

**“[Metal]–Catalyzed Carbon–Carbon and Carbon–
Heteroatom Bond Formation: Synthesis of Biologically
Active Heterocyclic Compounds”**

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

TO
UNIVERSITY OF PUNE

BY
Yadagiri Kommagalla

Dr. C. V. Ramana
(Research Guide)

ORGANIC CHEMISTRY DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE-411008
MARCH-2014

DEDICATED TO
MY Elder Brother
With tons of memory

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, National Chemical Laboratory, Pune – 411008. 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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March – 2014

Dr. C. V. Ramana

(Research Guide)

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Yadagiri Kommagalla

DEFINATIONS AND ABBREVIATIONS

Ac	–	Acetyl
Ac ₂ O	–	Acetic anhydride
AcOH	–	Acetic acid
BSA	–	<i>N,O</i> -Bis(trimethylsilyl)acetamide
Bu	–	Butyl
^t BuOH	–	Tertiary butyl alcohol
Cat.	–	Catalytic/catalyst
DCM	–	Dichloromethane
Conc.	–	Concentrated
DMP	–	2,2'-Dimethoxypropane
DMF	–	<i>N,N</i> -Dimethylformamide
DMAP	–	<i>N,N'</i> -Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
Et	–	Ethyl
EC	–	Effective concentration
HRMS	–	High Resolution Mass Spectroscopy
IBX	–	2-Iodobenzoic acid
Liq.	–	Liquid
Me	–	Methyl
MIC	–	Minimum Inhibitory Concentration
NMR	–	Nuclear Magnetic Resonance
piv	–	Pivoyl
Py	–	Pyridine
<i>p</i> -TSA	–	<i>para</i> -Toluenesulfonic acid
Ph	–	Phenyl
<i>i</i> -PrOH	–	<i>iso</i> -Propanol
rt	–	Room temperature
Sat.	–	Saturated
TBAF	–	Tetra- <i>n</i> -butylammonium fluoride
THF	–	Tetrahydrofuran
TMSOTf	–	Trimethylsilyl trifluoromethanesulfonate

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet

GENERAL REMARKS

- ^1H 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-50 MHz, AV-100 MHz, JEOL AL-100 (100 MHz) and DRX-125 MHz spectrometer.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 eV using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1} .
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- 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, I_2 , and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60-120), (100-200), and (230-400) mesh were used for column chromatography.

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ABSTRACT

Research Student	:	Yadagiri Kommagalla
Research Guide	:	Dr. C. V. Ramana
Title of Thesis	:	[Metal]–Catalyzed Carbon–Carbon and Carbon–Heteroatom Bond formation: Synthesis of Biologically Active Heterocyclic Compounds
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The thesis entitled “[Metal]–Catalyzed Carbon–Carbon and Carbon–Heteroatom Bond Formation: Synthesis of Biologically Active Heterocyclic Compounds” is divided into three chapters. The first chapter reveals the design and synthesis of two 1,4-disubstituted 1,2,3-triazole compounds their evaluation as anticancer agents (Section-A, Chapter 1) and as antifungal agents (Section-B, Chapter 1). The Synthesis of benzofuran conjugated sugar/nucleoside derivatives and the Synthesis of anti-inflammatory 2-arylbenzofurans *via* branched selective acrylate insertion are described respectively in Chapters 2 and 3.

Chapter-I: [Cu]-Catalyzed [3+2] Azide–Alkyne Cycloaddition: Synthesis of the PIP-3 antagonist PITENIN–1 analogues and their evaluation as potential anti-cancer and anti-fungal agents

PITENINS (Fig.1) are a class of small molecules which inhibit phosphoinositide 3-kinase (PI3K or PI3-kinase). PI3K plays a critical role in many cellular functions, including survival, proliferation, metabolism and motility. Hyper-activation of this pathway is known to play an important role in tumorigenesis.

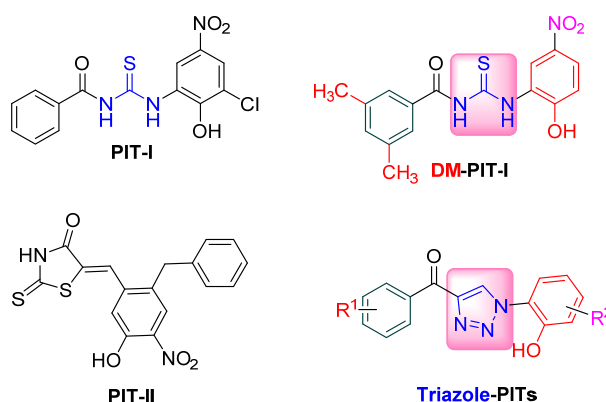
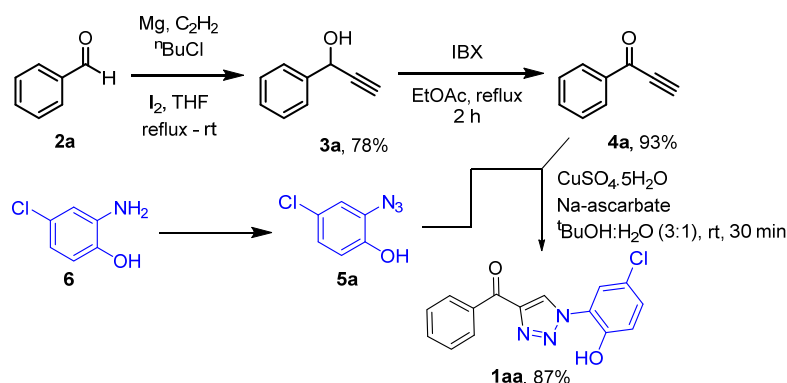


Figure 1: Structures of the two classes (PIT-1 and PIT-2) of inhibitors of phosphatidylinositol-3 kinase (PI3K) signaling pathway, termed PITENINs (PITs) and the newly designed 2nd generation triazole-PITs

Considering some of the drawbacks with these PITENINS (high micromolar activity and low stability for DMPIT-I the $T_{1/2} < 2$ min in mouse liver microsomal stability assay *in vitro*), the present investigations have been undertaken as means of improving the activity and pharmaceutical features of this new class of drug, have been under taken. As a first step, the possibility of replacing the susceptible thiourea unit with a 1,2,3-triazole structural motif has been examined. The simple triazole derivative **1aa** was prepared by the cycloaddition of alkynone **4a** (Scheme 1) with azidophenol **5a** under copper catalyzed click reaction conditions. The initial screening of **1aa** against growth of A2780 human ovarian cancer cells revealed that **1aa** has a comparable activity with the corresponding PIT-1 analogue.



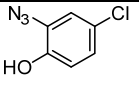
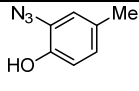
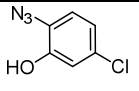
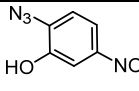
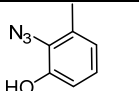
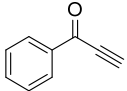
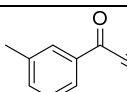
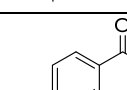
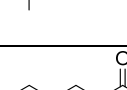
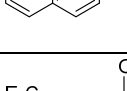
Scheme 1: Synthesis of selected alkynol and alkynone

This initial promise has motivated us to synthesize a collection of triazole derivatives by varying the functional groups on both the aryl rings for optimization and for studying the structure activity relationship. A wide range of alkynones **4b–4e** have been synthesized by following the established procedure and by employing the azido phenols **5a–5e** as the dipolarophiles for the Cu-catalyzed azide-alkyne [3+2]-cycloaddition. Table 1 summarizes the details of the compounds synthesized and also their anticancer data. This has ultimately resulted in the identification of **1ea** that has shown activity 20 times higher than that of the DM-PIT-1.

The activity of **1ea** was further tested in lipid overlay assay, measuring binding of Akt PH domain with PIP3, spotted on micro cellulose membrane as previously described. Compound **1ea** displayed substantially higher activity compared to DM-PIT-1. The inhibition of PI3K/Akt signaling in human glioblastoma U87MG and ovarian carcinoma A-2780 cells was further examined with compound **1ea**. Interestingly, while a limited inhibition of Akt phosphorylation of Akt itself and several of its effectors by **1ea** was observed, it displayed robust inhibition of TORC1/p70S6K/S6 pathway downstream from Akt, suggesting that the increased activity of **1ea** translated into more specific inhibition of a particular pathway downstream from PI3K/Akt. Other targets of **1ea** in the PI3K/Akt signaling pathway remain to be fully elucidated in the future. Finally, one of the major goals of our study was to improve the pharmacological properties of PIT-1/DM-PIT-1. The compound **1ea** displayed $T_{1/2}=119$ min in mouse liver microsomal stability assay *in*

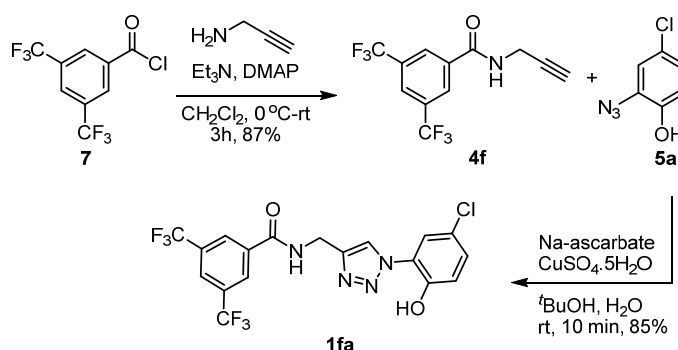
vitro (for DM-PIT-1 it was $T_{1/2} < 2$ min). Overall, our SAR analysis describes a new analog of PIT-1 with significantly improved anti-cancer activity and pharmacological properties.

Table 1: Variously substituted 1,2,3-triazoles synthesized and their inhibition of PIP3

					
	1aa $EC_{50} = 103.6 \mu M^a$ $= 51.6 \mu M^b$	1ab $EC_{50} > 100 \mu M^a$ $> 100 \mu M^b$	1ac $EC_{50} = 48.9 \mu M^a$ $= 42.3 \mu M^b$	— —	1ae $EC_{50} = 8.1 \mu M^a$ $= 8.0 \mu M^b$
	1ba $EC_{50} = 57.8 \mu M^a$ $= 30.6 \mu M^b$	1bb $EC_{50} > 100 \mu M^a$ $> 100 \mu M^b$	1bc $EC_{50} = 100 \mu M^a$ $= 64.4 \mu M^b$	1bd $EC_{50} = 89.1 \mu M^a$ $= 70.5 \mu M^b$	1be $EC_{50} = 104.0 \mu M^a$ $= 98.4 \mu M^b$
	1ca $EC_{50} = 64.1 \mu M^a$ $= 41.6 \mu M^b$	1cb $EC_{50} > 100 \mu M^a$ $> 100 \mu M^b$	— —	— —	1ce $EC_{50} > 100 \mu M^a$ $> 100 \mu M^b$
	1da $EC_{50} > 100 \mu M^a$ $> 100 \mu M^b$	1db $EC_{50} > 100 \mu M^a$ $> 100 \mu M^b$	— —	— —	1de $EC_{50} = 85.2 \mu M^a$ $= 74.9 \mu M^b$
	1ea $EC_{50} = 11.99 \mu M^a$ $= 3.15 \mu M^b$	— —	— —	— —	— —

^aalone with compounds, ^balong with TRIAL, TRIAL-tumor necrosis factor-related apoptosis-inducing ligand

Compound **1fa** which is closely related to **1ea** was synthesized from 3,5-bis(trifluoromethyl)benzoyl chloride **7** by coupling with propargyl amine to procure the key intermediate **4f**, which was further subjected for the cycloaddition reaction with azidophenol **5a**. The compound **1fa** has showed good activity, but not found to be better than **1ea**.



Scheme 2: Synthesis of substituted 1,2,3-triazole (**1fa**)

Synthesis, characterization, antifungal evaluation and mechanistic studies of new 1,2,3-triazole derivatives

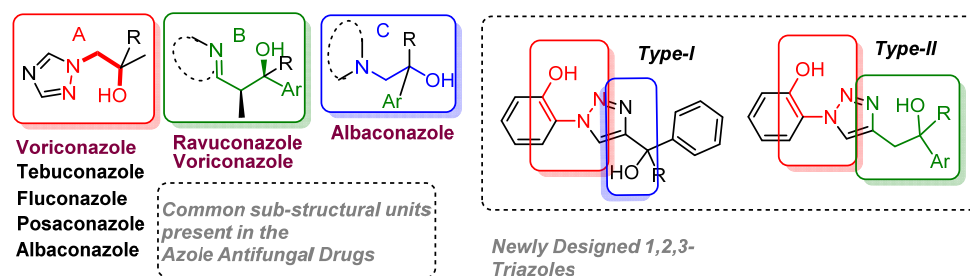
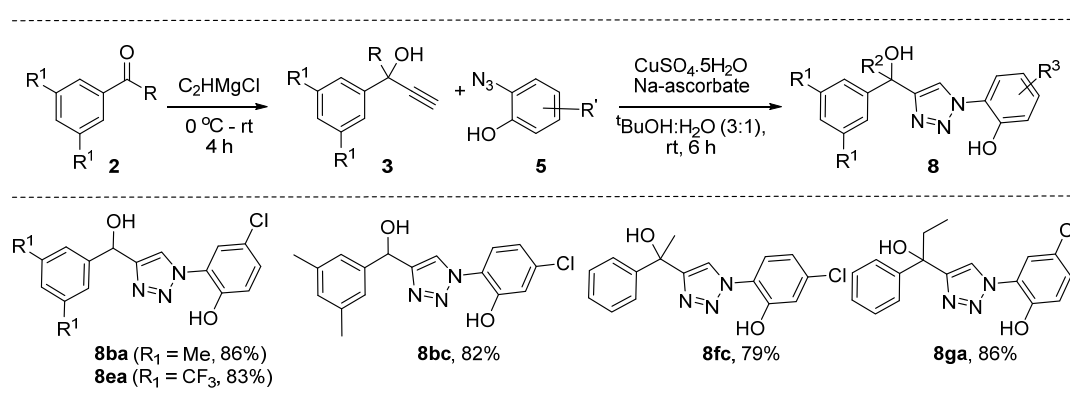


Figure 2. Common sub-structural units A–C found in the commercial azole-based antifungals and newly designed 1,2,3-triazole having any two of these A–C sub-structural units

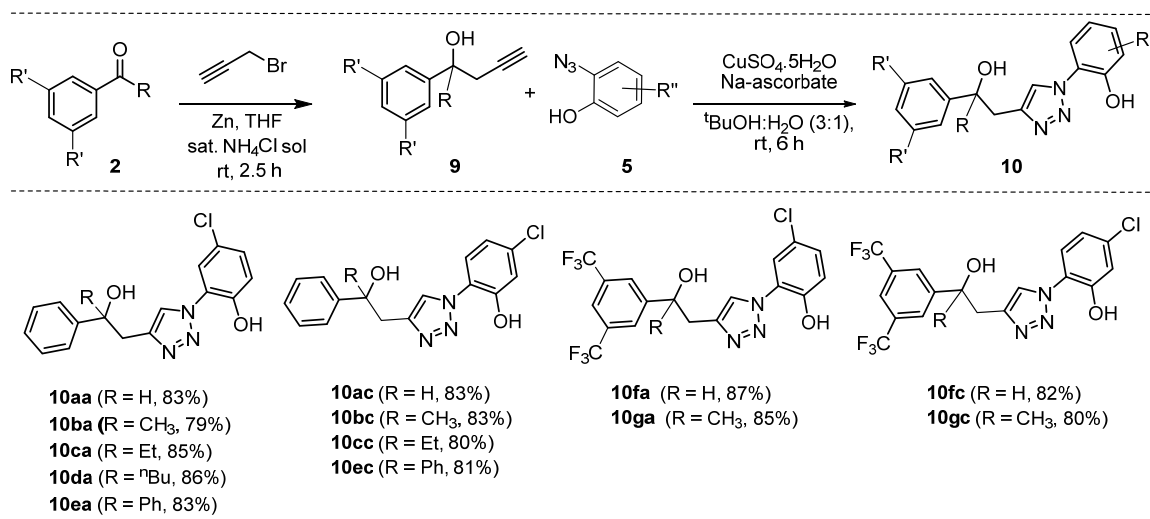
In recent years, studies have revealed that many of the cancer drugs have the potential to be antifungal agents and conversely anti-fungal compounds also show potential anti-cancer properties. Considering this, and aided by some sub-structural elements in azole antifungal drugs two classes of 1,4-disubstituted 1,2,3-triazole compounds have been designed as potential antifungal candidates (Fig. 2).

Scheme 3 saliently describes the synthesis of some Type I precursors following simple synthetic transformations. The aromatic alkynol intermediates were synthesized by treating aryl aldehydes/ketones with ethynylmagnesium chloride and then the resulting alkynols were subjected for 1,3-dipolar cycloaddition with chloroazidophenols **5a** and **5c** under established conditions.



Scheme 3: Synthesis of Triazole Compounds of Type-I

The synthesis of the compounds of Type 2 started with the reaction of aryl aldehydes/ketones with propargyl bromide under Zn-mediated Barbier reaction conditions (Scheme 4). The 1,3-dipolar cycloaddition of chloroazidophenols **5a** and **5c** with different alkynols **9a–9g** (Scheme 1B.3) was carried out under established CuAAC reaction conditions.



Scheme 4: Synthesis of Type II 1,2,3-Triazoles

These two classes of 1,2,3-triazoles were screened against *C. albicans* ATCC 24433, *C. albicans* ATCC 10231, *C. glabrata* NCYC 388, *C. neoformans*, *C. neoformans* ATCC 34664, *A. fumigatus* MCC 1046, *A. niger* ATCC 10578(CLSI M27-A3) and *F. oxysporum* (CLSI M38-A2). Based on the MIC results, compounds **8bc**, **10cc**, **10fa**, **10fc**, **10ga**, **10gc** and **10da** were identified as lead molecules. The mechanism of antifungal action of these compounds was investigated by different assays. Detailed experiments on the depletion of ergosterol revealed that the antifungal activity of the compounds **10ca**, **10fa** and **10ga** was due to lanosterol 14 α -demethylase inhibition. On the other hand, with compounds **8bc**, **10cc**, **10fc**, **10gc**, **10da**, there was no ergosterol depletion and later it has been identified that their antifungal activity was because of generation of intracellular reactive oxygen species (ROS). Compounds **10da** and **10fc** were most effective and showed ROS generation in >99% cells at 2X MIC 4X MIC concentration, respectively.

Chapter 2: [Pd]-Catalyzed Cycloisomerization: Synthesis of benzofuran conjugated sugar/nucleoside derivatives

The modification on the sugar back bone in nucleosides is an important strategy for the development of antiviral and anticancer drugs. The sugar modifications, in particular, C-3' modified sugar unit in the nucleosides have gained significant attention for therapeutic development.

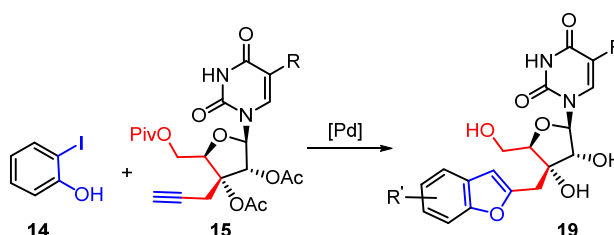
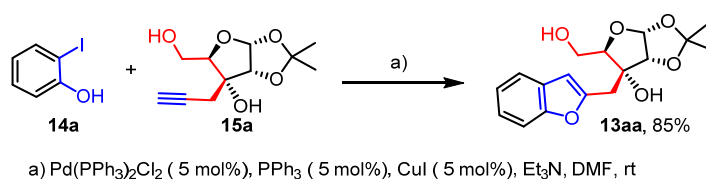


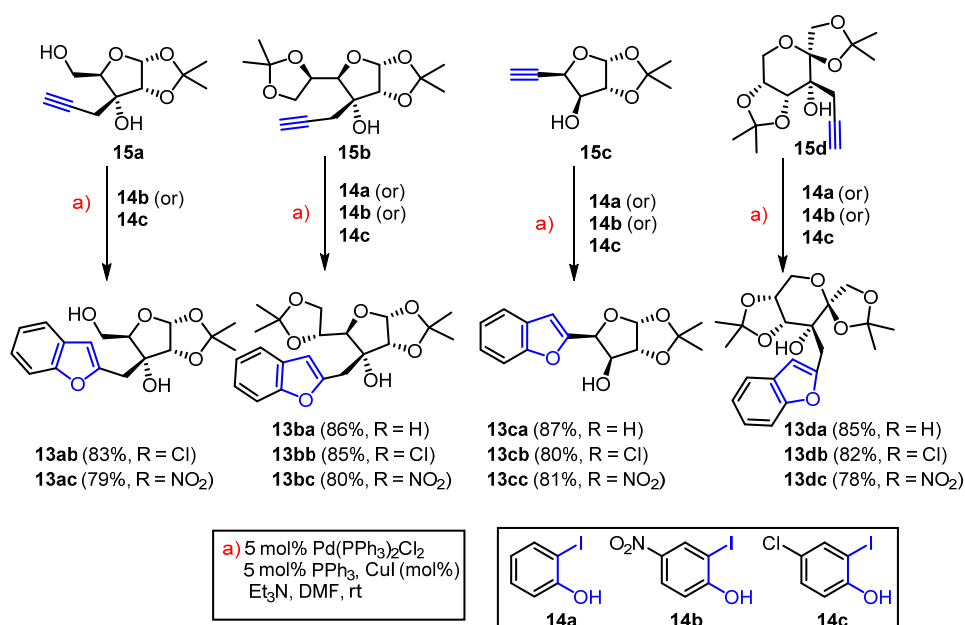
Figure 3: Strategy for benzofuran-conjugated nucleosides

Considering the widespread occurrence of the benzofuran unit in a variety of biologically active molecules, we designed the modified nucleosides having a pendant C-3'-*(2-benzofuranlymethyl)* unit. Figure 3 reveals our intended strategy featuring a Pd-catalyzed Sonogashira coupling *cum* cyclization reaction of C3'-propargyl nucleoside with *o*-iodophenol substrates. Our initial studies in this direction started with exploring the feasibility of this approach with simple sugar derived alkynols. The optimization of the Pd-catalyzed reaction was performed with xylose derived alkyne **15a** and 2-iodophenol (Scheme 5). The reaction was carried at rt by employing 5 mol% each of Pd(PPh₃)₂Cl₂ and PPh₃ and CuI in a mixture of Et₃N and DMF. The reaction proceeded smoothly and the requisite benzofuran-conjugated xylose derivative **13aa** was obtained in very good yield



Scheme 5: The synthesis of sugar- benzofuran conjugates.

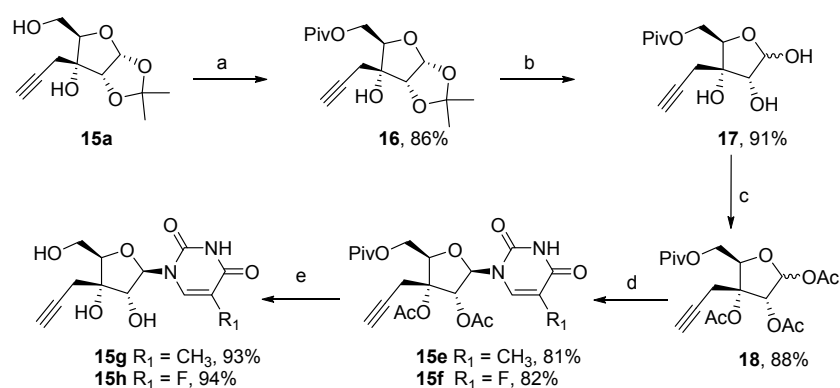
Scheme 6 shows the scope of this reaction on four sugar templates **15a–15d** employing three representative iodophenols **14a–14c**. The reactions were facile with all the four alkynes employed and gave the corresponding sugar–benzofuran conjugates in very good yields.



Scheme 6: Scope of [Pd]-catalyzed benzofurannulation of sugar derivatives.

Having established the [Pd]-catalyzed benzofuran synthesis on simple sugar derivatives, we next focused on the feasibility of this reaction with unprotected C(3)-propargylated nucleosides. Our initial intention was to carry out this benzofurannulation reaction on free nucleosides **15h–15j**, thereby making a provision of substrate flexibility at the final stage and providing an easy access to synthesis of a collection of C(3)-modified nucleosides (Scheme 7).

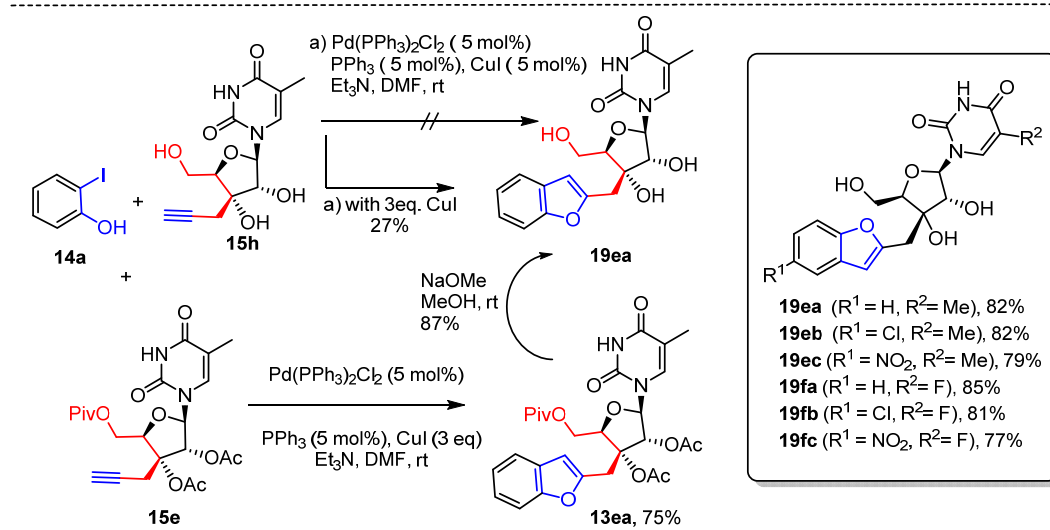
The synthesis of the alkynyl nucleosides **15g–15h** started with the selective protection of the C(5)–OH of alkynol **15a** as its pivaloate **16** by using pivaloyl chloride in the presence of triethylamine in dichloromethane. The hydrolysis of the acetone group followed by peracetylation of the intermediate lactol gave an anomeric mixture of C(3)-propargyl ribose derivatives **18**. The *N*-glycosidation of the anomeric mixture **18** was carried out under modified Vorbrüggen conditions employing thymine, and 5-fluorouracil to afford the protected nucleosides **15e–15f**, respectively. The deacetylation of **15e–15f** employing catalytic amounts of NaOMe in methanol gave the nucleosides **15g–15h** (Scheme 7) in good yields.



Scheme 7: Reagents and conditions: a) Piv-Cl, Et₃N, DMAP, CH₂Cl₂, 4 h; b) 70% ACOH, reflux 6h; c) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 4 h; d) BSA, TMSOTf, CH₃CN, 4 h; e) NaOMe, MeOH, rt, 20 min.

Our initial experiments dealing with the Sonogashira coupling reaction of alkyne **15g** (Scheme 8) were unsuccessful under the conditions described in Scheme 5 and 6. Optimization of the reaction conditions has been carried out by increasing the amounts of the copper iodide. These experiments revealed that the presence of 3 eq. of copper iodide (with respect to the alkyne) is essential. However, the isolation of pure nucleosides turned out to be a difficult proposition as the samples were always found to be contaminated with the triethylamine salts. Considering these difficulties, we next moved to the corresponding protected nucleosides **15e–15f**. The Sonogashira coupling of **15e** with **14a** proceeded smoothly in the presence of 3 equivalent of CuI and the corresponding benzofuran– nucleoside conjugate **13ea** was obtained in excellent yields. The deacetylation of **13ea** with NaOMe in methanol provided the desired free nucleoside **19ea**.

We have utilized the optimized sonogashira coupling reaction for the synthesis of the remaining benzofuran conjugated nucleoside derivatives employing nucleoside derived alkynes with three Iodophenols (**14a-14c**), obtained in good yields and these were subsequently hydrolyzed with NaOMe in methanol to provide the desired free nucleoside **19ea-19fc**.



Scheme 8: Reaction optimization for benzofuran-conjugated nucleosides synthesis.

Chapter 3: [Ru]-Catalyzed C-H activation: Synthesis of anti-inflammatory 2-arylbenzofurans via linear/branched selective acrylate insertion

The 2,3-disubstituted benzo[*b*]furan derivatives of Type 1–4 (Fig. 4) have been established as novel anti-inflammatory and/or class 3 antiarrhythmic agents. The reported procedures for the syntheses of these compounds are multistep in nature and involve harsh reaction conditions such as the Friedel-Crafts acylation and acid/base mediated condensations.

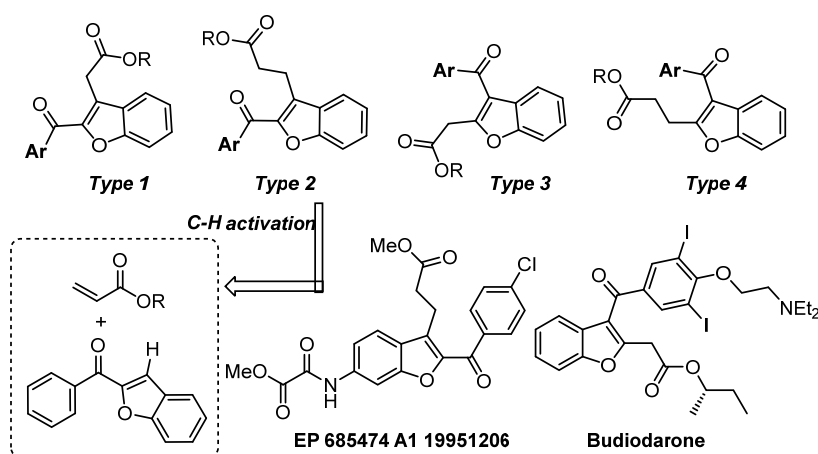
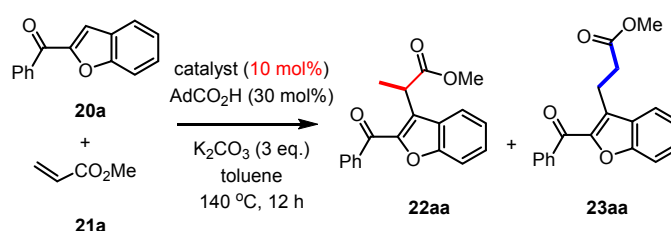


Figure 4. Categorization of medicinally important 2/3-arylbenzo[*b*]furans and the structure of related drug Budiodarone

As a part of our ongoing studies on “C–H activation & functionalization”, we intended to synthesize the aroylbenzofurans of Type 2 *via* carbonyl directed C–H activation and alkylation with acrylates. The ruthenium-catalyzed direct addition of the *ortho* C–H bonds of aryl ketones employing vinylsilanes reported by Murai *et al.* is one of the early examples in this area that has been subsequently expanded rapidly. However, the ruthenium-catalysed hydroarylation of acrylates has not yet been documented. Considering this, and given the industrial relevance of the products, as well as the challenging Ru-catalyzed hydroarylation of acrylates, the current exercise has been taken up.

Table 2. Catalyst screening for directed hydroarylation



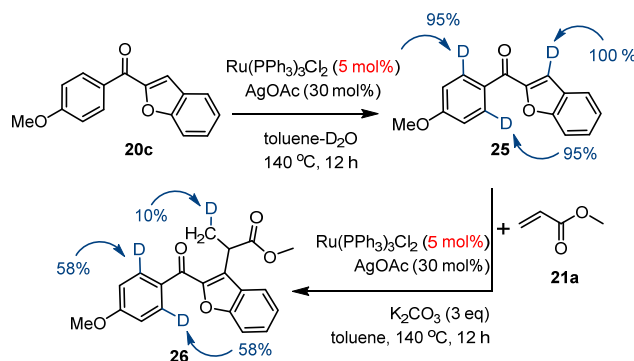
S.No	Catalyst	Yield (%) ^a /(22aa/23aa)
1	[Ru(<i>p</i> -cymene)Cl ₂] ₂	23 (28/72)
2	Ru ₃ (CO) ₁₂	31(83/17)
3	RuCl ₃ .H ₂ O	nd
4	RuO ₂	No reaction
5	(PPh ₃) ₃ Ru(CO)H ₂	73 (89/11)
6	Ru(PPh ₃) ₃ Cl ₂	82 (94/6)

^aisolated yield; nd = not determined (complex reaction mixture)

Initial studies using various complexes revealed that the desired alkylation of **20a** is viable and, quite interestingly, branched alkylated products being formed predominantly (Table 2). The optimization experiments have been carried with Ru(PPh₃)₃Cl₂ in order to identify to right conditions for the best branched-selective alkylation. To this end, we found that the use of 5 mol% Ru(PPh₃)₃Cl₂ and 30 mol% silver acetate as the additive, 3 equivalent of K₂CO₃ as base and toluene as the solvent provided the best selectivity and the yield.

Next, the compatibility of various α , β -unsaturated esters as coupling partners has been examined under the optimized conditions employing **20a** as the substrate (Table 3). The reactions with ethyl-, butyl-, and cyclohexyl acrylates (**21b–21d**) gave the corresponding products in very good isolated yields without substantial difference in the branched/linear selectivity. In case of methyl crotonate (**21e**), the reaction proceeded smoothly and the corresponding branched adduct **22ae** was obtained as the major product and the 1,5-addition linear adduct **24** was obtained as the minor isomer with an overall yield of 84%. However, with both methyl- and butyl methacrylates (**21g**, **21h**), the

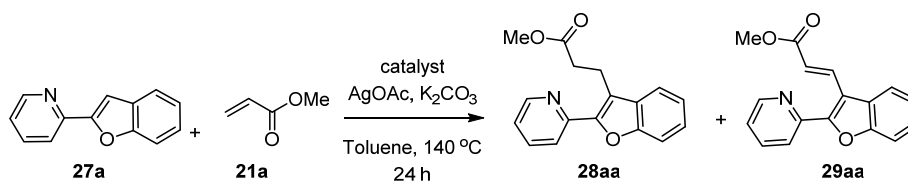
of 2-acetyl benzofuran did the reaction proceed smoothly, with the product formation occurring in good yield. However, the regioselectivity dropped to ~1:1. Coming to the olefins, the coupling of **20a** with styrene was facile and gave a 1:1 mixture. On the other hand, for the same reaction with dodec-1-ene, complete branched selectivity with partial conversion resulted.



Scheme 10. Deuterium labeling experiments with **25**

Next, the deuterium labelling experiments were conducted to understand the course of the mechanism of the branched selective alkylation. As shown in Scheme 10, the deuterium incorporation was observed at the C3 position of benzofuran and also at the C2'/C6' position of the pendant aryl ring. Quite interestingly, when compound **25** was subjected for alkylation with methyl acrylate, the incorporation of deuterium at the β -position of the branched product was observed. However, the percentage of deuterium incorporation was quite nominal (<10%).

Table 4. Catalyst screening for directed hydroarylation



S.No	catalyst	K ₂ CO ₃	28aa (yield %)	29aa (yield %)
1	Ru(PPh ₃) ₃ Cl ₂	presence	no	59
2	Ru(PPh ₃) ₃ Cl ₂	absence	75	no
3	Ru ₃ (CO) ₁₂	absence	no	68
4	[Ru(p-cymene)Cl ₂] ₂	absence	66	no

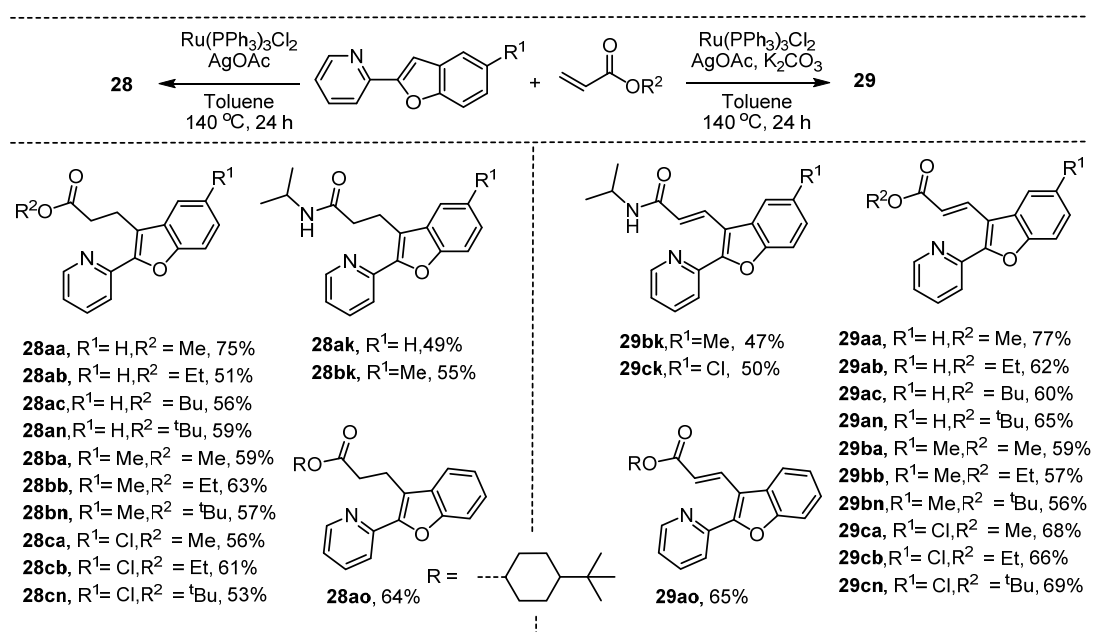
With this available information and considering the previous reports, a tentative mechanistic proposal for the branched selective alkylation has been put forward. The large steric effect of PPh₃ around the metal center and the non-polar nature of the Ru–C bond in the intermediate ruthena-cycle have been attributed as influences in the insertion

of the alkene into the Ru–C bond taking the functional group far from the PPh₃ ligands and thus leading to the branched-selective alkylation.

Considering our experiments with 2-acetylbenzofuran, where a 1:1 mixture of branched- and linear alkylation products were formed, to further explore in the direction of the influence of the coordinating ligand, the pyridine has been selected as a directing group. Surprisingly when 2-(2-pyridyl)-benzofuran **27a** was subjected for the C–H activation and alkylation with methyl acrylate under optimized conditions, only the cross dehydrogenative adduct **29aa** was formed with complete linear selectivity.

Intrigued by this, the reaction of **27a** with methyl acrylate has been examined with various other complexes. Quite interestingly, with the [Ru(p-cymene)Cl₂]₂ complex, the linear selective alkylation product **28aa** was exclusively observed. To our surprise, the optimization experiments with the Ru(PPh₃)₃Cl₂ complex revealed that even with this complex, when K₂CO₃ was absent, the alkylation product **28aa** was obtained exclusively.

Table 5. Substrate scope for alkylation and alkynylation with acrylates



Having discovered two complementary conditions for alkylation or alkynylation, we explored the generality of these reactions by employing a wide range of olefins and differently substituted benzofuran derivatives. The reactions with various acrylates such as ethyl-, butyl-, *tert*.butyl- and 4-*t*-butylcyclohexyl- acrylates (**21b**, **21c**, **21n** and **21o** respectively) were compatible and gave the corresponding products in moderate to good isolated yields. However, the reactions with *N*-isopropylacrylamide as well as with methyl crotonate were sluggish and the products were obtained in poor yields. Quite interestingly, with acrylonitrile (**21j**), under both conditions, the alkylated **28aj** and alkynylation product **29aj** were obtained in a 1:1 ratio.

Coming to the mechanism, a hypothesis founded upon the more polar Ru–C bond due to the pyridine directing group and approach of the electrophilic β -carbon close to the nucleophilic Ru-C carbon atom is provided for the exclusive linear selectivity. Coming to the role of base, after the coordinative insertion, the resulting organo-Ru intermediate can undergo either protodemetallation (by the released AcOH, in absence of base) or beta-elimination (*via* the base-mediate hydride abstraction through the anchimeric assistance of the metal centre) to afford respectively alkylation and alkenylation products.

CHAPTER I:

**[Cu]-Catalyzed [3+ 2] Azide–Alkyne Cycloaddition:
Synthesis of the PIP-3 antagonist PITENIN–1
analogues and their evaluation as potential anti-
cancer and anti-fungal agents**

SECTION A

**Synthesis of the PIP-3 antagonist PITENIN-1 analogues and
their evaluation as potential anti-cancer Agents**

1A.1.1. Over View of Cancer

Cancer is a deadly disease, which is known for uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion or by implantation into distant sites by metastasis.¹ According to the GLOBOCAN 2012 worldwide survey report, in 2012 there were 32.6 million people (over the age of 15 years) alive who were diagnosed with a cancer (2007-2012). In 2012, about 14.1 million new cancer cases have been reported and around 8.2 million cancer-related deaths.² This was quite alarming when compared with the 2008 statistics (12.7 million cancer cases and 7.6 million cancer-related deaths). It was estimated that the number will increase to 19.3 million new cancer cases per year by 2025, because of the increase of the aged population. Very importantly, 56.8% of all cancers and 64.9% cancer deaths in 2012 occurred in the poor and developing countries. According to a WHO report, nearly 0.7 million Indians die of cancer every year, while over 1 million are newly diagnosed with some form of the disease. Thus, there is an urgent need for cancer control today through the development of effective and affordable drugs for less developed countries.

1A.1.2. Treatment

There are 200 different types of cancer diseases known till date, affecting various parts of the body which are all unique in their causes and symptoms.³ Cancer treatment is usually a combination of a number of different modalities. Most common types of cancer treatment are:

- Surgery
- Chemotherapy
- Radiation therapy
- Targeted therapy
 - Antibody therapy
 - Small molecule inhibitors
- Immunotherapy
- Hyperthermia
- Stem cell transplant and laser treatment

The severe side-effects caused by some of the early cancer treatment methods such as chemo-, surgery, and radiation; sometimes give a feeling that cancer treatment is worse than cancer. Once the treatment begins, people often begin to feel quite sick. Targeted therapy is another option, which has a significant impact in the treatment of

some types of cancer, and is currently a very active research area.⁴ For targeted therapy, which became available from the late 1990s, most conventional anticancer drugs have been designed with deoxyribonucleic acid (DNA) synthesis as their target. Most targeted therapies are either small-molecule drugs or monoclonal antibodies.⁵ Most monoclonal antibodies cannot penetrate the cell's plasma membrane and are directed against targets that are outside cells or on the cell surface. The past two decades has witnessed antibody-based therapy for cancer.⁶

Small molecule inhibitors are one of the active research areas in targeted therapy in present scenario. Small-molecule drugs are typically able to diffuse into cells and can act on targets that are found inside the cell.⁷ The newly introduced drugs have shifted the targets from the direct synthesis of DNA to basic function, which is responsible for tumor formation.⁸ One such target, the protein kinase family, has become increasingly important over the past 20 years, with approximately 30 distinct kinase enzymes being targeted by drugs under development for clinical trials. Kinases, which are part of the larger family of phosphotransferases are critical in cellular functions such as metabolism, cell signaling, protein regulation, cellular transport, secretory processes, and myriad other cellular pathways. Kinase is a type of enzyme that transfers phosphate groups from high-energy donor molecules, such as ATP, to specific substrates. The deregulation of kinase activity affects the signals that promote or regulate the cell cycle, growth factors and their receptors, signal transduction pathways and thus has emerged as a major mechanism by which cancer cells evade normal physiological constraints on growth and survival, leading to tumorigenesis. Thus, the kinase signaling pathway is an important potential target for inhibition.

Two examples of small molecule anticancer kinase inhibitors in the clinic are Gleevec (Imatinib), which is approved for the treatment of chronic myeloid leukaemia⁹ and gastrointestinal stromal tumours and Iressa (gefitinib) which is approved for the treatment of non-small-cell lung cancer.¹⁰ These drugs were designed to inhibit receptor tyrosine kinases that are associated with development and progression of the tumor. Targeted molecular therapies, such as, the receptor tyrosine kinase inhibitors, have shown greater tolerance than traditional non-specific chemotherapeutic drugs towards normal tissues, presenting, a larger therapeutic window.

This approach seems applicable to certain classes of intracellular signaling proteins and pathways that possess heavily mutated hotspots. Three major signaling pathways that have been identified as playing important roles in cancer include the mitogen-activated protein kinase (MAPk)/Ras, the protein kinase C (PKC) and the PI3K/AKT signaling cascade. The PI3K/AKT signaling pathway plays a vital role in the cellular functions and the deregulation or disruption of this pathway causes tumorigenesis.¹¹

1A.1.3. Phosphatidylinositol 3-kinases (PI3Ks)

Phosphatidylinositol 3-kinases (PI3Ks) belong to an enzyme family of vitally important regulators for intracellular signaling pathways. PI3Ks catalyze the phosphorylation of phosphatidylinositol at the 3'-position of the inositol ring producing secondary messenger lipids which control cellular activities including cell survival, growth and proliferation. A large proportion of cell-surface receptors, especially those linked to tyrosine kinases activate PI3Ks.¹² Dysregulation of the PI3K pathway has been implicated in many human diseases. Hyper activation of this pathway is known to play an important role in tumorigenesis, whereas the deficiencies in the PI3K pathway contribute to the development of type II diabetes. Therefore, this pathway offers promising targets for the development of drugs to combat this diseases.^{13, 14}

The PI3K family is divided into three different classes: Class I, Class II, and Class III, based on their primary structure, mode of regulation, substrate specificity, tissue distribution and function within the cell.^{15, 16} The class I PI3Ks are responsible for the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3). Class I PI3Ks (α , β , and γ) are recruited to the plasma membrane in response to growth factor and hormone stimulation to mediate the phosphorylation of lipid phosphatidylinositol-4,5-bisphosphate (PIP2), generating PIP3, which orchestrates multiple downstream intracellular signaling events. PIP3 signaling is terminated by the phosphatase PTEN, which dephosphorylates PIP3. Genetic alterations targeting PTEN are among the most frequent mutations in human cancers, indicating a critical role of uncontrolled signaling through PIP3 in tumorigenesis and metastasis.¹⁷ This conclusion is reinforced by transgenic studies establishing that loss of PTEN leads to tumorigenesis.

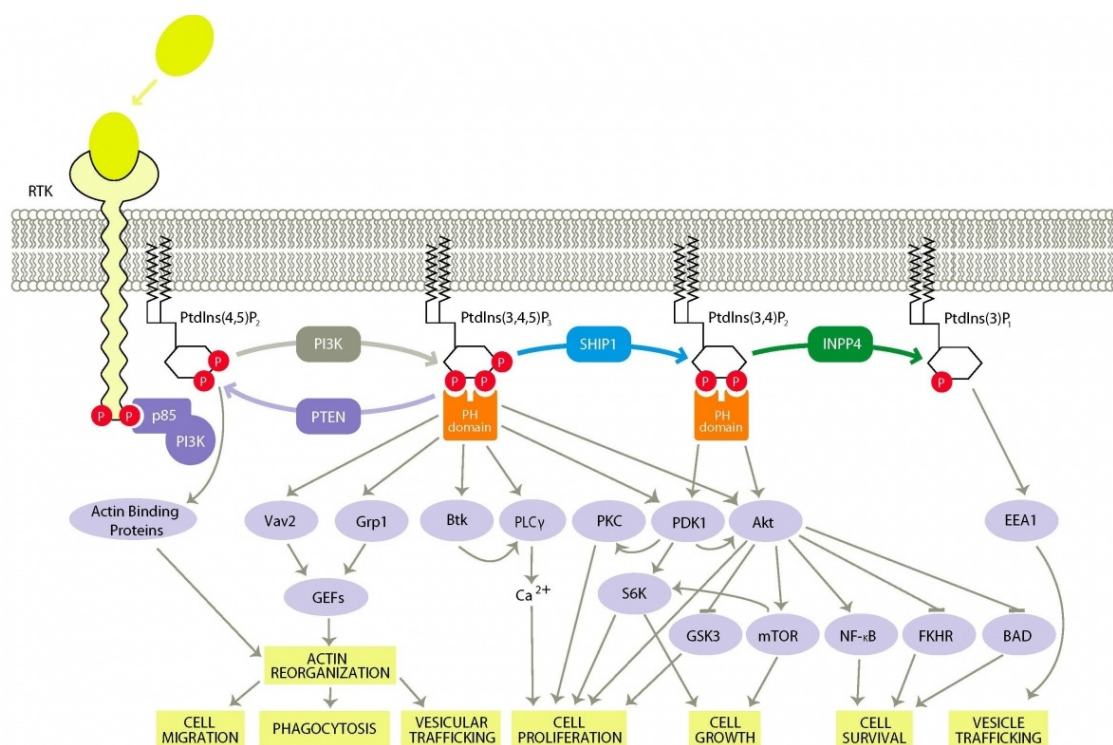


Figure S1.1: The PI3K signalling pathway¹⁸

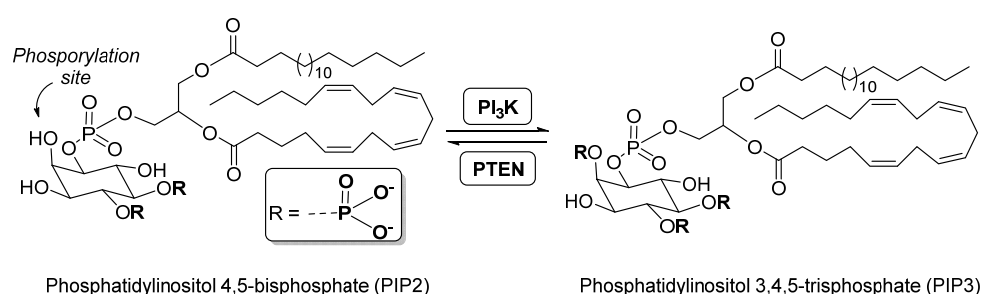


Figure S1.2: Phosphate transfer reaction catalyzed by Class I PI3K isoforms

PIP3 controls a complex cellular signaling network regulating cell growth, proliferation, and survival. The PIP3 target proteins are located in the cytosol of unstimulated cells and are recruited to the membrane through pleckstrin-homology (PH) domain-mediated binding to newly formed PIP3. Membrane translocation and activation of the PIP3 target proteins initiate a variety of local responses, including assembly of signaling complexes and priming of protein kinase cascades.^{13, 14} PIP3 regulates an array of PH domain-containing proteins,¹⁹ such as serine-threonine kinases Akt and PDK1, GRP1, a GDP/GTP exchange factor of ADP ribosylating factor, and protein tyrosine kinases of the Bruton's tyrosine kinase (Btk) and Tec families.^{20, 21} This diversity in PIP3 signaling makes it one of the most important second messengers downstream from growth factor and oncogene signals. A

particularly important example of PIP3-dependent activation is that of serine-threonine kinase Akt. It is achieved both through the binding of the Akt PH domain to PIP3 and membrane translocation of another target of PIP3, PDK1, which phosphorylates and activates Akt. The Akt family plays a fundamental role in cell survival, growth, and energy metabolism.²²

Although lipid–protein interactions mediate PI3K signaling and are frequently deregulated in cancer, most therapeutic strategies targeting the PI3K pathway have focused on inhibitors for downstream targets, including PDK1²³ and Akt.²⁴ Phospholipid–protein interactions have not been as actively targeted, even though lipid molecules are among the most important classes of second messengers. This is surprising considering that they represent “prototypic” small molecule–protein interactions usually involving well-defined binding sites.²⁵ Conceptually, protein–lipid interactions may be more readily targetable compared with protein–protein interactions, which frequently involve interactions of extended flat protein surfaces difficult to disrupt by small molecules.

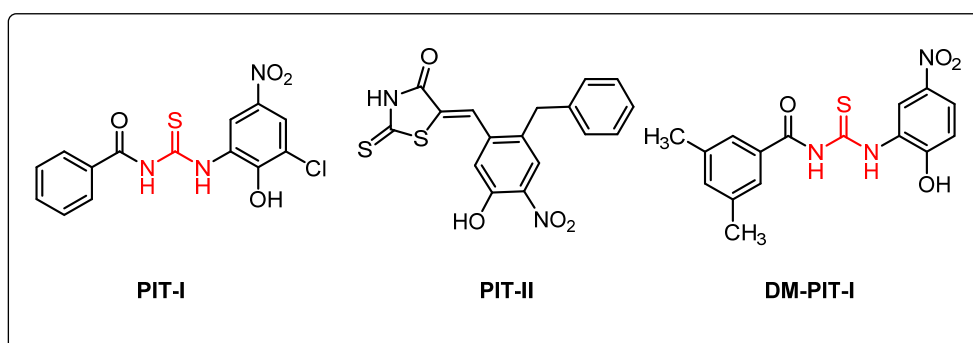


Figure S1.3: *Small molecule antagonists of PIP3*

There are many approaches focused on targeting enzymatic activities in the PI3K network. We have recently described a new approach aimed at targeting a universal central step in PI3K signal transduction, i.e. binding of PIP3 to PH domains of effector proteins.²⁶ In particular, we have developed two selective new classes of small molecule nonphosphoinositide PIP3 inhibitors, termed PITenins (PITs), PIT-1 (N-((3-chloro-2-hydroxy-5-nitrophenyl)carbamo-thioyl)benzamide) and PIT-2 ((Z)-5-(2-benzyl-5-hydroxy-4-nitrobenzylidene)-2-thioxothiazolidin-4-one).^{27,28}

Surprisingly, these two structurally dissimilar molecules displayed very similar anti tumor activities, including induction of apoptosis and metabolic stress and inhibition of cell migration and invasion. Particularly, both PIT-1 and PIT-2 displayed

synergistic toxicity with TRAIL in human glioblastoma U87MG cells. These activities have been linked to the inhibition of Akt signaling and actin remodeling by ARF6, two pathways regulated by PI3K. These *in vitro* activities of PITs translated into the significant inhibition of tumor growth and lung metastasis formation in 4T1 and B16-F10 syngeneic xenograft models by the dimethyl analogue of PIT-1.

Despite the promising initial results, PITs have displayed some obvious limitations, including high micromolar activity, this means, that the particular compound required more quantity and as well as multiple non-drug-like features. In particular, nitrophenyl and thiourea moieties of PIT-1 described potential toxicity concerns and metabolic liabilities. The initial analysis of the PIT-1 series revealed surprisingly specific SAR for a micromolar compound suggesting several changes to the molecule, leading to some increase in activity and changes in targeting different PH domains. In particular, the addition of two methyl groups to the phenyl ring in PIT-1 (DM-PIT-1, Fig. S1.3) resulted in some increase in activity and improved incorporation into long-circulating PEG-PE micelles for *in vivo* delivery.^{27, 29} DM-PIT-1 displayed $T_{1/2} < 2$ min in mouse liver microsomal stability assay *in vitro*. Furthermore, changes to the nitrophenyl ring were identified. However, these results did not address the main limitations of the PIT-1 series. Due to these limitations, the present inventions were undertaken to explore and seek to improve activity and pharmaceutical features of this new class of anti-cancer lead molecule. Our first concern was to replace the susceptible thiourea unit with a stable bioisostere and the nitro (NO₂) group with different functional groups.

1A.1.4. Bioisosters

Over the years, the medicinal research mainly focused on the development of a clinically useful drug, providing either a cure for a particular disease or symptomatic relief from a physiological disorder. Sometimes the lead compound with a desired pharmacological activity may have associated with it undesirable side effects, characteristics that limit its bioavailability, or structural features which adversely influence its metabolism and excretion from the body.³⁰ There is a strong necessity to overcome from these issues.³¹ The medicinal chemists successfully demonstrated the alternative approach such as 'Bioisosterism' after Friedman introduced this concept in 1951 for the rational modification of lead compounds into safer and more clinically

effective agents.³² This concept was well exploited for drug development by using atoms and small molecules as bioisosters.³³

The hetero cycle molecular units are found to be prominent bioisosters.^{32, 33} In recent years the 1,2,3-triazole units have attracted major attention for bioisosteric replacement. The 1,2,3-triazole units have been well explored as bioequivalent surrogates for the amide bond,³⁴ due to the structural similarities, including: a) three nitrogens of triazole mimicking the carbonyl group of amide, b) the C-H bond of triazoles as hydrogen bond donors similar to the N-H bond of amide and as electrophilic and c) the polarized two carbons of triazole are electronically similar to the carbonyl carbon of amide.³⁵

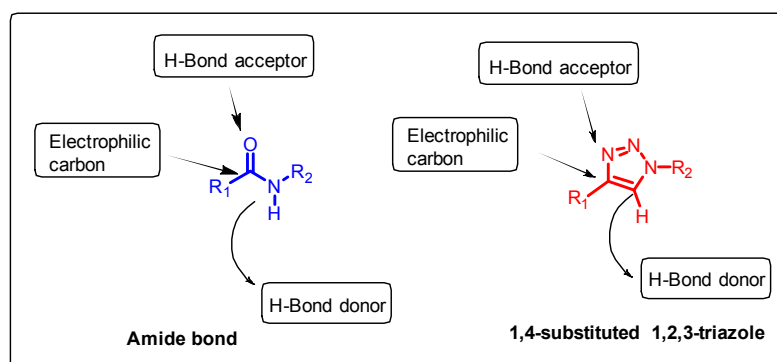


Figure S1.4: Structural comparison of amide and 1,2,3-triazole

Besides the potential bioisosteric replacement of amide bond in peptides, triazoles have also been predicted that they might act as bioisosteres of the acyl-phosphate³⁶ and *trans*-olefinic moieties. The phosphate unit has replaced by 1,2,3-triazole in the search of inhibitors of enzymes.³⁶ The substitution of a *trans*-olefinic group with a triazole in resveratrol proved to be more rewarding. This idea was supported by molecular modeling calculations (MM2) that suggested that this modification did not alter the spatial positioning of the phenolic hydroxyls that determine the biological activity of this phytoalexin. The effective *trans*-olefinic/1,4-disubstituted triazole replacement is not limited to resveratrol,³⁷ as it was possible to maintain estrogenic activity in diethylstilbestrol analogues.³⁸

Grimm's bioisosteric rule would suggest that obvious candidates for bioisosteric substitution with triazoles should be five-membered rings containing two nitrogen atoms. Some of the 1,4 regioisomers, but not their 1,5 counterparts, were more potent competitive inhibitors compared to fipronil. The potency and selectivity

were determined by substituents, strengthening the idea that triazole is a Grimm's bioisostere of pyrazole (Fig. S1.5).³⁹ This claim is reinforced by experiments on carbocyclic nucleosides. The adenine has been replaced with several heterocyclic moieties, with the 1,4-disubstituted triazole derivative showing the most potent antiviral activity against the vaccinia virus among the five-membered rings tested (Fig. S1.5).⁴⁰

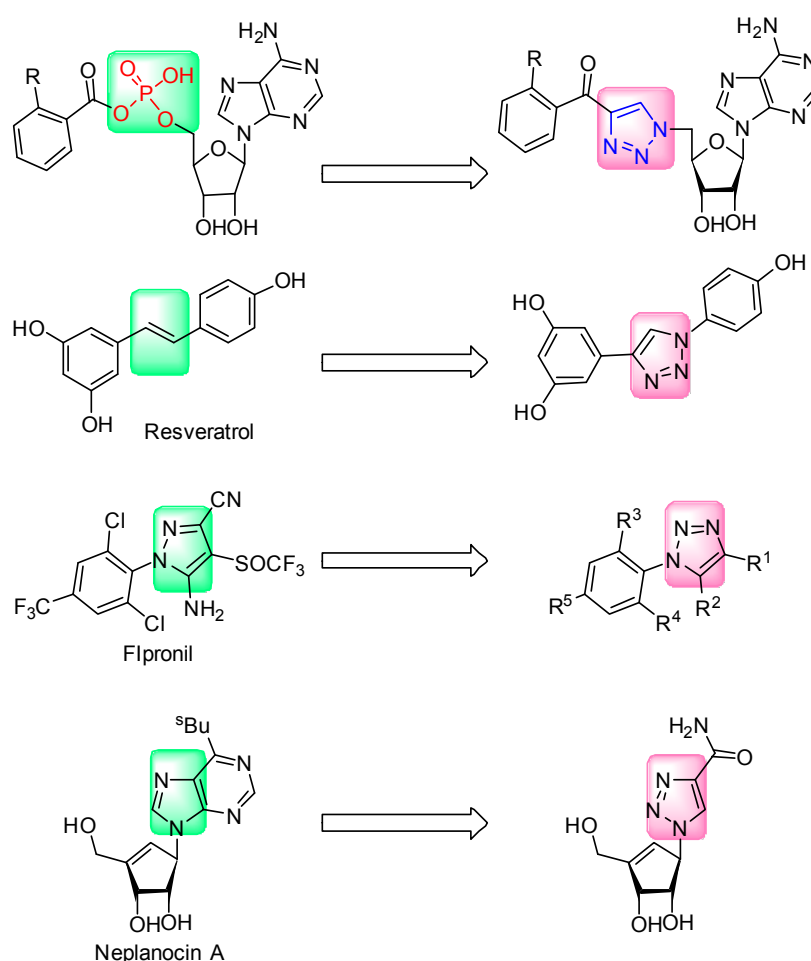
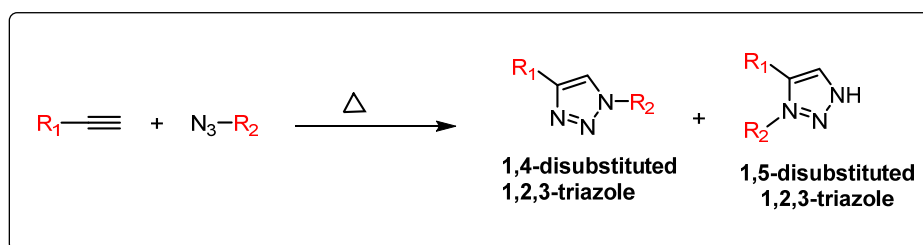


Figure S1.5: Some examples on triazole unit used as potential bioisoster

1A.1.5. Synthesis of 1,2,3-triazole

The 1,2,3-triazoles have been well known since the early 20th century. Dimroth discovered the formation of triazoles by the addition of organic azides to acetylenes.⁴¹ Later, Alder and Stein described in 1931, the reaction of phenylazide with bicyclo-[2,2,1] hept-2-ene and its derivatives, producing the 1,2,3-triazole.⁴² However, the synthesis of 1,2,3-triazoles has required harsh and laborious reaction methods. In 1961, Rolf Huisgen has introduced the [3 + 2] cycloaddition between a

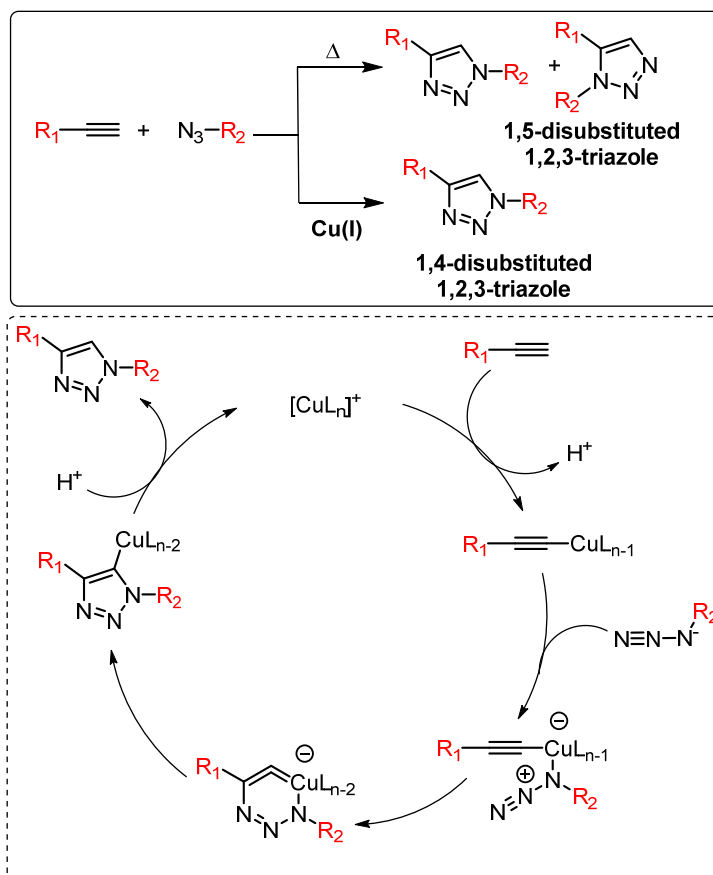
terminal alkyne and an azide to generate substituted 1,2,3-triazoles as a mixture of the 1,4-adduct and the 1,5-adduct at 98 °C in 18 hours (Scheme S1.1).⁴³ The regiomer mixture of this reaction outcome was a major disadvantage. However, in the beginning of the last decade, the seminal reports by Meldal and Sharpless has introduced a highly 1,4-regioselective version and, more importantly, conducted the reaction at rt by employing the copper-catalyst and have initiated the understanding the scope of this organic reaction.^{44, 45} Sharpless has referred to this cycloaddition as "the cream of the crop" of click chemistry and "the premier example of a click reaction." Later the metal catalyzed version of this reaction has been well explored.



Scheme S1.1: Classical Huisgen's 1,3 dipolar addition

1A.1.5.1. Copper Catalysis

In 2002, two chemists, Sharpless and Meldal independently reported the metal catalyzed version of Huisgen's azide-alkyne cycloaddition.^{44, 45} The seminal contribution of Sharpless and coworkers was later referred to as the "Click Chemistry" concept (Scheme S1.2). This copper(I) catalyzed variant of the Huisgen 1,3-dipolar cycloaddition is a noteworthy example in that it is no longer a true concerted cycloaddition, in which organic azides and terminal alkynes are united to afford 1,4-disubstituted 1,2,3-triazoles as sole products. Later, this reaction was termed the copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC). In the presence of a base, the terminal hydrogen, being the most acidic is deprotonated first to give a Cu acetylide intermediate, after which the azide displaces another ligand and binds to the copper. Then, an unusual six-membered copper(III) metallacycle is formed. Ring contraction to a triazolyl-copper derivative is followed by protonolysis that which delivers the triazole product and closes the catalytic cycle.

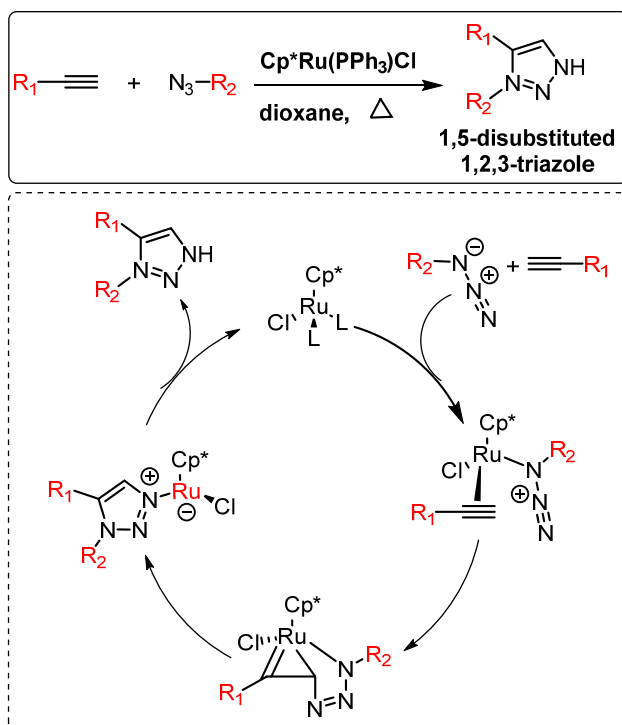


Scheme S1.2: Copper variation of 1,3 dipolar cycloaddition reaction of azide and alkyne (Click Reaction)

1A.1.5.2. Ruthenium Catalysis

The ruthenium-catalysed 1,3-dipolar azide-alkyne cycloaddition (**RuAAC**) gives the 1,5-triazole.⁴⁶ Unlike CuAAC in which only terminal alkynes react, in RuAAC, both terminal and internal alkynes can participate in the reaction (Scheme S1.3). This suggests that ruthenium acetylides are not involved in the catalytic cycle. The proposed mechanism suggests that in the first step, the spectator ligands undergo the displacement reaction to produce an activated complex which is converted, via oxidative coupling of an alkyne and an azide to the ruthenium containing metallacycle (Ruthenacycle). The new C-N bond is formed between the more electronegative and less sterically demanding carbon of the alkyne and the terminal nitrogen of the azide. The metallacycle intermediate then undergoes reductive elimination releasing the aromatic triazole product and regenerating the catalyst or the activated complex for further reaction cycles. $\text{Cp}^*\text{RuCl}(\text{PPh}_3)_2$, $\text{Cp}^*\text{Ru}(\text{COD})$ and $\text{Cp}^*[\text{RuCl}_4]$ are commonly used ruthenium catalysts. Catalysts containing the cyclopentadienyl(Cp) group are also employed. However, better results are observed with the

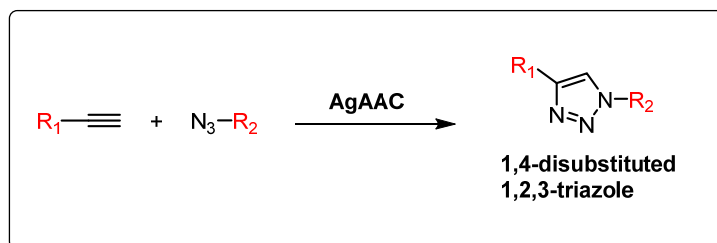
pentamethylcyclopentadienyl(Cp*) version. This may be due to the sterically demanding Cp* group which facilitates the displacement of the spectator ligands.⁴⁷



Scheme S1.3: Ruthenium catalyzed of 1,3 dipolar cycloaddition reaction of azide and alkyne

1A.1.5.3. Silver Catalysis

Recently, the discovery of a general Ag(I)-catalyzed azide–alkyne cycloaddition reaction (Ag-AAC) leading to 1,4-triazoles has been reported.⁵³ The mechanistic features are similar to the generally accepted mechanism of the copper(I)-catalyzed process.



Scheme S1.4: Ag(I)-catalyzed azide–alkyne cycloaddition reaction

Interestingly, silver(I)-salts alone are not sufficient to promote the cycloaddition. However the ligated Ag(I) source has proven to be exceptional for the AgAAC reaction. Curiously, pre-formed silver acetylides do not react with azides; however, silver acetylides do react with azides under catalysis with copper(I).⁴⁸

1A.1.6. Click Chemistry Overview

Click chemistry is a modular synthetic approach towards the assembly of new molecular entities and has recently emerged to become one of the most powerful tools in drug discovery, chemical biology, and proteomic applications.⁵⁰ The wide scope of CuAAC is firmly demonstrated by its use in different areas of life and material sciences such as drug discovery,⁵¹ bioconjugation,⁵² polymer and materials science⁵³ and related areas including supramolecular chemistry. DNA labeling and oligonucleotide synthesis, the assembly of glycoclusters and glycodendrimers,⁵⁴ the preparation of stationary phases for HPLC column, the development of microcontact printing, the conjugation of molecular cargos to the head group of phospholipids,⁵⁵ and the construction of bolaamphiphilic structures are further examples of the use of CuAAC.

1A.1.6.1. Click Chemistry in Drug Discovery

Current drug discovery relies on massive screening of chemical libraries against various extracellular and intracellular molecular targets to find novel chemotypes with the desired mode of action. Click chemistry simplifies compound synthesis, enabling faster lead discovery and optimization.^{55, 56} Click chemistry-based drug discovery mainly falls into three types: (1) high-throughput screening, (2) fragment-based drug discovery, and (3) dynamic template-assisted strategies in fragment-based drug discovery. In recent years, high-throughput technologies have gained the attention of pharmaceutical and biotechnology companies for lead drug discovery leads and it is now also being used for basic and applied research in academia. It comprises the screening of large chemical libraries for activity against biological targets via the use of automation, miniaturized assays, and large-scale data analysis.

The copper catalyzed click reaction has several applications in the drug discovery of enzyme inhibitors. The malfunctioning of PTP1B (protein tyrosine phosphatase 1B) leads to various human diseases like cancer, diabetes, obesity, and inflammation. Zhang and co-workers prepared a highly potent and selective mPTPB inhibitor (**S1.1**, Fig. S1.6) using a novel, double click chemistry strategy.⁵⁷ Later Xie et al. also reported new PTP inhibitor entities. Triazolyl glucosyl, galactosyl, and mannosyl serine and threonine derivatives were efficiently synthesized via the click

reaction, one of which (compound **S1.1**, Fig. S1.6) was identified as a potent and selective PTP1B inhibitor against a panel of homologous PTPs with $IC_{50} = 5.9 \pm 0.4 \mu M$.⁵⁸ Zhou and co-workers recently reported a potent and selective mPTPB inhibitor (**S1.2** and **S1.3**, Fig. S1.6) with highly efficacious cellular activity, from a combinatorial library of bidentate benzofuran salicylic acid derivatives assembled by click chemistry.⁵⁹

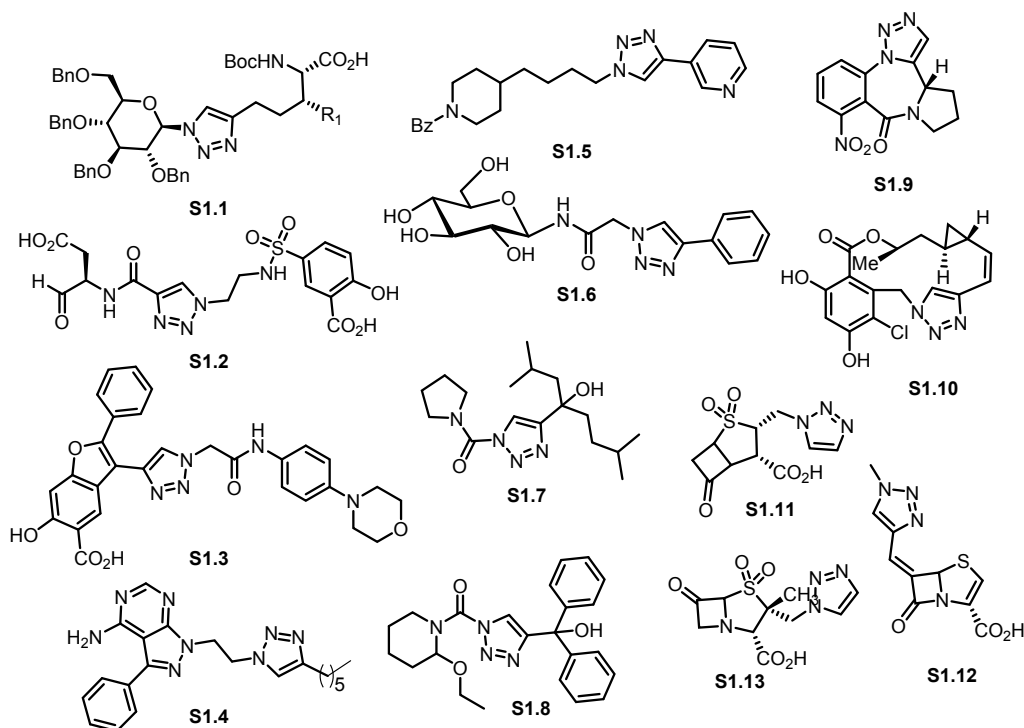


Figure S1.6: Biologically active compounds via click chemistry

Kumar and co-workers have recently reported the synthesis of 3-phenylpyrazolopyrimidine-1,2,3-triazole conjugates using the click chemistry approach and revealed that they displayed promising Protein Kinase inhibition. The hexyl triazolyl-substituted 3-phenylpyrazolopyrimidine (**S1.4**, Fig. S1.6) exhibited potent inhibition of the SRC kinase with an IC_{50} value of $5.6 \mu M$. Canonico et al. successfully constructed a small library of triazole analogues of antitumoral drug FK866 using click chemistry techniques. Among the synthesized triazole analogues, compound **S1.5** (Fig. S1.6) displayed nanomolar potency against depletion of NAD levels. Xie and co-workers also employed click chemistry for the synthesis of novel nucleoside conjugates between uridine and N-acetylglucosamine or oleanolic acid derivatives. Compound **S1.6** (Fig. S1.6) showed good inhibitory activity against glycogen phosphorylase with $IC_{50} = 13.6 \mu M$. Cravatt et al. recently

developed the triazole urea inhibitors **S1.7** and **S1.8** (Fig. S1.6), which were highly potent inhibitors against their respective serine hydrolase targets in mouse T-cell proteomes. Mohapatra and co-workers reported one-pot synthesis of novel tetracyclic scaffolds that incorporate a fusion of a proline, 1,2,3-triazole ring with [1,4]-benzodiazepin-8(4H)-one ring systems following click chemistry. Compound **S1.9** (Fig. S1.6) has showed good serine protease inhibition activity with $IC_{50} = 108.2 \mu M$. Danishefsky et al. employed click chemistry for the synthesis of novel heat shock protein 90 (Hsp90)-based anticancer agent, triazole-cyclopropanedicol derivative, **S1.10** (Fig. S1.6). Among the best-known examples of triazole-containing structures is tazobactam, a β -lactamase inhibitor that is marketed in combination with the broad spectrum antibiotic piperacillin. Tazobactam (**S1.11**) and related triazole-containing compounds (**S1.12** and **S1.13**; Fig. S1.5) turned out to be potent β -lactamase inhibitors with higher potency than clavulanic acid and sulbactam, and the triazole ring appears to play a pivotal role its potency.⁵⁰

1A.2. Present Work:

The aim of the present work was to optimize the anti cancer activity of the initially identified structural scaffold of the PIT1, and to explore the SAR analysis. In this scenario, our first concern was to replace the susceptible thiourea unit with a stable bioisostere and the nitro (NO₂) group with different functional groups. The 1,2,3-triazole structural motif has attracted our attention to as a replacement for the thiourea unit.^{32, 33} While 1,2,3-triazoles are not present in naturally occurring compounds, the triazole unit has been identified as the bioequivalent surrogate for the amide bond.⁴⁰ This concept has been well exploited for the development of potential anticancer agents as well as for developing non-nucleoside reverse transcriptase inhibitors. We are anticipating the best anti tumor activity with the 1,4-disubstituted-1,2,3-triazole derivatives (**Triazole-PITs**). These **Triazole-PITs** have been designed as the structural mimics of **DM-PIT-1** and as potential second-generation PITenins (PITs) as shown in Figure 1.1. The triazole unit was divided into three rings for a better understanding of the synthetic strategy and SAR analysis. As shown below, this led us to identify two structural units for the synthesis of – i. alkynone; ii. substituted *o*-azidophenol.

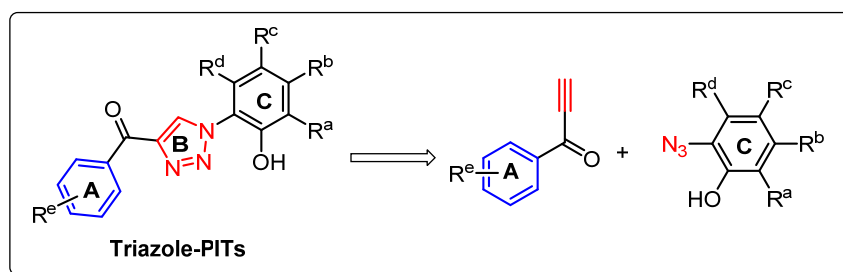


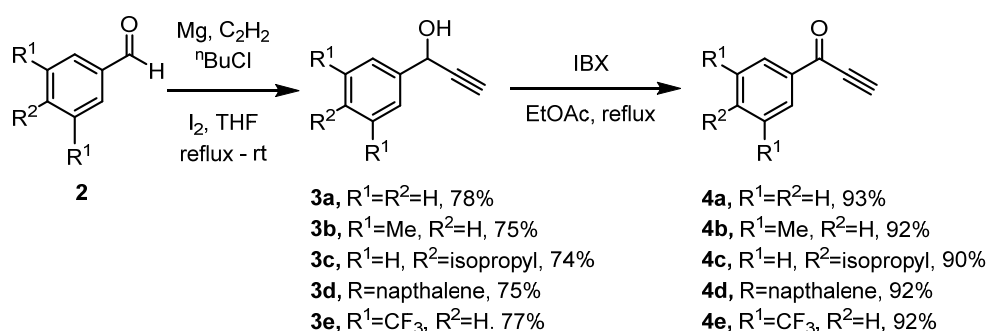
Figure 1.1: Anticipated potential second-generation PITenins

1A.2.1. Chemistry

1A.2.1.1. Synthesis of Alkynone (4a–4e)

A total of five different alkynones (**4a–4e**) having different substituted on the benzene ring or having a naphthalene unit have been designed in this context. Scheme 1.1 reveals the general approach that has been followed for their synthesis. For example, the synthesis of alkynone **4a** started with the addition of ethenyl magnesium chloride in THF to commercially available benzaldehyde in order to furnish the alkynol **3a** in good yield.⁶⁰ The compound was confirmed by ¹H, ¹³C NMR and IR spectroscopic techniques. In the ¹H NMR of the compound **3a**, the acetylenic proton

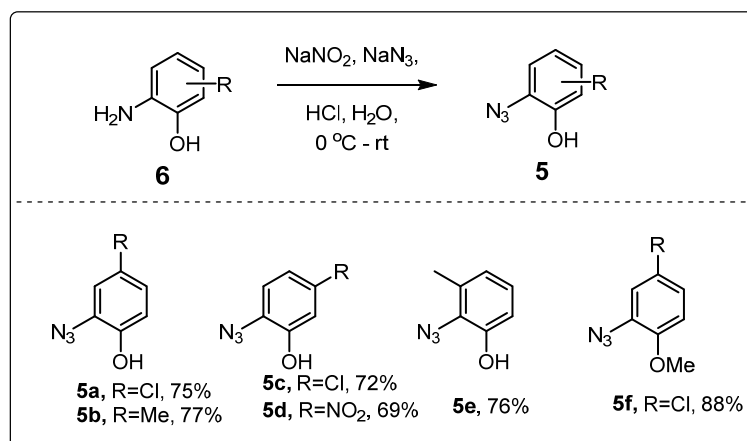
appeared at δ 2.26 ppm as a doublet with $J = 2.3$ Hz and the benzylic proton resonated at δ 5.43 ppm as a singlet. The presence of acetylenic group was also evident from the IR spectrum, where the absorption was observed at 3307 cm^{-1} . The compound **3a** was subjected for oxidation with IBX (in EtOAc, reflux for 2 h)⁶¹ on order to procure the alkynone **4a** in excellent yield. The structure of the compound **4a** has confirmed by ^1H and ^{13}C NMR. In the ^1H nmr spectrum of compound **4a**, the benzylic CH has disappeared and in the ^{13}C spectrum, the carbonyl carbon has appeared as a singlet at δ 196.4 ppm.



Scheme 1.1: Synthesis of selected alkynone

1A.2.1.2. Synthesis of 4-chloroazidophenol

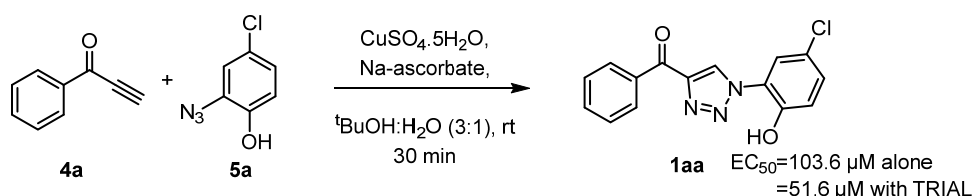
The 4-chloroazidophenol was prepared from commercially available 2-amino, 4-chlorophenol by a sequence of diazotization followed by azide substitution, affording the compound **5** with good yield (Scheme 1.2).⁶²



Scheme 1.2: Synthesis of selected azidophenols

1A.2.1.3. Synthesis of 1,4-substituted 1,2,3-triazole (1aa)

The resulting alkynone **4a** was subjected for the cycloaddition with 4-chloroazidophenol **5a** by using the well established copper catalyzed click reaction conditions. One equivalent of alkynone **4a** and one equivalent of 4-chloroazidophenol **5a** were dissolved in *tert*-BuOH/water (3:1) and the resulting solution was treated with 20 mol% CuSO₄·5H₂O and 20 mol% sodium ascorbate. The reaction mixture was stirred at room temperature (0.5-1 h) for completion of cycloaddition to deliver the requisite 1,2,3-triazole **1aa** (Scheme 1.3).⁶³ The constitution of compound **1aa** was confirmed with the help of ¹H, ¹³C NMR and HRMS data. For example, in the ¹H NMR spectra of the compound **1aa**, the characteristic triazole-C–H resonated at δ 9.07 ppm as a singlet. In the ¹³C NMR spectra, the carbonyl carbon appeared at δ 184.7 ppm (see the experimental section). In the HRMS, the exact mass of the compound showed, as calculated, for C₁₅H₁₀O₂N₃ClNa [M+Na]⁺: 322.0354 and it was found to be 322.0357. The initial screening of **1aa** against the growth of U87MG human glioblastoma cells revealed that **1aa** has a comparable activity with the corresponding PIT-1 analogue. The compound **1aa** alone depicted EC₅₀ value 103.6 μM and, with the combination of TRIAL depicted the EC₅₀ value with further improvement such as 51.6 μM (table-1.1).



Scheme 1.3: Synthesis of 1,4-disubstituted 1,2,3-triazole (**1aa**)

1A.2.1.4 Synthesis and SAR analysis of designed 1,4-disubstituted 1,2,3-triazoles

This initial promising result has motivated us to synthesize a collection of triazole derivatives by varying the functional groups; the basic skeleton of the triazole has been divided into three rings A, B and C, for the convenience of indication. We have synthesized three 1,2,3-triazoles such as **1ab**, **1ac** and **1ae** (Fig. 1.2), then tested in U87MG human glioblastoma cells (the antitumor activity has been shown in the table 1.1). The compound **1ac** showed some improved activity as EC₅₀ 48.9 μM alone and 42.3 μM with combination of TRIAL by changing the position of the chloro

group and, interestingly, with the replacement of position and functional group with the methyl group, compound **1ae** produced the better activity (entry 6, table 1.1). However **1ab** doesn't show any significant activity in U87MG cells. These results indicated that the nature and position of the substituent or functional group has an important role in the tumor suppression activity.

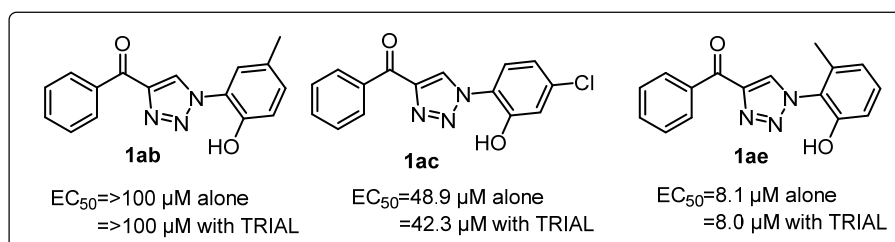
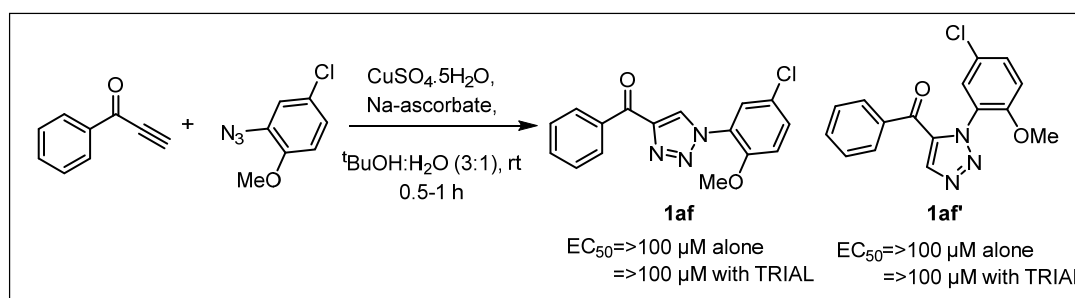


Figure 1.2: Selected variously substituted triazoles

To pursue the phenolic hydroxyl group and orientation of triazole ring influence on the tumor growth, we have protected the hydroxyl group 4-chloroazidophenol **5a** as its methoxy ether **5f**. Compound **5f** has been subjected for the CuSO₄ catalyzed click reaction with alkynone **4a** under the conditions as used in the synthesis of **1aa-1ad**. Surprisingly, the regiomer mixture of 1,4-disubstituted (**1af**) and 1,5-disubstituted triazole (**1af'**) adducts were observed. The compounds were confirmed by ¹H, ¹³C and HRMS. However, these molecules have not showed any impressive results and again lacked activity in A2780 cells. These results suggested that the orientation of the triazole ring and the phenol hydroxy group is essential for activity.



Scheme 1.4: Synthesis of phenol hydroxyl protected 1,2,3-triazole regiomers

Next, we pursued modification of the substituents on the phenyl ring A. A wide range of alkynones **4b-4e** have been synthesized by following the established procedure (Scheme 1.1) and the azido phenols **5a-5e** (Scheme 1.2) have been used as the dipolarophiles for the Cu-catalyzed azide-alkyne [3+2]-cycloaddition. All the new

compounds have been characterized completely with the help of spectral and analytical data.

In this course of SAR studies, the compounds **1ba**, **1bb**, **1bc**, **1bd** and **1be** having dimethyl groups on the ring A and differing in the functional groups on the ring C have been synthesized and were taken forward for screening against human ovarian cancer cells. However, structurally modified DM-PIT-1 analogues have shown only limited cellular activity (Fig. 1.3 and Table 1.1).

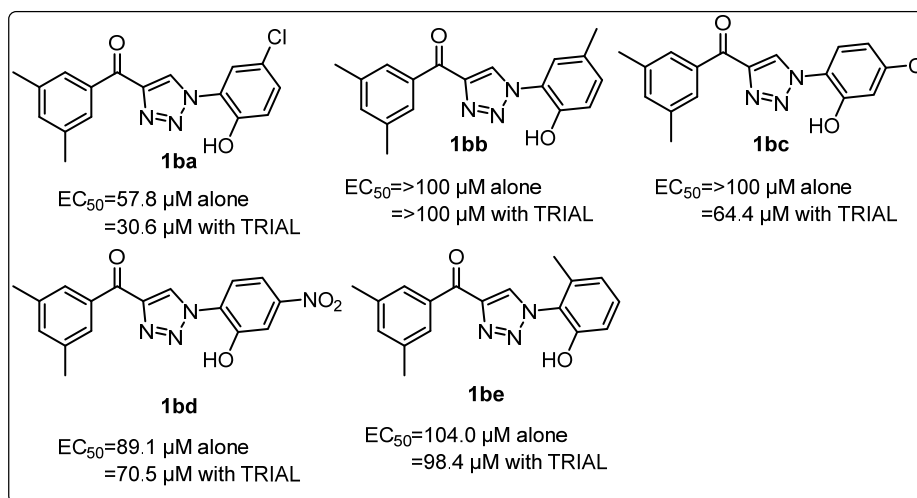


Figure 1.3: Selected variously substituted triazoles

Next, **1ca**, **1cb**, and **1ce** having a *p*-isopropyl group on the ring A and differing in the functional groups on the ring C, have been synthesized. The screening of these compounds against human ovarian cancer cells revealed that only, the chloro substituted compound **1ca** has shown moderate activity, while other compounds were ineffective (Fig. 1.4 and Table 1.1).

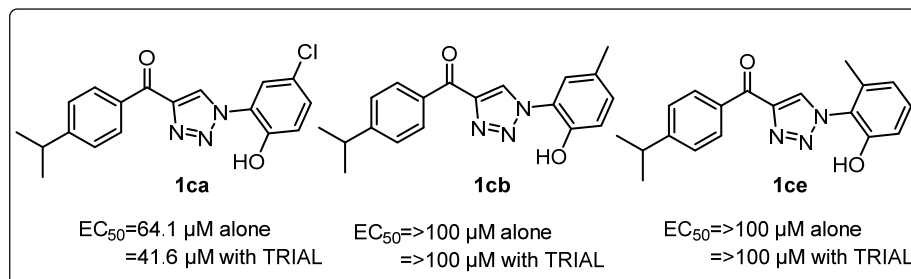


Figure 1.4: Selected variously substituted triazoles

Next, the replacement of the aryl ring A with a naphthyl has also been examined. Compounds **1da**, **1db** and **1de** having the naphthyl unit in place of the ring A have been synthesized and screened. However, there was no improvement in the activity (Figure 1.5 and Table 1.1).

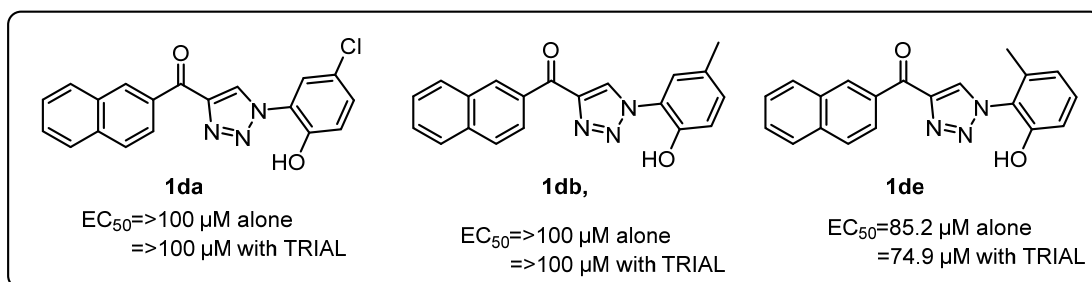
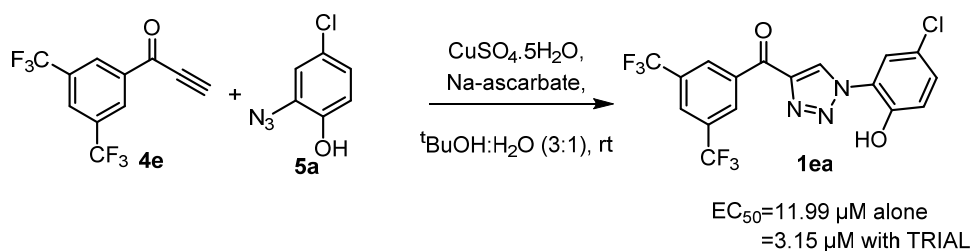


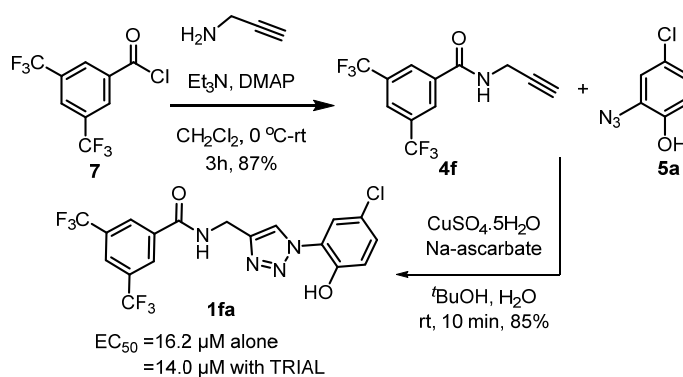
Figure 1.5: Selected variously substituted triazoles

Next, we intended to incorporate the CF₃ group in the triazole unit. Very interestingly, all the endeavors indicated that the addition of the CF₃ group at the C-3 and C-5 positions on ring A in combination with a chloro group at C-4 position of the ring C (YK-NCL-240, **1ea**) showed excellent improvement (17 times higher than that of the **DM-PIT-1** in anti-tumor activity).



Scheme 1.5: Synthesis of 1,4-disubstituted 1,2,3-triazole (**1ea**)

Next, we have synthesized **1fa** which contained an amide moiety of **DM-PIT-1**, but otherwise resembled **1ea**. The compound **1fa** was synthesized from 3, 5-bis(trifluoromethyl)benzoyl chloride **7** by nucleophilic displacement with propargyl amine to procure the key intermediate **4f**,⁷⁰ which was further subjected for the cycloaddition reaction with 4-chloro, 2-azidophenol **5a** (Scheme 1.6). The compound **1fa** has showed good activity, but the activity was seen to be lower than that of **1ea**.



Scheme 1.6: Synthesis of substituted 1,2,3-triazole (**1fa**)

1A.2.3. Chemistry

Table 1.1 : Anti-tumor activity Data of 1,4-disubstituted 1,2,3-triazole **1aa-1fa**^{a,b}

S.No	Compound no./code	EC ₅₀ (μM)	EC ₅₀ +TRAIL(μM)
1.	1aa (YK-NCL-176)	103.6	51.6
2.	1af (YK-NCL-177)	>100	>100
3.	1af (YK-NCL-178)	>100	>100
4.	1bc (YK-NCL-183)	>100	64.4
5.	1ab (YK-NCL-184)	>100	>100
6.	1ae (YK-NCL-185)	8.1	8.0
7.	1da (YK-NCL-186)	>100	>100
8.	1de (YK-NCL-187)	85.2	74.9
9.	1db (YK-NCL-188)	>100	>100
10.	1ba (YK-NCL-190)	57.8	30.6
11.	1ac (YK-NCL-191)	48.9	42.3
12.	1be (YK-NCL-192)	104.0	98.4
13.	1bb (YK-NCL-193)	>100	>100
14.	1bd (YK-NCL-194)	89.1	70.5
15.	1ca (YK-NCL-195)	64.1	41.6
16.	1ce (YK-NCL-196)	>100	>100
17.	1cb (YK-NCL-197)	>100	>100
18.	1fa (YK-NCL-234)	16.2	14.0
19.	1ea (YK-NCL-240)	11.99	3.15

^acompounds were tested in U87MG human glioblastoma Cells and ^btested in A2780 human ovarian cancer Cells

Based on the preliminary experiments and SAR analysis, the results indicated that the compound **1ea** showed better activity among all the triazole analogues that were tested. The compound **1ea** has been selected for further progress in the direction of examining its pharmacological properties. The *in vitro* and *in vivo* studies with compound **1ea** have been carried by Alexei's group at Tufts University. Following are some important features need to highlight!

1. The lipid overlay assay (measuring the binding of the Akt PH domain with PI(3,4)P2, spotted on microcellulose membrane) revealed that **1ea** displayed substantially higher activity compared to PIT-1.
2. The studies on the inhibition of PI3K/Akt signaling in human glioblastoma U87MG and ovarian carcinoma A-2780 cells suggested that increased activity of **1ea** might be due to more specific inhibition of a particular pathway downstream from PI3K/Akt .

3. *In vitro* cell viability studies with A2780 human ovarian cancer cells indicated that the EC₅₀ value for **1ea** was improved to 15-fold over DM-PIT1 and that was 17-fold in combination with TRAIL. A similar trend was observed with the other human cancer cell lines: U87MG human glioblastoma cells, T47D human breast cancer cells, and DU145 human prostate cancer cells.
4. In addition to activation of cell death, PITs displayed several additional important properties. First, it was found that PIT-1 analogues reverse resistance of cancer cells to anti-cancer cytokine TRAIL. This led to synergistic cytotoxicity of PIT-1 and TRAIL when applied in combination. This useful property was retained with **1ea**.
5. *In Vitro* inhibition of cellular migration by using wound healing assay model with T47D, U87MG, and DU145 cells revealed that **1ea** has not only increased cell death, but also suppressed cell migration and invasion through the attenuation of actin cytoskeleton remodeling.
6. *In Vivo* tumor inhibition studies in mice models by **1ea** revealed that the administration of the combination of TRAIL and **1ea** resulted in significantly reduced tumor weight. These formulations were also found to be well tolerated in mice, as there was no apparent toxicity or loss of body weight.
7. Finally, for compound **1ea**, the $T_{1/2}=119$ min ($CL=19.4 \mu L \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$) was determined through the mouse liver microsomal stability assay. In the same assay DM-PIT-1 displayed $T_{1/2}=1.8$ min ($CL=1262 \mu L \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$).
8. Pharmacokinetics analysis following intravenous injection of 1 mg/kg of the drug showed reasonable $T_{1/2}=3.22$ hr with a CL of 930 mL/hr/kg and a bioavailability of 85.1% following intraperitoneal administration.

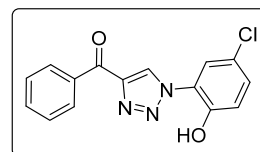
Overall, our SAR analysis describes a new analogue of PIT-1 with significantly improved anti-cancer activity and pharmacological properties, which may present a promising molecule for further analysis in mouse xenograft models.

General experimental procedure: To a solution of azide **5** (1.0 eq.) and alkyne **4** (1.1 eq.) in ^tBuOH:H₂O (3:1) at rt, sodium ascorbate (0.2 eq.) and CuSO₄·5H₂O (0.2 eq.) were added and the resulting brick reddish mixture was stirred vigorously for 30 min. The reaction mixture was diluted and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and the solvents were evaporated under reduced pressure. The product was purified by column chromatography.

(1-(5-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1aa):

Isolated by column chromatography (pet.ether/AcOEt = 8:2, *R_f* = 0.2). The title compound was determined as colourless solid

(87%). mp: 210–211 °C; ¹H NMR (200 MHz, CDCl₃ + MeOH (D₄)): δ 7.07 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H),

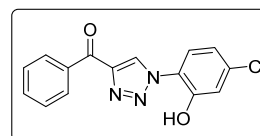


7.57–7.64 (m, 3H), 7.89 (s, 1H), 8.31 (d, *J* = 5.7 Hz, 2H), 9.07 (s, 1H) ppm; ¹³C NMR (50 MHz, CDCl₃ + MeOH (D₄)): δ 117.3 (d), 123.0 (d), 123.5 (s), 127.3 (2C, d), 129.1 (3C, d), 129.3 (d), 132.2 (d), 135.7 (s), 145.8 (s), 147.1 (s, 2C), 184.7 (s) ppm.; IR(cm⁻¹):ν 3070, 3010, 2774, 1622, 1596, 1425, 1222, 1095, 902, 721, 681; HRMS(ESI) calcd for C₁₅H₁₀O₂N₃ClNa (M⁺+Na): 322.0354; found: 322.0357.

(1-(4-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1ac):

Isolated by column chromatography (pet.ether/AcOEt = 8:2, *R_f*

= 0.2). The title compound was determined as colourless solid (87%). Mp: 238–239 °C; ¹H NMR (500 MHz, CDCl₃ + MeOH

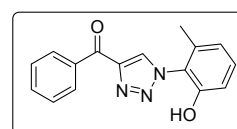


(D₄)): δ 7.55 (d, *J* = 8.6 Hz, 1H), 7.13 (s, 1H), 7.54–7.59 (m, 2H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 8.33 (d, *J* = 7.3 Hz, 2H), 9.01 (s, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃ + MeOH (D₄)): δ 116.7 (d), 119.7 (d), 122.5 (s), 124.9 (d), 128.0 (d, 3C), 129.8 (d, 2C), 133.0 (d), 135.3 (s), 136.3 (s), 146.4 (s), 149.5 (s), 186.1 (s) ppm; IR (cm⁻¹):ν 2954, 2913, 2846, 1510, 1453, 1419, 1243, 1160, 890, 854, 725, 682; HRMS(ESI) calcd for C₁₅H₁₀O₂N₃ClNa (M⁺+Na): 322.0354; found: 322.0355.

(1-(2-Hydroxy-6-methylphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1ae):

Isolated by column chromatography (pet.ether/AcOEt = 8:2, *R_f*

= 0.3). The title compound was determined as colourless solid (84%). Mp: 182–184 °C; ¹H NMR (200 MHz, CDCl₃ + MeOH



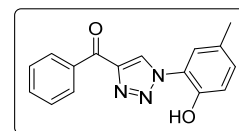
(D₄)): δ 2.35 (s, 3H), 6.83 (dd, *J* = 1.1, 8.2 Hz, 1H), 6.90 (s, 1H), 7.50–7.62 (m, 3H), 7.67 (d, *J* = 8.2 Hz, 1H), 8.31–8.37 (m, 2H), 8.97 (s, 1H) ppm; ¹³C NMR (50 MHz,

CDCl₃ + MeOH (D₄)) δ 20.6 (q), 117.2 (d), 120.5 (d), 121.2 (s), 123.5 (d), 128.1 (2C, d), 129.8 (d), 129.9 (d, 2C), 133.0 (d), 136.4 (s), 140.8 (s), 146.3 (s), 148.5 (s), 186.3 (s) ppm; IR (cm⁻¹): ν 2993, 2415, 1601, 1569, 1515, 1421, 1260, 1158, 981, 897, 723, 683; HRMS(ESI) calcd for C₁₆H₁₃O₂N₃Na (M⁺+Na): 302.0900; found: 302.0896.

(1-(2-Hydroxy-5-methylphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1ab):

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f =

0.3). The title compound was determined as colourless solid (91%). Mp: 200–202 °C; ¹H NMR (200 MHz, CDCl₃ + MeOH

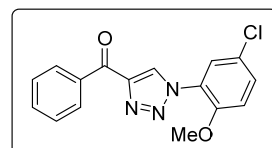


(D₄)) δ 2.27 (s, 3H), 6.90 (d, *J* = 8.3, 1H), 7.05 (dd, *J* = 1.6, 8.3, 1H), 7.42–7.61 (m, 4H), 8.28–8.32 (m, 2H), 8.90 (s, 1H) ppm; ¹³C NMR (50 MHz, CDCl₃ + MeOH (D₄)) δ 19.6 (q), 116.5 (d), 123.1 (s), 124.0 (d), 128.0 (d), 129.3 (s, 2C), 129.9 (d), 130.7 (d, 4C), 133.0 (d), 136.4 (s), 146.3 (s), 173.1 (s) ppm; IR (cm⁻¹): ν 3176, 3148, 2956, 2921, 1649, 1521, 1448, 1225, 1180, 1050, 907, 816, 722, 685; calcd for C₁₆H₁₃O₂N₃ (M + Na⁺): 302.0900; found: 302.0889.

(1-(5-Chloro-2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (1af):

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f

= 0.2). The title compound was determined as colourless solid (43%). Mp: 135–137 °C; ¹H NMR (200 MHz, CDCl₃): δ 3.94

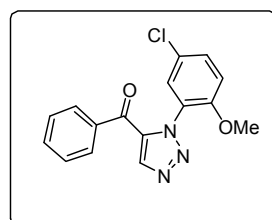


(s, 3H), 7.04 (d, *J* = 9.0 Hz, 1H), 7.44 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.51–7.64 (m, 3H), 7.95 (d, *J* = 2.7 Hz, 1H), 8.43–8.48 (m, 2H), 8.87 (bs, 1H) ppm; ¹³C NMR (50 MHz, CDCl₃): δ 56.4 (q), 113.5 (d), 125.1 (d), 126.4 (s, 2C), 128.4 (d, 2C), 130.3 (d), 130.6 (d, 3C), 133.3 (d), 149.5 (s, 2C), 175.7 (s), 197.8 (s) ppm; IR (neat): ν 3020, 1647, 1498, 1239, 1132, 1014, 986, 894, 813, 719, 640 cm⁻¹; HRMS(ESI) calcd for C₁₆H₁₂O₂N₃ClNa (M⁺+Na): 336.0510; found: 336.0510.

(1-(5-Chloro-2-methoxyphenyl)-1H-1,2,3-triazol-5-yl)(phenyl)methanone (1af''):

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f

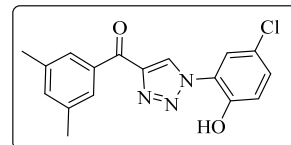
= 0.3). The title compound was determined as colourless solid (41%). Mp: 200–202 °C; ¹H NMR (200 MHz, CDCl₃): δ



3.95 (s, 3H), 6.82 (d, *J* = 8.7 Hz, 1H), 7.03 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.46–7.60 (m, 3H), 7.64–7.69 (m, 2H), 8.49 (d, *J* = 2.5 Hz, 1H), 10.9 (bs, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 56.3 (q), 105.0 (s), 110.9 (d), 120.1 (d), 123.5 (d), 127.1 (d, 2C), 128.6 (s), 129.1 (d, 3C), 132.8 (d), 134.0 (s), 158.6 (s, 2C), 187.9 (s)

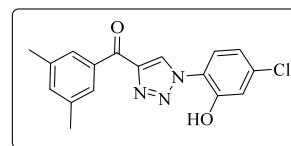
ppm; IR(cm^{-1}): ν 3278, 3061, 2984, 1732, 1645, 1599, 1448, 1300, 1200, 1093, 876, 752, 680; HRMS(ESI) calcd for $\text{C}_{16}\text{H}_{12}\text{O}_2\text{N}_3\text{ClNa}$ ($\text{M}^+ + \text{Na}$): 336.0510; found: 336.0510.

(1-(5-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(3,5-dimethylphenyl)methanone (1ba): Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.2). The title



compound was determined as colourless solid (83%). Mp: 232–234 °C; ^1H NMR (200 MHz, CDCl_3 + DMSO (D_6)): δ 2.40 (s, 6H), 7.01 (d, J = 8.7 Hz, 1H), 7.22–7.29 (m, 2H), 7.84 (d, J = 2.5 Hz, 1H), 7.95 (s, 2H), 8.97 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + DMSO (D_6)): δ 21.2 (q, 2C), 118.7 (d), 123.2 (d, 2C), 128.16 (d, 3C), 129.20 (s), 130.02 (d), 135.20 (s, 2C), 138.07 (s, 2C), 147.50 (s), 151.82 (s), 175.3 (s) ppm; IR(cm^{-1}): ν 3174, 2958, 2918, 2114, 1623, 1589, 1496, 1295, 1258, 1212, 1021, 801, 731, 651; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 328.0847; found: 328.0847.

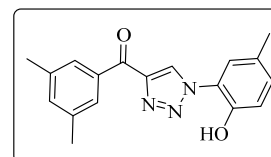
(1-(4-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(3,5-dimethylphenyl)methanone (1bc): Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.2). The title



compound was determined as colourless solid (91%). Mp: 149–151 °C; ^1H NMR (400 MHz, CDCl_3 + DMSO (D_6)) δ 2.35 (s, 6H), 6.95 (dd, J = 2.0, 8.6 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.22 (bs, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.85 (s, 2H), 8.91 (s, 1H) 11.0 (bs, 1H) ppm; ^{13}C NMR (101 MHz, CDCl_3 + DMSO (D_6)) δ 19.7 (q, 2C), 115.8 (d), 118.2 (d), 121.4 (s), 124.03 (d), 126.3 (d, 2C), 128.6 (d), 133.2 (d), 133.4 (s), 135.3 (s), 136.2 (s, 2C), 145.4 (s), 148.8 (s), 184.0 (s) ppm; IR(cm^{-1}): ν 3067, 2950, 2400, 1587, 1499, 1424, 1297, 1228, 1022, 854, 797, 765; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 328.0847; found: 328.0833.

(3,5-Dimethylphenyl)(1-(2-hydroxy-5-methylphenyl)-1H-1,2,3-triazol-4-

yl)methanone (1bb): Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.3). The title compound was

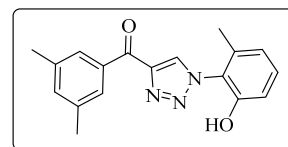


determined as colourless solid (85%). Mp: 188–190 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4) + DMSO (D_6)) δ 2.34 (s, 3H), 2.40 (s, 6H), 6.99 (d, J = 8.34 Hz, 1H), 7.09–7.20 (m, 1H), 7.29 (s, 1H), 7.56–7.63 (m, 1H), 7.88 (s, 2H), 8.94 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + MeOH (D_4) + DMSO (D_6)): δ 18.7 (q), 19.6 (q, 2C), 115.9 (d), 122.6 (s), 123.6 (d), 126.8 (d, 2C), 128.5 (s), 129.3

(d), 130.0 (d), 133.8 (d), 136.0 (s), 137.1 (s, 2C), 145.7 (s), 145.9 (s), 185.4 (s) ppm; IR(cm^{-1}): ν 3182, 2956, 2921, 2859, 1616, 1593, 1521, 1298, 1253, 1208, 1151, 1019, 805, 767, 696; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}_3$ (M^+H): 308.1394; found: 308.1387.

(3,5-Dimethylphenyl)(1-(2-hydroxy-6-methylphenyl)-1H-1,2,3-triazol-4-

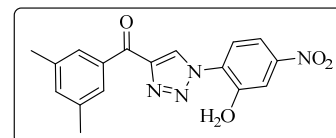
yl)methanone (1be): Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.3). The title compound was determined as colourless solid (91%). Mp: 188–190 °C; ^1H



NMR (200 MHz, CDCl_3 + MeOH (D_4)): δ 2.37 (s, 3H), 2.42 (s, 6H), 6.85 (d, J = 8.2 Hz, 1H), 6.91 (s, 1H), 7.31 (s, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.88 (s, 2H), 8.92 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + MeOH (D_4)): δ 19.6 (q, 3C), 116.3 (d), 119.7 (d), 120.7 (s), 123.3 (d), 126.8 (d, 2C), 129.3 (d), 133.8 (d), 136.0 (s), 137.1 (s, 2C), 140.1 (s), 145.7 (s), 148.1 (s), 185.4 (s) ppm; IR(cm^{-1}): ν 3402, 2918, 2254, 2128, 1626, 1595, 1521, 1430, 1234, 1022, 996, 824, 761; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}_3$ (M^+H): 308.1394; found: 308.1381.

(3,5-Dimethylphenyl)(1-(2-hydroxy-4-nitrophenyl)-

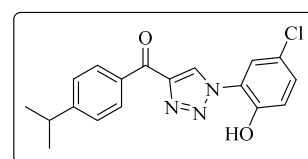
1H-1,2,3-triazol-4-yl)methanone (1bd): Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f =



0.2). The title compound was determined as yellow solid (86%). Mp: 237–239 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4) + DMSO (D_6)): δ 2.38 (s, 6H), 6.21 (d, J = 8.1 Hz, 1H), 7.18 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.55 (s, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.73–7.88 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3 + MeOH (D_4) + DMSO (D_6)): δ 20.3 (q, 2C), 109.3 (d), 110.9 (d), 115.9 (d), 124.6 (d, 2C), 133.0 (d), 134.6 (s), 137.4 (s, 2C), 138.2 (s), 141.1 (d), 141.2 (s), 141.7 (s), 145.0 (s), 191.4 (s) ppm; IR(cm^{-1}): ν 3377, 3311, 3091, 2885, 2198, 1929, 1627, 1594, 1521, 1428, 1262, 1182, 1081, 948, 870, 742, 643; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{N}_4\text{O}_4$ (M^+H): 339.1089; found: 339.1093.

(1-(5-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(4-

isopropylphenyl)methanone (1ca): Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.2). The title

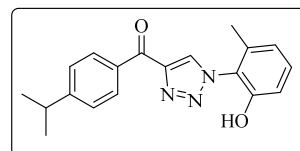


compound was determined as colourless solid (86%). Mp: 187–189 °C; ^1H NMR (400 MHz, CDCl_3 + MeOH (D_4) + DMSO (D_6)): δ 1.23 (d, J = 6.9 Hz, 6H), 2.95 (spt, J =

6.9 Hz, 1H), 7.05 (d, $J = 8.8$ Hz, 1H), 7.29 (dd, $J = 2.5, 8.8$ Hz, 1H), 7.36 (d, $J = 8.31$ Hz, 2H), 7.75 (d, $J = 2.7$ Hz, 1H), 8.20 (d, $J = 8.1$ Hz, 2H), 8.97 (s, 1H) ppm; ^{13}C NMR (100 MHz, $\text{CDCl}_3 + \text{MeOH} (D_4) + \text{DMSO} (D_6)$): δ 21.9 (q, 2C), 33.0 (d), 117.2 (d), 122.9 (s), 123.0 (d), 123.5 (s), 125.3 (d, 2C), 129.0 (d), 129.2 (d), 129.3 (d, 2C), 133.4 (s), 145.8 (s), 147.2 (s), 153.8 (s), 184.1 (s) ppm; IR(cm^{-1}): ν 3459, 2989, 1621, 1575, 1515, 1286, 1250, 1196, 1027, 785, 762; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{17}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 342.1004; found: 342.1009.

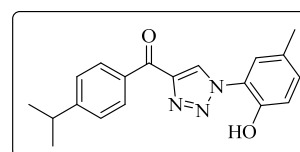
(1-(2-Hydroxy-6-methylphenyl)-1H-1,2,3-triazol-4-yl)(4-

isopropylphenyl)methanone (1ce): Isolated by column chromatography (pet.ether/AcOEt = 8:2, $R_f = 0.3$). The title compound was determined as colourless solid (82%). Mp: 172–174 °C; ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{MeOH} (D_4) + \text{DMSO} (D_6)$): δ 1.26 (s, 3H), 1.27 (s, 3H), 2.33 (s, 3H), 2.98 (spt, $J = 6.87$ Hz, 1H), 6.83 (d, $J = 7.3$ Hz, 1H), 6.99 (s, 1H), 7.44 (d, $J = 8.2$ Hz, 2H), 7.60 (d, $J = 8.2$ Hz, 1H), 8.29 (d, $J = 8.2$ Hz, 2H), 9.01 (s, 1H) ppm; ^{13}C NMR (125 MHz, $\text{CDCl}_3 + \text{MeOH} (D_4) + \text{DMSO} (D_6)$): δ 21.3 (q), 23.9 (q, 2C), 34.5 (d), 118.1 (d), 121.1 (d, 2C), 122.4 (s), 125.3 (d), 127.1 (d, 2C), 131.1 (d, 2C), 135.2 (s), 141.6 (s), 147.4 (s), 150.1 (s), 155.2 (s), 185.5 (s) ppm; IR(cm^{-1}): ν 3176, 2960, 1629, 1604, 1520, 1504, 1425, 1267, 1159, 1049, 907, 820, 770; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{O}_2\text{N}_3$ ($\text{M}^+ + \text{H}$): 322.1550; found: 322.1550.



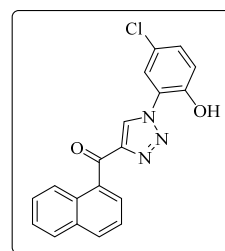
(1-(2-Hydroxy-5-methylphenyl)-1H-1,2,3-triazol-4-yl)(4-

isopropylphenyl)methanone (1cb): Isolated by column chromatography (pet.ether/AcOEt = 8:2, $R_f = 0.3$). The title compound was determined as colourless solid (83%). Mp: 131–133 °C; ^1H NMR (500 MHz, MeOH (D_4)): δ 1.48 (d, $J = 6.8$ Hz, 6H), 2.52 (s, 3H), 3.20 (spt, $J = 6.9$ Hz, 1H), 7.20–7.35 (m, 2H), 7.59 (d, $J = 8.3$ Hz, 2H), 7.78 (s, 1H), 8.50 (d, $J = 8.3$ Hz, 2H), 9.18 (s, 1H) ppm; ^{13}C NMR (125 MHz, MeOH (D_4)): δ 20.6 (q), 24.2 (q, 2C), 35.7 (d), 118.1 (d), 125.1 (s), 126.0 (d), 127.8 (d, 2C), 131.0 (s), 131.7 (d), 131.8 (d, 2C), 132.4 (d), 136.1 (s), 148.1 (s), 148.5 (s), 156.5 (s), 187.1 (s) ppm; IR(cm^{-1}): ν 3177, 2961, 2925, 2869, 1622, 1600, 1523, 1416, 1348, 1274, 1187, 1047, 907, 814, 773; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{O}_2\text{N}_3$ ($\text{M}^+ + \text{H}$): 322.1550; found: 322.1548.

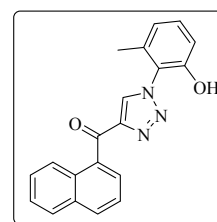


(1-(5-Chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)(naphthalen-1-yl)methanone (1da):

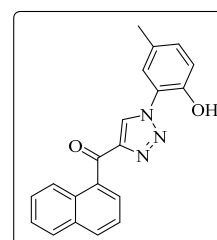
Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.2). The title compound was determined as colourless solid (87%). Mp: 255–257 °C; ^1H NMR (500 MHz, MeOH (D_4) + DMSO (D_6)): δ 7.12 (d, J = 8.9 Hz, 1H), 7.38 (dd, J = 2.4, 8.5 Hz, 1H), 7.56 (dd, J = 3.4, 6.4 Hz, 2H), 7.61 (t, J = 7.9 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 7.3 Hz, 2H), 8.13 (d, J = 8.2 Hz, 1H), 7.54 (dd, J = 3.1, 5.8 Hz, 1H), 9.07 (s, 1H); ^{13}C NMR (125 MHz, MeOH (D_4) + DMSO (D_6)): δ 119.2 (d), 123.9 (s), 125.2 (d), 125.3 (s), 125.4 (d), 125.7 (d), 127.1 (d), 128.2 (d), 129.2 (d), 130.1 (d), 130.9 (s), 131.1 (d), 131.6 (d), 132.8 (d), 134.3 (s), 135.5 (s), 148.1 (s), 149.5 (s), 188.8 (s) ppm; IR(cm^{-1}): ν 3067, 2950, 1942, 1736, 1645, 1598, 1437, 1303, 1233, 1158, 880, 748, 624; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{12}\text{O}_2\text{N}_3\text{ClNa}$ ($\text{M}^+ + \text{Na}$): 372.0510; found: 372.0507.

**(1-(2-Hydroxy-6-methylphenyl)-1H-1,2,3-triazol-4-yl)(naphthalen-1-yl)methanone (1de):**

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.3). The title compound was determined as colourless solid (84%). Mp: 221–223 °C; ^1H NMR (500 MHz, DMSO (D_6)): δ 2.27 (s, 3H), 6.72 (d, J = 8.2 Hz, 1H), 6.87 (s, 1H), 7.47–7.51 (m, 2H), 7.53 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.86–7.88 (m, 1H), 7.99 (t, J = 7.5 Hz, 2H), 8.27–8.29 (m, 1H), 8.85 (s, 1H), 10.21 (bs, 1H) ppm; ^{13}C NMR (125 MHz, DMSO (D_6)): δ 20.3 (q), 116.8 (d), 119.7 (d), 120.7 (s), 123.0 (d), 123.5 (d), 124.3 (d), 125.5 (d), 126.5 (d), 127.5 (d), 128.5 (d), 129.1 (d), 129.6 (s), 131.3 (d), 132.7 (s), 133.9 (s), 139.7 (s), 146.5 (s), 147.9 (s), 187.5 (s) ppm; IR(cm^{-1}): ν 3161, 2921, 1628, 1608, 1522, 1436, 1283, 1254, 1032, 902, 786, 764; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{16}\text{O}_2\text{N}_3$ ($\text{M}^+ + \text{H}$): 330.1237; found: 330.1221.

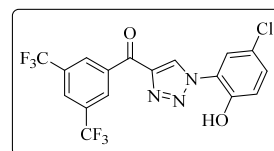
**(1-(2-Hydroxy-5-methylphenyl)-1H-1,2,3-triazol-4-yl)(naphthalen-1-yl)methanone (1db):**

Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.3). The title compound was determined as colourless solid (91%). Mp: 222–223 °C; ^1H NMR (400 MHz, CDCl_3 + MeOH (D_4)): δ 2.36 (s, 3H), 6.98 (d, J = 8.3 Hz, 1H), 7.14–7.16 (m, 1H), 7.56–7.65 (m, 5H), 7.96–7.98 (m,



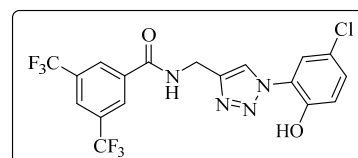
1H), 8.04 (dd, $J = 1.0, 7.1$ Hz, 1H), 8.11 (d, $J = 8.1$ Hz, 1H), 8.35–8.41 (m, 1H), 8.96 (s, 1H) ppm; ^{13}C NMR (100 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 19.5 (q), 116.4 (d), 123.0 (s), 123.9 (d), 124.0 (d), 124.7 (d), 126.0 (d), 127.1 (d), 128.0 (d), 129.0 (d), 129.2 (s), 130.0 (d), 130.2 (s), 130.7 (d), 132.2 (d), 133.5 (s), 134.3 (s), 146.3 (s), 146.9 (s), 188.6 (s) ppm; IR(cm^{-1}): ν 3070, 2920, 1627, 1522, 1457, 1368, 1286, 1256, 1164, 1031, 903, 786; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{16}\text{O}_2\text{N}_3$ ($\text{M}^+ + \text{H}$): 330.1237; found: 330.1243.

(3,5-Bis(trifluoromethyl)phenyl)(1-(5-chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)methanone (1ea): Isolated by column chromatography (pet.ether/AcOEt = 8:2, $R_f = 0.2$). The title compound was determined as colourless solid (82%). Mp: 210–212 °C; ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 7.08 (d, $J = 8.9$ Hz, 1H), 7.32 (dd, $J = 2.4, 8.9$ Hz, 1H), 7.94 (d, $J = 2.4$ Hz, 1H), 8.17 (bs, 1H), 8.99 (bs, 2H), 9.22 (s, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 118.0 (d), 121.6 (s), 123.6 (d, 2C), 123.8 (s), 124.0 (s), 124.4 (s), 126.0 (d, t, $J = 3.6$ Hz), 130.1 (d), 130.4 (d, $J = 2.7$ Hz), 130.5 (d), 131.4 (s, d, $J = 33.6$ Hz), 131.9 (s, d, $J = 34.5$ Hz), 137.8 (s), 146.1 (s), 147.5 (s), 182.5 (s) ppm; IR(cm^{-1}): ν 3187, 2959, 1640, 1527, 1419, 1280, 1134, 910, 819, 768; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_9\text{O}_2\text{N}_3\text{ClF}_6$ ($\text{M}^+ + \text{H}$): 436.0282; found: 436.0289..



N-((1-(5-chloro-2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3,5-

bis(trifluoromethyl)benzamide (1fa): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.5$). The title compound was determined as colourless solid (85%). Mp: 204–206 °C; ^1H NMR (200 MHz, CDCl_3): δ 4.43 (s, 2H), 6.69 (d, $J = 8.8$ Hz, 1H), 6.93 (dd, $J = 2.7, 8.7$ Hz, 1H), 7.40 (d, $J = 8.6$ Hz, 1H), 7.71 (bs, 1H), 8.12 (s, 3H) ppm; ^{13}C NMR (50 MHz, CDCl_3): δ 34.6 (t), 117.6 (d), 119.8 (d), 123.4 (d), 123.8 (s), 124.3 (d), 124.5 (d), 125.2 (s), 127.4 (d, $J = 2.9$ Hz), 129.1 (d), 130.6 (s), 130.7 (s, d, $J = 33.7$ Hz), 131.6 (s, d, $J = 34.0$ Hz), 135.6 (s), 143.5 (s), 147.4 (s, 2C), 164.8 (s) ppm; IR(cm^{-1}): ν 3085, 2926, 1645, 1597, 1460, 1376, 1280, 1176, 1132, 906, 773, 689; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{12}\text{O}_2\text{N}_4\text{ClF}_6$ ($\text{M}^+ + \text{H}$): 465.0547; found: 465.0533.



SECTION B

Synthesis, characterization, antifungal evaluation and mechanistic studies of new 1,2,3 triazole derivatives

1B.1. Introduction

1B.1.1. History of Fungal diseases

Fungal infections constitute an ever-growing medical problem causing an enormous economical burden for healthcare with high annual costs exceeding billions not only in India but also in the western world.⁶³ In developing countries like India, high costs associated with nosocomial infectious diseases often preclude efficient therapies. The major fungi infecting humans include *Candida* spp (*C. albicans*, *glabrata* and especially *parapsilosis* in India) accounting for 75% of all infections and representing the fourth leading cause of nosocomial diseases. Further, filamentous *Aspergillus* spp (i.e. *A. fumigatus*) or the yeast *Cryptococcus neoformans* and rare emerging fungal pathogens cause up to 25% of disseminated fungal infections. In the developing world, there are ~1 million new cases of cryptococcal disease reported per year resulting in 675000 deaths.⁶⁴ The mortality of about 40% just for candidemias exceeds that of all Gram-negative bacterial septicemias, emphasizing the medical importance of fungal diseases. Life threatening systemic fungemias develops in patients with severely impaired immunity (organ/bone marrow transplants, AIDS, cancer, neonates, and intensive care unit patients). The high mortalities are to a significant extent owing to inaccurate diagnostics, but also because current therapies rely upon a limited spectrum of high cost drugs. Hence, invasive fungal diseases are serious medical conditions, demanding a permanent attention in basic and clinical research, but also in translational antifungal drug discovery.⁶⁵

The term mycosis refers to conditions in which fungi invade the resistance barriers of the human body and establish infections. There are approximately 1.5 million different species of fungi on Earth, but only about 300 of those are known to cause infection.⁶⁶ These mycoses are of different types. Infections can be superficial that is situated at or close to the surface of the skin, or systemic, which means they can affect the body as a whole rather than individual parts or organs. Fungal infections are divided in the following groups⁶⁶

1. Superficial mycoses
2. Cutaneous mycoses
3. Subcutaneous mycoses

4. Systemic mycoses due to primary pathogens
5. Systemic mycoses due to opportunistic pathogens

The fungal pathogens are divided majorly into two classes - i. primary true pathogens (*Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides immitis*), and ii. opportunistic pathogens. Increase in the population of immunocompromised patients and increase in resistance against currently used drugs led to changing epidemiology and the emergence of fungal pathogens which were previously considered clinically insignificant. Most infections are caused by *Candida albicans* and *Aspergillus* sp. (*A. fumigatus* and *A. flavus*).⁶⁷ However in the last 2–3 decades, their percent share has declined due to emergence of pathogenic fungi which include - *Acremonium* sp., *Acremonium terreus*, non-*albicans Candida* sp. (*C. glabrata*, *C. parapsilosis*, *C. krusei*), *Cryptococcus neoformans*, *Fusarium* sp., *Microsporum* sp., *Paecilomyces* sp., *Penicillium marneffeii*, *Rhizopus oryzae*, *Trichoderma* sp., *Trichophyton* sp., *Trichosporon* sp. etc.

Over the past two decades, fungal infections have increased significantly in frequency and have become the major reason for morbidity and mortality.⁶⁸ As advances in medical care have improved is has the survival of patients with severe and life-threatening illnesses. The more aggressive nature of such care has led to a rapid increase in the number of immunosuppressed population which includes the patients with AIDS, autoimmune diseases, burns, radiotherapy, chemotherapy and transplantation. These changes have been correlated with a substantial increase in the rate of invasive fungal infections (IFIs). Apart from the increased number of immunocompromised hosts, the limited repertoire of antifungal drugs and resistance development against current anti-fungal drugs has aggravated the situation.⁶⁹

1B.1.2. History of antifungal agents

In disparity to the steep rise in the number of fungal infection cases, only a few drugs have been developed over the past 5-6 decades (Fig. S1.7). Currently, five classes of compounds are used clinically to treat systemic mycoses. Just after the Second World War the treatments available for fungal infections were weak acids and phenolic dyes. In the early 1950s the available systemic antifungal drugs were nystatin and amphotericin B, but toxicity limited their use.⁷⁰ In the early 1960's

Griseofulvin, the first orally effective antibiotic was used for dermatophytosis management and later broad-spectrum agents arrived, with the first being iodinated trichlorophenol haloprogin, which functioned by disrupting the fungal cell membrane. After two decades without any progress, the field of medical mycology was revolutionized by the development of the azole antifungal agents. Imidazole agents such as clotrimazole, miconazole, sulconazole and bifonazole acted by binding to cytochrome p-450, thus blocking ergosterol synthesis in the fungal cell membrane.⁷¹ However, the azole group of drugs is known to have caused anaphylaxis like side effects. This caused the scientific community to look for new drugs.

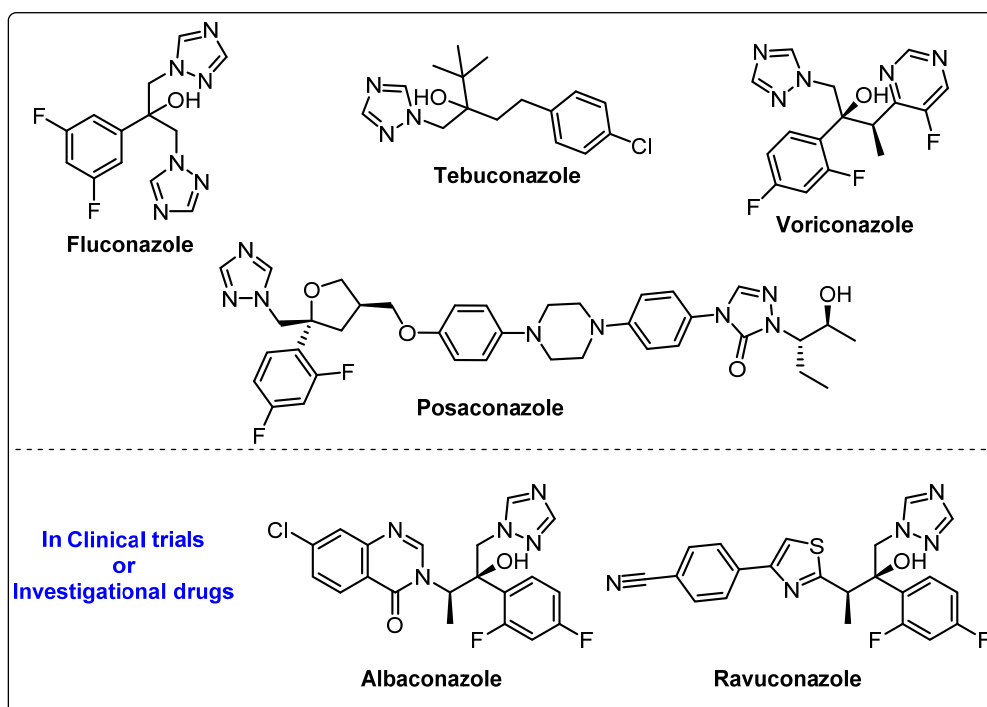


Figure S1.6: *Triazole-based antifungal agents*

The long haul was accounted with for the development of triazole antifungal agents that were less likely to cause hepatotoxicity, possibly due to their diminutive effects on cytochrome p-450-dependent enzymes. Terconazole was the first triazole developed, followed by itraconazole and then fluconazole. Fluconazole was marketed as Diflucan in the US and UK and over 30 countries worldwide. The new millennium brought echinocandins to the markets, which are the newest class of antifungals.⁷⁰ They are characterized by their inhibition of the synthesis of (1,3)- β -D-glucan (a key component of many fungal cell walls) and are therefore the first class of antifungal agents that act against a specific component of the fungal organisms and not

mammalian cells. Then second generation 1,2,4-triazoles, Voriconazole in 2002 and Posaconazole in 2005 (Fig. S1.6), were later introduced in the market. Very recently, Ravuconazole has invented new drugs beginning from tertiary alcohol, which is currently undergoing phase II clinical trials. It is highly active against a wide range of fungi.⁷² The timeline for the development of antifungal agents is shown in Figure S1.7.

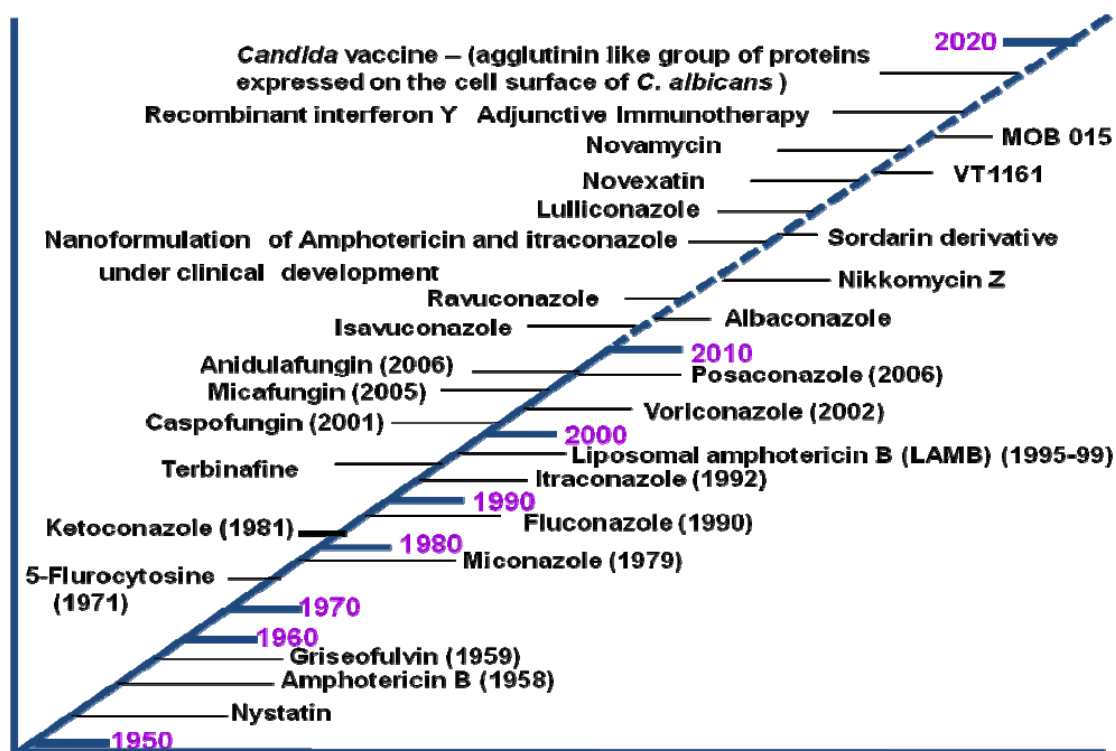


Figure S1.7. Progress of antifungal drugs development (Compiled from – Lewis, 2009; Ostrosky-Zeichner et al. 2010)

The antifungal agents available in the market have various drawbacks such as toxicity, a narrow spectrum of activity and fungistatic rather than fungicidal profiles. Some also exhibit drug–drug interactions. Secondly, currently available agents act on targets that are also found in mammalian cells. The discovery of antifungal agents that possess selective toxicity against the eukaryotic fungal cell remains an important scientific challenge.⁷³

Ideally, a selectively toxic antifungal agent should be developed that interacts with a fungal target not found in other eukaryotic cells. This strategy involves selective inhibition of the biosynthesis of important structural elements in the fungal cell. Ergosterol, a major component of fungal plasma membrane is one such target

and polyenes, azoles, morpholines and allylamines act either on ergosterol or different enzymes involved in ergosterol synthesis. For instance, azoles inhibit 14 α -lanosterol demethylase in the ergosterol biosynthesis pathway leading to depletion of ergosterol and accumulation of intermediate C-14 methyl-substituted sterols (Fig. S1.8).^{70, 74}

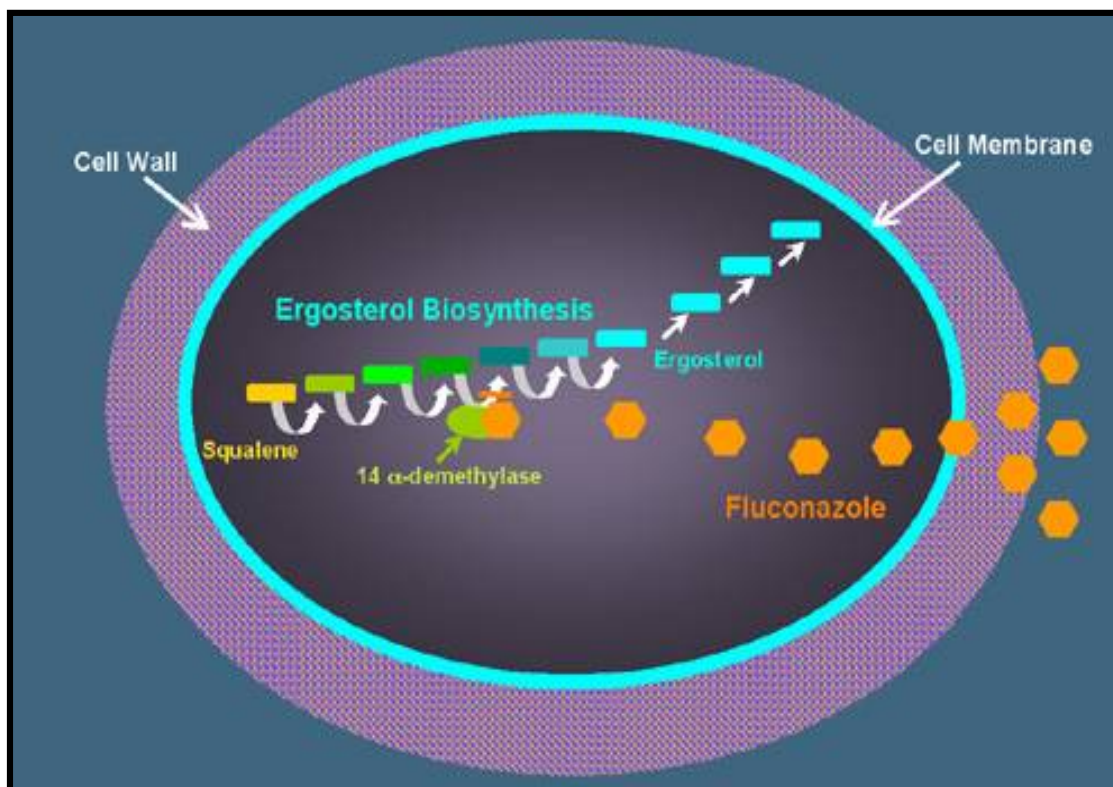


Fig. S1.8: Mechanism of antifungal action of azoles

Ergosterol depletion leads to disruption of membrane integrity and subsequently, inhibition of the fungal pathogen (Fig. S1.8). Even with the advent of ketoconazole, the search for improved antifungal azole agents has continued due in part to concerns over the potential for toxicity and poor penetration into cerebrospinal fluid associated with ketoconazole. Fluconazole is the current drug of choice for the treatment of severe infections caused by the *Candida* species and *Candida neoformans*. However, Fluconazole has only weak activity against isolates of *Aspergillus* species. Some of the fluconazole derivatives exhibited significant variations in plasma pharmacokinetics besides having weak anti-*aspergillus* activity.⁷⁵ Voriconazole also shows non-linear pharmacokinetics but has raised some concern with respect to its ocular toxicity.⁷⁶

The continuing demand for safe and effective broad spectrum antifungal agents with favorable pharmacokinetic properties has spurred both the design and development of new systemically active antifungal triazoles. The chemistry of triazoles has received considerable attention in recent years due to their biological activity. The triazole moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favorable in binding biomolecular targets as well as in increasing solubility. Moreover, triazoles can function as attractive linker units which could connect two pharmacophores to give an innovative bifunctional drug, and thus have become increasingly useful and important in constructing bioactive and functional molecules. Additionally, many investigations have shown that the addition of alkyl chains and/or various aromatic substituents, especially containing halogen atoms, has an important effect on the antimicrobial activities. Secondly, as compared to imidazoles (clotrimazole, ketoconazole, miconazole), 1,2,3-triazoles are less susceptible to metabolic degradation and have much greater target specificity, increased potency and an expanded spectrum of activity.⁷⁷ Therefore, the present work was initiated with an aim towards developing new 1,2,3 triazoles with variable functional groups and having potent biological activity, especially antifungal activity.⁴⁹

1B.2. Present Work

In recent years, studies have revealed that many of the cancer drugs have the potential to be anti-fungal agent vice versa anti-fungal compounds also show potential anti-cancer properties.⁷⁸ For example, thiabendazole, an orally available antifungal drug in clinical use for 40 years, also potently inhibits angiogenesis in animal models and in human cells. Thiabendazole reversibly disassembles newly established blood vessels, marking it as a vascular disrupting agent (VDA) and thus as a potential complementary therapeutic agent for use in combination with current anti-angiogenic therapies.⁷⁹

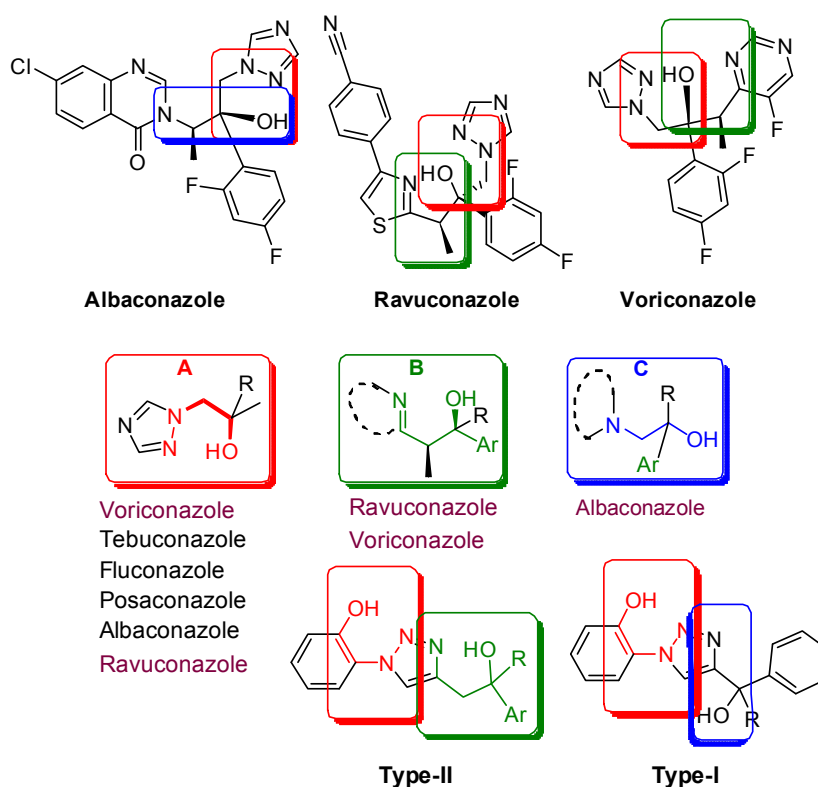


Figure 1B.1: Structures of the sub-structural units A – C noticed in theazole-class of antifungals and of the two types of newly designed triazole scaffolds

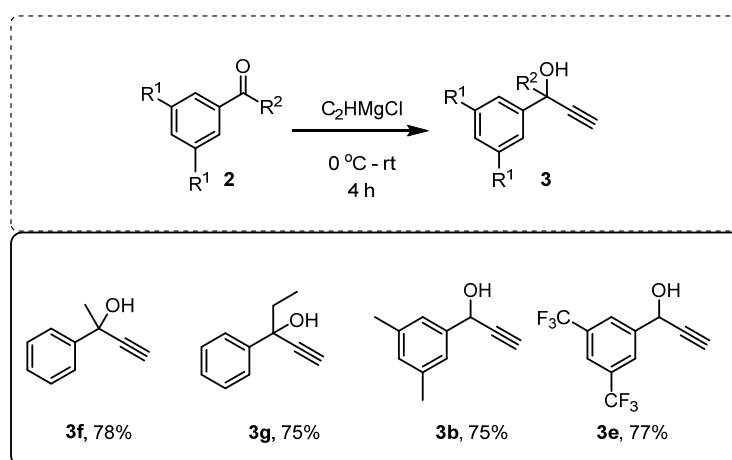
Similarly, recent Phase II studies have revealed the anti-fungal azole drug itraconazole for advanced prostate cancer treatment.⁸⁰ Having the building blocks of the newly developed 1,2,3-triazole anti-cancer hits in hand, we reasoned that a slight structural/functional group modification of **1ea** keeping some of the key aspects of 1,2,4-triazole antifungals, shall lead to new anti-fungal compounds. In this context, two classes of 1,4-disubstituted 1,2,3-triazole compounds have been designed as

potential candidates for antifungal screenings. The following figure reveals the salient features of our design. A dissection of the triazole antifungals revealed three key central structural elements. We designed the compounds in such a way that in type-I, the commonly noticed **N-N-C-C-OH** (Structural Unit A, Fig. 1b.1) in all azole-antifungal compounds has been retained. Whereas in type-II, along with this, another structural unit **N-C-C-C-OH** (Structural Unit B, Figure 1B.1) has been also incorporated.⁷⁶

1B.2.1. Chemistry:

1B.2.1.1 Synthesis of alkyne precursors for type-I triazoles

The aromatic alkynol intermediates (**3f** and **3g**) were synthesized by treating *in situ* prepared ethynylmagnesium chloride with two aromatic ketones such as acetophenone and propeophenone in THF respectively (scheme 1B.1).⁶⁰ The structures were confirmed by ¹H, ¹³C NMR and IR. For example, in the ¹H NMR spectrum of compound **3f**, the acetylenic proton was identified as a singlet at δ 2.67 ppm, the methyl protons (CH₃) resonated as singlet at 1.78 ppm and the quaternary hydroxyl proton appeared at δ 2.65 ppm as a broad singlet. In the ¹³C spectrum, the carbonyl carbon disappeared at δ 198 ppm and the quaternary carbon atom appeared at δ 69.7 ppm as singlet and the terminal acetylenic proton resonated at δ 73.0 ppm. The presence of the acetylenic group was also evident from the IR spectrum where the absorption was observed at 3318 cm⁻¹.

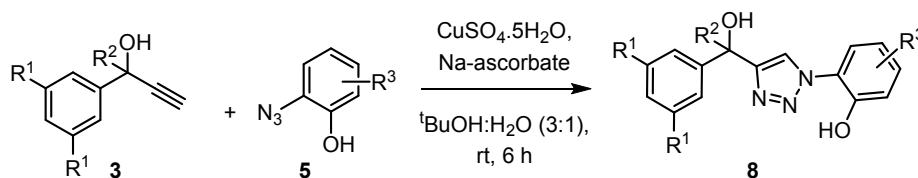


Scheme 1B.1: Synthesis of alkyne precursors for Type-I

1B.2.1.2. Synthesis of aryl 1,4-substituted-1,2,3-triazolyl compounds (Type-I)

1,3 Dipolar cycloaddition of two different chloroazidophenols **5a** and **5c** with different alkynols **3b**, **3e**, **3f** and **3g** was carried out using the click reaction. One equivalent of alkynols **3b**, **3e**, **3f** and **3g** were taken in separate round bottom flasks and one equivalent of each chloroazidophenols **5a** and **5c** were dissolved in *t*butanol/water (3:1) the resulting solution was treated with 20 mol% CuSO₄·5H₂O and 20 mol% sodium ascorbate.⁶³ The reaction mixture was stirred at room temperature (6 h) for completion of cycloaddition leading to the final compounds **8ba**, **8bc**, **8ea**, **8fc** and **8ga** (Scheme 1B.2 and Fig. 1B.2).

All 1,2,3-triazolyl derivatives **8ba–8ga** were characterized by IR, ¹H and ¹³C NMR and HRMS. For instance for **8fc**, the IR spectrum showed characteristic stretching frequencies at 3160 and 1443 cm⁻¹. In the ¹H NMR spectrum, the methyl (CH₃) appeared at δ 2.02 ppm as a singlet and the characteristic triazolyl proton appeared at δ 8.20 ppm as a singlet. The remaining aromatic protons resonated between δ 6.96–7.63 ppm. In the ¹³C NMR spectrum, the methyl (CH₃) appeared at δ 28.9 ppm as quartet and benzylic quaternary carbon appeared at δ 70.9 ppm as a singlet. In the HRMS, the exact mass of the compound showed as calculated for C₁₆H₁₅O₂N₃Cl [M+H]⁺ was 316.0847 and it was found as 316.0846. For another representative triazole **8bc**, in the ¹H NMR spectrum, the benzylic CH appeared at δ 6.03 as singlet, methyl protons (CH₃) appeared as a singlet at δ 2.31 ppm and the triazolyl proton appeared at δ 7.88 ppm as a singlet. In the ¹³C NMR spectrum, two methyl carbons appeared at δ 21.3 ppm as quartet and the benzylic carbon appeared at δ 69.4 ppm. In the HRMS, the exact mass of the compound calculated for C₁₇H₁₇O₂N₃Cl [M+H]⁺ was 330.1004 and it was found as 330.1005.



Scheme 1B.2: Preparation of Type-I triazoles

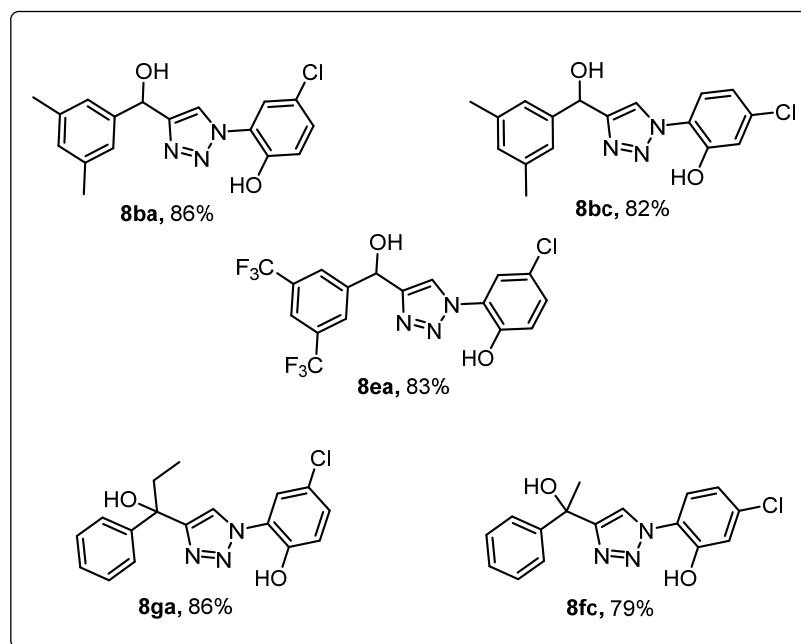
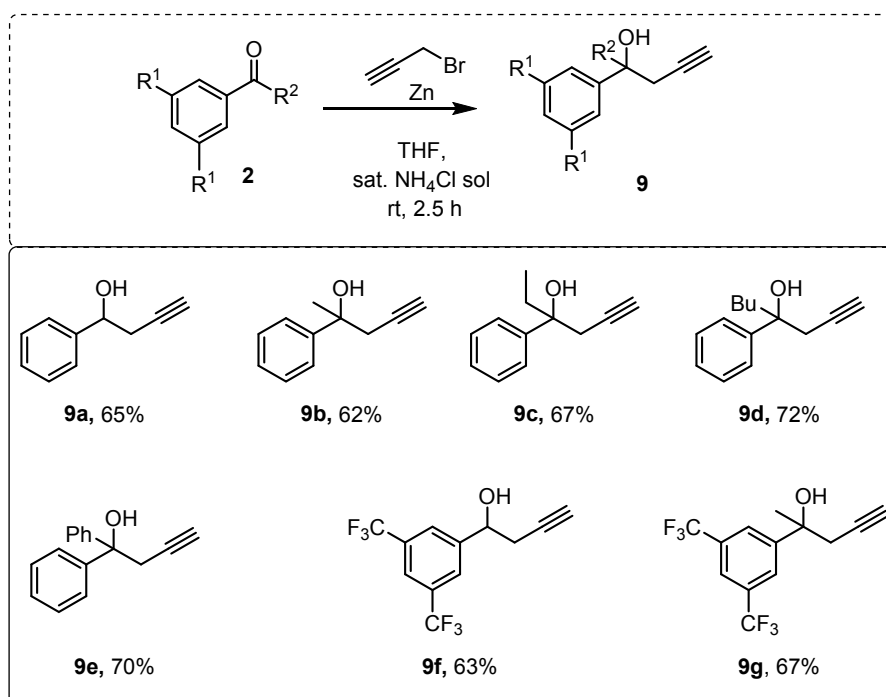


Figure 1B.2: Type-I 1,2,3-triazoles

1B.2.1.3. Synthesis of alkyne precursors for Type-II triazoles

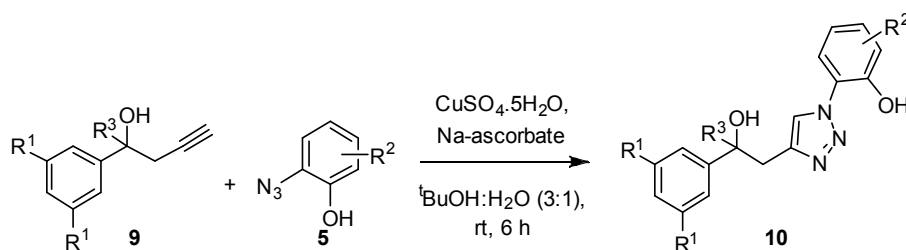
The aromatic alkynol intermediates (**9a** and **9g**) were synthesized by treating propargyl bromide with aromatic aldehydes and ketones (**2a–2j**) under Zn-mediated Barbier reaction conditions (Scheme 1B.3).⁸¹



Scheme 1B.3: Synthesis of alkyne precursors for Type-II

The products were confirmed by ^1H NMR and IR. For example, in the ^1H NMR spectrum of compound **9a** the acetylenic proton was identified as a triplet at δ 2.05 ppm with $J = 2.7$ Hz, the methylene protons resonated as a doublet of doublet at 2.61 ppm with $J = 2.7, 6.3$ Hz and the benzylic CH appeared at δ 4.83 ppm as a triplet with $J = 6.3$ Hz. The presence of the acetylenic group was also evident from the IR spectrum wherein the absorption was observed at 3309 cm^{-1} .

1B.2.1.4. Synthesis of Type-II 1,2,3-triazolyl compounds



Scheme 1B.4: Synthesis of 3°-alkynol derived 1,2,3 triazoles

The 1,3-dipolar cycloaddition of chloroazidophenols **5a** and **5c** with different alkynols **9a–9g** (scheme 1B.3) were carried out under established CuAAC reaction conditions. One equivalent of alkynols **9a–9g** taken in different round bottom flasks and one equivalent of chloroazidophenol **5a** and **5c** were dissolved in $t\text{BuOH}$ /water (3:1) and the resulting solution was treated with 20 mol% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and 20 mol% of sodium ascorbate. The reaction mixture was stirred at room temperature (6 h) for completion of cycloaddition leading to the final compounds **10** (scheme 1B.4 and Fig. 1B.3). All 1,2,3-triazolyl derivatives **10aa–10gc** were characterized by IR, ^1H and ^{13}C NMR and HRMS. For the representative compound **10ba**, the IR spectrum showed characteristic stretching frequencies at 3067 and 1645 cm^{-1} . In the ^1H NMR spectrum of compound **10ba**, the methyl-H (CH_3) resonated at δ 1.61 ppm as a singlet, methylene-H (CH_2) appeared at δ 3.28 ppm as a singlet and the triazolyl proton appeared at δ 7.83 ppm as a singlet. In the ^{13}C NMR spectrum, the CH_3 carbon resonated at δ 27.9 ppm as a quartet, the methylene carbon appeared at δ 39.5 ppm as a triplet and the benzylic carbon appeared at δ 73.0 ppm as a singlet. In the HRMS, the exact mass of the compound showed as calculated for $\text{C}_{17}\text{H}_{17}\text{O}_2\text{N}_3\text{Cl}$ $[\text{M}+\text{H}]^+$ was 330.1004 and it was found to be 330.0999.

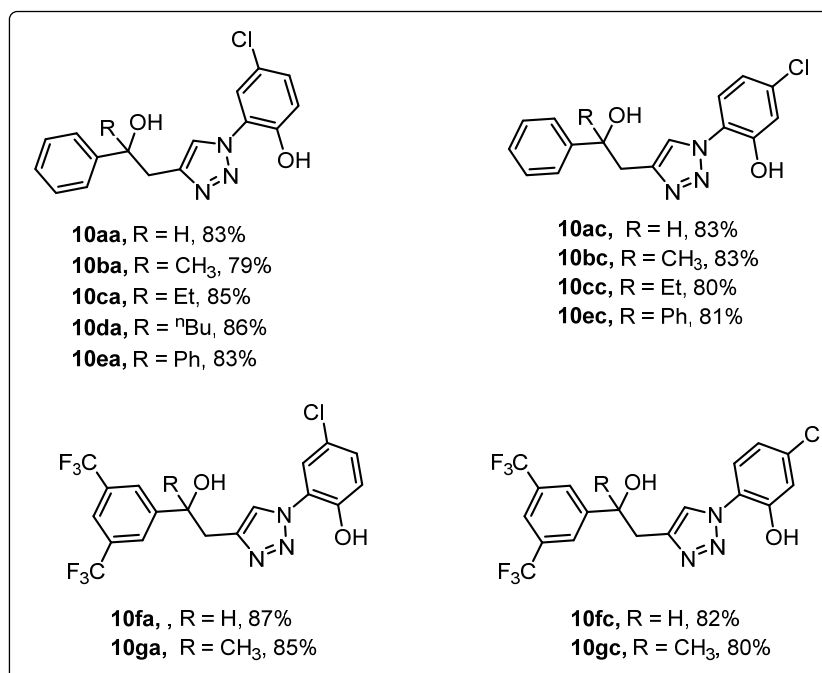


Figure 1B.3: Type II 1,2,3-triazoles

After the successful synthesis of type-I and type-II 1,2,3-triazoles, we have proceeded further for their antifungal evaluation against some human fungal pathogens.

1B.2.2. Biology:

1B.2.2.1. Microorganisms and growth conditions

Human pathogens *C. albicans* ATCC 24433, *C. albicans* ATCC 10231, *C. glabrata* NCYC 388, *C. neoformans*, *C. neoformans* ATCC 34664, *A. fumigatus* MCC 1046, *A. niger* ATCC 10578 were maintained on YPG (yeast extract, 0.3%; peptone, 0.5%; and glucose, 1%) agar slants, Whereas, *Fusarium oxysporum* (plant pathogen) was maintained on PD (potato, 20%; dextrose, 2%) agar slants at 4 °C. *Saccharomyces cerevisiae* wild type and *S. cerevisiae erg11* haploinsufficient mutant were a kind gift from Dr. A. Bacchawat, IISER, Mohali, India. The wild type and mutant *S. cerevisiae* strains were maintained on 2 x YPG agar slants. For different assays, the inoculum of the yeasts was prepared by growing them in YPG broth at 28°C for 24 h.

1B.2.2.2. Antifungal susceptibility assay

Antifungal activities of the synthesized compounds, type-I and type-II (in terms of Minimum Inhibitory Concentrations (MICs)) against *C. albicans* ATCC

24433, *C. albicans* ATCC 10231, *C. glabrata* NCYC 388, *C. neoformans*, *C. neoformans* ATCC 34664, *A. fumigatus* MCC 1046, *A. niger* ATCC 10578 (CLSI M27-A3) and *F. oxysporum* (CLSI M38-A2) were determined by broth microdilution assay with some modification.⁸² The only modification was that instead of RPMI-1640, YPG medium was used as a growth medium. Briefly, appropriate amount of compounds were dissolved in dimethyl sulfoxide to get 100X final strength. The stock was then diluted 1:50 in YPG medium and 200 μ l from this was added to the first row of a 96-well microtitre plate.

