Stereoselective Synthesis of C27-C35 Eribulin Fragment and Related Macrocycles

A Thesis
Submitted for Degree of
DOCTOR OF PHILOSOPHY
In Chemistry

By

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DEDICATED

TO MY

FATHER

DECLARATION

I, hereby, declare that the matter embodied in the thesis is the result of research investigation carried out by me at the Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Hyderabad, India, under the supervision of **Professor Prabhat Arya**.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

Dr. Reddy's Institute of Life Sciences
University of Hyderabad
August 2015

Saidulu Konda

CERTIFICATE

This is to certify that the thesis entitled ***"Stereoselective Synthesis of C27-C35 Eribulin Fragment and Related Macrocycles"*** being submitted by ***Mr. Saidulu Konda*** to University of Hyderabad for the award of ***Doctor of Philosophy*** in ***Chemistry*** has been carried out by him under my supervision and the same has not been submitted elsewhere for a degree. I am satisfied that the thesis has reached to the standard of fulfilling the requirements of the regulations relating to the nature of the degree.

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I thank the Almighty for giving me the strength and patience to work through all these years so that today I can stand proud with my head held high.

Dr. Reddy's Institute of Life Sciences **Saidulu Konda**
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Synopsis

This thesis entitled**, "Stereoselective Synthesis of C27-C35 Eribulin Fragment and Related Macrocycles"** contains five chapters

Chapter 1: Synthesis and Biological Evaluation of Cytoskeleton (Actin and Tubulin) Modulaters

This chapter deals with the literature of chemistry and biology cytoskeleton (actin and tubulin) modulaters in drug discovery arena and breifly discuss about a selected few examples as the small molecule modulators of actin and tubulin.

Chapter 2: Stereoselective Synthesis of C27-C35 Eribulin Fragment and its Related Analogs *(Submitted for publication).*

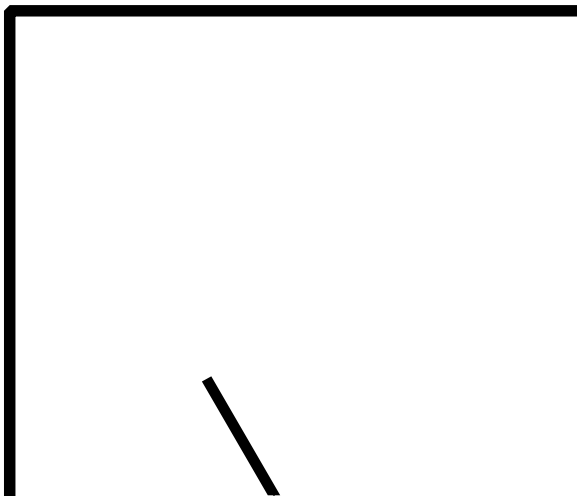
Section A: Literature Work on C27-C35 Eribulin Fragment

This section covers the literature synthesis of C27-C35 fragment of eribulin, reported over the years by several leading research groups.

Section B: Stereoselective Synthesis of C27-C35 Eribulin Fragment and its Related Analogs

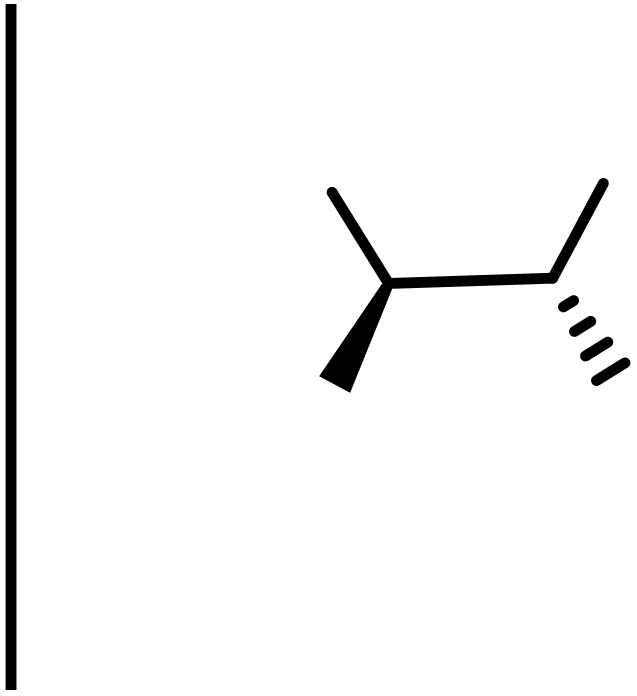
Figure 1: Three Key Fragments

Our plan was to develop a practical and scalable new methodology to the synthesis of compound **F1.2**. The retrosynthetic approach to compound **F1.2** is shown in **Scheme 1**. Compound **F1.2** is planned to be synthesized by using an asymmetric oxa-Michael approach from **1.1**. We propose to obtain **1.1** by vinylation and the cross metathesis reaction on **1.2**. The sulfone **1.2** can be obtained from *SS*-tartaric acid (**1.3**).



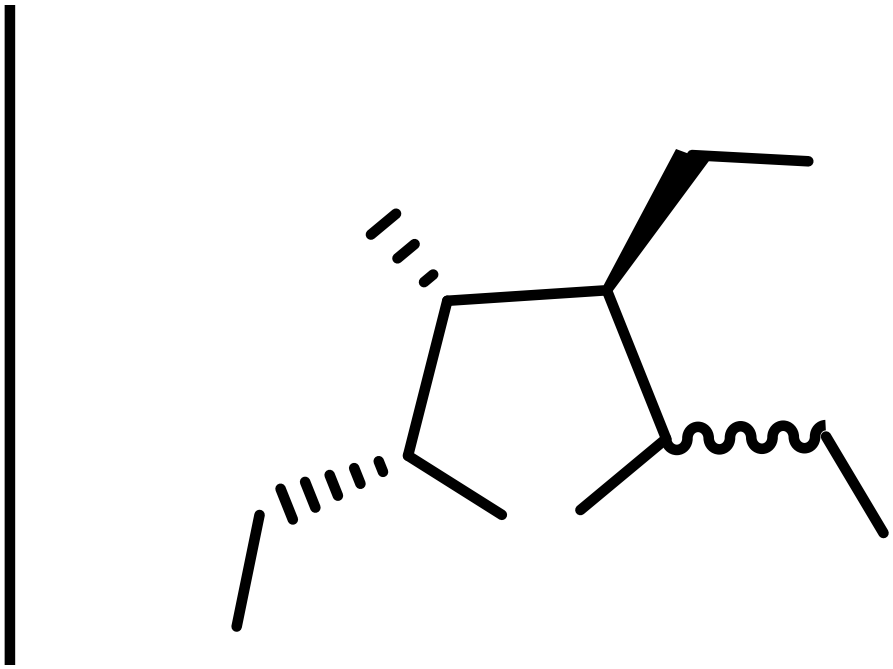
Scheme 1: Retrosynthesis of Eribulin Fragment, **F1.2**

We started the synthesis of **3.4,** from **1.3** esterification and an acetonide protection in one pot followed by $NaBH_4$ reduction, which gave **2.1**. This was then subjected to selective benzyl protection, oxidation of other hydroxyl to aldehyde followed by sulfone Wittig reaction and this afforded **2.2**. Vinylation using vinylmagnesium bromide and CuI gave **2.3** as a single diastereomer. The cross metathesis of an obtained olefin with ethyl acrylate using Grubbs' 2nd generation catalyst followed by an acetonide removal with pTSA led us the synthesis of **2.4** in a good yield. An asymmetric oxy-Michael addition of **2.4** using NaH condition furnished **2.5** and **2.5**[1] as an inseparable diastereomeric mixture.



Scheme 2: Tetrahydrofuran Ring Formation

Further, we subjected a mixture of **2.5** and **2.5**[1] to the next reaction directly. The $LiAlH_4$ reduction of the carboxyl ester, TBDPS protection of obtained primary alcohol and methylation of secondary alcohol, gave **3.1** (minor) and **3.1**[1] (major). We further moved with major (**3.1**[1]**),** and debenzylation and the hydroxyl moiety to iodo group afforded compound **3.2**. The replacement of an iodo group by vinyl and then the dihydroxylation of an olefin completed the synthesis of **3.4**. The product was thoroughly assigned using NMR and MS and the relative stereochemistry was assigned by nOe studies (**Figure 2)**.

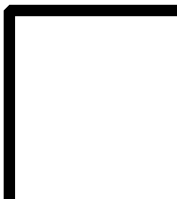


Scheme 3: Synthesis of C27-C35 Eribulin Fragment **3.4**

Figure 2: nOe of Compound **3.4**

We synthesized other related analogs using iodocyclization strategy as the key reaction. The retrosynthetic approach to compound **4.1** is shown in **Scheme 4**. Compound **4.1** was planned to be synthesized by using an iodocyclization approach

from **4.2**. The synthesis of **4.2** was planned from **4.3** by vinylation. Finally, in our synthesis planning, **4.3** was also planned from *SS*-tartaric acid **1.3**.



Scheme 4: Retrosynthesis of Iodocyclization Approach

For the synthesis of **5.1** and **5.2**, we then started with **2.3** (**Scheme 2**) and subjected this to an iodocyclization. For the synthesis of **5.8**, we prepared **5.3** from **2.2** in three simple steps and then subjected to vinylation and this gave **5.4** as 13:1 diastereomeric mixture. We further moved with the mixture and the steps included: removal of acetonide in 2N HCl gave us **5.5** and **5.6** as a separable mixture. Further, we moved with **5.5**: (i) DCB (2,6-dichlorobenzyl) protection, and (ii) $LiAlH_4$ reduction of lactone gives diol. The TBDPS protection of primary alcohol, methylation of secondary alcohol afforded **5.7,** finally iodocyclization led us producing **5.8** in a good yield.

Scheme 5: Synthesis of Fragments **5.1,5.2** and **5.8**

A few key references

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Chapter 3: Synthesis of Eribulin Fragment Based Macrocyclic Toolbox.

Our goal was to develop various modular approches to obtain different macrocyles to explore their biological properties. Utilizing some of the fragments from **Chapter 2**, as the key building blocks (**Scheme 5**), our next plan was to design the synthesis of different macrocyclic compounds having 14-membered rings (**Figure 3**).

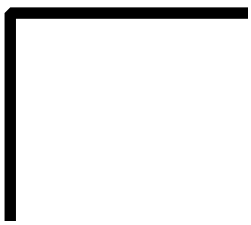
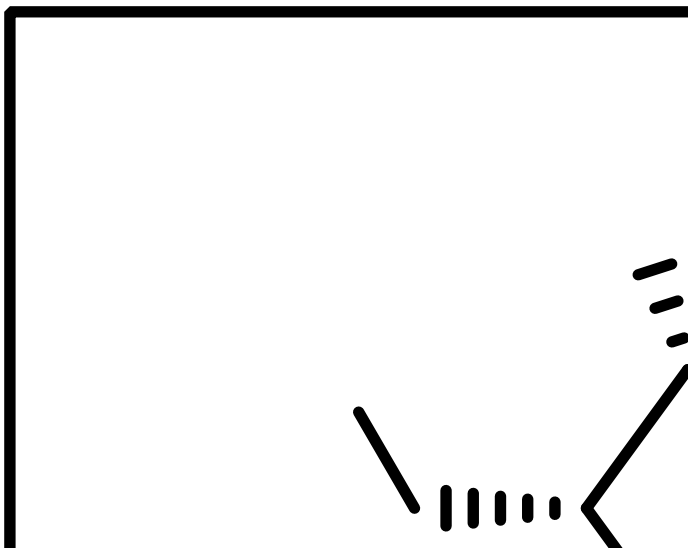


Figure 3: Our Modular Macrocyclic Design

We started the synthesis of key fragments from **5.1, 5.2** & **5.8** (**Scheme 5**), and subjected all the three fragments to vinylmagnesium bromide in the presence of CuI and HMPA at -30 ^{o}C. This approach afforded olefin compounds and further methylation of free hydroxyl groups in two cases led us completing the synthesis of **6.2** and **6.3** (**Scheme 6**).



Scheme 6: Synthesis of Key Fragments

To start the synthesis of macrocycles from **6.1** and **6.2**, the debenzyaltion of both isomers with $TiCl_4$, coupling of N-alloc amino acid building block using EDCI, DMAP and the ring closing metathesis with Grubbs' 2nd generation catalyst 10 mol% at 0.001 mM dilution in DCM afforded the macrocycles **7.1** and **7.2**. The generality of our approach was demonstrated by synthesizing four macrocycles each in both cases.

Using another, a slightly modified approach, fragment **6.3** led us obtain **7.3** by : (i) TBDPS removal with TBAF, (ii) coupling, (iii) RCM and (iv) hydrogenation using Pd/C, another series of macrocycles. In a similar manner, the macrocyclic synthesis of **7.4** was accomplished. .

Scheme 7: Synthesis of Various Macrocyclic Compounds

All these macrocyclic compounds and various acyclic intermediates were then sent to our key collaborator, Dr. Satish Srinivas Kitambi, Biochemistry Dept, Karolinksa Institute, Sweden to search for a new family of cytoskeleton modulators and as novel anti-cancer agents through testing on patient-derived brain tumor cells.

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Chapter 4: Synthesis of Novel Glycohybrids Using 1,3-dipolar Cycloaddition Approach

In this chapter, I discussed a novel tricyclic monosaccharide triazole hybrids, namely, aryl substituted hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine derivatives from an intramolecular 1,3-dipolar cycloaddition of 6-azido-4-*O*-propargyl glycopyranosides. (*RSC Adv*. **2014**, *4*, 63962-63965*)*

Figure 4: Triazole Hybrids

Our synthesis was started with methyl-D-glucopyranoside **8.1** which upon 1,3 diol protection with benzaldehyde dimethyl acetal gave **8.2**. Benzylation of remaining

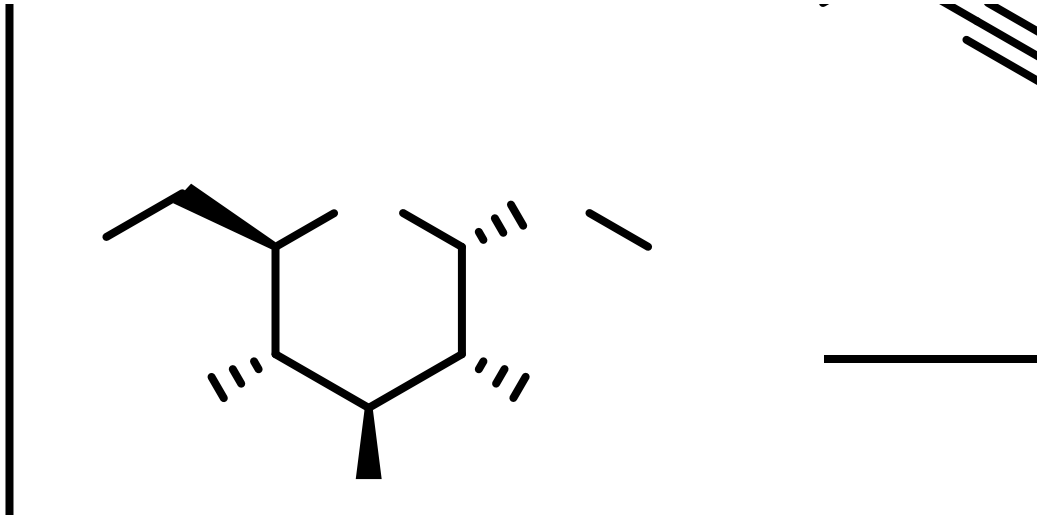
alcohols with benzyl bromide and removal of benzylidine with pTSA afforded **8.4**. The selective primary tosylation and refluxing with NaN_3 provided us **8.6**. This key intermediate was further used for making the triazole compounds. Initially, we utilized simple tosylated propargyl alcohol to obtain **8.7** and then subjected **8.7** to 1,3-dipolar cycloaddition in DMF at 80 ^oC for obtaining **8.8** in a good yield. This was further subjected to hydrogenation to complete the synthesis of **8.9**.

Scheme 8: Synthesis of Key Sugar Moiety **8.6**

We synthesized different tosyl derivatives (**9.4a-9.4f**) by Sonogashira coupling using propargyl alcohol **9.1**, with different aryl bromides (**9.2**) followed by tosylation using TsCl and KOH.

Scheme 9: Synthesis of Different Tosylates

Further, we synthesized substituted triazoles using **8.6**, propargylation in NaH, DMF conditions. Subjection to 1,3-dipolar addition on heating without CuI, followed by hydrogenation with Pd/C, MeOH, we finally succeeded preparing substituted triazoles (**10.3a**-**10.3f**).



Scheme 10: Synthesis of Novel Glycohybrids

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Chapter 5: $InCl_3$ Catalyzed Three Component Synthesis of α-Benzylamino Coumarins and Diketones (*Tetrahedron. Lett*., **2012**, *53*, 5314–5317)

In this chapter, I discussed a convenient and practical $InCl_3$ catalyzed three-component reaction of 4-hydroxy coumarin/1,3 diones, aromatic aldehyde, and secondary amine for the synthesis of α-benzylamino coumarins and diketones in good yields.

Scheme 11: Synthesis of Coumarin and Dimedone Derivatives

We optimized the reaction conditions with different catalysts, solvents and different time scale, and found that 10 mol% $InCl_3$ in toluene for 3 h was the best condition, giving the product in 90% yield.

Table 1: Optimized Conditions of $InCl_3$ Catalyzed Reaction of α-Benzylamino Coumarins

A few key references

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ABBREVIATIONS

Ag_2O	:	Silver oxide
aq.	:	Aqueous
Ar	:	Aryl
$AlCl_3$	:	Alluminium trichloride
Alloc-AA	:	N-Alloc amino acid
$BF_3 \cdot OEt_2$	:	Borontrifluoride-etherate complex
BnBr	:	Benzyl bromide
CH_3CN	:	Acetonitrile
$CDCl_3$	:	Deuterated chloroform
CuI	:	Copper Iodide
DCM	:	Dichloromethane
DMF	:	Dimethylformamide
DMAP	:	4-Dimethylaminopyridine
EDCI	:	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EtOAc	:	Ethyl acetate
Et_3N or TEA	:	Triethylamine
$EtO_2CCH_2PO(OEt)_2$	:	Triethyl phosphonoacetate
Eq	:	Molar equivalent(s)
ES	:	Electro Spray
G-II	:	Grubbs 2nd generation catalyst
H_2	:	Hydrogen
HMPA	:	Hexamethyl phosphoramide
2N HCl	:	2 Normal Hydrochloric acid
h	:	Hour
IBX	:	2-iodoxybenzoic acid
$InCl_3$	:	Indium Trichloride
Im	:	Imidazole
I_2	:	Iodine
K_2CO_3	:	Potassium carbonate
KOH	:	Potassium hydroxide

$LiAlH_4$	:	Lithium aluminium hydride
MeI	:	Methyl iodide
NH_4Cl	:	Ammonium chloride
$NaHCO_3$	:	Sodium bicarbonate
Na_2SO_4	:	Sodium sulphate
NaH	:	Sodium hydride
$NaBH_4$	:	Sodium borohydride
NMO	:	N-methyl morpholine N-Oxide
NMR	:	Nuclear magnetic resonance
NaN_3	:	Sodium azide
Me	:	Methyl
MeOH	:	Methanol
OsO_4	:	Osmium tetroxide
$PhO_2SCH_2PO(OEt)_2$	:	Methanesulfonylphosphate
*p*TSA	:	*para*-toluene sulfonic acid
Pd/C	:	10% Palladium on Carbon
$PhCH(OMe)_2$	:	Benzaldehyde dimethylacetal
PPh_3	:	Triphenylphosphene
$Pd(PPh_3)_4$	:	Tetrakis(triphenylphosphine)palladium
Rt	:	Room temperature
Rf	:	Retardation factor
TBDPSCl	:	tert-Butylchlorodiphenylsilane
TBAF	:	Tetra-n-butylammonium fluoride
THF	:	Tetrahydrofuran
TLC	:	Thin Layer Chromatography
$TiCl_4$	:	Titanium tetrachloride
TsCl	:	*para*-toluenesulfonyl chloride

General Information

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Varian 400 MHz NMR spectrometer at the frequency indicated. Where indicated, the NMR peak assignments were made using COSY experiments. All chemical shifts are quoted on the δ-scale and were referenced to the residual solvent as an internal standard. Combinations of the following abbreviations are used to describe NMR spectra: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Mass spectra and LCMS were recorded using electron impact, chemical ionisation or electrospray ionisation techniques, on Agilent-6430 mass spectrometer. High-performance liquid chromatography was carried out on Agilent-1200 instrument using X-BRIDGE C-18 150×4.6mm 5µ column . Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel $60F_{254}$ (Merck, 1.05554) and the spots were visualized with UV light at 254 nm or alternatively by staining with aqueous basic potassium permanganate or ceric ammonium molybdate or ninhydrin. Flash column chromatography was performed using silica gel (Merck, 60A, 230-400 Mesh). Commercially available reagents were used as supplied and some of them were distilled before use. All reactions were performed in oven dried glassware. DMF, DCM, MeOH and THF were dried immediately prior to use according to standard procedures: Dimethylformamide, Dichloromethane was distilled under N_2 from CaH_2, Methanol was distilled under N_2 over Mg and Tetrahydrofuran was distilled under N_2 over Na. All solvents were removed by evaporation under reduced pressure.

Chapter 1

Synthesis and Biological Evaluation of Cytoskeleton (Actin and Tubulin) Modulators

Synthesis and Biological Evaluation of Cytoskeleton (Actin and Tubulin) Modulators

In this section, I am going to discuss about the synthesis and biological evaluation of cytoskeleton (actin and tubulin) modulators.

1.1. Cytoskeleton

The cytoskeleton of eukaryotic cells has three major components, which includs microfilaments (actin filaments), microtubules, and intermediate filaments.[1] These filaments form a network of fibers through the association of monomeric proteins, such as actin, tubulin, keratin *etc*. and stabiliztion or de-stabilization of various protein:protein interactions (PPIs)[1] of such cytoskeletal proteins directly leads to the regulation of cytoskeletal dynamics.[2]

1.2. Tubulin

1.2.1a. Introduction to Tubulin

Tubulin is a small protein unit of microtubules and was isolated in 1967 by Borisy and Taylor.[3] It is an important sub-unit of microtubules which play a key role in several cellular functions. The term tubulin was given by Mohri and co-workers[4] and the purification of tubulin protein from brain was carried-out by Weisenberg and co-workers in 1968,[5] whereas it was obtained from the sperm tails by Shelanski and Taylor.[5-6] The microtubules are present in all eukaryotic cytoskeleton and participate in several biological functions.

Microtubules consist of polymerized α- and β-tubulin heterodimers, and play important roles in cell proliferation[7], traficking[8], cell-signaling[9], and migration.[8,10] Most approved anti-cancer drugs function through the targeting of tubulins.[11] The microtubule stabilizers, for example taxols (**F4.8**), epothilones (**F4.1**), laulimalide (**F4.3**), discodermolide (**F4.5**) *etc*. increases the formation of microtubules by stabilizing the interaction between tubulin heterodimers. Microtubule destabilizers include vinca alkaloids[12] and calchicines[13] and these compounds destabilize the microtubule formation by disrupting the tubulin oligomerization.[10,12,14] Microtubule minus ends can elongate *in viro* but at a lower speed compared to the plus ends and they are mostly stable or depolarizing in cells (**Figure 1**).[14] The plus ends explore the cytoplasm in a very dynamic manner.[15] Microtubules undergo the phases of growth, pause and shrinkage and separated by the rescue or catastrophe events, this dynamic

behavior was termed as "dynamic instability". At the time of microtubules polymerization, the heterodimers of GTP bound tubulin are added at plus end. A slight delay between polymerization and the hydrolysis of GTP by β-tubulin creates a GTP-tubulin cap and a loss of this cap induces the depolymerization of microtubules.[2,11]

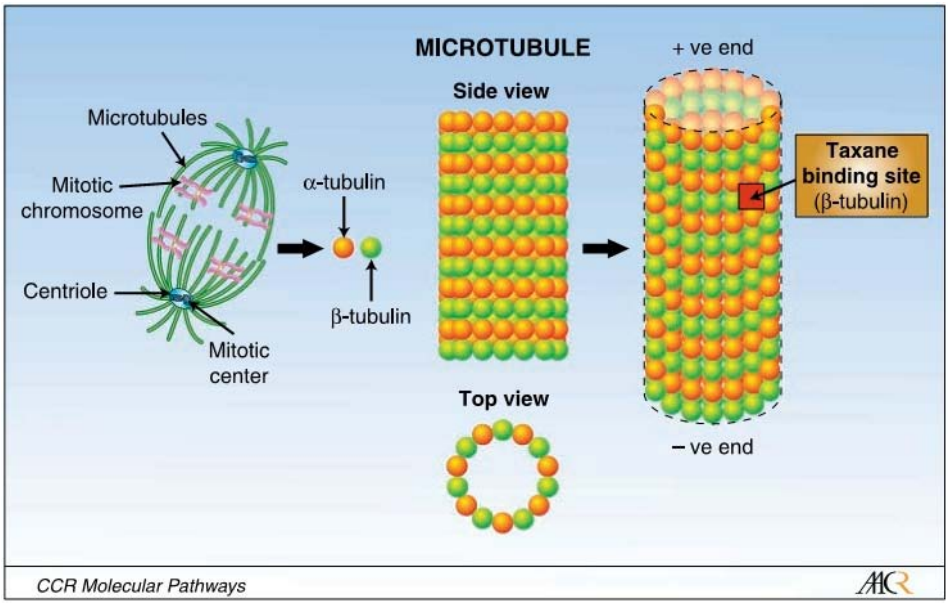


Figure 1: Structure and Function of Microtubules[14]

(this figure is directly taken from *Clin.Cancer Res*. **2008**, 14, 7167-7172)

1.2.1b. Regulation of Microtubule Dynamics

The intrinsic processes such as the presence of GTP-cap and GTP-islands thus regulate the microtubule dynamics.[14] Whereas an extrinsic regulatation of microtubule is due to the numerous microtubule associated proteins (MAPs), especially proteins that bind to the plus end of the microtubules. The most studied stabilizing MAPs are Tau, MAP2 and MAP4.[16] Proteins such as katanin, spastin and fidgetin regulates the number and length of the microtubules by their severing activity. Recent studies have shown that a fraction of the Tubulin Ring Complex (γ-TuRC) regulate the microtubule dynamics by inducing pauses.[17] Tyrosination of tubulin is carried-out by the tubulin-tyrosine ligase, and the tubulin tyrosination seems to be necessary for the binding of CLIP170 and CLIP115 or p150Glued at the plus tip of the microtubules.[18] Glutamylation and glycylation are essentially found in cilia and flagella in mammalian cells whereas in neurons most microtubules are poly-

glutamylated.[19] Tubulin acetylation also increases the binding of motors to microtubules, and microtubule acetylation enhances the ER sliding in addition to mitochondria, but not endosomes, which bind preferencially to acetylated microtubules.[20] The dynamic behavior of microtubule results from a balance of many regulatory processes or due to its interactions with regulatory proteins (**Figure 2**).[15a,18,20]

Figure 2: Regulation of Microtubule Dynamics[15a]
(this figure is drawn from *Int. J. Biochem. Cell Biol.* **2012**, *44*, 266)

Drugs that interfere with the microtubules structure and function are divided into two types: (i) stabilizers and (ii) destabilizers. Most of the current approved drugs targets tubulin and not actin. For example, vinca alkaloids which is a tubulin destabilizer binds to β-tubulin and these are the oldest class of cytotoxic agents which show activity against lymphomas, non-small cell lung cancer and breast cancer.[21] The next generation cytotoxic agents which belong to the family of microtubule stabilizers are

taxanes and these are used in ovarian cancer gastroesophagal cancer germ cell tumors and head and neck cancer.[22] Other tubulin stabilizers which show activity like taxanes are epothilones and they also function by binding to β-tubulin.[23] Laulimalides binds to α-tubulin; the binding sites for some other drugs are shown in **Figure 3**.[14]

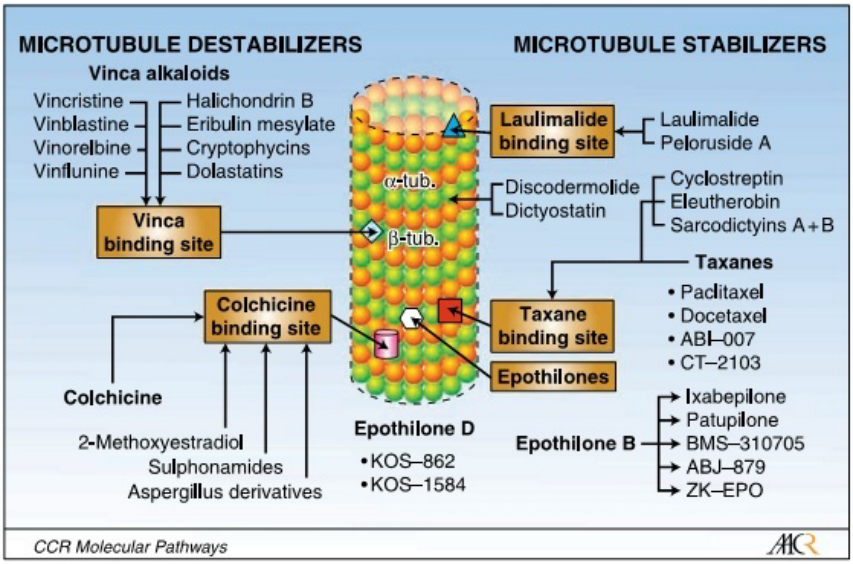


Figure 3: Microtubule Stabilizers and Destabilizers their Binding Sites on Tubulin[14] (this figure is directly taken from *Clin.Cancer Res*. **2008**, 14, 7167-7172)

1.2.2. Microtubule Stabilizing Agents

1.2.2a. Taxanes (F4.8): Taxanes are amongst most promissing antitumor agents available in market today. Several ongoing experimental and clinical trials have supported the fact that even with their side effects and poor solubilities, taxanes are still the first lines of treatment chosen for breast, ovary, lung and other metastatic cancers.[23]

1.2.2b. Epothilones (F4.1): Epothilones are novel class of microtubule stabilizing agents, isolated by myxobacterium *sorangium cellulosam.*[24] The binding site of these natural products is close to the taxane-binding site. The mechanism of action of epothilones is also similar to taxanes whereas they are structurally different. Intially, there were limitations in the use of epothilones in early times but newer structural analogs appear to be highly promising and one of them has succeeded in reaching the market.

1.2.2c. Ixabepilone (F4.2): A semisynthetic derivative of epothilone B, which has a modified lactone ring to lactam is now utilized for overcoming from the hepatic degradation. In 2007, ixabepilone was approved by FDA.[25]

1.2.2d. Laulimalide and peloruside: Laulimalide (**F4.3**) is derived from marine sponge which is active against paclitaxel-resistant cells.[26] Laulimalide binds to α-tubulin.[27] It has a narrow therapeutic index and marked toxicity. Peloruside A (**F4.6**) was isolated from marine sponge *Mycale hentscheli* in New Zealand which is having similar structure as epothilone.[27] The binding site is the same as for laulimalide, and also, it is less lipophilic than paclitaxel.[26]

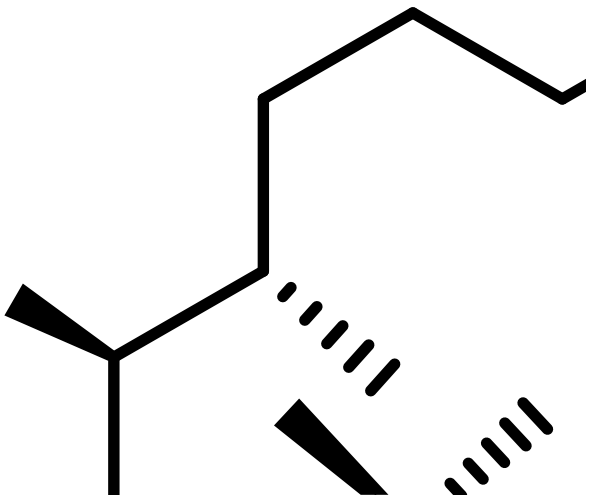


Figure 4: Few Examples of Tubulin Stabilizers

1.2.2e. Other agents: In addition to the different class of natural products discussed above, a number of other naturally occuring compounds have been reported to stabilize tubulin and some of these are: cyclostreptin (**F5.1**)[28], eleutherobin (**F5.2**)[29]

and sarcodictyins (**F5.3**).[30] These compounds are chemically related and reach for the similar binding site as for taxanes. In addition to these examples, jatrophanes (**F5.4, F5.5, F5.6**)[31], tubercidin (**F5.7**)[32] and dicumarol (**F5.8**)[33] are also reported to stabilize microtubules.

Figure 5: Other Natural Products that Stabilizes Tubulin or Microtubule

1.2.3. Microtubule Destabilizing Agents

1.2.3a. Halichondrins and Eribulin: Halichondrin B (**F7.1**) act as a tubulin destabilizing agent with subtle differences in the mechanism of action from other anti-mitotic agents, like: vinca alkaloids.[12] Eribulin mesylate (Halaven®) (**F6.6**) is a synthetic analog of halichondrin B, a non-taxane microtubule dynamics destabilizer, and it is approved for the treatment of late-stage metastatic breast cancer.[34]

1.2.3b. Colchicines: Colchicine itself has no clinical use but there are many compounds which bind to the colchicine binding site and some of these include 2-methoxyestradiol (**F6.8**),[35] sulfonamide derivatives (**F6.7**)[35b] and synthetic derivatives of *Aspergillus sp.*[13]

1.2.3c. Vinca alkaloids: Vinca alkaloids which include vinblastine (**F6.1**), vincristine (**F6.2**), vindoline (**F6.3**) *etc.*[12] are the well-established compounds.[36] There are

several synthetic derivatives which function through the vinca binding site and are undergoing further clinical investigation. Cryptophycins (**F6.4**) are isolated from blue algae and cryptophycin 52 (**F6.5**) is a synthetic analog of cryptophycin which shows activity against ovarian cancer.[37]

1.2.3d. Dolastatins (F6.9): It is isolated from *Dolabella aurincularia* found in Indian Ocean and its binding site is close to vinca binding site for inhibiting microtubules.[38]

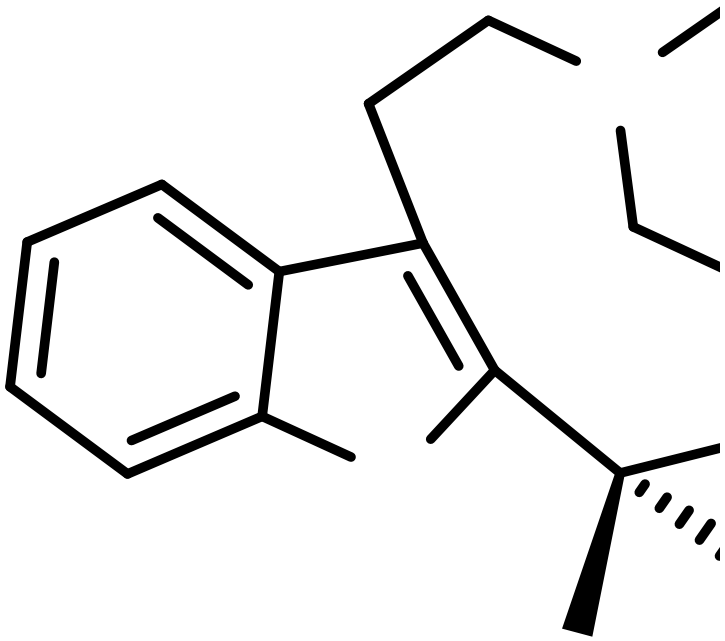


Figure 6: Few Structures of Tubulin Destabilizers

1.3. Synthesis of Microtubule Stabilizing Agents

1.3.1a. Dictyostatin: Dictyostatin (**1.1**) is a potent cytotoxic macrolide isolated by Pettit and co-workers[39] from a marine sponge. It has an unsaturated 22-membered macrolactone, and also contains 11 stereo-centers. This macrolide has endocyclic 2Z, 4E dienoate and a pendant Z-diene moity at C21. Herein, I have outlined the total synthesis of dictyostatin reported by Paterson and co-workers in 2004.[40]

1.3.1b. Retrosynthesis: The late stage reduction of the enone **1.2** was controlled by the ring conformation. The 10Z alkene was obtained from Still-Gennari olefination[41] of the fragment **1.3** and aldehyde **1.4**, whereas the 2Z, 4E dienoate from Stille coupling with **1.5**. The macrocyclization was then carried-out through Yamaguchi macrolactonization. Subunit **1.4** was synthesized from HWE (Horner-Wadsworth-Emmons) reaction between aldehyde **1.6** and phosphonate **1.7** which were prepared from a common intermediate **1.8**.[42]

Scheme 1: Retrosynthesis of Dictyostatin

1.3.1c. Synthesis: Synthesis of dictyostatin was started with *bis*-TBS protection of **1.8**, and a selective removal of the primary TBS with *p*TSA followed by an iodo conversion to obtain alcohol, giving **2.1**. Alkylation of enolate of Myers'

propionamide (**2.2**)[43] afforded **2.3** in an exellent selectivity. The removal of chiral auxiliary followed by an oxidation with DMP delivered **1.6**.

Schem 2: Synthesis of Fragment **1.6**

Fragment **1.7** was also accessed from **1.8** and all the steps are shown in **Scheme 3** . The TBS protection of primary alcohol, subjection to DDQ for PMB group conversion to PMP through 1,3-diol protection followed by DIBAL-H reaction to PMP removal from primary to the secondary hydroxyl provided compound **3.1**. Oxidation of primary hydroxyl and Takai methylation[44] furnished **3.3** in a good yield. The TBS removal and DMP oxidation gave **3.4**, which upon the addition of dimethyl methylphosphonate using *n*BuLi followed by an oxidation completed the synthesis of **1.7**.

Scheme 3: Synthesis of Subunit **1.7**

Synthesis of fragment **1.4** was afforded by HWE reaction between **1.6** and **1.7** giving an enone **4.1**, which was further subjected to reduction of a conjugate enone by the Stryker reagent.[45] This upon oxidative removal of PMB group with DDQ followed by 1,3-*syn* selective reduction with $Zn(BH_4)_2$[46] afforded a triol **4.2**. The selective TBS protection of C11 and C19 hydroxyl groups, a selective removal of C11 TBS with TBAF, AcOH, and finally, the TEPMO oxidation of the primary hydroxyl completed the synthesis of **1.4**.

Scheme 4: Synthesis of Subunit **1.4**

The synthesis of subunit **1.3** was finished from alcohol **5.2** which was easily accessed by Brown's crotylation of **5.1**. Further, the TBS protection, ozonolysis and Takai methylation[47] led to the synthesis of alcohol **5.4** in good yields. Next, the selective removal of TBS followed by oxidation of primary alcohol gave acid **5.5**. This acid was then converted to an acid chloride using the Ghosez reagent[48] and this was then added to a freshly prepared reagent $(F_3CCH_2O)_2P(O)CH_2Li$ at -100 ^oC, which completed the synthesis of **1.3**.

Scheme 5: Synthesis of Subunit **1.3**

Having all the subunits in hand, the synthesis was completed by a HWE reaction with an exess K_2CO_3, which gave Z enone **6.1**. Liebeskind-type, Stille coupling[49] (CuTC) of vinyl iodide **6.1** and Z alkenyl stannane **1.5** afforded **6.2**. The TIPS ester was converted to an acid by KF and the Yamaguchi macrolactonization of the seco acid gave 22-membered macrocycle **1.2**. Finally, the Luche reduction[50] of **1.2** and the removal of TBS groups completed the synthesis.

Scheme 6: Completion of Synthesis

1.4. Synthesis of Microtubule Destabilizing Agents

1.4.1a. Eribulin: Eribulin mesylate (Halaven®) (**F6.6)** is a non-taxane microtubule dynamics destabilizer and is approved for the treatment of late-stage metastatic breast cancer.[51] It is a macrocyclic ketone, non-peptidic, and fully synthetic drug that is derived from the truncated version of halichondrin B (**F7.1**).[52] Halichondrins are a class of polyether macrolides, first isolated from the marin sponge *Halichondria okadai* Kadota,[53] which is commonly located along the pacific coast of Japan. The potent *in vivo* activity of the crude extracts from *Halichondria okadai* Kadota, led the isolation and identification nor-halichondrin A (**F7.2**) with the cytotoxicity, IC_{50} = 5 ng/mL vs B16 melanoma as shown by the Uemura team.[54] Later, Uemera and co-workers collected 600 kg of *H. Okadai*, and further identified seven halichondrins.

Figure 7: Halichondrin B and nor-Halichondrin A

Halichondrin family is having an unusual 2,6,9-trioxatricyclo[3.3.2.0]decane ring system, as well as a 22-membered macrolactone ring, two exocyclic olefins, and, an array of poly-oxygenated pyran and furan rings that define three major classes of halichondrins A, B and C. The detailed isolation and structural elucidation of the halichondrin family is nicely reviewed by Phillips and co-workers in 2009.[55]

First, the total synthesis of halichondrin and norhalichondrin was achieved by Kishi and co-workers in 1992.[56] Second, the total synthesis of norhalichondrin B was reported by Phillips and co-workers in 2009.[57] Some other groups also worked on the total synthesis of halichondrin family natural products (**Figure 8**).[58]

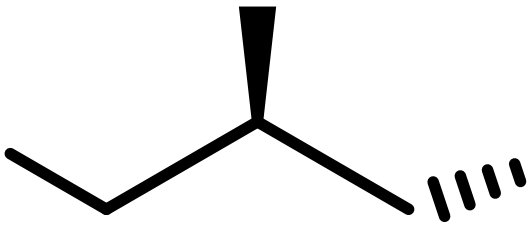


Figure 8: Chemical Structures of Eribulin (**F6.6)**, ER-076349 (**F8.1)** and Diol (**F8.2)**

1.4.1b. Discovery and Development of Eribulin: During the biological evaluation of halichondrin B and its intermediates, a macrocyclic macrolactone diol **F8.2** was discovered as a more potent compound than halichondrin B against DLD-1 human colon cancer cells.[59] Among these several derivatives, compounds having the ketone moiety were the most promising, and, thus, **F8.1** (ER-076349) and **F6.6** showed prominence in activity (E7389, previously ER-086526). Halaven (**F6.6)** is a non-taxane, first-in-class microtubule dynamics inhibitor. The FDA approved this compound for the metastatic breast cancer.[60] The novel mechanism of action of eribulin, differs from other known classes of tublin-targeted agents (**Figure 9**).[34] These known compounds bind to an interdimer interface or the β-tubulin subunit alone, and, inhibits the microtubular growth phase of microtubular dynamics instability in interphase cells without any effect on shortening.[61] In addtion to this, moreover, it also promotes the centromere spindle relaxation without affecting the rate of stretching.[61a]

Figure 9: Eribulin Mechanism of Action[62]

(this figure is drawn from *Mol. Cancer Ther.* **2005**, *4*, 1086)

The preclinical studies of eribulin showed a broad spectrum of anti-tumour activity against a wide variety of human cancer types.[63] The phase II trials of eribulin in chemotherapy pre-treated advanced breast cancer patients showed a manageable tolerability profile with most common drug-related adverse effect. Peripheral neuropathy is a common toxicity associated with tubulin-targeted chemotherapeutic agents, the phase II study compared the incidence and severity of neuropathy associated with eribulin or ixabepilone in metastatic breast cancer was designed to detect a difference in neuropathy rate of 35% for eribulin versus 63% for ixabepilone. These studies have shown the incidence of neuropathy (any grade) to be 33.3 and 48.0%, and peripheral neuropathy as 31.4 and 44.0% for eribulin and ixabepilone respectively eventhough these results were not significant. The phase III trial, 762 women with LABC or MBC were randomly allotted in 2:1 ratio to eribulin 1.4mg/m^2 over 2-5 min on days 1 and 8 of 21-day cycle (n=508) or treatment of physicians

choice (TPC) (n=254), result showed a significant increase in OS for eribulin (13.1 months) compared with TPC (10.6 months).[64] Based on the result, the FDA approved eribulin mesylate as a third-line treatment for MBC (metastatic breast cancer) refractory to anthracyclines and taxanes.

1.4.1c. Key Fragments of Eribulin: The Eisai synthesis of ER-076349 and E7389 utilized most of the technology that was adopted from Kishi's approaches. ER-076349 was readily synthesized from three fragments, and, they are shown in **Scheme 7**. A practical gram scale synthesis of eribulin was reported by Yu and co-workers[65]

Scheme 7: Key Fragments of ER-O76349

1.4.1d. Recent Developments in the Synthesis of Eribulin Fragments

Fragment C27-C35: Herein, I am going to explain the recent synthesis of C27-C35 fragment from Chandrasekhar and co-workers.[66]

Scheme 8: Retrosynthesis of Fragment **8.1**

This synthesis involves a tandem α-chlorination/aldol reaction[67] as the key step. The retrosynthetic analysis is shown in **Scheme 8**. The fragment **8.1** could be synthesized from **8.2** which was derived from **8.3**. This is a key intermediate which was brought from the two substrates, **8.4** and **8.5**.

The key intermediate chlorohydrin **8.3** was prepared from the protected dihydroxyacetone **8.5** and pentenal **8.4** using D-proline as a catalyst in the presence of N-chlorosuccinamide in 62% yield and 91% ee (**Scheme 9**).

Scheme 9: Synthesis of Key Intermediate **8.3**

The key fragment **8.3** was converted to C28-C35 fragment **8.1** as shown in **Scheme 10**. The hydroxyl directed reduction of the keto group with tetramethylammonium triacetoxyborohydride, and the acetonide removal with $MeOH/H_2O$ at 60 ^oC underwent cyclization which then followed by 1,3-diol protection with anisaldehyde dimethyl acetal to obtain **10.1**. Further, **10.1** was subjected Mitsunobu conditions[68] that gave **10.2**. The methylation of hydroxyl group with MeI and NaH and Sharpless dihydroxylation for introducing the C34 stereocenter.[69] Finally, the azide group at C35 was brought in using the standard conditions, which then completed the synthesis of **8.1**.

Scheme 10: Completion of Synthesis of **8.1**

Fragment C14-C26: Here, I am discussing the recent synthesis of C14-C26 fragment of eribulin from D-Quinic acid, which was obtained by Belanger and co-workers. (**Figure 10**).[70]

A key feature of this synthesis was the crystallization-induced diastereoselective transformation of an α-methyl nitrile. It is a non-chromatographic synthesis and an α-methyl nitrile substrate was derived from D-quinic acid. The stereoselective iodoetherification of **F10.1** provided **F10.2** and the zinc-mediated reductive elimination of **F10.2** then produced **F10.1**. The fragment **F10.2** was obtained from D-quinic acid as a readily available chiral source to access all the needed stereogenic centers.

Figure 10: Synthetic Strategy Towards C14-C26 Fragment

The D-quinic acid (**F10.3**) was converted into crystalline diacetate **11.1** through four steps and these are: (i) diol protection, (ii) lactonization,[71] (iii) reduction and (iv) peracetylation. The *C*-glycosylation of **11.1** with **11.2** followed by NaOMe treatment gave C20 and C23 stereogenic centers. The reduction of an moiety ester followed by mesylation afforded compound **11.3**.

The cyanide displacement and LDA treatment followed by quenching with MeI gave α-methyl nitrile in 1:1 ratio. The treatment with KHMDS converted the undesired epimer to the desired crystallized compound (**11.4**) and this also improved the selectivity to >4:1.[72]

Scheme 11: Synthesis of α-methyl Nitrile

Cyclohexylidine cleavage and a regioselective bromoacetate formation[73] then led to producing **12.1.** This was then subjected to several transformations and these are: (i) dehydrobromination, (ii) ozonolysis, (iii) borohydride quench and (iv) the periodate cleavage afforded the crystalline lactol which was then followed by a HWE reaction, finally giving **12.2**. The hydrogenation and triflate-mediated iodination then gave the crystalline iodo-ester intermediate. The reduction of the ester moiety with $LiBH_4$ followed by zinc-mediated Vasella fragmentation[74] afforded an exocyclic double bond. The HCl treatment to form a cyclic imidate hydrochloride which upon hydrolytic lactonization led to producing **12.3**. The protection of primary alcohol with TBDPS, lactone opening to Weinreb amide synthesis, protection of C23 hydroxy with TBS, finally gave **12.4**. This was then subjected to three simple steps to complete the synthesis of **F10.1**.

Scheme 12: Completion of Synthesis

Fragment C1-C19: Here, I am explaining the recent synthetic strategy developed for the C1-C19 fragment of eribulin/ halichondrin by the Kishi's group.[75]

Scheme 13: New Approach to the Synthesis of C1-C19 Fragment

The Cr-mediated coupling of organic halides or triflates with aldehydes belong to a class of 1,2-carbonyl addition reactions.[76] Ni- or Cr-mediated coupling of alkenyl halides or triflates were originally reported by Takai, Hiyama, Nozaki and co-workers in 1983.[77] In this process, the active nucleophiles $RCrX_2$ are generated from their corresponding halides or triflates *in situ*.

Scheme 14: Optimized Conditions

The researchers first studied the coupling efficiency of β-iodoenones (**14.1a-c**) with an aldehyde (**14.4**) using 10 mol% Cr catalyst prepared from sulfonamide **14.6**[78] and 1 mol% **14.7**. In addition to this, different types of catalysts,[79] aldehydes and β-bromoenones were also tested. Moreover, the computational experiments were also performed to study the reactivity between β-bromoenones and vinyl iodides.[78b,80]

Finally, good results were obtained in the methodology development to achieve the coupling of **13.1** and **13.2**. Having success in this direction, the researchers then opted for the following conditions for coupling the aldehyde **13.1** and the vinylogous acyl anion of β-bromoenone **13.2** with Cr-catalyst which was prepared from sulfonamide **14.6** and Ni-complex **15.3**.

The furan ring formation was carried-out by an acylation of allylic alcohol as the *p*-nitrobenzoate which was then followed by an aqueous TFA hydrolysis of cyclohexilidene group, giving the diol. This was then treated with aqueous K_2CO_3 to *p*-nitrobenzoate hydrolysis and this was then followed by an oxy-Michael addition of C9-hydroxyl group with an α,β-unsaturated ketone giving 1:2 mixture. This was then subjected to an ion exchange resin to converting to the desired polycyclic compound **13.4**.[81]

Scheme 15: Reaction Conditions Applied

1.5. Actin

1.5.1. Introduction

Actin is the most abundant intracellular protein in eukaryotic cells, and, play a key role in many essential cellular functions, including maintaining cell shape, cell

motility, cell signaling, cell division and cytokinesis.[82] In 1942, Banga and Szent-Györgyi extracted a new protein, actin, from the rabbit's muscle tissue and calculated that 1.0 gm of muscle contains 25-30 mg actin.[83] In 1943, Strauband co-workers showed that, in physiological conditions, the newly extracted protein existed in two forms: globular actin or G-actin (monomeric form) that was stable in the absence of salt, and in the presence of ions (Mg^{2+}, K^{+}, or Na^{+}) it can polymerize into a long double-stranded helical polymer with non-covalent interactions, called fibrous actin or F-actin (polymeric form).[82] Actin strongly binds one adenosine nucleotide, and the polymerization process from G to F-actin also activates the ATPase.[82] The ATPase activity drives the actin filament treadmilling, in which, the polymerization at the one end and de-polymerization at the other end occurs at the same time. This biological process happens with the help of numerous accessory proteins which can influence several aspects of actin filament dynamics.[84]

G-actin (see **Figure 11**) appears globular in the electron microscope but x-ray crystallographic analysis reveals that it is separated into two lobes and it has four sub-domains having a deep cleft.[85] The ATP, along with Mg^{2+}, binds within the deep cleft between sub-domains 2 and 4, and this could be hydrolyzed to ADP-Pi. When ATP or ADP is bound to G-actin, the nucleotide effects the conformation of the molecule and without a bound nucleotide, G-actin gets denatured very rapidly. In the presence of ions, the transition from G-actin to F-actin takes place and this process is reversible, if the ionic strength is lower, which then leads to depolymerization of F-actin to G-actin.[86]

A diverse group of natural products are found to specifically target and modulate the actin filament dynamics and these compounds have been isolated from a variety of sources plants, sponges, marine and soil organisms, algae, fungi and bacteria.[87] Bioactive natural products, such as actin, modulators are two types: (1) actin filament stabilizers, and (2) actin filament de-stabilizers that inhibit the filament assembly.[88]

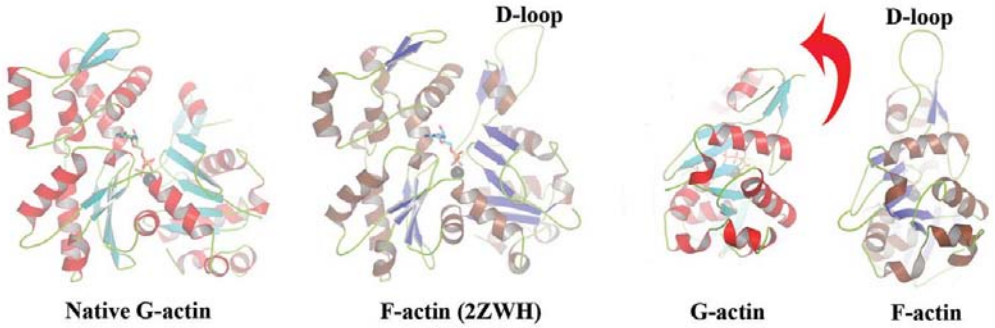


Figure 11: Actin Structures[89]
(this figure is directly taken from *Cytoskeleton* **2010**, *67*, 456)

1.5.2. Actin Filament Stabilizers

Natural products that stabilize actin filaments or induce the actin polymerization are shown to be extremely useful as chemical tools to understanding the actin filament assembly and organization, as well as, the actin-mediated cellular functions.[88a] Some of these natural products are jasplakinolide (**F12.1**)[90], Doliculide (**F12.2**)[91], chondramides (**F12.3**)[92], amphidinolide H (**F12.4**)[93], hectochlorin (**F12.5**) [94], seragamides (**F12.6**)[95], bisbromoamide (**F12.7**)[96], and phalloidin (**F12.8**)[97].[88b]

Figure 12: Actin Filament Stabilizers

1.5.3. Jasplakinolide

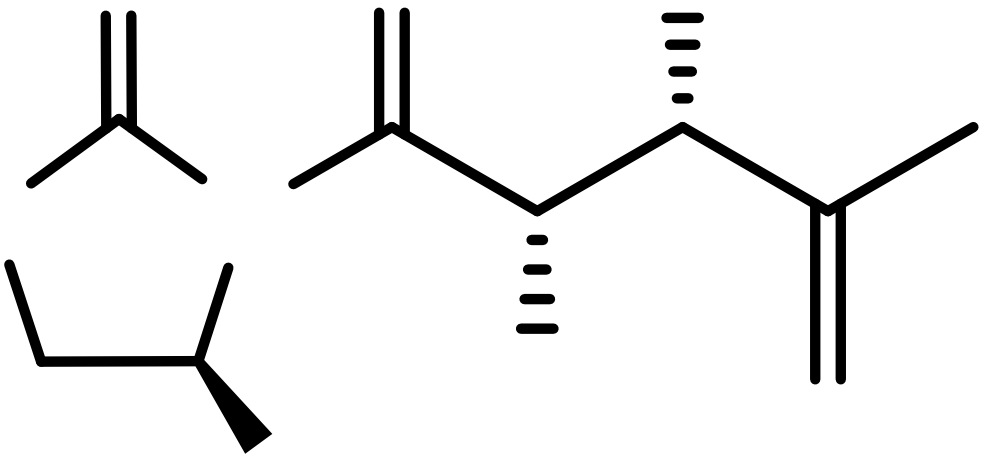
Jasplakinolide (**F12.1**) is a novel cyclic peptide isolated from the marine sponge, *Jaspis splendens*.[98] It contains (*S*)-alanine and two unusual amino acids, β-tyrosine and 2- bromoabrine, both possessing the less common R absolute configuration. Along with this, it also contains a non-enoic acid fragment with three chiral centers.[99]

Like phalloidin, jasplakinolide stabilizes F-actin and promotes the actin polymerization. Modification of the actin cytoskeleton impacts upon the signal transduction thus leading to apoptosis which has experimentally proved by an addition of jasplakinolide to CTLL-20 cells which enhances the apoptosis.[100]

Here, I outlined the total synthesis of (+)-jasplakinolide (**F12.1**) by Gosh and co-workers that was reported in 2007.[101] The disconnection approach is shown in **Scheme 16**, Compound **F12.1** could be obtained from **16.1** using a macrolactonization strategy. This could be obtained from the coupling of polypropionic acid **16.2** and tripeptide **16.3**.

Scheme 16: Retrosynthesis of (+)-Jasplakinolide

The aldol adduct **17.1**, obtained from an asymmetric aldol between Evans' oxazolidinone and methacrolein was subjected to an ortho ester Claisen rearrangement with triethyl orthopropionate in the presence of a catalytic amount of propionic acid at 140 ^{o}C. This resulted in the γ,δ-unsaturated ester **17.3** (7:1 mixture by NMR). The reaction proceeded via a cyclic six membered transition state (**17.2**) as shown in **Scheme 17**. This Claisen rearrangement is very useful in the diastereoselective transfer of 1,4-chirality to obtain α-methyl carbonyl compounds. Compound **17.3** was then subjected to $LiBH_4$ reduction for converting an auxiliary to primary alcohol. This was followed by Mitsunobu reaction with DEAD, PPh_3 and the acetone cynohydrin gave the nitrile **17.4**. Nitrile group in **8.4** was partially reduced to an aldehyde using Ra-Ni, NaH_2PO_3, Py and AcOH conditions. It was further treated with MeMgBr which yielded the secondary alcohols **17.5** and **16.2** as a 1:1 mixture. Secondary alcohol **17.5** converted to the required secondary alcohol **16.2** via Mitsunobu reaction. Finally, compound **16.2** was coupled with tripeptide **16.3** using the DCC coupling reagent and this approach gave compound **16.1** in 80% yield. The natural product (+)-Jasplakinolde (**F12.1**) was obtained from the **16.1** in five steps.



Scheme 17: Synthesis of (+)-Jasplakinolide

1.5.4. Actin Filament Destabilizers

The dynamics of actin assembly that are regulated by a number of endogenous proteins along with these natural products that destabilize actin filaments or induce the actin polymerization have also been discovered.[102] Some of these selected natural products are bistramides (**F13.1**)[103], iejimalides (**F13.2**)[104], swinholides (**F13.3**)[105], mycalolides (**F13.4**)[106], reidispongiolides (**F13.5**)[107] and aplyronines (**F15.1**, **F15.2**).[102,108]

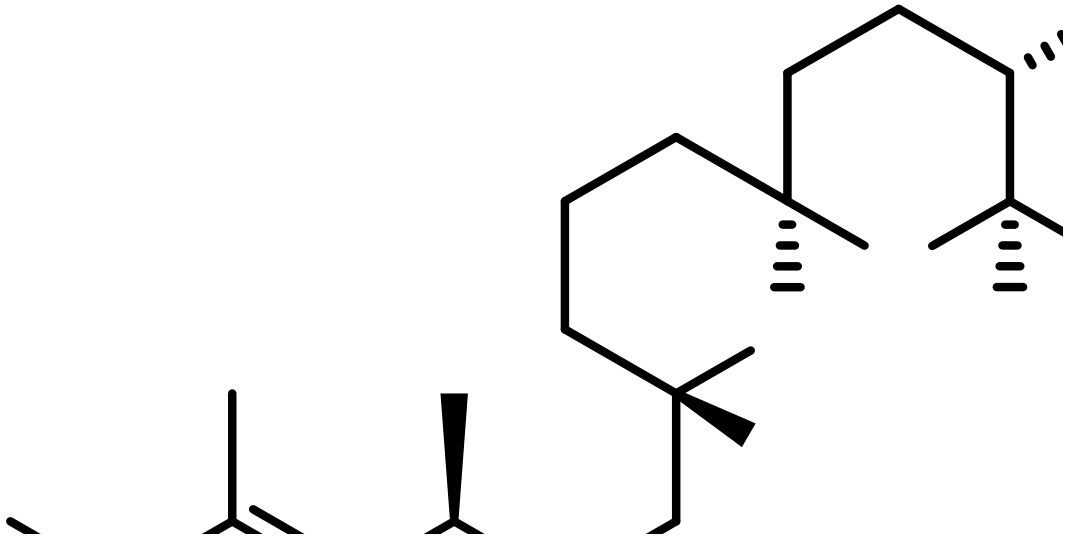


Figure 13: Actin Filament Destabilizers

1.5.5. Aplyronine A

Recently Kigoshi group[109] discovered that aplyronine A (**F15.1**) and aplyronine C (**F15.2**) , a derivative of aplyronine A that lacks the trimethylserine ester moiety, inhibit actin polymerization to the same extent, where aplyronine A forms a 1:1:1 heterotrimeric complex with actin and tubulin (see **Figure 14**), in association with actin synergistically binding to tubulin, and then inhibits the tubulin polymerization. There are no previous reports of microtubule inhibitors that also bind to actin and affects the microtubule assembly.

Figure 14: Model Diagram of Aplyronine A Binding to Actin and Tubulin[109]
(this figure is drawn from *J. Am. Chem. Soc.* **2013**, *135*, 18089)

Herein, I am going to explain the synthesis of C1-C19 segment of aplyronine A which was reported by Kigoshi team in 2011 (**Figure 15**).[108c]

Figure 15: Design for the Synthesis of Aplyronine A

The retrosynthetic analysis is shown in **Scheme 18**. Aplyronine A (**F15.1**) could be obtained from **18.1**. The precursor **18.1**was planned to derive from the NHK (Nozaki-Hiyama-Kishi) reaction of **18.2**, which was constructed from the segments **18.3** and **18.4**. The carboxylic acid segment **18.3** can be obtained from an asymmetric NHK reaction between an aldehyde **18.5** and the iodo-olefin **18.6**.

Scheme 18: Retrosynthetic Analysis of Aplyronine A

Synthesis of C5-C11 segment: This synthesis was started from alcohol **19.1** which is an intermediate of the previous work by the same group. The silyl protection of **19.1**, debenzylation, conversion of alcohol to the tosyl moiety led the synthesis of **19.2**. Homologation with allylmagnesium bromide afforded **19.3** with the concomitant cleavage of the pivolyl group. Finally, the protection of an alcohol moiety to pivolyl again followed by the dihydroxylation and cleavage afforded, the segment **18.5**.

Scheme 19: Synthesis of C5-C11 Segment

Synthesis of C14-C19 segment: Synthesis of segment **18.6** was started from alcohol **20.1**, oxidation of **20.1** followed by Ohira-Bestmann reagent[110] to furnish **20.2**. The ester was reduced with DIBAL-H and the TBS protection of alcohol gave **20.3**. Introducing the methyl group was then followed by a regioselective hydrozirconation[111] which afforded **18.6**.

Scheme 20: Synthesis of C14-C19 Segment

Having both fragments **18.5** and **18.6** in hand, the NHK reaction using $CrCl_2/NiCl_2$ and the ligand **21.1** produced the the coupling product **21.2** in a good yield.

Scheme 21: Coupling of **18.5** and **18.6**

Synthesis of C1-C19 segment: To complete the synthesis of C1-C19 fragment, methylation of **21.2**, removal of TES with acetic acid to obtain secondary hydroxyl product (with 80% of primary TBS removal product) and then the conversion of primary hydroxyl group to TBS, finally gave **22.1**. The secondary hydroxyl was then protected with MTM, which was then followed by the cleavage of the pivolyl group with DIBAL. The DMP oxidation of alcohol moiety then furnished **22.2**. HWE reaction of aldehyde **22.2** followed by an ester hydrolysis with LiOH completed the synthesis of **18.3**.

Scheme 22: Synthesis of C1-C19 Segment

1.6. References:

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Chapter 2

Stereoselective Synthesis of C27-C35 Eribulin Fragment and its Related Analogs

Part A: Literature Synthesis of C27-C35 Eribulin Fragment

In this section, the literature synthesis of C27-C35 eribulin fragment is covered.

2.1. Literature Synthesis of C27-C35 Eribulin Fragment, 1.7

The first synthesis of the fragment **1.7 (Scheme 1)** proceeded from the stock intermediate which was prepared from L-arabinose in 9 steps.[1] It was converted to C30a modified derivative (structure not shown) in 14 synthetic transformations in 23 steps from the commercially available starting material with an overall yield of 1.3%.[1] Later, Kishi and co-workers team further developed a practical synthesis of fragment **1.7** from a commercially available starting material, D-(+)-Glucurono-6,3-lactone.[2] In the second generation synthesis of fragment **1.7**, the C30 $PhSO_2CH_2$ group was introduced stereoselectively (>100:1) via hydrogenation using the Crabtree catalyst[3], and, this synthesis was practically free from any chromatographic separation.[4] Recently, Arya group reported a practical and scalable synthesis of the analog of fragment **1.7** and its other related diastereomers.[5]

Kishi's Approach 1

In 2004, Kishi and co-workers developed a new methodalogy that led to the synthesis of fragment **1.7** and various steps involved are outlined in **Scheme 1**.

Scheme 1: The Synthesis of the C27-C35 Tetrahydrofuran Fragment

Synthesis of fragment **1.7** was started with a regioselective opening of an epoxide **1.2** which was prepared from the corresponding allylic epoxy alcohol[6] protected with the MPM group, with the lithium anion of **1.1**[7] in the presence of $BF_3{\cdot}OEt_2$. This gave 3:1 mixture of structural isomers, favoring the desired product **1.3**. Hydrogenation

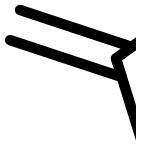
using Lindlar's catalyst was followed by an acetylation which furnished the *cis*-olefin **1.4**. Further, the dihydroxylation with osmium tetraoxide afforded 8:1 mixture of diastereomers, which was directly converted to the corresponding dimesylates, **1.5.** The desired isomer **1.5** was separated by column chromatography and then subjected to cyclization in the presence of triton B. This was further subjected to desulfonylation with methyl magnesium bromide, followed by methylation of the corresponding alcohol, thus giving **1.6**. Through adjusting the protecting groups on the C32 side chain, a selective cleavage of the benzyl ether under Raney-Nickel conditions and Swern oxidation, finally afforded the fragment **1.7.**[8]

Kishi's Approach 2

In 2003, Kishi group synthesized C27-C35 fragment of eribulin from D-(+)-glucurono-6,3-lactone.[2,4] D-Glucurono-6,3-lactone was converted to 1,2-*O*-isopropy lidene-α-D-5-deoxyglucurono-6,3-lactone **2.1** by a simple modification, and DIBAL reduction of **2.1**, followed by a Wittig reaction and then O-benzylation, which provided an olefin. An asymmetric dihydroxylation of terminal olefin is known to proceed with the relatively low asymmetric induction. This was achieved with Sharpless' approach $(DHQ)_2PYR$, yielding 3:1 mixture of the C-34 diastereomers. The C30 stereocenter was stereospecifically introduced via $NaBH(OAc)_3$ reduction under the influence of the C31 hydroxyl group, followed by protection as the benzyl ether.[2] Although the first-generation synthesis was long, it has attractive features, including a high overall yield and only one chromatographic purification. With the two major modifications, the second generation synthesis was more practical, and it is outlined in **Scheme 2**.[4] The synthesis began with 1,2-*O*-isopropylidene-α-D-5-deoxyglucurono-6,3-lactone, DIBAL reduction followed by Wittig reaction and *O*-methylation with NaH/MeI conditions to obtain **3.2** in a good yield. The catalytic asymmetric dihydroxylation of **2.2** was best achieved with Sharpless approach $(DHQ)_2PYR$, to obtain a 3:1 mixture of the C34 diastereomers. This was directly subjected to benzoylation **2.3**, and then *C*-allylation gave α-*C*-allylated product with dr > 60:1 and then separated by crystallization **2.4**.

Oxidation of secondary hydroxyl group with DMP, followed by sulfonyl Wittig-Horner-Emmons reaction with $PhSO_2CH_2P(O)(OEt)_2$/LiHMDS in toluene, furnished the corresponding α,β-unsaturated phenylsulfone as a 30:1 mixture of the Z/E-

isomers. The terminal olefin **2.5** was then selectively cleaved and followed by reduction, to furnish the primary alcohol **2.6** as a 30:1 Z/E-mixture. Hydrogenation of **2.6** in the presence of Crabtree catalyst **2.7** in DCM at 0 °C smoothly proceeded to furnish the C27-C35 building block **2.8** in 95% yield with >100:1 stereoselectivity.



Scheme 2: Second Generation Synthesis of the C27-C35 Tetrahydrofuran Fragment

Arya's Approach

In 2015, the Arya group reported a divergent approach of C27-C35 eribulin fragment using a cheap commercially available starting material, D-xylose.[5]

The Arya team developed a modular approach to the synthesis of C27-C35 fragment of eribulin and its C29 and C32 diastereomers of eribulin fragment via Evans' asymmetric *syn* aldol and an asymmetric oxa-Michael reactions as the key steps.

The stereoselective synthesis of aldehyde **3.4** was started with a suitable chiral starting material, D-xylose. Initially, the team synthesized (R)-α-hydroxyester **3.3** from D-xylose, in six steps with an overall yield 27.5% as reported by Okabe and co-workers.[9] The α-hydroxyester **3.3** was protected as its silyl ether, reduction of ester with lithium borohydride then gave the secondary alcohol product. It was then subjected to oxidation with DMP to obtain an aldehyde **3.4** in 85% yield after column chromatography.

For model studies, the synthesis of C29 and C32 diastereomers of **1.7,** was easily achieved from **3.4** by using a chiral auxiliary-mediated *syn* aldol reaction (**3.6**). This was then subjected to a chiral auxiliary cleavage and the selective oxidation of the primary alcohol to aldehyde using TEMPO reagent (**3.7**). The -OTBS removal of **3.7** followed by an oxa-Michael reaction occurred in one-pot by using TBAF to obtain compound **3.8**. It was found to be a single diastereomer from ^{1}H NMR and the relative stereochemistry was assigned using nOe studies.

Scheme 3: Synthesis of the C29-C35 Diastereomeric Fragment Eribulin

Similarly, compound **4.6** was synthesized from a chiral aldehyde **4.1.** In this series,, two diastereomers in 1:1 ratio were obtained and these were separated through a column chromatography. The relative stereochemistry of both products was assigned using nOe studies.

Scheme 4: Synthesis of Precise Fragment

Part B: Stereoselective Synthesis of C27-C35 Fragment of Eribulin and its Related Analogs (Our Approach)

In this section, I discuss our second generation synthesis of C27-C35 fragment of eribulin and its related analogs using *SS*-tartaric acid as the starting material.

2.2. Introduction

In continuation of our interest in obtaining a series of different types of macrocyclic compounds that utilize the western tetrahydrofuran ring fragment, herein, our next generation synthesis plan and its execution are described. Our first goal was to develop a practical and scalable stereoselective synthesis of several forms of the western furan ring fragment in which the commercially available *SS*-tartaric acid was utilized as the cheap starting material. Once the synthetic route to obtain analogs is thoroughly developed, our next plan is to obtain different types of macrocyclic compounds.

2.3. Retrosynthesis

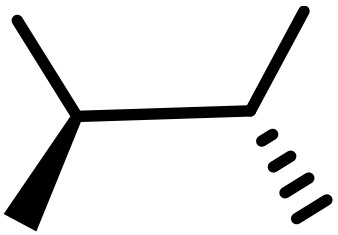
Retrosynthetic analysis of our target **1.7** is shown in **Scheme 5.** The two hydroxyl groups in **1.7** could be obtained from Sharpless dihydroxylation. The tetrahydrofuran ring formation could be achieved through an asymmetric oxy-Michael reaction of **5.1**. This unsaturated ester can be obtained from **5.2**, in three simple transformations: (i) vinylation, (ii) cross metathesis with ethyl acrylate and (iii) acetonide deprotection.

This unsaturated sulfone derivative could be synthesized by *SS*-tartaric acid (**5.3**) in 6 steps.

Scheme 5: Retrosynthesis of Fragment **1.1**

2.4. Synthesis of C27-C35 Fragment of Eribulin

Our synthetic path started with *SS*-tartaric acid (**6.1**). In one pot, the esterification and an acetonide protection with 2,2-dimethoxy propane and a catalytic amount of *p*TSA in methanol at 65 ^{o}C produced **6.2**.[10] The reduction of two ester moieties in **6.2** with $NaBH_4$ in methanol condition gave **6.3** as colorless oil.[11] Further, the selective benzylation of one of the hydroxyl groups with BnBr, NaH in THF afforded mono-protected compound **6.4**[12] as colorless liquid. Oxidation of obtained alcohol with IBX in acetonitrile under refluxing conditions,[13] followed by sulfone Wittig reaction[14] with metanesulfonylphosphate and NaH in THF afforded **6.5** as a single isomer. Here, we generated one more chiral center by our vinylation approach[15] with vinylmagnesium bromide and CuI in THF at -20 ^{o}C. This strategy afforded us **6.6** as a single diastereomer and the stereochemistry was assigned following the cyclization. The subjection of **6.6** to cross metathesis[16] using ethylacrylate and Grubbs' 2nd generation catalyst in toluene reflux conditions furnished **6.7** in 80% yield. Acetonide removal with the catalytic amount of *p*TSA gave the diol compound **6.8** as colorless liquid. Further, the subjection of **6.8** to an oxa-Michael addition with NaH and THF conditions at 0 ^{o}C afforded a mixture of inseparable diastereomers (**6.9a:6.9b**) in 1:4 ratio.



Scheme 6: Synthesis of Tetrahydrofuran Ring

Further, we moved with the mixture of diastereomers (**6.9a+6.9b**) and subjected this to $LiAlH_4$ in THF, which furnished an inseparable mixture of **7.1a+7.1b**. The TBDPS protection then gave **7.2a+7.2b** as colorless liquid. The secondary hydroxyl moiety was then subjected to methylation using MeI, NaH conditions and this afforded a separable mixture of **7.3a** and **7.3b** in 1:4 ratio. Further, the next steps were planned with the major isomer, **7.3b**. It was subjected to debenzylation using Pd/C, H_2 in EtOAc which gave **7.4** in a good yield. The hydroxyl group was then converted to an iodo moiety the presence of PPh_3, iodine and imidazole (Apple reaction)[17] in DCM as a solvent giving **7.5**. Further, the conversation of an iodo group to vinyl moiety was carried-out using vinylmagnesium bromide and CuI in presence of HMPA and this afforded an olefin compound **7.6**. Finally, the dihydroxylation[4] of obtained olefin with OsO_4 and $(DHQ)_2PYR$ as a chiral catalyst, I was able to complete the synthesis of C27-C35 fragment (**1.7**) of eribulin and herein, I obtained 5:1 diastereomeric mixture based on NMR studies (see **Figure 1**).

Scheme 7: Completion of Synthesis **1.7**

Figure 1: nOe of Compound **1.7**

2.5. Retrosynthesis of C27-C35 Eribulin Fragment Related Analogs

Using iodocyclization[18] as the key reaction, we further developed the synthesis of related analogs and our plan and execution are covered in this section. The retrosynthetic approach to compound **8.1** is shown in **Scheme 8**. For the synthesis of **8.1**, we plan to use an iodocyclization approach from **8.2**. In our planning strategy, we proposed the synthesis of **8.2** by vinylation on **8.3** which in turn can be obtained from *SS*-tartaric acid **8.4**.

Scheme 8: Retrosynthesis of C27-C35 Eribulin Fragment Analogs

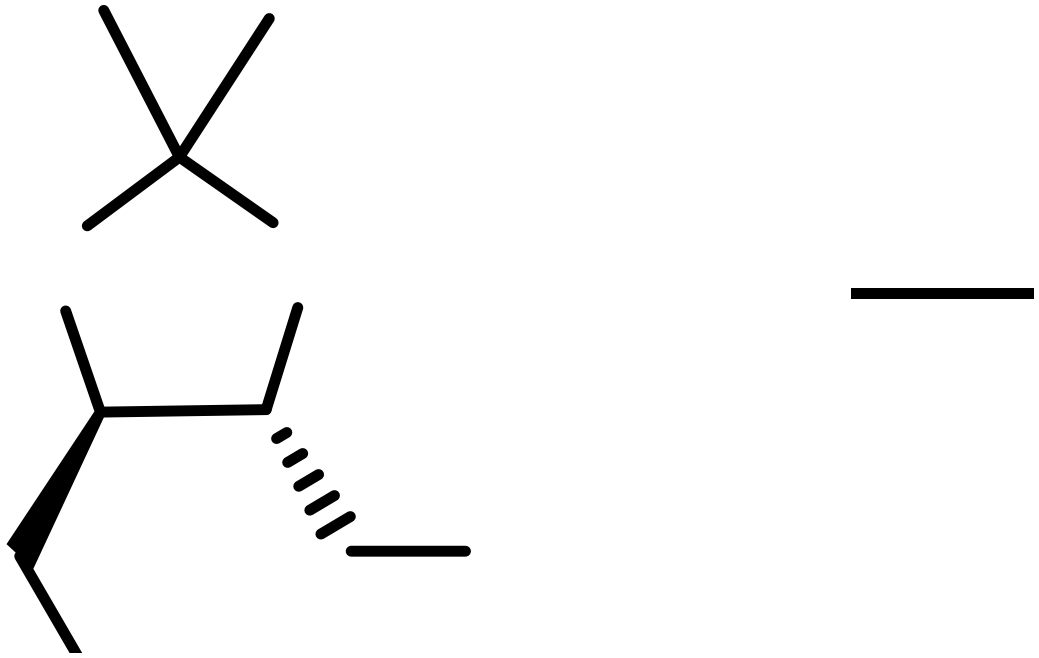
2.6. Synthesis of C27-C35 Eribulin Fragment Related Analogs

Utilizing compound **6.6** from **Scheme 6**, we synthesized the analogs of eribulin fragment, which is shown in **Scheme 9**. The subjection of **6.6** to 2N HCl for an acetonide removal in THF:H_2O gave **9.1** as yellowish solid. This upon iodocyclization[18] of the diol with iodine in acetonitrile at -20 ^oC afforded a separable 7:3 mixture of diastereomers **9.2** (major) and **9.3** (minor).

Scheme 9: Synthesis of Analogs **9.2** and **9.3**

In another similar approach, we started with **6.4**, which was obtained from **6.1**. Oxidation of **6.4** with IBX gave aldehyde and it was then followed by a Wittig reaction with triethylphosphonoacetate (TEPA) in NaH, THF conditions affording **10.1** as a single isomer. Further, subjection of **10.1** to vinylmagnesium bromide in the presence of a catalytic CuI and TMSCl, HMPA as additives at -78 ^oC produced 13:1 diastereomeric mixture of **10.2** as colorless oil.[19] This upon acetonide deprotection with 2N HCl in THF:H_2O gave the separable diastereomeric mixture **10.3** (major)

and **10.4** (minor) in a good yield. We then moved forward with the major isomer **10.3**. The DCB (2,6-dichlorobenzyl chloride)[20] protection of the secondary hydroxyl group with Ag_2O, TBAI condition in DMF afforded **10.5** and this upon treatment with $LiAlH_4$ at 0 ^oC, gave us the reduced product **10.6** as colorless oil. The TBDPS protection of the primary hydroxyl and methylation of the secondary hydroxyl using MeI, NaH, furnished **10.7** in an excellent yield. Finally, iodocyclization[18,21] of **10.7** with iodine in acetonitrile at -20 ^oC, produced **10.8** as a single diastereomer with the *in situ* removal of the DCB.



Scheme 10: Synthesis of Analog **10.8**

Figure 2: nOe of Compound **10.8**

2.7. Experimental section

2.7.1. Synthesis of Fragment 1.7

((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol

(6.2):

To a stirred solution of **6.1** (100 g) in MeOH (20 mL) was added catalytic amount of *p*TSA and 2,2-dimethoxy propane (2 eq). Then reflux for 16 h, after consumption of starting material (monitored by TLC) concentrated under reduced pressure and purified by column chromatography (9:1 hexanes/ethylacetate) to provide **6.1.1** as colorless liquid. Then **6.1.1** was dissolved in MeOH (100 mL) and added $NaBH_4$ (2 eq) portion wise at 0 ^oC. After 16 h the crude reaction mixture was concentrated and extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture **6.2** (92 g, 85%) was subjected to next step directly.

Molecular Formula: $C_7H_{14}O_4$

R_f: 0.5 (5:5 Hexanes/Ethylacetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.05-4.00 (m, 2H), 3.85-3.80 (m, 2H), 3.75-3.70 (m, 2H), 2.35-2.30 (m, 2H), 1.45 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.1, 139.9, 137.4, 133.5, 131.1, 129.3, 128.4, 127.8, 127.7, 127.7, 110.4, 79.0, 73.6, 69.0, 26.8, 26.5.

(4R,5R)-4-(Benzyloxymethyl)-2,2-dimethyl-5-((E)-2-(phenylsulfonyl)vinyl)-1,3-dioxolane

(6.5):

To a stirred solution of **6.2** (92 g) in THF (100 mL) was added NaH (1 eq) portion wise at 0 ^{o}C and followed by BnBr (1 eq). After 12 h the reaction mixture was quenched with water and extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 Hexane/Ethylacetate) to provide **6.3** (98 g) as a colorless liquid. The compound **6.3** (98 g) was dissolved in CH_3CN (100 mL) and added IBX (2 eq), then refluxed at 80 ^{o}C for 1 h. After consumption of total starting material (monitored by TLC) was filtered through celite and concentrated under reduced pressure to provide crude **6.4** as pale yellow liquid (98 g) which is subjected for next step directly. The crude **6.4** (98 g) was dissolved in THF and was added to the freshly prepared wittig ylide which prepared from $PhO_2SCH_2PO(OEt)_2$ and NaH at 0 ^{o}C. Then the reaction mixture was stirred at same temperature for 2 h. After 2 h the reaction mixture was quenched with water and extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 Hexane/Ethylacetate) to provide **6.5** (110 g) as a white solid.

Molecular Formula: $C_{21}H_{24}O_5S$

R_f: 0.4 (8:2 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 263.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87-7.83 (m, 2H), 7.60 (t, *J* = 7.20 Hz, 1H), 7.51 (t, *J* = 7.70 Hz, 2H), 7.37-7.25 (m, 5H), 6.96 (dd, *J* = 14.95, 4.09 Hz, 1H), 6.61 (dd, *J* = 14.96, 1.64 Hz, 1H), 4.61-4.51 (m, 2H), 4.48 (ddd, *J* = 8.36, 4.07, 1.64 Hz, 1H), 3.95-3.89 (m, 1H), 3.62 (dq, *J* = 10.30, 4.88 Hz, 2H), 1.40 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.2, 139.9, 137.5, 133.5, 131.2, 129.3, 128.5, 127.9, 127.7, 110.4, , 79.1, 73.7, 69.1, 26.8, 26.6;

(4R,5R)-4-(Benzyloxymethyl)-2,2-dimethyl-5-((S)-1-(phenylsulfonyl)but-3-en-2-yl)-1,3-dioxolane

(6.6):

To a stirred solution of CuI (1.8 g, 9.538 mmoles) in dry THF (10 mL) was added vinylmagnesium bromide (37 mL, 38.1 mmoles) dropwise at -78 ^{o}C and allowed to stir at same temperature for 10 min Then sulphone **6.5** (3.7 g, 9.538 mmoles) was added in THF (2 mL) dropwise over 20 min Then the reaction mixture was stirred at -78 ^{o}C to -20 ^{o}C for 40min and at -20 ^{o}C for 5 h. After completion of the reaction was quenched with NH_4Cl and NH_4OH (1:1) solution at same temperature and extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hexanes/ethylacetate) to provide **6.6** (1.45 g, 75%) as colorless oil.

Molecular Formula: $C_{15}H_{18}O_4$

R_f: 0.35 (8:2 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 417.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.31 Hz, 2H), 7.67-7.58 (m, 1H), 7.54 (d, *J* = 7.70 Hz, 2H), 7.37-7.26 (m, 6H), 5.53-5.41 (m, 1H), 5.14 (s, 1H), 5.04 (d, *J* = 11.00 Hz, 1H), 4.54 (s, 2H), 3.97-3.91 (m, 1H), 3.73 (s, 1H), 3.60-3.50 (m, 2H), 3.49-3.41 (m, 1H), 3.20-3.11 (m, 1H), 2.82-2.72 (m, 1H), 1.35 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.8, 134.8, 133.6, 129.4, 129.2, 128.4, 128.1, 127.7, 127.3**,** 119.4, 109.5, 79.0, 78.2, 73.3, 70.4, 57.2, 43.5, 27.1, 27.1.

(S,E)-Ethyl 4-((4R,5R)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(phenylsulfonyl)pent-2-enoate

(6.7):

To a stirred solution of **6.6** (1 g, 2.403 mmoles) in toluene (50 ml) was added **G-II** (101 mg, 0.120 mmoles) and ethylacrylate (1.27 mL, 12.015 mmoles) then refluxed for 16 h. After completion of the reaction was filtered through celite and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 Hexanes/ethylacetate) to provide **6.7** (780 mg) as light yellow oil.

Molecular Formula: $C_{26}H_{32}O_7S$

R_f: 0.5 (8:2 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 489.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.55-7.52 (m, 2H), 7.39-7.29 (m, 5H), 6.58 (dd, *J* = 9.60 Hz, 15.60 Hz, 1H), 5.84 (d, *J* = 15.60 Hz, 1H), 4.54 (s, 2H), 4.15 (q, *J* = 7.40 Hz, 2H), 3.95-3.85 (m, 2H), 3.58 (dd, *J* = 2.80 Hz, 15.60 1H), 3.50 (t, *J* = 4.37 Hz, 2H), 3.25 (dd, *J* = 9.60 Hz, 14.40 Hz, 1H), 3.04-2.96 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30-1.28 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 143.8, 139.3, 137.6, 133.8, 129.3, 128.4, 128.1, 127.7, 127.6, 124.9, 109.9, 78.6, 78.1, 73.5, 70.2, 60.5, 56.3, 40.9, 31.9, 30.0, 2 9.7, 27.0, 22.7, 14.2.

(4S,5R,6R,E) -Ethyl 7-(benzyloxy)-5,6-dihydroxy-4-(phenylsulfonylmethyl)hept-2-enoate

(6.8):

To a stirred solution of starting material **6.7** (780 mg, 1.639 mmoles) in THF:H_2O (1:1, 20 mL) was added *p*TSA (281 mg, 1.639 mmoles) and refluxed for 16 h. After consuming total starting material (monitored by TLC), extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (5:5 hexanes/ethylacetate) to provide **6.8** (588 mg) as white solid.

Molecular Formula: $C_{23}H_{28}O_7S$
R_f: 0.2 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 449.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.62 (t, *J* = 7.41 Hz, 1H), 7.55-7.52 (m, 2H), 7.38-7.27 (m, 5H), 6.58 (dd, *J* = 15.60, 9.57 Hz, 1H), 5.85 (d, *J* = 15.60 Hz, 1H), 4.52 (s, 2H), 4.14 (q, *J* = 7.15 Hz, 2H), 3.77 (dd, *J* = 14.16, 2.40 Hz, 1H), 3.72 (t, *J* = 4.06 Hz, 1H), 3.58 (d, *J* = 4.83 Hz, 2H), 3.52 (d, *J* = 7.94 Hz, 1H), 3.21 (dd, *J* = 14.16, 9.20 Hz, 1H), 3.16-3.08 (m, 1H), 2.97-2.91 (bs, 1H), 2.63-2.56 (bs, 1H), 1.27 (t, *J* = 7.13 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 144.4, 137.1, 133.7, 129.3, 128.6, 128.1, 127.9, 125.2, 110.0, 73.8, 73.0, 72.6, 68.7, 60.5, 56.6, 41.0, 14.2.

Ethyl 2- ((3R,4R,5R)-5-(benzyloxymethyl) -4-hydroxy-3-(phenylsulfonylmethyl) tetrahydrofuran-2-yl)acetate

(6.9a+6.9b):

To a stirred solution of **6.8** (400 mg, 0.892 mmoles) in dry THF (15 mL) was added 60% NaH (21 mg, 0.892 mmoles) at 0 ^oC and allowed to stir for 30 min After completion of the reaction was quenched with water and extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (3:7 Hexanes/ethylacetate) to provide **6.9a & 6.9b** (360 mg) inseparable mixture as white gummy liquid.

Molecular Formula: $C_{23}H_{28}O_7S$

R_f: 0.3 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 449.7 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.88 (m, 2H), 7.67 (t, *J* = 7.45 Hz, 1H), 7.58-7.54 (m, 2H), 7.38-7.26 (m, 5H), 4.62-4.48 (m, 2.6H), 4.24-4.18 (m, 1H), 4.11 (q, *J* = 7.14 Hz, 2H), 4.03 (dd, *J* = 11.92, 5.52 Hz, 0.68H), 3.94 (dd, *J* = 9.59, 4.66 Hz,

0.68H), 3.79-3.65 (m, 2.2H), 3.26 (d, *J* = 6.99 Hz, 1.3H), 3.23-3.15 (m, 1H), 2.87-2.76 (m, 1.5H), 2.71-2.65 (m, 1H), 2.59-2.50 (m, 0.8H), 2.48-2.44 (m, 0.5H), 1.25-1.22 (t, *J* = 9.6 Hz, 3H).

(2R,3R,4R)-2-(Benzyloxymethyl)-5-(2-hydroxyethyl)-4-(phenylsulfonylmethyl) tetrahydrofuran-3-ol

(7.1a+7.1b):

To a stirred solution of **6.9a+6.9b** (340 mg, 0.7589 mmoles) in dry THF (15 mL) was added $LiAlH_4$ (43 mg, 1.138 mmoles) at 0 ^oC and allowed to stir for 3 h then the reaction mixture was quenched with aq. NaOH solution(2 mL), filtered through celite and concentrated under reduced pressure. The residue (**7.1a+7.1b,** 260 mg) was directly subjected to next reaction.

Molecular Formula: $C_{21}H_{26}O_6S$;

R_f: 0.2 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 407.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.89 (m, 2H), 7.70-7.64 (m, 1H), 7.58-7.54 (m, 2H), 7.37-7.27 (m, 5H), 4.59-4.44 (m, 3H), 4.29 (t, *J* = 4.40 Hz, 0.7H), 4.22 (q, *J* = 7.14 Hz, 0.3H), 4.00 (q, *J* = 5.20 Hz, 0.7H), 3.80-3.69 (m, 5H), 3.24-3.12 (m, 2H), 2.73 (bs, 2H), 2.67-2.62 (m, 1H), 2.47-2.41 (m, 2H), 1.95—1.79 (m, 1.6H), 1.67-1.51 (m, 0.8H).

(2R,3R,4R)-2-(Benzyloxymethyl)-5-(2-(tert-butyldiphenylsilyloxy)ethyl)-4-(phenylsulfonylmethyl)tetrahydrofuran-3-ol

(7.2a+7.2b):

To a stirred solution of **7.1a+7.1b** (200 mg, 0.492 mmoles) in dry DCM (10 mL) was added imidazole (100 mg, 1.479 mmoles) and TBDPSCl (0.15mL, 0.5911 mmoles) at 0 ^{o}C. Then the reaction was stirred for 3 h at room temperature. After completion of the reaction was quenched with water and extracted with DCM (3×10 mL). Then the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (7.5:2.5 Hexanes/ethylacetate) to provide **7.2a+7.2b** (280 mg) as gummy liquid.

Molecular Formula: $C_{37}H_{44}O_6SSi$

R_f: 0.5 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 645.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.23 Hz, 2H), 7.68-7.60 (m, 5H), 7.56-7.51 (m, 2H), 7.44-7.27 (m, 11H), 4.61-4.52 (m, 2H), 4.51-4.41 (m, o.7H), 4.37 (t, *J* = 4.80 Hz, 1H), 4.11 (q, *J* = 4.80 Hz, 0.3H), 3.97 (q, *J* = 4.80 Hz, 0.7H), 3.81-3.66 (m, 5H), 3.23-3.11 (m, 2H), 2.60-2.54 (m, 0.7H), 2.33-2.25 (m, 1H), 1.91-1.81 (m, 1H), 1.76-1.61 (m, 1.3H), 1.03-1.01 (m, 9H).

(2-((2S,3S,4R,5R)-5-(Benzyloxymethyl)-4-methoxy-3-(phenylsulfonylmethyl) tetrahydrofuran-2-yl)ethoxy)(tert-butyl)diphenylsilane

(7.3a+7.3b):

To a stirred solution of **7.2a+7.2b** (120 mg, 0.1863 mmoles) in dry DMF (15 mL) was added silver oxide (243 mg, 0.931 mmoles) and MeI (0.12mL, 1.863 mmoles) at 0 ^{o}C. Then the reaction was stirred for 48 h at room temperature in dark place. After completion of the reaction was filtered through celite and extracted with ethylacetate and cool water. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 Hexanes/ethylacetate) to provide **7.3b** as colorless liquid (85 mg), **7.3a** as white solid (10 mg).

7.3a:

Molecular Formula: $C_{38}H_{46}O_6SSi$

R_f: 0.65 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 659.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.69 Hz, 2H), 7.67-7.60 (m, 5H), 7.55 (t, *J* = 7.76 Hz, 2H), 7.44-7.25 (m, 11H), 4.55 (dd, *J* = 41.73, 12.20 Hz, 2H), 4.35-4.24 (m, 3H), 3.74-3.64 (m, 2H), 3.62-3.51 (m, 2H), 3.37 (s, 3H), 3.15 (dd, *J* = 14.26, 3.23 Hz, 1H), 2.85 (dd, *J* = 14.20, 10.61 Hz, 1H), 2.72-2.65 (m, 1H), 1.67-1.58 (m, 2H), 1.03 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 138.3, 135.5, 133.9, 133.7, 129.6, 129.4, 128.3, 127.8, 127.7, 127.6, 127.5, 84.5,78.6, 75.7, 73.3, 68.9, 61.2, 58.0, 53.2, 41.2, 3 3.2, 26.8, 19.2.

7.3b:

Molecular Formula: $C_{38}H_{46}O_6SSi$

R_f: 0.6 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 659.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.78 Hz, 2H), 7.66-7.63 (m, 5H), 7.53 (t, *J* = 7.72 Hz, 2H), 7.46-7.25 (m, 11H), 4.64-4.50 (dd, *J* = 41.73, 12.20 Hz, 2H), 4.01 (d, *J* = 3.68 Hz, 1H), 3.96-3.91 (m, 1H), 3.80-3.64 (m, 5H), 3.39 (s, 3H), 3.17-3.06 (m, 2H), 2.55-2.48 (m, 1H), 1.97 (dt, *J* = 13.61, 6.57 Hz, 1H), 1.74 (dt, *J* = 13.61, 6.57 Hz, 1H), 1.02 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5,138.1, 135.5, 133.9, 133.8, 133.6, 129.6, 129.4, 128.3, 127.8, 127.7, 127.6, 85.5, 80.8, 80.7, 73.4, 68.4, 60.8, 57.8, 43.9, 37.9, 2 6.8, 19.1.

((2R,3R,4S,5S)-5-(2-(tert-Butyldiphenylsilyloxy)ethyl)-3-methoxy-4-(phenylsulfonylmethyl)tetrahydrofuran-2-yl)methanol

(7.4):

To a stirred solution of **7.3b** (160 mg) in dry EtOAc (15 mL) was added Pd/C (20 mg) and stirred for 24 h in H_2 atmosphere. Then filtered through celite pad, filtrate

was concentrated under reduced pressure. The residue was purified by column chromatography (6:4 Hexanes/ethylacetate) to provide **7.4** (118mg) as colorless gummy liquid.

Molecular Formula: $C_{31}H_{40}O_6SSi$

R_f: 0.3 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 569.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.83 Hz, 2H), 7.67-7.63 (m, 5H), 7.55 (t, *J* = 7.72 Hz, 2H), 7.46-7.34 (m, 6H), 4.11 (bs, 1H), 3.87-3.70 (m, 6H), 3.43 (s, 3H), 3.16-3.11 (m, 2H), 2.57-2.52 (m, 1H), 2.20 (bs, 1H), 1.93 (dt, *J* = 13.68, 5.80 Hz, 1H), 1.79 (dt, *J* = 13.13, 12.77, 5.84 Hz, 1H), 1.01 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5,135.5, 133.9, 133.7, 133.6, 129.6, 129.4, 127.8, 127.7, 127.6, 86.5, 81.0, 80.5, 61.5, 60.7, 57.9, 57.6, 44.2, 37.7, 26.8, 19.2.

tert-Butyl (2-((2S,3S,4R,5S)-5-(iodomethyl)-4-methoxy-3-(phenylsulfonylmethyl) tetrahydrofuran-2-yl)ethoxy)diphenylsilane

(7.5):

To a stirred solution of **7.4** (50 mg, 0.088 mmoles) in dry DCM (10 mL) was added PPh_3 (115 mg, 0.440 mmoles) and imidazole (29 mg, 0.440 mmoles) at room temperature. Then bring it to 0 ^oC then added iodine (110 mg, 0.440 mmoles) and stir for 16 h. After consumption of starting material (monitored by TLC), quenched with saturated solution of sodium thiosulphate and extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then the residue was purified by column chromatography (9.5:0.5 Hexanes ethylacetate) to provide **7.5** (45 mg) as white solid.

Molecular Formula: $C_{31}H_{39}IO_5SSi$

R_f: 0.2 (9:1 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 679.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.98 Hz, 2H), 7.67-7.63 (m, 5H), 7.55 (t, *J* = 7.76 Hz, 2H), 7.44-7.34 (m, 6H), 4.05-4.02 (m, 1H), 4.01-3.98 (m, 1H), 3.87 (td, *J* = 8.03, 5.05 Hz, 1H), 3.79-3.67 (m, 2H), 3.45 (s, 3H), 3.32 (t, *J* = 8.78 Hz, 1H), 3.21 (dd, *J* = 9.41, 5.73 Hz, 1H), 3.12 (d, *J* = 6.99 Hz, 2H), 2.61 (dd, *J* = 12.01, 6.62 Hz, 1H), 1.91 (td, *J* = 13.67, 6.85 Hz, 1H), 1.76 (td, *J* = 13.19, 6.15 Hz, 1H), 1.01 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 135.5, 133.9, 129.6, 129.5, 127.8, 127.6, 84.9, 82.2, 81.6, 60.6, 58.0, 57.8, 43.7, 38.2, 29.7, 26.8, 19.2.

(2-((2S,3S,4R,5R)-5-Allyl-4-methoxy-3-(phenylsulfonylmethyl)tetrahydrofuran-2-yl)ethoxy)(tert-butyl)diphenylsilane

(7.6):

To a stirred solution of compound **7.5** (25 mg, 0.0368 mmoles) in dry THF (2 mL) was added CuI (3 mg, 0.0184 mmoles) and HMPA (0.07 mL, 0.368 mmoles) at 23 ^oC. Then the reaction mixture temperature was bring to -30 ^oC and added vinylmagnesium bromide dropwise. After stirring reaction mixture 3 h at same temperature, was quenched with saturated NH_4Cl solution and extracted with ethylacetate (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (7:3 Hexanes/ethylacetate) to provide **7.6** (15 mg) as colorless oil.

