Total Synthesis of Proposed Structures of Potent Anti-Inflammatory Agents Solomonamides and Analogs

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

By

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Under the guidance of
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Dedicated

To My Mother

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Total Synthesis of Proposed Structures of Potent Anti-Inflammatory Agents Solomonamides and Analogs"** submitted by **Mr. Kashinath K** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, "**Total Synthesis of Proposed Structures of Potent Anti-Inflammatory Agents Solomonamides and Analogs**" submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. D. Srinivasa Reddy**, Senior Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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Kashinath

List of Abbreviations

AcOH	acetic acid
AcCl	acetyl chloride
Ac_2O	acetic anhydride
Å	angstrom
Ar	aryl
MeCN	acetonitrile
Bn	benzyl
Boc	*tertiary*-butyloxycarbonyl
Br	bromo
brs	broad singlet
Bu	butyl
t-Bu	*tertiary*-butyl
calcd.	Calculated
cm^{-1}	1/centimetre
C–C	carbon-carbon
C–H	carbon-hydrogen
C–N	carbon-nitrogen
C–O	carbon-oxygen
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethyl aminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
DMSO-d_6	deutriated dimethylsulphoxide
dd	doublet of doublet
d	doublet (in NMR) or day(s) (in Scheme)

Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
equiv	equivalent
EWG	electron withdrawing group
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectrometry
HSQC	homonuclear single bond correlation
HMBC	Heteronuclear Multiple Bond Correlation
Hz	hertz
IR	infrared
J	coupling constant (in NMR)
mass (ESI+)	electron spray ionization mass spectroscopy
min	minute(s)
m	multiplet
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
m/z	mass to charge ratio
Me	methyl
MHz	megahertz
N	normality
nM	nanomolar(s)
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
R_f	retention factor

rt	room temperature
s	singlet
S_N	nucleophilic substitution
sec	secondary
t	triplet
tert	tertiary
TBHP	*tert*-Butyl hydroperoxide
TEA	triethyl amine
THF	tetrahydrofuran
TFA	trifluroacetic acid
TFAA	trifluroacetic anhydride
TLC	thin layer chromatography
TEA	triethyl amine
Ts	*para*-toluenesulphonyl
UV	ultraviolet
v/v	volume by volume
wt/v	weight by volume
^{o} C	degree celsius
µM	micromolar

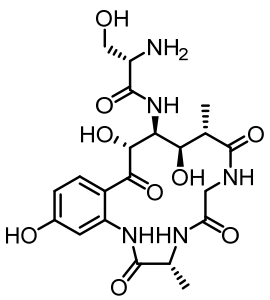
Synopsis

Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	**Mr. Kashinath K**
Degree Enrolment No. & Date	**Ph. D in Chemical Sciences (10CC11J26086); January 2011**
Title of the Thesis	**Total Synthesis of Proposed Structures of Potent Anti-Inflammatory Agents Solomonamides and Analogs**
Research Supervisor	**Dr. D. Srinivasa Reddy**

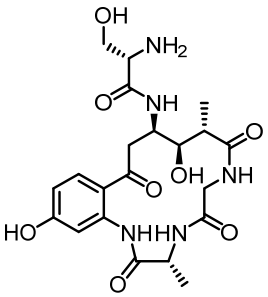
The thesis is divided into three sections. Section 1 describes a brief introduction to the importance of macrocyclic compounds in drug discovery and selected strategies to access macrocyclic frame works. Section 2 describes results and discussion part which includes design and experimental efforts toward total synthesis of target macrocyclic natural products solomonamide A, B and its analogs. Complete experimental details including compounds characterization using various analytical tools are part of Section 3.

Introduction

From many years, natural products have been a rich source of biologically active compounds. Among the natural products, macrocyclic compounds have their own significance because of interesting biological properties and structural features. A macrocycle provides diverse functionality and stereochemical complexity in a conformationally pre-organized ring structure. This can result in high affinity and selectivity for protein targets, while preserving sufficient bioavailability to reach intracellular locations. These valuable characteristics are proven by the success of more than 68 marketed macrocycle drugs. In early 2011, two macrocyclic peptides solomonamide A & B were isolated by Zampella's group. Solomonamide A showed potent anti-inflammatory activity in carrageenan induced mouse model with 60% reduction in paw edema at 100 µg/Kg (ip) in a dose dependent manner, another closely related compound solomonamide B was not tested due to scarcity of the material.[1]



Solomonamide A



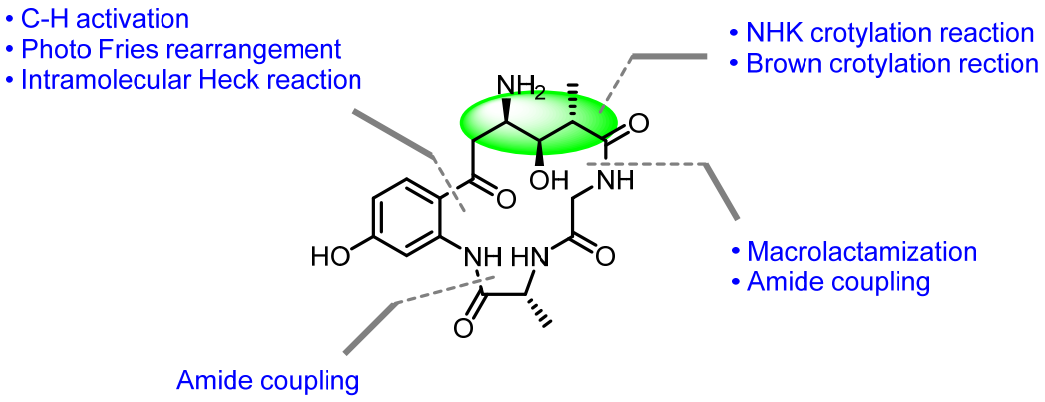
Solomonamide B

Statement of the Problem

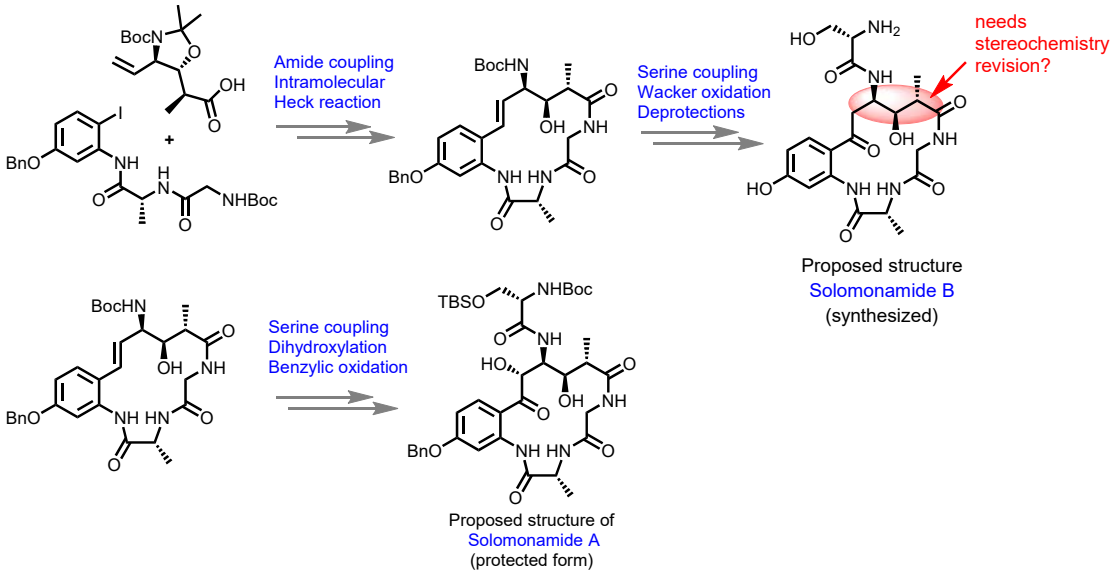
Humans suffer from many inflammatory diseases, including arthritis, allergy, atherosclerosis, cancer, and autoimmune diseases. There is always demand for new medicines with novel mechanisms. Macrocyclic structural class has been poorly explored in drug discovery. This is mainly due to inability to access these classes of compounds and they do not follow the classical Lipinski's rules that are commonly applied in traditional drug discovery arena. However, because of new understanding and development of science, macrocycles started gaining the momentum. Solomonamides are one such class of macrocyclic, which showed potent *in vivo* biological activity and offers a novel chemotype. The scarcity of the material and considering importance of macrocylic compounds in drug discovery, we have taken up task of synthesizing solomonamides and their analogs in sufficient quantities which can be helpful for further biological evaluation and ultimately may deliver optimized compound for treating various inflammatory diseases.

Methodology used

Several strategies were designed and executed for the synthesis of solomonamides. The key disconnections and reactions used for the constructuion of targets are outlined below.[2-4]

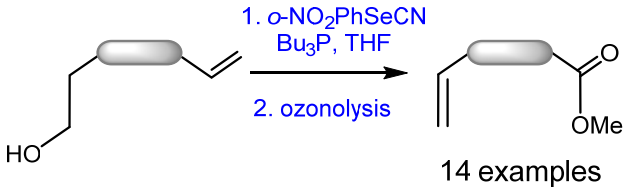


After having the optimized route to access the solomonamide skeleton we have turned our attention toward the synthesis of solomonamides. Initially we have started the synthesis of solomonamide B where intramolecular Heck reaction was used to construct the macrocyclic skeleton. The double bond was transformed into benzylic ketone in a highly regioselective manner by using hydroxy group directed Wacker oxidation. Removal of protecting groups afforded the solomonamide B. After careful analysis of NMR spectral data it was confirmed that there is a discrepancy in original structural assignment of natural product. So, there is a need to revise the stereo chemistry of the natural product, in particular non amino acid partner.



The stereochemistry of solomonamide B was assigned based on solomonamide A, suggesting that the stereochemistry of solomonamide A is also incorrect. However, to check the feasibility of our strategy towards solomonamide A, the styrene double bond was oxidized (dihydroxylation followed benzylic oxidation) to give 7:3 diastereomeric mixtures of compounds. Although we do not have proof, major compound is expected to have the desired stereochemistry present in the proposed structure of solomonamide A. Thus, we have completed the total synthesis of proposed structure of solomonamide B and solomonamide A (in protected form).

While working on total synthesis we have developed a simple and practical one-pot, two-directional approach to access olefinic esters. The scope of the method was generalized with 14 examples and the end products obtained using developed method can serve as useful building blocks.[5]



Noteworthy Findings

a) Macrocyclizations using different methods were demonstrated to form 15-membered solomonamide skeleton.
b) Accomplished the first total synthesis of solomonamide B (proposed structure).
c) Proposed structure of solomonamide A was synthesized in protected form.
d) Our efforts suggest that there is a need for structural revision of solomonamides, particularly in the region of non-peptide portion.
e) Synthesized several analogs of solomonamides, which are currently being evaluated in anti-inflammatory assays.

f) Developed a mild and practical one-pot method to access olefinic esters using ozonolysis in a two-directional approach and demonstrated its utility with the various useful examples.

References

1. C. Festa, S. De Marino, V. Sepe, M. V. D'Auria, G. Bifulco, C. Débitus, M. Bucci, V. Vellecco, A. Zampella, *Org. Lett.* **2011**,*13*,1532.

2. **K. Kashinath**, N. Vasudevan, D. S. Reddy, *Org. Lett.* **2012**, *14*, 6222

3. D. S. Reddy, **K. Kashinath**, N. Vasudevan, A process for the preparation of solomonamide analogues. W. O. Patent 2014083578 A1, June 5, 2014

4. N. Vasudevan, **K. Kashinath**, D.S. Reddy, *Org. Lett.* **2014**, *16*, 6148

5 **K. Kashinath**, S. Dhara, D. S. Reddy, *Org. Lett.* **2015**, *17*, 2090.

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Section 1

Introduction to Macrocyclic Compounds

1.1. Introduction

1.1.1. Natural product based macrocycles in drug discovery

Natural products are chemical entities produced by living organism. These compounds may be isolated from plants, animals, microorganism, fermentation broths or marine organisms. In the history of drug discovery, natural products have been a prime source and always played an important role in discovering medicines for human well being. A substantial number of molecules are clinically validated and marketed for numerous indications such as immunosuppressive agents, antibiotics, anti-inflammatory and anti-tumor agents. From an analysis of last 20 year period (1994-2014), it is estimated that ~35% of available drugs are either natural products or derived from natural products (Figure 1).[1]

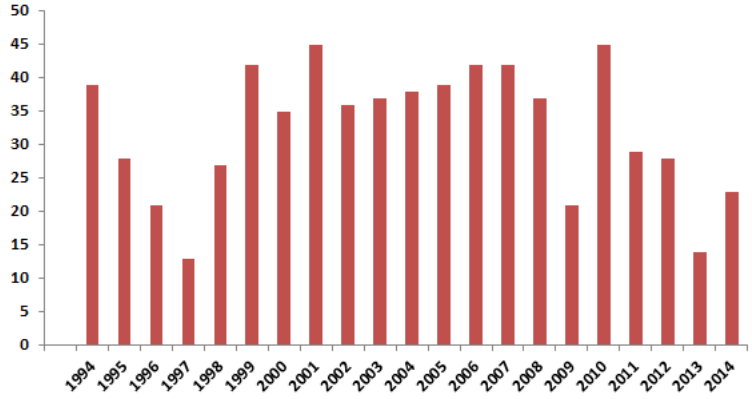


Figure 1. Percentage of drugs based on natural products from 1994-2014

Among the natural products, macrocyclic compounds occupy a special space, due to its interesting biological properties and structural features. A macrocycle provides varied functionality and stereochemical complexity in a conformationally preorganized ring structure which results in high binding affinity and selectivity toward protein targets. At the same time, they retain sufficient bioavailability to reach intracellular components. These valuable characteristics were upheld by the success of more than 68 marketed macrocycle drugs and 35 macrocyclic compounds that are in clinical development as per a recent review by Fabrizio Giordanetto and Jan Kihlberg.[2] Out of 68 marketed drugs, 48

are natural products and 18 are natural product-derived drugs, remaining 2 are synthetic. Out of 35 clinical candidates, 17 are natural products 8 are derived from natural products and 10 are de novo design (Figure 2).

According to a recent document,[2] out of the 68 identified macrocyclic drugs registered:

- 34 are used for bacterial infections
- 10 are used for the treatment of cancers
- 28 are used in immunological and cardiovascular therapeutic areas.

In the case of 35 drugs which are in clinical development

- 14 are for the treatments of different cancers
- 10 are anti-infective agents and
- 11 are under examination for indications from ophthalmology to endocrinology.

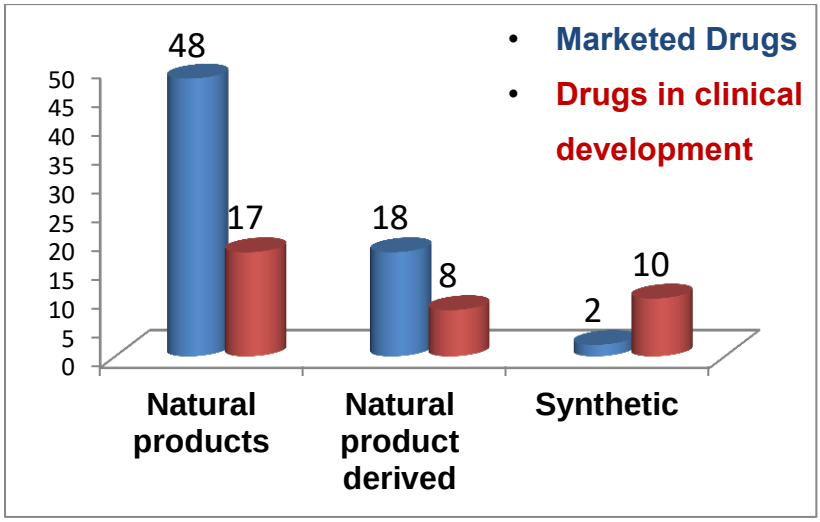


Figure 2. Macrocyclic compounds as drugs

Numerous reviews, articles and book chapters are published describing the importance of macrocycles in drug discovery.[3] Here, selected macrocyclic drugs and compounds in clinical trials are described with their biological relevance and current status. Cyclosporin A (**1**)[4] was isolated from the fungus *Tolypocladium inflatum*. It is a 11 amino acid containing non-ribosomal cyclic peptide used as an immunosuppressant in organ transplantation.

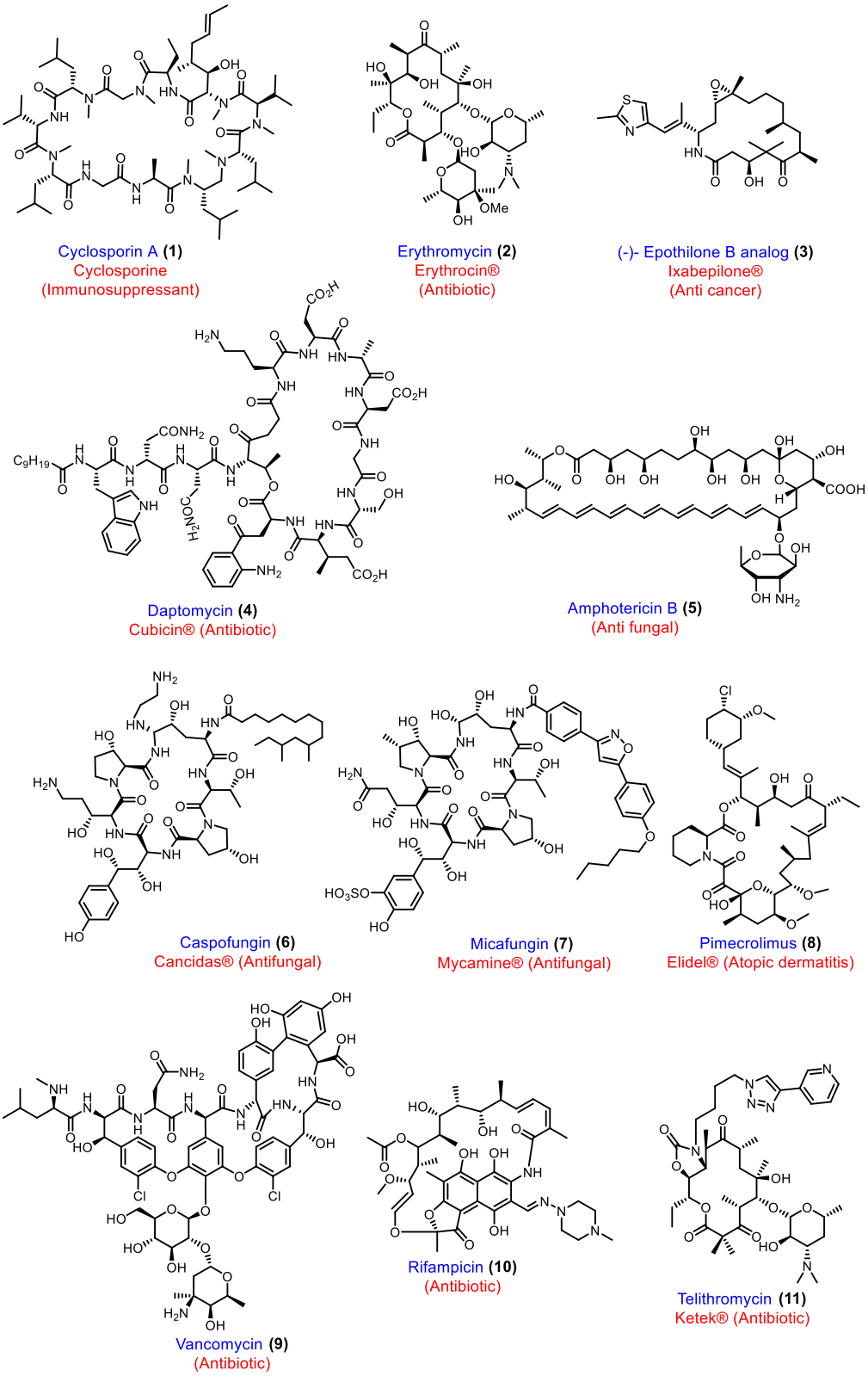


Figure 3. Selected marketed macrocyclic compounds

Erythromycin (**2**)[5] is a macrolide, isolated from the bacteria *Saccharopolysporaerythraea* useful for treating various bacterial infections. Ixabepilone® (**3**)[6] is an aza analog of natural product epothilone B. It is used as an anticancer drug for treating metastatic or locally advanced breast cancer, where taxanes and anthracyclines failed in treatment. Daptomycin (Cubicin®) (**4**)[7] isolated from saprotroph *Streptomyces roseosporus* is an antibiotic drug used for infections caused by gram-positive bacteria. Amphotericin B (**5**)[8] is an antifungal drug used for serious fungal infections. Caspofungin (Cancidas®) (**6**)[9] and Micafungin (Mycamine®) (**7**)[10] are antifungal drugs used for the infections caused by *Aspergillus* and *Candida* species. Pimecrolimus (Elidel®) (**8**)[11] is an immunomodulating agent used for the treatment of atopic dermatitis. Vancomycin (**9**)[12] is an antibiotic used for the treatment of various bacterial infections. Rifampicin (**10**)[13] is used for the treatment of tuberculosis, an infectious disease caused by bacteria *mycobacterium tuberculosis.* Telithromycin (Ketek®) (**11**)[14] is used for the treatment of community-acquired pneumonia, it is the only ketolide marketed till date (Figure 3). Among these drugs Cyclosporin A (**1**), Erythromycin (**2**), Amphotericin B (**5**), Vancomycin (**9**) and Rifampicin (**10**) are the drugs present in "19th WHO Model List of Essential Medicines -April 2015".[15]

Voclosporin (**12**)[16] Anidulafungin (**13**)[17] are in phase 3 clinical trials for treating immune disorders (immunosuppressant) and invasive candidiasis, a fungal infection respectively. Pacritinib (**14**)[18] is in phase-3 clinical trials for treating primary myelofibrosis. Solithromycin (**15**),[19] a erythromycin (**2**) derivative, is in phase-2 clinical trials for treating chronic obstructive pulmonary diseases (COPD). MK-5172 (**16**)[20] which is a close analog of vaniprevir in phase-2 clinical trials for hepatitis C virus infection. TMC647055 (**17**)[21] is under phase-2 clinical trials as an HCV inhibitor, which targets the NS5b RNA-dependent RNA-polymerase. SCY-635 (**18**)[22] is in phase-2 clinical trials for treating hepatitis C infection. Zotarolimus (**19**)[23] and Ridaforolimus (**20**)[24] belongs to rapamycin subclass. Zotarolimus (**19**) is being evaluated in phase-2 clinical trials as an immunosuppressant. Ridaforolimus (**20**) is in phase-1 clinical trials for treating breast cancer. JNJ-26483327 (**21**)[25] is in phase-1 clinical trials for advanced solid tumors. E7389

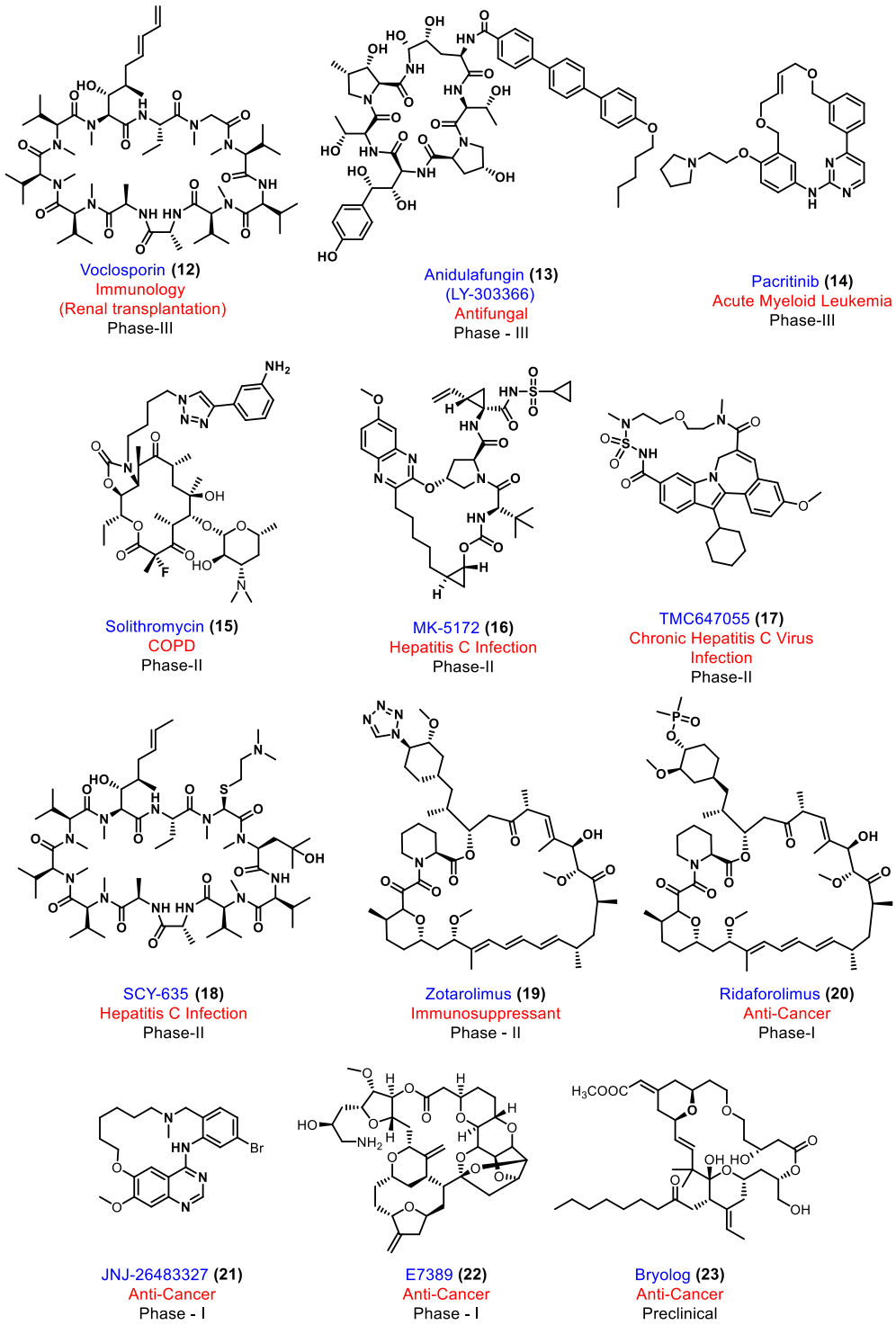


Figure 4. Selected macrocyclic compounds in clinical development

(**22**),[26] eastern hemisphere of halichondrin B is fully synthetic and is in phase-1 clinical development for treating cancer. Bryolog (**23**)[27] is a simpler analog of bryostatin which is

in pre-clinical development for treating various cancers (Figure 4). (Information on the current status of drugs presented here is taken from www.clinicaltrials.gov.in)

1.1.2. Properties of macrocyclic compounds

Ring architecture with 12 or more atoms with molecular weight 500-2000 Da are considered as macrocyclic compounds. Usually, pharmaceutical industries work mostly on small molecules, which are having a molecular weight less than 500 Da (infact, Lipinski rule suggests to keep it below 500 for oral drugs). This is mainly due to the enormous study was done, numerous tools are available for the synthesis, and it is easy for researchers to modify small molecules to attain desired pharmacokinetic/ pharmacodynamic properties. However, during the last 20 years, understanding of disease mechanisms has grown, in particular with the discoveries around the etiology of cancer and inflammatory diseases. These disease targets are components of PPIs (protein-protein interactions), which have large protein surfaces. Small molecules have a limited affinity to bind to the extended binding targets because these molecules lack the physical reach to enable them to effectively interact.

Biological drugs are also called as biologics or large molecules. The molecular weight of these compounds is around 10000 Da to 50000 Da, and represents a class of molecules based on proteins. Because of extreme affinity and selectivity for their binding to target proteins they have been developed as drugs. For example adalimumab (HUMIRA®) an antagonist of TNF (tumor necrosis factor) is prescribed for rheumatoid arthritis and other inflammatory diseases. Although, biologics are so effective they often suffer from poor oral bioavailability.

Macrocyclic compounds can be a potential solution for targets like PPIs, its large surface area enables them to bind to extended binding sites. Macrocycles are close to small molecules and behave like biological compounds, thus, macrocycles are often called as small molecule biologics (Figure 5). For example, cyclosporine is an immunosuppressant drug used in organ transplantation. It inhibits calcineurin by binding to cyclophilin thereby suppressing the activity of T cells. It is a cyclic peptide with

molecular weight of 1,200 daltons, this size is required for binding to the cyclophilin surface.[28]

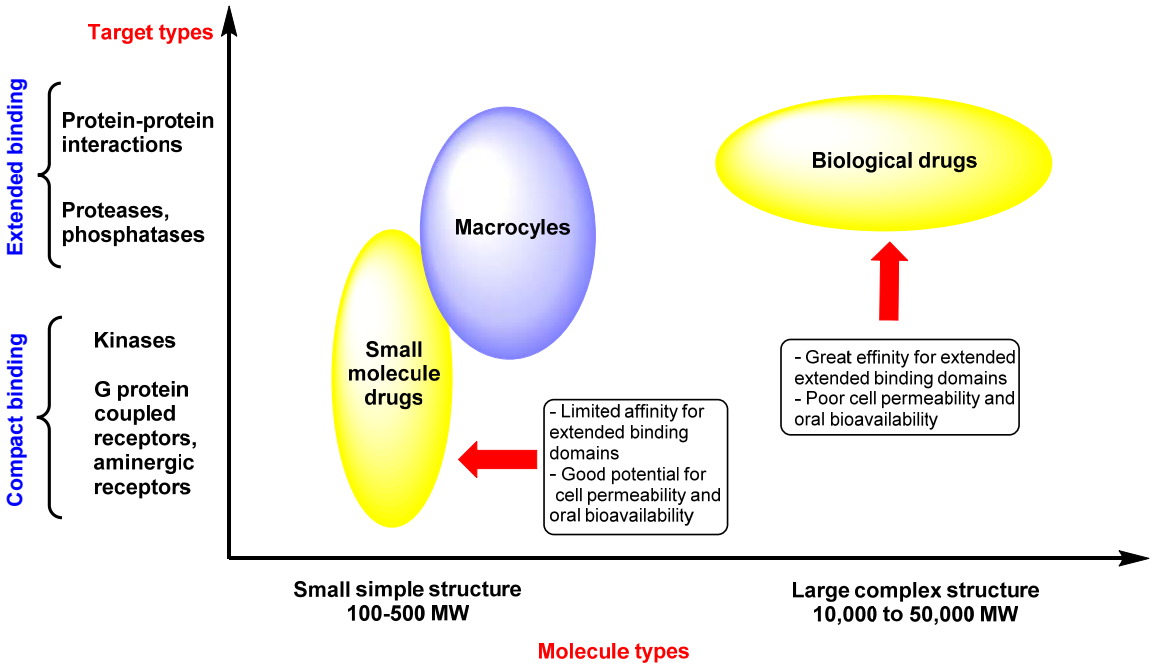


Figure 5. Target *vs.* drug complexity

Oral bioavailability of macrocycles

A drug which is administrated orally should have enough bio-availability to reach the required target and show the activity. In general, it is known that the molecules which follow the Lipinski rule of 5 (Molecular weight <500, LogP <5, total hydrogen bond acceptors <10, and total hydrogen bond donors <5) possess good oral bio-availability. Most of the macrocycles do not follow the Lipinski rule but there are few macrocyclic compounds which are orally bioavailable known in the literature. A detailed study was carried out by Fabrizio Giordanetto and Jan Kihlberg[2] on 68 marketed macrocyclic drugs and 35 clinical candidates. According to their study 19/68 market drugs and 15/35 clinical candidates are administrated orally. This study shows although macrocycles do not follow the Lipinski rule they can demonstrate a good oral bioavailability.

Improving potency through macrocyclization

Cyclization of drug-like compounds helps in conformational restriction, is one of the common strategy practiced in medicinal chemistry to improve the potency of compounds towards a target. For a compound to bind successfully to a protein, the molecule has to adopt a bioactive conformation. Macrocycles although not completely rigid, have restricted internal bond rotations thus, these are considered as conformationally restricted. Macrocycles have enough flexibility to efficiently interact with binding sites in proteins.

Here, we illustrate one example from the literature to explain the effect of macrocyclization to improve the activity of compounds. Tao *et al.* during the development of urea-based Chk1 inhibitors, studied the effect of macrocyclization effect compared to their corresponding acyclic intermediates.[29] The Compound **24,** which is linear had an IC_{50} value of 22 nM. The authors hypothesized that macrocyclization of the compound **24** may improve the potency of the inhibitor, accordingly they have synthesized macrocyclic compound **25** which showed an IC_{50} of 10 nM (Figure 6). Encouraged by the results, further study was initiated by altering the size of the macrocycle, accordingly, compounds **26**, **27**, **28** were synthesized. Compound **26 (**14 membered macrocycle) and compound **27** (15 membered macrocycle) showed a promising activity of 6 nM and 7 nM respectively. Compound **28** (16-membered

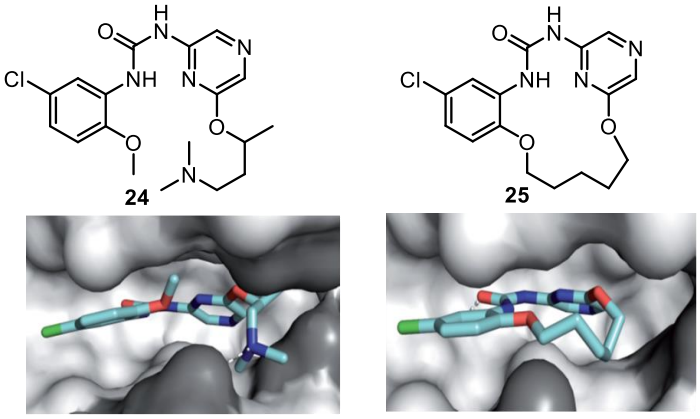
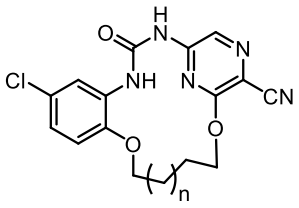


Figure 6. Acyclic and macrocyclic Chk1 inhibitors

macrocycle) showed slightly less activity 28 nM. The decrease in activity can be attributed to increased steric interactions with the target protein as larger alkyl linker has to be accommodated in the binding pocket (Figure 7). Thus, the introduction of constraints through macrocyclization proved to be a good strategy.

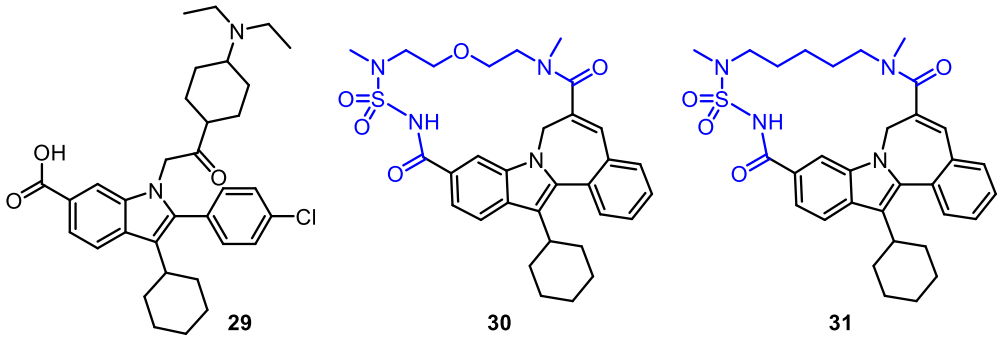


n = 1; ring size 14, IC_{50} 6 nM **(26)**
n = 2; ring size 15, IC_{50} 7 nM **(27)**
n = 3; ring size 16, IC_{50} 28 nM **(28)**

Figure 7. Macrocyclic Chk1 inhibitors

Improving pharmacokinetic properties through macrocyclization

As mentioned above cyclization is the one of the strategies to improve the drug-like properties of a compound. Rigidification of the molecule through macrocyclization can lead to an improvement in PK (pharmacokinetic) parameters. Cummings et. al. utilized this concept to improve the PK properties in a series of indole-based HCV inhibitors which target the NS5B (Nonstructural protein 5B) RNA polymerase.[30] From the crystal structure of compound **29** and related compounds, it was clear that the carboxylic acid is outside the hydrophobic binding pocket, and forms a salt bridge at the edge of the binding pocket. The carboxylic acid undergoes glucuronidation in vivo and results in toxic metabolites. Several modifications were made to improve the PK parameters of these compounds by different groups, but was not successful. Cummings group designed macrocyclic analogs **30** and **31** keeping in mind that the macrocyclization of the exposed acid functionality may lead to an improvement in PK. Accordingly, the sulfonamide macrocycles synthesized preserves all the important interactions observed in the parent open chain inhibitors. The additional binding interactions arising from macrocyclization led to an increase in binding affinity. The macrocycles showed good PK properties which were a concern in non-macrocyclic compounds (Figure 8).[30,31]



29 F (%) = 10 EC_{50} (nM) = 127

30 F (%) = >66 EC_{50} (nM) = 81

31 F (%) = 76 EC_{50} (nM) = 75

F = oral bioavailability; EC_{50} = half maximal effective concentration

Figure 8. HCV inhibitors which target the NS5B RNA polymerase

1. 2. General strategies for the construction of macrocycles

In the synthesis of macrocyclic compounds, construction of macrocyclic skeleton is considered to be crucial. There are several methods reported in the literature for the macrocyclization and several reviews are published.[32] The macrocyclization can be classified based on the mode of cyclization. Some of the selected macrocyclization methods are covered here in this section.

1. Macrolactonization
2. Macrolactamization
3. Palladium-catalyzed coupling reactions
   Suzuki-Miyaura, Heck, Stille, Buchwald
4. Ring-Closing Metathesis (RCM)
5. Click reaction
6. Wittig reaction
7. Mitsunobu reaction
8. Nucleophilic Aromatic Substitution SNAr

1.2.1 Macrolactonization

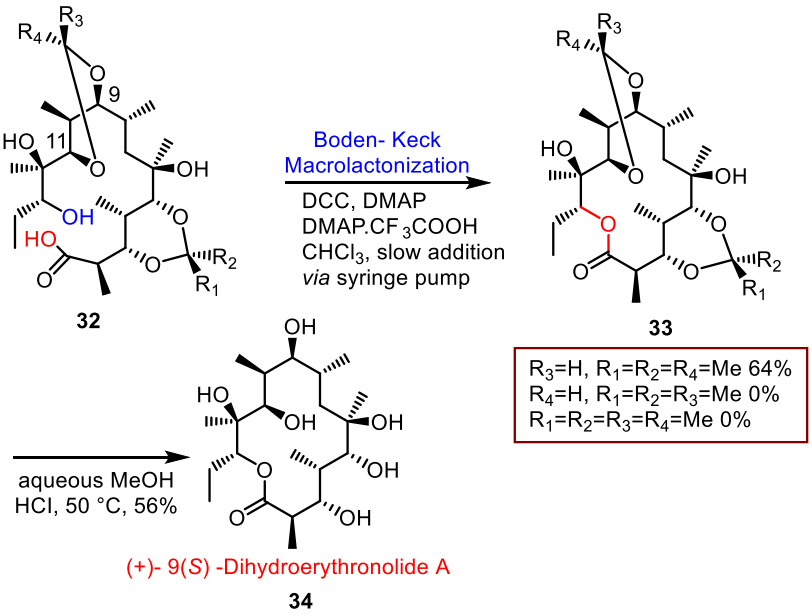
In general, the most commonly used methods for lactonization of acids and alcohols (*seco*-acids) can be classified into three based on activation.[33]

(1) Activation of acid group

(2) Conversion of alcohol group into an easily leaving group

(3) Activating both acid and alcohol functionality simultaneously using a double activation approach.

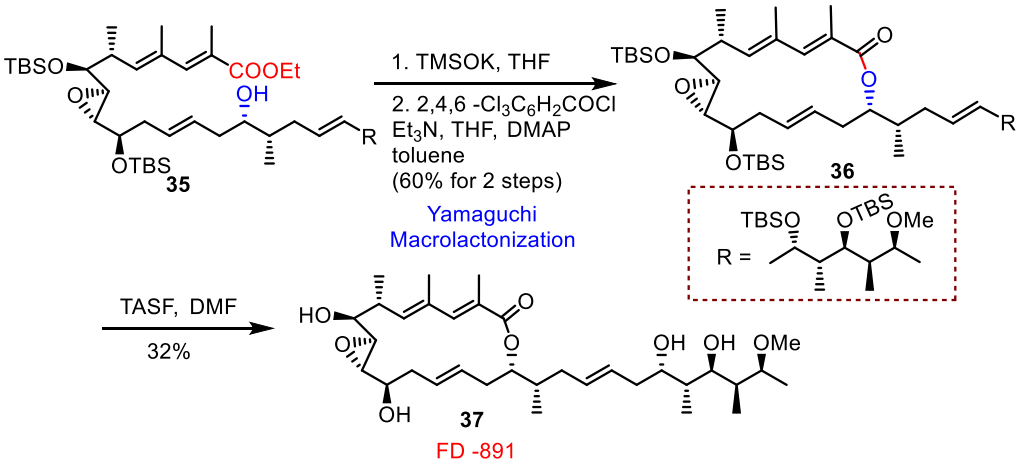
Here we have described some examples from the literature. Gilbert Stork and Scott D. Rychnovsky, utilized Boden-Keck macrolactonization condition for the construction of macrocyclic skeleton in the synthesis of **(+)**-9(*S*) dihydroerythronilide (Scheme 1).[34] The *seco* acid (**32**) on treating with DCC, DMAP and its trifluoro acetic acid salt underwent macrolactonization to afford macrocyclic lactone (**33**) in 64% yield. The cyclization depends on the conformation of the 9,11 cyclic ketal. When R_4=H, R_1=R_2=R_3=Me and R_1=R_2=R_3=R_4=Me cyclization failed to give the desired compound, when R_3 is methyl a 1,3 diaxial interaction between R_3 methyl and C8 made cyclization of the *seco* acid (**32**) unfavorable. When R_3=H, R_1=R_2=R_4=Me, there is no 1,3 diaxial interaction and cyclization was achieved with 64% yield. Deprotection of acetal group in acidic condition afforded **(+)**-9(*S*) dihydroerythronilide A (**34**).



Scheme 1. Synthesis of (+)-9(*S*)-dihydroerythronlide A

One of the most popular methods for the macrolactonization is Yamaguchi macrolactonization. Marco and coworkers utilized the Yamaguchi macrolactonization in

the synthesis of naturally occurring, cytotoxic macrolide FD-891 (**37**). Hydrolysis of the ethyl ester group in compound **35** under mild condition using TMSOK followed by macrolactonization of the resulting hydroxyl acid was achieved at high dilution (0.006M) using 2,4,6-trichlorobenzoyl chloride (TCBC), Et_3N, DMAP in THF afforded compound **36**. Finally, cleavage of all the silyl groups using TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate) in compound **36** gave cytotoxic macrolide FD-891 (**37**) (Scheme 2).[35]



Scheme 2. Synthesis of FD-891

Other bioactive macrocyclic compounds like potent immunosuppressive FK506 binding protein (FKBP) ligands **38**[36] and microtubule stabilizing agents **39**,[37] an antifungal agent Sch-725674 (**40**)[38] were synthesized by using Yamaguchi conditions for ring closure (Figure 9).

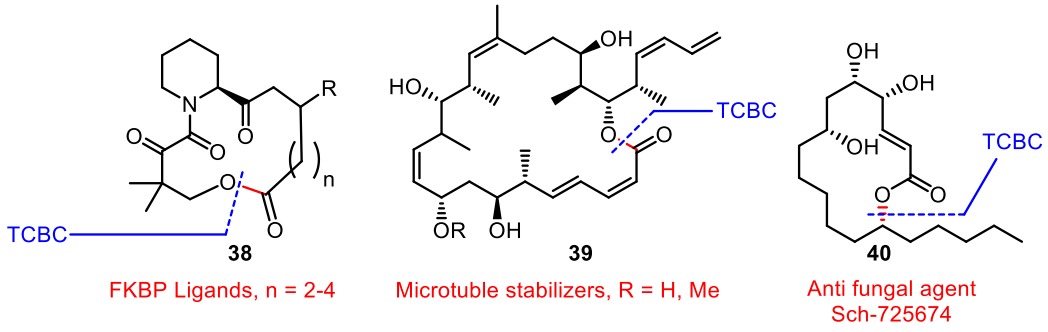


Figure 9. Representative macrocyclic compounds from macrolactonization

1.2.2. Macrolactamization

In general, most of the macrolactamizations[39] proceed through formation of an amide bond. This involves activation of acid **41** into activated ester **42** followed by a nucleophilic attack of amine leads to the formation of macrolactam **43** (Figure 10).

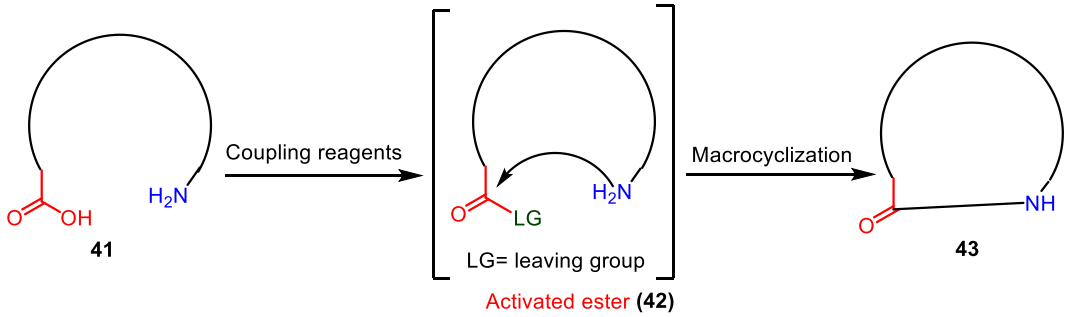


Figure 10. Schematic representation of macrolactamization

For macrolactamization, a wide range of coupling agents is available, which includes carbodiimides (DCC, EDC), phosphoniumsalts (HATU, BOP, PyBOP), boronate salts (TBTU), acylazoles, pyridinium salts (Mukaiyama reagent) and triazines (DEPBT) (Figure 11).

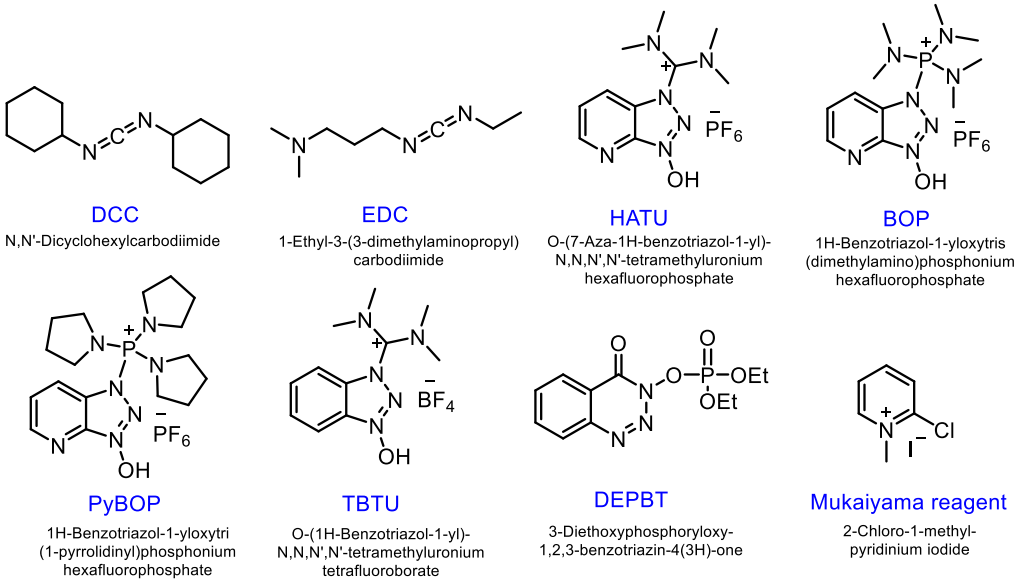
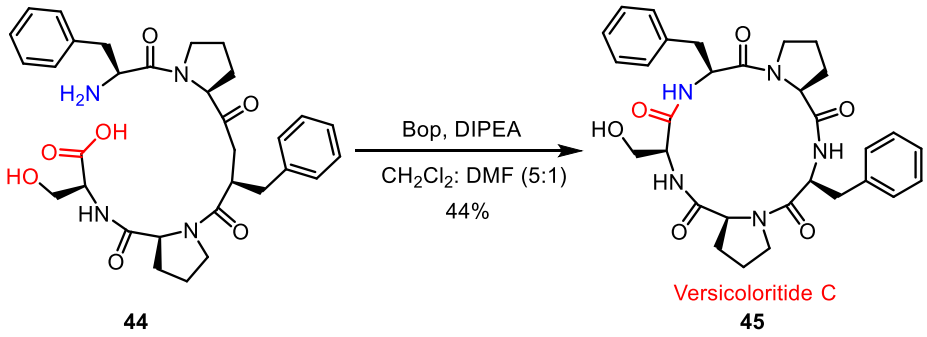


Figure 11. Selected amide coupling reagents

Macrolatamization in versicoloritide C (**45**) was achieved by using amide coupling reagent BOP in CH_2Cl_2:DMF (5:1) as solvent with 44% yield by Brimble group (Scheme 3).[40]



Scheme 3. Synthesis of versicoloritide C

Macrolactamization is often the method of choice for peptidomimetic macrocycles and has been successfully employed for the synthesis of thrombin inhibitors **46**[41] and small ring inhibitors neutral endopeptidase (NEP) inhibitors **46**[41](Figure 12).

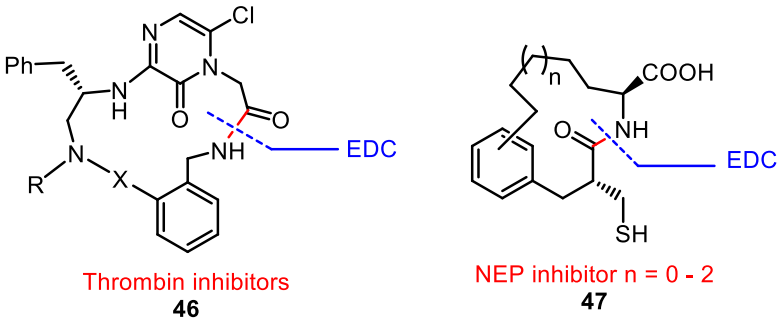
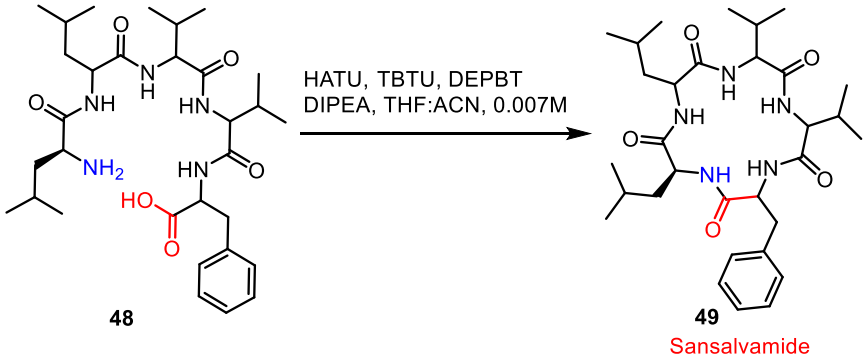


Figure 12. Representative macrocyclic compounds from macrolactamization

All amide coupling reagents may not help in achieving the desired macrolactamization, it requires a lot of trials to come up with the required amide coupling reagent. To avoid the number of trials, the use of a combination of coupling reagents is proposed and this concept gives moderate to good yields depending upon the substrate. McAlpine and co-workers utilized this concept very well in the synthesis of cytotoxic sansalvamide (**49**) and its derivatives.[43] Compound **48** on treating with a combination of peptide coupling reagents (HATU, TBTU, DEPBT) at high dilution gave desired

macrolide sansalvamide (**49**) in good yield (Scheme 4). Several analogs were synthesized by varying amino acids residues and *N*-methylated compounds. The macrocyclization was achieved with 5-76% yields at 0.007-0.0007 M concentration.



Scheme 4. Mc Alpine synthesis of sansalvamide

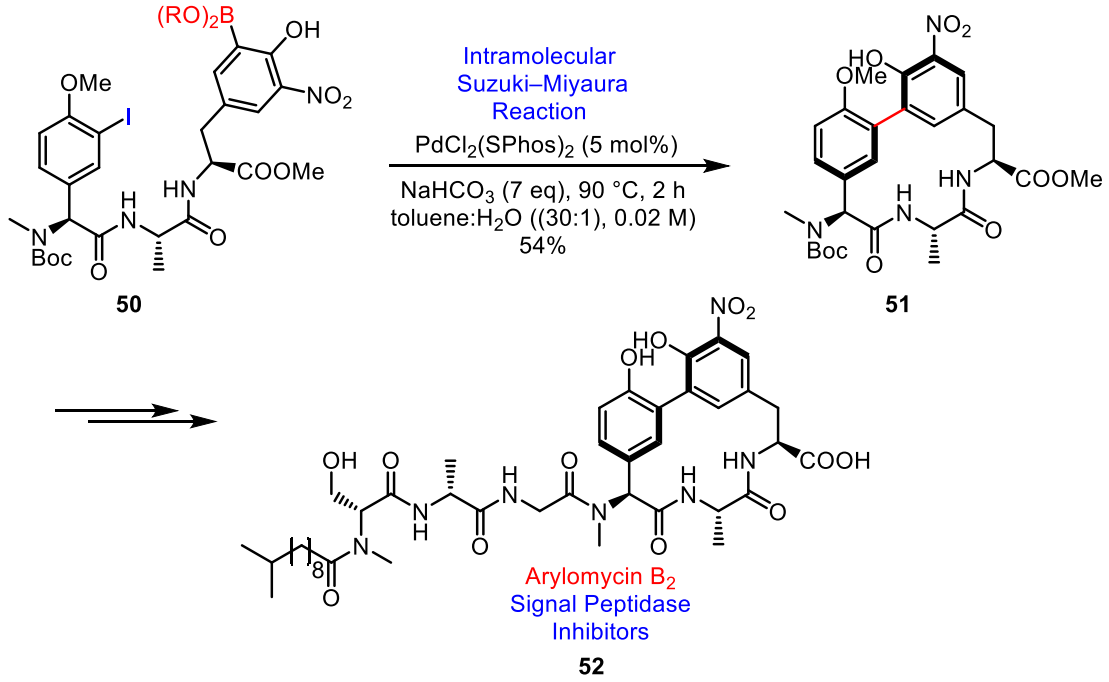
1.2.3. Palladium- catalyzed coupling reactions

Over the past few decades, Pd-catalyzed cross-coupling reactions gained more importance and became a prominent tool for making new C-C, C-O or C-N bonds. The ease of making new C-C, C-O, C-N and other carbon-hetero (C-X) bonds make these reactions remarkable tools in natural product synthesis.[44] These reactions also played a major role in the synthesis of macrocyclic compounds.

Suzuki-Miyaura coupling reaction

Suzuki couplings of aryl or vinyl boronic esters/acids with aryl or vinyl halides/triflates also have a great impact on the synthesis of macrocyclic compounds. For example, arylomycins[45]are lipo hexapeptides act as potent signal peptidase I (SPase I) inhibitors. The aromatic rings of 4-hydroxy phenyl glycine and Tyr are in compound **50** cross-linked by an aryl–aryl bond, which forms a 14-membered meta, meta-cyclophane. The macrocyclization was achieved by Suzuki-Miyura cross-coupling reaction. ($[PdCl_2(SPhos)_2]$, *C* = 0.02 M in toluene/H_2O (30:1) and $NaHCO_3$ (7 equiv)). This macrocycle **51** was further transformed to natural product arylomycin B, **52** (Scheme 5). It is noteworthy that the intramolecular Suzuki–Miyaura reaction was the only successful

way to build the cyclophane unit of the arylomycins. Other trials, for macrolactamization were found to be inefficient.[46]



Scheme 5. Synthesis of signal peptidase inhibitor arylomycin B_2

The cyclization in Mycocyclosin (**53**)[47] and Acerogenin E (**54**)[48] was achieved by intramolecular Suzuki reaction (Figure 13).

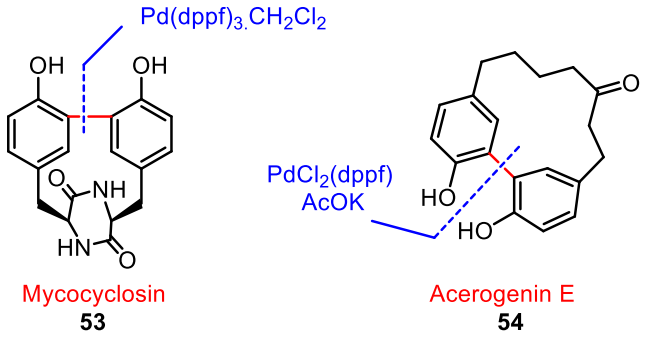
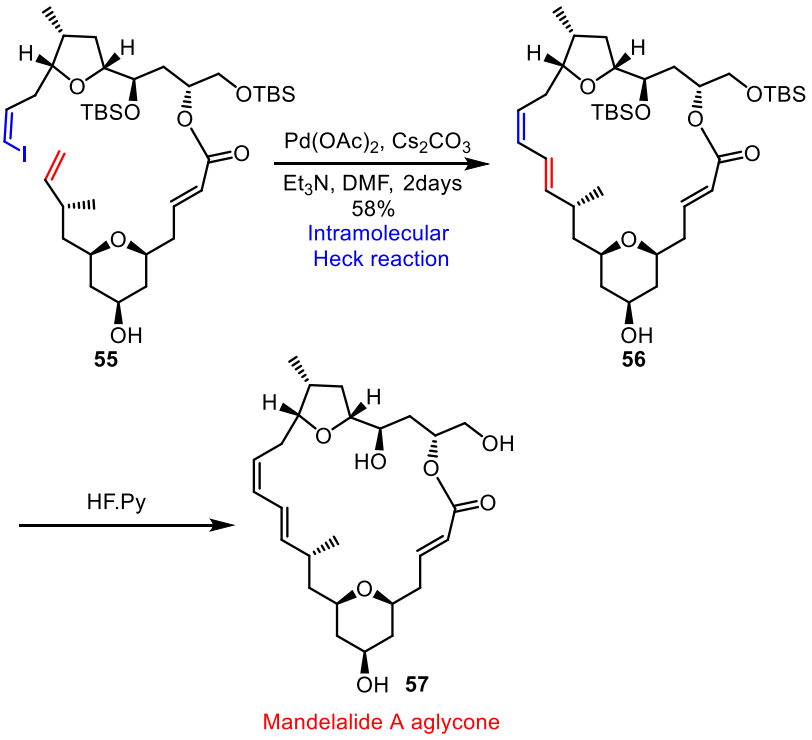


Figure 13: Representative examples for macrocyclization through intramolecular Suzuki reaction

Heck coupling reaction

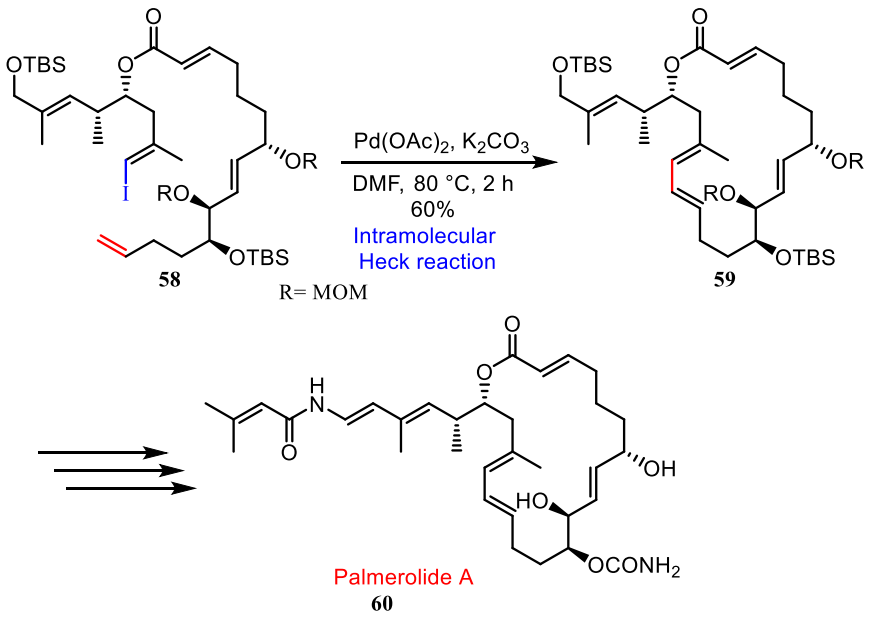
A coupling reaction between aryl/vinyl halides and alkenes in the presence of Pd catalyst and a base is known as Heck reaction. The Intramolecular Heck reaction is one of the key tools for the construction of macrocyclic frameworks. One such example is the synthesis of mandelalide A aglycone,[49] by Subhash Ghosh group. The macrocyclization of compound **55** was achieved through an intramolecular Heck reaction using $Pd(OAc)_2$ as catalyst and Cs_2CO_3 as base in DMF solvent. The macrolide **56** was obtained in 58% yield with exclusive *E*–stereochemistry. The removal of silyl protecting groups (HF.Py) afforded mandelalide A aglycone (**57**) (Scheme 6).



Scheme 6. Synthesis of mandelalide A aglycone

The intramolecular Heck reaction was successfully applied in the synthesis of an anticancer agent Palmerolide A (**60**)[50] by K. R. Prasad et. al. Intramolecular Heck coupling ($Pd(OAc)_2$, K_2CO_3, DMF) was performed on compound **58** to afford

macrolactone **59** in 60% yields, which was further converted to natural product palmerolide A (**60**) in a few steps (Scheme 7).



Scheme 7. Synthesis of palmerolide A

The intramolecular Heck reaction was also successfully employed in the synthesis of β-turn mimics **61**,[51] HCV protease inhibitors **62**[52] and complex structures like macrocyclic taxoid **63** (Figure 14).[53]

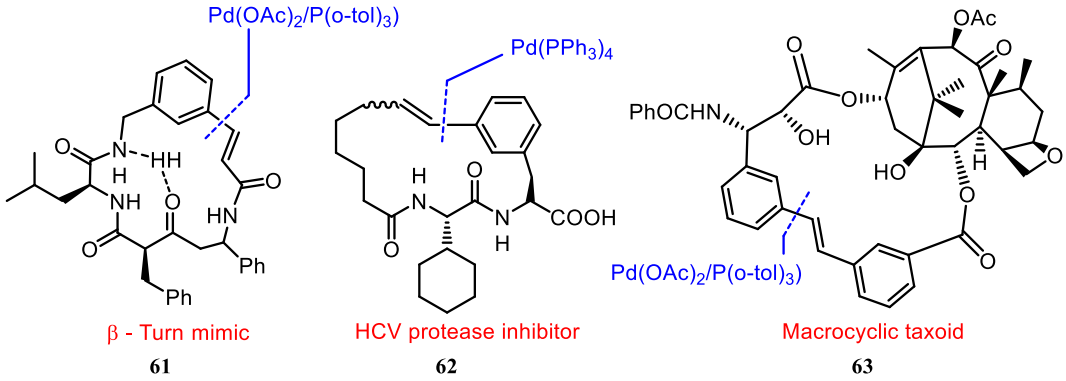
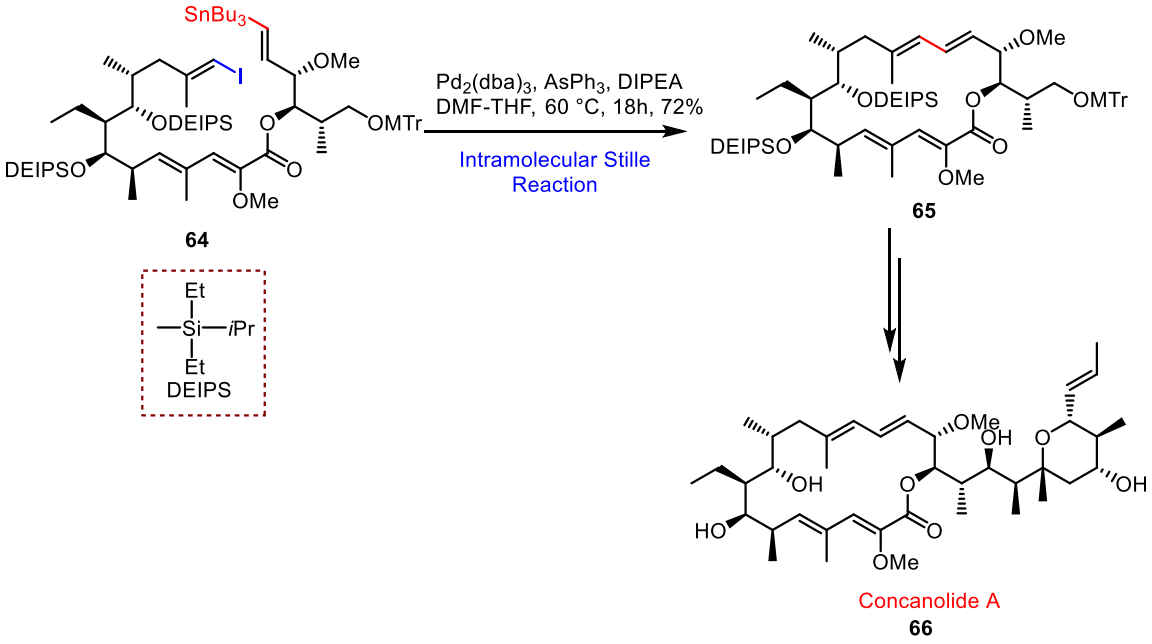


Figure 14. Representative macrocyclic compounds synthesized using intramolecular Heck reaction

Stille Coupling

Stille coupling between organo tin reagent and aryl/vinyl halides is another palladium-catalysed coupling reaction, used for the construction of macrocycle.[54] Toshima et al. have described an impressive illustration of the use of the intramolecular Stille reaction in their total synthesis concanolide A (**66**).[55] Compound **64** was converted into macrolide **65** using $Pd_2(dba)_3$, $AsPh_3$, DIPEA in DMF-THF in a very good yield. This macrolide **65** was further transformed into natural product concanolide A (**66**) in a few steps (Scheme 8).

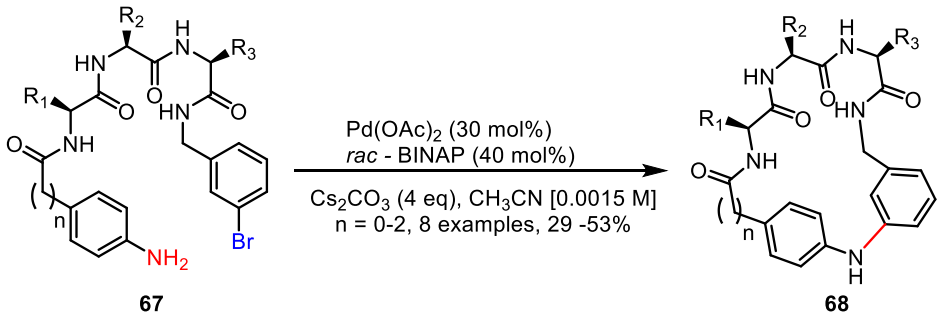


Scheme 8. Synthesis of concanolide A

Buchwald–Hartwig coupling reaction

Buchwald – Hartwig reaction is a C-N bond forming reaction between amine and aryl halides catalyzed by Pd catalyst. Although this reaction is less common in macrocyclization, there are few examples in the literature where macrocycle was constructed through this reaction. For example, Iqbal et al. used Buchwald coupling reaction as the key cyclization step in the synthesis of cyclic peptides constrained with

biarylamine linkers.[56] The cyclization was achieved by using $Pd(OAc)_2$, *rac*-BINAP and Cs_2CO_3 as base under dilute condition. By using this method 8 compounds were synthesized in 29-53% yields, and obtained products were 16 to 22-membered macrocycles (Scheme 9).

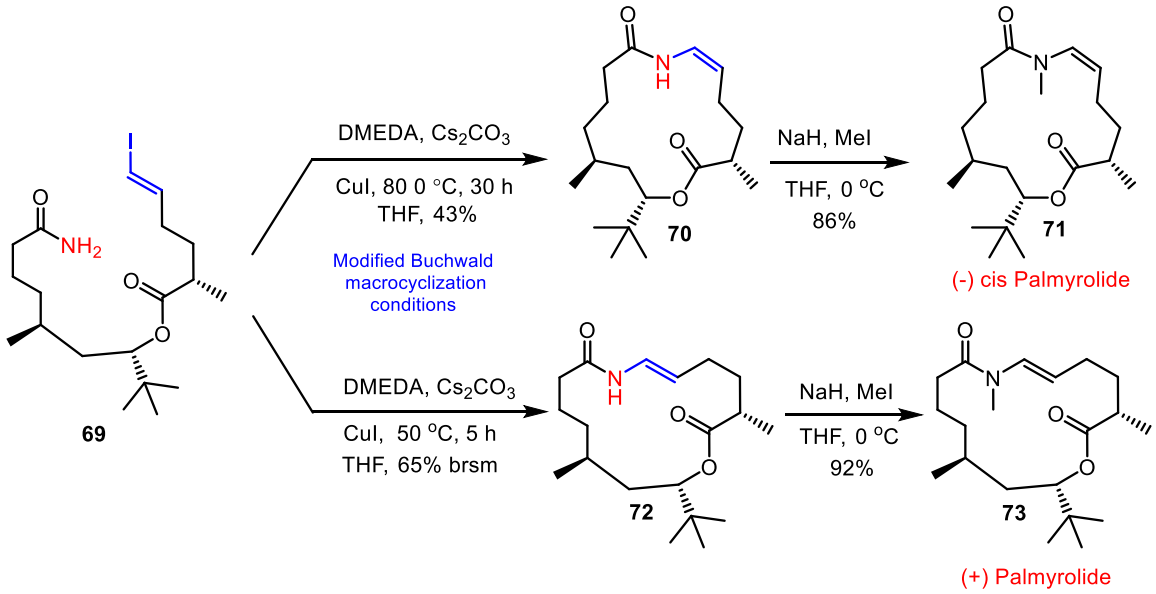


67 **68**

R = H, R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3, n = 0, 42%
R = H, R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3, n = 1, 50%
R = H, R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3, n = 2, 53%
R = H, R_1 = -CH_2Ph, R_2 = - CH_3, R_3 = -$CH_2CH(CH_3)_2$, n = 0, 44%
R = H, R_1 = -CH_2Ph, R_2 = -$CH_2CH(CH_3)_2$, R_3 = - CH_3, n = 0, 41%
R = H, R_1 = -$CH(CH_3)_2$, R_2 = -$CH(CH_3)CH_2CH_3$, R_3 = - CH_3, n = 0, 46%
R = H, R_1 = -$CH(CH_3)_2$, R_2 = -$CH_2CH(CH_3)_2$, R_3 = - CH_3, n = 0, 36%
R = CH_3, R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = - CH_3, n = 0, 29%

Scheme 9. Macrocyclization through Buchwald- Hartwig reaction

D. S. Reddy and co-workers utilized the modified Buchwald condition for the synthesis of (+)-palmyrolide A and (-)-*cis*-palmyrolide.[57] It is worth noting that, change in the temperature and, reaction time afforded two different end products. Compound **69** on treating with DMEDA, Cs_2CO_3, CuI, at 80 °C for 30 h afforded *cis*- macrocycle, **70** which was converted into *cis*-palmyrolide (**71**) by *N*-methylation (NaH, MeI) and cyclization of compound **69** at 50 °C for 5 h gave *trans*-macrocycle **72**, which on *N*-methylation (NaH, MeI) afforded (+)-palmyrolide A **73** (Scheme 10).



Scheme 10. Synthesis of *cis*- palmyrolide and palmyrolide A by D. S. Reddy and co-workers

1.2.4. Ring-closing metathesis (RCM)

Ring-closing metathesis (RCM) is an intramolecular reaction in which two terminal alkenes react to form cycloalkene with the loss of ethylene. The reaction is mediated

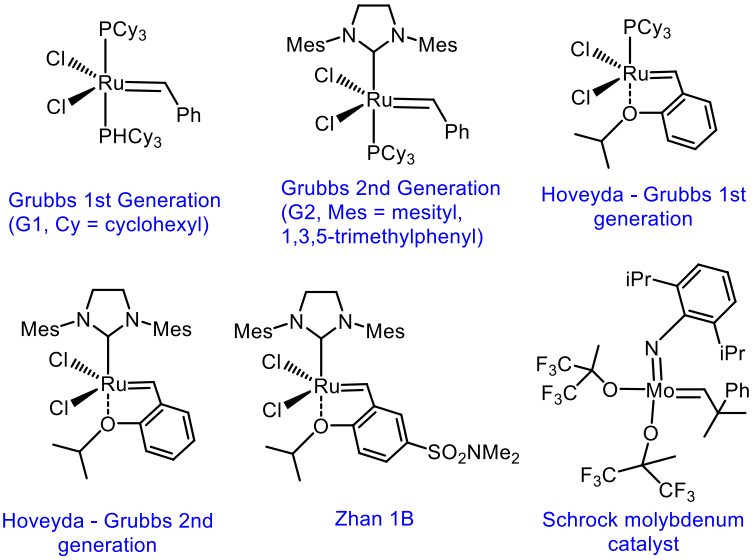
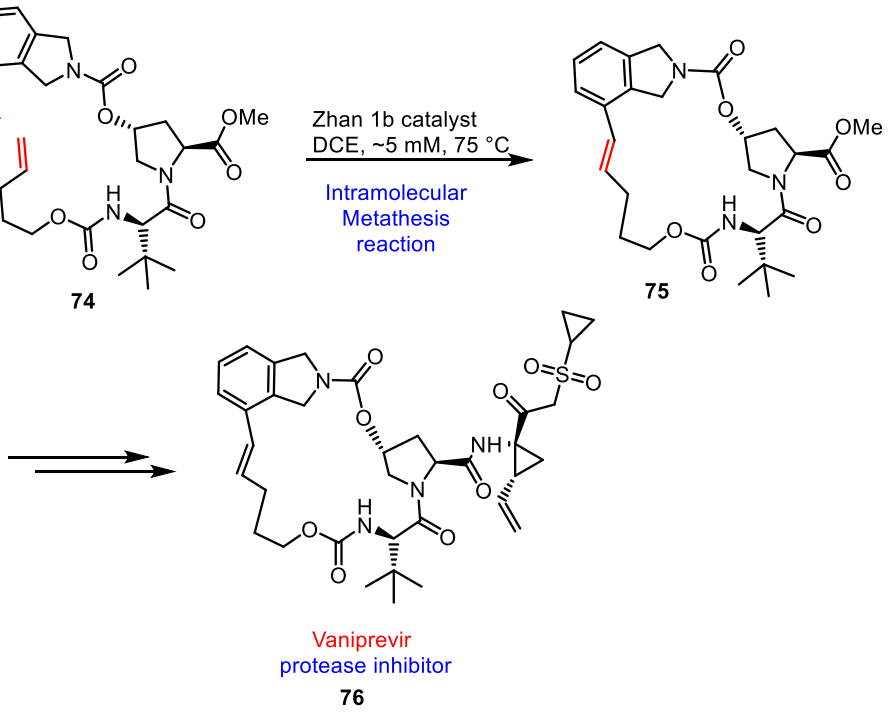


Figure 15. Generally used metathesis catalysts

by an organometallic catalyst. Although Ru, Mo, W catalysts can promote RCM, Ru catalysts are used more frequently because of functional group tolerance, air stability, and commercial availability (Figure 15).

The RCM has been extensively used in the construction of macrocycles.[58]The most substantial impact of RCM has been utilized in the development of the macrocyclic HCV NS3/4A protease inhibitors. Mc Cauley et al. in their synthesis of vaniprevir (**76**)[59] the key macrocyclization was achieved by Zhan 1b catalyst with trans-olefin selectivity (Scheme 11).



Scheme 11. Synthesis of vaniprevir

A wide range of molecular architectures can be accessed through RCM. This strategy has been successfully applied for the synthesis of macrocyclic anticancer taxoids **77**,[60] Hsp90 inhibitors **78**,[61] SGLT2 inhibitors **79**,[62] and a series of multi-kinase inhibitors which are in clinical trials. SB1317 (TG02) **80**,[63] an inhibitor of CDK/JAK2/FLT3 for treating cancers, pacritinib (SB1518) **81**,[64] a JAK2, inhibitor for the treatment of myelofibrosis, SB1578, **82**,[65] an inhibitor of JAK2, for treating rheumatoid arthritis, HIV protease inhibitor (-)-

petrosin, **83**,[66] and antifungal agent Sch-725674 analog **83.**[38] It is worth highlighting that the synthesis of compound **83**, RCM was carried out in gram scale (1.2g) with 71% yield. (site of cyclization indicated along with the catalyst in Figure 16).

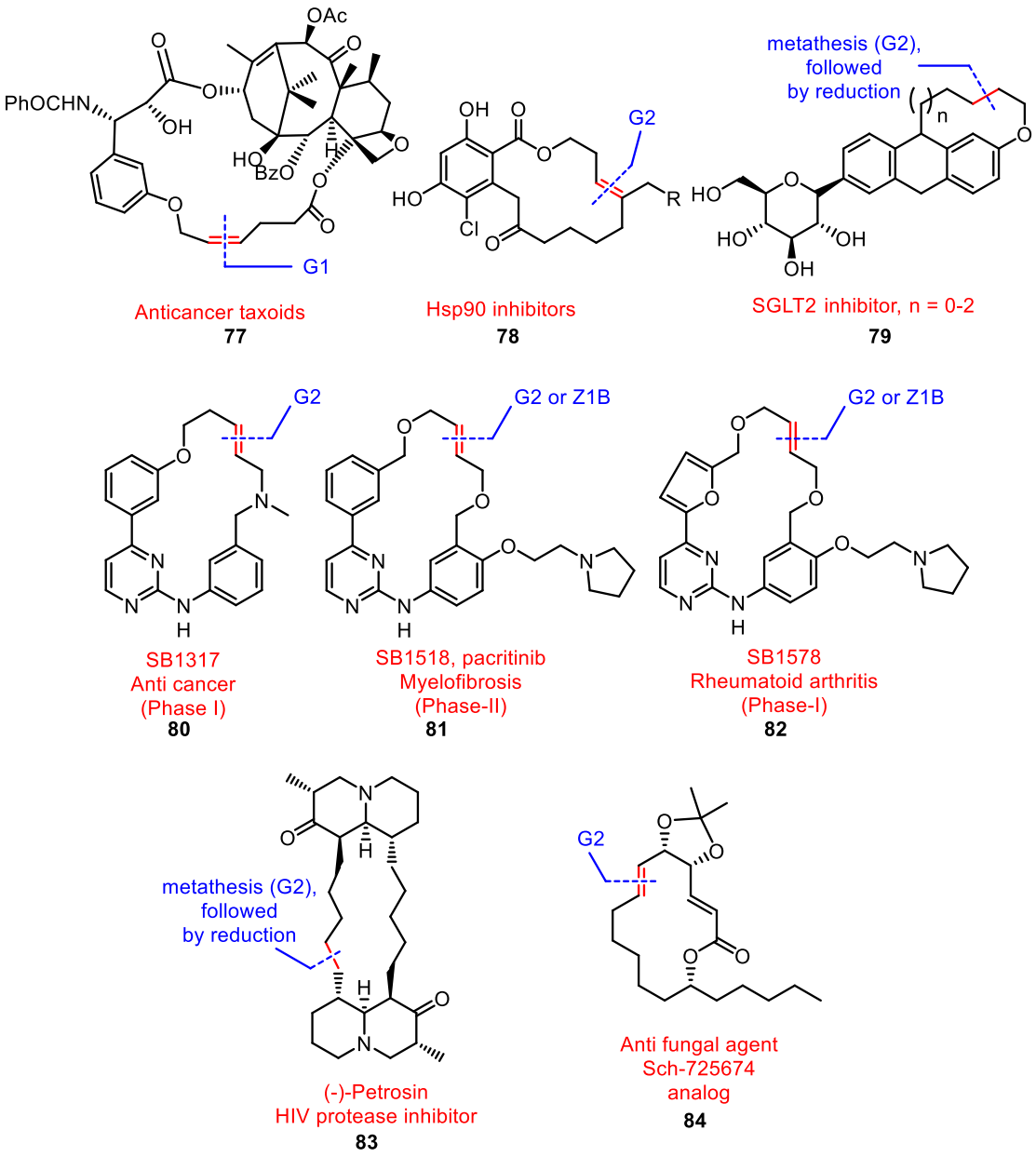
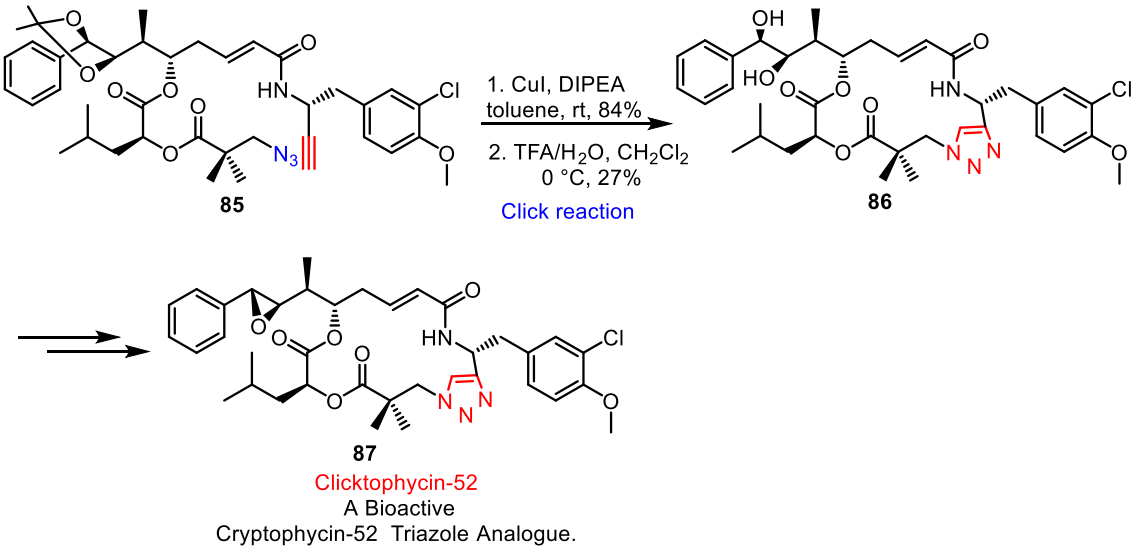


Figure 16. Representative macrocyclic compounds synthesized by RCM

1.2.5. Click reaction

Huisgen reaction, [3+2]-cycloaddition of azides with alkynes, is commonly referred as ‘‘Click’’reaction.[67] The transformation is usually conducted in the presence of copper (I). Since the triazole moiety is considered to be a *trans*-amide mimic, this chemistry was widely used in the synthesis of macrocyclic peptidomimetic structures.[68]

Sewald and co-workers achieved the macrocyclization of the triazole analog of cryptophcin-52 analog clicktophycin-52 (**87**) by Cu(I)-mediated “Click”-cyclization (Scheme 12).[69]



Scheme 12. Synthesis of clicktophycin-52

Macrocyclization using Click chemistry was also used in the synthesis of macrocyclic peptidomimetic structures, such as β–strand **88**,[70] HDAC inhibitor **89**[71] and SST receptor ligands **90**[72] (Figure 17).

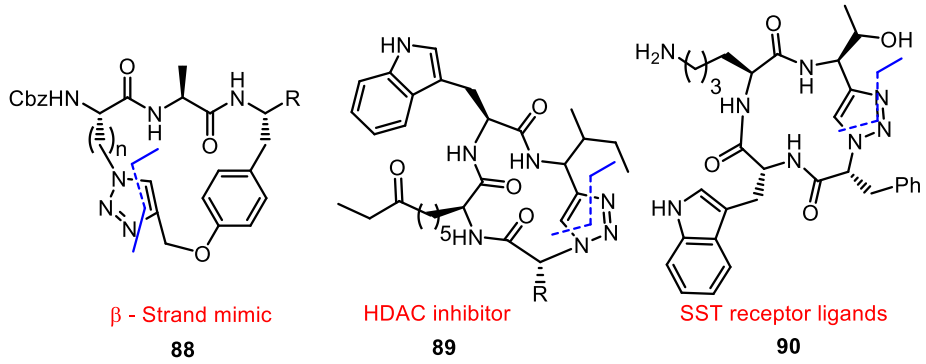
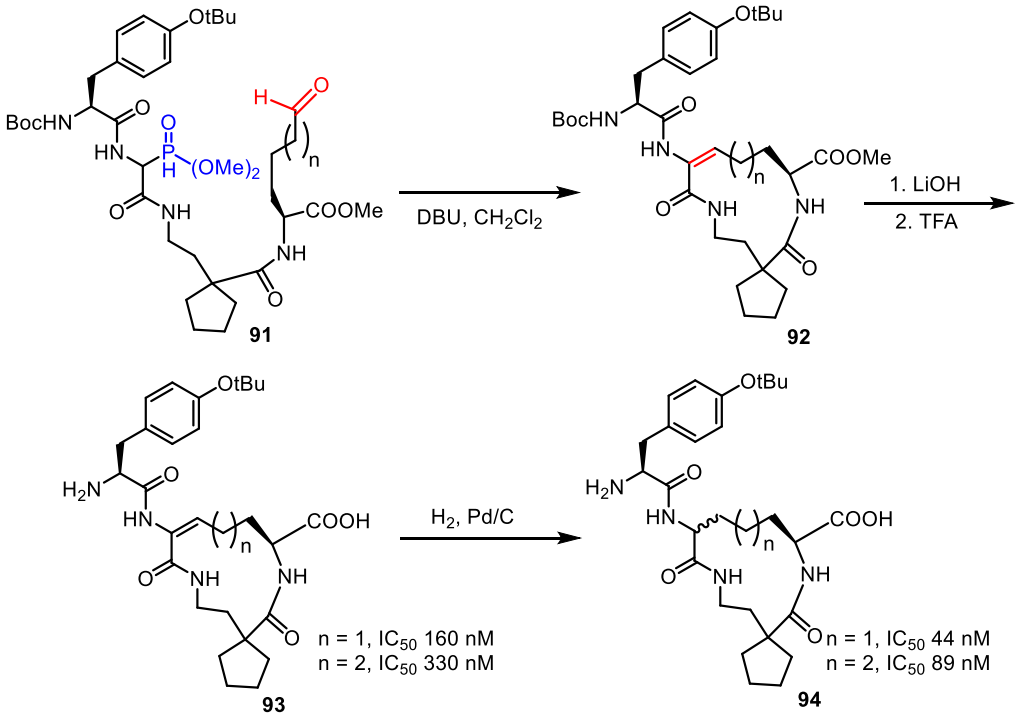


Figure 17. Representative examples for macrocyclization through Click reaction

1.2.6. Wittig reaction

Wittig-type reactions have only limited application in macrocyclization. One example is synthesis of VCAM-VLA-4 antagonists.[73] Jefferson Tilley constructed macrocyclic skeleton **92** by the intramolecular Wittig reaction of an aldehyde **91** with a phosphonoglycine moiety. Ester hydrolysis followed by subsequent reduction of the



Scheme 13. Synthesis of VCAM-VLA-4 antagonists

olefin gave the desired compounds **94**, which showed activity in the nM range. 13-membered rings showed better activity than the14-membered analogs (Scheme 13).

1.2.7. Mitsunobu reactions

Mitsunobu reaction is moderately used for macrocycle ring closure.[74] The mild reaction conditions, known stereochemical outcome, and ease of execution, led to the popularity of this reaction. Generally used Mitsunobu reagents are shown in Figure 19.

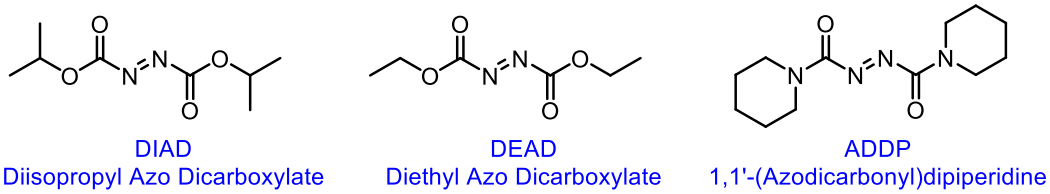
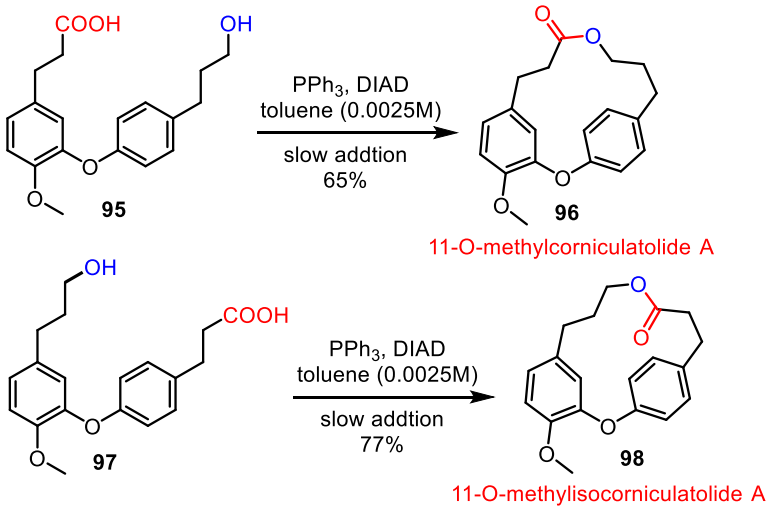


Figure 19. Selected Mitsunobu reagents

11-*O*-methylcorniculatolide A, **96** and 11-*O*-methylisocorniculatolide A, **98** were synthesized by using Mitsunobu reaction (PPh_3, DIAD) from corresponding hydroxy acid (**95** and **97** respectively**)** in good yields by D. S. Reddy group (Scheme 14).[75]



Scheme 14. Synthesis of 11-*O*-methylcorniculatolide A **(96)** and 11-*O*-methylisocorniculatolide A **(98)**

Mitsunobu reaction was also utilized for the synthesis of compounds like TACE inhibitor intermediates **99**,[75] MMP inhibitor intermediate **100**[76] and HCV protease inhibitors **101**[77] (Figure 18). In the first case, the nitrogen of a sulfonamide is a nucleophile, while in the other two cases oxygen of phenol served as a nucleophile.

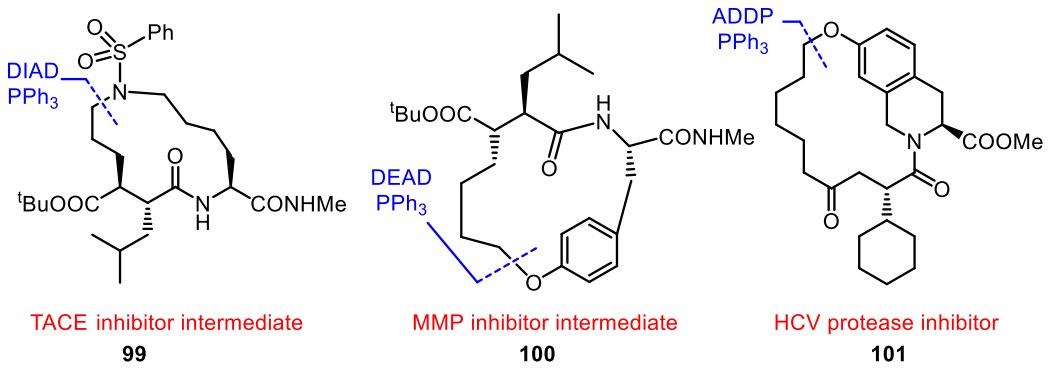
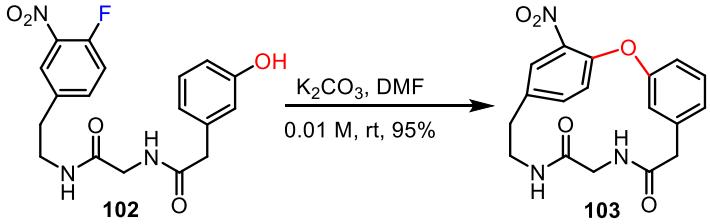


Figure 18. Representative examples for macrocyclization through Mitsunobu reaction

1.2.8. Nucleophilic aromatic substitution S_NAr reaction

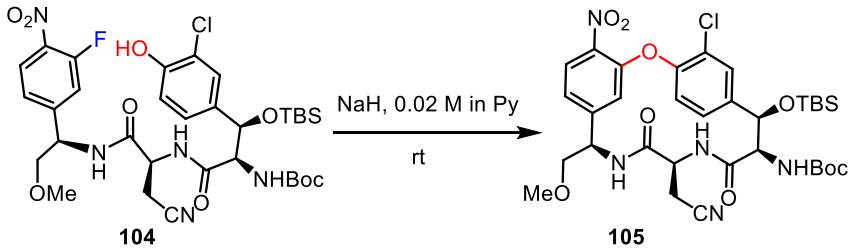
Aromatic substitution reactions have also been applied for the construction of macrocyclic skeletons. Precisely, in the synthesis of biaryl ether moiety in natural products. The first example of S_NAr based macrocyclization was the synthesis of model carboxylate-binding pockets of vancomycin reported by Rene Beugelmans.[78] Treatment of DMF solution of **102** with K_2CO_3 at room temperature for 6 h afforded macrocycle **103** as a single compound in 95% yield (Scheme 15).



Scheme 15. Synthesis of model carboxylate-binding pockets of vancomycin

A.V. Rama Rao and co-workers were successful in achieving the synthesis of the right-hand binding pocket of vancomycin **105** from compound **104** by employing S_NAr

based macrocylization (NaH, 0.02 M py, rt) (Scheme 16).[79] In these reactions a fluoro group (more preferably) adjacent to a nitro group can be displaced by OH compared to a bromo group. This concept was also used by Nicolaou and Evan's groups in their synthesis of vancomycin.[80]



104 105

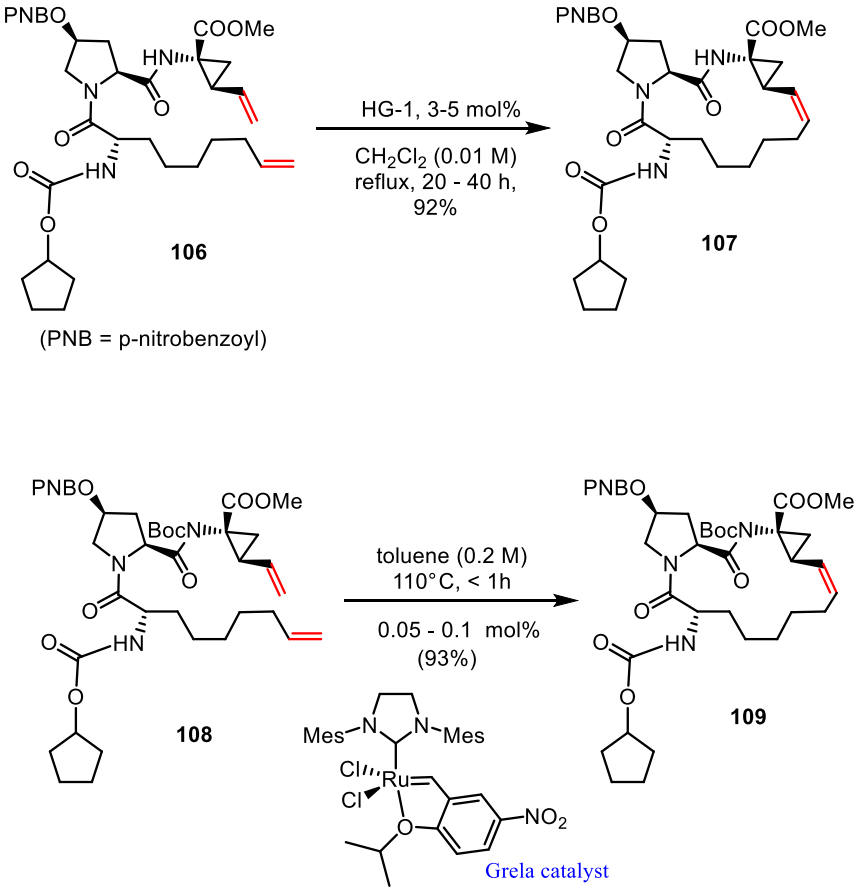
Scheme 16. Synthesis of the right-handed binding pocket of vancomycin by A. V. Ramarao

1.2.9. Scalable synthesis of macrocycles

One of the major issues regarding macrocyclic compounds is the difficulty in accessing these compounds in a necessary scale for advanced preclinical/clinical investigations. However, because of increase in attention on macrocyclic compounds, in recent times more research is going on this area and there are few reports in literature for scalable synthesis, one such example is synthesis of HCV protease inhibitor BILN 2061 (ciluprevir) by Boehringer Ingelheim pharmaceuticals.

The synthesis of ciluprevir, an HCV NS3/4A protease inhibitor was relied on the RCM based macrocyclization. In the first generation synthesis compound **106** was converted into compound **107** using HG-1 catalyst. The synthesis was done in 100 kg scale and yields were also promising. But, the synthesis required 3-5 mol% of costly HG-1 catalyst, high dilution (requires more solvent), and long reaction times 20 h, some times upto 40 h. To address these problems an additional study was carried out and second generation approach was developed. The compound **108** was synthesized by introducing a Boc protection on one of the amide and RCM was carried out by using modified ruthenium catalyst (Grela) to give compound **109**.[81] By using this second generation approach the reaction efficiency was improved significantly in terms consumption of

solvent (decreased from 0.01 to 0.2 M concentration), catalyst loading (3 -5 mol% to 0.05 - 0.1 mol%) and time (decreased from 20 h to <1 h) (Scheme 17). This example clearly demonstrates that macrocyclizations can be done in a large scale.



Scheme 17. Process improvement for ciluprevir intermediate

1.3. Conclusions

Macrocycles have been playing an important role in drug discovery. There are several macrocyclic compounds that are marketed as drugs and many are in clinical trials. Macrcocylization makes a molecule conformationally restricted which helps the molecule to bind to the target with greater affinity, which in turn may help in improving the potency, physicochemical and ADME properties. Despite many benefits of macrocyclic compounds in drug discovery, this class of compounds was underexplored because of the difficulties in developing an efficient synthetic route for the macrocyclization. However,

in recent years, enormous studies in this field led to the development of several synthetic methodologies for the construction of macrocycle, which opened the way for further research in macrocycle based drug discovery. The new advancements in synthetic tools and deeper understanding of chemical biology including informatics encouraged many medicinal chemists/drug discovery scientists to take up macrocyclic structures as valuable scaffolds for their programs. Along these lines, our research group also got attracted to this field of exciting research and we have identified the solomonamide scaffold as a working platform.

1.4. References

1. D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2016, **79**, 629.

2. F. Giordanetto and J. Kihlberg, *J. Med. Chem.,* 2014, **57**, 278.

3. Selected publications related to importance of macrocycles in drug discovery.(a) EM. Driggers, S. P. Hale, J. Lee, and N. K. Terrett, *Nat. Rev. Drug Discov.*, 2008, **7**, 608. (b) A. K. Oyelere, *Curr. Top. Med. Chem.* 2010, **10**, 1359. (c) E. Marsault, M. L., *J. Med. Chem.* 2011, **54**, 1961. (d) J. Mallinson, and I. Collins, *Future Med. Chem.,* 2012, **4**, 1409. (e) X. Yu and D. Sun., *Molecules,* 2013, **18**, 6230. (f) D. J. Newman, and G. M. Cragg, *RSC Macrocyclies in drug discovery*, Chapter 1, pp 1-34, 2014. (g) V. Martí-Centelles, M. D. Pandey, M. I. Burguete, and S. V. Luis, *Chem. Rev.*, 2015, **115**, 8736.

4. H. Svarstad, H. C. Bugge and S. S. Dhillion, *Biodiversity and Conservation,* 2000, **9**, 1521.

5. Abbott Laboratories. Erythrocin stearate (erythromycin stearate) tablets prescribing information (dated 2000 Nov). In Physicians' desk reference. 56th ed. Montvale, NJ: Medical Economics Company Inc; 2002:452-4.

6. S. Goodin, *Am. J. HealthSyst. Pharm.,* 2008, **65**, S10.

7. (a) F. P. Tally, and M. F. DeBruin, *J Antimicrob Chemother.*, 2000, **46,** 523. (b) PG. Charles, and ML Grayson, *Med J Aust.* 2004, **181**, 549.

8. T. J. Walsh, E. J. Anaissie, and D. W. Denning., *Clin Infect Dis*., 2008, **46**, 327.

9. S. C. Deresinski, and D. A. Stevens, *Clin Infect Dis.,* 2003, **36,** 1445.

10. P. G. Pappas, C. M. Rotstein, R. F. Betts, M. Nucci, D. Talwar, J. J. De Waele, J. A. Vazquez, B. F. Dupont, D. L. Horn, L. Ostrosky-Zeichner, A. C. Reboli, B. Suh, R. Digumarti, C. Wu, L. L. Kovanda, L. J. Arnold, and D. N. Buell, *Clin Infect Dis.*, 2007, **45**, 883.

11. B. R. Allen, M. Lakhanpaul, A. Morris, S. Lateo, T. Davies, G. Scott, M. Cardno, M. E. Ebelin, P. Burtin, and T. J. Stephenson, *Arch Dis Child.*, 2003, **88,** 969.

12. C. Liu, A. Bayer, S. E. Cosgrove, R. S. Daum, S. K. Fridkin, R. J. Gorwitz, S. L. Kaplan, A. W. Karchmer, D. P. Levine, B. E. Murray, M. Rybak, D. A. Talan, H. F. *Clin Infect Dis.*, 2011, **52**, 285.

13. (a) Oxford Handbook of Infectious Diseases and Microbiology. OUP Oxford. 2009. p. 56. ISBN 978-0-19-103962-1. (b) McHugh, Timothy D. (2011). Tuberculosis: diagnosis and treatment. Wallingford, Oxfordshire: CABI. p. 219. ISBN 978-1-84593-807-9.

14. K. D. Clay, J. S. Hanson, S. D. Pope, R. W. Rissmiller, P. P. Purdum, and P. M. Banks, *Ann Intern Med.*, 2006, **144**, 415.

15. http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf

16. L. Aspeslet, D. Freitag, D. Trepanier, M. Abel,S. Naicker, N. Kneteman, R.Foster, and R. Yatscoff, *Transplant. Proc.* 2001, **33**, 1048.

17. DS. Krause, J. Reinhardt, JA. Vazquez, A. Reboli, BP. Goldstein, M. Wible, and T. Henkel, *Antimicrob Agents Chemother.*, 2004, **48,** 2021.

18. A. D. William, A. C.-H Lee, S.Blanchard, A. Poulsen, E. L. Teo,H. Nagaraj, E.Tan,D. Chen, M. Williams, E. T. Sun, K. C. Goh, W. C. Ong, S. K. Goh, S. Hart, R.Jayaraman, M. K. Pasha, K. Ethirajulu, J. M. Wood and B. W. Dymock, *J. Med. Chem.*, 2011, **54**, 4638.

19. J. G. Still, J. Schranz, T. P Degenhardt, D. Scott, P. Fernandes, M. J. Gutierrez and K. Clark,*Antimicrob. Agents Chemother.*, 2011, **55**, 1997.

20. V. Summa, S. W. Ludmerer, J. A. McCauley, C. Fandozzi, C. Burlein, G. Claudio, P. J. Coleman, J. M. DiMuzio, M. Ferrara, M. Di Filippo, A. T. Gates, D. J. Graham, S. Harper, D. J.Hazuda, C. McHale, E.Monteagudo, V. Pucci, M. Rowley, M. T. Rudd, A.

Soriano, M. W. Stahlhut, J. P. Vacca, D. B. Olsen, N. J. Liverton, and S. S Carroll, *Antimicrob. Agents Chemother.*, 2012, **56**, 4161.

21. S. Vendeville, T. I. Lin, L. Hu, A. Tahri, D. McGowan, M. D. Cummings, K.Amssoms, M. Canard, S. Last, I. Van den Steen, B. Devogelaere, M. C. Rouan, L. Vijgen, J. M Berke, P. Dehertogh, E. Fransen, E. Cleiren, L. Van der Helm, G. Fanning, K. Van Emelen, O. Nyanguile, K. Simmen and P. Raboisson, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4437.