Table 1B.1. Minimum Inhibitory Concentration (MIC in μ g/ml) of the synthesized compounds against human pathogenic fungi

Organism Compound	<i>Candida albicans</i> ATCC 24433	<i>Candida Albicans</i> ATCC 10231	<i>Candida glabrata</i> NCYC388	<i>Cryptococcus Neoformans</i> ATCC 34664	<i>Aspergillus Fumigates</i> MCC 1046	<i>Aspergillus niger</i> ATCC 10578
Type-I						
8ba	64	ND	32	32	64	64
8bc	32	32	32	32	32	>128
8ea	128	ND	128	16	>128	>128
8ga	128	ND	128	64	>128	>128
8fc	>128	ND	128	>128	128	>128
Type-II						
10aa	64	ND	128	>128	128	64
10ba	128	ND	128	>128	128	64
10ca	64	32	32	32	32	128
10da	16	16	8	16	8	>128
10ea	64	>128	64	64	>128	>128
10fa	16	16	8	16	>128	>128
10ga	16	16	8	16	32	>128
10ac	64	ND	128	>128	128	>128
10bc	>128	128	64	128	128	128
10cc	32	32	64	32	128	64
10ec	64	>128	64	32	>128	>128
10fc	16	32	8	16	>128	>128
10gc	16	16	8	8	8	>128
Fluconazole	2	8	>128	32	>128	>128

The compounds were serially diluted two fold in successive wells to get a range of 1-128 µg/ml. Fungal yeast cells ($\sim 2 \times 10^3$ cfu/mL), freshly grown in YPG broth in logarithmic phase, were suspended in the medium and inoculated (100 µl) in the wells of the plate. For *F. oxysporum*, 2×10^4 spores/mL were added. The microtitre plate was incubated for 48 h, and the absorbance was measured at 600 nm by using the microtitre plate reader (xMark™ Microplate Absorbance Spectrophotometer, Bio-Rad, CA, USA) to assess cell growth. The MIC was defined as the lowest concentration exhibiting >90% inhibition of visible growth as compared to growth of the control. All the results were summarized in table 1B.1. Based on the MIC results, compounds **8bc**, **10cc**, **10fa**, **10fc**, **10ga**, **10gc**, and **10da** were identified as lead molecules. Mechanism of antifungal action of these compounds was investigated by different assays.

1B.2.2.3. Haploinsufficiency assay for identification of ergosterol synthesis inhibitors

A yeast genome-wide drug induced haploinsufficiency screen using *S. cerevisiae* as a model organism has been developed by Giaever *et al.*⁸³ Lowering the dosage of a single gene from two copies to one copy in diploid yeast results in a heterozygote. The resulting mutant strain becomes sensitive to any drug that acts on the product of this gene as compared to wild type strain. This haploinsufficient phenotype thereby identifies the gene product of the heterozygous locus as the likely drug target.⁸⁴

For instance, diploid wild type *S. cerevisiae* strain and its mutant (haploid for the targeted gene *erg11* – lanosterol 14 α -demethylase gene) were used for the screening of the ergosterol synthesis inhibitors. As the mutant has only one copy of *erg11*, the effect of azole inhibitors (targeting ergosterol synthesis) on growth will be more pronounced on it as compared to the wild type, whereas other agents will exert similar effect on both the strains. The synthesized compounds were checked for antifungal activity against both *S. cerevisiae* strains in 2X YPG medium by broth microdilution assay (CLSI M27-A3).⁸² (Table 1B.2). Concentration of compounds **10ca**, **10fa**, **10ga** required to inhibit growth of the mutant was half than the concentration required for wild type *S. cerevisiae* growth inhibition identifying lanosterol 14 α -demethylase as their target.

Table 1B.2: Haploinsufficiency assay for target identification using *S. cerevisiae* wild type and mutant for *erg11* gene

Organism Compound	<i>S. cerevisiae</i> 1536 (wild strain)	<i>S. cerevisiae</i> 1500 (mutant for <i>erg11</i>)
	MIC in µg/ml	
Type-I		
8ea	128	128
8bc	32	32
8ba	64	64
8ga	128	128
8fc	>128	>128
Type-II		
10aa	>128	128
10ba	>128	>128
10ca	128	64
10da	32	32
10ea	64	64
10fa	32	16
10ga	32	16
10ac	64	64
10bc	128	128
10cc	64	64
10ec	32	32
10fc	16	16
10gc	16	16
Fluconazole	32	16

1B.2.2.4. Effect of the compounds on sterol profile of *C. albicans* ATCC 24433

The depletion of ergosterol as a result of inhibition of the lanosterol 14 α -demethylase by the compounds was quantified by spectrophotometry⁸⁵. Briefly, overnight grown *C. albicans* ATCC 24433 (1×10^6 cfu/ml) cells were inoculated in a series of flasks with 50 ml of YPG broth containing 0.5MIC and MIC of the compounds **10ca**, **10fa**, **10ga**, **8bc**, **10da** and Fluconazole. The flasks were incubated on a rotary shaker (180 rpm, 30 °C) for 24 h. After incubation, the cells were harvested by centrifugation (3000rpm for 5 min) and washed with sterile distilled water. The net wet weight of the cell pellet was determined. Three ml of 25% alcoholic potassium hydroxide solution

(25 g of KOH and 35 ml of sterile distilled water, brought to 100 ml with 100% ethanol), was added to 125 mg of pellet and vortex mixed for 1 min. Cell suspensions were transferred to sterile borosilicate glass screw-cap tubes and were incubated in an 85 °C water bath for 1 h. Following incubation, tubes were allowed to cool to room temperature. Sterols were then extracted by addition of a mixture of 1 ml of sterile distilled water and 3 ml of *n*-heptane followed by vigorous mixing for 3 min. The heptane layer was scanned between 220 and 300 nm with a spectrophotometer (Spectrascan UV-2600 Spectrophotometer, Chemito).

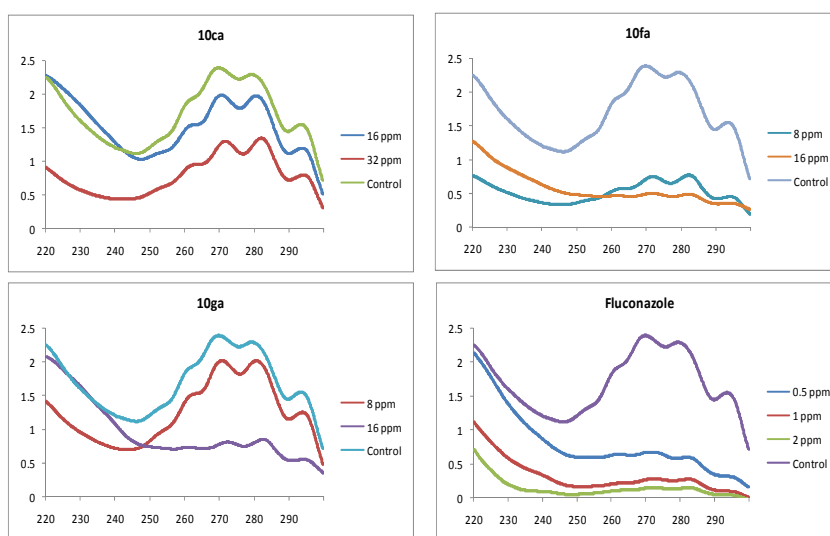


Figure 1B.4: Sterol profile of *C. albicans* ATCC 24433 in presence of a) **10ca**, b) **10fa**, c) **10ga** and d) fluconazole

The presence of ergosterol and the late sterol intermediate 24(28)DHE in the extracted sample resulted in a characteristic four-peaked curve. A dose-dependent decrease in the height of the absorbance peaks was evident and corresponded to decreased ergosterol concentration for fluconazole and **10fa**, **10ga** and **10ca**. The sterol profile for negative control compounds **8bc** and **10da** was similar to control. The results confirmed lanosterol 14 α -demethylase enzyme as a target for these compounds, thereby exerting their antifungal action through ergosterol depletion.

For compounds **8bc**, **10cc**, **10fc**, **10gc**, **10da** and no ergosterol depletion was observed, which indicated a different mode of action. Apart from lanosterol 14 α -demethylase inhibition, few azoles like miconazole are known to exert their antifungal action by reactive oxygen species (ROS) generation. Therefore ROS production was evaluated for these compounds by using dichlorofluorescein diacetate dye.

1B.2.2.5. Detection of Reactive Oxygen Species (ROS) production

Intracellular reactive oxygen species (ROS) generation was assessed by 2',7'-dichlorofluorescein diacetate (DCFH-DA) staining. After incubation of the cells with different concentrations of the compounds for 120 min, 10 μ M DCFH-DA in Phosphate Buffer Saline (PBS) was added and incubated further for 30 min. The cells were then harvested, washed with PBS and directly viewed using epifluorescence microscope (Leitz Laborlux S, Germany) equipped with a 50 W mercury lamp and a filter set (I3 filter block with excitation filter BP 450-490, and suppression filter LP520). The digital images were acquired with a Canon Power shot S80 camera and Zoom Browser EX 5.5 software for image acquisition and management. The percentage of fluorescent cells for each treatment was determined from the total number of cells (>300) and the fluorescent cells counted.

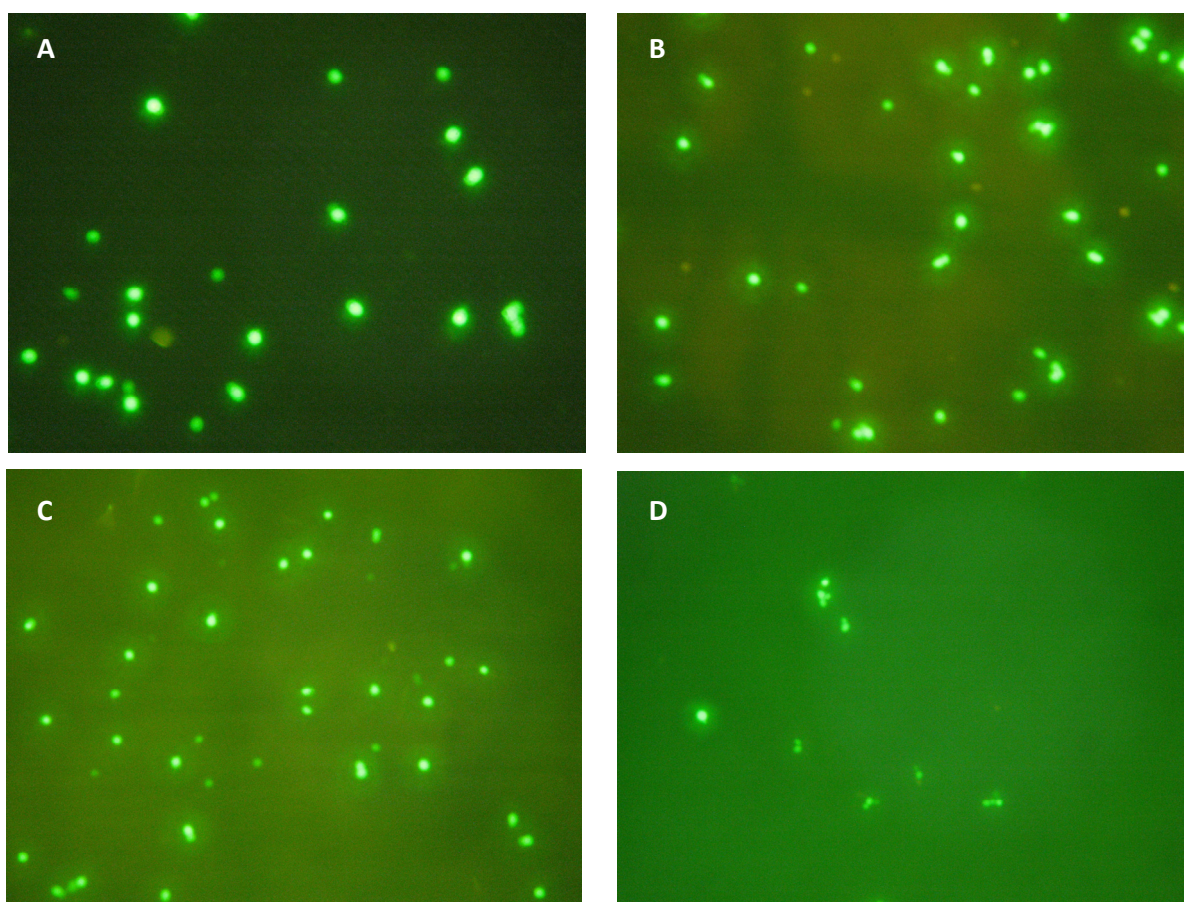


Fig.1B.5: DCFH-DA staining of *C. albicans* ATCC 24433 cells exposed to A) 32 μ g/ml **10da**; B) 64 μ g/ml **10cc**; C) 64 μ g/ml **10fc** and D) 64 μ g/ml **8bc**.

Based on these experiments the compounds **10cc**, **10gc**, **10fc**, **10da** and **8bc** were found to show antifungal activity through the ROS generation. For compound

10gc ROS generation was not observed. Compounds **10da** and **10fc** were most effective and showed ROS generation in >99% cells at 2X MIC 4X MIC concentration, respectively.

1B.2.3. Analysis

Based on the results obtained from the anti fungal studies of selected compounds, screening against some of the fungal pathogens followed by the mode of action such as enzyme inhibition and/or reactive oxygen species (ROS) generation and the structural features of the lead compounds following are some important observations need to be highlighted. First, as expected, compounds of Type II having the structural units **A** and **B** have shown better antifungal activity when compared with the Type 1 compounds which are having the structural units **A** and **C**.

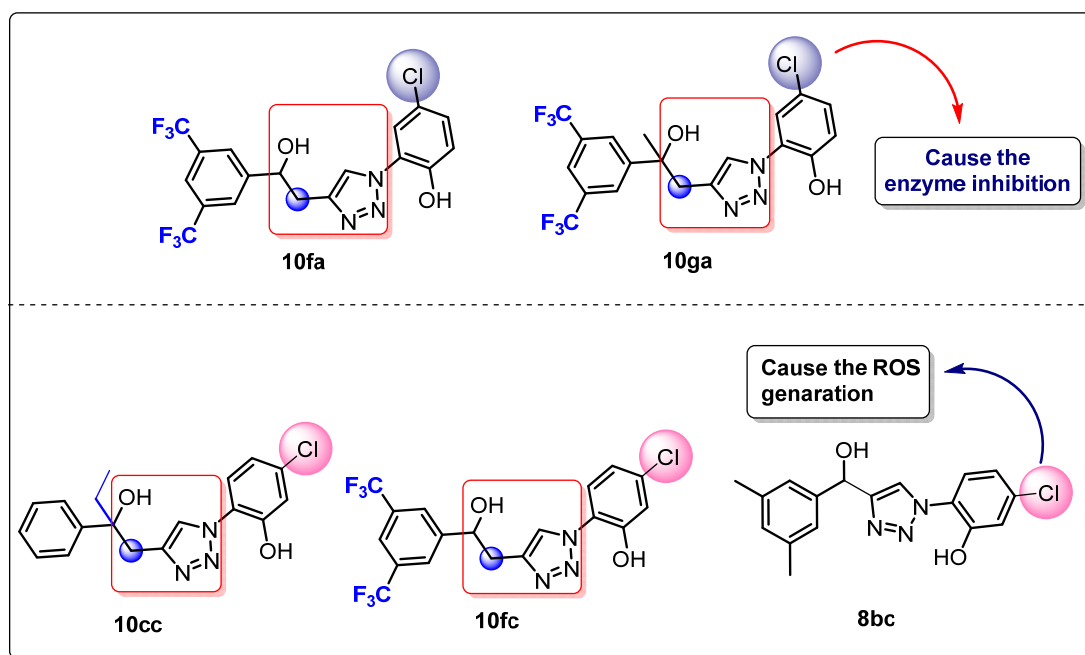


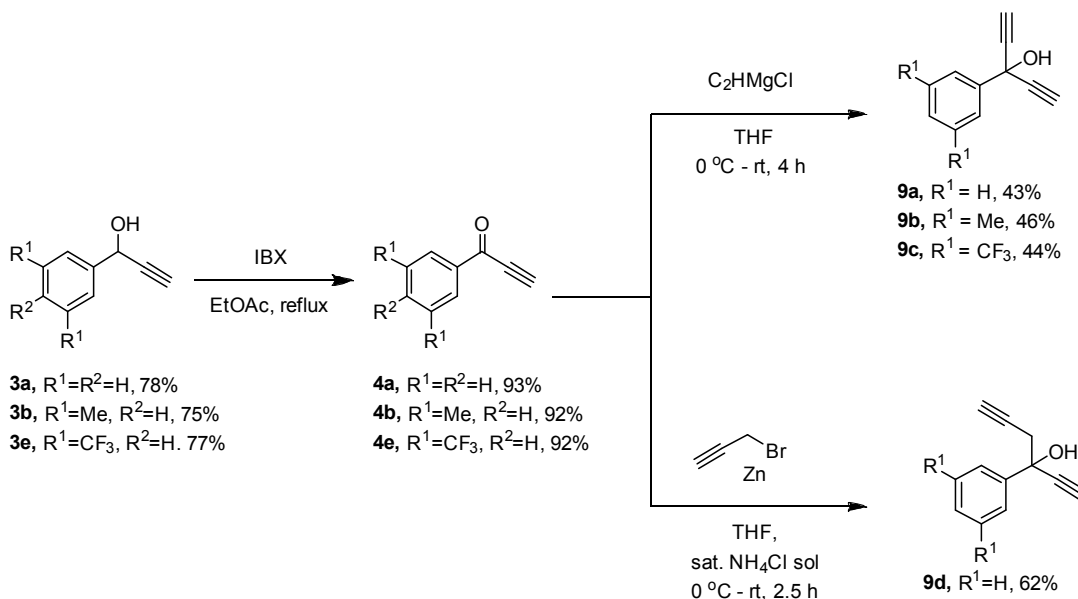
Figure 1B.6. Structure activity relationship of type I and II azoles

The results are indicative of the importance of a flexible methylene (CH_2) linker in between the two aryl ring for better antifungal activity. Another interesting and important feature that we noticed was how the position of the halo group changed the mode of action. When the chloro group was at the C-5 position of the phenyl ring (or *meta*) to the triazole unit, the molecule (compounds **10fa** and **10ga**) inhibited the fungal pathogen through the inhibition of enzyme, lanosterol 14 α -demethylase. Whereas, when the chloro group was at para position of the phenyl ring to the triazole

unit (compounds **10cc**, **10fc** and **8bc**), the inhibition of the fungi was due to ROS generation. Interestingly, for **10da**, though the chloro group was at C-5 position of the phenyl ring (or *meta*) to the triazole unit, ROS generation was observed as antifungal mode of action, which might be due to the presence of long alkyl chain at benzylic junction. The structure activity relationship will be useful in further optimization of lead molecules.

1B.2.4.1. Synthesis of dialkyne with 3^o-hydroxy group

After having a couple of antifungal hits in hand, we next turned our attention towards the synthesis of another set of compounds which were designed mainly around the antifungal drug fluconazole. The structure of the fluconazole is characterized by the presence of a 1,3-di(1*H*-1,2,4-triazol-1-yl)propan-2-ol unit. We were interested to synthesize ditriazolyl compounds and see whether the addition of another triazole unit has any significant advancement.



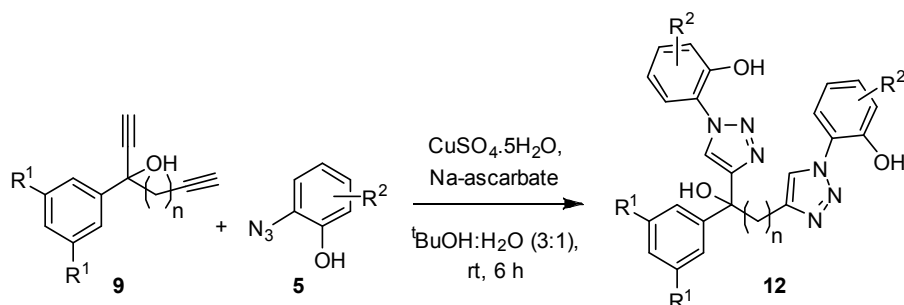
Scheme 1B.5: *Synthesis of dialkynol*

Scheme 1B.5, saliently describes the synthesis of symmetric dialkynols **9a-9c**. The synthesis started with the reactions of alkynones **4a**, **4b** and **4e** with excess ethynyl magnesium chloride in THF. However modest yields were obtained in Grignard reaction. The non-symmetric dialkynol **9d** was synthesized from alkynone **4a** by treating it with propargyl bromide under Zn-mediated Barbier reaction conditions (Scheme 1B.5). The structures of the dialkynol compounds (**9a**–

9d) were confirmed by NMR and IR spectroscopy. In the ^1H NMR spectrum of the compound **9a**, the terminal alkyne two protons were resonated at δ 2.79 ppm as singlet and the hydroxyl proton was resonated at δ 3.23 ppm while aromatic protons were resonated in between δ 7.36–7.84 ppm as two multiplets.

1B.2.4.2. Synthesis of aryl bis(1,4-substituted-1,2,3-triazolyl) compounds

Next the dialkynols **9a–9d** were subjected for the Cu(I) catalyzed 1,3-cycloaddition reaction strategy with azidophenols **5a**, **5b**, **5c** and **5e** to afford a set of eight triazoles (Scheme 1B.6).



Scheme 1B.6: Synthesis of bis triazoles

All 1,2,3-triazolyl derivatives **12aa–12ce** were characterized by ^1H and ^{13}C NMR and HRMS. For the representative compound **12da**, in the ^1H NMR spectrum, the methylene proton appeared as two doublet at δ 3.80 ppm and δ 3.99 ppm with $J = 14.9$ Hz, respectively and the two triazolic protons were resonated as two separate singlets at δ 7.85 and δ 8.31 ppm respectively. In ^{13}C NMR spectrum the methylene carbon resonated at δ 38.3 ppm as triplet and the benzylic quaternary carbon appeared at δ 73.5 ppm as singlet. In the HRMS, the exact mass of the compound showed as calculated for $\text{C}_{24}\text{H}_{19}\text{O}_3\text{N}_6\text{Cl}_2$ ($\text{M}^+ + \text{H}$) was 509.0890 and it was found as 509.0891.

The anti-fungal activity of all the bis triazoles was checked against the fungal pathogens as described in section 1B.2.2.2. All the symmetric bis-triazoles (Fig.1B.4) were ineffective as anti-fungals. The only unsymmetric bis-triazole **12da** showed antifungal activity with MIC values of 16, 16 and 8 $\mu\text{g/ml}$ for *C. albicans* ATCC 24433, *C. glabrata* NCYC 388 and *C. neoformans* ATCC 34664, respectively. Similar MIC (32 $\mu\text{g/ml}$) for *S. cerevisiae* wild type and *erg11* mutant indicated that

mode of the action for **12da** was different than inhibition of lanosterol 14 α -demethylase enzyme.

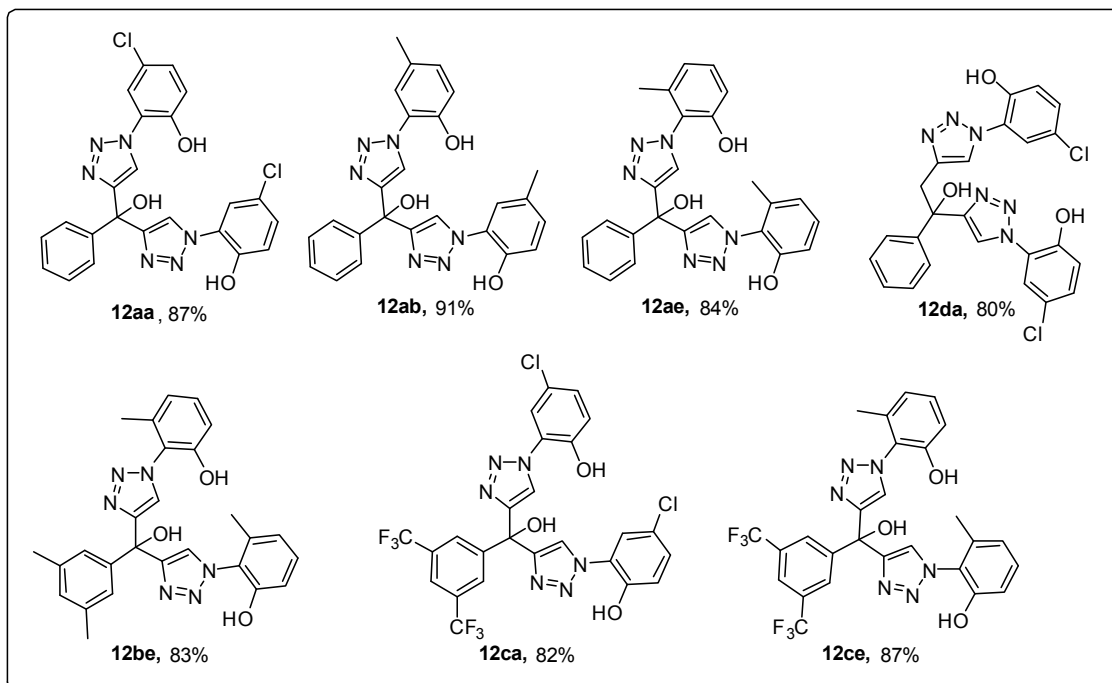


Figure 1B.7: Synthesized bis 1,2,3-triazoles

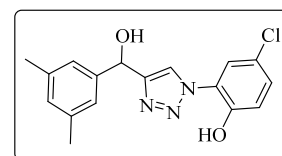
Conclusion:

To conclude, three sets of compounds have been designed by integrating some of the key structural elements present in theazole antifungals in the structure of one the novel anti-cancer hit that we have identified. Screening of focused collection of newly synthesized 1,2,3-triazoles lead to identify a couple of hits having promising antifungal activities. The mechanistic investigations revealed the possibility of two-complimentary modes of action for these 1,2,3-triazole derivatives. Further investigations on SAR of this new series of hits are currently under progress.

General experimental procedure B: To a solution of alkyne (**9** or **3**) (1.0 eq.) and azide **5** (2.2 eq.) in ^tBuOH:H₂O (3:1) at rt, sodium ascorbate (0.95 eq.) and CuSO₄ 5H₂O (0.2 eq.) were added and the resulting brick reddish mixture was stirred vigorously for 6 hrs. The reaction mixture was diluted and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and the solvents were evaporated under reduced pressure. The product was purified by column chromatography.

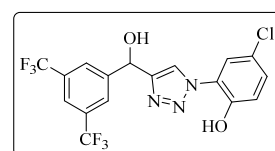
4-Chloro-2-(4-((3,5-dimethylphenyl)(hydroxy)methyl)-1H-1,2,3-triazol-1-yl)phenol (8ba**):**

Isolated by column chromatography (pet.ether/AcOEt = 6:4, *R_f* = 0.3). The title compound was determined as colourless solid (86%). Mp: 191–193 °C; ¹H NMR (200 MHz, CDCl₃): δ 2.34 (s, 6H), 2.74 (d, *J* = 3.5 Hz, 1H), 6.06 (d, *J* = 2.9 Hz, 1H), 7.00 (s, 1H), 7.08–7.16 (m, 2H), 7.26 (dd, *J* = 2.3, 8.8 Hz, 2H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.88 (s, 1H), 9.91 (s, 1H) ppm; ¹³C NMR (50 MHz, CDCl₃ + MeOH (D₄)): δ 21.3 (q, 2C), 69.4 (d), 119.1 (d), 119.6 (d), 120.2 (d), 120.4 (d), 121.4 (s), 124.1 (d, 2C), 130.1 (d), 135.0 (s), 138.5 (s, 2C), 141.2 (s), 150.0 (s), 151.6 (s) ppm; IR (cm⁻¹): 3306, 3136, 2944, 1645, 1564, 1442, 1318, 1262, 1063, 875, 751, 669; HRMS (ESI) calcd for C₁₇H₁₇O₂N₃Cl (M⁺+H): 330.1004; found: 330.1004.



2-(4-((3,5-Bis(trifluoromethyl)phenyl)(hydroxy)methyl)-1H-1,2,3-triazol-1-yl)-4-chlorophenol (8ea**):**

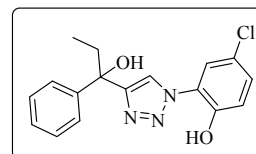
Isolated by column chromatography (pet.ether/AcOEt = 6:4, *R_f* = 0.3). The title compound was determined as colourless solid (83%). Mp: 211–213 °C; ¹H NMR (200 MHz, CDCl₃ + MeOH (D₄)): δ 5.99 (s, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 7.06 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.64 (bs, 1H), 7.86 (bs, 2H), 8.11 (s, 1H) ppm; ¹³C NMR (50 MHz, CDCl₃ + MeOH (D₄)): δ 67.1 (d), 117.9 (d), 120.3 (s), 120.5 (d, t, *J* = 3.7 Hz), 123.1 (d), 123.5 (d, 2C), 124.2 (s), 124.6 (s), 125.7 (s), 126.4 (d, *J* = 1.8 Hz), 129.1 (d), 130.6 (s, d, *J* = 33.3 Hz), 131.9 (s, d, *J* = 33.7 Hz), 145.2 (s), 147.4 (s), 149.7 (s) ppm; IR (cm⁻¹): 3393, 3133, 2959, 1647, 1448, 1300, 1260, 876, 751, 724; HRMS (ESI) calcd for C₁₇H₁₁O₂N₃ClF₆ (M⁺+H): 438.0439; found: 438.0445.



4-Chloro-2-(4-(1-hydroxy-1-phenylpropyl)-1H-1,2,3-triazol-1-yl)phenol (8ga**):**

Isolated by column chromatography (pet.ether/AcOEt = 6:4, *R_f* = 0.4). The title compound was determined as yellow solid (86%). Mp: 177–179 °C; ¹H NMR (200

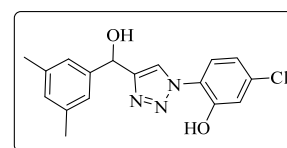
MHz, CDCl₃ + MeOH (D₄): δ 0.73 (t, J = 7.3 Hz, 3H), 2.04–2.40 (m, 2H), 6.82 (d, J = 8.8 Hz, 1H), 6.99–7.24 (m, 4H), 7.32–7.43 (m, 2H), 7.55 (d, J = 2.5 Hz, 1H), 8.05 (s, 1H) ppm; ¹³C



NMR (50 MHz, CDCl₃ + MeOH (D₄): δ 7.3 (q), 34.6 (t), 74.3 (s), 118.1 (d), 122.6 (d), 123.2 (d), 124.2 (s), 124.6 (s), 125.3 (d, 2C), 126.6 (d), 127.7 (d, 2C), 129.1 (d), 144.8 (s), 147.4 (s), 154.1 (s) ppm; IR(cm⁻¹): 3359, 3121, 2960, 1647, 1547, 1428, 1373, 1251, 1163, 966, 855, 754, 673; HRMS(ESI) calcd for C₁₇H₁₇O₂N₃Cl (M⁺+H): 330.1004; found: 330.1007.

5-Chloro-2-(4-((3,5-dimethylphenyl)(hydroxy)methyl)-1H-1,2,3-triazol-1-

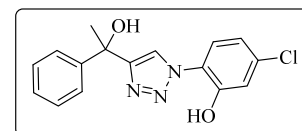
yl)phenol (8bc): Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.3). The title compound was determined as colourless solid (82%). Mp: 223–224 °C; ¹H



NMR (200 MHz, CDCl₃): δ 2.31 (s, 6H), 6.03 (s, 1H), 6.94 (d, J = 2.2, 8.7 Hz, 2H), 7.08 (s, 2H), 7.17 (d, J = 2.3 Hz, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 21.3 (q, 2C), 69.4 (d), 119.1 (d), 119.6 (d), 120.2 (d), 120.4 (d), 121.4 (s), 124.1 (d, 2C), 130.1 (d), 135.0 (s), 138.5 (s, 2C), 141.2 (s), 150.0 (s), 151.6 (s) ppm; IR (cm⁻¹): 3325, 3122, 2987, 2405, 1648, 1567, 1460, 1336, 1226, 1058, 874, 760, 664; HRMS(ESI) calcd for C₁₇H₁₇O₂N₃Cl (M⁺+H): 330.1004; found: 330.1005.

5-Chloro-2-(4-(1-hydroxy-1-phenylethyl)-1H-1,2,3-triazol-1-yl)phenol (8fc):

Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.4). The title compound was determined as colourless solid (79%). Mp: 232–234 °C; ¹H NMR (200 MHz, CDCl₃ +

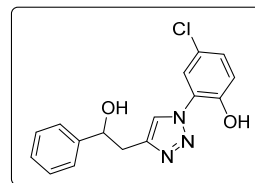


MeOH (D₄): δ 2.02 (s, 3H), 6.96 (dd, J = 2.2, 8.6 Hz, 1H), 7.07 (d, J = 2.3 Hz, 1H), 7.22–7.36 (m, 3H), 7.50–7.56 (m, 2H), 7.63 (d, J = 8.6 Hz, 1H), 8.20 (s, 1H) ppm; ¹³C NMR (50 MHz, CDCl₃ + MeOH (D₄): δ 28.9 (q), 70.9 (s), 116.2 (d), 119.1 (d), 122.4 (d), 122.8 (s), 124.5 (d, 2C), 124.7 (d), 126.1 (d), 127.2 (d, 2C), 134.3 (s), 146.1 (s), 149.4 (s), 154.3 (s) ppm; IR(cm⁻¹): 3309, 3160, 2987, 1642, 1555, 1443, 1362, 1266, 1109, 1013, 975, 871, 753, 678; HRMS(ESI) calcd for C₁₆H₁₅O₂N₃Cl (M⁺+H): 316.0847; found: 316.0846.

4-Chloro-2-(4-(2-hydroxy-2-phenylethyl)-1H-1,2,3-triazol-1-yl)phenol (10aa):

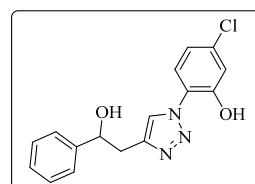
Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.3). The title compound was determined as colourless solid (83%). Mp: 148–150 °C; ¹H NMR

(200 MHz, CDCl_3 + MeOH (D_4)): δ 3.22 (d, J = 5.3 Hz, 2H), 5.04 (t, J = 6.6 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 7.22–7.43 (m, 6H), 7.71 (d, J = 2.5 Hz, 1H), 8.08 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + MeOH (D_4)) δ 34.8 (t), 72.5 (d), 117.7 (d), 123.3 (d), 123.8 (s), 123.9 (d), 124.6 (s), 125.3 (d, 2C), 126.9 (d), 127.8 (d, 2C), 129.0 (d), 143.2 (s), 143.7 (s), 147.4 (s) ppm; IR (cm^{-1}): 3363, 3131, 2998, 1643, 1552, 1314, 1253, 1044, 863, 764, 661; HRMS(ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 316.0847; found: 316.0847.



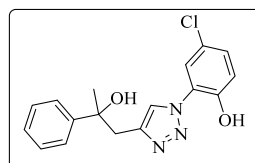
5-Chloro-2-(4-(2-hydroxy-2-phenylethyl)-1H-1,2,3-triazol-1-yl)phenol (10ac):

Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.3). The title compound was determined as colourless solid (83%). Mp: 171–172 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4)) δ 3.19 (s, 2H), 5.01 (s, 1H), 6.95 (d, J = 8.3 Hz, 1H), 7.06 (s, 1H), 7.25–7.36 (m, 5H), 7.58 (d, J = 8.0 Hz, 1H), 8.01 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + MeOH (D_4)) δ 34.7 (t), 72.4 (d), 116.4 (d), 119.3 (d), 122.9 (s), 124.7 (d), 125.2 (d, 2C), 126.8 (d), 127.6 (d, 3C), 134.4 (s, 2C), 143.2 (s), 149.5 (s) ppm; IR (cm^{-1}): 3341, 3142, 2972, 1651, 1563, 1324, 1221, 1063, 873, 750, 668; HRMS(ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 316.0847; found: 316.0854.



4-Chloro-2-(4-(2-hydroxy-2-phenylpropyl)-1H-1,2,3-triazol-1-yl)phenol (10ba):

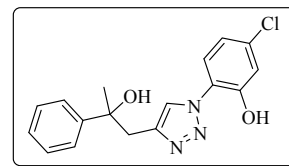
Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.4). The title compound was determined as colourless solid (79%). Mp: 180–181 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4)) δ 1.61 (s, 3H), 3.28 (s, 2H), 6.98 (d, J = 8.8 Hz, 1H), 7.20–7.37 (m, 4H), 7.43–7.49 (m, 2H), 7.65 (d, J = 2.5 Hz, 1H), 7.83 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + MeOH (D_4)) δ 27.9 (q), 39.5 (t), 73.0 (s), 117.6 (d), 123.3 (d), 123.7 (s), 124.3 (d, 3C), 124.5 (s), 126.0 (d), 127.4 (d, 2C), 128.9 (d), 142.9 (s), 146.7 (s), 147.4 (s) ppm; IR (cm^{-1}): 3344, 3067, 2950, 1942, 1736, 1645, 1598, 1437, 1303, 1233, 1158, 880, 748, 624; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{17}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 330.1004; found: 330.0999.



5-Chloro-2-(4-(2-hydroxy-2-phenylpropyl)-1H-1,2,3-triazol-1-yl)phenol (10bc):

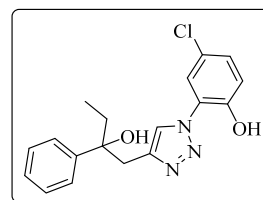
Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.4). The title compound was determined as colourless solid (83%). Mp: 189–190 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4)) δ 1.61 (s, 3H), 3.28 (s, 2H), 6.95 (dd, J = 2.3, 8.6 Hz,

1H), 7.05 (d, $J = 2.3$ Hz, 1H), 7.22–7.36 (m, 3H), 7.44–7.49 (m, 2H), 7.55 (d, $J = 8.6$ Hz, 1H), 7.76 (s, 1H) ppm; ^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 28.2 (q), 39.6 (t), 73.1 (s), 116.6 (d), 119.4 (d), 122.9 (s), 124.4 (d, 3C), 124.7 (d), 126.1 (d), 127.5 (d, 2C), 134.5 (s), 142.9 (s), 146.7 (s), 149.6 (s) ppm; IR(cm^{-1}): 3448, 3162, 3022, 2929, 1643, 1552, 1445, 1364, 1263, 1155, 1006, 923, 874, 763; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{17}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 330.1004; found: 330.1009.



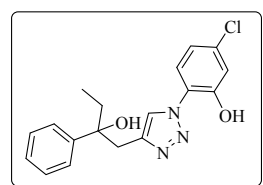
4-Chloro-2-(4-(2-hydroxy-2-phenylbutyl)-1H-1,2,3-triazol-1-yl)phenol (10ca):

Isolated by column chromatography (pet.ether/AcOEt = 6:4, $R_f = 0.4$). The title compound was determined as colourless solid (85%). Mp: 153–155 °C; ^1H NMR (400 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 0.80 (t, $J = 7.0$ Hz, 3H), 1.85–2.02 (s, 1H), 3.32 (s, 2H), 6.97 (d, $J = 8.0$ Hz, 1H), 7.18–7.22 (m, 2H), 7.31 (t, $J = 7.3$ Hz, 2H), 7.37–7.42 (m, 2H), 7.57 (s, 1H), 7.71 (s, 1H) ppm; ^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 7.5 (q), 34.7 (t), 38.4 (t), 76.5 (s), 118.7 (d), 122.8 (d), 123.4 (d), 124.4 (s, 2C), 125.3 (d, 2C), 126.4 (d), 127.9 (d, 2C), 129.4 (d), 143.5 (s), 144.7 (s), 147.7 (s) ppm; IR(cm^{-1}): 3329, 3173, 2953, 1632, 1558, 1558, 1431, 1373, 1264, 1161, 971, 872, 748, 720, 683; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{19}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 344.1160; found: 344.1164.



5-Chloro-2-(4-(2-hydroxy-2-phenylbutyl)-1H-1,2,3-triazol-1-yl)phenol (10cc):

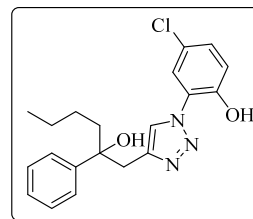
Isolated by column chromatography (pet.ether/AcOEt = 6:4, $R_f = 0.4$). The title compound was determined as yellow solid (80%). Mp: 129–131 °C; ^1H NMR (400 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 0.79 (t, $J = 7.4$ Hz, 3H), 1.83–2.05 (m, 2H), 3.32 (s, 2H), 6.88 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.05 (d, $J = 2.3$ Hz, 1H), 7.18–7.22 (m, 1H), 7.28–7.34 (m, 3H), 7.38–7.40 (m, 2H), 7.57 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 7.8 (q), 35.1 (t), 38.5 (t), 76.7 (s), 118.6 (d), 120.2 (d), 122.0 (d), 125.4 (d, 3C), 126.6 (d), 128.1 (d, 2C), 134.8 (s, 2C), 144.7 (s, 2C), 149.8 (s) ppm; IR(cm^{-1}): 3333, 3329, 2972, 1642, 1547, 1428, 1363, 1271, 1167, 971, 872, 747, 684; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{19}\text{O}_2\text{N}_3\text{Cl}$ ($\text{M}^+ + \text{H}$): 344.1161; found: 344.1164.



4-chloro-2-(4-(2-hydroxy-2-phenylhexyl)-1H-1,2,3-triazol-1-yl)phenol (10da):

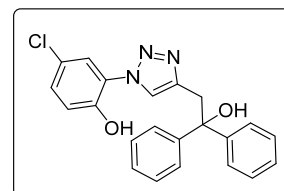
Isolated by column chromatography (pet.ether/AcOEt = 6:4, $R_f = 0.5$). The title compound was determined as colourless solid (86%). Mp: 165–167 °C; ^1H NMR (400

MHz, CDCl₃ + MeOH (D₄)): δ 0.83 (t, J = 7.3 Hz, 3H), 1.01–1.11 (m, 1H), 1.20–1.36 (m, 3H), 1.81–1.89 (m, 1H), 1.91–1.99 (m, 1H), 3.32 (t, J = 15.3 Hz, 1H), 4.03 (bs, 2H), 6.98 (d, J = 8.8 Hz, 1H), 7.19–7.23 (m, 2H), 7.32 (t, J = 7.8 Hz, 1H), 7.40 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 2.3 Hz, 1H), 7.69 (s) ppm; ¹³C NMR (100 MHz, CDCl₃ + MeOH (D₄)): δ 13.4 (q), 22.6 (t), 25.2 (t), 38.7 (t), 41.7 (t), 76.0 (s), 118.2 (d), 123.2 (d), 123.9 (d), 124.1 (s), 124.6 (s), 125.1 (d, 2C), 126.1 (d), 127.7 (d, 2C), 129.2 (d), 143.2 (s), 145.0 (s), 147.6 (s) ppm; IR(cm⁻¹): 3459, 3116, 2980, 1639, 1547, 1334, 1231, 1056, 869, 750; HRMS(ESI) calcd for C₂₀H₂₃O₂N₃Cl (M⁺+H): 372.1473; found: 372.1471.



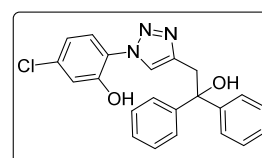
4-Chloro-2-(4-(2-hydroxy-2,2-diphenylethyl)-1H-1,2,3-triazol-1-yl)phenol (10ea):

Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.5). The title compound was determined as colourless solid (83%). Mp: 194–196 °C; ¹H NMR (200 MHz, CDCl₃ + MeOH (D₄)): δ 3.82 (s, 2H), 6.96 (d, J = 8.7 Hz, 1H), 7.17–7.35 (m, 7H), 7.46–7.51 (m, 6H), 7.58 (d, J = 2.5 Hz, 1H), 7.66 (s, 1H) ppm; ¹³C NMR (50 MHz, CDCl₃ + MeOH (D₄)): δ 37.9 (t), 77.2 (s), 118.0 (d), 123.3 (d), 124.0 (s), 124.2 (d), 124.5 (s), 125.8 (d, 4C), 126.5 (d, 2C), 127.6 (d, 4C), 129.1 (d), 143.1 (s), 146.0 (s, 2C), 147.5 (s) ppm; IR(cm⁻¹): 3355, 3173, 2988, 1637, 1529, 1435, 1263, 1152, 984, 873, 759, 620; HRMS(ESI) calcd for C₂₂H₁₉O₂N₃Cl (M⁺+H): 392.1160; found: 392.1162.

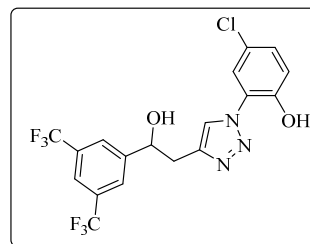


5-Chloro-2-(4-(2-hydroxy-2,2-diphenylethyl)-1H-1,2,3-triazol-1-yl)phenol (10ec):

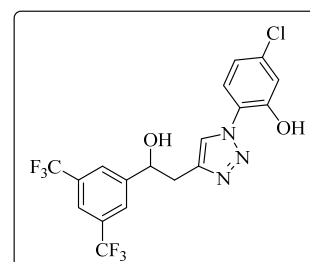
Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.5). The title compound was determined as colourless solid (81%). Mp: 210–212 °C; ¹H NMR (200 MHz, CDCl₃ + MeOH (D₄)): δ 3.81 (s, 2H), 6.89 (dd, J = 2.2, 8.6 Hz, 1H), 7.02 (m, 1H), 7.15–7.33 (m, 6H), 7.38 (d, J = 1.6 Hz, 1H), 7.43–7.50 (m, 4H), 7.54 (s, 1H) ppm; ¹³C NMR (50 MHz, CDCl₃ + MeOH (D₄)): δ 38.0 (t), 77.2 (s), 117.3 (d), 119.8 (d), 122.8 (s), 123.9 (d), 124.2 (d), 125.9 (d, 4C), 126.7 (d, 2C), 127.8 (d, 4C), 134.7 (s), 143.2 (s), 146.0 (s, 2C), 149.7 (s) ppm; IR(cm⁻¹): 3321, 3137, 2970, 1639, 1598, 1543, 1437, 1323, 1236, 1152, 870, 740, 625; HRMS(ESI) calcd for C₂₂H₁₉O₂N₃Cl (M⁺+H): 392.1160; found: 392.1158.



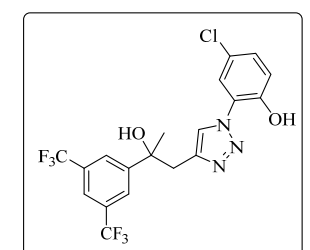
2-(4-(2-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethyl)-1H-1,2,3-triazol-1-yl)-4-chlorophenol (10fa): Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.3). The title compound was determined as colourless solid (87%). Mp: 181–183 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4)): δ 3.22 (d, J = 6.4 Hz, 2H), 5.19 (t, J = 6.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.26 (dd, J = 2.7, 8.6 Hz, 1H), 7.76 (d, J = 2.7 Hz, 1H), 7.79 (bs, 2H), 7.90 (bs, 2H), 8.17 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + MeOH (D_4)): δ 34.8 (t), 72.1 (d), 117.7 (d), 120.5 (s), 120.6 (d, J = 4.0 Hz), 123.5 (d, 2C), 123.9 (s, 2C), 124.2 (d), 124.6 (s), 125.7 (d, J = 2.9 Hz), 129.1 (d), 130.6 (s, d, J = 33.3 Hz), 131.6 (s, d, J = 33.3 Hz), 142.8 (s), 146.7 (s), 147.5 (s) ppm; IR(cm^{-1}): 3316, 3097, 2400, 1645, 1563, 1438, 1321, 1220, 1042, 867, 751, 660; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{13}\text{O}_2\text{N}_3\text{ClF}_6$ ($\text{M}^+ + \text{H}$): 452.0595; found: 452.0600.



2-(4-(2-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethyl)-1H-1,2,3-triazol-1-yl)-5-chlorophenol (10fc): Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.3). The title compound was determined as colourless solid (82%). Mp: 192–194 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4)): δ 3.21 (d, J = 6.4 Hz, 2H), 5.19 (t, J = 6.3 Hz, 1H), 6.98 (dd, J = 2.2, 8.6 Hz, 1H), 7.08 (d, J = 2.2 Hz, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.79 (bs, 2H), 7.88 (bs, 2H), 8.09 (bs, 1H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + MeOH (D_4)): δ 34.9 (t), 71.2 (d), 116.7 (d), 119.6 (d, 2C), 120.3 (s), 120.6 (d, t, J = 3.3 Hz), 122.9 (s), 124.8 (d, 2C), 125.8 (d, J = 3.3 Hz), 130.3 (s, d, J = 33.3 Hz), 131.6 (s, d, J = 32.9 Hz), 134.7 (s, 2C), 146.7 (s, 2C), 149.7 (s) ppm; IR(cm^{-1}): 3298, 3161, 2984, 1645, 1599, 1443, 1309, 1211, 1095, 871, 757, 682; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{13}\text{O}_2\text{N}_3\text{ClF}_6$ ($\text{M}^+ + \text{H}$): 452.0595; found: 452.0599.



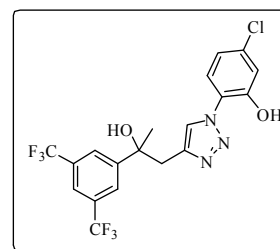
2-(4-(2-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)-4-chlorophenol (10ga): Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.4). The title compound was determined as colourless solid (85%). Mp: 164–166 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4)): δ 1.67 (s, 3H), 3.30 (s, 2H), 7.00 (d, J = 8.8 Hz, 1H), 7.24 (dd, J = 2.5, 8.8 Hz,



1H), 7.69 (d, $J = 2.5$ Hz, 1H), 7.76 (bs, 1H), 7.97 (s, 2H), 8.08 (s, 1H) ppm; ^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{MeOH}$ (D_4)): δ 28.1 (q), 39.4 (t), 72.7 (s), 117.7 (d), 119.9 (d, $J = 4.0$ Hz), 120.3 (s), 123.4 (d, 2C), 123.9 (s, 2C), 124.5 (d), 125.1 (d, d, $J = 2.9$ Hz), 125.7 (s), 129.1 (d), 130.7 (s, d, $J = 32.9$ Hz), 143.2 (s, 2C), 147.7 (s) 150.3 (s) ppm; IR(cm^{-1}): 3453, 3152, 2993, 1640, 1600, 1555, 1437, 1363, 1248, 1160, 1023, 983, 871, 764; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{15}\text{O}_2\text{N}_3\text{ClF}_6$ ($\text{M}^+ + \text{H}$): 466.00752; found: 466.0755.

2-(4-(2-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxypropyl)-1H-1,2,3-triazol-1-yl)-5-chlorophenol (10gc): Isolated by column chromatography

(pet.ether/AcOEt = 6:4, $R_f = 0.4$). The title compound was determined as colourless solid (80%). Mp: 156–158 °C; ^1H NMR (200 MHz, $\text{CDCl}_3 + \text{MeOH}$ (D_4)): δ 1.68 (s, 3H), 3.29 (s, 2H), 6.96 (dd, $J = 2.2, 8.6$ Hz, 1H), 7.07 (d, $J = 2.2, 1\text{H}$),



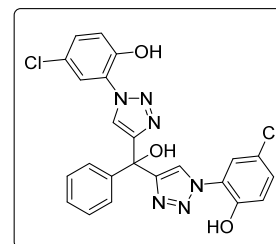
7.58 (d, $J = 8.6$ Hz, 1H), 7.76 (bs, 1H), 7.97 (s, 2H), 8.01 (s, 1H) ppm; ^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{MeOH}$ (D_4)): δ 28.1 (q), 39.4 (t), 72.8 (s), 116.6 (d), 119.4 (d), 119.9 (d, $J = 4.0$ Hz), 120.3 (s), 122.9 (s), 124.6 (d), 124.8 (d, 2C), 125.1 (d, d, $J = 2.9$ Hz), 125.7 (s), 130.1 (s, d, $J = 32.9$ Hz), 131.4 (s, d, $J = 32.9$ Hz), 134.6 (s), 142.2 (s), 149.6 (s), 150.2 (s) ppm; IR(cm^{-1}): 3322, 3129, 2983, 1633, 1600, 1535, 1427, 1363, 1248, 1170, 1027, 989, 878, 754; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{15}\text{O}_2\text{N}_3\text{ClF}_6$ ($\text{M}^+ + \text{H}$): 466.00752; found: 466.0750.

General experimental procedure C: To a solution of di alkyne **11** (1.0 eq.) and azide **5** (2.2 eq.) in $t\text{BuOH}:\text{H}_2\text{O}$ (3:1) at rt, sodium ascorbate (0.95 eq.) and CuSO_4 (0.2 eq.) were added and the resulting brick reddish mixture was stirred vigorously for 6 hrs. The reaction mixture was diluted and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. The product was purified by column chromatography.

2,2'-((Hydroxy(phenyl)methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(4-

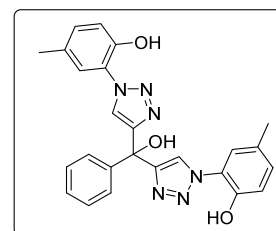
chlorophenol) (12aa): Isolated by column chromatography (pet.ether/AcOEt = 6:4, $R_f = 0.2$). The title compound was determined as yellow solid (87%). Mp: 208–209 °C; ^1H NMR (200 MHz, $\text{CDCl}_3 + \text{MeOH}$ (D_4)): δ 7.01 (d, $J = 8.8$ Hz, 2H), 7.26 (dd, J

= 2.5, 8.8 Hz, 2H), 7.30–7.42 (m, 3H), 7.61–7.66 (m, 2H), 7.76 (d, $J = 2.5$ Hz, 2H), 8.35 (s, 2H) ppm; ^{13}C NMR (100 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 71.4 (s), 117.9 (d), 123.6 (d, 2C), 123.9 (s, 2C), 124.1 (d), 124.6 (s), 126.0 (d, 3C), 127.3 (d, 3C), 127.6 (d, 2C), 129.3 (d), 143.6 (s), 147.6 (s, 2C), 152.3 (s, 3C) ppm; IR(cm^{-1}): 3371, 3159, 2980, 1638, 1557, 1432, 1373, 1281, 1163, 973, 872, 750, 694; HRMS(ESI) calcd for $\text{C}_{23}\text{H}_{17}\text{O}_3\text{N}_6\text{Cl}_2$ ($\text{M}^+ + \text{H}$): 495.0734; found: 495.0738.



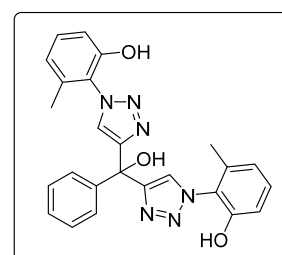
2,2'-((Hydroxy(phenyl)methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(4-methylphenol) (12ab): Isolated by column chromatography

(pet.ether/AcOEt = 6:4, $R_f = 0.2$). The title compound was determined as colourless solid (91%). Mp: 191–193 °C; ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 2.20 (s, 6H), 6.84 (d, $J = 8.2$ Hz, 2H), 6.98 (d, $J = 7.9$ Hz, 2H), 7.26 (d, $J = 3.7$ Hz, 5H), 7.50 (d, $J = 7.3$ Hz, 2H), 8.06 (s, 2H) ppm; ^{13}C NMR (125 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 20.0 (q, 2C), 77.3 (s), 117.6 (d), 123.4 (d), 123.6 (d, 2C), 126.2 (d, 3C), 127.7 (d), 128.0 (d, 3C), 129.6 (s, 3C), 130.6 (d, 2C), 143.7 (s), 145.4 (s), 146.9 (s, 2C), 152.6 (s, 2C) ppm; IR(cm^{-1}): 3423, 3153, 2987, 1635, 1558, 1441, 1347, 1234, 1159, 1046, 878, 750; HRMS(ESI) calcd for $\text{C}_{25}\text{H}_{23}\text{O}_3\text{N}_6$ ($\text{M}^+ + \text{H}$): 455.1826; found: 455.1827.



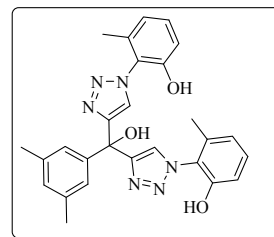
2,2'-((Hydroxy(phenyl)methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(3-methylphenol) (12ae): Isolated by column chromatography

(pet.ether/AcOEt = 6:4, $R_f = 0.2$). The title compound was determined as colourless solid (84%). Mp: 173–175 °C; ^1H NMR (200 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 2.34 (s, 6H), 6.78 (d, $J = 8.1$ Hz, 2H), 6.86 (s, 2H), 7.30–7.38 (m, 3H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.76 (d, $J = 7.6$ Hz, 2H), 8.17 (s, 2H) ppm; ^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 20.6 (q, 2C), 71.5 (s), 117.5 (d, 2C), 120.5 (d, 2C), 121.5 (s), 123.5 (d, 2C), 123.8 (d), 126.1 (d, 2C), 127.4 (d), 127.8 (d, 3C), 140.4 (s, 3C), 143.7 (s), 148.8 (s, 2C), 152.2 (s, 2C) ppm; IR(cm^{-1}): 3459, 3155, 2989, 1642, 1433, 1589, 1314, 1232, 1053, 872, 743; HRMS(ESI) calcd for $\text{C}_{25}\text{H}_{23}\text{O}_3\text{N}_6$ ($\text{M}^+ + \text{H}$): 455.1826; found: 455.1829.



2,2'-(((3,5-dimethylphenyl)(hydroxy)methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(3-methylphenol) (12be):

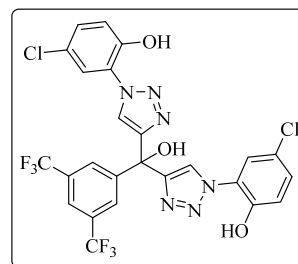
Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.2). The title compound was determined as colourless solid (83%). Mp: 177–178 °C; ^1H NMR (500 MHz, CDCl_3 + MeOH (D_4)): δ 2.30 (s, 6H), 2.35 (s, 6H), 6.79 (d, J = 7.9 Hz, 2H), 6.87 (s, 2H), 6.94 (s, 1H), 7.22 (s, 2H), 7.46 (d, J = 7.9 Hz, 2H), 8.16 (s, 2H) ppm;



^{13}C NMR (125 MHz, CDCl_3 + MeOH (D_4)): δ 20.6 (q, 2C), 20.9 (q, 2C), 71.5 (s), 117.7 (d, 2C), 120.5 (d, 2C), 121.5 (s), 123.3 (d, 2C), 123.6 (d), 123.9 (d, 3C), 129.1 (d), 137.4 (s, 3C), 140.4 (s, 3C), 143.6 (s), 148.9 (s), 152.5 (s, 2C) ppm; IR(cm^{-1}): 3377, 3170, 2988, 1638, 1562, 1447, 1358, 1239, 1167, 1025, 872, 741; HRMS(ESI) calcd for $\text{C}_{27}\text{H}_{27}\text{O}_3\text{N}_6$ ($\text{M}^+ + \text{H}$): 483.2141; found: 483.2138.

2,2'-(((3,5-Bis(trifluoromethyl)phenyl)(hydroxy)methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(4-chlorophenol) (12ca):

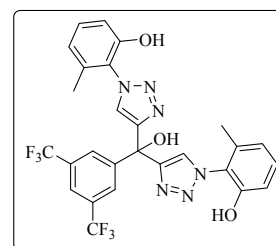
Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.2). The title compound was determined as colourless solid (82%). Mp: 213–214 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4)): δ 7.01 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 2.5, 8.8 Hz, 2H), 7.76



(d, J = 2.5 Hz, 2H), 7.84 (bs, 1H), 8.28 (bs, 2H), 8.43 (s, 2H) ppm; ^{13}C NMR (50 MHz, CDCl_3 + MeOH (D_4)): δ 70.9 (s), 118.1 (d, 2C), 120.3 (s), 121.2 (d, J = 3.7 Hz), 123.7 (d, 3C), 124.1 (s, 2C), 124.2 (d, 2C), 124.5 (s), 125.7 (s), 126.7 (d, J = 2.9 Hz), 129.5 (d, 2C), 130.3 (s, d, J = 33.3 Hz), 131.7 (s, d, J = 32.6 Hz), 146.9 (s), 147.6 (s, 3C), 151.5 (s, 2C) ppm; IR(cm^{-1}): 3373, 3173, 2978, 1641, 1599, 1550, 1435, 1333, 1231, 1150, 973, 877, 746, 624; HRMS(ESI) calcd for $\text{C}_{25}\text{H}_{15}\text{O}_3\text{N}_6\text{Cl}_2\text{F}_6$ ($\text{M}^+ + \text{H}$): 631.0481; found: 631.0482.

2,2'-(((3,5-Bis(trifluoromethyl)phenyl)(hydroxy)methylene)bis(1H-1,2,3-triazole-4,1-diyl))bis(3-methylphenol) (12ce):

Isolated by column chromatography (pet.ether/AcOEt = 6:4, R_f = 0.2). The title compound was determined as colourless solid (87%). Mp: 244–246 °C; ^1H NMR (200 MHz, CDCl_3 + MeOH (D_4)): δ 2.35 (s, 6H), 6.80 (dd, J = 1.5, 8.2 Hz, 2H), 6.86 (s, 2H), 7.54

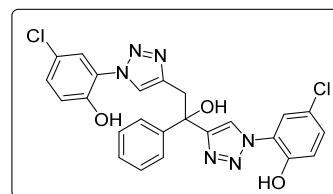


(dd, J = 1.8, 8.1 Hz, 1H), 7.84 (s, 2H), 8.31 (bs, 2H), 8.34 (s, 1H), 8.43 (s, 1H) ppm;

^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 20.2 (q, 2C), 86.8 (s), 116.9 (d), 117.0 (d), 120.2 (d, 3C), 121.4 (d, t, $J = 3.7$ Hz), 122.9 (d), 123.5 (d), 123.6 (d), 124.1 (d), 126.0 (s, d, $J = 3.7$ Hz), 126.6 (d), 129.5 (s), 130.4 (s, d, $J = 33.7$ Hz), 131.7 (s, d, $J = 34.0$ Hz), 140.3 (s, 3C), 146.0 (s), 147.1 (s), 148.5 (s, 2C), 148.6 (s), 151.5 (s) ppm; IR(cm^{-1}): 3411, 3177, 2990, 1645, 1538, 1437, 1313, 1232, 1158, 881, 745, 620; HRMS(ESI) calcd for $\text{C}_{27}\text{H}_{21}\text{O}_3\text{N}_6\text{F}_6 (\text{M}^+ + \text{H})$: 591.1574; found: 591.1570.

2,2'-((1-Hydroxy-1-phenylethane-1,2-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(4-chlorophenol) (12da): Isolated by column chromatography (pet.ether/AcOEt = 6:4,

$R_f = 0.2$). The title compound was determined as colourless solid (80%). Mp: 131–133 °C; ^1H NMR (200 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 3.54 (d, $J = 14.9$ Hz, 1H), 3.73 (d, $J = 14.9$ Hz, 1H), 6.67 (dd, $J = 4.7, 8.7$ Hz, 2H),



6.92–7.12 (m, 5H), 7.32 (s, 1H), 7.36 (d, $J = 1.0$ Hz, 2H), 7.48 (d, $J = 2.5$ Hz, 1H), 7.59 (bs, 1H), 8.05 (s, 1H) ppm; ^{13}C NMR (50 MHz, $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$): δ 38.3 (t), 73.5 (s), 117.8 (d, 2C), 123.3 (d, 3C), 123.9 (s, 2C), 124.0 (s, 2C), 124.6 (s, 2C), 125.2 (d, 2C), 126.8 (d), 127.6 (d, 4C), 129.1 (d), 144.2 (s), 147.4 (s), 147.5 (s) ppm; IR(cm^{-1}): 3378, 3170, 2989, 1643, 1600, 1552, 1453, 1368, 1258, 1163, 1039, 873, 751; HRMS(ESI) calcd for $\text{C}_{24}\text{H}_{19}\text{O}_3\text{N}_6\text{Cl}_2 (\text{M}^+ + \text{H})$: 509.0890; found: 509.0891.

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CHAPTER II:

**[Pd]-Catalyzed Cycloisomerization: Synthesis of
benzofuran conjugated sugar/nucleoside derivatives**

2.1. Introduction:

Benzofurans are a class of highly privileged structural motifs of heterocyclic compounds existing widely in natural products and unnatural synthetic compounds with biological and pharmacological potential.¹ They have been found to exist in nature since the late 19th century.² Since that time their investigations have revealed many avenues of understanding their properties. The simple benzofuran heterocyclic compound consists of fused benzene and furan rings, which is usually extracted from coal tar.

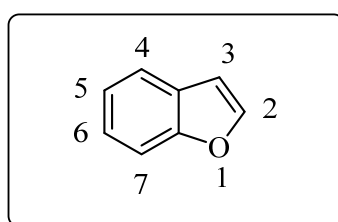


Figure S2.1: *The basic benzofuran motif*

2.1.1. Over view of benzofuran

2.1.1.1. Benzo[b]furan in natural products

Benzo[b]furan (Later it has been described as benzofuran) is the parent of many related compounds with more complex structures, particularly in a myriad number of natural products.³ In particular many of these natural products are biologically more active than Egonol, and it has a wide spectrum of biological activities including insecticidal, fungicidal, antimicrobial, antisweet, antiproliferative, cytotoxic and antioxidant properties.⁴ In nature's collection of biologically active benzofurans, 2-heteroarylbenzofuran ring systems are widely distributed in nature and have been reported to have antiviral, antioxidant and antifungal activities. For example, cicerfuran, obtained from the roots of a wild species of chickpea, *Cierbijugum*, was reported to be a major factor in the defense system against *Fusarium* wilt.⁵ The similar type of natural products such as Furomollugin, Viniferifuran, Anigopreissin A are also of biological significance.⁶ Most of the benzofuran containing natural products are known for their cytotoxic and antitumor activity, such as Rubicordifolin and its analogous. The highly substituted benzofuran contain novel oligostilbenes, such as malibatol A and B, viniferifuran and

Shoreaphenol and exhibit a wide variety of pharmacological activities including anti-inflammatory, antioxidant, antifungal, antibacterial, anti-HIV, and anticarcinogenic activities. The marine natural products such as Liphagal, show PI3K signaling inhibitory activity and Frondosin B plays an important role in tumor progression and metastasis in several human cancers, including lung cancers.⁷

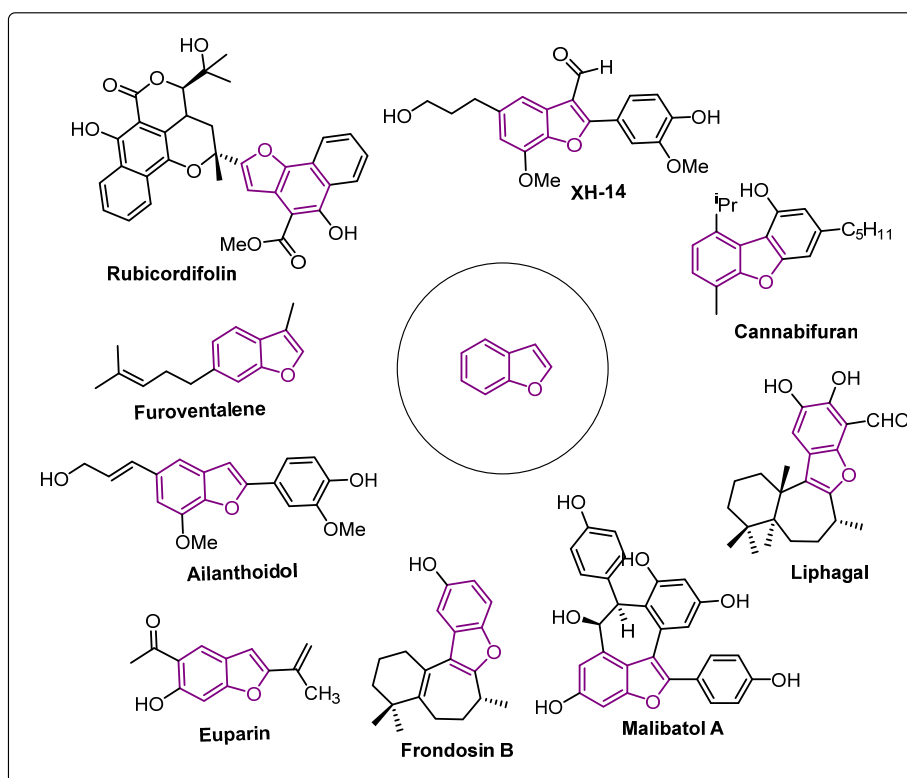


Figure S2.2: *Wide spectrum of Benzofuran containing natural products*

2.1.1.2. Benzofuran in Pharmaceuticals

Benzofuran derivatives are an important class of heterocyclic compounds that exhibit biological activity on a wide range of targets.⁸ The synthetic and natural benzofuran derivatives are best known for their pharmaceutical potential. Recently, benzofurans have been identified as selective adenosine A_{2A} receptor antagonists⁹ for a novel nondopaminergic approach to PD therapy and nonacidic benzofuran EP1 receptor antagonists for the treatment of inflammatory pain.¹⁰ The unnatural benzofuran scaffold, Aminodarone and its synthetic analog Dronedarone were found as antiarrhythmic agent, available in the market with different trade names.¹¹ There are several benzofuran containing molecules that have showed anti tumor activity, such as **CRA-024781**, found as a novel synthetic inhibitor of histone

deacetylase enzymes with antitumor activity *in vitro* and *in vivo*. Befunolol is a beta-adrenoceptor blocking agent, which is clinically used in the treatment of glaucoma, which is available under different trade names in the market. The natural product Psoralen and its isomers have shown very good biological activity, a case in point being the important use of psoralen is in PUVA treatment for skin problems such as psoriasis. Angelicin has shown antiviral property. In particular, the natural product, Coumestrol also shows pharmaceutical, because of its estrogenic activity.¹²

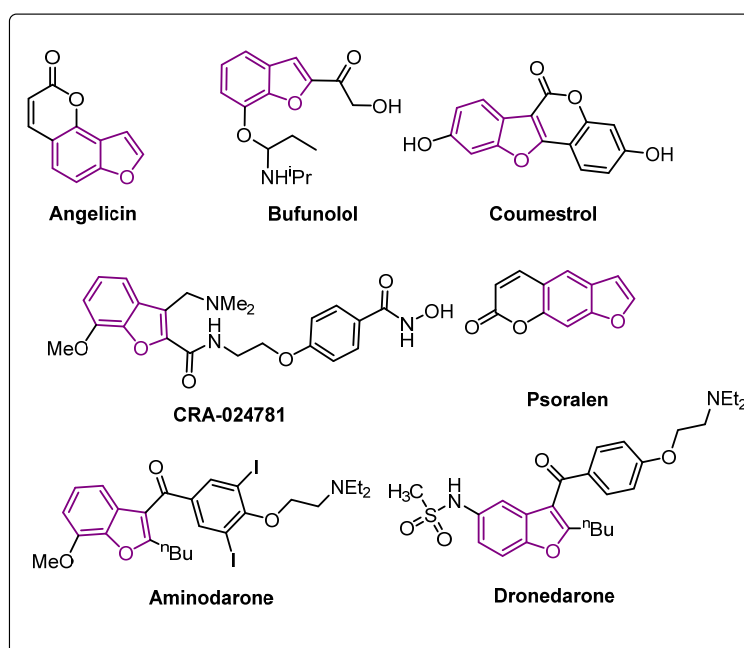


Figure S2.3: Molecules containing the benzofuran motif

2.1.1.3. Benzofuran in Functional materials

Benzofuran is known for its wonderful structure, it expands from organic chemistry to the interdisciplinary field of science. Despite its applications in biological systems and pharmaceuticals, it has shown several applications in the field of material science as well.¹³ Finally, benzofurans have also emerged recently as important structural elements for organic materials, such as organic transistors. Some of the benzofuran derivatives have shown optoelectronic properties, Benzodifuran (**BDF**) derivatives developed as organic light-emitting diode (OLED) devices have demonstrated that BDFs function as efficient hole transporting materials (**HTMs**).^{13c} The benzotrifuran has also shown very good optoelectronic properties. The recent results indicated that the benzofuran based polymeric material **PBDFDODTBT** is a

promising candidate for high-efficiency polymer solar cells and the benzo[1,2-b:4,5-b']difuran unit may be an excellent electron donating building block for organic electronic materials.¹⁴ Benzofuran-containing oligoaryls are known to be highly fluorescent and good hole transporting materials. Small molecules and conjugated polymers based on benzofuran chromophores have been used for electroluminescent devices, solar cell applications, and field effect transistors.¹⁵

In particular, benzodifuran (BDF), is of prime interest as organic semiconductors due to their fascinating features including structural symmetry and planarity, as well as rigid and π -extended conjugation which can enhance electron delocalization and intermolecular interactions to improve charge mobility.

2.1.2. Synthetic strategies towards benzofurans:

The widespread occurrence and important biological-/material applications associated benzofuran derivatives has led to the development of a broad range of methods for their synthesis. All the known methods for the synthesis of benzofurans can be arranged into two groups. The first group involves the formation of an annulated heterocyclic ring (in this case furan) by the intramolecular cyclization of benzene derivatives. The methods of the second group are encountered very rarely and involve the creation of an annulated carbocyclic ring. In this chapter, mainly the methods of the first group followed by few examples of the second group are going to be discussed. Coming to the first group – i.e annulation of the furan ring, the methods can be grouped in the following four possible types depending upon the bond which is being constructed. Following are some representative examples selected for each group.

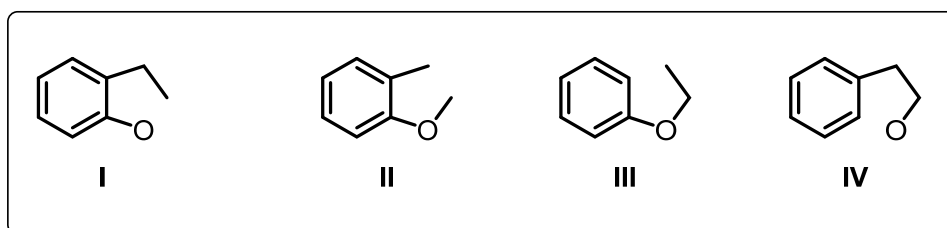
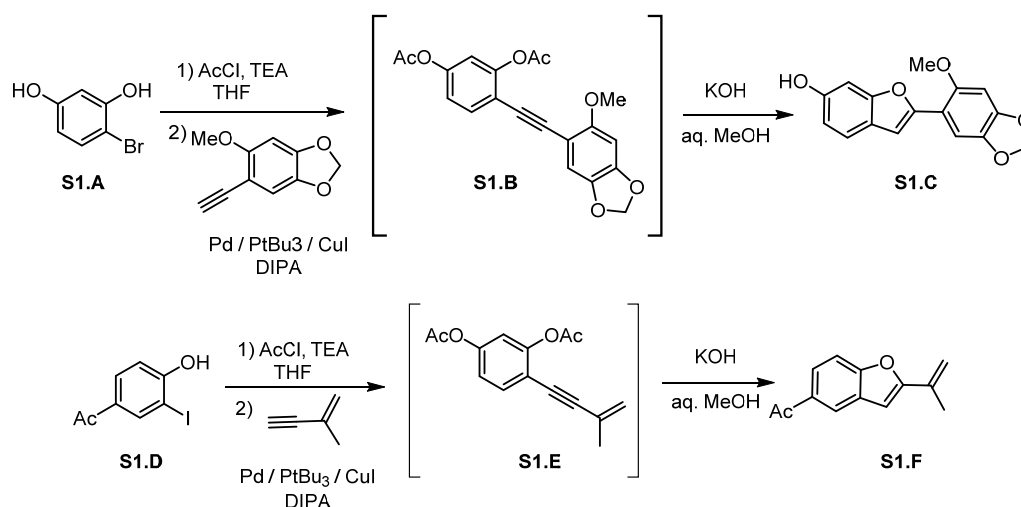


Figure S2.4: Strategy for the benzofuran construction

2.1.2. 1. Ring closure by the formation of the O-C2 bond (Type-I)

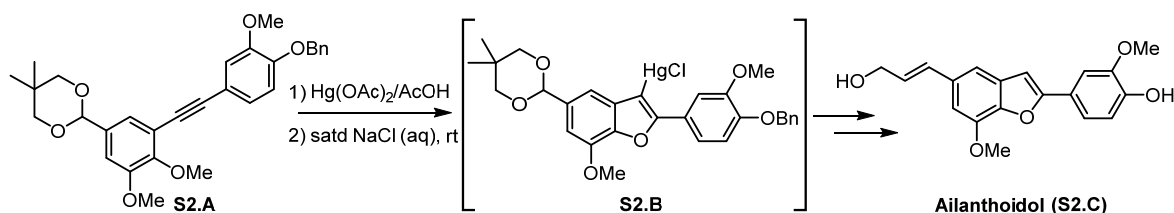
The majority of the condensation methods involve the formation of C2–O bond, which belongs to the first type. The starting compounds are ortho-substituted phenols. Substituents at the ortho position must contain an electron-deficient β -carbon atom, which is the structural unit of some unsaturated fragment or is attached to an atom characterized by a sufficiently strong M effect. In literature, there are a large number of reports of this type of approach. Some notable ones are mentioned below.

Kotschy *et al.* reported a simple one-pot procedure for the preparation of substituted benzofurans starting from acetylated halogenated phenols and their coupling with a suitable alkyne and subsequent base-mediated saponification and cyclization. This method has been applied successfully to the total synthesis of natural products such as Cicerfuran and dehydrotremetone (**S1.C** and **S1.F**, scheme S2.1 respectively).¹⁶



Scheme S2.1: Kotschy's approach for the Cicerfuran and dehydrotremetone

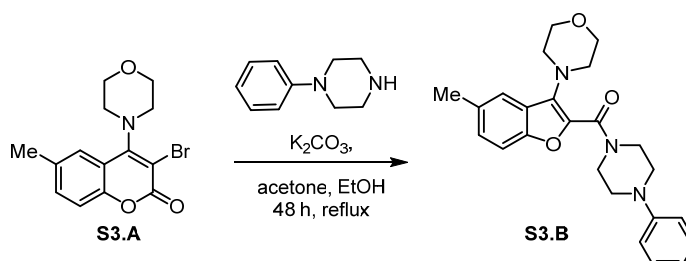
A mercury-mediated cycloetherification of *o*-alkynylphenylmethyl ethers has been reported by Chern and coworkers in the synthesis of ailanthoidol, XH-14, and obovaten.



Scheme S2.2: Chern's approach for the synthesis of ailanthoidol

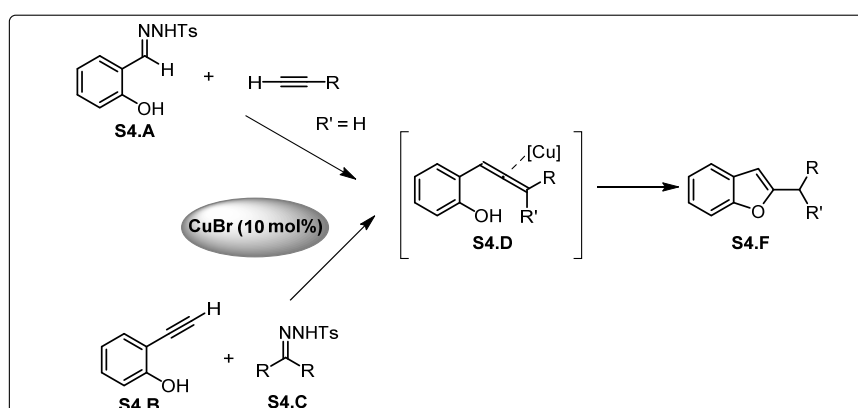
In this synthetic strategy 2-substituted phenyl-3-chloromercuriobenzofuran could be a key intermediate for the successful synthesis of these natural products (Scheme S2.2).¹⁷

Ling-Yi Kong *et al.* have developed an unusual rearrangement of a benzopyran group to a benzofuran group during a synthesis of coumarins to obtain new candidates for treating Alzheimer's disease (AD). The rearrangement occurred under moderate conditions such as piperazine substituents reacted with **S3.A** in the presence of K_2CO_3 in acetone and ethanol at reflux temperature for 48 h and offered a facile and practical preparation of biologically active benzofuran derivatives (Scheme S2.3).¹⁸



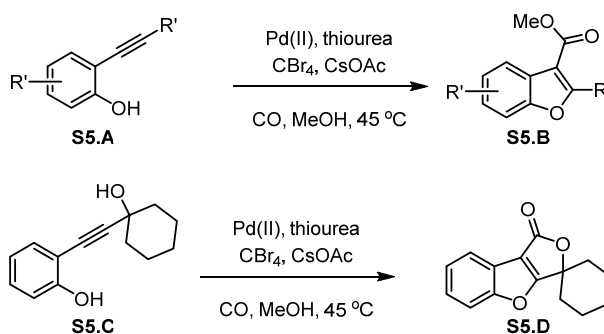
Scheme S2.3: Kong's approach for the benzofuran derivatives

Lei Zhou *et al.* described a general and practical method for synthesizing 2-substituted benzofurans. This method employs easily accessible *N*-tosylhydrazones and *o*-alkynylphenols as substrates. The reaction proceeds through a CuBr-catalyzed coupling–allenyl–cyclization sequence under ligand-free conditions. In this reaction, a di-substituted allene intermediate is formed *via* the migratory insertion of a copper carbene species, which smoothly undergoes copper-catalyzed intramolecular cyclization to afford 2-substituted benzofurans (Scheme S2.4).¹⁹



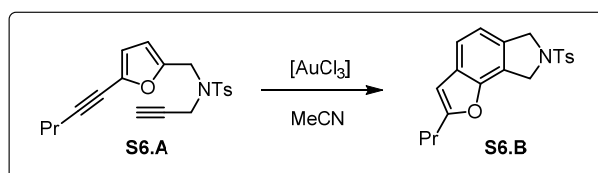
Scheme S2.4: Zhou's approach for the Cu catalyzed benzofuran derivatives

Zhen Yang and coworkers reported the carbonylative annulation of *o*-alkynylphenols mediated by $\text{PdCl}_2(\text{PPh}_3)_2$ and dppp in the presence of CsOAc and CO leading to functionalized benzo[*b*]furo[3,4-*d*]furan-1-ones in good yields. This novel synthetic approach provides a highly efficient method for diversification of the benzofuran scaffold for combinatorial synthesis (Scheme S2.5).²⁰



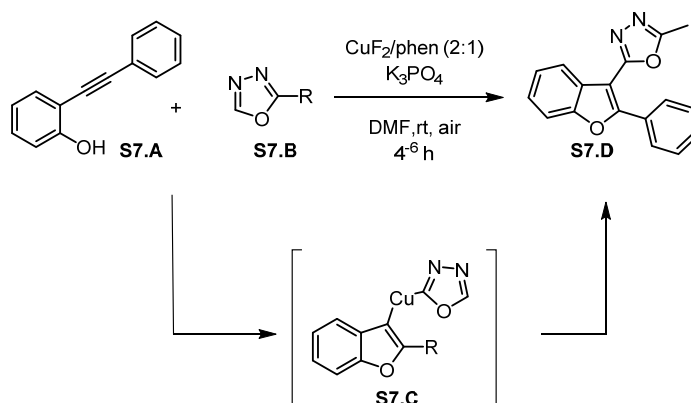
Scheme S2.5: Yang's approach for the synthesis of benzofuran derivatives

Hashmi *et al.* demonstrated the gold-catalyzed phenol synthesis of an intramolecular migration of the oxygen atom which leads to the doubly annulated benzofuran derivatives. In this strategy, the oxygen atom is transferred intramolecularly and also the reaction proceeds through cationic intermediates (Scheme S2.6).²¹



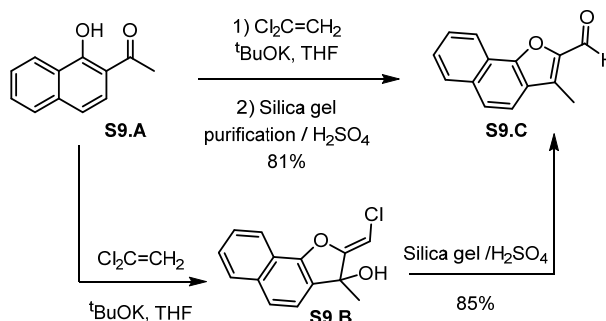
Scheme S2.6: Hashmi's approach for the gold-catalyzed benzofuran derivatives

Miura and coworkers reported a copper-mediated annulative direct coupling of *o*-alkynylphenols with 1,3,4-oxadiazoles. This proceeds smoothly even under ambient conditions to afford the corresponding biheteroaryls. The conditions employed involve the use of CuF_2/phen as catalyst with the experiments being conducted in the presence of K_3PO_4 in DMF at rt and in the open atmosphere. The reaction system represents a new avenue for the construction of biheteroaryl molecules of interest in their biological and physical properties (Scheme S2.7).²²



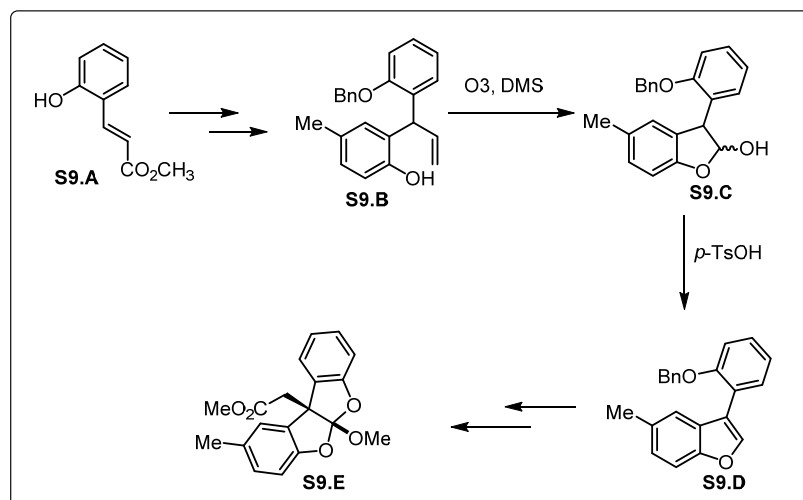
Scheme S2.7: *Cu-catalyzed benzofuran synthesis*

Marko *et al.* have reported a unique approach for the synthesis of highly functionalized benzofurans employing the base-catalyzed ($t\text{BuOK}$) condensation of *o*-hydroxyphenones with 1,1-dichloroethylene. As shown in the following scheme S2.8, initially this leads to the formation of the corresponding chloromethylene furans. These labile intermediates undergo a facile rearrangement into benzofuran carbaldehydes under mild acidic conditions.²³



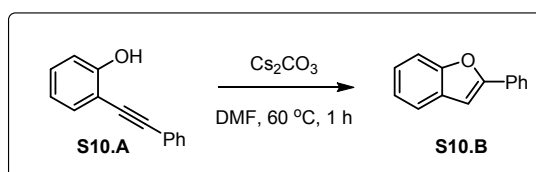
Scheme S2.8: *Marko's approach for synthesis of benzofuran*

Wood and coworkers have demonstrated a strategy for the synthesis of Diazonamide A. The strategy commenced with commercially available hydroxycinnamate **S9.A**, which was converted into the olefin **S9.B** after few steps. Reductive ozonolysis followed by dehydration of the resulting hemiacetal **S9.C** afford benzofuran **S9.D**, a very versatile intermediate, which leads to the Diazonamide A after few steps (Scheme S2.9).²⁴



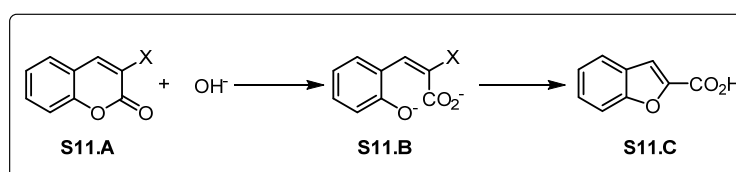
Scheme S2.9: Wood's approach for the synthesis of Diazonamide A

Wang *et al.* reported a base promoted synthesis of 2-substituted benzofurans from 2-alkynylphenols. These cyclizations were carried out with Cs_2CO_3 in DMF at 60 °C for 1 h. The deprotonation of the phenol hydroxyl group by a base was probably the driving force for the reaction (Scheme S2.10).²⁵



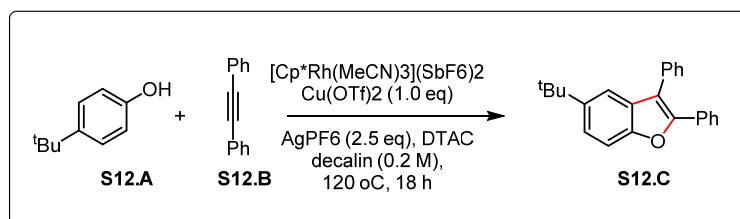
Scheme S2.10: Wang's approach for the base catalyzed benzofurans synthesis

Wesby *et al.* reported that the 3-halocoumarins are readily converted into benzofuran-2-carboxylic acids *via* a Perkin (coumarin–benzofuran ring contraction) rearrangement reaction. This rearrangement entails initial base catalyzed ring fission. The resulting phenoxide anion then attacks a vinyl halide to produce the final benzofuran moiety and this reaction was explored under microwave reaction conditions (Scheme S2.11).²⁶



Scheme S2.11: Wesby's approach for coumarin–benzofuran ring contraction

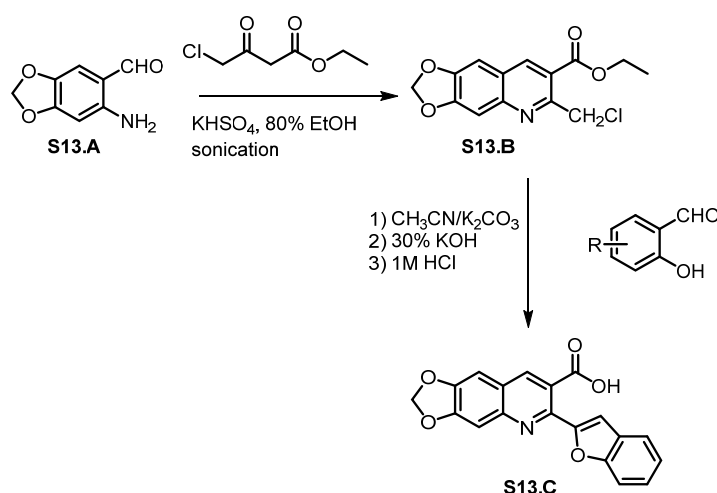
Zhangjie Shi *et al.* reported recently the first example of copper-mediated oxidative annulations of phenols and unactivated internal alkynes to afford benzofuran derivatives. Starting from commercially available phenols and alkynes, the direct one step/pot synthesis of benzofuran derivatives has been achieved with high efficiency. The mechanistic pathway indicates that the process is likely to initiate with the reversible electrophilic carbocupration, followed by alkyne insertion and cyclization to afford the desired product (Scheme S2.12).²⁷



Scheme S2.12: Shi's approach for Cu-catalyzed benzofurans synthesis

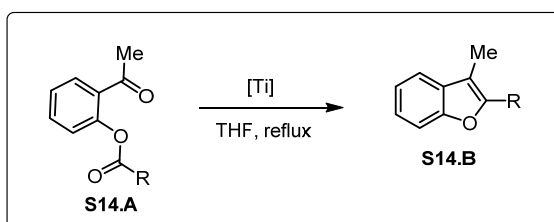
2.1.2. 2. Ring closure by the formation of the C(2)-C(3) bond (Type-II)

Gao *et al.* described a method which offers a straight forward and facile synthetic route for the preparation of a variety of 2-benzofuranyl-6,7-methylenedioxyquinoline-3-carboxylic acids *via* the one-pot reaction of ethyl 2-chloromethyl-6,7-methylenedioxyquinoline-3-carboxylate (**S13.B**) with various substituted salicylaldehydes (Scheme S2.13). Most of these products are anticipated have high biological significance.²⁸



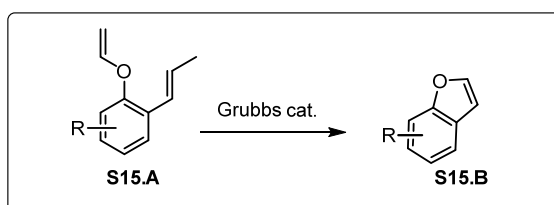
Scheme S2.13: Gao's approach for the synthesis of benzofuran derivatives

Jumbam *et al.* reported the titanium-mediated synthesis of 2,3-disubstitutedbenzofurans via McMurray coupling of esters of *o*-hydroxyacetophenone derivatives. Despite the fact that this reaction requires stoichiometric amounts of the titanium reagent, however, is the method of choice for the synthesis of 2,3-disubstitutedbenzofurans (Scheme S2.14).²⁹



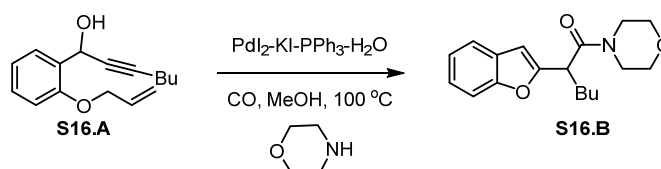
Scheme S2.14: Jumbam's approach for the synthesis of benzofuran derivatives

Wang and coworkers developed a ring closing metathesis (RCM) method for the synthesis of benzofurans. The metathesis reaction of various O-vinyl and C-propenylphenyl as precursor (S15.A) proceeded smoothly with the Grubbs' 1st generation catalyst to furnish the desired benzofurans in high yields (Scheme S2.15).³⁰



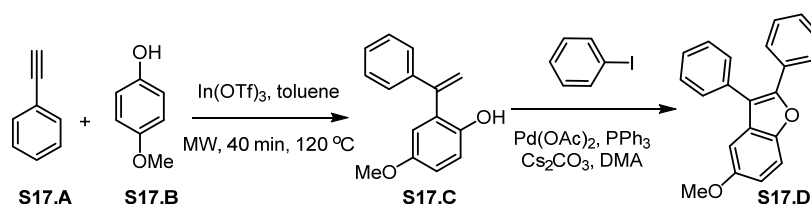
Scheme S2.15: Wang's approach for the synthesis of benzofuran derivatives

A concept founded upon the "sequential homobimetallic catalysis- a process in which two different complexes of the same metal, but in two different oxidation states, promote two catalytic cycles in sequence" Gabriele *et al.*, reported a simple approach for the synthesis of 2-benzofuran-2-ylacetamides. The conditions employed involve the treatment of a mixture of 1-(2-allyloxyaryl)-2-yn-1-ols (S16.A), amines, and CO with catalytic amounts of PdI₂ in conjunction with PPh₃ and KI (Scheme S2.16).³¹



Scheme S2.16: Gabriele's approach for the synthesis of benzofuran derivatives

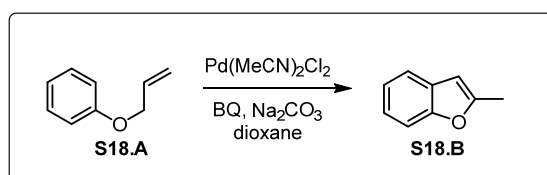
Kumar *et al.* reported an efficient and simple strategy for the synthesis of 2,3-diarylbenzofurans involving Pd-catalyzed one pot arylation *cum* intramolecular oxy-cyclization of o-hydroxystyrene derivatives. This approach involves a sequence of hydroarylation of phenols and alkynes in the presence of $\text{In}(\text{OTf})_3$ under microwave irradiation followed by a one-pot Heck-oxyarylation of generated 1-substituted-R-hydroxy styrenes and trapping of the intermediate organometallic species with aryl halides leading to a 2,3-diarylbenzofuran (Scheme S2.17).³²



Scheme S2.17: Kumar's approach for sequential In and Pd catalyzed synthesis of 2,3-disubstituted benzofuran derivatives

2.1.2.3. Ring closure by the formation of the Ar-C(3) bond (Type-III)

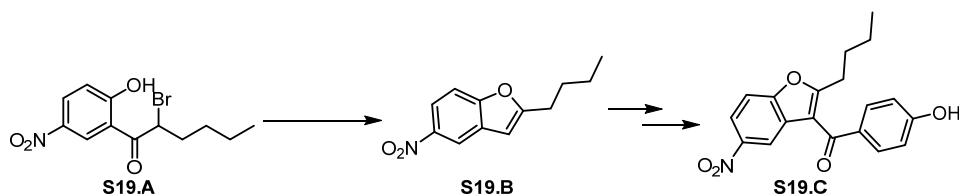
Youn *et al.* developed one-pot procedures for the conversion of allyl aryl ethers to 2-methylbenzofurans *via* sequential Claisen rearrangement and oxidative cyclization. The employed conditions for the reaction involve the use of $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ as catalyst, benzoquinone as the oxidation agent (Scheme S2.18).³³



Scheme S2.18: Youn's approach for the synthesis of benzofuran derivatives

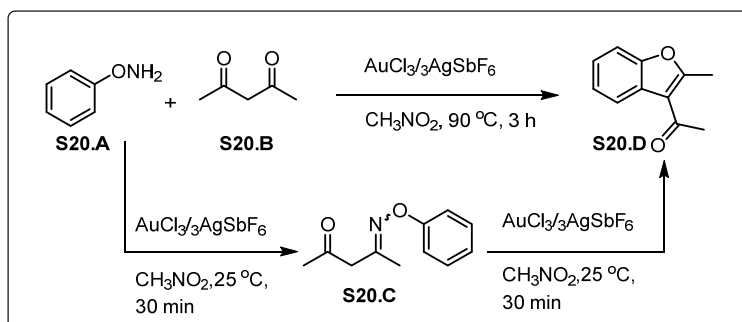
Rajgopal *et al.* reported a practical and an alternative approach for the synthesis of (2-butyl-5-nitrobenzofuran-3-yl)(4-hydroxyphenyl)methanone, a key intermediate used in the preparation of the antiarrhythmic drug, Dronedaron hydrochloride. The base (TEA) mediated intramolecular nucleophilic displacement of 2-bromo-1-(2-hydroxy-5-nitrophenyl)hexan-1-one has been used as the key reaction in this approach. Accordingly, the 2-butyl-5-nitrobenzofuran (**S19.B**) was prepared in

70–75% of yield after two steps. This key intermediate has been taken forward for the preparation of Dronedarone (Scheme S2.19).³⁴



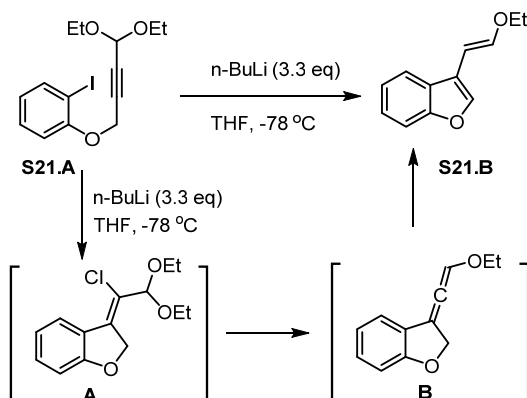
Scheme S2.19: Rajgopal's approach for the synthesis of benzofuran derivatives

Liu *et al.* described a regioselective protocol for the synthesis of 3-carbonylated benzofuran (**3-CBF**) involving the gold(III)-catalyzed tandem condensation/rearrangement/cyclization reaction of *O*-arylhydroxylamines with 1,3-dicarbonyl compounds. The best feature of this strategy is the minimum loading of catalyst (3 mol% of AuCl₃/AgSbF₆) and a highly selective protocol for the synthesis of 3-CBFs (Scheme S2.20).³⁵



Scheme S2.20: Liu's approach for the synthesis of benzofuran derivatives

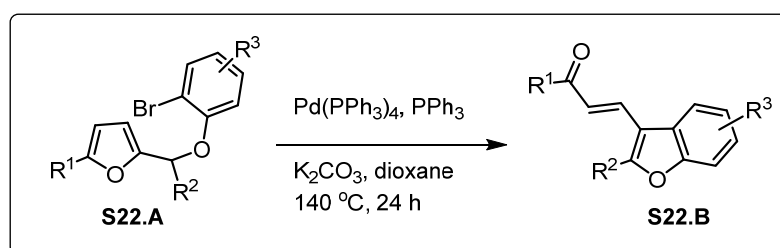
Maddaluno and Le Strat reported a simple route to 3-vinylbenzofurans *via* the internal addition of aryl-anions on the triple bond and the subsequent anionic cascade.



Scheme S2.21: Maddaluno's approach for the synthesis of 3-vinylbenzofurans

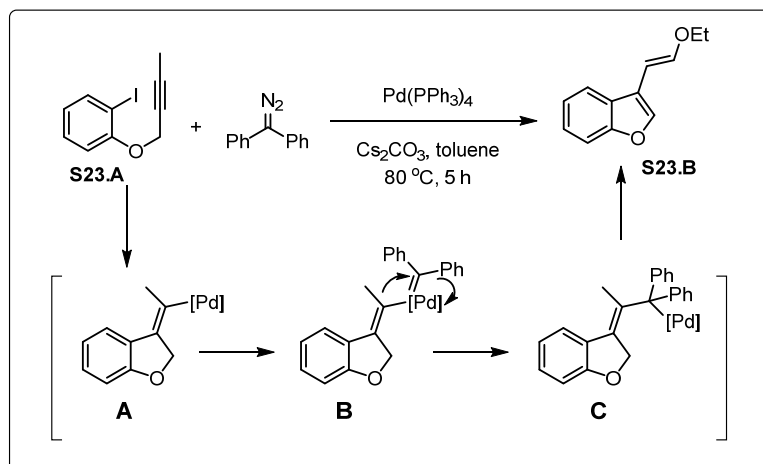
As shown in scheme S2.21, the iodine-lithium exchange with an excess of *n*-BuLi followed by a 5-*exo*-dig addition of the aryllithium on the triple bond leads to a vinyl lithium intermediate which after loss of lithium ethoxide leads to an exocyclic allene. The intermediate exocyclic allene then rearranges to 3-vinylbenzofuran.³⁶

Yin *et al.* described a novel method for the synthesis of functionalized benzofurans from furans. This protocol involves palladium (0)-catalyzed dearomatizing C2 arylation of the furan ring, the formation of a π -allylic palladium complex, furan ring opening, and β -hydride elimination, resulting in a benzofuran derivative (Scheme S2.22).³⁷



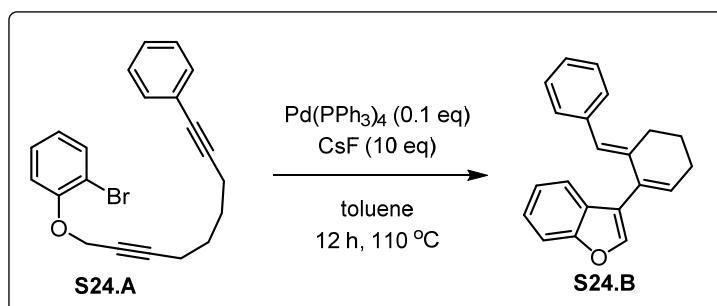
Scheme S2.22: Yin's method for the synthesis benzofurans

Wang *et al.* reported a Pd-catalyzed synthesis of 3-vinylbenzofurans. Interestingly the key step involved in this approach is the migratory insertion of the Pd carbene B to form intermediate C, which subsequently undergoes a β -hydride elimination. Notably, in this transformation, C–C single bond formation (the cyclization) and the C=C double bond formation (carbene coupling) have been achieved in a single catalytic cycle (Scheme S2.23).³⁸



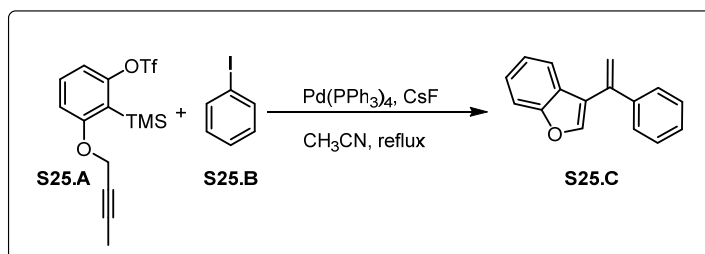
Scheme S2.23: Wang's approach for the synthesis of 3-vinylbenzofurans

Werz *et al.* reported a novel domino reaction of diynyl-substituted bromoarenes leading to highly functionalized benzofuran systems through a sequence of C–C bond formations. In the mechanistic study the two consecutive carbopalladation steps were anticipated, but it is not clear so far whether double bond isomerization as followed by a sigmatropic rearrangement or the involvement of Pd(IV) species is assumed. A slight change of the substrates opened another reaction pathway resulting in the annulation of benzene moieties (Scheme S2.24).³⁹



Scheme S2.24: Werz's method for the synthesis of 3-substituted benzofurans

Ma *et al.* reported a palladium (0)-catalyzed cascade reaction for the efficient synthesis of 3-vinylbenzofuran derivatives (**S25.C**) employing the benzyne chemistry. In this method, first, the benzyne intermediate was formed *in situ* upon the treatment of **S25.A** with CsF; an instant intramolecular ene reaction produces readily allene intermediate, obviously due to the aromaticity of the benzene ring; the insertion reaction with ArPdI forms a π -allylic palladium intermediate and the subsequent β -H elimination would afford the unexpected isomeric benzofuran derivative **S25.C**.⁴⁰

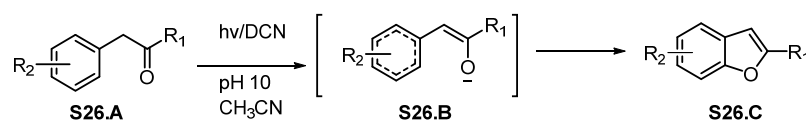


Scheme S2.25: Ma's method for the synthesis of 3-substituted benzofurans

2.1.2.4. Ring closure by the formation of the Ar-O bond (Type IV)

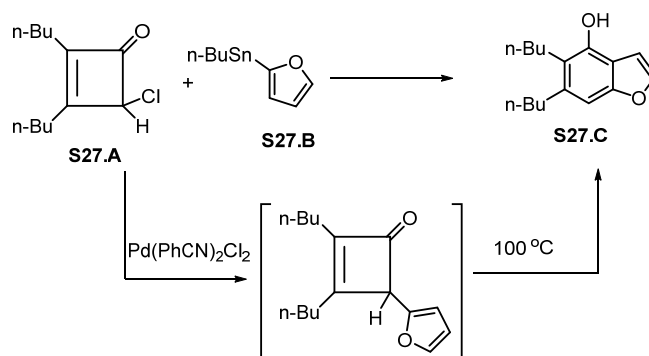
Pandey *et al.* reported the synthesis of 2-substituted benzofurans. The enolates of 2-aryl-1-substituted ethane-1-ones **S26.A** can undergo photo-induced intramolecular

cyclization to form 2-substituted benzofurans **S26.C**. The general reaction procedure involved uses a 125 W mercury lamp to irradiate a mixture of **S26.A** and 1,4-dicyanonaphthalene (DCN) in a molar ratio of approximately 10:1, at > 230 nm in a Pyrex filter. A mixture of acetonitrile and water (8:2), with sodium hydroxide added to bring the pH to ~ 10 , was used as the solvent.⁴¹



Scheme S2.26: The photo-induction methodology of Pandey *et al.*

2.1.2.5. Synthesis from furans and dihydrofurans



Scheme S2.27: Liebeskind's approach for Pd catalyzed benzofuran synthesis

4-Chloro-2-cyclobutanone **S27.A** can undergo Pd-catalysed cross-coupling with 2-stannylated furans **S27.B**, followed by heating, to give 4-hydroxybenzofurans **S27.C**. (Scheme S2.27) **S27.C** was easily prepared in good yield by reacting 4-Chloro-2-cyclobutanone **S27.A** with 2-(tri-n-butylstannyl)furan. In the presence of 5 mol% Pd(PhCN)₂Cl₂ and 10 mol% tris-2-furylphosphine acted as the Stille cross-coupling catalyst in the first step of the reaction, which proceeded at 50 °C for 4 hours and at 100 °C for another 4 hours. (Dioxane was used as the solvent). The overall yield of this reaction was 94%.⁴²

2.2. Introduction:

Carbohydrates are the most abundant organic compounds in living organisms and account for one of the four major biomolecular classes including proteins, lipids, and nucleic acids.⁴⁴ Before the 1970s, scientists solely considered carbohydrates as energy sources, structural components, and protective agents. In particular, they serve as fuel molecules as well as fundamental constituents of living organisms.⁴⁵ However recent scientific innovations have revealed that carbohydrates play an important role in many biological functions. In the living cells, the carbohydrates play key roles in many crucial recognition processes. It has been realized that these compounds may provide important leads for drug discovery.⁴⁶ To reveal the biological roles of saccharides, it is very important to have sufficient amounts of pure and well-defined (poly)saccharides of different sizes and compositions. The chemical synthesis of oligosaccharides is much more complicated than the synthesis of other biopolymers such as peptides and oligonucleotides and many challenging problems still need to be addressed.

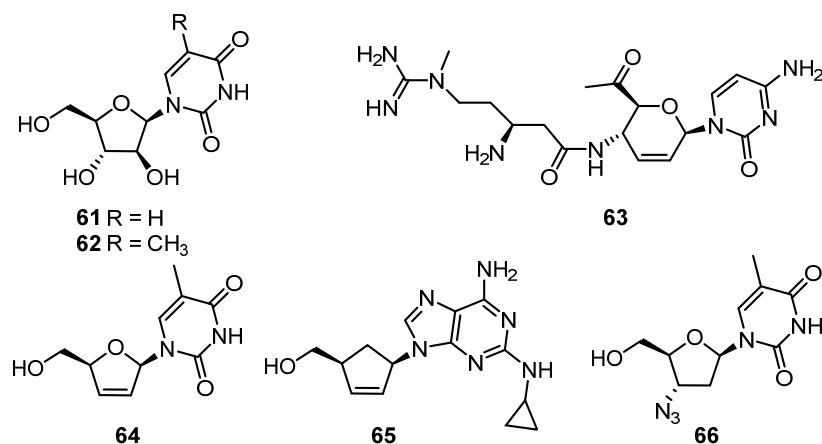


Figure S2.5 *Natural Nucleosides having other than ribo sugar part and some important nucleoside-based anti-HIV agents*

In recent years, the mimicking of carbohydrates for the synthesis of better drug candidate as well as organic materials has drawn major attention from both academia and industry.⁴⁷ The interaction of sugars with proteins initiates many biological processes. One can achieve control of these processes by using sugar-like structures to antagonize the natural ligands at the protein receptor level. Nucleoside analogues are pharmacologically diverse family that includes cytotoxic compounds, antiviral agents and immunosuppressive molecules.⁴⁷ Considerable progress has been

made in the search for novel nucleoside structures with anticancer and/or antiviral activity by modifications in the nucleobase and/or in the sugar moiety and several branched-chain sugar nucleosides have shown potent antitumor activity.

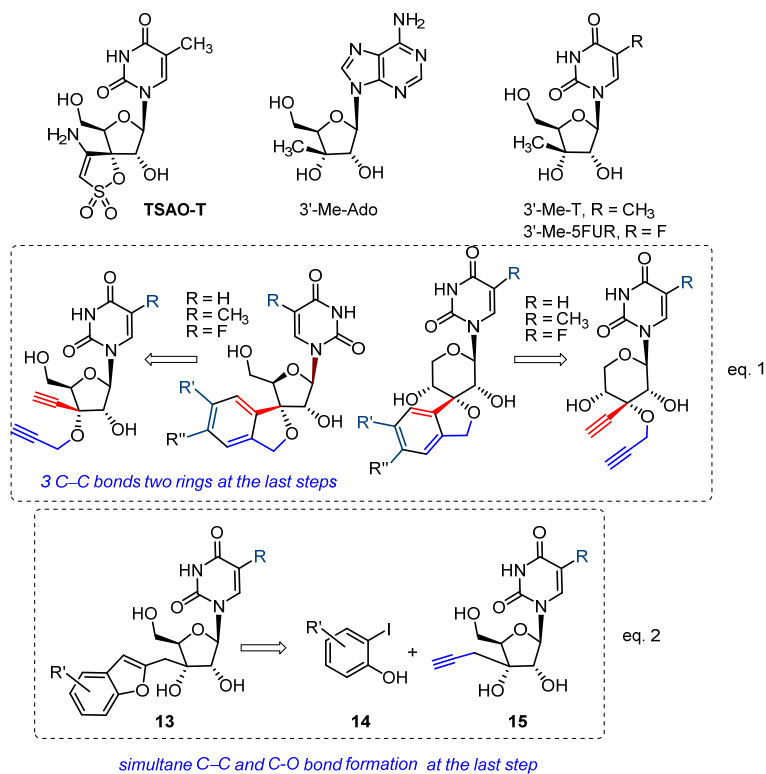


Figure 2.1: C-3' modified nucleosides

Nucleosides are glycosylamines consisting of a nucleobase bonded to a ribose or deoxyribose sugar. Nucleosides can be phosphorylated by specific kinases in the cell on the sugar's primary alcohol group, producing nucleotides, which are the molecular building block of DNA and RNA. In medicine, several natural nucleosides and their analogues are used as antiviral or anticancer agents (Fig. S2.5).⁴⁸⁻⁵² The sugar modifications, in particular, C-3' modified sugar unit in the nucleosides, have gained significant attention for therapeutic development. In 1992, Camarasa *et al.* produced an entirely new class of molecules, designated as TSAO ([2,5-bis-O-(*tert*-butyldimethylsilyl)- β -D-ribofuranosyl]-3-spiro-5'-(4'-amino-1',2'-oxathiole 2',2'-dioxide)), which showed potent HIV-1 inhibitory activity.⁵³ The prototype compound is TSAO-T, in which the simple modification is at C-3' position (Fig. 2.1). From this initial success, later few groups focused on the synthesis of C-3' modified nucleosides for antiviral and anticancer evaluation.^{54, 55} These agents behave as antimetabolites that interact with a number of intracellular targets blocking the DNA chain elongation

or interfering with the biosynthesis of nucleosides and nucleotides, a limiting process in cell proliferation.

2.3. Present Work

In our group, earlier, we had reported a modular approach for the synthesis of a focused collection of C3 isobenzofuran-spiroannulatedribo-configured nucleosides either in furanose or in pyranose forms. As shown in Figure 2.1 (eq. 1), the key reaction employed was alkyne cyclotrimerization and more importantly, this reaction was conducted on a free nucleoside diyne.⁵⁶ Since this reaction was executed as the last step and one of the partners is a simple alkyne, this provided an opportunity for synthesizing a large collection of C3' modified nucleosides. Our strategy is quite striking as the other spironucleosides in general are synthesized in a target oriented route – i.e one approach for one nucleoside. In continuation, we have been interested at looking at the possibility of appending a benzofuran unit at C3', considering that fact that it occurs in diverse natural, medicinally important compounds such as drug candidates and organic materials.

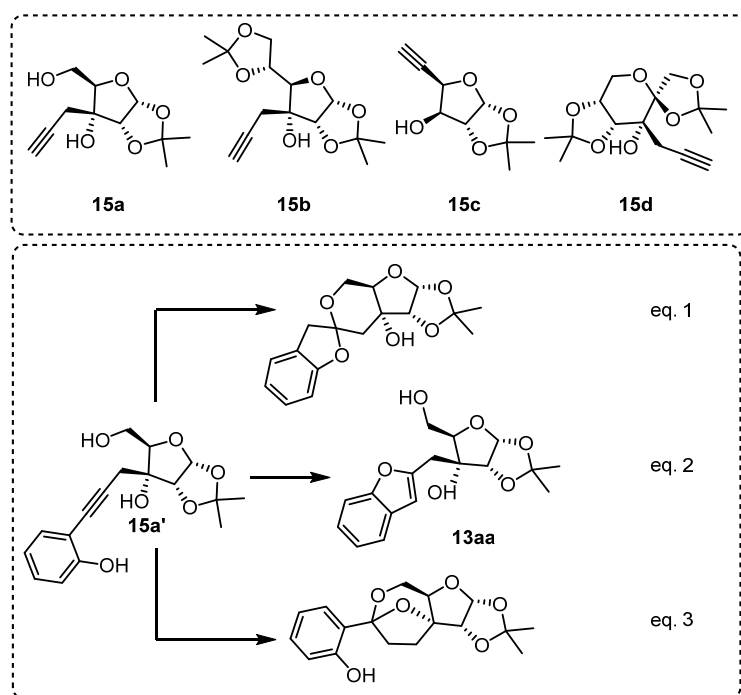


Figure 2.2: Selected sugar alkynols **15a** – **15d** and possible cyclization with **15a**

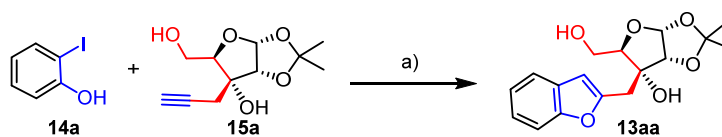
Coming to our synthetic plan, amongst the several methods available in the literature for the synthesis of the benzofuran unit, the coupling-*cum*-cyclization of o-iodophenols with alkynes in particular (both being catalyzed by various metal complexes) has attracted our attention. We have intended this strategy to explore the

target *cum* flexibility to make the combinatorial library of desired product collection in an efficient manner. This method is a mild one with tolerance for various functional groups. It also provides an opportunity for synthesizing diverse analogues by simple variation of either the iodophenol **14** employed (final event) or the nucleobase used (just two steps prior to the final event). The salient features of our approach are described in Figure 2.1 (eq. 2).⁵⁷

As a first step in this direction, to establish a platform for the final cyclization event on an unprotected nucleobase, we have set up our first objective to check the feasibility of this reaction with simple sugar alkynols. As shown in Figure 2.2, we have different sugar alkynols **15a–15d** having free –OH groups at different positions that we have selected as model substrates in this context. The possible cyclizations of one of the important alkynol **15a** are given in Figure 2.2. This reveals our concern in this regard and also why these model studies are important in the direction of conducting the projected benzofuran unit synthesis *via* the coupling-*cum*-cyclization of *o*-iodophenols with the free nucleoside alkynol. There exist three possibilities. If the C5-OH participates in the cyclization, depending upon the mode of cyclization i.e. 5-*exo* or 6-*endo*, it leads to two possible ketals i.e. either a bridged bicyclic ketal (eq. 3, Fig. 2.2)⁵⁸ or a spiroketal (eq. 1, Fig. 2.2).⁵⁹ In case if the Ar-OH participates in the cyclization, it provides the desired benzofuran **13aa**.⁵⁷ Indeed, the sugar alkynol **15a** will serve as the starting point for our synthesis of key nucleoside alkynols. Having set the initial objectives, we proceeded next for the synthesis of the key alkynols **15a–15d** from the suitable sugar precursors.^{59, 60}

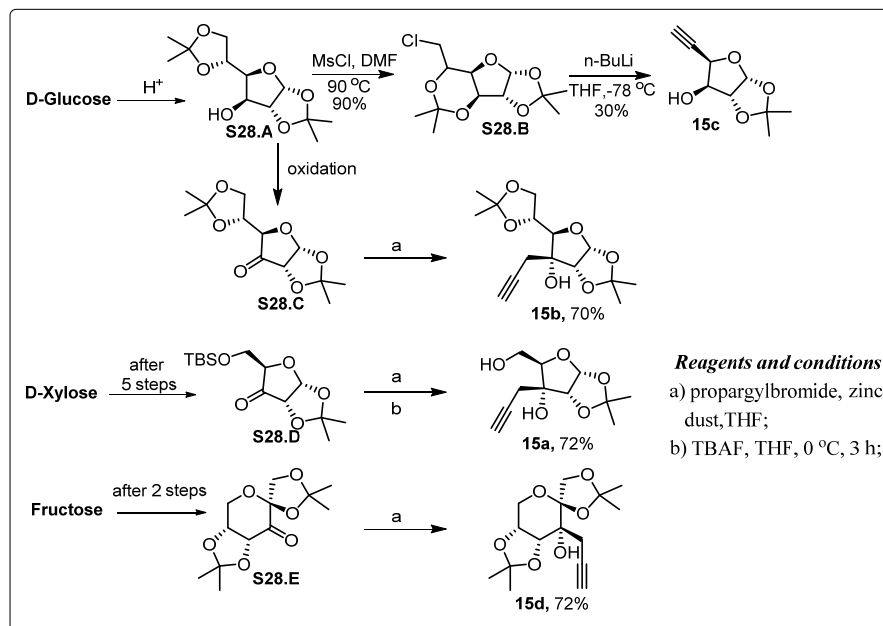
Our journey started with the preparation of known the xylose derived alkynol **1a** from D-xylose in 5 steps. The key [Pd]-mediated Sonogashira coupling of the xylose derived alkynol **15a** with *o*-iodophenol **14a** proceeded smoothly and provided exclusively one single product in 85% yield.⁶¹ The conditions employed involve the use Pd(PPh₃)₂Cl₂ (5 mol%), as a catalyst along with PPh₃ (5 mol%), and CuI (5 mol%) in a mixture of Et₃N and DMF and the reaction was conducted at rt. The structure of isolated product was determined as the desired benzofuran derivative **13aa** with the help of spectral and analytical data. For example, in the ¹H NMR spectrum of **13aa**, the characteristic C(3)–H of the benzofuran ring is present at δ 6.63 ppm as a singlet and the 2H of the methylene unit appeared as doublets at δ 2.86 and δ 3.13 ppm with a large geminal coupling (15.5 Hz). As expected, the C(3) of the

benzofuran ring resonated at up field (103.5 ppm, d) and the methylene unit attached to the C(2) appeared at δ 30.5 ppm.



Scheme 2.1: The intended cycloisomerization and the synthesis of sugar-benzofuran conjugates. Reaction conditions and reagents: a) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (5 mol%), PPh_3 (5 mol%), CuI (5 mol%), Et_3N , DMF, rt

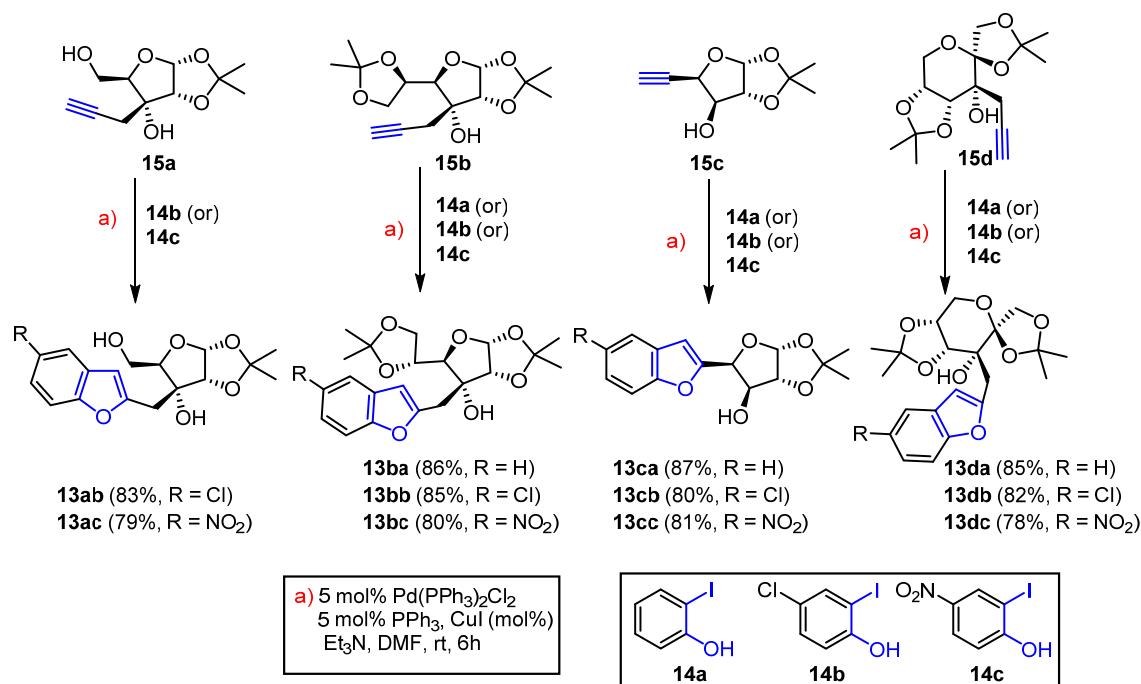
Having established the key benzofuran synthesis with the complicated model substrate **15a**, our next objective was to show the generality of this reaction by varying both the coupling partners i.e. iodophenol and the sugar alkyne. The sugar alkynols **15b–15d** having the alkyne integrated on different sugar platforms have been synthesized by following the established procedures. Scheme 2.2 provides a glimpse of the protocols that we have adopted for their syntheses.^{59, 60}



Scheme 2.2: Preparation of sugar alkyne precursors

The iodophenols **14a–14c** have been selected as the partners for conducting the Pd-catalyzed coupling-*cum*-cyclization with the sugar alkynols **15a–15d** and thus establish the generality of this reaction in the direction of the synthesis of sugar derived benzofuran conjugates. As shown in Scheme 2.3, the Sonogashira coupling of sugar alkyne, **15a–15d** with the three iodophenols **14a–14c** proceeded smoothly in the presence of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI and Et_3N in DMF at rt within 6 h. The reactions are facile with all the four alkynes employed and gave the corresponding sugar–

benzofuran conjugates in very good yields. The substituents on the iodophenol in general have no influence on the yields except in case of the NO₂ group where the yields dropped slightly. All the new compounds synthesized have been fully characterized by using spectroscopic techniques and the results have been summarized in Scheme 2.3.



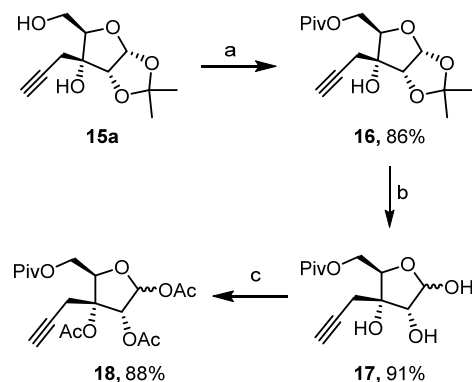
Scheme 2.3: Scope of [Pd]-catalyzed benzofurannulation of sugar derivatives.

2.2.1 Synthesis of glycosyl donor (18).

After successful implementation of the target *cum* flexibility strategy employing the [Pd]-catalyzed benzofuran synthesis on simple sugar derivatives, we intended to check the feasibility of this reaction with unprotected C(3) C-propargylated nucleosides **15g** and **15h**. The modification of the sugar unit in the nucleosides is one of the promising approaches for the derivation of new antiviral agents. Our initial intention was to carry out this benzofurannulation reaction on free nucleosides **15g** and **15h**, thereby making a provision of substrate flexibility at the final stage and providing an easy access for synthesizing a collection of C(3')-modified nucleosides (Scheme 2.5). The synthesis of the key intermediate alkynyl nucleosides **15g** and **15h** started from the known xylose derived alkynol **15a**.

We have earlier established that if the C5-OH is free and undergoes the hydrolysis and peracetylation, in general it leads to a pyranose derivative. However, we have handled this problem by protecting the C5-OH with an acid stable protecting

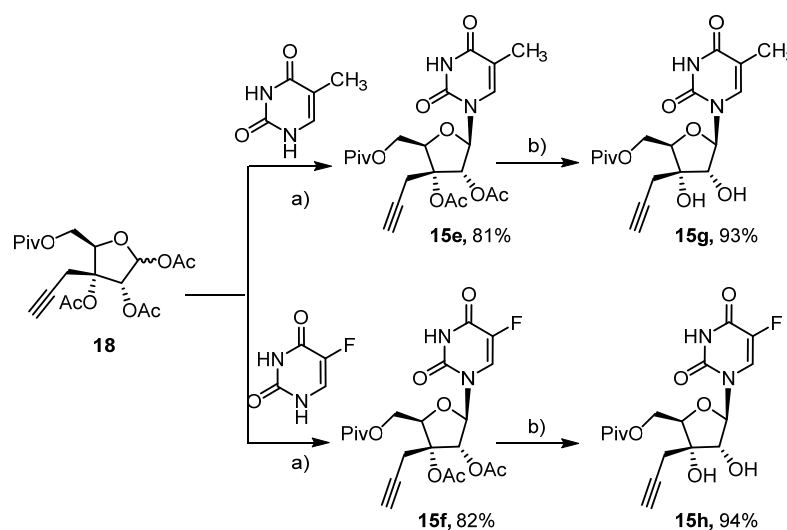
group and then carrying out the acetonide hydrolysis with acid followed by peracetylation, which exclusively leads to a desired furanose derivative.⁵⁶ We intended to follow a similar approach in the present case as well. Thus the selective protection of C(5)-OH of alkynol **15a** as its pivaloate **16** has been carried out by using pivaloyl chloride in the presence of triethyl amine in dichloromethane. The resulting compound **16** has been subjected for the selective hydrolysis of the 1,2-acetonide group by employing 70% AcOH in water reflux for 6h to offer the anomeric mixture of intermediate lactols **17**, which have been subsequently subjected for peracetylation employing acetic anhydride in the presence of triethyl amine (TEA) and DMAP in dichloromethane to furnish a 1:1 anomeric mixture of triacetyl C(3)-propargyl ribose derivatives **18** (scheme 2.4).



Scheme 2.4: Reagents and conditions: a) Piv-Cl, Et₃N, DMAP, CH₂Cl₂, 4h; b) 70% ACOH, reflux 6h; c) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 4h.

The compound **18** was fully characterized by spectral and analytical data. In the ¹H NMR spectrum of compound **18**, the methylene unit appeared as two doublet of doublets at δ 2.88 ppm and 3.05 ppm with a large geminal coupling ($J = 2.5, 17.7$ Hz) and the methyl protons of pivaloyl appeared at δ 1.07 ppm as a singlet and the methyl protons of acetate appeared at δ 1.91, 1.92 and 1.95 ppm as singlets respectively. In the ¹³C NMR spectrum, the alkyne carbons and quaternary carbon C(3) showed at δ 82.3, 82.2 singlet and doublet respectively and the methylene carbon at δ 21.1 ppm. The remaining carbonyl quaternary carbons appeared as singlets at δ 168.5, 168.7, 168.9 and 177.1 ppm. The acetylenic C–H stretching frequency was appeared at 3308 cm⁻¹ and the C $\equiv$ C stretching frequency at 2121 cm⁻¹ in the IR spectrum of compound **18**.

After successful synthesis of the anomeric mixture of triacetates **18**, our next concern was the *N*-glycosidation. The glycosidation of triacetate **18** was carried out under modified Vorbrüggen conditions.⁶² The conditions employed involve the treatment of **18** with thymine or with 5-fluorouracil in the presence of *N,O*-bis(trimethylsilyl)acetamide and TMSOTf in acetonitrile, then after completion at 0 °C and then heating the contents at 50 °C for 2 h to afford the protected nucleosides **15e** and **15f** respectively. The anomeric configuration of the protected nucleosides **15e** and **15f** was established with the help of spectral data analysis.



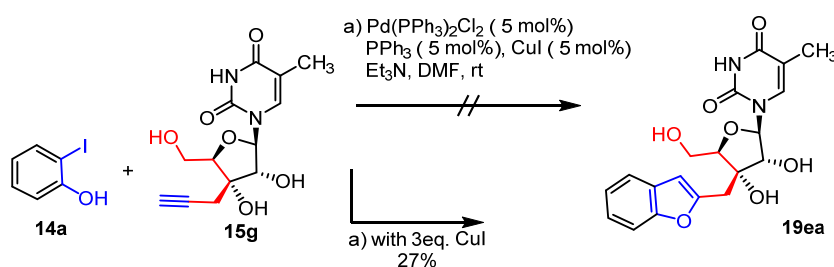
Scheme 2.5: a) BSA, TMSOTf, CH₃CN, 4h; b) NaOMe, MeOH, rt, 20 min.

For example, in the ¹H NMR spectrum of compound **15e**, the anomeric–H and C(2)–H resonated at δ 6.19 and 5.45 respectively as a doublets with a characteristic large *J*_{1,2} coupling constant *J* = 7.8 Hz which is indicative of a β-configuration. The characteristic C-3 CH₃ appeared at δ 1.92 as singlet and the C-2 olefinic proton resonated at down field δ 7.24 as a singlet. The two protons of CH₂, which were adjacent to alkyne (CH₂ of propargyl) resonated as two separate doublet of doublets at δ 3.04 and δ 3.25 with a coupling constant *J* = 2.5, 17.3 Hz. The amide N–H of **15e** showed a broad singlet at δ 9.35 ppm. In the ¹³C NMR spectrum of compound **15e**, the C-3 appeared as singlet at δ 112.0 and C-2 olefin proton appeared as a doublet at δ 134.3 ppm. Quite interestingly, in the case of **15f**, the anomeric–H appeared as a doublet of doublet at 6.19 (dd, ⁵*J*_(H1,F) = 1.5, 7.8 Hz) while it was a doublet in the case of compound **15e**. The second coupling was due to the long range coupling with a fluorine atom. The other couplings associated with the fluorine have been seen both in ¹H and the ¹³C NMR spectra of compound **15f**. The deacetylation of **15e** and **15f** employing catalytic amounts of NaOMe in methanol gave the free alkynol

nucleosides **15g** and **15h** (Scheme 2.5) in good yields. The spectral data of the free nucleoside alkyne **15g** and **15h** were in accordance with the assigned structure. For example, the disappearance of characteristic peaks of pivaloyl, acetyl methyl group in ^1H NMR spectra was supportive of the assigned structures of **15g** and **15h**.

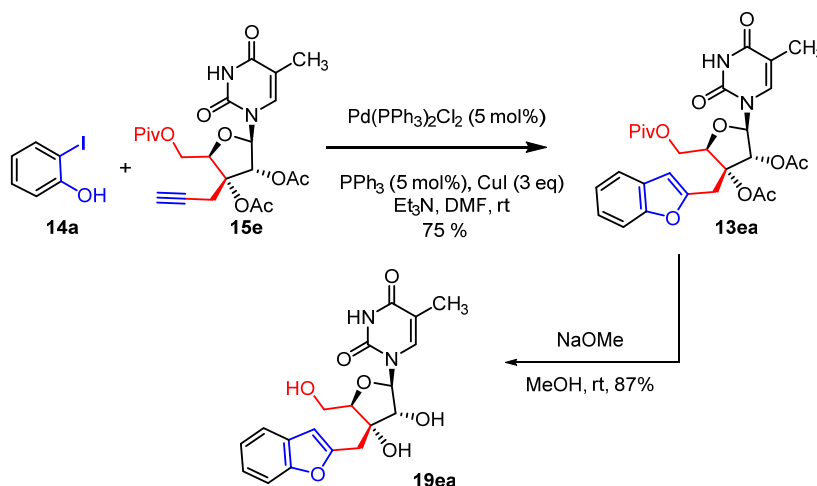
2.2.2. Synthesis of Nucleoside derived benzofuran conjugates

Our initial experiments dealing with the Sonogashira coupling reaction of alkyne **15g** (Scheme 2.6) were unsuccessful under the conditions described in Schemes 2.1 and 2.3.



Scheme 2.6: The substrate and reaction optimization for the synthesis of benzofuran-conjugated nucleosides.

Optimization of the reaction conditions has been carried out by changing the reagents. Initial attempts at replacing the base TEA with Cs_2CO_3 , K_2CO_3 or with Na_2CO_3 met failure.



Scheme 2.7: The synthesis of benzofuran-conjugated nucleosides.

Next we moved to look at the amount of CuI as all the $-\text{OH}$ groups are free and also the presence of free base. When 1 eq of CuI was employed, we could see the formation of the desired products with the help of mass spectra analysis. However, the conversion was unsatisfactory. When we switched to 2eq. CuI , the Sonogashira reaction provided the desired **19ea** in 10% yield, despite the fact that the conversion

was about 63%. Finally, when 3 eq of CuI was employed, the product **19ea** was isolated in 27% yield and disturbingly; the conversion was almost 100%. These experiments revealed that the presence of 3 equivalents of copper iodide (with respect to the alkyne) is essential and it indicated that activation of this alkyne required a stoichiometric amount of CuI. Despite the fact that the yield was poor (27%), the isolation of pure nucleosides turned out to be a difficult proposition as the samples are always contaminated with the triethylamine salts. Considering these difficulties, we next moved to the corresponding protected nucleosides **15e** and **15f**. Our preliminary experiments with the Sonogashira coupling of **15e** with simple *o*-iodophenol (**14a**) revealed that even in this case, the presence of 3 equivalents of CuI is essential for obtaining the corresponding benzofuran **13ea** in respectable yields.

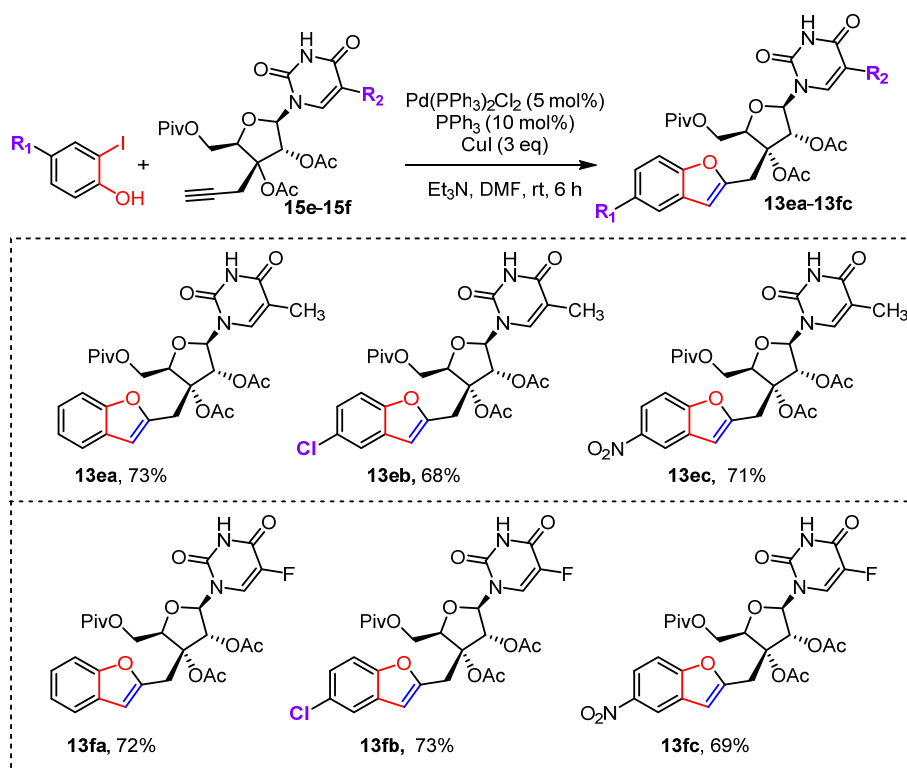


Table 2.1. Generalization of the benzofuran synthesis on nucleoside templates

The compound **13ea** was fully characterized by spectral and analytical data. In the ¹H NMR spectrum of compound **13ea**, the characteristic benzofuran C3-H appeared at δ 6.43 as singlet and the disappearance of alkyne proton was observed. The remaining aromatic protons resonated in the range of δ 7.20–7.50 ppm. The C3'–CH₃ appeared as singlet at δ 1.94. The methylene (CH₂) protons, which are adjacent to the benzofuran appeared as two separate doublets at δ 3.15 and 4.13 with a large germinal coupling of *J* = 15.3 Hz. In the ¹³C NMR spectrum of compound **13ea**, the

benzofuran C3 carbon resonated at δ 110.8 as a doublet and the remaining aromatic carbons were also observed at the expected positions.

Subsequently, we conducted the Sonogashira coupling of **15e** and **15f** with the other iodophenols **14a–14c**. All the reactions were facile and afforded the corresponding benzofurans in good yields and the details of all these reactions are summarized in Table 2.1. All the compounds were completely characterized with the help of analytical and spectroscopic techniques.

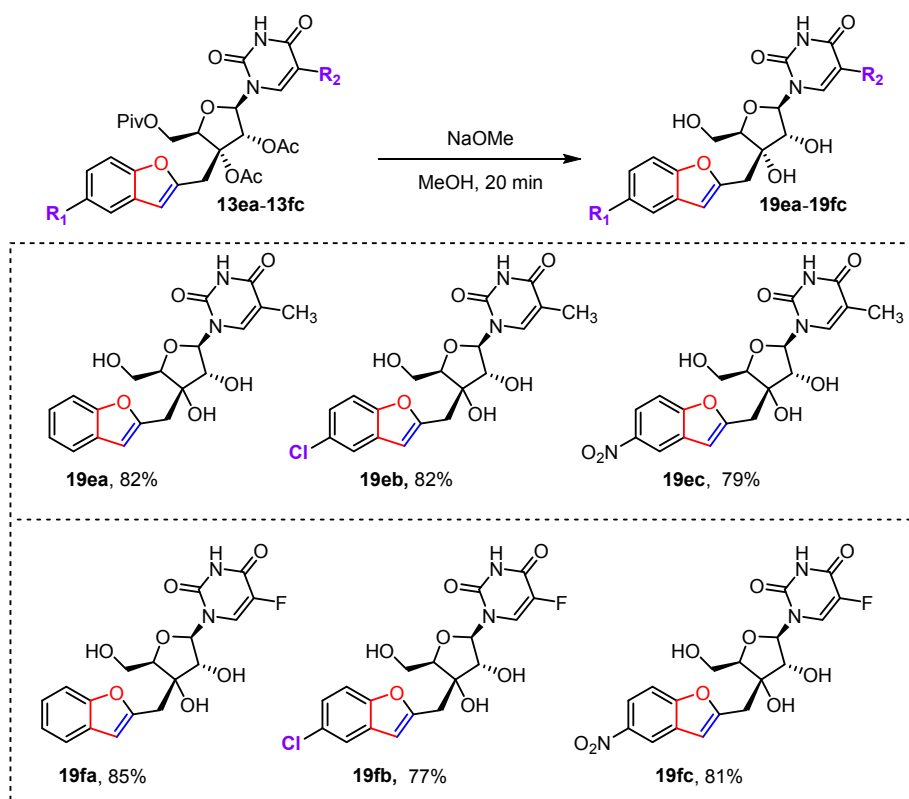


Table 2.2. Generalization of the benzofuran synthesis on nucleoside templates

The global deprotection of the resulting nucleoside conjugated benzofuran derivatives was carried out under Zemplan's conditions (NaOMe in MeOH) to afford the corresponding fully deprotected benzofuran conjugated nucleosides (**19ea**, **19eb**, **19ec**, **19fa**, **19fb**, **19fc**) in good yields. The details of the synthesis of all these compounds have been summarized in Table 2.2. The structures of all the compounds were confirmed with the help of analytical and spectroscopy techniques. For example, the disappearance of the characteristic peaks of the pivaloyl, acetyl methyl group in ^1H NMR was supportive of the assigned structures of **19ea–19fc**.

Conclusion

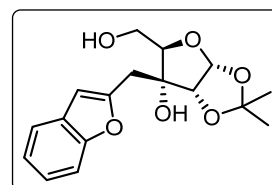
To conclude, the suitability of [Pd]-mediated coupling *cum* cyclization of *o*-iodophenols with alkynes leading to benzofurans has been examined on various sugar and nucleoside derived alkynes. The reactions of sugar alkynes proceeded smoothly under the standard Sonogashira conditions employing both palladium and copper complexes in catalytic amounts. However, with the nucleoside derived alkynes, the presence of 3 equivalents of copper salt (with respect to the alkyne) is essential. Since the key benzofuran ring construction was the penultimate step in the synthesis of C(3)-modified nucleosides, and since it is an intermolecular coupling event, the present approach provides ample room for the synthesis of the corresponding benzofuran conjugated nucleosides collection.

4.3. General procedure for benzofuran synthesis

To a solution of alkyne (1.0 mmol), iodophenol (1.0 mmol) in Et₃N (5.0 mL) and DMF (2.5 mL), PPh₃ (0.05 mmol) was added followed by Pd(PPh₃)₂Cl₂ (0.05 mmol), and the reaction mixture was flushed with argon for 30 min. CuI (0.05 mmol) was added and flushed with argon for 10 min and stirred at rt for 6 h. The reaction mixture was partitioned between ethyl acetate and water. Then the organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated. The crude residue was purified by column chromatography.

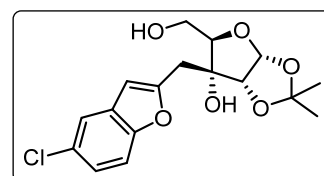
1,2-*O*-Isopropylidene-3-*C*-(benzofuran-2'-yl)methylene)- α -D-allofuranose (**13aa**):

Isolated by column chromatography (pet.ether/AcOEt = 1:1, *R_f* = 0.4). The title compound **13aa** was determined as offwhite solid (85%). mp: 152–154 °C; [α]_D²⁵: + 0.1 (*c* 0.5, CHCl₃); IR (CHCl₃): ν 3448, 3233, 2985, 1599, 1453, 1217, 1027, 878, 768, 668 cm⁻¹; ¹H NMR (200MHz, CDCl₃): δ 1.30 (s, 3H), 1.56 (s, 3H), 2.40 (br s, 1H), 2.86 (d, *J* = 15.5 Hz, 1H), 3.03 (br s, 1H), 3.13 (d, *J* = 15.5 Hz, 1H), 3.90–4.06 (m, 3H), 4.42 (d, *J* = 3.9 Hz, 1H), 5.85 (d, *J* = 3.9 Hz, 1H), 6.63 (s, 1H), 7.16–7.29 (m, 2H), 7.43–7.54 (m, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 26.4 (q), 26.5 (q), 30.5 (t), 60.1 (t), 78.5 (s), 80.7 (d), 82.2 (d), 103.5 (d), 106.0 (d), 110.9 (d), 112.6 (s), 120.6 (d), 122.7 (d), 123.7 (d), 128.6 (s), 153.5 (s), 154.6 (s) ppm; ESI-MS *m/z*: 343.30 (100%, [M+Na]⁺), 359.28 (11%, [M+K]⁺); Annl. Calcd for C₁₇H₂₀O₆: C, 63.74; H, 6.29% Found: C, 63.77; H, 6.26%.



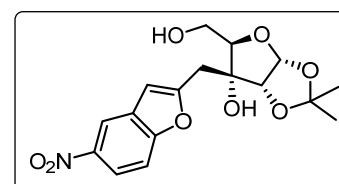
1,2-*O*-Isopropylidene-3-*C*-(6'-chlorobenzofuran-2'-yl)methylene)- α -D-allofuranose (**13ab**):

Isolated by column chromatography (pet.ether/AcOEt = 1:1, *R_f* = 0.4). The title compound **13ab** was determined as offwhite solid (83%). mp: 170–172 °C; [α]_D²⁵: + 0.1 (*c* 0.5, CHCl₃); IR (CHCl₃): ν 3684, 3019, 2937, 2400, 1729, 1598, 1448, 1004, 871, 756, 669 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.32 (s, 3H), 1.58 (s, 3H), 2.09 (br s, 1H), 2.86 (d, *J* = 15.7 Hz, 1H), 2.94 (br s, 1H), 3.14 (d, *J* = 15.7 Hz, 1H), 3.88–4.04 (m, 3H), 4.39 (d, *J* = 3.9 Hz, 1H), 5.85 (d, *J* = 3.9 Hz, 1H), 6.60 (s, 1H), 7.20 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 2.2 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 26.4 (q), 26.5 (q), 30.5 (t), 60.0 (t), 78.5 (s), 80.7 (d), 82.2 (d), 103.5 (d), 105.7 (d), 111.8 (d), 112.7 (s), 120.2 (d), 123.8 (d), 128.3 (s), 130.0 (s), 153.0 (s), 155.2 (s) ppm; ESI-MS *m/z*: 377.25 (100%, [M+Na]⁺), 393.28 (18%, [M+K]⁺); Anal. Calcd for C₁₇H₁₉ClO₆: C, 57.55; H, 5.40% Found: C, 57.85; H, 5.40%.



1,2-*O*-Isopropylidene-3-*C*-(6'-nitrobenzofuran-2'-yl)methylene)- α -D-allofuranose (**13ac**):

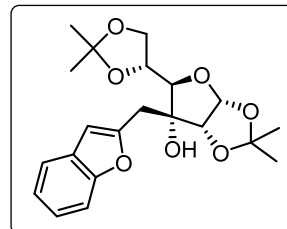
Isolated by column chromatography (pet.ether/AcOEt = 1:1, *R_f* = 0.5). The title compound **13ac** was determined as offwhite solid (79%). mp: 171–172 °C; [α]_D²⁵: + 0.04 (*c* 0.5, CHCl₃); IR (CHCl₃): ν 3436, 3019, 2400, 1599, 1347, 1215, 1020, 757, 669 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.32 (s, 3H), 1.57 (s, 3H), 1.89 (br s, 1H), 2.87 (br s, 1H), 2.93 (d, *J* = 15.3 Hz, 1H), 3.23 (d, *J* = 15.7 Hz, 1H), 3.92–4.04 (m, 3H), 4.39 (d, *J* = 4.0 Hz, 1H), 5.88 (d, *J* = 4.0 Hz, 1H), 6.80 (s, 1H), 7.51 (d, *J*



= 9.0 Hz, 1H), 8.20 (dd, J = 9.0, 2.3 Hz, 1H), 8.45 (d, J = 2.2 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 26.4 (q), 26.6 (q), 30.6 (t), 60.0 (t), 78.5 (s), 80.6 (d), 82.1 (d), 103.6 (d), 106.8 (d), 111.3 (d), 112.9 (s), 117.1 (d), 119.7 (d), 129.1 (s), 144.1 (s), 157.4 (s), 157.4 (s) ppm; ESI-MS m/z : 388.22 (100%, $[\text{M}+\text{Na}]^+$); Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_8$: C, 55.89; H, 5.24; N, 3.83% Found: C, 55.73; H, 5.44; N, 3.83%.

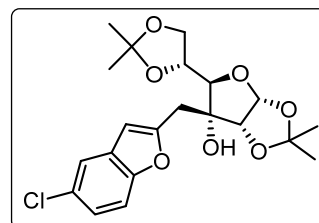
1,2:5,6-Di-*O*-isopropylidene-3-*C*-(benzofuran-2'-yl)methylene)- α -D-allofuranose (13ba):

Isolated by column chromatography (pet.ether/AcOEt = 4:1, R_f = 0.4). The title compound **13ba** was determined as offwhite solid (86%). mp: 100–102 °C; $[\alpha]_{\text{D}}^{25}$: +0.08 (c 0.5, CHCl_3); IR (CHCl_3): ν 3461, 2988, 1600, 1455, 1383, 1219, 1072, 853, 753 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.21 (s, 3H), 1.30 (s, 3H), 1.41 (s, 3H), 1.49 (s, 3H), 2.84 (dd, J = 15.5, 3.2 Hz, 1H), 2.88 (br s, 1H), 3.28 (dd, J = 15.5, 3.2 Hz, 1H), 3.79–3.91 (m, 2H), 4.04–4.23 (m, 2H), 4.35 (d, J = 3.8 Hz, 1H), 5.68 (d, J = 3.8 Hz, 1H), 6.61 (s, 1H), 7.11–7.19 (m, 2H), 7.34–7.46 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 25.3 (q), 26.4 (q), 26.6 (q), 26.7 (q), 31.4 (t), 68.1 (t), 73.2 (d), 79.1 (s), 81.3 (d), 81.9 (d), 103.6 (d), 106.0 (d), 109.9 (s), 110.9 (d), 112.7 (s), 120.6 (d), 122.7 (d), 123.6 (d), 128.7 (s), 153.6 (s), 154.6 (s). ppm; ESI-MS m/z : 413.30 (100%, $[\text{M}+\text{Na}]^+$), 429.25 (26%, $[\text{M}+\text{K}]^+$); Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{O}_7$: C, 64.60; H, 6.71% Found: C, 64.60; H, 6.73%.



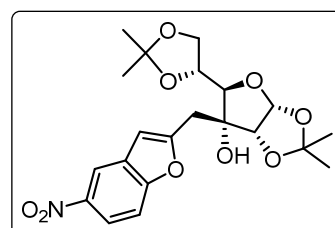
1,2:5,6-Di-*O*-isopropylidene-3-*C*-(6'-chlorobenzofuran-2'-yl)methylene)- α -D-allofuranose (13bb):

Isolated by column chromatography (pet.ether/AcOEt = 4:1, R_f = 0.4). The title compound **13bb** was determined as offwhite solid (85%). mp: 130–132 °C; $[\alpha]_{\text{D}}^{25}$: +21.13 (c 0.5, CHCl_3); IR (CHCl_3): ν 3436, 3019, 1618, 1448, 1215, 1071, 843, 756, 668 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.24 (s, 3H), 1.33 (s, 3H), 1.44 (s, 3H), 1.53 (s, 3H), 2.83 (d, J = 15.4 Hz, 1H), 2.97 (s, 1H), 3.30 (d, J = 15.4 Hz, 1H), 3.82–3.94 (m, 2H), 4.07–4.23 (m, 2H), 4.35 (d, J = 3.8 Hz, 1H), 5.72 (d, J = 3.8 Hz, 1H), 6.59 (s, 1H), 7.12 (dd, J = 8.7, 2.2 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.40 (dd, J = 2.2 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 25.1 (q), 26.2 (q), 26.4 (q), 26.5 (q), 31.1 (t), 67.9 (t), 73.0 (d), 78.8 (s), 81.1 (d), 81.8 (d), 103.4 (d), 105.5 (d), 109.7 (s), 111.6 (d), 112.5 (s), 119.9 (d), 123.5 (d), 128.0 (s), 129.9 (s), 152.7 (s), 155.2 (s) ppm; ESI-MS m/z : 447.13 (100%, $[\text{M}+\text{Na}]^+$), 463.05 (22%, $[\text{M}+\text{K}]^+$); Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{ClO}_7$: C, 59.36; H, 5.93%; Found: C, 59.39; H, 5.91%.



1,2:5,6-Di-*O*-isopropylidene-3-*C*-(6'-nitrobenzofuran-2'-yl)methylene)- α -D-allofuranose (13bc):

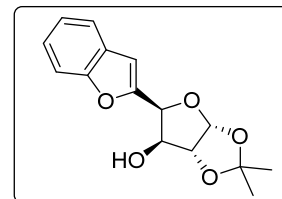
Isolated by column chromatography (pet.ether/AcOEt = 4:1, R_f = 0.4). The title compound **13bc** was determined as offwhite solid (80%). mp: 138–140 °C. $[\alpha]_{\text{D}}^{25}$: + 20.77 (c 0.5, CHCl_3); IR (CHCl_3): ν 3437, 3020, 2991, 1592, 1525, 1346, 1216, 1071, 844, 755 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.33 (s, 3H), 1.39 (s, 3H), 1.50 (s, 3H), 1.60 (s, 3H), 2.95 (d, J = 15.7 Hz, 1H), 3.05 (s, 1H), 3.46 (d, J = 15.7 Hz, 1H), 3.88–4.01 (m, 2H), 4.14–4.27 (m, 2H), 4.42



(d, $J = 3.8$ Hz, 1H), 5.83 (d, $J = 3.8$ Hz, 1H), 6.88 (s, 1H), 7.52 (d, $J = 9.1$ Hz, 1H), 8.17 (dd, $J = 9.1, 2.2$ Hz, 1H), 8.43 (d, $J = 2.2$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 25.1 (q), 26.3 (q), 26.4 (q), 26.6 (q), 31.2 (t), 68.0 (t), 73.1 (d), 78.9 (s), 81.1 (d), 81.9 (d), 103.5 (d), 106.7 (d), 109.9 (s), 111.0 (d), 112.8 (s), 116.9 (d), 119.4 (d), 129.1 (s), 144.0 (s), 157.3 (s), 157.5 (s) ppm; ESI-MS m/z : 458.42 (100%, $[\text{M}+\text{Na}]^+$); Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_9$: C, 57.93; H, 5.79; N, 3.22%; Found: C, 57.81; H, 5.86; N, 3.22%.

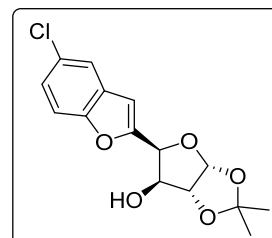
1,2-*O*-Isopropylidene-4-*C*-(5-benzofuran-2'-yl)- α -D-xylobutanofuranose (**13ca**):

Isolated by column chromatography (pet.ether/AcOEt = 5:1, $R_f = 0.4$). The title compound **13ca** was determined as white solid (87%). mp: 124–126 °C; $[\alpha]_D^{25}$: -32.4 (c 1.6, CHCl_3); IR (CHCl_3): ν 3445, 3019, 2935, 1635, 1455, 1216, 1075, 754, 667 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.35 (s, 3H), 1.57 (s, 3H), 2.24 (br s, 1H), 4.42 (d, $J = 2.5$ Hz, 1H), 4.66 (d, $J = 3.7$ Hz, 1H), 5.38 (d, $J = 2.5$ Hz, 1H), 6.08 (d, $J = 3.7$ Hz, 1H), 6.86 (s, 1H), 7.19–7.33 (m, 2H), 7.44–7.49 (m, 1H), 7.56 (dd, $J = 2.4, 6.6$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 26.1 (q), 26.7 (q), 75.9 (d), 77.1 (d), 84.7 (d), 104.8 (d), 106.4 (d), 111.2 (d), 112.1 (s), 121.2 (d), 123.1 (d), 124.5 (d), 127.7 (s), 151.4 (s), 154.9 (s) ppm; ESI-MS m/z : 277.25 (27% $[\text{M}+\text{H}]^+$), 299.27 (100% $[\text{M}+\text{Na}]^+$); Annl. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_5$: C, 65.21; H, 5.84%; found: C, 65.18; H, 5.84%.



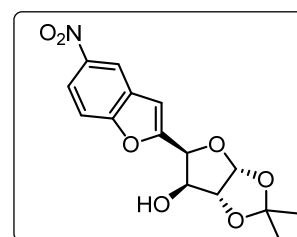
1,2-*O*-Isopropylidene-4-*C*-(5(6'-chlorobenzofuran-2'-yl)- α -D-xylobutanofuranose (**13cb**):

Isolated by column chromatography (pet.ether/AcOEt = 4:1, $R_f = 0.4$). The title compound **13cb** was determined as brown gummy liquid (80%). $[\alpha]_D^{25}$: -28.6 (c 0.9, CHCl_3); IR (CHCl_3): ν 3444, 2926, 1728, 1614, 1447, 1217, 1143, 1074, 751, 694 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.37 (s, 3H), 1.57 (s, 3H), 4.45 (d, $J = 2.5$ Hz, 1H), 4.69 (d, $J = 3.5$ Hz, 1H), 5.37 (d, $J = 2.3$ Hz, 1H), 6.10 (d, $J = 3.5$ Hz, 1H), 6.82 (s, 1H), 7.25 (dd, $J = 2.3, 8.8$ Hz, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 7.54 (d, $J = 2.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.1 (q), 26.8 (q), 76.0 (d), 77.1 (d), 84.7 (d), 104.8 (d), 106.0 (d), 112.3 (s and d, 2C), 120.8 (d), 124.8 (d), 128.7 (s), 129.1 (s), 153.2 (s), 153.4 (s) ppm; ESI-MS m/z : 350.88 (100%, $[\text{M}+\text{K}]^+$); Annl. Calcd for $\text{C}_{15}\text{H}_{15}\text{ClO}_5$: C, 57.98; H, 4.87%; found: C, 57.95; H, 4.88%.



1,2-*O*-Isopropylidene-4-*C*-(5(6'-nitrobenzofuran-2'-yl)- α -D-xylobutanofuranose (**13cc**):

Isolated by column chromatography (pet.ether/AcOEt = 5:1, $R_f = 0.4$). The title compound **13cc** was determined as off white solid (81%). mp: 131–133 °C; $[\alpha]_D^{25}$: -34.8 (c 1.0, CHCl_3); IR (CHCl_3): ν 3445, 2989, 1644, 1523, 1347, 1217, 1071, 753, 683 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.38 (s, 3H), 1.58 (s, 3H), 2.17 (br s, 1H), 4.51 (br s, 1H), 4.70 (d, $J = 3.7$ Hz, 1H), 5.40 (d, $J = 2.4$ Hz, 1H), 6.12 (d, $J = 3.7$ Hz, 1H), 7.00 (s, 1H), 7.54 (d, $J = 9.1$ Hz, 1H), 8.18 (dd, $J = 2.3, 9.1$ Hz, 1H), 8.46 (d, $J = 2.3$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 26.1 (q), 26.8 (q), 75.8 (d), 77.0 (d), 84.8 (d), 104.8 (d), 106.7 (d), 111.5 (d), 112.4 (s), 117.6 (d), 120.3 (d), 128.3 (s), 144.1 (s), 155.5 (s), 157.6 (s) ppm; ESI-MS m/z : 344.08 (54%

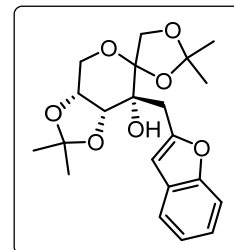


$[M+Na]^+$), 360.05 (100% $[M+K]^+$); Annl. Calcd for $C_{15}H_{15}NO_7$: C, 56.08; H, 4.71; N, 4.36%; found: C, 56.11; H, 4.68; N, 4.37%.

1,2:4,5-Di-*O*-isopropylidene-3-*C*-(benzofuran-2'-yl)methylene)- α -D-psicopyranose (13da):

Isolated by column chromatography (pet.ether/AcOEt = 5:1, R_f = 0.4).

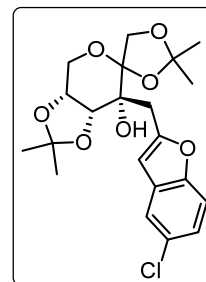
The title compound **13da** was determined as off white solid (85%). mp: 76–78 °C; $[\alpha]_D^{25}$: –94.5 (c 0.5, $CHCl_3$); IR ($CHCl_3$): ν 3554, 2988, 2936, 1600, 1586, 1455, 1076, 995, 849, 752 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.45 (s, 6H), 1.52 (s, 3H), 3.09 (s, 2H), 4.06 (d, J = 9.5 Hz, 2H), 4.09 (d, J = 12.3 Hz, 1H), 4.17 (d, J = 12.3 Hz, 2H), 4.36 (d, J = 5.8 Hz, 1H), 4.40 (d, J = 9.5 Hz, 1H), 6.58 (s, 1H), 7.15–7.22 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0 (q), 25.4 (q), 25.6 (q), 26.0 (q), 34.4 (t), 59.6 (t), 71.2 (d), 71.3 (s), 71.9 (t), 74.3 (d), 105.2 (d), 106.2 (s), 108.6 (s), 110.5 (d), 112.1 (s), 120.1 (d), 122.1 (d), 123.1 (d), 128.6 (s), 154.0 (s), 154.6 (s) ppm; ESI-MS m/z : 413.31 (100%, $[M+Na]^+$), 429.22 (33%, $[M+K]^+$); Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71%; Found: C, 64.69; H, 6.64%.



1,2:4,5-Di-*O*-isopropylidene-3-*C*-(6'-chlorobenzofuran-2'-yl)methylene)- α -D-psicopyranose (13db):

Isolated by column chromatography (pet.ether/AcOEt = 5:1, R_f = 0.4).

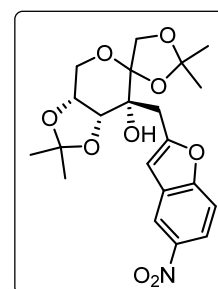
The title compound **13db** was determined as a pale yellow solid (82%). mp: 103–105 °C. $[\alpha]_D^{25}$: –92.0 (c 0.4, $CHCl_3$); IR ($CHCl_3$): ν 3436, 3019, 2993, 2400, 1598, 1448, 1259, 1215, 756 cm^{-1} ; ^1H NMR (200MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.42 (s, 3H), 1.45 (s, 3H), 1.51 (s, 3H), 3.00 (s, 1H), 3.06 (s, 2H), 4.03 (d, J = 9.7 Hz, 1H), 4.12 (d, J = 2.4 Hz, 1H), 4.14–4.18 (m, 1H), 4.19–4.23 (m, 1H), 4.33 (d, J = 5.7 Hz, 1H), 4.38 (d, J = 9.7 Hz, 1H), 6.53 (s, 1H), 7.16 (dd, J = 2.2, 8.7 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1 (q), 25.5 (q), 25.8 (q), 26.3 (q), 34.7 (t), 59.8 (t), 71.2 (d), 71.3 (s), 72.2 (t), 74.4 (d), 105.1 (d), 106.2 (s), 108.9 (s), 111.7 (d), 112.4 (s), 120.0 (d), 123.5 (d), 127.9 (s), 153.3 (s), 156.0 (s) ppm; ESI-MS m/z : 425.81(23%, $[M+H]^+$), 447.22 (100%, $[M+Na]^+$); Anal. Calcd for $C_{21}H_{25}ClO_7$: C, 59.36; H, 5.93%; Found: C, 59.53; H, 5.83%.