Molecular Formula: $C_{33}H_{42}O_5SSi$

R_f: 0.2 (6:4 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 579.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.87 (m, 2H), 7.70-7.64 (m, 4H), 7.62-7.59 (m, 1H), 7.55-7.49 (m, 2H), 7.46-7.36 (m, 6H), 5.58-5.48 (m, 1H), 5.25-5.16 (m, 2H), 4.04 (dd, *J* = 6.11, 3.16 Hz, 1H), 3.98 (dd, *J* = 4.90, 2.53 Hz, 1H), 3.88-3.80 (m, 2H),

3.31-3.29 (m, 2H), 3.22 (s, 3H), 2.27-2.21 (m, 2H), 1.77-1.73 (m, 2H), 1.02 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.7, 135.6, 135.5, 134.9, 133.6, 133.5, 133.3, 129.7, 129.2, 128.0, 127.8, 127.7, 118.4, 110.0, 81.2, 70.6, 62.2, 56.6, 52.8, 42.7, 37.3 , 31.9, 29.7, 29.6, 29.3, 26.9, 26.8, 22.7, 19.1, 14.1.

(S)-3-((2R,3R,4S,5S)-5-(2-(tert-Butyldiphenylsilyloxy)ethyl)-3-methoxy-4-(phenylsulfonylmethyl)tetrahydrofuran-2-yl)propane-1,2-diol

(1.7):

To a stirred solution of **7.6** (5mg, 0.086 mmoles) in THF:H_2O (1:1, 1 mL) was added NMO and OsO4 and reaction mixture was stirred for 16 h. after consumption of complete starting material was added sodium thiosulphate and extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **1.7** (4 mg) as colorless oil (ref. *Org. Lett.* 2009, *11*, 4516-4519) .

Molecular Formula: $C_{33}H_{44}O_7SSi$

R_f: 0.2 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 613.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.93 (d, *J* = 7.91 Hz, 2H), 7.68-7.65 (m, 5H), 7.59 (t, *J* = 7.68 Hz, 2H), 7.49-7.40 (m, 6H), 4.08-4.02 (m, 1H), 3.98-3.75 (m, 5H), 3.68-3.64 (m, 2H), 3.49-3.45 (m, 1H), 3.42 (s, 3H), 3.14-3.06 (m, 1H), 2.72-2.65 (m, 1H), 2.10-1.85 (m, 3H), 1.82-1.68 (m, 3H), 1.06 (s, 9H).

2.7.2. Synthesis of Fragment 9.2 & 9.3

(2R,3R,4S)-1-(benzyloxy)-4-(phenylsulfonylmethyl)hex-5-ene-2,3-diol

(9.1):

To a stirred solution of starting material **6.5** (1 g, 2.87 mmoles) in THF:H_2O (1:1) was added 2N HCl (1 ml) and refluxed for 16 h. After consumtion of total starting material (monitored by TLC), extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (5:5 hexanes/ethylacetate) to provide **9.1** (760 mg) as light yellow solid.

Molecular Formula: $C_{20}H_{24}O_5S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 393.2 (M+17)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.89 (m, 2H), 7.66-7.62 (m, 1H), 7.57-7.53 (m, 2H), 7.39-7.29 (m, 6H), 5.65-5.56 (m, 1H), 5.17-5.11 (m, 2H), 4.54 (s, 2H), 3.89-3.84 (m, 1H), 3.71 (dd, *J* = 14.31, 2.97 Hz, 1H), 3.62-3.58 (m, 2H), 3.50-3.46 (m, 1H), 3.19 (dd, *J* = 14.30, 8.94 Hz, 1H), 2.96 (dq, *J* = 18.00, 2.80 Hz, 1H), 2.31-2.16 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 137.3, 135.8, 133.6, 129.2, 128.6, 128.1, 127.8, 119.4, 73.2, 73.0, 68.4, 57.2, 42.5, 28.1.

(2R,3R,4R,5R)-2-(benzyloxymethyl)-5-(iodomethyl)-4-(phenylsulfonylmethyl) tetrahydrofuran-3-ol

(9.2+9.3):

The compound **9.1** (1 g, 2.645 mmoles) was dissolved in CH_3CN (20 mL) in round bottom flask and iodine (1 g, 3.968 mmoles) was dissolved in 2 mL CH_3CN and added slowly at -20 ^oC. Then stirred for 3 h at -20 ^oC. After completion of the reaction was quenched with saturated solution of sodium thiosulphate and extracted with EtOAc (3× 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by

column chromatography (8:2 Hexanes/ethylacetate) to provide **9.2** (600 mg) as white solid and **9.3** (250 mg) colorless liquid.

9.2:

Molecular Formula: $C_{20}H_{23}IO_5S$

R_f: 0.3 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 502.8 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.56 Hz, 2H), 7.68 (t, *J* = 7.41 Hz, 1H), 7.58 (t, *J* = 7.67 Hz, 2H), 7.39-7.28 (m, 5H), 4.72 (bs, 1H), 4.61-4.50 (m, 3H), 4.33 (q, *J* = 5.60 Hz, 1H), 3.74 (d, *J* = 4.24 Hz, 2H), 3.29-3.21 (m, 2H), 3.19-3.03 (m, 3H), 2.76-2.68 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.2, 134.1, 129.5, 128.5, 128.1, 127.8, 78.4, 78.2, 75.6, 73.9, 69.4, 53.0, 45.3, 3.6.

9.3:

Molecular Formula: $C_{20}H_{23}IO_5S$

R_f: 0.2 (7:3 Hexanes/Ethyl acetate)

LRMS (ES+) m/z = 502.8 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.17 Hz, 2H), 7.70 (t, *J* = 7.01 Hz, 1H), 7.61 (t, *J* = 7.72 Hz, 2H), 7.41-7.30 (m, 5H), 4.60 (s, 2H), 4.44 (t, *J* = 4.37 Hz, 1H), 4.10 (q, *J* = 4.78 Hz, 1H), 3.83-3.77 (m, 2H), 3.77-3.72 (m, 1H), 3.47 (dd, *J* = 10.31, 5.73 Hz, 1H), 3.38 (dd, *J* = 10.28, 5.54 Hz, 1H), 3.32-3.22 (m, 2H), 2.53-2.45 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 137.5, 134.2, 129.6, 128.5, 128.2, 127.9, 127.8, 81.7, 79.8, 77.8, 73.8, 68.8, 58.0, 48.2, 29.7, 8.4.

2.7.3. Synthesis of Fragment 10.8

(4R,5R)-4-(Benzyloxymethyl)-2,2-dimethyl-5-((E)-2-(phenylsulfonyl)vinyl)-1,3-dioxolane

(10.1):

To a stirred solution of 60% NaH (2.85 g, 119.047 mmoles) in dry THF was added Triethyl phosphonoacetate (TEPA; 23.6 mL, 119.047 mmoles) dropwise over 30 min. at 0 ^{o}C. After stirring the reaction mixture at same temperature for 30 min. starting material **6.4.1** (10 g, 39.682 mmoles) was added slowly. Then the reaction was stirred for 2 h at 0 ^{o}C. After completion of the reaction (monitored by TLC) was quenched with water and extracted with EtOAc (3×100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hexane/Ethylacetate) to provide **10.1** (11.2 g, 90%) as a yellowish liquid.

Molecular Formula: $C_{18}H_{24}O_5$

R_f: 0.5 (9:1 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 337.1 (M+17)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 6.90 (dd, *J* = 15.63, 5.6 Hz, 1H), 6.10 (dd, *J* = 15.64, 1.20 Hz, 1H), 4.64-4.56 (m, 2H), 4.45-4.41 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.98-3.94 (m, 1H), 3.64 (d, *J* = 4.80 Hz, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 1.30 (t, *J* = 7.20 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 144.0, 137.6, 128.4, 127.7, 127.6, 122.5, 110.1, 79.5, 73.6, 69.2, 60.5, 26.9, 26.6, 14.20.

(S)-Ethyl 3-((4R,5R)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-enoate

(10.2):

To a stirred solution of CuI (77 mg, 4.062 mmoles) in dry THF (10 mL) was added vinylmagnesium bromide (8.1 mL, 8.12 mmoles) dropwise at -78 ^{o}C and allowed to stir at same temperature for 40 min. Then TMSCl (1 mL, 8.12 mmoles) and ester **10.1** (1.3 g, 4.062 mmoles) was added in THF (2 mL) dropwise over 20 min followed by

HMPA (2.8 mL, 16.24 mmoles). Then the reaction mixture was stirred at -78 ^{o}C for 7 h and at room temperature for 12 h. After completion of the reaction was quenched with NH_4Cl and NH_4OH (1:1) solution at same temperature and extracted with EtOAc (3×100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hexanes/ethylacetate) to provide **10.2** (990 mg, 75%) as colorless oil.

Molecular Formula: $C_{20}H_{28}O_5$

R_f: 0.5 (9:1 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 349.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.37-7.26 (m, 5H), 5.53 (td, *J* = 17.20 Hz, 1H), 5.14 (d, *J* = 17.20 Hz, 1H), 5.03 (dd, *J* =10.29, 1.19 Hz, 1H), 4.58 (s, 2H), 4.14-4.06 (m, 2H), 4.02-3.96 (m, 1H), 3.74 (t, *J* = 7.66 Hz, 1H), 3.59 (dd, *J* = 10.52, 2.98 Hz, 1H), 3.48 (dd, *J* = 10.52, 5.95 Hz, 1H), 2.78-2.68 (m, 2H), 2.37-2.28 (m, 1H), 1.40 (s, 6H), 1.23 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 138.0, 136.3, 128.3, 127.7, 118.0, 109.2, 79.4, 78.8, 73.3, 70.6, 60.3, 45.1, 36.7,27.2, 14.2.

(4S,5R)-5-((R)-2-(Benzyloxy)-1-hydroxyethyl)-4-vinyldihydrofuran-2(3H)-one and (4R,5R)-5-((R)-2-(benzyloxy)-1-hydroxyethyl)-4-vinyldihydrofuran-2(3H)-one

(10.3 + 10.4):

To a stirred solution of starting material **10.2** (1 g, 2.87 mmoles) in THF:H_2O (1:1) was added 2N HCl (1 ml) and refluxed for 16 h. After consumption of total starting material (monitored by TLC), extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure. The residue was purified by column chromatography (8:2 hexanes/ethylacetate) to provide **10.3** (650 mg) and **10.4** (50 mg) in 13:1 ratio.

10.3:

Molecular Formula: $C_{15}H_{18}O_4$

R_f: 0.3 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 279.7 (M+17)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 5.79-5.70 (m, 1H), 5.22-5.14 (m, 2H), 4.59-4.52 (m, 2H), 4.23 (dd, *J* = 7.6, 2.00 Hz, 1H), 3.91-3.88 (m, 1H), 3.64-3.56 (m, 2H), 3.30 (p, 1H), 2.80 (dd, *J* = 17.60, 9.20 Hz, 1H), 2.42 (dd, *J* = 17.60, 9.20 Hz, 1H), 2.32 (d, *J* = 6.00 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 137.5, 136.0, 128.5, 127.9, 127.8, 118.0, 83.4, 73.5, 71.1, 69.4, 41.0**,** 34.9.

10.4:

Molecular Formula: $C_{15}H_{18}O_4$

R_f: 0.5 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 279.7 (M+17)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 5.68-5.59 (m, 1H), 5.37 (d, *J* = 3.60 Hz, 1H), 5.34 (d, *J* = 2.80 Hz, 1H), 4.54 (s, 2H), 4.34 (dd, *J* = 9.60, 2.40 Hz, 1H), 3.88 (bt, 1H) 3.68-3.57 (m, 3H), 1.90-1.83 (m, 1H), 1.74-1.67 (m, 1H), 1.66-1.62 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 137.8, 136.8, 136.6, 132.9, 130.2, 128.4, 128.4, 127.7, 117.3, 83.4, 76.1, 73.6, 69.1, 67.0, 40.6, 34.9.

(4S,5R)-5-((R)-2-(benzyloxy)-1-(2,6-dichlorobenzyloxy)ethyl)-4-vinyldihydrofuran-2(3H)-one

(10.5):

To a stirred solution of starting material **10.3** (1.2 g, 4.58 mmoles) in dry DMF (10 mL) was added Ag_2O (1.8 g, 6.87 mmoles), TBAI (3.38 g, 9.16 mmoles) and 2,6-dichlorobenzylchloride (1.78 g, 9.16 mmoles) at inert atmosphere and the reaction mixture was stirred for 48 h in dark place. After completion of the reaction was filtered through celite and extracted with ethylacetate and cool water. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 hexanes/ethylacetate) to provide **10.5** (1.35 g, 70%)as colorless oil.

Molecular Formula: $C_{22}H_{22}Cl_2O_4$

R_f: 0.5 (8:2 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 437.6 (M+17)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 7H), 7.21 (dd, *J* = 8.67, 7.40 Hz, 1H), 5.71 (dt, *J* = 17.10, 10.16, 8.37 Hz, 1H), 5.09-4.95 (m, 3H), 4.83 (d, *J* = 10.50 Hz, 1H), 4.62-4.53 (m, 2H), 4.40 (dd, *J* = 6.80, 1.60 Hz, 1H), 3.88 (dd, *J* = 8.82, 4.85 Hz, 1H), 3.75-3.67 (m, 2H), 3.17 (p, 1H), 2.77 (dd, *J* = 17.60, 9.00 Hz, 1H), 2.37 (dd, *J* = 17.60, 9.00 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 137.8, 136.8, 136.6, 132.9, 130.3, 128.5, 128.4, 127.8, 117.4, 83.4, 76.1, 73.6, 69.1, 67.1, 40.7, 34.9.

(2R,3R,4R,5R)-2-(benzyloxymethyl)-4-(2-(tert-butyldiphenylsilyloxy)ethyl)-5-(iodomethyl)tetrahydrofuran-3-ol

(10.7):

To a stirred solution of starting material **10.5** (2.3 g, 5.476 mmoles) in dry THF (20 mL) was added $LiAlH_4$ (312 mg, 8.21 mmoles) portion wise at 0 ^oC. After 16 h the reaction mixture was quenched with NaOH solution and filtered through celite. The filtrate was concentrated under reduced pressure and residue (**10.6**) was subjected to next reaction. The residue (2 g, 6.896 mmoles) was dissolved in dry DCM (20 mL)

and add imidazole (1.4 g, 20.688 mmoles), TBDPSCl (2.2 mL, 8.275 mmoles) at 0 ^{o}C. The reaction mixture was stirred for 3 h. After completion of the reaction was quenched with water and extracted with DCM (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9.6:0.4 Hexanes/ethylacetate) to provide **10.6.1** (2.5 g) as colorless oil. Then the compound **10.6.1** (2.5 g) was dissolved in DMF (20 mL) and NaH was added slowly at 0 ^{o}C. Then MeI was added at same temperature, after 1 hour reaction mixture was quenched with water and extracted with EtOAc (3× 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9.5:0.5 Hexanes/ethylacetate) to provide **10.7** (1.8 g) as colorless oil. (50%, 3 steps)

10.6:

Molecular Formula: $C2_2H_{26}Cl_2O_4$

R_f: 0.4 (8:2 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 425.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38-7.28 (m, 7H), 7.22-7.16 (m, 1H), 5.66-5.57 (m, 1H), 5.07-4.96 (m, 3H), 4.83-4.80 (m, 1H), 4.61-4.53 (m, 2H), 3.79-3.66 (m, 4H), 3.60-3.53 (m, 2H), 2.47 (dq, *J* = 8.77, 4.41 Hz, 1H), 2.27 (s, 3H), 2.01-1.91 (m, 1H), 1.62-1.53 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 137.8, 136.8, 133.2, 130.0, 128.3, 128.3, 127.7, 127.6, 116.9, 74.2, 73.6, 70.2, 66.5, 60.9, 44.7, 33.9, 30.8.

10.6.1:

Molecular Formula: $C_{38}H_{44}Cl_2O_4Si$

R_f: 0.5 (9:1 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 663.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.66 (d, *J* = 6.99 Hz, 4H), 7.43-7.28 (m, 13H), 7.21-7.15 (m, 1H), 5.53 (td, *J* = 17.39, 9.82 Hz, 1H), 5.05-4.93 (m, 3H), 4.86-4.81 (m, 1H), 4.60-4.54 (m, 2H), 3.80-3.59 (m, 5H), 3.53 (t, *J* = 7.80 Hz, 1H), 2.61-2.51 (m, 1H), 2.45 (d, *J* = 7.71 Hz, 1H), 2.10-2.02 (m, 1H), 1.61 (s, 1H), 1.54-1.43 (m, 1H), 1.03 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.1, 136.9, 135.6, 135.2, 134.8, 134.0,

133.9, 133.5, 135.6, 130.0, 129.7, 129.5, 128.4, 127.7, 127.7, 127.6, 127.6, 117.2, 74.1, 73.6, 70.5, 66.8, 61.8, 43.8, 33.0, 26.9, 26.6, 19.2, 19.0.

10.7:
Molecular Formula: $C_{39}H_{46}Cl_2O_4Si$

R_f: 0.6 (9:1 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 677.7 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.71-7.67 (m, 5H), 7.45-7.27 (m, 13H), 7.17-7.11 (m, 1H), 5.56 (td, *J* = 17.08, 9.58 Hz, 1H), 5.00-4.93 (m, 2H), 4.86 (q, *J* = 10.21 Hz, 2H), 4.55 (s, 2H), 3.75-3.57 (m, 5H), 3.42 (s, 3H), 3.25 (dd, *J* = 7.57, 1.83 Hz, 1H), 2.68 (dt, *J* = 10.09, 2.06 Hz, 1H), 2.04-1.93 (m, 1H), 1.52-1.41 (m, 1H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 138.2, 137.0, 135.6, 134.1, 134.1, 133.7, 129.8, 129.5, 128.3, 128.3, 127.8, 127.6, 127.5, 116.8, 83.7, 78.6, 73.5, 69.2, 67.0, 62.0, 60.7, 41.9, 32.7, 26.9, 19.2.

(2R,3R,4R,5R)-2-(benzyloxymethyl)-4-(2-(tert-butyldiphenylsilyloxy)ethyl)-5-(iodomethyl)tetrahydrofuran-3-ol

(10.8):

To stirred solution of **10.7** (1.8 gr) in acetonitrile (50 mL) was added iodine solution dropwise at -30 ^oC after 3 h was added saturated solution of sodium thiosulphate and extracted with EtOAc (3× 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hexanes/ethylacetate) to provide **10.8** (1.45 g) as colorless oil.

Molecular Formula: $C_{32}H_{41}IO_4Si$

R_f: 0.5 (9.5:0.5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 645.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.71-7.68 (m, 4H), 7.46-7.32 (m, 11H), 4.58 (dd, *J* = 43.23, 12.13 Hz, 2H), 4.10 (td, *J* = 6.65, 4.58 Hz, 1H), 3.80 (dt, *J* = 6.69, 3.73 Hz, 1H), 3.76-3.69 (m, 3H), 3.64 (dd, *J* = 10.05, 6.74 Hz, 1H), 3.56 (dd, *J* = 4.00, 1.09 Hz, 1H), 3.29-3.28 (m, 2H), 3.24 (s, 3H), 2.51-2.44 (m, 1H), 1.70-1.62 (m, 1H), 1.57-1.50 (m, 1H), 1.07 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 135.6, 135.5, 134.8, 133.5, 135.5, 129.8, 129.7, 129.6, 128.3, 127.8, 127.7, 127.6, 86.2, 84.3, 81.2, 73.4, 69.1, 61.6, 57.0, 45.2, 35.2, 29.7, 26.9, 26.5, 19.2, 9.8.

2.8. References:

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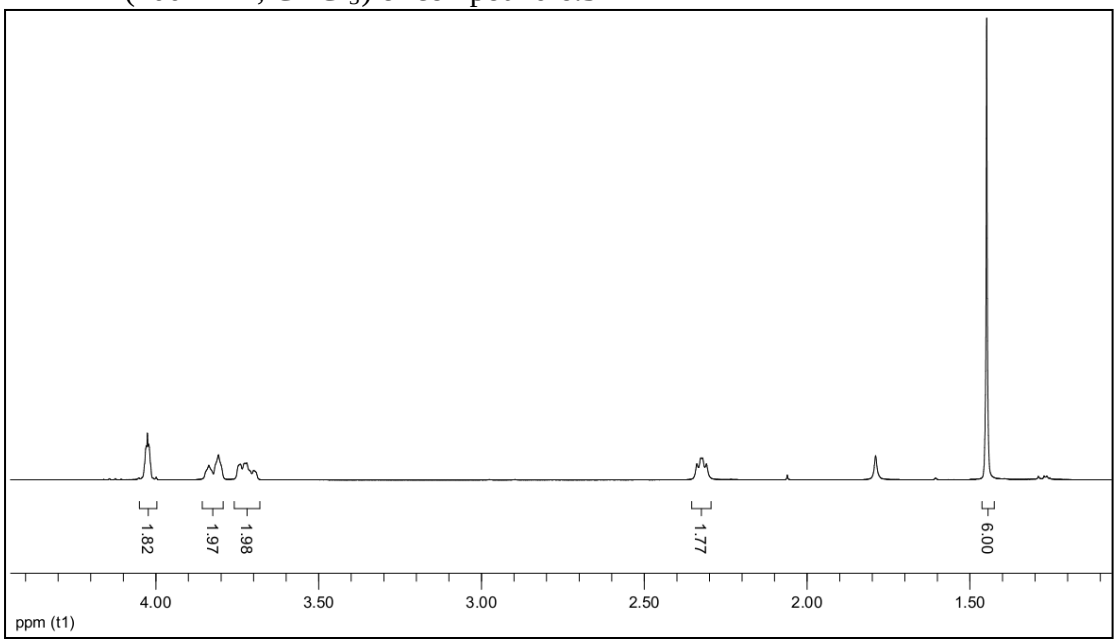
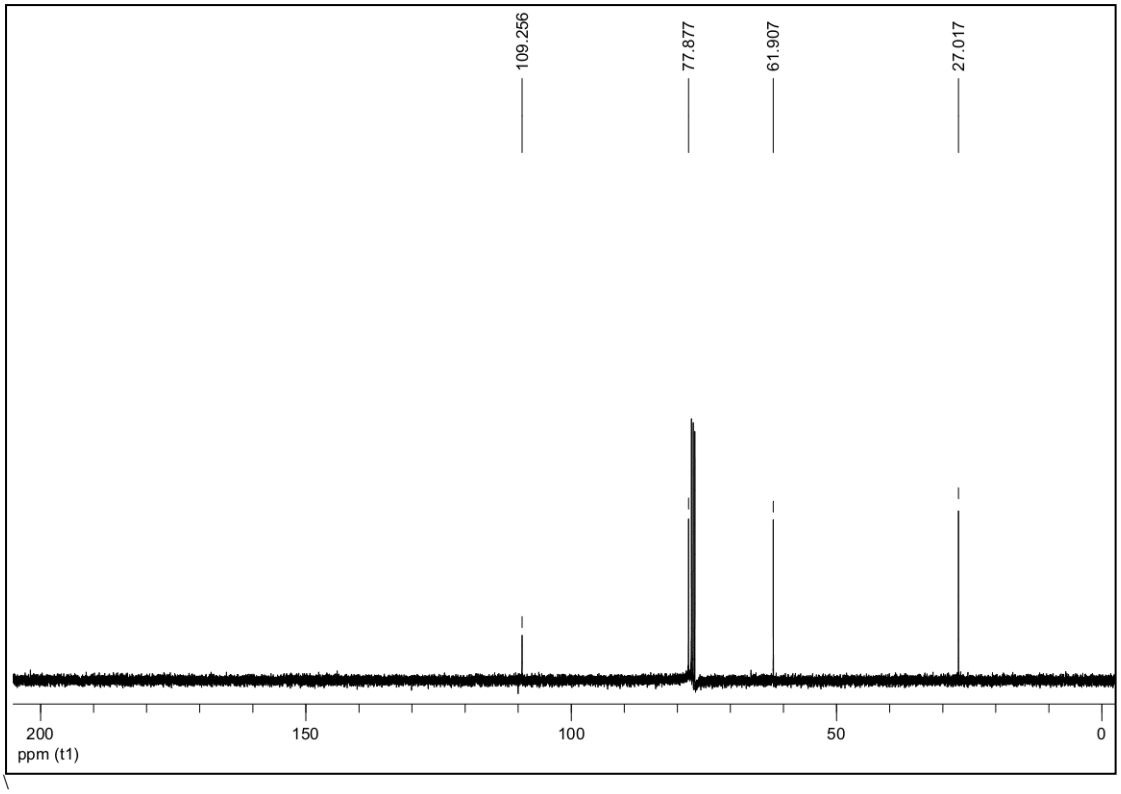
2.9. Spectral Data:

^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.3**



^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.3**



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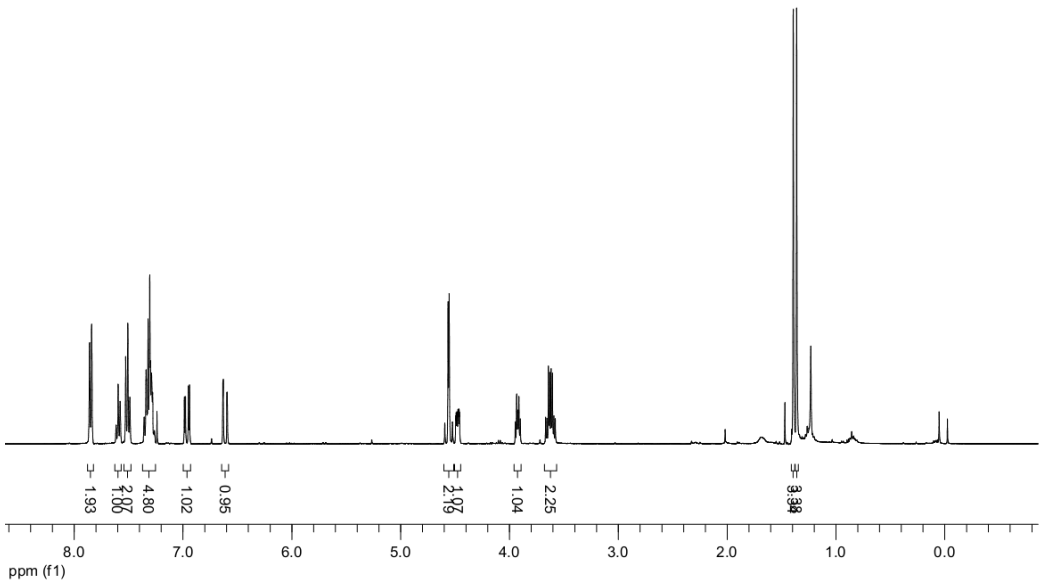
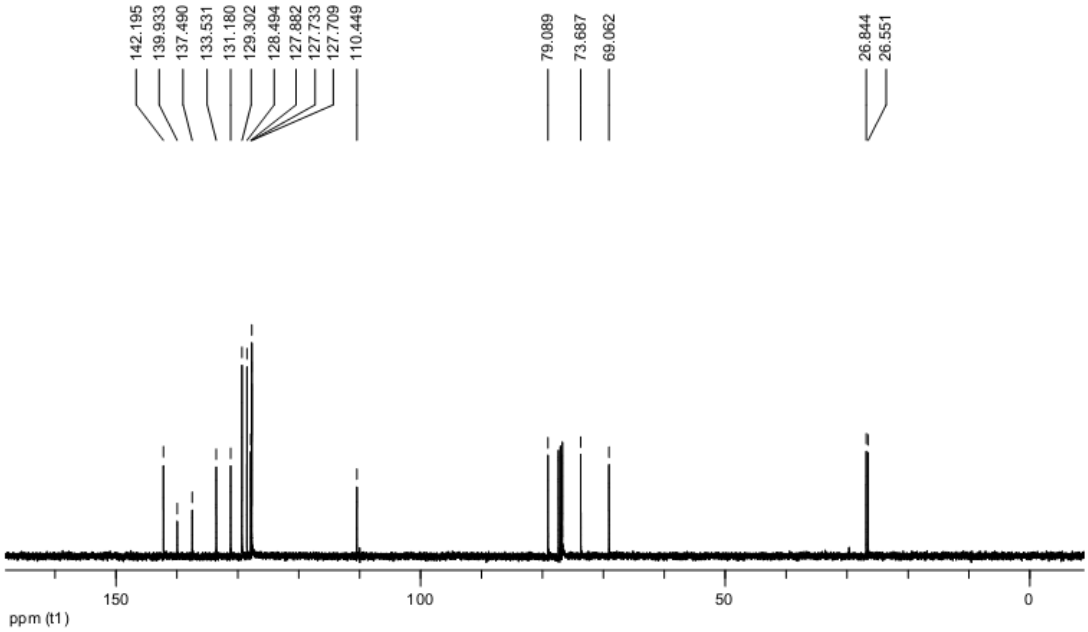


^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.5**



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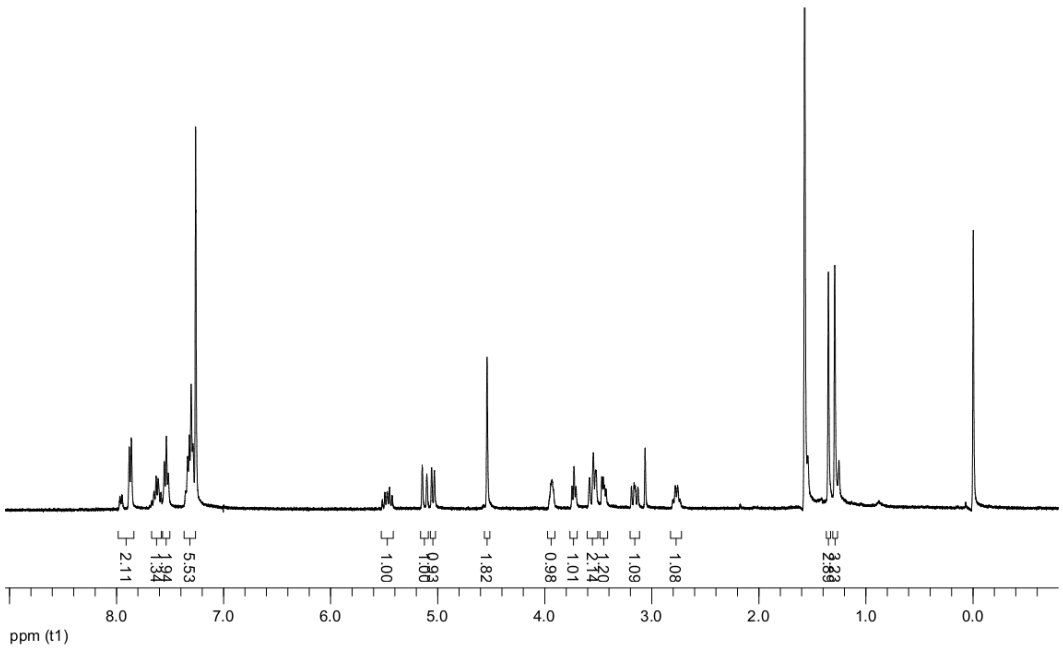
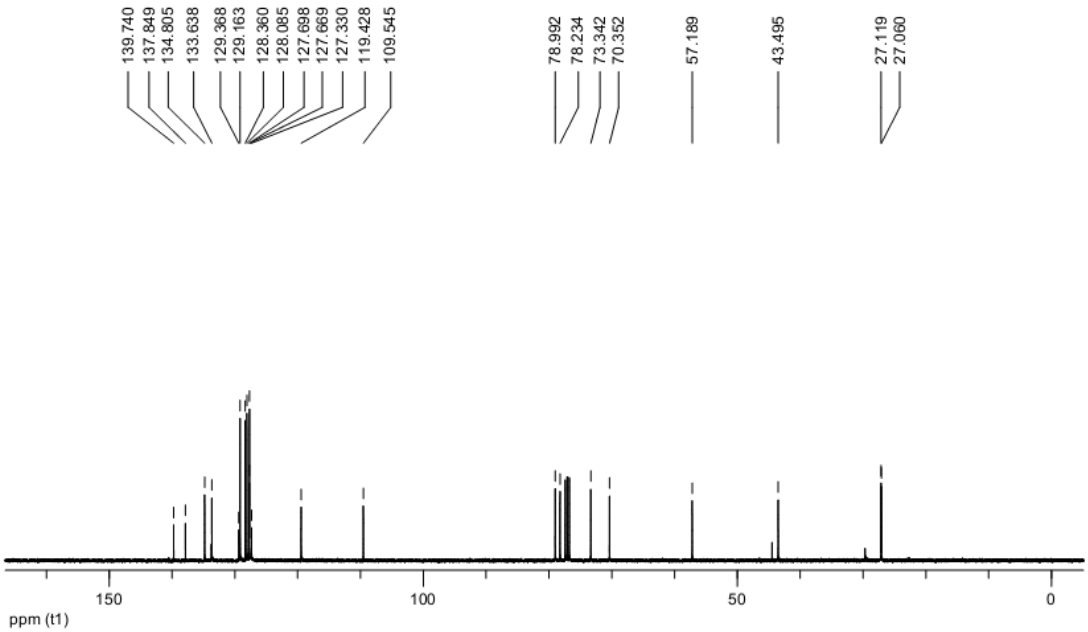
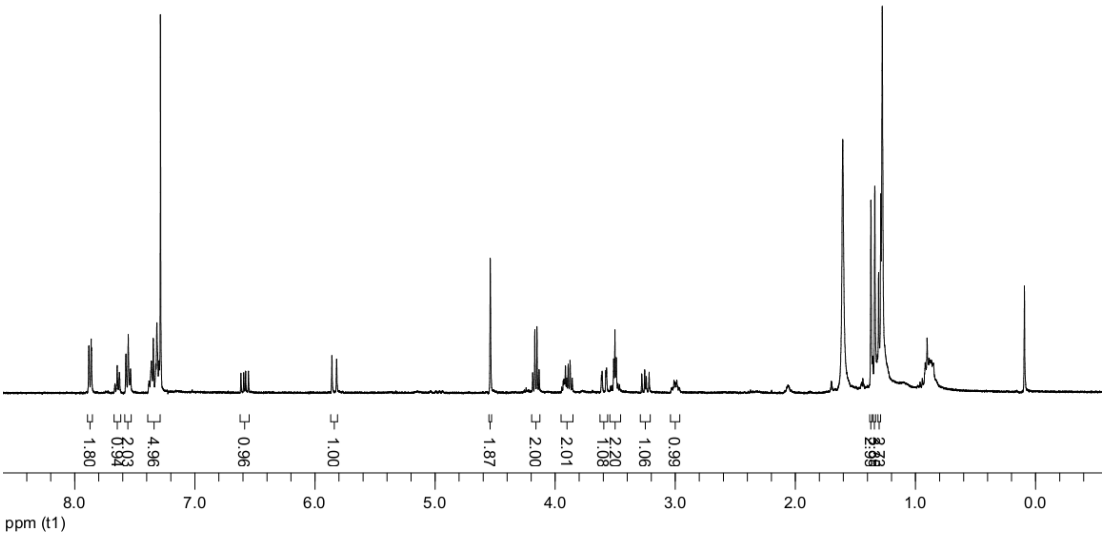


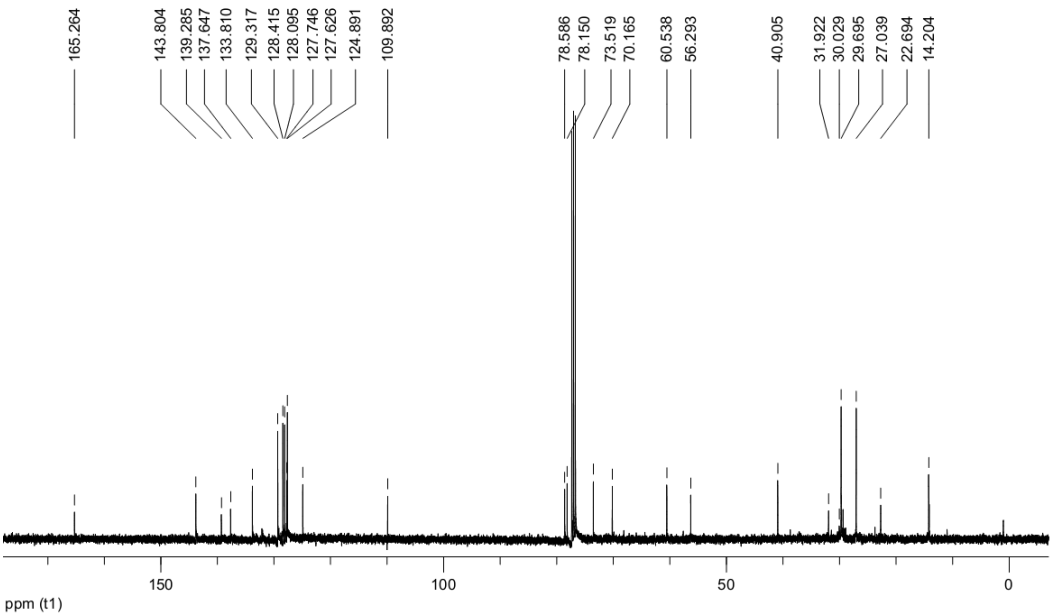
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.6**



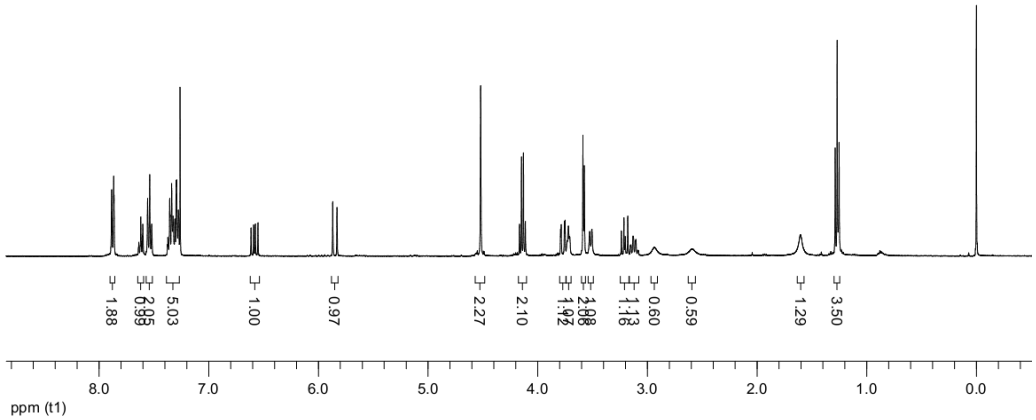
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.7**



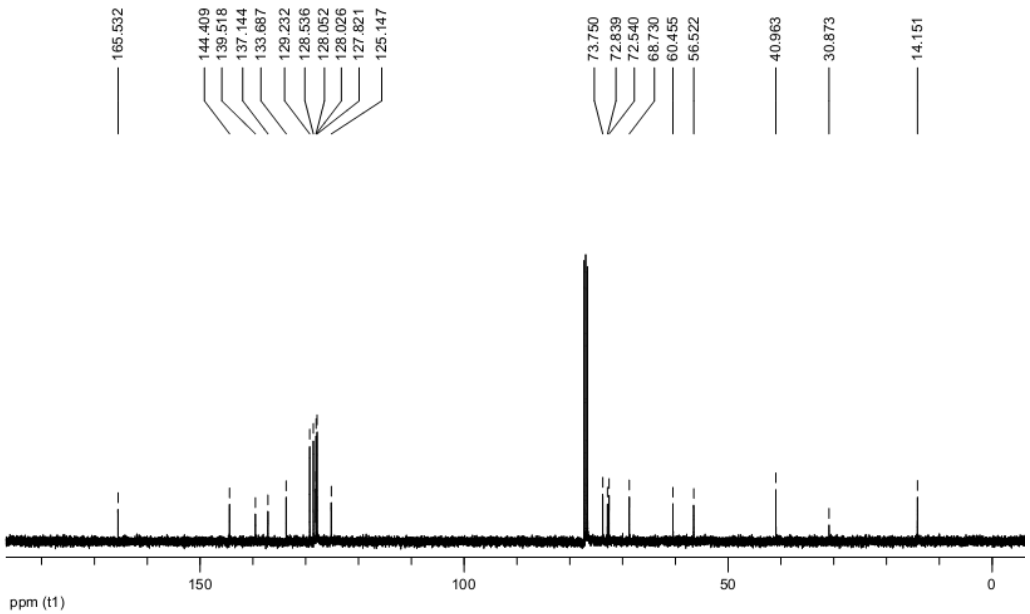
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.7**



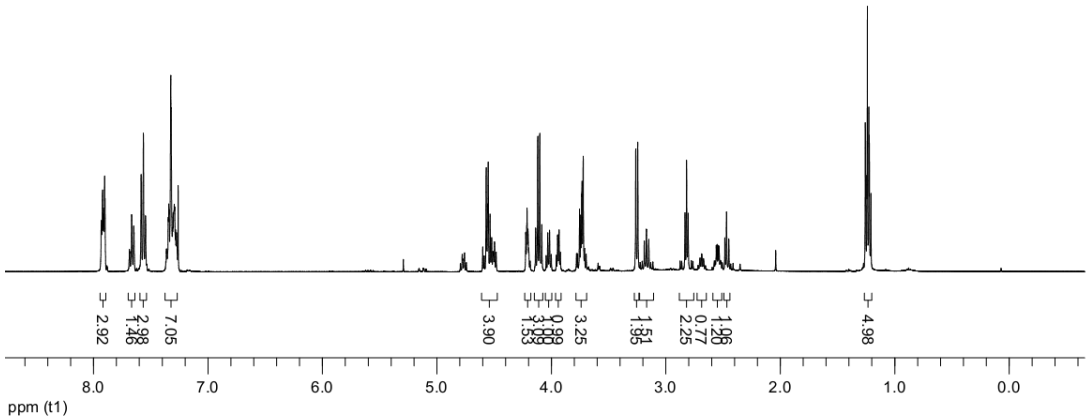
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.8**



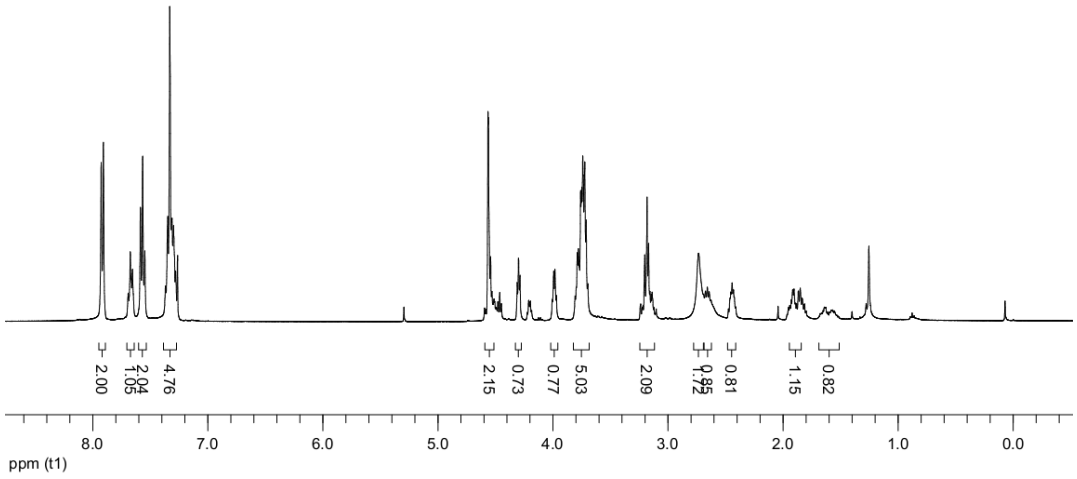
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.8**



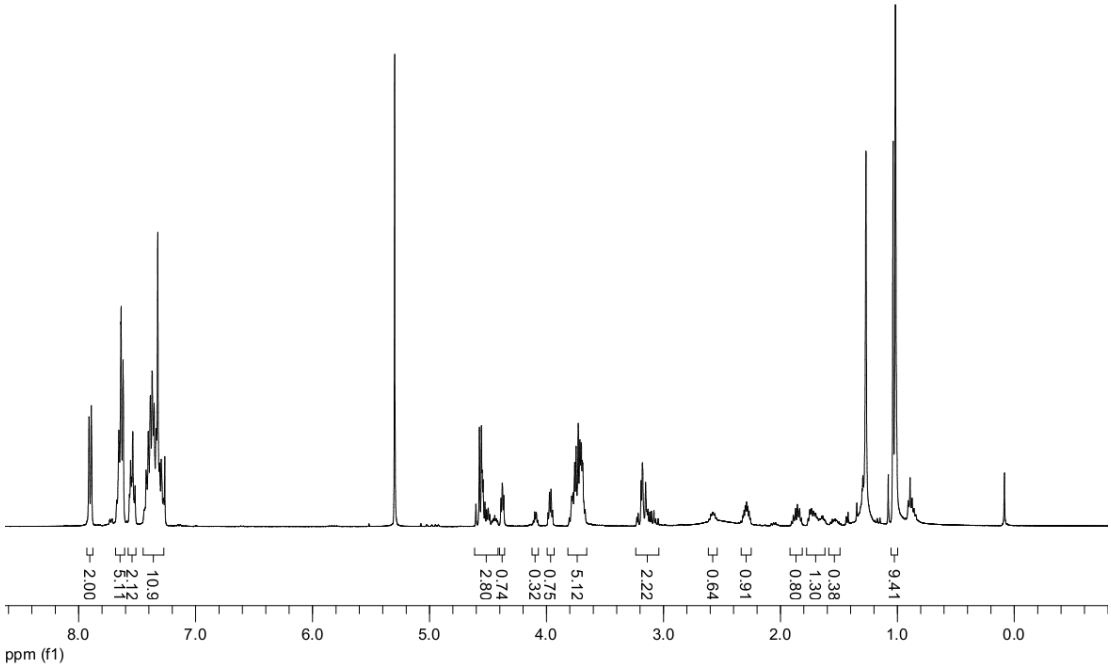
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.9a+6.9b**



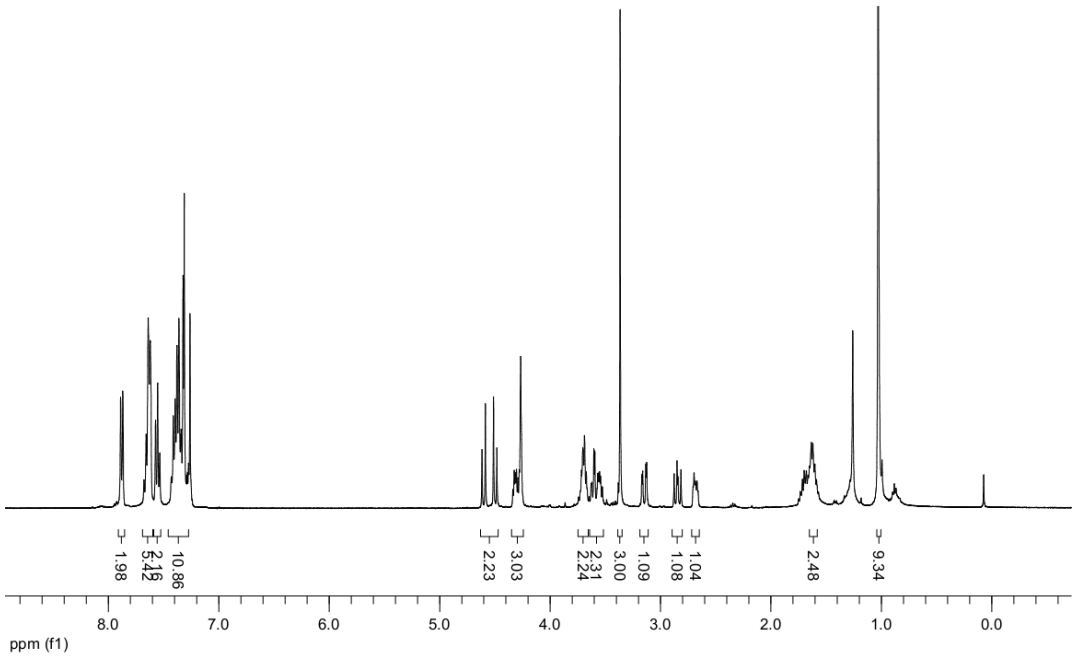
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7.1a+7.1b**



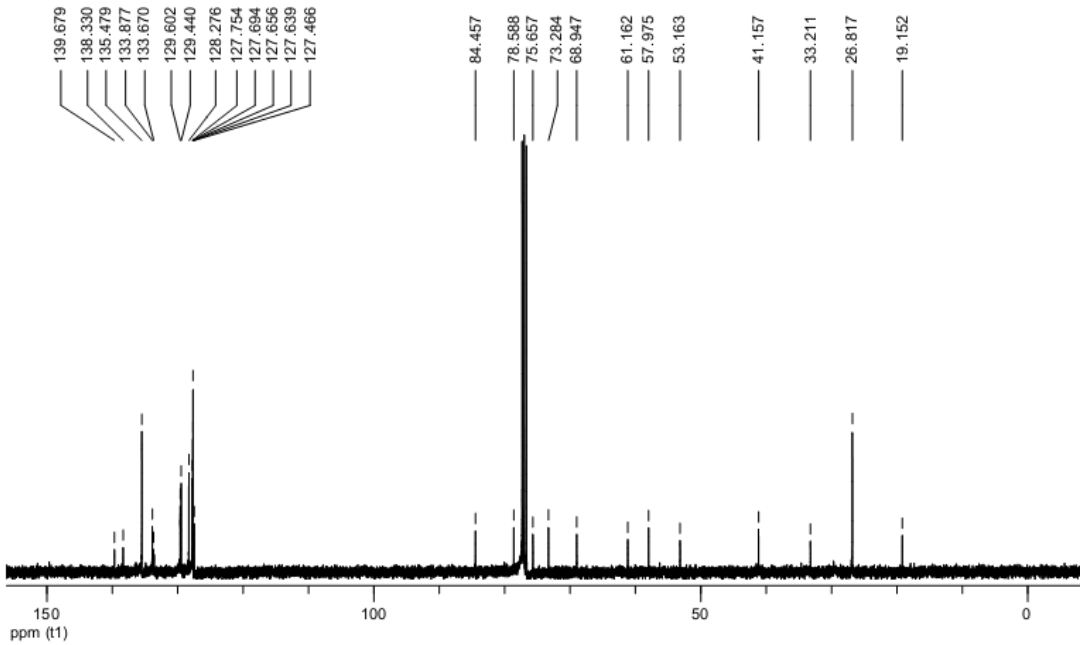
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7.2a+7.2b**



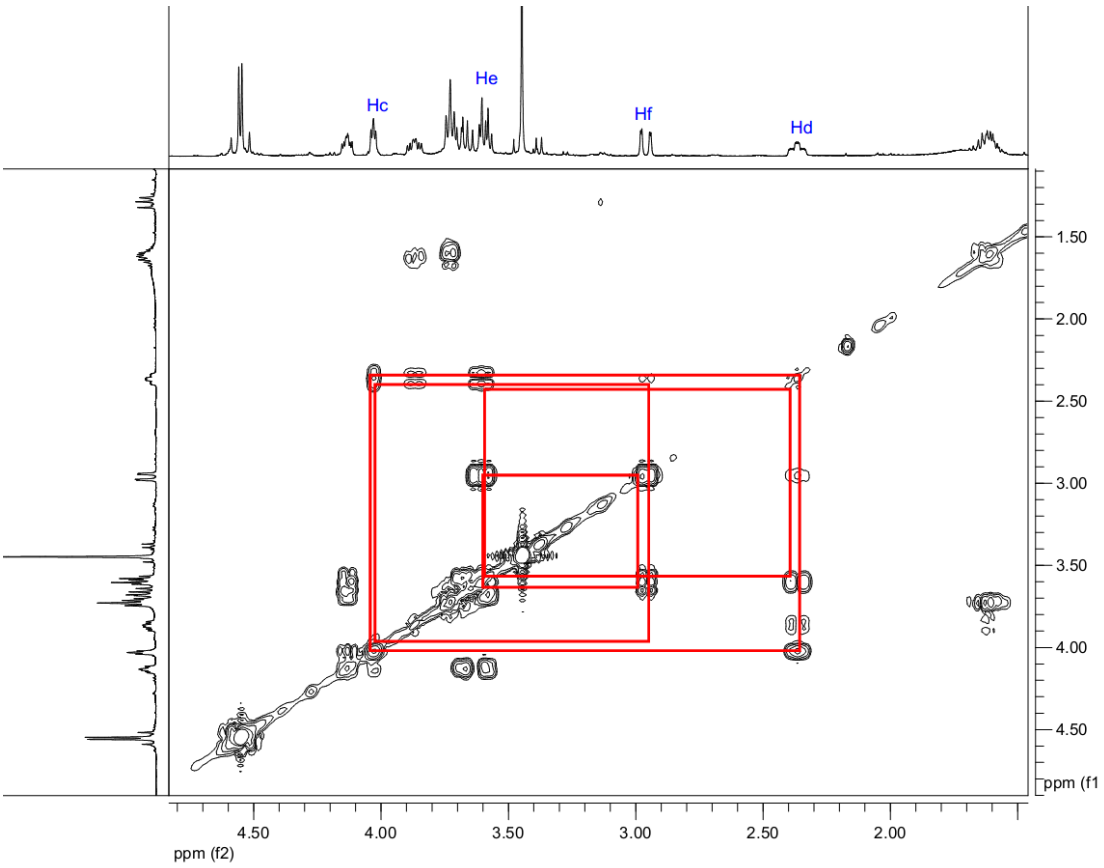
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7.3a**



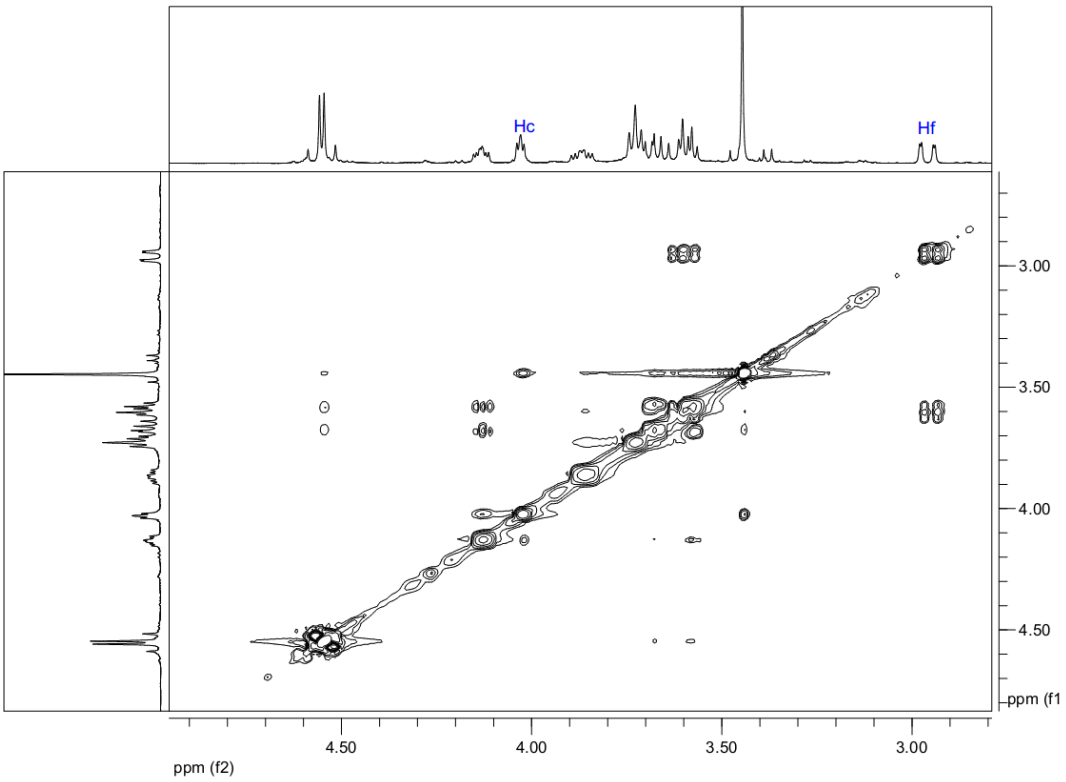
^{13}C NMR (100 MHz, $CDCl_3$) of compound **7.3a**



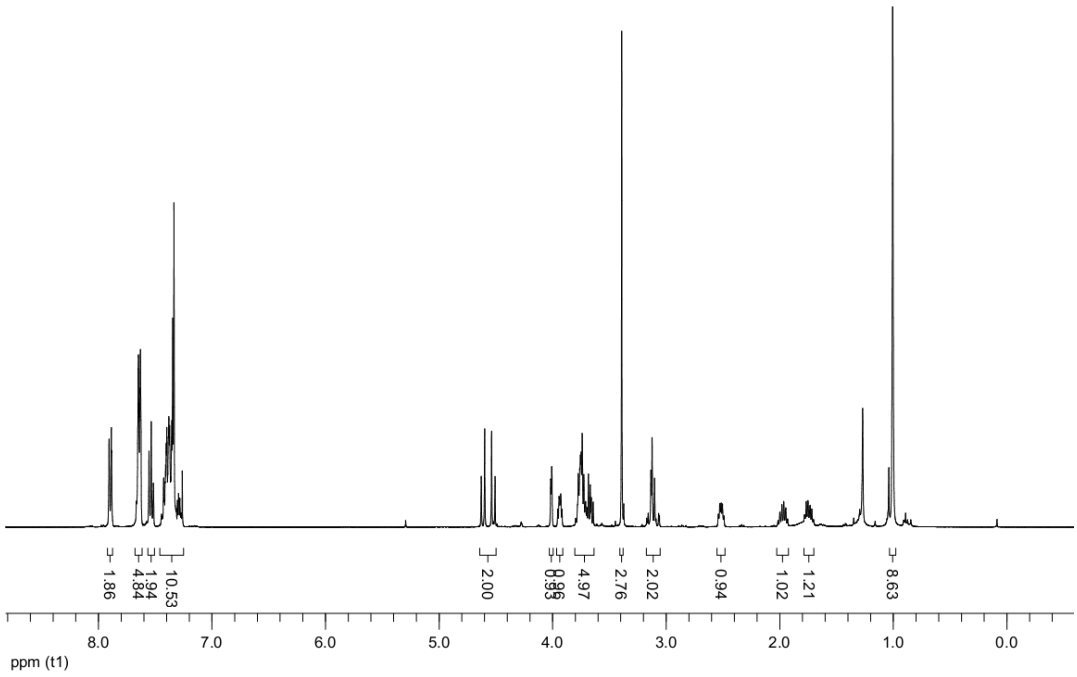
^{1}H -^{1}H COSY (400 MHz, $CDCl_3$) of compound **7.3a**



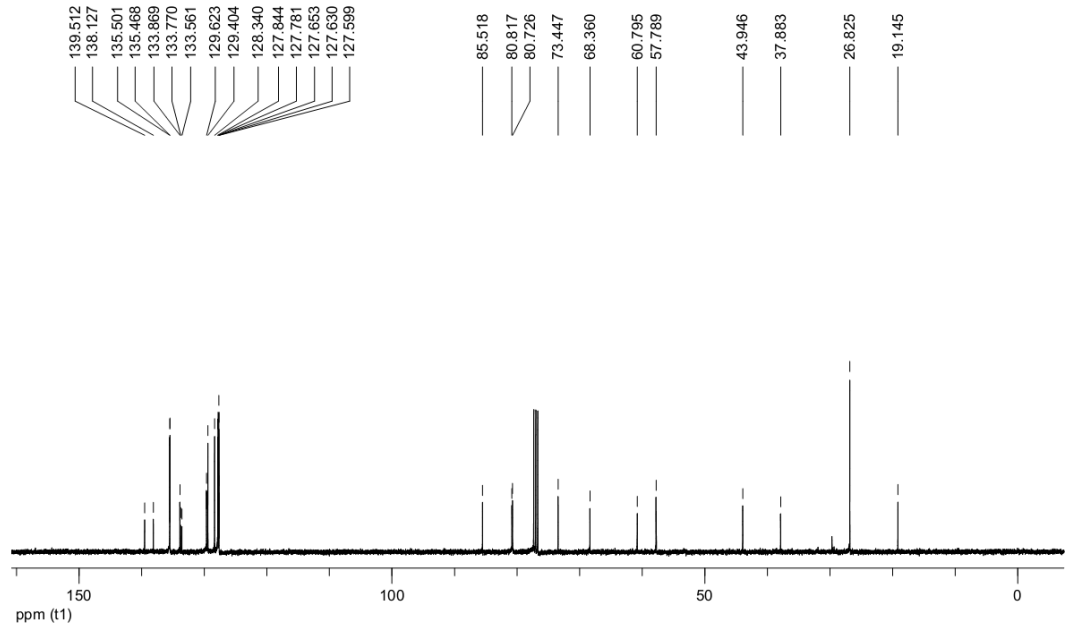
NOESY (400 MHz, $CDCl_3$) of compound **7.3a**



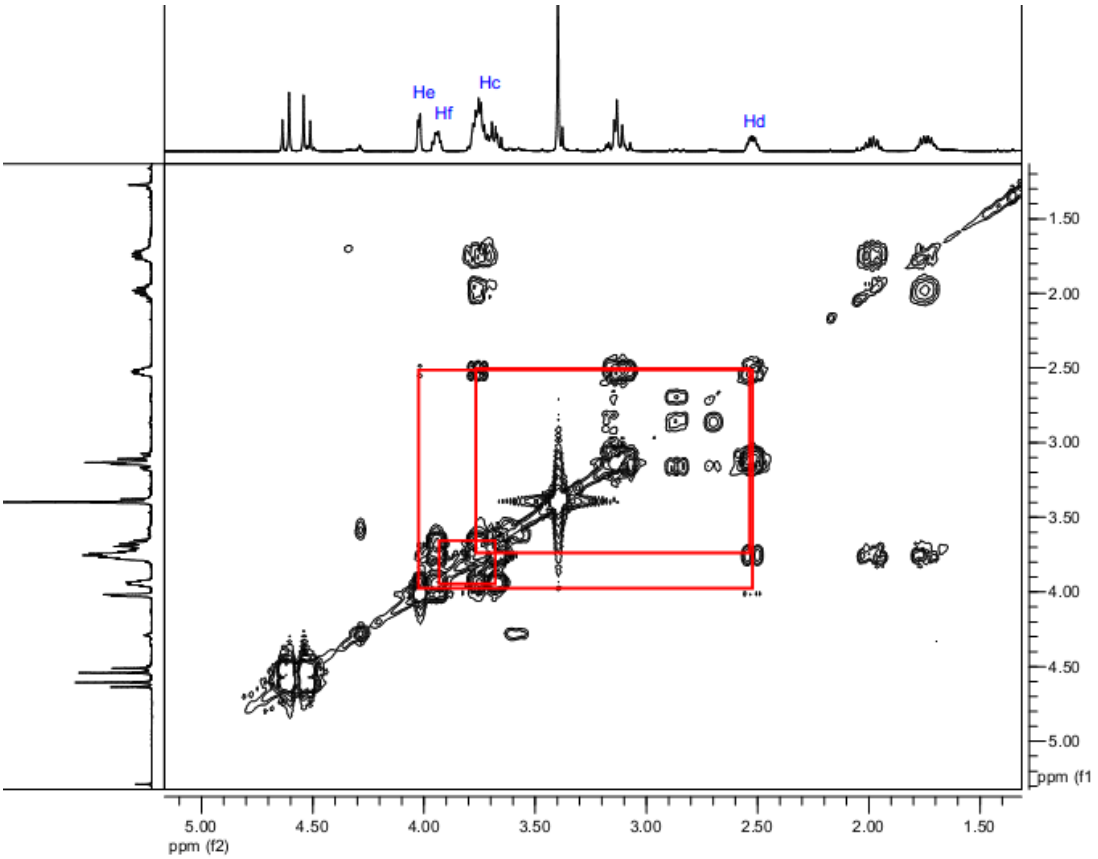
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7.3b**



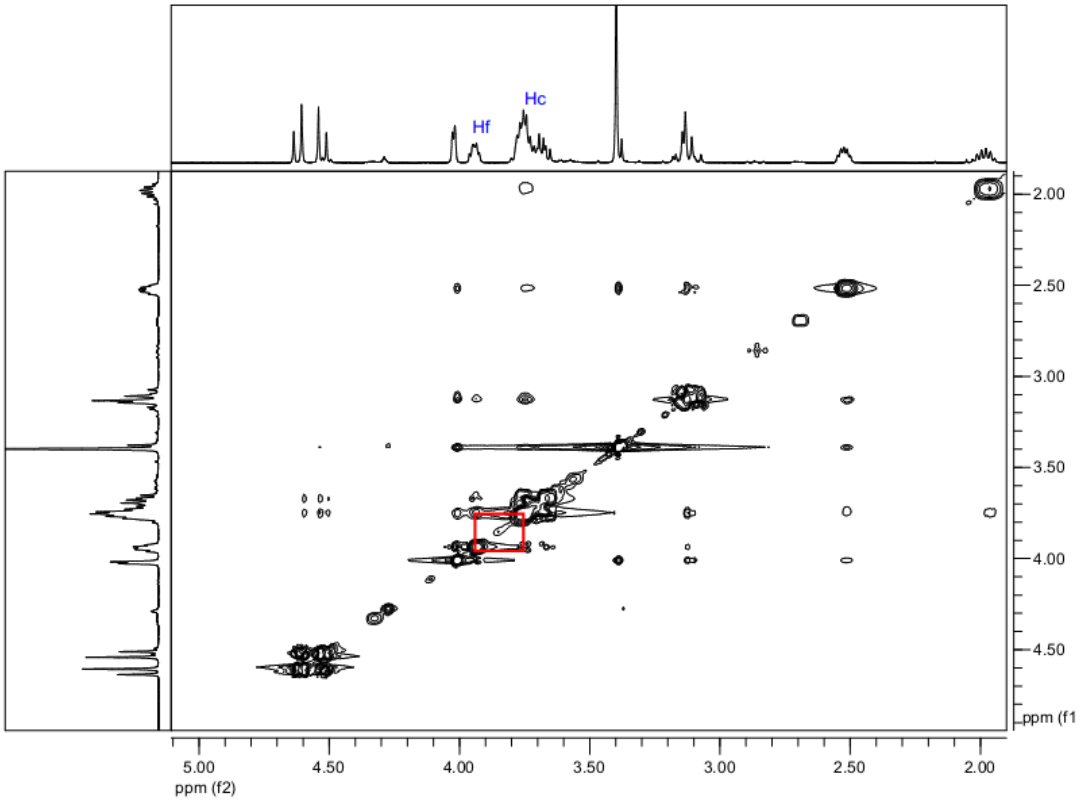
^{13}C NMR (100 MHz, $CDCl_3$) of compound **7.3b**



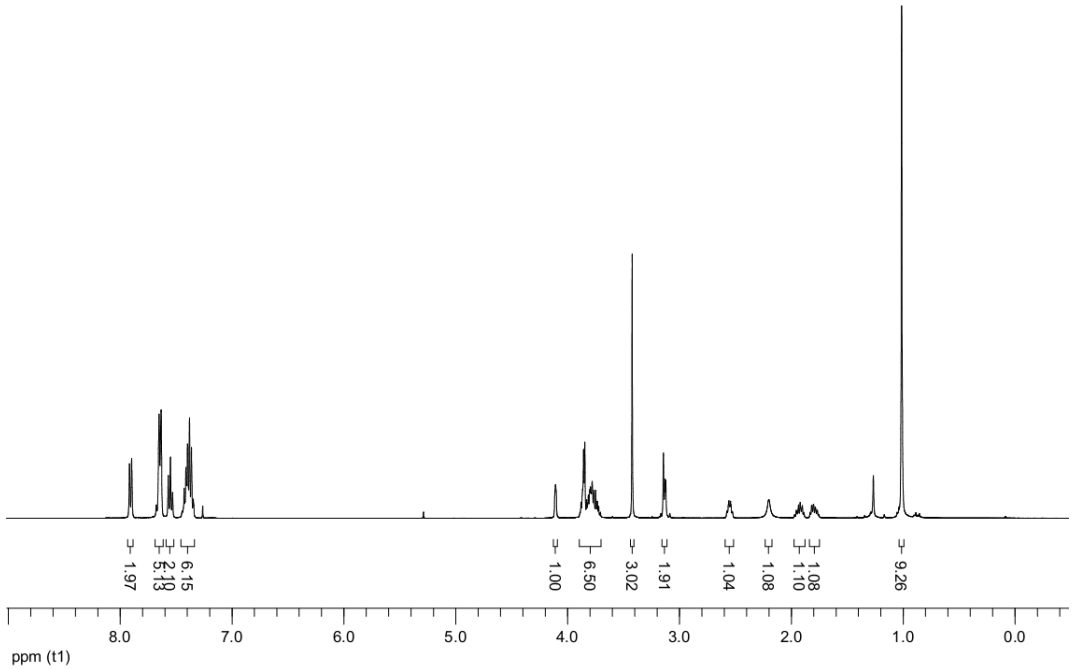
^{1}H -^{1}H COSY (400 MHz, $CDCl_3$) of compound **7.3b**



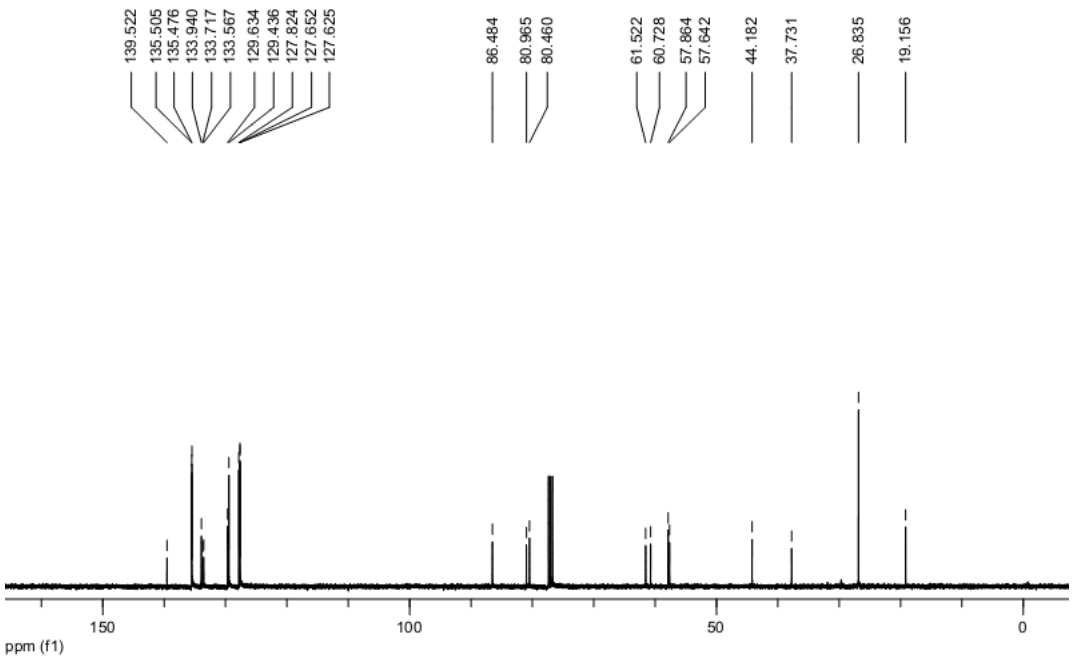
NOESY (400 MHz, $CDCl_3$) of compound **7.3b**



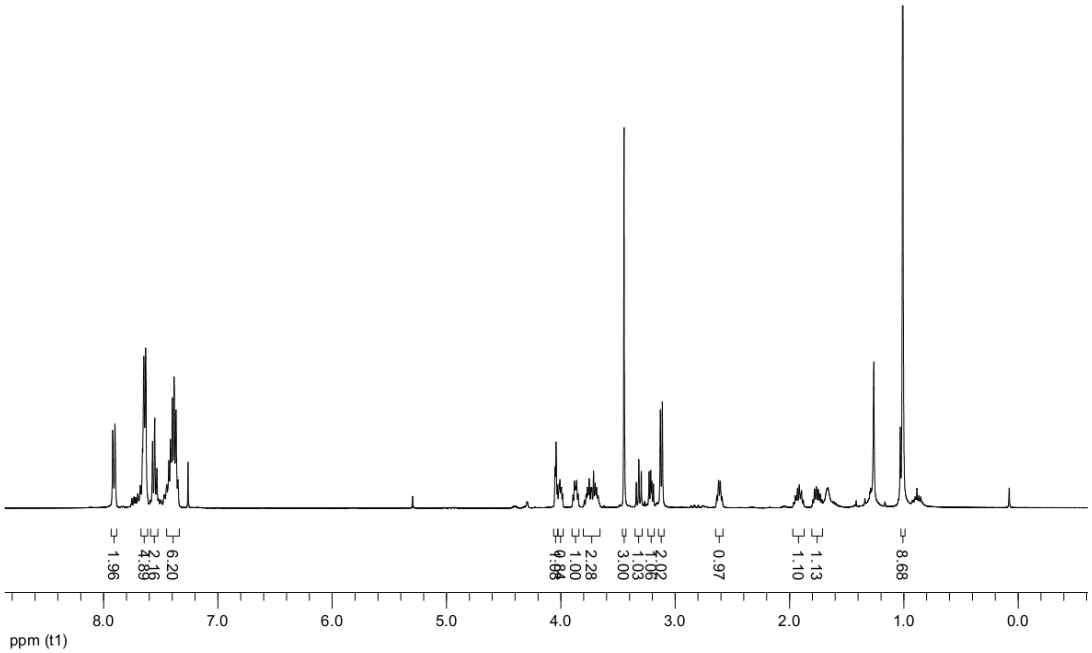
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7.4**



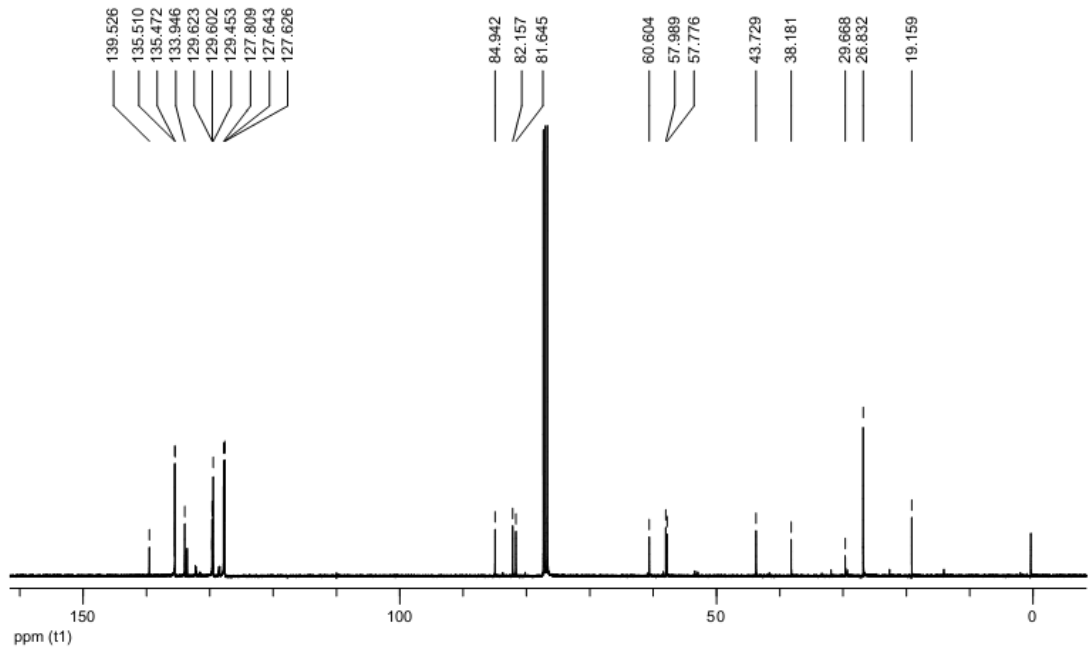
^{13}C NMR (100 MHz, $CDCl_3$) of compound **7.4**



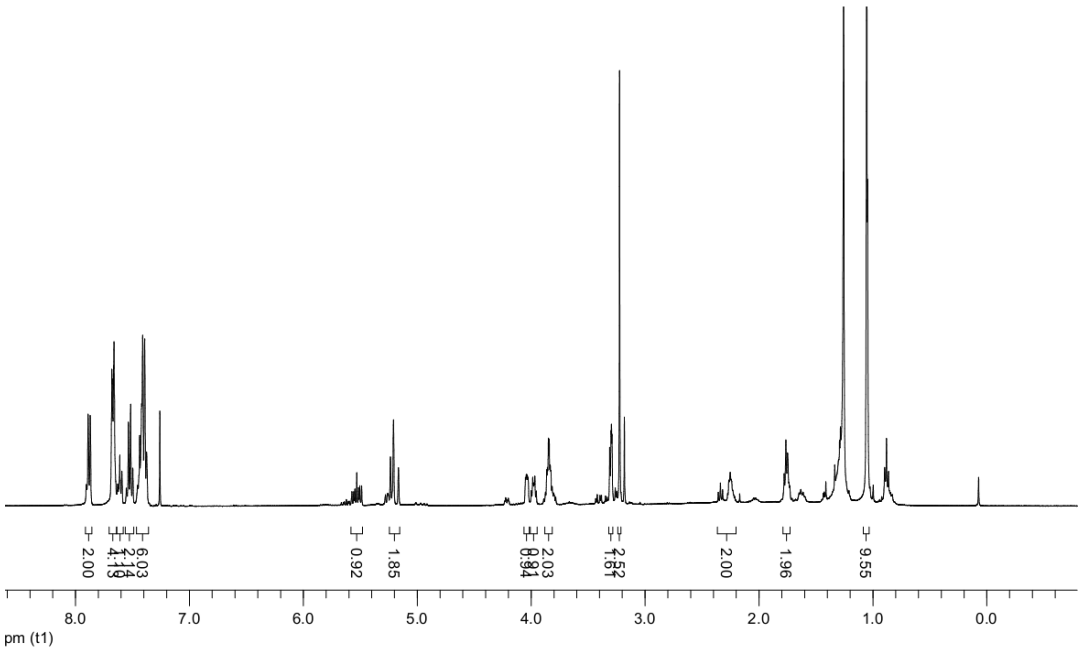
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7.5**



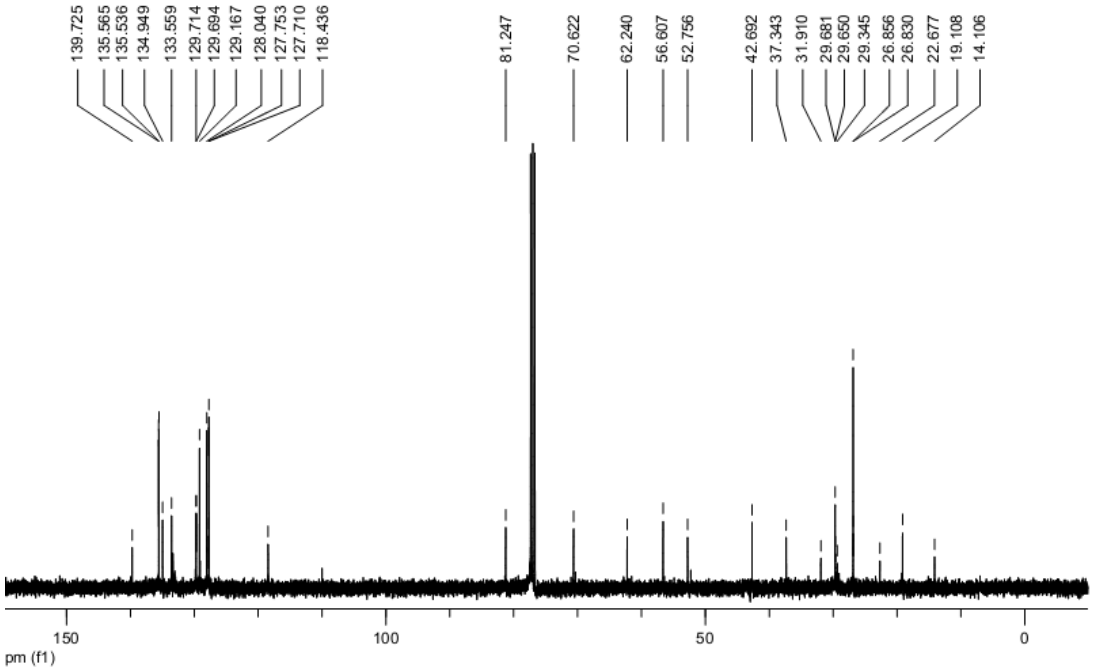
^{13}C NMR (100 MHz, $CDCl_3$) of compound **7.5**



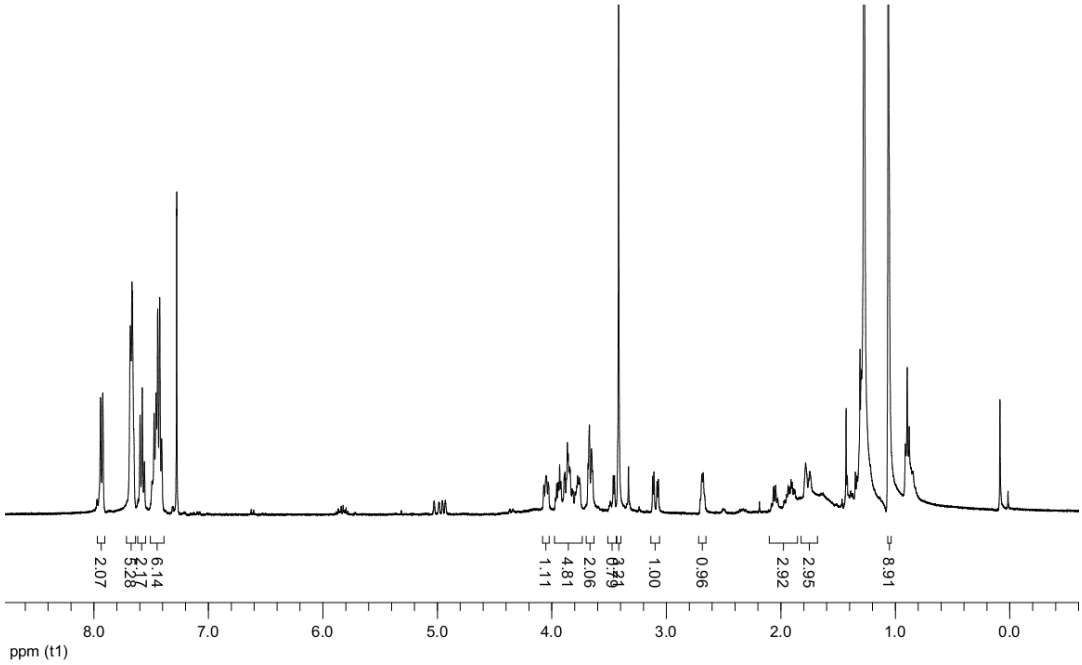
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7.6**



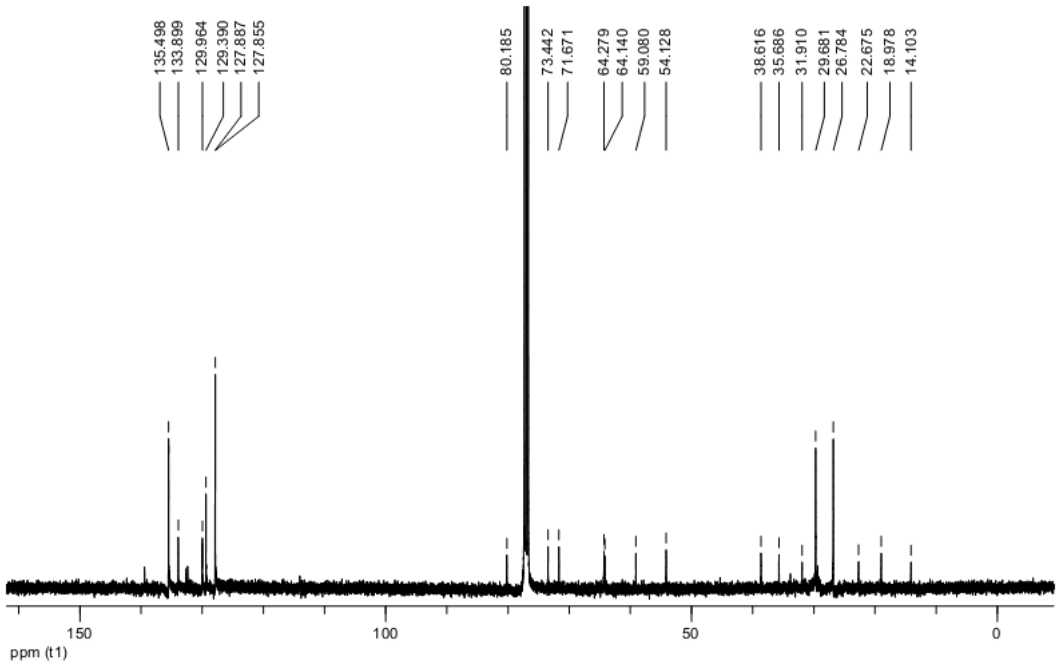
^{13}C NMR (100 MHz, $CDCl_3$) of compound **7.6**



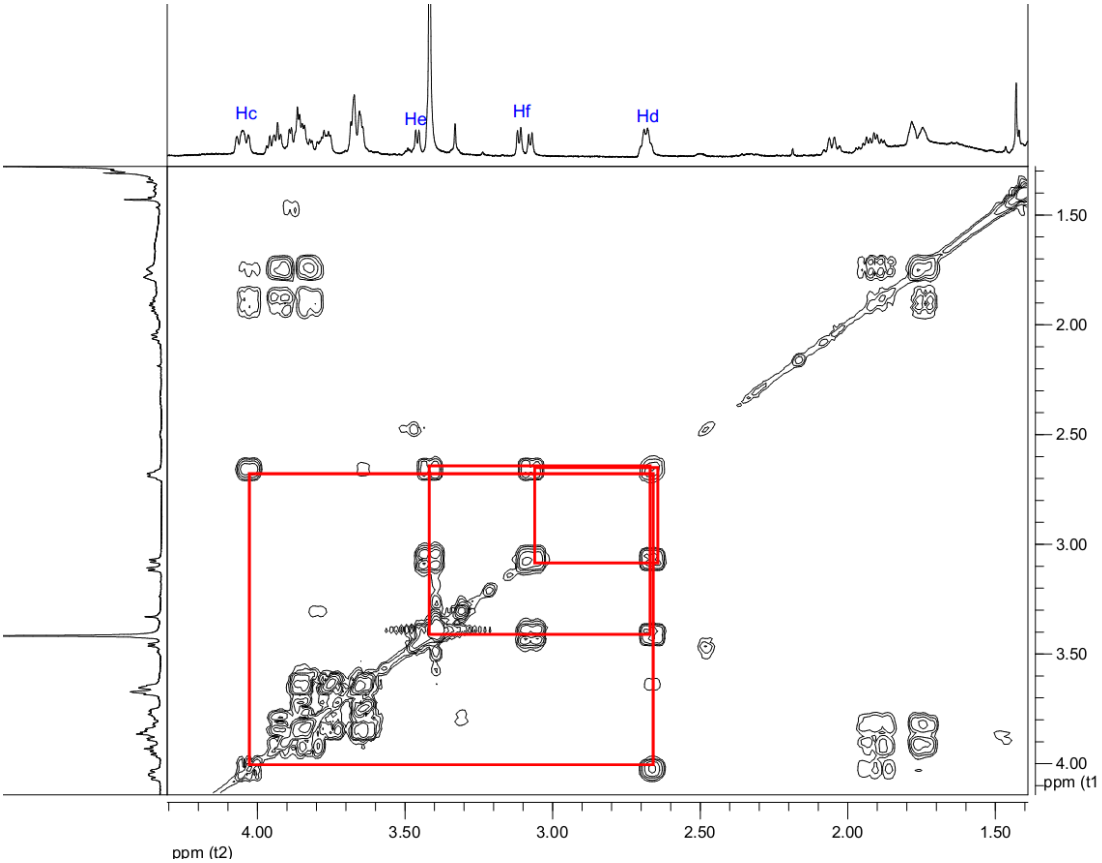
^{1}H NMR (400 MHz, $CDCl_3$) of compound **1.7**



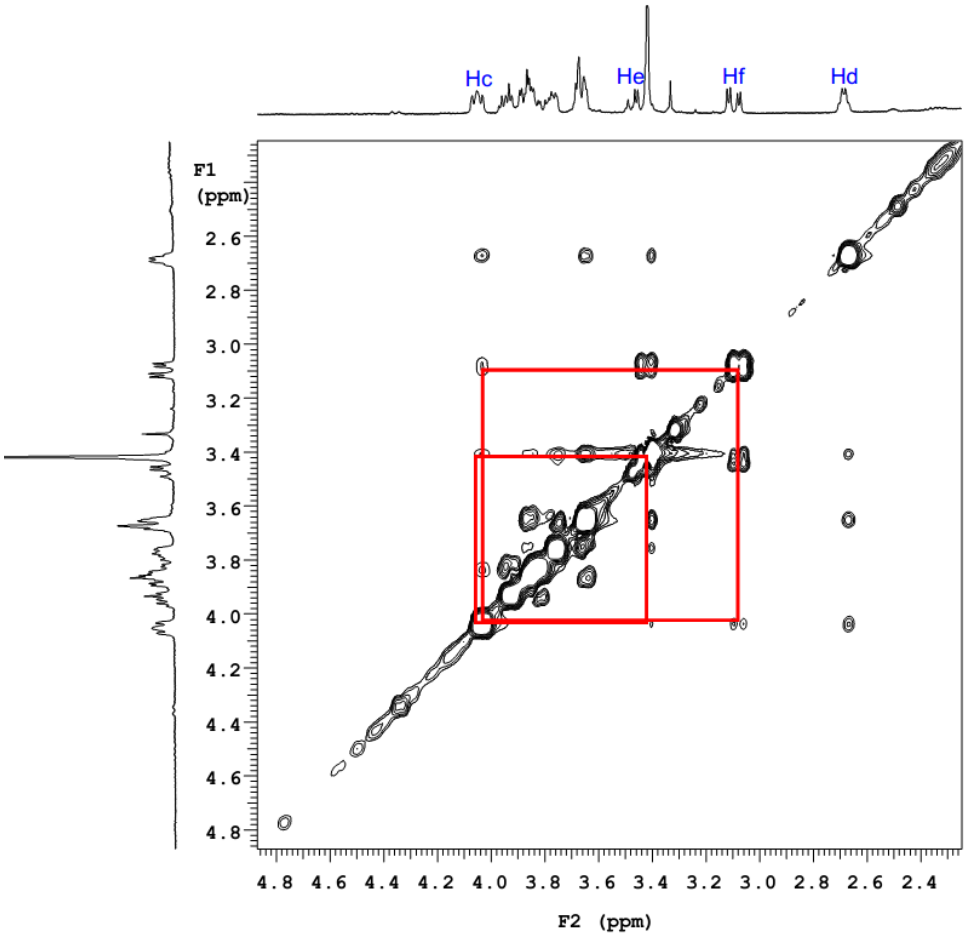
^{13}C NMR (100 MHz, $CDCl_3$) of compound **1.7**



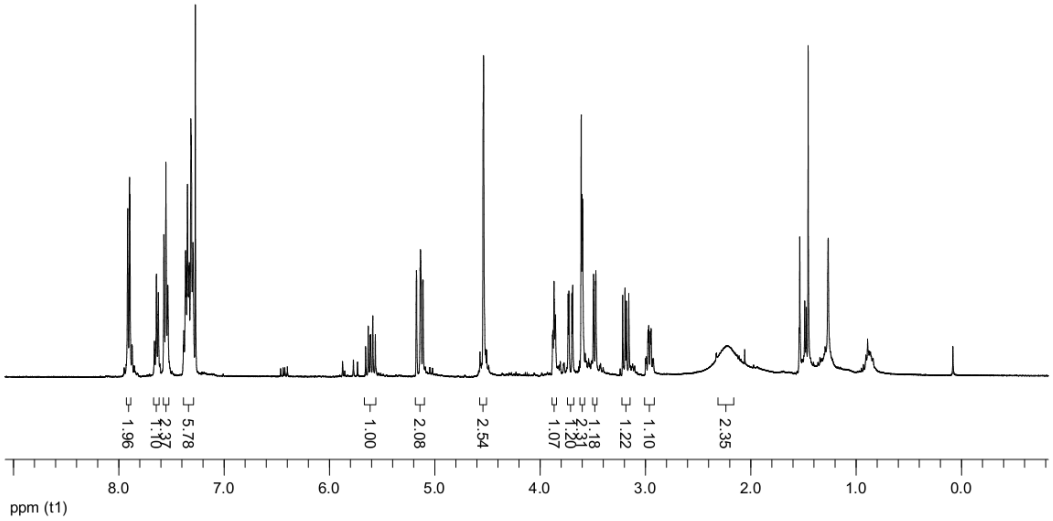
^{1}H -^{1}H COSY (400 MHz, $CDCl_3$) of compound **1.7**



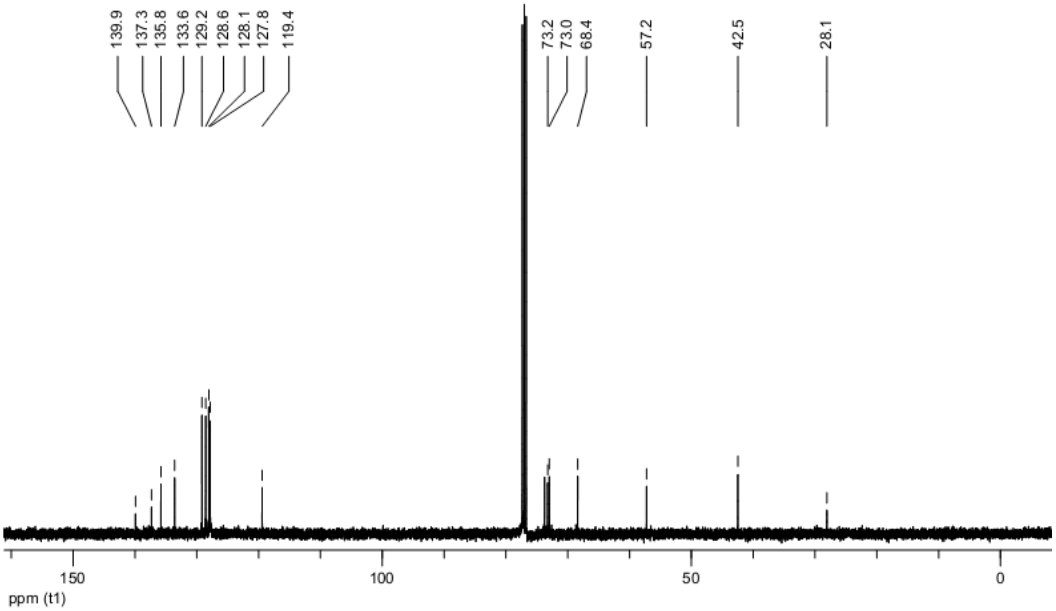
NOESY (400 MHz, $CDCl_3$) of compound **1.7**



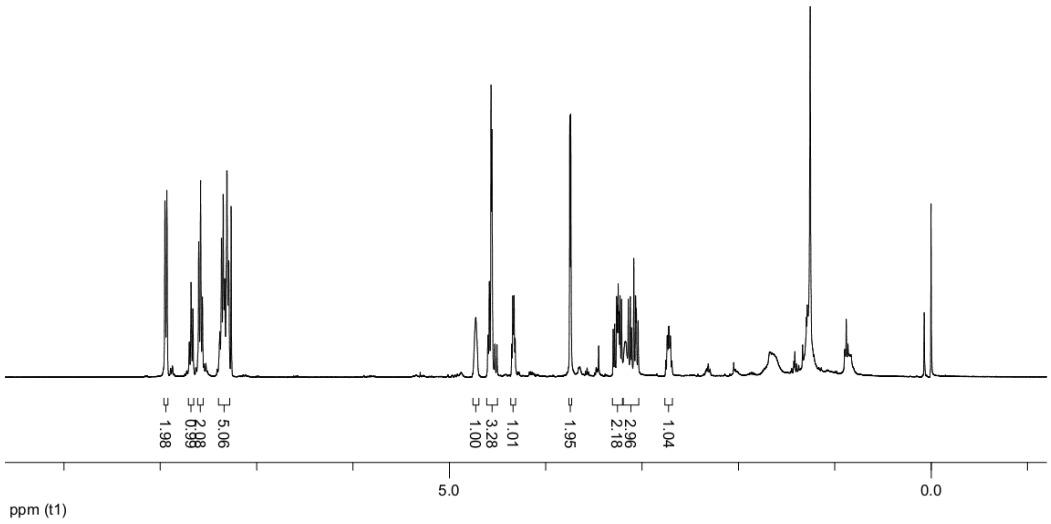
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9.1**



^{13}C NMR (100 MHz, $CDCl_3$) of compound **9.1**



^{1}H NMR (400 MHz, $CDCl_3$) of compound **9.2**



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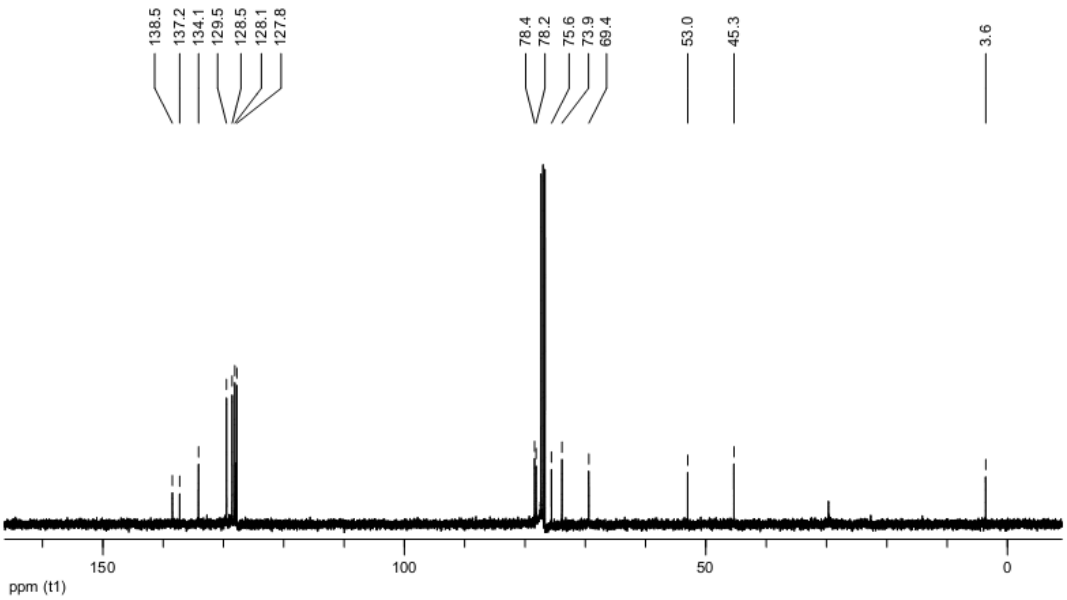