22. S. Hopkins, B. DiMassimo, P. Rusnak, D. Heuman, J. Lalezari, A. Sluder, B.Scorneaux, S. Mosier, P. Kowalczyk, Y. Ribeill, J. Baugh and P. J. Gallay, *Hepatol.*, 2012, **57**, 47.

23. S. E. Burke, R. E. Kuntz, and L. B. Schwartz, *Adv. Drug Delivery Rev.* 2006, **58**, 437.

24. (a) M. M Mita, A. C. Mita, Q. S. Chu, E. K. Rowinsky, G. J. Fetterly, M. Goldston, A. Patnaik, L. Mathews, A. D. Ricart, T. Mays, H. Knowles, V. M. Rivera, J. Kreisberg, C. L. Bedrosian, and A. W. Tolcher, *J. Clin. Oncol.* 2008, **26**, 361. (b) G. J. Fetterly, M. M. Mita, C. D. Britten, E. Poplin, W. D. Tap, A. Carmona, L. Yonemoto, C. L. Bedrosian, E. H. Rubin, and A. W. Tolcher, *J. Clin. Oncol.* 2008, **26**, 14555.

25. I. R. H. M. Konings, M. J. A. de Jonge, H. Burger, A. van der Gaast, L. E. C van Beijsterveldt, H. Winkler, J. Verweij, Z. Yuan, P. Hellemans, and F. A. L. M. Eskens, *Br. J. Cancer.*, 2010, **103**, 987.

26. Eisai Pharmaceuticals Annual Report 2003, pp 18

27. P. A. Wender, J. L. Baryza, S. E. Brenner, M. O. Clarke, M. L. Craske, J. C. Horan and T. Meyer, *Curr. Drug Discovery Technol.*, 2004, **1**, 1.

28. K. Nicholas, *Innovations in Pharmaceutical Technology*, 2014, **51,** 26.

29. Z-F. Tao, L. Wang, K. D. Stewart, Z. Chen, W. Gu, Mai-Ha Bui, P. Merta, H. Zhang, P. Kovar, E. Johnson, C. Park, R. Judge, S. Rosenberg, T. Sowinand and N.-H. Lin, *J. Med. Chem.*, 2007, **50**, 1514.

30. M. D. Cummings, T-I Lin, L. Hu, A. Tahri, D. McGowan, K. Amssoms, S. Last, B. Devogelaere, M.-C Rouan, L. Vijgen, J. M. Berke, P. Dehertogh, E. Fransen, E. Cleiren, L. Helm, G. Fanning, K. Van Emelen, O. Nyanguile, K. Simmen, P. Raboisson, and S. Vendeville, *Angew. Chem.*, 2012, **124**, 4715 and referances cited therein.

31. S. Harper, S. Avolio, B. Pacini, M. Di Filippo, S. Altamura, L. Tomei, G. Paonessa, S. Di Marco, A. Carfi, C. Giuliano, J. Padron, F. Bonelli, G. Migliaccio, R. D. Francesco, R. Laufer, M. Rowley, and F. Narjes, *J. Med. Chem.* 2005, **48**, 4547.

32. Selected publication for macrocylization. (a) C. M. Madsen and M. H. Clausen, *Eur. J. Org. Chem.* **2011**, 3107. (b) X. Yu and D. Sun, *Molecules* 2013, **18**, 6230. (C) D. J. Newman, and G. M. Cragg, *RSC Macrocyclies in drug discovery*, Chapter 11, pp 398-486, 2014 and referances cited therein.

33. (a) A. Parenty, X. Moreau, G. Niel and J. M. Campagne, *Chem. Rev.* 2013, **113**, PR1. (b) E. J.Corey and K. C. Nicolaou, *J. Am. Chem. Soc.* 1974, **96**, 5614. (c) C. Palomo, M. Oiarbide, J. M García, A. González, R. Pazos, J. M. Odriozola, P. Bañuelos, M. Tello, and A. Linden, *J. Org. Chem.*, 2004, **69**, 4126.

34. G. Stork and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 1987, **109**, 1565.

35. J. García-Fortanet, J. Murga, M. Carda and J. A. Marco, *Org. Lett.*, 2006, **8**, 2695.

36. J. I. Luengo, A. Konialian-Beck, M. A. Levy, M. Brandt, D. S. Eggleston and D. A. Holt, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 321.

37. I. Paterson, G. J. Naylor, N. M. Gardner, E. Guzman and A. E. Wright, *Chem. - Asian J.*, 2011, **6**, 459.

38. B. Seetharamsingh, P. V. Khairnar, and D. S. Reddy, *J. Org. Chem.* 2016, **81**, 290.

39. A. El-Faham and F. Albericio, *Chem. Rev.*, 2011, **111**, 6557.

40. H. Kaur, A.M. Heapy and M. A. Brimble *Synlett*, 2012, **23**, 2284.

41. (a) G. M. Ksander, R. de Jesus, A. Yuan, R. D. Ghai, A. Trapani, C. McMartin and R. Bohacek, *J. Med. Chem.*, 1997, **40**, 495. 17. (b) G. M. Ksander, R. de Jesus, A. Yuan, R. D. Ghai, C. Mc Martin and R. Bohacek, *J. Med. Chem.*, 1997, **40**, 506.

42. (a) M. N. Greco, E. T. Powell, L. R. Hecker, P. Andrade-Gordon, J. A. Kauffman, J. M. Lewis, V. Ganesh, A. Tulinsky and B. E. Maryanoff, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2947.(b) P. G. Nantermet, J. C. Barrow, C. L. Newton, J. M. Pellicore, M. Young, S. D. Lewis, B. J. Lucas, J. A. Krueger, D. R. McMasters, Y. Yan, L. C. Kuo, J. P. Vacca and H. G. Selnick, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2781.

43. (a) V. Ardi, L. Alexander, V. Johnson and S. R. Mc Alpine, *ACS Chem. Bio*., 2011, **6**, 1357. (b) J. B. Kunicki, M. N. Petersen, L. D. Alexander, V. C. Ardi, J. R. McConnell, S. R. McAlpine, *Bioorg. Med. Chem. Lett.,* 2011, **21**, 4716.

44. Selected reviews for Palladium-Catalyzed Cross-Coupling Reactions in natural product synthesis (a) K. C. Nicolaou, P. G. Bulger, and D. Sarlah, *Angew. Chem. Int. Ed.* 2005, **44**, 4442, (b) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885.

45. J. Dufour, L. Neuville and J. Zhu, *Chem. - Eur. J.*, 2010, **16**, 10523.

46.T. C. Roberts, P. A. Smith, R. T. Cirz and F. E. Romesberg, *J. Am. Chem. Soc.*, 2007, **129**, 15830.

47. J. R. Cochrane, J. M. White, U. Wille, and C. A. Hutton, *Org. Lett.*, 2012, **14**, 2402.

48. T. Ogura, and T. Usuki, *Tetrahedron*, 2013, **69**, 2807.

49. K. Mahender Reddy, V. Yamini, K. K. Singarapu, and Subhash Ghosh, *Org. Lett.*,2014, **16**, 2658.

50. K. R. Prasad and A. B. Pawar, *Org. Lett.*, 2011, **13,** 4252.

51. P. Rajamohan Reddy, V. Balraju, G. R. Madhavan, B. Banerji and J. Iqbal, *Tetrahedron Lett.*, 2003, **44**, 353.

51. K. X. Chen, F. G. Njoroge, A. Prongay, J. Pichardo, V. Madison and V. Girijavallabhan, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4475.

53. (a) T. C. Boge, Z. J. Wu, R. H. Himes, D. G. Vander Velde and G. I. Georg, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3047. (b) X. Geng, M. L. Miller, S. Lin and I. Ojima, *Org. Lett.*, 2003, **5**, 3733.

54. M. A. J. Duncton and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1,* 1999, 1235.

55. T. Jyojima, N. Miyamoto, M. Katohno, M. Nakata, S. Matsumura, K. Toshima, *Tetrahedron Lett.*, 1998, **39**, 6007.

56. V. Balraju and J. Iqbal, *J. Org. Chem.*, 2006, **71**, 8954.

57. S. C. Philkhana,B. Seetharamsingh B, Y. B. Dangat, K.Vanka, and D. S. Reddy, *Chem. Commun*. 2013, **49**, 3342.

58. (a) R. H. Grubbs, S. J. Miller, and G. C. Fu, *Acc. Chem. Res.*, 1995, ***28***, 446. (b) A. Fürstner, *Angew. Chem. Int. Ed.* 2000, **39**, 3012. (c) R. R. Schrock, A. H. Hoveyda,

Angew. Chem. Int. Ed. 2003, **42**, 4592. (c) S. J. Connon, and S. Blechert, *Angew. Chem. Int. Ed.,* 2003, **42**, 1900. (d) A. Deiters, and S. F. Martin, *Chem. Rev.* 2004, 104, 2199. (e) A. Gradillas, and J. Pérez-Castells, *Angew. Chem. Int. Ed.* 2006, **45**, 6086. (f) B. Alcaide, P. Almendros, L. A. Grubbs' *Chem. Rev.* 2009, **109**, 3817. (g) H.M.A. Hassan, *Chem. Commun.,* 2010**, 46,** 9100.

59. J. A. Mc Cauley , C. J. McIntyre, M. T. Rudd,K. T. Nguyen, J. J. Romano, J. W. Butcher, K. F. Gilbert, K. J. Bush, M. K. Holloway, J. Swestock, B. –L. Wan, S. S.Carroll, J. M. DiMuzio, D. J. Graham, S. W. Ludmerer, S.-S. Mao, M. W. Stahlhut, C. M. Fandozzi, N. Trainor, D. B. Olsen, J.P. Vacca, and N. J. Liverton, *J. Med. Chem.,* 2010, **53**, 2443.

60. I. Ojima and M. Das, *J. Nat. Prod.,* 2009, **72**, 554.

61. (a) J. E. Day, S. Y. Sharp, M. G. Rowlands, W. Aherne, P. Workman and C. J. Moody, *Chem. - Eur. J.,* 2010, **16**, 2758. (b) J. E. Day, S. Y. Sharp, M. G. Rowlands, W. Aherne, A. Hayes, F. I. Raynaud, W. Lewis, S. M. Roe, C. Prodromou, L. H. Pearl, P. Workman and C. J. Moody, *ACS Chem. Biol.,* 2011, **6**, 1339.

62.. S. Y. Kang, M. J. Kim, J. S. Lee and J. Lee, *Bioorg. Med. Chem. Lett.,* 2011, **21**, 3759.

63. (a) A. D. William, A. C. Lee, K. C. Goh, S. Blanchard, A. Poulsen, E. L. Teo, H. Nagaraj, C. P. Lee, H. Wang, M. Williams, E. T. Sun, C. Hu, R. Jayaraman, M. K. Pasha, K. Ethirajulu, J. M. Wood and B. W. Dymock, *J. Med. Chem.,* 2012, **55**, 169. (b) A. Poulsen, A. William, S. Blanchard, H. Nagaraj, M. Williams, H. Wang, A. Lee, E. Sun, E. L. Teo, E. Tan, K. C. Goh and B. Dymock, *J. Mol. Model.,* 2013, **19**, 119.

64. (a) A. D. William, A. C. Lee, S. Blanchard, A. Poulsen, E. L. Teo, H. Nagaraj,E. Tan, D. Chen, M. Williams, E. T. Sun, K. C. Goh, W. C. Ong,S. K. Goh, S. Hart, R. Jayaraman, M. K. Pasha, K. Ethirajulu, J. M. Wood and B. W. Dymock, *J. Med. Chem.,* 2011, **54**, 4638. (b) A. Poulsen, A. William, S. Blanchard, A. Lee, H. Nagaraj, H. Wang,E. Teo, E. Tan, K. C. Goh and B. Dymock, *J. Comput.-Aided Mol. Des.*,2012, **26**, 437.

65. A. D. William, A. C. Lee, A. Poulsen, K. C. Goh, B. Madan, S. Hart, E. Tan, H. Wang, H. Nagaraj, D. Chen, C. P. Lee, E. T. Sun, R. Jayaraman, M. K. Pasha, K.

Ethirajulu, J. M. Wood and B. W. Dymock, *J. Med. Chem.,* 2012, **55**, 2623.

66. H. Toya, K. Okano, K. Takasu, M. Ihara, A. Takahashi, H. Tanaka, and H. Tokuyama, *Org. Lett.,* 2010, **12**, 5196.

67. (a) G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba and A. A. Genazzani, *Med. Res. Rev.,* 2008, 28, 278. (b) C. Hein, X.-M. Liu and D. Wang, *Pharm. Res.,* 2008, **25**, 2216. (c) P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.,* 2013,**113**, 4905.

68. (a) Y. L. Angell and K. Burgess, *Chem. Soc. Rev.,* 2007, **36**, 1674. (b) J. M. Holub and K. Kirshenbaum, *Chem. Soc. Rev.,* 2010, **39**, 1325.

69. M. Nahrwold, T. Bogner, S. Eissler, S. Verma, and N. Sewald, *Org. Lett.,* 2010, **12,** 1064.

70. A. D. Pehere and A. D. Abell, *Org. Lett.,* 2012, **14**, 1330.

71. W. S. Horne, C. A. Olsen, J. M. Beierle, A. Montero and M. R. Ghadiri, *Angew. Chem., Int. Ed.,* 2009, **48**, 4718.

72. J. M. Beierle, W. S. Horne, J. H. van Maarseveen, B. Waser, J. C. Reubi and M. R. Ghadiri, *Angew. Chem., Int. Ed.,* 2009, **48**, 4725.

73. J. Tilley, G. Kaplan, N. Fotouhi, B. Wolitzky and K. Rowan, *Bioorg. Med.Chem. Lett.,* 2000, **10**, 1163.

74. K. C. K. Swamy, N. N. B. Kumar, E. Balaraman and K. V. P. P. Kumar,*Chem. Rev.,* 2009, **109**, 2551.

75. G. N. Raut, K. Chakraborty, P. Verma, R. S. Gokhale, and D. S. Reddy, *Tetrahedron Lett.,* 2012, **53,** 6343.

76. A. Arasappan, K. X. Chen, F. G. Njoroge, T. N. Parekh and V. Girijavallabhan, *J. Org. Chem.,* 2002, **67**, 3923.

77. A. Arasappan, F. G. Njoroge, K. X. Chen, S. Venkatraman, T. N. Parekh, H. Gu, J. Pichardo, N. Butkiewicz, A. Prongay, V. Madison and V. Girijavallabhan, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 3960. (c) K. X. Chen, F. G. Njoroge, J. Pichardo, A. Prongay, N. Butkiewicz, N. Yao, V. Madison and V. Girijavallabhan, *J. Med. Chem.,* 2006, **49**, 567.

78. R. Beugelmans, J. Zhu, N. Husson, M. B. Choussy and G. P. Singh *J. Chem. Soc., Chem,Commun.,* 1994, 439.

79. A.V. Rama Rao, *Pure and Appl. Chem*. 1998, **70**, 391.

80. (a) D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, and J. L. Katz, *Angew. Chem. Int. Ed.* 1998, **37**, 2700. (b) K. C. Nicolaou, C. N. C. Boddy, S. Natarajan, T.-Y. Yue, H. Li, S. Bra¨se, and J. M. Ramanjulu, *J. Am. Chem. Soc.* 1997, **119**, 3421.

81. V. Farina, C. Shu, X. Zeng, X. Wei, Z. Han, N. K. Yee and C. H. Senanayake, *Org. Process Res. Dev.*, 2009, **13**, 250.

Section 2

Studies toward Total Synthesis of Solomonamides A and B

2.1. Introduction

2.1.1. Isolation and structural elucidation of solomonamides

Theonella swinhoei, a marine sponge which belongs to Lithistida order sponges (Figure 1) is a rich source of biologically active compounds for many years, which include potent cytotoxic complex polyketides such as swinholide A and misakinolide A,[1] antifungal aurantosides,[2] sterols (swinhosterols, theonellasterols, solomonsterol A & B).[3] Peptides are most significant among the bioactive metabolites of *Theonella swinhoei*. Acyclic peptides such as polytheonamides,[4] koshikamides A1 and A2,[5] cyclic peptides, such as cyclotheonamides,[6] ombamide,[7] orbiculamide,[8] keramamides,[9] cupolamide,[10] oriamide[11] large-ring bicyclic peptides, such as theonellamides[12] depsipeptides headed by theonellapeptolides,[13] koshikamides A and B,[14] nagahamide[15] and glycopeptides,[16] and perthamides C-F[17] (Figure 2). The extraordinary chemical diversity found in the metabolites of *Theonella* sponges may be partly due to the biosynthetic capability of bacteria that this sponge host. This hypothesis also has been supported in the case of omnamides, swinholide A, and theopederins.

Taxonomy

Kingdom: Animalia
Phylum : Porifera
Class : Demospongiae
Order : Lithistida
Family : Theonellidae
Genus : Theonella

Image source: http://www.dafni.com/spongia/Theonella_Levin_Large.jpg

Figure 1. *Theonella swinhoei*

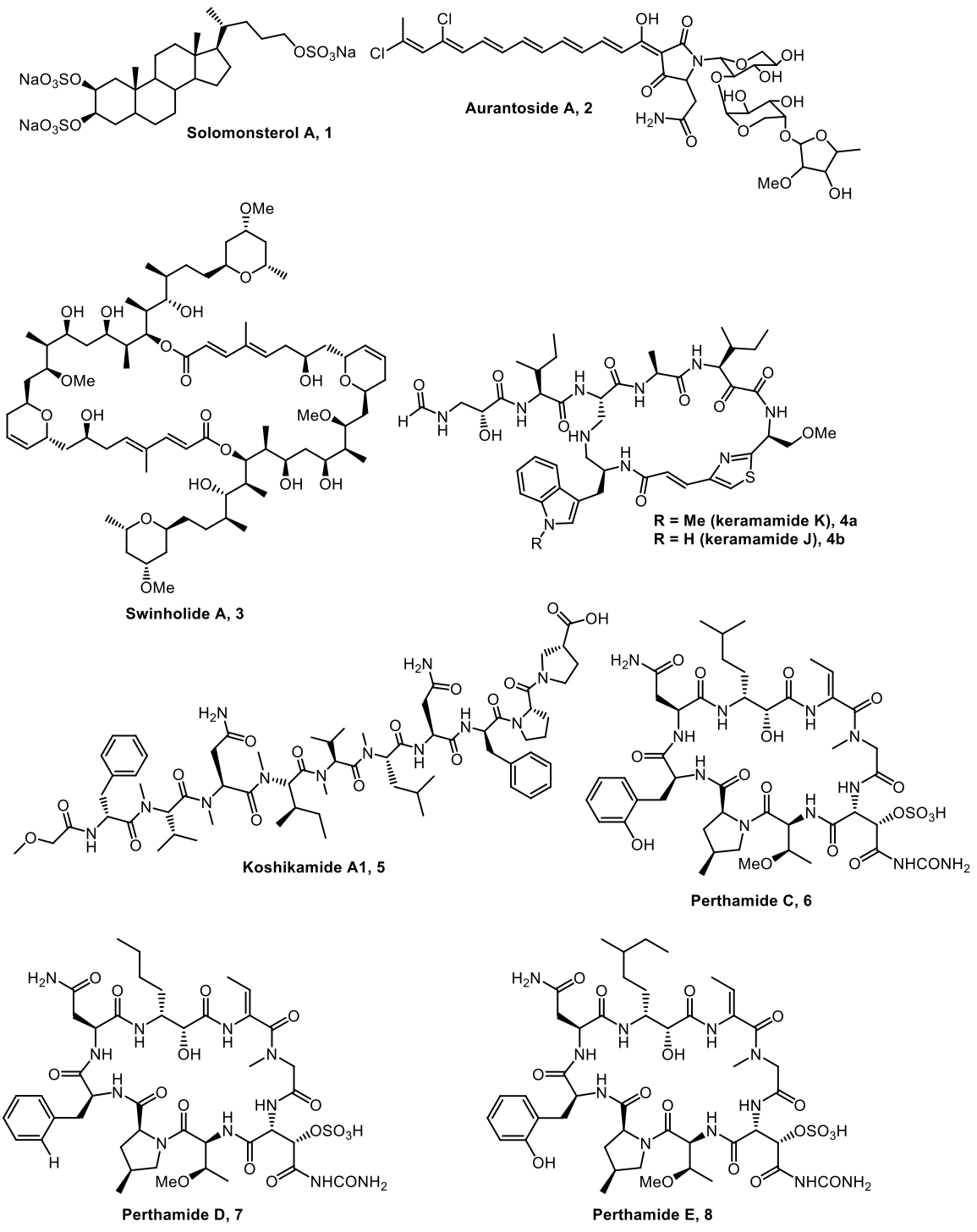


Figure 2. Selected compounds isolated from *Theonella sp.*

Solomonamides A and B were isolated from *Theonella swinhoei* in early 2011 (collected from Solomon Islands), by Zampella's group from Italy (Figure 3).[18a] Both the compounds were obtained by HPLC purification on a C-12 Jupiter proteo column with 20% MeOH/H_2O + 0.1% of TFA as eluent. Solomonamide A was obtained in 6.2 mg as a white amorphous solid ($[\alpha]^{25}_D$ + 2.3° (c 0.17, CH_3OH)) and solomonamide B was obtained in 3.6 mg as white amorphous solid ($[\alpha]^{25}_D$ + 4.8° (c 0.28, CH_3OH)).

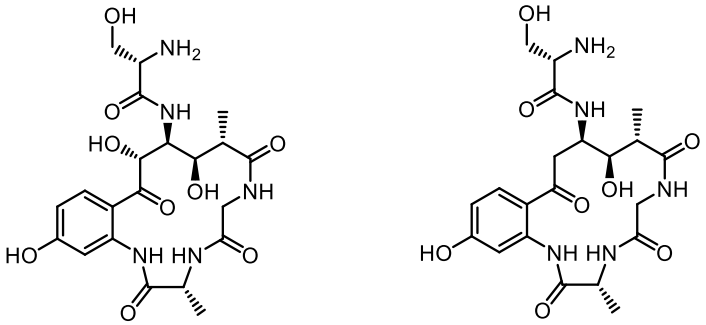
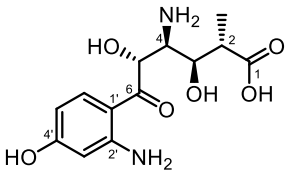
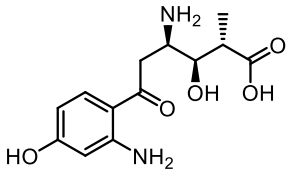


Figure 3. Structures of solomonamides A and B

The gross structures of solomonamides were established by Marfey's method and advanced NMR spectroscopic methods. By Marfey's method, it was confirmed that both natural products contain amino acids L-Serine, D-Alanine, and Glycine. The non-amino acid fragment of solomonamide A was established by extensive 2D NMR studies and defined as 4-amino (2'-amino-4'-hydroxyphenyl)-3, 5-dihydroxy-2-methyl-6-oxohexanoic acid **11** (ADMOA). The most challenging task of stereochemical assignment of the non-peptide unit of these compounds was carried out by QM *J* based analysis and DFT $J/^{13}C$ calculations. The HR-ESIMS of solomonamide B was 16 mass units lower than solomonammide A and comparison of 2D NMR data of the both the compounds revealed that in solomonamide B there is a methylene group at the C-5 position of non-amino acid partner. Hence, the residue was named as 4-amino-6-(2'-amino-4'-hydroxyphenyl) -3-hydroxy-2-methyl-6-oxohexanoic acid **12** (AHMOA) (Figure 4).



ADMOA, 11
4-amino(2' -amino-4' -hydroxyphenyl) -3,5 -dihydroxy-2-methyl-6-oxohexanoic acid



AHMOA, 12
4-amino-6-(2' -amino-4' - hydroxyphenyl) -3-hydroxy-2-methyl-6-oxohexanoic acid

Figure 4. Non-amino acid portions (key fragments) in solomonamide A and solomonamide B.

2.1.2 Biological activity of solomonamides

Solomonamide A showed potent anti-inflammatory activity in carrageenan induced mouse paw edema model. It was administrated immediately before the injection of carrageenan and after 24 h and paw volume was measured immediately before the injection and 2, 4, 6, 24, 48, 72 and 96 h thereafter, by using an hydropletismometer. The increase in paw volume was calculated (the difference between the paw volume measured at each time point and the basal paw edema). Solomonamide A was injected in three different doses 30, 100, 300 µg/kg or vehicle (PEG) and it was observed that it

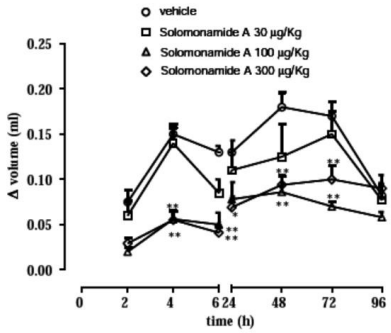


Image source: Adapted with permission from (*Org. Lett*. 2011, 13, 1532; SI). Copy right (2011)

Figure 5. Dose-dependent inhibition of carrageenan-induced paw edema by solomonamide A[18a]

significantly reduced carrageenan-induced paw edema both in the 0-6 h and in 24-96 h as shown in Figure 5. A 60% reduction of edema was observed in mice at the dose of 100 μg/kg (i.p.). However, the closely related solomonamide B could not be tested due to the unavailability of natural product.

2.2. Inflammation

Inflammation is a protective response of our body to any external stimuli. It can be a response of the body to a damage or immune process. When a damage or wound takes place inflammation initiates the healing process, so it is a necessary process for the body. The process of inflammation need to be in control, otherwise, it can lead to severe consequences called inflammatory disorders, which comprises various diseases like asthma, allergies, autoimmune disorders, atherosclerosis, cancers, and rheumatoid arthritis. Inflammation is broadly classified into two types.

1. Acute inflammation: It is the immediate response of tissue to damage or injury. Acute inflammation is usually of short duration and occurs before the immune response is established. The primary aim of acute inflammation is to remove the injurious agent. It is often resolved shortly on its own but sometimes turns into chronic inflammation.

2. Chronic inflammation: Persistent infection for a prolonged time (weeks or months) leads to chronic inflammation. This can be caused by physical injury, infections like bacterial, viral, burns, chemical irritants, and many others. The main signs of inflammation are increased heat, redness, pain, swelling, and loss of function. There are many cells (Leukocytes, Monocytes, etc.) and proteins (bradykinin, plasmin, thrombin, factor XII etc.) involved in inflammation. Factors like Histamines, Nitric oxide (NO), prostaglandins, TNF-alpha, IL-1, IL-8, IFN-γ are also involved in mediating the inflammation.[19]

There are two types of medications available to treat inflammatory diseases.

1. Steroids
2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

As the inflammation is responsible for several diseases listed above, working on anti-inflammatory compounds will help to come up with new drug leads which can be further optimized and developed into drug candidates. Considering the potent biological activity and interesting structural features, total synthesis of solomonamides was initiated in our research group to come up with novel anti-inflammatory agents.

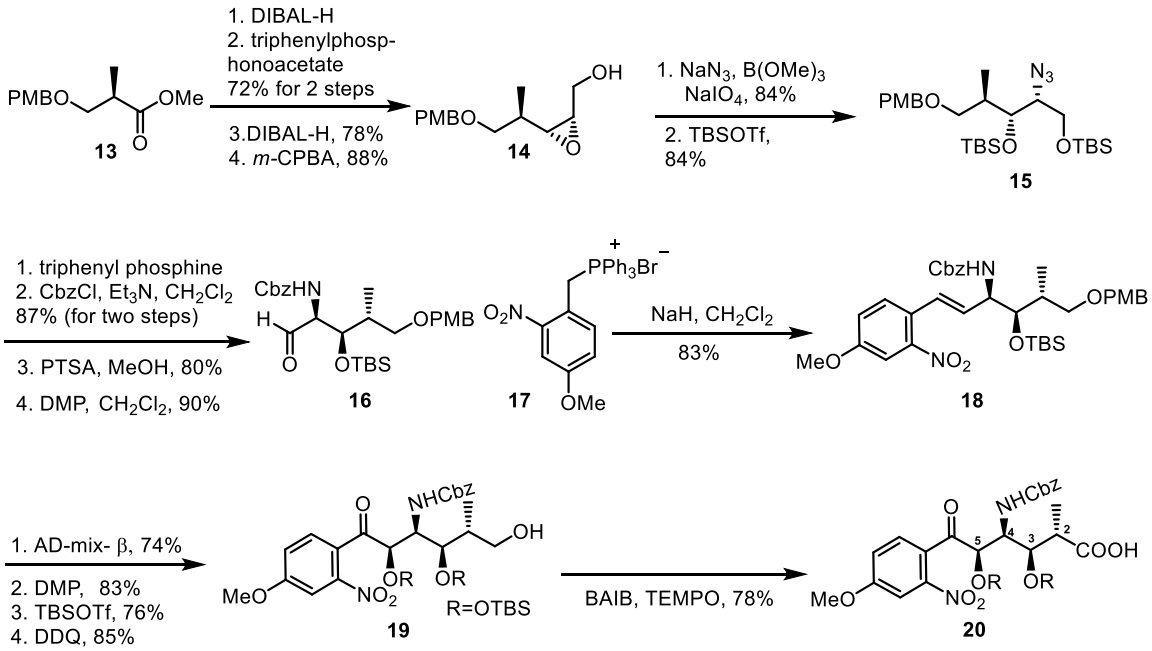
2.3. Reported approaches towards synthesis of solomonamide A

Solomonamides A and B were highlighted as part of a "Hot off the press" natural products review published by the Royal Society of Chemistry (RSC) in the month May, 2011 which indicates the importance of these molecules.[18b] The tremendous potential of solomonamides in treating inflammatory diseases prompted many synthetic groups, including our group to synthesize and evaluate them using appropriate biological assays. Although no total synthesis is reported till date, apart from reports from our lab[20a-d] there are only two approaches reported from Chandrasekhar group[20e,f] towards total synthesis. Before going to our work on this project, here we describe the efforts of Chandrasekhar group.

S. Chandrasekhar group approach

Immediately after the first publication from our group on the efforts towards total synthesis, Chandrasekhar group at the CSIR-Indian Institute of Chemical Technology, India, reported the synthesis of unusual γ-amino acid part of solomonamide A in the fully protected form.[20e] Their synthesis commenced from PMB- protected *R*-Roche ester **13**, which was converted to epoxide **14** using simple functional group transformations. The epoxide **14** was opened regioselectively with NaN_3 followed by protection of alcohol as TBS afforded compound **15**, with three required stereocentres. Reduction of azide to amine (Staudinger conditions), after a few protection and deprotection steps and oxidation of one of the primary alcohol to aldehyde (DMP) afforded fragment **16**. The aldehyde compound **16** was treated with Wittig salt **17** under basic conditions to afford compound **18** as 7:3 *E*/*Z* diastereomeric mixture in 83% yields. The major *E*-

diastereomer was subjected to Sharpless asymmetric dihydroxylation using AD mix-β to afford dihydroxy compound followed by selective oxidation of benzylic alcohol using DMP, protection of remaining alcohol as TBS and removal of PMB gave compound **19** with all the four requisite stereocenters. Oxidation of primary alcohol in compound **19** to acid using Epp and Widlanski protocol (BAIB, TEMPO, CH_3CN) under neutral conditions resulted in desired unusual amino acid **20** in good yields.

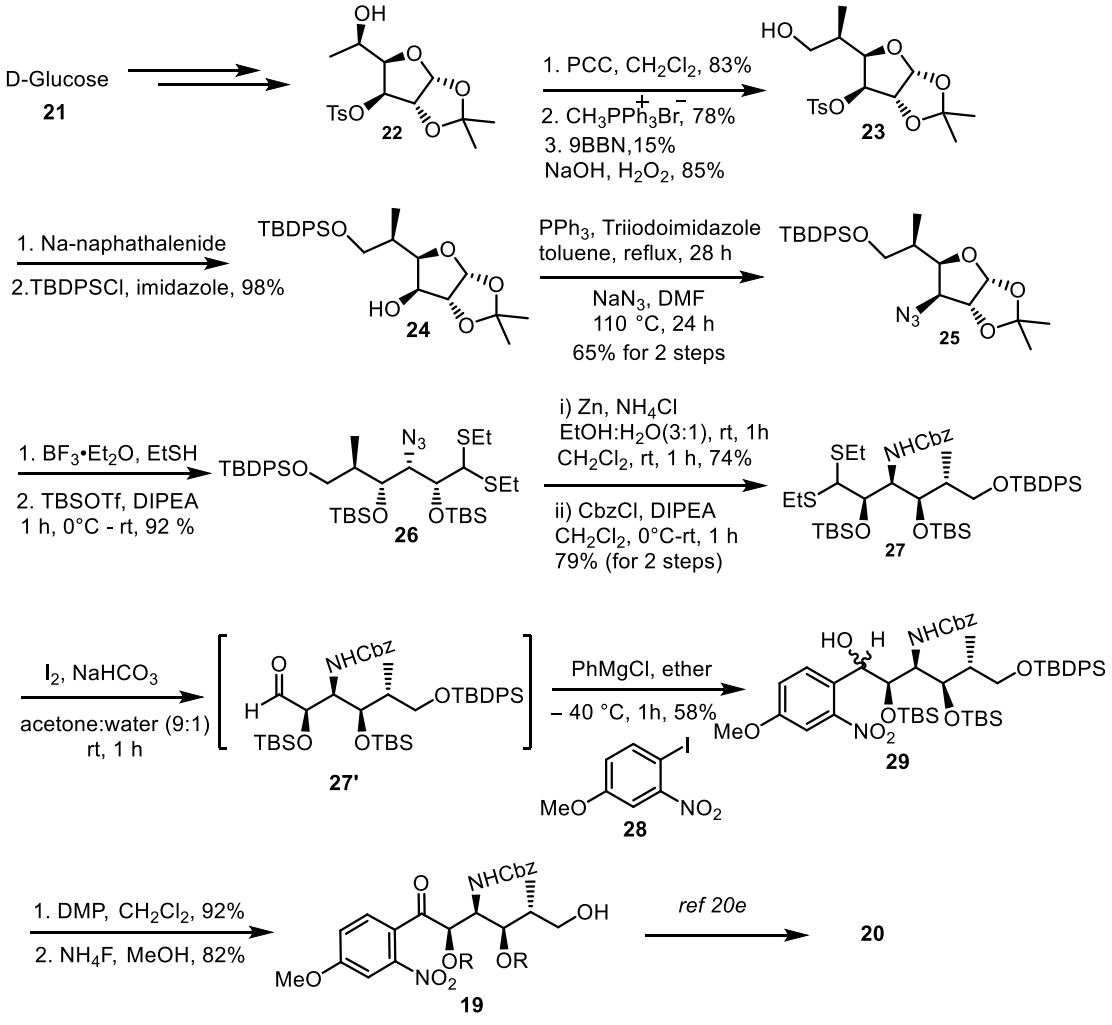


Scheme 1. Synthesis of ADMOA

In summary, Chandrasekhar group accomplished the synthesis of ADMOA, an unusual γ-amino acid fragment of solomonamide A in protected form. The synthesis was accomplished in 15 steps. The methyl stereocenter at C2 was obtained from *R*-Roche ester, amino alcohol at C3 and C4 were introduced by regioselective opening of epoxide with NaN_3, and the remaining hydroxy group at C5 was installed by Sharpless asymmetric dihydroxylation.

Very recently, Chandrasekhar group reported another approach[20f] for the synthesis of the same ADMOA fragment starting from D-glucose. In this route, the synthesis commenced from known furanose derivative **22** synthesized from D-Glucose, **21** by using literature

procedures. The alcohol in **22** was oxidized (PCC) to methyl ketone followed by one carbon homologation of the compound and diastereoselective hydroboration of the olefin in the presence of 9-BBN furnished furano alcohol **23**, with 20:1 *de* in favor of the required isomer. The tosyl group at the 3′ position in **23** was removed using Na-naphthalenide to give the diol followed by selective protection of the primary alcohol as TBDPS ether gave **24** in good yields. The alcohol in compound **24** was converted into azide compound **25** using a double inversion technique. The opening of 1,2-*O*-isopropylidene furan in **25** with EtSiH using $BF_3 \cdot OEt_2$ followed by protection of alcohol groups as TBS ether gave compound **26**. The Reduction of azide to amine (Zn/NH_4Cl)



Scheme 2. Second approach for the synthesis of ADMOA fragment

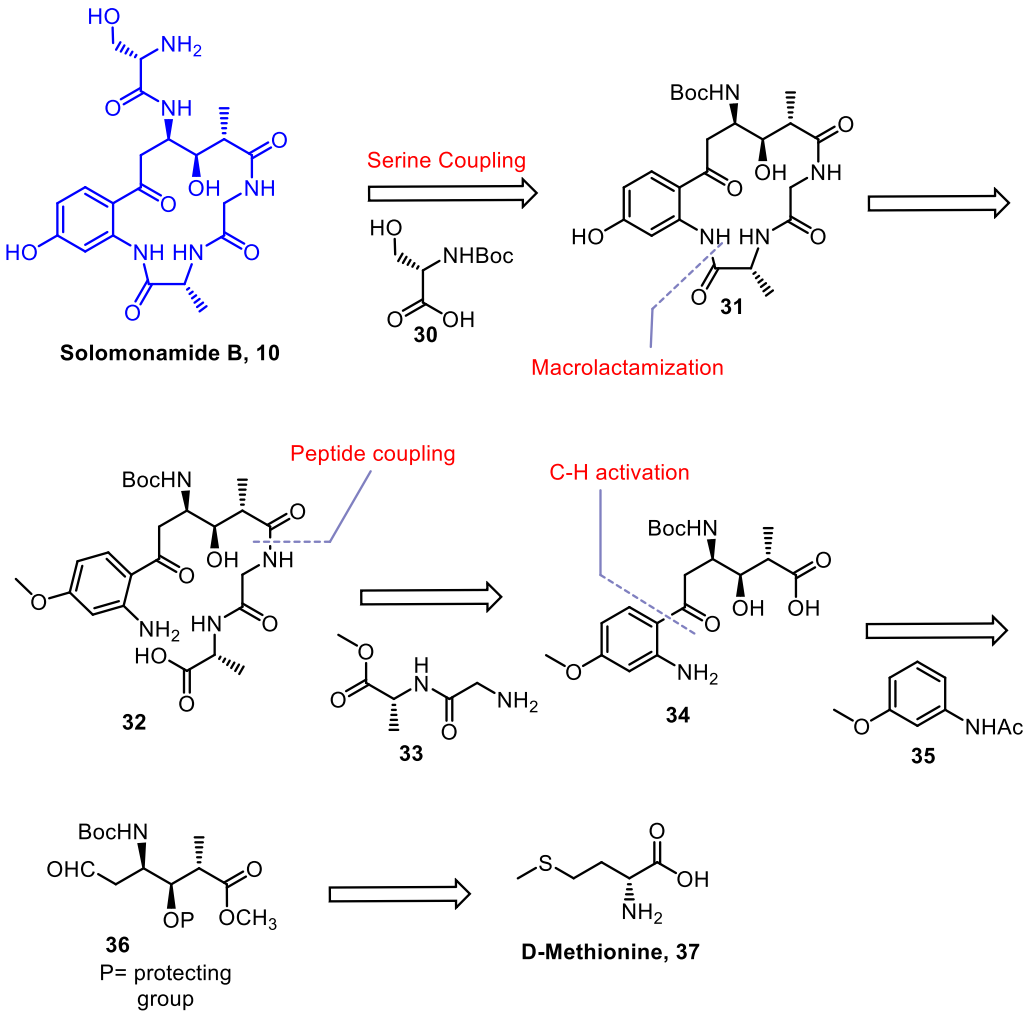
followed by treatment with Cbz–Cl gave the compound **27** in good yields. The dithiane compound **27** was treated with I_2/$NaHCO_3$ to release free aldehyde **27'** which underwent Grignard reaction with nitro aryl iodide **28** in the presence of PhMgCl (metal–halogen exchange) to furnish the diastereomeric alcohol **29** in 58% yield. Oxidation of **25** using Dess–Martin periodinane (DMP) followed by selective deprotection of the TBDPS group with NH_4F in methanol gave the compound **19** which was reported earlier by the same group. The compound **19** was converted into acid compound **17** in a similar manner to their previous approach (Scheme 1). Thus, the authors completed another synthesis of ADMOA fragment using a different approach. The synthesis was of total 15 steps from known compound and it is scalable.

2.4. Present work

The importance of macrocyclic compounds in drug discovery, potent anti-inflammatory activity of solomonamides and novel chemotype with interesting structural features prompted us to choose this target for the total synthesis and analogs synthesis followed by biological evaluation. Initially, it was planned to synthesize solomonamide B considering that it was not evaluated biologically. Various approaches were followed for the total synthesis, which are depicted below in detail.

2.4.1. Approach 1: Macrolactamization at aniline –NH_2

The initial retrosynthetic analysis is compiled in Scheme 3. Solomonamide B, **10** was envisioned through pendant L-serine (**30**)[21a] coupling on macrocycle **31** in the end game. The macrocyclic compound could be obtained from the macrolactamization of amino acid **32**, which can be easily accessed from the coupling of the dipeptide NH_2-D-Ala-Gly-OMe (**33**)[21b] to non-amino acid fragment **34** which in turn could be accessed from *N*-acetyl *m*- anisidine **35** and key aldehyde fragment **36** using C-H activation reaction. The aldehyde **36** can be obtained from unnatural amino acid D-methionine (**37**) by functional group transformations.

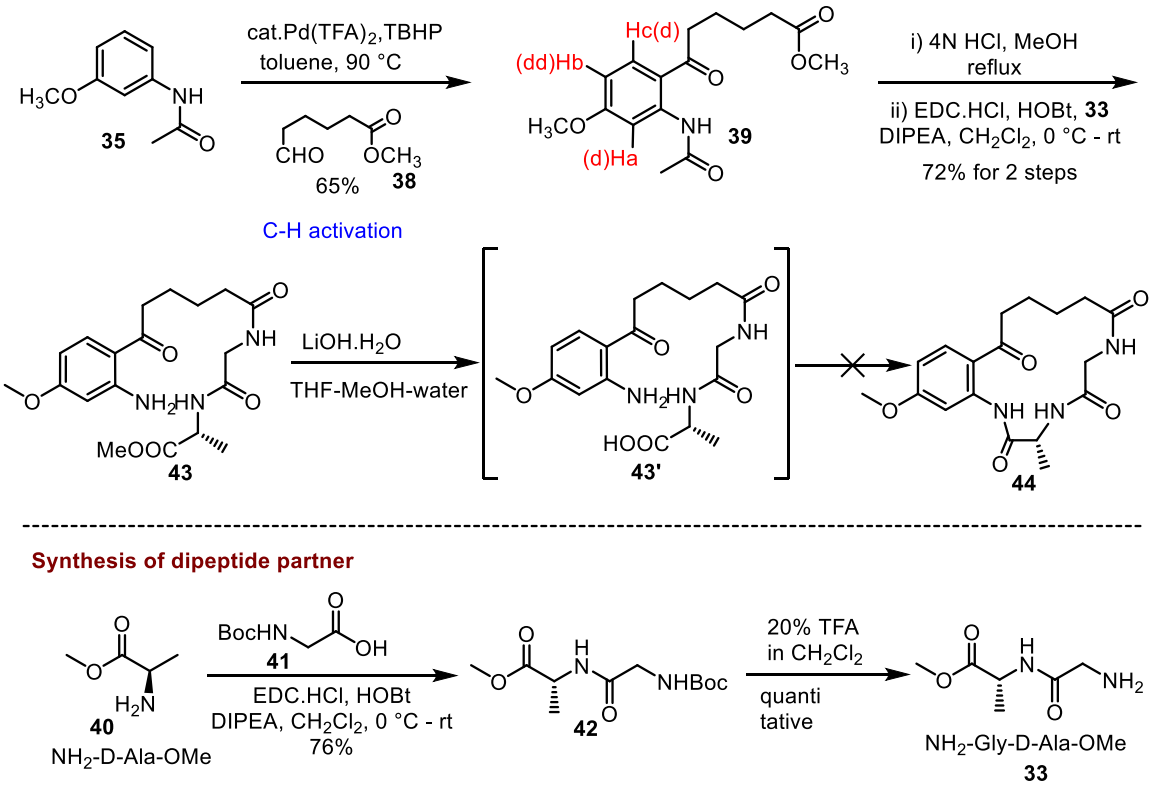


Scheme 3. Retrosynthesis of solomonamide B

Before embarking on the synthesis of the actual molecule, it was decided to explore the feasibility of the strategy, particularly the macrolactamization at aniline. Accordingly, synthesis commenced with C-H activation reaction on *N*-acetyl *m*-anisidine **35**,[22] with known aldehyde methyl 6-oxohexanoate **38**[23] using a method developed by Knowng and co-workers[24] to give desired keto compound **39** as a single regioisomer in 65% yield. Appearance of signals in the ^{13}C NMR spectrum at δ 202.7 ppm corresponding to benzylic –C=O and signals in the ^{1}H NMR spectrum at δ 3.01- 2.91 (m, 2H), 2.38-2.34 (m, 2H), 1.76 -1.65 (m, 4H) corresponding to aliphatic chain confirmed the formation of desired compound **39**. The regiochemistry of the obtained product was confirmed by the

coupling constants of the aromatic protons signals in the ^{1}H NMR spectrum at 8.42 (d, *J* = 2.7 Hz, 1Ha); *meta* coupling, 7.82 (d, *J* = 9.0 Hz, 1Hc); *ortho* coupling and 7.03 (dd, *J* = 2.7, 9.0 Hz, 1Hb); *ortho* and *meta* coupling. The coupling pattern supports the 1, 3, 5 substitution on the aromatic ring. In addition to this, the HRMS (ESI) analysis showed a peak at m/z 308.1491corresponding to $[M+H]^+$ with molecular formula $C_{16}H_{22}O_5N$ further confirmed the formation of the product **39.**

After having the required non-amino acid fragment in hand, both ester and acetyl groups were deprotected using 4N HCl in methanol under reflux conditions followed by coupling of dipeptide NH_2-Gly-D-Ala-OMe, **33** (synthesized from D-alanine ester, **40** and Boc-glycine **41** in a 2 step manner through the intermediacy of **42** by following literature procedures)[21] afforded compound **43**. The ester **43** on hydrolysis using LiOH gave macrocyclization precursor **43'** which was confirmed by the presence of a peak at m/z 380.1816 in HRMS (ESI) corresponding to $[M+H]^+$ with molecular formula



Scheme 4. Attempts toward the synthesis of macrocyclic skeleton of solomonamides

$C_{18}H_{26}O_6N_3$. The crude compound was subjected to macrolactamization under various conditions listed in Table1. But, attempts to synthesize the macrocyclic compound **44** were not successful (Scheme 4). This can be explained by the poor basicity or nucleophilicity of the aryl-NH_2, which is in an extended conjugation with the *ortho* acyl group (such as vinylogous amide)[25] or intramolecular hydrogen bonding between aniline -NH and *O*-acyl carbonyl as shown in Figure 6.

Sl.No	Conditions	Observations
1	HATU, DIPEA, DMF,70 °C	Complex reaction mixture
2	PyBop, DIPEA, toluene, 100 °C	Complex reaction mixture
3	Mukaiyama reagent, DIPEA, toluene	Complex reaction mixture
4	Isobutyl chloroformate, NMM, THF	Complex reaction mixture

Table 1. Conditions tried for macrolactamization

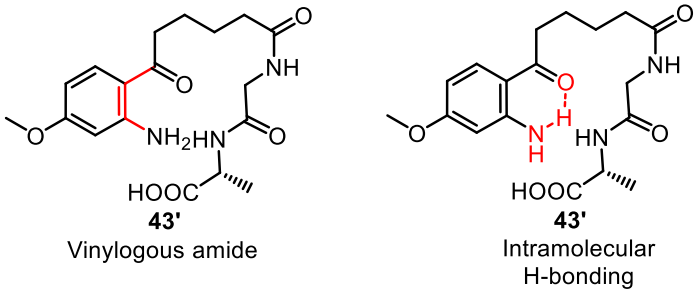
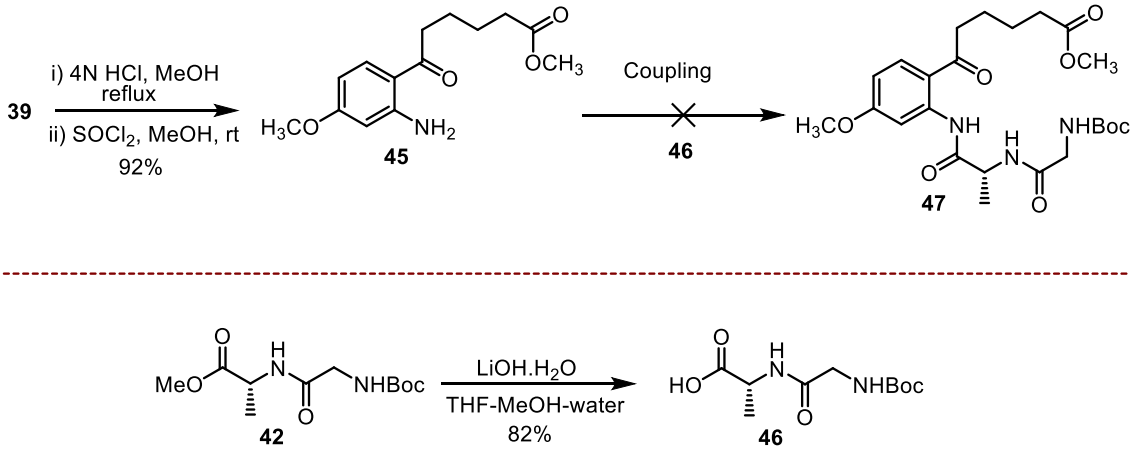


Figure 6. Possible explanation for the unsuccessful macrocyclization attempts

2.4.2. Approach 2: Macrolactamization at Gly-NH_2

When macrolactamization at aniline -NH_2 was not successful, attempts were diverted towards macrolactamization at Gly-NH_2 position and carboxylic acid terminal from a non-amino acid partner. For this purpose compound **39** was treated with 4N HCl in methanol in reflux condition, where both ester and *N*-acetyl got deprotected to give an acid, which was converted to methyl ester **45** using $SOCl_2$ in MeOH. The dipeptide acid

46 was synthesized from hydrolysis of corresponding dipeptide ester **42** in 82% yields under basic condition (LiOH) using literature procedures.[21] Despite several attempts listed in Table 2, no success was achieved in coupling the dipeptide acid **46** to amine **45** (Scheme 5).



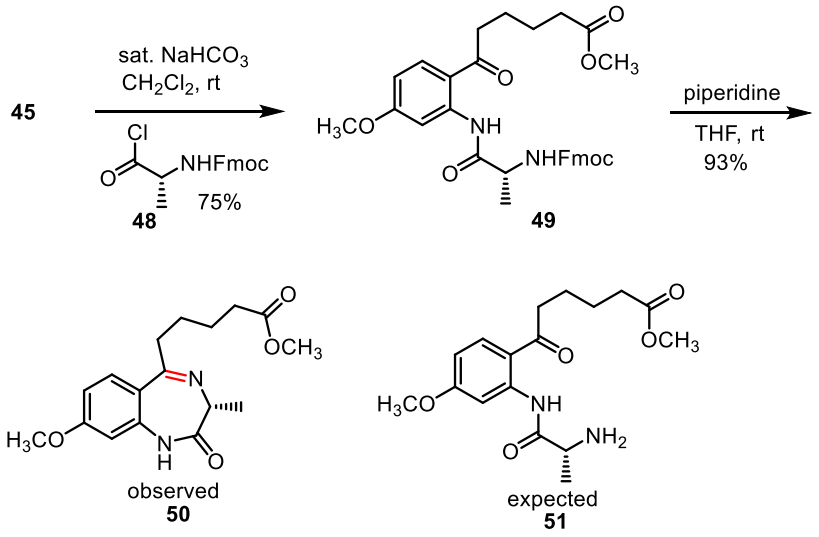
Scheme 5. Coupling of dipeptide **46** to **45**

S.No	Conditions	Observations
1	HATU, DIPEA, DMF, rt - 100 °C	No Reaction
2	DCC, DMAP, DMF, rt -100 °C	No Reaction
3	PyBOP, DIPEA, Toluene, 100 °C	No Reaction
4	Isobutyl chloroformate, NMM, THF, 40 °C	No Reaction
5	T_3P, DIPEA, THF, rt-reflux	No Reaction

Table 2. Conditions tried for dipeptide (**46**) coupling

After several attempts, coupling of Fmoc-D-Ala-Cl **48**[26] with amine **45** was successful using saturated $NaHCO_3$ in CH_2Cl_2 to afford alanine coupled compound **49** in 75% yield. The appearance of signals in the ^1H NMR spectrum at δ 1.54 (d, J = 7.0 Hz, 3H) and at δ 19.0 in ^{13}C NMR spectrum corresponding to alanine $–CH_3$ confirmed the formation of

compound **49**. In addition, the HRMS (ESI) analysis showed a peak at m/z 559.2439 corresponding to $[M+H]^+$ with a molecular formula $C_{32}H_{35}O_7N_2$ further confirmed the formation of desired product **49**. Next, deprotection of the Fmoc group in **49** was performed using piperidine. However, the desired compound **51** was not formed, instead, benzodiazepinone **50** was isolated in 93% yield (Scheme 6). The ^{13}C NMR spectrum displayed absence of signal for the carbonyl carbon at δ 200 and HRMS (ESI) analysis showed a peak at 319.1653 corresponding to $[M+H]^+$ with molecular formula $C_{17}H_{23}O_4N_2$ confirmed the formation of benzodiazepinone **50**. Although it is not the desired outcome, this method can be used for the synthesis of different benzodiazepinone derivatives, as this scaffold is a privileged structure in the field of medicinal chemistry.



Scheme 6. Formation of benzodiazepinones

There are several benzodiazepinone scaffold based compounds used as drugs and many are under biological evaluation.[27,28] For example, Devazepide, **52**, is a CCKA (Cholecystokinin A) receptor antagonist, used for the treatment of gastrointestinal problems such as gastroparesis, dyspepsia, and gastric reflux. Lorazepam, **53**, used to treat anxiety disorders. It reduces anxiety, agitation, and induces sleep. The benzodiazepinone scaffold is also found as neurokinin-1 antagonists, **54**, enzyme inhibitors such as κ-secretase inhibitors, **55**, and farnesyl protein transferase inhibitors

like compound **56**, and ion channel ligands such as compound **57** (delayed rectifier K+ current modulator) (Figure 8).[27]

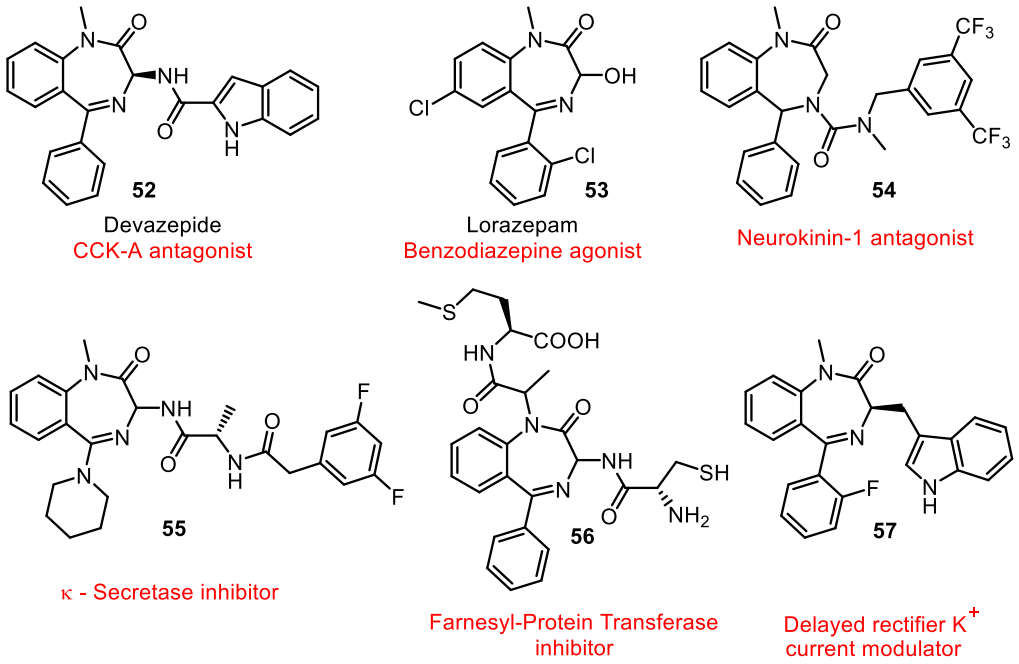
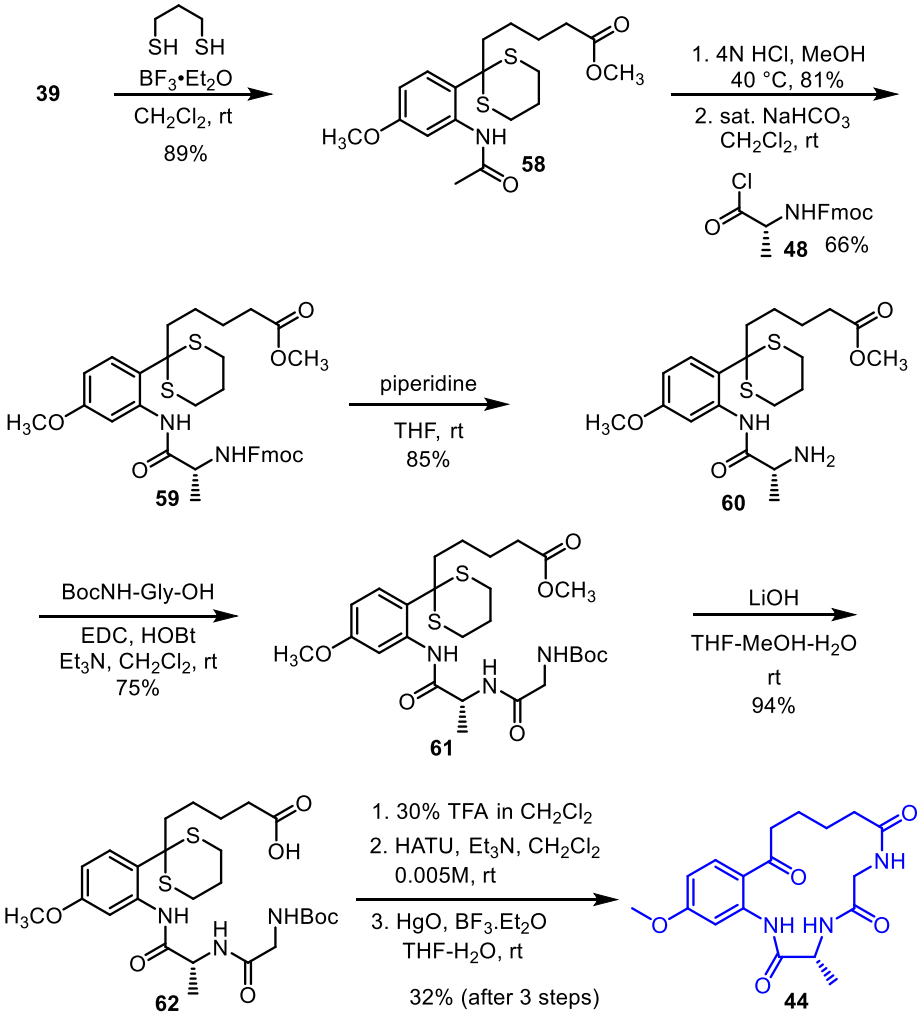


Figure 8. Representative examples for benzodiazepinone scaffold with biological activities

To avert the problem of benzodiazepinone formation, the ketone present in compound **39** was protected with propanedithiol in the presence of $BF_3 \cdot Et_2O$ to give thioketal **58** in 89% yield. At this stage, the coupling of dipeptide Boc-Gly-D-Ala-OH (**46**) was attempted on compound **58** considering that the protection of ketone removed the vinylogous amide character. Nevertheless, the coupling of dipeptide was not successful. Hence, the compound **58** was transformed to compound **59** in a two-step process (deacetylation followed by coupling of Fmoc-D-Ala-Cl). Deprotection of Fmoc group in piperidine condition gave the desired free amine **60**, which was coupled with Boc-Gly-OH (**41)** to produce **61**. Hydrolysis of compound **61** furnished the acyclic precursor **62** in good yields. The crude acyclic amino acid resulting from Boc deprotection was subjected to the key macrolactamization using HATU followed by thioketal deprotection under standard conditions (HgO, $BF_3 \cdot Et_2O$) resulted in the formation of the macrocyclic core of

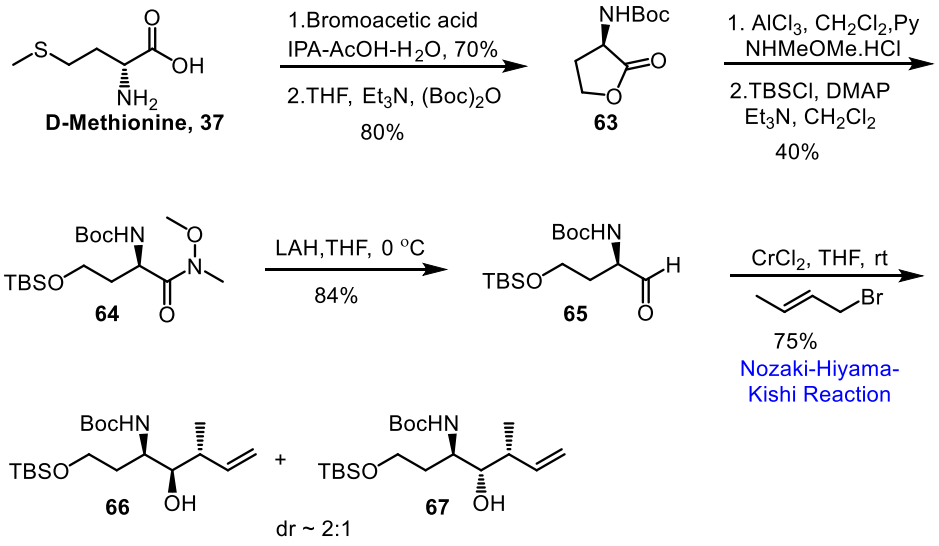
solomonamides, **44** (Scheme 7). Appearance of signals in the ^{1}H NMR spectrum at δ 4.54 (d, *J* = 15.1 Hz, 1H), 3.68 (d, *J* = 15.1 Hz, 1H) corresponding to Gly-CH_2 (characteristic peaks for macrocycle, same was observed in natural product) confirms the macrocyclization. The signals in the ^{13}C NMR spectrum at δ 203.3 corresponding to benzylic –C=O confirms the thioketal deprotection. HRMS (ESI) analysis showed a peak at m/z 362.1713 corresponding to $[M+H]^+$ with molecular formula $C_{18}H_{24}O_5N_3$ further confirmed the gross structure of macrocycle **44** as shown in Scheme 7.



Scheme 7. Synthesis of macrocyclic core of solomonamide B

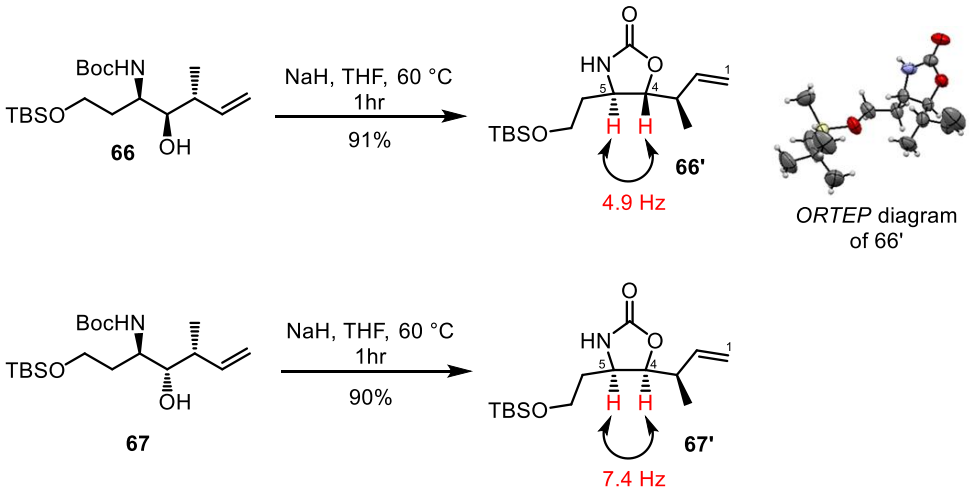
2.4.3. Efforts toward the total synthesis of solomonamide B

After the successful completion of the synthesis of model macrocyclic core, **44**, the next objective was to synthesize the natural product solomonamide B, **10**. For this purpose, aldehyde fragment with requisite stereochemistry is needed to perform the key C-H activation reaction. The synthesis commenced with the conversion of D-methionine (**37**) to Boc-protected D-homoserine lactone (**63**) in two steps by following literature procedures.[29a] The lactone in compound **63** was opened with *N,O*-dimethyl hydroxyl amine hydrochloride in the presence of $AlCl_3$, pyridine to provide Weinreb amide with terminal alcohol, which was found to be unstable thus, immediately protected as TBS ether **64**. The ^1H, ^{13}C NMR, and optical rotation values were compared with the literature values and found to be identical.[29a] It is worth noting that previously, this particular transformation (lactone opening) was carried out by using $AlMe_3$ which is a pyrophoric and expensive reagent.[29b] Here, it was accomplished using relatively less pyrophoric and cheaply available $AlCl_3$. Later, the Weinreb amide **64** was reduced to an aldehyde **65**[30] by treating with $LiAlH_4$ at 0 °C for 1 h. The ^1H, ^{13}C NMR, and optical rotation values were compared with the literature values and found to be identical.[30] The aldehyde **65** on reaction with crotyl bromide/$CrCl_2$ underwent Nozaki-Hiyama-Kishi type of reaction to afford compounds **66** and **67** in a 2:1 diastereomeric ratio.[31] Appearance of signals in the ^{13}C NMR spectrum at δ 115.8, 141.0 ppm in compound **66**, δ 115.7, 141.0 ppm in compound **67** corresponding to alkene carbons and appearance of signals in the ^1H NMR spectrum at δ 1.01 (d, J = 6.4 Hz, 3H) corresponding to $–CH_3$ and δ 5.84-5.82 (m, 1H), 5.09-5.05 (m, 2H) corresponding to terminal olefin in compound **66** and δ 1.03 (d, J = 7.4 Hz, 3H) corresponding to $–CH_3$ and δ 5.83-5.78 (m, 1H), 5.10-5.08 (m, 2H) corresponding to terminal olefin in compound **67** indicated the gross structures of compounds **66** and **67** as drawn. In addition, the HRMS (ESI) analysis showed a peak at m/z 374.2718 for compound **66** and peak at m/z 374.2717 for compound **67** corresponding to $[M+H]^+$ with molecular formula $C_{19}H_{40}O_4NSi$ which further confirmed the formation of desired products **66** and **67** (Scheme 8).



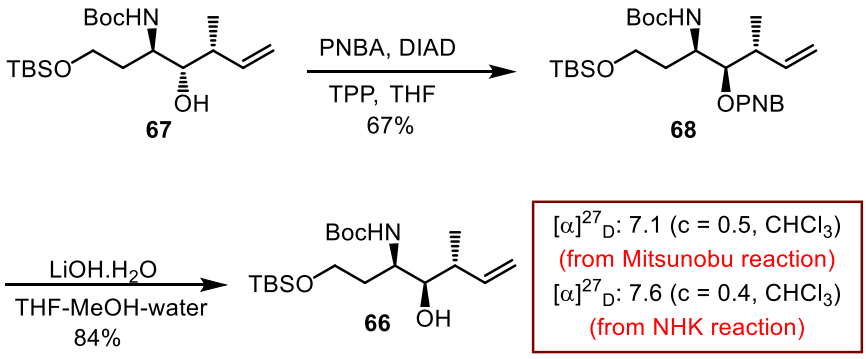
Scheme 8. Synthesis of key fragment

The next task was to confirm the stereochemistry of the obtained compounds, one of the methods to confirm the relative stereochemistry of the amino alcohol is converting into corresponding oxazolidinones and measuring the corresponding coupling constants. It was documented in the literature that the coupling constant 2-5 Hz indicates *syn* and 6-8 Hz indicates *anti* stereochemistry.[31a] Accordingly, both the isomers **66** and **67** were converted into their corresponding oxazolidinones **66'** and **67'** using NaH, THF reflux condition in very good yield. In the ^{1}H NMR spectrum of compound **66'**, C5 attached proton was merged with C7 attached protons and appeared at δ 3.70-3.64 (m, 3H), C4 attached proton was observed at 4.15 (t, J = 4.9 Hz, 1H). The coupling constant of C4 confirmed the stereochemistry of the **66'** which in turn confirmed that the major compound **66** is required isomer with 3*R*, 4*R*, 5*R* stereochemistry. The stereochemistry was further confirmed by X-ray crystal structure analysis of carbamate **66'**. Similarly, In ^{1}H NMR spectrum of compound **67'** the appearance of a peak at δ 4.32 (t, J = 7.4 Hz, 1H) corresponding to C4 attached proton confirmed the stereochemistry **67'** which in turn confirmed the stereochemistry of compound **67** as 3*R*, 4*S*, 5*R* (Scheme 9).



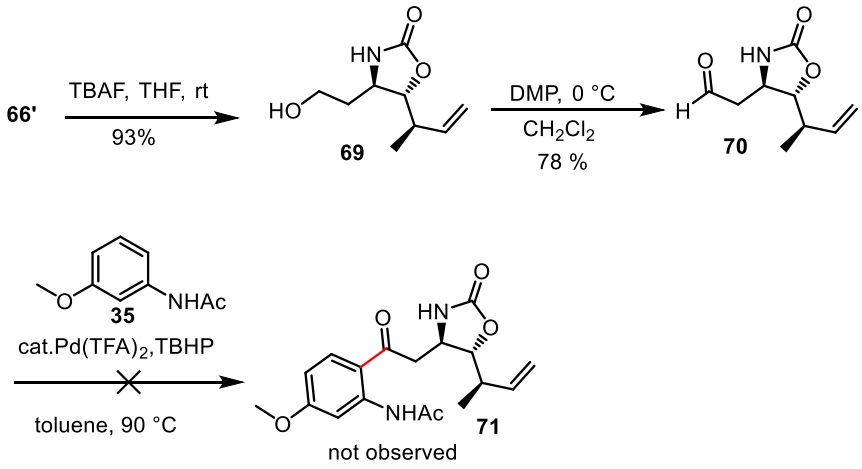
Scheme 9. Confirmation of stereochemistry of compounds **66** and **67**

It is also worth noting that the unrequired isomer **67** was converted into required isomer **66** by inverting the – OH stereocenter using Mitsunobu protocol. The compound **67** was treated with *p*-nitrobenzoic acid (PNBA) in the presence of DIAD, TPP afforded **68** in 69% yield. The appearance of ^{1}H NMR signal in aromatic region δ 8.13 - 8.40 (m, 4H), and in ^{13}C NMR spectrum, signal at δ 164.4 confirmed the coupling of *p*-nitrobenzoic acid. The compound **68** on hydrolysis (LiOH) afforded compound **66** in 86% yield. The ^{1}H, ^{13}C NMR and optical rotation values were compared with initially synthesized compound and found to be identical (Scheme 10).



Scheme 10. Conversion of compound **67** to **66**

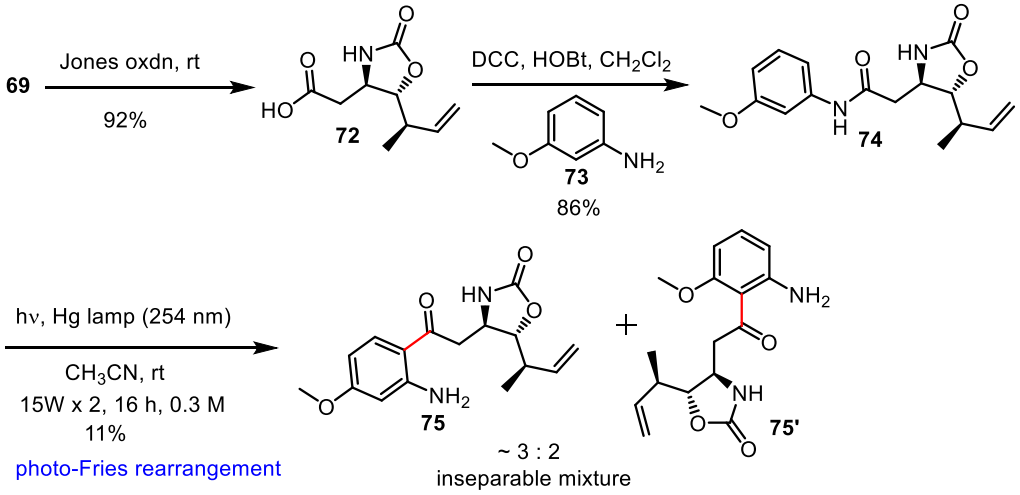
Once the stereochemistry was established, the silyl protection of primary alcohol (TBS) in compound **66'** was detached using TBAF to afford alcohol **69**. The disappearance of NMR signals (^{1}H & ^{13}C) related to TBS group and MS value confirmed the structure of **69**. The alcohol present in **69** was oxidized to the aldehyde using Dess-Martin periodinane (DMP) to afford an aldehyde **70** in 78% yields, the product was confirmed by the appearance of a signal at δ 9.78 ppm in ^{1}H NMR which corresponds to aldehyde moiety. ESI-HRMS showed a peak at 184.0970 corresponding to $[M+H]^{+}$ with molecular formula $C_9H_{14}O_3N$ further confirmed the desired product formation. After synthesizing the desired aldehyde, **70**, it was subjected to C-H activation reaction with *m*- anisidine, **35,** under similar and optimized conditions (cat Pd $(TFA)_2$, TBHP). However, it was observed that the aldehyde got decomposed and the desired product **71** was not observed (Scheme 11).



Scheme 11. C-H activation reaction

To circumvent the stability problem of the aldehyde, a completely different strategy using photochemistry was planned. For that purpose, the alcohol **69** was transformed to acid **72** using Jones oxidation followed by coupling with *m*-anisidine **73** with the help of DCC, HOBt to afford amide compound **74** in 86% yield. To migrate the acyl group in compound **74**, to its *ortho* position to get desired non-amino acid fragment **75** photo-Fries rearrangement was chosen. The compound **74** was subjected to photolysis under the Hg vapor lamp (254 nm) 15 w x 2 bulbs, at 0.1 M concentration in ACN afforded

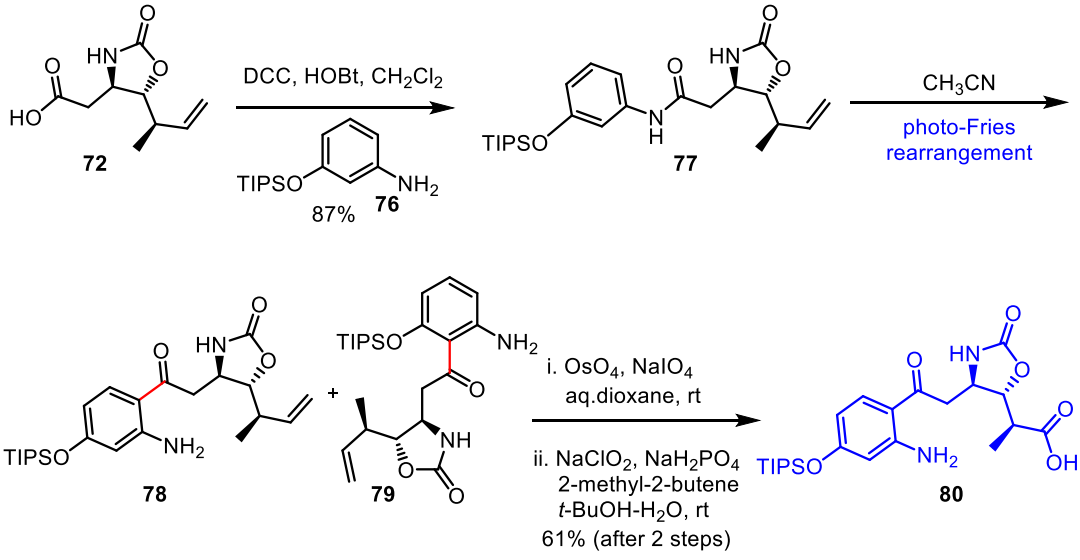
compounds **75** and **75'** as an inseparable regioisomeric mixture in 3:2 ratio and in less yield[32](Scheme 12). In ^{1}H and ^{13}C NMR spectrum two sets of signals were observed which confirms the mixture of two compounds. In ^{13}C NMR spectrum the appearance of a signal at δ 201.4, 197.3 ppm corresponding to benzylic –C=O of two compounds confirmed the migration of acyl group. The product was further confirmed by the observance of ESI- HRMS peak at 305.1493 corresponding to $[M+H]^{+}$ with molecular formula $C_{16}H_{21}O_4N_2$. Although migration of the acyl moiety through photo-Fries rearrangement was successful, the reaction suffered from poor regioselectivity and low yields. It was believed that replacement of phenolic methyl with bulky groups like TBS or TIPS may induce steric hindrance which ultimately may avoid the formation of another regioisomer.



Scheme 12. Photo-Fries rearrangement

Accordingly, the acid component **72** was coupled with the known TIPS protected *m*-amino-phenol **76**[33] to afford compound **77** in 87% yield. The compound **77** on photo-Fries rearrangement afforded the desired isomer **78** as major compound. After several trials mentioned in Table 3, the yields were improved up to 36% using a 16 W bulb, 0.0015 M concentration in ACN and stirring for 5h. The appearance of signals in the ^{13}C NMR spectrum at δ 197.3 corresponding to benzylic –C=O confirmed the migration of carbonyl group to give desired compound **78**. The regiochemistry of the obtained product

was confirmed by the coupling constants of the aromatic protons signals in the ^{1}H NMR spectrum at δ 7.49 (d, *J* = 8.8 Hz, 1H); *ortho* coupling, 6.19 (dd, *J* = 8.8 Hz, 2.1 Hz, 1H); *ortho* and *meta* coupling and 6.10 (d, *J* = 2.1 Hz, 1H) *meta* coupling. The coupling pattern supports the 1,2,5 substitution on an aromatic ring. In addition to this, the ESI-HRMS analysis showed a peak at m/z 447.2673 corresponding to $[M+H]^+$ with molecular formula $C_{24}H_{39}N_2O_4Si$ further confirmed the formation of desired product **78.** The other regioisomer **79** was obtained as minor product and was easily separated by column chromatography. The regiochemistry of the compound **79** was confirmed by the coupling constants of the aromatic proton signals in the ^{1}H NMR spectrum at δ 7.03 (t, *J* = 7.93 Hz, 1H), 6.24 (d, *J* = 7.93 Hz, 1H), 6.12 (d, *J* = 7.93 Hz, 1H), the coupling pattern supports the 1,2,3 substitution on the aromatic ring. After having the desired compound **78** in hand, it was subjected to oxidative cleavage (OsO_4, $NaIO_4$) to give an aldehyde followed by Pinnick oxidation to afford corresponding acid **80** in 61% over two steps. Thus, the key fragment AHMOA of solomonamide B in a protected form was prepared (Scheme 13).

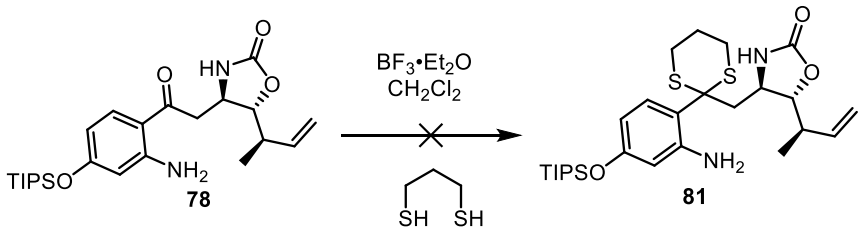


Scheme 13. Synthesis of 4-amino-6-(2'-amino-4'-hydroxyphenyl)-3-hydroxy-2-methyl-6-oxohexanoic acid residue (AHMOA).

S. No	Conc. of Reaction mix.	U.V lamp	Time	% of Yield (Required)	% of Yield (Unrequired)
1	0.1 M	15W x 2	16 h	Poor conversion	Not observed
2	0.1 M	8W x 2	24h	10% conversion	Not observed
3	0.0015M	80 W	8 h	18 %	< 5%
4	0.0015M	80 W	6h	20 %	< 5%
5	0.0015M	80 W	5 h	30%	< 5%
6	0.0015M	80 W	4 h	25%	< 5%
7	0.0015M	80 W	3h	22%	< 5%
8	0.0015M	16W	3h	25%	< 5%
9	0.0015M	16 W	4h	29%	< 5%
10	0.0015M	16W	5h	36% (42% brsm)	< 5%

Table 3. Optimization study of photo-Fries rearrangement.

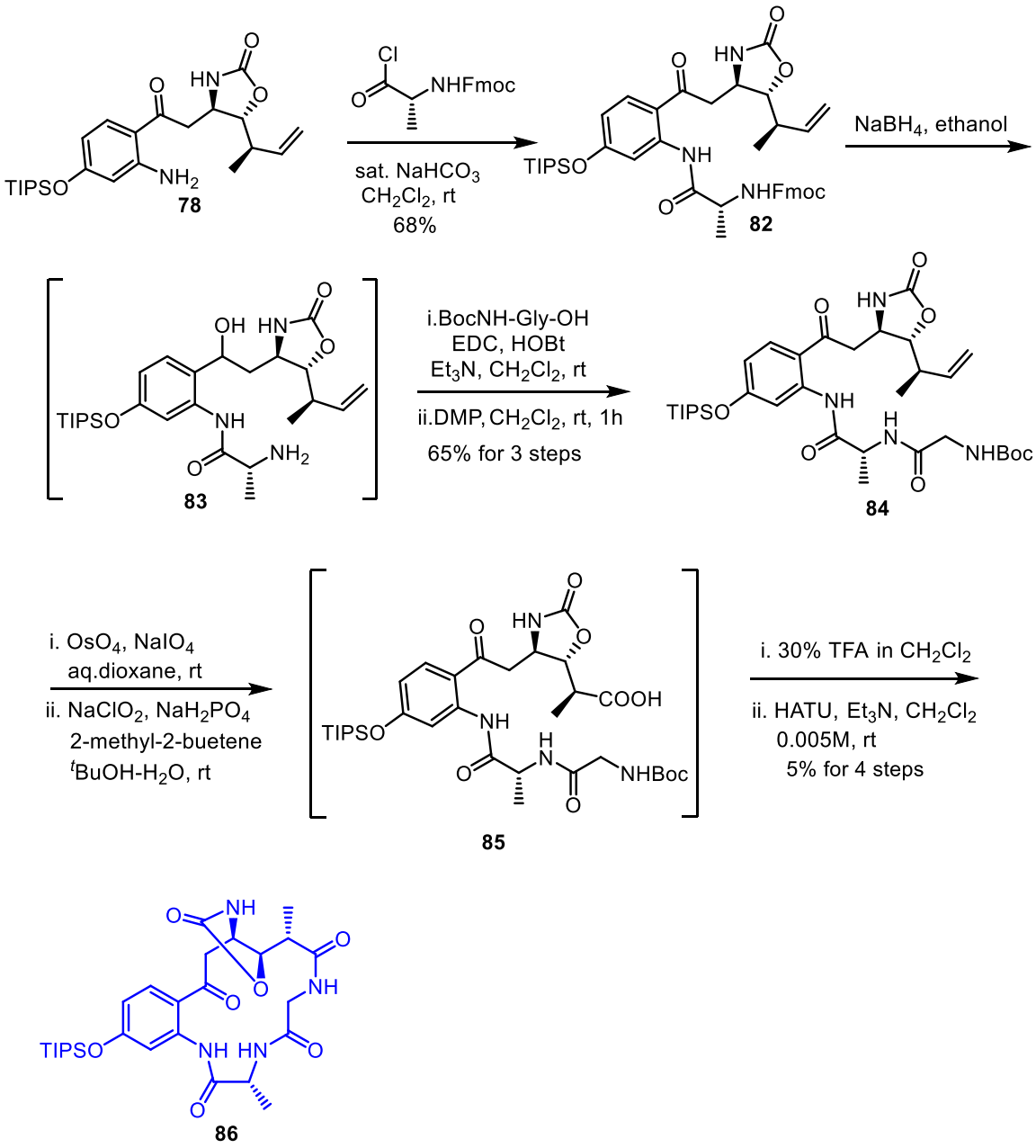
Next, the coupling of the dipeptide fragment was initiated. The first step was the protection of the benzylic carbonyl group of **78** as thioketal **81** to avoid the benzodiazepinone formation in later steps (as we encountered the problems previously; see Scheme 6). However, the protection of carbonyl moiety through dithiane was not successful under the previously optimized condition ($BF_3{\cdot}Et_2O$, and 1,3 propane dithiol). This may be because of the steric hindrance of rigid oxazolidinone moiety. (Scheme 14)



Scheme 14. Protection of keto group

Next, the Fmoc-D-Ala-Cl was coupled to **78** in optimized condition to afford compound **82** in 68% yield. To avoid benzodiazepinone formation, the carbonyl group in compound **82** was reduced using $NaBH_4$ to give compound **83** as a diastereomeric mixture, where

the Fmoc protecting group also got deprotected. As we need to convert alcohol to ketone at a later stage, we did not put efforts to understand the stereochemical outcome of the reaction. The crude alcohol mixture was taken forward and coupled with NHBoc-Gly-OH under EDC, HOBt conditions followed by subsequent oxidation (DMP) to afford the compound **84** in 65% yield over 3 steps. The appearance of the signal at δ 1.47 (s, 9H) corresponding to the ^{t}Bu of Boc protecting group in ^{1}H NMR spectrum confirmed the coupling of Boc-Gly-OH and in ^{13}C NMR presence of a signal at δ 202.1 ppm corresponding to benzylic carbonyl group indicated the formation of required compound. HRMS (ESI) analysis of compound **84** showed a peak at m/z 675.3782 corresponding to $[M+H]^+$ with molecular formula $C_{34}H_{55}N_4O_8Si$ further confirmed the formation of desired compound **84.** The Compound **84** on oxidative cleavage followed by Pinnick oxidation gave macrocyclization precursor **85**, which was confirmed by mass analysis and Boc deprotection followed by macrolactamization under optimized conditions (HATU, Et_3N) gave the desired macrocycle **86** in very poor yield (Scheme 15). The ^{1}H NMR data indicated the gross structure as drawn. HRMS (ESI) analysis of compound **86** showed a peak at m/z 575.2903 corresponding to $[M+H]^+$ with molecular formula $C_{28}H_{43}N_4O_7Si$ further confirmed the formation of desired macrocyclic compound **86** (Scheme 14). Although macrocyclic compound was synthesized with all the required stereochemistry, we could not go forward using this route because of following reasons. (1) Lack of sufficient quantities, (2) poor yields in the final step, (3) purification problems, (4) failed attempts to open the carbamate for the further transformations and also (5) a long synthetic sequence made us explore other alternatives. Thus, for the completion of the total synthesis, there was a need to come up with another approach where all these issues can be solved to complete the total synthesis. Accordingly, a new strategy was planned and the details are described in the following sections.

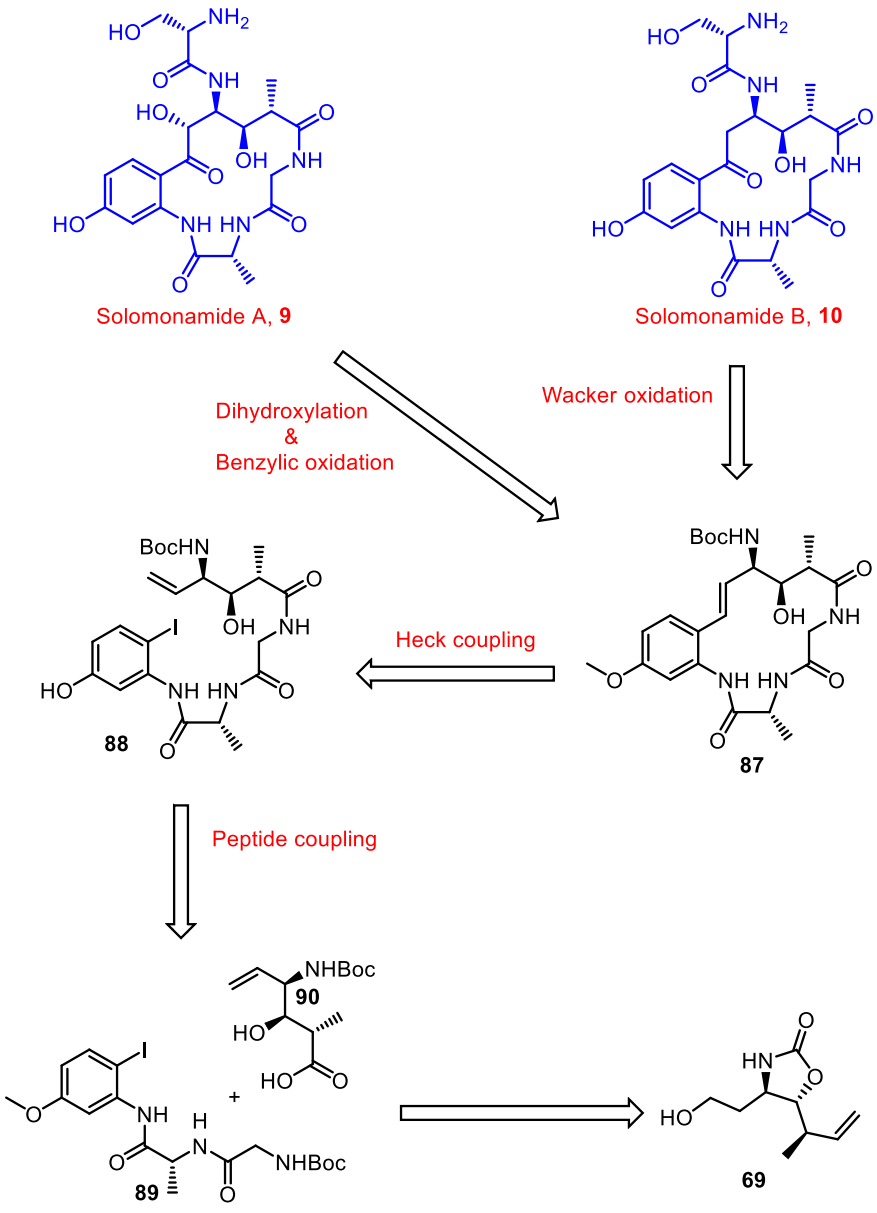


Scheme 15. Synthesis of the macrocyclic skeleton of solomonamide B with desired stereochemistry.

2.4.4. Approach 3: Macrocyclization using intramolecular Heck reaction

In the revised approach, both the natural products were planned from a common macrocyclic intermediate **87**. Solomonamide B was planned through Wacker oxidation

from the key macrocycle **87**. At the same time, solomonamide A was planned through dihydroxylation followed by chemoselective benzylic oxidation in the key macrocycle. The macrocycle **87** was envisaged from the intramolecular Heck reaction of acyclic precursor **88**. The compound **88** could be readily synthesized from appropriate intermediates, dipeptide derivative **89** and acid fragment **90**. The compound **90** can be synthesized from compound **69** which was previously prepared (Scheme 16).

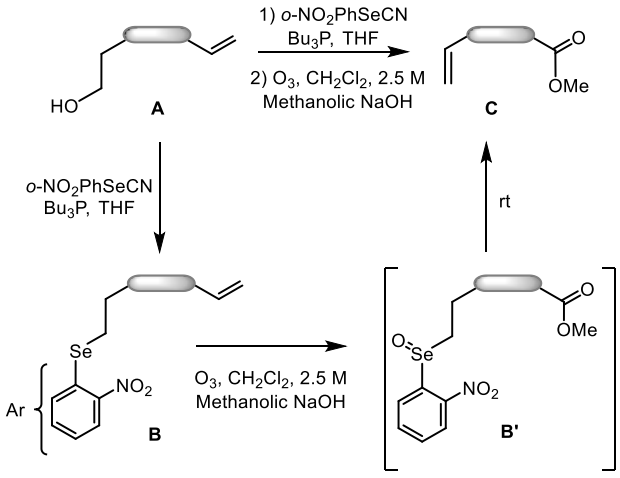


Scheme 16. Revised retrosynthetic analysis

In this approach, the first target was to synthesize the acid fragment **90** from previously synthesized compound **69**. If the transformation is performed by employing conventional routes it requires multiple steps (first olefin end has to be converted into the corresponding acid, and acid should be protected as an ester or any other, then alcohol at the other end has to be converted into olefin). The general methods to convert terminal olefins to the corresponding acids are 1) oxidative cleavage using OsO_4, $NaIO_4$ followed by Pinnick oxidation 2) Oxidative ozonolysis reaction. The general methods for the conversion of alcohols to an alkene are 1) Chugaev elimination 2) pyrolysis 3) treating with strong acids[34] and 4) Grieco elimination.[35] Grieco elimination is a mild method to convert the alcohol to the corresponding olefin. In this method, the alcohol is first converted into corresponding phenyl/ aryl selenide, which on oxidation to selenoxide using H_2O_2 or *m*-CPBA or ozonolysis[36,37] undergoes *syn* elimination to afford olefin with the expulsion of selenol. Considering multi-utility of ozonolysis reaction in various functional group transformations,[38] a method to produce olefinic esters was developed from corresponding alkenols using a two-directional approach which is depicted below.

Breaking and making of olefins simultaneously

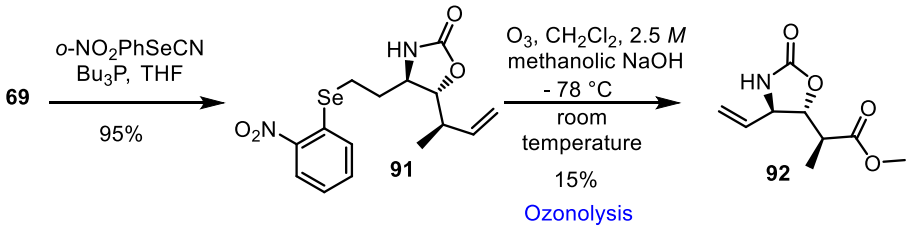
A general outline of the developed method is outlined in Scheme 17. First, conversion of alkenol A to the corresponding arylselenide B using *o*-NO_2PhSeCN, Bu_3P followed by



Scheme 17. General synthetic approach for the conversion of alkenol to olefinic ester

ozonolysis in methanolic NaOH solution to produce the desired olefinic ester C, which forms through the intermediate selenoxide B′.

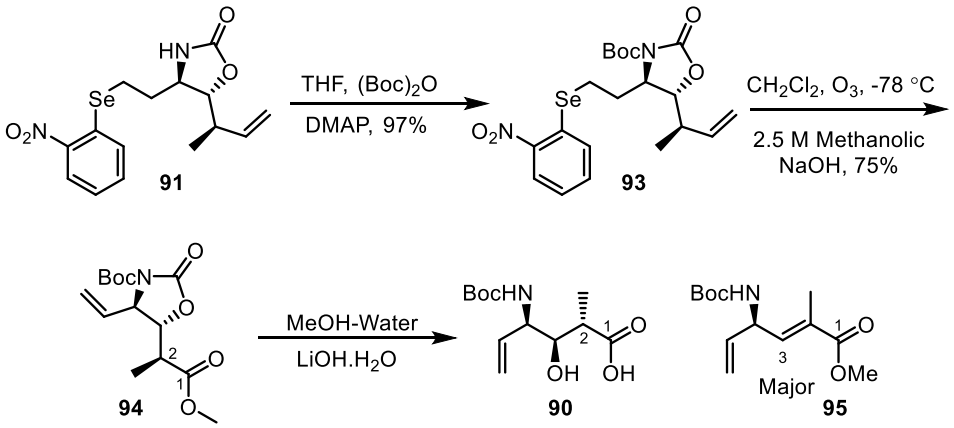
As per the plan, the compound, **69** was converted into corresponding alkenyl aryl selenide **91** using *o*-NO_2PhSeCN, Bu_3P in 95% yield. Ozonolysis of compound **91** at −78 °C in CH_2Cl_2 and 5 equiv of 2.5 M methanolic NaOH followed by stirring the reaction mixture at room temperature for 3−4 h furnished the desired olefinic ester **92** in 15% yield (scheme 18). The ^{1}H NMR displayed the absence of the signals in δ 7-9 ppm corresponding to aromatic protons confirms the elimination of selenium and on the other hand, the appearance of signals at 5.86 (ddd, *J* = 7.3, 10.0, 17.2 Hz, 1H), 5.41 - 5.25 (m, 2H) confirms the formation of terminal olefin. The signal at 3.71 (s, 3H) corresponding to ester –CH_3 in ^{1}H NMR and appearance of δ 172.7 ppm in ^{13}C NMR corresponding to ester carbonyl further confirms the desired product formation. ESI- HRMS of the compound **92** has shown the peak at 200.0916 corresponding to $[M+H]^+$ with molecular formula $C_9H_{14}O_4N$ further confirmed the formation of required compound.



Scheme 18. Breaking and making of olefins simultaneously

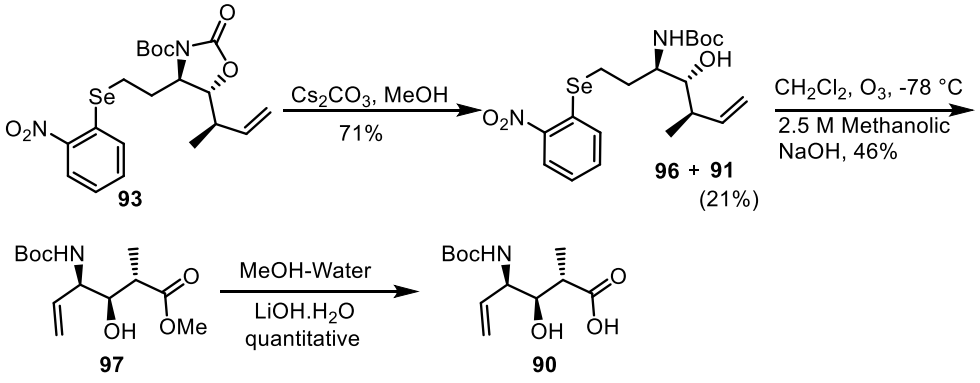
For the improvement in yield, compound **91** was protected as Boc to give compound **93,** which on ozonolysis afforded desired olefinic ester **94** in 75% yield. Hydrolysis of ester **94** under basic conditions (LiOH) afforded α, β unsaturated ester **95** as a major compound and desired acid **90** in a minor quantities. The compound **95** was confirmed by the shift of ^{1}H NMR signal at δ 1.26 (d, *J* = 7.3 Hz, 3H) to a signal at δ 1.92 (s, 3H) corresponding to –CH_3 and appearance of signal at δ 6.50 (d, *J* = 8.80 Hz, 1H) corresponding to internal olefinic –CH. HRMS (ESI) has showed the peak at 278.1359 corresponding to $[M+Na]^+$ with molecular formula $C_{13}H_{21}O_4NNa$ further confirmed the formation of compound **95**.

The acid **90** was confirmed by the presence of a signal at 1.25 (d, J = 6.95 Hz, 3H), 2.56 - 2.75 (m, 1H) corresponding to methyl at C2 and and disappearance of 3.71 (s, 3H) corresponding to ester –CH_3 in ^{1}H NMR spectrum (Scheme 19).



Scheme 19. Attempts toward the synthesis of key fragment **90**

The compound **95** was obtained form **94** with a loss of – CO_2. So, we thought that the removal of carbamate followed by ozonolysis will solve this problem. Accordingly, amino alcohol **96** was synthesized from compound **93** under basic conditions (Cs_2CO_3/MeOH) (during deprotection 21% of compound **91** also formed). The compound **96** on ozonolysis in methanolic NaOH afforded ester **97** in moderate yield. The ester upon hydrolysis in basic condition (LiOH) gave the desired acid fragment **90** in quantitative yield without any eliminated product as expected (Scheme 20).



Scheme 20. Synthesis of key fragment **90**

Encouraged by the success of this reaction (simultaneous cleavage and formation of double bonds) on three compounds **91**, **93**, and **96** it was decided to expand the scope of the method. Accordingly, various examples were picked up and all the results are compiled in the Table 4 below. In the first example, *β*-citronellol **1a** was transformed into corresponding olefinic ester **1c,** a known intermediate in the synthesis of myxobacterial pheromone, reported by Mori et al. where they have reported the synthesis in six steps (Figure 8).[39] It is important to note that corresponding carboxylic acid of **1c** was used in natural product synthesis by different groups.[40]

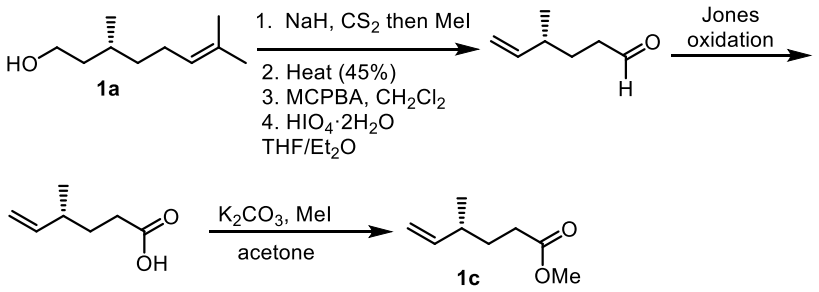


Figure 8. Reported synthetic sequence for the synthesis of 1c by Mori et al.

Undecenol **2a** was converted to corresponding selenide **2b** followed by ozonolysis afforded olefinic ester **2c** in good yield. Alkenol **3a** was synthesized by *O*-alkylation on ethylene glycol with decenyl bromide and converted to selenide **3b**, followed by ozonolysis, afforded *O*-vinyl ester **3c**. It is worth highlighting that vinyl ethers are difficult to prepare under mild conditions.[41] Triazole compound **4a**, obtained by click reaction between 3-butynol and the corresponding azide, was converted to 4-vinyl-1,2,3-triazole derivative **4c**, an important building block in the new class of polymers.[42]

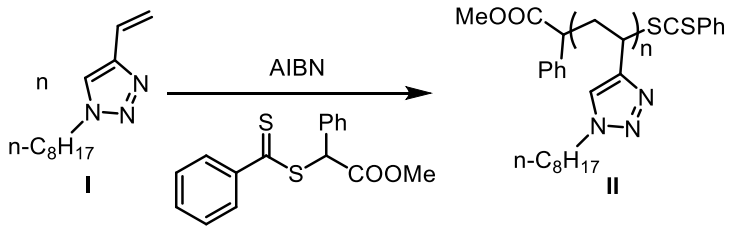


Figure 9. Polymerization of 1-Octyl-4-vinyl-1,2,3-triazole

For example, a polymer such as **II,** was synthesized from its corresponding monomer 1-Octyl-4-vinyl-1,2,3-triazole, **I** by Craig J. Hawker group. This polymeric material was having unique physical properties, with many attractive features.[42a] Similarly, aromatic alkenol **5a** was converted in to **5c**. The reaction worked well with the (−)-nopol **6a**, which is having an internal olefin to afford cyclobutyl derivative **6c** with fixed stereochemistry in good yields. Alkenols **7a**, **8a**, and **9a** were synthesized by the opening of *N*-Boc-L-homoserine lactone[29] with allylamine, *N*-methyl allylamine, and diallyl amine, respectively. These compounds on conversion to the corresponding selenides followed by ozonolysis afforded the desired dipeptide vinyl Gly-Gly derivatives (7c, 8c and 9c) which can be used in peptide research. As can be seen from the literature, vinyl glycine derivatives are generally prepared from methionine derivatives using high temperatures and they often suffer from the side products formation due to the migration of the double bond.[43] The present method is useful for the synthesis of vinyl glycine derivatives without any migration. Further, to increase the scope, compound **10a**[44] having an electron donating group (methyl) and compound **11a** having an electron withdrawing group (ester) at the beta position, were synthesized. The compounds **10a** and **11a** were coverted into corresponding selenium compounds **10b** and **11b**, which on ozonolysis afforded corresponding olefinic esters **10c** and **11c** in good yields. It was observed that reaction was faster in the case of **11a** which demonstrates that an electron withdrawing group enhances the rate of the reaction.

