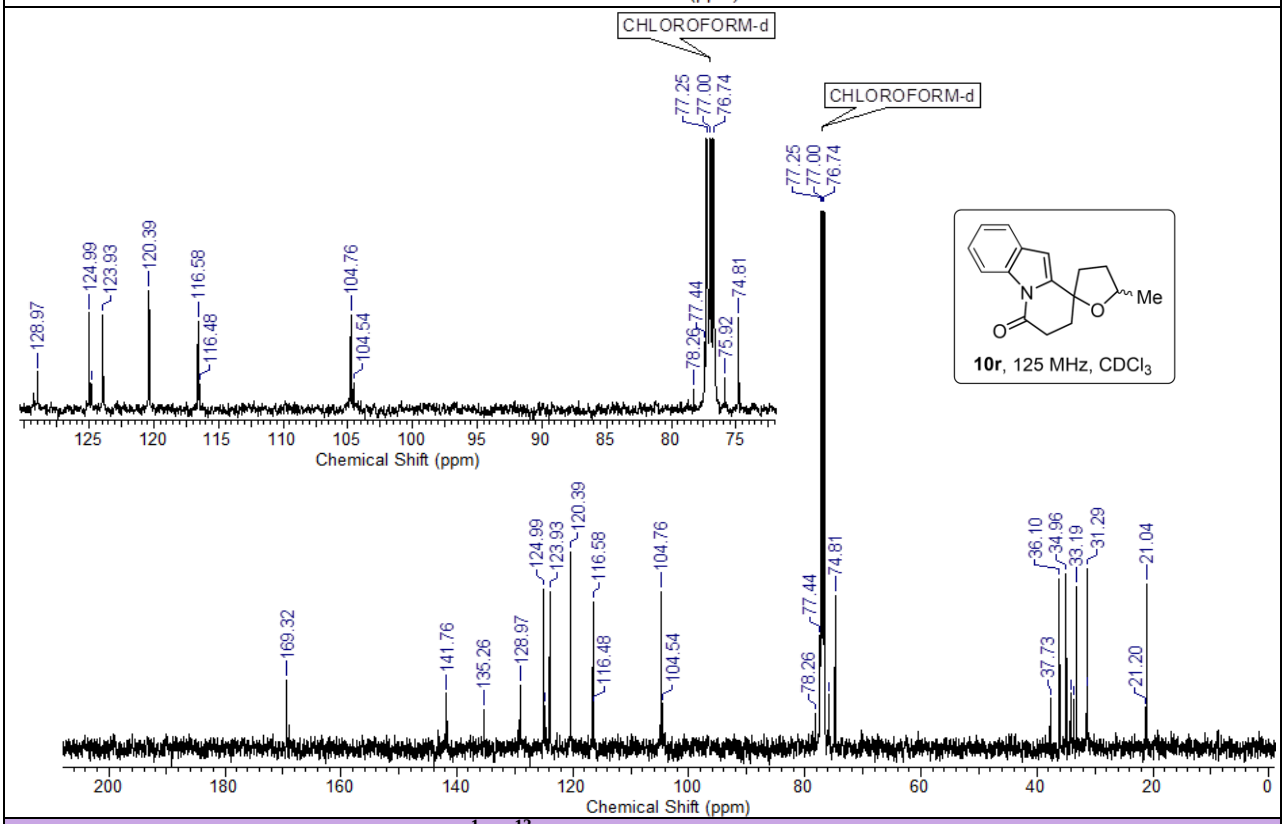
^{1}H /^{13}C NMR Spectrum of 10l





^{1}H /^{13}C NMR Spectrum of 10q





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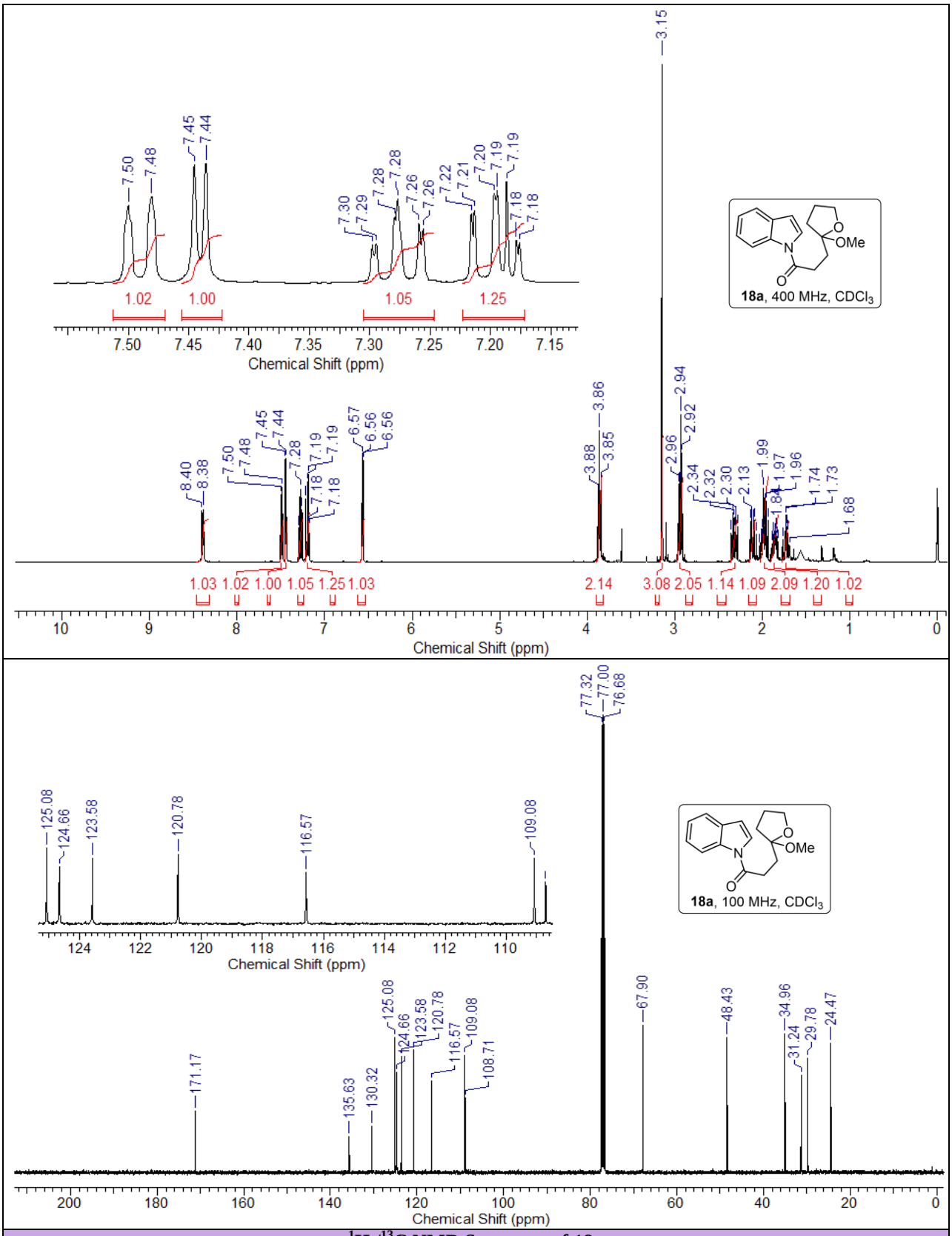

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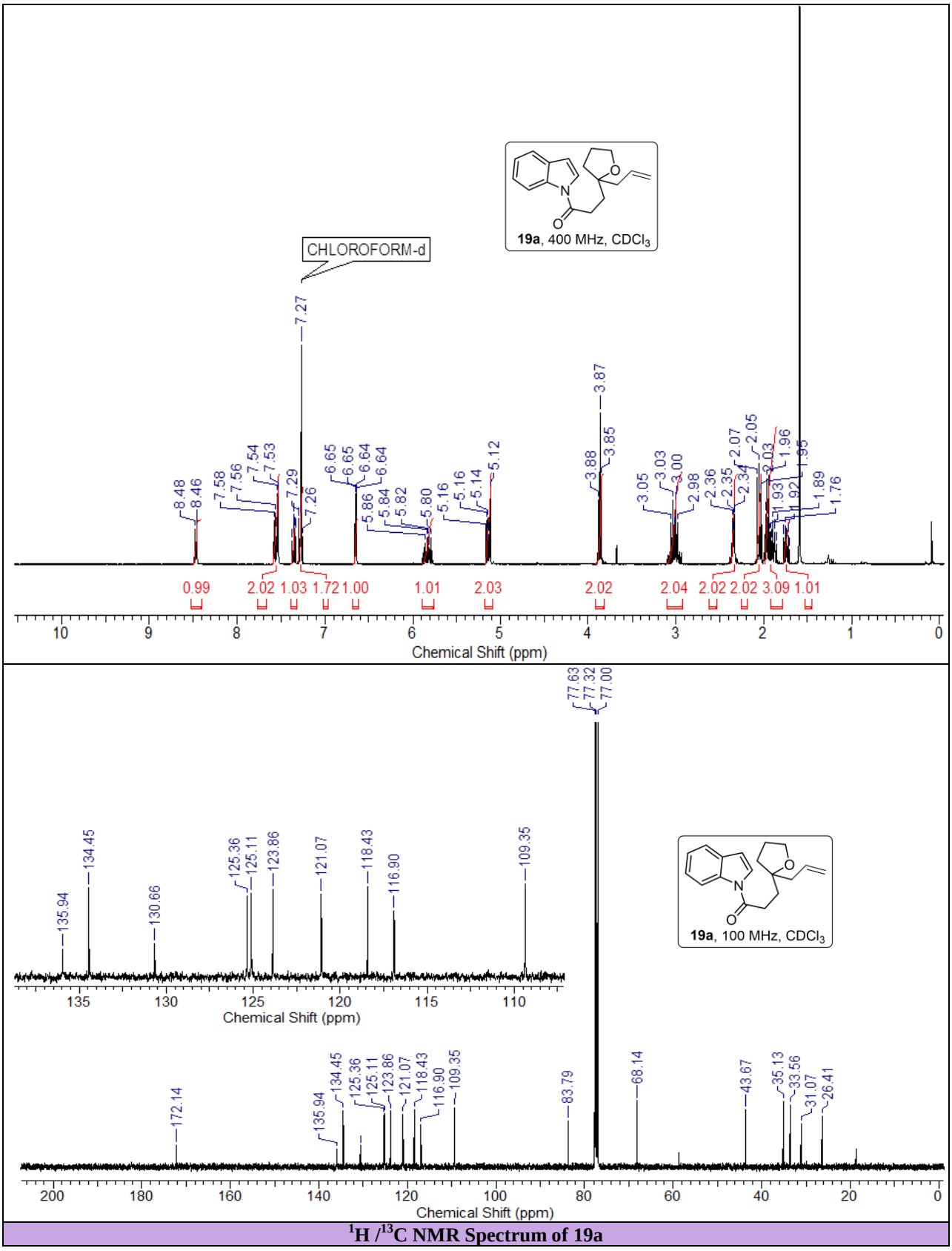

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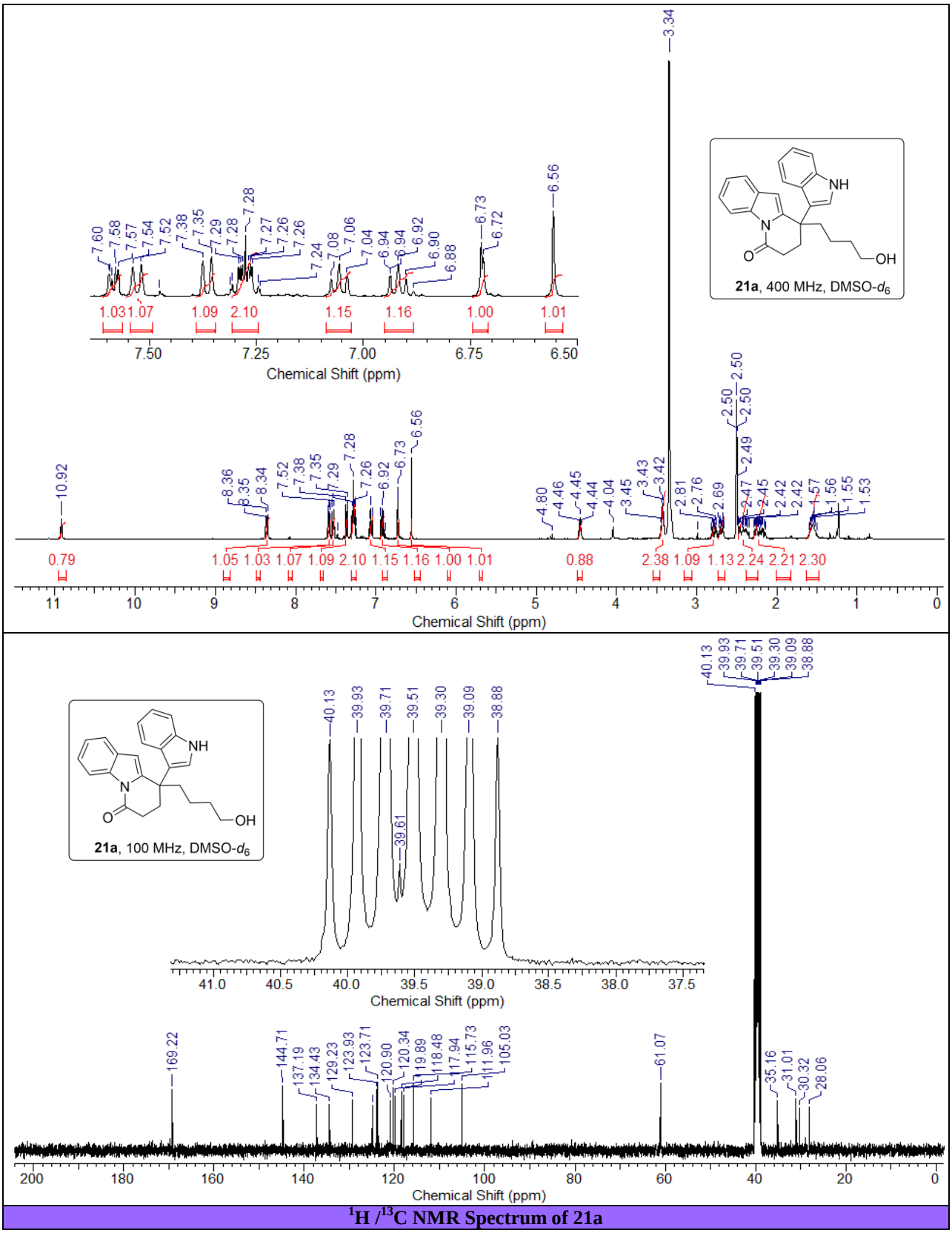

^{1}H /^{13}C NMR Spectrum of 21a

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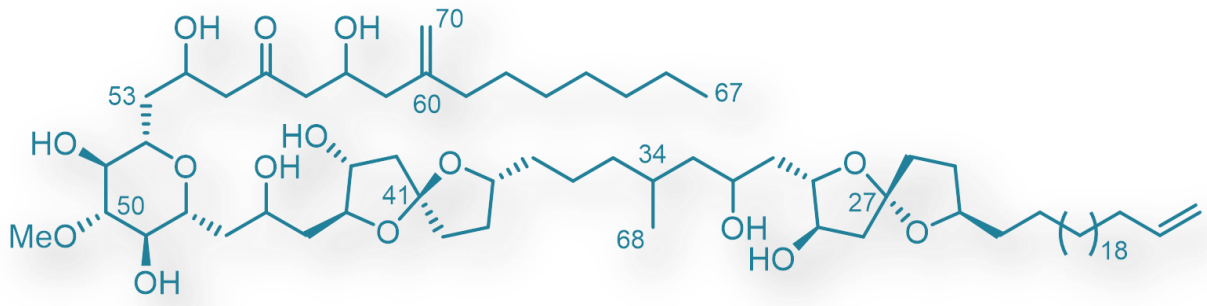
Chapter II

Gold Catalysed Alkynediol Spiroketalization: Studies Toward the Synthesis of the C35–C53 Fragment of Symbiospirol A/B/C



1.1 Introduction to Bicyclic Acetals

The primary and secondary metabolic pathways in plants, animals, bacteria, and fungi are a source of a huge collection of bioactive natural products like carbohydrates, alkaloids, steroids and terpenoids.[1] Natural products are complex structures with distinguished structural and stereochemical arrangements, which accounts for their affinity and selectivity towards a range of biological targets. The millions of millions untraced of natural products are widely distributed in nature, but only a few million have been isolated and characterised. Nature has categorised them into sub-divisions depending upon the association in combination.

Arguably, natural products are a great source of motivation for synthetic chemists to unravel novel transformations to match the complexity found in nature. The highly functionalised or unsubstituted bicyclic acetal is one of the crucial substructures present in natural products or biological targets.[2] Bicyclic acetals interact with biomacromolecules, where the conformations of acetals show a major role.[3] The bicyclic acetals are classified into three different categories: fused, spiro, and bridged, depending upon their framework or connection pattern.

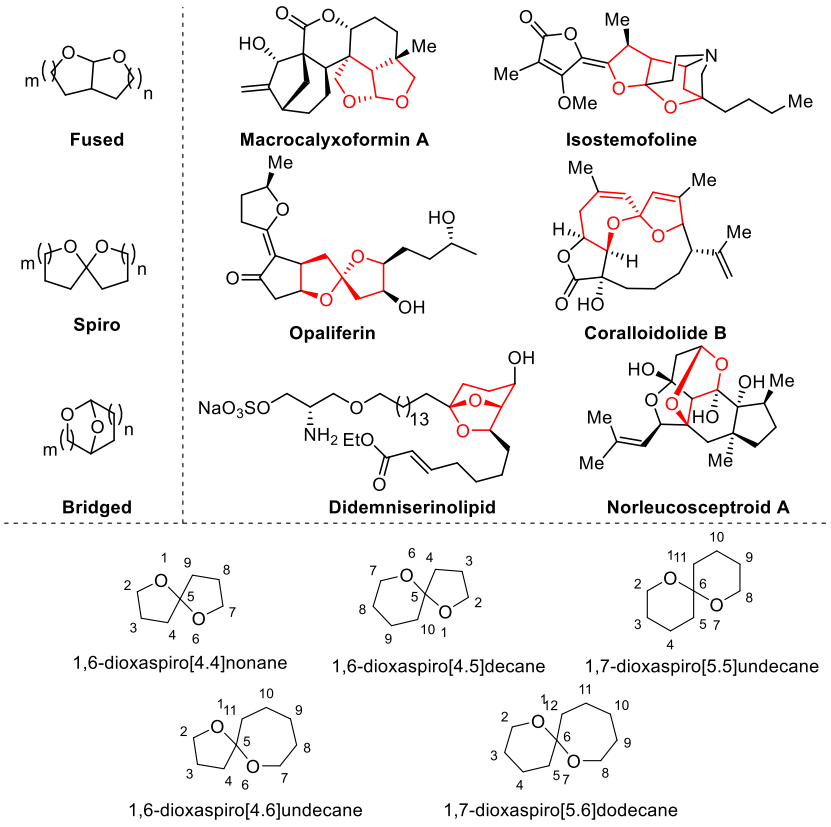


Figure 1. Different Bicyclic Acetals and the Nomenclature of Spiroketals

According to a latest report, a large set 466238 natural products were analysed from the Universal Natural Product Database (UNPD), where 1578 fused bicyclic acetals, 2633 spiroacetal moieties and 2159 bridged bicyclic acetal natural products were identified.[4] The most common ring combinations [5,5], [6,6], and [6,6] were found to be present in fused bicyclic acetals or spirocyclic acetals. However 6,8-dioxabicyclo[3.2.1]octane is a popular framework in bridged bicyclic acetals. Figure 1 shows basic structures of different bicyclic acetals and representative natural products of the class, and the nomenclature for the spiroketal skeleton.

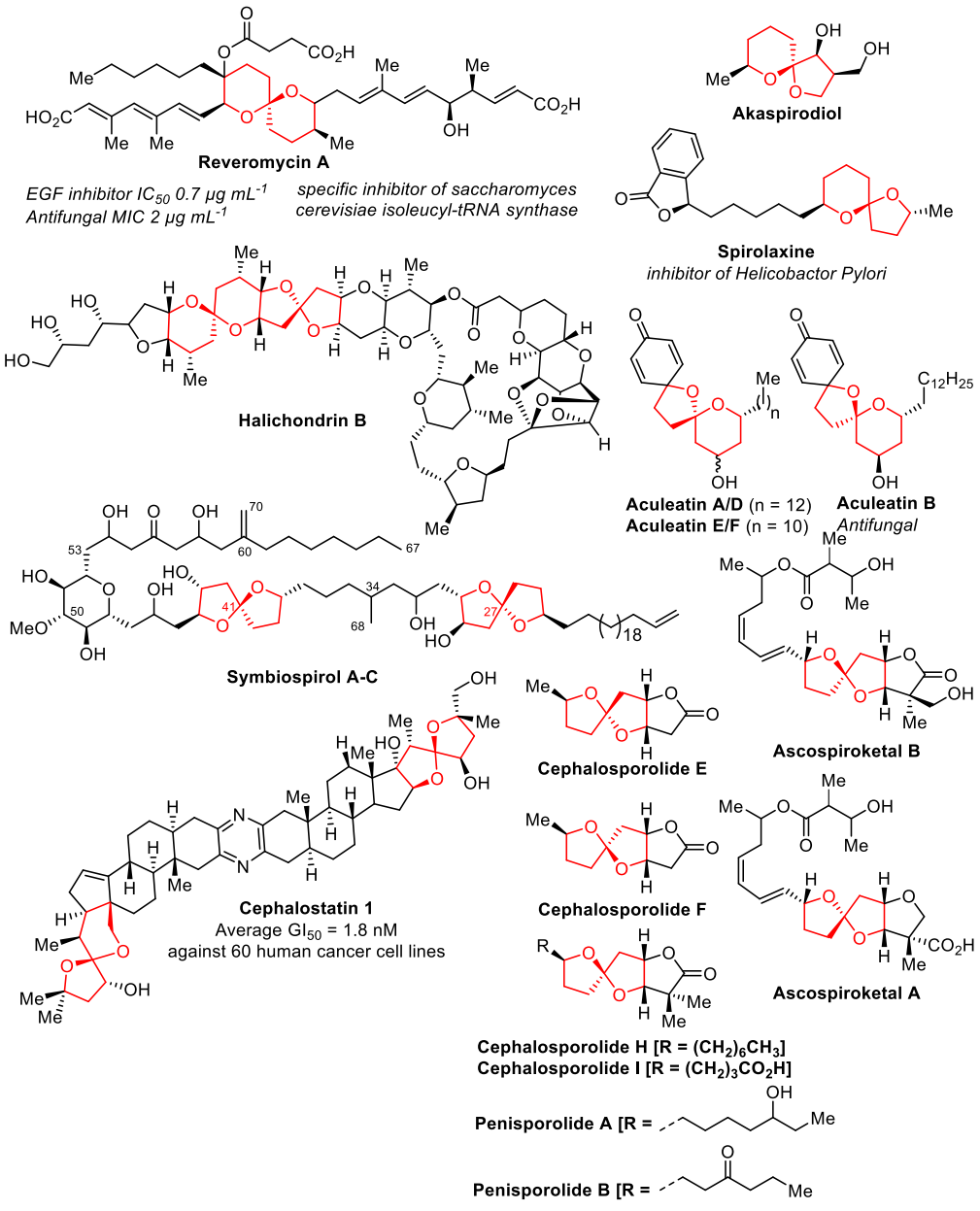
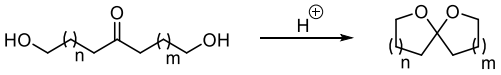


Figure 2. Selected Bioactive Spiroketal Natural Products

Spiroketal natural products possessing a cyclic ketal unit integrated in between two rings are privileged skeletons present in numerous biologically active natural products, and appreciated targets in medicinal chemistry.[5] In general, the unfunctionalized spiroketals are obtained from flying insects and are identified for their pheromone activity. Over the past few decades, the spiroketal motif has received noteworthy consideration from organic chemists. Previously, a wide range of new synthetic methods have been tested in order to accomplish the total synthesis of simple targets of this class. However, the classical method to construct a spiroketal is the intramolecular ketalisation of a suitably positioned ketonediol.[6]



Scheme 1. Classical Spiroketal Synthesis

It was noted that the bridged bicyclic ketal is a rigid structure. However, the spiroketal unit is labile and is therefore a major concern while planning the retrosynthesis of spiroketal natural products. The synthesis or isolation of natural products (Aculeatins, Cephalosporolide E and F) with an epimeric spirocenter is proof of the labile nature of spiroketals.[7] Figure 2 describes structures of some selected natural products having a spiroketal core, and their varied biological activities. In this regard, recently published work by the Brimble group involves the formal synthesis of γ-rubromycin, the synthesis of a *bis*-spiroacetal core of spirastrellolide B, and pectenotoxin.[8] Over the last two decades, our group has been involved in the design and development of transition metal catalysed cycloisomerization in the context of the spiroketal core or the corresponding natural products synthesis.[9] Although several exciting methods have been reported earlier, the most common methods are based and varied upon the handling of the carbonyl unit. The next set of discussions will emphasize mainly the development of metal catalysed cycloisomerization and consequently, the representative total synthesis of spiroketal natural products.

1.2 Transition Metal Catalysed Alkynol Spiroketalization:

As shown in Scheme 1, the spiroketals architecture was commonly synthesized by the acid catalysed cyclisation of dihydroxyketones. A short time ago, the synthesis of oxygen enclosed heterocycles such as furans, benzopyran, pyran, and bicyclicketal skeletons was explored *via* transition metal catalysed cycloisomerization reactions.[10]

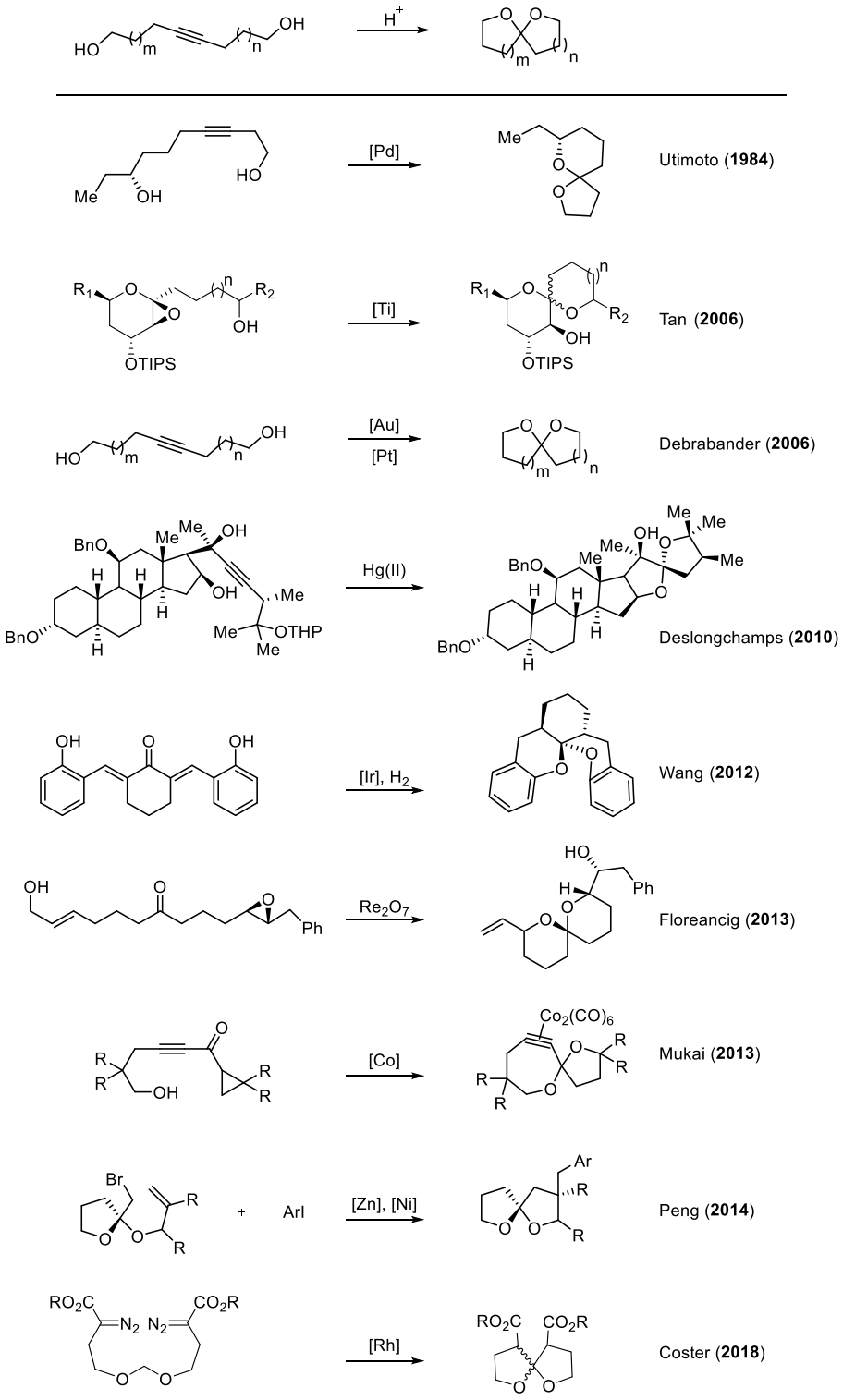
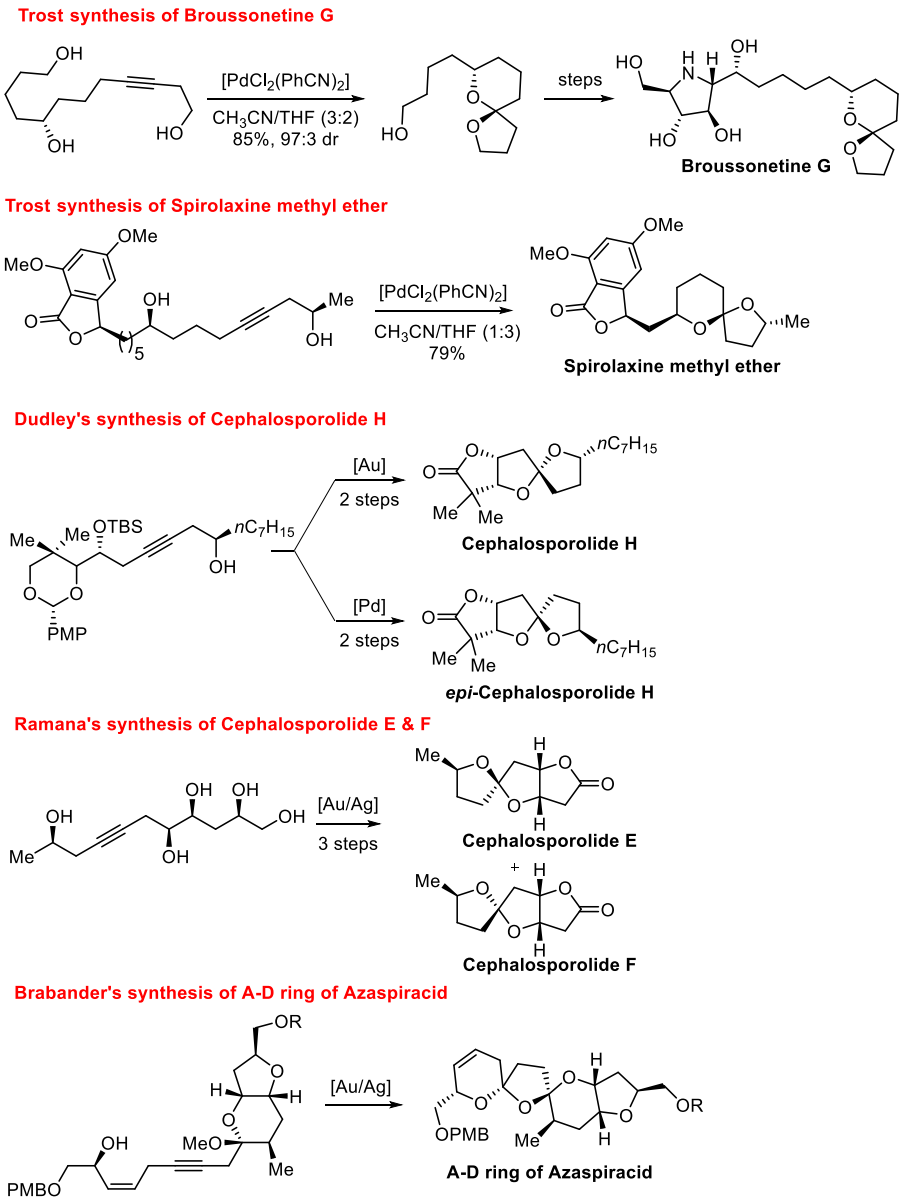


Figure 3. Development of Metal Catalysed Spiroketalization

Figure 3 saliently describes the development of the spiroketalization reaction over the past two–three decades by employing several transition metal complexes. The first report of Pd-catalysed alkynediol spiroketalization to construct a spiroketal unit appeared from the Utimoto group.[11] Subsequently, several metals complexes such as [Ti], [Au], [Pt], [Hg], [Ir],

[Re], [Co], [Zn], and [Rh] have been employed for spiroketalization reactions and to construct the spiroketal unit.[12] These approaches have been used in the total synthesis of some of the spiroketal natural products or fragments of natural products depending upon the flexibility in the starting material and the metal catalyst to be used. Natural products like Broussonetine G, Spirolaxine methyl ether, Cephalosporolides E/F/H, and the A–D rings of Azaspiracid have been accomplished by employing the metal catalysed spiroketalization as the key step of the synthesis (Scheme 2).[13]



Scheme 2. Transition Metal Catalysis in the Synthesis of Spiroketal Natural Products

We have earlier disclosed how the regioselectivity of the [Pd]- and [Au]-catalysed alkynol cycloisomerization is influenced by the substituents present on the alkyne unit, and

also employed the same guiding principles to design the substrates and accomplished the total synthesis of Cephalosporolides E/F having a spiro ketal unit and the formal synthesis of didemniserinolipid B that contains a bridged bicyclic core.[14] In continuation of our interest in this domain, the recently isolated symbiospirols A/B/C have been selected as targets for the total synthesis by employing metal catalysed cycloisomerization reactions to construct the central spiro-*bis*-THF unit and the tetrahydropyran unit in general and also fixing the missing stereochemistry of some of stereogenic centers present in these molecules.

1.3 Introduction to Symbiospirols A/B/C:

Symbiospirols A, B, and C were isolated from the cultured symbiotic dinoflagellate *symbiodinium sp*. and their structures were elucidated using NMR and degradation reactions.[15] The structures of symbiospirols were characterized with the presence of a long chain, and a polyhydroxyl and polyether backbone. In general, Symbiospirols possess a *bis*-spiroketal and tetrahydropyran core at their center. As shown in Figure 4, Symbiospirol A and B are diastereomers at the spirocenter C27, whereas the symbiospirol A and C are diastereomers at spirocenter C41. Symbiospirol A inhibited the PS-stimulated activation of PKC and hence is a promising target. Till date, there are no reports documented that are aimed at the total synthesis of symbiospirols A/B/C.

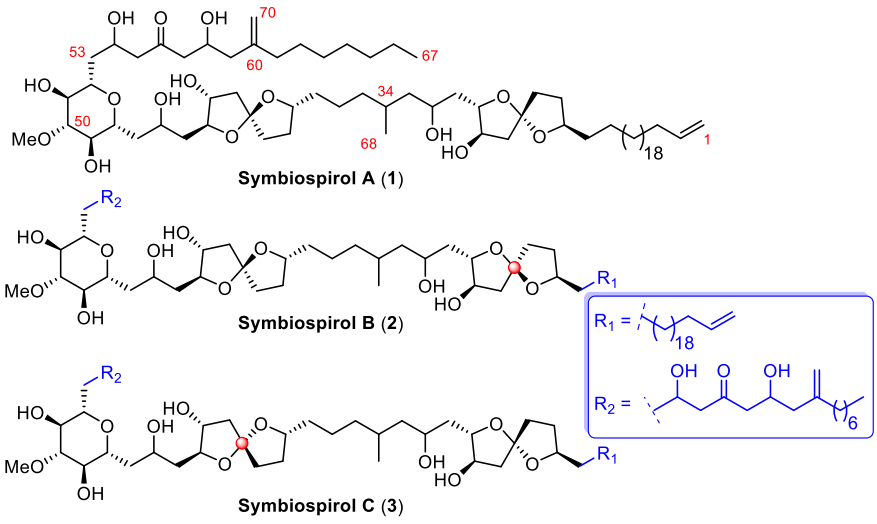
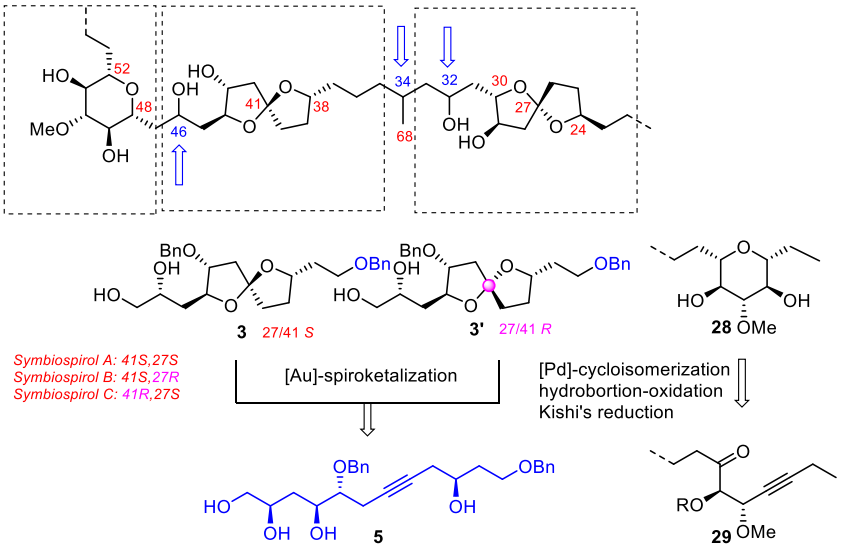


Figure 4. Structure of the Symbiospirols A/B/C

The presence of two spiroketal units and a *C*-pyranoside in symbiospirols has attracted our interest, as they provide an opportunity of extending the applicability of in-house developed C-glycosides synthesis and alkynediol spiroketalization, both being metal-

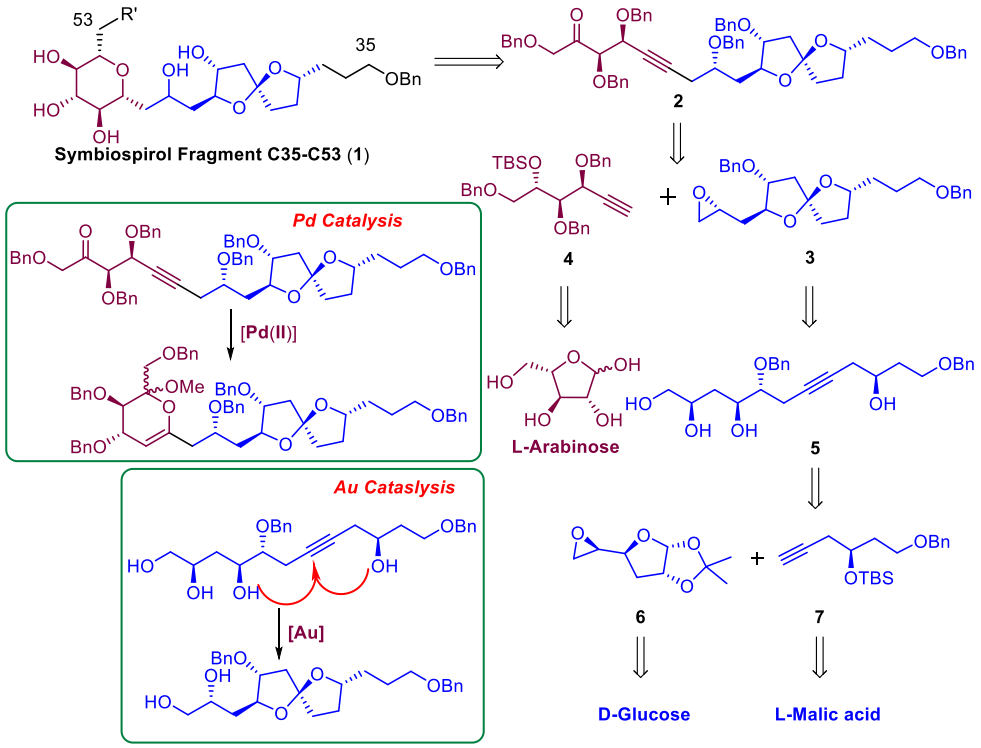
catalysed ones. As shown in Scheme 3, the basic skeletons of symbiospirols could be a combination of **3** & **3'** and a pyranoside **28**. The spiroketals **3** and **3'** are epimeric at the spirocenter. In case of symbiospirol A, it comprises of two units of **3** whereas, in case of symbiospirols B and C, either C24-C30 (B) or the C38-C44 (C) will be having the R configuration at the spiroketal carbon. Keeping all this information, we have devised our program to synthesize the spiroketals **3** and **3'** with an appropriate protecting group for orthogonal chain extension. However, fixing the relative stereochemistry of the spirocenters needs substantial NMR studies, as well as the synthesis of other possible diastereomers for an unambiguous structure determination, is warranted. Coming to the *C*-pyranoside unit that contains *gluco*-configuration, we have earlier documented the synthesis of a similar *gluco*-configured 1,5-*cis*-pyranoside by employing a one-pot palladium-catalysed alkynone cycloisomerization and Kishi's reduction.[9b-d] In the present case, the C3-OH of the pyranose ring needs to be selectively methylated. With these interim objectives in mind, we have proceeded further and the details of our efforts in this direction have been provided in the next section.



Scheme 3. Key Spiroketalization or Cycloisomerization Steps

1.4. Retrosynthetic Analysis:

As mentioned previously, as a part of the total synthesis of symbiospirols, the C35–C53 fragment of these compounds has been taken as the initial target. This fragment contains a *bis*-spiroketal unit and a tetrahydropyran core. The relative stereochemistry of the tetrahydropyran core is common in all the three natural products. However, as indicated earlier, in case of the symbiospirol C, the C41 spirocarbon is epimeric to that present in the other two natural products. However, one of the problems with the metal-catalysed spiroketalization, especially from the alkynediols, was the lack of selectivity during the spiroketalization. In the current case, this will be an added advantage, as it will provide an opportunity to synthesize both the epimeric spiroketal units present in these natural products and also determine the possible conformation and the relative stereochemistry of this portion of the molecules. Keeping this in mind, the gold-catalysed spiroketalization of alkynediol was intended to construct the two spiro-*bis*-THF units of symbiospirols A/B/C. Coming to the construction of the central tetrahydropyran ring of symbiospirols A/B/C, a palladium-catalysed cycloisomerization of alkynone, followed by hydroboration-oxidation and Kishi reduction of (Scheme 5) have been opted in this regard. Accordingly, after having the desired fragment, it can be stitched with the next spiro- *bis*-THF unit (C22–C33).

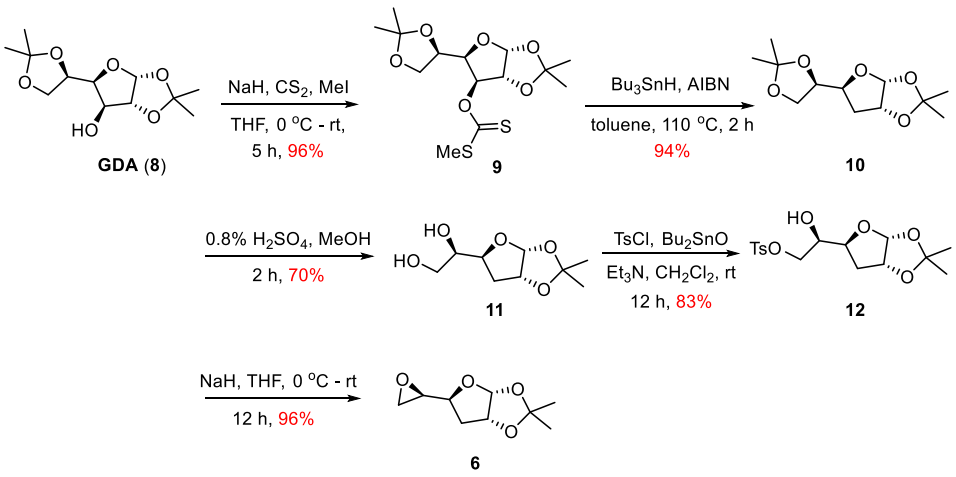


Scheme 5. Retrosynthetic Strategy

As shown in Scheme 5, the opening of spiroketal-epoxide **3** with L-arabinose derived alkyne **4**, followed by –OTBS deprotection and alcohol oxidation, could afford the desired alkynone **2**. The alkyne **4** could be obtained from the known 2,3,5-*tri*-O-benzyl-L-arabinofuranose *via* Colvin rearrangement followed by the –OTBS protection of the resultant alkynol. Coming to the synthesis of the key epoxide fragment **3**, it was planned from the gold-catalysed spiroketalization of tetrol **5**, with the subsequent conversion of terminal 1,2-diol to the corresponding epoxide. The synthesis of tetrol **5** was planned from the opening of the D-glucose derived known epoxide **6** with L-malic acid derived alkyne **7**, followed by –OTBS, acetonide deprotection and the reduction of the resultant lactol.