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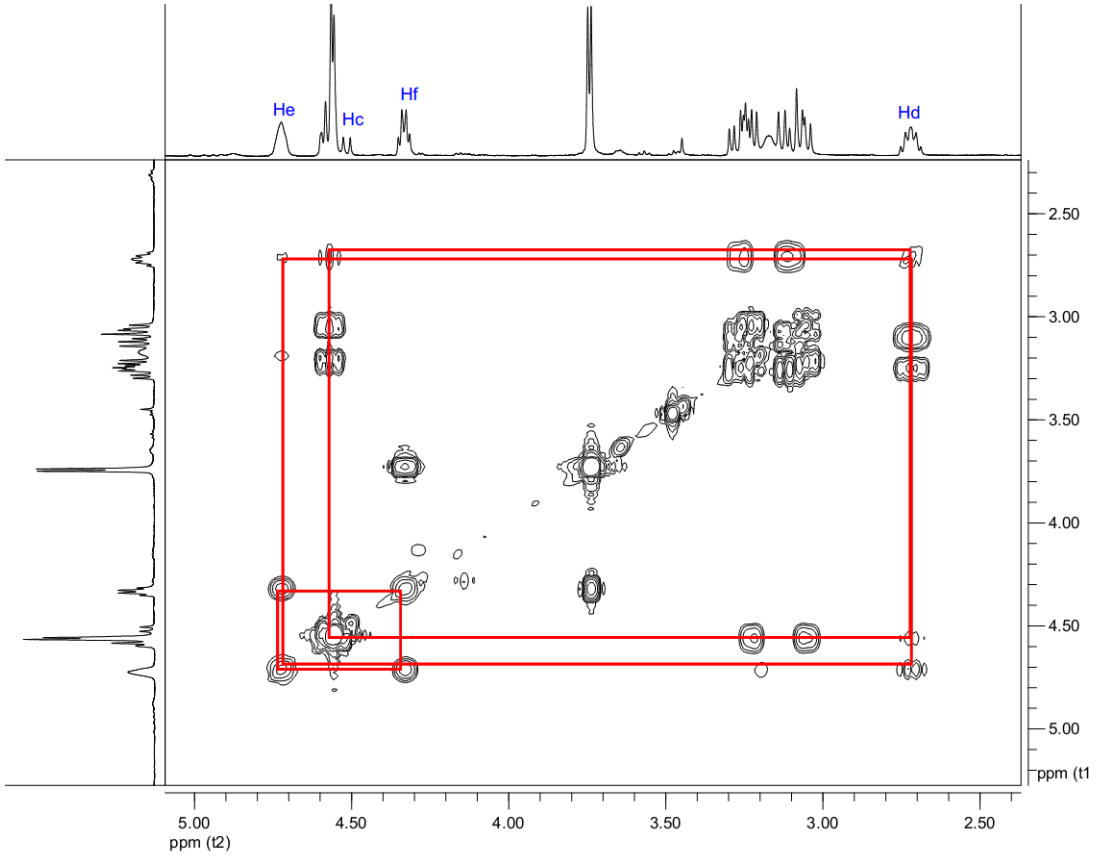

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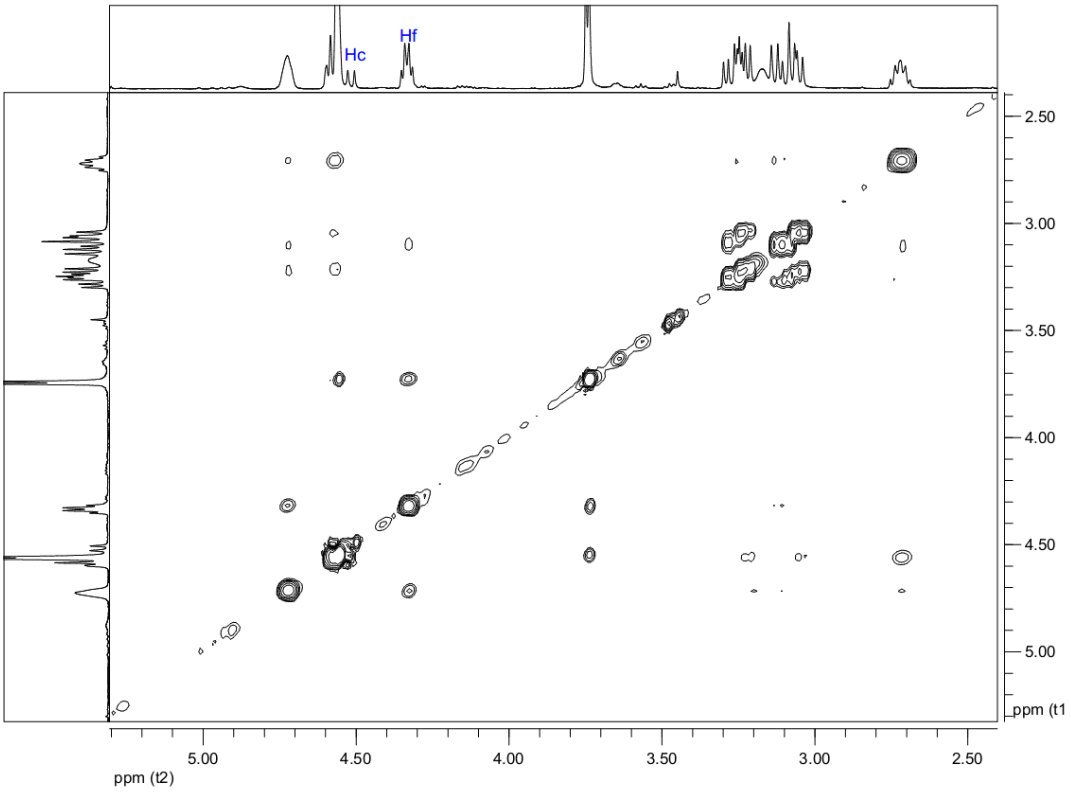

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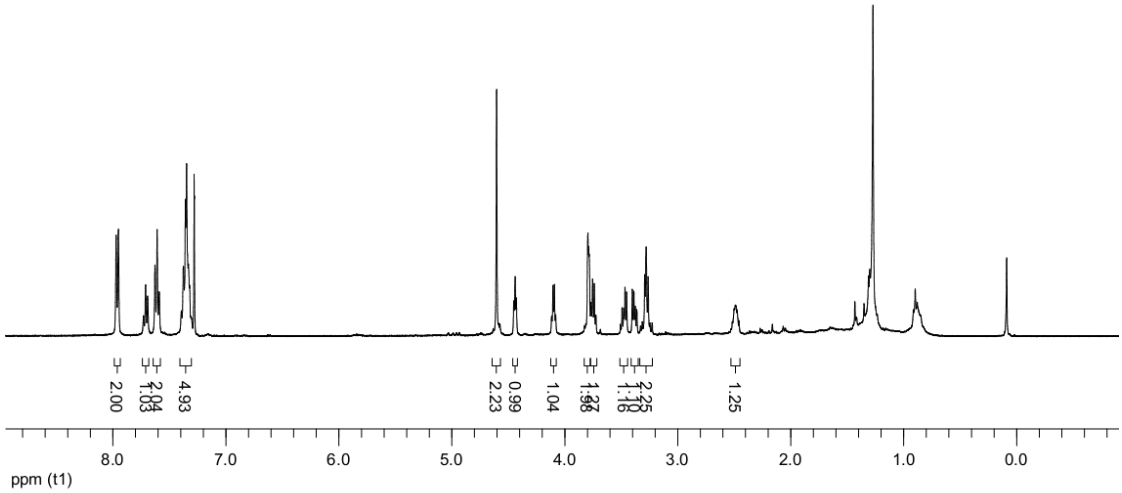
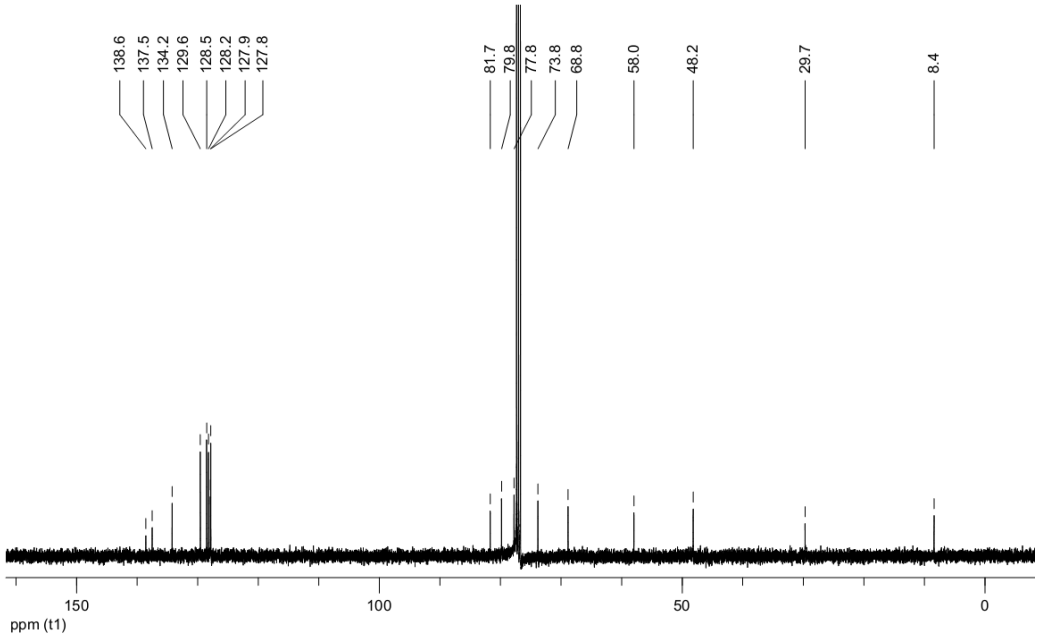
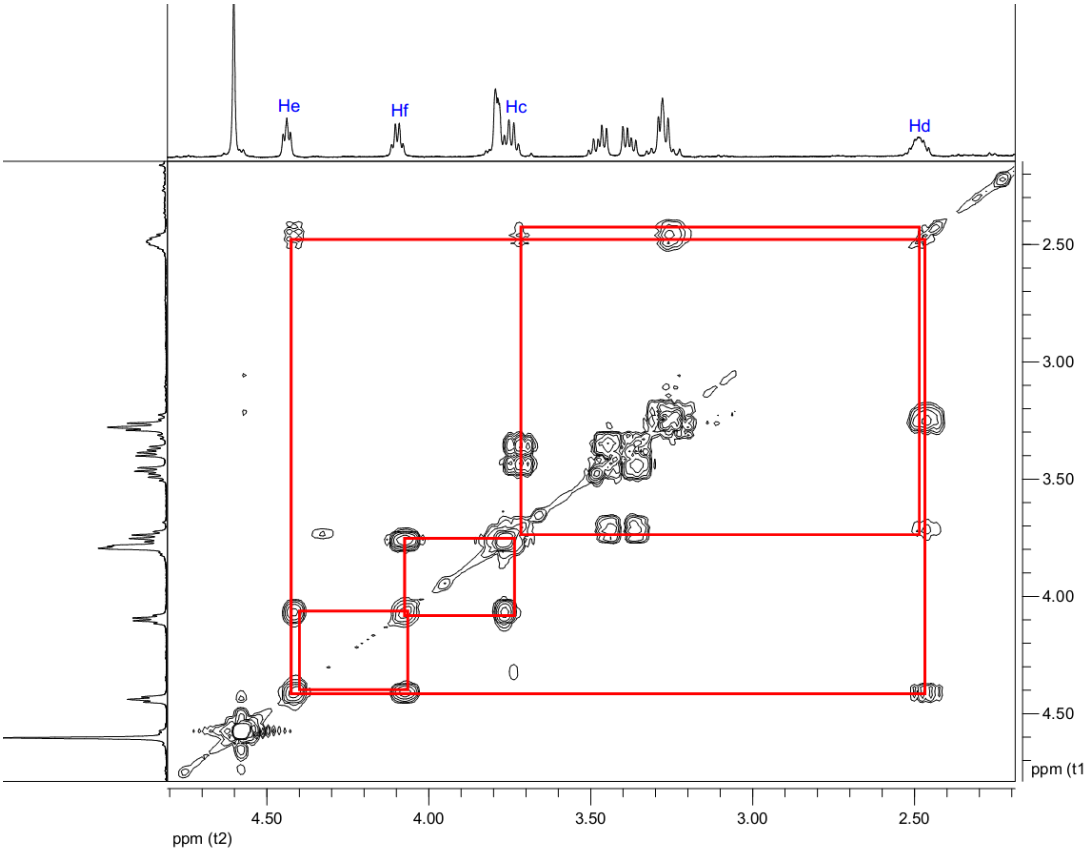


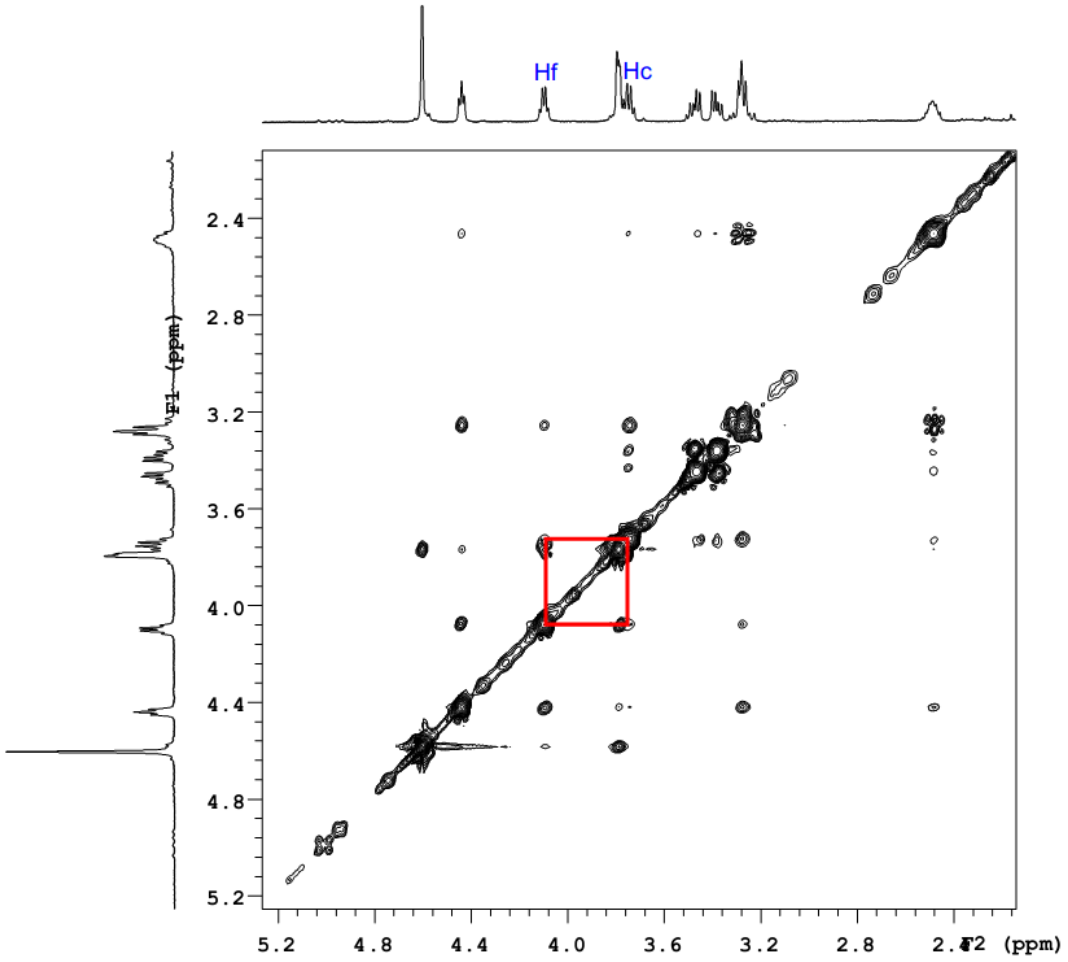
^{13}C NMR (100 MHz, $CDCl_3$) of compound **9.3**



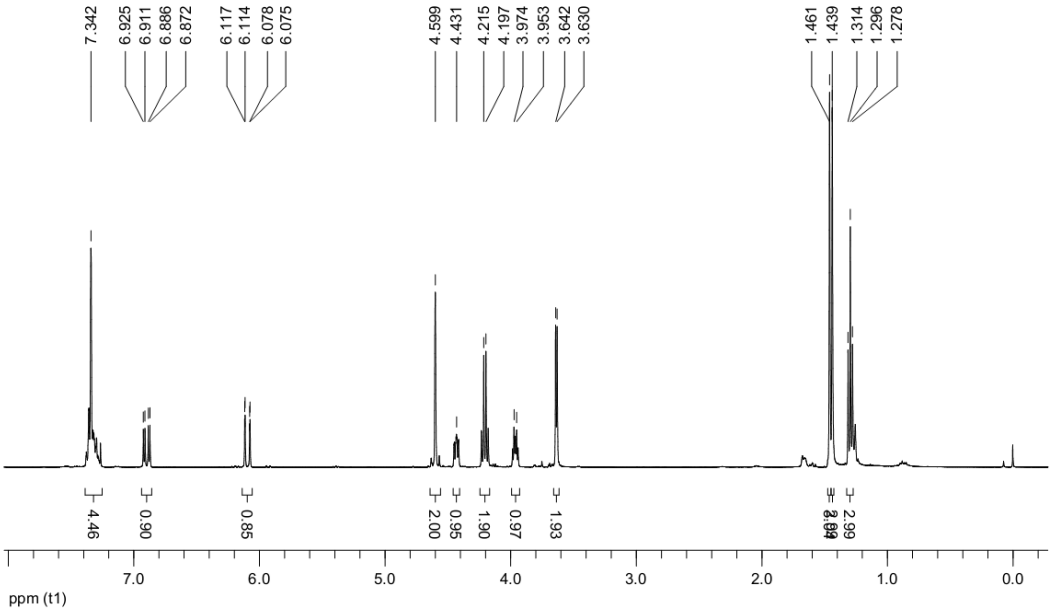
^{1}H -^{1}H COSY (400 MHz, $CDCl_3$) of compound **9.3**



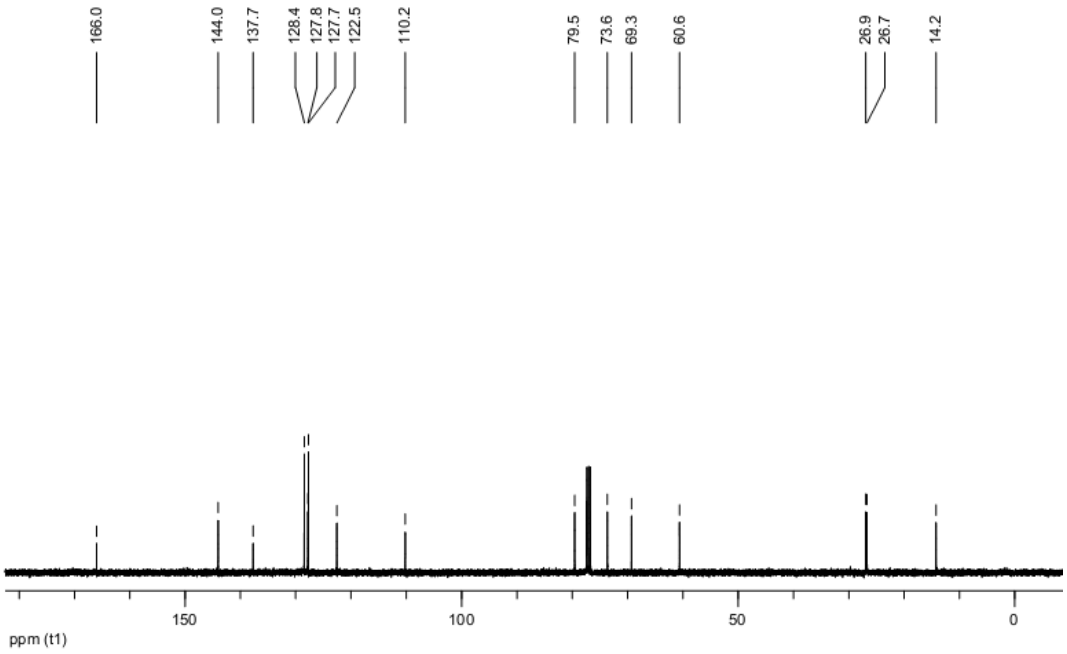
NOESY (400 MHz, $CDCl_3$) of compound **9.3**



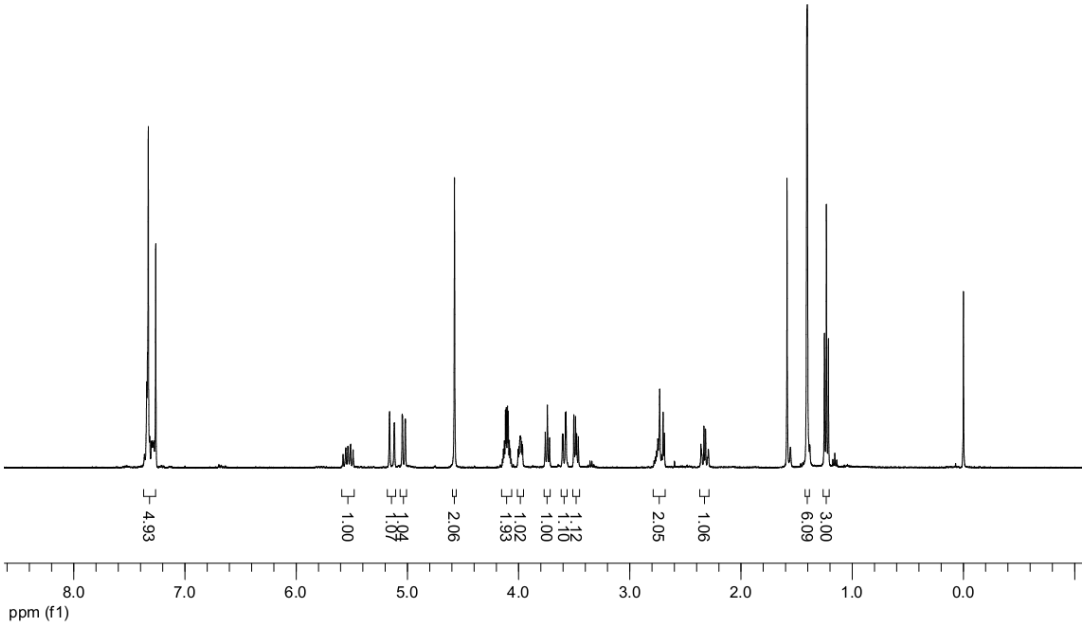
^{1}H NMR (400 MHz, $CDCl_3$) of compound **10.1**



^{13}C NMR (100 MHz, $CDCl_3$) of compound **10.1**



^{1}H NMR (400 MHz, $CDCl_3$) of compound **10.2**



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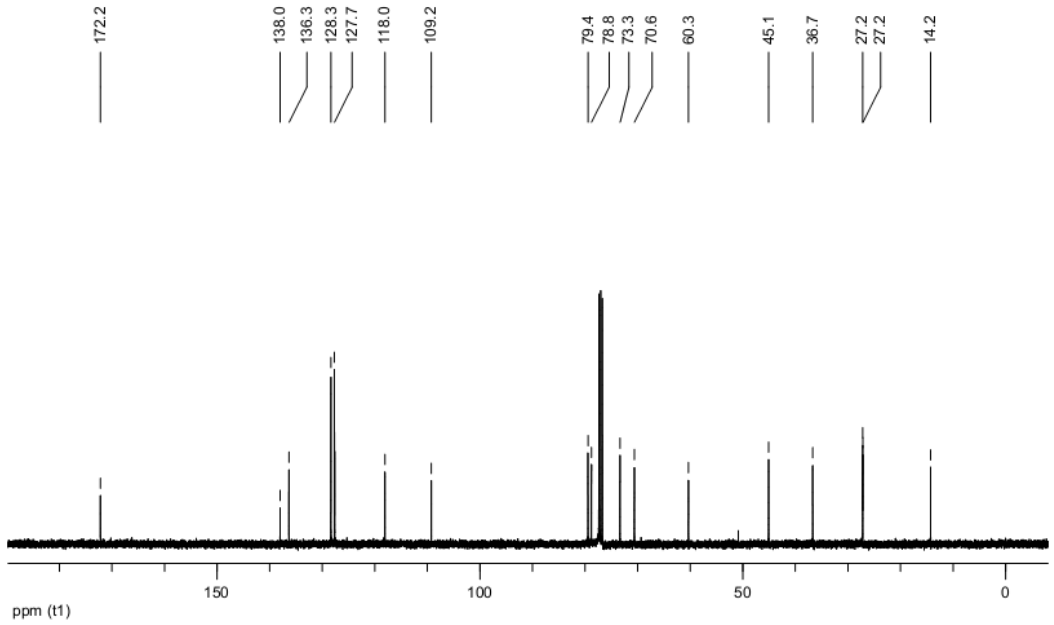
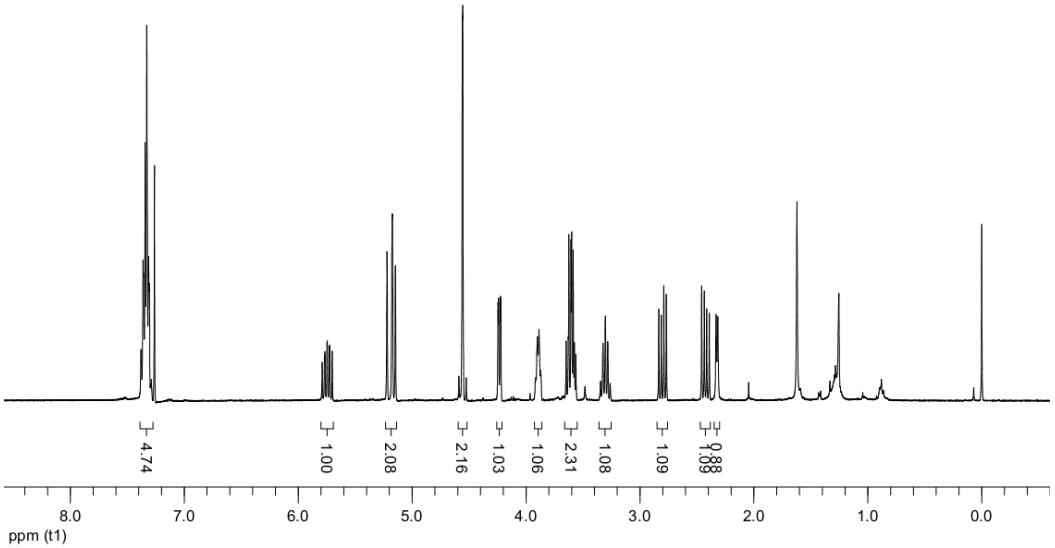


^{1}H NMR (400 MHz, $CDCl_3$) of compound **10.3**



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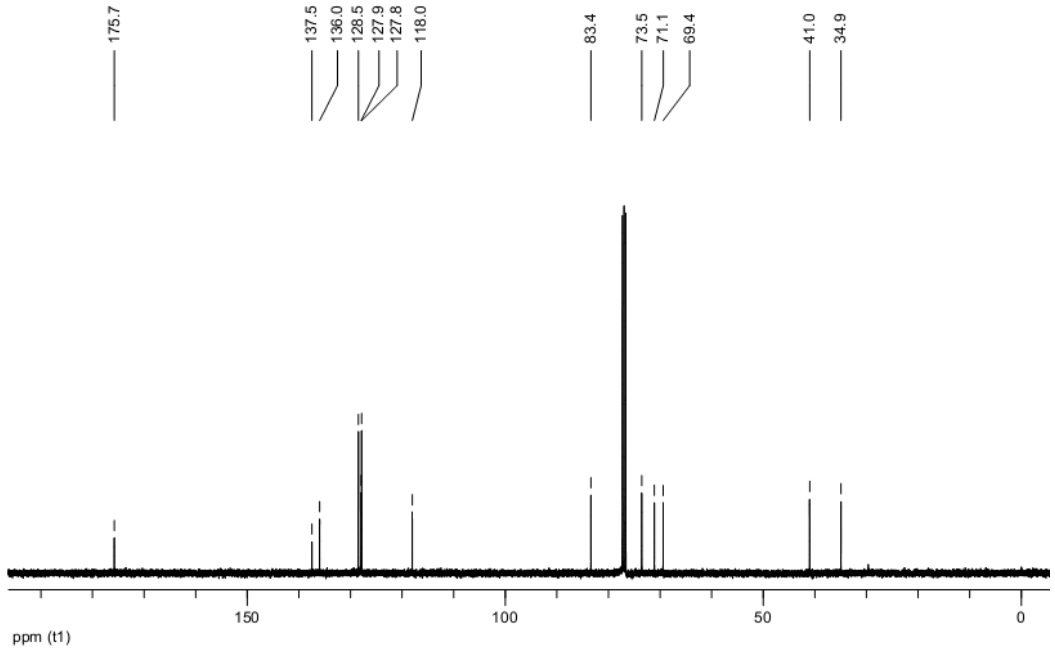

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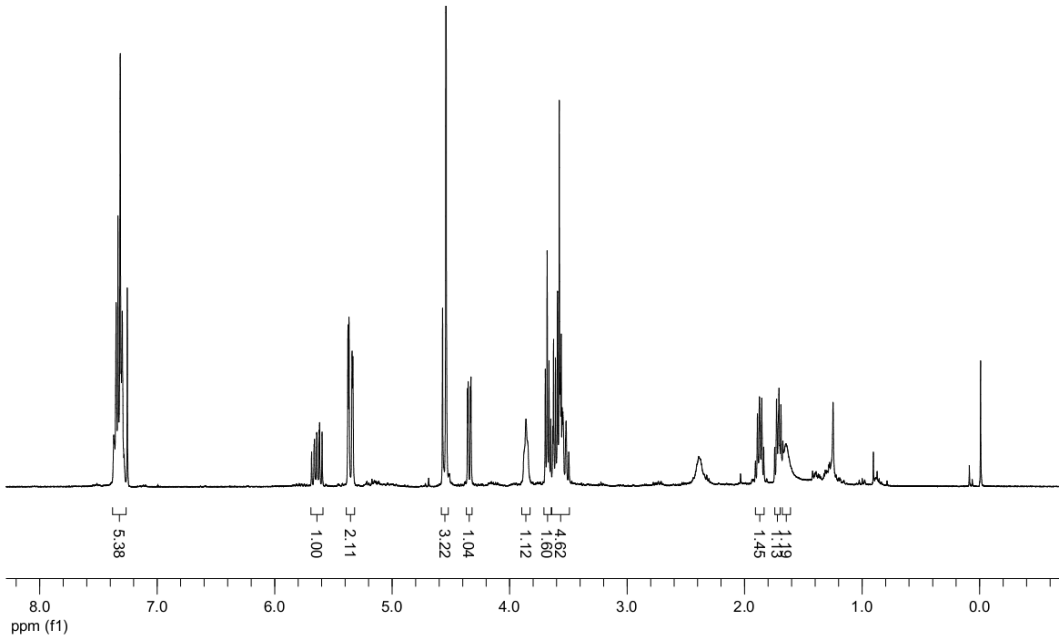

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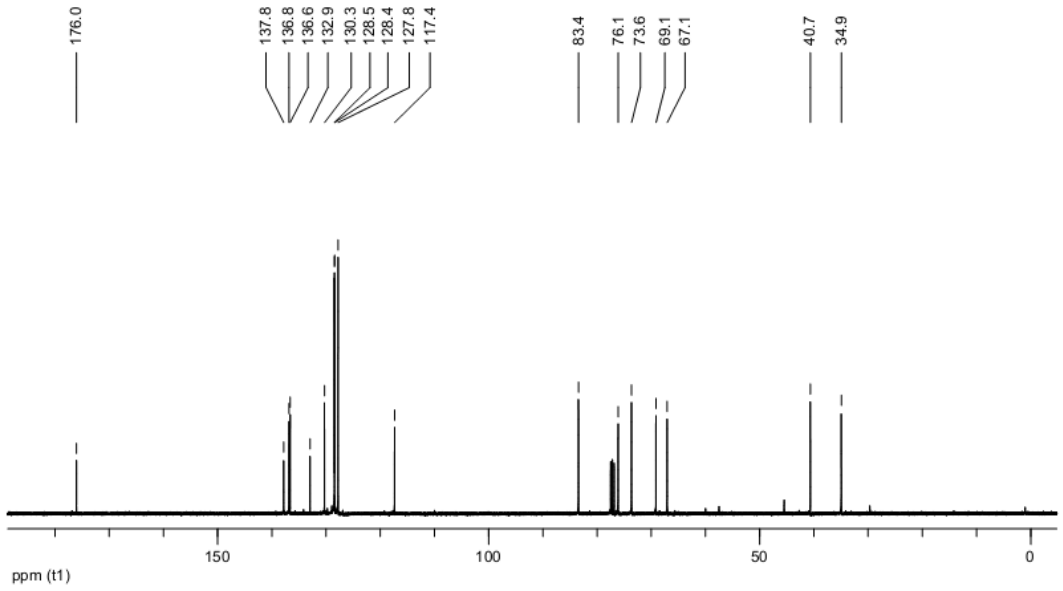
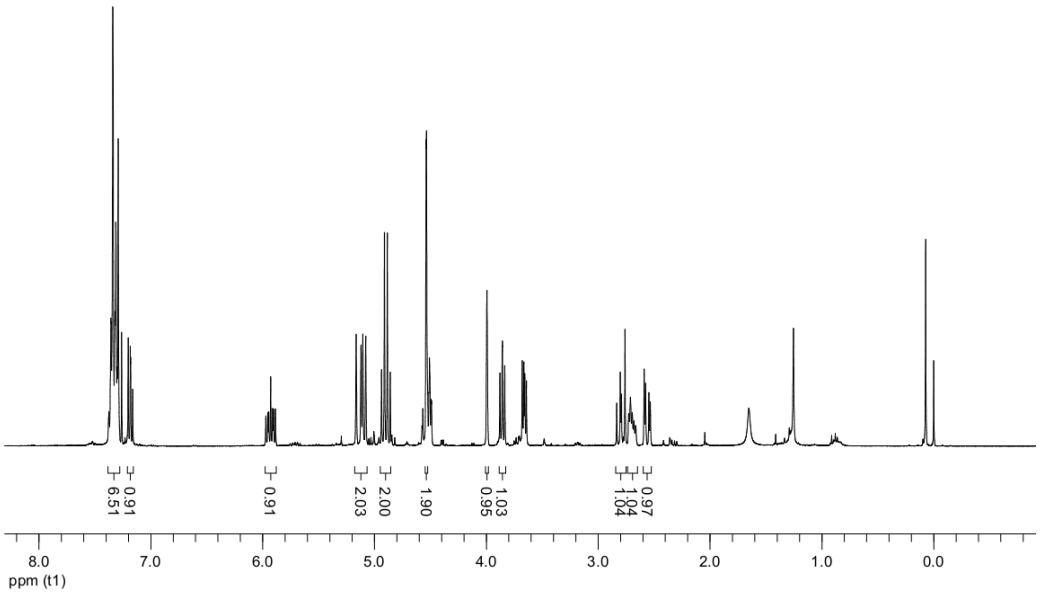
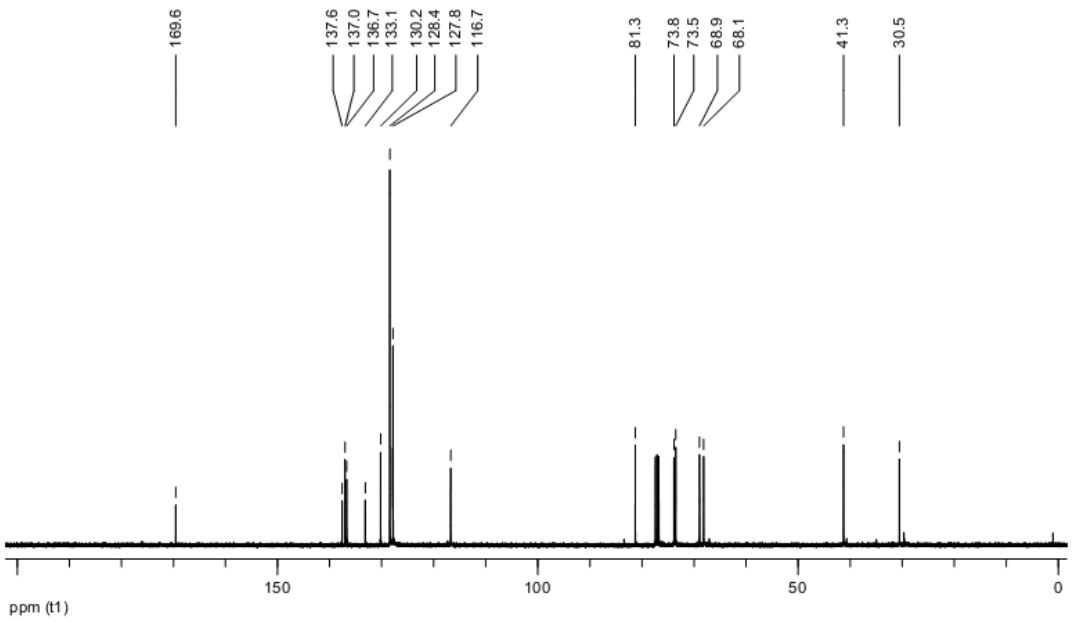


^{1}H NMR (400 MHz, $CDCl_3$) of compound **10.5**



^{13}C NMR (100 MHz, $CDCl_3$) of compound **10.5**



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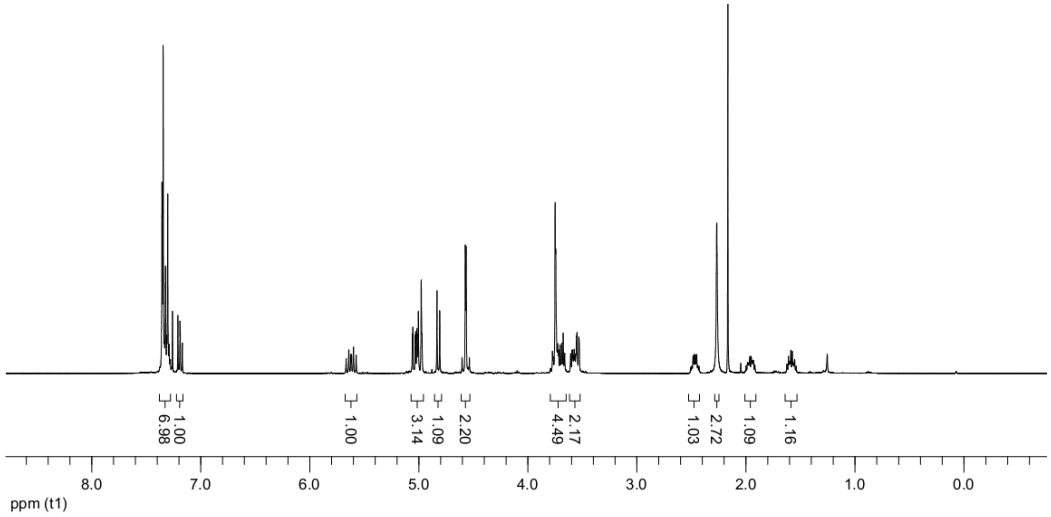

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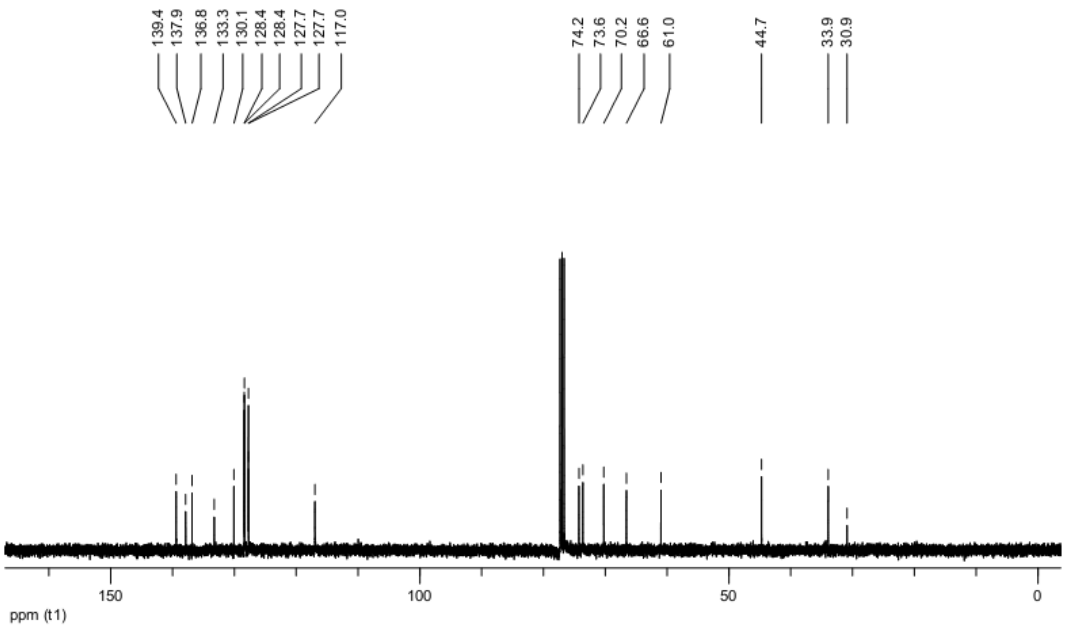
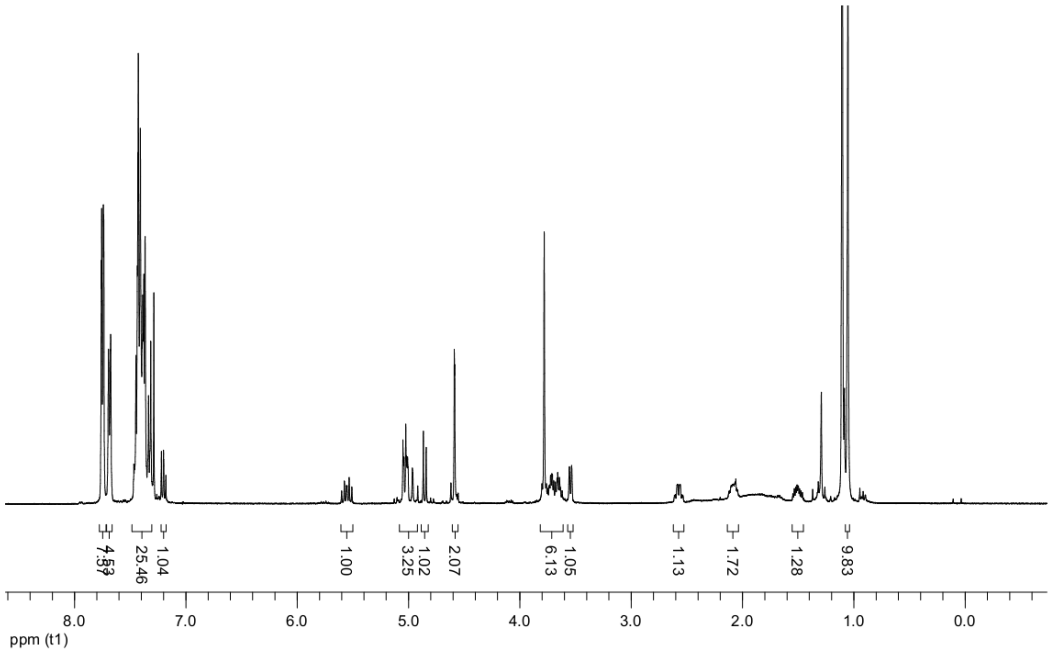
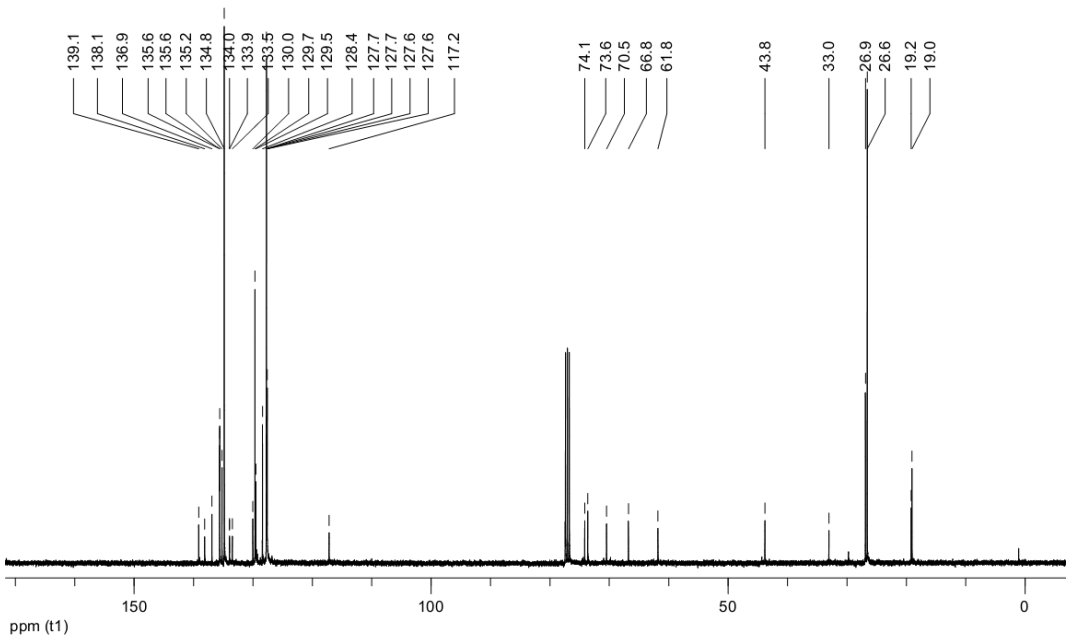


^{1}H NMR (400 MHz, $CDCl_3$) of compound **10.6.1**



^{13}C NMR (100 MHz, $CDCl_3$) of compound **10.6.1**



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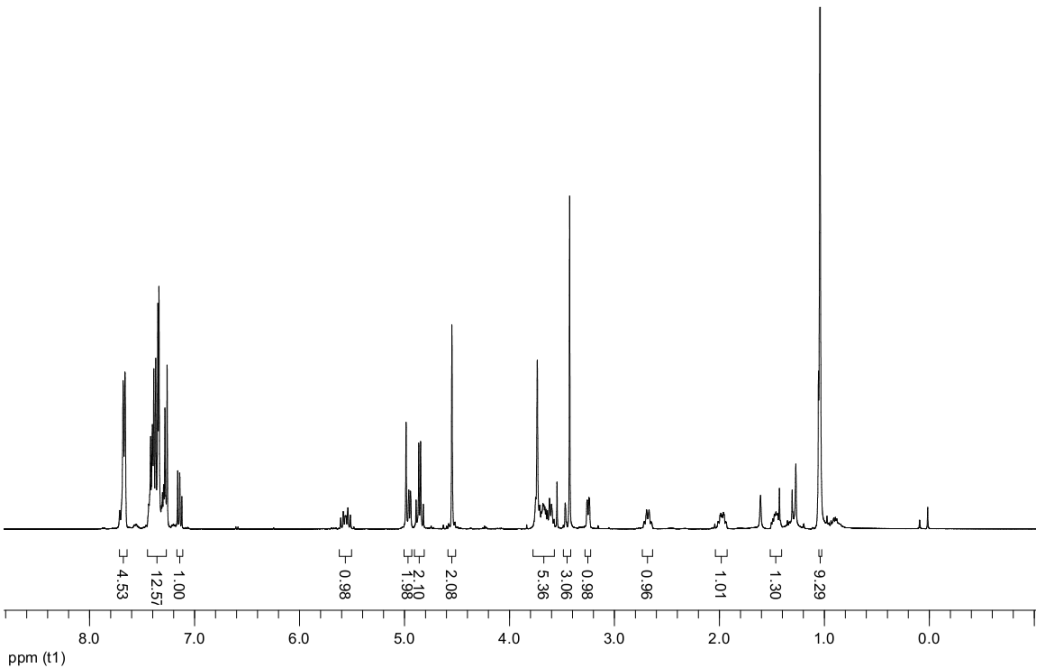
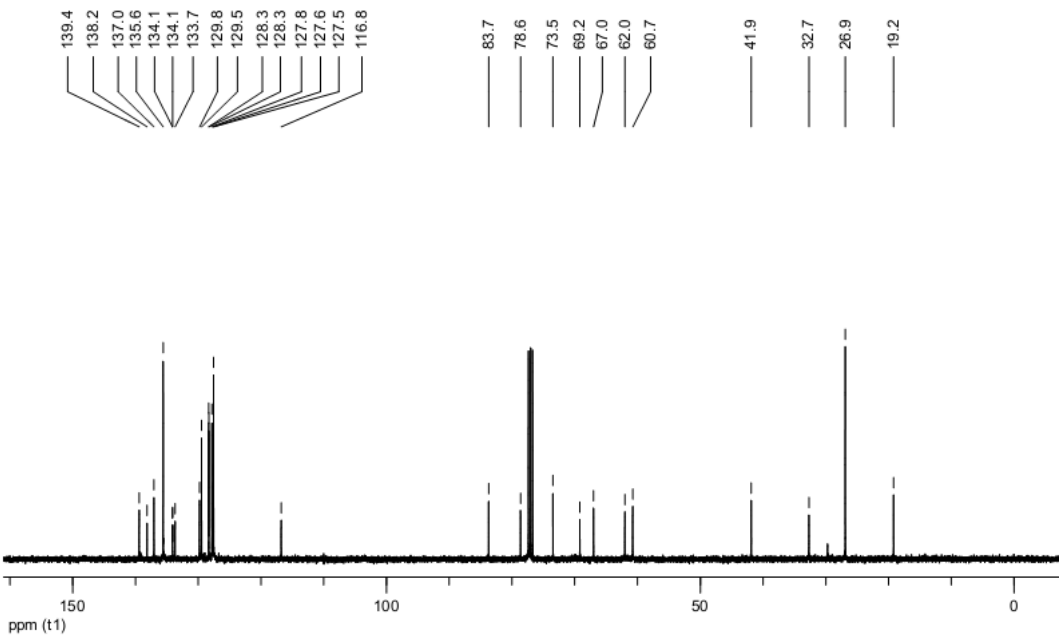
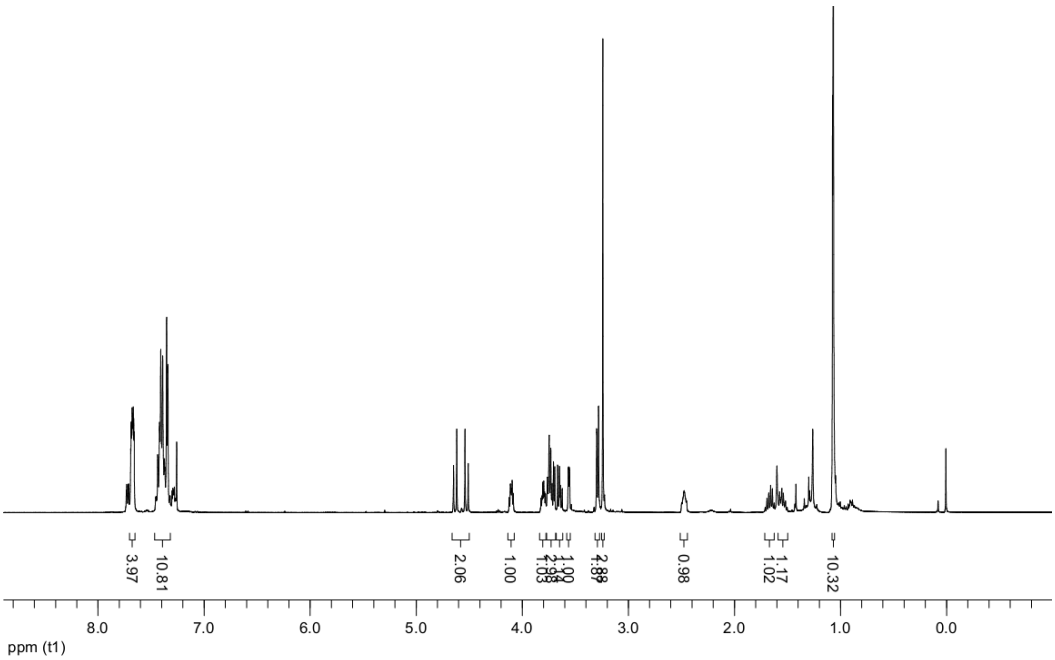


^{13}C NMR (100 MHz, $CDCl_3$) of compound **10.7**



^{1}H NMR (400 MHz, $CDCl_3$) of compound **10.8**



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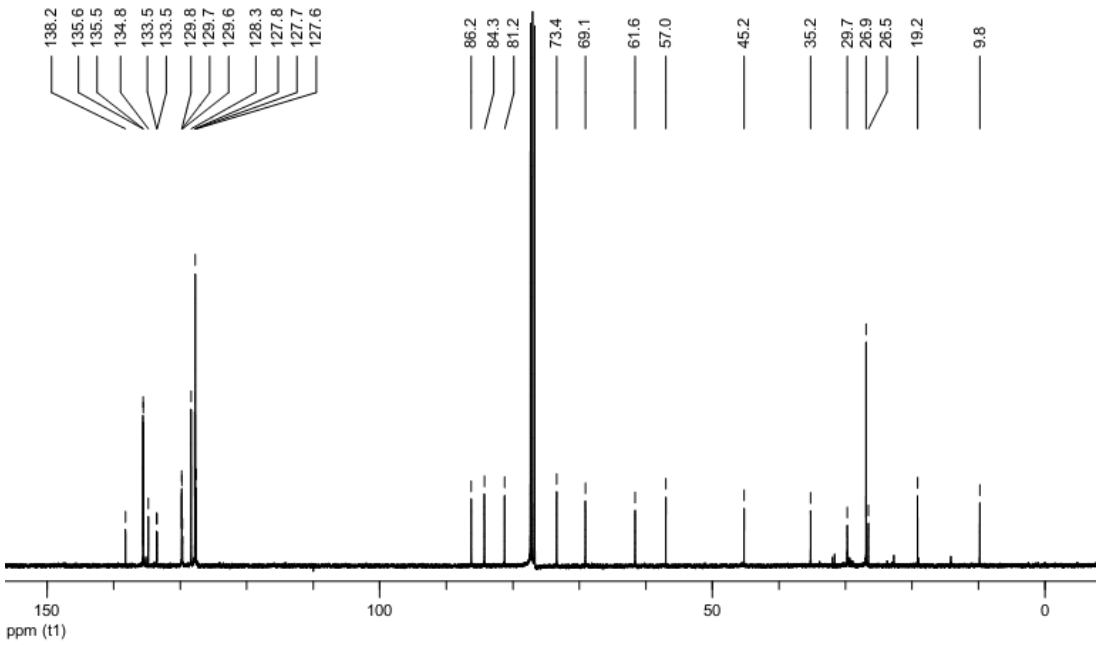
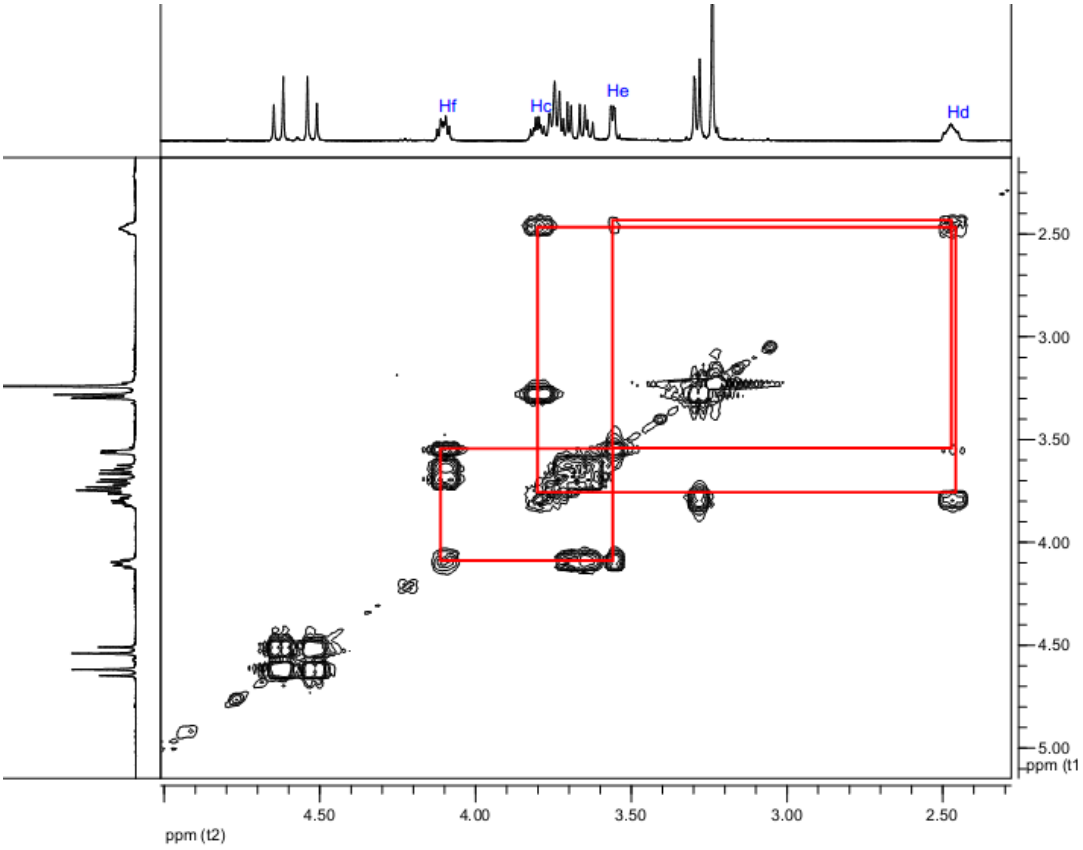
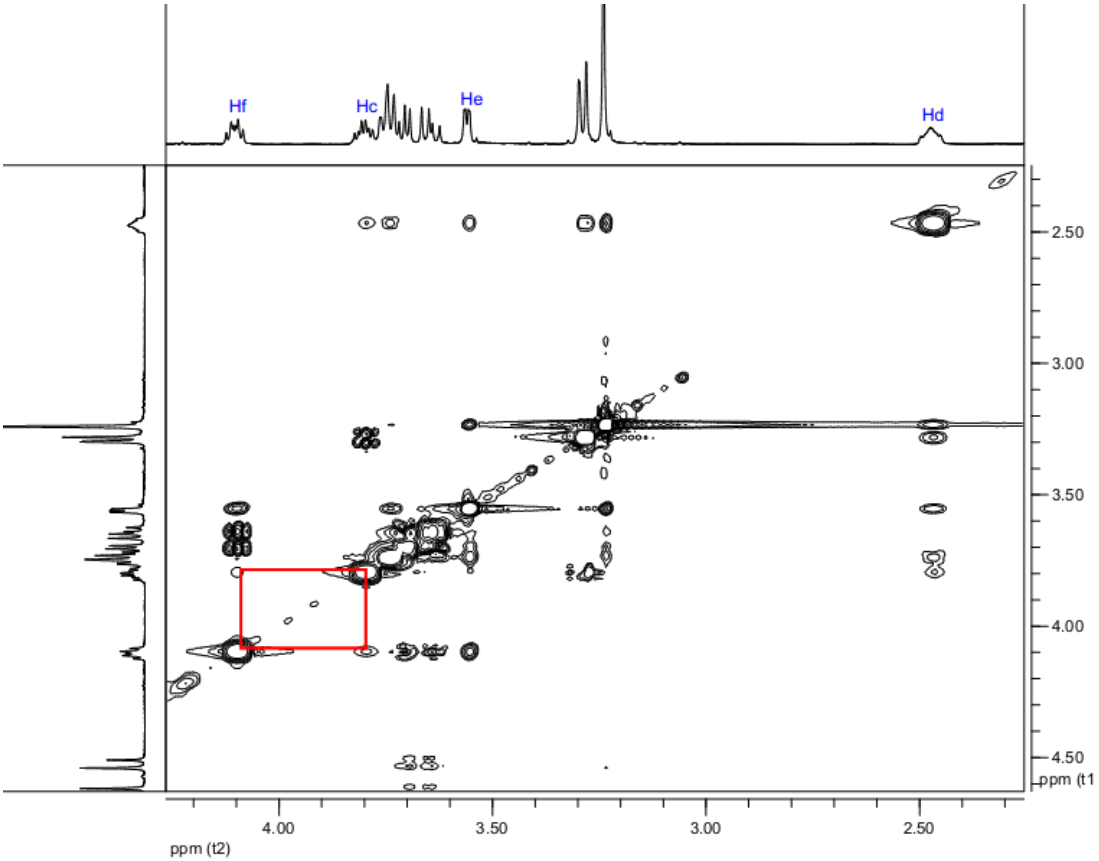


^{1}H -^{1}H COSY (400 MHz, $CDCl_3$) of compound **10.8**



NOESY (400 MHz, $CDCl_3$) of compound **10.8**


Hf
Hc
He
Hd
2.50
3.00
3.50
4.00
4.50
ppm (t1
4.00
3.50
3.00
2.50
ppm (t2)

Chapter 3

Synthesis of Eribulin Fragment Based Macrocyclic Toolbox

3.1. Protein-Protein Interactions (PPIs)

Several factors have contributed to the limited success of small molecules as modulators of protein-protein interactions (PPIs).[1] In general, protein-protein interactions involve shallow surfaces cover a relatively large surface area. PPIs are largely driven by hydrophobic interfaces.[2] The Hydrogen bonds and electrostatic interactions play crucial roles,[3] and the covalent bonds are also considered important for PPIs. The physico-chemical principles of protein-protein interactions are general, and many of the interactions observed *in vitro* are an outcome of experimental over-expression or of the crystal effects, complicating the functional prediction. Proteins also have areas known as "*hot spots*".[4] In several cases, it has been observed that these "*hot spots*" contribute significantly to an overall binding, and, the targeting of these "focused surface areas" has successfully led to the design of small-molecule binders. There are a few examples in literature where the structural information of protein-protein complex led to the design of small molecules that exploit the "*hot spots*".[1a] One such example of a rationally designed molecule involved the synthesis of small-molecule modulators capable of interfering with Caspase 9-IAP BIR 3 domain interactions.[5] Whereas a typical enzyme inhibition based approach involves seeking the structural information of an enzyme and then working closely with organic synthesis/medicinal and computational chemists. As in most cases, the enzymes present well-defined, often deep pockets and this information gives a good starting point to develop the medicinal chemistry program in the drug discovery arena.[6]

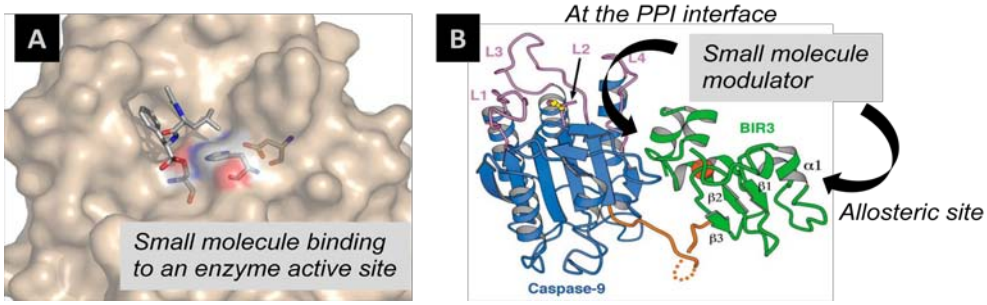


Figure 1: (A) An illustration of a small molecule binding to an enzyme active site; (B) small molecule modulators of protein-protein interactions via interface or an allosteric site[4] (this figure is directly taken from *Nat. Rev. Drug Discov.* **2004**, *3*, 301)

A practical way to predict protein function is through the identification of the binding partners. Since the majority of protein chores in living cells are mediated by protein-protein interactions, if the function of at least one of the components with which the protein interacts is identified, it is then expected to facilitate its functional and the pathway assignment. Through the network of protein-protein interactions, we can map cellular pathways and their intricate cross-connectivity.[7] For example, two protein partners cannot simultaneously bind at the same (or overlapping) site, the discovery of the ways in which proteins associate can also assist in the inferring dynamic regulation. The identification of protein-protein interactions is at the heart of functional genomics. The prediction of protein-protein interactions is also crucial for developing the drug discovery program. The knowledge of the signaling pathways and its topology, length, and dynamics should provide useful information in forecasting the side effects.[1b]

3.2. Importance of Macrocycles

Macrocycles are small molecules having ring size of 12 or more atoms. Macrocycles are pre-organized ring structures which are having stereochemical complexity and diverse functionality within the molecule.[8] These characteristics provides high affinity and selectivity for protein targets. The approved macrocyclic drugs which are in market,[9] mostly derived from natural products, for example erythromycin (**F4.1**)[10], rifampicin (**F2.9**)[11] and avermectin (**F2.10**)[12] *etc*. More than 70 macrocycles are presently in the market as drugs, which derived from natural products that are bacteria, fungi and plants.[9] There are some literature examples which shows the advantage of cyclic over acyclic molecules.[13] There are four types of the structural diversity in literature and these are: i) appendage diversity ii) functional group diversity iii) stereochemical diversity, and iv) skeletal diversity.[14]

Macrocycles possess a lower number of rotatable bonds and more conformationally restricted than their acyclic analogs, topologically macrocycles have the unique ability to span large surface areas while remaining conformationally restricted compared to molecules of equivalent molecular weight.[8b] Macrocyclic drugs are available primarily from two sources, one of them is natural products and some specific examples include epothilone (**F2.1)**[15] ixabepilone (**F2.2**),[16] rapamycin (**F2.3**),[17] bicyclomycin (**F2.4**),[18]

geldanamycin (**F2.5**, **F2.6**),[19] kendomycin (**F2.7**)[20] and cryptophycin (**F2.8**)[21] *etc*. (see **Figure 2**).

Figure 2: Biologically Active Natural Products

The second source of macrocyclic compounds is the synthetic, they may be peptides or natural product-like small molecules. The use of drug-like macrocycles is emerging as an exciting area in medicinal chemistry.[22] With the increasing awareness of concepts of drug-likeness and the dangers of 'molecular obesity', the functionalized macrocyclic scaffolds have the potential in providing a way to generating ligand-efficient molecules with enhanced biological and pharmacokinetic properties.[22a]

Figure 3: Synthetic Bioactive Macrocycles[22a]

Shown in **Figure 3** are some synthetic macrocycles which are in clinical trials and these are for example: (i) a dual JAK2/FLT3 inhibitor pacritinib (**F3.1**)[23] in phase II trials, (ii) SB1317 (**F3.2**)[24] the CDK2/JAK2/FLT3 inhibitor in phase I trial, (iii) cilengitide (**F3.3**)[25] a synthetic cyclic peptide in phase III trials for the treatment of glioblastoma and (iv) the Pan-CDK inhibitor Compound M (**F3.4**)[26] in further development.

3.3. 14-Membered Macrocycles

There are several biologically active natural products which are having 14-membered macrocyclic ring structure, for example erythromycin (**F4.1**),[27] cytochalasins (**F4.2**),[28] migrastatin (**F4.3**)[29] and amphidinolide V (**F4.4**).[30]and these compounds are isolated from different types of natural sources.

Erythromycin is medicinally important macrolide antibiotic produced by a strain of *Streptomyces erythreus.*[31] It contains a 14-membered lactone ring with ten chiral centers and two sugars L-cladinise and D-desosamine. The first total synthesis of erythromycin was reported by Woodword and co-workers in 1981.[10]

Cytochalasans (**F4.2**) is a group of fungal polyketide amino acid hybrid metabolites with a wide range of biological functions.[32] Cytochalasins A and B were isolsted from *Phoma* strain S 298, and *Helminthosporium dematioideum* respectively.[33] These are characterized by a highly substituted perhydro-isoindolone moiety to which typically a macrocyclic ring either a carbocycle, a lactone or a cycle carbonate is fused.[32] Cytochalasans specifically interact with the actin filament network by capping the barbed ends , and thereby altering the dynamic properties of microfilaments.[34]

Migrastatin (**F4.3**) is a 14-membered macrolide isolated from two different strains of *Streptomyces*, inhibits human tumor cell migration.[29a] It was first isolated from cultures of *Streptomyces* sp. MK929-43F1, then from strain NRRL 18993 in 2002.[35]

Amphidinolide V (**F4.4**) is one of the member of amphidinolide family extracted from marine dinoflagellate *Amphidinium* strain Y-5.[36] This cytotoxic polyene macrolide contains four exomethylene groups decorating the 14-membered ring.[37]

Figure 4: Biologically Active 14-membered Macrocycles.

3.4. Tetrahydrofuran Ring Containing Macrocycles

Here, I am showing a few natural products (see **Figure 5**) which are having tetrahydrofuran ring as an important part of their macrocyclic strucutral architecutres. Eribulin (**F5.1**)[38] is a synthetic analog of the marine natural product halichondrin B[39] and is approved for the treatment of metastatic breast cancer by FDA (Food and Drug

Administration) in November 2010.[40] It interferes with the microtubule dynamics by inhibiting the growth of microtubules and by sequestering tubulin into non-productive aggregates, it contains two tetrahydrofuran rings within the molecule.[41]

The haterumalides (**F5.2**)[42] which are also having a tetrahydrofuran ring, are a series of chlorinated macrolides isolated from an Okinawan sea sponge of the species *Ircinia*.[43] Amphidinolides are a family of biologically active macrolides and many of them exhibit potent antitumor activity against murine lymphoma L1210 and human carcinoma KB cells.[44] These compounds are isolated from cultured symbiotic dinoflagellate *Amphidinium* species.[45]

Amphidinolide E (**F5.3**)[46] is a unique 18-membered macrolide isolated from Y-5 strain of *Amphidinium* sp. and Amphidinolide F (**F5.4**)[47] is most complex and densely functionalized compound in this family. this is a 25-membered macrolactone and it contain eleven stereogenic centers and two *trans* fused tetrahydrofuran rings. Amphidinolide E (**F5.3**) is a 18-membered macrolactone and contains eight stereogenic centers and one *cis* fused tetrahydrofuran ring.[48]

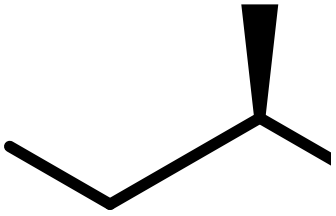


Figure 5: Macrocycles with Tetrahydrofuran Ring

3.5. Working Hypothesis

In particular, the interest in accessing functionalized large ring derivatives (i.e., macrocyclic compounds) is growing due to several reasons, and, these are: (i) medium-to-large ring structures present an opportunity to map a large surface area to interact with protein targets, (ii) the pre-organization in large rings allow several functional groups to display in specific orientations, (iii) cyclic compounds, in general, known to exhibit better cell permeation properties.[49] Despite all of these attractive features that large rings offer, and, having an excellent track record of several macrocyclic natural products as drugs, the full potential of this area remains to be explored thoroughly.[50] One of the challenges in this arena is the development of synthesis methods that are modular, and, practical in nature, and, that would allow an access to different types of functionalized medium to large rings. With this objective, we designed different types of 14-membered macrocycles using some of the key fragments from our second chapter.

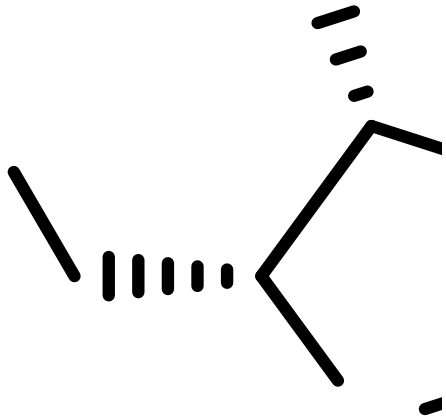
3.6. Results and Discussion

Our goal was to develop modular approches in obtaining different types of macrocyclic architectures to explore their biological properties. Utilizing some of our fragments that we discussed in **Chapter 2** as the key building blocks (**Chapter 2, Scheme 9 and 10**), our plan is to design the synthesis of different macrocyclic compounds that are having 14-membered rings (see **Figure 6**). One of the key features in all our designs is the presence of an amino acid moiety in the macrocyclic ring that can allow us exploring the use of various chiral side chains ranging from non-polar to polar groups.

Figure 6: Our Macrocyclic Designs

3.7. Synthesis of Key Fragments

The synthesis of the key fragments was started from **1.1, 1.2** & **1.3** (taken from **Chapter 2**). As a general approach, all the three fragments were subjected to vinylmagnesium bromide[51] in the presence of CuI and HMPA at -30 ^{o}C and this approach furnished olefinic compounds respectively. This was then followed by methylation of free hydroxyl groups in two cases, **1.1** and **1.2** and this completed the synthesis of key fragments **1.4**, **1.5** and **1.6 (Scheme 1)**.[52]



Scheme 1: Synthesis of Key Fragments

3.8. Retrosynthesis of Macrocycles F6.1 and F6.2

Retrosynthetic analysis of macrocycles **F6.1** and **F6.2** is shown in **Scheme 2**. The macrocyclic ring formation was planned to achieve by the ring closing metathesis approach (RCM) for obtaining **F6.1** or **F6.2** from **2.1 and 2.1.**[1] This could be obtained from the primary alcohol **2.2** and **2.2**[1] which can be easily prepared from the benzyl protected compounds, **2.3** and **2.3**[1].

Scheme 2: Retrosynthesis of Macrocycles **F6.1** and **F6.2**

3.9. Synthesis of Macrocycle F6.1

We started the synthesis of a macrocyclic compound from **1.4** having 1,3-*trans* groups at C-29 and C-32. The debenzylation using 2.0 equivalents of $TiCl_4$ in DCM at room temperature, gave the corresponding alcohol,[53] which was then subjected to a coupling with different *N*-alloc amino acid building blocks using EDCI, DMAP in DCM at room temperature. This pathway afforded **3.1a-3.1d** and various amino acids, such as phenylalanine, isoluecine, valine and pipecolic acid were utilized in this approach. Finally, the ring closing metathesis with Grubbs' 2nd generation catalyst (**3.2**) using 10 mol% at 0.001 mM dilution in DCM afforded the macrocycles **F6.1a** to **F6.1d**. In one macrocyclic case study, an olefin geometry was assigned as *trans* by NMR. In this series, we synthesized four macrocycles and their structures are shown in **Figure 7**.

Scheme 3: Synthesis of Macrocycles **F6.1a-F6.1d**

Figure 7: Derivatives of Macrocycle **F6.1**

3.10. Synthesis of Macrocycle F6.2

In a similar approach, I also synthesized four macrocycles (**F6.2a-F6.2d**) using *N*-alloc protected phenylalanine, leucine, D-proline and pipecolic acid respectively in which we utilized compound **1.6** having 1,3 *cis* relationship for the groups at C-29 and C-32 as the starting material and it is shown in **Figure 8**.

Scheme 4: Synthesis of Macrocycles **F6.2a-F6.2d**

Figure 8: Derivatives of Macrocycle **F6.2**

3.11. Retrosynthesis of Macrocycles F6.3

For this series, we started the synthesis of macrocycle **F6.3** from the fragment **1.6**, and our retrosynthetic planning is shown in **Scheme 5** . The fully de-protected version of the macrocyclic compound **F6.3** was then obtained by Pd/C in EtOAc condition from **5.1**. The macrocycle **5.1** can be obtained from **5.2** using the ring closing metathesis approach. The amino acid building block coupled product **5.2** could be prepared from **1.6** by the TBDPS removal with TBAF.

Scheme 5: Retrosynthesis of Macrocycle **F6.3**

3.12. Synthesis of Macrocycle F6.3

Using another fragment **1.6** having 1,3-*cis* relationship between groups at C-29 and C-32, we designed another two series of macrocycles **F6.3** and **F6.4**. In this approach,

we first started with the TBDPS removal of **1.6** using TBAF in THF at room temperature. This was then coupled with different *N*-alloc amino acid building blocks using EDCI and DMAP in DCM to access **6.1a-6.1d**. The ring closing metathesis approach using Grubbs' 2nd generation catalyst in 0.001mM DCM as a solvent furnished the desired macrocycles, **6.2a-6.2a**. Finally, we succeeded the hydrogenation approach (Pd/C) in this series for the benzyl removal and the double bond reduction to provide us with fully deprotected and reduced macrocycles **F6.3a-F6.3d** as shown in **Scheme 6**.

Scheme 6: Synthesis of Macrocycles **F6.3a-F6.3d**

Figure 9: Derivatives of Macrocycle **F6.3**

3.13. Retrosynthesis of Macrocycle F6.4

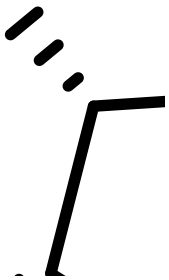
We started the synthesis of macrocycle **F6.4** from the fragment **1.6**, and the retrosynthetic analysis of macrocycle **F6.4** is shown in **Scheme 7**. The fully deprotected version of macrocycle **F6.4** could be achieved by Pd/C in EtOAc conditions. The macrocycle **7.1** could be obtained from **7.2** using the ring closing metathesis strategy. The amino acid building block coupled product **7.2** could be prepared from **1.6** by TBDPS removal with TBAF and methylation of obtained alcohol followed by debenzylation with $TiCl_4$.

Scheme 7: Retrosynthesis of Macrocycle **F6.4**

3.14. Synthesis of Macrocycle F2.4

Further, we tried to stitch the amino acid building blocks from the down side of the **1.6**. For this we tried to remove the benzyl group in presence of TBDPS with $TiCl_4$, $SnCl_4$ and Na/Liq.NH_3 but TBDPS also coming off with $TiCl_4$ and $SnCl_4$ whereas with the use of Na/Liq.NH_3, the starting material remains the same. Because of this unsuccessful attemptt for the benzyl group deprotection, we then decided to remove TBDPS group with TBAF to obtain a primary alcohol. It was further methylated in NaH, DMF conditions using methyl iodide to furnish **8.1** in 80% yield. Then, we removed the benzyl group with $TiCl_4$ in DCM which was followed by a coupling of amino acid building blocks with EDCI, DMAP conditions producing **8.2a** and **8.2b**.

Finally, the ring closing metathesis with Grubbs' 2nd generation catalyst for building the macrocyclic compounds, further hydrogenation with Pd/C, H_2 conditions in EtOAc gave macrocycles **F6.4a and F6.4b** with the fully reduced version.



Scheme 8: Synthesis of Macrocycles **F6.4a and F6.4b**

Figure 10: Derivatives of Macrocycles **F6.4**

3.15. Experimental Procedures

(2R,3R,4R,5R)-5-allyl-2-(benzyloxymethyl)-4-(phenylsulfonylmethyl)tetrahydrofuran-3-ol (1.1.1):

To a stirred solution of compound **1.1** (500 mg, 0.793 mmoles) in dry THF (5 mL) was added CuI (75 mg, 0.396 mmoles) and HMPA (1.41 mL, 7.93 mmoles) at 23 ^{o}C. Then the reaction mixture temperature was bring to -30 ^{o}C and added vinylmagnesium bromide dropwise. After stirring the reaction mixture 3 h at same temperature was quenched with saturated NH_4Cl solution and extracted with ethylacetate (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (7:3 Hexanes/ethylacetate) to provide **1.1.1** (300 mg) as white solid.

Molecular Formula: $C_{22}H_{26}O_5S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 402.8 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$ δ ppm 7.92-7.87 (m, 2H), 7.64-7.61 (m, 1H), 7.54 (t, *J* = 7.60 Hz, 2H), 7.38-7.27 (m, 5H), 5.66-5.55 (m, 1H), 5.16-5.10 (m, 2H), 4.53 (d, *J* = 1.45 Hz, 2H), 3.86-3.84 (m, 1H), 3.70 (dd, *J* = 14.29, 2.98 Hz, 1H), 3.62-3.57 (m, 2H), 3.48 (d, *J* = 8.72 Hz, 1H), 3.18 (dd, *J* = 14.30, 8.84 Hz, 1H), 2.95 (dq, *J* = 8.88, 2.89 Hz, 1H), 2.16-1.61 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 137.4, 135.8, 133.6, 129.1, 128.5, 128.0, 127.8, 119.3, 73.7, 73.2, 73.0, 68.4, 57.2, 42.4.

(2R,3S,4R,5R)-2-allyl-5-(benzyloxymethyl)-4-methoxy-3-(phenylsulfonylmethyl) tetrahydrofuran

(1.4):

To a stirred solution of **1.1.1** (320 mg) in DMF (20 mL) was added Ag_2O (2 eq), MeI (5 eq) at dark environment after stirring 16 h the reaction mixture was filtered through celite and extracted with ethylacetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hexanes/ethylacetate) to provide **1.4** (240 mg) as white solid.

Molecular Formula: $C_{23}H_{28}O_5S$

R_f: 0.6 (9:1 Hexanes/Ethylacetate);

LRMS (ES+) m/z = 417.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89-7.84 (m, 2H), 7.63-7.59 (m, 1H), 7.52 (t, *J* = 7.59 Hz, 2H), 7.36-7.27 (m, 5H), 5.75-5.62 (m, 1H), 5.13-5.06 (m, 2H), 4.51 (s, 2H), 3.62-3.52 (m, 3H), 3.44-3.39 (m, 1H), 3.37-3.36, (m, 6H), 3.30 (dd, *J* = 6.52, 3.21 Hz, 1H), 3.21 (dd, *J* = 14.28, 10.09 Hz, 1H), 3.05-2.98 (m, 1H).

^{13}CNMR (100 MHz,$CDCl_3$) δ 140.0, 137.7, 136.8, 133.4, 129.0, 128.3, 128.0, 127.7, 118.2, 82.6, 80.1, 73.4, 68.4, 60.7, 58.6, 56.8, 41.1, 29.6.

((2R,3R,4S,5R)-5-Allyl-3-methoxy-4-(phenylsulfonylmethyl)tetrahydrofuran-2-yl)methanol

(1.4.1):

To a stirred solution of **1.4** (250 mg, 0.664 mmol) in DCM (100 mL) was added $TiCl_4$ (0.14 mL, 1.329 mmol) and stirred for 3 h at room temperature, after consumption of complete starting material was quenched with saturated NH_4Cl and extracted with DCM (3×50 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **1.4.1** (150 mg) as colorless oil.

Molecular Formula: $C_{16}H_{22}O_5S$

R_f: 0.35 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 327.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91-7.87 (m, 2H), 7.63 (t, *J* = 7.43 Hz, 1H), 7.54 (t, *J* = 7.55 Hz, 2H), 5.73 (dt, *J* = 17.16, 8.85 Hz, 1H), 5.11-5.06 (m, 2H), 3.75 (dd, *J* = 11.52, 5.02 Hz, 1H), 3.67 (dd, *J* = 11.53, 4.41 Hz, 1H), 3.49 (dd, *J* = 14.40, 2.93 Hz, 1H), 3.42 (d, *J* = 7.78 Hz, 6H), 3.32 (dt, *J* = 9.56, 9.31, 4.49 Hz, 2H), 3.22 (dd, *J* = 14.38, 9.47 Hz, 1H), 3.04-2.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.0, 137.0, 133.6, 129.1, 128.0, 118.0, 83.6, 81.5, 60.9, 60.4, 58.5, 56.6, 40.7, 30.9, 29.6.

(3.1a-3.1d):

To a stirred solution of **1.4.1** (30 mg) in DCM (20 mL) was added EDCI (2 eq), DMAP (2 eq) and Alloc-AA (2 eq) the reaction was stirred for 3 h at room temperature, after consumption of complete starting material was quenched with water and extracted with DCM. The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (7:3 Hexanes/ethylacetate) to provide **3.1a-3.1d** (35 mg) as colorless oil.

3.1a:

Molecular Formula: $C_{25}H_{35}NO_8S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 510.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89-7.87 (m, 2H), 7.64-7.60 (m, 1H), 7.55-7.52 (m, 2H), 5.94-5.84 (m, 1H), 5.74-5.63 (m, 1H), 5.34-5.17 (m, 3H), 5.10 (dd, *J* = 13.83, 2.73 Hz, 2H), 4.55 (d, *J* = 5.57 Hz, 2H), 4.29-4.19 (m, 3H), 3.55-3.45 (m, 2H),

3.40-3.38 (m, 6H), 3.25-3.18 (m, 2H), 3.06-3.01 (m, 1H), 2.18-2.09 (m, 1H), 0.97 (d, *J* = 6.84 Hz, 3H), 0.89 (d, *J* = 6.87 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.8, 156.0, 140.0, 136.4, 133.6, 132.5, 129.1, 128.0, 118.6, 117.8, 82.3, 79.0, 65.8, 63.7, 60.5, 59.0, 58.9, 56.7, 40.9, 31.1, 19.0, 17.5.

3.1b:

Molecular Formula: $C_{26}H_{37}NO_8S$

R_f: 0.5 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 524.6 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (d, *J* = 7.69 Hz, 2H), 7.63 (t, *J* = 7.39 Hz, 1H), 7.54 (t, *J* = 7.71 Hz, 2H), 5.95-5.84 (m, 1H), 5.75-5.63 (m, 1H), 5.34-5.18 (m, 3H), 5.11 (dd, *J* = 13.59, 2.64 Hz, 2H), 4.55 (d, *J* = 5.43 Hz, 2H), 4.34-4.19 (m, 3H), 3.56-3.45 (m, 2H), 3.41-3.39 (m, 5H), 3.25-3.17 (m, 2H), 3.08-3.02 (m, 1H), 1.83-1.79 (m, 2H), 1.46-1.35 (m, 1H), 1.23-1.12 (m, 1H), 0.94-0.89 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.8, 155.9, 140.0, 136.4, 133.6, 132.5, 129.1, 128.0, 118.6, 117.9, 82.3, 79.0, 65.8, 63.7, 60.5, 59.0, 58.3, 56.7, 40.9, 37.8, 30.9, 29.6, 24.9, 15.5, 11.5.

3.1c:

Molecular Formula: $C_{27}H_{31}NO_8S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 530.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (d, *J* = 7.97 Hz, 2H), 7.65-7.61 (m, 1H), 7.54 (t, *J* = 7.57 Hz, 2H), 7.32-7.21 (m, 4H), 7.13 (t, *J* = 8.01 Hz, 2H), 5.91-5.81 (m, 1H), 5.69-5.48 (m, 1H), 5.31-5.04 (m, 5H), 4.60-4.52 (m, 3H), 4.29-4.06 (m, 2H), 3.81-3.64 (m, 1H), 3.57-3.26 (m, 4H), 3.24-2.93 (m, 5H), 2.16 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.5, 155.6, 139.8, 136.0, 133.7, 132.5, 129.2, 128.7, 128.1, 128.0, 127.2, 119.6, 119.0, 117.9, 81.6, 72.3, 69.0, 65.9, 64.4, 60.6, 58.9, 57.5, 56.6, 54.9, 42.5, 41.2, 38.2.

3.1d:

Molecular Formula: $C_{24}H_{31}NO_8S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 494.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87 (d, *J* = 7.43 Hz, 2H), 7.62 (t, *J* = 7.34 Hz, 1H), 7.53 (t, *J* = 7.57 Hz, 2H), 5.96-5.81 (m, 1H), 5.73-5.61 (m, 1H), 5.34-5.07 (m, 4H), 4.95-4.82 (m, 1H), 4.58-4.56 (m, 2H), 4.31 (dd, *J* = 11.36, 5.87 Hz, 1H), 4.24-4.14 (m, 1H), 4.13-3.98 (m, 1H), 3.56-3.43 (m, 2H), 3.38-3.36 (m, 6H), 3.26-3.16 (m, 2H), 3.06-3.04 (m, 2H), 2.24-2.14 (m, 1H), 1.85-1.57 (m, 4H), 1.50-1.35 (m, 1H), 1.28-1.20 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.3, 156.2, 140.0, 136.4, 133.6, 132.7, 129.1, 128.0, 118.7, 117.4, 82.3, 78.9, 66.2, 63.4, 60.6, 58.9, 56.8, 54.2, 41.8, 41.7, 41.0, 26.6, 24.6, 20.6.

(F6.1a-F6.1d):

To a stirred solution of **3.1a-3.1d** (30 mg) in DCM (100 mL) was added Grubbs-II catalyst (**3.2**, 10 mol%), the reaction was stirred for 16 h at 40 ^{o}C, after consumption of complete starting material was concentrated under reduced pressure and the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **F6.1a-F6.1d** (18-20 mg) as colorless oil.

F6.1a:

Molecular Formula: $C_{23}H_{31}NO_8S$

R_f: 0.2 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 482.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (d, *J* = 7.47 Hz, 2H), 7.67-7.62 (m, 1H), 7.56 (d, *J* = 7.72 Hz, 2H), 5.88-5.82, (m, 1H), 5.75-5.64 (m, 1H), 5.30-5.22 (m, 1H), 5.13-5.09 (m, 2H), 4.57 (bs, 2H), 4.33-4.19, (m, 3H), 3.54-3.48 (m, 2H), 3.42-3.40 (m, 5H), 3.25-3.19 (m, 2H), 3.10-3.02 (m, 1H), 2.20-2.10 (m, 1H), 0.98 (d, *J* = 6.80 Hz, 3H), 0.90 (d, *J* = 6.56 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.8, 155.9, 140.0, 136.4, 133.6, 129.2, 128.1, 128.0, 118.7, 82.3, 78.9, 64.6, 63.7, 60.5, 59.0, 56.7, 53.4, 40.9, 31.9, 31.1, 29.7, 29.6, 29.3, 22.7, 19.0, 17.5, 14.1.

F6.1b:

Molecular Formula: $C_{24}H_{33}NO_8S$

R_f: 0.25 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 496.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.65-7.61 (m, 1H), 7.57-7.52 (m, 2H), 7.38-7.37 (m, 1H), 7.33-7.30 (m, 1H), 5.76-5.64 (m, 1H), 5.37-5.24 (m, 1H), 5.18-5.10 (m, 2H), 4.73 (d, *J* = 6.16 Hz, 1H), 4.38-4.19 (m, 3H), 3.55-3.46 (m, 2H), 3.44-3.38 (m, 5H), 3.24-3.19 (m, 2H), 3.11-3.02 (m, 1H), 1.94-1.82 (m, 1H), 1.75-1.70 (m, 2H), 0.96-0.89 (m, 6H).

F6.1c:

Molecular Formula: $C_{27}H_{31}NO_8S$

R_f: 0.1 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 530.6 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.92-7.84 (m, 2H), 7.70-7.60 (m, 1H), 7.56-7.53 (m, 2H), 7.34-7.28 (m, 3H), 7.187.17 (m, 2H), 6.02-5.38 (m, 2H), 5.05-4.25 (m, 4H), 3.76-3.38 (m, 5H), 3.33-2.74 (m, 5H), 2.35-1.58 (m, 5H).

F6.1d:

Molecular Formula: $C_{24}H_{31}NO_8S$

R_f: 0.2 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 494.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87 (d, *J* = 7.43 Hz, 2H), 7.64 (t, *J* = 7.43 Hz, 1H), 7.54 (t, *J* = 7.61 Hz, 2H), 5.99-5.53 (m, 2H), 4.84-4.55 (m, 1H), 4.45-3.75 (m, 4H), 3.52-2.97 (m, 12H), 2.91-2.75 (m, 1H), 2.25 (d, *J* = 13.73 Hz, 1H), 1.86-1.66 (m, 4H), 1.45-1.41 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.8, 143.4, 133.8, 129.3, 128.0, 128.0, 127.9, 110.0, 102.7, 84.9, 82.3, 62.1, 56.5, 36.8, 31.9, 31.4, 29.7, 25.7, 24.2, 22.7, 20.4, 14.1.

(2R,3R,4R,5S)-5-allyl-2-(benzyloxymethyl)-4-(phenylsulfonylmethyl) tetrahydrofuran-3-ol

(1.2.1):

To a stirred solution of compound **1.2** (500 mg, 0.793 mmoles) in dry THF (5 mL) was added CuI (75 mg, 0.396 mmoles) and HMPA (1.41 mL, 7.93 mmoles) at 23 ^{o}C. Then the reaction mixture temperature was bring to -30 ^{o}C and added vinylmagnesium bromide dropwise. After stirring the reaction mixture 3 h at same temperature was quenched with saturated NH_4Cl solution and extracted with ethylacetate (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (7:3 Hexanes/ethylacetate) to provide **1.2.1** (300 mg) as white solid.

Molecular Formula: $C_{22}H_{26}O_5S$

R_f: 0.5 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 403.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.87 (m, 2H), 7.66-7.60 (m, 1H), 7.53 (dd, *J* = 10.40, 4.69 Hz, 2H), 7.38-7.26 (m, 5H), 5.66-5.55 (m, 1H), 5.17-5.08 (m, 2H), 4.53 (d, *J* = 1.57 Hz, 2H), 3.87-3.84 (m, 1H), 3.70 (dd, *J* = 14.31, 3.01 Hz, 1H), 3.61-3.55 (m, 2H), 3.47 (dd, *J* = 8.72, 1.37 Hz, 1H), 3.18 (dd, *J* = 14.32, 8.86 Hz, 1H), 2.95 (dd, *J* = 8.91, 2.88 Hz, 1H), 2.28 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 137.4, 135.8, 133.6, 129.1, 128.5, 128.0, 127.8, 119.3, 73.7, 73.2, 73.0, 68.4, 57.2, 42.4.

(2S,3S,4R,5R)-2-Allyl-5-(benzyloxymethyl)-4-methoxy-3-(phenylsulfonylmethyl) tetrahydrofuran

(1.5):

To a stirred solution of **1.2.1** (320 mg) in DMF (20 mL) was added Ag_2O (2 eq), MeI (5 eq) at dark environment after stirring 16 h the reaction mixture was filtered through celite and extracted with ethylacetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hexanes/ethylacetate) to provide **1.5** (250 mg) as colorless oil.

Molecular Formula: $C_{22}H_{26}O_5S$

R_f: 0.6 (9:1 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 416.8 (M+1)

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.92-7.85 (m, 2H), 7.64-7.60 (m, 1H), 7.53 (t, *J* = 7.56 Hz, 2H), 7.38-7.27 (m, 5H), 5.66-5.54 (m, 1H), 5.14-5.10 (m, 2H), 4.54-4.48 (m, 2H), 3.71 (dd, *J* = 14.25, 2.66 Hz, 1H), 3.61 (dq, *J* = 9.93, 5.15 Hz, 2H), 3.52-3.35 (m, 6H), 3.16 (dd, *J* = 14.24, 9.31 Hz, 1H), 2.97 (dq, *J* = 9.08, 2.52 Hz, 1H), 2.57 (d, *J* = 7.96 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 137.8, 136.8, 133.5, 129.1, 129.1, 128.4, 128.1, 128.0, 127.8, 127.7, 118.3, 82., 80.0, 73.4, 68.4, 60.8, 58.7, 56.8, 41.2.

((2R,3R,4S,5S)-5-allyl-3-methoxy-4-(phenylsulfonylmethyl)tetrahydrofuran-2-yl)methanol

(1.5.1):

To a stirred solution of **1.5** (250 mg, 0.664 mmol) in DCM (100 mL) was added $TiCl_4$ (0.14 mL, 1.329 mmol) and stirred for 3 h at room temperature, after consumption of complete starting material was quenched with saturated NH_4Cl and extracted with DCM (3×50 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **1.5.1** (150 mg) as colorless oil.

Molecular Formula: $C_{16}H_{22}O_5S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 327.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87-7.85 (m, 2H), 7.64-7.60 (m, 1H), 7.56-7.51 (m, 2H), 5.71 (td, *J* = 17.19, 8.92 Hz, 1H), 5.10-5.05 (m, 2H), 3.05-2.95 (m, 1H), 3.77-3.69 (m, 1H), 3.69-3.62 (m, 1H), 3.49 (dd, *J* = 14.40, 2.90 Hz, 1H), 3.41-3.38 (m, 5H), 3.31 (dt, *J* = 9.41, 4.35 Hz, 2H), 3.22 (dd, *J* = 14.39, 3.02-3.95 (m, 1H), 9.59 Hz, 1H), 2.17 (bs, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.9, 136.9, 133.6, 129.2, 128.0, 118.1, 83.5, 81.4, 60.9, 60.5, 58.5, 56.6, 40.8, 29.7.

(4.1a-4.1d):

To a stirred solution of **1.5.1** (30 mg) in DCM (20 mL) was added EDCI (2 eq), DMAP (2 eq) and Alloc-AA (2 eq) the reaction was stirred for 3 h at room temperature, after consumption of complete starting material was quenched with water and extracted with DCM (3×30 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (7:3 Hexanes/ethylacetate) to provide **4.1a-4.1d** (35 mg) as colorless oil.

4.1a:

Molecular Formula: $C_{29}H_{35}NO_8S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 558.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.88 (d, *J* = 7.23 Hz, 2H), 7.65-7.61 (m, 1H), 7.56-7.52 (m, 2H), 7.34-7.21 (m, 4H), 7.13 (s, 1H), 5.92-5.82 (m, 1H), 5.71-5.59 (m, 1H), 5.31-5.16 (m, 3H), 5.15-5.08 (m, 2H), 4.62 (dd, *J* = 14.26, 6.35 Hz, 1H), 4.54 (d, *J* = 5.56 Hz, 3H), 4.20 (d, *J* = 5.91 Hz, 2H), 3.50 (dd, *J* = 14.15, 2.50 Hz, 1H), 3.37-3.35 (m, 3H), 3.33 (s, 3H), 3.24-3.01 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.4, 155.5, 140.0, 136.4, 135.5, 133.6, 132.5, 129.3, 129.3, 129.2, 128.7, 128.0, 127.3, 118.7, 117.9, 110.0, 82.2, 78.8, 65.9, 64.0, 60.5, 59.0, 56.8, 54.8, 40.9, 38.2, 29.7, 29.6.

4.1b:

Molecular Formula: $C_{26}H_{37}NO_8S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 524.6 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.92-7.86 (m, 2H), 7.66-7.60 (m, 1H), 7.55-7.52 (m, 2H)5.95-5.82 (m, 1H), 5.74-5.51 (m, 1H), 5.33-5.24 (m, 1H), 5.22-5.07 (m, 4H), 4.54-4.53 (m, 2H), 4.37-4.28 (m, 1H), 4.28-4.22 (m, 1H), 4.19-4.09 (m, 1H), 3.68 (dd, *J* = 14.24, 2.42 Hz, 1H), 3.55-3.32 (m, 5H), 3.26-3.12 (m, 2H), 3.07-2.94 (m, 1H), 2.47-2.42 (m, 1H), 1.74-1.47 (m, 4H), 0.92 (dd, *J* = 6.41, 1.66 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.0, 155.9, 140.0, 136.0, 133.6, 132.5, 129.2, 128.0, 119.6, 117.8, 81.7, 72.3, 69.1, 65.9, 64.1, 60.7, 58.9, 57.5, 56.5, 52.5, 42.5, 41.2, 29.7, 24.7, 22.8, 21.7, 14.1.