Towards the completion of total synthesis of solomonamide B, the required dipeptide fragment **89** was synthesized from the coupling of 2-iodo-5-methoxy aniline **98**[45] and dipeptide NHBoc-Gly-D-Ala-OH (**56**) in 63% yield using HATU as amide coupling reagent. The appearance of signals in ^{1}H NMR spectrum at δ 3.65 (d, J = 5.6 Hz, 2H), corresponding to Gly-CH_2 and 1.38 (s, 12H, alanine –CH_3 and Boc-^{t}Bu) and the presence of signals at δ 171.5, 169.9 in ^{13}C NMR spectrum corresponding to amide carbonyl groups confirmed the dipeptide coupling. HRMS (ESI) has shown the peak at 500.0648 corresponding to $[M+Na]^+$ with molecular formula $C_{17}H_{24}O_5N_3INa$ confirmed the desired product formation. After having both the fragments in hand, the Boc

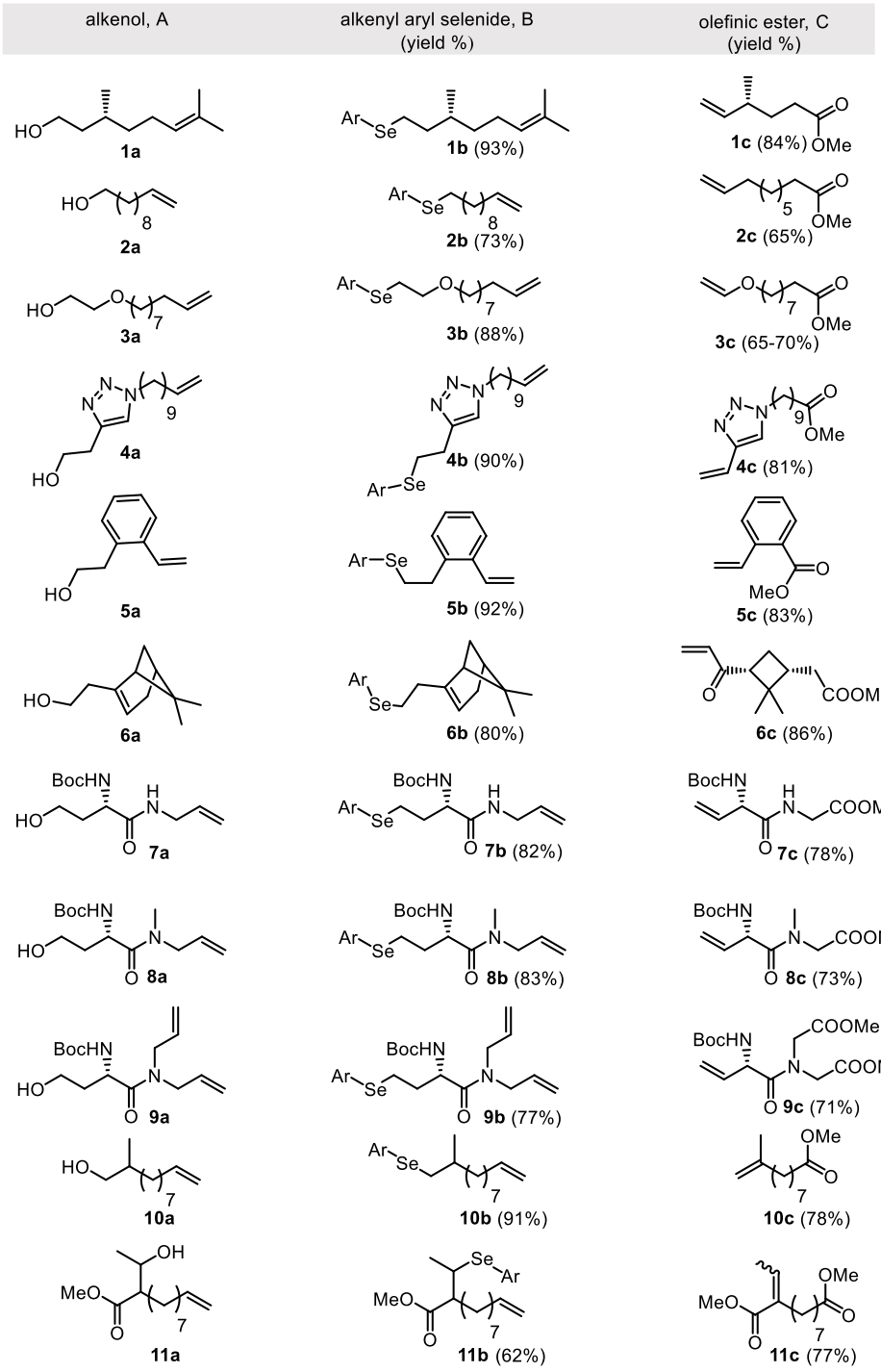
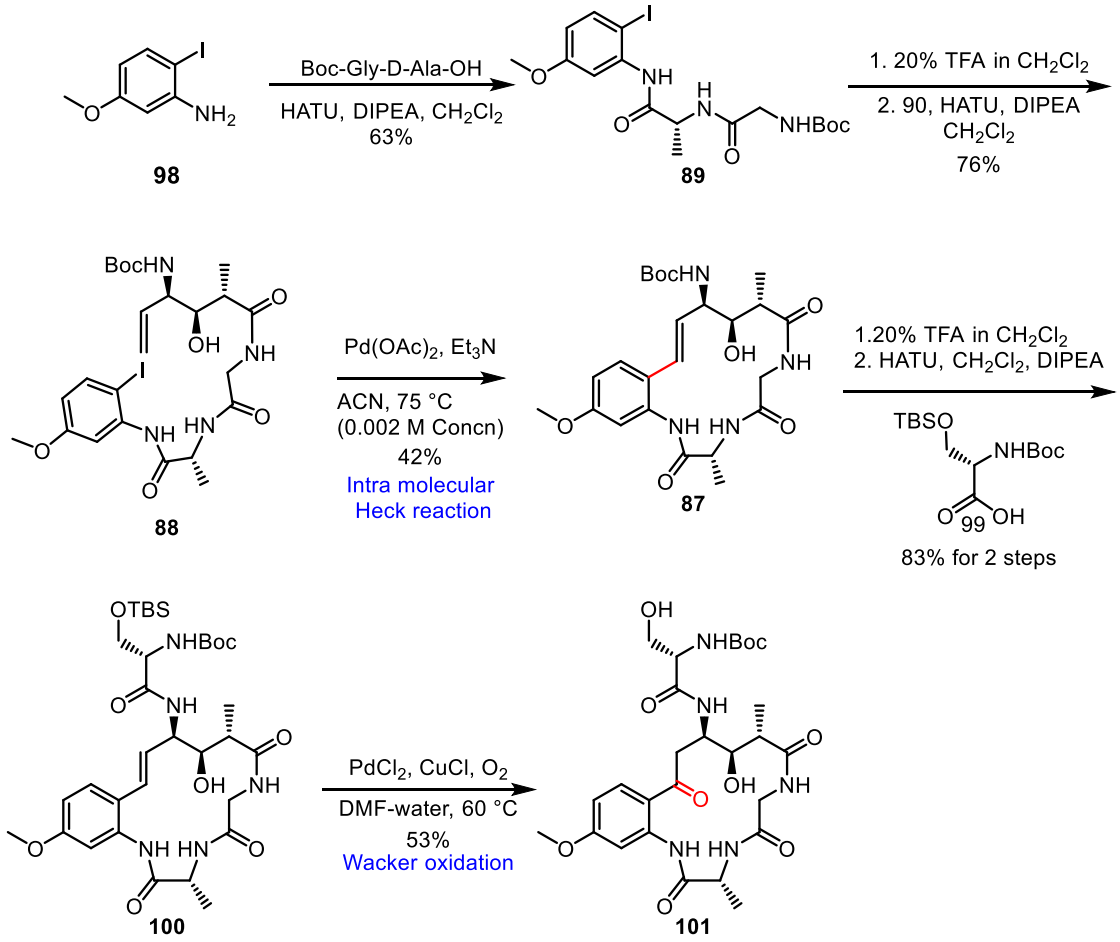


Table 4: Scope of the method

protecting group in compound **89** was removed using 20% TFA in CH_2Cl_2 followed by coupling of acid **90** (synthesized from hydrolysis of **97**) in the presence of HATU,

DIPEA afforded macrocyclization precursor **88** in 76% yield. All the spectral data is in agreement with the assigned structure. Intramolecular Heck reaction was chosen for the cyclization and after several attempts the cyclization was achieved using $Pd(OAc)_2$, Et_3N under dilute conditions (0.002 M conc.), to furnish the macrocycle **87** in 42% yield with exclusive trans double bond. The appearance of signals in the ^1H NMR spectrum at δ 6.62 (d, *J* = 15.9 Hz, 1H), 6.01 - 5.90 (m, 1H) indicated the presence of 1,2-substituted double bond and confirmed the formation of the macrocycle. In addition to this, the HRMS (ESI) analysis showed a peak at m/z 513.2311 corresponding to $[M+Na]^+$ with molecular formula $C_{24}H_{34}O_7N_4Na$ further confirmed the formation of desired macrolide **87**. It is noteworthy to mention that macrocyclizations using Heck reactions are very rare in the literature,[46] in particular, on this type of macrocyclic scaffolds. The synthesized compound **87** represents the complete macrocyclic core of the solomonamides with all the requisite stereochemistry pattern. As per the planned strategy, deprotection of Boc group in macrocycle **87** followed by coupling of the serine derivative **99**[47] gave the desired compound **100** in 83% yield. The presence of signals correspond to serine moiety in the product indicates the formation of the desired product. The next task was to introduce oxygen functionality at the benzylic carbon. After a few trials, it was possible. The double bond present in compound **100** was subjected to Wacker-type oxidation[48] using $Pd(OAc)_2$ as a catalyst and CuCl as co-catalyst in DMF/water, under O_2 atmosphere to furnish the macrocyclic ketone **101** in good yield (Scheme 21). The pleasing outcome of the reaction was the observed exclusive regioselectivity. In the same reaction condition, the unwanted TBS also got deprotected which was confirmed by disappearace of the signal in ^1H and ^{13}C at 0.89 (s, 9H), 0.08 (s, 6H) and 26.2, -5.0 respectively corresponding to silyl attached dimethyl and *tert*-butyl. The signal at δ 201.1 in ^{13}C NMR spectrum confirmed the formation of benzylic – C=O and HRMS (ESI) analysis showed a peak at m/z 616.2589 corresponding to $[M+Na]^+$ with molecular formula $C_{27}H_{39}O_{10}N_5Na$ further confirmed the formation of **101.** It is worth mentioning that oxidation of substituted double bond in a macrolide ring is the first of this kind. As this transformation is interesting, it was decided to explore further on the scope of the

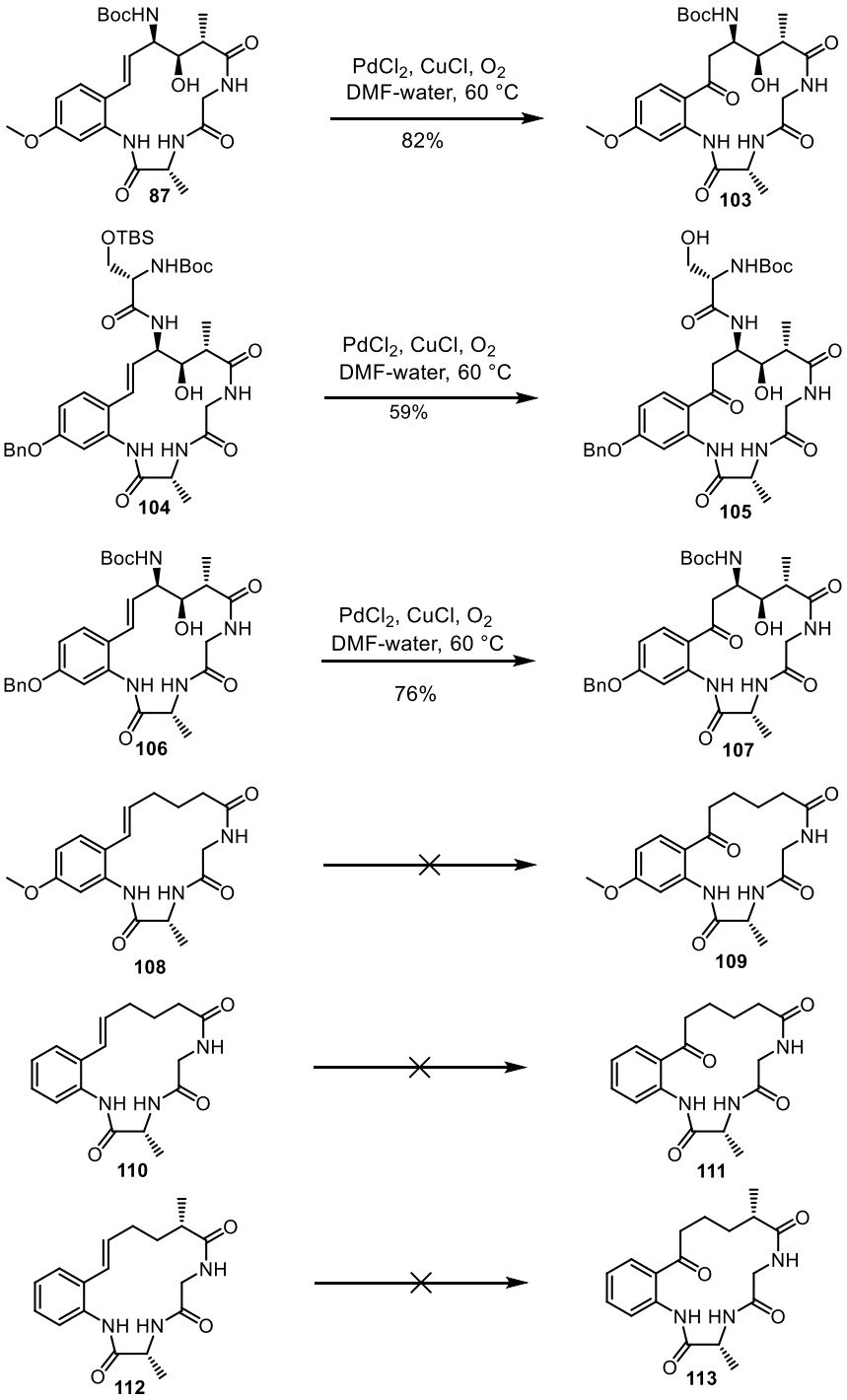
reaction. Accordingly, the reaction on six different macrocycles was attempted under the same conditions (Scheme 22).



Scheme 21: Efforts toward solomonamide B

Macrocyclic compounds **87**, **104**, and **106** underwent Wacker oxidation smoothly with complete regioselectivity and afforded the expected keto compounds **103**, **105**, and **107**, respectively. Whereas, macrocyclic compounds **108**, **110** and **112**[20b] did not undergo the reaction to produce the oxidized compounds (Scheme 19). These experimental results indicate that the presence of homoallylic alcohol is essential for the desired transformation. Probably, the success of the reaction on selected macrocycles can be explained by the OH group co-ordination with a double bond through a Pd species

(Figure 9).[49] (Note: The compounds **104** and **106** were synthesized in the later part of the synthesis, for understanding purpose shown here)



Scheme 22: Scope of Wacker oxidation

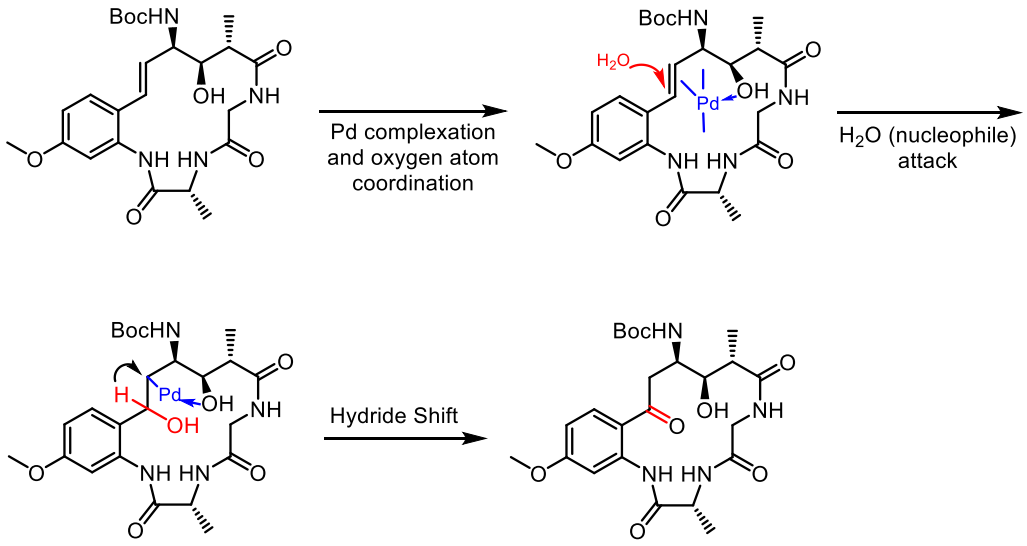
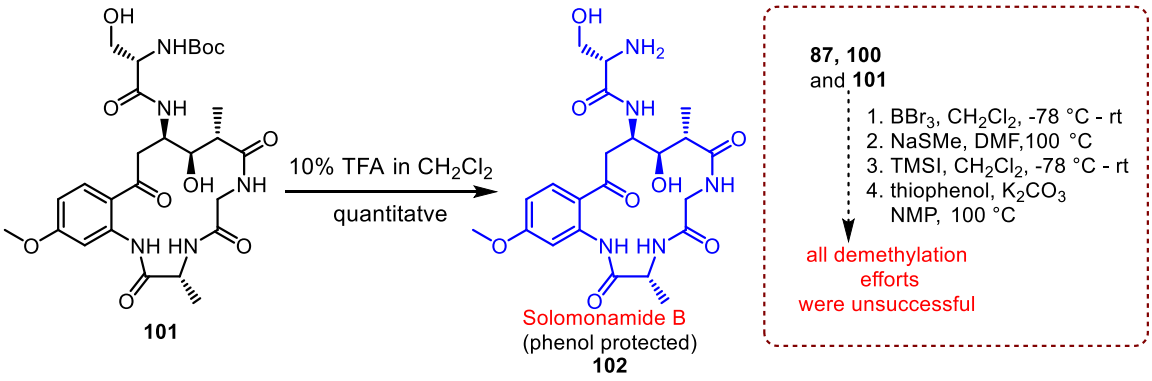


Figure 9. Plausible mechanism for hydroxyl-directed wacker oxidation

The only task left for the completion of the total synthesis was deprotection of phenolic methyl group. Despite a few trials under various conditions shown in scheme 19, this transformation could not be achieved at final stages on compound **101** or any of the intermediate stages **87** and **100**. Finally, exposure of compound **101** to 10% TFA in CH_2Cl_2 and evaporation of solvent furnished solomonamide B methyl ether **102** in quantitative yield (Scheme 23). The disappearance of signals related to Boc protecting group in ^{1}H and ^{13}C NMR Spectrum confirmed the Boc deprotection. HRMS (ESI) analysis showed a peak at m/z 494.2245 corresponding to $[M+H]^+$ with molecular formula $C_{22}H_{32}O_8N_5$ further confirmed the formation of compound **102**.

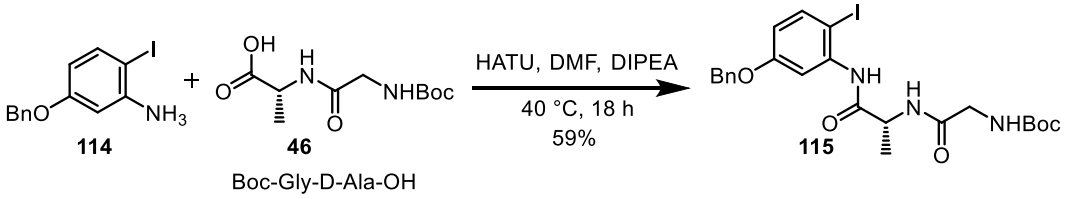


Scheme 23: Synthesis of phenol protected solomonamide B

The synthesized compound **102** represents the complete structure of solomonamides with the requisite stereochemistry pattern and desired functionalities. Thus, the total synthesis of solomonamide B was achieved in protected form.

2.4.5. Change of protecting group and completion of solomonamide B synthesis

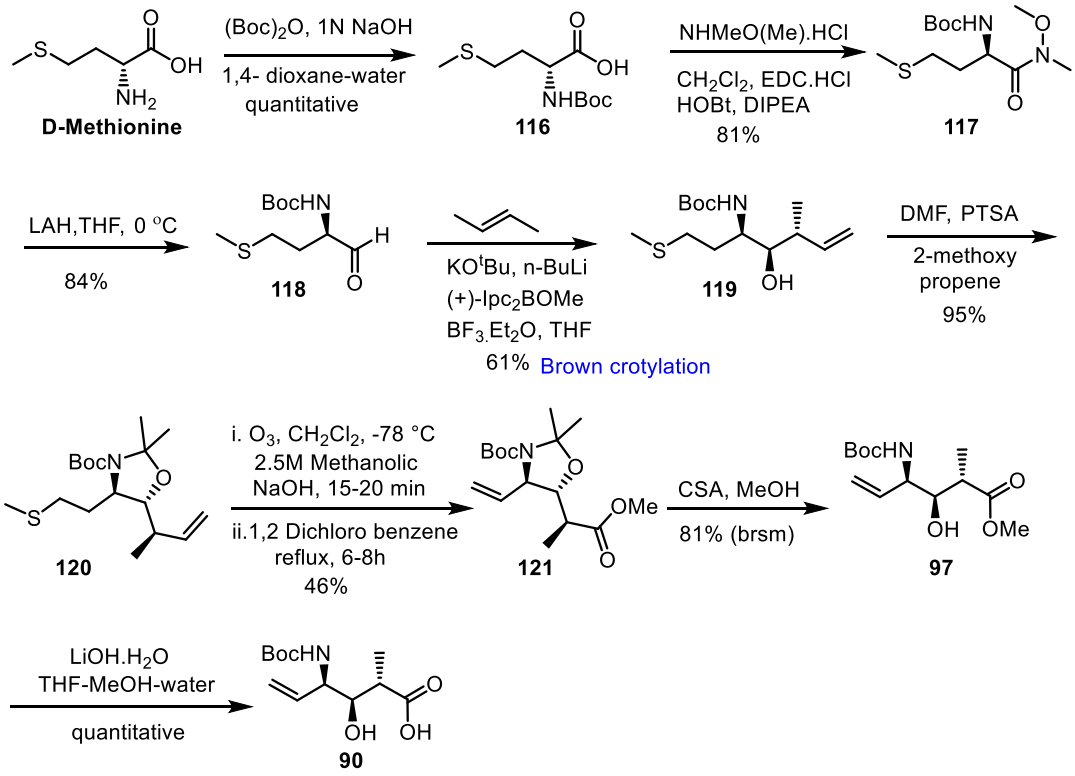
An appropriate protecting group was needed to circumvent the problem of deprotection of phenolic methyl group.It was decided to go with benzyl protection because it could be deprotected under mild and neutral conditions such as hydrogenation. Accordingly, aniline derivative **114**[50] was prepared by following literature procedures in which phenolic hydroxy group was protected with a benzyl group. Then it was coupled with the dipeptide, Boc-Gly-D-Ala-OH (**56**) to obtain compound **115** in 59% yield (Scheme 24).



Scheme 24: Synthesis of dipeptide fragment with benzyl protection

At the same time, another approach was developed for the synthesis of non- amino acid partner to improve the overall efficiency of our total synthesis. The amino acid D-methionine was converted to corresponding Weinreb amide **117**, through the intermediate **116**. Then, it was reduced to aldehyde **118** by following literature procedures.[51] The aldehyde **118** on Brown crotylation reaction using (+)–(B)-*E*- crotyldiisopinocamphenyl borane afforded compound **119** with desired stereochemistry in 61% yield as a single isomer. The stereochemistry was assigned based on literature reports.[52] The amino alcohol in compound **119** was protected as acetonide to give the compound **120** in very good yield. The compound **120** on ozonolysis (in methanolic NaOH) followed by refluxing in 1,2-dichloro benzene[53] afforded olefinic ester **121** in 46% yield for 2 steps. Deprotection of acetonide in compound **121** using CSA/MeOH afforded compound **97** in 81% yield based on recovered starting material. The ^{1}H, ^{13}C NMR, and rotation values

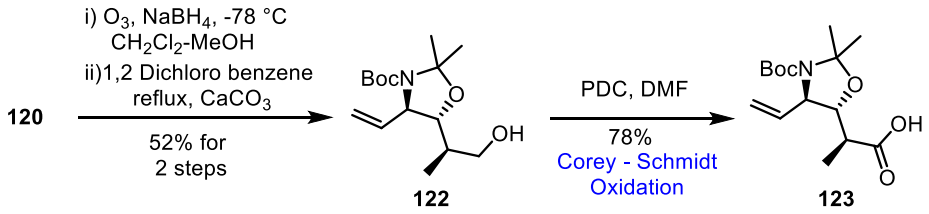
are identical with the previously synthesized compound **97.** The compound **97** on hydrolysis afforded acid compound **90** in quantitative yield (Scheme 25).



Scheme 25. Alternate approach for the synthesis of non-amino acid fragment

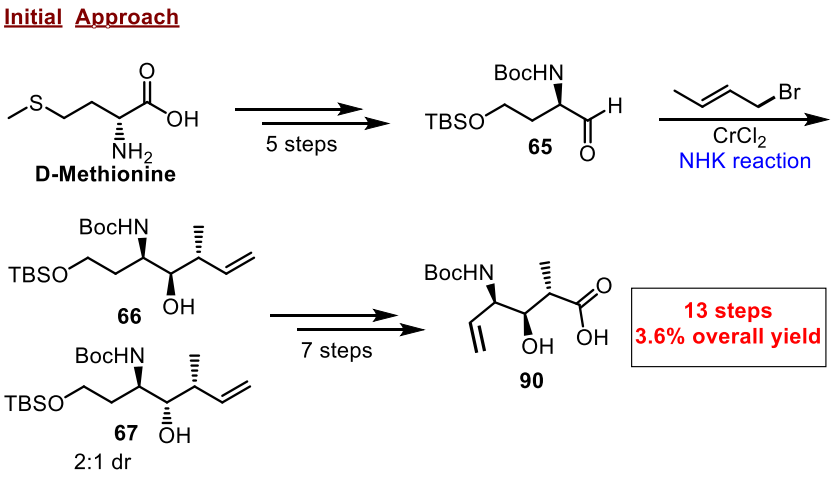
In previous approach and present approach, ozonolysis reaction and ester hydrolysis reactions were carried out under basic conditions. Although we were confident that there will not be any epimerization in reaction condition based on literature precedence, to avoid ambiguity in final stages the approach was slightly modified. The compound **120** on reductive ozonolysis (O_3, $NaBH_4$),[54] followed by refluxing in 1, 2 dichlorobenzene afforded alkenol **122** in 52% yield over 2 steps. The appearance of signals in ^{1}H NMR spectrum at δ 5.76 - 5.57 (m, 1H), 5.14 (d, J = 10.0 Hz, 2H) and signals at 138.0, 117.2 in ^{13}C NMR spectrum corresponding to olefin confirmed the desired product formation. In addition to this, the HRMS (ESI) analysis showed a peak at m/z 308.1833 corresponding to $[M+Na]^+$ with molecular formula $C_{15}H_{27}O_4NNa$ further confirmed the formation of **122**. The alcohol was converted into desired key unnatural amino acid component **123**

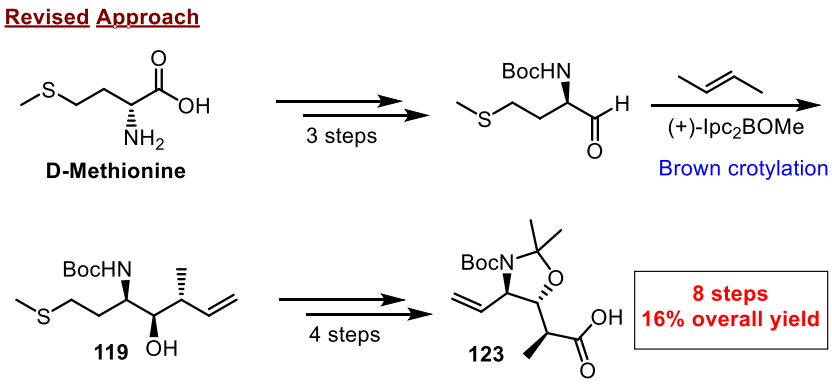
using Corey- Schmidt condition (PDC/DMF)[55] (Scheme 26). The appearance of signal at δ 178.9 corresponding to acid carbonyl confirmed the oxidation of alcohol to acid. HRMS (ESI) analysis showed a peak at m/z 322.1622 corresponding to $[M+Na]^+$ with molecular formula $C_{15}H_{25}O_5NNa$ further confirmed the formation of the required non-amino acid fragment **123**.



Scheme 26. Improved synthetic approach for the synthesis of non-amino acid fragment

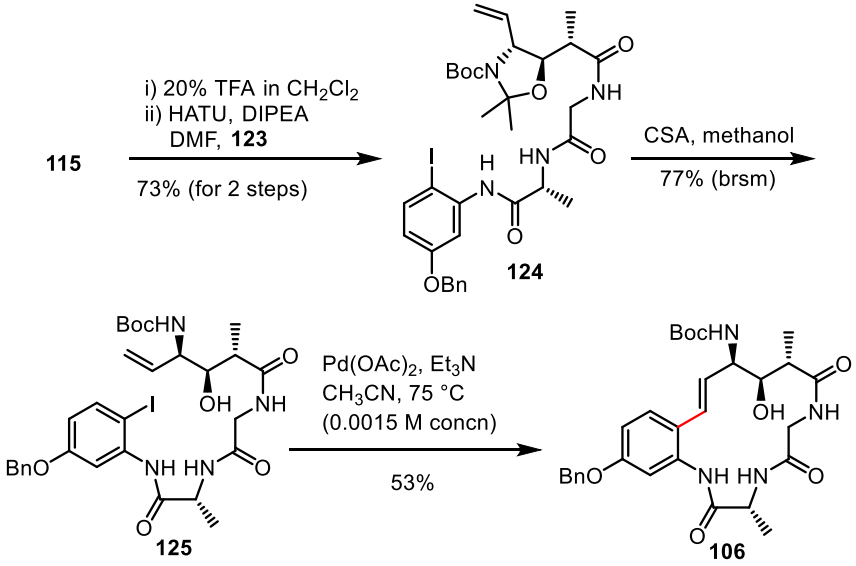
In the first approach, the non-amino acid fragment was achieved in 13 steps with 3.6% overall yield starting from D-methionine. NHK reaction was used to install the stereochemistry and selenium elimination was used to synthesize Olefin. It is worth noting that in the revised approach NHK reaction was replaced with Brown crotylation reaction, where exclusively one isomer was synthesized and sulfoxide elimination was used to synthesize olefin. Thus, in modified approach, the key non-amino acid **123** was synthesized in 8 steps with 16% overall yield starting from commercially available same starting material, i.e D-methionine (Scheme 27).





Scheme 27. Comparison of approaches for the synthesis of unnatural amino acid fragment

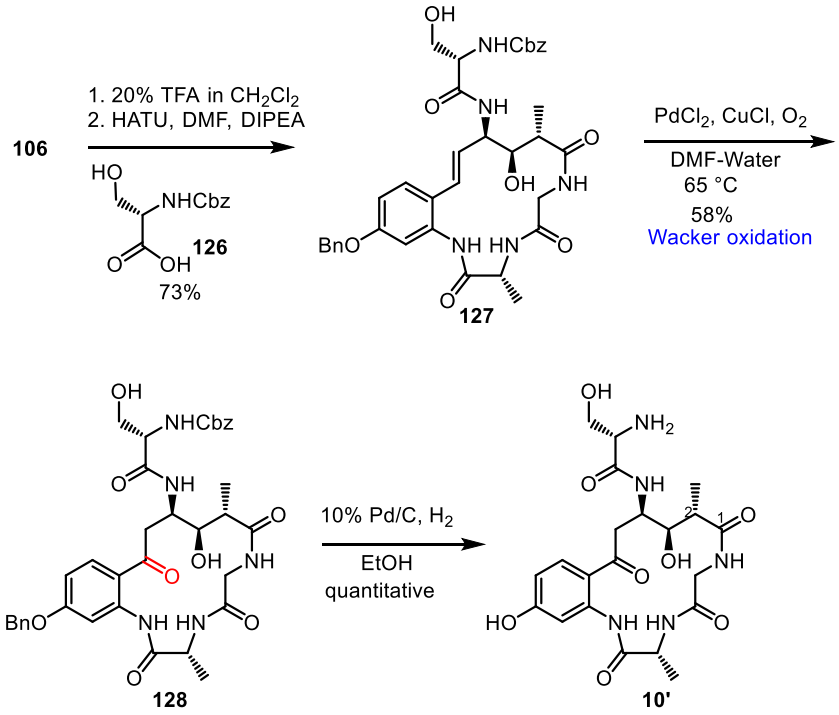
The unnatural amino acid component **123** was coupled (HATU-DIPEA) with the free amine prepared from **115** to yield compound **124** in 73% yield for 2 steps. Acetonide deprotection in compound **124** afforded macrocyclic precursor **125** in good yields based on recovered starting material. Compound **125** was subjected to intramolecular Heck reaction under optimized conditions ($Pd(OAc)_2$, Et_3N) to furnish the macrocycle **106** in moderate yields (Scheme 28). Compound **106** represents the complete macrocyclic core of the proposed structure of solomonamides with appropriate functionalities and



Scheme 28: Synthesis of macrocyclic skeleton of solomonamide B (benzyl protection)

stereochemistry pattern. The macrocyclization worked well like in the case of –OMe series and the compound wasa obtained with a slight improvement in yield. (43% for OMe compound to 53% for OBn compound). The appearance of ^{1}H NMR signals at 6.60 (d, *J* = 15.7 Hz, 1H), 5.91 (dd, *J* = 8.9, 15.8 Hz, 1H) corresponding to substituted double bond and HRMS (ESI) peak at 589.2628 corresponding to $[M+Na]^+$ with molecular formula $C_{30}H_{38}O_7N_4Na$ confirmed the desired product formation.

After having the macrocycle core **106**, the next task was coupling of the serine moiety. Accordingly, Boc was deprotected in 20% TFA in CH_2Cl_2 followed by coupling with CbzNH-L-ser-OH **126**[56] afforded compound **127.** In previous approach BocNH-OTBS-L-ser-OH was utilized (See: Scheme 19), which was replaced with CbzNH- L-serine-OH **126,** considering both OBn and Cbz groups can be deprotected simultaneously under hydrogenation condition. The compound **127** when subjected to Wacker oxidation under optimized condition afforded keto compound **128.** As per the plan compound, **128** was treated with Pd/C and stirred under H_2 atmosphere to afford compound **10'.** The disappearance of peaks at δ 7.29 - 7.53 (m, 10H) in ^{1}H NMR confirms that both OBn and Cbz were getting deprotected. HRMS (ESI) analysis showed a peak at m/z 480.2084 corresponding to $[M+H]^+$ with molecular formula $C_{29}H_{30}O_8N_5$ corresponding to solomonamide B. However, to our surprise, the NMR (^{1}H & ^{13}C NMR) values are not identical with the reported values and in ^{1}H NMR the $–CH_3$ peak corresponding C2 appeared at δ 0.92 as dd with coupling constant *J* = 6.94, 13.87 Hz which in principle has to be a doublet (d). The actual reason for the typical behavior of $– CH_3$ group could not be figured out, but it was observed that this splitting pattern (dd) was seen only when Pd was used in the final step.



Scheme 29: Efforts toward total synthesis of solomonamide B

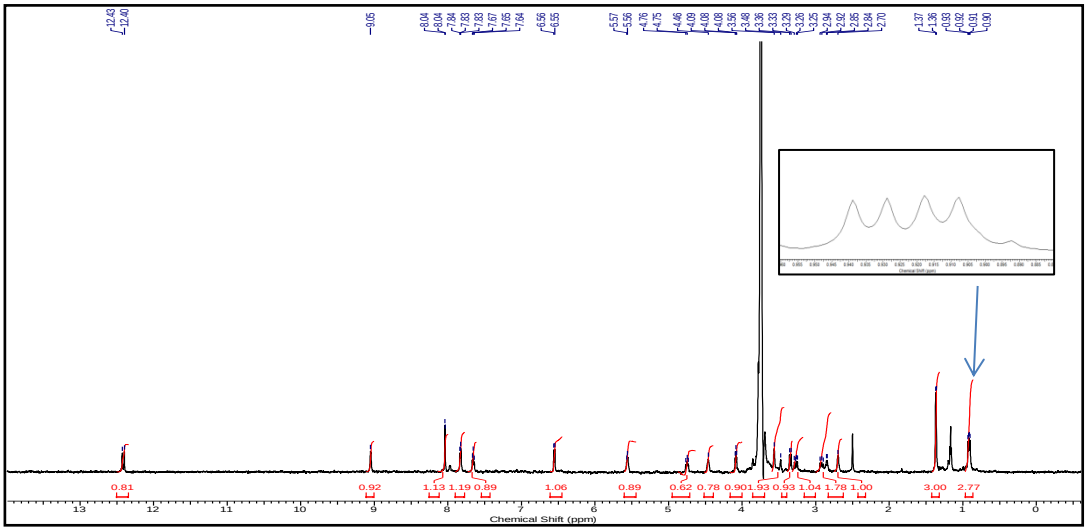
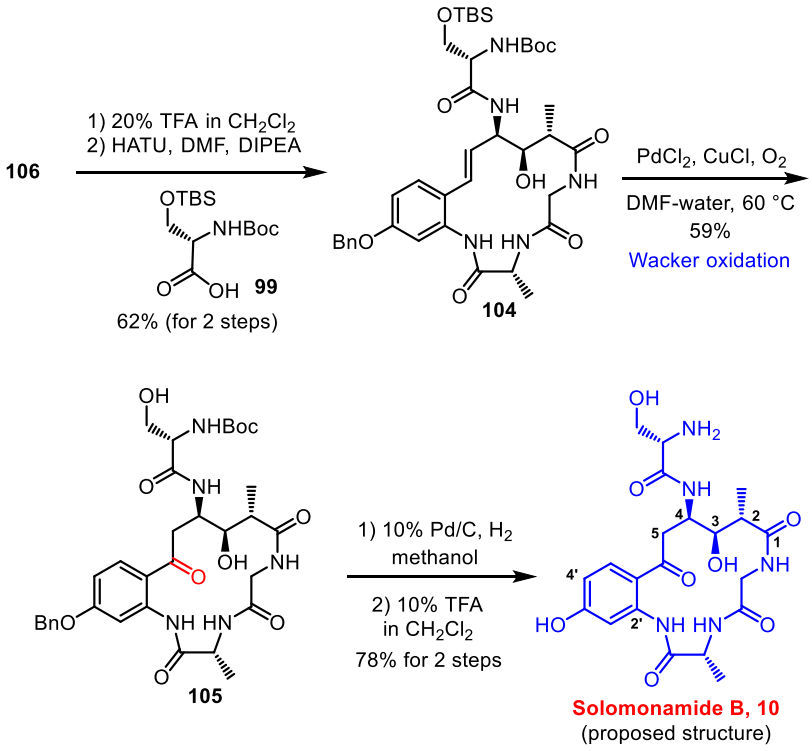


Figure 10: ^{1}H NMR spectrum of **10'**

At this stage, we decided to go with our previous approach, followed for the synthesis of solomonamide B methyl ether (see Scheme 21 and 23). Accordingly, removal of Boc

group in macrocycle **106** followed by coupling of the serine derivative **99** gave the compound **104** in 62% yield. Compound **104** was subjected to Wacker oxidation under the optimized condition to afford solomonamide B in protected form, **105.** Deprotection of the benzyl group in **105** furnished the phenolic compound which was filtered through the column and treated with 10% TFA in CH_2Cl_2 to afford the target compound solomonamide B. The disappearance of signal at δ 1.41 (s, 9H), in ^1H NMR spectrum confirmed the Boc deprotection and disappearance of signals corresponding to benzyl group in ^1H and ^{13}C NMR spectrum indicated the gross structure as drawn. The HRMS (ESI) showed a peak at 480.2085 corresponding to $[M+H]^+$ with molecular formula $C_{29}H_{30}O_8N_5$ further confirmed desired product formation (Scheme 30).



Scheme 30: Total synthesis of proposed structure of solomonamide B

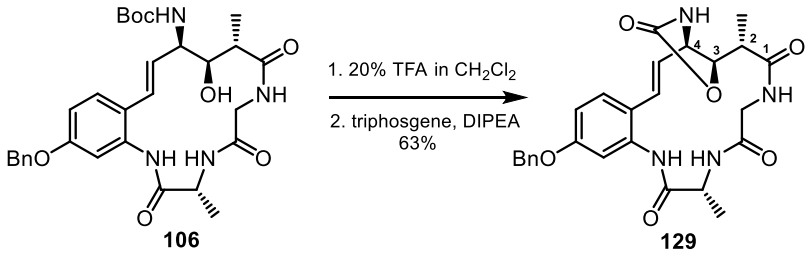
Table 5: ^{1}H and ^{13}C chemical shift data of **10** in comparison to the reported values

Residue	Notation	δ_H (δ_H reported), multiplicity, J_{HH}	δ_C (δ_C reported)
Gly			
	1 (CO)	--	169.84 (169.0)
	2a	4.81(4.19), dd, $J_{H\alpha\text{-}H\alpha'}$=15.2, $J_{NH\text{-}H\alpha}$=9.0	42.06 (42.4)
	2b ′	3.34(3.78), dd, $J_{H\alpha\text{-}H\alpha'}$=15.2	--
	3 (NH)	7.73(7.30), dd, $J_{NH\text{-}H\alpha}$=9.0	--
D-Ala			
	1 (CO)	--	172.15(179.2)
	2a	4.12(4.29), dq, $J_{H\alpha\text{-}H\beta}$=7.4, $J_{NH\text{-}H\alpha}$=6.2	50.73 (49.7)
	3	1.39 (1.36), d, $J_{H\alpha\text{-}H\beta}$=7.4	16.99(16.0)
	4 (NH)	9.09 (8.79), d, $J_{NH\text{-}H\alpha}$=6. 2	--
L-Ser			
	1 (CO)	--	165.66(166.7)
	2	3.95 (3.98), br	53.67(53.6)
	3a	3.71 (3.69), br	60.61 (60.3)
	3b	3.71 (3.69), br	--
	4 (OH)	5.46(5.46),br, ol	--
	5 (NH_2)	8.06(8.08), br	--
Non peptide portion			
	1 (CO)	--	172.61(173.2)
	2	2.76 (2.35), dq, $J_{H2\text{-}H7}$=7.1	45.23(45.4)
	3	3.59 (3.39), br	71.40(72.2)
	4	4.52(4.52), br, m	45.23(48.0)
	5a	3.32 (3.34), dd, $J_{H\alpha\text{-}H\alpha'}$=17.6	42.29(41.2)
	5b	2.91 (2.87), $J_{H\alpha\text{-}H\alpha'}$=17.6	--
	6	--	200.17(201.1)
	7	0.97 (1.08), d, $J_{H2\text{-}H7}$=7.1	9.38 (13.6)
	8 (OH-3)	5.44 (5.53), br, ol	--
	9 (NH-4)	7.87 (7.98), br, ol	--
	1′	--	113.96 (115.8)
	2′	--	142.41 (141.3)
	3′	8.13 (7.92), d, $J_{H3'\text{-}H5'}$=2.5	105.66 (106.1)
	4′	--	163.36 (162.9)
	5′	6.58 (6.57), dd, $J_{H5'\text{-}H6'}$=8.9, $J_{H3'\text{-}H5'}$=2.5	110.15 (110.0)
	6′	7.86(7.77), d, $J_{H5'\text{-}H6'}$=8.9	133.67 (132.9)
	10 (OH-4′)	10.75 (10.70), br, s	--
	11 (NH-2′)	12.52 (11.50), br, s	

Multiplicities and *J* coupling constants are provided only for the resonances that are without any overlaps or wherever the unambiguous measurements were possible.

The NMR spectroscopic data for the compound **10** was obtained in DMSO-d_6 at 300 K on a 500 MHz spectrometer. The complete ^{1}H and ^{13}C chemical shift assignment (Table 5) was done by 1D and 2D (DQF-COSY, TOCSY, ROESY, HSQC, and HMBC) homo and heteronuclear experiments. Clearly, the chemical shifts data for the synthesized solomonomide B did not match with the reported values (Table 5), which is more likely due to the misassignment of the stereochemistry in the isolated natural product by Zampella's group.

Despite the relative stereochemistry at 2, 3 and 4 carbons were concretely established from stereoselective synthetic schemes 22, 23, 24 and 26. To ensure the same in the final stages, supporting NMR studies were carried out on a derivative of **106**. For this purpose, a pentacyclic carbamate derivative **129** has been synthesized from **106** by Boc deprotection followed by treating with triphosgene. This derivatization was necessary so as to induce some conformational rigidity into the macrolide ring of **106**, which otherwise might be flexible.



Scheme 31: Rigidification of macrocycle **106** for NMR studies

The ^{1}H NMR chemical shift data for **129** in DMSO-d_6 showed near identical values for protons at 3 and 4, so the NMR studies were repeated in Acetone-d_6 at 300 K. The observed ROE pattern H2-H3 (very strong), H6-H3 (strong), H6-H4 (strong), H5-H3 (strong), H5-H9 (medium), H7-H3 (strong), Gly-NH-H2 (strong), Gly-NH-H3 (strong), Gly-NH-H4 (weak), Gly-NH-H7 (very weak), H4-H7 (very strong) and H9-H7 (very weak) well support the relative stereochemistry (Figure 10).

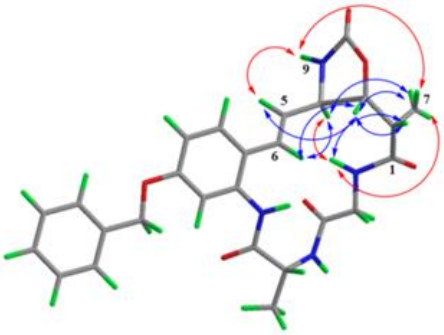


Figure 10: The key ROE pattern in **129** (shown in curved double-headed arrows - very strong and strong ROEs in blue; medium to weak ROEs in red) observed for 23 in support of the relative stereochemical configuration at positions 2, 3 and 4. The core structure is drawn in chem.3D for an appropriate representation of the ROE pattern.

Along with the NMR studies, crystallization on various macrocyclic compounds was also tried simultaneously. Although the attempts to obtain suitable crystals of the macrocyclic intermediates were not successful, fortunately, compound **129** was crystallized in the NMR tube upon long standing and its crystal structure analysis further confirmed the presence of the required stereochemistry in **129** (Figure 11). Thus, the total synthesis of the proposed structure of solomonamide B was accomplished for the first time. Careful analysis and head-to-head comparison of the ^{1}H and ^{13}C NMR spectral data of the synthesized compound and natural solomonamide B suggests there is a problem with the original structure assignment, in particular in the stereochemistry of non-peptide portion.

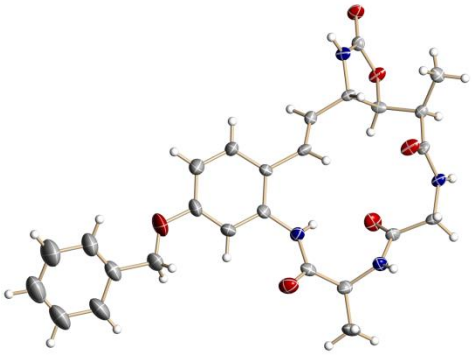
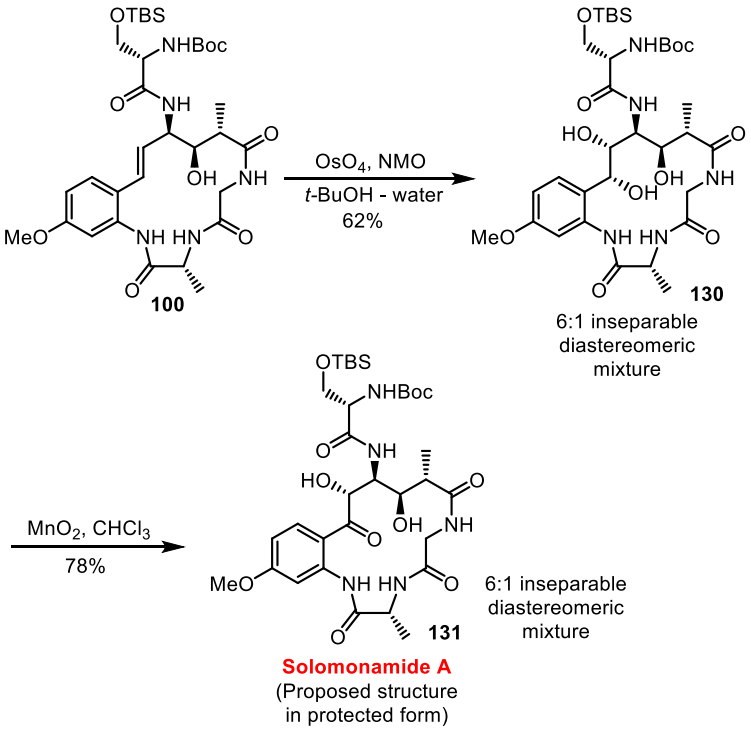


Figure 11: *ORTEP* diagram of **129**

2.4.6. Attempts toward total synthesis of proposed structure of solomonamide A

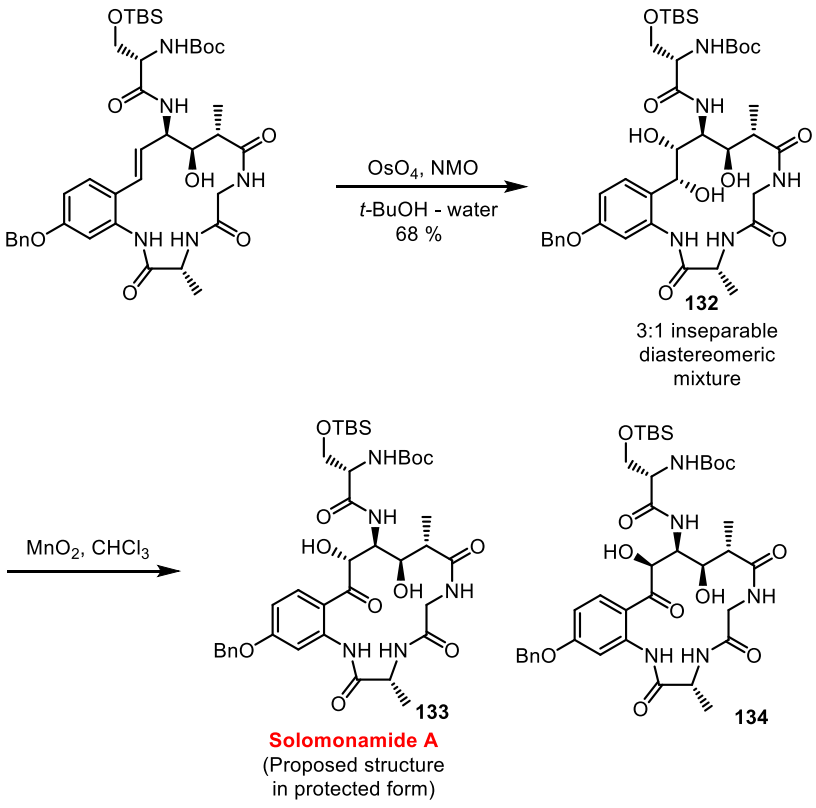
The solomonamide B structure was assigned based on solomonamide A, which suggests that the structure of solomonamide A also needs to be revised. Although the structure is wrong, the synthesis of the proposed structure was initiated to check the feasibility of designed strategy. Initially, the OMe series was tried, accordingly the macrocycle **100** was dihydroxylated using Upjohn conditions (OsO_4, NMO)[57] to afford **130** as a 6:1 inseparable diastereomeric mixture. The appearance of two sets of signals in ^1H and ^{13}C NMR confirmed the mixture of diastereomers. Disappearance of signals in ^1H NMR at 6.63 (d, J = 16.1 Hz, 1H), 6.08 - 6.04 (m, 1H) corresponding to substituted styrene and peak at m/z 748.3558 in the HRMS (ESI) analysis corresponding to $[M+Na]^+$ with molecular formula $C_{33}H_{55}O_{11}N_5Na$ confirmed the formation of dihydroxy compound **130.** The compound **130** on benzylic oxidation afforded **131,** solomonamide A and its epimer in protected form as 6:1 diastereomeric mixture. The benzylic oxidation was confirmed



Scheme 32. Total synthesis of proposed structure of solomonamide A in protected form (methyl ether)

by the appearance of a signal at δ 194.3 in ^{13}C NMR spectrum corresponding to the benzylic carbonyl. In addition, the HRMS (ESI) analysis showed a peak at m/z 746.3406 corresponding to $[M+Na]^+$ with a molecular formula $C_{33}H_{53}O_{11}N_5NaSi$ further confirmed the formation of **131**. Although there is no experimental support for the stereochemical outcome, it was expected that major compound may be required isomer considering that the dihydroxylation takes place from the less hindered side. It is purely based on the assumption and we have no support for the same.

Later, same reaction sequence was carried out with OBn series, dihydroxylation on **104** afforded compound **132** as 3:1 diastereomeric mixture which was inseparable like in –OMe series. Benzylic oxidation of **132** afforded compounds **133** and **134** which could be separated by column chromatography (Scheme 29). The major compound **133** is expected

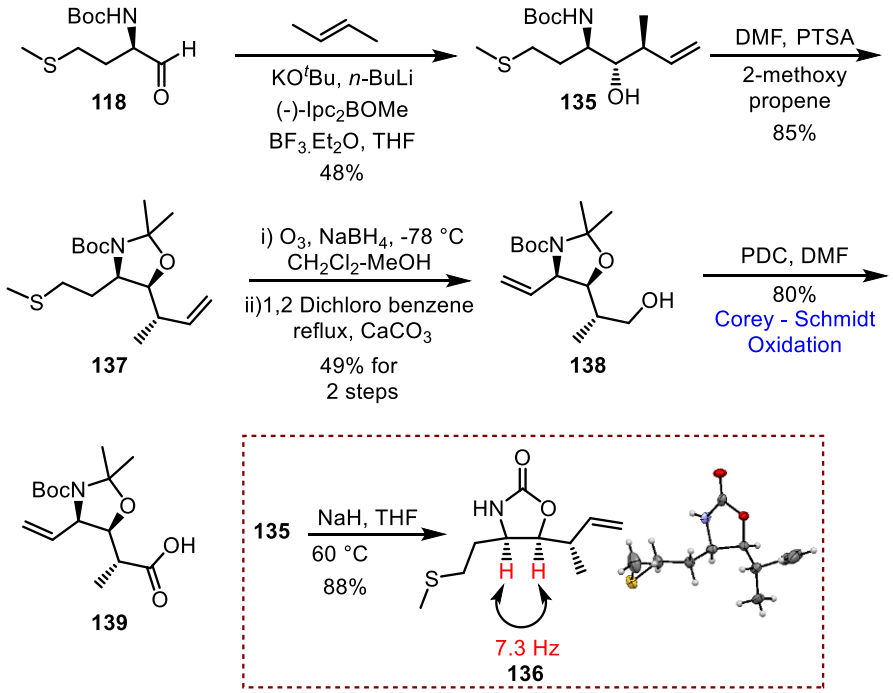


Scheme 33. Total synthesis of proposed structure of solomonamide A in protected form (benzyl ether)

to be proposed structure of solomonamide A. Thus, we have developed a route for the synthesis of solomonamide A.

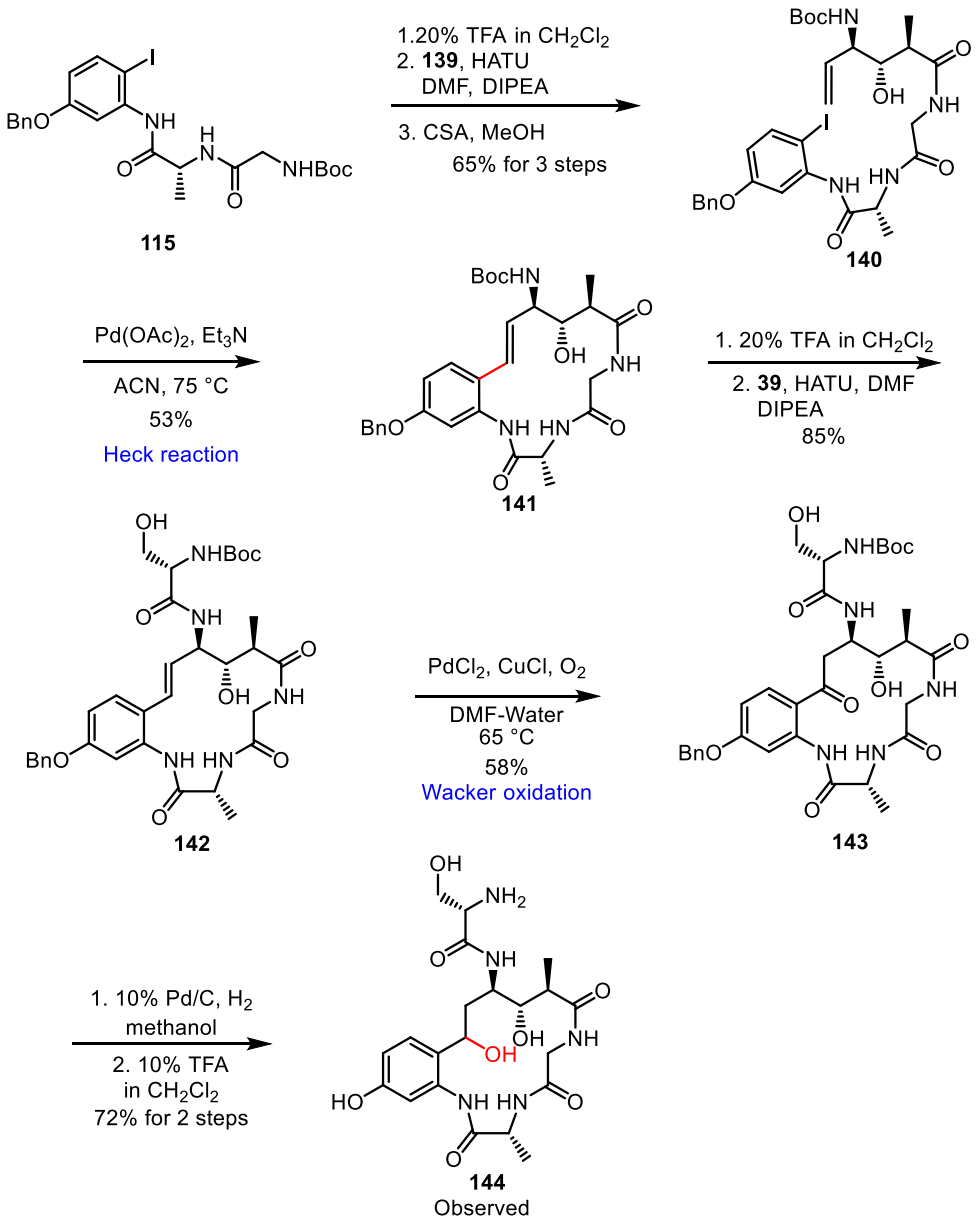
2.4.7. Efforts toward structural revision of solomonamide B

After accomplishing the total synthesis of proposed structures of both the natural products, The next task was to establish the stereochemistry of non-amino acid portion and structural revision of natural products. As an initial effort, it was planned to reverse the stereochemistry of the hydroxyl and methyl groups, considering the information from Zampella's group, where both the methyl and hydroxyl group are to be in *anti*- relation and the major discrepancy in ^{1}HNMR was the appearance of –CH_3 attached proton (C2 carbon) at 2.7 ppm instead of 2.35 ppm. Accordingly, the key non-amino acid fragment was synthesized from methionine aldehyde **118**. The aldehyde **118** on brown crotylation using (-)-Ipc_2BOMe afforded fragment **135** with desired stereochemistry. X-ray crystal structure of corresponding carbamate **136** further confirmed the stereochemistry.



Scheme 34. Synthesis of non-amino acid fragment with change in C2-C3 stereochemistry

Later, compound **135** was converted to key non-amino acid **139** through the intermediacy of **137** and **138** by following a similar synthetic sequence like in the previous scheme (see scheme 25 and 26). The unnatural amino acid component **139** was coupled (HATU-DIPEA conditions) with the free amine prepared from **115** followed by acetonide deprotection afforded macrocyclic precursor **140** in 65% yield for 3 steps. Compound

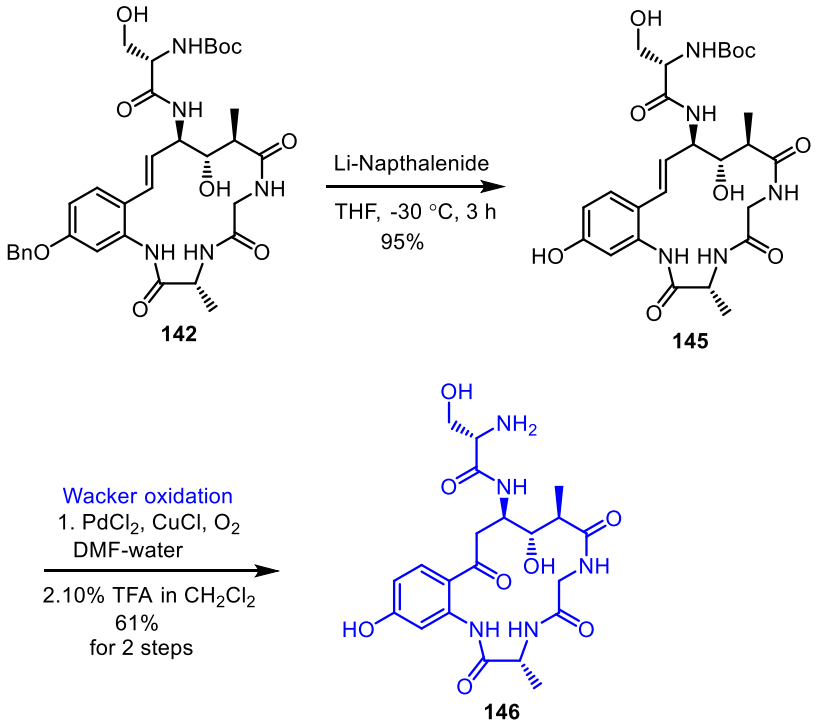


Scheme 35. Efforts toward synthesis of compound **144**

140 was subjected to intramolecular Heck reaction under optimized conditions ($Pd(OAc)_2$, Et_3N) to furnish the macrocycle **141** in moderate yields (Scheme 35). Like in previous scheme deprotection of Boc group in macrocycle **141** followed by coupling of the serine derivative **39**[21a] (Boc-Serine-OH was used instead of TBS protected serine) gave the desired compound **142** in 85% yield. Compound **142** was subjected to Wacker oxidation under optimized conditions to afford compound **143** in moderate yield. Deprotection of the benzyl group in Pd/C, H_2 atmosphere followed by treatment with 10% TFA in CH_2Cl_2 afforded the carbonyl reduced compound **144** as a single diastereomer with unknown stereochemistry in 72% yield for 2 steps. The carbonyl reduction in compound **144** was confirmed by the disappearance of the peak at δ 200.3 and appearance of an additional peak at δ 83.3 in ^{13}C NMR. In addition to this, the HRMS (ESI) analysis showed a peak at m/z 482.2242 corresponding to $[M+H]^+$ with a molecular formula $C_{21}H_{32}O_8N_5$ further confirmed the formation of product **144.** Replacement of Pd/C with $Pd(OH)_2$ or use of Pd/C poisoned with $CaCO_3$ or barium sulfate or adding external alkene compound like cyclohexene in reaction mixture did not solve the problem.

To circumvent this problem of carbonyl reduction, benzyl protection was removed in penultimate compound **142**. The benzyl deprotection was achieved using Li-napthalenide, to afford compound **145** in a very good yield. The compound **145** was subjected to Wacker oxidation and followed by Boc deprotection in 10% TFA in CH_2Cl_2 afforded the target compound **146**. The HRMS (ESI) analysis showed a peak at m/z 480.2087 corresponding to $[M+H]^+$ with a molecular formula $C_{29}H_{30}O_8N_5$ further confirmed the formation of product **146**.

Thus, the putative structure of solomonamide B and analog with C2-C3 inversion was synthesized. Unfortunately, the NMRs of both the compounds did not match with the reported values which necessitate a structural revision. Synthesizing different isomers by changing the stereochemistry of non-amino acid partner may help in revising the structure. The efforts towards the structural revision of solomonamides are currently ongoing in our lab.



Scheme 31. Synthesis of **146**

2.5. Analogs synthesized

Several analogs were synthesized by keeping dipeptide portion intact, varying non-amino acid partner and with/without serine moiety. A compound such as **44** represents simplified macrocyclic skeleton of solomonamide B without any chiral centers in the non- amino acid portion. The biological activity of this compound can explain the importance of stereocenters in non- amino acid portion. Compound **129** is a macrolide with required stereocenters and amino alcohol was protected as a carbamate. The carbamate carbonyl can serve as a serine carbonyl. The compounds **87**, **106**, **129** can explain the importance of benzylic carbonyl. **103**, **107** are the compounds without serine moiety and phenol is protected as methyl/benzyl ether can reveal the importance of serine and phenolic-OH. The compound **102** is a methyl ether of proposed structure of solomonamide B (**7**). The biological evaluation of **102** and **7** can explain the relevance of phenolic-OH. The difference between **146** and **7** is an inversion of C2, C3 centers. This can help to find out the importance of absolute configuration of C2 and C3 centers.

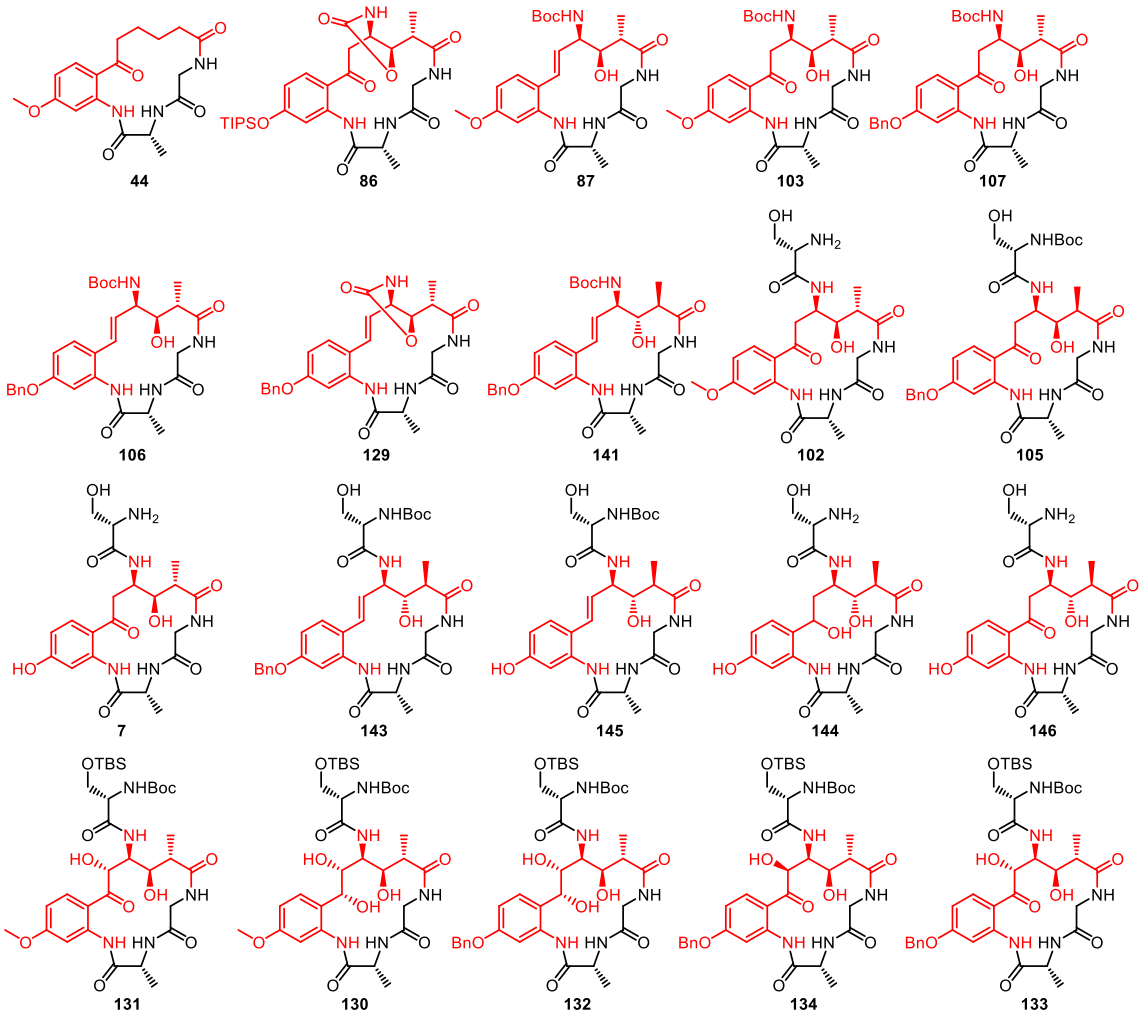


Figure 12. Synthesized analogs

Dihydroxy compounds **130**, **132** and alpha hydroxyl carbonyl compounds **131, 133** and **134** which are close to the proposed structure of solomonamide A and can be tested after deprotections. All these modifications will help to understand the SAR better. In addition, more compounds with varying stereochemical pattern are being synthesized in our group. All these compounds will be evaluated in anti-inflammatory assays to come up with better molecules for the generation of anti-inflammatory leads.

2.6. Conclusions

- Macrocyclizations using different methods were demonstrated to form solomonamide skeleton.
- Total synthesis of solomonamide B showed there is a discrepancy in NMR which suggests that there is a need for structural revision.
- The proposed structure of solomonamide A was synthesized in protected form.
- Prepared several analogs of solomonamides, which are to be evaluated in anti-inflammatory assays.
- Developed a mild and practical one-pot method to access olefinic esters using ozonolysis in a two-directional approach and demonstrated its utility with various useful examples.

Thus, the experimental research work carried out during the last five years is described in this section clearly lays the foundation for the future work on solomonamides, in particular, who are practicing medicinal chemistry towards the identification of lead molecules based on macrocyclic scaffolds.

2.7. References

1.(a) I. Kitagawa, M. Kobayashi, T. Katori, M. Yamashita, J.Tanaka, M. Doi, and T. J. Ishida, *Am Chem Soc*, 1990, **112**, 3710 (b) M. Kobayashi, S. Tsukamoto, A. Tanabe, T. Sakai, and M. J. Ishibashi, *J. Chem. Soc. Perkin trans1*., 1991, **112**, 2379.

2. A. S. Ratnayake, R. A. Davis, M. K. Harper, C. A. Veltri, C. D. Andjelic, L. R. Barrows, and C. M. Ireland, *J. Nat. Prod*., 2005, **68**, 104.

3. (a) E. Kho, D. K. Imagawa, M. Rohmer, Y. Kashman, and C. Djerassi, *J. Org.Chem*., 1981, **46**, 1836. (b) T. Hamada, T. Sugawara, S. Matsunaga, and N. Fusetani, *Tetrahedron Let*., 1994, **35**, 609. (c) C. Festa, S. De Marino, M. V. D'Auria, G. Bifulco, B. Renga, S. Fiorucci, S. Petek, and A. Zampella, *J. Med. Chem.* 2011, **54**, 401.

4. (a) T. Hamada, S. Matsunaga, G. Yano, and N. Fusetani, *J. Am. Chem. Soc*., 2005, **127**, 110 (b) N. Fusetani, K. Warabi, Y. Nogata, Y. Nakao, S. Matsunaga, and R. R. M.. Van Soest, *Tetrahedron Lett*., 1999, **40**, 4687.(c) T. Araki, S. Matsunaga, and N. Fusetani, *Biosci. Biotechnol. Biochem*., 2005, **69**, 1318 (d) N. Fusetani, S. Matsunaga, H.

Matsumoto, and Y. Takebayashi, *J. Am. Chem.Soc.*, 1990, **112**, 7053.

5. (a) Y. Nakao, S. Matsunaga, and N. Fusetani, *Bioorg. Med. Chem*., 1995, **3**, 1115. (b) Y. Nakao, N. Oku, S. Matsunaga, and N. Fusetani, *J. Nat. Prod*., 1998, **61**, 667.

6. (a) J. Kobayashi, M. Sato, T. Murayama, M. Ishibashi, M. R. Walchi, M. Kanai, J. Shoji, and Y. Ohizumi, *J. Chem. Soc. Chem. Commun*., 1991, 1050.(b) N. Fusetani, T. Sugawara, S. Matsunaga, and H. Hirota, *J. Am. Chem. Soc*., 1991, **113**, 7811.

7. M. C. Roy, I. I. Ohtani, J. Tanaka, T. Higa, and R. Satari, *Tetrahedron Lett.*, 1999, **40**, 5373.

8. J. Kobayashi, M. Sato, M. Ishibashi, H. Shigemori,T. Nakamura, and Y. Ohizumi, *J. Chem.Soc.PerkinTrans*.,1991,**1**,2609.

9.(a) F. Itagaki, H. Shigemori, M. Ishibashi, T. Nakamura, T. Sasaki, and J. Kobayashi, *J. Org. Chem*., 1992, **57**, 5540. b) J. Kobayashi, F. Itagaki, H. Shigemori, T. Takao, and Y. Shimonishi, *Tetrahedron*, 1995, **51**, 2525. c) H. Uemoto, Y. Yahiro, H. Shigemori, M.Tsuda, T. Takao, Y. Shimonishi, and J. Kobayashi, *Tetrahedron*, 1998, **54**, 6719. d) M. Tsuda, H. Ishiyama, K. Masuko, T. Takao, Y. Shimonishi, and J. Kobayashi, *Tetrahedron*, 1999, **55**, 12543. e) L. S. Bonnington, J. Tanaka, T. Higa, J. Kimura, Y. Yoshimura, Y. Nakao, W. Y. Yoshida, and P. J. Scheuer, *J. Org. Chem.*, 1997, **62**, 7765.

10. L. Chill, Y. Kashman, and M. Schleyer, *Tetrahedron*, 1997, **53**, 16147.

11. S. Matsunaga, N. Fusetani, K. Hashimoto, and M. Walchli, *J. Am. Chem. Soc*., 1989, **111**, 2582.

12. M. Kobayashi, K. Kanzaki, S. Katayama, K. Ohashi, H. Okada, S. Ikegami, and I. Kitagawa, *Chem. Pharm. Bull*., 1994, **42**, 1410.

13. (a) I. Kitagawa, M. Kobayashi, N. K. Lee, H. Shibuya, Y. Kawata, and F. Sakiyama, *Chem. Pharm. Bull.*, 1986, **34**, 2664. b) D. P. Clark, J. Carroll, S. Naylor, and P. Crews, *J. Org. Chem*., 1998, **63**, 8757. c) T. Araki, S. Matsunaga, Y. Nakao, K. Furihata, L. West, D. J. Faulkner, and N. Fusetani, *J. Org. Chem*., 2008, **73**, 7889.

14. (a) P. W. Ford, K. R. Gustafson, T. McKee, N. Shigematsu, L. K. Maurizi, D. E. Williams, E. Dilip de Silva, P. Lassota, T. M. Allen, R.Van Soest, R. J. Andersen, and M. R Boyd, *J. Am. Chem. Soc*., 1999, **121**, 5899. b) Y. Okada, S. Matsunaga, R. W. M.Van Soest, and N. Fusetani, *Org. Lett*., 2002, **4**, 3039.

15. A. S. Ratnayake, T. S. Bugni, X. Feng, M. K. Harper, J. J. kalicky, K. A. Mohammed, C. D. Andjelic, L. R. Barrows, and C. M. Ireland, *J. NatProd*., 2006, **69**, 1582.

16. (a) C. A. Bewley, and D. J. Faulkner, *J. Org. Chem*., 1994, **59**, 4849. (b) E. W. Schmidt, C. A. Bewley, and D. J. Faulkner, *J. Org. Chem*., 1998, **63**, 1254.

17. C. Festa, S. De Marino, V. Sepe, M. V. D'Auria, G. Bifulco, R. Andres, M. C.Terencio, M. Paya, C. Debitus and A. Zampella, *Tetrahedron* 2011, **67**, 7780.

18. (a) C. Festa, S. De Marino, V. Sepe, M. V. D'Auria, G. Bifulco, R. C. Debitus, M. Bucci, V. Vellecco, and A. Zampella, *Org. Lett*. 2011, **13**, 1532 (b) R. A. Hill, and A. Sutherland, *Nat. Prod. Rep*., 2011, **28**, 1031.

19. A. Gosslau1, S. Li1 , C.-T. Ho, K. Chen and N. E. Rawson, *Mol. Nutr. Food Res.* 2011,**55**,74.

20. a) K. Kashinath, N. Vasudevan, and D. S. Reddy, *Org. Lett.* 2012, **14**, 6222 b) D. S. Reddy, K. Kashinath, and N. Vasudevan, A process for the preparation of solomonamide analogues. W. O. Patent 2014083578 A1, June 5, 2014; C) N. Vasudevan, K. Kashinath, and D.S. Reddy, *Org. Lett.* 2014, 16, 6148; d) K. Kashinath, S. Dhara,and D. S. Reddy, *Org. Lett*. 2015, **17**, 2090. e) N. Kavitha, V. P. Kumar, and S. Chandrasekhar, *Tetrahedron Lett.* 2013, **54**, 2128;f) N. Kavitha, and S. Chandrasekhar, *Org. Biomol. Chem.,* 2015, **13**, 6242.

21. a) . D. Sellanes, F. Campot, I. Núñez, G. Lin, P. Espósito, S. Dematteis, J. Saldaña, L. Domínguez, E. Manta, and G. Serra *Tetrahedron*, 2010, **66**, 5384. b) K. Asif, M. Himaja, M.V. Ramana, and M. S. Sikarwar, *Asian J. Chem.* 2012, **24**, 2739.

22. V. Belov, M. Bossi, J. Folling, V. Boyarskiy, and S. Hell, *Chem. Eur. J*., 2009, **15**, 10762.

23. L. Rogers, Z. Konstantinou, M. Reddy, and M. Organ, *Eur. J. Org. Chem.*, 2011, 5374.

24. Y. Wu, B. Li, Li, X. Mao, and F. Kwong, *Org. Lett.* 2011, **12**, 3258.

25. (a) A-Z. A. Elassar, and A. A. El-Khai, *Tetrahedron*, 2003, **59**, 8463 (b) *The Chemistry of Enamines Part 1*; Z., Ed. Rappoport, John Wiley and Sons: Chichester, New York, Brisbane, Toronto, Singapore, 1994.

26. S. J. Tantry, R. Venkataramanarao, G. Chennakrishnareddy, and V. V. Sureshbabu, .

J. Org. Chem. 2007, **72**, 9360.

27. D. A. Horton, G. T. Bourne, and M. L. Smythe, *Chem. Rev*. 2003, **103**, 893.

28. Selected refs related to synthesis of benzodiazepinones (a) S.Ferrini, F. Ponticelli, and M. Taddei, *J. Org. Chem.* 2006, **71**, 9217. (b) I. Im, T. R.Webb, Y.-D. Gong, J.-I. Kim, and Y.-C. Kim, *J. Comb. Chem.* 2004, **6,** 207. (c) P. R. Carlier, H. Zhao, J. DeGuzman, and P. C.-H. Lam, *J. Am. Chem. Soc.* 2003, **125**, 11482.

29. (a) B. T. Kelley and M. M. Joullié, *Org. Let.*, 2010, **12**, 4244.

30. B. A. Aleiwi, C. M. Schneider, and M. Kurosu, *J. Org. Chem.* 2012, **77**, 3859. (b) Commercial availability and safety documentation of trimethyl aluminium can be can be accessed sigma Aldrich through following link http://www.sigmaaldrich.com/catalog/product/aldrich/257222?lang=en&region=IN

31. (a) P. Ciapetti, M. Falorni, and T. Maurizo, *Tetrahedron*, 1996, **52**, 7379. (b) P. Ciapetti, M. Falorni, T. Maurizo, and P. Ulivi, *Tetrahedron Lett.* 1994, **35**, 3183. (c) A. Frustner, and N. Shi, *J. Am. Chem. Soc*. 1996, **118**, 12349. (d) A. Frustner, *Chem. Rev.*, 1999, **99**, 991 (e) P. Cintas, *Synthesis*, 1991, 248.

32. (a) G. Guerrini, F. Ponticelli, and M. Taddei, *J. Org. Chem.*, 2011, **76** , 7597. (b) S. Ferrini, F. Ponticelli, and M. Taddei, *Org. Lett.* 2007, **9**, 69.

33. J. Choy, S. Figueroa, L. Jiang, and P. Wagner, *Syn. Commun*., 2008, **38**, 3840.

34. Selected publications: (a) L. Tschugaeff, *Ber. Dtsch. Chem. Ges.*1900, **33**, 3118. (b) L. A. Paquette, R. A. Roberts, and G. J. Drtina, *J. Am. Chem. Soc.* 1984, **106**, 6690. (c) M.-H. Lee, S.-W. Lee, Y.-M. Jeon, D.-Y. Park, and J.-Y. Ryu, **2005**, WO2005035468. (d) J. Magolan, C. A. Carson, and M. A. Kerr, *Org. Lett.* 2008, **10**, 1437.

35. (a) K. B. Sharpless, and M. W. Young, *J. Org. Chem.* 1975, **40**, 947. (b) P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.* 1976, **41**, 1485.

36. A. J. Waring, and J. H. Zaidi, *J. Chem. Soc., Perkin Trans. 1* 1985, 631.

37. D. L. J. Clive, and M. H. D. Postema, *J. Chem. Soc., Chem. Commun.* 1994, 235.

38. Selected reviews and publications: (a) J. A. Marshall, and A. W. Garofalo, *J. Org. Chem.* 1993, **58,** 3675. (b) J. A. Marshall, A. W. Garofalo, and R. C. Sedrani, *Synlett* 1992, 643. (c) D. F. Taber, and K. Nakajima, *J. Org. Chem.* 2001, **66**, 2515. (d) K. M. Miller, W.-S. Huang, and T. F. Jamison, *J. Am. Chem. Soc.* 2003, **125**, 3442. (e) S. G.

Van Ornum, R. M. Champeau, and R. Pariza, *Chem.Rev.* 2006, **106,** 2990. (f) H. Lu, and C. Li, *Org. Lett.* 2006, **8**, 5365. (g) X. Mollat du Jourdin, M. Noshi, and P. L. Fuchs, *Org. Lett.* 2009, 11, 543. (h) S. Kyasa, T. J. Fisher, and P. H. Dussault, *Synthesis* 2011**, 2011**, 3475. (i) R. Willand-Charnley, and P. H. Dussault, *J. Org. Chem.* 2013, **78,** 42. (j) L. Kersten, K. Harms, and G. Hilt, *J. Org. Chem.* 2014**, 79**, 11661. (k) R. Ramesh, and D. S. Reddy, *Org. Biomol.* Chem. 2014**, 12**, 4093.

39. K. Mori, and M. Takenaka, *Eur. J. Org. Chem.* 1998, **1998**, 2181.

40. Selected publications: (a) G. Venkateswar Reddy, R. Satish Chandra Kumar, G. Shankaraiah, K. Suresh Babu, and J. Madhusudana Rao, *Helv. Chim. Acta.* 2013, **96**, 1590. (b) Y. C. Hwang, and F. W. Fowler, *J. Org. Chem.*, 1985, **50**, 2719.

41. (a) W. H. Watanabe, and L. E. Conlon, *J. Am. Chem. Soc.* 1957, **79**, 2828. (b) M. Bosch, and M. Schlaf, *J. Org. Chem.* 2003, 68, 5225.

42. Selected publications: (a) Thibault, R. J.; Takizawa, K.; Lowenheilm, P.; Helms, B.; Mynar, J. L.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 12084. (b) Praud, A.; Bootzeek, O.; Blache, Y. *Green Chem.* **2013**, *15*, 1138.

43. Selected publications: (a) A. Afzali-Ardakani, and H. Rapoport, *J. Org. Chem.*1980, **45**, 4817. (b) P. Meffre, L. Voquang, Y. Voquang, F. Le Goffic, *Synth. Commun.* 1989, **19**, 3457. (c) S. J. Miller, H. E. Blackwell, and R. H. Grubbs, *J. Am. Chem. Soc.* 1996, **118,**9606.

44. (a) S. Takano, M. Yamanaka, K. Okamoto, and F. Saito, *J. Soc. Cosmet. Chem.* 1983, **34**, 116. (b) J. S. Yadav, K. U. Gayathri, N. Thrimurtulu, and A. R. Prasad, *Tetrahedron* 2009, **65**, 3536.

45. C. Ma, X. Liu, X. Li, J. Flippen-Anderson, S. Yu, and J. M. Cook, *J. Org. Chem.* 2001, **66**, 4525.

46. Selected reviews and publications for intramolecular Heck reaction: (a) S. E. Gibson, and R. J. Middleton, *Contemp. Org. Synth.* 1996, **3**, 447. (b) P. Rajamohan Reddy, V. Balraju, G. R. Madhavan, B. Banerji, and J. Iqbal, *Tetrahedron Lett.* 2003, **44**, 353. (c) A. V. Kalinin, B. A. Chauder, S. Rakhit, and V. Snieckus, *Org. Lett.* 2003, **5**, 3519. (d) J. Jägel, and M. E. Maier, *Synthesis* 2009, 2881. (e) K. R. Prasad, and A. B. Pawar, *Org. Lett.* 2011, **13**, 4252. (f) K. M. Reddy, V. Yamini, K. K. Singarapu, and S. Ghosh, *Org.*

Lett. 2014, **16**, 2658.

47. D. Yoo, J.S. Oh, D.-W. Lee, and Y. G. Kim, *J. Org. Chem.* 2003, **68**, 2979.

48. Selected publications on Wacker oxidation a) D. G Miller, and D. D. M Wayner, *J. Org. Chem*. 1990, **55**, 2924; b) S.-K. Kang, K.-Y. Jung, J.-U. Chung, E.-Y. Namkoong, and T.-H. Kim, *J. Org. Chem.* 1995, **60**, 4678; c) P. R. Skaanderup, and R. Madsen, *J. Org. Chem.* 2003, **68**, 2115; d) P. Mukherjee, and T. K. Sarkar, *Org. Biomol. Chem.* 2012, **10**, 3060; e) B. Morandi, Z. K Wickens, and R. H. Grubbs, *Angew. Chem., Int. Ed.* 2013, **52,** 2944.

49. E. Keinan, K. K. Seth, and R. Lamed, *J. Am. Chem. Soc.* 1986, **108**, 3474.

50. K .Hatakeyama, K. Ohmori, and K.Suzuki, *Synlett,* 2005,1311.

51. G. S. Sheppard, J. Wang, M. Kawai, N. Y. BaMaung, R. A. Craig, S. A. Erickson, L. Lynch, J. Patel, F. Yang, X. B. Searle, P. Lou, C. Park, K. H. Kim, J. Henkin, and R. Lesniewski*, Bioorg. Med. Che. Lett.* 2004, **14**, 865.

52. a) H. C. Brown, and K. S. Bhat, *J. Am. Chem. SOC.* 1986, **108**, 293; b) H. C. Brown, K. S. Bhat, and R. S. Randad, *J. Org. Chem.* 1989, **54**, 1570.

53. G. Wei, J. M. Chalker, and T. Cohen, *J. Org. Chem.* 2011, **76**, 7912.

54. M. Ojika, H. Kigoshi, Y. Yoshida, T. Ishigaki, M. Nisiwaki, I. Tsukada, M. Arakawa, H. Ekimoto, and K. Yamada, *Tetrahedron,* 2007, **63**, 3138.

55. G. Tojo, M. Fernández, in Oxidation of Primary Alcohols to Carboxylic Acids, Springer New York, 2007, pp. 33-41.

56. A. M. King, C. Salomé, J. Dinsmore, E. Salomé-Grosjean, M. De Ryck, R. Kaminski, A. Valade, and H. Kohn, *J. Med. Chem.,* 2011, **54**, 4815.

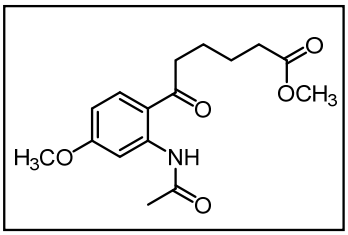
57. V. Rheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.* **1976**, 1973.

Section C

Experimental Details

3.1. Experimental procedures

Methyl 6-(2-acetamido-4-methoxyphenyl)-6-oxohexanoate (39):



N-(3-Methoxyphenyl)acetamide **35** (1.0 g, 6 mmol) and $Pd(TFA)_2$ (0.1 g, 0.3 mmol) were loaded in sealed tube with a stir bar under nitrogen atmosphere. Toluene (12 mL) was added into the tube. The solution was then stirred for about 1-2 min. Methyl 6-oxohexanoate **38** (1.74 g, 12 mmol), TBHP (6M in decane, 2 mL) were introduced into the tube. The reaction mixture was stirred at 90 °C for 24 h, concentrated under reduced pressure and purified by column chromatography (silica gel 100-200 mesh, 1:9 ethyl acetate - pet ether) to afford **39** (1.18 g, 65%) as a pale yellow solid.

Mp : 88 - 89 °C

IR υ_{max}(film): cm^{-1} 3446, 2925, 1738, 1698, 1526, 1435, 1246

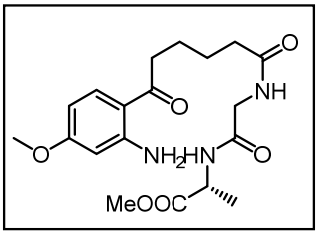
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.12 (bs,1H), 8.42 (d, *J* = 2.7 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.03 (dd, *J* = 2.7, 9.0 Hz, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 3.01- 2.91 (m, 2H), 2.38-2.34 (m, 2H), 2.23 (s, 3H), 1.76 -1.65 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.7, 173.8, 169.9, 164.7, 143.9, 132.7, 114.7, 109.6, 104.0, 55.6, 51.6, 39.2, 33.9, 25.7, 24.5, 24.1

MS: 330 $(M+Na)^+$

HRMS: calculated for $C_{16}H_{22}O_5N$ $[M+H]^+$: 308.1492, found 308.1491.

Methyl (6-(2-amino-4-methoxyphenyl)-6-oxohexanoyl)glycyl-D-alaninate (43):



To a solution of **39** (300 mg, 1.0 mmol) in methanol (5 mL), 4N HCl (10 mL) was added and refluxed for 4 h. After the completion of reaction (monitored by TLC), reaction mass was evaporated to dryness. The dipeptide ester compound **42** (254 mg, 1.0 mmol) was stirred in 20% TFA in CH_2Cl_2 to afford amine as TFA salt **33**. Above acid and this salt were taken in 20 mL CH_2Cl_2. EDC (206 mg, 1.1 mmol), HOBt (145 mg, 1.1 mmol) were added at 0 °C followed by Et_3N (0.3 Ml, 2.0 mmol) was added and stirred at room temperature for 14 h. Diluted the reaction mixture with 10 mL of CH_2Cl_2 washed with 5% citric acid (10 mL) and saturated $NaHCO_3$. Organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (silica gel 100-200 mesh, 4:96 MeOH- CH_2Cl_2) to afford compound **43** (275 mg, 72%) as off white solid.

Mp : 114 -116 °C

$[\alpha]_D^{24}$: 8.8 (*c* = 0.3, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3334, 2920, 1731, 1640, 1611, 1597.

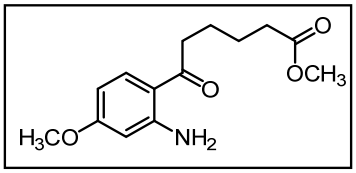
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 9.05 Hz, 1H), 7.01 (d, *J* = 6.60 Hz, 1H), 6.74 (brs, 1H), 6.20 (dd, *J* = 2.08, 8.93 Hz, 1H), 5.99 - 6.12 (m, 1H), 4.55 (quin, *J* = 7.15 Hz, 1H), 3.91 - 4.08 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 2.79 - 2.95 (m, 2H), 2.26 - 2.38 (m, 2H), 1.72 (brs, 4H), 1.40 (d, *J* = 7.09 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 173.6, 173.2, 168.8, 164.3, 152.9, 133.2, 112.4,

104.5, 99.3, 55.2, 52.5, 48.1, 43.2, 38.4, 36.1, 25.2, 24.3, 18.1

HRMS: calculated for $C_{19}H_{28}O_6N_3$ $[M+H]^+$: 394.1793, found 394.1791.

Methyl 6-(2-amino-4-methoxyphenyl)-6-oxohexanoate (45)



To a solution of **39** (500 mg, 1.6 mmol) in methanol (5 mL), 4N HCl (10 mL) was added and refluxed for 4 h. After the completion of reaction (monitored by TLC), reaction mass was evaporated to dryness, dissolved in dry methanol (20 mL), $SOCl_2$ (0.13 mL, 1.8 mmol) was added at 0 °C, stirred for 16 h at room temperature. Reaction mass was evaporated to dryness, basified with saturated aq. $NaHCO_3$ solution, extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200 mesh, 1:9 ethyl acetate - pet ether) to afford **45** (400 mg, 92%) as a pale yellow solid.

Mp: 65 - 66 °C

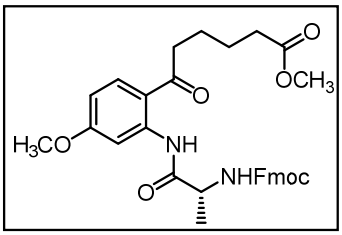
IR υ_{max}(film): cm^{-1} 3459, 3334, 1732, 1615, 1587, 1456

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.9 Hz, 1H), 6.41 (bs, 2H), 6.22 (dd, *J* = 2.3, 8.9 Hz, 1H), 6.06 (d, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 2.91-2.84 (m, 2H), 2.40-2.33 (m, 2H), 1.75 -1.66 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 174.0, 164.2, 152.8, 133.2, 112.4, 104.4, 99.3, 55.2, 51.5, 38.5, 33.9, 24.7, 24.4

HRMS calculated for $C_{14}H_{20}O_4N$ $[M+H]^+$: 266.1387, found 266.1387.

(*R*)-Methyl 6-(2-(2-((((9H-fluoren-9- yl)methoxy)carbonyl)amino) propanamido-4-methoxyphenyl)-6-oxohexanoate (49)



To a solution of **45** (75 mg, 0.28 mmol) in dry CH_2Cl_2 (2 mL), D-Fmoc-Ala-Cl **48**(110 mg, 0.33 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise followed by saturated aq. $NaHCO_3$ solution (1 mL) was added and the mixture was stirred for 6 h at room temperature. Reaction mass was diluted with CH_2Cl_2 (20 mL), organic layer was separated, washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 230-400 mesh, 1:19 MeOH - CH_2Cl_2) to afford **49** (118 mg, 75%) as a yellow solid.

Mp: 120 - 121 °C

$[\alpha]_D^{24}$: 8.8 (*c* = 0.3, $CHCl_3$)

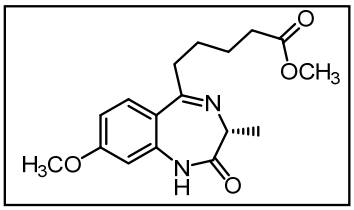
IR υ_{max}(film): cm^{-1} 3335, 2926, 1730, 1645, 1611, 1576, 1523, 1456

^{1}H NMR (200 MHz, $CDCl_3$): δ 12.6 (s, 1H), 8.42 (d, *J* = 2.5 Hz, 1H), 7.85-7.75 (m, 5H), 7.40 (m, 4H), 6.64 (dd, *J* = 2.5, 8.9 Hz, 1H), 5.50 (bs, 1H), 4.52-4.27 (m, 4H), 3.89 (s, 3H), 3.64 (s, 3H), 2.94 (m, 2H), 2.27 (m, 2H), 1.58-1.68 (m, 4H), 1.54 (d, *J* = 7.0 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 173.8, 172.1, 164.6, 155.9, 144.2, 143.7 (2C), 143.2, 141.2, 132.6, 127.6 (2C), 127.0 (2C), 125.3, 125.2, 119.9 (2C), 115.2, 110.0, 104.2, 67.2, 55.6, 52.1, 51.5, 47.2, 39.1, 33.7, 24.4, 24.0, 19.0;

HRMS calculated for $C_{32}H_{35}O_7N_2$ $[M+H]^+$: 559.2439, found 559.2439.

(*R*)-Methyl 5-(8-methoxy-3-methyl-1-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)pentanoate (50):



To a solution of **49** (100 mg, 0.18 mmol) in THF (5 mL), piperidine (0.3 mL) was added, stirred for 4 h at room temperature. Reaction mass was concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel 230-400 mesh, 1:15 MeOH - CH_2Cl_2) to afford compound **50** (53 mg, 93%) as a pale yellow solid.

Mp: 87 - 88 °C

$[\alpha]_D^{25}$: 80.0 (*c* = 0.3, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3019, 2937, 1727, 1690, 1557, 1514, 1462

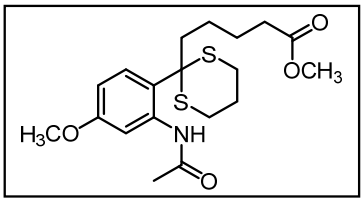
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 6.75 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H), 3.58-3.57 (m, 4H), 2.79-2.63 (m, 2H), 2.26-2.23 (m, 2H), 1.60-1.46 (m, 7H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 172.8, 170.7, 161.5, 138.8, 129.5, 121.3, 111.1, 104.9, 57.7, 55.5, 51.5, 38.5, 33.7, 27.2, 24.5, 16.7

MS: 341 $(M+Na)^+$

HRMS: calculated for $C_{17}H_{23}O_4N_2$ $[M+H]^+$: 319.1652, found 319.1653.

Methyl 5-(2-(2-acetamido-4-methoxyphenyl)-1,3-dithian-2-yl)pentanoate (58):



To a solution of **39** (1.0 g, 3.2 mmol) in dry CH_2Cl_2 (20 mL), 1,3-propanedithiol (0.81 mL, 8.1 mmol), $BF_3.Et_2O$ (1 mL, 8.1 mmol) were added and stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL), saturated aq. $NaHCO_3$ solution (10 mL) was added and the organic layer was separated, and dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200, 1:5 ethyl acetate - pet ether) to afford **58** (1.16 g, 89%) as a colourless liquid.

IR υ_{max}(film): cm^{-1} 2949, 1736, 1694, 1525, 1464, 1424

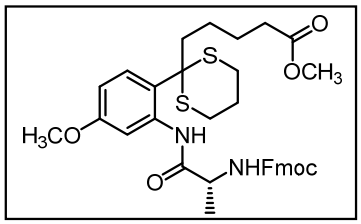
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (bs,1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.68 (bs, 1H), 6.66 (dd, *J* = 2.7, 8.9 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 2.83-2.73 (m, 4H), 2.20-2.17 (m, 2H), 2.15 (s, 3H), 2.11-2.07 (m, 2H), 2.00-1.95 (m, 2H); 1.53-1.46 (m, 2H), 1.30-1.17 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 167.8, 159.5, 137.7, 133.2, 119.8, 110.1, 110.0, 57.4, 55.3, 51.5, 40.5, 33.6, 28.1 (2C), 25.1, 24.9, 24.8, 23.7

MS: 420 $(M+Na)^+$

HRMS: calculated for $C_{19}H_{28}O_4NS_2$ $[M+H]^+$: 398.1454 found 398.1453.

(*R*)-Methyl 5-(2-(2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-Methoxyphenyl)-1,3-dithian-2-yl)pentanoate (59) :



To a stirred solution of **58** (200 mg, 0.5 mmol) in methanol (5 mL) was added 4N HCl (3 mL) and then heated at 40-50 °C for 4 h. The reaction mass was concentrated under reduced pressure, the residue was basified with saturated aq. $NaHCO_3$ (pH ~10) and extracted with ethyl acetate (15 mL x 2). The combined organics were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford free amine (methyl 5-(2-(2-amino-4-methoxyphenyl)-1,3-dithian-2-yl)pentanoate) (145 mg, 81%) as a colourless liquid. This compound was used for next reaction without further purification.

To a solution of above free amine (145 mg, 0.4 mmol) and D-Fmoc-Ala-Cl **48**(148 mg, 0.4 mmol) in dry CH_2Cl_2 (5 mL), saturated aq. $NaHCO_3$ (2.5 mL) was added and stirred for 6 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was separated, dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200, 3:7 ethyl acetate - pet ether) to afford **59** (175 mg, 66%) as a colourless viscous liquid.

$[\alpha]_D^{27}$: - 25.0 (*c* = 0.3, $CHCl_3$)

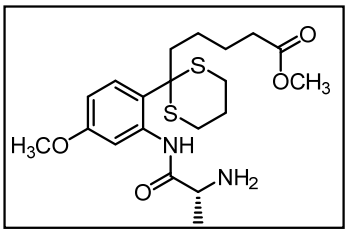
IR υ_{max}(film): cm^{-1} 3273, 1732, 1682, 1610, 1575

^{1}H NMR (200 MHz, CD_3OD): δ 7.87-7.69 (m, 5H), 7.42-7.29 (m, 5H), 6.75 (dd, *J* = 2.9, 8.9 Hz, 1H), 4.48-4.15 (m, 4H), 3.77 (s, 3H), 3.52 (s, 3H), 2.72-2.54 (m, 4H), 2.21-1.88 (m, 6H),1.43 (d, *J* = 7.0 Hz, 3H), 1.38-1.28 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 170.2, 159.5, 155.8, 143.8 (2C), 141.3 (2C), 137.1, 133.3, 127.7 (2C), 127.1 (2C), 125.1(2C), 120.5, 120.0 (2C), 110.6, 109.8, 67.1, 57.4, 55.4 (2C), 51.9, 51.5, 47.2, 40.4, 33.6, 28.0, 24.7 (2C), 23.7, 19.0;

HRMS: calculated for $C_{35}H_{41}O_6N_2S_2$ $[M+H]^+$:649.2401, found 649.2397.

(*R*)-Methyl 5-(2-(2-(2-aminopropanamido)-4-methoxyphenyl)-1,3-dithian-2-l)pentanoate (60)



To a solution of **59** (250 mg, 0.4 mmol) in THF (5 mL), piperidine (0.2 mL) was added and stirred at room temperature for 2 h. Reaction mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200, 1:24 methanol - CH_2Cl_2) to afford **60** (140 mg, 85%) as a colourless viscous liquid.

$[\alpha]_D^{25}$: - 5.8 (*c* = 0.6, $CHCl_3$)

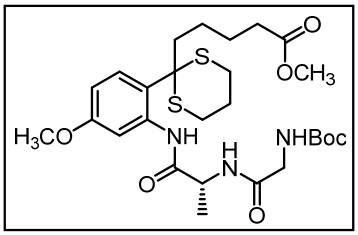
IR υ_{max}(film): cm^{-1} 3245, 2950, 1735, 1679, 1608, 1043;

^{1}H NMR (400 MHz, CD_3OD): δ 7.84 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 2.7 Hz, 1H), 6.76 (dd, *J* = 2.7 Hz, 9.0 Hz, 1H), 3.81 (s, 3H), 3.59 (s, 3H), 3.58-3.53 (m, 1H), 2.84-2.79 (m, 4H), 2.23-2.17 (m, 4H), 2.02-1.90 (m, 2H), 1.53-1.45 (m, 2H), 1.39 (d, *J* =7.0 Hz, 3H), 1.27-1.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 175.5, 160.7, 137.9, 134.1, 124.2, 113.1, 110.9, 57.3, 55.8, 52.6, 51.9, 40.8, 34.4, 28.9, 25.9, 25.8 (2C), 25.1, 21.3;

MS: 449 $(M+Na)^+$

HRMS calculated for $C_{20}H_{31}O_4N_2S_2$ $[M+H]^+$: 427.1720, found 427.1729.