1.5 Synthesis of Epoxide 6:

The synthesis began with xanthate protection of alcohol **8** (GDA) in the presence of sodium hydride (60% oil suspension), carbon disulphide and methyl iodide in THF solvent at 0 ^{o}C – rt for 5 h to afford xanthate **9** in 96% yield (Scheme 6). Next, the xanthate **9** was exposed to (Barton–McCombie deoxygenation) tributyltin hydride (Bu_3SnH) and azobisisobutyronitrile (AIBN) in toluene solvent at 110 °C for 2 h to obtain compound **10** in 94% yield. The ^{1}H NMR spectrum showed the disappearance of a singlet at δ 2.58 (s, 3H) and the existence of two new multiplets around δ 1.5–2.25, which conformed the formation of C3-deoxy-glucose diacetonide. The selective deprotection of the 5,6-*O*-isopropylidene group in presence of 0.8% H_2SO_4 in methanol solvent gave the diol **11** in 70% yield. The selective tosylation of diol **11** in the presence of cat. dibutyltin oxide (Bu_2SnO), tosyl chloride and triethylamine in dichloromethane solvent gave compound **12** in 83% yield. The resulting compound **12** was immediately exposed to sodium hydride (60% oil suspension) in THF



Scheme 6. Synthesis of Epoxide **6**

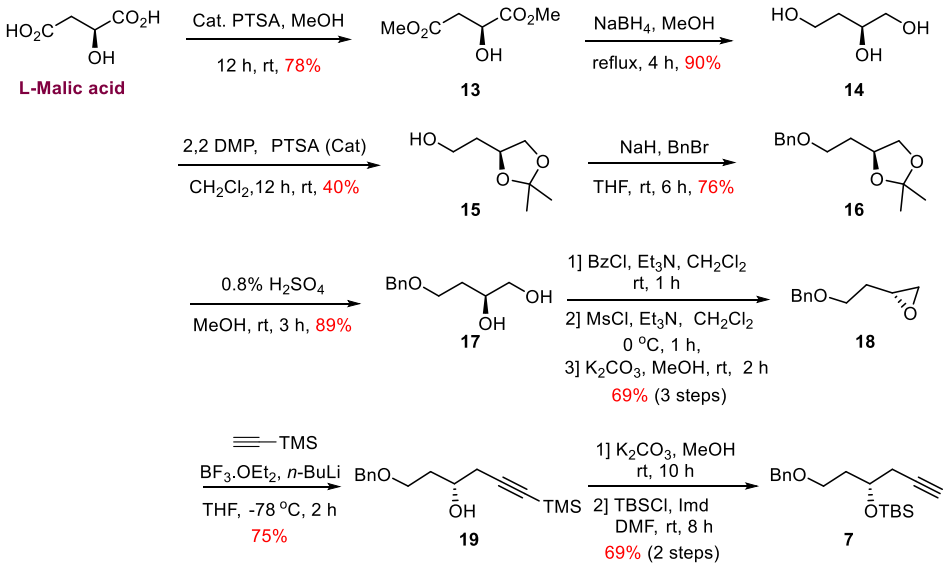
solvent at 0 ^{o}C – rt to obtain the desired epoxide **6** in 96% yield. The ^{1}H NMR spectrum of epoxide **6** showed two singlets at δ 1.33 (s, 3H), and 1.51 (s, 3H) representing the 1,2-*O*-isopropylidene group and a doublet at δ 5.84 (d, *J* = 3.6 Hz, 1H) corresponding to the C1 proton. The ^{13}C NMR spectrum displayed two quartets of methyls of acetonide at δ 26.1 (q), and 26.7 (q) and a methylene carbon (C3) of the ring at δ 34.2 (s), and 45.1 (s) (methylene of epoxide). Also, the C1 carbon appeared as doublet at δ 105.5 (d), whereas the quaternary carbon of 1,2-*O*-isopropylidene was observed at δ 111.3 (s). The ESI-MS (HRMS) base peak appeared at 209.0782 supporting the formation of the desired epoxide **6**. The specific rotation of the compound **6** was found to be $[\alpha]_D^{28}$ –21.7 (*c* 3.6, $CHCl_3$), which is in agreement with the reported data.[14d]

1.6 Synthesis of Alkyne 7 from L-Malic Acid:

The synthesis of alkyne **7** commenced with the esterification of L-malic acid in the presence of cat. *p*-toluenesulfonic acid and in methanol at rt for 12 h to form the di-ester **13** in 78% yield (Scheme 7). Compound **13** was reduced with sodium borohydride in refluxing methanol for 4 h to afford the triol **14** in 90% yield. The protection of 1,2-diol as its 1,2-*O*-isopropylidene derivative was carried out with 2,2-dimethoxy propane (2,2-DMP) in the presence of cat. *P*-toluenesulfonic acid in dichloromethane solvent at rt for 12 h. Next, the stepwise benzyl protection of alcohol **15** with sodium hydride (60% oil suspension) and benzyl bromide followed by the acetonide deprotection in the presence of cat. *P*-toluenesulfonic acid gave the desired diol **17** in 89% yield. The ^{1}H NMR of diol **17** showed a multiplet at 7.15–7.26 (m, 5H) in the aromatic region and a doublet at δ 4.40 (d, *J* = 15.0 Hz, 2H), representing the benzyl group. The diol **17** was converted to its inverse epoxide **18** by following a 3 steps procedure (69% yield over 3 steps), comprising of the selective benzoylation of the primary hydroxyl in the presence of benzoyl chloride, triethylamine, followed by mesylation of the secondary hydroxyl group with methanesulfonyl chloride (MsCl), triethylamine, and eventually benzoyl deprotection, followed by epoxidation employing potassium carbonate (K_2CO_3) in methanol. The ^{1}H NMR spectrum of epoxide **18** exhibits a multiplet at δ 7.20–7.30 (m, 5H) and a singlet at 4.46 (s, 2H), corresponding to benzyl group. The epoxide ring protons appeared at δ 2.41 (dd, *J* = 4.9, 2.6 Hz, 1H), 2.66 (t, *J* = 4.5 Hz, 1H), and 2.98–3.03 (m, 1H). The ^{13}C NMR spectrum displayed four methylenes at δ 33.0 (t), 47.1 (t), 67.1 (t), and 73.1 (t) and a doublet of the epoxide ring at δ 50.1 (d) to confirm the epoxide formation. In the ESI-MS (HRMS), the base peak appeared at 179.1066

and the specific rotation was found to be $[\alpha]_D^{28}$ +10.7 (*c* 2.0, $CHCl_3$), identical with the reported values.[16]

Next, the alkyne group was introduced by the opening of the epoxide **18** with trimethylsilyl acetylene in the presence of *n*-BuLi and $BF_3.OEt_2$ at -78 °C for 2 h to obtain the alkynol **19** in 75% yield.[17] The ^1H NMR spectrum of compound showed a singlet at δ 0.00 (s, 9H), indicating the presence of the trimethylsilyl group, whereas the multiplet of five protons in the aromatic region and a singlet at δ 4.38 (s, 2H) specifies the presence of the benzyl group. The appearance of a peak at δ 2.29 (dd, *J* = 11.3, 5.1 Hz, 2H) is characteristic of a methylene next to alkyne, and hence confirms the opening of epoxide **18**. The deprotection of the –TMS group in K_2CO_3 methanol followed by protection of the resultant alkynol as –OTBS ether in *tert*-butyldimethylsilyl chloride (TBS), and imidazole base afforded the desired alkyne **7** in 69% yield over 2 steps. The ^1H NMR evidenced the formation of alkyne **7**, where the singlet peaks at δ 0.00 (s, 3H), 0.03 (s, 3H), and 0.83 (s, 9H) indicate the presence of the –OTBS group. However, the characteristic alkyne proton appeared at δ 1.75 (dd, *J* = 7.8, 13.7 Hz, 1H). The ^{13}C NMR shows representative alkyne carbons at δ 70.1 (d) and 81.4 (s) respectively. The ESI-MS (HRMS) base peak was observed at 319.2094 and the specific rotation was found to be $[\alpha]_D^{28}$ +13.8 (*c* 1.82, $CHCl_3$).

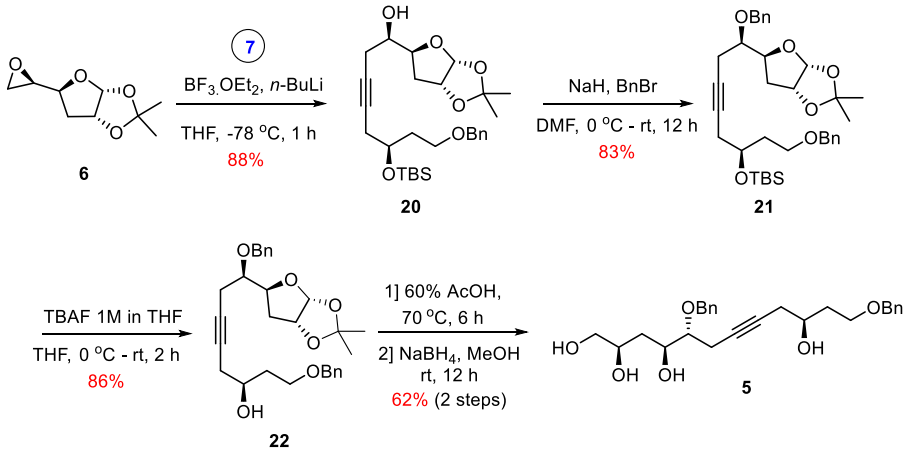


Scheme 7. Synthesis of Alkyne **7** from Inverse L-Malic Acid Epoxide

1.7 Synthesis of Tetrol 5:

After successful synthesis of the requisite epoxide **6** and alkyne **7**, these fragments were coupled in the presence of *n*-BuLi and $BF_3.OEt_2$ at -78 °C for 1h to give alcohol **20** in

88% yield (Scheme 8).[14d] The structure of alcohol **20** was established with the help of ^{1}H and ^{13}C NMR spectral data. In the ^{1}H NMR spectrum of compound **20**, the singlet at δ -0.02 (s, 3H), 0.00 (s, 3H), and 0.81 (s, 9H) indicated the presence of the –OTBS group whereas the methyls of acetonide group were found to be resonating at δ 1.25 (s, 3H) and 1.44 (s, 3H). Along with this, the distinguishing C1 proton appeared as a doublet at δ 5.74 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR also supported the presence of the –OTBS group as well as acetonide group. The presence of two shielded quartets at δ -4.85 (q) and -4.52 (q) and an intense quartet at δ 25.8 (q, 3C) represented the –OTBS group. Another two quartets present at δ 26.2 (q) and 26.8 (q) accounted for the methyls of the acetonide group. The representative alkyne carbons appeared at δ 77.2 (s) and 78.0 (s) as singlets, whereas a doublet at δ 105.4 (d) denotes the C1 proton. The ESI-MS (HRMS) supported the formation of alcohol **20** by showing the corresponding base peak at 527.2783 and the observed specific rotation of the compound was $[\alpha]^{28}_{D}$ +6.2 (*c* 1.63, $CHCl_3$). The resulting alcohol **20** was treated with sodium hydride (60% oil suspension) and benzyl bromide in DMF solvent at 0 °C – rt for 12 h to obtain the benzyl ether **21** in 83% yield.

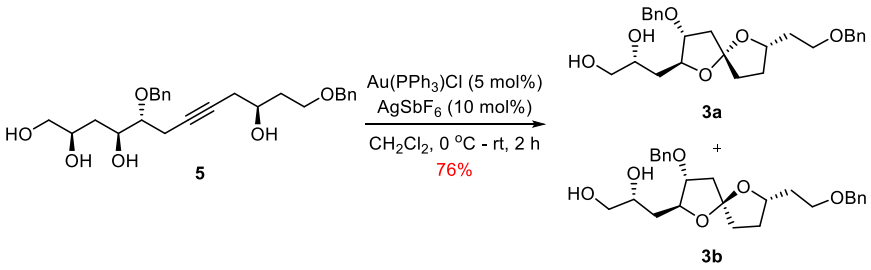


Scheme 8. Synthesis of Tetrol **5**

Immediately, compound **21** was treated with *tetra-n*-butylammonium fluoride (TBAF, 1M in THF) at 0 °C – rt for 2 h to afford the alkynol **22** in 86% yield. The structure of compound **22** was established with the help of NMR spectral data analysis. The disappearance of peaks corresponds to the –TBS group (0 – 1.3 ppm) in ^{1}H NMR and (-5 – 25 ppm) in ^{13}C NMR, indicating the successful deprotection. Also, the increase in the number of aromatic protons 7.27–7.37 (m, 10H) and the benzylic methylene in the region of ~ 4.5 ppm, the appearance of 72.9 (t) and 73.3 (t) in the ^{13}C NMR spectrum indicated the presence of two O-benzyl groups. The characteristic C1 proton resonated at δ 5.79 (d, *J* = 3.6 Hz, 1H)

and the same carbon in ^{13}C NMR appeared as a doublet at δ 105.3 (d). The ESI-MS (HRMS) base peak appeared at 481.2583, whereas the observed specific rotation is $[\alpha]_D^{28}$ -6.7 (*c* 3.86, $CHCl_3$). Subsequently, the desired tetrol **5** was synthesised from compound **22** *via* a one pot acetonide deprotection and lactol reduction. The acetonide deprotection was accomplished by exposing compound **22** with 60% acetic acid at 70 °C for 6 h. Upon completion of the reaction, the solvents were removed to dryness under reduced pressure and with the crude compound, we proceeded to the next step. The conversion of lactol to the desired tetrol **5** was done by reduction in the presence of sodium borohydride in methanol solvent at rt for 12 h to give tetrol in 62% yield over 2 steps. The structure of tetrol **5** was established with ^1H and ^{13}C NMR spectral data analysis. For example, in the ^1H NMR spectrum, the presence of two benzyl groups was evident from an aromatic-H multiplet δ 7.29–7.37 (m, 10H) and one of the benzylic methylenes appeared as a singlet at 4.52 (s, 2H), and the other benzylic group gave two doublets at δ 4.55 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H). The characteristic methylene next to the alkyne appeared as a doublet of doublet at δ 2.38 (dd, *J* = 2.2, 5.8 Hz 2H) and two multiplets at δ 2.45–2.54 (m, 1H), 2.55–2.62 (m, 1H). The ^{13}C NMR showed distinguishing alkyne carbons at δ 78.5 (s) and 78.8 (s) ppm. The representative four methylene (66.6, 68.5, 72.1, and 73.3) and four methine carbons (69.5, 72.0, 72.5, and 80.2) attached to oxygen atom appeared around δ ~ 65–80 ppm. The formation of tetrol **5** was supported by the presence of a ESI-MS (HRMS) base peak at 465.2240, and the specific rotation of compound was observed at a $[\alpha]_D^{28}$ -16.3 (*c* 2.24, $CHCl_3$). After completing the synthesis of tetrol **5** successfully, the stage was all set to go for the gold catalysed spiroketalization and to check the diastereoselectivity of the reaction.

1.8 Gold Catalysed Spiroketalization:



Scheme 9. Synthesis of Spiro Diastereomers **3a** and **3b**

The tetrol **5** was treated with $AuPPh_3Cl$ (5 mol%) catalyst and $AgSbF_6$ (10 mol%) was generally employed as additive in dichloromethane solvent at 0 ^oC – rt for 2 h. As per

our expectation, a mixture of inseparable diastereomers **3a** and **3b** was obtained in 76% yield (2:1 dr from ^{1}H NMR).

In order to assign the stereochemistry of the newly formed spiro-centre in both the diastereomers, we separated the mixture of **3a** and **3b** by high-performance liquid chromatography (HPLC) using YMC HPLC, chiral art 250 X 10.0 mml. D., S-5 µm column. The methods details: solvent system = 25% IPA–*n*-Hexane, flow rate = 0.5 mL/min, run time = 120 min, wave length = 250 nm. As shown in Figure 5, the ratio of diastereomers calculated from the HPLC peak areas was found to be 4:7. The specific rotation of **3a** and **3b** were found to be completely different: $[\alpha]_D^{28}$ +24.0 (*c* 2.34, $CHCl_3$) and $[\alpha]_D^{28}$ -66.13 (*c* 1.72, $CHCl_3$) respectively.

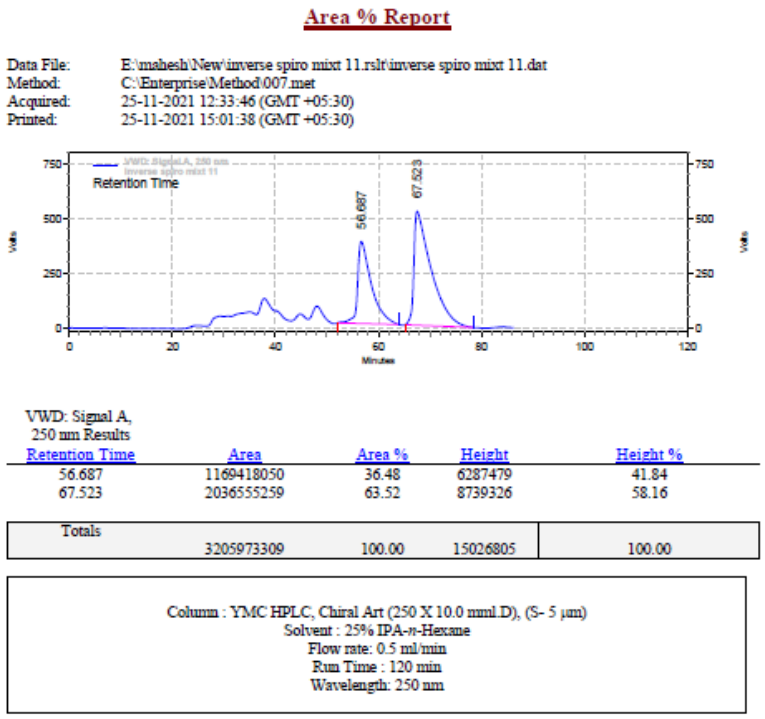


Figure 5. HPLC Data of Compounds **3a** and **3b**

The 2D NMR of separated diastereomers was recorded to assign the stereochemistry of spiro-centres by extensive NMR analysis. Figure 6 is a COSY spectrum of the major diastereomer **3a**, which shows a separate peak at δ 3.94 (dt, *J* = 5.1, 8.7 Hz, 1H) corresponding to the methine (C**H**-OH) proton of C11. This proton showed a correlation cross peak with protons of C12 (H12a and H12b) which resonate at δ 3.61 (dd, *J* = 3.7, 11.2 Hz, 1H) and 3.48 (dd, *J* = 5.8, 11.1 Hz, 1H). Also the cross peak of H11 was observed with protons of C10 resonating at δ 1.79–1.84 (td, *J* = 1.7, 6.2 Hz, 2H). The C8 proton was found

to be in correlation with the C7 proton resonating at δ 2.41 (dd, *J* = 6.5, 13.0 Hz, 1H) and C10 protons.

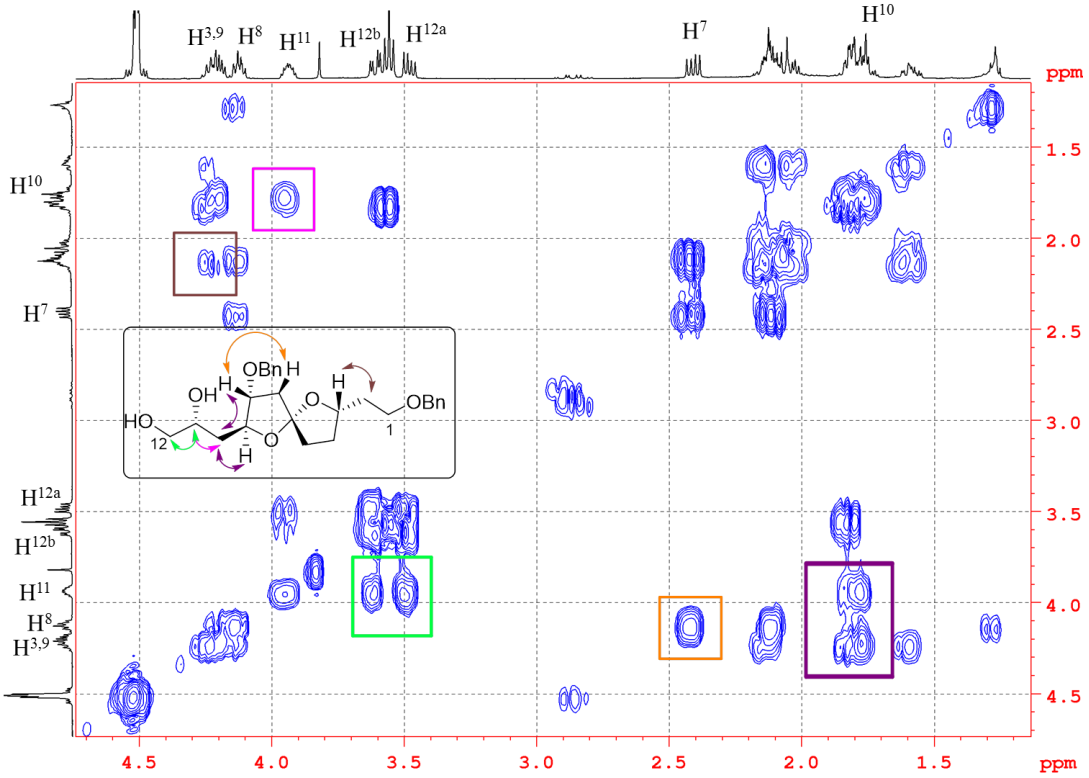


Figure 6. COSY Spectrum of Compound **3a** (Major isomer)

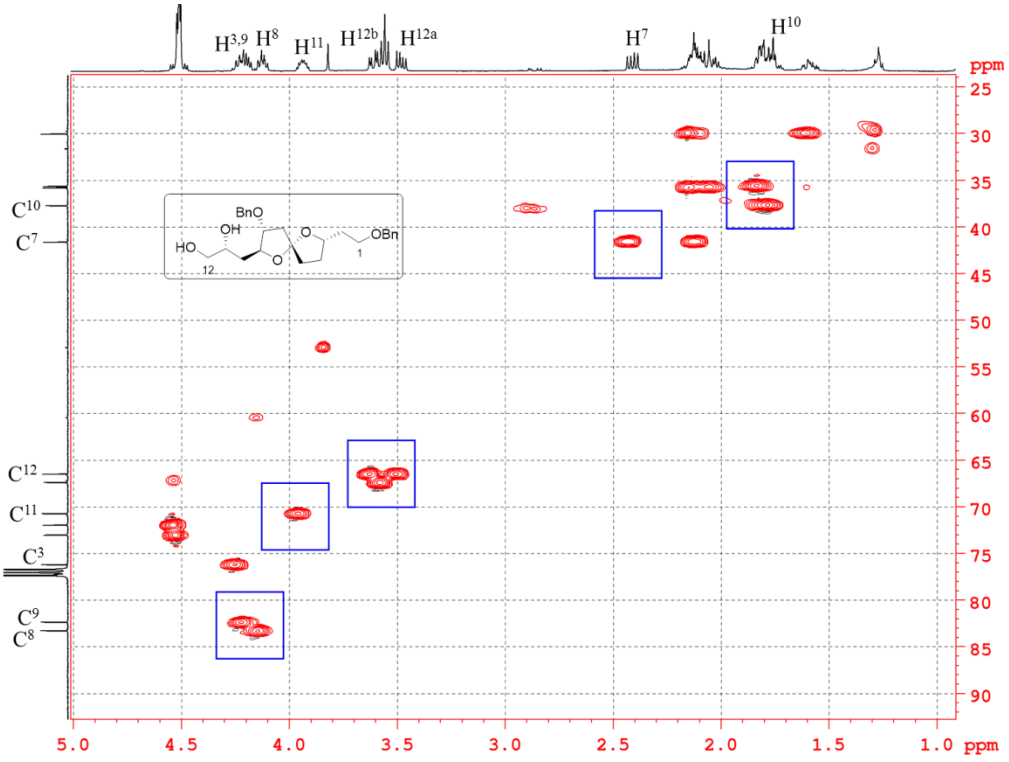


Figure 7. HSQC Spectrum of Compound **3a** (Major isomer)

After establishing the left half of the spirocenter we went to assign the protons at another side of the spirocenter. It was observed that the C3 proton resonates at close to the δ value to the C9 proton and a correlation cross peak with C2 protons. After successful analysis of the COSY spectrum to confirm the connectivity of protons, it was needed to assign their corresponding carbon atoms by HSQC analysis. Figure 7 shows the HSQC spectrum of compound **3a**, where protons and their respective carbons cross peaks are highlighted. The NOESY spectrum of compound **3a** was difficult to analyse because of the overlapped peaks which caused some trouble for the assignment of the stereochemistry of spirocenter. Our effort towards the crystallisation of diols **3a** or **3b** or the corresponding 3,5-dinitrobenzoate ester derivatives (monobezoate of the primary hydroxyl was formed and the secondary –OH group was intact even when excess of reagent was employed) were disappointing and the compounds were obtained as syrups.

Next, we decided to compare the data of the synthesised diastereomers with reported compounds having a similar spiro-*bis*-THF unit in their structure. The literature search ended up finding a report (*Org. Chem. Front.*, **2017**, *4*, 140–146) for the assignment of stereochemistry at the spiro center in cephalosporolides, penisporolides and related synthetic analogues. The paper reported a reliable method to determine the relative configuration of the tricyclic [5,5]-spiroacetal-*cis*-fused-γ-lactone (SAFL) based upon the combination of 2D-NMR [spin-spin coupling (SSC)] and X-ray diffraction [conformational study] analysis. As shown in Figure 8, there is a significant difference in the chemical shift values of C5 protons, which has been explained with the help of X-ray diffraction studies and diamagnetic anisotropic effects. The fully eclipsed conformation might cause steric compression or orbital distortions of H5 protons and because of that, the H5a has been shifted to downfield ~2.5 ppm. In the other conformation, H5b has been shifted to downfield ~2.1 ppm. This can be further explained by diamagnetic anisotropic effects: when the flanking groups are *cis* to each

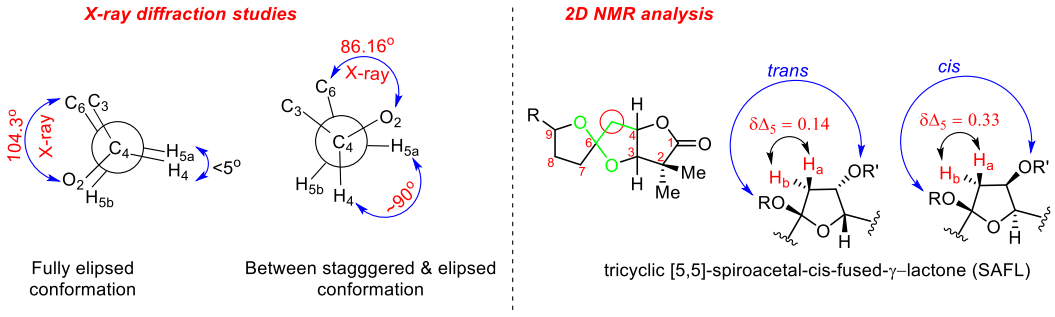


Figure 8. Justification of Chemical Shift Difference by X-ray Diffraction and NMR Analysis

other, the chemical shift difference is larger. However, the *trans* orientation leads to small differences.[18]

Inspired with this report, we focused on C7 protons to check the chemical shift differences. As shown in Figure 9, in case of the major diastereomer, the (H7a and H7b) $\Delta\delta_7$ = 0.28 which revealed that the spiro oxygen and the flanking group are *cis* to each other. However, the observed difference of minor diastereomer was $\Delta\delta_7$ = 0.13, which indicated the *trans* stereochemistry of the flanking groups.

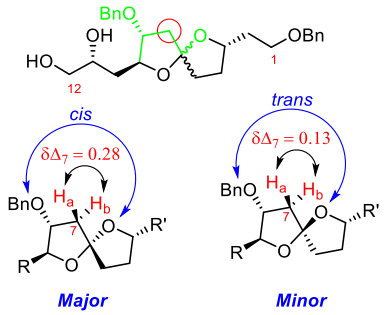


Figure 9. Observed Chemical Shift Difference in NMR Analysis

The successful characterisation of spiro compounds and the assignment of the stereochemistry of the spiro center encouraged us to investigate the rationality of the method. For this purpose, the C3 diastereomers (**3'a** and **3'b**) were intended, which could be synthesised by the opening of epoxide **6** with alkyne **7'** (figure 10). The L-malic acid derived intermediate diol **17** could be converted to the desired alkyne **7'** by following a 5 step sequence.

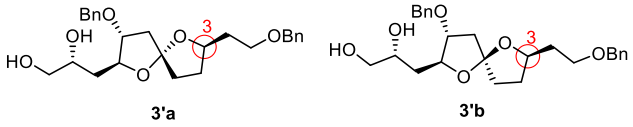
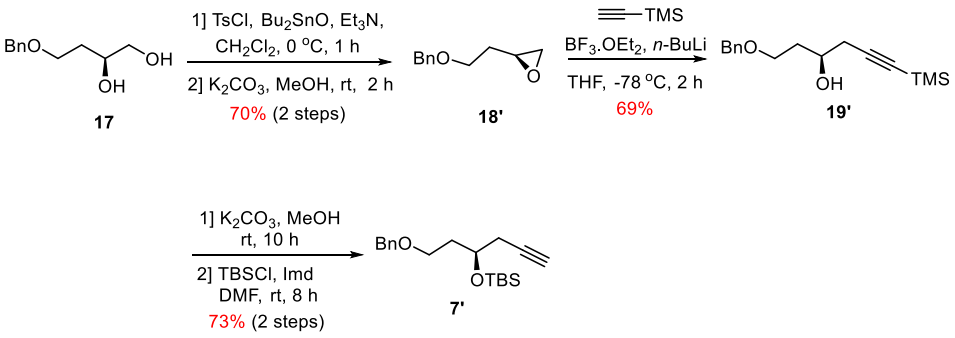


Figure 10. Synthesis of C3 (**3'a** and **3'b**) diastereomers of diols **3a** and **3b**

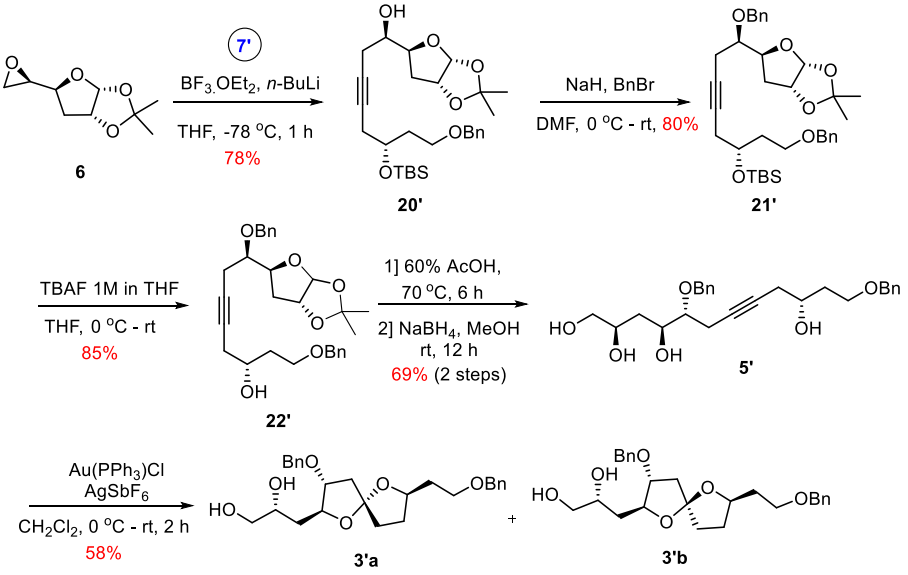
Accordingly, for the selective tosylation of the primary –OH group, diol **17** was treated with *p*-toluenesulfonyl chloride and triethylamine in the presence of cat. Bu_2SnO in dichloromethane solvent at 0 °C – rt for 1 h to obtain the tosylate, which was further reacted with potassium carbonate in methanol to afford epoxide **18'** in 70% yield over 2 steps (Scheme 10). The subsequent opening of epoxide with trimethylsilyl acetylene in the presence of *n*-BuLi and $BF_3.OEt_2$ at -78 °C for 2 h delivered the alkynol **19'** in 69% yield.

The sequential –TMS deprotection followed by –TBS protection of alkynol afforded the requisite alkyne **7'** in 73% yield over 2 steps. The spectral data of compounds **18'**, **19'**, and **7'** was in agreement with their previously synthesized corresponding enantiomers. However, the sign of the specific rotation was opposite $[\alpha]_D^{28}$ -12.5 (*c* 2.3, $CHCl_3$).[19]



Scheme 10. Synthesis of Alkyne **7'** from L-Malic acid Epoxide

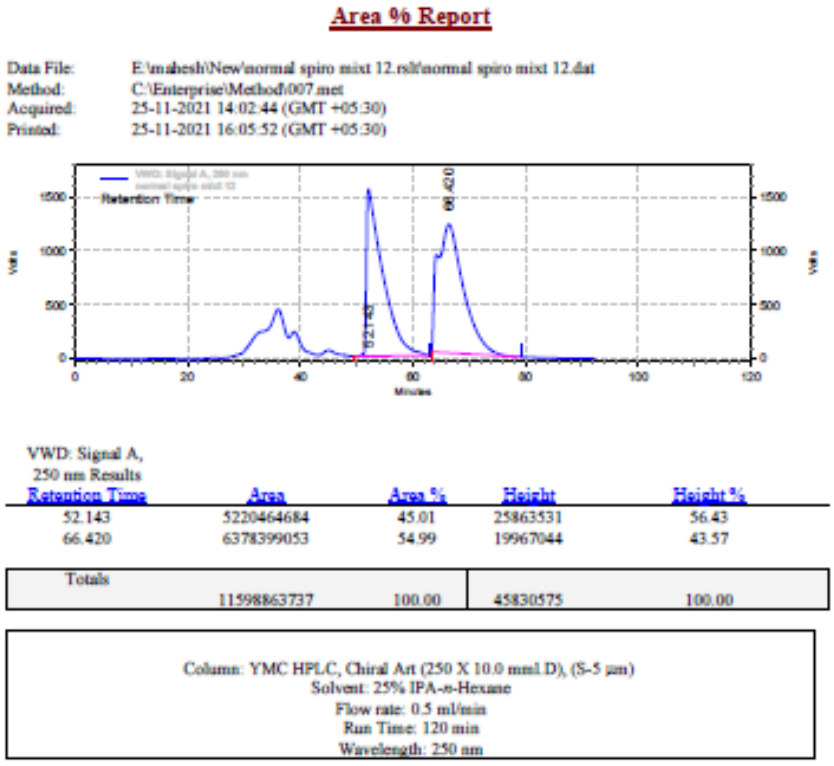
As shown in Scheme 11, the epoxide **6** was reacted with alkyne **7'** in the presence of *n*-BuLi and $BF_3.OEt_2$ at -78 °C for 1 h to deliver the alkynol **20'** in 78% yield. The structure of **20'** was established with the help of ^1H and ^{13}C NMR spectra analysis. For example, in the ^1H NMR spectrum, three characteristic singlets at 0.00 (s, 3H), 0.03 (s, 3H), and 0.83 (s, 9H) indicate the presence of the –OTBS group and two singlets at 1.28 (s, 3H) and 1.46 (s, 3H) represented the acetonide group. The characteristic C1 proton appeared as a doublet at δ 5.75 (d, *J* = 3.6 Hz, 1H). In the ^{13}C NMR spectrum, the alkyne carbons were seen to resonate at δ 77.2 (s) and another carbon signal overlapped with the ring carbon at δ 79.9 (d) (more intense



Scheme 11. Synthesis of Spiro-diastereomers **3'a** and **3'b**

peak compared with other singlet). The representative C1 carbon appeared as a doublet at δ 105.4 (d) and a quaternary carbon of acetonide was seen to resonate as a singlet at 111.3 (s). The structure was further supported by the appearance of the ESI-MS HRMS) base peak at 527.2802.

Next, by following the established steps, alkynol **20'** was converted to the respective tetrol **5'** in 69% yield over the last 2 steps. The tetrol **5'** was then subjected for the gold catalysed spiroketalization and the expected mixture of inseparable diastereomers **3'a** and **3'b** were isolated (11:9 dr from ^{1}H NMR). The mixture of diastereomers was separated by chiral HPLC (11:9 dr).



Area % Report

Data File: E:\mahesh\New\normal spiro mixt 12.rslt\normal spiro mixt 12.dat
Method: C:\Enterprise\Method\007.met
Acquired: 25-11-2021 14:02:44 (GMT +05:30)
Printed: 25-11-2021 16:05:52 (GMT +05:30)

VWD: Signal A, 250 nm Results

Retention Time	Area	Area %	Height	Height %
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66.420	6378399053	54.99	19967044	43.57
Totals	11598863737	100.00	45830575	100.00

Column: YMC HPLC, Chiral Art (250 X 10.0 mm I.D), (S-5 µm)
Solvent: 25% IPA-n-Hexane
Flow rate: 0.5 ml/min
Run Time: 120 min
Wavelength: 250 nm

Figure 11. HPLC Data of Compounds **3'a** and **3'b**

The 2D NMR of separated diastereomers was recorded in order to assign the stereochemistry at the spiro center. Figure 12 shows the COSY spectrum and Figure 13 shows the HSQC spectrum of major diastereomer **3'a**. Similar to the previous spiro compounds, the assignment of stereochemistry of the spiro center with the help of 2D NMR was a tough task.

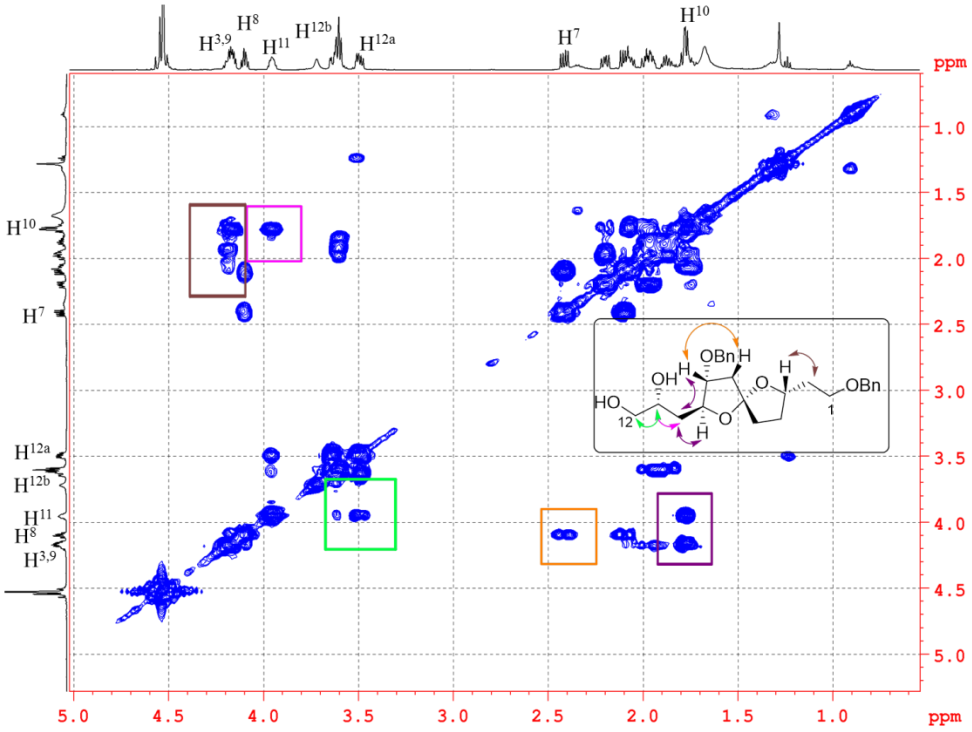


Figure 12. COSY Spectrum of Compound **3'a** (Major isomer)

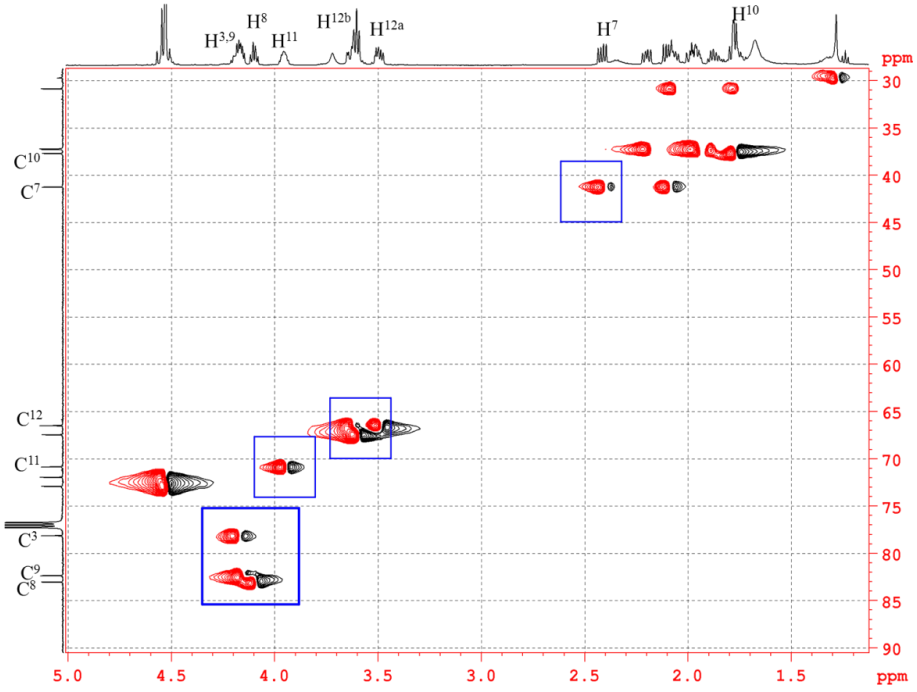


Figure 13. HSQC Spectrum of Compound **3'a** (Major isomer)

Eventually, we employed the formerly used NMR analysis method to assign the configuration of the spiro centers. The major diastereomer showed (H7a and H7b) $\Delta\delta_7 = 0.31$ and hence we assigned it as the *cis* isomer **3'a**. The observed difference in other diastereomer was $\Delta\delta_7 = 0.12$, which indicated that the flanking groups are oriented in a *trans*

fashion, as shown in **3'b**. The observed specific rotations of compound **3'a** and **3'b** are $[\alpha]_D^{28}$ -108.0 (*c* 0.44, $CHCl_3$) and $[\alpha]_D^{28}$ -2.16 (*c* 0.42, $CHCl_3$) respectively.

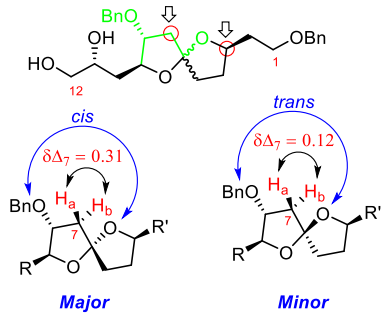


Figure 14. Observed Chemical Shift Difference in the NMR Analysis

After having a set of diastereomeric spiro-derivatives, we have compiled the ^{13}C-NMR chemical shifts to examine how the variation of the relative stereochemistry of the spirocenter/THF ring carbon will influence the chemical shifts of the other centers.