1,2:4,5-Di-*O*-isopropylidene-3-*C*-(6'-nitrobenzofuran-2'-yl)methylene)- α -D-psicopyranose (13dc):

Isolated by column chromatography (pet.ether/AcOEt = 4:1, R_f = 0.4).

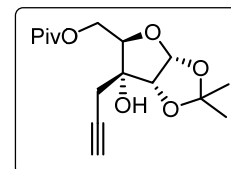
The title compound **13dc** was determined as a off white solid (78%). mp: 110–112 °C; $[\alpha]_D^{25}$: –94.8 (c 0.4, $CHCl_3$); IR ($CHCl_3$): ν 3436, 3019, 2936, 2400, 1592, 1346, 1215, 1071, 756 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.40 (s, 3H), 1.47 (s, 3H), 1.52 (s, 3H), 2.99 (s, 1H), 3.10 (d, J = 1.8 Hz, 2H), 4.04 (d, J = 9.8 Hz, 1H), 4.12 (d, J = 12.3 Hz, 1H), 4.21 (d, J = 10.8 Hz, 1H), 4.35 (d, J = 5.8 Hz, 1H), 6.73 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 8.17 (dd, J = 2.3, 8.8 Hz, 1H), 8.44 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0 (q), 25.3 (q), 25.6 (q), 26.2 (q), 34.5 (t), 59.7 (t), 71.3 (d), 71.6 (s), 72.1 (t), 74.3 (d), 106.1 (d), 106.2 (s), 108.8 (s), 110.8 (d), 112.4



(s), 116.7 (d), 119.2 (d), 129.1 (s), 143.8 (s), 157.6 (s), 158.2 (s) ppm; ESI-MS m/z : 458.30 (48%, $[M+Na]^+$); Anal. Calcd for $C_{21}H_{25}NO_9$: C, 57.93; H, 5.79; N, 3.22%; Found: C, 58.06; H, 5.75; N, 3.32%.

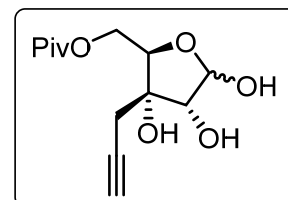
1,2-*O*-Isopropylidene-3-*C*-prop-2-ynyl-5-*O*-pivaloyl- α -D-ribofuranose (16):

At 0 °C a solution of compound **15a** (9.9 g, 0.043 mol), TEA (12.1 ml, 0.08 mol) and catalytic DMAP in dry CH_2Cl_2 (150 ml) was treated with pivaloyl chloride (5.35 ml, 65.0 mmol) stirred at rt for 3 h. The reaction mixture was cooled to 0 °C and quenched with water and extracted with CH_2Cl_2 . Combined organic phase washed with sat. $NaHCO_3$ and water, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (pet.ether/AcOEt = 4:1, R_f = 0.4) gave compound **16** (86% yield) as a pale yellow syrup. $[\alpha]_D^{25}$: +19.9 (c 3.0, $CHCl_3$); IR ($CHCl_3$): ν 3488, 3278, 2979, 2123, 1958, 1731.6, 1481, 1284, 1166, 1006, 874, 757, 642 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.26 (s, 3H), 1.46 (s, 3H), 2.03 (t, J = 2.5 Hz, 1H), 2.24 (dd, J = 17.2, 2.5 Hz, 1H), 2.42 (dd, J = 17.2, 2.5 Hz, 1H), 3.05 (br s, 1H), 3.95 (dd, J = 3.5, 11.0 Hz, 1H), 4.04 (dd, J = 4.5, 7.2 Hz, 1H), 4.19 (dd, J = 3.3, 12.1 Hz, 1H), 4.37 (d, J = 3.8 Hz, 1H), 5.71 (d, J = 3.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4 (t), 26.2 (q), 26.3 (q), 26.8 (q, 3C), 38.4 (s), 61.3 (t), 71.5 (s), 78.0 (s), 78.9 (d, 2C), 81.3 (d), 103.4 (d), 122.2 (s), 177.8 (s) ppm; ESI-MS m/z : 335.14 (11%, $[M+Na]^+$), 351.11 (100%, $[M+K]^+$); Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74%; found C, 61.54; H, 7.73%.



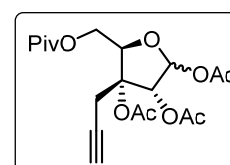
3-*C*-(2-Propynyl)-5-*O*-pivaloyl- α/β -D-ribofuranose (17):

Compound **16** (11.6 g, 0.037 mol) in 60% acetic acid (100 mL) was heated under reflux temperature for 2 h. The maximum acetic acid was removed by using reduced pressure, then the reaction mixture was neutralized by slow addition of solid K_2CO_3 and extracted in ethyl acetate. Combined ethyl acetate extracts were dried (Na_2SO_4) and filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (CH_2Cl_2/CH_3OH = 9:1, R_f = 0.6) gave a mixture of triol **17** (91% yield) as a colorless syrup. IR ($CHCl_3$): ν 3434.0, 3308.9, 2974.0, 2121.8, 1957.6, 1728.6, 1481.3, 1285.2, 1158.6, 859.85, 758.1, 666.7 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (s, 9H), 2.15 (t, J = 2.6 Hz, 1H), 2.51 (dd, J = 2.8, 17.2 Hz, 1H), 2.68 (dd, J = 2.6, 17.2 Hz, 1H), 3.24 (br s, 2H), 3.42 (br s, 1H), 4.05–4.23 (m, 2H), 4.31–4.42 (m, 2H), 5.07 (d, J = 6.8 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.4 (t), 27.1 (q, 3C), 38.7 (s), 62.8 (t), 72.0 (d), 74.2 (d), 77.6 (s), 78.7 (s), 82.3 (d), 96.0 (d), 178.2 (s) ppm; ESI-MS: m/z 295.1222 (31 % $M+Na$), 311.0832 (100 % $[M + K]^+$). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40%; found C, 57.28; H, 7.34%.



1,2,3-Tri-*O*-acetyl-3-*C*-(2-propynyl)-5-*O*-pivaloyl- α/β -D-ribofuranose (18):

The triol **17** was dissolved in dry CH_2Cl_2 (150 mL). TEA (8 mL) and catalytic DMAP was added and the mixture was cooled to 0 °C. To this, acetic anhydride (6.8 mL, 0.072 mol) was added and the contents were stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was neutralized slow addition of sat. $NaHCO_3$ and extracted with CH_2Cl_2 , dried over Na_2SO_4 , and filtered and concentrated under reduced



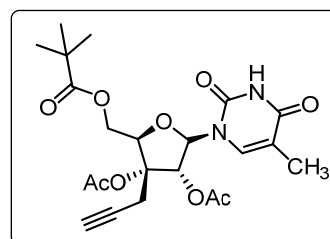
pressure. Purification of the residue by silica gel column chromatography (pet.ether/AcOEt = 4:1, R_f = 0.3) gave a mixture of triacetates **18** (88% yield) as a colorless syrup. IR (CHCl₃): ν 3434, 3308, 2974, 2121, 1957, 1728, 1481, 1285, 1158, 859, 758, 666 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.07 (s, 9H), 1.91 (s, 3H), 1.91–1.92 (alkyne protone has been merged, 1H), 1.92 (s, 3H), 1.95 (s, 3H), 1.91 (t, J = 2.6 Hz, 1H), 2.88 (dd, J = 2.5, 17.7 Hz, 1H), 3.05 (dd, J = 2.5, 17.2 Hz, 1H), 4.03–4.10 (m, 1H), 4.28 (m, 2H), 5.36 (d, J = 2.8 Hz, 1H), 5.9 (d, J = 2.8 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 20.1 (q), 20.4 (q), 20.6 (q), 21.1 (t), 26.6 (q, 3C), 38.2 (s), 61.8 (t), 71.5 (s), 76.8 (d), 77.7 (d), 82.2 (d), 82.3 (s), 97.3 (d), 168.5 (s), 168.7 (s), 168.9 (s), 177.1 (s) ppm; ESI-MS m/z : 421.43 (16%, [M+Na]⁺), 437.14 (100%, [M+K]⁺); Anal. Calcd for C₁₉H₂₆O₉: C, 57.28; H, 6.58%; found: C, 57.26; H, 6.59%.

General procedure for *N*-glycosidation

A solution of acetate **18** (2.51 mmol), nucleobase (5.02 mmol), and *N,O*-bis(trimethylsilyl)acetamide (3.06 mL, 12.54 mmol) in anhydrous CH₃CN (15 mL) was heated to reflux for 15 min. The reaction mixture was cooled to 0 °C and TMSOTf (932 μ L, 5.0 mmol) was added. The reaction mixture was stirred at 50 °C for 2 h, quenched with cold aq. NaHCO₃ and extracted with EtOAc. The combined organic layer was washed with water, dried over Na₂SO₄, and filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography.

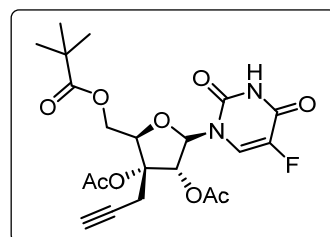
1-[2,3-Di-*O*-acetyl-3-*C*-propynyl]-5-*O*-pivaloyl- β -D-ribo-pentofuranosyl]thymidine (**15e**):

Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.3). The title compound **15e** was determined as a colorless syrup (81%). $[\alpha]_D^{25}$: -7.26 (c 2.5, CHCl₃); IR (CHCl₃): ν 3276, 3023, 2976, 1697, 1464, 1371, 1279, 1060, 904, 756, 666 cm⁻¹; ¹H NMR (200MHz, CDCl₃): δ 1.24 (s, 9H), 1.90 (s, 3H), 2.08 (t, J = 2.3 Hz, 1H), 2.09 (s, 3H), 2.17 (s, 3H), 3.02 (dd, J = 2.5, 17.3 Hz, 1H), 3.23 (dd, J = 2.5, 17.3 Hz, 1H), 4.39 (dd, J = 3.3, 12.8 Hz, 1H), 4.49 (dd, J = 4.8, 12.8 Hz, 1H), 4.64 (t, J = 4.3 Hz, 1H), 5.43 (d, J = 7.8 Hz, 1H), 6.17 (d, J = 7.8 Hz, 1H), 7.22 (s, 1H), 9.33 (br s 1H); ¹³C NMR (50 MHz, CDCl₃): δ 12.5 (q), 20.7 (q), 21.6 (q), 22.2 (t), 27.2 (q, 3C), 38.8 (s), 62.5 (t), 72.1 (s), 75.5 (d), 81.1 (2C, d), 82.5 (s), 83.9 (d), 112.0 (s), 134.3 (d), 150.7 (s), 163.4 (s), 169.9 (s), 170.1 (s), 177.7 (s) ppm; ESI-MS m/z : 486.83 (100%, [M+Na]⁺), 502.78 (86%, [M+K]⁺); Anal. Calcd for C₂₂H₂₉N₂O₉: C, 56.89; H, 6.08; N, 6.03%. found: C, 56.89; H, 6.06; N, 6.05%.



1-[2,3-Di-*O*-acetyl-3-*C*-propynyl]-5-*O*-pivaloyl- β -D-ribo-pentofuranosyl]5-fluorouridine (**15f**):

Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.3). The title compound **15f** was determined as a colorless syrup (82%). $[\alpha]_D^{25}$: +11.4 (c 0.8, CHCl₃); IR (CHCl₃): ν 3478, 3025, 2977, 2365, 1732, 1694, 1602, 1527, 1455, 1346, 1216, 1068, 960, 753, 666 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.26 (s, 9H), 2.08 (t, J = 2.5 Hz, 1H), 2.11 (s, 3H), 2.19 (s, 3H), 2.97 (dd, J = 2.5, 17.3 Hz, 1H), 3.25 (dd, J = 2.6, 17.2 Hz, 1H), 4.39 (dd, J = 3.3, 13.0 Hz, 1H), 4.47 (dd, J = 3.8, 13.0 Hz, 1H), 4.73 (t, J =



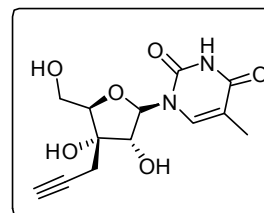
3.8 Hz, 1H), 5.40 (d, $J = 7.8$ Hz, 1H), 6.19 (dd, $J = 1.5, 7.8$ Hz, 1H), 7.59 (d, $J = 5.8$ Hz, 1H), 9.22 (br s, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 20.7 (q), 21.6 (q), 22.0 (t), 27.2 (3C, q), 38.8 (s), 62.8 (t), 75.9 (d), 81.5 (d), 82.8 (d), 84.3 (d), 122.8 (d), 123.1 (d), 139.7 (s), 142.1 (s), 149.2 (s), 156.4 (d), 170.0 (s), 170.3 (s), 177.7 (s) ppm; ESI-MS m/z : 491.16 (100%, $[\text{M}+\text{Na}]^+$), 507.22 (97%, $[\text{M}+\text{K}]^+$); Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{FN}_2\text{O}_9$: C, 53.84; H, 5.38; N, 5.98%; found: C, 53.86; H, 5.35; N, 5.97%.

General procedure for ester hydrolysis

A solution of **15e–15f** (1.0 mmol) and catalytic NaOMe in methanol (5 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated under reduced pressure and the crude was purified by silica gel column chromatography.

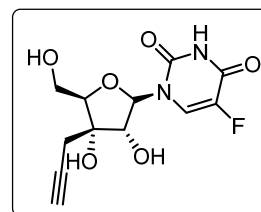
1-[(3-*C*-Propynyl)- β -D-ribo-pentofuranosyl]thymidine (**15g**):

Isolated by column chromatography (5% MeOH in CH_2Cl_2 , $R_f = 0.3$). The title compound **15g** was determined as a white sticky solid (93%). $[\alpha]_D^{25}$: -6.1 (c 0.8, CH_3OH); IR (neat): ν 3439, 3276, 3023, 2976, 1697, 1464, 1371, 1279, 1060, 904, 756, 666 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.62 (d, $J = 1.0$ Hz, 3H), 1.91 (t, $J = 2.6$ Hz, 1H), 2.40 (dd, $J = 2.5, 17.1$ Hz, 1H), 2.50 (dd, $J = 2.6, 17.1$ Hz, 1H), 3.58 (dd, $J = 2.7, 12.3$ Hz, 1H), 3.71 (dd, $J = 1.9, 12.3$ Hz, 1H), 3.86 (t, $J = 2.2$ Hz, 1H), 3.90 (d, $J = 7.8$ Hz, 1H), 5.67 (d, $J = 7.8$ Hz, 1H), 7.66 (d, $J = 1.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.5 (q), 25.1 (t), 62.0 (t), 77.9 (d, 2C), 78.8 (s, 2C), 88.1 (d), 88.5 (d), 111.8 (s), 140.0 (d), 153.1 (s), 166.3 (s) ppm; ESI-MS: m/z 297.28 (83%, $[\text{M}+\text{H}]^+$), 319.30 (100%, $[\text{M}+\text{Na}]^+$); Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_6$: C, 52.70; H, 5.44; N, 9.46%; found: C, 52.68; H, 5.42; N, 9.95%.



1-[3-*C*-Propynyl-D-ribo-pentofuranosyl]5-fluorouridine (**15h**):

Isolated by column chromatography (5% MeOH in CH_2Cl_2 , $R_f = 0.3$). The title compound **15h** was determined as a white sticky solid (94%). $[\alpha]_D^{25}$: $+0.7$ (c 2.3, CH_3OH); IR (neat): ν 3447, 3275, 3025, 2977, 2365, 1732, 1694, 1602, 1527, 1455, 1346, 1216, 1068, 960, 753, 666 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.95 (t, $J = 2.5$ Hz, 1H), 2.49 (dd, $J = 2.5, 17.1$ Hz, 1H), 2.56 (dd, $J = 2.5, 17.1$ Hz, 1H), 3.67 (dd, $J = 1.4, 12.3$ Hz, 1H), 3.79 (dd, $J = 1.1, 12.3$ Hz, 1H), 3.81 (d, $J = 7.4$ Hz, 1H), 3.96 (t, $J = 2.0$ Hz, 1H), 5.82 (d, $J = 1.1, 7.4$ Hz, 1H), 8.21 (d, $J = 6.3$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 23.7 (t), 60.5 (t), 76.7 (d), 77.3 (2C, s), 86.5 (2C, d), 87.7 (d), 125.5 (d), 149.9 (s), 157.7 (s), 157.9 (s) ppm; ESI-MS m/z : 301.26 (83%, $[\text{M}+\text{H}]^+$), 323.28 (100%, $[\text{M}+\text{Na}]^+$); Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_6$: C, 48.00; H, 4.36; N, 9.33%; found: C, 48.03; H, 4.33; N, 9.32%.

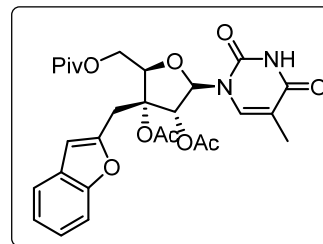


4.3. General procedure for Sonogashira coupling

To a solution of alkyne (1 mmol), iodobenzene (1.5 mmol) in Et_3N (4 mL) and DMF (2 mL), PPh_3 was added followed by $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.1 mmol), and the reaction mixture was flushed with argon for 30 min. CuI (3 mmol) was added and flushed with argon for 10 min and stirred at rt for 12 h. The reaction mixture was partitioned between ethyl acetate, water and the organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography.

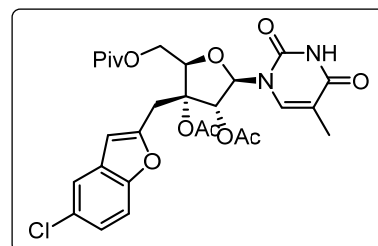
1-[2,3-Di-*O*-acetyl-3-*C*-(benzofuran-2-yl)methylene))-5-*O*-pivaloyl-β-*D*-ribo-pentofuranosyl]thayamidine (13ea):

Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.3). The title compound **13ea** was determined as a brown gummy liquid (87%). $[\alpha]_D^{25}$: –47.0 (c 1.2, CHCl₃); IR (CHCl₃): ν 3199, 3021, 2975, 1701, 1602, 1586, 1455, 1371, 1216, 1058, 960, 753, 666 cm^{–1}; ¹H NMR (200 MHz, CDCl₃): δ 1.34 (s, 9H), 1.53 (s, 3H), 1.69 (s, 2H), 1.94 (s, 3H), 2.23 (s, 3H), 3.15 (d, J = 15.3 Hz, 1H), 4.13 (d, J = 15.3 Hz, 1H), 4.44 (dd, J = 3.4, 13.1 Hz, 1H), 4.61 (dd, J = 3.7, 13.1 Hz, 1H), 4.96 (t, J = 3.4 Hz, 1H), 5.53 (d, J = 8.2 Hz, 1H), 6.16 (d, J = 8.2 Hz, 1H), 6.43 (s, 1H), 7.20 (dt, J = 1.0, 7.6 Hz, 1H), 7.26 (dt, J = 1.5, 7.6 Hz, 1H), 7.31 (d, J = 1.2 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 8.66 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.5 (q), 20.0 (q), 22.1 (q), 27.3 (q, 3C), 29.7 (t), 38.9 (s), 62.9 (t), 75.5 (d), 81.4 (d), 83.6 (d), 84.1 (s), 105.8 (d), 110.8 (d), 111.7 (s), 120.6 (d), 123.0 (d), 124.3 (d), 128.0 (s), 134.2 (d), 150.8 (s), 151.5 (s), 154.6 (s), 163.2 (s), 170.1 (s), 170.9 (s), 177.0 (s) ppm; ESI-MS m/z : 557.43 (76%, [M+H]⁺), 579.42 (100%, [M+Na]⁺); Anal. calcd for C₂₈H₃₂N₂O₁₀: C, 60.42; H, 5.80; N, 5.03%; found: C, 60.45; H, 5.81; N, 5.06%.



1-[2,3-Di-*O*-acetyl-3-*C*-(6'-chlorobenzofuran-2'-yl)methylene))-5-*O*-pivaloyl-β-*D*-ribo-pentofuranosyl]thayamidine (13eb):

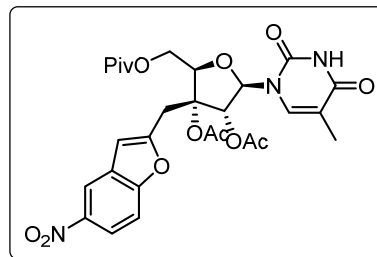
Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.3). The title compound **13eb** was determined as a brown gummy liquid (68%). $[\alpha]_D^{25}$: –55.3 (c 1.6, CHCl₃); IR (CHCl₃): ν 3445, 3025, 2957, 1708, 1604, 1449, 1371, 1216, 1062, 960, 804, 756, 666 cm^{–1}; ¹H NMR (200 MHz, CDCl₃): δ 1.34 (s, 9H), 1.57 (s, 3H), 1.94 (s, 3H), 2.22 (s, 3H), 3.15 (d, J = 15.3 Hz, 1H), 4.12 (d, J = 15.3 Hz, 1H), 4.44 (dd, J = 3.3, 13.0 Hz, 1H), 4.61 (dd, J = 3.4, 13.0 Hz, 1H), 4.95 (t, J = 3.3 Hz, 1H), 5.53 (d, J = 8.2 Hz, 1H), 6.16 (d, J = 8.2 Hz, 1H), 6.39 (s, 1H), 7.22 (dd, J = 2.0, 8.7 Hz, 1H), 7.28 (s, 1H), 7.31 (d, J = 1.3 Hz, 1H), 7.48 (d, J = 1.9 Hz, 1H), 9.24 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.5 (q), 20.0 (q), 22.0 (q), 27.3 (q, 3C), 29.7 (t), 38.9 (s), 62.8 (t), 75.5 (d), 81.3 (d), 83.6 (d), 84.0 (s), 105.4 (d), 111.7 (d), 111.8 (s), 120.2 (d), 124.5 (d), 128.6 (s), 129.3 (s), 134.1 (d), 150.8 (s), 153.2 (2C, s), 163.4 (s), 170.0 (s), 170.8 (s), 177.7 (s) ppm; ESI-MS m/z : 592.21 (27%, [M+H]⁺), 613.53 (100%, [M+Na]⁺); Anal. calcd for C₂₈H₃₁ClN₂O₁₀: C, 56.90; H, 5.29; N, 4.74%; found: C, 56.90; H, 5.27; N, 4.76%.



1-[2,3-Di-*O*-acetyl-3-*C*-(6'-nitrobenzofuran-2'-yl)methylene))-5-*O*-pivaloyl-β-*D*-ribo-pentofuranosyl]thayamidine (13ec):

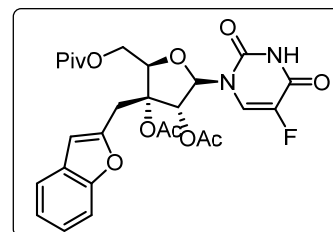
Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.3). The title compound **13ec** was determined as a brown gummy liquid (71%). $[\alpha]_D^{25}$: –62.4 (c 1.6, CHCl₃); IR (CHCl₃): ν 3478, 3025, 2977, 1694, 1602, 1527, 1455, 1346, 1216, 1068, 960, 753, 666 cm^{–1}; ¹H NMR (200 MHz, CDCl₃): δ 1.34 (s, 9H), 1.60 (s, 3H), 1.95 (d, J = 1.0 Hz, 3H), 2.25 (s, 3H), 3.24 (d, J = 15.3 Hz, 1H), 4.19 (d, J = 15.3 Hz, 1H), 4.47 (dd, J = 3.3, 13.0 Hz, 1H), 4.62 (dd, J = 3.4, 13.0 Hz, 1H), 4.95 (t, J = 3.2 Hz, 1H), 5.57 (d, J = 8.1 Hz, 1H), 6.16 (d, J = 8.1

Hz, 1H), 6.61 (s, 1H), 7.31 (d, $J = 1.1$ Hz, 1H), 7.48 (d, $J = 9.0$ Hz, 1H), 8.23 (dd, $J = 2.4, 9.0$ Hz, 1H), 8.48 (d, $J = 2.4$ Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.5(q), 20.1 (q), 22.0 (q), 27.3 (3C, q), 29.8 (t), 38.9 (s), 62.8 (t), 75.5 (d), 81.3 (d), 83.8 (d), 83.9 (s), 106.5 (d), 111.1 (d), 111.8 (s), 117.2 (d), 120.3 (d), 128.3 (s), 134.1(d), 144.3 (s), 150.7 (s), 155.4 (s), 157.4 (s), 163.4 (s), 169.9 (s), 170.7 (s), 177.6 (s) ppm; ESI-MS m/z : 602.49 (100%, $[\text{M}+\text{H}]^+$), 624.48 (97%, $[\text{M}+\text{Na}]^+$); Anal calcd for $\text{C}_{28}\text{H}_{31}\text{N}_3\text{O}_{12}$: C, 55.90; H, 5.19; N, 6.99%; found : C, 55.92; H, 5.18; N, 7.02%.



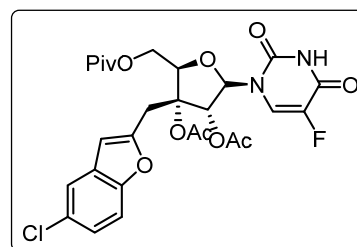
1-[2,3-Di-O-acetyl-3-C-(benzofuran-2-yl)methylene)-5-O-pivaloyl- β -D-ribo-pentofuranosyl]5-fluorouridine (13fa):

Isolated by column chromatography (pet.ether/AcOEt = 7:3, $R_f = 0.3$). The title compound **13fa** was determined as a brown gummy liquid (72%). $[\alpha]_D^{25}$: -24.4 (c 2.1, CHCl_3); IR (CHCl_3): ν 3446, 3034, 2925, 1719, 1642, 1454, 1369, 1215, 1142, 751, 666 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.35 (s, 9H), 1.51 (s, 3H), 2.24 (s, 3H), 3.10 (d, $J = 15.2$ Hz, 1H), 4.13 (d, $J = 15.2$ Hz, 1H), 4.44 (dd, $J = 2.9, 13.3$ Hz, 1H), 4.60 (dd, $J = 2.5, 13.3$ Hz, 1H), 5.03 (t, $J = 2.6$ Hz, 1H), 5.49 (d, $J = 8.0$ Hz, 1H), 6.15 (dd, $J = 1.8, 8.0$ Hz, 1H), 6.42 (s, 1H), 7.23 (t, $J = 2.1$ Hz, 1H), 7.33–7.35 (m, 2H), 7.50 (dd, $J = 2.1, 5.8$ Hz, 1H), 7.68 (d, $J = 5.8$ Hz, 1H), 9.40 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.9 (q), 22.1 (q), 27.2 (q, 3C), 29.4 (t), 38.8 (s), 63.2 (t), 76.0 (d), 81.7 (d), 84.3 (d), 105.7 (d), 110.8 (d), 120.6 (d), 123.0 (d), 124.3 (2C, d), 128.0 (s), 149.3 (s), 151.2 (3C, s), 154.8 (s), 156.8 (d), 170.3 (s), 170.9 (s), 177.7 (s) ppm; ESI-MS: m/z 561.29 (12.5%, $[\text{M}+\text{H}]^+$), 583.26 (100%, $[\text{M}+\text{Na}]^+$), 599.24 (50%, $[\text{M}+\text{K}]^+$); Anal calcd for $\text{C}_{27}\text{H}_{29}\text{FN}_2\text{O}_{10}$: C, 57.85; H, 5.21; N, 5.00%; found C, 57.83; H, 5.19; N, 5.02%.



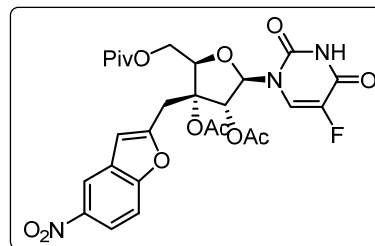
1-[2,3-Di-O-acetyl-3-C-(6'-chlorobenzofuran-2'-yl)methylene)-5-O-pivaloyl- β -D-ribo-pentofuranosyl]5-fluorouridine (13fb):

Isolated by column chromatography (pet.ether/AcOEt = 7:3, $R_f = 0.3$). The title compound **13fb** was determined as a brown gummy liquid (73%). $[\alpha]_D^{25}$: -33.1 (c 1.2, CHCl_3); IR (CHCl_3): ν 3212, 3023, 2976, 1728, 1600, 1449, 1371, 1214, 1061, 963, 757, 666 cm^{-1} ; ^1H NMR (200MHz, CDCl_3): δ 1.35 (s, 9H), 1.56 (s, 3H), 2.23 (s, 3H), 3.09 (d, $J = 15.3$ Hz, 1H), 4.13 (d, $J = 15.3$ Hz, 1H), 4.44 (dd, $J = 2.9, 13.3$ Hz, 1H), 4.59 (dd, $J = 2.5, 13.3$ Hz, 1H), 5.02 (t, $J = 2.5$ Hz, 1H), 5.49 (d, $J = 8.1$ Hz, 1H), 6.15 (dd, $J = 1.8, 8.1$ Hz, 1H), 6.38 (s, 1H), 7.22 (dd, $J = 1.9, 8.7$ Hz, 1H), 7.28 (s, 1H), 7.48 (d, $J = 1.8$, Hz, 1H), 7.67 (d, $J = 5.8$ Hz, 1H), 9.47 (br s, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 20.0 (q), 22.1 (q), 27.2 (q, 3C), 29.5 (t), 38.8 (s), 63.1 (t), 75.9 (d), 81.6 (d), 84.2 (d and s, 2C), 105.4 (d), 111.7 (d), 120.3 (d), 124.5 (d), 128.6 (2C, s), 129.3 (d), 149.3 (s), 153.0 (3C, s), 153.1 (s), 170.2 (s), 170.8 (s), 177.6 (s) ppm; ESI-MS m/z : 595.16 (100%, $[\text{M}+\text{H}]^+$), 617.14 (97%, $[\text{M}+\text{Na}]^+$); Anal calcd for $\text{C}_{27}\text{H}_{28}\text{ClFN}_2\text{O}_{10}$: C, 54.51; H, 4.74; N, 4.71%; found: C, 54.53; H, 4.74; N, 4.74%.



1-[2,3-Di-O-acetyl-3-C-(6'-nitrobenzofuran-2'-yl)methylene)-5-O-pivaloyl-β-D-ribo-pentofuranosyl]5-fluorouridine (13fc):

Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.3). The title compound **13fc** was determined as a brown gummy liquid (69%). $[\alpha]_D^{25}$: -37.3 (c 0.9, CHCl₃); IR (CHCl₃): ν 3216, 3098, 2976, 1714, 1600, 1526, 1346, 1215, 1069, 963, 753, 666 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.36 (s, 9H), 1.59 (s, 3H), 2.25 (s, 3H), 3.15 (d, J = 15.3 Hz, 1H), 4.18 (d, J = 15.3 Hz, 1H), 4.46 (dd, J = 2.8, 13.3 Hz, 1H), 4.61 (dd, J = 2.1, 13.3 Hz, 1H), 5.02 (s, 1H), 5.51 (d, J = 8.0 Hz, 1H), 6.15 (dd, J = 1.1, 8.0 Hz, 1H), 6.60 (s, 1H), 7.48 (dd, J = 9.0 Hz, 1H), 7.66 (d, J = 5.8, Hz, 1H), 8.23 (dd, J = 2.0, 9.0 Hz, 1H), 8.47 (d, J = 2.0 Hz, 1H), 9.47 (br s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 20.0 (q), 22.1 (q), 27.2 (3C, q), 29.7 (t), 38.9 (s), 63.1 (t), 76.1 (d), 81.7 (d), 84.1 (s), 84.4 (d), 106.6 (d), 111.1 (d), 117.2 (d), 120.3 (2C, d), 128.4 (s), 144.3 (2C, s), 149.2 (s), 155.2 (2C, s), 157.4 (s), 170.0 (s), 170.7 (s), 177.6 (s) ppm; ESI-MS m/z : 627.71 (100%, $[M+Na]^+ - 1$), 643.67 (97%, $[M+K]^+ - 1$); Anal calcd for C₂₇H₂₈ClF₃N₃O₁₂: C, 53.56; H, 4.66; N, 6.94%; found: C, 53.53; H, 4.68; N, 6.94%.

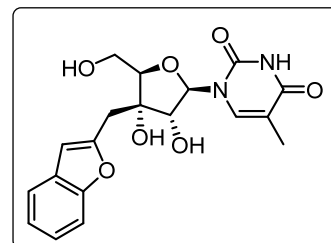


General procedure for global deprotection of esters

A solution of **13ea-13fc** (1.0 mmol) and catalytic NaOMe in methanol (5 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated under reduced pressure and the crude was purified by silica gel column chromatography.

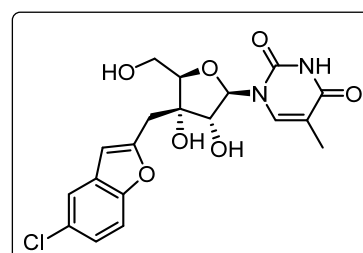
1-[3-C-(Benzofuran-2-yl)methylene]-β-D-ribo-pentofuranosyl]thayamidine (19ea):

Isolated by column chromatography (5% MeOH in CH₂Cl₂, R_f = 0.3). The title compound **19ea** was determined as a off white solid (82%). mp: 240–242 °C; $[\alpha]_D^{25}$: -18.0 (c 0.3, CH₃OH); IR (neat): ν 3444, 3078, 2922, 2851, 1659, 1542, 1456, 1021, 704 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.92 (s, 3H), 3.32 (s, 2H), 3.89 (dd, J = 2.5, 12.0 Hz, 1H), 4.01 (dd, J = 2.5, 12.0 Hz, 1H), 4.17 (d, J = 2.0 Hz, 1H), 4.35 (d, J = 7.8 Hz, 1H), 6.03 (d, J = 7.8 Hz, 1H), 6.66 (s, 1H), 7.15–7.23 (m, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 6.5 Hz, 1H), 8.08 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 11.1 (q), 31.8 (t), 60.5 (t), 76.2 (d), 77.6 (s), 86.2 (d), 87.3 (d), 104.5 (d), 109.9 (d), 110.1 (s), 119.6 (d), 121.8 (d), 122.7 (d), 128.2 (s), 137.4 (d), 151.2 (s), 153.8 (s), 154.1(s), 164.5 (s) ppm; ESI-MS: 411.43(100%, $[M+Na]^+$); Anal calcd for C₁₉H₂₀N₂O₇: C, 58.76; H, 5.19; N, 7.21%; found: C, 58.73; H, 5.21; N, 7.18%.



1-[3-C-(6'-Chlorobenzofuran-2'-yl)methylene]-β-D-ribo-pentofuranosyl]thayamidine (19eb):

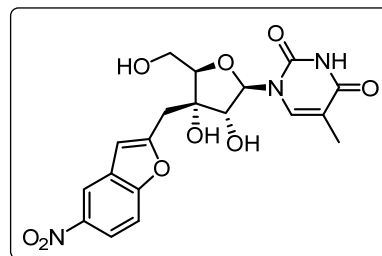
Isolated by column chromatography (5% MeOH in CH₂Cl₂, R_f = 0.3). The title compound **19eb** was determined as a off white sticky solid (82%). $[\alpha]_D^{25}$: -9.6 (c 0.5, CH₃OH); IR (neat): ν 3445, 3046, 2925, 2852, 2090, 1645, 1456, 1380, 1016, 658 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.92 (s, 3H), 3.31 (bs, 2H), 3.89 (dd, J = 2.4, 12.0 Hz, 1H), 3.99 (dd, J =



2.5, 12.0 Hz, 1H), 4.18 (t, $J = 1.9$ Hz, 1H), 4.37 (d, $J = 7.6$ Hz, 1H), 5.97 (d, $J = 7.6$ Hz, 1H), 6.63 (s, 1H), 7.19 (dd, $J = 2.2, 8.7$ Hz, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.48 (d, $J = 2.1$ Hz, 1H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.4 (q), 32.0 (t), 60.6 (t), 76.3 (d), 77.7 (s), 86.2 (d), 87.7 (d), 104.4 (d), 110.4 (d), 111.2 (s), 119.4 (d), 123.0 (d), 127.6 (s), 129.7 (s), 137.6 (d), 151.3 (s), 152.6 (s), 155.8 (s), 164.6 (s) ppm; ESI-MS: 445.23 (100%, $[\text{M}+\text{Na}]^+$); Anal calcd for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_7$: C, 53.97; H, 4.53; N, 6.63%; found: C, 53.94; H, 4.56; N, 6.62%.

1-[3-C-(6'-Nitrobenzofuran-2'-yl)methylene]- β -D-ribo-pentofuranosyl]thymidine (19ec).

Isolated by column chromatography (5% MeOH in CH_2Cl_2 , $R_f = 0.3$). The title compound **19ec** was determined as a off white sticky solid (79%). $[\alpha]_D^{25}$: -26.0 (c 0.1, CH_3OH); IR (neat): ν 3444, 3082, 2927, 2852, 2077, 1668, 1521, 1472, 1344, 1265, 1018, 753, 579 cm^{-1} ; ^1H NMR (500 MHz, $\text{CDCl}_3+\text{MeOH}(\text{D}_4)$): δ 1.91 (s, 3H), 3.37 (d, $J = 3.9$ Hz, 2H), 3.88 (dd, $J = 2.7, 12.2$ Hz, 1H), 3.97 (dd, $J = 1.7, 12.7$

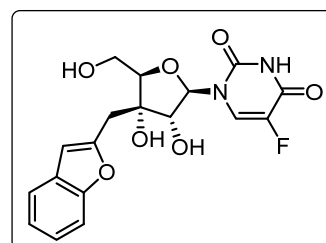


Hz, 1H), 4.15 (t, $J = 2.2$ Hz, 1H), 4.34 (d, $J = 7.8$ Hz, 1H), 6.06 (d, $J = 7.6$ Hz, 1H), 6.89 (s, 1H), 7.59 (d, $J = 9.1$ Hz, 1H), 8.11 (d, $J = 1.0$ Hz, 1H), 8.18 (dd, $J = 2.5, 9.1$ Hz, 1H), 8.48 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (125 MHz, $\text{CDCl}_3+\text{MeOH}(\text{D}_4)$): δ 10.5 (q), 31.6 (t), 60.2 (t), 75.9 (d), 77.2(s), 85.9 (d), 86.6 (d), 105.0 (d), 109.8 (s), 110.1 (d), 115.7 (d), 118.3 (d), 128.6 (s), 137.0 (d), 143.3 (s), 151.1 (s), 156.8 (s), 158.0 (s), 164.2 (s) ppm; ESI-MS: 456.68 (100%, $[\text{M}+\text{Na}]^+$); Anal calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_9$: C, 52.66; H, 4.42; N, 9.70%; found: C, 52.69; H, 4.40; N, 9.73%.

1-[3-C-(Benzofuran-2'-yl)methylene]- β -D-ribo-pentofuranosyl]5-fluorouridine (19fa):

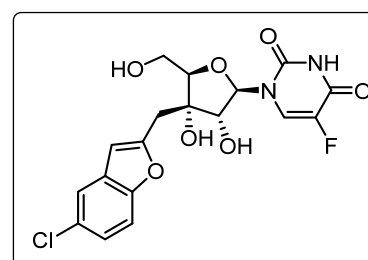
Isolated by column chromatography (5% MeOH in CH_2Cl_2 , $R_f = 0.4$). The title compound **19fa** was determined as a off white solid (85%). mp: 177–179 $^{\circ}\text{C}$ $[\alpha]_D^{25}$: -15.8 (c 0.8, CH_3OH); IR

(neat): ν 3419, 3084, 2924, 2852, 1712, 1642, 1455, 1253, 1125, 1068, 948, 751 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 3.31 (s, 2H), 3.90 (dd, $J = 2.5, 12.1$ Hz, 1H), 4.03 (dd, $J = 1.6, 12.1$ Hz, 1H), 4.22 (t, $J = 1.5$ Hz, 1H), 4.31 (d, $J = 7.3$ Hz, 1H), 6.03 (dd, $J = 1.8, 7.4$ Hz, 1H), 6.66 (s, 1H), 7.18–7.24 (m, 2H), 7.39–7.44 (m, 1H), 7.49–7.55 (m, 1H), 8.42 (d, $J = 6.7$ Hz, 1H); ^{13}C NMR (125 MHz, $\text{CDCl}_3 + \text{MeOH}(\text{D}_4)$): δ 32.1 (t), 60.7 (t), 77.0(d), 78.1 (s), 86.7 (d), 87.9 (d), 104.9 (d), 110.3 (d), 120.1 (2C, d), 122.3 (d), 123.2 (d), 125.5 (d, $^2J_{\text{C,F}} = 34.5$ Hz), 128.3 (s), 140.4 (s, d, $^3J_{\text{C,F}} = 234.3$ Hz), 149.9 (s), 153.8 (2C, s), 154.4(s) ppm; ESI-MS: 415.30 (100%, $[\text{M}+\text{Na}]^+$); Anal calcd for $\text{C}_{18}\text{H}_{17}\text{FN}_2\text{O}_7$: C, 55.10; H, 4.37; N, 7.14%; found C, 52.06; H, 4.35; N, 7.17%.



1-[3-C-(6'-Chlorobenzofuran-2'-yl)methylene]- β -D-ribo-pentofuranosyl]5-fluorouridine (19fb):

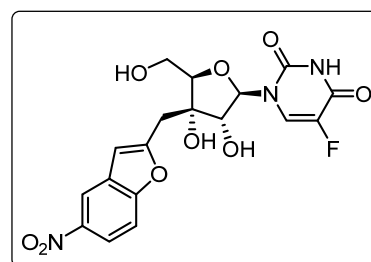
Isolated by column chromatography (5% MeOH in CH_2Cl_2 , $R_f = 0.3$). The title compound **19fb** was determined as a off white sticky solid (77%). $[\alpha]_D^{25}$: -7.2 (c 0.1, CH_3OH); IR (neat): ν 3419, 3096, 2976, 1728, 1600, 1449, 1371, 1140, 1061, 963, 757, 666 cm^{-1} ; ^1H NMR (500 MHz, $\text{CDCl}_3+\text{MeOH}(\text{D}_4)$): δ 3.30 (s, Hz, 2H), 3.88 (dd, $J = 2.4,$



12.2 Hz, 1H), 4.00 (dd, $J = 1.5$, 12.2 Hz, 1H), 4.16 (br s, 1H), 4.27 (d, $J = 7.5$ Hz, 1H), 4.5 (br s, 1H), 6.09 (dd, $J = 1.2$, 7.6 Hz, 1H), 6.65 (s, 1H), 7.18 (dd, $J = 2.1$, 8.6 Hz, 1H), 7.36 (d, $J = 8.6$ Hz, 1H), 7.48 (d, $J = 2.1$ Hz, 1H), 8.55 (d, $J = 6.7$ Hz, 1H); ^{13}C NMR (125 MHz, $\text{CDCl}_3 + \text{MeOH}(\text{D}_4)$): δ 31.6 (t), 60.2 (t), 76.7 (d), 77.7 (s), 86.2 (d), 86.9 (d), 104.1 (d), 110.9 (d), 119.1 (d, 2C), 122.7 (d), 124.9 (d, $J_{\text{C,F}} = 34.3$ Hz), 127.3 (s), 129.6 (s, 2C), 152.4 (s), 155.8 (s, 3C), ppm; ESI-MS: 449.06 (100%, $[\text{M} + \text{Na}]^+$); Anal calcd for $\text{C}_{18}\text{H}_{16}\text{ClFN}_2\text{O}_7$: C, 50.66; H, 3.78; N, 6.56%; found: C, 50.64; H, 3.78; N, 6.53%.

1-[3-*C*-(6'-Nitrobenzofuran-2'-yl)methylene]- β -D-ribo-pentofuranosyl]5-fluorouridine (19fc):

Isolated by column chromatography (5% MeOH in CH_2Cl_2 , $R_f = 0.4$). The title compound **19fc** was determined as a off white solid (81%). M.P: 200–202 °C $[\alpha]_D^{25}$: -11.9 (c 0.74, CH_3OH); IR (neat): ν 3447, 3102, 2924, 2853, 1700, 1642, 1523, 1456, 1339, 1122, 963, 753, 666 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 3.37 (s, 2H), 3.90 (dd, $J = 2.5$, 12.1 Hz, 1H), 3.99 (dd, $J = 1.0$, 12.1 Hz, 1H), 4.18 (t, $J = 1.5$ Hz 1H), 4.29 (d, $J = 7.4$ Hz, 1H), 6.10 (dd, $J = 1.9$, 8.3 Hz, 1H), 6.88 (s, 1H), 7.58 (d, $J = 9.6$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 8.18 (dd, $J = 2.5$, 9.4 Hz, 1H), 8.48 (d, $J = 2.5$ Hz, 1H), 8.56 (d, $J = 7.0$ Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 31.6 (t), 60.2 (t), 76.6 (d), 77.6 (s), 86.1 (d), 86.8 (d), 105.2 (d), 110.3 (d), 115.9 (d), 118.5 (d), 124.9 (d, $^2J_{\text{C,F}} = 34.5$ Hz), 128.7 (s), 140.0 (s, d, $^3J_{\text{C,F}} = 234.3$ Hz), 143.6 (s), 149.6 (s), 156.9 (s), 157.9 (2C, s) ppm; ESI-MS: 460.01 (100%, $[\text{M} + \text{Na}]^+$); Anal calcd for $\text{C}_{18}\text{H}_{16}\text{FN}_3\text{O}_9$: C, 49.43; H, 3.69; N, 9.61%; found: C, 49.43; H, 3.66; N, 9.64%.



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CHAPTER III:

[Ru]-Catalyzed C-H activation: Synthesis of anti-inflammatory 2-arylbenzofurans via linear/branched selective acrylate insertion

3.1. Introduction

The construction of C–C bond is central to the Organic Synthesis. Since the first synthesis of urea in the laboratory by *Wöhler* in 1828, the organic chemists were searching for more efficient, economic methods to construct the C–C, C–H, and C–hetero atom bonds for the value added products.¹ The progression of aldol reaction, Claisen and related condensations are the initial breakthroughs in this arena which amply explored the potential of carbonyl compounds and active methylene groups.² Subsequently, the Zn-mediated addition of α -bromoesters (Reformatsky reaction)³ and allyl-, propargyl halides (Barbier reaction)⁴ have revealed that functionalized yet not active methylene groups can be also added to the carbonyl compounds. The pioneering work of Grignard on organomagnesium reagents made new insights in organic synthesis by efficient construction of C–C bond and it utilized for synthesis of complex organic molecules.⁵ The pre and post Grignard reaction, there has been numerous classical organic transformations taken place in 19th and 20th centuries and which are paved the way for the development of modern organic synthesis.⁶

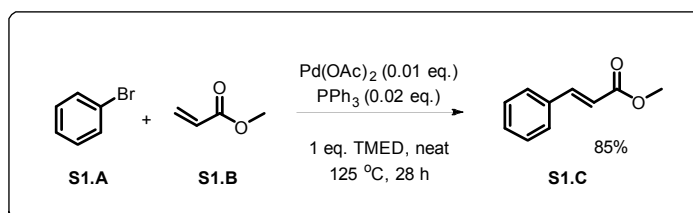
The shining light had been blink, as the transition metal complexes utilized for the cultivation of C–C and C–hetero atom bond formation.⁷ The post Ullmann reaction, copper metal complexes efficiently used for the construction of C–C and C–hetero atom bond with prefunctional aromatic compounds.⁸ Despite its good catalytic properties, advances in organocopper chemistry, still there is a large number of other problems persist. For example, the reactions were sluggish and involved homo couplings. The mid and late 20th century has witnessed for many changes, a long range of transition and organometallic complexes, such as Cu, Ni or Pd, used as catalysts for myriad of organic transformations for C–C and C–hetero atom bond formation.^{7, 9} The palladium complexes occupied the major room for C–C bond formation by cross coupling reactions, such as Heck, Suzuki, Negishi, Sonogashira and Stille reactions and their modifications.¹⁰ These Pd-catalyzed reactions are addressed the molecular complexity in the synthesis of organic molecules. Despite their low catalyst loading and high catalytic activity, there are several limitations were associated. For example all these catalysts are working on only pre-functional aromatic and aliphatic compounds.

In the late 20th and early 21st century chemists have aggressively searching for new efficient, economic and environment friendly method for the organic

transformations. A long range of early and late transition metals have been used, finally succeeded and introduced the word C–H bond activation and functionalization, which brings the great revolution and it provides a sustainable alternative to both traditional cross coupling and classical Friedal-Craft's alkylation.¹¹ In particular, a variety of methods have been developed to allow for the formation of a number of types of bonds, including C–C, C–H, C–N, C–O, C–S, and C–P. These developments have allowed for the synthesis of myriad complex molecules in a manner never before possible.

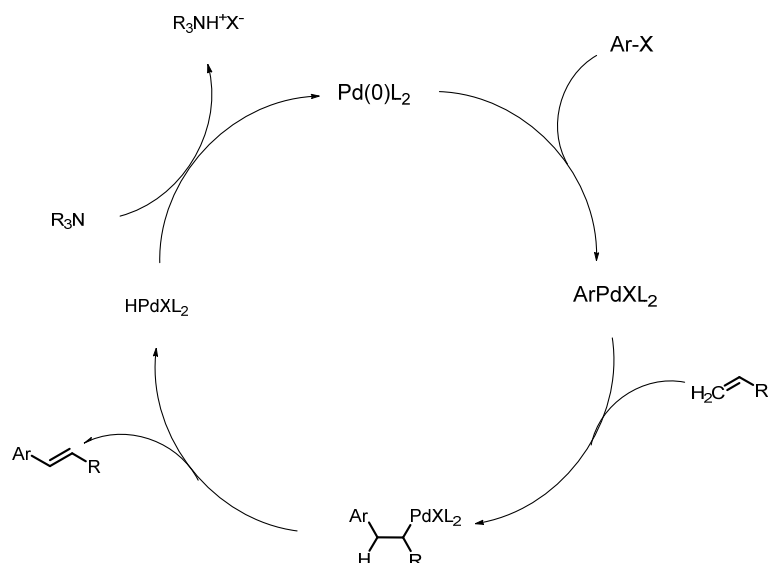
3.1.1. Cross Coupling Reactions with Acrylate

Transition metal catalyzed cross coupling reactions with acrylates have been developed as an important tool for constructing new carbon-carbon bonds in modern organic synthesis, to accomplish the synthesis of natural products, pharmaceuticals, dyes, organic conductors and semi-conductors, polymers and many value added industrial applications.⁷ Among the many reactions, first foremost, Heck reaction is well known transformation of aryl/heteroaryl halide and acrylate into olefinated adducts.¹² One of the benefits of the Heck Reaction is its outstanding *trans* selectivity. In the early 1970s, Heck reported that acrylates could be arylated by reacting with stoichiometric amounts of Ar-Pd-X or Ar-Pd-OAc complexes. Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being amenable to the Heck Reaction.



Scheme S3.1: Pd(OAc)_2 catalyzed Heck reaction with acrylates

A mechanism was proposed which involved a *syn* migratory insertion of the olefin into the arylpalladium species, followed by a *syn* β -hydride elimination of a hydridopalladium [HPdX] ($\text{X} = \text{Cl}, \text{OAc}$) (Scheme S3.2). Subsequently, a reaction using organo-palladium salts, formed by the direct reaction of aryl iodides with finely divided palladium, to react with acrylate (alkene) was developed by Heck, and discovered independently by Mizoroki at the same time. This discovery opened the way to a new reaction later it called the Mizoroki-Heck reaction.¹³



Scheme S3.2: *Catalytic cycle for Heck reaction*

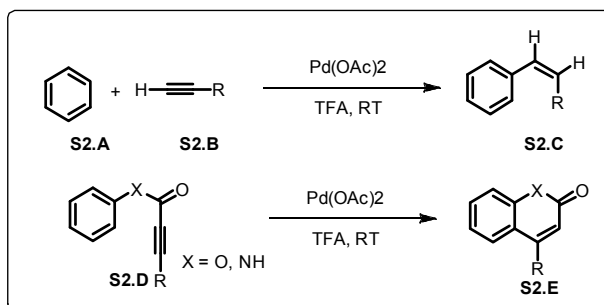
3.1.2. C–H activation

Over the years based on these initial studies, a broad range of new reaction conditions were developed to directly transform C–H bonds into C–C or C–heteroatom bonds *via* C–H activation by avoiding the pre-functional groups.¹¹ These C–H activation reactions brought the tremendous change, by shorting the synthetic routs in modern organic synthesis by utilizing ubiquitous C–H bonds. This C–H functionalization is a class of reactions that could lead to a paradigm shift in organic synthesis, relying on the selective activation of ubiquitous C–H bonds in organic molecules instead of the standard approach of conducting transformations on pre-existing functional groups. Since the first example of C–H oxidative addition of benzene to a soluble transition metal complex was observed by Chatt and Davidson in 1965,¹⁴ the understanding and potential of C–H activation reactions has been extensively studied. Throughout the 1980's and into the 1990's, a significant amount of research was focused on better understanding C–H bond activation through investigations of intermediates, thermodynamics and kinetics, and selectivity of various stoichiometric reactions. These reactions further divided into two wide categories, direct C–H activation reactions and directing group assisted C–H activation reactions.¹⁵

3.1.2.1. Direct C–H Activation:

Reaction without directing group assistance refers to those where the C–H bond is cleaved through direct metal insertion without the presence of heteroatoms for

metal chelation or to act as directing groups. The challenges of discriminating between various *activation* types of chemically similar C–H bonds within the hydrocarbon skeleton and also regio selective C–H activation remain to be addressed.

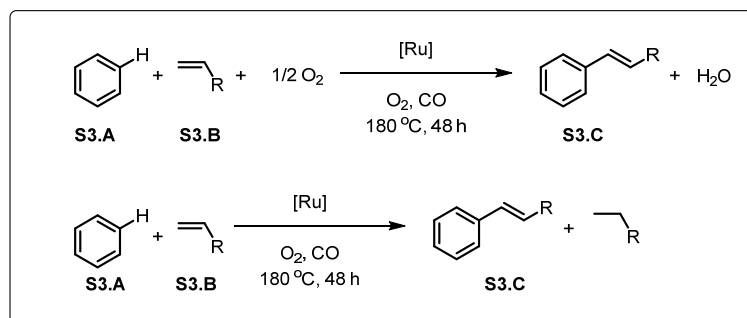


Scheme S3.3: *Inter and Intramolecular palladium catalyzed direct C–H*

The seminal work on direct C–H activation reported by Fujiwara, address the effective metalation of aromatic C–H bonds at room temperature using highly-electrophilic, *in situ* generated, Pd(II) and Pt(II) cationic species in trifluoroacetic acid (TFA), leading to the regioselective inter- and intramolecular addition of simple arenes to C–C multiple bonds (Scheme S3.3).¹⁶ In most cases, the addition of alkynes exclusively affords the thermodynamically less stable *cis*-aryl alkene. The intramolecular hydroarylation of C≡C bonds is facile and regiospecific because of the electrophilic metalation of aromatic C–H bonds by the Pd(II) cationic species which is assisted by ethynyl coordination. In fact, this intramolecular reaction combines both chelation assistance and electrophilic metalation.

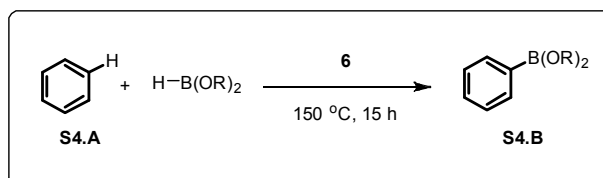
The next effective contribution for direct C–H activation was Milstein's Heck-type oxidative coupling reaction, which was found to be promoted by molecular oxygen, is one of the most remarkable examples of ruthenium catalyzed arene C–H bond insertion reactions (Scheme S3.4).¹⁷ The catalytic oxidative coupling of arenes with alkenes to generate aryl alkenes, in which the double bond is preserved, is a highly desirable goal. Since the reaction does not require the utilization of reactive substituent and does not form any byproducts, it has a unique advantage over other methods for the preparation of aromatic alkenes, especially when compare to the well-known Heck reaction for the vinylation of aryl halides. In Milstein's Heck type coupling, dioxygen can be directly used as the oxidant, while still retaining good catalytic activity. The reaction is catalyzed by ruthenium complexes under a CO atmosphere condition. Readily available ruthenium complexes such as RuCl₃·3H₂O

(1), $[\text{Ru}(\text{CO})_3\text{Cl}_2]_2$ (2), $[(\eta^6\text{-C}_6\text{H}_6)\text{RuCl}_2]_2$ (3), $\text{Ru}(\text{NO})\text{Cl}_3 \cdot 5\text{H}_2\text{O}$ (4), and $\text{Ru}(\text{F}_3\text{CCOCHCOCF}_3)_3$ (5) show essentially the same type of catalytic activity.



Scheme S3.4: Ruthenium catalyzed direct arene C–H bond activation and functionalization with alkenes

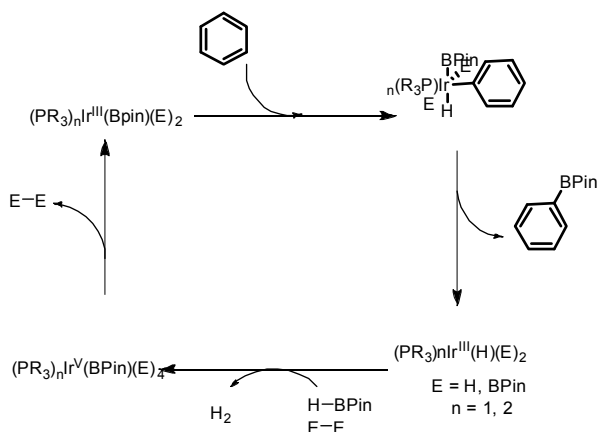
Later Smith also described that iridium catalysts $(\text{MesH})\text{Ir}(\text{BPin})_3$ ($\text{MesH} = \eta^6\text{-mesitylene}$, $\text{BPin} = \text{oxaborolane}$) (6) were efficient for direct synthesis of arylboron compounds from aromatic hydrocarbons and boranes under “solvent-less” conditions (Scheme S3.5).¹⁸ The Ir catalysts are highly selective for C–H bond activation and do not interfere with subsequent transformations, including Pd-mediated cross-coupling with aryl halides. By virtue of their favorable activities and exceptional selectivities, these Ir catalysts impart the synthetic versatility of arylboron reagents to C–H bonds both aromatic and heteroaromatic hydrocarbons.



Scheme S3.5: Iridium catalyzed boryllation of aromatic compounds by C–H activation

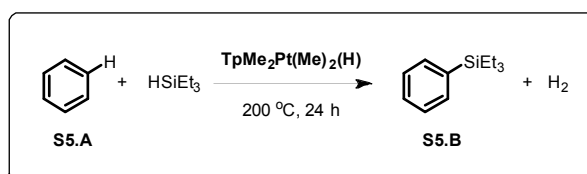
Smith proposed the reaction mechanism involving Ir(III) and Ir(V) intermediates as shown in Scheme S3.6. The following evidence supports the mechanism proposed in Scheme S3.6: (a) Borylation products of iodobenzene are not obtained when Ir(I) sources are used under stoichiometric or catalytic conditions, whereas Ir(III) complexes effect both stoichiometric and catalytic borylations. (b) Improved catalytic activity is observed with chelating phosphines and inhibition was observed when $[\text{phosphine}]:[\text{iridium}]$ ratios equal or exceed 3:1, strongly supporting the viability of bisphosphine intermediates (Scheme S3.6, $n = 2$), which could be generated via E–E reductive elimination ($\text{E} = \text{H}, \text{BPin}$) from an 18 electron

bisphosphine Ir(V) resting state. (c) The 18 electron bisphosphine compound, $\text{IrH}_5(\text{PMe}_3)_2$, is an efficient precatalyst for the borylation.



Scheme S3.6: Catalytic cycle for borylation

Hartwig discovered a highly selective, acceptor-less dehydrogenative coupling of silanes with arene C–H bonds in good yields in the presence of $\text{TpMe}_2\text{PtMe}_2\text{H}$ ($\text{TpMe}_2 = \text{hydridotris}(3,5\text{-dimethylpyrazolyl})\text{borate}$) and related platinum(IV) complexes (Scheme S3.7).¹⁹ The reaction of the arenes occurred selectively at the least sterically hindered C – H bonds and preferentially with more electron-poor arenes. If the dehydrogenative coupling of simple silanes with aromatic and aliphatic C–H bonds could be developed, then useful reactions could result. Because of the higher stability of silanes toward disproportionation than boranes, they could undergo tandem or sequential reactions that would be impossible using borane or even disilane reagents.



Scheme S3.7: Platinum catalyzed direct C–H activation

3.1.2.2. Chelation Assisted C–H functionalization

The directed or chelation assisted C–H activation, the reaction facile through the metal chelation with heteroatom. In the area of C–H bond functionalization chemistry, the directed or chelation assisted C–H bond activation reactions with some of the transition metal catalysts were found to be very efficient tools for their substrate tolerance of functional groups and wide range of synthetic utility.^{11b, 20}

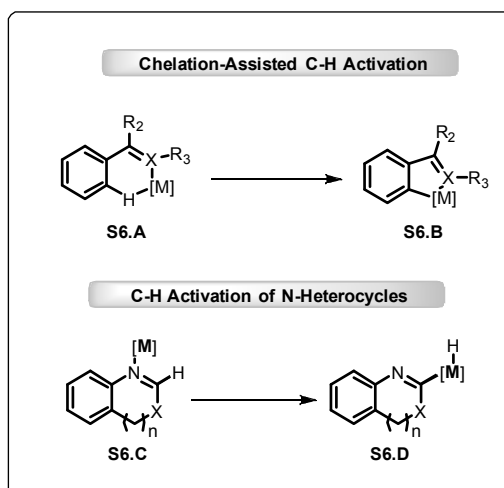


Figure S3.1: *schematic representation of chelation assisted C–H activation*

Over the past decade, chelation-controlled (functional group directed) C–H bond activation reactions by various transition metal catalysts have been reported by many research groups using directing (functional) group containing arenes and heteroarenes. Two mechanistically distinct reaction pathways are now proposed with modes of C–H bond activation by metal (Figure S3.1).

First of all, the heteroatom could be used as a chelating group to bind the metal catalyst, facilitating reactivity at the substrate *ortho* position. In this case, the formation of the heterometallacycle with oxygen or nitrogen provides a favorable driving force inducing regiochemistry. In the case of heteroatom initially coordinates to the metal center, acts to stabilize the formation of a metal-carbon bond using a proximal C–H bond from the substrate and then the functionalization occurs.

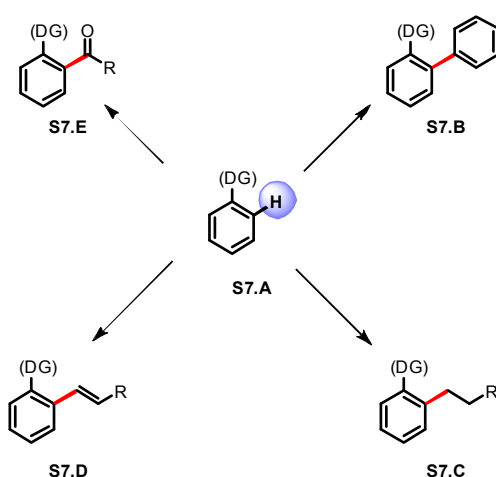


Figure S3.2: *Types of chelation assisted C–H activation*

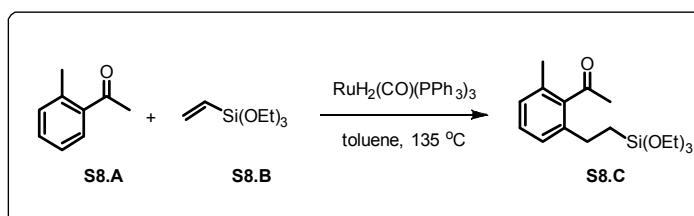
The use of chelation control in C–H bond functionalization offers several advantages with respect to substrate scope and application to total synthesis. Pioneering work in this field such as rhodium-catalyzed C–H alkylation was

developed by Lim and Kang using pyridine as the directing group. More recently, imine functional groups have been employed in the C–H bond alkylation using Rh(I) catalysts. In addition, the limited scope of intermolecular hydroarylation due to olefin isomerization leads to research on intramolecular C–H alkylation reactions. These alkylation methods were applied in natural products synthesis like mescaline and (+)-lithospermic acid. While the hydroarylation of olefins showed great success in organic chemistry, research into Rh-catalyzed alkenylation and annulations has been examined by only a few chemists. In most cases, *N*-directed alkenylation was commonly used with alkyne derivatives, whereas *N*-benzyl chelating groups afforded annulation products with phenylacetylenes under higher temperature and at prolonged reaction times. The development of C–H arylation reactions is now another subject of active investigation that can be addressed by Rh compounds. Various aryl sources have been employed in C–H arylation reactions, despite the production of unwanted di-arylation side product. Additionally, the carbonylation reactions were also reported using chelation-assisted arenes and CO as the carbonyl source. Unfortunately, a limited substrate scope only was possible because of harsh reaction conditions that degrade certain functionalization.

An alternative method for achieving selectivity in C–H bond functionalization is to apply an electronic stabilizing group which makes metal-carbon bond at proximal site on compounds easily. This approach has been previously utilized in the Rh-catalyzed alkylation and arylation. The initial approach of azole reactions using Rh catalysts were reported by Ellman and Bergman. Both intramolecular and intermolecular versions of alkylation reactions have been researched that involve a wide scope of substrates. Although, high temperature was needed in this transformation, heterocycles including pyridines and azolines were activated by this method. Additionally, the fascinating mode of activation and excellent functional group tolerance that Rh catalysts offer, led to arylation reactions with various azoles. Azoles as well as arenes with a single heteroatom also were activated by rhodium to yield functionalized products.²²

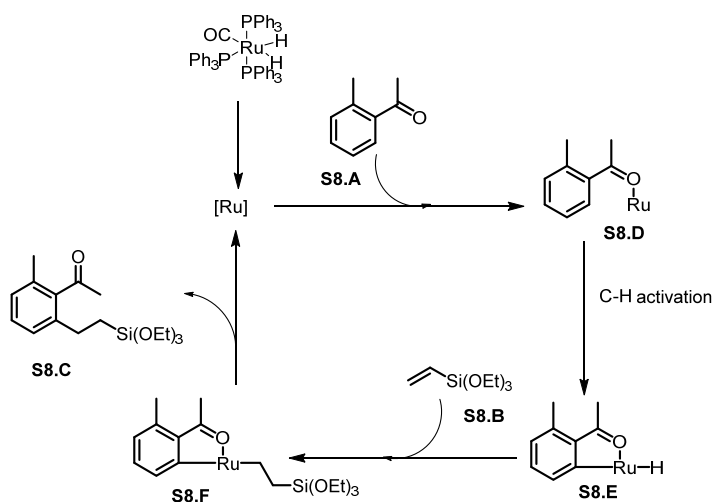
The unique reactivity of rhodium catalyst leads to a new avenue for C–C and C–N bond formation. This system shows high regioselectivity with a broad substrate scope. Owing to high functional group tolerance, both chelation-assisted and heteroatom-directed C–H bond functionalization have been employed in the synthesis of complex molecules.

Murai pioneered chelate-assisted, regioselective, catalytic C–H bond activation of arene and olefin coupling reaction. For example, acetophenone was added to vinyl silane to yield regioselectively alkylated product at the ortho position (Scheme S3.8).²³ The ruthenium complex $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (**7**) was found to be an efficient catalyst for this coupling reaction. This reaction is a quite effective synthetic method, and, in many cases, gave nearly quantitative yields.



Scheme S3.8: *[Ru] catalyzed C–H functionalization with vinylsilanes*

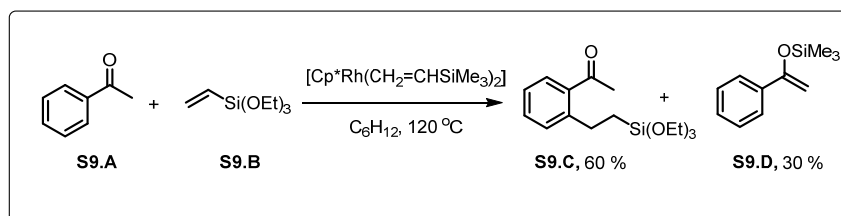
As shown Scheme S3.9, Murai proposed that the reaction involves the coordination of the carbonyl group of aryl ketones to the ruthenium center and is placed in a favorable position for the cleavage of the C–H bond. The ruthenium hydride complex **8** has been suggested as a key intermediate species. The rate-limiting step of the coupling reaction is the C–C bond forming step instead of C–H activation step.²³



Scheme S3.9: *Catalytic cycle for [Ru] catalyzed heteroatom directed C–H activation*

The reaction was extended to various arene and olefin coupling reactions. One of the most important findings in elucidation of the mechanism of coupling reaction is that the C–H bond cleavage step is not the rate-limiting step. Instead a rapid equilibrium exists prior to the reductive elimination step that leads to the C–C bond formation. Murai has established that the reductive elimination of alkylated products is the rate-determining step.

The rhodium bis-olefin complex $[\text{Cp}^*\text{Rh}(\text{CH}_2=\text{CHSiMe}_3)_2]$ (**9**) has also been shown to be an effective catalyst for selective addition of olefins to the ortho position of arylketones (Scheme S3.10). A main difference between scheme S3.8 and scheme S3.10 is that in the ruthenium catalyzed process, carbonyl coordination is presumed to be the first step, which directs the C–H bond activation to the ortho position of the aromatic substrate.

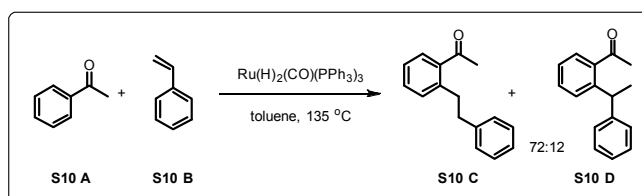


Scheme S3.10: *[Rh] catalyzed C–H functionalization with vinylsilanes*

H/D exchange experiments established that *para* and *meta* C–H bonds are not activated in the ruthenium system. The rhodium catalytic processes, on the other hand, are not discriminating in the C–H bond activation step and activation of all sites (*ortho*, *meta*, and *para*) of the substrate was observed. Murai has established that the C–H bond activation is fast and reversible in the ruthenium case and reductive elimination of the alkylated product is the rate-limiting step. It is believed that the similar features are applied to the rhodium system as well, but no conclusive evidence is available concerning this point. In the both systems, the energy barrier for reductive elimination which then forms the product is decreased by chelation of the carbonyl group to the metal center.

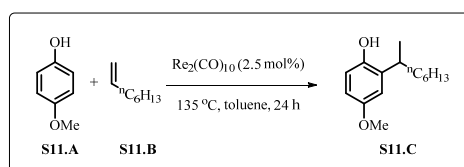
3.1.2.3. C–H Activation and Branched Selective Alkylations:

The branched selective hydroarylation via C–H activation is one of the demanding tasks till date. Reports are available in literature, wherein, when styrene was employed an olefin counterpart in Murai reaction, the formation of the branched selective alkylation has been noticed (Scheme S3.11).²⁴ Use of bulky phosphines as additives has increased the linear selectivity. Despite its occurrence, there has been little attention paid on the possibility of branched-selective alkylation until recently.



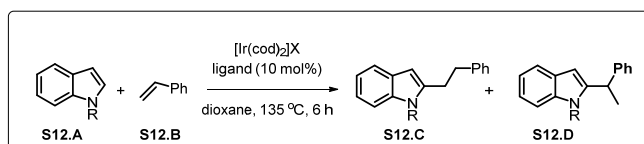
Scheme S3.11: *[Ru] catalyzed C–H functionalization with styrene*

In 2009, Takai *et al.* reported the Rhenium catalyzed branched selective alkylation of phenol, which is the first report with phenolic hydroxy has a directing group.²⁵ The paramount importance in this methodology was regioselective introduction of long chain olefins at the ortho or para position of hydroxyl group selectively with $\text{Re}_2(\text{CO})_{10}$ complex (Scheme S3.12). Some of the selected rhenium complexes were screened, but among them $\text{Re}_2(\text{CO})_{10}$ showed better activity and excellent selectivity. The scope and limitations of phenol derivatives with 1-octene were investigated in toluene at 135 °C and also scope of aliphatic olefins examined, in which ortho or para and some cases both ortho and para alkylated mixture were also observed.



Scheme S3.12: *[Re] catalyzed C–H functionalization with olefines*

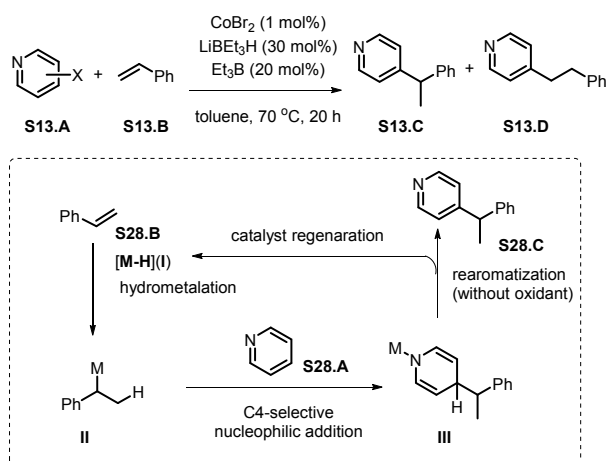
Shibata *et al.* reported the Iridium catalyzed C2-alkylation of *N*-substituted indole derivatives with various alkene with a remarkable linear or branched selectivities.²⁶ This protocol relies on the use of the carbonyl group on the nitrogen atom of indole as a directing group, a linear product was predominant when an acetyl group was used as a directing group, and a branched product was predominant with a benzoyl group. The selectivity of linear or branched product was controlled by the directing group and ligand (Scheme S3.13). Albeit the results provided on regioselective hydroarylation of olefines using indoles are path breaking, however, the details on factors behind this unusual activity and how the directing group and ligand tuned the same, have been not yet addressed.



Scheme S3.13: *[Ir] catalyzed regioselective alkylation with olefines*

Very recently Kanai *et al.* reported the cobalt catalyzed C4-alkylation of pyridines with excellent linear or branched selectivity depending upon the nature of the olefine employed. A new hypothesis based on catalytic nucleophilic addition/rearomatization has been executed.²⁷ A catalytic amount of CoBr_2 in combination with LiBEt_3H gave branched adducts from styrene derivatives, and linear

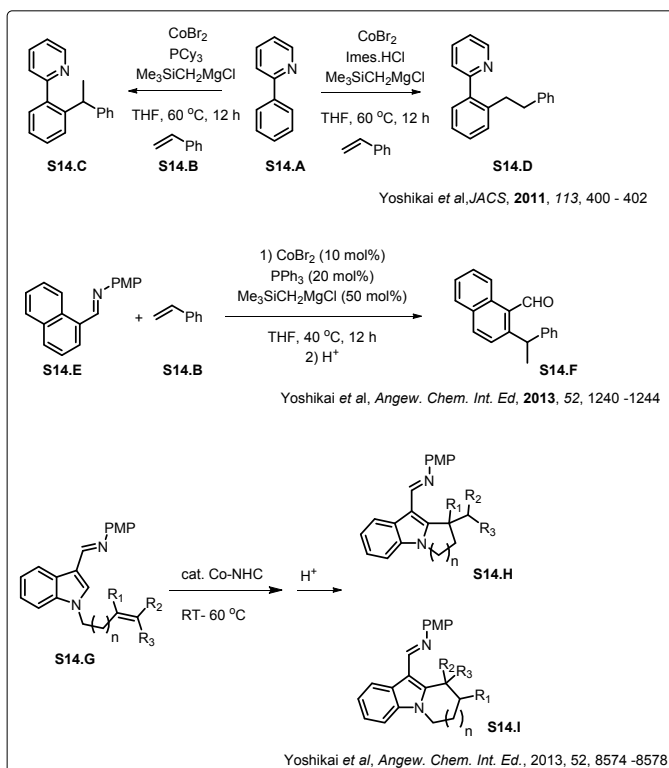
adducts from aliphatic alkenes. As shown in Scheme xx, the reaction proceeds via hydrometalation of alkenes and subsequent nucleophilic addition of the resulting alkyl–metal species to pyridine C4 affords a dihydropyridine intermediate. The rearomatization of pyridine leads to the regeneration of the metalhydride catalyst. The high catalyst turnover numbers (up to 3440; s/c=4000) observed in the reaction with styrene are noteworthy. However, the mechanistic studies also couldn't make any clear evidence on the variation on the mode of alkylation with styrene and aliphatic 1-alkene.



Scheme S3.14: *[Co] catalyzed regioselective alkylation with styrene*

Yoshikai et al developed the concept of regioselective hydroarylation switch by using low valent cobalt catalysis. The investigation commenced the development of chelation assisted hydroarylation reactions of styrenes particularly. The beauty of this concept is ligand-controlled regioselectivity switch and the study of orthogonal scope and selectivity of the Lewis acid. This low valent metal catalyzed hydroarylation reactions, in particular, the branched selectivity hydroarylation with the Co-PCy₃ catalysis is highly attractive. Their inaugural application on this concept was delivered with pyridine directed regioselective hydroarylation with CoBr₂ and Me₃SiCH₂MgBr, PCy₃ ligand has used for tuning the branched selective alkylation and IMes•HCl has been used for tuning the linear selective alkylation.²⁸ This seminal contribution later taken forward with aldamine nitrogen directed branched selective alkylation on naphthyl ring with styrene derivatives²⁹ and it was followed by the intramolecular aldamine nitrogen directed branched selective C2-alkylation on indole moiety.³⁰ In this case the regioselectivity of the cyclization reaction is primarily dependent on the structure of the olefin tether, but is controllable by the steric nature of the NHC ligand when the tether is a parent homoallyl group, which is an example

of catalytic regiodivergent synthesis. The results were summarized in scheme, SIMes·HCl was identified as a promising pre-ligand, affording the expected cyclization products **S14H** and **S14I** with a ratio of 4:1.



Scheme S3.15: [Co] catalyzed regioselective alkylation with olefines

3.1.3. Metal catalyzed coupling of acrylates:

Acrylates are esters of acrylic acids. They are also known as propenoates, they contain vinyl groups, that is, two carbon atoms double bonded to each other, directly attached to the carbonyl carbon.

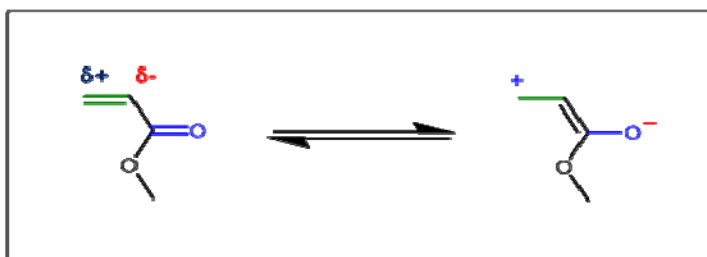


Figure S3.3: Resonance structures of acrylates

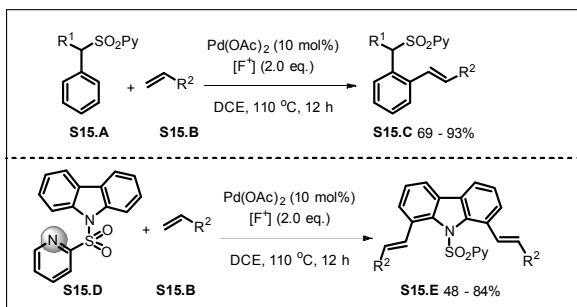
The conjugation of alkene with the carbonyl group provides special properties. The carbonyl group draws electrons away from the alkene, and the alkene group is, therefore, deactivated towards an electrophile. These compounds are activated towards nucleophiles for conjugate additions. The involvement of acrylates as

coupling partners/electrophiles in the C–H activation reactions can be divided in to two types:

- i. alkenylation (cross dehydrogenative coupling)
- ii. alkylation (Murai reaction)

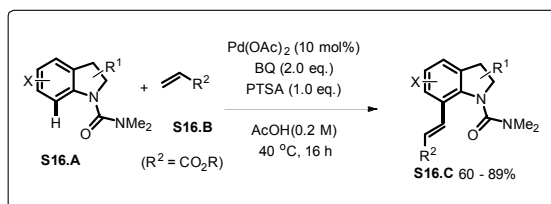
3.1.3.1. Cross Dehydrogenative Coupling (Alkenylation) of Acrylate *via* C–H activation

Carretero *et al* reported the Pd(OAc)₂ catalyzed, sulfonyl group directed ortho alkenylation with acrylates on N-alkyl N-(2-pyridyl)sulfonyl anilines and arylalkylamines and also extended the C–H functionalization to di *ortho* olefination on carbzole (Scheme S3.16).³¹



Scheme S3.16: [Pd] catalyzed sulfonyl directed alkenylation with olefines

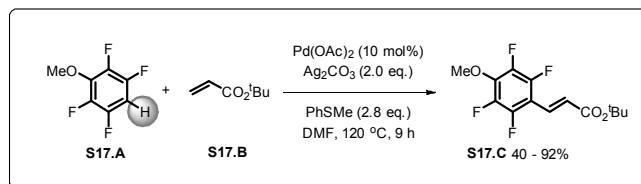
Oestreich *et al* has documented recently Pd(OAc)₂ catalyzed, C-7 selective C–H bond alkenylation of indolines. BQ was used as oxidant, but it was also possible to perform the cross coupling under aerobic conditions, infrequently used urea has been utilized as directing group and good to excellent yield was obtained (Scheme S3.17).³² Yu and other groups^{32b} also benefited to achieve the alkenylation by utilizing urea as directiong group.



Scheme S3.17: [Pd] catalyzed urea directed alkenylation with olefins

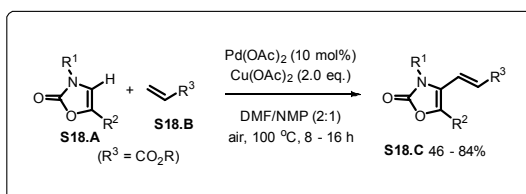
Zhang *et al* reported the Pd(OAc)₂ catalyzed direct C–H bond functionalization strategy for the olefination of polyfluoroarenes, which represents one of the rare examples of catalytic direct olefination of electron-deficient arenes. This transformation has been promoted by thioether (PhSMe) (Scheme S3.18). They

have demonstrated the power of the new ligand PhSMe, has shown the reaction of those previous ‘inert’ substrates to provide high yields.³³



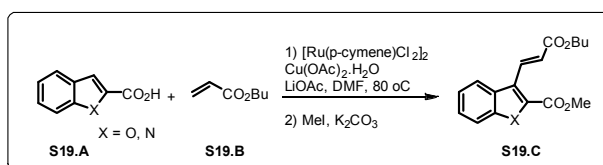
Scheme S3.18: *[Pd] catalyzed alkenylation with olefins*

Zhu *et al* established a novel and general method for the synthesis of 4-alkenyl-2-oxazolones featuring the first Pd catalyzed direct C–H activation and functionalization on 2-oxazolones and Cu(OAc)₂ used as oxidant to promote the reaction (Scheme S3.19).³⁴



Scheme S3.19: *[Pd] catalyzed alkenylation with olefins*

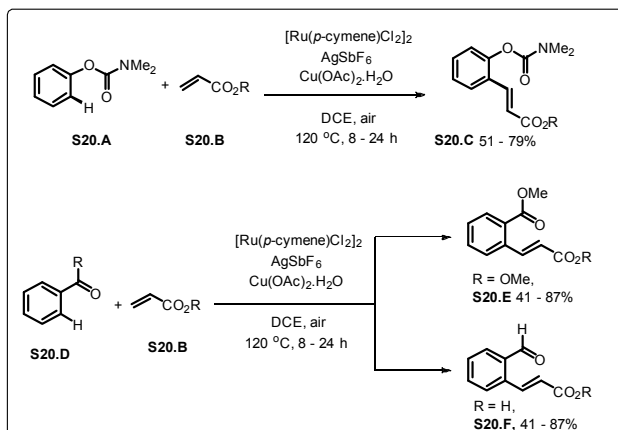
The first examples on the use of Ru-complexes for the carbonyl directed dehydrogenative cross coupling reaction with acrylates has been reported by Miura in 2009 employing heterocyclic systems such as benzofuran and indole derivatives (Scheme S3.20).³⁵



Scheme S3.20: *[Ru] catalyzed alkenylation with olefins*

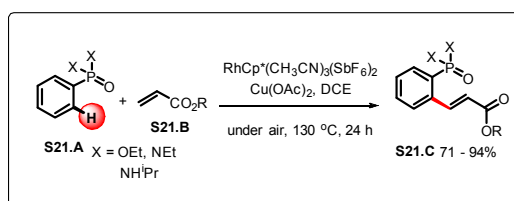
The employed conditions involve the use of Ru(*p*-cymene)Cl₂ as a catalyst and Cu(OAc)₂.H₂O oxidant. This initial success with Ru-complexes has been later well explored by various other systems and with diverse directing groups mainly by Ackermann and Jeganmohan groups. Wang, Ackermann and Jeganmohan independently reported Ru catalyzed phenol carbamate directed *ortho* alkenylation (Scheme S3.21).³⁶ Advantage from this initial success, later they have independently reported Ru catalyzed ester directed *ortho* alkenylation on arenes³⁷ followed by

Jeganmohan's Ru catalyzed aldehyde directed *ortho* alkenylation on arenes³⁸ is a noteworthy example.



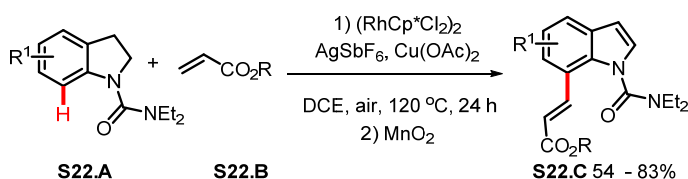
Scheme S3.21: *[Ru] catalyzed carbonyl directed alkenylation with olefins*

Glorius *et al* documented very recently, Rh catalyzed phosphonate and phosphonamide directed C–H activation for alkenylation of arylphosphonates and phosphonamides at *ortho* position. The cationic rhodium species $\text{RhCp}^*(\text{CH}_3\text{CN})_3(\text{SbF}_6)_2$ successfully catalyzed when $\text{Cu}(\text{OAc})_2$ used as oxidant in DCE under air at 130 °C for 24h and furnished good to excellent yields (Scheme S3.22).³⁹



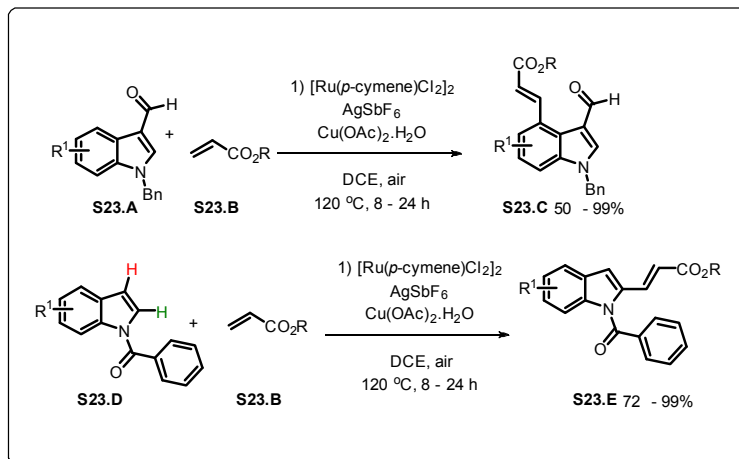
Scheme S3.22: *[Rh] catalyzed directed alkenylation with olefins*

Antonchick *et al* reported recently Rh catalyzed, regioselective C-7 C–H bond alkenylation of indolines by using infrequently used urea as a directing group. This has achieved after Oestreich's contribution with $\text{Pd}(\text{OAc})_2$. $\text{Cu}(\text{OAc})_2$ was used as oxidant instead of BQ with cationic $[\text{RhCp}^*(\text{SbF}_6)]_2$, to furnish the excellent yields of olefination (Scheme S3.23).⁴⁰



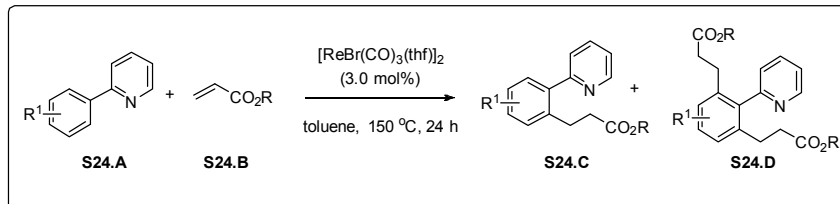
Scheme S3.23: *[Rh] catalyzed directed alkenylation with olefins*

Prabhu *et al* recently documented the Ru catalyzed a selective C2-alkenylation of indole using carbonyl oxygen as a directing group and C4-alkenylation also reported *via* the C–H functionalization using carbonyl oxygen of an aldehyde as a directing group (Scheme S3.24).⁴¹



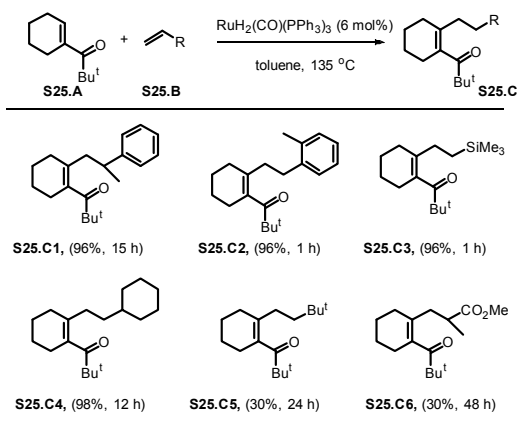
Scheme S3.24: *[Ru] catalyzed directed alkenylation with olefins*

Takai *et al* reported the Re catalyzed pyridine directed acrylate insertion into an Aromatic C–H Bond at the ortho position of a directing group (Scheme S3.25).⁴²



Scheme S3.25: *[Re] catalyzed directed alkenylation with olefins*

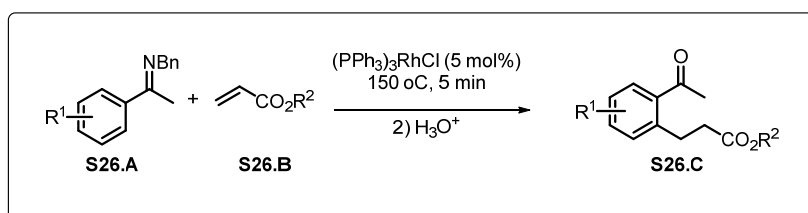
Unlike the cross dehydrogenative coupling, the alkylation with acrylates *inter alia* the use of acrylates in the Murai reaction have been less explored.



Scheme S3.26: *[Rh] catalyzed directed alkenylation with olefins*

In the initial disclosures, Murai has attempted the use of acrylates as coupling partners employing the dihydropyran derivatives, unlike the simple olefins where excellent yields are obtained, with methyl methacrylate, the product was formed in very poor yields. This observation with acrylates has been taken granted in general that they are poor substrates in Murai reaction (Scheme S3.26).⁴³

However, recently, Jun and Takai independently reported the Rh and Re catalyzed imene directed ortho hydroarylation with acrylates (Scheme S3.27).⁴⁴

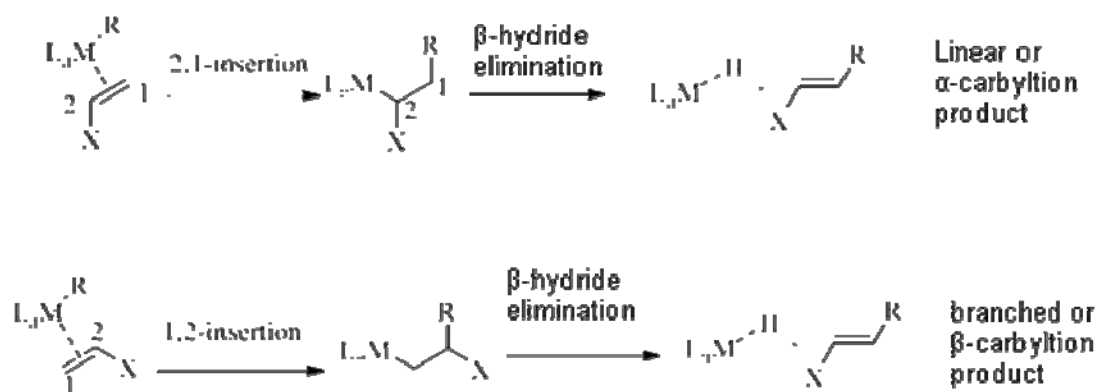


Scheme S3.27: *[Rh] catalyzed directed alkenylation with olefins*

Very recently, while our work was in progress, Chatani and co-workers reported the first successful Ru-catalyzed Murai reaction with enone systems.⁴⁵

From the examples given above it is evident that the Murai reaction with acrylates has been yet to be addressed. Another interesting observation is, either in the classical cross-coupling reactions or in the cross dehydrogenative couplings, when acrylates are employed as the electrophiles, in general, linear products are observed exclusively. Only, in 2011, the first example on the regio-irregular coupling with acrylates has been documented by Wucher and co-workers in the Mizoroki–Heck coupling reaction. However, the Pd-complex was used in stoichiometric amounts.⁴⁶

Wucher and coworkers reported the remarkable strategy for the carbon–carbon bond formation. The authors illustrated the results by reinventing the regioselective rule in the Mizoroki–Heck coupling, which is the most prominent example in organic synthesis and also by catalytic insertion polymerization. Usually electron-deficient olefins insert selectively in a 2,1 fashion for electronic reasons. The authors have commenced the regioselective insertion of acrylate by destabilizing the transition state of 2,1-insertion via steric interactions, the regioselectivity of methyl acrylate insertion into palladium–methyl and phenyl bonds can be inverted entirely to yield the opposite “regioirregular” products in stoichiometric reactions. Insights from these experiments will aid the rational design of complexes which enable a catalytic and regioirregular Mizoroki–Heck reaction of electron-deficient olefins (Scheme S3.28).



Scheme S3.28: *[Pd] catalyzed regioselective acrylate insertion*

The concept which allows reversal of the commonly valid regioselectivity rule for the insertion of the electron-deficient olefin MA into palladium carbon bonds. Appropriately arranged steric bulk of the ligands bound to the palladium center results in a severe steric repulsion with the incoming substrate in the electronically favored 2,1-insertion transition states. This steric repulsion makes the less sterically encumbered 1,2-insertion transition states competitive and strongly favored, thus overriding the usual distinct electronic determination of the insertion reaction. But they used bulky phosphine ligands and the palladium complex used in stoichiometric ratio. However this results certainly aid the rational design of catalysts that provide selective access to a catalytic regioirregular Mizoroki–Heck reaction.

Introduction

Benzofuran is one of the commonly encountered structural units in natural products as well as in medicinally important small molecules. The 2,3-disubstituted benzofurans deserves a special mention as they have served as building blocks for a number of natural products synthesis and possess unique biological activities. For example, the 2-(2-arylbenzofuran-3-yl)acetates (Type I); 3-(2-arylbenzofuran-3-yl)propanoates (Type II) and their regiomer counterparts (Types III and IV respectively, Fig.3.1) have been identified as novel anti-inflammatory agents and Antiarrhythmic agents respectively.⁴⁷ The compounds of Type I are known to inhibit the type IV phosphodiesterase, which results in the elevation of cellular cAMP that regulate the production of superoxide by polymorphonuclear leukocytes (PMN).⁴⁸

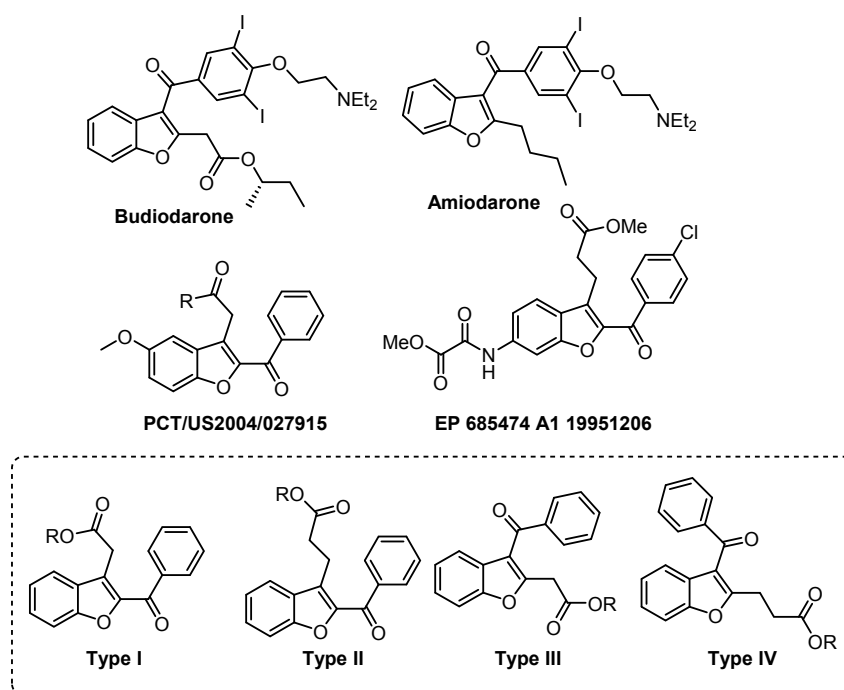
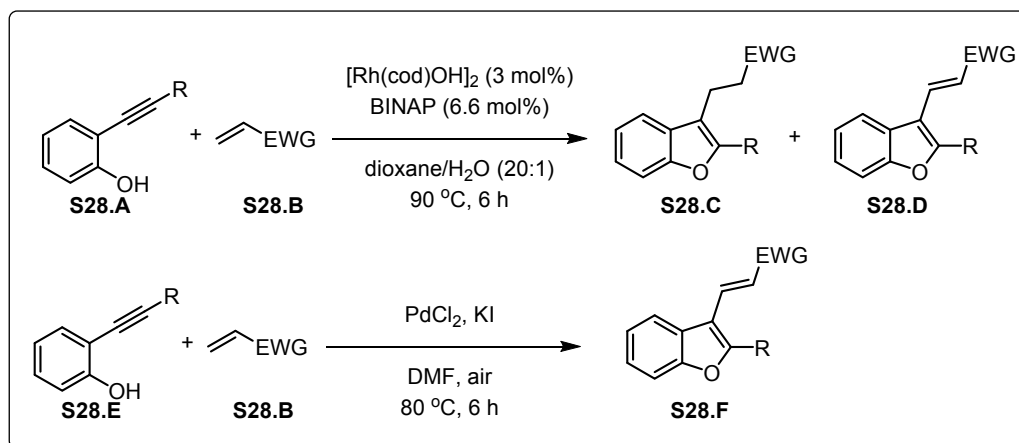


Figure 3.1: Structures of selected drugs/investigational drugs having the 2,3-disubstituted benzofuran core and classification of the 2-/3-arylbenzofuran class of molecules

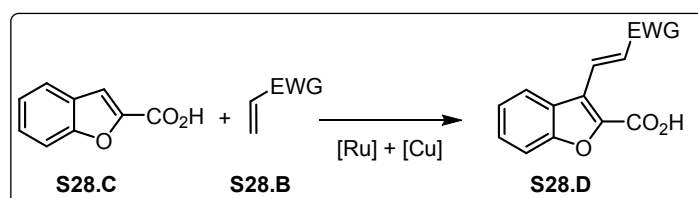
The reported procedure for the synthesis of these compounds is multistep in nature and involves harsh reaction conditions such as Fridel-Crafts acylation and acid/base mediated condensations.⁴⁹ A plausible approach will be the one-pot sequential metal-catalyzed cyclization of 2-alkynylphenols followed by the trapping of the intermediate aryl metal species with α,β -unsaturated carbonyl compounds. In 2009, two research groups (Aurrecoechea and Lautens) independently reported the [Pd] and [Rh]-catalyzed tandem cyclization *cum* Heck-type coupling between 2-alkynylphenols and alkenes, which led to 2,3-disubstitutedbenzofurans (Scheme 3.1).⁵⁰ In both the cases, the reaction proceeds *via* the

cyclization of 2-alkynylphenols and subsequent trapping of the intermediate benzo[*b*]furanyl-C3-metal species with α,β -unsaturated carbonyl compounds. However, substituents at the C2 are limited mainly to the alkyl or aryl group and β -substituted acrylates found as poor substrates.



Scheme 3.1: Reported Rh-/Pd-catalyzed cyclization-conjugate addition cascade

In 2011, Satoh, Miura and co-workers reported a complementary method for this purpose that involves the C2 carboxylate directed cross-dehydrogenative coupling of alkyl acrylates and benzo[*b*]furan-2-carboxylate derivatives (Scheme-S3.20).³⁵ The cheap and inexpensive $[\text{RuCl}_2(\text{p-cymene})]_2$ has been employed as the catalyst and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the stoichiometric oxidant. The reactions proceeded with complete linear selective alkenylation. As mentioned in the introduction, this initial success with ruthenium (II)-mediated cross dehydrogenative couplings has been explored further by several other groups employing a wide range of directing groups on both aryl and heteroaryl rings. The recent report of the Pd-catalyzed C3 arylation of 1-aryl benzofuran derivatives by Bertounesque and co-workers needs a special mention here.⁵¹



Scheme S3.20: Miura's landmark approach on first Ru-catalyzed cross-dehydrogenative coupling

Given the biological significance of the compounds of Type I–IV, and the presence of a weak coordinating group such as aroyl on the benzofuran ring, the C-H elaboration of activation methods for these heterocycles will be a suitable facile alternative for the synthesis of these important pharmaceuticals. We have been interested in exploring the possibility of

the C2-carbonyl directed C3 alkylation of benzo[*b*]furans using the α,β -unsaturated carbonyl compounds as electrophiles. Needless to say that with α, β -unsaturated esters (acrylates) it is still a big challenge to do regioselective hydroarylation on aryl or heteroaryl groups with any metal catalyst. Many endeavours end up with only dehydroarylation (alkenylation) and very few reports deal with Rh and Re providing linear alkylation.^{44, 42} There have been strong debates on commonalities and differences of the directing group influence on the outcome of the reaction and the elaboration of its mechanistic studies. However the investigations have been limited.

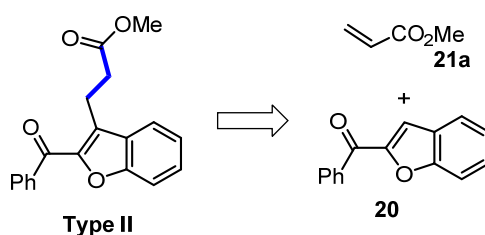
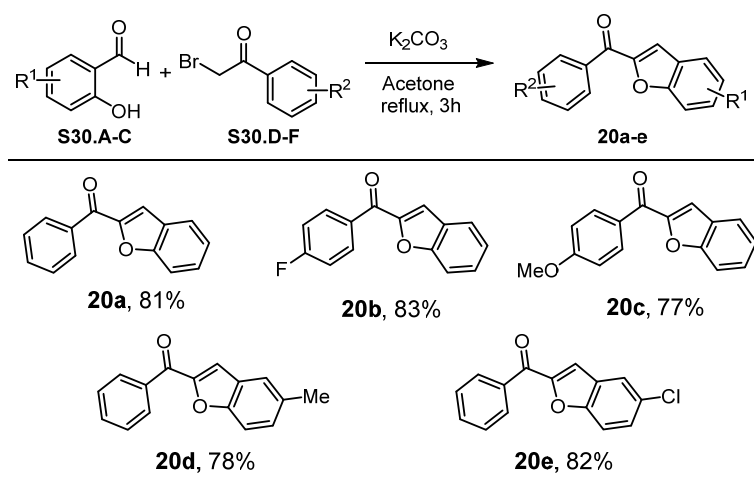


Figure 3.2: C–H activation approach for the requisite branched/linear alkylation on benzofurans

Figure 3.2 reveals our intended strategy for the synthesis of 3-substituted 2-arylabenzofurans of Type II derivatives *via* carbonyl directed C–H activation. Considering the fact that the earlier reports on similar reactions in general employ re-oxidants such as $\text{Cu}(\text{OAc})_2$ for cross-dehydrogenative coupling,^{37, 38} we intended to explore the possibility of alkylation with acrylates without using any such oxidant. Since cationic Ru-arene complexes have been employed for the cross dehydrogenative couplings, our concern was whether the neutral ruthenium-complexes will pave the path for the alkylation with acrylates.



Scheme 3.2: Synthesis of 2-arylabenzofuran substrates

The starting 2-arylabenzofuran derivatives **20a–20e** have been synthesized by following the established procedures.⁵² As shown in Scheme 3.2, the synthesis involves the

treatment of a salsiladehyde derivative with 2-bromo acetophenone in the presence of K_2CO_3 in acetone for 3 h at its reflux temperature.

After having a diverse set of substrates, the initial studies began with the identification of the optimal catalyst for the requisite alkylation with methyl acrylate. Some selected ruthenium complexes have been screened as catalysts for this purpose using benzo[*b*]furan **20a** as the substrate and methyl acrylate **21a** as an acceptor and the conditions used were those that have been commonly prescribed for the directed C–H bond activations (Table 3.1). The employed conditions in the exploratory experiments involved the heating of a mixture of **20a** with excess acrylate (3 eq.) in the presence of the catalyst (10 mol %), K_2CO_3 (3.0 eq.) and adamantane-1-carboxylic acid ($AdCO_2H$, 0.3 eq.) in toluene at 140 °C for 12 h in a screw-capped sealed tube. These preliminary experiments revealed that the desired alkylation of **20a** was viable. Quite interestingly, the formation of substantial amounts of branched alkylated products **22aa** along with the linear product **23aa** was noticed. The ratio of linear vs branched products seems to be catalyst dependent. Among the various ruthenium complexes screened, the best branched selectivity was obtained with $Ru_3(CO)_{12}$, $RuH_2(CO)(PPh_3)_3$ and $Ru(PPh_3)_3Cl_2$. The results have been summarized in table 3.1.

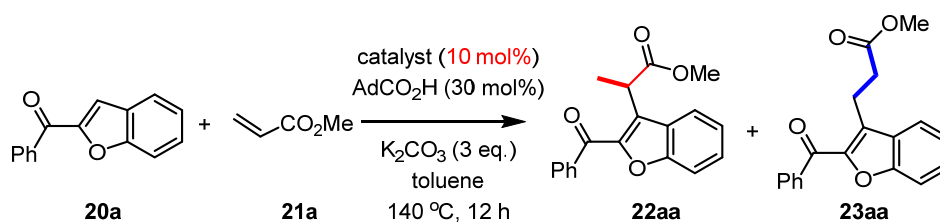


Table 3.1. Catalyst screening for directed hydroarylation

S.No	Catalyst	Yield (%) ^a (22aa / 23aa)
1	$[Ru(p\text{-cymene})Cl_2]_2$	23 (28/72)
2	$Ru_3(CO)_{12}$	31(83/17)
3	$RuCl_3 \cdot H_2O$	nd
4	RuO_2	No reaction
5	$(PPh_3)_3Ru(CO)H_2$	73 (89/11)
6	$Ru(PPh_3)_3Cl_2$	82 (94/6)

^aisolated yield; nd = not determined (complex reaction mixture)

The products were confirmed by NMR and HRMS. In the ^1H NMR spectrum the branched alkylated product **22aa**, the C2'–H and C6'–H were seen to resonate at δ 8.10–8.16 ppm as a multiplet and the characteristic benzofuran C3–H was seen to disappeared. The

methoxy group of the propionate unit resonated at δ 3.68 ppm as a singlet and the terminal methyl group at δ 1.67 ppm as doublet with $J = 7.2$ Hz and methyne (CH) at δ 4.96 ppm resonated as quartet with $J = 7.2$ Hz. In the ^{13}C NMR spectrum of compound **22aa**, the characteristic benzofuran C3 carbon appeared as a singlet at δ 126.7 ppm and the corresponding propionate methoxy carbon resonated at 52.2 ppm as a quartet. The terminal methyl carbon resonated at 16.8 ppm as quartet, the methyne (CH) carbon at δ 35.9 as a doublet and the carbonyl carbon resonated at δ 185.9 ppm as a singlet. In the HRMS, the exact mass of the compound showed, as calculated, for $\text{C}_{19}\text{H}_{16}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 331.0941 and it was found to be 331.0938. Considerations of the cost, stability and the good yield obtained, when compared with $\text{Ru}_3(\text{CO})_{12}$ and $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$, led us to select the $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ complex for further optimization studies.

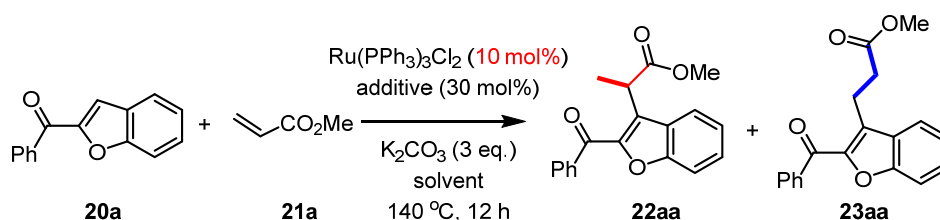


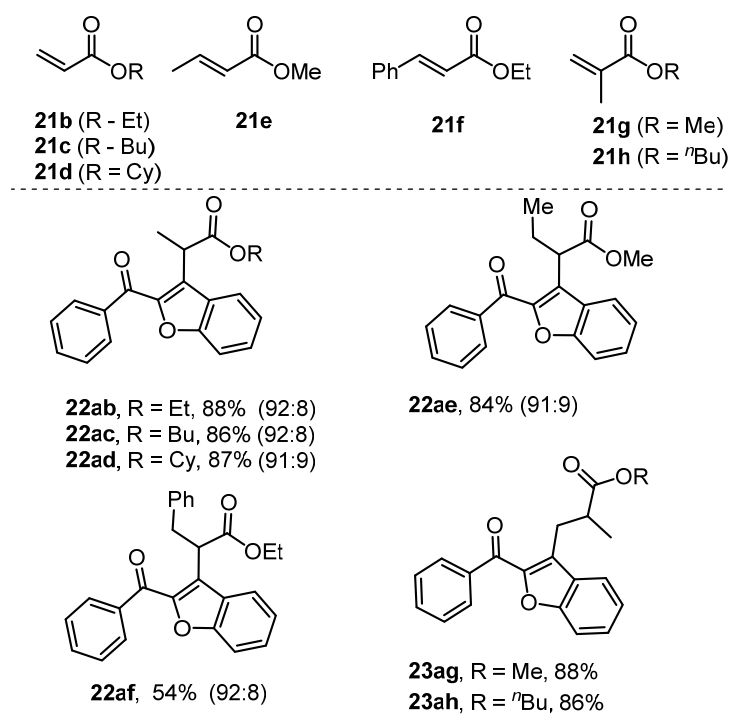
Table 3.2. Catalyst screening for directed hydroarylation

S.No	Additive	Solvent	Base	Yield% (3/4) ^b
1.	PivCO ₂ H	Toluene	K ₂ CO ₃	74 (91/9)
2.	CCl ₃ CO ₂ H	Toluene	K ₂ CO ₃	77 (96/4)
3.	MesCO ₂ H	Toluene	K ₂ CO ₃	72 (95/5)
4.	Cu(OAc) ₂	Toluene	K ₂ CO ₃	74 (94/6)
5.	AgOAc	Toluene	K ₂ CO ₃	87 (94/6) ^c
6.	No additive	Toluene	K ₂ CO ₃	61 (90/10) ^d
7.	AgOAc	DMSO	K ₂ CO ₃	nd
8.	AgOAc	DMF	K ₂ CO ₃	nd
9.	AgOAc	DCE	K ₂ CO ₃	0 ^e
10.	AgOAc	NMP	K ₂ CO ₃	0 ^f
11.	AgOAc	Dioxane	K ₂ CO ₃	67 (79/21)
12.	AgOAc	Toluene	K ₂ CO ₃ (1 eq.)	56
13.	AgOAc	Toluene	K ₂ CO ₃ (2 eq.)	63
14.	AgOAc	Toluene	K ₂ CO ₃ (5 eq.)	86
15.	AgOAc	Toluene	No Base	No reaction

^a**Reaction conditions:** benzofuran (1 eq.), methylacrylate (3 equiv), $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ catalyst (10 mol%), K_2CO_3 (unless otherwise mentioned, 3 equivalents with respect to **20**), Additive (30 mol%), 140 °C, solvent, 24 h; ^b isolated yield after column chromatographic purification; ^c clean reaction; ^d intractable compounds increased in the reaction mixture; ^e recovered unreacted starting material; ^f keto group was reduced; nd = not determined (complex reaction mixture); NR = no reaction.

The optimization experiments were carried out for improving the yield and regio selectivity by using 5 mol% catalyst, 3 equivalents of K_2CO_3 and 30 mol% of additive. Various additives have been used (entries 1-5, Table 3.2), Silver acetate has been found to be the best additive for improving the selectivity and consequently, the products were isolated in excellent yield. Coming to the solvents screened, DMSO (Entry 7), DMF (Entry 8) and DCE (Entry 9) were found to be completely ineffective. Reduction of the keto group was observed when NMP was used as the solvent (Entry 10).⁵³ In 1,4-dioxane, the reaction gave good yield, but the selectivity was reduced (Entry 11), Thus, toluene has been identified as the solvent of choice for which both the yield and the selectivity were found to be the best. Control experiments revealed that the reaction also proceeds without AgOAc (entry 12, Table 3.2), but with a high increase in the amount of intractable compounds in the mixture. Experiments with varying concentrations of K_2CO_3 revealed that its presence is essential (entries 12–15, Table 3.2).

Table 3.3: Acrylate substrate scope^{a,b}

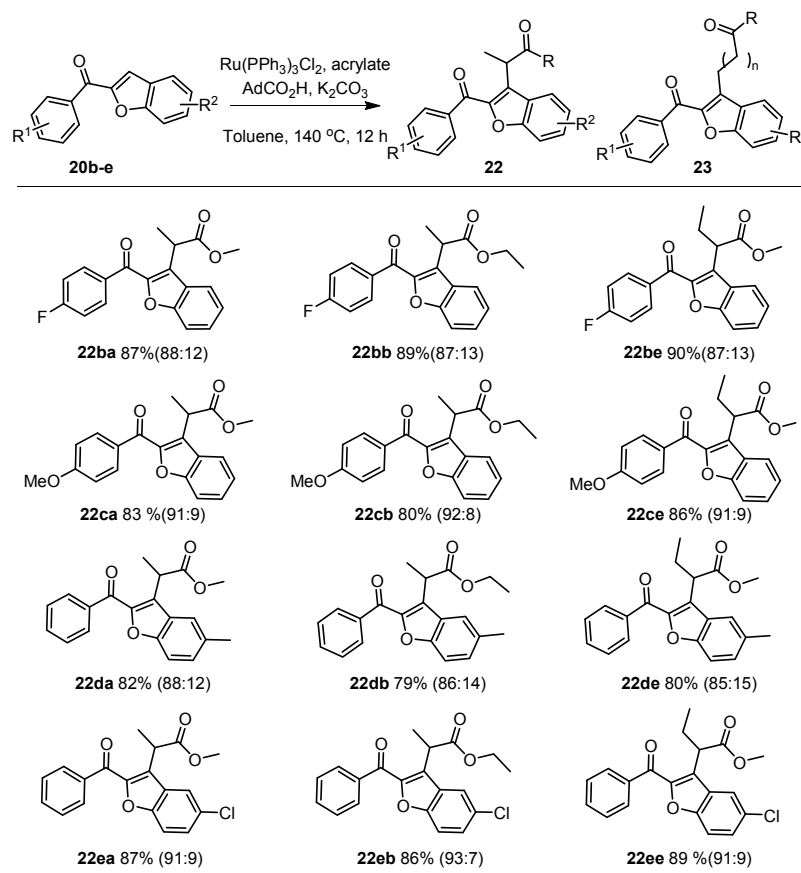


^a**Reaction conditions:** benzofuran (1 equiv), acrylate (3 equiv), $Ru(PPh_3)_3Cl_2$ (5 mol%), K_2CO_3 (3equiv), AgOAc (30 mol%), 140 °C, toluene, 24 h. ^bisolated yield after column chromatographic purification. The ratio has been confirmed by HPLC and ^1H NMR.

The compatibility of various α,β -unsaturated esters as coupling partners has been explored under the optimized conditions employing **20a** as the substrate. The reaction of **20a** with ethyl-, butyl-, and cyclohexyl acrylates (**21b–21d**) gave the corresponding products in

very good isolated yields without substantial difference in the branched/linear selectivity. In case of methyl crotonate (**21e**), the reaction proceeded smoothly and the corresponding branched adduct **22ae** was obtained as the major product and the 1,5-addition linear adduct was obtained as the minor isomer (**24**) with an overall yield of 84%.⁴⁴ The minor isomer (**24**) has been confirmed by NMR and HRMS (see the experimental section). In the ¹H NMR spectrum of the linear alkylated product **24**, the protons of threemethylenes (CH₂) were resonated at δ 2.12 ppm as quintate ($J = 7.5$ Hz, 2H), 2.46 ppm as triplet ($J = 7.5$ Hz, 2H), 3.22 ppm as triplet ($J = 7.6$ Hz, 2H). In the ¹³C NMR spectrum these three methylene carbons were appeared as triplets at δ 23.7, 24.7 and 33.5 ppm. However, with both methyl- and butyl methacrylates (**21g** and **21h**), the corresponding linear adducts **23ag** and **23ah** were formed as the only products. This result indicates that steric factors might be playing a substantial role in deciding the linear vs branched selectivity. In the case of ethyl cinnamate (**21f**), the reaction was sluggish and the branched adduct **22af** was obtained as the major product in moderate yield/conversion (Table 3.3).

Table 3.4: Acrylate scope and structural variations to the benzofuran counterpart.

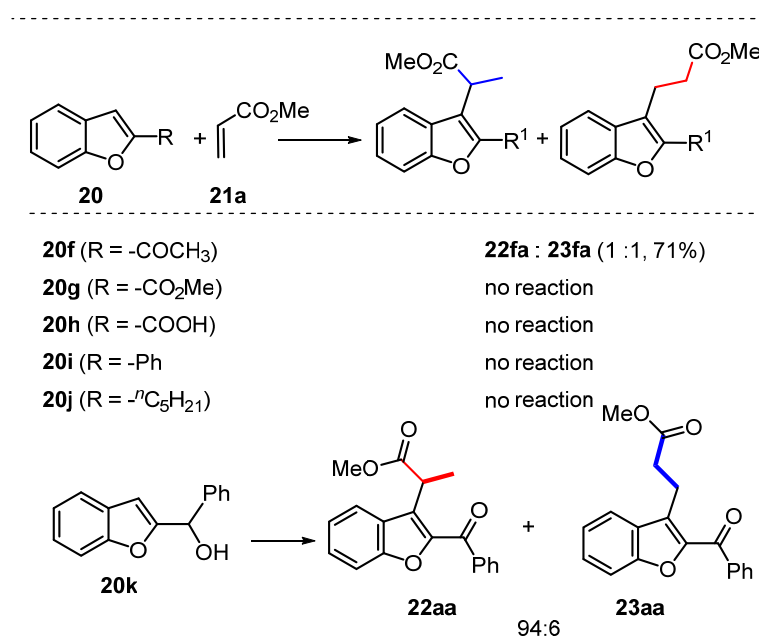


^a**Reaction conditions:** benzofuran (1 equiv), acrylate (3 equiv), Ru(PPh₃)₃Cl₂ (5 mol%), K₂CO₃ (3equiv), AgOAc (30 mol%), 140°C, toluene, 24h. ^bisolated yield after column chromatographic purification. ^crecovered unreacted starting material. nd = not determined (complex reaction mixture).

The generality of the branched selective alkylation with **21a**, **21b** and **21e** has been examined further by employing variously substituted 2-arylbenzofurans **20b–20e**, and all the reactions were seen to be facile with the optimized conditions and furnished excellent yield. As indicated in Table 3.4, the presence of the electron withdrawing group on the phenyl ring led to the increase in the linear product formation. On the other hand, the presence of the electron donating groups on the phenyl ring enhanced the branched selectivity. The presence of the electron withdrawing substituent on the benzofuran ring has, at most, only nominal influence on the selectivity. Interestingly, when a methyl group is present in place of chlorine, the selectivity was found to drop slightly. These observations indicate that the coordinating ability of the carbonyl group with the metal center has some influence on the branched *vs* linear selectivity.

Next, in order to learn about the role of the directing group, the reaction has been conducted with different C2 substituted benzofuran derivatives (Scheme 3.3). As expected, both 2-alkyl-, 2-phenyl and 2-carboxylate derivatives were intact under these conditions. In case of 2-acetyl benzofuran, the reaction proceeded smoothly, with the product formation occurring in good yield. However, the regioselectivity dropped to ~1:1. Very interestingly, in case of benzofuran-2-yl(phenyl)methanol, both the oxidation and alkylation are facile and resulted in **22aa**.

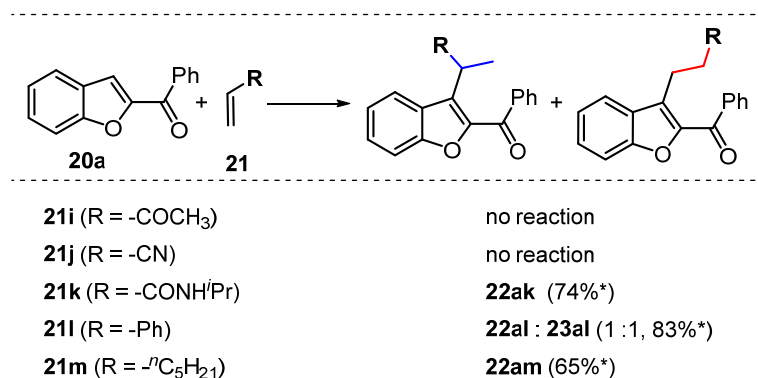
Scheme 3.3: Scope of directing groups ^{a,b}



^a**Reaction conditions:** **20** (1 mmol), **21** (3 mmol), Ru(PPh₃)₃Cl₂ (5 mol%), K₂CO₃ (3 mmol), AgOAc (30 mol%); ^bisolated yield and ratio determined by ¹H NMR

These observations clearly reveal the necessity of a carbonyl group for the desired alkylation and the steric influence of the pendant alkyl/aryl group on regioselectivity. Later, we have examined the scope of this reaction with respect to the substituents on alkene by employing *N*-isopropylacrylamide, acrylonitrile, methylvinyl ketone, styrene and dodecene as representative olefin partners and 2-benzoylbenzofuran (**20a**) as a substrate (Scheme 3.4).

Scheme 3.4: Scope of olefin partners^a



^a**Reaction conditions:** **20** (1 eq.), **21** (3 eq.), Ru(PPh₃)₃Cl₂ (5 mol%), K₂CO₃ (3 eq.), AgOAc (30 mol%); *Yield based on the recovered starting material

The reactions with acrylonitrile and methylvinyl ketone were not found to be encouraged under these conditions. The reaction was sluggish with *N*-isopropyl acrylamide (74% yield based on 48% conversion). However, the reaction exclusively gave the branched product (**22ak**). A 1:1 regioisomeric mixture was obtained with styrene.⁵⁴ On the other hand, with dodec-1-ene, the reaction was incomplete (65% yield based on 42% conversion),⁵⁵ but interestingly, the reaction gave exclusively the linear alkylation product (**22am**).

Mechanistic Study

Having encountered and then established the unprecedented branched selective alkylation with acrylates, our next concern was to understand the mechanism of this reaction. The two important issues to be addressed in this context are –i. the mechanism of deprotonation; ii. The possibility of a Ru–H intermediate and subsequent hydrometallation (Murai's type mechanism).²³ There have been four possible mechanisms proposed for the C–H deprotonation – i. oxidative addition; ii. sigma-bond metathesis; iii. electrophilic substitution and iv. 1,2-addition.⁵⁶ Coming to the Ru(II)-complexes, in many of the instances it has been proposed that the reaction proceeds *via* the electrophilic substitution. The generally proposed mechanism proceeding *via* electrophilic substitution involves an intramolecular deprotonation assisted by a carbonate or carboxylate. However, in case of ruthenium-arene complexes, especially when pyridine was a directing group, Dixneuf and co-workers have revealed that

this is intermolecular in nature and is an autocatalytic process – i.e the released carboxylic acid will enhance the rate of deprotonation (Fig. 3.3).⁵⁷

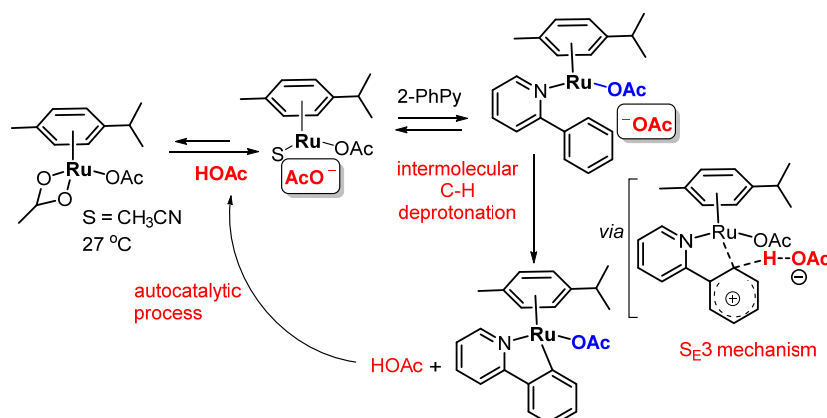
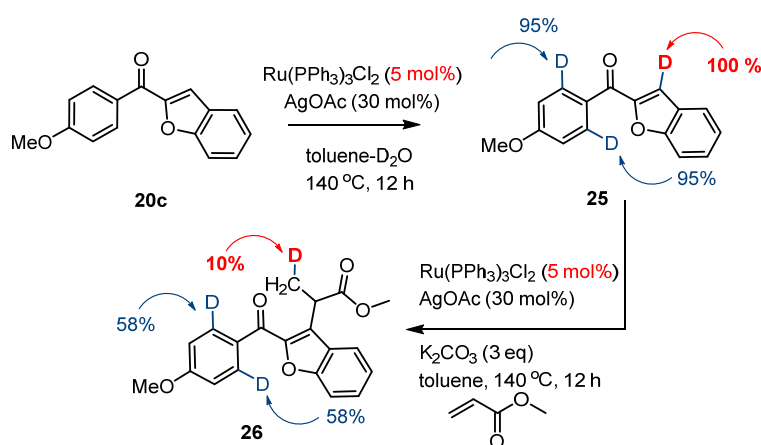


Figure 3.3: *Dixneuf's approach for possibility of deprotonation by acetate*⁵⁷

Considering these issues, the deuterium labelling experiments have been carried out in order to understand the course of the deprotonation and also the possibility of the hydrometalation.



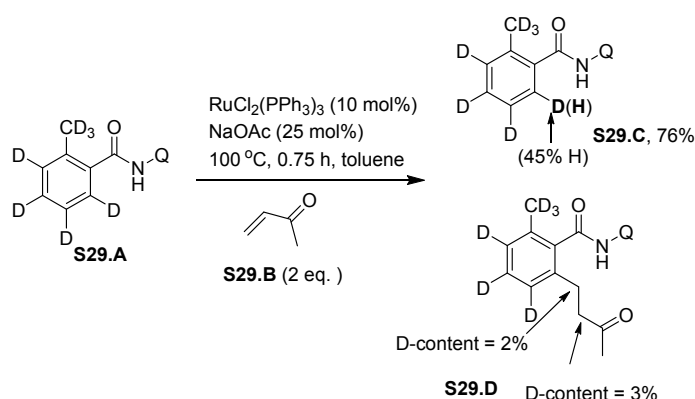
Scheme 3.5. *Deuterium labeling experiments*

Table 3.5. Deuterium labeling experiments with 20c

S.No	Additive	% of deuterium labelling	
		C3 (%)	C2'+C6' (%)
1	AgOAc (30 mol%)	100	95
2	K ₂ CO ₃ (3 eq.)	53	46
3	no additive and base	87	75.5
4	AgOAc (30 mol%) K ₂ CO ₃ (3 eq.)	58	15.5

The reactions were conducted in the presence of D_2O and without acrylate. As shown in Scheme 3.5, the deuterium incorporation was observed at the C3 position of benzofuran and also at the C2'/C6' position of the pendant aryl ring. The magnitude of the deuterium incorporation seems to depend upon the presence and/or absence of the additives (Table 3.5). With the $Ru(PPh_3)_3Cl_2$ alone, the deuterium incorporation was found to be better than when all the other additives were present. The maximum deuterium incorporation (100% at C3 and 95% at C2'/C6') was observed when silver acetate was used as an additive along with the ruthenium complex. This observation reveals that the path of the reaction presumably involves an acetate assisted deprotonation of the C–H bond, as proposed by Dixneuf and others in the [Ru]-catalyzed directed arylations. Surprisingly, the reactions, either with potassium carbonate (3 eq. with respect to the benzofuran) alone or along with $AgOAc$, resulted in a dramatic decrease in the deuterium labelling at both the carbons.

Having been prepared the C3 deuterated benzofuran **20c**, next we examined its alkylation with acrylate under the optimized conditions. As shown in Scheme 3.5, quite interestingly, the incorporation of deuterium at the β -position of the branched product was observed. However, the percentage of deuterium incorporation was quite nominal (<10%). Similarly, the loss of deuterium at C2' and C6' of the benzoyl group was also noticed. These experiments revealed that the C–H activation process is reversible and also that maybe there was no hydride mechanism involved. Very recently, Rouquet and Chatani have revealed a similar observation in the [Ru]-catalyzed *o*-alkylation of aromatic amides with α,β -unsaturated ketones and remarked that the involvement of [Ru]–H species in the catalytic cycle is yet to be clarified (Scheme 3.6).⁴⁵



Scheme 3.6: Chatani's approach for deuterium labelling study⁴⁵

After having obtained some clues from the deuterium labelling experiments next we proceeded further in the direction of understanding the course of the branched selective alkylation. Some of the observations need to be highlighted (Fig.3.4). As shown in Figure

3.4, the outcome of the C–H functionalization completely depends upon the electronic nature of the olefin employed. In general, with the electron deficient olefins, the branched selectivity is greater. Whereas with partially polarized styrene, a 1:1 mixture of both linear and branched products was obtained and with dodec-1-ene, the complete linear product was obtained. On the other hand, when acetyl was a directing group (with more nucleophilic carbonyl), the selectivity dropped to 1:1. Also, when dioxane was employed as a solvent in lieu of toluene that has been generally used, the selectivity dropped to 4:1. Another important point to be mentioned here is, during our initial exploratory experiments, under similar conditions, the linear selective alkylation was noticed with the Ru-arene complex.

This catalyst dependent regioselectivity under the similar conditions suggests that the active catalysts involved in these two processes are different in both their steric and their electronic preferences. With the complex B ($\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$), the observed branched selectivity with methyl acrylate, the lack of regioselectivity with partially polarized styrene and the complete linear selectivity with dodec-1-ene reveals that the partial charge present on the metal centre, *inter alia* the low polarity of the Ru–C bond in the ruthenocycle intermediate involved does not alone decide the orientation of the olefin for its insertion into the Ru–C bond. However, the exclusive formation of linear products with methyl methacrylate indicates steric crowding around the metal centre and therefore suggests the presence of overriding steric effects. The large steric effect of $\text{L}_3 = (\text{PPh}_3)_3$ with respect to $\text{L}_3 = \text{arene}$ likely influences the insertion of the alkene into the Ru–C bond, taking the functional group far from the PPh_3 ligands.

All these observations indicate that in the course of the reaction, Ru–C bond of the intermediate ruthena-cycle involved is non-polar in nature and is susceptible for electronic perturbations from either side. When either directing group is strong or the reaction medium is polar, there is a chance for partial polarization of this bond and thus the selectivity drops. Finally, the exclusive formation of linear products with methyl methacrylate indicates steric crowding around the metal center and therefore suggests the presence of overriding steric effects.

The discrimination in the olefin orientation seems to be originating from the electronic influence as the sterically demanding methacrylate exclusively gave the linear product. Such a type of electronic discrimination and regioselectivity switching either by polarity of the substrate or because of the electronic nature of the ligands around the metal

centre has been revealed earlier in the hydrometalation step by the groups of Spencer and Yu.^{58, 59}

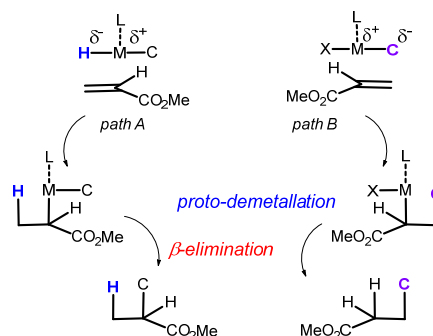
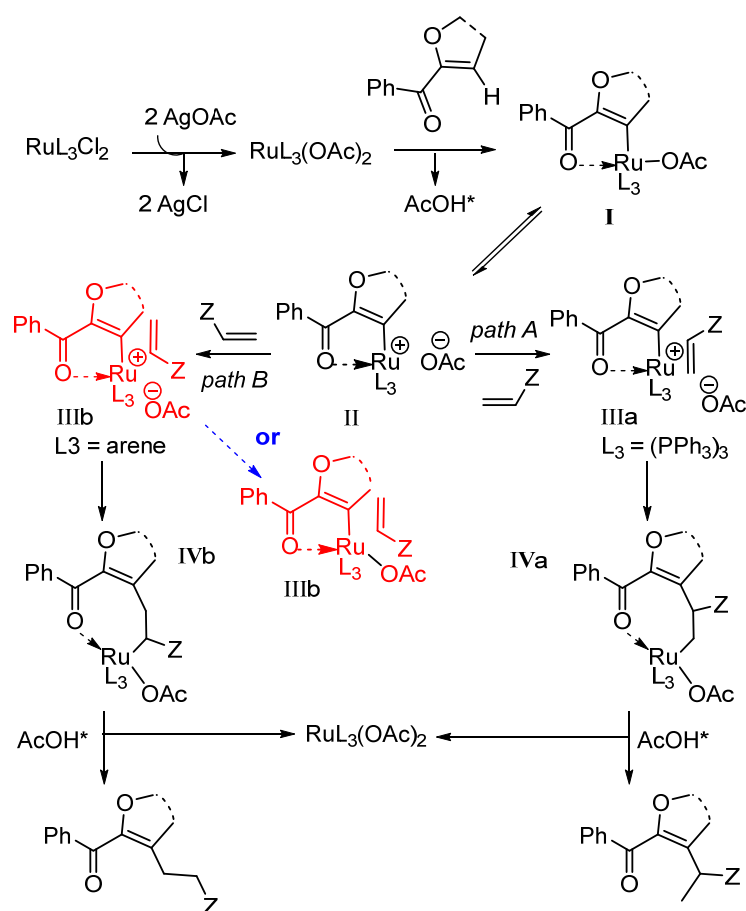


Figure 3.4: Hydroarylation (Yu's proposal) on the hydrometalation and similar proposal

Analogous to the hypothesis that has been extended by Yu and co-workers in case of hydroarylation and with the information available in hand, herein, we propose that, there exist two possible pathways for the coordinative insertion. In path A, the β -carbon of the acrylate is oriented close to the metal centre whereas in path B, the α -carbon is close to the metal centre. While the former leads to the branched product the latter should provide the linear product. The preference for paths A and B will be determined by the partial charge present on the metal centre. In case the metal-carbon bond is non polar, the path A is preferred on the steric grounds, which we believe is indeed operational in the present case. The increase in the branched selectivity in case of **20c** where a methoxy group is present at *para*-to the carbonyl group and can retard the metal back donation to the π -system of the carbonyl group, the lack of regioselectivity with partially polarized styrene and the complete linear selectivity with 1-dodecene supports our arguments.

On this basis, and considering previous reports, a plausible pathway is proposed (Scheme 3.7). The reaction of complex **B** with 2 eq. of AgOAc generates $\text{Ru}(\text{OAc})_2(\text{PPh}_3)_3$. The coordination of the carbonyl group and the subsequent acetate-mediated deprotonation leads to the intermediate ruthenacycle **I** and releases AcOH. The easy dissociation of the $\text{AcO}-\text{Ru}(\text{II})$ bond from complex **I** favours the cationic intermediate **II**. Here, there exist two possible pathways for the olefin coordination and its insertion. In path A, observed for $\text{L}_3 = (\text{PPh}_3)_3$, the β -carbon of the acrylate is oriented close to the metal center due to steric interactions of the functional group (**IIIa**). On the other hand in path B for $\text{L}_3 = \text{arene}$, the $\text{Ru}-\text{C}$ bond is more polar (**IIIb**) and the α -carbon is close to the metal center. While the former pathway leads to the branched product precursor **IVa** the latter pathway should provide the linear product precursor **IVb**. Subsequent insertion of the acrylate and a final protodemetalation by AcOH affords **22a/23a** and thus regenerates the ruthenium acetate complex.



Scheme 3.7: Proposed mechanism for the hydroarylation

An alternative mechanism involving a $[\text{Ru}]\text{-H}$ (like in the Murai reaction) intermediate and subsequent hydrometalation and final reductive elimination is also possible for $\text{Ru}_3(\text{CO})_{12}$ and $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ leading to regioselectivity similar to catalyst **B** ($\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$). However, under the conditions employed in the present case, the possibility of a $\text{Ru}[0]$ species generation for insertion into the C–H bond is doubtful.

C–H functionalization pyridine as directing group

After the initial success documented by Miura on the Ru-catalyzed carboxylate directed oxidative cross coupling, reactions with acrylates via C–H activation (cross dehydrogenative coupling) has seen a wide range of applications in this area. Apart from the carbonyl group, various other functional groups have been deployed as the directing ligands in this context. Amongst them, pyridine is one of the important directing groups that have been employed recently by Takai and co-workers in the area of Re-catalyzed cross dehydrogenative couplings. As has been indicated in the introduction, with simple 2-arylpyridine derivatives, the reaction with acrylates in general proceeds in a linear fashion resulting in the cross-dehydrogenative coupling products. However, such pyridine directed couplings on benzofuran or on any other heterocyclic systems have not yet been documented.

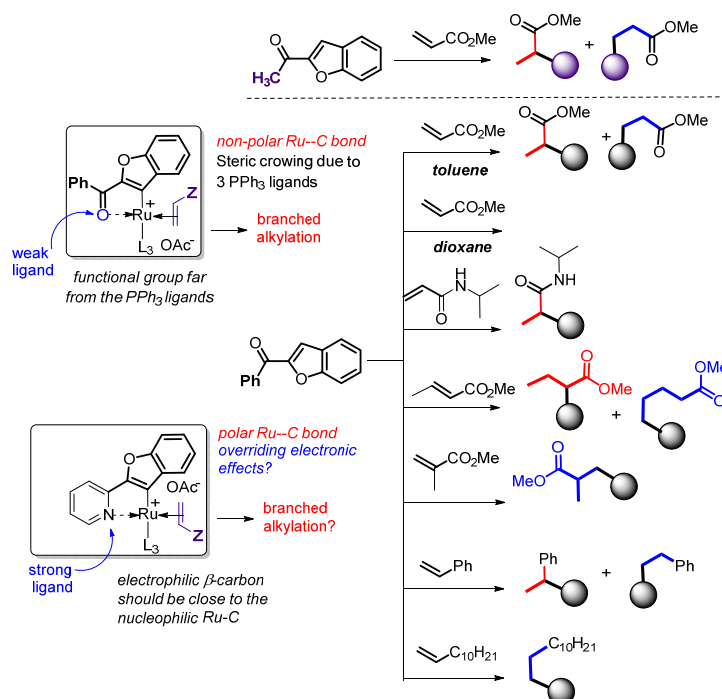


Figure 3.5: Directing group influence on mode of C-H functionalization

After having established benzoyl as a directing group for alkylation, and having studied the factors that influence the branched selectivity as well as, the directing group influence on the mode of C-H functionalization, our next concern was what happens if the directing group is strongly ligating like pyridine. As given in the above Figure 3.5, one can see that the competition between linear and branched alkylation depends upon both the electronic preferences of the directing group and also of olefin. Under the same conditions, conjugated olefin gave mainly branched alkylation whereas the simple dodec-1-ene gave exclusively linear alkylation. On the other hand, with same methyl acrylate, when the directing group was acetyl, the proportion of the linear alkylation (when compared with benzoyl directing group) was increased. Also, the branched selective alkylation with acrylate was higher in toluene and decreased when dioxane was employed as the solvent. As mentioned in the previous mechanistic discussion, we reasoned that this was because of the low polarity of the Ru-C bond in the involved ruthenacycle intermediate was susceptible for simple electronic effects induced by the substituents present on either the aryl or the benzofuran rings. Funded upon these observations and to provide further support to the hypothesis on the involvement of the lowpolarity of the Ru-C bond, we have been further interested to look at the C3 alkylation of benzofuran employing pyridine as a directing group. As shown in Figure 3.5, we reasoned that due to the strong donation from the pyridine ring the Ru-C in the intermediate ruthena cycle will be more polarized and thus favour the

coordination of the olefin based upon the electronic preferences i.e – the electrophilic β -carbon of the acrylate should be close to the nucleophilic Ru–C bond and thus should provide the linear alkylation product.

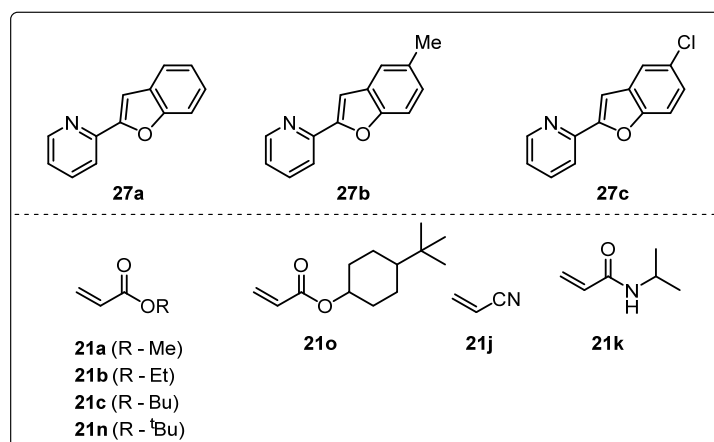


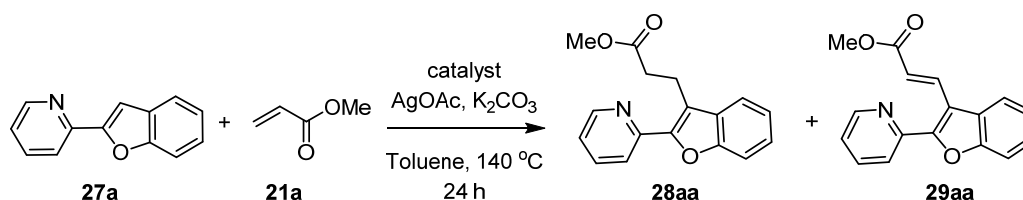
Figure 3.6: The starting compounds for the alkylation.

Our ventures in this direction started with the preparation of the 2(2'-pyridyl)benzofurans **27a–27c** by the Sonogashira coupling of 2-ethynylpyridine with the corresponding 2-iodophenols. Our initial studies were carried out by employing **27a** as a substrate and methyl acrylate as the coupling partner. Under the same conditions that have been employed with the 2-benzoylbenzofuran, the reaction of **27a** with methyl acrylate gave exclusively one product the structure of which has been established as given in Table 3.6 with the help of spectral data analysis. For example in the ^1H NMR spectrum of the compound **29aa**, olefinic protons were seen to resonate at δ 6.74 and 9.02 ppm as two doublets respectively with the coupling constant of 16.5 Hz indicating the presence of a double bond with E-configuration. The methoxy protons resonated at δ 3.86 ppm as a singlet, and most importantly, the disappearance of C3-H was observed. In the HRMS, the exact mass of the compound showed as calculated for $\text{C}_{17}\text{H}_{14}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$) was 280.0968 and it was found as 280.0968.

Although the linear selectivity is anticipated on the basis of the above mentioned hypothesis of strong coordinative ability of the pyridine unit, however, the observed complete cross-dehydrogenative coupling without any alkylation product was surprising, since no co-oxidant was employed. However, considering the fact that the base was employed in excess and that in Heck-like couplings it is known that the base plays the essential role of facilitating the final reductive β -elimination step, control experiments were carried out in the absence of base. Interestingly, when the reaction was conducted under identical conditions except the absence of base, the reaction provided exclusively the linear alkylation product with complete

regioselectivity. This is an important observation which revealed that with this Ru-complex, the alkylation reactions are proceeding through the commonly proposed coordinative insertion mechanism and that there is no involvement of any Ru-H intermediate.

Table 3.6. Catalyst screening for directed hydroarylation^{a,b}



S.No	catalyst	K ₂ CO ₃	28aa (yield %)	29aa (yield %)
1	Ru(PPh ₃) ₃ Cl ₂	presence	no	59
2	Ru(PPh ₃) ₃ Cl ₂	absence	75	no
3	Ru ₃ (CO) ₁₂	absence	no	68
4	[Ru(p-cymene)Cl ₂] ₂	absence	66	no

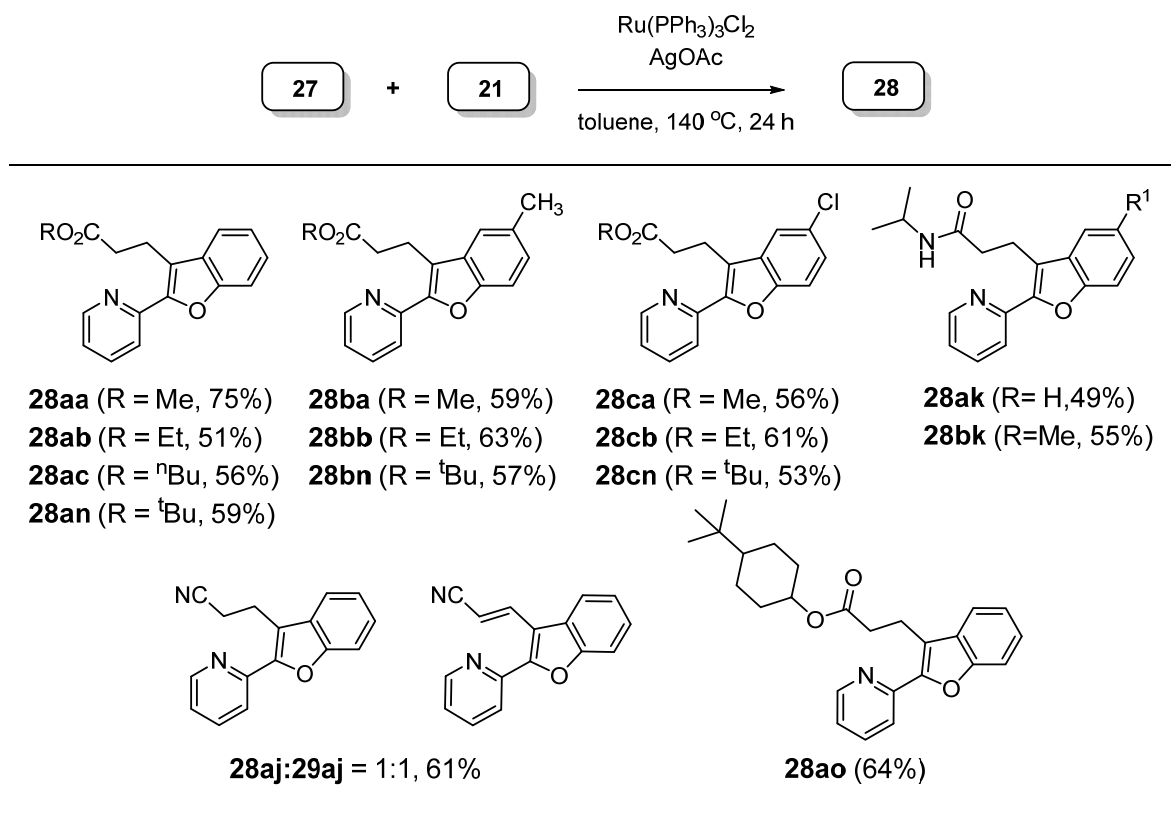
^a**Reaction conditions:** benzofuran (1 eq.), acrylate (3 eq.), catalyst (5 mol%), K₂CO₃ (3eq. and otherwise it mentioned), AgOAc (30 mol%), 140 °C, toluene, 24 h. ^bisolated yield after column chromatographic purification.

The structure of the linear alkylation product **28aa** has been confirmed by ¹H, ¹³C NMR and HRMS. In ¹H NMR spectrum of compound **28aa**, the two CH₂ protons were seen to resonate at δ2.83 and δ3.58ppm as two triplets with a coupling constant *J* = 8.1 Hz and most importantly, the disappearance of the C3-H was observed. In the HRMS, the exact mass of the compound showed as calculated for C₁₇H₁₆O₃N (M⁺+H) was 282.1125 and it was found as 282.1125. The results are summarized in Table 3.6.

Having discovered two complementary conditions for alkylation or alkenylation, we explored the generality of these reactions by employing a wide range of olefins and differently substituted benzofuran derivatives. Table 3.7 summarizes the results obtained with the alkylation reaction (absence of K₂CO₃). Various acrylates such as ethyl-, butyl-, tert.butyl- and 4-tert.butylcyclohexyl- acrylates (**21b**, **21c**, **21n** and **21o** respectively) were compatible and gave the corresponding products in moderate to good isolated yields. However, the reactions with *N*-isopropylacrylamide as well as with methyl crotonate, were found to be sluggish and the products were obtained in poor yields. Quite interestingly, with acrylonitrile (**21j**), the reaction proceeded smoothly and both the alkylated product **28aj** and the alkenylated product **29aj** were obtained in a 1:1 ratio as indicated in Table 3.7. The presence of the electron withdrawing substituent on the benzofuran ring has, at most, only nominal

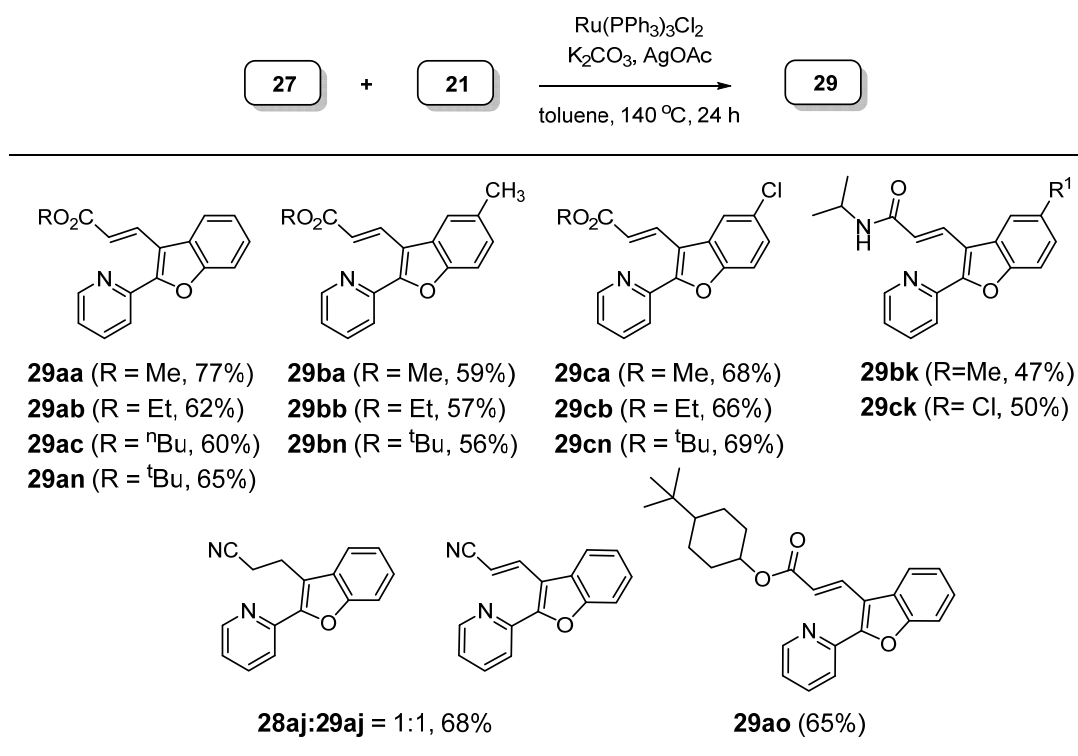
influence on the selectivity. Interestingly, when a methyl group is present in place of chlorine, the yields were found to drop slightly. These observations indicate that the C–H bond strength of the C3 carbon of benzofuran and the steric environment of the substrate has some influence on the yield of the reaction.

Table 3.7: Acrylate and substrate scope for alkylation^{a,b}



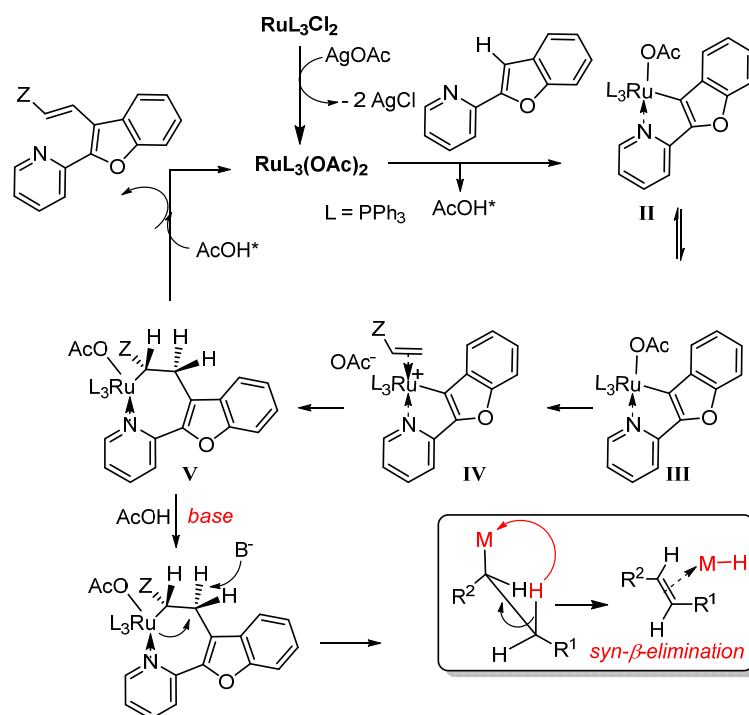
^a**Reaction conditions:** benzofuran (1 eq.), acrylate (3 eq.), Ru(PPh₃)₃Cl₂ (5 mol%), AgOAc (30 mol%), 140 °C, toluene, 24 h. ^bisolated yield after column chromatographic purification.

Table 3.8 shows the generality of the alkenylation (presence of K₂CO₃) of various 2-pyridylbenzofurans. Various olefin counterparts such as ethyl-, butyl-, tert.butyl- and 4-tert.butylcyclohexyl- acrylates (**21b**, **21c**, **21n** and **21o** respectively) were compatible and gave the corresponding linear selective alkenylated products in moderate to good isolated yields. In this case too the reaction with *N*-isopropylacrylamide was seen to be sluggish. Surprisingly, with acrylonitrile (**21j**), even in the presence of the base, both the alkylated product **28aj** and the alkenylated product **29aj** were obtained in a 1:1 ratio (Table 3.8).

Table 3.8: Acrylate and substrate scope for alkenylation^{a,b}

^a**Reaction conditions:** benzofuran (1 eq.), acrylate (3 eq.), Ru(PPh₃)₃Cl₂ (5 mol%), K₂CO₃ (3 eq.), AgOAc (30 mol%), 140 °C, toluene, 24 h. ^bisolated yield after column chromatographic purification.

Funded upon our initial hypothesis we extended the following mechanism for these two reactions. The reaction of RuCl₂(PPh₃)₃ complex with 2 eq. of AgOAc generates Ru(OAc)₂(PPh₃)₃. The coordination of the pyridyl nitrogen and the subsequent acetate-mediated deprotonation leads to the intermediate ruthenacycle **I** and releases AcOH. The easy dissociation of the AcO–Ru(II) bond from complex **I** favours the coordination of the olefin to the cationic intermediate **II**. Due to the more polar Ru–C bond present in complex **IIIb**, the electrophilic β-carbon is close to the nucleophilic Ru–C carbon atom. After the olefin insertion and acetate addition, the linear product precursor **IV** will be obtained. When there was no base present, this intermediate upon protodemetalation by the released AcOH affords the linear alkylation product and thus regenerates the ruthenium acetate complex. When the base is present, since the β-elimination (commonly encountered in Heck-coupling) is not possible as it requires that M–C_α and C_β–H bonds align in a syn coplanar arrangement, we propose that this happens *via* the base-mediate hydride abstraction through the anchimeric assistance of the metal centre present on the next carbon.



Scheme 3.7: *Proposed mechanism for the alkylation and alkenylation*

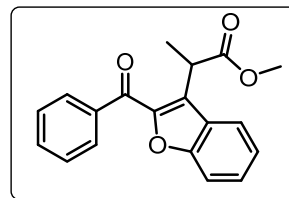
Conclusions

We have documented a first report on the hydroarylation of alkyl acrylates *via* C–H activation. This is the much awaited Murai Reaction with acrylates employing Ru-catalysts and more importantly, the substrates employed are pharmaceutically relevant. The remarkable features of the present transformations are – i. the unprecedented regioselectivity of the coupling process when the directing group was a benzoyl; ii. the base switch for the alkylation or alkenylation when the pyridine ring was the directing group. Overall we have provided the first examples in this direction – how the regioselectivity of acrylate insertion depended upon the steric and their electronic preferences of the active catalysts involved and how the electronic preferences around the metal centre will vary with the directing group employed. We believe that these findings will provide fresh impetus for further efforts on understanding the “hydroarylation process *via* C–H activation”, especially in the direction of how the nature of the substrate, catalyst, ligand, and base will be fine-tuned in order to achieve the alkylations with the desired regioselectivity.

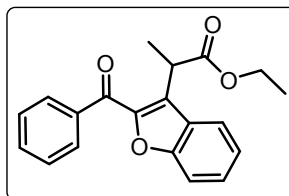
General procedure A: Hydroarylation of acrylates employing $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ complex

2-arylbenzo[b]furan (0.1 mmol) was placed in a screw cap pressure tube and dissolved in anhydrous toluene, which was then evacuated and back filled with argon. To the reaction vessel alkene (acrylate) (0.3 mmol), K_2CO_3 (0.3 mmol), $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ (0.005 mmol) and AgOAc (0.03 mmol) were added. The solution was then stirred at 140 °C (bath temperature) for 12h. The reaction mixture was cooled to room temperature. The solvent were evaporated and the crude products were purified by column chromatography (pet ether/AcOEt) to give analytically pure.

Methyl 2-(2-benzoylbenzofuran-3-yl)propanoate (22aa): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil (87%), and the ratio of branch to linear product is (94:6). ^1H NMR (200 MHz, CDCl_3): δ 1.67 (d, J = 7.2 Hz, 3H), 3.68 (s, 3H), 4.96 (q, J = 7.2 Hz, 1H), 7.32 (ddd, J = 1.4, 6.8, 8.1 Hz, 1H), 7.45–7.68 (m, 5H), 7.75 (d, J = 8.0 Hz, 1H), 8.10–8.16 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 16.8 (q), 35.9 (d), 52.2 (q), 112.5 (d), 122.2 (d), 123.7 (d), 126.7 (s), 128.1 (d), 128.3 (d, 2C), 128.8 (s), 129.9 (d, 2C), 132.9 (d), 137.3 (s), 147.7 (s), 154.3 (s), 173.7 (s), 185.9 (s) ppm; IR(neat): ν 3020, 2400, 1735, 1645, 1563, 1261, 1215, 1059, 877, 757, 669 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{16}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 331.0941; found: 331.0938.

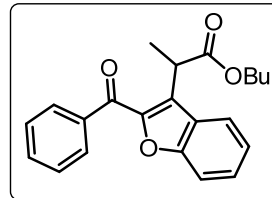


Ethyl 2-(2-benzoylbenzofuran-3-yl)propanoate (22ab): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil (88%) and the ratio of branch to linear product is (92:8). ^1H NMR (200 MHz, CDCl_3): δ 1.15 (t, J = 7.2 Hz, 3H), 1.67 (d, J = 7.3 Hz, 3H), 4.16 (q, J = 7.2 Hz, 2H), 4.91 (q, J = 7.3 Hz, 1H), 7.32 (ddd, J = 1.4, 6.8, 8.1 Hz, 1H), 7.44–7.67 (m, 5H), 7.77 (d, J = 8.0 Hz, 1H), 8.09–8.14 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 14.1 (q), 16.9 (q), 36.1 (d), 61.0 (t), 112.4 (d), 122.3 (d), 123.5 (d), 126.7 (s), 128.0 (d), 128.3 (d, 2C), 129.0 (s), 129.9 (d, 2C), 132.9 (d), 137.4 (s), 147.7 (s), 154.3 (s), 173.2 (s), 185.8 (s) ppm; IR(neat): ν 3278, 3061, 2984, 1908, 1732,

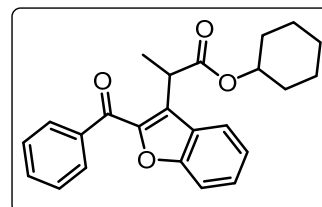


1645, 1599, 1448, 1300, 1200, 1093, 876, 752, 680 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{18}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 345.1097; found: 345.1095.

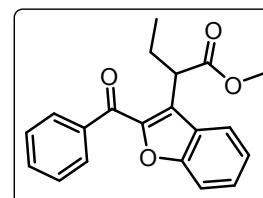
Butyl 2-(2-benzoylbenzofuran-3-yl)propanoate (22ac): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil (86%), and the ratio of branch to linear product is (92:8). ^1H NMR (400 MHz, CDCl_3): δ 0.79 (t, J = 7.3 Hz, 3H), 1.10–1.30 (m, 2H), 1.43–1.54 (m, 2H), 1.67 (d, J = 6.9 Hz, 3H), 4.11 (t, J = 6.6 Hz, 2H), 4.92 (q, J = 7.3 Hz, 1H), 7.33 (td, J = 0.9, 7.6 Hz, 1H), 7.46–7.58 (m, 4H), 7.60–7.64 (m, 1H), 7.77 (d, J = 7.8 Hz, 1H), 8.10–8.14 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.5 (q), 16.8 (q), 18.9 (t), 30.5 (t), 36.1 (d), 64.9 (t), 112.4 (d), 122.4 (d), 123.6 (d), 126.8 (s), 128.1 (d), 128.3 (d, 2C), 129.0 (s), 129.9 (d, 2C), 132.9 (d), 137.4 (s), 147.7 (s), 154.4 (s), 173.3 (s), 185.9 (s) ppm; IR(neat): ν 3393, 2959, 1735, 1647, 1448, 1300, 1260, 876, 751, 724 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{22}\text{H}_{23}\text{O}_4$ ($\text{M}^+ + \text{H}$): 351.1591; found: 351.1589.