(*R*)-Methyl 5-(2-(2-(2-(2-((*tert*-butoxycarbonyl)amino)acetamido)propanamido)-4-methoxyphenyl)-1,3-dithian-2-yl)pentanoate (61) :



To a solution of **60** (120 mg, 0.3 mmol) and Boc-Gly-OH (**41)** (55 mg, 0.3 mmol) in dry CH_2Cl_2 (5 mL) EDC.HCl (48 mg, 0.3 mmol), HOBt (42 mg, 0.3 mmol), Et_3N (0.1 mL, 0.6 mmol) were added and stirred for 14 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 1N HCl (10 mL), saturated aq. $NaHCO_3$ solution (10 mL) and dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200, 1:30 methanol - CH_2Cl_2) to afford **61** (120 mg, 75%) as a colorless viscous liquid.

$[\alpha]_D^{24}$: 18.3 (*c* = 1.0, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3294, 2937, 1718, 1676, 1609, 1169, 1045

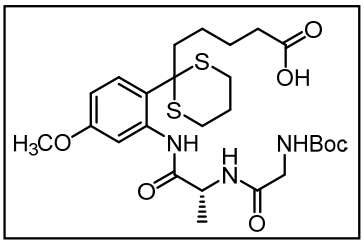
^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (d, *J* = 8.9 Hz, 1H), 7.41 (d, *J* = 2.3 Hz, 1H), 6.80 (dd, *J* = 2.3, 8.8 Hz, 1H), 4.45 (q, *J* = 7.0 Hz, 1H), 3.84 (s, 2H), 3.80 (s, 3H), 3.60 (s, 3H), 2.81- 2.73 (m, 4H), 2.23-2.19 (m, 2H), 2.11-1.91 (m, 4H), 1.50-1.45 (m, 14H), 1.21 -1.14 (m, 2H)

^{13}C NMR (100 MHz, CD_3OD): δ 175.7, 172.8, 172.6, 160.8, 158.2, 137.6, 134.7, 123.9, 113.1, 111.3, 80.7, 57.9, 55.8, 52.0, 51.7, 44.7, 41.2, 34.3, 29.0 (2C), 28.7 (3C), 26.0, 25.7, 24.8, 17.7

MS : 606 $(M+Na)^+$

HRMS: calculated for $C_{27}H_{42}O_7N_3S_2$ $[M+H]^+$: 584.2459, found 584.2456.

(*R*)-5-(2-(2-(2-(2-((*tert*-Butoxycarbonyl)amino)acetamido)propanamido)-4-methoxyphenyl)-1,3-dithian-2-yl) pentanoic acid (62) :



To a solution of **61** (120 mg, 0.2 mmol) in THF:MeOH (3:2, 5 mL), LiOH (26 mg, 0.6 mmol, in 1 mL water) was added and stirred for 3 h at room temperature. Solvent was removed under reduced pressure and the residue was acidified with 1 N HCl (pH ~3) and extracted with ethyl acetate (10 mL X 2). The combined organics were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford **62** (110 mg, 94%) as colourless liquid.

$[\alpha]_D^{25}$: - 5.0 (*c* = 0.5, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3307, 2933, 1714, 1669, 1610, 1245, 1045

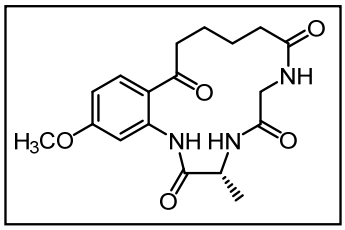
^{1}H NMR (400 MHz, CD_3OD): δ 7.88 (d, *J* = 8.8 Hz, 1H), 7.40 (bs, 1H), 6.77 (dd, *J* = 2.5, 8.8 Hz, 1H), 4.46 (q, *J* = 7.3 Hz, 1H), 3.83 (s, 2H), 3.79 (s, 3H), 2.87-2.72 (m, 4H), 2.19-2.07 (m, 4H), 2.09 -1.93 (m, 2H), 1.48 -1.43 (m, 14H), 1.22 -1.20 (m, 2H);

^{13}C NMR (100 MHz, CD_3OD): δ 177.7, 175.6, 173.2, 173.0, 161.1, 138.0, 135.1, 124.3, 113.5, 111.7, 81.0, 58.3, 56.2, 52.1, 45.1, 41.7, 35.0, 31.2, 29.4 (3C), 26.4, 26.3, 25.3, 21.2, 18.2;

MS: 592 $(M+Na)^+$

HRMS calculated for $C_{26}H_{40}O_7N_3S_2$ $[M+H]^+$:570.2302, found 570.2304.

(*R*)-16-Methoxy-3-methyl-3,4,6,7,9,10,11,12-octahydro-1H- benzo[h] [1,4,7] triazacyclo- pentadecine-2,5,8,13-tetraone (44) :



To a solution of **62** (40 mg, 0.07 mmol) in CH_2Cl_2 (3 mL), TFA (0.9 mL) was added and stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the residue was taken up in dry CH_2Cl_2 (14 mL), HATU (80 mg, 0.21 mmol) and Et_3N (0.05 mL, 0.35 mmol) were added and the resulting reaction solution was stirred at room temperature for 16 h. Reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1N HCl (5 mL) and saturated aq. $NaHCO_3$ solution (5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue (20 mg, 0.04 mmol) obtained after the evaporation of the solvent was dissolved in THF-water (85:15, 3 mL), HgO (22 mg, 0.1 mmol) and $BF_3.Et_2O$ (0.01 mL, 0.1 mmol) were added and stirred at room temperature for 4 h. The reaction mixture was filtered and the filtrate was diluted with ethyl acetate (5 mL), washed with brine (5 mL), dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 230-400, 1:19 methanol: CH_2Cl_2) to afford **44** as a white solid (8 mg, 32% over 3 steps).

Mp: 158 - 160 °C

$[\alpha]_D^{24}$: 29.0 (*c* = 0.2, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 2924, 2854, 1632, 1540, 1040

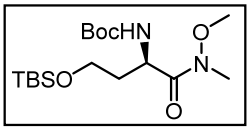
^{1}H NMR (400 MHz, CD_3OD): δ 8.21 (d, *J* = 2.8 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 6.71 (dd, *J* = 9.2, 2.8 Hz, 1H), 4 .54 (d, *J* = 15.1 Hz, 1H), 4.30 (q, *J* = 7.4 Hz, 1H), 3.85 (s, 3H), 3.68 (d, *J* = 15.1 Hz, 1H), 3.01-2.98 (m, 2H), 2.11-1.96 (m, 2H), 1.79-1.58 (m, 4H), 1.49 (d, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 203.3, 175.8, 173.5, 171.3, 165.3, 142.8, 133.6, 117.0, 109.6, 105.4, 55.5, 52.1, 43.4, 38.3, 36.1, 26.9, 21.4, 16.6

MS : 384 $(M+Na)^+$

HRMS: calculated for $C_{18}H_{24}O_5N_3$ $[M+H]^+$:362.1710, found 362.1713.

***tert*-butyl (*R*)-(3,9,9,10,10-pentamethyl-4-oxo-2,8-dioxa-3-aza-9-silaundecan-5-yl)carbamate (64):**



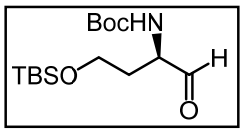
To solution of NHMe(OMe).HCl (14.5 gm, 150 mmol) and $AlCl_3$ (19.9 gm, 150 mmol) in dry CH_2Cl_2 (150 mL), pyridine (12 mL, 150 mmol) was added at 0 °C and stirred for 15 min. A solution of homoserine lactone **63** (10 gm, 50 mmol, dissolved in 50 mL of CH_2Cl_2) was added dropwise over 30 min and stirred at room temperature for 16 h. Reaction was quenched with saturated sodium potassium tartarate (20 mL) and extracted with EtOAc (50 mL X 3). Combined organic layers were washed with water (30 mL) and brine (30 mL) and concentrated under reduced pressure and the curde was taken in dry CH_2Cl_2 (100 mL), Et_3N (13.9 mL, 100 mmol), TBSCl (8.2 gm, 54 mmol) and DMAP (0.1 eq) were added at 0 °C and stirred at room temperature for 12 h. The reaction mixture was washed with water (30 mL), brine (30 mL) and organic layer was dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 230-400, 3:7 ethil acetate : pet ether) to afford **64** as a white solid (7.6 gm, 40% for 2 steps) and starting material lactone **63** 2.5 gm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (brs, 1H), 4.73 (brs., 1H), 3.76 (s, 3H), 3.64 - 3.72 (m, 2H), 3.18 (brs., 3H), 1.94 (brs, 1H), 1.63 - 1.76 (m, 1H), 1.40 (s, 9H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 155.6, 79.3, 61.5, 59.7, 48.7, 34.7, 32.1, 28.3, 25.9, 18.2, -5.6

The ^{1}H NMR and ^{13}C NMR and rotation values are identical with the reported values.

***tert*-Butyl (*R*)-(4-((tert-butyldimethylsilyl)oxy)-1-oxobutan-2-yl)carbamate (65)**



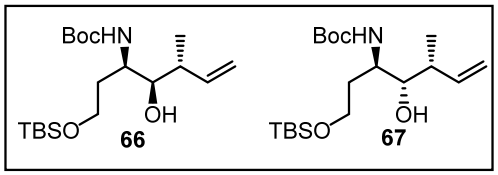
To a solution of Weinrab amide **64** (3.8 gm, 10.1 mmol) in dry THF (50 mL), LAH (1.0 gm, 26.2 mmol) was added portion wise at 0 °C for 15 min. After 1 h reaction was quenched with saturated Na_2SO_4 solution until effervescences stopped. Filtered the reaction mixture through celite pad, organic layer diluted with EtOAc (80 mL), washed with water (20 mL) brine solution (20 mL), dried over anhydrous Na_2SO_4. The crude aldehyde **65** (2.7 gm, 84%) obtained after removal of solvent was enough pure by NMR and used further without purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 4.19 (q, J = 5.19 Hz, 1H), 3.68 (t, J = 5.40 Hz, 2H), 1.89 - 2.11 (m, 2H), 1.42 (s, 9H), 0.85 (s, 9H), 0.01 (s, 3H), 0.01 (s, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 199.9, 155.7, 79.7, 59.2, 58.6, 31.7, 28.2, 25.8, 25.8, 25.6, 18.0, -5.7

The ^{1}H and ^{13}C NMR values are compared with reported values and found to be identical.

***tert*-butyl ((*3R,4R,5R*)-1-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-5-methylhept-6-en-3-yl)carbamate (66) and *tert*-Butyl ((*3R,4S,5R*)-1-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-5-methylhept-6-en-3-yl)carbamate (67)**



Anhydrous chromium (II) chloride (4.6 g, 37.5 mmol) was transfered into a round bottomed flask under argon atmosphere and heated upto 200 °C for 40 min under high vaccum. (*R*)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-1-oxobutan-2-yl)carbamate **65** (4.0 g, 12.6 mmol) in THF (40 mL) was added at 0 °C followed by *trans*- crotyl bromide (2.6 mL, 25 mmol) and the reaction mixture was stirred at room temperature for 8 h. Reaction mass was quenched with saturated aq. NH_4Cl (20 mL) and extracted with Et_2O (4 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200 mesh, 1:15 to 1:10 ethyl acetate - pet ether) to afford **66** and **67** respectively (~2:1 ratio, 75%).

66: (2.3 g, 49%) as a colourless oil

$[\alpha]_D^{27}$: 7.6 (*c* = 0.4, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3443, 2957, 2859, 1716, 1473

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83-5.78 (m, 1H), 5.10-5.08 (m, 3H), 3.84-3.83 (m, 1H), 3.70-3.67 (m, 2H), 3.32 (bs, 1H), 3.06 (bs, 1H), 2.24-2.22 (m, 1H), 1.81-1.70 (m, 2H), 1.41 (s, 9H), 1.03 (d, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 1.6 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 141.0, 115.7, 79.0, 76.3, 60.0, 49.6, 41.6, 35.8, 28.4 (3C), 25.9 (3C), 18.2, 16.9, -5.5 (2C)

MS: 396 $(M+Na)^+$

^{1}HRMS: calculated for $C_{19}H_{40}O_4NSi$ $[M+H]^+$: 374.2727 found 374.2717

67: (1.2 g, 26%) as a colourless oil.

$[\alpha]_D^{27}$: 5.7 (*c* = 0.9, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3441, 2958, 2885, 1701, 1500

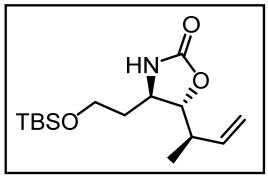
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 -5.82 (m, 1H), 5.09-5.05 (m, 3H), 3.85 (bs, 1H), 3.70-3.69 (m, 2H), 3.36 (bs, 1H), 2.86-2.85 (m, 1H), 2.30-2.24 (m, 1H), 1.82 -1.66 (m, 2H), 1.41 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 141.0, 115.8, 79.1, 76.6, 59.8, 50.3, 41.2, 31.1, 28.4 (3C), 25.9 (3C), 18.2, 16.9, -5.5 (2C)

MS: 396 $(M+Na)^+$

^{1}HRMS calculated for $C_{19}H_{40}O_4NSi$ $[M+H]^+$: 374.2727 found 374.2718.

(*4R,5R*)-5-((*R*)-But-3-en-2-yl)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)oxazolidin-2-one (66'):



To a stirred solution of **66** (0.3 g, 0.8 mmol) in dry THF (10 mL), NaH (60% in mineral oil, 0.070 g, 1.7 mmol) was added at 0 °C then reaction mass was heated at 60 °C for 2 h. The Reaction mass was cooled to 0 °C and quenched with saturated aq. NH_4Cl solution (5 mL), extracted with ethyl acetate (2 x 20 mL), dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200 mesh, 3:7 ethyl acetate - pet ether) to afford **66'** as a white crystalline solid (0.22 g, 91%).

Mp: 60 – 61 °C

$[\alpha]_D^{26}$: 43.0 (*c* = 0.5, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3242, 2929, 1756, 1256, 1100

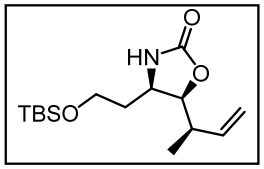
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (bs, 1H), 5.78-5.69 (m, 1H), 5.12 (s, 1H), 5.08 (d, *J* = 5.1 Hz, 1H), 4.15 (t, *J* = 4.9 Hz, 1H), 3.70-3.64 (m, 3H), 2.40-2.45 (m, 1H), 1.73-1.64 (m, 2H), 1.09 (d, *J* = 7.4 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 137.0, 117.1, 85.0, 60.2, 53.4, 41.3, 38.3, 25.8 (3C), 18.1, 15.2, -5.4 (2C);

MS: 322 $(M+Na)^+$;

HRMS**:** calculated for $C_{15}H_{30}O_3NSi$ $[M+H]^+$: 300.1995, found 300.1986.

(4*R*,5*S*)-5-((*R*)-but-3-en-2-yl)-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)oxazolidin-2-one (67'):



Prepared from **67** in 90% yield as a white solid by following the procedure for the synthesis of **66'**.

Mp : 66 - 67 °C

$[\alpha]_D^{26}$: 1.1 (*c* = 0.5, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3246, 2954, 2929, 1767, 1249, 1111

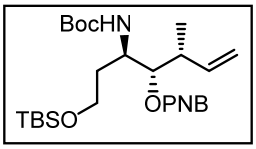
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (m, 1H), 5.83 (bs, 1H), 5.17-5.11 (m, 2H), 4.32 (t, *J* = 7.4 Hz, 1H), 3.88 (m, 1H), 3.77 (m, 2H), 2.53 (m, 1H), 1.74 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 138.5, 115.9, 82.8, 61.2, 54.9, 37.2, 31.2, 25.8 (3C), 18.1, 16.6, -5.4 (2C)

MS : 322 $(M+Na)^+$

HRMS: calculated for $C_{15}H_{30}O_3NSi$ $[M+H]^+$: 300.1995, found 300.1986.

(3*R*,4*S*,5*R*)-5-((*tert*-Butoxycarbonyl)amino)-7-((*tert*-butyldimethylsilyl)oxy)-3-methylhept-1-en-4-yl 4-nitrobenzoate (68):



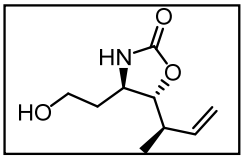
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 - 8.40 (m, 4H), 5.80 (ddd, *J* = 7.33, 10.23, 17.31 Hz, 1H), 5.10 (dd, *J* = 5.75, 14.21 Hz, 3H), 4.77 (d, *J* = 9.73 Hz, 1H), 4.04 - 4.29 (m, 1H), 3.59 - 3.79 (m, 2H), 2.67 (qd, *J* = 6.49, 13.37 Hz, 1H), 1.72 - 1.95 (m, 1H), 1.45 (br. s., 1H), 1.31 (s, 9H), 1.11 (d, *J* = 6.82 Hz, 3H), 0.00 - 0.11 (m, 6H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 164.4, 155.3, 150.6, 139.1, 135.4, 123.6, 116.2, 79.6, 79.2, 59.7, 48.8, 38.9, 35.3, 28.2, 26.0, 18.2, 14.4, 5.5.

$[\alpha]_D^{26}$: 10.6 (*c* = 0.3, $CHCl_3$)

HRMS: calculated for $C_{16}H_{43}O_7N_2Si$ $[M+H]^+$: 523.2840, found 523.2837

(4*R*,5*R*)-5-((R)-but-3-en-2-yl)-4-(2-hydroxyethyl)oxazolidin-2-one (69) :



To a solution of **66'** (1.0 g, 3.3 mmol) in THF (20 mL), TBAF (1M in THF, 5 mmol) was added and stirred for 5 h at room temperature. Reaction mass was quenched with saturated aq. NH_4Cl solution (10 mL), extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by

column chromatography (silica gel 100-200 mesh, 1:19 MeOH - CH_2Cl_2) to afford (*4R,5R*)-5-((*R*)-but-3-en-2-yl)-4-(2-hydroxyethyl)oxazolidin-2-one **69** (0.57 g, 93%) colourless oil.

$[\alpha]_D^{27}$: 37.2 (*c* = 1.3, $CHCl_3$)

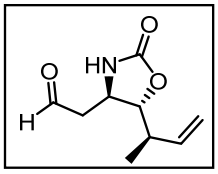
IR υ_{max} (film): cm^{-1} 3310, 2936, 1735, 1420, 1013

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, 1H), 5.75-5.66 (m, 1H), 5.12 (d, *J* = 4.2 Hz, 1H), 5.08 (s, 1H), 4.10 (t, *J* = 5.0 Hz, 1H), 3.72-3.61 (m, 4H), 2.45-2.40 (m, 1H),1.70 (q, *J* =6.0 Hz, 2H), 1.06 (d, *J* = 6.7 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 136.9, 117.2, 85.5, 59.03, 53.3, 41.2, 38.0, 14.9

HRMS: calculated for $C_9H_{16}O_3N$ $[M+H]^+$:186.1125, found 186.1125.

2-((4R,5R)-5-((R)-but-3-en-2-yl)-2-oxooxazolidin-4-yl)acetaldehyde (70):

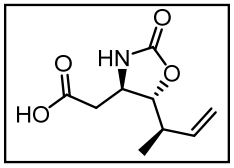


To a solution of compound **69** (120 mg, 0.6 mmol) in dry CH_2Cl_2 (10 mL), DMP (302 mg, 0.7 mmol) was added at 0 °C and stirred for 2 hr at same temperature. Diluted the reaction mixture with 15 mL of CH_2Cl_2 washed with sat sodium thiosulfate (5 mL) and brine (5 mL). organic layer was concentrated to afford aldehyde **70** (92 mg, 78%) as acolorless sticky liquid. The compound was used further without any purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 5.68 - 5.87 (m, 2H) (NH proton merged), 5.04 - 5.33 (m, 2H), 4.12 - 4.17 (m, 1H), 3.97 (d, *J* = 6.02 Hz, 1H), 2.82 (d, *J* = 6.53 Hz, 2H), 2.45 - 2.59 (m, 1H), 1.13 (s, 3H)

HRMS: calculated for $C_9H_{14}O_3N$ $[M+H]^+$:184.0973, found 184.0970

2-((*4R,5R*)-5-((*R*)-But-3-en-2-yl)-2-oxooxazolidin-4-yl)acetic acid (72) :



To a solution of (*4R,5R*)-5-((*R*)-but-3-en-2-yl)-4-(2-hydroxyethyl)oxazolidin-2-one **69** (0.5 g, 2.7 mmol) in acetone (20 mL), Jones reagent (0.7 M solution, 15 mL) was added drop wise at 0 °C and the reaction mixture was stirred for 3.5 h at same temperature. Reaction mass was quenched with isopropanol, the solid thus formed was filtered through a celite bed and the filtrate was evaporated to dryness. The crude material was taken up in ethyl acetate (50 mL), washed with water (10 mL) and brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **72** (0.49 g, 92%) as a white solid.

Mp: 98 - 100 °C

$[\alpha]_D^{25}$: 56.0 (*c* = 0.5, $CHCl_3$)

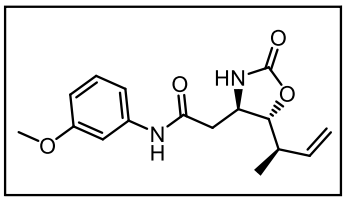
IR υ_{max}(film): cm^{-1} 3309, 2974, 1732, 1419, 1240

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.84 (bs, 1H), 7.16 (s, 1H), 5.83-5.66 (m, 1H), 5.22 (s, 1H), 5.15 (d, *J* = 5.5 Hz, 1H), 4.19 (t, *J* = 4.9 Hz, 1H), 3.95 (q, *J* =6.4 Hz, 1H), 2.63 (d, *J* =6.8 Hz, 2H), 2.58-2.44 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 174.0, 160.3, 136.1, 118.0, 84.5, 51.4, 41.0, 39.9, 14.6; **MS:** 222 $(M+Na)^+$

^{1}HRMS: calculated for $C_9H_{12}O_4N$ $[M-H]^+$:198.0761, found:198.0768.

2-((4*R*,5*R*)-5-((*R*)-but-3-en-2-yl)-2-oxooxazolidin-4-yl)-*N*-(3- thoxyphenyl)acetamide (74):



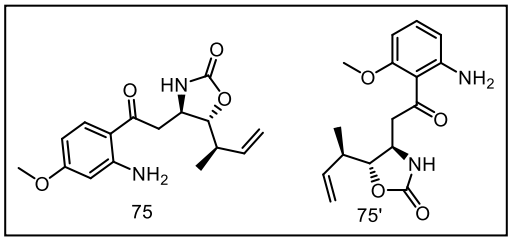
To a solution of **72** (90 mg, 0.4 mmol) and HOBt (83 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL), DCC (111 mg, 0.5 mmol) was added at 0 °C, stirred for 10 min. Then *m*- anisidine (**73**) (75 µL, 0.6 mmol) was introduced and stirring continued for 16 h at room temperature. White solid thus formed was filtered through a celite bed, filtrate was evaporated and purified by column chromatography (silica gel 100-200, 1:19 MeOH - CH_2Cl_2) to afford **74** (119 mg, 86%) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.73 (brs., 1H), 7.21 (brs., 1H), 7.16 (t, *J* = 8.19 Hz, 1H), 7.07 (d, *J* = 8.56 Hz, 1H), 6.62 (dd, *J* = 2.20, 8.07 Hz, 1H), 6.55 (brs., 1H), 5.75 - 5.89 (m, 1H), 5.03 - 5.20 (m, 2H), 4.21 (s, 1H), 4.07 - 4.16 (m, 1H), 3.75 (s, 3H), 2.51 - 2.58 (m, 2H), 2.36 - 2.46 (m, 1H), 1.00 (d, *J* = 6.85 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 159.9, 159.4, 139.2, 138.4, 129.7, 116.1, 112.4, 109.9, 105.9, 82.8, 55.3, 52.9, 36.9, 36.8, 16.3.

^{1}HRMS: calculated for $C_{16}H_{21}O_4N_2$ $[M+H]^+$:305.1496, found: 305.1491.

(4*R*,5*R*)-4-(2-(2-Amino-4-methoxyphenyl)-2-oxoethyl)-5-((*R*)-but-3-en-2-yl)oxazolidin-2-one (75) and (4*R*,5*R*)-4-(2-(2-amino-6-methoxyphenyl)-2-oxoethyl)-5-((*R*)-but-3-en-2-yl)oxazolidin-2-one (75'):



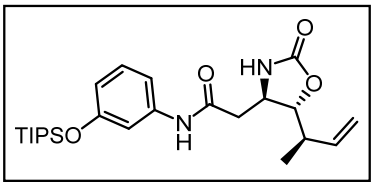
Compound **74** (100 mg, 0.32 mmol) was dissolved in dry acetonitrile (10 mL) and purged with argon for 15 min. This solution was irradiated with low pressure Hg vapour lamp (254 nm, 15W X 2) for 16 h. The residue obtained after the removal of the solvent under reduced pressure was purified by column chromatography (silica gel 230-400, 0.4:99.6 MeOH - CH_2Cl_2) to afford **75** and **75'** as inseparable regioisomeric mixture. (11 mg, 11%).

^{1}H NMR (500 MHz, $CDCl_3$): (mixture of isomers) δ 7.52 (d, *J* = 8.85 Hz, 1H), 7.15 (t, *J* = 8.24 Hz, 1H), 6.21 - 6.30 (m, 2H), 6.18 (d, *J* = 8.24 Hz, 1H), 6.07 (d, *J* = 2.44 Hz, 1H), 5.95 (ddd, *J* = 7.48, 10.22, 17.40 Hz, 2H), 5.60 (br. s., 1H), 5.55 (br. s., 1H), 5.08 - 5.25 (m, 4H), 4.43 (td, *J* = 7.55, 15.41 Hz, 2H), 4.19 - 4.30 (m, 2H), 3.86 (s, 2H), 3.81 (s, 3H), 3.30 (d, *J* = 6.71 Hz, 1H), 3.14 - 3.22 (m, 2H), 2.57 (td, *J* = 7.10, 13.89 Hz, 2H), 1.10 (d, *J* = 6.71 Hz, 5H)

^{13}C NMR (125 MHz, $CDCl_3$): (mixture of isomers) δ 201.4, 197.3, 164.9, 161.5, 158.8, 158.6, 153.2, 151.4, 138.6, 134.4, 132.7, 116.2, 112.0, 110.3, 105.3, 99.2, 98.6, 82.4, 82.3, 55.6, 55.3, 52.4, 52.0, 44.6, 38.0, 37.7, 17.0, 16.9;

^{1}HRMS: calculated for $C_{16}H_{21}O_4N_2$ $[M+H]^+$:305.1496, found: 305.1493.

2-((*4R,5R*)-5-((*R*)-But-3-en-2-yl)-2-oxooxazolidin-4-yl)-N-(3-((triisopropylsilyl)oxy) phenyl)acetamide (77):



To a solution of **72** (0.2 g, 1 mmol) and HOBt (0.16 g, 1.2 mmol) in dry CH_2Cl_2 (10 mL), DCC (0.25 g, 1.2 mmol) was added at 0 °C, stirred for 10 min. Then 3-((triisopropylsilyl)oxy) aniline **76** (0.26 g, 1 mmol) was introduced and stirring continued for 16 h at room temperature. White solid thus formed was filtered through a celite bed, filtrate was evaporated and purified by column chromatography (silica gel 100-200, 1:19 MeOH - CH_2Cl_2) to afford **77** (0.4 g, 87%) as a white solid.

Mp: 110 - 111 °C

$[\alpha]_D^{25}$: - 5.0 (*c* = 0.5, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 2945, 2868, 1748, 1668, 1607

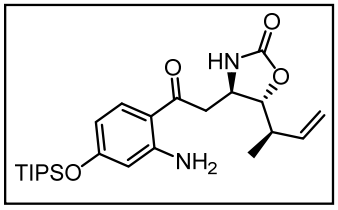
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (m, 1H), 7.23 (s, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.64 (m, 1H), 5.86 (m, 1H), 5.75 (m, 1H), 5.20-5.16 (m, 2H), 4.28 (m, 1H), 4.05 (m, 1H), 2.67-2.50 (m, 3H), 1.31-1.25 (m, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.6 Hz, 18H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 158.4, 156.6, 138.5, 136.4, 129.6, 117.8, 116.1, 112.3, 111.6, 84.3, 51.6, 42.8, 41.3, 17.9 (3C), 14.8, 12.6 (6C)

MS: 469 $(M+Na)^+$

^{1}HRMS: calculated for $C_{24}H_{39}N_2O_4Si$ $[M+H]^+$: 447.2674, found: 447.2673.

(*4R,5R*)-4-(2-(2-Amino-4-((triisopropylsilyl)oxy)phenyl)-2-oxoethyl)-5-((R)-but-3-en-2-yl)oxazolidin-2-one (78):



Compound **77** (100 mg, 0.2 mmol) was dissolved in dry acetonitrile (150 mL) and purged with argon for 15 min. This solution was irradiated with low pressure Hg vapour lamp (254 nm, 16W) for 4.5 h. The residue obtained after the removal of the solvent under reduced pressure was purified by column chromatography (silica gel 230-400, 0.4:99.6 MeOH - CH_2Cl_2) to afford **78** (36 mg, 36%, 5 mg of starting material was recovered) as a white solid and compound **79** (4 mg) as off white solid.

Mp: 131 - 132 °C;

$[\alpha]_D^{26}$: 33.8 (*c* = 0.2, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3437, 3327, 2945, 2869, 1744, 1636, 1619, 1589

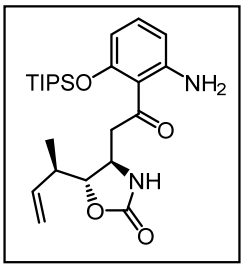
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=8.8 Hz, 1H), 6.30 (bs, 2H), 6.19 (dd, *J* = 8.8 Hz, 2.1 Hz, 1H), 6.10 (d, *J* = 2.1 Hz, 1H), 5.80 (m, 1H), 5.62 (bs, 1H), 5.20-5.16 (m, 2H), 4.23 (t, *J* = 5.2 Hz, 1H), 4.06 (m, 1H), 3.15 (m, 2H), 2.57 (m, 1H), 1.29-1.23 (m, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 7.3 Hz, 18H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 162.0, 158.2, 153.0, 136.7, 132.8, 117.6, 112.3, 109.8, 106.3, 84.2, 51.1, 44.6, 41.2, 17.8 (3C), 14.9, 12.7 (6C)

MS: 469 $(M+Na)^+$

^{1}HRMS: calculated for $C_{24}H_{39}N_2O_4Si$ $[M+H]^+$: 447.2674, found 447.2673.

(4*R*,5*R*)-4-(2-(2-amino-6-((triisopropylsilyl)oxy)phenyl)-2-oxoethyl)-5-((*R*)-but-3-en-2-yl)oxazolidin-2-one (79):



Mp: 140 - 141 °C

$[\alpha]_D^{26}$: 25.2 (*c* = 0.1, $CHCl_3$)

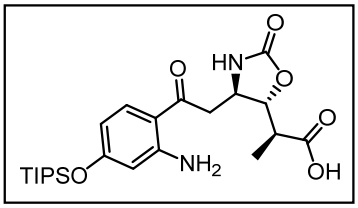
IR υ_{max}(film): cm^{-1} 3431, 2942, 2865, 1744, 1630, 1618

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (t, *J* = 7.93 Hz, 1H), 6.24 (d, *J* = 7.93 Hz, 1H), 6.12 (d, *J* = 7.93 Hz, 1H), 5.84 (brs., 1H), 5.71 - 5.82 (m, 1H), 5.55 (brs., 1H), 4.14 (dd, *J* = 4.58, 5.80 Hz, 1H), 3.95 - 4.06 (m, 1H), 3.39 (d, *J* = 3.36 Hz, 1H), 3.23 - 3.31 (m, 1H), 2.45 - 2.56 (m, 1H), 1.29 - 1.39 (m, 3H), 1.14 (d, *J* = 7.02 Hz, 3H), 1.11 (d, *J* = 1.22 Hz, 18H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 158.2, 158.0, 136.8, 133.9, 117.6, 113.1, 110.0, 106.9, 84.2, 51.4, 50.7, 41.3, 18.0, 15.1, 13.4

HRMS: calculated for $C_{24}H_{39}N_2O_4Si$ $[M+H]^+$: 447.2674, found 447.2672.

(*S*)-2-((*4R,5R*)-4-(2-(2-Amino-4-((triisopropylsilyl)oxy)phenyl)-2-oxoethyl)-2-oxooxazolidin-5-yl)propanoic acid (80):



To a cooled (0 °C) solution of **78** (50 mg, 0.1 mmol**)** in dioxane-water (3:1, 4 mL) OsO_4 (2.5% in *t*-BuOH, 0.1 mL, 0.01 mmol), $NaIO_4$ (96 mg, 0.4 mmol) and 2,6-lutidine (0.03 mL, 0.2 mmol) were added. The reaction mixture was stirred at room temperature for 3 h, filtered, and concentrated under vacuum. The residue obtained was taken up in ethyl acetate (10 mL), washed with aq.$Na_2S_2O_3$ (5 mL) followed by brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford colourless oil.

To this crude material dissolved in *t*-BuOH-water (5:1, 3 mL), NaH_2PO_4 (20 mg, 0.16 mmol), 2-methyl-2-butene (0.03 mL, 0.3 mmol) and $NaClO_2$ (10 mg, 0.1 mmol) were added. After the reaction mixture was stirred at room temperature for 6 h, the reaction mixture was evaporated to dryness, dissolved in ethyl acetate (10 mL), washed with water (5 mL), and dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200 mesh, 1 : 12, MeOH - CH_2Cl_2) to afford **80** (32 mg, 61%**)** as an off white solid.

Mp: 105 - 106 °C

$[\alpha]_D^{25}$: 80.5 (*c* = 0.5, $CHCl_3$)

IR υ_{max} (film): cm^{-1} : 3338, 2925, 2854, 1738, 1614, 1519, 1015

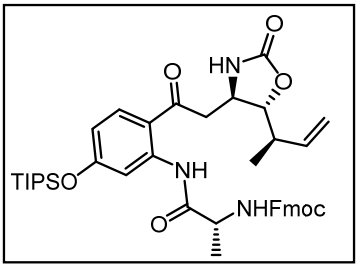
^{1}H NMR (400 MHz, CD_3OD): δ 7.63 (d, *J* = 8.8 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 6.15 (dd, *J* = 2.2, 8.8 Hz, 1H), 4.64-4.59 (m, 1H), 4.23-4.20 (m, 1H),3.29-3.25 (m, 2H), 2.89-2.83 (m, 1H), 1.29-1.27 (m, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.15-1.11 (m, 18H)

^{13}C NMR (100 MHz, CD_3OD): δ 198.8, 162.9, 161.2, 134.4, 113.6, 110.0, 107.0, 83.8, 53.0, 46.0, 45.5, 18.4 (6C), 13.9 (3C), 12.4.

MS: 487 $(M+Na)^+$

HRMS: calculated for $C_{23}H_{35}N_2O_6Si$ $[M-H]^+$: 463.2259, found: 463.2282.

(9*H*-fluoren-9-yl)methyl ((*R*)-1-((2-(2-((4*R*,5*R*)-5-((*R*)-but-3-en-2-yl)-2-oxooxazolidin-4-yl)acetyl)-5-((triisopropylsilyl)oxy)phenyl)amino)-1-oxopropan-2-yl)carbamate (82):



Compound **82** (170 mg, 68%) was synthesized by following the similar procedure used for the synthesis of **60.**

Mp: 137 - 139 °C

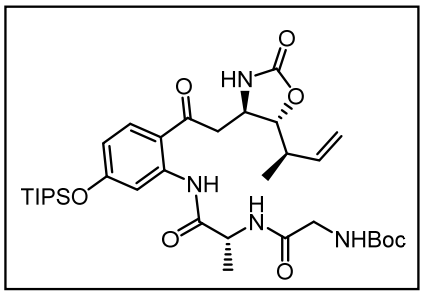
$[\alpha]_D^{25}$: 55.5 (*c* = 0.4, $CHCl_3$)

^{1}H NMR (400 MHz, CD_3OD): δ 8.41 (d, *J* = 2.26 Hz, 1H), 7.96 (d, *J* = 9.03 Hz, 1H), 7.87 (d, *J* = 7.53 Hz, 1H), 7.82 (d, *J* = 7.53 Hz, 2H), 7.71 (d, *J* = 7.28 Hz, 1H), 7.40 (dd, *J* = 3.01, 7.28 Hz, 2H), 7.29 - 7.37 (m, 2H), 6.63 - 6.79 (m, 1H), 5.55 - 5.66 (m, 1H), 4.97 (d, *J* = 17.32 Hz, 2H), 4.61 (dd, *J* = 6.02, 9.79 Hz, 1H), 4.23 - 4.29 (m, 2H), 4.16 - 4.22 (m, 2H), 3.80 - 3.88 (m, 1H), 3.38 (d, *J* = 8.53 Hz, 1H), 3.19 - 3.27 (m, 1H), 2.19 - 2.32 (m, 1H), 1.52 (d, *J* = 7.28 Hz, 3H), 1.33 - 1.41 (m, 3H), 1.13 - 1.15 (m, 18H), 0.83 (d, *J* = 6.78 Hz, 3H);

^{13}C NMR (100 MHz, CD_3OD): δ 201.7, 175.0, 163.5, 161.2, 158.8, 145.8, 145.0, 143.9, 142.8, 142.7, 138.5, 135.0, 129.0, 128.4, 127.0, 126.5, 121.1, 117.7, 117.5, 116.1, 112.1, 85.7, 68.5, 54.1, 52.8, 46.7, 42.7, 18.5, 18.0, 15.7, 14.0

HRMS: calculated for $C_{42}H_{54}O_7N_3Si$ $[M+H]^+$: 740.3731, found: 740.3730.

***tert*-Butyl (2-(((*R*)-1-((2-(2-((4*R*,5*R*)-5-((*R*)-but-3-en-2-yl)-2-oxooxazolidin-4-yl)acetyl)-5-((triisopropylsilyl)oxy)phenyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)carbamate (84)**



To a solution of compound **82** (160 mg, 0.2 mmol) was taken in ethanol (5 mL) $NaBH_4$ (32 mg, 0.8 mmol) was added at 0 °C and stirred for 10 h at room temperature. Concentrated the reaction mixture and quenched with ice and extracted with EtOAc (10 mL X 2). Combined organic layers were washed with brine (5 mL) and concentrated . The Ms of the compound showed peak at 542 confirmed that along with carbonyl reduction Fmoc also got deprotected. The crude compound was taken in dry CH_2Cl_2 (5 mL), NHBoc-Gly-OH (37 mg, 0.2 mmol), EDC(33 mg, 0.2 mmol), HOBt (29 mg, 0.2 mmol) were added followed by Et_3N (60 μL) was added and stirred at room temperature for 24 h. diluted the reaction mixture with EtOAc (10 mL) washed with brine 3 mL. organic layer was concentrated to afford glycine coupled compound. Compound was confirmed by appearance of mass peak at 699 (M+Na). The crude compound was taken in CH_2Cl_2 cooled to 0 °C, DMP (137 mg) was added and stirred for 1 h at same temperature. Filtered the reaction mixture washed with sat. $NaHCO_3$. Organic layer was dried over Na_2SO_4 the crude material obtained after removal of solvent was purified by column chromatography (silica gel 100-200 mesh, 4: 96, MeOH - CH_2Cl_2) to afford **84** (95 mg, 65% for 3 steps**)** as an off white solid.

Mp: 112 - 113 °C

$[\alpha]_D^{24}$: 81.8 (*c* = 0.5, $CHCl_3$)

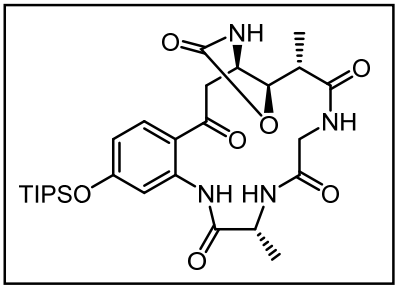
IR υ_{max} (film): cm^{-1} : 3338, 2925, 2854, 1738, 1614, 1519, 1015

^{1}H NMR (500 MHz, CD_3OD): δ 8.38 (d, *J* = 2.45 Hz, 1H), 8.00 (d, *J* = 8.80 Hz, 1H), 6.72 (dd, *J* = 2.45, 8.80 Hz, 1H), 5.84 (ddd, *J* = 7.95, 10.03, 17.48 Hz, 1H), 5.17 - 5.28 (m, 2H), 4.51 (q, *J* = 7.09 Hz, 1H), 4.39 (t, *J* = 4.40 Hz, 1H), 4.12 - 4.21 (m, 1H), 4.01 (d, *J* = 5.62 Hz, 1H), 3.41 (d, *J* = 6.11 Hz, 2H), 2.56 - 2.67 (m, 1H), 1.51 (d, *J* = 7.34 Hz, 3H), 1.47 (s, 9H), 1.33 - 1.41 (m, 3H), 1.17 (d, *J* = 7.34 Hz, 3H), 1.15 (d, *J* = 7.58 Hz, 18H)

^{13}C NMR (125 MHz, CD_3OD): δ 202.1, 174.1, 173.1, 163.6, 161.5, 158.5, 143.9, 138.4, 136.6, 135.1, 135.0, 133.4, 132.2, 127.8, 118.1, 117.4, 116.1, 111.9, 85.9, 80.9, 52.9, 52.8, 52.1, 46.5, 46.4, 44.8, 43.1, 28.9, 18.5, 17.6,16.2, 14.0

HRMS: calculated for $C_{34}H_{55}N_4O_8Si$ $[M+H]^+$: 675.3784, found: 675.3782.

(3a*R*,4*S*,10*R*,18a*R*)-4,10-Dimethyl-14-((triisopropylsilyl)oxy)-3a,4,6,7,9,10,18,18a-octahydro-2*H*-benzo[h]oxazolo[4,5-l][1,4,7]triazacyclopentadecine-2,5,8,11,17(1H,12H)-pentaone (86):



To a cooled (0 °C) solution of **85** (60 mg, 0.01 mmol**)** in dioxane-water (3:1, 4 mL) OsO_4 (2.5% in *t*-BuOH, 3 µL), $NaIO_4$ (76 mg, 0.04 mmol) and 2,6-lutidine (20 µL, 0.02 mmol) were added. The reaction mixture was stirred at room temperature for 3 h, filtered, and concentrated under vacuum. The residue obtained was taken up in ethyl acetate (10 mL),

washed with aq.$Na_2S_2O_3$ (5 mL) followed by brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford colourless oil.

To this crude material dissolved in *t*-BuOH-water (5:1, 3 mL), NaH_2PO_4 (16 mg, 0.015 mmol), 2-methyl-2-butene (28 µL, 0.03 mmol) and $NaClO_2$ (8 mg, 0.01 mmol) were added. After the reaction mixture was stirred at room temperature for 6 h, the reaction mixture was evaporated to dryness dissolved in ethyl acetate (10 mL), washed with water (5 mL), and dried over anhydrous Na_2SO_4. The crude material **(85')**obtained after removal of solvent was treated with 20 % TFA in CH_2Cl_2 and stirred for 2 h. concentrated the reaction mixture and the residue was taken up in dry CH_2Cl_2 (20 mL), HATU (101 mg, 0.03 mmol) and Et_3N (0.06 mL, 0.05 mmol) were added and the resulting reaction solution was stirred at room temperature for 16 h. Reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1N HCl (5 mL) and saturated aq. $NaHCO_3$ solution (5 mL). The organic layer was dried over anhydrous Na_2SO_4. The crude material obtained after removal of solvent was purified by repititive column chromatography (silica gel 230-400, 4: 96 methanol: CH_2Cl_2) to afford **86** a white solid (3 mg, 5% over 4 steps).

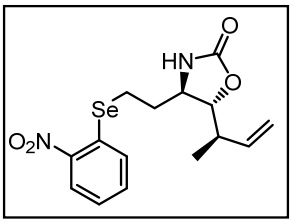
^{1}H NMR (400 MHz, CD_3OD): δ 8.31 (d, *J* = 2.29 Hz, 1H), 7.92 (d, *J* = 9.16 Hz, 1H), 6.68 (dd, *J* = 2.29, 9.16 Hz, 1H), 4.63 (dd, *J* = 1.83, 4.12 Hz, 1H), 4.30 (q, *J* = 7.63 Hz, 1H), 4.18 - 4.23 (m, 1H), 3.48 - 3.51 (m, 1H), 3.44 - 3.47 (m, 2H), 3.31 - 3.33 (m, 1H), 3.00 - 3.06 (m, 1H), 1.48 (d, *J* = 7.33 Hz, 3H), 1.33 – 1.35 (m, 3H), 1.14 (d, *J* = 6.87 Hz, 3H), 1.12 (d, *J* = 2.29 Hz, 9H), 1.10 (d, *J* = 2.29 Hz, 9H)

HRMS: calculated for $C_{28}H_{43}N4O_7Si$ $[M+H]^+$: 575.2901, found: m/z 575.2903

General procedure A: procedure for the synthesis of alkenyl aryl selenides: Bu_3P (2 mmol) was added dropwise to a solution of alkenol (1 mmol) and 2-nitrophenyl selenocyanate (2 mmol) in 5 mL of THF under nitrogen atmosphere. After 2-3 h TLC indicated almost complete disappearance of the starting material, and the mixture was concentrated *in vacuo* and purified by column chromatography using ethyl acetate and pet ether to afford desired alkenyl aryl selenides.

General procedure B: Procedure for ozonolysis reaction: A solution of alkenyl selenide (1 mmol) in 30 mL of CH_2Cl_2 and 2.5 M methanolic NaOH (5 mmol) was stirred at −78 °C as ozone was passed through the solution. After 20-30 min, initially reaction mixture color changed to yellow then yellow precipitate was observed. Once blue color observed oxygen was passed to remove excess of ozone until reaction mixture was become colorless. The reaction mixture was allowed to warm up to room temperature, and then stirred for additional 3-4 h. The reaction mixture was diluted with water (10 mL) extracted with CH_2Cl_2 (10 mL x 2). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the crude material on a silica gel column chromatography ethyl acetate and pet ether afforded desired olefin esters.

(4*R*,5*R*)-5-((*R*)-But-3-en-2-yl)-4-(2-((2-nitrophenyl)selanyl)ethyl)oxazolidin-2-one (91):



The compound **91** (1.8 gm, 95%) synthesized from compound **69** by following general procedure A, as yellow color solid.

Mp: 120- 121 °C

$[\alpha]_D^{27}$ + 48.30 (*c* 1.26, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3233, 2975, 1730, 1499

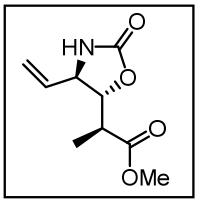
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.3 Hz, 1H), 7.62 - 7.46 (m, 2H), 7.39 - 7.20 (m, 2H), 5.83 - 5.65 (m, 1H), 5.25 - 5.06 (m, 2H), 4.17 (t, *J* = 4.9 Hz, 1H), 3.75 (q, *J* = 5.9 Hz, 1H), 3.00 (td, *J* = 7.6, 11.9 Hz, 1H), 2.94 - 2.81 (m, 1H), 2.58 - 2.41 (m, 1H), 2.06 - 1.89 (m, 2H), 1.11 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 146.8, 136.5, 134.0, 132.4, 128.9, 126.5, 125.8, 117.7, 84.7, 54.9, 41.4, 34.6, 20.9, 14.7

MS: 393 $(M+Na)^+$

HRMS: calculated for $C_{15}H_{19}O_4N_2Se$ $[M+H]^+$: 371.0505, found 371.0497.

Methyl (*S*)-2-((4*R*,5*R*)-2-oxo-4-vinyloxazolidin-5-yl)propanoate (92):



The compound **92** (16 mg, 15%) was synthesized from compound **91** by following general procedure B, as a pale yellow liquid.

$[\alpha]_D^{29}$: + 9.07 (*c* 1.33, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 2935, 1758, 1671, 1644, 1529

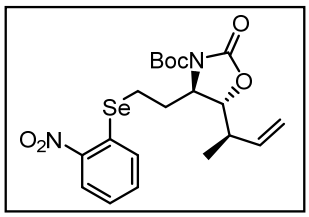
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (ddd, *J* = 7.3, 10.0, 17.2 Hz, 1H), 5.41 - 5.25 (m, 3H), 4.53 (t, *J* = 6.1 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 2.95 (t, *J* = 7.0 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 158.1, 136.1, 118.8, 82.0, 57.6, 52.2, 43.0, 11.5

MS: 222 $(M+Na)^+$

HRMS: calculated for $C_9H_{14}O_4N$ $[M+H]^+$: 200.0917, found 200.0916.

***tert*-Butyl (4*R*,5*R*)-5-((*R*)-but-3-en-2-yl)-4-(2-((2-nitrophenyl)selanyl)ethyl)-2-oxooxazolidine-3-carboxylate (93) :**



To a solution of **91** (500 mg, 1.3 mmol) in THF (10 mL) was added di-tert-butyl dicarbonate (590 mg, 2.7 mmol) and 4-dimethylaminopyridine (DMAP) (33 mg, 0.3

mmol) and the whole was stirred at room temperature for overnight. The reaction mixture was concentrated *in vaccuo* and the crude material was purified by column chromatography (silica gel 100-200 mesh 15% ethyl acetate - pet ether) to afford **93** (615 mg, 97%) as yellow color solid.

Mp: 103- 105 °C

$[\alpha]_D^{27}$: + 5.65 (*c* 0.97, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3211, 2932, 1654, 1544

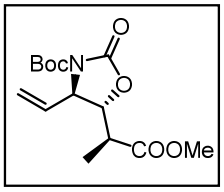
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (dd, *J* = 1.4, 8.2 Hz, 1H), 7.54 (ddd, *J* = 1.4, 7.0, 8.1 Hz, 1H), 7.43 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.33 (ddd, *J* = 1.4, 7.2, 8.4 Hz, 1H), 5.68 (ddd, *J* = 8.2, 10.3, 17.2 Hz, 1H), 5.24 - 5.07 (m, 2H), 4.18 - 4.09 (m, 2H), 2.97 - 2.86 (m, 1H), 2.85 - 2.71 (m, 1H), 2.53 - 2.38 (m, 1H), 2.25 - 2.04 (m, 2H), 1.49 (s, 9H), 1.11 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 149.2, 146.8, 135.7, 134.1, 132.6, 128.7, 126.7, 125.9, 118.4, 84.4, 80.9, 57.2, 42.1, 32.0, 28.0, 19.8, 14.8

MS: 493 $(M+Na)^+$

HRMS: calculated for $C_{20}H_{26}O_6N_2SeNa$ $[M+Na]^+$: 493.0848, found 493.0839.

tert-Butyl (4*R*,5*R*)-5-((*S*)-1-methoxy-1-oxopropan-2-yl)-2-oxo-4-vinyloxazolidine-3-carboxylate (94):



The compound **94** (120 mg, 75%) was synthesized from compound **93** by following general procedure B, as a pale yellow color liquid.

$[\alpha]_D^{26}$: + 12.00 (*c* 1.17, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3023, 1813, 1728, 1597

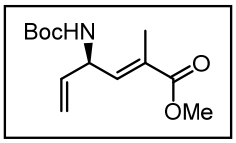
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 - 5.74 (m, 1H), 5.40 - 5.25 (m, 2H), 4.50 (dd, *J* = 4.1, 7.3 Hz, 1H), 4.39 (dd, *J* = 4.1, 6.4 Hz, 1H), 3.72 (s, 3H), 3.02 - 2.80 (m, 1H), 1.51 (s, 9H), 1.26 (d, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 151.3, 148.9, 134.9, 118.8, 84.3, 78.6, 59.6, 52.3, 43.0, 28.0, 11.6

MS: 322 $(M+Na)^+$

HRMS: calculated for $C_{14}H_{21}O_6NNa$ $[M+Na]^+$: 322.1261, found 467.1255.

Methyl (*R*,*E*)-4-((tert-butoxycarbonyl)amino)-2-methylhexa-2,5-dienoate (95):



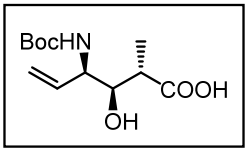
Compound **94** (100 mg, 0.33 mmol) was taken in THF-MeOH (1 mL, 3:2) cooled to 0 °C, LiOH. H_2O (15 mg, 0.375 mmol) dissolved in 0.5mL water was added and stirred for 3 h. After completion of the reaction (monitored by TLC), concentrated the reaction mixture to remove THF and MeOH. Acidified to P^H 3 with 1N HCl, extracted with ethylacetate (5 mL X 2). Organic layer was concentrated purified by column chromate graphy (silica gel 100-200 mesh 25% ethyl acetate - pet ether) to afford **95** (62 mg, 73%) as colorless liquid and compound **90** (12 mg, 14%). (Note: acid compound **90** found to unsatable).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (d, *J* = 8.80 Hz, 1H), 5.76 (ddd, *J* = 5.2, 10.5, 16.9 Hz, 1H), 5.13 - 5.24 (m, 2H), 4.99 (brs., 1H), 4.68 (brs., 1H), 3.74 (s, 3H), 1.92 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 154.9, 139.4, 135.6, 116.1, 79.9, 52.0, 51.0, 28.4, 12.8.

HRMS: calculated for $C_{13}H_{21}O_4NNa$ $[M+Na]^+$: 278.1363, found 278.1359.

(2*S*,3*R*,4*R*)-4-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-2-methylhex-5-enoic acid (90)

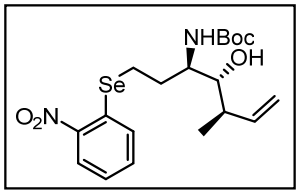


^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (brs., 1H), 5.74 - 5.99 (m, 1H), 5.14 - 5.33 (m, 2H), 4.17 - 4.38 (m, 1H), 3.79 – 3.75 (m, 1H), 2.56 - 2.75 (m, 1H), 1.44 (s, 9H), 1.25 (d, *J* = 6.95 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 179.8, 156.1, 136.5, 116.4, 80.0, 75.0, 53.7, 42.3, 28.3, 14.0.

HRMS: calculated for $C_{12}H_{22}O_5N$ $[M+H]^+$: 260.14979 found 260.1492.

***tert*-Butyl ((3*R*,4*R*,5*R*)-4-hydroxy-5-methyl-1-((2-nitrophenyl)selanyl)hept-6-en-3-yl)carbamate (96):**



To a solution of compound **93** (300 mg, 0.63 mmol) in dry methanol Cs_2CO_3 (104 mg, 0.32 mmol) was added and stirred for 8 h. Methanol was removed under reduced pressure diluted with ethyl acetate (15 mL) washed with water (5 mL), brine (5 mL). The organic layer was dried over Na_2SO_4 and the crude material obtained after removal of the solvent was purified by column chromatography (silica gel 100-200 mesh 15% ethyl acetate - pet ether) to afford **96** (202 mg, 71%) as yellow color solid and compound **91** (61 mg, 21%).

Mp: 118-120 °C

$[\alpha]_D^{29}$: + 4.73 (*c* 0.89, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3023, 1595, 1217

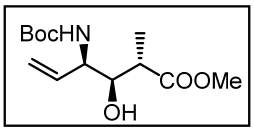
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.1 Hz, 1H), 7.61 - 7.49 (m, 2H), 7.39 - 7.29 (m, 1H), 5.80 - 5.54 (m, 1H), 5.26 - 5.17 (m, 2H), 4.94 (d, *J* = 9.5 Hz, 1H), 4.01 - 3.88 (m, 1H), 3.30 (d, *J* = 8.6 Hz, 1H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.26 (td, *J* = 7.5, 15.1 Hz, 1H), 2.18 - 2.07 (m, 1H), 2.07 - 1.90 (m, 2H), 1.48 (s, 9H), 1.08 (d, *J* = 6.6 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 146.9, 140.6, 133.6, 129.0, 126.4, 125.3, 117.7, 79.5, 75.6, 51.4, 42.5, 33.0, 28.4, 22.7, 16.4

MS: 467 $(M+Na)^+$

HRMS: calculated for $C_{19}H_{28}O_5N_2SeNa$ $[M+Na]^+$: 467.1056, found 467.1045.

Methyl (2*S*,3*R*,4*R*)-4-((*tert*-butoxycarbonyl)amino)-3-hydroxy-2-methylhex-5-enoate (97):



The compound **97** (60 mg, 46%) was synthesized from compound **96** by following general procedure B, as a colorless liquid.

$[\alpha]_D^{30}$: + 29.10 (*c* 2.95, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3016, 2977, 1707, 1501

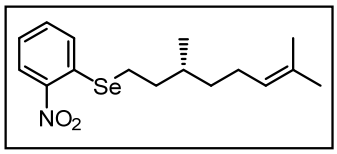
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 - 5.78 (m, 1H), 5.31 - 5.19 (m, 2H), 5.03 - 4.93 (m, 1H), 4.30 (brs, 1H), 3.79 (d, *J* = 7.8 Hz, 1H), 3.71 (s, 3H), 3.04 (brs, 1H), 2.67 (t, *J* = 7.3 Hz, 1H), 1.44 (s, 9H), 1.22 (d, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 155.7, 136.9, 116.2, 79.6, 74.9, 53.7, 52.0, 42.5, 28.3, 14.1

MS: 296 $(M+Na)^+$

HRMS: calculated for $C_{13}H_{23}O_5NNa$ $[M+Na]^+$: 296.1468, found 296.1467.

(*R*)-(3,7-Dimethyloct-6-en-1-yl)(2-nitrophenyl)selane (1b):



The compound **1b** (205 mg, 93%) synthesized from *β*-citronellol by following general procedure A, as a yellow color liquid.

$[\alpha]_D^{25}$: + 8.16 (*c* 1.10, $CHCl_3$)

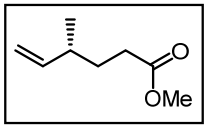
IR υ_{max}(film): cm^{-1} 3022, 2964, 2923, 1594, 1516, 1301, 1216

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.2 Hz, 1H), 7.57 - 7.47 (m, 2H), 7.37 - 7.27 (m, 1H), 5.18 - 5.00 (m, 1H), 3.05 - 2.80 (m, 2H), 2.12 - 1.89 (m, 2H), 1.85 - 1.53 (m, 9H), 1.91 -1.46 (m, 2H), 0.97 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 146.7, 134.0, 133.5, 131.4, 129.0, 126.4, 125.2, 124.4, 36.6, 35.1, 33.1, 25.7, 25.4, 24.0, 19.2, 17.7

HRMS: calculated for $C_{16}H_{24}O_2NSe$ $[M+H]^+$: 342.0967, found 342.0963.

Methyl (*R*)-4-methylhex-5-enoate (1c):



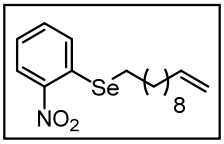
Compound **1c** (35 mg, 84%) was synthesized from compound **1b** by following general procedure B, as a colorless liquid.

$[\alpha]_D^{25}$: − 14.65 (*c* 0.50, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 - 5.54 (m, 1H), 5.05 - 4.92 (m, 2H), 3.67 (s, 3H), 2.32 - 2.27 (m, 2H), 2.22 - 2.07 (m, 1H), 1.76 - 1.54 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 143.4, 113.6, 51.5, 37.5, 31.9, 31.3, 20.1. Spectral data and rotation were compared with reported values and found to be identical.

(2-Nitrophenyl)(undec-10-en-1-yl)selane (2b)



The compound **2b** (155 mg, 73%) was synthesized from undec-10-en-1-ol by following general procedure A, as a yellow color liquid.

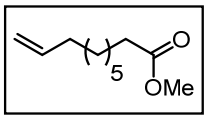
IR υ_{max}(film): cm^{-1} 3022, 2928, 2856, 1595, 1216

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.1 Hz, 1H), 7.57 - 7.47 (m, 2H), 7.29 (ddd, *J* = 3.4, 4.9, 8.3 Hz, 1H), 5.80 (tdd, *J* = 6.6, 10.3, 17.1 Hz, 1H), 5.05 - 4.84 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.03 (q, *J* = 6.8 Hz, 2H), 1.77 (quin, *J* = 7.5 Hz, 2H), 1.47 (quin, *J* = 7.3 Hz, 2H), 1.40 - 1.25 (m, 10H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 139.1, 134.0, 133.5, 129.0, 126.4, 125.1, 114.1, 33.7, 30.1, 29.4, 29.1, 29.0, 28.8, 28.2, 26.2

HRMS: calculated for $C_{17}H_{26}O_2NSe$ $[M+H]^+$: 356.1123, found 356.1116.

Methyl dec-9-enoate (2c)



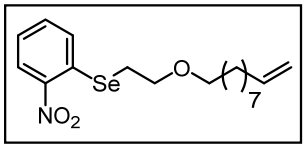
Compound **2c** (25 mg, 65%) was synthesized from compound **2b** by following general procedure B, as a colorless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 - 5.74 (m, 1H), 5.08 - 4.87 (m, 2H), 3.67 (s, 3H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.65 - 1.59 (m, 2H), 1.40 - 1.27 (m, 8H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 139.1, 114.2, 51.4, 34.1, 33.7, 29.1, 28.9, 28.8, 24.9.

Spectral data and rotation were compared with reported values and found to be identical.

(2-(Dec-9-en-1-yloxy)ethyl)(2-nitrophenyl)selane (3b):



The compound **3b** (186 mg, 88%) was synthesized from compound **3a** by following general procedure A, as a yellow color liquid.

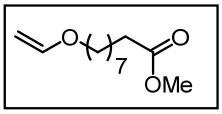
IR υ_{max}(film): cm^{-1} 3073, 3011, 2929, 2857, 1637, 1515, 1337 1218

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 1.2, 8.3 Hz, 1H), 7.67 - 7.57 (m, 1H), 7.57 - 7.44 (m, 1H), 7.40 - 7.18 (m, 1H), 5.93 - 5.70 (m, 1H), 5.07 - 4.81 (m, 2H), 3.87 - 3.66 (m, 2H), 3.58 - 3.34 (m, 2H), 3.22 - 2.98 (m, 2H), 2.10 - 1.94 (m, 2H), 1.62 - 1.47 (m, 2H), 1.43 - 1.16 (m, 10H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 139.2, 133.5, 133.2, 129.1, 126.4, 125.4, 114.1, 71.3, 69.1, 33.8, 29.6, 29.4, 29.0, 28.9, 26.1, 25.8

HRMS: calculated for $C_{18}H_{28}O_3NSe$ $[M+H]^+$: 386.1229, found 386.1221.

Methyl 9-(vinyloxy)nonanoate (3c)



The compound **3c** (~27 mg, 65-70%, decomposition was observed in $CDCl_3$) was synthesized from compound **3b** by following general procedure B, as colorless liquid.

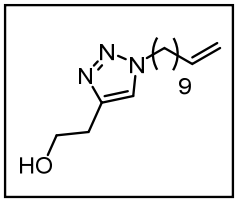
IR υ_{max}(film): cm^{-1} 3023, 2357, 1726, 1596, 1216, 1031

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.39 (dd, *J* = 6.8, 14.3 Hz, 1H), 4.10 (dd, *J* = 1.9, 14.4 Hz, 1H), 3.90 (dd, *J* = 1.9, 6.8 Hz, 1H), 3.68 - 3.50 (m, 5H), 2.29 - 2.16 (m, 2H), 1.66 - 1.51 (m, 4H), 1.25 - 1.21 (m, 8H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 152.0, 86.2, 68.1, 51.4, 34.1, 29.1, 29.0, 25.9, 24.9

HRMS: calculated for $C_{12}H_{23}O_3$ $[M+H]^+$: 215.1642, found 215.1640.

2-(1-(Undec-10-en-1-yl)-1H-1,2,3-triazol-4-yl)ethan-1-ol (4a):



Mixture of 11-azidoundec-1-ene (200 mg, 1.02 mmol) and but-3-yn-1-ol (70 mg, 1.02 mmol) in 6 mL of (1 : 1) t-BuOH and water in presence of $CuSO_4.5H_2O$ (12.5 mg, 5 mol%) and Na-Ascorbate (20.2 mg, 10 mol%) were heated at 80 ^oC for 1 h. After completion of reaction (monitored by TLC), t-BuOH was removed under reduced pressure and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to get the crude product which was purified by silica gel column chromatography (silica gel 100-200 mesh 2% MeOH - CH_2Cl_2) to afford the compound **4a** (225 mg, 83%) as colorless solid.

Mp: 70- 82 °C

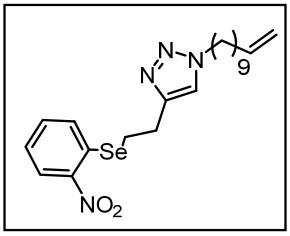
IR υ_{max}(film): cm^{-1} 3390, 3019, 2930, 1456, 1217

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (s, 1H), 5.91 - 5.68 (m, 1H), 5.06 - 4.86 (m, 2H), 4.30 (t, *J* = 7.3 Hz, 2H), 3.94 (t, *J* = 5.8 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.10 - 1.96 (m, 2H), 1.88 (t, *J* = 6.7 Hz, 2H), 1.44 - 1.26 (m, 12H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.4, 139.1, 121.3, 114.1, 61.6, 50.2, 33.7, 30.2, 29.3, 29.0, 28.9, 28.8, 28.6, 26.4

HRMS: calculated for $C_{15}H_{28}ON_3$ $[M+H]^+$: 266.2227, found 266.2227.

4-(2-((2-Nitrophenyl)selanyl)ethyl)-1-(undec-10-en-1-yl)-1H-1,2,3-triazole (4b):



The compound **4b** (189 mg, 90%) was synthesized from compound **4a** by following general procedure A, as a yellow color liquid.

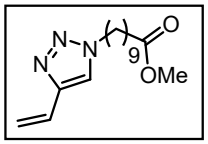
IR υ_{max}(film): cm^{-1} 2959, 2865, 1639, 1678, 1459, 1499, 1220, 1146

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 - 8.15 (m, 1H), 7.63 - 7.46 (m, 2H), 7.36 (s, 1H), 7.34 - 7.28 (m, 1H), 5.94 - 5.74 (m, 1H), 5.05 - 4.86 (m, 2H), 4.29 (t, *J* = 7.2 Hz, 2H), 3.31 - 3.23 (m, 2H), 3.22 - 3.14 (m, 2H), 2.02 (q, *J* = 7.0 Hz, 2H), 1.86 (t, *J* = 7.0 Hz, 2H), 1.39 - 1.24 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 145.9, 139.2, 133.7, 132.9, 129.0, 126.5, 125.5, 121.1, 114.2, 50.3, 33.8, 30.3, 29.3, 29.3, 29.0, 29.0, 28.9, 26.5, 25.4, 25.1

HRMS: calculated for $C_{21}H_{31}O_2N_4Se$ $[M+H]^+$: 451.1607, found 451.1613.

1-(Undec-10-en-1-yl)-4-vinyl-1*H*-1,2,3-triazole (4c):



The compound **4c** (35 mg, 81%) was synthesized from compound **4b** by following general procedure B, as colorless liquid.

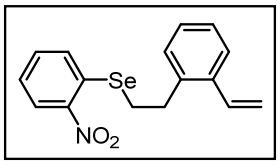
IR υ_{max}(film): cm^{-1} 3021, 2933, 2358, 1729, 1598, 1499, 1217

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 6.72 (dd, *J* = 11.1, 17.7 Hz, 1H), 5.88 (dd, *J* = 1.0, 17.9 Hz, 1H), 5.33 (dd, *J* = 1.0, 11.2 Hz, 1H), 4.32 (t, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.88 (d, *J* = 6.8 Hz, 2H), 1.60 (t, *J* = 7.2 Hz, 2H), 1.35 - 1.23 (m, 10H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 146.3, 125.8, 120.0, 115.9, 51.5, 50.3, 34.1, 30.3, 29.1 (2C), 29.0, 28.9, 26.4, 24.9

HRMS: calculated for $C_{15}H_{26}O_2N_3$ $[M+H]^+$: 280.2020, found 280.2018.

(2-Nitrophenyl)(2-vinylphenethyl)selane (5b):



The compound **5b** (210 mg, 92%) was synthesized from compound **5a**[5] by following general procedure A, as a yellow color liquid.

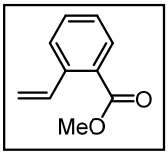
IR υ_{max}(film): cm^{-1} 3021, 2939, 1584, 1516, 1301, 1216

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 - 8.17 (m, 1H), 7.47 - 7.38 (m, 3H), 7.23 (ddd, *J* = 2.1, 6.2, 8.3 Hz, 1H), 7.20 - 7.09 (m, 3H), 6.91 (dd, *J* = 11.0, 17.4 Hz, 1H), 5.62 (dd, *J* = 1.2, 17.4 Hz, 1H), 5.28 (dd, *J* = 1.1, 10.9 Hz, 1H), 3.06 - 3.01 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 137.8, 136.5, 134.0, 133.5, 133.3, 129.4, 129.0, 128.1, 127.2, 126.4, 126.2, 125.4, 116.5, 32.2, 26.5

HRMS: calculated for $C_{16}H_{16}O_2NSe$ $[M+H]^+$: 334.0341, found 334.0336.

Methyl 2-vinylbenzoate (5c):

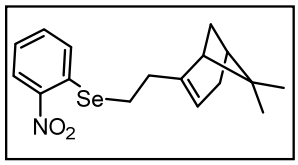


The compound **5c** (30 mg, 83%) was synthesized from compound **5b** by following general procedure B, as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 - 7.84 (m, 1H), 7.61 - 7.57 (m, 1H), 7.51 - 7.42 (m, 2H), 7.35 - 7.29 (m, 1H), 5.65 (dd, *J* = 1.2, 17.4 Hz, 1H), 5.36 (dd, *J* = 1.2, 11.0 Hz, 1H), 3.90 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 139.6, 135.9, 132.1, 130.3, 128.6, 127.4, 127.2, 116.5, 52.1.

(2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)(2-nitrophenyl)selane (6b):



The compound **6b** (175 mg, 80%) was synthesized from compound **6a** (−) - Nopol by following general procedure A, as a yellow color liquid.

$[\alpha]_D^{25}$: − 22.8 (*c* 0.60, $CHCl_3$)

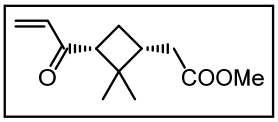
IR υ_{max}(film): cm^{-1} 3022, 2923, 1586, 1516, 1336, 1216

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 3.4 Hz, 2H), 7.39 - 7.22 (m, 1H), 5.36 (brs, 1H), 3.05 - 2.86 (m, 2H), 2.49 - 2.38 (m, 3H), 2.38 - 2.16 (m, 2H), 2.16 - 2.01 (m, 2H), 1.30 (s, 3H), 1.21 (d, *J* = 8.6 Hz, 1H), 0.88 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 143.4, 133.9, 133.5, 129.0, 126.4, 125.2, 117.9, 45.6, 40.7, 38.1, 35.4, 31.7, 31.2, 26.3, 23.9, 21.3

HRMS: calculated for $C_{17}H_{22}NO_2Se$ $[M+H]^+$: 352.0810, found 352.0811.

Methyl 2-((1*R*,3*R*)-3-acryloyl-2,2-dimethylcyclobutyl)acetate (6c):



The compound **6c** (26 mg, 86%) was synthesized from compound **6b** by following general procedure B, as a pale yellow color liquid.

$[\alpha]_D^{25}$: − 41.8 (*c* 1.00, $CHCl_3$)

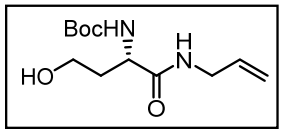
IR υ_{max}(film): cm^{-1} 3022, 2928, 1730, 1676, 1266, 1217

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.30 (dd, *J* = 10.7, 17.4 Hz, 1H), 6.15 (d, *J* = 17.4 Hz, 1H), 5.77 (d, *J* = 10.7 Hz, 1H), 3.62 (s, 3H), 3.17 (t, *J* = 8.5 Hz, 1H), 2.46 - 2.36 (m, 1H), 2.36 - 2.24 (m, 2H), 2.09 (q, *J* = 10.8 Hz, 1H), 2.00 - 1.89 (m, 1H), 1.28 (s, 3H), 0.78 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 173.2, 137.0, 128.0, 51.5, 50.8, 43.4, 38.1, 34.9, 30.1, 22.6, 17.4

HRMS: calculated for $C_{12}H_{19}O_3$ $[M+H]^+$: 211.1329, found 211.1326.

***tert*-Butyl (*S*)-(1-(allylamino)-4-hydroxy-1-oxobutan-2-yl)carbamate (7a):**



Mixture of N-Boc-L-Homoserine lactone (100 mg, 0.5 mmol) and allyl amine (37 µL, 0.5 mmol) in 2 mL of toluene irradiated under microwave at 130 °C for 30 min. concentrated the reaction mixture, diluted with ethylacetate (10 ml) washed with 1N HCl (2 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, concentrated and purified by

column chromatography (silica gel 100-200 mesh 30% ethyl acetate - CH_2Cl_2) to afford **7a** (79 mg, 62%, 92% based on recovered starting material) as colorless solid.

Mp: 80- 82 °C

$[\alpha]_D^{25}$: −1.41 (*c* 0.87, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3020, 2930, 1669, 1593,1217

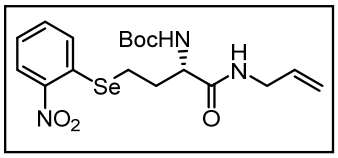
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (brs, 1H), 5.90 - 5.68 (m, 2H), 5.24 - 5.01 (m, 2H), 4.44 - 4.30 (m, 1H), 3.90 - 3.81 (m, 2H), 3.68 (brs, 2H), 2.03 - 1.93 (m, 1H), 1.81 - 1.63 (m, 1H), 1.41 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 156.6, 133.8, 116.3, 80.3, 58.5, 51.4, 41.9, 36.4, 28.3

MS: 281 $(M+Na)^+$

HRMS: calculated for $C_{12}H_{22}O_4N_2Na$ $[M+Na]^+$: 281.1472, found 281.1466.

***tert*-Butyl (*S*)-(1-(allylamino)-4-((2-nitrophenyl)selanyl)-1-oxobutan-2-yl)carbamate (7b):**



The compound **7b** (140 mg, 82%) was synthesized from compound **7a** by following general procedure A, as a yellow color solid.

Mp: 113- 114 °C

$[\alpha]_D^{25}$: +1.43 (*c* 0.64, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 2929, 1672, 1595, 1515, 1217

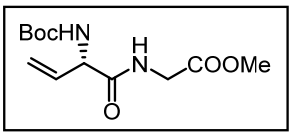
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 3.7 Hz, 2H), 7.35 - 7.27 (m, 1H), 6.56 (brs, 1H), 5.90 - 5.72 (m, 1H), 5.33 (d, *J* = 8.3 Hz, 1H), 5.23 - 5.07 (m, 2H), 4.32 (d, *J* = 6.1 Hz, 1H), 3.94 - 3.84 (m, 2H), 3.05 - 2.87 (m, 2H), 2.37 - 2.23 (m, 1H), 2.13 - 2.01 (m, 1H), 1.43 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 155.8, 146.8, 133.8, 133.6, 132.9, 128.9, 126.5, 125.6, 116.6, 80.5, 54.5, 41.9, 31.7, 28.3, 21.6

MS: 466 $(M+Na)^+$

HRMS: calculated for $C_{18}H_{25}O_5N_3NaSe$ $[M+Na]^+$: 466.0852, found 466.0844.

Methyl (*S*)-(2-((*tert*-butoxycarbonyl)amino)but-3-enoyl)glycinate (7c):



The compound **7c** (80 mg, 78%) was synthesized from compound **7b** by following general procedure B, as a colorless liquid.

$[\alpha]_D^{29}$: + 10.17 (*c* 3.5, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 2982, 1749, 1678, 1499, 1217

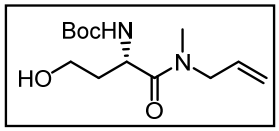
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (brs, 1H), 5.90 (ddd, *J* = 6.4, 10.4, 17.0 Hz, 1H), 5.46 (d, *J* = 6.6 Hz, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.32 - 5.23 (m, 1H), 4.75 (brs, 1H), 4.03 (d, *J* = 5.4 Hz, 2H), 3.73 (s, 3H), 1.42 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.1, 155.3, 133.8, 118.2, 80.2, 56.8, 52.4, 41.3, 28.3

MS: 295 $(M+Na)^+$

HRMS: calculated for $C_{12}H_{20}O_5N_2Na$ $[M+Na]^+$: 295.1264, found 295.1261.

***tert*-Butyl (*S*)-(1-(allyl(methyl)amino)-4-hydroxy-1-oxobutan-2-yl)carbamate (8a):**



The compound **8a** (106 mg, 68%) was synthesized from N-Boc-L-homoserine lactone and *N*-Methyl allylamine by following the similar procedure for the synthesis of **7a**, as a colorless liquid.

$[\alpha]_D^{29}$: +6.80 (*c* 7.8, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3021, 1601, 1587

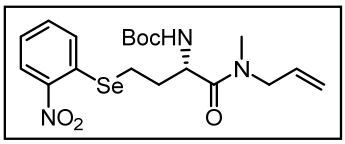
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 - 5.58 (m, 2H), 5.24 - 5.05 (m, 2H), 4.76 - 4.59 (m, 1H), 4.04 - 3.82 (m, 2H), 3.62 (d, *J* = 7.8 Hz, 2H), 2.98 - 2.88 (N-Methyl observed as two singlets, 3H), 1.95 - 1.79 (m, 1H), 1.55 - 1.41 (m, 1H), 1.39 (d, *J* = 1.7 Hz, 9H)

^{13}C NMR (400 MHz, $CDCl_3$): (mixture of rotamers) δ 172.3, 171.8, 156.8, 156.6, 132.1, 117.8, 117.7, 80.2, 57.9, 51.9, 50.3, 47.4, 47.2, 36.8, 36.2, 34.5, 33.6, 28.2

MS: 295 $(M+Na)^+$

HRMS: calculated for $C_{13}H_{24}O_4N_2Na$ $[M+Na]^+$: 295.1628, found 295.1624.

***tert*-Butyl (*S*)-(1-(allyl(methyl)amino)-4-((2-nitrophenyl)selanyl)-1-oxobutan-2-yl)carbamate (8b):**



The compound **8b** (112 mg, 83%) was synthesized from compound **8a** by following general procedure A, as a yellow color liquid.

$[\alpha]_D^{29}$: + 3.52 (*c* 3.3, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 2979, 1643, 1512, 1217

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.3 Hz, 1H), 7.56 - 7.48 (m, 2H), 7.31 (t, *J* = 5.5 Hz, 1H), 5.79 - 5.66 (m, 1H), 5.60 - 5.50 (m, 1H), 5.25 - 5.09 (m, 2H), 4.82 - 4.68 (m,

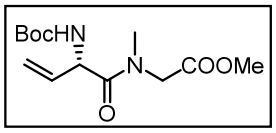
1H), 4.06 - 3.87 (m, 2H), 3.04 - 2.89 (m, 5H), 2.20 - 2.07 (m, 1H), 2.05 - 1.93 (m, 1H), 1.44 (d, *J* = 3.7 Hz, 9 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 170.9, 155.6, 155.5, 146.9, 133.7, 133.0, 132.1, 128.9, 128.8, 126.5, 125.6, 117.9, 117.6, 80.0, 52.0, 50.6, 50.5, 50.3, 34.6, 33.8, 32.9, 32.3, 28.3, 21.5, 21.4 (mixture of rotamers)

MS: 480$(M+Na)^+$

HRMS: calculated for $C_{19}H_{27}O_5N_3NaSe$ $[M+Na]^+$: 480.1008, found 480.1003.

Methyl (*S*)-N-(2-((*tert*-butoxycarbonyl)amino)but-3-enoyl)-*N*-methylglycinate (8c):



The compound **8c** (46 mg, 73%) was synthesized from compound **8b** by following general procedure B, as a colorless liquid.

$[\alpha]_D^{29}$: + 5.79 (*c* 3.01, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3022, 1748, 1705, 1657, 1487, 1217

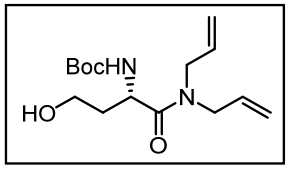
^{1}H NMR (400 MHz, $CDCl_3$): (mixture of rotamers) 5.87 - 5.76 (m, 1H), 5.60 (d, *J* = 7.6 Hz, 1H), 5.42 (d, *J* = 17.4 Hz, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 5.12 (t, *J* = 7.0 Hz, 1H), 4.34 (d, *J* = 17.4 Hz, 1H), 3.92 (d, *J* = 17.4 Hz, 1H), 3.73 (s, 3H), 3.10 (s, 3H), 1.42 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 169.3, 155.0, 132.7, 118.6, 79.8, 53.3, 52.2, 49.7, 36.3, 28.3

MS: 309 $(M+Na)^+$

HRMS: calculated for $C_{13}H_{22}O_5N_2Na$ $[M+Na]^+$: 309.1421, found 309.1418.

***tert*-Butyl (*S*)-(1-(diallylamino)-4-hydroxy-1-oxobutan-2-yl)carbamate (9a):**



The compound **9a** (106 mg, 72%) was synthesized from N-Boc-L-homoserine lactone with diallylamine by following the similar procedure for the synthesis of **7a**, as a pale yellow color liquid.

$[\alpha]_D^{29}$: − 0.94 (*c* 0.82, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3023, 1595, 1521, 1426, 1216

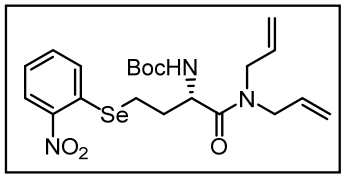
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 - 5.61 (m, 3H), 5.30 - 5.08 (m, 4H), 4.71 (t, *J* = 7.7 Hz, 1H), 4.13 (dd, *J* = 5.5, 15.3 Hz, 1H), 4.05 - 3.95 (m, 1H), 3.95 - 3.81 (m, 2H), 3.72 - 3.57 (m, 2H), 2.00 - 1.83 (m, 1H), 1.60 - 1.48 (m, 1H), 1.44 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 156.7, 132.4, 118.0, 117.7, 80.3, 57.9, 49.1, 47.8, 47.4, 37.0, 28.3

MS: 321 $(M+Na)^+$

HRMS: calculated for $C_{15}H_{26}O_4N_2Na$ $[M+Na]^+$: 321.1785, found 321.1782.

***tert*-Butyl (*S*)-(1-(diallylamino)-4-((2-nitrophenyl)selanyl)-1-oxobutan-2-yl)carbamate (9b):**



The compound **9b** (105 mg, 77%) was synthesized from compound **9a** by following general procedure A, as a yellow color liquid.

$[\alpha]_D^{29}$ + 8.35 (*c* 1.4, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3019, 1691, 1641, 1432, 1218

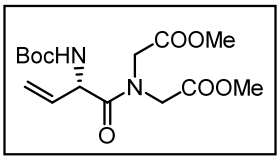
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.8 Hz, 1H), 7.57 - 7.47 (m, 2H), 7.32 (ddd, *J* = 2.6, 5.8, 8.3 Hz, 1H), 5.80 - 5.65 (m, 2H), 5.45 (d, *J* = 8.3 Hz, 1H), 5.23 - 5.07 (m, 4H), 4.78 - 4.66 (m, 1H), 4.08 - 3.80 (m, 4H), 2.94 (t, *J* = 7.7 Hz, 2H), 2.17 - 2.07 (m, 1H), 2.07 - 1.95 (m, 1H), 1.44 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 155.5, 146.9, 133.7, 133.0, 132.5, 132.4, 128.8, 126.5, 125.5, 117.8, 117.6, 80.0, 50.5, 49.2, 48.1, 32.9, 28.3, 21.5

MS: 506 $(M+Na)^+$

HRMS: calculated for $C_{21}H_{29}O_5N_3NaSe$ $[M+Na]^+$:506.1165, found 506.1164.

Dimethyl 2,2'-((2-((*tert*-butoxycarbonyl)amino)but-3-enoyl)azanediyl)(*S*)-diacetate (9c):



The compound **9c** (45 mg, 71%) was synthesized from compound **9b** by following general procedure B, as a yellow color liquid.

$[\alpha]_D^{30}$: + 3.28 (*c* 0.82, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 2972, 1751, 1708, 1493, 1217

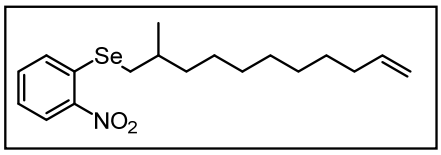
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 - 5.73 (m, 1H), 5.59 (d, *J* = 7.6 Hz, 1H), 5.42 (d, *J* = 17.1 Hz, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 4.99 (t, *J* = 7.1 Hz, 1H), 4.38 (d, *J* = 17.9 Hz, 1H), 4.32 - 4.21 (m, 1H), 4.21 - 4.05 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 1.43 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 169.3, 168.8, 154.8, 132.8, 119.0, 79.9, 53.4, 52.6, 52.3, 49.5, 48.1, 28.3

MS: 367 $(M+Na)^+$

HRMS: calculated for $C_{15}H_{24}O_7N_2Na$ $[M+Na]^+$: 367.1476, found 367.1472.

(2-Methylundec-10-en-1-yl)(2-nitrophenyl)selane (10b) :



The compound **10b** (310 mg, 91%) was synthesized from compound **10a**[8] by following general procedure A, as a yellow color liquid.

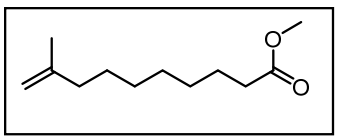
IR υ_{max}(film): cm^{-1} 2922, 1512, 1331, 1300

^{1}H NMR (400MHz ,$CDCl_3$) δ 8.29 (d, *J* = 8.3 Hz, 1H), 7.59 - 7.47 (m, 2H), 7.35 - 7.26 (m, 1H), 5.90 - 5.73 (m, 1H), 5.09 - 4.89 (m, 2H), 2.97 (dd, *J* = 5.6, 11.2 Hz, 1H), 2.78 (dd, *J* = 7.6, 11.2 Hz, 1H), 2.06 (q, *J* = 7.0 Hz, 2H), 1.87 (dd, *J* = 5.9, 12.2 Hz, 1H), 1.58 - 1.48 (m, 1H), 1.41 - 1.28 (m, 11H), 1.11 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 139.2, 134.1, 133.4, 129.2, 126.4, 125.2, 114.2, 37.3, 34.4, 33.8, 32.6, 29.7, 29.4, 29.1, 28.9, 27.0, 20.5

HRMS: calculated for $C_{18}H_{27}O_2NNaSe$ $[M+Na]^+$: 392.1099, found 392.1095.

Methyl 9-methyldec-9-enoate (10c):



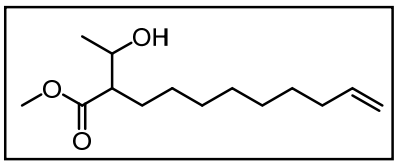
The compound **10c** (46 mg, 78%) was synthesized from compound **10b** by following general procedure B, as a pale yellow color liquid.

^{1}H NMR (400MHz ,$CDCl_3$): δ 4.66 (d, *J* = 11.5 Hz, 2H), 3.66 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.98 (t, *J* = 7.6 Hz, 2H), 1.70 (s, 3H), 1.66 - 1.57 (m, 2H), 1.47 - 1.38 (m, 2H), 1.34 - 1.25 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 146.2, 109.7, 51.4, 37.8, 34.1, 29.1 (3C), 27.5, 24.9, 22.4

HRMS: calculated for $C_{12}H_{23}O_2$ $[M+H]^+$: 199.1693, found 199.1694.

Methyl 2-(1-hydroxyethyl)undec-10-enoate (11a):



To a stirred solution of diisopropylamine (0.42 mL, 3.0 mmol) in THF (4 mL), n-BuLi (3.0 mL, 3.0 mmol, 1.6 M in hexane) was slowly added at −10 ^oC under nitrogen atmosphere. After 30 min, the reaction mixture was cooled to −78 ^oC and to it, Methyl 10-undecenoate (0.4 g, 2.0 mmol) dissolved in THF (5 mL) was slowly added and stirred at the same temperature for 30 min. Acetaldehyde (0.22 mL, 4.0 mmol) dissolved in THF (2 mL) was added and stirring was continued for further 1 h at same temperature. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (5 mL), diluted with ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to obtain the crude mass which on purified by column chromatography (silica gel 100-200 mesh 5% ethyl acetate - pet ether) afforded the desired compound **11a** (380 mg, 78%, mixture of diastereomers) as a colorless liquid.

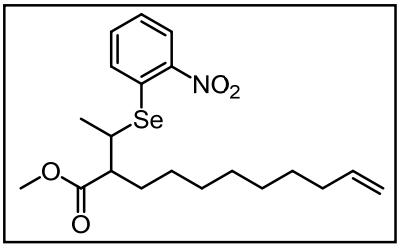
IR υ_{max}(film): cm^{-1} 2925, 1729, 1439

^{1}H NMR (400MHz, $CDCl_3$): δ (mixture of diastereomers) 5.93 - 5.67 (m, 1H), 5.05 - 4.81 (m, 2H), 3.97 (t, *J* = 5.7 Hz, 1H), 3.71 - 3.70 (2 singlets from two diastereomers, 3H), 2.56 - 2.34 (m, 2H), 2.02 (q, *J* = 7.2 Hz, 2H), 1.70 - 1.56 (m, 2H), 1.40 - 1.32 (m, 2H), 1.27 (brs, 8H), 1.22 - 1.17 (two doublets from two diastereomers, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 175.8, 139.2, 114.2, 68.4, 68.3, 52.7, 52.3, 51.6, 51.6, 33.8, 29.5, 29.5, 29.2, 29.0, 28.9, 27.7, 27.3, 27.3, 21.6, 20.3

HRMS: calculated for $C_{14}H_{26}O_3Na$ $[M+Na]^+$: 265.1774, found 265.1773.

Methyl 2-(1-((2-nitrophenyl)selanyl)ethyl)undec-10-enoate (11b):



The compound **11b** (163 mg, 62%) was synthesized from compound **11a** by following general procedure A, as a yellow color liquid.

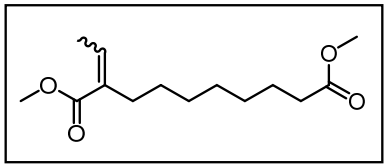
IR υ_{max}(film): cm^{-1} 2924, 1732, 1566, 1443

^{1}H NMR (400MHz ,$CDCl_3$): δ (major isomer) 8.21 (dd, *J* = 1.2, 8.3 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.55 - 7.50 (m, 1H), 7.36 - 7.30 (m, 1H), 5.93 - 5.74 (m, 1H), 5.05 - 4.87 (m, 2H), 3.71 (s, 3H), 3.67 - 3.59 (m, 1H), 2.75 - 2.54 (m, 1H), 2.06 - 1.99 (m, 2H), 1.76 (brs, 2H), 1.52 (d, *J* = 7.1 Hz, 3H), 1.39 - 1.32 (m, 2H), 1.26 (brs, 8H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 148.1, 139.1, 133.4, 131.9, 130.3, 126.3, 125.9, 114.2, 51.7, 51.1, 38.9, 33.8, 31.6, 29.3, 29.2, 29.0, 28.8, 27.6, 19.6

HRMS: calculated for $C_{20}H_{29}O_4NNaSe$ $[M+Na]^+$: 450.1154, found 450.1150.

Dimethyl 2-ethylidenedecanedioate (11c):



The compound **11c** (56 mg, 77%) was obtained as 3: 1 (Z:E) mixture from compound **11b** by following general procedure B, as a pale yellow color liquid and it was observed that reaction went for completion in 1 h.

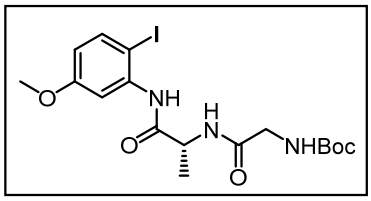
IR υ_{max}(film): cm^{-1} 2933, 1737, 1716, 1438

^{1}H NMR (400MHz ,$CDCl_3$): δ (major isomer) 5.96 (q, *J* = 7.1 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.93 (d, *J* = 7.1 Hz, 3H), 1.63 - 1.56 (m, 2H), 1.40 - 1.34 (m, 2H), 1.31 - 1.24 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): (mixture of *E*, *Z* isomers) δ 174.3, 168.7, 168.4, 137.3, 136.2, 136.1, 133.3, 132.9, 51.6, 51.4, 51.1, 34.5, 34.1, 29.3, 29.1, 29.0, 28.9, 28.8, 27.0, 26.3, 24.9, 22.0, 15.7, 14.2

HRMS: calculated for $C_{14}H_{24}O_4Na$ $[M+Na]^+$: 279.1567, found 279.1568

***tert*-Butyl (*R*)-(2-((1-((2-iodo-5-methoxyphenyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)carbamate (89):**



To a mixture of 2-iodo 5-methoxy aniline **98** (1.0 g, 4.0 mmol), Boc-Gly-D-Ala-OH (**56)** (987 mg, 4.0 mmol) in 20 mL CH_2Cl_2. HATU (2.3 g, 6.0 mmol), diisopropyl ethylamine (2.0 mL) were added and stirred for 14 h at 25^{o}C, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 1N HCl (15 mL) and sat. $NaHCO_3$ solution (15 mL) organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure.

Purification by column chromatography (silica gel 100-200 mesh 40% ethyl acetate - CH_2Cl_2) yielded compound **89** (1.2 g, 63%) as a white color solid.

Mp: 87- 88 °C

$[\alpha]_D^{26}$: + 17.34 (*c* 2.22, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3020, 1584, 1165

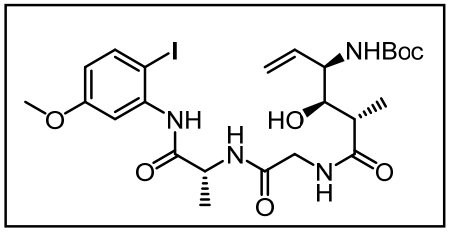
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (brs, 1H), 8.19 (d, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.29 - 7.18 (m, 1H), 6.99 (t, *J* = 5.5 Hz, 1H), 6.64 (dd, *J* = 2.8, 8.7 Hz, 1H), 4.59 - 4.42 (m, 1H), 3.74 (s, 3H), 3.65 (d, *J* = 5.6 Hz, 2H), 1.38 (s, 12H)

^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 169.9, 160.2, 156.3, 140.0, 139.5, 114.0, 112.0, 83.7, 78.6, 55.9, 49.2, 43.7, 28.6, 18.5

MS: 500 $(M+Na)^+$

HRMS: calculated for $C_{17}H_{24}O_5N_3INa$ $[M+Na]^+$: 500.0653, found 500.0648.

***tert*-Butyl ((3*R*,4*R*,5*S*)-4-hydroxy-6-((2-(((*R*)-1-((2-iodo-5-methoxyphenyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)amino)-5-methyl-6-oxohex-1-en-3-yl)carbamate (88):**



To a solution of **89** (100 mg, 0.2 mmol) in CH_2Cl_2 (5 mL), TFA (1.0 mL) was added at 0 °C and stirred at 25 °C for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure to afford the amine as TFA salt.

Compound **97** (57 mg, 0.2 mmol) was taken in THF-MeOH (1 mL, 3:2) cooled to 0 °C, LiOH. H_2O (11 mg, 0.25 mmol) dissolved in 0.3 mL water was added and stirred for 3 h. After completion of the reaction (monitored by TLC), concentrated the reaction mixture to remove THF and MeOH. Acidified to P^H 3 with 1N HCl, extracted with ethylacetate (5

mL X 2). Organic layer was concentrated to afford compound **90**, the residue was taken up in dry CH_2Cl_2 (5 mL), added to above amine salt, then HATU (79 mg, 0.2 mmol), DIPEA (0.1 mL, 0.62 mmol) were added and the resulting solution was stirred at ambient temperature for 16 h. Reaction mass was diluted with CH_2Cl_2 (5 mL) washed with saturated solution of $NaHCO_3$ (3 mL), brine (3 mL) and then evaporated to dryness. Purification by column chromatography (silica gel 230-400 mesh 4% methanol - CH_2Cl_2) yielded compound **88** (98 mg, 76%) as an off white solid.

Mp: 170- 172 °C

$[\alpha]_D^{26}$: + 7.63 (*c* 1.0, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3021, 2931, 1672, 1576

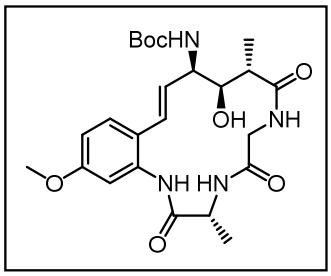
^{1}H NMR (400MHz, CD_3OD): δ 7.73 - 7.64 (m, 1H), 7.25 (d, *J* = 2.7 Hz, 1H), 6.67 - 6.58 (m, 1H), 5.88 (ddd, *J* = 5.5, 10.4, 17.1 Hz, 1H), 5.25 - 5.12 (m, 2H), 4.64 - 4.47 (m, 1H), 4.24 (brs, 1H), 4.12 - 4.03 (m, 1H), 3.82 (s, 1H), 3.77 (s, 3H), 3.71 (d, *J* = 8.2 Hz, 1H), 2.63 - 2.40 (m, 1H), 1.47 (d, *J* = 7.3 Hz, 3H), 1.45 - 1.41 (m, 9H), 1.13 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 179.5, 174.5, 172.9, 163.0, 159.1, 141.6, 139.6, 117.1, 116.3, 114.1, 84.3, 81.5, 77.6, 57.1, 56.5, 52.1, 46.3, 44.7, 29.8, 19.1, 15.5.

MS: 641 $(M+Na)^+$

HRMS: calculated for $C_{24}H_{35}O_7N_4INa$ $[M+Na]^+$: 641.1443, found 641.128.

***tert*-Butyl ((3*R*,9*S*,10*R*,11*R*,*E*)-10-hydroxy-16-methoxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)carbamate (87) :**



To a solution of compound **88** (60 mg, 0.1 mmol) in anhydrous acetonitrile (60 mL), $Pd(OAc)_2$ (5 mol%) and triethylamine (0.14 mL, 1.0 mmol) were added and heated at 75 °C for 12h. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (silica gel 230-400 mesh 4% methanol - CH_2Cl_2) yielded compound **87** (20 mg, 42%) as an off white solid.

Mp: 140 - 142 °C

$[\alpha]_D^{26}$: − 30.43 (*c* 0.46, $CHCl_3$)

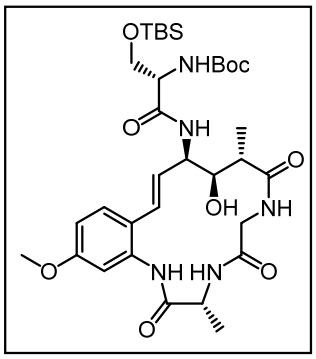
^{1}H NMR (400MHz, CD_3OD): δ 7.37 (d, *J* = 8.5 Hz, 1H), 7.21 (brs, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.01 - 5.90 (m, 1H), 4.47 - 4.35 (m, 2H), 4.05 (d, *J* = 14.3 Hz, 1H), 3.81 (s, 3H), 3.72 (d, *J* = 7.9 Hz, 1H), 3.65 (d, *J* = 14.3 Hz, 1H), 2.54 (brs, 1H), 1.54 (d, *J* = 6.7 Hz, 3H), 1.48 (s, 11H), 1.30 (d, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 177.3, 171.5, 170.8, 159.5, 156.7, 134.9, 128.2, 127.6, 127.1, 123.4, 112.0, 110.2, 79.0, 75.4, 58.8, 54.4, 50.4, 43.7, 42.2, 27.4, 15.3, 15.0

MS: 513 $(M+Na)^+$

HRMS: calculated for $C_{24}H_{34}O_7N_4Na$ $[M+Na]^+$: 513.2320, found 513.2311.

***tert*-Butyl((*S*)-3-((*tert*-butyldimethylsilyl)oxy)-1-(((3*R*,9*S*,10*R*,11*R*,*E*)-10-hydroxy-16-methoxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*- benzo [*h*] [1,4,7] triazacyclopentadecin-11-yl)amino)-1-oxopropan-2-yl)carbamate (100):**



To a solution of compound **87** (45 mg, 0.091 mmol) in CH_2Cl_2 (5mL) trifluoro acetic acid (1.0 mL) was added at 0 °C and the resulting suspension was stirred for 2 h at the same temperature. Reaction was monitored by TLC, and then concentrated. This residue was dissolved in dry DMF (4 mL), then HATU (38 mg, 0.10 mmol), DIPEA (40 µL, 0.22 mmol) and *N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyldimethylsilyl)-*L*-serine **99** (29 mg, 0.091 mmol) was added. The resulting solution was stirred at ambient temperature for 16h. Reaction mass was diluted with ethylacetate (15 mL), washed with saturated solution of $NaHCO_3$ (5 mL), H_2O (5 mL). The organic layer was dried over Na_2SO_4 and the crude material obtained after removal of the solvent was purified by column chromatography (silica gel 230-400 mesh 4% methanol - CH_2Cl_2) to afford **100** (52 mg, 83%) as off white solid.

Mp: 146-148 °C

$[\alpha]_D^{26}$: + 27.10 (*c* 0.49, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3023, 2403, 1523, 1595, 1427

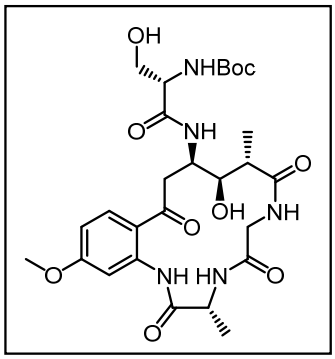
^{1}H NMR (400MHz, CD_3OD): δ 7.31 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 2.7, 8.6 Hz, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 6.08 - 6.04 (m, 1H), 4.79 (t, *J* = 7.6 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 1H), 4.30 - 4.21 (m, 1H), 4.09 (d, *J* = 15.2 Hz, 1H), 3.95 (d, *J* = 6.8 Hz, 1H), 3.87 (d, *J* = 5.9 Hz, 2H), 3.81 (s, 3H), 3.68 (d, *J* = 15.2 Hz, 1H), 2.62 (d,

J = 5.6 Hz, 1H), 1.53 (d, *J* = 7.3 Hz, 3H), 1.48 (s, 9H), 1.28 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H)

^{13}C NMR (125 MHz, DMSO-d$_6$): 175.9, 170.7, 170.0, 169.6, 159.1, 155.5, 135.9, 129.0, 127.8, 127.0, 122.9, 111.3, 109.7, 78.7, 75.2, 63.7, 56.8, 55.7, 50.1, 43.8, 41.5, 28.6, 26.2, 18.4, 16.8, -5.0

HRMS: calculated for $C_{33}H_{53}O_9N_5NaSi$ $[M+Na]^+$: 714.3505, found 714.3489.

***tert*-Butyl ((*S*)-3-hydroxy-1-(((3*R*,9*S*,10*R*,11*R*)-10-hydroxy-16-methoxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-benzo[*h*] [1,4,7] triazacyclopentadecin-11-yl)amino)-1-oxopropan-2-yl)carbamate (101):**



To a stirred solution of $PdCl_2$ (10 mol%), CuCl (6 mg, 0.06 mmol) in DMF-water (3 mL, 2:1) compound **100** (40 mg, 0.06 mmol) was added and heated at 65 °C under O_2 atmosphere for 8h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed water (5 mL) and brine (5 mL) organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure. Purification by column chromatography (silica gel 230-400 mesh 6% methanol - CH_2Cl_2) yielded compound **101** (18 mg, 53%) as a white color solid.

Mp: 134-136 °C

$[\alpha]_D^{26}$: + 0.85 (*c* 0.16, CH_3OH)

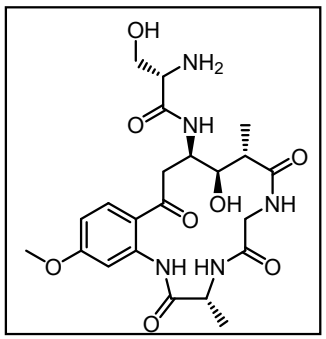
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.46 (s, 1H), 9.09 (d, *J* = 5.9 Hz, 1H), 8.21 (d, *J* = 2.4 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 5.45 (d, *J* = 4.6 Hz, 1H), 4.87 (t, *J* = 5.4 Hz, 1H), 4.79 (dd, *J* = 9.0, 15.4 Hz, 1H), 4.35 (t, *J* = 8.4 Hz, 1H), 4.11 (quin, *J* = 6.9

Hz, 1H), 3.94 - 3.88 (m, 1H), 3.82 (s, 3H), 3.62 - 3.52 (m, 3H), 3.32 (s, 1H), 3.16 (d, *J* = 5.1 Hz, 1H), 2.95 (d, *J* = 17.1 Hz, 1H), 2.78 - 2.64 (m, 1H), 1.40 (s, 9H), 1.38 (d, *J* = 7.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 201.1, 172.9, 172.8, 170.4, 169.3, 164.5, 155.9, 142.6, 134.0, 115.6, 109.1, 104.7, 78.9, 71.7, 61.7, 57.3, 56.1, 51.2, 45.8, 45.0, 42.8, 42.5, 28.6, 17.4, 9.5

HRMS: calculated for $C_{27}H_{39}O_{10}N_5Na$ $[M+Na]^+$: 616.2589, found 616.2589.