Table 1. Comparison of ^{13}C NMR values of all four diastereomers

Inverse malic epoxide			**Normal malic epoxide**		
Carbon number	**Major 3a**	**Minor 3b**	**Carbon number**	**Major 3'a**	**Minor 3'b**
1	67.3	67.6	**1**	67.4	67.5
2	35.8	37.7	**2**	37.1	35.7
3	76.2	77.9	**3**	78.1	76.3
4	35.6	37.1	**4**	37.2	36.2
5	30.0	30.4	**5**	30.8	29.9
6	115.0	113.7	**6**	114.9	113.8
7	41.5	40.4	**7**	41.2	40.9
8	83.2	82.3	**8**	83.0	82.4
9	82.3	80.8	**9**	82.5	81.0
10	37.7	36.6	**10**	37.6	36.6
11	70.7	71.3	**11**	70.8	71.2
12	66.5	66.4	**12**	66.4	66.4

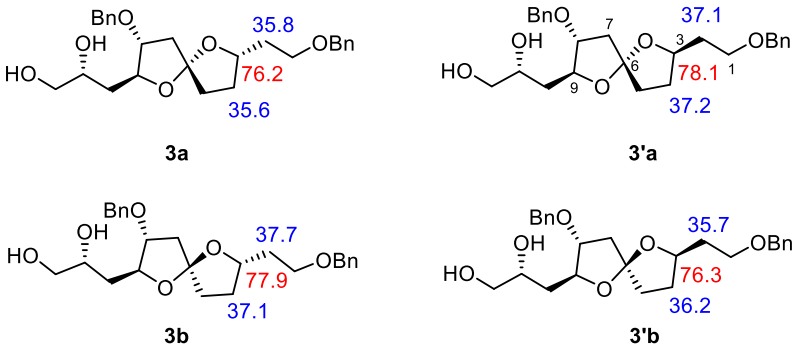
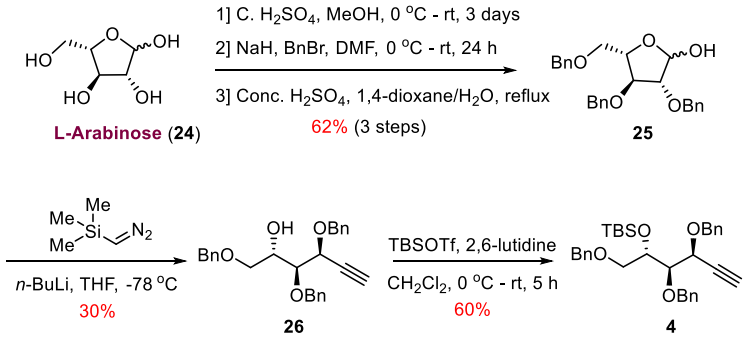


Figure 15. Characteristic ^{13}C NMR Chemical Shift Variation

It was noticed that the values of C2–C4 vary in all the diastereomers and the stereochemistry at the spirocenter relative to the C3 makes a significant change in their ^{13}C NMR. However, as one could notice, the change in the stereochemistry at C3 does not have any influence on the chemical shifts of the spiro-carbon.

After successful assignment of the spiro center stereochemistry, we moved in the forward direction to complete the synthesis of the other coupling partner. By following the reported 3 steps (glycosylation, benzylation, and glycoside hydrolysis) procedure, lactol **25** was synthesised in 62% yield over 3 steps from L-arabinose (Scheme 12).[20] The conversion of lactol **25** to the desired alkyne **26** was attempted by employing the Ohira-Bestmann reagent and also under Corey-Fuchs conditions. However, in both the cases we failed to get the desired product. When we switched to the Colvins' procedure employing trimethylsilyl diazomethane and *n*-BuLi, the desired alkyne **26** was obtained in 30% yield.[21] The resultant alkynol **26** was treated with *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine base and dichloromethane to obtain the desired alkyne fragment **4** in 60% yield. The structure of alkyne **4** was established with the help of ^{1}H and ^{13}C NMR spectral data analysis. For example, in the ^{1}H NMR spectrum of compound **4**, a multiplet at δ 7.18–7.34 (m, 15H) indicated the presence of three benzyl groups. The existence of –OTBS group was indicated by three characteristic singlets at δ 0.00 (s, 3H), 0.01 (s, 3H), and 0.83 (s, 9H). The terminal alkyne proton appeared at δ 2.50 (m, 1H). In the ^{13}C NMR spectrum, the alkyne carbons appeared as singlets at δ 75.9 (s), and 81.1 (s), along with the four triplets corresponding to the methylene carbons (71.0, 71.4, 73.2, 75.2). The ESI-MS (HRMS) base peak appeared at 553.2747.

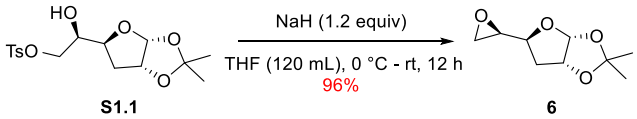


Scheme 12. Synthesis of Alkyne **27** from L-Arabinose

To this end, the synthesis of the desired fragment symbiospirols needed the conversion of spirodiols **3a** and **3b** to the corresponding epoxides and subsequent opening with the alkyne **4**. However, the tedious separation of these diastereomers by HPLC and also the poor yields in synthesizing the alkyne fragment **4** did not allow us to move forward in this direction. Currently, an alternative strategy to construct the pyran core first and postpone the spiroketalization to a later stage is in progress in our laboratory.

In conclusion, the gold catalysed spiroketalization of alkyne diol was successfully employed in the synthesis of the spiro-*bis*-THF unit of the Symbiospirols A/B/C. The stereochemistry of synthesised diastereomers was assigned based upon the reported NMR analysis method. The chiral building blocks (D-glucose, L-malic acid, L-arabinose) were successfully utilised in the synthesis of the necessary intermediates of the desired fragment of symbiospirols.

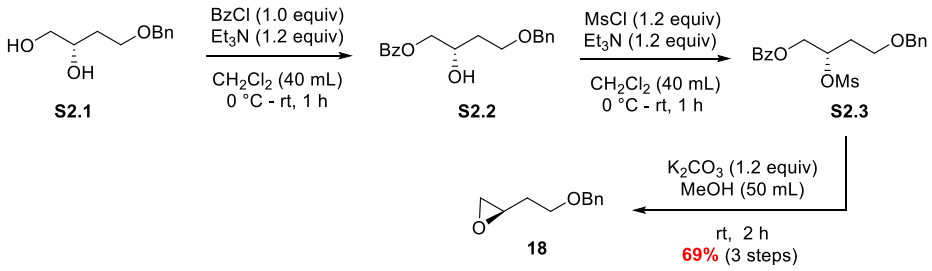
Synthesis of Epoxide 6 from D-Glucose:



Scheme S1. Synthesis of Epoxide **6**

(3a*R*,5*S*,6a*R*)-2,2-dimethyl-5-((*R*)-oxiran-2-yl)tetrahydrofuro[2,3-*d*][1,3]dioxole (6): At 0 °C, to a solution of tosylate **S1.1** (10.0 g, 27.9 mmol) in THF (120 mL), sodium hydride (60% oil suspension, 1.34 g, 33.48 mmol) was added in portions and the reaction mixture was warmed to room temperature with stirring for 12 h. Then the mixture was cooled to 0 °C and quenched with water, extracted with EtOAc (300 mL X 2). The combined organic layer was washed with brine (50 mL X 2), and dried over (Na_2SO_4), evaporated under reduced pressure. The resulting crude product was purified by column chromatography (05:95% ethyl acetate/petroleum ether) to afford compound **6** (5.0 g, 96%) as colourless oil. R_f = 0.8 (30% EtOAc/petroleum ether); $[\alpha]_D^{28}$ –21.7 (*c* 3.6, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.50 (s, 3H), 1.72 (td, *J* = 3.0, 13.3 Hz, 1H), 2.06 (dd, *J* = 3.0, 13.3 Hz, 1H), 2.61 (d, *J* = 2.3 Hz, 1H), 2.82 (m, 1H), 3.15 (m, 1H), 4.17–4.25 (m, 1H), 4.75 (m, 1H), 5.84 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 26.1 (q), 26.7 (q), 34.2 (t), 45.1 (t), 51.6 (d), 77.9 (d), 80.2 (d), 105.5 (d), 111.3 (s) ppm; **HRMS** (ESI) calcd for $C_9H_{14}NaO_4$: 209.0784 $[M + Na]^+$; found 209.0782.

Synthesis of Inverse Epoxide 18 from L-Malic Acid:



Scheme S2. Synthesis of Epoxide **18**

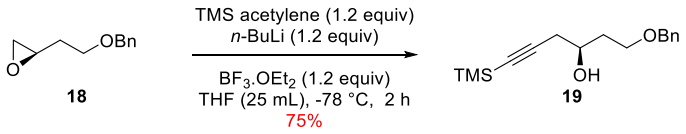
(*R*)-2-(2-(benzyloxy)ethyl)oxirane (18): At 0 °C, the L-malic acid derived diol **S2.1** (3.0 g, 15.29 mmol) was dissolved in CH_2Cl_2 (40 mL). To this, dibutyl tin oxide (Bu_2SnO 380 mg, 1.53 mmol) was added and the reaction mixture was stirred for 10 min followed by sequential

addition of Et_3N (2.56 mL, 18.34 mmol), DMAP (186 mg, 1.53 mmol), benzoyl chloride (1.78 mL, 15.29 mmol). Then reaction mixture was warmed to room temperature and continued stirring for 1 h. After completion, it was quenched with water (25 mL), extracted with CH_2Cl_2 (50 mL X 2), combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure, crude product was purified by column chromatography to afford benzoate **S2.2** as colourless liquid (3.5 g).

The solution of benzoate **S2.2** (3.5 g, 11.65 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C. To this, was sequentially added Et_3N (1.95 mL, 13.98 mmol), methanesulfonyl chloride (1.08 mL, 13.98 mmol), and DMAP (142 mg, 1.17 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was quenched with water (25 mL), extracted with CH_2Cl_2 (50 mL X 2). The combined organic layer was dried (Na_2SO_4), concentrated to dryness under reduced pressure to afford crude product **S2.3** (4.4 g).

The crude product **S2.3** (4.4 g, 10.27 mmol) was dissolved in methanol (50 mL) and added K_2CO_3 (1.93 g, 13.95 mmol) at room temperature with stirring for 2 h. After completion, it was filtered through celite and concentrated to dryness. The solid mass was extracted with EtOAc (75 mL X 2), washed with saturated aq. $NaHCO_3$ (50 mL), brine (25 ml), dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography to afford epoxide **18** as colourless oil in 1.9 g (69% after 3 steps). R_f = 0.8 (20% EtOAc/petroleum ether); $[\alpha]_D^{28}$ +10.7 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.72 (dt, *J* = 6.1, 13.0 Hz, 1H), 1.83 (dt, *J* = 6.1, 13.0 Hz, 1H), 2.45 (dd, *J* = 4.9, 2.6 Hz, 1H), 2.71 (t, *J* = 4.5 Hz, 1H), 2.98–3.03 (m, 1H), 3.51–3.57 (m, 2H), 4.46 (s, 2H), 7.21–7.25 (m, 1H), 7.26–7.32 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 32.9 (t), 47.0 (t), 50.0 (d), 67.0 (t), 73.0 (t), 127.6 (d, 3C), 128.3 (d, 2C), 138.2 (s) ppm; **HRMS** (ESI) calcd for $C_{11}H_{15}O_2$: 179.1067 $[M + H]^+$; found 179.1066.

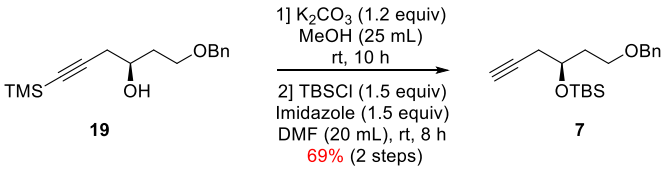
Synthesis of Alkynol 19:



(*S*)-1-(benzyloxy)-6-(trimethylsilyl)hex-5-yn-3-ol (19): An oven dried two neck round bottom flask fitted with septum and argon balloon, filled with solution of trimethylsilyl acetyelene (1.82

mL, 12.79 mmol) in THF (25 mL) and cooled it to -78 °C. To this, was added sequentially, 1.6 M *n*-butyl lithium (8.0 mL, 12.79 mmol), and $BF_3.OEt_2$ (1.58 mL, 12.79 mmol) with stirring for 15 min, followed by the addition of THF (15 mL) solution of epoxide **18** (1.9 g, 10.66 mmol) in drop wise fashion. The reaction mixture was continued stirring at the same temperature for 2 h. Then, it was quenched with saturated aq. NH_4Cl (20 mL), extracted with EtOAc (30 mL X 2). The combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography to afford alkynol **19** as colourless liquid (2.23 g, 75%). R_f = 0.6 (10% EtOAc/petroleum ether); $[\alpha]_D^{28}$ +2.7 (*c* 1.18, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.08 (s, 9H), 1.71–1.80 (m, 1H), 1.82–1.89 (m, 1H), 2.37 (dd, *J* = 0.6, 5.1 Hz, 2H), 2.97 (dd, *J* = 0.8, 2.2 Hz, 1H), 3.58 (ddd, *J* = 4.5, 7.6, 12.2 Hz, 1H), 3.67 (ddd, *J* = 4.7, 9.5, 11.1 Hz, 1H), 3.85–3.92 (m, 1H), 4.45 (s, 2H), 7.20–7.24 (m, 1H), 7.25–7.28 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 0.03 (q, 3C), 28.5 (t), 35.3 (t), 68.5 (t), 69.3 (d), 73.2 (t), 87.0 (s), 103.3 (s), 127.6 (d, 2C), 127.7 (d), 128.4 (d, 2C), 137.9 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{25}SiO_2$: 277.1618 $[M + H]^+$; found 277.1619.

Synthesis of Alkyne 7:

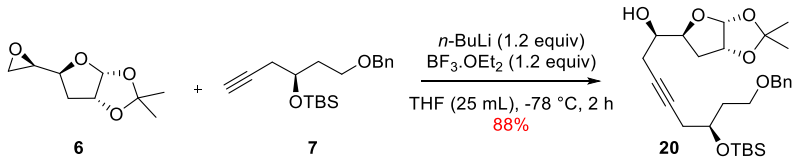


(*S*)-((1-(benzyloxy)hex-5-yn-3-yl)oxy)(*tert*-butyl)dimethylsilane (7): To the solution of alkynol **19** (2.23 g, 8.07 mmol) in methanol (25 mL) was added K_2CO_3 (1.34 g, 9.68 mmol) in one portion at room temperature and the reeaction mixture was conituned stirring for 10 h. Then, the content was filetered through celite and concentrated to dryness. The solid residue was diluted with water (30 mL), extracted with EtOAc (50 mL X 2), washed with brine (30 mL), dried (Na_2SO_4), concentrated under reduced pressure, and crude product was purified by column chromatography to afford alkynol as colourless liquid (1.45 g).

To the solution of alkynol (1.45 g, 7.10 mmol) in DMF (20 mL) was added *tert*-butyldimethylsilyl chloride (1.6 g, 10.65 mmol) and imidazole (725 mg, 10.65 mmol) at room temperature and continued stirring for 8 h. the reaction was quenched by addition of water (30 mL) and extracted with EtOAc (30 mL X 2), washed with brine (30 mL X 2), dried (Na_2SO_4),

concentrated under reduced pressure, purified by column chromatography to afford alkyne **7** as colourless liquid (1.79 g, 69% over 2 steps). R_f = 0.9 (10% EtOAc/petroleum ether); $[\alpha]_D^{28}$ +13.8 (*c* 1.82, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ -0.01 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 1.52 (s, 1H), 1.75 (dd, *J* = 7.8, 13.7 Hz, 1H), 1.88–1.96 (m, 2H), 2.29 (dd, *J* = 5.9, 2.6 Hz, 2H), 3.45–3.55 (m, 2H), 3.95 (tt, *J* = 1.8, 6.0 Hz, 1H), 4.43 (dd, *J* = 7.0, 18.8 Hz, 2H), 7.20–7.23 (m, 1H), 7.25–7.31 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.8 (q), -4.5 (q), 18.0 (s), 25.8 (q, 3C), 27.7 (t), 36.6 (t), 66.7 (t), 68.0 (d), 70.1 (d), 72.9 (t), 81.4 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.5 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{31}SiO_2$: 319.2093 $[M + H]^+$; found 319.2094.

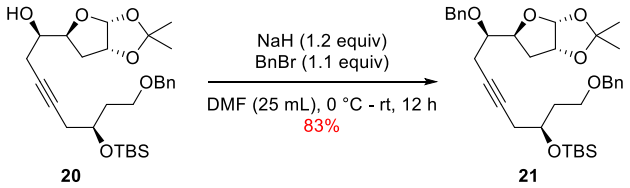
Synthesis of Compound 20:



(1*R*,6*S*)-8-(benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)-1-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)oct-3-yn-1-ol (20): At -78 °C, *n*-butyl lithium 1.6 M (3.42 mL, 5.48 mmol), and $BF_3.OEt_2$ (0.67 mL, 5.48 mmol) were added slowly to the THF (20 mL) solution of alkyne **7** (1.74 g, 5.48 mmol). After 20 min., a THF (10 mL) solution of epoxide **6** (850 mg, 4.54 mmol) was added in drop wise fashion and continued stirring at the same temperature for additional 2 h. After completion, the reaction was quenched with saturated aq. NH_4Cl (20 mL), extracted with EtOAc (30 mL X 2). The combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography to afford compound **20** as colourless liquid (2.04 g, 88%). R_f = 0.5 (10% EtOAc/petroleum ether); $[\alpha]_D^{28}$ +6.2 (c 1.63, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27–7.31 (m, 4H), 7.22–7. 25 (m, 1H), 5.76 (d, *J* = 3.6 Hz, 1H), 4.69 (t, *J* = 4.2 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.23 (dt, *J* = 4.5, 10.6 Hz, 1H), 3.88–3.97 (m, 1H), 3.85 (d, *J* = 4.7, 1.5 Hz, 1H), 3.51 (dd, *J* = 7.0, 5.5 Hz, 2H), 2.31–2.37 (m, 2H), 2.26–2.31 (m, 2H), 2.03 (dd, *J* = 4.5, 13.3 Hz, 1H), 1.90 (qd, *J* = 7.0, 4.0 Hz, 1H), 1.67–1.84 (m, 2H), 1.46 (s, 3H), 1.28 (s, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.4 (s), 128.3 (d, 2C), 127.7 (d, 2C), 127.5 (d), 111.3 (s), 105.4 (d), 80.6 (d), 80.0 (s), 79.9 (d), 77.2 (s), 72.9 (t), 70.1 (d), 68.2 (d), 66.7 (t), 36.6 (t), 33.0 (t), 28.0 (t), 26.8 (q), 26.2 (q), 25.8 (q, 3C), 24.0 (t), 18.0 (s), -4.5

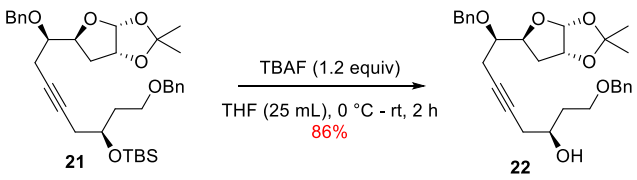
(q), -4.9 (q) ppm (one alkyne carbon peak is getting merged with the $CDCl_3$ triplet); **HRMS** (ESI): m/z [M + Na]+ calcd for $C_{28}H_{44}SiNaO_6$: 527.2799; found 527.2783.

Synthesis of Compound 21:



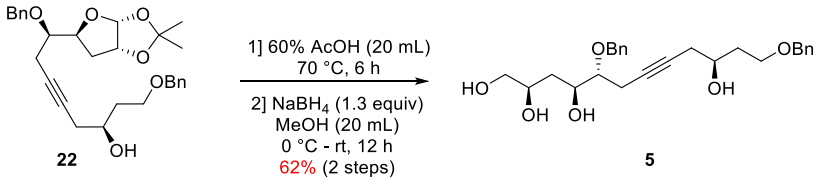
(((3*S*,8*R*)-1,8-bis(benzyloxy)-8-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)oct-5-yn-3-yl)oxy)(*tert*-butyl)dimethylsilane (21): At 0 °C, sodium hydride (60% oil suspension, 190 mg, 4.75 mmol) was added in portions to the DMF (25 mL) solution of alcohol **20** (2.0 g, 3.96 mmol). After stirring for 15 min., benzyl bromide (0.52 mL, 4.36 mmol) was added to the mixture at the same temperature. The reaction was quenched by slow addition of water (20 mL) to the cooled mixture, extracted with EtOAc (50 mL X 2), organic layer was washed with water (20 mL X 2), brine (20 mL) and the combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure and crude compound was purified by column chromatography to afford compound **21** as colourless liquid (1.96 g, 83%). R_f = 0.4 (10% EtOAc/petroleum ether); $[\alpha]_D^{28}$ +5.6 (c 3.17, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.19–7.30 (m, 10H), 5.72 (d, *J* = 3.6 Hz, 1H), 4.63–4.68 (m, 2H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.41 (d, *J* = 7.5 Hz, 2H), 4.34 (td, *J* = 1.6, 10.3 Hz, 1H), 3.85–3.91 (m, 1H), 3.68 (dd, *J* = 6.1, 10.2 Hz, 1H), 3.44–3.52 (m, 2H), 2.31–2.40 (m, 2H), 2.21–2.28 (m, 2H), 2.03 (dd, *J* = 4.6, 13.3 Hz, 1H), 1.88–1.96 (m, 1H), 1.81 (ddd, *J* = 4.8, 10.5, 15.3 Hz, 1H), 1.65–1.74 (m, 1H), 1.43 (s, 3H), 1.25 (s, 3H), 0.81 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.6 (s), 138.6 (s), 128.3 (d, 2C), 128.2 (d, 2C), 127.7 (d, 2C), 127.6 (d, 2C), 127.5 (d), 127.4 (d), 111.2 (s), 105.3 (d), 80.6 (d), 79.9 (d), 78.8 (s), 78.0 (s), 77.8 (d), 73.0 (t), 72.9 (t), 68.3 (d), 66.8 (t), 36.6 (t), 33.3 (t), 28.1 (t), 26.9 (q), 26.3 (q), 25.8 (s, 3C), 22.3 (t), 18.0 (s), -4.5 (q), -4. 9 (q) ppm; **HRMS** (ESI): m/z [M + H]+ calcd for $C_{35}H_{51}SiO_6$: 595.3449; found 595.3435.

Synthesis of Compound 22:



(3*S*,8*R*)-1,8-bis(benzyloxy)-8-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)oct-5-yn-3-ol (22): At 0 °C, TBAF 1M in THF (*tetra-n*-butyl ammonium fluoride) (3.93 mL, 3.93 mmol) was added to the solution of compound **21** (1.95 g, 3.28 mmol) in THF (25 mL) and the mixture was continued stirring at rt for 2 h. The reaction was quenched with slow addition of water (20 mL), extracted with EtOAc (30 mL X 2), combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography to afford compound **22** as colourless liquid (1.36 g, 86%). R_f = 0.3 (30% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -6.7 (*c* 3.86, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.21–7.42 (m, 10H), 5.79 (d, *J* = 3.6 Hz, 1H), 4.70–4.75(m, 2H), 4.67 (d, *J* = 11.4, 1H), 4.53 (s, 2H), 4.41 (dd, *J* = 9.7, 4.3 Hz, 1H), 3.94 (br. s., 1H), 3.68–3.80 (m, 2H), 3.64 (dd, *J* = 4.2, 8.1 Hz, 1H), 3.10 (br. s., 1H), 2.39–2.50 (m, 4H), 1.73–1.96 (m, 4H), 1.52 (s, 3H), 1.34 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 138.4 (s), 137.9 (s), 128.4 (d, 2C), 128.2 (d, 2C), 127.6 (d, 2C), 127.6 (d, 2C), 127.5 (d, 2C), 111.2 (s), 105.2 (d), 80.5 (d), 79.7 (d), 78.5 (s), 78.4 (s), 77.7 (d), 73.2 (t), 72.8 (t), 69.6 (d), 68.5 (t), 35.4 (t), 33.6 (t), 27.5 (t), 26.8 (q), 26.2 (q), 22.1 (t) ppm; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{37}O_6$: 481.2585; found 481.2583.

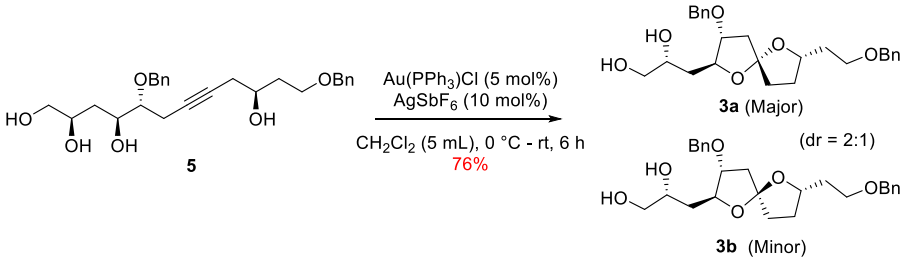
Synthesis of Tetrol 5:



(2*R*,4*S*,5*R*,10*S*)-5,12-bis(benzyloxy)dodec-7-yne-1,2,4,10-tetraol (5): The round bottom flask fitted to reflux condenser was charged with compound **22** (1.35 g, 2.81 mmol) and 20 mL 60% aq. acetic acid. The content was stirred at 70 °C for 6 h and the solvents were removed to dryness under reduced pressure to give crude lactol in 1.24 g.

To the solution of crude lactol (1.24 g, 2.81 mmol) in 20 mL Methanol, was added the sodium borohydride (138 mg, 3.66 mmol) at 0 °C. The reaction mixture was warmed to rt and continued stirring for 12 h. After completion, reaction was quenched with 1 mL of sat. NH_4Cl, solvents were removed under reduced pressure, and crude was purified by column chromatography to obtain tetrol **5** as colourless liquid (775 mg, 62% 2 steps). R_f = 0.2 (80% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -16.3 (*c* 2.24, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28–7.38 (m, 10H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.55(d, *J* = 11.6 Hz, 1H), 4.52 (s, 2H), 4.11 (d, *J* = 7.6 Hz, 1H), 3.87–4.02 (m, 2H), 3.67–3.76 (m, 1H), 3.59–3.67 (m, 2H), 3.48–3.55 (m, 2H), 3.17 (br. s., 1H), 2.45–2.62 (m, 2H), 2.38 (dd, *J* = 2.2, 5.8 Hz, 2H), 1.71–1.92 (m, 4H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.8 (s), 137.8 (s), 128.5 (d, 2C), 128.5 (d, 2C), 128.0 (d), 127.9 (d, 2C), 127.8 (d), 127.7 (d, 2C), 80.1 (d), 78.5 (s), 77.2 (s), 73.3 (t), 72.6 (d), 72.2 (t), 72.0 (d), 69.6 (d), 68.5 (t), 66.6 (t), 35.6 (t), 34.5 (t), 27.6 (t), 19.9 (t) ppm; **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{34}NaO_6$: 465.2248; found 465.2240.

Synthesis of Diastereomers 3a and 3b:



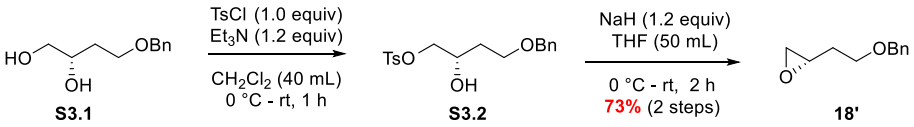
To the solution of tetrol **5** (150 mg, 0.338 mmol) in CH_2Cl_2 (5 mL) was added $Au(PPh_3)Cl$ (8.38 mg, 16.95 µmol) and $AgSbF_6$ (11.65 mg, 33.89 µmol) at room temperature and continued stirring for 6 h. After completion, it was concentrated under reduced pressure, and purified by column chromatography (230-400 silica) to afford mixture of diastereomers **4a** and **4b** as colourless liquid (114 mg, 76%).

(*R*)-3-((2*S*,3*R*,5*R*,7*S*)-3-(benzyloxy)-7-(2-(benzyloxy)ethyl)-1,6-dioxaspiro[4.4]nonan-2-yl)propane-1,2-diol (3a): colourless liquid (76 mg); R_f = 0.2 (80% EtOAc/petroleum ether); $[\alpha]_D^{28}$ +24.0 (*c* 2.34, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.54–1.64 (m, 1H), 1.72–1.78 (m, 2H), 1.79–1.84 (td, *J* = 1.7, 6.2 Hz, 2H), 2.03 (dd, *J* = 5.5, 9.6 Hz, 1H), 2.07–2.18 (m, 3H), 2.41 (dd, *J* = 6.5, 13.0 Hz, 1H), 3.48 (dd, *J* = 5.8, 11.1 Hz, 1H), 3.56 (t, *J* = 6.5 Hz, 2H), 3.61 (dd, *J* =

3.7, 11.2 Hz, 1H), 3.94 (dt, *J* = 5.1, 8.7 Hz, 1H), 4.12 (dd, *J* = 6.5, 11.2 Hz, 1H), 4.17– 4.27 (m, 2H), 4.46– 4.57 (m, 4H), 7.28–7.39 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 30.0 (t), 35.6 (t), 35.8 (t), 37.7 (t), 41.6 (t), 66.5 (t), 67.4 (t), 70.7 (d), 71.9 (t), 73.0 (t), 76.2 (d), 82.3 (d), 83.2 (d), 115.0 (s), 127.6 (d), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d), 128.4 (d, 2C), 128.5 (d, 2C), 137.9 (s), 138.4 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{34}NaO_6$: 465.2248 $[M + Na]^+$; found 4865.2245.

(*R*)-3-((2*S*,3*R*,5*S*,7*S*)-3-(benzyloxy)-7-(2-(benzyloxy)ethyl)-1,6-dioxaspiro[4.4]nonan-2-yl)propane-1,2-diol (3b): colourless liquid (38 mg); R_f = 0.2 (80% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -66.13 (*c* 1.72, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.54 (dt, *J* = 9.6, 14.1 Hz, 1H), 1.64–1.72 (m, 2H), 1.73 (dd, *J* = 2.5, 5.7 Hz, 1H), 1.76–1.83 (m, 1H), 1.86 (dd, *J* = 4.0, 10.7 Hz, 1H), 1.90 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.93–2.03 (m, 2H), 2.08 (dd, *J* = 4.5, 13.8 Hz, 1H), 2.19 (dd, *J* = 8.2, 13.8 Hz, 1H), 3.39 (dd, *J* = 5.6, 11.1 Hz, 1H), 3.49–3.58 (m, 3H), 3.65 (ddd, *J* = 4.5, 5.9, 8.1 Hz, 1H), 3.80 (td, *J* = 2.8, 5.8 Hz, 1H), 4.11 (ddd, *J* = 3.2, 6.2, 10.0 Hz, 1H), 4.21 (t, *J* = 6.2 Hz, 1H), 4.35–4.41 (d, *J* = 12.0 Hz, 1H), 4.41–4.48 (d, *J* = 4.5 Hz, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 7.16–7.30 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 30.4 (t), 36.6 (t), 37.1 (t), 37.7 (t), 40.4 (t), 66.4 (t), 67.6 (t), 71.3 (d), 71.9 (t), 72.9 (t), 77.8 (d), 80.7 (d), 82.3 (d), 113.7 (s), 127.5 (d), 127.6 (d, 2C), 127.8 (d, 2C), 127.8 (d), 128.3 (d, 2C), 128.4 (d, 2C), 137.8 (s), 138.5 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{34}NaO_6$: 465.2248 $[M + Na]^+$; found 4865.2242.

Synthesis of Epoxide 18' from L-Malic Acid:



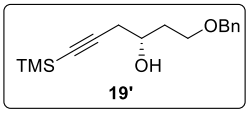
Scheme S3. Synthesis of Epoxide **18'**

(*S*)-2-(2-(benzyloxy)ethyl)oxirane (8'): At 0 °C, the L-malic acid derived diol **S3.1** (3.0 g, 15.29 mmol) was dissolved in CH_2Cl_2 (40 mL) and was treated with dibutyl tin oxide (Bu_2SnO 380 mg, 1.53 mmol), Et_3N (2.56 mL, 18.34 mmol), DMAP (186 mg, 1.53 mmol), 4-methylbenzenesulfonyl chloride (2.91 g, 15.29 mmol). The mixture was warmed to room temperature with stirring for 6 h. The reaction was quenched with water (25 mL), extracted with CH_2Cl_2 (80 mL X 2), combined organic layer was dried (Na_2SO_4), concentrated under reduced

vacuum, crude product was purified by column chromatography to afford tosylate **S3.2** as colourless liquid (4.2 g).

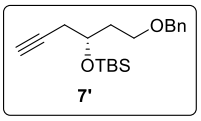
The tosylate **S3.2** (4.2 g, 11.99 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. To this, sodium hydride (60% oil suspension, 575 mg, 14.38 mmol) was added in small portions and the content was warmed to room temperature for 2 h. After completion of the reaction it was cooled to 0 °C and quenched with water (20 mL), extracted with EtOAc (75 mL X 2), dried over (Na_2SO_4), concentrated under reduced pressure, purified by column chromatography to afford epoxide **18'** as colourless liquid (1.99 g, 73% over 2 steps). R_f = 0.8 (20% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -12.5 (*c* 2.3, $CHCl_3$); **HRMS** (ESI) calcd for $C_{11}H_{14}NaO_2$: 201.0886 $[M + Na]^+$; found 201.0885.

(*R*)-1-(benzyloxy)-6-(trimethylsilyl)hex-5-yn-3-ol (19'):



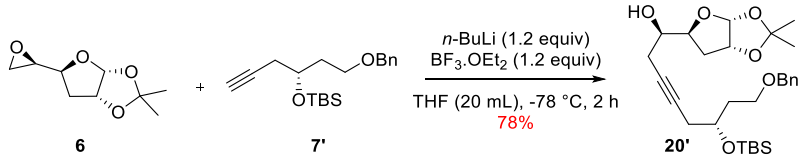
Synthesized by following the procedure used in the synthesis of compound **19**. Epoxide **18'** (1.99 g, 11.17 mmol), trimethylsilyl acetyelene (1.91 mL, 13.40 mmol), *n*-BuLi (8.37 mL, 13.40 mmol), $BF_3.OEt_2$ (1.65 mL, 13.40 mmol), THF (40 mL), -78 °C, 2 h, (2.15 g, 69%), $[\alpha]_D^{28}$ -3.5 (*c* 1.25, $CHCl_3$); **HRMS** (ESI) calcd for $C_{16}H_{24}SiNaO_2$: 299.1438 $[M + Na]^+$; found 299.1432.

(*R*)-((1-(benzyloxy)hex-5-yn-3-yl)oxy)(*tert*-butyl)dimethylsilane (7'):



Synthesized by following the procedure used in the synthesis of compound **20**. **Step 1:** alkynol **19'** (2.15 g, 7.78 mmol), K_2CO_3 (1.29 g, 9.33 mmol), MeOH (40 mL), rt, 10 h. **Steps 2:** alkynol (1.42 g, 6.95 mmol), *tert*-butyldimethylsilyl chloride (1.57 g, 10.43 mmol), imidazole (710 mg, 10.43 mmol), DMF (20 mL), rt, 8 h (1.81 g, 73%, 2 steps), $[\alpha]_D^{28}$ -12.05 (*c* 1.17, $CHCl_3$); **HRMS** (ESI) calcd for $C_{19}H_{30}SiNaO_2$: 341.1907 $[M + Na]^+$; found 341.1902.

Synthesis of Alkynol 20':

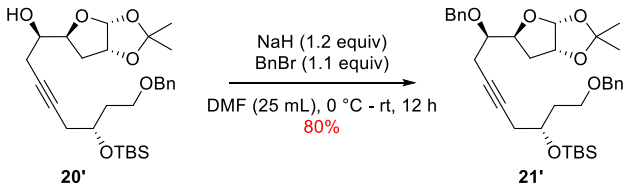


It was synthesized by following the procedure used in the synthesis of compound **20**.

Epoxide **6** (1.0 g, 5.37 mmol), alkyne **7'** (2.05 g, 6.44 mmol), *n*-BuLi 1.6 M (4.03 mL, 6.44 mmol), $BF_3.OEt_2$ (0.795 mL, 6.44 mmol), THF (20 mL), -78 °C, 2 h, (2.12 g, 78%).

(1*R*,6*R*)-8-(benzyloxy)-6-((tert-butyldimethylsilyl)oxy)-1-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)oct-3-yn-1-ol (20'): colourless liquid; R_f = 0.5 (10% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -19.1 (*c* 1.48, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.28 (s, 3H), 1.46 (s, 3H), 1.67–1.84 (m, 2H), 1.91 (qd, *J* = 7.0, 4.0 Hz, 1H), 2.03 (dd, *J* = 4.5, 13.3 Hz, 1H), 2.26–2.31 (m, 2H), 2.31–2.37 (m, 2H), 3.51 (dd, *J* = 7.0, 5.5 Hz, 2H), 3.83 (dd, *J* = 4.7, 10.5 Hz, 1H), 3.89–3.97 (m, 1H), 4.23 (dt, *J* = 4.6, 10.6 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.69 (t, *J* = 4.2 Hz, 1H), 5.76 (d, *J* = 3.6 Hz, 1H), 7.20–7.25 (m, 1H), 7.27–7.32 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.9 (q), -4.5 (q), 18.0 (s), 23.9 (t), 25.8 (q, 3C), 26.2 (q), 26.8 (q), 28.0 (t), 32.9 (t), 36.6 (t), 66.7 (t), 68.2 (d), 70.1 (d), 72.9 (t), 77.2 (s), 79.9 (d, 2C), 80.6 (d), 105.4 (d), 111.3 (s), 127.5 (d), 127.7 (d, 2C), 128.3 (d, 2C), 138.5 (s) ppm (one alkyne carbon peak is getting merged with the $CDCl_3$ triplet); **HRMS** (ESI) calcd for $C_{28}H_{44}SiNaO_6$: 527.2804 $[M + Na]^+$; found 527.2802.

Synthesis of Alkyne 21':



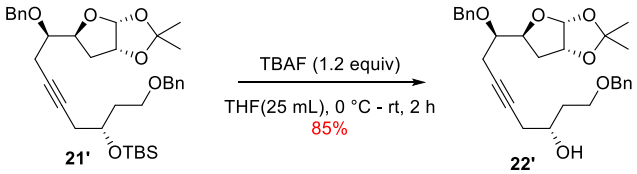
It was synthesized by following the procedure used in the synthesis of compound **21**.

Alcohol **20'** (2.1 g, 4.16 mmol), sodium hydride 60% oil suspension (200 mg, 4.99 mmol), benzyl bromide (0.543 mL, 4.58 mmol), DMF (25 mL), 0 °C – rt, 12 h, (1.99 g, 80%).

(((3*R*,8*R*)-1,8-bis(benzyloxy)-8-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)oct-5-yn-3-yl)oxy)(tert-butyl)dimethylsilane (21'): colourless liquid; R_f = 0.4 (10% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -15.6 (*c* 1.95, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ -0.02 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.25 (s, 3H), 1.43 (s, 3H), 1.70 (dt, *J* = 5.5, 13.5 Hz, 1H), 1.81 (ddd, *J* = 4.8, 10.5, 13.5 Hz, 1H), 1.87–1.97 (m, 1H), 2.03 (dd, *J* = 4.6, 13.3 Hz, 1H), 2.21–2.28 (m, 2H), 2.31–2.40 (m, 2H), 3.44–3.52 (m, 2H), 3.68 (dd, *J* = 6.1, 10.2 Hz, 1H), 3.84–3.92 (m, 1H), 4.34 (dd, *J* = 3.2, 7.7 Hz, 1H), 4.39–4.46 (m, 2H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.62–4.69 (m,

2H), 5.72 (d, *J* = 3.6 Hz, 1H), 7.17–7.24 (m, 2H), 7.25–7.28 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* -4.9 (q), -4.5 (q), 18.0 (s), 22.3 (t), 25.8 (q, 3C), 26.3 (q), 26.9 (q), 28.1 (t), 33.3 (t), 36.6 (t), 66.8 (t), 68.3 (d), 72.9 (t), 73.0 (t), 77.8 (d), 78.0 (s), 78.8 (s), 79.9 (d), 80.6 (d), 105.3 (d), 111.2 (s), 127.4 (d), 127.5 (d), 127.6 (d, 2C), 127.7 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 138.6 (s), 138.6 (s) ppm; **HRMS** (ESI) calcd for $C_{35}H_{50}SiNaO_6$: 617.3274 $[M + Na]^+$; found 617.3272.

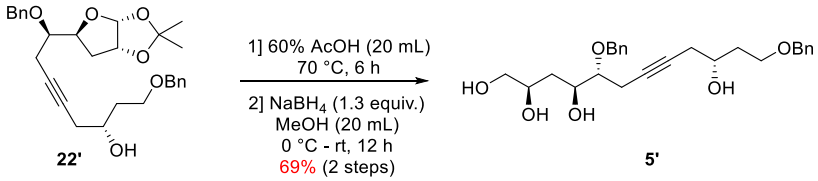
Synthesis of Alkynol 22':



It was synthesized by following the procedure used in the synthesis of compound **22**.
Alkyne **21'** (1.95 g, 3.28 mmol), TBAF 1M in THF (3.61 mL, 3.61 mmol), THF (25 mL), 0 °C – rt, 2 h, (1.35 g, 85%).

(3*S*,8*R*)-1,8-bis(benzyloxy)-8-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)oct-5-yn-3-ol (22'): colourless liquid; R_f = 0.3 (30% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -5.7 (*c* 1.86, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 1.34 (s, 3H) , 1.52 (s, 3H), 1.76–1.95 (m, 4H), 2.15 (dd, *J* = 4.2, 13.3 Hz, 1H), 2.32–2.50 (m, 4H), 3.10 (br., s. 1H), 3.64 (dd, *J* = 8.0, 12.2 Hz, 1H), 3.68–3.78 (m, 2H), 3.94 (br., s. 1H), 4.42 (dd, *J* = 4.9, 10.3 Hz, 1H), 4.53 (s, 2H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.74 (dd, *J* = 4.9, 10.3 Hz, 2H), 5.80 (d, *J* = 4.0 Hz, 1H), 7.27–7.39 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 22.1 (t), 26.2 (q), 26.8 (q), 27.5 (t), 33.6 (t), 35.4 (t), 68.5 (t), 69.6 (d), 72.8 (t), 73.2 (t), 77.7 (d), 78.4 (s, 2C), 79.7 (d), 80.5 (d), 105.2 (d), 111.2 (s), 127.5 (d, 2C), 127.6 (d, 2C), 127.6 (d, 2C), 128.2 (d, 2C), 128.4 (d, 2C), 137.9 (s), 138.4 (s) ppm; **HRMS** (ESI) calcd for $C_{29}H_{36}NaO_6$: 503.2409 $[M + Na]^+$; found 503.2416.

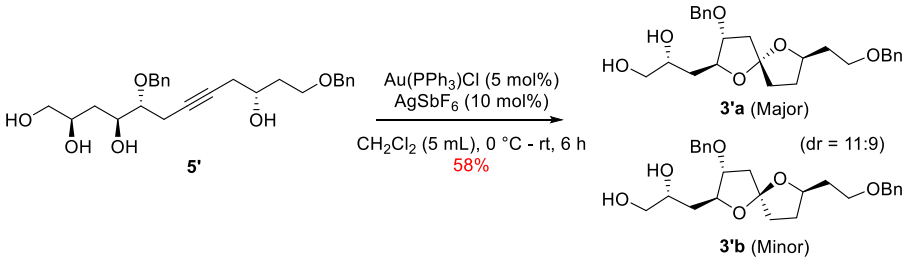
Synthesis of Tetrol 5':



It was synthesized by following the procedure used in the synthesis of compound **5**.
Step 1: alkynol **22'** (1.35 g, 2.81 mmol), 60% AcOH (20 mL), 70 °C, 6 h, **Step 2:** $NaBH_4$ (138 mg, 3.66 mmol), MeOH (20 mL), 0 °C – rt, 12 h, (860 mg, 69% 2 steps).

(2*R*,4*S*,5*R*,10*S*)-5,12-bis(benzyloxy)dodec-7-yne-1,2,4,10-tetraol (5'): colourless liquid; R_f = 0.2 (80% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -22.2 (*c* 1.66, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.71–1.92 (m, 4H), 2.37 (dt, *J* = 2.2, 5.8 Hz, 2H), 2.49 (ddd, *J* = 2.2, 6.3, 10.7 Hz, 1H), 2.57 (ddd, *J* = 2.7, 7.5, 10.0 Hz, 1H), 3.17 (br. s., 1H), 3.51 (dd, *J* = 5.5, 10.8 Hz, 2H), 3.59–3.66 (m, 2H), 3.70 (dt, *J* = 5.3, 9.5 Hz, 1H), 3.94 (dd, *J* = 5.7, 11.1 Hz, 2H), 4.11 (d, *J* = 7.6 Hz, 1H),4.52 (s, 2H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 7.28–7.38 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.9 (t), 27.6 (t), 34.5 (t), 35.6 (t), 66.6 (t), 68.5 (t), 69.6 (d), 72.0 (d), 72.2 (t), 72.6 (d), 73.3 (t), 78.5 (s), 78.9 (s), 80.1 (d), 127.7 (d, 2C), 127.8 (d), 127.9 (d, 2C), 127.9 (d), 128.5 (d, 2C), 128.5 (d, 2C), 137.8 (s), 137.8 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{35}O_6$: 443.2433 $[M + Na]^+$; found 443.2433.