Cyclohexyl 2-(2-benzoylbenzofuran-3-yl)propanoate (22ad): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil (87%), and the ratio of branch to linear product (91:9). ^1H NMR (500 MHz, CDCl_3): δ 1.13–1.47 (m, 8H), 1.63–1.65 (m, 1H), 1.66 (d, J = 7.3 Hz, 3H), 1.79–1.83 (m, 1H), 4.80–4.86 (m, 1H), 4.87 (q, J = 7.3 Hz, 1H), 7.30 (dt, J = 0.6, 7.9 Hz, 1H), 7.47 (ddd, J = 1.2, 7.3, 8.4 Hz, 1H), 7.51–7.55 (m, 3H), 7.63 (tt, J = 1.2, 7.9 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 8.08–8.12 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 16.9 (q), 23.4 (t), 23.6 (t), 25.3 (t), 31.2 (t), 31.5 (t), 36.4 (d), 73.2 (d), 112.4 (d), 122.6 (d), 123.5 (d), 126.8 (s), 128.0 (d), 128.3 (d, 2C), 129.2 (s), 129.9 (d, 2C), 132.9 (d), 137.5 (s), 147.7 (s), 154.4 (s), 172.6 (s), 185.9 (s) ppm; IR(neat): ν 2936, 2858, 1729, 1648, 1560, 1448, 1298, 1201, 1017, 876, 750, 723 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{24}\text{H}_{25}\text{O}_4$ ($\text{M}^+ + \text{H}$): 377.1747; found: 377.1746.



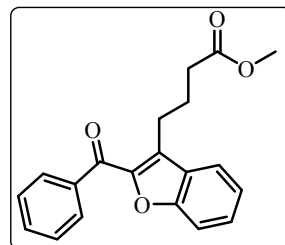
Methyl 2-(2-benzoylbenzofuran-3-yl)butanoate (22ae): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless



oil (84%), and the ratio of branch to linear product (91:9). ^1H NMR (200 MHz, CDCl_3): δ 0.94 (t, J = 7.5 Hz, 3H), 1.91–2.13 (m, 1H), 2.26–2.47 (m, 1H), 3.67 (s, 3H), 4.84 (dd, J = 6.7, 8.6 Hz, 1H), 7.32 (dt, J = 1.3, 8.6 Hz, 1H), 7.44–7.67 (m, 5H), 7.84 (d, J = 7.6 Hz, 1H), 8.07–8.13 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 12.0 (q), 24.8 (t), 42.9 (d), 52.1 (q), 112.4 (d), 122.9 (d), 123.6 (d), 126.9 (s), 127.0 (s), 128.0 (d), 128.3 (d, 2C), 129.9 (d, 2C), 132.9 (d), 137.4 (s), 148.5 (s), 154.3 (s), 173.3 (s), 185.9 (s) ppm; IR(neat): ν 3279, 3060, 2968, 1944, 1734, 1647, 1598, 1447, 1361, 1264, 1112, 1002, 979, 875, 752, 680 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{18}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 345.1097; found: 345.1095.

Methyl 4-(2-benzoylbenzofuran-3-yl)butanoate (24): Isolated by column

chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). ^1H NMR (400 MHz, CDCl_3): δ 2.12 (quin, J = 7.5 Hz, 2H), 2.46 (t, J = 7.5 Hz, 2H), 3.22 (t, J = 7.6 Hz, 2H), 3.68 (s, 3H), 7.36 (t, J = 7.3 Hz, 1H), 7.47–7.58 (m, 4H), 7.63 (t, J = 7.3 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 7.1 Hz, 2H); ^{13}C NMR (101

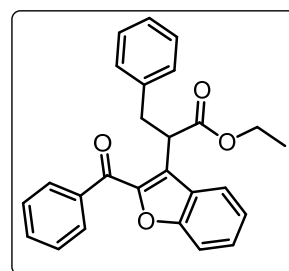


MHz, CDCl_3) δ 23.7 (t), 24.7 (t), 33.5 (t), 51.5 (q), 112.3 (d), 121.6 (d), 123.5 (d), 128.2 (d), 128.3 (d, 2C), 128.5 (s), 129.8 (d, 2C), 130.3 (s), 132.7 (d), 137.7 (s), 148.3 (s), 154.3 (s), 173.8 (s), 185.7 (s) ppm; IR(neat): ν 3067, 2950, 1942, 1736, 1645, 1598, 1437, 1303, 1233, 1158, 880, 748, 624 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{O}_4$ ($\text{M}^+ + \text{H}$): 323.1278; found: 323.1280.

Ethyl 2-(2-benzoylbenzofuran-3-yl)-3-phenylpropanoate (22af): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5).

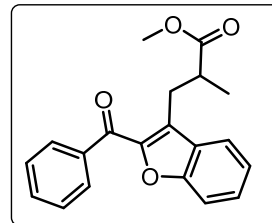
The title compound was determined as colourless oil (54%), and the ratio of branch to linear product (94:6).

^1H NMR (400 MHz, CDCl_3): δ 1.15 (t, J = 7.3 Hz, 3H), 3.22 (dd, J = 8.2, 13.3 Hz, 1H), 3.63 (dd, J = 7.3, 13.3 Hz, 1H), 4.15 (dq, J = 2.8, 7.0 Hz, 2H), 5.17 (dd, J = 6.9, 8.2 Hz, 1H), 7.04–7.13 (m, 5H), 7.29–7.35 (m, 1H), 7.45–7.50 (m, 3H), 7.52 (d, J = 8.2 Hz, 1H), 7.57–7.63 (m, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.87–7.92 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1 (q), 37.7 (t), 43.5 (d), 61.2 (t), 112.4 (d), 122.8 (d), 123.6 (d), 126.3 (d), 126.8 (s), 127.9 (d), 128.1 (d, 2C), 128.2 (d, 2C), 129.0 (d, 2C), 129.7 (d, 2C), 132.8 (d), 137.4 (s), 138.5 (s, 2C), 148.5 (s), 154.2 (s), 172.2 (s), 186.0 (s) ppm; IR(neat): ν 3448, 3062, 3028, 2927,



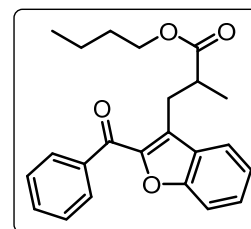
1946, 1732, 1648, 1561, 1447, 1366, 1291, 1175, 1002, 929, 876, 752 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{26}\text{H}_{22}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 421.1410; found: 421.1407.

Methyl 3-(2-benzoylbenzofuran-3-yl)-2-methylpropanoate (23ag): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil (88%). ^1H NMR (400 MHz, CDCl_3): δ 1.29 (d, J = 6.9 Hz, 3H), 3.02–3.08 (m, 1H), 3.30 (dd, J = 7.3, 13.3 Hz, 1H), 3.44 (dd, J = 7.3, 13.3 Hz, 1H), 3.56 (s, 3H), 7.35 (dt, J = 1.4, 8.2 Hz, 1H), 7.46–7.51



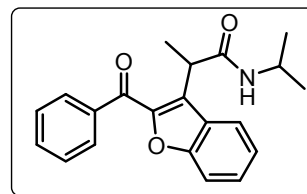
(m, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.59–7.65 (m, 1H), 7.77 (d, J = 7.79 Hz, 1H), 8.11–8.14 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 17.4 (q), 28.4 (t), 39.9 (d), 51.7 (q), 112.3 (d), 121.9 (d), 123.5 (d), 128.2 (d), 128.3 (d, 2C), 128.6 (s), 128.8 (s), 129.8 (d, 2C), 132.7 (d), 137.5 (s), 148.7 (s), 154.2 (s), 176.5 (s), 185.6 (s) ppm; IR(neat): ν 3061, 2950, 1735, 1644, 1598, 1558, 1447, 1373, 1291, 1267, 1171, 974, 875, 750, 722, 693 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{18}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 345.1097; found: 345.1094.

Butyl 3-(2-benzoylbenzofuran-3-yl)-2-methylpropanoate (23ah): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil (86%). ^1H NMR (400 MHz, CDCl_3): δ 0.83 (t, J = 7.3 Hz, 3H), 1.12–1.22 (m, 2H), 1.29 (d, J = 6.9 Hz, 3H), 1.36–1.45 (m, 2H), 3.03 (hexatet, J = 7.3 Hz, 1H), 3.31 (dd, J = 6.9, 13.3 Hz, 1H), 3.41 (dd, J = 8.2, 13.3 Hz, 1H), 3.86–3.99 (m, 2H), 7.31–7.35 (m, 1H), 7.45–7.56 (m, 4H), 7.63 (tt, J = 1.4, 7.3 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 8.09–8.13 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.6 (q), 17.5 (q), 18.9 (t), 28.5 (t), 30.4 (t), 40.0 (d), 64.3 (t), 112.2 (d), 122.0 (d), 123.5 (d), 128.2 (d), 128.3 (d, 2C), 128.6 (s), 129.0 (s), 129.8 (d, 2C), 132.7 (d), 137.6 (s), 148.6 (s), 154.2 (s), 176.2 (s), 185.6 (s) ppm; IR(neat): ν 3061, 2960, 1908, 1731, 1644, 1557, 1448, 1373, 1291, 1173, 976, 875, 750, 693 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{23}\text{H}_{24}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 387.1567; found: 387.1563.



2-(2-Benzoylbenzofuran-3-yl)-N-isopropylpropanamide (22ak): Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.4). The title compound was determined as colourless oil (74%). ^1H NMR (500 MHz, CDCl_3) δ 0.97 (d, J = 6.7 Hz, 3H), 1.19 (d, J = 6.7 Hz, 3H), 1.69 (d, J = 7.3 Hz, 3H), 4.02 (dd, J = 14.0, 6.7 Hz,

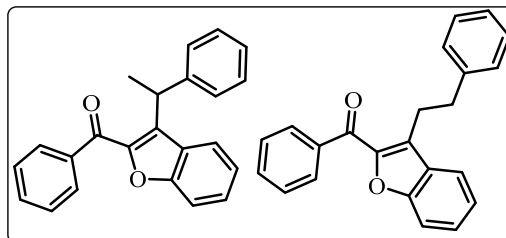
1H), 4.64 (q, $J = 7.1$ Hz, 1H), 6.57 (d, $J = 7.3$ Hz, 1H), 7.31–7.36 (m, 1H), 7.46–7.51 (m, 1H), 7.53 (d, $J = 8.2$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 2H), 7.67 (t, $J = 7.5$ Hz, 1H), 8.09 (d, $J = 7.9$ Hz, 1 H), 8.11–8.16 (m, 2H); ^{13}C NMR (125



MHz, CDCl_3) δ 15.8 (q), 22.4 (q), 22.7 (q), 37.3 (d), 41.4 (d), 112.2 (d), 123.7 (d), 124.2 (d), 126.6 (s), 128.3 (d), 128.4 (d, 3C), 130.2 (d, 3C), 131.0 (s), 133.3 (d), 136.92 (s), 147.8 (s), 154.6 (s), 171.2 (s), 186.7 (s) ppm; IR(neat): ν 3333, 3061, 2973, 1644, 1549, 1449, 1360, 1261, 1174, 1023, 966, 826, 752 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{O}_3\text{NNa}$ ($\text{M}^+ + \text{Na}$): 358.1414; found: 358.1411.

(3-Phenethylbenzofuran-2-yl)(phenyl)methanone (22a) and phenyl(3-(1-phenylethyl)benzofuran-2-yl)methanone (23a): Isolated by column

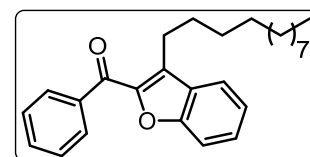
chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.5$). The title compound was determined as colourless oil (83%), and the ratio of branch to linear product is (1:1). ^1H NMR



(200 MHz, CDCl_3): δ 1.88 (d, $J = 7.3$ Hz, 3H), 3.04–3.08 (m, 2H), 3.43–3.47 (m, 2H), 5.43 (q, $J = 7.3$ Hz, 1H), 7.18–7.20 (m, 3H), 7.26–7.28 (m, 5H), 7.30–7.34 (m, 3H), 7.42 (d, $J = 8.6$ Hz, 2H), 7.46–7.49 (m, 3H), 7.54–7.57 (m, 5H), 7.61–7.64 (m, 3H), 8.09 (d, $J = 7.3$ Hz, 2H), 8.12 (d, $J = 7.3$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 19.2 (q), 26.8 (t), 34.5 (d), 35.9 (t), 112.3 (d), 112.3 (d), 121.4 (d), 123.1 (d), 123.3 (d), 123.4 (d), 126.0 (d), 126.3 (d), 127.0 (s), 127.5 (d, 2C), 127.6 (d), 128.1 (d), 128.2 (d), 128.3 (d, 2C), 128.3 (d, 6C), 128.4 (s), 128.5 (d, 2C), 129.7 (d, 2C), 129.9 (d), 130.5 (s), 132.6 (d), 132.7 (d), 134.3 (s), 137.7 (s), 137.8 (s), 141.4 (s), 143.5 (s), 147.4 (s), 148.2 (s), 154.2 (s), 154.6 (s), 185.7 (s), 186.3 (s) ppm; IR (neat): ν 2993, 2415, 1730, 1646, 1566, 1263, 1219, 1065, 869, 754, 667 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{O}_2$ ($\text{M}^+ + \text{H}$): 327.1380; found: 327.1383.

Phenyl(3-undecylbenzofuran-2-yl)methanone (22am): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.6$). The title

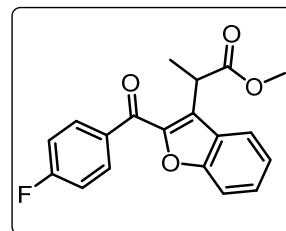
compound was determined as colourless oil (65%). ^1H NMR (500 MHz, CDCl_3): δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.26 (bs, 14H), 1.30–1.37 (m, 2H), 1.39–1.47 (m, 2H), 1.71–1.79 (m, 2H), 3.09–3.17 (m, 2H), 7.34 (t, $J = 7.48$ Hz, 1H), 7.46–7.57 (m, 4H), 7.62 (d, $J = 7.3$ Hz, 1H), 7.74 (d, $J =$



7.93 Hz, 1H), 8.09 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 14.1 (q), 22.7 (d), 24.6 (d), 29.4 (d), 29.5 (d), 29.6 (d, 3C), 29.6 (d), 29.8 (d), 29.8 (d), 31.9 (d), 112.3 (d), 121.7 (d), 123.2 (d), 128.0 (d), 128.3 (d, 2C), 128.7 (s), 129.7 (d, 2C), 131.8 (s), 132.5 (d), 137.9 (s), 148.0 (s), 154.3 (s), 185.9 (s) ppm.

Methyl 2-(2-(4-fluorobenzoyl)benzofuran-3-yl)propanoate (22ba): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.5$).

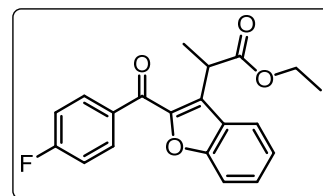
The title compound was determined as colourless oil (87%), and the ratio of branch to linear product (88:12). ^1H NMR (200 MHz, CDCl_3): δ 1.67 (d, $J = 7.2$ Hz, 3H), 3.68 (s, 3H),



4.95 (q, $J = 7.2$ Hz, 1H), 7.15–7.26 (m, 2H), 7.29–7.37 (m, 1H), 7.46–7.54 (m, 1H), 7.57 (d, $J = 8.3$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 8.15–8.25 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 16.8 (q), 35.9 (d), 52.2 (q), 112.4 (d), 115.5 (d, $J = 21.6$ Hz, 2C), 122.3 (d), 123.7 (d), 126.7 (s), 128.2 (d), 129.2 (s), 132.7 (d, $J = 9.1$ Hz, 2C), 133.5 (s, $J = 2.9$ Hz), 147.5 (s), 154.3 (s), 165.1 (s, $J = 255.1$ Hz), 173.6 (s), 184.0 (s) ppm; IR(neat): ν 3459, 2989, 1910, 1739, 1646, 1599, 1304, 1232, 1059, 879, 749 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{15}\text{O}_4\text{FNa}$ ($\text{M}^+ + \text{Na}$): 349.0847; found: 349.0843.

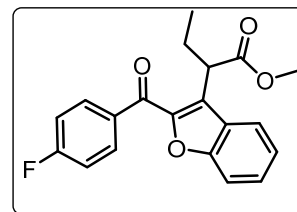
Ethyl 2-(2-(4-fluorobenzoyl)benzofuran-3-yl)propanoate (22bb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.5$).

The title compound was determined as colourless oil (89%), and the ratio of branch to linear product (87:13). ^1H NMR (200 MHz, CDCl_3): δ 1.15 (t, $J = 7.1$ Hz, 3H), 1.67

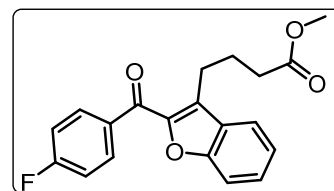


(d, $J = 7.2$ Hz, 3H), 4.16 (q, $J = 7.2$ Hz, 2H), 4.91 (q, $J = 7.2$ Hz, 1H), 7.15–7.26 (m, 2H), 7.32 (ddd, $J = 1.4, 6.8, 8.1$ Hz, 1H), 7.50 (ddd, $J = 1.3, 8.3, 15.2$ Hz, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 8.14–8.24 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 14.1 (q), 16.8 (q), 36.1 (d), 61.0 (t), 112.4 (d), 115.5 (d, $J = 21.6$ Hz, 2C), 122.4 (d), 123.6 (d), 126.7 (s), 128.2 (d), 129.3 (s), 132.7 (d, $J = 9.1$ Hz, 2C), 133.7 (s), 147.5 (s), 154.3 (s), 165.1 (s, $J = 255.1$ Hz), 173.1 (s), 184.1 (s) ppm; IR(neat): ν 3444, 3069, 2982, 1909, 1735, 1645, 1598, 1446, 1347, 1234, 1159, 1046, 878, 750 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{17}\text{O}_4\text{FNa}$ ($\text{M}^+ + \text{Na}$): 363.1003; found: 363.1002.

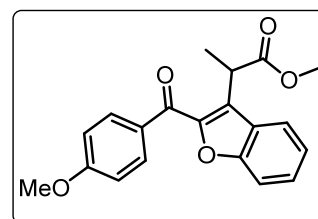
Methyl 2-(2-(4-fluorobenzoyl)benzofuran-3-yl)butanoate (22be): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil (90%), and the ratio of branch to linear product (87:13). ^1H NMR (200 MHz, CDCl_3): δ 0.94 (t, J = 7.5 Hz, 3H), 1.91–2.13 (m, 1H), 2.26–2.48 (m, 1H), 3.67 (s, 3H), 4.84 (dd, J = 6.7, 8.7 Hz, 1H), 7.15–7.26 (m, 2H), 7.32 (ddd, J = 1.4, 6.7, 8.1 Hz, 1H), 7.50 (dt, J = 1.3, 8.3 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 8.13–8.23 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 12.1 (q), 24.8 (t), 42.9 (d), 52.1 (q), 112.3 (d), 115.5 (d, J = 22.0 Hz, 2C), 123.0 (d), 123.7 (d), 126.9 (s), 127.4 (s), 128.2 (d), 132.6 (d, J = 9.2 Hz, 2C), 133.7 (s), 148.3 (s), 154.3 (s), 165.1 (s, J = 254.7 Hz), 173.2 (s), 184.2 (s) ppm; IR(neat): ν 3073, 2968, 1944, 1737, 1647, 1599, 1560, 1435, 1263, 1231, 1158, 980, 877, 749, 625 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{17}\text{O}_4\text{FNa}$ ($\text{M}^+ + \text{Na}$): 363.1003; found: 363.1001.



Methyl 4-(2-(4-fluorobenzoyl)benzofuran-3-yl)butanoate (23be): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil. ^1H NMR (500 MHz, CDCl_3): δ 2.10 (qt, J = 7.5 Hz, 2H), 2.44 (t, J = 7.3 Hz, 2H), 3.20 (t, J = 7.3 Hz, 2H), 3.66 (s, 3H), 7.17–7.21 (m, 2H), 7.34 (dt, J = 1.1, 7.1 Hz, 1H), 7.49 (dt, J = 1.2, 7.0 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 8.15–8.18 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 23.7 (t), 24.7 (t), 33.5 (t), 51.5 (q), 112.3 (d), 115.5 (d, J = 21.0 Hz, 2C), 121.7 (d), 123.6 (d), 128.3 (d), 128.4 (s), 130.7 (s), 132.5 (d, J = 9.5 Hz, 2C), 133.9 (s), 148.1 (s), 154.3 (s), 165.1 (s, J = 254.6 Hz), 173.8 (s), 183.9 (s) ppm; IR(neat): ν 3067, 2950, 1942, 1736, 1645, 1598, 1437, 1303, 1233, 1158, 880, 748, 624 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{17}\text{O}_4\text{FNa}$ ($\text{M}^+ + \text{Na}$): 363.1003; found: 363.1001.

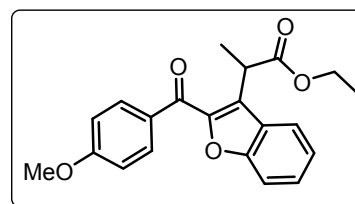


Methyl 2-(2-(4-methoxybenzoyl)benzofuran-3-yl)propanoate (22ca): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil (83%), and the ratio of branch to linear product (91:9). ^1H NMR (400 MHz, CDCl_3): δ 1.67 (d, J = 7.3 Hz, 3H), 3.68 (s, 3H), 3.93 (s, 3H), 4.95 (q, J = 7.2 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 7.33 (dt, J = 0.9, 7.8



Hz, 1H), 7.49 (dt, $J = 1.4, 8.7$ Hz, 1H), 7.57 (d, $J = 8.3$ Hz, 1H), 7.75 (d, $J = 8.3$ Hz, 1H), 8.19 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.9 (q), 35.9 (d), 52.2 (q), 55.5 (q), 112.4 (d), 113.7 (d, 2C), 122.2 (d), 123.6 (d), 126.8 (s), 127.8 (d), 128.2 (s), 130.1 (s), 132.5 (d, 2C), 148.1 (s), 154.2 (s), 163.6 (s), 173.9 (s), 184.2 (s) ppm; IR(neat): ν 3453, 2953, 1954, 1736, 1643, 1600, 1437, 1364, 1258, 1170, 1027, 989, 878, 754 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{O}_5$ ($\text{M}^+ + \text{H}$): 339.1227; found: 339.1226.

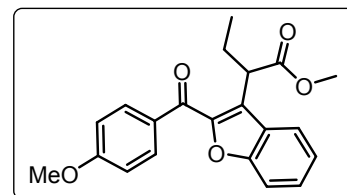
Ethyl 2-(2-(4-methoxybenzoyl)benzofuran-3-yl)propanoate (22cb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.5$). The title compound was determined as colourless oil (80%), and the ratio of branch to linear product (92:8). ^1H NMR (200 MHz, CDCl_3): δ 1.15 (t, $J = 7.2$ Hz, 3H), 1.66



(d, $J = 7.2$ Hz, 3H), 3.92 (s, 3H), 4.15 (q, $J = 7.1$ Hz, 2H), 4.89 (q, $J = 7.2$ Hz, 1H), 7.02 (d, $J = 8.8$ Hz, 2H), 7.33 (d, $J = 1.3, 6.8$ Hz, 1H), 7.47 (dt, $J = 1.1, 8.3$ Hz, 1H), 7.57 (d, $J = 8.2$ Hz, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 8.18 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 14.1 (q), 16.9 (q), 36.1 (d), 55.5 (q), 61.0 (t), 112.4 (d), 113.7 (d, 2C), 122.3 (d), 123.5 (d), 126.8 (s), 127.8 (d), 128.3 (s), 130.2 (s), 132.5 (d, 2C), 148.1 (s), 154.2 (s), 163.5 (s), 173.4 (s), 184.2 (s) ppm; IR(neat): ν 3070, 2981, 1732, 1638, 1600, 1572, 1456, 1298, 1258, 1167, 1029, 878, 749 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{O}_5$ ($\text{M}^+ + \text{H}$): 353.1384; found: 353.1382.

Methyl 2-(2-(4-methoxybenzoyl)benzofuran-3-yl)butanoate (22ce): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.5$).

The title compound was determined as colourless oil (86%), and the ratio of branch to linear product (91:9). ^1H



NMR (200 MHz, CDCl_3): δ 0.94 (t, $J = 7.5$ Hz, 3H), 1.90–2.13 (m, 1H), 2.25–2.46 (m, 1H), 3.67 (s, 3H), 3.91 (s, 3H), 4.82 (dd, $J = 6.8, 8.6$ Hz, 1H), 7.02 (d, $J = 8.6$ Hz, 2H), 7.26–7.35 (m, 1H), 7.43–7.51 (m, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 8.16 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 12.1 (q), 24.8 (t), 42.9 (d), 52.0 (q), 55.5 (q), 112.3 (d), 113.7 (d, 2C), 122.9 (d), 123.5 (d), 126.4 (s), 126.9 (s), 127.7 (d), 130.2 (s), 132.5 (d, 2C), 148.9 (s), 154.2 (s), 163.5 (s), 173.4 (s), 184.3 (s) ppm; IR(neat): ν 3017, 2967, 1736, 1639, 1599, 1509, 1460, 1360, 1260, 1113, 1030, 877, 752, 626 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{O}_5$ ($\text{M}^+ + \text{H}$): 353.1384; found: 353.1383.

Methyl 2-(2-benzoyl-5-methylbenzofuran-3-yl)propanoate (22da): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5).

The title compound was determined as colourless solid (82%),

and the ratio of branch to linear product (88:12). Mp: 114-115

°C; ^1H NMR (400 MHz, CDCl_3): δ 1.67 (d, J = 7.3 Hz, 3H),

2.48 (s, 3H), 3.69 (s, 3H), 4.95 (q, J = 7.3 Hz, 1H), 7.31 (dd, J = 1.8, 8.7 Hz, 1H),

7.45 (d, J = 8.2 Hz, 1H), 7.50–7.56 (m, 3H), 7.63 (tt, J = 1.4, 7.3 Hz, 1H), 8.11–8.14

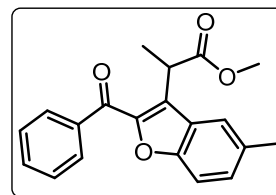
(m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.8 (q), 21.5 (q), 35.9 (d), 52.2 (q), 112.0

(d), 121.6 (d), 126.8 (s), 128.3 (d, 2C), 128.6 (s), 129.8 (d), 130.0 (d, 2C), 132.8 (d),

133.4 (s), 137.4 (s), 147.9 (s), 152.9 (s), 173.8 (s), 185.9 (s) ppm; IR(neat): ν 2949,

1739, 1645, 1563, 1448, 1300, 1206, 1057, 905, 804, 720 cm^{-1} ; HRMS(ESI) calcd for

$\text{C}_{20}\text{H}_{19}\text{O}_4$ ($\text{M}^+ + \text{H}$): 323.1278; found: 323.1276.



Ethyl 2-(2-benzoyl-5-methylbenzofuran-3-yl)propanoate (22db): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5).

The title compound was determined as colourless oil (79%),

and the ratio of branch to linear product (86:14). ^1H NMR

(500 MHz, CDCl_3): δ 1.16 (t, J = 7.3 Hz, 3H), 1.6 (d, J = 7.0

Hz, 3H), 2.47 (s, 3H), 4.16 (q, J = 7.3 Hz, 2H), 4.88 (q, J = 7.0 Hz, 1H), 7.31 (dd, J =

1.5, 8.5 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.50–7.54 (m, 3H), 7.63 (tt, J = 1.2, 7.3 Hz,

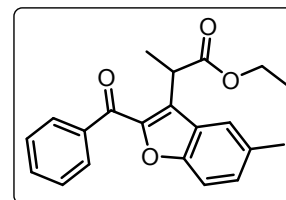
1H), 8.08–8.11 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 14.2 (q), 16.9 (q), 21.5 (q),

36.1 (d), 61.1 (t), 112.0 (d), 121.8 (d), 126.9 (s), 128.3 (d, 2C), 128.8 (s), 129.7 (d),

130.0 (d, 2C), 132.8 (d), 133.3 (s), 137.5 (s), 147.9 (s), 153.0 (s), 173.3 (s), 185.9 (s)

ppm; IR(neat): ν 2981, 1945, 1743, 1648, 1447, 1373, 1259, 1180, 1027, 856, 722, 696

cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{O}_4$ ($\text{M}^+ + \text{H}$): 337.1434; found: 337.1430.



Methyl 2-(2-benzoyl-5-methylbenzofuran-3-yl)butanoate (22de): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title

compound was determined as colourless oil (80%), and the

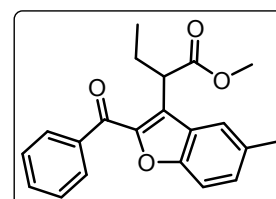
ratio of branch to linear product (85:15). ^1H NMR (400 MHz,

CDCl_3): δ 0.94 (t, J = 7.3 Hz, 3H), 1.97–2.06 (m, 1H), 2.29–

2.38 (m, 1H), 2.48 (s, 3H), 3.69 (s, 3H), 4.83 (dd, J = 6.9, 8.7 Hz, 1H), 7.31 (dd, J =

1.8, 8.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.50–7.55 (m, 2H), 7.60–7.65 (m, 2H),

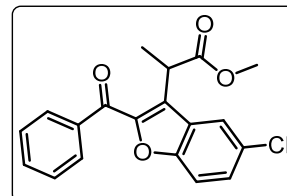
8.08–8.11 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.1 (q), 21.5 (q), 24.7 (t), 42.9



(d), 52.1 (q), 111.9 (d), 122.3 (d), 126.9 (s), 127.0 (s), 128.3 (d, 2C), 129.7 (d), 129.9 (d, 2C), 132.8 (d), 133.3 (s), 137.6 (s), 148.7 (s), 152.9 (s), 173.4 (s), 186.0 (s) ppm; IR(neat): ν 3350, 2929, 1944, 1736, 1648, 1560, 1436, 1267, 1159, 1042, 907, 803, 694 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{O}_4$ (M^+H): 337.1434; found: 337.1432.

Methyl 2-(2-benzoyl-5-chlorobenzofuran-3-yl)propanoate (22ea): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5).

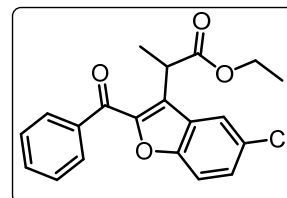
The title compound was determined as colourless solid (87%), the ratio of branch to linear product (91:9). Mp: 90–91 °C; ^1H NMR (500 MHz, CDCl_3): δ 1.65 (d, J = 7.3 Hz, 3H),



3.69 (s, 3H), 4.89 (q, J = 7.3 Hz, 1H), 7.43 (dd, J = 2.1, 8.9 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.51–7.54 (m, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 8.07–8.08 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 16.9 (q), 35.8 (d), 52.4 (q), 113.6 (d), 121.8 (d), 128.0 (s, 2C), 128.4 (d, 2C), 128.5 (d), 129.4 (s), 129.9 (d, 2C), 133.2 (d), 137.1 (s), 148.8 (s), 152.7 (s), 173.4 (s), 185.7 (s) ppm; IR(neat): ν 2953, 1956, 1735, 1653, 1437, 1369, 1257, 1199, 1173, 988, 857, 757 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{16}\text{O}_4\text{Cl}$ (M^+H): 343.0732; found: 343.0733.

Ethyl 2-(2-benzoyl-5-chlorobenzofuran-3-yl)propanoate (22eb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5).

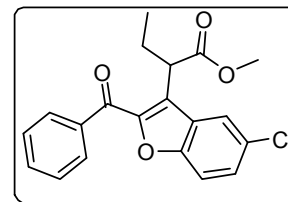
The title compound was determined as colourless oil (86%), and the ratio of branch to linear product (93:7). ^1H NMR (200 MHz, CDCl_3): δ 1.19 (t, J = 7.1 Hz, 3H), 1.66 (d, J = 7.3 Hz,



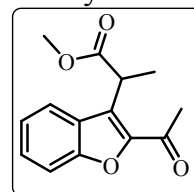
3H), 4.18 (q, J = 7.1 Hz, 2H), 4.86 (q, J = 7.3 Hz, 1H), 7.43–7.46 (m, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.55 ((t, J = 7.8 Hz, 2H),), 7.61–7.67 (m, 1H), 7.76 (d, J = 1.8 Hz, 1H), 8.05–8.11 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1 (q), 16.9 (q), 36.1 (d), 61.2 (t), 113.6 (d), 122.0 (d), 128.0 (s), 128.2 (s), 128.4 (d, 3C), 129.3 (s), 129.9 (d, 2C), 133.1 (d), 137.1 (s), 148.8 (s), 152.7 (s), 172.9 (s), 185.7 (s) ppm; IR(neat): ν 3036, 2928, 1733, 1650, 1598, 1557, 1447, 1295, 1197, 1068, 961, 806, 723, 694 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{18}\text{O}_4\text{Cl}$ (M^+H): 357.0888; found: 357.0887.

Methyl 2-(2-benzoyl-5-chlorobenzofuran-3-yl)butanoate (22ee): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless solid (89%), and the ratio of branch to linear product (91:9). Mp: 88–89 °C; ^1H NMR (500 MHz, CDCl_3): δ 0.95 (t, J = 7.6 Hz, 3H), 1.95–2.04 (m,

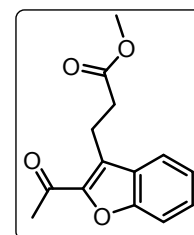
1H), 2.28–2.39 (m, 1H), 3.71 (s, 3H), 4.79 (dd, $J = 6.4, 8.8$ Hz, 1H), 7.45 (dd, $J = 1.9, 8.5$ Hz, 1H), 7.49 (d, $J = 8.5$ Hz, 1H), 7.51–7.56 (m, 2H), 7.63 (tt, $J = 1.2, 7.3$ Hz, 1H), 7.85 (d, $J = 2.1$ Hz, 1H), 8.07–8.08 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 12.1 (q), 24.9 (t), 42.9 (d), 52.2 (q), 113.5 (d), 122.5 (d), 126.3 (s), 128.1 (s), 128.4 (d, 2C), 128.5 (d), 129.4 (s), 129.9 (d, 2C), 133.1 (d), 137.2 (s), 149.6 (s), 152.7 (s), 173.0 (s), 185.8 (s) ppm; IR(neat): ν 3019, 2970, 2400, 1734, 1648, 1559, 1447, 1292, 1215, 986, 808, 756, 669 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{18}\text{O}_4\text{Cl}$ ($\text{M}^+ + \text{H}$): 357.0888; found: 357.0888.



Methyl 2-(2-acetylbenzofuran-3-yl)propanoate (22fa): Isolated by column chromatography (pet.ether/AcOEt = 9.5:0.5, $R_f = 0.4$). The title compound was determined as colourless oil (71%), and the ratio of branch to linear product is (48:52). ^1H NMR (500 MHz, CDCl_3): δ 1.60 (d, $J = 7.0$ Hz, 3H), 2.66 (s, 3H), 3.67 (s, 3H), 5.02 (q, $J = 7.0$ Hz, 1H), 7.30 (td, $J = 0.9, 8.2$ Hz, 1H), 7.49 (ddd, $J = 1.2, 7.0, 8.2$ Hz, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 7.70 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 16.7 (q), 27.9 (q), 35.4 (q), 52.2 (q), 112.4 (d), 122.5 (d), 123.6 (d), 126.3 (s), 126.9 (s), 128.1 (d), 147.3 (s), 154.1 (s), 173.7 (s), 191.7 (s) ppm; IR(neat): ν 2986, 2401, 1733, 1645, 1564, 1260, 1215, 1060, 876, 759, 668 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 269.0784; found: 269.0782.



Methyl 3-(2-benzoylbenzofuran-3-yl)propanoate (23fa): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.2$). ^1H NMR (400 MHz, CDCl_3): δ 2.64 (s, 3H), 2.73 (t, $J = 7.5$ Hz, 2H), 3.38 (t, $J = 7.5$ Hz, 2H), 3.63 (s, 3H), 7.33 (dd, $J = 6.8, 7.8$ Hz, 1H), 7.47–7.50 (m, 1H), 7.53 (d, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.6 (t), 27.7 (q), 33.4 (t), 51.7 (q), 112.2 (d), 121.8 (d), 123.4 (d), 126.9 (s), 128.2 (d), 128.4 (s), 148.2 (s), 154.0 (s), 173.2 (s), 191.2 (s) ppm; IR (neat): ν 2987, 2409, 1735, 1648, 1562, 1260, 1214, 1066, 874, 753, 666 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$): 269.0784; found: 269.0783.

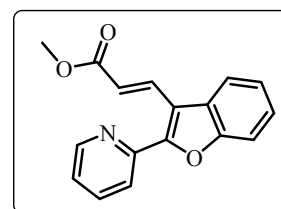


General procedure B: Linear alkenylation using $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$:

2-(benzofuran-2-yl)pyridine (0.1 mmol) was placed in a screw cap pressure tube and dissolved in anhydrous toluene (2 mL), which was then evacuated and back filled with argon. To the reaction vessel alkene (acrylate) (0.3 mmol), K_2CO_3 (3.0 mmol), $Ru(PPh_3)_3Cl_2$ (0.005 mmol) and $AgOAc$ (0.03 mmol) were added. The solution was then stirred at 140 °C (bath temperature) for 24 h. The reaction mixture was cooled to room temperature. The solvent were evaporated and the crude products were purified by column chromatography (pet ether/AcOEt) to give analytically pure.

Methyl (*E*)-3-(2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29aa): Isolated by column chromatography (pet.ether/AcOEt = 8:2, R_f = 0.5). The title compound was determined as pale yellow colour solid (77%).

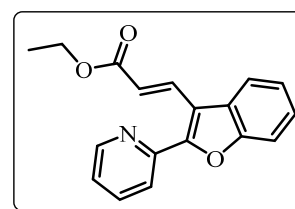
Mp: 116-117 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.74 (d, J = 16.5 Hz, 1H), 7.29 (dd, J = 0.9, 4.6 Hz, 1H), 7.35



(dt, J = 0.9, 7.9 Hz, 1H), 7.41 (dt, J = 1.5, 8.2 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.82 (dt, J = 1.8, 7.9 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 7.9 Hz, 1H), 8.79 (dddd, J = 0.9, 1.5, 2.4, 4.6 Hz, 1H), 9.02 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 51.7 (q), 111.7 (d), 115.5 (s), 119.7 (d), 121.7 (d), 122.1 (d), 123.2 (d), 124.0 (d), 126.0 (d), 126.9 (s), 136.6 (d), 137.6 (d), 149.9 (d), 149.9 (s), 153.5 (s), 154.4 (s), 167.8 (s) ppm; IR (neat): ν 3030, 1735, 1644, 1598, 1438, 1206, 1043, 870, 758, 669 cm^{-1} ; HRMS(ESI) calcd for $C_{17}H_{14}O_3N$ ($M^+ + H$): 280.0968; found: 280.0968.

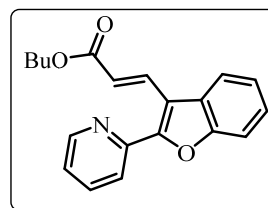
Ethyl (*E*)-3-(2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29ab): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as yellow colour solid (62%).

Mp: 124-125 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.38 (t, J = 7.3 Hz, 3H), 4.32 (q, J = 7.3 Hz, 2H), 6.74 (d, J

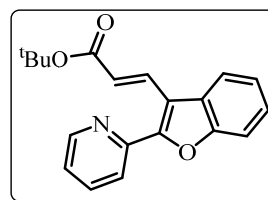


= 16.5 Hz, 1H), 7.29 (dddd, J = 0.9, 4.9, 7.6, 12.5 Hz, 1H), 7.35 (dt, J = 0.9, 7.9 Hz, 1H), 7.41 (dt, J = 1.2, 8.2 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.82 (dt, J = 1.8, 7.9 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 8.79 (dddd, J = 0.9, 1.5, 2.4, 4.6 Hz, 1H), 9.02 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (q), 60.4 (t), 111.7 (d), 115.6 (s), 120.1 (d), 121.8 (d), 122.1 (d), 123.1 (d), 123.9 (d), 126.0 (d), 126.9 (s), 136.6 (d), 137.3 (d), 149.9 (s), 149.9 (d), 153.4 (s), 154.4 (s), 167.4 (s) ppm; IR (neat): ν 3033, 1742, 1648, 1597, 1438, 1215, 1066, 874, 752, 653 cm^{-1} ; HRMS(ESI) calcd for $C_{18}H_{16}O_3N$ ($M^+ + H$): 294.1125; found: 294.1125.

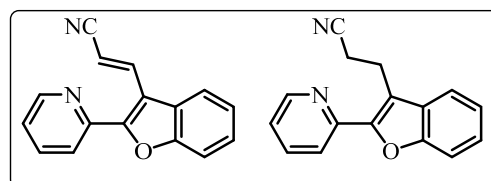
Butyl (*E*)-3-(2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29ac): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as brown colour gum (60%). ^1H NMR (400 MHz, CDCl_3): δ 1.01 (t, J = 7.3 Hz, 3H), 1.46–1.56 (m, 2H), 1.71–1.78 (m, 2H), 4.27 (t, J = 6.5 Hz, 2H), 6.74 (d, J = 16.3 Hz, 1H), 7.30 (dd, J = 4.8, 7.5 Hz, 1H), 7.37 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.83 (dt, J = 1.8, 8.0 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.79 (d, J = 4.5 Hz, 1H), (d, J = 16.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.8 (q), 19.2 (t), 30.8 (t), 64.3 (t), 111.7 (d), 115.6 (s), 120.1 (d), 121.8 (d), 122.1 (d), 123.2 (d), 123.9 (d), 126.0 (d), 126.9 (s), 136.6 (d), 137.3 (d), 149.9 (d), 149.9 (s), 153.4 (s), 154.4 (s), 167.5 (s) ppm; IR (neat): ν 3021, 2992, 1731, 1637, 1420, 1230, 1041, 868, 752, 671 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 322.1438; found: 322.1438.



***Tert*-butyl (*E*)-3-(2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29an):** Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as white colour solid (65%). Mp: 131–133 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.59 (s, 9H), 6.68 (d, J = 16.6 Hz, 1H), 7.29 (dd, J = 5.3, 7.3 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.82 (dt, J = 1.5, 8.0 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 8.79 (d, J = 4.3 Hz, 1H), 8.97 (d, J = 16.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 28.3 (q, 3C), 80.3 (s), 111.7 (d), 115.7 (s), 121.8 (d), 121.9 (d), 122.1 (d), 123.1 (d), 123.8 (d), 125.9 (d), 127.0 (s), 136.3 (d), 136.6 (d), 149.9 (d), 149.9 (s), 153.2 (s), 154.4 (s), 166.7 (s) ppm; IR (neat): ν 3061, 2977, 1736, 1640, 1596, 1210, 1042, 869, 761, 650 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 322.1438; found: 322.1431.



(*E*)-3-(2-(Pyridin-2-yl)benzofuran-3-yl)acrylonitrile (29aj) and 3-(2-(pyridin-2-yl)benzofuran-3-yl)propanenitrile (28aj) : Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as white colour

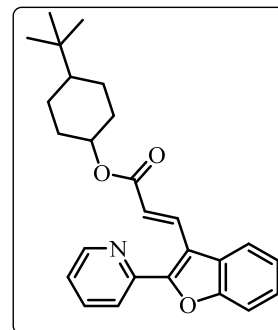


solid (68%). Mp: 71–72 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.90 (t, J = 7.3 Hz, 2H), 3.61 (t, J = 7.3 Hz, 2H), 6.16 (d, J = 16.9 Hz, 1H), 7.24 (ddd, J = 1.4, 5.0, 7.8 Hz, 1H), 7.30–7.36 (m, 2H), 7.37–7.41 (m, 2H), 7.45 (dt, J = 1.4, 8.2 Hz, 1H), 7.53 (d, J = 7.8

Hz, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.66 (dd, $J = 0.9, 7.8$ Hz, 1H), 7.78–7.83 (m, 2H), 7.85 (dt, $J = 1.8, 7.8$ Hz, 1H), 7.98 (d, $J = 8.2$ Hz, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 8.68 (d, $J = 5.0$ Hz, 1H), 8.76 (d, $J = 4.6$ Hz, 1H), 9.03 (d, $J = 16.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 17.2 (t), 20.8 (t), 97.2 (d), 111.4 (d), 111.9 (d), 115.0 (s), 116.8 (s), 119.1 (s), 119.6 (d), 120.0 (s), 120.6 (d), 121.2 (d), 122.0 (d), 122.4 (d), 123.1 (d), 123.6 (d), 124.3 (d), 125.7 (d), 126.1 (s), 126.3 (d), 129.5 (s), 136.6 (d), 136.8 (d), 143.9 (d), 149.5 (s), 149.6 (d), 149.8 (d), 150.4 (s), 153.2 (s), 153.9 (s), 154.3 (s, 2C) ppm; IR (neat): ν 3020, 2988, 2213, 1735, 1639, 1601, 1266, 1040, 861, 758, 662 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{16}\text{H}_{11}\text{ON}_2$ ($\text{M}^+ + \text{H}$): 247.0866; found: 247.0867.

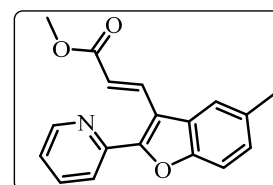
4-(*Tert*-butyl)cyclohexyl (*E*)-3-(2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29ao):

Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.4$). The title compound was determined as brown colour gum (65%). ^1H NMR (500 MHz, CDCl_3): δ 0.89 (s, 9H), 1.03–1.13 (m, 1H), 1.18 (dq, $J = 3.4, 13.7$ Hz, 1H), 1.39–1.50 (m, 2H), 1.53–1.60 (m, 1H), 1.66 (d, $J = 11.0$ Hz, 1H), 1.87 (d, $J = 13.1$ Hz, 1H), 2.08–2.18 (m, 2H), 4.79–4.85 (m, 1H), 6.73 (d, $J = 16.2$ Hz, 1H), 7.27–7.30 (m, 1H), 7.35 (t, $J = 7.3$ Hz, 1H), 7.39–7.43 (m, 1H), 7.57 (d, $J = 8.2$ Hz, 1H), 7.81 (dt, $J = 1.5, 7.9$ Hz, 1H), 7.96 (d, $J = 8.2$ Hz, 1H), 8.00 (d, $J = 7.6$ Hz, 1H), 8.79 (d, $J = 4.6$ Hz, 1H), 9.00 (d, $J = 16.2$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 21.8 (t), 25.5 (t), 27.6 (q, 3C), 30.8 (t), 32.2 (t), 41.3 (s), 47.1 (d), 73.8 (d), 111.7 (d), 115.6 (s), 120.5 (d), 121.8 (d), 122.1 (d), 123.1 (d), 123.9 (d), 125.9 (d), 126.9 (s), 136.6 (d), 137.1 (d), 149.9 (s), 149.9 (d), 153.4 (s), 154.4 (s), 167.0 (s) ppm; IR (neat): ν 3025, 2996, 1740, 1644, 1603, 1233, 1055, 873, 762, 660 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{26}\text{H}_{30}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 404.2220; found: 404.2219.



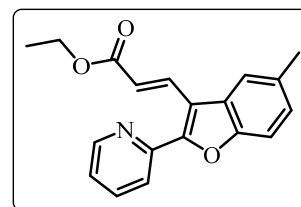
Methyl (*E*)-3-(5-methyl-2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29ba):

Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.4$). The title compound was determined as white colour solid (59%). Mp: 110–111 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 2.51 (s, 3H), 3.87 (s, 3H), 6.74 (d, $J = 16.6$ Hz, 1H), 7.23 (d, $J = 8.5$ Hz, 1H), 7.28–7.31 (m, 1H), 7.46 (d, $J = 8.5$ Hz, 1H), 7.73 (s, 1H), 7.83 (dt, $J = 1.8, 8.0$ Hz, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 8.80 (d, $J = 4.5$ Hz, 1H), 9.01 (d, $J = 16.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.5 (q), 51.7 (q), 111.2 (d), 115.4

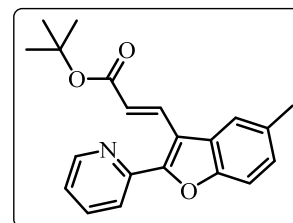


(s), 119.5 (d), 121.6 (d), 122.1 (d), 123.1 (d), 126.9 (s), 127.3 (d), 133.6 (s), 136.7 (d), 137.7 (d), 149.8 (d), 149.9 (s), 152.9 (s), 153.6 (s), 167.9 (s) ppm; IR (neat): ν 3054, 2999, 1743, 1640, 1599, 1223, 1045, 850, 758, 669 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{16}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 294.1125; found: 294.1122.

Ethyl (E)-3-(5-methyl-2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29bb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as yellow colour gum (57%). ^1H NMR (500 MHz, CDCl_3): δ 1.40 (t, J = 7.3 Hz, 3H), 2.52 (s, 3H), 4.32 (q, J = 7.3 Hz, 2H), 6.74 (d, J = 16.2 Hz, 1H), 7.23 (d, J = 5.8 Hz, 1H), 7.30 (t, J = 5.8 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.74 (s, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 8.80 (br s, 1H), 9.00 (d, J = 16.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 14.4 (q), 21.5 (q), 60.5 (t), 111.2 (d), 115.5 (s), 119.9 (d), 121.6 (d), 122.1 (d), 123.1 (d), 126.9 (s), 127.3 (d), 133.6 (s), 136.8 (d), 137.4 (d), 149.7 (d), 149.8 (s), 152.9 (s), 165.4 (s), 167.5 (s) ppm; IR (neat): ν 3033, 2987, 1731, 1644, 1600, 1210, 1043, 870, 750, 657 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{18}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 308.1281; found: 308.1283.

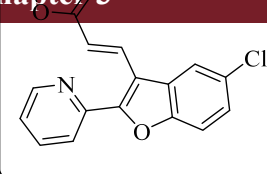


Tert-butyl (E)-3-(5-methyl-2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29bn): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as yellow colour gum (56%). ^1H NMR (500 MHz, CDCl_3): δ 1.59 (s, 9H), 2.52 (s, 3H), 6.66 (d, J = 16.2 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.28–7.29 (m, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.74 (s, 1H), 7.82 (dt, J = 1.5, 7.9 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 8.79 (d, J = 4.3 Hz, 1H), 8.94 (d, J = 16.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 21.5 (q), 28.3 (q, 3C), 80.3 (s), 111.2 (d), 115.5 (s), 121.7 (d, 2C), 122.1 (d), 123.0 (d), 127.0 (s), 127.2 (d), 133.5 (s), 136.4 (d), 136.6 (d), 149.8 (d), 150.0 (s), 152.9 (s), 153.3 (s), 166.8 (s) ppm; IR (neat): ν 3028, 2971, 1736, 1634, 1598, 1240, 1035, 868, 781, 673 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 336.1594; found: 336.1594.



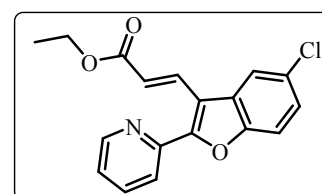
Methyl (E)-3-(5-chloro-2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29ca): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as white colour solid (68%). Mp: 122–123 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 3.87 (s, 3H), 6.74 (d, J = 16.5 Hz, 1H), 7.32 (ddd, J = 0.9, 4.6, 7.3 Hz, 1H),

7.37 (dd, $J = 2.3, 8.7$ Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 1H), 7.84 (dt, $J = 1.8, 8.2$ Hz, 1H), 7.89 (d, $J = 1.8$ Hz, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 8.80 (d, $J = 4.6$ Hz, 1H), 8.96 (d, $J = 16.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 51.8 (q), 112.7 (d), 115.0 (s), 119.9 (d), 121.3 (d), 122.2 (d), 123.5 (d), 126.2 (d), 128.1 (s), 129.7 (s), 136.7 (d), 136.9 (d), 149.4 (s), 150.0 (d), 152.7 (s), 154.5 (s), 167.6 (s) ppm; IR (neat): ν 3041, 2993, 1739, 1654, 1620, 1597, 1255, 1035, 870, 652, 669 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{13}\text{O}_3\text{NCl}$ ($\text{M}^+ + \text{H}$): 314.0578; found: 314.0580.



Ethyl (E)-3-(5-chloro-2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29cb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.4$). The title compound was

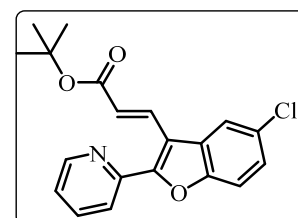
determined as white colour solid (66%). Mp: 117-118 °C;



^1H NMR (400 MHz, CDCl_3): δ 1.39 (t, $J = 7.1$ Hz, 3H), 4.33 (q, $J = 7.1$ Hz, 2H), 6.64 (d, $J = 16.4$ Hz, 1H), 7.31 (dd, $J = 4.9, 6.9$ Hz, 1H), 7.36 (dd, $J = 2.0, 8.6$ Hz, 1H), 7.48 (d, $J = 8.6$ Hz, 1H), 7.8 (dd, $J = 1.5, 7.8$ Hz, 1H), 7.89 (d, $J = 1.7$ Hz, 1H), 7.96 (d, $J = 8.1$ Hz, 1H), 8.79 (d, $J = 4.7$ Hz, 1H), 8.96 (d, $J = 16.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.7 (q), 60.8 (t), 113.0 (d), 115.4 (s), 120.7 (d), 121.7 (d), 122.5 (d), 123.8 (d), 126.5 (d), 128.5 (s), 129.9 (s), 137.0 (d, 2C), 149.7 (s), 150.3 (d), 153.0 (s), 154.7 (s), 167.5 (s) ppm; IR (neat): ν 3039, 2996, 1731, 1649, 1618, 1601, 1232, 1045, 854, 751, 660 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{15}\text{O}_3\text{NCl}$ ($\text{M}^+ + \text{H}$): 328.0735; found: 328.0737.

Tert-butyl (E)-3-(5-chloro-2-(pyridin-2-yl)benzofuran-3-yl)acrylate (29cn):

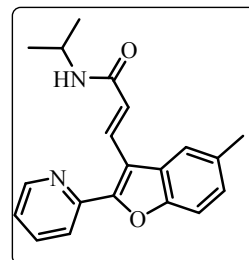
Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.4$). The title compound was determined as white colour solid (69%). Mp: 136-137 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.59 (s, 9H), 6.59 (d, $J = 16.3$ Hz, 1H), 7.31 (dd, $J = 4.8, 7.5$ Hz, 1H), 7.38 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 1H), 7.83 (dt, $J = 1.8, 8.0$ Hz, 1H), 7.93 (d, $J = 2.0$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 8.79 (td, $J = 0.8, 4.8$ Hz, 1H), 8.90 (d, $J = 16.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 28.3 (q, 3C), 80.6 (s), 112.7 (d), 115.2 (s), 121.5 (d), 122.2 (d), 122.3 (d), 123.4 (d), 126.1 (d), 128.3 (s), 129.6 (s), 135.6 (d), 136.7 (d), 149.5 (s), 150.0 (d), 152.8 (s), 154.3 (s), 166.5 (s) ppm; IR (neat): ν 3028, 2991, 1741, 1659, 1611, 1604,



1263, 1040, 857, 751, 662 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{O}_3\text{NCl}$ (M^+H): 356.1048; found: 356.1043.

(*E*)-*N*-isopropyl-3-(5-methyl-2-(pyridin-2-yl)benzofuran-3-yl)acrylamide (29bk):

Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as pale yellow colour solid (47%). Mp: 222–223 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 1.29 (d, J = 7.1 Hz, 6H), 2.51 (s, 3H), 4.24–4.33 (m, 1H), 6.67 (d, J = 15.9 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.28–7.30 (m, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.69 (s, 1H), 7.82 (dt, J = 1.7, 8.1 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 8.78 (d, J = 15.9 Hz, 1H), 8.79 (d, J = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.6 (q), 22.9 (q, 2C), 41.6 (d), 111.3 (d), 115.5 (s), 121.4 (d), 122.1 (d), 122.9 (d), 123.1 (d), 127.1 (d), 127.2 (s), 133.0 (d), 133.2 (s), 136.6 (d), 149.9 (d), 150.0 (s), 152.9 (s), 153.1 (s), 165.6 (s) ppm; IR (neat): ν 3020, 2400, 1731, 1644, 1438, 1215, 1045, 850, 758, 669 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{O}_2\text{N}_2$ (M^+H): 321.1598; found: 321.1599.

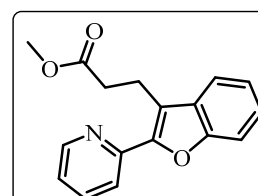


General procedure B: Linear alkylation using $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$:

2-(benzofuran-2-yl)pyridine (0.1 mmol) was placed in a screw cap pressure tube and dissolved in anhydrous toluene (2 mL), which was then evacuated and back filled with argon. To the reaction vessel alkene (acrylate) (0.3 mmol), $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ (0.005 mmol) and AgOAc (0.03 mmol) were added. The solution was then stirred at 140 $^{\circ}\text{C}$ (bath temperature) for 24 h. The reaction mixture was cooled to room temperature. The solvent were evaporated and the crude products were purified by column chromatography (pet ether/AcOEt) to give analytically pure.

Methyl 3-(2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28aa):

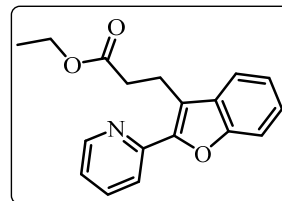
Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as yellow colour gum (75%). ^1H NMR (200 MHz, CDCl_3): δ 2.83 (t, J = 8.1 Hz, 2H), 3.58 (t, J = 8.2 Hz, 2H), 3.65 (s, 3H), 7.17–7.24 (m, 1H), 7.28–7.39 (m, 2H), 7.52 (dd, J = 1.4, 7.1 Hz, 1H), 7.65–7.69 (m, 1H), 7.78 (dt, J = 1.8, 7.9 Hz, 1H), 7.95 (dd, J = 0.9, 7.9 Hz, 1H), 8.69 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.7 (t), 33.9 (t), 51.5 (q), 111.2 (d), 118.7 (s), 120.1 (d), 120.6 (d), 122.0 (d), 122.7 (d), 125.3 (d), 130.0 (s), 136.4 (d), 149.4 (s), 149.6 (d),



150.8 (s), 153.9 (s), 173.9 (s) ppm; IR (neat): ν 3028, 2985, 1733, 1645, 1620, 1437, 1218, 1051, 859, 768, 660 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 282.1125; found: 282.1125.

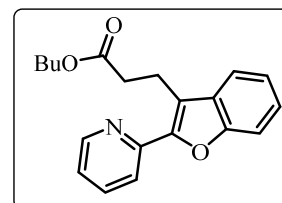
Ethyl 3-(2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28ab): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless gum (51%). ^1H

NMR (400 MHz, CDCl_3): δ 1.20 (t, J = 7.3 Hz, 3H), 2.81 (t, J = 8.0 Hz, 2H), 3.58 (t, J = 8.0 Hz, 2H), 4.11 (q, J = 7.3 Hz, 2H), 7.21 (dd, J = 4.8, 7.5 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.3 Hz, 1H), 7.78 (dt, J = 1.8, 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 8.69 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.2 (q), 19.8 (t), 34.1 (t), 60.3 (t), 111.2 (d), 118.8 (s), 120.2 (d), 120.6 (d), 122.0 (d), 122.7 (d), 125.3 (d), 130.1 (s), 136.4 (d), 149.3 (s), 149.6 (d), 150.9 (s), 153.9 (s), 173.5 (s) ppm; IR (neat): ν 3038, 2986, 1741, 1634, 1431, 1235, 1025, 870, 721, 663 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{18}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 296.1281; found: 296.1281.



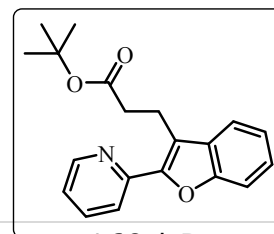
Butyl 3-(2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28ac): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless gum (56%). ^1H NMR (400 MHz,

CDCl_3): δ 0.90 (t, J = 7.3 Hz, 3H), 1.27–1.37 (m, 2H), 1.51–1.59 (m, 2H), 2.81 (t, J = 7.8 Hz, 2H), 3.58 (t, J = 7.8 Hz, 2H), 4.05 (t, J = 7.3 Hz, 2H), 7.21 (dd, J = 4.8, 7.5 Hz, 1H), 7.26–7.30 (m, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.78 (dt, J = 1.3, 7.8 Hz, 1H), 7.94 (dd, J = 0.8, 8.0 Hz, 1H), 8.69 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7 (q), 19.1 (t), 19.8 (t), 30.6 (t), 34.1 (t), 64.3 (t), 111.2 (d), 118.9 (s), 120.2 (d), 120.6 (d), 122.0 (d), 122.7 (d), 125.3 (d), 130.1 (s), 136.4 (d), 149.3 (s), 149.6 (d), 150.9 (s), 153.9 (s), 173.6 (s) ppm; IR (neat): ν 3033, 2991, 1736, 1638, 1448, 1223, 1042, 869, 748, 661 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 324.1594; found: 324.1592.



Tert-butyl 3-(2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28an): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as white colour solid (59%).

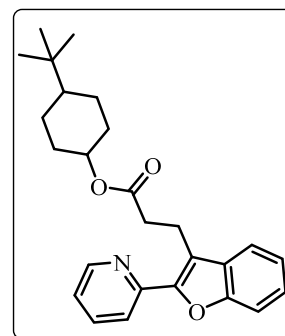
Mp: 149–150 $^{\circ}\text{C}$; ^1H NMR (500 MHz, CDCl_3): δ 1.41 (s, 9H),



2.71 (t, $J = 7.9$ Hz, 2H), 3.55 (t, $J = 7.9$ Hz, 2H), 7.21 (dd, $J = 4.6, 7.6$ Hz, 1H), 7.26–7.30 (m, 1H), 7.34 (dt, $J = 1.2, 8.2$ Hz, 1H), 7.51 (d, $J = 8.2$ Hz, 1H), 7.69 (d, $J = 7.6$ Hz, 1H), 7.77 (dt, $J = 1.8, 7.9$ Hz, 1H), 7.93 (d, $J = 7.9$ Hz, 1H), 8.70 (d, $J = 4.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.8 (t), 28.1 (q, 3C), 35.3 (t), 80.1 (s), 111.2 (d), 119.0 (s), 120.3 (d), 120.6 (d), 121.9 (d), 122.6 (d), 125.2 (d), 130.1 (s), 136.3 (d), 149.3 (s), 149.6 (d), 150.9 (s), 153.9 (s), 172.8 (s) ppm; IR (neat): ν 3029, 2993, 1741, 1644, 1600, 1448, 1245, 1055, 852, 751, 662 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 324.1594; found: 324.1589.

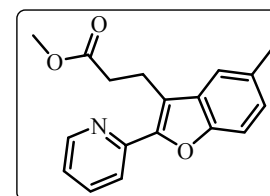
4-(*Tert*-butyl)cyclohexyl 3-(2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28ao):

Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.4$). The title compound was determined as pale yellow colour gum (64%). ^1H NMR (400 MHz, CDCl_3): δ 0.85 (s, 9H), 0.96–0.99 (m, 1H), 1.09 (dq, $J = 2.6, 7.6$ Hz, 2H), 1.18–1.34 (m, 2H), 1.78 (d, $J = 12.7$ Hz, 2H), 1.93 (d, $J = 9.1$ Hz, 2H), 2.78 (t, $J = 7.6$ Hz, 2H), 3.57 (t, $J = 7.6$ Hz, 2H), 4.58–4.65 (m, 1H), 7.22 (dd, $J = 4.7, 6.9$ Hz, 1H), 7.26–7.30 (m, 1H), 7.35 (dt, $J = 1.0, 7.3$ Hz, 1H), 7.51 (d, $J = 8.3$ Hz, 1H), 7.68 (d, $J = 7.6$ Hz, 1H), 7.78 (t, $J = 7.6$ Hz, 1H), 7.94 (d, $J = 8.1$ Hz, 1H), 8.70 (d, $J = 3.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.8 (t), 25.4 (t, 2C), 27.6 (q, 3C), 32.0 (t, 2C), 32.3 (s), 34.4 (t), 47.0 (d), 73.7 (d), 111.2 (d), 119.0 (s), 120.3 (d), 120.6 (d), 122.0 (d), 122.6 (d), 125.3 (d), 130.1 (s), 136.5 (d), 149.2 (s), 149.5 (d), 150.8 (s), 153.9 (s), 173.1 (s) ppm IR (neat): ν 3063, 2989, 1737, 1643, 1462, 1227, 1055, 873, 763, 662 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{26}\text{H}_{32}\text{O}_3\text{N}$ ($\text{M}^+ + \text{H}$): 406.2377; found: 406.2377.



Methyl 3-(5-methyl-2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28ba): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.4$).

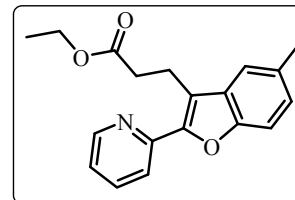
The title compound was determined as pale yellow colour gum (59%). ^1H NMR (400 MHz, CDCl_3): δ 2.48 (s, 3H), 2.81 (t, $J = 8.1$ Hz, 2H), 3.55 (t, $J = 8.1$ Hz, 2H), 3.66 (s, 3H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.22 (dd, $J = 5.1, 7.0$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.43 (s, 1H), 7.79 (t, $J = 7.7$ Hz, 1H), 7.93 (d, $J = 8.1$ Hz, 1H), 8.71 (d, $J = 3.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.8 (t), 21.4 (q), 33.8 (t), 51.6 (q), 110.8 (d), 118.8 (s), 119.8 (d), 120.7 (d), 122.0 (d), 126.8 (d), 130.0 (s), 132.2 (s), 136.7 (d), 149.1 (s), 149.3 (d), 150.6 (s), 152.4 (s), 173.9 (s) ppm; IR (neat): ν 3027, 2989, 1743, 1640,



1458, 1233, 1045, 863, 753, 662 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{18}\text{O}_3\text{N}$ (M^+H): 296.1281; found: 296.1282.

Ethyl 3-(5-methyl-2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28bb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4).

The title compound was determined as pale yellow colour gum (63%). ^1H NMR (400 MHz, CDCl_3): δ 1.21 (t, J = 7.1 Hz, 3H), 2.48 (s, 3H), 2.80 (t, J = 7.6 Hz, 2H), 3.55 (t, J = 7.6

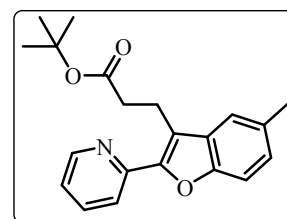


Hz, 2H), 4.11 (q, J = 7.1 Hz, 2H), 7.18 (d, J = 8.3 Hz, 1H), 7.27 (s, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 8.74 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.2 (q), 19.8 (t), 21.4 (q), 34.0 (t), 60.4 (t), 111.0 (d, 2C), 119.9 (s), 119.9 (d, 2C), 121.0 (d), 122.2 (d), 127.1 (d), 132.3 (s, 2C), 152.6 (s, 3C), 173.4 (s) ppm; IR (neat): ν 3051, 2995, 1742, 1640, 1600, 1463, 1224, 1040, 870, 753, 662 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{O}_3\text{N}$ (M^+H): 310.1438; found: 310.1439.

***Tert*-butyl 3-(5-methyl-2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28bn):**

Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as pale yellow

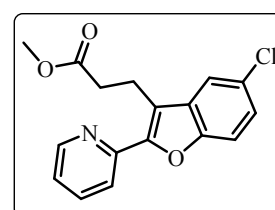
colour gum (57%). ^1H NMR (500 MHz, CDCl_3): δ 1.42 (s, 9H), 2.48 (s, 3H), 2.70 (t, J = 7.9 Hz, 2H), 3.51 (t, J = 7.9 Hz,



2H), 7.15 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 5.5, 6.7 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.44 (s, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 8.70 (d, J = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.9 (t), 21.4 (q), 28.1 (q, 3C), 35.3 (t), 80.2 (s), 110.7 (d), 118.9 (s), 120.0 (d), 120.7 (d), 121.9 (d), 126.6 (d), 130.1 (s), 132.1 (s), 136.5 (d), 149.2 (s), 149.3 (d), 150.8 (s), 152.4 (s), 172.8 (s) ppm; IR (neat): ν 3020, 2400, 1731, 1644, 1438, 1215, 1045, 850, 758, 669 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{21}\text{H}_{24}\text{O}_3\text{N}$ (M^+H): 338.1751; found: 338.1753.

Methyl 3-(5-chloro-2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28ca): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4).

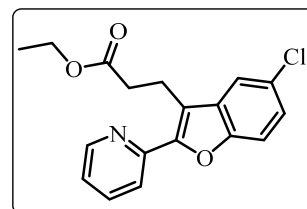
The title compound was determined as white colour solid (56%). Mp: 87-88 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 2.81 (t, J = 7.8 Hz, 2H), 3.53 (t, J = 8.0 Hz, 2H), 3.66 (s, 3H), 7.23 (ddd, J = 1.0, 5.0, 7.5 Hz, 1H), 7.29 (dd, J = 2.3, 8.5 Hz, 1H), 7.43 (d, J = 8.5 Hz,



1H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.79 (dt, $J = 1.8, 8.0$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 8.69 (d, $J = 4.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.7 (t), 33.7 (t), 51.6 (q), 112.3 (d), 118.3 (s), 119.7 (d), 120.7 (d), 122.4 (d), 125.4 (d), 128.4 (s), 131.5 (s), 136.5 (d), 149.7 (d), 150.4 (s), 150.7 (s), 152.2 (s), 173.7 (s) ppm; IR (neat): ν 3051, 2999, 1731, 1644, 1430, 1215, 1046, 850, 750, 663 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{O}_3\text{NCl}$ ($\text{M}^+ + \text{H}$): 316.0735; found: 316.0736.

Ethyl 3-(5-chloro-2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28cb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.4$).

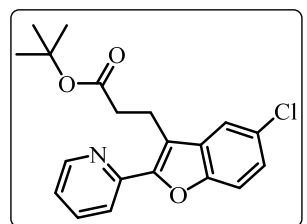
The title compound was determined as white colour solid (61%). Mp: 84-85 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 1.22 (t, $J = 7.3$ Hz, 3H), 2.79 (t, $J = 7.3$ Hz, 2H), 3.53 (t, $J = 7.3$



Hz, 2H), 4.11 (t, $J = 7.3$ Hz, 2H), 7.23 (ddd, $J = 0.9, 5.0, 7.3$ Hz, 1H), 7.29 (dd, $J = 1.8, 8.7$ Hz, 1H), 7.43 (d, $J = 8.7$ Hz, 1H), 7.63 (d, $J = 2.3$ Hz, 1H), 7.79 (dt, $J = 1.8, 8.2$ Hz, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 8.69 (d, $J = 4.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1 (q), 19.6 (t), 34.0 (t), 60.4 (t), 112.2 (d), 118.4 (s), 119.8 (d), 120.7 (d), 122.4 (d), 125.4 (d), 128.4 (s), 131.5 (s), 136.5 (d), 149.7 (d), 150.4 (s), 150.7 (s), 152.2 (s), 173.2 (s) ppm; IR (neat): ν 3020, 2996, 1734, 1644, 1602, 1438, 1215, 1045, 850, 758, 669 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{18}\text{H}_{17}\text{O}_3\text{NCl}$ ($\text{M}^+ + \text{H}$): 330.0891; found: 330.0892.

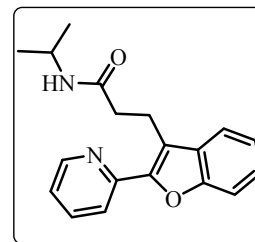
tert-butyl 3-(5-chloro-2-(pyridin-2-yl)benzofuran-3-yl)propanoate (28cn): Isolated by column chromatography (pet.ether/AcOEt = 9:1, $R_f = 0.4$).

The title compound was determined as white colour solid (53%). Mp: 90-91 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 1.41 (s, 9H), 2.69 (t, $J = 8.0$ Hz, 2H), 3.49 (t, $J = 7.8$ Hz,

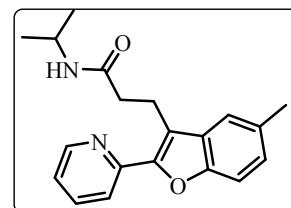


2H), 7.23 (dd, $J = 5.0, 6.5$ Hz, 1H), 7.29 (dd, $J = 2.0, 8.5$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 1H), 7.64 (d, $J = 1.8$ Hz, 1H), 7.78 (dt, $J = 1.8, 8.0$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 8.70 (d, $J = 4.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.8 (t), 28.1 (q, 3C), 35.2 (t), 80.3 (s), 112.2 (d), 118.6 (s), 119.9 (d), 120.8 (d), 122.3 (d), 125.4 (d), 128.3 (s), 131.5 (s), 136.4 (d), 149.7 (d), 150.4 (s), 150.7 (s), 152.3 (s), 172.6 (s) ppm; IR (neat): ν 3056, 2999, 1736, 1644, 1599, 1433, 1219, 1043, 860, 751, 665 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{O}_3\text{NCl}$ ($\text{M}^+ + \text{H}$): 358.1204; found: 358.1207.

***N*-isopropyl-3-(2-(pyridin-2-yl)benzofuran-3-yl)propanamide (28ak):** Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as white colour solid (49%). Mp: 149-150 °C; ^1H NMR (400 MHz, CDCl_3): δ 0.97 (d, J = 6.6 Hz, 6H), 2.81 (t, J = 7.1 Hz, 2H), 3.56 (t, J = 7.1 Hz, 2H), 3.97–4.06 (m, 1H), 6.82 (d, J = 6.9 Hz, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.32–7.39 (m, 2H), 7.52 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.91 (t, J = 7.6 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 8.73 (d, J = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.2 (t), 22.5 (q, 2C), 36.3 (t), 41.2 (d), 111.3 (d, 2C), 120.2 (s), 120.7 (d, 2C), 121.6 (d), 122.6 (d), 123.1 (d), 125.9 (d), 129.6 (s, 2C), 154.2 (s, 2C), 171.6 (s) ppm; IR (neat): ν 3043, 2995, 1748, 1644, 1600, 1438, 1219, 1055, 859, 750, 660 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{O}_2\text{N}_2$ ($\text{M}^+ + \text{H}$): 309.1598; found: 309.1600.



***N*-isopropyl-3-(5-methyl-2-(pyridin-2-yl)benzofuran-3-yl)propanamide (28bk):** Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless gum (55%). ^1H NMR (400 MHz, CDCl_3): δ 0.94 (d, J = 6.6 Hz, 6H), 2.47 (s, 3H), 2.78 (t, J = 7.3 Hz, 2H), 3.57 (t, J = 7.3 Hz, 2H), 3.99–4.07 (m, 1H), 6.73 (d, J = 3.9 Hz, 1H), 7.11 (dd, J = 3.9, 6.1 Hz, 1H), 7.16 (d, J = 3.9 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 8.69 (d, J = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.1 (t), 21.4 (q), 22.6 (q, 2C), 36.5 (t), 40.9 (d), 110.7 (d), 119.1 (s), 120.3 (d), 121.0 (d), 122.2 (d), 126.9 (d), 132.4 (s), 136.9 (d), 139.3 (s), 149.0 (d), 151.1 (s), 151.1 (s), 161.9 (s), 171.4 (s) ppm; IR (neat): ν 3333, 3061, 2973, 1644, 1549, 1449, 1360, 1261, 1174, 1023, 966, 826, 752 cm^{-1} ; HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{23}\text{O}_2\text{N}_2$ ($\text{M}^+ + \text{H}$): 323.1754; found: 323.1756.

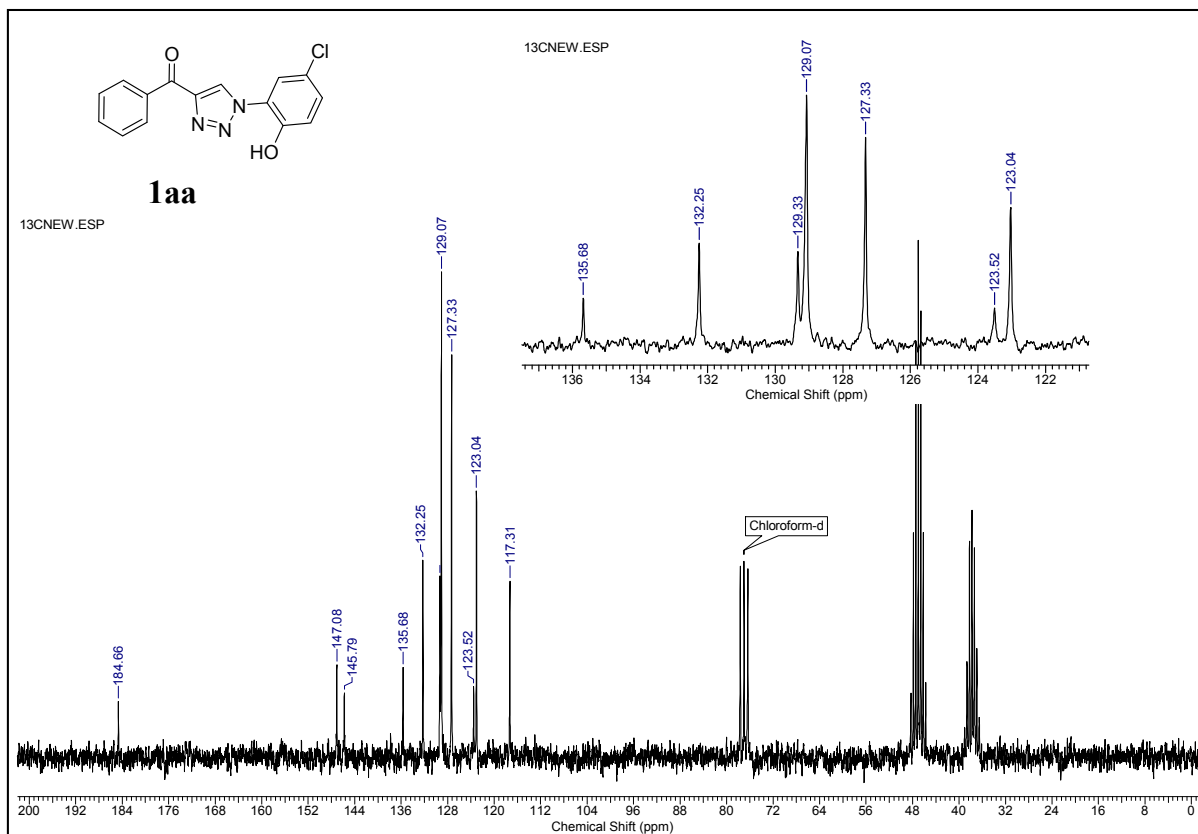


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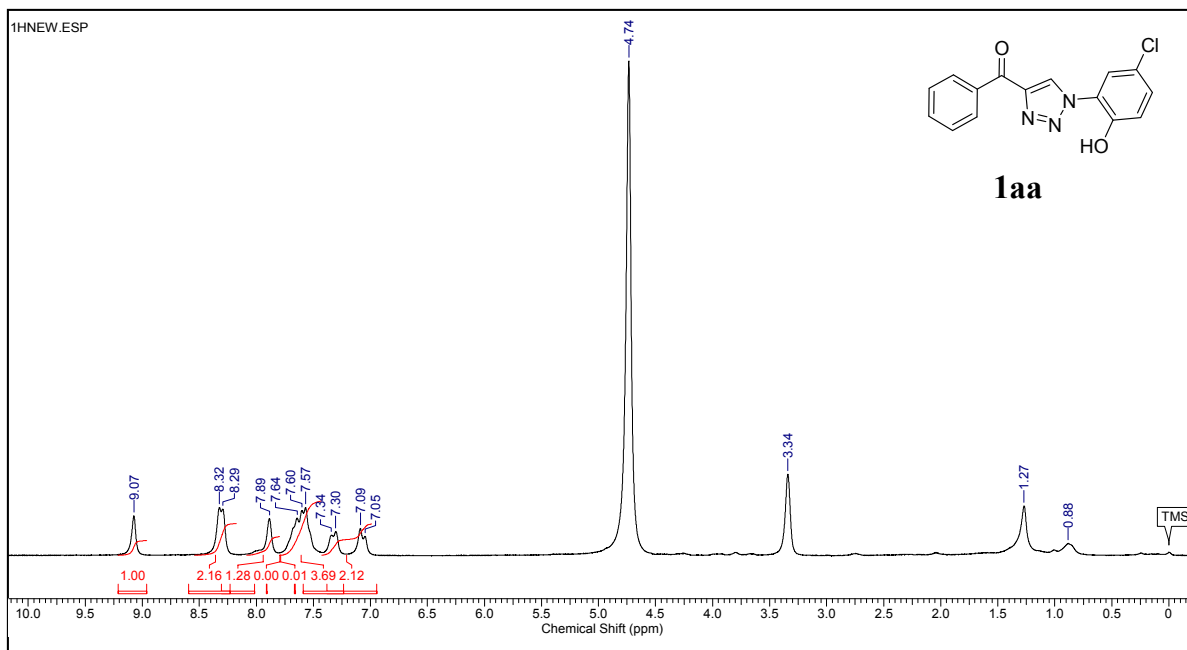
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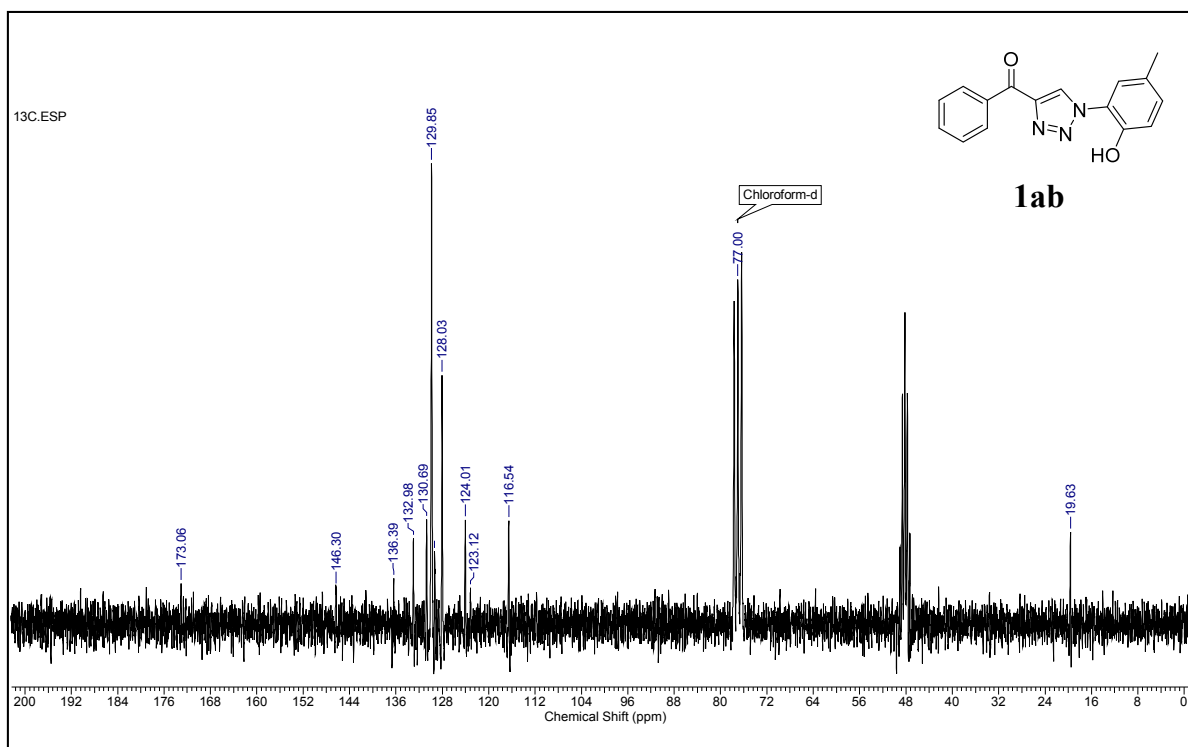
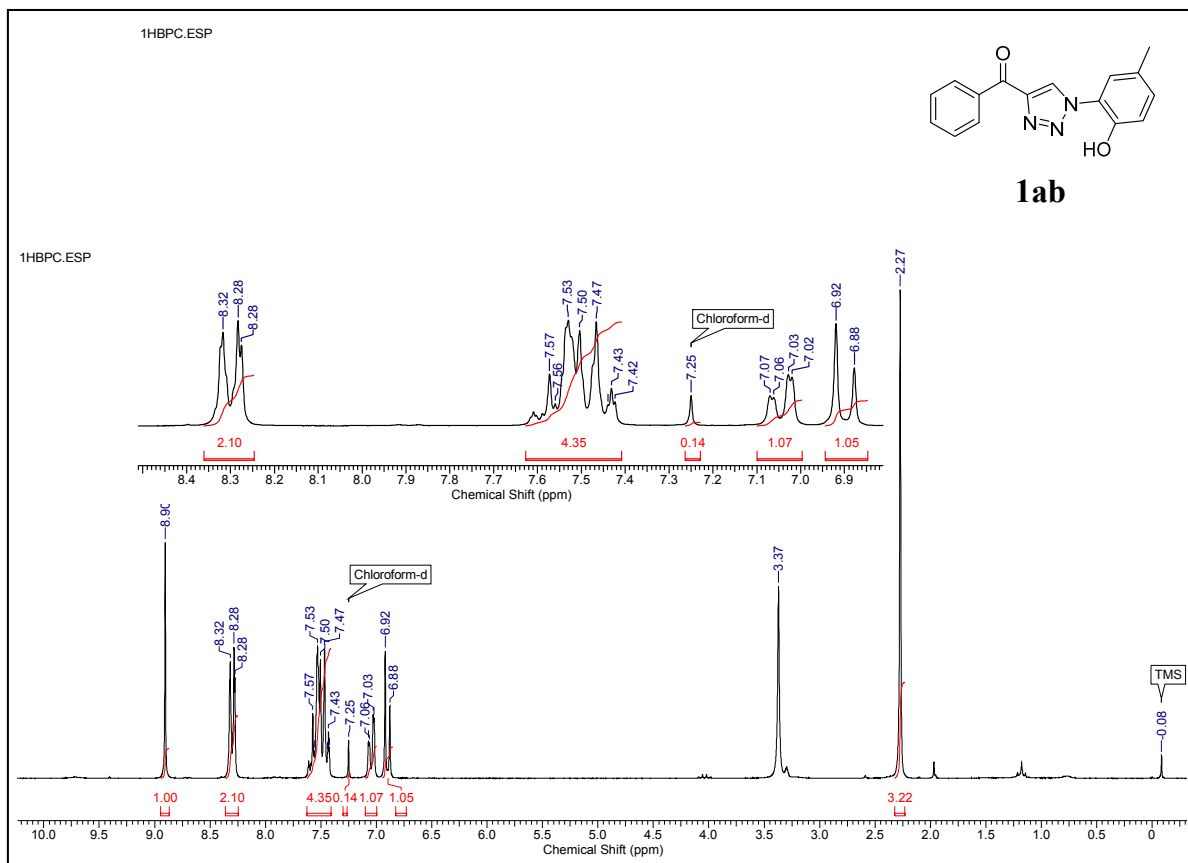
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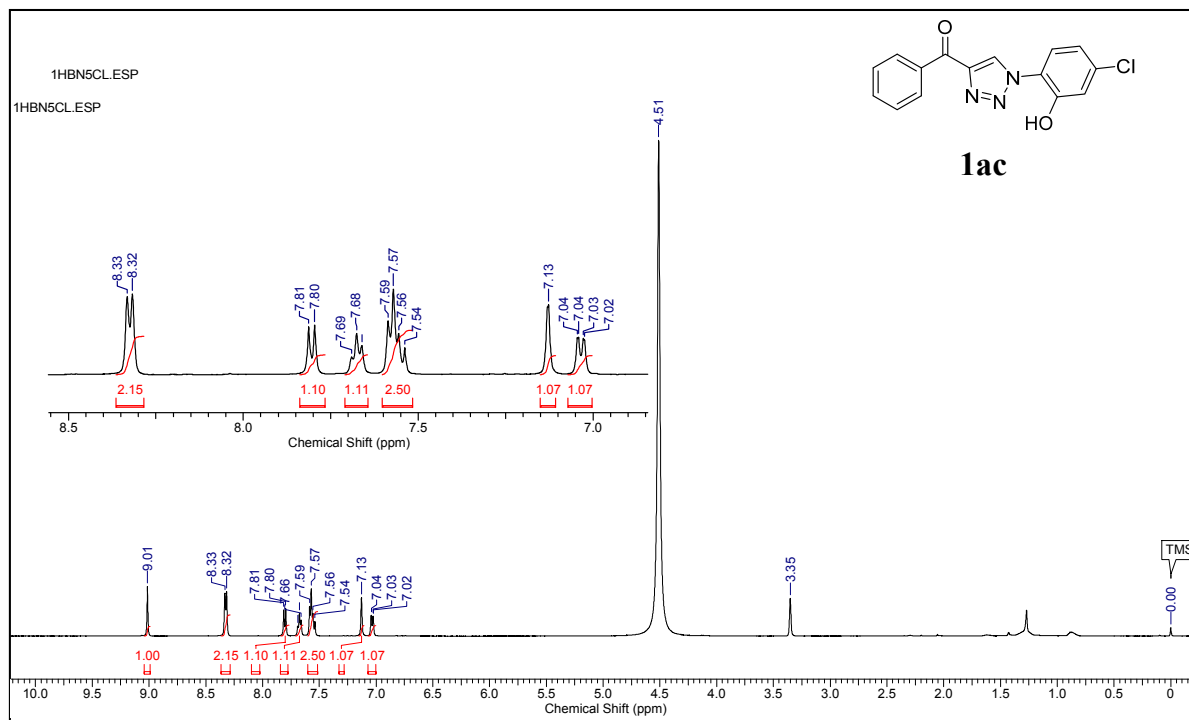


¹H NMR Spectrum of **1aa** in CDCl₃ + MeOH (D₄) (200 MHz)

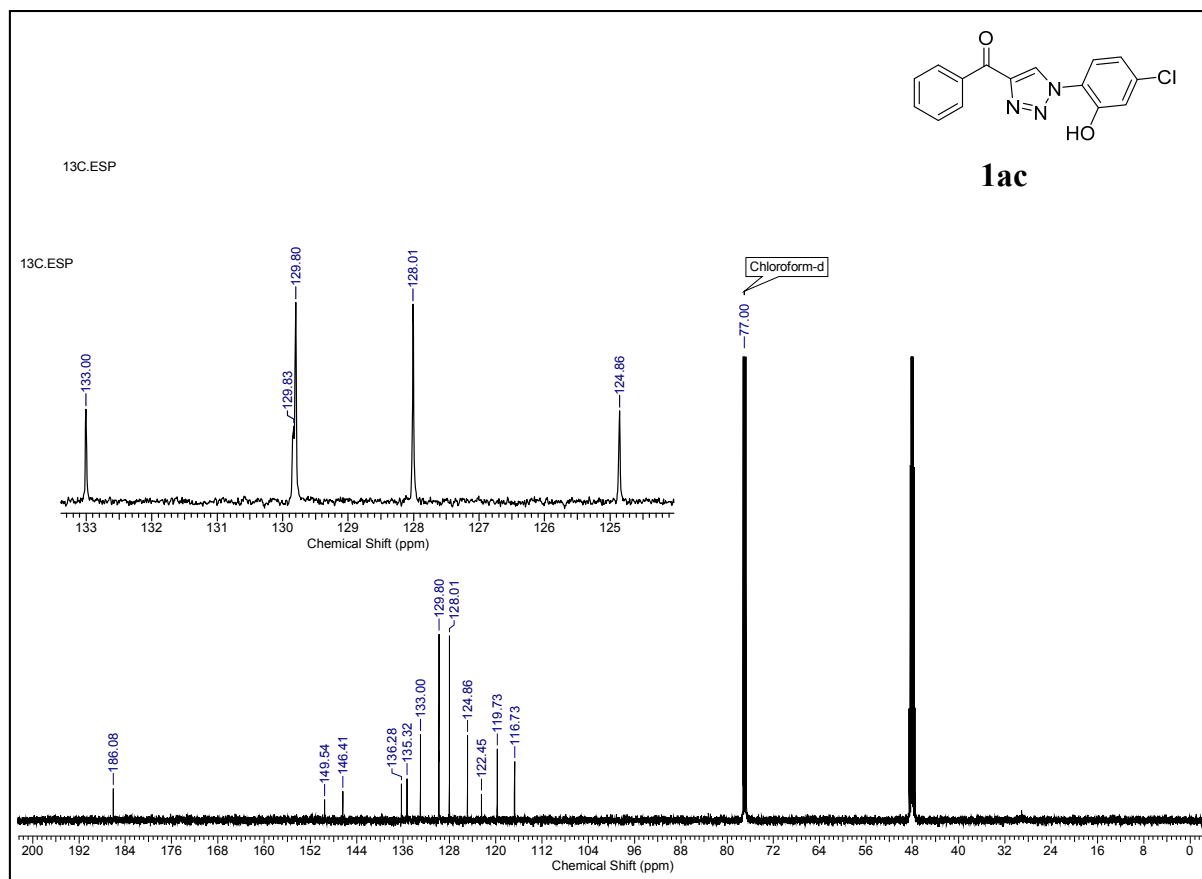


¹³C NMR Spectrum of **1aa** in CDCl₃ + MeOH (D₄) (50 MHz)

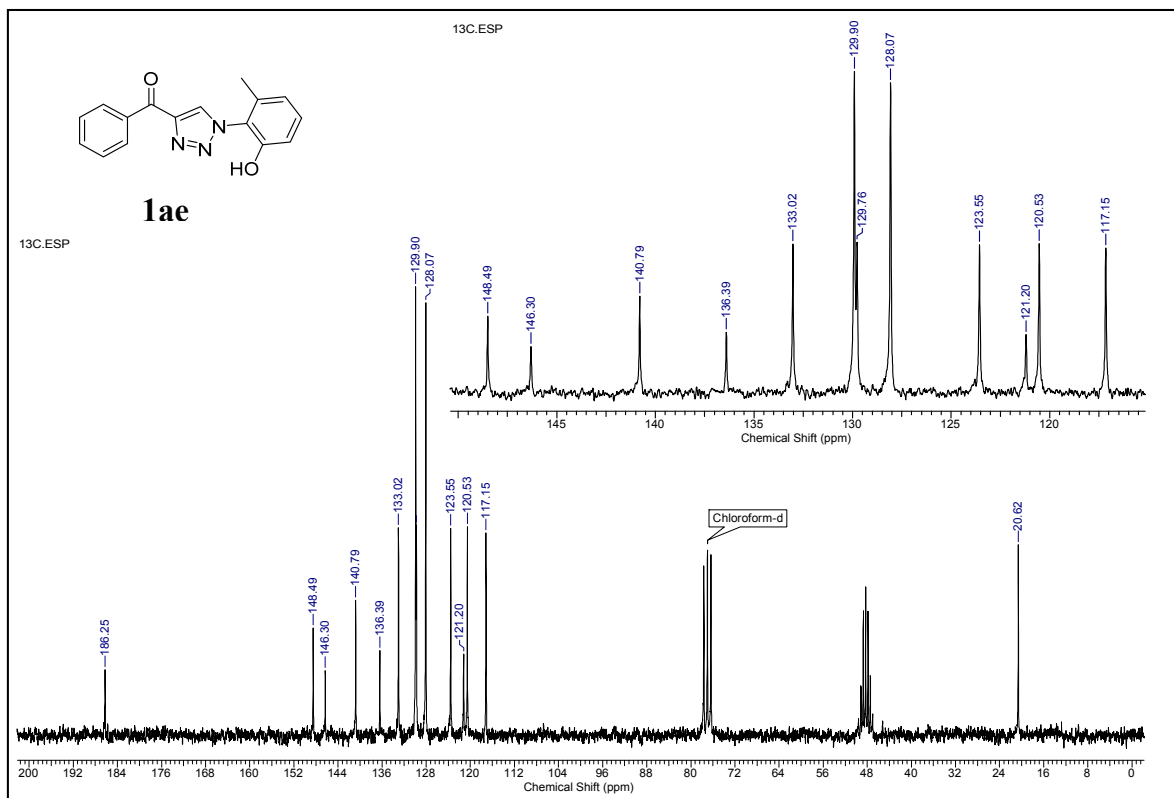




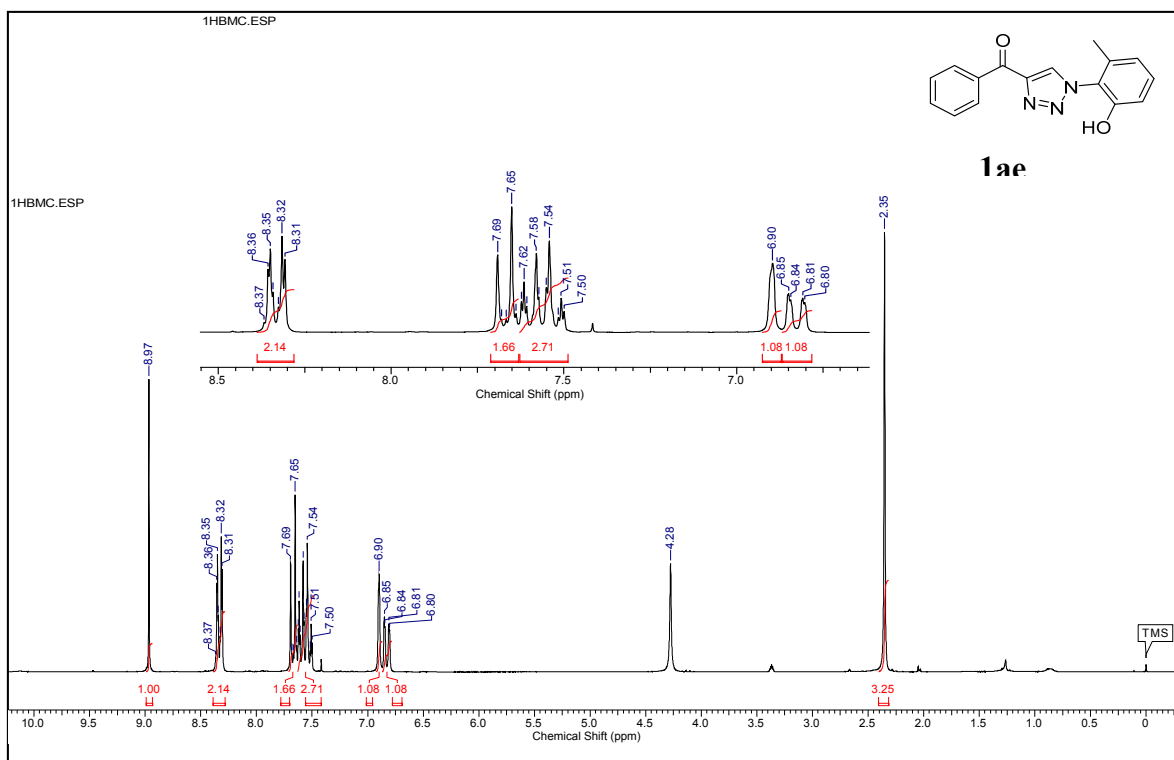
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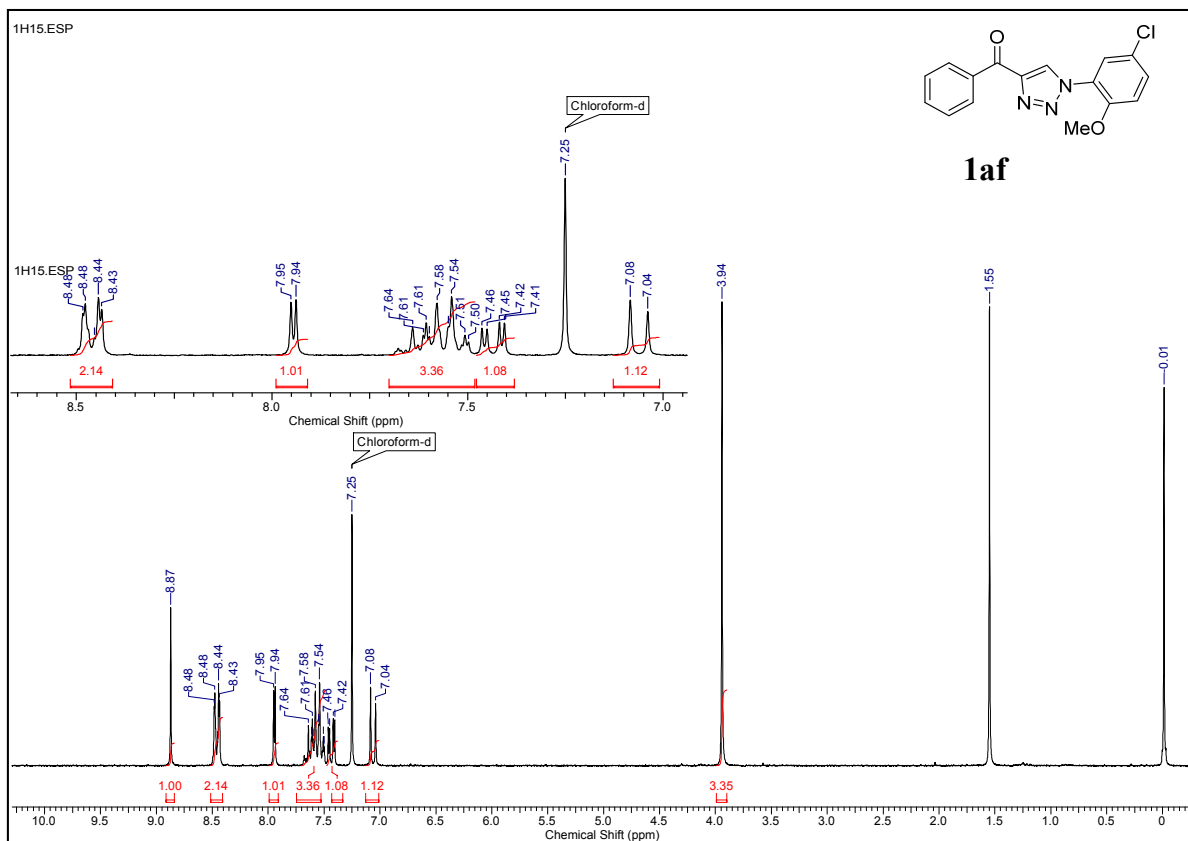
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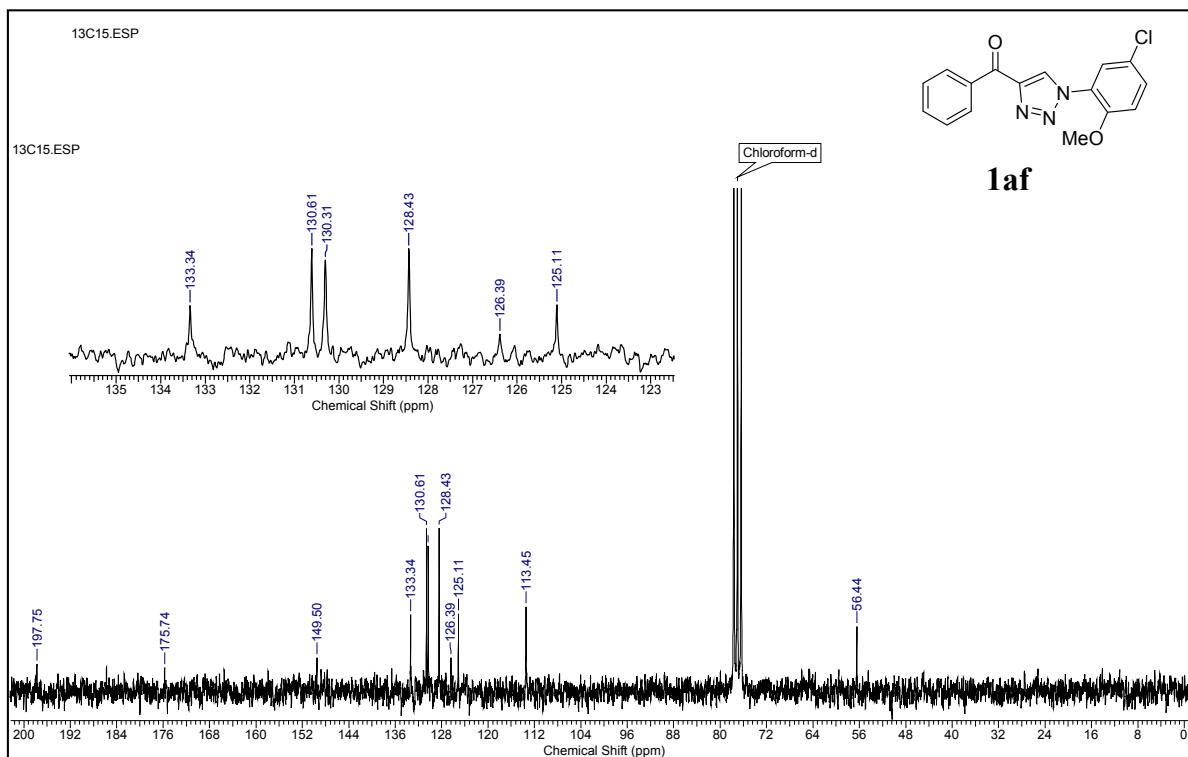
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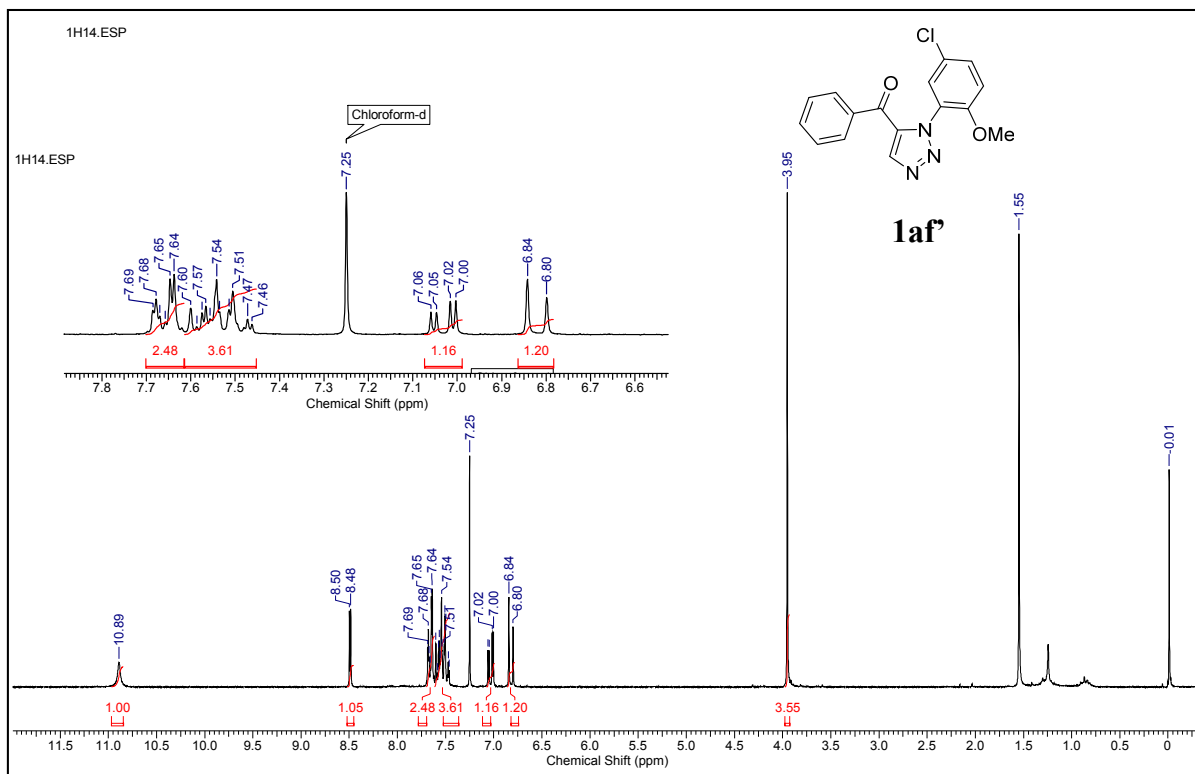
¹³C NMR Spectrum of **1ae in CDCl₃ + MeOH (D₄) (50 MHz)**



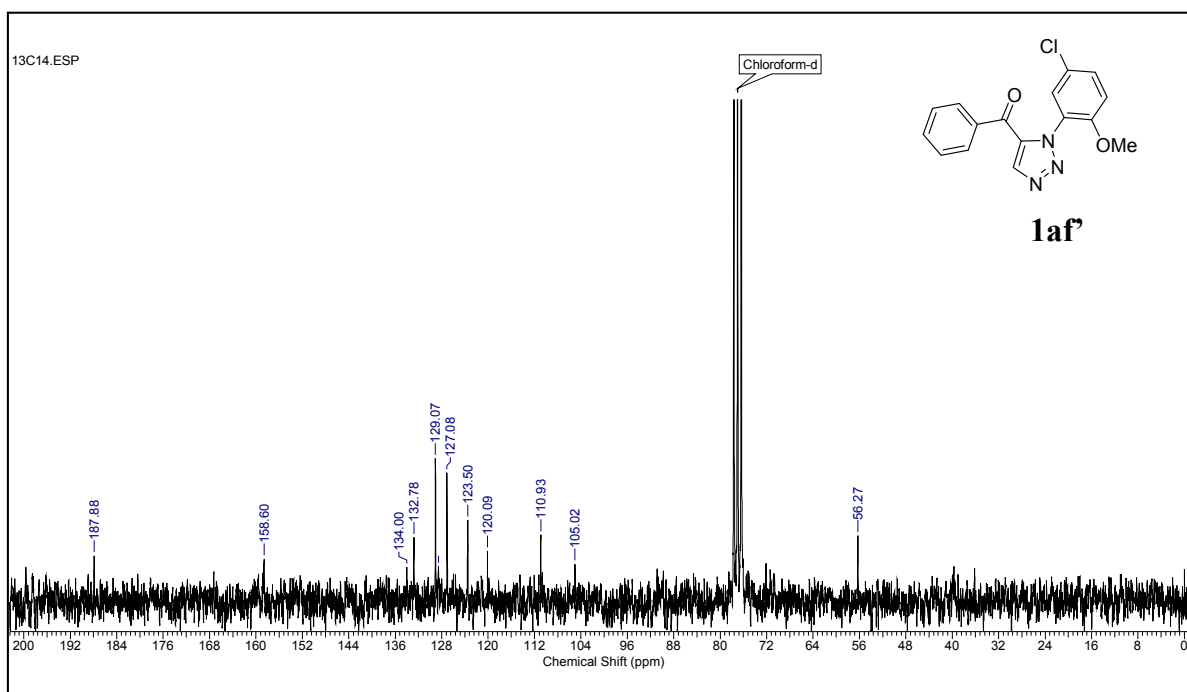
¹H NMR Spectrum of **1af** in CDCl₃ (200 MHz)



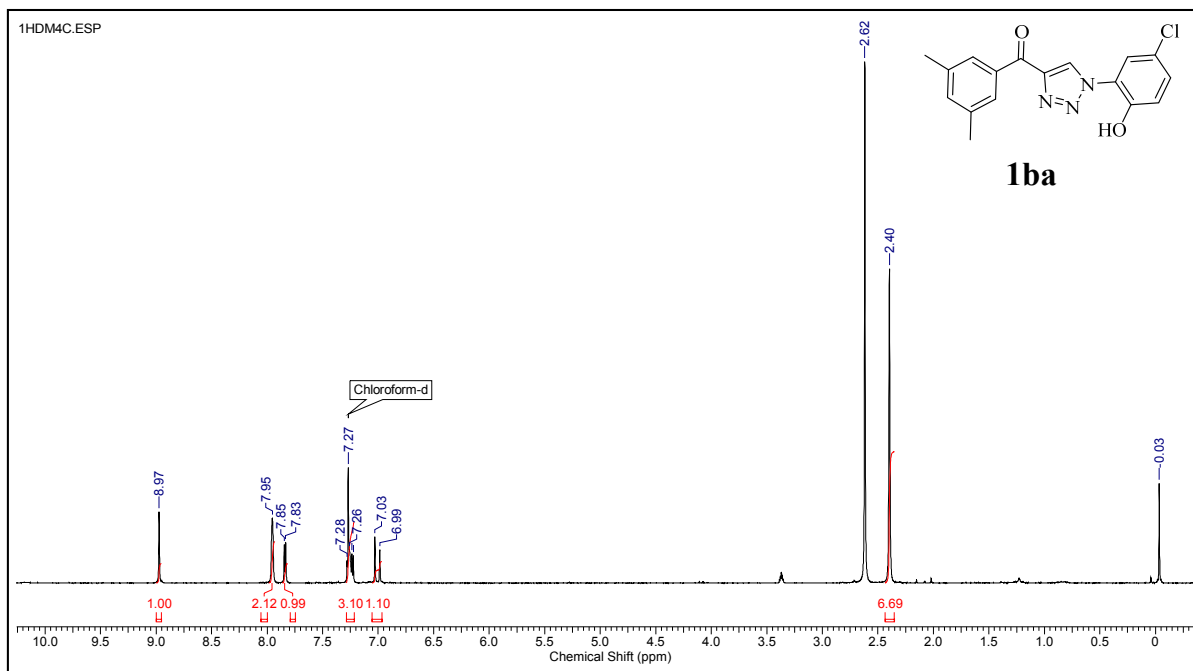
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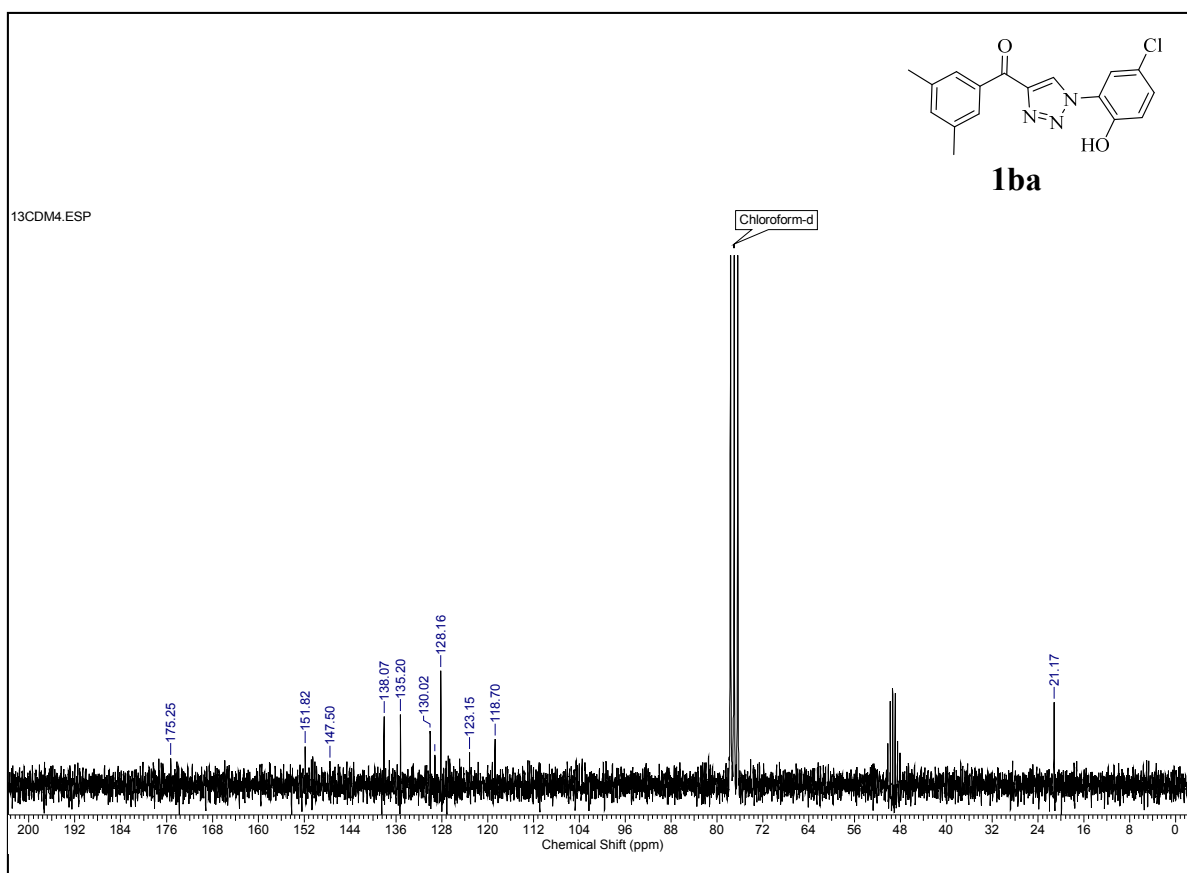
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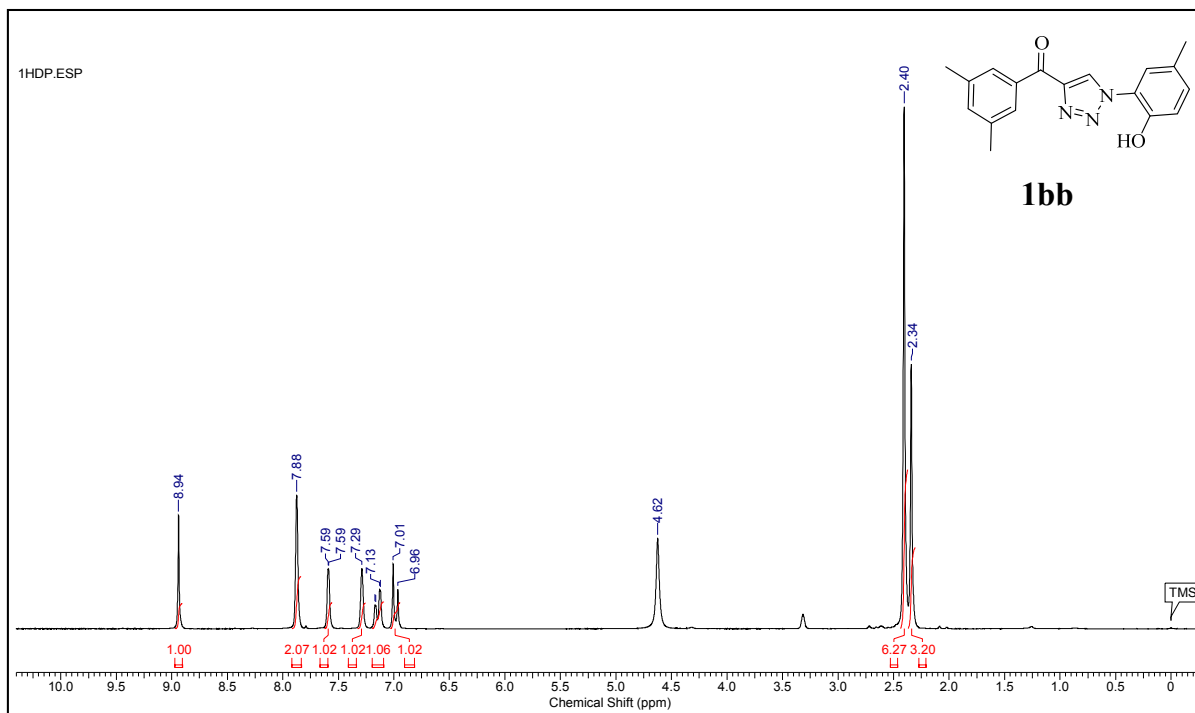
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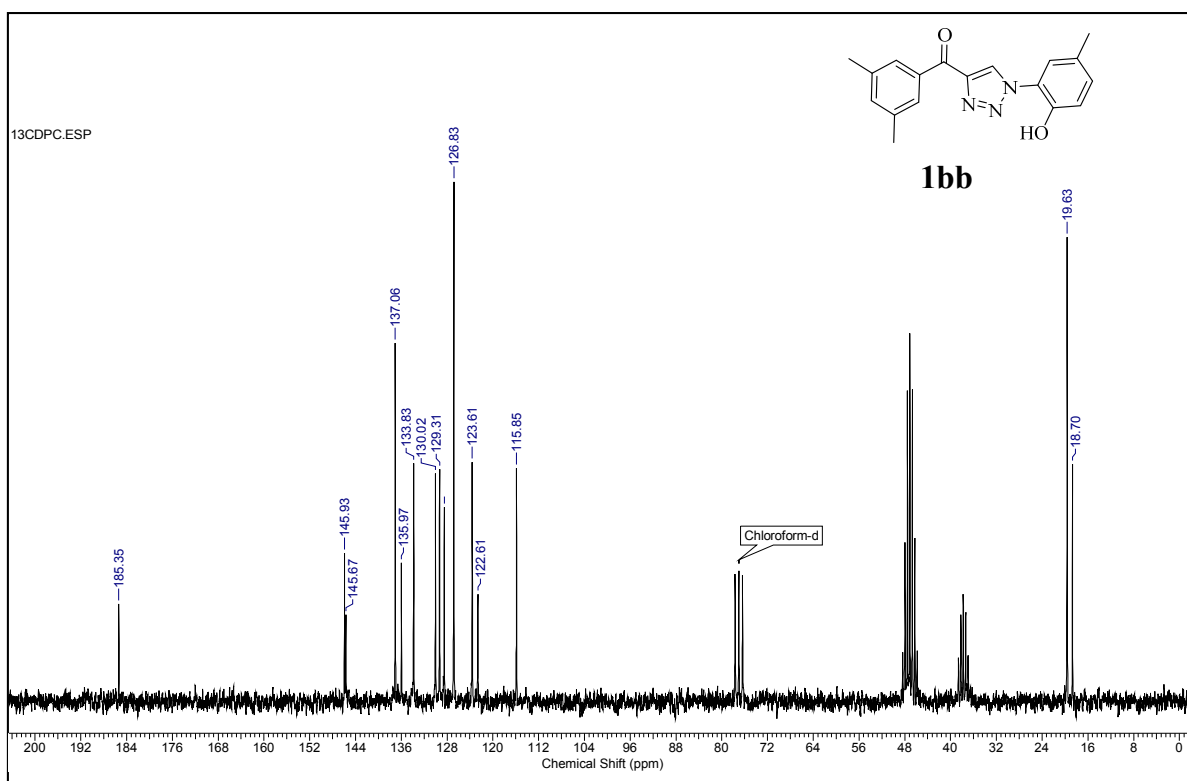
¹H NMR Spectrum of **1ba** in CDCl₃ + DMSO (D₆) (200 MHz)



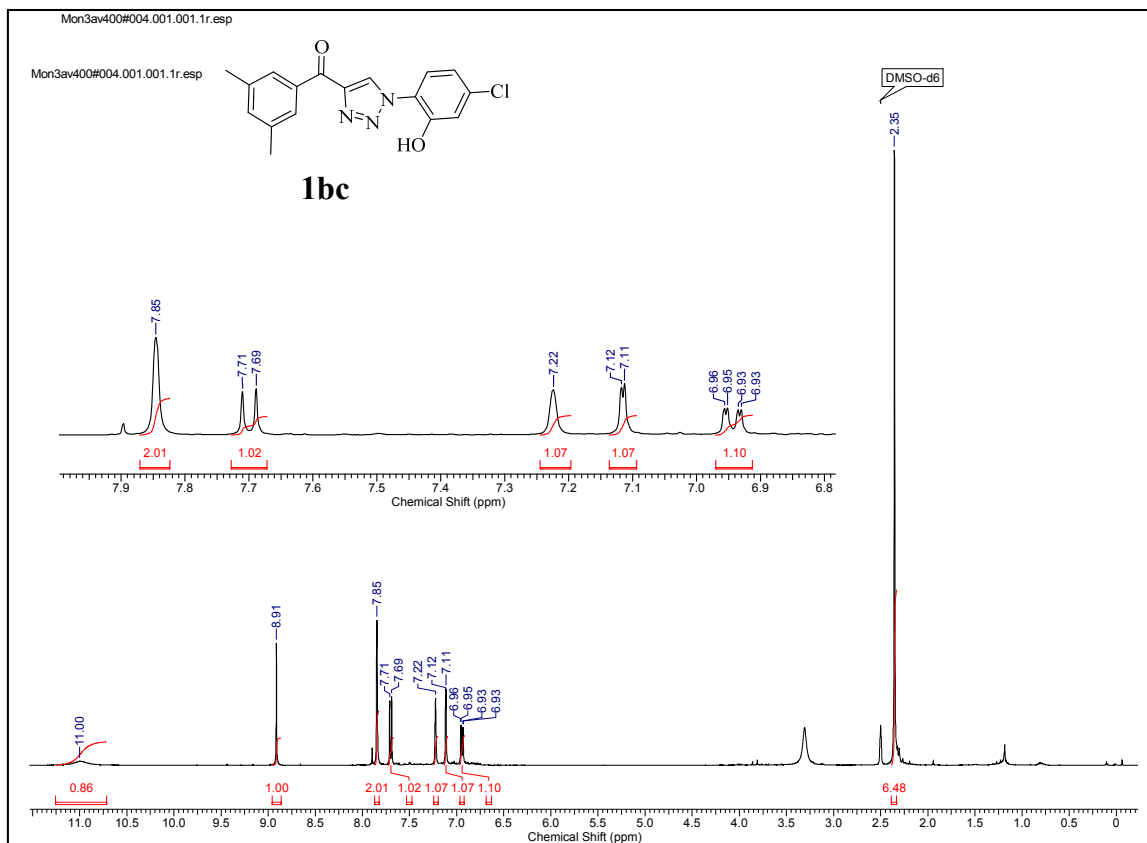
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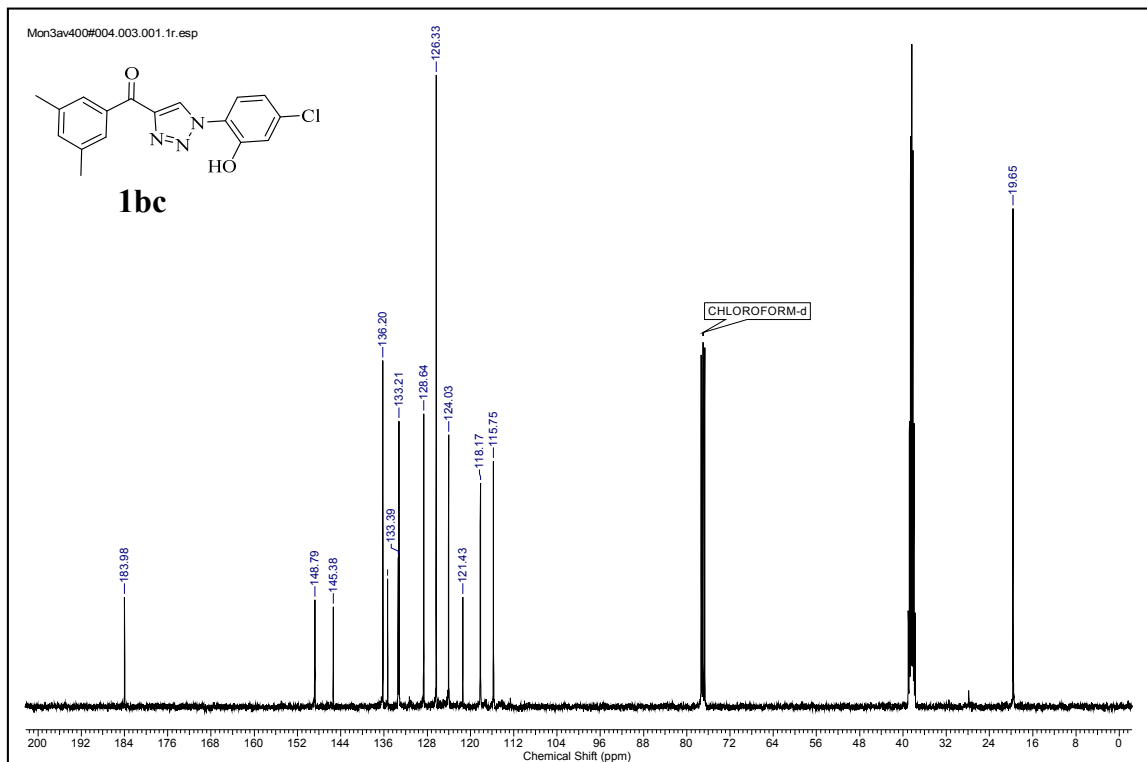
^1H NMR Spectrum of **1ba** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4) + \text{DMSO} (\text{D}_6)$ (200 MHz)



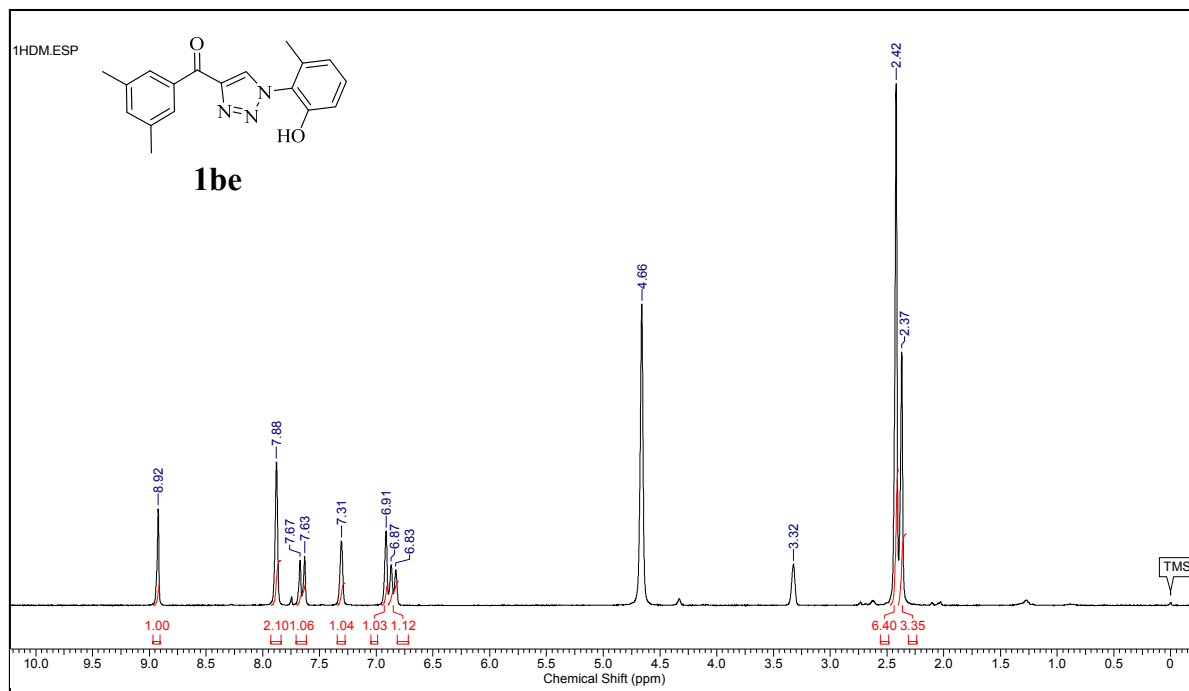
^{13}C NMR Spectrum of **1bb** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4) + \text{DMSO} (\text{D}_6)$ (200 MHz)



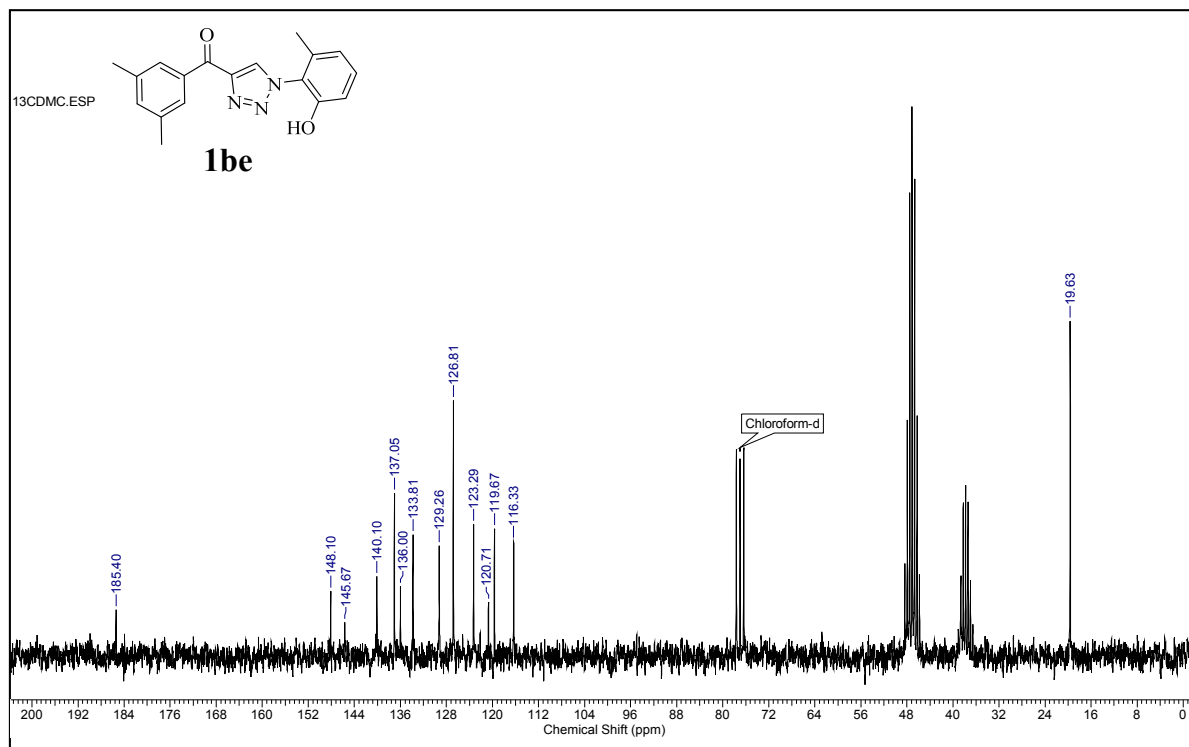
¹H NMR Spectrum of **1bc** in CDCl₃ + DMSO (D₆) (400 MHz)



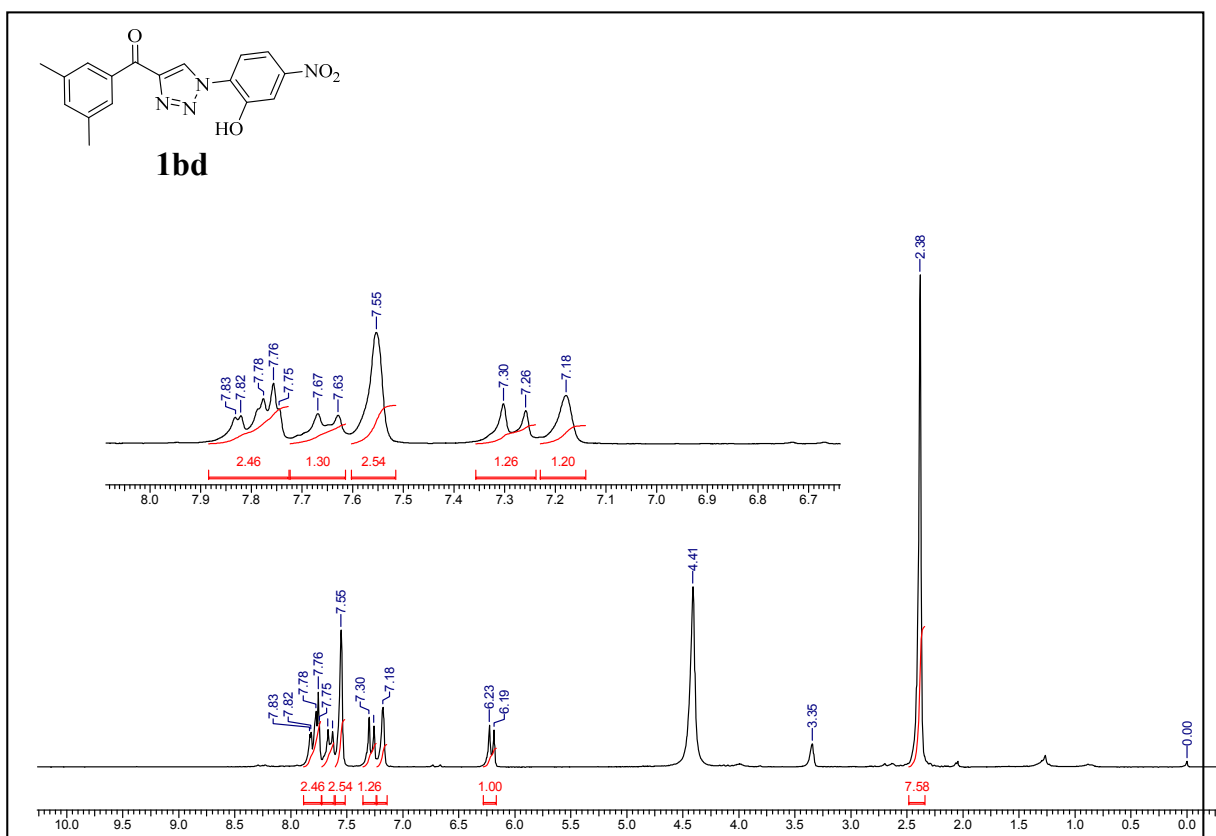
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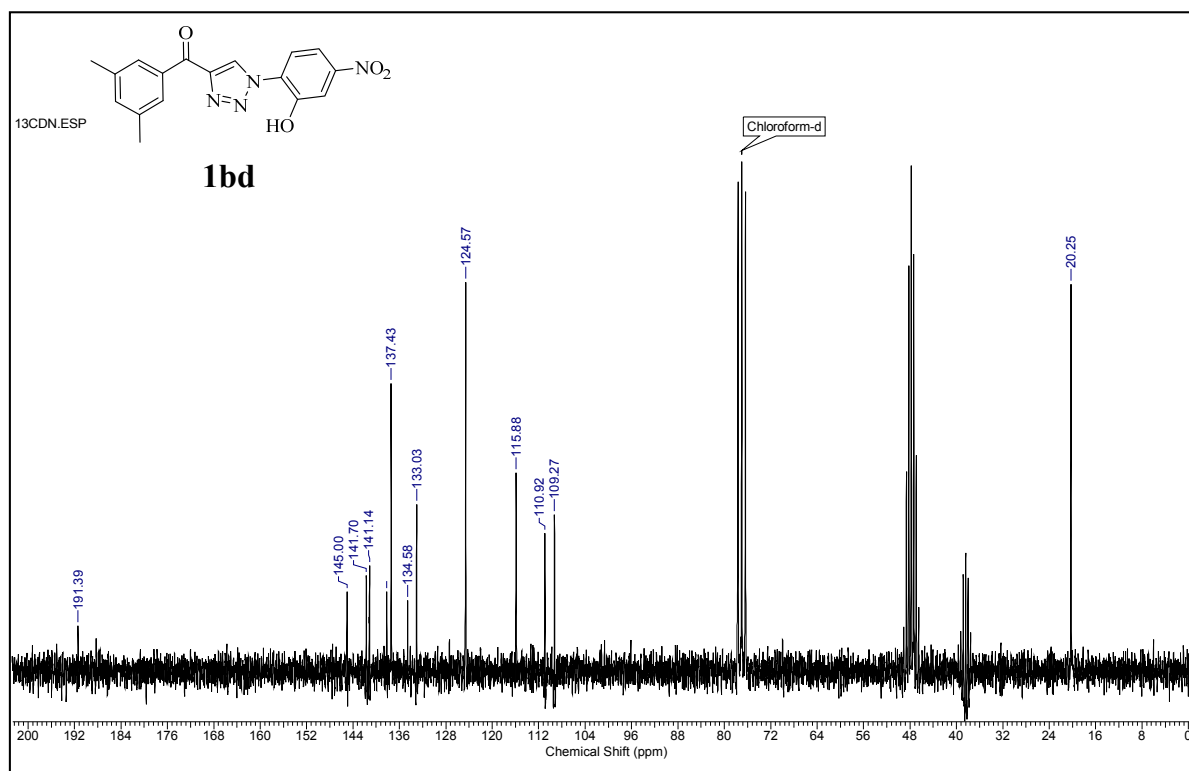
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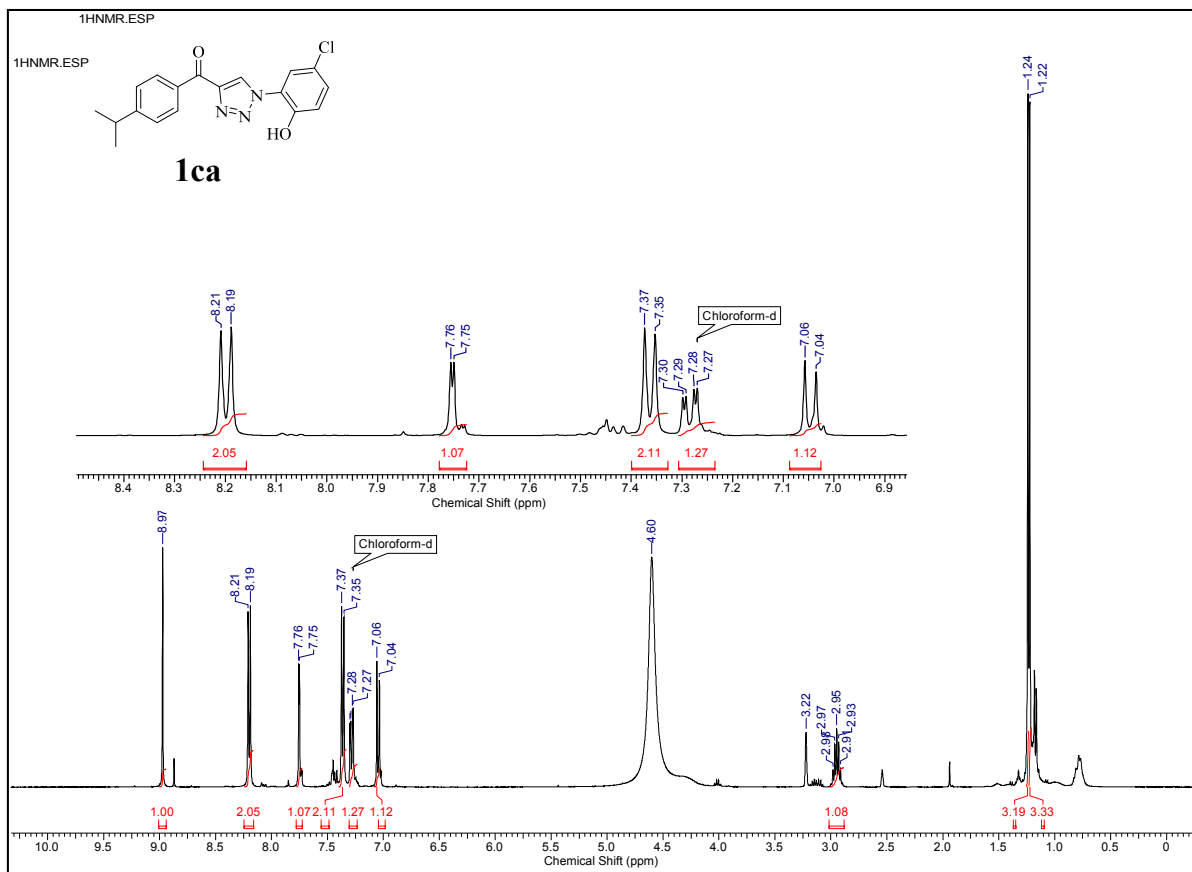
¹³C NMR Spectrum of **1be** in CDCl₃ + MeOH (D₄) (50 MHz)



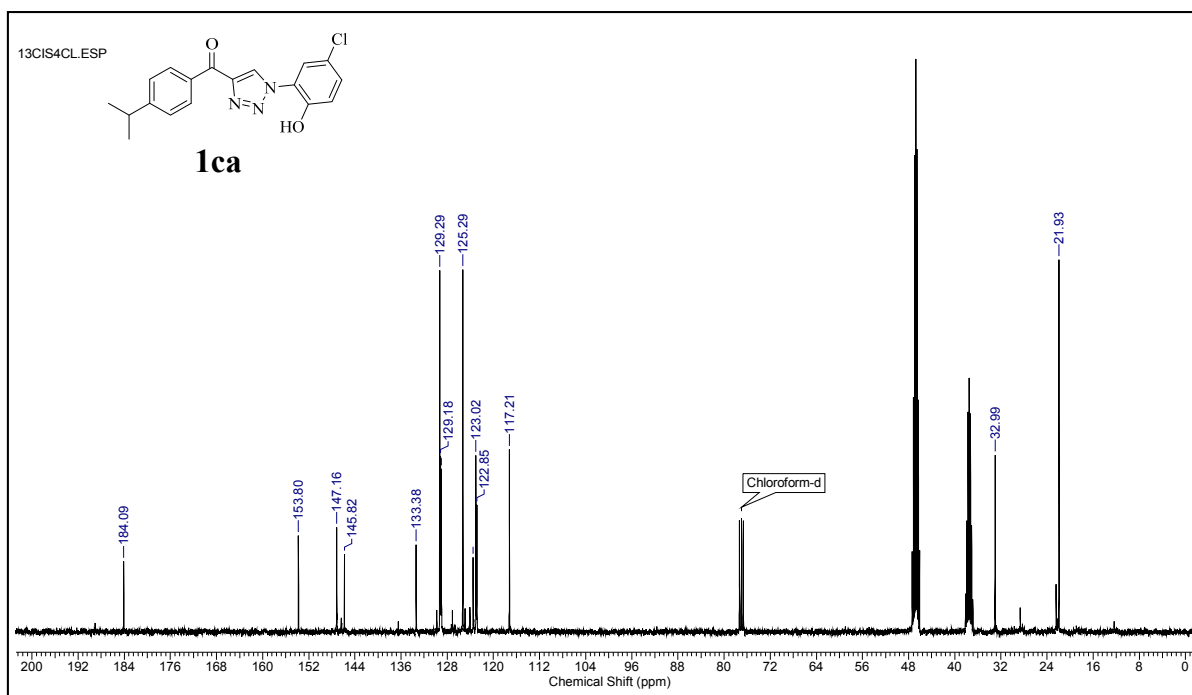
¹H NMR Spectrum of **1bd** in CDCl₃ + MeOH (D₄) + DMSO (D₆) (200 MHz)



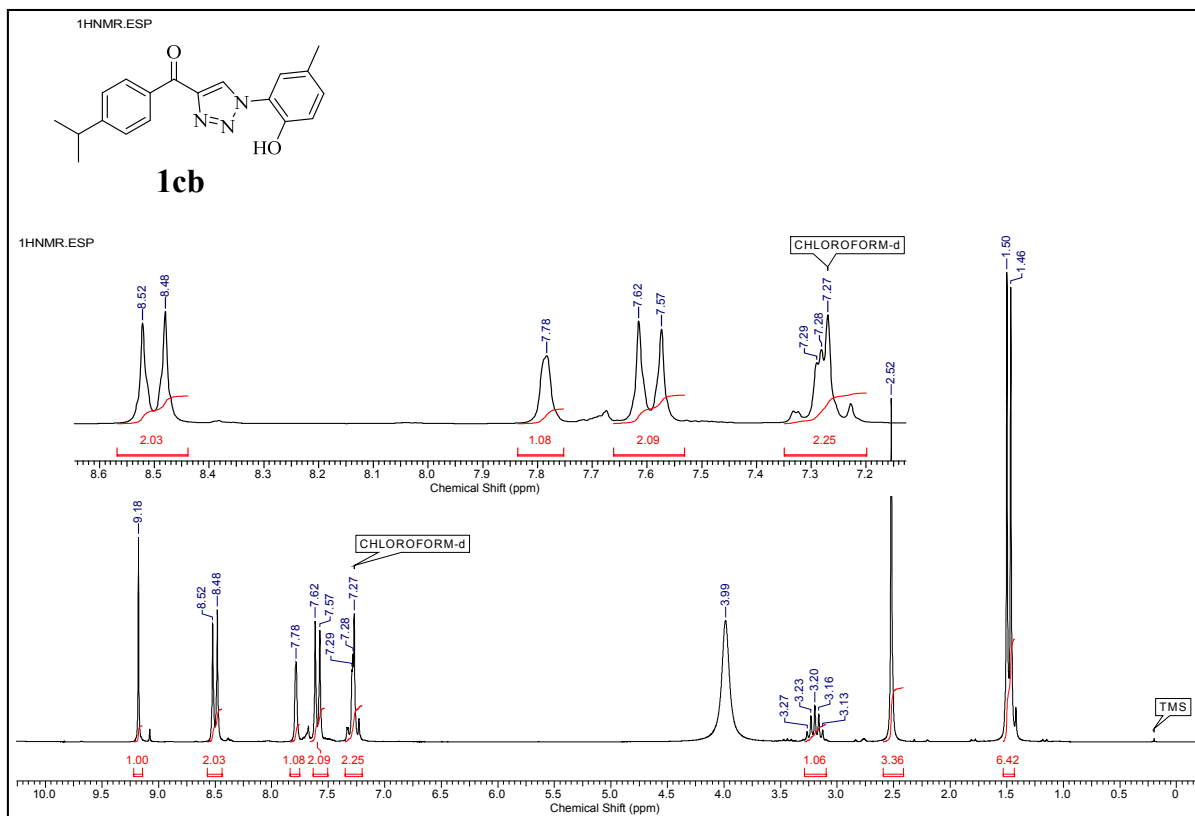
¹³C NMR Spectrum of **1ba** in CDCl₃ + MeOH (D₄) + DMSO (D₆) (50 MHz)



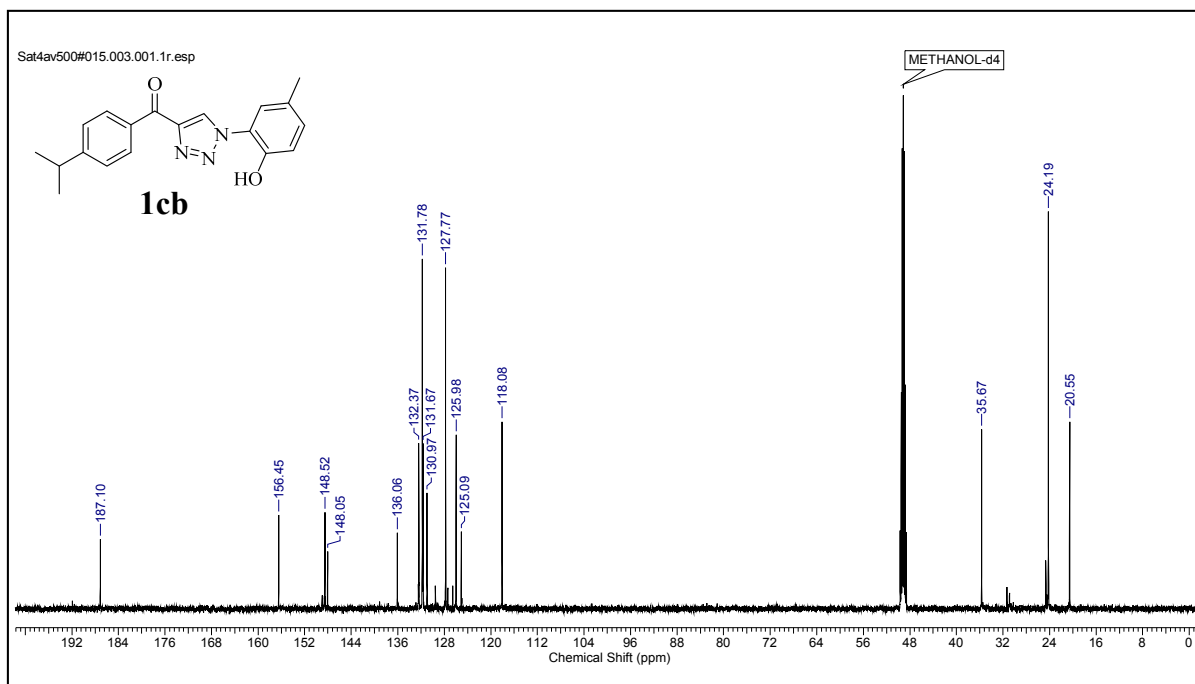
¹H NMR Spectrum of **1ca** in CDCl₃ + MeOH (D₄) + DMSO (D₆) (400 MHz)



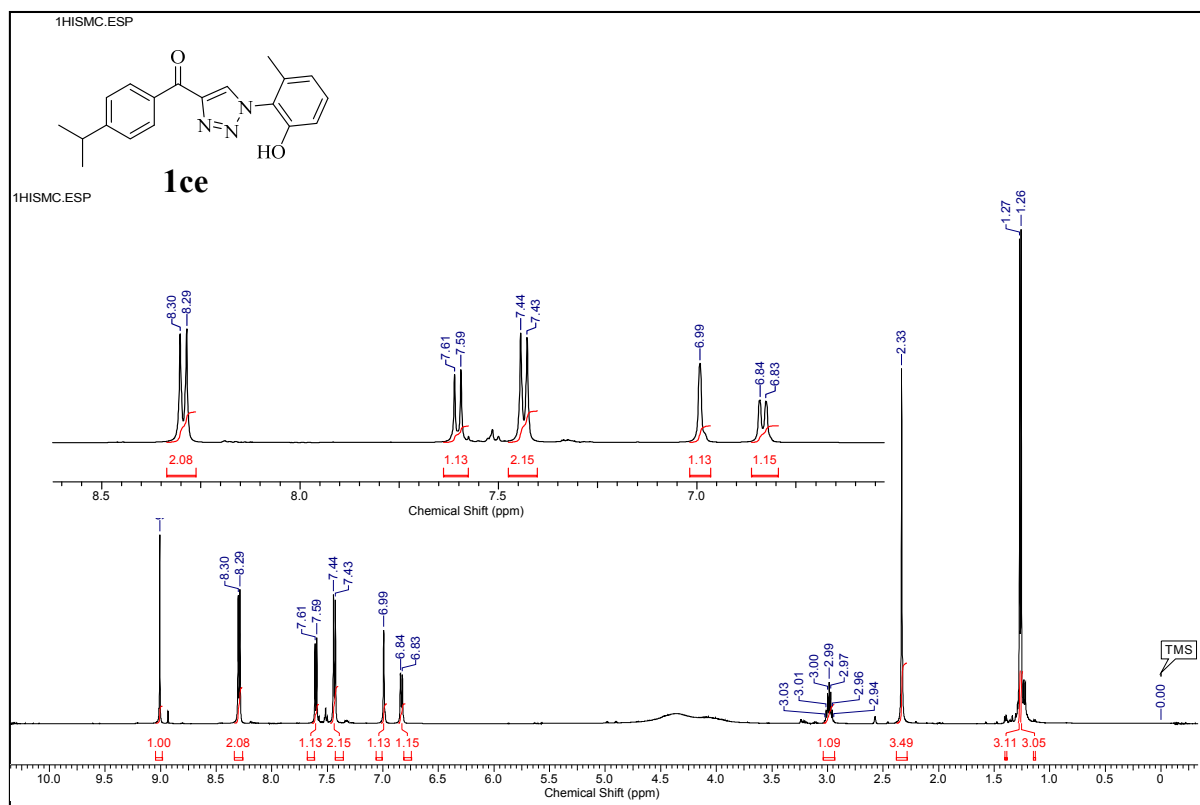
¹³C NMR Spectrum of **1ba** in CDCl₃ + MeOH (D₄) + DMSO (D₆) (100 MHz)



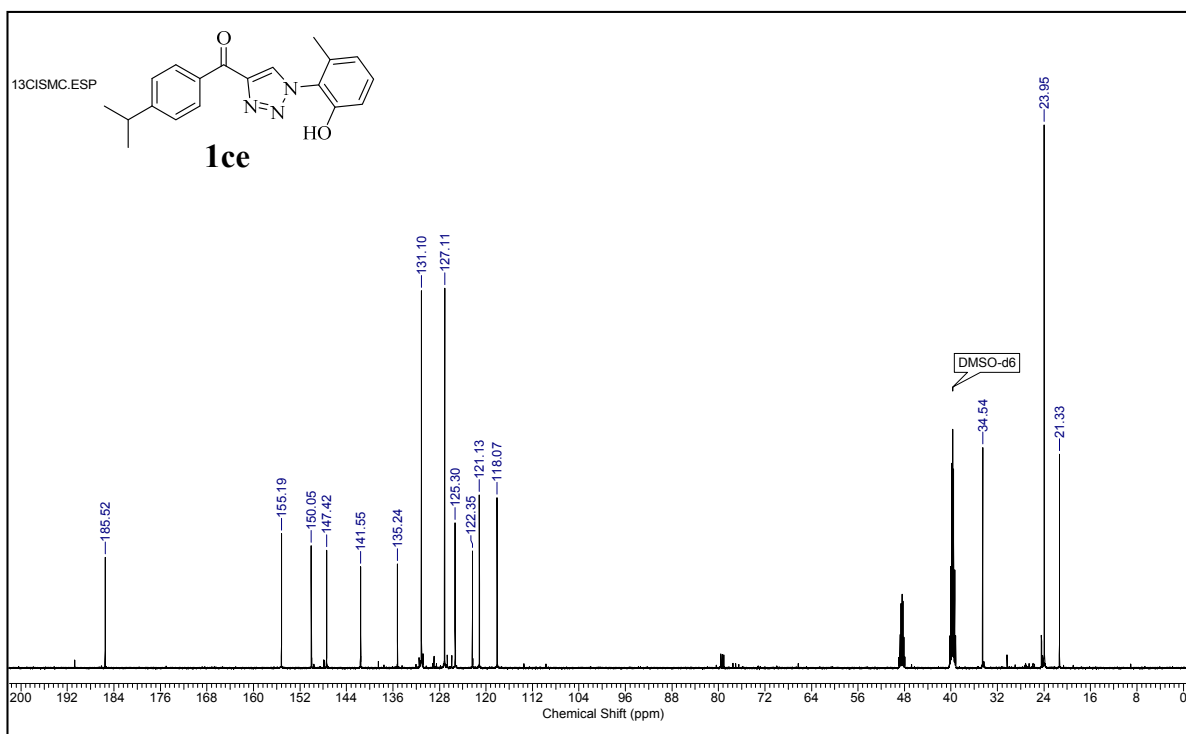
¹H NMR Spectrum of **1ba** in MeOH (D₄) (500 MHz)



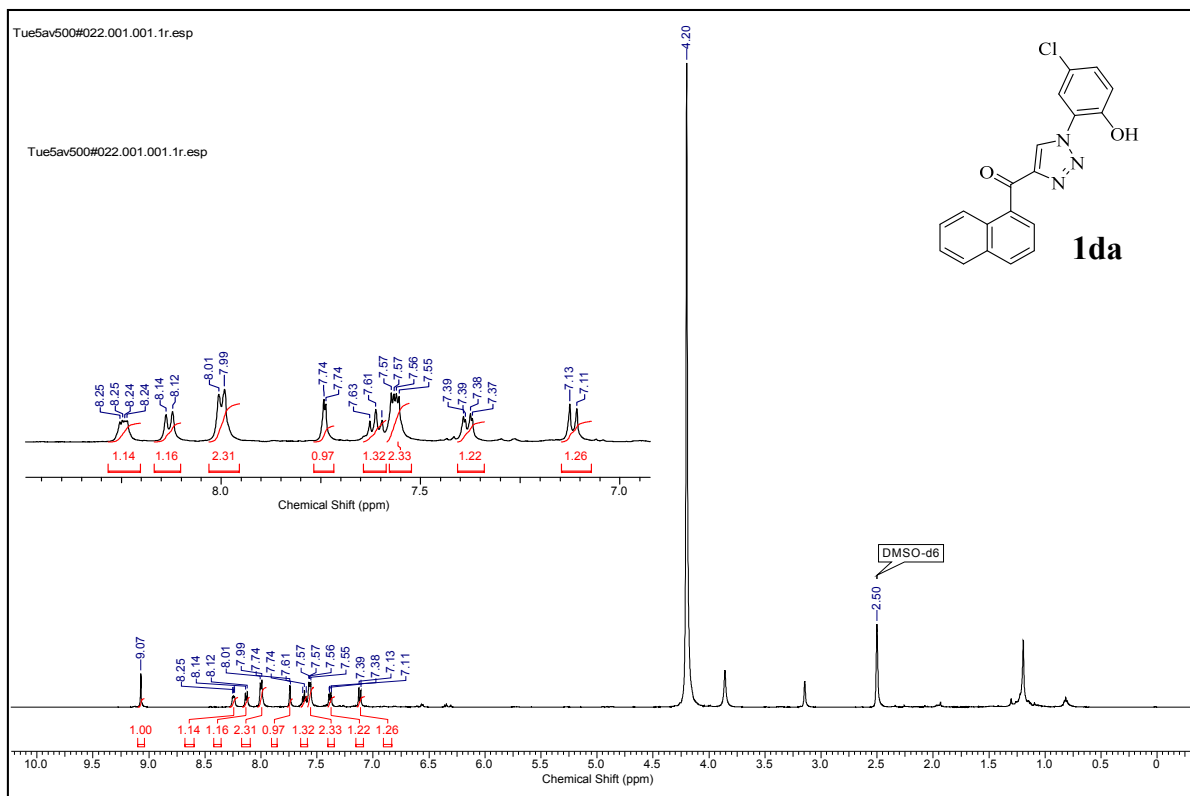
¹³C NMR Spectrum of **1cb** in MeOH (D₄) (125 MHz)



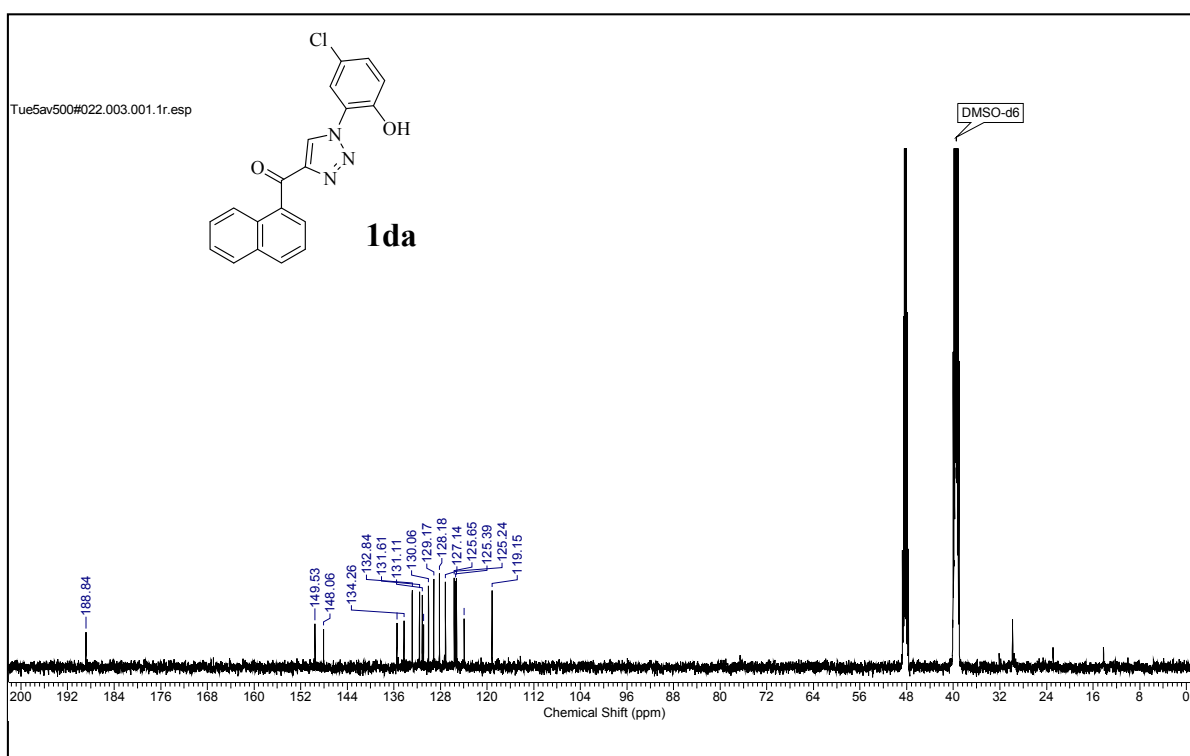
¹H NMR Spectrum of **1ce** in CDCl₃ + MeOH (D₄) + DMSO (D₆) (500 MHz)