(*S*)-2-Amino-3-hydroxy-N-((3*R*,9*S*,10*R*,11*R*)-10-hydroxy-16-methoxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1H-benzo[h] [1,4,7] triazacyclopentadecin-11-yl)propanamide (102):



To a solution of compound **101** (12 mg, 0.02 mmol) in CH_2Cl_2 (3 mL) trifluoro acetic acid (0.3 mL) was added at 0 °C and the resulting suspension was stirred for 2 h at the same temperature.Reaction was monitored by TLC, and then concentrated and triturated with diethyl ether (3 mL) and dried under vacuum to afford compound **102** in a quantitative yield.

Mp: 194 – 196 °C

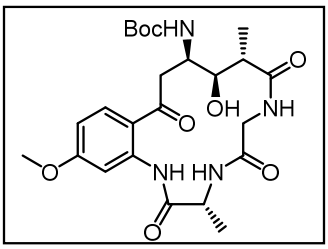
$[\alpha]_D^{26}$: + 0.58 (*c* 0.1, CH_3OH)

^{1}H NMR (500 MHz, DMSO-d$_6$): δ 12.51 (s, 1H), 9.10 (d, *J* = 5.7 Hz, 1H), 8.24 (d, *J* = 2.6 Hz, 1H), 8.09 - 8.04 (m, 2H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 6.77 (dd, *J* = 2.6, 9.0 Hz, 1H), 4.81 (dd, *J* = 9.0, 15.1 Hz, 1H), 4.57 - 4.46 (m, 1H), 4.20 - 4.10 (m, 1H), 4.00 - 3.87 (m, 1H), 3.84 (s, 3H), 3.74 - 3.70 (m, 3H), 3.58 (d, *J* = 3.1 Hz, 2H), 3.33 (d, *J* = 10.9 Hz, 2H), 2.95 (d, *J* = 16.8 Hz, 1H), 2.79 - 2.71 (m, 1H), 1.40 (d, *J* = 7.3 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 201.1, 173.1, 172.9, 170.4, 166.1, 164.6, 142.7, 134.0, 115.5, 109.2, 104.6, 71.9, 61.1, 56.1, 54.2, 51.2, 45.7, 43.0, 42.5, 17.4, 9.8

HRMS: calculated for $C_{22}H_{32}O_8N_5$ $[M+H]^+$: 494.2245, found 494.2245.

***tert*-Butyl ((3*R*,9*S*,10*R*,11*R*)-10-hydroxy-16-methoxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)carbamate (103) :**



The compound **103** (20 mg, 82%) as off white solid was synthesized from compound **87** by following similar procedure for the synthesis **101.**

Mp 216 - 218 °C

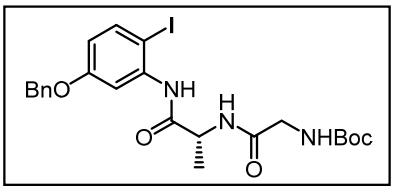
$[\alpha]_D^{26}$: + 23.31 (*c* 1.41, $CHCl_3$)

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.45 (s, 1H), 9.11 (d, *J* = 5.6 Hz, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.73 (d, *J* = 9.3 Hz, 1H), 6.74 (dd, *J* = 2.4, 8.8 Hz, 1H), 5.55 (d, *J* = 8.8 Hz, 1H), 5.26 (d, *J* = 5.4 Hz, 1H), 4.79 (dd, *J* = 9.0, 15.2 Hz, 1H), 4.24 - 4.10 (m, 2H), 4.08 - 4.03 (m, 1H), 3.84 (s, 3H), 3.74 (brs, 1H), 3.54 - 3.46 (m, 1H), 2.97 (d, *J* = 17.4 Hz, 1H), 2.81 - 2.68 (m, 1H), 1.39 (s, 12H), 0.93 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 201.3, 172.8, 170.4, 164.5, 154.4, 142.6, 134.2, 115.7, 109.0, 104.7, 78.3, 72.1, 56.1, 51.2, 46.2, 45.1, 43.8, 42.5, 28.7, 17.4, 12.8;

HRMS calculated for $C_{24}H_{34}O_8N_4Na$ $[M+Na]^+$: 529.2269, found 529.2267.

***tert*-Butyl (*R*)-(2-((1-((5-(benzyloxy)-2-iodophenyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)carbamate (115):**



To a mixture of 5-(benzyloxy)-2-iodoaniline **114** (1.0 g, 3.0 mmol), Boc-Gly-D-Ala-OH (**46**) (756 mg, 4.0 mmol) in DMF (5 mL). HATU (1.7 g, 4.6 mmol), diisopropyl ethylamine (1.0 mL, 6.0 mmol) were added at 0 ^{o}C and stirred for 14 h at 25^{o}C, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with 1N HCl (15 mL) and sat. $NaHCO_3$ solution (15 mL) organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure. Purification by column chromatography (silica gel 100-200 mesh 40% ethyl acetate - CH_2Cl_2) yielded compound **115** (1.0 g, 59 %) as a white color solid.

Mp: 103- 104 °C

$[\alpha]_D^{27}$: + 29.51 (*c* 1.28, $CHCl_3$)

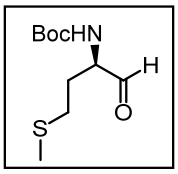
IR υ_{max}(film): cm^{-1} 3362, 3020, 1695, 1584, 1514

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (s, 1H), 8.20 (d, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.50 - 7.28 (m, 6H), 7.01 (t, *J* = 5.7 Hz, 1H), 6.72 (dd, *J* = 2.8, 8.7 Hz, 1H), 5.09 (s, 2H), 4.50 (d, *J* = 6.8 Hz, 1H), 3.64 (d, *J* = 5.9 Hz, 2H), 1.47 - 1.27 (m, 12H) (Boc 9H and Methyl 3H merged)

^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 169.8, 159.2, 156.3, 140.1, 139.5, 137.1, 128.9, 128.4, 128.1, 114.7, 113.1, 84.3, 78.5, 69.9, 49.2, 43.6, 28.7, 18.5

HRMS: calculated for $C_{23}H_{28}O_5N_3INa$ $[M+Na]^+$: 576.0966, found 576.0963.

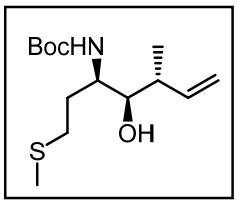
***tert*-Butyl (*R*)-(4-(methylthio)-1-oxobutan-2-yl)carbamate (118):**



Compound **118** (15 gm, 84%) was synthesized by following similar procedure for the synthesis of **117**

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.64 (s, 1H), 5.06 - 5.33 (m, 1H), 4.23 - 4.45 (m, 1H), 2.49 - 2.69 (m, 2H), 2.18 - 2.34 (m, 1H), 2.08 (s, 3H), 1.83 - 2.01 (m, 1H), 1.45 (s, 9H)
^{13}C NMR (50 MHz, $CDCl_3$): δ 199.1, 59.1, 29.8, 28.8, 28.3, 15.4

***tert*-Butyl ((3*R*,4*R*,5*R*)-4-hydroxy-5-methyl-1-(methylthio)hept-6-en-3-yl)carbamate (119)**



(*E*)-2-butene (3 mL, 17 mmol, 2 equiv) was condensed into flask containing KOtBu (2.4 g, 21.5 mmol, 1.25 equiv) in THF (20 mL) cooled to –78 °C. After careful addition of n-BuLi (13.4 mL, 1.6 M in hexanes, 21.5 mmol, 1.25 equiv) over 1 hour (maintaining internal temperature below –70 °C), the reaction mixture was warmed to –50 °C for 15 min. The mixture was cooled to –78 °C once again, and a solution of (+)-B-methoxydiisopinocampheylborane (25 mL, 1M in THF, 25 mmol, 1.45 equiv) was added slowly over 30 min. Next, BF3•Et2O (4.1 mL, 29.1 mmol, 1.7 equiv) was added at –78 °C over 30 minutes, then the solution of reagent was treated with a solution of compound **118** (4.3 g, 17.1 mmol) in THF (25 mL). The reaction mixture was stirred at –78 °C for 12 h, then warmed to –15 °C. A mixture of 3 N NaOH (8.3 mL) and 30% hydrogen peroxide (2.9 mL) was added dropwise to the reaction. After being heated to reflux for 1 h, the mixture was cooled to 0 °C. Concentrated the reaction mixture, diethylether (50

mL) was added and washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na2SO4 and the crude material obtained after removal of the solvent was purified by column chromatography (silica gel 230-400 mesh 10% ethylacetate - petether) to afford **119** (3.25 g, 61%) as colorless liquid as a single diastereomer.

$[\alpha]_D^{30}$: + 9.38 (*c* 4.53, $CHCl_3$)

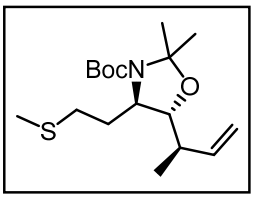
IR υ_{max}(film): cm^{-1} 3439, 3017, 2977, 1701, 1501, 1442

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (td, *J* = 9.2, 18.0 Hz, 1H), 5.21 - 5.10 (m, 2H), 4.83 (d, *J* = 9.5 Hz, 1H), 3.93 - 3.76 (m, 1H), 3.24 (d, *J* = 8.6 Hz, 1H), 2.58 - 2.46 (m, 2H), 2.26 - 2.18 (m, 1H), 2.13 (brs, 1H), 2.09 (s, 3H), 1.93 - 1.76 (m, 2H), 1.43 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 140.8, 117.2, 79.2, 75.7, 50.3, 42.3, 33.4, 30.9, 28.4, 16.5, 15.6

HRMS: calculated for $C_{14}H_{27}O_3NNa$ $[M+Na]^+$: 312.1604, found 312.1599.

***tert*-Butyl (4*R*,5*R*)-5-((*R*)-but-3-en-2-yl)-2,2-dimethyl-4-(2-(methylthio) ethyl) oxazolidine-3-carboxylate (120):**



To a stirred solution of compound **119** (7.0 g, 24.2 mmol), and 2-methoxypropene (5.82 mL, 60.5 mmol) in dry DMF (20 mL) PTSA.H_2O (93 mg, 4.8 mmol) was added at 0 °C under argon atmosphere. The resulting solution was stirred at room temperature for 4 h. The reaction was then diluted with H_2O (5 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with cold saturated $NaHCO_3$ solution (15 mL), H_2O (10 mL), brine (10 mL), and evaporated in *vacuo*. Purification by column chromatography (silica gel 100-200 mesh 10% ethyl acetate – pet ether) yielded compound **120** (7.53 g, 95%) as a pale yellow color liquid.

$[\alpha]_D^{30}$: – 8.9764 (*c* 0.97, $CHCl_3$)

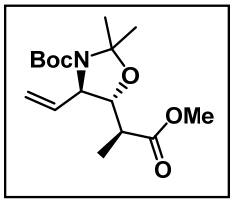
IR υ_{max}(film): cm^{-1} 3020, 2978, 1684, 1597

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 - 5.75 (m, 1H), 5.11 - 4.96 (m, 2H), 3.88 (brs, 1H), 3.62 (dd, *J* = 3.7, 7.8 Hz, 1H), 2.53 - 2.28 (m, 3H), 2.10 (s, 3H), 1.92 (dd, *J* = 6.6, 7.3 Hz, 2H), 1.55 (brs, 3H), 1.46 (s, 12H), 1.02 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 139.7, 115.5, 94.3, 83.7, 80.0, 59.4, 41.4, 33.1, 32.3, 30.3, 28.4, 27.9, 27.3, 17.0, 15.5

HRMS: calculated for $C_{17}H_{31}O_3NNaS$ $[M+Na]^+$: 352.1917, found 352.1914.

***tert*-Butyl (4*R*,5*R*)-5-((*S*)-1-methoxy-1-oxopropan-2-yl)-2,2-dimethyl-4-vinyloxazolidine-3-carboxylate (121)**



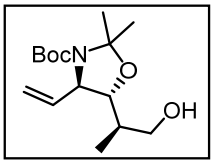
To a solution of compound **120** (400 mg, 1.2 mmol) in CH_2Cl_2 (30 mL) 2.5 M methanolic NaOH 2.4 mL was added than ozone was bubbled at –78 °C until the colour becomes blue, once the blue color appears oxygen was bubbled to remove excess ozone, Concentrated the reaction mixture, diluted with ethyl acetate (20 mL) and washed with H_2O (5 mL), brine (5 mL), and evaporated in *vacuo* the residue was taken in 1,2 dichloro benzene (10 mL) $CaCO_3$ (486 mg, 4.8 mmol) was added and refluxed for 6 h. The crude reaction mixture was purified by column chromatography (silica gel 230-400 mesh 20% ethylacetate - CH_2Cl_2) to afford **121** (175 g, 46 % for 2 steps) as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (td, *J* = 8.59, 16.81 Hz, 1H), 5.16 (d, *J* = 9.78 Hz, 2H), 4.05 - 4.27 (m, 1H), 3.97 - 4.05 (m, 1H), 3.67 (s, 3H), 2.75 (quin, *J* = 7.09 Hz, 1H), 1.56 (brs., 3H), 1.48 (s, 3H), 1.42 (brs., 9H), 1.17 (d, *J* = 7.09 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 151.9, 136.9, 117.1, 81.1, 62.4, 51.7, 43.2, 28.4, 26.8, 13.4

HRMS: calculated for $C_{16}H_{17}O_5NNa$ $[M+Na]^+$: 336.1781, found 336.1788.

***tert*-Butyl (4*R*,5*R*)-5-((*R*)-1-hydroxypropan-2-yl)-2,2-dimethyl-4-vinyloxazolidine-3-carboxylate (122):**



To a solution of compound **120** (4.0 g, 9.1 mmol) in CH_2Cl_2-MeOH(1:1, 60 mL) Ozone was bubbled at –78 °C until the colour becomes blue, once the blue color appears oxygen was bubbled to remove excess ozone, then $NaBH_4$ (1. 38 g, 36.5 mmol) was added and reaction mixture was allowed to room temperature and stirred for 8-10 h. Concentrated the reaction mixture, diluted with ethyl acetate (50 mL) cooled to 0 °C and quenched with 1 N HCl (5 mL). The organic layer was H_2O (10 mL), brine (10 mL), and evaporated in *vacuo* to afford alcohol compound **9a,** here sulfur also got oxidized to sulfoxide. The crude sulfoxide compound was taken in 1,2 dichloro benzene (30 mL) $CaCO_3$ (3.64 g, 36.5 mmol) was added and refluxed for 6 h. The crude reaction mixture was purified by column chromatography (silica gel 230-400 mesh 20% ethylacetate - CH_2Cl_2) to afford **122** (1.35 g, 52 % for 2 steps) as colorless liquid.

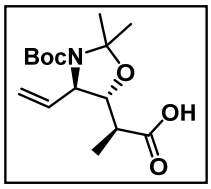
$[\alpha]_D^{30}$: + 15.83 (*c* 0.41, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 - 5.57 (m, 1H), 5.14 (d, *J* = 10.0 Hz, 2H), 4.06 (brs, 1H), 3.71 (t, *J* = 6.8 Hz, 1H), 3.66 - 3.57 (m, 2H), 2.56 (brs, 1H), 1.97 - 1.83 (m, 1H), 1.57 (s, 3H), 1.46 (s, 3H), 1.39 (brs, 9H), 0.93 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 138.0, 117.2, 94.3, 83.6, 80.1, 65.9, 63.7, 38.3, 28.4, 26.8, 25.9, 14.0

HRMS: calculated for $C_{15}H_{27}O4NNa$ $[M+Na]^+$: 308.1832, found 308.1833.

(*S*)-2-((4*R*,5*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidin-5-yl)propanoic acid (123):



To a stirred solution of compound **122** (0.5 g, 1.7 mmol) in DMF (6 mL), Pyridinium dichromate (PDC) (2.64 g, 7.0 mmol) was added and stirred at room temperature for 4 h. To the reaction mixture water (5 mL) was added and extracted with diethyl ether (20 mL x 2), combined the organic layers and washed with brine (5 mL) concentrated under reduced pressure. Purification by column chromatography (silica gel 100-200 mesh 30% ethyl acetate – CH_2Cl_2) yielded compound **123** (0.34 g, 65%) as a colorless liquid.

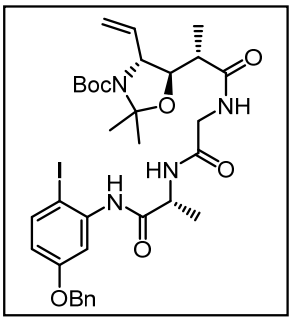
$[\alpha]_D^{30}$: + 25.09 (*c* 0.80, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 - 5.67 (m, 1H), 5.20 (d, *J* = 10.0 Hz, 2H), 4.28 - 4.12 (m, 1H), 4.03 (dd, *J* = 5.3, 7.7 Hz, 1H), 2.85 - 2.70 (m, 1H), 1.62 (s, 3H), 1.53 (s, 3H), 1.45 (brs, 9H), 1.25 (d, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 151.9, 137.5, 117.4, 94.2, 81.1, 80.2, 62.7, 43.3, 28.4, 26.7, 26.4, 13.8

HRMS: calculated for $C_{15}H_{25}O_5NNa$ $[M+Na]^+$: 322.1625, found 322.1622.

***tert*-Butyl (4*R*,5*R*)-5-((*S*)-1-((2-(((*R*)-1-((5-(benzyloxy)-2-iodophenyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)amino)-1-oxopropan-2-yl)-2,2-dimethyl-4-vinyloxazolidine-3-carboxylate (124):**



To a solution of **115** (665 mg, 1.2 mmol) in CH_2Cl_2 (5 mL), TFA (1.0 mL) was added at 0 °C and stirred at 25 °C for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure to afford the amine as TFA salt.

Compound **123** (300 mg, 1.0 mmol) was taken in dry DMF (5 mL), added above amine salt, then HATU (457 mg, 1.2 mmol), DIPEA (0.43 mL, 2.5 mmol) were added and the resulting solution was stirred at ambient temperature for 16h. Reaction mass was diluted with ethylacetate (50 mL) washed with saturated solution of aq $NaHCO_3$ (5 mL), brine (5 mL) and then evaporated to dryness. Purification by column chromatography (silica gel 230-400 mesh 4% methanol - CH_2Cl_2) yielded compound **124** (535 mg, 73 %, for 2 steps) as an off white solid.

Mp: 92- 94 °C

$[\alpha]_D^{30}$: + 36.0985 (*c* 0.81, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3020, 1687, 1584, 1518, 1381, 1217

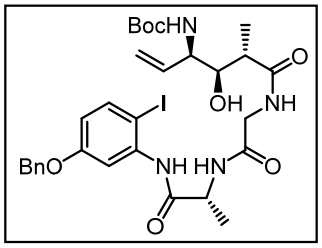
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.15 (d, *J* = 5.4 Hz, 1H), 8.04 (d, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.51 - 7.30 (m, 5H), 7.26 (brs, 1H), 6.80 - 6.61 (m, 1H), 5.85 - 5.65 (m, 1H), 5.15 (d, *J* = 15.7 Hz, 2H), 5.08 (s, 2H), 4.60 - 4.41 (m, 1H),

4.18 - 4.00 (m, 1H), 3.97 - 3.91 (m, 1H), 3.85 (d, *J* = 6.4 Hz, 1H), 3.77 - 3.62 (m, 1H), 2.69 - 2.58 (m, 1H), 1.54 (s, 3H), 1.46 - 1.25 (m, 15H), 1.01 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 176.9, 173.3, 171.4, 161.1, 153.6, 140.6, 139.4, 138.2, 129.7, 129.2, 128.8, 118.2, 116.0, 113.8, 95.9, 83.0, 81.6, 71.4, 64.5, 51.0, 46.3, 43.8, 28.8, 27.3, 26.8, 18.2, 14.8

HRMS: calculated for $C_{33}H_{43}O_7N_4INa$ $[M+Na]^+$: 757.2069, found 757.2056.

***tert*-Butyl ((3*R*,4*R*,5*S*)-6-((2-(((*R*)-1-((5-(benzyloxy)-2-iodophenyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)amino)-4-hydroxy-5-methyl-6-oxohex-1-en-3-yl)carbamate (125) :**



To a solution of compound **124** (500 mg, 0.6 mmol) in methanol (4 mL), Camphorsulphonic acid (31 mg, 0.3 mmol) was added and stirred for 18 h. reaction was monitored by TLC showed only 50% conversion. Concentrated the reaction mixture diluted with ethylacetate (30 mL), washed with saturated solution of aq $NaHCO_3$ (5 mL), brine (5 mL) and then evaporated to dryness. Purification by column chromatography (silica gel 230-400 mesh 4 - 6 % methanol - CH_2Cl_2) yielded compound **125** (190 mg, 77%, brsm) as an off white solid and starting material **124** (240 mg) .

Mp: 85- 86 °C

$[\alpha]_D^{27}$: + 27.67 (*c* 0.3, $CHCl_3$)

IR υ_{max}(film): cm^{-1} 3021, 2931, 1647, 1576

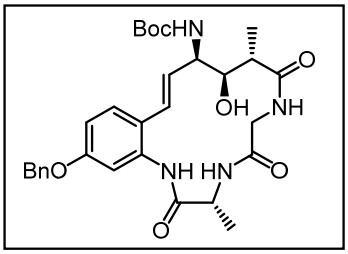
^{1}H NMR (400MHz, CD_3OD): δ 7.71 (d, *J* = 8.6 Hz, 1H), 7.51 - 7.23 (m, 6H), 6.69 (dd, *J* = 2.6, 8.7 Hz, 1H), 5.97 - 5.83 (m, 1H), 5.29 - 5.15 (m, 2H), 5.06 (s, 2H), 4.62 - 4.57

(m, 1H) 4.28 (brs, 1H), 4.14 - 4.04 (m, 1H), 3.91 - 3.81 (m, 1H), 3.76 (d, *J* = 8.1 Hz, 1H), 2.66 - 2.47 (m, 1H), 1.51 (d, *J* = 7.1 Hz, 3H), 1.46 (s, 9H), 1.17 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 177.0, 171.9, 170.4, 159.5, 156.6, 139.1, 137.1, 136.7, 128.2, 127.7, 127.3, 114.7, 114.6, 112.6, 82.2, 79.1, 75.1, 69.9, 54.0, 49.7, 43.9, 42.3, 27.4, 16.6, 13.1

HRMS: calculated for $C_{30}H_{39}O_7N_4INa$ $[M+Na]^+$: 717.1756, found 717.1746.

***tert*-Butyl ((3*R*,9*S*,10*R*,11*R*,*E*)-16-(benzyloxy)-10-hydroxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)carbamate (106):**



To a solution of compound **125** (120 mg, 0.17 mmol) in anhydrous acetonitrile (120 mL), $Pd(OAc)_2$ (5 mol%) and triethylamine (0.24 mL, 1.7 mmol) were added and heated at 75 °C for 12h. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (silica gel 230-400 mesh 4% methanol - CH_2Cl_2) yielded compound **106** (52 mg, 53%) as an off white solid.

Mp: 130 - 132 °C

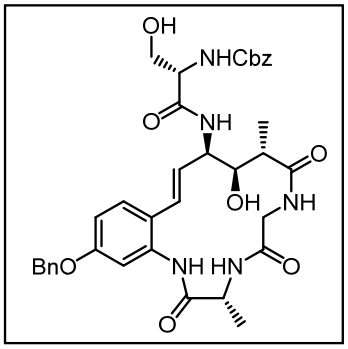
$[\alpha]_D^{27}$: − 20.48 (*c* 0.81, $CHCl_3$)

^{1}H NMR (400MHz, CD_3OD): δ 7.45 - 7.40 (m, 2H), 7.39 - 7.33 (m, 3H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.28 - 7.25 (m, 1H), 6.90 - 6.78 (m, 1H), 6.60 (d, *J* = 15.7 Hz, 1H), 5.91 (dd, *J* = 8.9, 15.8 Hz, 1H), 5.11 - 5.03 (m, 2H), 4.46 - 4.27 (m, 2H), 4.02 (d, *J* = 14.4 Hz, 1H), 3.69 (dd, *J* = 2.2, 8.3 Hz, 1H), 3.62 (d, *J* = 14.4 Hz, 1H), 2.58 - 2.45 (m, 1H), 1.52 (d, *J* = 7.3 Hz, 3H), 1.45 (s, 9H), 1.27 (d, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 180.9, 175.4, 174.7, 162.3, 160.7, 143.0, 141.0, 138.8, 132.0, 131.5, 131.1, 116.9, 115.3, 79.3, 73.6, 62.6, 54.3, 47.6, 46.1, 31.3, 19.3, 19.0

HRMS: calculated for $C_{30}H_{38}O_7N_4Na$ $[M+Na]^+$: 589.2633, found 589.2628.

Benzyl ((*S*)-1-(((3*R*,9*S*,10*R*,11*R*,*E*)-16-(benzyloxy)-10-hydroxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (127):



To a solution of compound **106** (20 mg, 0.035 mmol) in CH_2Cl_2 (5mL) trifluoro acetic acid (1.0 mL) was added at 0 °C and the resulting suspension was stirred for 2 h at the same temperature. Reaction was monitored by TLC, and then concentrated. This residue was dissolved in dry DMF (3 mL), then HATU (15 mg, 0.04 mmol), DIPEA (18 μL, 0.1) mmol) and NHCbz-L-Ser-OH **126** (9 mg, 0.05 mmol) was added. The resulting solution was stirred at ambient temperature for 16h. Reaction mass was diluted with ethylacetate (10 mL), washed with saturated solution of $NaHCO_3$ (5 mL), H_2O (5 mL). The organic layer was dried over Na_2SO_4 and the crude material obtained after removal of the solvent was purified by column chromatography (silica gel 230-400 mesh 4% methanol - CH_2Cl_2) to afford **127** (17.5 mg, 73%) as off white solid.

Mp: 203 - 205 °C

$[\alpha]_D^{27}$: +13.90 (*c* 0.35, $CHCl_3$)

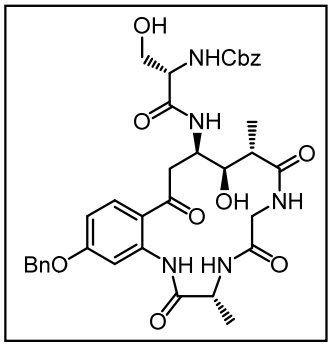
IR υ_{max}(film): cm^{-1} 3022, 2403, 1659, 1522, 1426;

^{1}H NMR (400MHz, CD_3OD): δ 7.40 - 7.51 (m, 3H), 7.23 - 7.40 (m, 10H), 6.78 - 6.91 (m, 1H), 6.60 (d, *J* = 16.14 Hz, 1H), 6.09 (dd, *J* = 7.21, 16.02 Hz, 1H), 5.11 - 5.19 (m, 2H), 5.09 (s, 2H), 4.75 - 4.83 (m, 1H), 4.40 (q, *J* = 7.01 Hz, 1H), 4.31 (brs, 1H), 4.06 (d, *J* = 15.16 Hz, 1H), 3.96 (d, *J* = 6.60 Hz, 1H), 3.85 (t, *J* = 4.77 Hz, 3H), 3.66 (d, *J* = 15.16 Hz, 1H), 2.44 - 2.68 (m, 1H), 1.48 (d, *J* = 7.09 Hz, 3H), 1.25 (d, *J* = 7.34 Hz, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 177.2, 171.6, 171.4, 171.3, 158.5, 157.2, 137.1, 136.6, 135.2, 128.1, 127.7, 127.6, 127.5, 127.2, 126.7, 123.4, 112.5, 110.6, 74.1, 69.7, 66.6, 61.9, 57.5, 56.7, 50.2, 42.9, 41.7, 26.2, 14.9, 14.8

HRMS: calculated for $C_{36}H_{42}O_9N_5$ $[M+H]^+$: 688.2977, found 688.2969.

Benzyl ((*S*)-1-(((3*R*,9*S*,10*R*,11*R*)-16-(benzyloxy)-10-hydroxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin -11-yl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (128):



Compound **128** (14 mg, 58%) was synthesized from **127** by following similar procedure used for the synthesis of compound **101**.

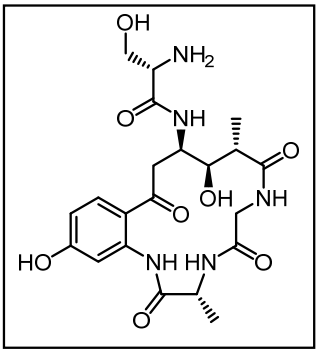
^{1}H NMR (500 MHz, DMSO-d_6): δ 12.44 (s, 1H), 9.09 (d, *J* = 5.80 Hz, 1H), 8.30 (d, *J* = 2.44 Hz, 1H), 7.91 (d, *J* = 8.85 Hz, 1H), 7.67 (d, *J* = 9.16 Hz, 1H), 7.29 - 7.53 (m, 10H), 7.26 (brs., 1H), 6.82 (d, *J* = 8.54 Hz, 1H), 5.48 (d, *J* = 4.88 Hz, 1H), 5.18 (s, 2H), 5.07 (s, 2H), 4.94 - 5.00 (m, 1H), 4.75 - 4.83 (m, 1H), 4.37 (t, *J* = 8.39 Hz, 1H), 4.09 - 4.16 (m, 1H), 3.97 - 4.05 (m, 1H), 3.60 - 3.67 (m, 2H), 3.57 (brs., 2H), 3.32 - 3.37 (m, 1H), 3.26

(dd, *J* = 13.12, 18.92 Hz, 1H), 2.95 (d, *J* = 17.70 Hz, 1H), 2.63 - 2.81 (m, 1H), 1.39 (d, *J* = 7.32 Hz, 3H), 0.89 (d, *J* = 6.71 Hz, 3H);

^{13}C NMR (125 MHz, DMSO-d_6): δ 200.8, 172.6, 172.5, 170.1, 168.8, 163.2, 156.3, 142.1, 137.0, 136.3, 133.7, 128.6, 128.5, 128.2, 127.9, 127.7, 115.4, 109.3, 105.4, 85.8, 71.5, 69.7, 65.7, 61.4, 57.4, 50.9, 45.5, 44.7, 42.6, 42.1, 17.0, 9.1

HRMS: calculated for $C_{36}H_{41}O_{10}N_5Na$ $[M+Na]^+$: 726.2746, found 726.2743.

(*S*)-2-amino-*N*-((3*R*,9*S*,10*R*,11*R*)-10,16-dihydroxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)-3-hydroxypropanamide (10'):



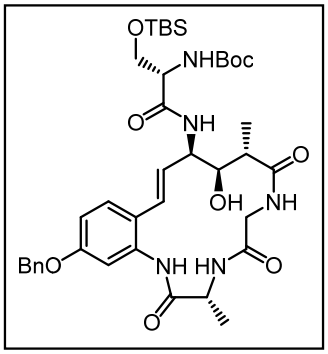
Compound **129** (10 mg, 0.014 mmol) was taken in ethanol (3 mL) and stirred for 4 h under H_2 atmosphere. Filtered the reaction mixture through celite pad to afford compound **10'**(6.5 mg) in a quantitative yield.

^{1}H NMR (700 MHz, DMSO-d_6): δ 12.41 (d, *J* = 19.65 Hz, 1H), 9.05 (d, *J* = 4.24 Hz, 1H), 8.00 - 8.14 (m, 1H), 7.83 (dd, *J* = 3.28, 8.67 Hz, 1H), 7.65 (t, *J* = 9.44 Hz, 1H), 6.55 (d, *J* = 8.09 Hz, 1H), 5.44 - 5.60 (m, 1H), 4.72 - 4.78 (m, 1H), 4.46 (br. s., 1H), 4.08 (t, *J* = 6.55 Hz, 1H), 3.56 (brs., 1H), 3.48 (brs., 1H), 3.35 (d, *J* = 15.41 Hz, 1H), 3.27 (dd, *J* = 11.37, 17.92 Hz, 1H), 2.88 - 3.00 (m, 1H), 2.85 (d, *J* = 6.94 Hz, 1H), 2.70 (brs., 1H), 1.36 (d, *J* = 7.32 Hz, 3H), 0.92 (dd, *J* = 6.94, 13.87 Hz, 3H)

^{13}C NMR (175 MHz, DMSO-d_6): δ 200.6, 200.5, 173.3, 172.7, 170.4, 166.3, 163.7, 142.7, 134.1, 114.7, 110.8, 106.5, 72.0, 70.2, 60.9, 60.3, 54.4, 51.3, 45.7, 45.6, 42.9, 42.6, 41.6, 40.2, 17.3, 9.5;

HRMS: calculated for $C_{29}H_{30}O_8N_5$ $[M+H]^+$: 480.2089, found 480.2086.

***tert*-Butyl ((*S*)-1-(((3*R*,9*S*,10*R*,11*R*,*E*)-16-(benzyloxy)-10-hydroxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (104):**



To a solution of compound **106** (45 mg, 0.079 mmol) in CH_2Cl_2 (5mL) trifluoro acetic acid (1.0 mL) was added at 0 °C and the resulting suspension was stirred for 2 h at the same temperature. Reaction was monitored by TLC, and then concentrated. This residue was dissolved in dry DMF (3 mL), then HATU (60 mg, 0.16 mmol), DIPEA (41µL, 0.23 mmol) and *N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyldimethylsilyl)-*L*-serine **99** (28 mg, 0.087 mmol) was added. The resulting solution was stirred at ambient temperature for 16h. Reaction mass was diluted with ethylacetate (15 mL), washed with saturated solution of $NaHCO_3$ (5 mL), H_2O (5 mL). The organic layer was dried over Na_2SO_4 and the crude material obtained after removal of the solvent was purified by column chromatography (silica gel 230-400 mesh 4% methanol - CH_2Cl_2) to afford **104** (38 mg, 62 %) as off white solid.

Mp: 87 - 89 °C

$[\alpha]_D^{27}$: + 63.22 (*c* 0.12, $CHCl_3$)

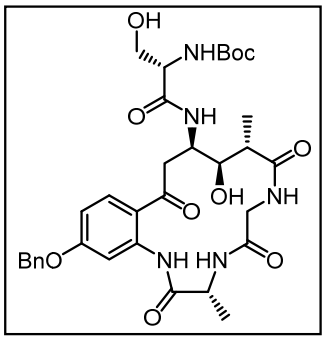
IR υ_{max}(film): cm^{-1} 3023, 2403, 1523, 1595, 1427

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.91 (d, *J* = 6.6 Hz, 1H), 8.56 (brs, 1H), 8.40 (d, *J* = 6.2 Hz, 1H), 8.01 (d, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.41 - 7.37 (m, 3H), 7.35 - 7.30 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.64 - 6.43 (m, 2H), 5.86 (dd, *J* = 8.4, 15.7 Hz, 1H), 5.27 (d, *J* = 6.9 Hz, 1H), 5.09 (s, 2H), 4.63 - 4.52 (m, 1H), 4.30 (quin, *J* = 7.2 Hz, 1H), 4.10 (brs, 2H), 3.79 - 3.72 (m, 1H), 3.66 (brs, 2H), 3.52 - 3.47 (m, 1H), 2.58 - 2.53 (m, 1H), 1.40 (s, 9H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3 H), 0.83 (s, 9H), 0.02 (s, 6H)

^{13}C NMR (125 MHz, DMSO-d_6): δ 175.9, 170.7, 170.0, 169.6, 158.1, 155.6, 137.4, 135.9, 129.1, 128.9, 128.3, 128.1, 127.8, 127.0, 123.2, 112.2, 110.8, 78.8, 75.1, 69.7, 63.8, 56.8, 50.2, 43.8, 41.5, 28.6, 26.2, 18.4, 16.8, -5.0

HRMS: calculated for $C_{39}H_{58}O_9N_5Si$ $[M+H]^+$: 768.3998, found 768.3994.

***tert*-Butyl ((*S*)-1-(((3*R*,9*S*,10*R*,11*R*)-16-(benzyloxy)-10-hydroxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-benzo[*h*] [1,4,7] triaza-cyclopentadecin-11-yl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (105):**



To a stirred solution of $PdCl_2$ (10 mol%), CuCl (6 mg, 0.06 mmol) in DMF-water (3 mL, 2:1) compound **104** (50 mg, 0.06 mmol) was added and heated at 65 °C under O_2 atmosphere for 8h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed water (5 mL) and brine (5 mL) organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure. Purification by column chromatography (silica gel

230-400 mesh 6% methanol - CH_2Cl_2) yielded compound **105** (26 mg, 59%) as a white color solid.

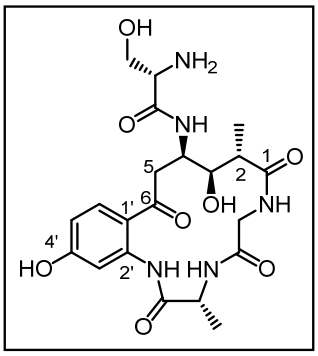
Mp: 242 - 244 °C

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.46 (s, 1H), 9.10 (d, *J* = 5.9 Hz, 1H), 8.32 (d, *J* = 2.2 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.50 - 7.44 (m, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.40 (d, *J* = 4.6 Hz, 1H), 5.20 (s, 2H), 4.88 - 4.74 (m, 2H), 4.36 (t, *J* = 9.3 Hz, 1H), 4.18 - 4.06 (m, 1H), 3.93 - 3.88 (m, 1H), 3.64 - 3.49 (m, 3H), 3.32 - 3.21 (m, 2H), 2.96 (d, *J* = 17.1 Hz, 1H), 2.80 - 2.62 (m, 1H), 1.41 (s, 9H), 1.37 (d, *J* = 4.2 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, DMSO-d$_6$): δ 201.2, 173.0, 172.8, 170.4, 169.3, 163.5, 155.9, 142.5, 136.6, 134.0, 129.0, 128.9, 128.6, 128.3, 128.1, 115.8, 109.7, 105.7, 78.8, 71.7, 70.0, 61.6, 57.3, 51.2, 45.8, 45.0, 42.8, 42.5, 28.6, 17.4, 9.6

HRMS: calculated for $C_{33}H_{44}O_{10}N_5$ $[M+H]^+$: 670.3083, found 670.3075.

***tert*-Butyl ((*S*)-1-(((3*R*,9*S*,10*R*,11*R*)-10,16-dihydroxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (10):**



To a solution of compound **131** (20 mg**,** 0.03 mmol) in methanol (3 mL), 10% Pd/C (~ 5 mg) was added and stirred under H_2 atmosphere for 2 h. The reaction mixture was then filtered through silica gel column, concentrated to afford phenolic compound. The

phenolic compound was dissolved in CH_2Cl_2 (3 mL), TFA (0.3 mL) was added at 0 °C and the resulting suspension was stirred for 2h at the same temperature. Concentrated the reaction mixture and azeotroped with toluene (3 mL x 3), acetonitrile (3 mL x 3) and dried under vacuum to afford compound **10** (11 mg, 78% for 2 steps) as off white solid. **$[\alpha]_D^{25}$:** − 10.89 (*c* 0.34, CH_3OH)

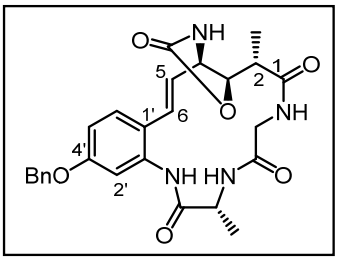
HRMS: calculated for $C_{29}H_{30}O_8N_5$ $[M+H]^+$: 480.2089, found 480.2085.

Table 1: ^1H and ^{13}C chemical shift data of **10** in comparison to the reported values

Residue	Notation	δ_H (δ_H reported), multiplicity, J_{HH}	δ_C (δ_C reported)
Gly			
	1 (CO)	--	169.84 (169.0)
	2a	4.81(4.19), dd, $J_{H\alpha\text{-}H\alpha'}$=15.2, $J_{NH\text{-}H\alpha}$=9.0	42.06 (42.4)
	2b ′	3.34(3.78), dd, $J_{H\alpha\text{-}H\alpha'}$=15.2	--
	3 (NH)	7.73(7.30), dd, $J_{NH\text{-}H\alpha}$=9.0	--
D-Ala			
	1 (CO)	--	172.15(179.2)
	2a	4.12(4.29), dq, $J_{H\alpha\text{-}H\beta}$=7.4, $J_{NH\text{-}H\alpha}$=6.2	50.73 (49.7)
	3	1.39 (1.36), d, $J_{H\alpha\text{-}H\beta}$=7.4	16.99(16.0)
	4 (NH)	9.09 (8.79), d, $J_{NH\text{-}H\alpha}$=6. 2	--
L-Ser			
	1 (CO)	--	165.66(166.7)
	2	3.95 (3.98), br	53.67(53.6)
	3a	3.71 (3.69), br	60.61 (60.3)
	3b	3.71 (3.69), br	--
	4 (OH)	5.46(5.46),br, ol	--
	5 (NH_2)	8.06(8.08), br	--
Non peptide portion			
	1 (CO)	--	172.61(173.2)
	2	2.76 (2.35), dq, $J_{H2\text{-}H7}$=7.1	45.23(45.4)
	3	3.59 (3.39), br	71.40(72.2)
	4	4.52(4.52), br, m	45.23(48.0)
	5a	3.32 (3.34), dd, $J_{H\alpha\text{-}H\alpha}$=17.6	42.29(41.2)
	5b	2.91 (2.87), $J_{H\alpha\text{-}H\alpha}$=17.6	--
	6	--	200.17(201.1)
	7	0.97 (1.08), d, $J_{H2\text{-}H7}$=7.1	9.38 (13.6)
	8 (OH-3)	5.44 (5.53), br, ol	--
	9 (NH-4)	7.87 (7.98), br, ol	--

	1′	--	113.96 (115.8)
	2′	--	142.41 (141.3)
	3′	8.13 (7.92), d, $J_{H3'-H5'}$=2.5	105.66 (106.1)
	4′	--	163.36 (162.9)
	5′	6.58 (6.57), dd, $J_{H5'-H6'}$=8.9, $J_{H3'-H5'}$=2.5	110.15 (110.0)
	6′	7.86(7.77), d, $J_{H5'-H6'}$=8.9	133.67 (132.9)
	10 (OH-4′)	10.75 (10.70), br, s	--
	11 (NH-2′)	12.52 (11.50), br, s	
Multiplicities and *J* coupling constants are provided only for the resonances that are without any overlaps or wherever the unambiguous measurements were possible.			

(3a*R*,4*S*,10*R*,18*aR*,*E*)-14-(Benzyloxy)-4,10-dimethyl-3a,4,6,7,9,10,12,18a-octahydro-2*H*-benzo[*h*]oxazolo[4,5-l][1,4,7]triazacyclopentadecine-2,5,8,11(1*H*)-tetraone (129):



To a solution of compound **106** (15 mg, 0.026 mmol) in CH_2Cl_2 (5 mL) trifluoro acetic acid (1.0 mL) was added at 0 °C and the resulting suspension was stirred for 2 h at the same temperature. Reaction was monitored by TLC, and then concentrated. This residue was dissolved in dry CH_2Cl_2 (4 mL), DIPEA (9 µL, 0.053 mmol) followed by triphosgene (9 mg, 0.029 mmol, in 1 mL CH_2Cl_2) was added at 0 °C and the resulting suspension was stirred for 2 h. Reaction mixture was diluted with EtOAc (10 mL) and washed with 1N HCl (3 mL), brine (3 mL). Organic layer was separated, dried under vacuum. Purification by column chromatography (silica gel 230-400 mesh 5% methanol - CH_2Cl_2) yielded compound **129** (8.2 mg, 63%) as white solid.

Mp: 236 - 238 °C

$[\alpha]_D^{27}$: +7.11 (*c* 0.25, CH_3OH)

HRMS: calculated for $C_{26}H_{29}O_6N_4$ $[M+H]^+$: 493.2082, found 493.2080.

Table 2: ^{1}H and ^{13}C chemical shift data of compound **129**			
Residue	Notation of the proton/carbon	δ_H, multiplicity, J_H	δ_C
Gly			
	1 (CO)	--	172.23
	2a (Hα)	4.27, dd, $J_{Hα\text{-}Hα'}$=15.8, $J_{NH\text{-}Hα}$=7.7	43.25
	2b (Hα′)	3.63, dd, $J_{Hα\text{-}Hα'}$=15.8, $J_{NH\text{-}Hα'}$=4.7	--
	3 (NH)	8.13, dd, $J_{NH\text{-}Hα}$=7.7, $J_{NH\text{-}Hα'}$=4.7	
D-Ala			
	1 (CO)	--	171.00
	2 (Hα)	4.41, q, $J_{Hα\text{-}Hβ}$=7.2, $J_{NH\text{-}Hα}$=7.2	51.56
	3 (Hβ)	1.43, d, $J_{Hα\text{-}Hβ}$=7.2	15.91
	4 (NH)	8.12, d, $J_{NH\text{-}Hα}$=7.2	--
Non peptide portion			
	1 (CO)	--	173.38
	2	3.07, dq, $J_{H2\text{-}H7}$=6.9, $J_{H2\text{-}H3}$=3.6	43.41
	3	4.69, t, $J_{H2\text{-}H3}$=3.6, $J_{H3\text{-}H4}$=3.7	82.48
	4	4.73, ddd, $J_{H4\text{-}H5}$=7.0, $J_{H3\text{-}H4}$=3.7, $J_{H4\text{-}H8}$=1.8	54.03
	5	6.02, dd, $J_{H5\text{-}H6}$=15.8, $J_{H4\text{-}H5}$=7.0	134.05
	6	6.48, d, $J_{H5\text{-}H6}$=15.8	127.72
	7	1.18, d, $J_{H2\text{-}H7}$=6.9	8.71
	8 (NH-4)	7.02, br	--
	1′	--	122.86
	2′	--	136.92
	3′	7.66, d, $J_{H3'\text{-}H5'}$=2.6	110.04
	4′	--	159.44
	5′	6.77, dd, $J_{H5'\text{-}H6'}$=8.6, $J_{H3'\text{-}H5'}$=2.6	112.11
	6′	7.28, d, $J_{H5'\text{-}H6'}$=8.6	128.70
	9 (NH-2′)	8.86, s	--
OBn-6′			
	1″	--	138.05

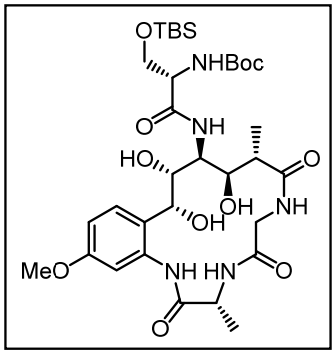
	2″	7.47, dd, , $J_{H2''\text{-}H3''}$=7.2, $J_{H2''\text{-}H4''}$=1.7	128.28
	3″	7.38, t, $J_{H2''\text{-}H3''}$=7.2, $J_{H3''\text{-}H4''}$=7.2	129.12
	4″	7.31, tt, $J_{H3''\text{-}H4''}$=7.2, $J_{H2''\text{-}H4''}$=1.7	128.28
	1 (CH_2-1″)	5.09, s	70.27

X-ray Crystal Structure Details: Single crystals of compound **129**, obtained from Acetone-d6. X-ray intensity data were collected on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 40 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[1] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2. All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* III view of both compounds were drawn with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. In the crystal structure benzyl group showed orientational disorder over two positions having occupancy 0.7 and 0.3. The anisotropic parameters of the benzyl group atoms were restraints using DELU, SIMU and ISOR commands integrated in SHELXTL package.

Crystallographic data for 129 (KKN-H-46) ($C_{26}H_{28}N_4O_6$): M = 492.52, Crystal dimensions 0.46 x 0.20 x 0.11 mm^3, monoclinic, space group $C2$, a = 21.150(10), b = 4.978(3), c = 24.550(11) Å, β = 104.86(3)°, V = 2498(2) $Å^3$, Z = 4, ρ_{calcd} = 1.310 gcm^{-3}, μ (Mo-K_α) = 0.094 mm^{-1}, *F(000)* = 1040, $2\theta_{max}$ = 50.00°, T = 296(2) K, 14707 reflections collected, 4389 unique reflections (R_{int}=0.1283), 2757 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.958, T_{max} = 0.990, 379 refined parameters, No. of restraints 199, S = 1.070, $R1$ = 0.0834, $wR2$ = 0.1716 (all data R = 0.1345, $wR2$=

0.1956), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.30, $\Delta\rho_{min}$= -0.23 (eÅ^{-3}). Crystallographic data for compound **129** (KKN-H-46) deposited with the Cambridge Crystallographic Data Centre as supplementary publication no.CCDC 1427296.

***tert*-Butyl ((2*S*)-3-((tert-butyldimethylsilyl)oxy)-1-oxo-1-(((3*R*,9*S*,10*R*,11*S*)-10,12,13-trihydroxy-16-methoxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1H-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)amino)propan-2-yl)carbamate (130)**



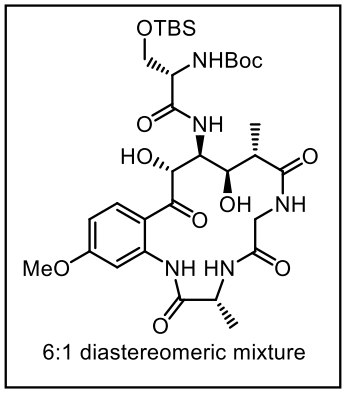
To a solution of compound **100** (25 mg, 0.036 mmol) in ^{t}BuOH-H_2O (2 ml, 1:1),NMO (8.4 mg, 0.073 mmol) and OsO_4 (46 µL, 0.1% solution in ^{t}BuOH) was added at 0 °C and stirred for 6h. ^{t}BuOH removed under vacuum, reaction mixture was diluted with EtOAc (5 mL) was hed with hypo solution (4 mL) and brine (4 ml). Organic layer was separated, dried under vacuum. Purification by column chromatography (silica gel 230-400 mesh 5% methanol - CH_2Cl_2) yielded compound **130** (16 mg, 62%) as white solid in 6:1 mixture of diastereomers.

^{1}H NMR (400MHz, CD_3OD): (major isomer) δ 7.49 (s, 1H), 7.17 (d, *J* = 8.56 Hz, 1H), 6.71 (dd, *J* = 2.57, 8.68 Hz, 1H), 4.72 (brs., 1H), 4.59 (brs., 1H), 4.42 - 4.49 (m, 1H), 4.33 (brs, 1H), 4.19 (t, *J* = 5.50 Hz, 1H), 4.10 - 4.14 (m, 1H), 3.91 (d, *J* = 5.38 Hz, 1H), 3.84 - 3.89 (m, 1H), 3.78 (s, 3H), 3.61 - 3.70 (m, 2H), 2.72 - 2.88 (m, 1H), 1.48 (s, 9H);1.45 (d, *J* = 7.05 Hz, 3H, 1.13 (d, *J* = 7.09 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 6H)

^{13}C NMR (100 MHz, CD_3OD): δ 174.7, 169.9, 169.6, 169.3, 157.7, 155.0, 136.2, 127.2, 123.2, 108.8, 107.8, 78.1, 76.7, 76.3, 76.1, 73.9, 70.5, 67.5, 61.3, 55.2, 52.9, 50.0, 43.1, 41.8, 27.8, 25.8, 23.5, 16.3, 14.7, 9.4, -8.2

HRMS: calculated for $C_{33}H_{55}O_{11}N_5Na$ $[M+Na]^+$: 748.3560, found 748.3558.

***tert*-Butyl ((2S)-3-((tert-butyldimethylsilyl)oxy)-1-(((3R,9S,10R,11S)-10,12-dihydroxy-16-methoxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1H-benzo[h][1,4,7]triazacyclopentadecin-11-yl)amino)-1-oxopropan-2-yl)carbamate (131):**



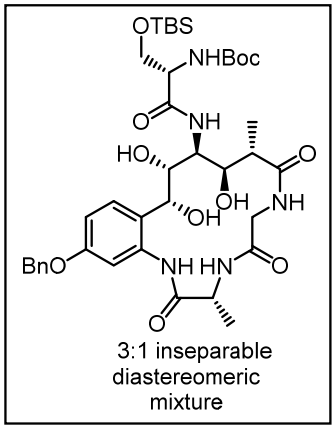
To a sloutuon of compound **130** (15 mg, 0.02 mmol) in $CHCl_3$ (5 mL) MnO_2 (18 mg, 0.2 mmol) was added and stirred for 4 h. filtered the reaction mixture through celite pad and purification by column chromatography (silica gel 230-400 mesh 4 % methanol - CH_2Cl_2) yielded compound **131** (11.7 mg, 78%) as white solid in 6:1 mixture of diastereomers.

^{1}H NMR (400MHz, CD_3OD): δ 9.70 - 9.89 (m, 1H), 8.22 - 8.32 (m, 1H), 7.78 (d, *J* = 8.31 Hz, 1H), 6.87 (d, *J* = 8.80 Hz, 1H), 4.66 (dd, *J* = 2.20, 5.14 Hz, 1H), 4.45 - 4.54 (m, 1H), 4.36 - 4.44 (m, 1H), 4.14 - 4.27 (m, 3H), 4.01 - 4.07 (m, 1H), 3.98 (d, *J* = 4.40 Hz, 1H), 3.92 (s, 4H), 3.86 (d, *J* = 5.38 Hz, 2H), 3.23 (q, *J* = 7.34 Hz, 1H), 2.42 - 2.58 (m, 1H), 1.43 - 1.51 (m, 15H), 1.10 (d, *J* = 6.85 Hz, 3H), 0.91 (s, 14H), 0.10 (s, 7H)

^{13}C NMR (100 MHz, CD_3OD): δ 194.3, 176.9, 174.8, 172.6, 171.7, 171.1, 166.0, 141.9, 138.3, 116.7, 109.4, 104.2, 79.2, 78.2, 77.9, 77.5, 69.8, 63.2, 55.0, 52.8, 50.8, 50.6, 48.7, 39.0, 29.4, 29.1, 27.3, 25.0, 17.8, 16.0, 10.9, 7.8, -6.7

HRMS: calculated for $C_{33}H_{53}O_{11}N_5NaSi$ $[M+Na]^+$: 746.3403, found 746.3406

***tert*-Butyl ((2S)-1-(((3R,9S,10R,11S)-16-(benzyloxy)-10,12,13-trihydroxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1H-benzo[h] [1,4,7]triazacyclopentadecin-11-yl)amino)-3-((tert-butyldimethylsilyl)oxy)-1-oxopropan-2-yl)carbamate (132):**



Compound **132** (28 mg, 68%) was synthesized by following similar procedure used for the synthesis of compound **130**. The compound was obtaines as 3:1 diastereomeric mixture.

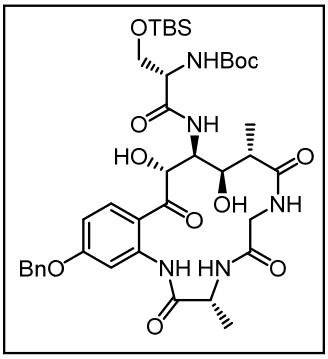
^{1}H NMR (400MHz, CD_3OD) (mixture of diastereomers): δ 7.60 (brs., 1H), 7.39 - 7.46 (m, 3H), 7.34 (d, *J* = 6.85 Hz, 3H), 7.30 (d, *J* = 6.36 Hz, 1H), 6.77 (d, *J* = 8.80 Hz, 1H), 5.07 (br. s., 3H), 4.72 (br. s., 1H), 4.45 (d, *J* = 6.85 Hz, 1H), 4.34 (br. s., 1H), 4.15 - 4.25 (m, 2H), 4.06 - 4.15 (m, 2H), 3.80 - 3.95 (m, 3H), 3.58 - 3.72 (m, 3H), 2.72 - 2.84 (m, 1H), 1.40 - 1.52 (m, 17H), 1.13 (d, *J* = 6.36 Hz, 3H), 0.88 - 0.96 (m, 13H), 0.05 - 0.19 (m, 9H)

^{13}C NMR (100 MHz, CD_3OD): δ 174.7, 170.0, 169.6, 169.3, 156.8, 137.6, 135.7, 127.3, 126.7, 126.6, 126.1, 126.0, 125.8, 125.7, 123.5, 111.2, 109.7, 108.8, 78.1, 73.8, 70.7,

69.7, 68.4, 68.1, 67.5, 61.9, 61.3, 55.2, 50.1, 50.0, 48.0, 46.8, 46.5, 46.3, 46.1, 45.9, 45.7, 45.5, 43.1, 41.8, 27.9, 25.8, 23.6, 16.3, 15.3, 14.7, 11.3, 9.4, -8.1, -8.1

HRMS: calculated for $C_{39}H_{59}O_{11}N_5NaSi$ $[M+Na]^+$: 824.3873, found 824.3868.

***tert*-Butyl ((*S*)-1-(((3*R*,9*S*,10*R*,11*S*,12*R*)-16-(benzyloxy)-10,12-dihydroxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1H-benzo[h][1,4,7]triazacyclopentadecin-11-yl)amino)-3-((tert-butyldimethylsilyl)oxy)-1-oxopropan-2-yl)carbamate (133):**



To a sloutuon of compound **132** (25 mg, 0.03 mmol) in $CHCl_3$ (5 mL) MnO_2 (27 mg, 0.3 mmol) was added and stirred for 4 h. filtered the reaction mixture through celite pad and purification by column chromatography (silica gel 230-400 mesh 4 % methanol - CH_2Cl_2) yielded compound **132** (10 mg,) and **134** (3 mg).

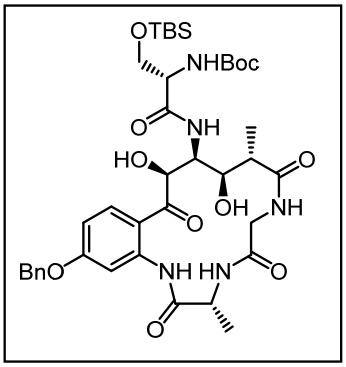
^{1}H NMR (400MHz, CD_3OD): δ 8.38 (d, *J* = 2.44 Hz, 1H), 7.77 (d, *J* = 8.54 Hz, 1H), 7.48 (d, *J* = 7.32 Hz, 2H), 7.41 (t, *J* = 7.48 Hz, 2H), 7.36 (d, *J* = 7.32 Hz, 1H), 6.92 - 6.94 (m, 1H), 5.41 (brs., 1H), 5.23 (s, 2H), 4.45 - 4.50 (m, 1H), 4.42 (d, *J* = 5.19 Hz, 1H), 4.39 (s, 1H), 4.19 - 4.23 (m, 2H), 4.06 (brs., 1H), 3.90 (d, *J* = 9.16 Hz, 2H), 2.94 - 3.01 (m, 1H), 1.47 (brs., 3H), 1.45 (s, 9H), 0.91 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H)

^{13}C NMR (100 MHz, CD_3OD): δ 194.3, 174.8, 172.7, 171.7, 171.1, 165.0, 156.4, 141.9, 138.3, 136.1, 128.2, 128.2, 127.9, 127.6, 127.4, 127.3, 116.8, 116.8, 110.2, 105.0, 79.6, 79.2, 73.2, 70.1, 69.8, 63.2, 56.7, 52.8, 50.8, 50.6, 48.7, 48.4, 48.2, 48.1, 47.9, 47.8, 47.6,

47.4, 47.3, 47.1, 42.3, 39.0, 31.7, 29.4, 29.3, 27.3, 27.2, 25.0, 24.9, 22.3, 17.9, 17.8, 16.0, 13.1, 12.9, 11.0, -6.7, -6.8;

HRMS: calculated for $C_{39}H_{57}O_{11}N_5NaSi$ $[M+Na]^+$: 822.3716, found 824.3697.

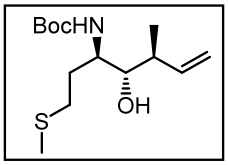
***tert*-butyl ((S)-1-(((3R,9S,10R,11S,12S)-16-(benzyloxy)-10,12-dihydroxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1H-benzo[h][1,4,7]triazacyclopentadecin-11-yl)amino)-3-((tert-butyldimethylsilyl)oxy)-1-oxopropan-2-yl)carbamate (134):**



The compound was obtained only in 3 mg which was not sufficient to record proper NMR. The compound was confirmed by HRMS.

HRMS: calculated for $C_{39}H_{57}O_{11}N_5NaSi$ $[M+Na]^+$: 822.3716, found 824.3689.

***tert*-Butyl ((3*R*,4*S*,5*S*)-4-hydroxy-5-methyl-1-(methylthio)hept-6-en-3-yl)carbamate (135):**



(*E*)-2-butene (3 mL, 17 mmol, 2 equiv) was condensed into flask containing KOtBu (2.9 g, 25.7 mmol, 1.5 equiv) in THF (20 mL) chilled to –78 °C. After careful addition of ^{n}-BuLi (16.1 mL, 1.6 M in hexanes, 25.7 mmol, 1.5 equiv) over 1 hour (maintaining internal temperature below –70 °C), the reaction mixture was warmed to –50 °C for 15

min. The mixture was chilled to –78 °C once more, and a solution of (-)-B-methoxydiisopinocampheylbora(8.1 gm in 30 mL THF, 25.7 mmol) was added slowly over 30 min. Next, BF_3•Et_2O (3.8 mL, 30.9 mmol, 1.8 equiv) was added at –78 °C over 30 minutes, then the solution of reagent was treated with a solution of compound **118** (4.0 g, 17.1 mmol) in THF (25 mL). The reaction mixture was stirred at –78 °C for 12 h, then warmed to –15 °C. A mixture of 3N NaOH (8.3 mL) and 30% hydrogen peroxide (2.9 mL) was added dropwise to the reaction. After being heated to reflux for 1 h, the mixture was cooled to 0 °C. Concentrated the reaction mixture, diethylether (50 mL) was added and washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and the crude material obtained after removal of the solvent was purified by column chromatography (silica gel 230-400 mesh 10% ethylacetate - petether) to afford **135** (2.4 gm, 48%) as colorless liquid as a single diastereomer

$[\alpha]_D^{30}$ +31.16 (*c* 1.66, $CHCl_3$)

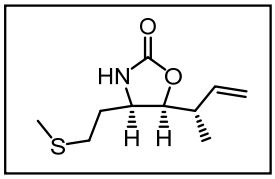
IR υ_{max}(film): cm^{-1} 3445, 3015, 2967, 1712, 1534, 1422

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (td, *J* = 8.93, 17.85 Hz, 1H), 5.01 - 5.20 (m, 2H), 4.94 (d, *J* = 9.29 Hz, 1H), 3.82 (t, *J* = 9.90 Hz, 1H), 3.38 (d, *J* = 5.38 Hz, 1H), 2.56 - 2.68 (m, 1H), 2.44 - 2.56 (m, 1H), 2.16 - 2.28 (m, 1H), 2.09 (s, 3H), 1.76 - 1.84 (m, 1H), 1.65 - 1.75 (m, 1H), 1.42 (s, 9H), 1.04 (d, *J* = 6.60 Hz, 3H)

^{13}H NMR (100 MHz, $CDCl_3$): δ 155.9, 140.6, 117.1, 79.4, 76.7, 51.4, 41.8, 31.0, 28.4, 16.3, 15.7;

HRMS: calculated for $C_{14}H_{27}O_3NNa$ $[M+Na]^+$: 312.1604, found 312.1602.

(4*R*,5*S*)-5-((*S*)-but-3-en-2-yl)-4-(2-(methylthio)ethyl)oxazolidin-2-one (136):

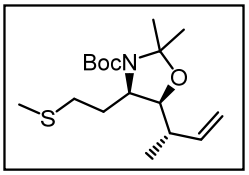


Compound **136** (58 mg, 88%) was synthesized by following similar procedure used for the synthesis of **66'**.

$[\alpha]_D^{26}$ +33.64 (*c* 0.74, $CHCl_3$)

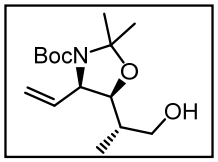
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (brs., 1H), 5.88 (ddd, *J* = 7.34, 10.27, 17.36 Hz, 1H), 5.08 - 5.22 (m, 2H), 4.3 (t, *J* = 7.34 Hz, 1H), 3.81 - 3.96 (m, 1H), 2.59 - 2.70 (m, 1H), 2.48 - 2.59 (m, 2H), 2.11 (s, 3H), 1.79 - 1.93 (m, 2H), 1.07 (d, *J* = 6.85 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): 159.4, 138.5, 116.1, 83.2, 54.7, 37.1, 30.8, 28.1, 16.7, 15.6
HRMS calculated for $C_{10}H_{18}O_2NS$ $[M+H]^+$: 216.1053, found 216.1052.

***tert*-Butyl (4*R*, 5*S*)-5-((*S*)-but-3-en-2-yl)-2,2-dimethyl-4-(2-(methylthio) ethyl) oxazolidine-3-carboxylate (137):**



Compound **137** (3.2 gm, 85%) was synthesized from **135** by following similar procedure used for the synthesis of **120**.
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.63 - 5.93 (m, 1H), 4.85 - 5.15 (m, 2H), 3.55 - 3.74 (m, 1H), 2.43 - 2.63 (m, 2H), 2.26 - 2.38 (m, 1H), 2.07 (s, 3H), 1.79 (br. s., 1H), 1.67 - 1.77 (m, 1H), 1.45 - 1.55 (m, 6H), 1.43 (s, 9H), 0.96 (t, *J* = 6.85 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): (mixture of rotamers)δ 152.9, 151.9, 140.6, 139.7, 115.4, 114.3, 93.2, 92.7, 80.7, 80.4, 80.0, 79.8, 77.4, 77.1, 76.8, 57.6, 41.4, 36.4, 31.2, 31.2, 30.3, 29.9, 29.6, 28.5, 28.4, 28.1, 27.3, 24.9, 23.5, 17.0, 16.5, 16.4, 15.6
HRMS calculated for $C_{17}H_{31}O_3NNaS$ $[M+Na]^+$: 352.1917, found 352.1911.

***tert*-Butyl (4*R*,5*S*)-5-((*S*)-1-hydroxypropan-2-yl)-2,2-dimethyl-4-vinyloxazolidine-3-carboxylate (138):**



Compound **138** (900 mg, 49% for 2 steps) was synthesized from **137** by following similar procedure used for the synthesis of **122**.

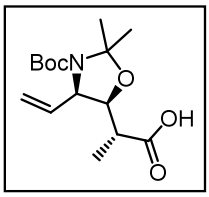
$[\alpha]_D^{30}$: + 45.45 (*c* 0.34, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 - 5.74 (m, 1H), 5.04 - 5.33 (m, 2H), 3.99 - 4.22 (m, 1H), 3.74 - 3.89 (m, 1H), 3.56 - 3.69 (m, 1H), 3.45 - 3.56 (m, 1H), 2.83 (brs., 1H), 1.86 (brs., 1H), 1.46 - 1.60 (m, 6H), 1.42- 1.37 (m, 9H), 0.76 (d, *J* = 6.36 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 132.9, 132.2, 119.0, 118.4, 93.6, 93.2, 81.5, 81.3, 80.3, 79.6, 67.5, 62.7, 62.4, 34.8, 34.7, 28.4, 28.0, 27.2, 25.1, 24.0, 12.3;

HRMS: calculated for $C_{15}H_{27}O4NNa$ $[M+Na]^+$: 308.1832, found 308.1830.

(*R*)-2-((4*R*,5*S*)-3-(tert-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidin-5-yl) pro panoic acid (139):



Compound **139** (710 mg, 80%) was synthesized from **138** by following similar procedure used for the synthesis of **123**.

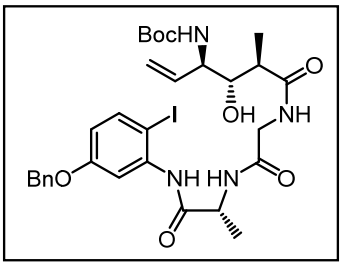
$[\alpha]_D^{27}$ + 25.09 (*c* 0.80, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 - 5.77 (m, 1H), 5.09 - 5.38 (m, 2H), 4.03 - 4.26 (m, 2H), 2.57 (brs, 1H), 1.49 - 1.41 (m, 15H), 1.12 (d, *J* = 5.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 179.9, 151.8, 151.6, 132.4, 131.7, 119.7, 119.0, 93.7, 93.3, 80.5, 79.8, 77.6, 77.4, 61.9, 61.6, 40.0, 29.7, 28.4, 27.9, 27.1, 24.8, 23.8, 13.3;

HRMS: calculated for $C_{15}H_{25}O_5NNa$ $[M+Na]^+$: 322.1625, found 322.1623.

***tert*-Butyl ((3R,4S,5R)-6-((2-(((R)-1-((5-(benzyloxy)-2-iodophenyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)amino)-4-hydroxy-5-methyl-6-oxohex-1-en-3-yl)carbamate (140):**



Compound **140** (300 mg, 65% for 3 steps) was was synthesized from **115** and **139** by following similar procedure used for the synthesis of **125**.

Mp: 84- 86 °C;

$[\alpha]_D^{27}$: + 25.51 (*c* 0.64, $CHCl_3$);

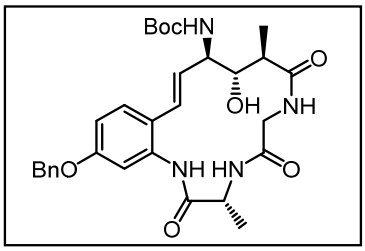
IR υ_{max}(film): cm^{-1} 3025, 2931, 1635, 1567;

^{1}H NMR (400MHz, CD_3OD): δ 7.70 (d, *J* = 8.80 Hz, 1H), 7.40 - 7.45 (m, 2H), 7.36 (t, *J* = 7.34 Hz, 3H), 7.31 (d, *J* = 7.58 Hz, 1H), 6.69 (dd, *J* = 2.45, 8.56 Hz, 1H), 5.93 (ddd, *J* = 7.34, 10.15, 17.24 Hz, 1H), 5.16 - 5.33 (m, 2H), 5.06 (s, 2H), 4.56 (q, *J* = 7.09 Hz, 1H), 4.16 (brs., 1H), 4.05 (d, *J* = 16.87 Hz, 1H), 3.84 (d, *J* = 16.87 Hz, 1H), 3.62 - 3.76 (m, 1H), 2.50 - 2.60 (m, 1H), 1.50 (d, *J* = 7.34 Hz, 3H), 1.43 (s, 9H), 1.16 (d, *J* = 6.85 Hz, 3H);

^{13}C NMR (100MHz, CD_3OD): δ 177.0, 172.0, 170.5, 159.6, 139.1, 136.7, 133.8, 128.2, 127.6, 127.3, 116.5, 114.7, 112.6, 79.1, 75.6, 69.8, 55.3, 49.8, 43.2, 42.4, 27.4, 16.4, 13.0;

HRMS: calculated for $C_{30}H_{39}O_7N_4INa$ $[M+Na]^+$: 717.1756, found 717.1747.

***tert*-Butyl ((3*R*,9*R*,10*S*,11*R*,*E*)-16-(benzyloxy)-10-hydroxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-1H-benzo[h][1,4,7]triazacyclopentadecin-11-yl)carbamate (141) :**



Compound **141** (202 mg, 53%) was was synthesized from **140** by following similar procedure used for the synthesis of **106**.

Mp: 132 - 134 °C

$[\alpha]_D^{27}$: + 75.78 (*c* 0.48, $CHCl_3$)

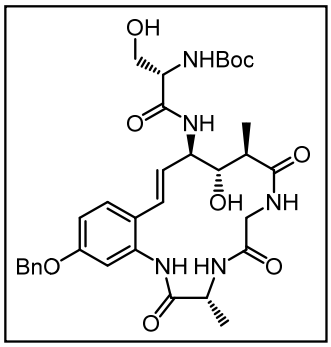
IR υ_{max}(film): cm^{-1} 3029, 2931, 1644, 1598

^{1}H NMR (400MHz, CD_3OD): δ 7.42 - 7.46 (m, 2H), 7.36 - 7.40 (m, 3H), 7.32 (d, *J* = 6.85 Hz, 1H), 7.24 (d, *J* = 1.96 Hz, 1H), 6.85 (d, *J* = 2.45 Hz, 1H), 6.58 (d, *J* = 15.89 Hz, 1H), 5.96 (dd, *J* = 5.50, 15.77 Hz, 1H), 5.09 (s, 2H), 4.64 (t, *J* = 5.26 Hz, 1H), 4.49 (q, *J* = 6.93 Hz, 1H), 3.94 - 4.14 (m, 1H), 3.78 - 3.91 (m, 2H), 2.44 - 2.53 (m, 1H), 1.52 (d, *J* = 7.34 Hz, 3H), 1.47 (s, 3H), 1.28 (d, *J* = 7.09 Hz, 3H)

^{13}C NMR (100MHz, CD_3OD): δ 177.4, 171.9, 171.7, 158.4, 139.1, 137.1, 135.1, 133.8, 128.2, 128.1, 127.5, 127.3, 127.2, 125.2, 124.5, 112.9, 111.5, 78.8, 73.5, 69.7, 56.4, 50.3, 43.3, 42.8, 27.4, 15.3, 14.7

HRMS: calculated for $C_{30}H_{38}O_7N_4Na$ $[M+Na]^+$: 589.2633, found 589.2623.

***tert*-Butyl ((S)-1-(((3R,9R,10S,11R,E)-16-(benzyloxy)-10-hydroxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-1H-benzo[h][1,4,7]triazacyclopentadecin-11-yl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (142):**



Compound **142** (100 mg, 83%) was was synthesized Ffrom **141** and **39** by following similar procedure used for the synthesis of **127**.

Mp: 145 - 147 °C

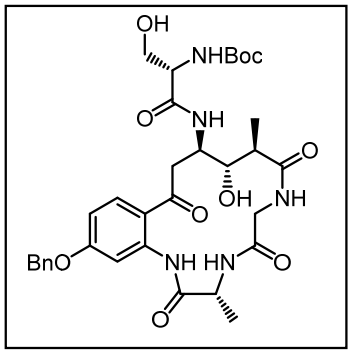
$[\alpha]_D^{27}$: + 55.64 (*c* 0.38, $CHCl_3$)

^{1}H NMR (400MHz, CD_3OD): δ 7.43 (d, *J* = 6.85 Hz, 2H), 7.28 - 7.40 (m, 4H), 7.20 (brs., 1H), 6.86 (d, *J* = 7.83 Hz, 1H), 6.65 (brs., 1H), 5.98 (d, *J* = 15.65 Hz, 1H), 5.09 (brs., 2H), 4.47 – 4.49 (m, 2H), 4.11 (brs, 1H), 3.97 - 4.07 (m, 1H), 3.82 (br s, 2H), 3.74 (d, *J* = 17.12 Hz, 2H), 2.43 (brs., 1H), 1.42 - 1.50 (m, 12H), 1.23 (d, *J* = 6.85 Hz, 3H);

^{13}C NMR (100MHz, CD_3OD): δ 179.5, 174.6, 173.4, 160.0, 158.0, 136.7, 129.7, 129.0, 128.7, 128.5, 127.6, 126.3, 114.6, 113.4, 80.8, 74.2, 71.2, 63.4, 58.5, 56.0, 55.1, 52.1, 45. 4, 44.6, 28.9, 16.9, 16.4.

HRMS calculated for $C_{33}H_{43}O_9N_5Na$ $[M+Na]^+$: 676.2953, found 676.2945.

***tert*-butyl ((S)-1-(((3R,9R,10S,11R)-16-(benzyloxy)-10-hydroxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1H-benzo[h] [1,4,7] triazacyclopentadecin-11-yl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (143):**



Compound **143** (18 mg, 58%) was was synthesized from **142** by following similar procedure used for the synthesis of **128**.

Mp: 130 - 132 °C

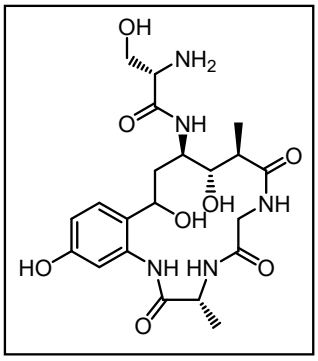
$[\alpha]_D^{27}$: + 2.9 (*c* 0.12, MeOH)

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (s, 1H), 9.28 (d, *J* = 4.40 Hz, 1H), 8.30 (s, 1H), 7.92 (d, *J* = 8.80 Hz, 1H), 7.83 (d, *J* = 7.83 Hz, 1H), 7.44 - 7.49 (m, 2H), 7.37 - 7.44 (m, 3H), 7.32 - 7.37 (m, 2H), 6.83 (d, *J* = 8.31 Hz, 1H), 6.48 - 6.58 (m, 1H), 6.14 (d, *J* = 6.36 Hz, 1H), 5.20 (s, 2H), 5.07 (d, *J* = 3.91 Hz, 1H), 4.81 (t, *J* = 5.14 Hz, 1H), 4.41 - 4.58 (m, 1H), 4.21 - 4.34 (m, 1H), 4.04 (brs., 1H), 3.89 - 3.98 (m, 1H), 3.44 - 3.59 (m, 4H), 3.38 - 3.43 (m, 1H), 2.60 (d, *J* = 16.14 Hz, 1H), 2.34 (brs., 1H), 1.43 (s, 9H), 1.38 (d, *J* = 6.40 Hz, 3H),1.10 (d, *J* = 7.34 Hz, 3H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 200.4, 174.4, 172.8, 170.4, 163.1, 155.5, 142.6, 136.8, 133.4, 129.0, 128.9, 128.5, 128.2, 128.0, 116.4, 109.3, 105.9, 78.7, 73.1, 69.9, 62.4, 57.0, 55.4, 52.0, 49.9, 49.1, 44.4, 44.1, 42.0, 28.6, 17.3, 17.1;

HRMS: calculated for $C_{33}H_{44}O_{10}N_5$ $[M+H]^+$: 670.3083, found 670.3076.

(2*S*)-2-amino-3-hydroxy-*N*-((3*R*,9*R*,10*S*,11*R*)-10,13,16-trihydroxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*- enzo[h] [1,4,7] triaza cyclopentadecin-11-yl)propanamide (144)



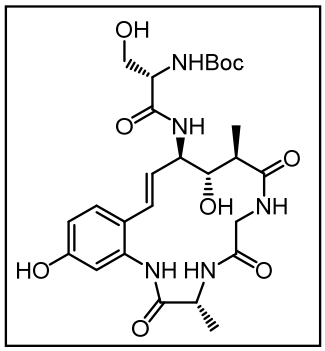
Compound **144** (8 mg, 72% for 2 steps) was was synthesized from **143** by following similar procedure used for the synthesis of **10**.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.64 (s, 1H), 9.09 (s, 1H), 8.61 - 8.79 (m, 1H), 8.12 (brs., 2H), 8.12 (br. s., 3H), 7.51 (d, *J* = 2.45 Hz, 1H), 7.01 (d, *J* = 8.56 Hz, 1H), 6.50 (dd, *J* = 2.45, 8.31 Hz, 1H), 5.58 (br. s., 1H), 5.17 (t, *J* = 7.09 Hz, 1H), 4.43 - 4.50 (m, 1H), 4.35 - 4.43 (m, 1H), 3.93 (dd, *J* = 7.95, 16.02 Hz, 2H), 3.81 (dd, *J* = 6.85, 10.03 Hz, 2H), 2.60 (dd, *J* = 6.60, 10.51 Hz, 1H), 2.23 - 2.31 (m, 1H), 1.31 (d, *J* = 7.34 Hz, 3H), 0.98 (d, *J* = 6.85 Hz, 3H)

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 175.8, 174.7, 170.9, 166.7, 157.5, 138.3, 127.4, 121.0, 110.8, 109.9, 83.4, 75.5, 60.6, 54.7, 53.8, 49.3, 45.4, 43.7, 36.4, 18.4, 13.9

HRMS: calculated for $C_{21}H_{32}O_8N_5$ $[M+H]^+$: 482.2245, found 482.2242.

***tert*-Butyl ((*S*)-1-(((3*R*,9*R*,10*S*,11*R*,*E*)-10,16-dihydroxy-3,9-dimethyl-2,5,8-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (145):**



Li-napthalenide (6 mL, 0.17 M in THF) was added to a stirred solution of compound **142** (46 mg, 0.7 mmol) at – 40 °C and stirred for 3 h at same temperature reaction was quenched with saturated NH_4Cl and reaction mass was diluted with ethylacetate (10 mL), washed with H_2O (5 mL) brine (5 mL). The organic layer was dried over Na_2SO_4 and the crude material obtained after removal of the solvent was purified by column chromatography (silica gel 230-400 mesh 7% methanol - CH_2Cl_2) to afford **145** (37 mg, 95%) as off white solid.

Mp: 160 - 162 °C

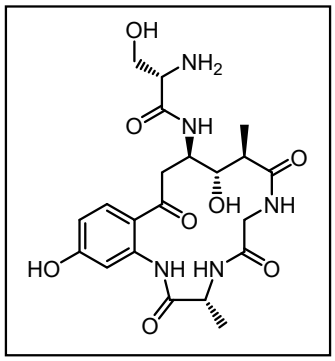
$[\alpha]_D^{27}$: + 22.8 (*c* 0.1, MeOH)

^{1}H NMR (400MHz, CD_3OD): δ 7.29 (d, *J* = 8.31 Hz, 1H), 7.00 (brs, 1H), 6.64 - 6.70 (m, 1H), 5.95 (dd, *J* = 3.18, 15.89 Hz, 1H), 5.17 (brs., 1H), 4.46 - 4.54 (m, 1H), 4.43 (brs, 1H), 4.16 (d, *J* = 13.20 Hz, 1H), 3.97 - 4.05 (m, 1H), 3.83 (brs., 2H), 3.69 - 3.80 (m, 1H), 2.41 - 2.49 (m, 1H), 1.54 (d, *J* = 7.34 Hz, 2H), 1.45 (s, 9H), 1.24 (d, *J* = 6.85 Hz, 3H)

^{13}C NMR (100MHz, CD_3OD): δ 177.9, 172.8, 171.8, 157.2, 156.5, 135.2, 129.1, 127.0, 125.3, 123.3, 113.4, 79.4, 65.5, 61.8, 57.0, 54.5, 53.7, 50.6, 42.9, 27.3, 15.3, 14.8.

HRMS: calculated for $C_{26}H_{37}O_9N_5Na$ $[M+Na]^+$: 586.2483, found 586.2491

(*S*)-2-amino-*N*-((3*R*,9*R*,10*S*,11*R*)-10,16-dihydroxy-3,9-dimethyl-2,5,8,13-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-benzo[*h*][1,4,7]triazacyclopentadecin-11-yl)-3-hydroxypropanamide (146) :

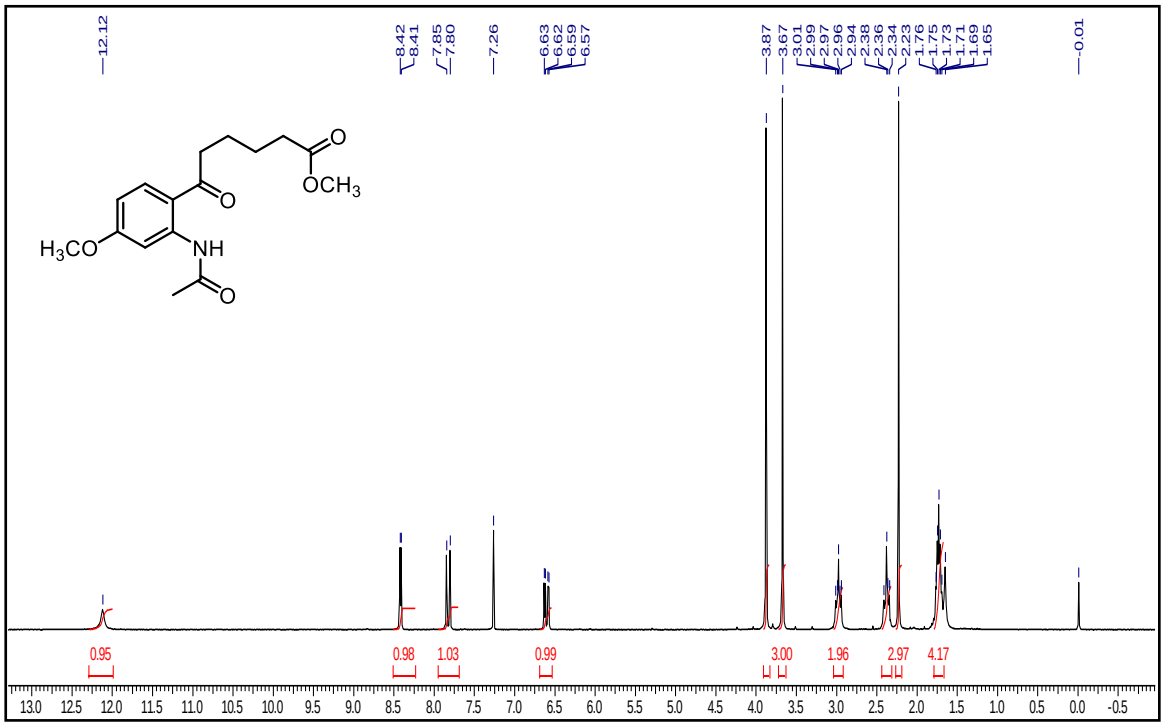


To a stirred solution of $PdCl_2$ (10 mol%), CuCl (5 mg, 0.05 mmol) in DMF-water (3 mL, 2:1) compound **145** (30 mg, 0.05 mmol) was added and heated at 65 °C under O_2 atmosphere for 8h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed water (5 mL) and brine (5 mL) organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure. The reaction mixture was filtered through the silica gel column and the residue was dissolved in CH_2Cl_2 (3 mL), TFA (0.3 mL) was added at 0 °C and the resulting suspension was stirred for 2h at the same temperature. Concentrated the reaction mixture and azeotroped with toluene (3 mL x 3), acetonitrile (3 mL x 3) and dried under vacuum to afford compound **146** (19 mg, 61% for 2 steps) as off white solid.

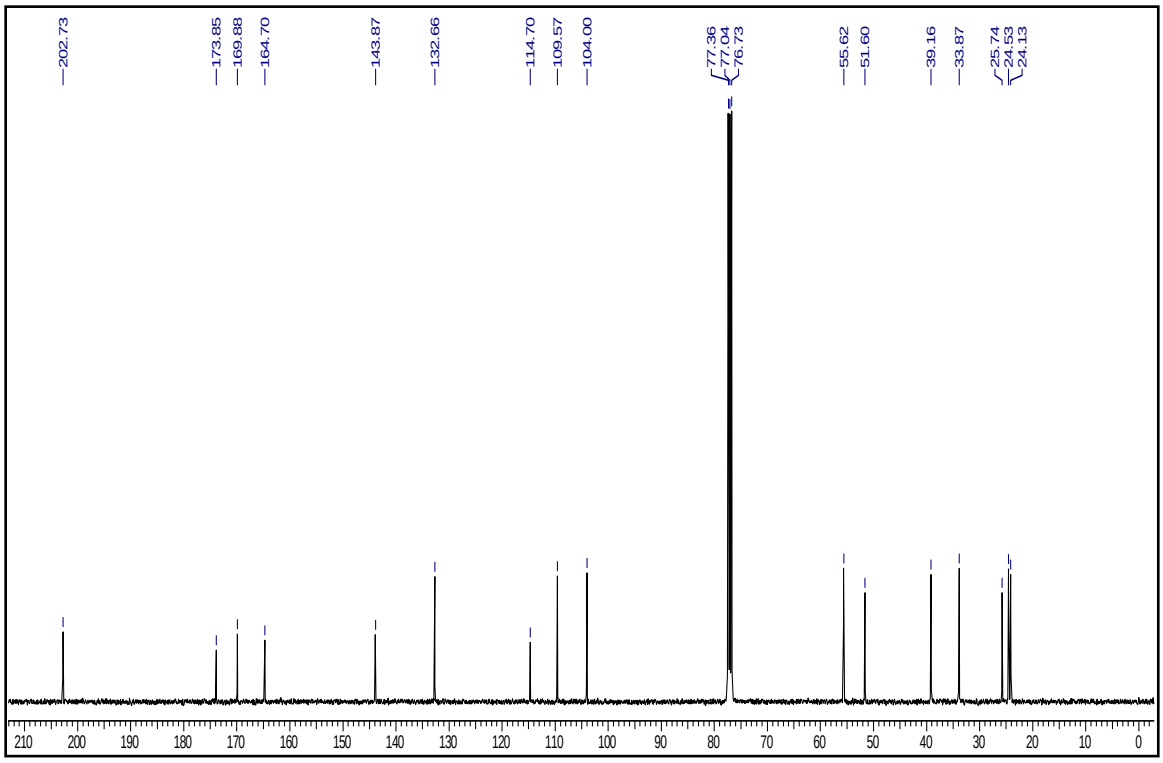
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (s, 1H), 10.60 (br. s., 1H), 9.24 (d, *J* = 4.89 Hz, 1H), 8.61 (s, 1H), 8.37 (d, *J* = 7.82 Hz, 1H), 8.09 (brs., 2H), 7.83 (d, *J* = 8.80 Hz, 1H), 7.35 (brs., 1H), 6.48 - 6.63 (m, 2H), 5.45 (brs., 1H), 4.59 (d, *J* = 9.29 Hz, 1H), 4.28 (d, *J* = 14.67 Hz, 1H), 3.65 - 3.82 (m, 3H), 3.50 (d, *J* = 13.20 Hz, 1H), 2.67 (brs., 1H), 1.39 (d, *J* = 7.34 Hz, 3H), 1.13 (d, *J* = 7.34 Hz, 3H)

HRMS: calculated for $C_{29}H_{30}O_8N_5$ $[M+H]^+$: 480.2089, found 480.2087.