Synthesis of Diastereomers 3'a & 3'b:



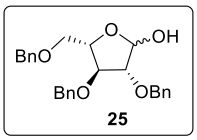
The solution of tetrol **5'** (150 mg, 0.338 mmol) in CH_2Cl_2 (5 mL) was added $Au(PPh_3)Cl$ (8.38 mg, 16.95 µmol) and $AgSbF_6$ (11.65 mg, 33.89 µmol) at room temperature and continued stirring for 6 h. After completion, it was concentrated under reduced pressure, purified by column chromatography (230-400 silica) to afford mixture diastereomers **3a** and **3'b** as colourless liquid (88 mg, 58%).

(*R*)-3-((2*S*,3*R*,5*R*,7*R*)-3-(benzyloxy)-7-(2-(benzyloxy)ethyl)-1,6-dioxaspiro[4.4]nonan-2-yl)propane-1,2-diol (3'a): colourless liquid (55 mg); R_f = 0.2 (80% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -108.0 (*c* 0.44, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65 (br. s., 2H), 1.72–1.79 (m, 3H), 1.81–1.88 (m, 1H), 1.92 (td, *J* = 2.2, 4.5 Hz, 1H), 1.97 (dt, *J* = 1.5, 12.0 Hz, 1H), 2.02–2.11

(m, 2H), 2.18 (dd, *J* = 7.6, 12.2 Hz, 1H), 2.40 (dd, *J* = 6.1, 12.9 Hz, 1H), 3.47 (dd, *J* = 5.7, 11.0 Hz, 1H), 3.55–3.64 (m, 3H), 3.90–3.97 (m, 1H), 4.08 (dt, *J* = 6.1, 11.4 Hz, 1H), 4.11–4.20 (m, 2H), 4.46–4.57 (m, 2H), 7.27–7.39 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 30.8 (t), 37.2 (t), 37.2 (t), 37.6 (t), 41.2 (t), 66.5 (t), 67.4 (t), 70.8 (d), 71.9 (t), 72.9 (t), 78.1 (d), 82.3 (d), 83.0 (d), 114.9 (s), 127.5 (d), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d), 128.3 (d, 2C), 128.5 (d, 2C), 137.8 (s), 138.4 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{34}NaO_6$: 465.2248 $[M + Na]^+$; found 465.2242.

(*R*)-3-((2*S*,3*R*,5*S*,7*R*)-3-(benzyloxy)-7-(2-(benzyloxy)ethyl)-1,6-dioxaspiro[4.4]nonan-2-yl)propane-1,2-diol (3'b): colourless liquid (33 mg); R_f = 0.2 (80% EtOAc/petroleum ether); $[\alpha]_D^{28}$ -2.16 (*c* 0.42, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.61–1.65 (m, 1H), 1.79 (dd, *J* = 3.0 Hz, 1H), 1.83 (dd, *J* = 3.0, 6.1 Hz, 1H), 1.92 (t, *J* = 6.8 Hz, 1H), 1.95–2.03 (m, 2H), 2.03–2.14 (m, 2H), 2.18 (dd, *J* = 4.5, 13.7 Hz, 1H), 2.30 (dd, *J* = 8.3, 13.7 Hz, 1H), 3.49 (dd, *J* = 5.3, 11.4 Hz, 1H), 3.56–3.66 (m, 3H), 3.73–3.77 (m, 1H), 3.92 (qd, *J* = 3.4, 5.9 Hz, 1H), 4.18 (td, *J* = 3.0, 6.4 Hz, 1H), 4.22 (dd, *J* = 6.8, 12.9 Hz, 1H), 4.45 (d, *J* = 12.2 Hz, 1H), 4.49 (d, *J* = 2.2 Hz, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 7.28–7.39 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 29.9 (t), 35.7 (t), 36.2 (t), 36.6 (t), 40.9 (t), 66.4 (t), 67.5 (t), 71.2 (d), 71.9 (t), 73.0 (t), 76.3 (d), 81.0 (d), 82.4 (d), 113.8 (s), 127.5 (d), 127.6 (d, 2C), 127.8 (d, 2C), 127.8 (d), 128.4 (d, 2C), 128.5 (d, 2C), 137.8 (s), 138.5 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{34}NaO_6$: 465.2248 $[M + Na]^+$; found 465.2246.

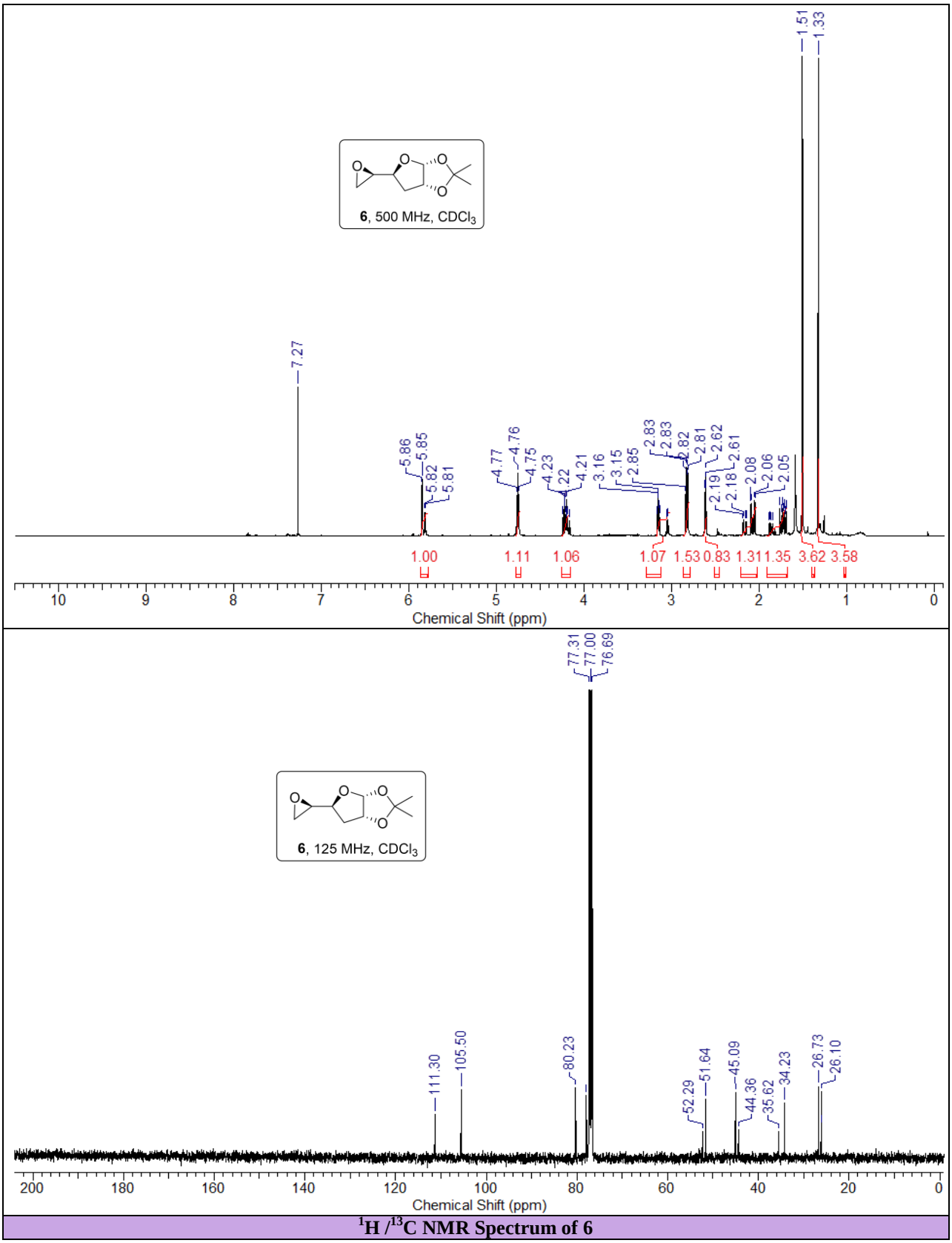
(3*R*,4*S*,5*S*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (25): It was synthesized by following reported procedure. Methyl *α*, *β*-L-Arabinofuranoside (15 g, 91.38 mmol) afforded mixture of 2,3,5-*Tri*-O-benzyl-*α*,*β*-L-arabinose **25** as colourless liquid (24 g, 62% yield over three steps); R_f = 0.6 (80% EtOAc/petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 3.53–3.65 (m, 2H) 3.97 (d, *J* = 3.8 Hz, 1H), 4.05 (t, *J* = 4.5 Hz, 1H), 4.12–4.21 (m, 1H), 4.49 (t, *J* = 4.5 Hz, 1H), 4.53–4.59 (m, 5H), 4.61–4.70 (m, 1H), 5.37–5.55 (m, 1H), 7.28–7.39 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 70.1 (t), 70.5 (t), 71.62 (t), 71.87 (t), 71.9 (t) 72.1 (t), 73.2 (t), 73.4 (t), 80.4 (d), 81.6 (d), 81.8 (d), 82.7 (d), 83.9(d), 86.7 (d), 96.0 (d), 101.0 (d), 127.6 (d), 127.7 (d, 4C), 127.8 (d, 2C), 127.9 (d), 128.3 (d), 128.4 (d, 5C), 137.2 (s, 2C), 137.3 (s, 2C), 137.7 (s), 137.9 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{28}NaO_5$: 443.1829 $[M + Na]^+$; found 443.1828.



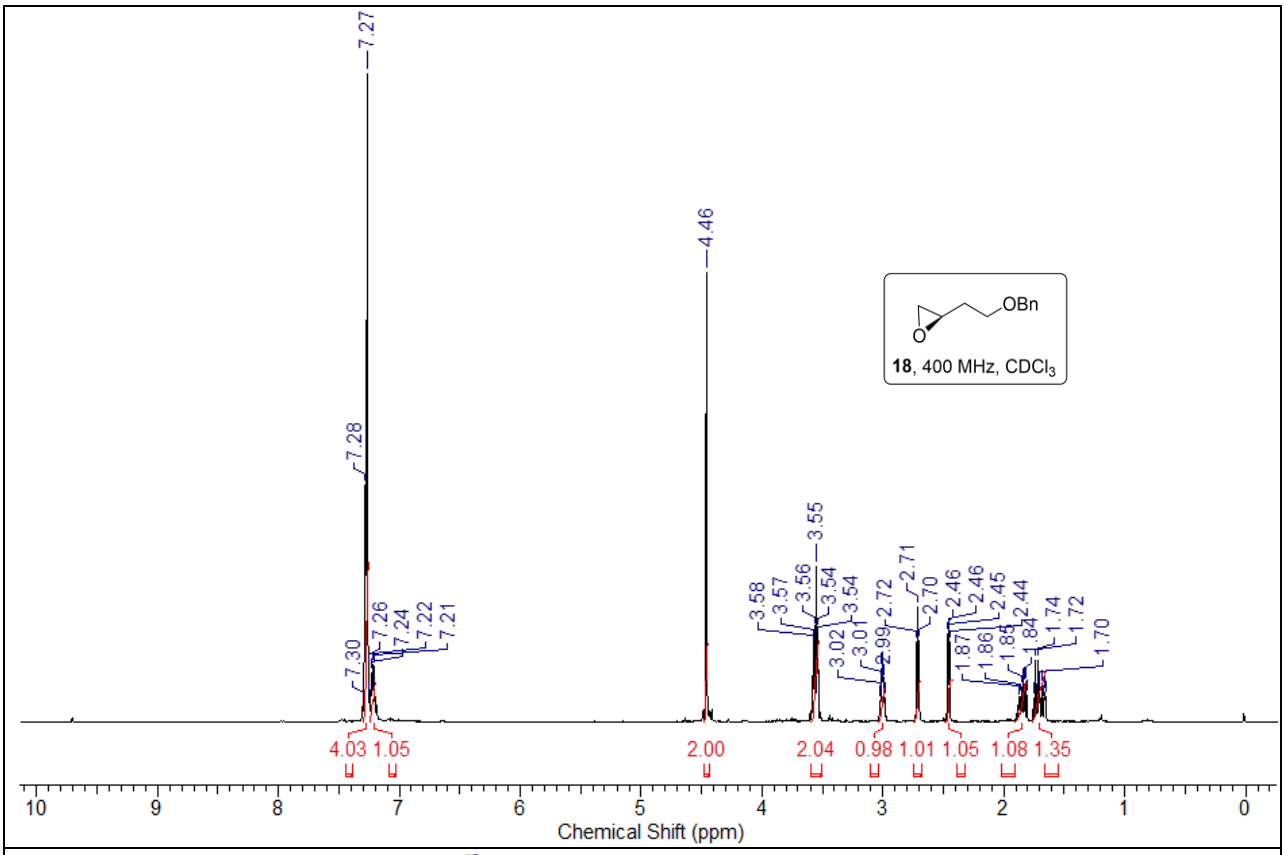
25

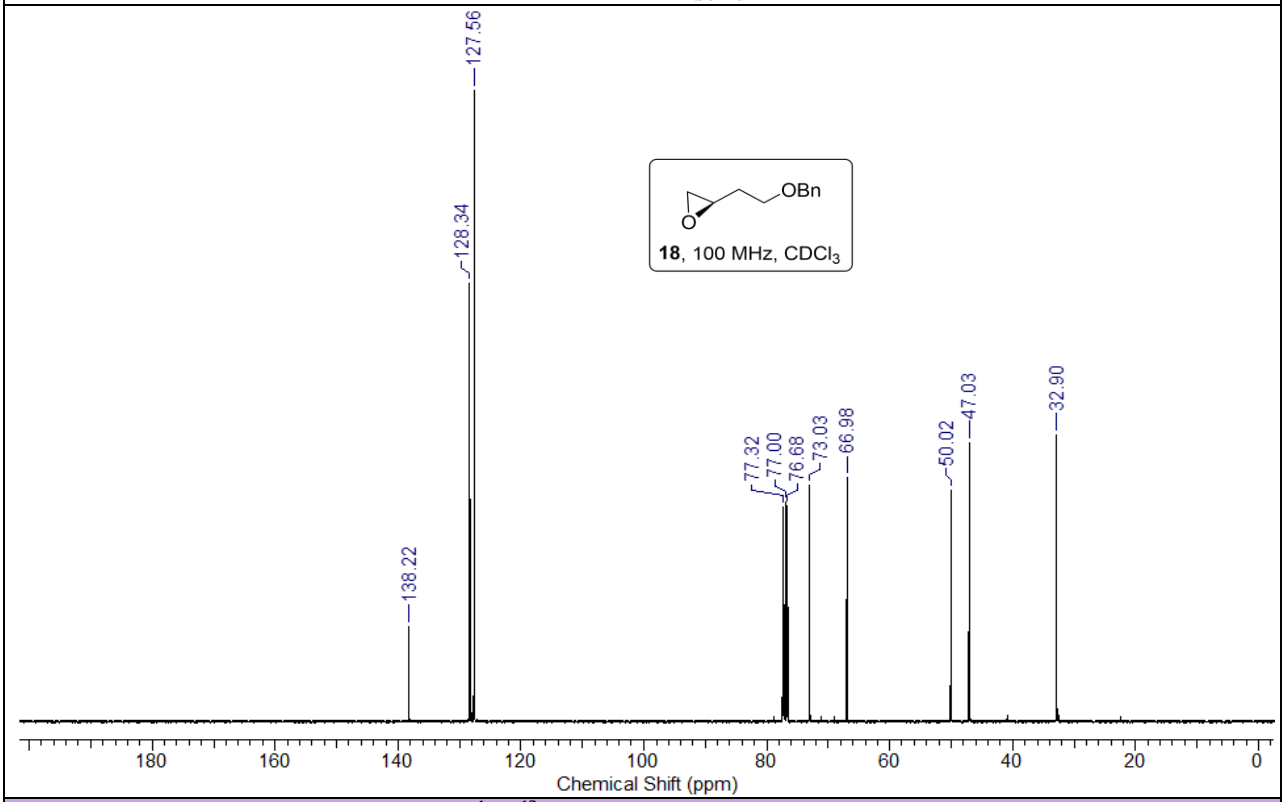
(2*S*,3*S*,4*S*)-1,3,4-tris(benzyloxy)hex-5-yn-2-ol (26): It was synthesized by following reported procedure. 2,3,5-*Tri*-O-benzyl-*α*,*β*-L-arabinose **25** (2.0 g, 4.76 mmol) afforded compound **26** as colourless liquid (600 mg, 30%); R_f = 0.8 (30% EtOAc/petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.35 (d, *J* = 2.1 Hz, 1H), 3.42 (ddd, *J* = 16.6, 9.8, 3.3 Hz, 2H), 3.55 (dd, *J* = 7.3, 3.8 Hz, 1H), 3.90–3.94 (m, 1H), 4.21 (dd, *J* = 3.8, 2.2 Hz, 1H), 4.29–4.33 (m, 2H), 4.38 (d, *J* = 16.8, 1H), 4.45 (d, *J* = 16.3 Hz, 1H), 4.65 (t, *J* = 11.5 Hz, 2H), 7.05–7.16 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 68.7 (d), 70.1 (d), 70.6 (t), 71.0 (t), 73.4 (t), 74.4 (t), 76.0 (s), 80.0 (d), 80.3 (s), 126.9 (s), 127.6 (d), 127.7 (d), 127.8 (d, 2C), 127.9 (d), 128.1 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 128.4 (d, 2C), 137.1 (s), 138.0 (s, 2C) ppm; **HRMS** (ESI) calcd for $C_{27}H_{28}NaO_4$: 439.1880 $[M + Na]^+$; found 439.1885.

***tert*-butyldimethyl(((2*S*,3*R*,4*S*)-1,3,4-tris(benzyloxy)hex-5-yn-2-yl)oxy)silane (4):** At 0 °C, Trimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.3 mL, 1.56 mmol) and 2,6-Lutidine (0.2 mL, 1.56 mmol) was added to the dichloromethane (10 mL) solution of alkynol **26** (500 mg, 1.2 mmol). The content was warmed to rt and continued stirring for 5 h. Then the reaction was quenched by addition of water (10 mL) at 0 °C, extracted with dichloromethane (25 mL X 2), dried (Na_2SO_4), concentrated under reduced pressure, purified by column chromatography to afford alkyne **4** as colourless liquid (385 mg, 60%). R_f = 0.2 (80% EtOAc/petroleum ether); $[\alpha]_D^{28}$ 26.2 (*c* 1.67, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.00 (s, 3H), 0.01 (s, 3H), 0.83 (s, 9H), 2.48–2.50 (m, 1H), 3.53 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.68 (dd, *J* = 9.8, 4.3 Hz, 1H), 3.76–3.79 (m, 1H), 4.24 (q, *J* = 4.7 Hz, 1H), 3.36–4.41 (m, 1H), 4.45 (d, *J* = 3.7 Hz, 2H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.83 (dd, *J* = 14.3, 11.7 Hz, 2H), 7.28–7.33 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* -4.9 (q), -4.5 (q), 18.1 (s), 25.9 (q, 3C), 69.5 (d), 71.0 (t), 71.4 (t), 71.8 (d), 73.2 (t), 75.2 (t), 75.9 (d), 81.1 (s), 84.0 (d), 127.4 (d, 2C), 127.5 (d), 127.6 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.2 (d, 4C), 137.9 (s), 138.4 (s), 138.8 (s); **HRMS** (ESI) calcd for $C_{33}H_{42}SiNaO_4$: 553.2745 $[M + Na]^+$; found 553.2747.