4.1c:

Molecular Formula: $C_{25}H_{33}NO_8S$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 508.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90-7.88 (m, 2H), 7.63-7.61 (m, 1H), 7.59-7.51 (m, 2H), 5.98-5.80 (m, 1H), 5.63-5.53 (m, 1H), 5.35-5.05 (m, 4H), 4.61-4.54 (m, 2H),

4.41-4.15 (m, 3H), 3.62-3.35 (m, 7H), 3.25-3.13 (m, 2H), 3.06-2.98 (m, 1H), 2.42-2.13 (m, 2H), 2.01-1.90 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.4, 154.7, 136.0, 132.7, 129.1, 128.0, 118.8, 117.4, 81.9, 72.2, 68.9, 66.0, 60.5, 58.8, 56.6, 46.4, 42.6, 41.3, 30.9, 29.7, 24.5, 24.4, 23.5.

4.1d:

Molecular Formula: $C_{27}H_{37}NO_8S$

R_f: 0.3 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 536.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.93-7.88 (m, 2H), 7.72-7.51 (m, 3H), 5.99-5.81 (m, 1H), 5.73-5.49 (m, 1H), 5.41-5.05 (m, 4H), 4.95-4.84 (m, 1H), 4.58-4.57 (m, 2H), 4.35-4.17 (m, 2H), 4.10-3.99 (m, 2H), 3.72-3.31 (m, 4H), 3.28-2.89 (m, 3H), 2.26-1.98 (m, 3H), 1.69-1.66 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.0, 139.7, 135.9, 132.7, 129.2, 129.1, 128.0, 119.6, 117.4, 110.0, 81.7, 72.3, 66.2, 63.5, 57.4, 56.5, 54.5, 54.3, 53.1, 41.8, 41.2, 29.6, 29.6, 26.6, 24.6, 22.6, 20.6, 20.6, 20.6, 14.1.

(F6.6a-F6.2d):

To a stirred solution of **4.1a-4.1d** (30 mg) in DCM (100 mL) was added Grubbs-II catalyst (10 mol%), the reaction was stirred for 16 h at 40 ^oC, after consumption of complete starting material was concentrated under reduced pressure and the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **F6.2a-F6.2d** (20 mg) as colorless oil.

F6.2a:

Molecular Formula: $C_{27}H_{31}NO_8S$

R_f: 0.2 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 530.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89-7.84 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.52 (m, 2H), 7.34-7.27 (m, 3H), 7.18 (d, *J* = 6.73 Hz, 2H), 5.72-5.63 (m, 1H), 5.58-5.49 (m, 1H), 4.98-4.90 (m, 1H), 4.76-4.67 (m, 1H), 4.42-4.27 (m, 1H), 4.12-4.02 (m, 1H), 3.73-3.63 (m, 2H), 3.40-3.34 (m, 2H), 3.26-3.10 (m, 3H), 2.99-2.87 (m, 3H), 1.61 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.6, 155.8, 133.6, 129.2, 129.0, 128.9, 128.9, 128.1, 127.5, 114.1, 113.8, 83.3, 59.1, 56.9, 56.4, 36.5, 31.9, 29.7, 22.7, 14.1.

F6.2b:

Molecular Formula: $C_{27}H_{31}NO_8S$

R_f: 0.25 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 596.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90-7.87 (m, 2H), 7.65-7.61 (m, 1H), 7.57-7.53 (m, 2H), 5.79-5.54 (m, 2H), 5.20-4.99 (m, 1H), 4.91 (d, *J* = 5.99 Hz, 1H), 4.86-4.78 (m, 1H), 4.72 (dd, *J* = 12.92, 6.22 Hz, 1H), 4.12-4.06 (m, 1H), 4.03-3.99 (m, 1H), 3.82 (dd, *J* = 14.23, 2.19 Hz, 1H), 3.61-3.55 (m, 1H), 3.47 (m, 3H), 3.23-3.12 (m, 2H), 2.83-2.73 (m, 1H), 2.09-2.02 (m, 1H), 1.76-1.45 (m, 4H), 0.95-0.90 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.2, 155.8, 140.1, 133.6, 133.6, 129.7, 129.2, 128.0, 128.0, 122.0, 114.0, 74.5, 63.3, 58.7, 57.2, 54.4, 40.1, 39.6, 29.7, 24.8, 22.7, 21.6.

F6.2c:

Molecular Formula: $C_{23}H_{29}NO_8S$

R_f: 0.1 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 480.6 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91-7.83 (m, 2H), 7.66-7.61 (m, 1H), 7.59-7.51 (m, 2H), 5.03-4.89 (m, 1H), 4.79-4.71 (m, 1H), 4.63-4.40 (m, 1H), 4.36-4.04 (m, 2H), 3.70-3.35 (m, 7H), 3.27-3.13 (m, 1H), 3.04-2.88 (m, 1H), 2.78-2.57 (m, 1H), 2.36-

2.19 (m, 1H), 2.09-1.82 (m, 4H), 1.77-1.55 (m, 2H), 6.00-5.78 (m, 1H), 5.76-5.40 (m, 2H).

F6.2d:

Molecular Formula: $C_{24}H_{31}NO_8S$

R_f: 0.1 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 494.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87-7.85 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.52 (m, 2H), 5.85-5.44 (m, 2H), 5.16-4.62 (m, 3H), 4.54-4.42 (m, 1H), 4.23-3.78 (m, 3H), 3.64 (d, *J* = 2.11 Hz, 1H), 3.51-3.35 (m, 5H), 3.27-3.13 (m, 2H), 3.00-2.83 (m, 3H), 2.34-2.07 (m, 1H), 1.79-1.60 (m, 4H), 1.49-1.38 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.3, 142.7, 133.6, 129.1, 128.1, 128.1, 128.0, 110.0, 63.2, 57.0, 55.4, 41.3, 31.9, 29.7, 29.6, 29.6, 29.3, 26.0, 24.3, 24.3, 24.3, 24.2, 22.7, 20.4, 14.1.

(2-((2S,3S,4R,5R)-2-allyl-5-(benzyloxymethyl)-4-methoxytetrahydrofuran-3-yl)ethoxy)(tert-butyl)diphenylsilane

(1.6):

To a stirred solution of compound **1.3** (500 mg, 0.793 mmoles) in dry THF (5 mL) was added CuI (75 mg, 0.396 mmoles) and HMPA (1.41 mL, 7.93 mmoles) at 23 ^oC. Then the reaction mixture temperature was bring to -30 ^oC and added vinylmagnesium bromide dropwise. After stirring the reaction mixture 3 h at same temperature was quenched with saturated NH_4Cl solution and extracted with ethylacetate (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (7:3 Hexanes/ethylacetate) to provide **1.6** (320 mg) as colorless oil.

Molecular Formula: $C_{34}H_{44}O_4Si$

R_f: 0.3 (9.5:0.5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 544.8 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69 (d, *J* = 6.68 Hz, 4H), 7.43-7.28 (m, 11H), 5.69-5.57 (m, 1H), 5.08-5.01 (m, 2H), 4.55 (s, 2H), 3.92-3.85 (m, 1H), 3.77-3.69 (m, 1H), 3.65 (dd, *J* = 16.50, 8.33 Hz, 1H), 3.57-3.49 (m, 2H), 3.44 (s, 3H), 3.17 (dd, *J* = 6.80, 2.64 Hz, 1H), 2.68-2.61 (m, 1H), 2.38-2.35 (m, 1H), 1.56-1.44 (m, 1H), 1.98-1.88 (m, 1H), 1.07 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 133.3, 130.8, 129.2, 124.8, 123.7, 123.0, 123.0, 122.8, 112.3, 78.5, 68.6, 66.9, 65.4, 57.1, 55.5, 37.5, 28.0, 22.2, 22.1, 14.5.

2-((2S,3S,4R,5R)-2-allyl-5-(benzyloxymethyl)-4-methoxytetrahydrofuran-3-yl)ethanol

(1.6.1):

To a stirred solution of **1.6** (500 mg) in THF (50 mL) was added TBAF (2 eq), the reaction was stirred for 3 h at rt, after consumption of complete starting material was concentrated under reduced pressure and the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **1.6.1** (245 mg) as colorless oil.

Molecular Formula: $C_{18}H_{26}O_4$

R_f: 0.5 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 307.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38-7.27 (m, 5H), 5.71-5.59 (m, 1H), 5.10-5.08 (m, 2H), 4.58-4.49 (m, 2H), 3.71-3.64 (m, 1H), 3.64-3.53 (m, 3H), 3.49-3.43 (m, 4H), 3.41 (s, 3H), 3.18 (dd, *J* = 7.98, 3.05 Hz, 1H), 2.62-2.53 (m, 1H), 1.97-1.86 (m, 2H), 1.57-1.46 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.4, 137.9, 128.4, 127.7, 117.0, 78.9, 74.5, 73.5, 71.5, 70.0, 60.9, 58.4, 45.2, 34.2.

(6.1a-6.1d):

To a stirred solution of **1.6.1** (60 mg, 0.196 mmol, 1 eq) in DCM (30 mL) was added EDCI (0.392 mmol, 2 eq), DMAP (0.392 mmol, 2 eq) and Alloc-AA (0.392 mmol, 2 eq)the reaction was stirred for 3 h at room temperature, after consumption of complete starting material was quenched with water and extracted with DCM (3×20 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (7:3 Hexanes/ethylacetate) to provide **6.1a-6.1d** (85 mg) as colorless oil.

6.1a:

Molecular Formula: $C_{31}H_{39}NO_7$

R_f: 0.5 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 538.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38-7.23 (m, 8H), 7.12 (d, *J* = 6.79 Hz, 2H), 5.93-5.83 (m, 1H), 5.59-5.46 (m, 1H), 5.32-5.03 (m, 6H), 4.66-4.50 (m, 6H), 4.23-4.17 (m, 1H), 4.08-4.01 (m, 1H), 3.68 (dd, *J* = 9.95, 5.29 Hz, 1H), 3.60 (dd, *J* = 9.96, 4.76 Hz, 1H), 3.46-3.41 (m, 4H), 3.10 (dq, *J* = 13.95, 6.01 Hz, 2H), 2.49 (d, *J* = 7.42 Hz, 1H), 2.38 (dq, *J* = 10.68, 10.48, 3.09 Hz, 1H), 2.22-2.11 (m, 1H), 1.79 (bs, 1H), 1.56-1.47 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.5, 155.5, 138.3, 137.9, 135.8, 132.6, 129.3, 128.6, 128.4, 127.8, 127.8, 127.7, 127.1, 118.1, 117.8, 78.6, 74.3, 73.6, 69.9, 65.8, 64.0, 58.4, 54.8, 44.9, 38.2, 29.2.

6.1b:

Molecular Formula: $C_{28}H_{41}NO_7$

R_f: 0.4 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 504.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38-7.27 (m, 5H), 5.90 (ddd, *J* = 22.68, 10.81, 5.61 Hz, 1H), 5.56 (td, *J* = 17.13, 9.94 Hz, 1H), 5.34-5.25 (m, 1H), 5.21-5.01 (m, 4H), 4.58-4.52 (m, 4H), 4.35 (dt, *J* = 8.86, 5.33 Hz, 1H), 4.20-4.15 (m, 1H), 4.07-3.98 (m, 1H), 3.66-3.57 (m, 2H), 3.48-3.41 (m, 4H), 3.40 (s, 3H), 3.16 (dd, *J* = 8.35, 2.50 Hz, 1H), 2.56 (dt, *J* = 11.30, 3.00 Hz, 1H), 2.12-2.02 (m, 1H), 1.74-1.46 (m, 4H), 0.94-0.92 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.1, 155.8, 138.5, 138.0, 132.6, 128.4, 127.7, 117.7, 117.7, 83.3, 79.8, 73.4, 68.8, 65.7, 63.9, 60.8, 58.8, 52.5, 43.1, 41.9, 28.8, 24.7, 22.8, 21.9.

6.1c:

Molecular Formula: $C_{28}H_{41}NO_7$

R_f: 0.45 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 504.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37-7.26 (m, 5H), 5.90 (ddd, *J* = 22.71, 10.88, 5.64 Hz, 1H), 5.52 (dt, *J* = 19.80, 6.80 Hz, 1H), 5.35-5.25 (m, 2H), 5.24-5.02 (m, 4H), 4.59-4.51 (m, 4H), 4.31-427 (m, 1H), 4.21-4.16 (m, 1H), 4.10-4.04 (m, 1H), 3.67 (dd, *J* = 9.94, 5.29 Hz, 1H), 3.60 (dd, *J* = 9.94, 4.79 Hz, 1H), 3.46-3.40 (m, 5H), 2.47 (d, *J* = 7.76 Hz, 1H), 2.44-2.35 (m, 1H), 2.27-2.16 (m, 1H), 1.58-1.47 (m, 1H), 1.44-1.37 (m, 1H), 1.21-1.11 (m, 1H), 0.92-0.88 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.0, 155.9, 138.3, 137.9, 132.7, 128.4, 127.8, 127.8, 127.7, 127.6, 118.1, 117.8, 78.6, 74.2, 73.6, 69.9, 65.8, 63.7, 58.4, 44.9, 38.0, 29.2, 24.9, 15.4, 11.6.

6.1d:

Molecular Formula: $C_{27}H_{39}NO_7$

R_f: 0.5 (7:3 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 490.2 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37-7.25 (m, 5H), 5.90 (qd, *J* = 10.79, 5.62 Hz, 1H), 5.57 (td, *J* = 17.05, 9.92 Hz, 1H), 5.33-5.25 (m, 2H), 5.23-5.17 (m, 1H), 5.12-5.06 (m, 2H), 4.59-4.50 (m, 4H), 4.28-4.16 (m, 2H), 4.06-4.00 (m, 1H), 3.85 (dt, *J* = 6.29, 1.98 Hz, 1H), 3.54-3.44 (m, 2H), 3.42 (s, 3H), 3.12 (dd, *J* = 7.97, 2.02 Hz, 1H),

2.51 (dt, *J* = 10.99, 3.06 Hz, 1H), 2.27 (bs, 1H), 2.19-2.10 (m, 1H), 2.09-2.00 (m, 1H), 1.60-1.50 (m, 1H), 0.95 (d, *J* = 6.84 Hz, 3H), 0.87 (d, *J* = 6.86 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.1, 156.1, 137.9, 132.7, 128.4, 127.8, 118.1, 117.8, 82.8, 73.4, 71.5, 69.9, 65.8, 63.6, 60.7, 58.9, 43.2, 31.3, 28.8, 19.0, 17.4.

(6.2a-6.2d):

To a stirred solution of **6.1a-6.1d** (85 mg) in DCM (100 mL) was added Grubbs-II catalyst (10 mol%), the reaction was stirred for 16 h at 40 ^{o}C, after consumption of complete starting material was concentrated under reduced pressure and the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **6.2a-6.2d** (65 mg) as colorless oil.

6.2a:

Molecular Formula: $C_{29}H_{35}NO_7$

R_f: 0.5 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 510.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38-7.25 (m, 8H), 7.15-7.10 (m, 2H), 5.77 (bs, 1H), 5.57 (dt, *J* = 17.2, 10.0 Hz, 1H), 5.28-5.20 (m, 1H), 5.12-5.06 (m, 2H), 4.65-4.57 (m, 1H), 4.54-4.50 (m, 4H), 4.23-4.15 (m, 1H), 4.00 (dd, *J* = 7.75, 2.87 Hz, 1H), 3.88-3.81 (m, 1H), 3.54-3.45 (m, 2H), 3.42 (s, 3H), 3.14-3.02 (m, 3H), 2.51-2.44 (m, 1H), 2.39-2.24 (m, 1H), 2.05-1.94 (m, 1H), 1.57-1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.5, 155.4, 137.9, 135.7, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.1, 127.8, 127.8, 127.7, 127.1, 118.1, 82.8, 73.4, 71.5, 69.9, 64.6, 63.9, 60.8, 54.7, 43.2, 38.3, 29.7, 29.7, 28.8.

6.2b:

Molecular Formula: $C_{26}H_{37}NO_7$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 476.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39-7.28 (m, 5H), 5.86-5.64 (m, 2H), 4.90-4.64 (m, 2H), 4.53 (s, 2H), 4.25-4.09 (m, 2H), 3.73-3.54 (m, 4H), 3.46-3.37 (m, 8H), 3.17-3.08 (m, 1H), 2.67-2.54 (m, 1H), 2.07-2.00 (m, 1H), 1.80-1.55 (m, 5H), 0.95-0.90 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.4, 141.5, 137.9, 128.4, 127.8, 127.8, 125.0, 110.0, 82.4, 82.4, 73.5, 68.8, 61.1, 58.9, 54.3, 45.8, 29.7, 24.8.

6.2c:

Molecular Formula: $C_{26}H_{37}NO_7$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 476.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.36-7.27 (m, 5H), 3.67 (dd, *J* = 9.93, 5.31 Hz, 1H), 3.61 (dd, *J* = 9.93, 4.79 Hz, 1H), 5.84 (bs, 1H), 5.52 (dt, *J* = 17.20 Hz, 9.60 1H), 5.29-5.25 (m, 1H), 5.15-5.04 (m, 2H), 4.56-4.53 (m, 4H), 4.29 (dd, *J* = 8.81, 4.86 Hz, 1H), 4.22-4.16 (m, 1H), 4.13-4.04 (m, 1H), 3.49-3.40 (m, 5H), 2.48-2.35 (m, 2H), 2.27-2.18 (m, 1H), 1.92-1.82 (m, 1H), 1.61-1.49 (m, 5H), 0.93-0.89 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.0, 155.8, 137.9, 137.9, 128.4, 128.2, 127.8, 127.8, 118.2, 82.8, 73.4, 71.5, 69.9, 64.6, 63.5, 60.7, 58.3, 43.2, 38.0, 28.8, 24.9, 15.5, 11.6.

6.2d:

Molecular Formula: $C_{25}H_{35}NO_7$

R_f: 0.5 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 462.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37-7.26 (m, 5H), 5.84 (bs, 1H), 5.57 (td, *J* = 17.09, 9.92 Hz, 1H), 5.28 (d, *J* = 7.57 Hz, 1H), 5.15-5.06 (m, 2H), 4.63-4.49 (m, 4H), 4.29-4.15 (m, 3H), 4.04 (td, *J* = 10.70, 8.39 Hz, 1H), 3.88-3.84 (m, 1H), 3.54-3.45 (m, 2H), 3.44 (s, 3H), 3.13 (dd, *J* = 7.93, 1.74 Hz, 1H), 2.51 (dt, *J* = 10.84, 3.05 Hz, 1H), 2.20-1.99 (m, 3H), 1.60-1.50 (m, 1H), 0.87 (d, *J* = 6.76 Hz, 3H), 0.95 (d, *J* = 6.82 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.0, 156.0, 137.8, 128.4, 127.8, 118.2, 82.8, 73.4, 71.5, 69.9, 64.6, 63.6, 60.8, 59.0, 43.2, 31.3, 29.7, 28.8, 19.0, 17.5.

(F6.3a & F6.3b):

To a stirred solution of **6.2c & 6.2d** (35 mg) in EtOAc (10 mL) was added Pd catalyst (10 mol%), the reaction was stirred for 16 h at H_2 atmosphere, after consumption of complete starting material was filtered through celite and concentrated under reduced pressure, the residue was purified by column chromatography (6:4Hexanes/ethylacetate)to provide **F6.3a & F6.3** (15 mg) as colorless oil.

F6.3a:

Molecular Formula: $C_{19}H_{33}NO_7$

R_f: 0.1 (3:7 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 388.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.40 (d, *J* = 8.63 Hz, 1H), 4.32-4.21 (m, 2H), 4.15-4.04 (m, 3H), 3.67-3.64 (m, 2H), 3.57-3.52 (m, 1H), 3.48 (s, 3H), 3.18 (bs, 1H), 1.84-1.78 (m, 2H), 1.68-1.59 (m, 4H), 1.54-1.36 (m, 4H), 1.00-0.85 (m, 10H). **^{13}CNMR** (100 MHz, $CDCl_3$) δ ppm 172.2, 156.5, 82.6, 72.4, 64.8, 64.3, 63.8, 60.8, 58.4, 38.5, 37.8, 31.9, 29.7, 28.2, 25.5, 25.0, 23.7, 15.5, 11.5.

F6.3b:

Molecular Formula: $C_{18}H_{31}NO_7$

R_f: 0.1 (3:7 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 374.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.42-5.34 (m, 1H), 4.30-4.09 (m, 6H), 3.72-3.63 (m, 2H), 3.59-3.52 (m, 1H), 3.48 (s, 3H), 3.19-3.17 (m, 1H), 2.94-2.76 (m, 1H), 2.18-2.08 (m, 1H), 1.89-1.76 (m, 1H), 1.74-1.36 (m, 8H), 0.97-0.91 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.3, 156.6, 82.6, 72.4, 63.9, 59.2, 38.6, 33.8, 31.9, 29.7, 28.2, 25.5, 23.7, 22.7, 19.1, 17.7, 14.1, 11.7.

(2S,3S,4R,5R)-2-allyl-5-(benzyloxymethyl)-4-methoxy-3-(2-methoxyethyl) tetrahydrofuran

To a stirred solution of **1.6.1** (200 mg) was dissolved in DMF (10 mL) and NaH was added slowly at 0 ^{o}C. Then MeI was added at same temperature, after 1 hour reaction mixture was quenched with water and extracted with EtOAc (3× 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (9.5:0.5 Hexanes/ethylacetate) to provide **8.1** (200 mg) as colorless oil.

Molecular Formula: $C_{19}H_{28}O_4$

R_f: 0.2 (8:2 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 321.4 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39-7.28 (m, 5H), 5.65-5.55 (dt, *J* = 9.60, 2.80 Hz, 1H), 5.13-5.02 (m, 2H), 4.54 (s, 2H), 3.66-3.58 (m, 2H), 3.48-3.42 (m, 4H), 3.41 (s, 3H), 3.39-3.32 (m, 1H), 3.30 (s, 3H), 3.16 (dd, *J* = 8.11, 2.82 Hz, 1H), 2.57-2.50 (m, 1H), 2.03-1.94 (m, 1H), 1.61 (bs, 2H), 1.51-1.41 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.3, 138.1, 128.4, 127.7, 127.7, 116.8, 83.5, 79.9, 73.4, 71.0, 69.0, 60.7, 58.7, 58.5, 43.0, 29.8.

((2R,3R,4S,5S)-5-allyl-3-methoxy-4-(2-methoxyethyl)tetrahydrofuran-2-yl)methanol

(8.1.1):

To a stirred solution of **8.1** (200 mg) in DCM (50 mL) was added $TiCl_4$ (0.14 mL, 1.329 mmol) and stirred for 3 h at room temperature, after consumption of complete starting material was quenched with saturated NH_4Cl and extracted with DCM (3×50 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **8.1.1** (110 mg) as colorless oil.

Molecular Formula: $C_{12}H_{22}O_4$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 231.3 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm

(8.2a & 8.2b):

To a stirred solution of **8.1.1** (50 mg) in DCM (20 mL) was added EDCI (2 eq), DMAP (2 eq) and Alloc-AA (2 eq) the reaction was stirred for 3 h at room temperature, after consumption of complete starting material was quenched with water and extracted with DCM. The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (7:3 Hexanes/ethylacetate) to provide **8.2a** and **8.2b** (55 mg) as colorless oil.

8.2a:

Molecular Formula: $C_{25}H_{35}NO_7$

R_f: 0.6 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 462.5 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28-7.21 (m, 4H), 7.15 (bs, 1H), 5.95-5.79 (m, 1H), 5.33-5.04 (m, 4H), 4.71-4.63 (m, 1H), 4.54-4.53 (m, 2H), 4.41-4.32 (m, 1H),

4.27-4.14 (m, 2H), 3.98-3.89 (m, 1H), 3.83-3.71 (m, 1H), 3.63-3.51 (m, 1H), 3.46-3.41 (m, 2H), 3.33-3.31 (m, 3H), 3.29-3.26 (m, 3H), 3.13-3.11 (m, 2H), 2.12-1.80 (m, 3H), 1.70-1.58 (m, 2H), 1.53 (t, *J* = 6.51 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.4, 155.5, 134.7, 132.6, 129.4, 128.5, 127.1, 117.7, 86.9, 81.4, 78.4, 70.4, 65.7, 64.6, 58.6, 57.0, 54.7, 46.7, 46.1, 39.7, 38.2, 32.0, 29.7, 26.1, 24.8.

8.2b:

Molecular Formula: $C_{22}H_{37}NO_7$

R_f: 0.6 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 427.5 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.93-5.83 (m, 1H), 5.30-5.01 (m, 4H), 4.54-4.53 (m, 2H), 4.45-4.11 (m, 4H), 4.00-3.93 (m, 1H), 3.80-3.67 (m, 1H), 3.58-3.56 (m, 1H), 3.46-3.38 (m, 2H), 3.34-3.24 (m, 6H), 2.08-1.78 (m, 4H), 1.70-1.56 (m, 2H), 1.42-1.37 (m, 1H), 1.20-1.12 (m, 1H), 0.95-0.86 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.9, 155.9, 134.7, 132.6, 117.7, 86.9, 81.2, 78.4, 70.4, 65.7, 64.3, 58.6, 57.0, 55.2, 46.0, 39.6, 38.1, 31.9, 29.6, 26.0, 24.9, 15.4, 11.6.

(8.2.1 & 8.2.1):

To a stirred solution of **8.2a** and **8.2b** (50 mg) in DCM (100 mL) was added Grubbs-II catalyst (10 mol%), the reaction was stirred for 16 h at 40 ^{o}C, after consumption of complete starting material was concentrated under reduced pressure and the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **8.2.1** and **8.2.2** (35 mg) as colorless oil.

8.2.1:

Molecular Formula: $C_{23}H_{31}NO_7$

R_f: 0.45 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 434.4 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32-7.22 (m, 3H), 7.20-7.13 (m, 2H), 5.81-5.71 (m, 1H), 5.63-5.54 (m, 1H), 5.28-5.21 (m, 1H), 5.00-4.73 (m, 2H), 4.66-4.63 (m, 1H), 4.54-4.50 (m, 1H), 4.42-4.31 (m, 1H), 4.29-4.11 (m, 2H), 3.98-3.80 (m, 1H), 3.75-3.67 (m, 1H), 3.59-3.54 (m, 1H), 3.48-3.39 (m, 2H), 3.17-3.11 (m, 1H), 2.57-2.44 (m, 1H), 2.23-2.16 (m, 1H), 2.10-1.87 (m, 2H), 1.73-1.46 (m, 4H), 3.37-3.25 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.2, 155.5, 136.4, 129.4, 128.7, 127.8, 127.0, 125.1, 87.9, 86.9, 79.9, 70.9, 70.4, 64.6, 63.6, 58.6, 57.0, 55.2, 54.5, 46.1, 43.6, 37.2, 30.2, 29.7, 26.1, 22.7, 14.1.

8.2.2:

Molecular Formula: $C_{20}H_{33}NO_7$

R_f: 0.4 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 400.4 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.88-5.79 (m, 1H), 5.73-5.55 (m, 1H), 5.33-5.24 (m, 1H), 5.08-4.80 (m, 1H), 4.59-4.51 (m, 1H), 4.41-4.12 (m, 4H), 4.013.78 (m, 2H), 3.76-3.64 (m, 1H), 3.61-3.58 (m, 1H), 3.45-3.40 (m, 3H), 3.32-3.27 (m, 7H), 2.30-2.08 (m, 2H), 2.00-1.80 (m, 3H), 1.53-1.50 (m, 2H), 0.97-0.89 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.8, 128.2, 86.9, 70.5, 70.4, 58.6, 58.6, 58.5, 58.3, 57.0, 46.0, 38.1, 32.0, 31.8, 24.9, 24.9, 24.7, 15.4, 15.4, 11.6.

(F6.4a & F6.4b):

To a stirred solution of **8.2.1 & 8.2.2** (30 mg) in EtOAc (10 mL) was added Pd catalyst (10 mol%), the reaction was stirred for 16 h at H_2 atmosphere, after consumption of complete starting material was filtered through celite and concentrated under reduced pressure, the residue was purified by column chromatography (5:5 Hexanes/ethylacetate) to provide **F6.4a & F6.4b** (15 mg) as colorless oil.

F6.4a:

Molecular Formula: $C_{23}H_{33}NO_7$

R_f: 0.3 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 436.1 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34-7.13 (m, 6H), 5.04-4.95 (m, 1H), 4.75-4.33 (m, 2H), 4.31-3.93 (m, 4H), 3.85-3.64 (m, 2H), 3.62-3.53 (m, 1H), 3.43-3.27 (m, 9H), 3.23-3.09 (m, 1H), 3.06-2.96 (m, 1H), 1.86-1.63 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 129.4, 129.0, 128.8, 128.7, 128.5, 127.1, 110.0, 87.4, 87.4, 75.2, 70.8, 58.6, 56.3, 45.8, 33.9, 31.9, 29.7.

F6.4b:

Molecular Formula: $C_{20}H_{35}NO_7$

R_f: 0.3 (5:5 Hexanes/Ethylacetate)

LRMS (ES+) m/z = 402.4 (M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.41-4.15 (m, 3H), 4.07-3.97 (m, 2H), 3.86-3.68 (m, 2H), 3.61-3.57 (m, 1H), 3.47-3.43 (m, 2H), 3.33-3.28 (m, 5H), 2.10-1.81 (m, 4H), 1.69-1.64 (m, 6.19 Hz, 4H), 1.57-1.48 (m, 3H), 0.98-0.85 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.3, 152.6, 86.9, 70.8, 70.5, 58.6, 58.6, 57.0, 46.6, 46.0, 38.1, 33.8, 32.0, 31.9, 29.7, 25.6, 25.0, 24.9, 22.7, 15.4, 14.1, 11.6.

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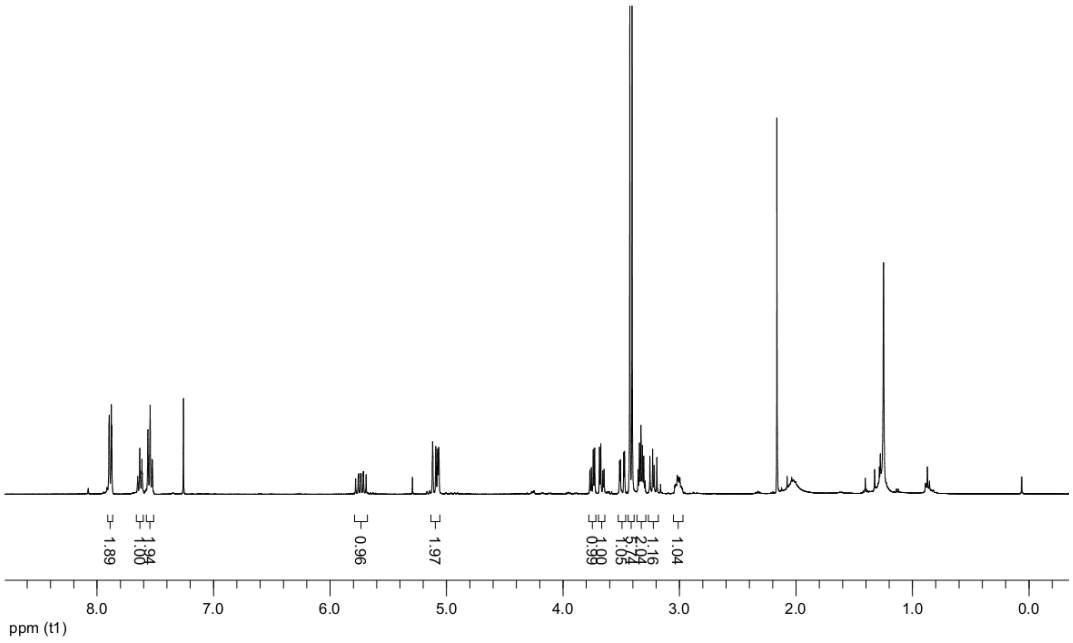
3.17. Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) of compound **1.4.1**



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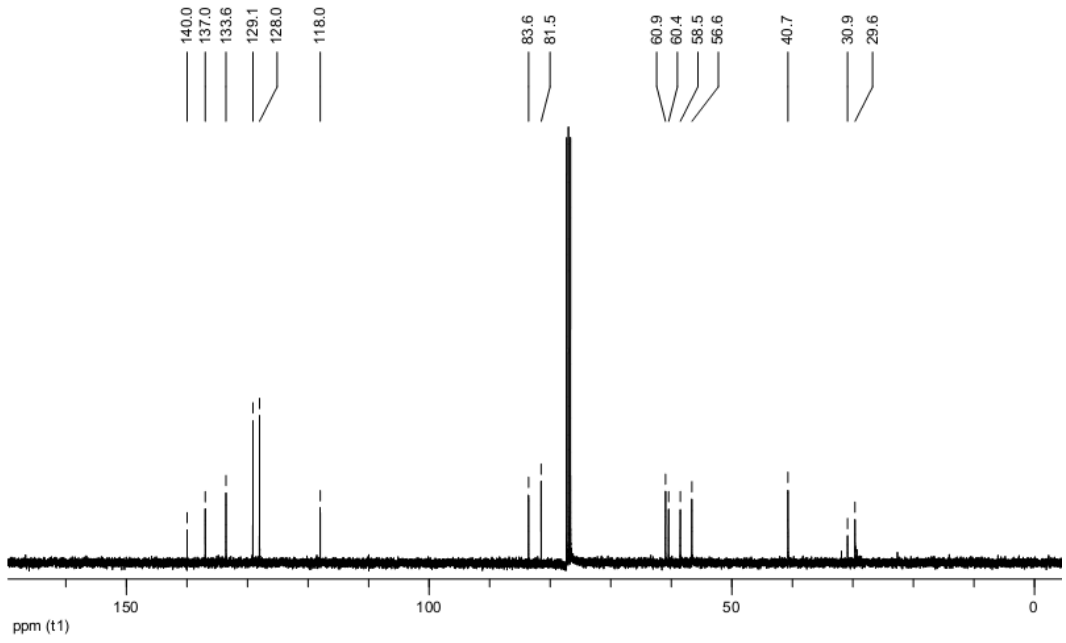

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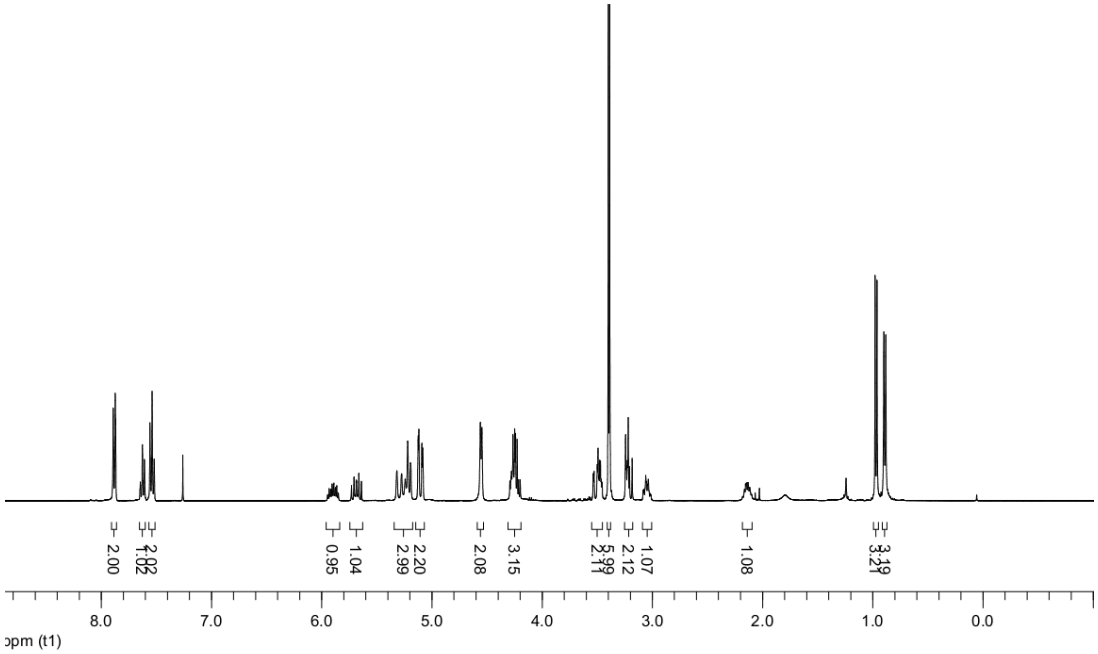

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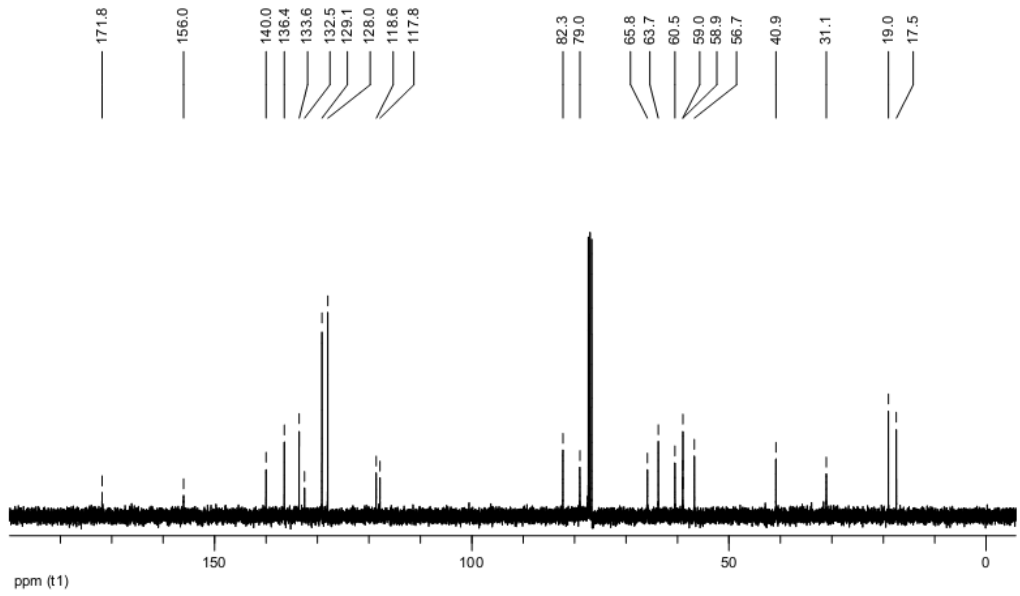

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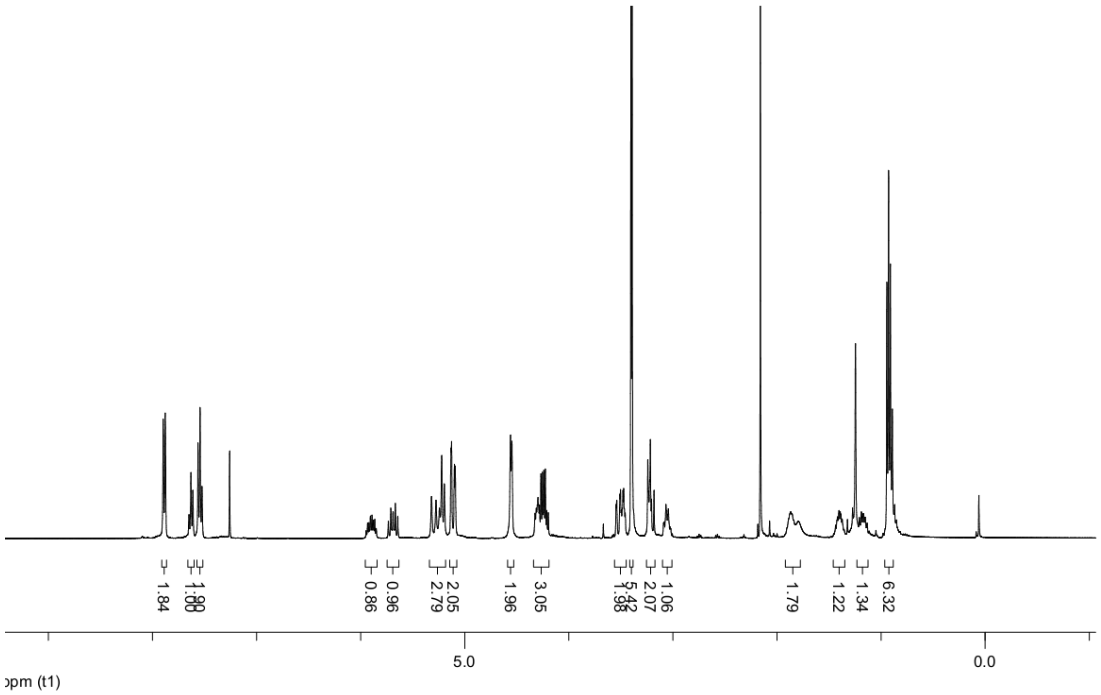

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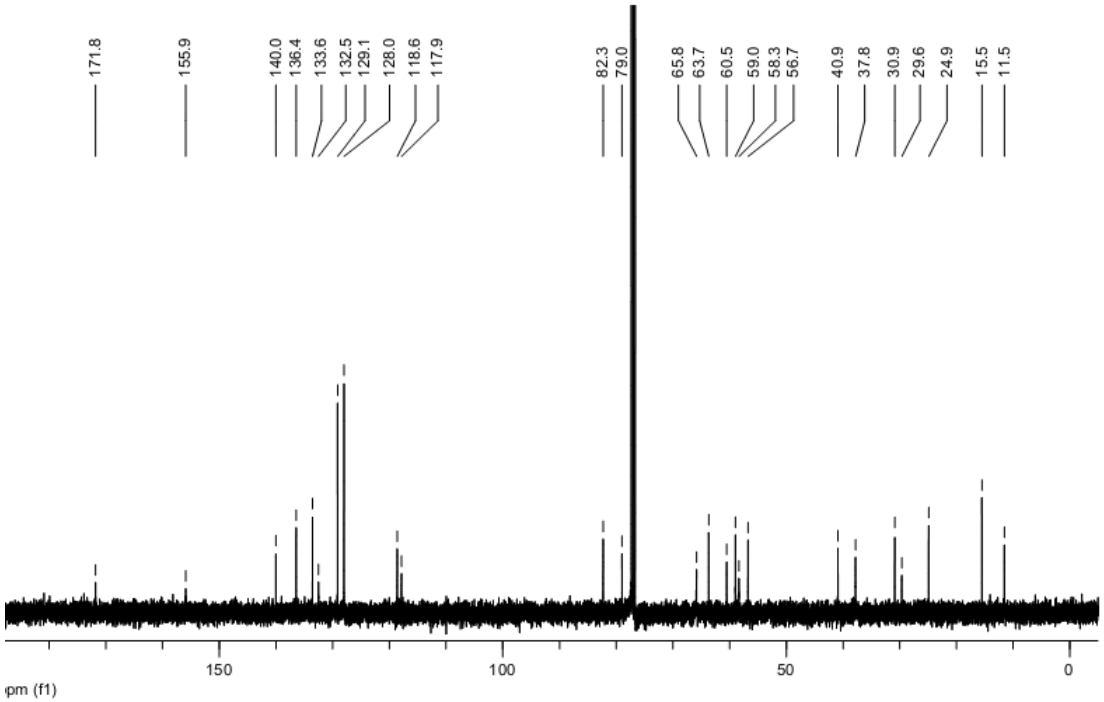

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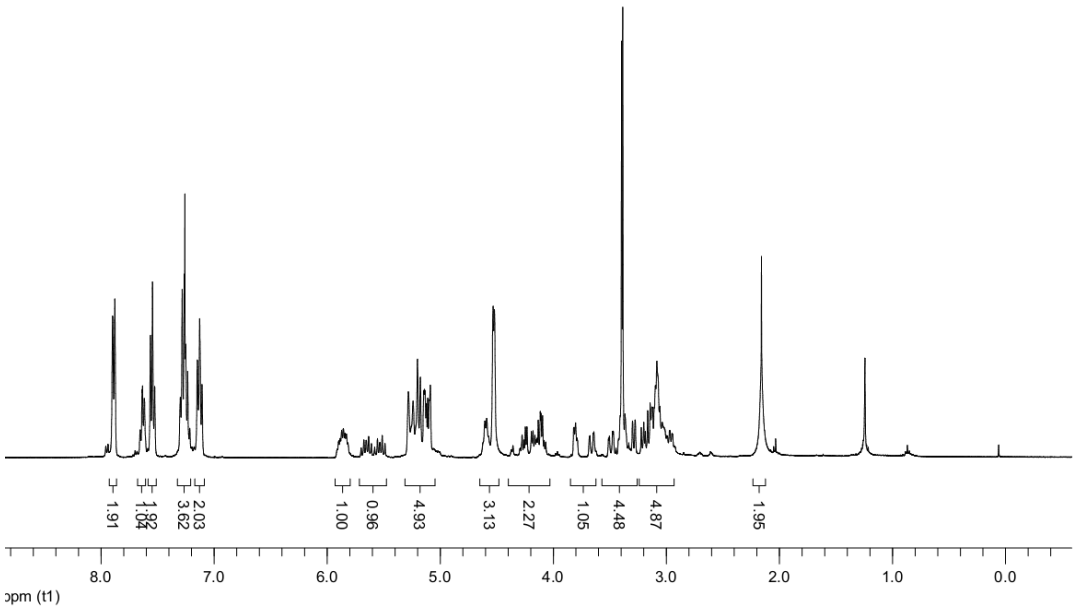

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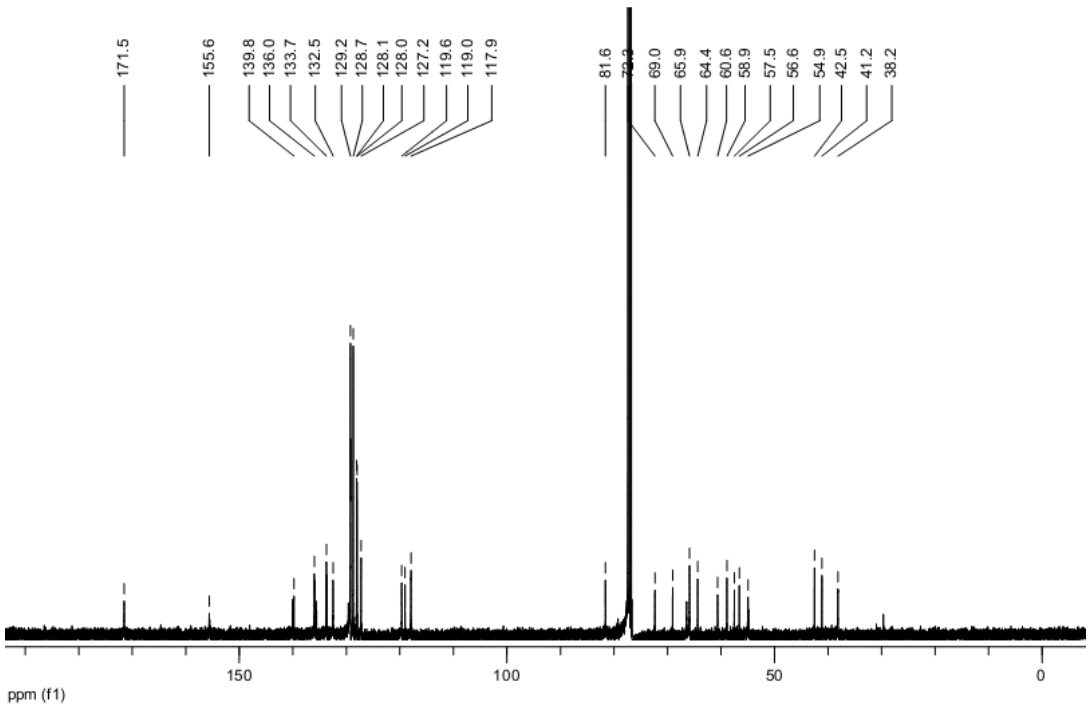

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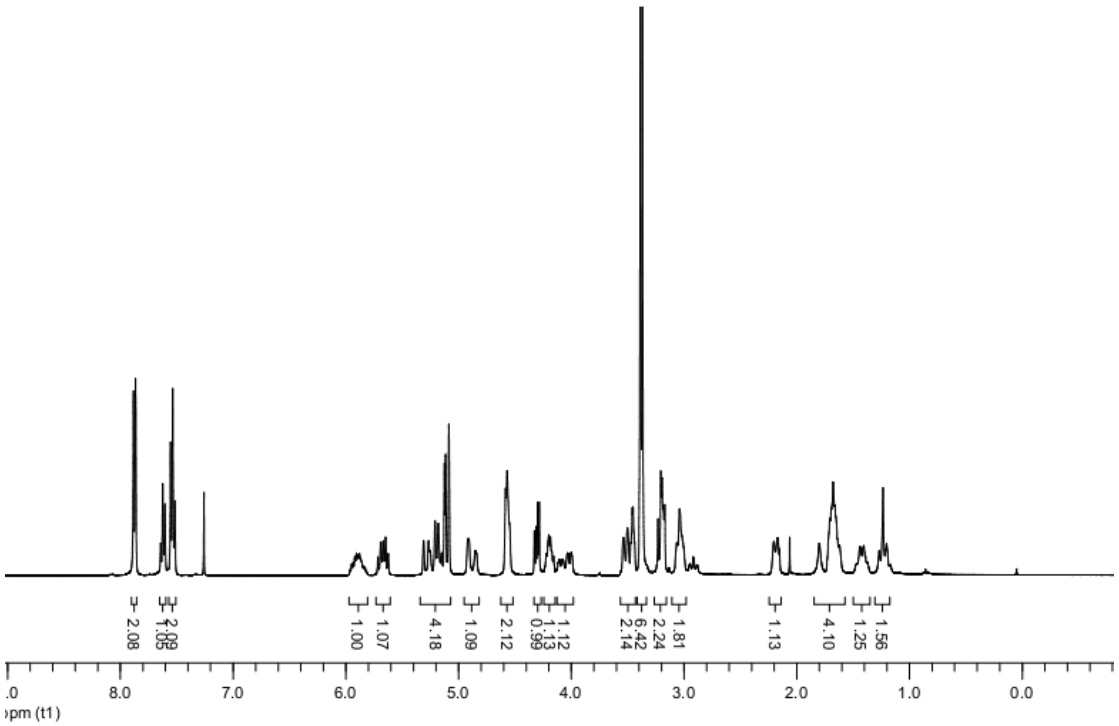

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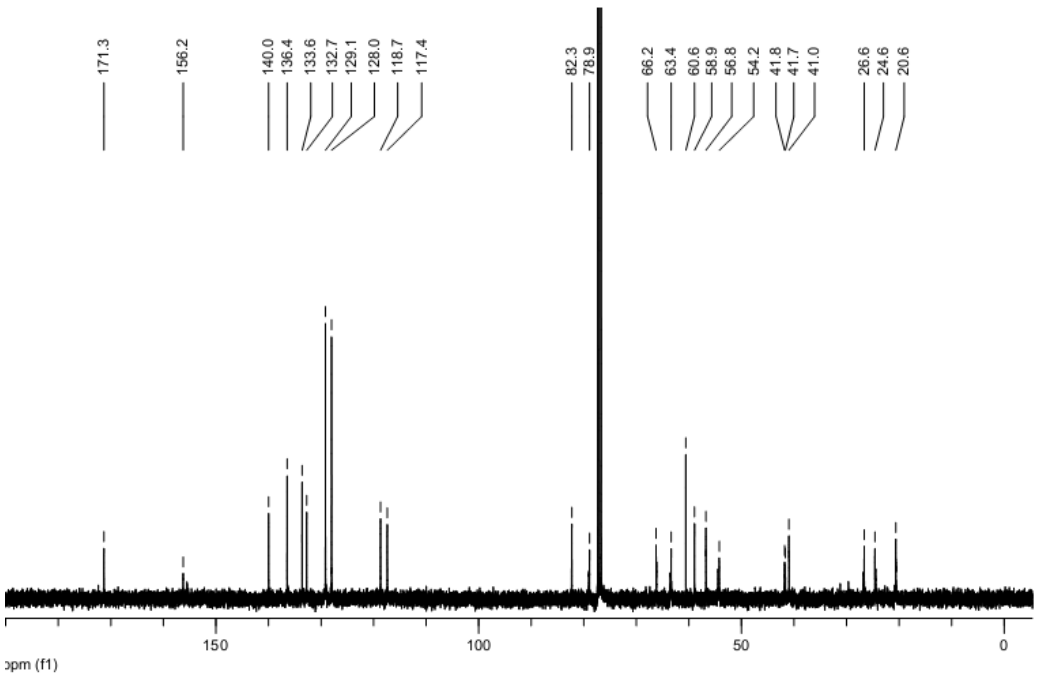
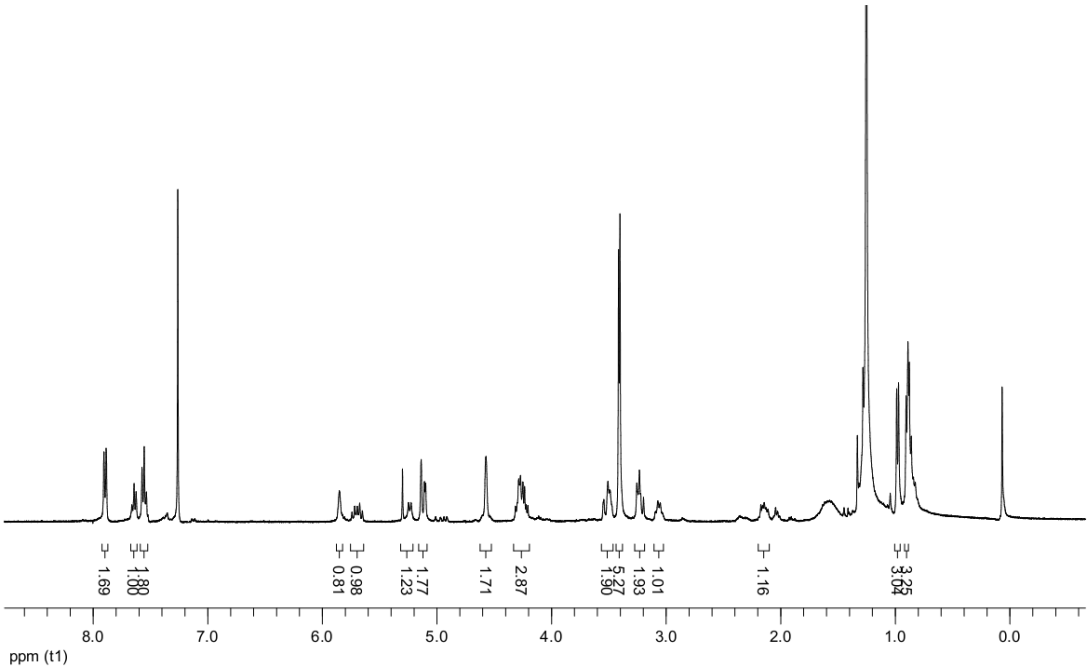


^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.1a**



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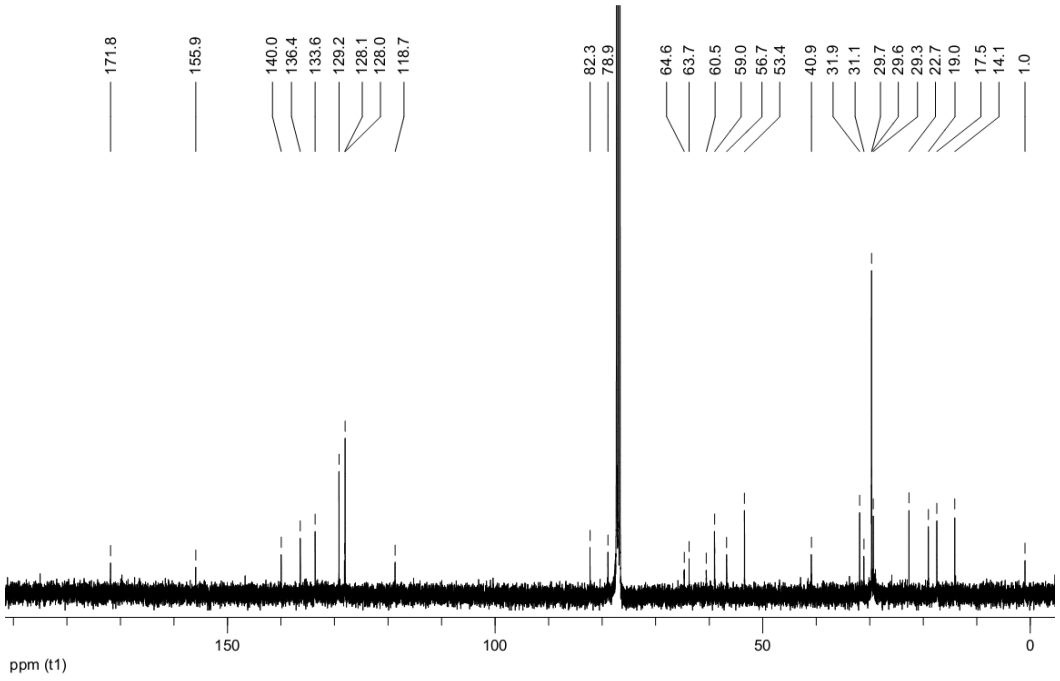
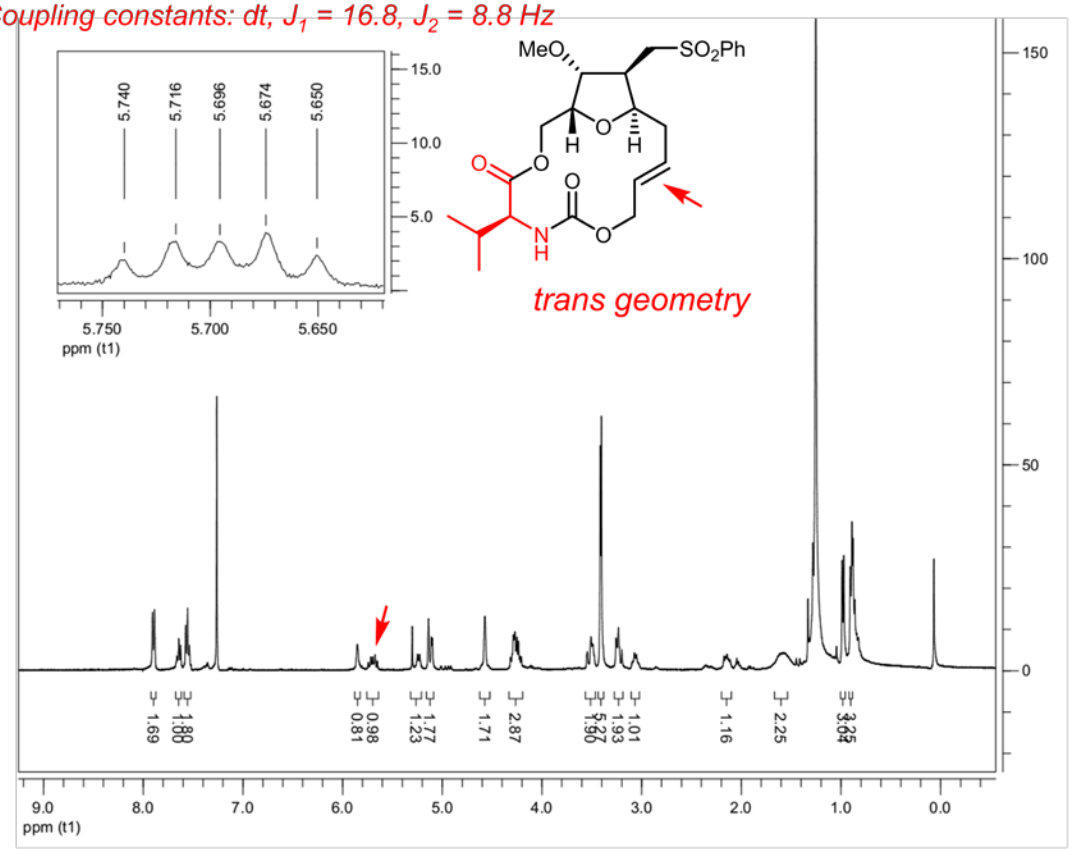
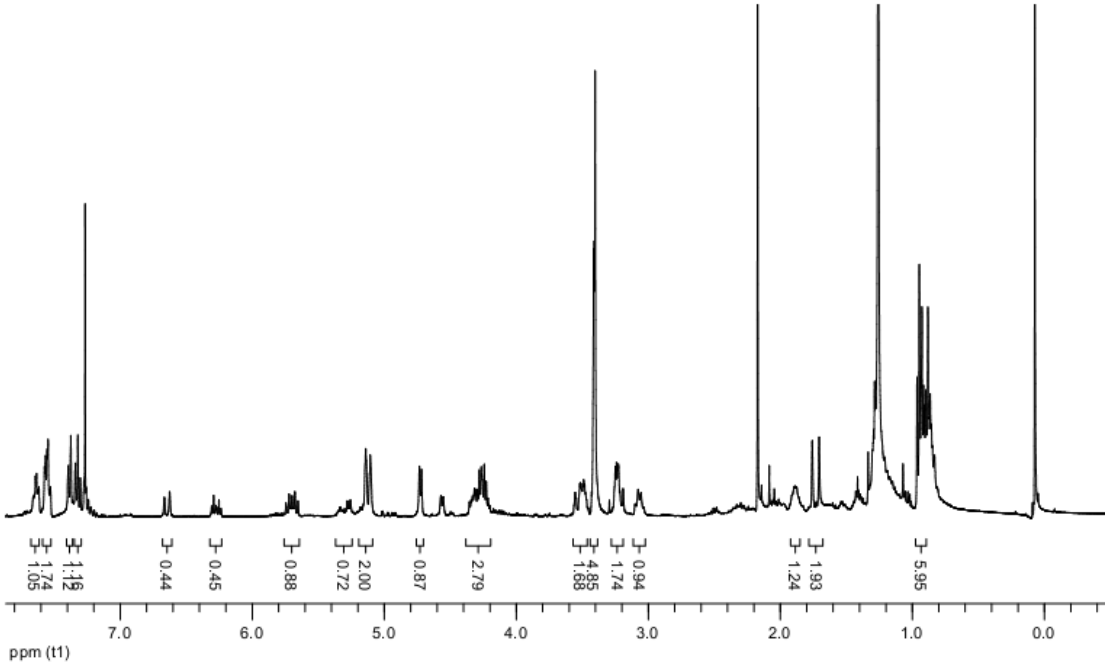


Olefin Geometry Assigned!

Coupling constants: dt, J_1 = 16.8, J_2 = 8.8 Hz



^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.1b**



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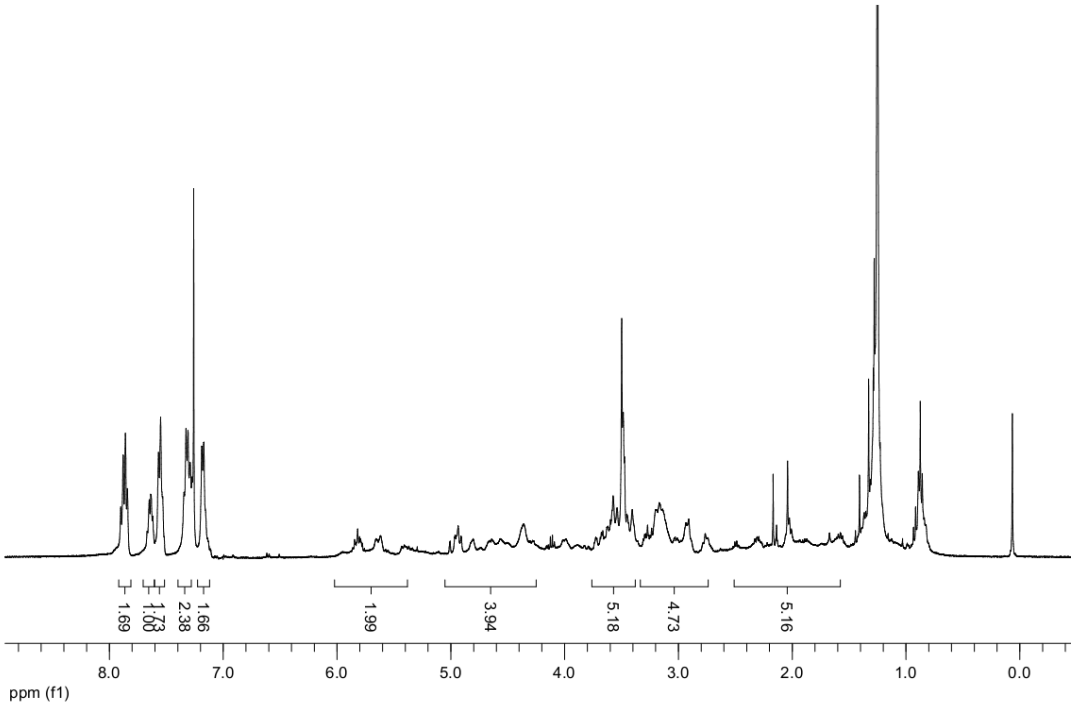

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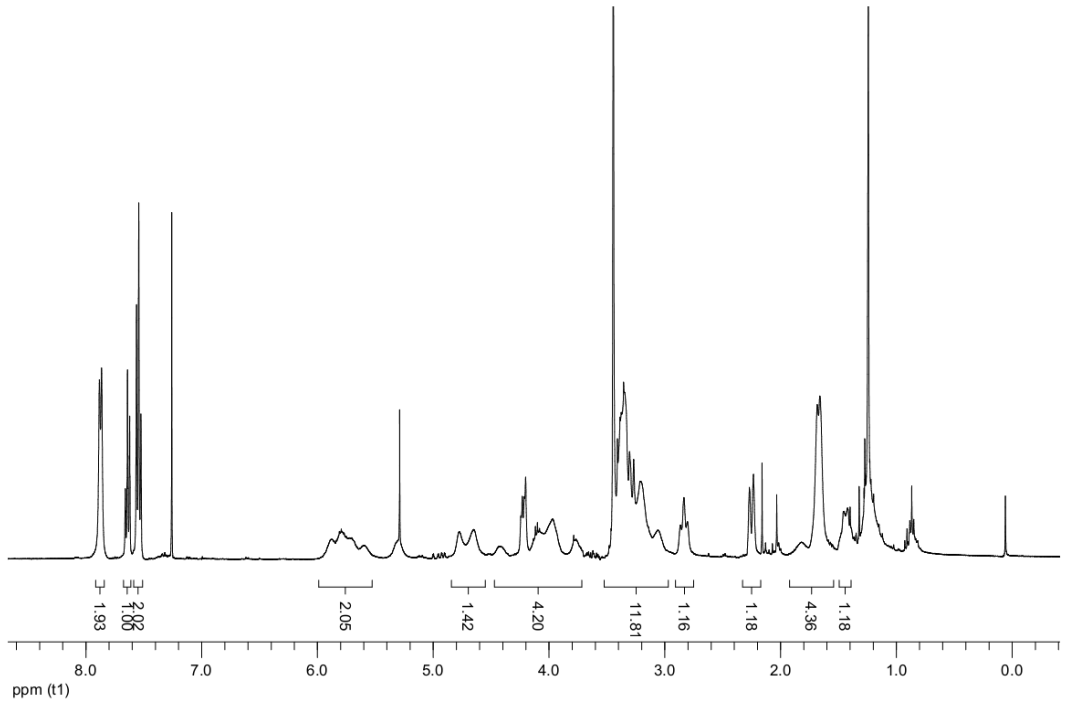

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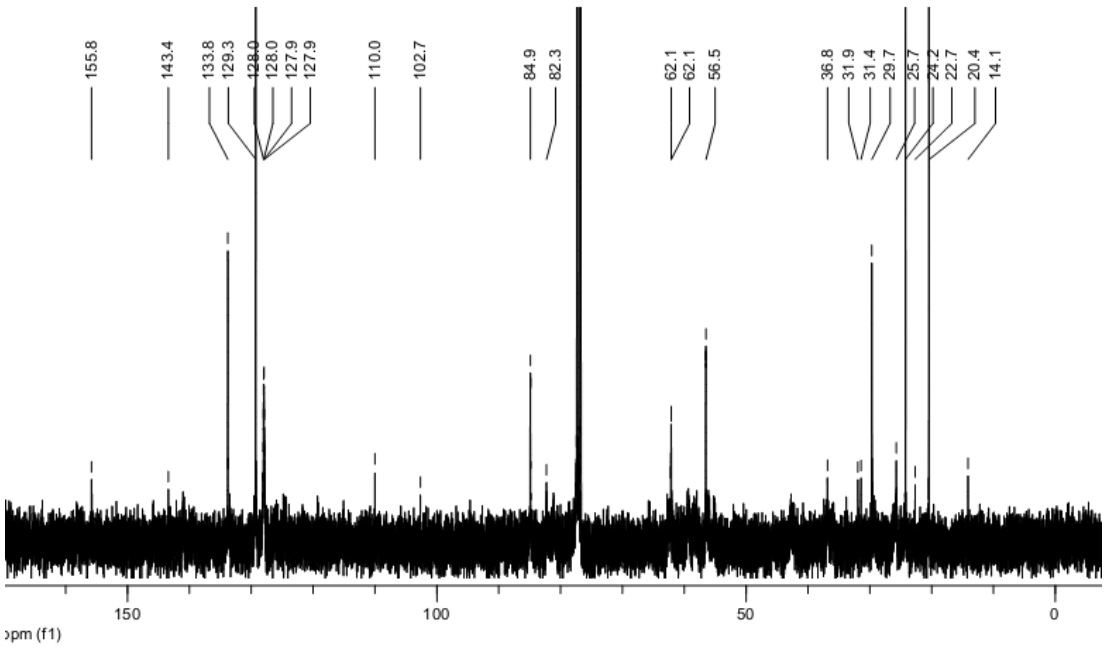

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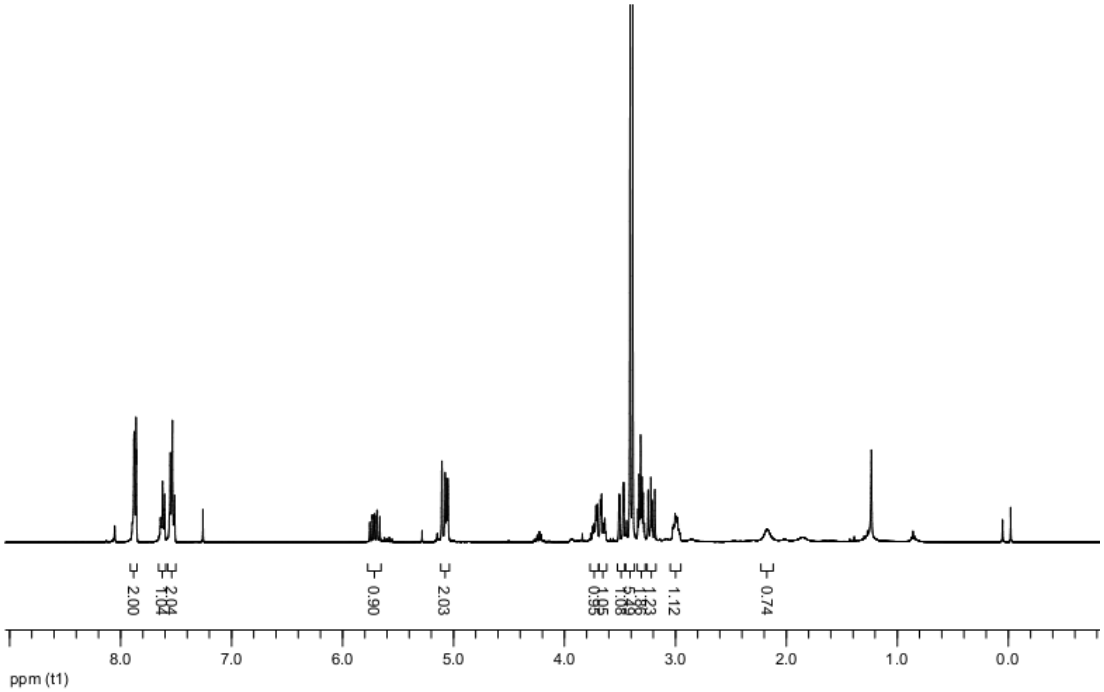

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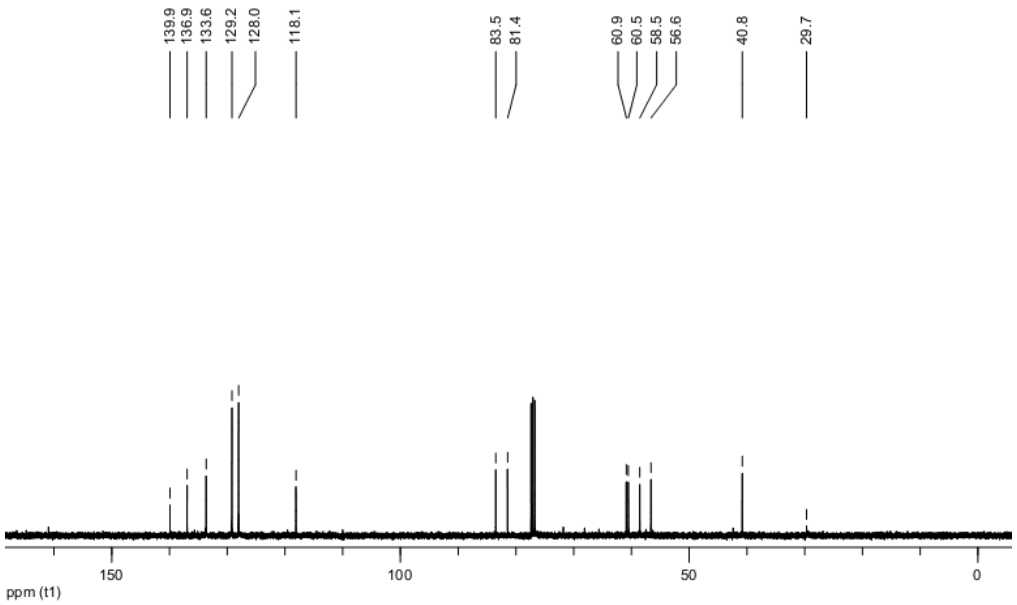

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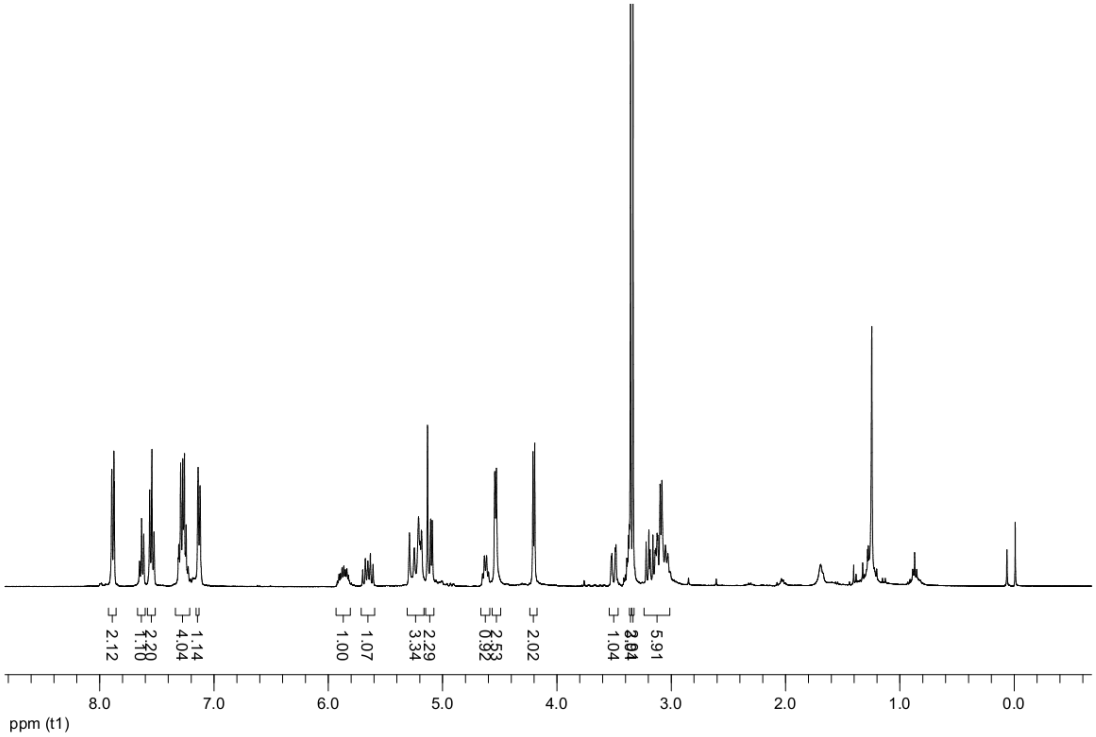

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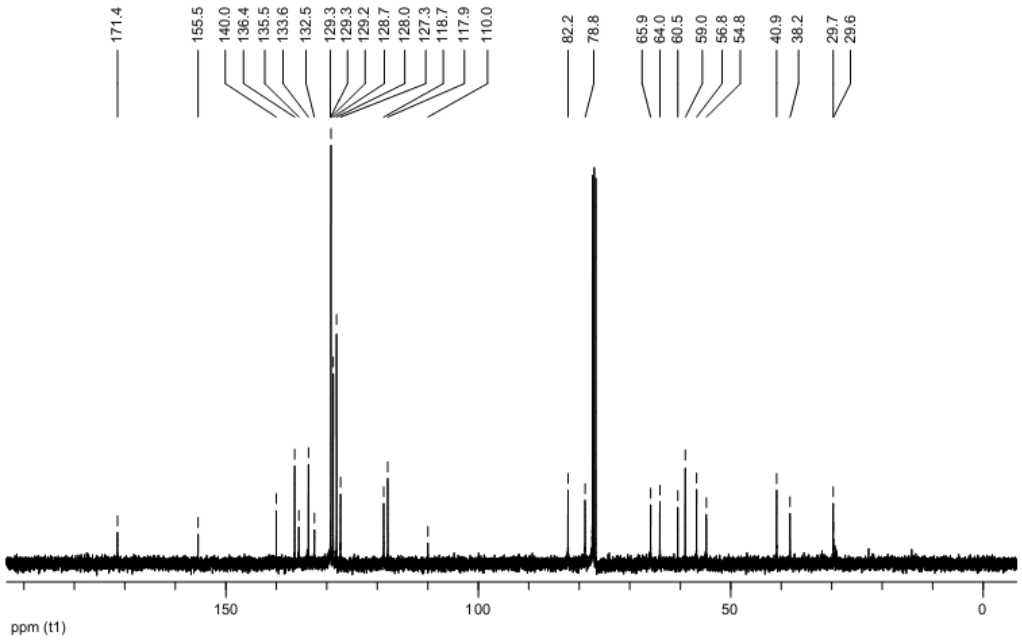

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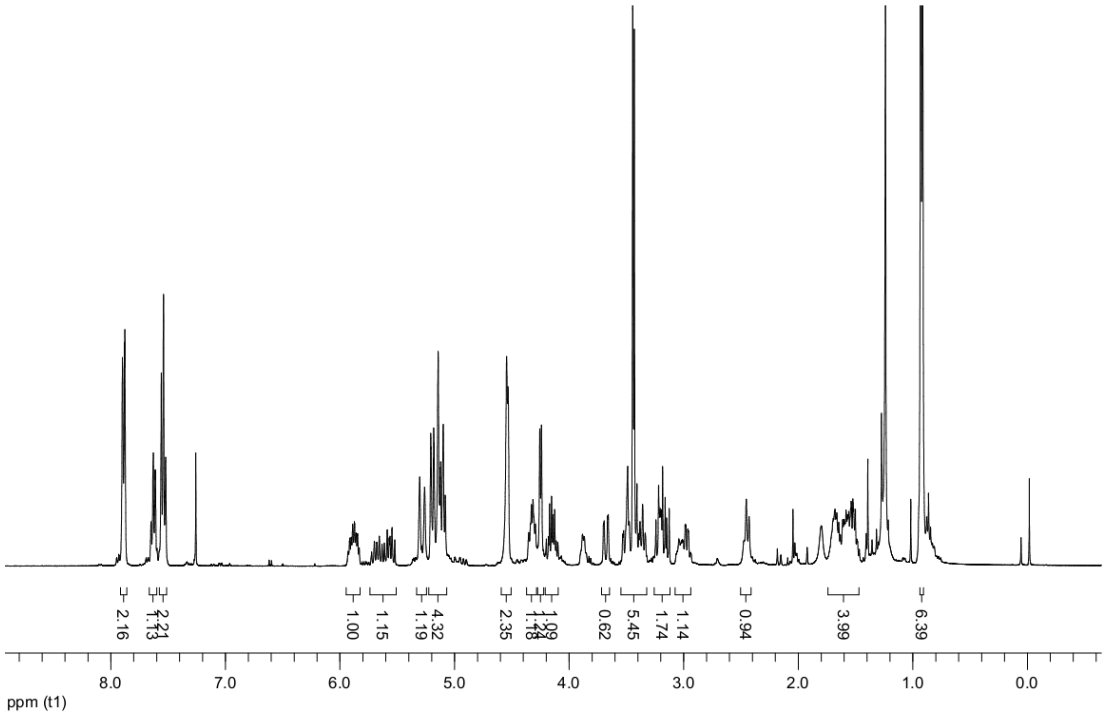

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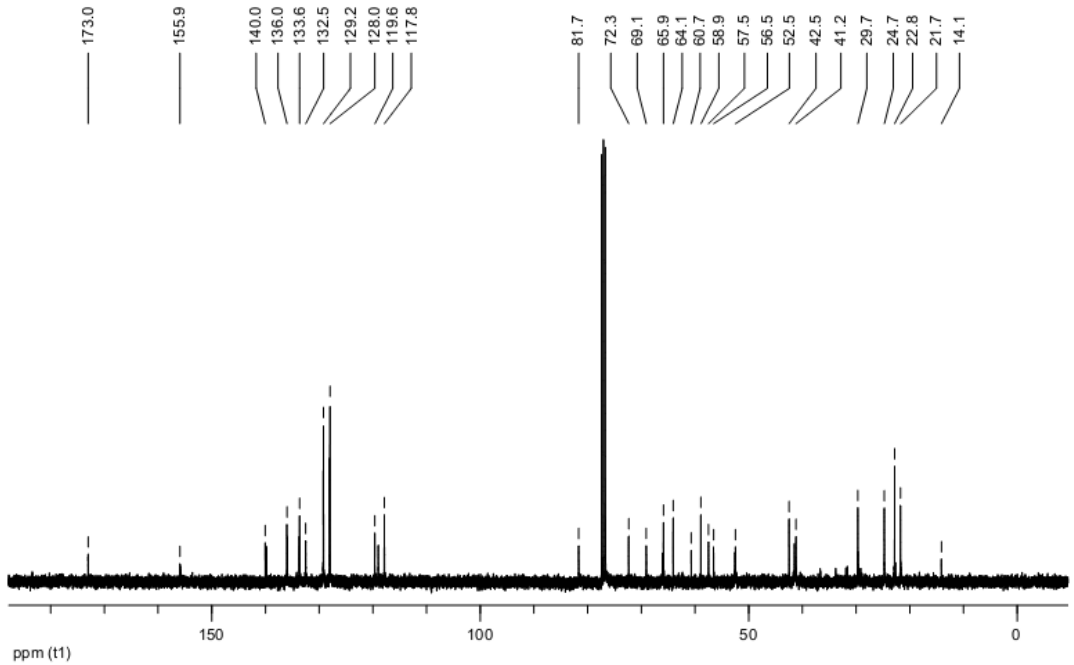

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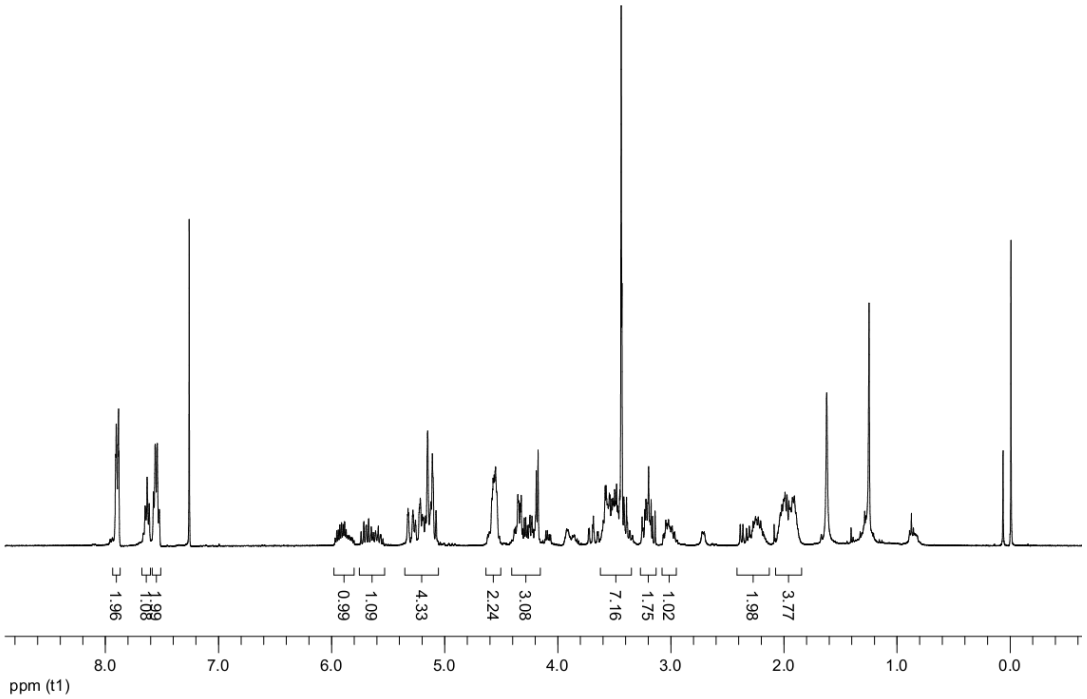

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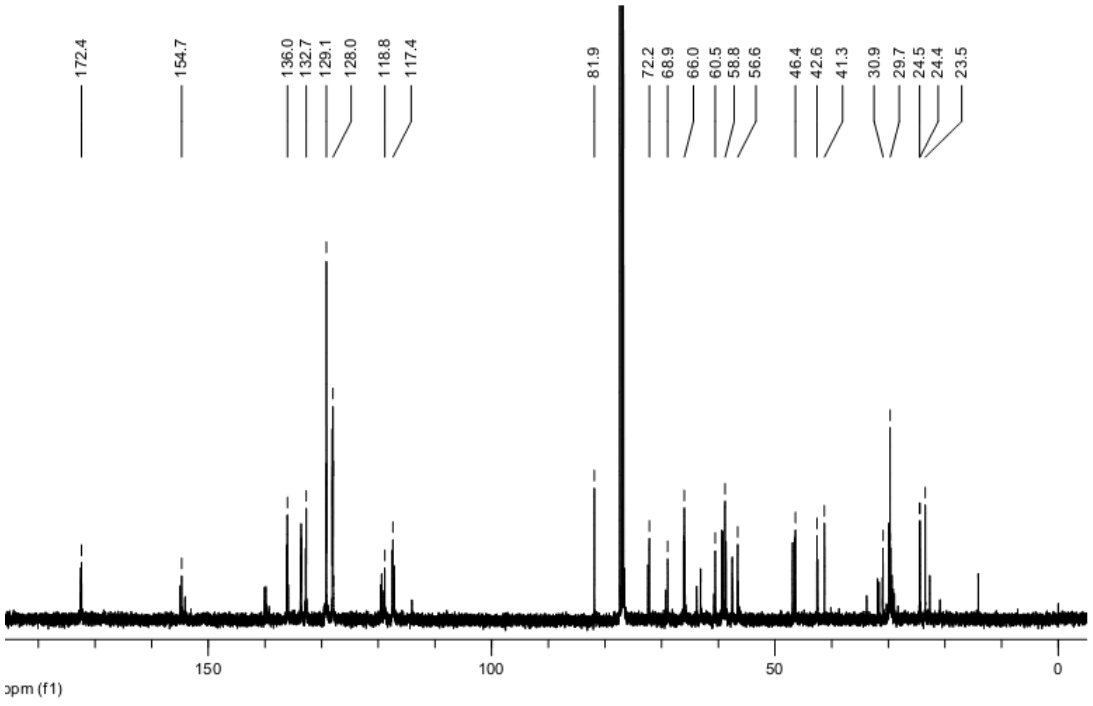

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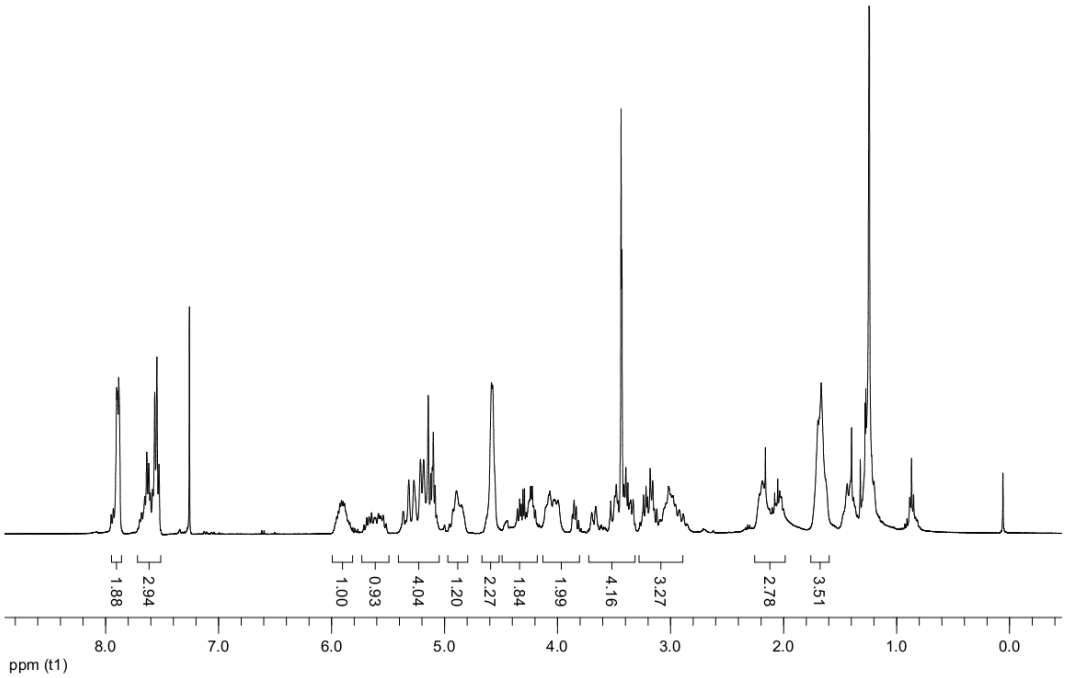

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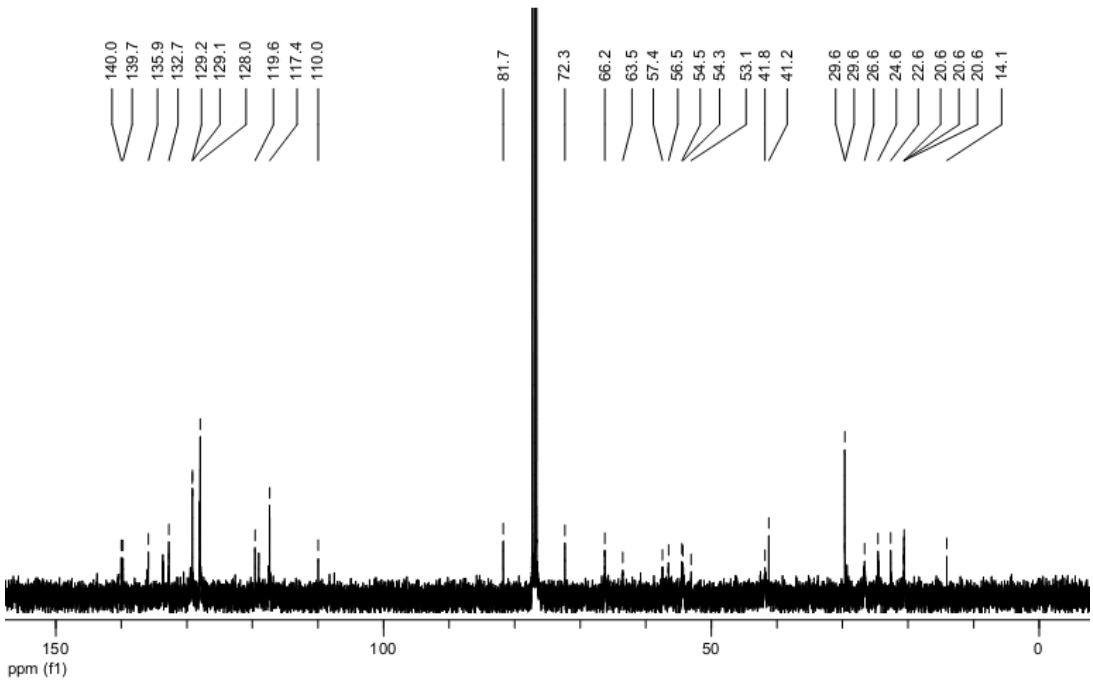

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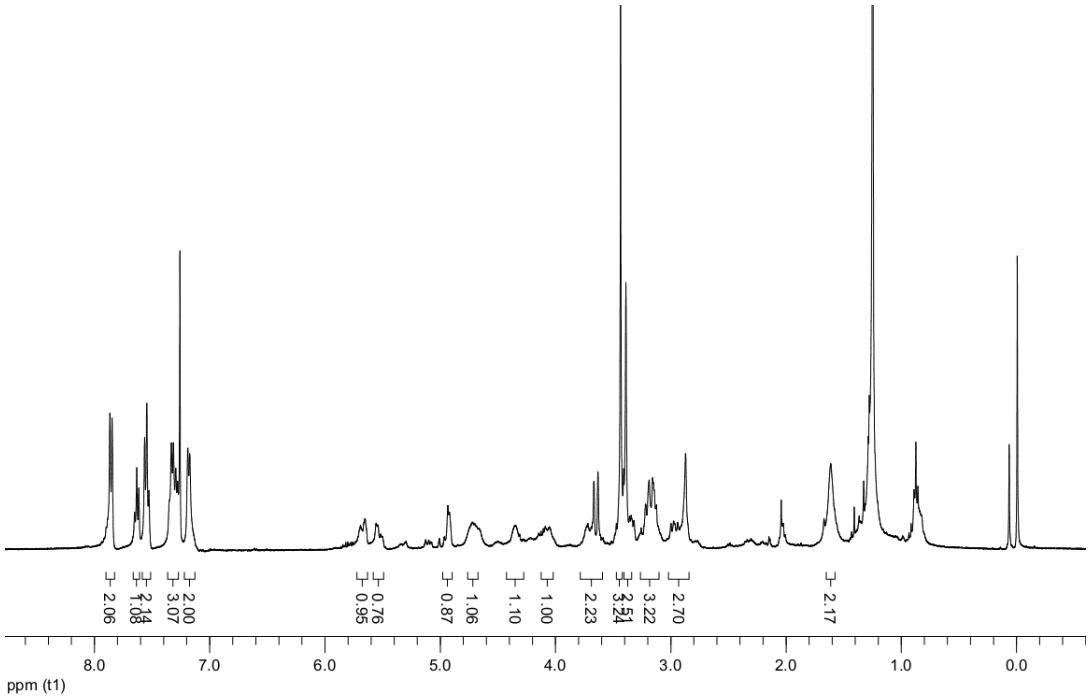
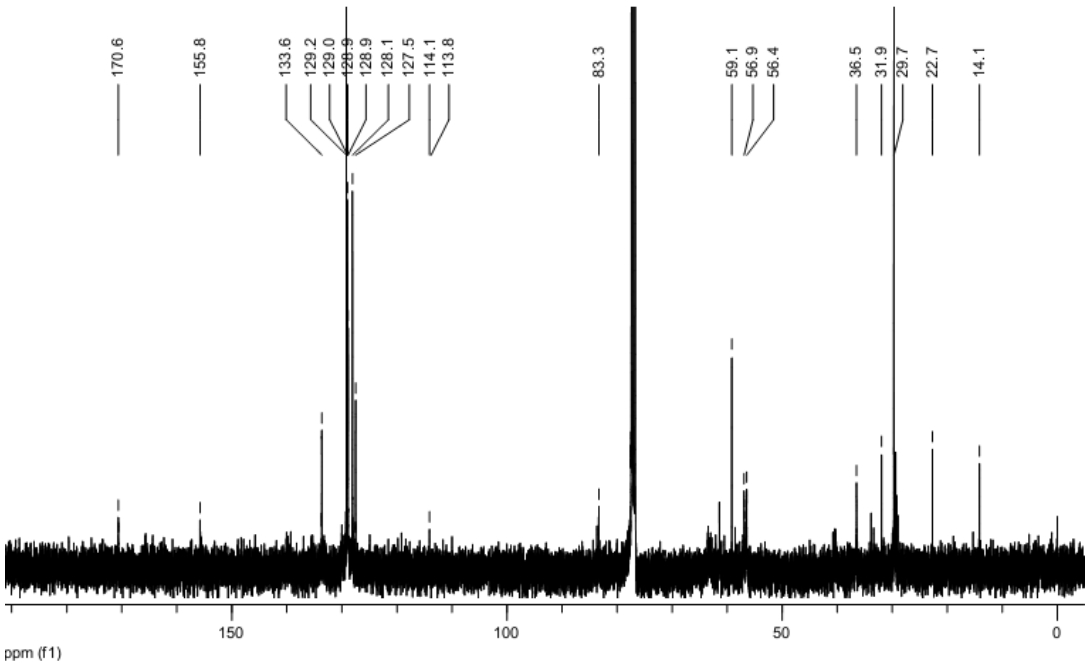
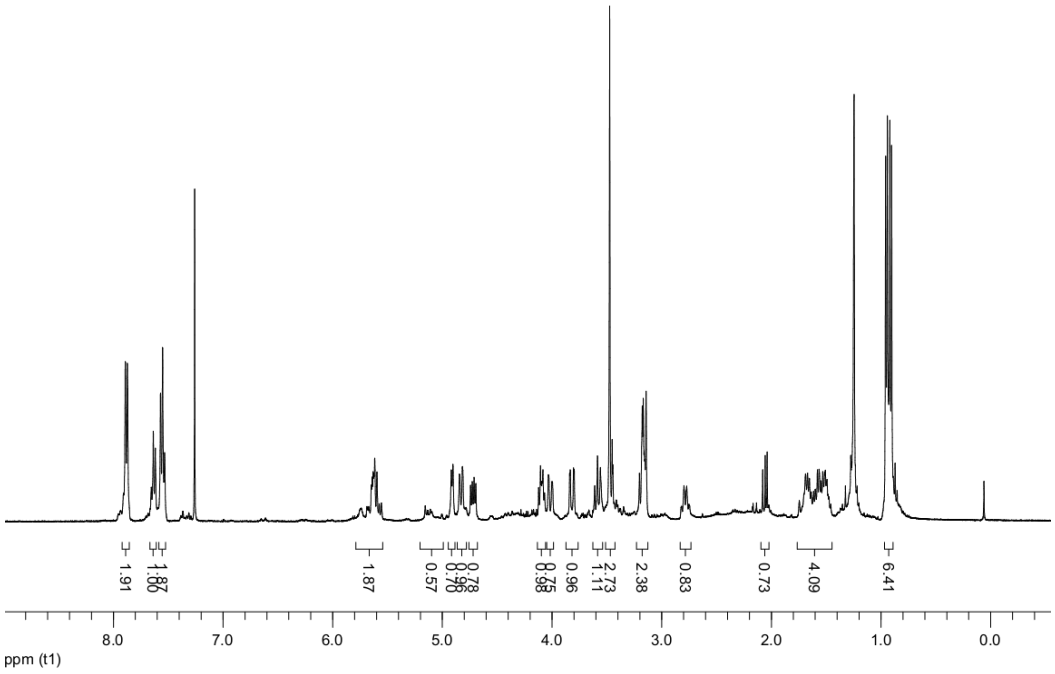