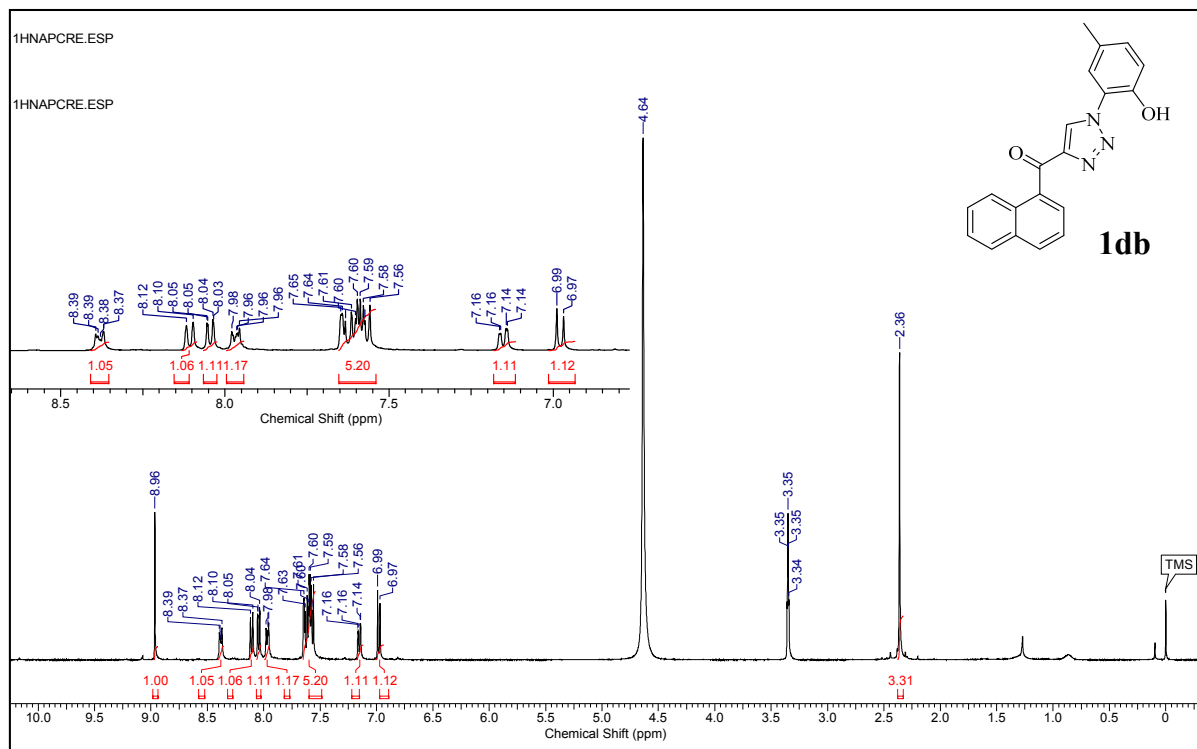
¹³C NMR Spectrum of **1ca** in CDCl₃ + MeOH (D₄) + DMSO (D₆) (125 MHz)



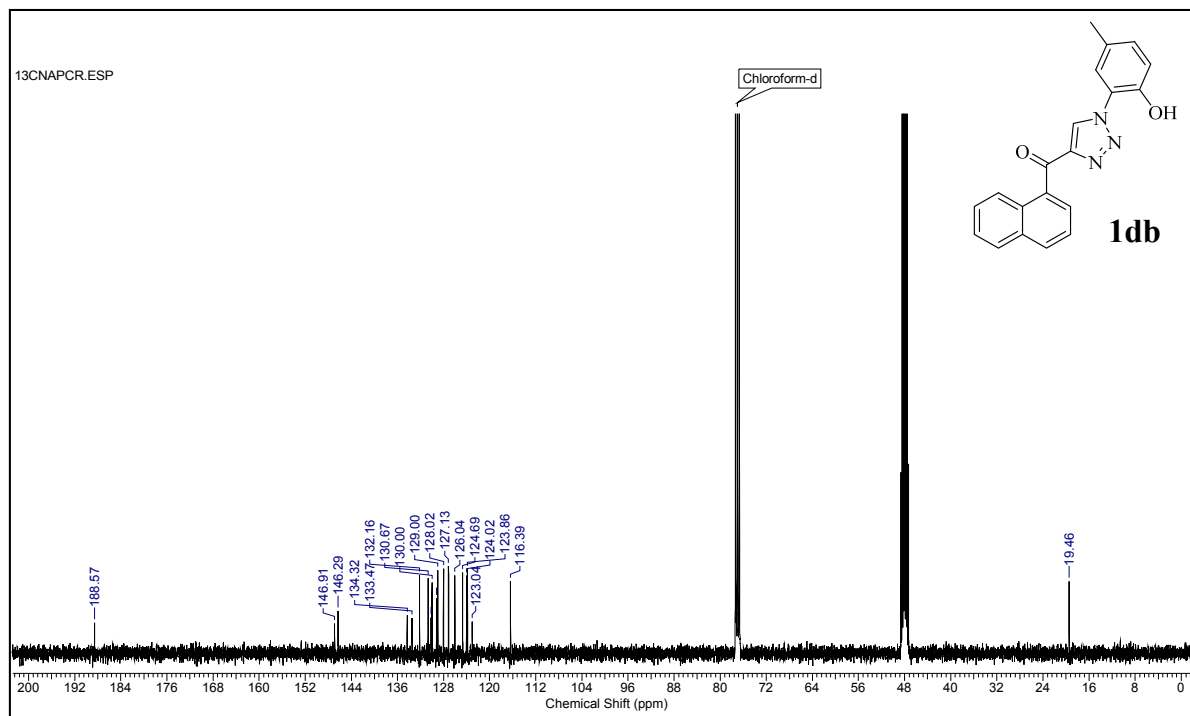
¹H NMR Spectrum of **1da** in CDCl₃ + MeOH (D₄) + DMSO (D₆) (500 MHz)



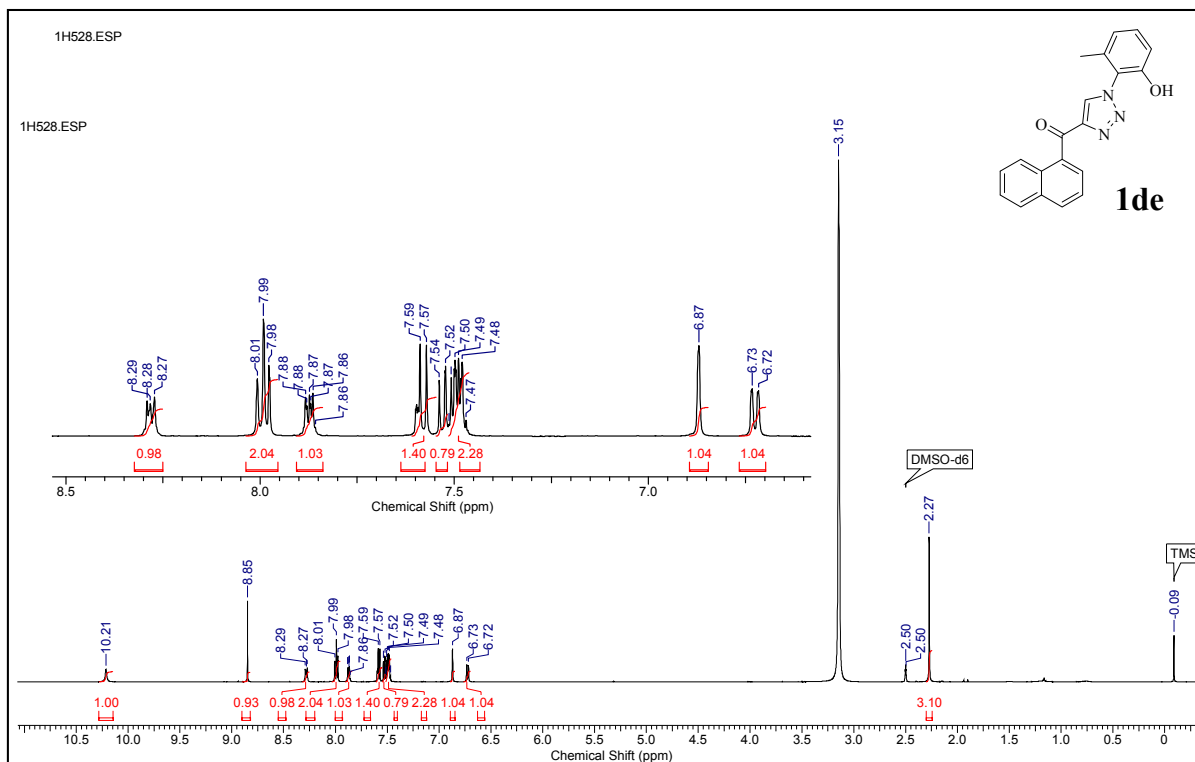
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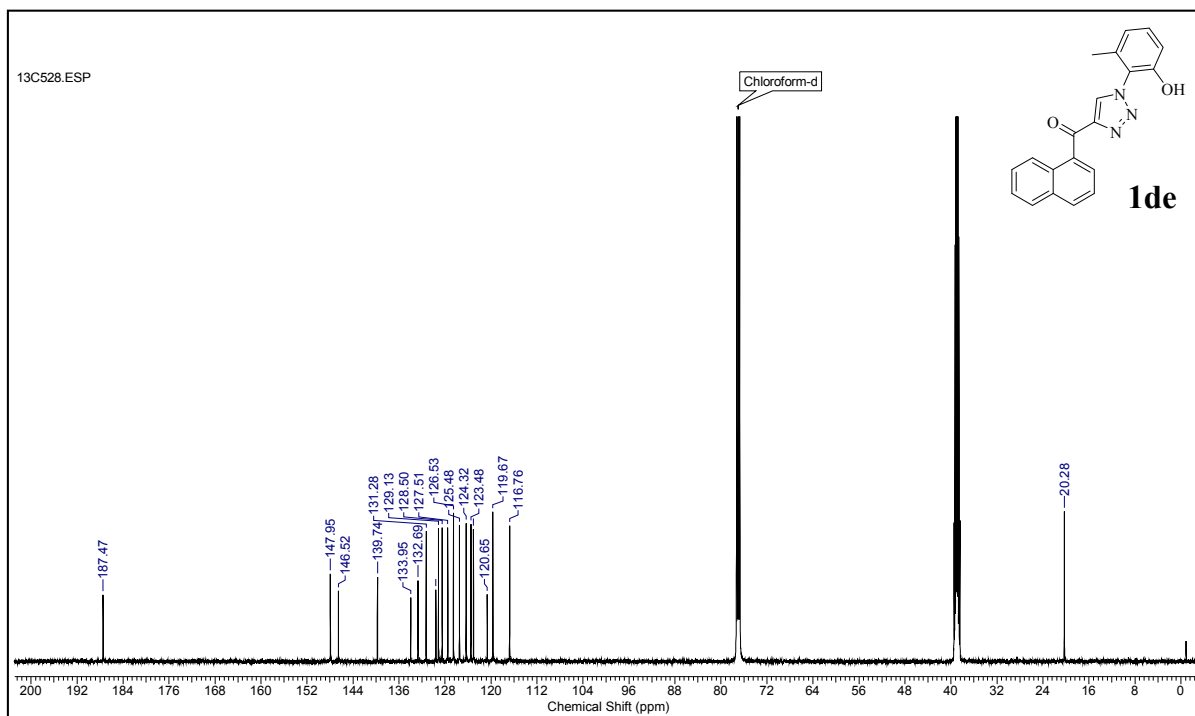
^1H NMR Spectrum of **1db** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4) + \text{DMSO} (\text{D}_6)$ (400 MHz)



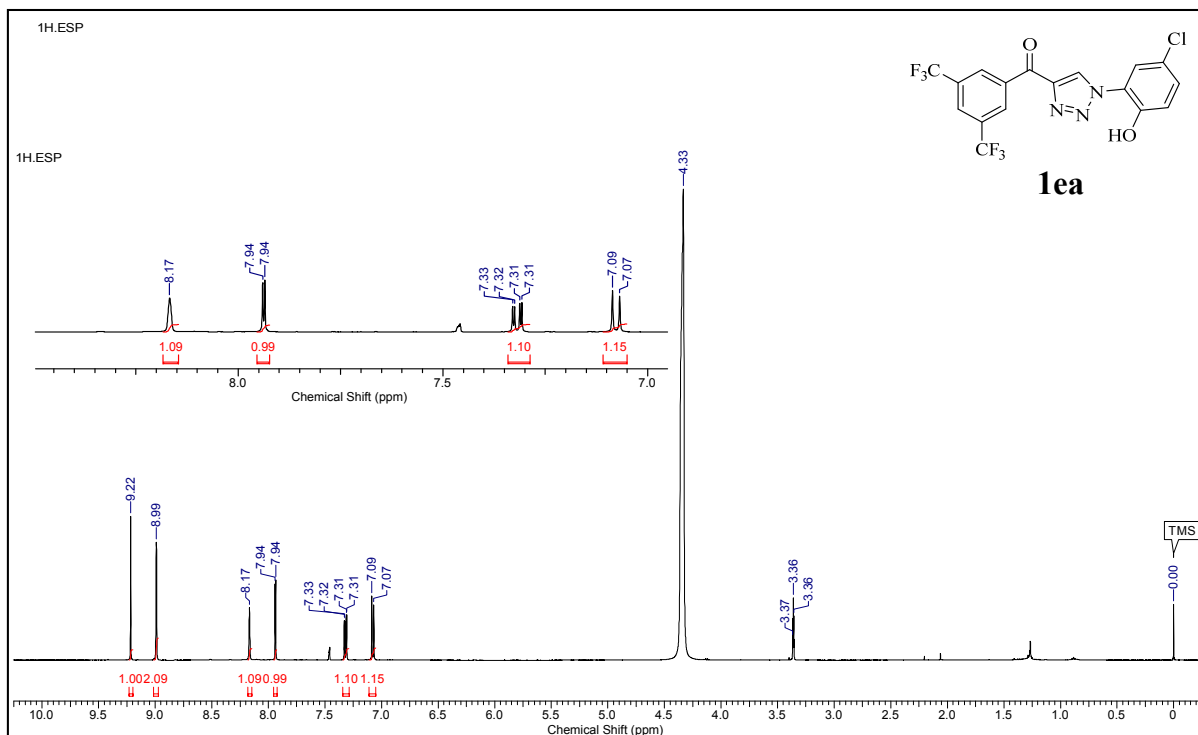
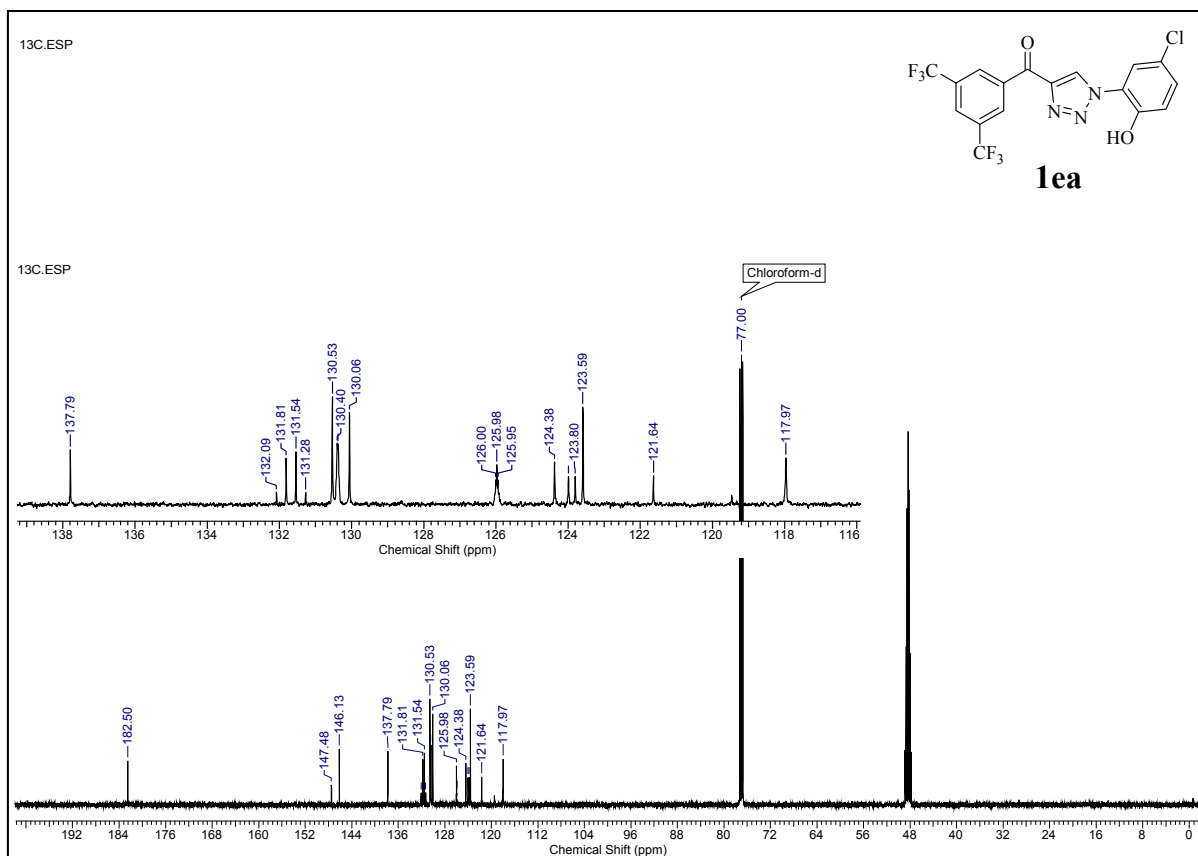
^{13}C NMR Spectrum of **1db** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4) + \text{DMSO} (\text{D}_6)$ (100 MHz)



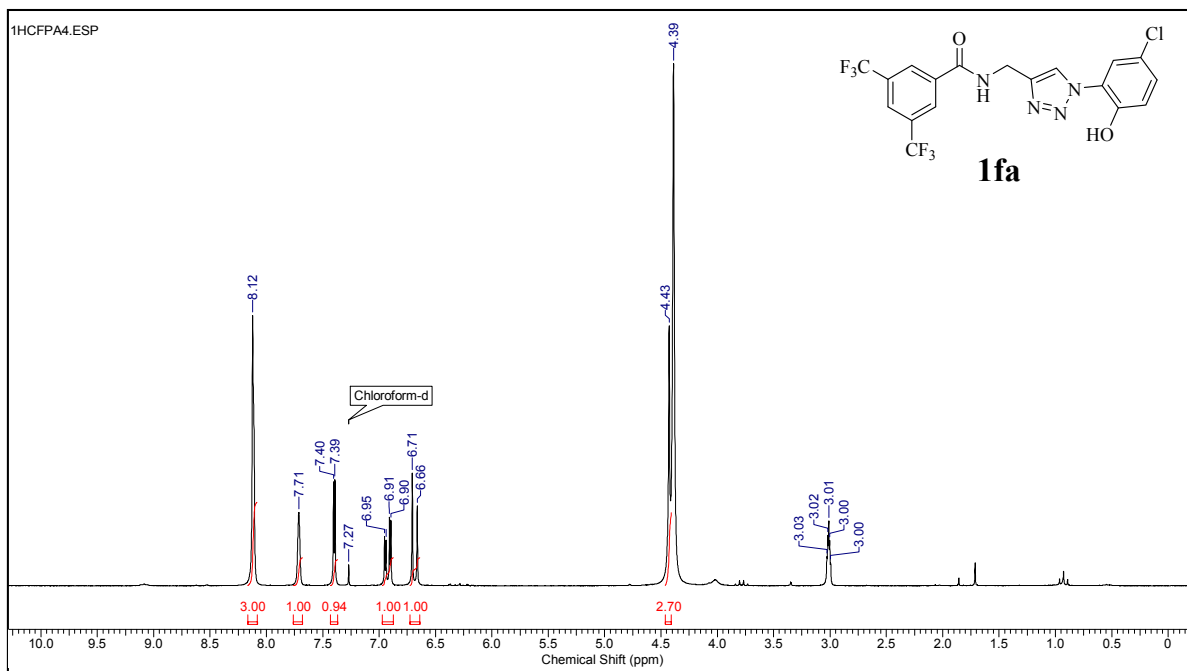
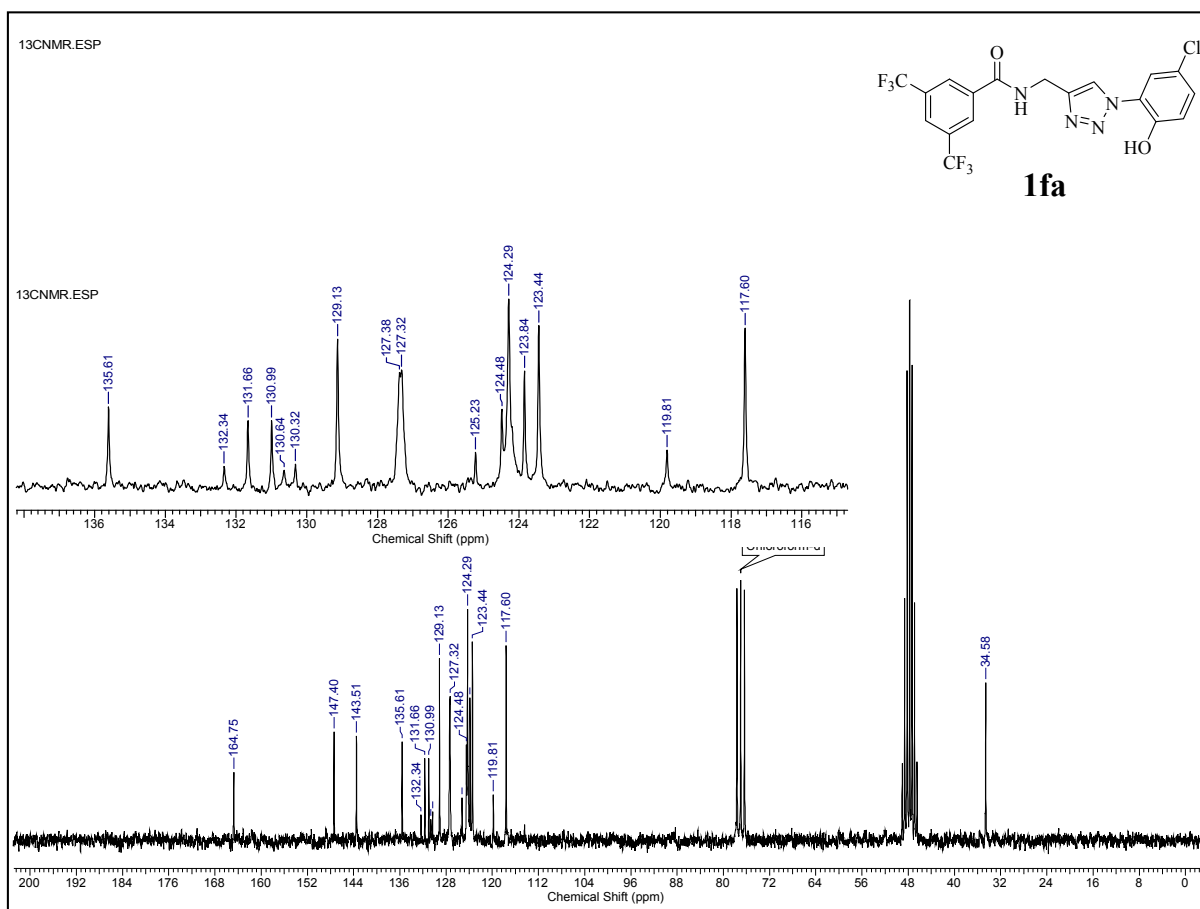
^1H NMR Spectrum of **1de** in DMSO (D_6) (500 MHz)

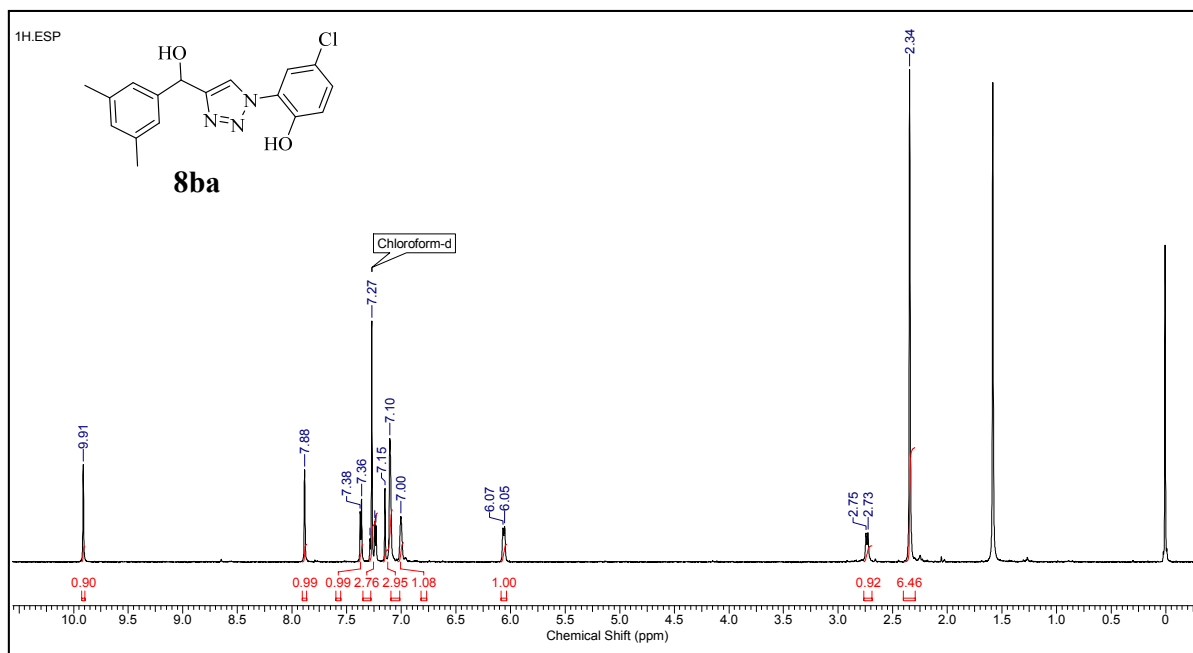


^{13}C NMR Spectrum of **1de** in DMSO (D_6) (125 MHz)

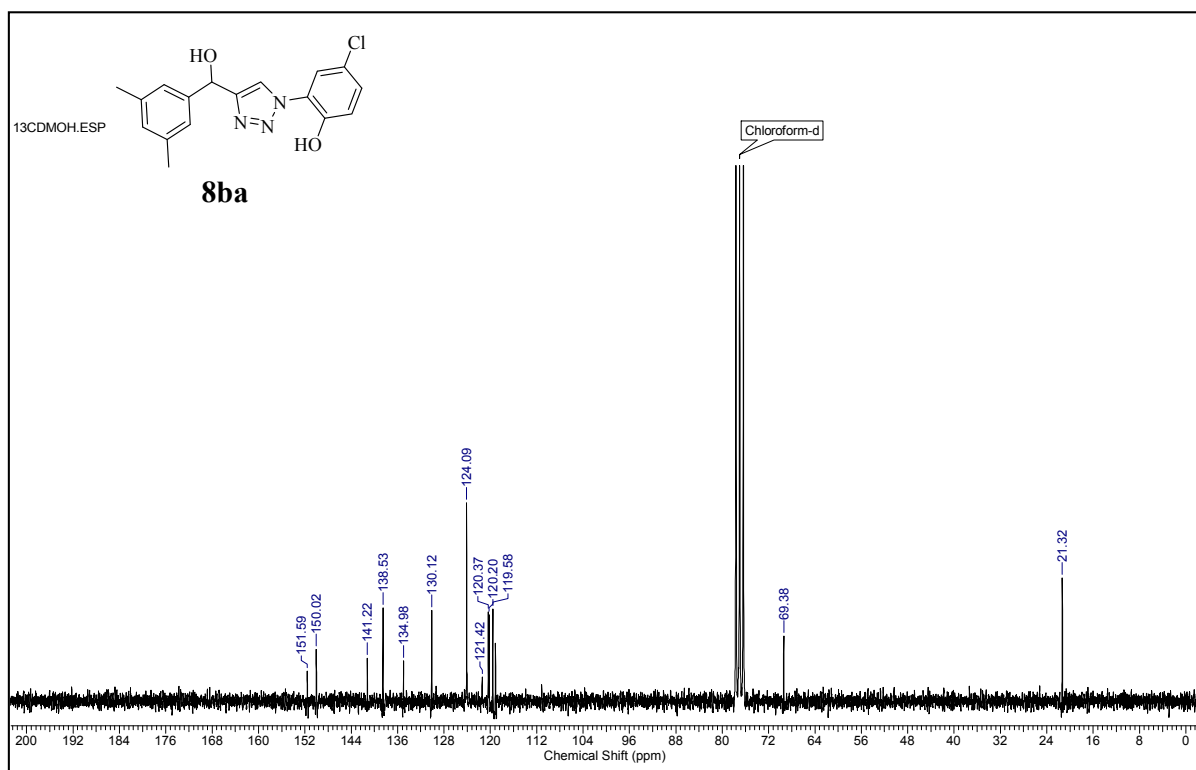
¹H NMR Spectrum of **1ea** in CDCl₃ + MeOH (D₄) (500 MHz)

¹³C NMR Spectrum of **1ea in CDCl₃ + MeOH (D₄) (125 MHz)**

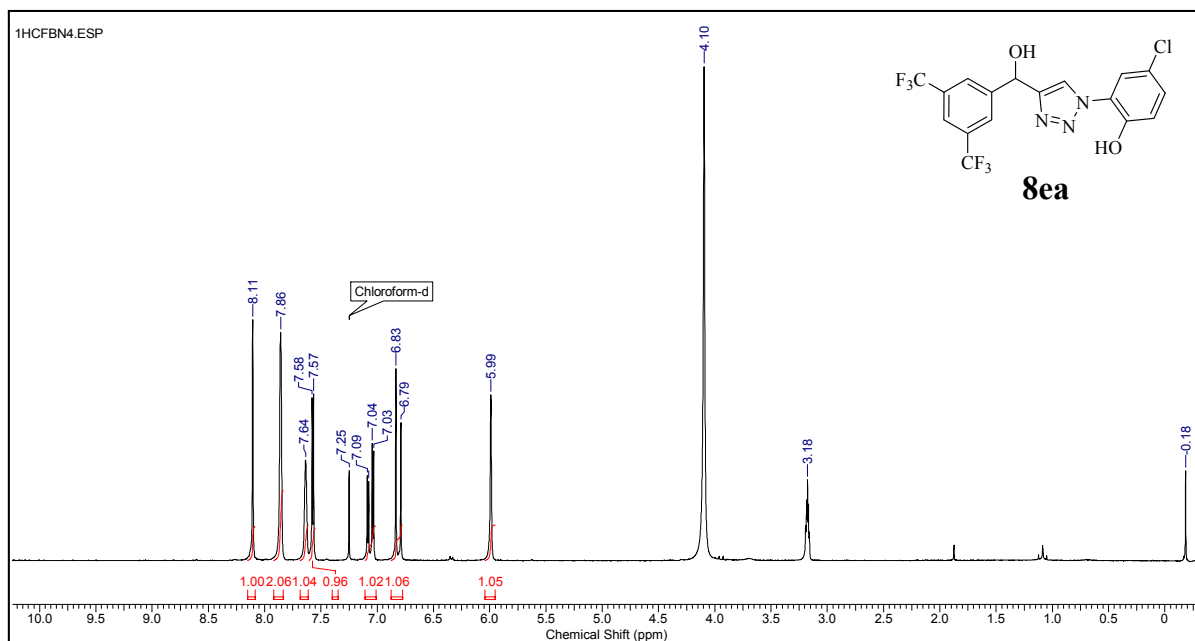
¹H NMR Spectrum of **1fa** in CDCl₃ + MeOH (D₄) (200 MHz) ^{13}C NMR Spectrum of **1fa** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (200 MHz)



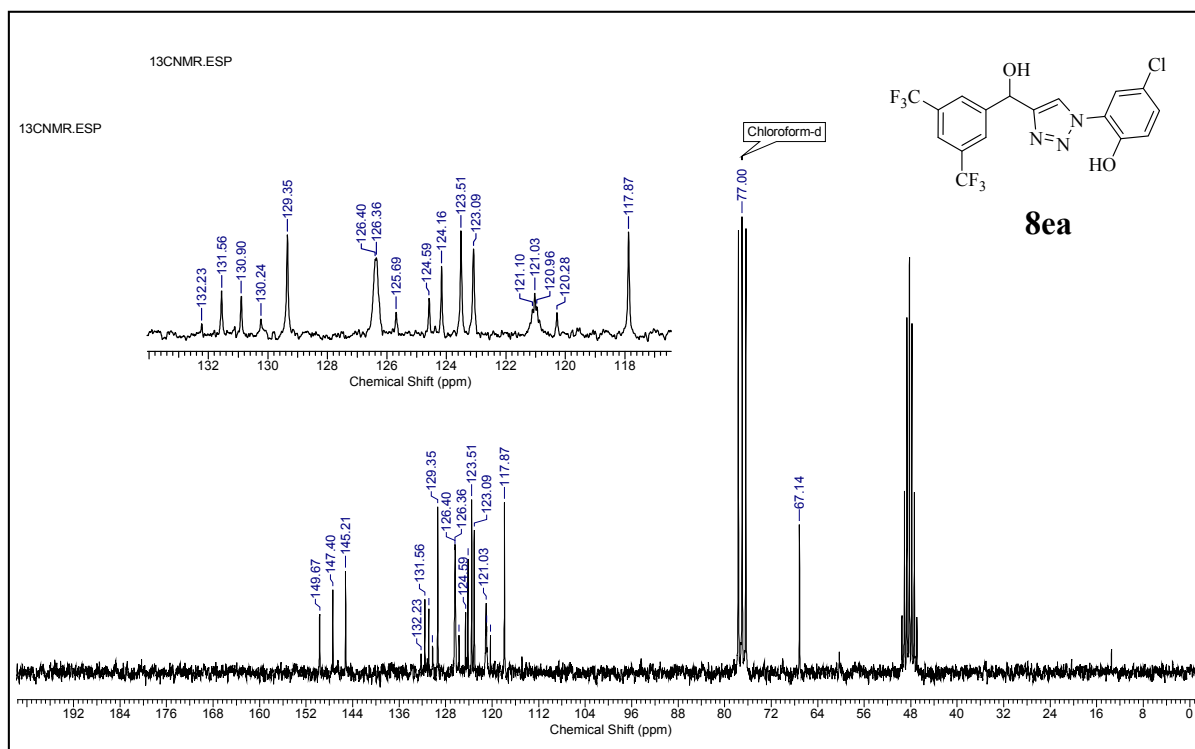
¹H NMR Spectrum of **8ba** in CDCl₃ + MeOH (D₄) (200 MHz)



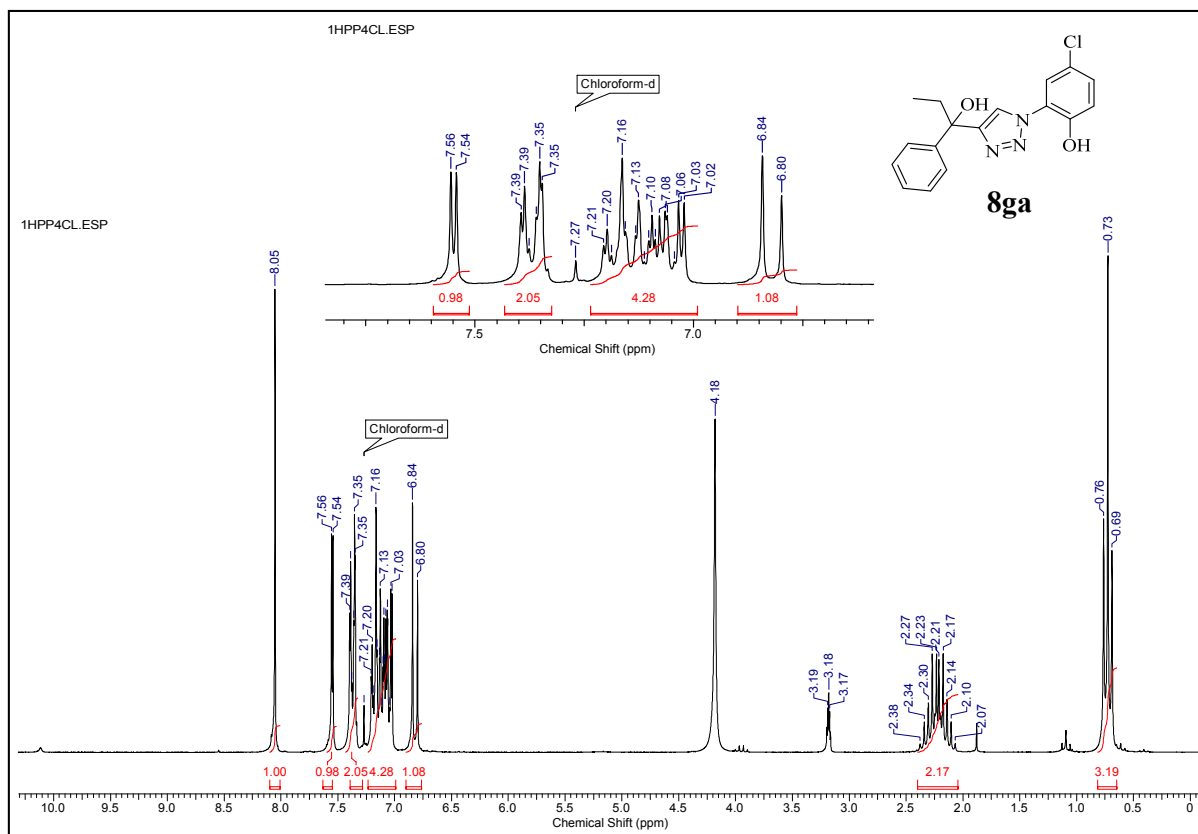
¹³C NMR Spectrum of **8ba** in CDCl₃ + MeOH (D₄) (50 MHz)



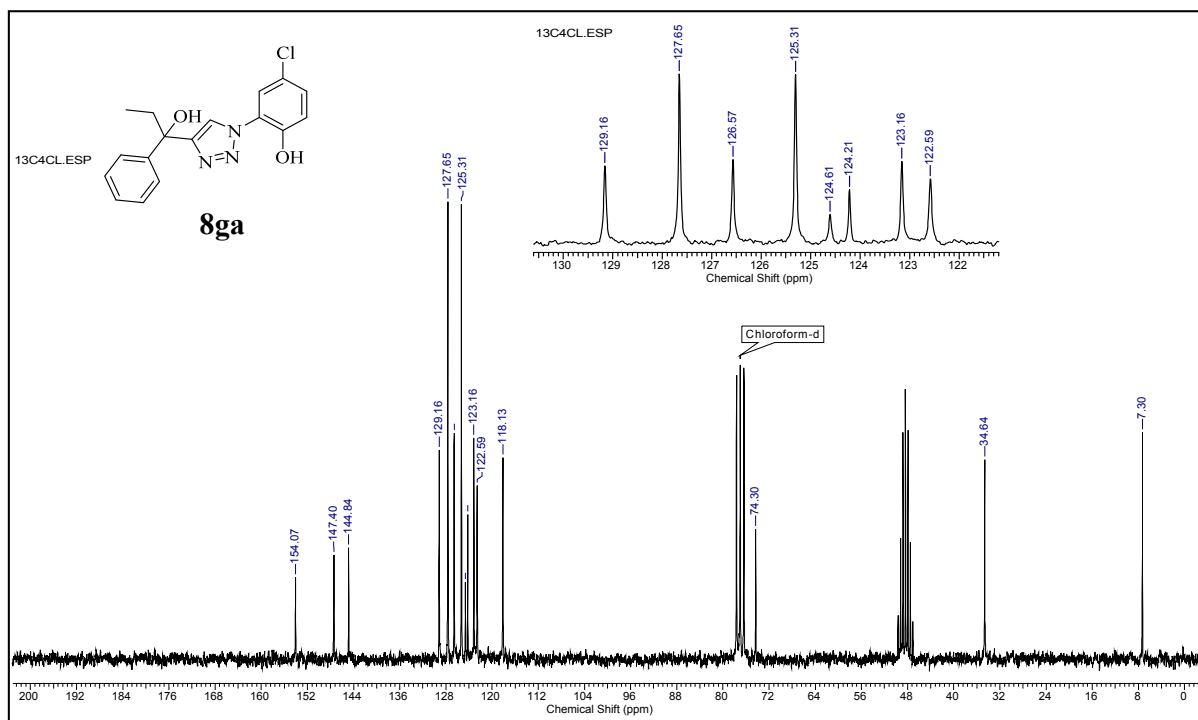
^1H NMR Spectrum of **8ea** in $\text{CDCl}_3 + \text{MeOH (D}_4\text{)}$ (200 MHz)



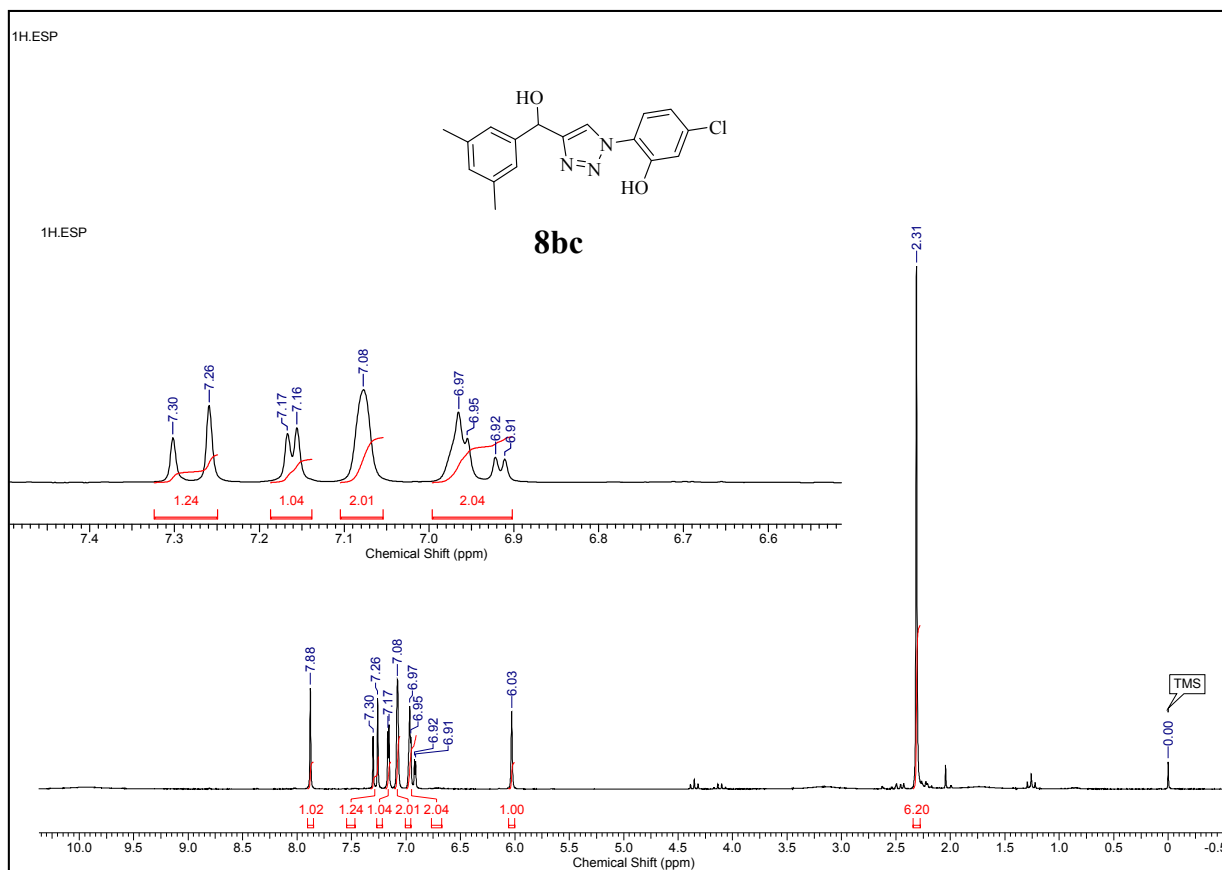
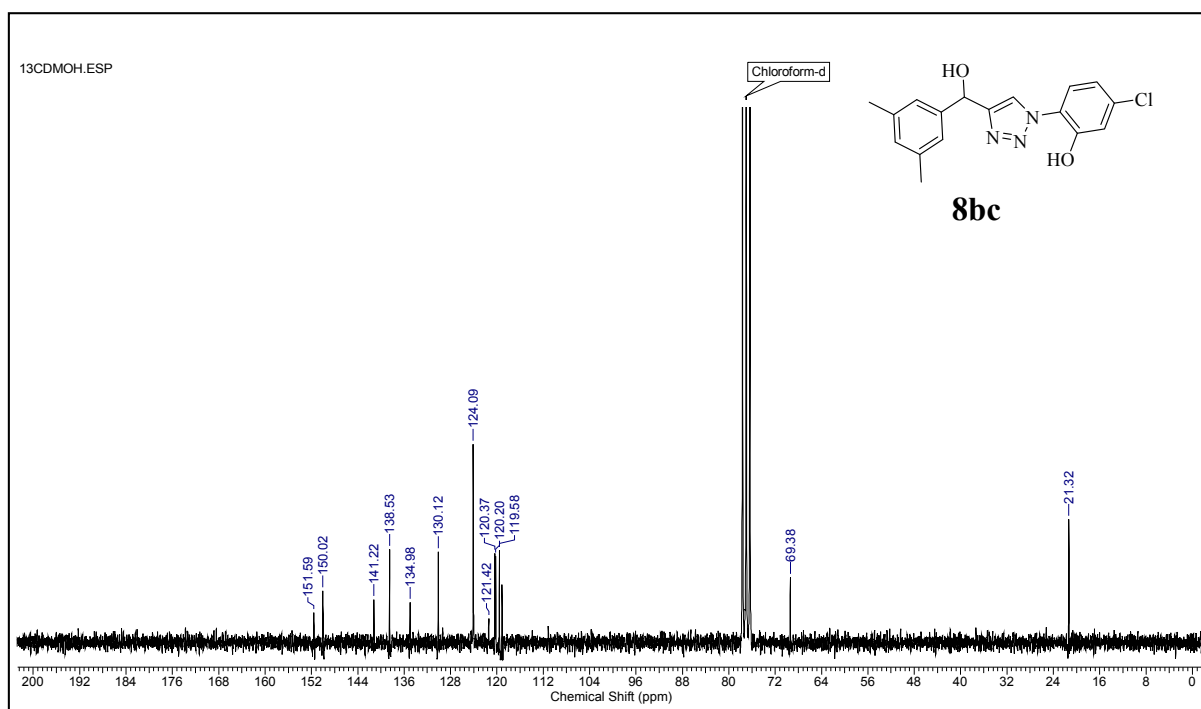
^{13}C NMR Spectrum of **8ea** in $\text{CDCl}_3 + \text{MeOH (D}_4\text{)}$ (50 MHz)



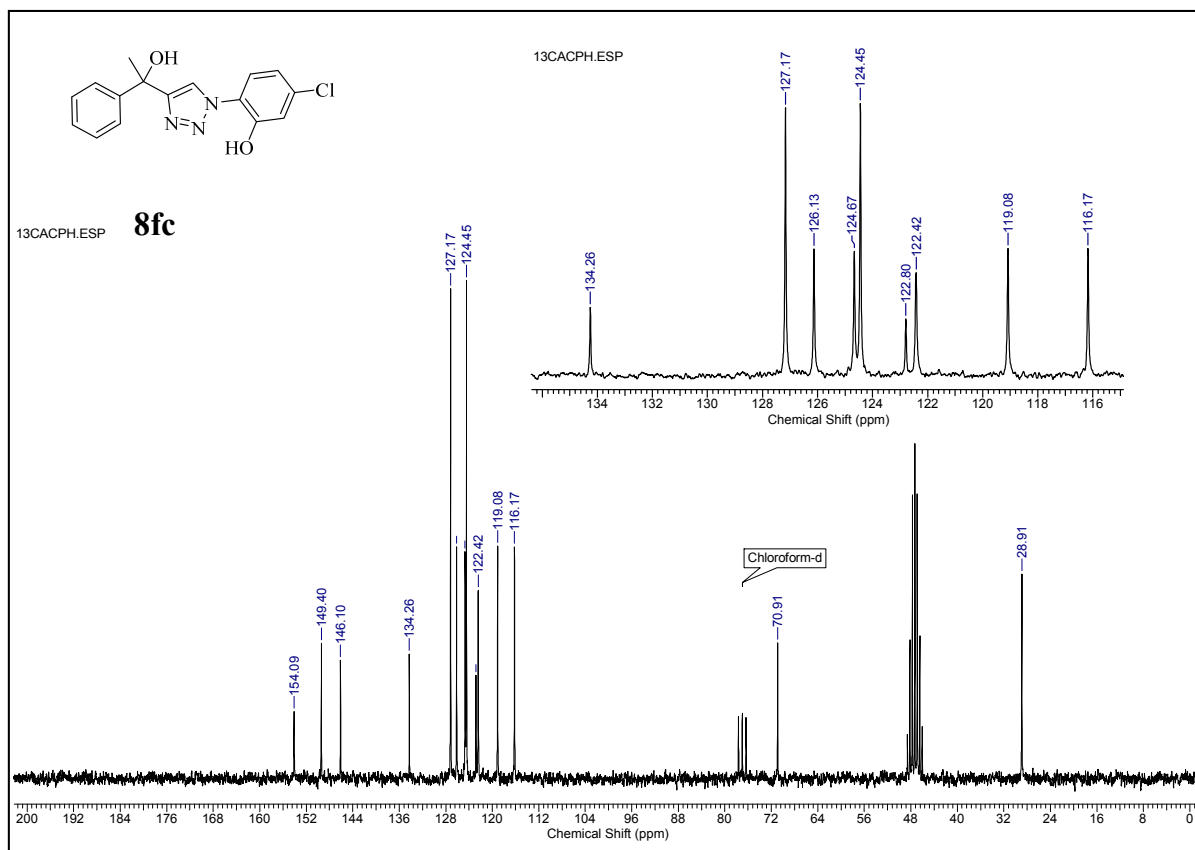
¹H NMR Spectrum of **8ga** in CDCl₃ + MeOH (D₄) (200 MHz)



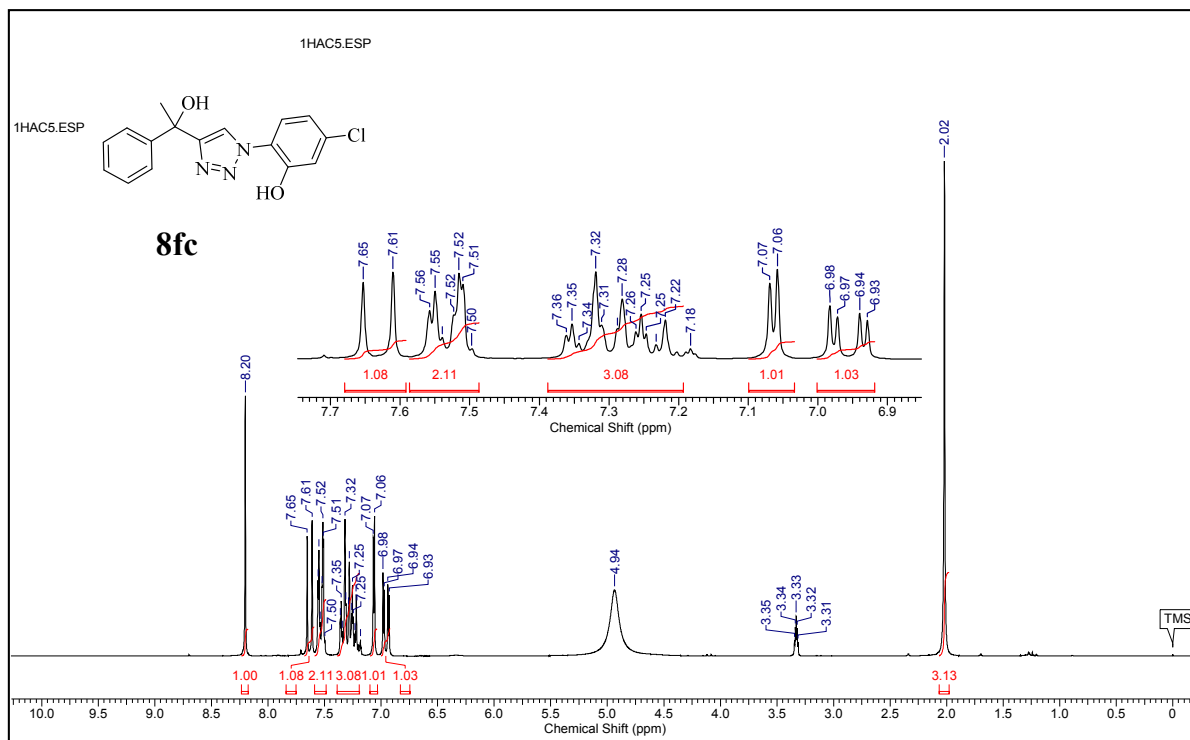
¹³C NMR Spectrum of **8ga** in CDCl₃ + MeOH (D₄) (50 MHz)

¹H NMR Spectrum of **8bc** in CDCl₃ + MeOH (D₄) (200 MHz)

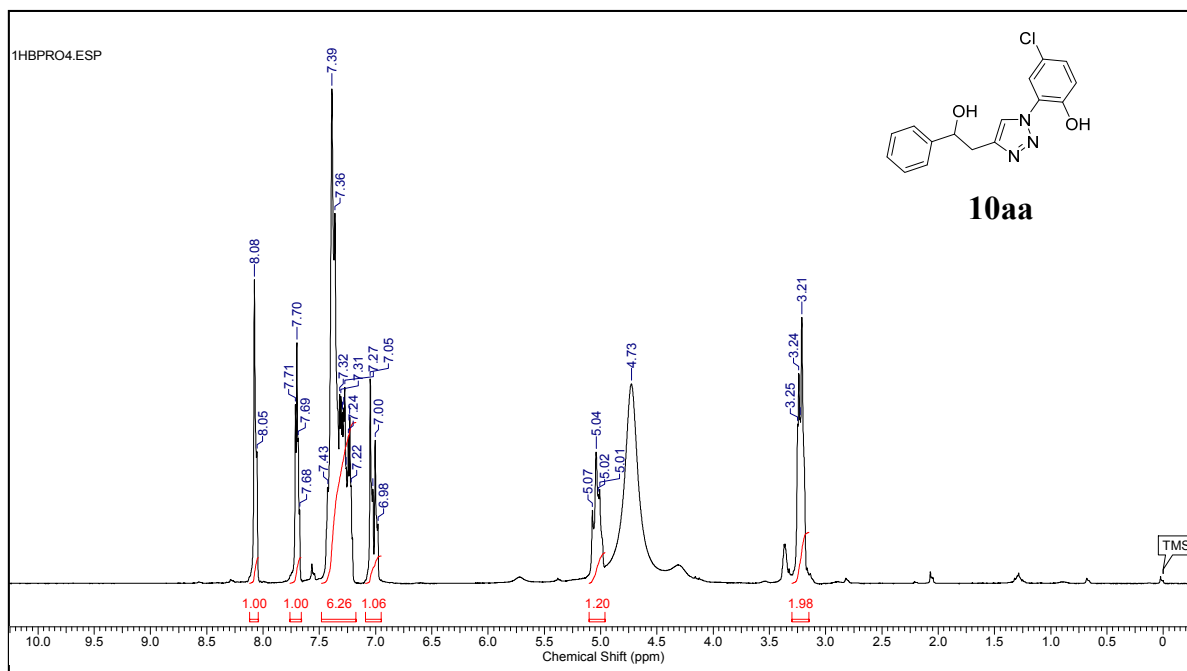
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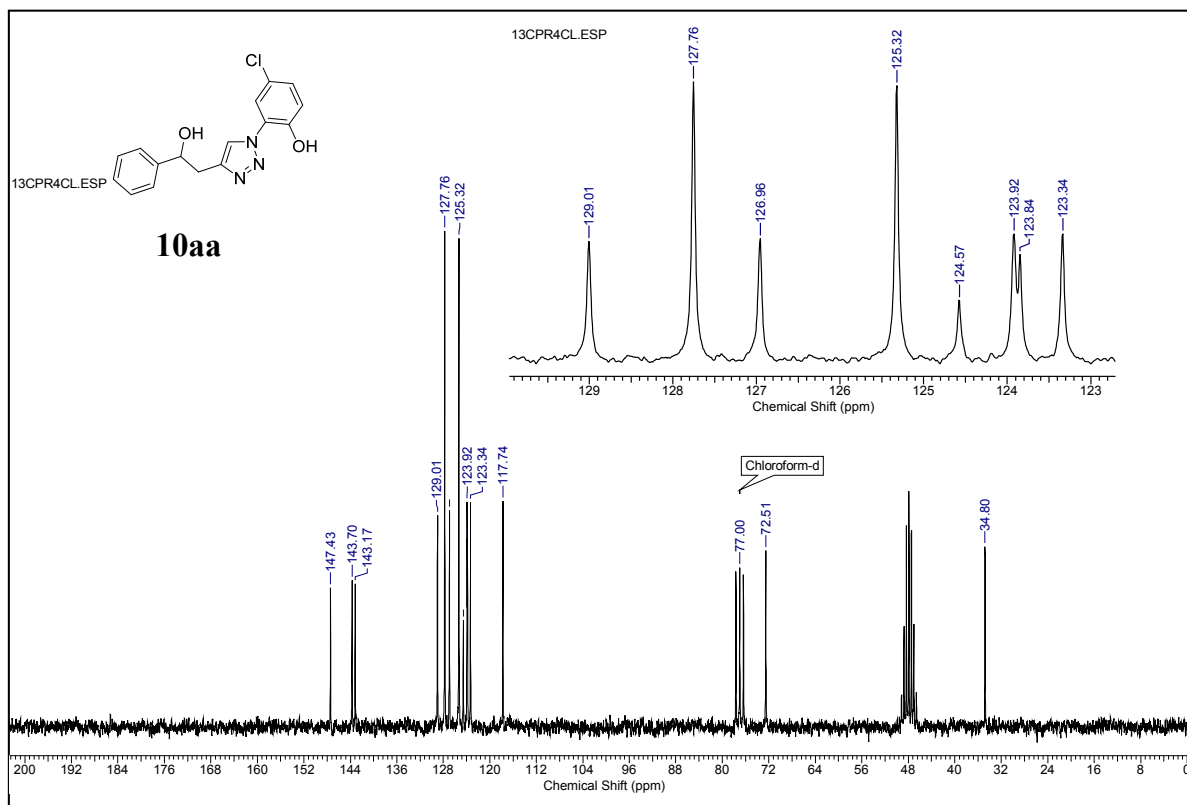
¹H NMR Spectrum of **8fc** in CDCl₃ + MeOH (D₄) (200 MHz)



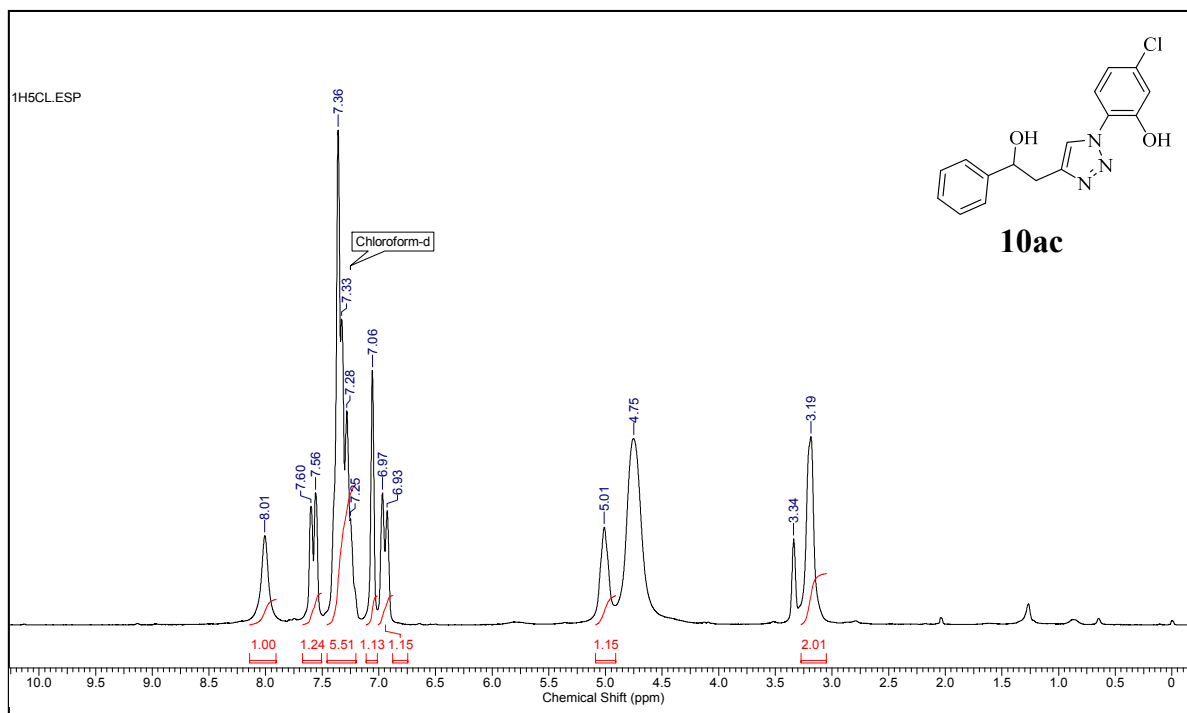
¹³C NMR Spectrum of **8fc** in CDCl₃ + MeOH (D₄) (50 MHz)



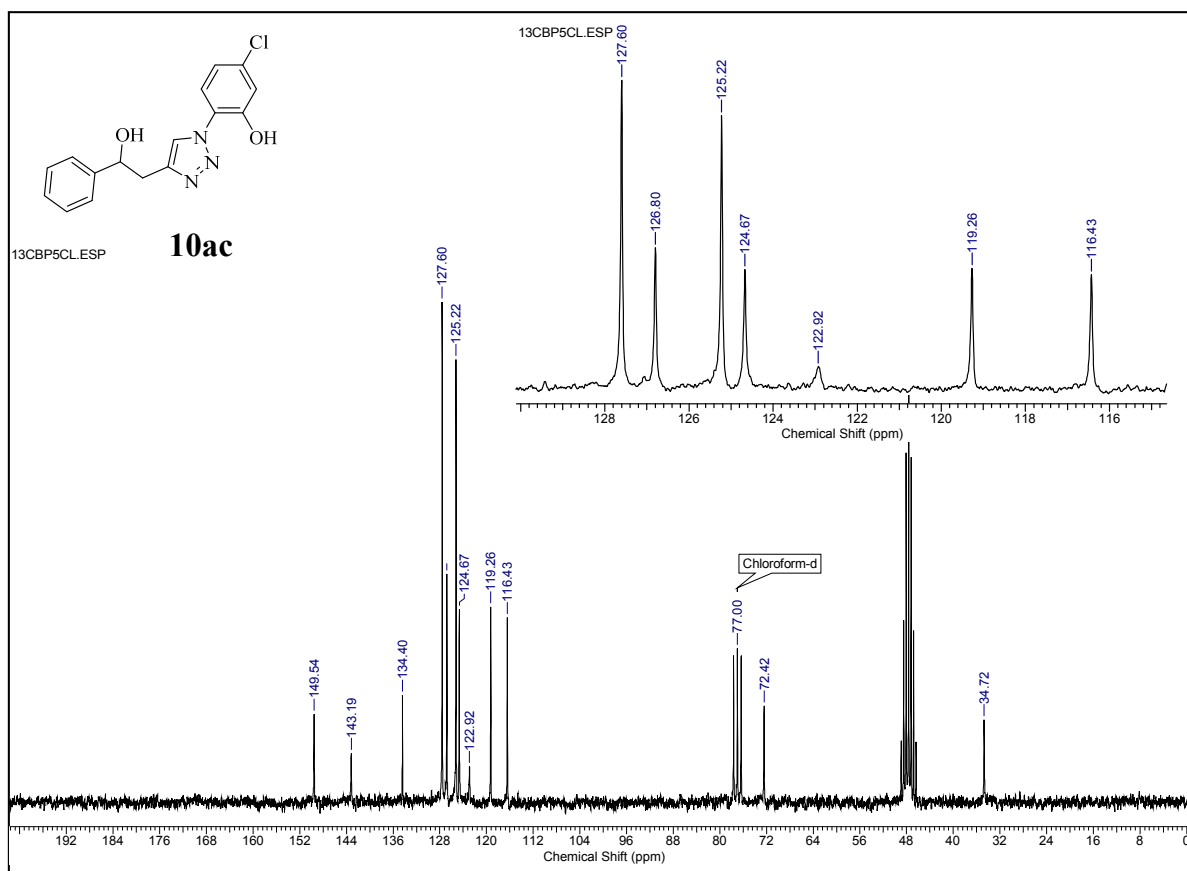
^1H NMR Spectrum of **10aa** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (200 MHz)



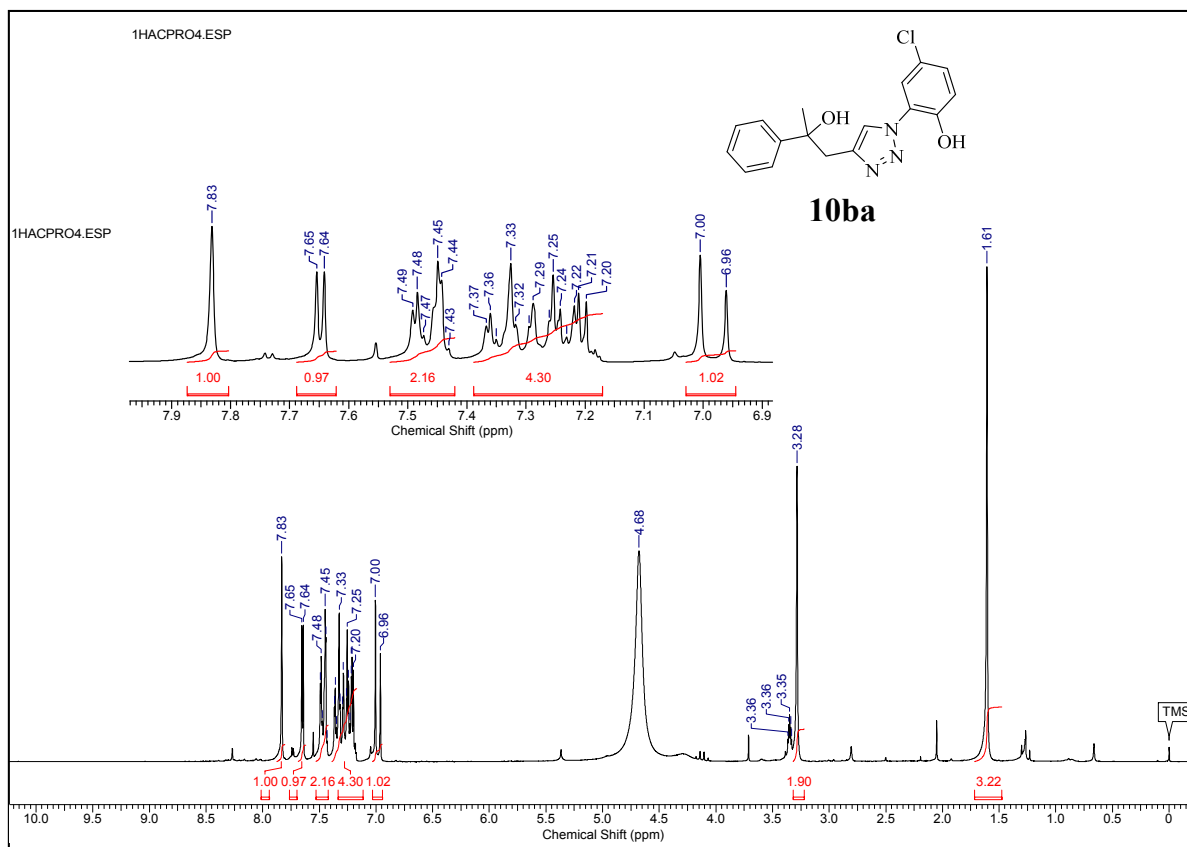
^{13}C NMR Spectrum of **10aa** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (50 MHz)



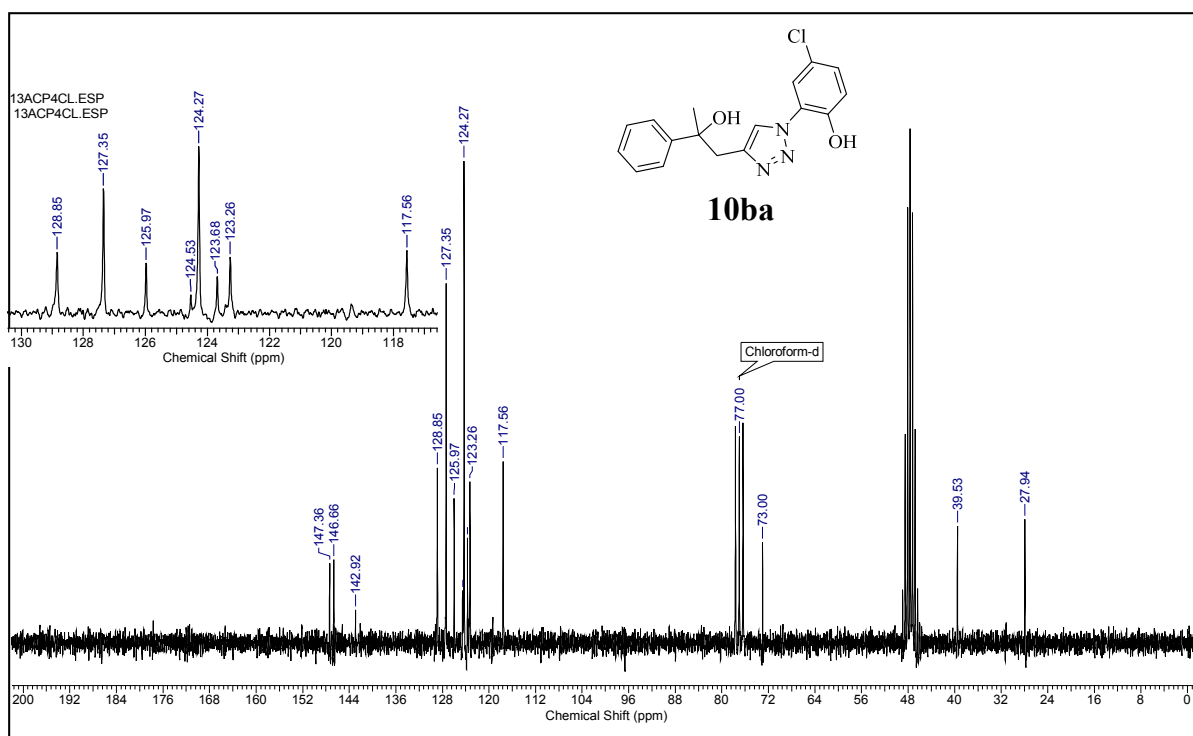
¹H NMR Spectrum of **10ac** in CDCl₃ + MeOH (D₄) (200 MHz)



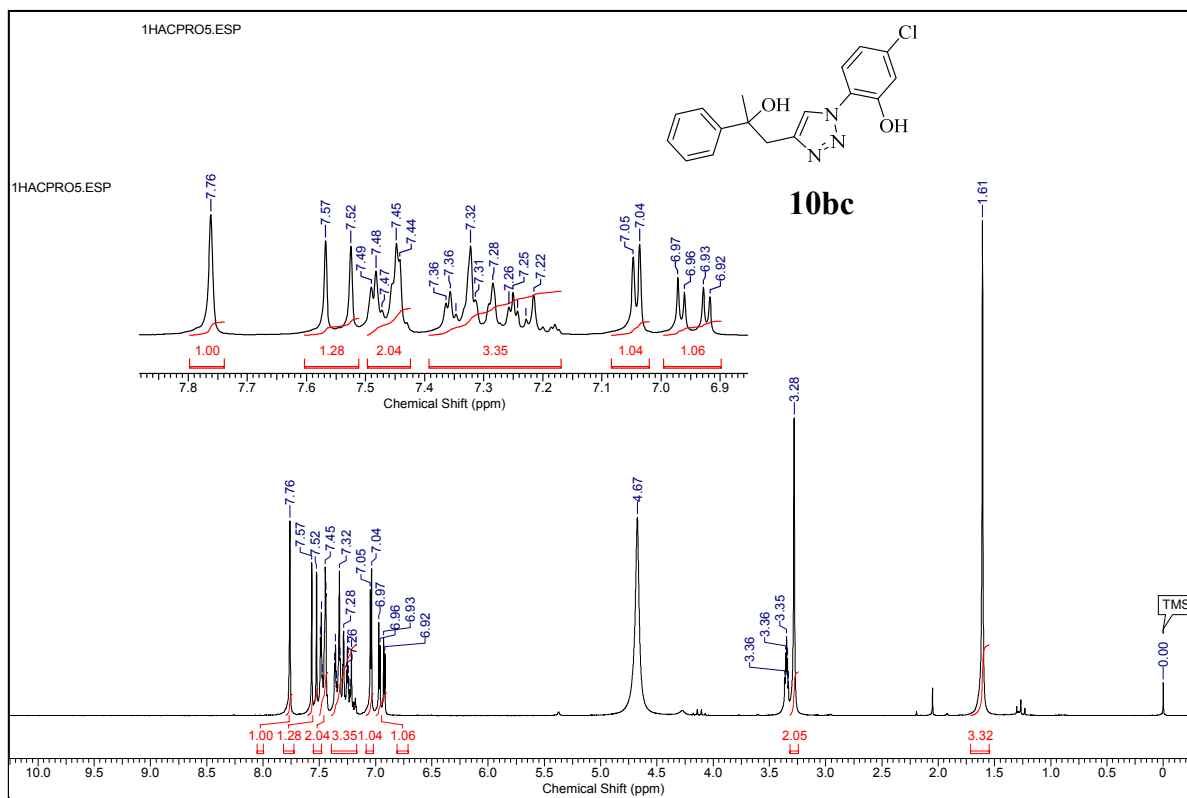
¹³C NMR Spectrum of **10ac** in CDCl₃ + MeOH (D₄) (50 MHz)



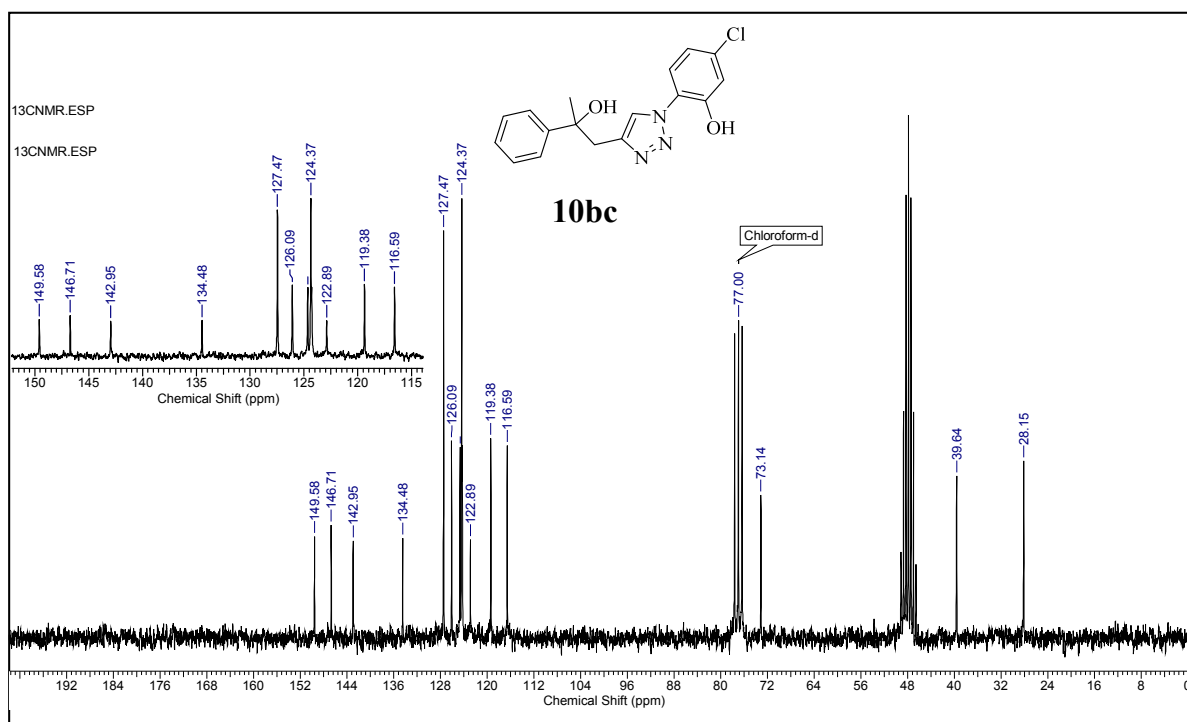
¹H NMR Spectrum of **10ba** in CDCl₃ + MeOH (D₄) (200 MHz)



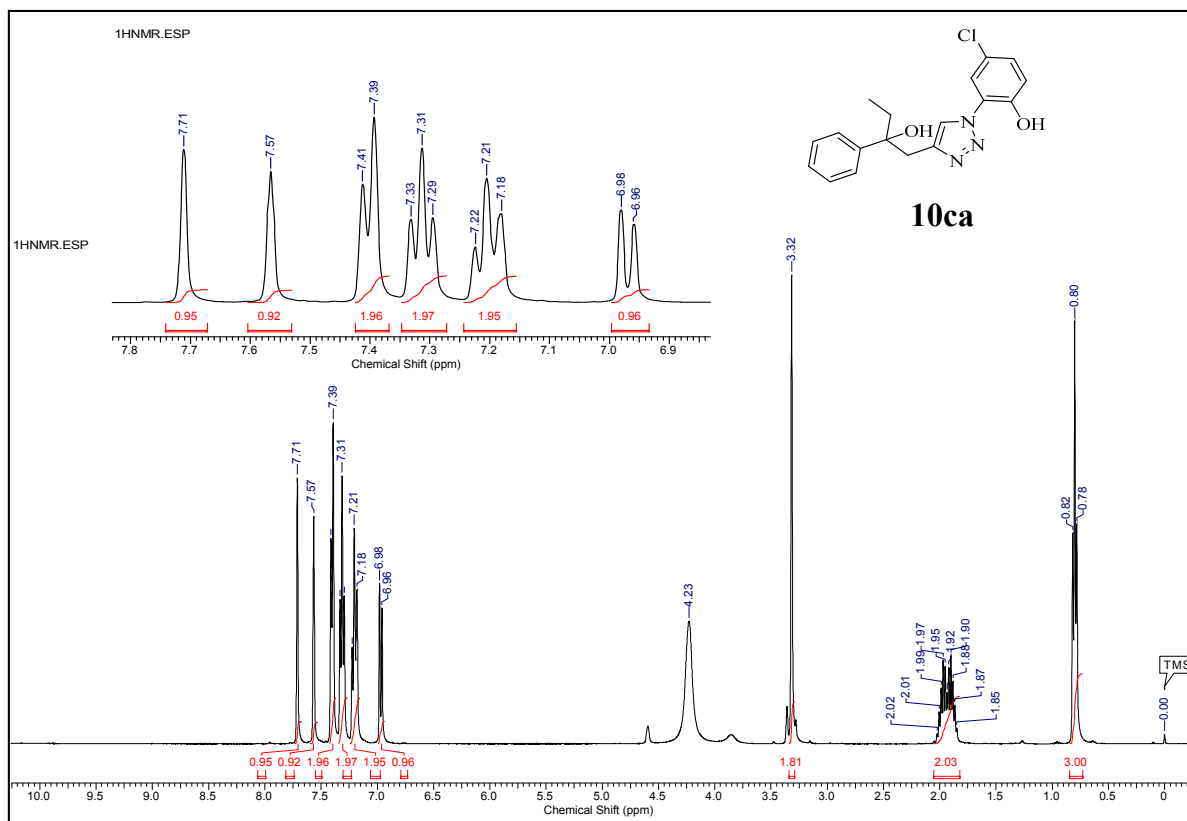
¹³C NMR Spectrum of **10ba** in CDCl₃ + MeOH (D₄) (50 MHz)



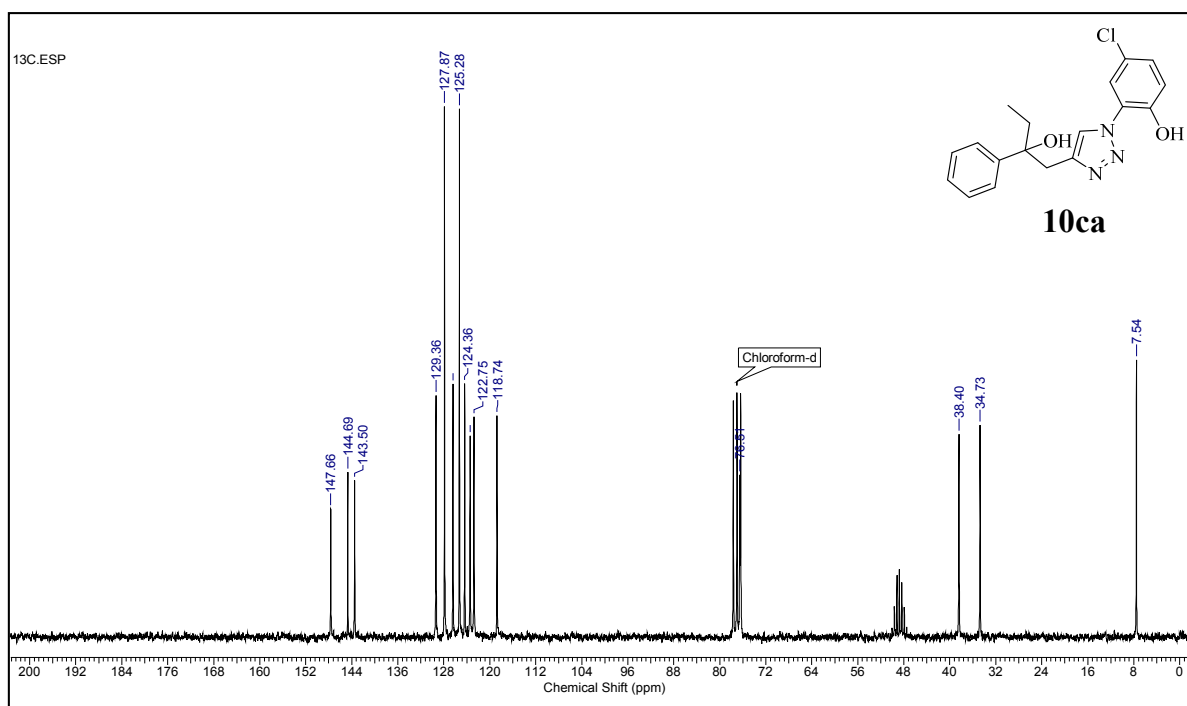
^1H NMR Spectrum of **10bc** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (200 MHz)



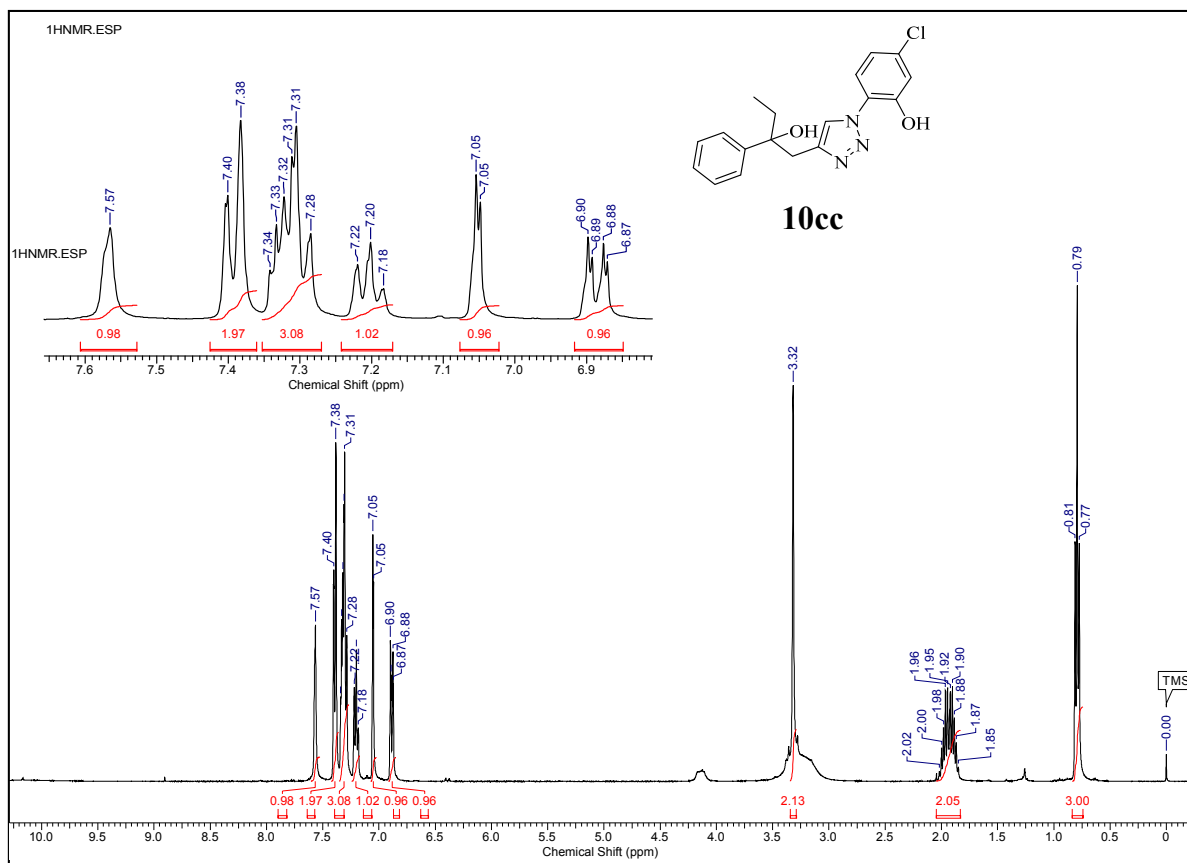
^{13}C NMR Spectrum of **10bc** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (50 MHz)



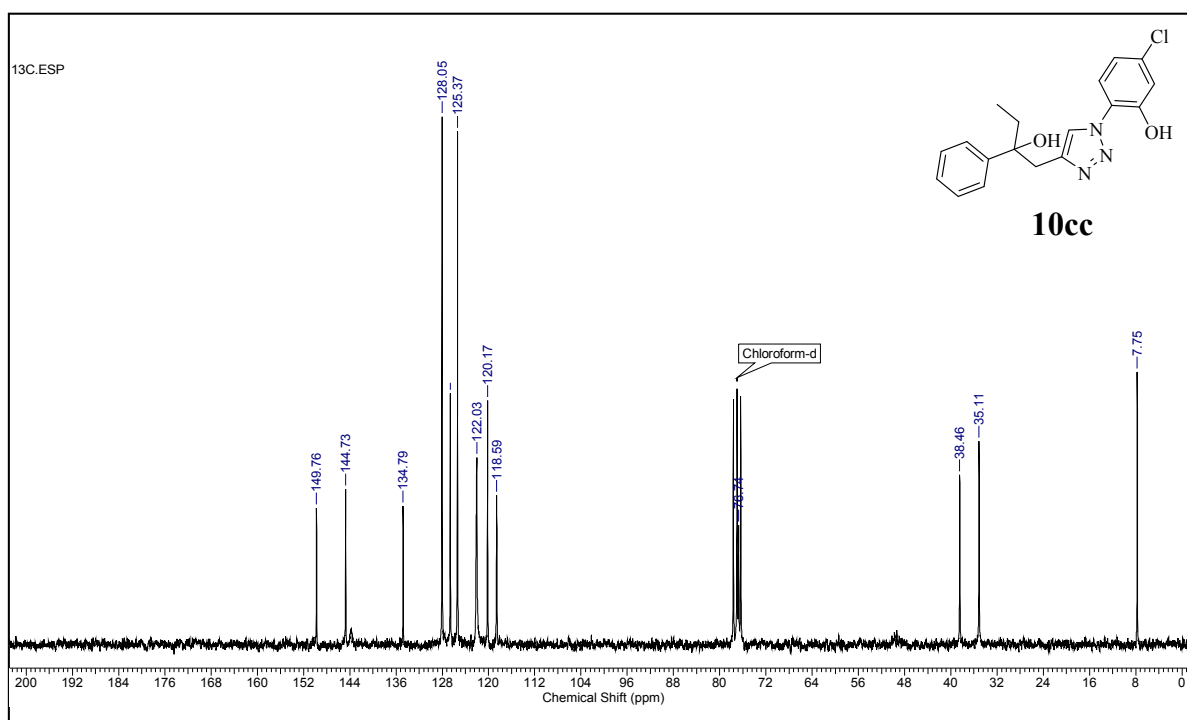
¹H NMR Spectrum of **10ca** in CDCl₃ + MeOH (D₄) (400 MHz)



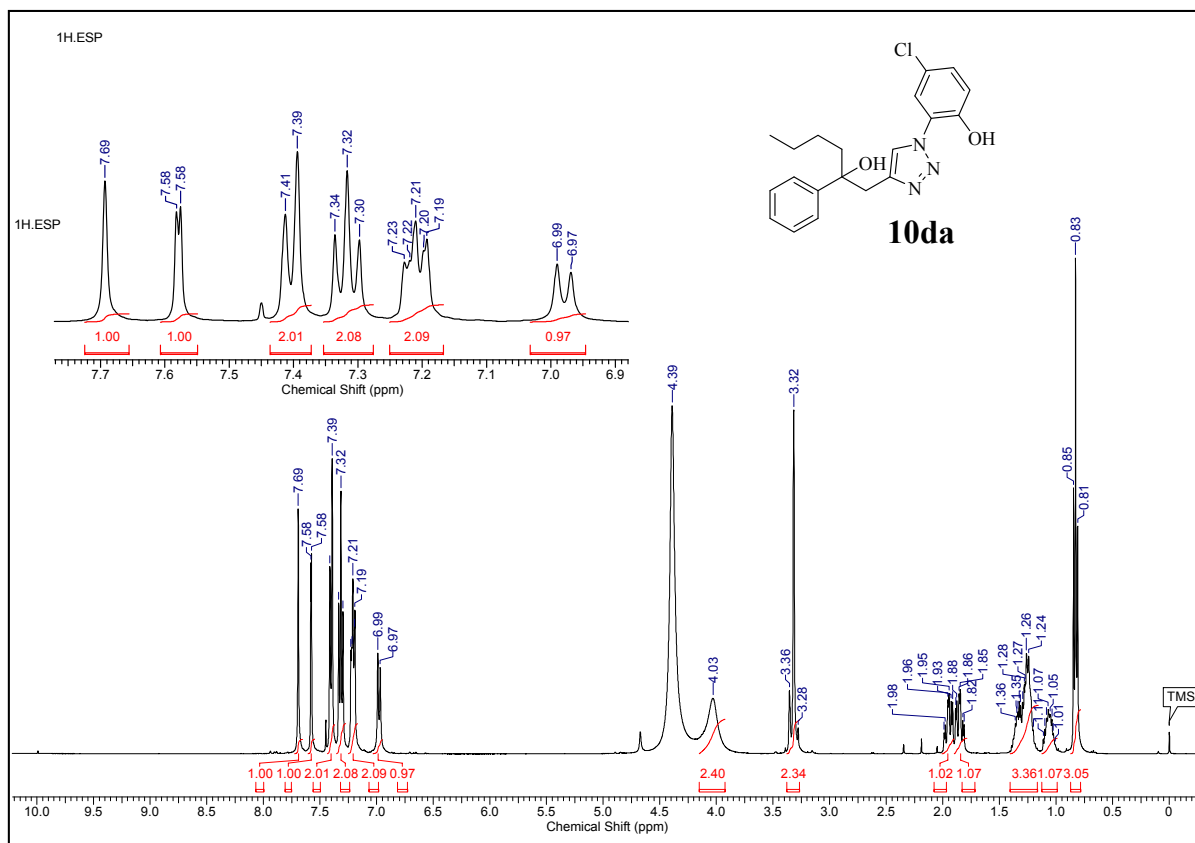
¹³C NMR Spectrum of **10ca** in CDCl₃ + MeOH (D₄) (50 MHz)



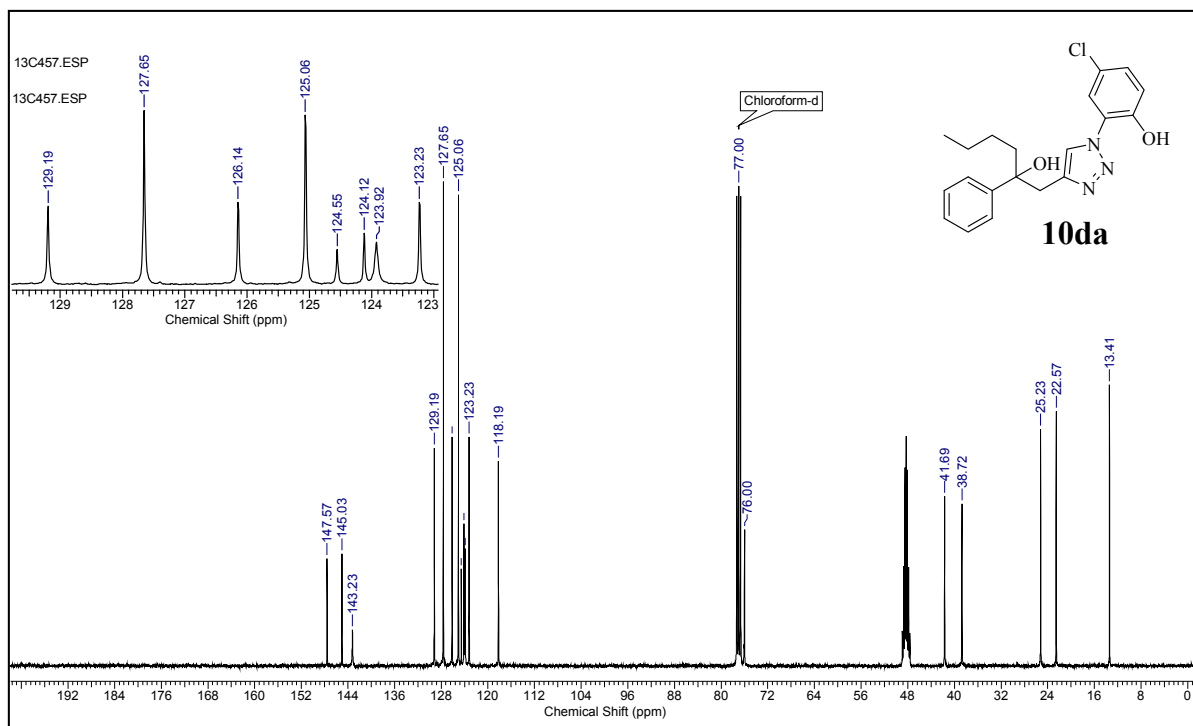
¹H NMR Spectrum of **10cc** in CDCl₃ + MeOH (D₄) (400 MHz)



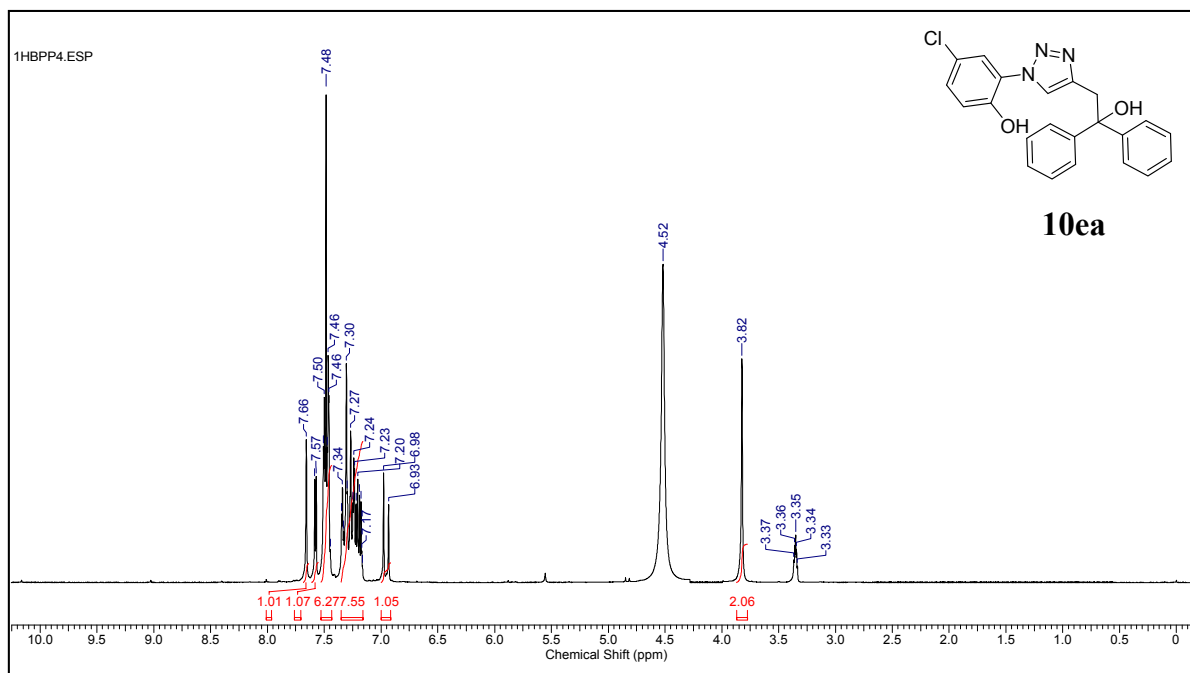
¹³C NMR Spectrum of **10cc** in CDCl₃ + MeOH (D₄) (50 MHz)



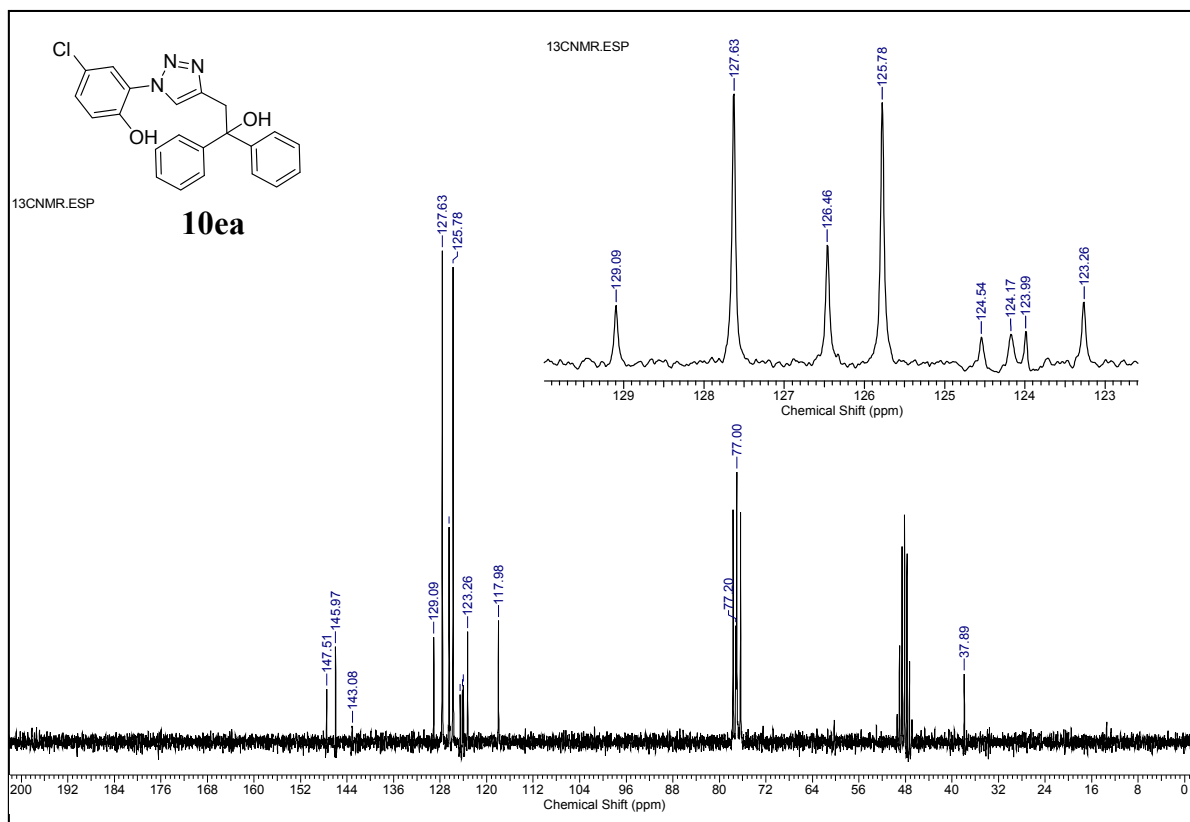
¹H NMR Spectrum of **10da** in CDCl₃ + MeOH (D₄) (400 MHz)



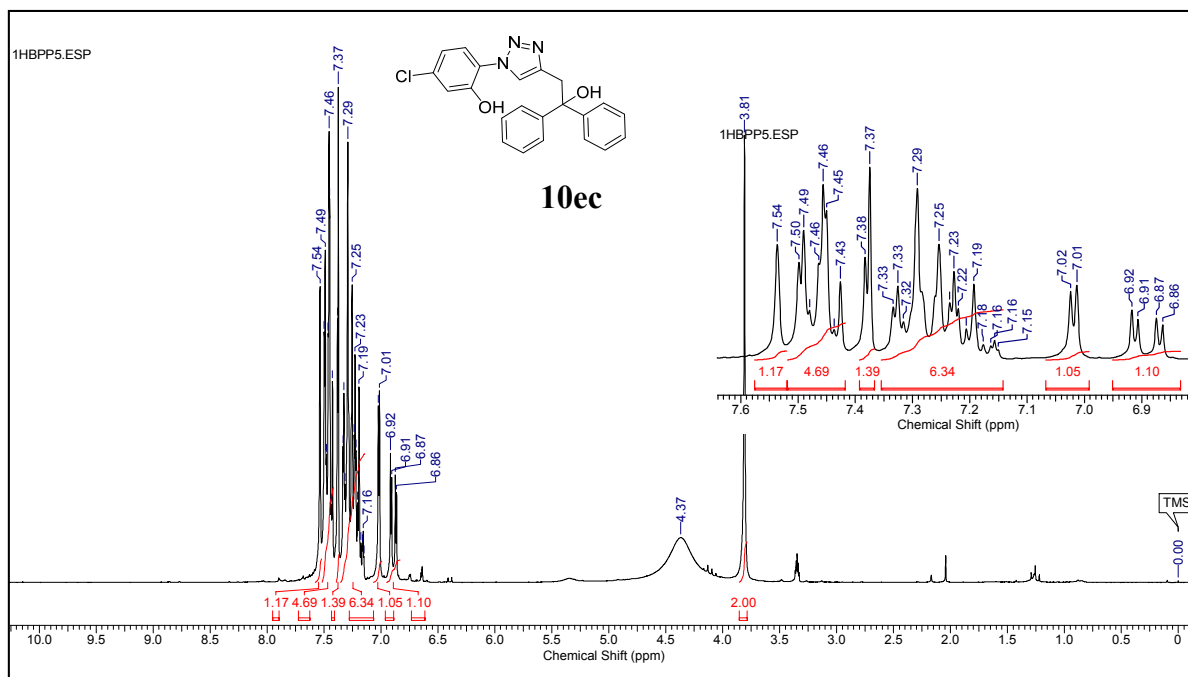
¹³C NMR Spectrum of **10da** in CDCl₃ + MeOH (D₄) (100 MHz)



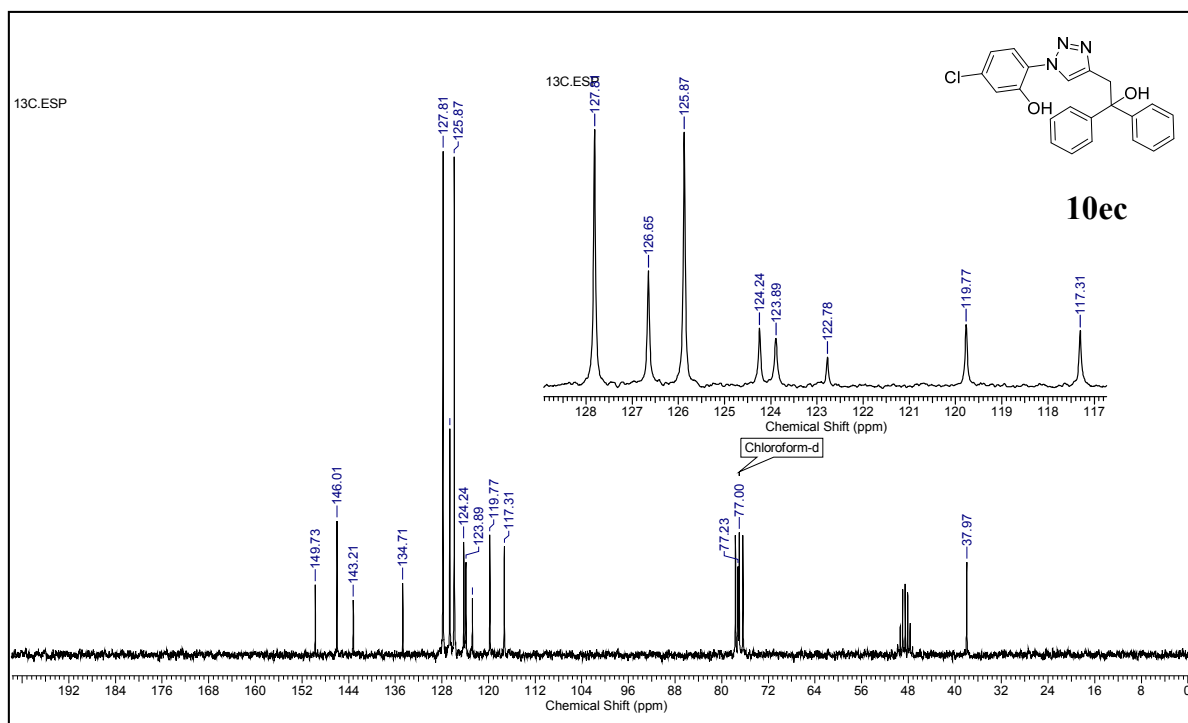
^1H NMR Spectrum of **10ea** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (200 MHz)



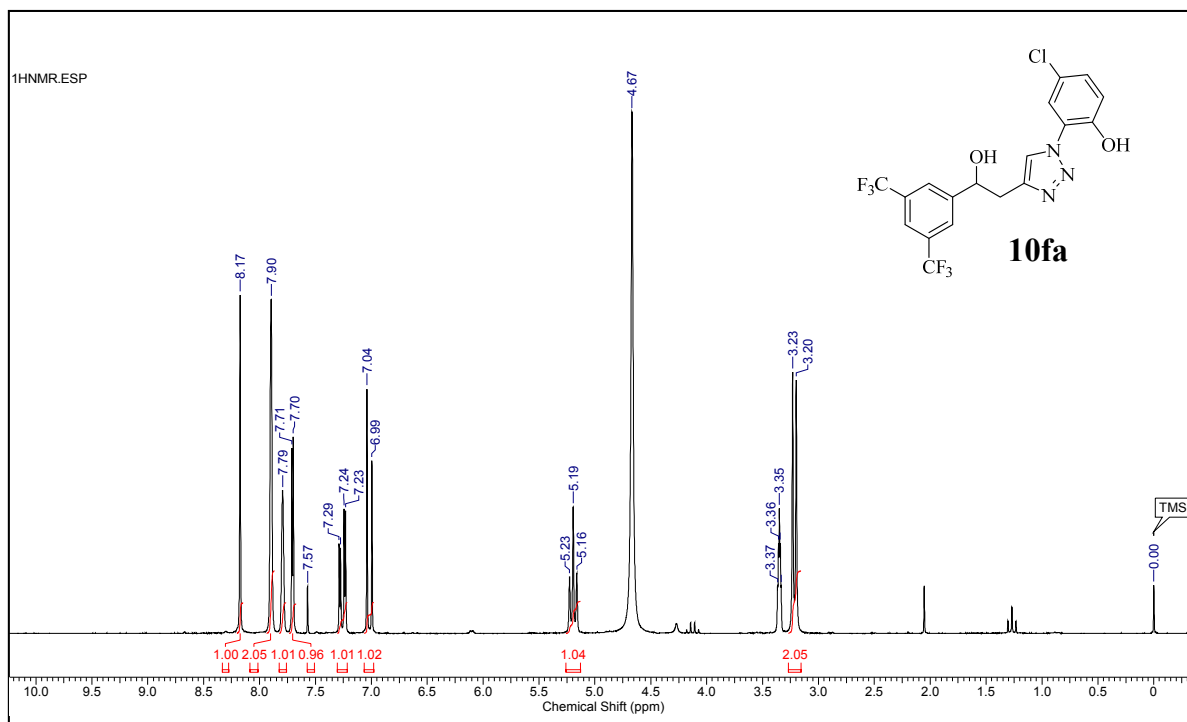
^{13}C NMR Spectrum of **10ea** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (50 MHz)



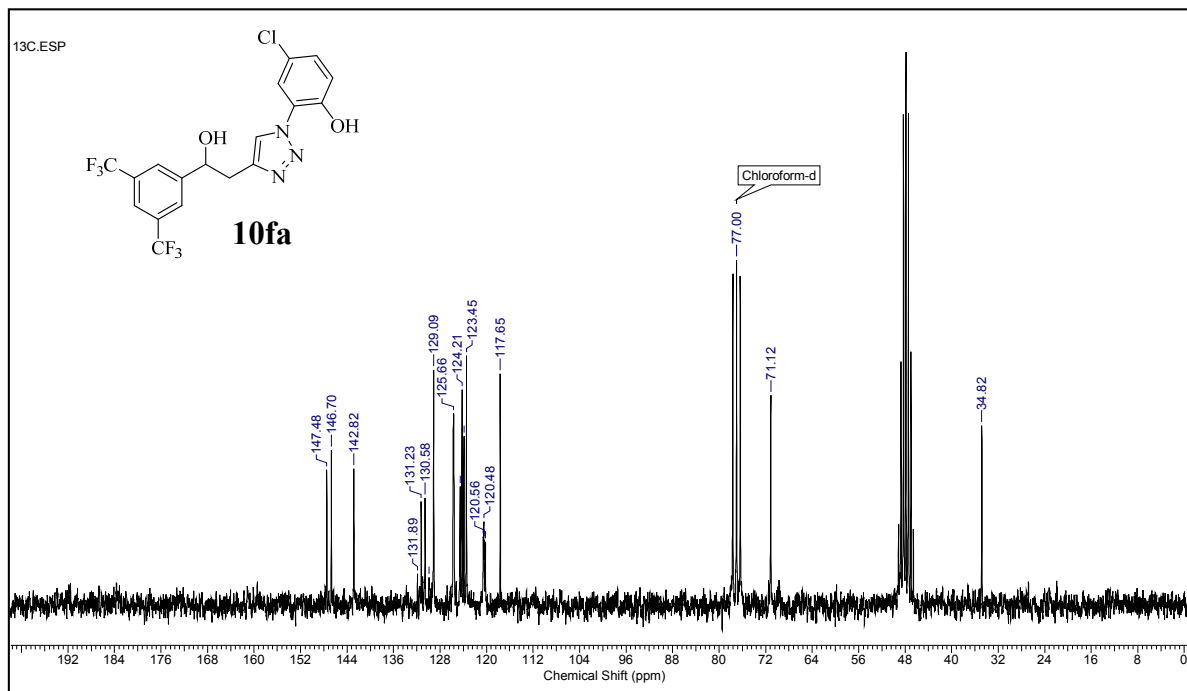
^1H NMR Spectrum of **10ec** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (200 MHz)



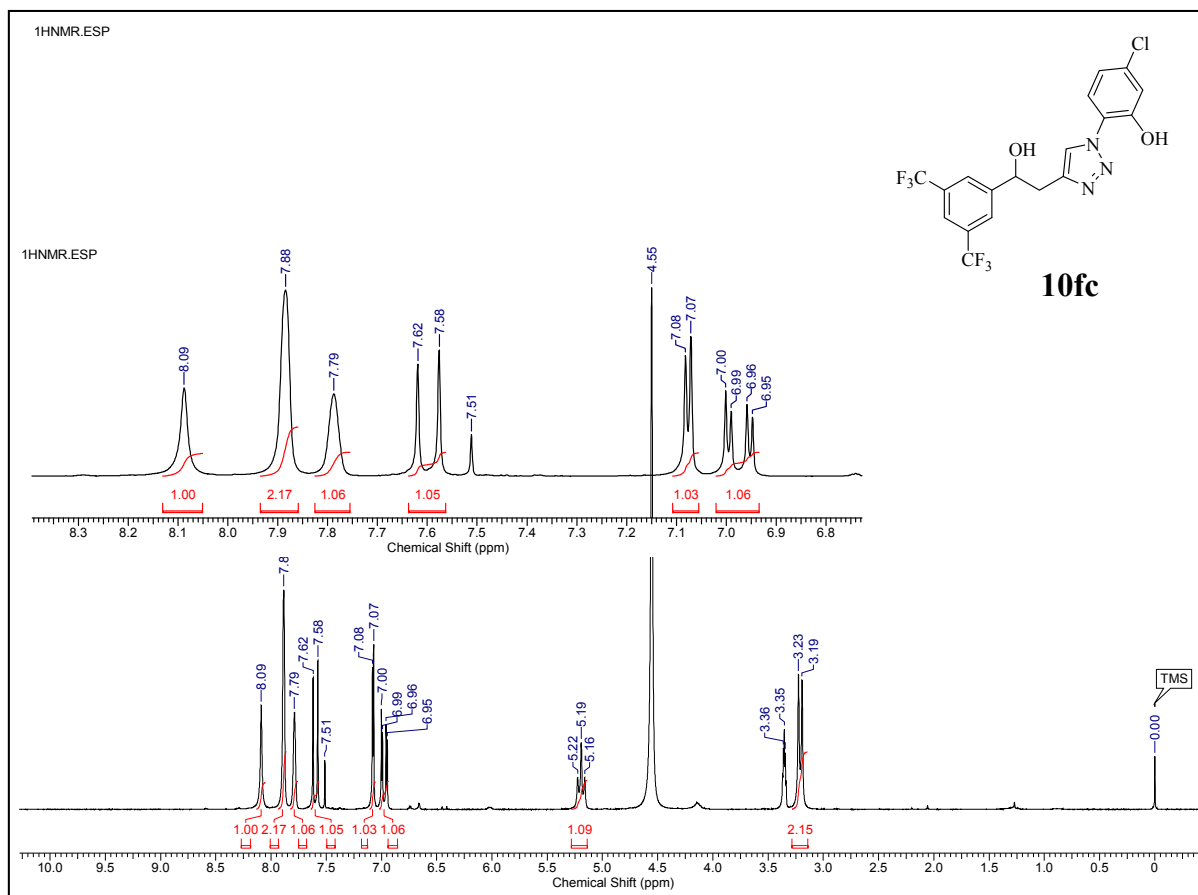
^{13}C NMR Spectrum of **10ec** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (50 MHz)



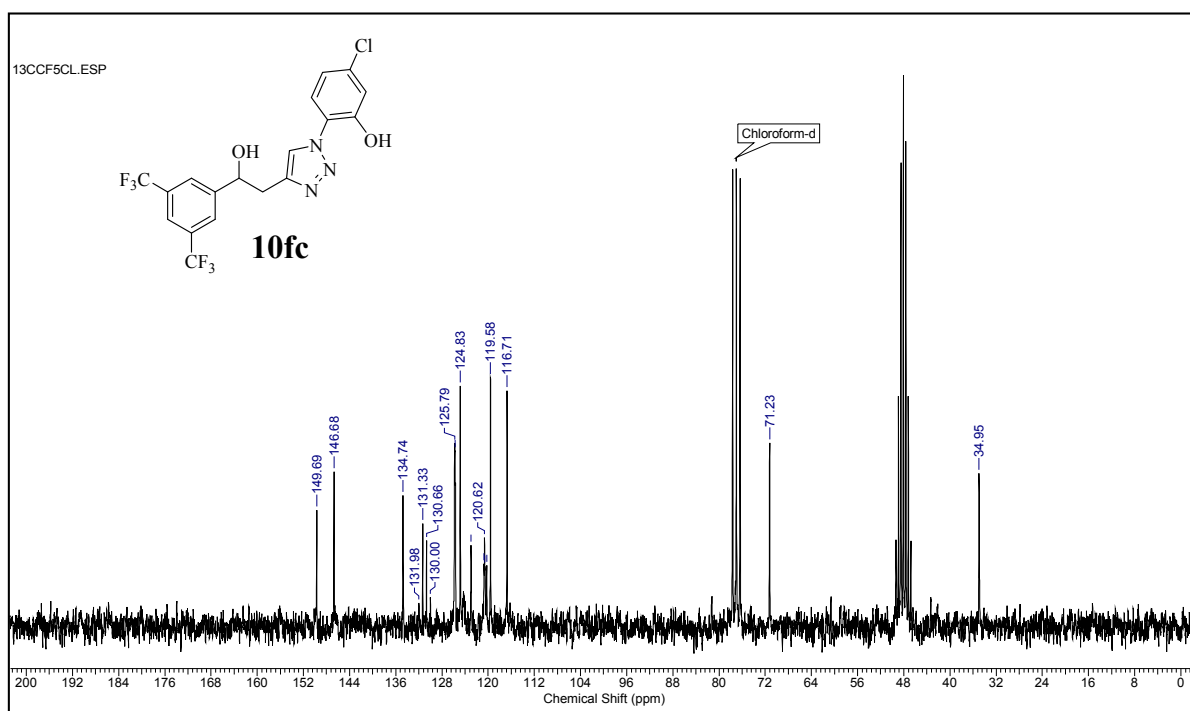
¹H NMR Spectrum of **10fa** in CDCl₃ + MeOH (D₄) (200 MHz)



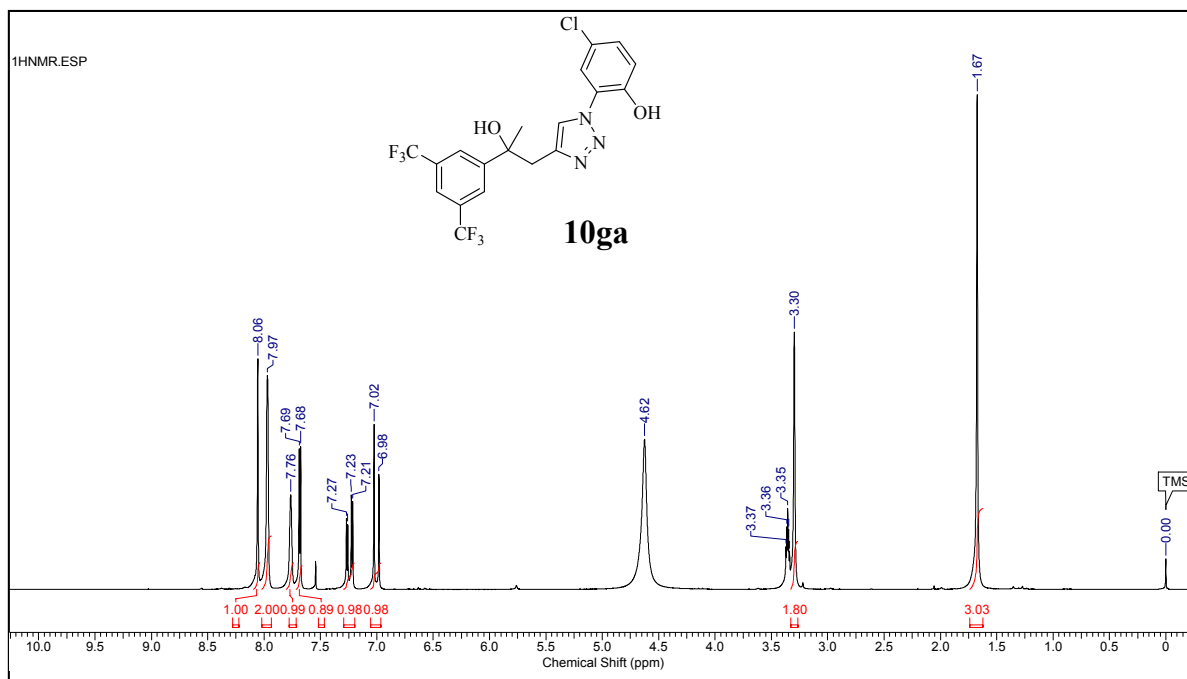
¹³C NMR Spectrum of **10fa** in CDCl₃ + MeOH (D₄) (50 MHz)



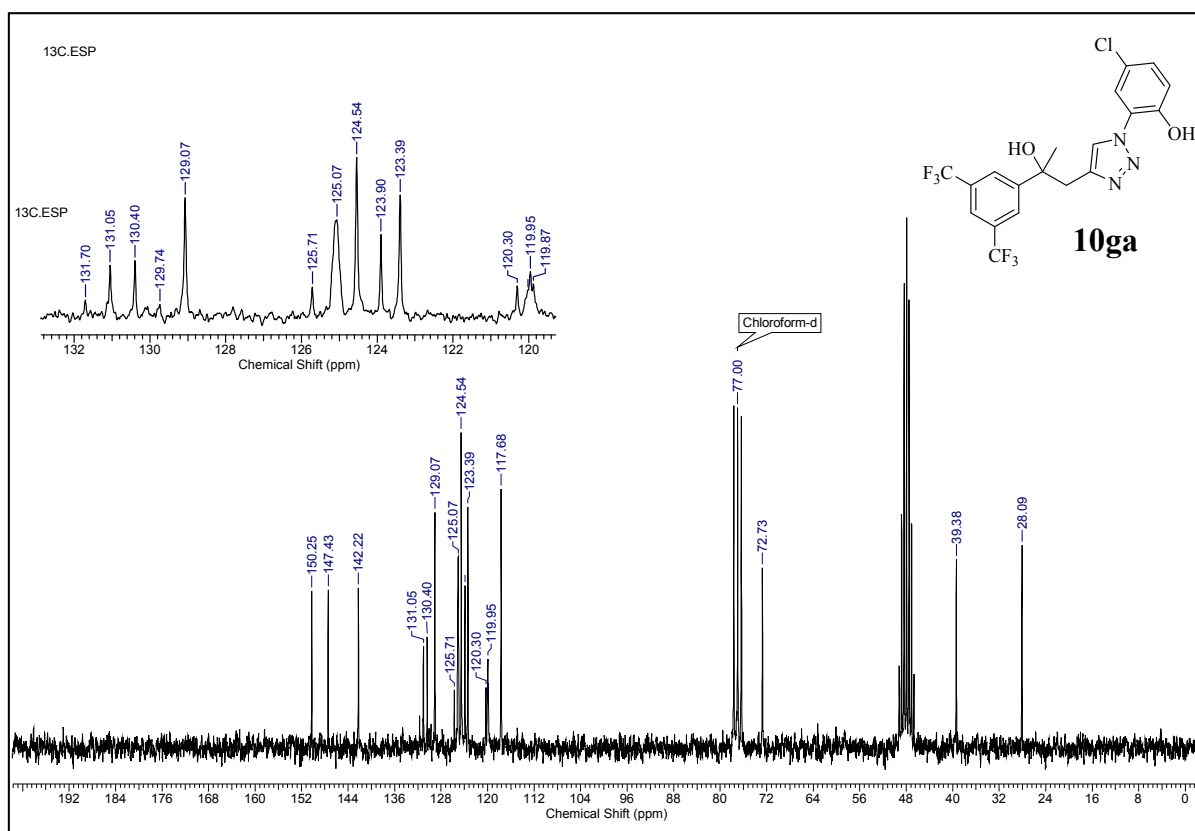
¹H NMR Spectrum of **10fc** in CDCl₃ + MeOH (D₄) (200 MHz)



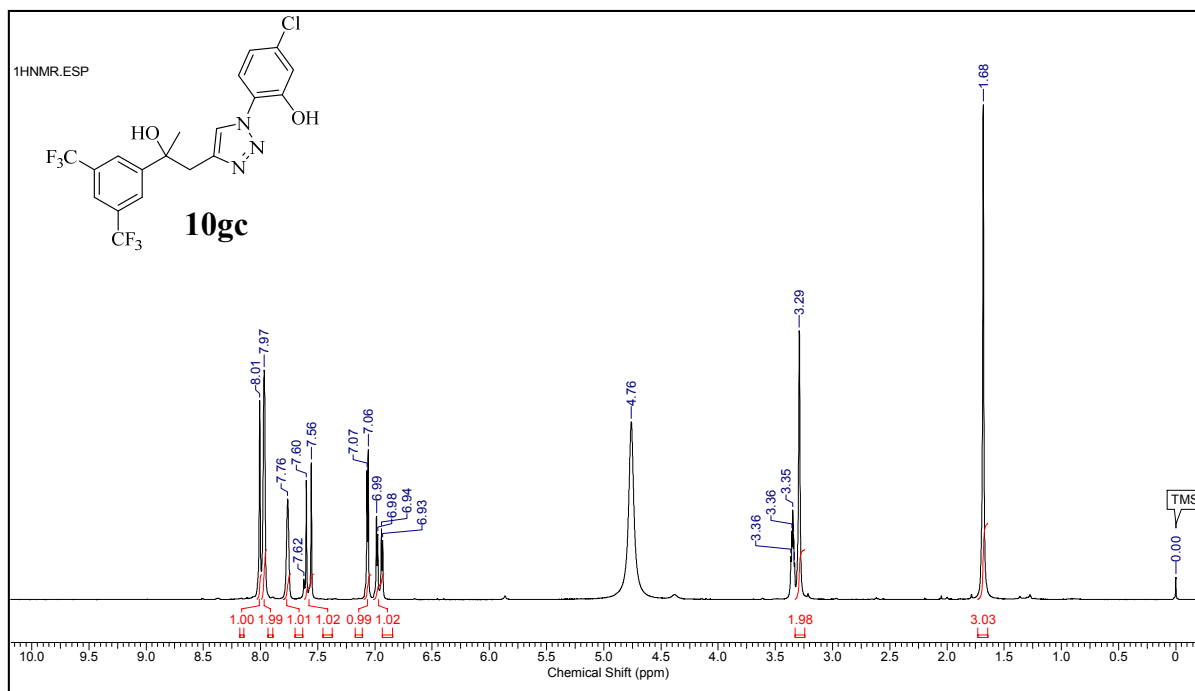
¹³C NMR Spectrum of **10fc** in CDCl₃ + MeOH (D₄) (50 MHz)



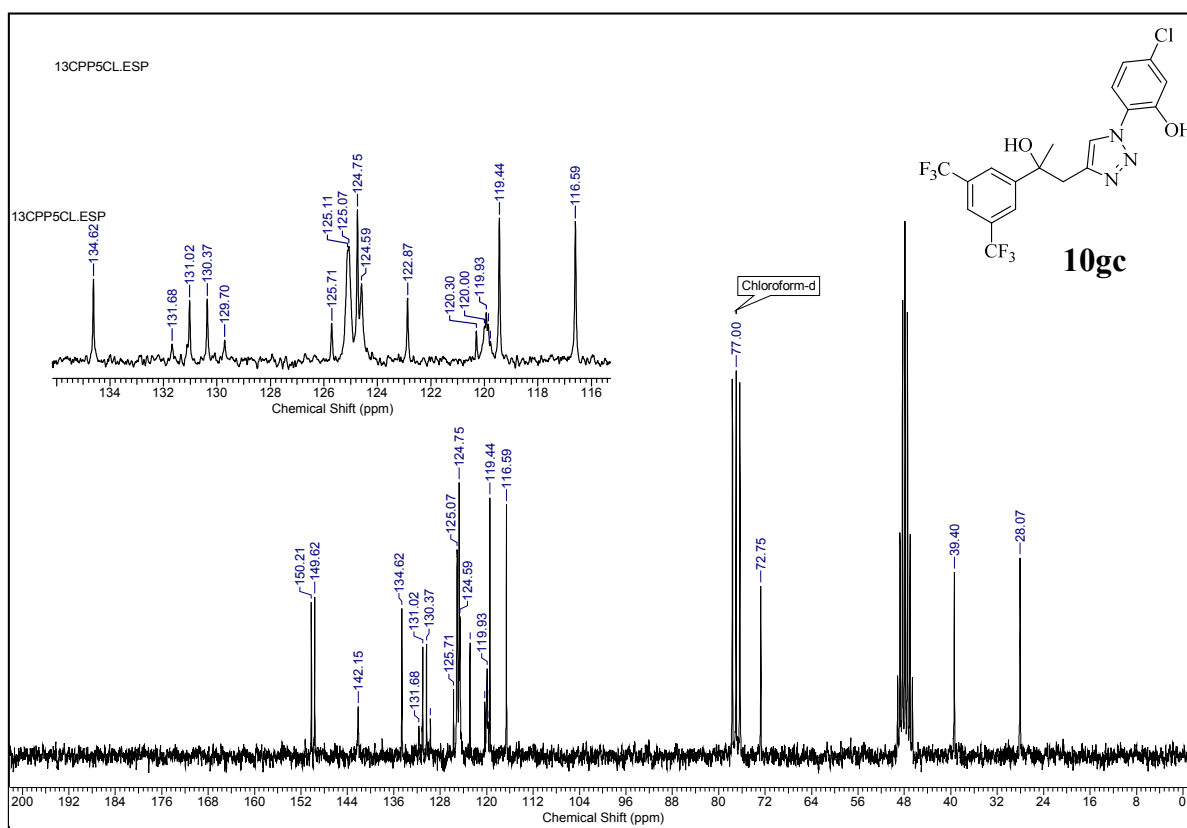
¹H NMR Spectrum of **10ga** in CDCl₃ + MeOH (D₄) (200 MHz)



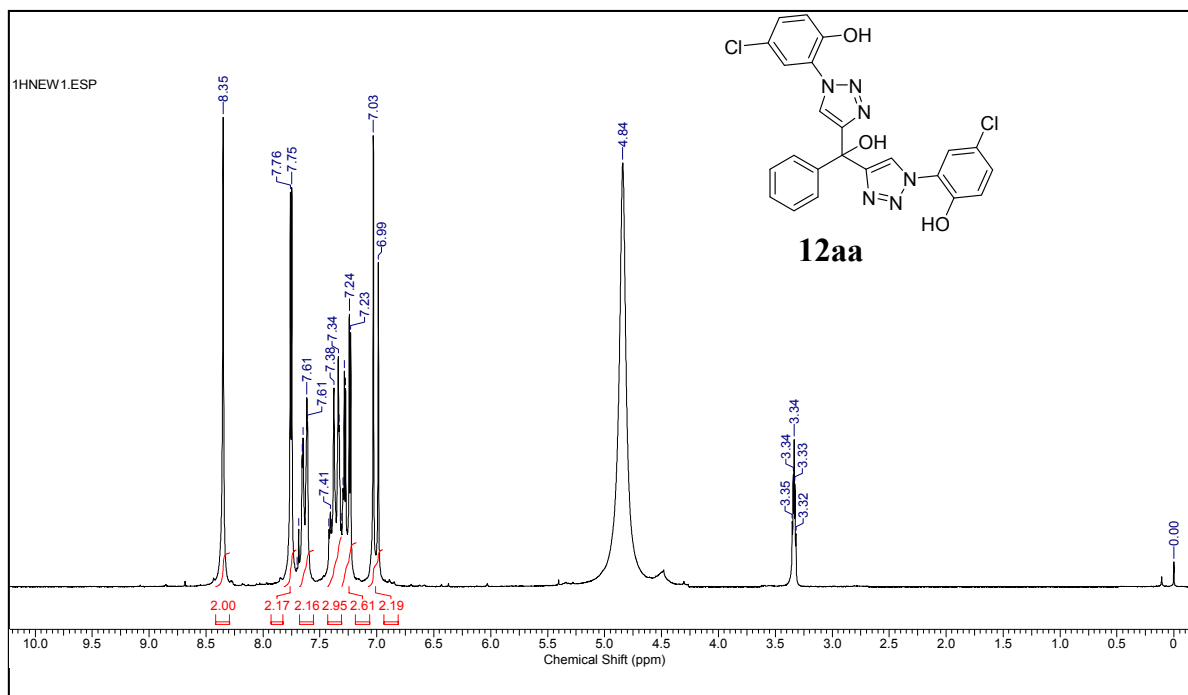
¹³C NMR Spectrum of **10ga** in CDCl₃ + MeOH (D₄) (50 MHz)



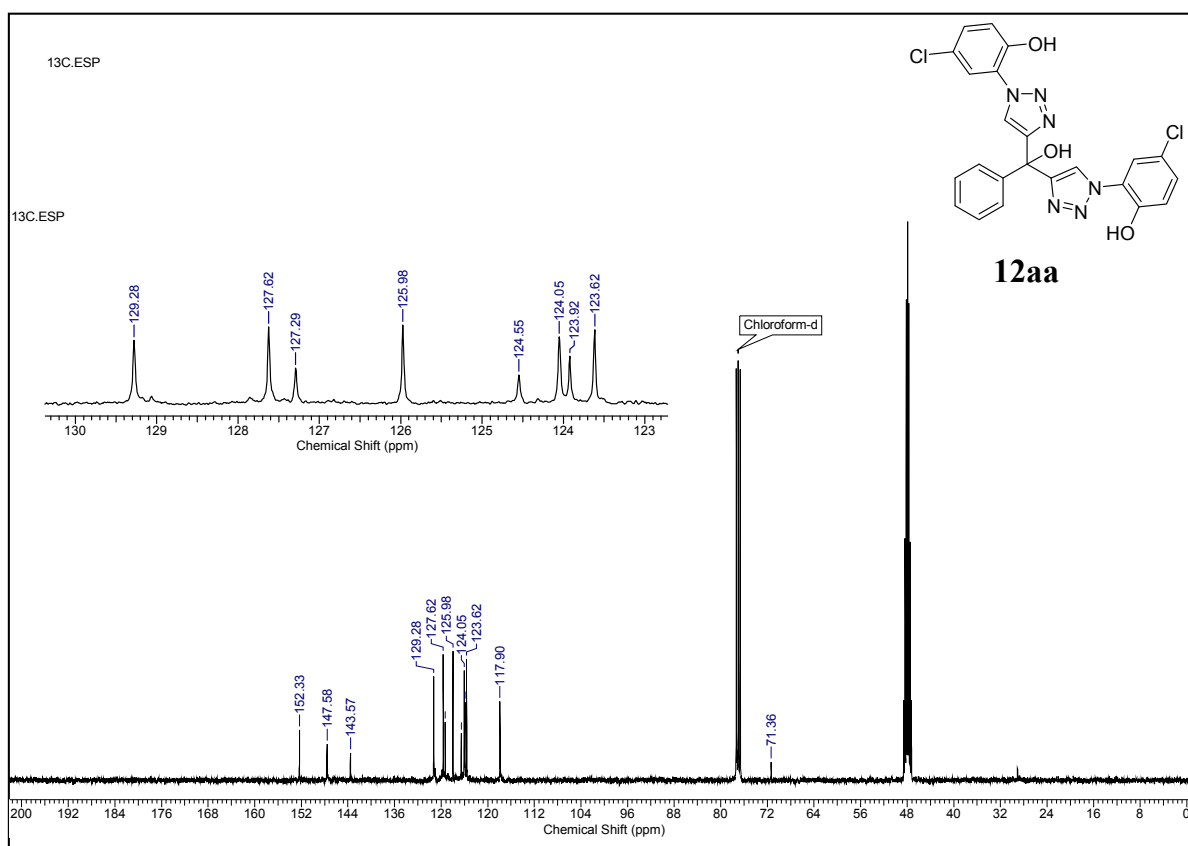
¹H NMR Spectrum of **10gc** in CDCl₃ + MeOH (D₄) (200 MHz)



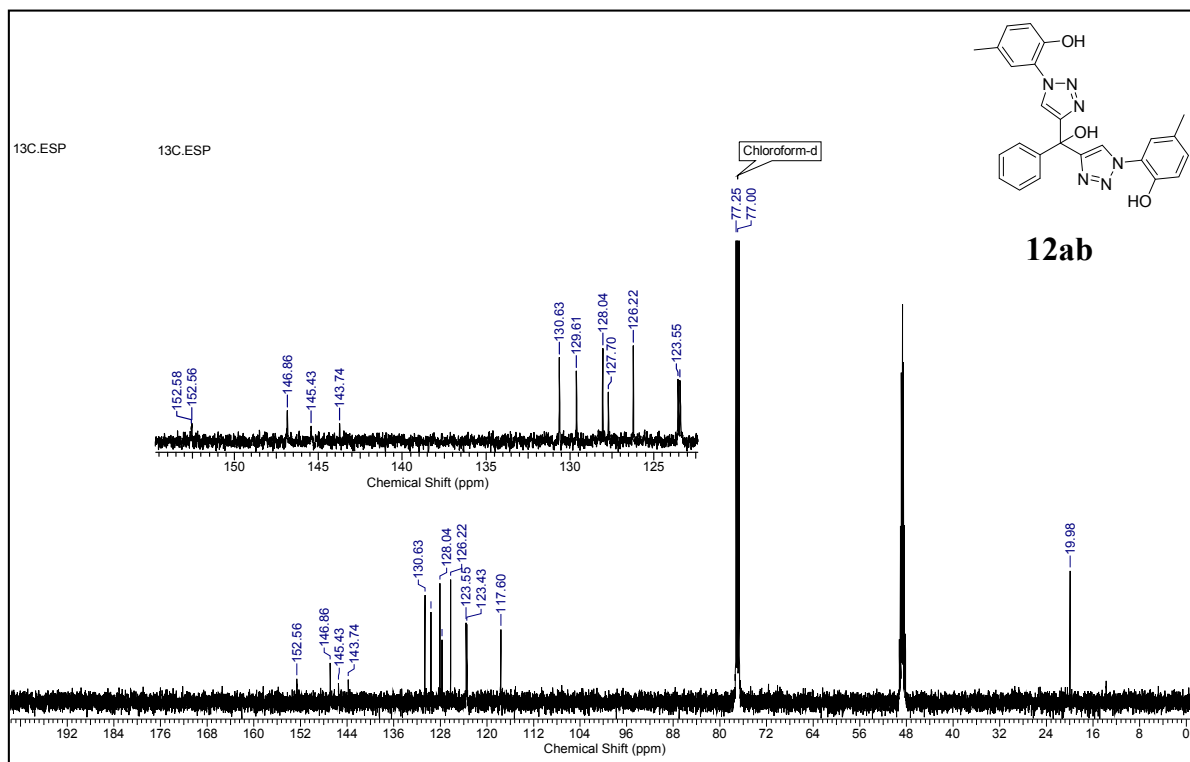
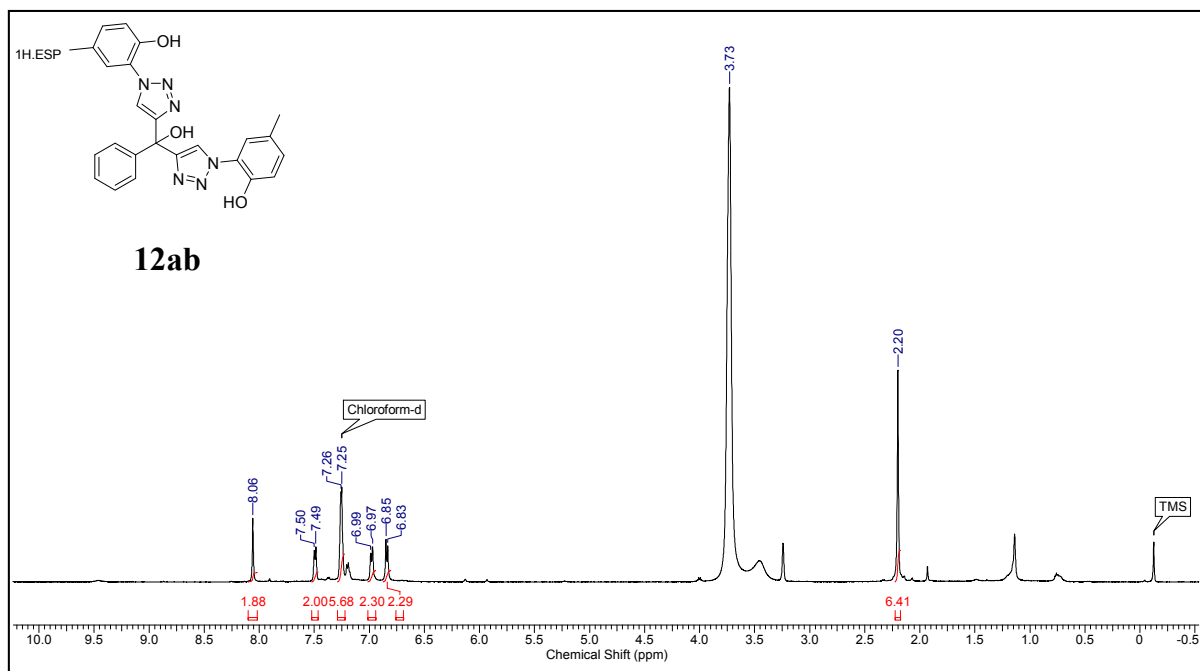
¹³C NMR Spectrum of **10gc** in CDCl₃ + MeOH (D₄) (50 MHz)

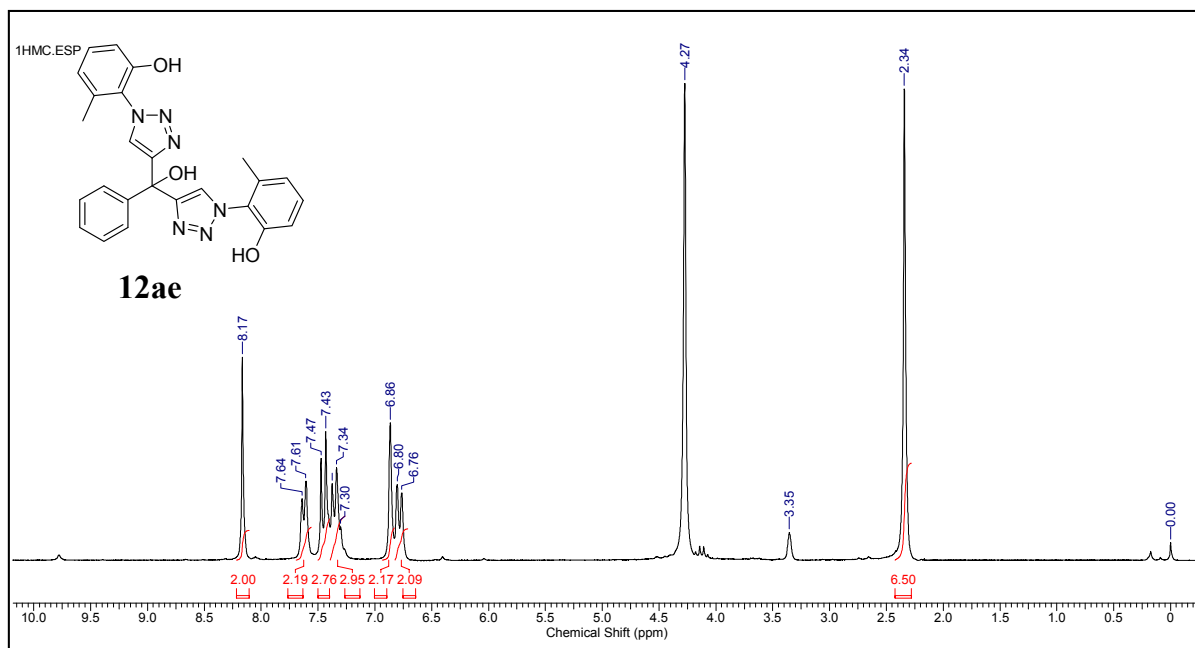


^1H NMR Spectrum of **12aa** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (200 MHz)

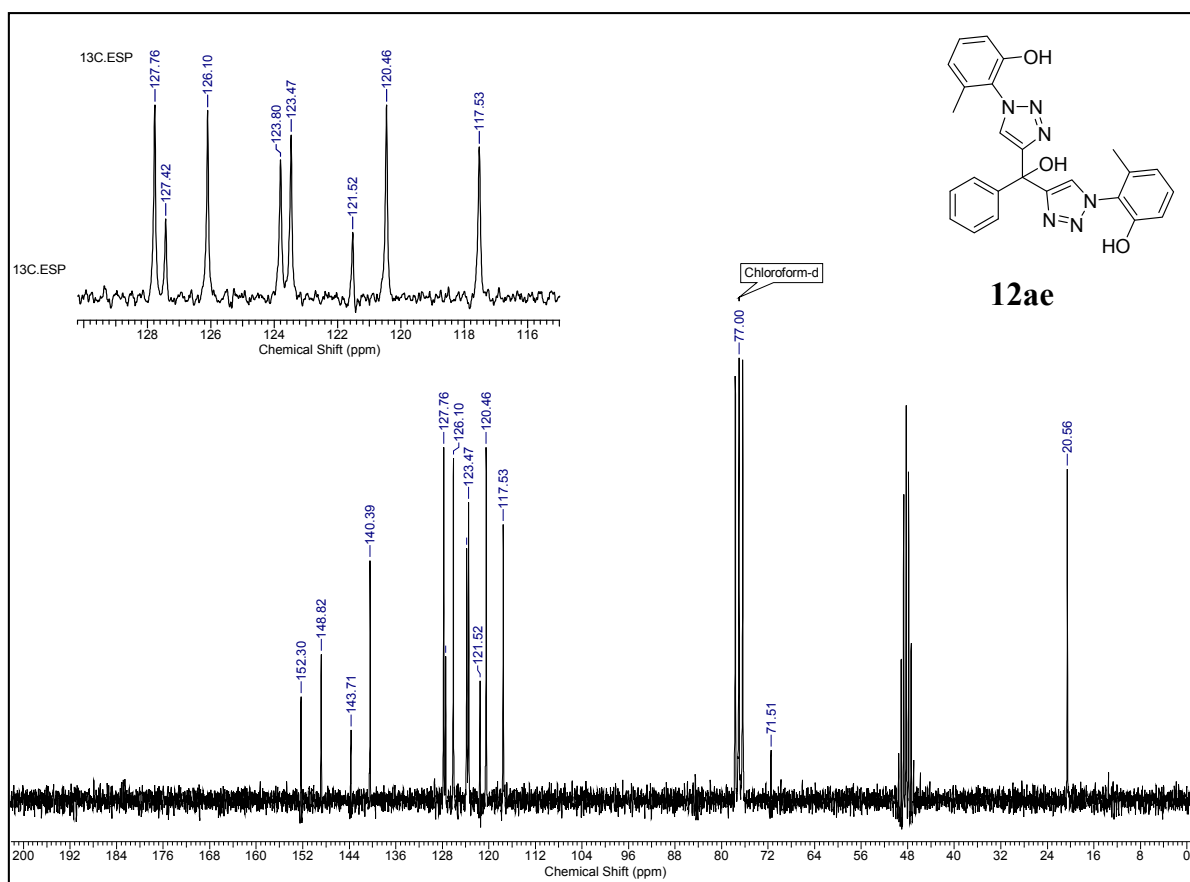


^{13}C NMR Spectrum of **12aa** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (100 MHz)

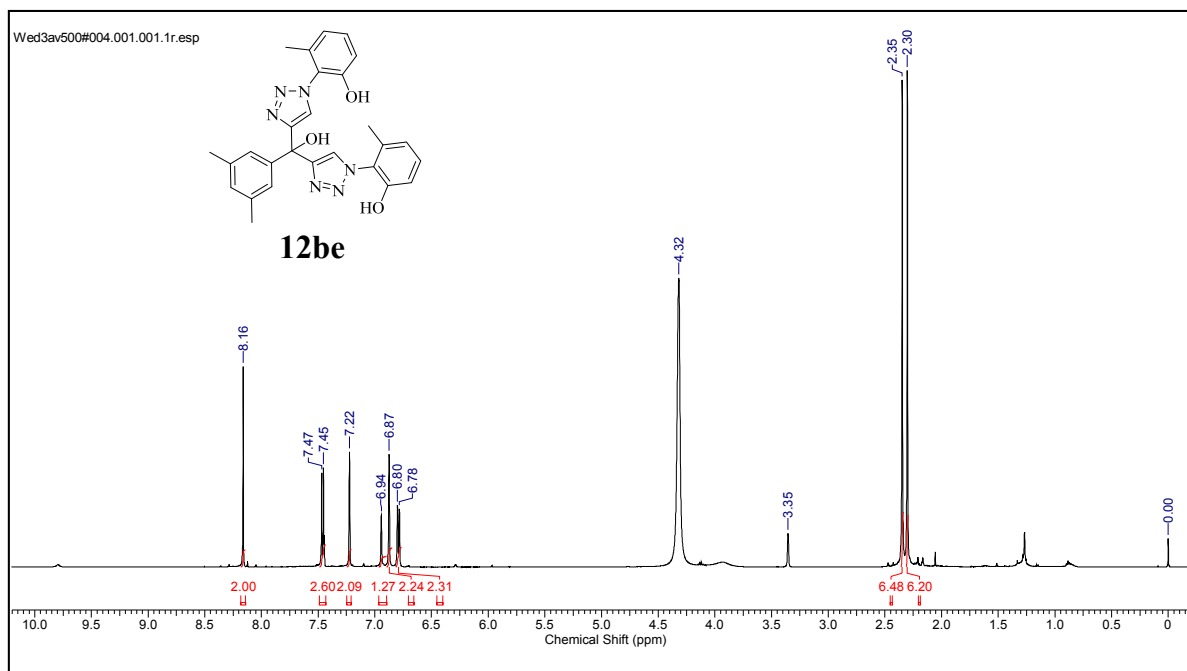




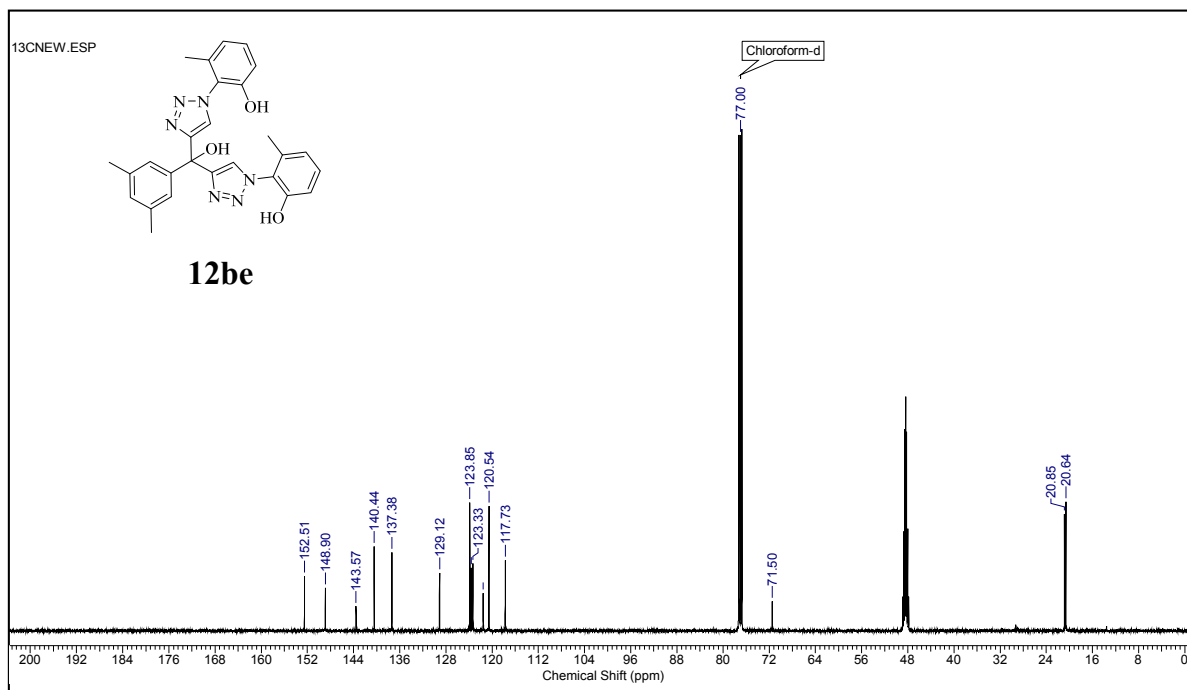
¹H NMR Spectrum of **12ae** in CDCl₃ + MeOH (D₄) (200 MHz)



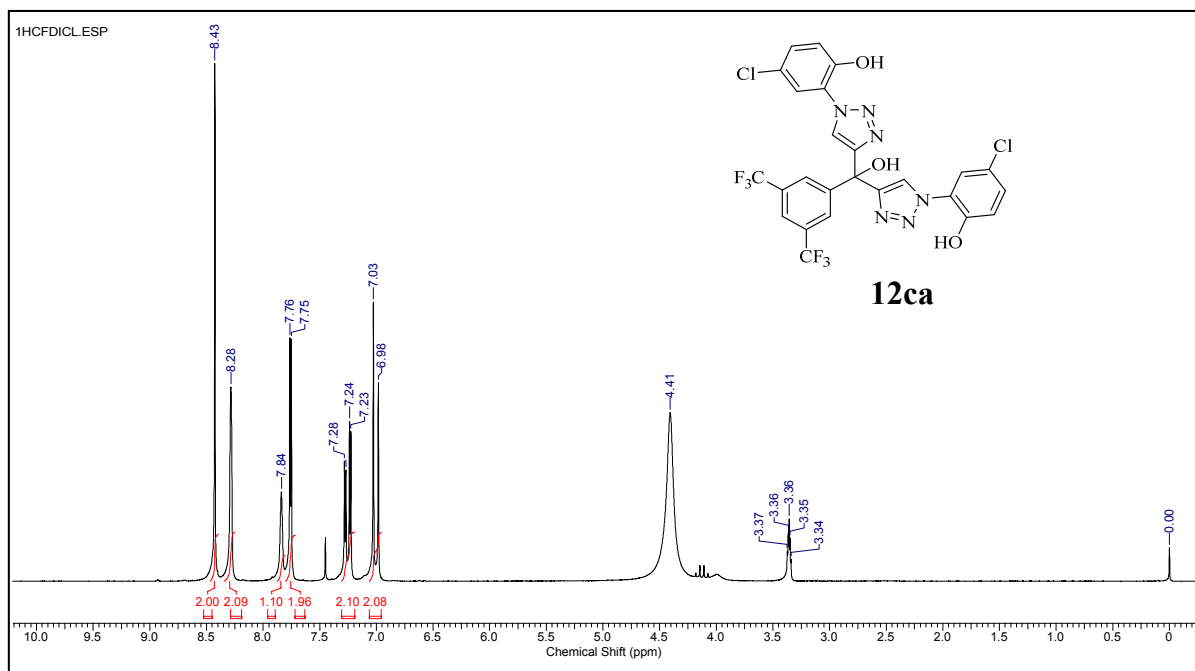
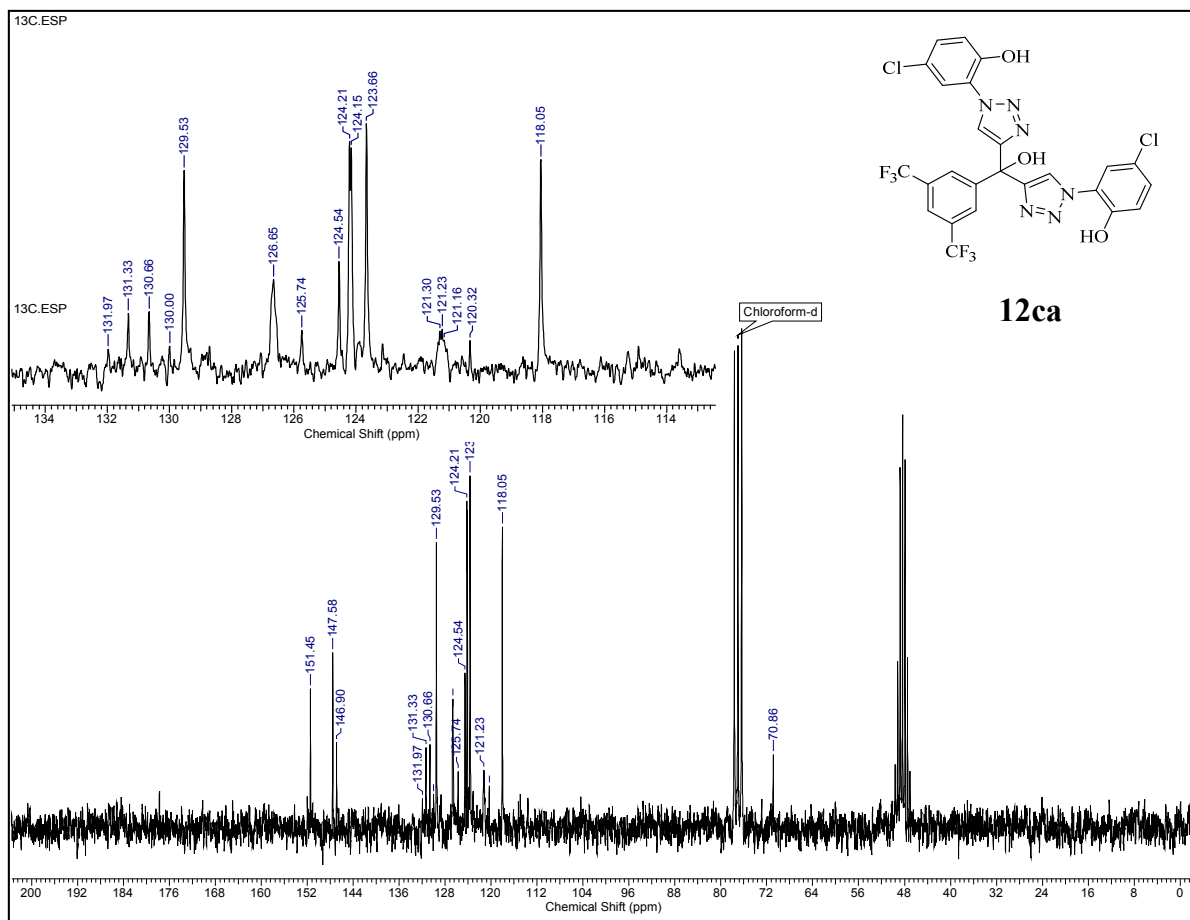
¹³C NMR Spectrum of **12ae** in CDCl₃ + MeOH (D₄) (50 MHz)



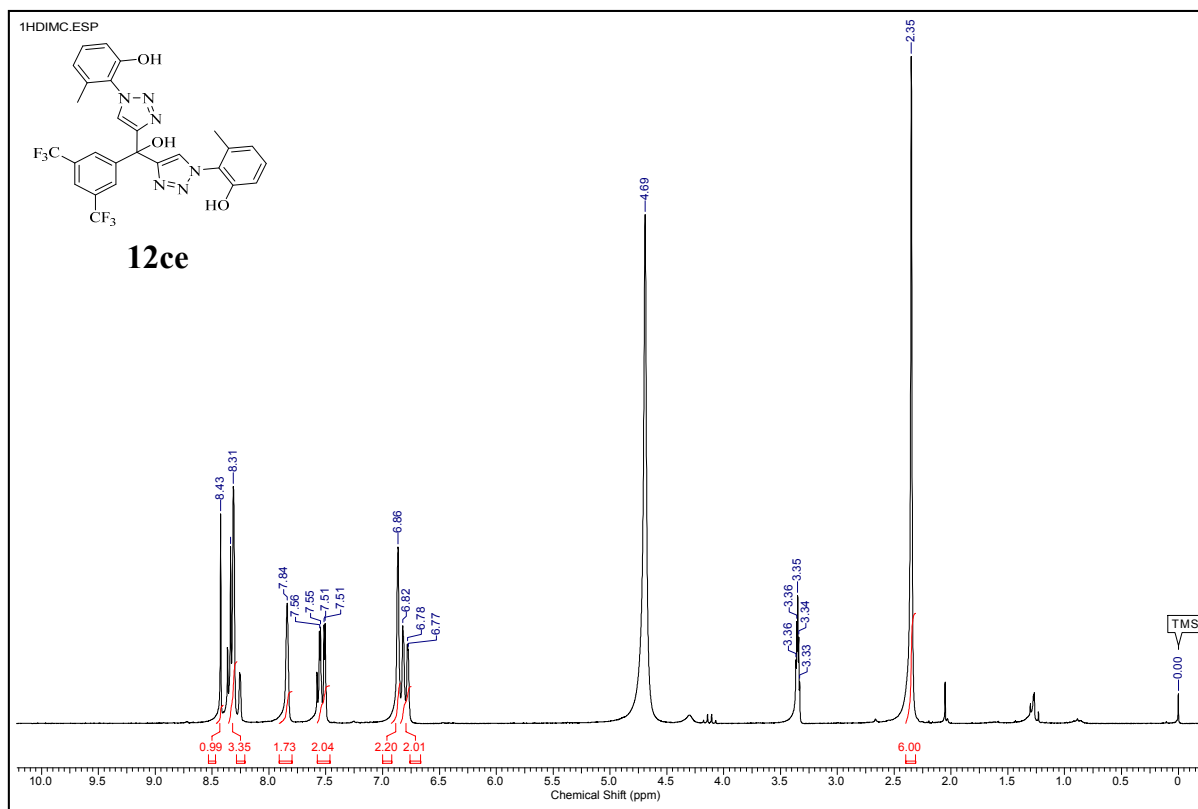
^1H NMR Spectrum of **12be** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (500 MHz)