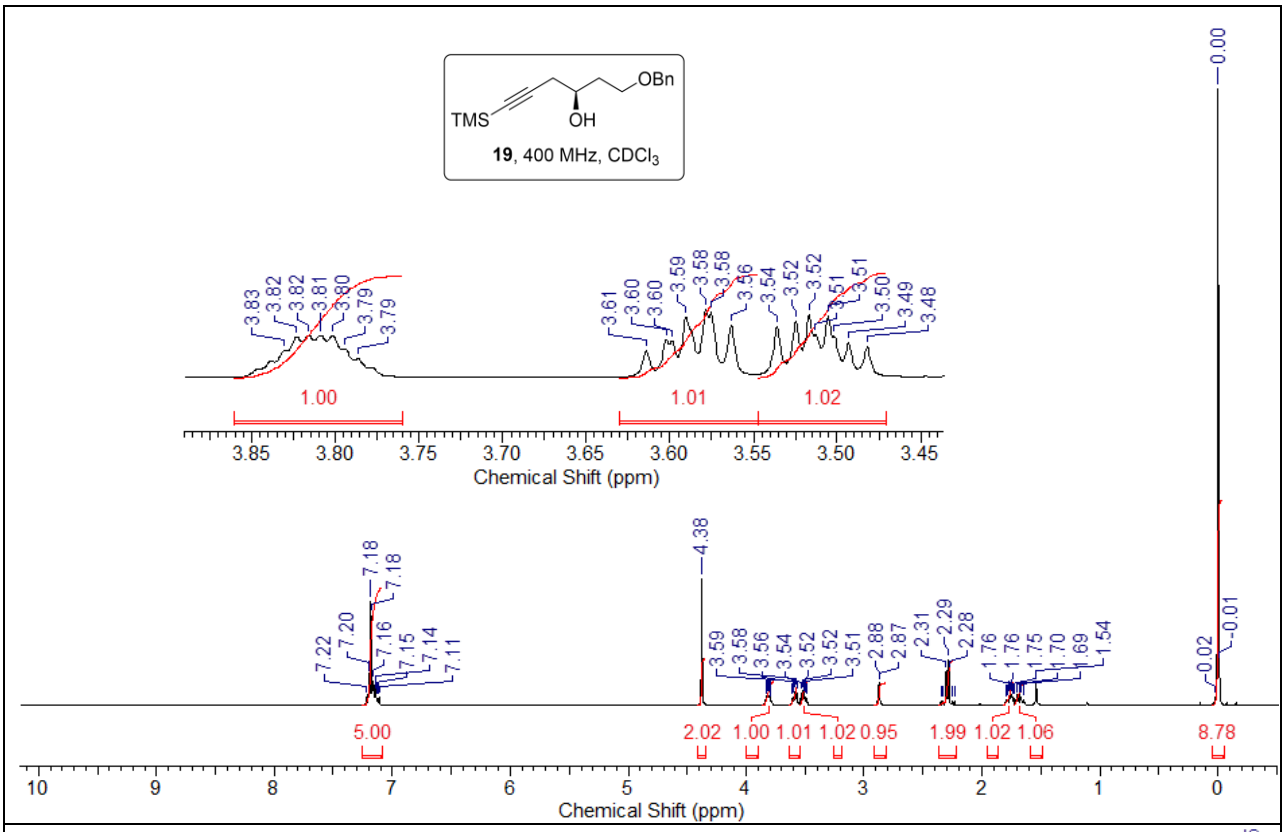


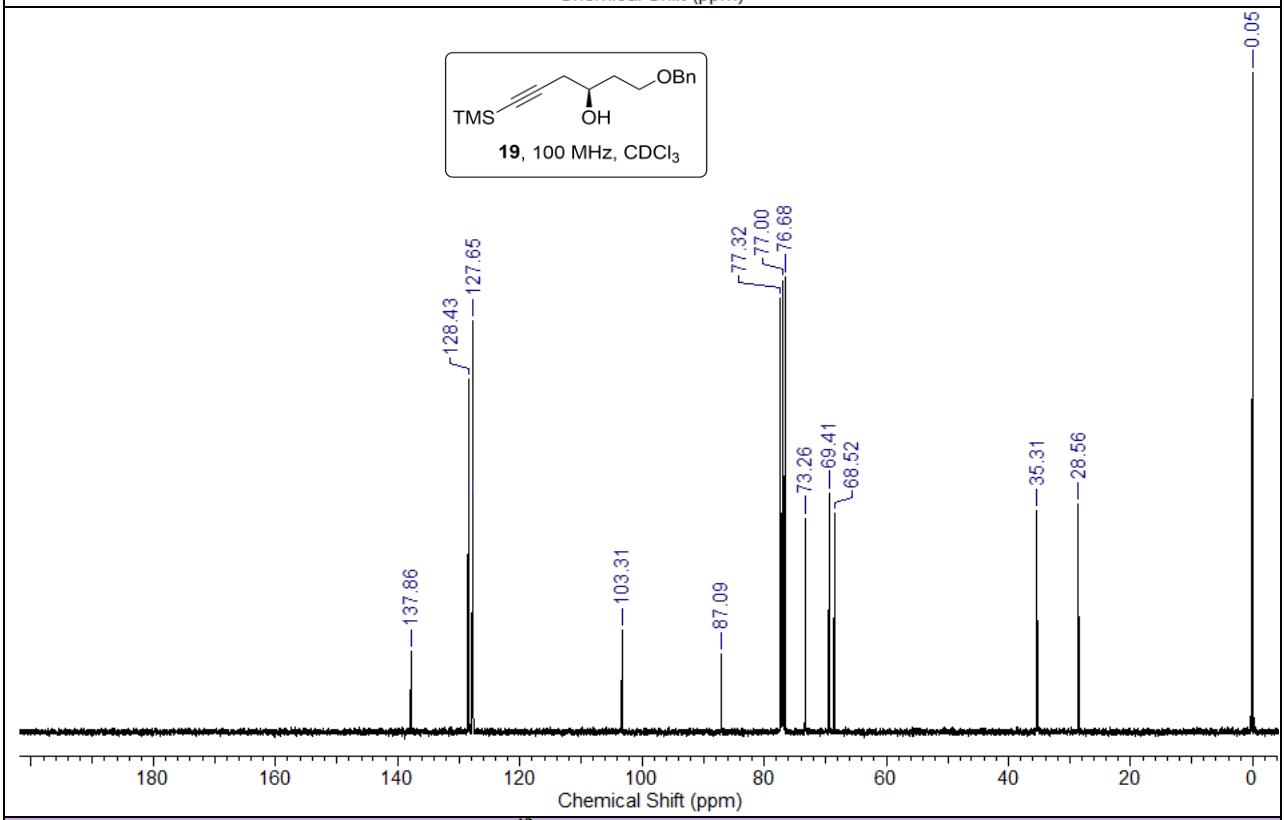
^{1}H /^{13}C NMR Spectrum of 6



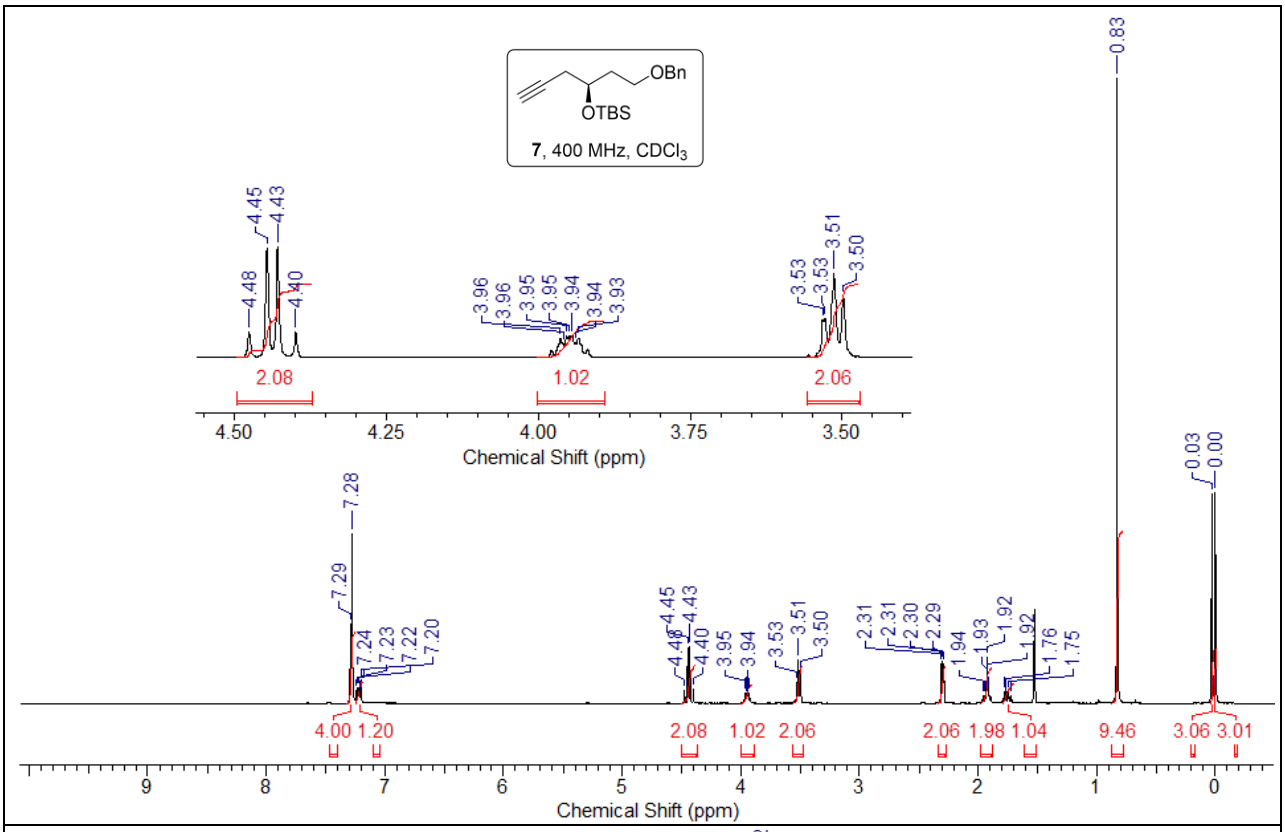


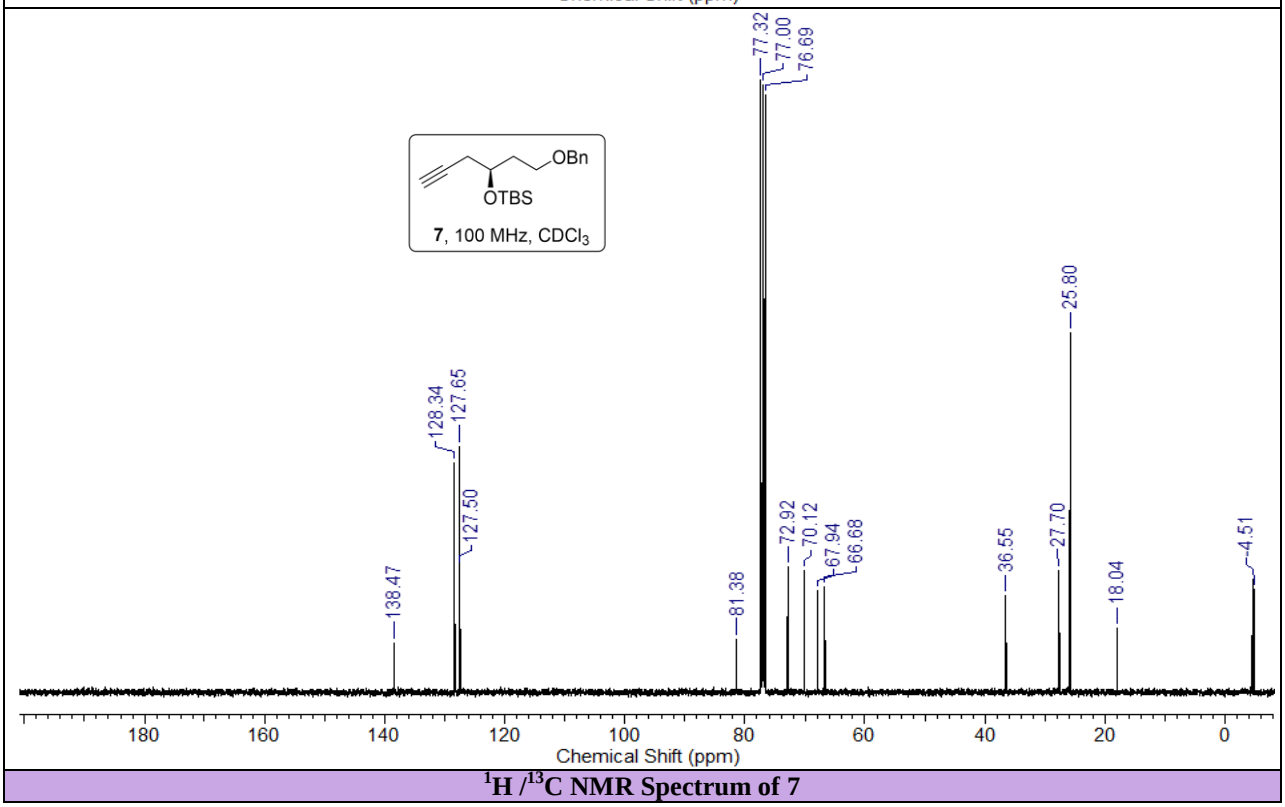
^{1}H /^{13}C NMR Spectrum of 18



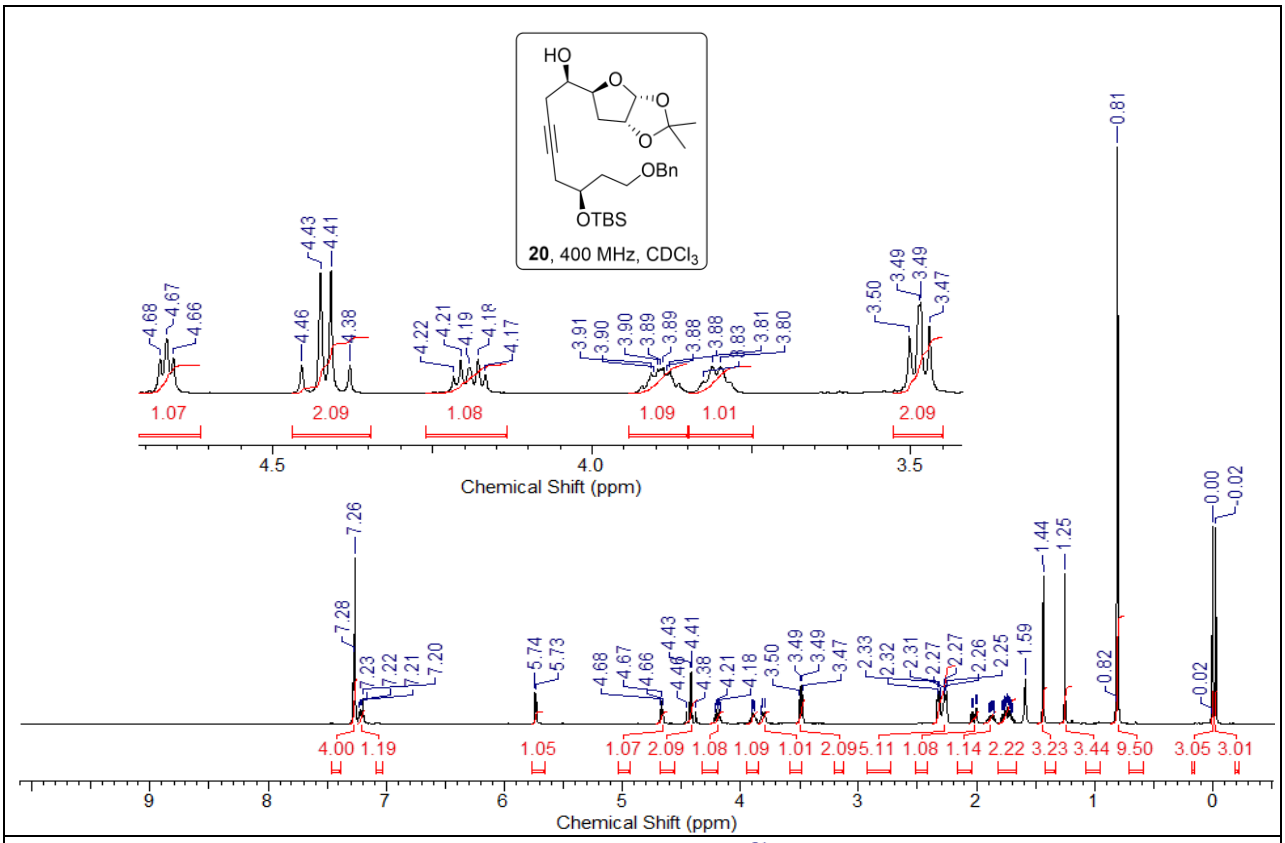


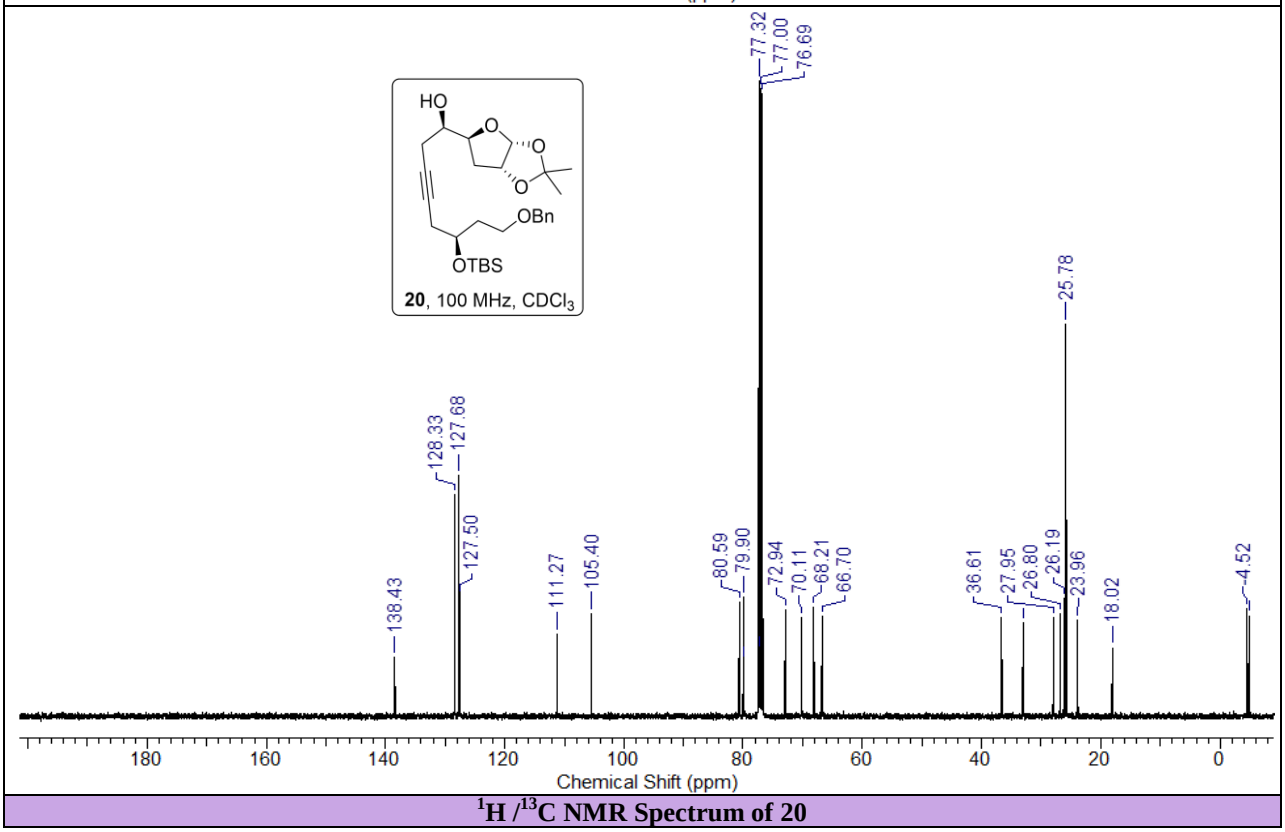
H /^{13}C NMR Spectrum of 19



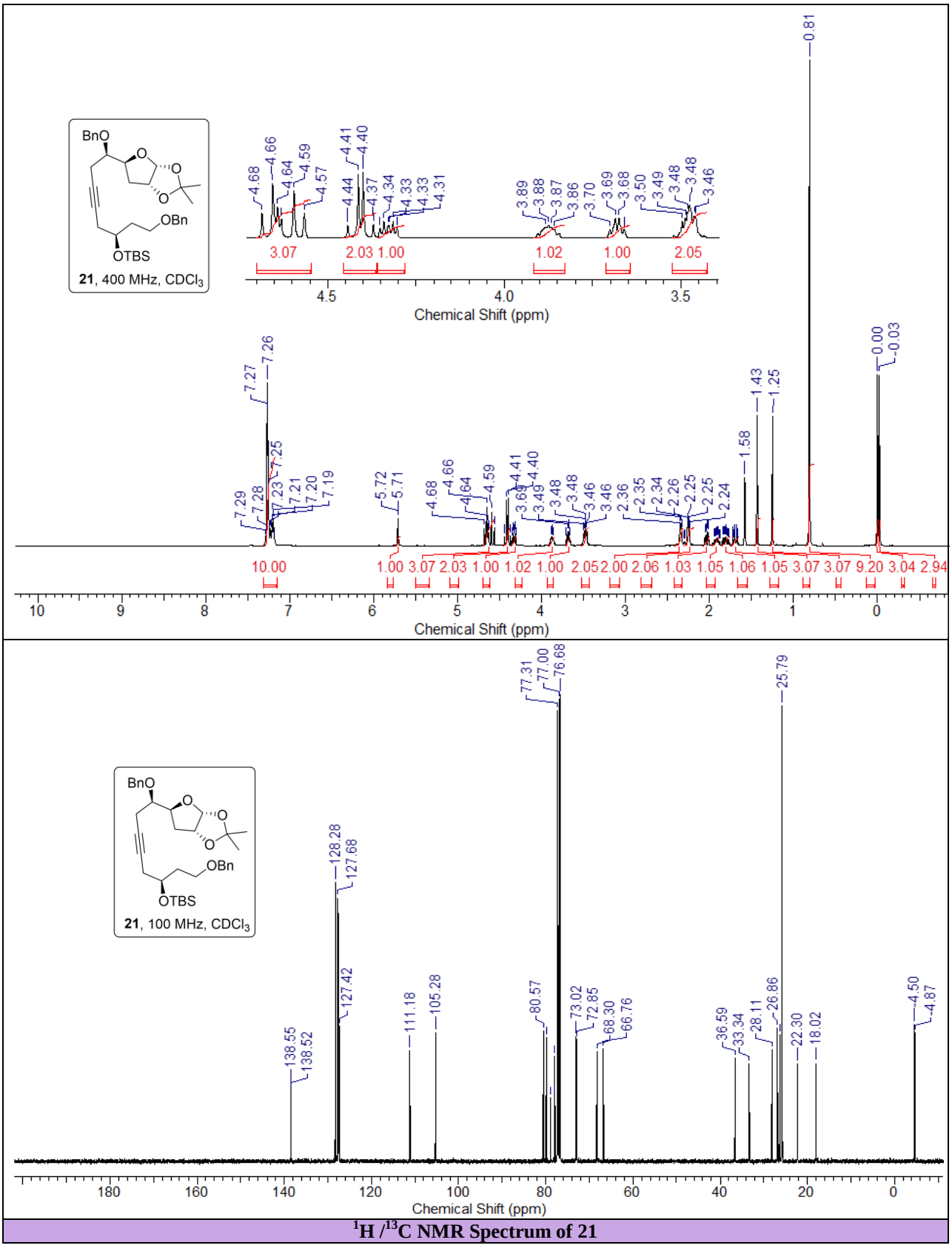


^{1}H /^{13}C NMR Spectrum of 7

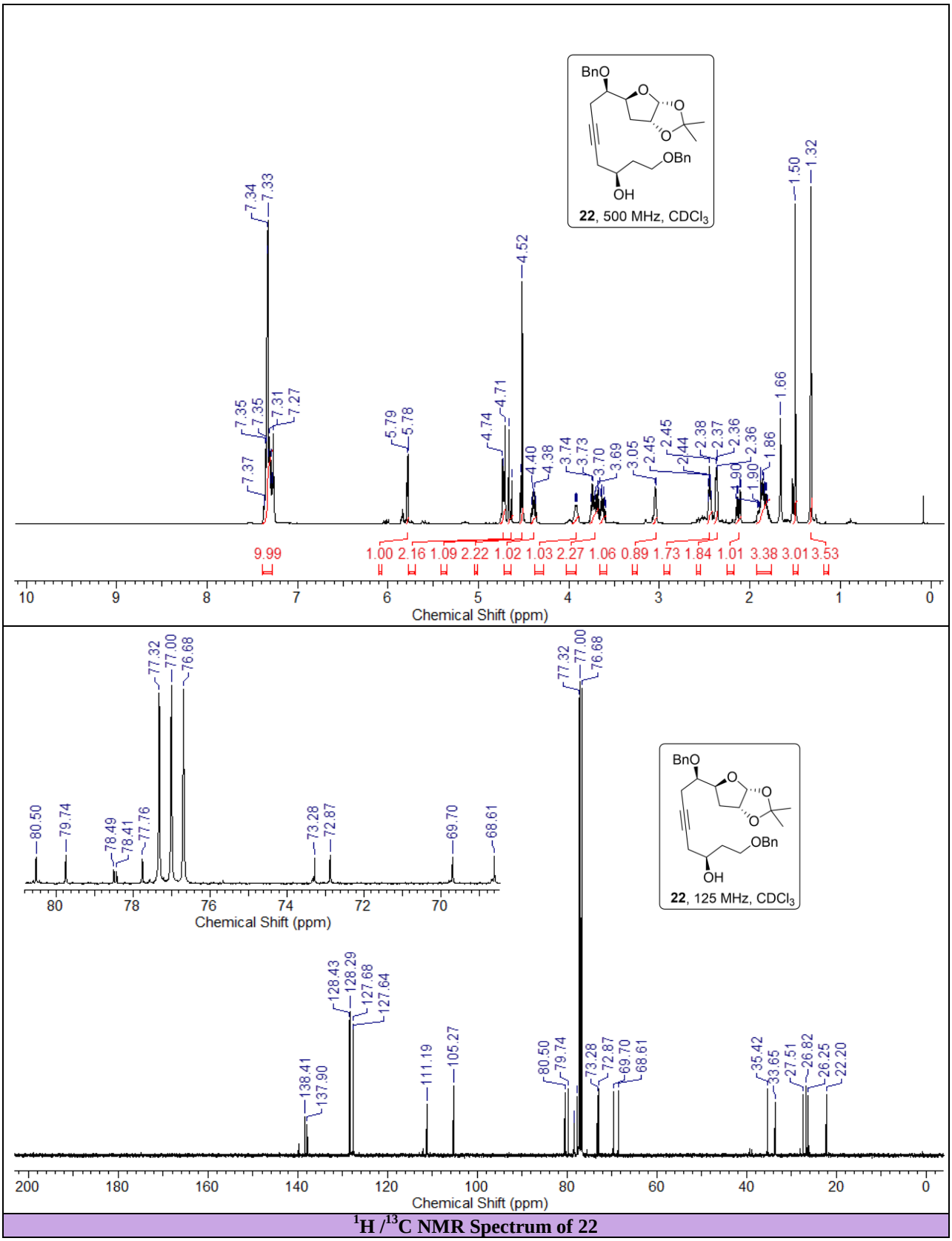




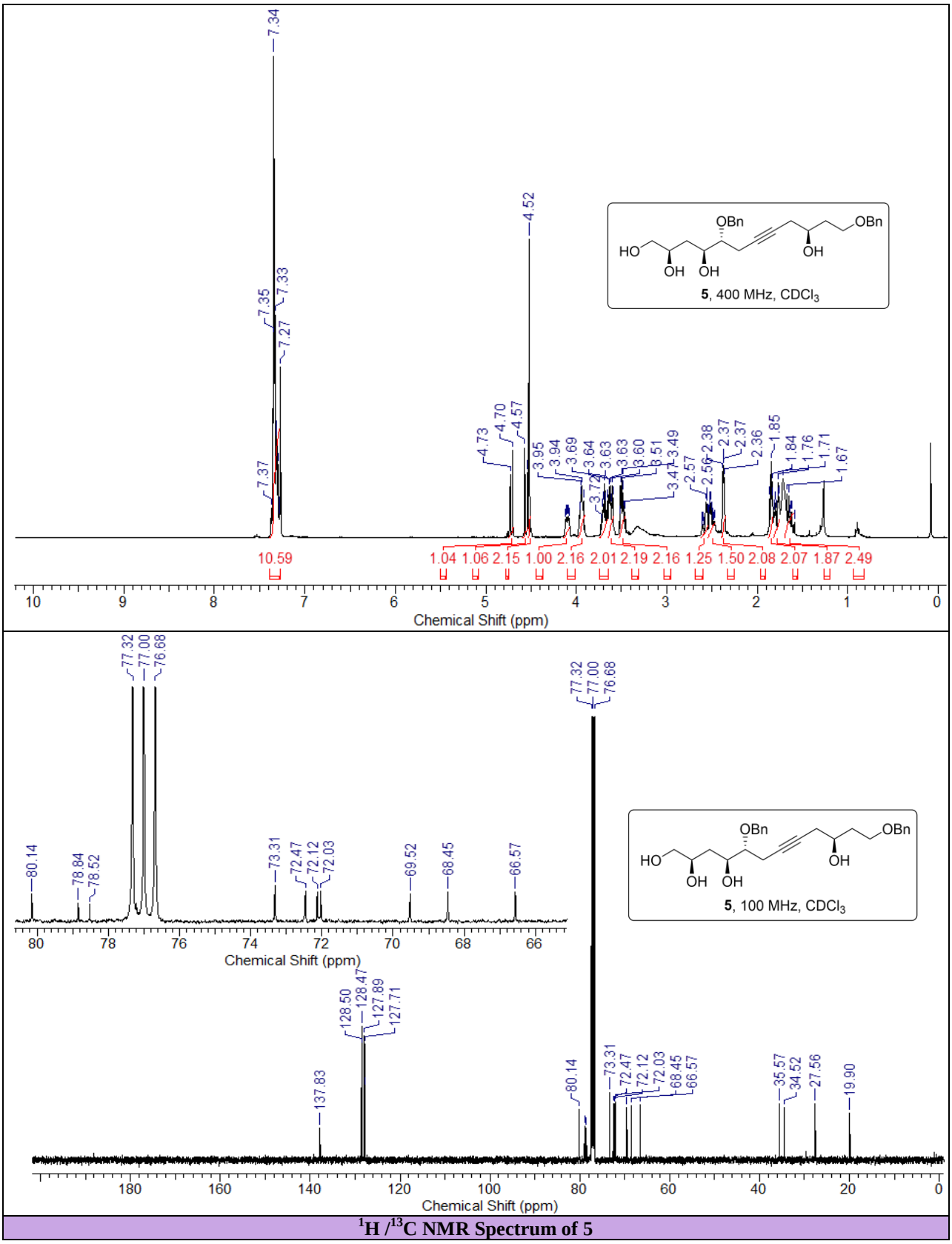
^{1}H /^{13}C NMR Spectrum of 20



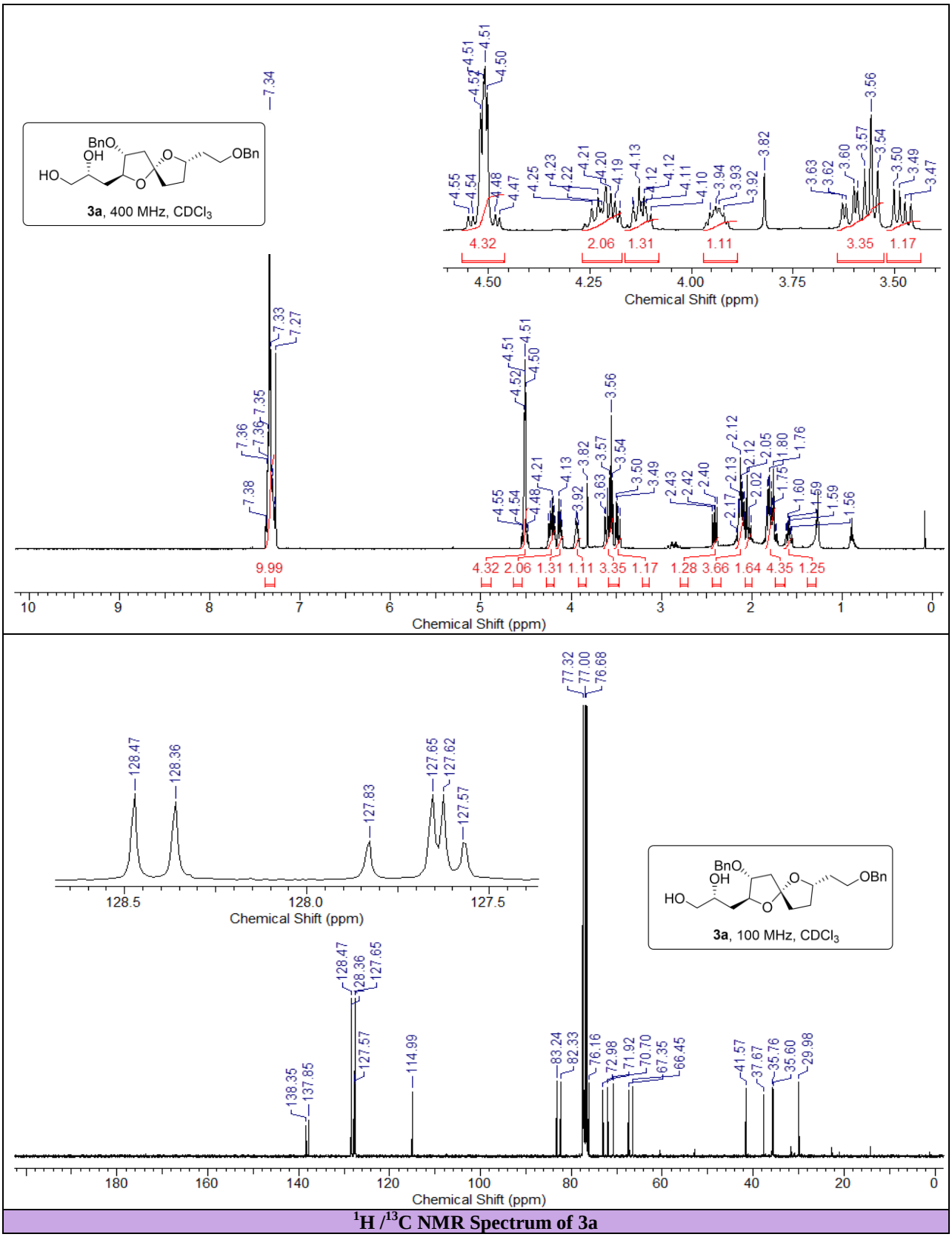
^{1}H /^{13}C NMR Spectrum of 21



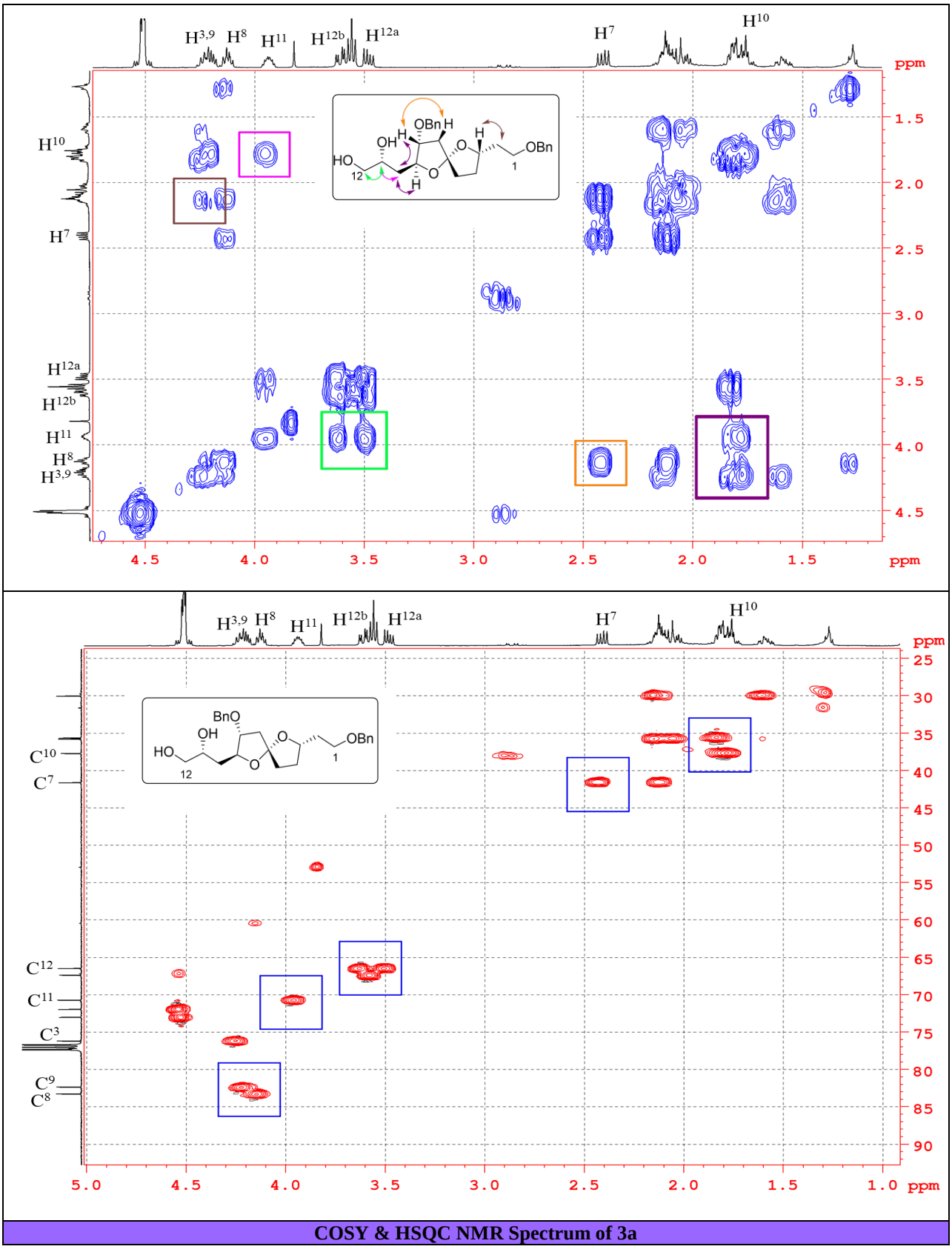
^{1}H /^{13}C NMR Spectrum of 22



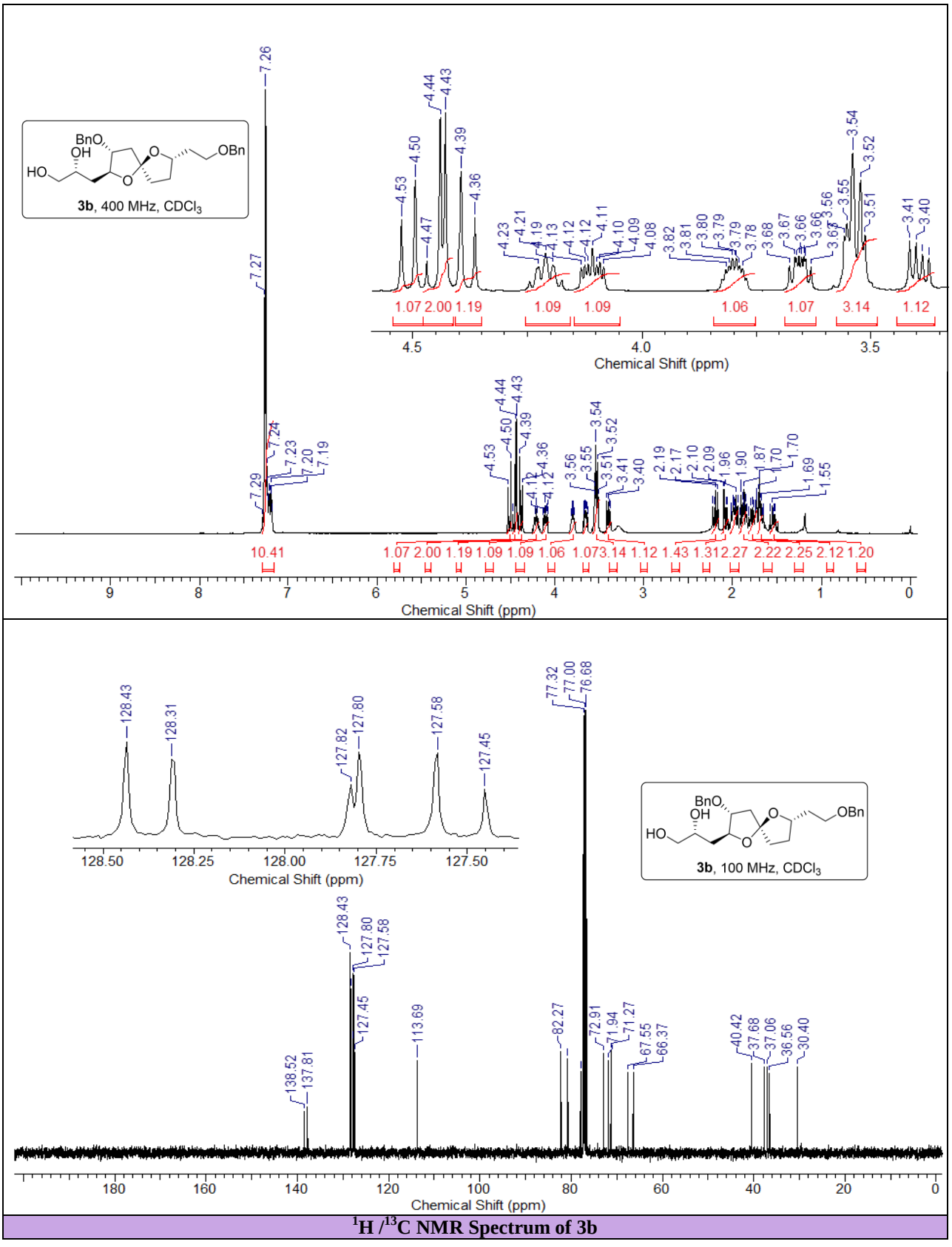
^{1}H /^{13}C NMR Spectrum of 5



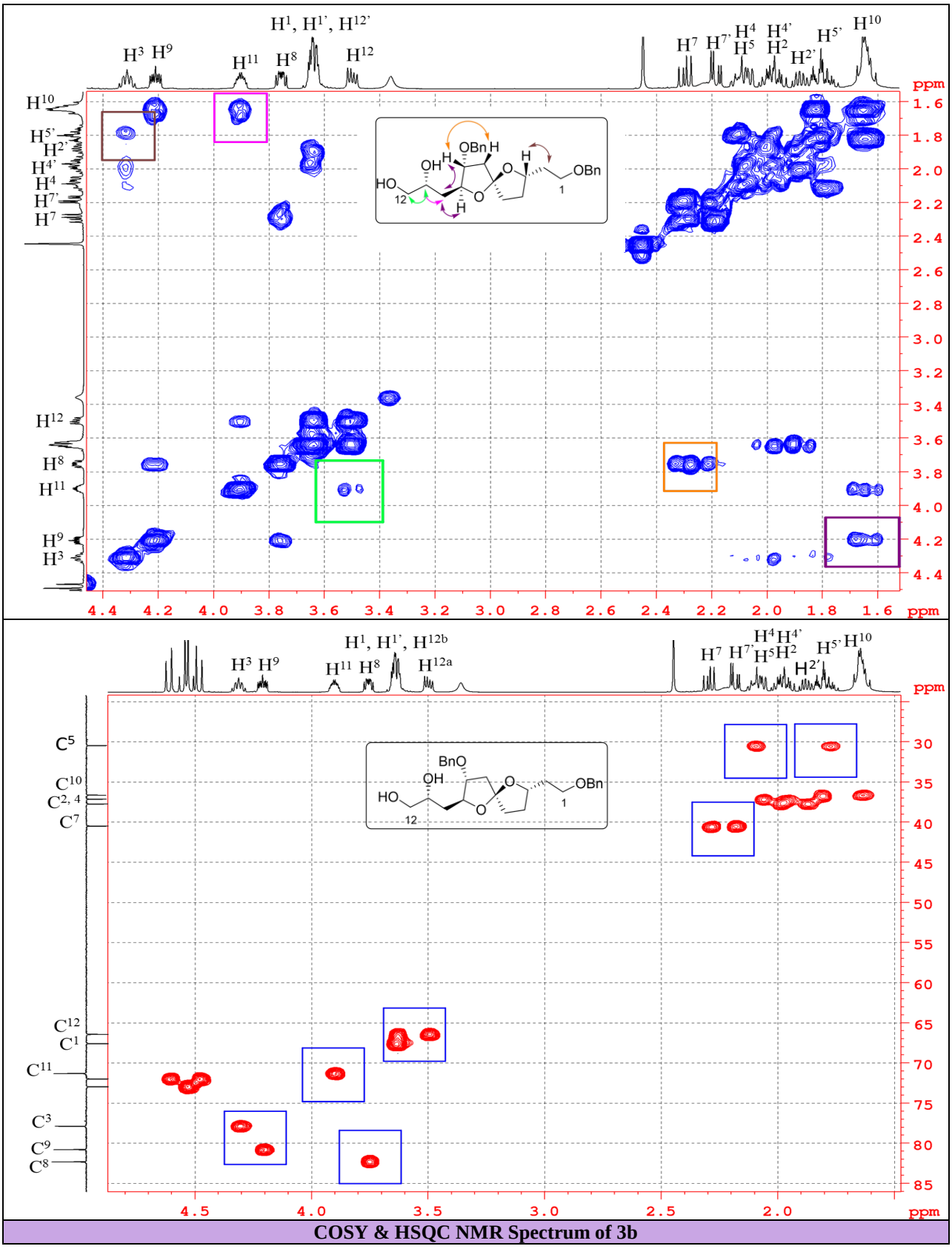
^{1}H /^{13}C NMR Spectrum of 3a



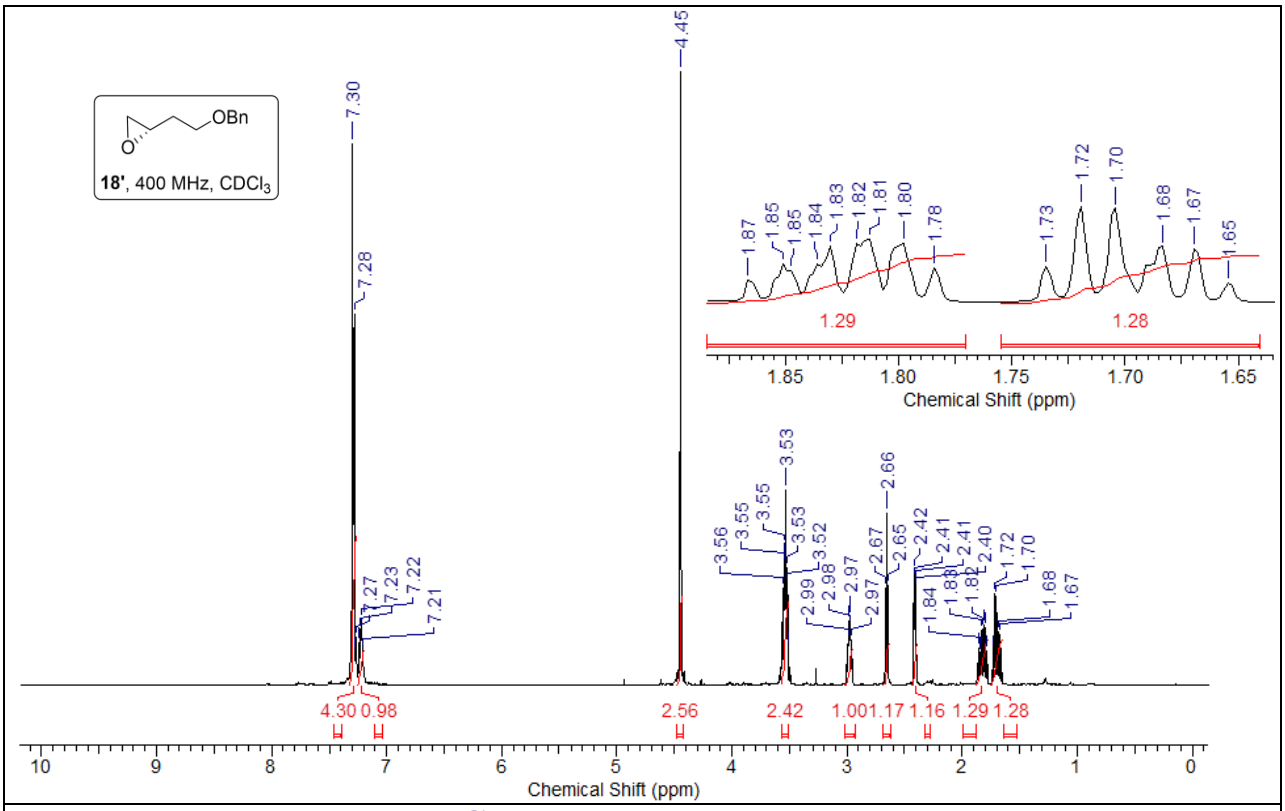
COSY & HSQC NMR Spectrum of 3a

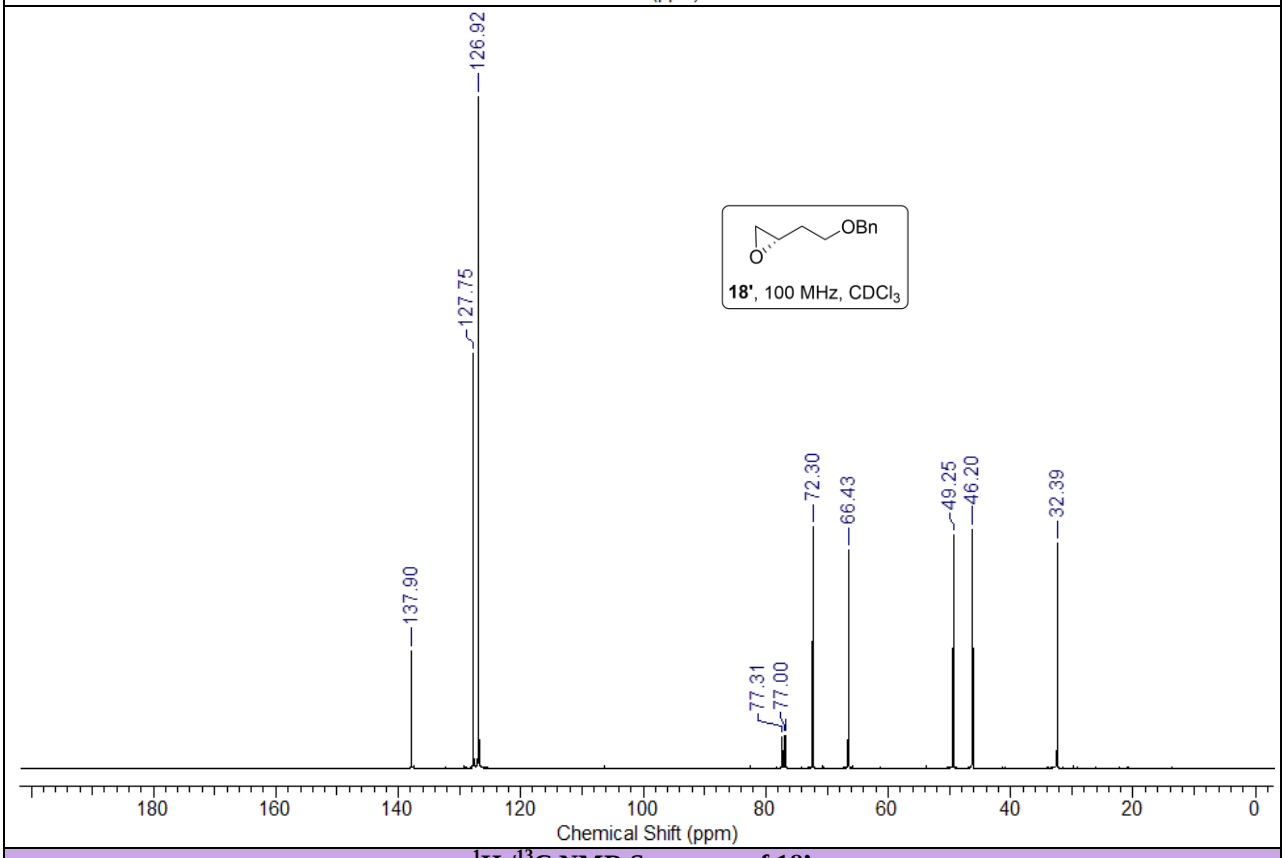


^{1}H /^{13}C NMR Spectrum of 3b

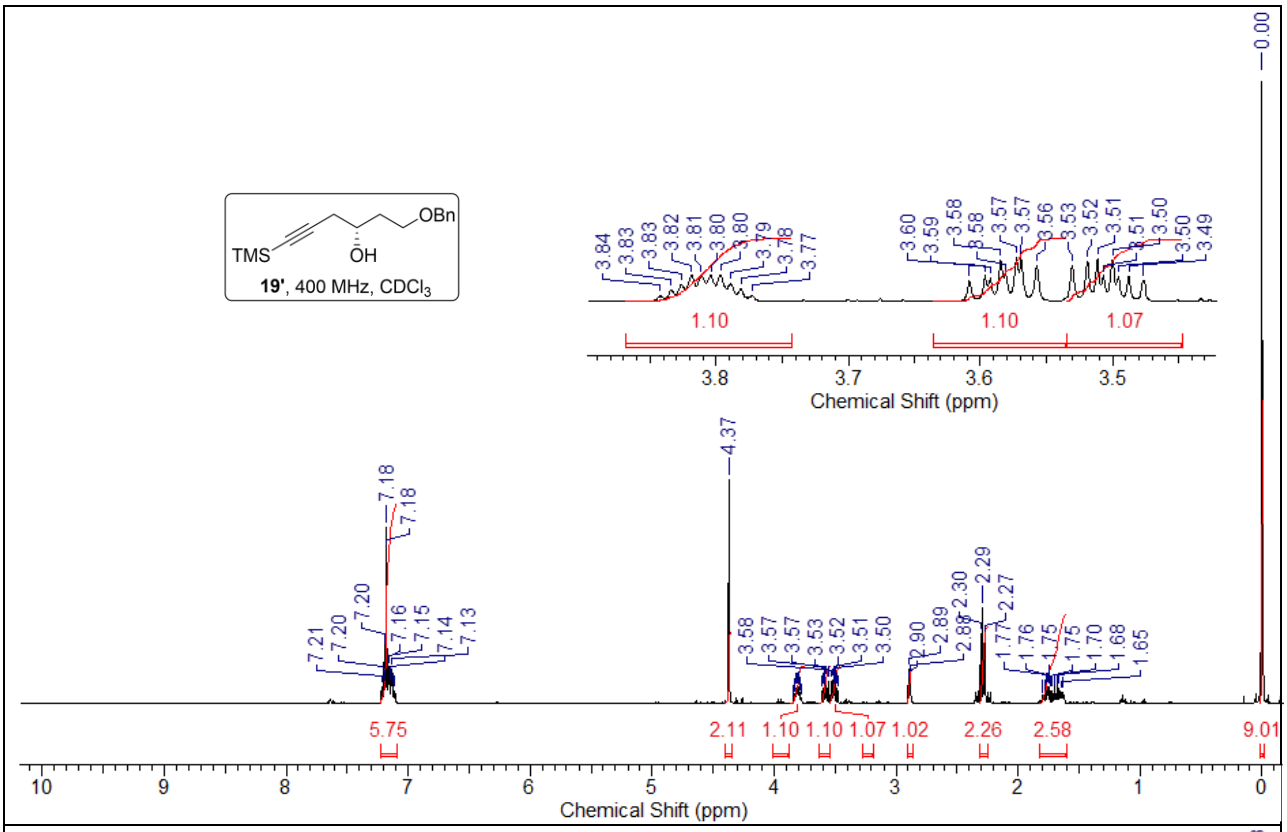


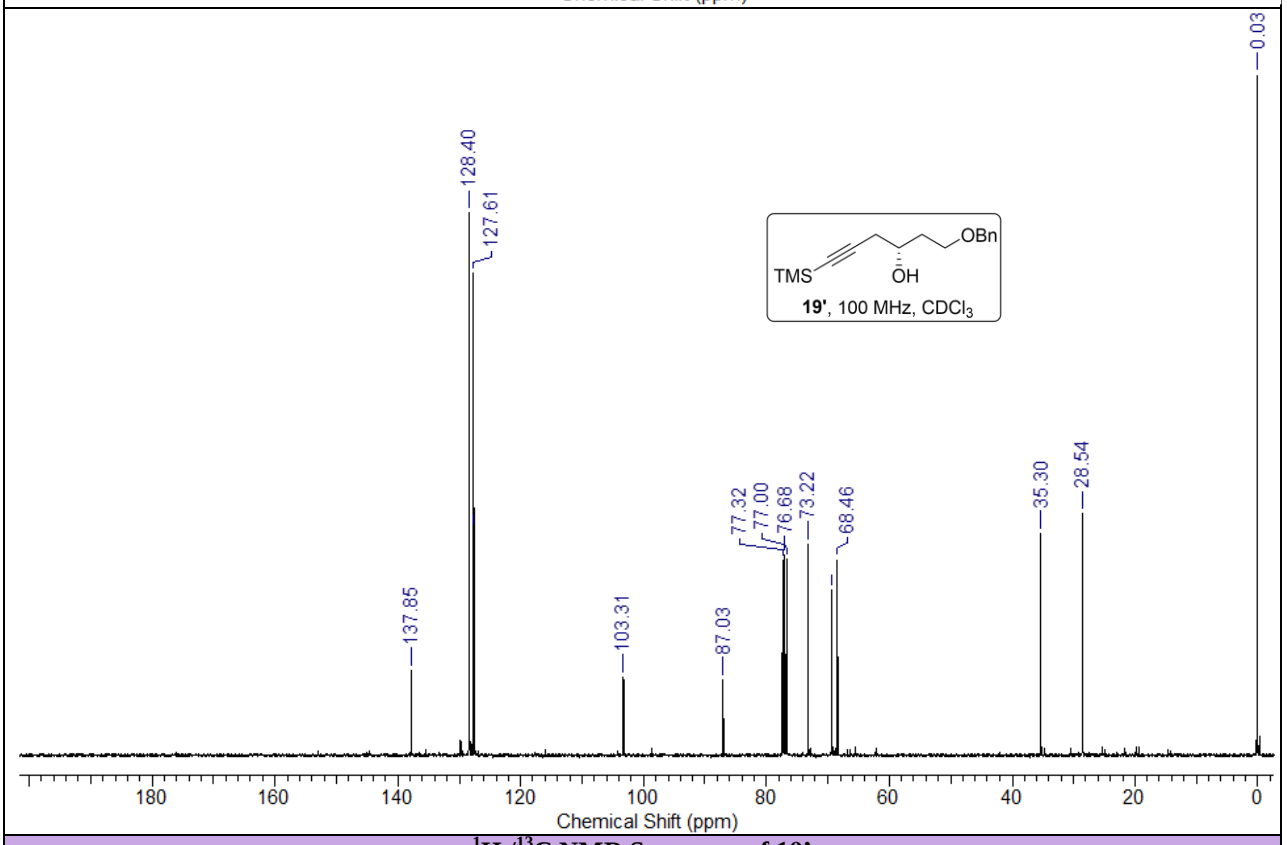
COSY & HSQC NMR Spectrum of 3b



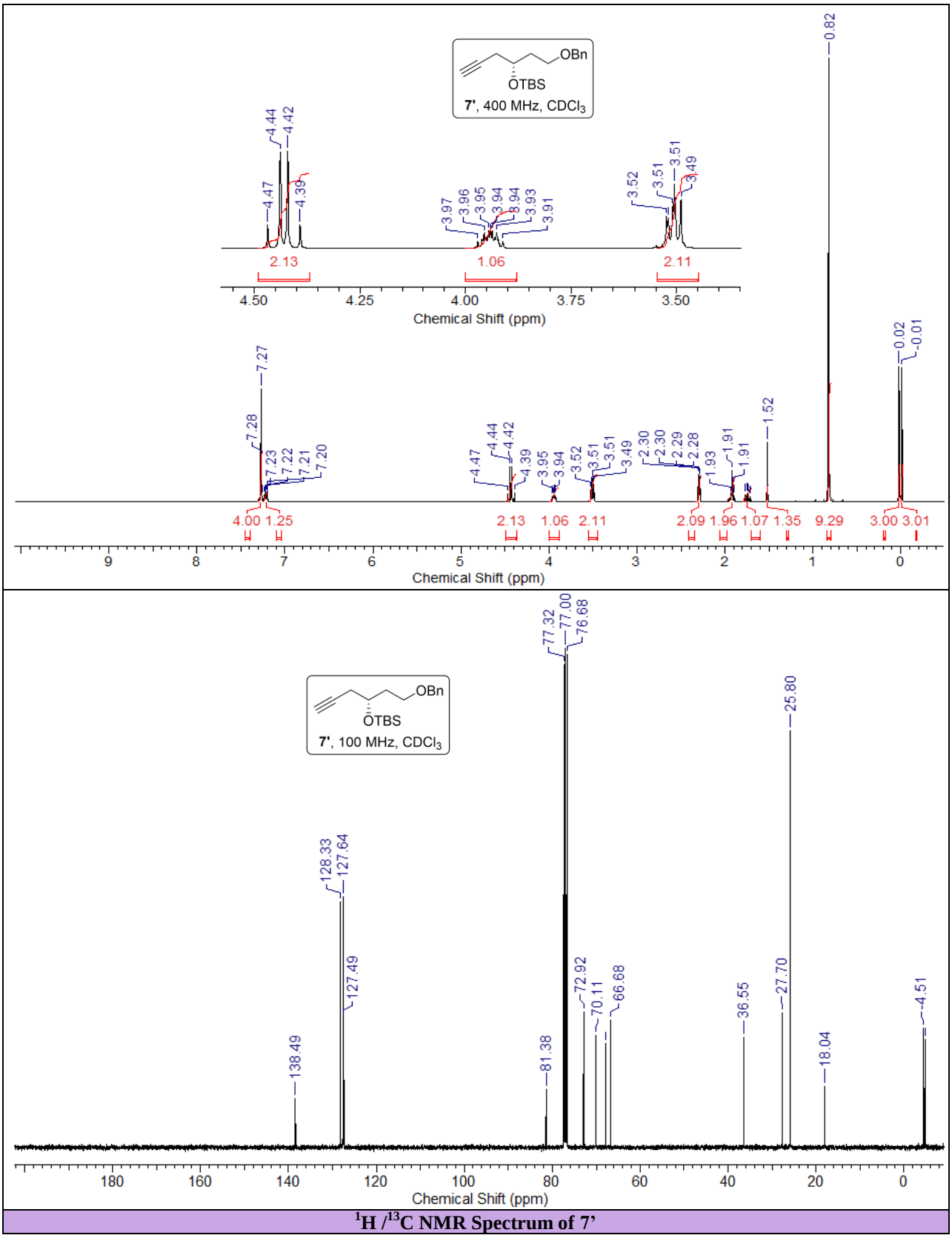


^{1}H /^{13}C NMR Spectrum of 18'

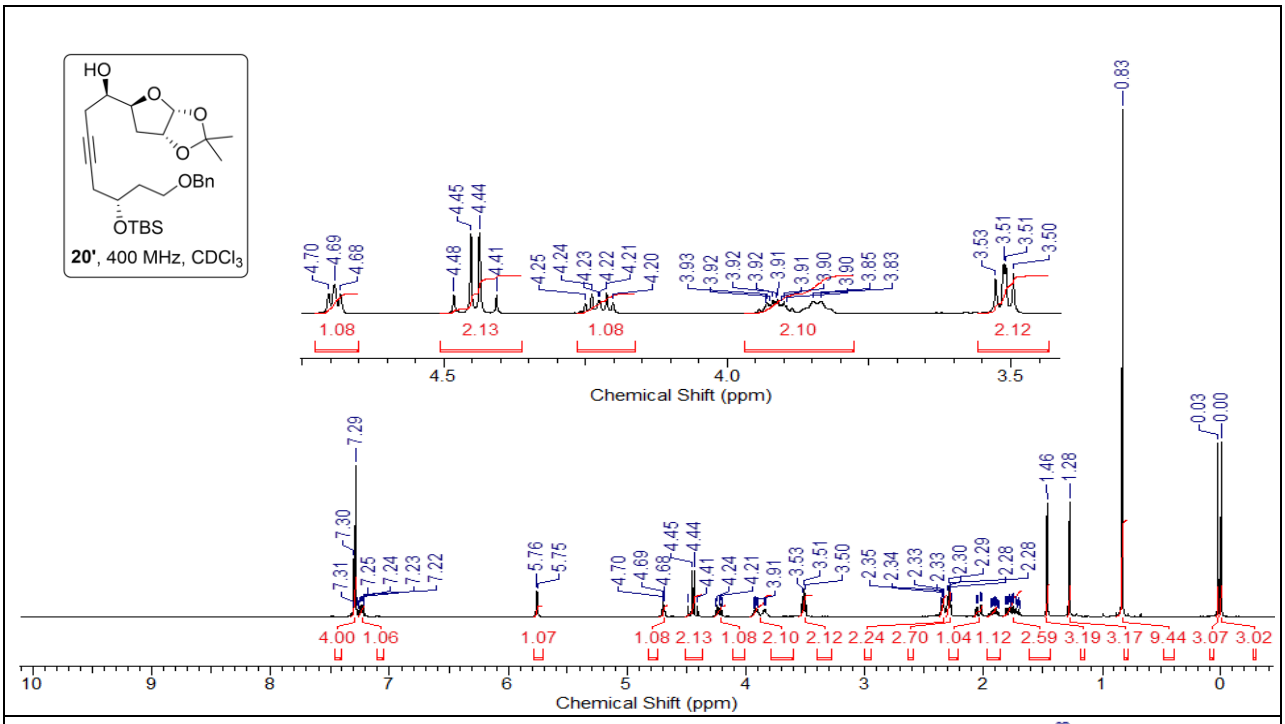


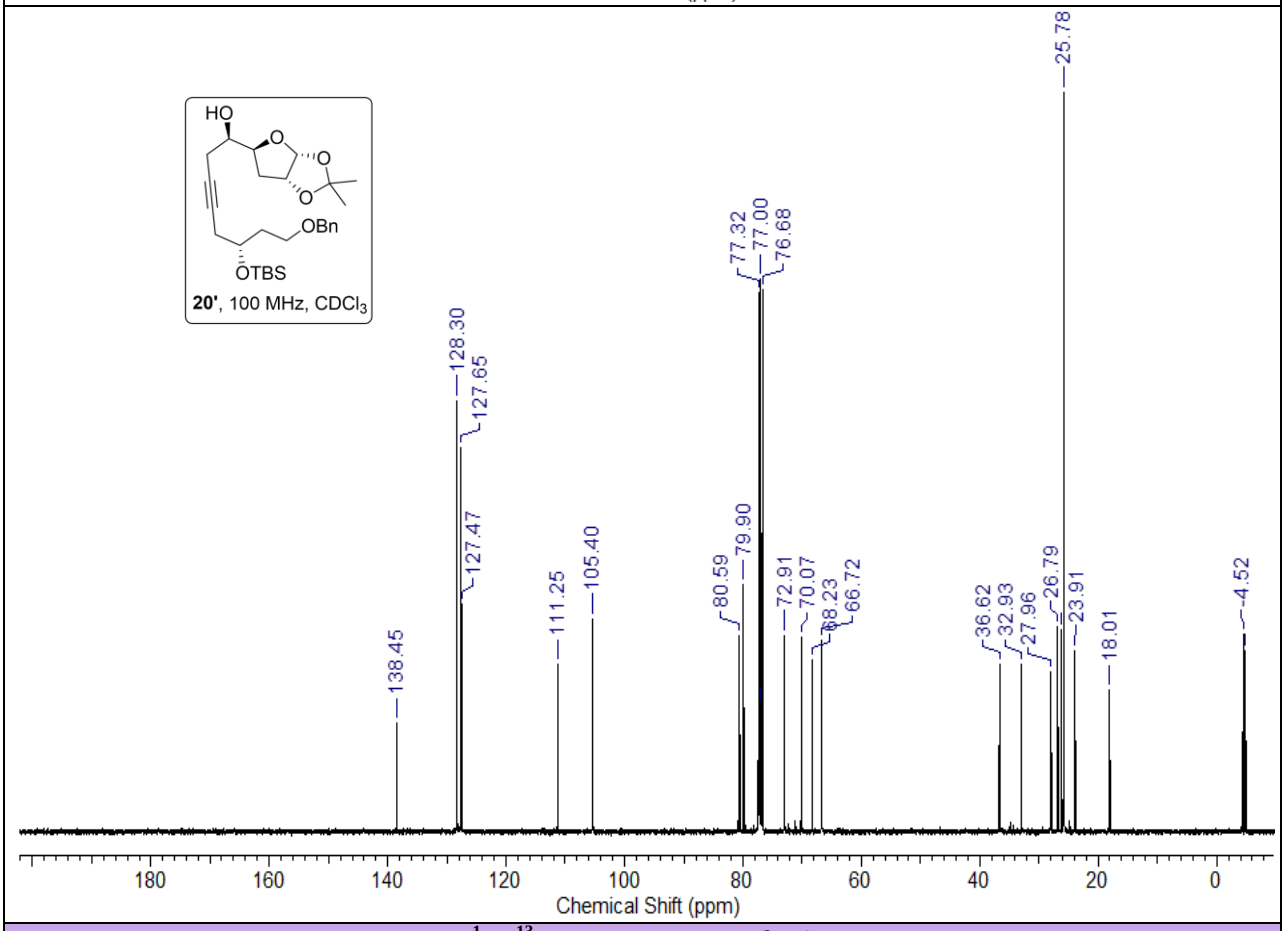


^{1}H /^{13}C NMR Spectrum of 19'