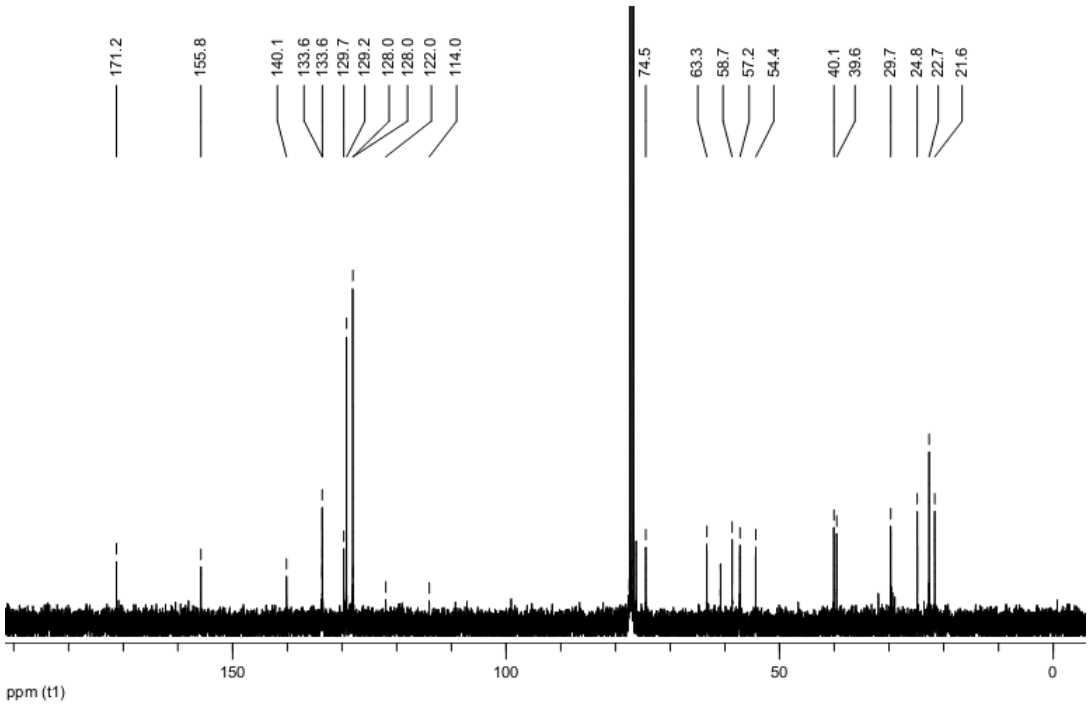
^{13}C NMR (100 MHz, $CDCl_3$) of compound **F6.2a**



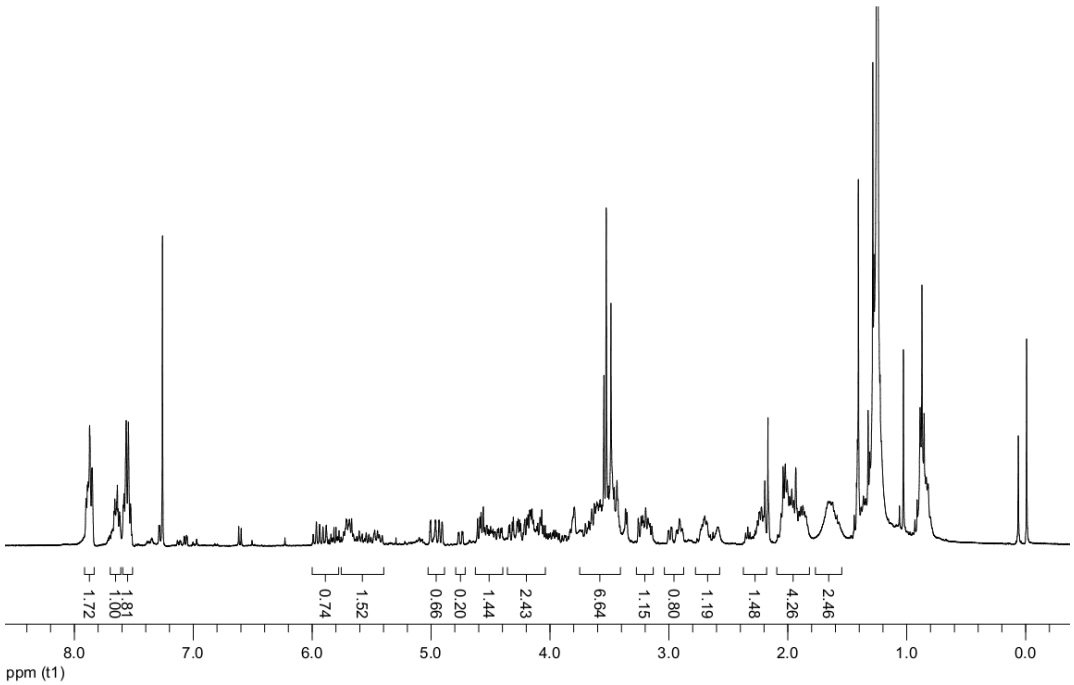
^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.2b**



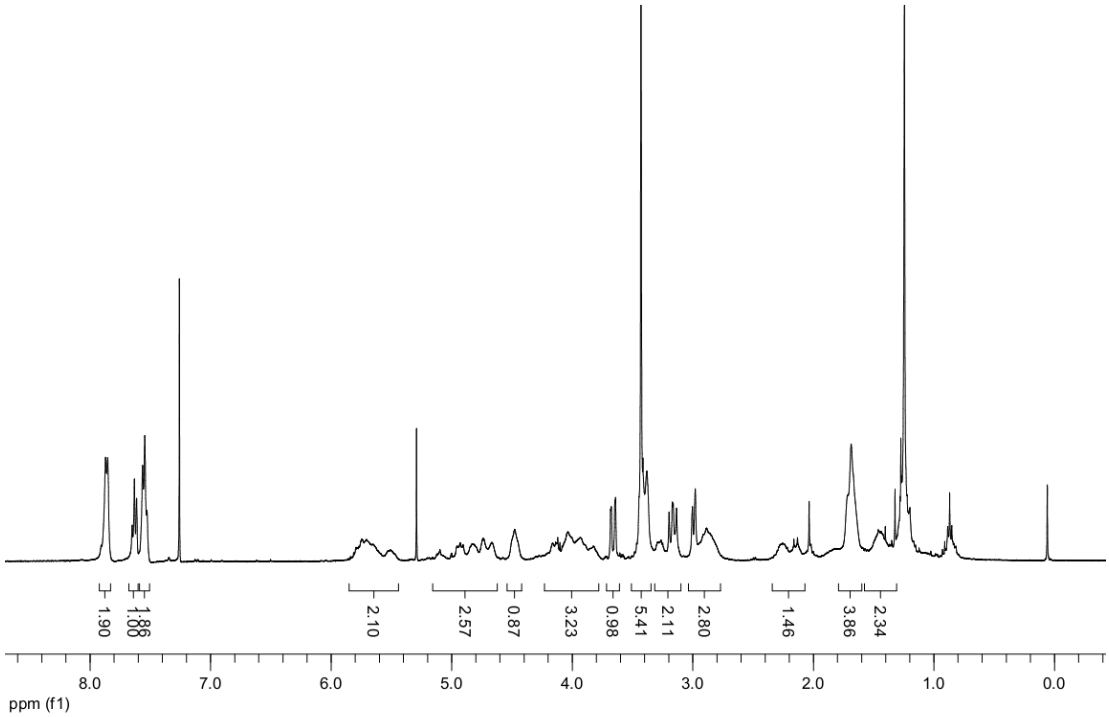
^{13}C NMR (100 MHz, $CDCl_3$) of compound **F6.2b**



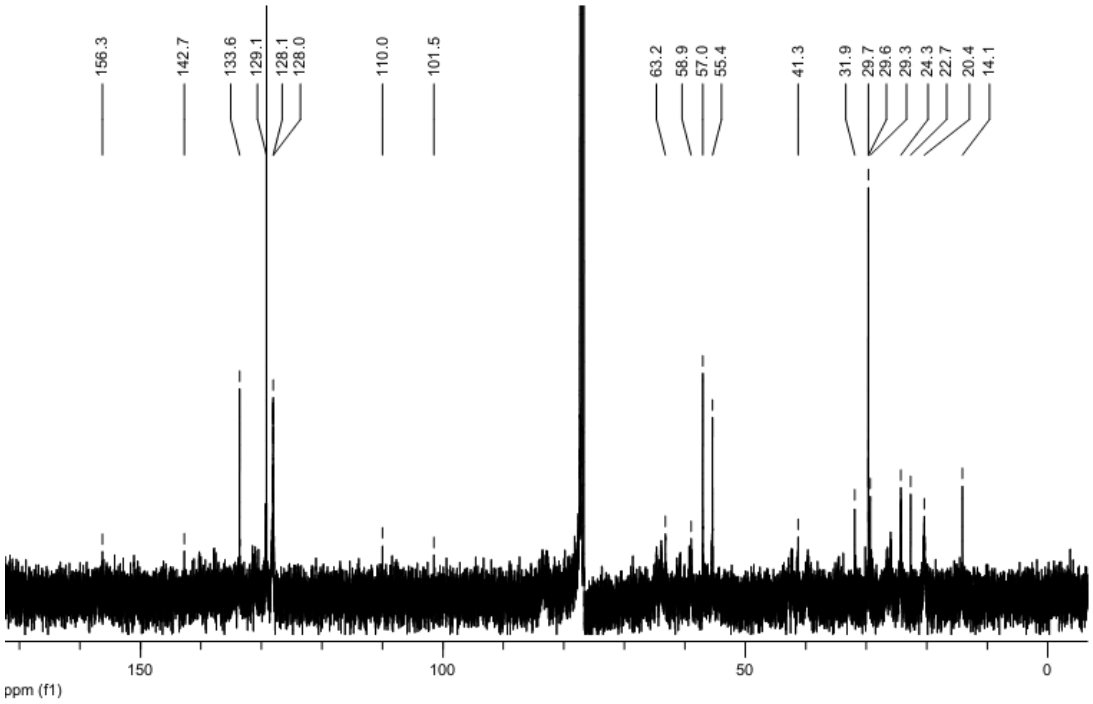
^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.2c**



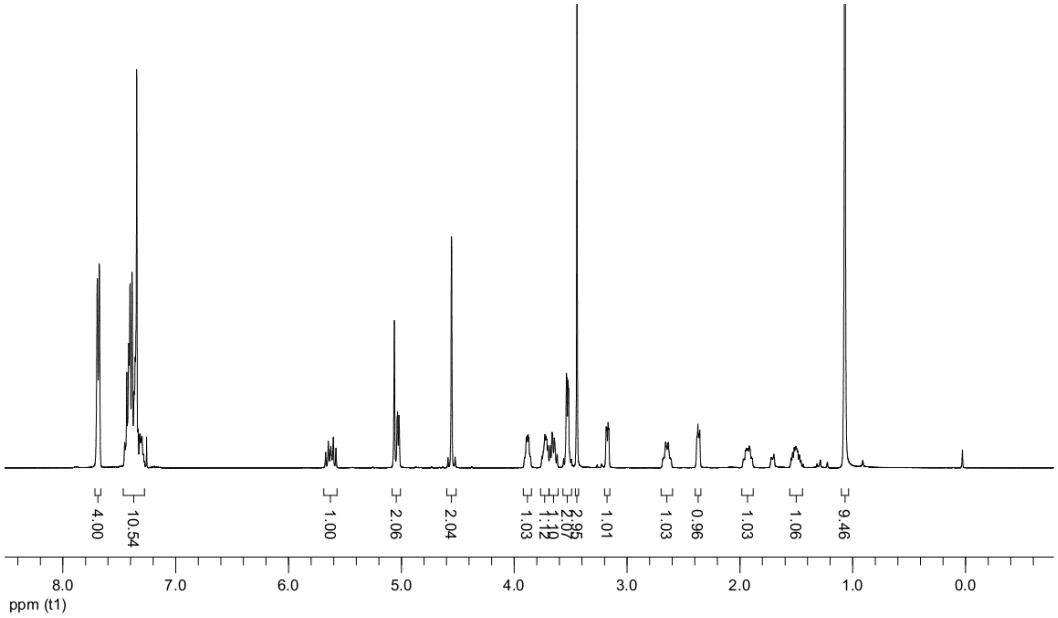
^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.2d**



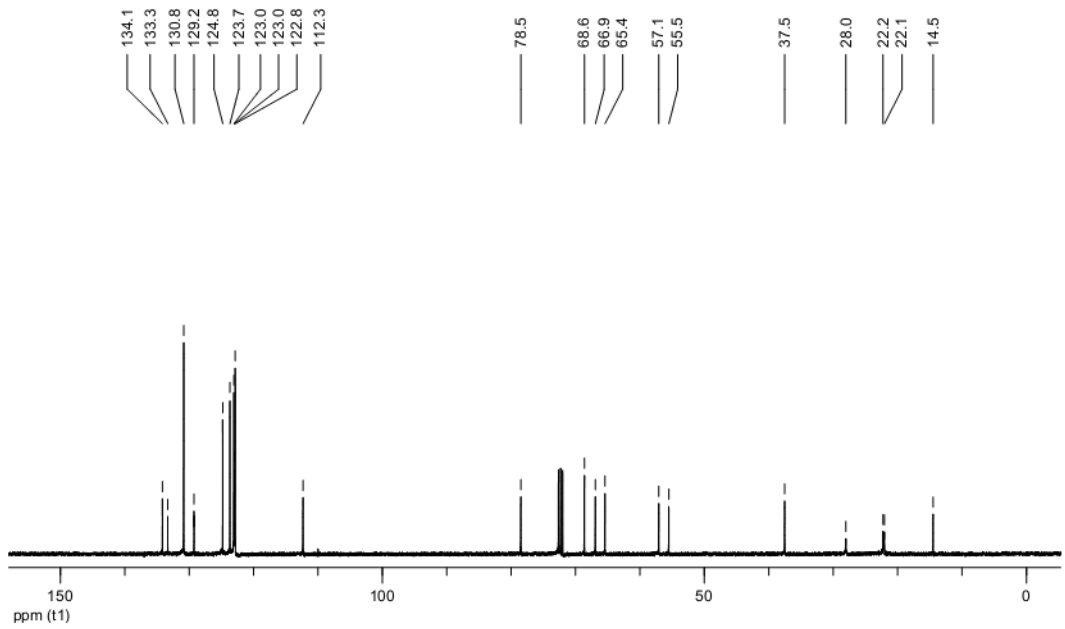
^{13}C NMR (100 MHz, $CDCl_3$) of compound **F6.2d**



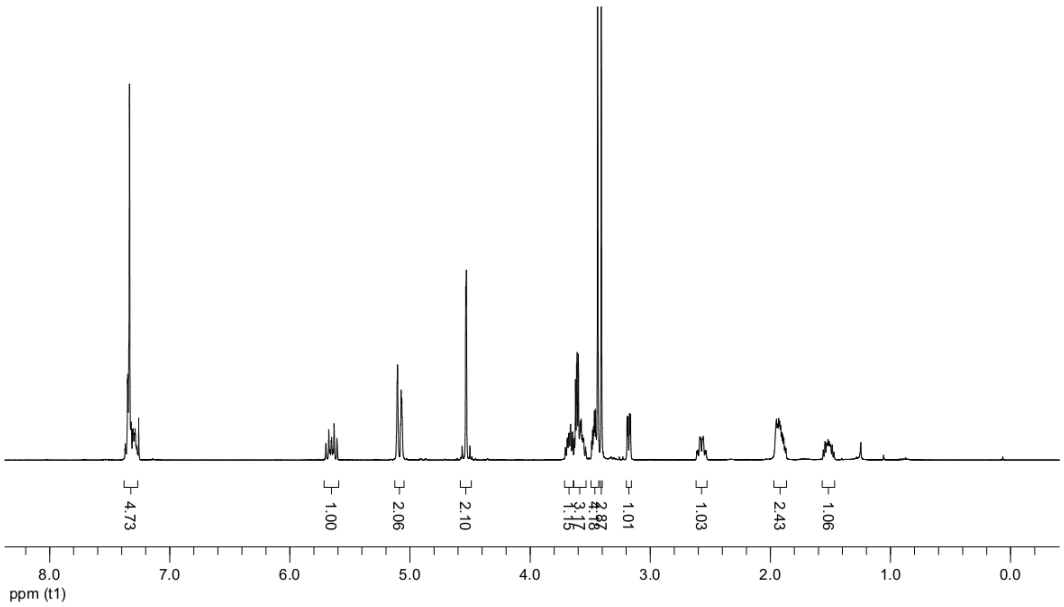
^{1}H NMR (400 MHz, $CDCl_3$) of compound **1.6**



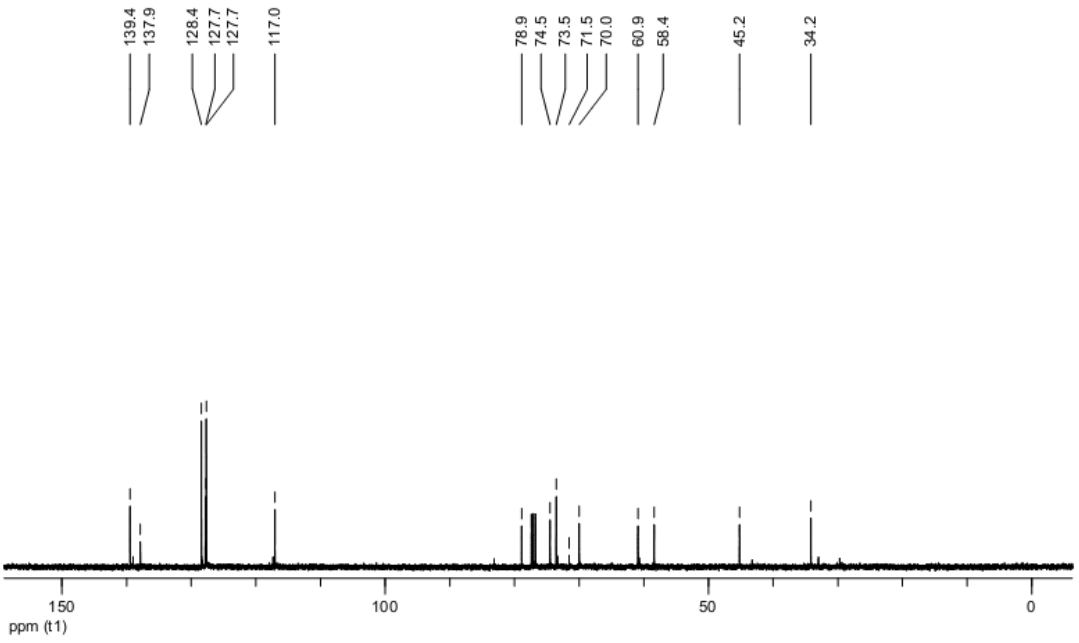
^{13}C NMR (100 MHz, $CDCl_3$) of compound **1.6**



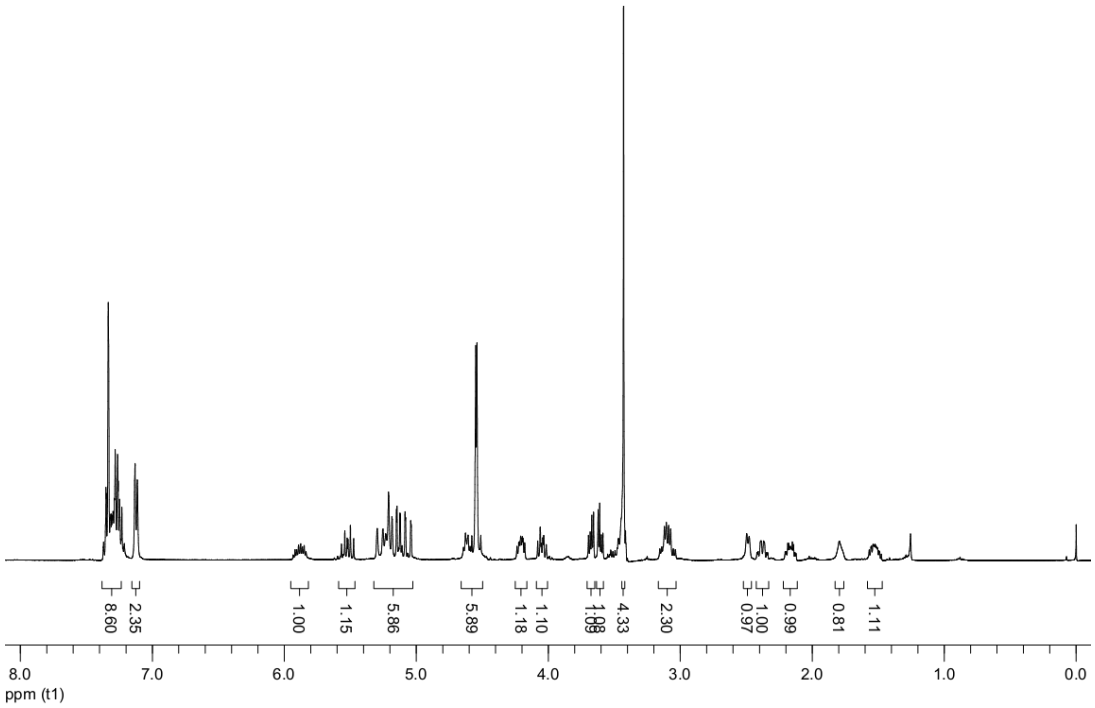
^{1}H NMR (400 MHz, $CDCl_3$) of compound **1.6.1**



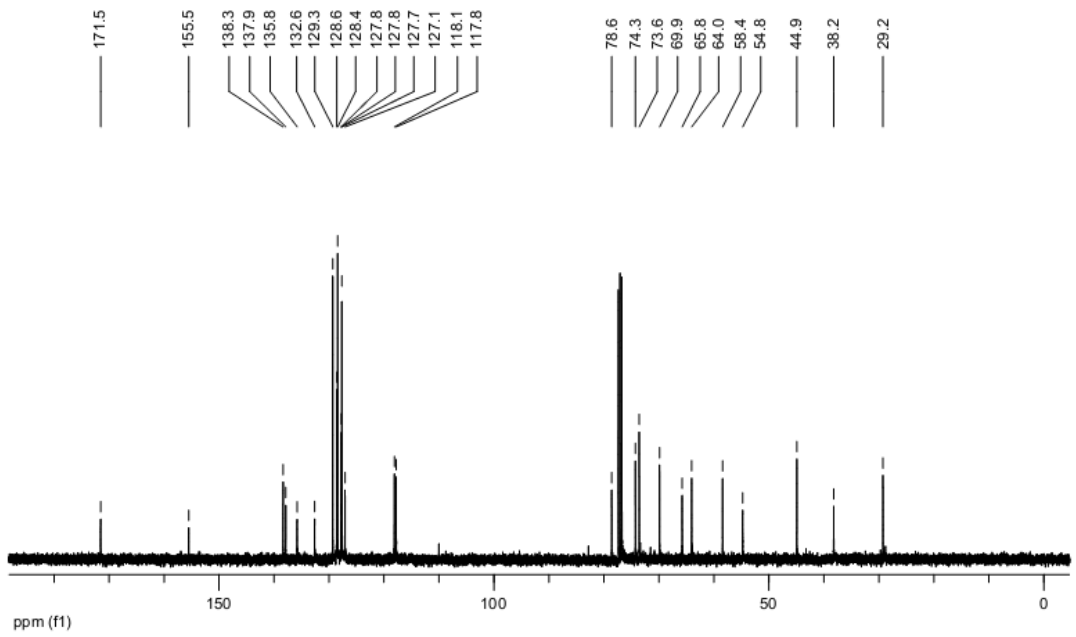
^{13}C NMR (100 MHz, $CDCl_3$) of compound **1.6.1**



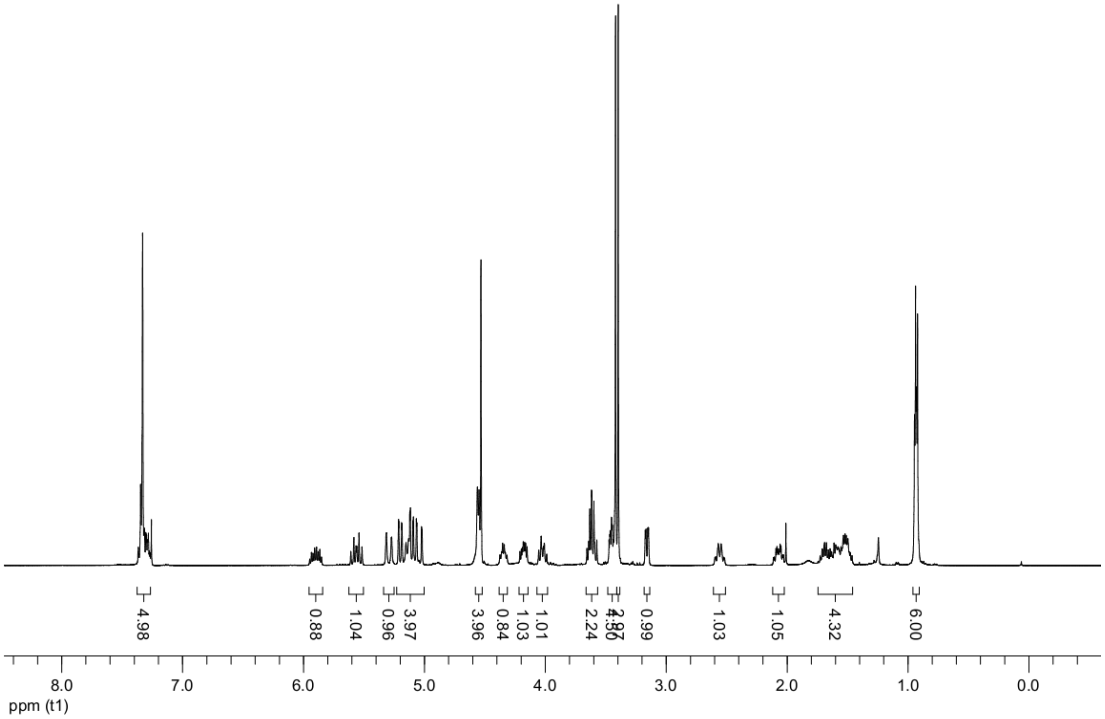
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.1a**



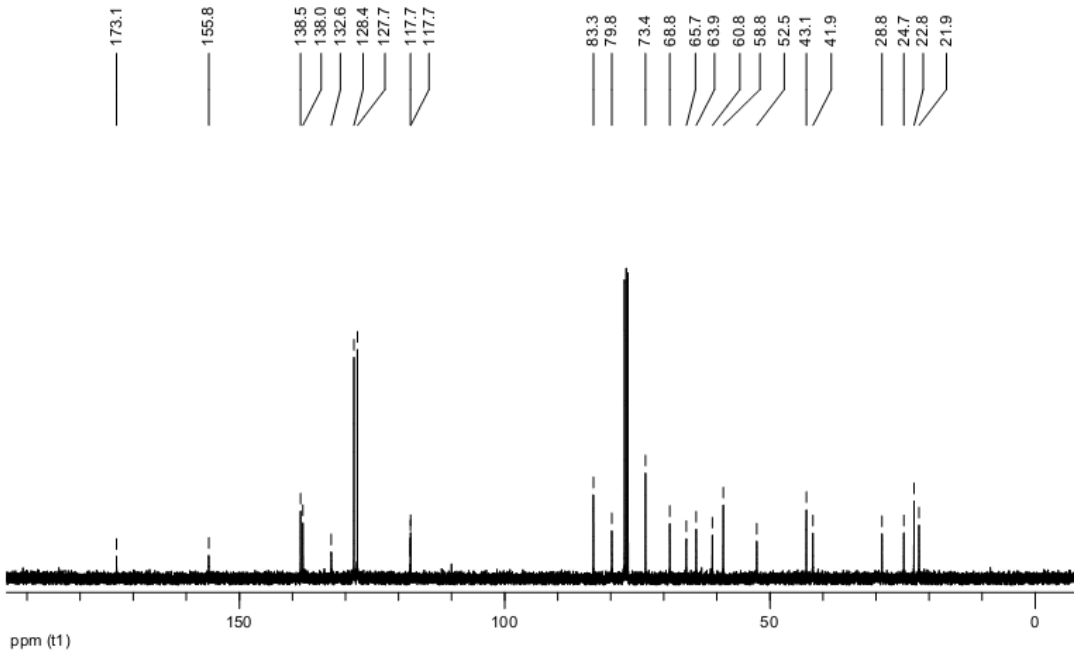
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.1a**



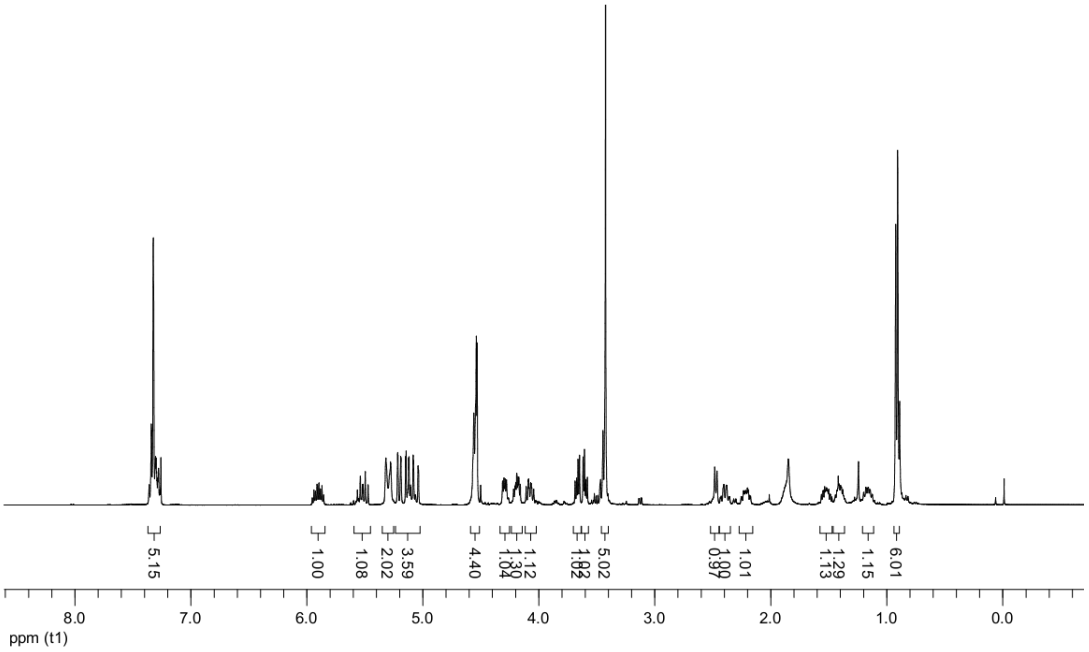
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.1b**



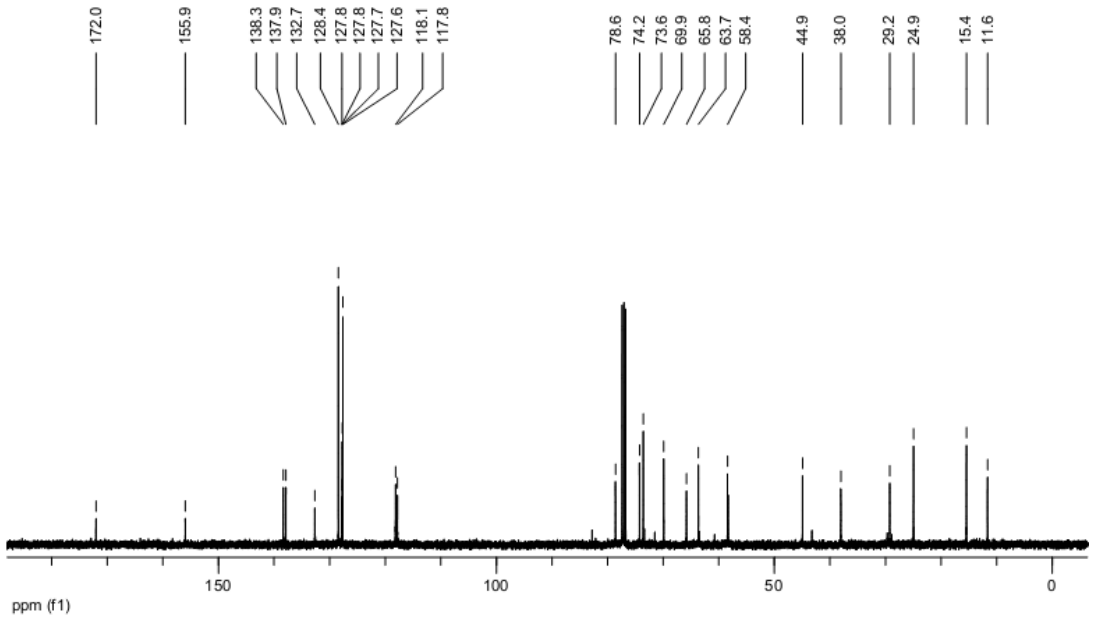
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.1b**



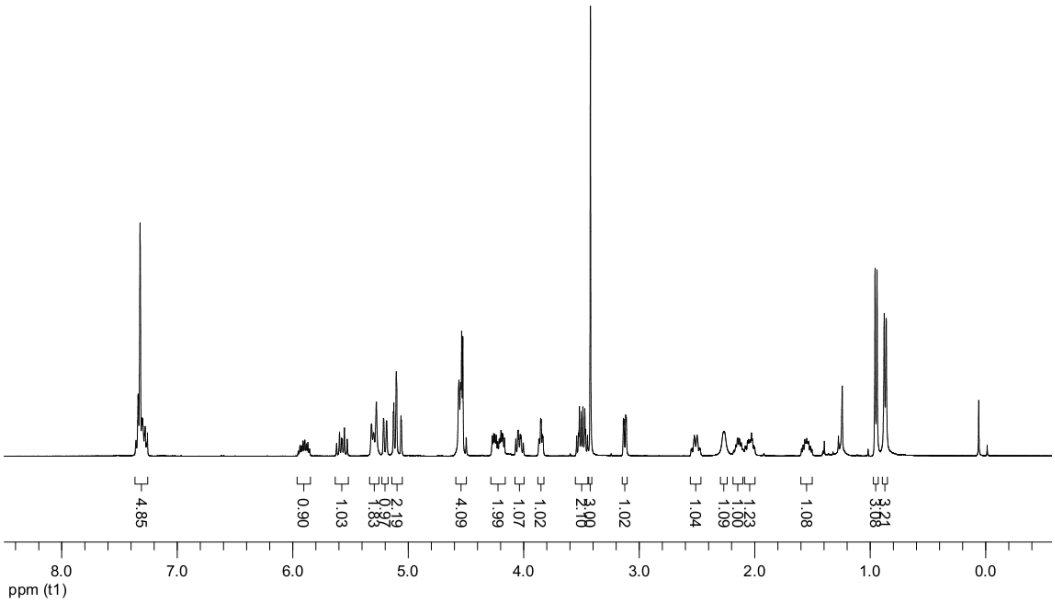
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.1c**



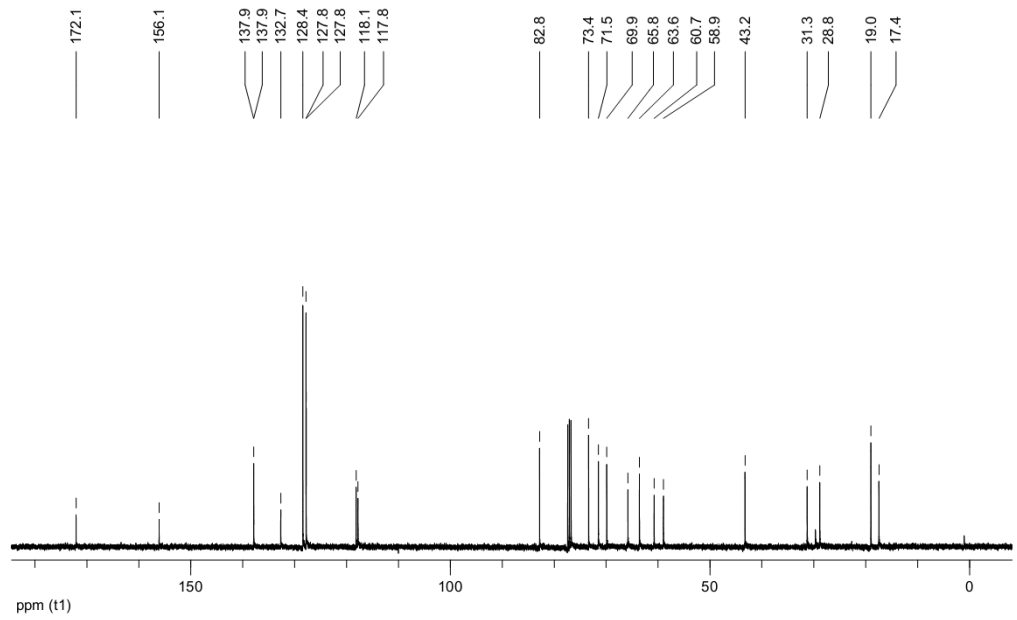
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.1c**



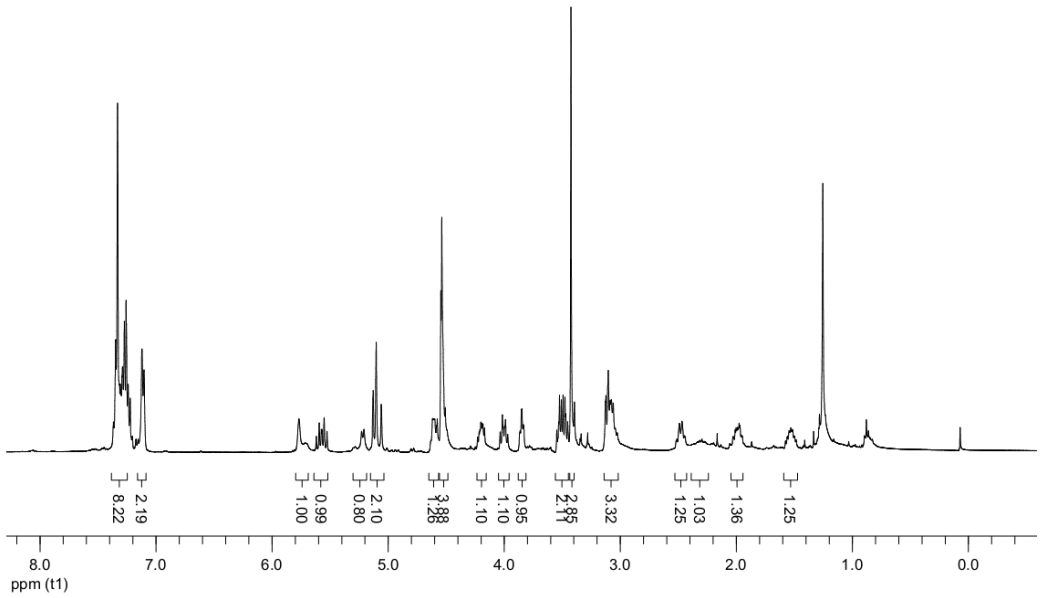
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.1d**



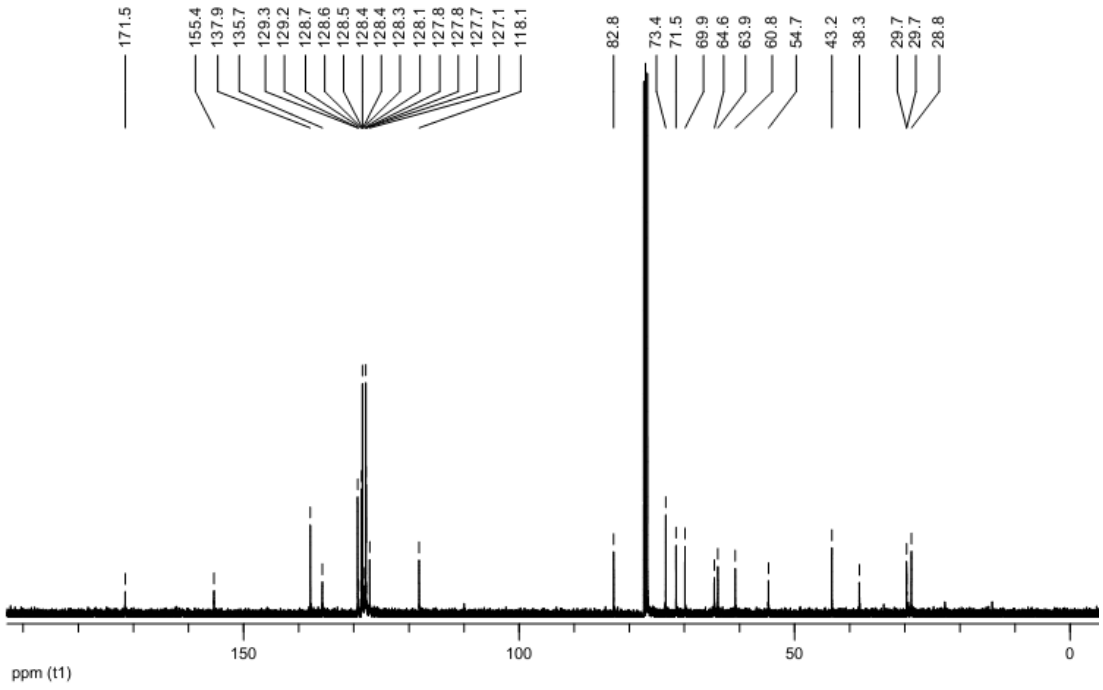
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.1d**



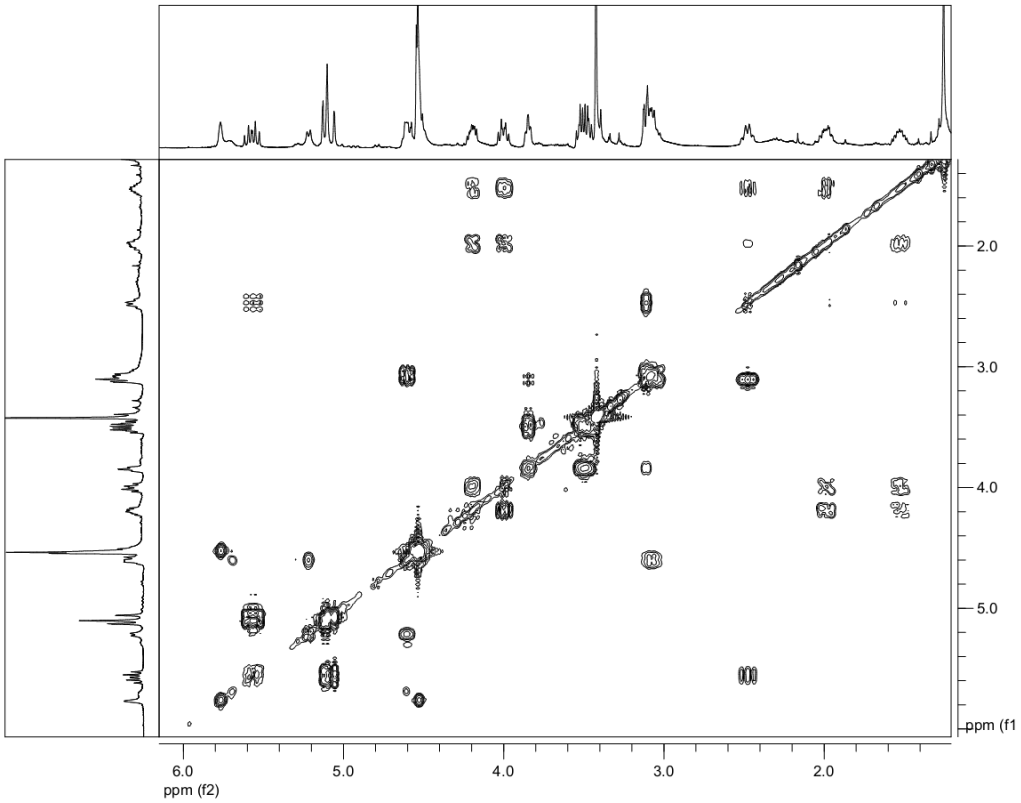
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.2a**



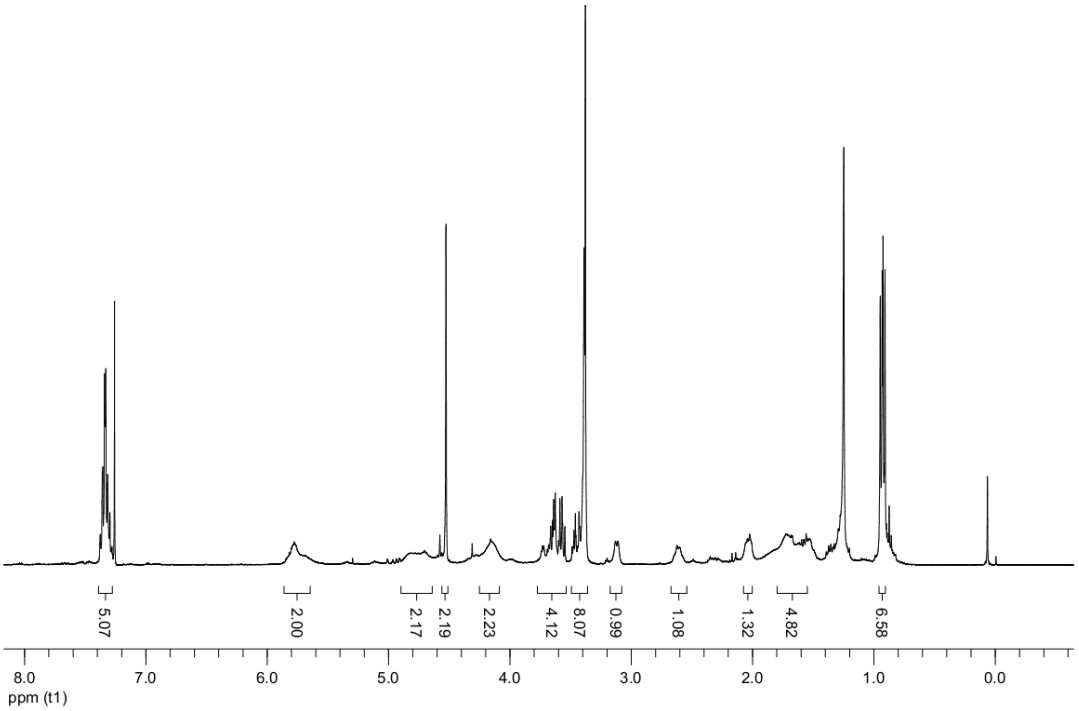
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.2a**



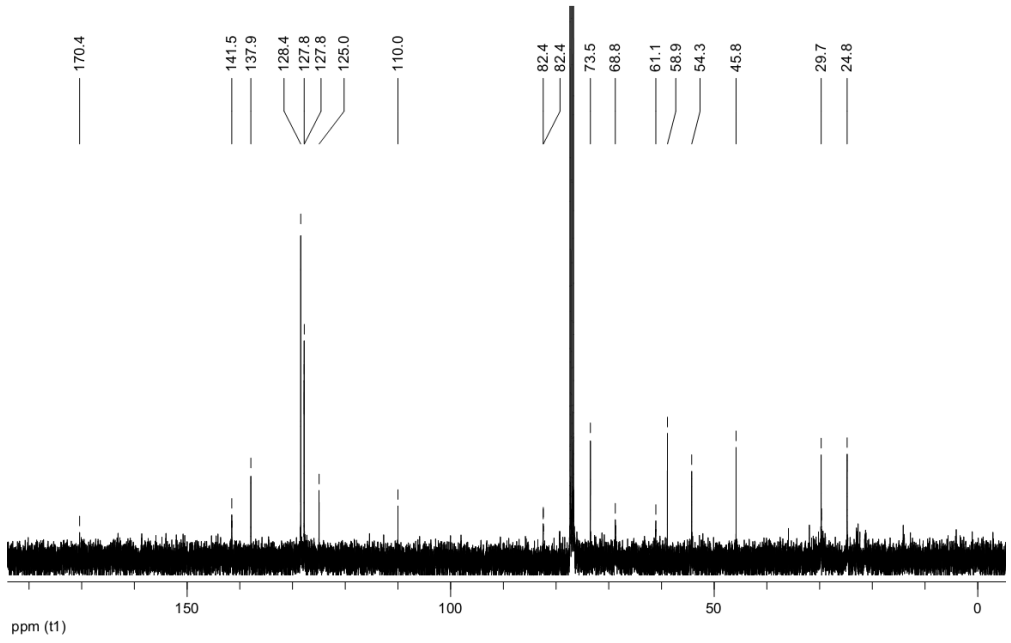
^{1}H -^{1}H COSY (400 MHz, $CDCl_3$) of compound **6.2a**



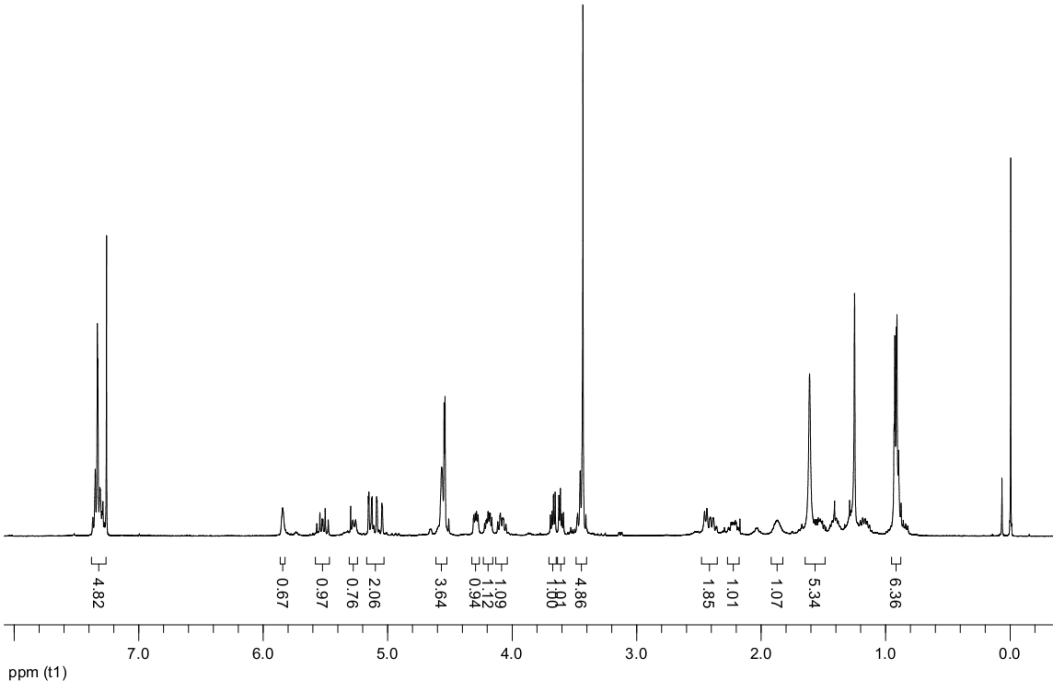
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.2b**



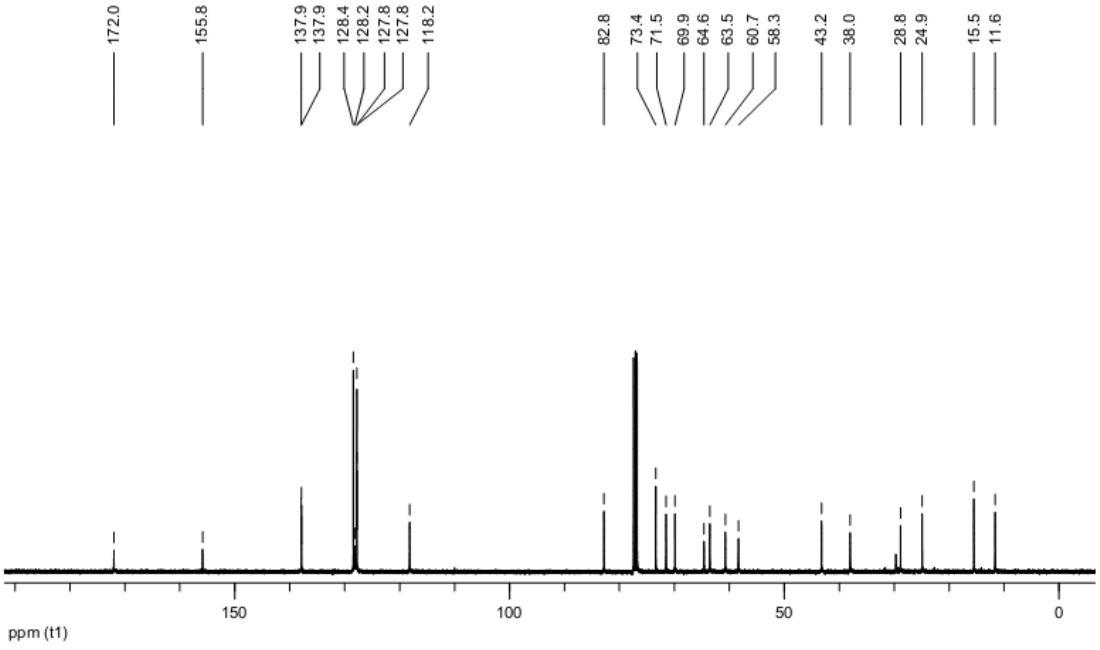
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.2b**



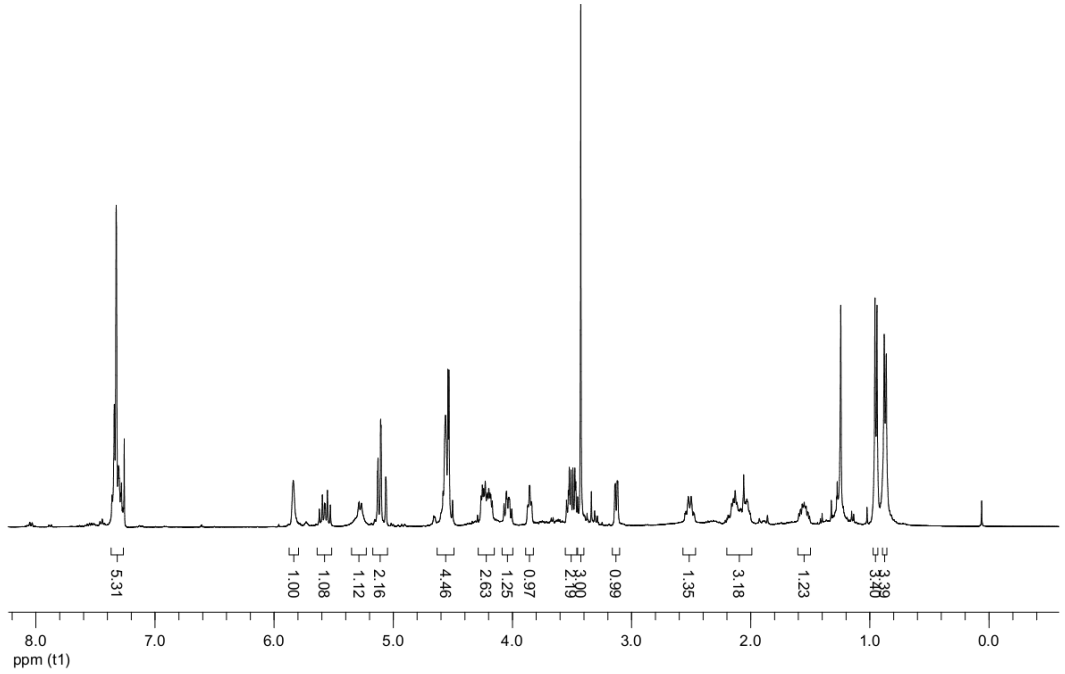
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.2c**



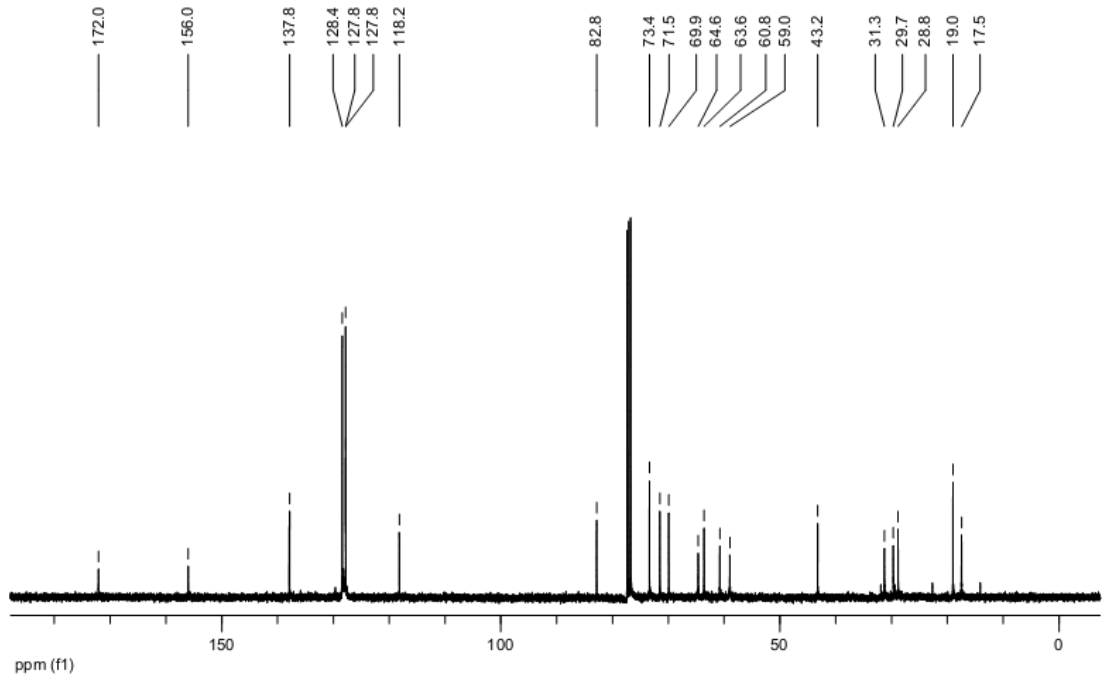
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.2c**



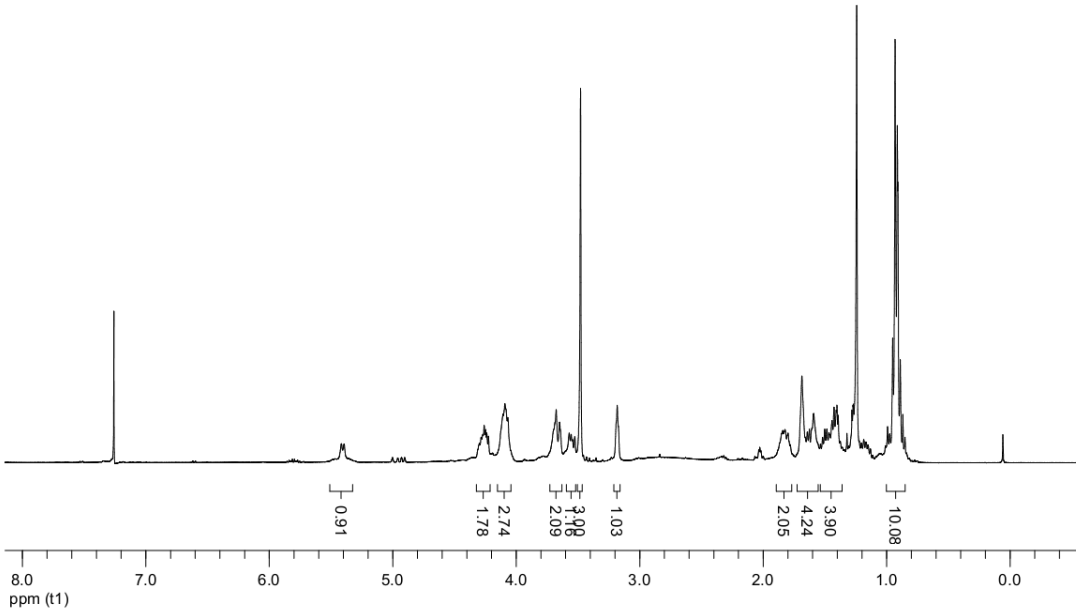
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.2d**



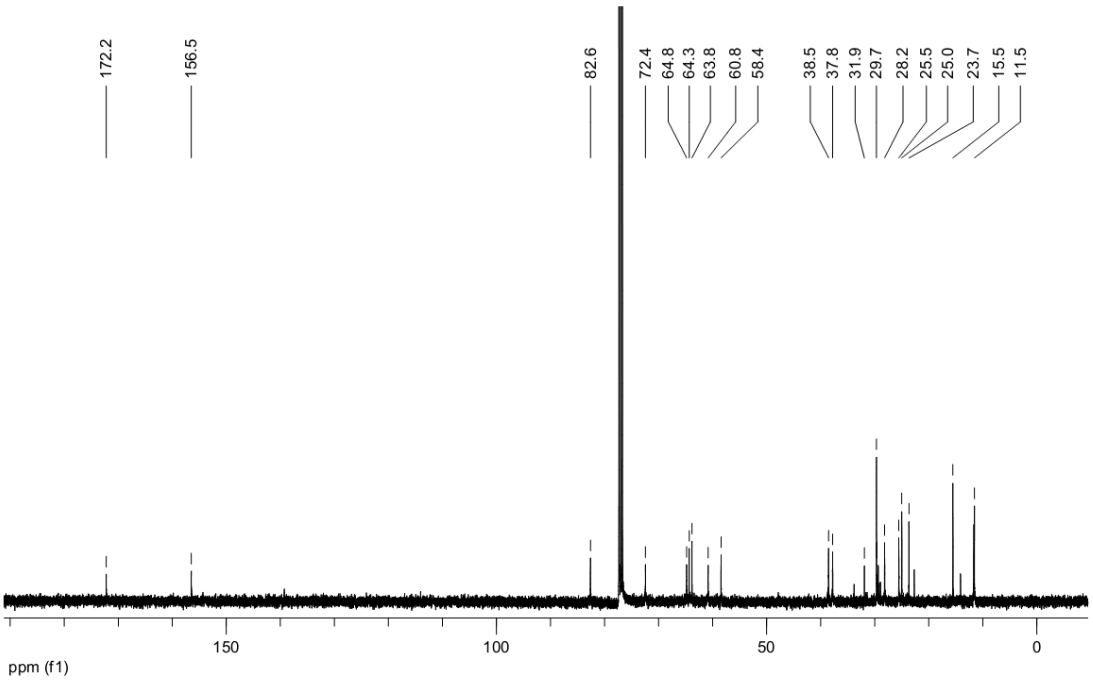
^{13}C NMR (100 MHz, $CDCl_3$) of compound **6.2d**



^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.3a**

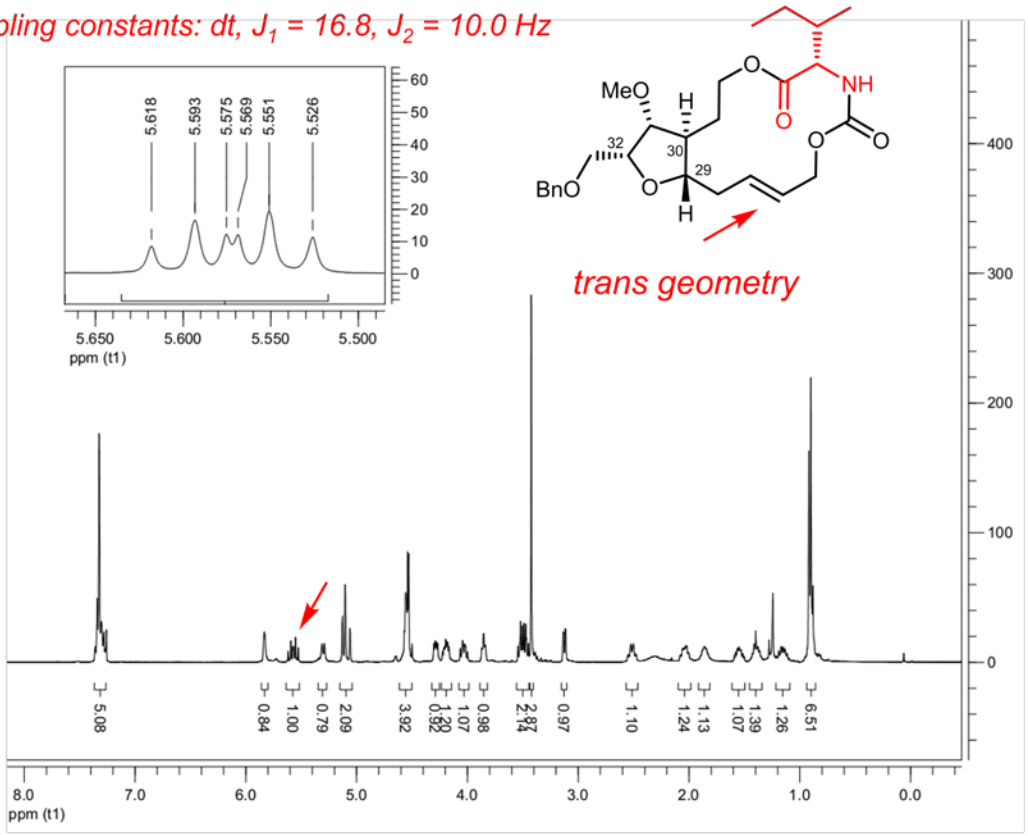


^{13}C NMR (100 MHz, $CDCl_3$) of compound **F6.3a**

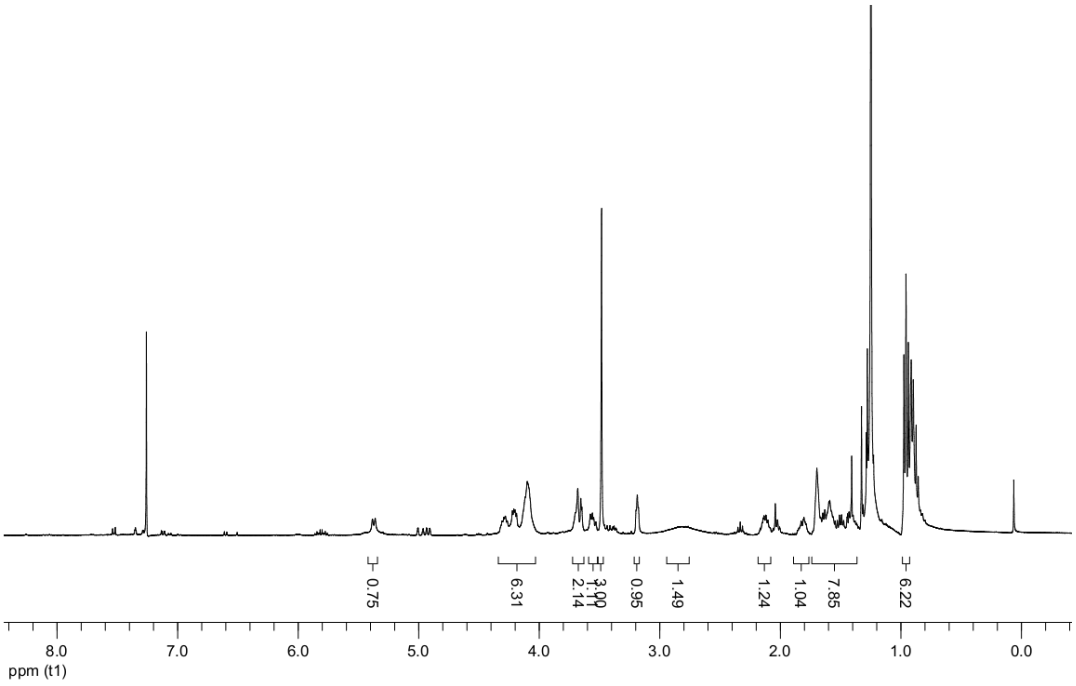


Olefin Geometry Assigned!

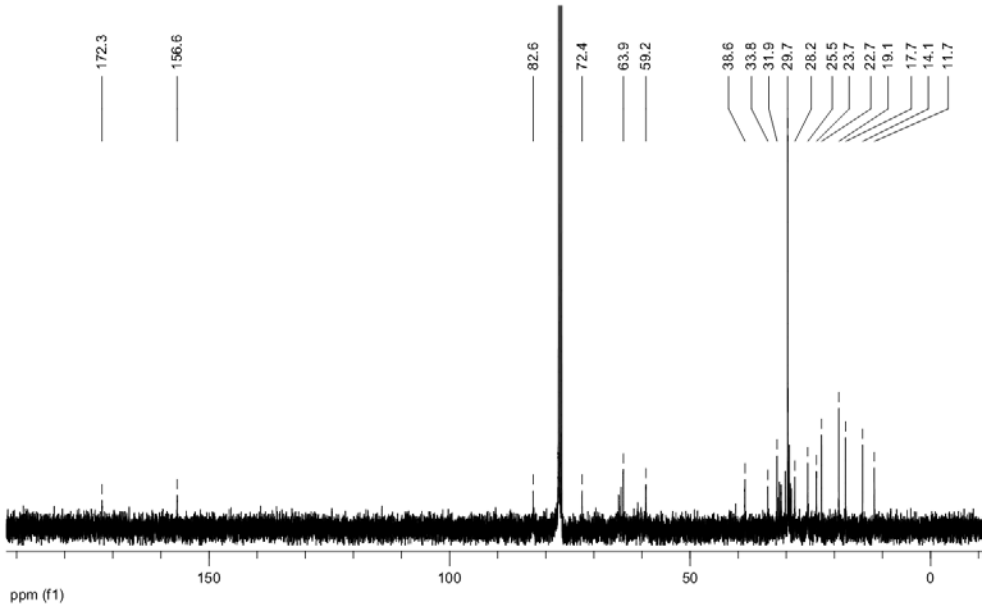
Coupling constants: dt, J_1 = 16.8, J_2 = 10.0 Hz



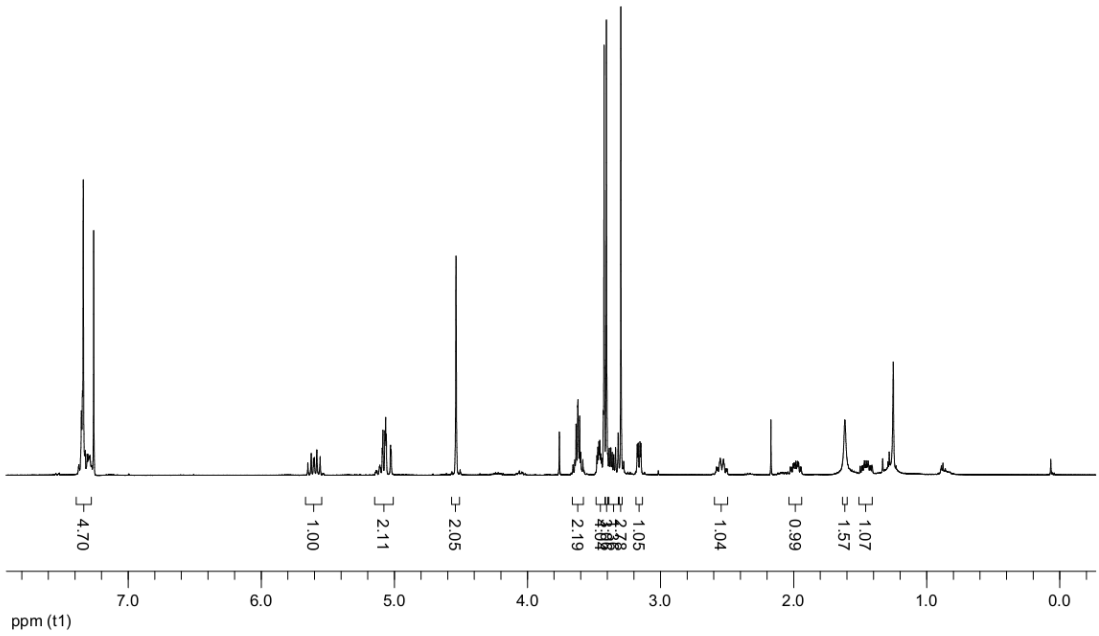
^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.3b**



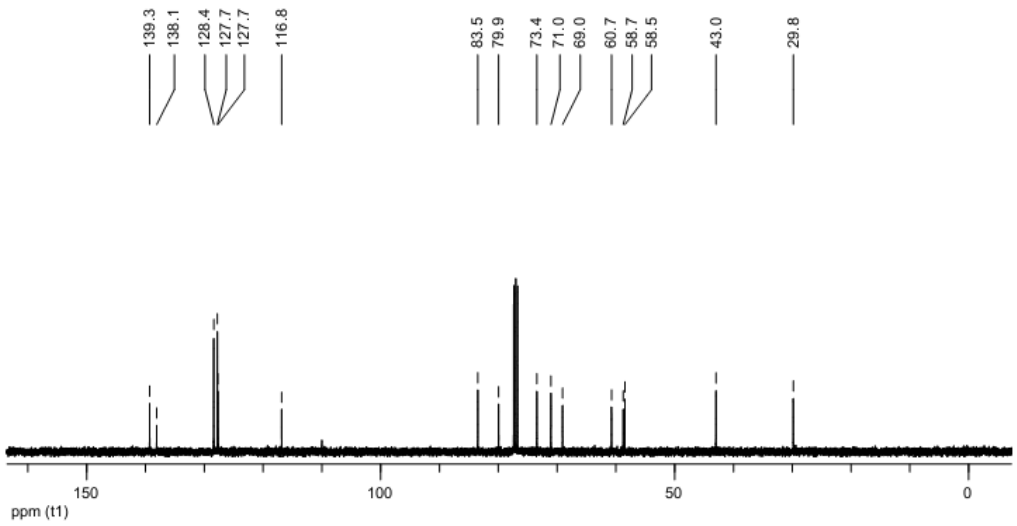
^{13}C NMR (100 MHz, $CDCl_3$) of compound **F6.3b**



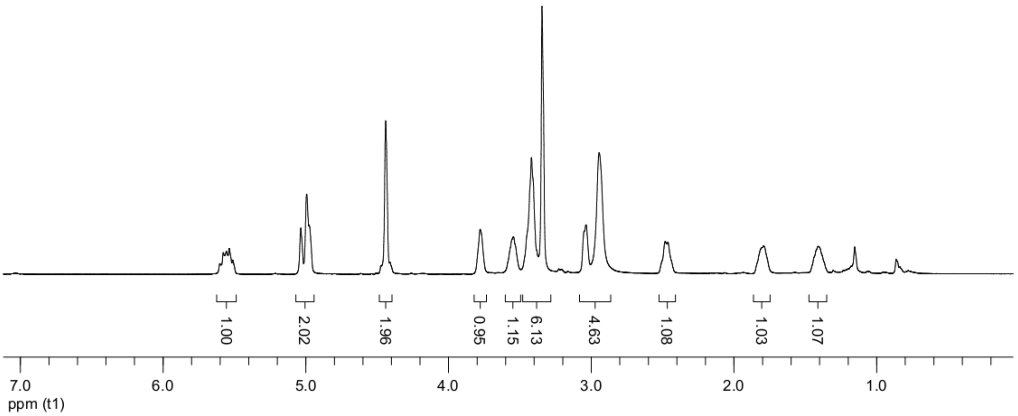
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8.1**



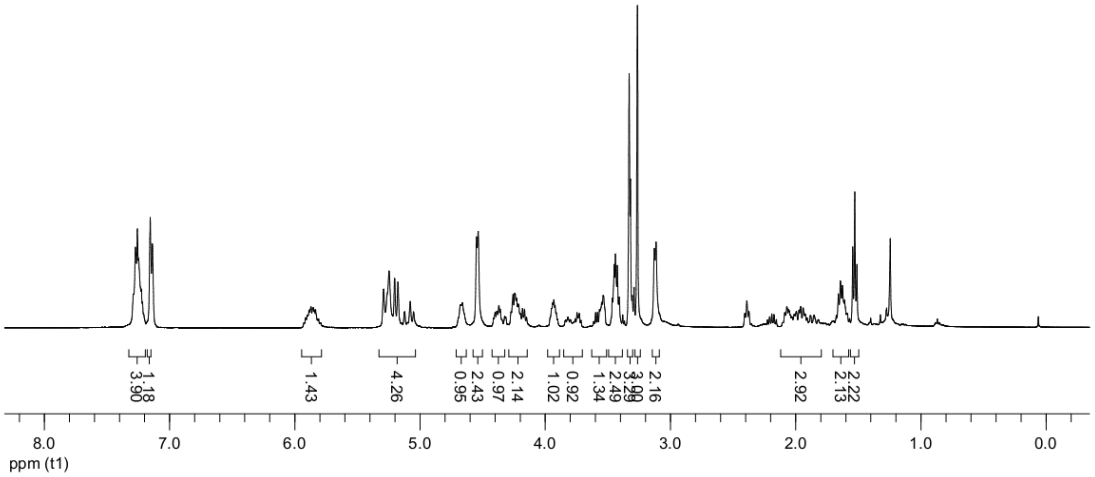
^{13}C NMR (100 MHz, $CDCl_3$) of compound **8.1**



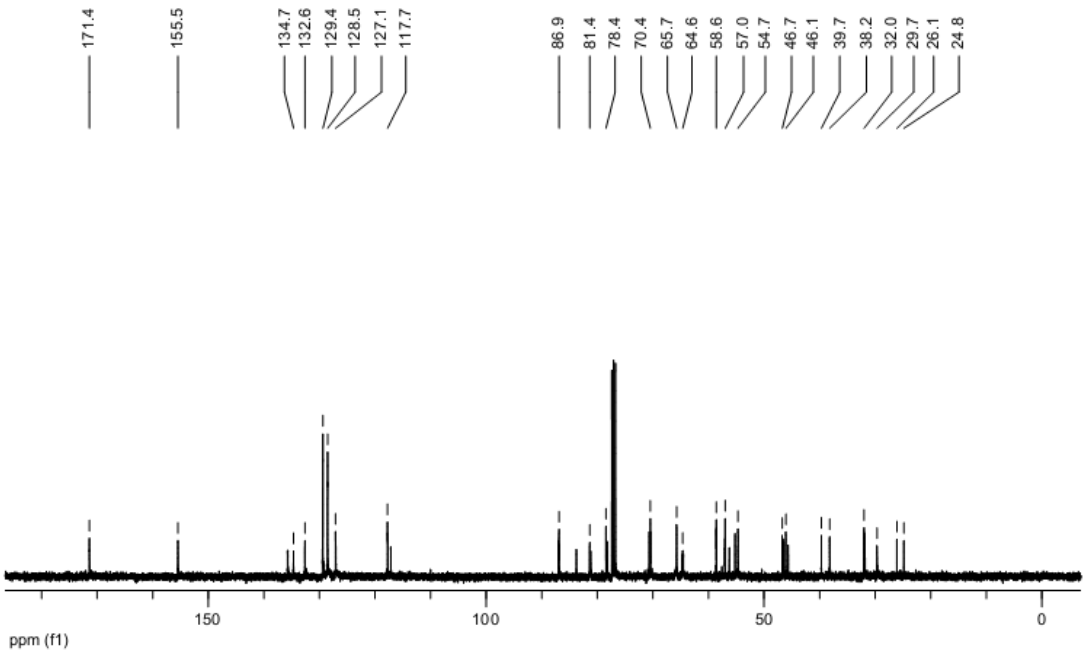
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8.1.1**



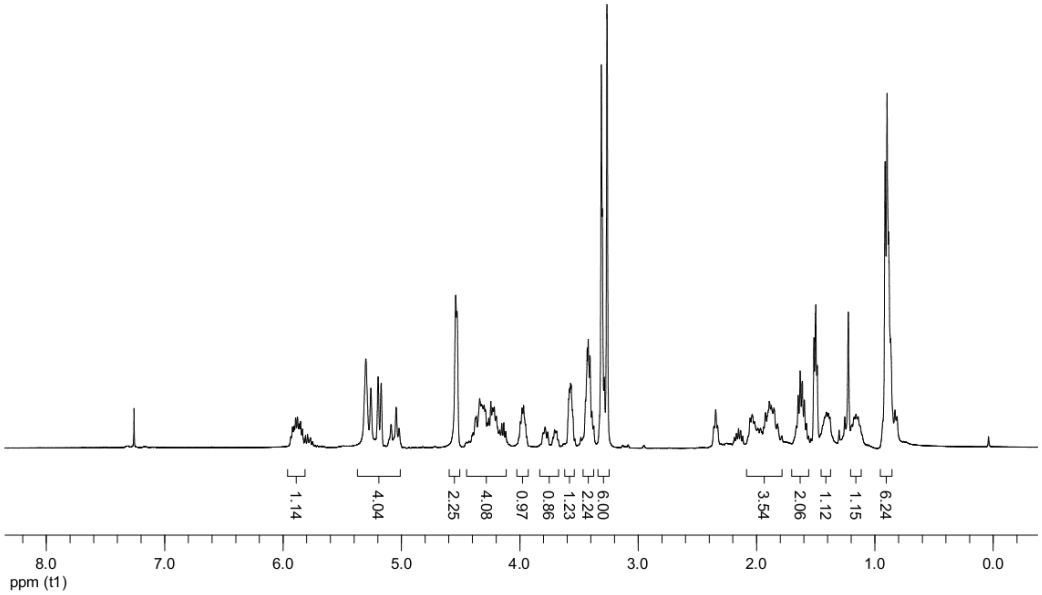
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8.2a**



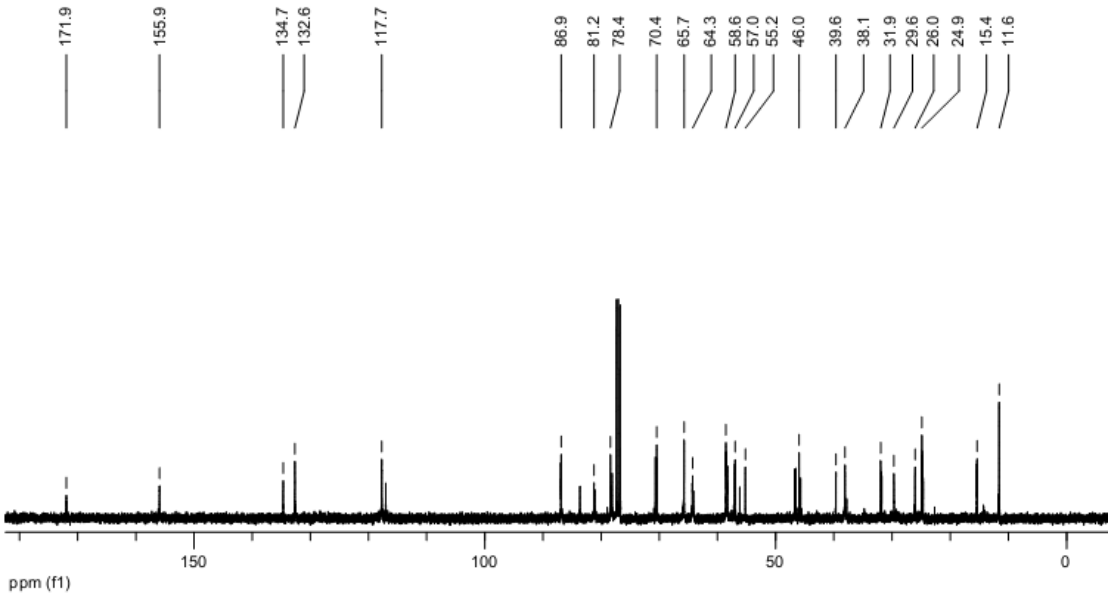
^{13}C NMR (100 MHz, $CDCl_3$) of compound **8.2a**



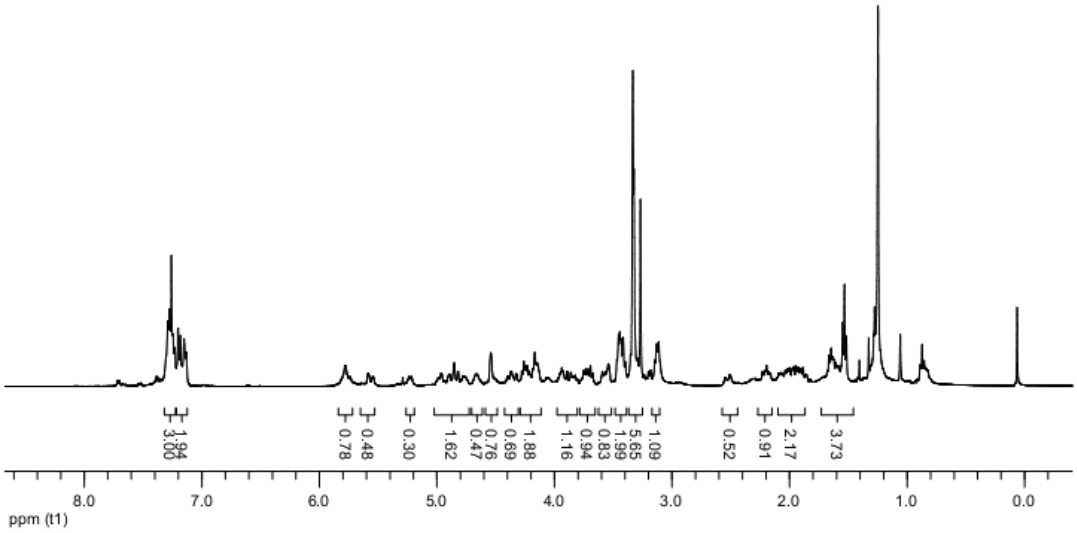
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8.2b**



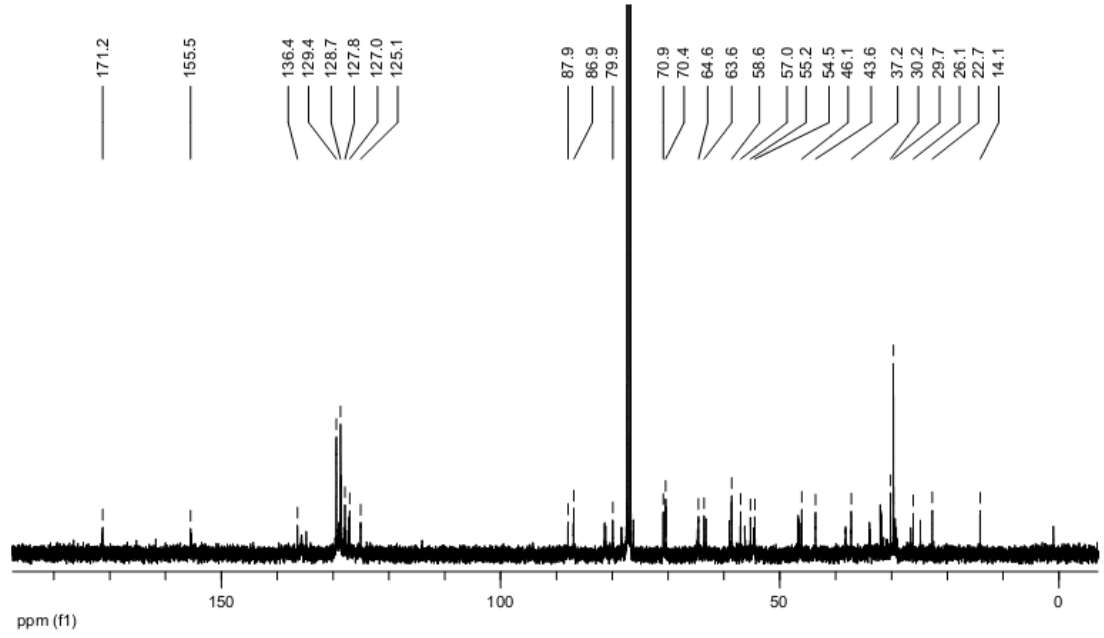
^{13}C NMR (100 MHz, $CDCl_3$) of compound **8.2b**



^{1}H NMR (400 MHz, $CDCl_3$) of compound **8.2.1**



^{13}C NMR (100 MHz, $CDCl_3$) of compound **8.2.1**



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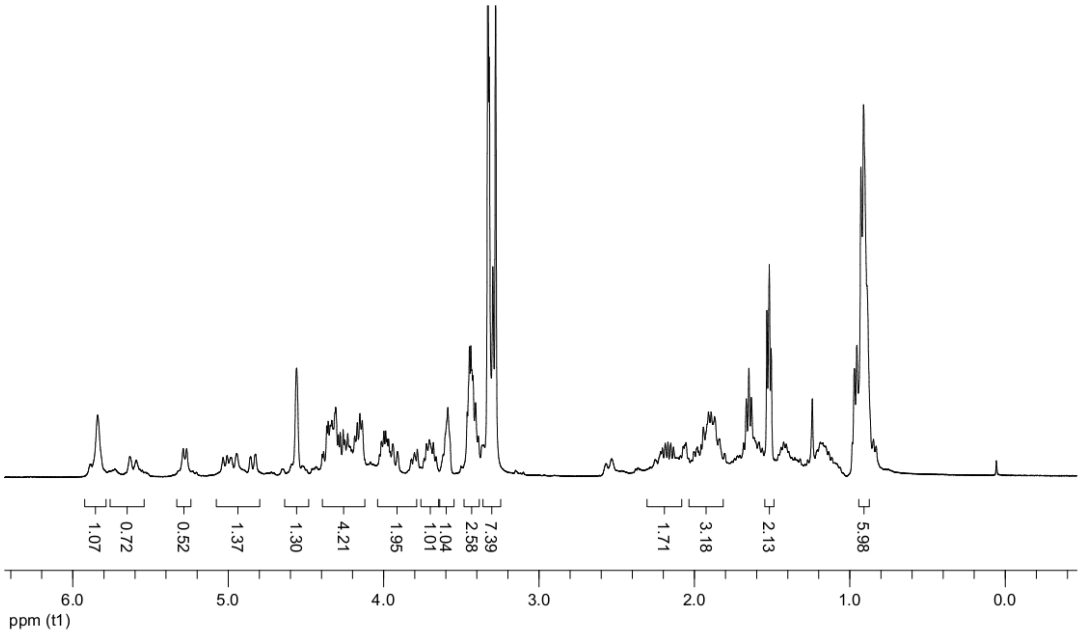
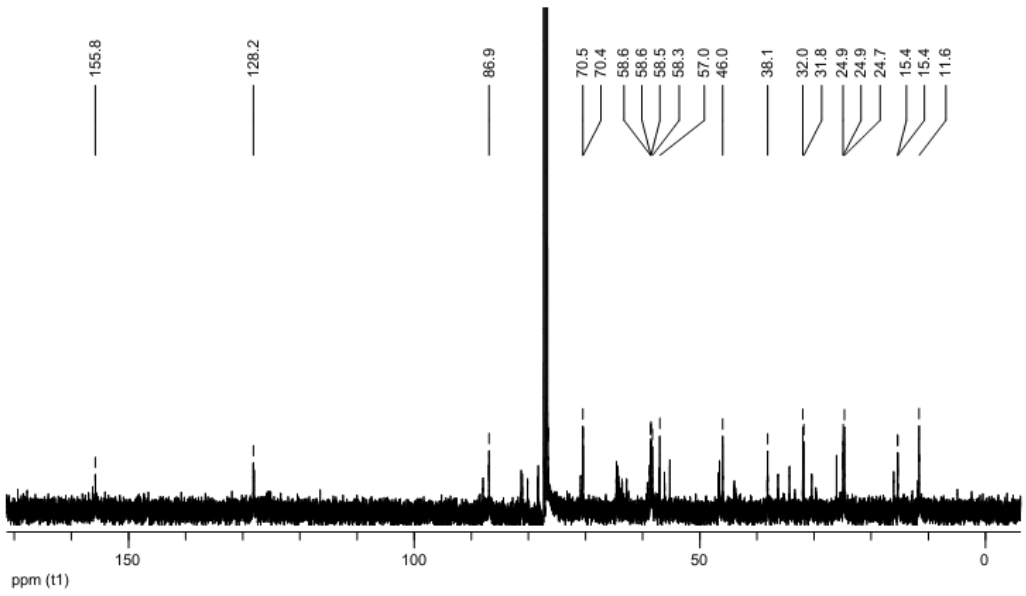
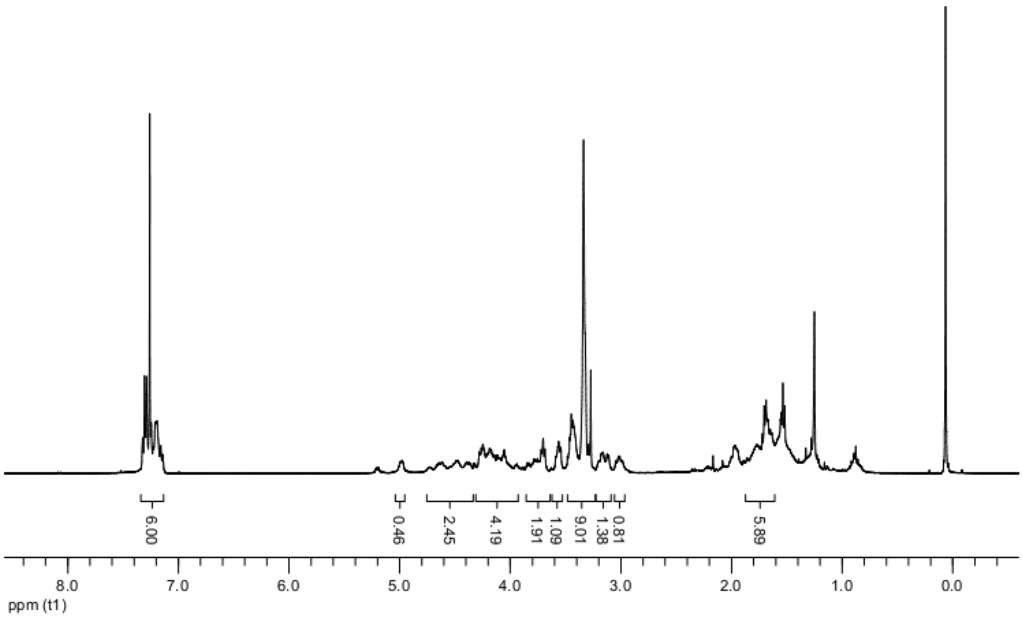


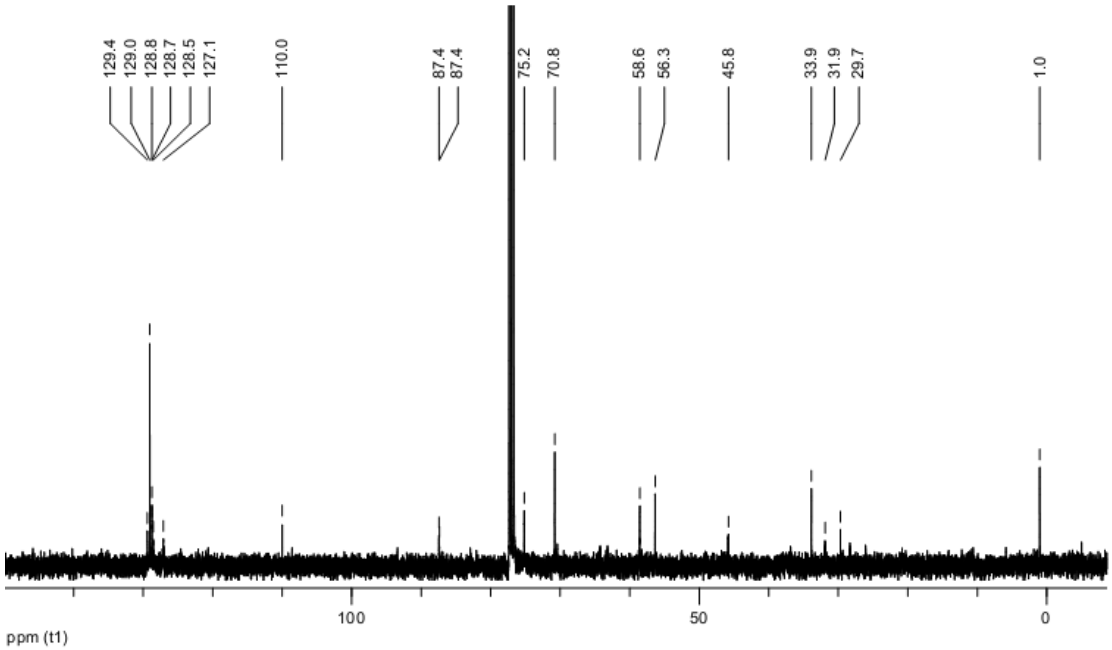
^{13}C NMR (100 MHz, $CDCl_3$) of compound **8.2.2**



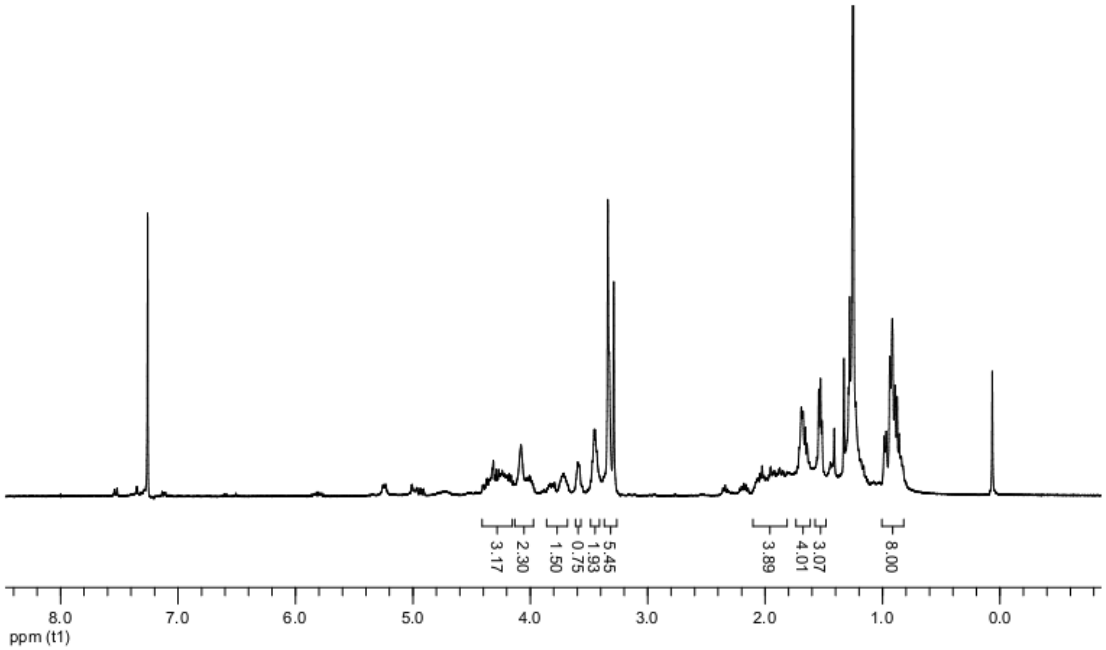
^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.4a**



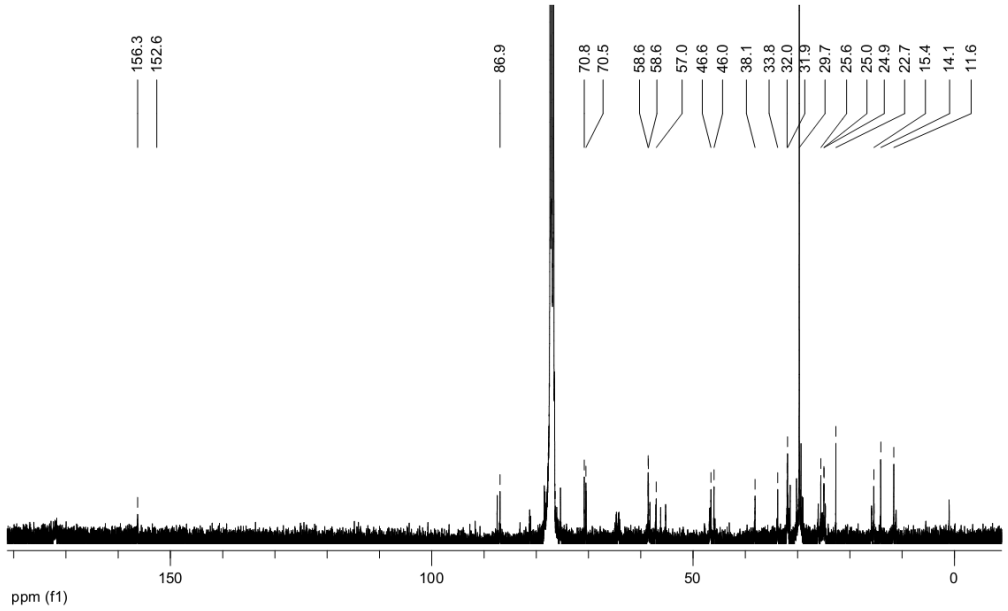
^{13}C NMR (100 MHz, $CDCl_3$) of compound **F6.4a**



^{1}H NMR (400 MHz, $CDCl_3$) of compound **F6.4b**



^{13}C NMR (100 MHz, $CDCl_3$) of compound **F6.4b**



Chapter 4

Synthesis of Novel Glycohybrids Using 1,3-Dipolar Cycloaddition Approach

In this chapter, I discussed a novel tricyclic monosaccharide triazole hybrids, namely, aryl substituted hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine derivatives from an intramolecular 1,3-dipolar cycloaddition of 6-azido-4-*O*-propargyl glycopyranosides.