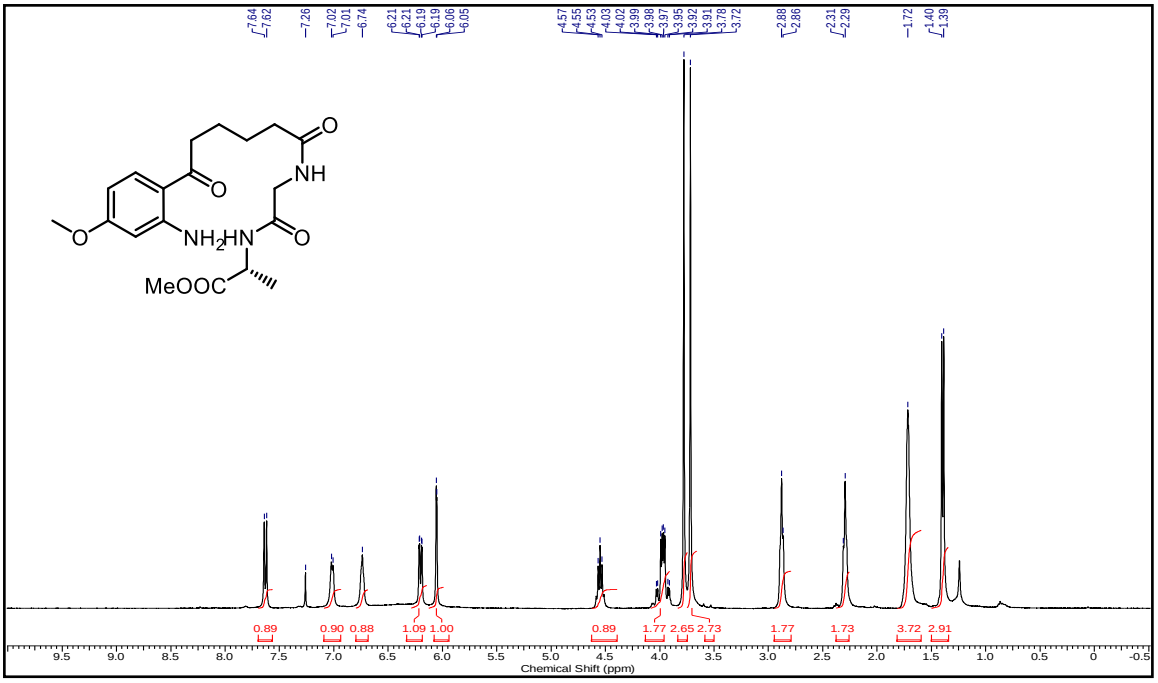
^{1}H NMR (400 MHz, $CDCl_3$) of compound 39



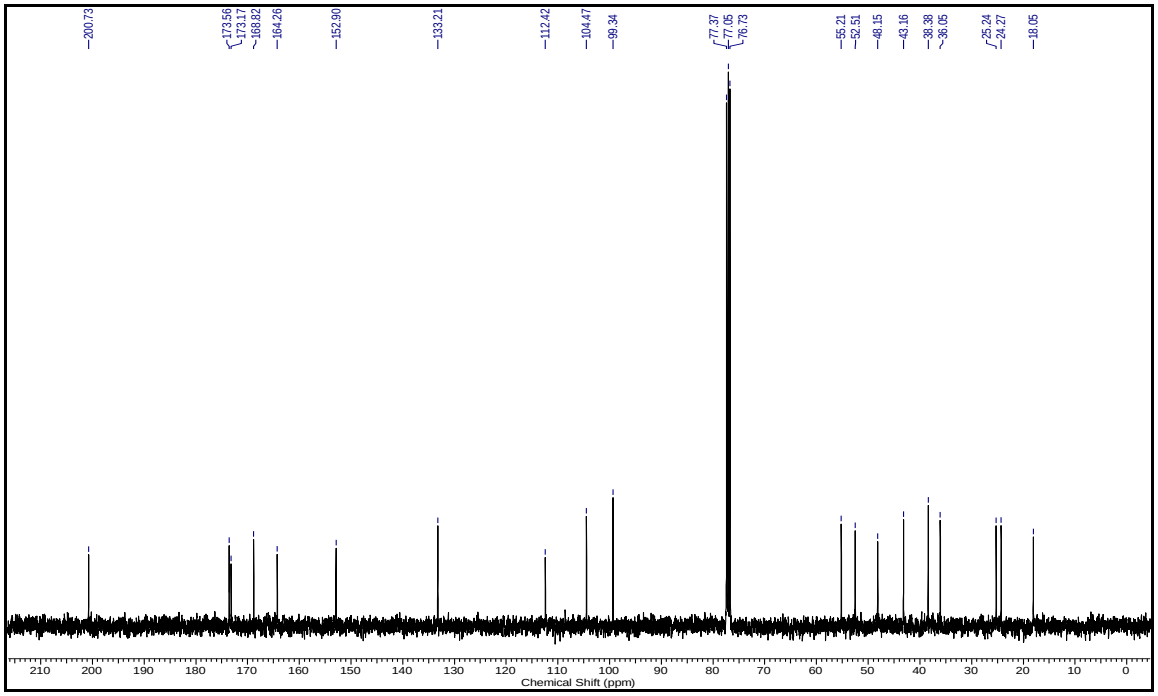
^{13}C NMR (100 MHz, $CDCl_3$) of compound 39



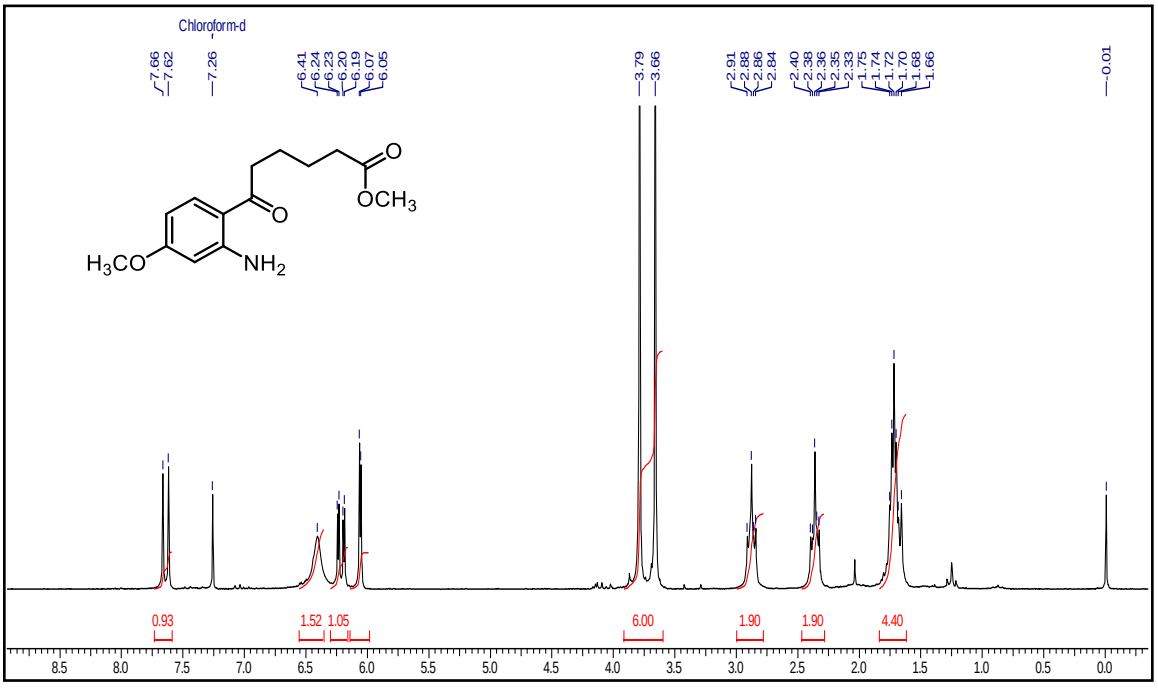
^{1}H NMR (400 MHz, $CDCl_3$) of compound 43



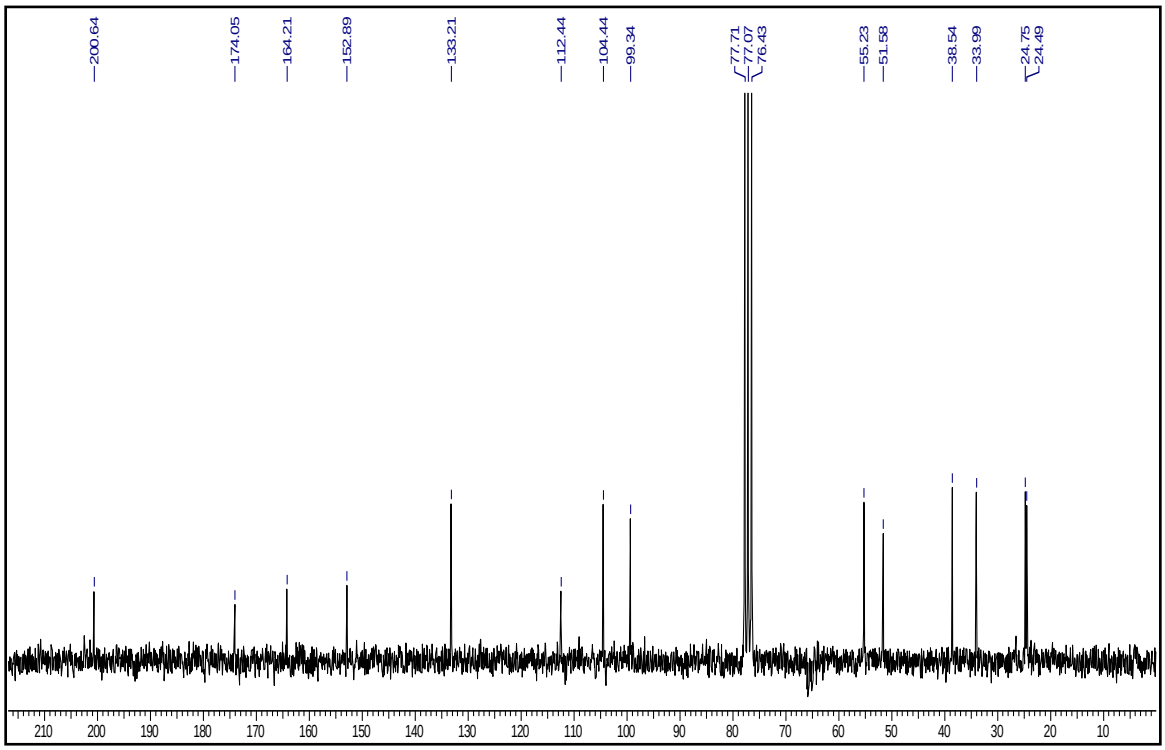
^{13}C NMR (100 MHz, $CDCl_3$) of compound 43



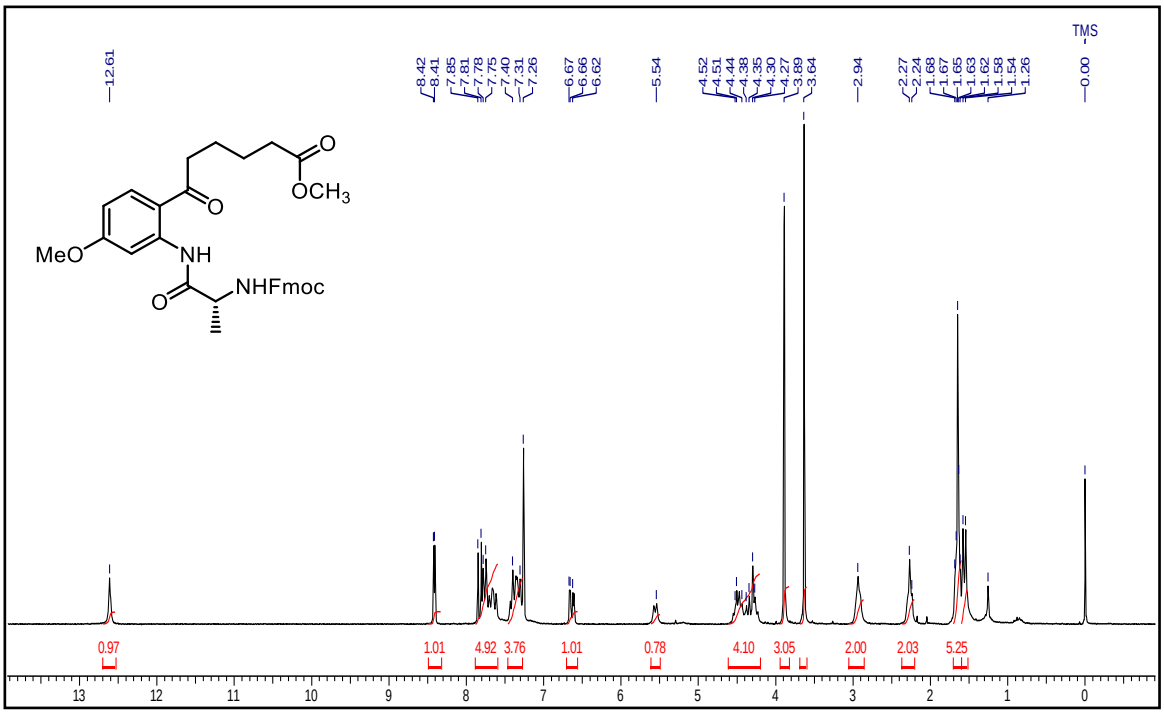
^{1}H NMR (200 MHz, $CDCl_3$) of compound 45



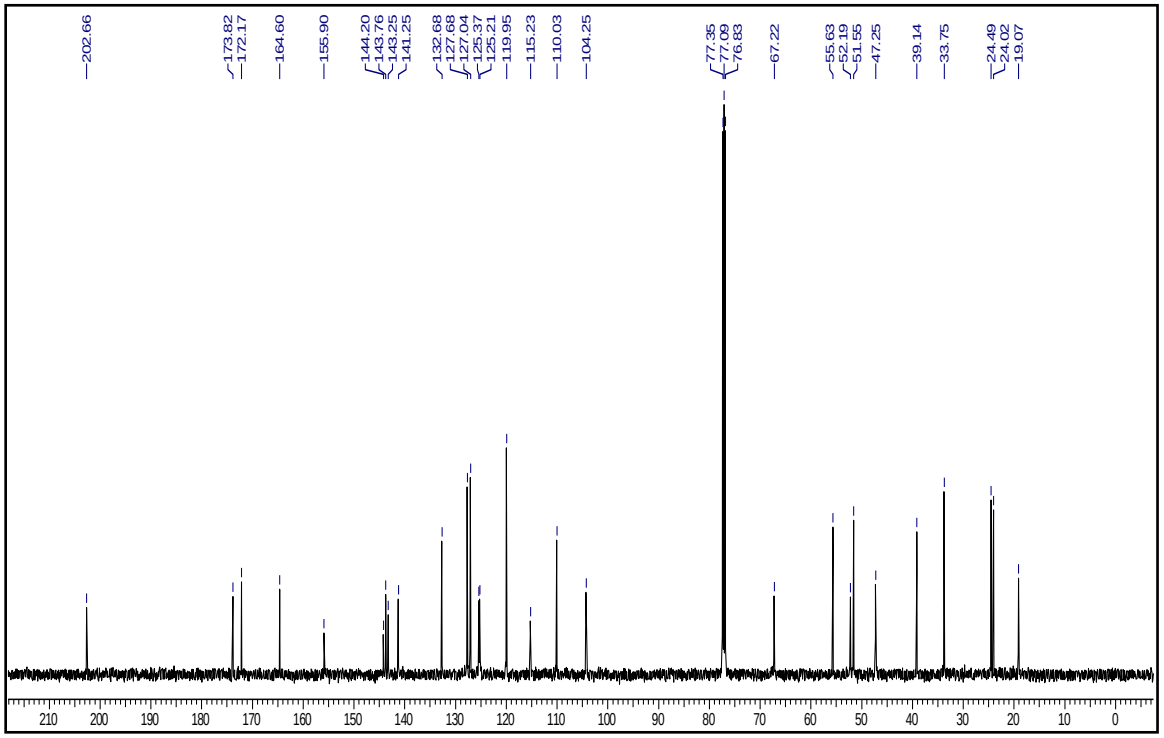
^{13}C NMR (100 MHz, $CDCl_3$) of compound 45



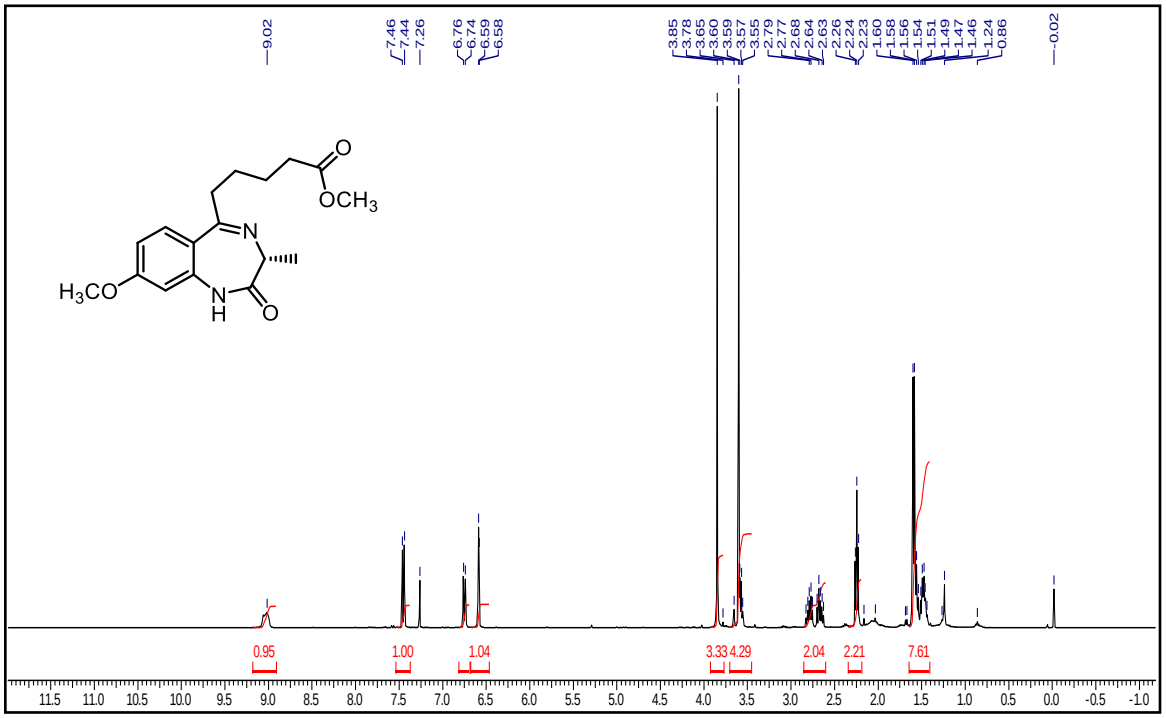
^{1}H NMR (200 MHz, $CDCl_3$ of compound 49



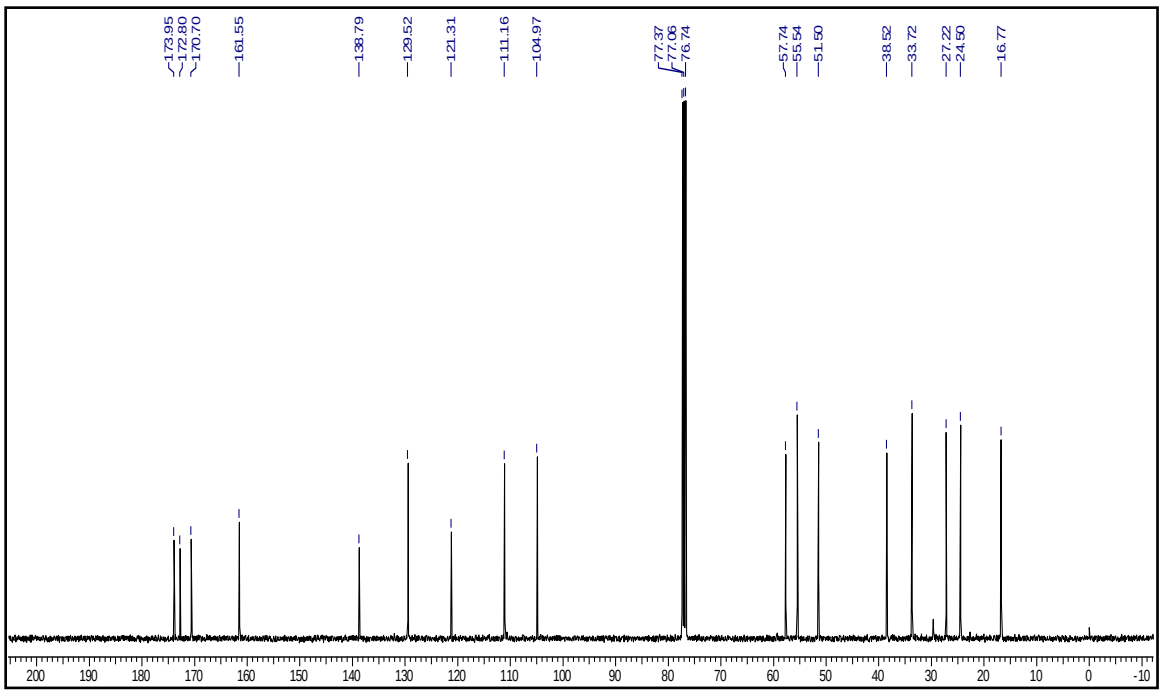
^{13}C NMR (125 MHz, $CDCl_3$) of compound 49



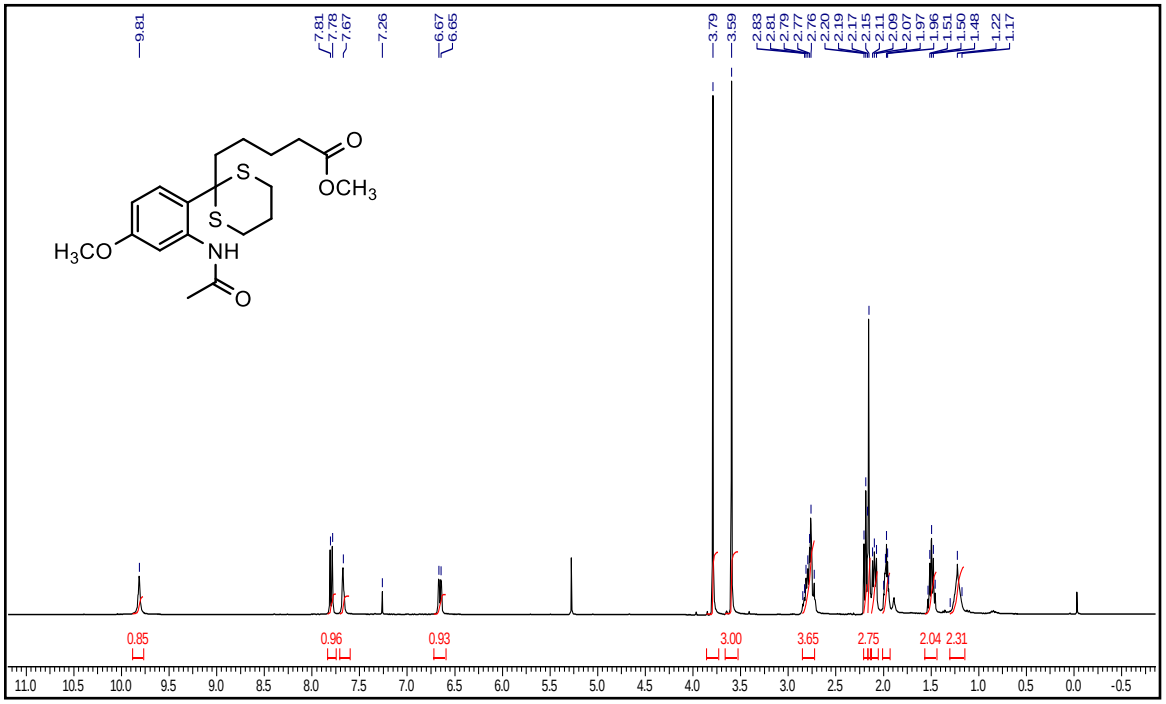
H NMR (400 MHz, $CDCl_3$ of compound 50



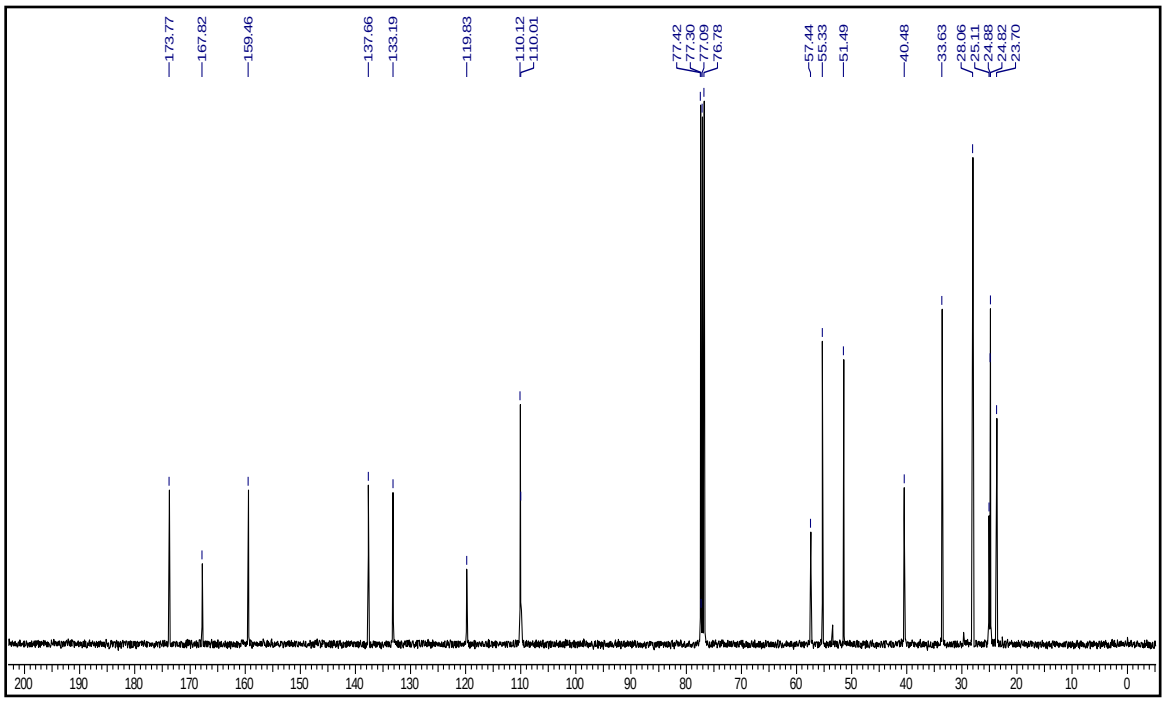
^{13}C NMR (100 MHz, $CDCl_3$ of compound 50



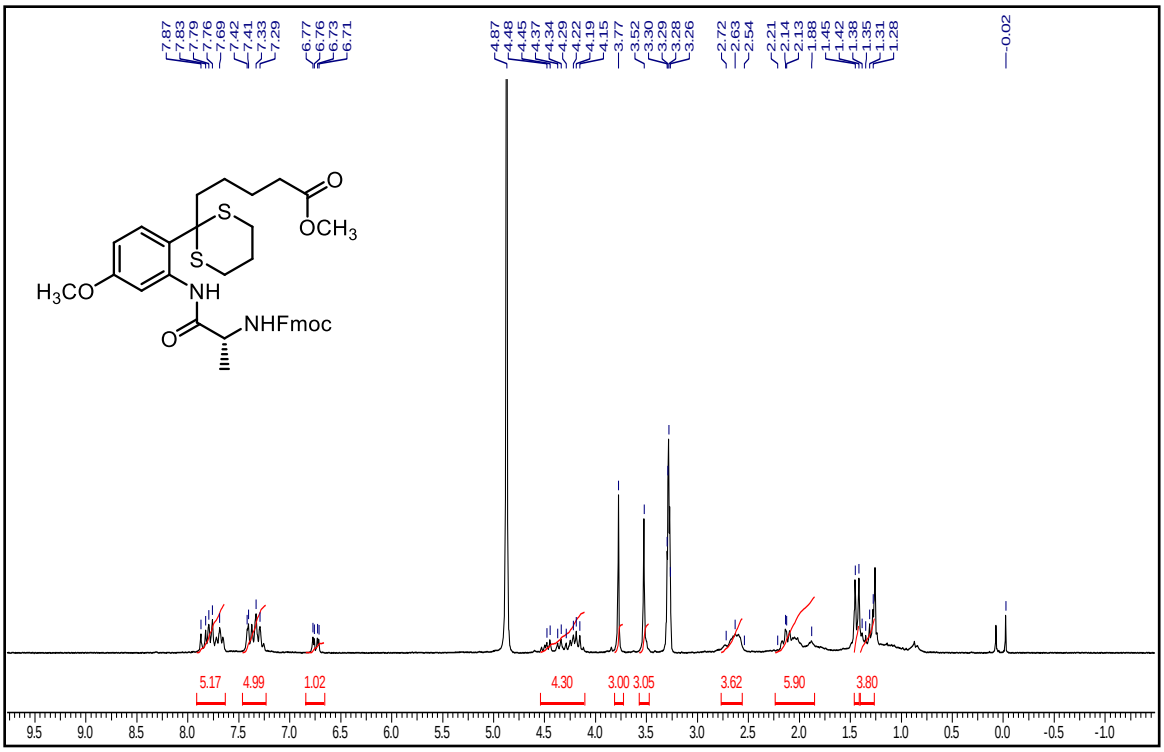
^{1}H NMR (400 MHz, $CDCl_3$ of compound 58



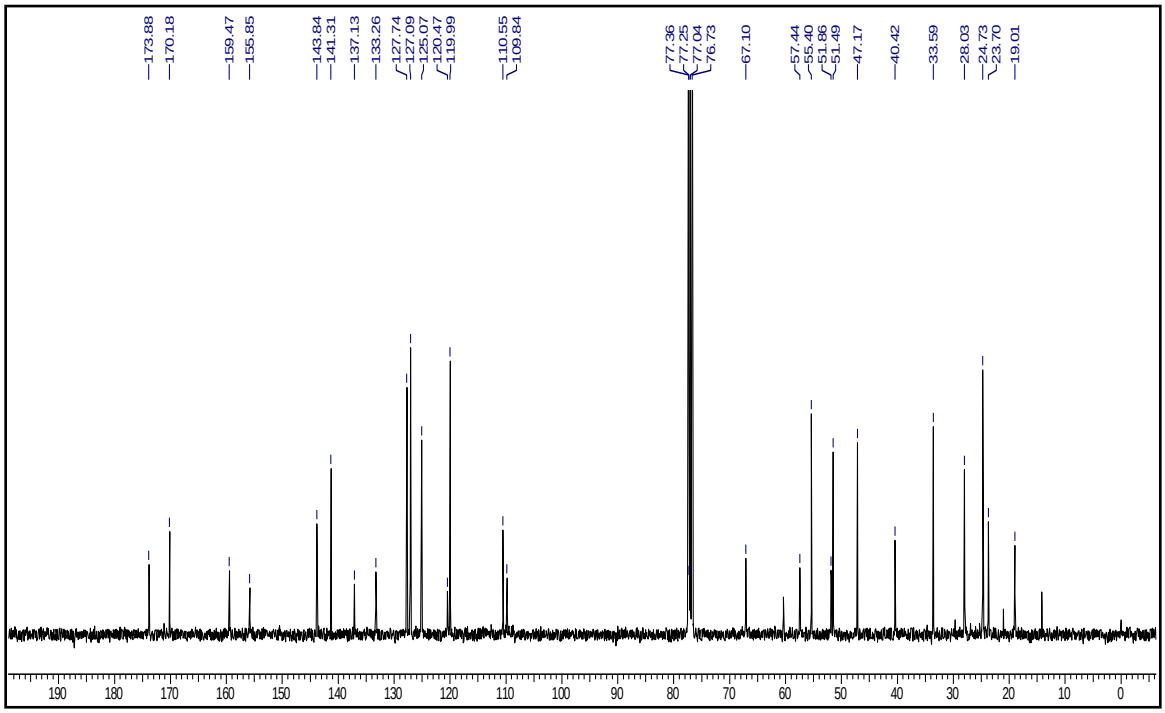
^{13}C NMR (100 MHz, $CDCl_3$) of compound 58



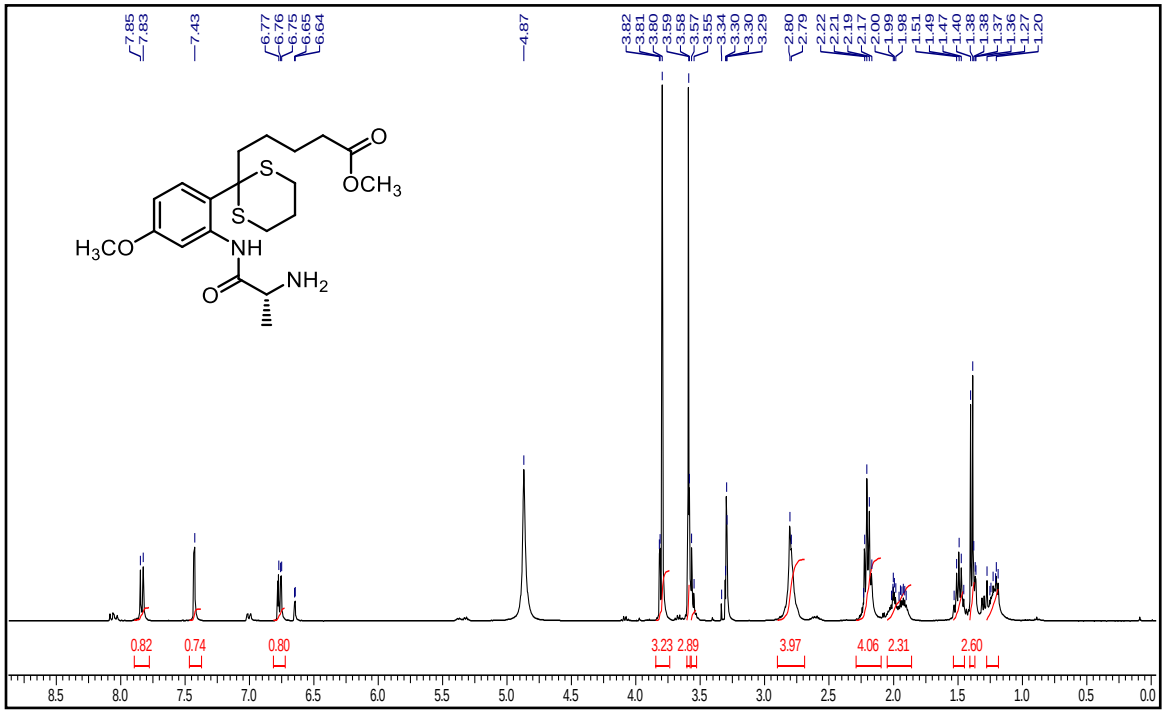
^{1}H NMR (200 MHz, CD_3OD) of compound 59



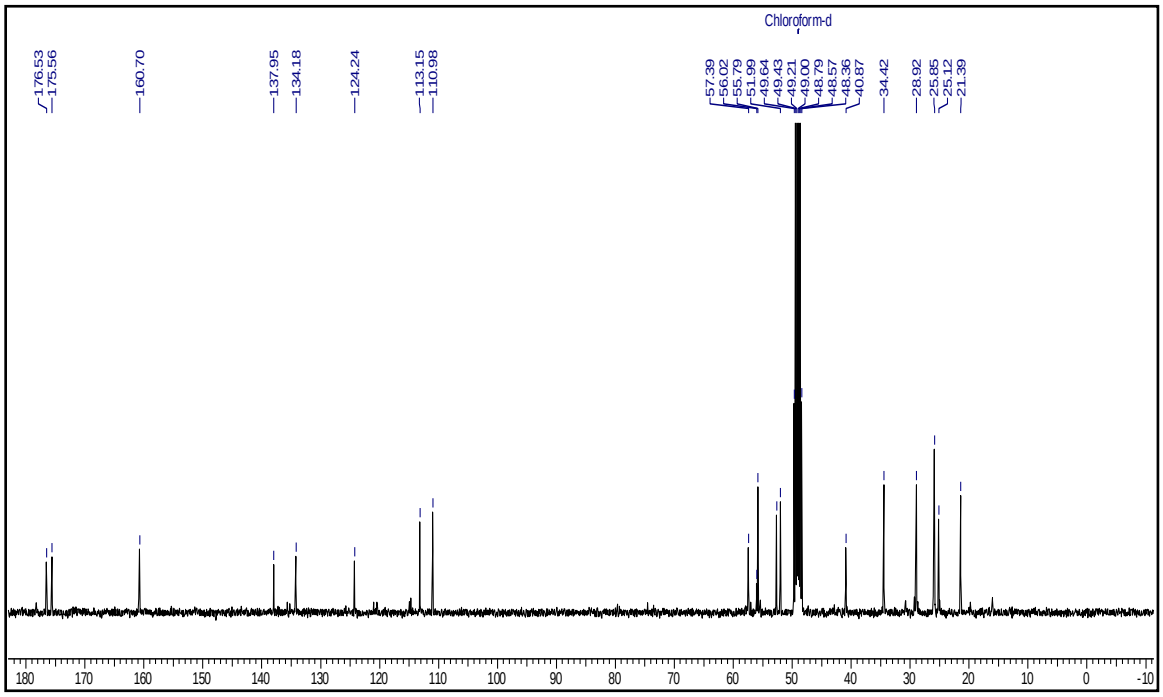
^{13}C NMR (100 MHz, $CDCl_3$) of compound 59



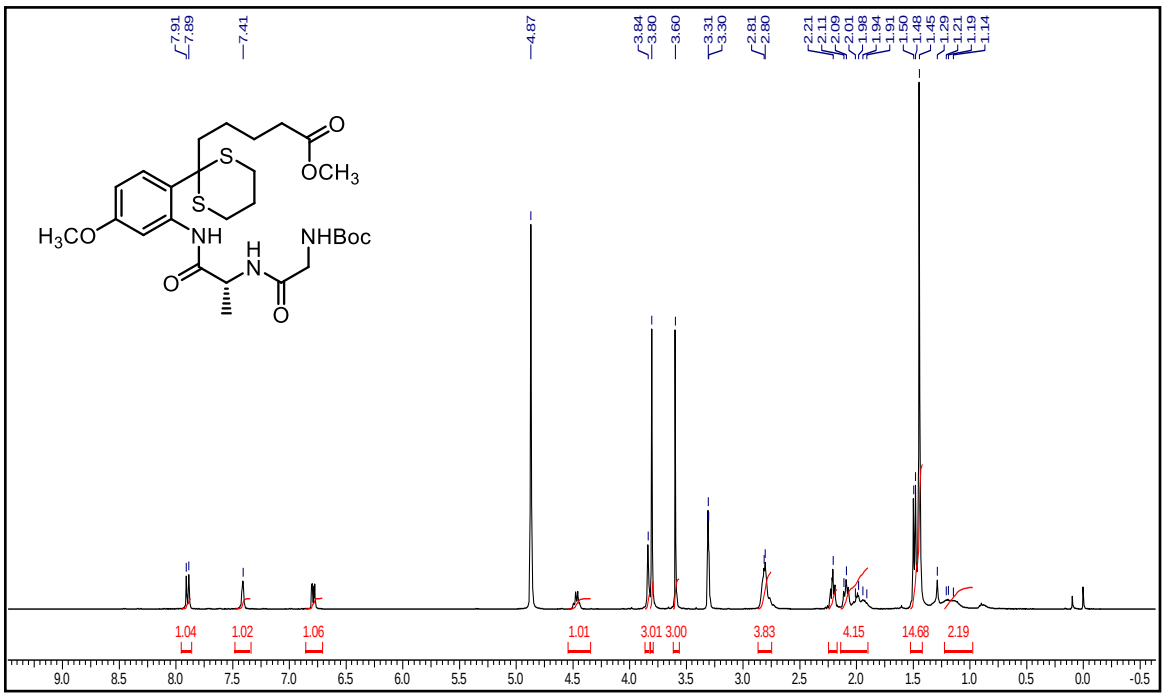
^{1}H NMR (400 MHz, CD_3OD) of compound 60



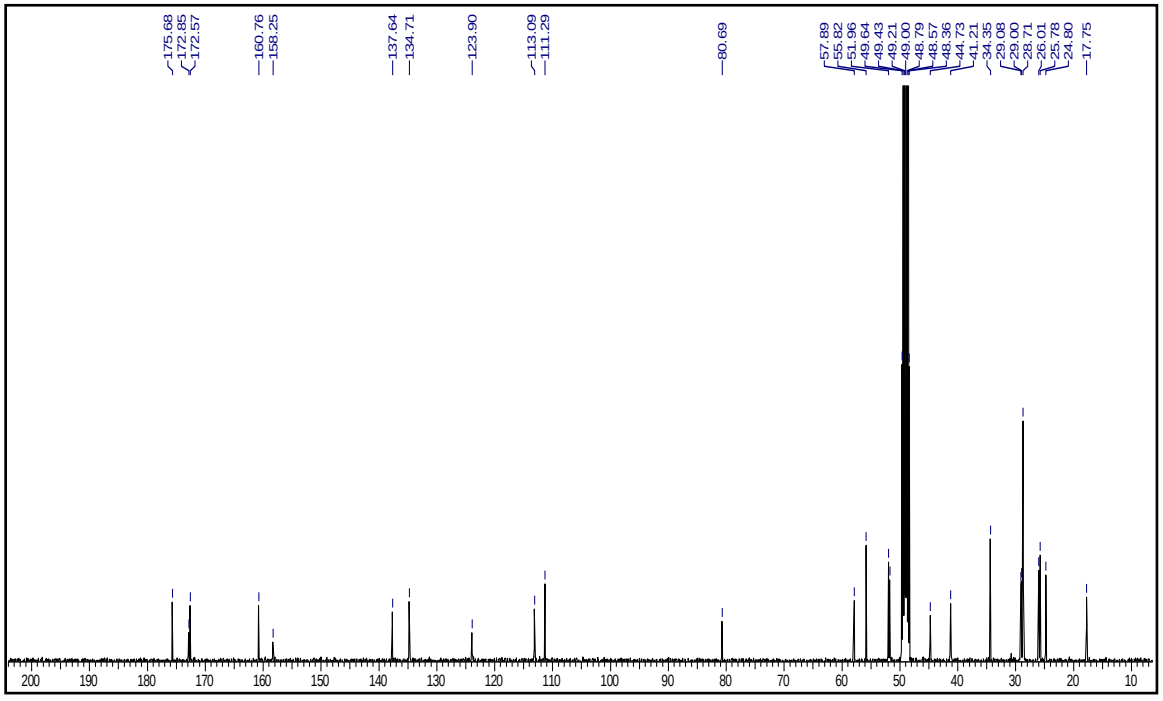
^{13}C NMR (100 MHz, $CDCl_3$) of compound 60



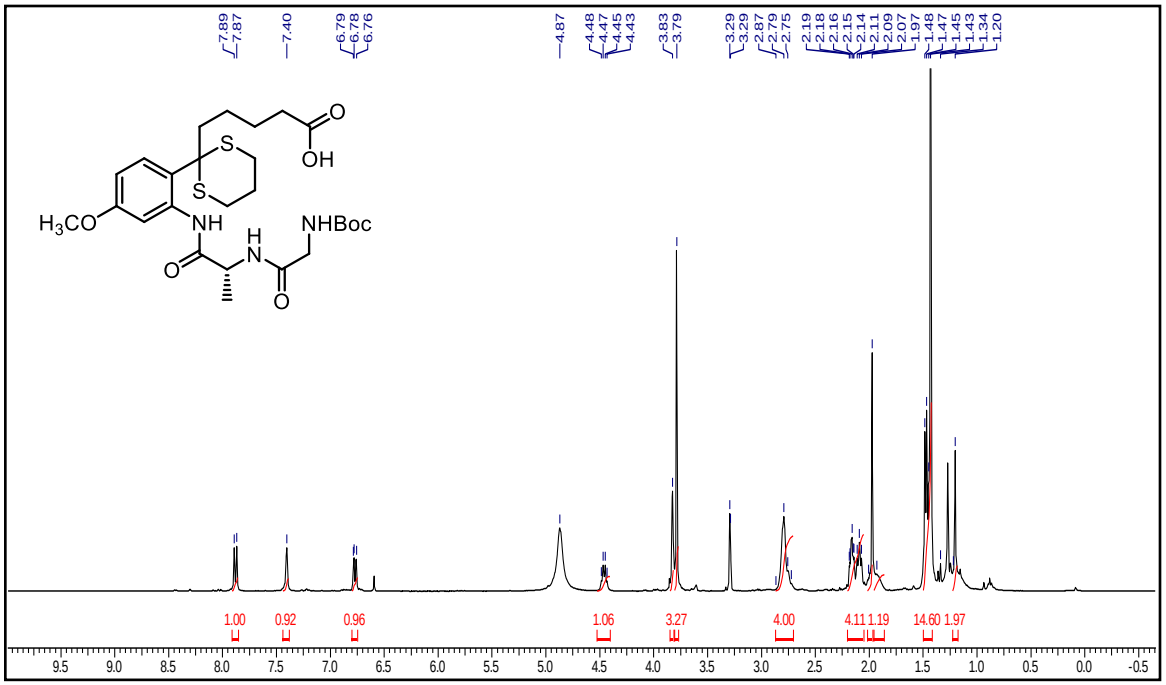
^{1}H NMR (400 MHz, CD_3OD) of compound 61



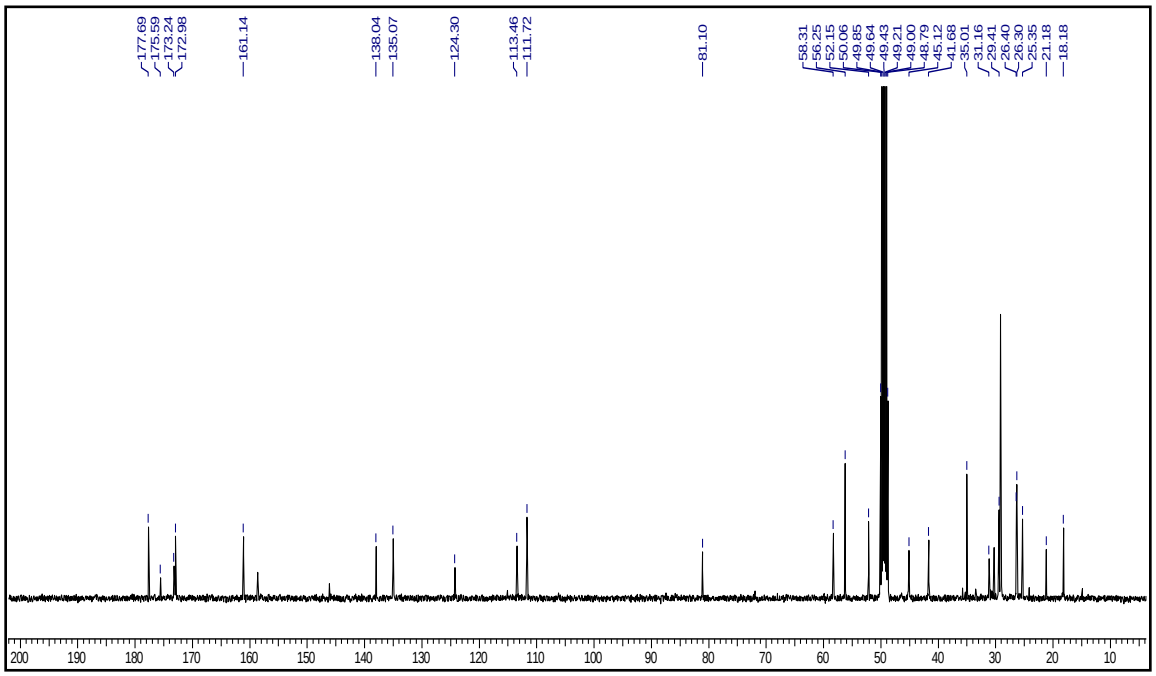
^{13}C NMR (100 MHz, CD_3OD) of compound 61



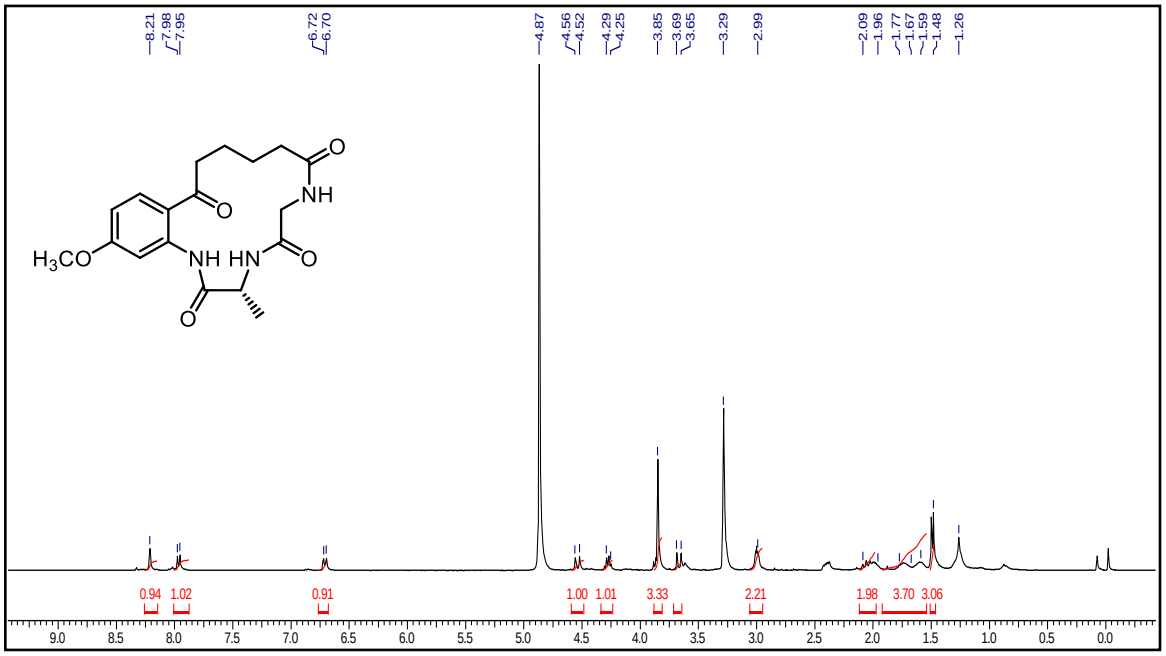
^{1}H NMR (400 MHz, CD_3OD) of compound 62



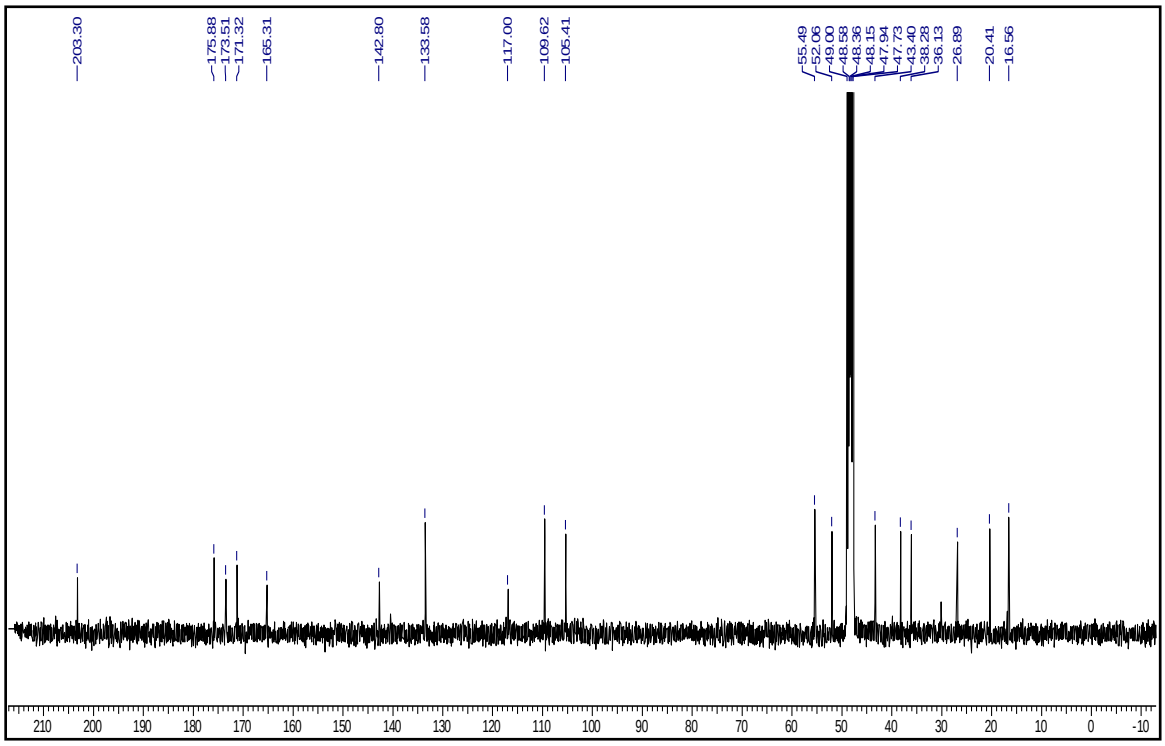
^{13}C NMR (100 MHz, CD_3OD) of compound 62



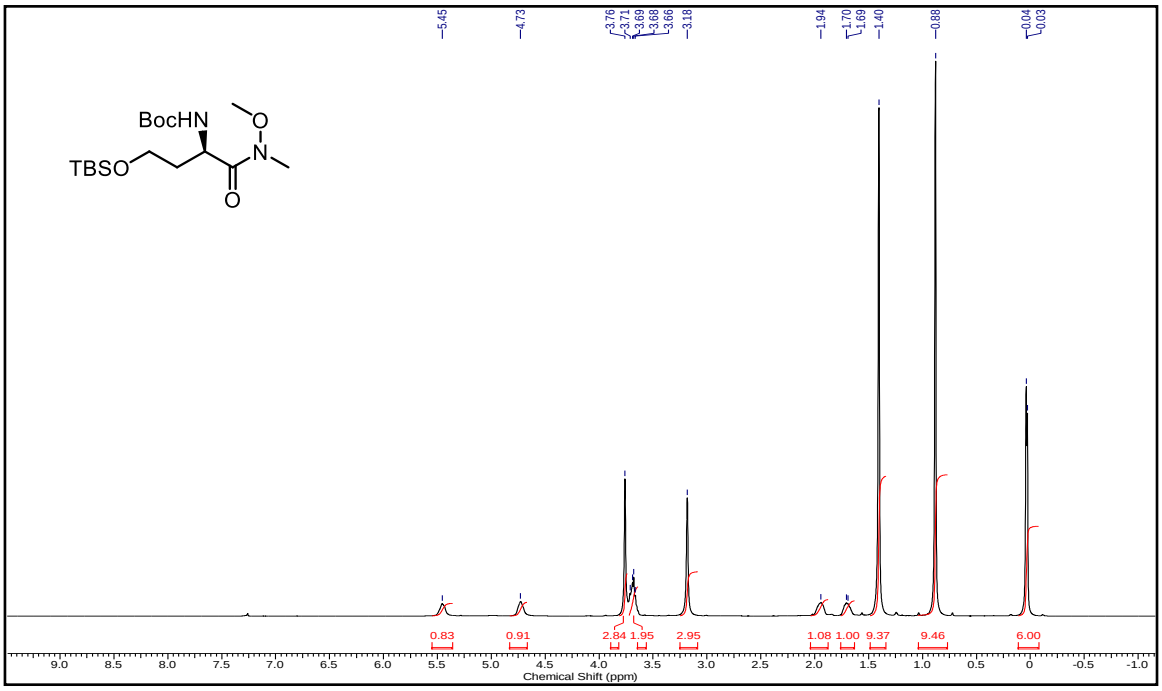
^{1}H NMR (400 MHz, CD_3OD) of compound 44



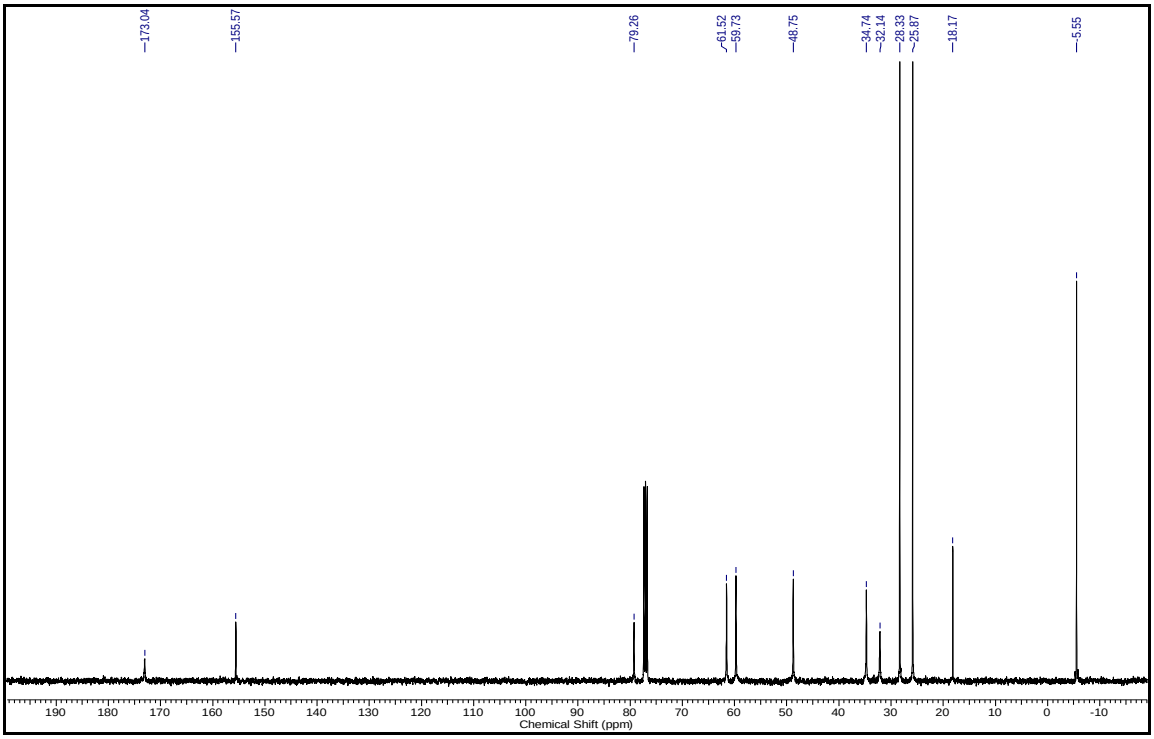
^{13}C NMR (100 MHz, CD_3OD) of compound 44



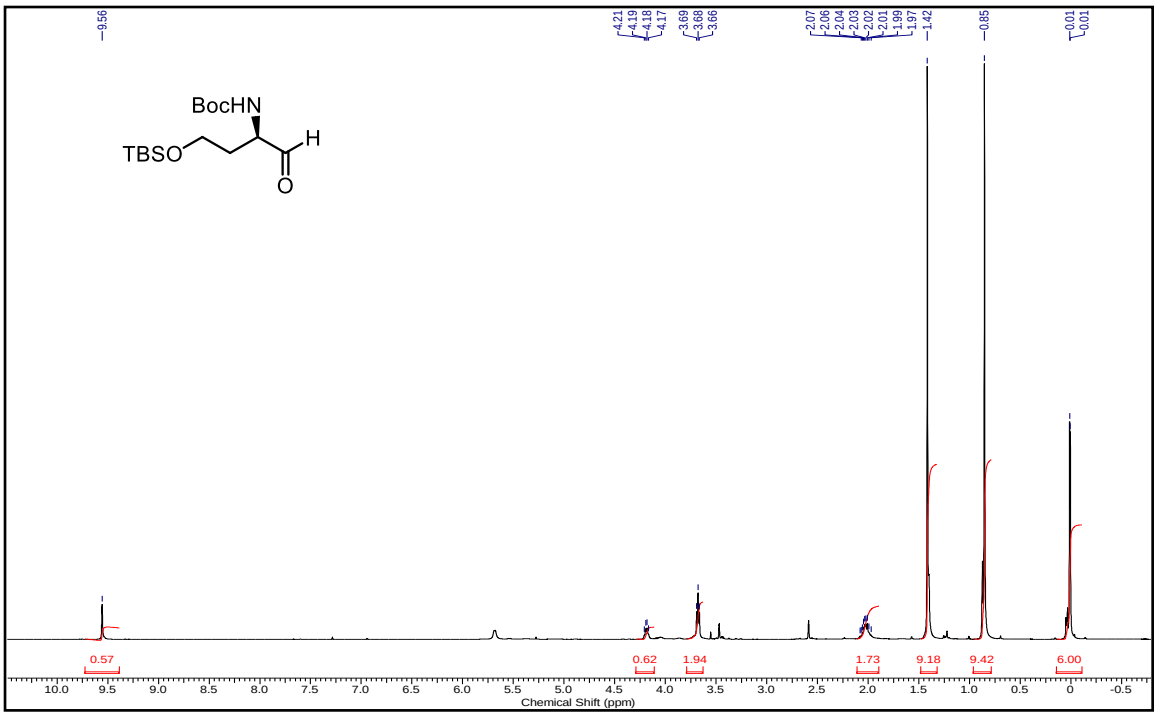
^{1}H NMR (400 MHz, $CDCl_3$) of compound 64



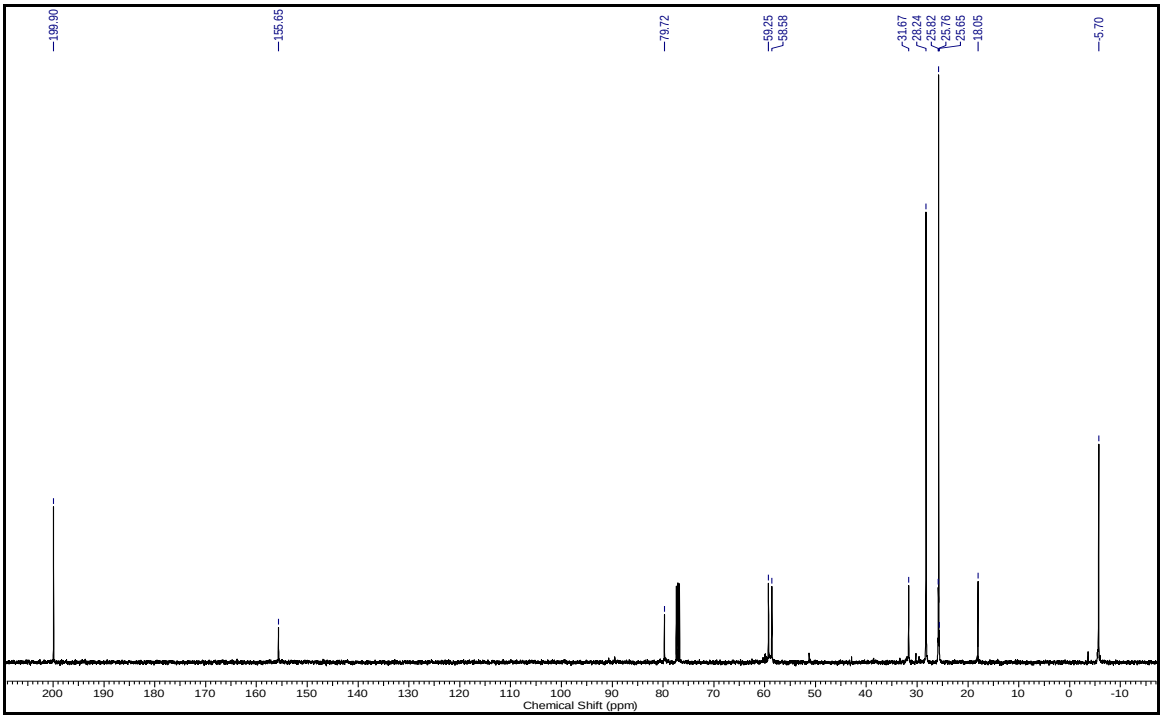
^{13}C NMR (100 MHz, $CDCl_3$) of compound 64



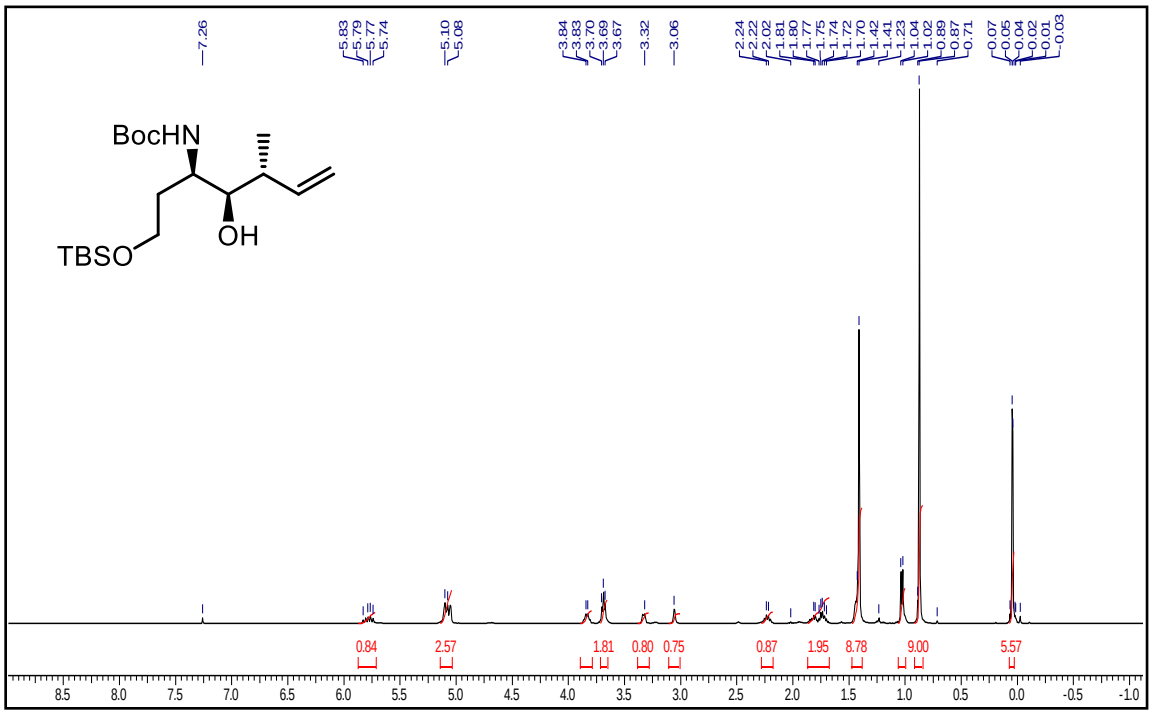
^{1}H NMR (400 MHz, $CDCl_3$) of compound 65



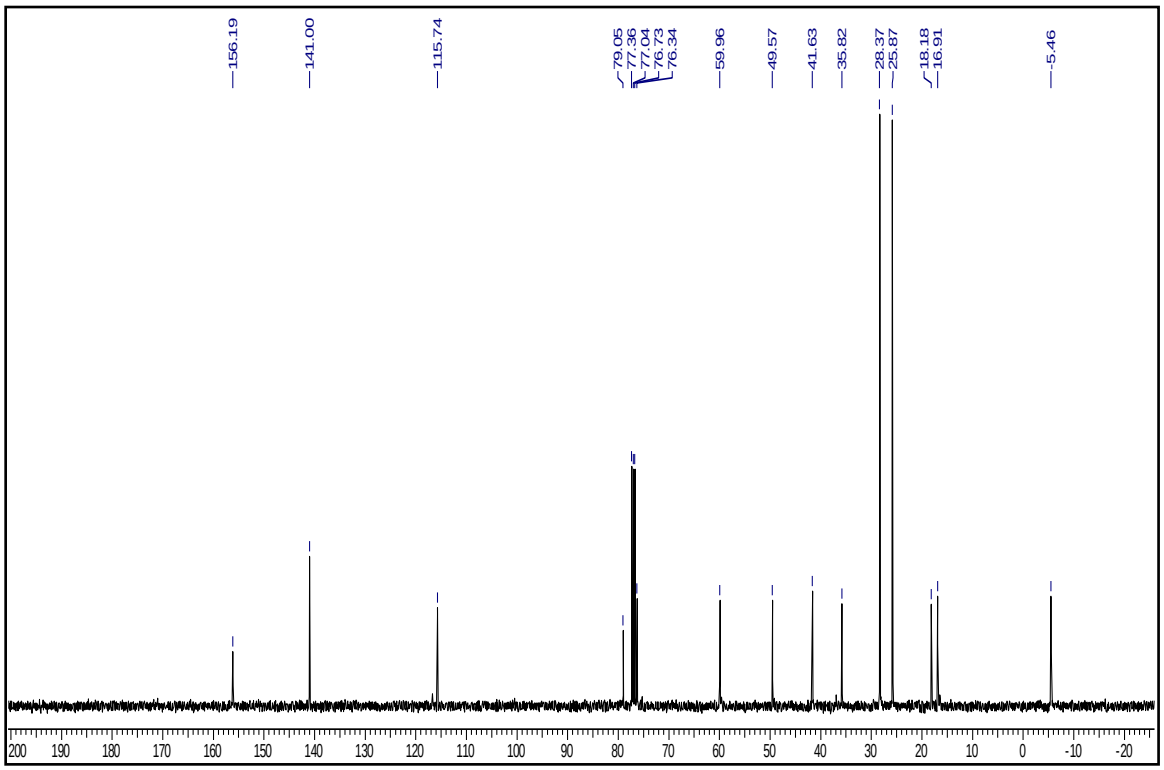
^{13}C NMR (100 MHz, $CDCl_3$) of compound 65



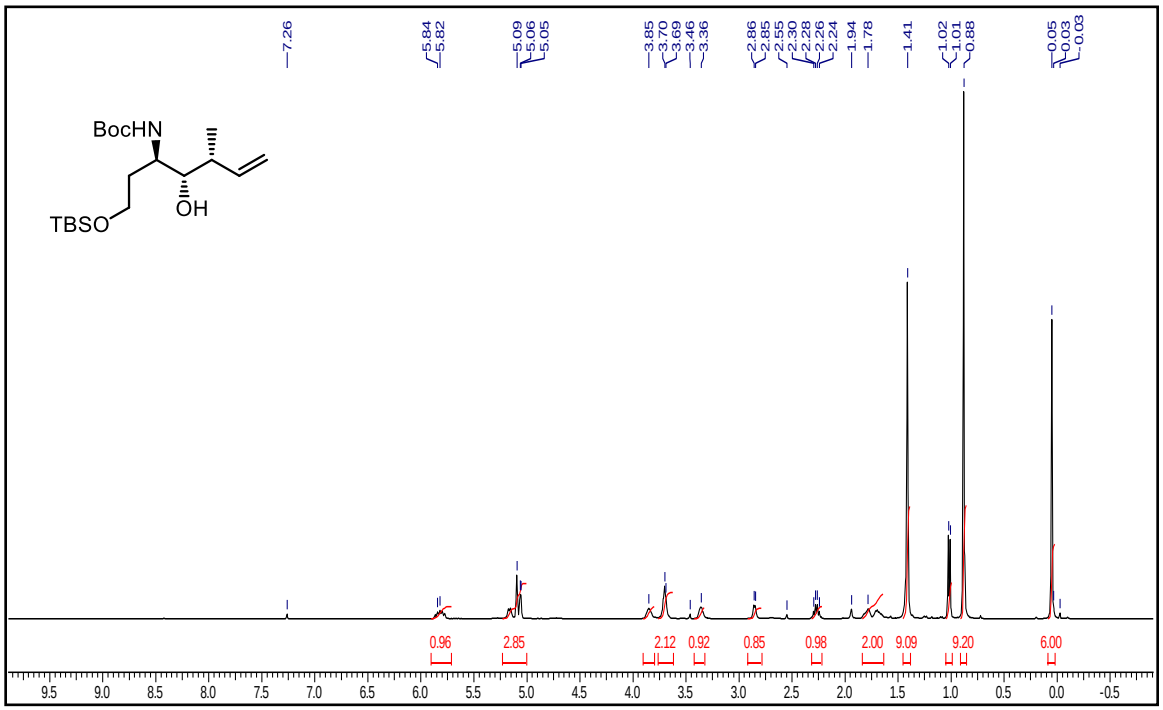
^{1}H NMR (400 MHz, $CDCl_3$) of compound 66



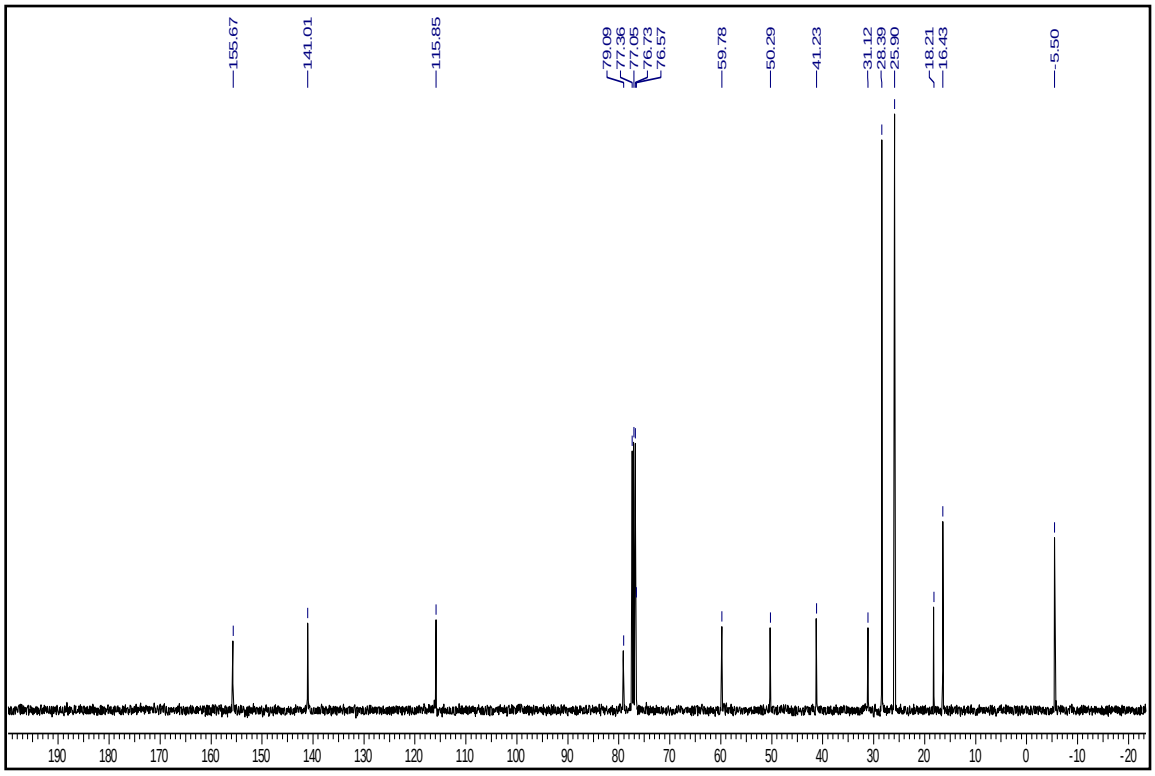
^{13}C NMR (100 MHz, $CDCl_3$) of compound 66



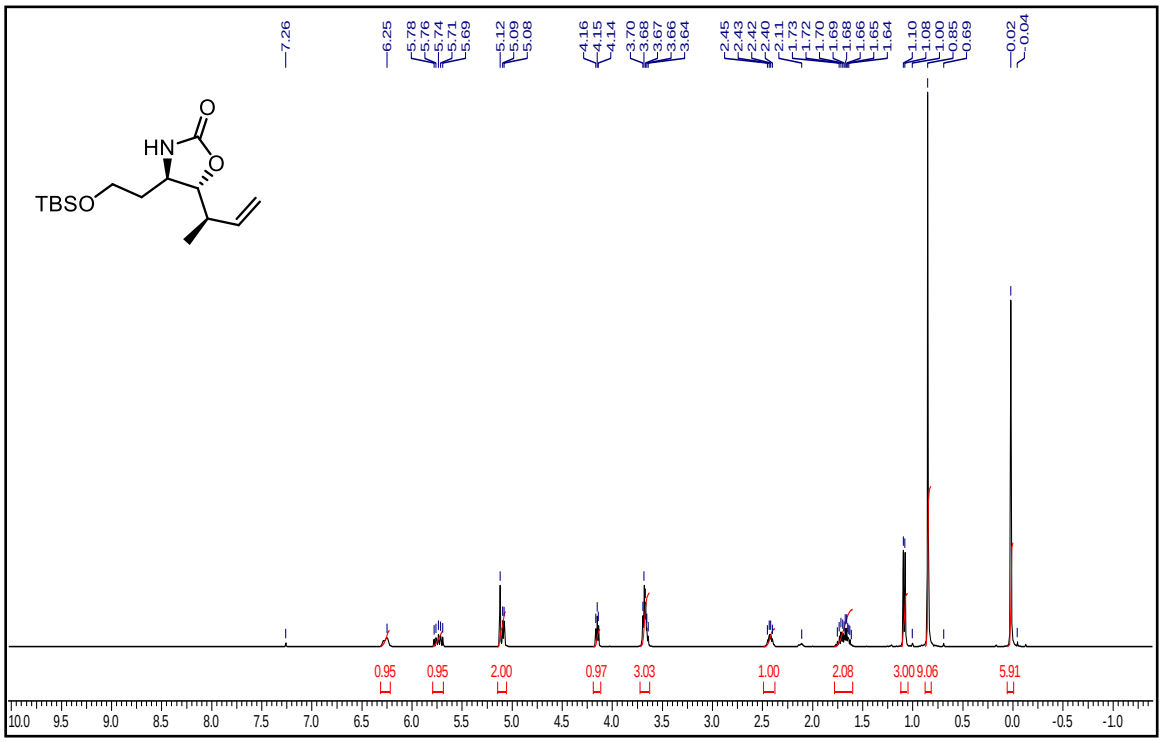
^{1}H NMR (400 MHz, $CDCl_3$) of compound 67



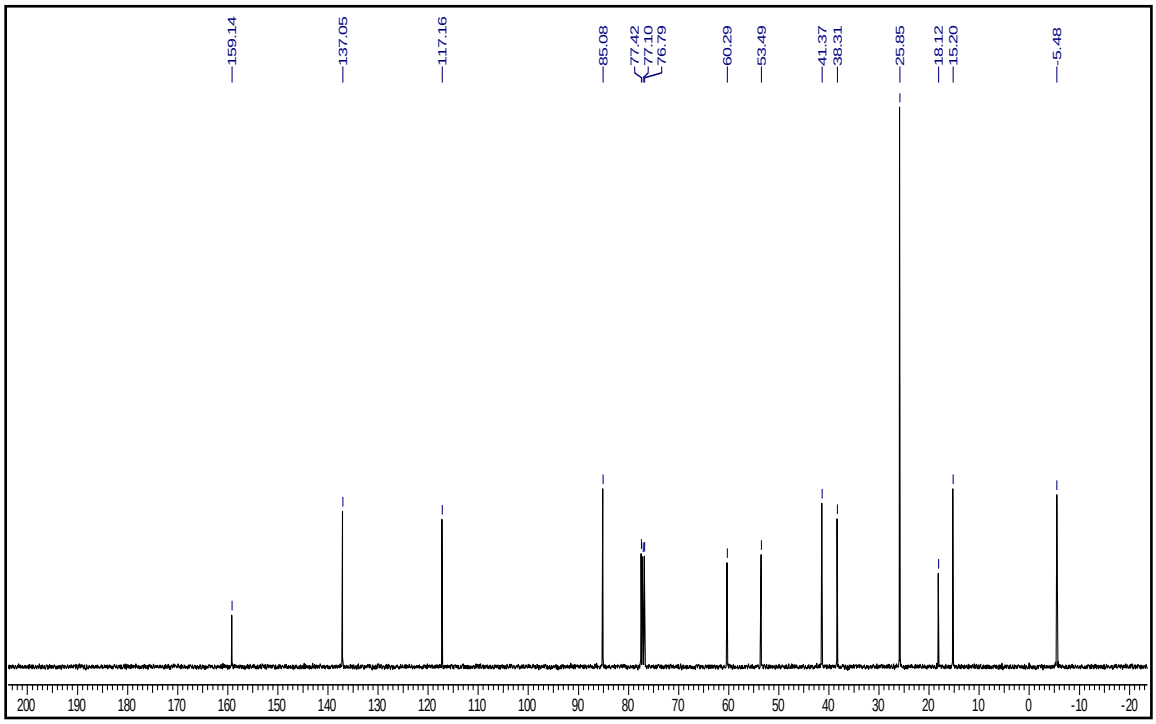
^{13}C NMR (100 MHz, $CDCl_3$) of compound 67



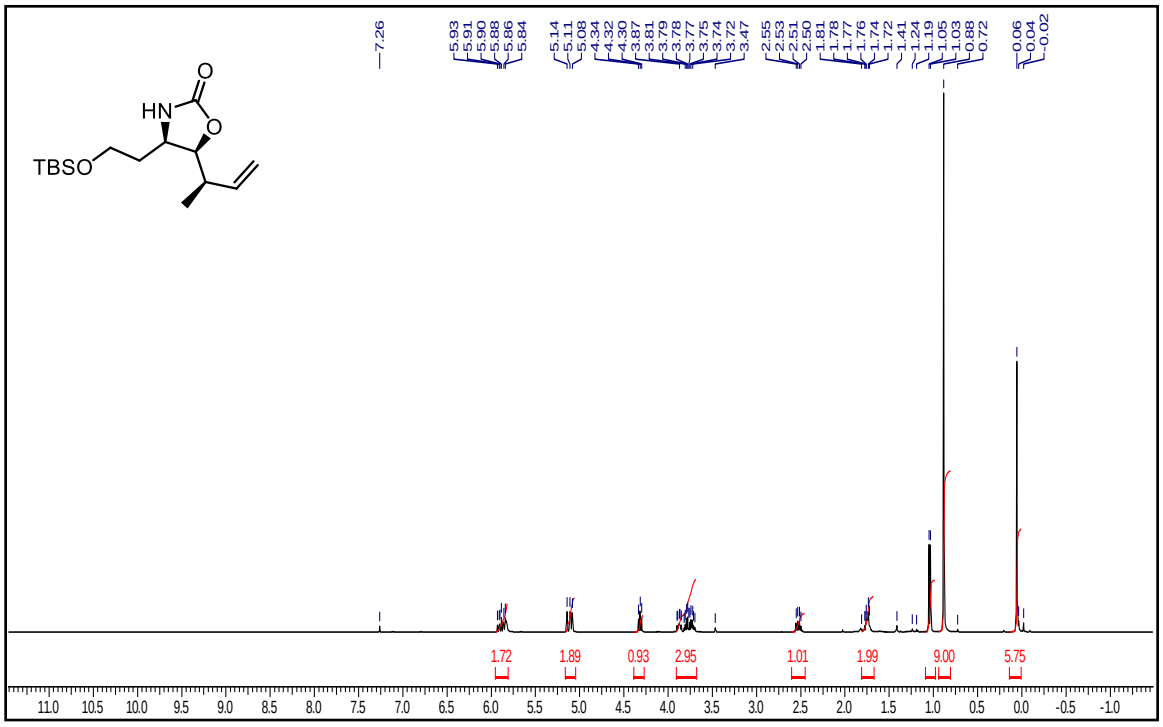
^{1}H NMR (400 MHz, $CDCl_3$) of compound 66'



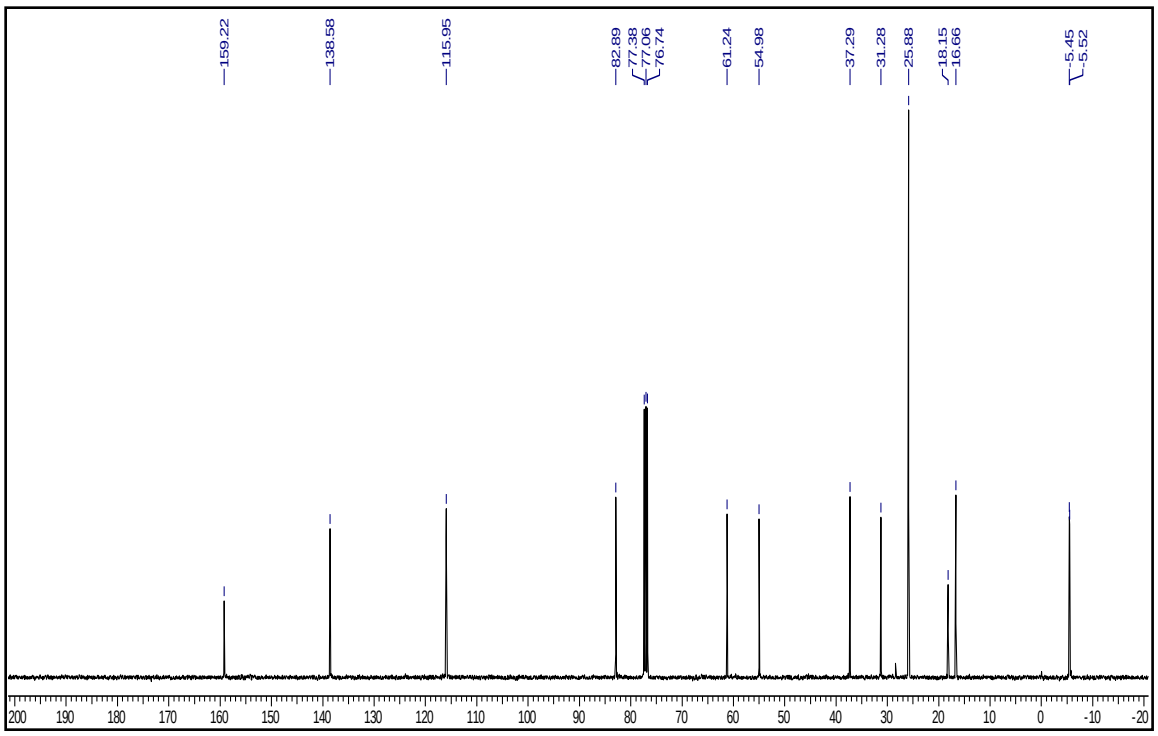
^{13}C NMR (100 MHz, $CDCl_3$) of compound 66'



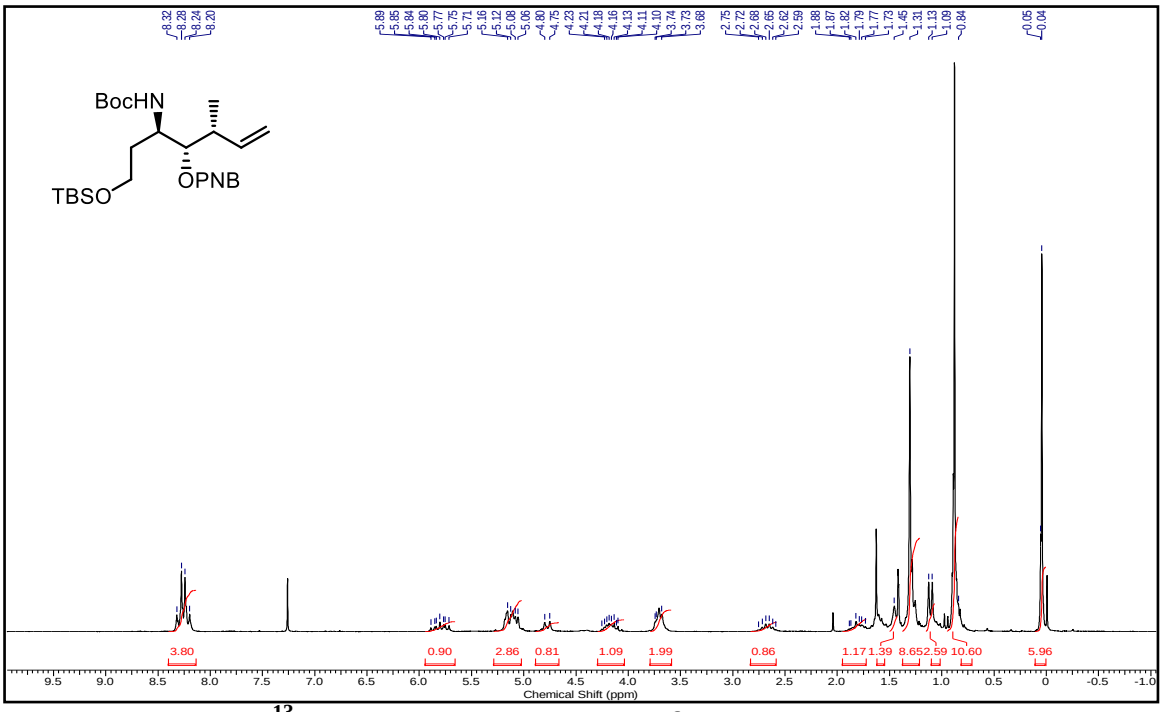
^{1}H NMR (400 MHz, $CDCl_3$) of compound 67'



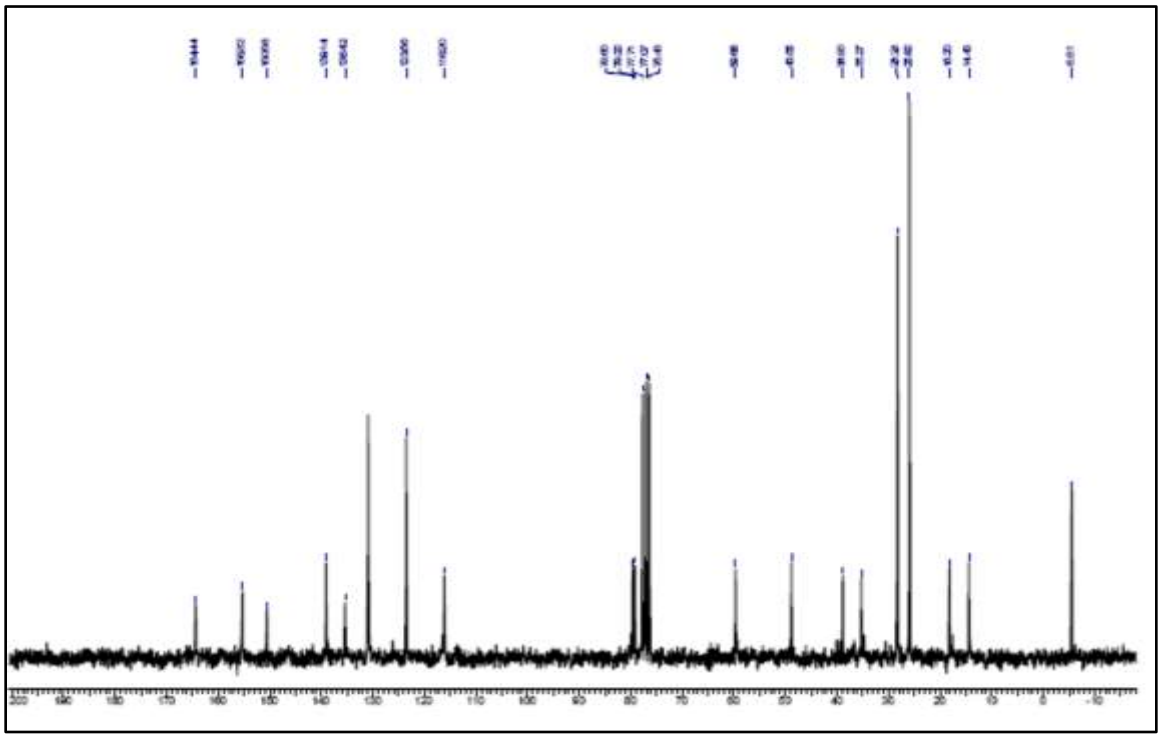
^{13}C NMR (100 MHz, $CDCl_3$) of compound 67'



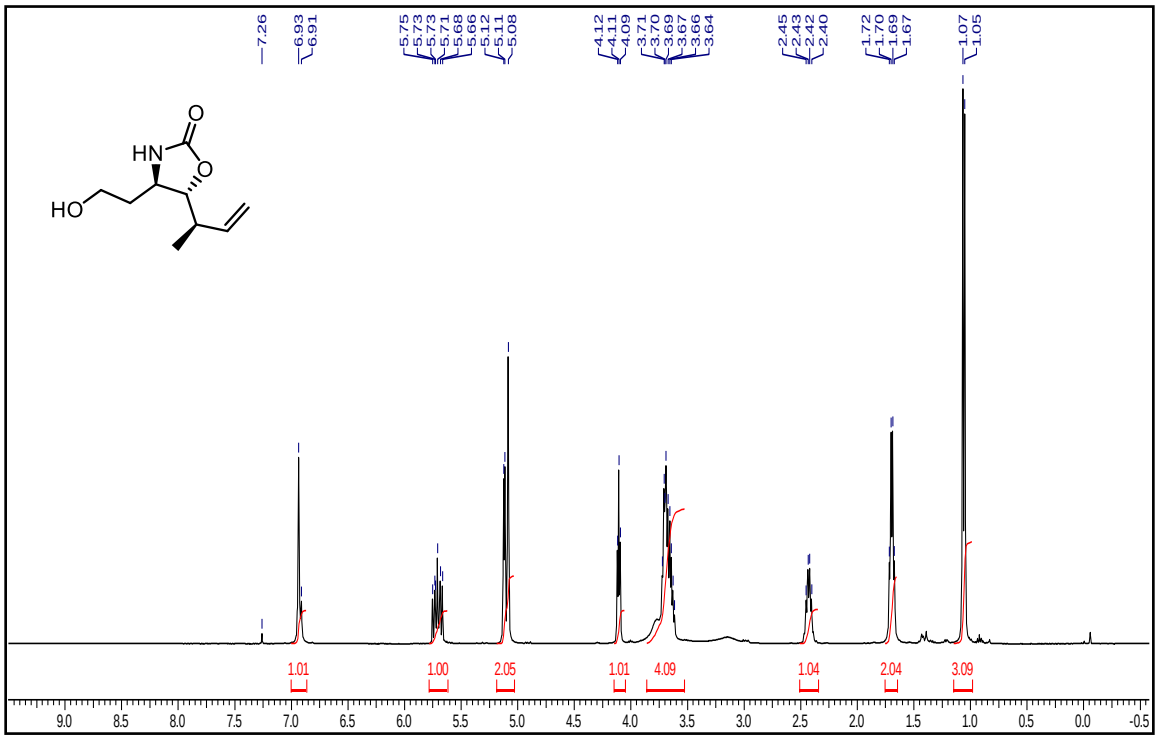
^{1}H NMR (200 MHz, $CDCl_3$) of compound 68



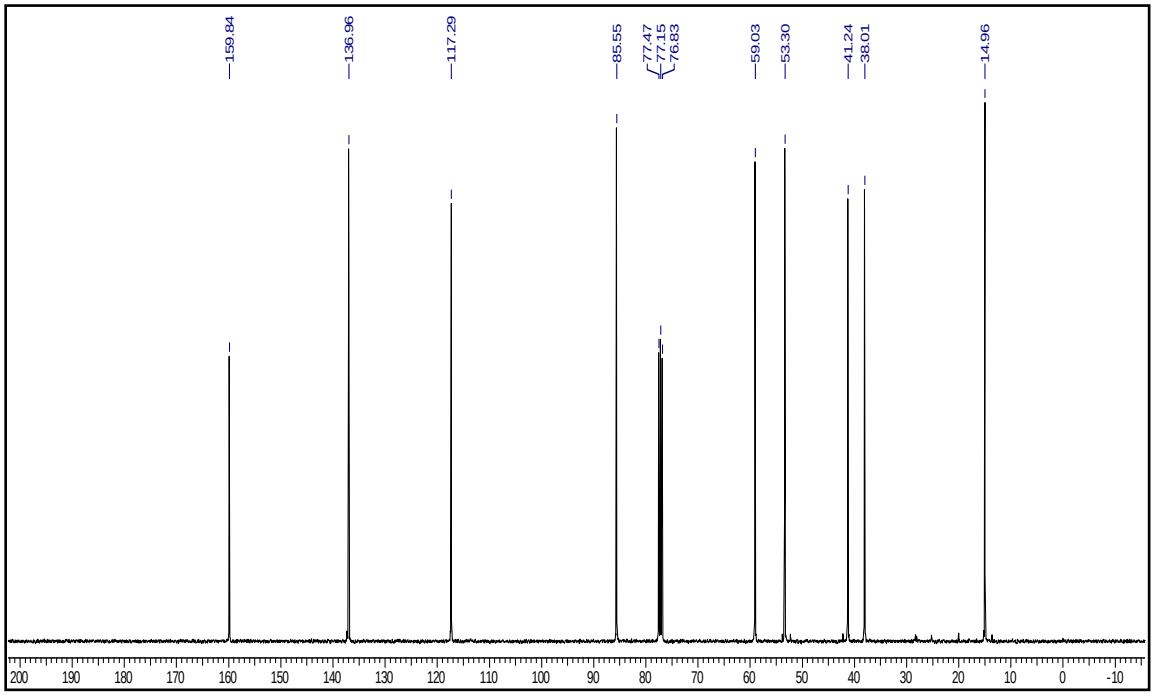
^{13}C NMR (50 MHz, $CDCl_3$) of compound 68



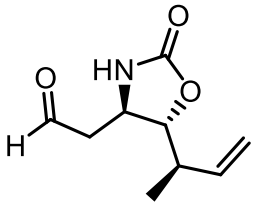
^{1}H NMR (400 MHz, $CDCl_3$) of compound 69

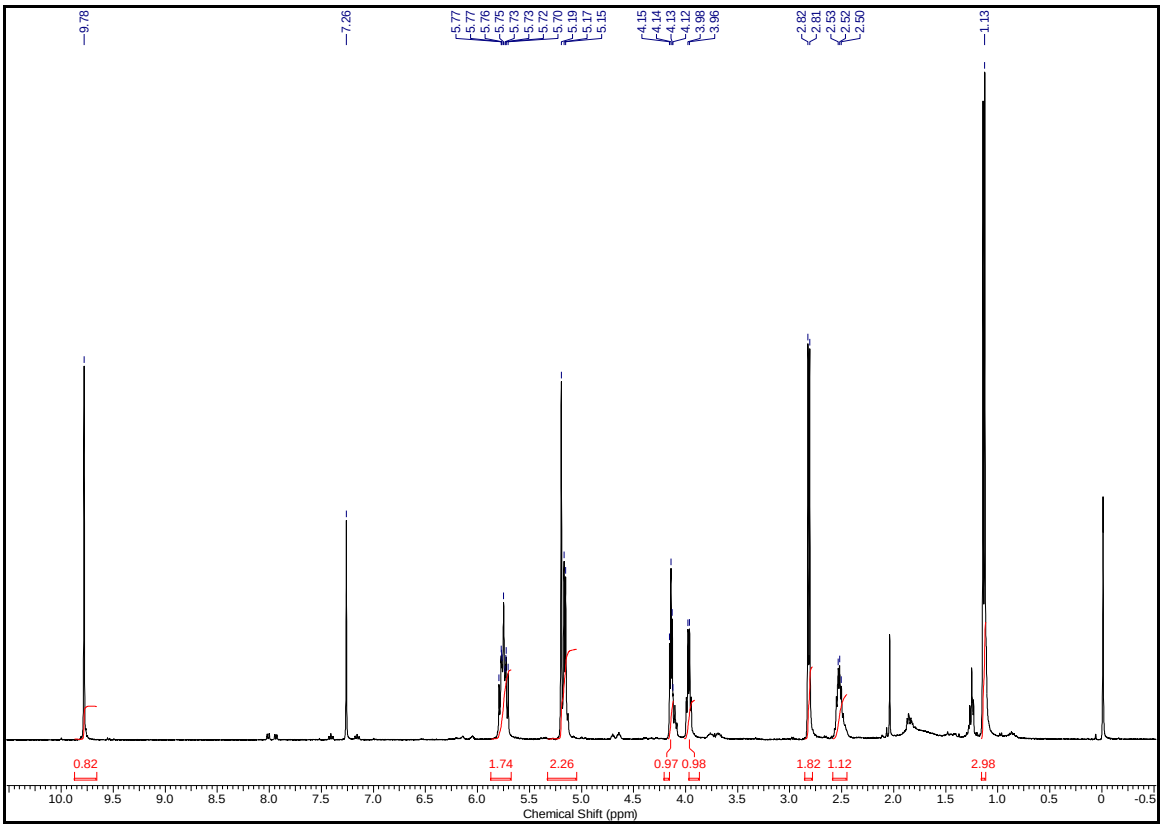


^{13}C NMR (100 MHz, $CDCl_3$) of compound 69

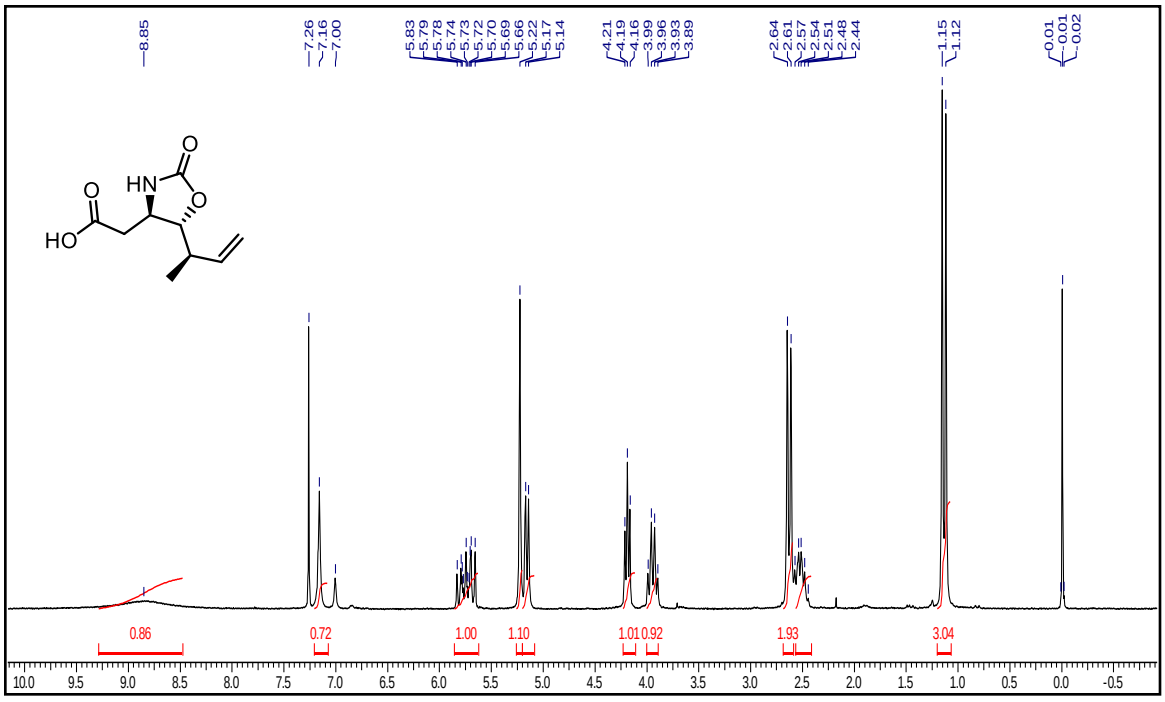


^{1}H NMR (400 MHz, $CDCl_3$) of compound 70

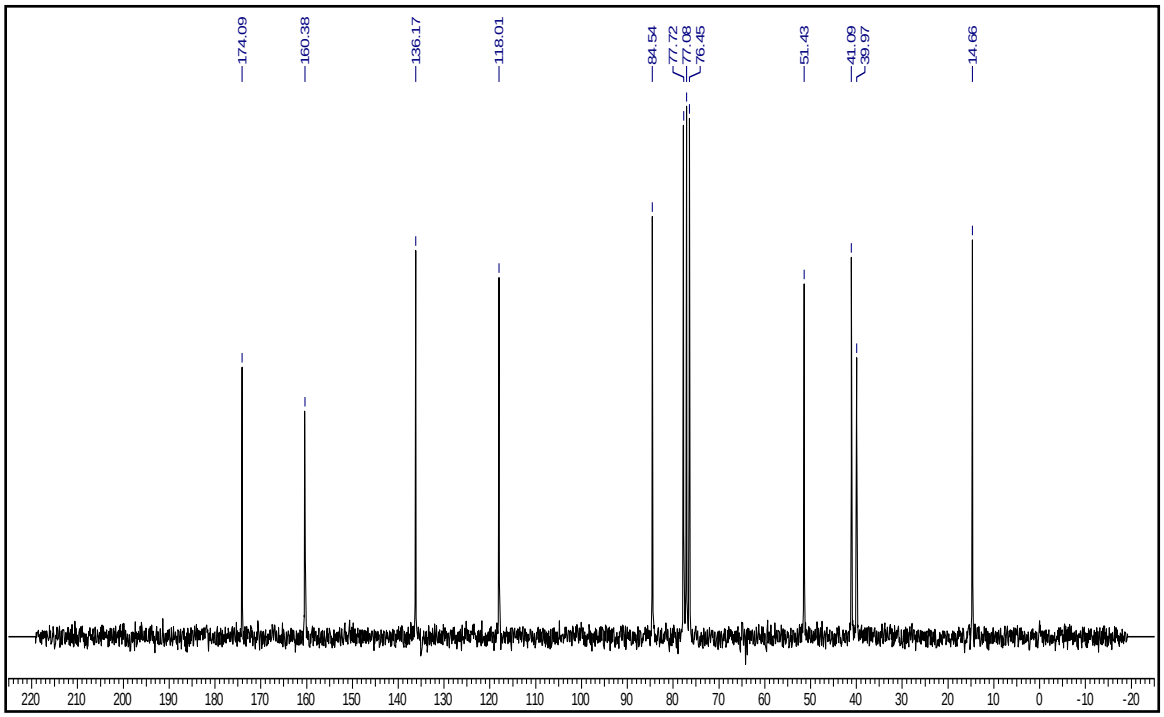




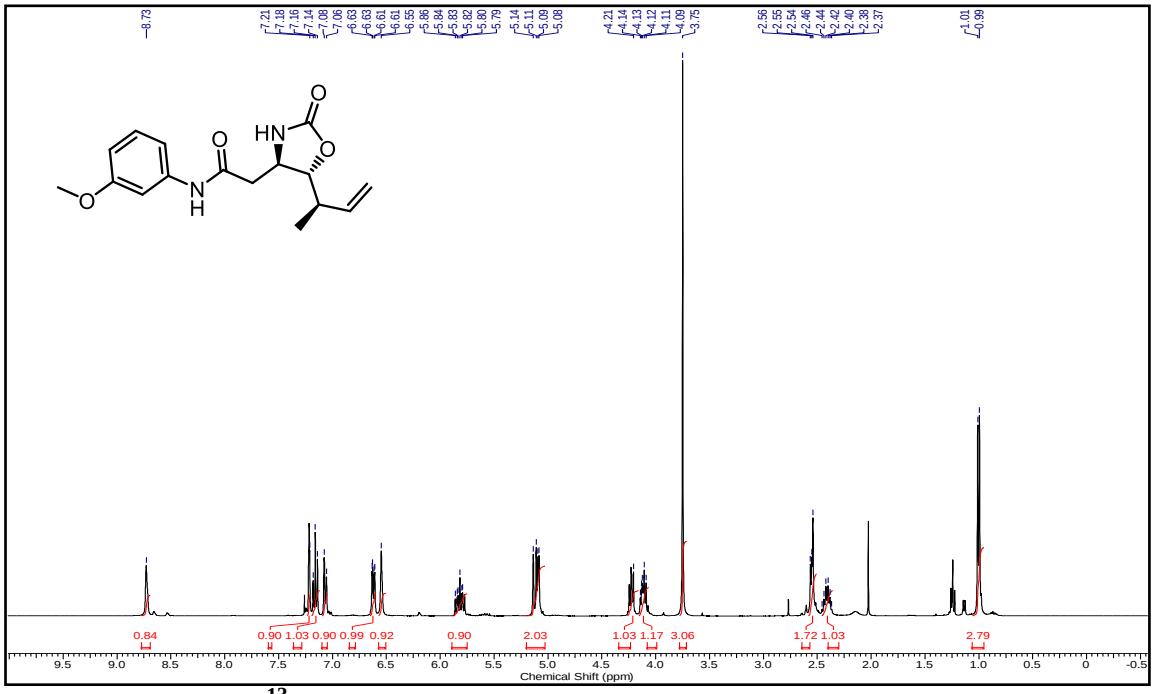
^{1}H NMR (200 MHz, $CDCl_3$) of compound 72



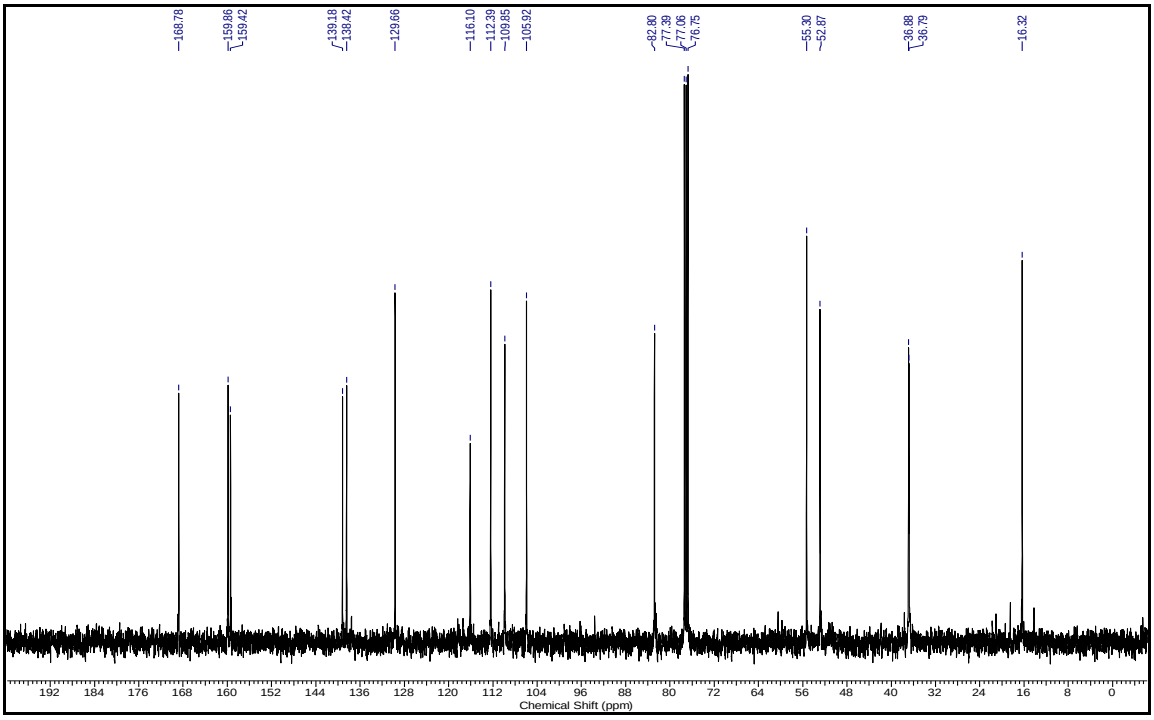
^{13}C NMR (50 MHz, $CDCl_3$) of compound 72



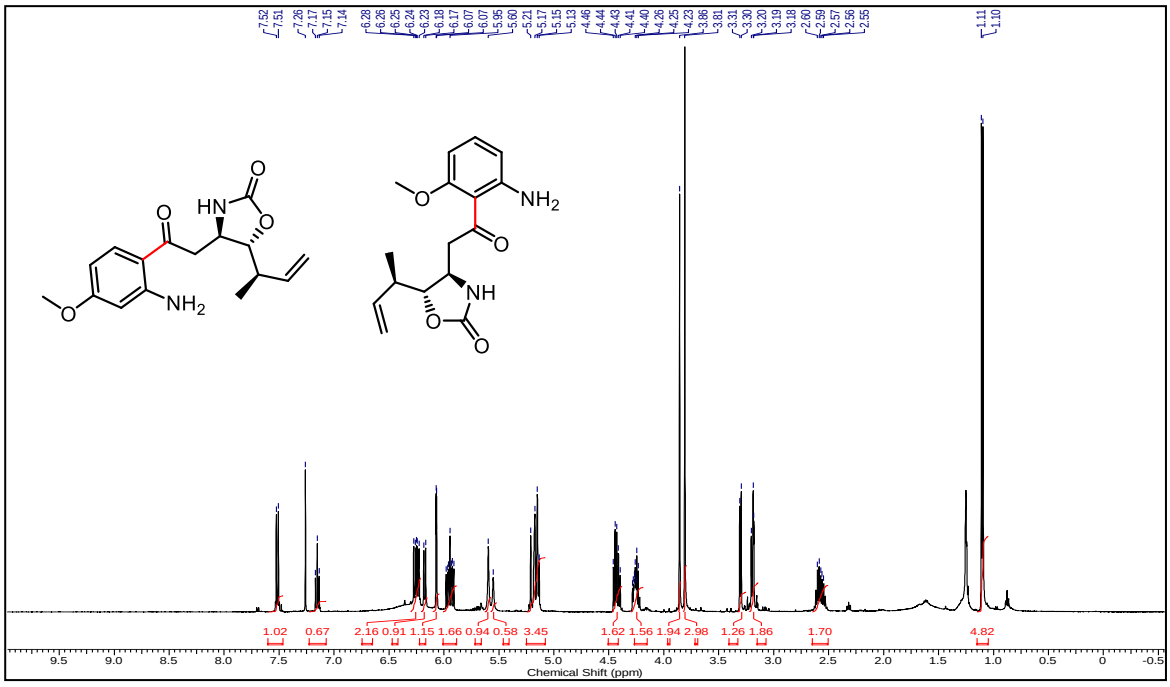
^{1}H NMR (400 MHz, $CDCl_3$) of compound 74



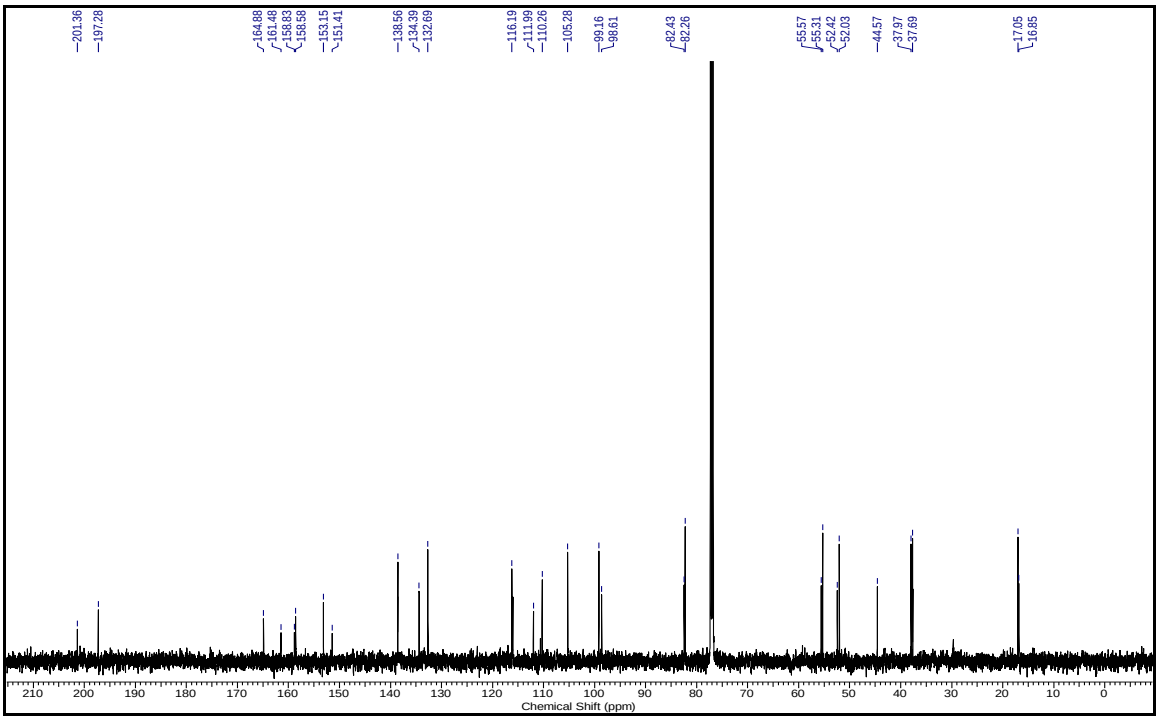
^{13}C NMR (100 MHz, $CDCl_3$) of compound 74



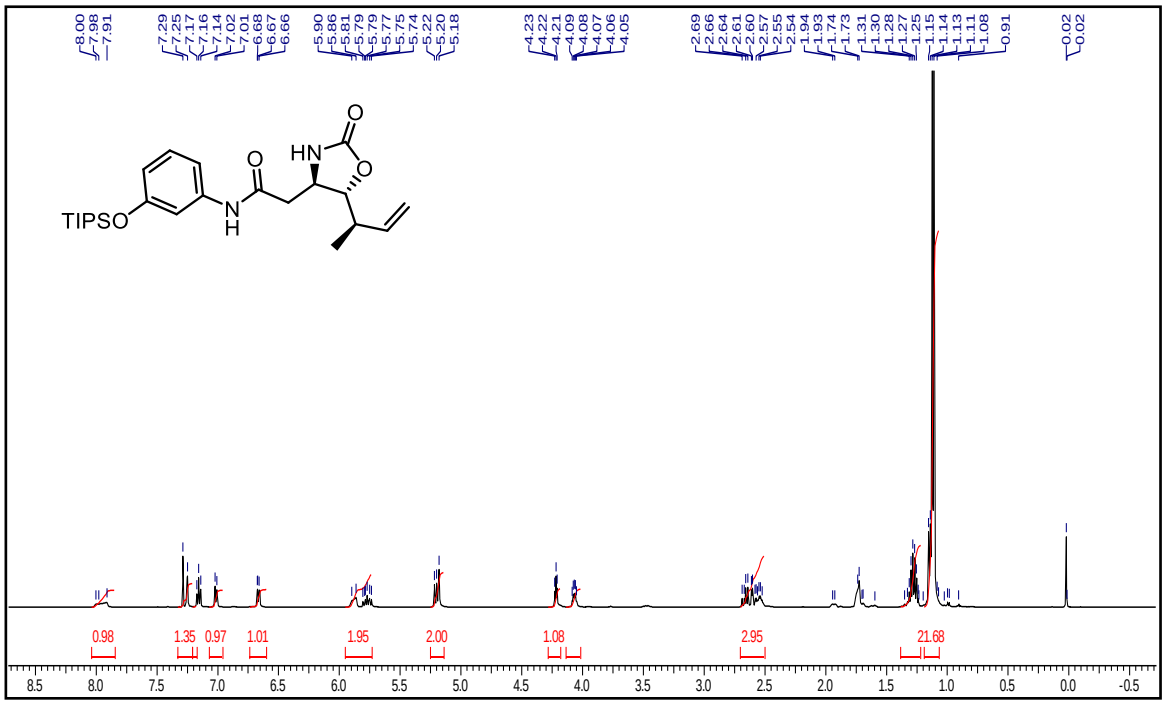
^{1}H NMR (500 MHz, $CDCl_3$) of compound 75 and 75'