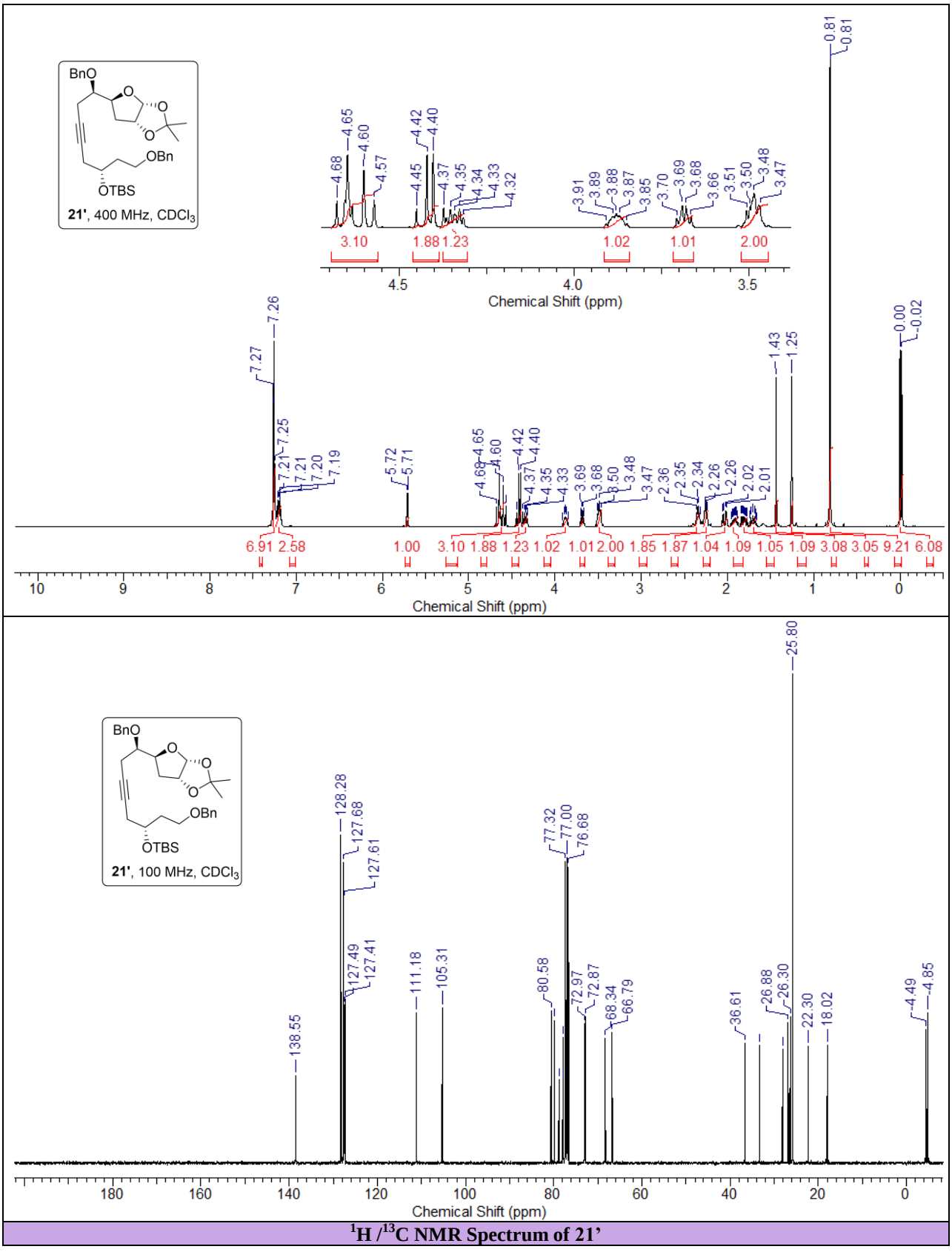


^{1}H /^{13}C NMR Spectrum of 7'





^{1}H /^{13}C NMR Spectrum of 20'



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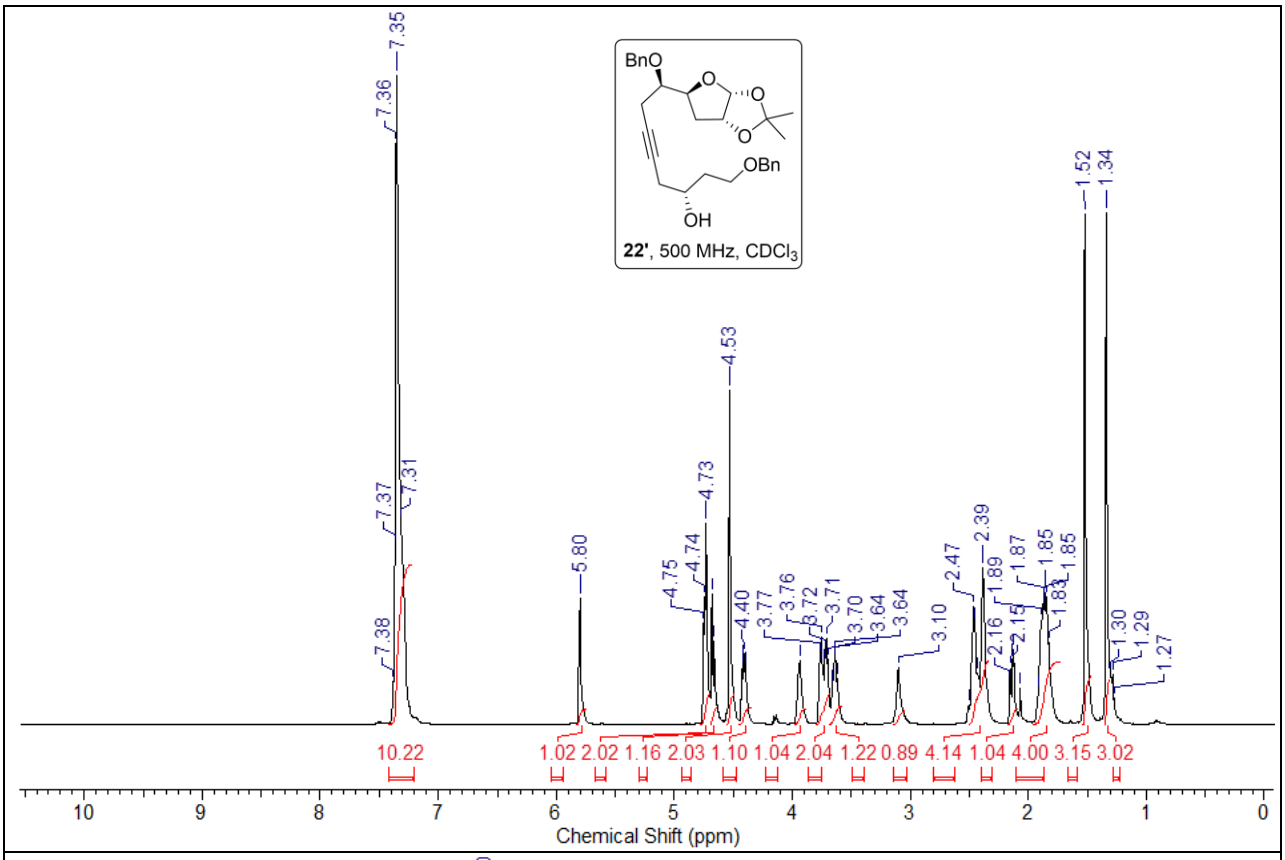
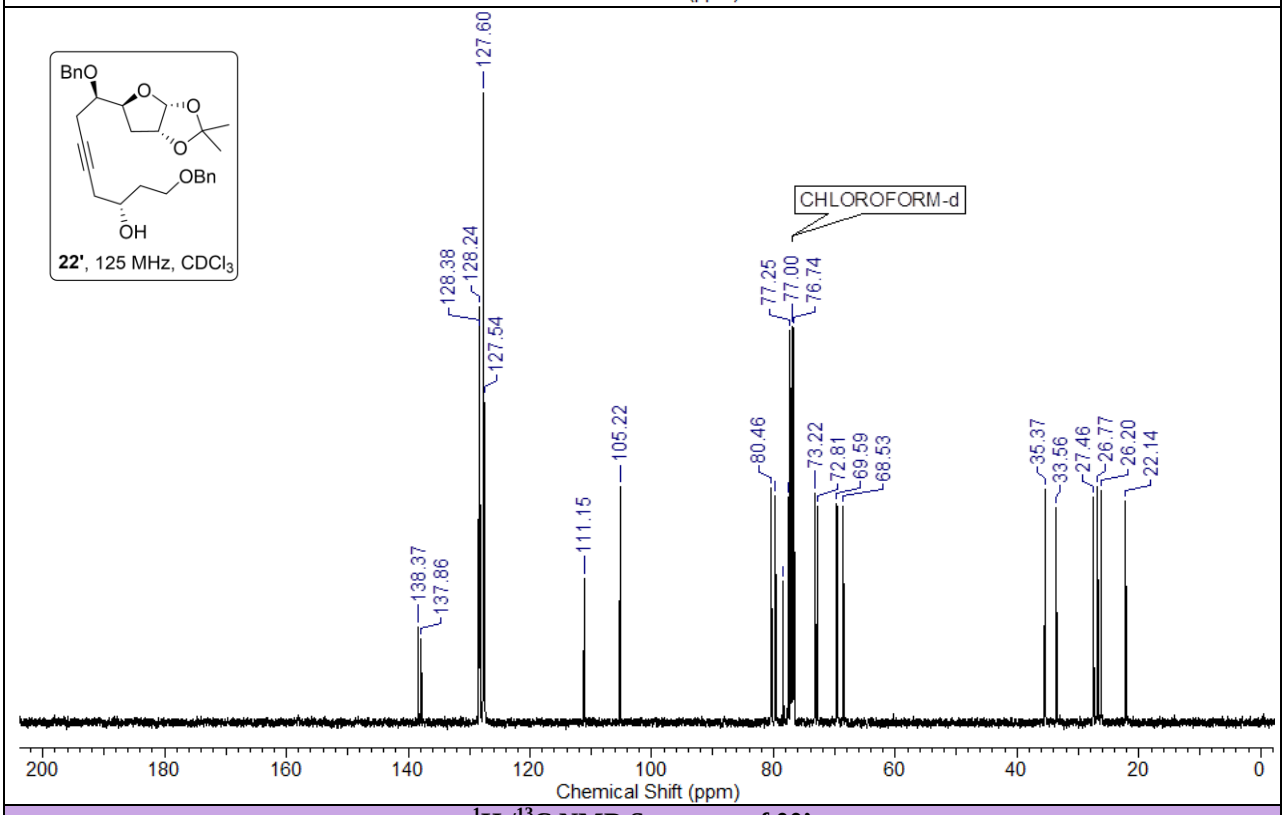
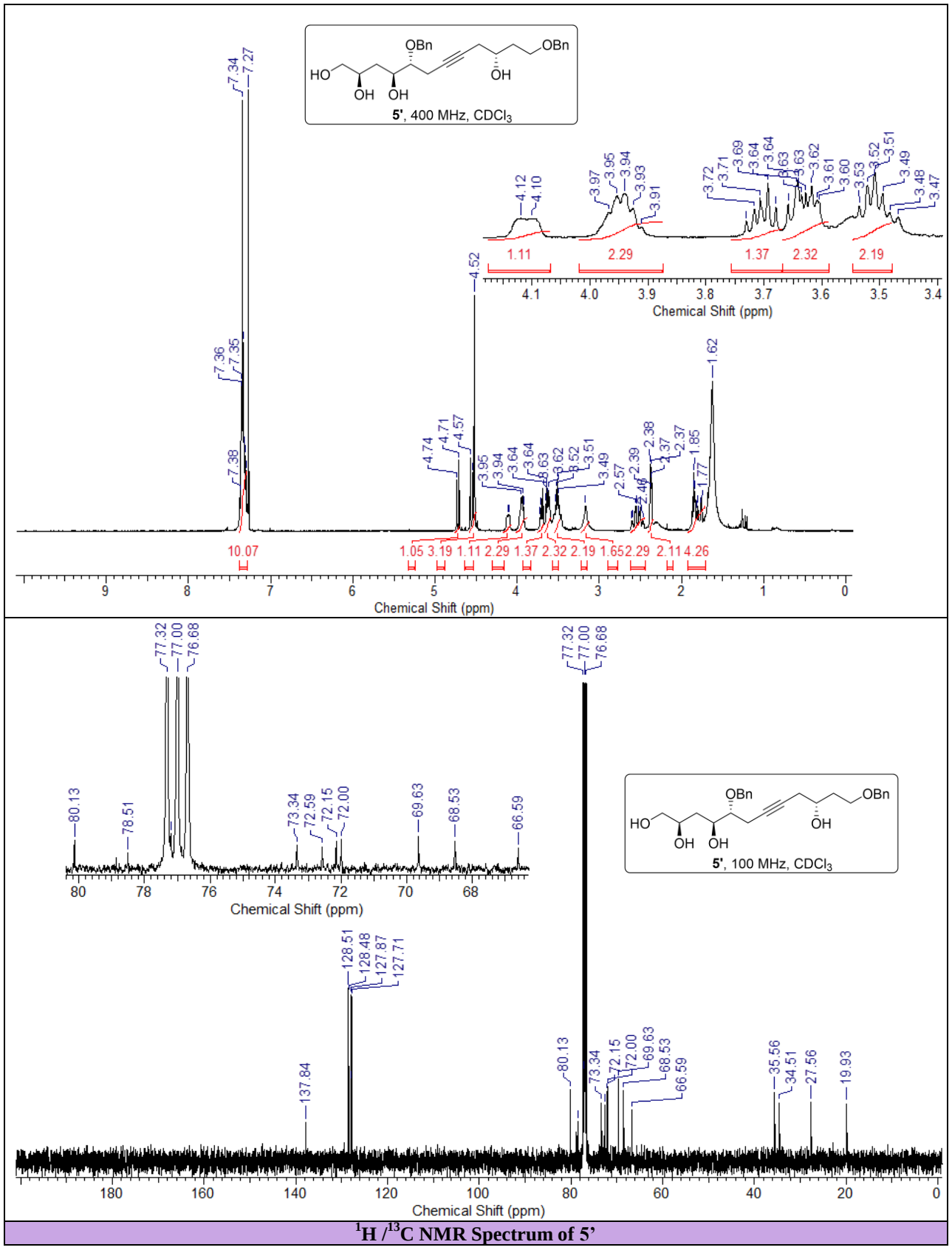




^{1}H /^{13}C NMR Spectrum of 22'



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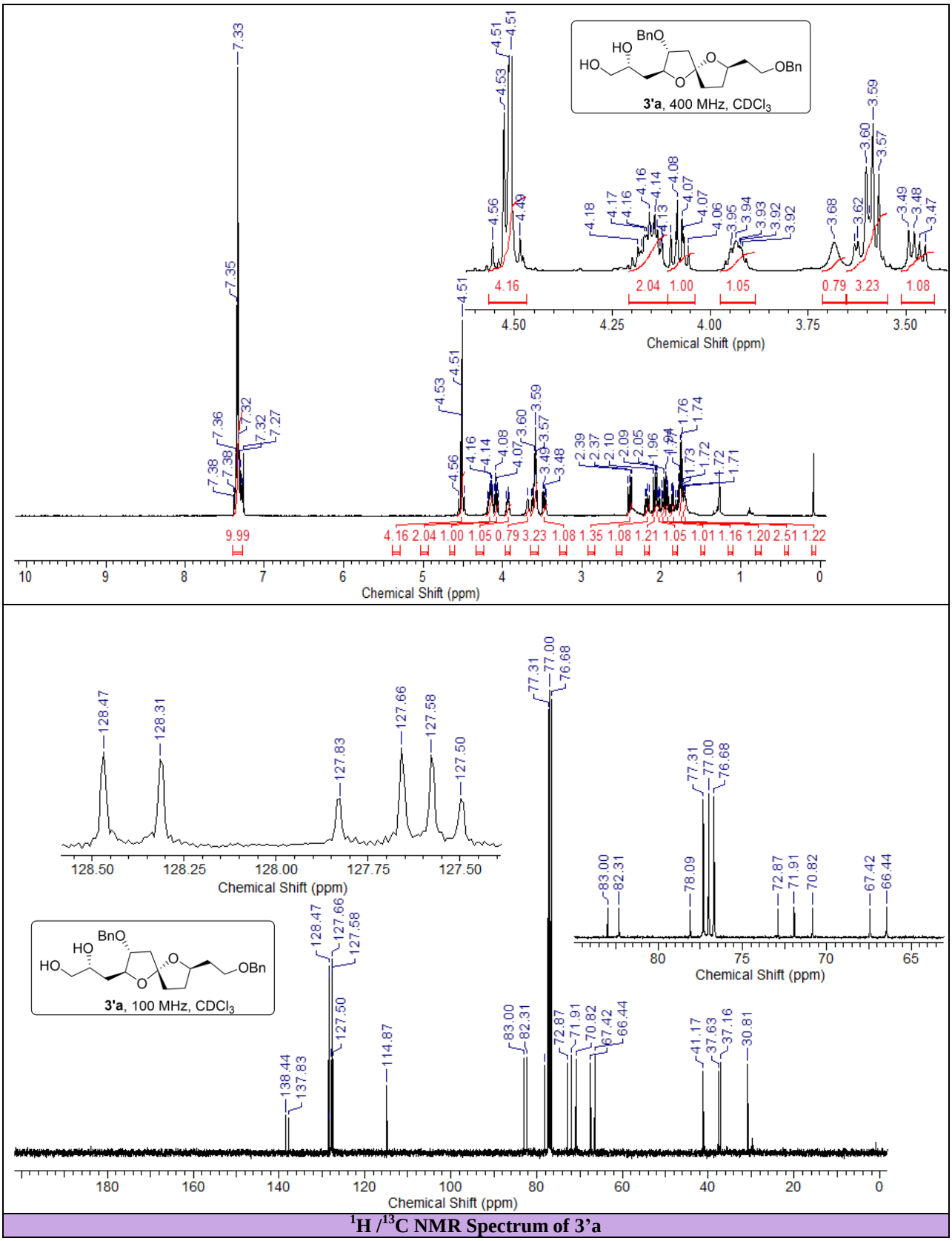
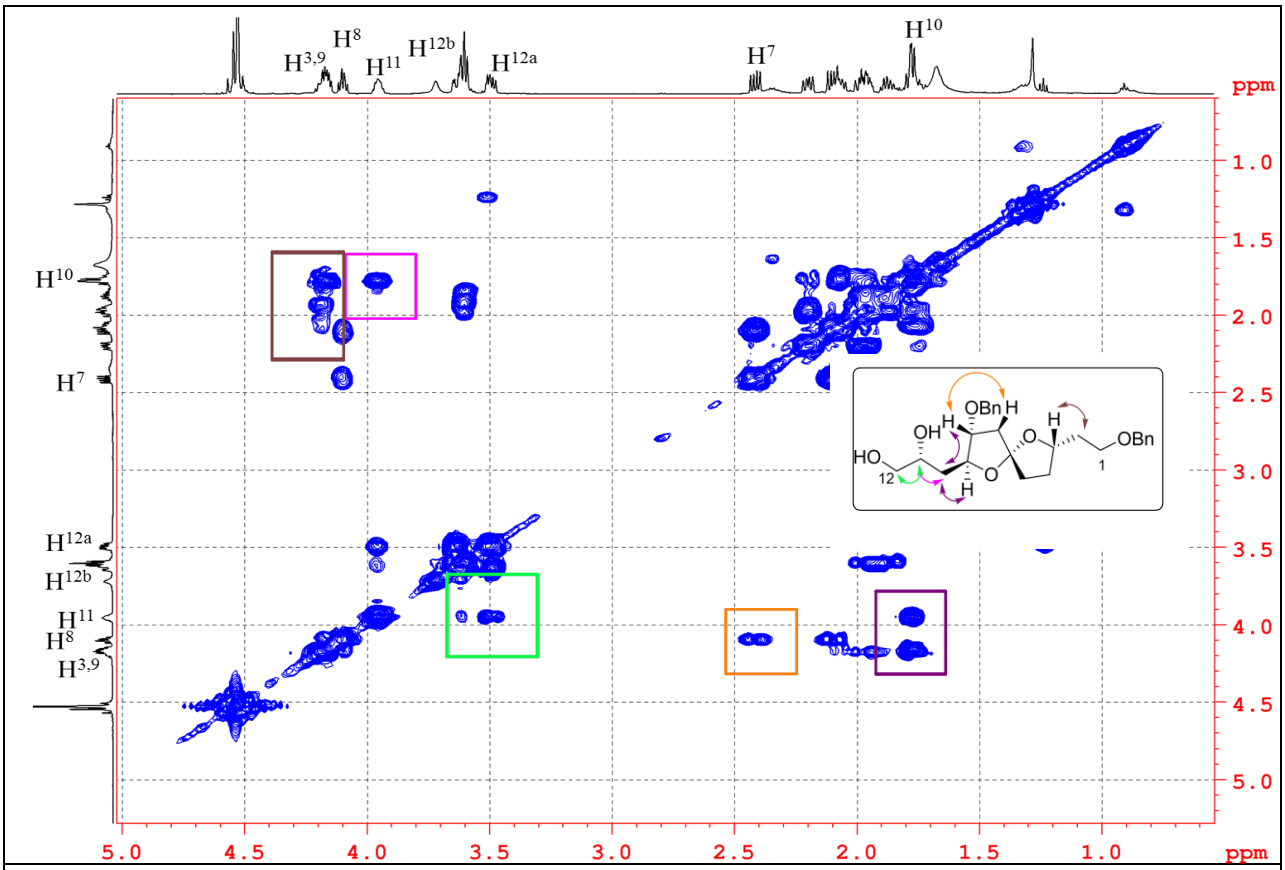
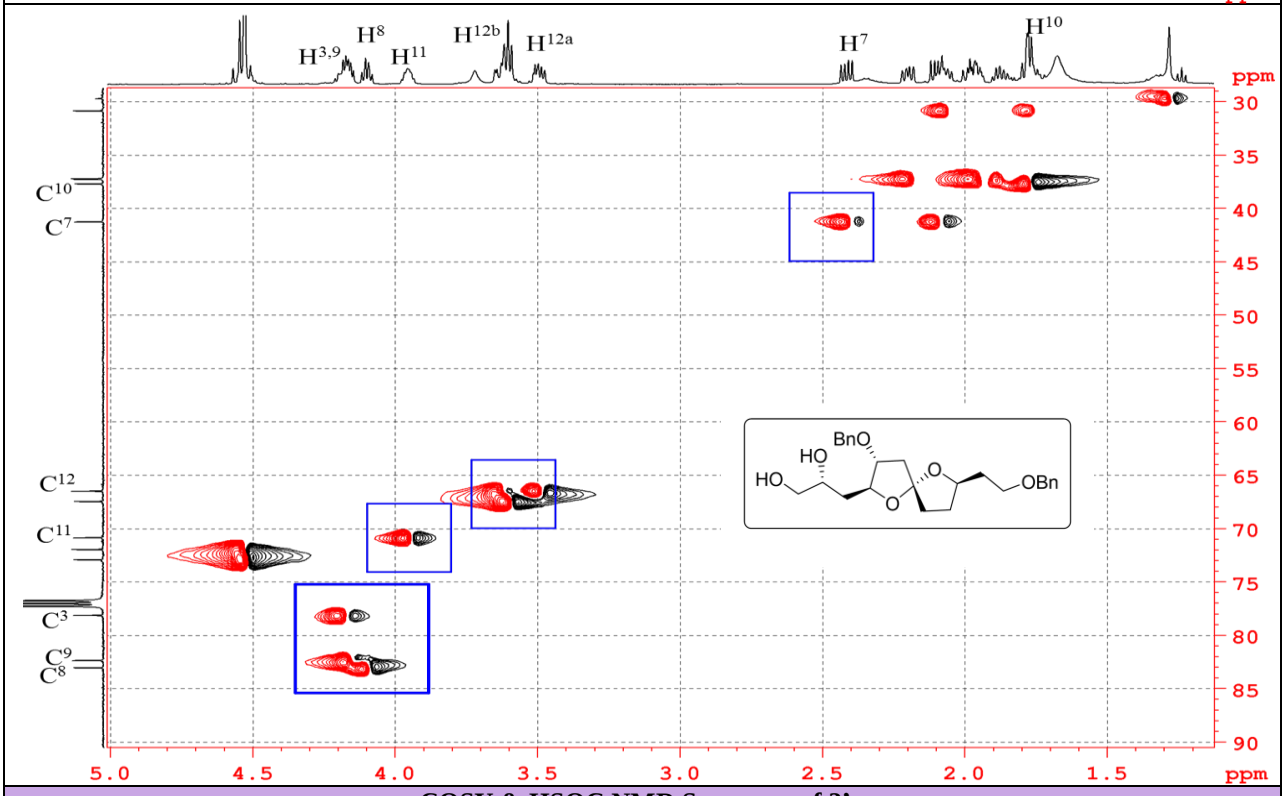
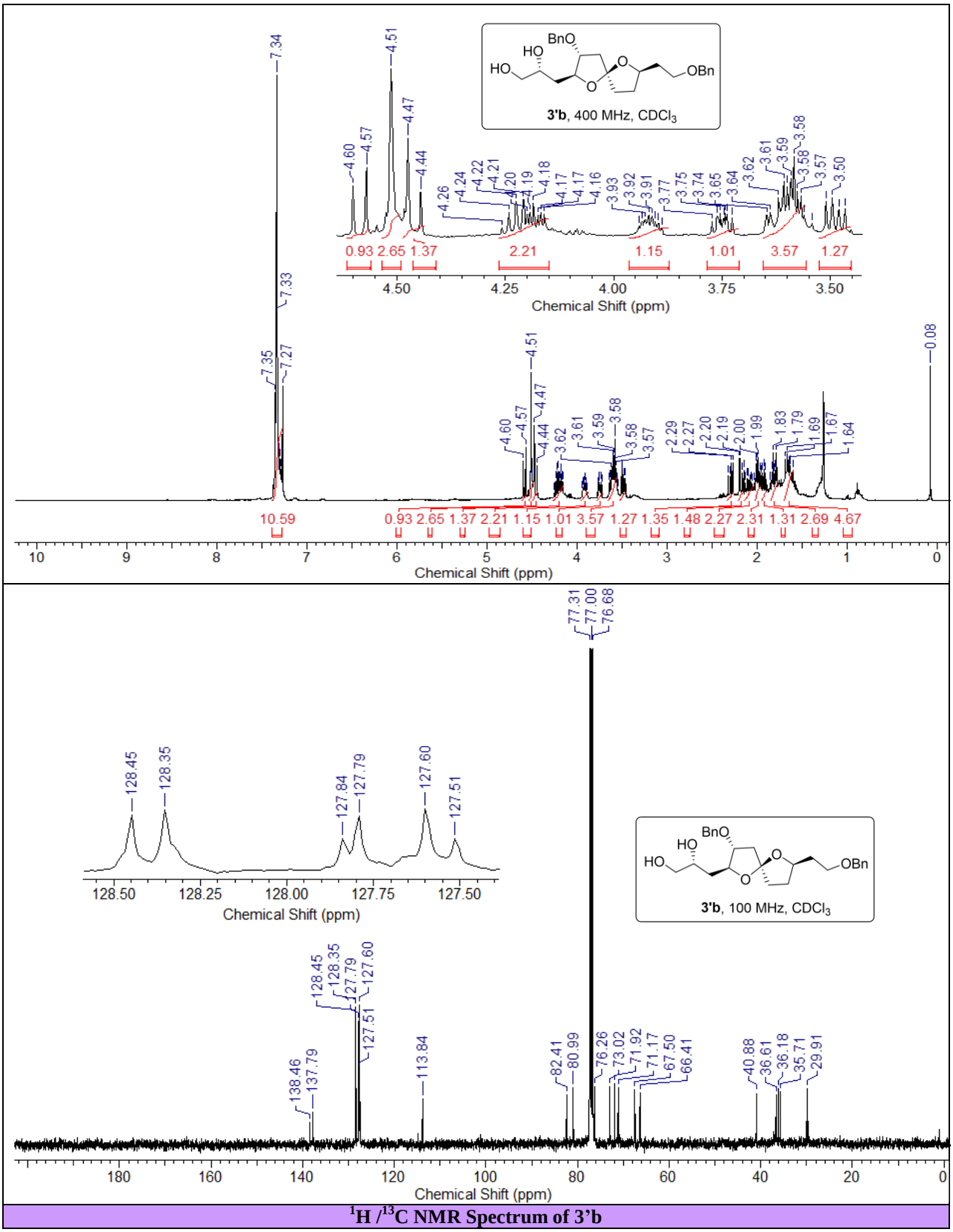


^{1}H /^{13}C NMR Spectrum of 3'a

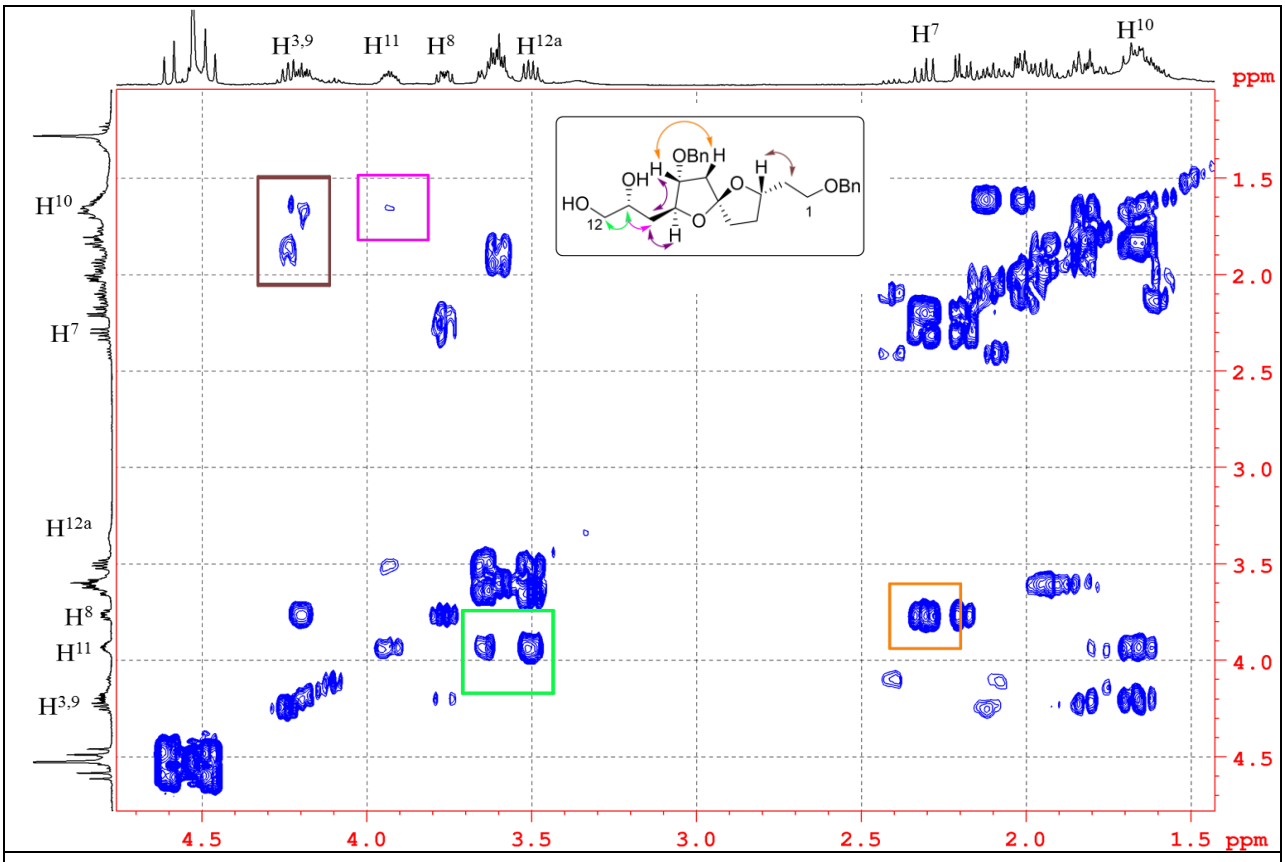


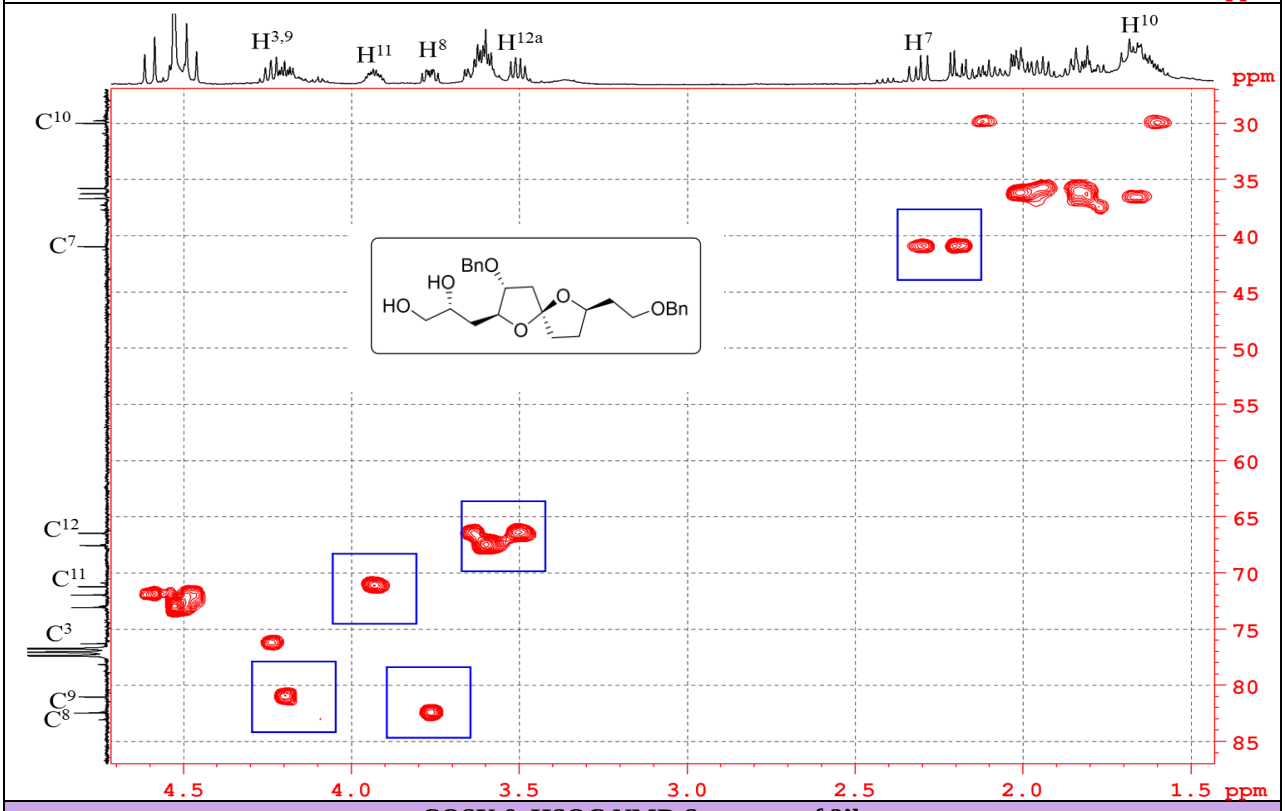


COSY & HSQC NMR Spectrum of 3'a

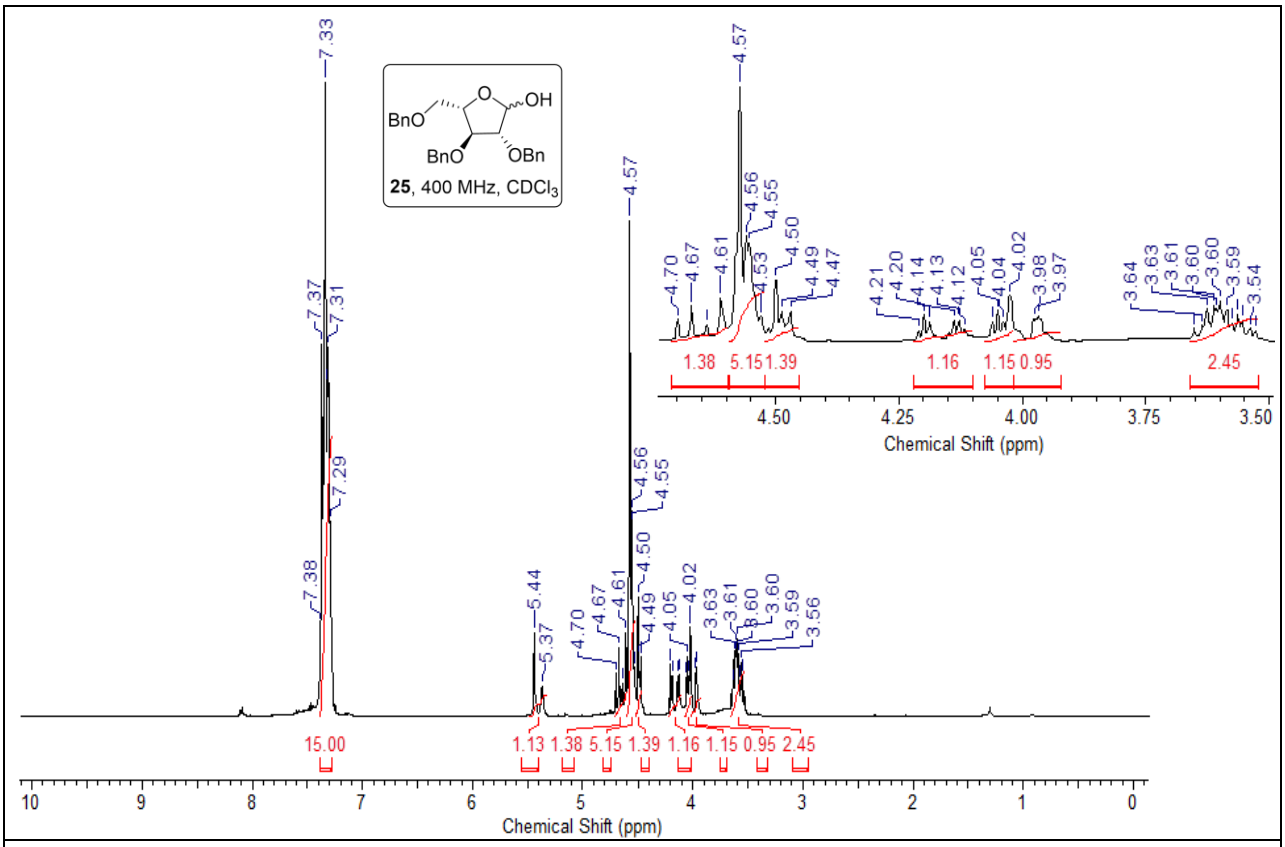


^{1}H /^{13}C NMR Spectrum of 3'b





COSY & HSQC NMR Spectrum of 3'b



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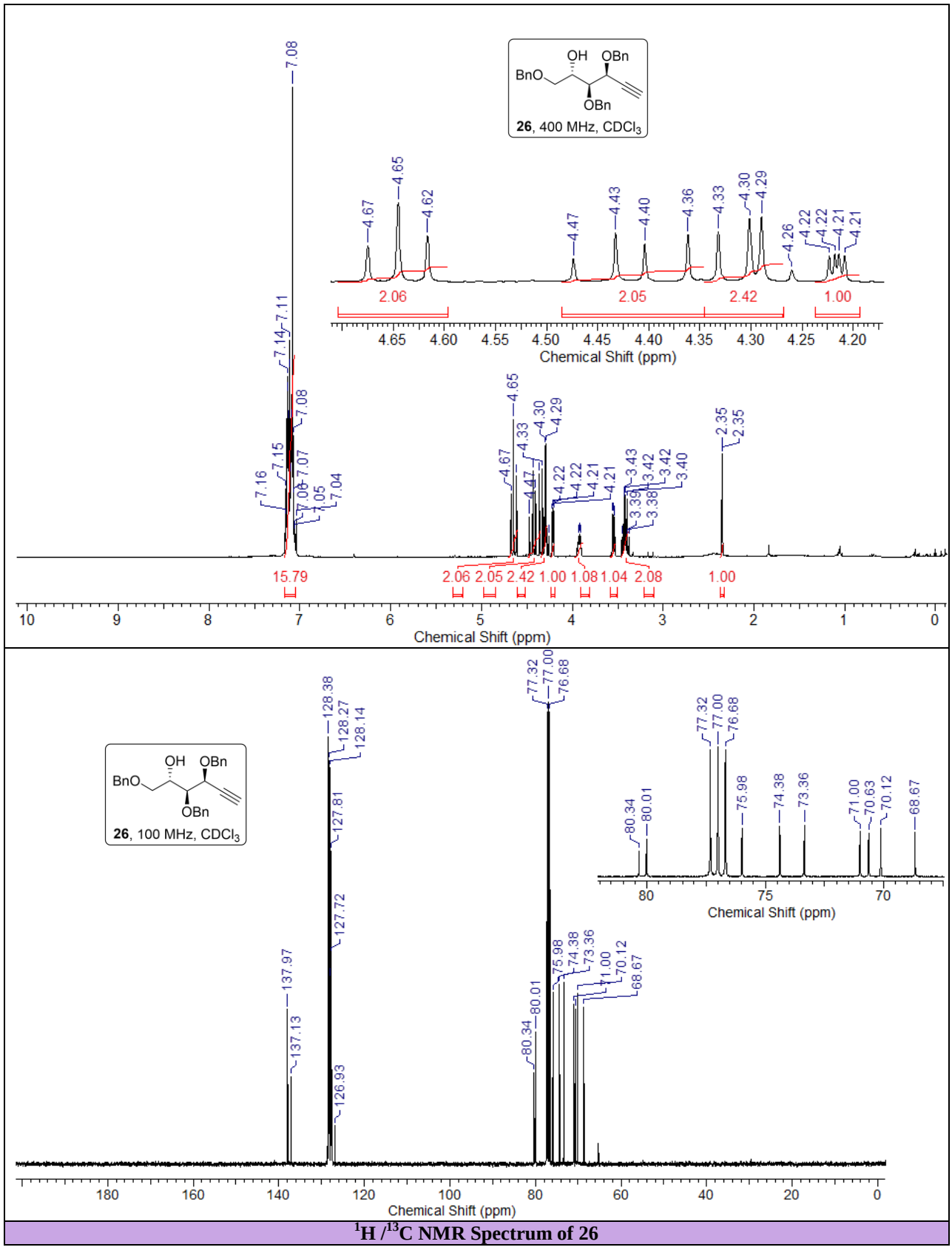
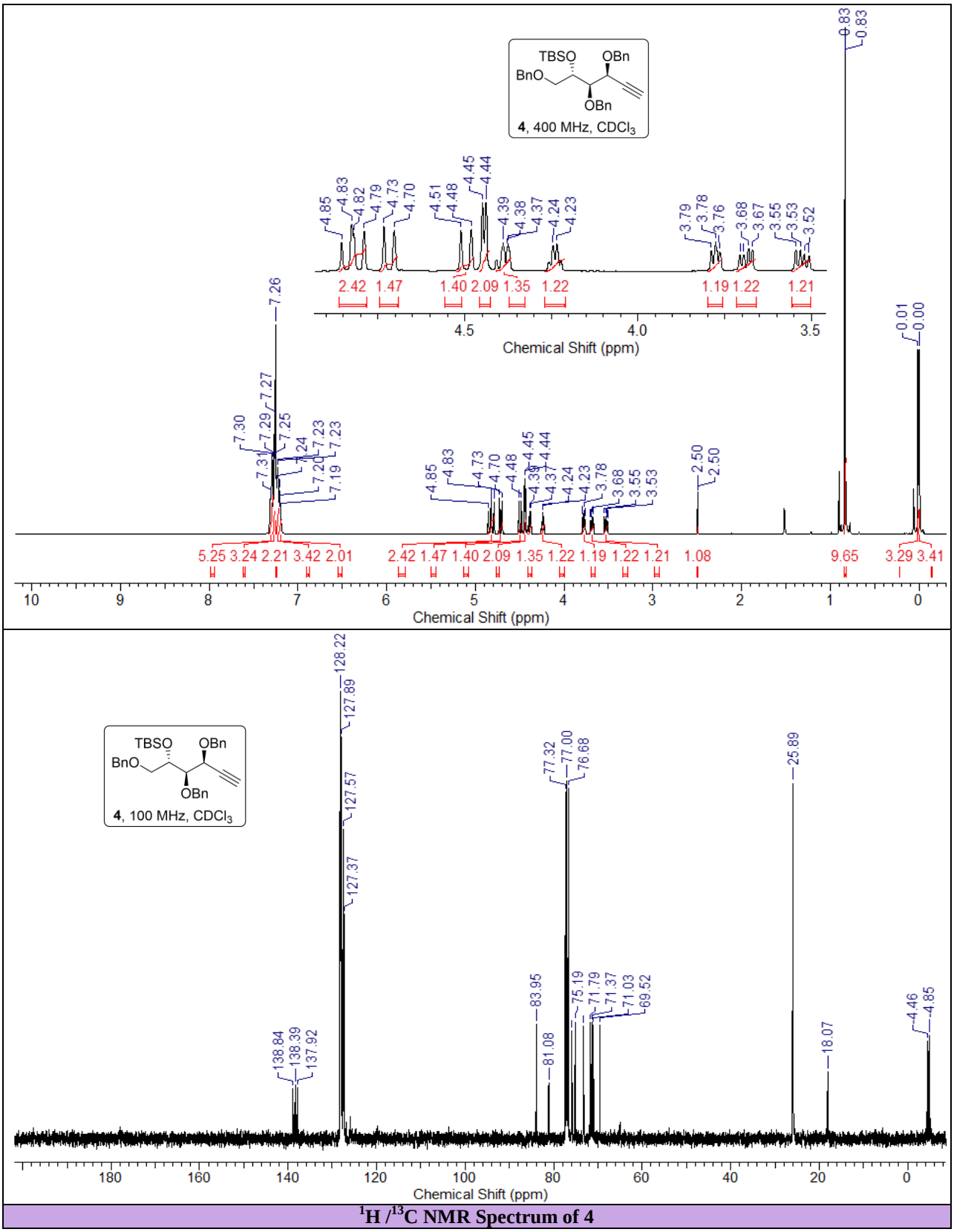


^{1}H /^{13}C NMR Spectrum of 26



^{1}H /^{13}C NMR Spectrum of 4

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ABSTRACT

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Registration No. : 10CC16A26017

Faculty of Study: Chemical Science

Year of Submission: 2022

AcSIR academic centre/CSIR Lab:

CSIR-National Chemical Laboratory, Pune

Name of the Supervisor(s): Dr. C. V. Ramana

Title of the thesis: Gold-Catalysed Cycloisomerization of Alkynols: Studies Toward the Total Synthesis of Mersicarpine and C35–C53 Fragment of Symbiospirols A/B/C

"Total synthesis" has an undeniable association with the progress of organic chemistry. The recent trends in chemical synthesis of natural products include transition metal catalysed cascade reactions to match the associated complexity. Gold-catalysed reactions are increasingly emerging in the literature over the past two decades. An interesting class of gold-catalysed reactions that needs a mention here are the cycloisomerization/cyclisation/hydroarylation processes. What we tried to address in this thesis is: intramolecular gold catalysed cycloisomerization/hydroarylation and the spiroketalization of suitable alkynols and the possibility of adding C, O, and N centred external nucleophiles to the *in situ* generated electrophiles. The developed protocols were investigated towards the total or fragment synthesis of natural products.