4.1. Introduction

A carbohydrate-inspired molecular hybridization approach incorporating natural chiral carbohydrate templates with heterocyclic rings offers an opportunity for the generation of an interesting array of structures and templates for drug discovery.[1] For instance, small molecule carbohydrate-triazole hybrids have been utilized either as drug candidates or mechanistic probes to unravel various intricate biological pathways (**Figure 1**).[2]

Figure 1: Bioactive Triazole Carbohydrate Hybrids

4.2 Results and Discussion

The design and synthesis of triazoles by Huisgen's 1,3-dipolar cycloaddition reaction[3] between alkynes and alkyl azides, termed as 'click-chemistry' by Sharpless[4], appeared to us as a preferred means to rapidly assemble the tricyclic framework. Though, similar approaches have been described earlier for the synthesis of triazole-carbohydrate analogs[2c,5], the triazole moiety in these cases was invariably fused at the reducing end of various pentoses and hexoses. We were interested to synthesize fused carbohydrate aryl triazole hybrids, wherein, the presence of aryl rings render the analogs drug-like with favourable ClogP values.

In the results described here-in, we have focussed on the introduction of a 4-aryl-triazole at the non-reducing end of the sugar by effecting an intramolecular [3+2] Huisgen's cycloaddition between a propargyl and an azide moiety anchored at the 4- and C-6-OH group of D-glucopyranoside derivative, to construct the triazole ring along with the concomitant formation of 1,4-oxazepine ring.

4.3. Retrosynthesis

Retrosynthetic analysis of glycohybrids is shown in **Scheme 1**. The triazole formation was planned from **1.2** by heating at 140 ^{o}C in DMF, which could be obtained from the propargylation of azide **1.3**. The key intermediate azide **1.3** could be synthesized from methyl-D-glucopyranoside (**1.4**) in five steps.

Scheme 1: Retrosynthesis of Glycohybrids

4.4. Synthesis

Our synthesis was started with methyl-D-glucopyranoside **2.1** which upon 1,3 diol protection with benzaldehyde dimethyl acetal, catalytic amount of iodine in DMF

gives **2.2**[6] in 80% yield. Further, the benzylation of remaining alcohols with benzyl bromide and NaH conditions in DMF afforded **2.3** as pale yellow solid in 95% yield.[7] The removal of benzylidine with pTSA in methanol furnished **2.4**. The selective tosylation of primary alcohol with TsCl and Py as a base gave **2.5**[8]. It was then treated with NaN_3 in DMF at 80 ^oC and this approach furnished **2.6** in an excellent yield[8-9].

This key intermediate was further used for obtaining different substituted triazole compounds. Initially, we tried with simple tosylated propargyl alcohol (**2.7**) to obtain **2.8** in NaH in DMF conditions, then subjection of **2.8** to 1,3-dipolar cycloaddition in DMF at 80 ^oC without any metal catalyst afforded **2.9** in an excellent yield. Finally, we removed the benzyl protecting groups by hydrogenation using Pd/C in methanol to complete the synthesis of **2.10**.

Scheme 2: Synthesis of**.....2.10**

Following this, we then prepared different tosyl derivatives (**3.4a-3.4f**) with the propargyl alcohol as a starting material. Sonogashira coupling[10] of propargyl alcohol **3.1**, with different aryl bromides (**3.2**) using palladium tetrakis treiphenyl phosphine, CuI, and K_2CO_3 in DMF at 80 ^oC produced **3.3** in good yields[11]. This was then followed by tosylation of the hydroxyl group using TsCl, KOH condition afforded the different tosylated compounds (**3.4a-3.4f**).[12]

Scheme 3: Synthesis of Different Tosyl Derivatives

Further, we synthesized various substituted triazoles using **2.6** as the starting material. The propargylation of **2.6** with different tosylated compounds (**3.4a-3.4f**) in NaH, DMF condition gave us **4.1**. This upon subjection to 1,3-dipolar addition on heating at 140 ^{o}C in DMF afforded the different triazoles (**4.2a-4.2f**)[13] in good yields. Further, hydrogenation with Pd/C, MeOH led to completing the synthesis of substituted triazoles (**F2.1-F2.6**).

Scheme 4: Synthesis of Novel Glycohybrids

Figure 2: Derivatives Synthesized

4.5. Conclusion

In conclusion, I developed an efficient route for the synthesis of tricyclic monosaccharide-triazole hybrids by employing 1,3-dipolar cycloaddition as the key reaction. These new chemical motifs can serve as promising leads as drug candidates or probes for several cell signaling, metabolic pathways.

4.6. Experimental Procedure

(4aR,6S,7R,8R,8aS)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol

(2.2).

To a solution of **2.1** (10 g, 51.54 mmol) in anhydrous DMF, iodine (1.29 g, 5.15 mmol), benzaldehyde dimethyl acetal (8.4 ml, 56.70 mmol) were added and the reaction mixture was stirred at ambient temperature for 12h. The reaction was quenched with aqueous sodium thiosulphate solution and extracted with ethylacetate (3 × 100 mL) and washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the crude product which was purified by flash column chromatography (EtOAc) to provide **2.2** (10.5 g, 75%) as a white solid.

Molecular Formula: $C_{14}H_{18}O_6$

R_f: 0.5 (8:2 DCM/MeOH)

LRMS (M+1): 282.7

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.38-7.36 (m, 3H), 5.54 (s, 1H), 4.80 (d, *J* = 4.0 Hz, 1H), 4.30 (dd, *J* = 9.64, 4.4 Hz, 1H), 3.93 (t, *J* = 9.6 Hz, 1H), 3.86-3.71 (m, 2H), 3.68-3.59 (m, 1H), 3.54-3.44 (m, 4H), 2.81 (s, 1H), 2.33 (d, *J* = 8.78 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 129.2, 128.3, 126.2, 101.9, 99.7, 80.9, 72.8, 71.7, 68.9, 62.3, 55.5.

(4aR,6S,7R,8S,8aR)-7,8-bis(benzyloxy)-6-methoxy-2-phenylhexahydropyrano [3,2-d][1,3]dioxine

(2.3):

To a solution (DMF) of **2.2** (1.0 equiv, 5.5 g, 19.51 mmol) was added NaH (3.0 equiv, 1.4 g, 58.51 mmol), benzyl bromide (1.0 equiv, 6.95 ml, 58.51 mmol) at 0 ^{o}C and the reaction was stirred at ambient temperature. After 24 h, the reaction mixture was quenched with water and extracted with ethylacetate (3 × 100 mL). Combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (9:1 hexanes/EtOAc) to provide **2.3** (9.0 g, 99%) as a white solid.

Molecular Formula: $C_{28}H_{30}O_6$

R_f: 0.6 (1:9 EtOAc/hexanes)

LRMS (M+1): 462.9

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.39-7.25 (m, 13H), 5.55 (s, 1H), 4.91 (d, *J* = 11.25 Hz, 1H), 4.85 (dd, *J* = 11.69, 7.45 Hz, 2H), 4.70 (d, *J* = 12.15 Hz, 1H), 4.59 (d, *J* = 3.60 Hz, 1H), 4.27 (dd, *J* = 10.04, 4.71 Hz, 1H), 4.05 (t, *J* = 9.29 Hz, 1H), 3.79-3.87 (m, 1H), 3.71 (t, *J* = 10.27 Hz, 1H), 3.63-3.60 (m, 1H), 3.57-3.54 (m, 1H), 3.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.1, 137.4, 128.9, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 126.0, 101.2, 99.2, 82.1, 79.2, 78.6, 75.3, 73.7, 69.0, 62.3, 55.3.

(2R,3R,4S,5R,6S)-4,5-bis(benzyloxy)-2-(hydroxymethyl)-6-methoxytetrahydro-2H-pyran-3-ol

(2.4):

To a solution (MeOH) of **2.3** (1.0 equiv, 8.0 g, 17.31 mmol) was added pTSA (1.0 equiv, 3.2 g, 17.31 mmol) and the reaction was stirred at ambient temperature. The

reaction mixture was quenched after 24h with water and extracted with ethylacetate (3 × 50 mL). Combined organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (1:1 hexanes/EtOAc) to provide **2.4** (6.0 g, 90%) as a pale yellow solid.

Molecular Formula: $C_{21}H_{26}O_6$

R_f: 0.2 (1:1 EtOAc/hexanes)

LRMS (M+1): 375.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 10H), 5.03 (d, *J* = 11.22 Hz, 1H), 4.78-4.59 (m, 4H), 3.81-3.72 (m, 3H), 3.63-3.60 (m, 1H), 3.55-3.47 (m, 2H), 3.38 (s, 3H), 2.38-2.31 (s, 1H), 2.04-1.88 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 137.9, 128.5, 128.4, 128.0, 127.9, 127.9, 127.8, 98.1, 81.3, 79.7, 75.3, 73.1, 70.7, 70.2, 62.2, 55.2.

((2R,3R,4S,5R,6S)-4,5-bis(benzyloxy)-3-hydroxy-6-methoxytetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate

(2.5):

To a solution (DCM) of **2.4** (1.0 equiv, 6.0 g, 16.04 mmol) was added pyridine (5.0 equiv, 6.4 mL, 80.21 mmol) at 0 ^oC and the reaction was stirred for 10 min. Tosyl chloride (2.0 equiv, 6.09 g, 32.08 mmol) was added and the reaction was stirred at ambient temperature. After 24 h, the reaction mixture was quenched with 1N HCl solution and extracted with DCM (3 × 50 mL). Combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced presssure. The crude residue

was purified by column chromatography (8:2 hexanes/EtOAc) to provide **2.5** (7.4 g, 90%) as a gummy liquid.

Molecular Formula: $C_{28}H_{32}O_8S$

R_f: 0.7 (1:1 EtOAc/hexanes)

LRMS (M+17): 529.1

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.29 Hz, 2H), 7.38-7.28 (m, 12H), 4.99 (d, *J* = 11.50 Hz, 1H), 4.75-4.61 (m, 3H), 4.55 (d, *J* = 3.2 Hz, 1H), 4.22 (d, *J* = 3.54 Hz, 2H), 3.76-3.67 (m, 2H), 3.48-3.39 (m, 2H), 3.32 (s, 3H), 2.43 (s, 3H), 2.27 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 138.5, 137.8, 132.9, 129.7, 128.6, 128.5, 128.0, 128.0, 127.9, 127.9, 98.0, 81.0, 79.4, 75.4, 73.1, 69.4, 68.9, 68.8, 55.3, 21.6.

(2R,3R,4S,5R,6S)-2-(azidomethyl)-4,5-bis(benzyloxy)-6-methoxytetrahydro-2H-pyran-3-ol

(2.6):

To a solution of **2.5** (1.0 equiv, 7.0 g, 13.25 mmol) in DMF was added NaN_3 (exess) and the reaction was refluxed at 80 ^oC. After 24 h, the reaction mixture was filtered through celite and extracted with ethylacetate (3 × 50 mL). Combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (9:1 hexanes/EtOAc) to provide **2.6** (5 g, 92%) as a pale yellow oil.

Molecular Formula: $C_{21}H_{23}N_3O_5$

R_f: 0.5 (3:7 EtOAc/hexanes)

LRMS (M+17): 400.2

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 10H), 5.03 (d, *J* = 11.56 Hz, 1H), 4.76 (d, *J* = 12.06 Hz, 1H), 4.71-4.63 (m, 3H), 3.78-3.69 (m, 2H), 3.53 (dd, *J* = 9.54, 3.54 Hz, 1H), 3.48 (dd, *J* = 13.12, 2.43 Hz, 1H), 3.45-3.36 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.8, 128.6, 128.5, 128.0, 128.0, 128.0, 127.9, 98.0, 81.0, 79.7, 75.3, 73.1, 70.6, 70.2, 55.3, 51.5.

General procedure for alkylation Compound

2.8 & 4.1a-f:

To a solution (DMF) of **2.6** (1.0 equiv, 0.225 mmol) was added NaH (1.5 equiv, 0.338 mmol), **2.8 & 4.1a-f** (2.0 equiv, 0.45 mmol) at 0 ^{o}C and the reaction was stirred at ambient temperature. After 2 h, the reaction mixture was quenched with water and extracted with ethylacetate (3 × 30 mL). Combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced presssure. The crude residue was purified by column chromatography (9:1 hexanes/EtOAc) to provide **2.8 & 4.1a-f** (90%).

(2.8):

Molecular Formula: $C_{24}H_{27}N_3O_5$

R_f: 0.6 (2:8 EtOAc/hexanes)

M.P: 146-148 ^{o}C

LRMS (M+1): 437.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H), 4.97 (d, *J* = 10.88 Hz, 1H), 4.76 (dd, *J* = 11.47, 5.39 Hz, 2H), 4.64 (d, *J* = 12.08 Hz, 1H), 4.60 (d, *J* = 3.52 Hz, 1H), 4.38 (dd, *J* = 15.68, 2.37 Hz, 1H), 4.33 (dd, *J* = 15.66, 2.34 Hz, 1H), 3.92 (t, *J* = 9.25 Hz, 1H), 3.75-3.69 (m, 1H), 3.58 (dd, *J* = 13.08, 2.32 Hz, 1H), 3.50 (dd, *J* = 9.64, 3.55 Hz, 1H), 3.45 (dd, *J* = 13.09, 6.24 Hz, 1H), 3.42-3.36 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 128.4, 128.3, 128.0, 127.9, 127.6, 97.8, 81.6, 79.8, 79.7, 75.6, 74.6, 73.2, 69.5, 59.8, 55.3, 51.3.

(2R,3R,4S,5R,6S)-2-(azidomethyl)-4,5-bis(benzyloxy)-6-methoxy-3-(3-phenylprop-2-ynyloxy)tetrahydro-2H-pyran

(4.1a):

Molecular Formula: $C_{30}H_{31}N_3O_5$

Pale yellow solid.

R_f: 0.6 (2:8 EtOAc/hexanes)

M.P: 152-154 ^oC

LRMS (M+1): 514.2

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.30 (m, 15H), 5.02 (d, *J* = 10.84 Hz, 1H), 4.82 (t, J = 10.00, 2H), 4.70-3.69 (m, 1H), 4.66-4.56 (m, 3H), 4.00 (t, *J* = 9.26 Hz, 1H), 3.82-3.78 (m, 1H), 3.65 (dd, *J* = 13.04, 2.06 Hz, 1H), 3.56 (dd, *J* = 9.64, 3.53 Hz, 1H), 3.53-3.46 (m, 2H), 3.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.9, 131.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7, 122.3, 97.9, 86.5, 85.1, 81.7, 79.8, 75.8, 73.3, 69.8, 60.7, 55.4, 51.5.

(2R,3R,4S,5R,6S)-2-(azidomethyl)-4,5-bis(benzyloxy)-6-methoxy-3-(3-m-tolylprop-2-ynyloxy)tetrahydro-2H-pyran

(4.1b):

Molecular Formula: $C_{31}H_{33}N_3O_5$

Pale yellow liquid

R_f: 0.6 (2:8 EtOAc/hexanes)

LRMS (M+1): 527.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.11 (m, 14H), 4.99 (d, *J* = 11.21, Hz, 1H), 4.79 (dd, *J* = 11.41, 8.22 Hz, 2H), 4.68-4.55 (m, 4H), 3.96 (t, *J* = 9.25 Hz, 1H), 3.80-3.74 (m, 1H), 3.62 (dd, *J* = 13.08, 2.18 Hz, 1H), 3.52 (dd, *J* = 9.66, 3.55 Hz, 1H), 3.49-3.42 (m, 2H), 3.41 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.0, 137.9, 132.2, 129.4, 128.7, 128.4, 128.4, 128.2, 128.1, 128.0, 128.0, 127.7, 122.1, 97.9, 86.7, 84.7, 81.7, 79.8, 75.7, 73.3, 69.8, 60.7, 55.3, 51.5, 21.2.

(2R,3R,4S,5R,6S)-2-(azidomethyl)-4,5-bis(benzyloxy)-6-methoxy-3-(3-(thiophen-2-yl)prop-2-ynyloxy)tetrahydro-2H-pyran

(4.1c):

Molecular Formula: $C_{28}H_{29}N_3O_5S$

Reddish brown liquid

R_f: 0.6 (2:8 EtOAc/hexanes)

LRMS (M+1): 519.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 10H), 7.26 (s, 1H), 7.20 (d, *J* = 3.54 Hz, 1H), 6.97 (dd, *J* = 5.05, 3.74 Hz, 1H), 4.99 (d, *J* = 10.88 Hz, 1H), 4.81-4.76 (m, 2H), 4.66 (d, *J* = 12.08 Hz, 1H), 4.59 (dd, *J* = 9.97, 3.92 Hz, 3H), 3.96 (t, *J* = 9.25 Hz, 1H), 3.78-3.72 (m, 1H), 3.60 (dd, *J* = 13.04, 2.21 Hz, 1H), 3.52 (dd, *J* = 9.65, 3.51 Hz, 1H), 3.49-3.43 (m, 2H), 3.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 132.4, 128.4, 128.4, 128.0, 127.9, 127.7, 127.5, 126.9, 97.8, 89.0, 81.7, 79.8, 75.7, 73.3, 69.7, 60.7, 55.3, 51.4.

(2R,3R,4S,5R,6S)-2-(azidomethyl)-4,5-bis(benzyloxy)-6-methoxy-3-(3-(4-methoxyphenyl)prop-2-ynyloxy)tetrahydro-2H-pyran

(4.1d):

Molecular Formula: $C_{31}H_{33}N_3O_6$

White solid

R_f: 0.6 (2:8 EtOAc/hexanes)

M.P: 140-143 ^oC

LRMS (M+1): 543.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.29 (m, 12H), 6.84 (d, *J* = 8.30 Hz, 2H), 4.98 (d, *J* = 10.80 Hz, 1H), 4.84-4.76 (m, 2H), 4.69-4.52 (m, 4H), 3.97 (t, *J* = 9.20 Hz, 1H), 3.81 (s, 3H), 3.79-3.74 (m, 1H), 3.63-3.60 (m, 1H), 3.56-3.50 (m, 1H), 3.47-3.41 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 138.4, 137.9, 133.1, 128.4, 128.4, 128.0, 128.0, 127.9, 127.7, 114.3, 113.9, 97.9, 86.4, 83.6, 81.7, 79.8, 75.7, 73.3, 69.8, 60.8, 55.3, 55.2, 51.5.

ethyl 3-(3-((2R,3R,4S,5R,6S)-2-(azidomethyl)-4,5-bis(benzyloxy)-6-methoxytetrahydro-2H-pyran-3-yloxy)prop-1-ynyl)benzoate

(4.1e):

Pale yellow solid

Molecular Formula: $C_{33}H_{34}N_3O_7$

R_f: 0.6 (2:8 EtOAc/hexanes)

M.P: 147-150 ^oC

LRMS (M+17): 602.4

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.00 (d, *J* = 7.86 Hz, 1H), 7.58 (d, *J* = 7.73 Hz, 1H), 7.42-7.27 (m, 11H), 5.00 (d, *J* = 10.86 Hz, 1H), 4.80 (dd, *J* = 11.47, 5.00 Hz, 2H), 4.67-4.54 (m, 4H), 4.38 (q, *J* = 7.13 Hz, 2H), 3.97 (t, *J* = 9.24 Hz, 1H), 3.81-3.74 (m, 1H), 3.61 (dd, *J* = 13.10, 2.17 Hz, 1H), 3.53 (dd, *J* = 9.67, 3.52 Hz, 1H), 3.50-3.43 (m, 2H), 3.40 (s, 3H), 1.39 (t, *J* = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 138.3, 137.8, 135.7, 132.7, 130.7, 129.5, 128.5, 128.4, 128.0, 128.0, 128.0, 127.7, 122.7, 97.9, 85.9, 85.5, 81.7, 79.8, 75.7, 73.3, 69.7, 61.2, 60.5, 55.4, 51.4, 14.2.

(2R,3R,4S,5R,6S)-2-(azidomethyl)-4,5-bis(benzyloxy)-6-methoxy-3-(3-(naphthalen-1-yl)prop-2-ynyloxy)tetrahydro-2H-pyran

(4.1f):

Pale yellow solid

Molecular Formula: $C_{34}H_{33}N_3O_5$

R_f: 0.6 (2:8 EtOAc/hexanes)

M.P: 174-176 ^oC

LRMS (M+1): 563.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.08 Hz, 1H), 7.88-7.82 (m, 2H), 7.67 (d, *J* = 7.08 Hz, 1H), 7.59-7.48 (m, 2H), 7.45-7.28 (m, 11H), 5.02 (d, *J* = 10.80, 1H), 4.88-4.72 (m, 4H), 4.70-4.60 (m, 3H), 4.01 (t, *J* = 9.22 Hz, 1H), 3.83-3.78 (m, 1H), 3.66 (dd, *J* = 13.07, 2.03 Hz, 1H), 3.59-3.45 (m, 4H), 3.42-3.40 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 133.1, 132.9, 130.6, 128.9, 128.3, 128.3, 128.1, 127.9, 127.8, 127.6, 126.6, 126.2, 125.8, 125.0, 119.8, 97.8, 89.7, 84.4, 81.6, 79.7, 75.6, 73.2, 69.7, 60.7, 55.2, 51.4.

General procedure for click reaction:

The solution (DMF) of **2.8** & **4.1a-f** (1.0 equiv, 0.183 mmol) was refluxed at 140 ^{o}C. After 24 h, the reaction mixture was filtered through celite and extracted with ethylacetate (3 × 30 mL). Combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced presssure. The crude residue was purified by column chromatography (8:2 hexanes/EtOAc) to provide **2.9 & 4.2a-f** (99%):

Compound 2.9: White solid

Molecular Formula: $C_{24}H_{27}N_3O_5$

R_f: 0.3 (1: 1 EtOAc/hexanes);

M.P: 148-150 ^{o}C

LRMS (M+1): 438.1;

HRMS calc for $C_{24}H_{27}N_3O_5$ $[M+H]^+$: 438.2023; found 438.1988.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.40-7.28 (m, 10H) 5.10-5.03 (m, 2H), 4.84-4.81 (m, 3H), 4.67 (d, *J* = 12.15 Hz, 1H), 4.58 (d, *J* = 3.55 Hz, 1H), 4.47 (d, *J* = 14.88 Hz, 1H), 4.23 (dd, *J* = 14.07, 10.63 Hz, 1H), 3.86 (t, *J* = 9.18 Hz, 1H), 3.75 (dt, *J* = 10.46, 2.98 Hz, 1H), 3.56-3.50 (m, 2H), 3.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 137.9, 136.4, 132.7, 128.4, 128.3, 128.0, 127.9, 127.9, 127.6, 98.4, 88.4, 79.4, 78.6, 76.2, 73.6, 65.9, 62.0, 55.8, 52.9.

(5aR,6S,7R,8S,9aR)-6,7-bis(benzyloxy)-8-methoxy-3-phenyl-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine

Compound (4.2a): White solid.

Molecular Formula: $C_{30}H_{31}N_3O_5$

R_f: 0.3 (1: 1 EtOAc/hexanes)

M.P: 158-161 ^oC

LRMS (M+1): 513.5

HRMS calc for $C_{30}H_{31}N_3O_5$ $[M+H]^+$: 514.2336; found 514.2307.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.47 (t, 2H), 7.43-7.26 (m, 11H), 5.27 (s, 1H), 5.08 (dd, *J* = 14.04, 2.99 Hz, 1H), 4.83 (t, 3H), 4.67 (d, *J* = 12.15 Hz, 1H), 4.60-4.54 (m, 2H), 4.29 (dd, *J* = 14.01, 10.68 Hz, 1H), 3.89-3.76 (m, 2H), 3.61-3.50 (m, 2H), 3.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 138.7, 137.9, 133.0, 130.3, 128.8, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 98.5, 88.5, 79.3, 78.6, 76.2, 73.6, 65.8, 62.1, 55.8, 53.3.

(5aR,6S,7R,8S,9aR)-6,7-bis(benzyloxy)-8-methoxy-3-m-tolyl-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine

Compound (4.2b): Pale yellow solid.

Molecular Formula: $C_{31}H_{33}N_3O_5$

R_f: 0.3 (1: 1 EtOAc/hexanes)

M.P: 156-158 ^oC

LRMS (M+1): 527.5

HRMS calc for $C_{31}H_{33}N_3O_5$ $[M+H]^+$: 528.2493; found 528.2431.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.20 (m, 14H), 5.28 (d, *J* = 8.00, 1H), 5.08 (dd, *J* = 14.04, 3.03 Hz, 1H), 4.84-4.81 (m, 3H), 4.67 (d, *J* = 12.16 Hz, 1H), 4.58-4.54 (m, 2H), 4.29 (dd, *J* = 14.01, 10.66 Hz, 1H), 3.90-3.76 (m, 2H), 3.60-3.49 (m, 2H), 3.40 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.6, 137.9, 132.8, 130.2, 129.1, 128.7, 128.6, 128.4, 128.3, 128.0, 127.9, 127.9, 127.6, 124.9, 98.4, 88.5, 79.3, 78.5, 76.1, 73.6, 65.8, 62.1, 55.7, 53.3, 21.4.

(5aR,6S,7R,8S,9aR)-6,7-bis(benzyloxy)-8-methoxy-3-(thiophen-2-yl)-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine

Compound (4.2c): Pale yellow solid

Molecular Formula: $C_{28}H_{29}N_3O_5S$

R_f: 0.3 (1: 1 EtOAc/hexanes)

M.P: 172-174 ^oC

LRMS (M+1): 519.4

HRMS calc for $C_{28}H_{29}N_3O_5S$ $[M+H]^+$: 520.1901; found 520.1865.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.26 (m, 12H), 7.13 (dd, *J* = 4.91, 3.71 Hz, 1H), 5.35 (d, *J* = 15.09 Hz, 1H), 5.06 (dd, *J* = 14.07, 2.97 Hz, 1H), 4.84-4.82 (m, 3H), 4.67 (d, *J* = 12.13 Hz, 1H), 4.58-4.53 (m, 2H), 4.27 (dd, *J* = 14.02, 10.69 Hz, 1H),

3.86 (t, *J* = 9.20 Hz, 1H), 3.79 (dt, *J* = 10.60, 2.88 Hz, 1H), 3.60-3.50 (m, 2H), 3.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.6, 137.9, 132.4, 131.7, 128.4, 128.3, 128.0, 128.0, 127.9, 127.6, 126.1, 125.6, 98.4, 88.5, 79.3, 78.5, 76.1, 73.6, 65.7, 61.9, 55.8, 53.3.

(5aR,6S,7R,8S,9aR)-6,7-bis(benzyloxy)-8-methoxy-3-(4-methoxyphenyl)-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine

Compound (4.2d): Colourless solid

Molecular Formula: $C_{31}H_{33}N_3O_6$

R_f: 0.3 (1: 1 EtOAc/hexanes)

M.P: 137-139 ^oC

LRMS (M+1): 543.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.61 Hz, 2H), 7.39-7.29 (m, 10H), 7.01 (d, *J* = 8.61 Hz, 2H), 5.23 (d, *J* = 14.96 Hz, 1H), 5.07 (dd, *J* = 14.04, 3.02 Hz, 1H), 4.85-4.82 (m, 3H), 4.67 (d, *J* = 12.15 Hz, 1H), 4.60-4.54 (m, 2H), 4.28 (dd, *J* = 14.02, 10.65 Hz, 1H), 3.89-3.76 (m, 5H), 3.58 (d, *J* = 9.04 Hz, 1H), 3.53 (dd, *J* = 9.49, 3.51 Hz, 1H), 3.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 138.6, 137.9, 129.1, 128.4, 128.3, 128.0, 127.9, 127.9, 127.6, 122.8, 114.2, 98.4, 88.5, 79.3, 78.5, 76.1, 73.6, 65.8, 62.1, 55.7, 55.3, 53.3.

ethyl 3-((5aR,6S,7R,8S,9aR)-6,7-bis(benzyloxy)-8-methoxy-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepin-3-yl)benzoate

Compound (4.2e): White solid

Molecular Formula: $C_{33}H_{35}N_3O_7$

R_f: 0.3 (1: 1 EtOAc/hexanes)

M.P: 144-146 ^oC

LRMS (M+17): 602.4

HRMS calc for $C_{33}H_{35}N_3O_7$ $[M+H]^+$: 586.2548; found 586.2443.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.09 (d, *J* = 7.83 Hz, 1H), 7.81 (d, *J* = 7.76 Hz, 1H), 7.56 (t, *J* = 7.76 Hz, 1H), 7.41-7.28 (m, 10H), 5.26 (d, *J* = 15.05 Hz, 1H), 5.10 (dd, *J* = 14.06, 3.03 Hz, 1H), 4.85-4.82 (m, 3H), 4.68.4.58 (m, 3H), 4.41 (q, *J* = 7.11 Hz, 2H), 4.31 (dd, *J* = 14.07, 10.66 Hz, 1H), 3.88-3.77 (m, 2H), 3.62-3.51 (m, 2H), 3.42 (s, 3H), 1.41 (t, *J* = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 145.0, 138.6, 137.9, 133.3, 132.2, 131.1, 130.6, 129.4, 129.0, 128.8, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 98.5, 88.6, 79.3, 78.5, 76.2, 73.6, 65.7, 62.0, 61.2, 55.8, 53.3, 14.3.

(5aR,6S,7R,8S,9aR)-6,7-bis(benzyloxy)-8-methoxy-3-(naphthalen-1-yl)-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine

Compound (4.2f): White solid

Molecular Formula: $C_{34}H_{33}N_3O_5$

R_f: 0.3 (1: 1 EtOAc/hexanes)

M.P: 168-170 ^oC

LRMS (M+1): 563.5

HRMS calc for $C_{34}H_{33}N_3O_5$ $[M+H]^+$: 564.2493; found 564.2434.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.91 (m, 3H), 7.58-7.50 (m, 3H), 7.46 (d, *J* = 6.88 Hz, 1H), 7.36-7.25 (m, 10H), 5.17 (dd, *J* = 14.11, 2.99 Hz, 1H), 4.95 (d, *J* = 14.97 Hz, 1H), 4.83-4.79 (m, 3H), 4.68 (d, *J* = 12.14 Hz, 1H), 4.61 (d, *J* = 3.42 Hz, 1H), 4.54 (d, *J* = 14.96 Hz, 1H), 4.39 (dd, *J* = 13.95, 10.78 Hz, 1H), 3.89 (t, *J* = 9.29 Hz, 2H), 3.63-3.51 (m, 2H), 3.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 138.5, 137.9, 134.6, 133.8, 131.8, 129.3, 128.4, 128.3, 128.3, 128.0, 128.0, 127.9, 127.6, 127.2, 126.7, 126.1, 125.4, 125.2, 98.5, 88.7, 79.3, 78.5, 76.2, 73.6, 65.9, 62.2, 55.8, 53.4.

General procedure for Hydrogenation:

To a solution of **2.9 & 4.2a-f** (1.0 equiv, 0.183 mmol) in MeOH was added 10% Pd/C (70 mg) and the reaction was stirred at ambient temperature under hydrogen atmosphere. After 24 h, the reaction mixture was filtered through silica gel and concentrated under reduced presssure. The crude residue was purified by column chromatography (EtOAc) to provide **2.10 & 4.3a-f** (95%).

(5aS,6R,7R,8S,9aR)-8-methoxy-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine-6,7-diol

Compound (2.10): White solid

Molecular Formula: $C_{10}H_{15}N_3O_5$

R_f: 0.2 (EtOAc)

$[\alpha]_D^{20}$ = +113.31 (*c* = 0.25, CH_3OH)

M.P: 147-150 ^oC

LRMS (M+1): 258.0

HRMS calc for $C_{10}H_{15}N_3O_5$ $[M+H]^+$: 258.1084; found 258.1068.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 5.13-5.09 (m, 2H), 4.82 (d, *J* = 3.75 Hz, 1H), 4.53 (d, *J* = 14.93 Hz, 1H), 4.31 (dd, 1H), 3.82-3.71 (m, 2H), 3.49-3.43 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.9, 99.1, 87.0, 72.1, 71.9, 65.8, 62.0, 56.0, 52.5, 29.6.

IR(KBr): υ 765, 1078, 2138, 3501 cm^{-1}

(5aS,6R,7R,8S,9aR)-8-methoxy-3-phenyl-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine-6,7-diol

Compound (4.3a): Pale red solid

Molecular Formula: $C_{16}H_{19}N_3O_5$

R_f: 0.2 (EtOAc)

$[\alpha]_D^{20}$ = +182.73 (c = 0.25, CH_3OH)

M.P: 150-154 ^oC

LRMS (M+1): 334.1

HRMS calc for $C_{16}H_{19}N_3O_5$ $[M+H]^+$: 334.1397; found 334.1377.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H), 7.50-7.47 (m, 2H), 7.44-7.40 (m, 1H), 5.23 (d, *J* = 15.06 Hz, 1H), 5.00 (dd, *J* = 13.93, 3.03 Hz, 1H), 4.80-4.75 (m, 2H), 4.60 (dd, *J* = 13.91, 10.70 Hz, 1H), 3.73-3.64 (m, 2H), 3.55-3.49 (m, 2H), 3.45 (s, 3H), 1.30-1.28 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 128.5, 128.2, 127.5, 100.0, 87.3, 71.7, 70.9, 65.8, 61.3, 54.6, 52.6.

IR(KBr): υ 1070, 2075, 3512 cm^{-1}

(5aS,6R,7R,8S,9aR)-8-methoxy-3-m-tolyl-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine-6,7-diol

Compound (4.3b): White solid

Molecular Formula: $C_{17}H_{21}N_3O_5$

R_f: 0.2 (EtOAc)

$[\alpha]_D^{20}$ = +158.37 (c = 0.25, CH_3OH)

M.P: 130-134 ^oC

LRMS (M+1): 348.1

HRMS calc for $C_{17}H_{21}N_3O_5$ $[M+H]^+$: 348.1554; found 348.1527.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.30 (m, 3H), 7.21 (d, *J* = 6.19 Hz, 1H), 5.33 (d, *J* = 13.73 Hz, 1H), 5.20-5.06 (m, 1H), 4.80-4.79 (m, 1H), 4.74-4.62 (m, 1H), 4.37-4.31 (m, 1H), 3.84-3.72 (m, 2H), 3.68-3.61 (m, 1H), 3.50-3.46 (m, 1H), 3.44 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 129.2, 128.7, 124.7, 99.3, 87.1, 71.8, 65.7, 55.9, 36.6, 31.5, 29.6, 21.4.

IR(KBr): υ 1073, 2240, 3415 cm^{-1}

(5aS,6R,7R,8S,9aR)-8-methoxy-3-(thiophen-2-yl)-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine-6,7-diol

Compound (4.3c): White solid

Molecular Formula: $C_{14}H_{17}N_3O_5S$

R_f: 0.2 (EtOAc)

$[\alpha]_D^{20}$ = +106.84 (c = 0.25, CH_3OH)

M.P: 145-150 ^{o}C

LRMS (M+23): 362.5

HRMS calc for $C_{17}H_{21}N_3O_6$ $[M+H]^+$: 364.1503; found 364.1482.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 4.91, 3.71 Hz, 1H), 7.23 (dd, *J* = 13.47, 8.07 Hz, 2H), 5.32 (d, *J* = 15.09 Hz, 1H), 5.03-5.01 (m, 1H), 4.53 (dd, *J* = 12.32, 9.40 Hz, 2H), 4.30-4.27 (m, 1H), 3.81 (t, *J* = 9.20 Hz, 1H), 3.72-3.70 (m, 1H), 3.58-3.47 (m, 2H), 3.38 (d, *J* = 4.85 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.6, 137.9, 132.4, 131.7, 125.6, 98.4, 88.5, 76.1, 73.6, 65.7, 61.9, 55.8, 53.3.

IR(KBr): υ 1055, 2093, 2951 cm^{-1}

(5aS,6R,7R,8S,9aR)-8-methoxy-3-(4-methoxyphenyl)-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine-6,7-diol

Compound (4.3d): White solid

Molecular Formula: $C_{17}H_{21}N_3O_6$

R_f: 0.2 (EtOAc)

$[\alpha]_D^{20}$ = +165.40 (c = 0.25, CH_3OH)

M.P: 230-234 ^{o}C

LRMS (M+1): 364.1

HRMS calc for $C_{16}H_{19}N_3O_5$ $[M+H]^+$: 334.1397; found 334.1377.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.40 Hz, 2H), 6.97 (d, *J* = 8.41 Hz, 2H), 5.27 (d, *J* = 14.93 Hz, 1H), 5.10 (dd, *J* = 14.06, 2.77 Hz, 1H), 4.81 (d, *J* = 3.57 Hz, 1H), 4.59 (d, *J* = 14.93 Hz, 1H), 4.34 (dd, *J* = 13.91, 10.83 Hz, 1H), 3.86-3.73 (m, 5H), 3.65 (dd, *J* = 9.38, 3.67 Hz, 1H), 3.50-3.44 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 145.7, 132.0, 129.1, 122.5, 114.3, 99.2, 87.0, 72.0, 71.9, 65.8, 62.0, 55.9, 55.3, 52.8

IR(KBr): υ 1058, 2057, 3508 cm^{-1}

ethyl3-((5aS,6R,7R,8S,9aR)-6,7-dihydroxy-8-methoxy-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepin-3-yl)benzoate

Compound (4.3e): White solid

Molecular Formula: $C_{19}H_{23}N_3O_7$

R_f: 0.2 (EtOAc)

$[\alpha]_D^{20}$ = +86.21 (c = 0.25, CH_3OH)

M.P: 131-134 ^oC

LRMS (M+1): 405.5

HRMS calc for $C_{19}H_{23}N_3O_7$ $[M+H]^+$: 406.1609; found 406.1582.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.09 (d, *J* = 7.82 Hz, 1H), 7.83 (d, *J* = 7.70 Hz, 1H), 7.55 (t, *J* = 7.77 Hz, 1H), 5.35 (d, *J* = 14.99 Hz, 1H), 5.16 (dd, *J* = 14.11, 3.13 Hz, 1H), 4.84 (d, *J* = 3.81 Hz, 1H), 4.67 (d, *J* = 15.02 Hz, 1H), 4.44-4.35 (m, 3H), 3.85-3.77 (m, 2H), 3.68 (dd, *J* = 9.48, 3.83 Hz, 1H), 3.56-3.47 (m, 4H), 1.41 (t, *J* = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 145.1, 132.9, 132.1, 131.1, 130.5, 129.5, 129.0, 128.6, 99.2, 87.1, 72.1, 71.9, 65.7, 61.9, 61.2, 56.0, 52.9, 14.3.

IR(KBr): υ 1082, 1715, 2077, 3398 cm^{-1}

(5aS,6R,7R,8S,9aR)-8-methoxy-3-(naphthalen-1-yl)-5a,6,7,8,9a,10-hexahydro-4H-pyrano[2,3-f][1,2,3]triazolo[5,1-c][1,4]oxazepine-6,7-diol

Compound (4.3f): White solid

Molecular Formula: $C_{20}H_{21}N_3O_5$

R_f: 0.2 (EtOAc)

$[\alpha]_D^{20}$ = +29.05 (*c* = 0.25, CH_3OH)

M.P: 183-187 ^oC

LRMS (M+1): 383.6

HRMS calc for $C_{20}H_{21}N_3O_5$ $[M+H]^+$: 384.1554; found 384.1526.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.89 (m, 1H), 7.55-7.44 (m, 2H), 7.40-7.30 (m, 1H), 7.14 (d, *J* = 4.62 Hz, 2H), 6.98 (t, *J* = 4.41 Hz, 1H), 5.13 (dd, *J* = 14.08, 3.13 Hz, 1H), 4.50 (d, *J* = 14.83 Hz, 1H), 4.37 (dd, *J* = 14.07, 10.68 Hz, 1H), 4.12 (d, *J* = 7.14 Hz, 1H), 3.82-3.79 (m, 2H), 3.68 (d, *J* = 3.74 Hz, 2H), 3.53-3.45 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 138.1, 136.8, 133.4, 130.0, 127.8, 125.3, 125.2, 99.1, 87.1, 72.1, 71.9, 65.9, 62.0, 56.0, 52.7.

IR(KBr): υ 1054, 2083, 3368 cm^{-1}

General procedure for synthesis of compound 3.3a-f: To a solution (DMF) of **3.1 (**1.0 equiv, 8.928 mmol) was added $Pd(PPh_3)_4$ (0.05 equiv, 0.44 mmol,) **Ar-Br** (**3.2a-f**, 1.0 equiv, 8.928 mmol), K_2CO_3 (10.0 equiv, 89.28 mmol), CuI (0.1 equiv, 0.892 mmol) was added and the reaction was stirred at 80 ^oC. After 24 h, the reaction mixture was filtered in celite and extracted with ethylacetate (3 × 30 mL). Combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced

pressure. The crude residue was purified by column chromatography (8:2 hexanes/EtOAc) to provide **3.3a-f** (80%): R_f: 0.3 (2:8 EtOAc/hexanes).

General procedure for synthesis of compound 2.7& 3.4a-f: To a solution (DCM) of **3.1 & 3.3a-f (**1.0 equiv, 2.89 mmol) was added TsCl (1.2 equiv, 3.47 mmol) then KOH powder (2.5 equiv, 3.62 mmol) was added portion wise about 30 min at 0 ^oC and the reaction was stirred at 0 ^oC. After 1 h, the reaction mixture was quenched with water and extracted with DCM (3×10 ml). Combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (9:1 hexanes/EtOAc) to provide **2.7 & 3.4a-f** (90%): R_f: 0.6 (2:8 EtOAc/hexanes);

4.6. References

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4.8. Spectral Data

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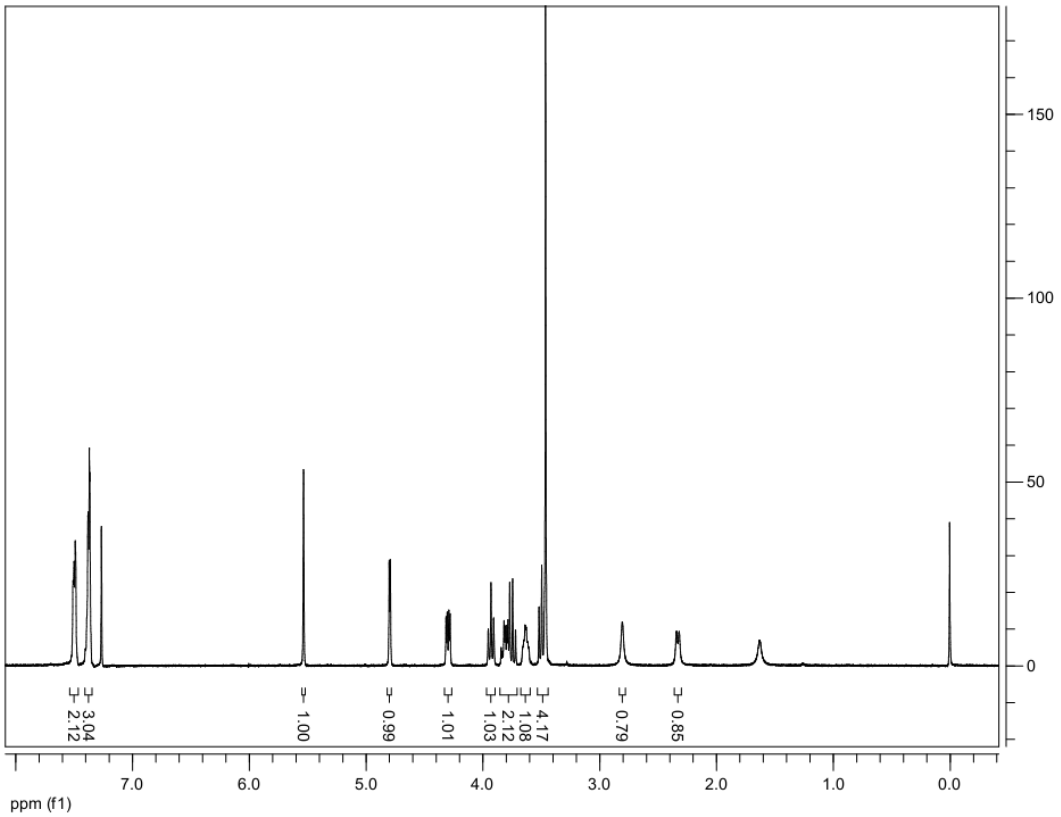

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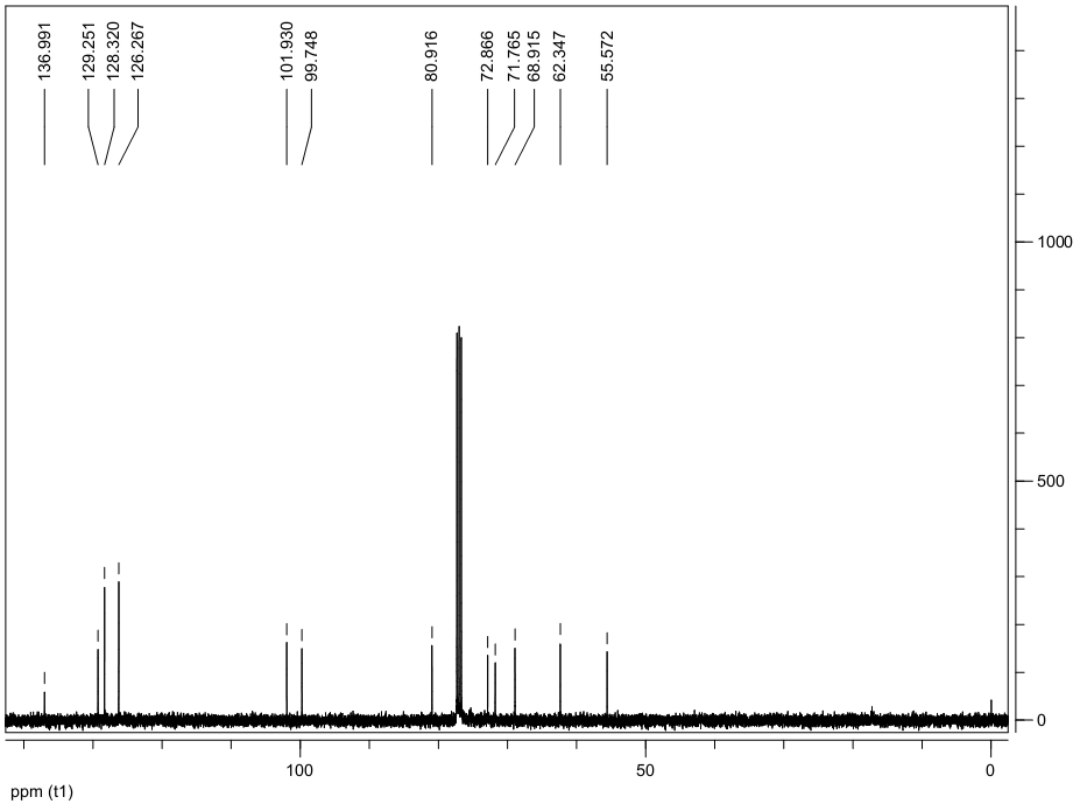

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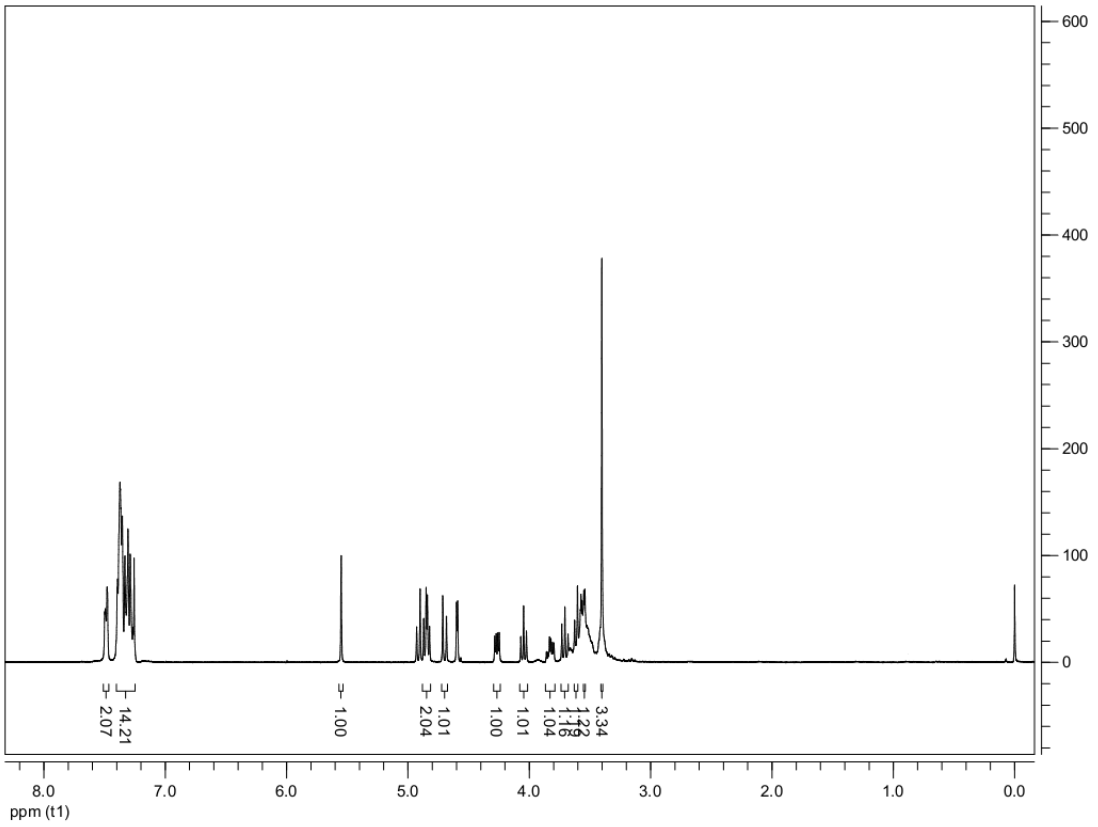

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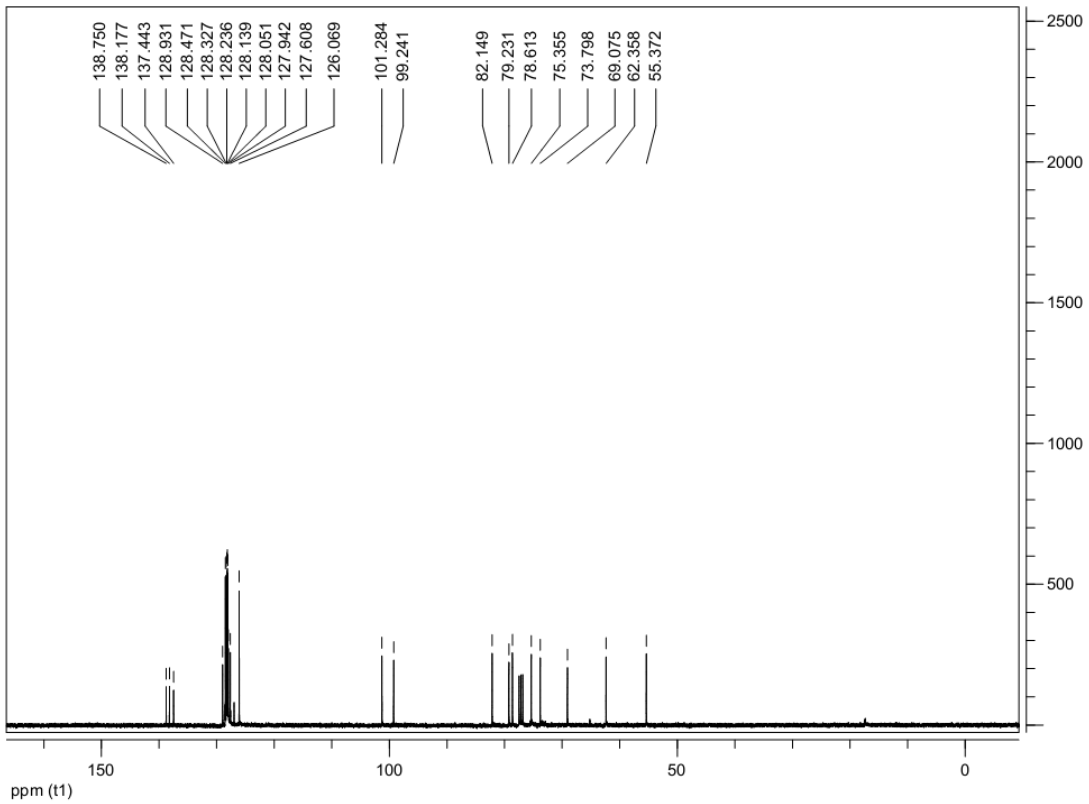

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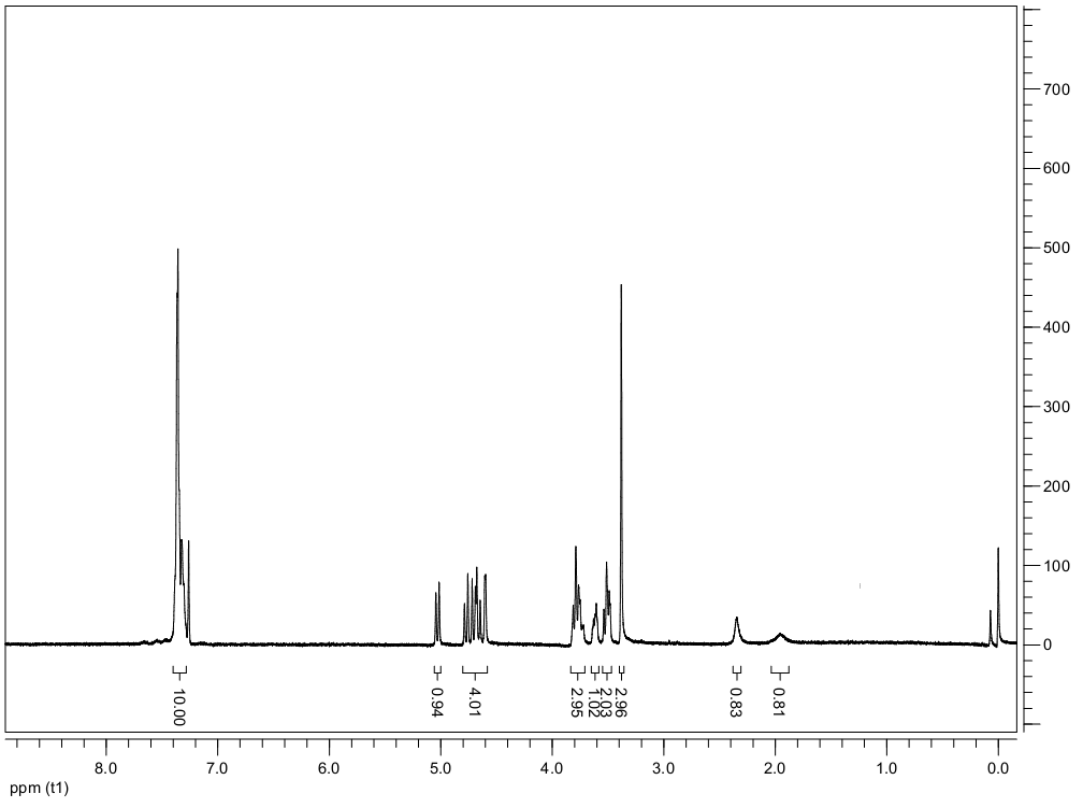

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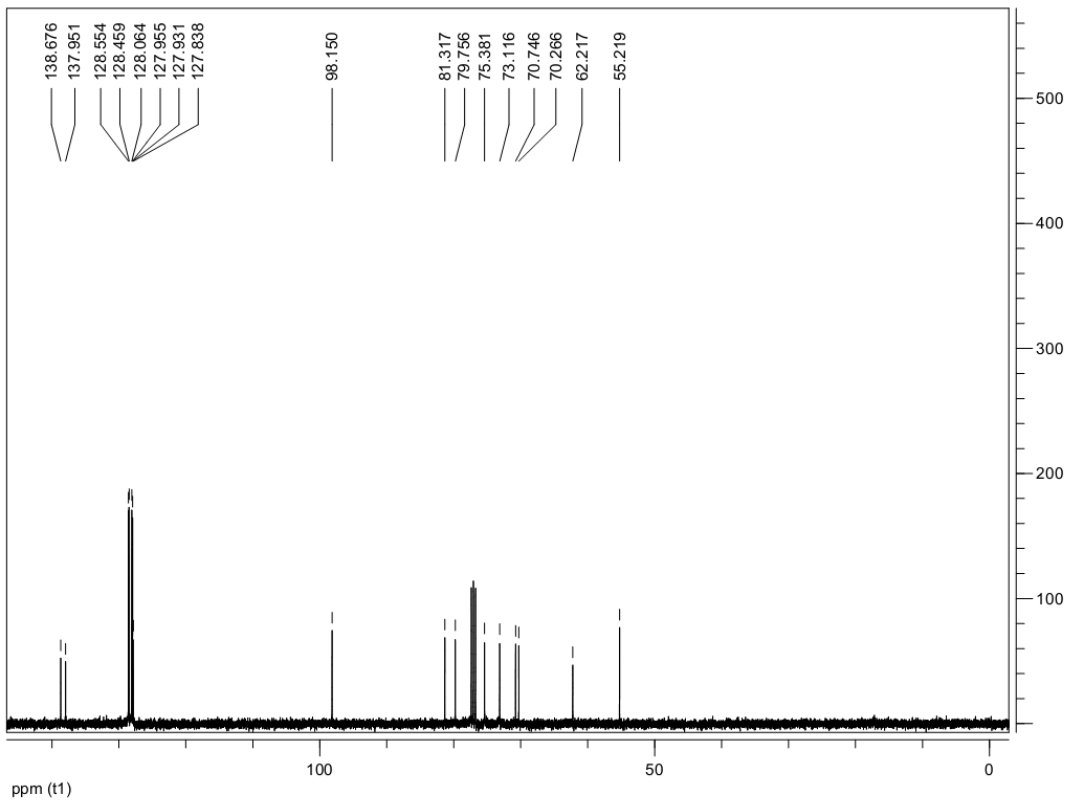

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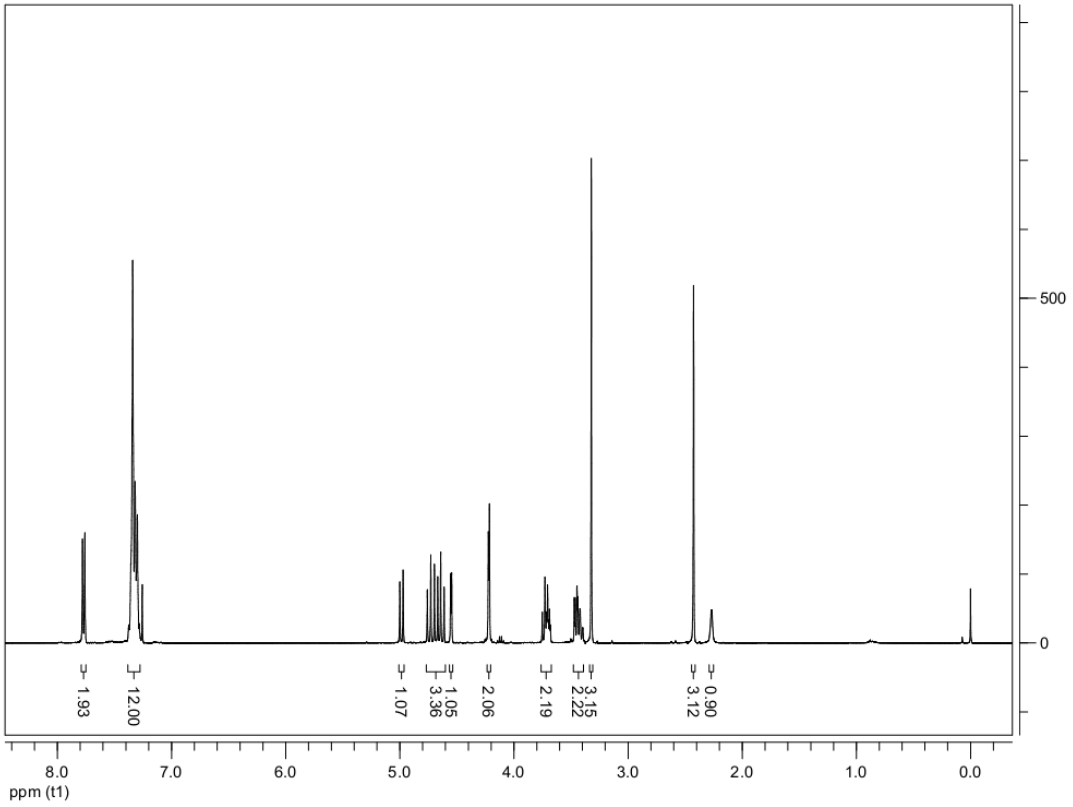

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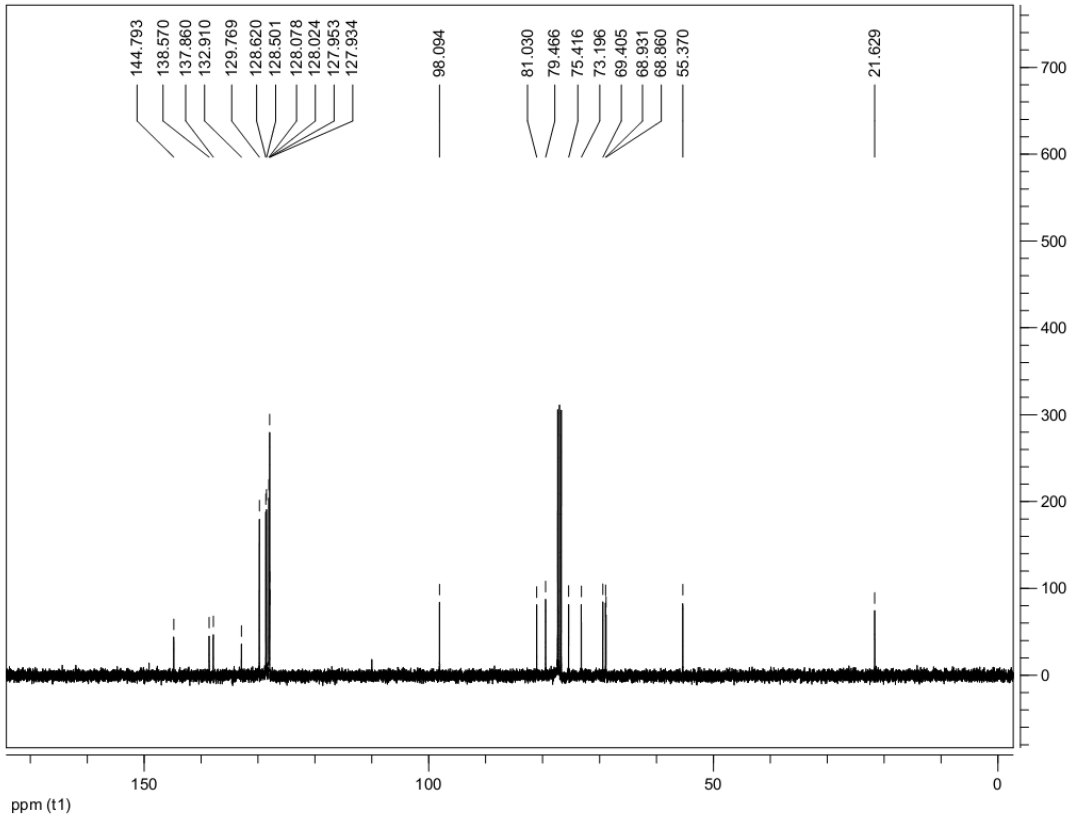

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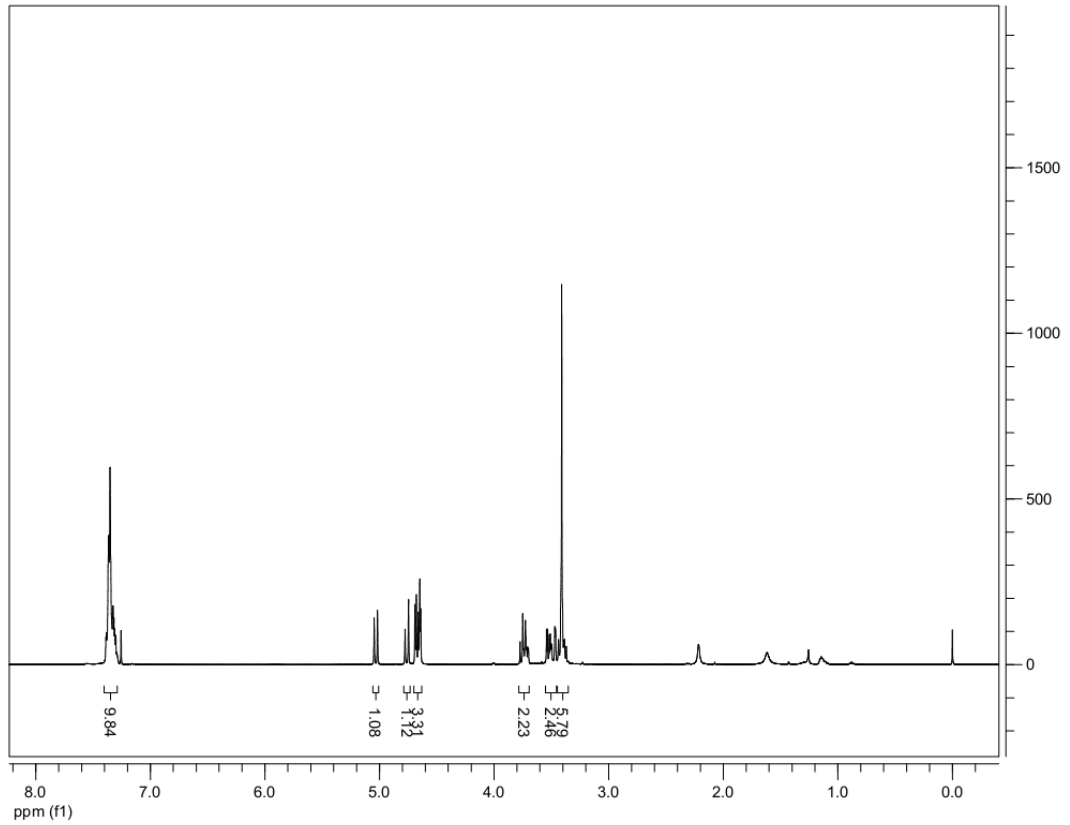

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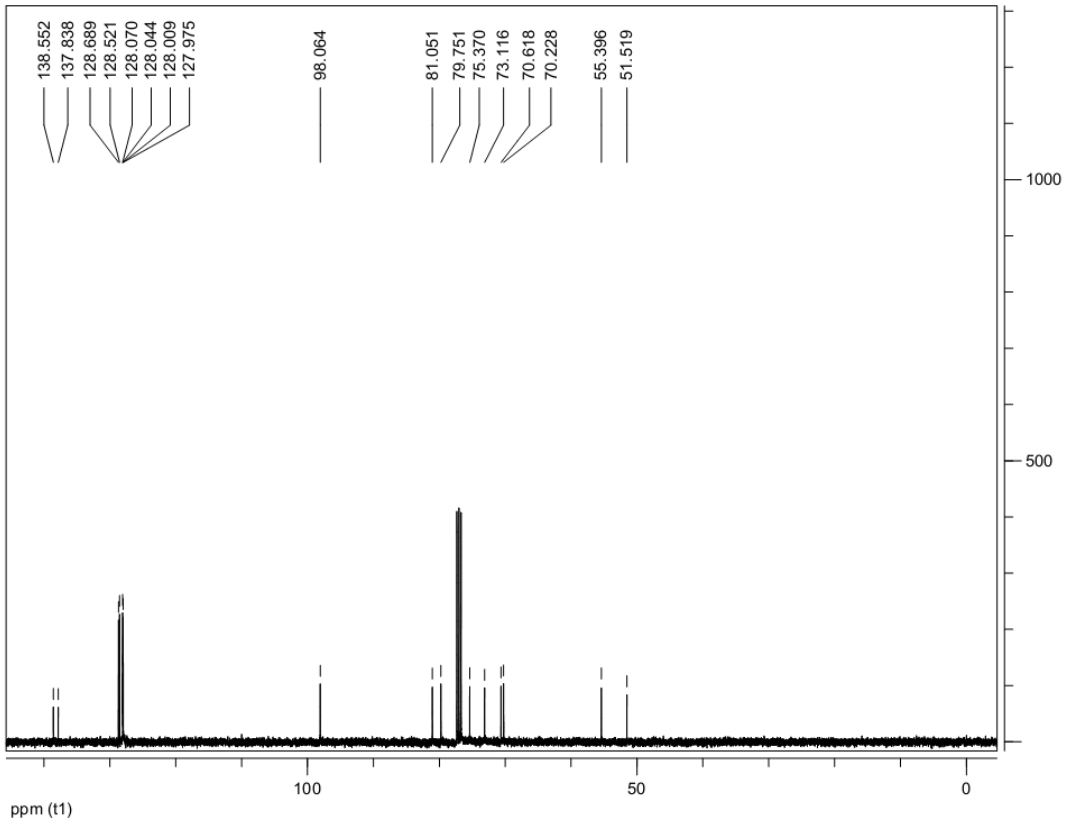

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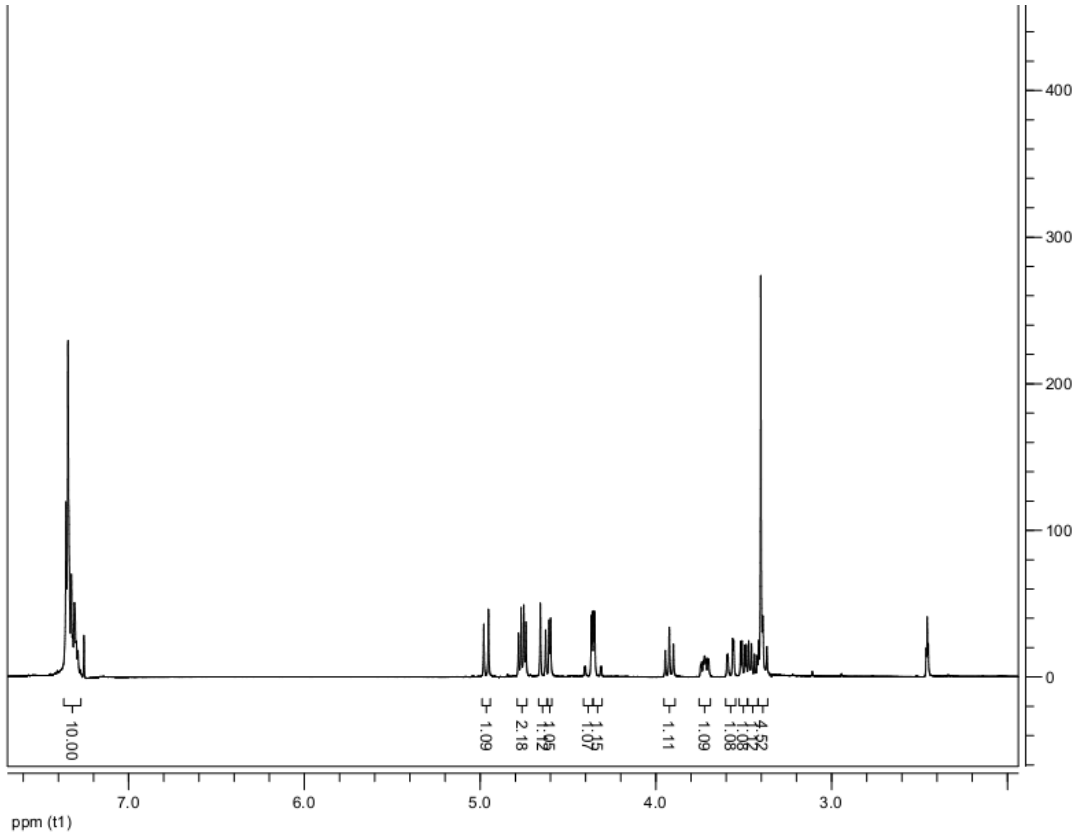

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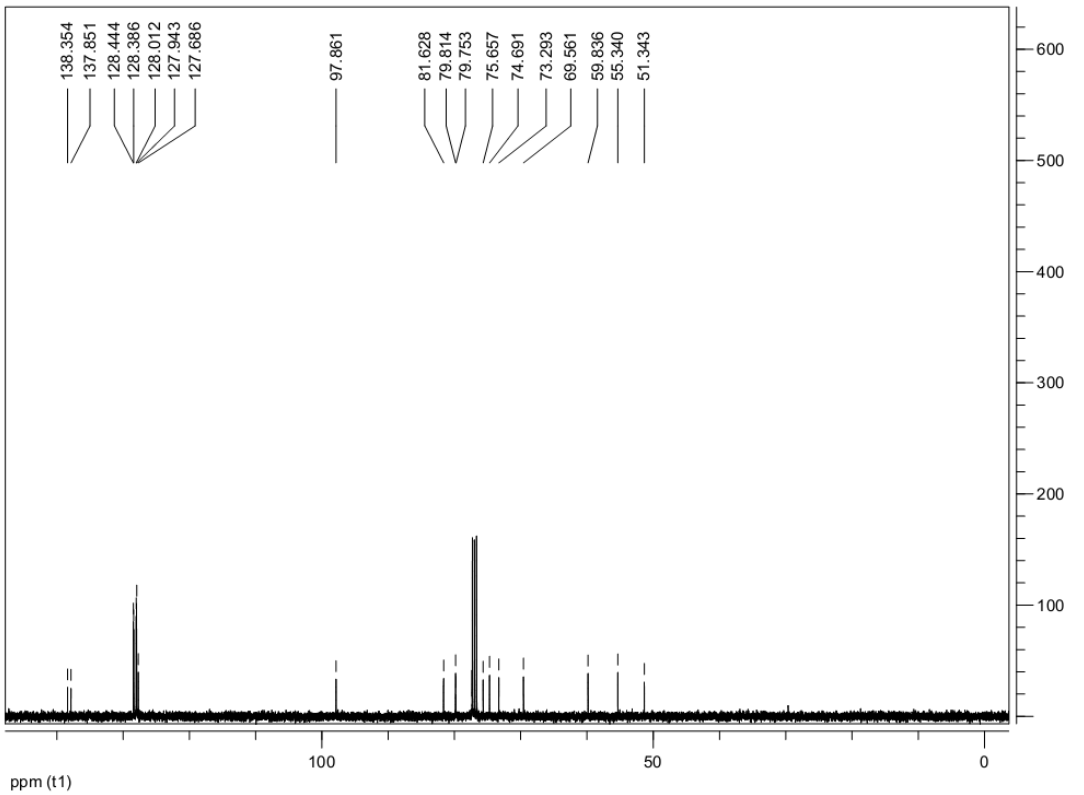

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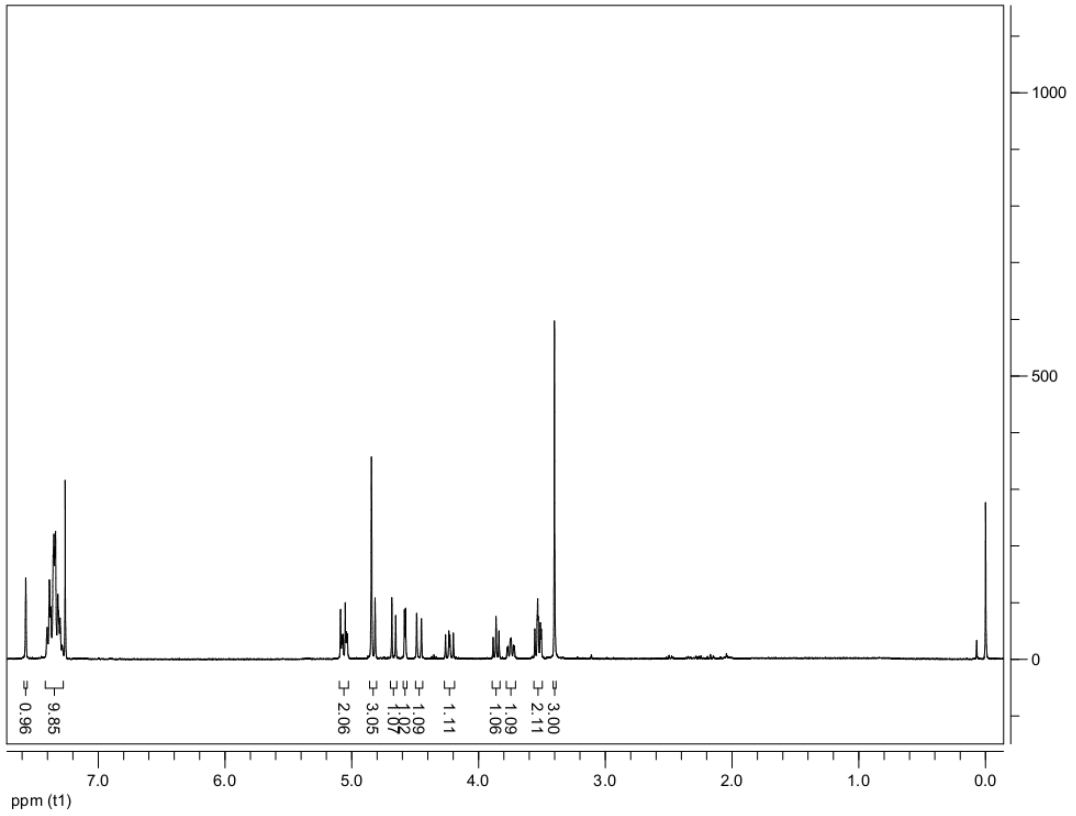

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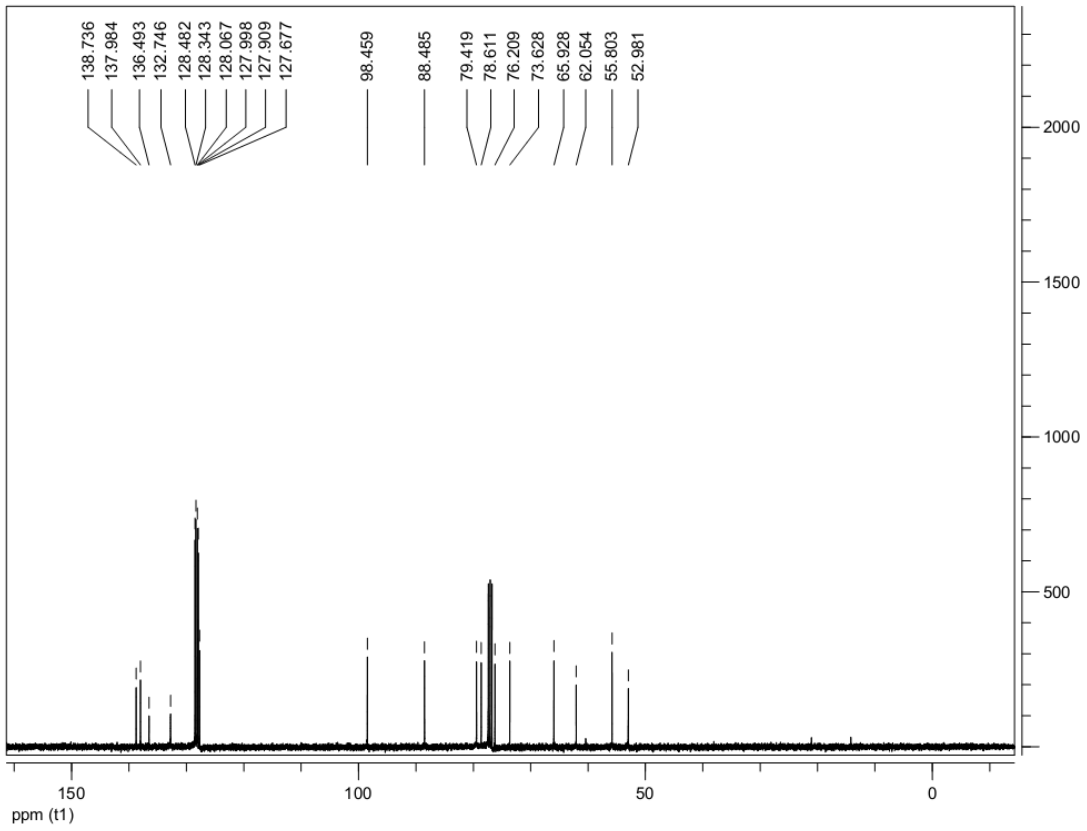

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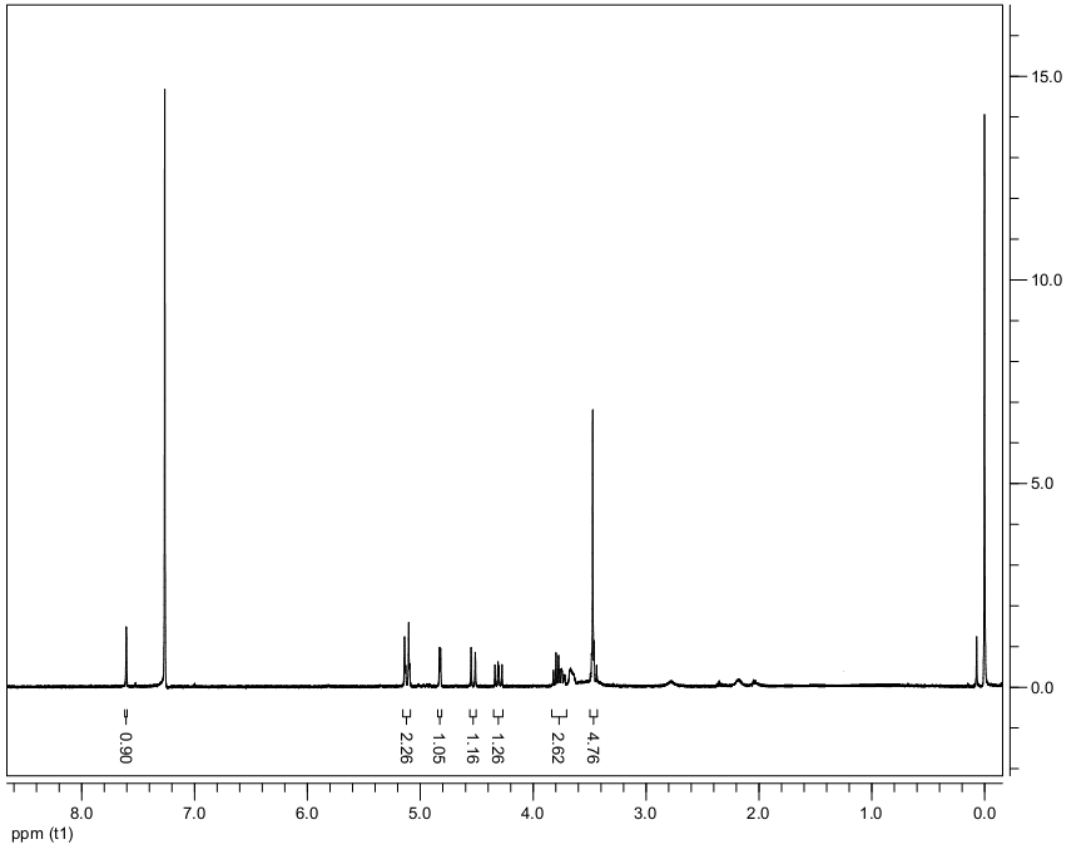

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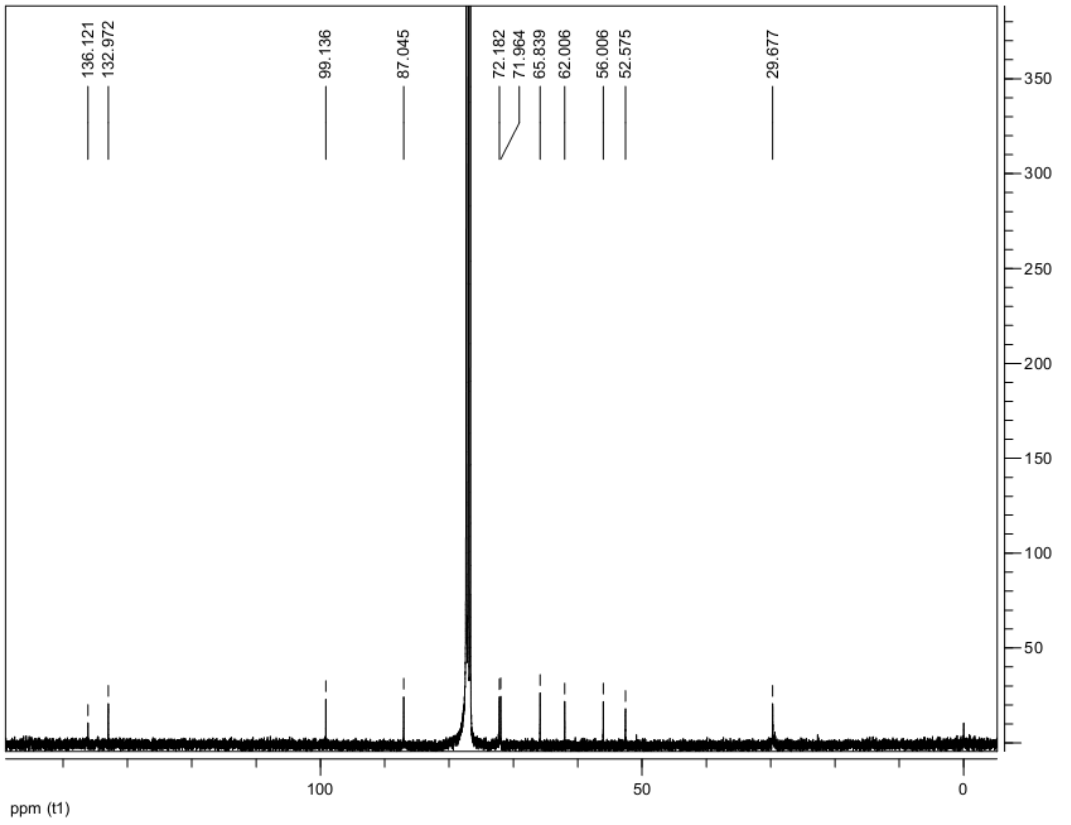

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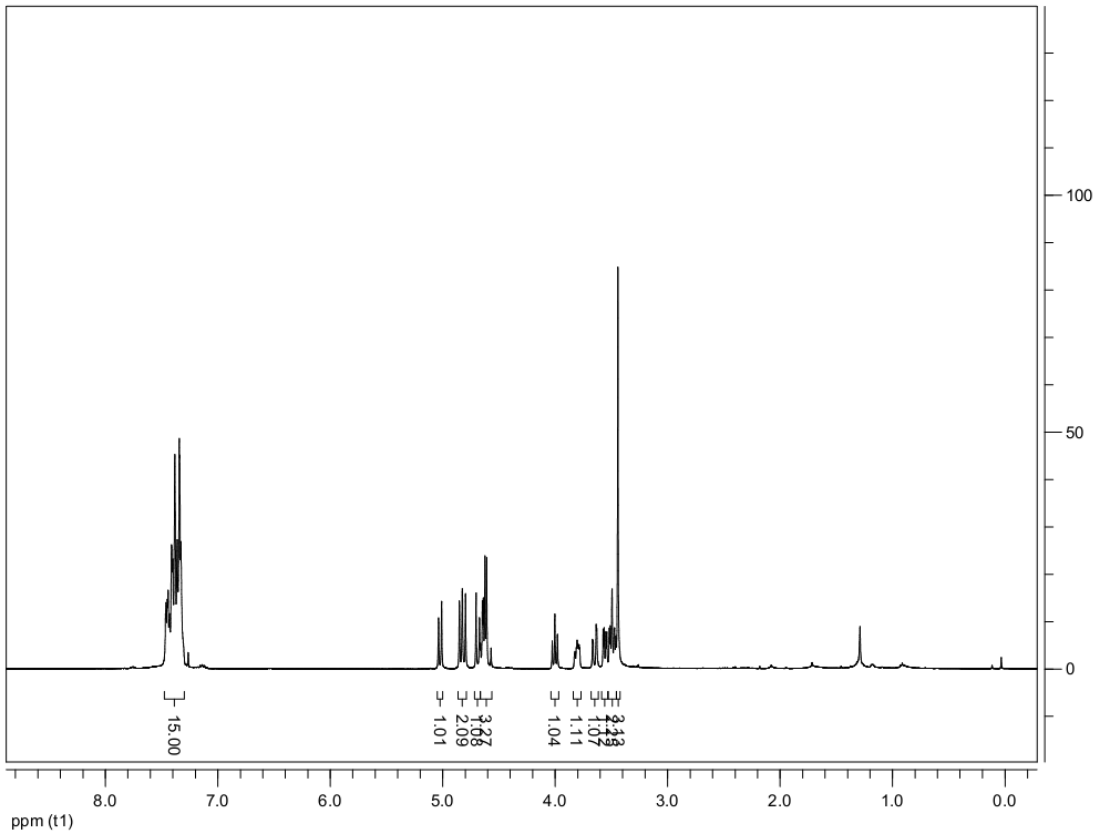

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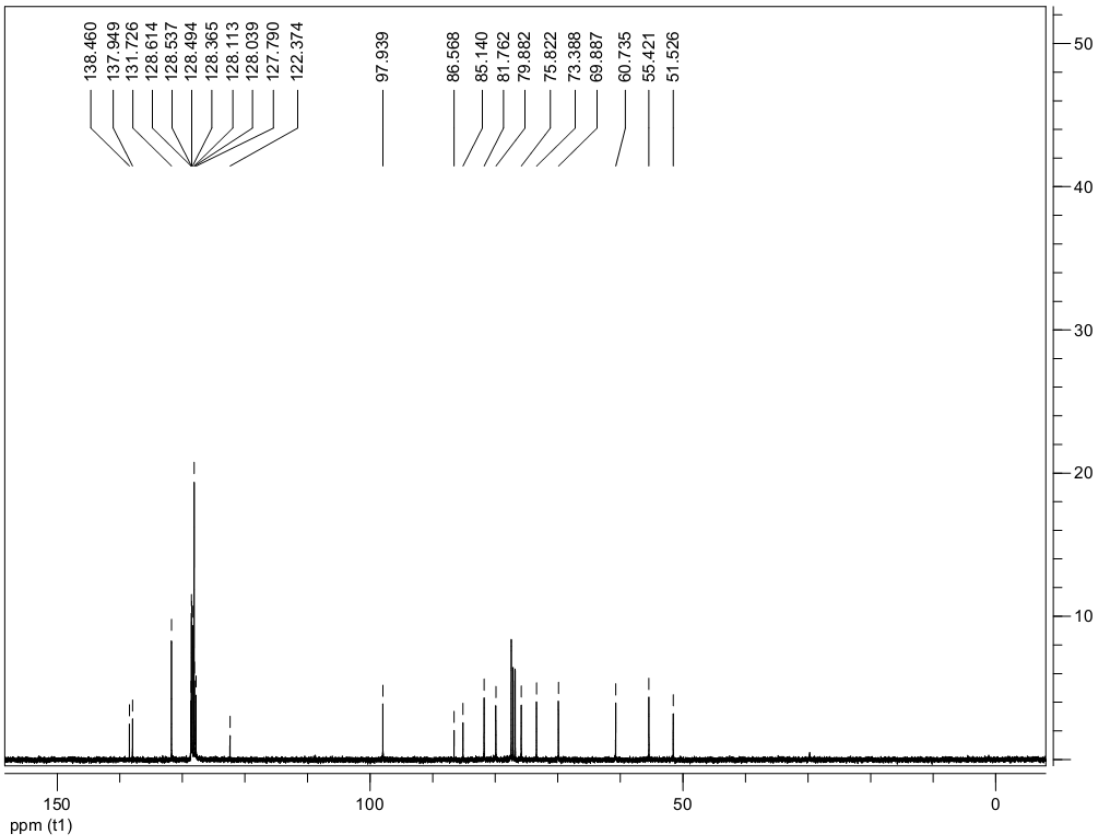

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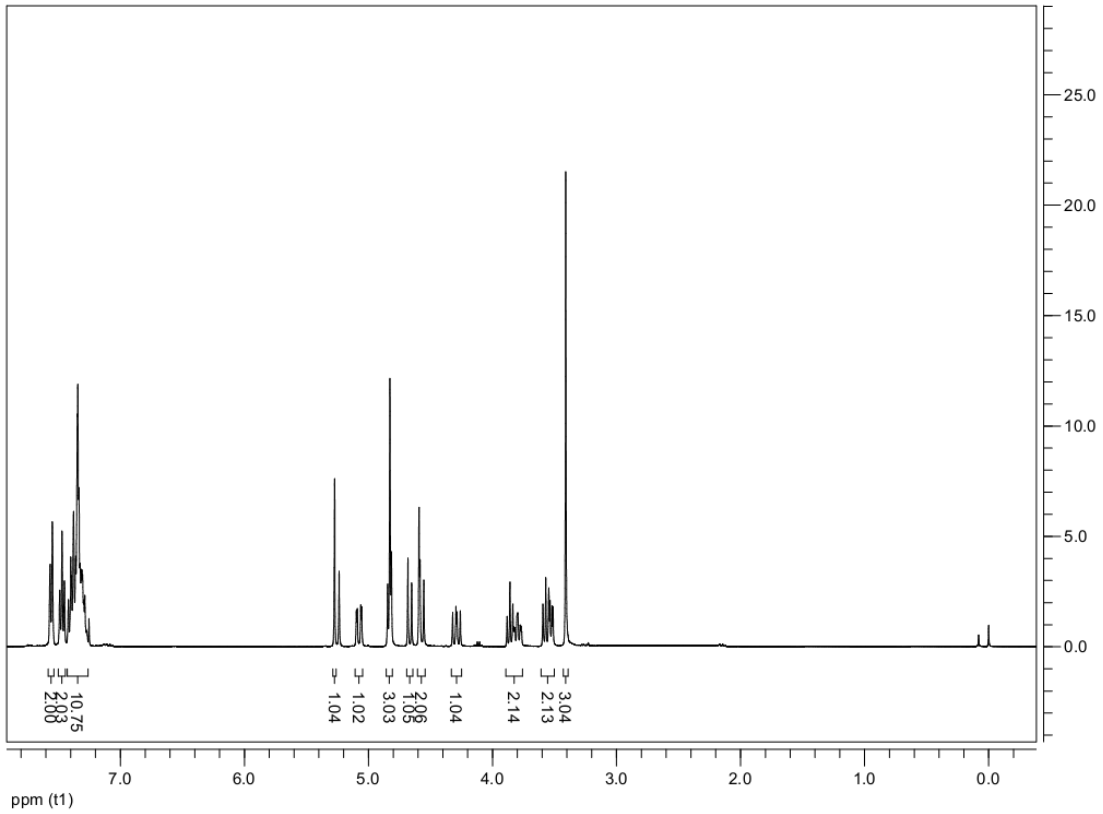