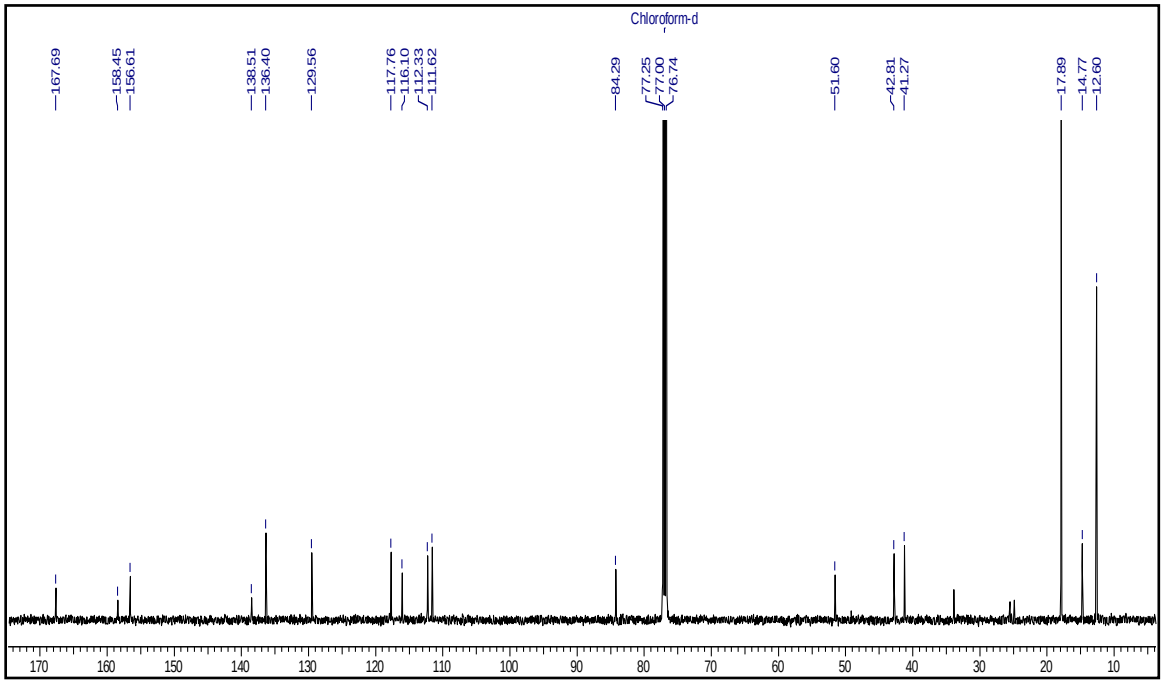
^{13}C NMR (125 MHz, $CDCl_3$) of compound 75 and 75'



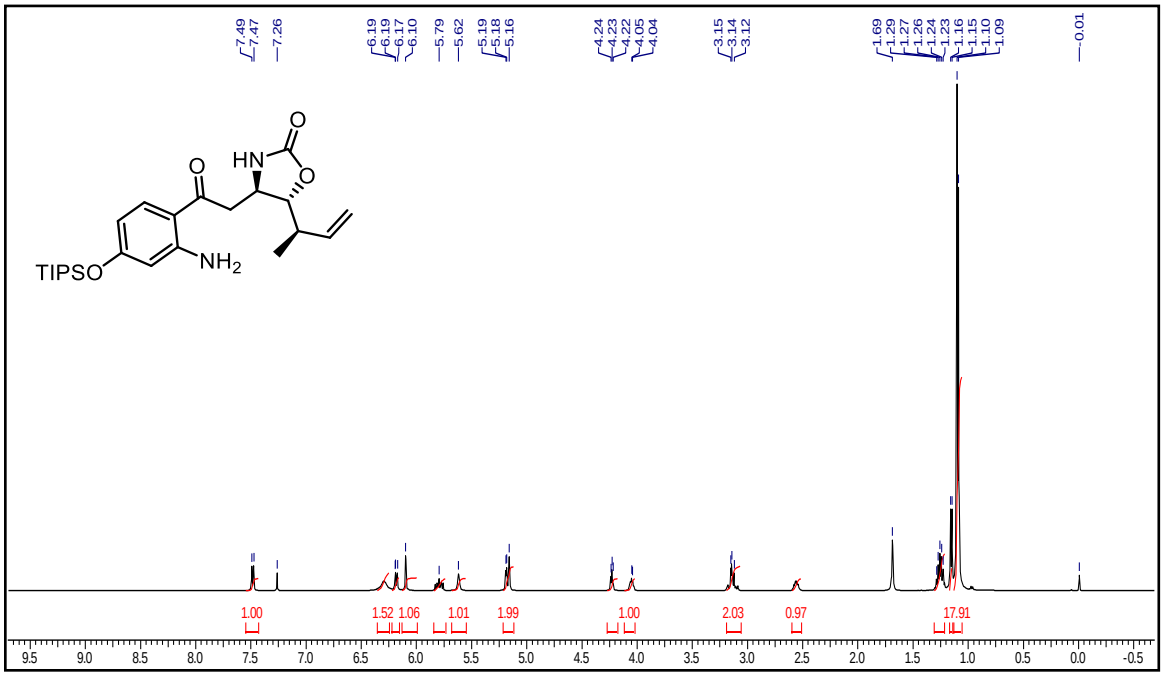
^{1}H NMR (400 MHz, $CDCl_3$) of compound 77



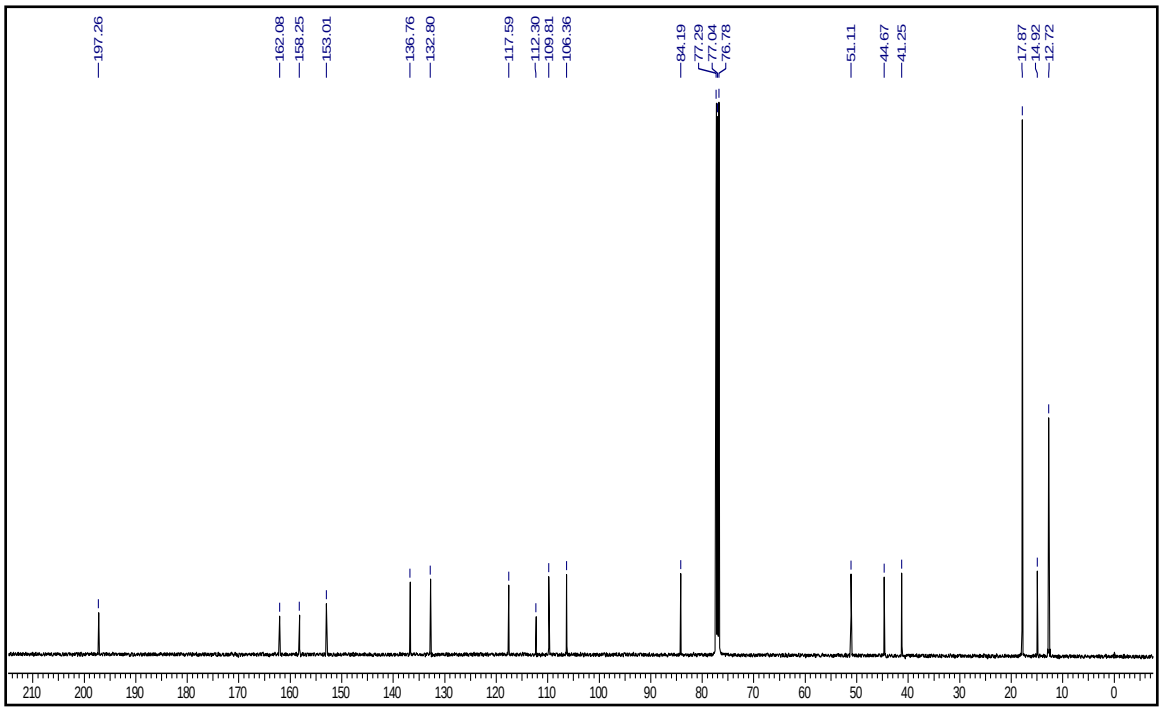
^{13}C NMR (100 MHz, $CDCl_3$) of compound 77



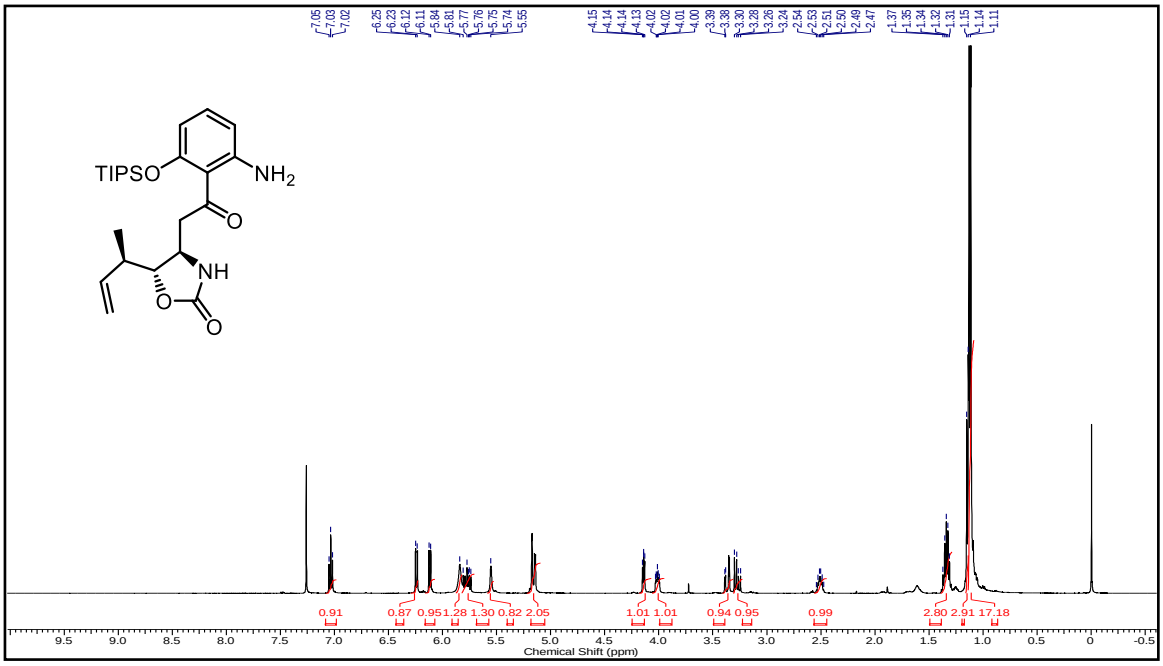
^{1}H NMR (400 MHz, $CDCl_3$) of compound 78



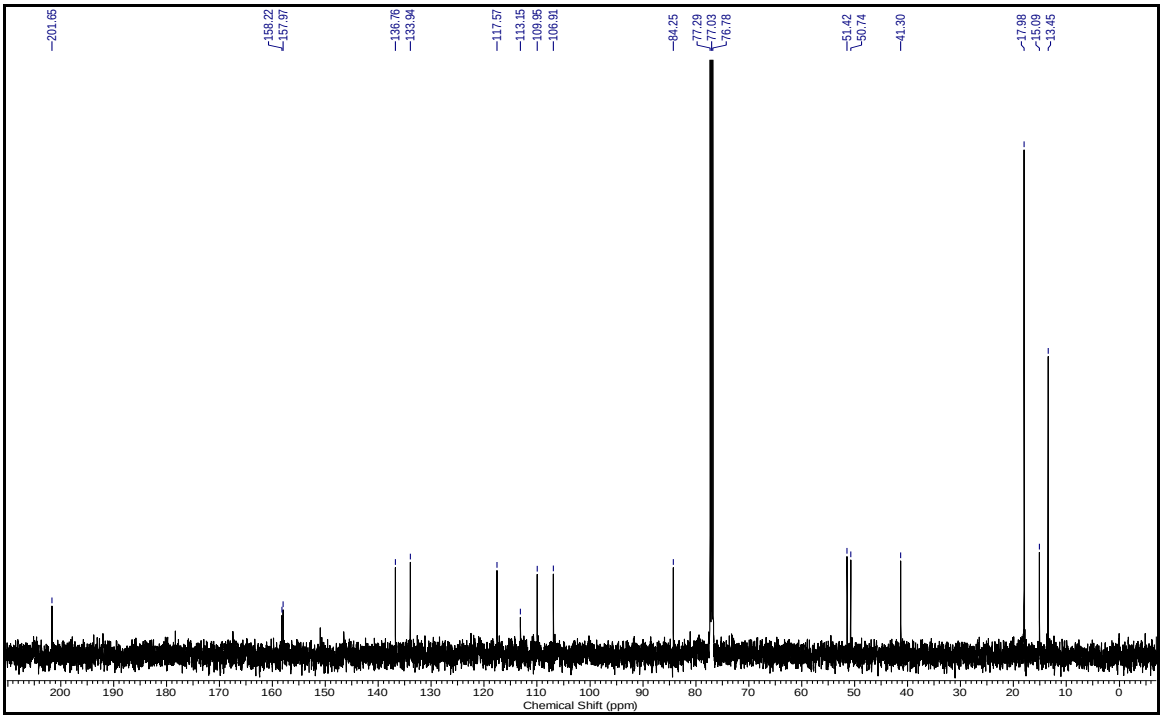
^{13}C NMR (100 MHz, $CDCl_3$) of compound 78



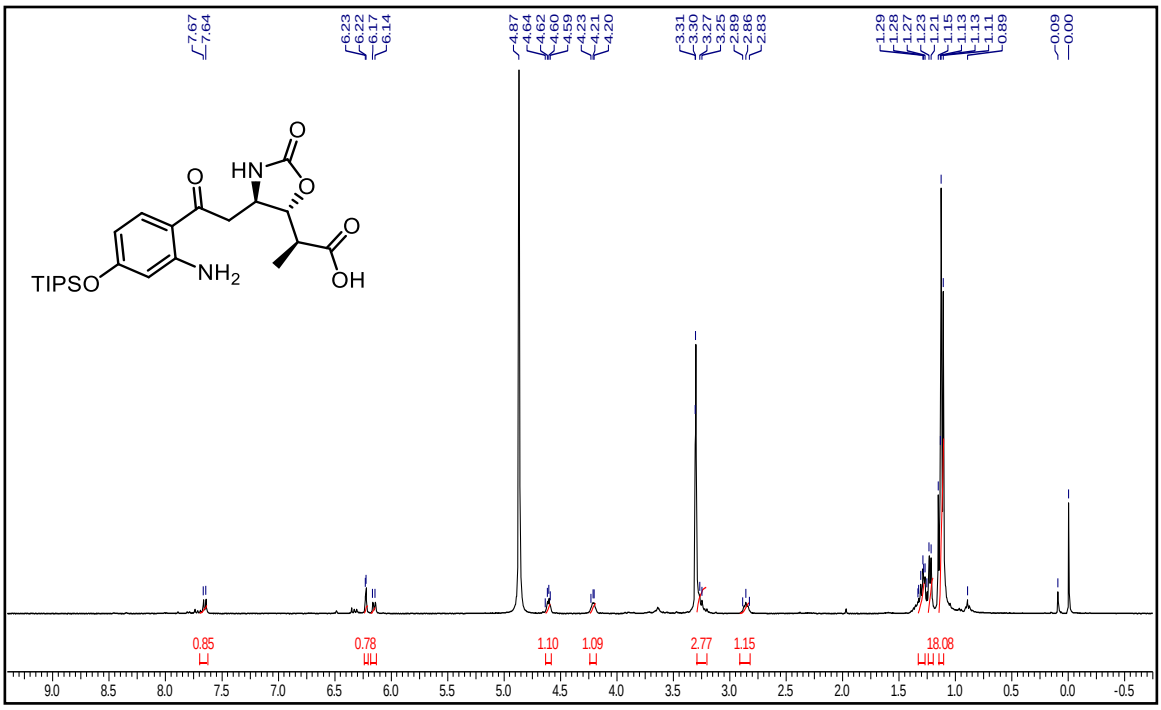
^{1}H NMR (500 MHz, $CDCl_3$) of compound 79



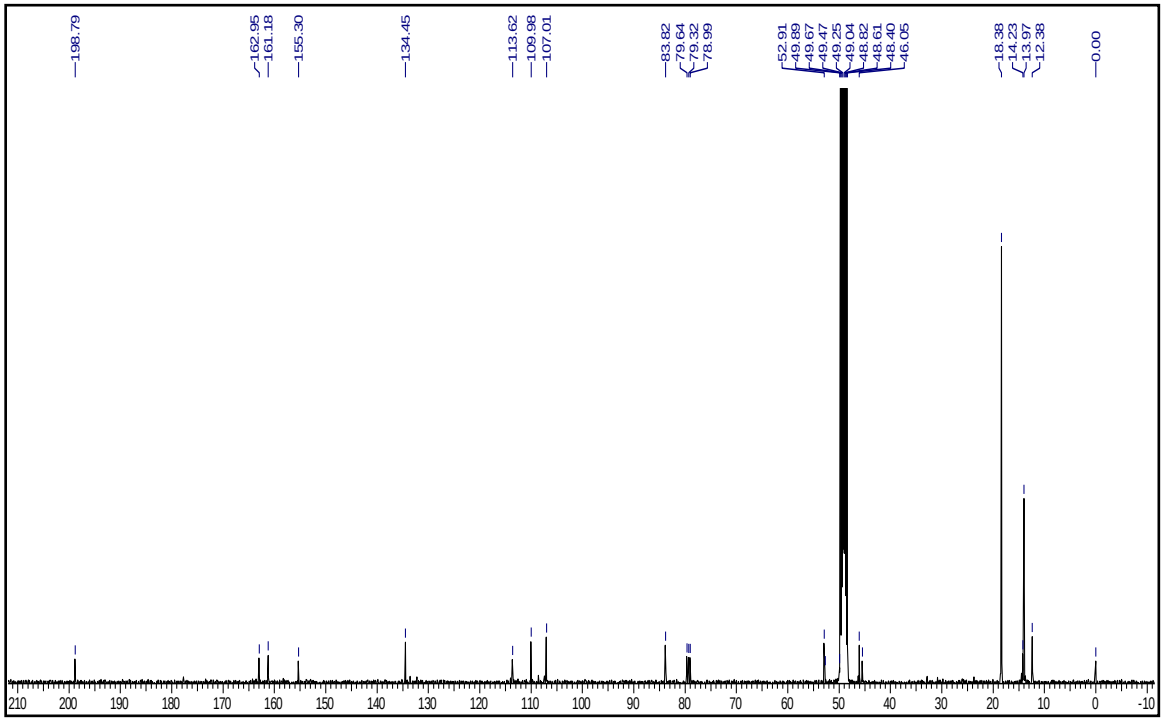
^{13}C NMR (125 MHz, $CDCl_3$) of compound 79



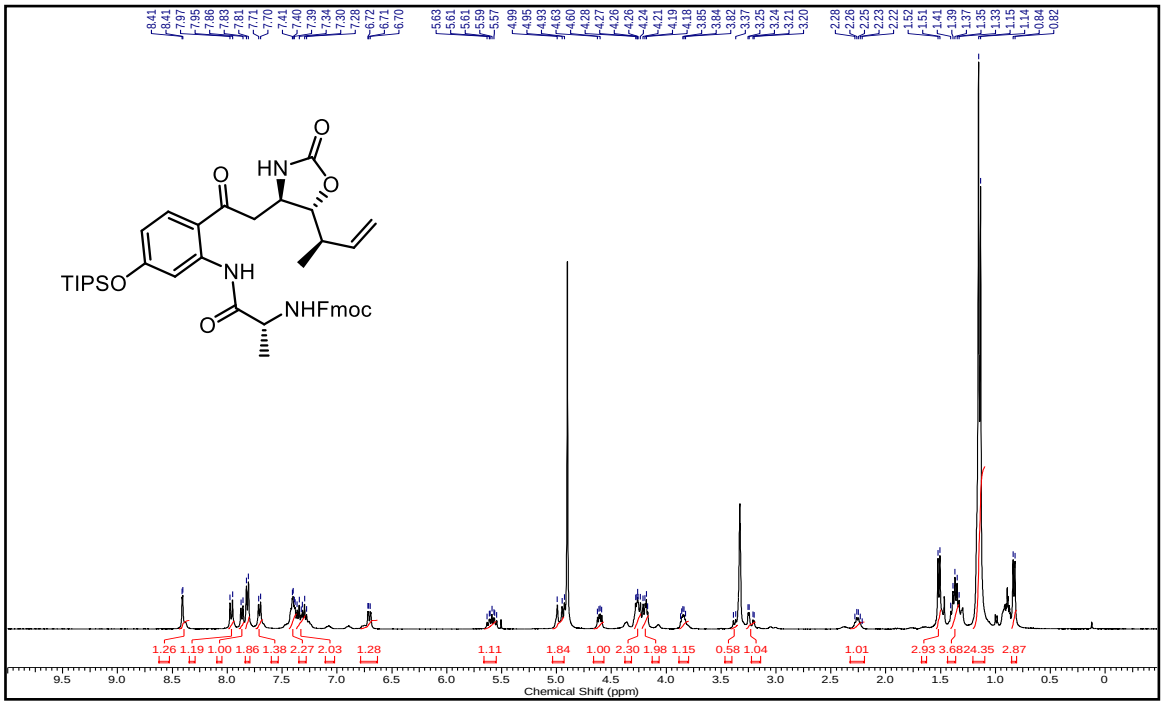
^{1}H NMR (400 MHz, CD_3OD) of compound 80



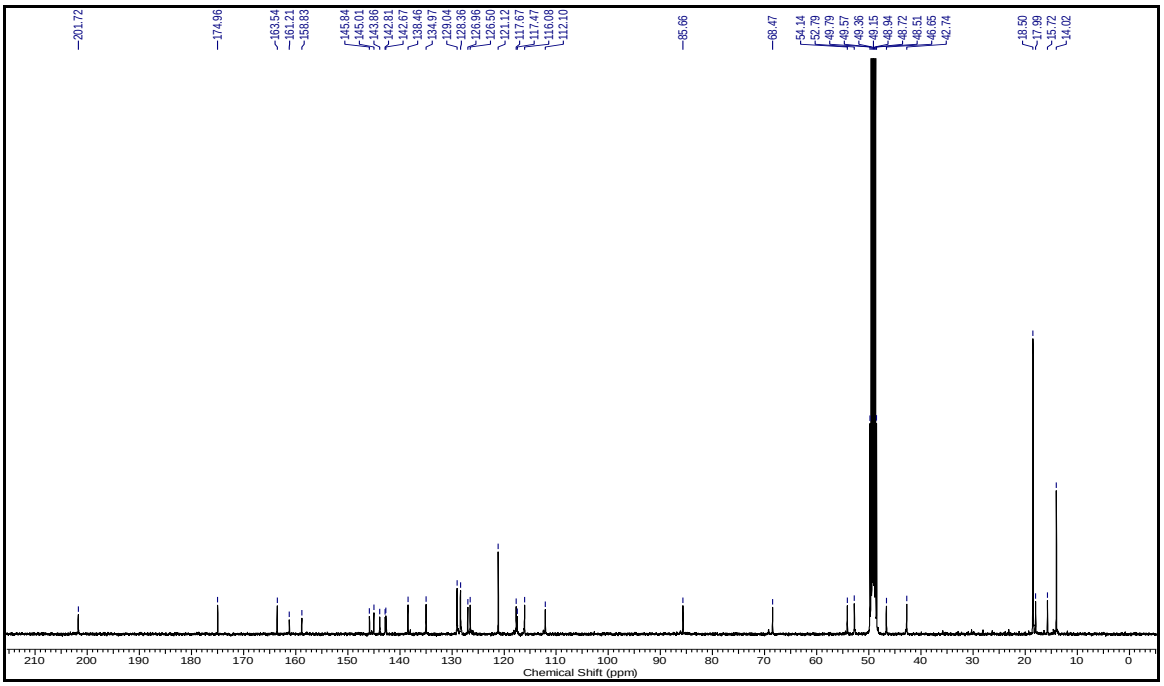
^{13}C NMR (100 MHz, CD_3OD) of compound 80



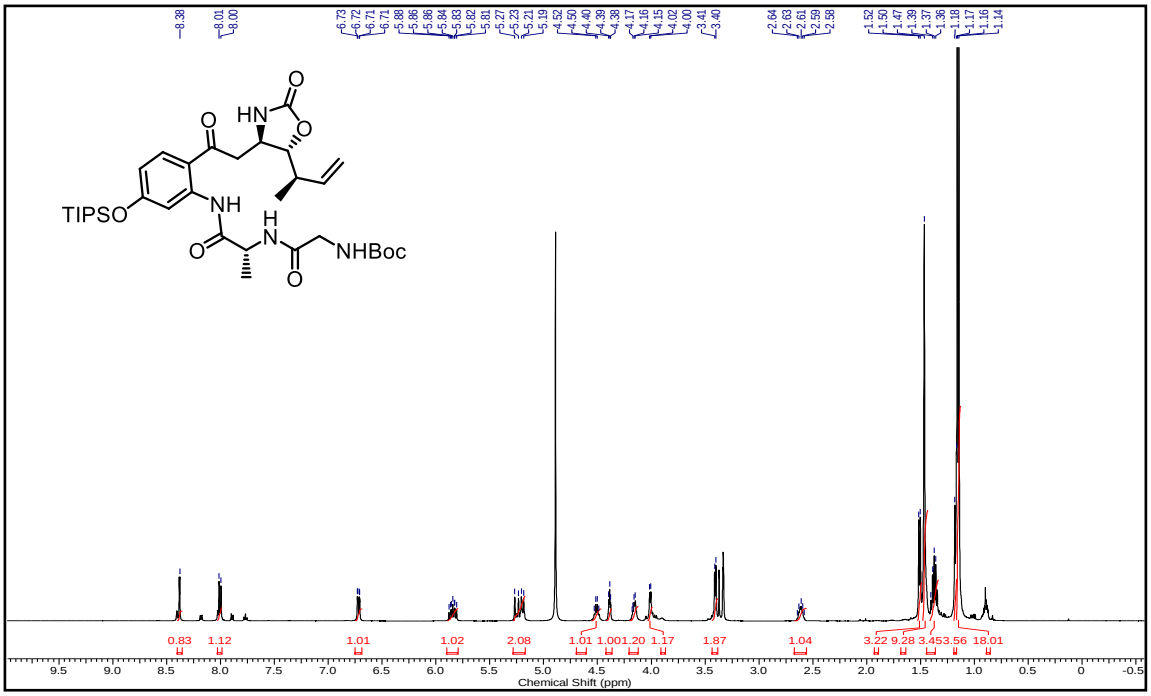
^{1}H NMR (400 MHz, CD_3OD) of compound 82



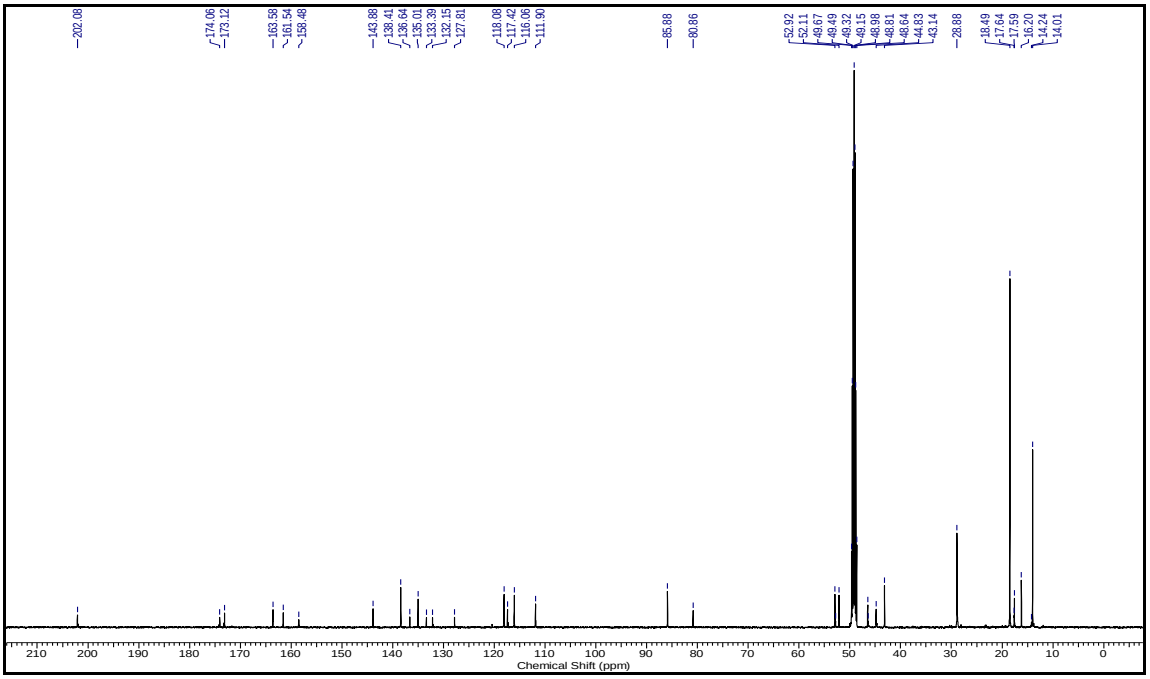
^{13}C NMR (100 MHz, CD_3OD) of compound 82



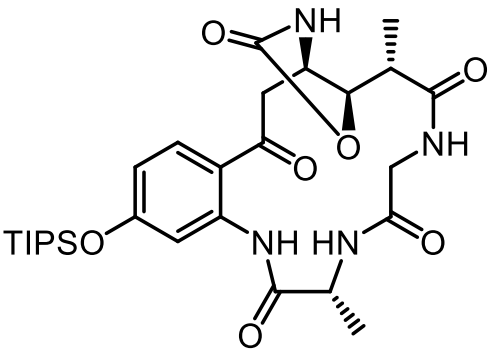
^{1}H NMR (500 MHz, CD_3OD) of compound 84

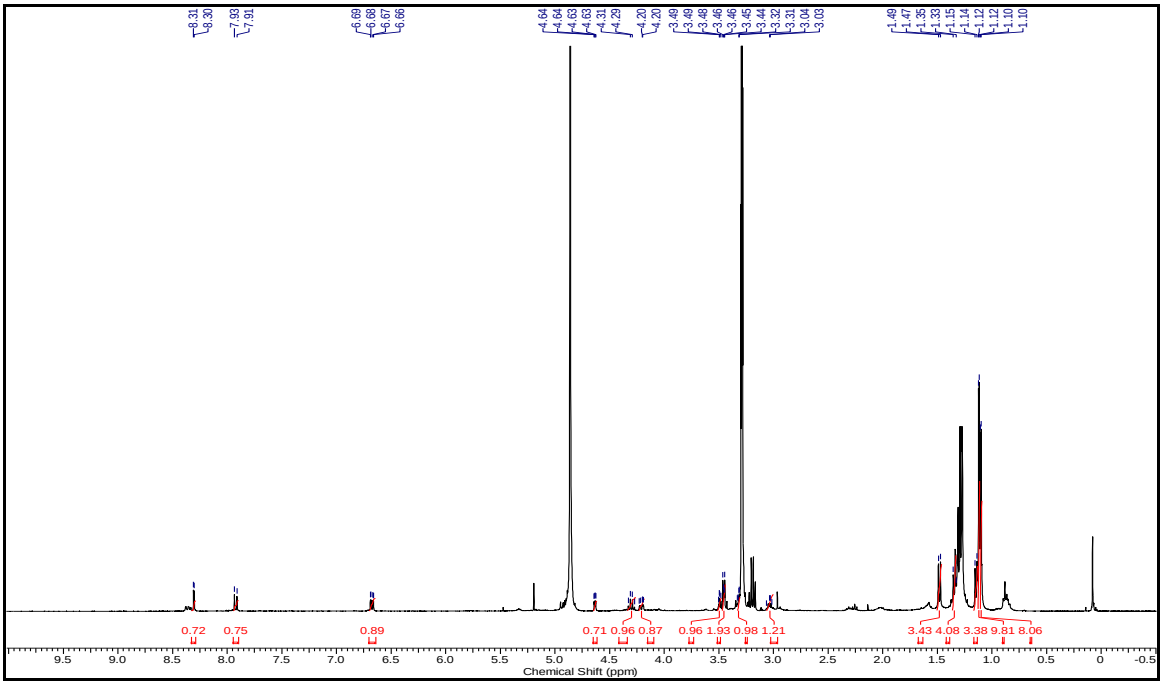


^{13}C NMR (125 MHz, CD_3OD) of compound 84

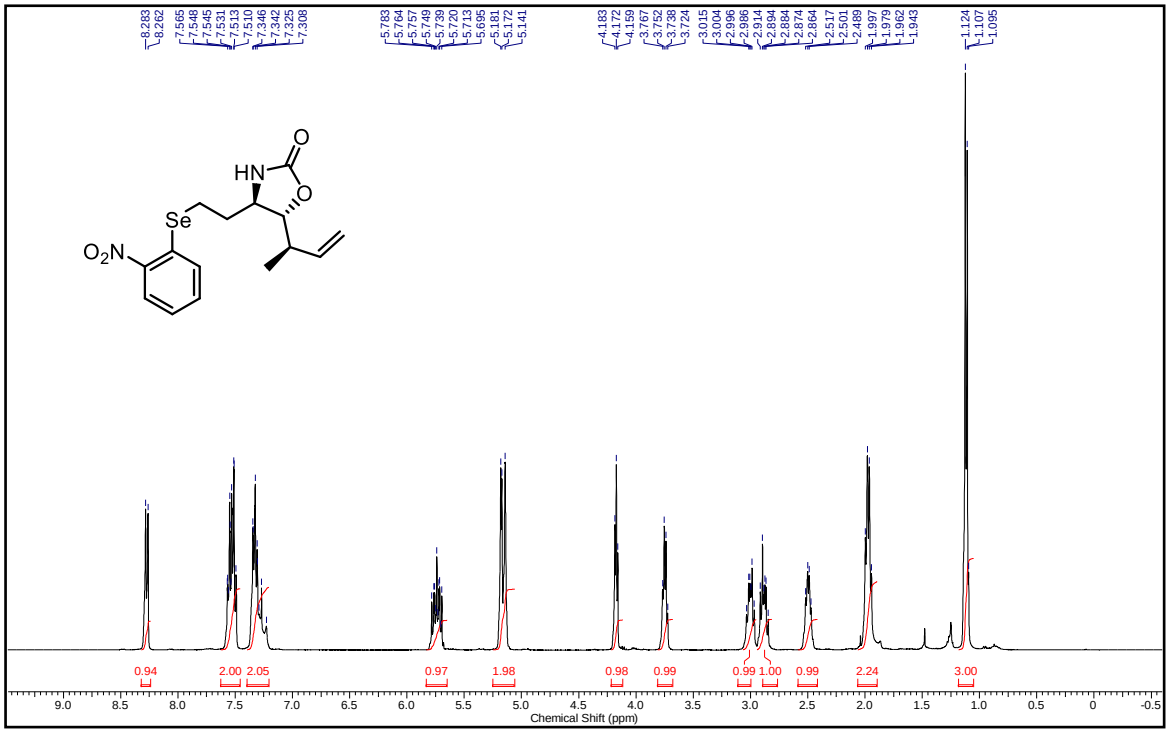


^{1}H NMR (400 MHz, CD_3OD) of compound 86

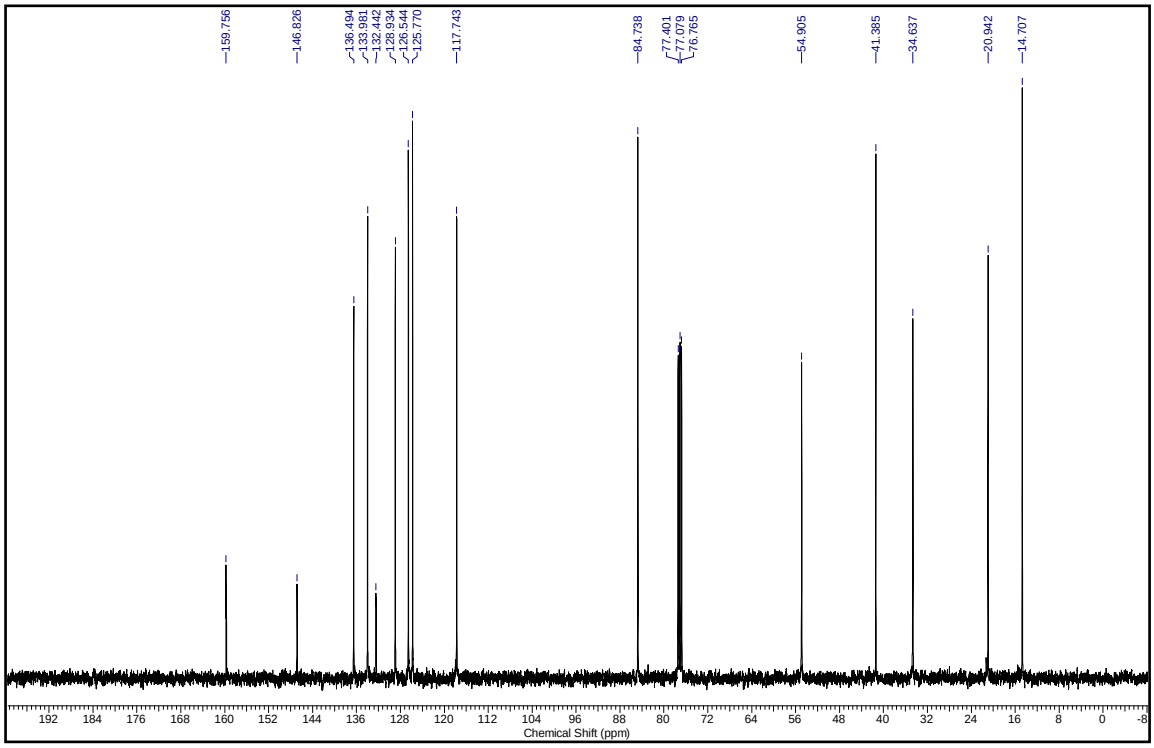




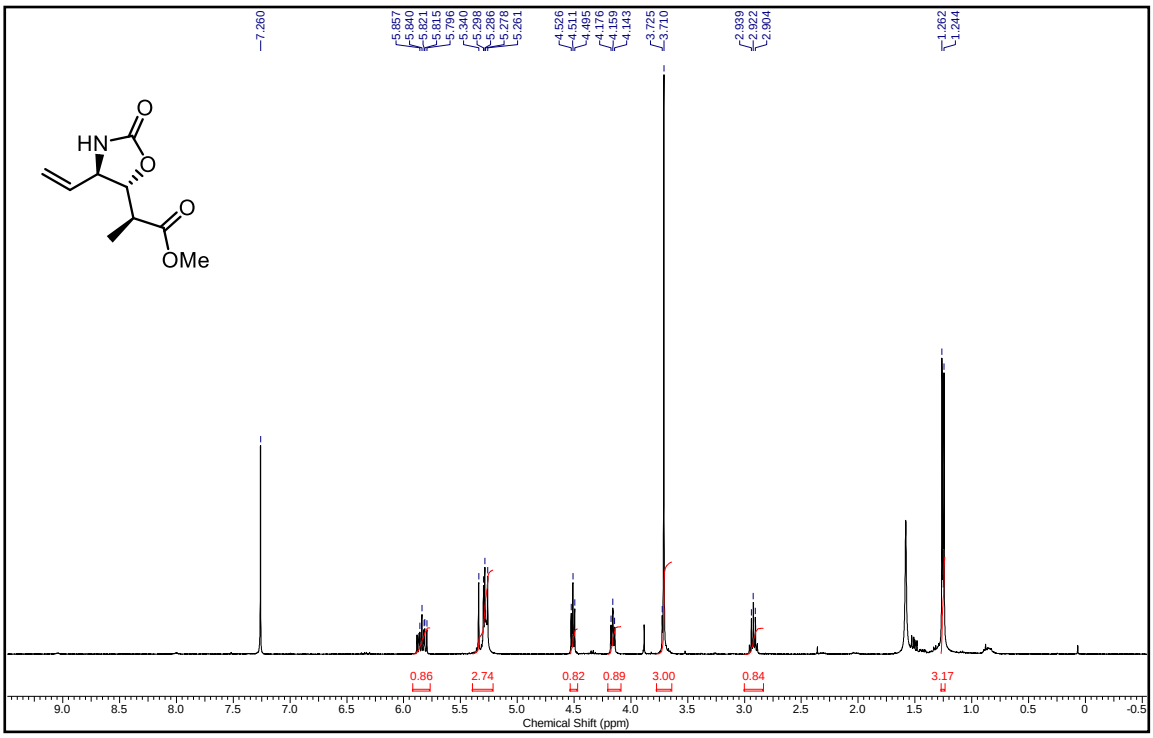
^{1}H NMR (400 MHz, $CDCl_3$) of compound 91



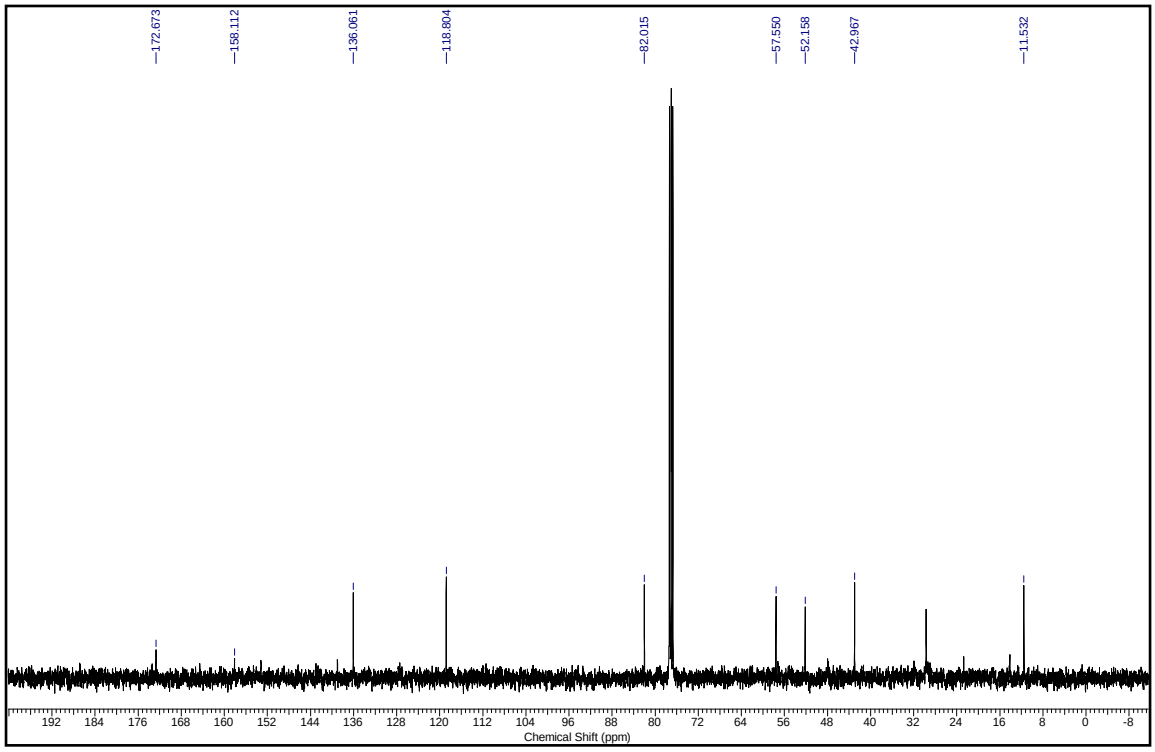
^{13}C NMR (100 MHz, $CDCl_3$) of compound 91



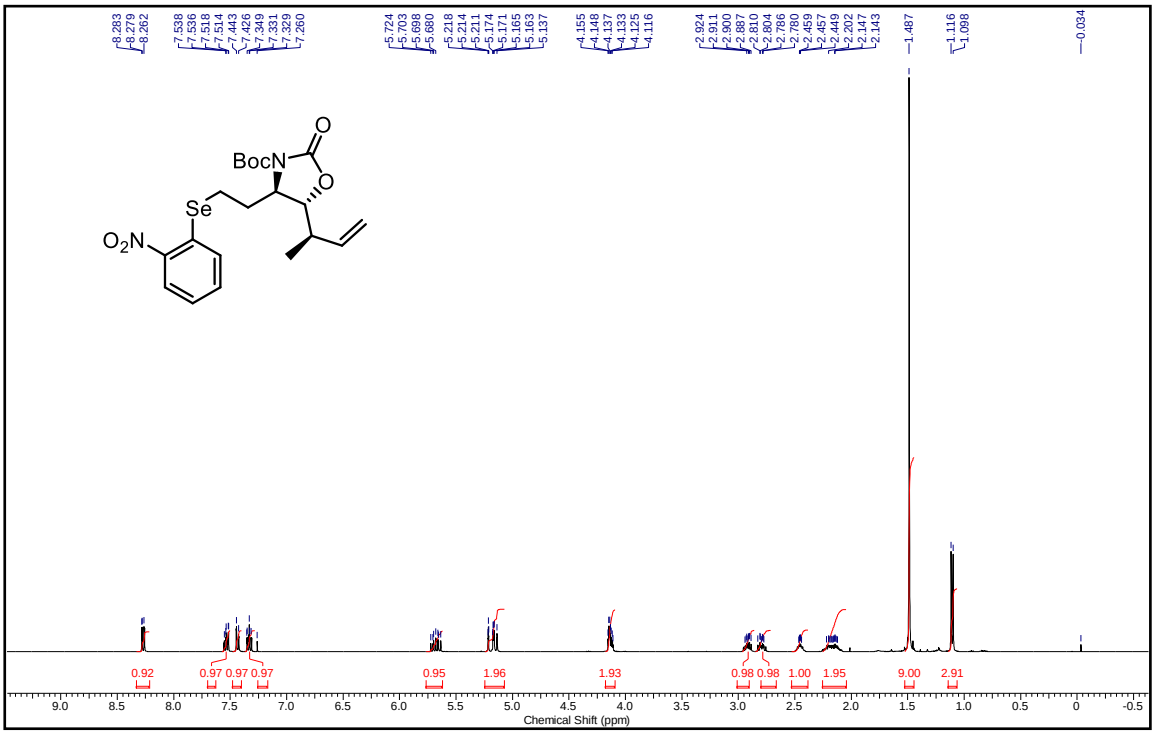
^{1}H NMR (400 MHz, $CDCl_3$) of compound 92



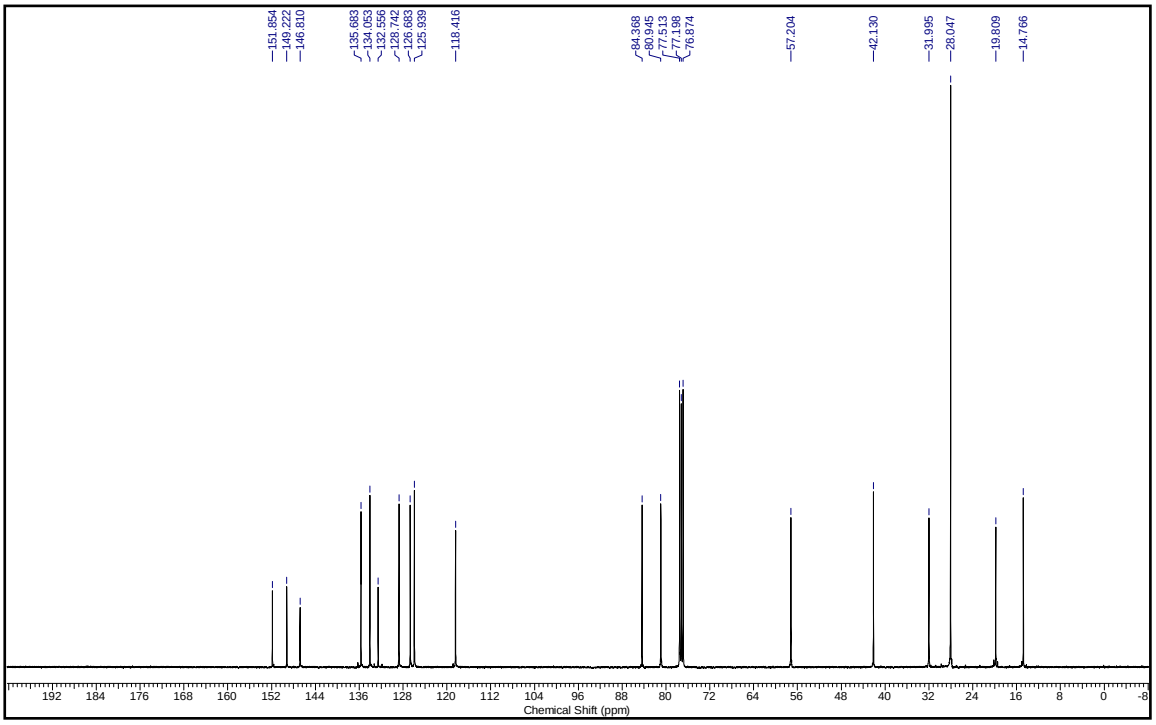
^{13}C NMR (100 MHz, $CDCl_3$) of compound 92



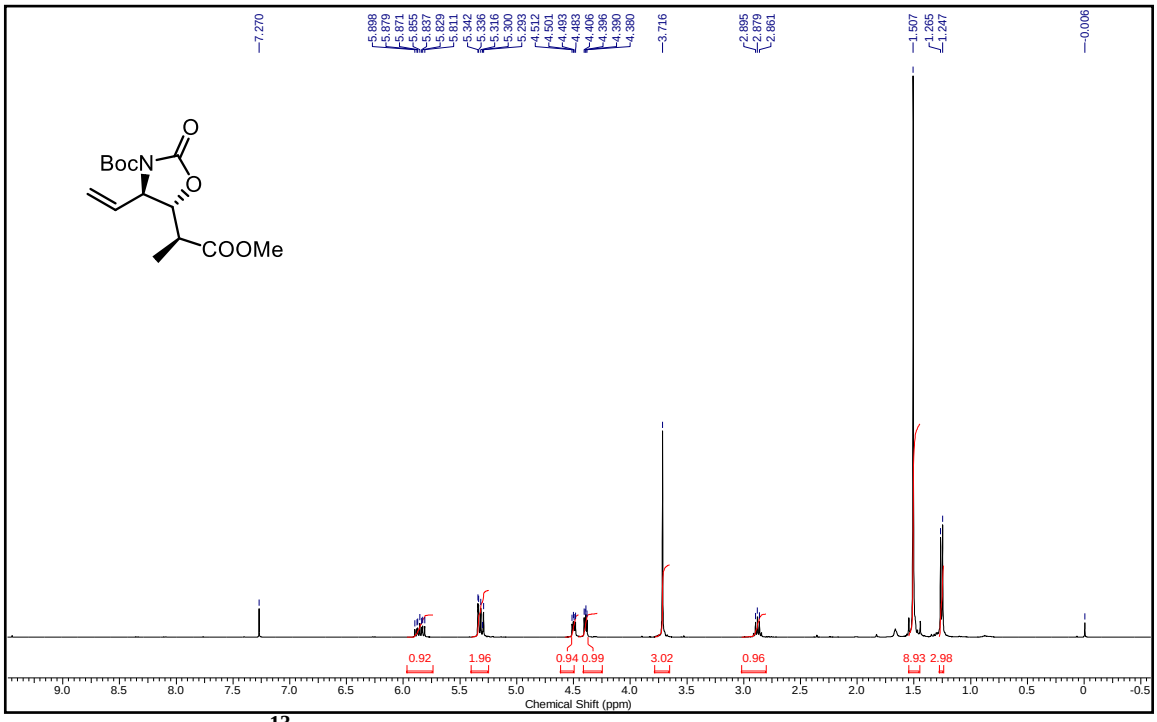
^{1}H NMR (400 MHz, $CDCl_3$) of compound 93



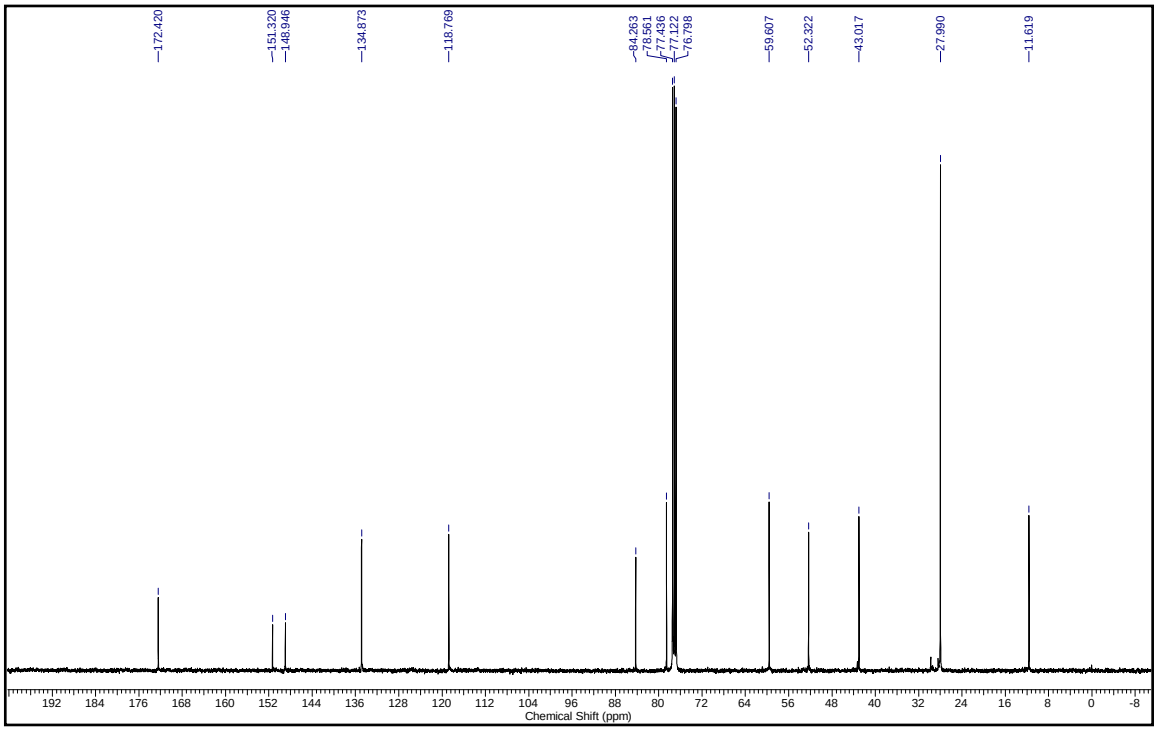
^{13}C NMR (100 MHz, $CDCl_3$) of compound 93



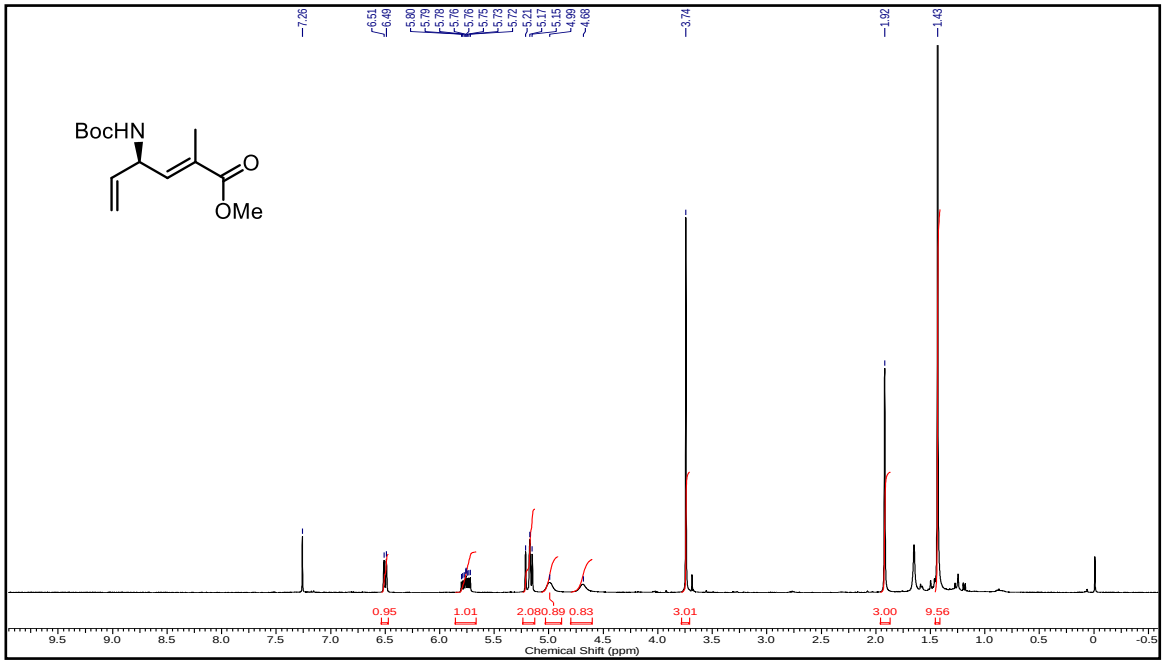
^{1}H NMR (400 MHz, $CDCl_3$) of compound 94



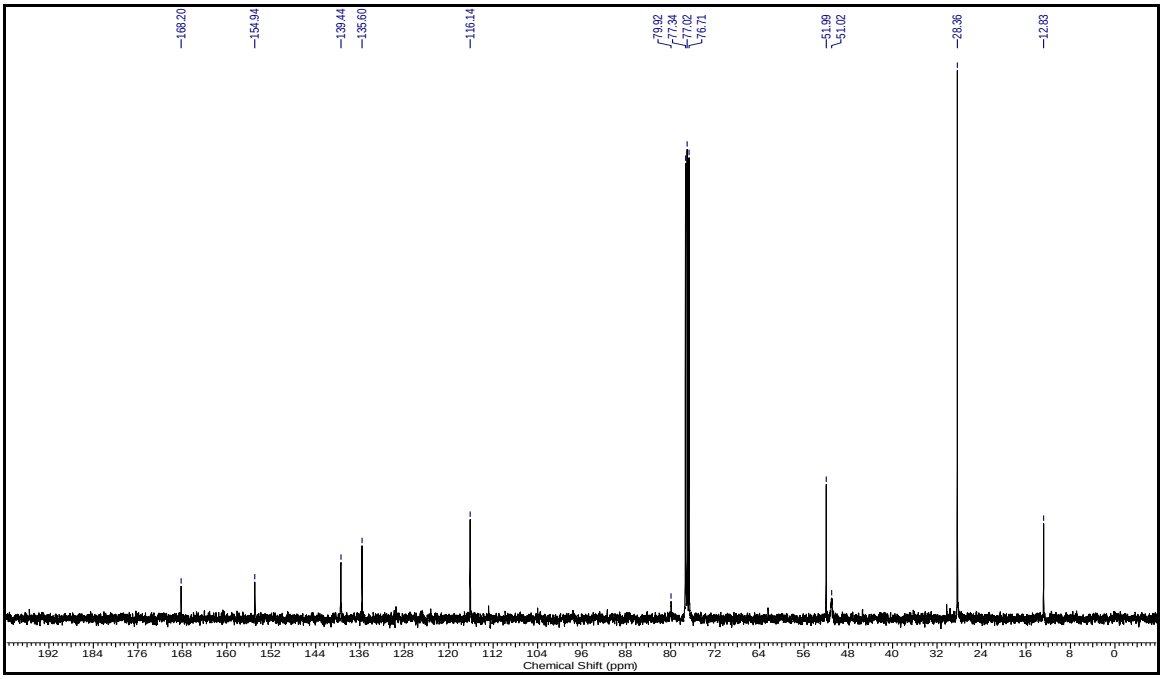
^{13}C NMR (100 MHz, $CDCl_3$) of compound 94



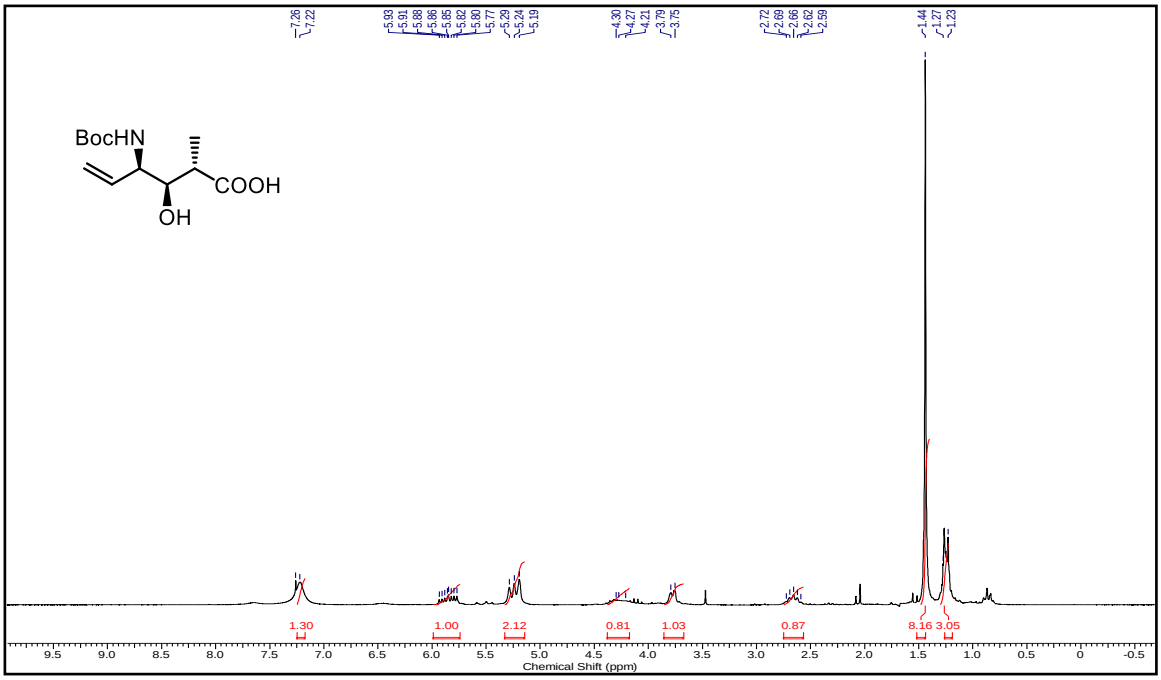
^{1}H NMR (400 MHz, $CDCl_3$) of compound 95



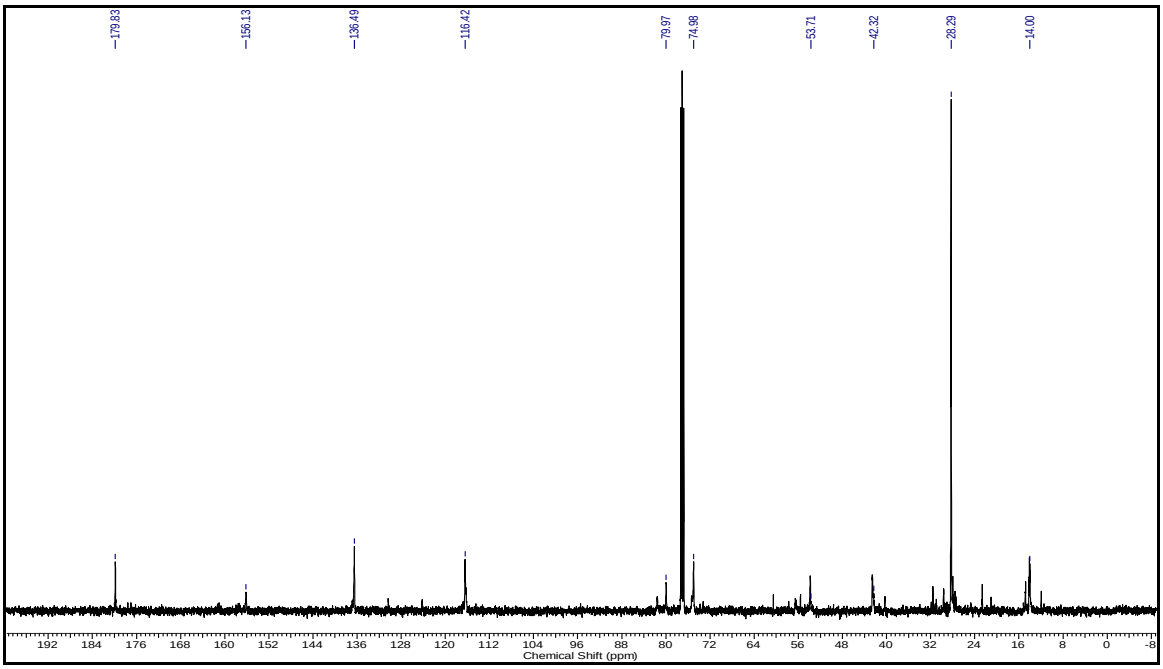
^{13}C NMR (100 MHz, $CDCl_3$) of compound 95



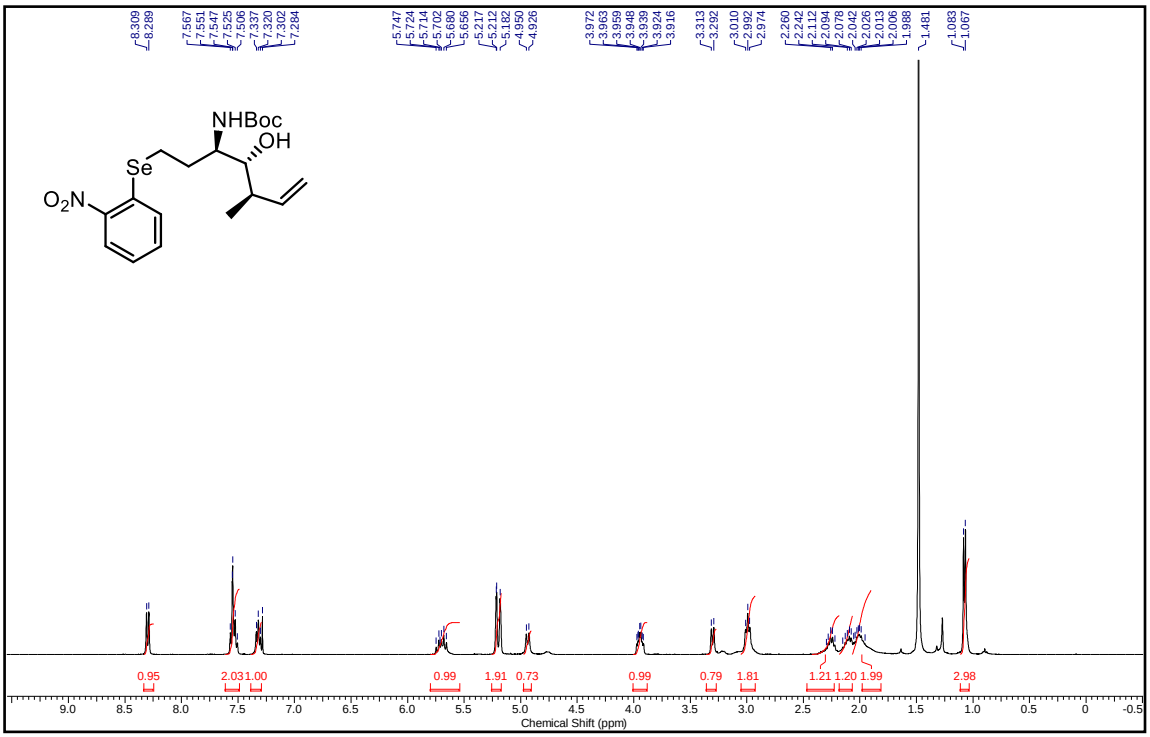
^{1}H NMR (200 MHz, $CDCl_3$) of compound 90



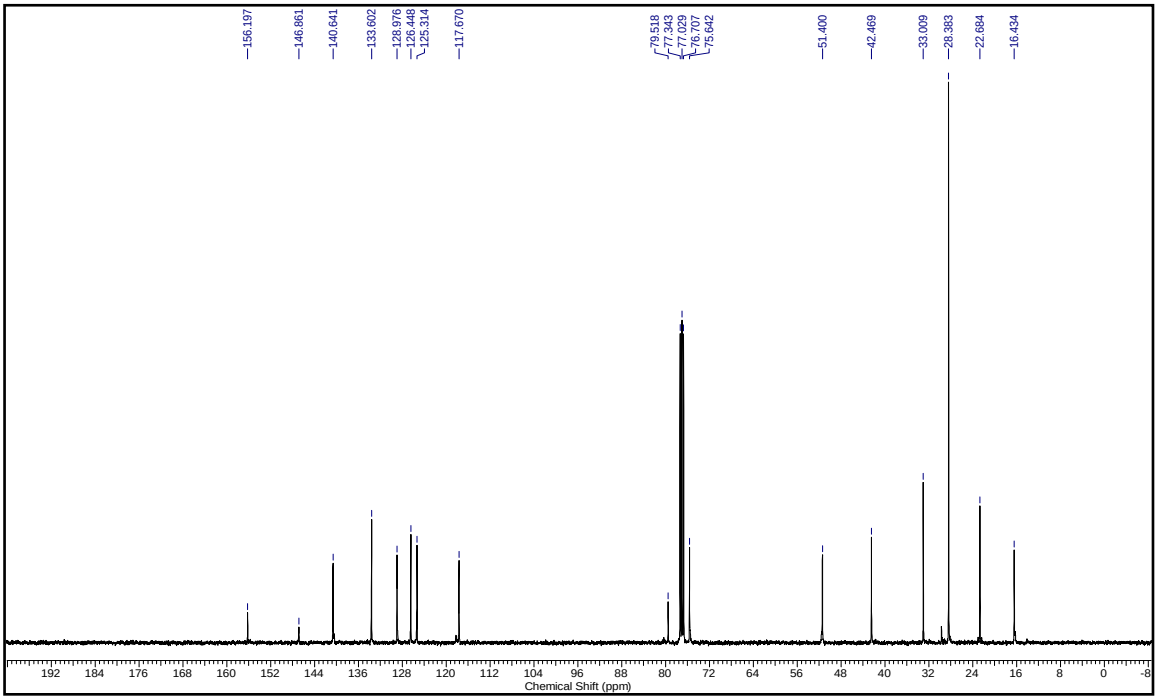
^{13}C NMR (125 MHz, $CDCl_3$) of compound 90



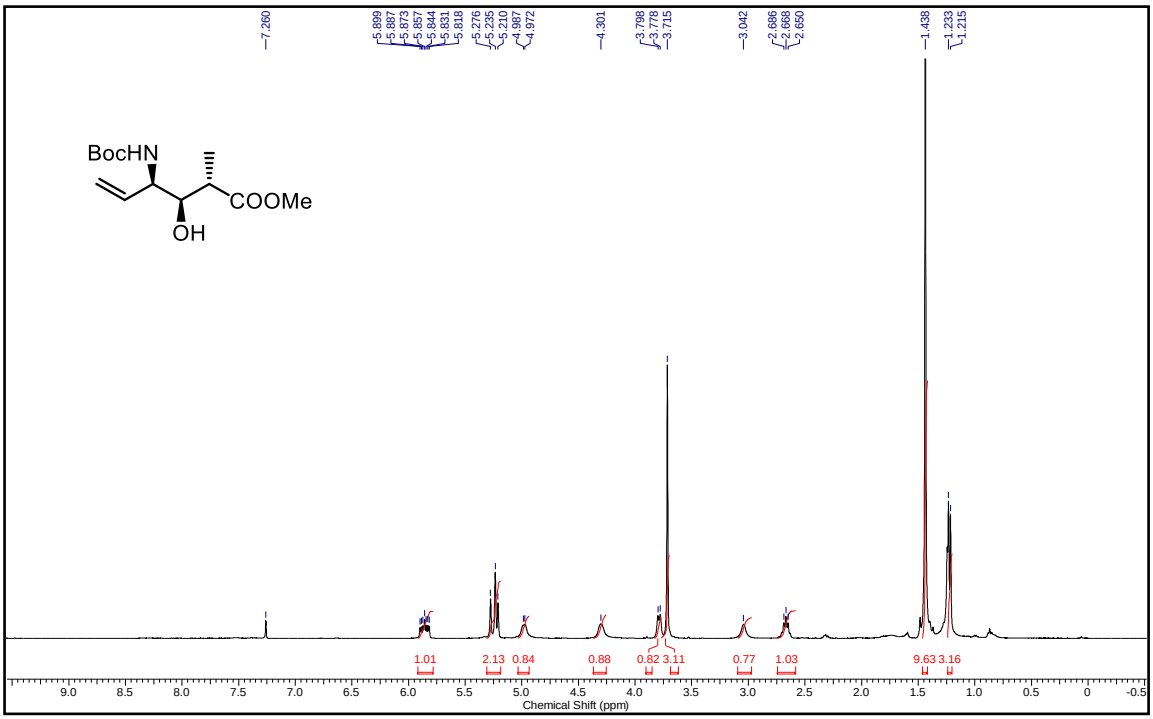
^{1}H NMR (400 MHz, $CDCl_3$) of compound 96



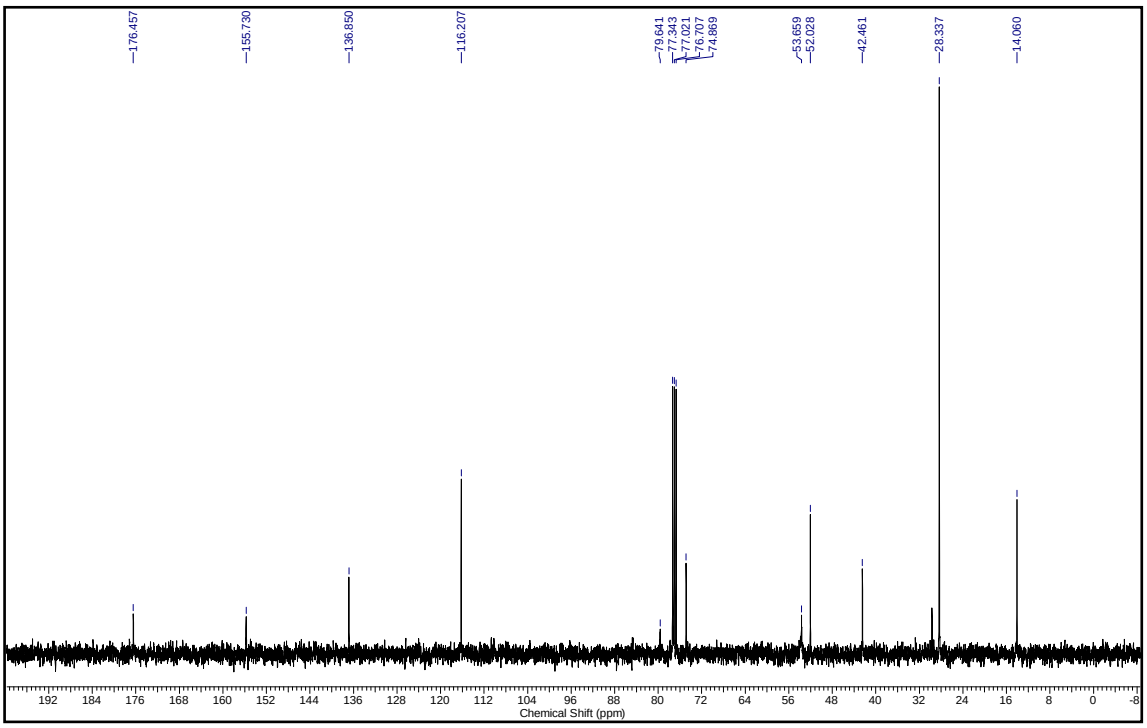
^{13}C NMR (100 MHz, $CDCl_3$) of compound 96



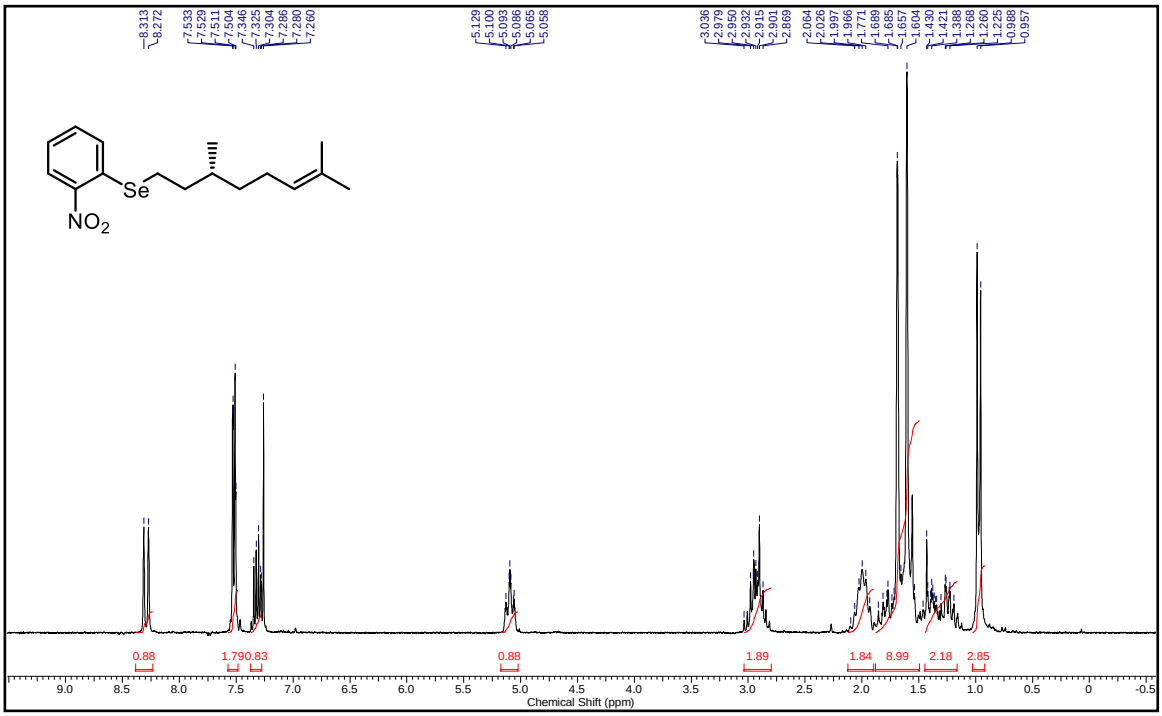
^{1}H NMR (400 MHz, $CDCl_3$) of compound 97



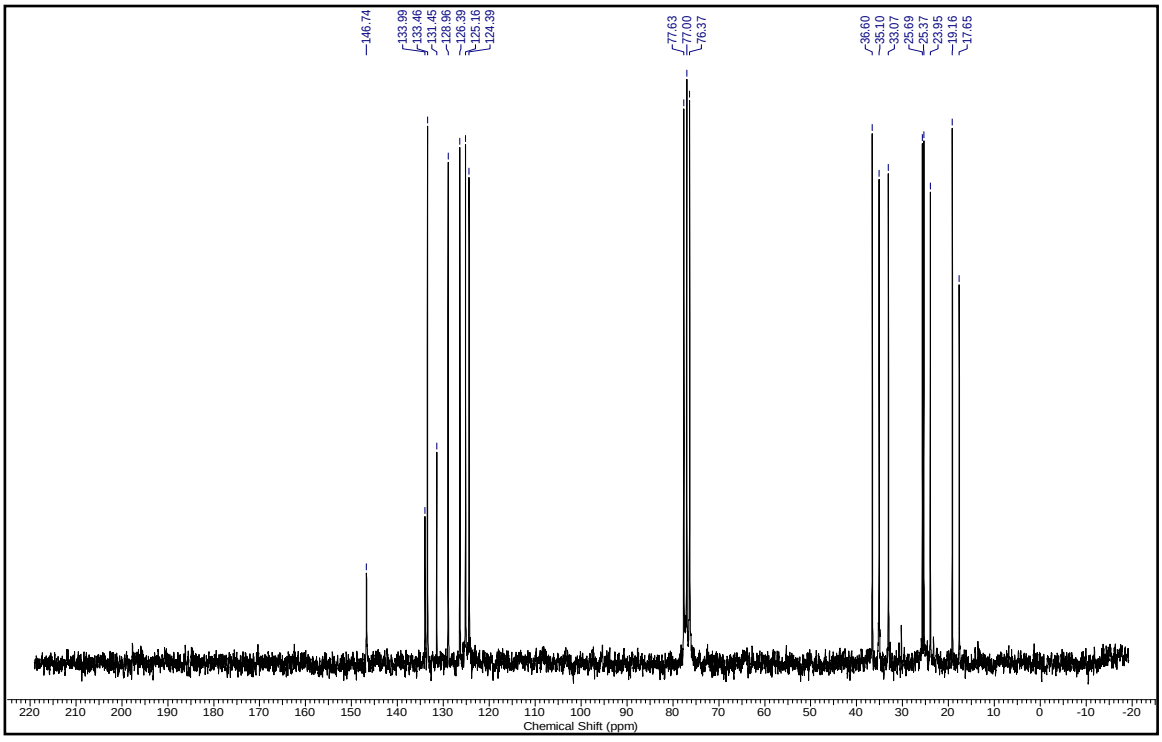
^{13}C NMR (100 MHz, $CDCl_3$) of compound 97



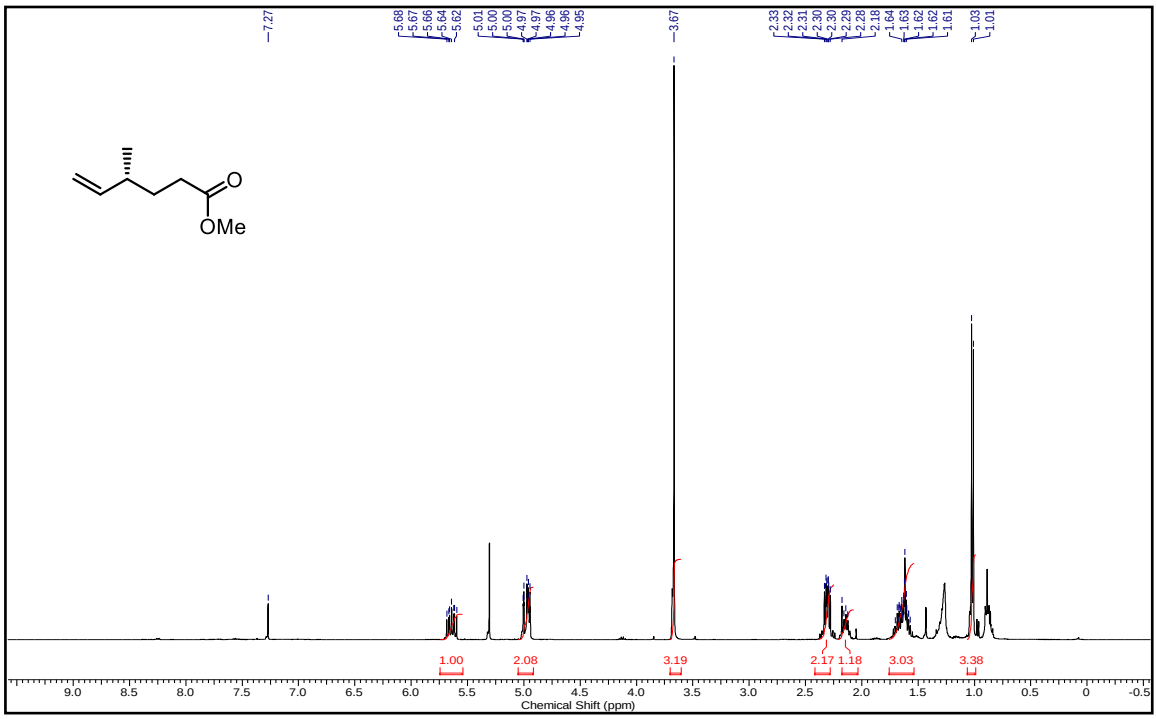
^{1}H NMR (200 MHz, $CDCl_3$) of compound 1b



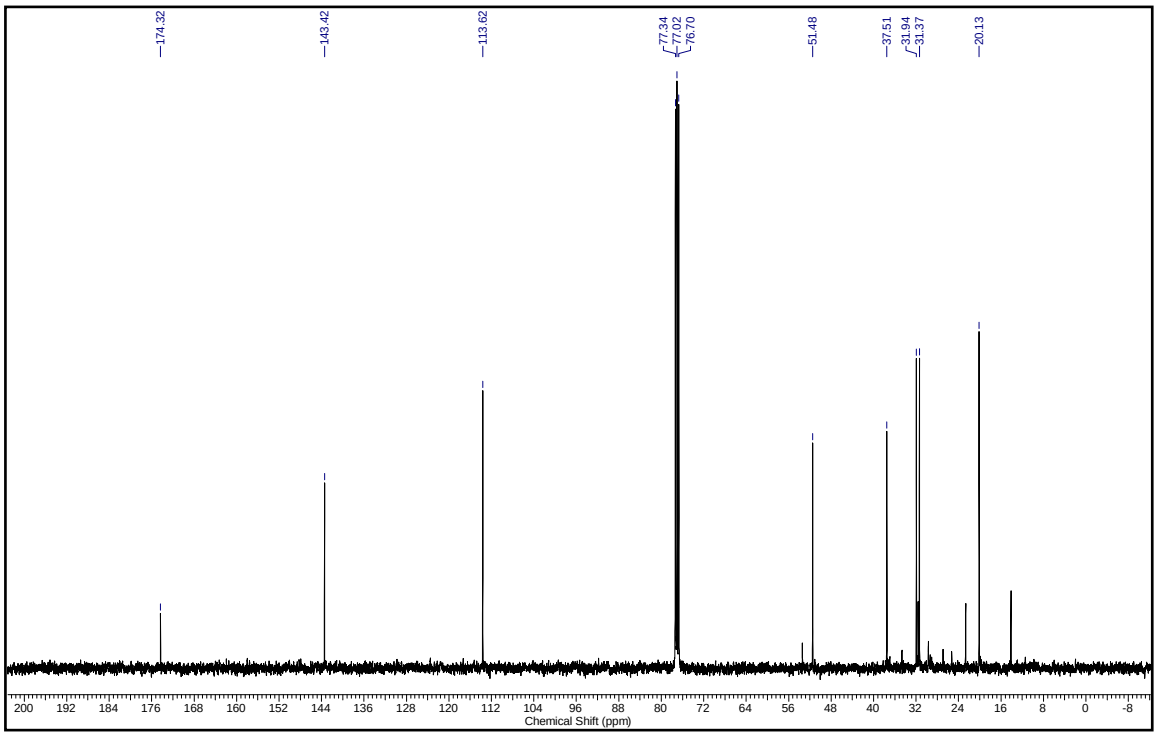
^{13}C NMR (50 MHz, $CDCl_3$) of compound 1b



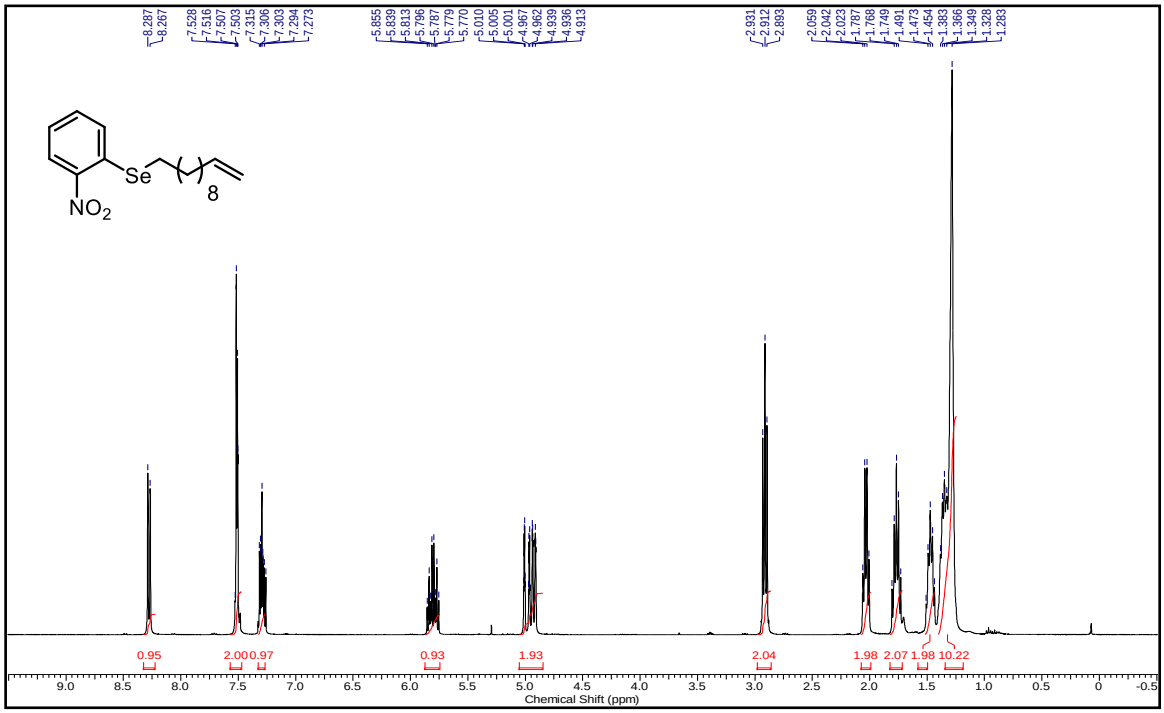
^{1}H NMR (400 MHz, $CDCl_3$) of compound 1c



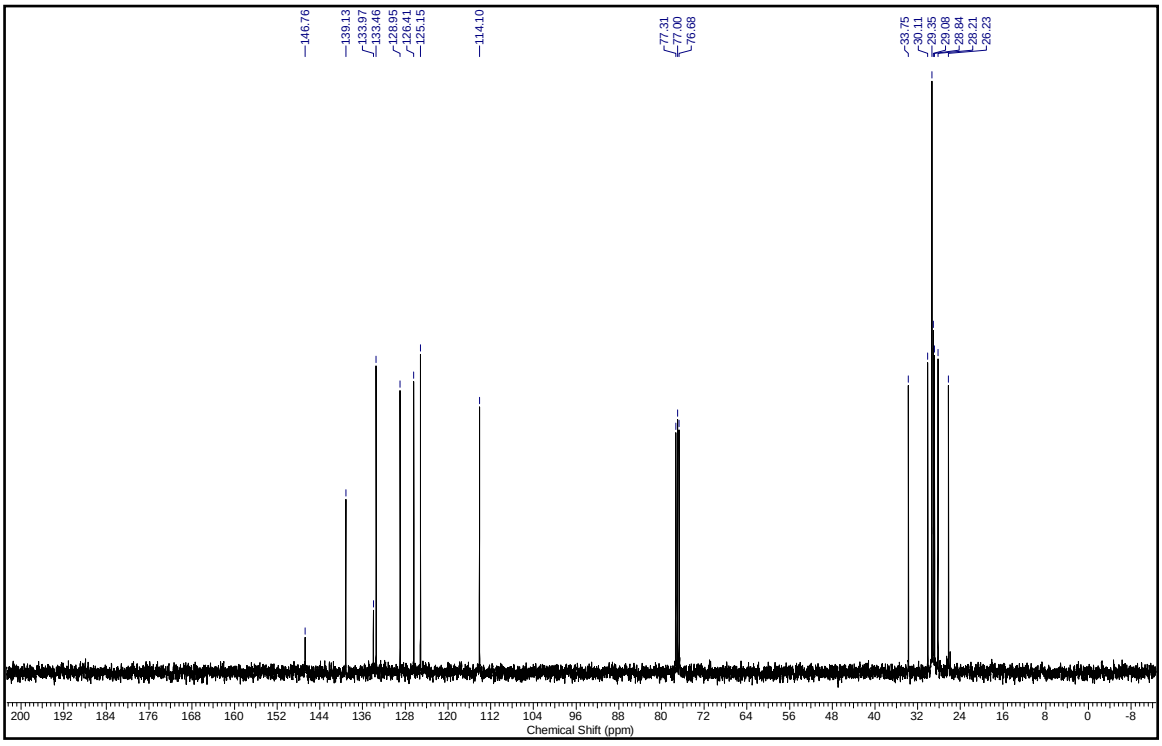
^{13}C NMR (100 MHz, $CDCl_3$) of compound 1c



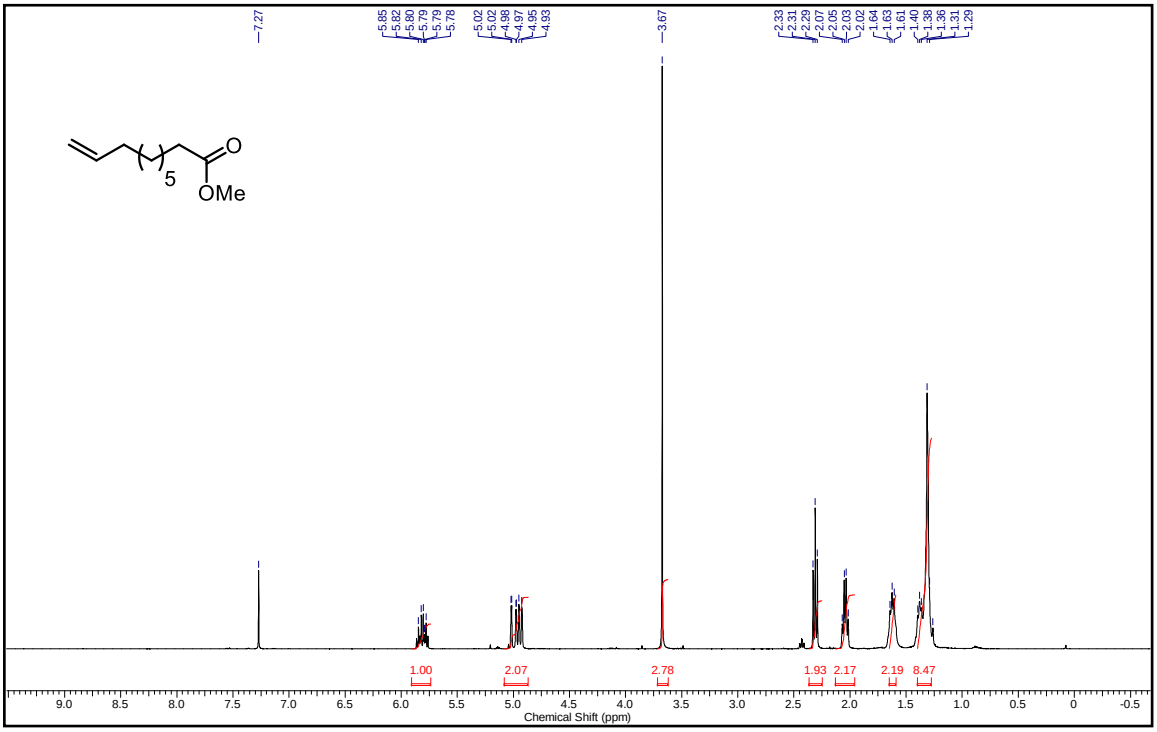
^{1}H NMR (400 MHz, $CDCl_3$) of compound 2b



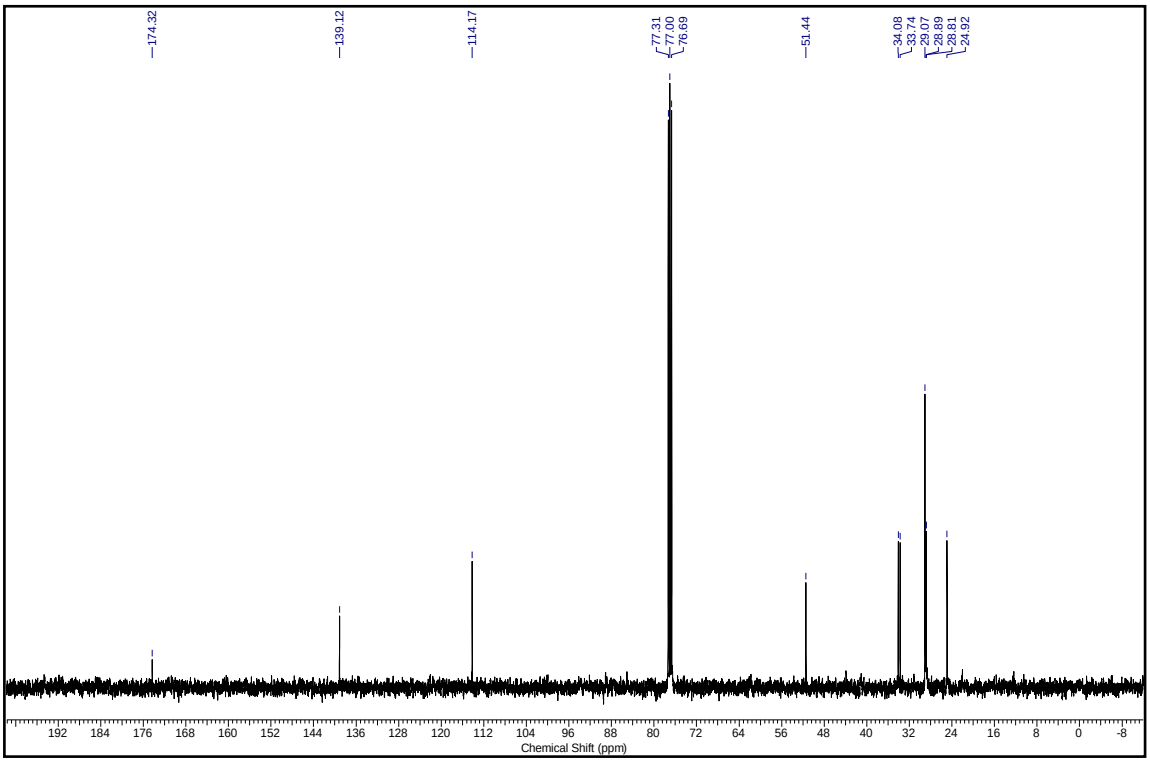
^{13}C NMR (100 MHz, $CDCl_3$) of compound 2b



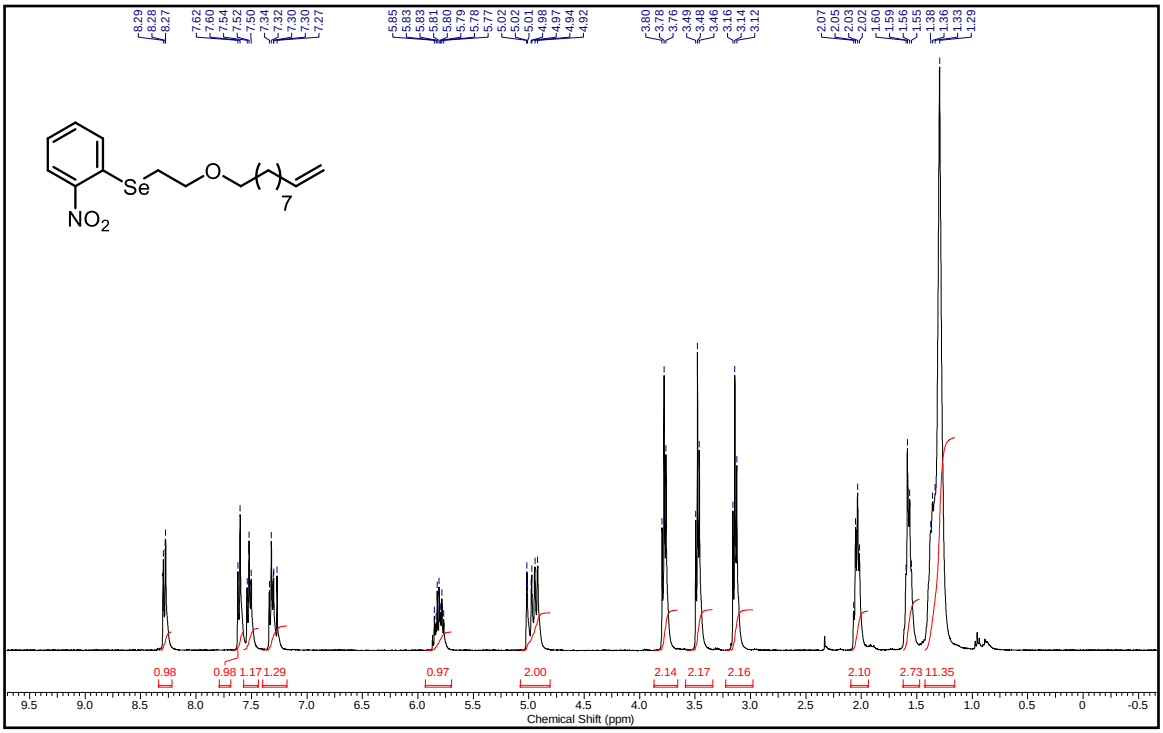
^{1}H NMR (400 MHz, $CDCl_3$) of compound 2c



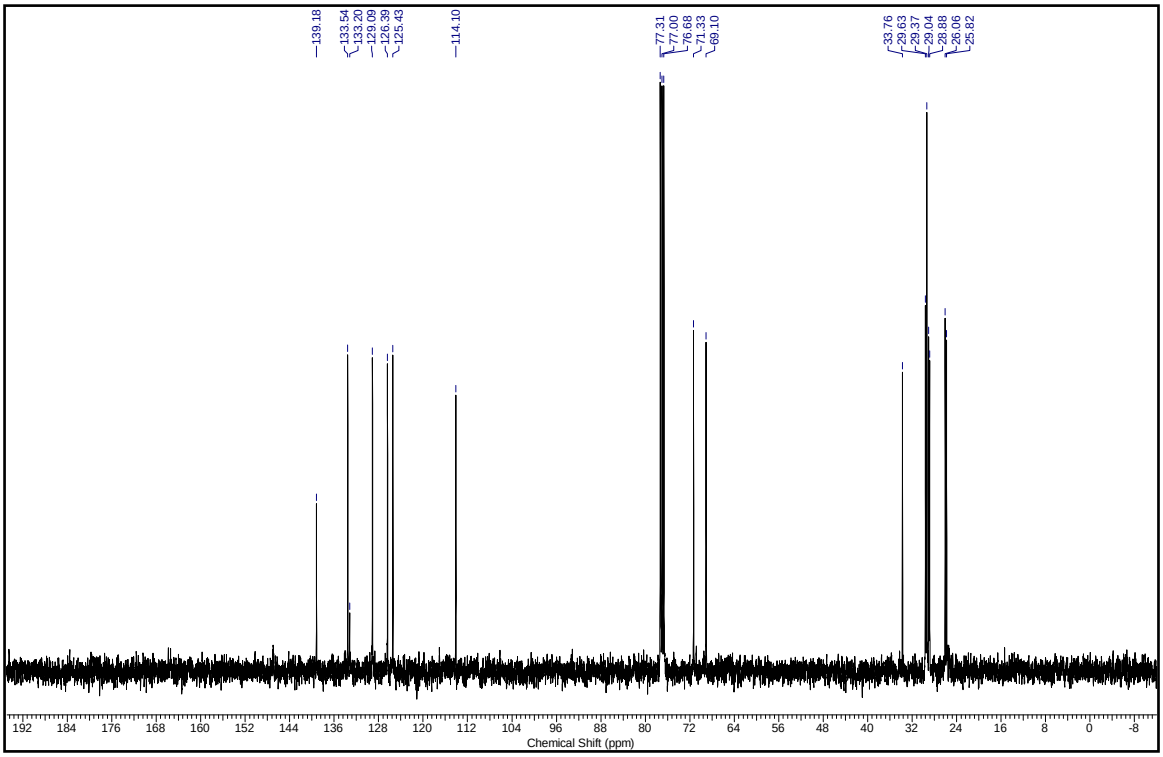
^{13}C NMR (100 MHz, $CDCl_3$) of compound 2c