Chapter 1 deals with exploring the possibility of [Au]-catalysed cycloisomerization of indole tethered alkynols and the Lewis acid mediated C3 allylation of indole. The reaction involves 5-endo-alkynol cycloisomerization and the dearomative addition of indole C2 to the intermediate oxocarbenium cation, to result in two equilibrating fused and spiro pentacyclic intermediates, which upon treatment with allyl silane in the presence of $BF_3 \cdot OEt_2$, undergo selective indole C3 allylation. The other nucleophiles, such as hydride, azide and indole, were also found to be compatible with this process.

Next, the alkynol was modified in order to exploit the developed protocol in the total synthesis of mersicarpine. Accordingly, the desired spiro-pyridoindolone intermediate was successfully synthesised. However, the proposed Lewis acid mediated addition of nucleophiles to the benzylic spiro center failed. Further exploration or modifications of this approach to complete the total synthesis are underway in our laboratory.

Chapter 2 covers the [Au]-catalysed spiroketalization of carbohydrate derived tetrol and its utility towards the synthesis of C35 to C53 fragment of symbiospirols A/B/C. The corresponding tetrol was synthesised by employing chiral building blocks such as D-glucose and L-malic acid. The desired spiro diastereomers were successfully synthesised and characterised by 2D NMR spectroscopy.

LIST OF PUBLICATIONS

List of Publications Emanating from the Thesis Work

1. **Shinde M. H.**; Ramana, C. V. An Apparent Umpolung Reactivity of Indole through [Au]-Catalysed Cyclisation and Lewis-Acid-Mediated Allylation. *Chem. Eur. J.* **2020**, *26*, 17171–17175.
2. **Shinde M. H.**; Ramana, C. V. Facile synthesis of the spiro-pyridoindolone scaffold via a gold-catalysed intramolecular alkynol cyclisation/hydroindolylation. *Org. Biomol. Chem.* **2022**, *20*, 2086–2095.
3. **Shinde M. H.**; Ramana, C. V. Synthesis of Central Spiro-*bis*-THF Fragments of Symbiospirols A/B/C. (*Manuscript under preparation*).

List of Publications Non-Emanating from the Thesis Work

1. More G. V.; Malekar P. V.; Kalshetti R. G.; **Shinde M. H.**; Ramana, C. V. Ru-Catalyzed Asymmetric Transfer Hydrogenation of α-Acyl Butyrolactone via Dynamic Kinetic Resolution: Asymmetric Synthesis of bis-THF Alcohol Intermediate of Darunavir. *Tetrahedron Lett.*, **2021**, *66*, 152831–152834.

Patents- *Nil*

List of Posters presented with details

1. Feb 2019- National Science Day at CSIR-NCL (Received Best Poster Award)

and

2. Nov 2020- 1st Virtual JNOST Conference for Research Scholars

Title:[Au]-Catalysed Cycloisomerization and Allylation - Simple Access to Functionalized Indolo[1,2-*b*]isoquinolin-6(11*H*)-ones

Abstract: A one-pot Gold-catalysed indole-alkynol cycloisomerization and $BF_3.OEt_2$ mediated regioselective C3 allylation has been established for synthesis of functionalized indoloisoquinolinone scaffold. The reaction involves 5-*endo*-alkynol cycloisomerization and dearomative addition of indole to the intermediate oxocarbenium cation that results in the two equilibrating fused and spiro pentacyclic intermediates which upon treatment with allylsilane in presence of $BF_3.OEt_2$ undergoes selective indole C3 allylation.

List of Conference Attended with Details

1. December 2016- International Conference on Organic Synthesis (ICOS 21)-IIT Bombay
2. July 2019- SU CHEM YUVA-IICT Hyderabad
3. Nov 2019- NCL-Research Foundation Annual Students Conference-NCL Pune
4. January 2020- Advances Organic Synthesis (AOS)- IISER/NCL Pune

Umpolung

An Apparent Umpolung Reactivity of Indole through [Au]-Catalysed Cyclisation and Lewis-Acid-Mediated Allylation

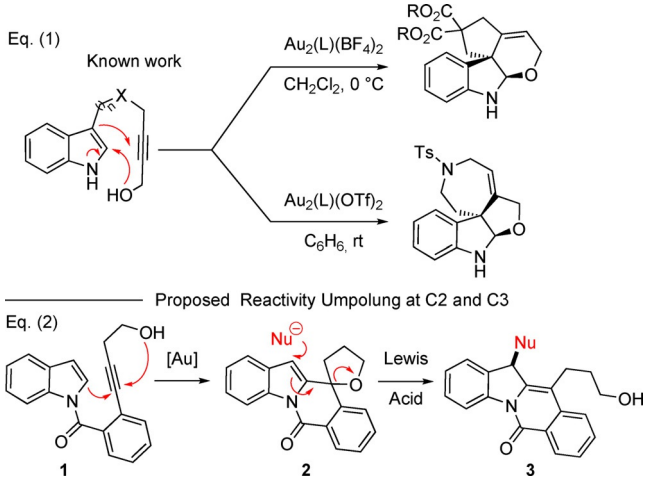
Mahesh H. Shinde[a, b] and Chepuri V. Ramana*[a, b]

Dedicated to Professor Pierre H. Dixneuf for his outstanding contributions to organometallic chemistry and Ru catalysis

Abstract: The sequential functionalization of indole C2 and C3 in an umpolung fashion was executed with a predesigned substrate and choice of reagents. The developed method comprises gold-catalysed alkynol cycloisomerisation/intramolecular addition of C2 of indole and subsequent BF_3·OEt_2-mediated regioselective C3 allylation, resulting in the synthesis of the functionalized indoloisoquinolinone scaffold. The reaction involves 5-*endo*-alkynol cycloisomerisation and the dearomative addition of indole C2 to the intermediate oxocarbenium cation, which results in two equilibrating fused and spiropentacyclic intermediates, which upon treatment with allyl silane in the presence of BF_3·OEt_2, undergo selective indole C3 allylation. Other nucleophiles, such as hydride, azide and indole, were also found to be compatible with this process.

Introduction

Indole is one of the privileged scaffolds present in a large number of active pharmaceutical ingredients and natural products.[1] Given their diverse and complex molecular architectures and importance in medicinal chemistry, the indole alkaloids have been attractive synthetic targets from the beginning.[2] As alkaloids of the indole class are characterized by their complex fused polycyclic frameworks, methods for the annulation around the indole nucleus have been explored in parallel to synthesis of the indole framework.[3] The inter/intramolecular trapping of indole C2 and/or C3 with electrophilic centres has been established as one of the promising approaches in this regard.[4] Specifically, the catalytic intramolecular hydroarylation of alkyne-tethered indoles in general, and by employing gold complexes in particular, has been well explored for (spiro)cycloannulations on indole templates.[5–9] These reactions proceed through indole dearomatization resulting from intramolecular addition of indole C3 on a π-activated gold complex, which leads to an iminium cation, which undergoes further reactions/rearrangement.[6] The strategic trapping of these iminium intermediates with an internal hydroxyl group [Eq. (1) in Scheme 1], revealed by Bandini and co-workers employing gold complexes, has emerged as a novel cascade cyclisation approach for the stereo/enantioselective synthesis of polycyclic indole scaffolds.[7] Similarly, Gong-Yang et al.[8] and Ohno[9] et al. have independently reported the gold-catalysed intramolecular tandem cyclisation of indole ynamides for the synthesis of the pyrrolo[2,3-*d*]carbazole core. The reported conventional ring formation and/or simultaneous 1,2- or 2,3-difunctionalization strategies on the indole-based skeleton[8–10] proceed through classical indole reactivity, that is, indole C3 acts as a nucleophile and C2 as an electrophilic centre. In this context, we hypothesised the possibility of inverting this reactivity through sequential functionalization of indole C2 and C3 with electrophilic and nucleophilic centres, respectively.[11]



Scheme 1. Gold-catalysed indole–alkynol cyclisation and the proposed reactivity umpolung at indole C2 and C3 through sequential functionalization.

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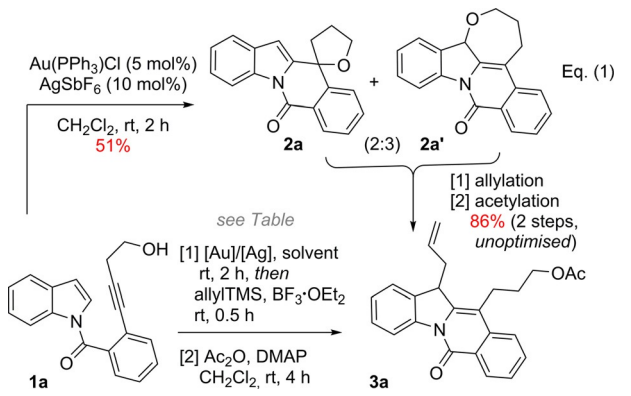
As shown in Scheme 1, we reasoned that *N*-[2-(4-hydroxy-but-1-yn-1-yl)benzoyl indoles when treated with a cationic gold complex should undergo an initial alkynol cyclisation followed by intramolecular indolylation (at C2),[5] leading to an indolo[1,2-*b*]isoquinolin-6(12*H*)-one bearing spiro-fused tetrahydrofuran at C4 of the isoquinolinone unit.[5–9] Subsequently, this intermediate, when treated with an external nucleophile such as allyl silane, should undergo an S_N2' reaction by addition at C3 of indole. This is an interesting proposal, as most of the reported indole allylations involve either electrophilic allylic sources or an internal Claisen rearrangement.[12]

Results and Discussion

For this proposition, the requisite substrate **1a** was prepared by *N*-benzoylation of indole with 2-iodobenzoic acid, followed by Sonogashira coupling with 3-butyn-1-ol, and subjected to cyclisation in the presence of 5 mol% $Au(PPh_3)Cl$ as catalyst and 10 mol% $AgSbF_6$ additive in dichloromethane at room temperature.[13] The starting compound **1a** disappeared completely within 2 h with the formation of two new products, as evidenced by TLC [Table 1, Eq. (1)]. The separation of these two compounds was found to be tedious, and they also appeared to be interconverting in $CDCl_3$ within a couple of hours. With great difficulty, the clean spectral data of these compounds could be obtained to establish the proposed structures. One of the compounds, **2a**, was found to be the proposed spirocyclic derivative, and the structure of the other compound, **2a′**, was determined to be a pentacyclic fused oxepane, which was further confirmed by single-crystal XRD.

Table 1. Reaction optimisation.



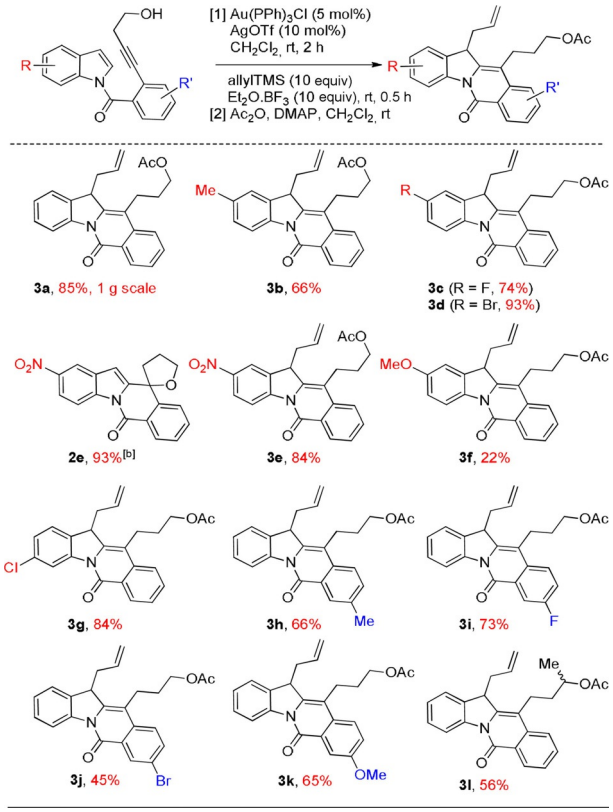
Entry	[Au] 5 mol%	[Ag] 10 mol%	Solvent	t[b] [h]	Yield of **3a** [%]
1	$Au(PPh_3)Cl$	$AgSbF_6$	CH_2Cl_2	2	51
2	$AuCl_3$	$AgSbF_6$	CH_2Cl_2	12	trace
3	$AuBr_3$	$AgSbF_6$	CH_2Cl_2	12	trace
4	*i*PrAuCl	$AgSbF_6$	CH_2Cl_2	12	hydration
5	$PtCl_4$	–	CH_2Cl_2	2	41
6	$Au(PPh_3)Cl$	$AgSbF_6$	$(CH_2)_2Cl_2$	2	52
7	$Au(PPh_3)Cl$	$AgSbF_6$	1,4-dioxane	2	58
8	$Au(PPh_3)Cl$	$AgSbF_6$	CH_3CN	2	–
9	$Au(PPh_3)Cl$	AgTFA	CH_2Cl_2	4	–
10	$Au(PPh_3)Cl$	Ag_2CO_3	CH_2Cl_2	4	–
11	$Au(PPh_3)Cl$	AgOTf	CH_2Cl_2	2	79
12	$Au(PPh_3)Cl$	$AgNTf_2$	CH_2Cl_2	4	54

[a] Reaction conditions: alkynol (1 equiv) in CH_2Cl_2 (3 mL) under argon, $Au(PPh_3)Cl$ (5 mol%), Ag salt (10 mol%) at RT for 2 h, trimethylallylsilane (allylTMS, 10 equiv), $BF_3{\cdot}OEt_2$ (10 equiv), Ac_2O (1 equiv), 4-dimethylaminopyridine (DMAP, 1 equiv), CH_2Cl_2 (5 mL). [b] Time for the [Au]-catalysed cyclisation.

The observed interconversion of these compounds in $CDCl_3$ reveals that the cleavage of the C–O bond in both **2a** and **2a′** is facile, and indicates that an intermediate allyl cation is readily formed. This prompted us to examine the allylation of purified and/or mixture of **2a** and/or **2a′** with an excess of trimethylallylsilane in the presence of $BF_3{\cdot}OEt_2$. Initially, we tried to isolate the allylation product, but it was found to be unstable on silica gel. To overcome this, the crude alcohol, subsequently isolated after work-up, was subjected to acetylation to obtain exclusively compound **3a** in up to 86% yield over two steps. The spectral data of the product **3a** clearly revealed the formation of an isoquinolin-1-one with a pendant allyl group at C3 and that the indole nucleus underwent dearomatization.

With this encouraging result in hand, next we examined combining both cyclisation with $Au(PPh_3)Cl/AgSbF_6$ and subsequent allylation in one pot. After exploring a couple of conditions, the addition of 10 equiv of each allyl silane and $BF_3{\cdot}OEt_2$ led to the complete consumption of the intermediates **2a**/**2a′** resulting from the initial cyclisation. The resulting crude alcohol isolated after work-up was subjected to acetylation to obtain the acetate **3a** in 51% overall yield (Table 1). Subsequent optimisation experiments identified (in)compatible [Au] complexes/additives for the initial cyclisation. As shown in Table 1, when $AuCl_3$ or $AuBr_3$ was employed as catalyst, the initial cyclisation itself was not facile. In the case of *i*PrAuCl/$AgSbF_6$, the cyclisation resulted in the formation of an inseparable 2:1 mixture of ketone **4a** (resulting from the alkyne hydration beta to the phenyl ring) and the known 3-(2-hydroxyethyl)-1*H*-isochromen-1-one[14] (resulting from either a 6-*endo*-dig cyclisation with the amide carbonyl group with concomitant amide bond cleavage or intramolecular lactonisation of the enol ether of the hydration product; see Scheme S1, Supporting Information). With $PtCl_4$, too, the reaction was facile, but the final product was isolated in poor yield. Also, the reaction seemed to be facile in 1,2-dichloroethane and 1,4-dioxane, in which it provided average yields (52 and 58%). However, there was no reaction in acetonitrile. For the same [Au] complex, when other silver additives were screened, it was observed that there was no reaction with silver trifluoroacetate (AgTFA) or Ag_2CO_3. With AgOTf, the product **3a** was isolated in 79% yield, whereas $AgNTf_2$ gave the final product **3a** in 54% yield. The possibility of effecting the initial cyclisation with $BF_3{\cdot}OEt_2$ as well as with other Lewis acids, such as $Sc(OTf)_3$, $Cu(OTf)_2$, $In(OTf)_3$, $InCl_3$, $Hg(OTf)_2$ and $Bi(OTf)_3$, revealed that they were not suitable for the current transformation.

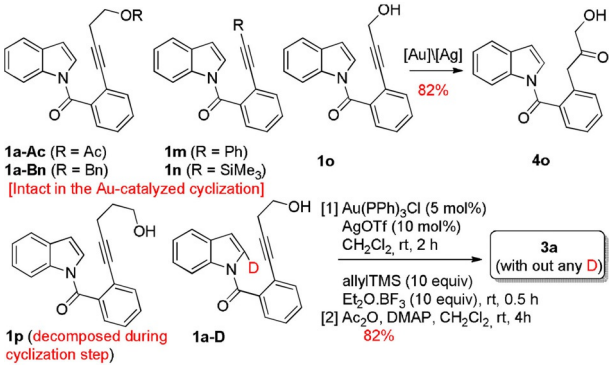
Having realised the simultaneous umpolung functionalization of indole C2 and C3, we next proceeded to generalise the scope of this reaction by employing alkyne substrates **1b**–**1k** having different substituents on indole and benzoic acid rings (Scheme 2). The reaction outcome seems to be influenced by the substituents, especially those on the indole ring. As shown in Scheme 2, substrates **1c**–**1e** having electron-withdrawing



Scheme 2. Substrate scope for the gold-catalysed cyclisation–allylation reaction.[a] [a] All reactions were carried out by employing 150 mg of alkynol substrate, and yields of isolated products are given. [b] Isolated after the initial [Au]-catalysed cyclisation.

groups at C5 of the indole ring gave better results (74–93%) compared with the corresponding methyl- and methoxy-substituted derivatives **1b** (66%) and **1f** (22%). Even with the substrate **1g** having a C6–Cl bond, the yield was excellent. Interestingly, with the C5-nitro substrate **1e**, the initial cyclisation gave exclusively the spiro derivative **2e**, which was found to be stable. In the case of substrates **3h**–**3k** having different substituents on the benzoyl ring situated *para* to the alkyne group, the yields were very good, with both electron-withdrawing and electron-donating groups. The reaction of the starting material having a secondary alcohol group under standard conditions yielded an inseparable mixture of diastereomers **3l** in 56% yield. Finally, to show the utility of the current methodology, the cyclisation/allylation of substrate **1a** was performed on 1 g scale. The reaction proceeded smoothly, and the yield of product **3a** was improved further from 79 to 85%.

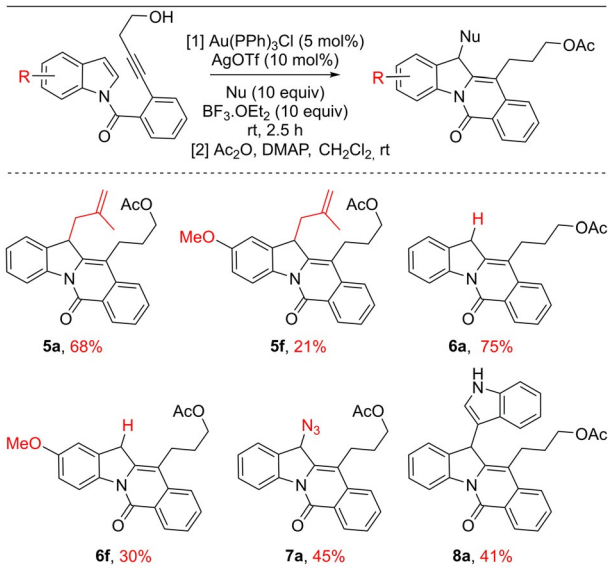
As a control and to understand the compatibility/course of the reaction, substrates having different substituents on the alkyne terminus were synthesized, and their [Au]-catalysed intramolecular hydroarylation reaction under the current conditions was examined. As shown in Scheme 3, the acetyl- and benzyl-protected alkynols **1a-Ac** and **1a-Bn** were found to be intact under these conditions. This clearly revealed that the presence of an OH group is essential for successful cycloisomerisation/indolylation and, importantly, the current domino process seems to be initiated by an alkynol cyclisation.



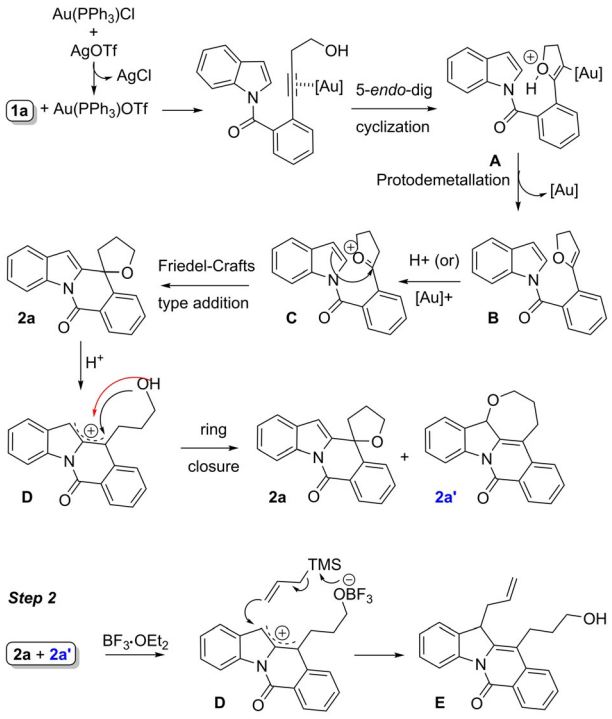
Scheme 3. Control experiments.

This was further supported by the control experiments with the phenyl- and trimethylsilyl-substituted alkynes **1m** and **1n**, respectively, which were also found to be intact under the current conditions. Interestingly, when the one-carbon truncated (**1o**) and homologated (**1p**) alkynols were employed as substrates, the hydration at the carbon atom next to the hydroxymethyl group was the major event, with alkyne **1o** providing compound **4o** and formation of a complex mixture being observed in case of the homologated alkyne **1p**. Interestingly, when the C2-deuterated analogue of **1a** was employed, product **3a** (without any deuterium label) was obtained exclusively, that is, there was no hydride-migration event.[8]

Next, we examined the compatibility of other nucleophiles such as methallyltrimethylsilane, Et_3SiH, Me_3SiN_3 and indole in the current sequence with alkynes **1a** and **1f**. As shown in Scheme 4, with the unsubstituted substrate **1a**, the reactions with all four nucleophiles were facile and provided the corresponding isoquinolin-1-ones in moderate to good yields. However, with the methoxy-bearing substrate **1f**, in general the re-



Scheme 4. Nucleophile scope in the gold-catalysed cyclisation–allylation reaction.



Scheme 5. Possible mechanism.

actions were sluggish and resulted in an intractable mixture when Me_3SiN_3 and indole were employed as the nucleophiles.

Regarding the mechanism, with the information available from the control experiments and considering the previous reports,[15] we propose the following tentative mechanism (Scheme 5). The catalytic cycle starts with the formation of the active catalyst [Au(PPh_3)OTf] and subsequent 5-*endo*-dig alkynol cycloisomerisation followed by protodemetallation leading to the intermediate dihydrofuran **B**.[16] The protonation of **B** (either with the [Au] complex or with the triflic acid generated in situ) results in oxocarbenium cation **C**, which, upon Friedel–Crafts-type addition of C2 of indole, leads to *spiro*-tetrahydrofuran **2a**.[17] As indicated by the control experiments, spiro compound **2a** seems to be susceptible and is in equilibration with the corresponding oxepin derivative **2a′**. The isolation of the stable spirocycle **2e** with 5-nitroindole derivative **1e** supports this argument, as the formation of a C3 cation is not favoured in this case under normal conditions. Next, exposure of the resulting compounds **2a** and **2a′** to BF_3·OEt_2 should lead to the allyl cationic species **D**, which undergoes allylation in S_N2' fashion with trimethylallylsilane to afford product **E**.[18]

Conclusion

The possibility of adding electrophilic and nucleophilic centres at indole C2 and C3, respectively, with a net reactivity umpolung was realized. Thus, a simple protocol for the synthesis of tetracyclic indoloisoquinolinones with a pendant allylic group at C3 of indole has been developed. This protocol comprises a cascade cyclisation of *N*-[2-(4-hydroxybut-1-yn-1-yl)]aroylindole derivatives involving gold-catalysed 5-*endo*-dig alkynol cycloisomerisation followed by intramolecular addition of C2 of indole and subsequent regioselective C3 allylation/azidation/reduction/indolylation. The polarity inversion of indole is challenging and less discovered, and it provides a complementary strategy for the synthesis of functionalized indole derivatives. Further exploration and studies on the applicability of this strategy in the context of total synthesis is ongoing.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allylation · cyclization · domino reactions · gold · umpolung

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Facile synthesis of the spiro-pyridoindolone scaffold *via* a gold-catalysed intramolecular alkynol cyclisation/hydroindolylation†

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A simple approach for the synthesis of pyridoindolone scaffolds with a spiroannulated tetrahydrofuran ring is described. The overall process comprises intramolecular sequential gold-catalysed 5-*endo*-*dig* alkynol cycloisomerization and subsequent addition of indole C2 to the *in situ* generated oxocarbenium cation.

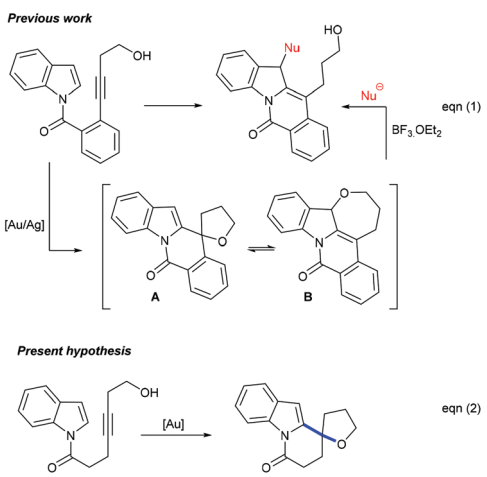
Introduction

During the last two decades, homogeneous gold-catalysis has emerged as a promising gold mine to unravel various organic transformations that are otherwise difficult to execute.[1] In particular, the gold-catalysed π-activation of unsaturated systems and the trapping of the electrophilic species obtained in inter- or intramolecular fashion with multiple nucleophilic centers led to the development of elegant domino processes to synthesize (hetero)cyclic scaffolds in a simple fashion.[2] In this context, domino processes that combine the gold-catalysed π-activation of alkynes and subsequent indole functionalization, have been established as a promising approach for the synthesis of complex polycyclic indole derivatives, and also for the synthesis of indole-based natural products.[3] The synthesis of the tetracyclic indole skeleton *via* the intramolecular cyclisation of indole-tethered alkynols/ynamides and the trapping of the resultant electrophilic intermediate with the oxygen-centred nucleophile in the presence of a gold complex has been pioneered by the groups of Bandini and Gong–Yang respectively.[4,5] Likewise, the addition of carbon centred nucleophiles to the C2 of indole was explored by the Ohno, Huang, and Liu groups.[6–8]

Recently, we documented the gold-catalysed cycloisomerization/cyclisation/allylation of alkyne-tethered indole derivatives that led to indoloisoquinolinone derivatives with a C3-allyl group on the indole ring.[9] This reaction proceeds *via* 5-*endo*-*dig* alkynol cycloisomerization followed by intramolecular addition of the C2 of indole, leading to the spiro-compound **A**.

However, as this spirocyclic carbon center is flanked in between the aromatic and heteroaromatic rings, the formation of the corresponding carbocation is facile. This leads the initially formed spiro compound **A** to be in equilibrium with the corresponding oxepin derivative **B** (eqn (1), Scheme 1) *via* the tetrahydrofuran ring opening and addition of the oxygen to the C3 of indole. In this context, we envisioned that with the simple alkynol substrate **1** without an annulated benzene ring in the chain, the gold-catalysed cyclisation should exclusively result in spiro-pyridoindolone **2**, as the formation of the carbocation is not as facile as in the former case.[10] This has been planned in the context of developing simple methods for the synthesis of a pyridoindolone skeleton, which is a privileged structural unit present in numerous alkaloids and investigational drugs (Fig. 1).[11,12]

The synthesis of functionalised pyridoindolone scaffolds has been explored over several decades. Transition metal cata-



Scheme 1 Previous work and present hypothesis.

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†Electronic supplementary information (ESI) available: Copies of NMR spectroscopy and spectral or analytical data. See DOI: 10.1039/d1ob02483c

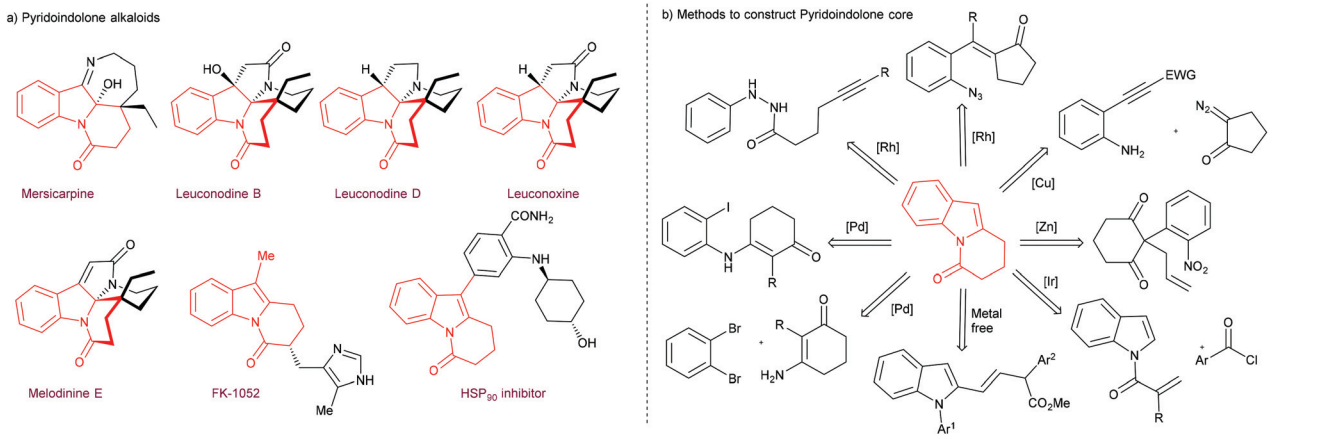
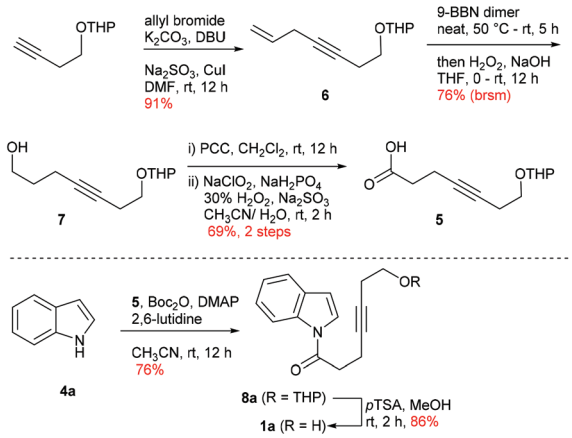


Fig. 1 (a) Pyridoindolone monoterpene indole alkaloids and bioactive compounds and (b) selected recent methods to construct the pyridoindolone core.

lysts like Pd, Rh, Cu, Zn and Ir, as well as metal-free approaches, have been documented in the context of the synthesis of the pyridoindolone core.[13–20] However, as shown in Scheme 1, the product that results in the present cases has the potential for further nucleophilic additions that can be modulated for the synthesis of advanced intermediates documented in the total synthesis of this class of natural products.[21] For example, a simple addition of the ethyl anion at this spiro-center should deliver the known key intermediate employed in the mersicarpine synthesis and, importantly, in a short and convergent manner.[22]

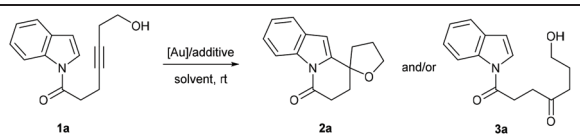
Results and discussion

The requisite alkynol **1a** has been prepared from the Boc_2O mediated coupling of indole **4a** and the THP-protected acid **5** (prepared in 4 steps, from the known THP-protected but-3-ynol, Scheme 2) and subsequent THP deprotection.[23] Next, the alkynol **1a** was subjected for the proposed gold-catalysed hydroarylation–spirocyclisation in the presence of the $AuPPh_3Cl$ catalyst and commonly employed $AgSbF_6$/AgOTf as activators in CH_2Cl_2 solvent (entries 1 & 2, Table 1).[24] The expected spirocyclic pyridoindolone **2a** was obtained in 42% and 36% yield respectively, along with a trace amount of the hydrated compound **3a**. When the same reaction was carried out in the presence of (JohnPhos)AuCl/$AgSbF_6$, the reaction yield was 36%, whereas the reaction with AuCl resulted in the isolation of compound **2a** in 60% yield (entries 3 & 4). Interestingly, the $AuCl_3$ catalyst without the [Ag] additive in CH_2Cl_2 solvent gave promising results (65% yield of spirocyclic compound **2a**, entry 5). This result prompted us to screen the $AuCl_3$ catalyst in different solvent systems. Accordingly, the reactions were carried out by employing THF, toluene, acetonitrile and 1,2-DCE to obtain **2a** in 26–93% yields (entries 6–9), where acetonitrile and 1,2-DCE, show the best results.[25]



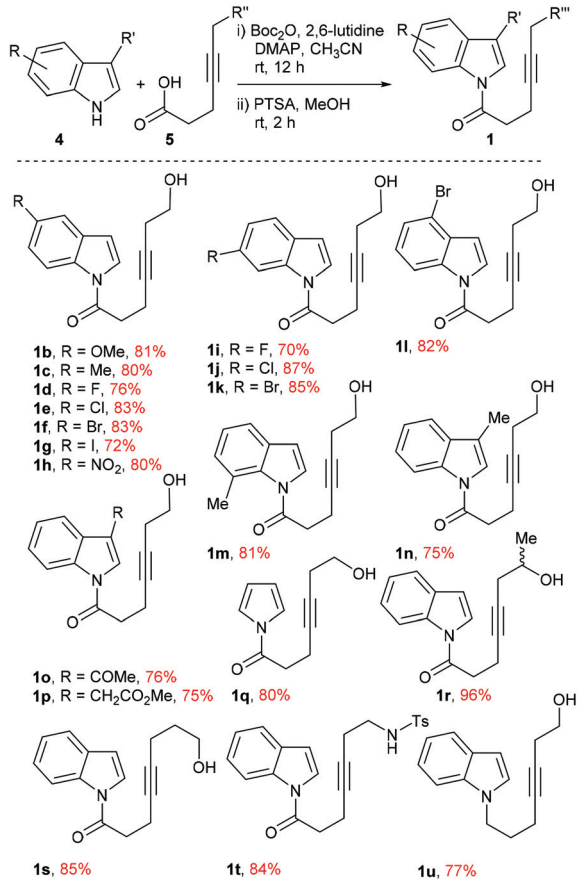
Scheme 2 The preparation of the starting acid **5** and alkynol **1a**.

Table 1 Optimization of gold-catalysed cyclisation[a]

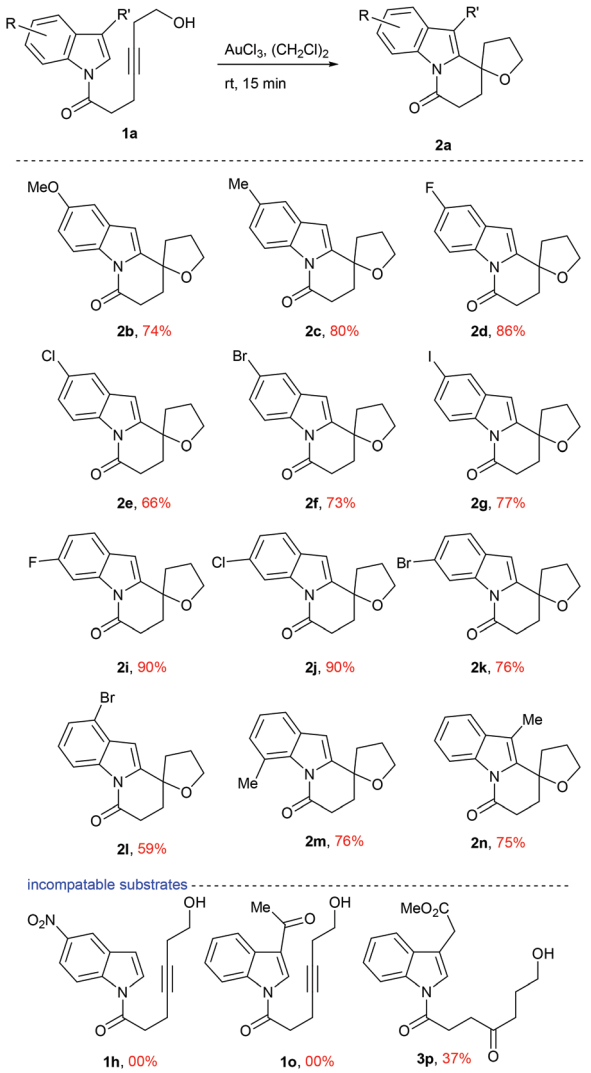


Entry	[Au]/[Ag]	Solvent	Temp./time (min)	Yield[b] (%) 2a	3a
1	$Au(PPh_3)Cl/AgSbF_6$	CH_2Cl_2	rt/15	42	15
2	$Au(PPh_3)Cl/AgOTf$	CH_2Cl_2	rt/15	36	22
3	(JohnPhos)$AuCl/AgSbF_6$	CH_2Cl_2	rt/15	36	13
4	AuCl/—	CH_2Cl_2	rt/15	60	5
5	$AuCl_3$/—	CH_2Cl_2	rt/15	65	12
6	$AuCl_3$/—	THF	rt/15	26	30
7	$AuCl_3$/—	PhMe	rt/15	66	5
8	$AuCl_3$/—	CH_3CN	rt/15	86	—
9	$AuCl_3$/—	$(CH_2Cl)_2$	rt/15	93	—

[a] In general, the reactions were carried out with **1a** (124.03 μmol), Au (5 mol%), and additive (10 mol%) in 3 ml dry solvent for 15 min. [b] Isolated yields.



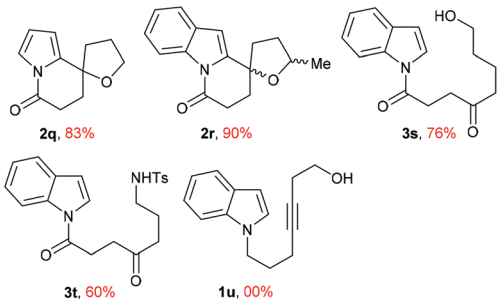
Scheme 3 Alkynols synthesized.



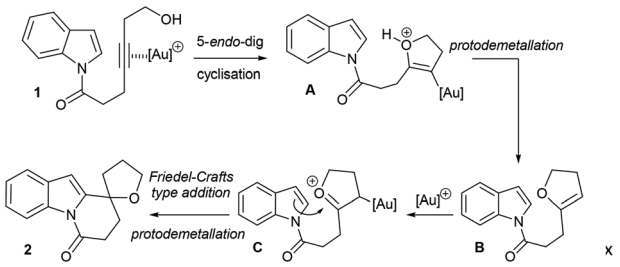
Scheme 4 Substrate scope.

After having the optimized conditions in hand, in order to extend the scope of the reaction, various indole templated alkynols (**1b–1n**) (70–87%) having different electron-donating/withdrawing groups on the indole ring were synthesized (Scheme 3) by following the established two-step sequence. In addition, pyrrolyl flanked alkynol **1q** (80%), alkynol **1r** (96%) with a 2°-OH group, and also the alkyne substrates (**1s–1u**) (where the flanking group around the alkyne was varied) have been synthesised to see the limitations of the current methodology.[26] Having a large set of differently substituted alkynols (**1b–1u**) in hand, the scope of the current methodology has been explored under the optimized conditions. In general, the reactions proceeded smoothly with the substrates **1b** and **1c** having strong (–OMe) or moderate (–Me) electron-donating groups at the C5 of indole respectively, and provided the corresponding cyclised products **2b** (74%) and **2c** (80%) in good yields (Scheme 4). Next, the halogenated substrates (**1d–1g**) having respectively an F, Cl, Br or I groups at the C5 position of indole afforded the corresponding spiro compounds (**2d–2g**) in good to excellent yields (66–86%). Likewise, the position of deactivators at the C4 and C6 of indole did not affect the outcome of the reaction, and afforded the desired spiro products (**2i–2l**) in moderate to excellent yields (59–90%). Similarly, the alkynols with C7 and C3 methyl indoles gave the spiropyridoindolone compounds (**2m** and **2n**) (76% & 75%). However, the substrates with strong electron-withdrawing groups, such as C5 nitro **1h** or C3 acetyl **1o**, blocked the conversion (Scheme 4). Along similar lines, when the alkynol flanked with indole-3-acetic acid **1p** was employed under optimised conditions, the hydration of alkyne was the major event, to yield 37% of compound **3p**.

Next, the scope of this transformation was examined by alkynols (**1q–1t**). The reaction of the pyrrole containing alkynol **1q** gave the corresponding spiro compound **2q** in 83% yield, revealing the suitability of this reaction for synthesizing the spiro-pyrrolopyridone scaffolds.[27] Similarly, with the substrate **1r** having the secondary alkynol, the reaction proceeded smoothly and provided the corresponding spiro compound **2r** in 90% yield as a mixture of diastereomers (1 : 0.3 dr from NMR). In case of the tosyl protected alkynyl amine **1t**, where the participating –OH was replaced with an –NHTs, under the current conditions, the hydration of the alkyne seemed to be facile. A similar observation was noticed with the homologated



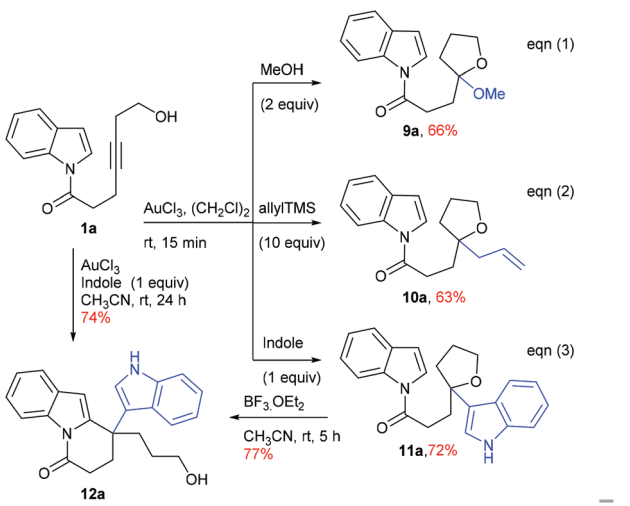
Scheme 5 Scope of the reaction with differently substituted alkynes.