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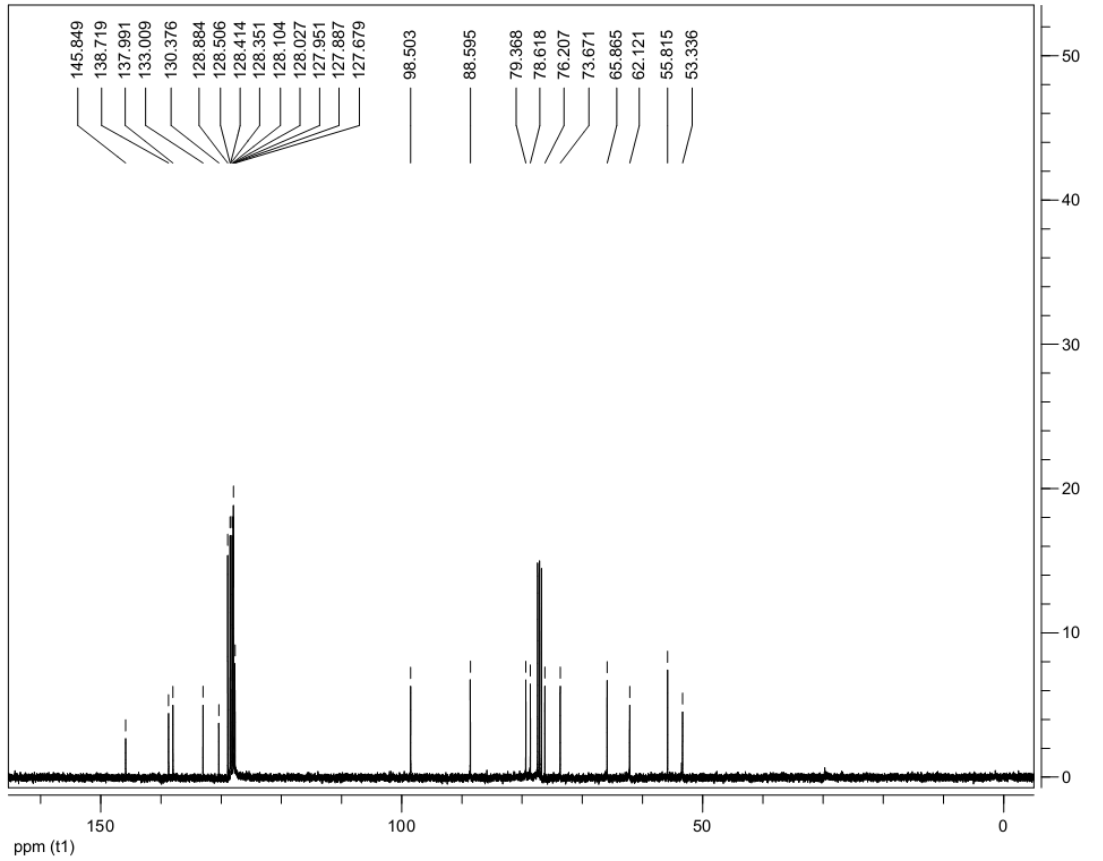

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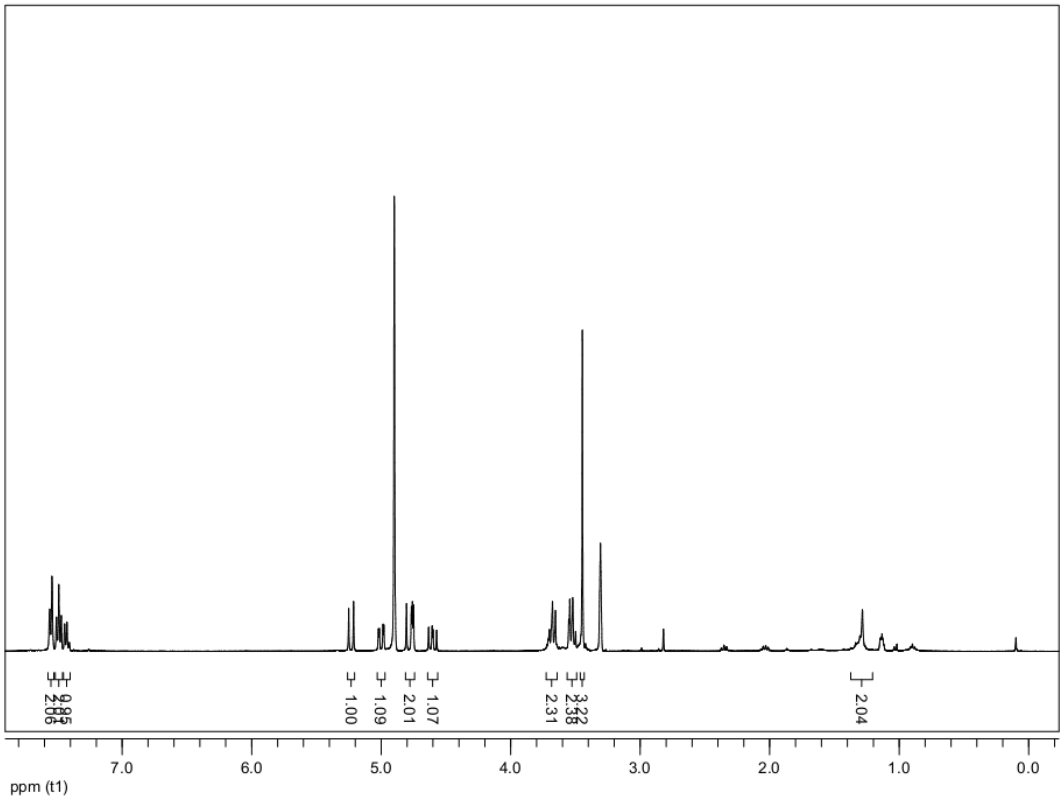

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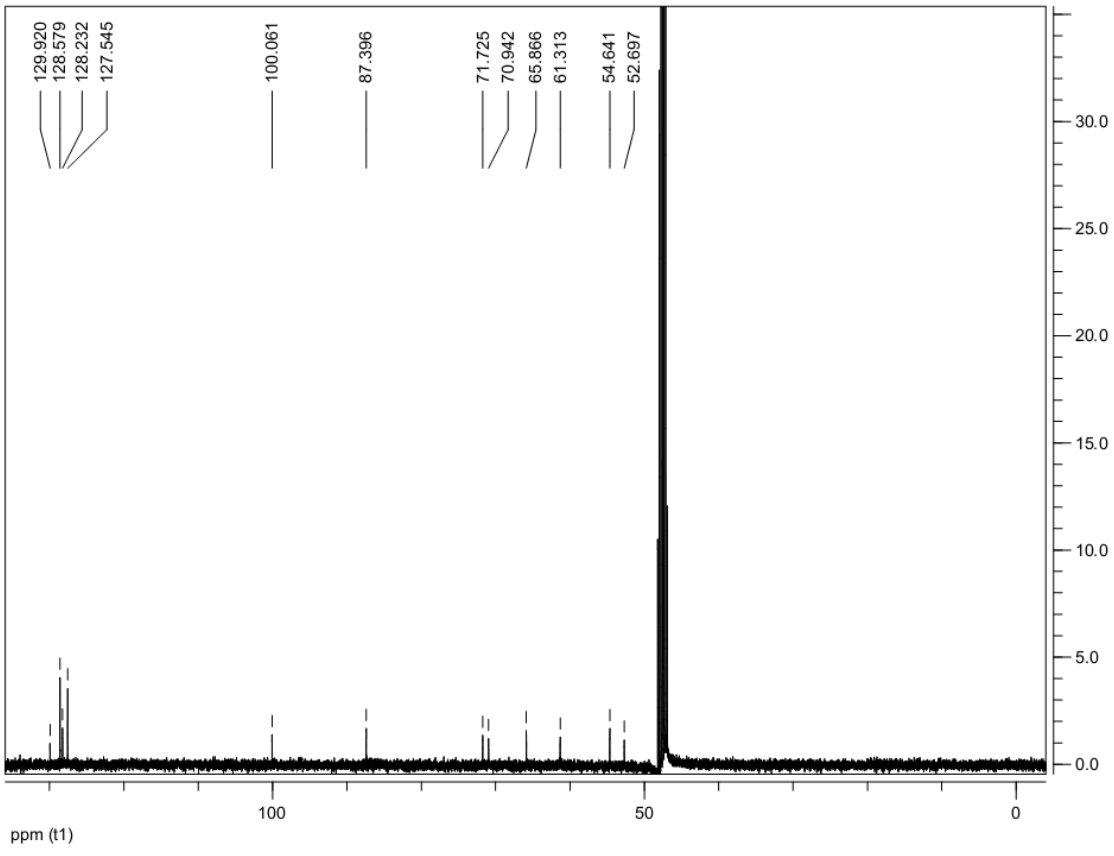

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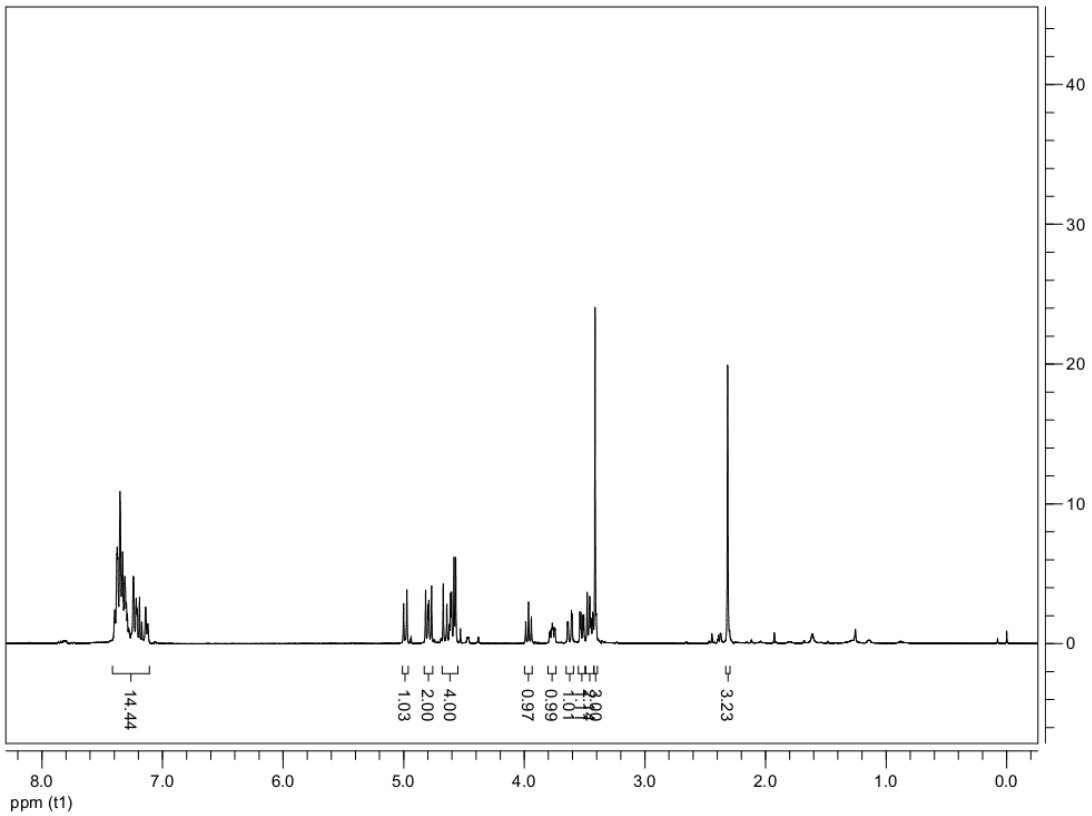

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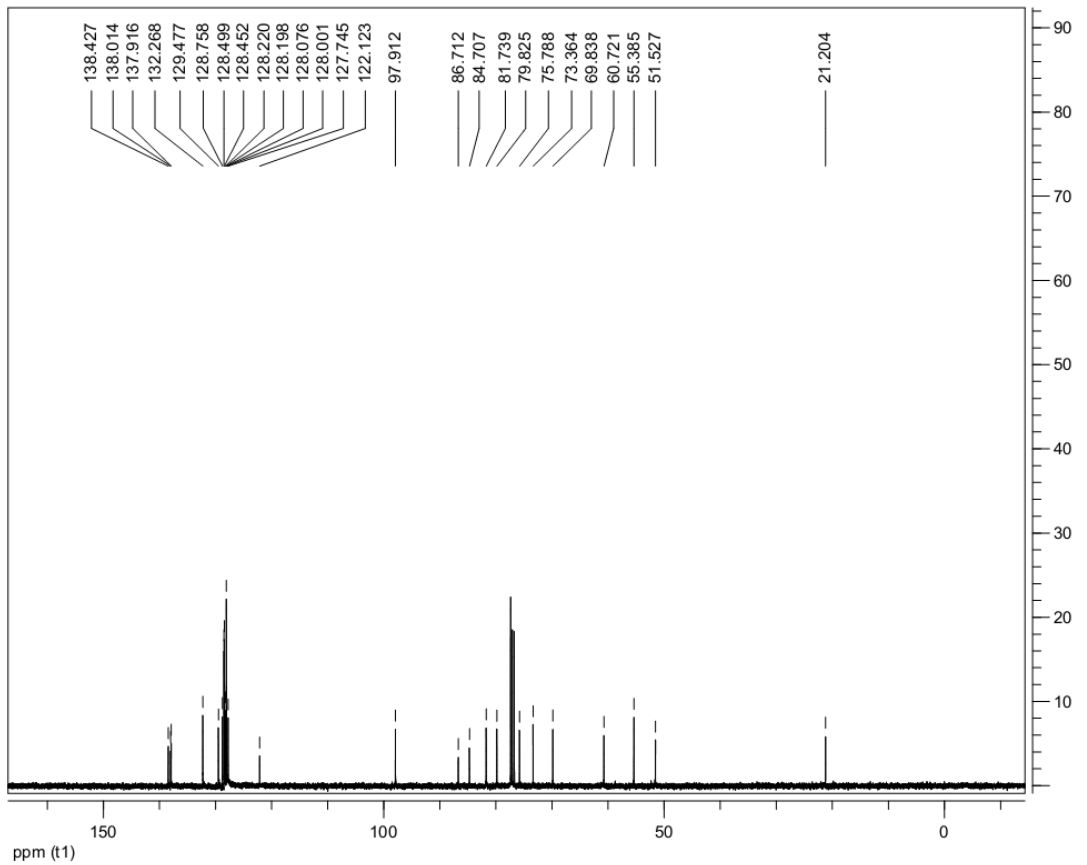

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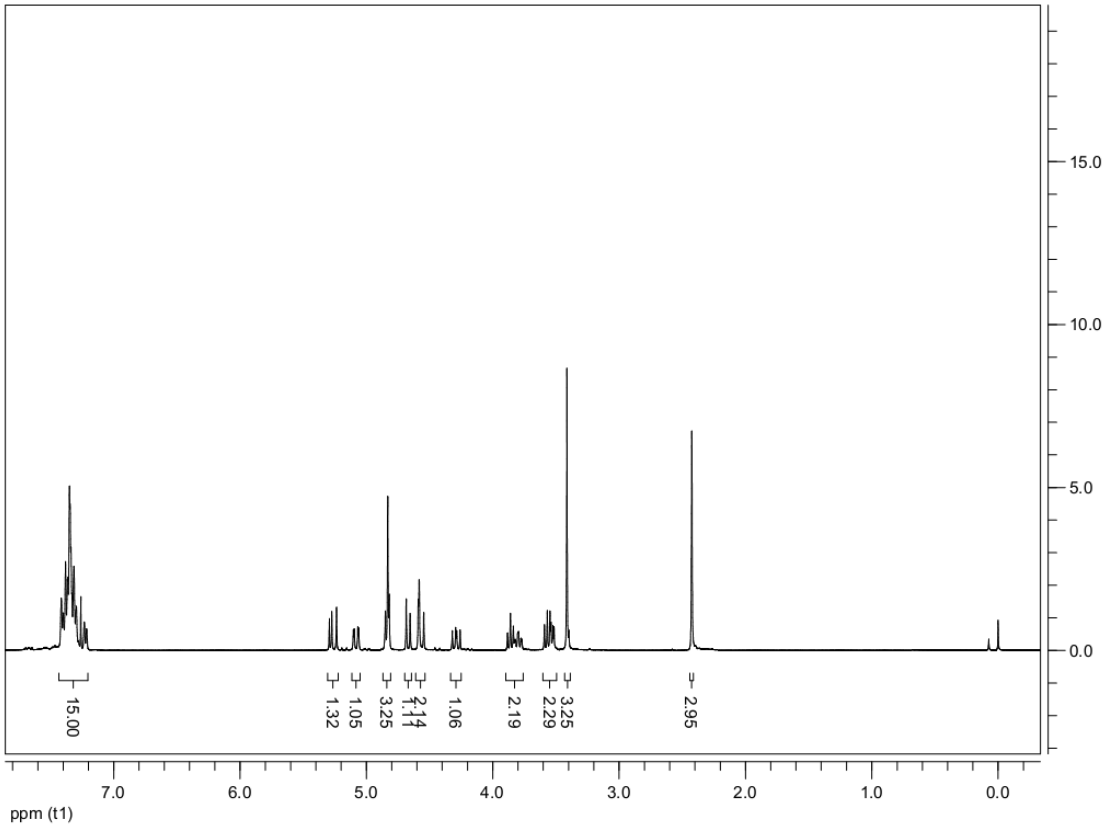

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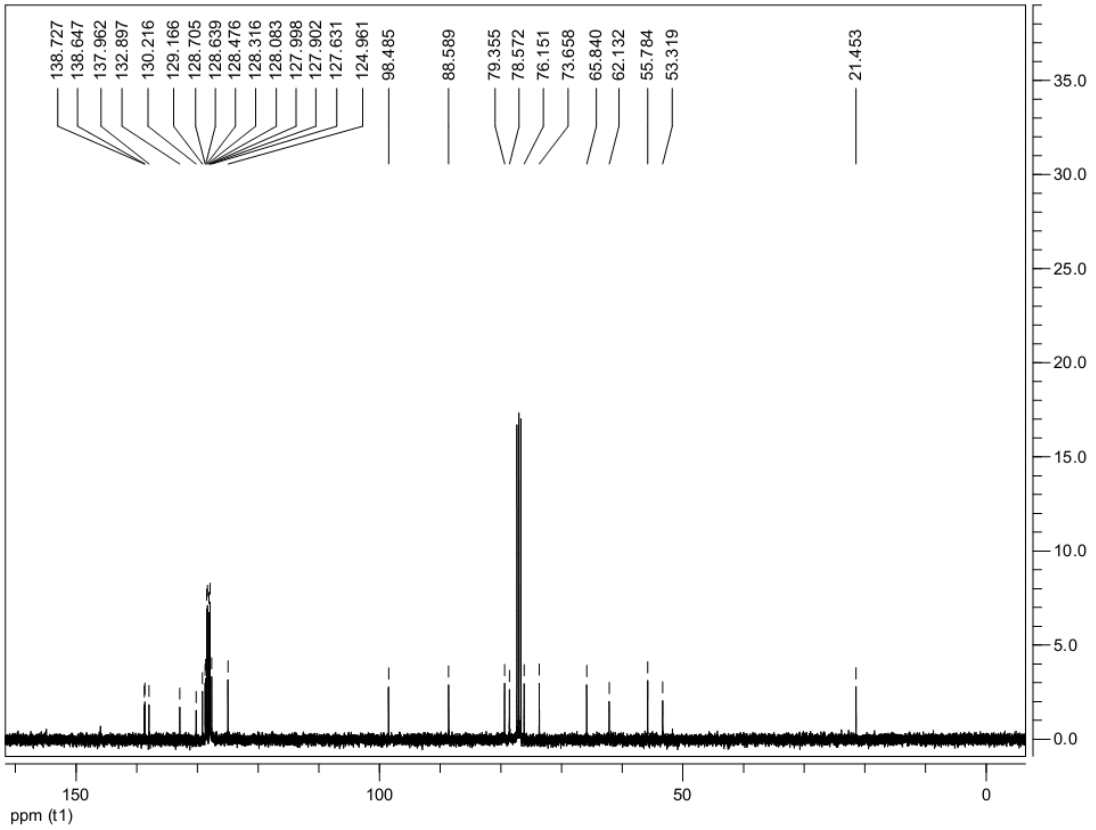

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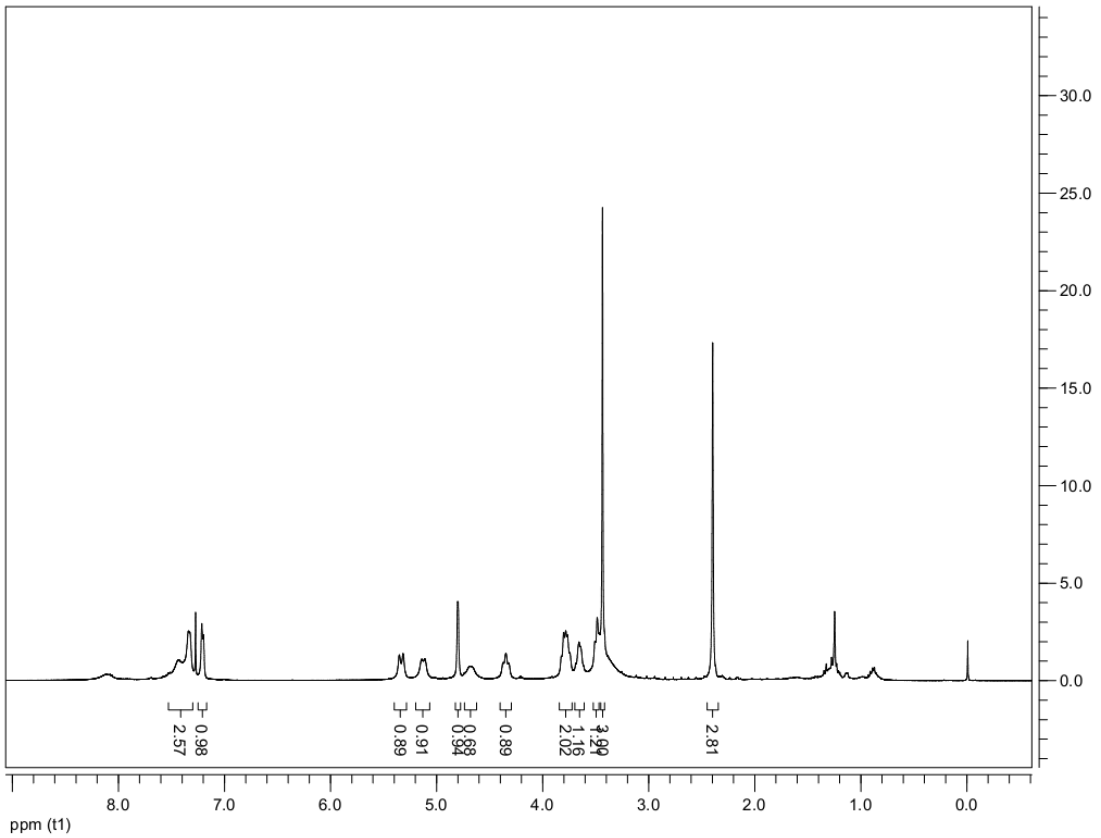

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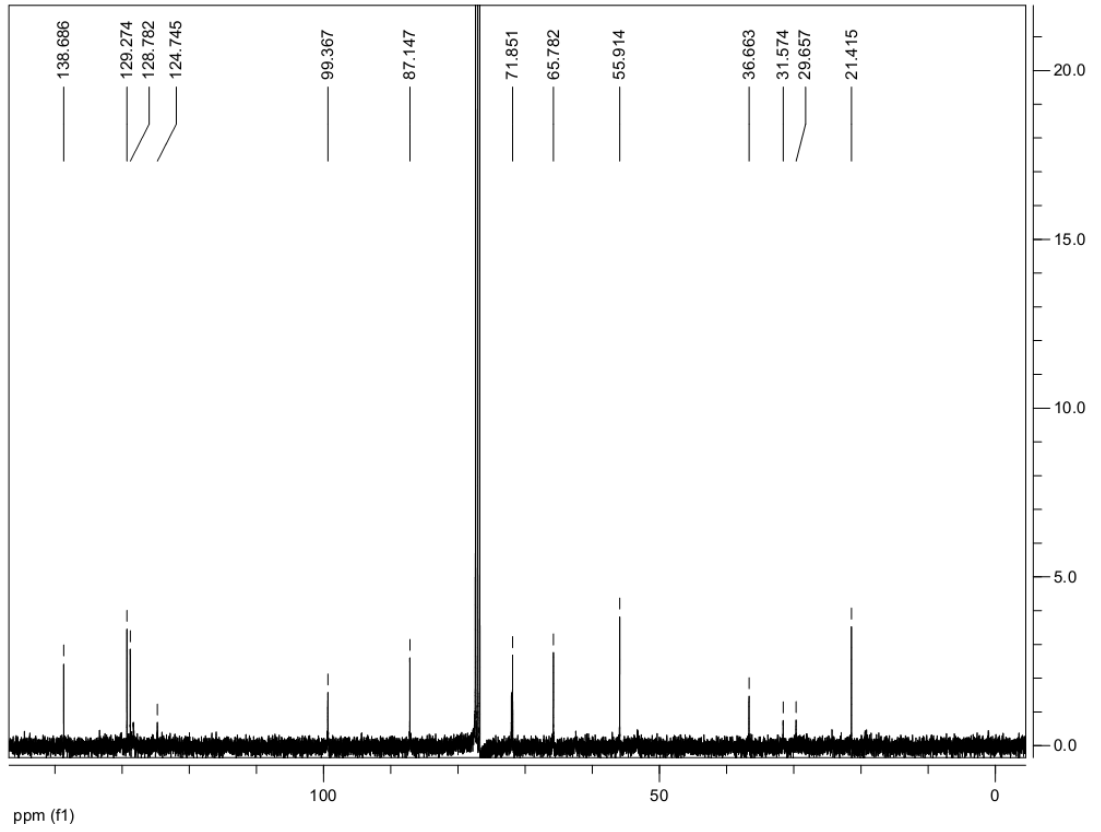

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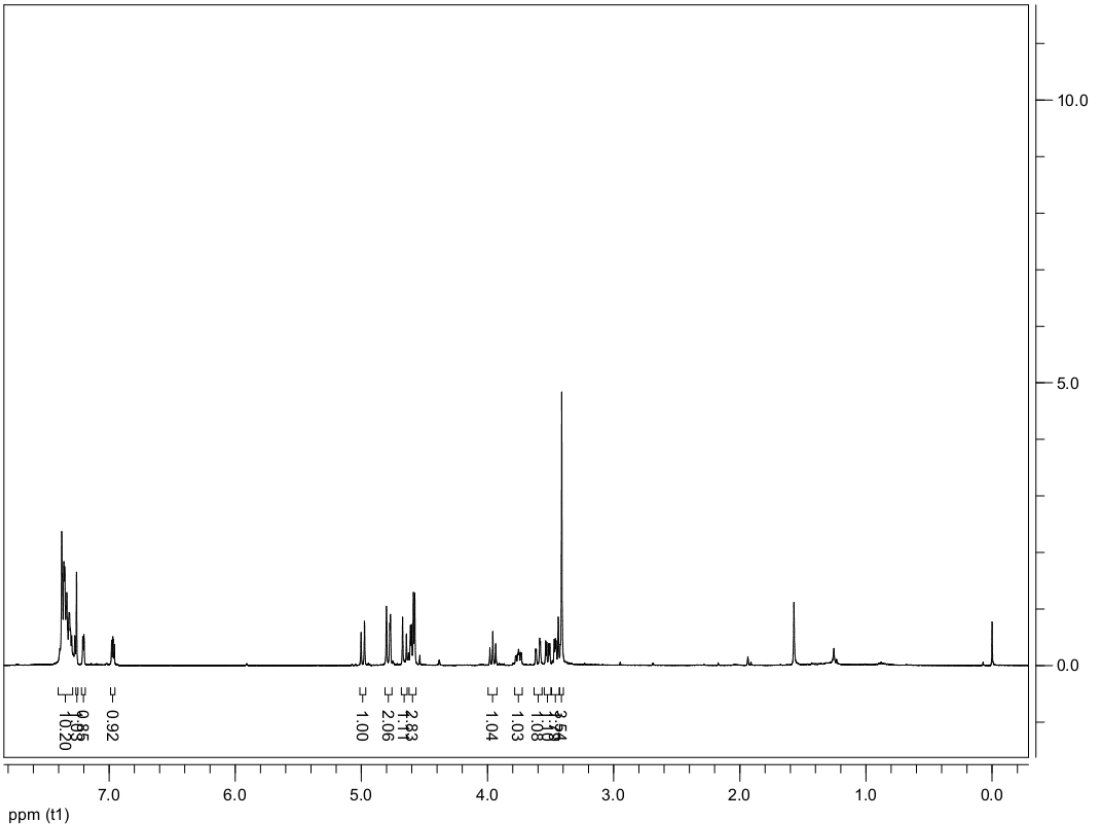

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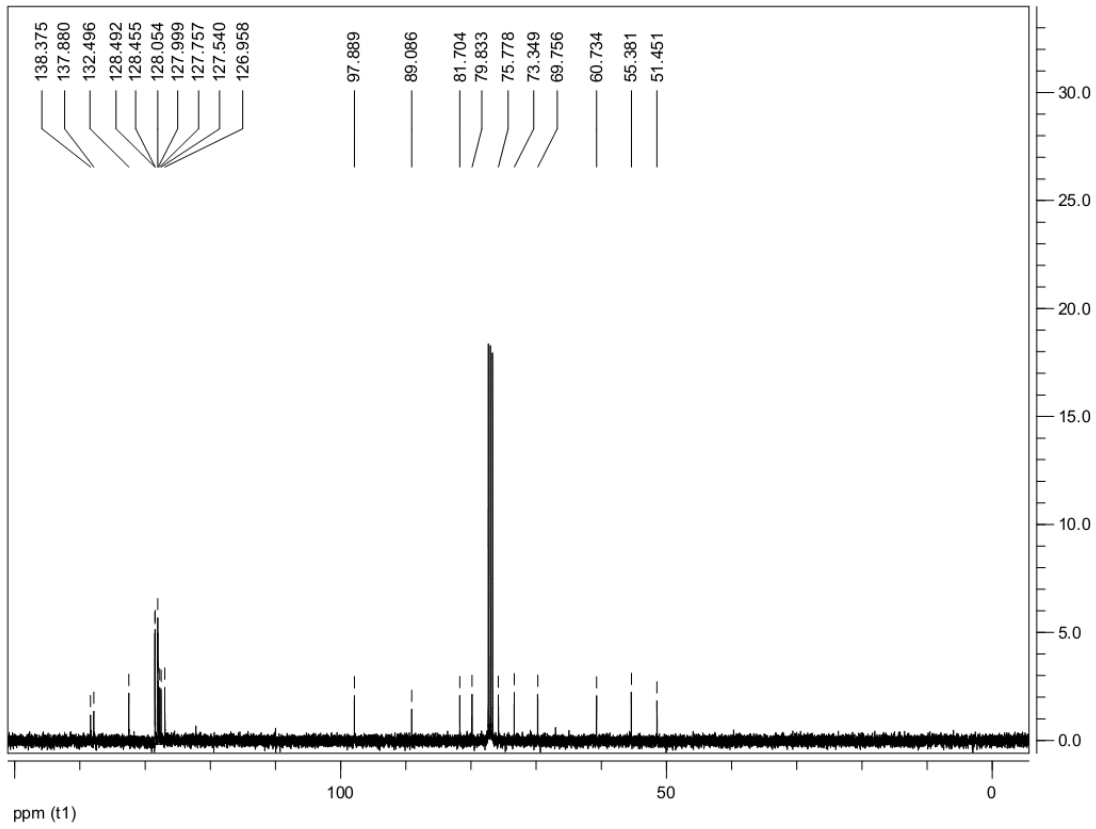

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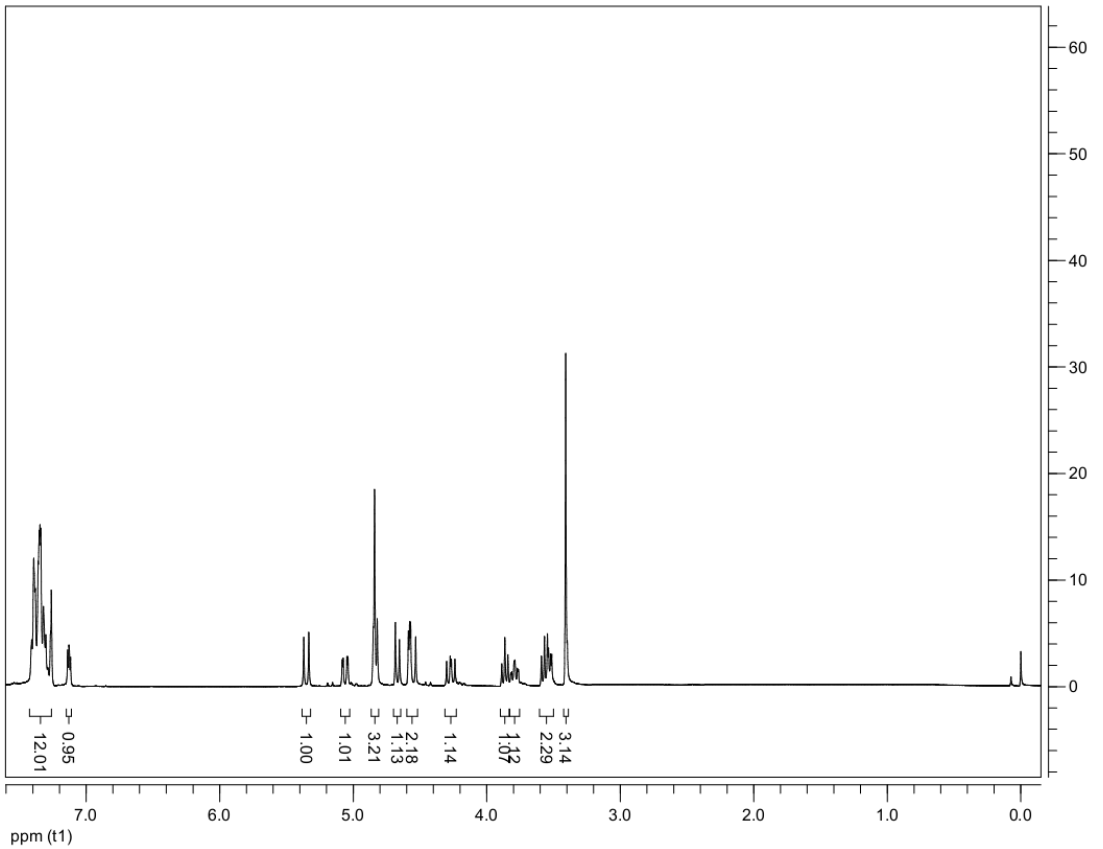

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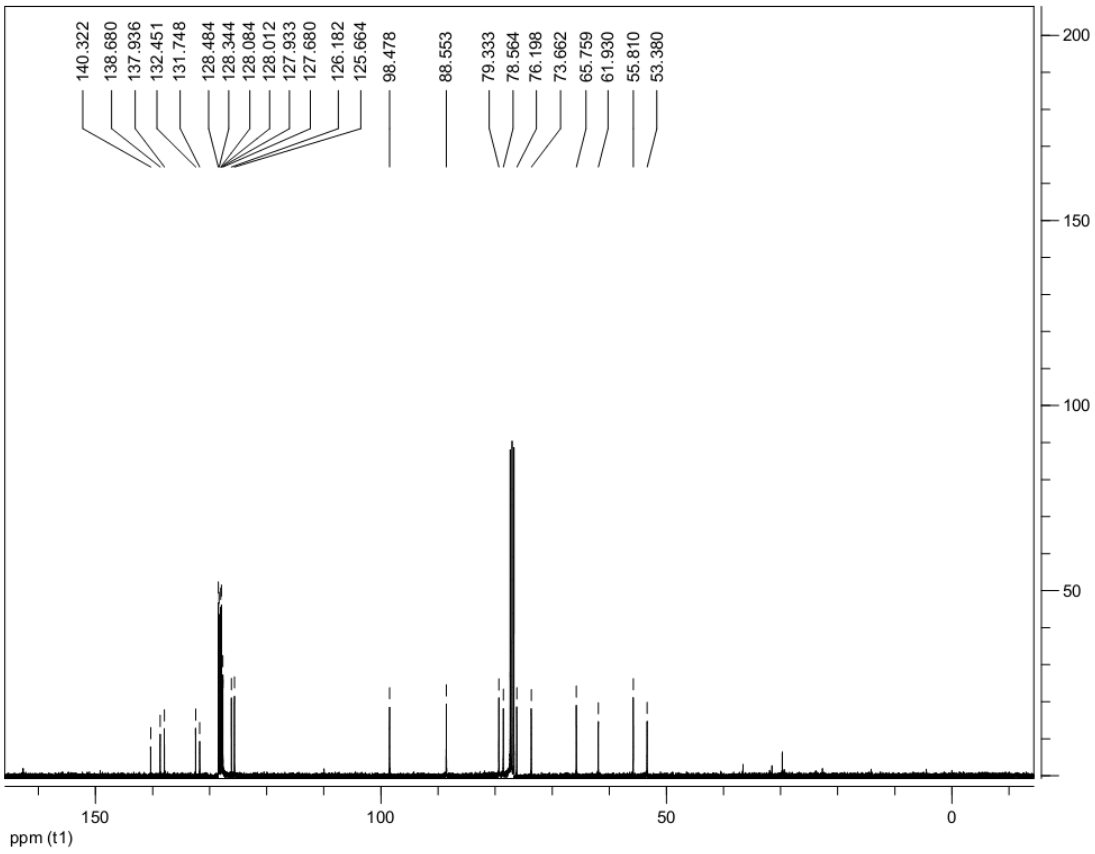

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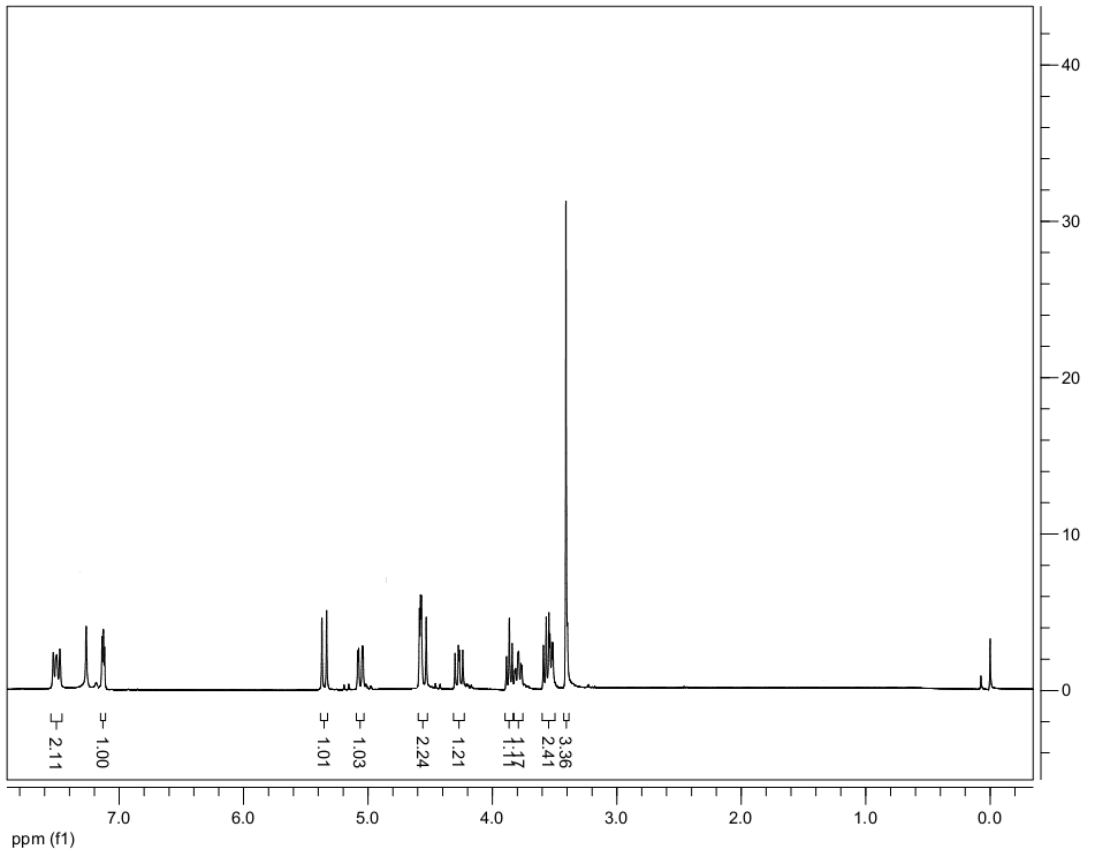

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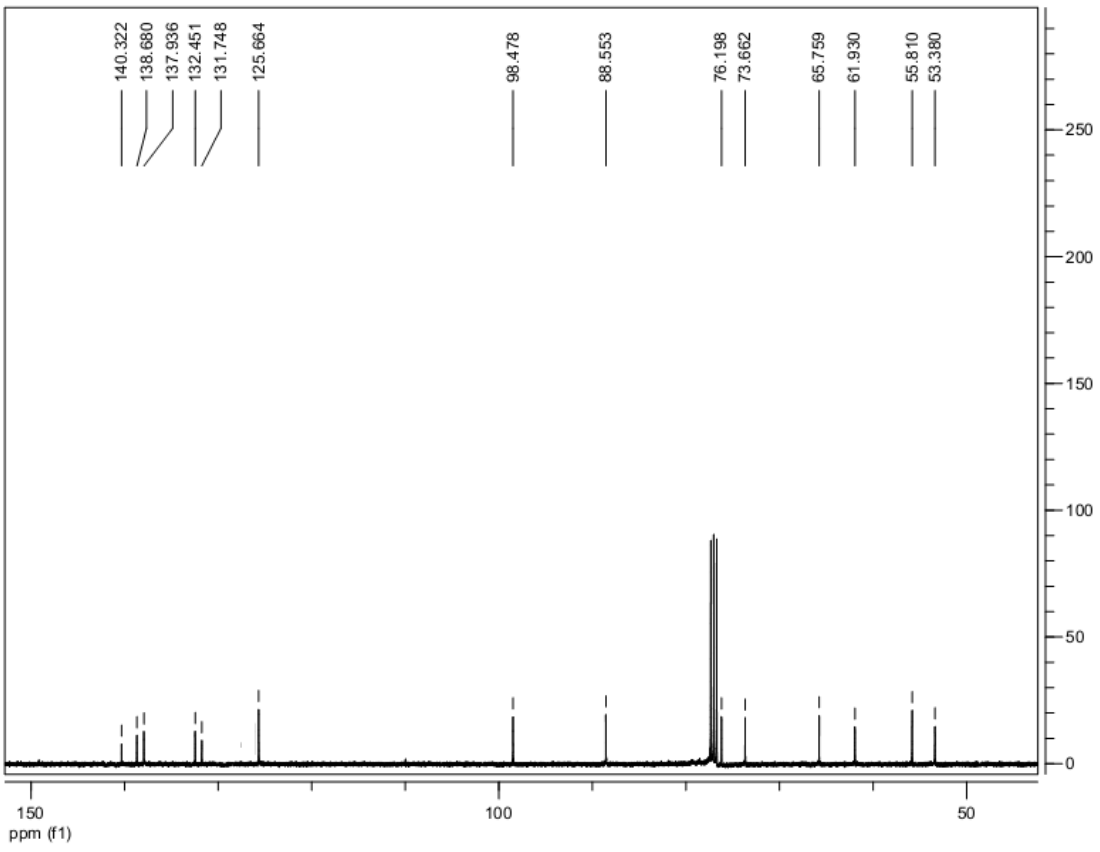

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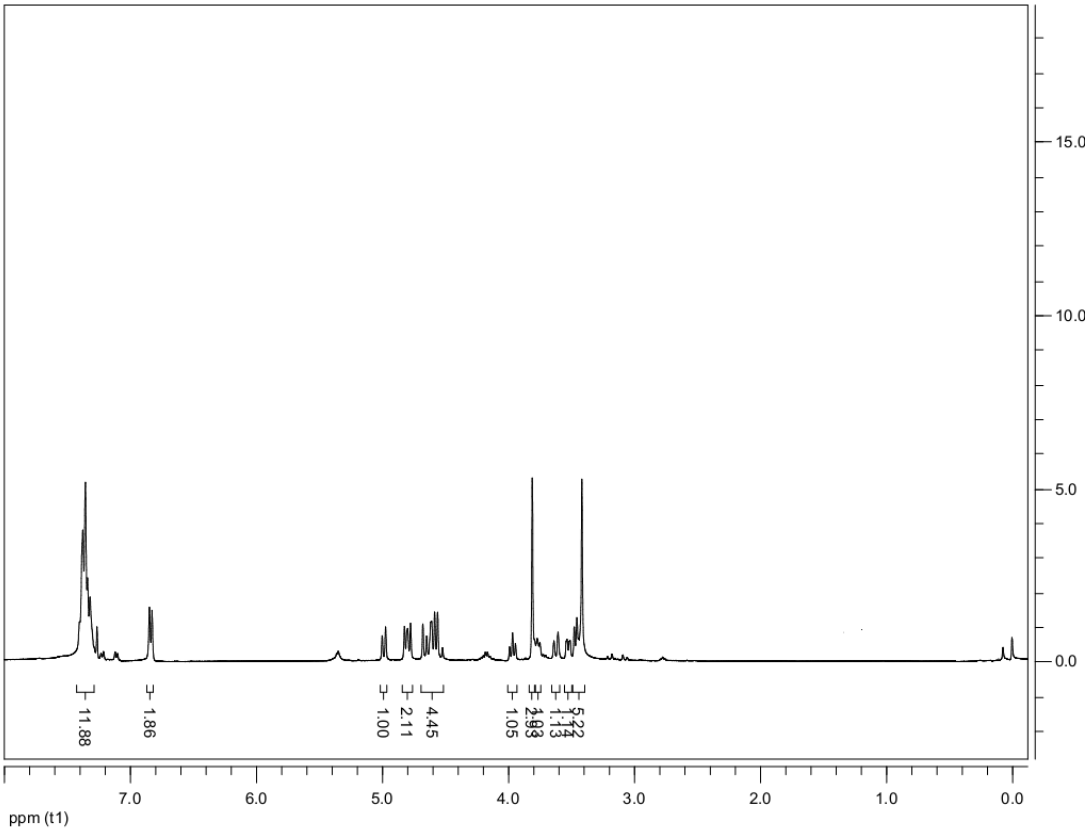

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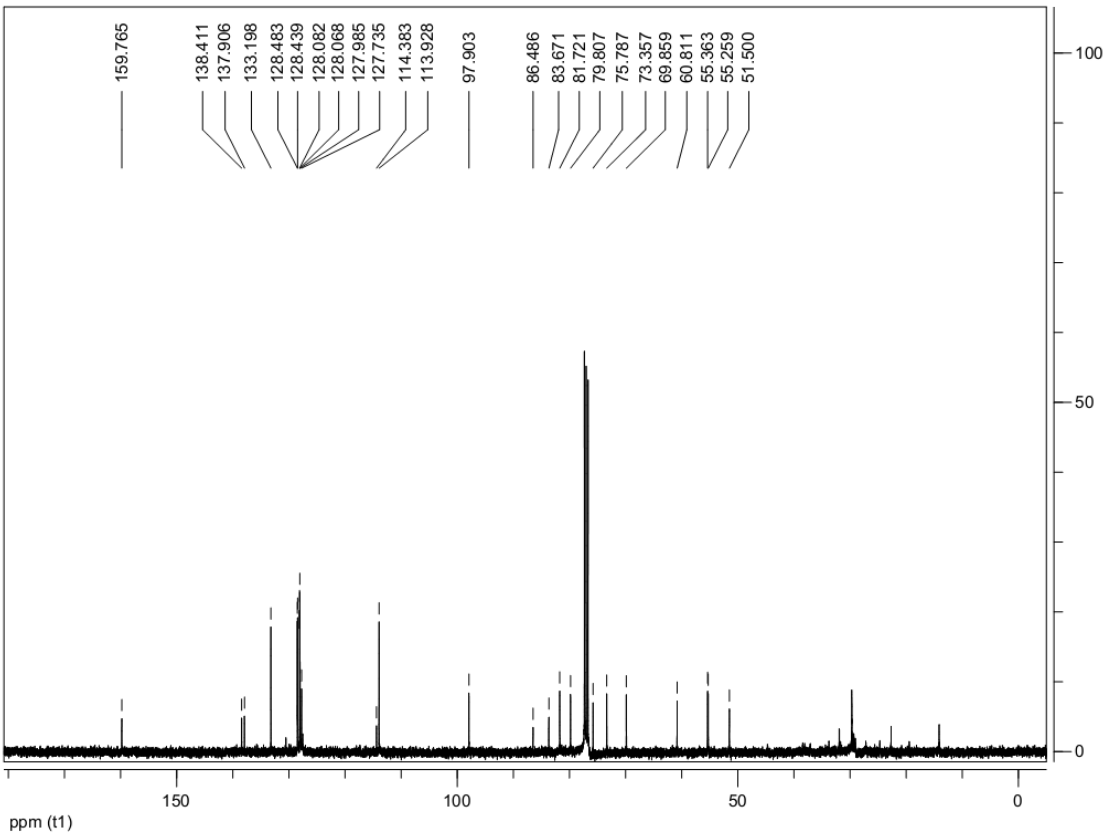

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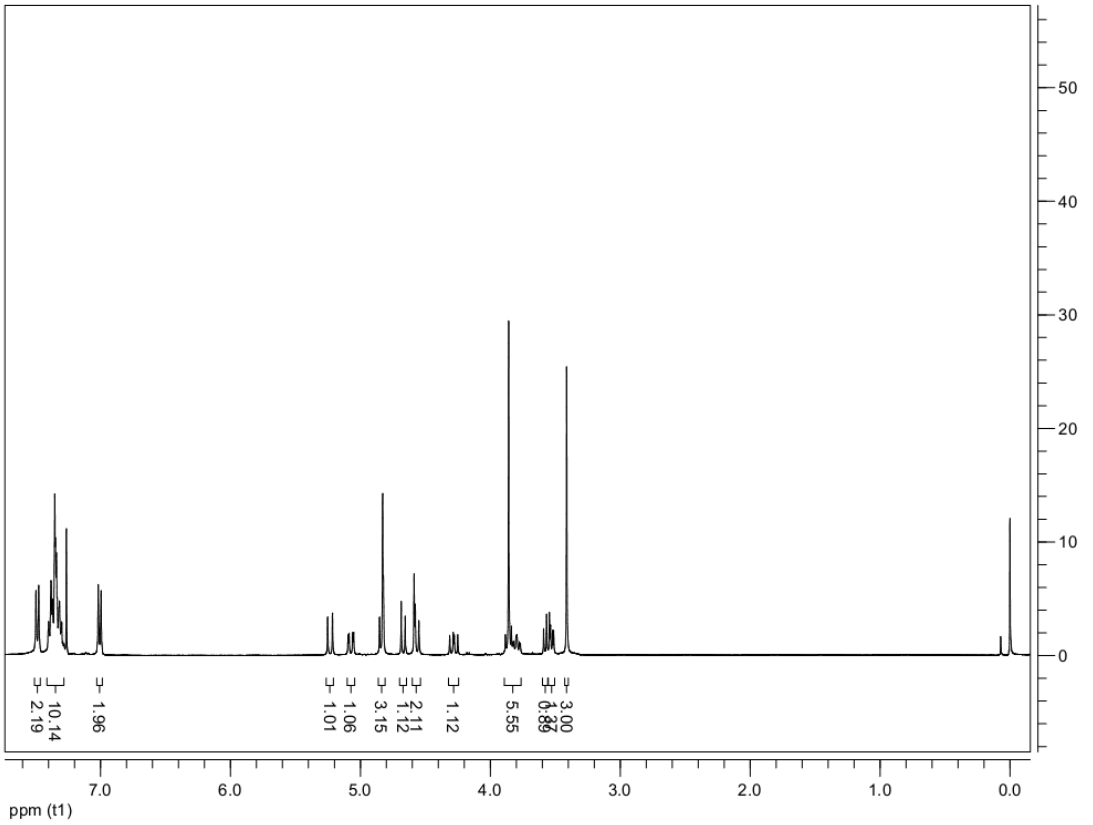

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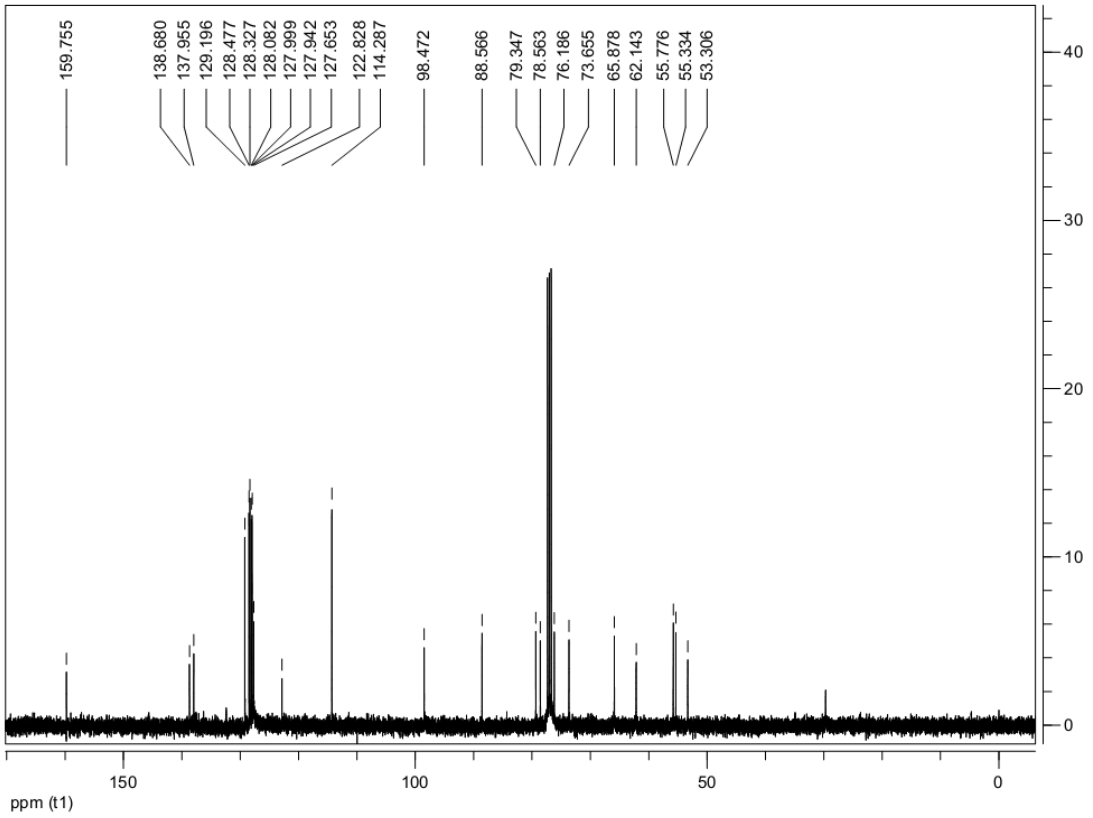

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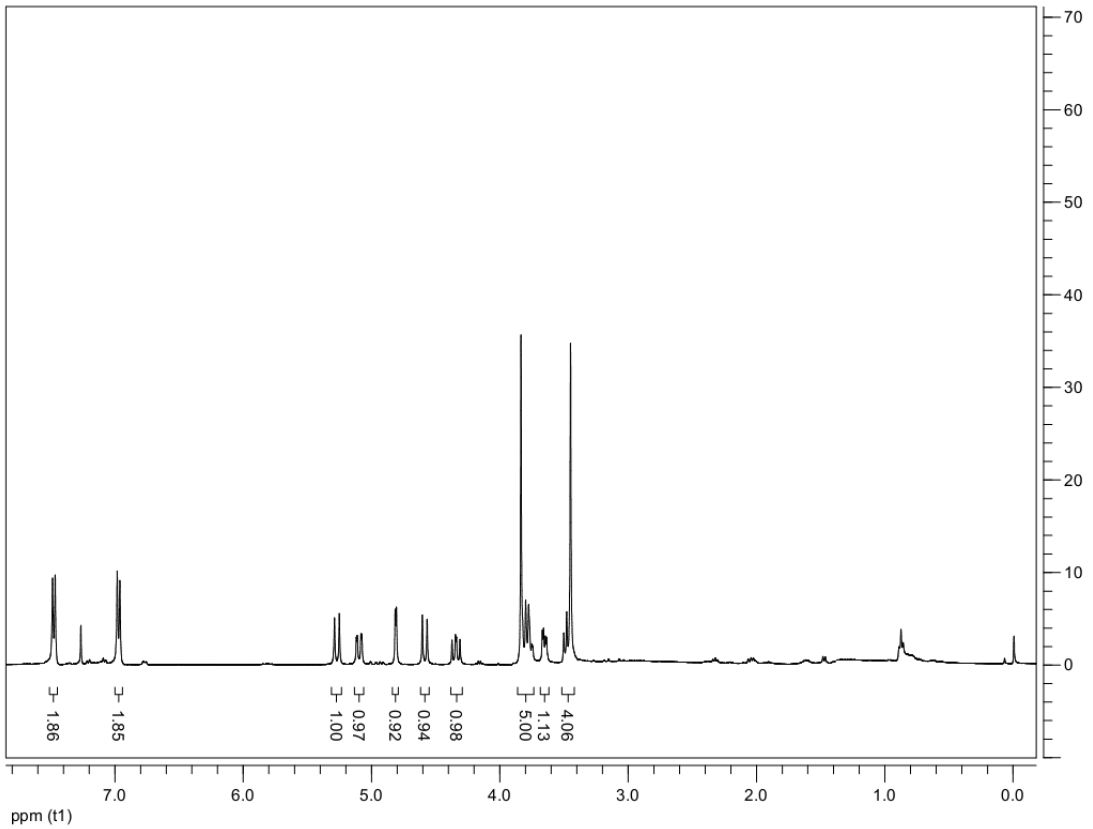
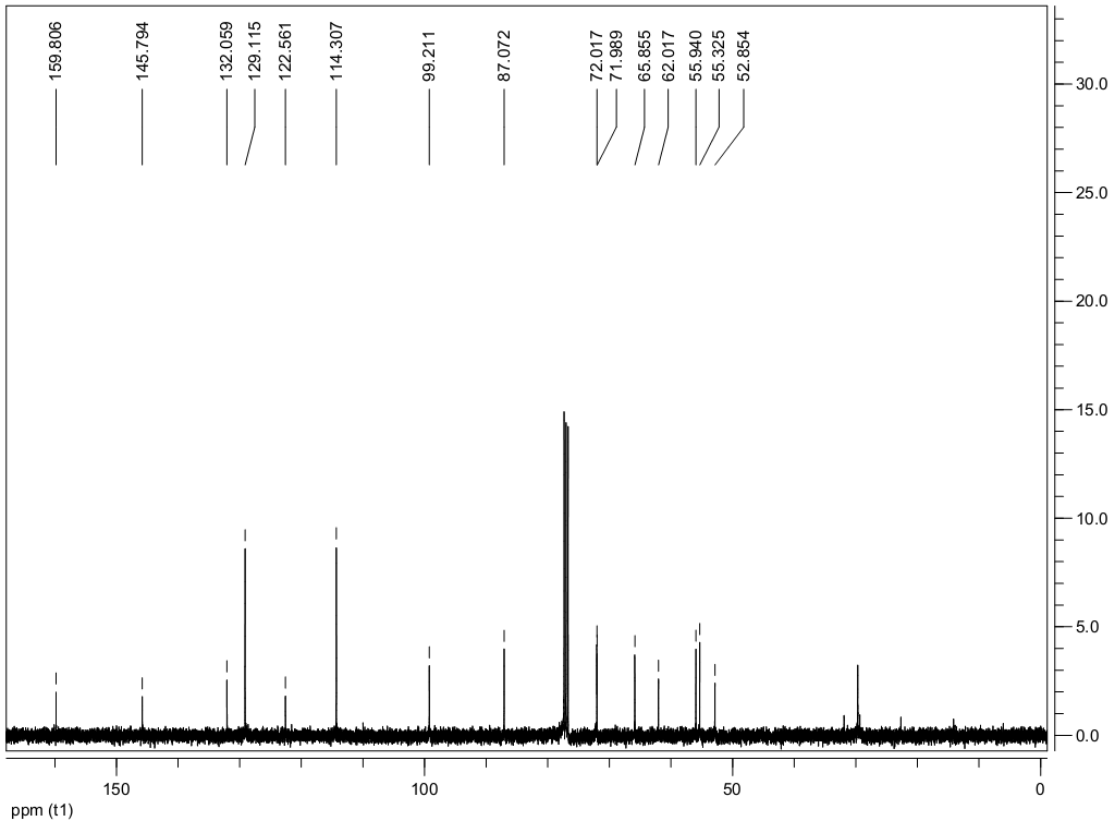
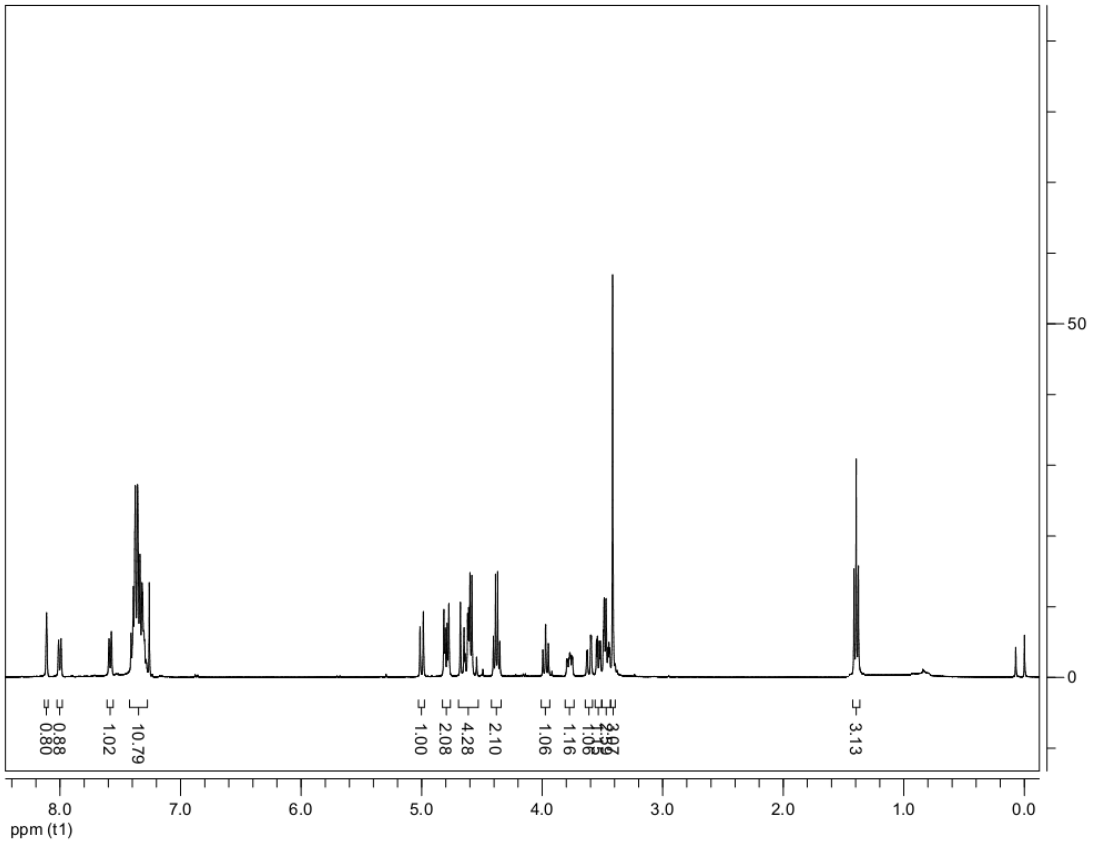


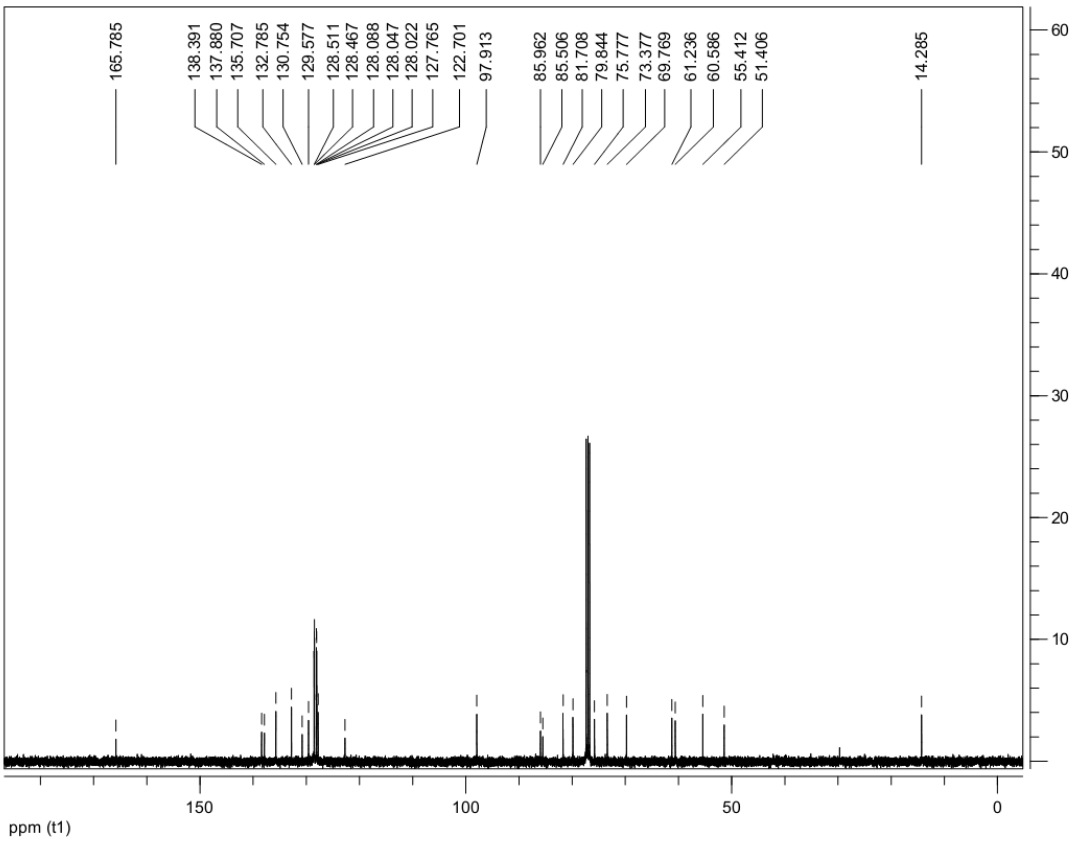
^{13}C NMR (100 MHz, $CDCl_3$)



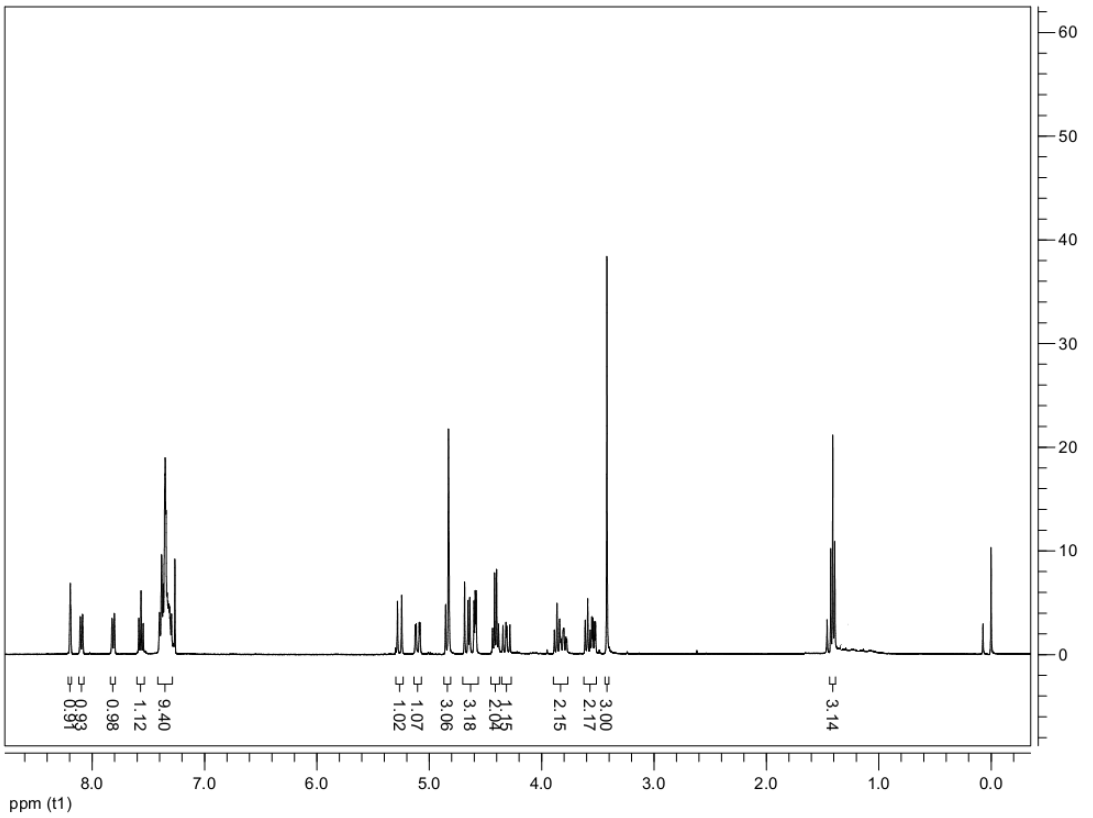
^{1}H NMR (400 MHz, $CDCl_3$)



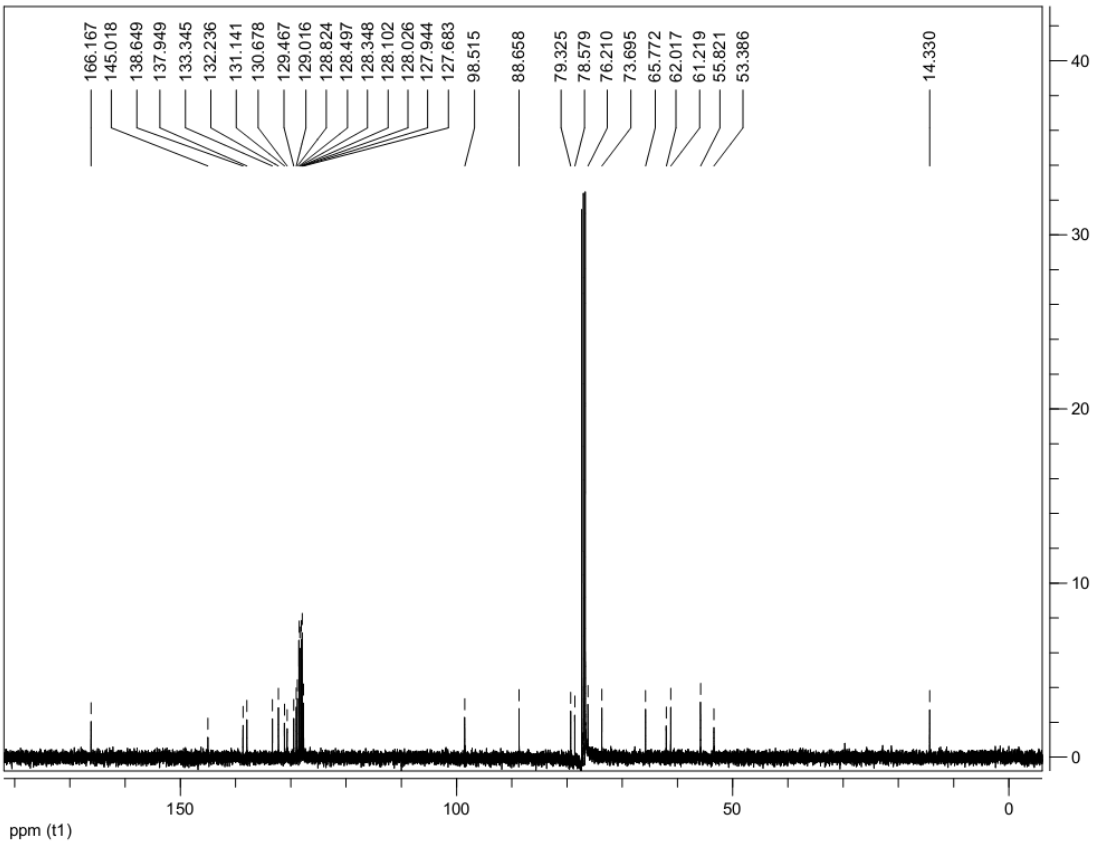
^{13}C NMR (100 MHz, $CDCl_3$)



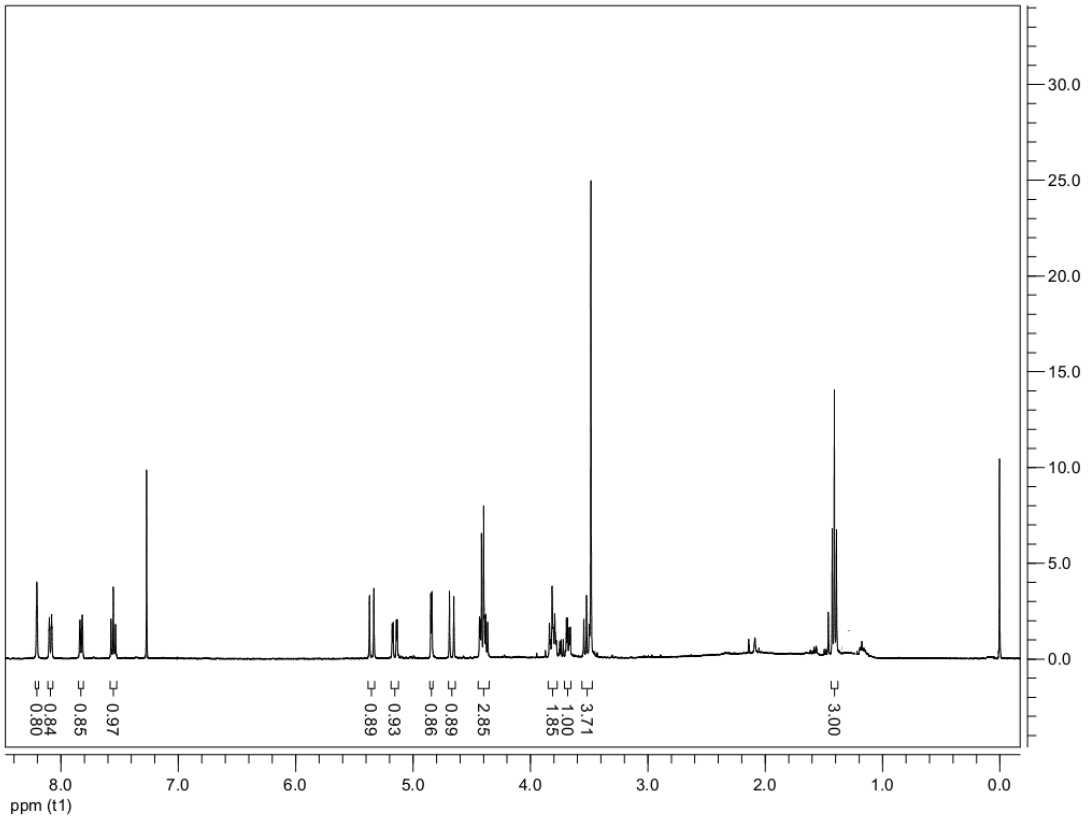
^{1}H NMR (400 MHz, $CDCl_3$)



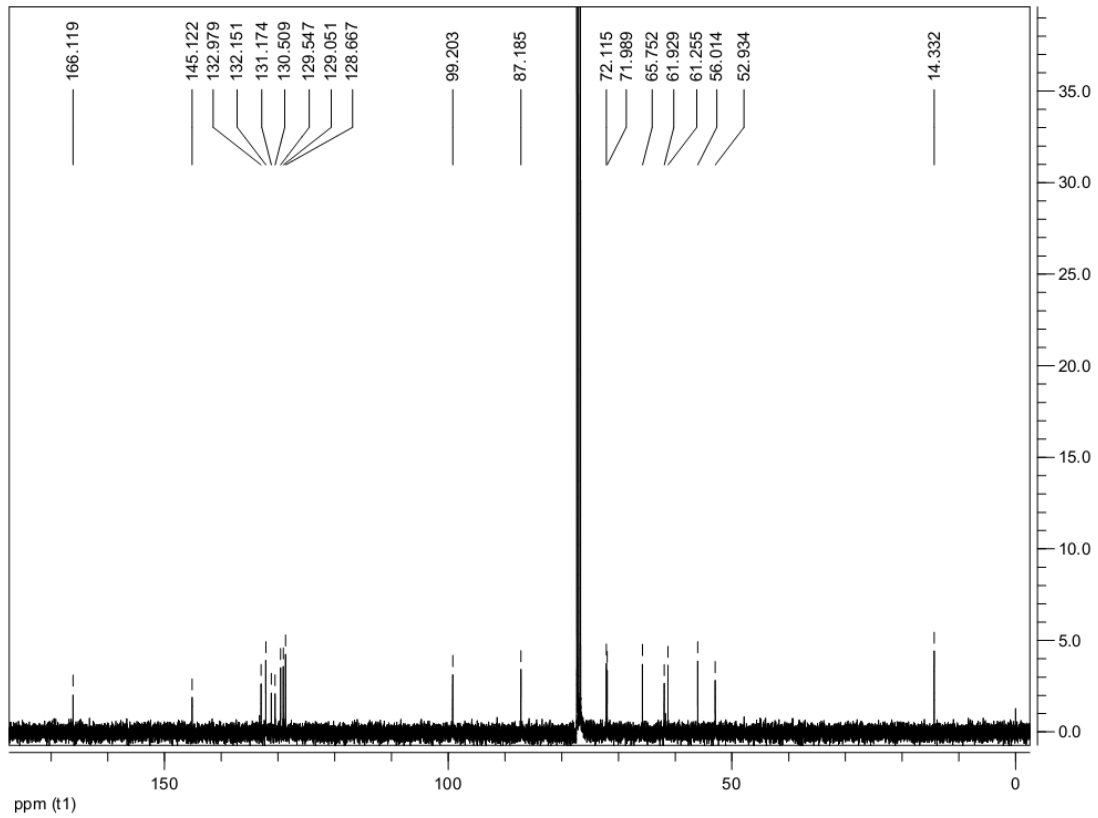
^{13}C NMR (100 MHz, $CDCl_3$)



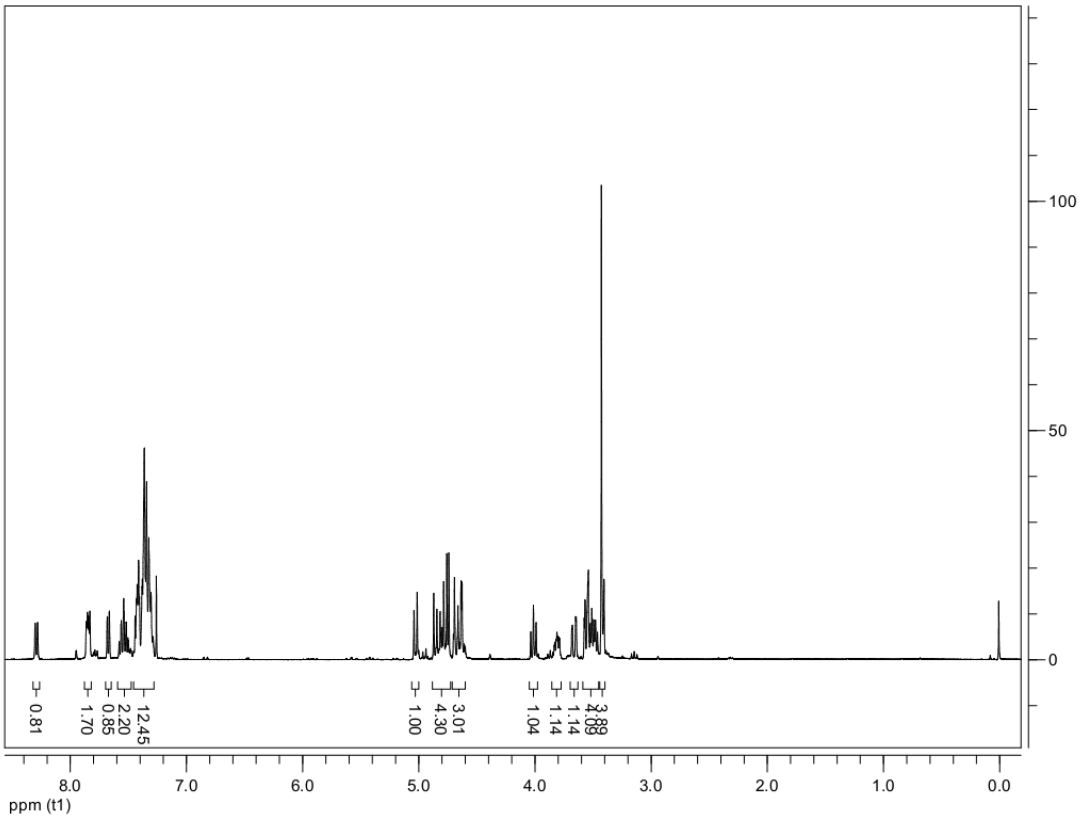
^{1}H NMR (400 MHz, $CDCl_3$)



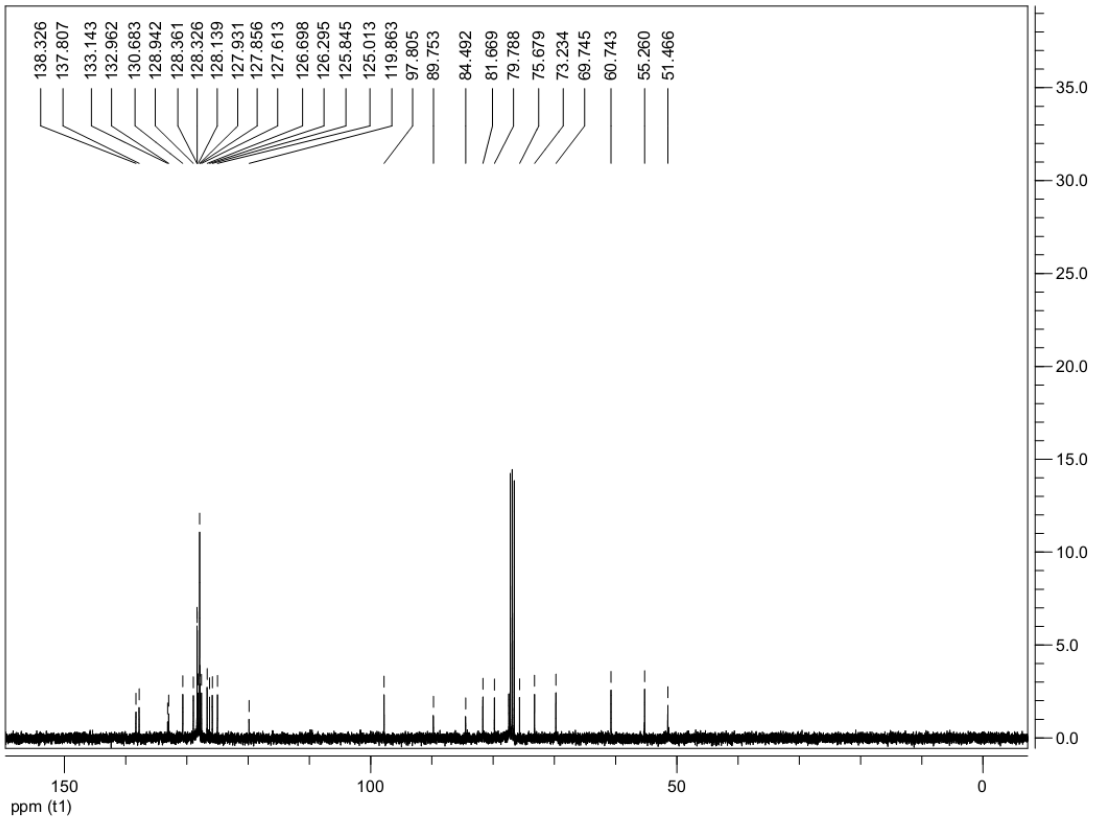
^{13}C NMR (100 MHz, $CDCl_3$)



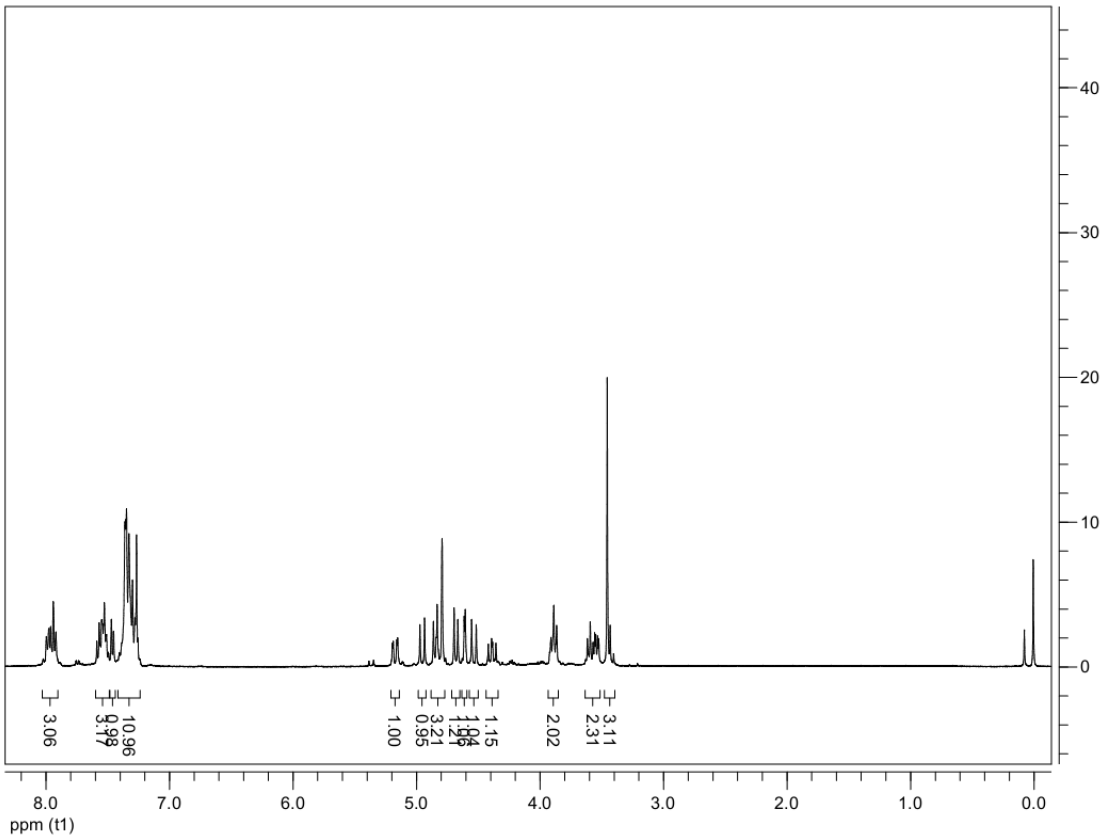
^{1}H NMR (400 MHz, $CDCl_3$)



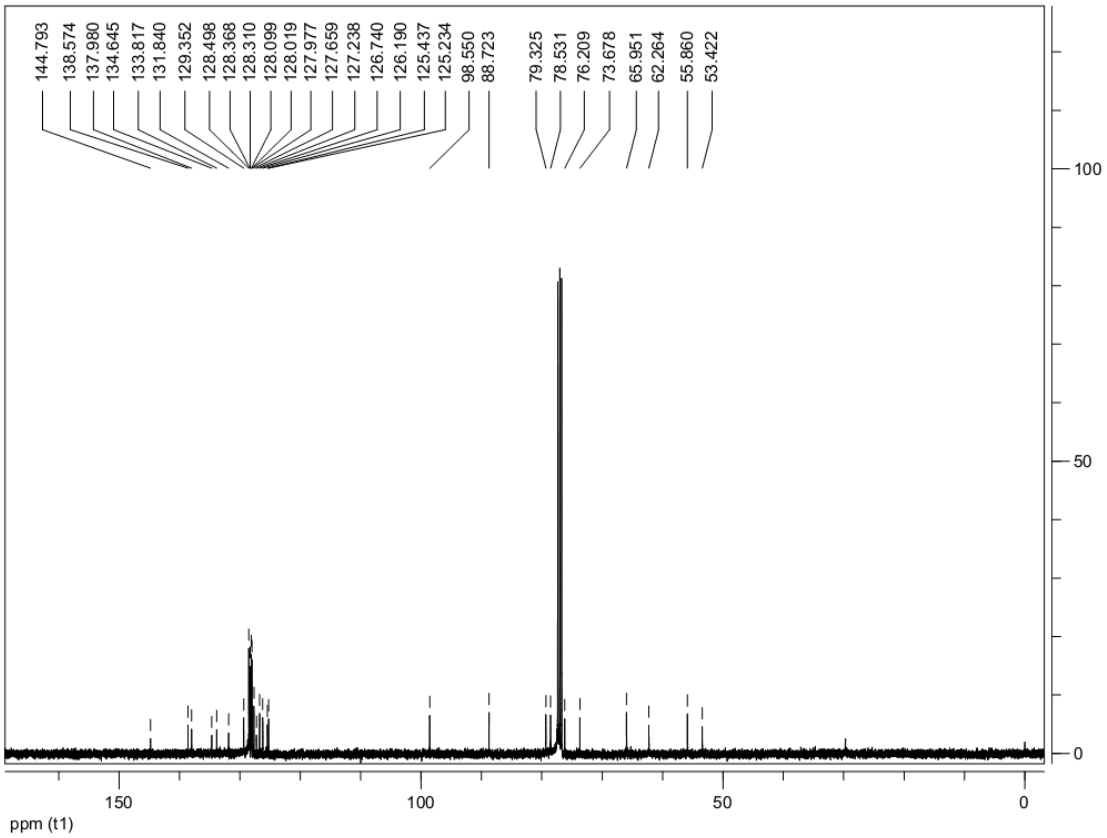
^{13}C NMR (100 MHz, $CDCl_3$)



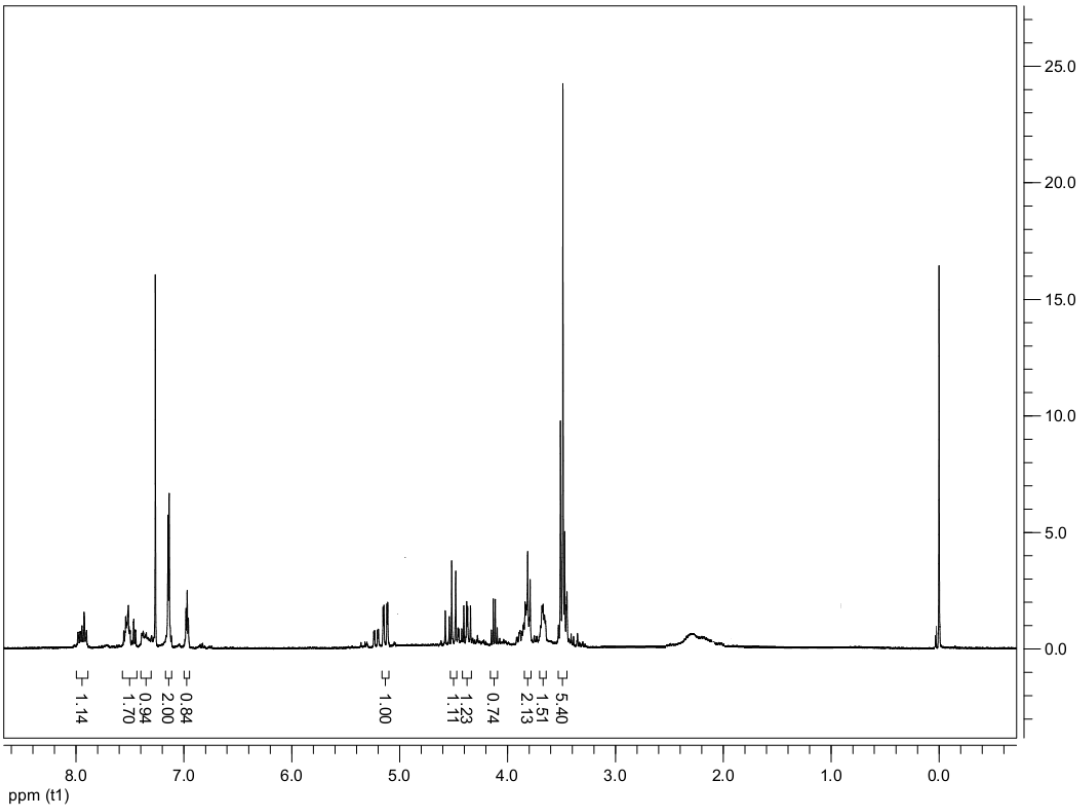
^{1}H NMR (400 MHz, $CDCl_3$)



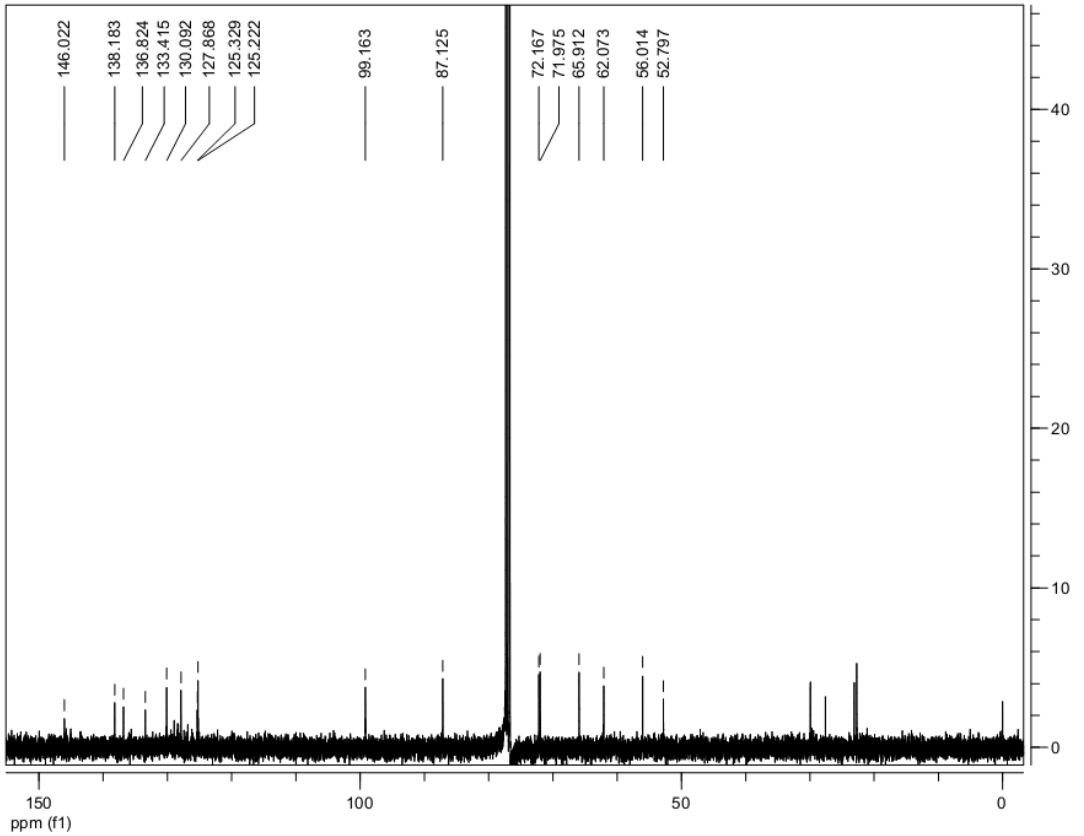
^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



Chapter 5

$InCl_3$ Catalyzed Three Component Synthesis of α-Benzylamino Coumarins and Diketones

5.1. Introduction

Multicomponent reactions (MCRs) typically involve more than two reactants to combine in a sequential manner, giving highly selective products, while retaining the majority of the atoms of the starting material.[1] MCRs have received considerable attention because of their wide range of applications in pharmaceutical chemistry for creating the structural diversity and combinatorial libraries in the drug discovery arena. [2]

In this chapter, I discussed a convenient and practical $InCl_3$ catalyzed three-component reaction of 4-hydroxy coumarin/1,3-diones, aromatic aldehyde, and secondary amine leading to the synthesis of α-benzylamino coumarins and diketones.

5.2. Importance of Coumarins

Coumarin and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products.[3] They exhibit wide range of biological activities such as anti-HIV[4], antimalarial[5], insecticidal[6], and antioxidant properties[7](**Figure 1**). Most significant coumarins are 3-substituted-4-hydroxy coumarin derivatives which have important clinical applications.[8]

Figure 1: Biologically Active Coumarins

5.3. Results and Discussion

We were interested in the development of one-pot MCR route to 3-substituted coumarin derivatives catalyzed by mild Lewis acids. Recently, indium(III)chloride has evolved as a mild and water tolerant Lewis acid imparting high regio-, chemo- and diastereoselectivity in various organic transformations.[9] Compared to

conventional Lewis acids, indium(III)chloride, in particular, has advantages of low catalyst loading, moisture stability and catalyst recycling.[10] In continuation of our interest in exploring the synthetic utility of indium(III)chloride,[11] we report a three-component reaction for the direct synthesis of α-benzylamino coumarin derivatives from 4-hydroxy coumarin, aromatic aldehyde and secondary amines.

Scheme 1: Synthesis of Coumarin and Dimedone Derivatives

We initially attempted a three-component reaction of 4-hydroxy coumarin, aryl aldehyde and secondary amines in the presence of various catalysts such as $FeCl_3$, $BF_3.OEt_2$, $AlCl_3$, $InCl_3$, amberlite IR-120 resin and I_2. Amongst these, $InCl_3$ was found to be an effective catalyst wherein the α-benzyl amino coumarin was obtained in good yields under mild conditions and with no traces of bis-coumarin product (**Scheme 1**). Except $BF_3.OEt_2$, all other Lewis acids studied, furnished the desired product, *albeit* in low yields (20-50% over 6-12 h).

Next, we studied the effect of solvent for this conversion. In polar solvents like ethanol and in chlorinated solvents like dichloromethane, the desired product was obtained in low yields. When the solvent was changed to a non-polar solvent such as toluene, excellent yields were obtained. We then examined the reaction under solvent-free conditions and observed that this reaction goes to completion in just 30 minutes at room temperature giving a modest 50% yield of the desired product (**Table 1**). In

the absence of $InCl_3$, the products were obtained in low yields (10-15%) and that also, after long reaction times (8-12 h).

Table 1: Optimized Conditions of $InCl_3$ Catalyzed Reaction of α-Benzylamino Coumarins

Mechanistically, we presume that the reaction proceeds *via* the formation of imine intermediate from secondary amine and aldehyde. Subsequent nucleophilic addition of 4-hydroxy coumarin results in the formation of only one product (**Figure 2**). To test the generality of this reaction, pyrrolidines, piperidines and indoles were reacted with 4-hydroxy coumarin and 1,3- dimedone (**Table 2**). All the products **1.4a-f** and **1.6a-f** were characterized and confirmed by ^{1}H NMR, ^{13}C NMR and MS. ^{1}H NMR spectra of compounds **1.6a-f** showed a characteristic singlet at around δ 5.01 indicating that the products exist exclusively in their enol forms.