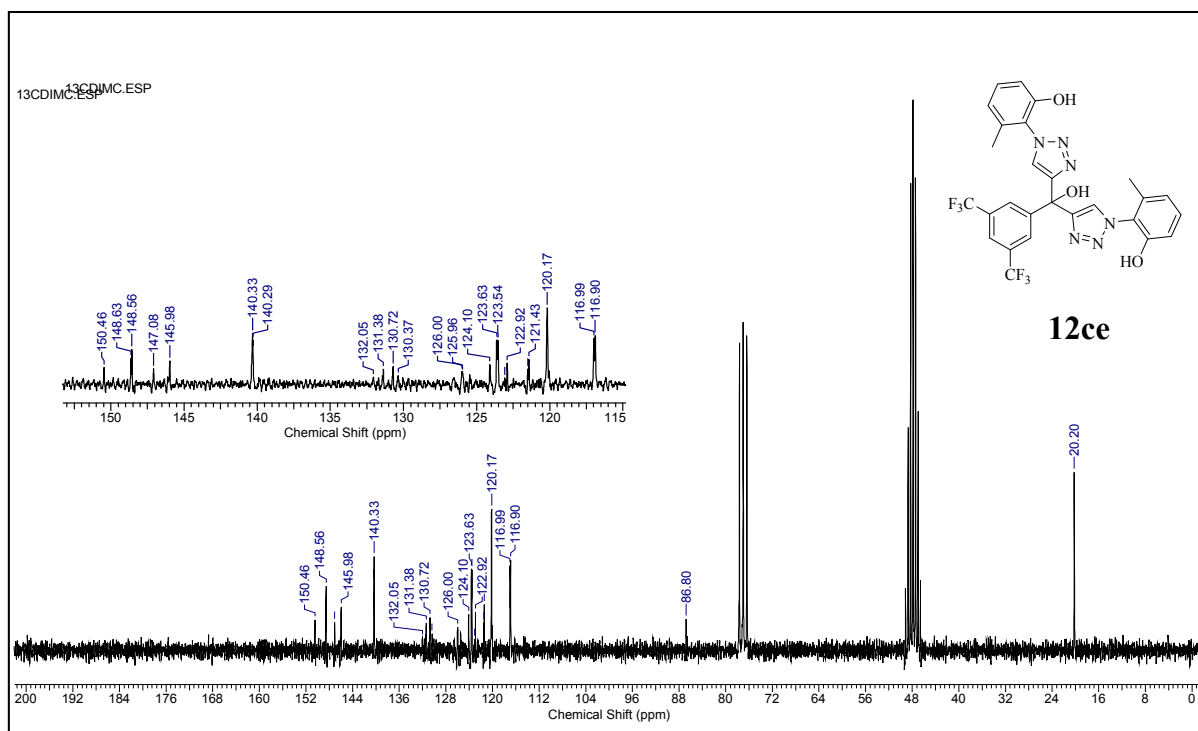
^{13}C NMR Spectrum of **12be** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (125 MHz)

¹H NMR Spectrum of **12ca** in CDCl₃ + MeOH (D₄) (200 MHz)

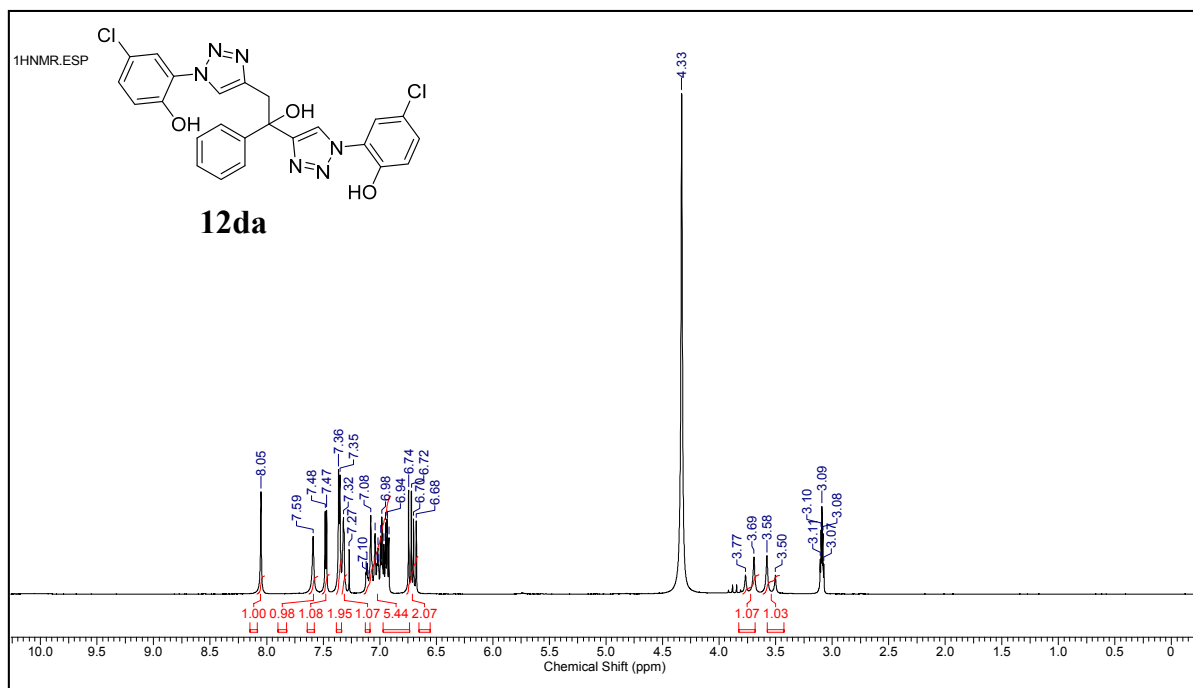
¹³C NMR Spectrum of **12ca** in CDCl₃ + MeOH (D₄) (50 MHz)



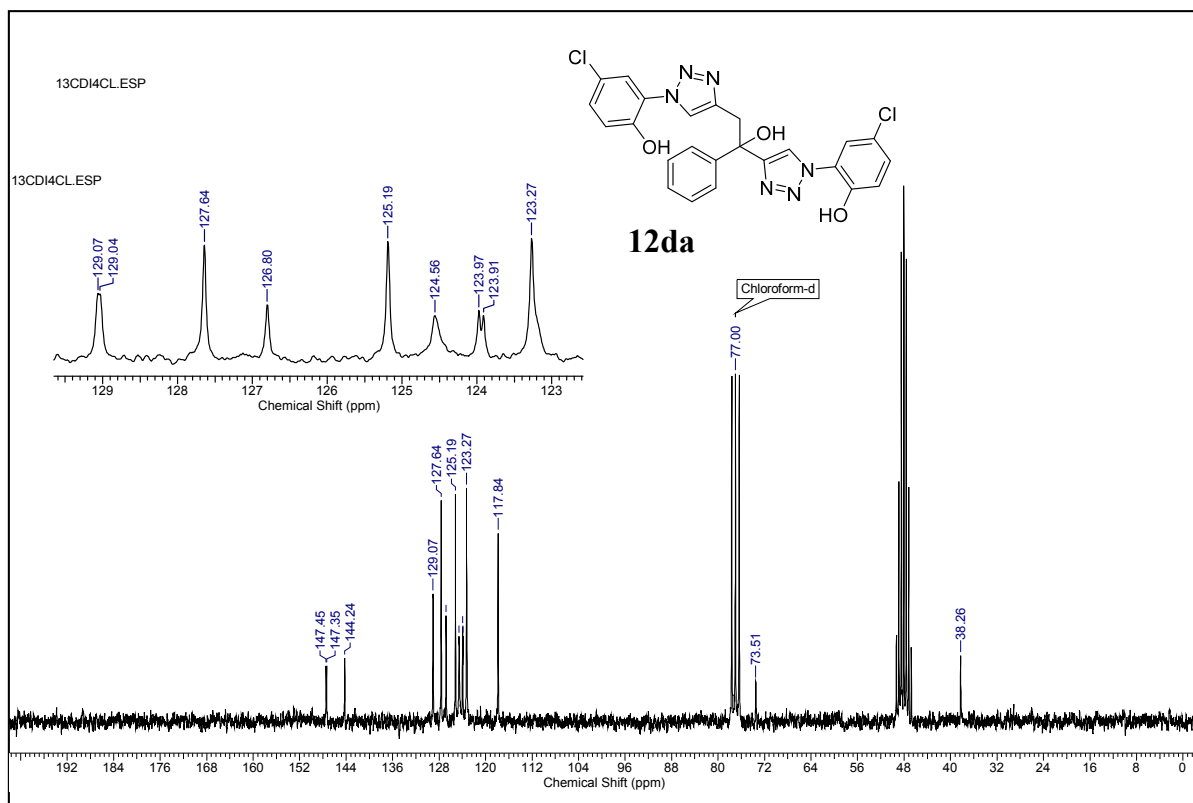
¹H NMR Spectrum of **12ce** in CDCl₃ + MeOH (D₄) (200 MHz)



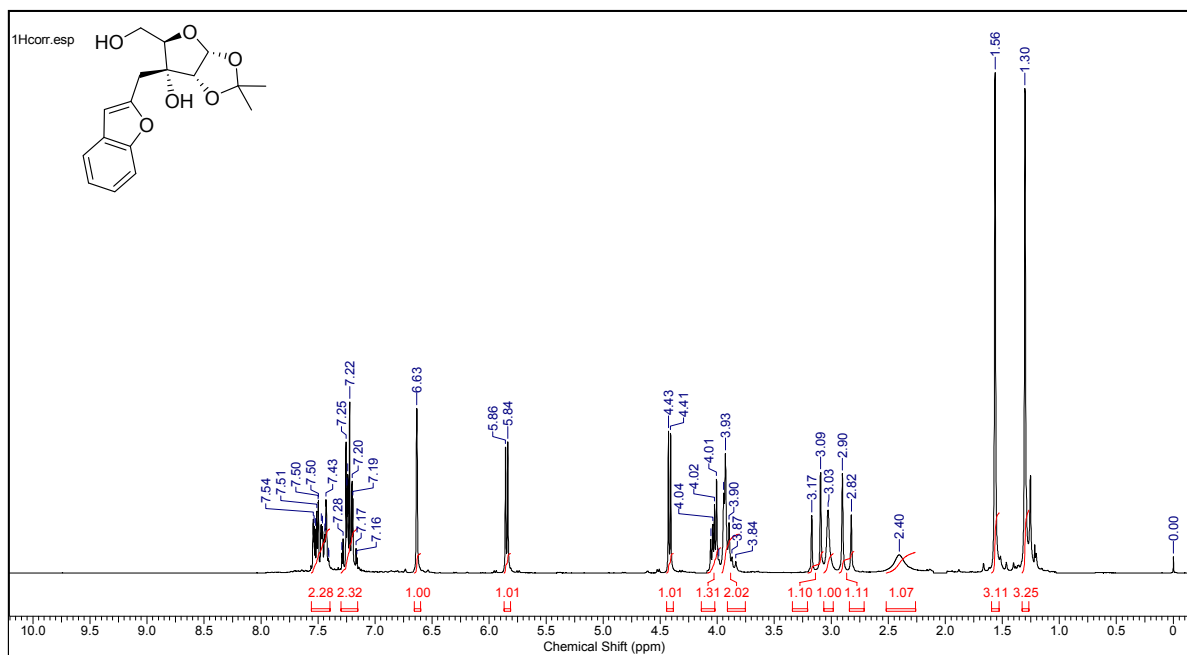
¹³C NMR Spectrum of **12ce** in CDCl₃ + MeOH (D₄) (50 MHz)



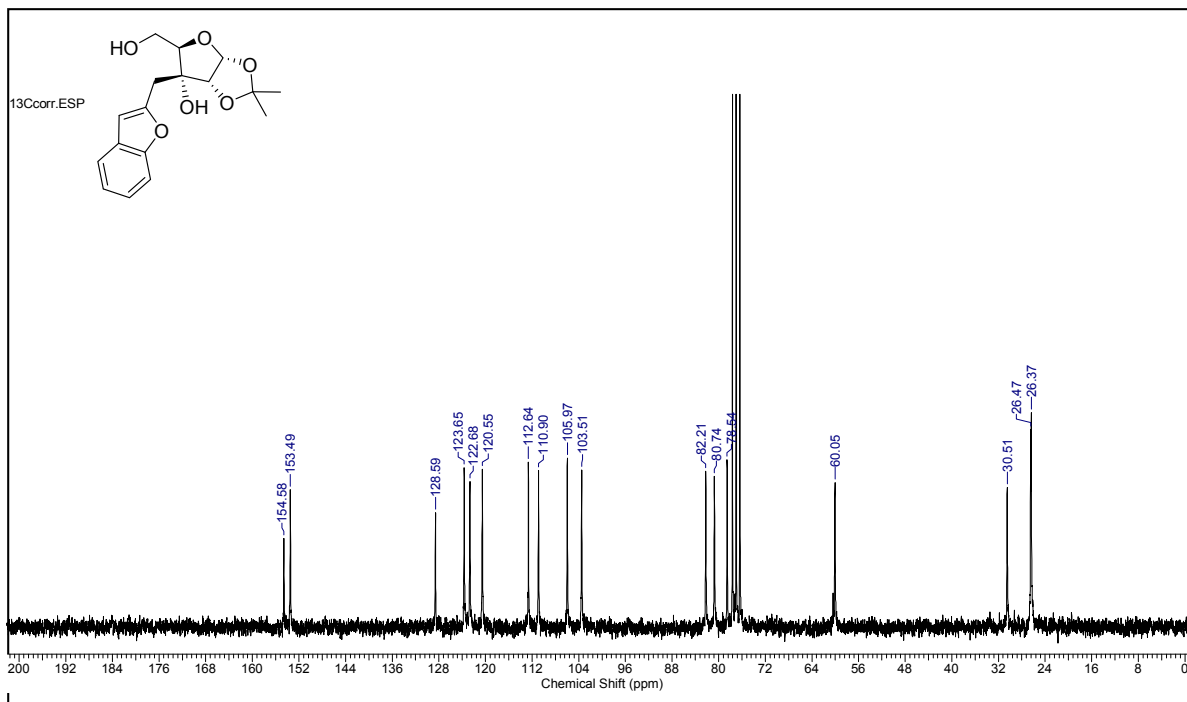
¹H NMR Spectrum of **12da** in CDCl₃ + MeOH (D₄) (200 MHz)



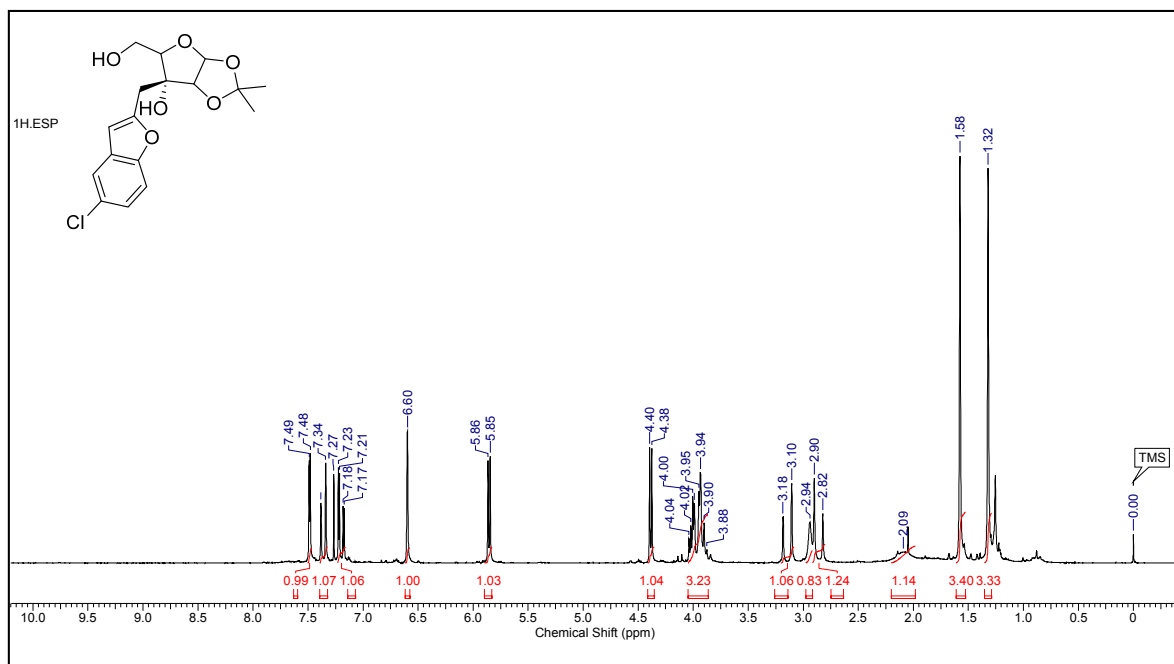
¹³C NMR Spectrum of **12da** in CDCl₃ + MeOH (D₄) (50 MHz)



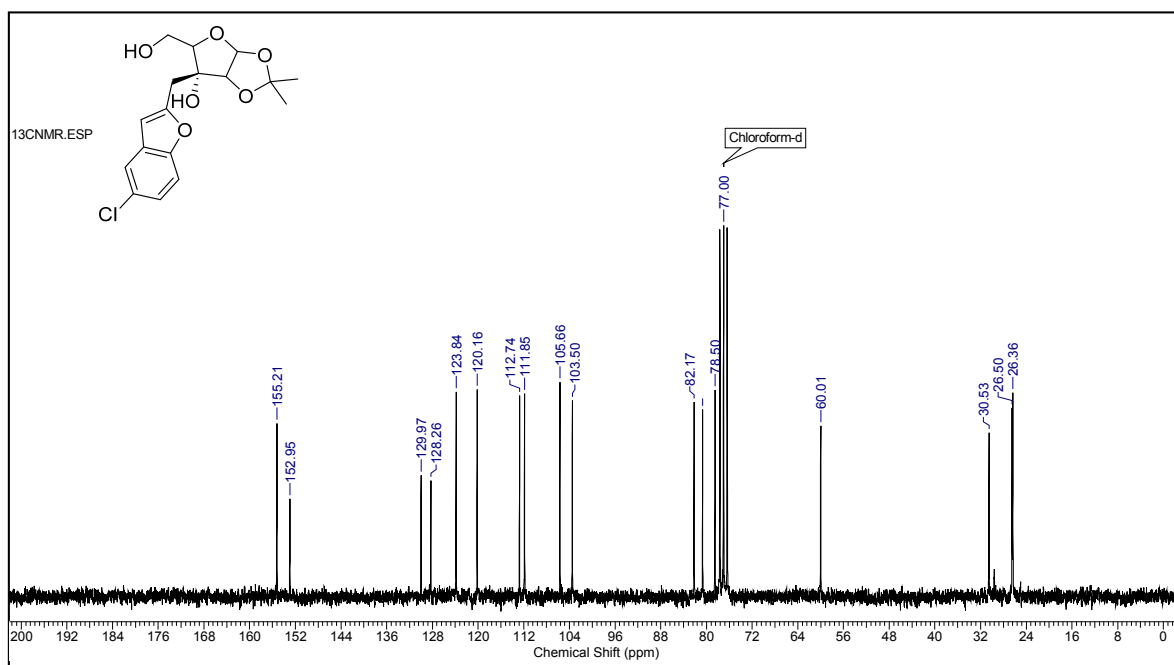
¹H NMR Spectrum of **13aa** in CDCl₃ (200 MHz)



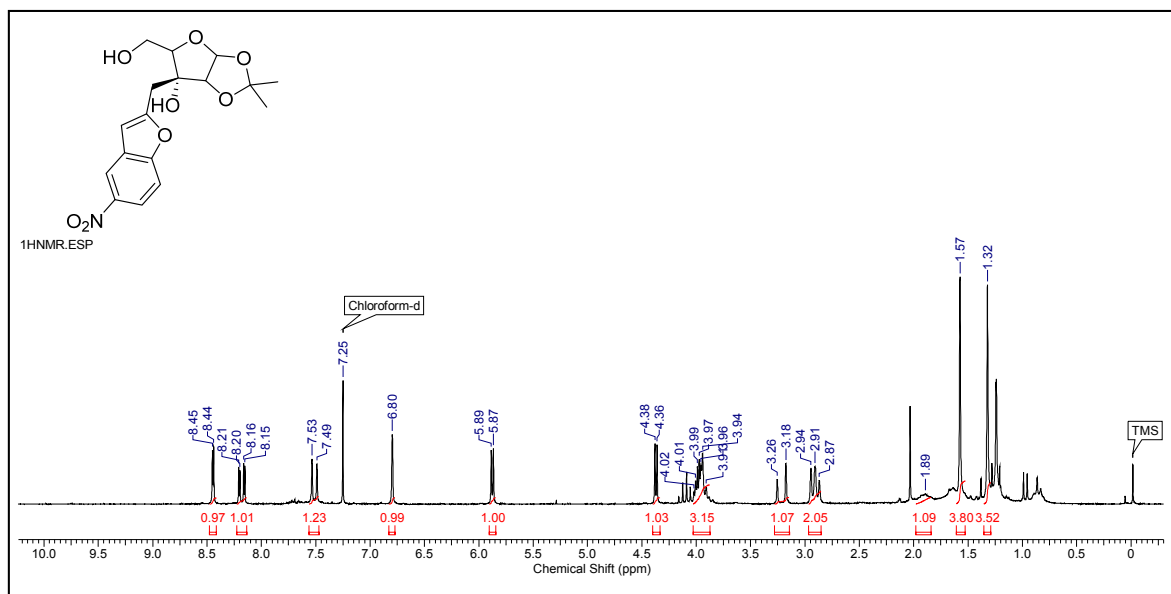
¹³C NMR Spectrum of **13aa** in CDCl₃ (50 MHz)



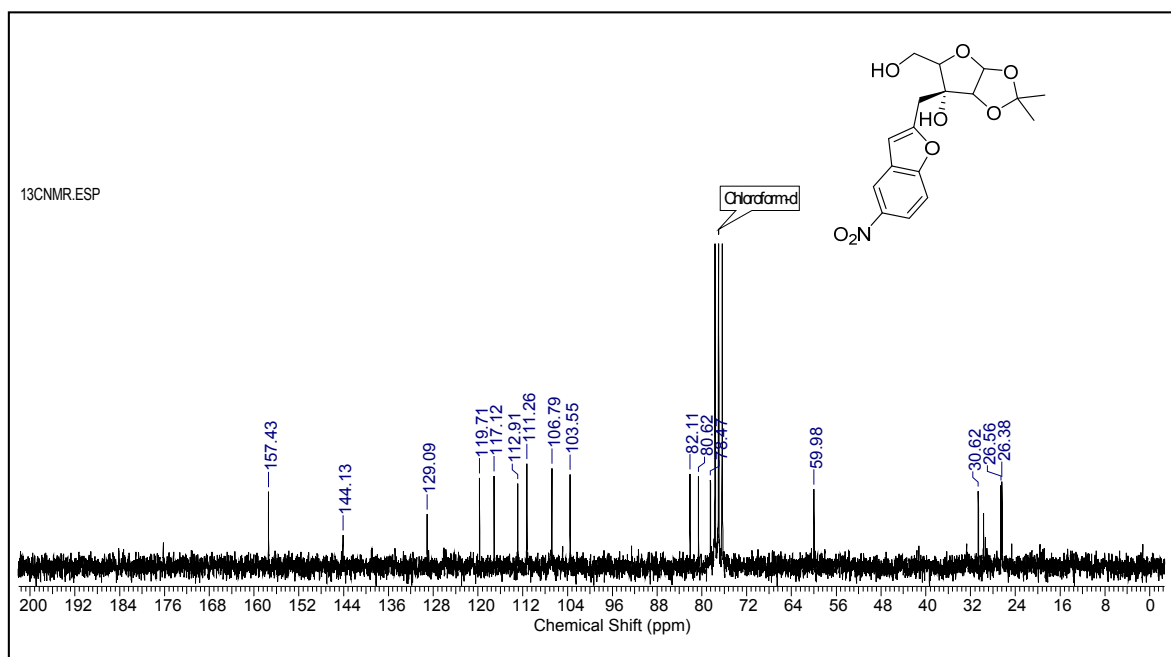
¹H NMR Spectrum of **13ab** in CDCl₃ (200 MHz)



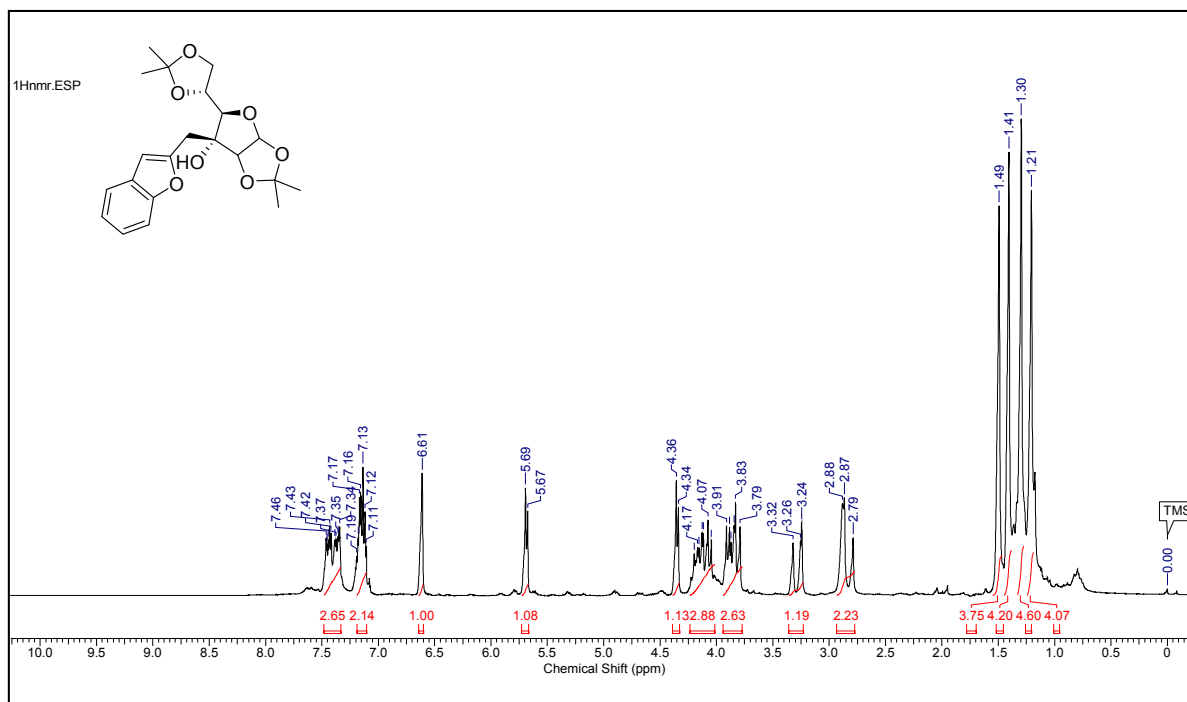
¹³C NMR Spectrum of **13ab** in CDCl₃ (50 MHz)



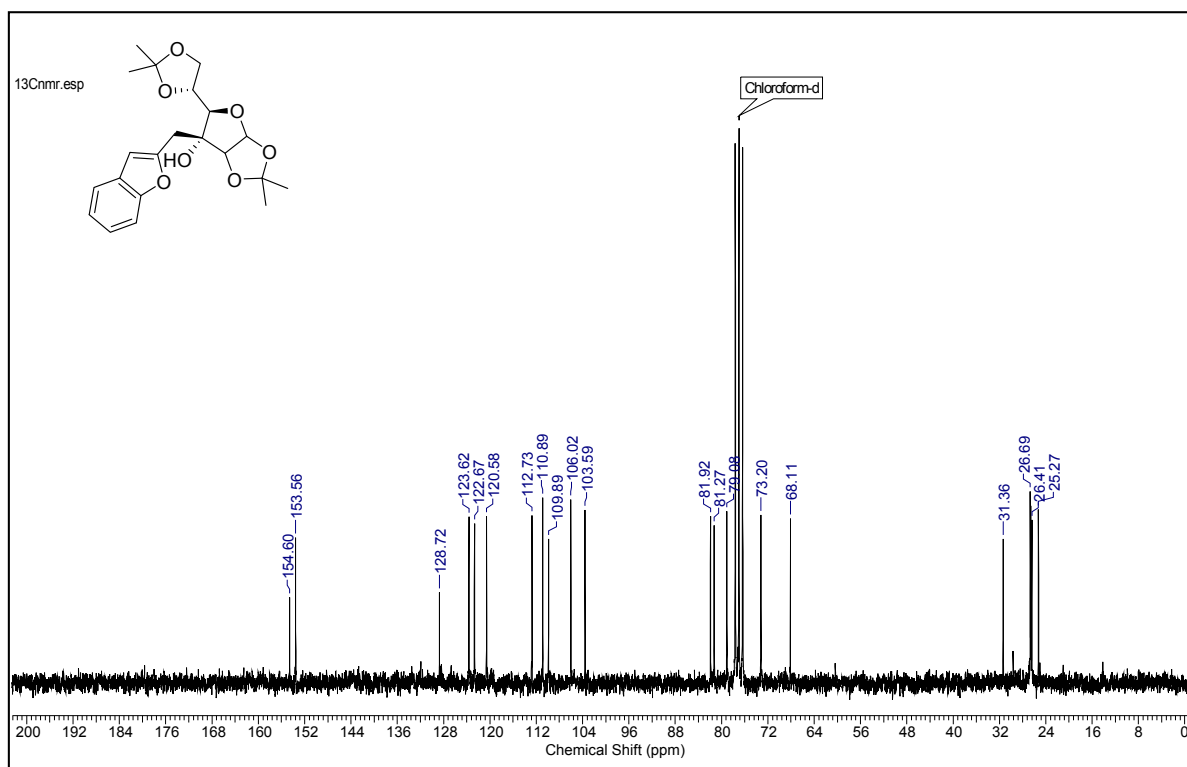
¹H NMR Spectrum of **13ac** in CDCl₃ (200 MHz)



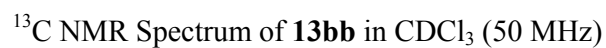
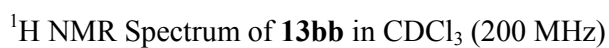
¹³C NMR Spectrum of **13ac** in CDCl₃ (50 MHz)

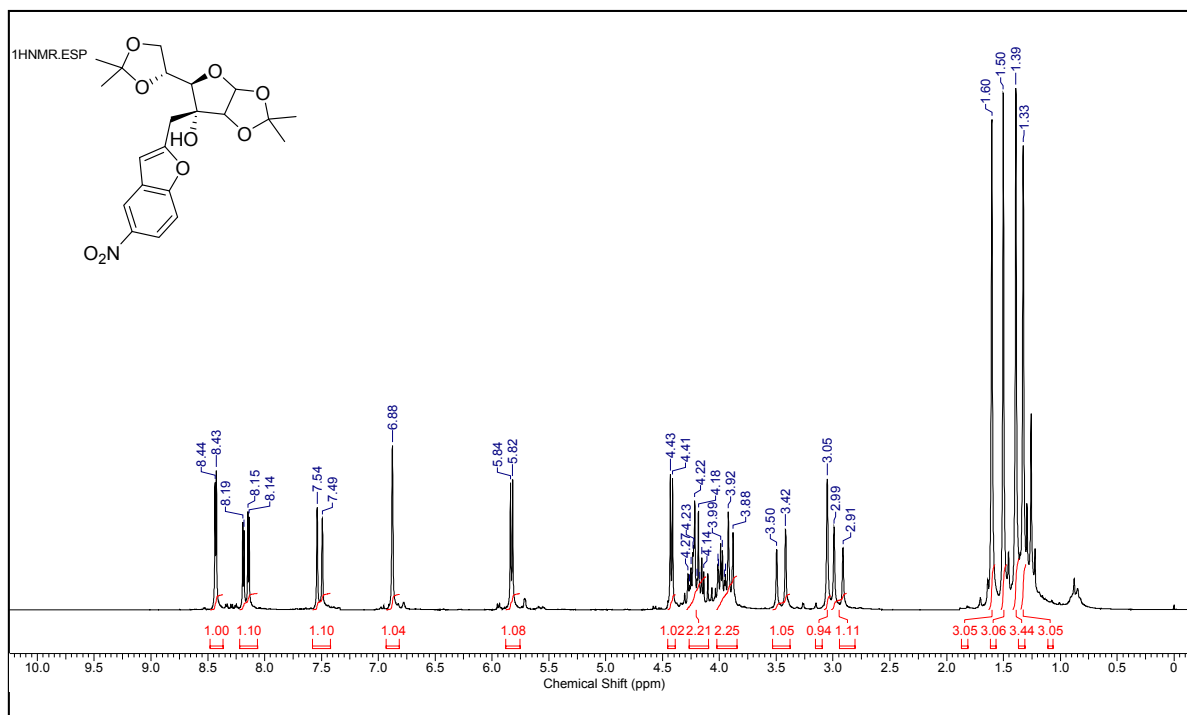


¹H NMR Spectrum of **13ba** in CDCl₃ (200 MHz)

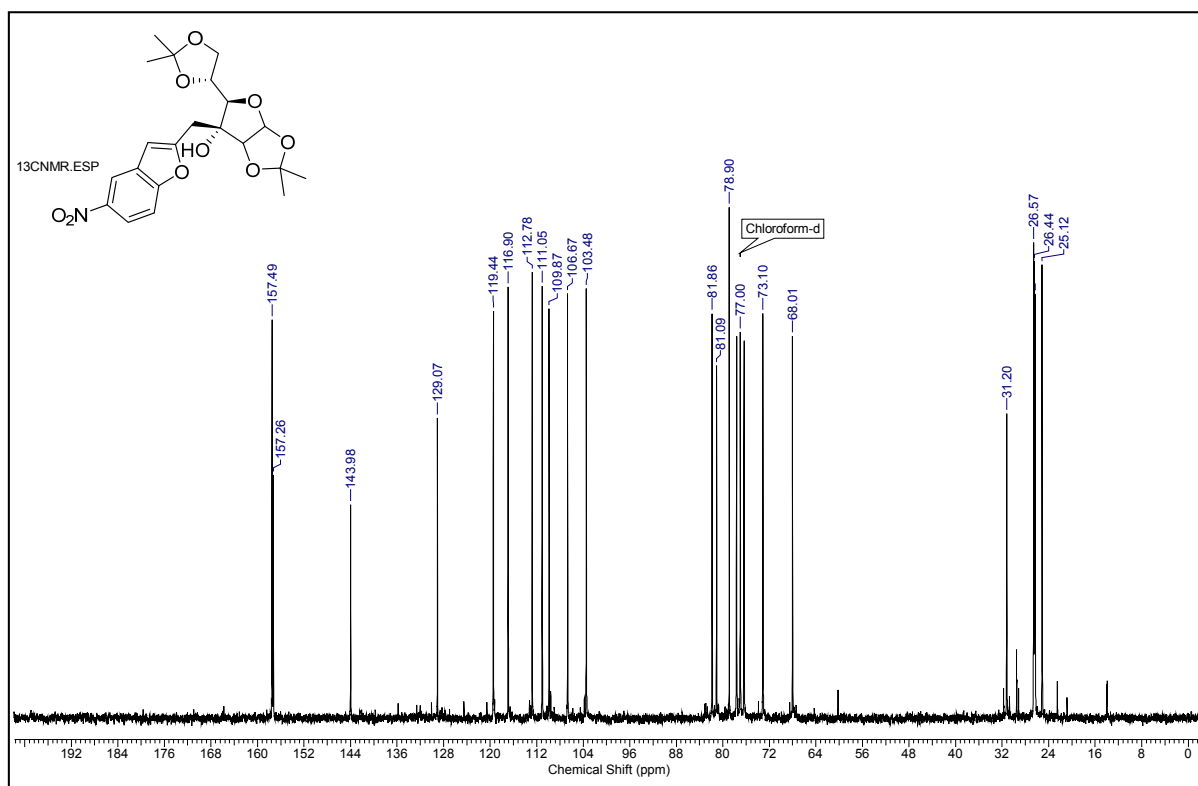


¹³C NMR Spectrum of **13ba** in CDCl₃ (50MHz)

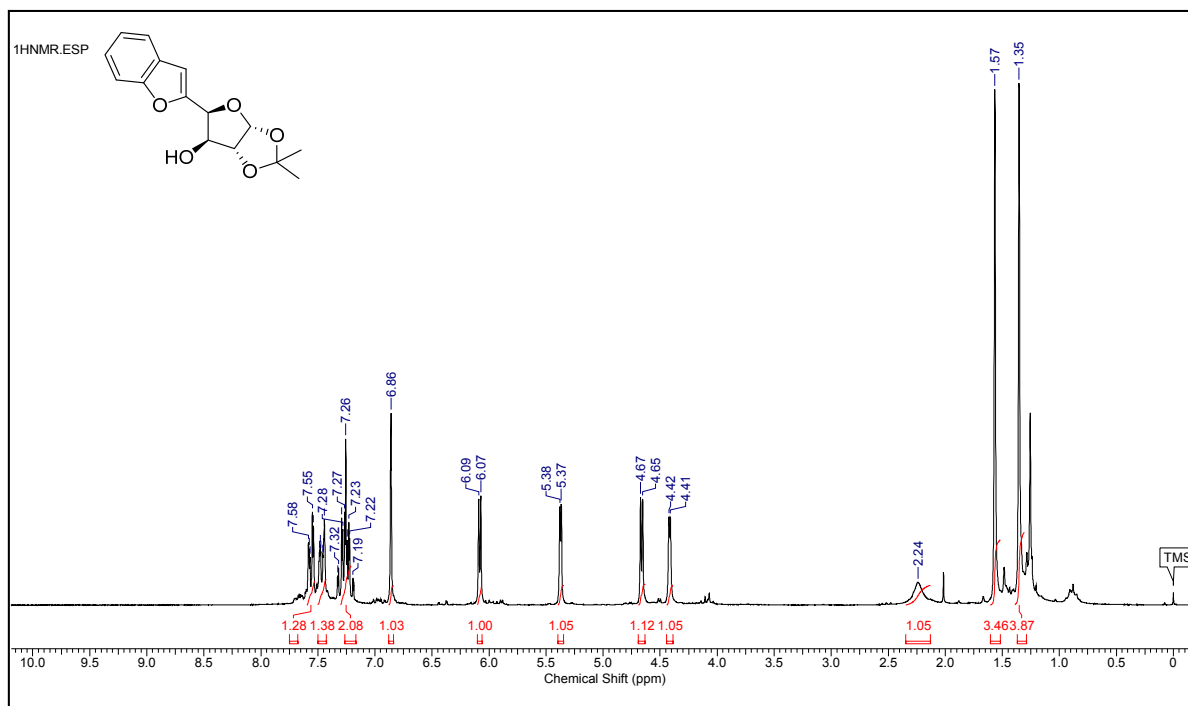




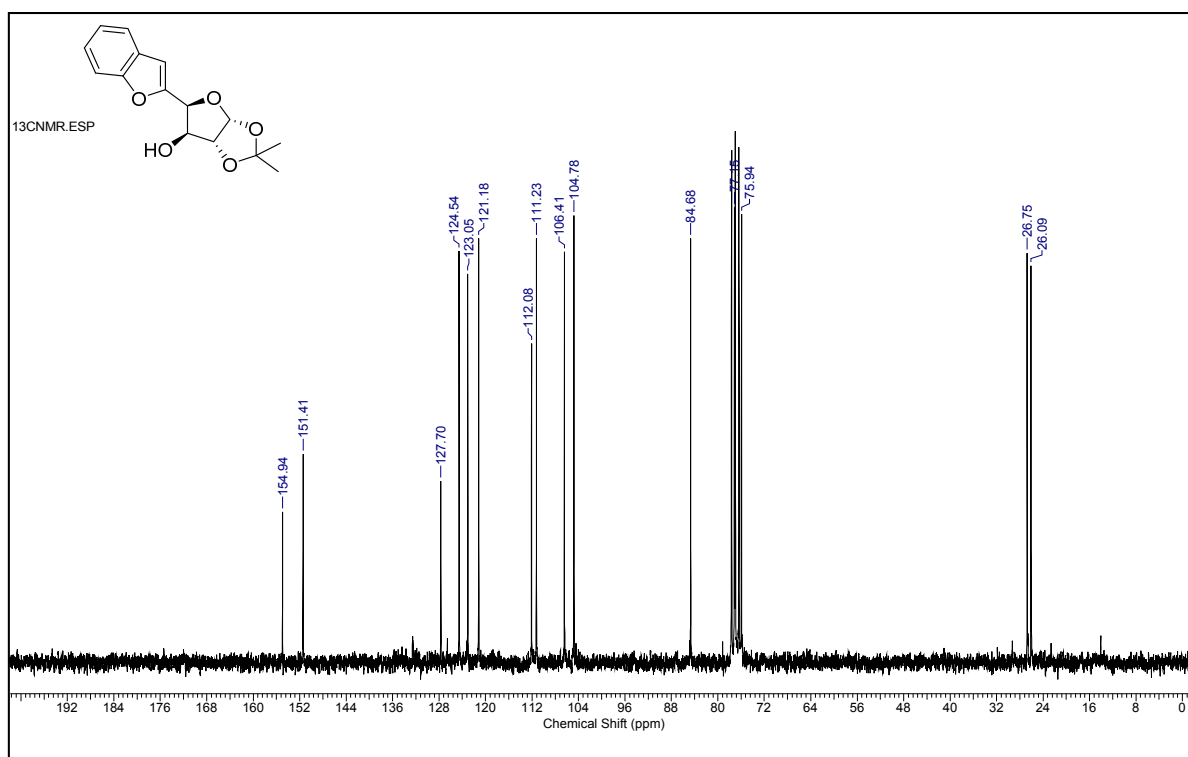
¹H NMR Spectrum of **13bc** in CDCl₃ (200 MHz)



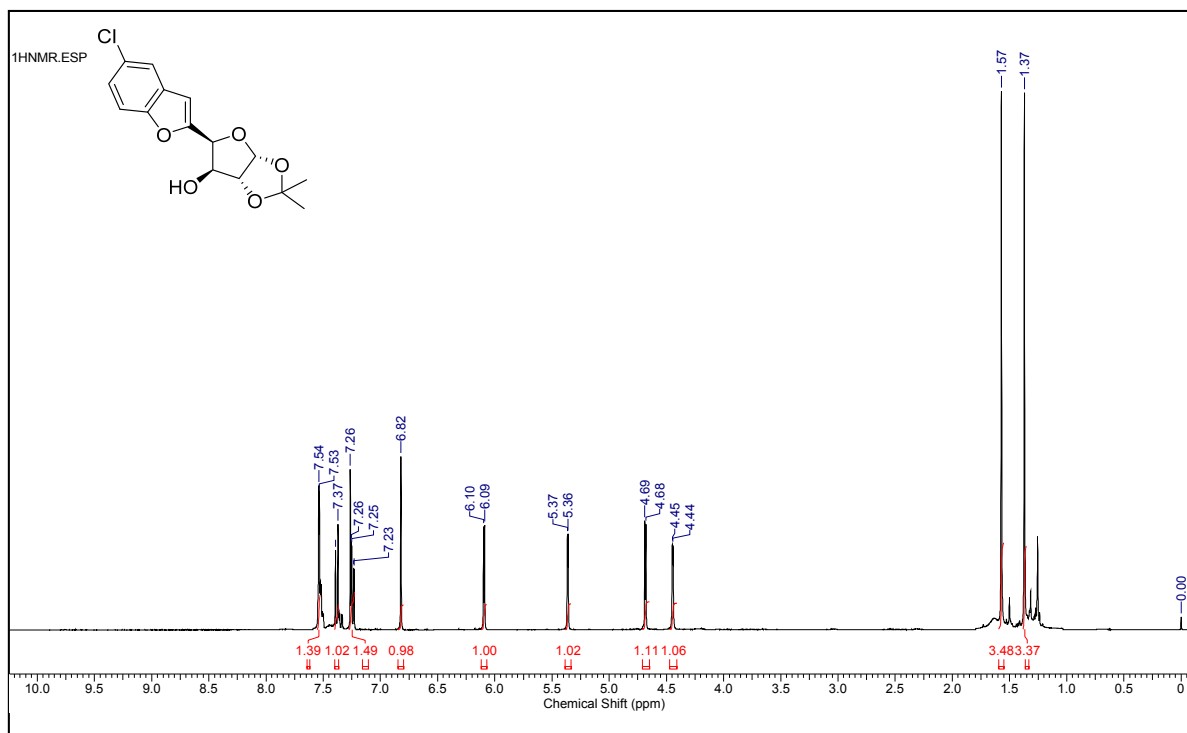
¹³C NMR Spectrum of **13bc** in CDCl₃ (50 MHz)



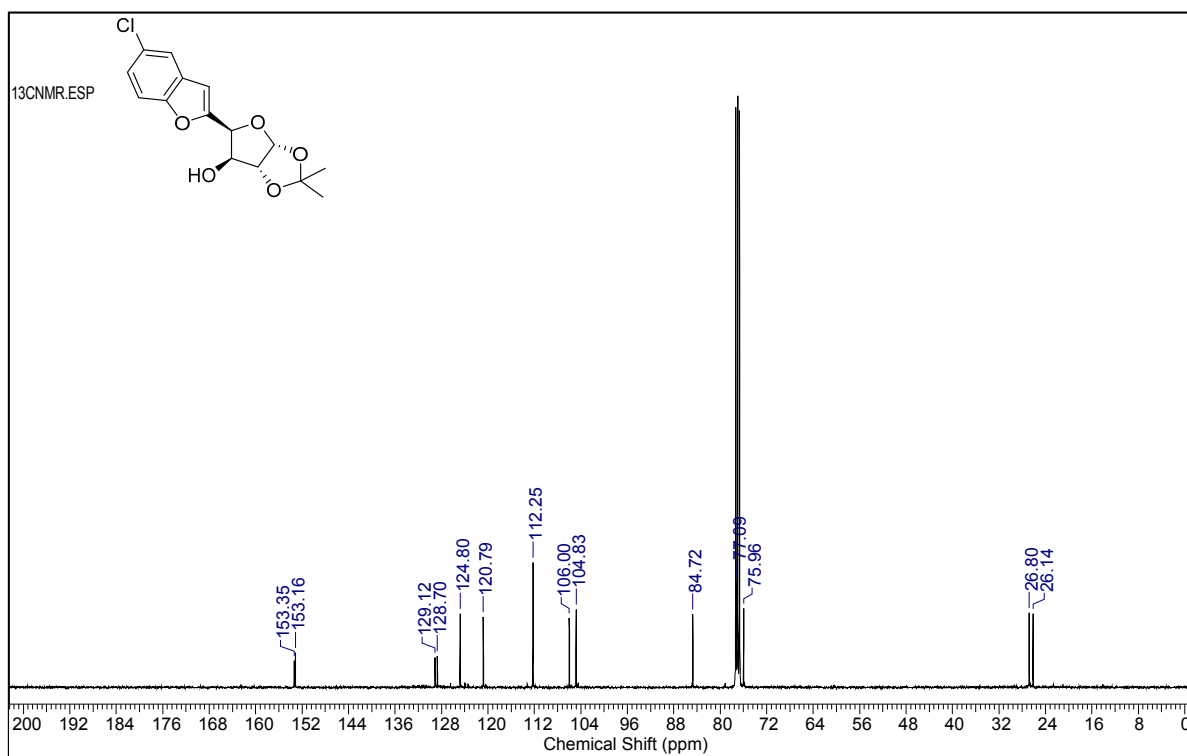
¹H NMR Spectrum of **13ca** in CDCl₃ (200 MHz)



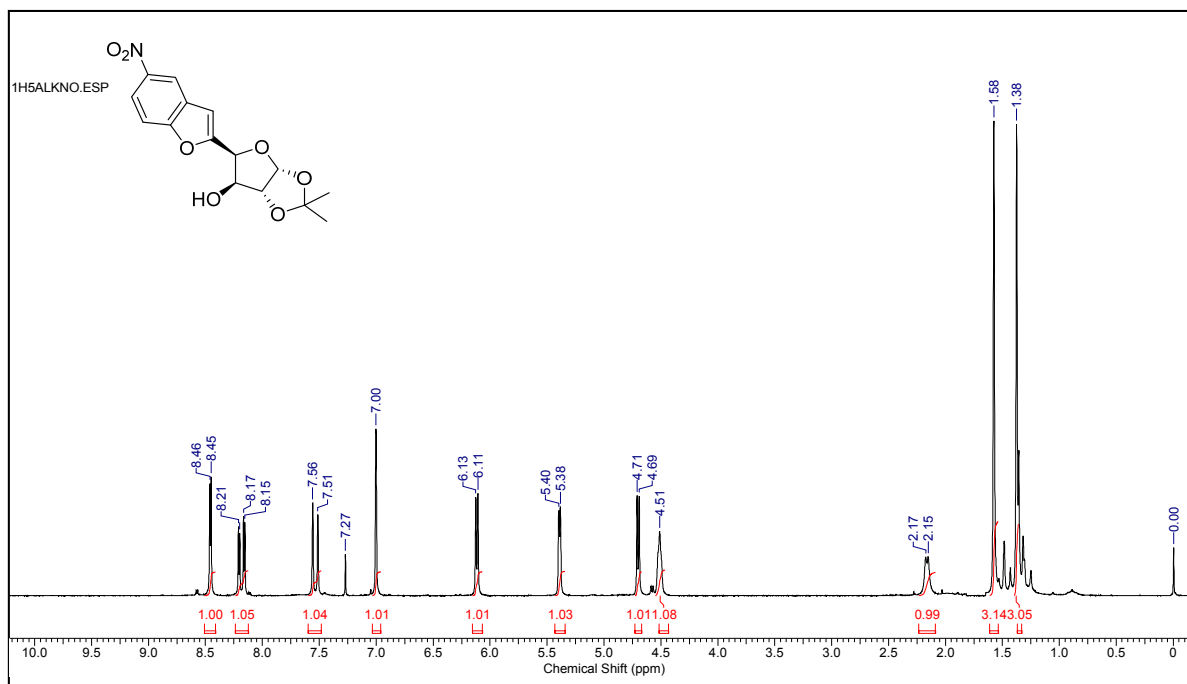
¹³C NMR Spectrum of **13ca** in CDCl₃ (50 MHz)



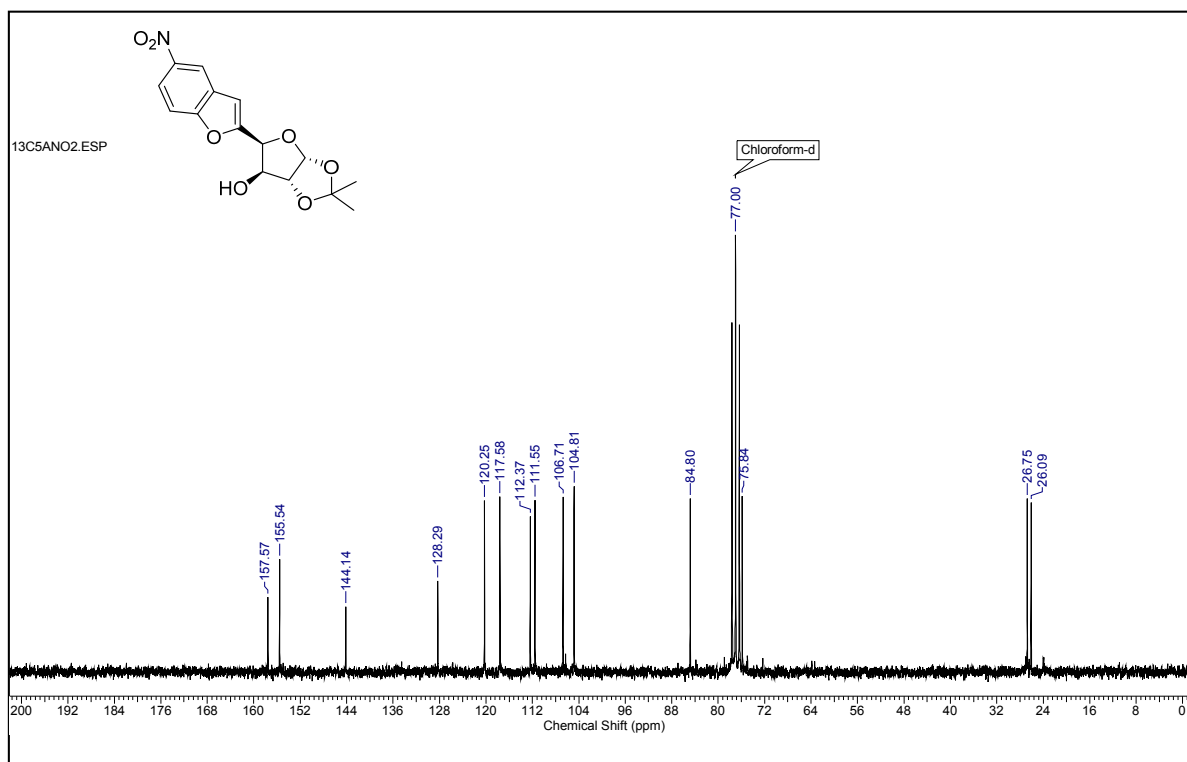
¹H NMR Spectrum of **13cb** in CDCl₃ (200 MHz)



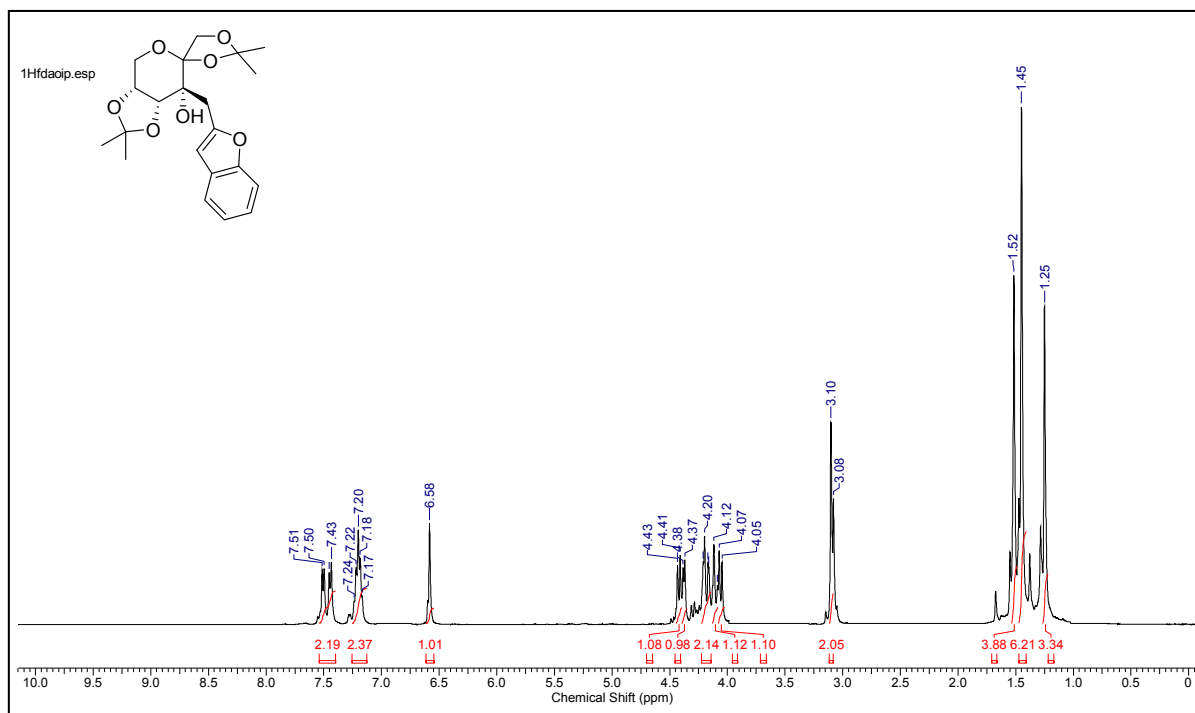
¹³C NMR Spectrum of **13cb** in CDCl₃ (50 MHz)



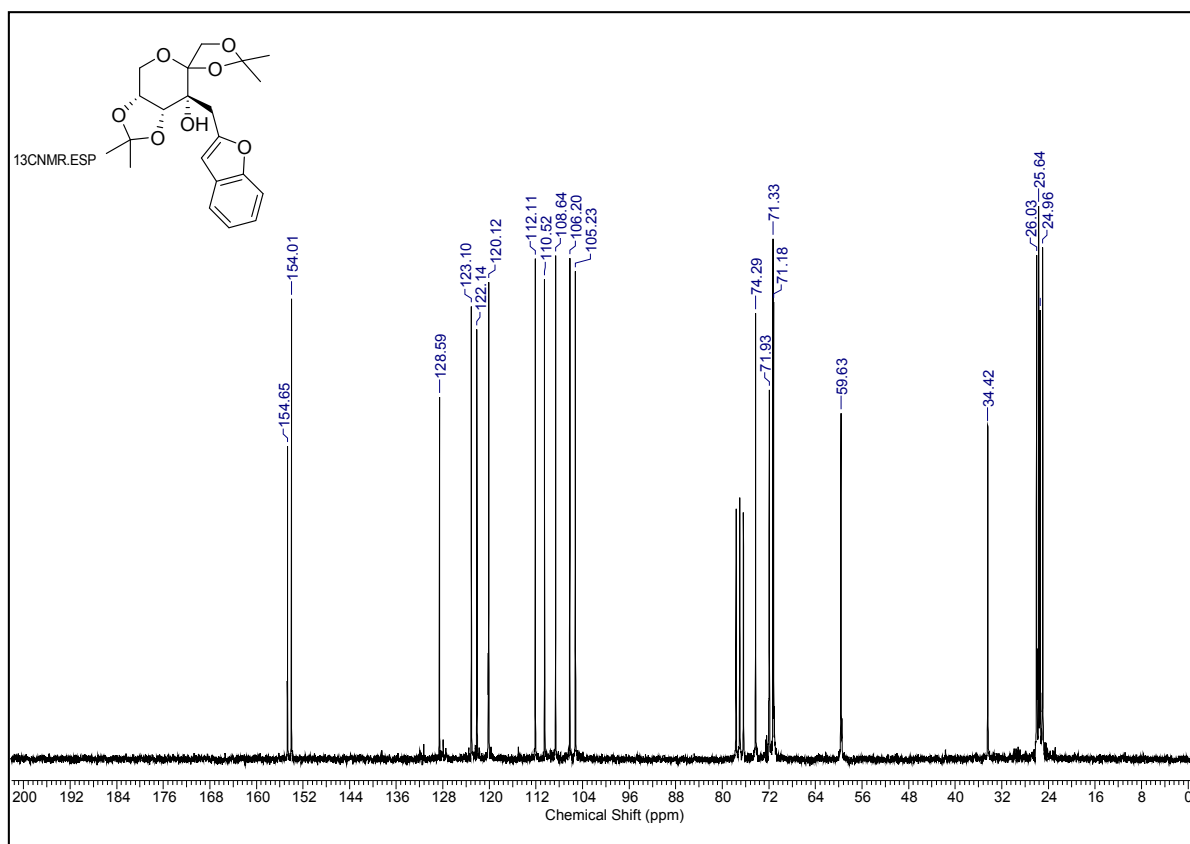
¹H NMR Spectrum of **13cc** in CDCl₃ (200 MHz)



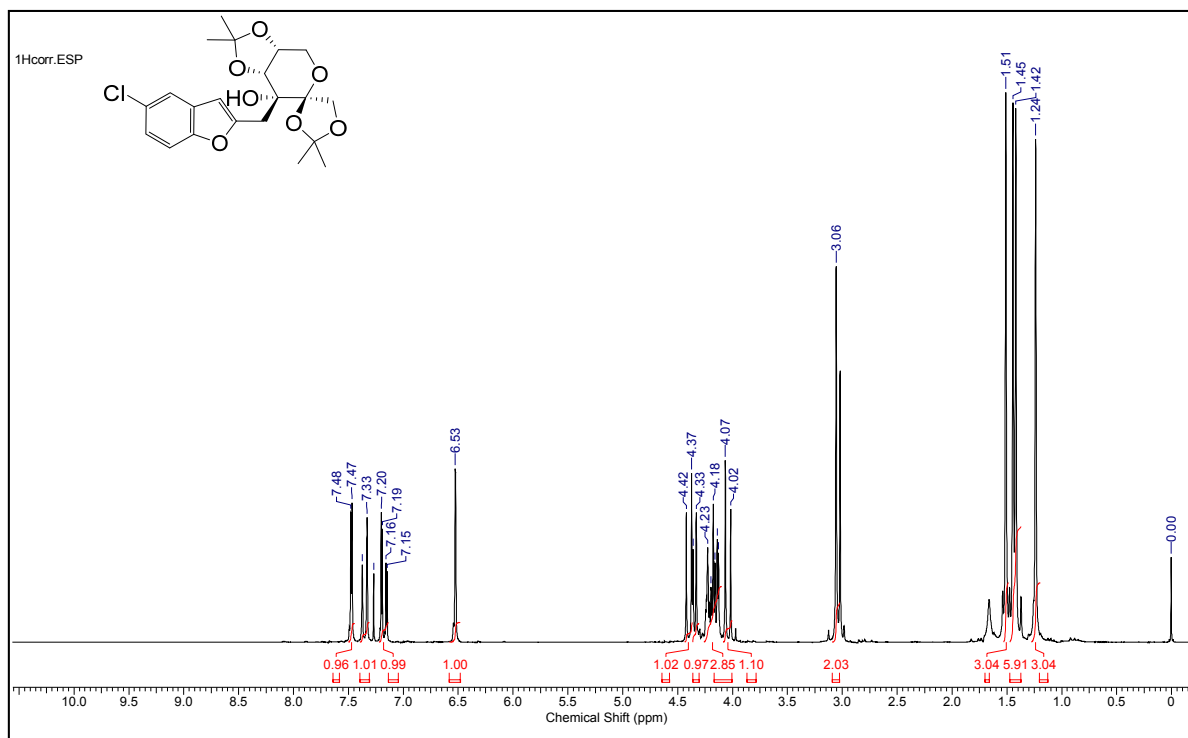
¹³C NMR Spectrum of **13cc** in CDCl₃ (50 MHz)



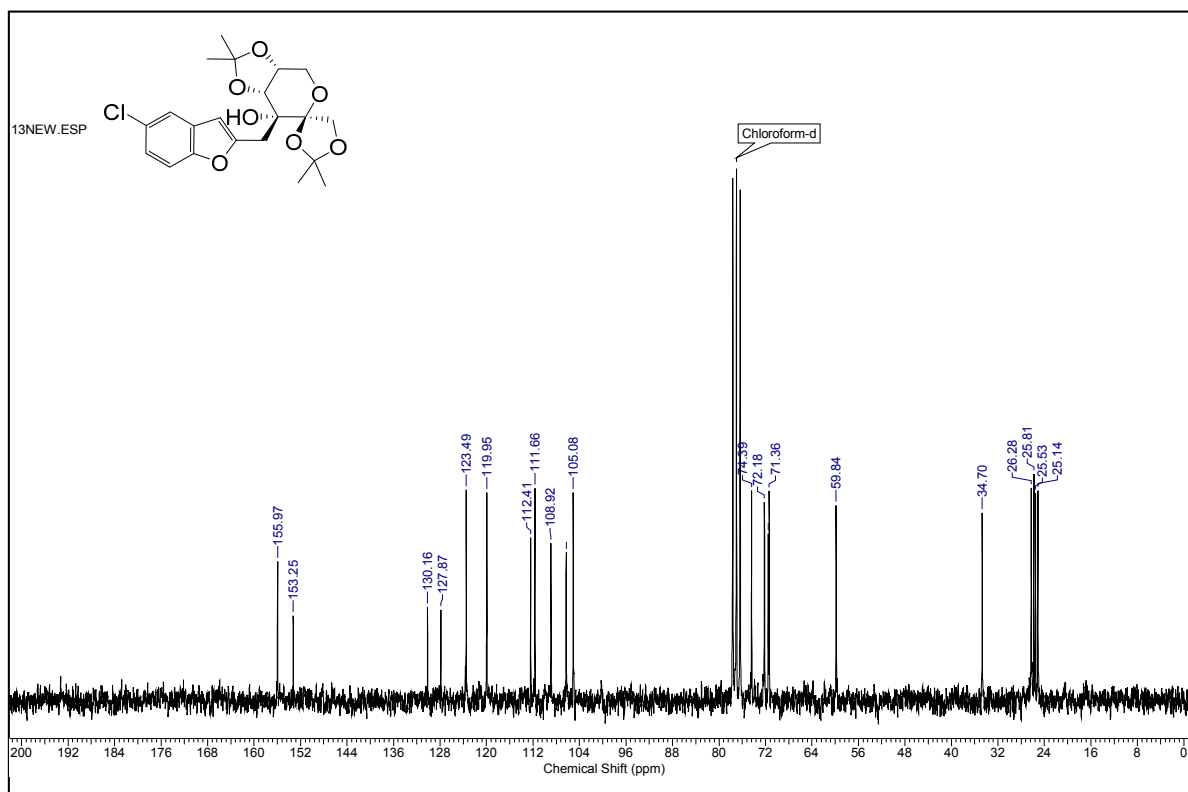
¹H NMR Spectrum of **13da** in CDCl₃ (200 MHz)



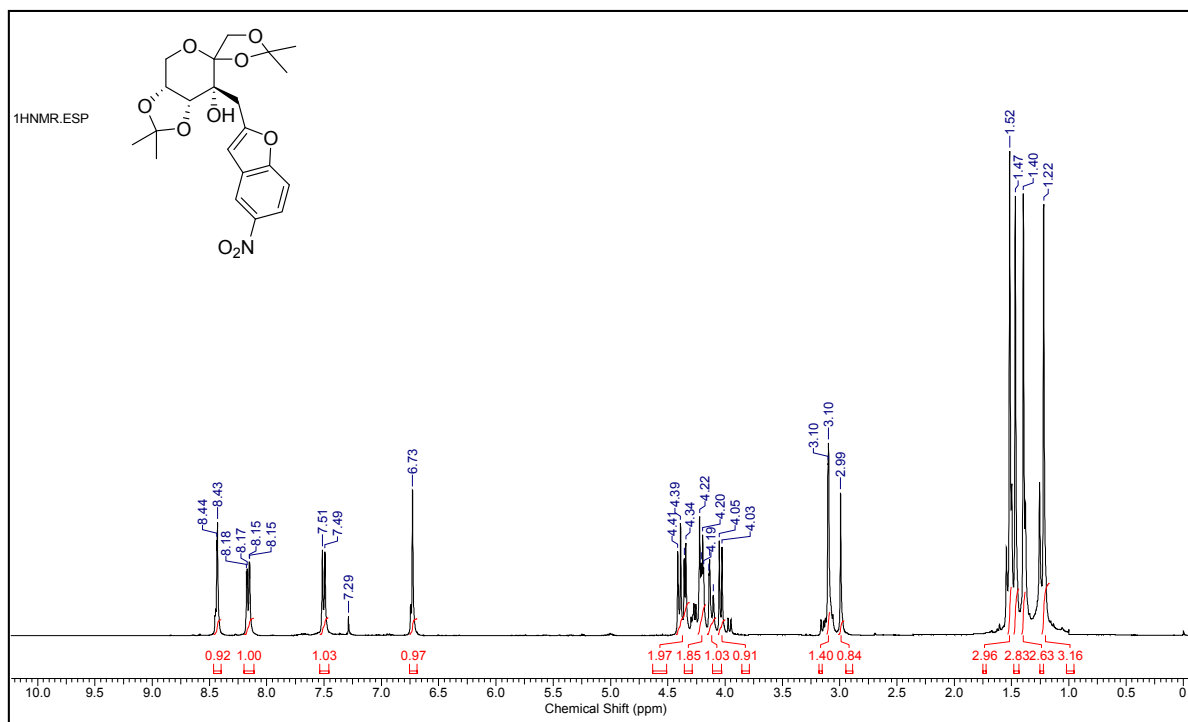
¹³C NMR Spectrum of **13da** in CDCl₃ (50 MHz)



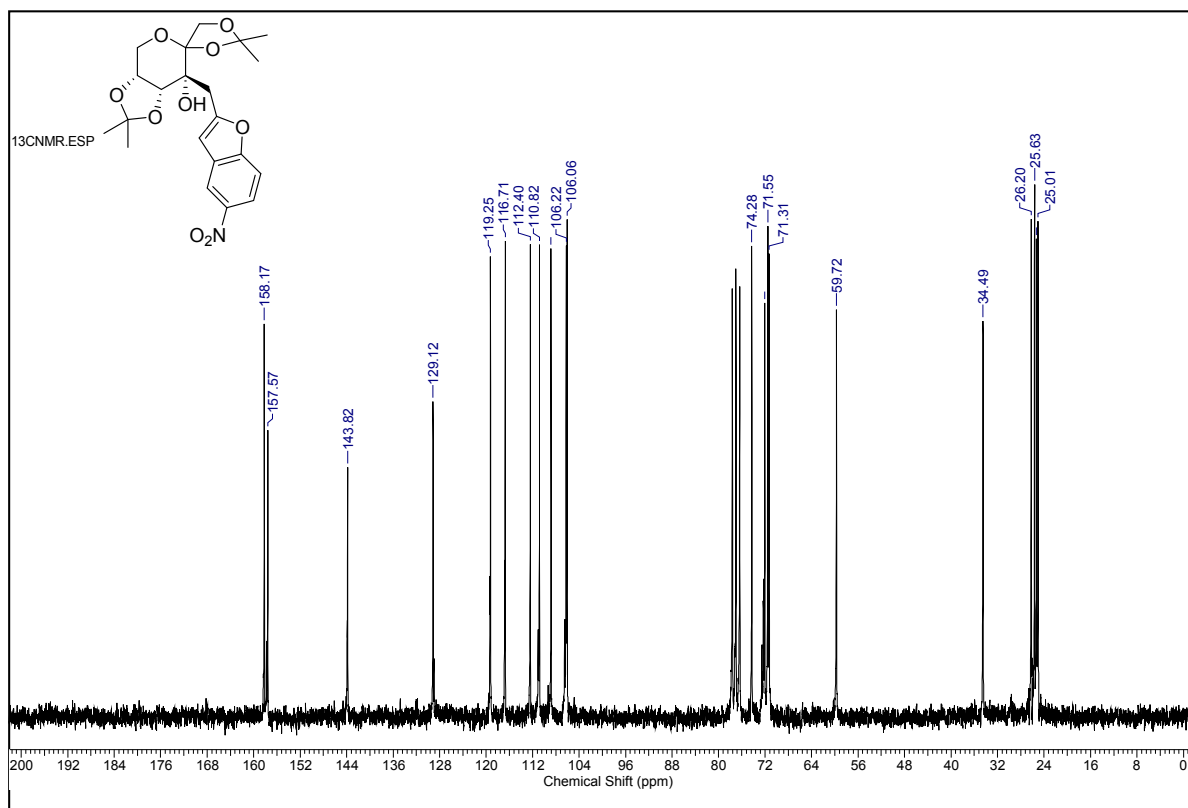
^1H NMR Spectrum of **13db** in CDCl_3 (200 MHz)



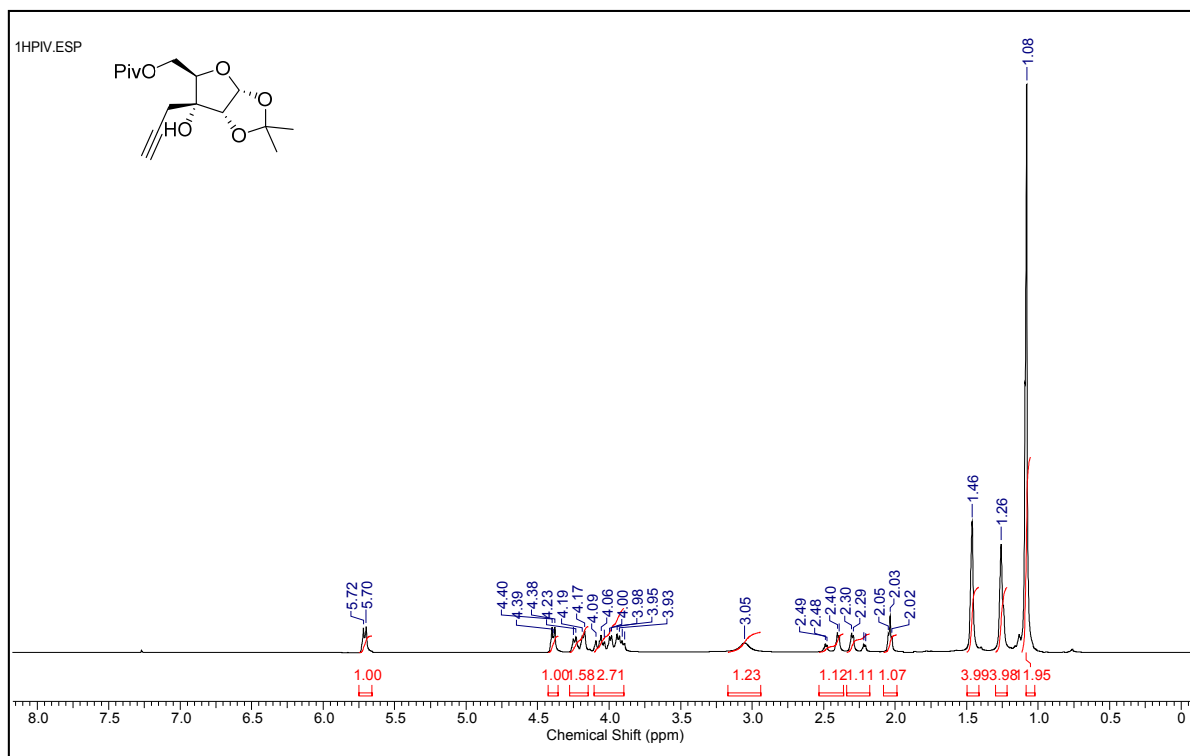
^{13}C NMR Spectrum of **13db** in CDCl_3 (50 MHz)



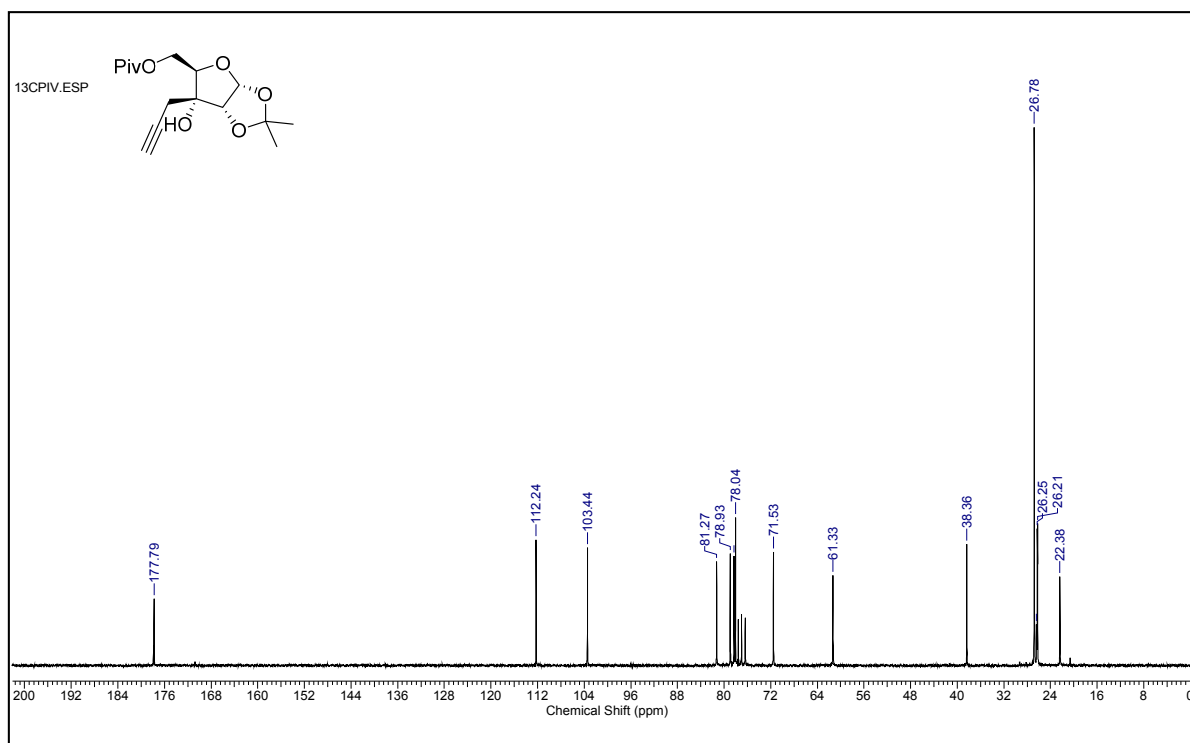
¹H NMR Spectrum of **13dc** in CDCl₃ (200 MHz)



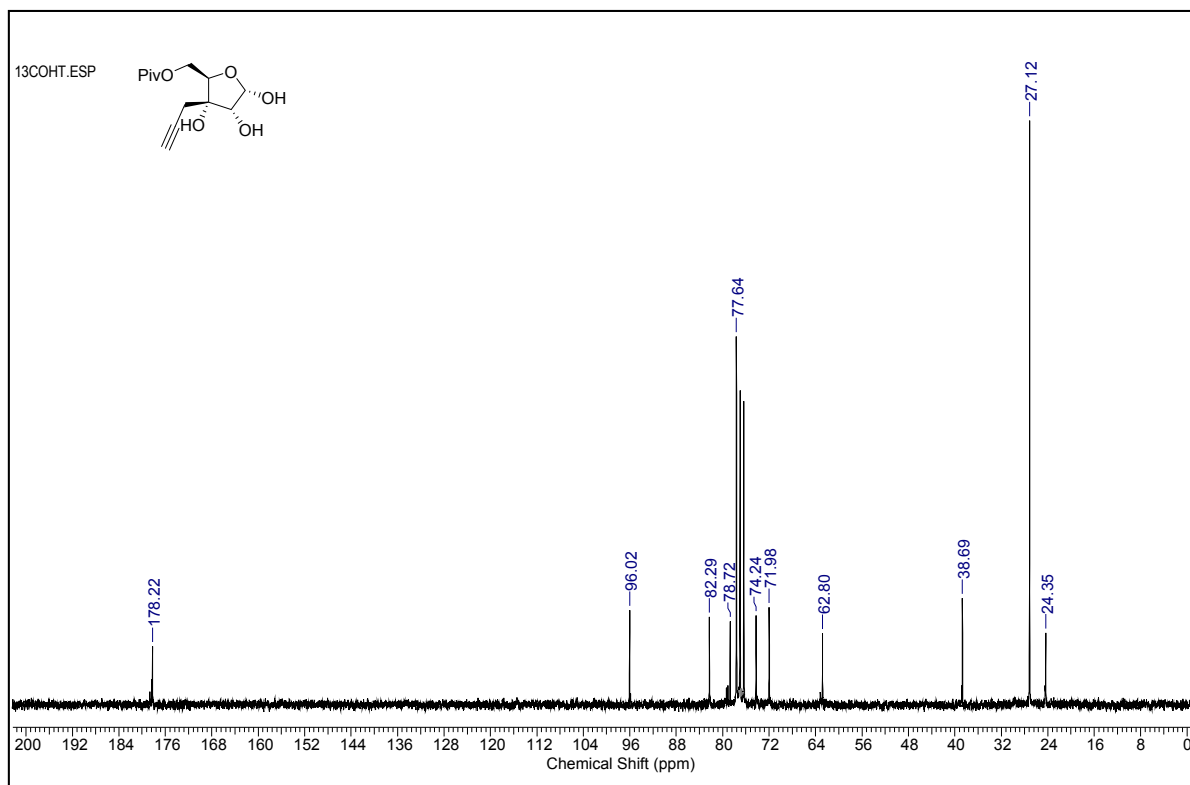
¹³C NMR Spectrum of **13db** in CDCl₃ (50 MHz)



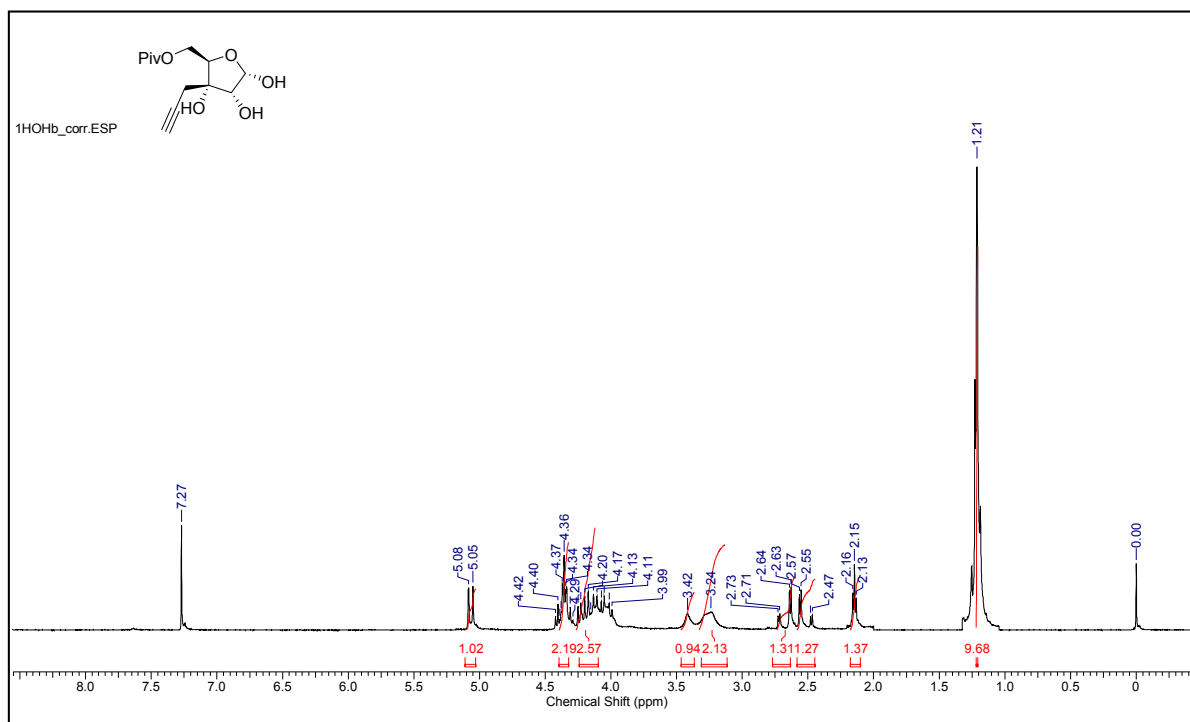
^1H NMR Spectrum of **16** in CDCl_3 (200 MHz)



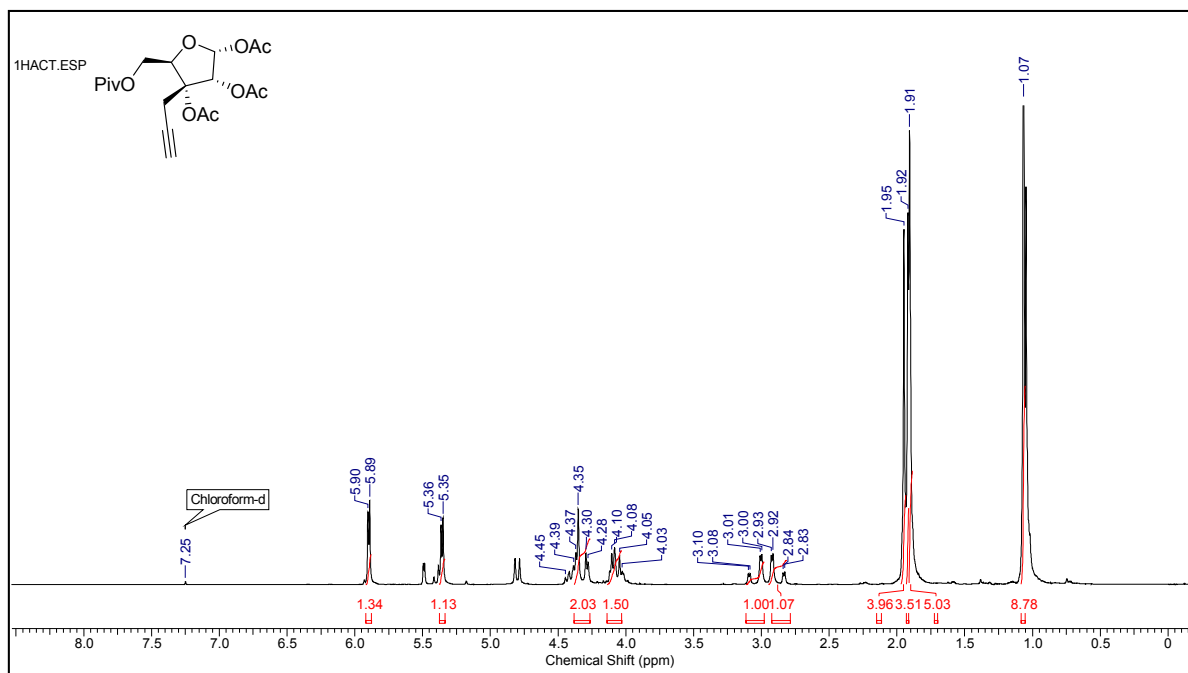
^{13}C NMR Spectrum of **16** in CDCl_3 (50 MHz)



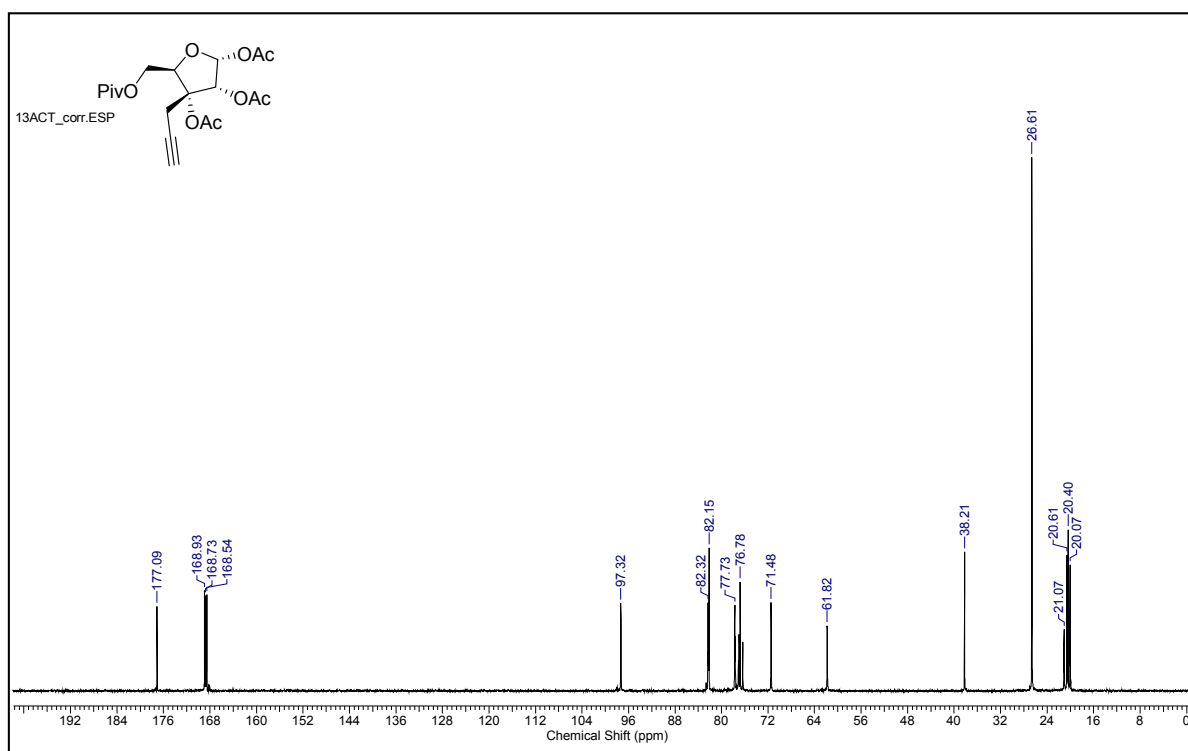
¹H NMR Spectrum of **17** in CDCl₃ (200 MHz)



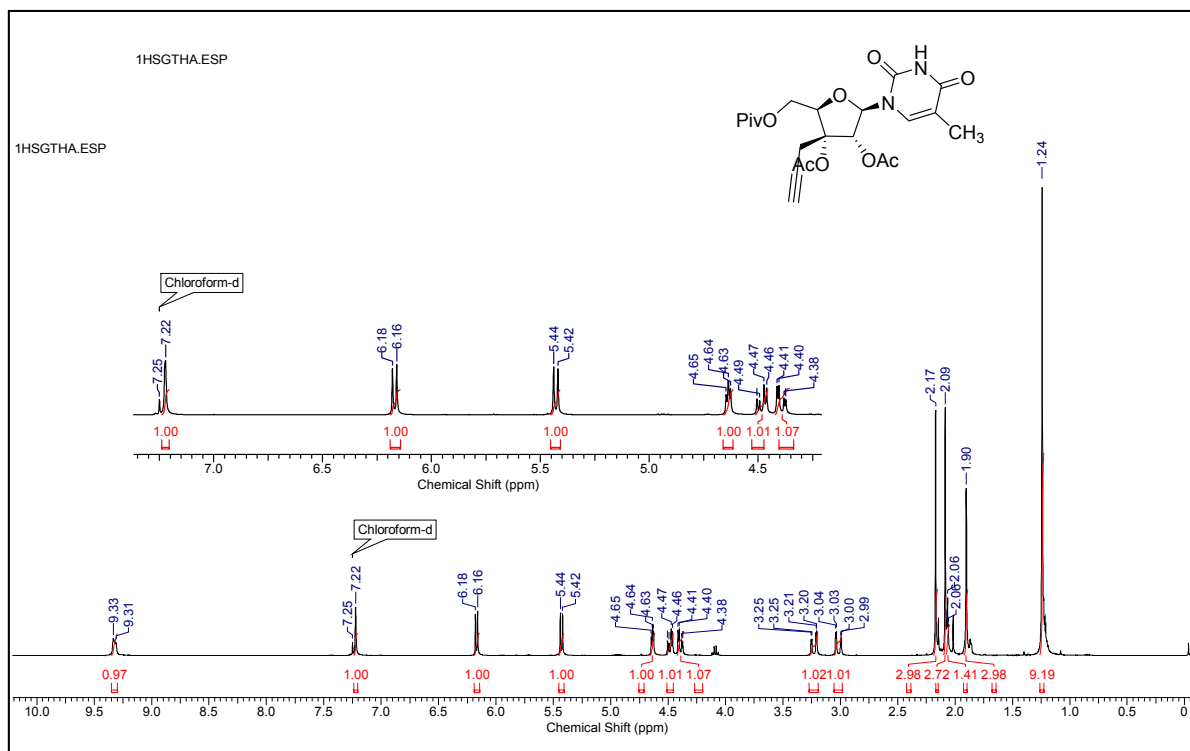
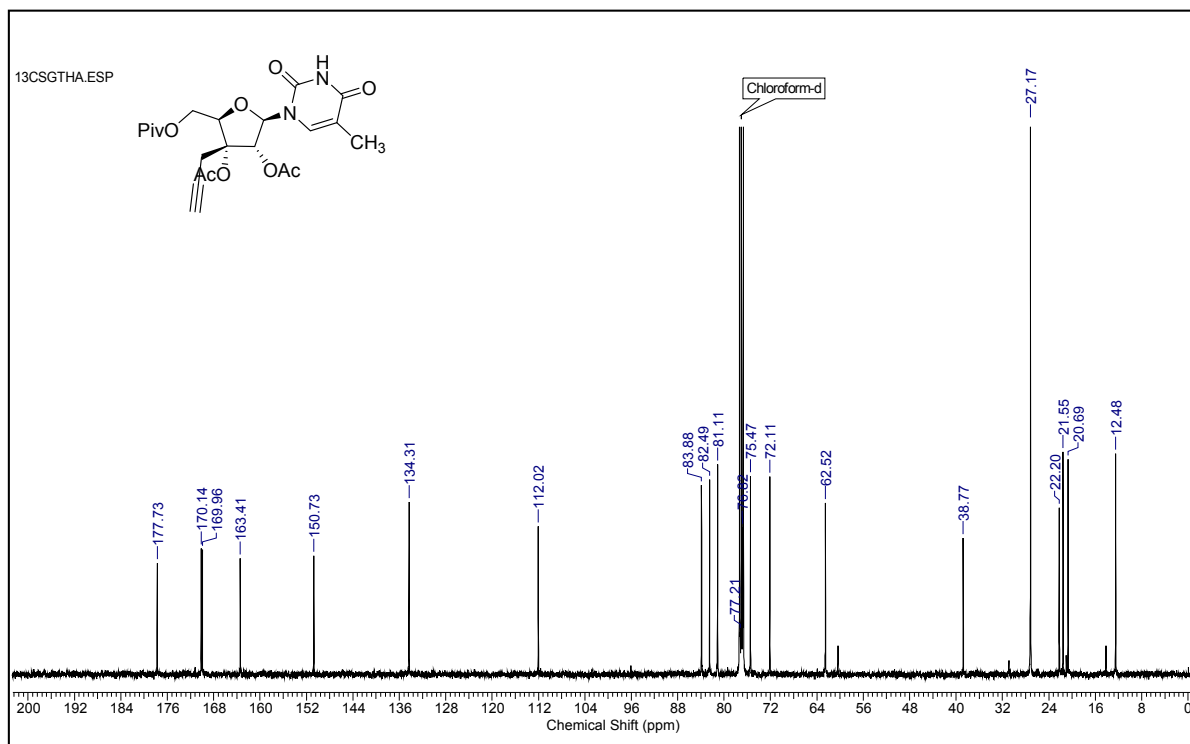
¹³C NMR Spectrum of **17** in CDCl₃ (50 MHz)

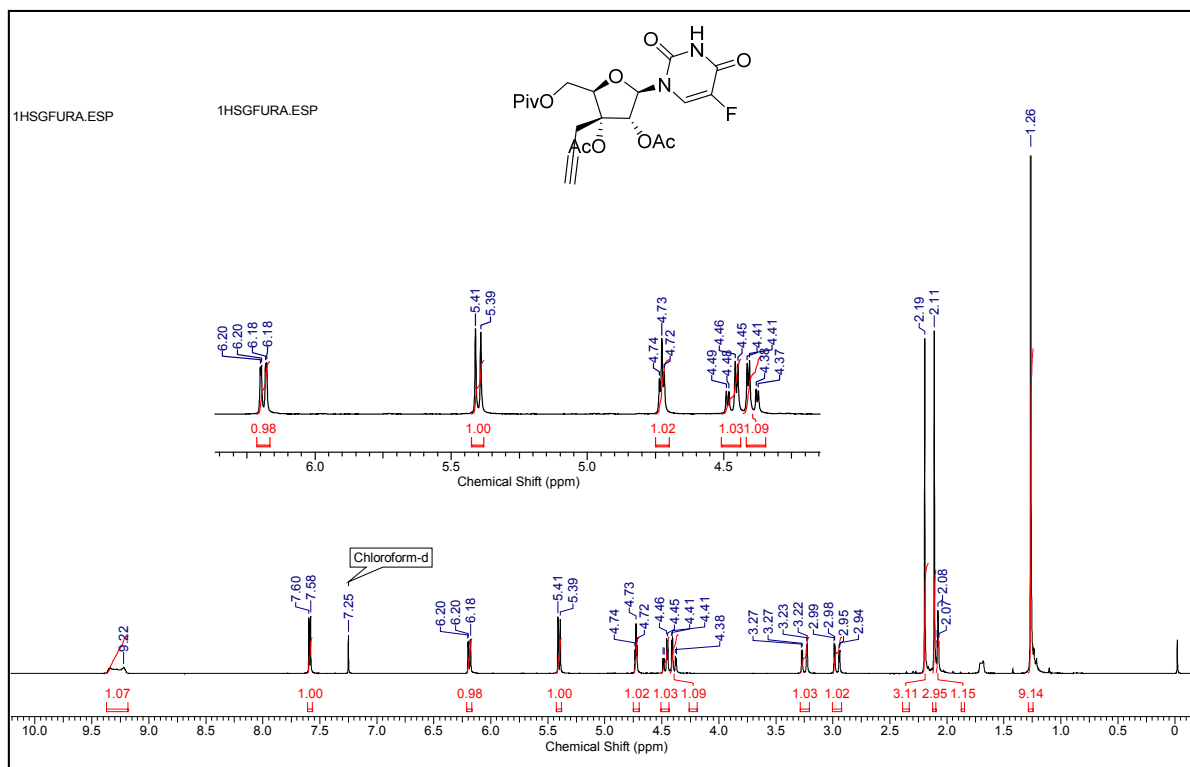


¹H NMR Spectrum of **18** in CDCl₃ (200 MHz)

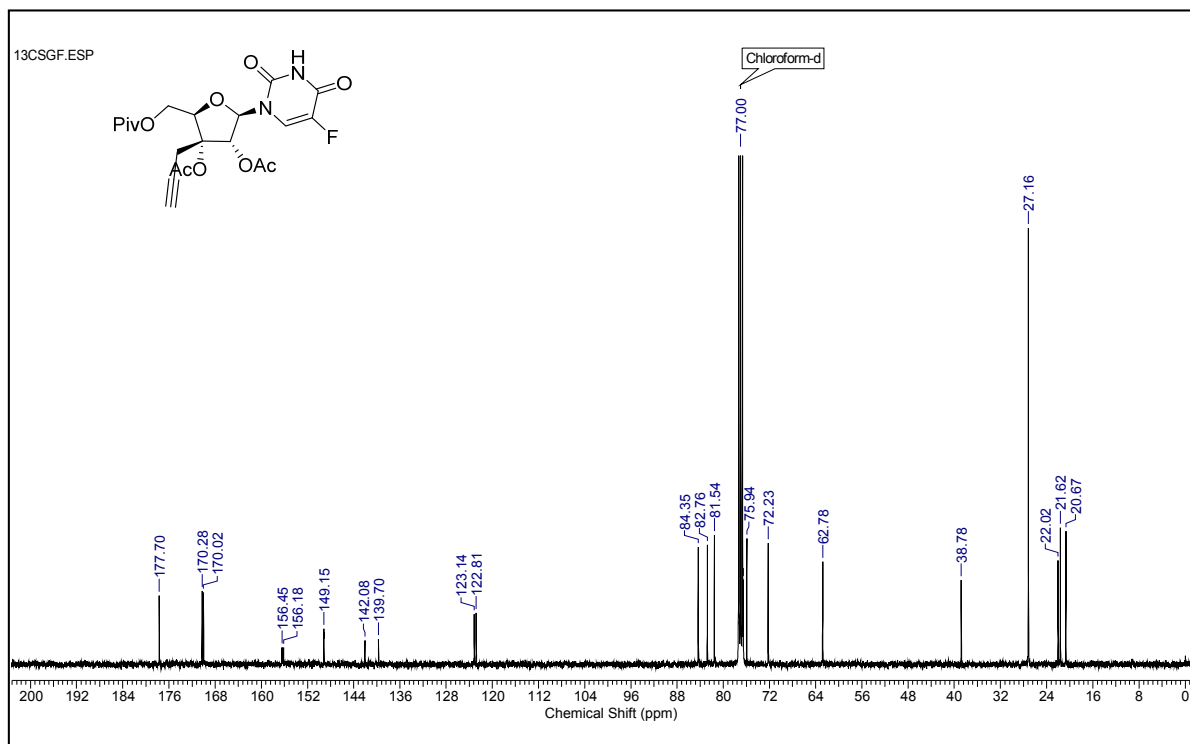


¹³C NMR Spectrum of **18** in CDCl₃ (50 MHz)


 ^1H NMR Spectrum of **15e** in CDCl_3 (200 MHz)

 ^{13}C NMR Spectrum of **15e** in CDCl_3 (50 MHz)



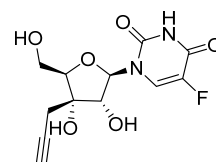
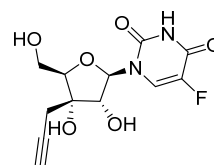
^1H NMR Spectrum of **15f** in CDCl_3 (200 MHz)

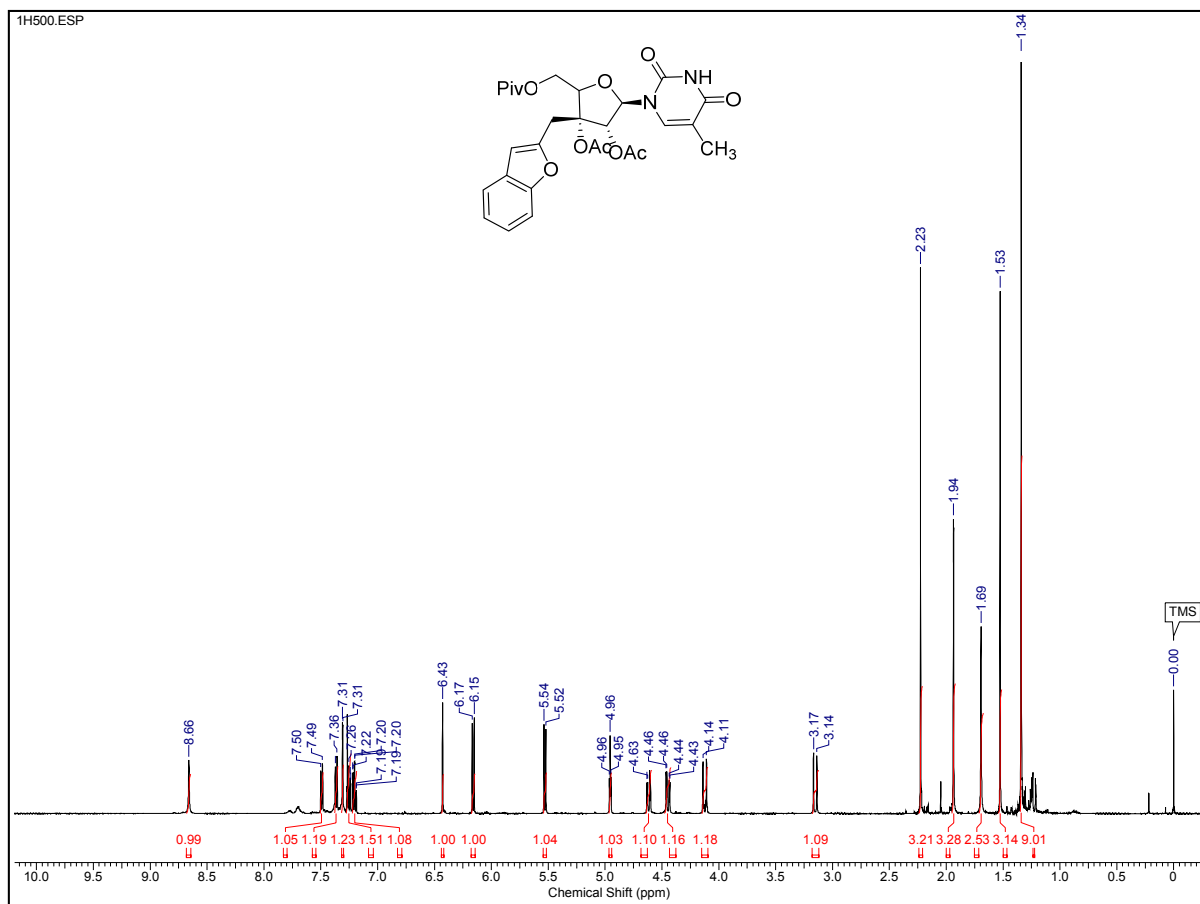


^{13}C NMR Spectrum of **15f** in CDCl_3 (50 MHz)

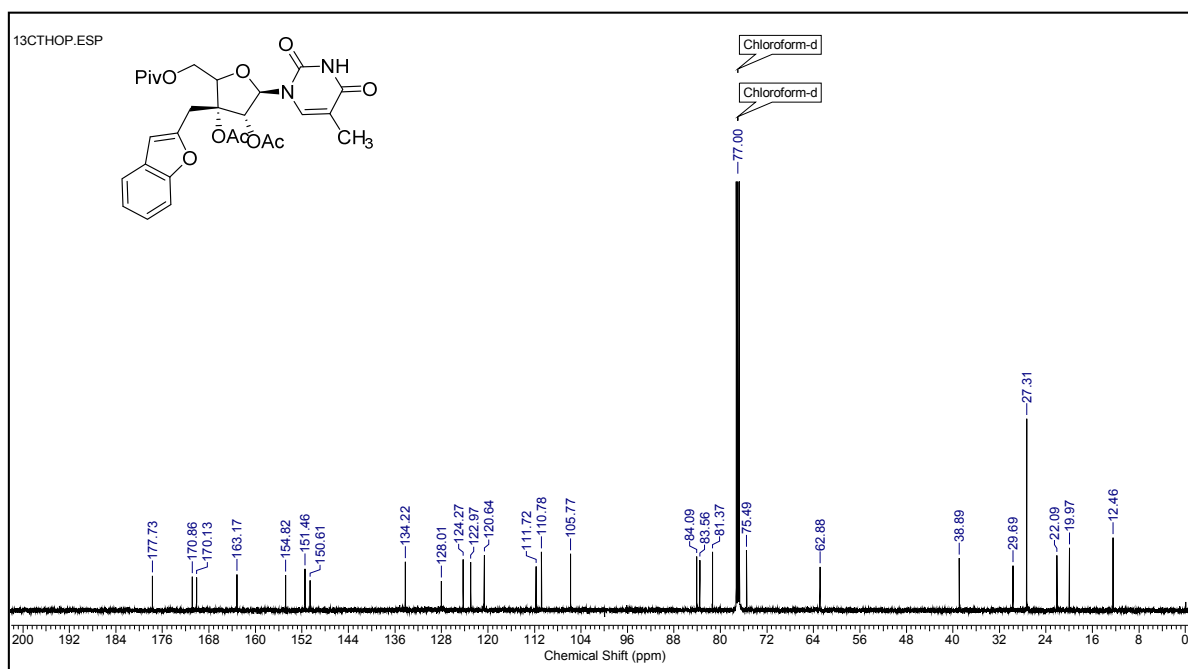
^1H NMR Spectrum of **15f** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (200 MHz)

^{13}C NMR Spectrum of **15f** in $\text{CDCl}_3 + \text{MeOH} (\text{D}_4)$ (50 MHz)

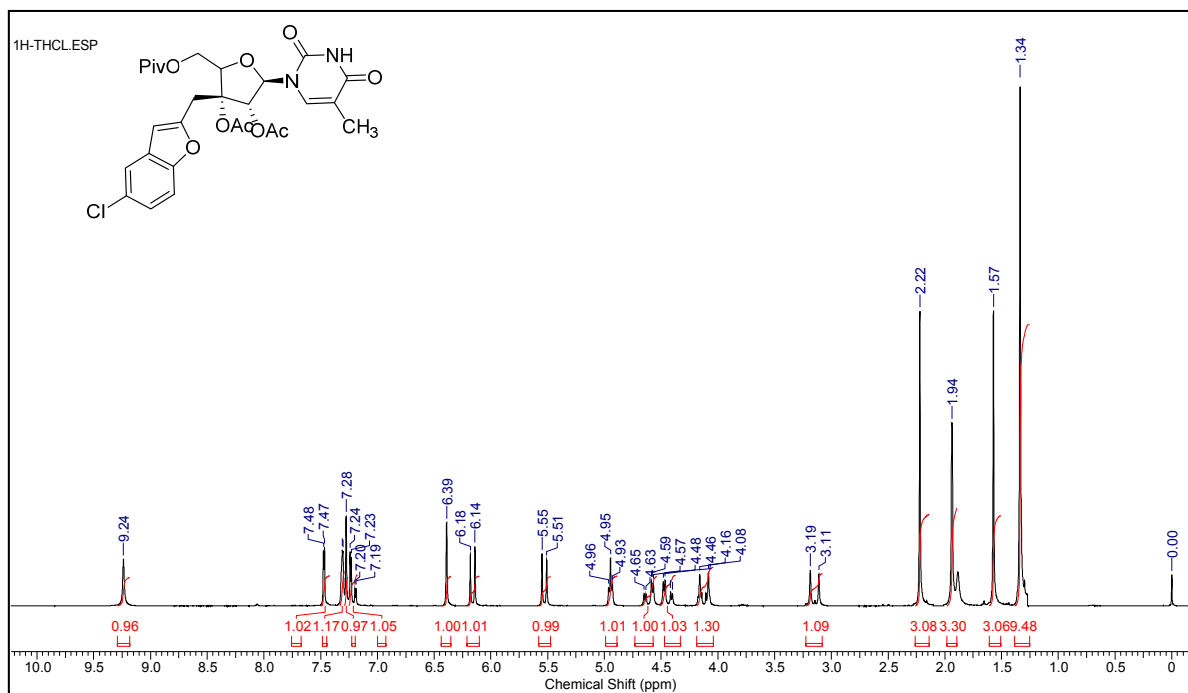




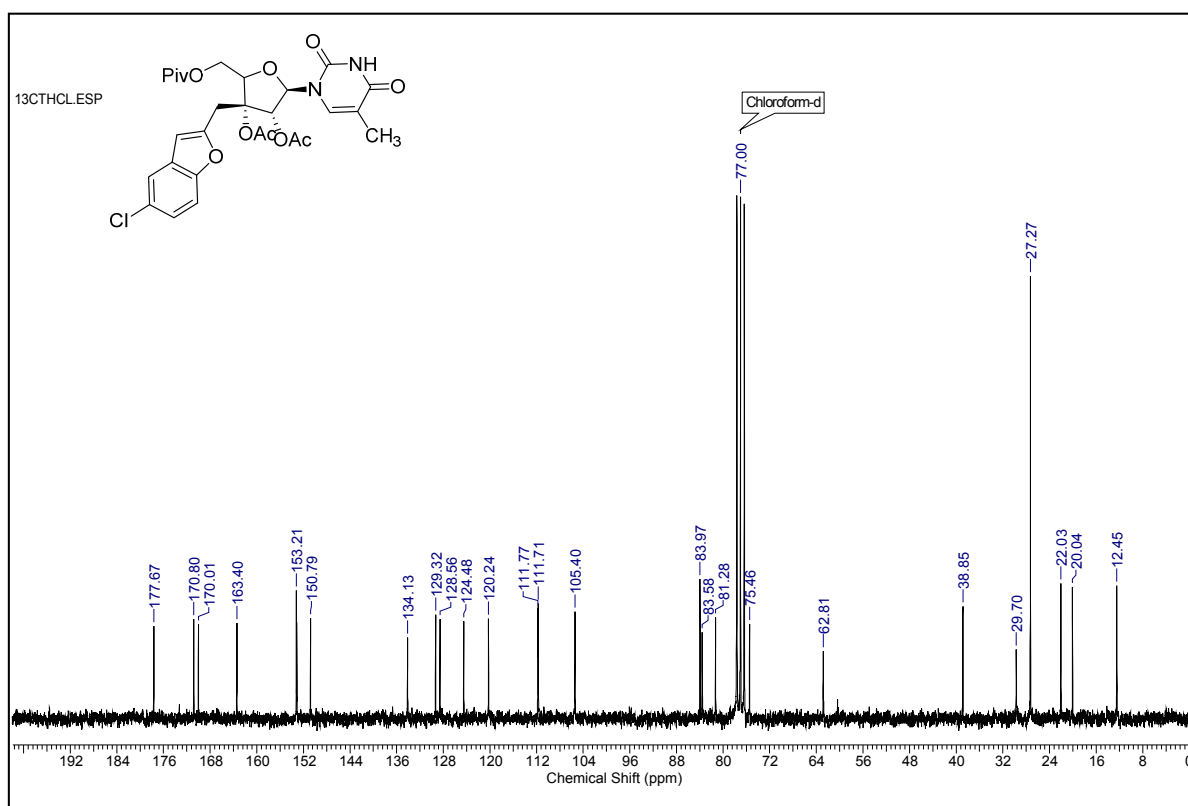
¹H NMR Spectrum of **13ea** in CDCl₃ (200 MHz)



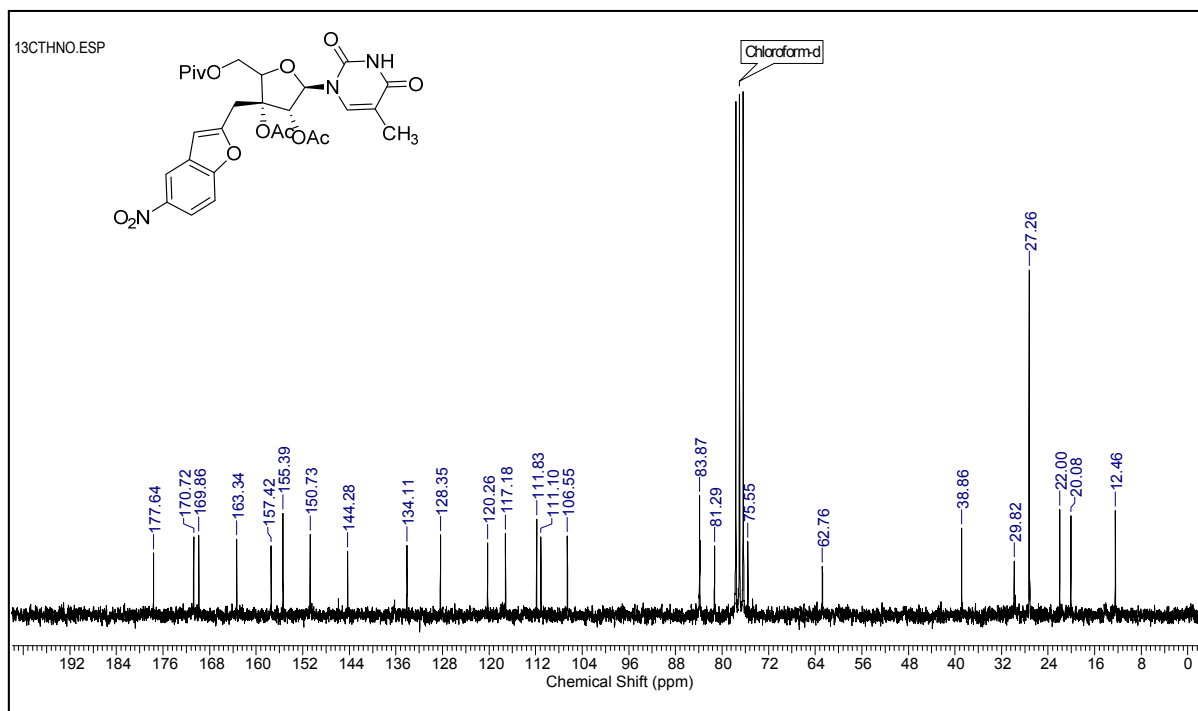
¹³C NMR Spectrum of **13ea** in CDCl₃ (50 MHz)



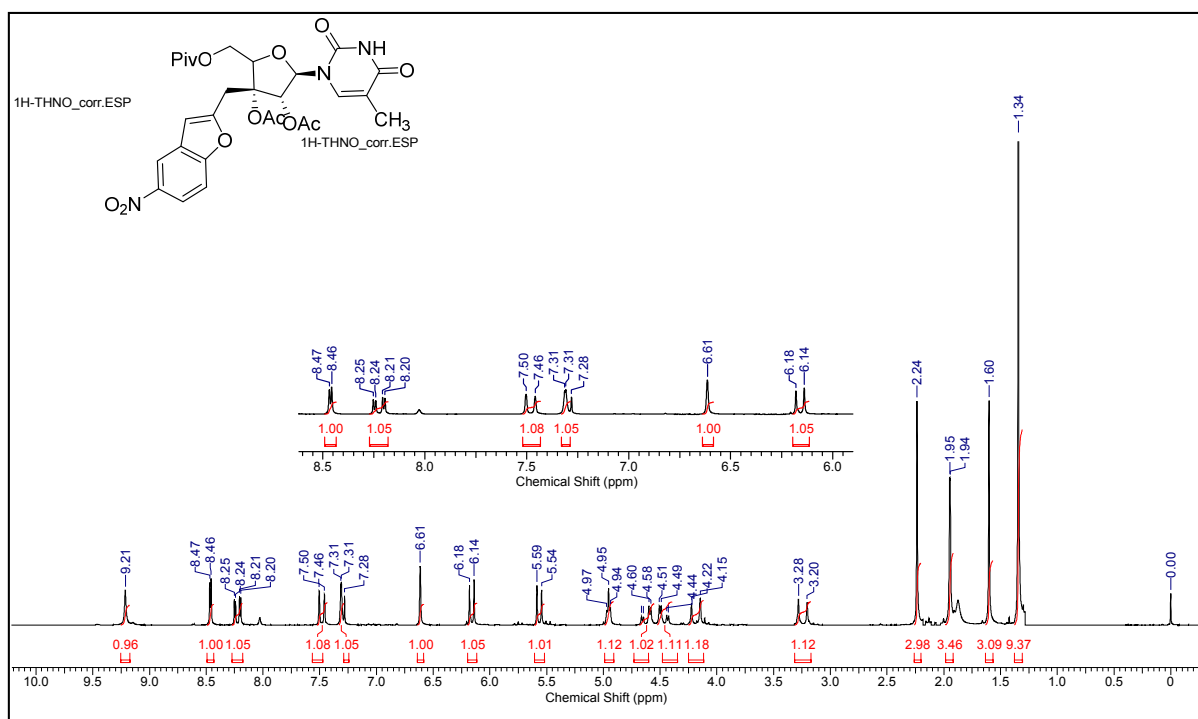
¹H NMR Spectrum of **13eb** in CDCl₃ (200 MHz)



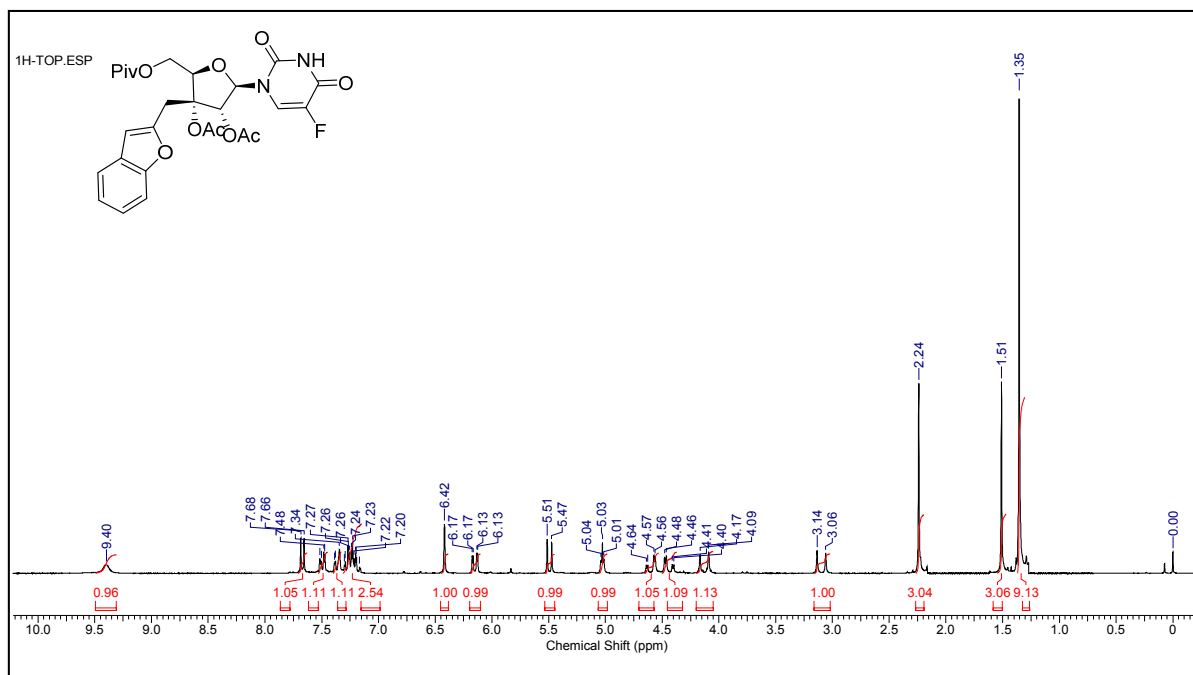
¹³C NMR Spectrum of **13eb** in CDCl₃ (50 MHz)



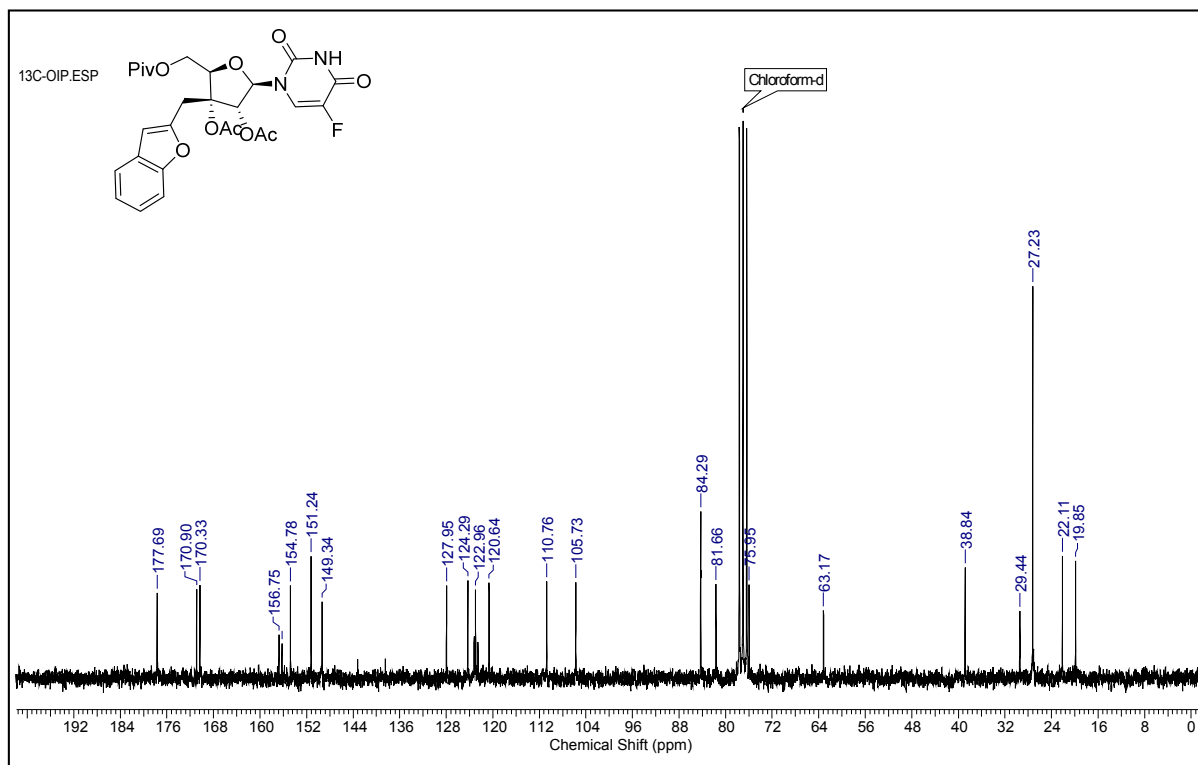
¹H NMR Spectrum of **13ec** in CDCl₃ (200 MHz)



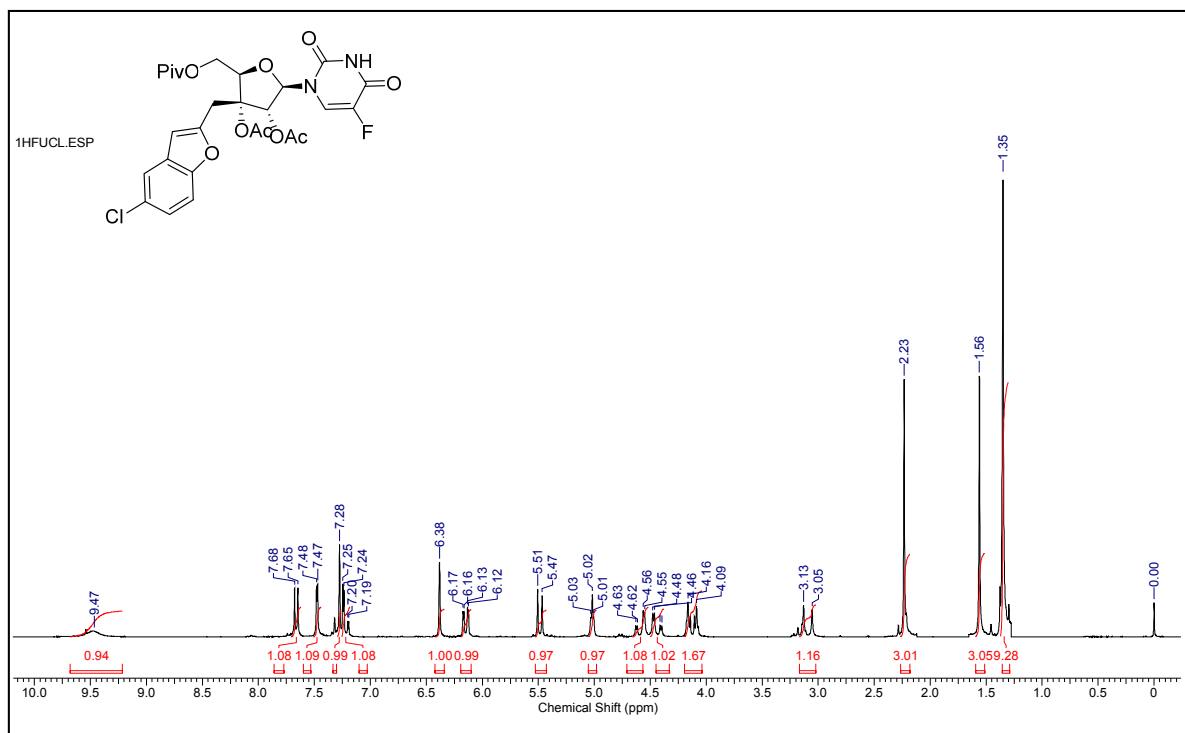
¹³C NMR Spectrum of **13ec** in CDCl₃ (50 MHz)



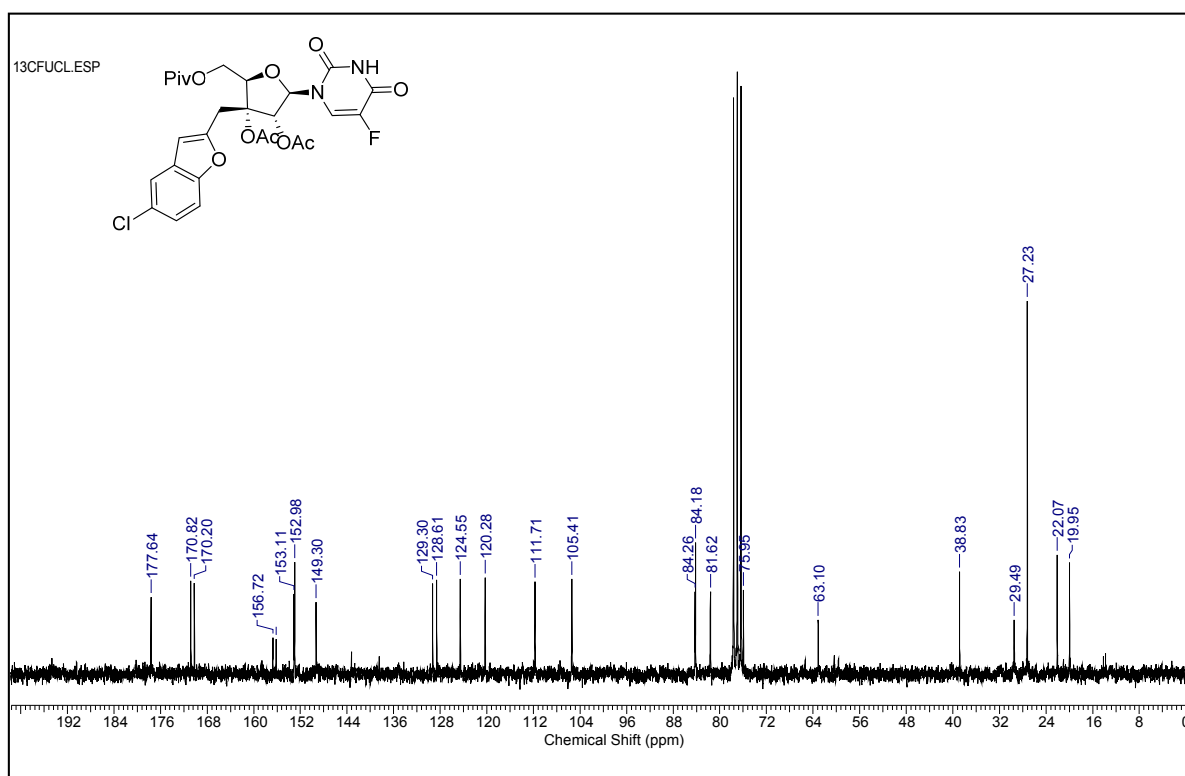
¹H NMR Spectrum of **13fa** in CDCl₃ (200 MHz)



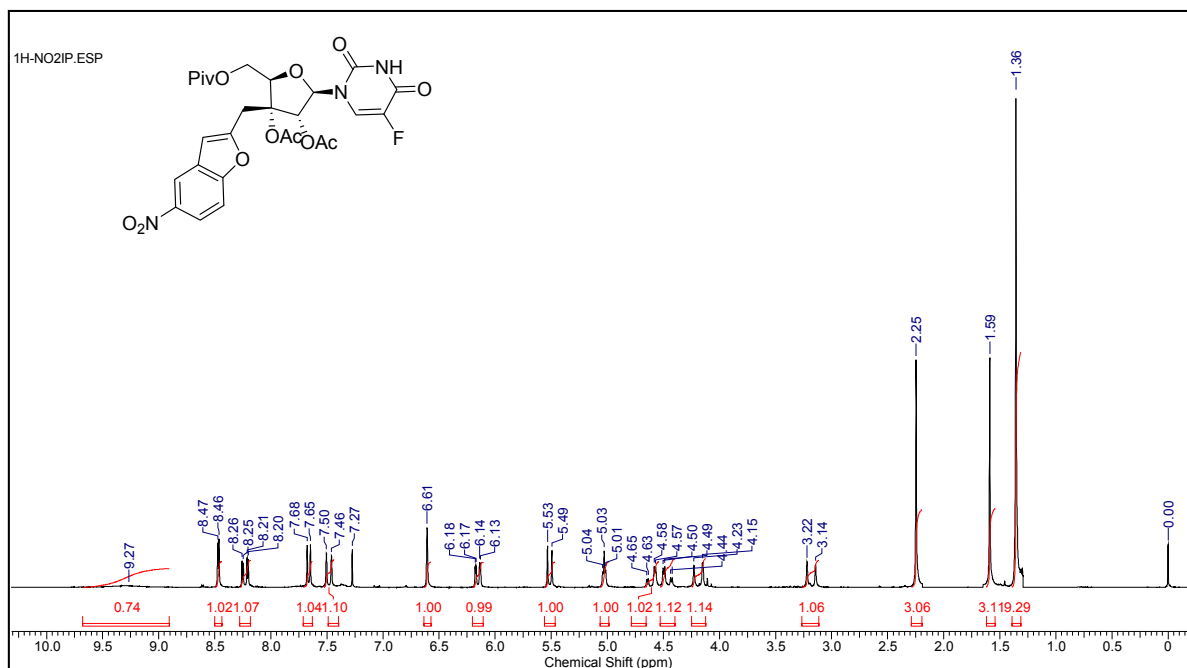
¹³C NMR Spectrum of **13fa** in CDCl₃ (50 MHz)



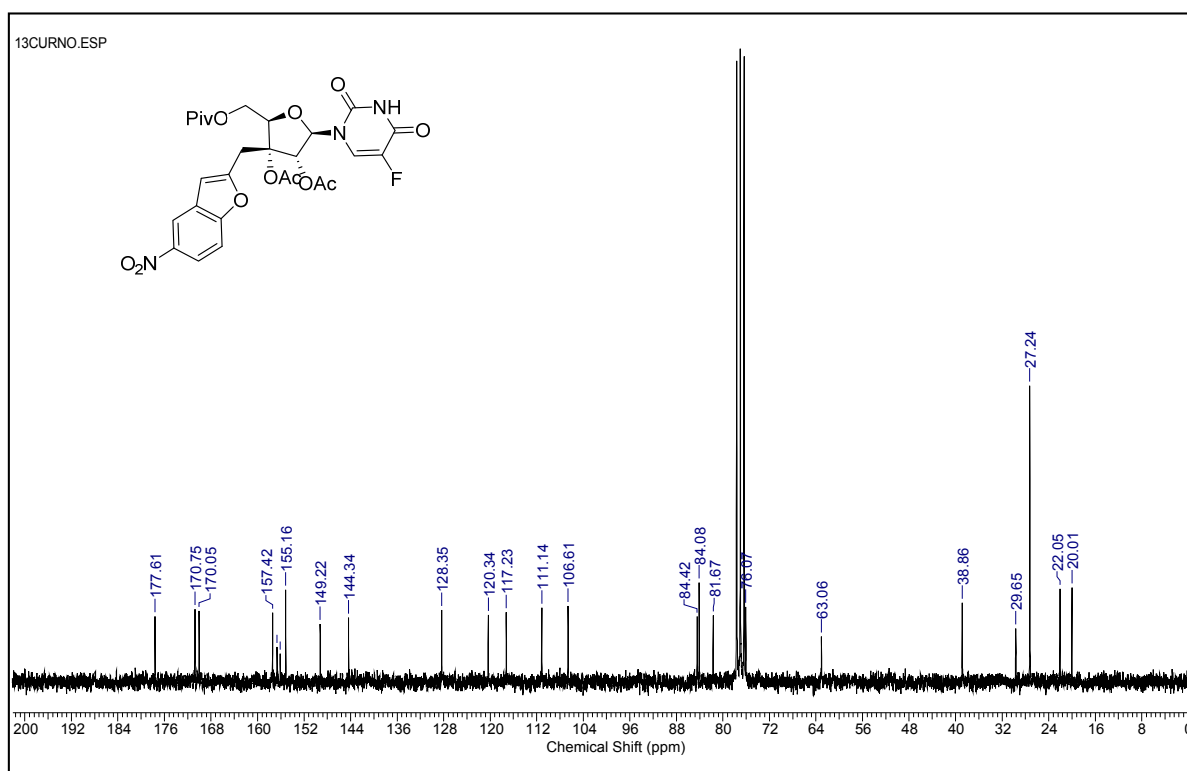
¹H NMR Spectrum of **13fb** in CDCl₃ (200 MHz)



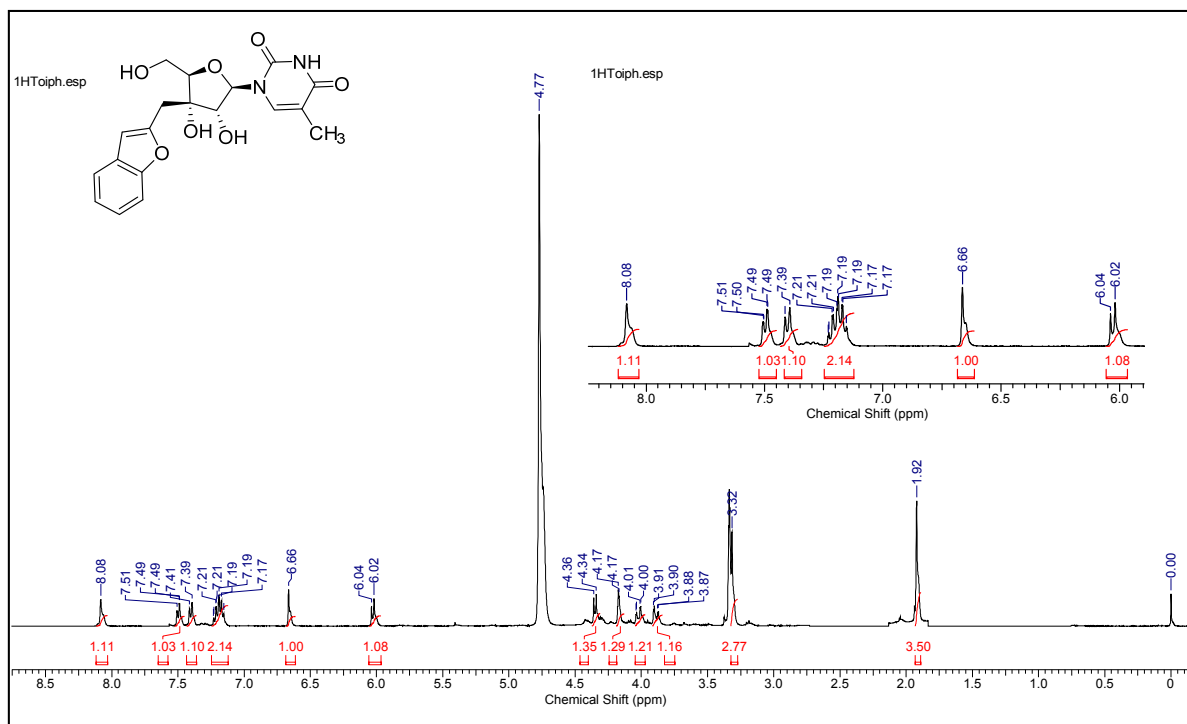
¹³C NMR Spectrum of **13fb** in CDCl₃ (50 MHz)



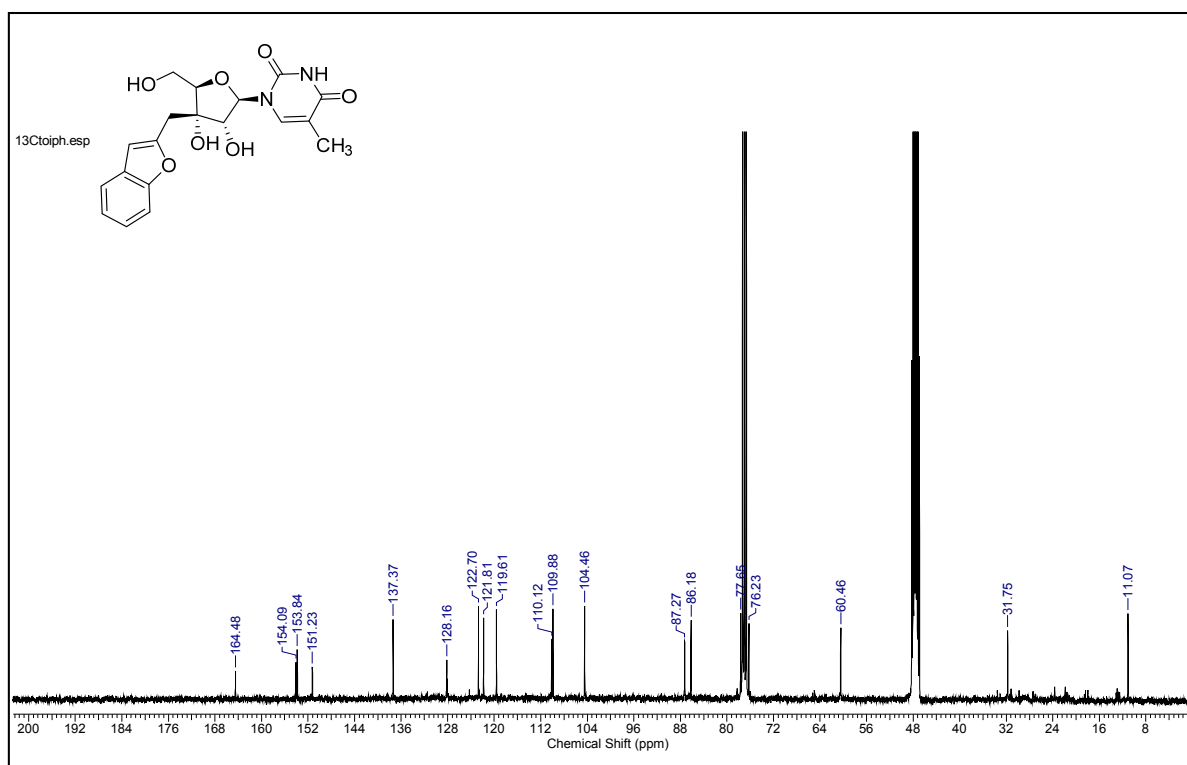
¹H NMR Spectrum of **13fc** in CDCl₃ (200 MHz)



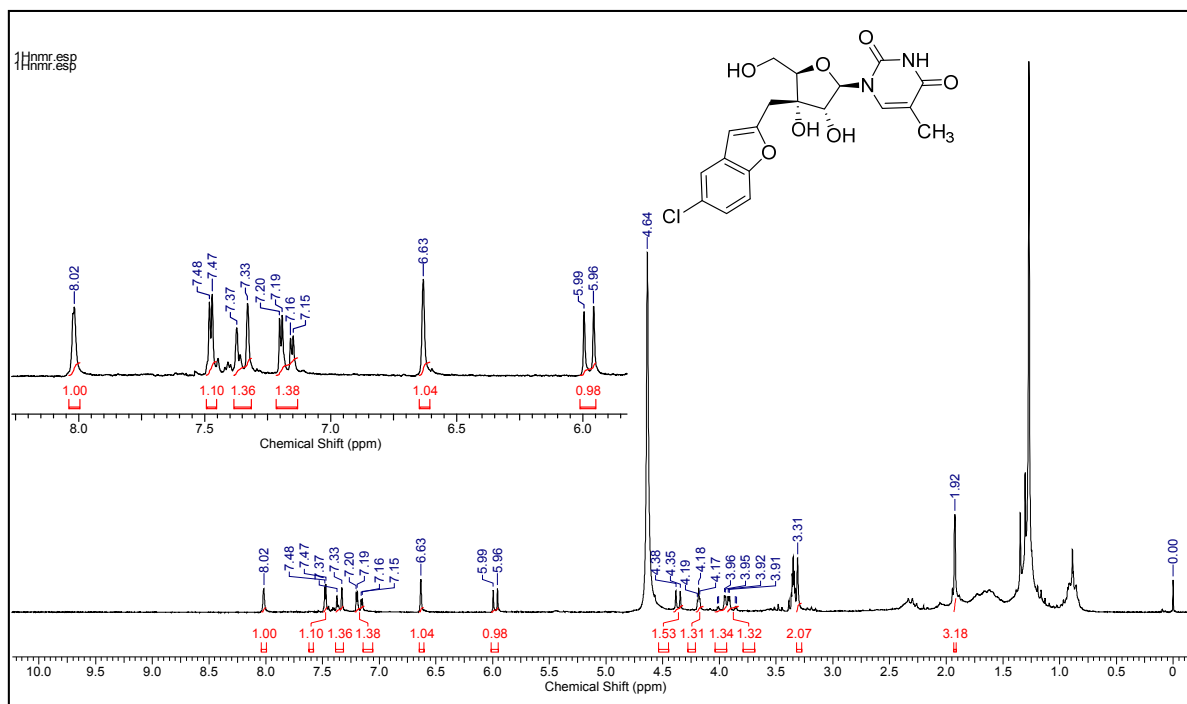
¹³C NMR Spectrum of **13fc** in CDCl₃ (50 MHz)



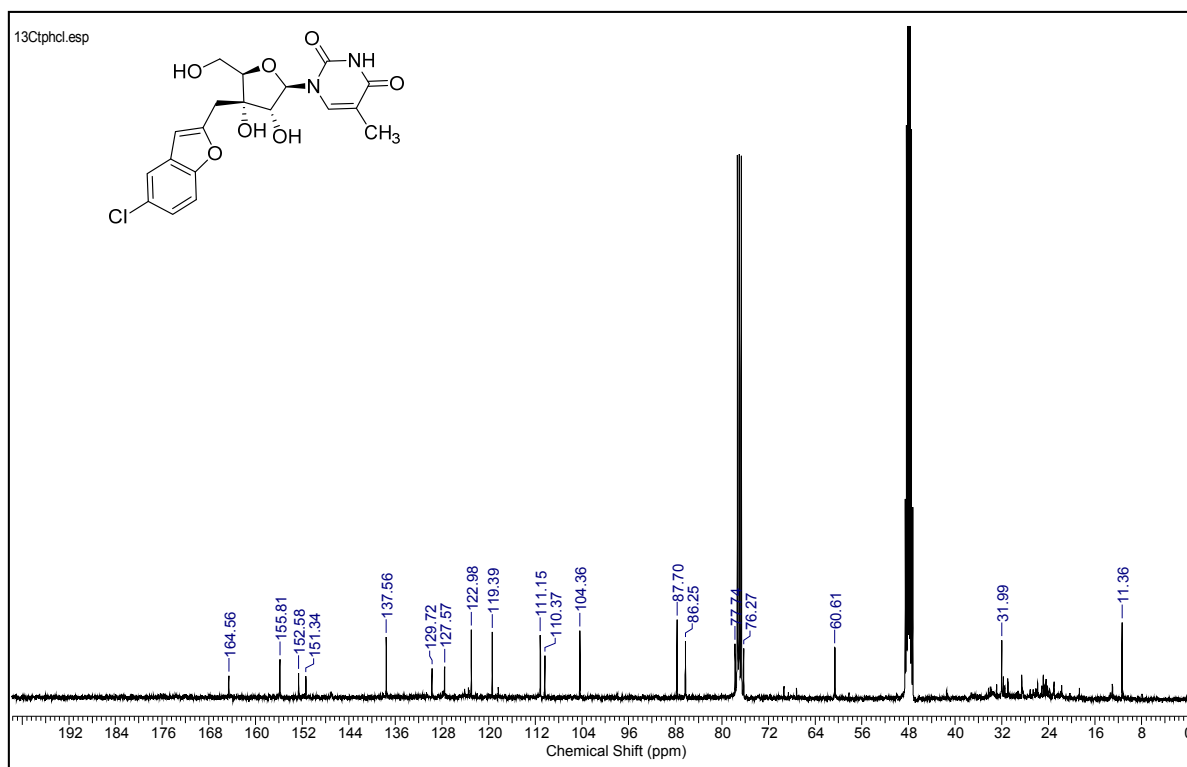
¹H NMR Spectrum of **19ea** in CDCl₃ (200 MHz)



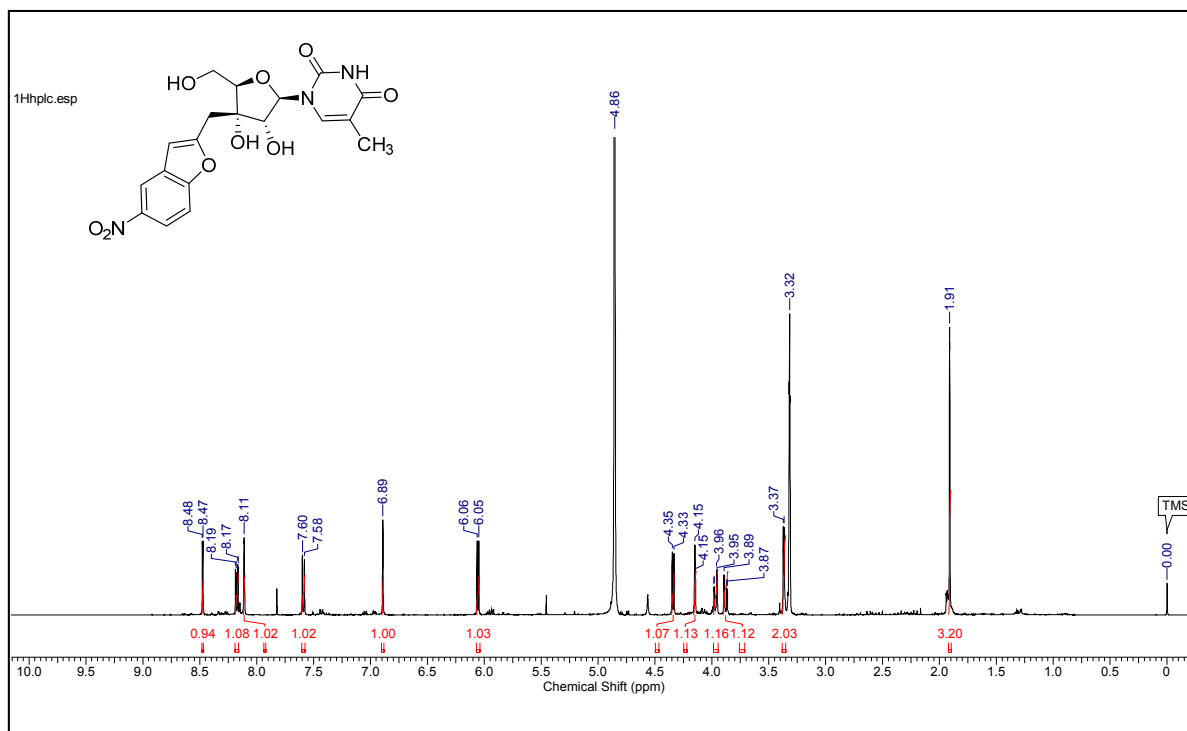
¹³C NMR Spectrum of **19ea** in CDCl₃ + MeOH (D₄) (50 MHz)



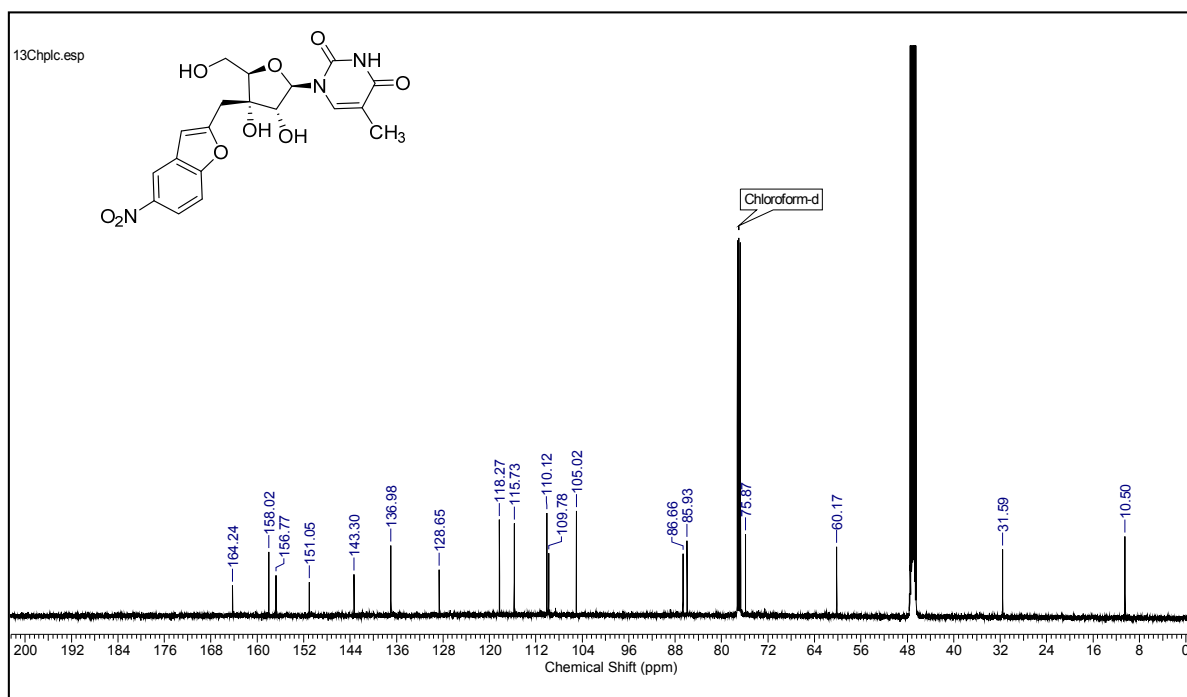
¹H NMR Spectrum of **19eb** in CDCl₃ (200 MHz)



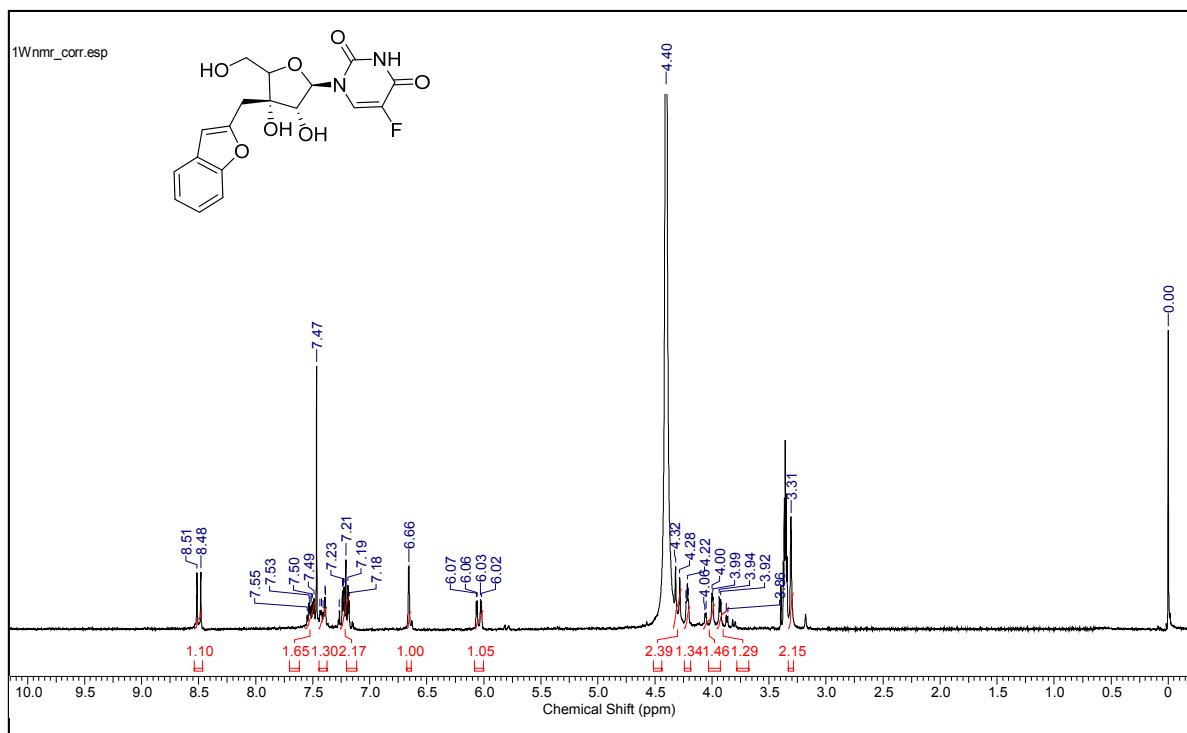
¹³C NMR Spectrum of **19eb** in CDCl₃ + MeOH (D₄) (50 MHz)



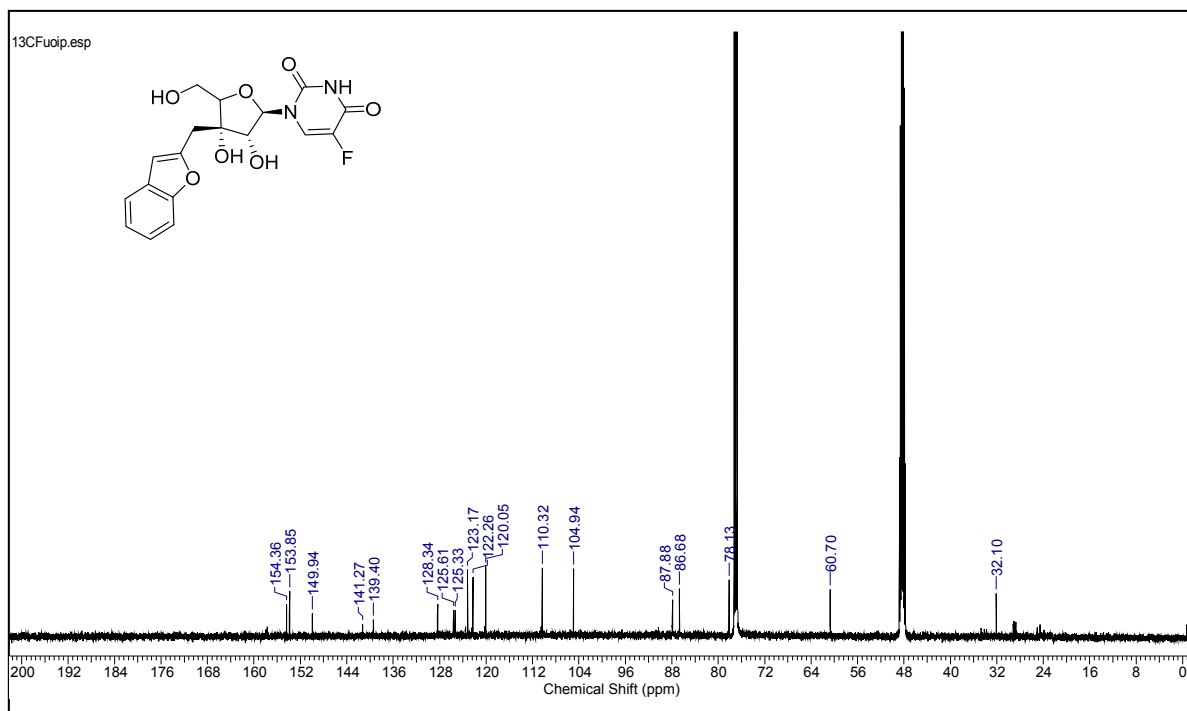
¹H NMR Spectrum of **19ec** in CDCl₃ + MeOH (D₄) (200 MHz)



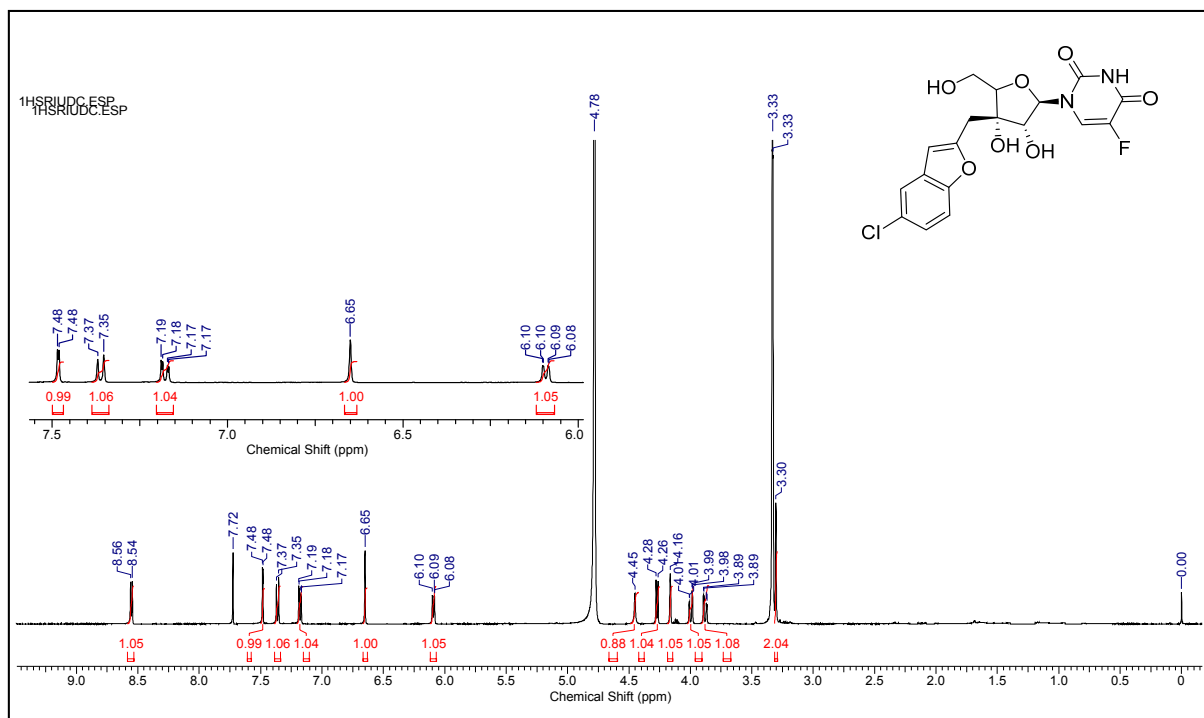
¹³C NMR Spectrum of **19ec** in CDCl₃ + MeOH (D₄) (50 MHz)



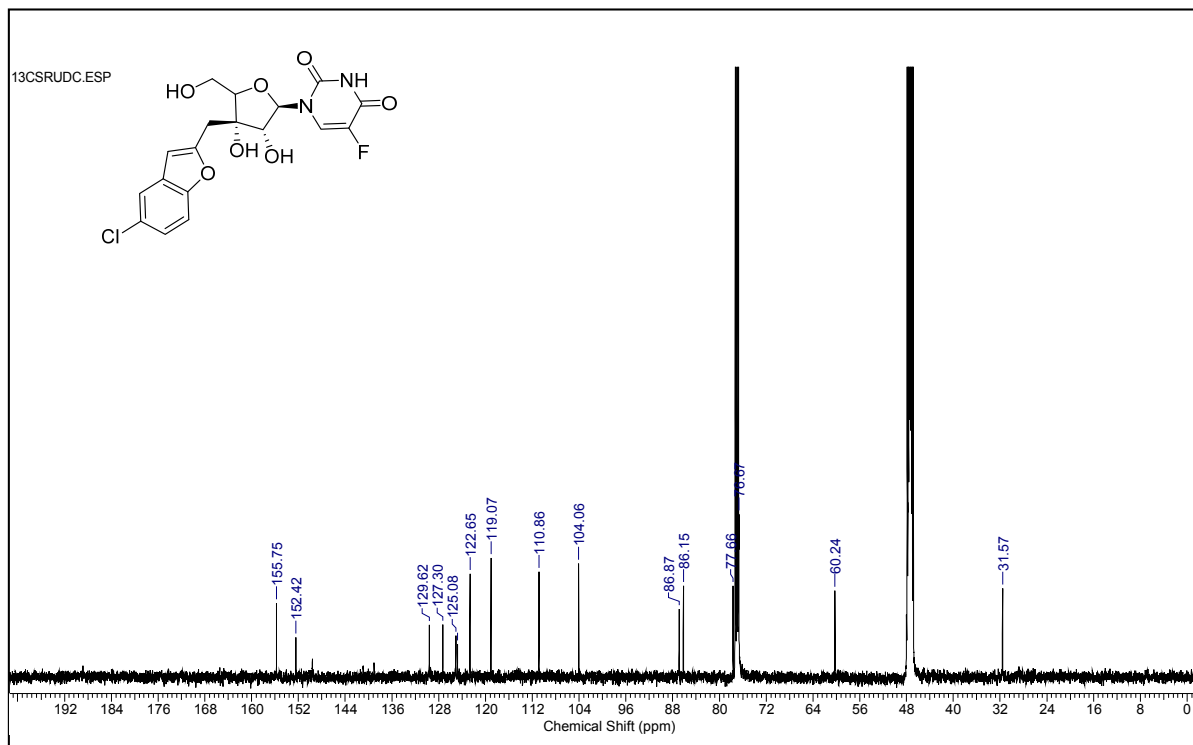
¹H NMR Spectrum of **19fa** in CDCl₃ + MeOH (D₄) (200 MHz)



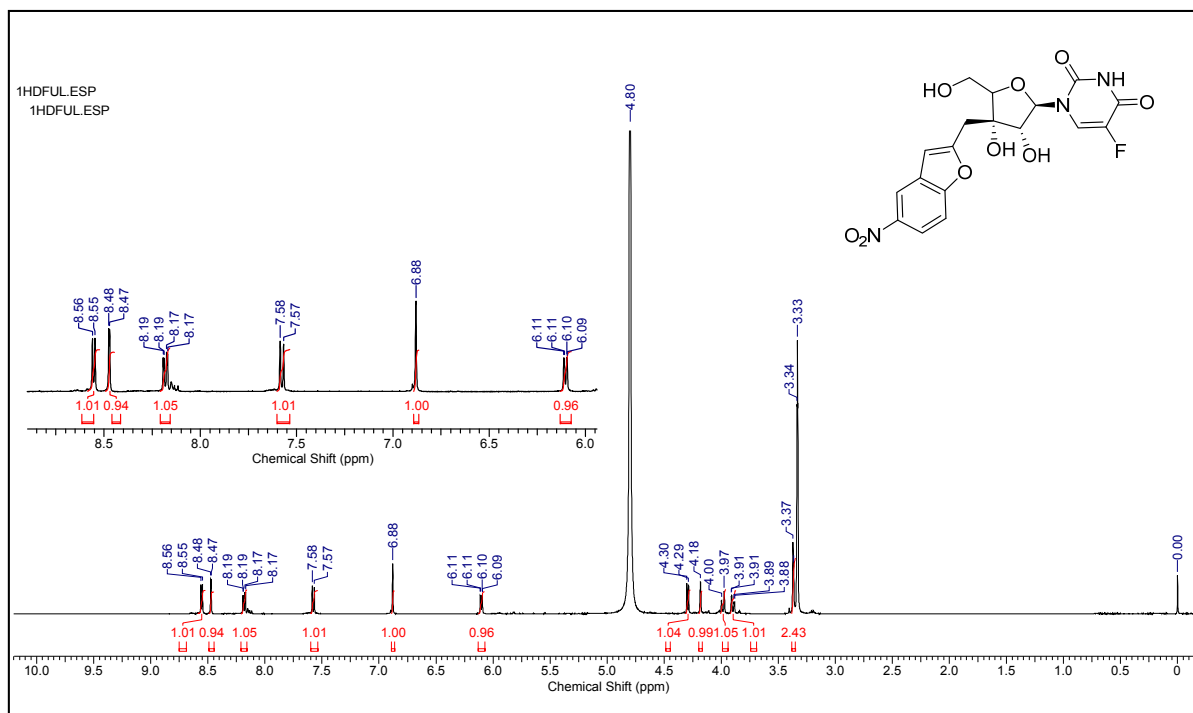
¹³C NMR Spectrum of **19fa** in CDCl₃ + MeOH (D₄) (50 MHz)