Scheme 7 Mechanistic pathway.

alkynol **1s**. When the alkynol **1u** (without amide carbonyl) was treated under the optimized conditions, like with the corresponding aryl templated alkynol, the starting material was seen to be intact (Scheme 5). The lack of reactivity in these cases is probably due to the competing formation of an indole-gold complex, causing catalyst deactivation.[28]

Next, in order to see the applicability of the current gold-catalysed spirocyclisation reaction in the context of the total synthesis of indolopyridone alkaloids, the possible addition of an external nucleophile to the reactive spiro center was attempted (Scheme 6). Accordingly, the cyclisation of alkynol **1a** was carried out under optimized conditions in the presence of different O- or C-centred nucleophiles such as MeOH (2 equiv.), trimethylallyl silane (10 equiv.), and indole (1 equiv.). Interestingly, as shown in Scheme 6, the cyclized products **9a**, **10a**, and **11a** were obtained in 66%, 63% and 72% yields respectively [eqn (1)–(3), Scheme 6] where the intermediate dihydrofuran was reacted with the external nucleophile and no intramolecular cyclisation was seen to take place. This clearly indicated that the reaction proceeds *via* initial alkynol cyclisation followed by intramolecular addition of the indolyl C2 to the intermediate oxo-carbenium cation. The possibility of carrying out the intramolecular cyclisation of the resulting product (**9a–11a**) was attempted with the addition of external Lewis acids. However, only in case of **11a**, the cyclisation was seen to be facile in the presence of borontrifluoride etherate in acetonitrile and provided the corresponding indole substituted indolopyridinone **12a** in good yield (77%). Alternatively, the same product **12a** was obtained in excellent yield (74%) when the cyclisation of alkynol **1a** in the presence of indole was conducted, with the change of the solvent from 1,2-DCE to acetonitrile.



Scheme 6 Cyclisation of alkynol **1a** in the presence of external nucleophiles.

Coming to the mechanism of the reaction (Scheme 7), the gold-catalysed 5-*endo-dig* cyclisation of alkynol **1** followed by protodemetallation leads to the dihydrofuran intermediate **B**.[29,30] Next, the π-activation of the alkene in dihydrofuran intermediate **B** by the gold-complex leads to the transient oxo carbenium cation **C** which undergoes subsequent Friedel–Crafts-type addition of C2 of indole C and concomitant protodemetallation leads to spiro-tetrahydrofuran **2**.[31]

Conclusions

A simple catalytic method for the construction of a spiro-pyridoindolone core present in the indole class of alkaloids has been established. The reaction involves a gold-catalysed 5-*endo-dig* mode of alkynol cyclisation followed by Friedel–Crafts-type addition of C2 indole to the resulting dihydrofuran intermediate. Initial studies on adding an external nucleophile to the resulting spiro-THF carbon were seen to have only limited success. Further exploration in this direction and its utility in natural product synthesis is underway in our laboratory.

Experimental section

General procedure for the deprotection of –OTHP group

A solution of alkyne **8** and pTSA (0.1 equiv.) in MeOH (5 mL) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography to afford alkynol **1**.

7-Hydroxy-1-(1*H*-indol-1-yl)hept-4-yn-1-one (1a). Prepared from alkyne **8a** (100 mg, 0.30 mmol). Colourless solid (64 mg, 86%); R_f = 0.4 (40% ethyl acetate in petroleum ether); mp:

84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (br. s., 1H), 2.44 (dt, J = 6.1, 2.0 Hz, 2H), 2.70–2.79 (dt, J = 7.1, 2.0 Hz, 2H), 3.17 (t, J = 7.1 Hz, 2H), 3.70 (t, J = 6.0 Hz, 2H), 6.68 (d, J = 3.7 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.3 Hz, 1H), 7.48 (d, J = 3.7 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.4 (t), 23.12 (t), 35.3 (t), 61.2 (t), 78.1 (s), 80.3 (s), 109.5 (d), 116.6 (d), 120.9 (d), 123.8 (d), 124.3 (d), 125.3 (d), 130.3 (s), 135.6 (s), 169.7 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{16}NO_2$: 242.1176 $[M + H]^+$; found 242.1173.

7-Hydroxy-1-(5-methoxy-1*H*-indol-1-yl)hept-4-yn-1-one (1b). Prepared from alkyne **8b** (100 mg, 0.28 mmol). Colourless solid (62 mg, 81%); R_f = 0.3 (40% ethyl acetate in petroleum ether); mp: 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (br. s., 1H), 2.43 (tt, J = 6.1, 2.3 Hz, 2H), 2.72 (tt, J = 7.2, 2.3 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H) 3.68 (dd, J = 4.2, 1.0 Hz, 2H), 3.87 (s, 3H), 6.59 (dd, J = 3.7, 0.6 Hz, 1H), 6.97 (dd, J = 9.0, 2.5 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 7.44 (d, J = 3.7 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.5 (t), 23.2 (t), 35.0 (t), 55.7 (q), 61.2 (t), 78.1 (s), 80.4 (s), 103.7 (d), 109.3 (d), 113.6 (d), 117.3 (d), 124.9 (d), 130.3 (s), 131.3 (s), 156.5 (s), 169.3 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_3$: 294.1101 $[M + Na]^+$; found 294.1106.

7-Hydroxy-1-(5-methyl-1*H*-indol-1-yl)hept-4-yn-1-one (1c). Prepared form alkyne **8c** (98 mg, 0.27 mmol). Colourless solid (60 mg, 80%); R_f = 0.3 (40% ethyl acetate in petroleum ether); mp: 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (br. s., 1H), 2.42 (tt, J = 6.1, 2.38 Hz, 2H), 2.45 (s, 3H), 2.72 (tt, J = 7.5, 2.3 Hz, 2H), 3.14 (t, J = 7.3 Hz, 2H), 3.69 (dd, J = 11.3, 6.0 Hz, 2H), 6.55–6.62 (dd, J = 3.8, 0.6 Hz, 1H), 7.18 (dd, J = 8.4, 1.5 Hz, 1H), 7.36 (t, J = 0.7 Hz, 1H) 7.43 (d, J = 3.7 Hz, 1H) 8.32 (d, J = 8.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.4 (t), 21.3 (q), 23.2 (t), 35.2 (t), 61.2 (t), 78.1 (s), 80.4 (s), 109.3 (d), 116.2 (d), 120.8 (d), 124.4 (d), 126.6 (d), 130.6 (s), 133.4 (s), 133.8 (s), 169.5 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}N\,Na\,O_2$: 278.1152 $[M + Na]^+$; found 278.1159.

1-(5-Fluoro-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (1d). Prepared from alkyne **8d** (100 mg, 0.29 mmol). Colourless solid (58 mg, 76%); R_f = 0.2 (40% ethyl acetate in petroleum ether); mp: 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (t, J = 5.8 Hz, 1H), 2.43 (tt, J = 6.1, 2.3 Hz, 2H), 2.73 (tt, J = 7.3, 2.3 Hz, 2H), 3.14 (t, J = 7.2 Hz, 2H), 3.64–3.73 (m, 2H), 6.63 (dd, J = 3.7, 0.6 Hz, 1H), 7.09 (td, J = 9.1, 2.6 Hz, 1H), 7.22 (dd, J = 8.7, 2.5 Hz, 1H), 7.50 (d, J = 3.8 Hz, 1H), 8.43 (dd, J = 9.1, 4.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.4 (t), 23.1 (t), 35.1 (t), 61.2 (t), 78.2 (s), 80.2 (s), 106.4 (dd, J_{C-F} = 24.4 Hz), 109.1 (dd, J_{C-F} = 3.8 Hz), 112.0 (dd, J_{C-F} = 24.4 Hz), 117.6 (dd, J_{C-F} = 9.1 Hz), 125.8 (s), 131.2 (sd, J_{C-F} = 7.6 Hz), 132.0 (s), 159.7 (sd, J_{C-F} = 240.3 Hz), 169.5 (s); ^{19}F NMR (376 MHz, $CDCl_3$): δ −119.12 ppm; HRMS (ESI) calcd for $C_{15}H_{14}NFNaO_2$: 282.0901 $[M + Na]^+$; found 282.0908.

1-(5-Chloro-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (1e). Prepared from alkyne **8e** (100 mg, 0.27 mmol). Pale yellow solid (64 mg, 83%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (br. s., 1H), 2.42 (tt, J = 6.1, 2.3 Hz, 2H), 2.72 (tt, J = 7.1, 2.3 Hz, 2H), 3.14 (t, J = 7.1 Hz, 2H), 3.69 (t, J = 6.0 Hz, 2H), 6.61 (d, J = 3.7 Hz, 1H), 7.32 (dd, J = 8.8, 2.0 Hz, 1H), 7.49 (d, J = 3.7 Hz, 1H), 7.54 (t, J = 2.1 Hz, 1H), 8.40 (d, J = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.1 (t), 61.2 (t), 78.3 (s), 80.1 (s), 108.7 (d), 117.6 (d), 120.5 (d), 125.4 (d), 125.5 (d), 129.4 (s), 131.5 (s), 133.9 (s), 169.6 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NClNaO_2$: 298.0605 $[M + Na]^+$; found 298.0614.

1-(5-Bromo-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (1f). Prepared from alkyne **8f** (100 mg, 0.24 mmol). Pale brown solid (66 mg, 83%); R_f = 0.2 (40% ethyl acetate in petroleum ether); mp: 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (br. s., 1H), 2.42 (tt, J = 6.0, 2.3 Hz, 2H), 2.72 (tt, J = 7.1, 2.3 Hz, 2H), 3.14 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H), 6.60 (d, J = 3.8 Hz, 1H), 7.41–7.50 (m, 2H), 7.70 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.2 (t), 61.2 (t), 78.3 (s), 80.1 (s), 108.6 (d), 117.1 (s), 118.0 (d), 123.5 (d), 125.4 (d), 128.1 (d), 132.0 (s), 134.3 (s), 169.6 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NBrNaO_2$: 342.0100 $[M + Na]^+$; found 342.0112.

7-Hydroxy-1-(5-iodo-1*H*-indol-1-yl)hept-4-yn-1-one (1g). Preapred from alkyne **8g** (100 mg, 0.22 mmol). Pale brown solid (59 mg, 72%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (br. s., 1H), 2.43 (tt, J = 6.1, 2.3 Hz, 2H), 2.72 (tt, J = 7.5, 2.3 Hz, 2H), 3.14 (t, J = 7.1 Hz, 2H), 3.69 (dd, J = 11.0, 4.8 Hz, 2H), 6.59 (dd, J = 3.8, 0.5 Hz, 1H), 7.44 (d, J = 3.8 Hz, 1H), 7.64 (dd, J = 8.7, 1.5 Hz, 1H), 7.92 (d, J = 1.5 Hz, 1H), 8.24 (d, J = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.2 (t), 61.12 (t), 80.1 (s), 88.0 (s), 108.4 (d), 118.4 (d), 125.1 (d), 129.8 (d), 132.6 (s), 133.8 (d, 2C), 134.9 (s), 169.7 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NINaO_2$: 389.9961 $[M + Na]^+$; found 389.9974.

7-Hydroxy-1-(5-nitro-1*H*-indol-1-yl)hept-4-yn-1-one (1h). Prepared from alkyne **8h** (100 mg, 0.27 mmol). Pale yellow solid (62 mg, 80%); R_f = 0.1 (40% ethyl acetate in petroleum ether); mp: 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (tt, J = 6.1, 2.3 Hz, 2H), 2.74 (tt, J = 7.2, 2.3 Hz, 2H), 3.19 (t, J = 7.1 Hz, 2H), 3.69 (t, J = 6.1 Hz, 2H), 6.82 (d, J = 3.8 Hz, 1H), 7.64 (d, J = 3.8 Hz, 1H), 8.25 (dd, J = 9.1, 2.3 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.59 (d, J = 9.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.2 (t), 23.1 (t), 35.3 (t), 61.1 (t), 78.5 (s), 79.8 (s), 109.8 (d), 116.8 (d), 117.1 (d), 120.5 (d), 127.2 (d), 130.2 (s), 138.5 (s), 144.3 (s), 169.9 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}N_2NaO_4$: 309.0846 $[M + Na]^+$; found 309.0853.

1-(6-Fluoro-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (1i). Prepared from alkyne **8i** (100 mg, 0.29 mmol). Pale yellow solid (53 mg, 70%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (tt, J = 6.1, 2.3 Hz, 2H), 2.67–2.76 (m, 2H), 3.13 (t, J = 7.2 Hz, 2H), 3.69 (t, J = 6.1 Hz, 2H), 6.63 (dd, J = 3.7, 0.6 Hz, 1H), 7.04 (td, J = 8.8, 2.5 Hz, 1H), 7.44 (d, J = 3.8 Hz, 1H), 7.48 (dd, J = 8.6, 5.3 Hz, 1H), 8.22 (dd, J = 10.3, 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.1 (t), 61.1 (t), 78.2 (s), 80.1 (s), 104.1(dd, J_{C-F} = 28.9 Hz), 109.2 (d), 111.9 (dd, J_{C-F} = 24.4 Hz), 121.3 (dd, J_{C-F} = 9.9 Hz), 124.5 (dd, J_{C-F} = 3.8 Hz), 126.4 (s), 135.6 (dd, J_{C-F} = 12.9 Hz), 161.3 (dd, J_{C-F} = 241.0 Hz),

169.8 (s) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.19 ppm; HRMS (ESI) calcd for $C_{15}H_{14}FNNaO_2$: 282.0901 $[M + Na]^+$; found 282.0892.

1-(6-Chloro-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (1j). Prepared from alkyne **8j** (100 mg, 0.27 mmol). Colourless solid (65 mg, 84%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (br. s., 1H), 2.44 (tt, J = 6.1, 2.3 Hz, 2H), 2.69–2.77 (m, 2H), 3.14 (t, J = 7.1 Hz, 2H), 3.66–3.75 (m, 2H), 6.64 (d, J = 3.8 Hz, 1H), 7.28 (dd, J = 1.7, 8.2 Hz, 1H), 7.44–7.50 (m, 2H), 8.54 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.2 (t), 61.2 (t), 78.2 (s), 80.1 (s), 109.1 (d), 116.9 (d), 121.5 (d), 124.4 (d), 124.8 (d), 128.7 (s), 131.2 (s), 135.8 (s), 169.7 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NClNaO_2$: 298.0605 $[M + Na]^+$; found 298.0611.

1-(6-Bromo-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (1k). Preapred from alkyne **8k** (100 mg, 0.24 mmol). Colourless solid (68 mg, 85%); R_f = 0.6 (40% ethyl acetate in petroleum ether); mp: 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (tt, J = 6.1, 2.3 Hz, 2H), 2.71 (ddt, J = 7.7, 6.7, 2.3 Hz, 2H), 3.13 (t, J = 6.8 Hz, 2H), 3.69 (t, J = 6.1 Hz, 2H), 6.63 (dd, J = 3.8, 0.6 Hz, 1H), 7.37–7.45 (m, 3H), 8.69 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.1 (t), 61.2 (t), 78.2 (s), 80.1 (s), 109.2 (d), 119.0 (s), 119.7 (d), 121.9 (d), 124.7 (d), 127.1 (d), 129.0 (s), 136.1 (s), 169.7 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NBrNaO_2$: 342.0100 $[M + Na]^+$; found 342.0090.

1-(4-Bromo-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (1l). Prepared from alkyne **8l** (100 mg, 0.24 mmol). Colourless solid (65 mg, 82%); R_f = 0.3 (40% ethyl acetate in petroleum ether); mp: 90–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (br. s., 1H), 2.44 (tt, J = 6.1, 2.3 Hz, 2H), 2.74 (tt, J = 7.1, 2.3 Hz, 2H), 3.17 (t, J = 7.2 Hz, 2H), 3.65–3.72 (m, 2H), 6.75 (dd, J = 3.3, 0.5 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H) 7.47 (dd, J = 7.8, 0.6 Hz, 1H), 7.53 (d, J = 3.7 Hz, 1H), 8.44 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 35.3 (t), 61.2 (t), 78.3 (s), 80.1 (s), 109.2 (d), 114.6 (s), 115.6 (d), 124.8 (d), 126.3 (d), 126.7 (d), 131.0 (s), 135.9 (s), 169.8 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{15}NBrO_2$: 320.0281 $[M + H]^+$; found 320.0288.

7-Hydroxy-1-(7-methyl-1*H*-indol-1-yl)hept-4-yn-1-one (1m). Prepared from alkyne **8m** (100 mg, 0.29 mmol). Colourless solid (61 mg, 81%); R_f = 0.4 (40% ethyl acetate in petroleum ether); mp: 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (tt, J = 6.2, 2.2 Hz, 2H), 2.49 (s, 3H), 2.65 (tt, J = 7.1, 2.3 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H), 3.60 (t, J = 6.1 Hz, 2H), 6.57 (d, J = 3.8 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H) 7.33 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 3.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 15.1 (t), 22.6 (q), 23.1 (t), 36.0 (t), 61.2 (t), 78.2 (s), 80.2 (s), 109.3 (d), 118.5 (d), 124.2 (d), 125.7 (d), 126.7 (s), 128.3 (d), 131.9 (s), 135.1 (s), 169.1 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1142.

7-Hydroxy-1-(3-methyl-1*H*-indol-1-yl)hept-4-yn-1-one (1n). Prepared from alkyne **8n** (100 mg, 0.29 mmol). Colourless solid (57 mg, 75%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (t, J = 6.0 Hz, 1H), 2.30 (d, J = 1.3 Hz, 3H), 2.43 (tt, J = 6.1, 2.3 Hz, 2H), 2.71 (tt, J = 7.5, 2.3 Hz, 2H), 3.11 (t, J = 7.3 Hz, 2H), 3.70 (dd, J = 11.8, 5.8 Hz, 2H), 7.23 (s, 1H), 7.31 (td, J = 7.4, 1.1 Hz, 1H), 7.37 (td, J = 7.7, 1.4 Hz, 1H), 7.51 (dq, J = 7.6, 0.7 Hz, 1H), 8.44 (d, J = 7.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 9.71 (q), 14.41 (t), 23.16 (t), 35.31 (t), 61.20 (t), 78.05 (s), 80.49 (s), 116.61 (d), 118.77 (s), 118.84 (d), 121.25 (d), 123.53 (d), 125.31 (d), 131.33 (s), 135.87 (s), 169.31 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1158.

1-(3-Acetyl-1*H*-indol-1-yl)-7-hydroxyhept-4-yn-1-one (1o). Preapred from alkyne **8o** (100 mg, 0.27 mmol). Pale brown solid (59 mg, 76%); R_f = 0.2 (50% ethyl acetate in petroleum ether); mp: 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (tt, J = 6.1, 2.3 Hz, 2H), 2.61 (s, 3H), 2.77 (tt, J = 7.5, 2.3 Hz, 2H), 3.24 (dd, J = 6.8, 1.0 Hz, 2H), 3.70 (t, J = 6.1 Hz, 2H), 7.37–7.47 (m, 2H), 8.11 (s, 1H), 8.33–8.37 (m, 1H), 8.39–8.44 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 28.0 (q), 35.4 (t), 61.1 (t), 78.5 (s), 79.8 (s), 116.2 (d), 122.1 (s), 122.5 (d), 125.3 (d), 126.4 (d), 127.2 (s), 130.3 (d), 136.1 (s), 169.9 (s), 193.7 (s) ppm; HRMS (ESI) calcd for $C_{17}H_{18}NO_2$: 290.1176 $[M + H]^+$; found 290.1174.

Methyl 2-(1-(7-hydroxyhept-4-ynoyl)-1*H*-indol-3-yl)acetate (1p). Prepared from alkyne **8p** (100 mg, 0.25 mmol). Colourless solid (59 mg, 75%); R_f = 0.1 (40% ethyl acetate in petroleum ether); mp: 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (br. s., 1H), 2.42 (tt, J = 6.1, 2.3 Hz, 2H), 2.71 (tt, J = 7.1, 2.3 Hz, 2H), 3.14 (t, J = 7.1 Hz, 2H), 3.68 (d, J = 4.2 Hz, 2H), 3.75 (s, 5H), 7.31 (td, J = 7.6, 1.0 Hz, 1H), 7.39 (td, J = 8.3, 1.2 Hz, 1H), 7.50–7.55 (m, 2H), 8.46 (d, J = 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.4 (t), 23.1 (t), 30.7 (t), 35.3 (t), 52.2 (q), 61.2 (t), 78.2 (s), 80.3 (s), 115.2 (s), 116.7 (d), 118.8 (d), 122.9 (d), 123.8 (d), 125.6 (d), 129.9 (s), 135.7 (s), 169.6 (s), 171.3 (s) ppm; HRMS (ESI) calcd for $C_{18}H_{19}NNaO_4$: 336.1206 $[M + Na]^+$; found 336.1193.

7-Hydroxy-1-(1*H*-pyrrol-1-yl)hept-4-yn-1-one (1q). Prepared from alkyne **8q** (94 mg, 0.34 mmol). Pale brown solid (56 mg, 80%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 62–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (br. s., 1H), 2.42 (tt, J = 6.1, 2.3 Hz, 2H), 2.66 (tt, J = 7.5, 2.3 Hz, 2H), 3.06 (dd, J = 7.0, 1.3 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H), 6.32 (t, J = 2.3 Hz, 2H), 7.33 (br. s., 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 23.1 (t), 34.1 (t), 61.2 (t), 78.1 (s), 80.10 (s), 113.3 (d, 2C), 119.0 (d, 2C), 168.9 (s) ppm; HRMS (ESI) calcd for $C_{11}H_{13}NNaO_2$: 214.0838 $[M + Na]^+$; found 214.0846.

7-Hydroxy-1-(1*H*-indol-1-yl)oct-4-yn-1-one (1r). Prepared from alkyne **8r** (100 mg, 0.29 mmol). Colourless solid (72 mg, 96%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, J = 6.1 Hz, 2H), 2.11 (br. s., 1H), 2.24–2.31 (m, 1H), 2.33–2.40 (m, 1H), 2.73 (tt, J = 7.2, 2.4 Hz, 2H), 3.16 (t, J = 7.0 Hz, 2H), 3.91 (sext, J = 6.1 Hz, 1H), 6.67 (d, J = 3.4 Hz, 1H), 7.26–7.32 (m, 1H), 7.37 (td, J = 8.3, 1.1 Hz, 1H), 7.47 (d, J = 3.4 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 8.47 (d, J = 8.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.4 (t), 22.2 (q), 29.4 (t), 35.3 (t), 66.4 (d), 77.9 (s), 80.8 (s), 109.5 (d), 116.6 (d), 120.9 (d), 123.8 (d), 124.3 (d), 125.3 (d), 130.3 (s), 135.6 (s), 169.7 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1141.

8-Hydroxy-1-(1*H*-indol-1-yl)oct-4-yn-1-one (1s). Prepared from alkyne **8s** (100 mg, 0.29 mmol). Pale yellow solid (64 mg,

85%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (br. s., 1H), 1.74 (quin, J = 6.5 Hz, 2H), 2.29 (tt, J = 6.9, 2.3 Hz, 2H), 2.72 (tt, J = 7.3, 2.3 Hz, 2H), 3.15 (t, J = 7.0 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 6.68 (d, J = 3.7 Hz, 1H), 7.27–7.34 (m, 1H), 7.38 (td, J = 8.3, 1.2 Hz, 1H), 7.49 (d, J = 3.8 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 8.49 (d, J = 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.4 (t), 15.3 (t), 31.3 (t), 35.4 (t), 61.8 (t), 78.7 (s), 80.7 (s), 109.4 (d), 116.6 (d), 120.9 (d), 123.8 (d), 124.4 (d), 125.2 (d), 130.3 (s), 135.6 (s), 169.8 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1143.

***N*-(7-(1*H*-Indol-1-yl)-7-oxohept-3-yn-1-yl)-4-methylbenzenesulfonamide (1t).** At 0 °C, a solution of amine **8t** (80 mg, 0.16 mmol) in MeOH (5 mL) was treated with oxalyl chloride (42 μL, 0.5 mmol) and stirring was continued at rt for 2 h. After completion of the reaction (indicated by TLC), the reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography to afford alkynyl amine **1t** (54 mg, 84% yield) as a colourless syrup. R_f = 0.4 (30% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (tt, J = 8.6, 2.2 Hz, 2H), 2.40 (s, 3H), 2.65 (tt, J = 9.5, 2.2 Hz, 2H), 3.01–3.14 (m, 4H), 5.15 (t, J = 6.2 Hz, 1H), 6.66 (d, J = 3.7 Hz, 1H), 7.23–7.32 (m, 3H), 7.36 (td, J = 7.7, 1.2 Hz, 1H), 7.45 (d, J = 3.7 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 8.47 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.3 (t), 20.0 (t), 21.5 (q), 35.1 (t), 42.0 (t), 77.5 (s), 80.9 (s), 109.5 (d), 116.6 (d), 120.9 (d), 123.8 (d), 124.3 (d), 125.3 (d), 127.0 (d, 2C), 129.7 (d, 2C), 130.3 (s), 135.5 (s), 137.1 (s), 143.4 (s), 169.7 (s) ppm; HRMS (ESI) calcd for $C_{22}H_{22}N_2O_3Na$: 417.1243 $[M + Na]^+$; found 417.1249.

7-(1*H*-indol-1-yl)hept-3-yn-1-ol (1u). At 0 °C, a solution of alkyne **8u** (800 mg, 2.97 mmol) in dry THF (20 mL) was treated drop wise with 1 N DIBAL-H in THF (3.56 mL, 3.56 mmol) and the stirring was continued for additional 2 h at the same temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with aq. sodium potassium tartarate (Rochelle's salt), diluted with EtOAc (50 mL), washed with water (20 mL × 2), brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting crude by column chromatography afforded the alkynol **1u** (522 mg, 77% yield) as a pale yellow liquid in. R_f = 0.5 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (quin, J = 6.6 Hz, 2H), 2.02–2.10 (m, 2H), 2.37 (tt, J = 6.2, 2.3 Hz, 2H), 3.61 (t, J = 6.2 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 6.41 (dd, J = 3.1, 0.5 Hz, 1H), 6.98–7.06 (m, 2H), 7.10–7.16 (m, 1H), 7.25–7.31 (m, 1H), 7.55 (d, J = 7.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1 (t), 23.0 (t), 29.1 (t), 44.8 (t), 61.3 (t), 77.8 (s), 80.8 (s), 101.1 (d), 109.3 (d), 119.2 (d), 120.9 (d), 121.4 (d), 127.9 (d), 128.6 (s), 135.9 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{17}NONa$: 250.1202 $[M + Na]^+$; found 250.1209.

General procedure for gold-catalysed spirocyclisation–hydroarylation

At rt, a solution of alkynol **1** (30 mg) in $(CH_2Cl)_2$ (3 mL) was stirred for 15 min in presence of $AuCl_3$ (5 mol%). After completion of the reaction, it was concentrated under reduced pressure, purified by column chromatography to afford spiroindolopyridones **2**.

4,5,7′,8′-Tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2a). Colourless solid (28 mg, 93%); R_f = 0.6 (40% ethyl acetate in petroleum ether); mp: 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (tt, J = 8.8, 3.1 Hz, 1H), 2.11–2.20 (m, 1H), 2.20–2.31 (m, 3H), 2.47 (ddd, J = 12.1, 8.2, 5.5 Hz, 1H), 2.79 (dt, J = 17.6, 5.1 Hz, 1H), 3.17 (ddd, J = 17.6, 9.9, 5.7 Hz, 1H), 3.99 (td, J = 6.8, 1.0 Hz, 2H), 6.51 (d, J = 0.5 Hz, 1H), 7.24–7.30 (m, 1H), 7.34 (td, J = 7.2, 1.3 Hz, 1H), 7.53 (ddd, J = 7.6, 1.3, 0.8 Hz, 1H), 8.49 (dd, J = 8.2, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.9 (t), 31.4 (t), 33.8 (t), 36.1 (t), 67.4 (t), 77.66 (s), 104.8 (d), 116.6 (d), 120.4 (d), 124.0 (d), 125.0 (d), 129.0 (s), 135.2 (s), 141.5 (s), 169.1 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{16}NNaO_2$: 242.1176 $[M + H]^+$; found 242.1174.

2′-Methoxy-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2b). Colourless solid (22.3 mg, 74%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.09 (m, 1H), 2.09–2.20 (m, 2H), 2.20–2.27 (m, 2H), 2.44 (ddd, J = 12.1, 8.2, 5.6 Hz, 1H), 2.77 (dt, J = 17.6, 5.1 Hz, 1H), 3.13 (ddd, J = 17.5, 9.8, 5.7 Hz, 1H), 3.85 (s, 3H), 3.98 (t, J = 6.6 Hz, 2H), 6.44 (d, J = 0.6 Hz, 1H), 6.93 (dd, J = 8.9, 2.5 Hz, 1H), 6.99 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 9.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.9 (t), 31.2 (t), 33.9 (t), 36.1 (t), 55.6 (q), 67.4 (t), 77.7 (s), 103.5 (d), 104.6 (d), 113.1 (d), 117.3 (d), 129.9 (s), 130.1 (s), 142.2 (s), 156.7 (s), 168.7 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_3$: 294.1101 $[M + Na]^+$; found 294.1108.

2′-Methyl-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2c). Colourless syrup (24 mg, 80%); R_f = 0.5 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (ddd, J = 12.0, 6.5, 2.1 Hz, 1H), 2.09–2.17 (m, 1H), 2.17–2.27 (m, 3H), 2.40–2.49 (m, 4H), 2.77 (dt, J = 17.6, 5.2 Hz, 1H), 3.14 (ddd, J = 17.5, 9.9, 5.7 Hz, 1H), 3.98 (td, J = 6.8, 0.7 Hz, 2H), 6.4 (d, J = 0.6 Hz, 1H), 7.15 (ddd, J = 8.3, 1.7, 0.5 Hz, 1H), 7.30 (dd, J = 1.5, 0.7 Hz, 1H), 8.34 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.4 (q), 25.9 (t), 31.3 (t), 33.8 (t), 36.1 (t), 67.4 (t), 77.7 (s), 104.6 (d), 116.1 (d), 120.4 (d), 126.3 (d), 129.2 (s), 133.4 (s), 133.5 (s), 141.5 (s), 168.9 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1158.

2′-Fluoro-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2d). Colourless solid (25.9 mg, 86%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (ddd, J = 11.5, 5.0, 1.6 Hz, 1H), 2.12–2.19 (m, 1H), 2.19–2.29 (m, 3H), 2.45 (ddd, J = 11.8, 5.3, 1.7 Hz, 1H), 2.79 (dt, J = 17.7, 5.2 Hz, 1H), 3.15 (ddd, J = 17.6, 9.9, 5.6 Hz, 1H), 3.95 (td, J = 6.8, 1.6 Hz, 2H), 6.47 (d, J = 0.6 Hz, 1H), 7.05 (td, J = 9.1, 2.6 Hz, 1H), 7.17 (dd, J = 8.7, 2.3 Hz, 1H), 8.43 (dd, J = 9.0, 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.9 (t), 31.23 (t), 33.8 (t), 36.1 (t), 67.5 (t), 77.6 (s), 104.4 (dd, J_{C-F} = 3.81 Hz), 106.0 (dd, J_{C-F} = 23.65 Hz), 112.5 (dd, J_{C-F} = 24.41 Hz), 117.5 (dd, J_{C-F} = 9.16 Hz), 130.1 (sd, J_{C-F} = 9.92 Hz), 131.6 (s), 143.2 (s), 159.9 (dd, J_{C-F} = 239.56 Hz), 168.8 (s); ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.85 ppm; HRMS (ESI) calcd for $C_{15}H_{14}NFNaO_2$: 282.0901 $[M + Na]^+$; found 282.0907.

2′-Chloro-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2e). Colourless solid (20 mg, 66%); R_f = 0.6 (40% ethyl acetate in petroleum ether); mp: 90–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04–2.12 (m, 1H), 2.12–2.18 (m, 1H), 2.19–2.30 (m, 3H), 2.39–2.49 (m, 1H), 2.79 (dt, J = 17.7, 5.1 Hz, 1H), 3.16 (ddd, J = 17.6, 9.9, 5.6 Hz, 1H), 3.93–4.03 (m, 2H), 6.45 (s, 1H), 7.27–7.32 (m, 1H), 7.49 (d, J = 2.0 Hz, 1H), 8.40 (d, J = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.9 (t), 31.3 (t), 33.8 (t), 36.1 (t), 67.5 (t), 77.6 (s), 103.9 (d), 117.5 (d), 120.1 (d), 125.1 (d), 129.5 (s), 130.3 (s), 133.6 (s), 143.0 (s), 168.9 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NClNaO_2$: 298.0605 $[M + Na]^+$; found 298.0615.

2′-Bromo-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2f). Colourless solid (22 mg, 73%); R_f = 0.5 (40% ethyl acetate in petroleum ether); mp: 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.11 (m, 1H), 2.11–2.19 (m, 1H), 2.19–2.29 (m, 3H), 2.39–2.48 (m, 1H), 2.79 (dt, J = 17.7, 5.2 Hz, 1H), 3.15 (ddd, J = 17.7, 9.8, 5.6 Hz, 1H), 3.92–4.03 (m, 2H), 6.44 (s, 1H), 7.42 (dd, J = 8.7, 2.0 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.9 (t), 31.3 (t), 33.7 (t), 36.1 (t), 67.5 (t), 77.5 (s), 103.8 (d), 117.2 (s), 117.9 (d), 123.1 (d), 127.8 (d), 130.8 (s), 133.9 (s), 142.8 (s), 169.0 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NBrNaO_2$: 342.0100 $[M + Na]^+$; found 342.0110.

2′-Iodo-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2g). Colourless syrup (23.3 mg, 77%); R_f = 0.4 (40% ethyl acetate in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.03–2.11 (m, 1H), 2.11–2.18 (m, 1H), 2.18–2.27 (m, 3H), 2.44 (ddd, J = 12.4, 8.2, 5.7 Hz, 1H), 2.78 (dt, J = 17.6, 5.2 Hz, 1H), 3.15 (ddd, J = 17.6, 10.0, 5.5 Hz, 1H), 3.93–4.02 (m, 2H), 6.42 (s, 1H), 7.60 (dd, J = 8.5, 1.7 Hz, 1H), 7.86 (d, J = 1.5 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 25.9 (t), 31.3 (t), 33.7 (t), 36.1 (t), 67.5 (t), 77.5 (s), 88.1 (s), 103.6 (d), 118.3 (d), 129.3 (d), 131.3 (s), 133.5 (d), 134.5 (s), 142.5 (s), 169.0 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{15}NIO_2$: 368.0142 $[M + H]^+$; found 368.0155.

3′-Fluoro-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2i). Colourless syrup (27 mg, 90%); R_f = 0.5 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.10 (m, 1H), 2.10–2.18 (m, 1H), 2.18–2.27 (m, 3H), 2.45 (ddd, J = 12.2, 8.2, 5.8 Hz, 1H), 2.78 (dt, J = 17.6, 5.0 Hz, 1H), 3.16 (ddd, J = 17.5, 10.0, 6.0 Hz, 1H), 3.92–4.03 (m, 2H), 6.48 (s, 1H), 7.02 (td, J = 8.9, 2.4 Hz, 1H), 7.43 (dd, J = 8.5, 5.3 Hz, 1H), 8.22 (dd, J = 10.1, 2.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.9 (t), 31.2 (t), 33.7 (t), 36.0 (t), 67.4 (t), 77.5 (s), 104.0 (dd, J_{C-F} = 28.2 Hz), 104.3 (d), 112.1 (dd, J_{C-F} = 24.4 Hz), 120.9 (dd, J_{C-F} = 9.9 Hz), 125.2 (sd, J_{C-F} = 1.5 Hz), 135.2 (sd, J_{C-F} = 12.9 Hz), 141.8 (sd, J_{C-F} = 3.8 Hz), 161.1 (sd, J_{C-F} = 240.3 Hz), 169.14 (s) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.47 ppm; HRMS (ESI) calcd for $C_{15}H_{14}NFNaO_2$: 282.0901 $[M + Na]^+$; found 282.0890.

3′-Chloro-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2j). Colourless oil (27 mg, 90%); R_f = 0.6 (40% ethyl acetate in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06 (dt, J = 8.7, 2.2 Hz, 1H), 2.10–2.18 (m, 1H), 2.18–2.27 (m, 3H), 2.45 (ddd, J = 12.4, 8.2, 5.7 Hz, 1H), 2.79 (dt, J = 17.6, 5.1 Hz, 1H), 3.15 (ddd, J = 17.6, 10.2, 5.7 Hz, 1H), 3.93–4.02 (m, 2H), 6.47 (s, 1H), 7.24 (dd, J = 8.3, 1.9 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 8.52 (d, J = 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 25.9 (t), 31.2 (t), 33.7 (t), 36.0 (t), 67.5 (t), 77.5 (s), 104.3 (d), 116.7 (d), 121.1 (d), 124.5 (d), 127.5 (s), 130.8 (s), 135.4 (s), 142.2 (s), 169.0 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NClNaO_2$: 298.0605 $[M + Na]^+$; found 298.0609.

3′-Bromo-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2k). Pale yellow solid (23 mg, 76%); R_f = 0.6 (40% ethyl acetate in petroleum ether); mp: 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.11 (m, 1H), 2.12–2.18 (m, 1H), 2.18–2.28 (m, 3H), 2.45 (dd, J = 6.6, 2.5 Hz, 1H), 2.79 (dt, J = 17.6, 5.1 Hz, 1H), 3.16 (ddd, J = 17.6, 10.0, 5.8 Hz, 1H), 3.93–4.02 (m, 2H), 6.47 (s, 1H), 7.34–7.42 (m, 2H), 8.68 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.9 (t), 31.3 (t), 33.7 (t), 36.1 (t), 67.5 (t), 77.5 (s), 104.4 (d), 118.5 (s), 119.6 (d), 121.5 (d), 127.2 (d), 127.9 (s), 135.8 (s), 142.1 (s), 169.0 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{15}BrNO_2$: 320.0281 $[M + H]^+$; found 320.0278.

1′-Bromo-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2l). Colourless oil (17.8 mg, 59%); R_f = 0.6 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04–2.20 (m, 2H), 2.20–2.31 (m, 3H), 2.50 (ddd, J = 12.3, 5.8, 1.7 Hz, 1H), 2.80 (dt, J = 17.7, 5.1 Hz, 1H), 3.12–3.23 (m, 1H), 4.01 (t, J = 6.6 Hz, 2H), 6.58 (s, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 7.3 Hz, 1H), 8.44 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 26.0 (t), 31.3 (t), 33.8 (t), 36.1 (t), 67.6 (t), 77.5 (s), 104.5 (t), 114.4 (s), 115.6 (d), 126.1 (d), 126.9 (d), 129.7 (s), 135.5 (s), 142.3 (s), 169.2 (s) ppm; HRMS (ESI) calcd for $C_{15}H_{14}NBrNaO_2$: 342.0100 $[M + Na]^+$; found 342.0110.

4′-Methyl-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2m). Colourless oil (23 mg, 76%); R_f = 0.6 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.17 (m, 2H), 2.17–2.30 (m, 3H), 2.40–2.50 (m, 1H), 2.63 (s, 3H), 2.81 (dt, J = 16.8, 5.5 Hz, 1H), 3.16 (ddd, J = 16.8, 9.8, 5.6 Hz, 1H), 3.99 (t, J = 6.6 Hz, 2H), 6.51 (s, 1H), 7.13 (d, J = 7.2 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.34 (d, J = 7.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 23.0 (q), 25.8 (t), 32.2 (t), 34.3 (t), 36.2 (t), 67.5 (t), 78.4 (s), 105.7 (d), 118.1 (d), 124.5 (d), 127.1 (s), 128.3 (d), 130.8 (s), 135.3 (s), 143.2 (s), 168.6 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_2$: 278.1152 $[M + Na]^+$; found 278.1141.

10′-Methyl-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2n). Pink syrup (22.5 mg, 75%); R_f = 0.5 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (dt, J = 13.0, 4.85 Hz, 1H), 2.13–2.23 (m, 3H), 2.23–2.33 (m, 2H), 2.36 (s, 3H), 2.76 (ddd, J = 17.5, 12.1, 5.0 Hz, 1H), 2.94 (dt, J = 17.6, 4.7 Hz, 1H), 4.04 (ddd, J = 6.8, 5.6, 1.3 Hz, 1H), 4.15–4.23 (m, 1H), 7.34 (ddd, J = 7.2, 2.6, 1.3 Hz, 2H), 7.48 (ddd, J = 2.6, 1.5, 0.6 Hz, 1H), 8.48 (ddd, J = 2.3, 1.7, 0.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 8.9 (q), 26.3 (t), 31.8 (t), 34.0 (t), 36.8 (t), 68.0 (t), 80.3 (s), 113.8 (s), 116.4 (d), 118.2 (d), 123.8 (d), 125.0 (d), 131.4 (s), 134.3 (s), 136.1 (s), 168.5 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_3$: 278.1152 $[M + Na]^+$; found 278.1159.

4,5,6′,7′-Tetrahydro-3*H*,5′*H*-spiro[furan-2,8′-indolizin]-5′-one (2q). Colourless syrup (25.2 mg, 83%); R_f = 0.5 (30% ethyl

acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (ddd, J = 12.2, 6.0, 2.7 Hz, 1H), 2.03–2.13 (m, 1H), 2.13–2.21 (m, 3H), 2.39 (ddd, J = 12.3, 8.3, 6.5 Hz, 1H), 2.70 (dt, J = 17.6, 4.3 Hz, 1H), 3.10 (ddd, J = 9.8, 7.6, 1.7 Hz, 1H), 3.83–3.98 (m, 2H), 6.18 (dd, J = 3.3, 1.5 Hz, 1H), 6.24 (t, J = 3.3 Hz, 1H), 7.39 (dd, J = 3.3, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.9 (t), 30.4 (t), 34.2 (t), 35.9 (t), 67.0 (t), 76.8 (s), 109.1 (d), 112.2 (d), 117.2 (d), 136.3 (s), 168.2 (s), ppm; HRMS (ESI) calcd for $C_{11}H_{13}NNaO_2$: 214.0838 $[M + Na]^+$; found 214.0846.

5-Methyl-4,5,7′,8′-tetrahydro-3*H*,6′*H*-spiro[furan-2,9′-pyrido[1,2-*a*]indol]-6′-one (2r). Colourless syrup (dr 1 : 0.3, 27 mg, 90%); R_f = 0.5 (30% ethyl acetate in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (d, J = 6.1 Hz, 3H), 1.39 (d, J = 6.1 Hz, 1H), 1.73 (ddd, J = 3.4, 9.1, 12.5 Hz, 1H), 1.83–1.91 (m, 0.3H), 2.09–2.19 (m, 1.77H), 2.20–2.27 (m, 2.5H), 2.27–2.34 (m, 1.45H), 2.44–2.56 (m, 1.4H), 2.80 (dt, J = 17.4, 4.8 Hz, 1.4H), 3.12 (ddd, J = 4.9, 8.0, 12.9 Hz, 0.3H), 3.23 (ddd, J = 17.4, 9.4, 7.0 Hz, 1H), 4.19–4.31 (m, 1.33H), 6.53 (s, 1H), 6.56 (s, 0.3H), 7.26–7.31 (m, 1.67H), 7.32–7.38 (m, 1.38H), 7.54 (d, J = 7.6 Hz, 1.3H), 8.47–8.53 (m, 1.3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 21.0 (q), 21.2 (q), 31.3 (t), 31.5 (t), 33.2 (t), 33.6 (t), 34.1 (t), 35.0 (t), 36.1 (t), 37.7 (t), 74.8 (d), 75.9 (d), 77.4 (s), 78.3 (s), 104.5 (d), 104.8 (d), 116.5 (d), 116.6 (d), 120.4 (d, 2C), 123.9 (d), 124.0 (d), 124.8 (d), 125.0 (d), 129.0 (s), 129.2 (s), 135.3 (s), 141.8 (s), 168.9 (s), 169.3 (s) ppm; HRMS (ESI) calcd for $C_{16}H_{18}NO_2$: 256.1332 $[M + H]^+$; found 256.1326.

Conflicts of interest

There are no conflicts to declare.

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