Figure 2: Possible Reaction Mechanism of α-Benzyl Amino Coumarins

The Reaction of 4-hydroxy coumarin with indole and aromatic aldehydes furnished product **1.8a-c** (**Table 3**), wherein, the most acidic C-3 proton of indole was involved. Compound **1.8** was obtained *via* the conjugate addition product of the enone formed from 4-hydroxy coumarin and aromatic aldehyde with indole.

Figure 3: Possible Reaction Mechanism of Aryl Indole Coumarins

Table 2: Compounds Synthesized with Coumarin.

Table 3: Compounds Synthesized with Dimedone.

Table 4: Compounds Synthesized with Indole

5.4. Conclusion

To summarize, I developed a convenient methodology for the synthesis of α-benzyl amino coumarin derivatives in high yields *via* a three-component reaction using $InCl_3$ catalyst. This reaction has been extended to α-benzyl amino diketone derivatives and represents a mild and convenient route.

5.5. Experimental Section

General procedure for the synthesis of compounds 1.4 and **1.6.** In a typical experiment, a solution of aldehyde (1 mmol), 4-hydroxy coumarin or diketone (1 mmol) and $InCl_3$ (0.1 mmol) in anhydrous toluene (1 mL), secondary amine (1 mmol) was added and the reaction mixture was vigorously stirred at room temperature for 3h. After the starting material disappeared (by TLC) the reaction mixture was quenched by water extracted with dichloromethane, dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure furnished the crude residue which was triturated in hexane to afford desired product in 80-90% yield.

4-hydroxy-3-(phenyl(pyrrolidin-1-yl)methyl)-2H-chromen-2-one

(1.4a):

Light yellow solid

M.P: 170-172 ^{o}C

LRMS (M+1): 321.9;

Yield: 90%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.99 Hz, 1H), 7.64 (d, *J* = 8.35 Hz, 2H), 7.49-7.44 (m, 1H), 7.31 (d, *J* = 8.41 Hz, 2H), 7.23 (d, *J* = 8.45 Hz, 3H), 5.15 (s, 1H), 3.68-3.62 (m, 1H), 3.18-3.07 (m, 2H), 2.72-2.64 (m, 1H), 2.10-2.0 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 167.2, 151.0, 148.5, 143.9, 127.1, 126.3, 125.7, 124.1, 124.1, 123.9, 123.4, 122.7, 122.2, 111.6, 105.5, 60.0, 50.7, 32.7, 30.6.

IR(KBr): 3068, 1657, 1456 cm^{-1}

4-hydroxy-3-(pyrrolidin-1-yl(p-tolyl)methyl)-2H-chromen-2-one

(1.4b):

Light yellow solid

M.P: 180-182 ^{o}C

LRMS (M+1): 335.9

Yield: 85%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.61 Hz, 1H), 7.57 (d, *J* = 8.00 Hz, 2H), 7.43-7.42 (m, 1H), 7.21 (d, *J* = 7.90 Hz, 2H), 7.13 (d, *J* = 7.88 Hz, 2H), 5.13 (s, 1H), 3.69-3.60 (m, 1H), 3.20-3.04 (m, 2H), 2.74-2.65 (m, 1H), 2.30 (s, 3H), 2.13-1.96 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 164.0, 154.1, 139.0, 134.7, 131.8, 130.5, 130.2, 128.8, 127.7, 124.3, 123.9, 123.5, 122.4, 121.2, 117.1, 95.5, 70.0, 69.7, 23.8, 23.3.

IR(KBr): 3079, 1653, 1456 cm^{-1}

3-((4-chlorophenyl)(pyrrolidin-1-yl)methyl)-4-hydroxy-2H-chromen-2-one

(1.4c):

White solid

M.P: 176-178 ^{o}C

LRMS (M+1): 355.9

Yield: 89%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, *J* = 7.28, 1.34 Hz, 1H), 7.73-7.67 (m, 2H), 7.48-7.42 (m, 1H), 7.33 (d, *J* = 6.08 Hz, 2H), 7.23 (d, *J* = 7.61 Hz, 2H), 5.18 (s, 1H), 3.71-3.63 (m, 1H), 3.22-3.06 (m, 2H), 2.75-2.65 (m, 1H), 2.14-1.97 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 163.9, 154.1, 136.3, 134.9, 130.2, 129.7, 129.2, 128.7, 124.3, 123.9, 123.6, 122.6, 120.9, 117.1, 95.4, 69.4, 69.0, 23.9, 23.3.

IR(KBr): 3077, 1649, 1456 cm^{-1}

3-((4-bromophenyl)(pyrrolidin-1-yl)methyl)-4-hydroxy-2H-chromen-2-one (1.4d):

Light yellow solid

M.P: 171-173 ^{o}C

LRMS (M+1): 400

Yield: 85%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 7.90, 1.27 Hz, 1H), 7.58 (d, *J* = 8.48 Hz, 2H), 7.49-7.44 (m, 3H), 7.23 (d, *J* = 8.60 Hz, 2H), 5.13 (s, 1H), 3.69-3.61 (m, 1H), 3.18-3.07 (m, 2H), 2.72-2.62 (m, 1H), 2.15-1.99 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 164.0, 153.9, 136.7, 132.8, 131.8,131.4, 130.4, 129.3, 123.8, 123.6, 123.0, 122.5, 120.9, 117.0, 95.2, 69.2, 68.8, 23.8, 23.2.

IR(KBr): 3076, 1648, 1456 cm^{-1}

4-hydroxy-3-((4-nitrophenyl)(pyrrolidin-1-yl)methyl)-2H-chromen-2-one (1.4e):

Light yellow solid

M.P: 170-172 ^{o}C

LRMS (M+1): 366.9

Yield: 82%

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.63 Hz, 2H), 7.97-7.93 (dd, *J* = 7.89, 1.56 Hz, 1H), 7.90 (d, *J* = 8.69 Hz, 2H), 7.5-7.46 (m, 1H), 7.23 (d, *J* = 3.60 Hz, 1H),

7.21 (d, *J* = 8.54 Hz, 1H), 5.30 (s, 1H), 3.27 (brs, 2H), 3.20-3.13 (m, 2H), 2.12-2.11 (m, 2H), 1.99 (brs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 163.9, 154.0, 147.9, 144.7, 132.4, 129.2, 128.7, 124.3, 124.1, 123.9, 122.9, 120.5, 117.1, 116.1, 95.2, 46.2, 45.3, 29.7, 24.4.

IR(KBr): 2966, 1652, 1456 cm^{-1}

4-hydroxy-3-((2-nitrophenyl)(pyrrolidin-1-yl)methyl)-2H-chromen-2-one (1.4f):

grey solid

M.P: 180-182 ^{o}C

LRMS (M+1): 366.9

Yield: 89%

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.12 (dd, *J* = 7.52, 1.23 Hz, 1H), 7.97 (dd, *J* = 7.76, 1.39 Hz, 1H), 7.86 (dd, *J* = 8.17, 1.26 Hz, 1H), 7.59-7.55 (m, 1H), 7.46 (t, *J* = 7.65 Hz, 2H), 7.21-7.15 (m, 2H), 5.91 (s, 1H), 3.75-3.67 (m, 1H), 3.25-3.14 (m, 3H), 2.29-1.99 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 163.6, 154.1, 149.3, 133.2, 132.5, 132.2, 130.0, 129.2, 124.1, 123.8, 122.6, 120.7, 117.1, 116.1, 95.7, 54.6, 50.8, 24.1, 23.6.

IR(KBr): 3073, 1666, 1534 cm^{-1}

5,5-dimethyl-2-(phenyl(pyrrolidin-1-yl)methyl)cyclohexane-1,3-dione

(1.6a):

Light yellow solid

M.P: 132-134 ^{o}C

LRMS (M+1): 300

Yield: 89%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 6.4 Hz, 2H), 7.32-7.28 (m, 3H), 5.07 (s, 1H), 3.53-3.44 (m, 1H), 2.96-2.90 (m, 2H), 2.57-2.47 (m, 1H), 2.25-2.17 (m, 4H), 2.05-1.87 (m, 4H), 0.99 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 162.7, 139.2, 129.2, 128.8, 128.2, 127.6, 110.0, 107.6, 69.6, 68.7 (2C), 49.2, 32.4 (2C), 28.6(2C), 23.8, 23.3.

IR(KBr): 2952, 1749, 1417 cm^{-1}

5,5-dimethyl-2-(pyrrolidin-1-yl(p-tolyl)methyl)cyclohexane-1,3-dione

(1.6b):

Yellow solid

M.P: 142-144 ^{o}C

LRMS (M+1): 313.9

Yield: 89%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.88 Hz, 2H), 7.09 (d, *J* = 7.52 Hz, 2H), 5.04 (s, 1H), 3.51-3.43 (m, 1H), 2.98-2.87 (m, 2H), 2.58-2.49 (m, 1H), 2.30 (s, 3H), 2.24-2.16 (m, 4H), 2.06-1.84 (m, 4H), 0.99 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 164.3, 138.0, 136.2, 130.2, 129.9, 128.9, 127.6, 107.6, 69.5, 68.5 (2C), 49.3, 32.4 (2C), 28.7 (2C), 28.6, 23.8, 23.4.

IR(KBr): 2953, 1722, 1417 cm^{-1}

2-((4-chlorophenyl)(pyrrolidin-1-yl)methyl)-5,5-dimethylcyclohexane-1,3-dione (1.6c):

Yellowish white solid

M.P: 128-130 ^{o}C

LRMS (M+1): 333.9

Yield: 90%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.45 Hz, 2H), 7.27 (d, *J* = 7.25 Hz, 2H), 5.01 (s, 1H), 3.50-3.42 (m, 1H), 2.96-2.85 (m, 2H), 2.51-2.43 (m, 1H), 2.25-2.16 (m, 4H), 2.07-1.89 (m, 4H), 0.99 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 159.4, 137.9, 134.0, 129.4, 129.0, 128.4, 110.0, 107.7, 68.7, 67.8 (2C), 49.0, 32.4 (2C), 28.5(2C), 23.8, 23.3.

IR(KBr): 3061, 1708, 1410 cm^{-1}

2-((4-bromophenyl)(pyrrolidin-1-yl)methyl)-5,5-dimethylcyclohexane-1,3-dione (1.6d):

Yellowish white solid

M.P: 131-133 ^{o}C

LRMS (M+1): 377.8

Yield: 85%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.4 (m, 4H), 4.99 (s, 1H), 3.49-3.40 (m, 1H), 2.96-2.84 (m, 2H), 2.50-2.42 (m, 1H), 2.24-2.14 (m, 4H), 2.05-1.85 (m, 4H), 0.98 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 155.1, 138.3, 131.3, 131.0, 130.4, 129.1, 122.1, 107.6, 68.7, 67.7 (2C), 49.0, 32.3 (2C), 28.6 (2C), 28.4, 23.5.

IR(KBr): 2952, 1705, 1514 cm^{-1}

5,5-dimethyl-2-((4-nitrophenyl)(pyrrolidin-1-yl)methyl)cyclohexane-1,3-dione (1.6e):

Yellow solid

M.P: 160-162 ^oC

LRMS (M+1): 345

Yield: 85%

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.59 Hz, 2H), 7.74 (d, *J* = 8.65 Hz, 2H), 5.13 (s, 1H), 3.53-3.43 (m, 1H), 3.08-2.96 (m, 1H), 2.92-2.81 (m, 1H), 2.49-2.36 (m, 1H), 2.25-2.16 (m, 4H), 2.06-1.96 (m, 4H), 0.97 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 159.2, 147.4, 146.4, 129.1, 128.1, 124.1, 123.8, 107.9, 68.1, 67.3, 67.0 (2C), 32.4 (2C), 28.5 (2C), 23.9, 23.4.

IR(KBr): 2951, 1590, 1418 cm^{-1}

5,5-dimethyl-2-((2-nitrophenyl)(pyrrolidin-1-yl)methyl)cyclohexane-1,3-dione (1.6f):

Yellow solid

M.P: 122-124 ^oC

LRMS (M+1): 344.9

Yield: 89%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.93 (d, *J* = 7.52 Hz, 1H), 7.74 (d, *J* = 8.10 Hz, 1H), 7.56-7.52 (m, 1H), 7.42-7.36 (m, 1H), 5.67 (s, 1H), 3.56-3.47 (m, 1H), 3.04-2.93 (m, 3H), 2.24-1.89 (m, 8H), 1.06-0.86 (brs, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 158.0, 149.5, 133.9, 132.5, 129.6, 124.4, 110.0, 107.9, 62.7, 62.1 (2C), 44.1, 32.4 (2C), 28.5 (2C), 23.7, 23.6.

IR(KBr): 3067, 1720, 1444 cm^{-1}

General procedure for the synthesis of compound 1.8. In a typical experiment, a solution of aldehyde (1 mmol), 4-hydroxy coumarin (1 mmol) and $InCl_3$ (0.1 mmol) in anhydrous toluene (1 mL), Indole (1 mmol) was added and the reaction mixture was refluxed for 3h. After the starting materials disappeared (by TLC) the reaction mixture was quenched by water extracted with dichloromethane, dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure furnished the crude residue which was purified by column chromatography (eluent ethyl acetate/hexanes, 1:4) to afford the desired product in 70-80% yield.

3-((1H-indol-3-yl)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one

(1.8a):

Brickred solid

M.P: 110-112 °C

LRMS (M+1): 367.9

Yield: 75%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (brs, 1H), 7.41-7.33 (m, 6H), 7.29 (d, *J* = 7.16 Hz, 1H), 7.23-7.14 (m, 3H), 6.99 (dd, *J* = 11.06, 3.97 Hz, 2H), 6.66 (d, *J* = 1.40 Hz, 2H), 5.89 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 167.8, 144.0, 136.6, 132.4, 128.9, 128.4, 128.4, 127.9, 127.0, 126.3, 125.9, 123.7, 123.5, 122.0, 121.6, 120.1, 119.6, 119.3, 119.0, 111.2, 110.8, 68.2, 40.0.

IR(KBr): 3413, 1721, 1454 cm^{-1}

3-((4-chlorophenyl)(1H-indol-3-yl)methyl)-4-hydroxy-2H-chromen-2-one (1.8b):

Brickred solid

M.P: 89-91 ^{o}C

LRMS (M-1): 399.9

Yield: 79%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (brs, 2H), 7.36 (dd, *J* = 7.22, 6.10 Hz, 4H), 7.30-7.23 (m, 3H), 7.19 (t, *J* = 7.60 Hz, 2H), 7.02 (t, *J* = 7.56 Hz, 2H), 6.63 (d, *J* = 1.54 Hz, 2H), 5.86 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 167.8, 142.5, 136.6, 131.7, 130.3, 129.7, 128.6, 128.0, 126.8, 123.7, 123.4, 122.8, 122.3, 121.8, 120.0, 119.5,119.5, 119.5, 119.1, 111.4, 111.4, 110.8, 39.5.

IR(KBr): 3412, 1721, 1455 cm^{-1}

3-((1H-indol-3-yl)(4-nitrophenyl)methyl)-4-hydroxy-2H-chromen-2-one (1.8c):

Yellow solid

M.P: 229-231 ^{o}C

LRMS (M+Na): 435.7

Yield: 75%

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (d, *J* = 8.64 Hz, 2H), 7.61 (d, *J* = 8.58 Hz, 2H), 7.37 (d, *J* = 8.12 Hz, 2H), 7.29 (d, *J* = 7.91 Hz, 2H), 7.05 (t, *J* = 7.49 Hz, 2H), 6.91-6.85 (m, 4H), 6.03 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 183.9, 153.6, 146.2, 137.0, 130.4, 129.3, 126.8, 125.0, 124.3, 123.9, 123.7, 123.5,122.2, 121.9, 119.8,119.6, 118.9, 118.2, 117.1, 112.5, 111.6, 110.0, 97.0, 55.4.

IR(KBr): 3388, 1737, 1413 cm^{-1}

5.6. References

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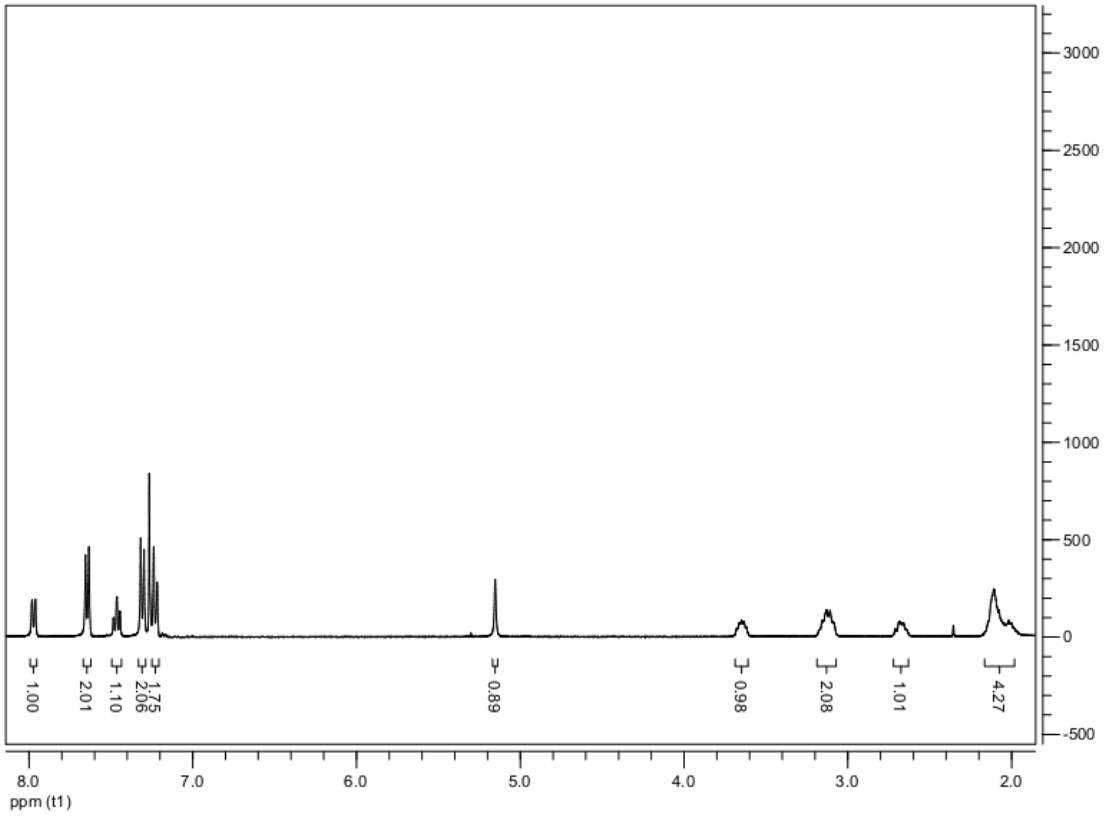
5.7. Spectral Data

^{1}H NMR (400MHz, $CDCl_3$)



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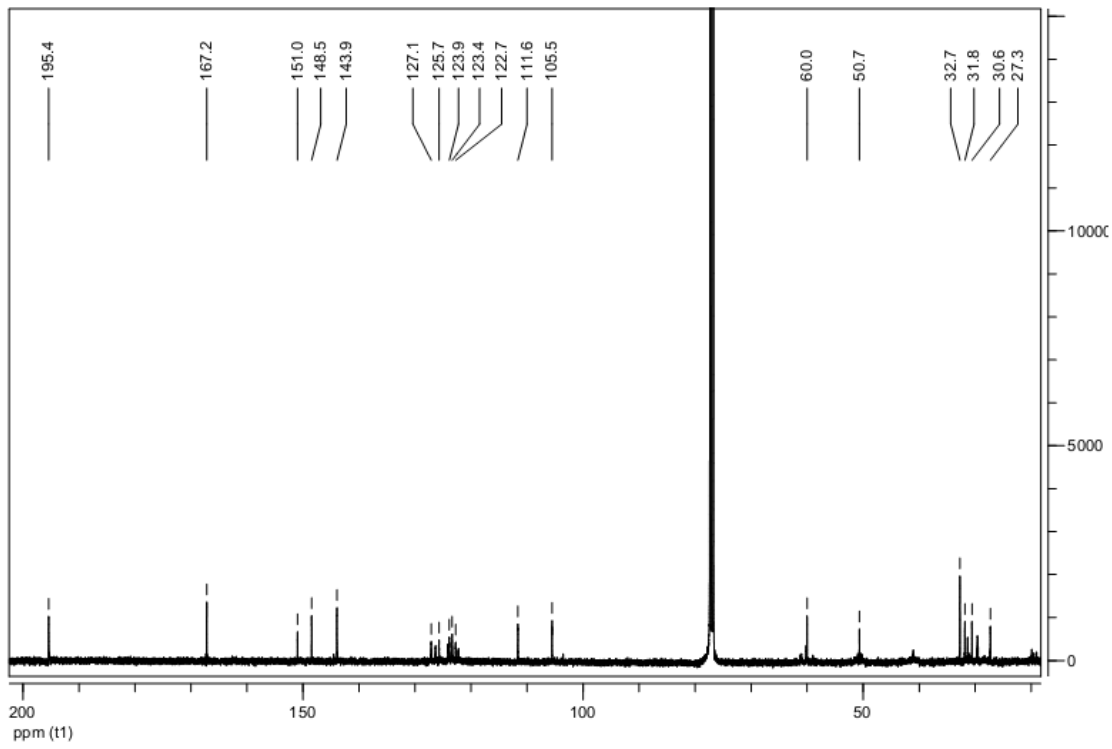

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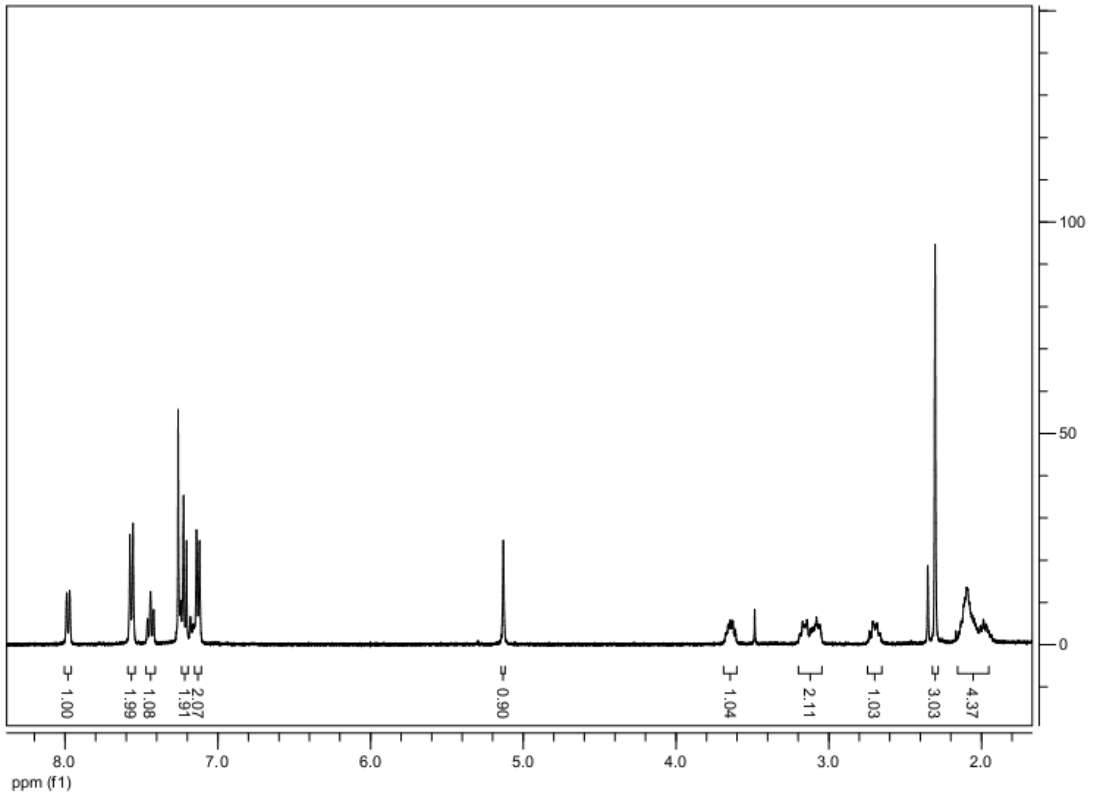

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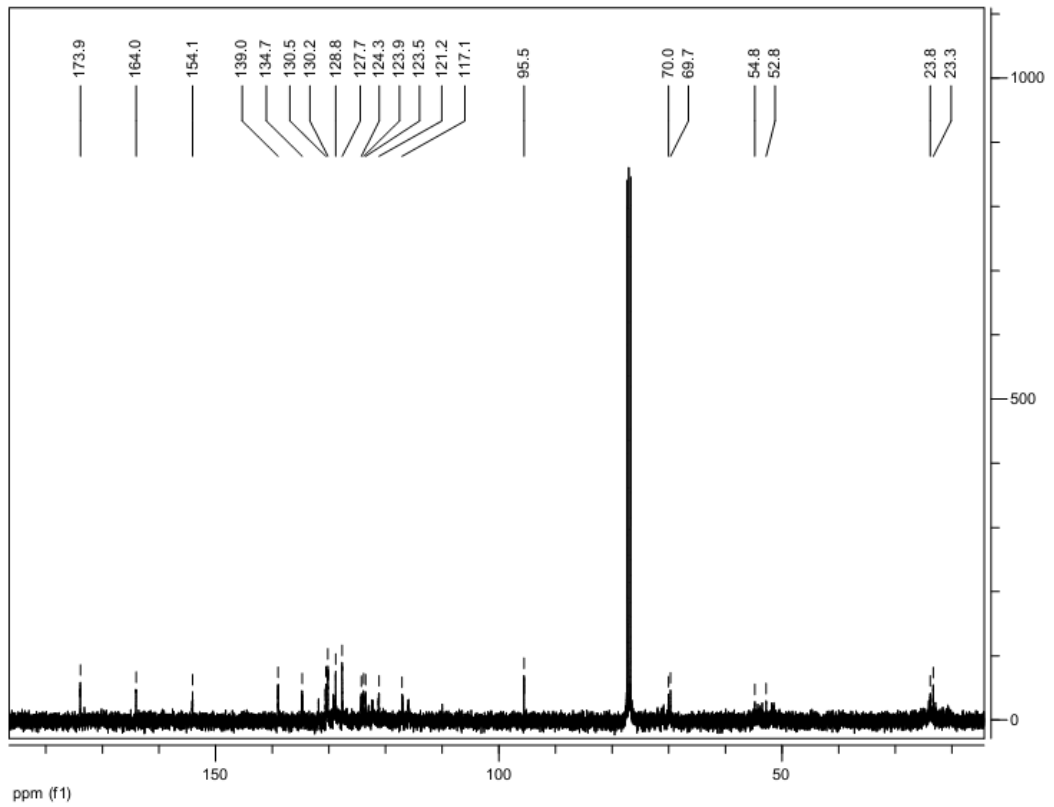

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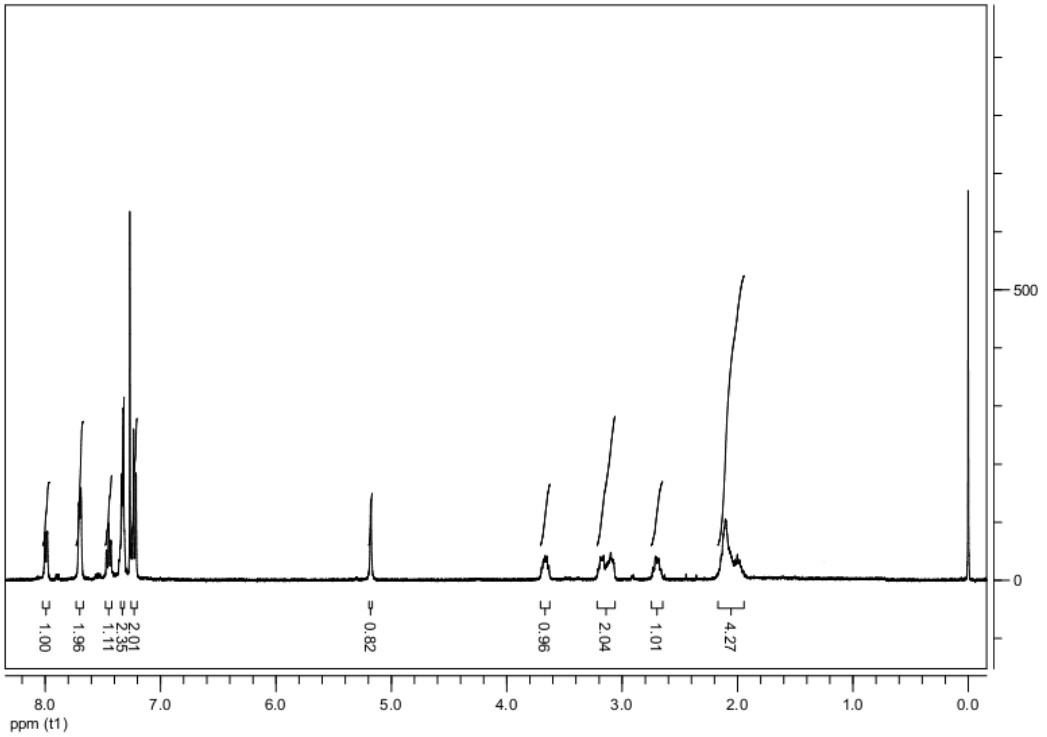

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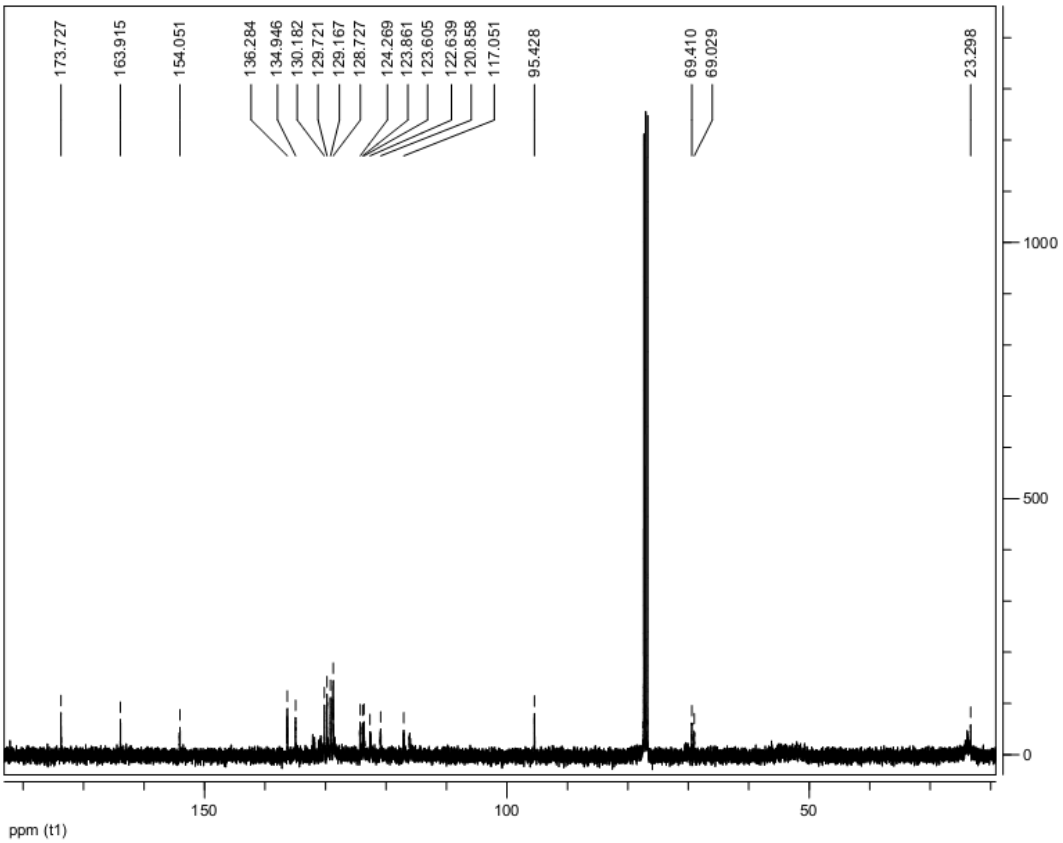

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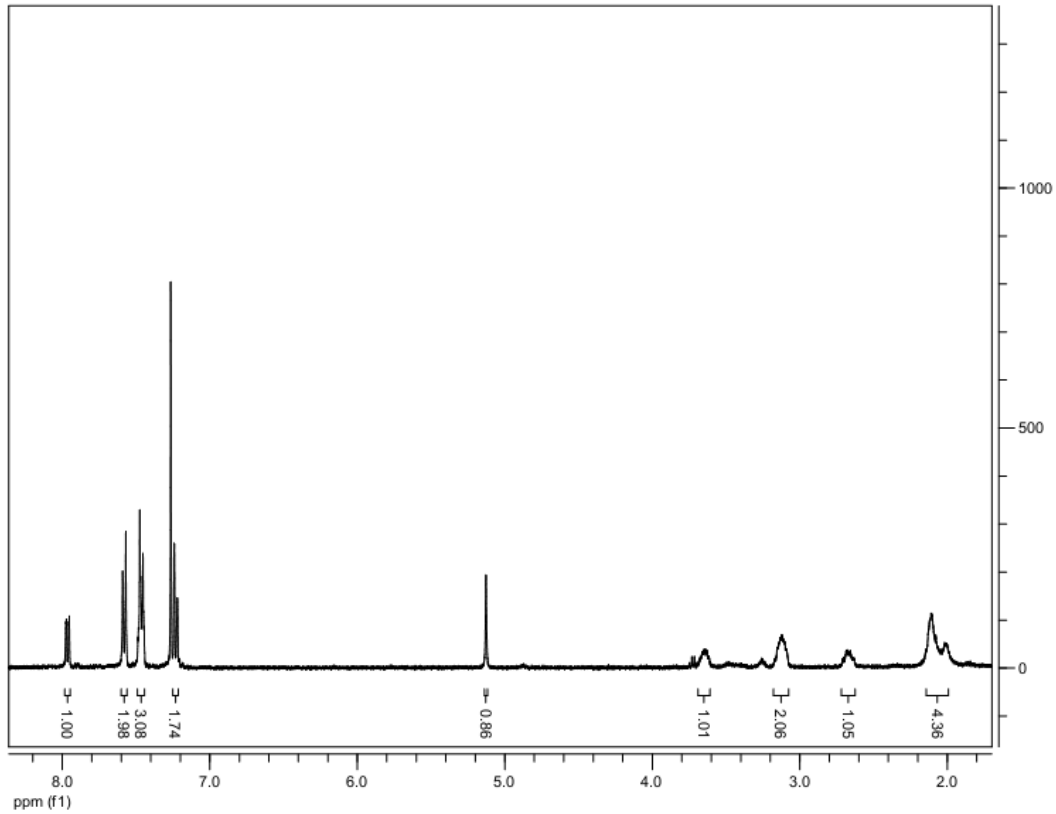

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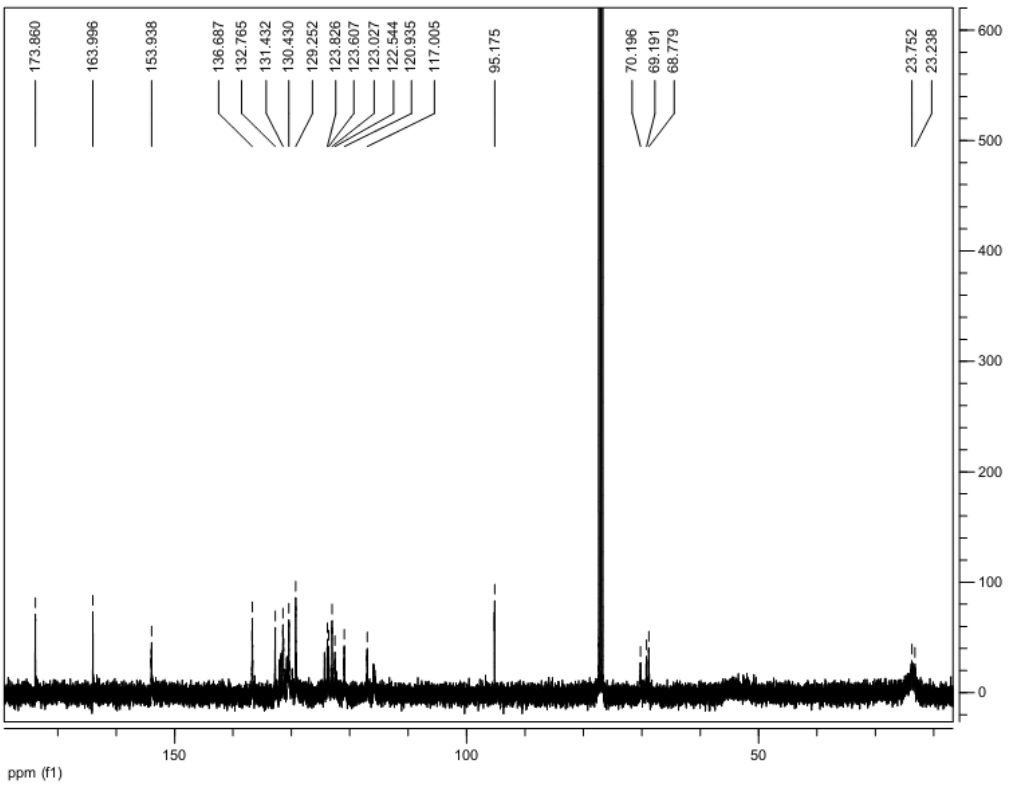

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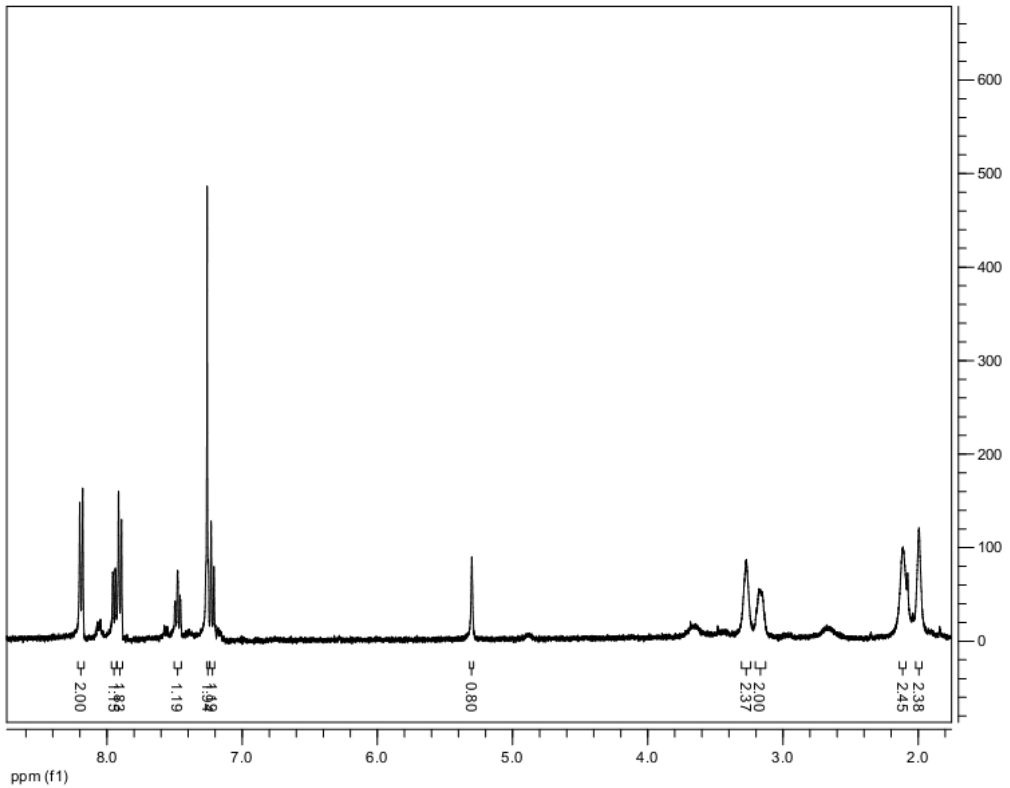

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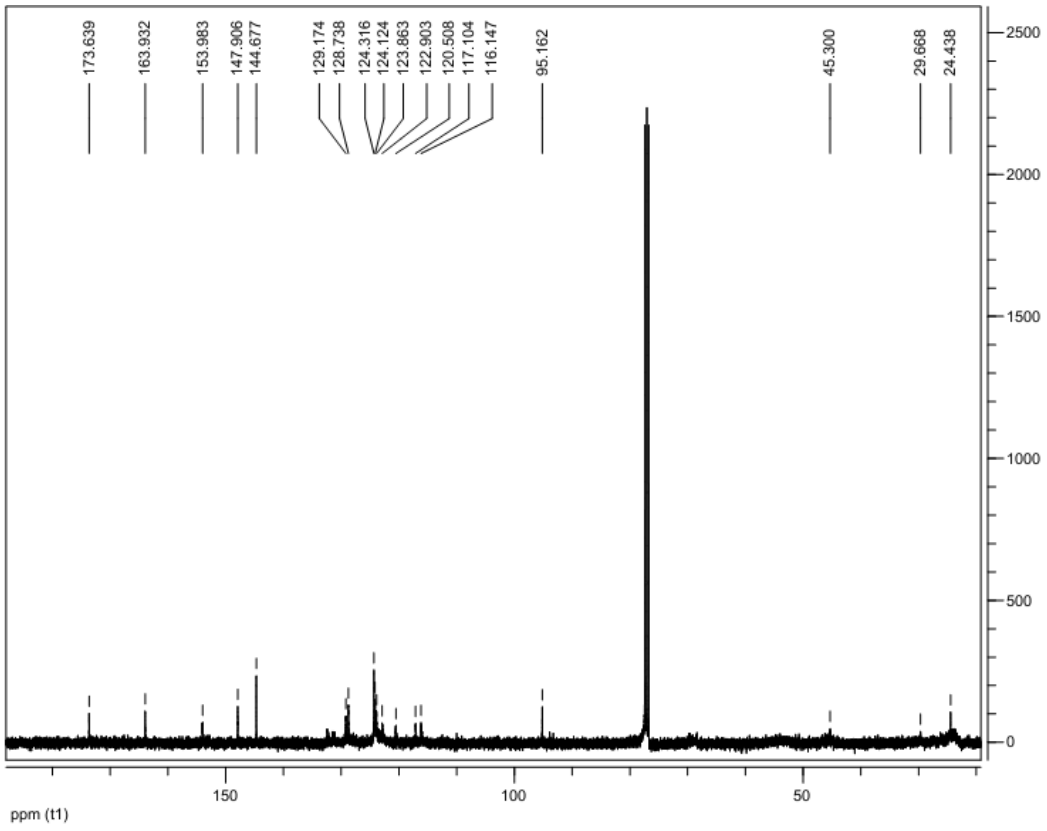

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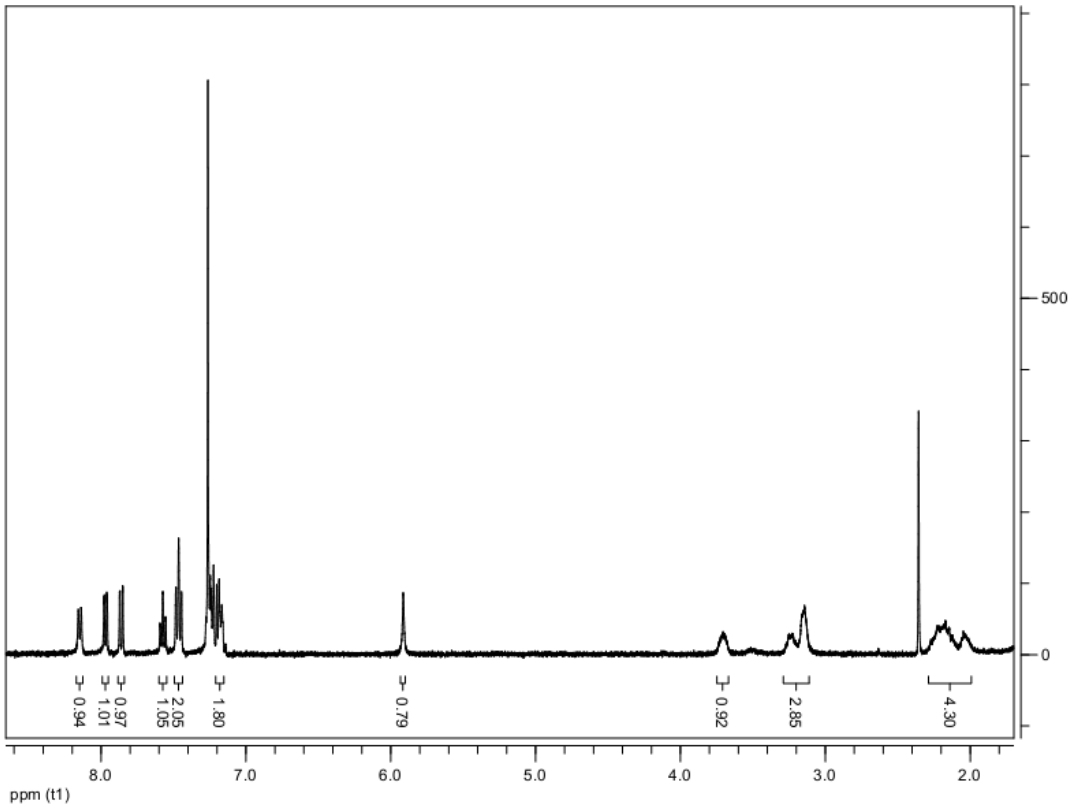

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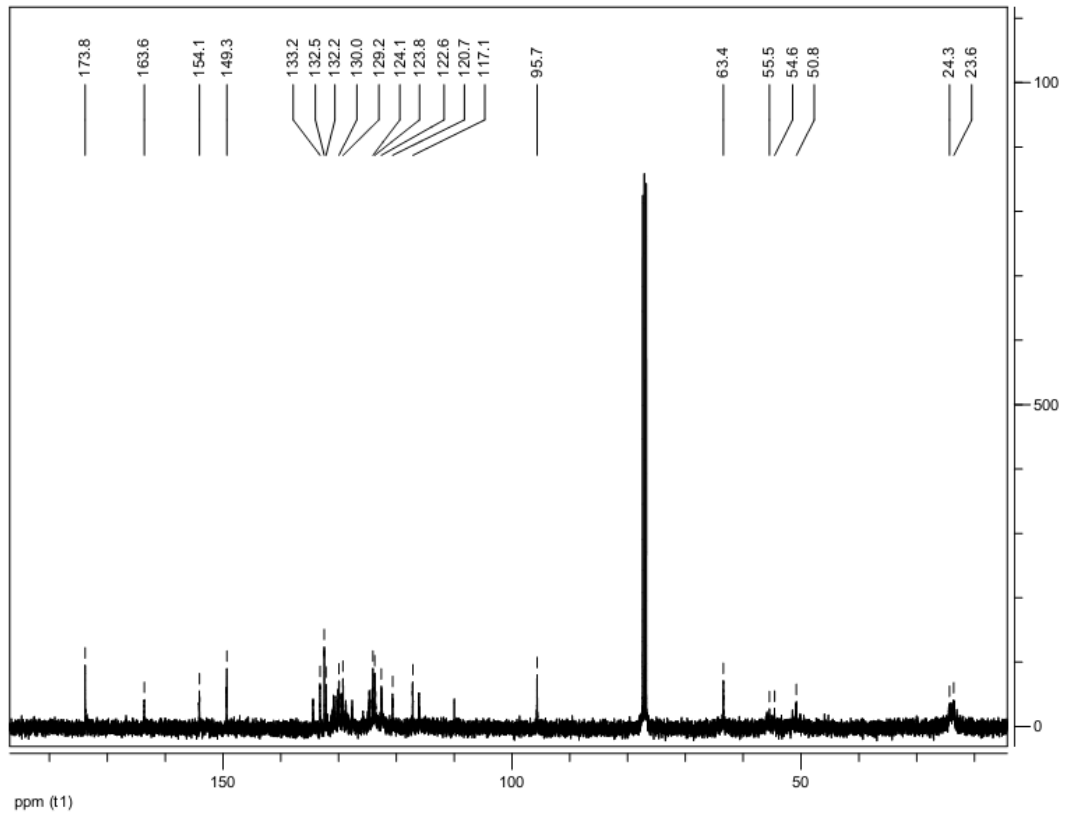

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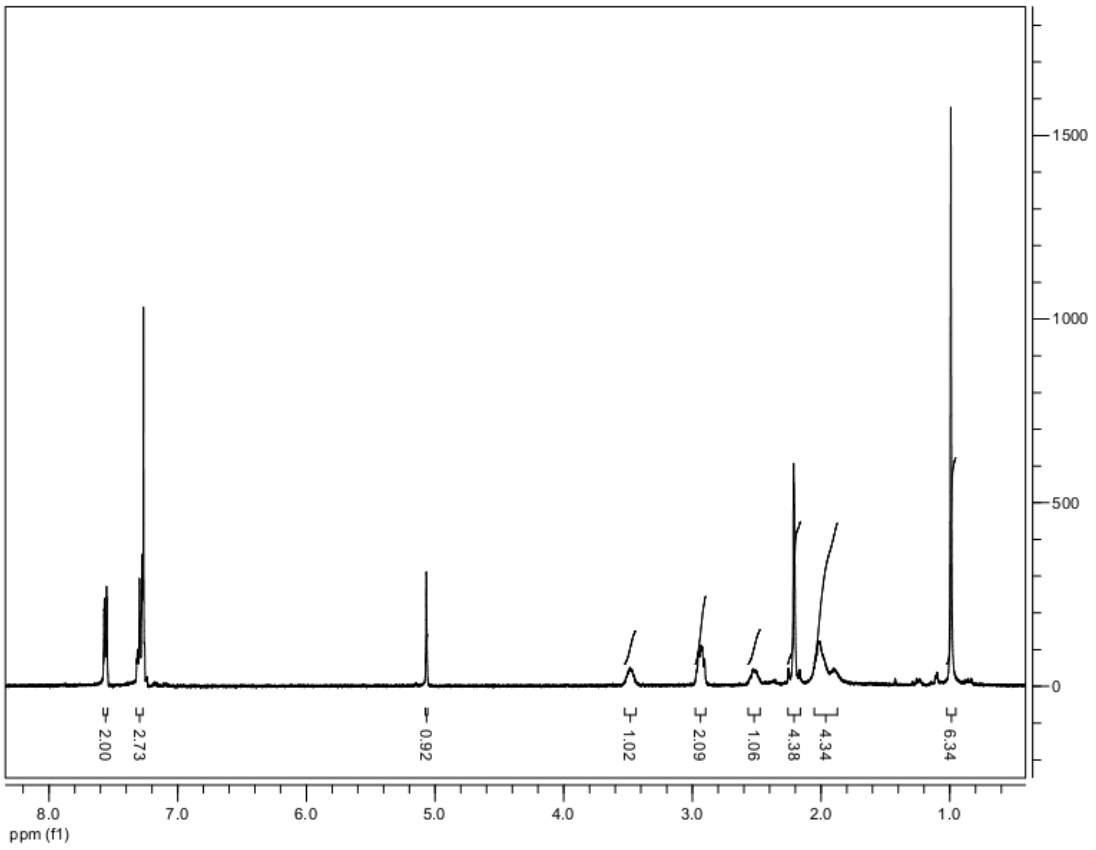

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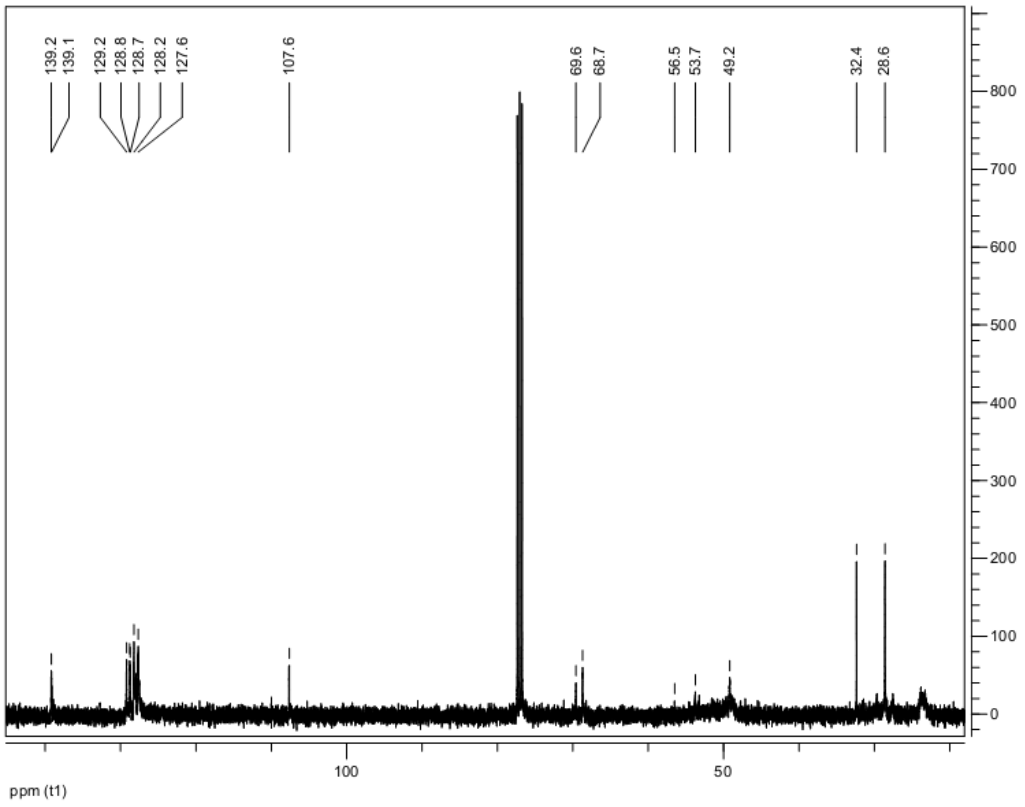

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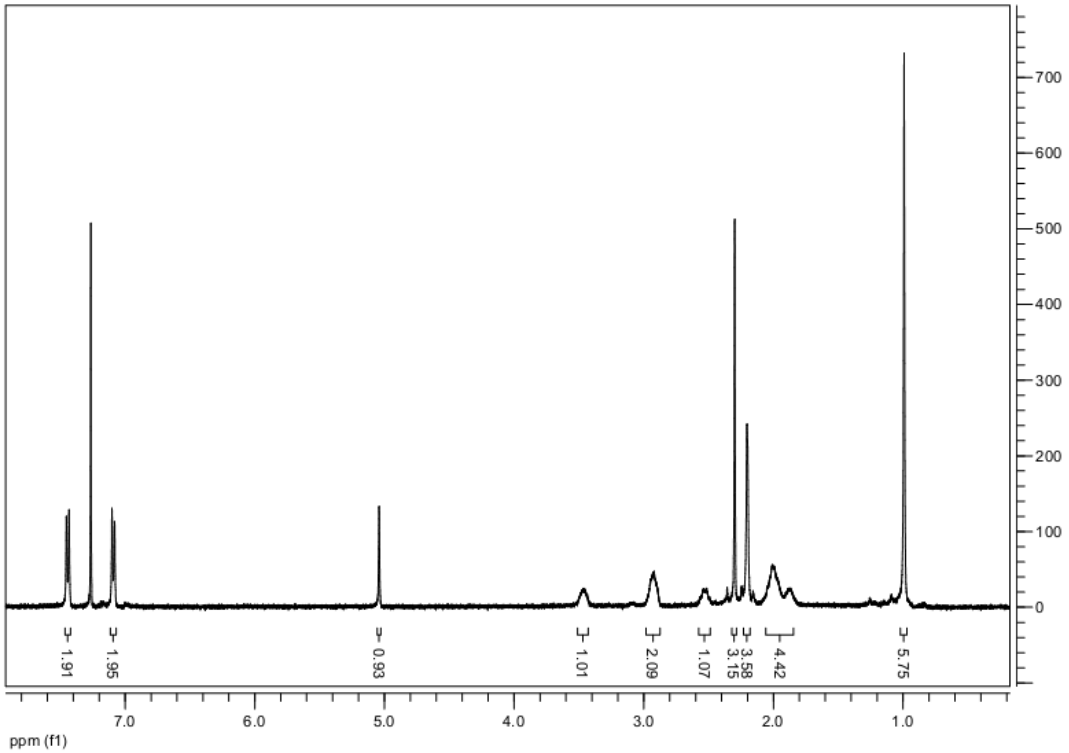

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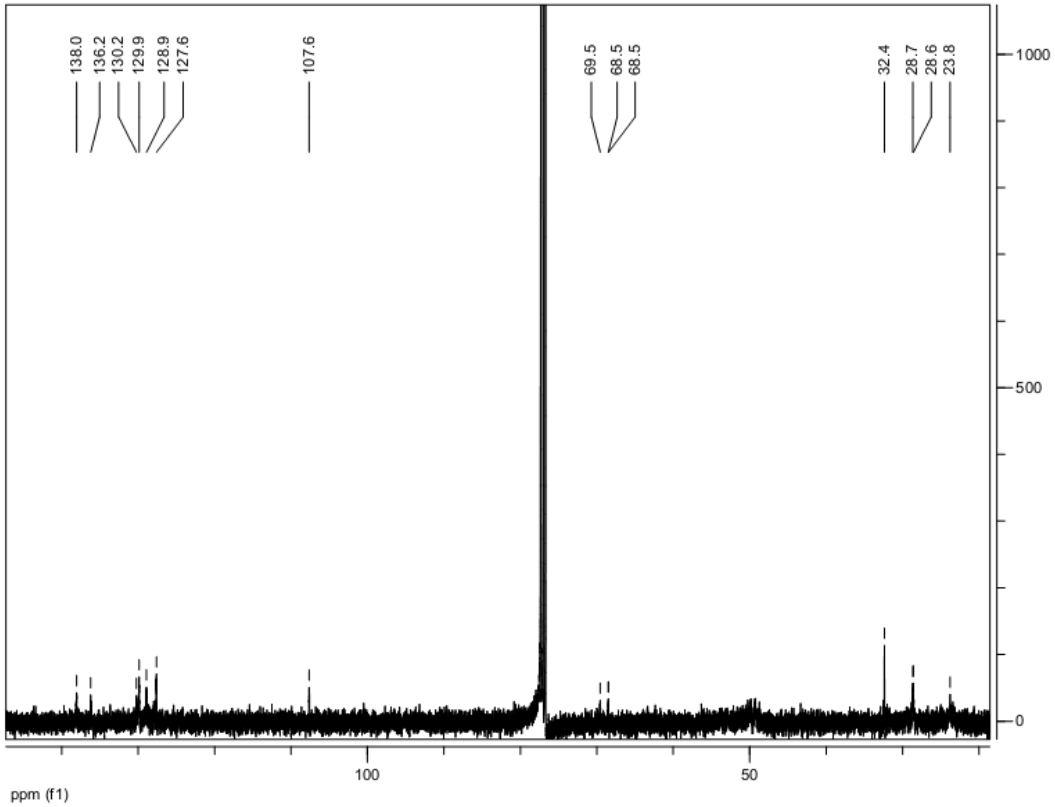

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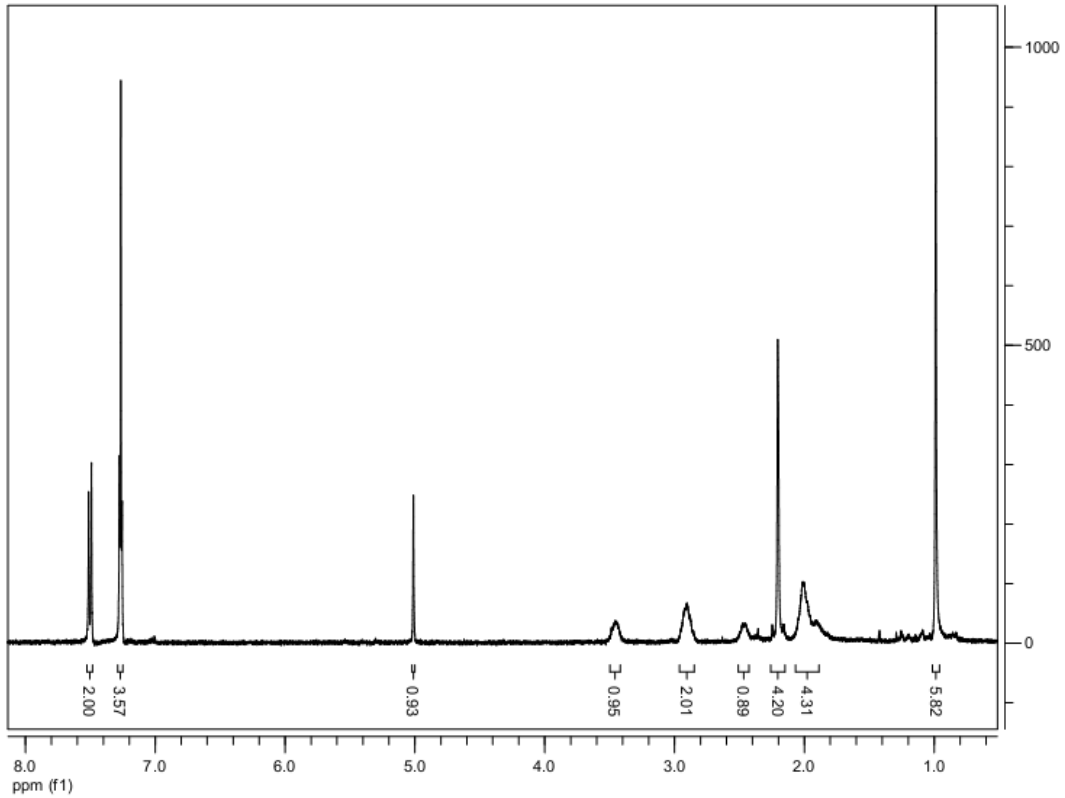

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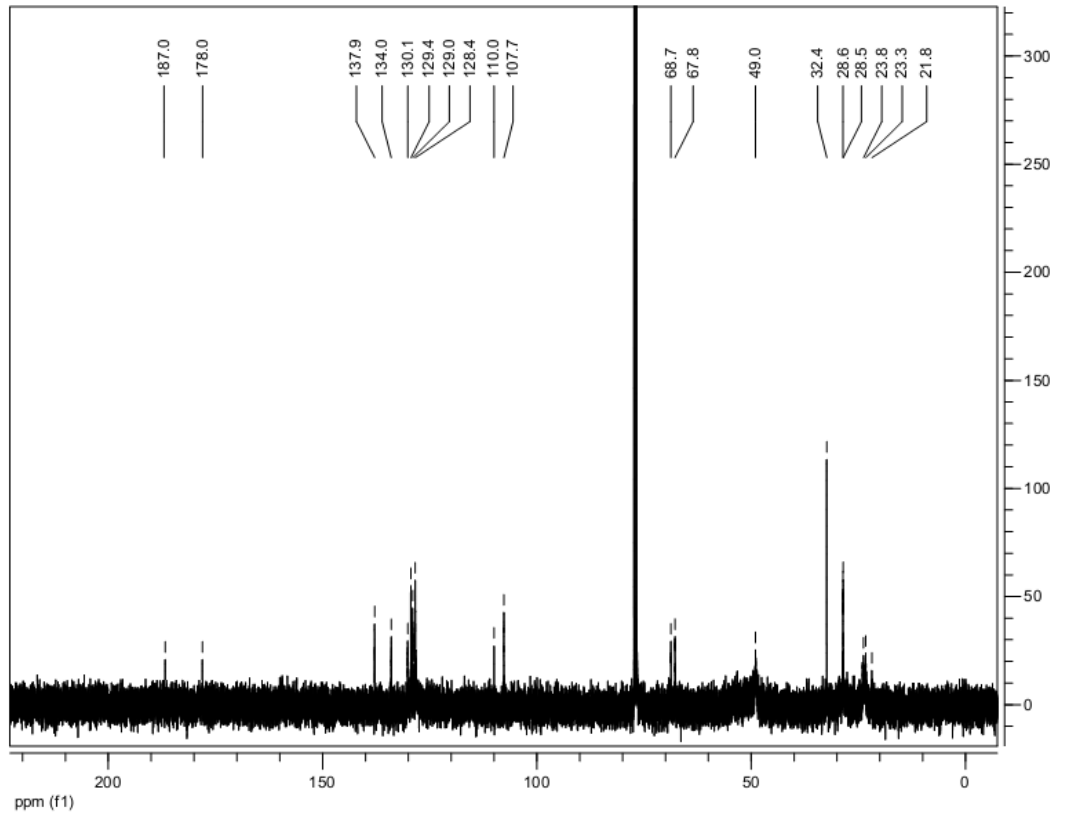

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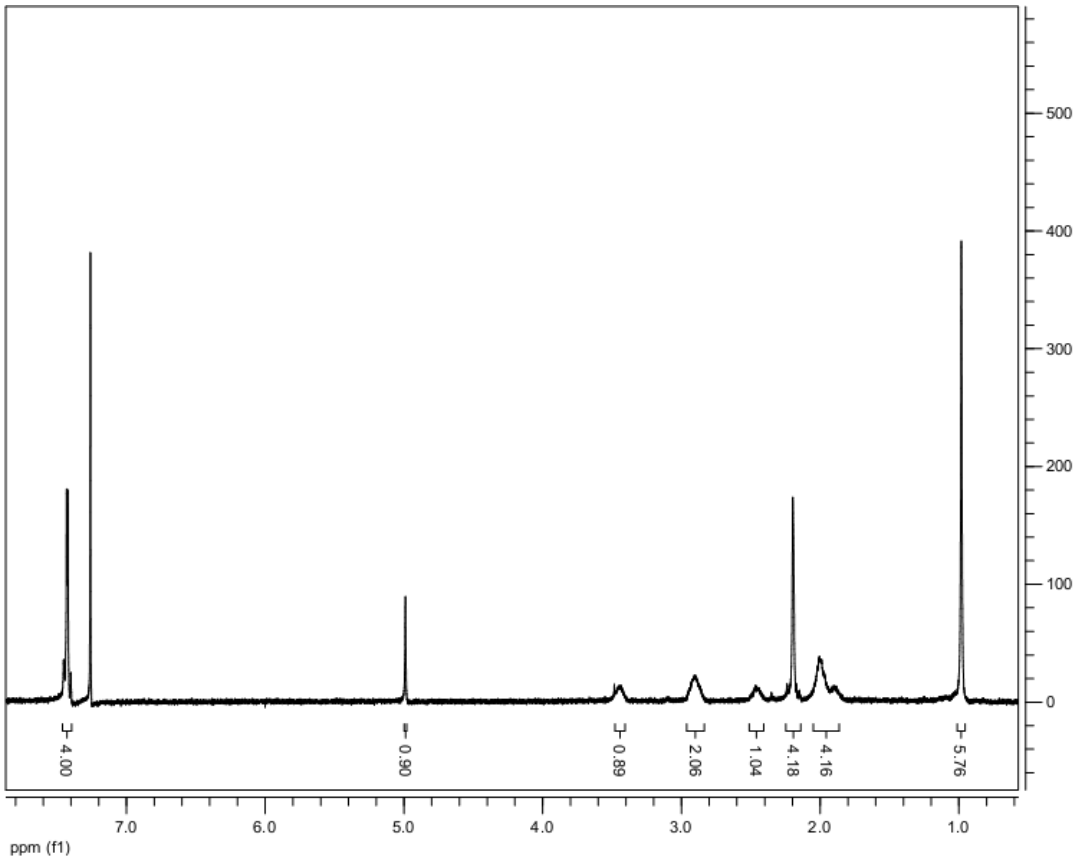

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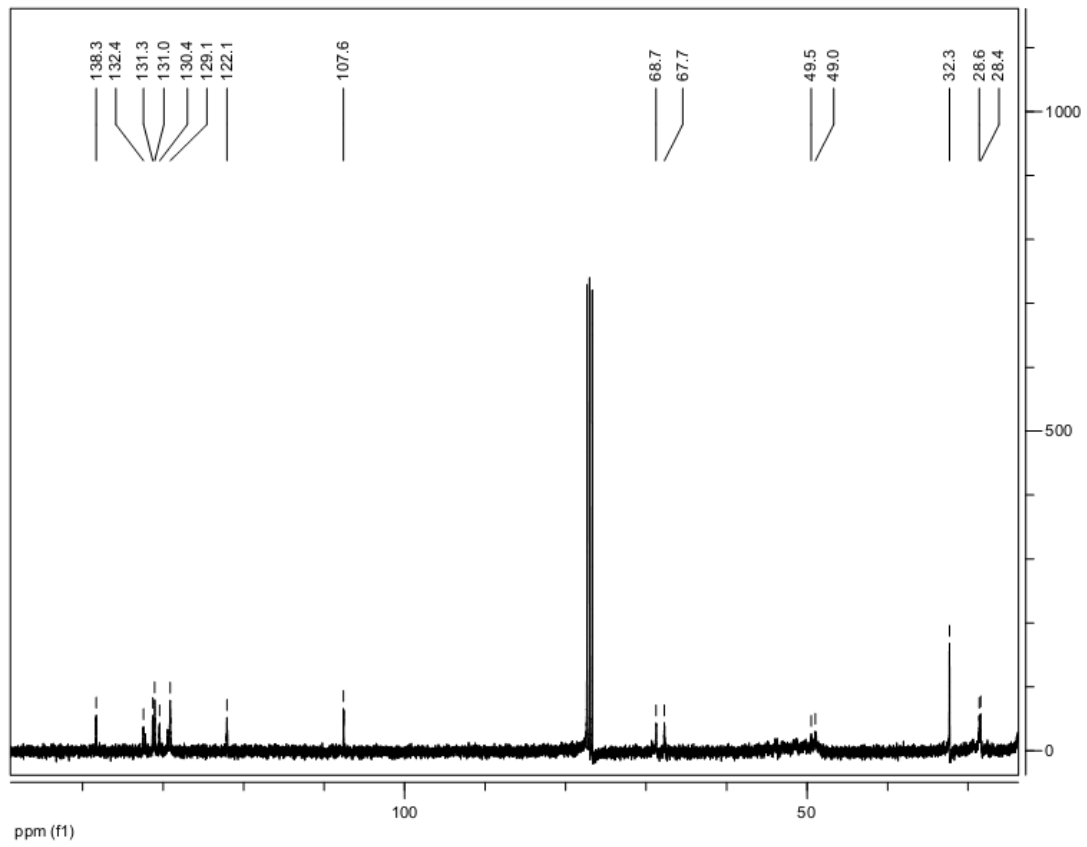

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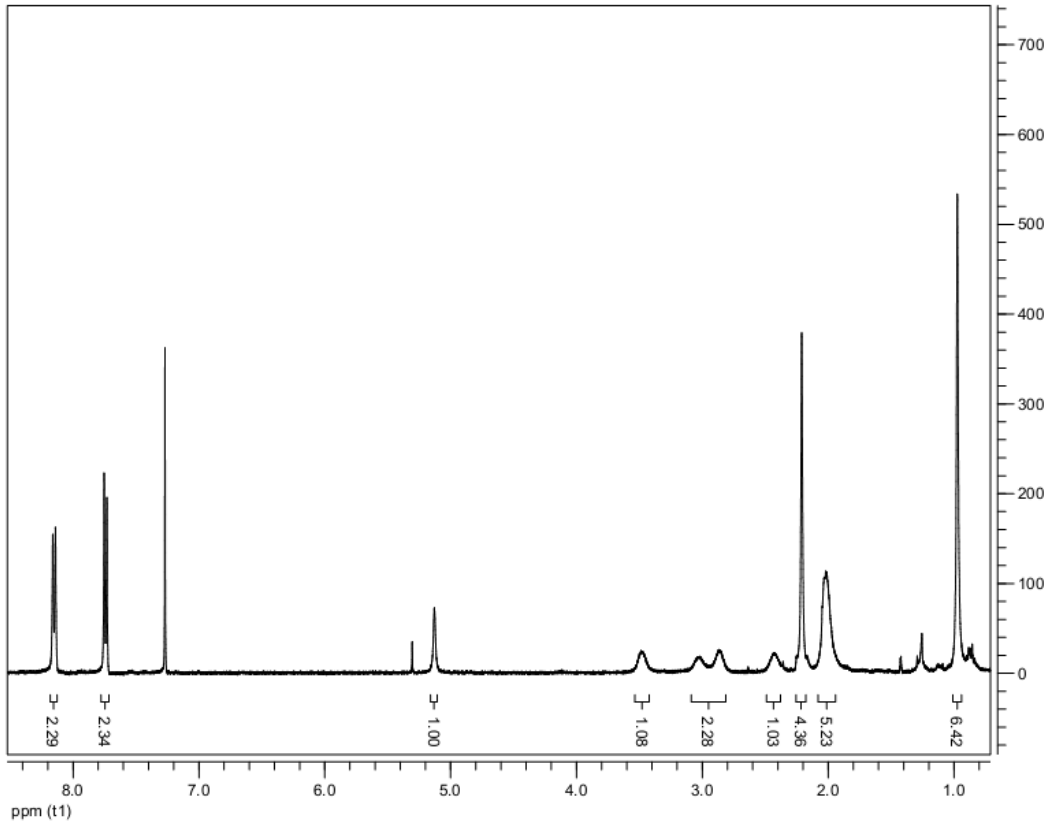

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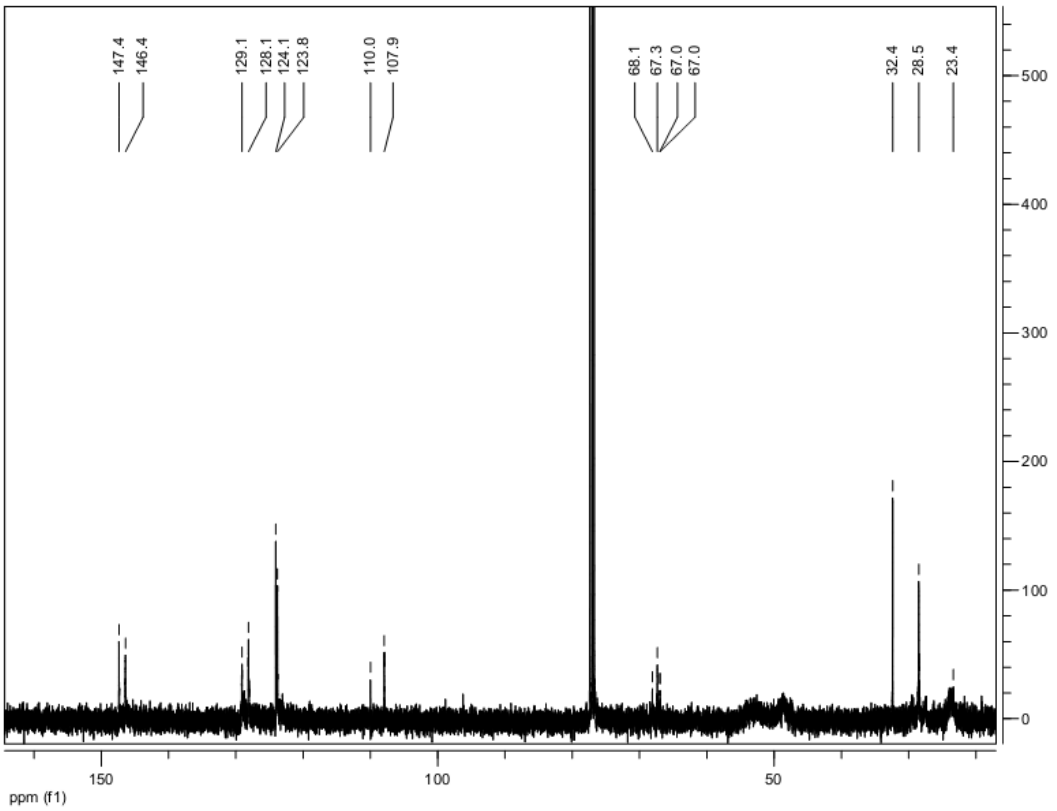

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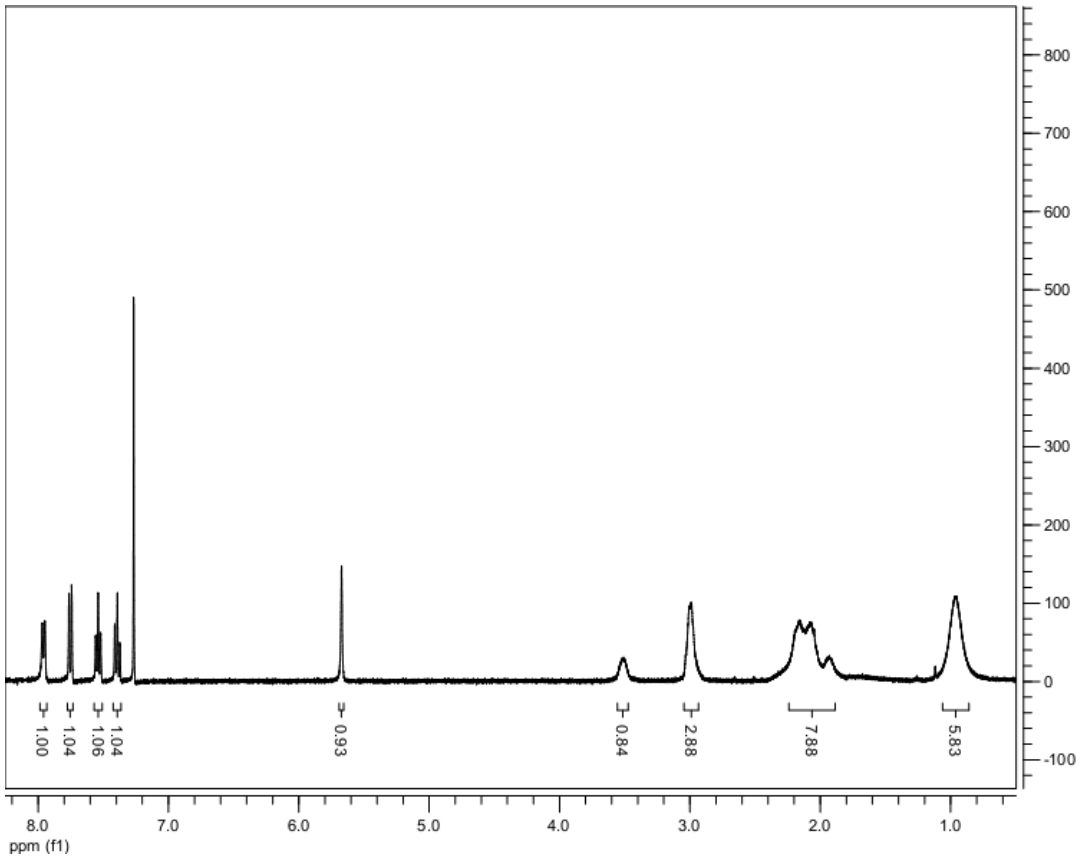

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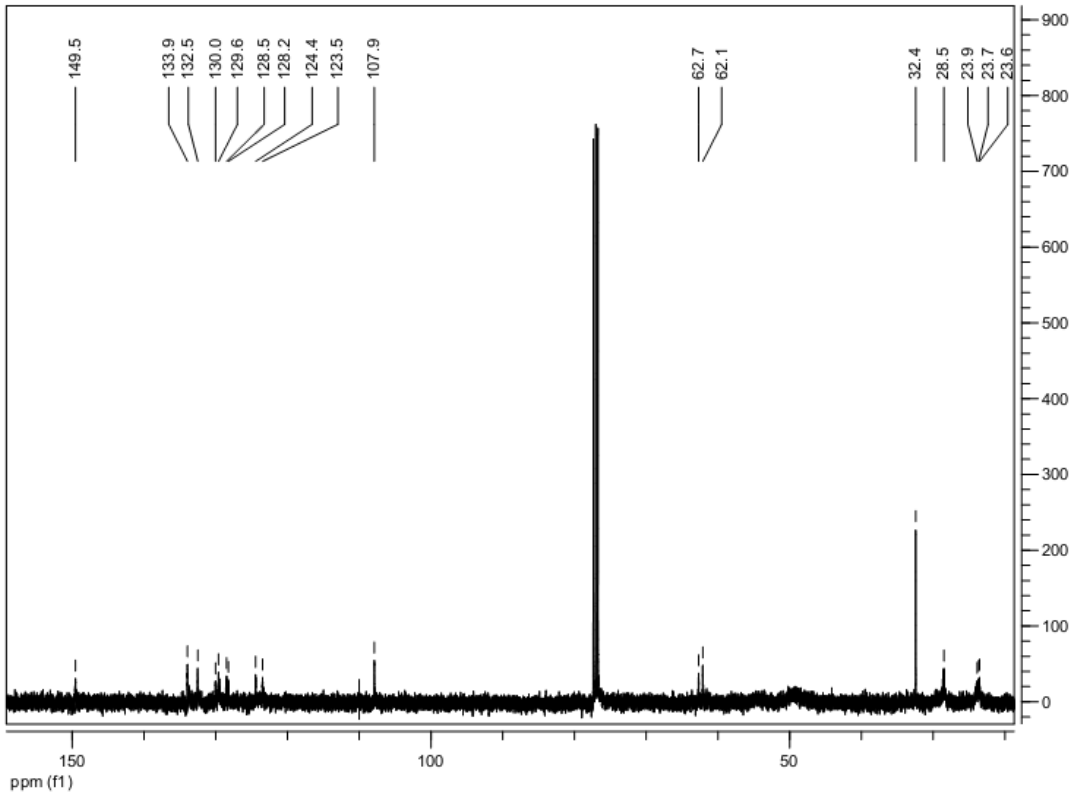

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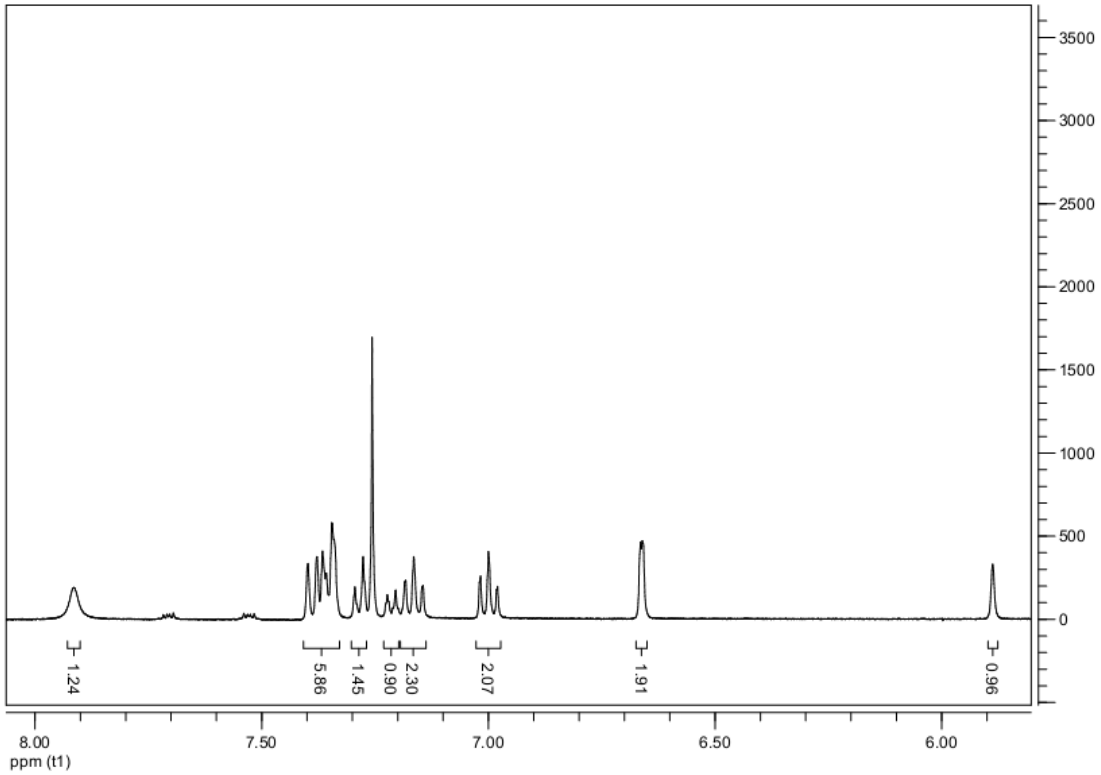

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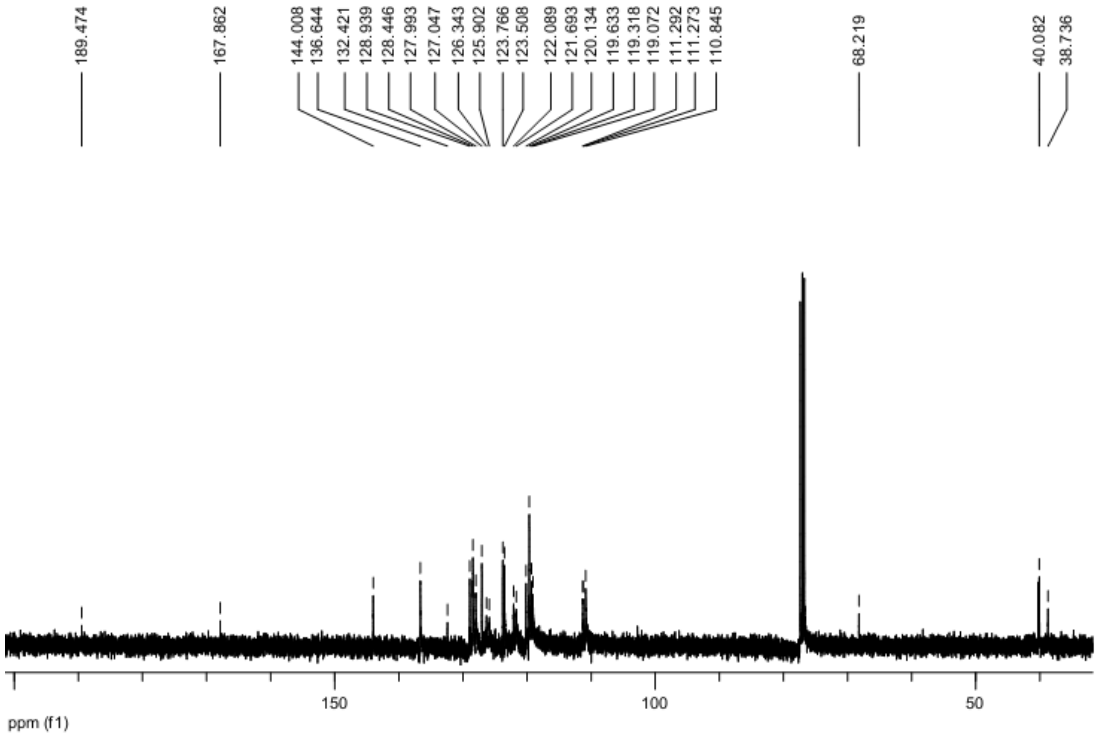

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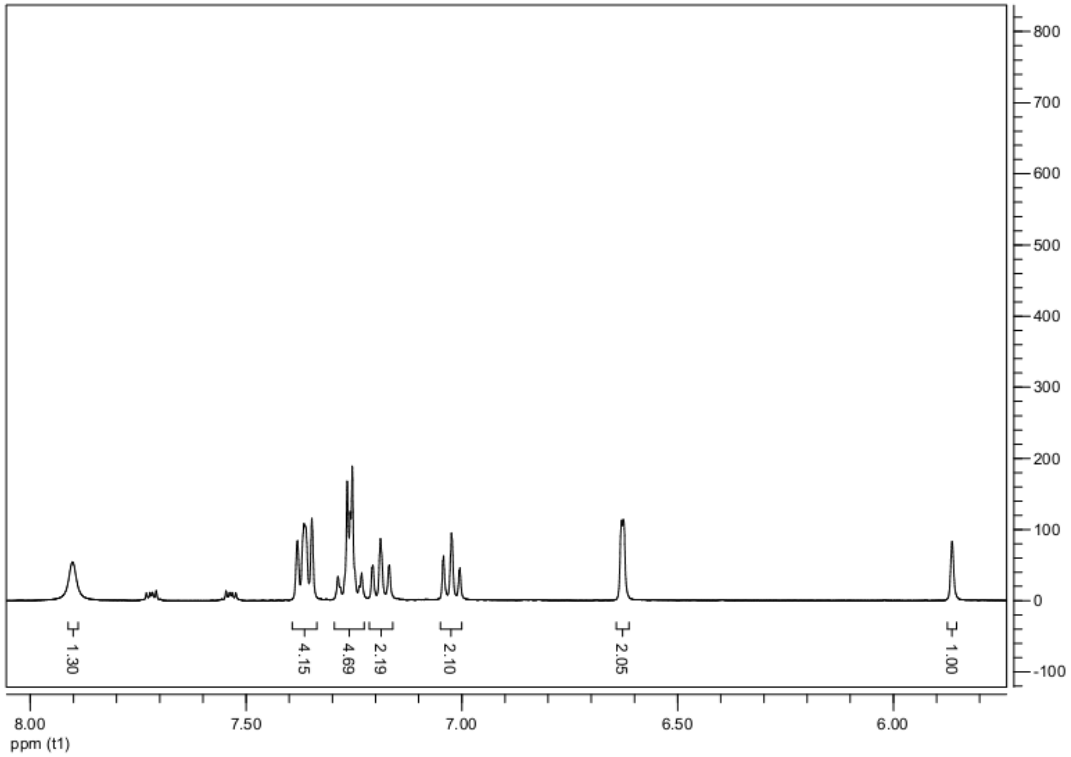

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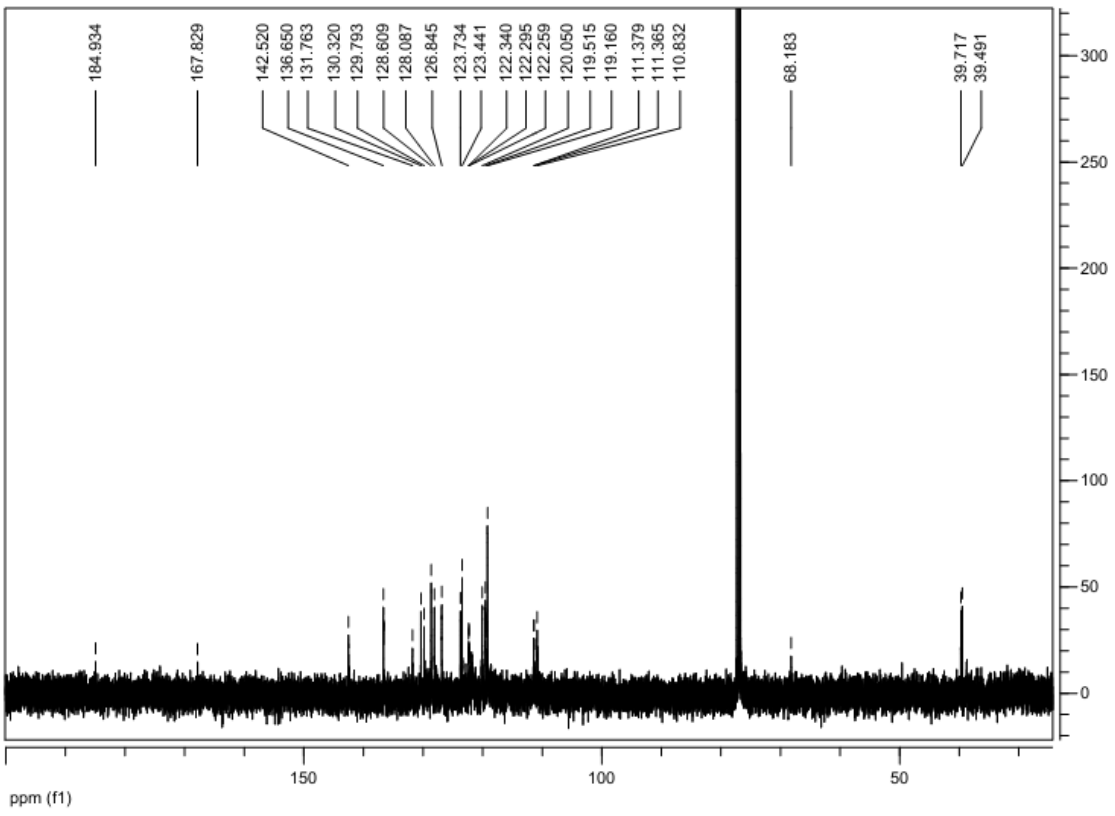

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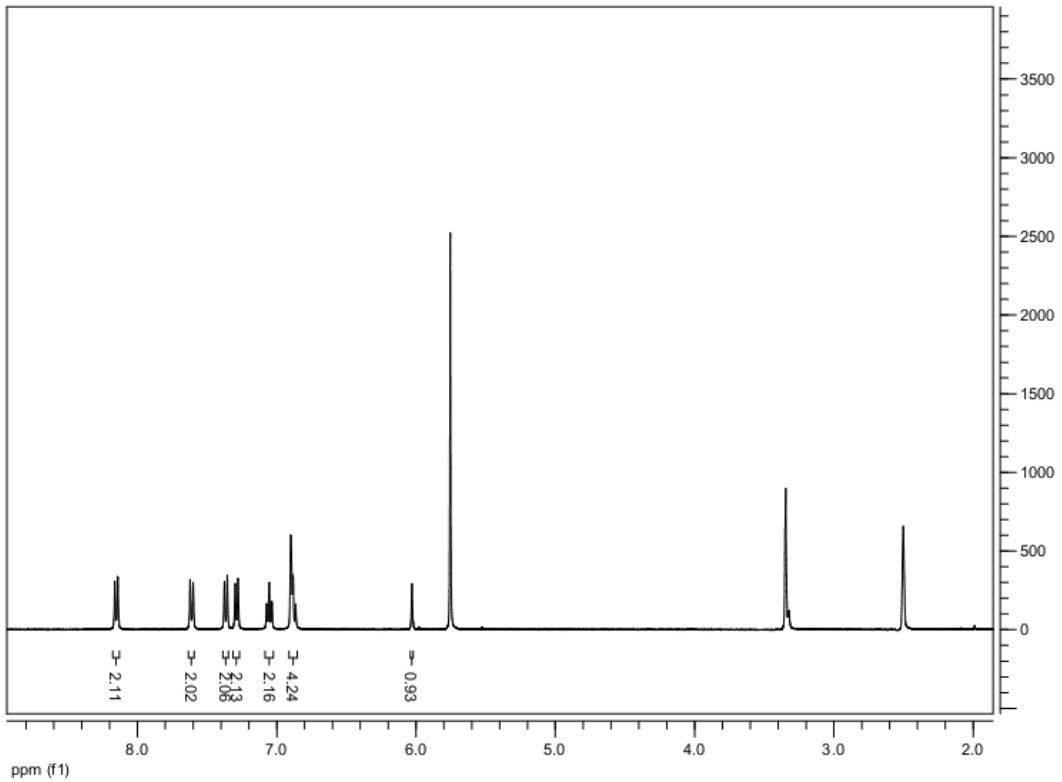

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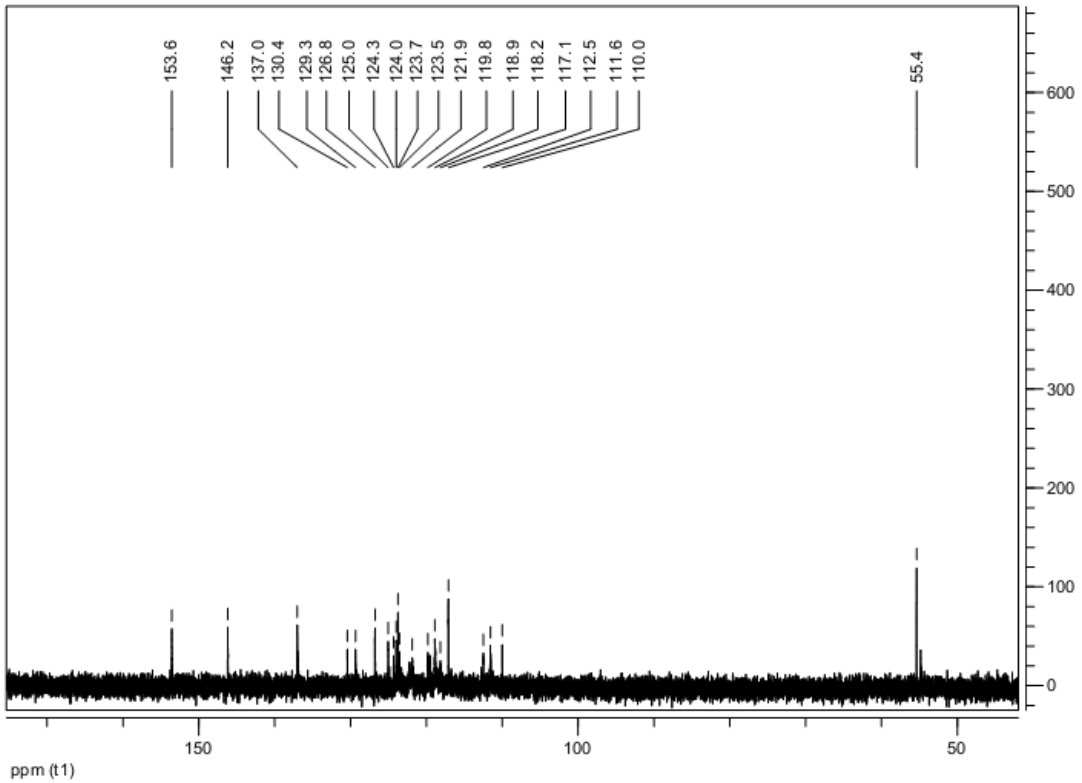

Saidulu Konda Peer Reviewed Publications:

1. $InCl_3$ catalyzed three component synthesis of α-benzylamino coumarins and diketones, *Tetrahedron. Lett*., **2012**, *53*, 5314–5317.

2. Click Chemistry route to tricyclic monosaccharide triazole hybrids: Design and Synthesis of Substituted Hexahydro-4H-pyrano [2,3-f] [1,2,3] triazolo[5,1-c][1,4] oxazepines, *RSC Adv*. **2014**, *4*, 63962-63965.

3. Scalable Stereoselective Synthesis of C27-C35 Eribulin Fragment for Building A Macrocyclic Diversity, **2015**, *submitted for publication.*

4. A Modular Approch to Building 17- and 18-Membered Macrocyclic Diversity from Eribulin C14-C21 Fragment, **2015**, *submitted for publication.*

5. Synthesis of C1-C10 Eribulin Fragment its Anologues for Building A Diverse Set of Macrocycles, **2015**, *submitted for publication.*

6. Review on Chemistry and Biology of Actin Modulators, **2015**, in progress.

Seminars/Conferences Attended:

2015 Presented a poster at DRILS, University of Hyderabad Campus, Young Scholar's Science Café Meet 2015.

2014 Presented a poster at X-JNOST 2014 international conference held in IIT Madras, India.

2013 Presented a poster at DRILS, University of Hyderabad Campus, India.

2009 Participated in one day seminar held on 3rd February, at MNR P.G College, Hyderabad on "New Perspectives in The Frontier of Drug Discovery".