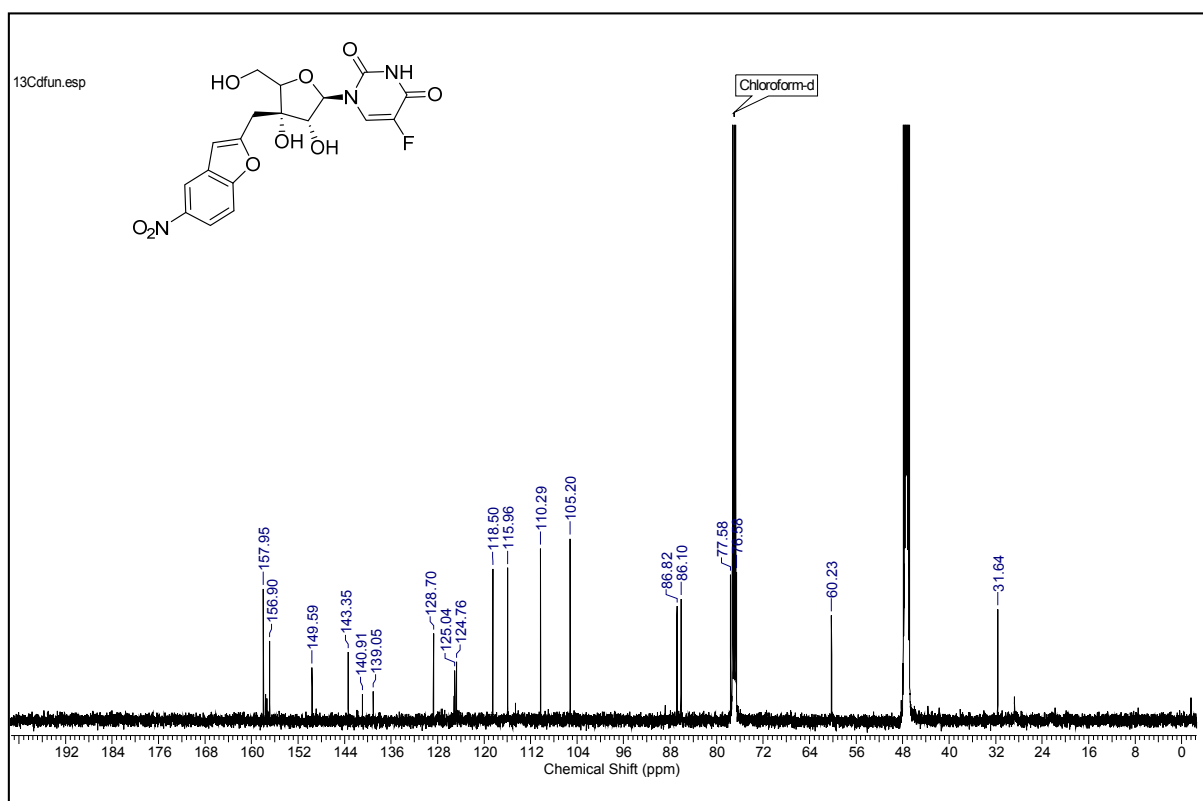
¹H NMR Spectrum of **19fb** in CDCl₃ + MeOH (D₄) (200 MHz)



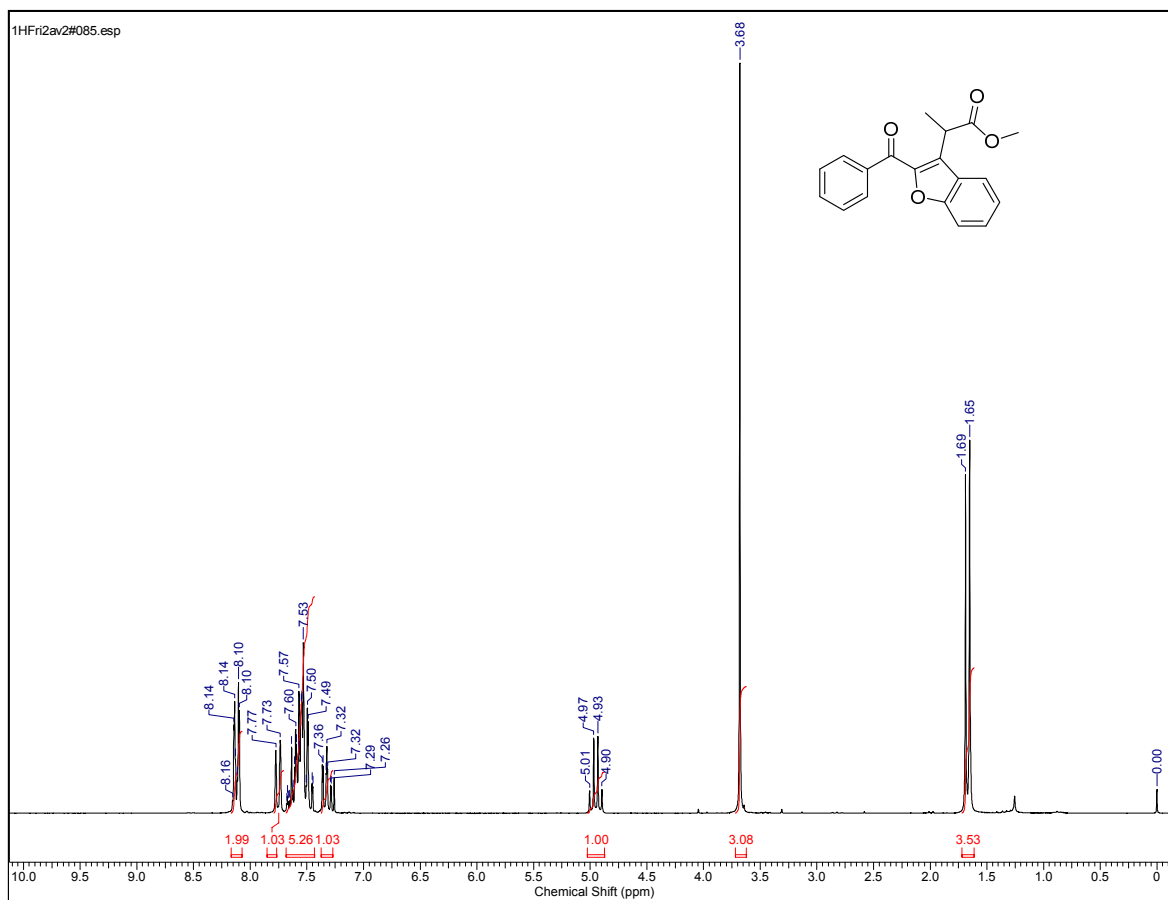
¹³C NMR Spectrum of **19fb** in CDCl₃ + MeOH (D₄) (50 MHz)



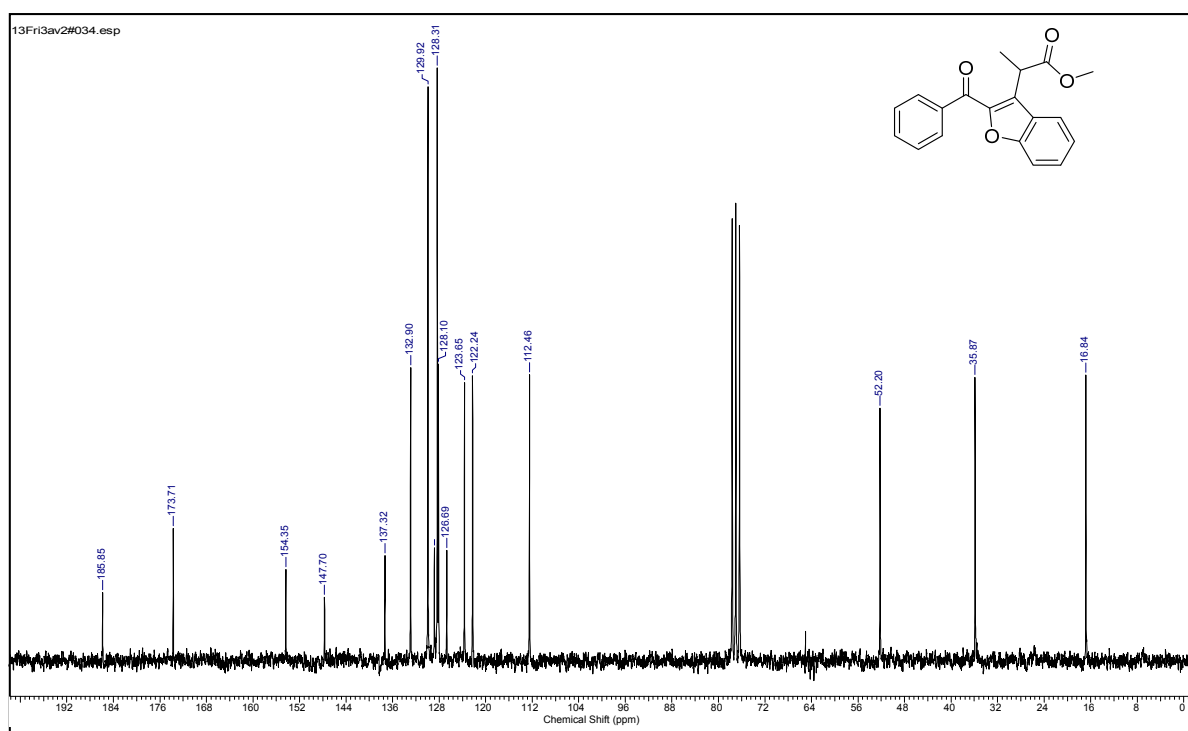
¹H NMR Spectrum of **19fc** in CDCl₃ + MeOH (D₄) (200 MHz)



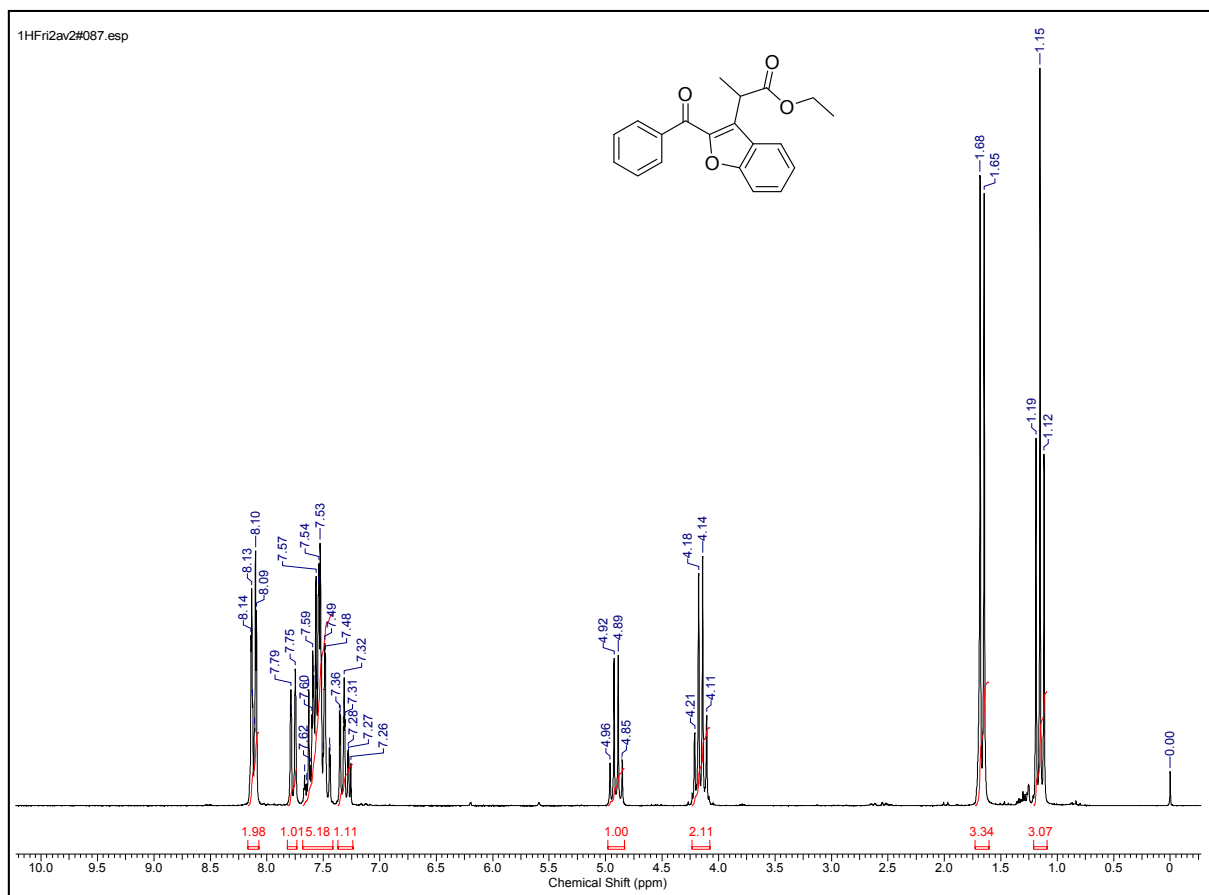
¹³C NMR Spectrum of **19fc** in CDCl₃ + MeOH (D₄) (50 MHz)



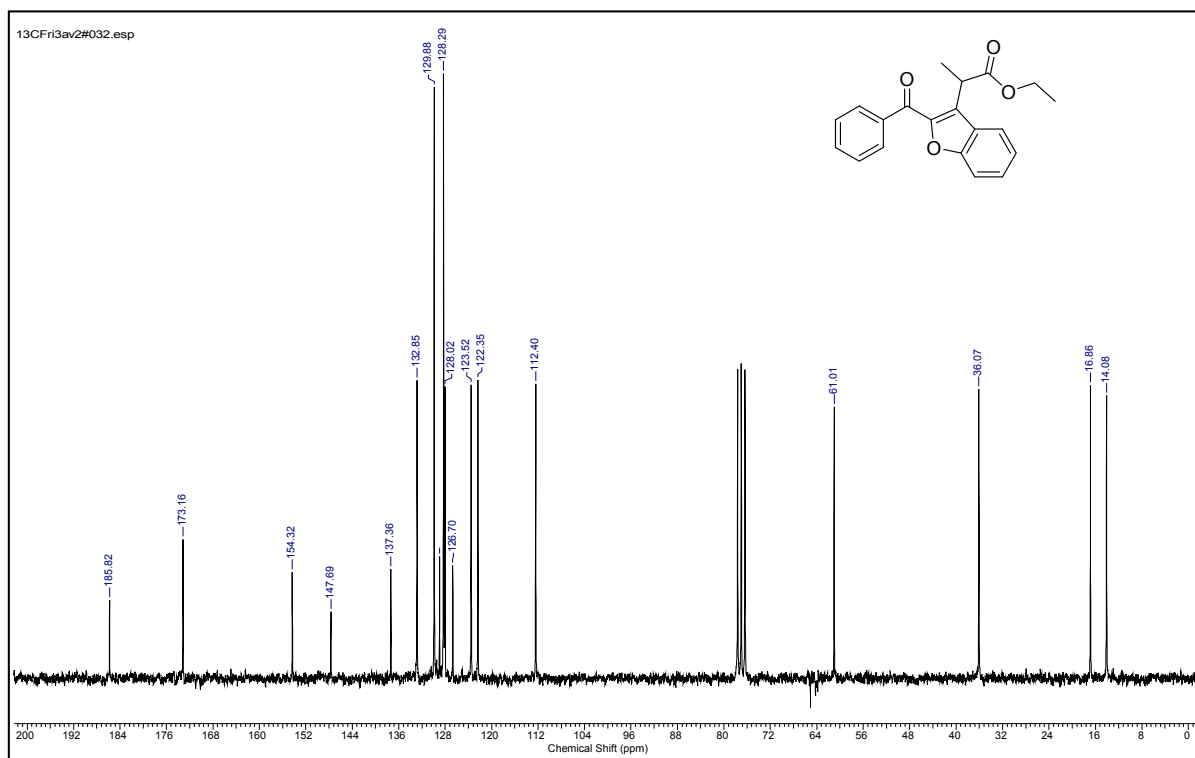
¹H NMR Spectrum of **22aa** in CDCl₃ (200 MHz)



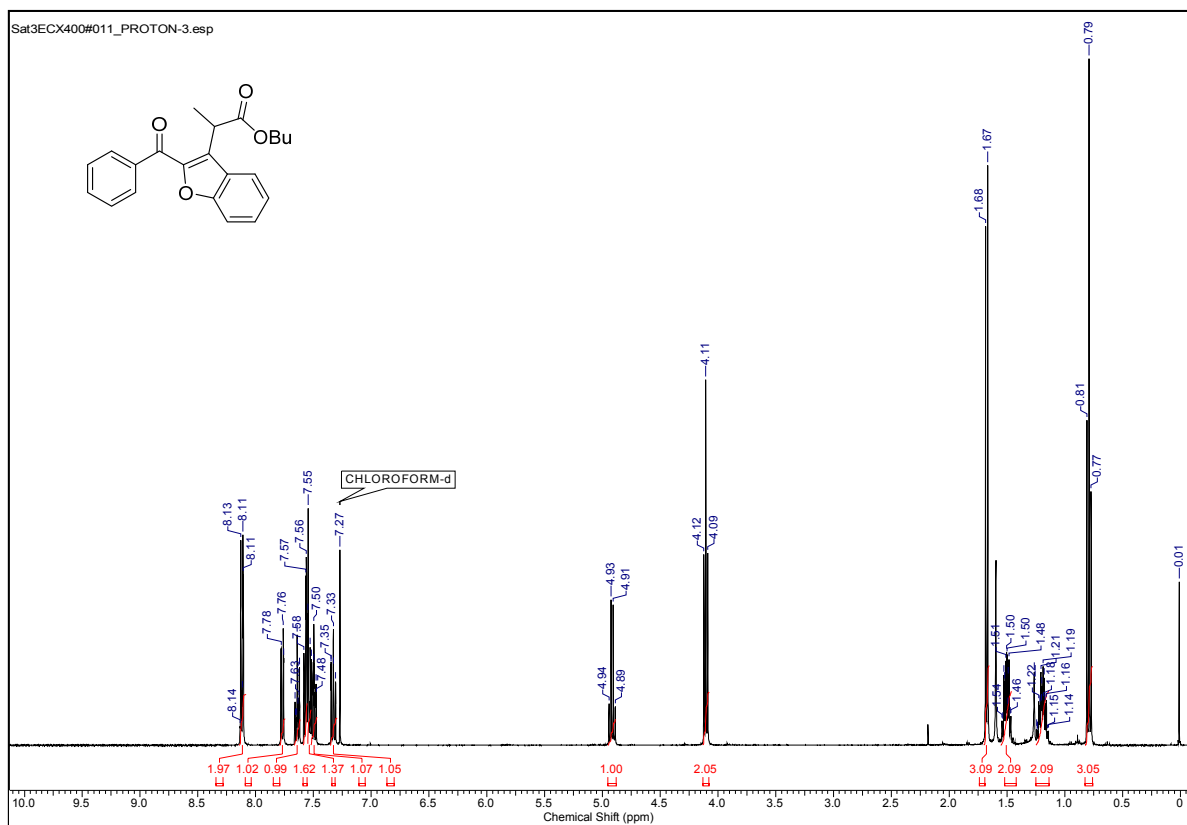
¹³C NMR Spectrum of **22aa** in CDCl₃ (50 MHz)



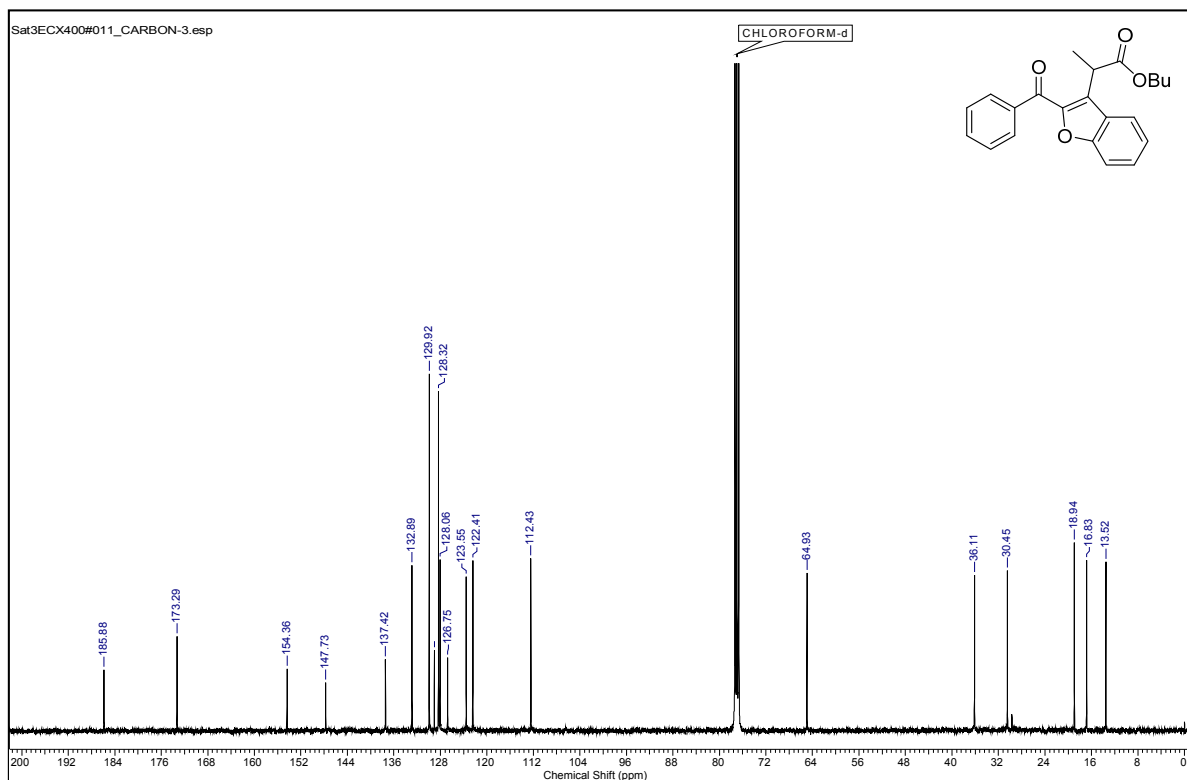
¹H NMR Spectrum of **22ab** in CDCl₃ (200 MHz)



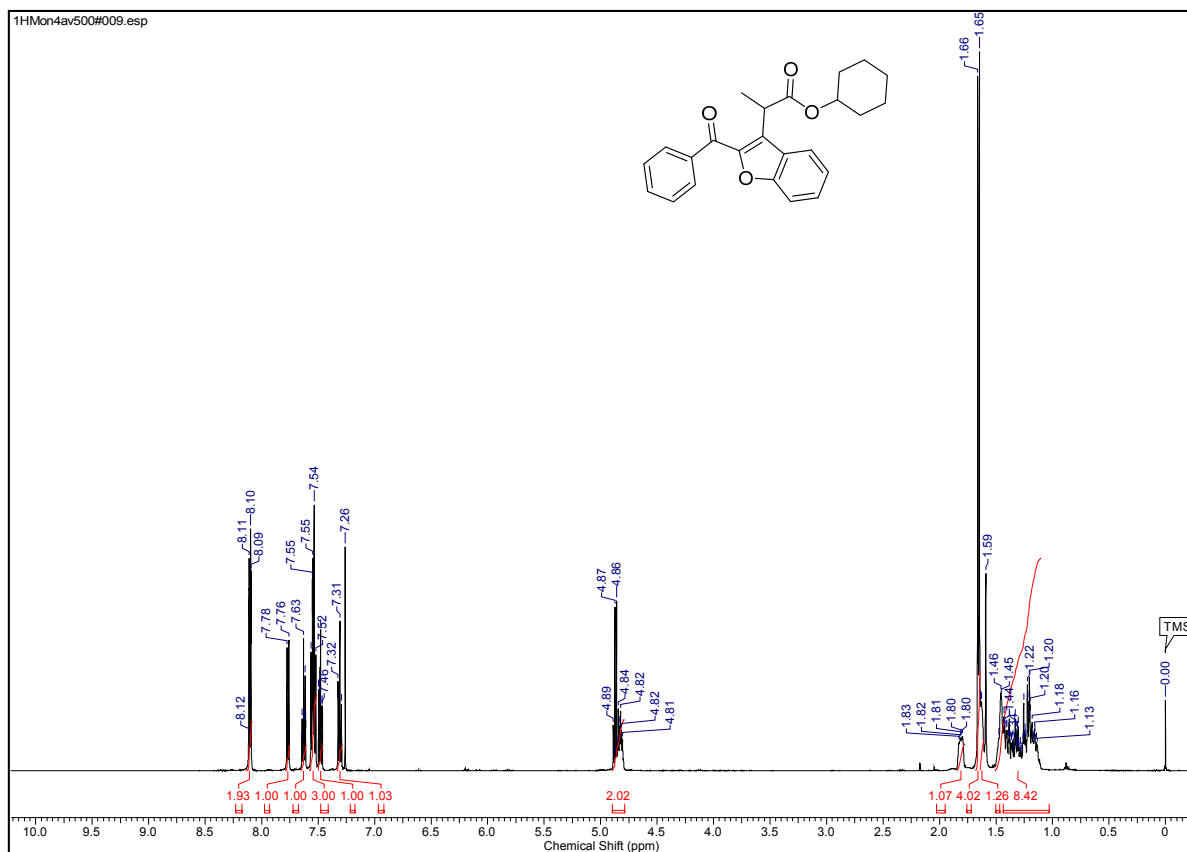
¹³C NMR Spectrum of **22ab** in CDCl₃ (50 MHz)



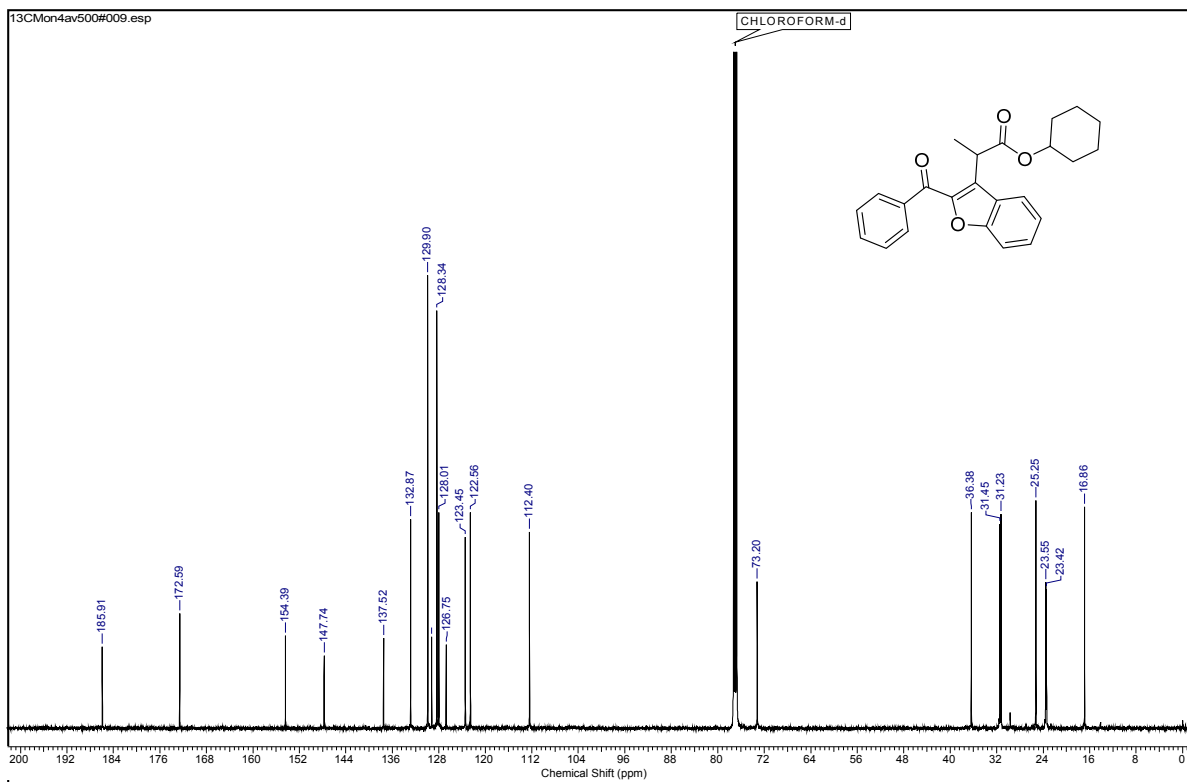
^1H NMR Spectrum of **22ac** in CDCl_3 (400 MHz)



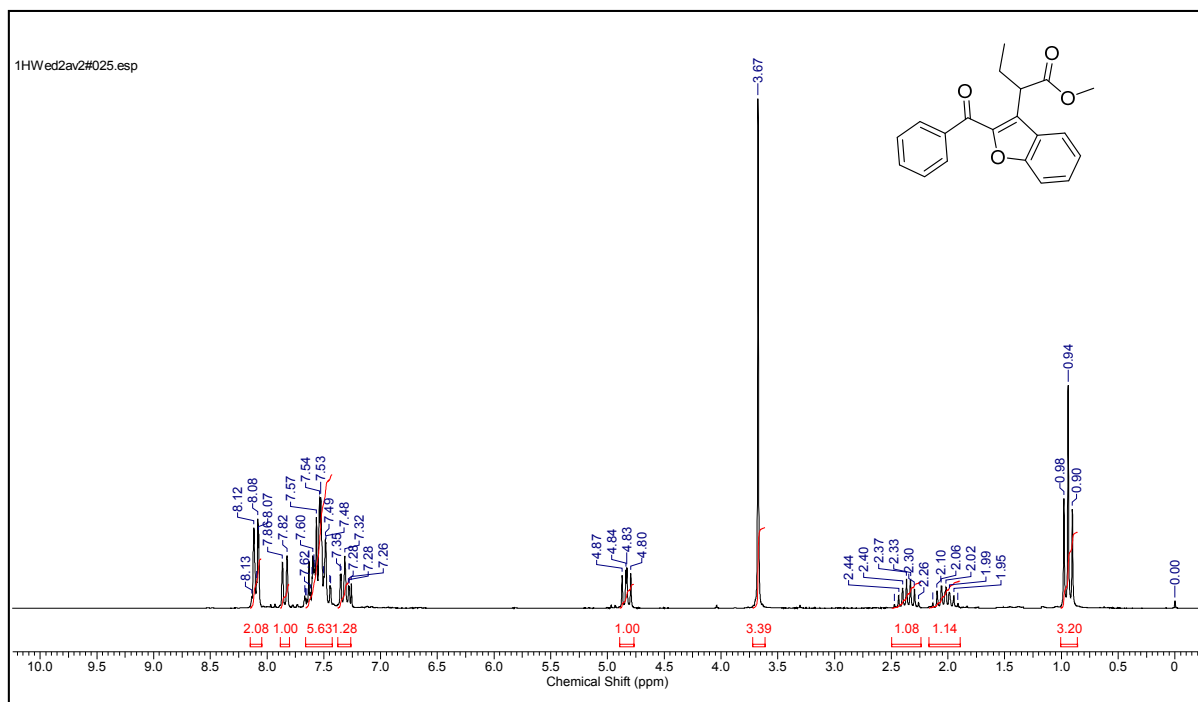
^{13}C NMR Spectrum of **22ac** in CDCl_3 (100 MHz)



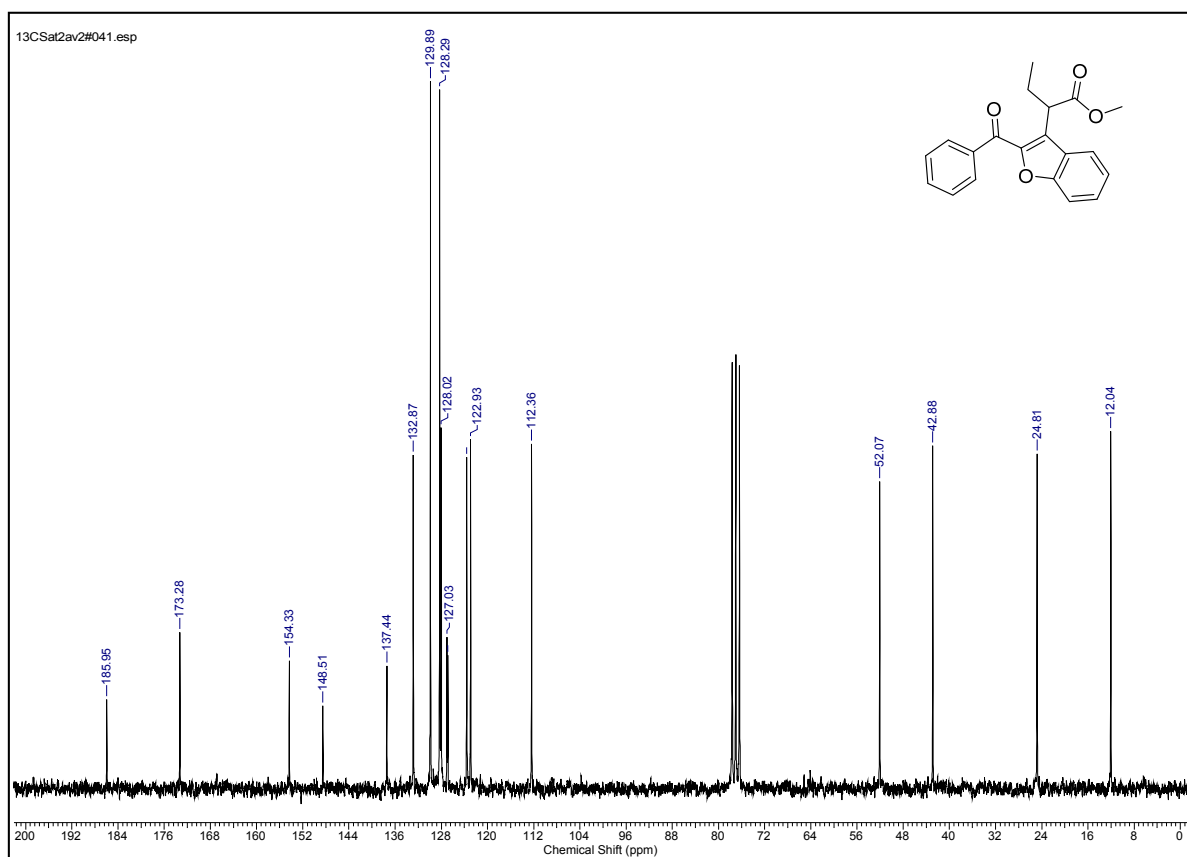
¹H NMR Spectrum of **22ad** in CDCl₃ (500 MHz)



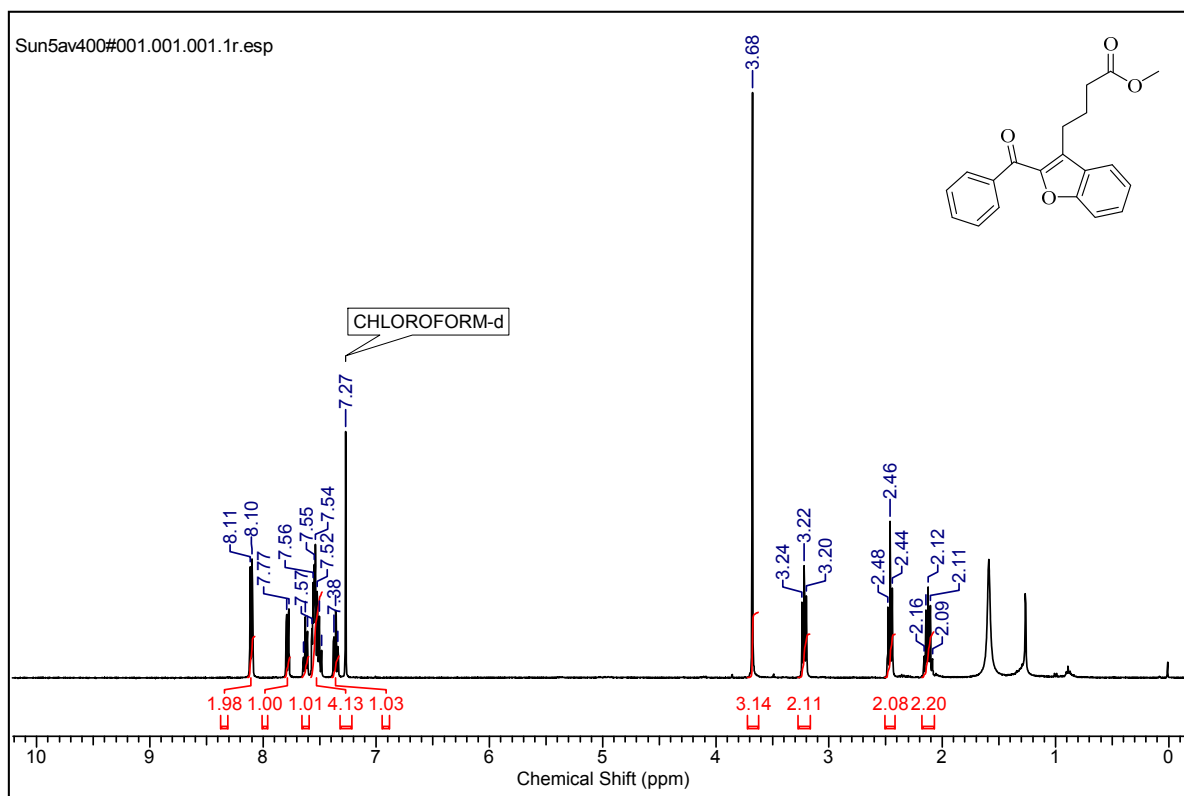
¹³C NMR Spectrum of **22ad** in CDCl₃ (125 MHz)



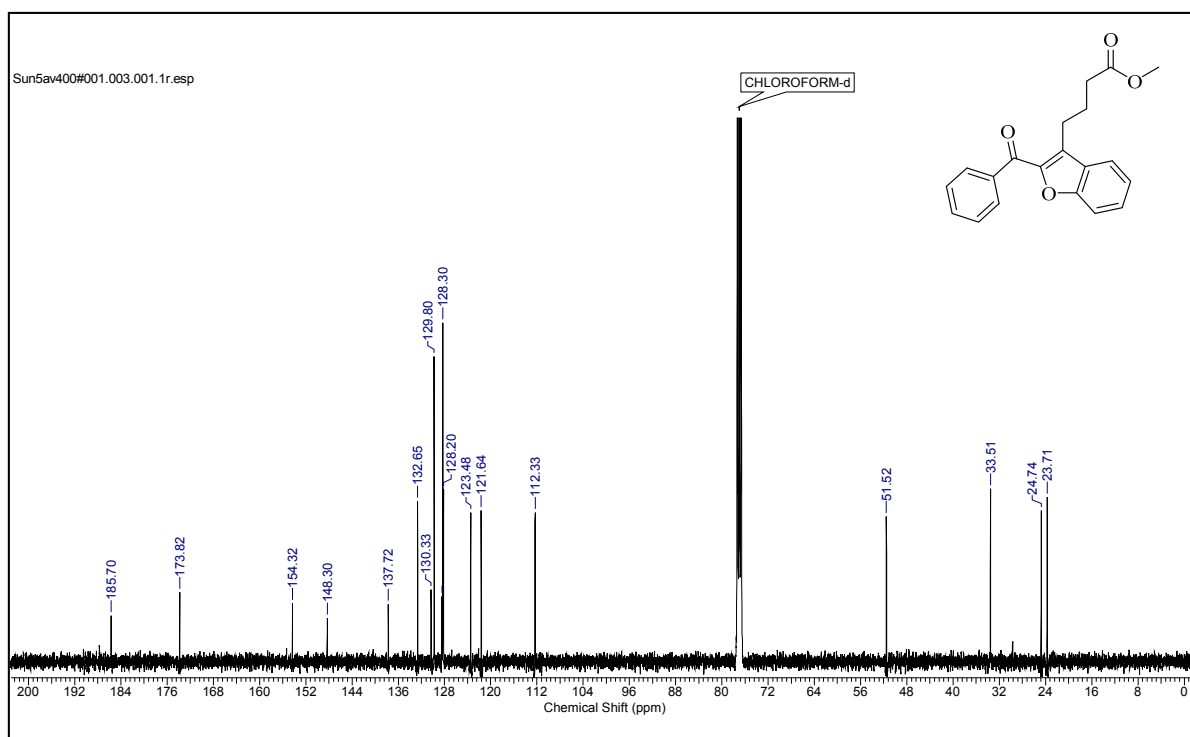
¹H NMR Spectrum of **22ae** in CDCl₃ (200 MHz)



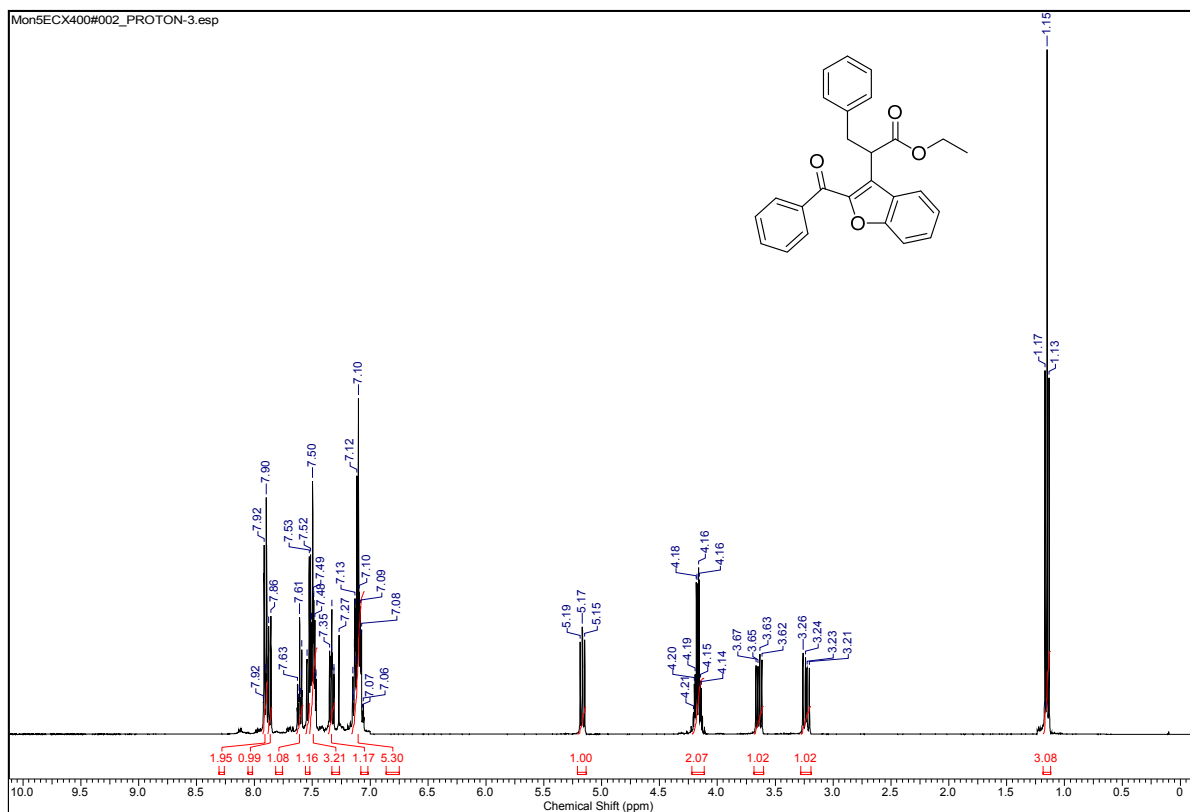
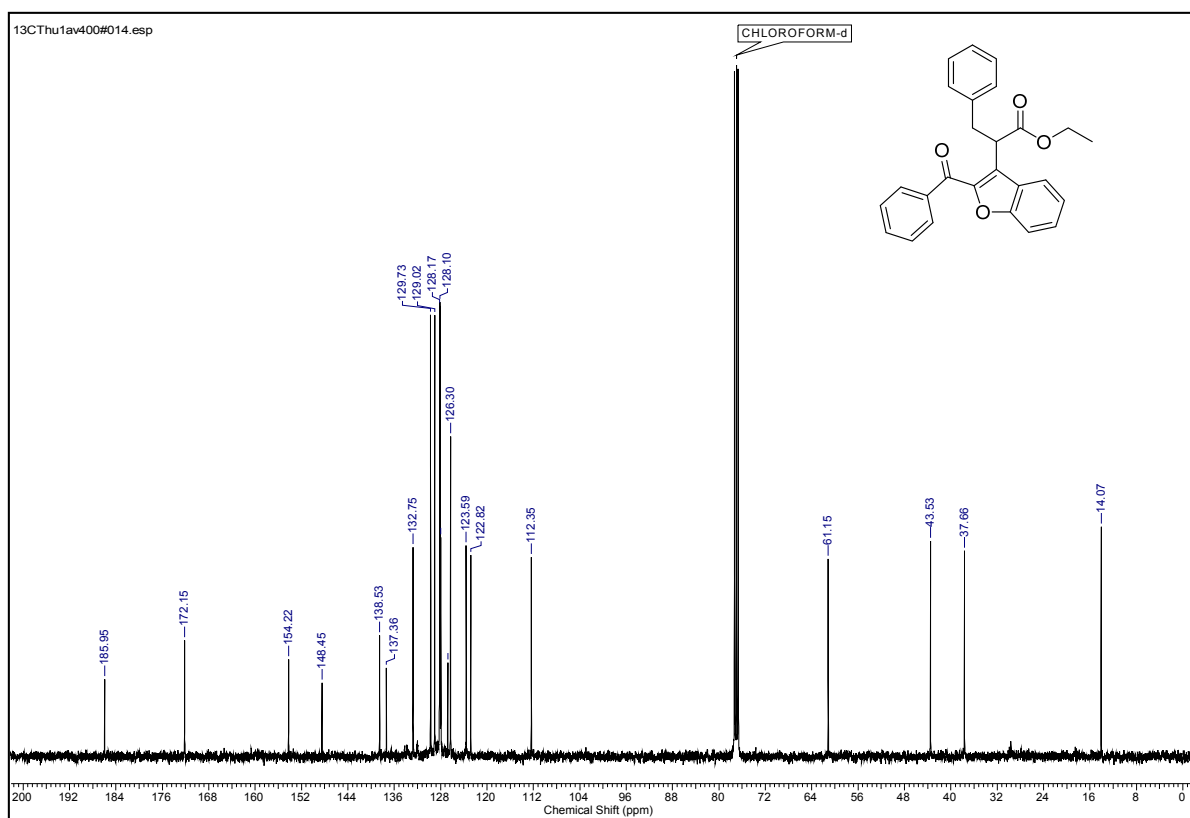
¹³C NMR Spectrum of **22ae** in CDCl₃ (50 MHz)

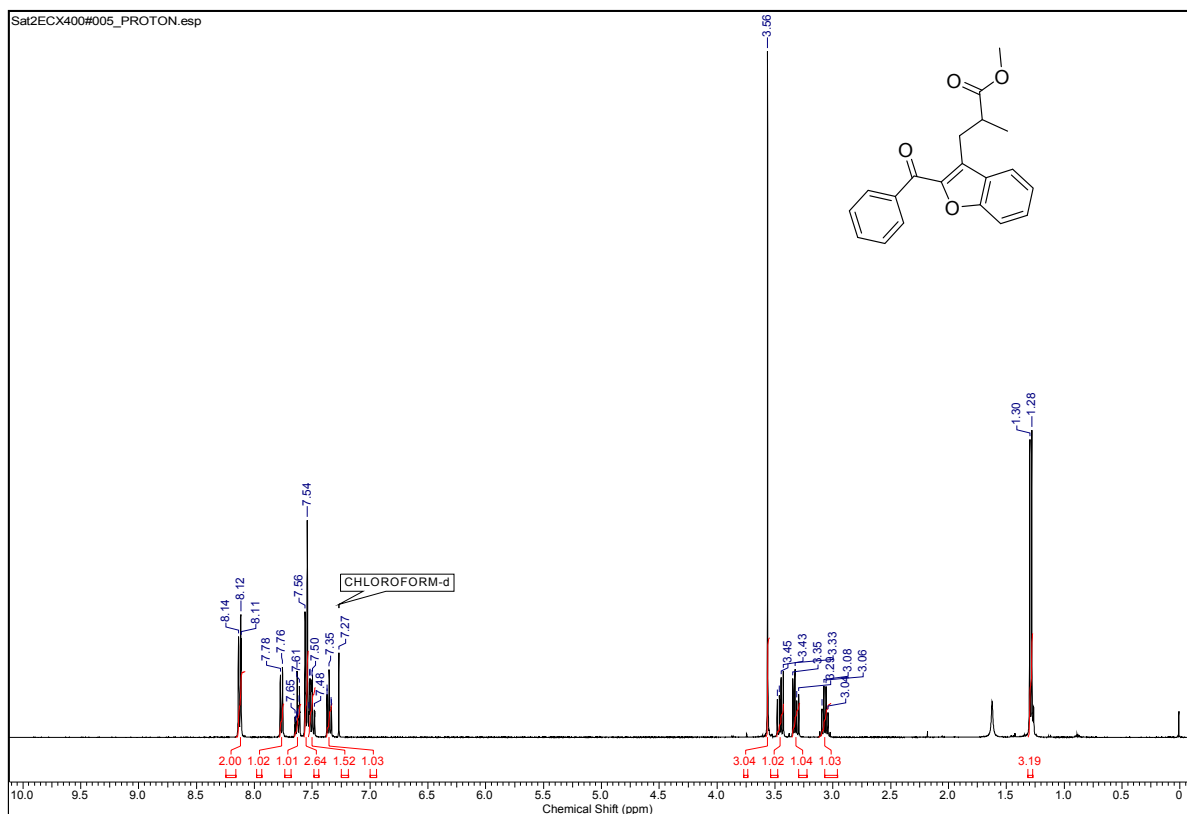


¹H NMR Spectrum of **24** in CDCl₃ (400 MHz)

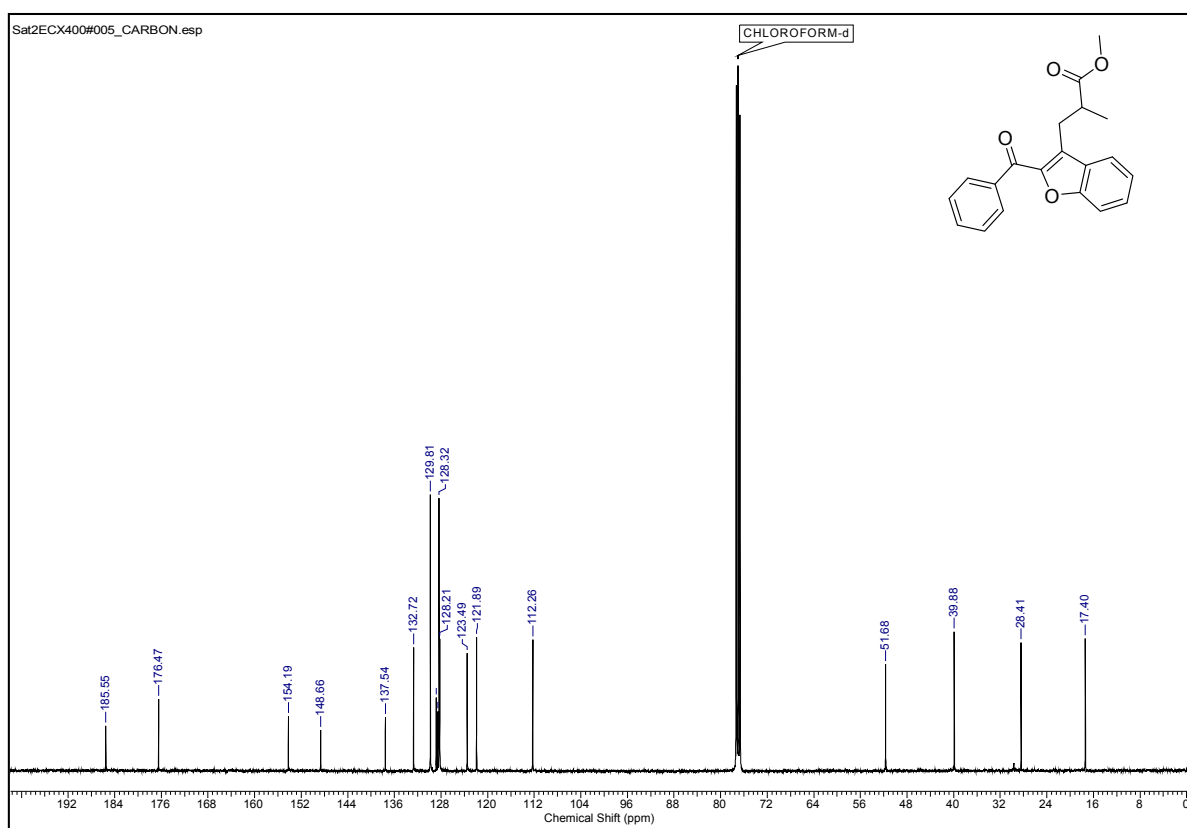


¹³C NMR Spectrum of **24** in CDCl₃ (100 MHz)

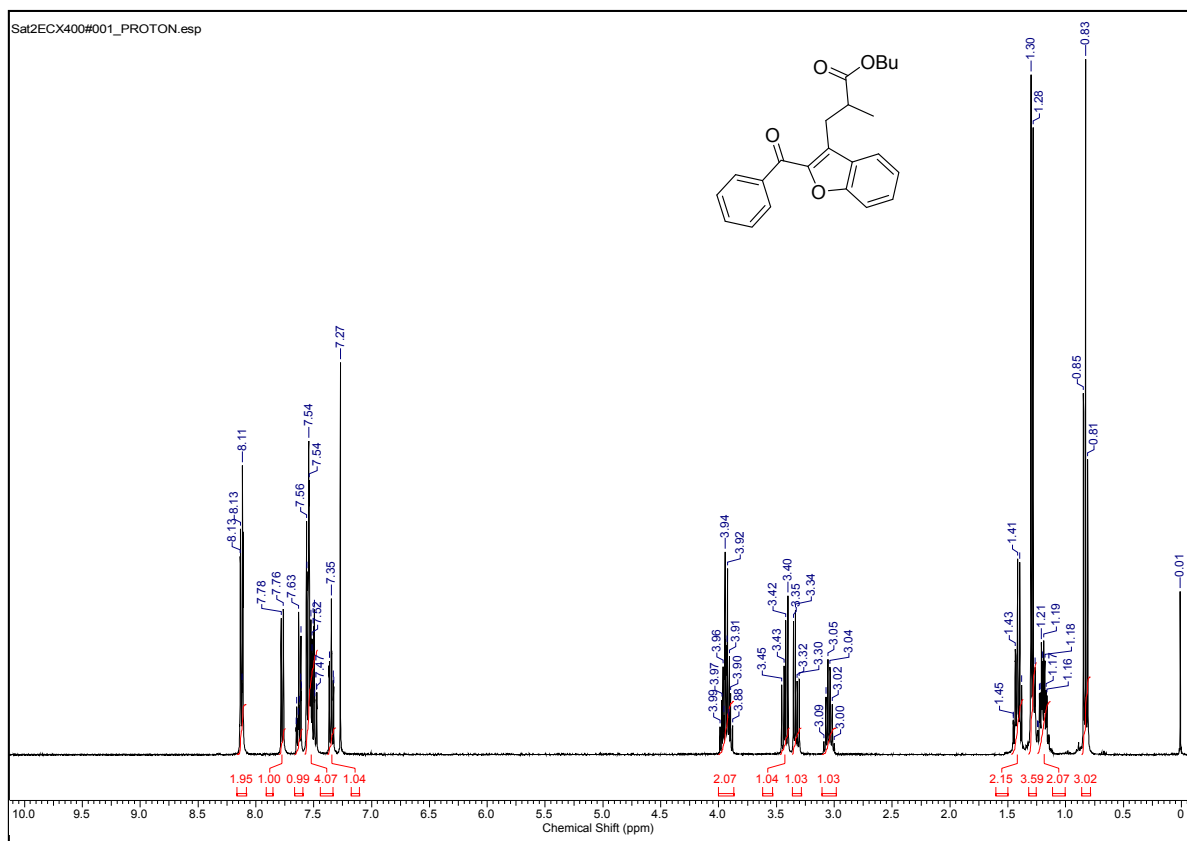
¹H NMR Spectrum of **22af** in CDCl₃ (400 MHz)¹³C NMR Spectrum of **22af** in CDCl₃ (100 MHz)



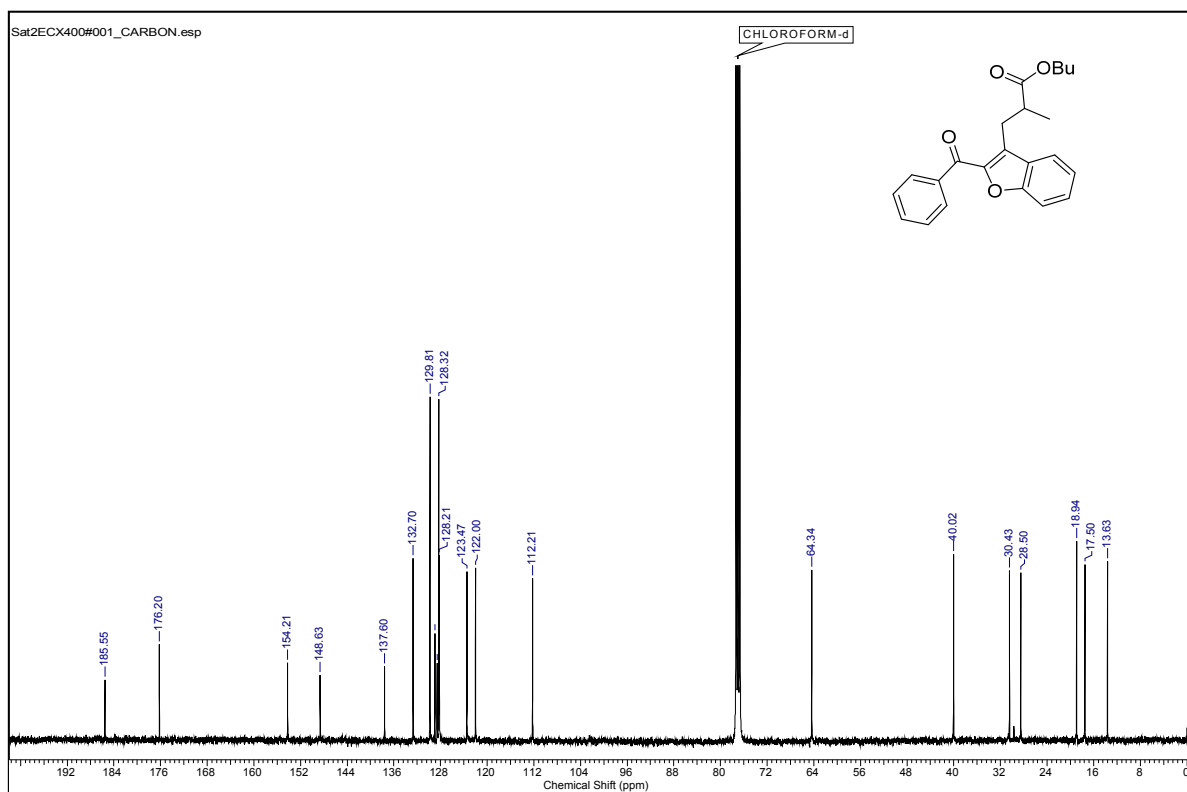
^1H NMR Spectrum of **23ag** in CDCl_3 (400 MHz)



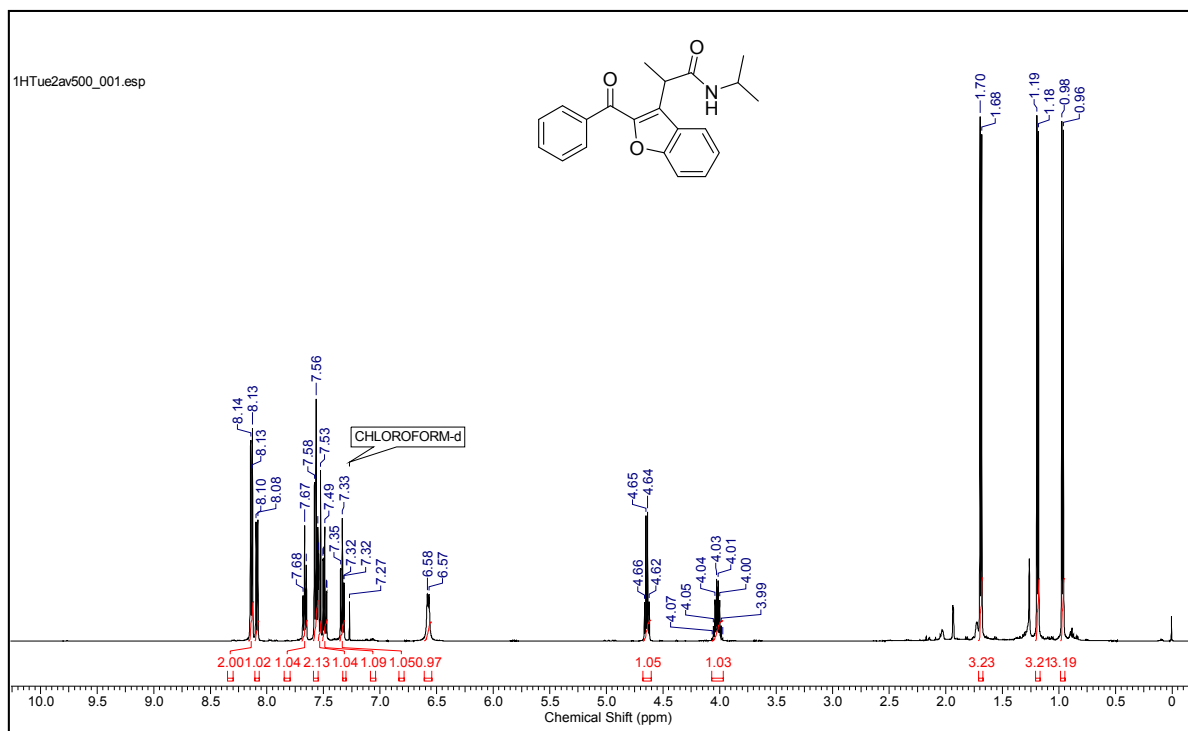
^{13}C NMR Spectrum of **23ag** in CDCl_3 (100 MHz)



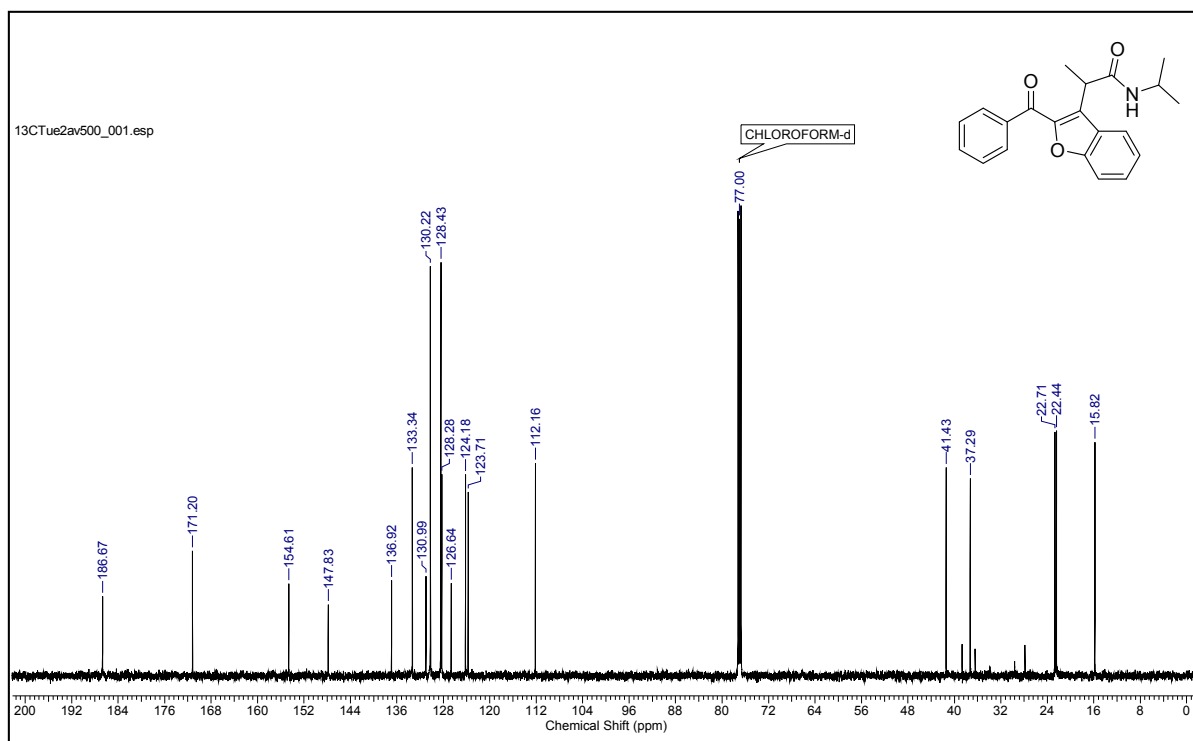
^1H NMR Spectrum of **23ah** in CDCl_3 (400 MHz)



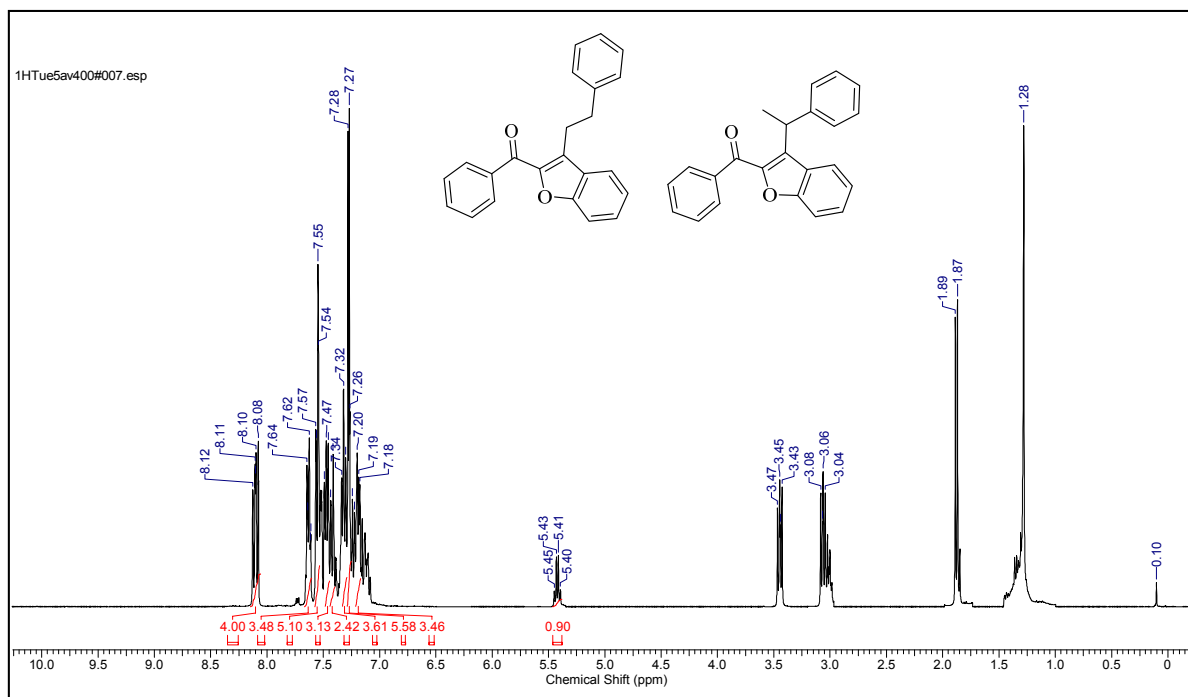
^{13}C NMR Spectrum of **23ah** in CDCl_3 (100 MHz)



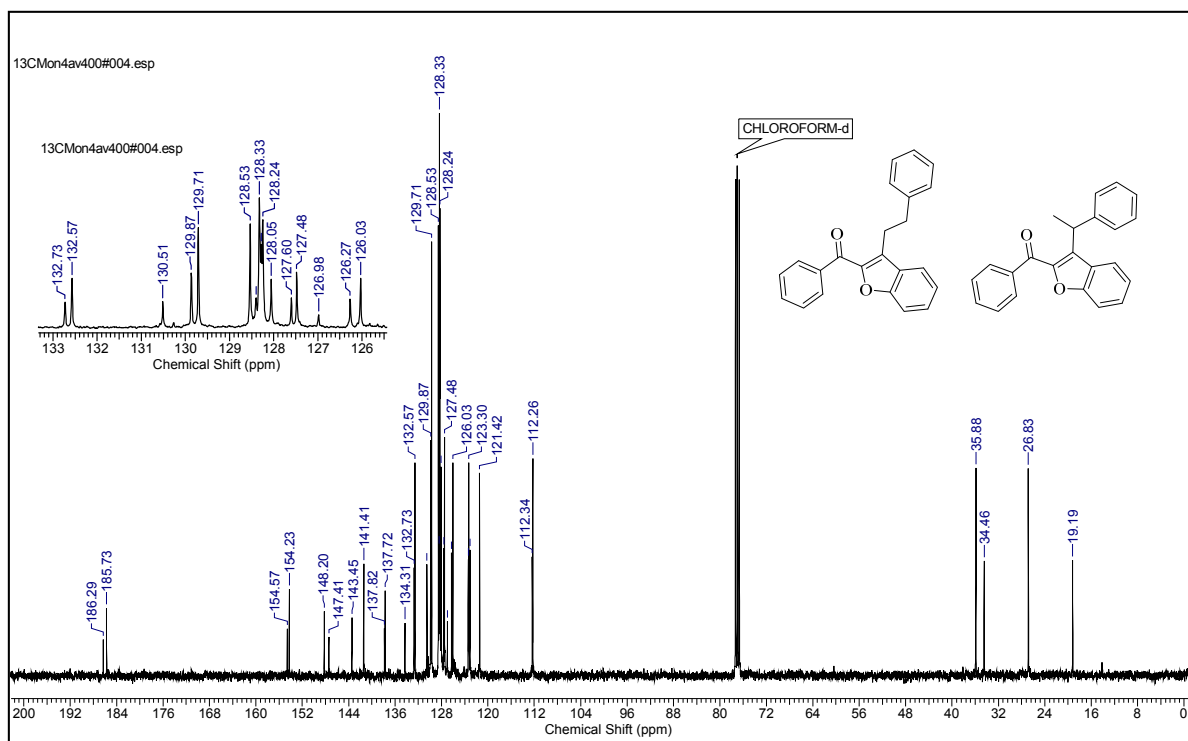
¹H NMR Spectrum of **22ak** in CDCl₃ (500 MHz)



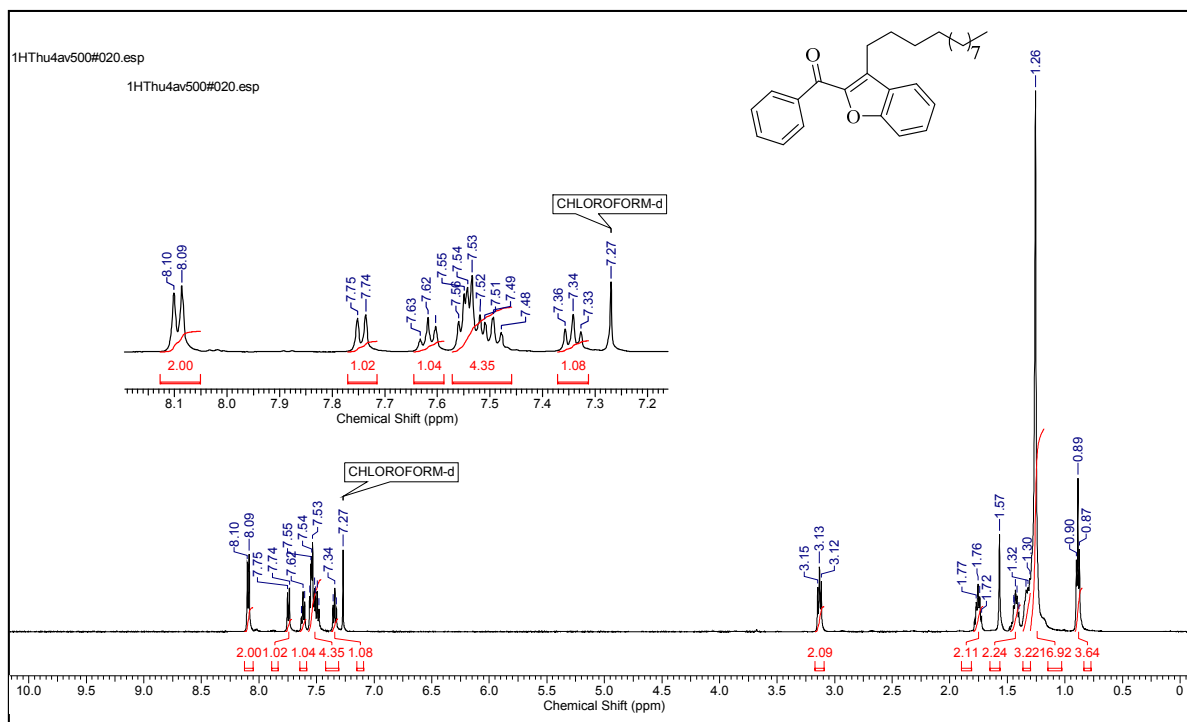
¹³C NMR Spectrum of **22ak** in CDCl₃ (125 MHz)



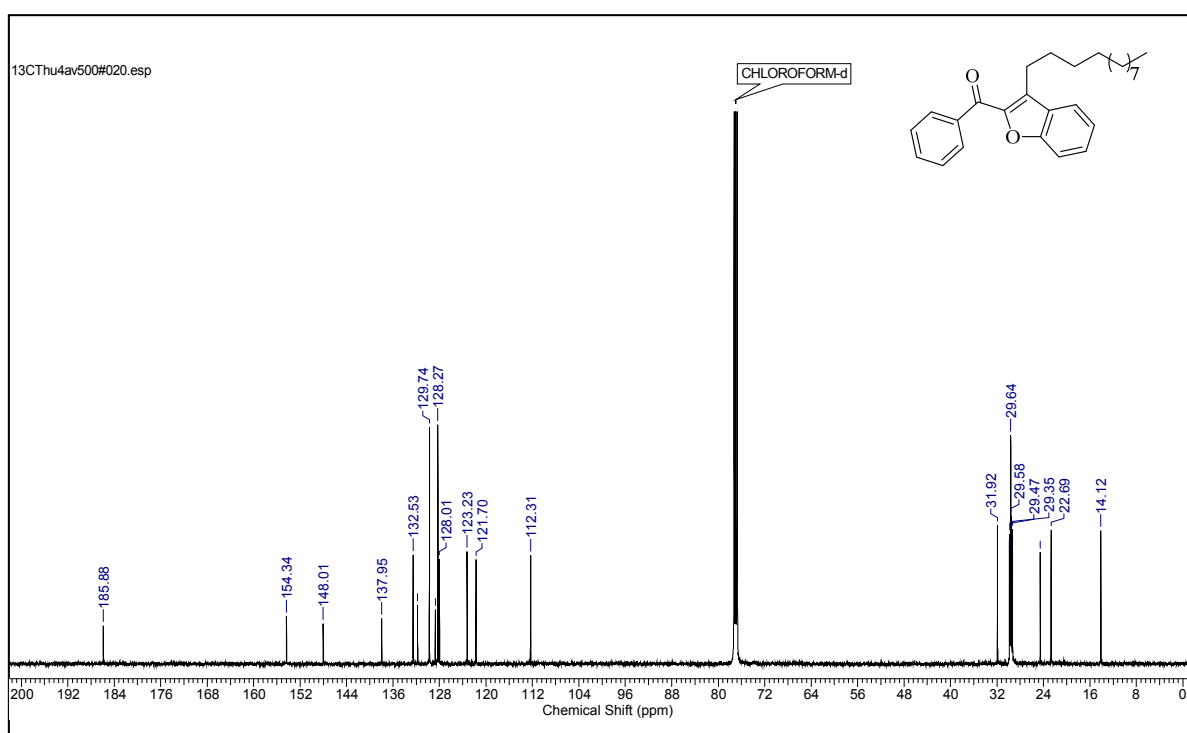
¹H NMR Spectrum of **22al** and **23al** in CDCl₃ (200 MHz)



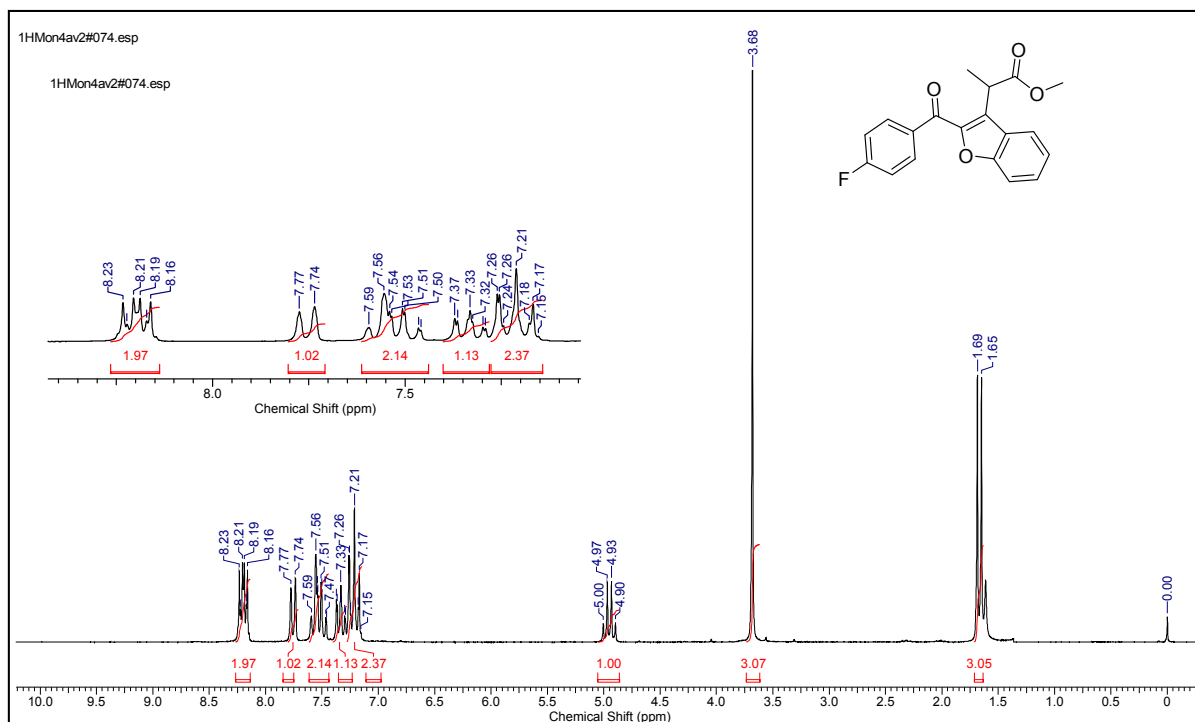
¹³C NMR Spectrum of **22al** and **23al** in CDCl₃ (100 MHz)



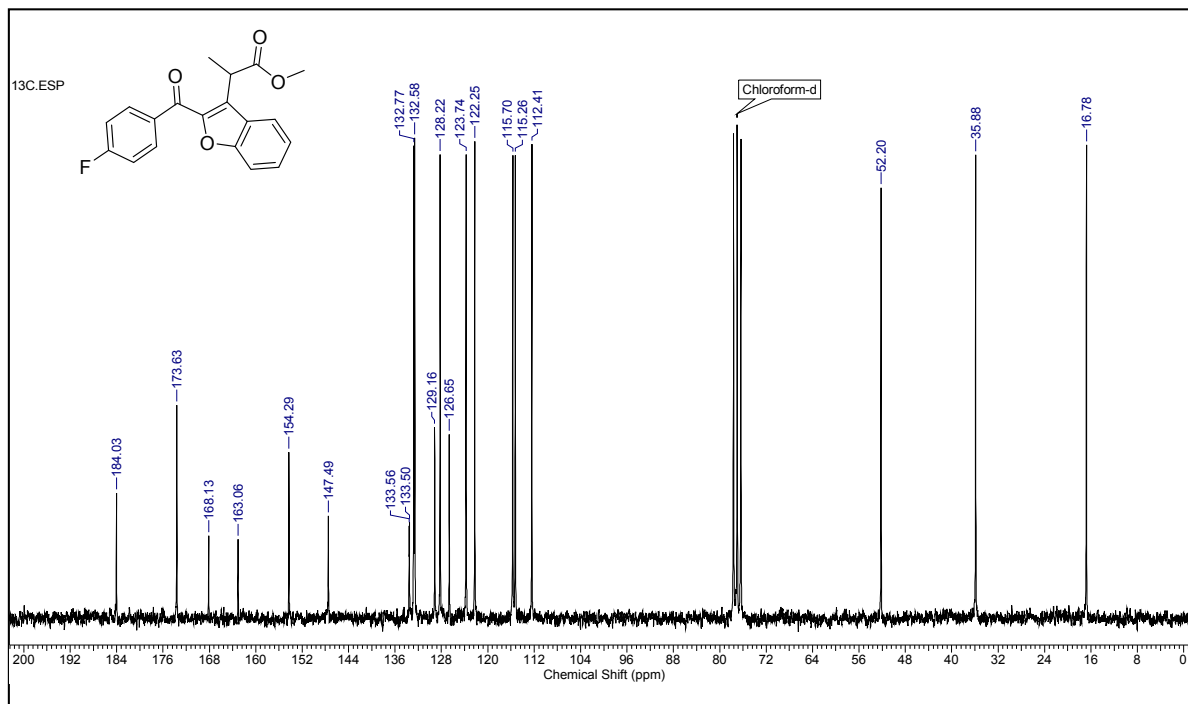
¹H NMR Spectrum of **22am** in CDCl₃ (500 MHz)



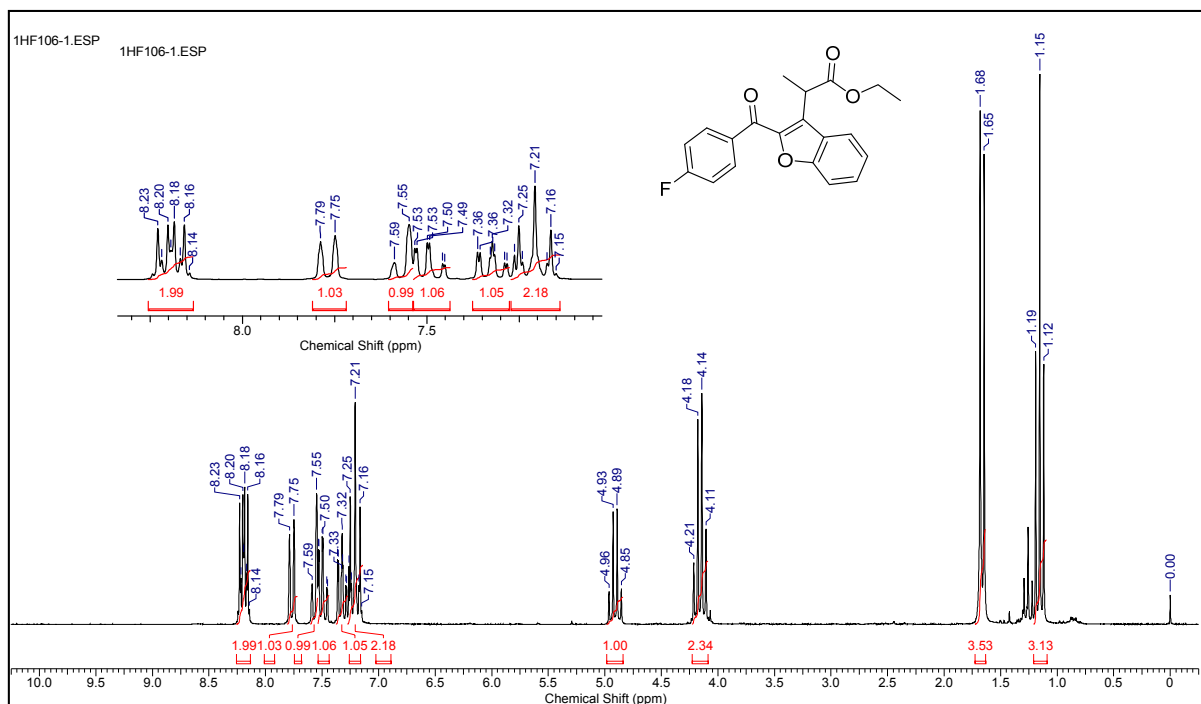
¹³C NMR Spectrum of **22am** in CDCl₃ (125 MHz)



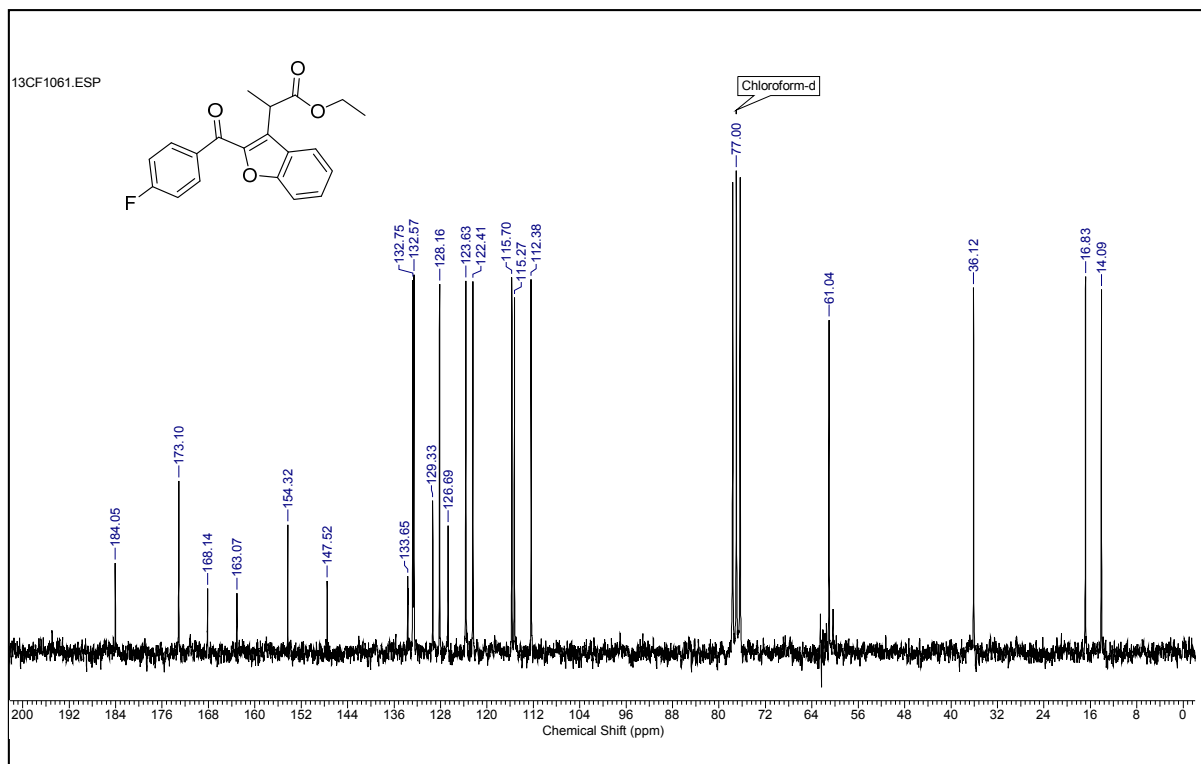
¹H NMR Spectrum of **22ba** in CDCl₃ (200 MHz)



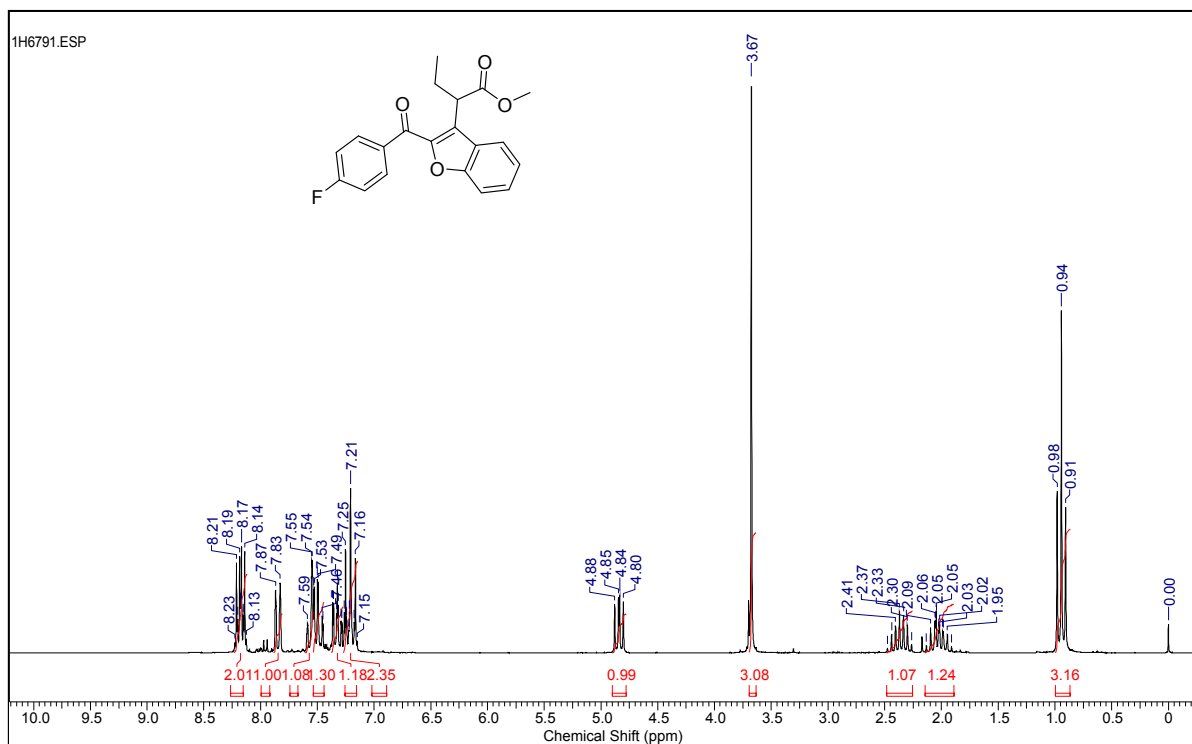
¹³C NMR Spectrum of **22ba** in CDCl₃ (50 MHz)



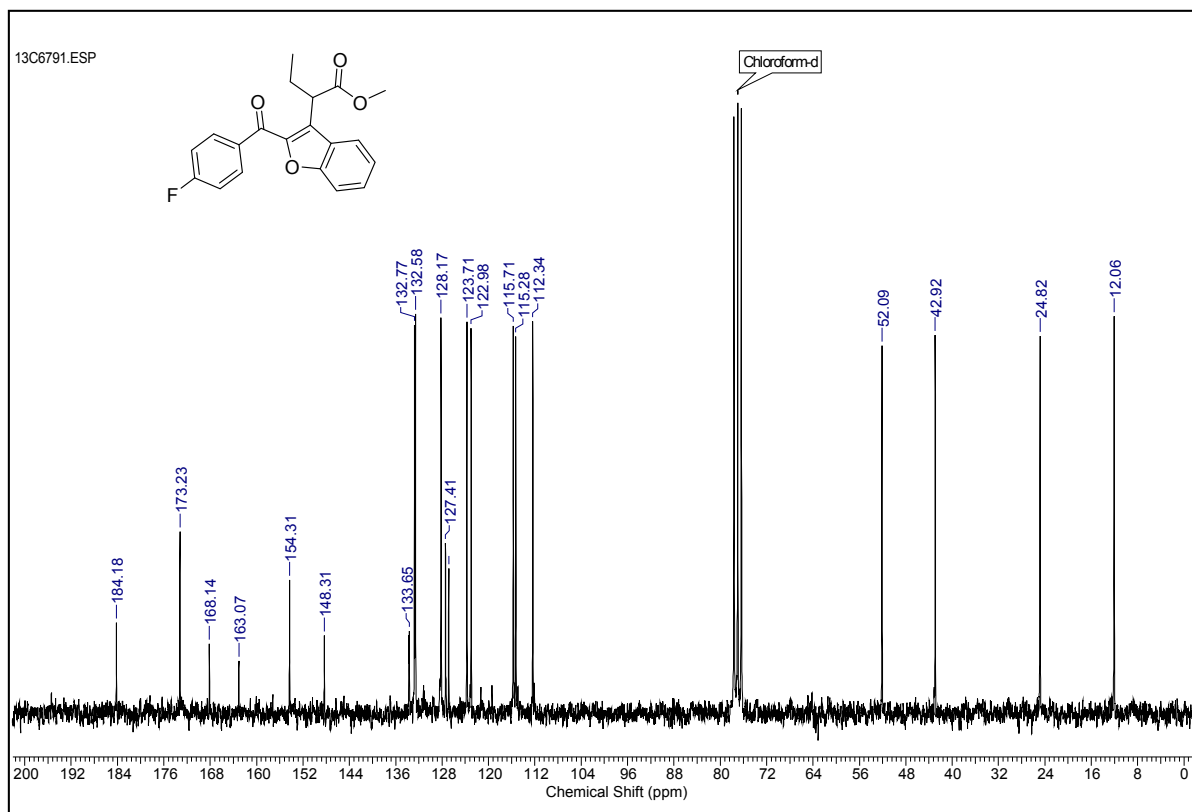
^1H NMR Spectrum of **22bb** in CDCl_3 (200 MHz)



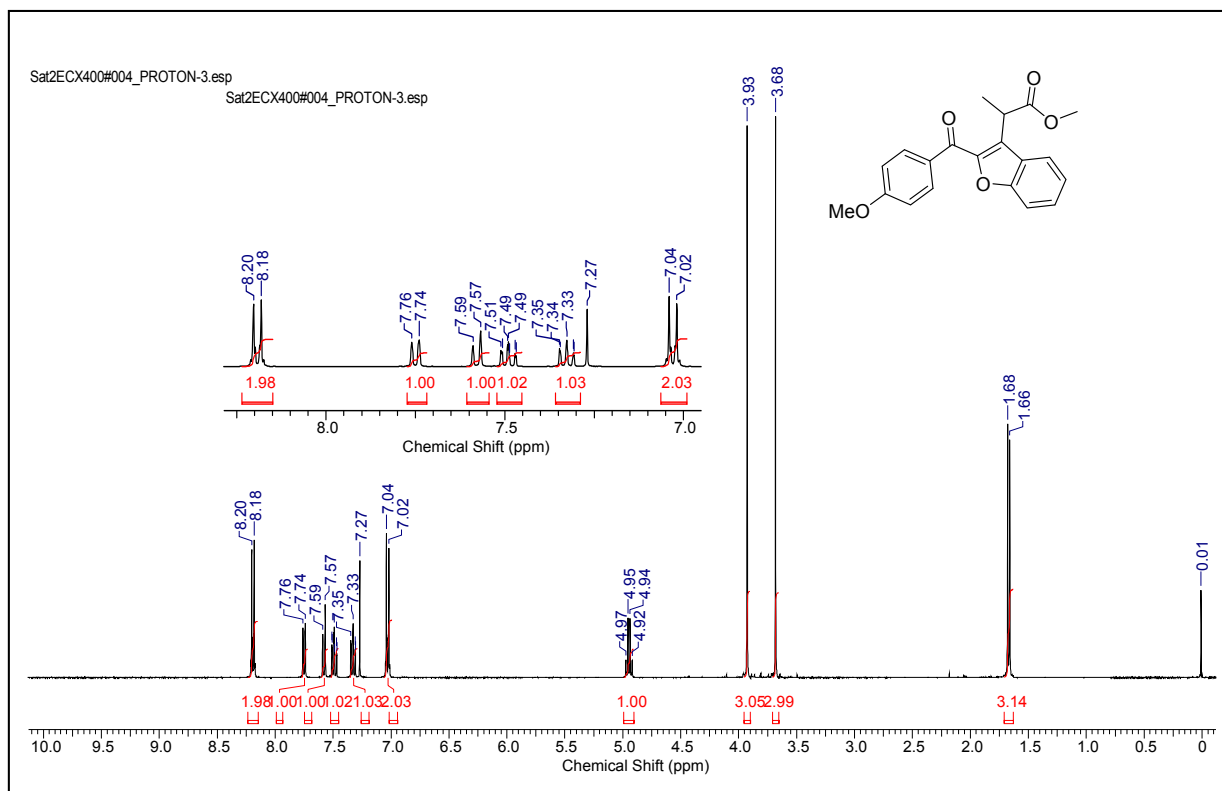
^{13}C NMR Spectrum of **22bb** in CDCl_3 (50 MHz)



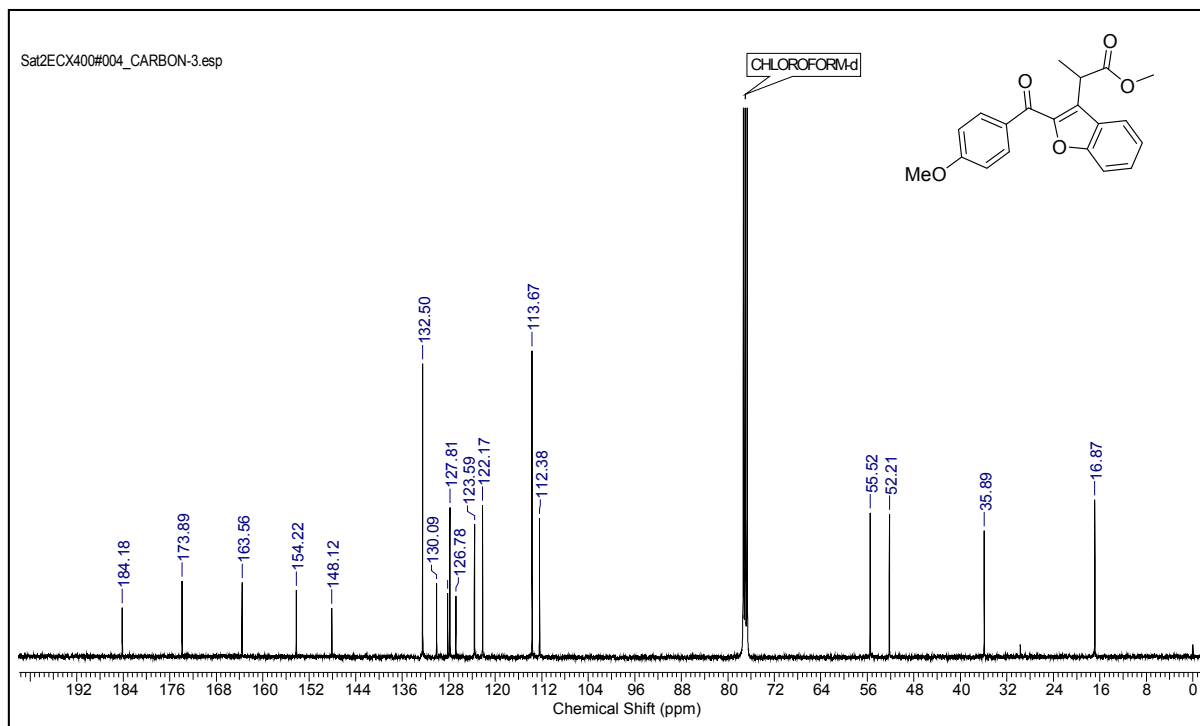
¹H NMR Spectrum of **22be** in CDCl₃ (200 MHz)



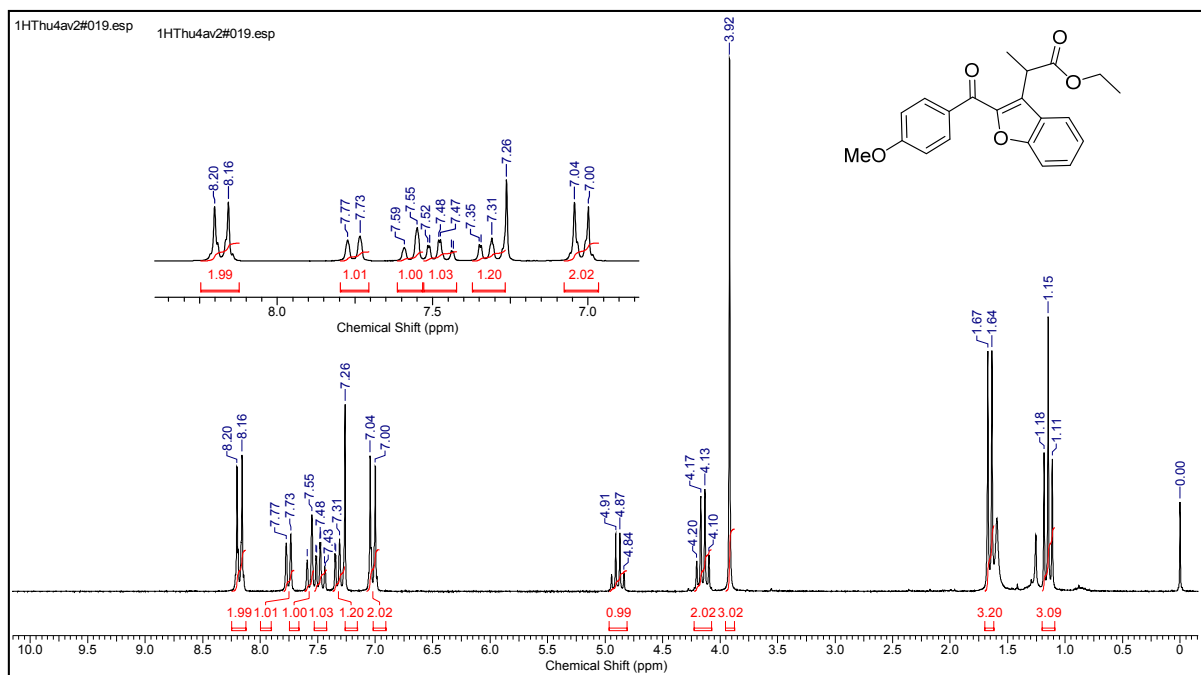
¹³C NMR Spectrum of **22be** in CDCl₃ (50 MHz)



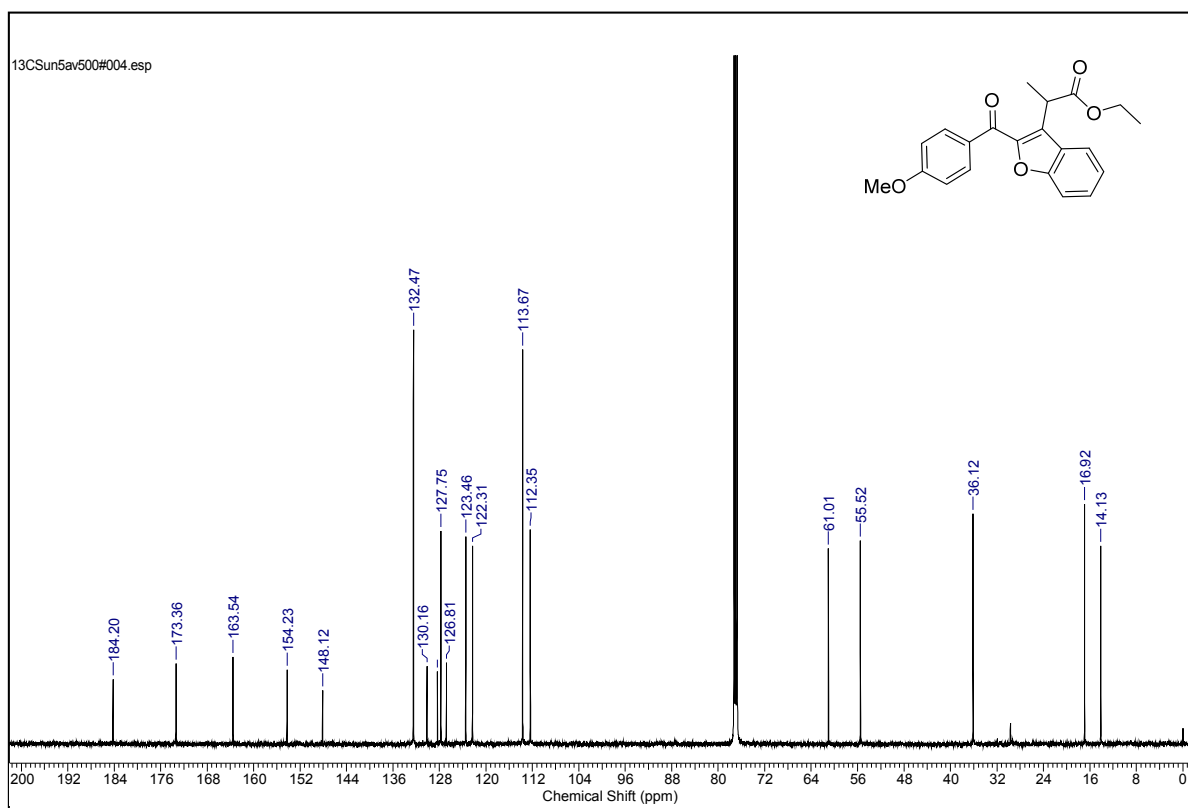
¹H NMR Spectrum of **22ca** in CDCl₃ (400 MHz)



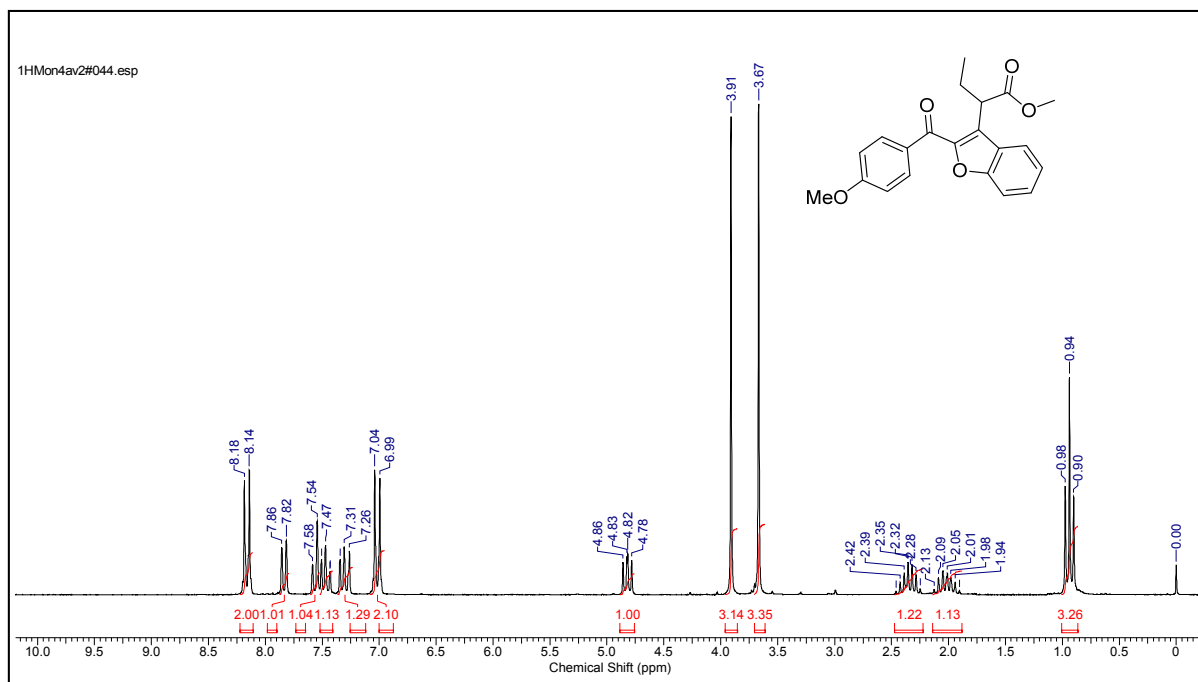
¹³C NMR Spectrum of **22ca** in CDCl₃ (100 MHz)



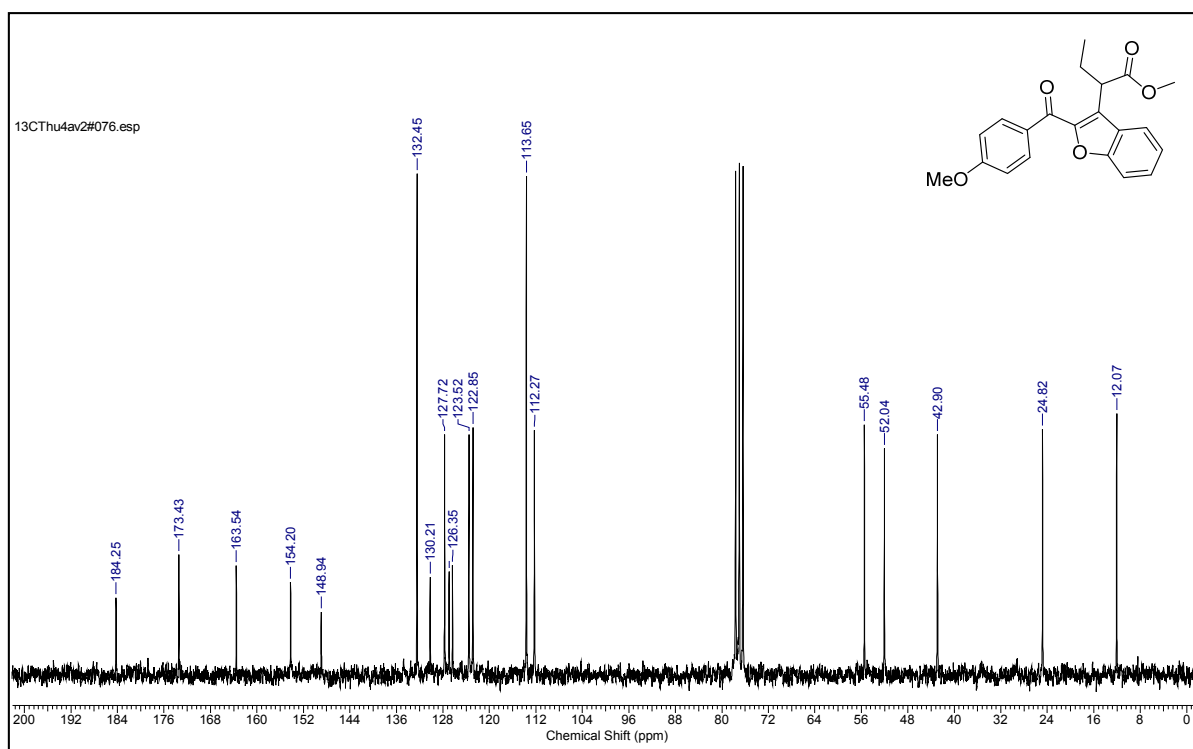
¹H NMR Spectrum of **22cb** in CDCl₃ (200 MHz)



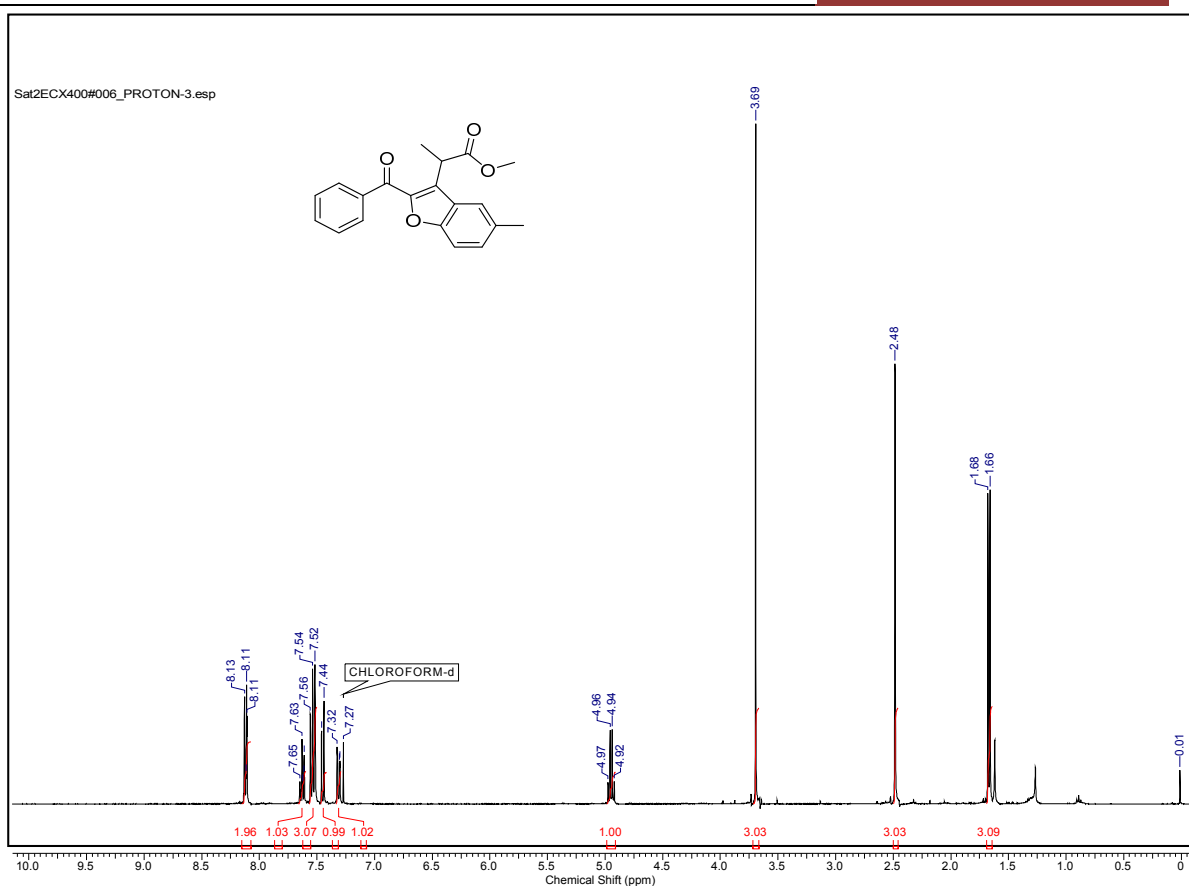
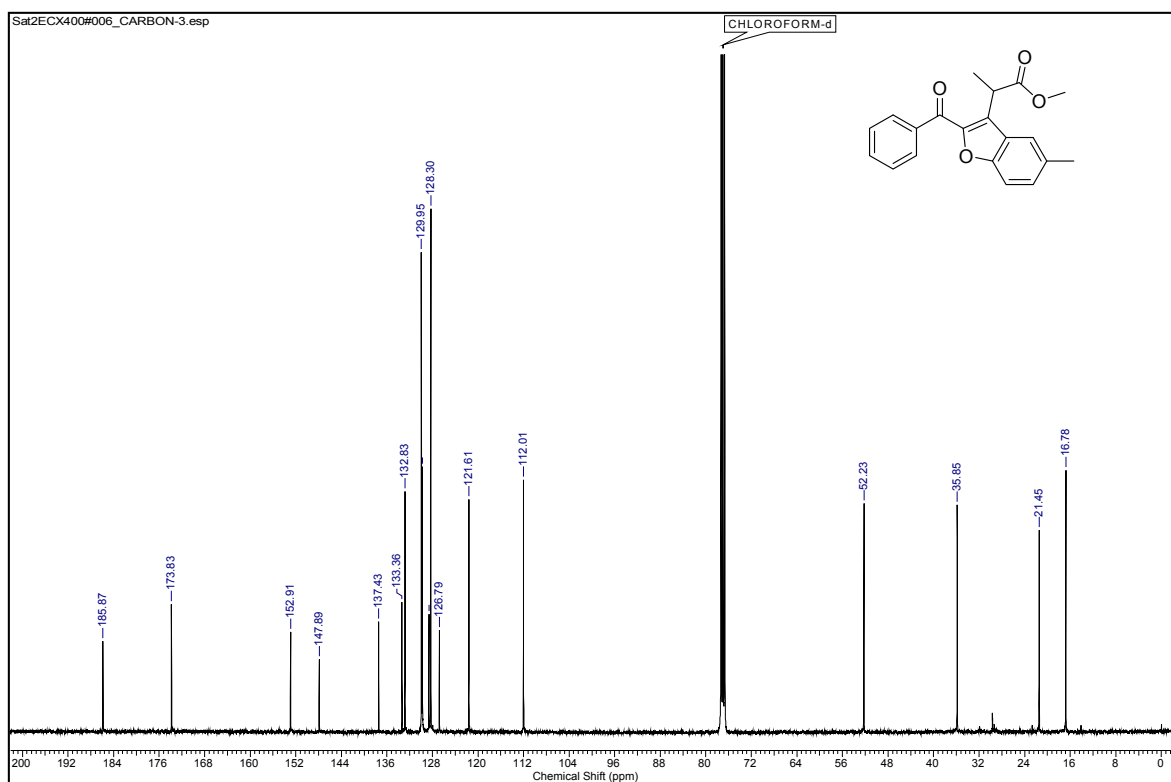
¹³C NMR Spectrum of **22cb** in CDCl₃ (125 MHz)

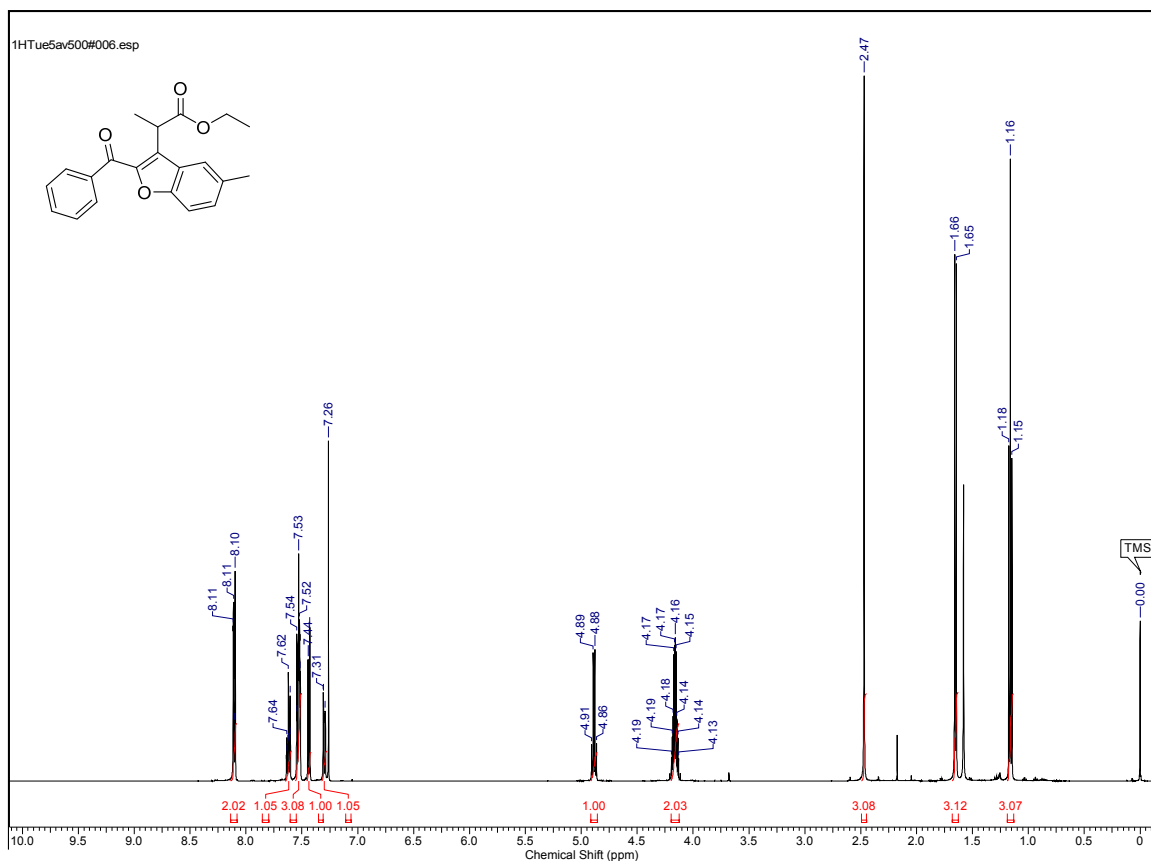
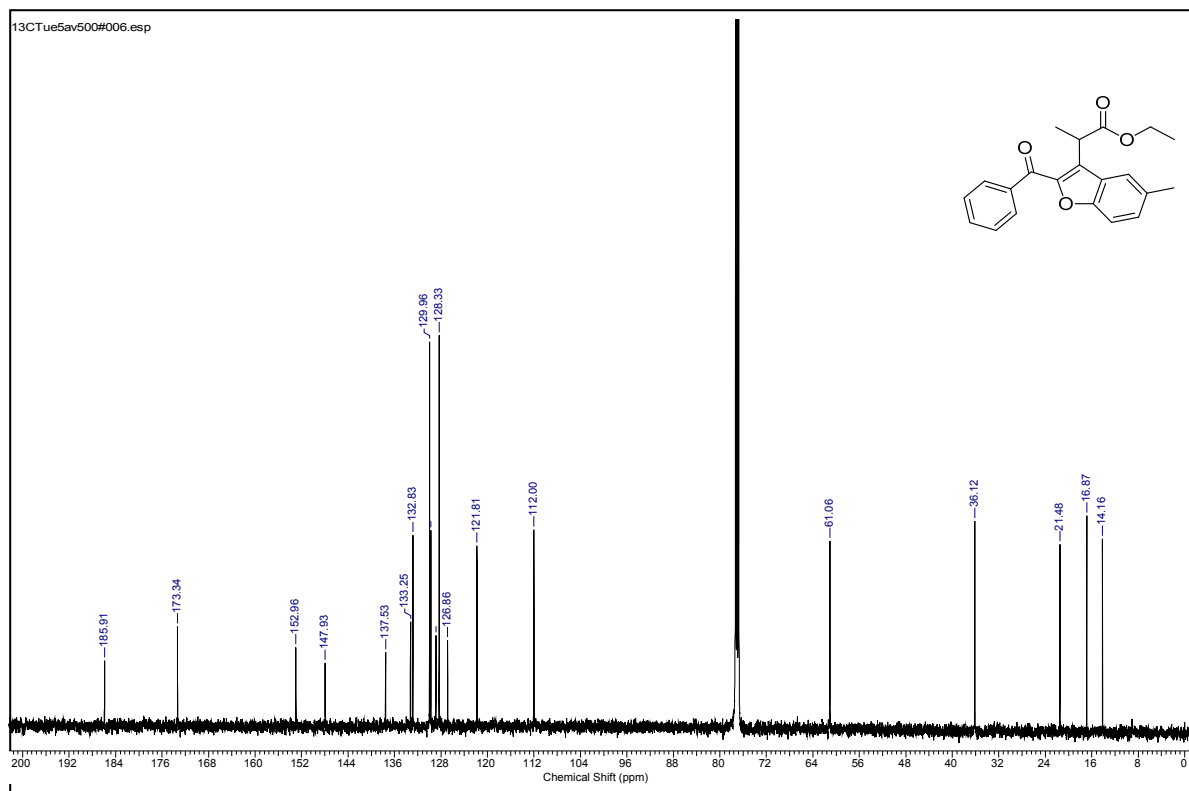


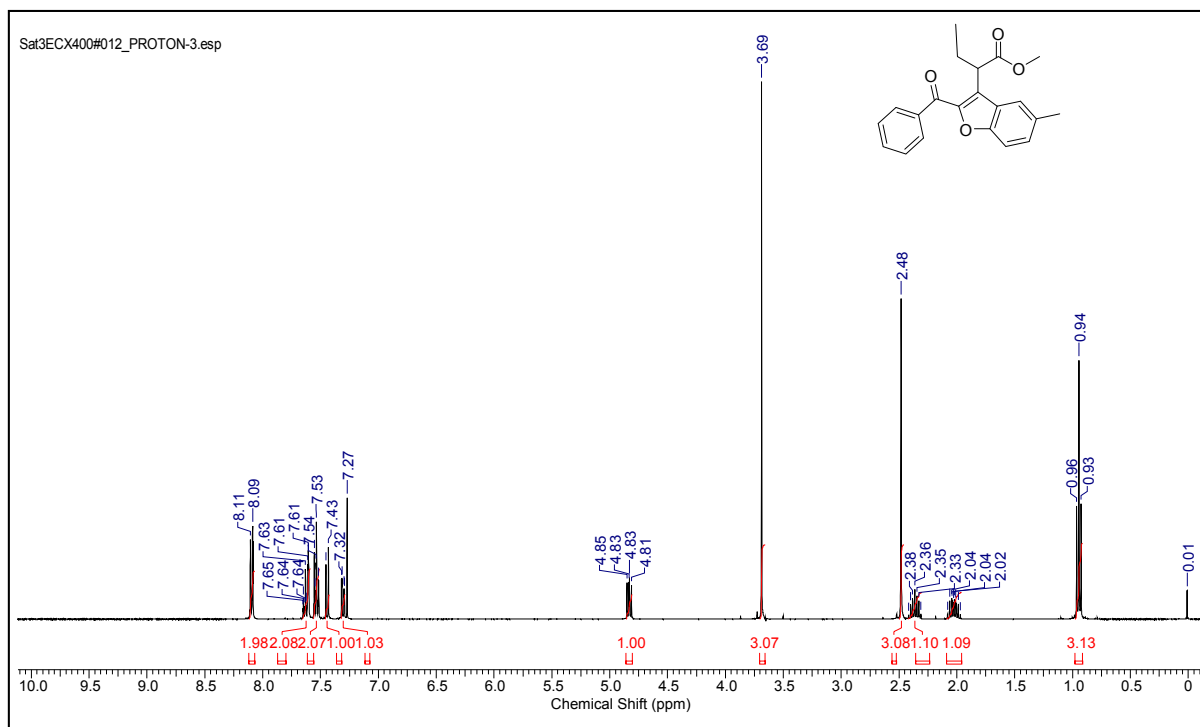
¹H NMR Spectrum of **22ce** in CDCl₃ (200MHz)



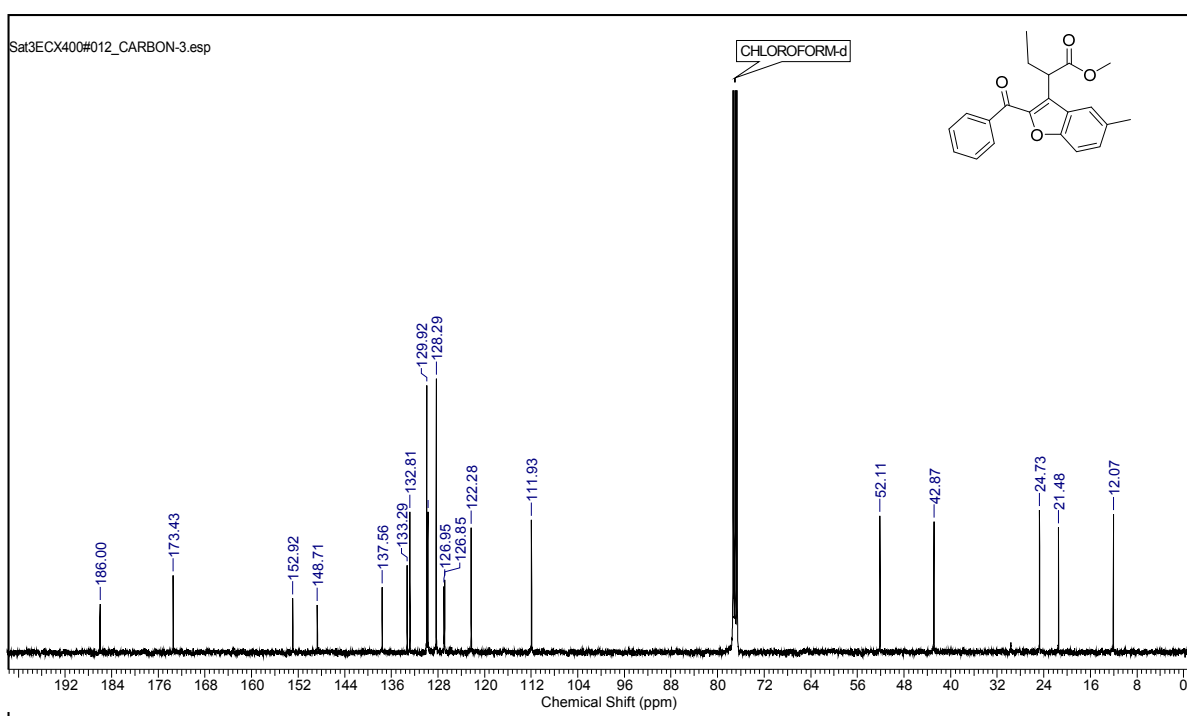
¹³C NMR Spectrum of **22ce** in CDCl₃ (50 MHz)

 ^1H NMR Spectrum of **22da** in CDCl_3 (400 MHz) ^{13}C NMR Spectrum of **22da** in CDCl_3 (100 MHz)

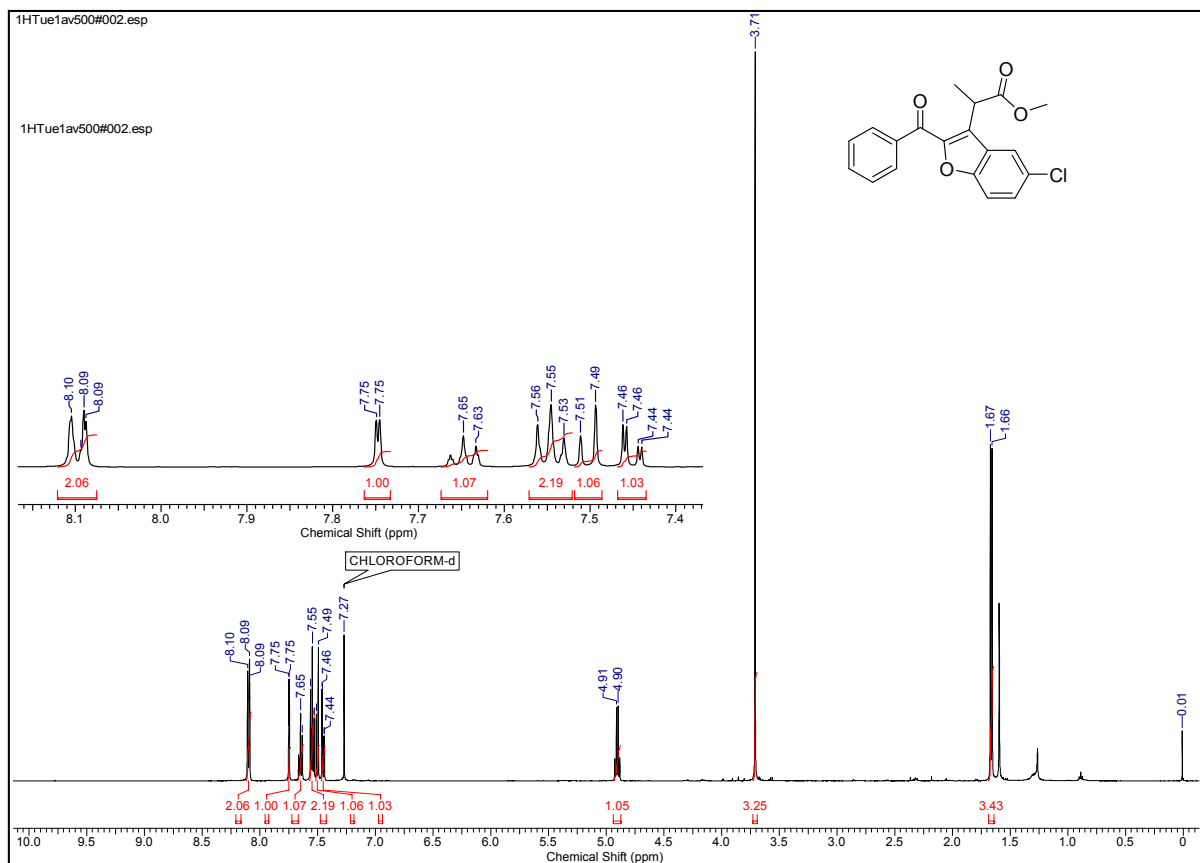
¹H NMR Spectrum of **22db** in CDCl₃ (500 MHz) ^{13}C NMR Spectrum of **22db** in CDCl_3 (125 MHz)



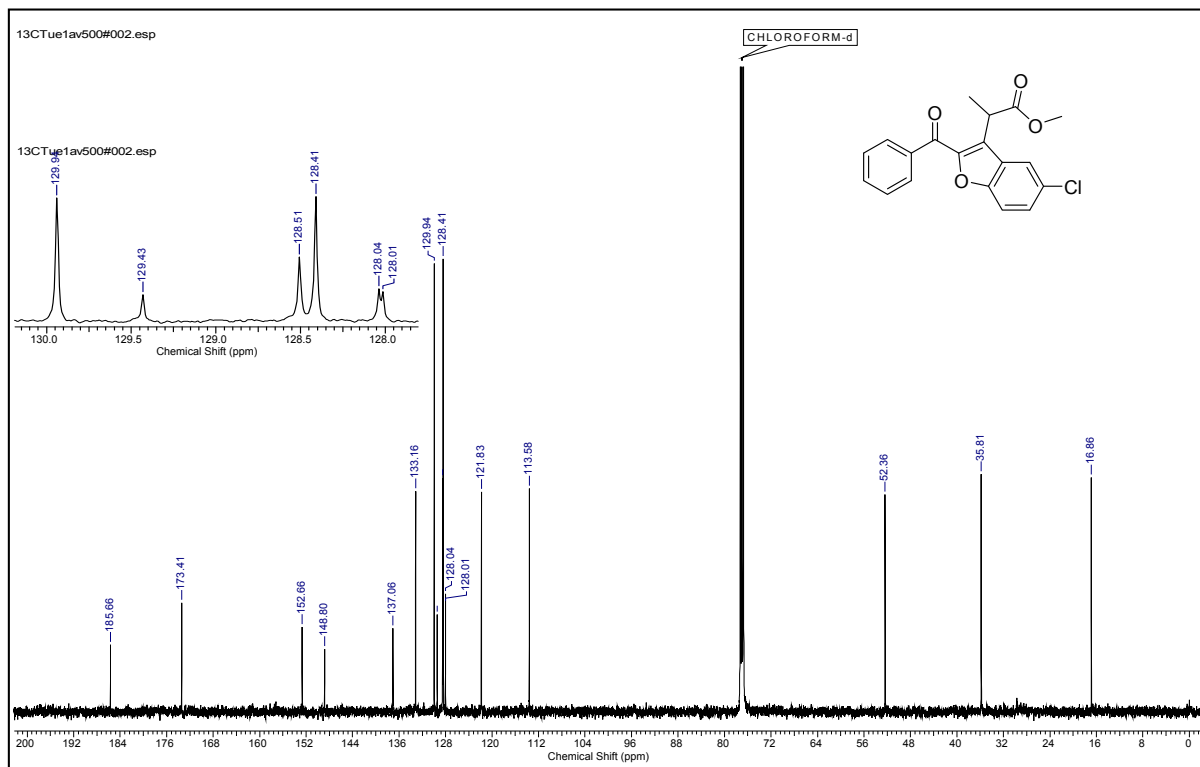
¹H NMR Spectrum of **22de** in CDCl₃ (400 MHz)



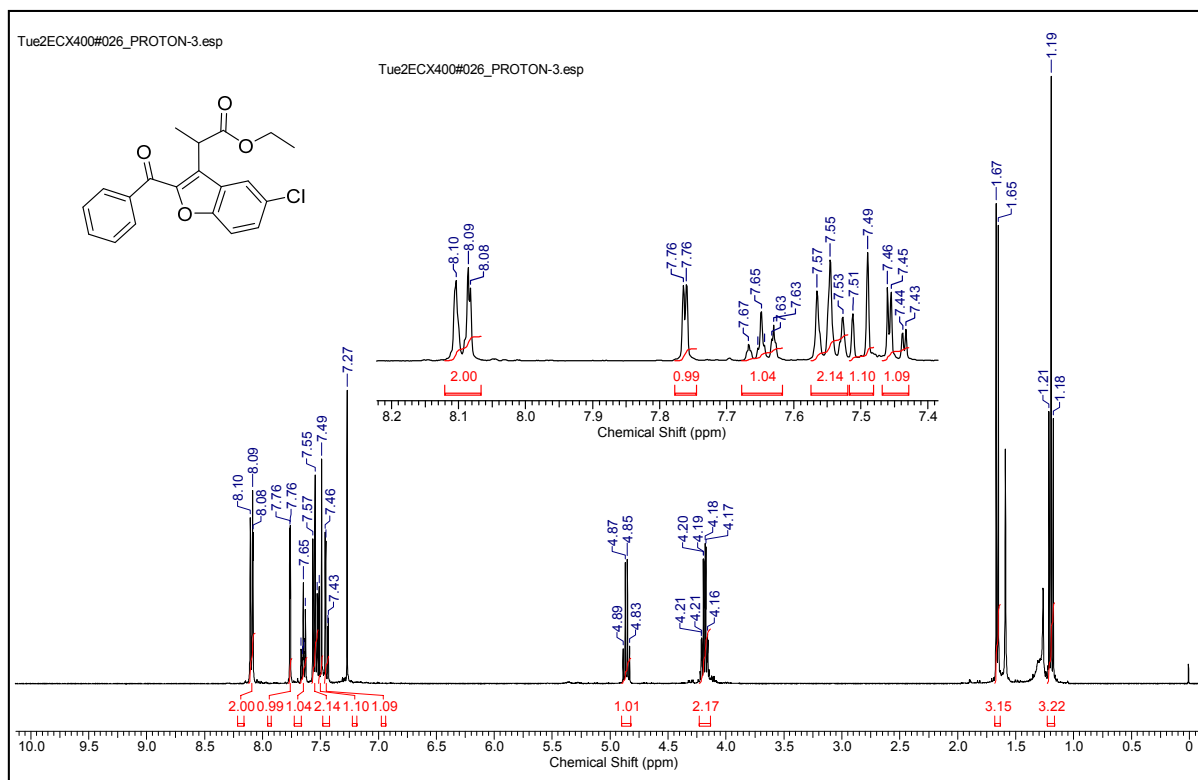
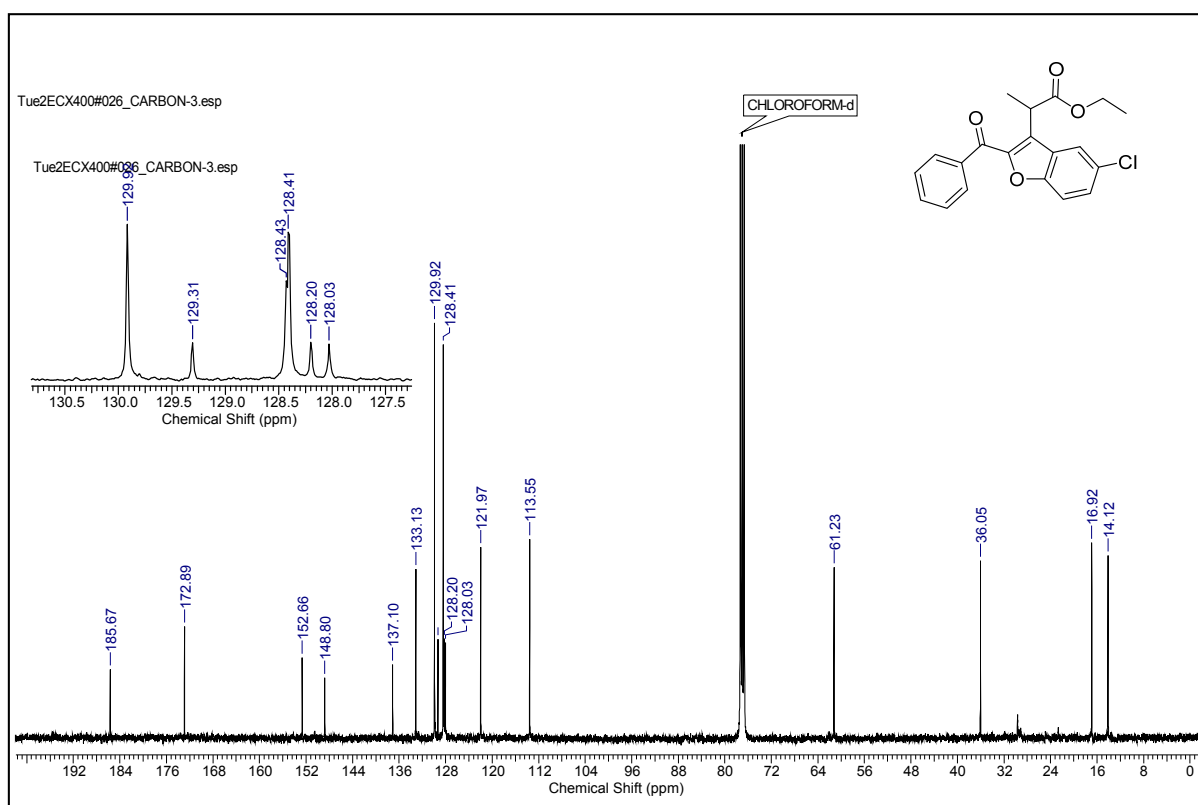
¹³C NMR Spectrum of **22de** in CDCl₃ (100 MHz)

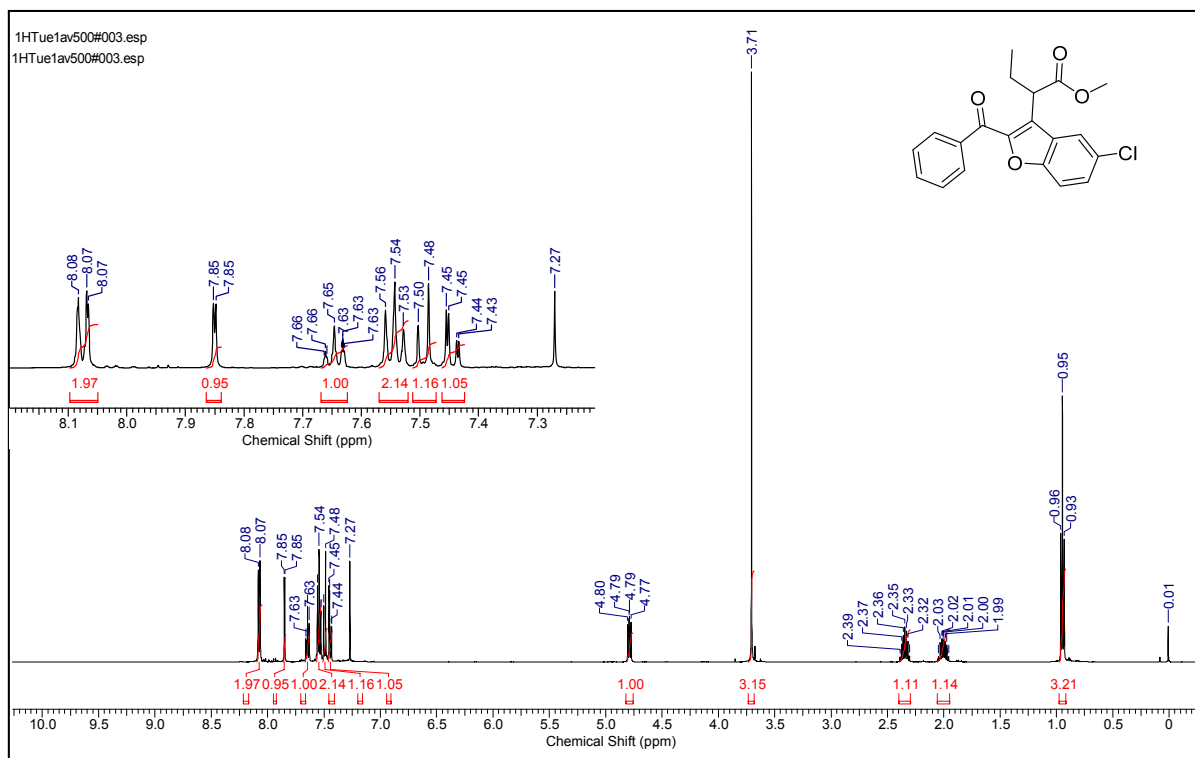


¹H NMR Spectrum of **27ea** in CDCl₃ (500 MHz)

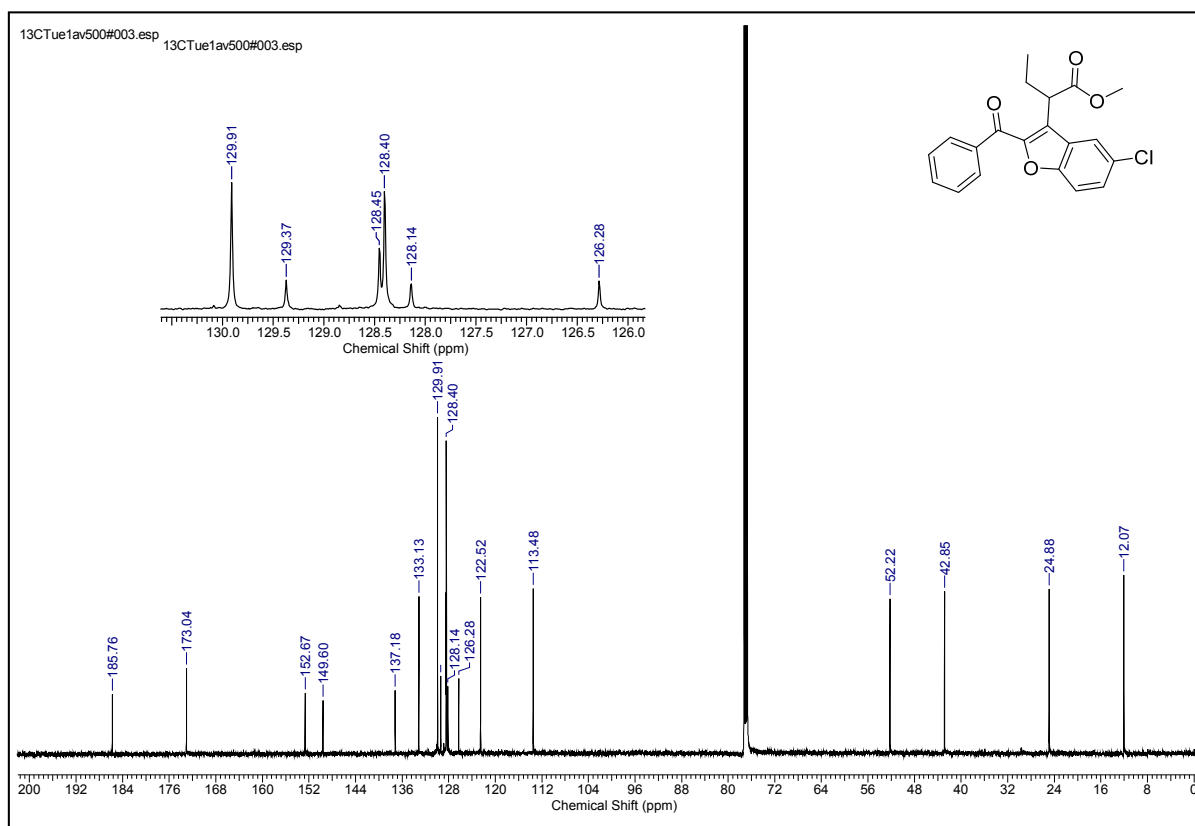


¹³C NMR Spectrum of **27ea** in CDCl₃ (125 MHz)

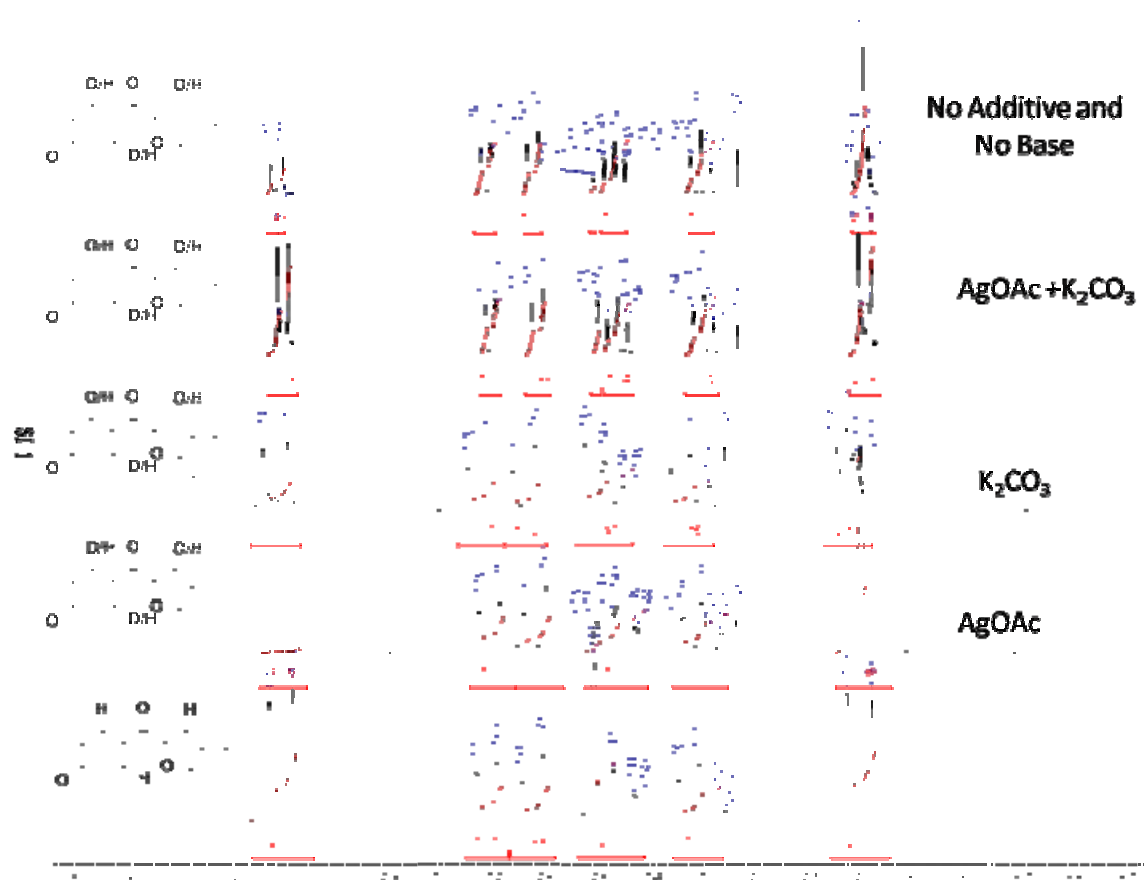
¹H NMR Spectrum of **22eb** in CDCl₃ (400 MHz)¹³C NMR Spectrum of **22eb** in CDCl₃ (100 MHz)

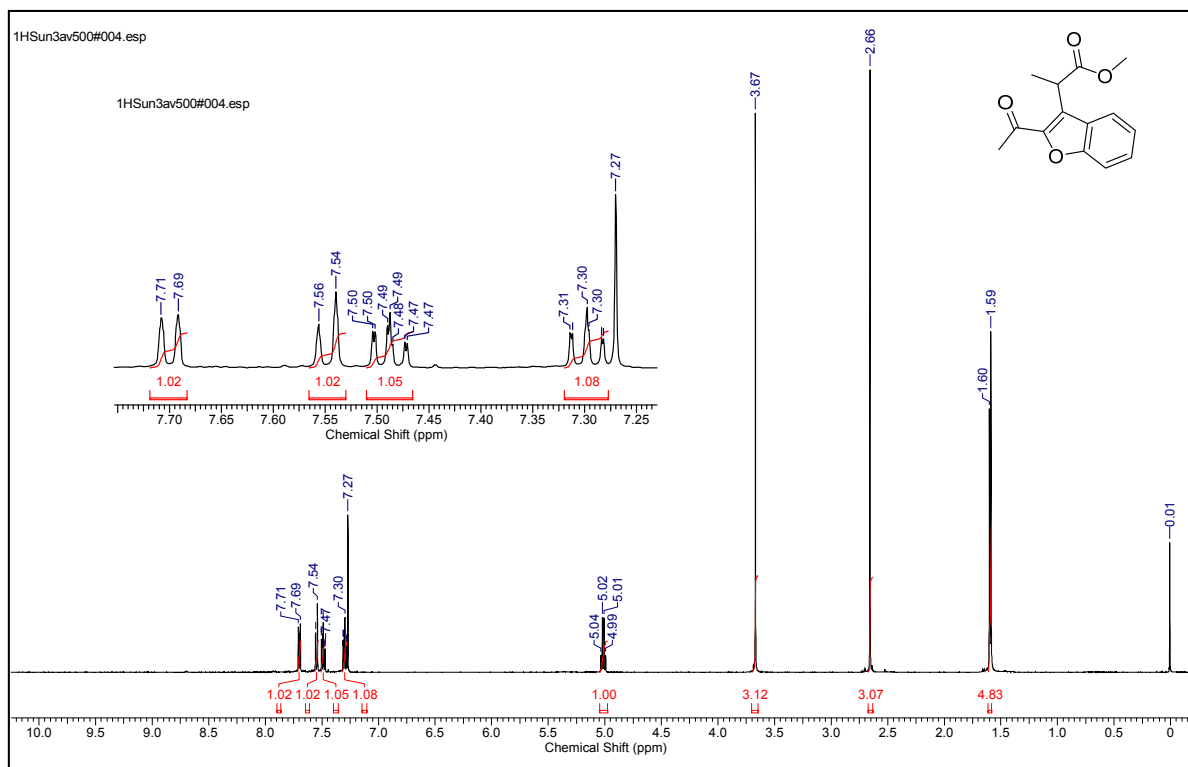


¹H NMR Spectrum of **22ee** in CDCl₃ (500 MHz)

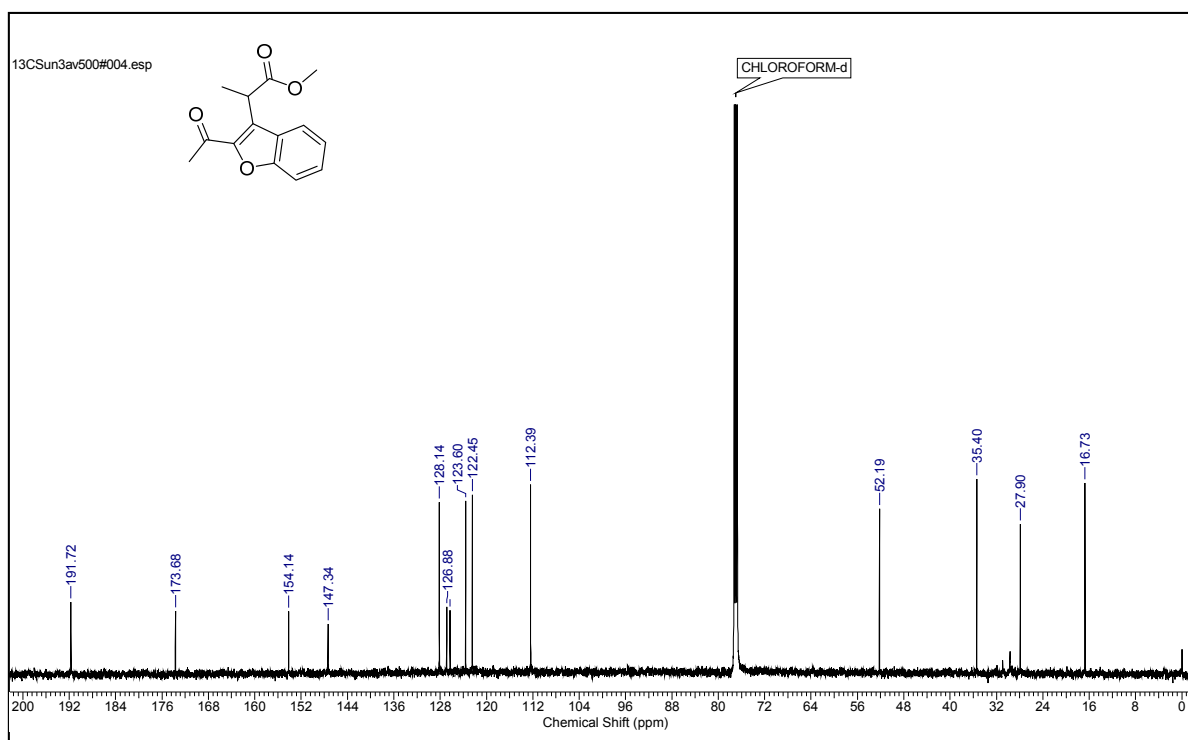


¹³C NMR Spectrum of **22ee** in CDCl₃ (125 MHz)

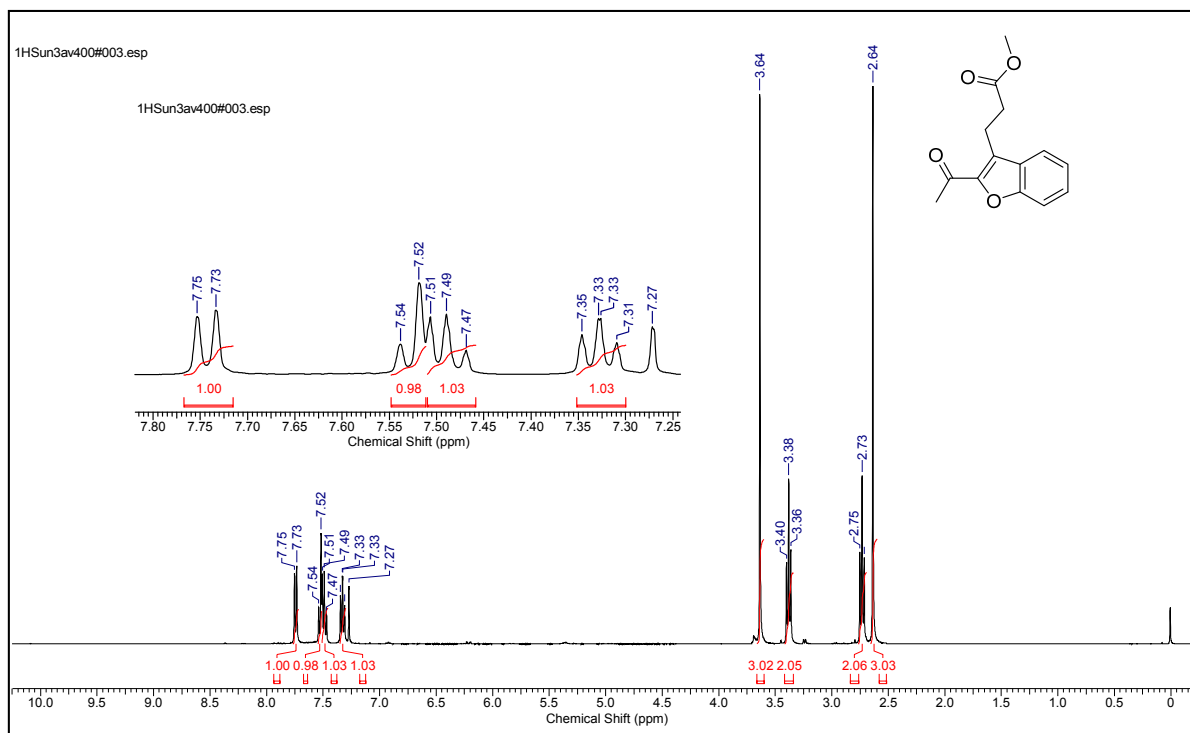




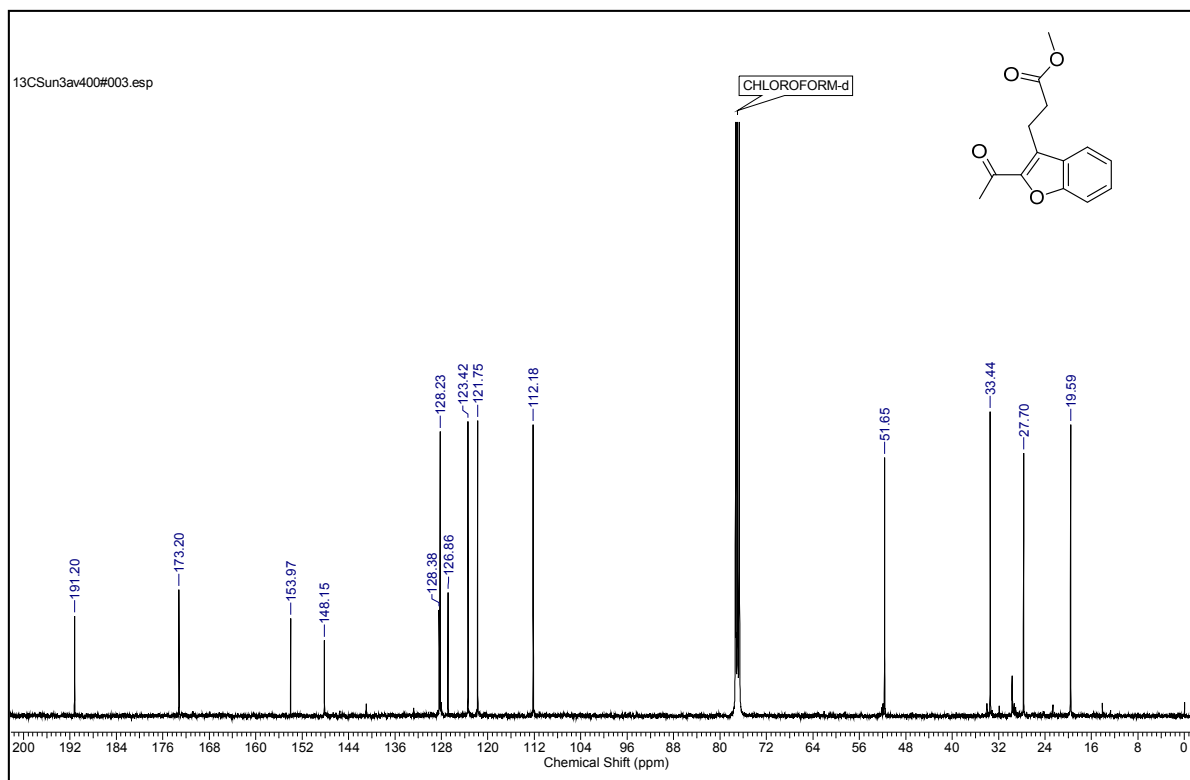
¹H NMR Spectrum of **22fa** in CDCl₃ (500 MHz)



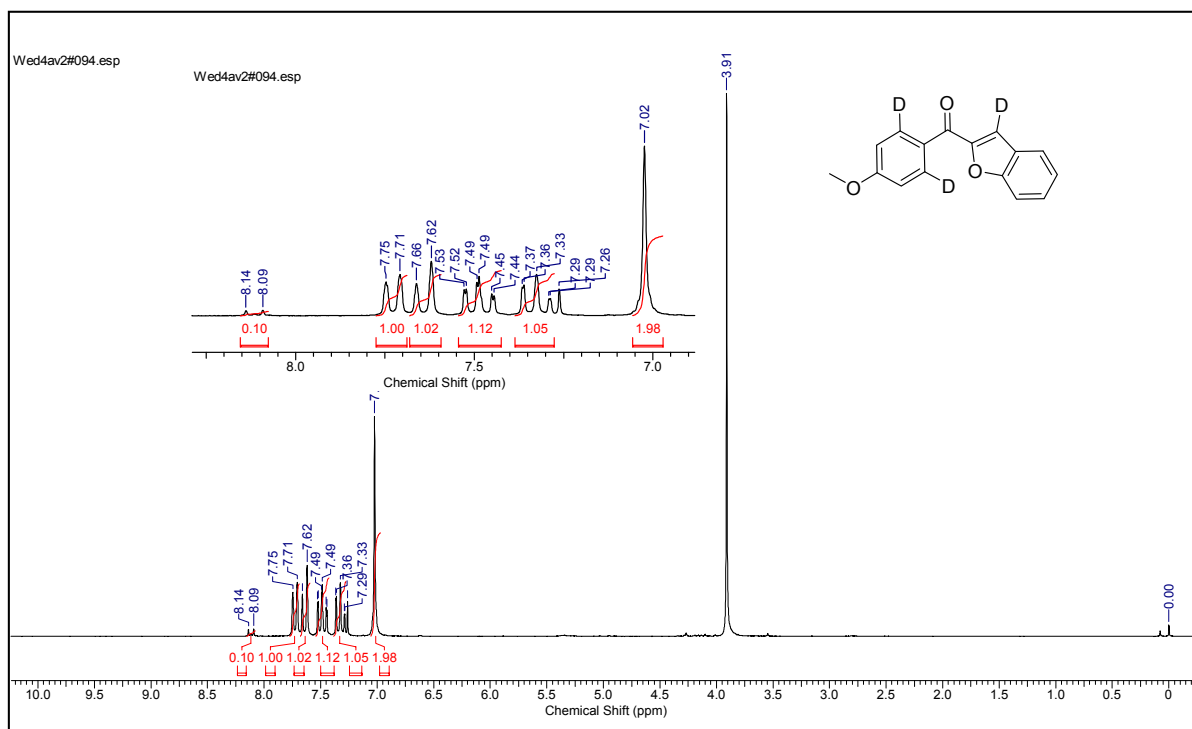
¹³C NMR Spectrum of **22fa** in CDCl₃ (125 MHz)



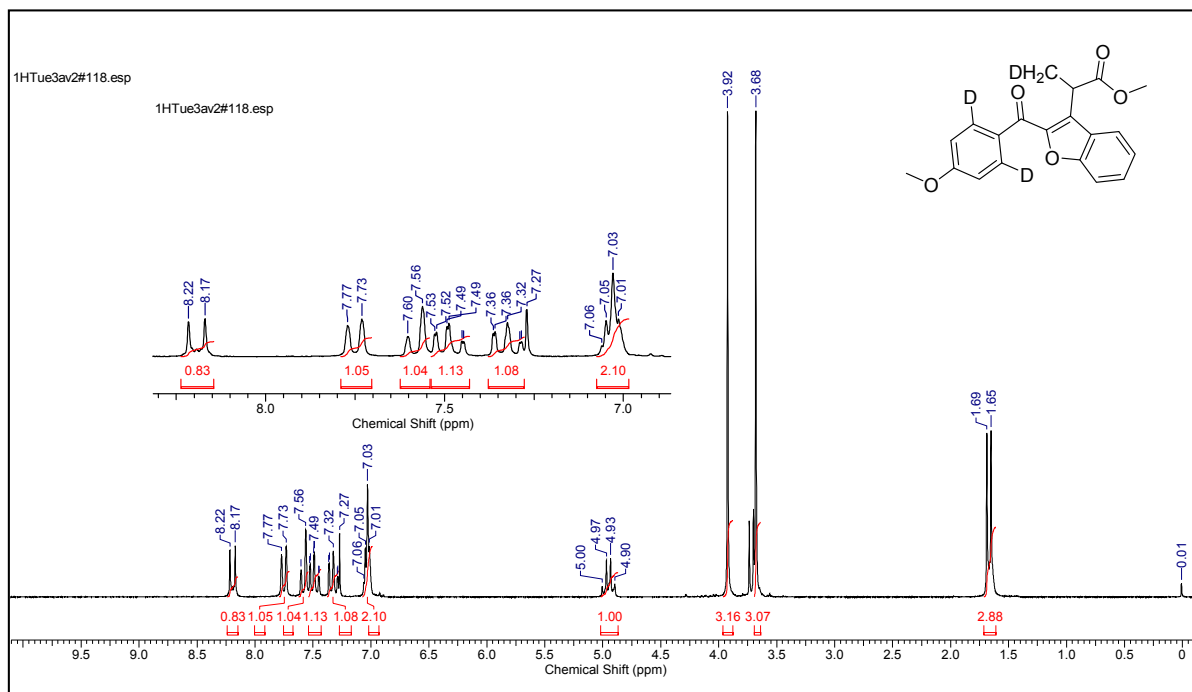
¹H NMR Spectrum of **23fa** in CDCl₃ (400 MHz)

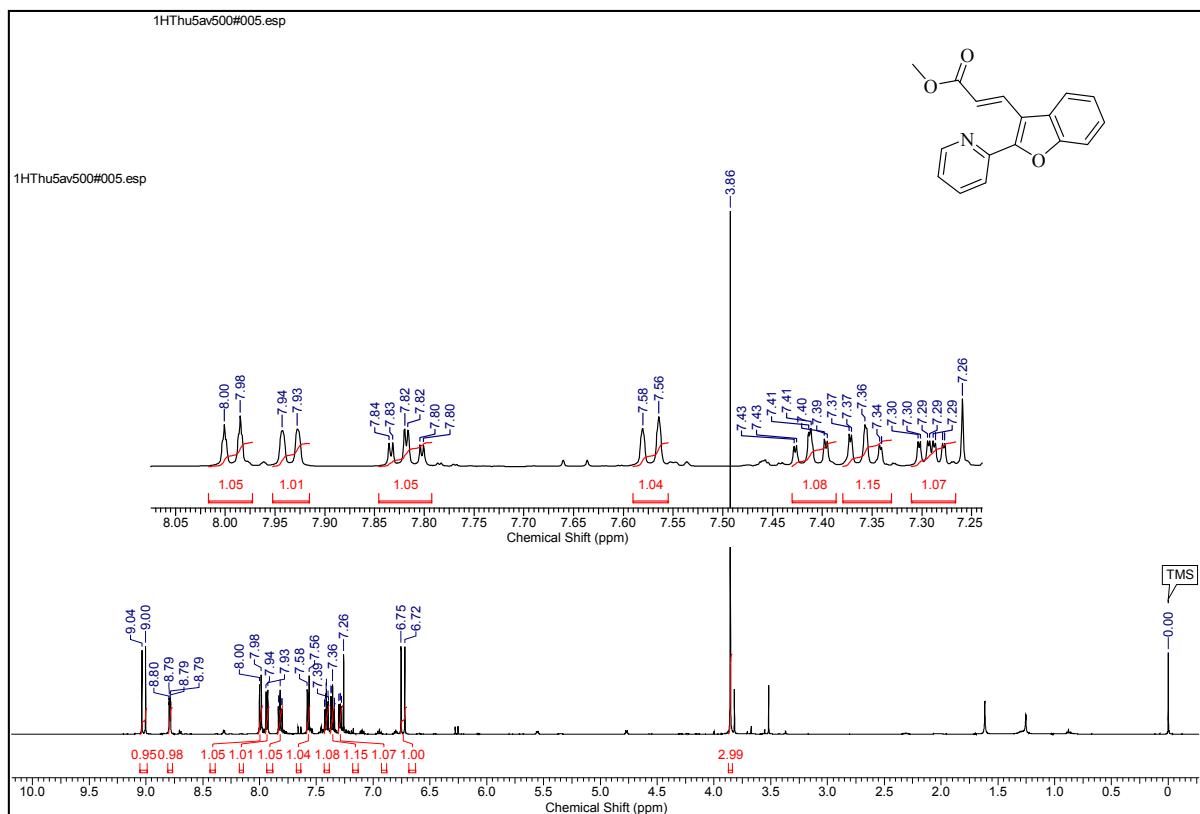


¹³C NMR Spectrum of **23fa** in CDCl₃ (100 MHz)

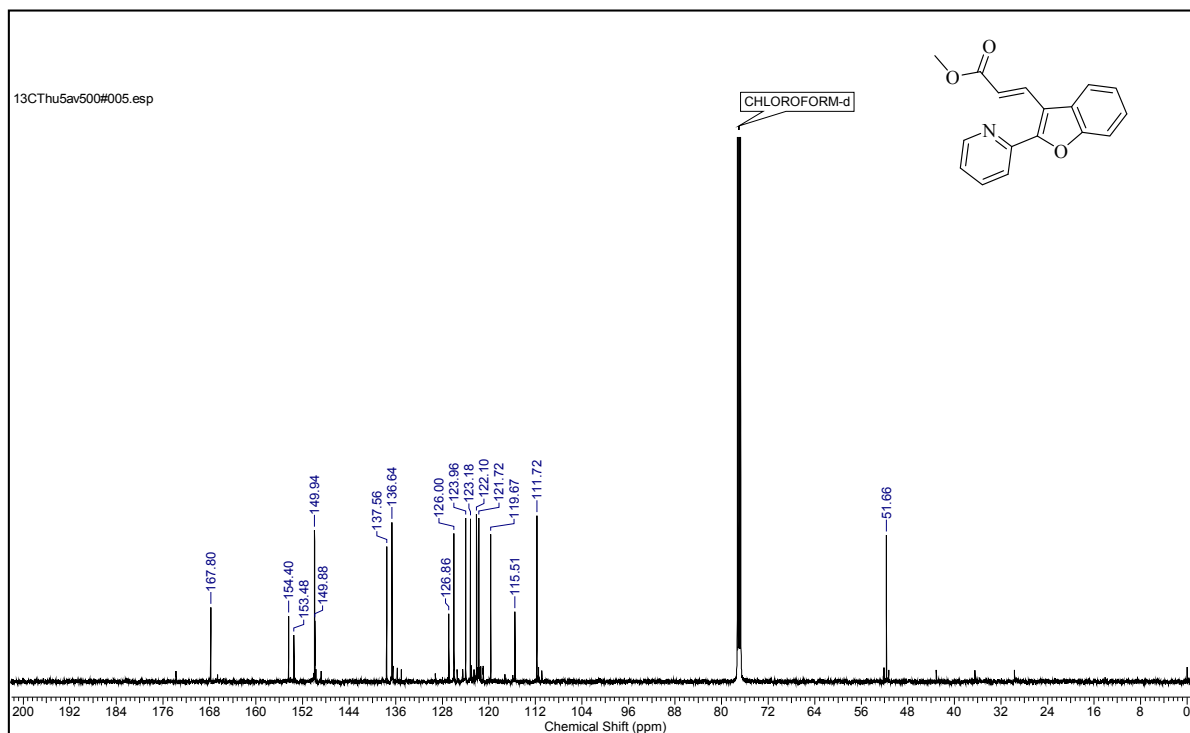


¹H NMR Spectrum of **25** in CDCl₃ (200 MHz)

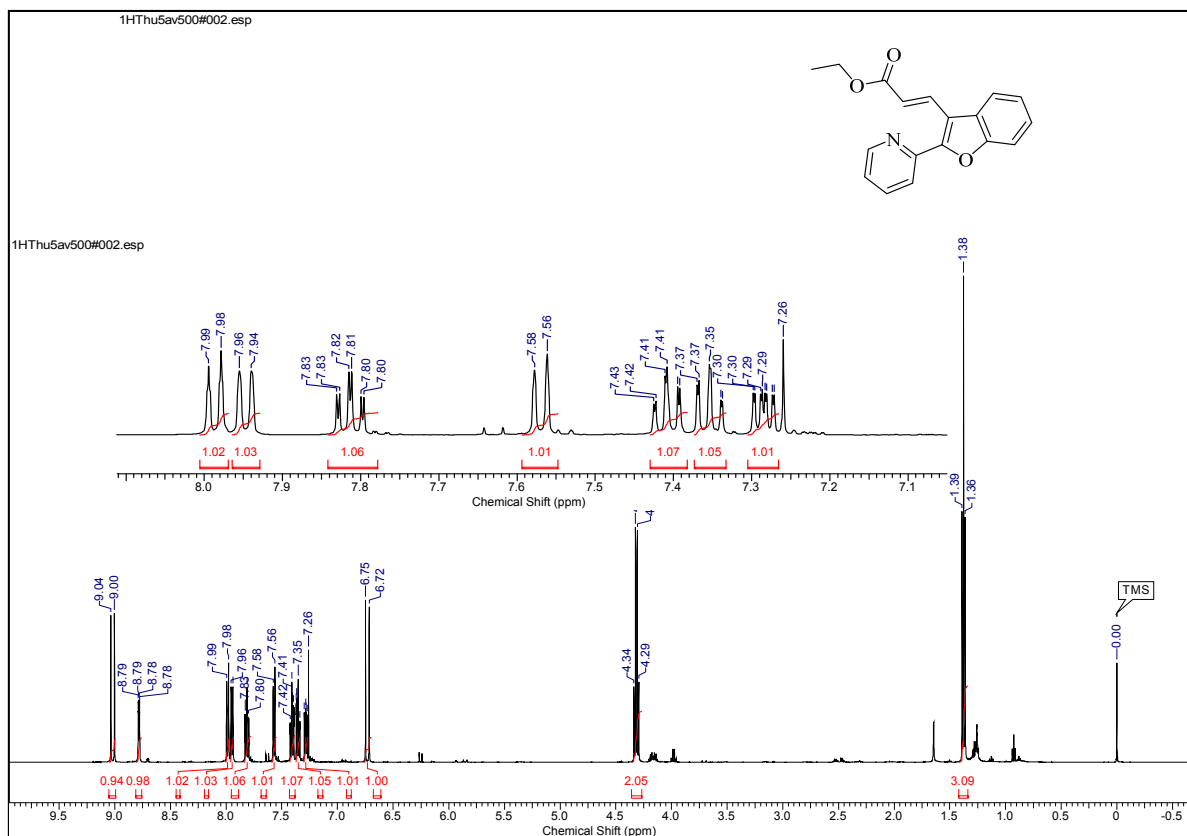
¹H NMR Spectrum of **26** in CDCl₃ (200 MHz)



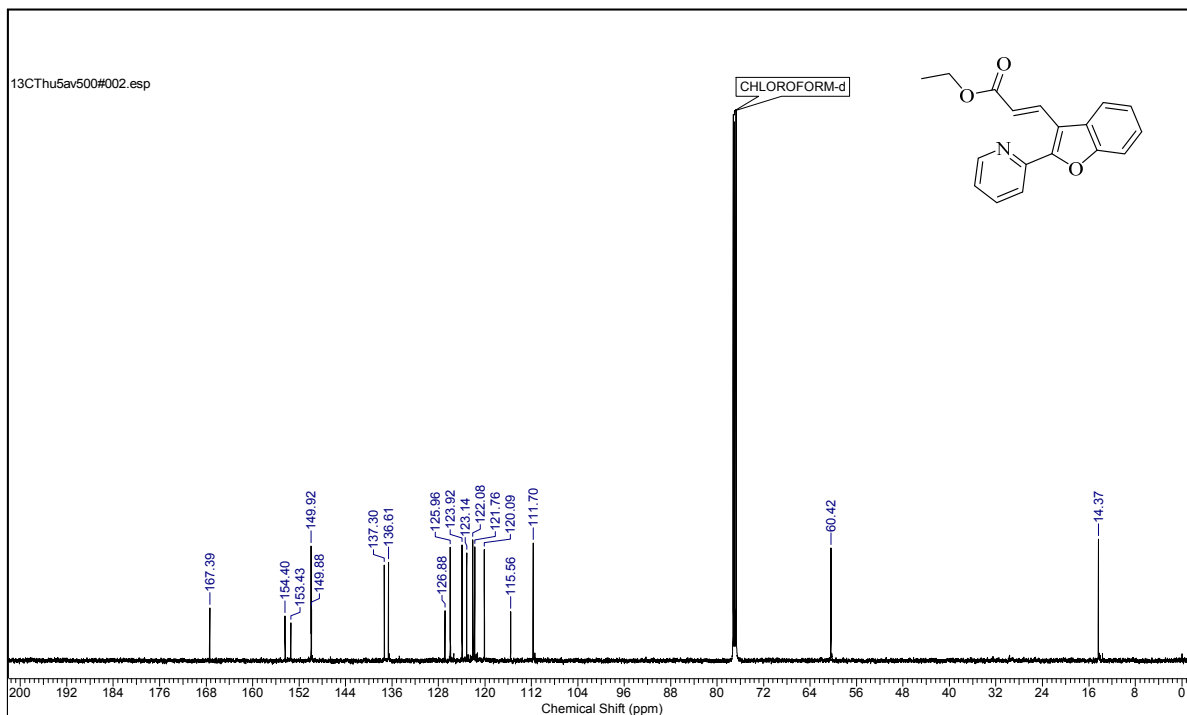
¹H NMR Spectrum of **29aa** in CDCl₃ (500 MHz)



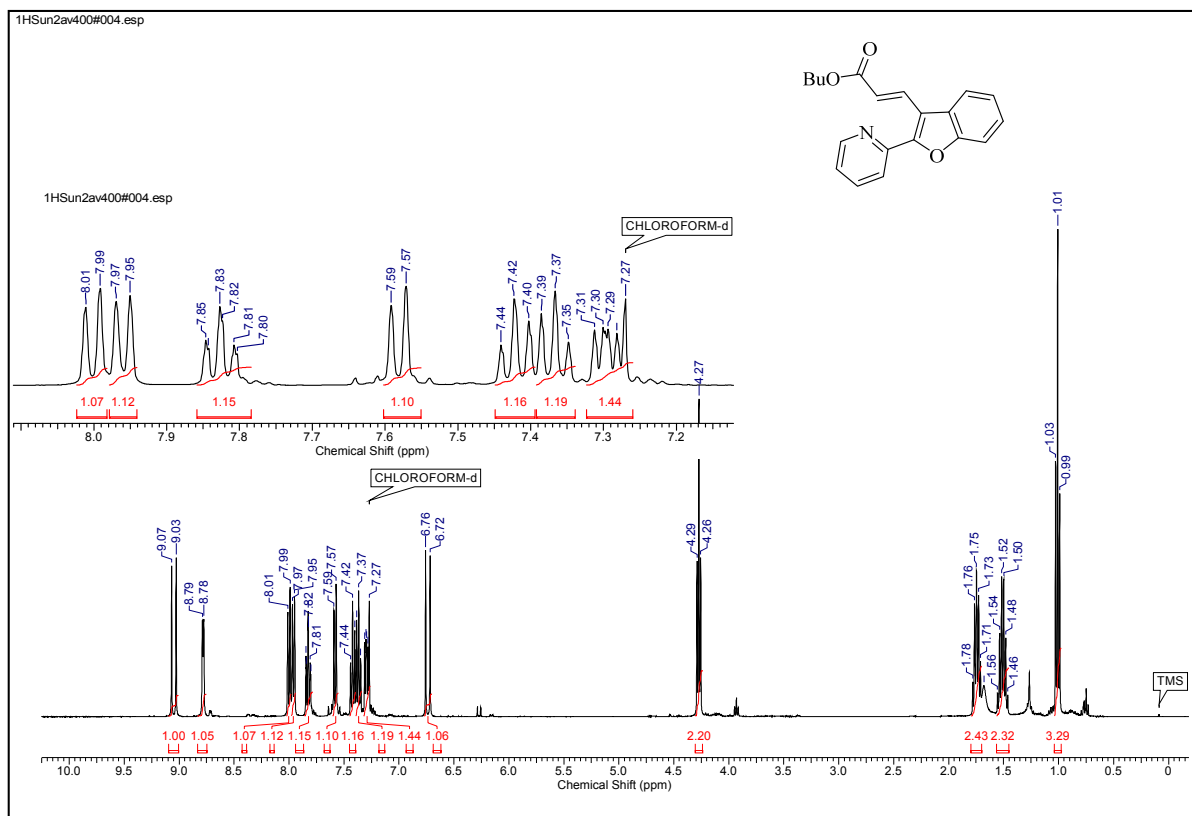
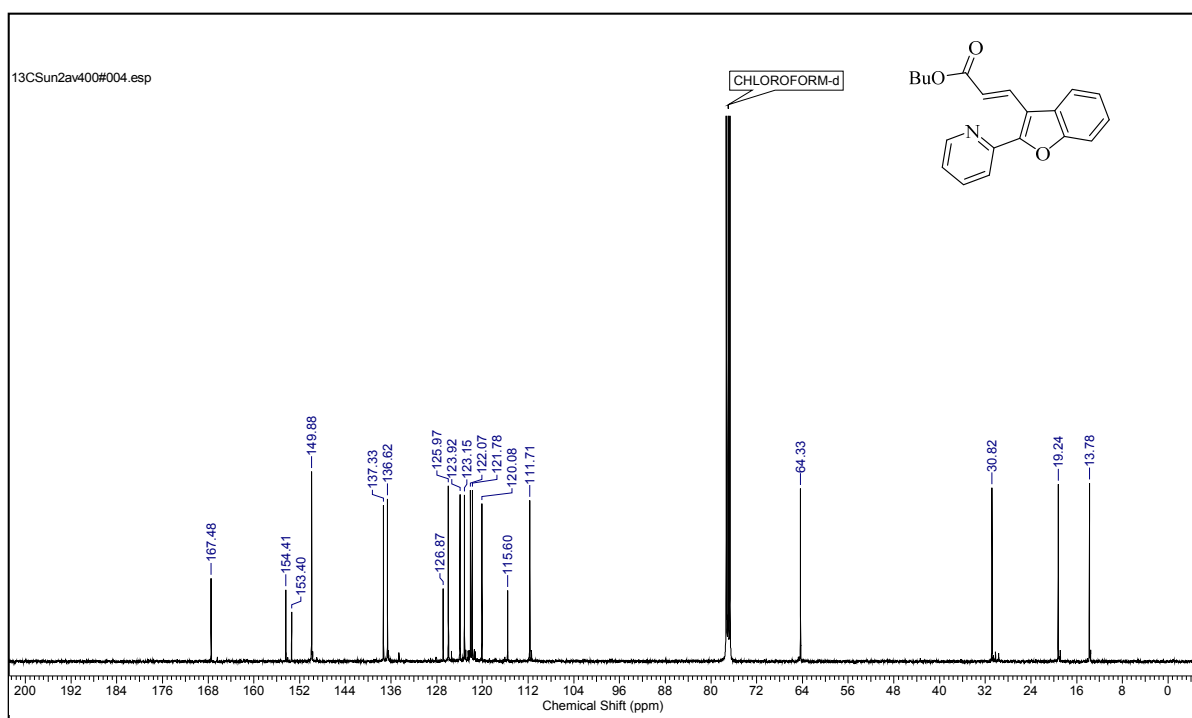
¹³C NMR Spectrum of **29aa** in CDCl₃ (125 MHz)

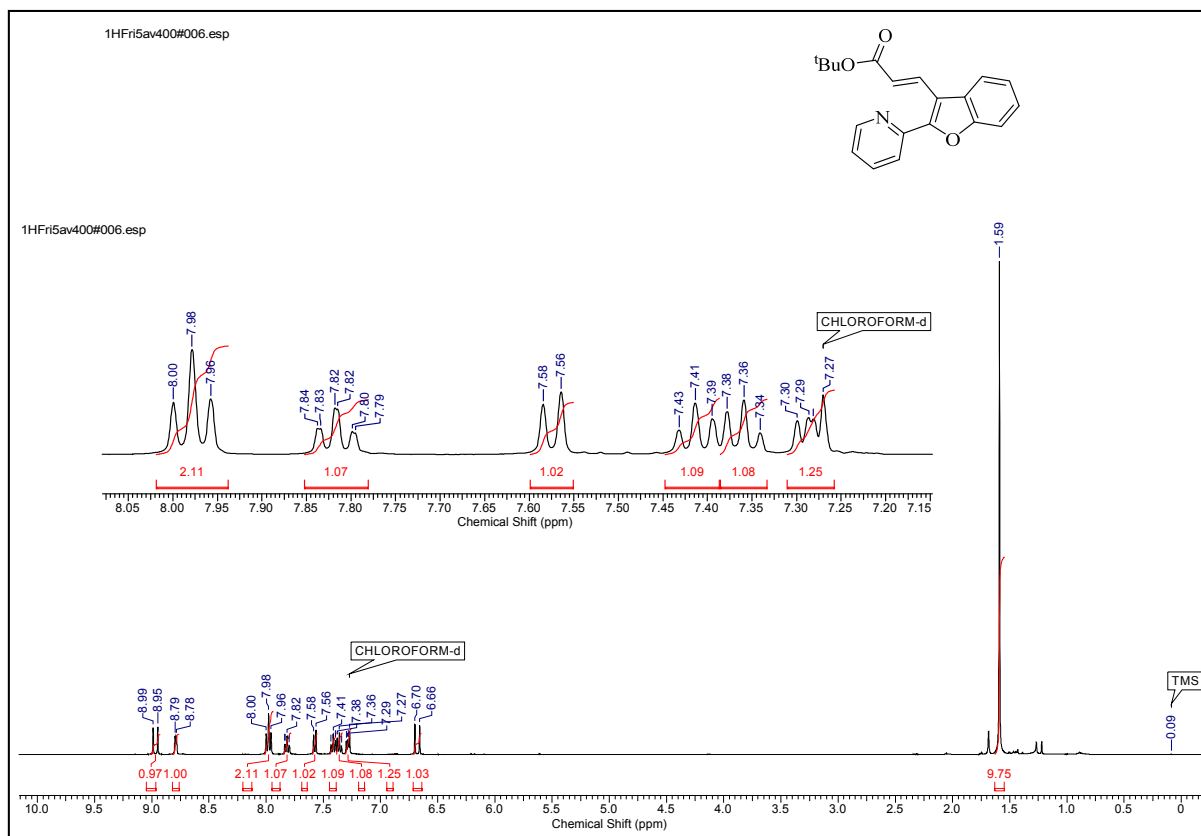


¹H NMR Spectrum of **29ab** in CDCl₃ (500 MHz)

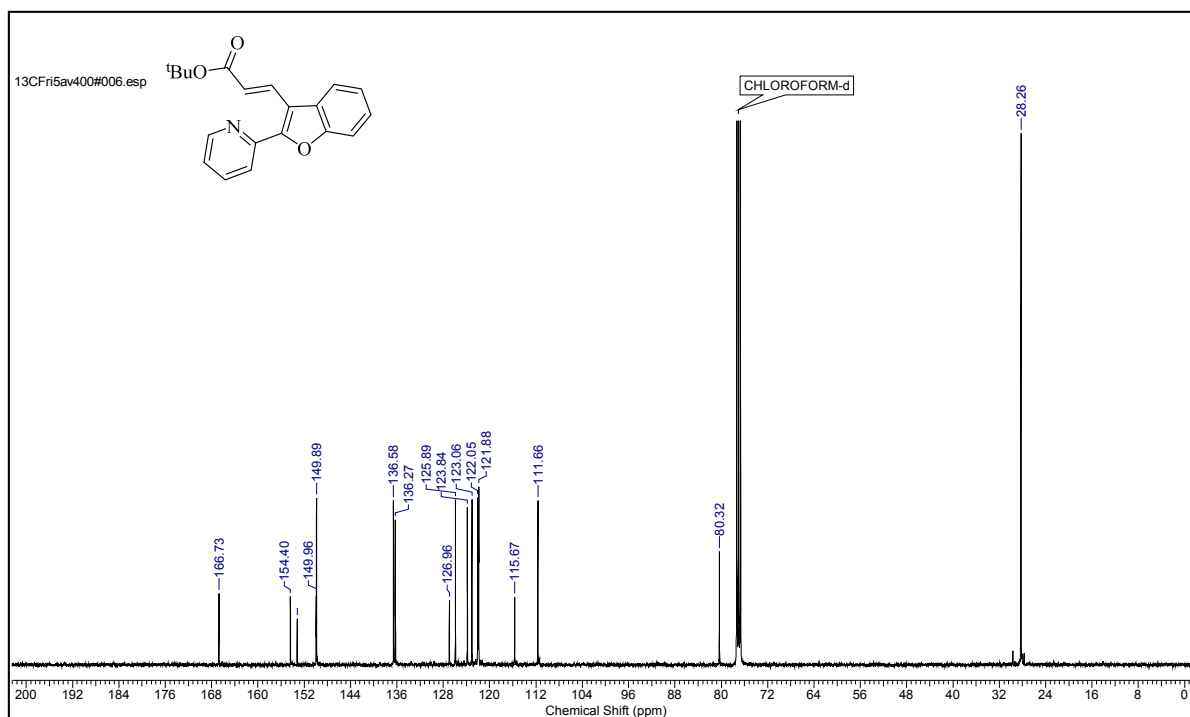


¹³C NMR Spectrum of **29ab** in CDCl₃ (125 MHz)

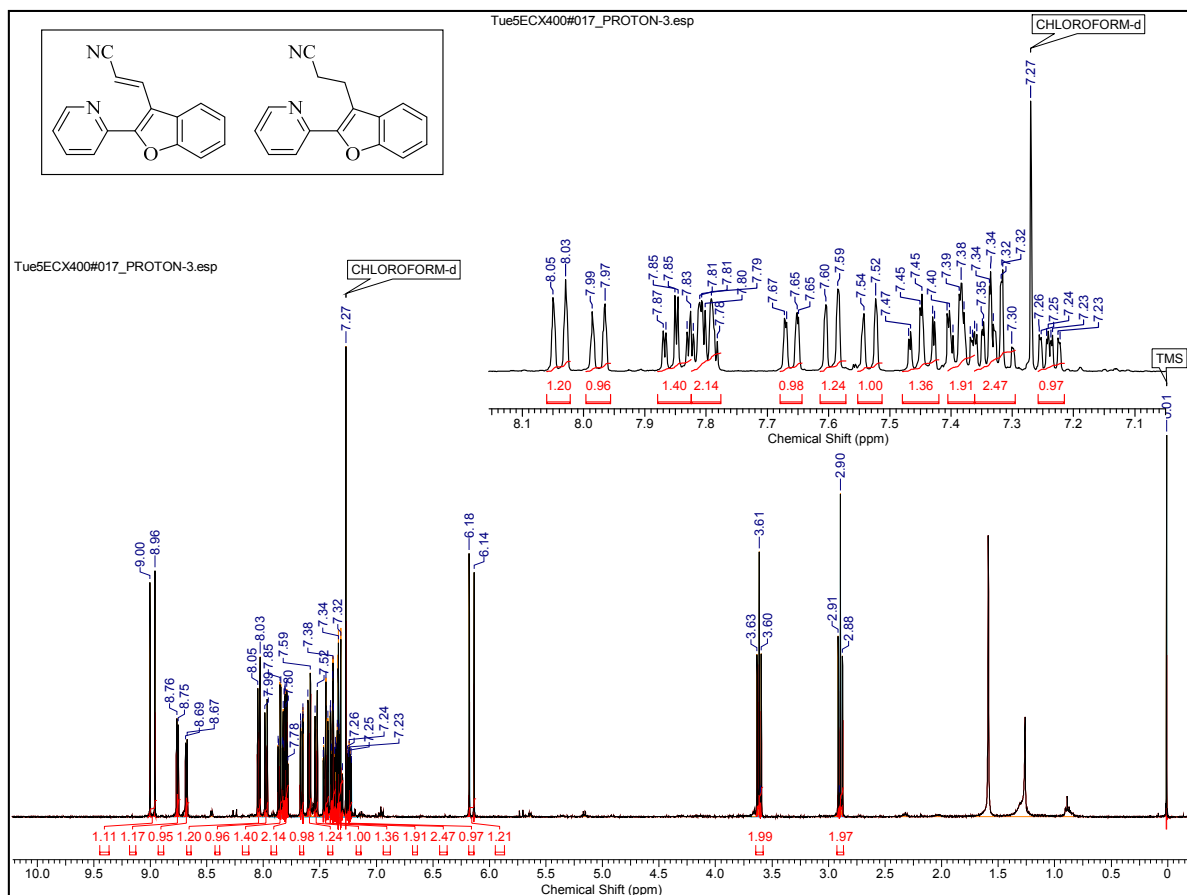
¹H NMR Spectrum of **29ac** in CDCl₃ (400 MHz)¹³C NMR Spectrum of **29ac** in CDCl₃ (100 MHz)



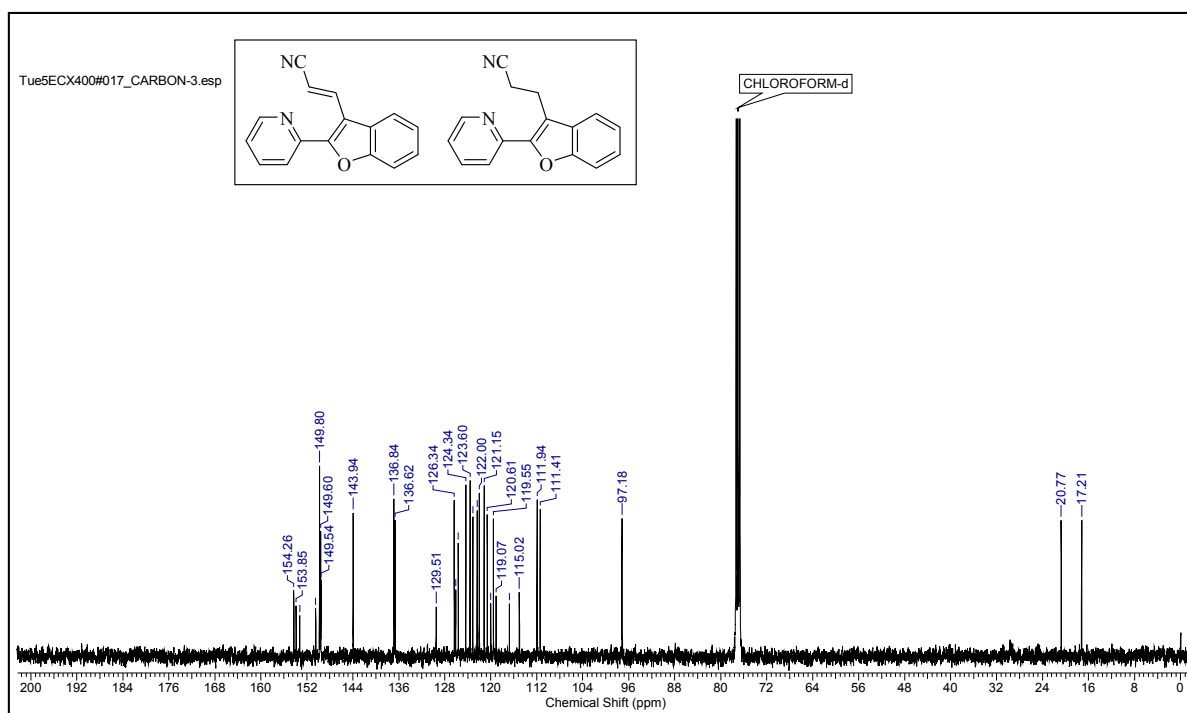
¹H NMR Spectrum of **29an** in CDCl₃ (400 MHz)

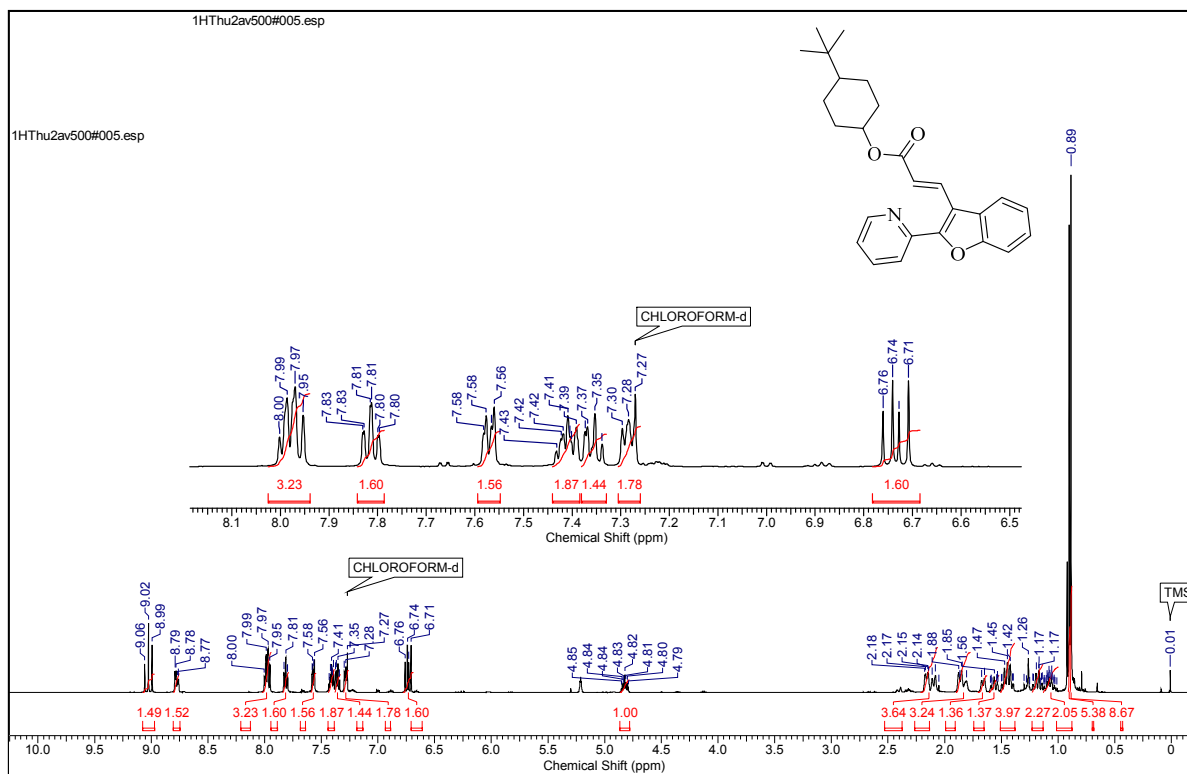


¹³C NMR Spectrum of **29an** in CDCl₃ (100 MHz)

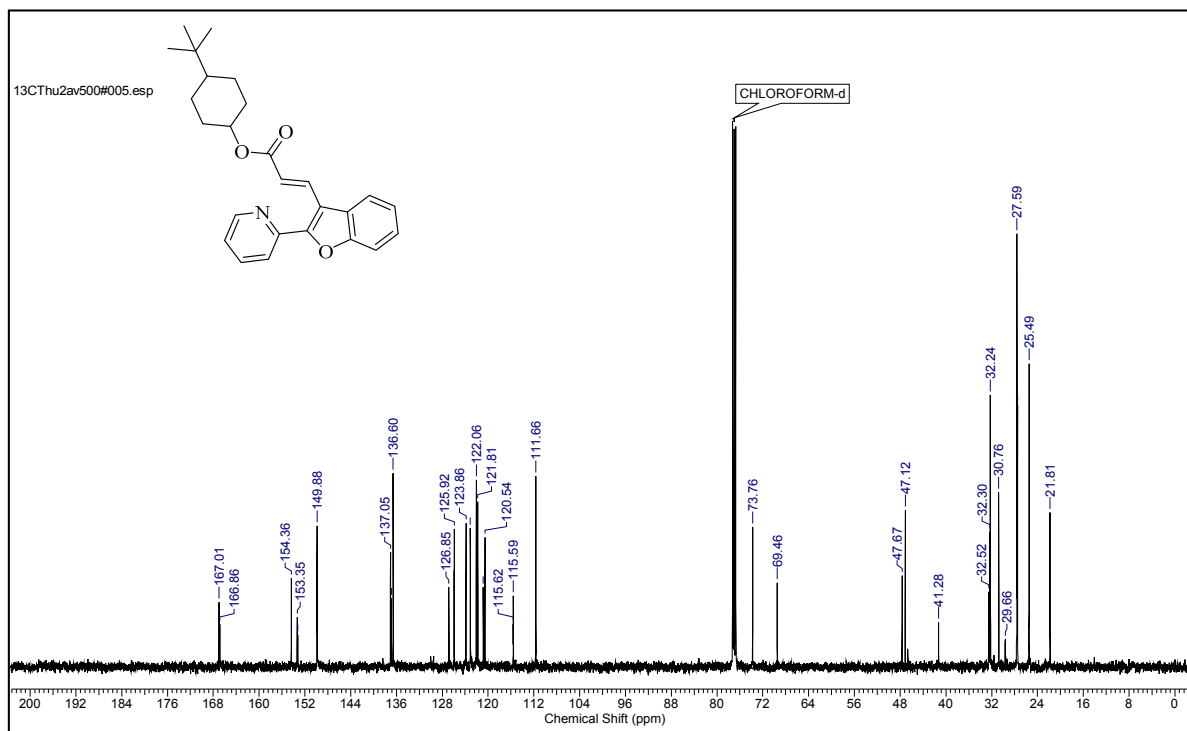


¹H NMR Spectrum of **29aj** and **28aj** in CDCl₃ (200 MHz)

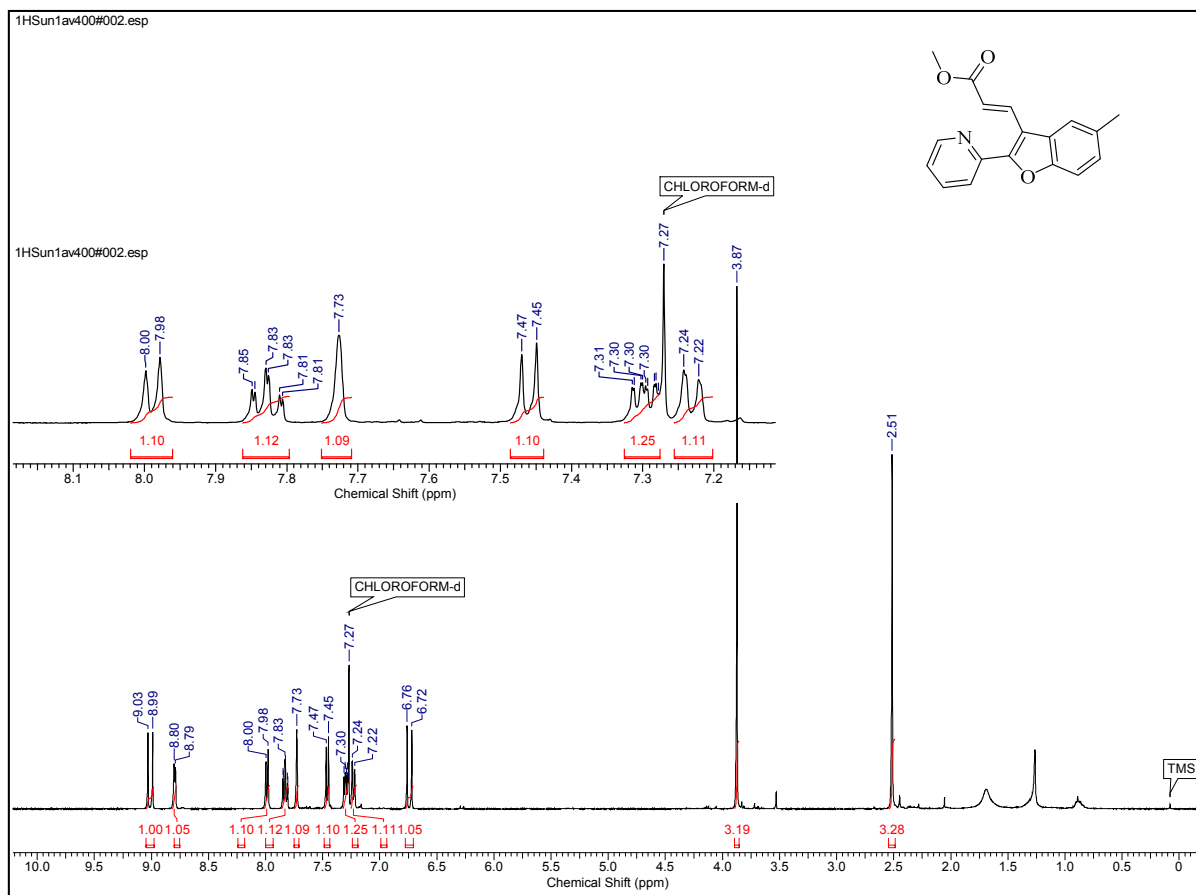
 ^{13}C NMR Spectrum of **29aj** and **28aj** in CDCl_3 (100 MHz)



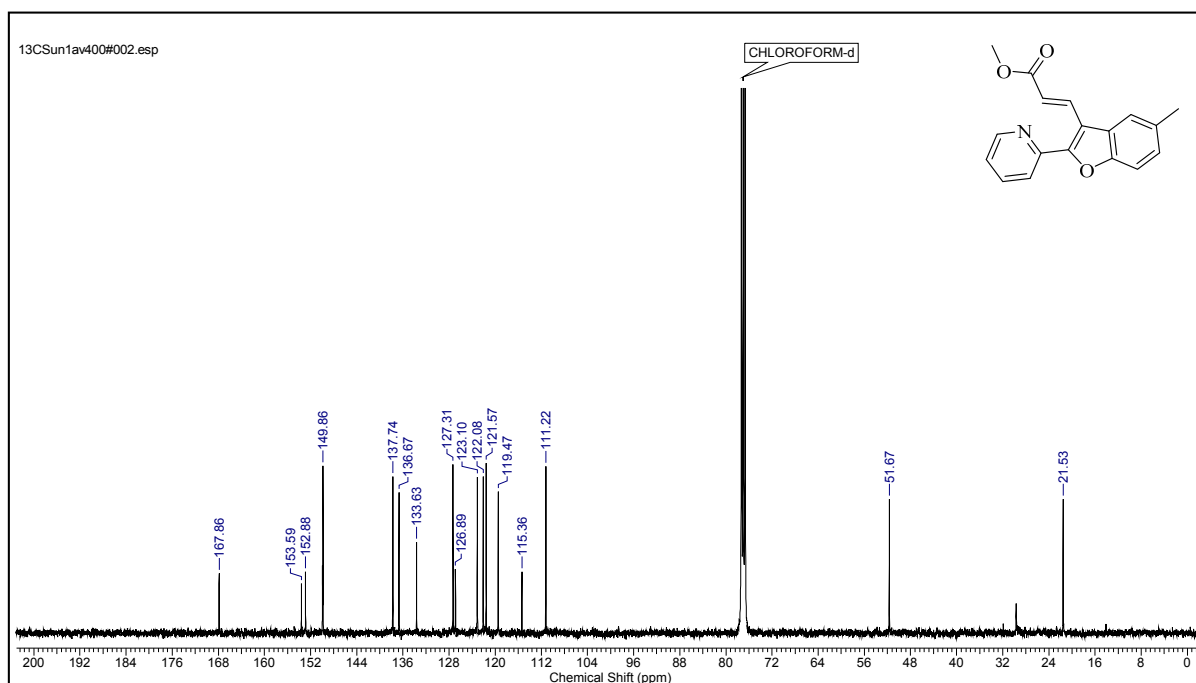
¹H NMR Spectrum of **29ao** in CDCl₃ (500 MHz)



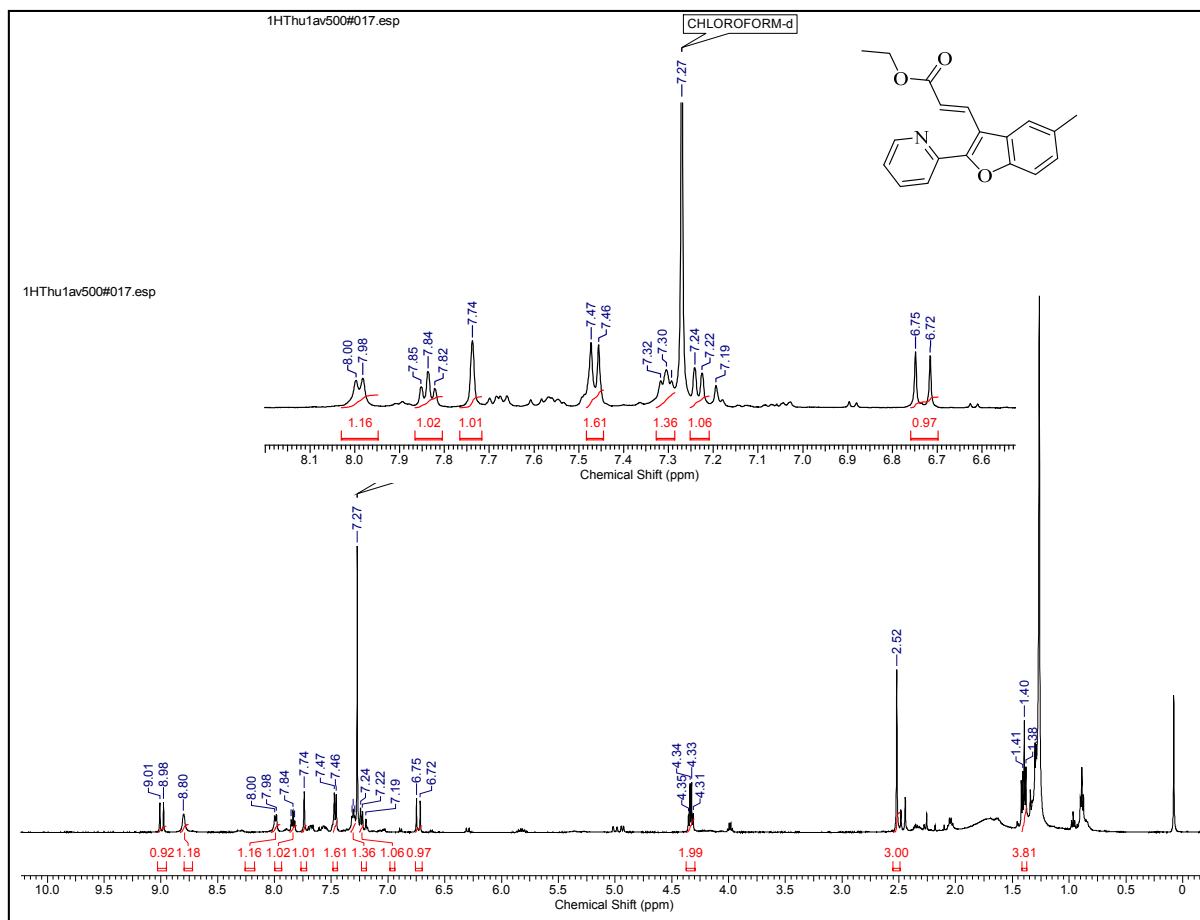
¹³C NMR Spectrum of **29ao** in CDCl₃ (125 MHz)



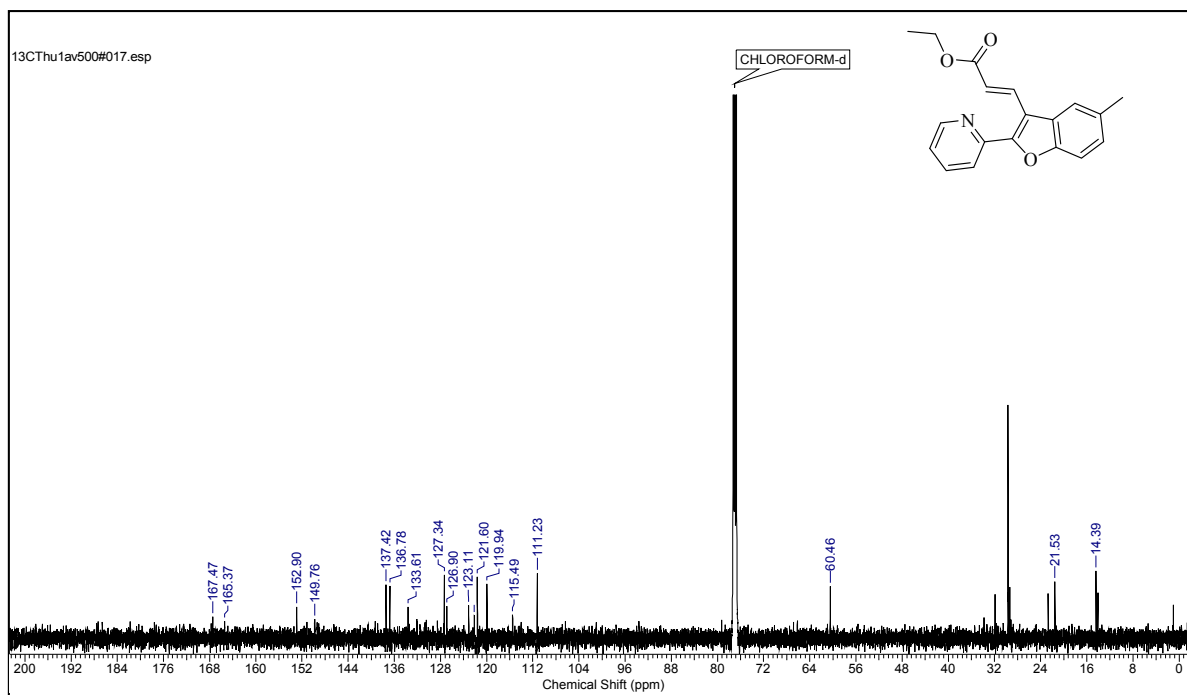
¹H NMR Spectrum of **29ba** in CDCl₃ (400 MHz)



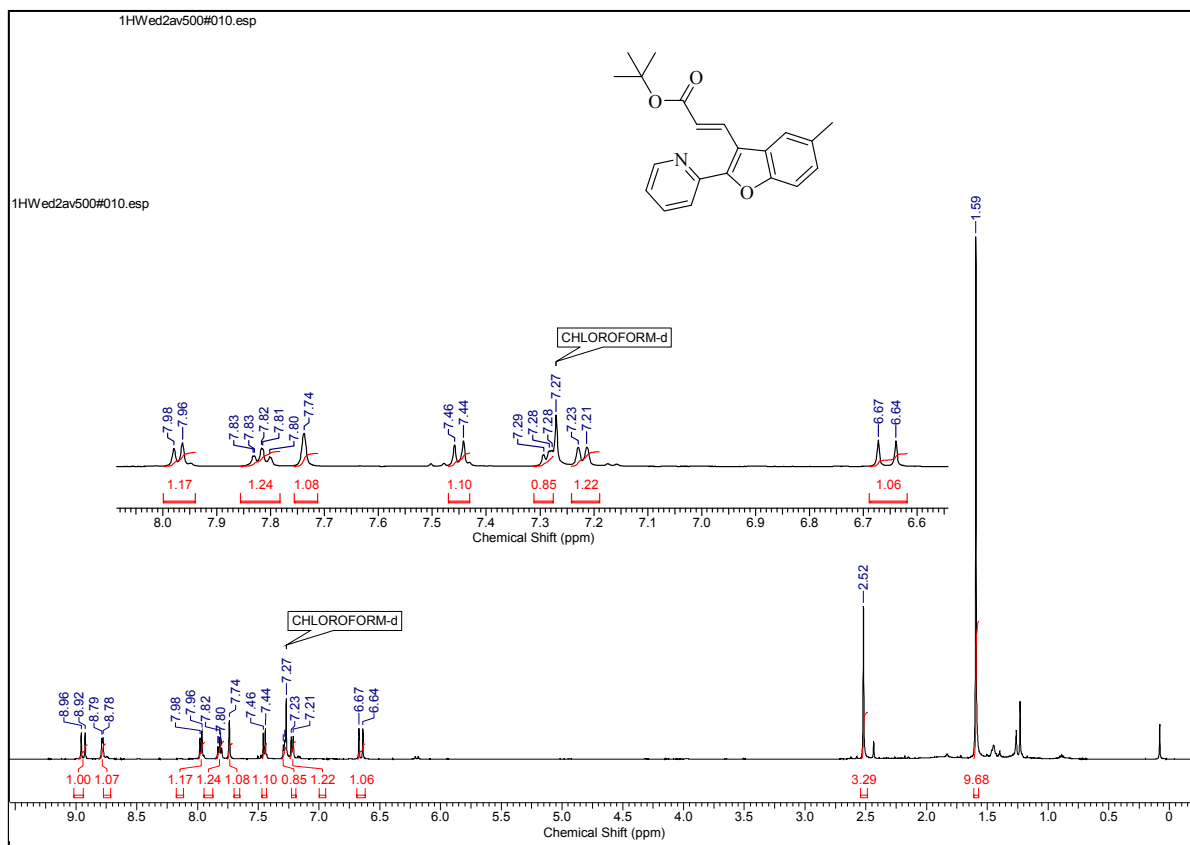
¹³C NMR Spectrum of **29ba** in CDCl₃ (100 MHz)



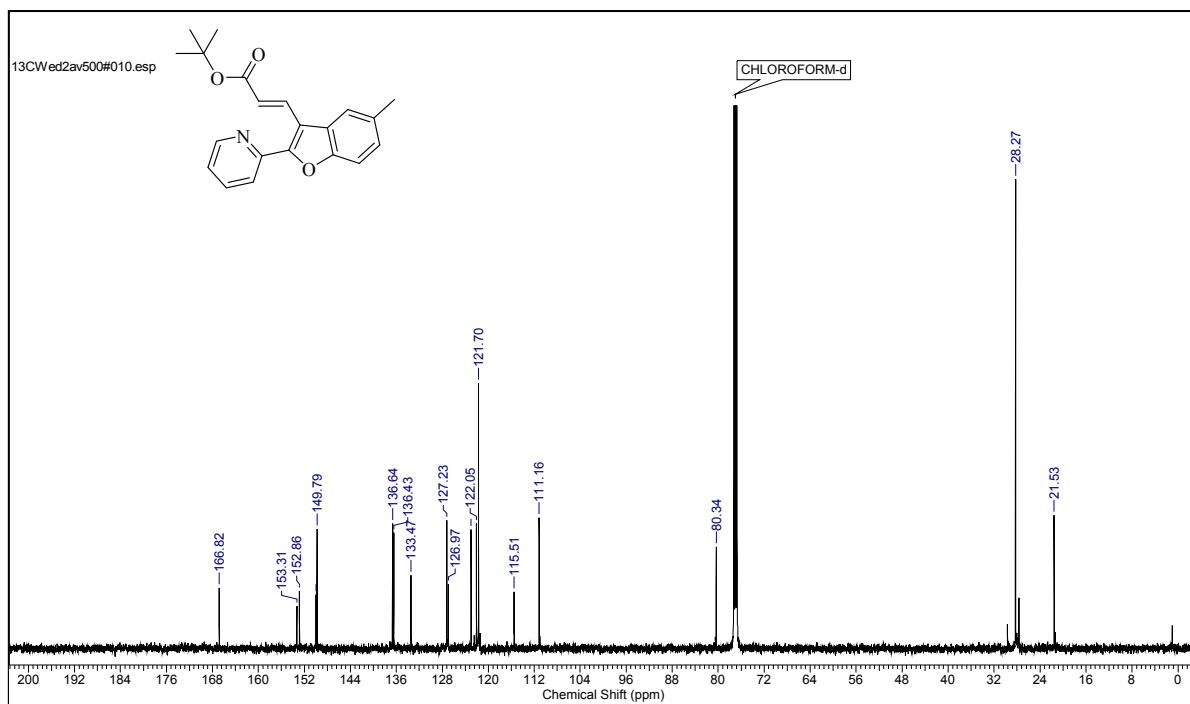
^1H NMR Spectrum of **29bb** in CDCl_3 (500 MHz)



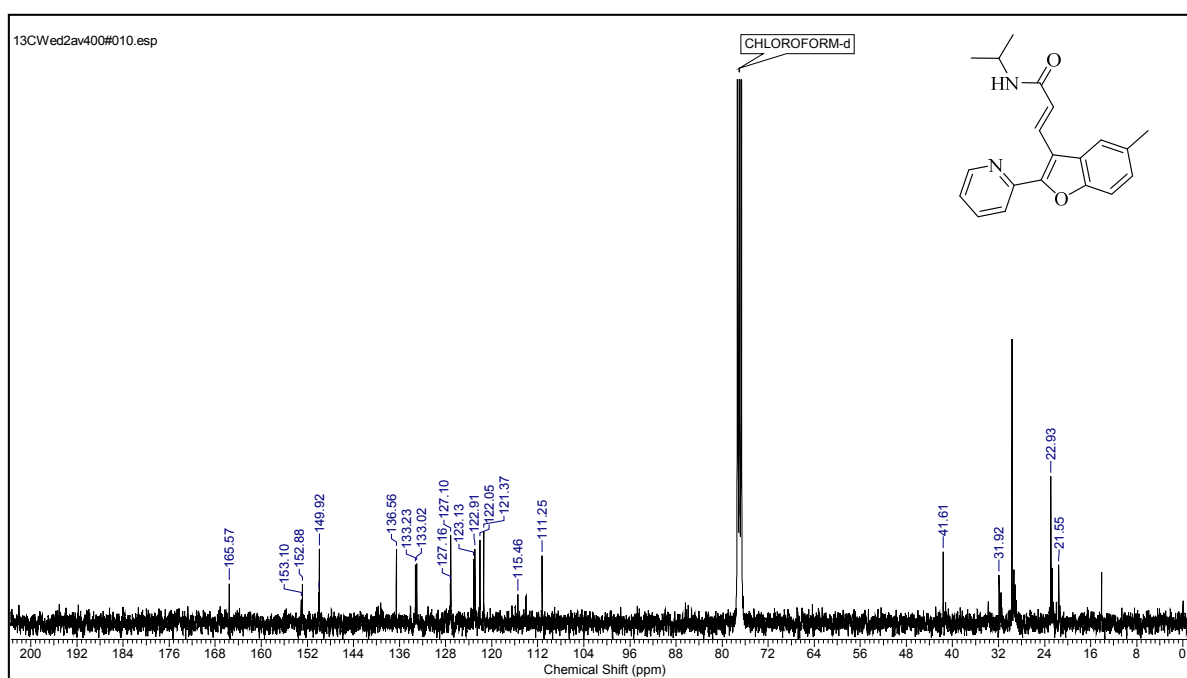
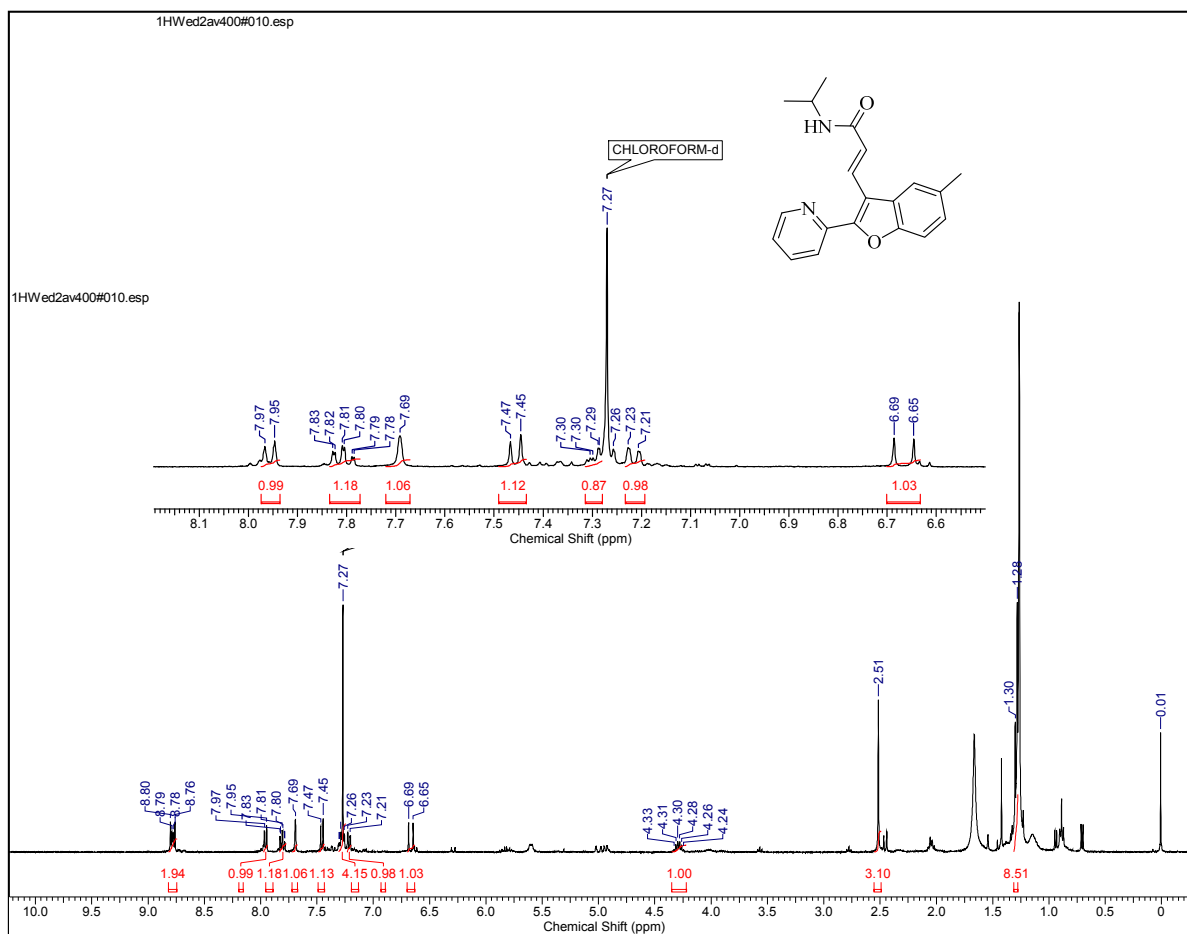
^{13}C NMR Spectrum of **29bb** in CDCl_3 (125 MHz)

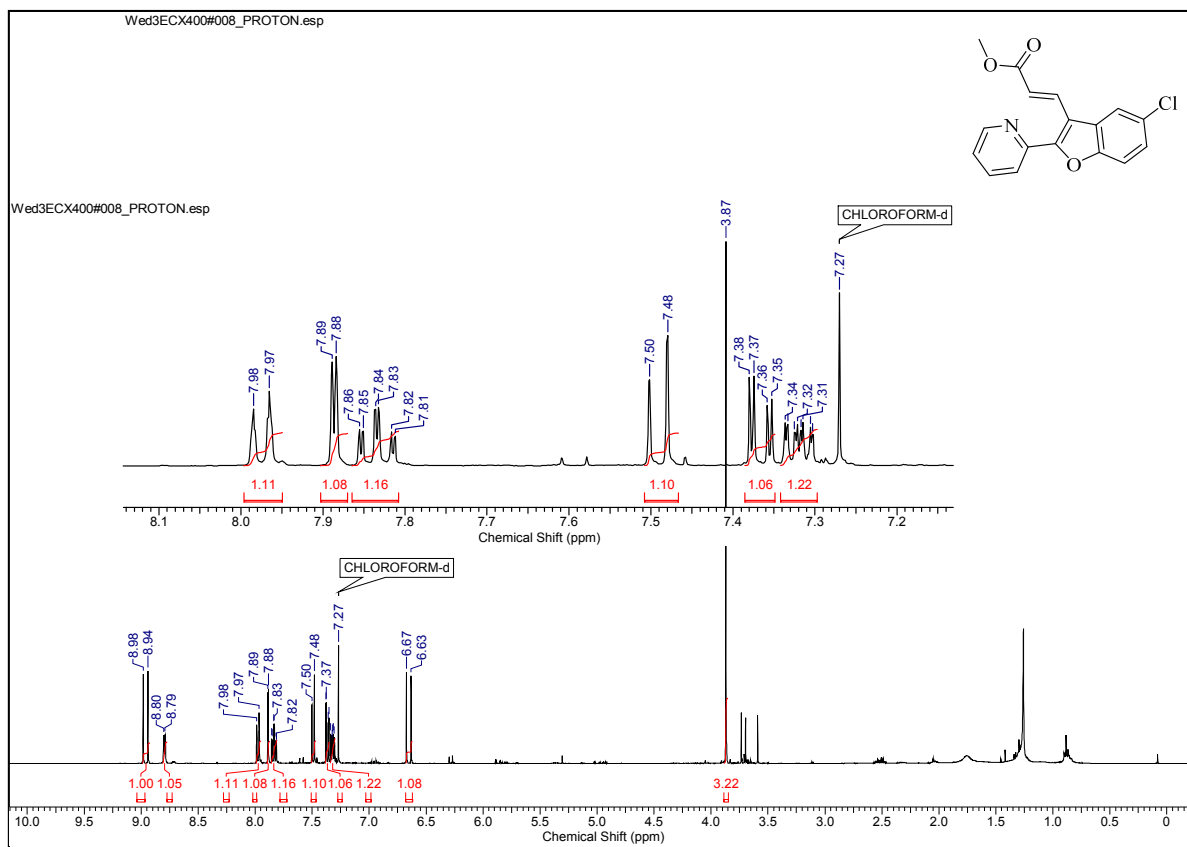


¹H NMR Spectrum of **29bn** in CDCl₃ (500 MHz)

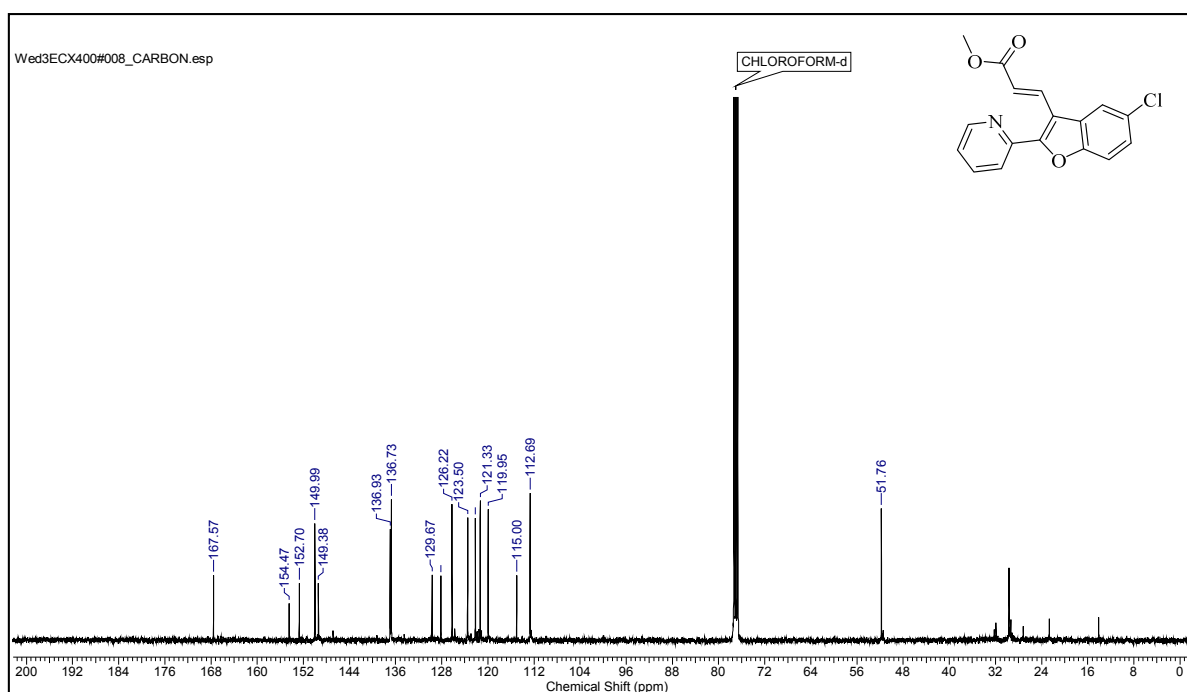


¹³C NMR Spectrum of **29bn** in CDCl₃ (125 MHz)

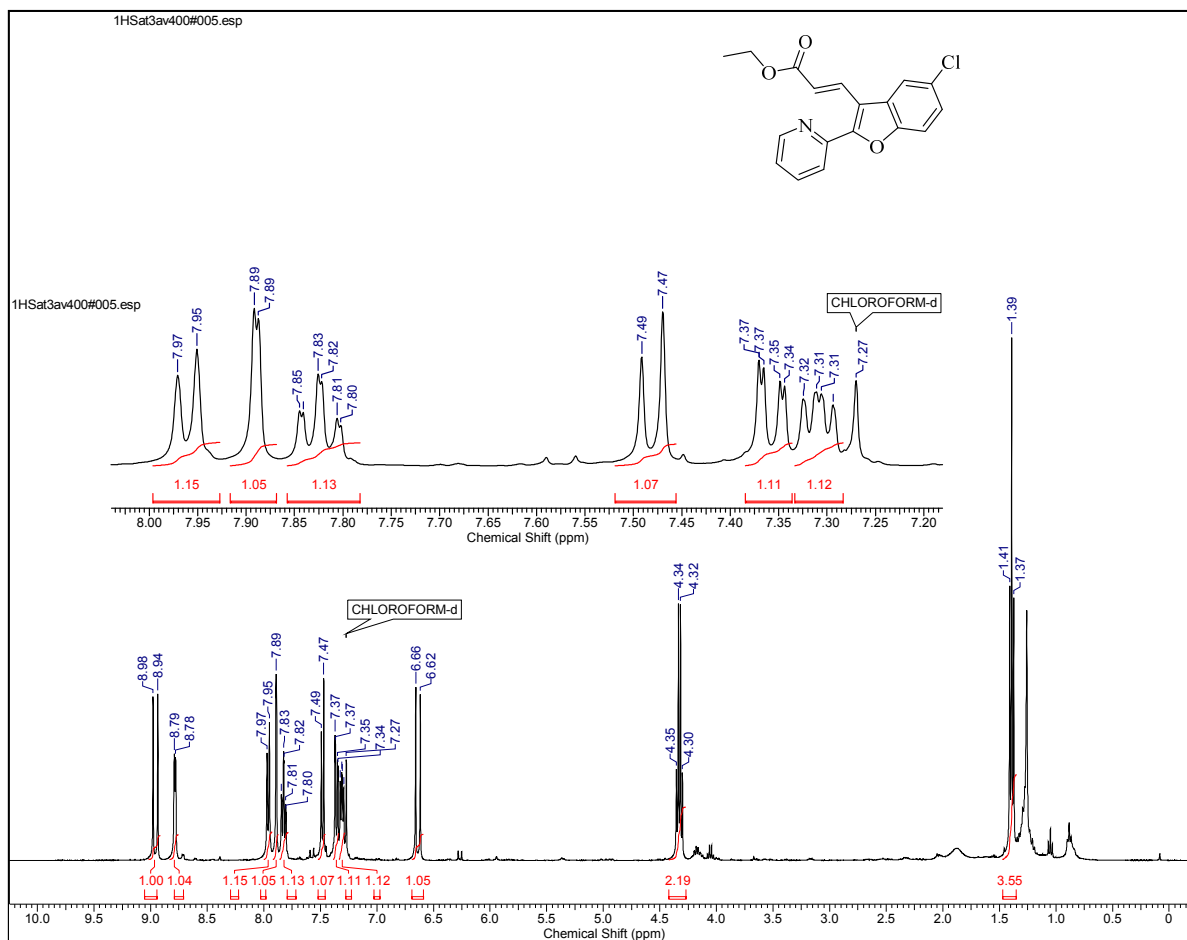




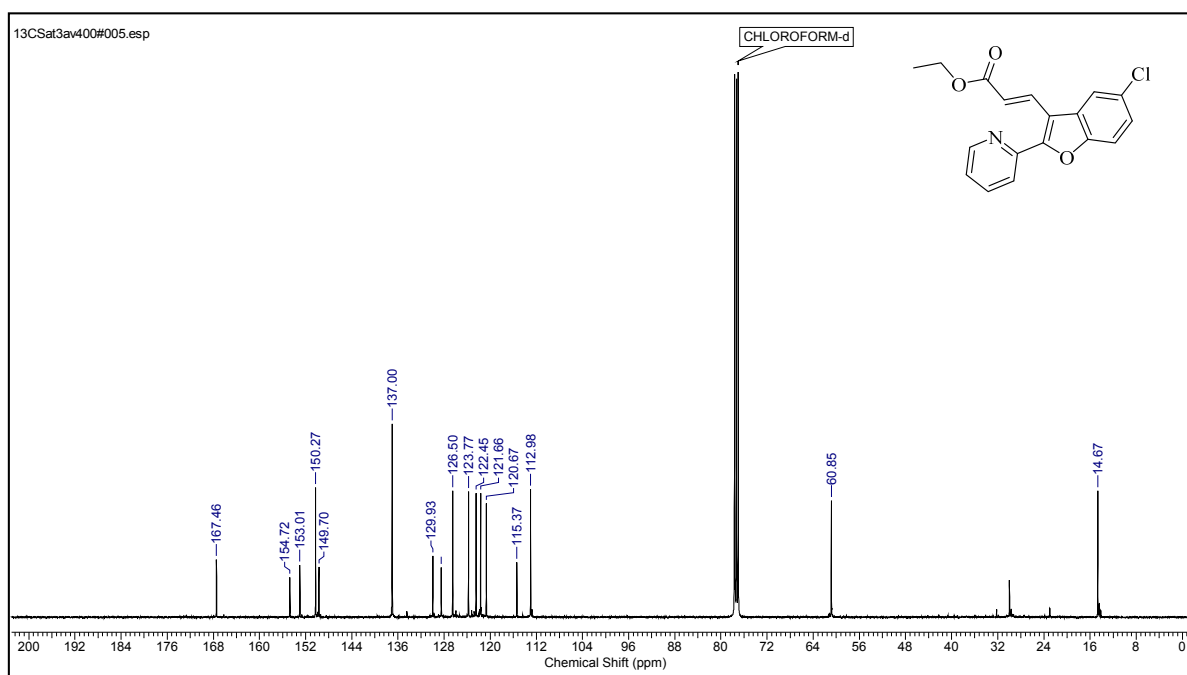
^1H NMR Spectrum of **29ca** in CDCl_3 (400 MHz)



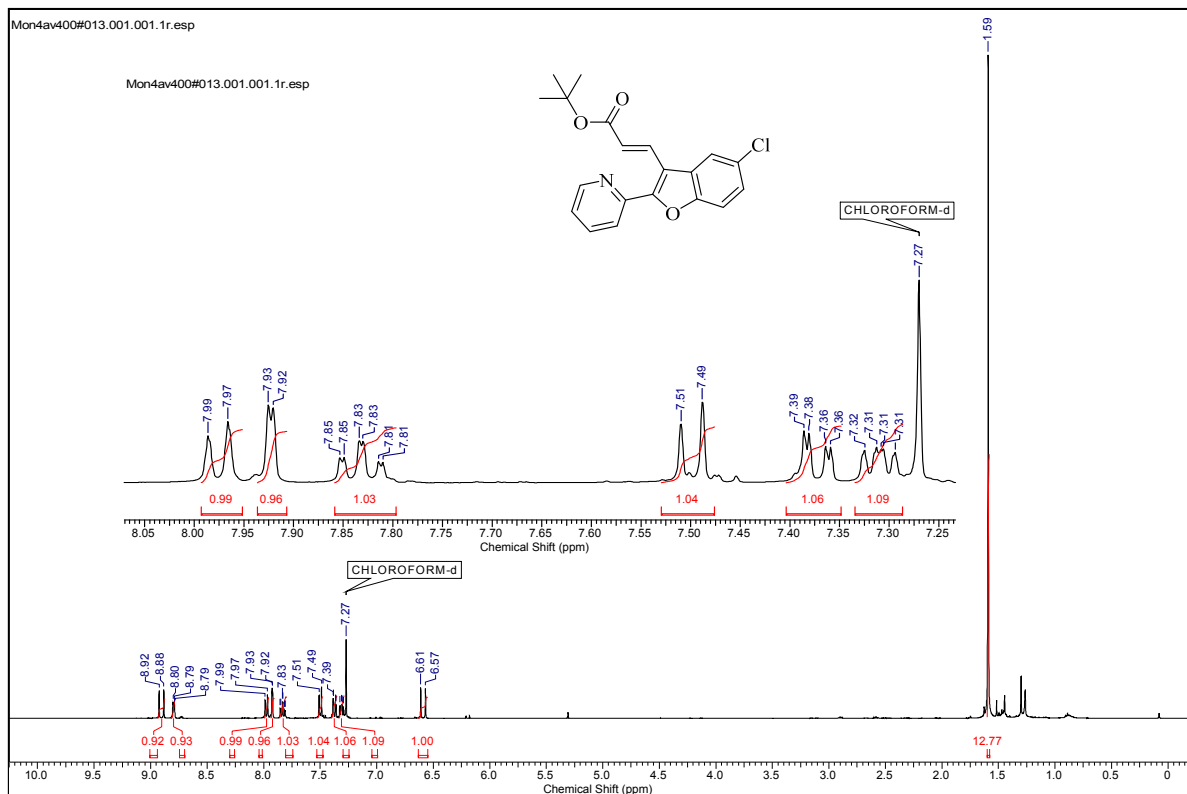
^{13}C NMR Spectrum of **29ca** in CDCl_3 (100 MHz)



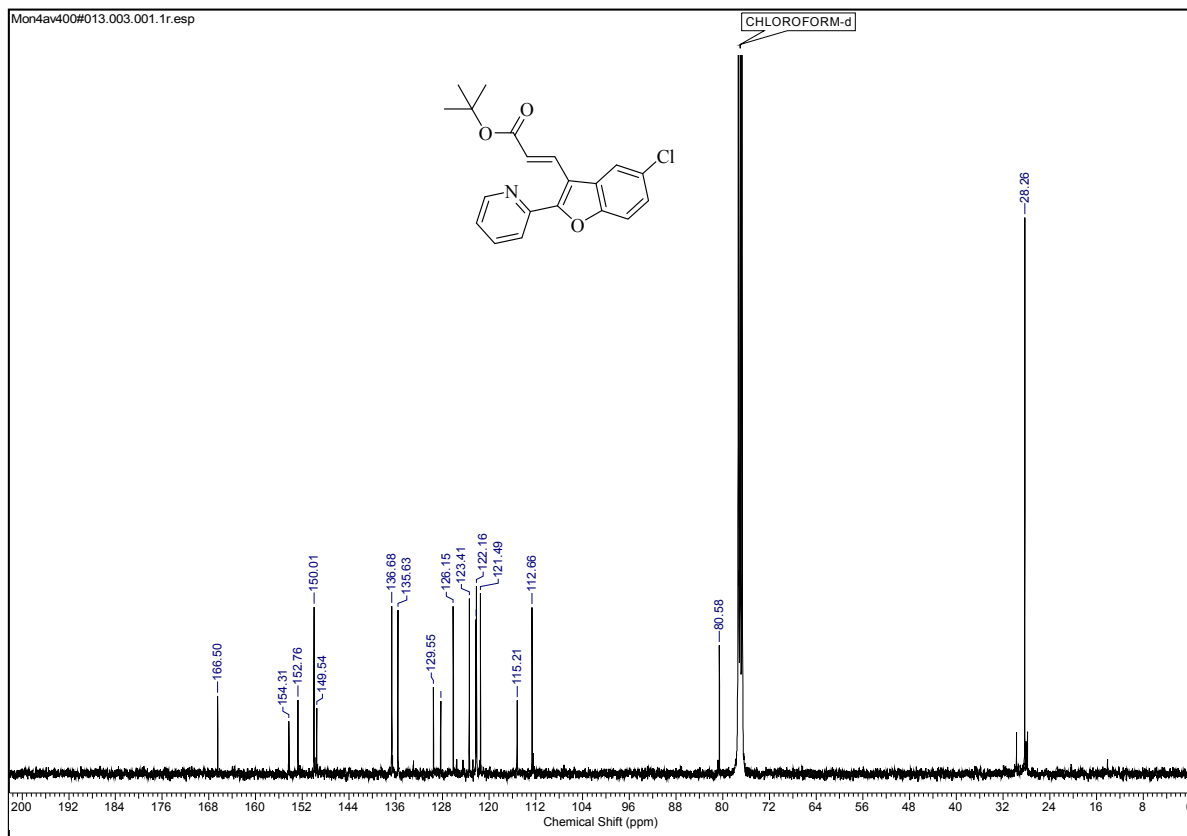
¹H NMR Spectrum of **29cb** in CDCl₃ (400 MHz)



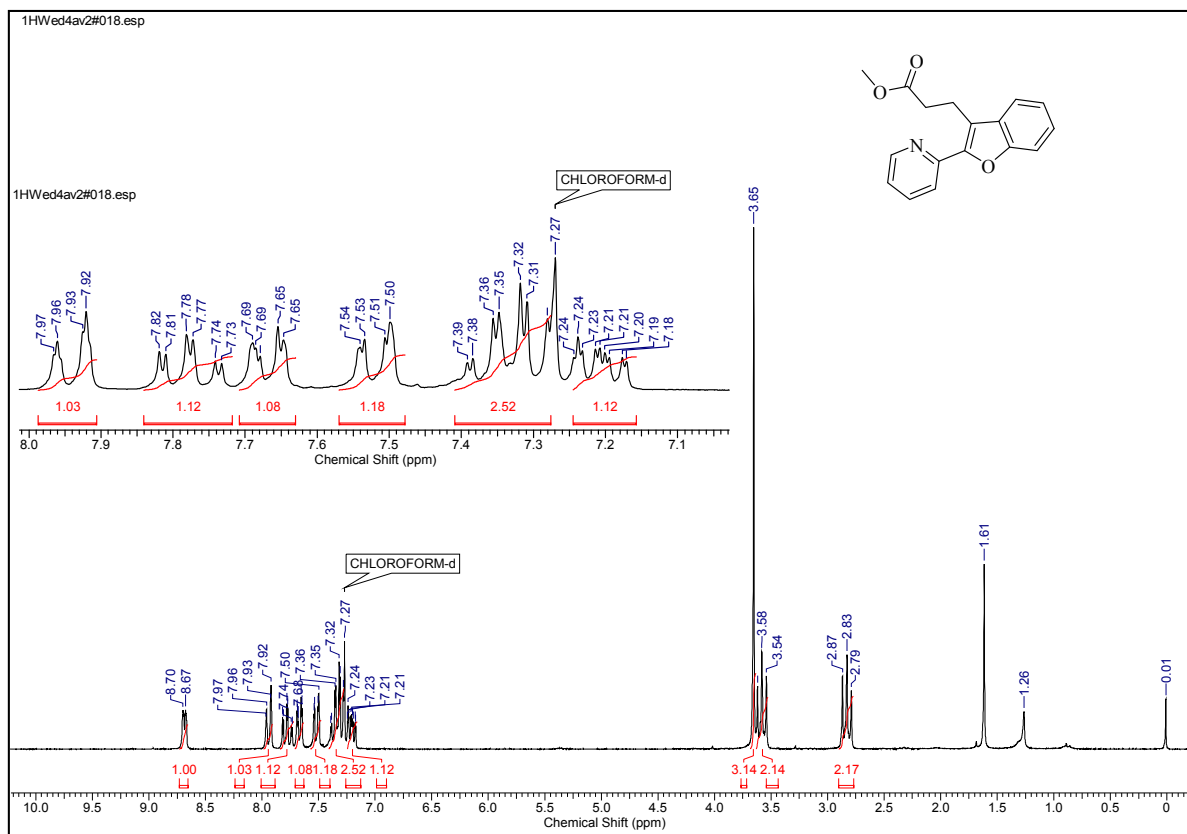
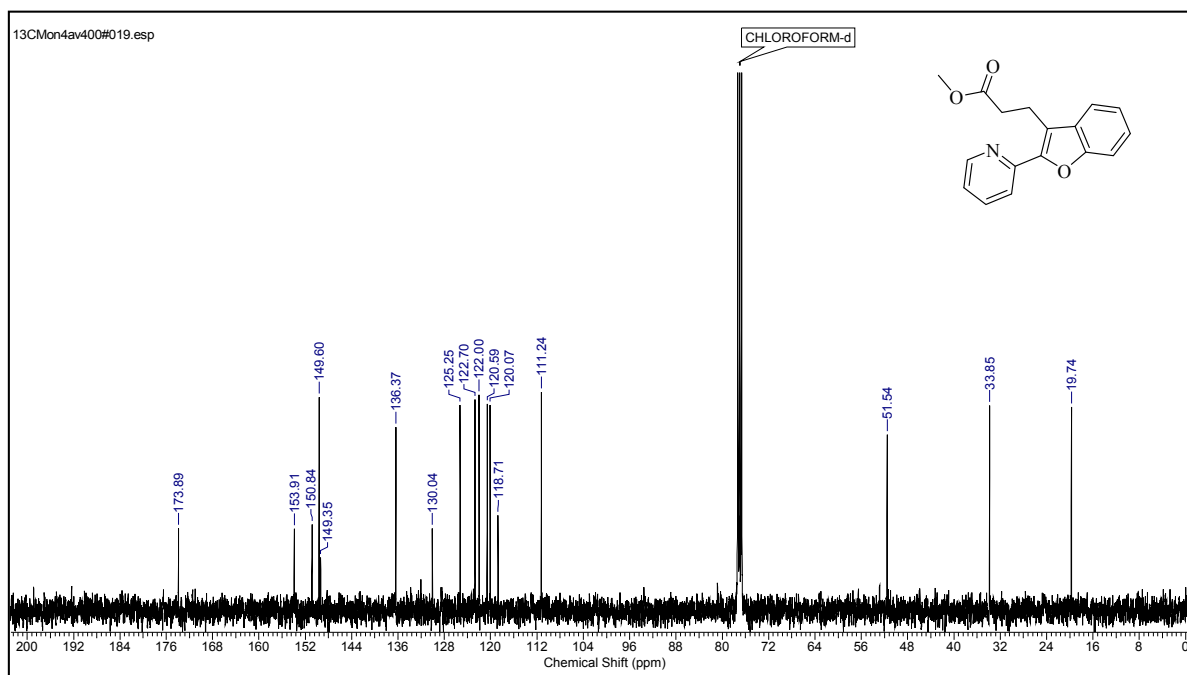
¹³C NMR Spectrum of **29cb** in CDCl₃ (100 MHz)

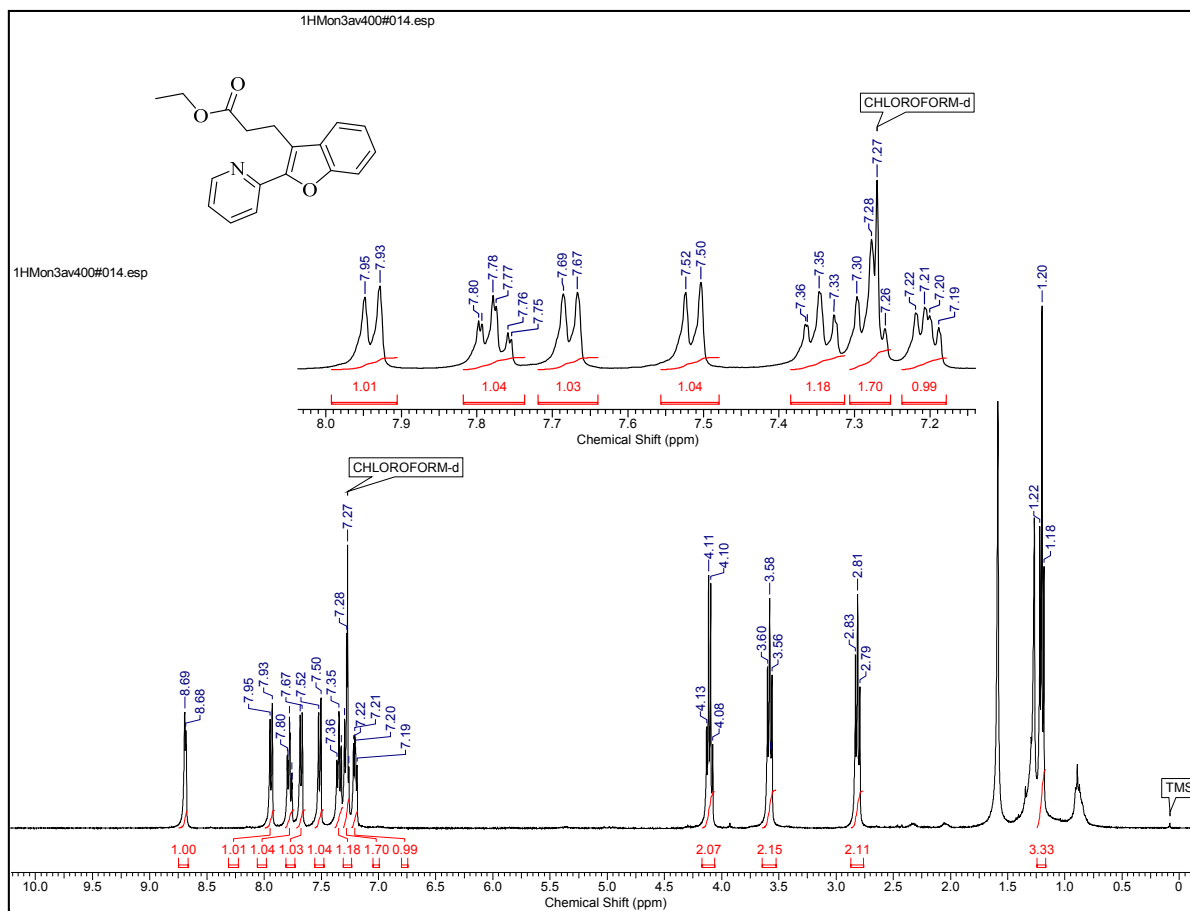
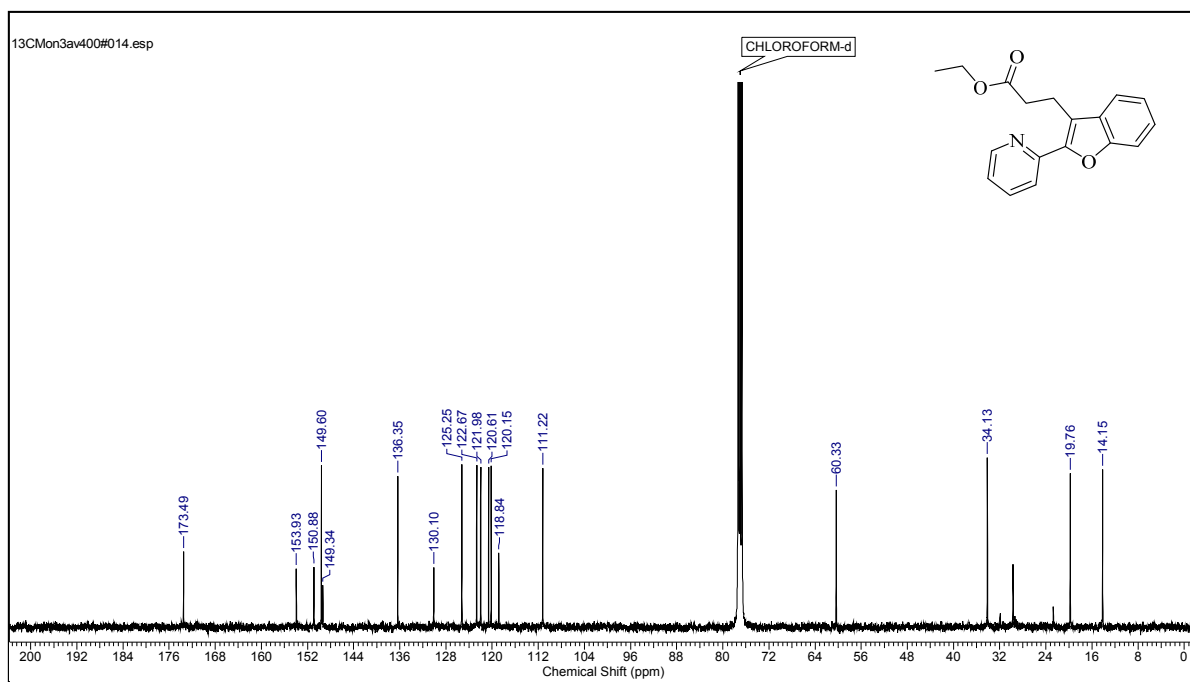


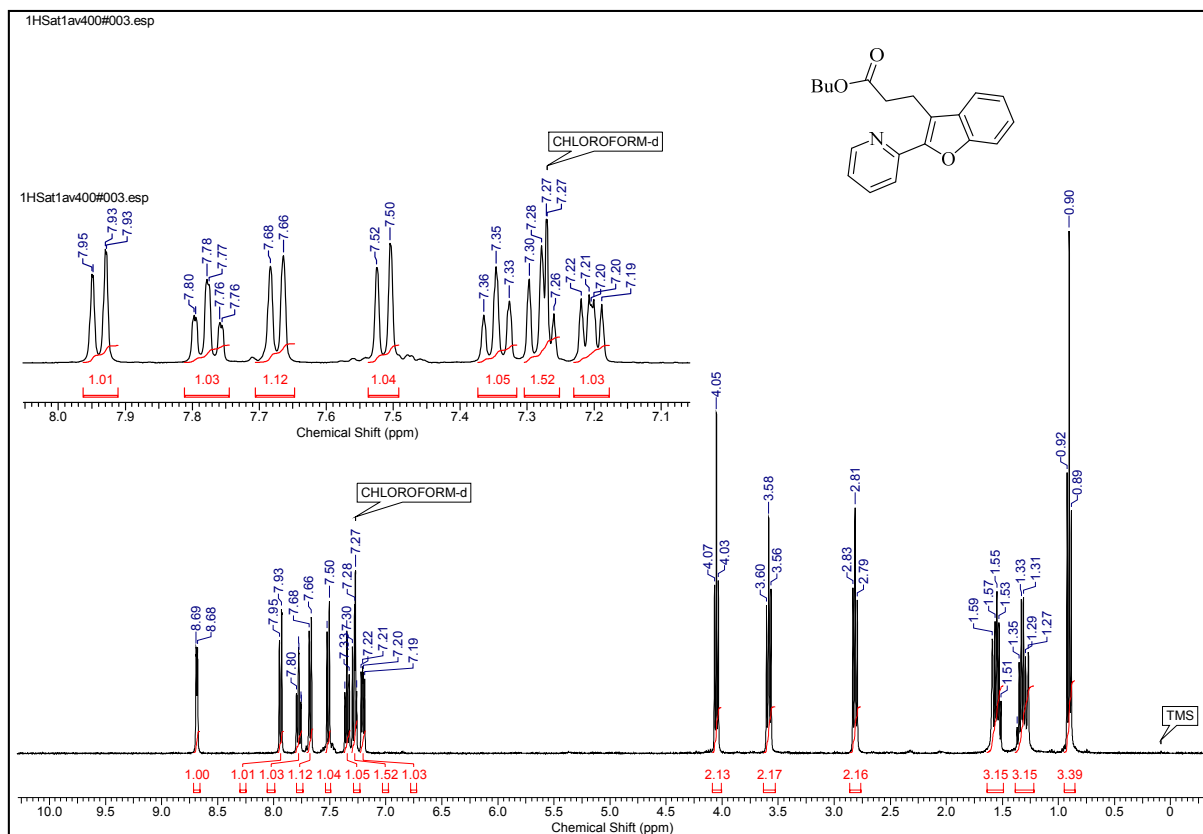
^1H NMR Spectrum of **29cn** in CDCl_3 (400 MHz)



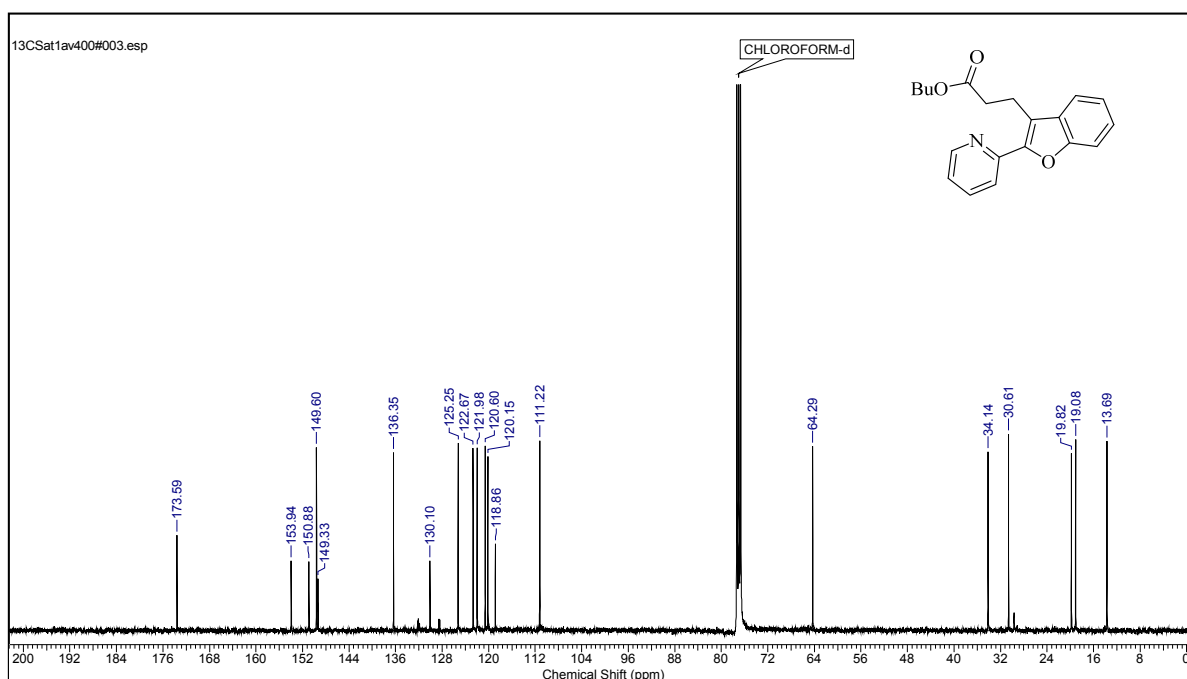
^{13}C NMR Spectrum of **29cn** in CDCl_3 (100 MHz)

¹H NMR Spectrum of **28aa** in CDCl₃ (200 MHz) ^{13}C NMR Spectrum of **28aa** in CDCl_3 (100 MHz)

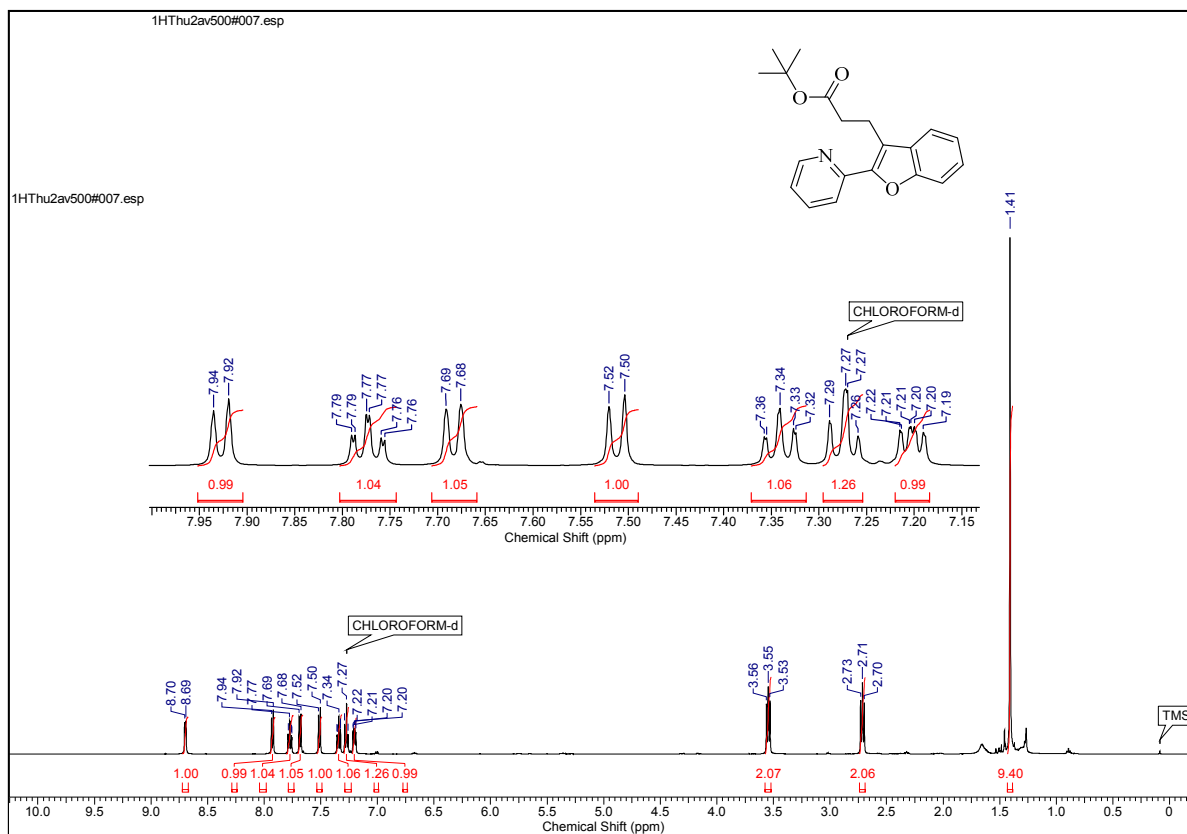
¹H NMR Spectrum of **28ab** in CDCl₃ (400 MHz)¹³C NMR Spectrum of **28ab** in CDCl₃ (100 MHz)



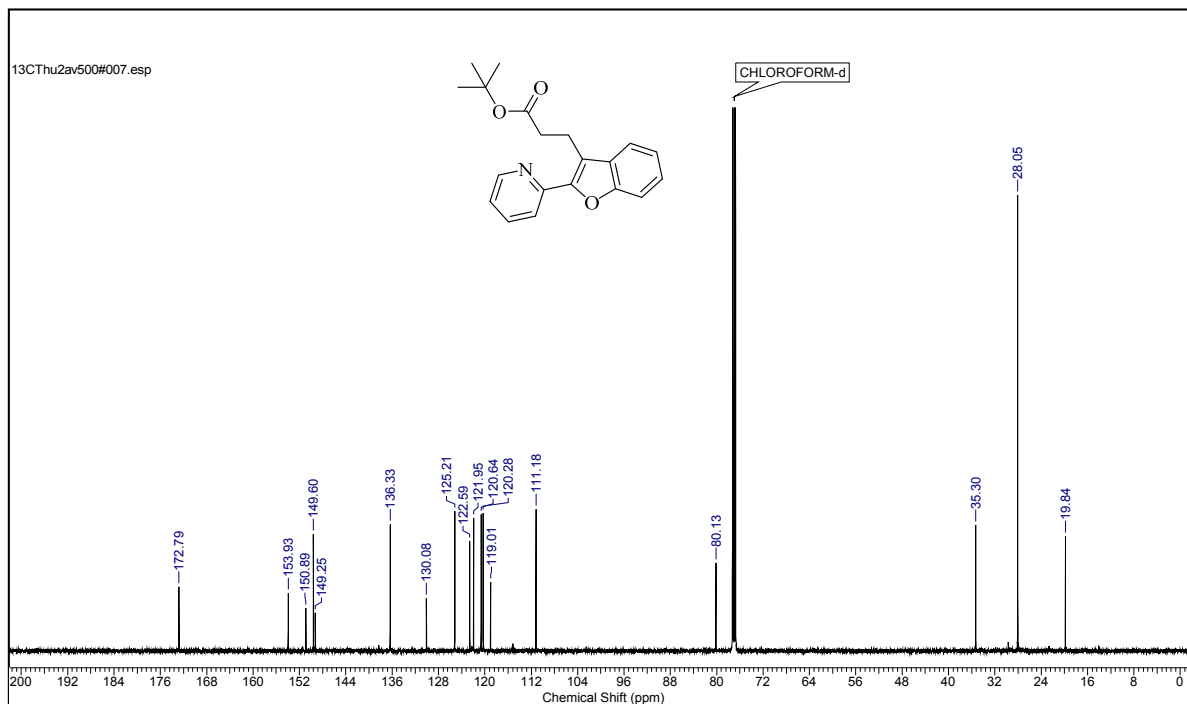
¹H NMR Spectrum of **28ac** in CDCl₃ (400 MHz)



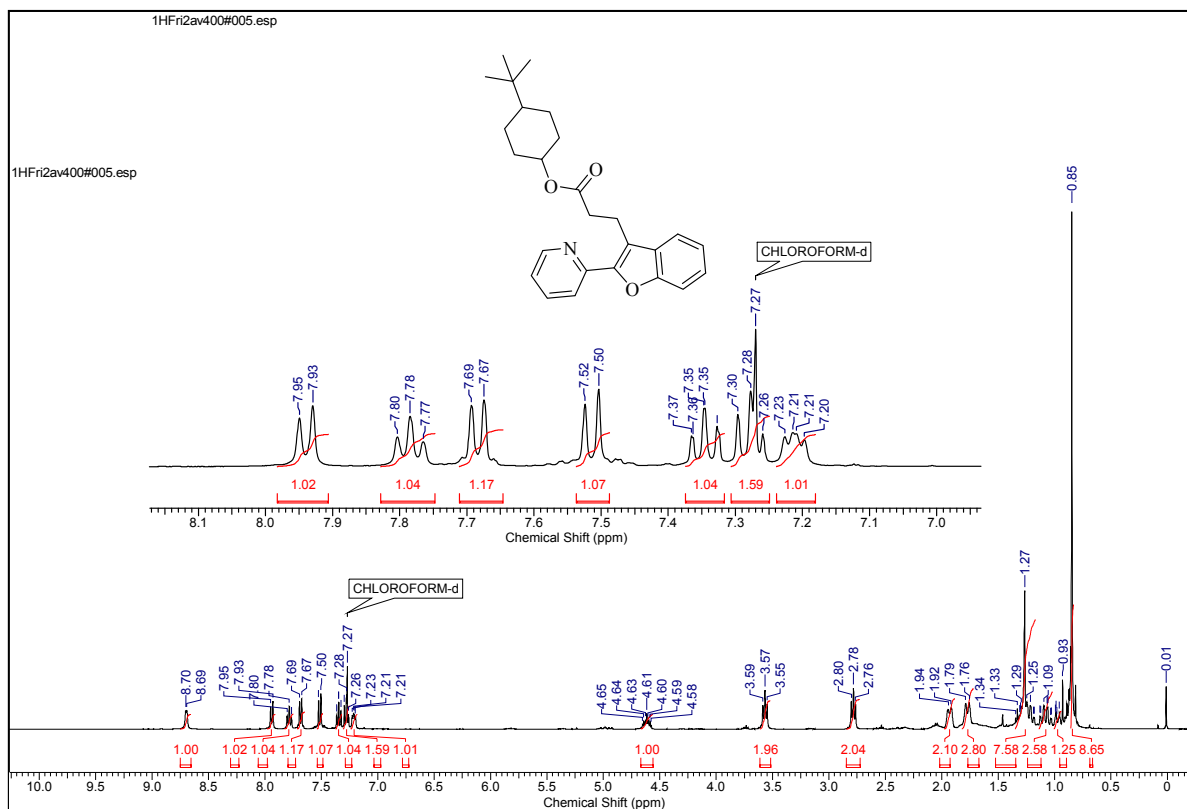
¹³C NMR Spectrum of **28ac** in CDCl₃ (100 MHz)



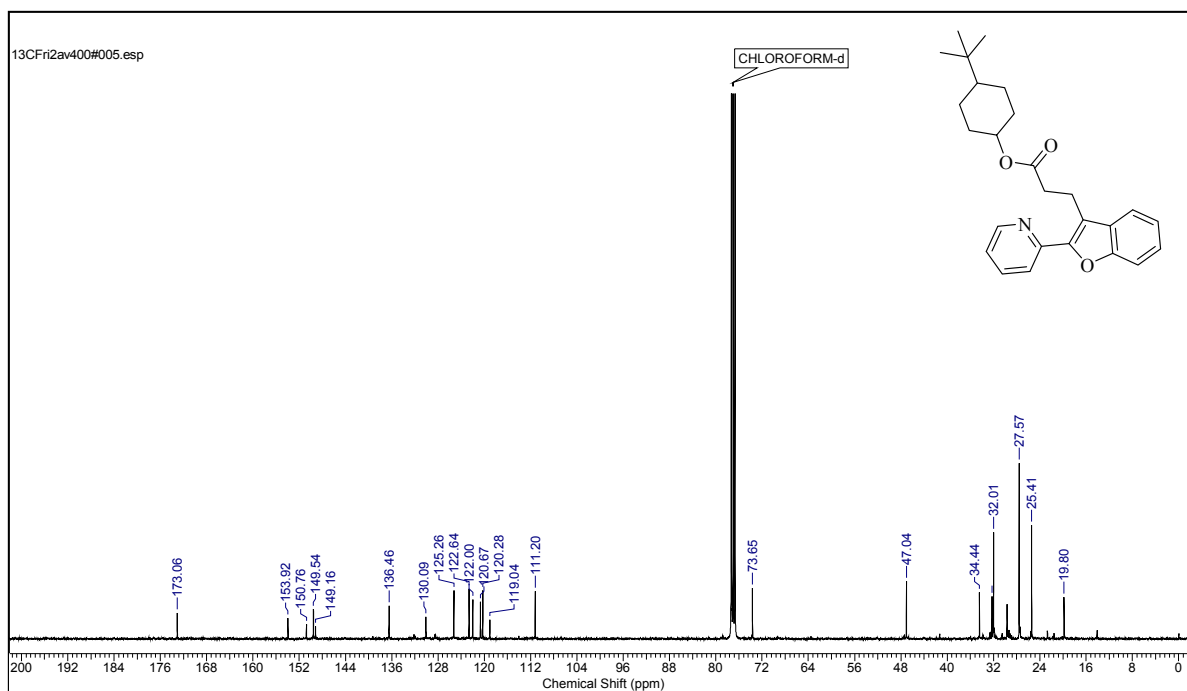
¹H NMR Spectrum of **28an** in CDCl₃ (500 MHz)



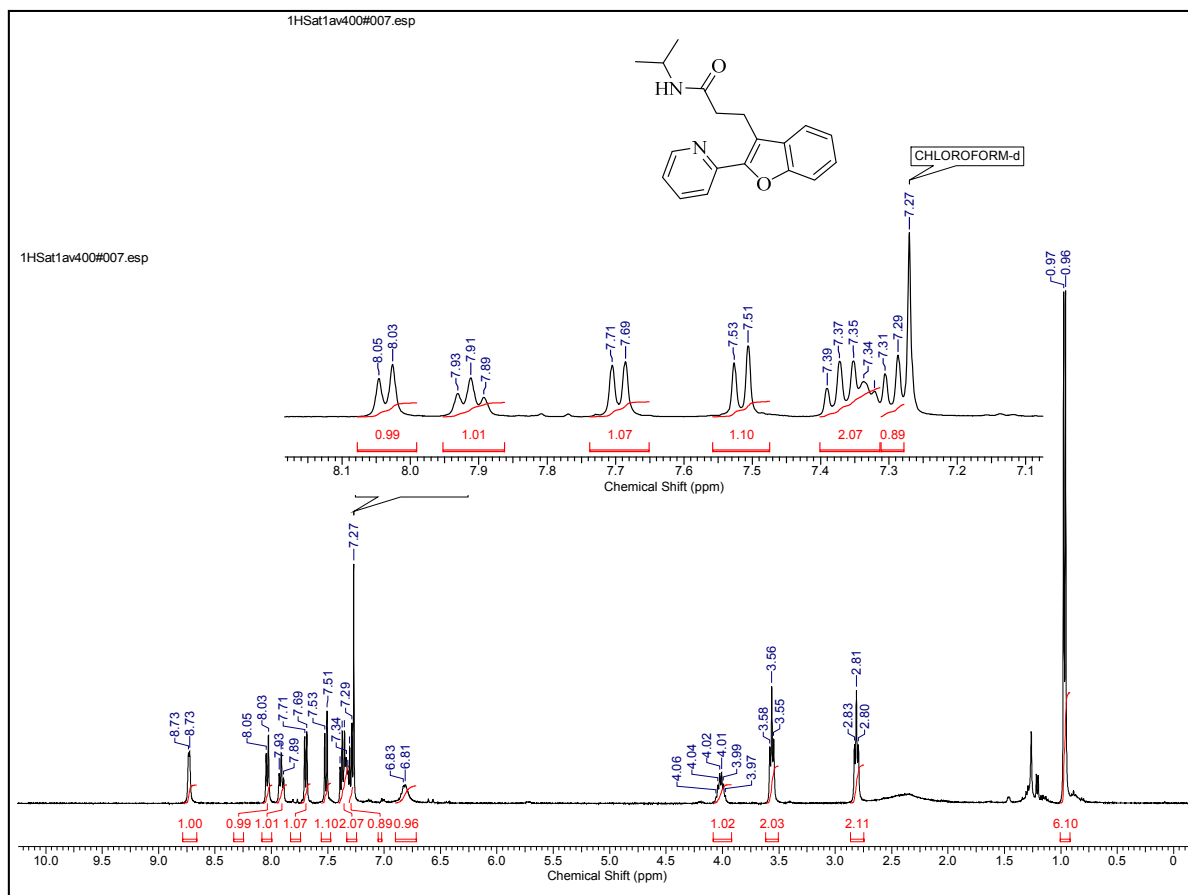
¹³C NMR Spectrum of **28an** in CDCl₃ (125 MHz)



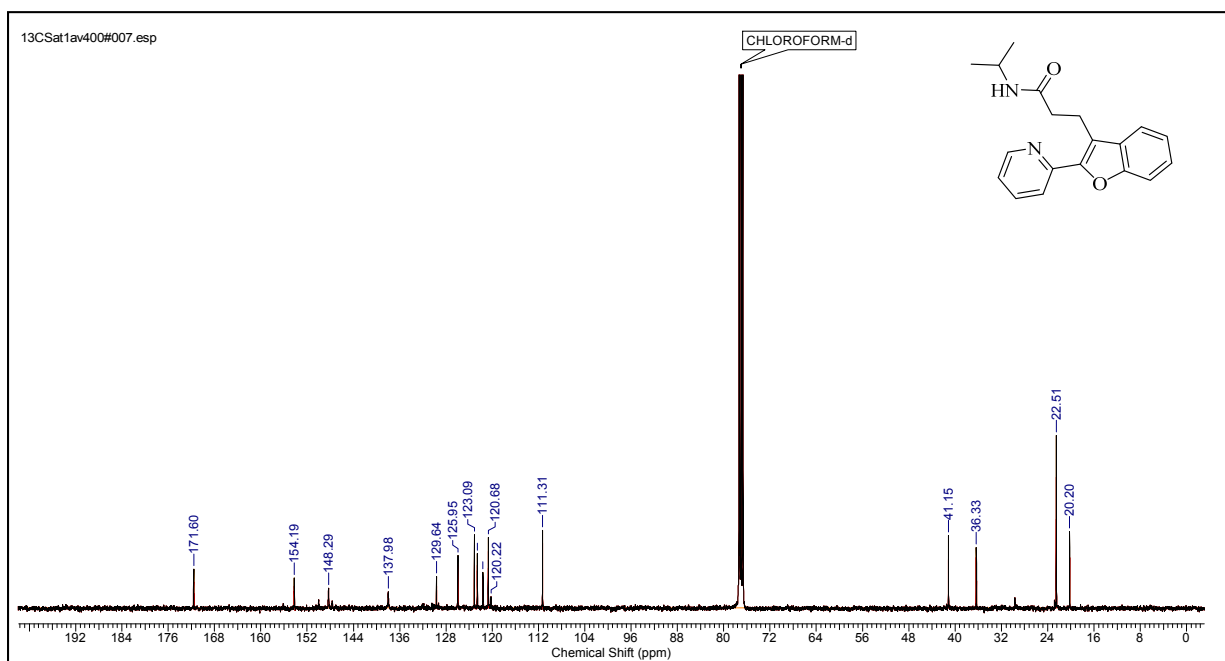
¹H NMR Spectrum of **28ao** in CDCl₃ (400 MHz)



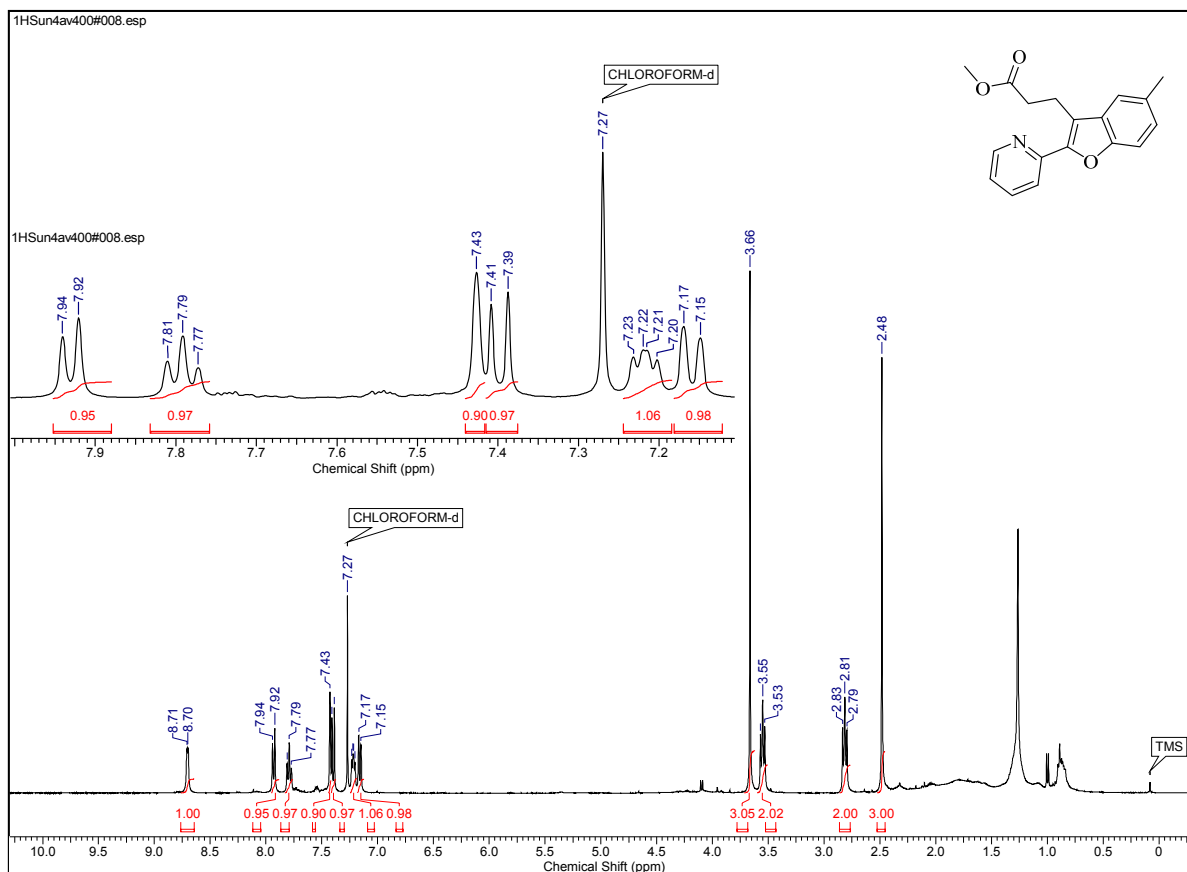
¹³C NMR Spectrum of **28ao** in CDCl₃ (100 MHz)



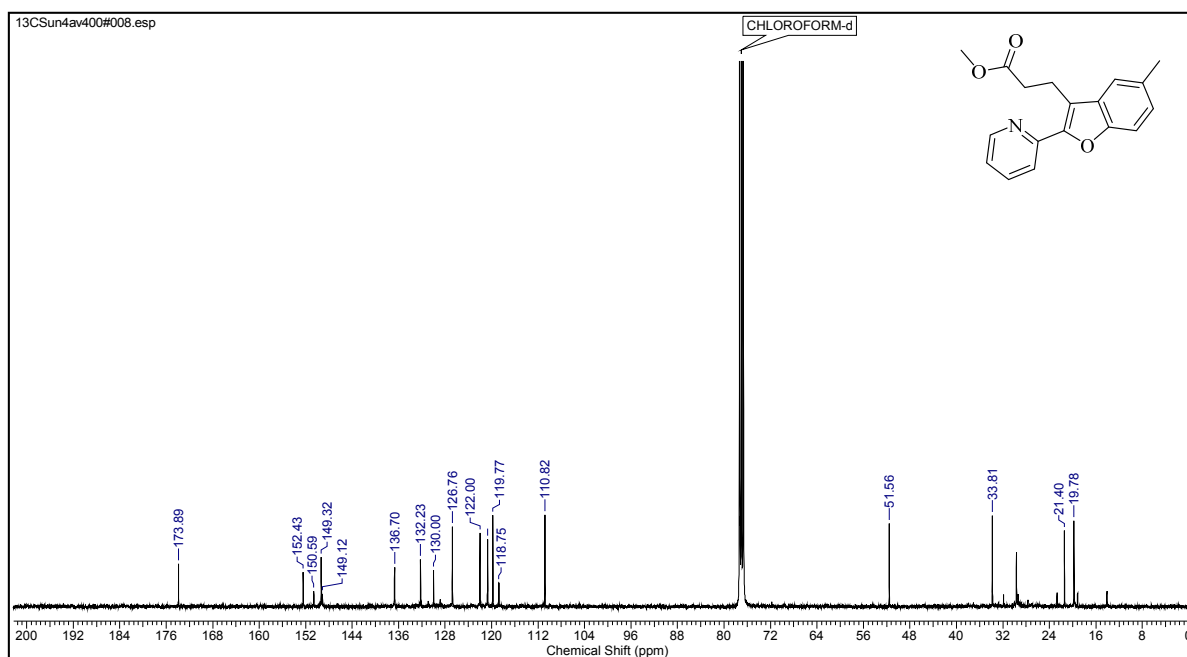
^1H NMR Spectrum of **28ak** in CDCl_3 (400 MHz)



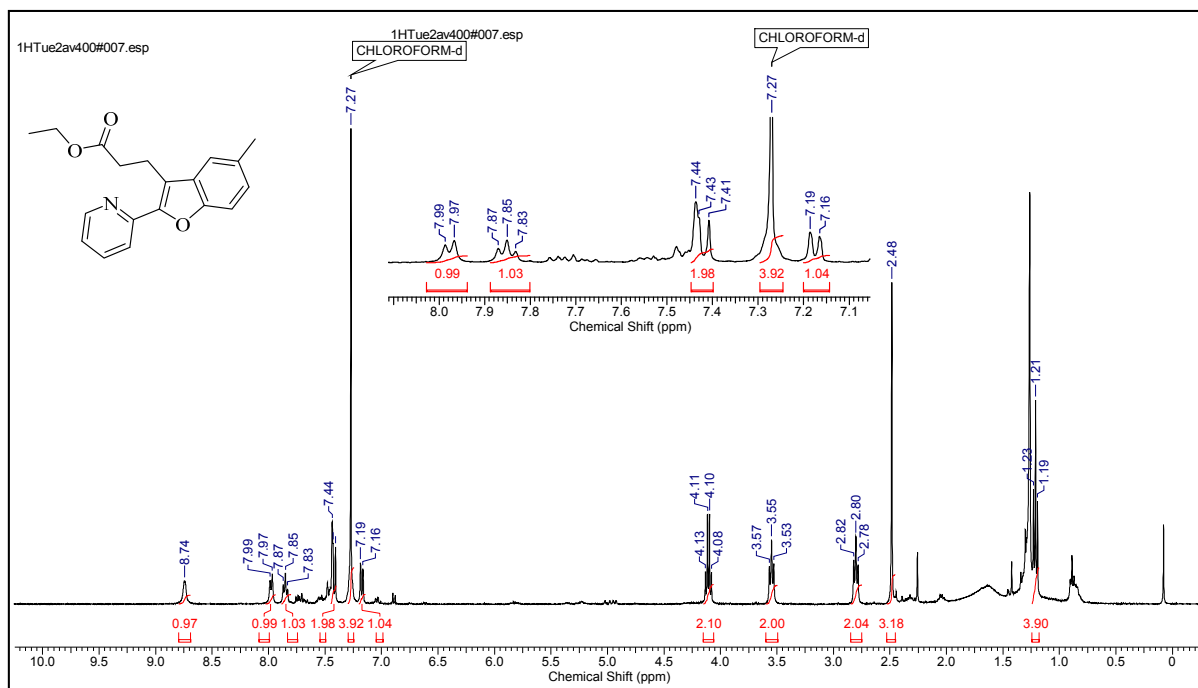
^{13}C NMR Spectrum of **28ak** in CDCl_3 (100 MHz)



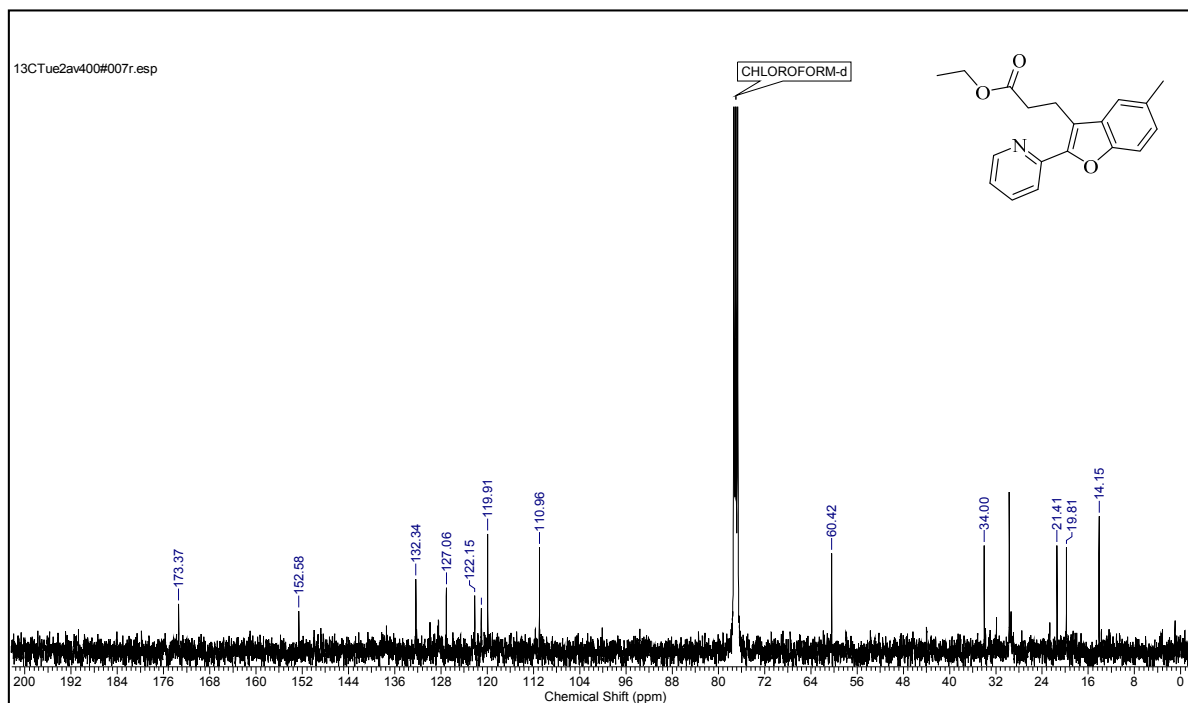
^1H NMR Spectrum of **28ba** in CDCl_3 (400 MHz)



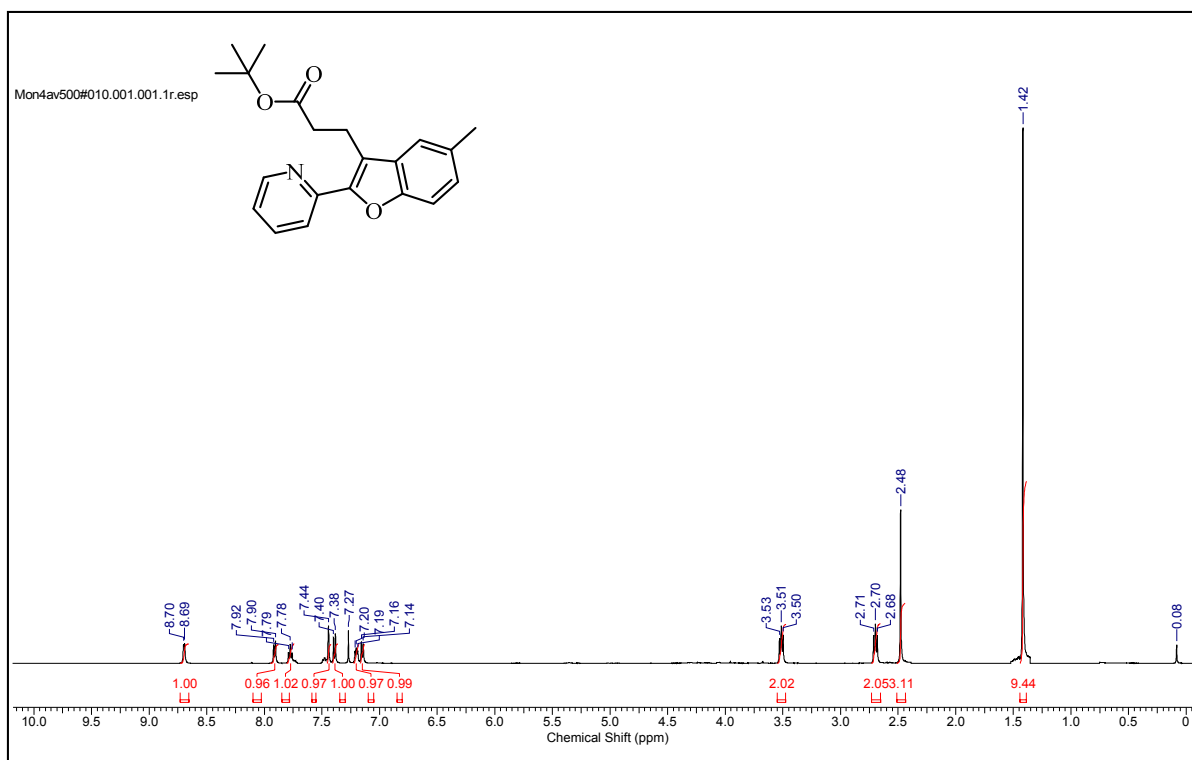
^{13}C NMR Spectrum of **28ba** in CDCl_3 (100 MHz)



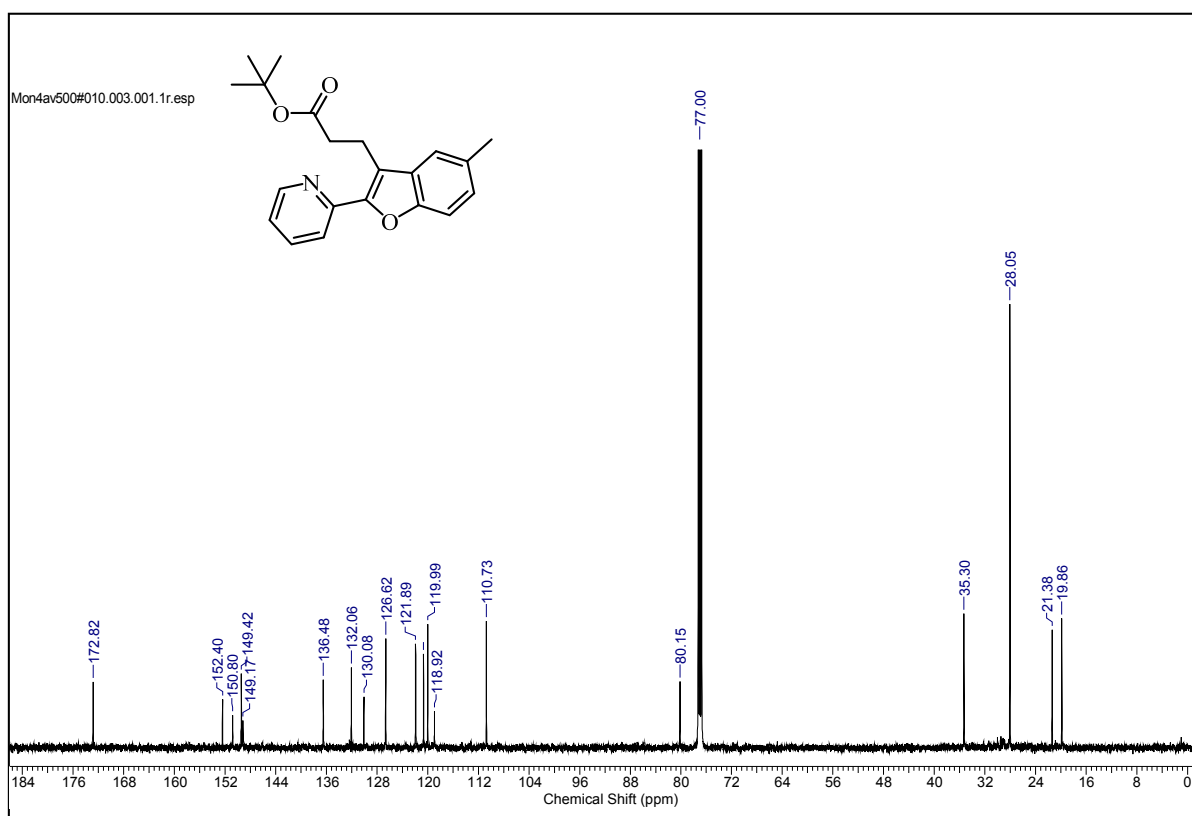
^1H NMR Spectrum of **28bb** in CDCl_3 (400 MHz)



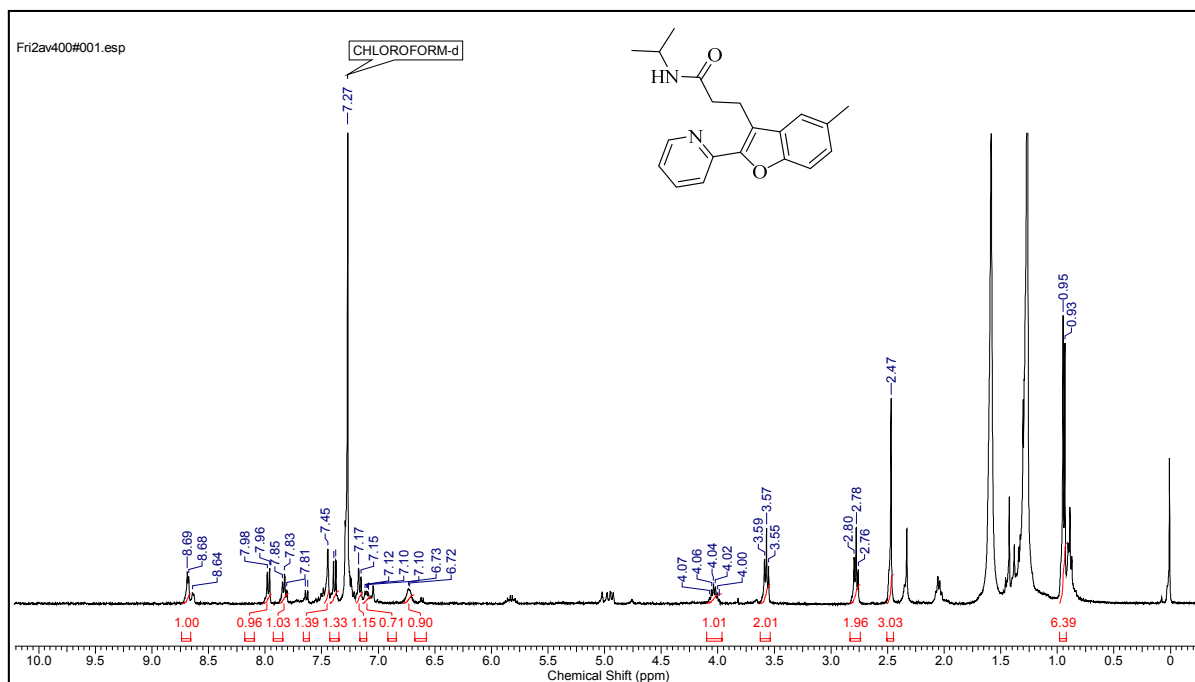
^{13}C NMR Spectrum of **28bb** in CDCl_3 (100 MHz)



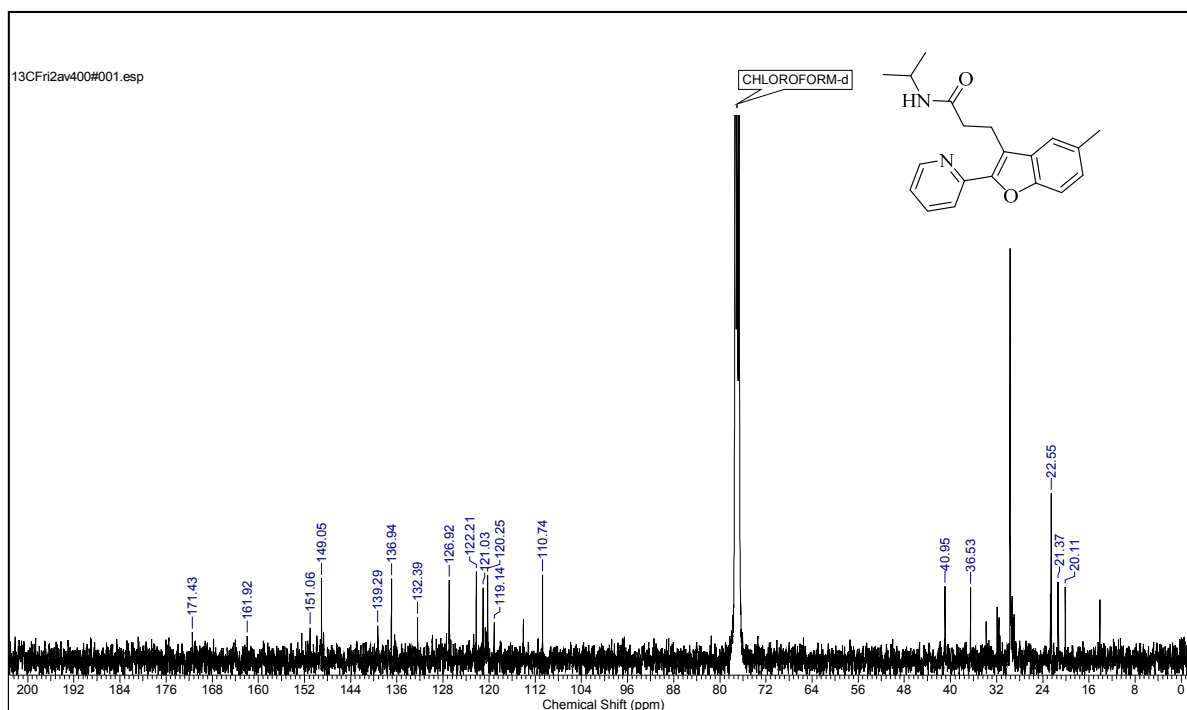
^1H NMR Spectrum of **28bn** in CDCl_3 (400 MHz)



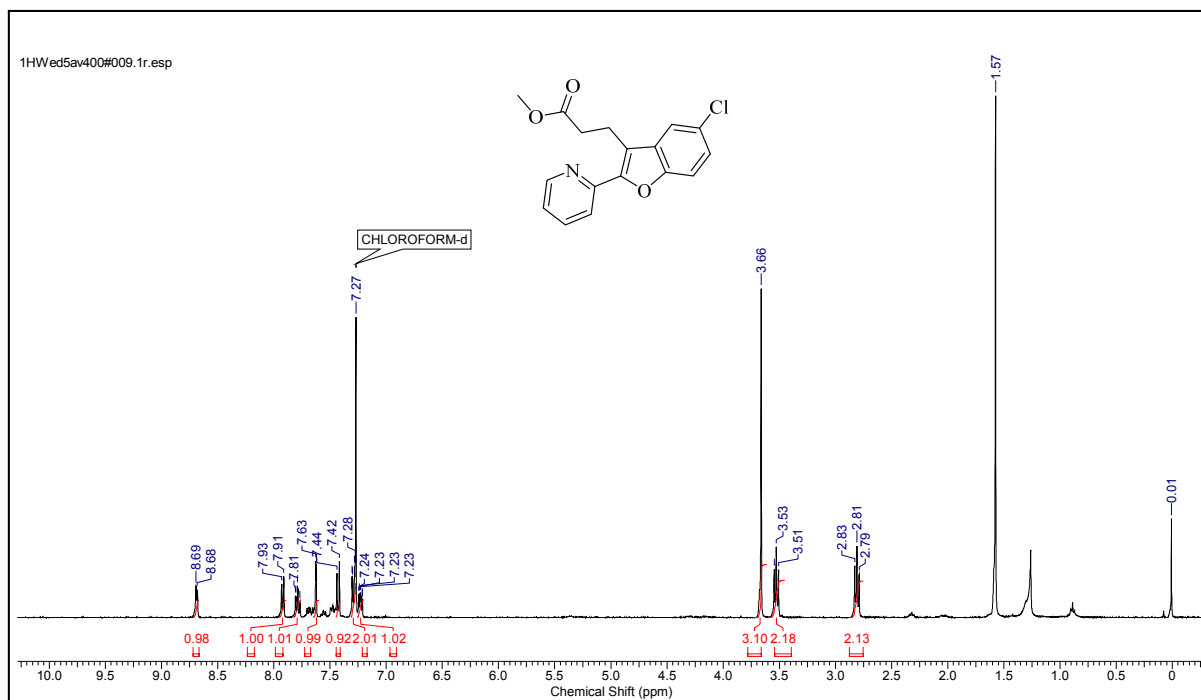
^{13}C NMR Spectrum of **28bn** in CDCl_3 (100 MHz)



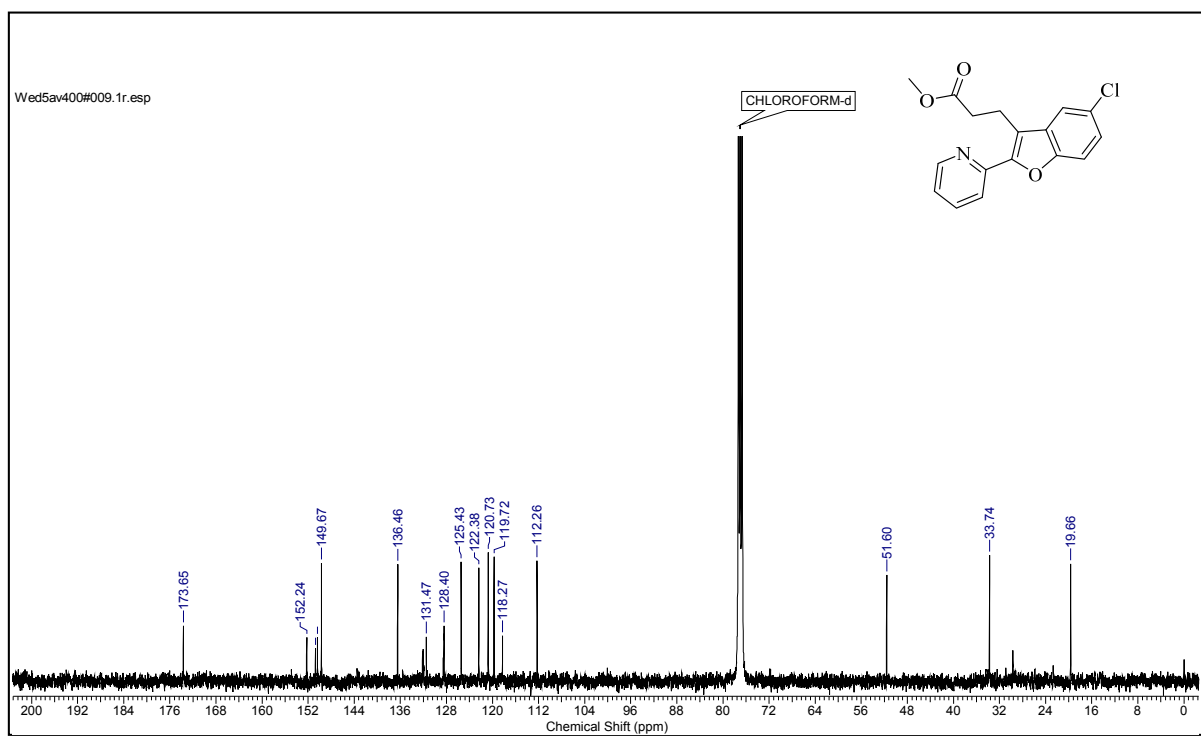
^1H NMR Spectrum of **28bk** in CDCl_3 (400 MHz)



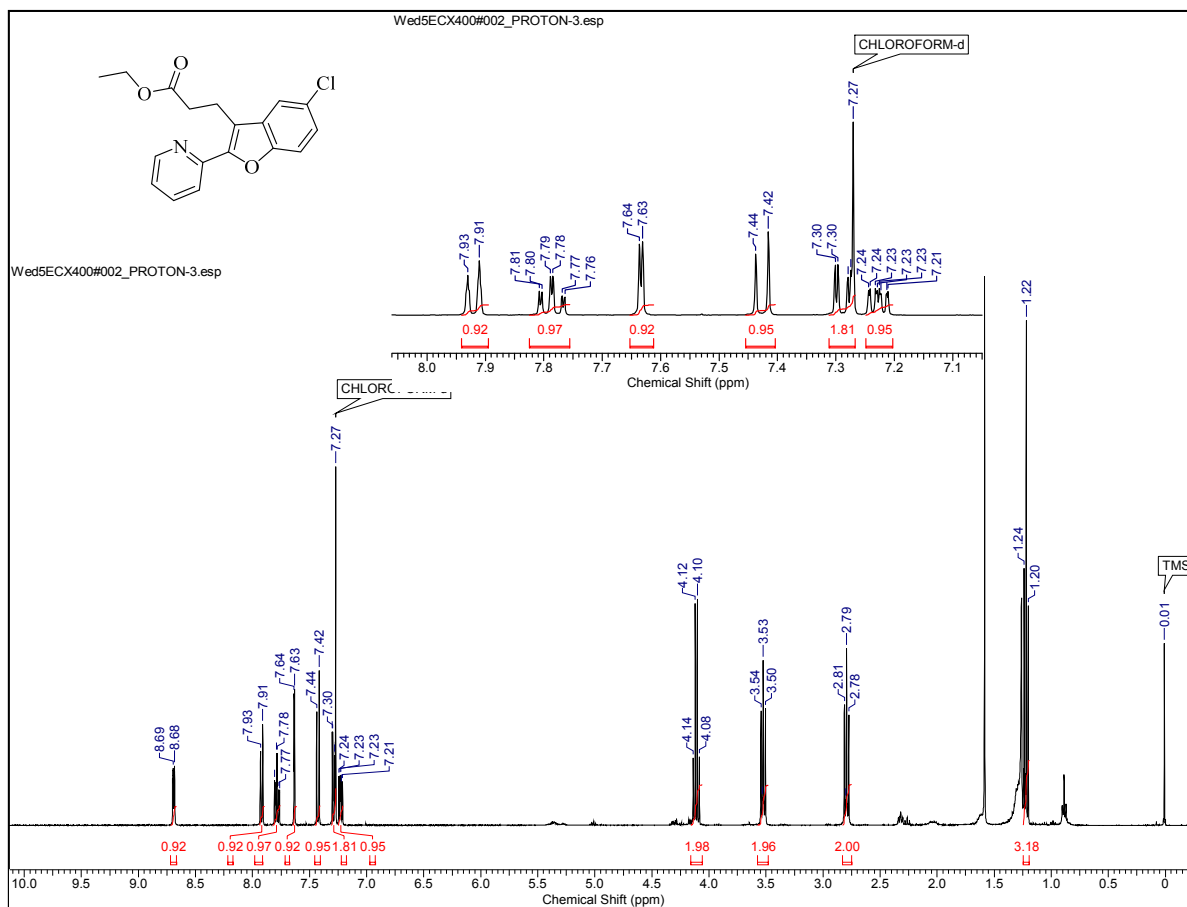
^{13}C NMR Spectrum of **28bk** in CDCl_3 (100 MHz)



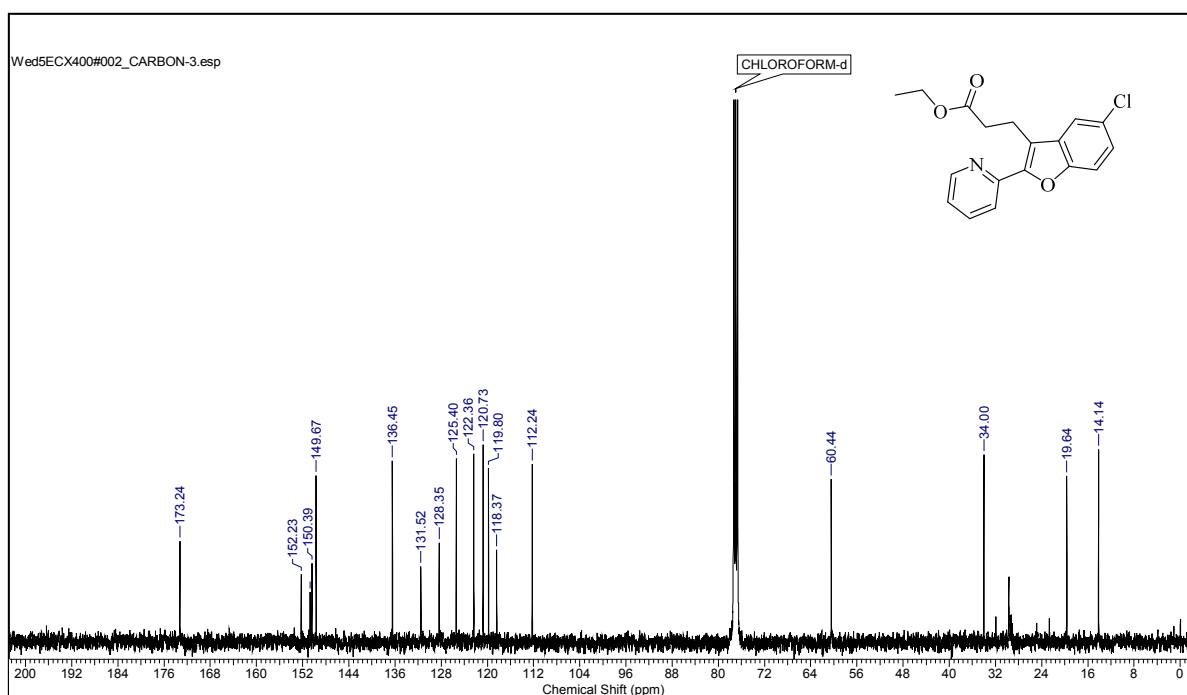
^1H NMR Spectrum of **28ca** in CDCl_3 (400 MHz)



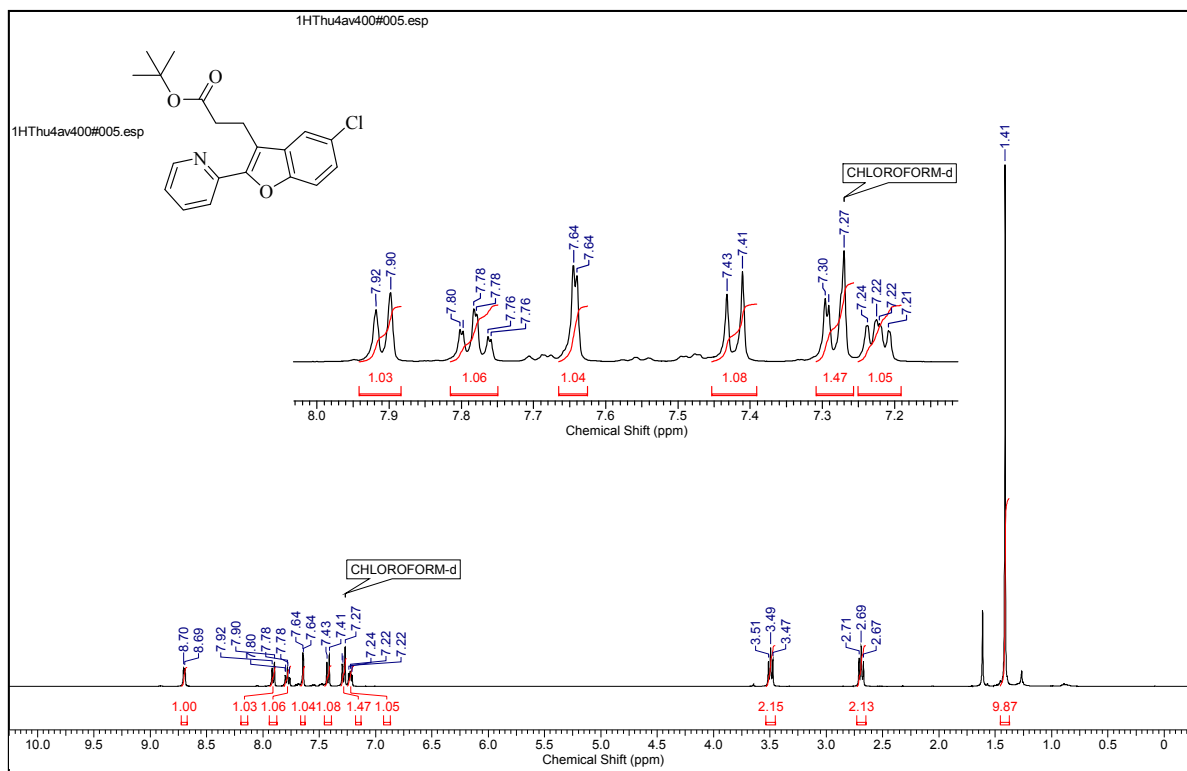
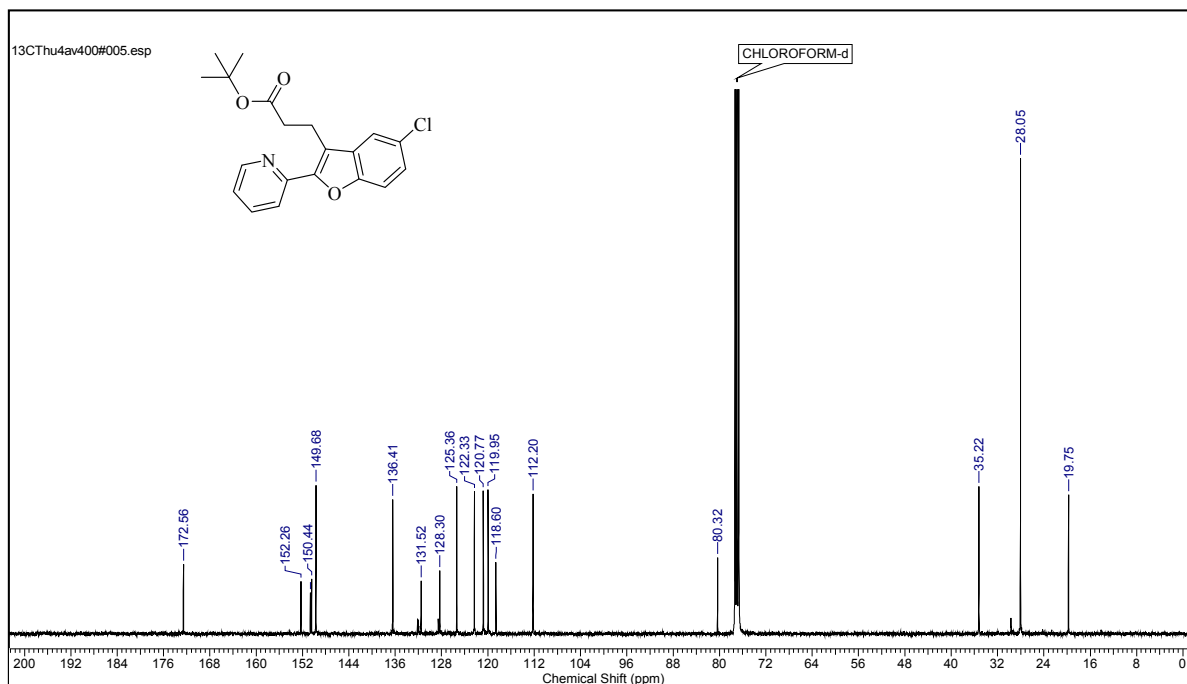
^{13}C NMR Spectrum of **28ca** in CDCl_3 (100 MHz)



¹H NMR Spectrum of **21cb** in CDCl₃ (400 MHz)



¹³C NMR Spectrum of **21cb** in CDCl₃ (100 MHz)


¹H NMR Spectrum of **28cn** in CDCl₃ (400 MHz)

¹³C NMR Spectrum of **28cn** in CDCl₃ (100 MHz)

LIST OF PUBLICATIONS:

- ☆ “The influence of electronic factors on Pd-mediated cycloisomerization: a systematic investigation of competitive 6-exo-dig *versus* 7-endo-dig cyclizations of sugar alkynols.” **Yadagiri Kommagalla**, I. Boddeti, B. Srinivas, M. N. Deshmukh, R.G. Gonnade and C.V. Ramana, *Tetrahedron*, **2009**, 65, 9819-9832.
- ☆ “Target cum flexibility: simple access to benzofuran conjugated sugar and nucleoside derivatives.” **Yadagiri Kommagalla**, Kolluru Srinivas and C.V. Ramana, *Tetrahedron Lett*, **2013**, 64, 1824-1827.
- ☆ “[Ru]-Catalysed Complementary Branched and Linear C(3)-Alkylation of 2-Aroylbenzofurans with Acrylates” **Yadagiri Kommagalla**, Kolluru Srinivas and C.V. Ramana, (manuscript under revision).
- ☆ “Optimization of the phosphoinositol-3, 4, 5-triphosphate antagonist PITENIN-1.” **Yadagiri Kommagalla**, Cornea, S., Riehle, R., Torchilin, V., Degterev, A., C.V. Ramana, (Communicated).
- ☆ “Synthesis, characterization, antifungal evaluation and mechanistic studies of new 1, 2, 3 triazole derivatives.” **Yadagiri Kommagalla**, Santosh G. Tupe, M. V. Deshpande and C.V. Ramana (to be Communicated).
- ☆ “[Ru]-Catalysed Switchable C-H activation: alkenylation and alkylation of benzofuranyl pyridine.” **Yadagiri Kommagalla** and C.V. Ramana (to be communicated).

List of Patents:

- ☆ Small Molecule Inhibitors of PI3-Kinase Signaling. Degterev, A., C.V. Ramana, Torchilin, V., **Yadagiri Kommagalla**, Cornea, S., (US provisional patent accepted, No: 61/802,960).
- ☆ A Novel Process for the Preparation of Anti-Inflammatory Compounds. C.V. Ramana, **Yadagiri Kommagalla**, K. Srinivas, (WO, IN provisional patent accepted, No:1876DEL2013).
- ☆ New 1,2,3 triazole derivatives as anti-fungal drugs. C.V. Ramana, M.V. Deshpande, **Yadagiri Kommagalla**, Santosh G. Tupe, (WO, IN provisional patent has filed).

Erratum