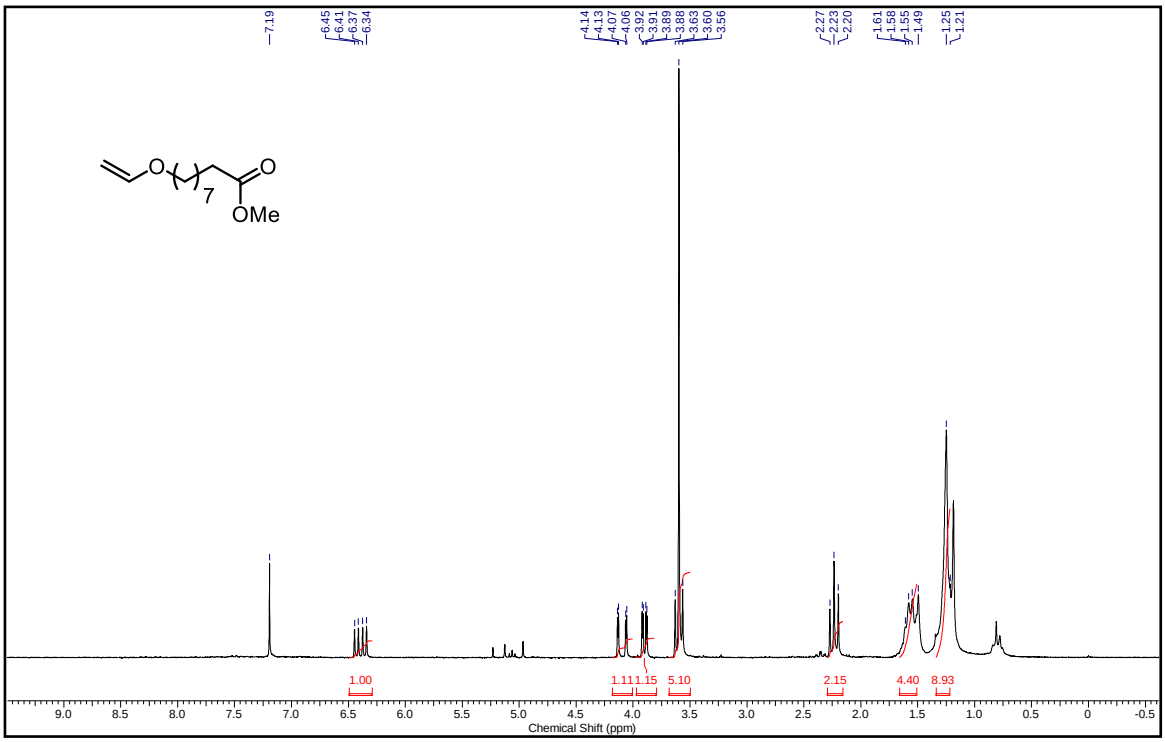
^{1}H NMR (400 MHz, $CDCl_3$) of compound 3b



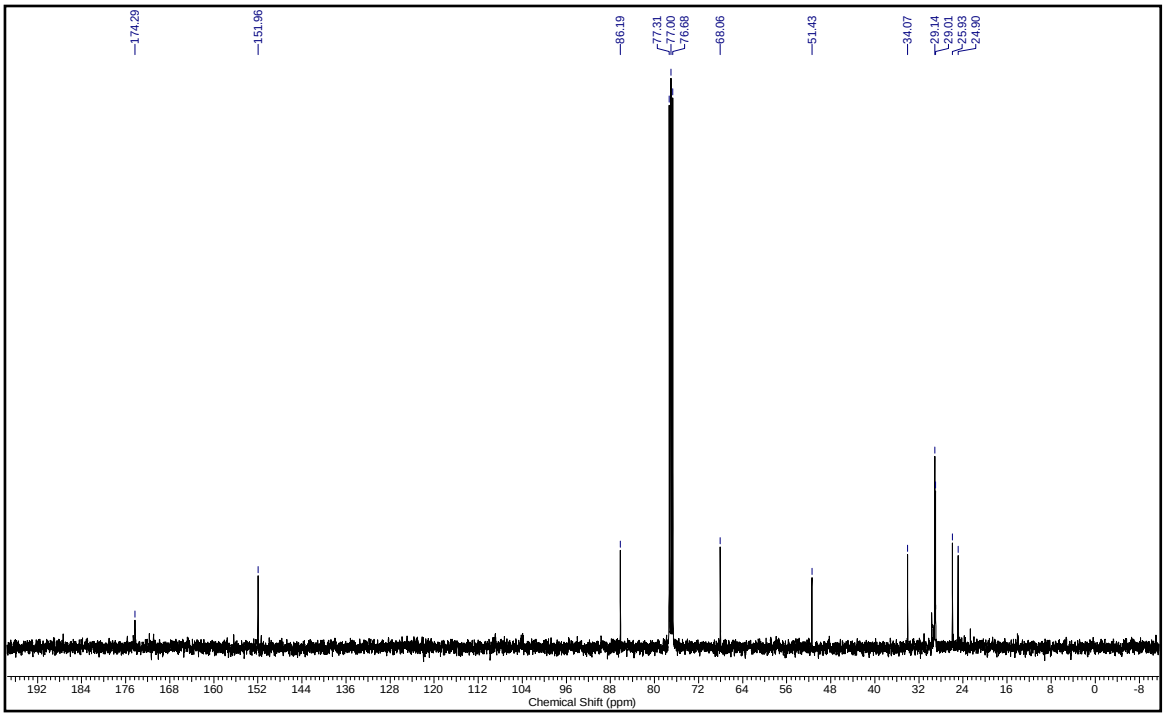
^{13}C NMR (50 MHz, $CDCl_3$) of compound 3b



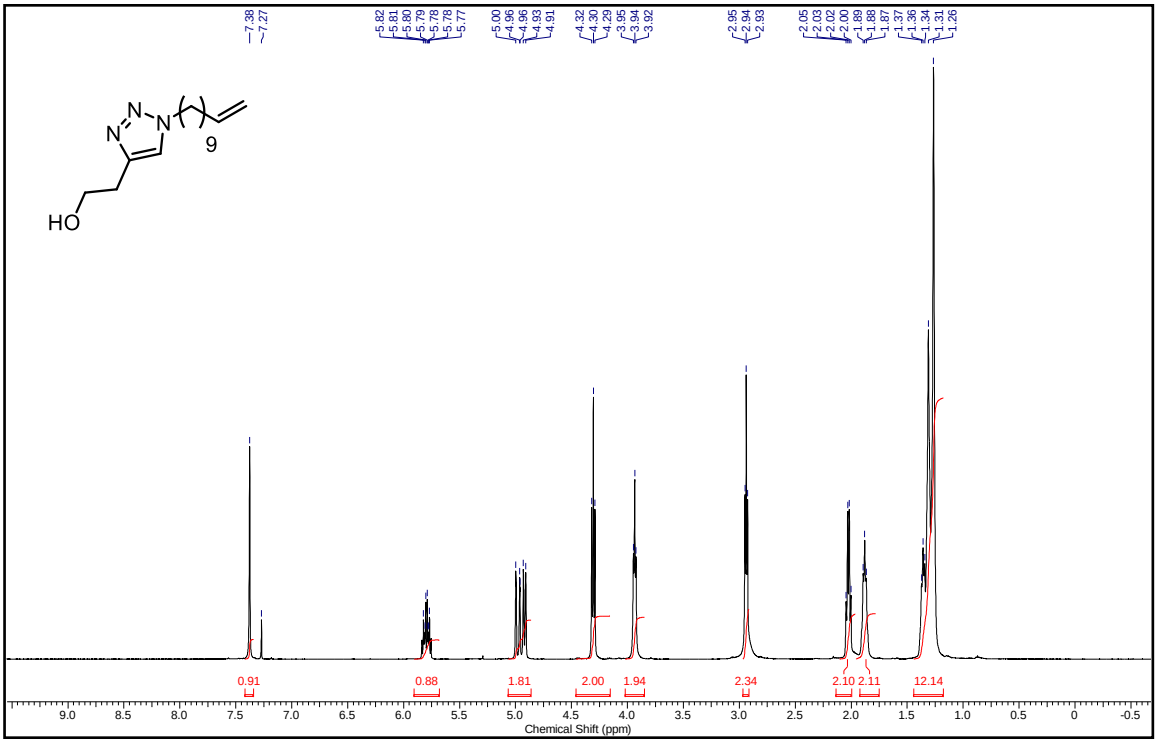
^{1}H NMR (200 MHz, $CDCl_3$) of compound 3c



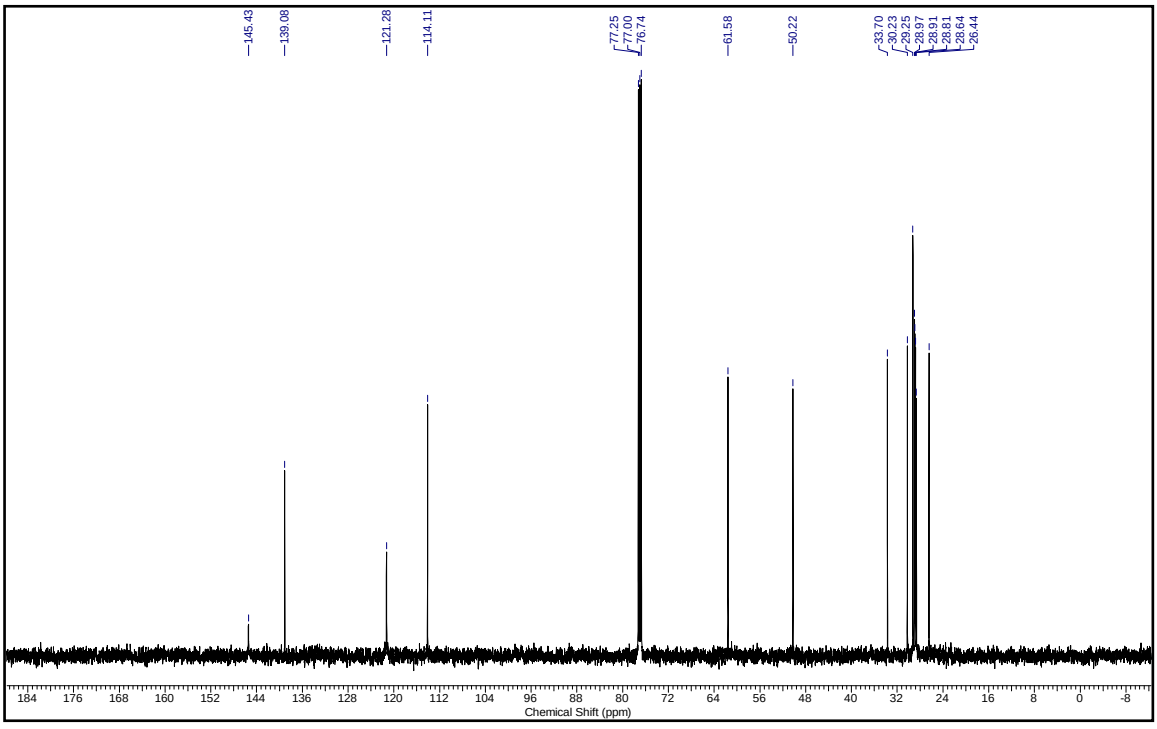
^{13}C NMR (100 MHz, $CDCl_3$) of compound 3c



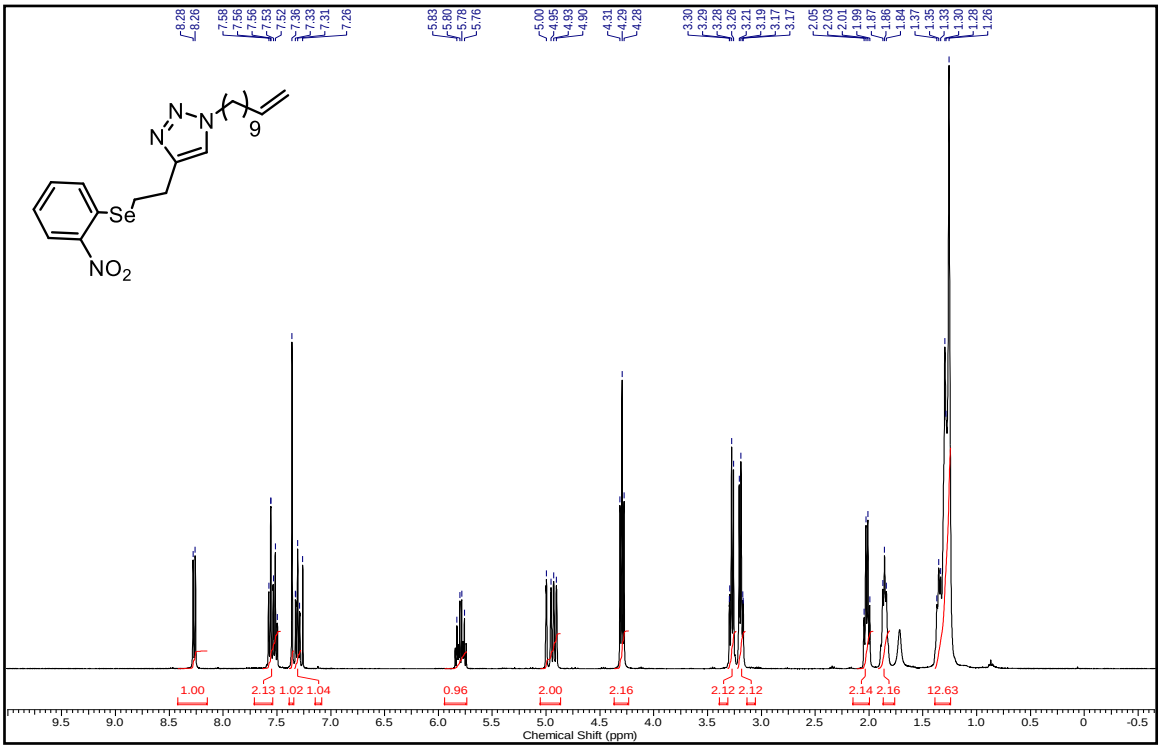
^{1}H NMR (500 MHz, $CDCl_3$) of compound 4a



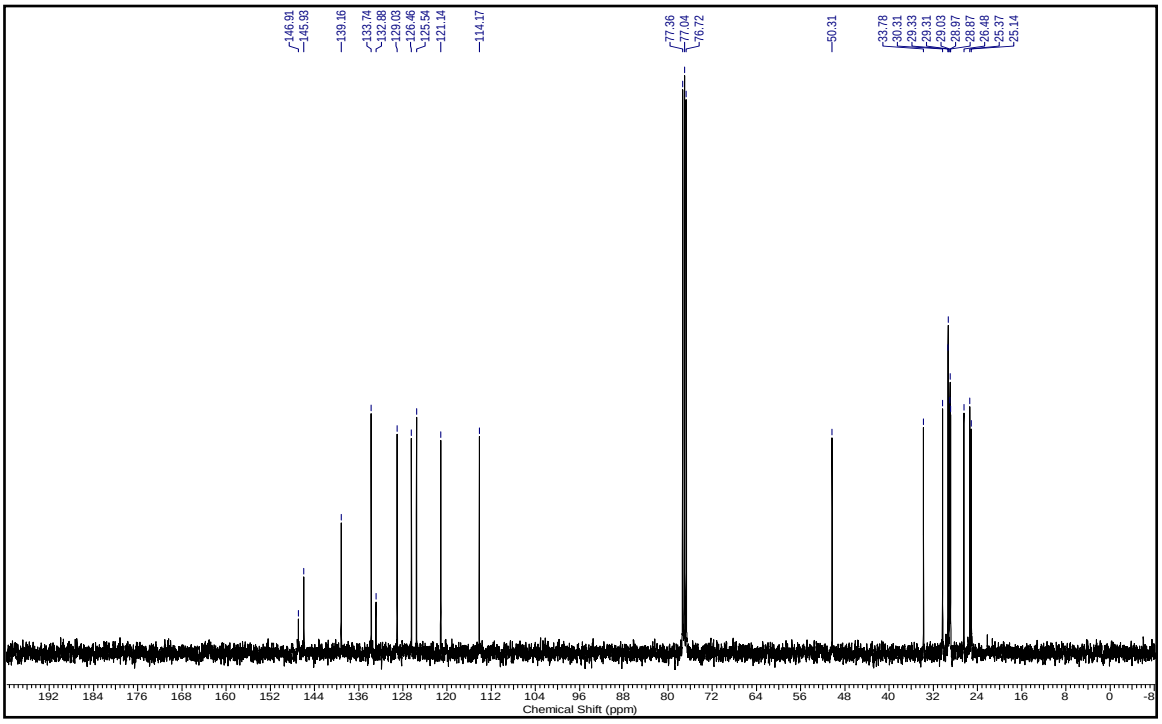
^{13}C NMR (125 MHz, $CDCl_3$) of compound 4a



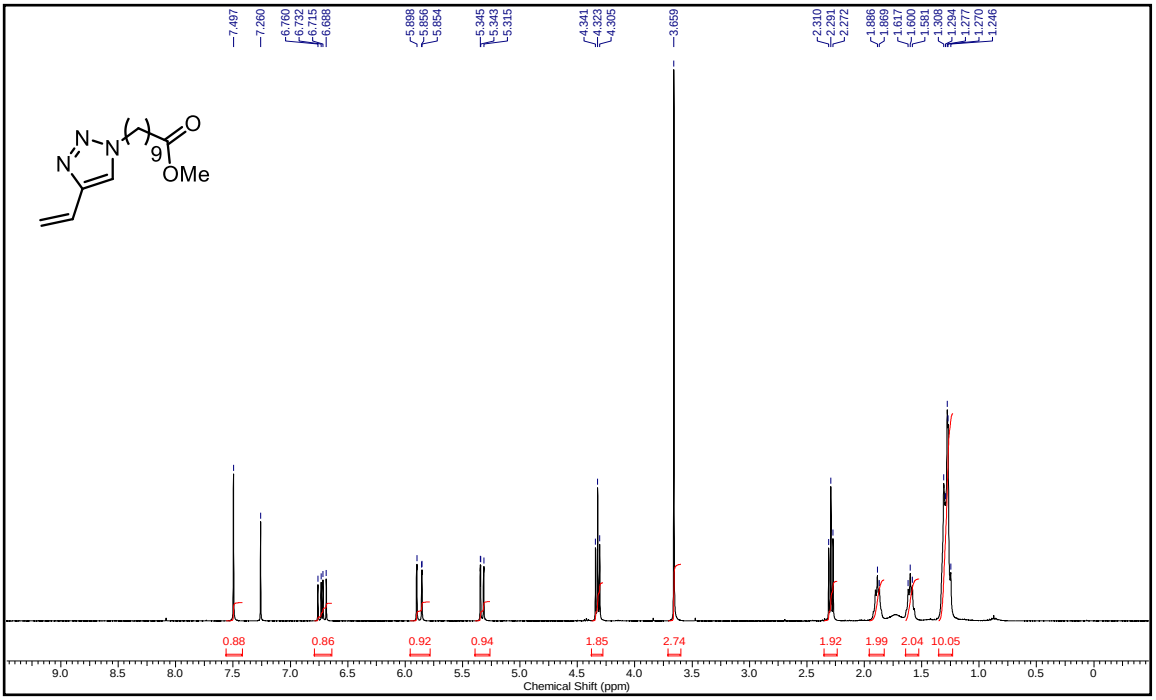
^{1}H NMR (400 MHz, $CDCl_3$) of compound 4b



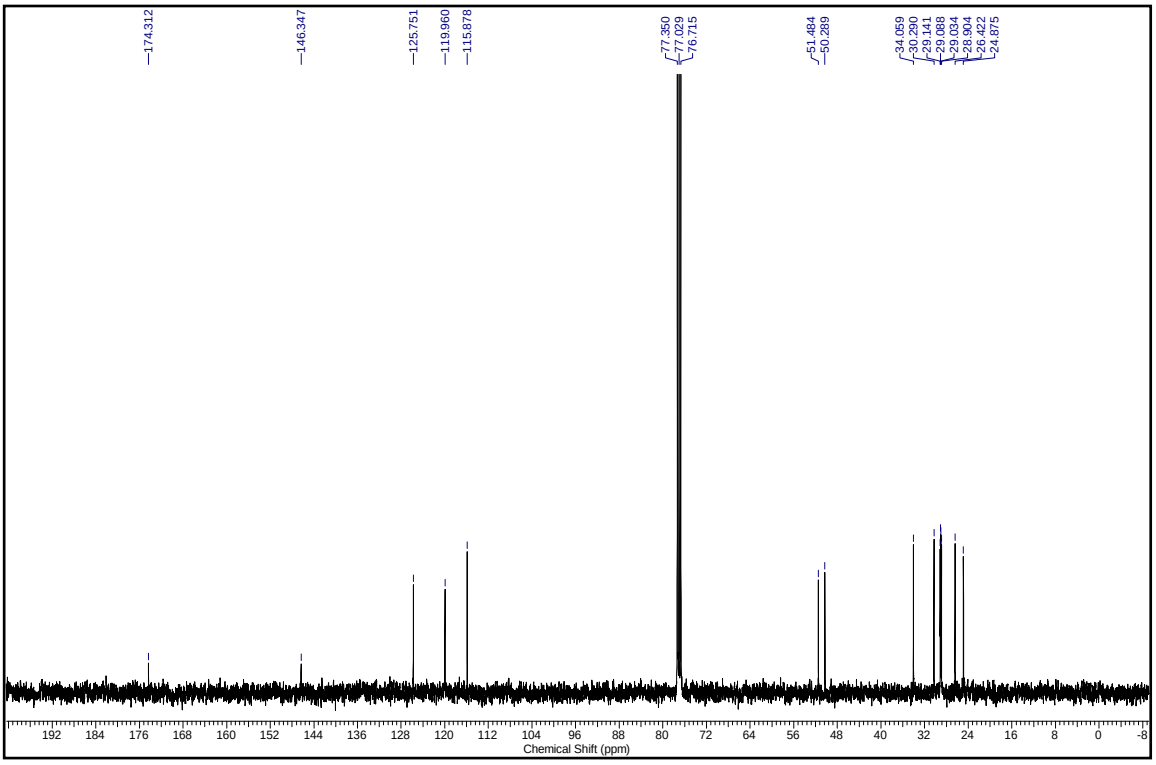
^{13}C NMR (100 MHz, $CDCl_3$) of compound 4b



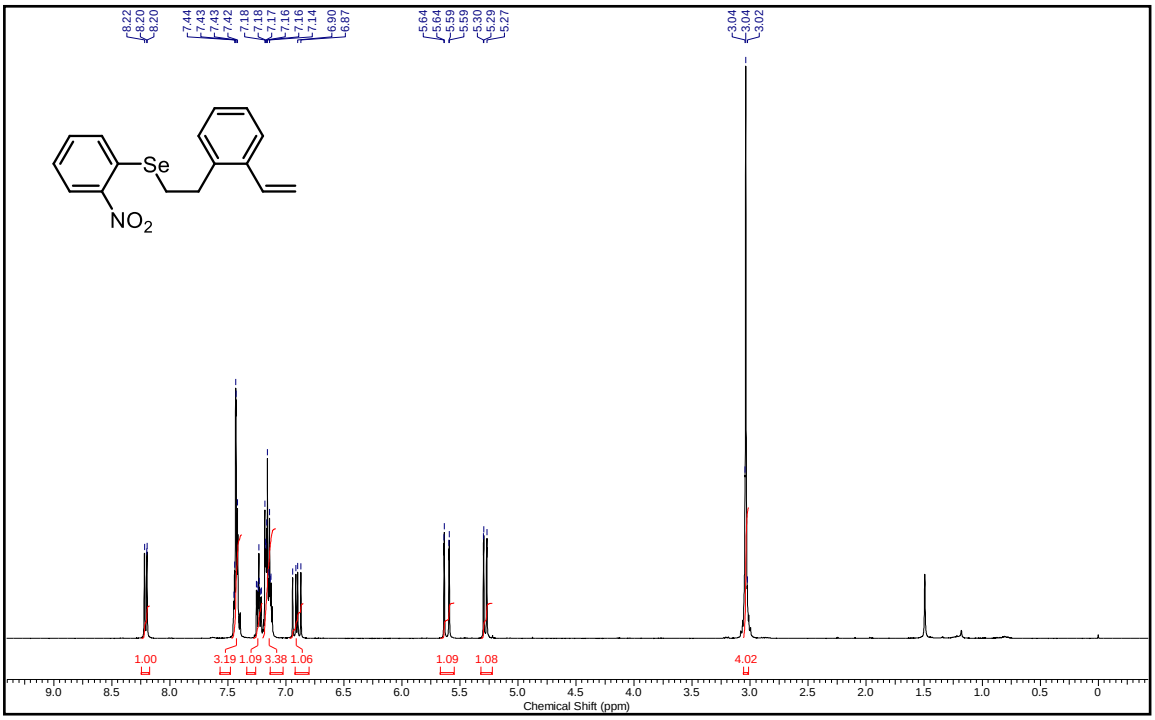
^{1}H NMR (400 MHz, $CDCl_3$) of compound 4c



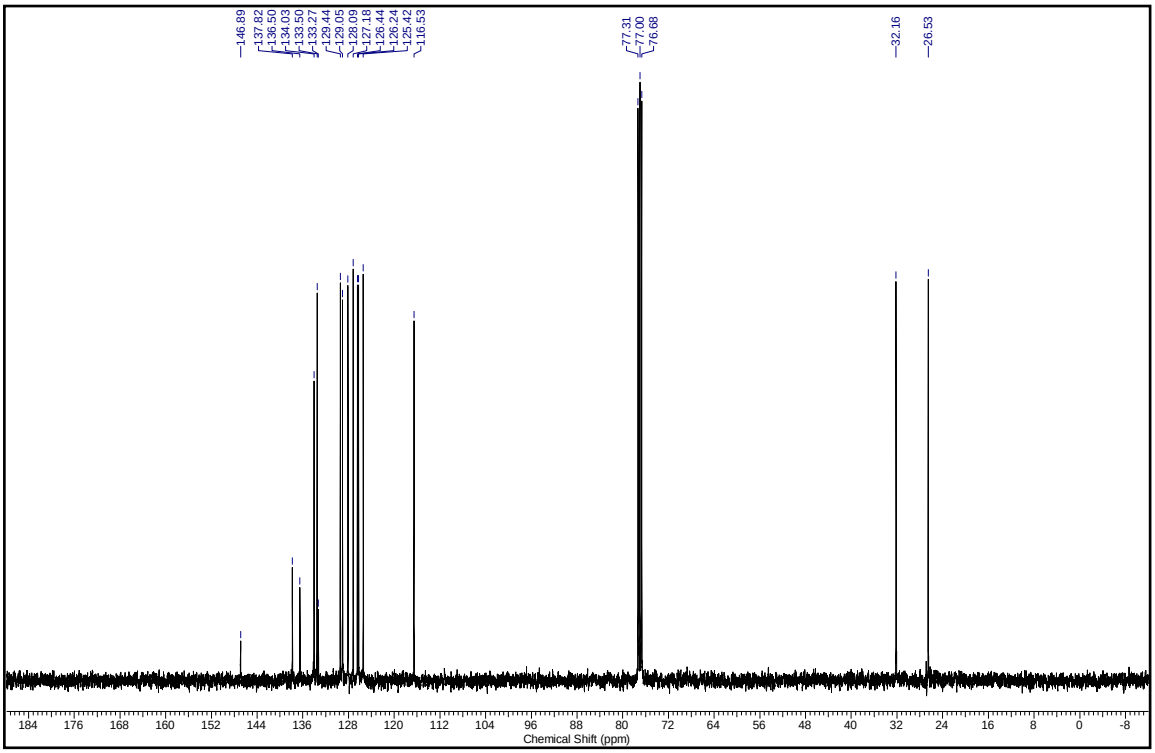
^{13}C NMR (100 MHz, $CDCl_3$) of compound 4c



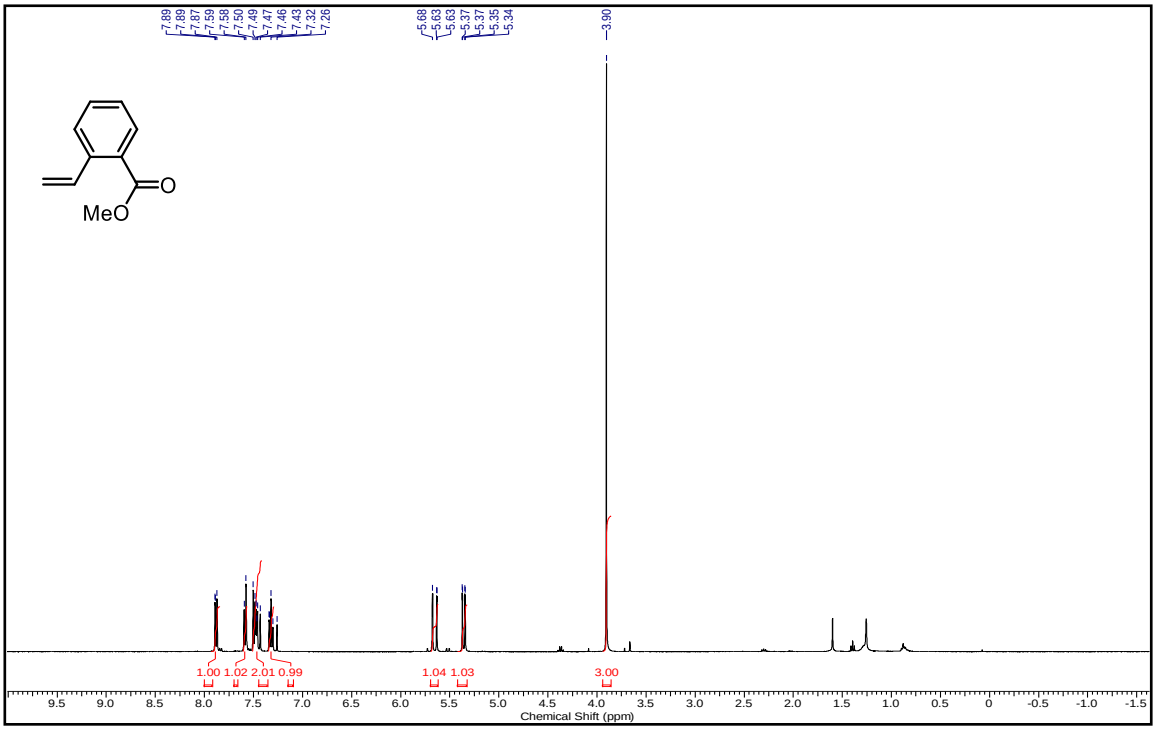
^{1}H NMR (400 MHz, $CDCl_3$) of compound 5b



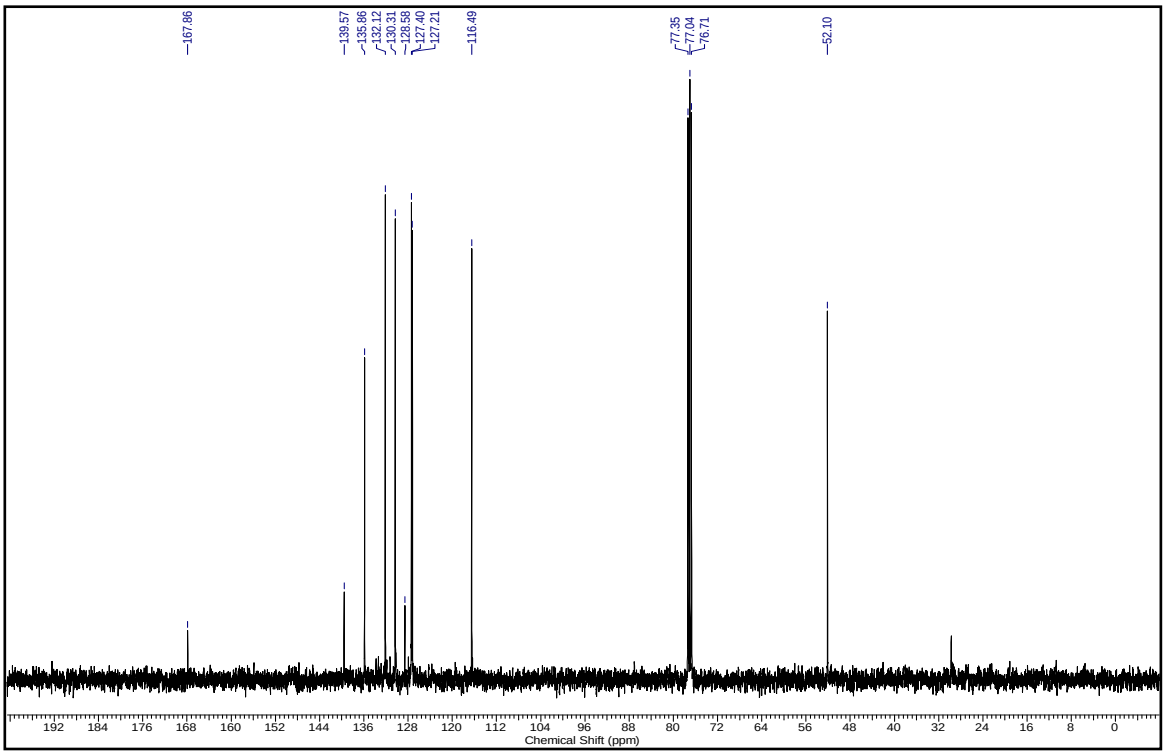
^{13}C NMR (100 MHz, $CDCl_3$) of compound 5b



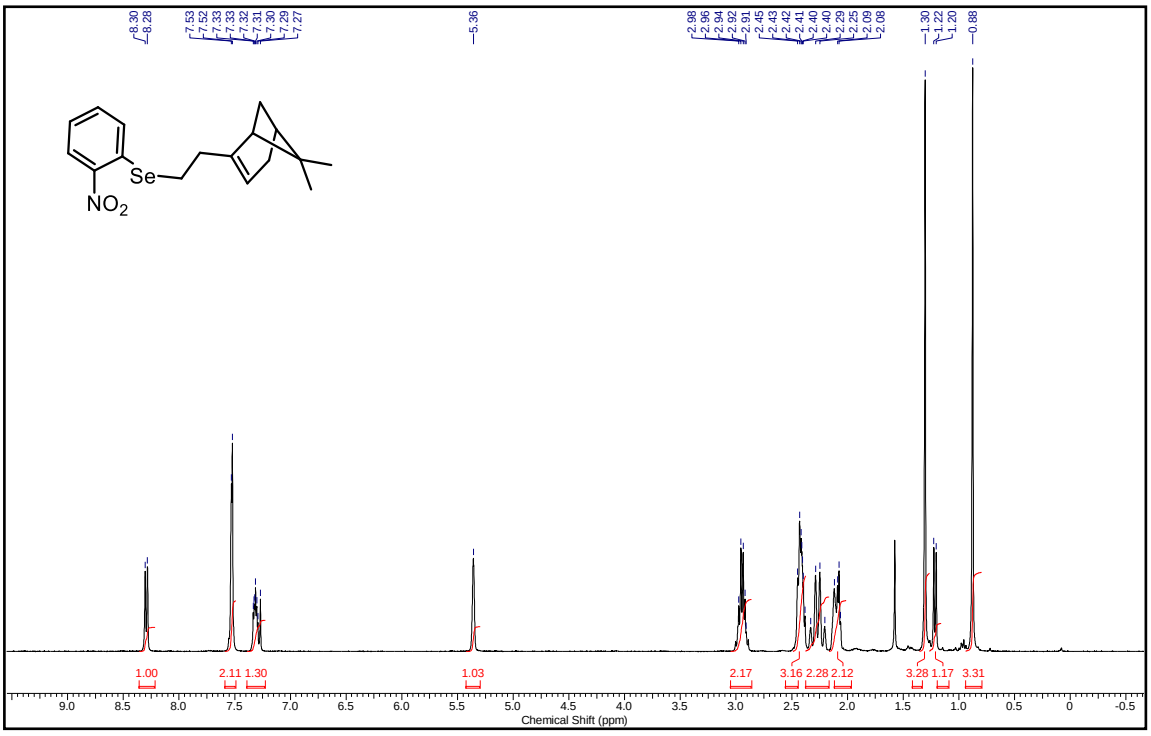
^{1}H NMR (400 MHz, $CDCl_3$) of compound 5c



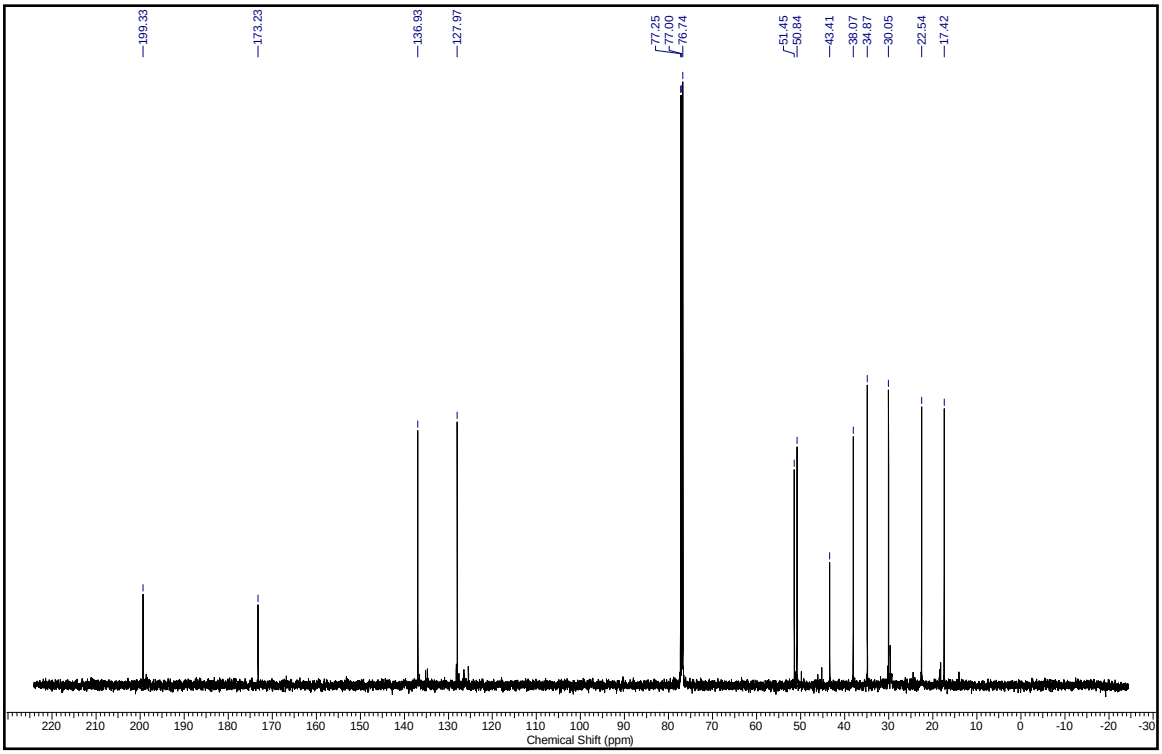
^{13}C NMR (100 MHz, $CDCl_3$) of compound 5c



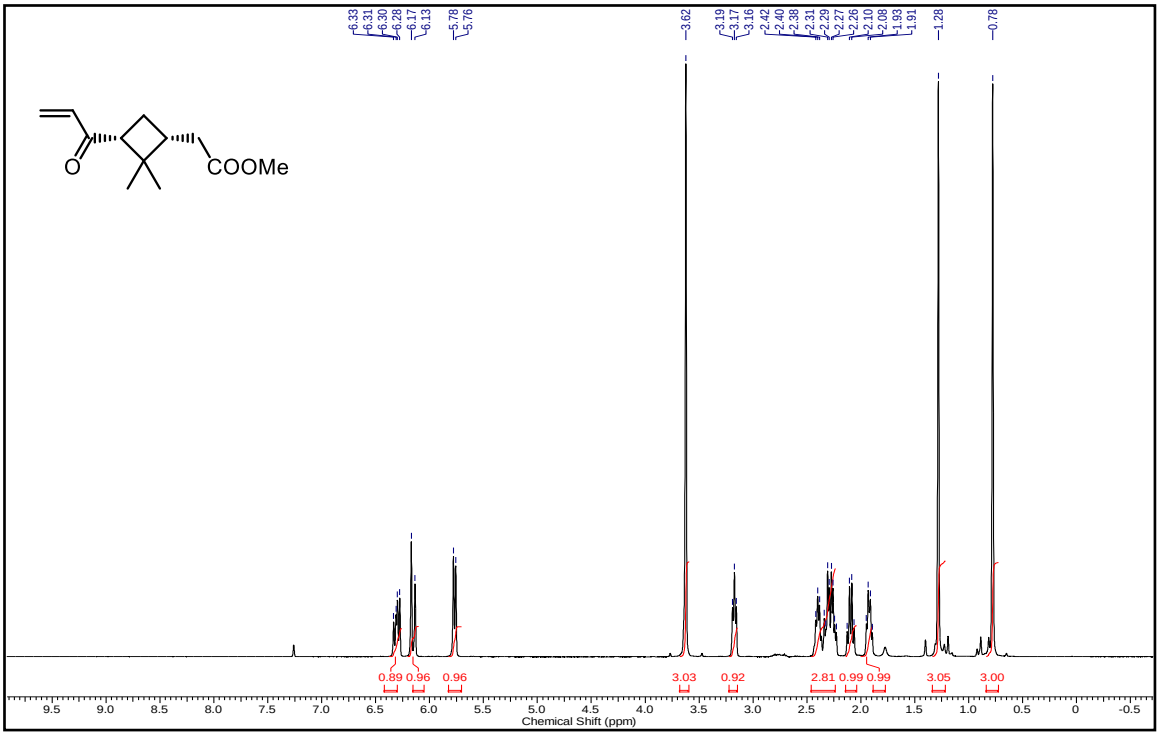
^{1}H NMR (400 MHz, $CDCl_3$) of compound 6b



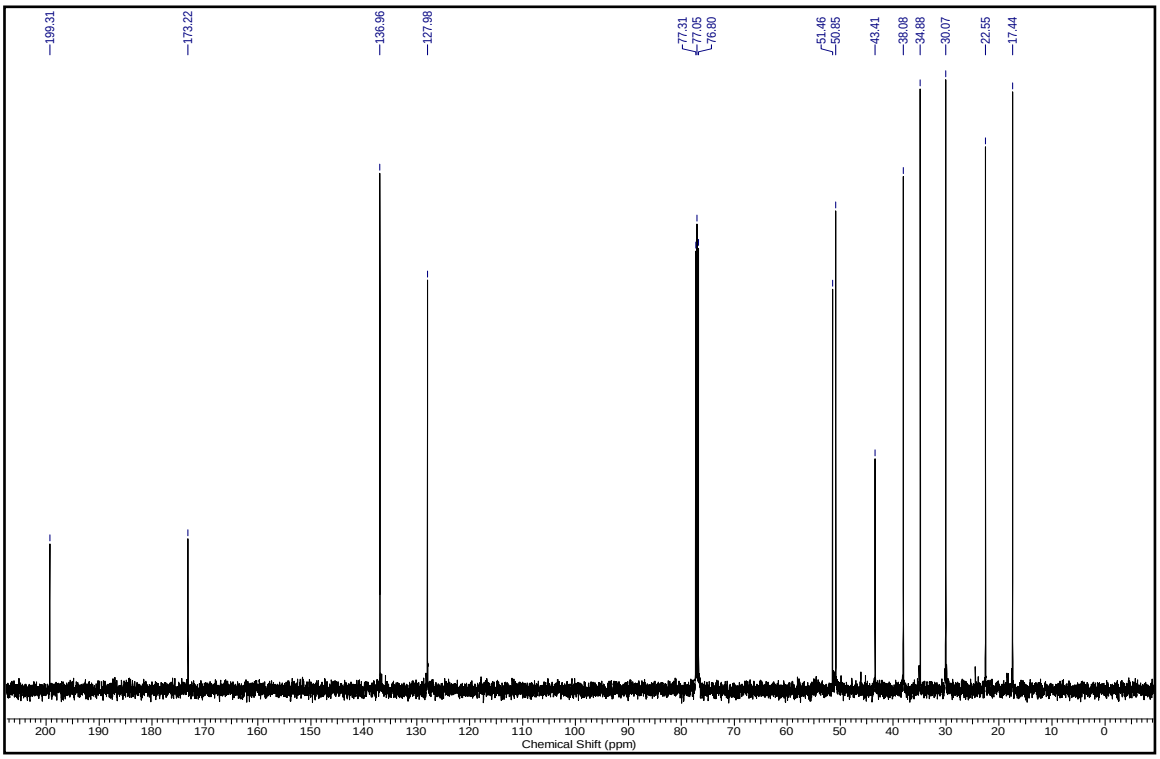
^{13}C NMR (100 MHz, $CDCl_3$) of compound 6b



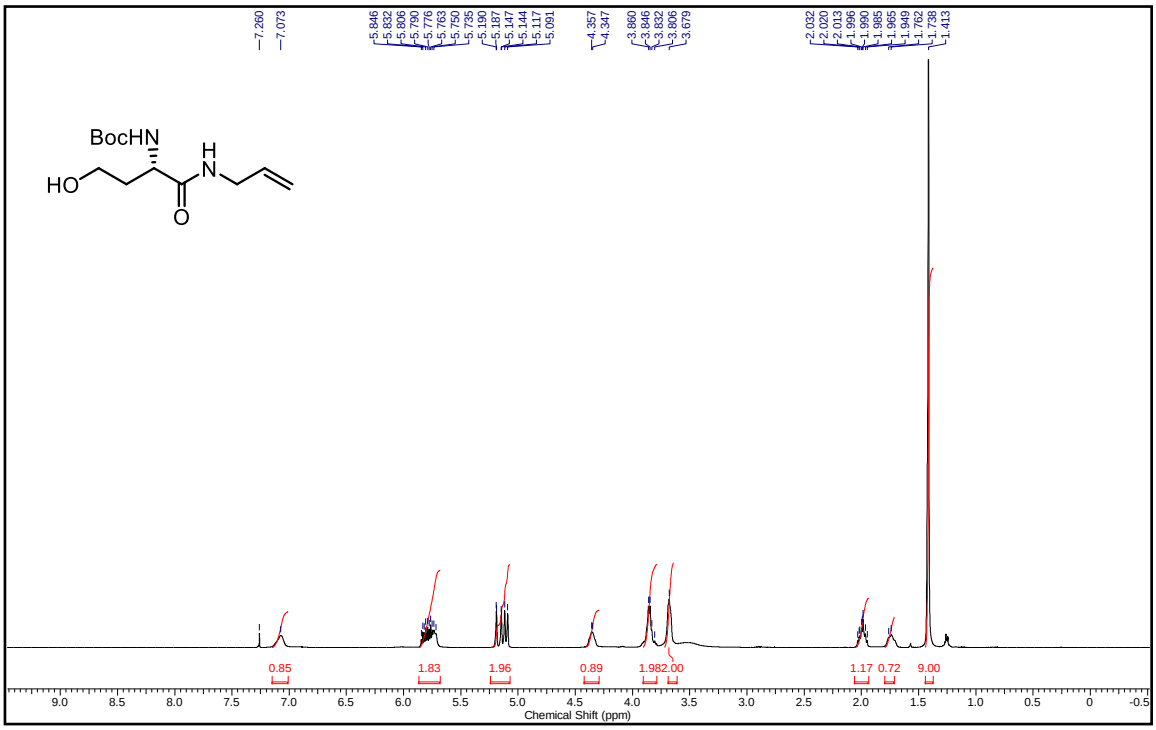
^{1}H NMR (500 MHz, $CDCl_3$) of compound 6c



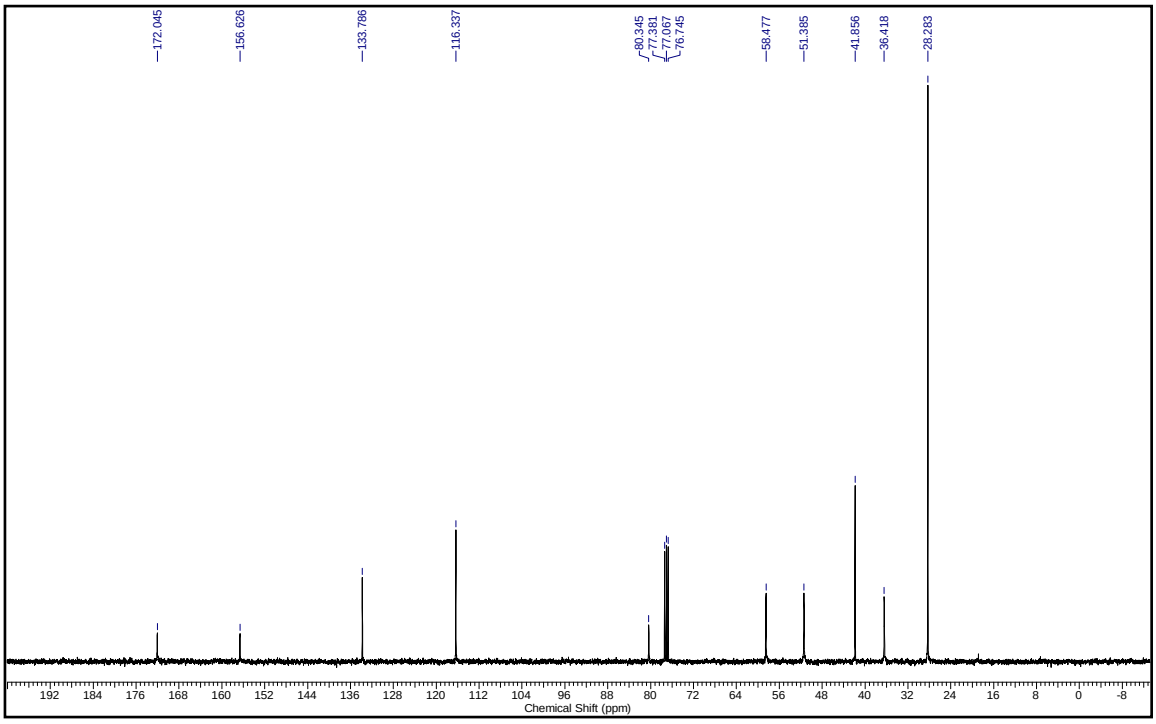
^{13}C NMR (100 MHz, $CDCl_3$) of compound 6c



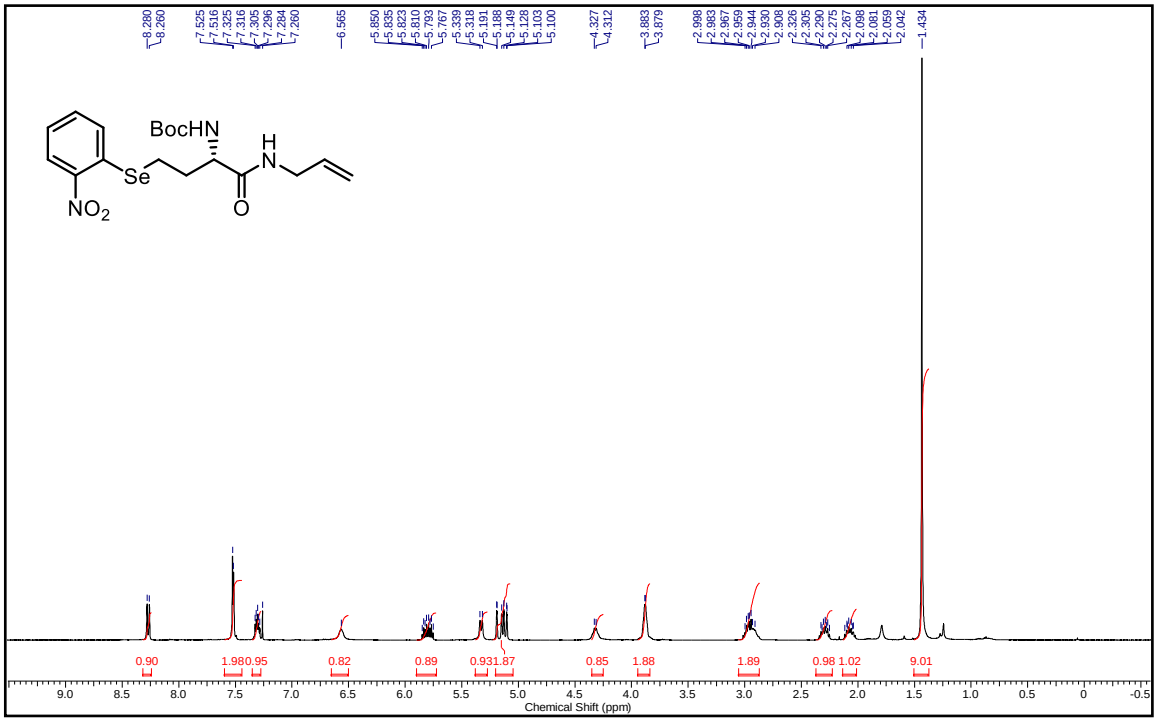
^{1}H NMR (400 MHz, $CDCl_3$) of compound 7a



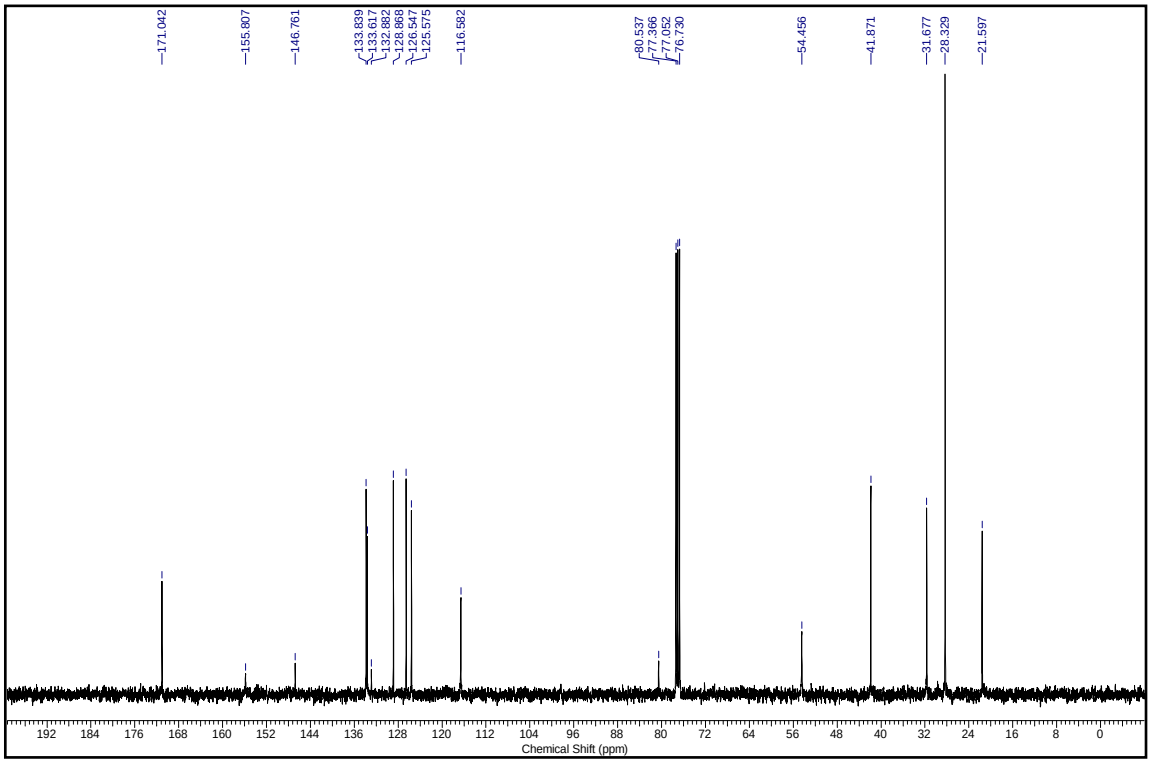
^{13}C NMR (100 MHz, $CDCl_3$) of compound 7a



H NMR (400 MHz, $CDCl_3$) of compound 7b



^{13}C NMR (100 MHz, $CDCl_3$) of compound 7b



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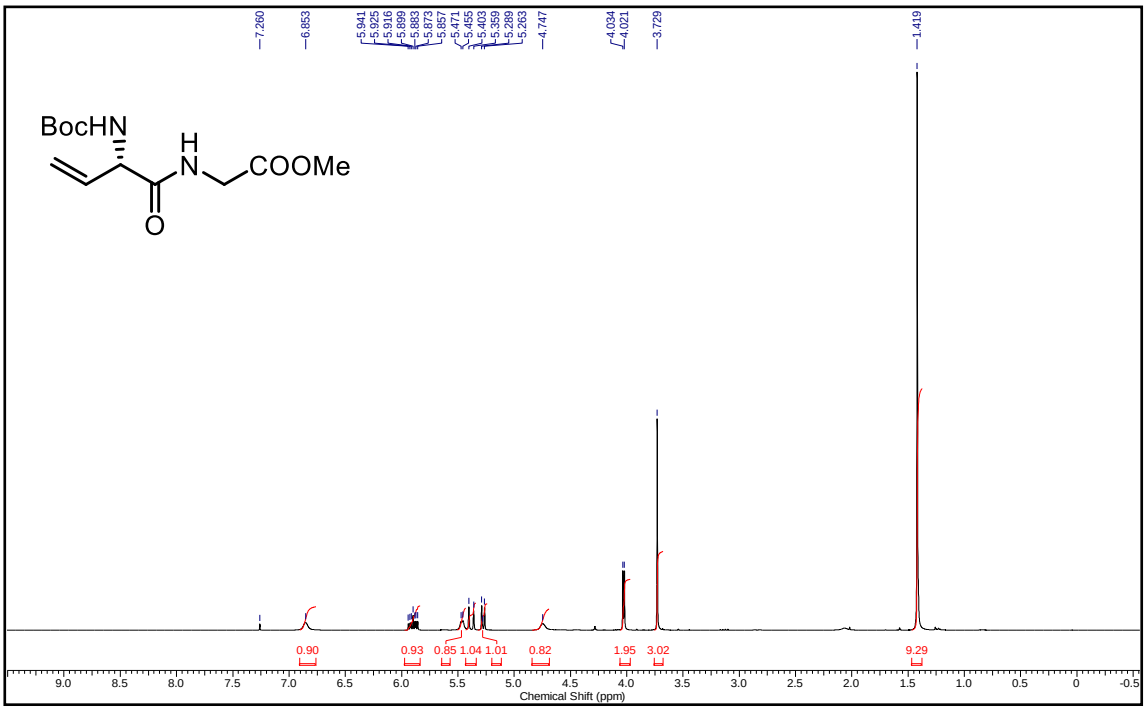

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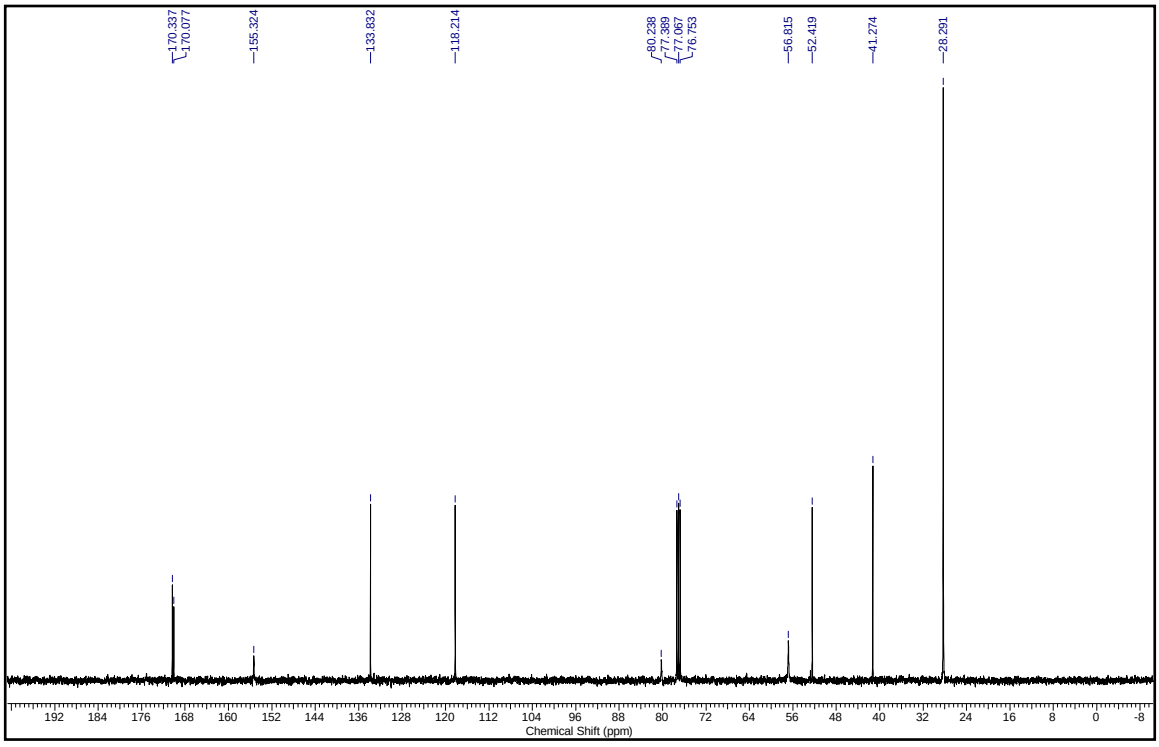
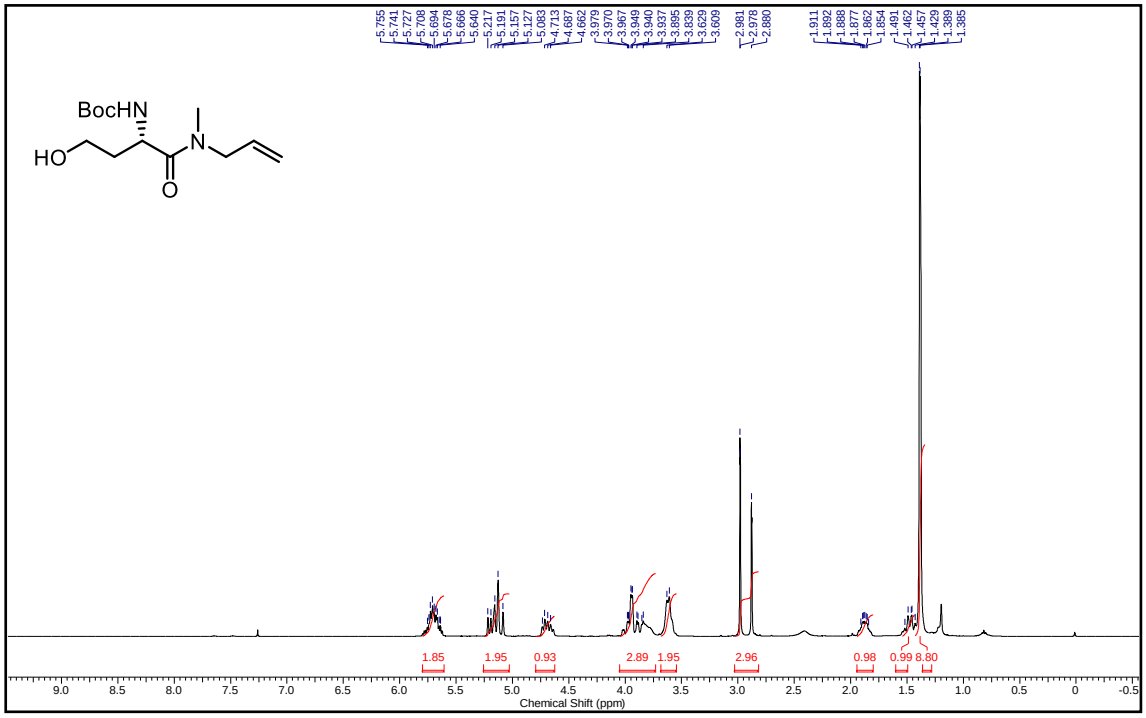
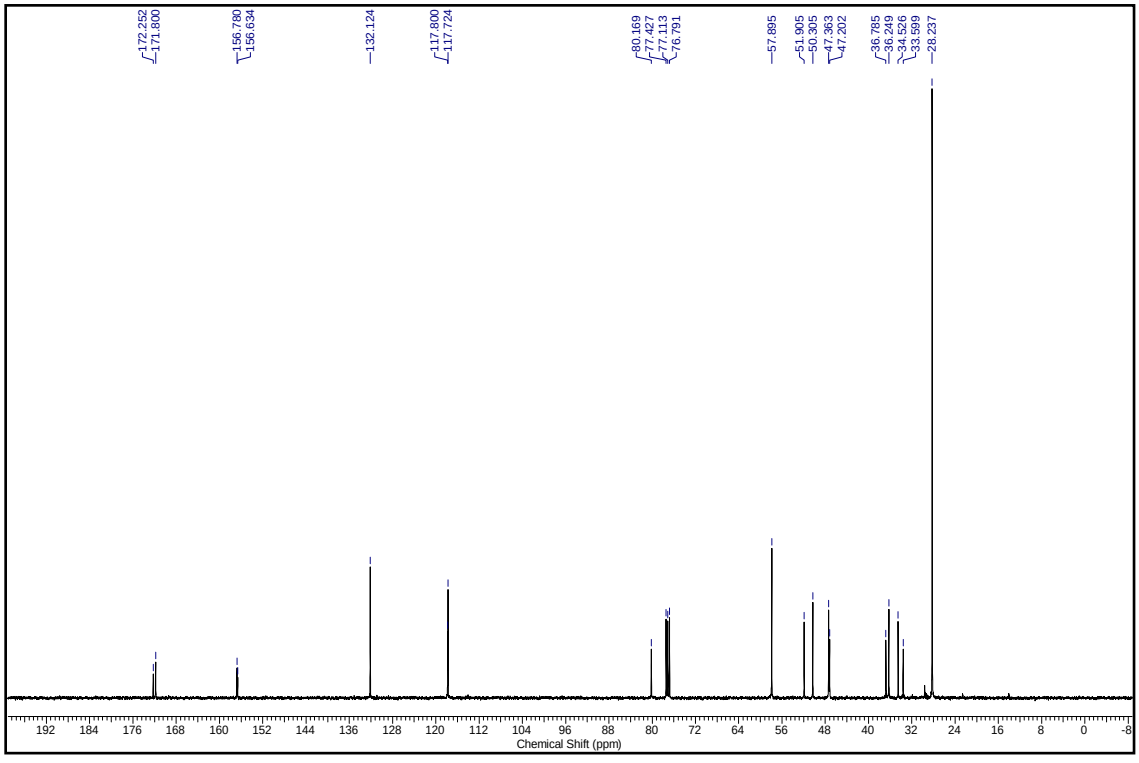


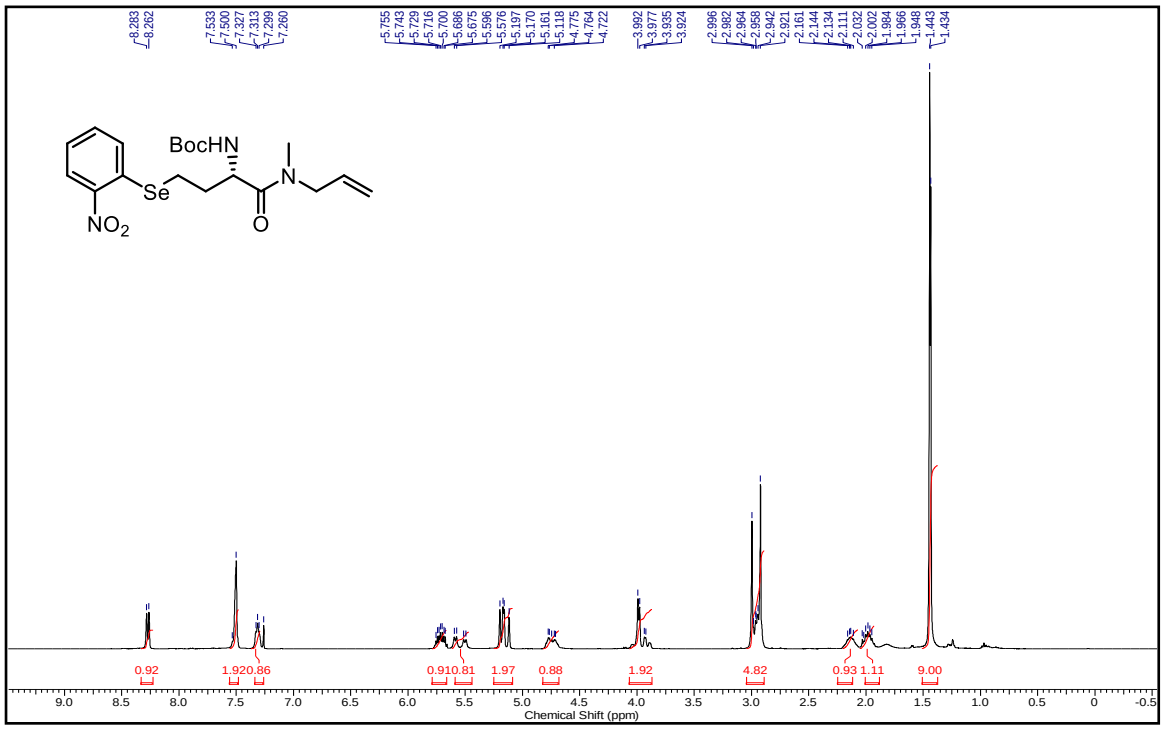
^{1}H NMR (400 MHz, $CDCl_3$) of compound 8a



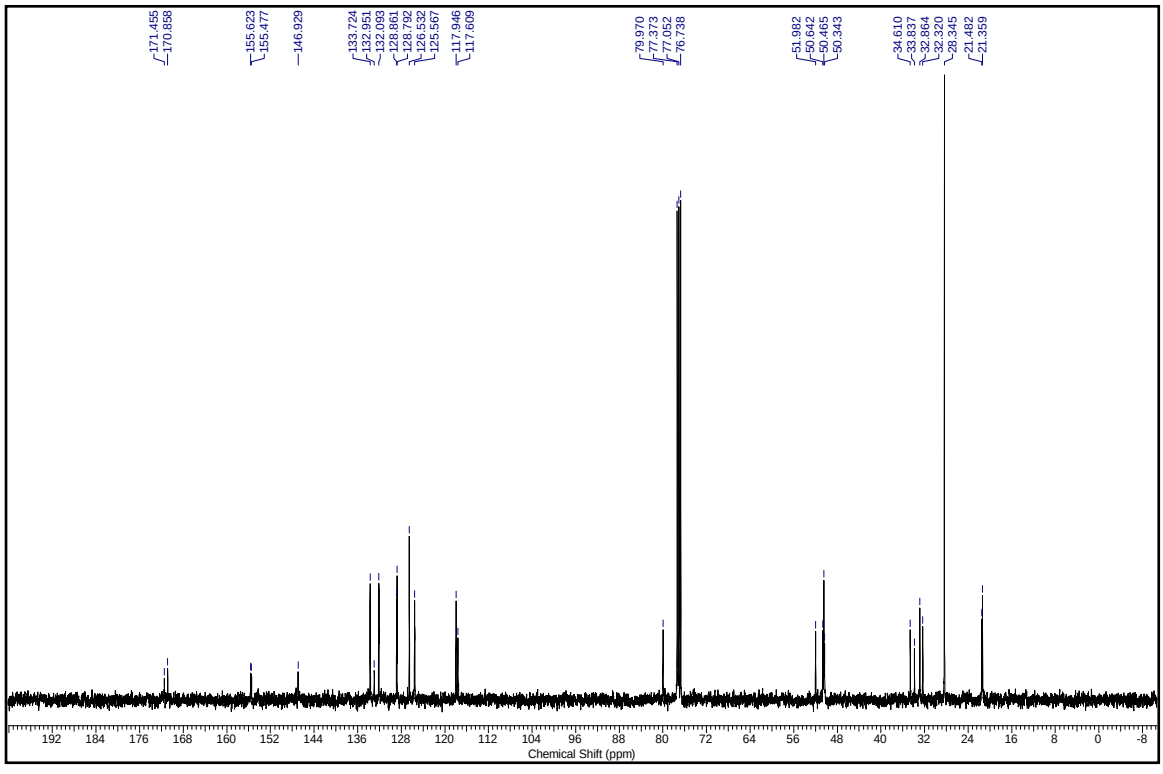
^{13}C NMR (400 MHz, $CDCl_3$) of compound 8a



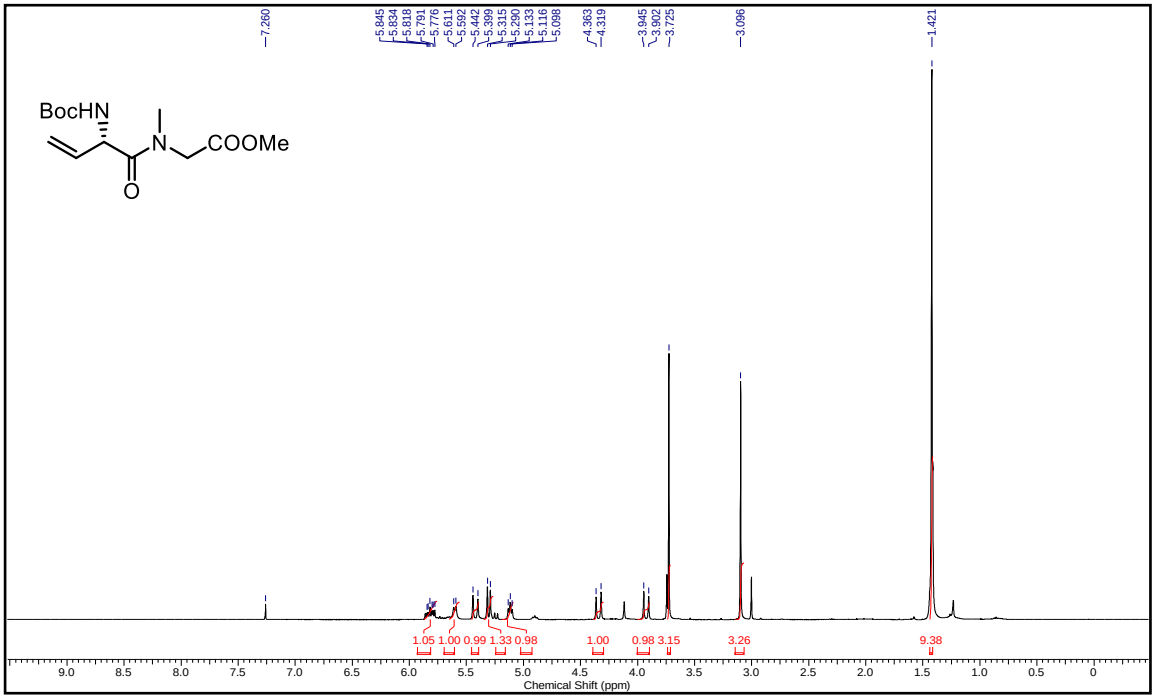
^{1}H NMR (400 MHz, $CDCl_3$) of compound 8b



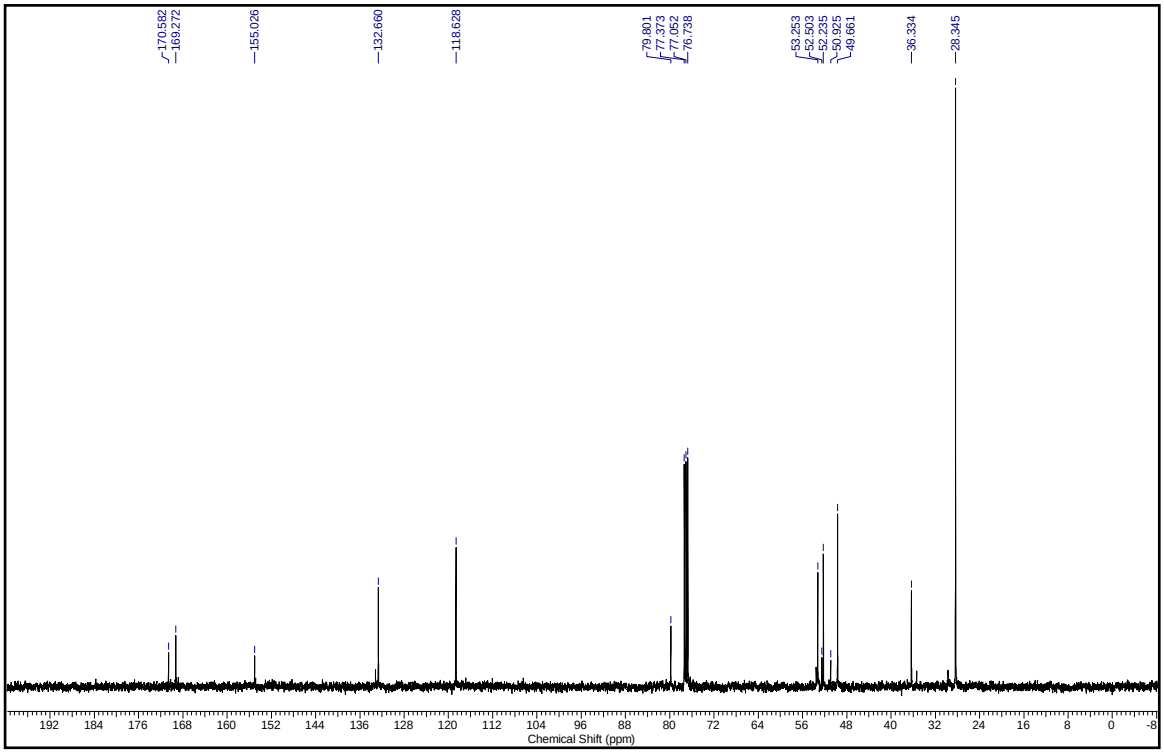
^{13}C NMR (100 MHz, $CDCl_3$) of compound 8b



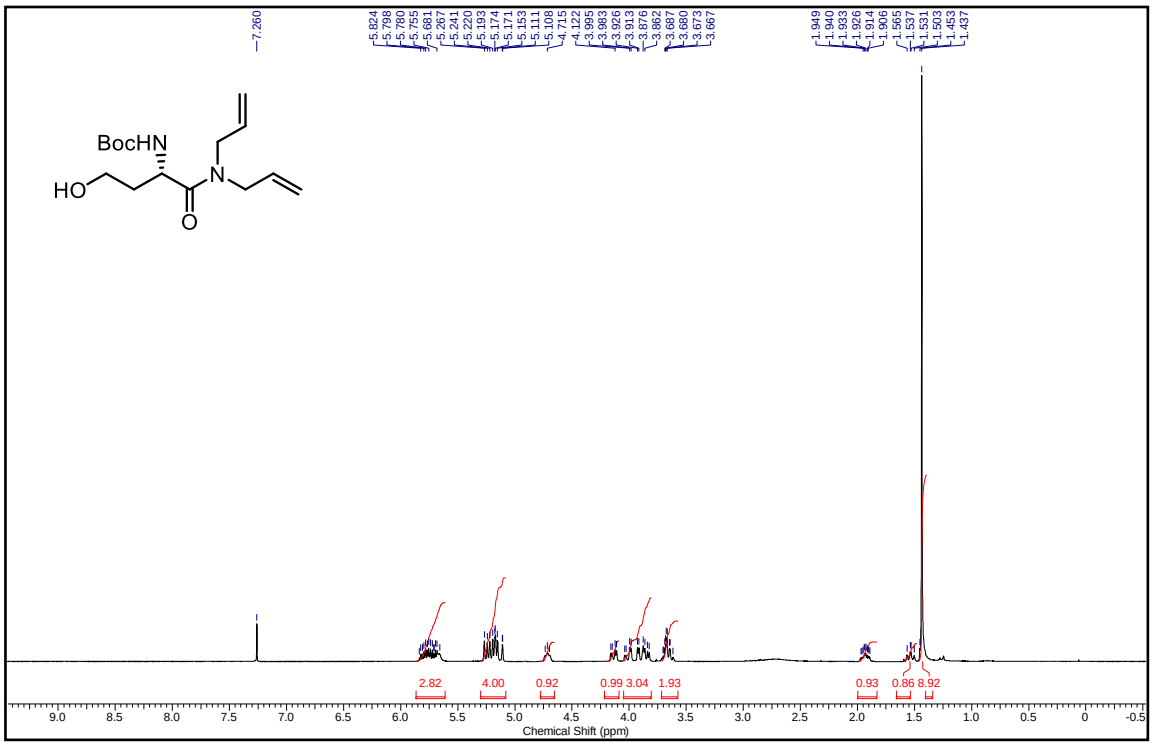
^{1}H NMR (400 MHz, $CDCl_3$) of compound 8c



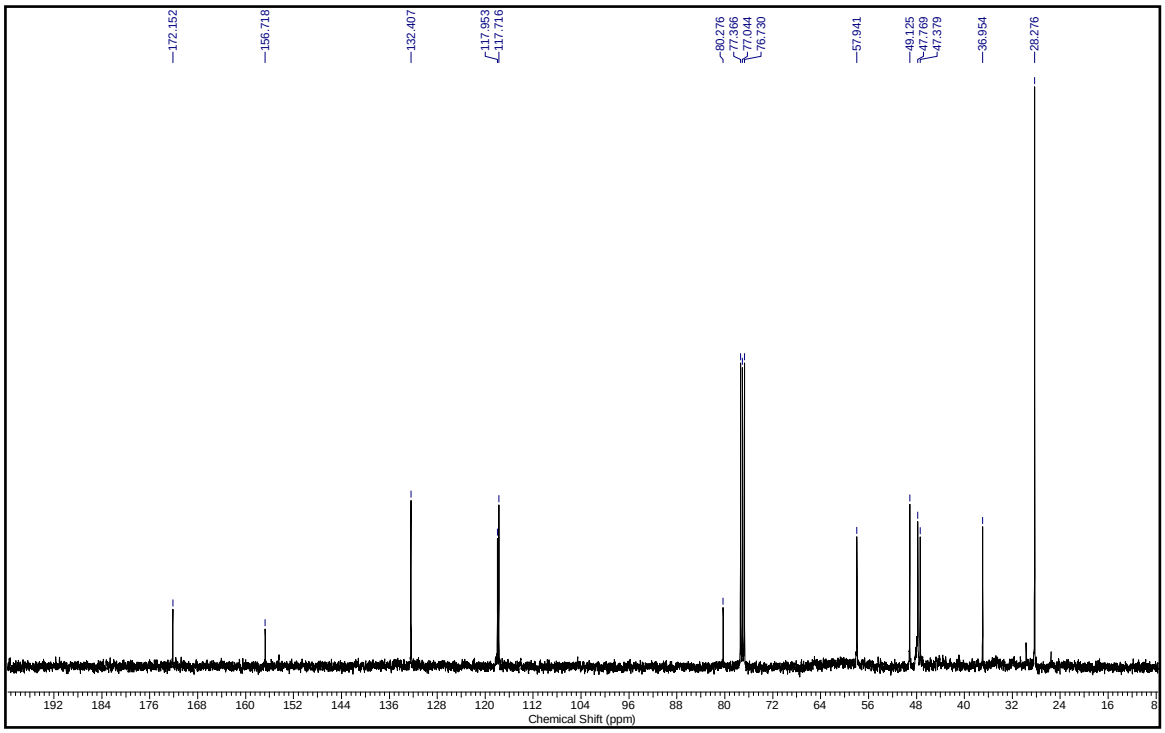
^{13}C NMR (100 MHz, $CDCl_3$) of compound 8c



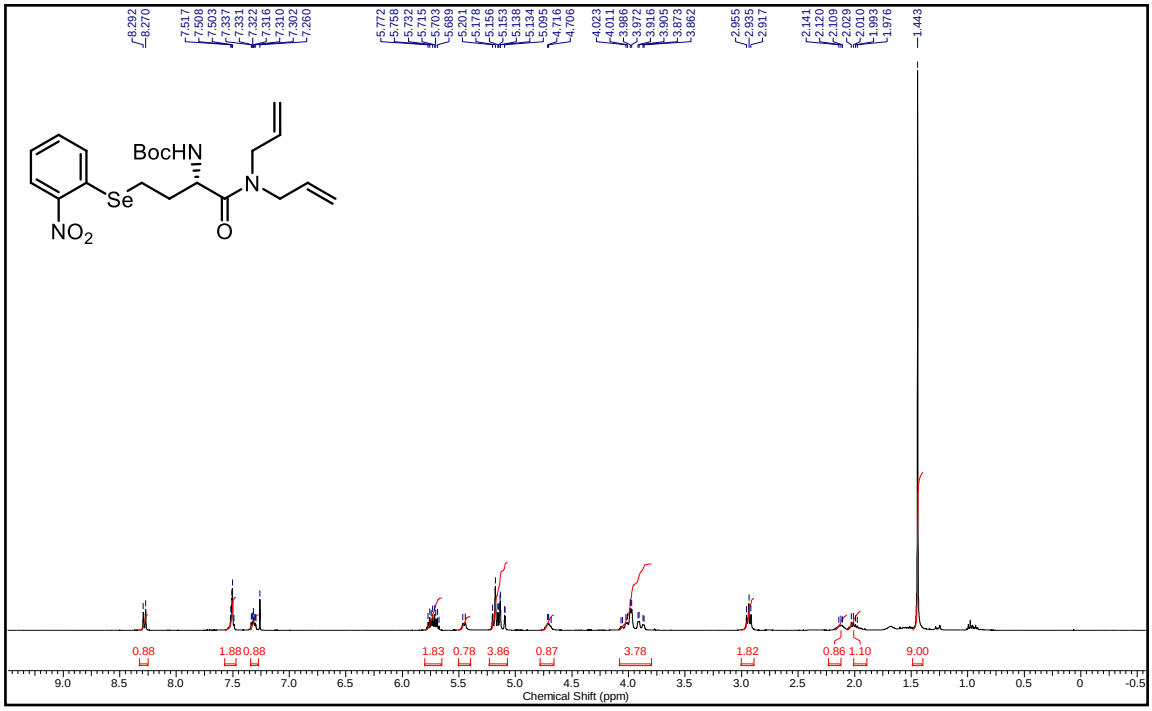
^{1}H NMR (400 MHz, $CDCl_3$) of compound 8c



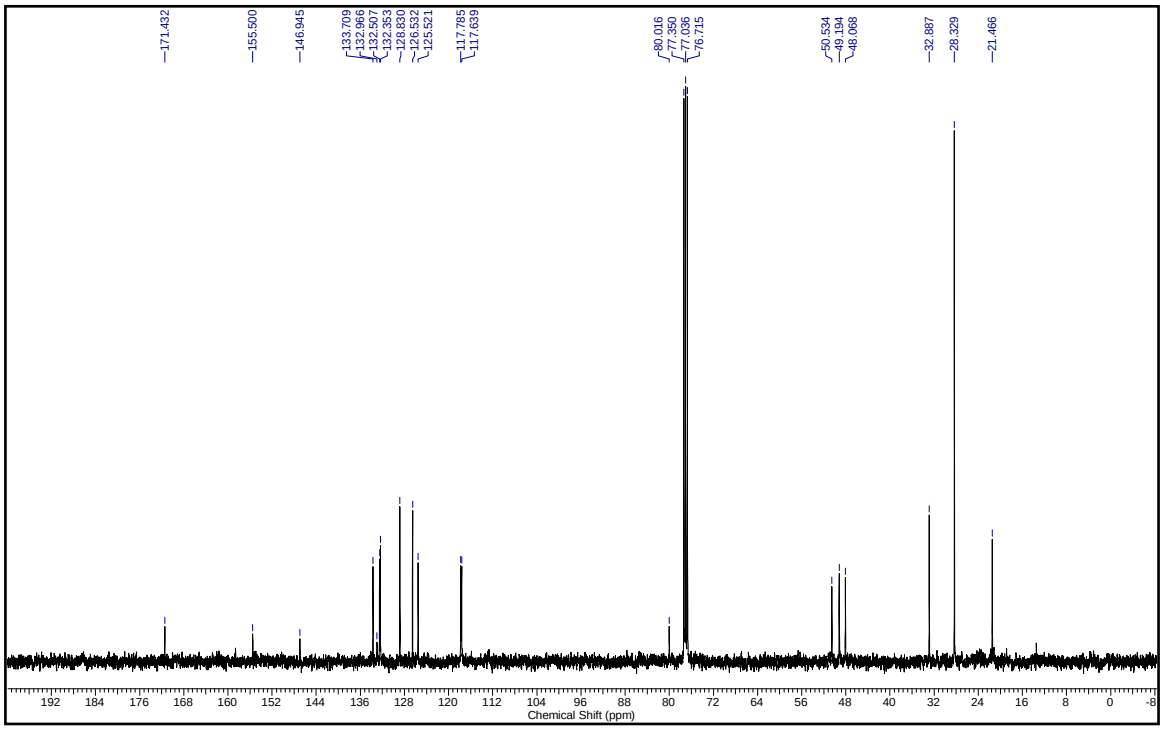
^{13}C NMR (100 MHz, $CDCl_3$) of compound 8c



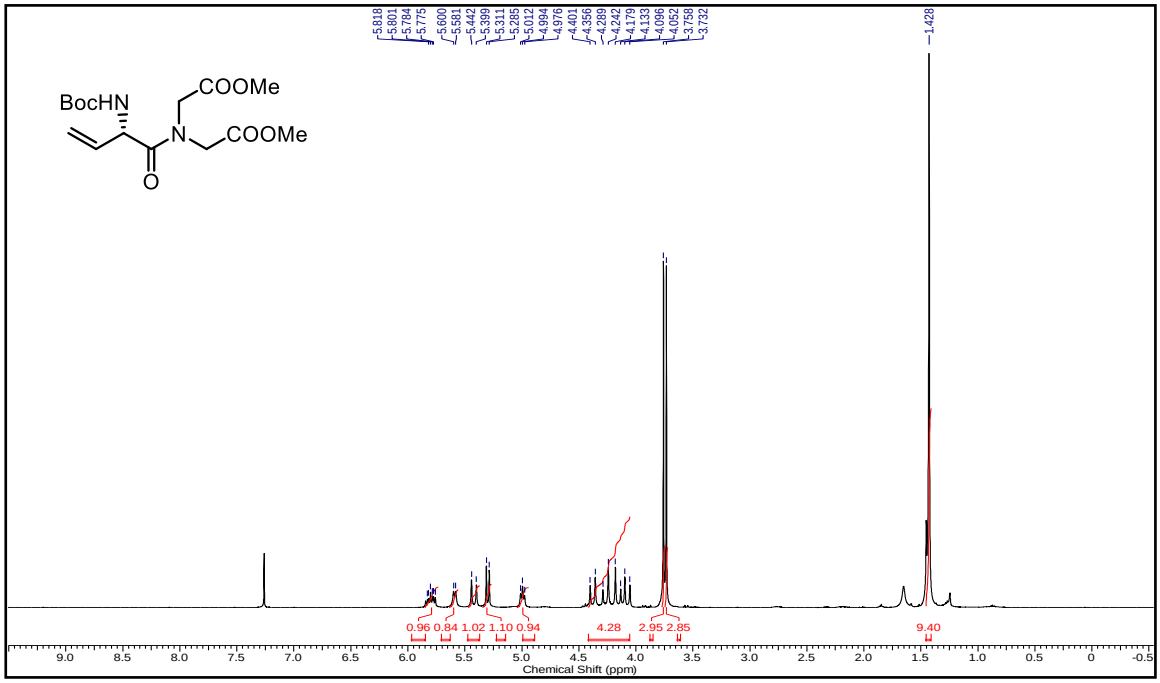
^{1}H NMR (400 MHz, $CDCl_3$) of compound 9b



^{13}C NMR (100 MHz, $CDCl_3$) of compound 9b



^{1}H NMR (400 MHz, $CDCl_3$) of compound 9c



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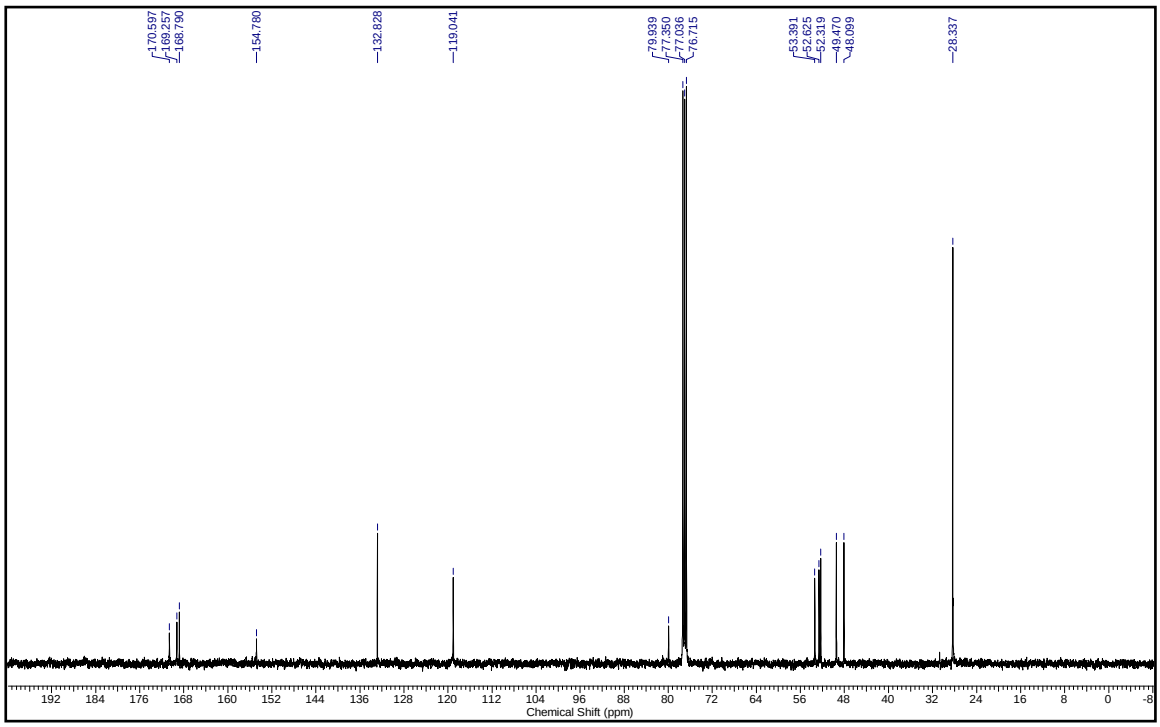
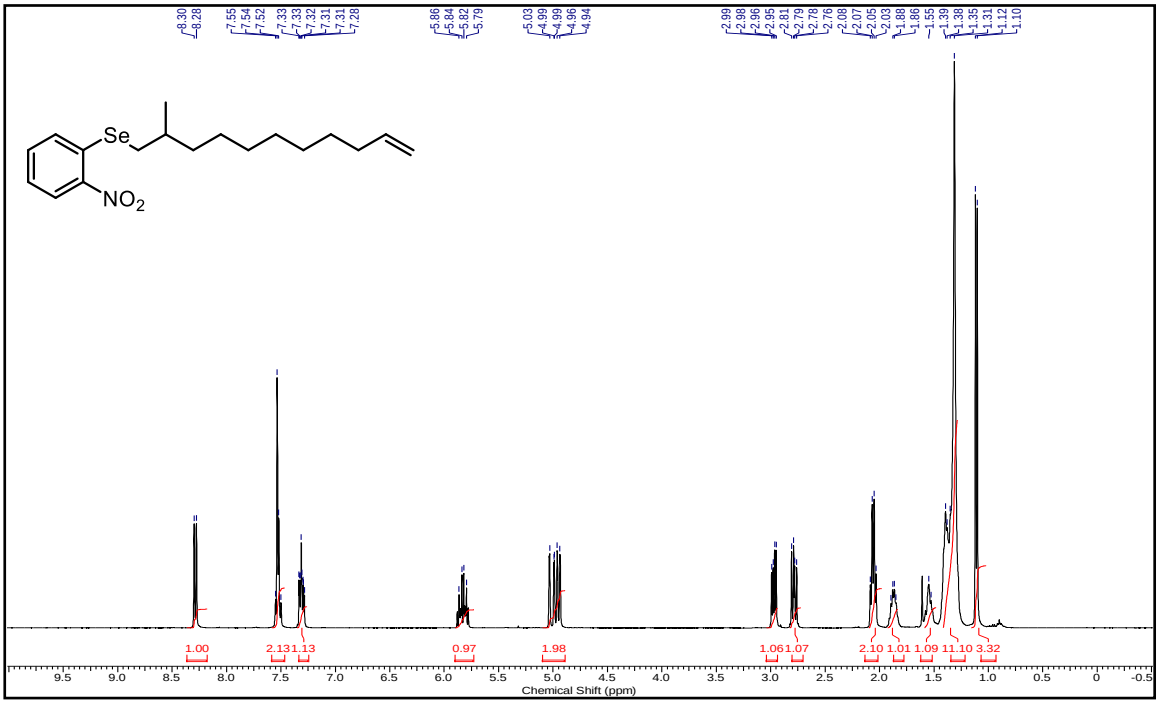
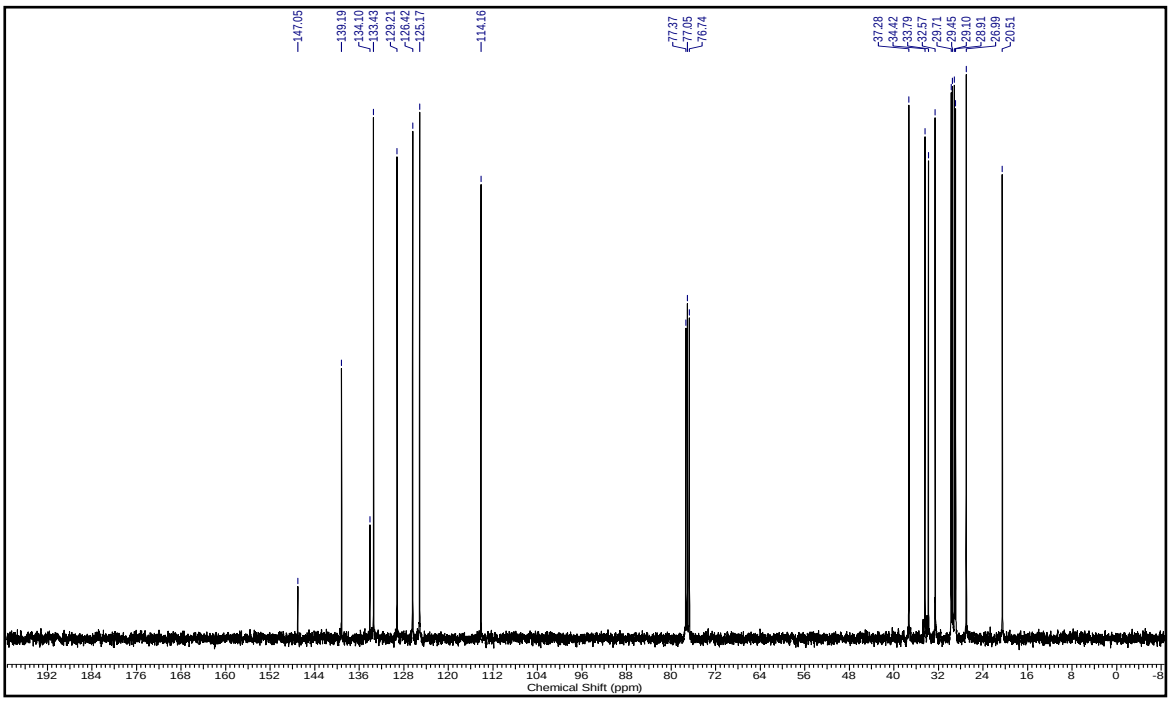


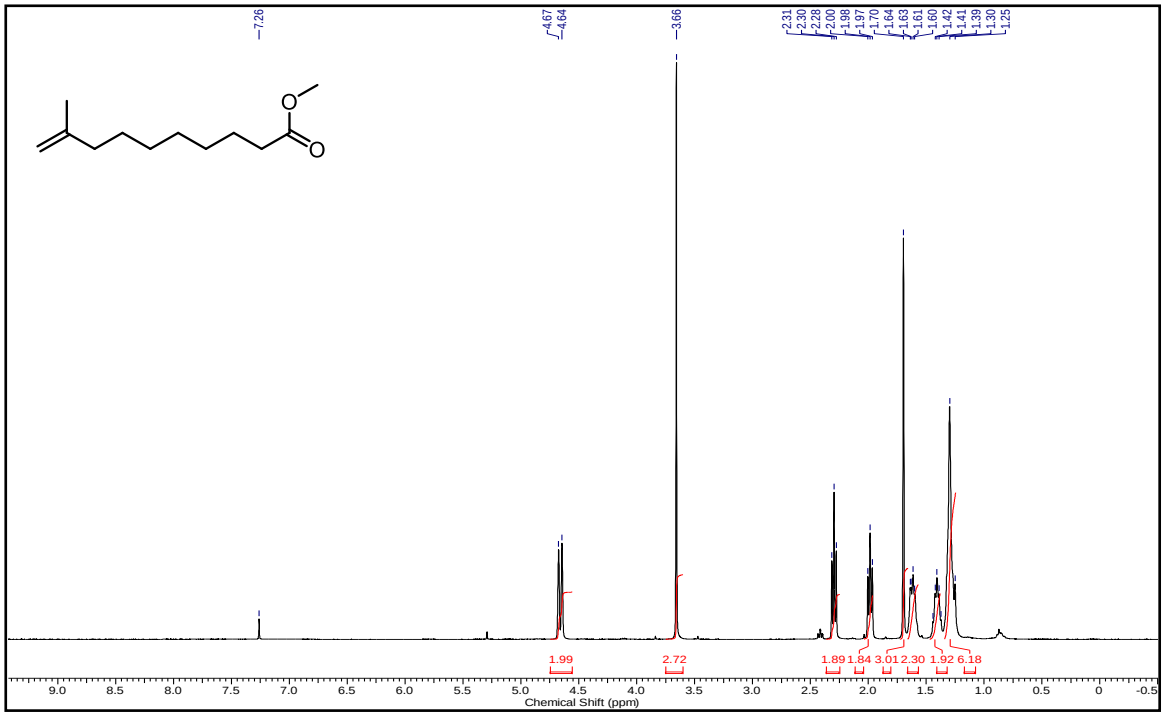
^{1}H NMR (400MHz ,$CDCl_3$) of compound 10b



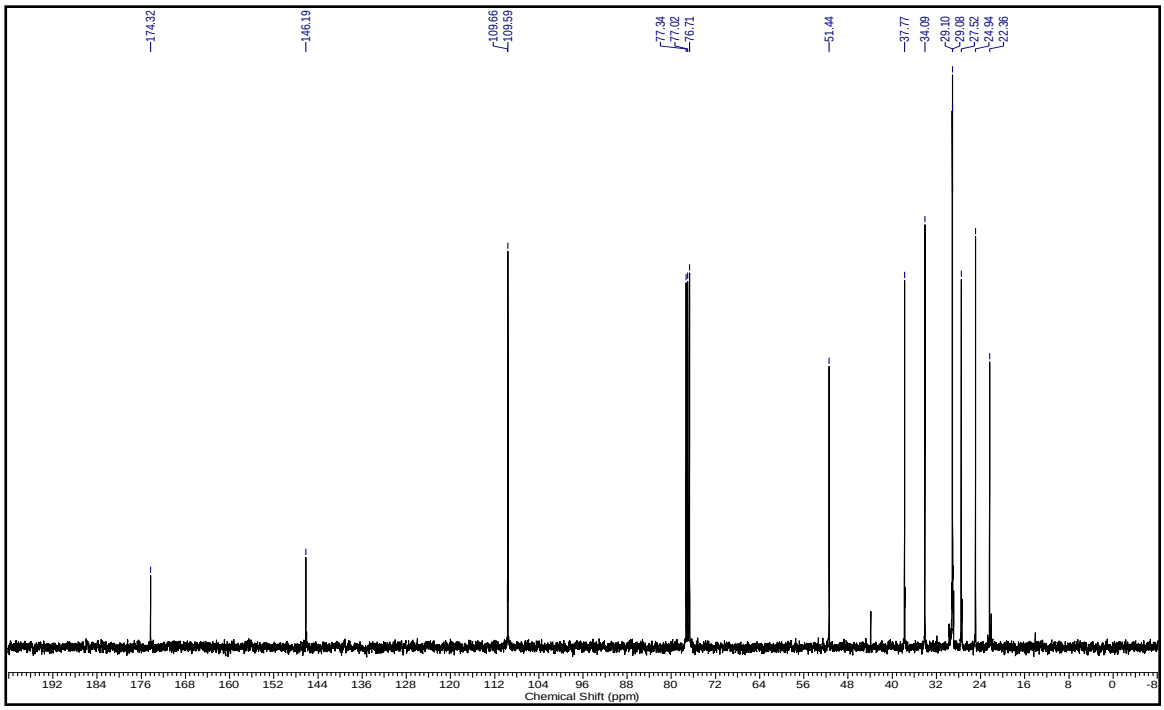
^{13}C NMR (100 MHz, $CDCl_3$) of compound 10b



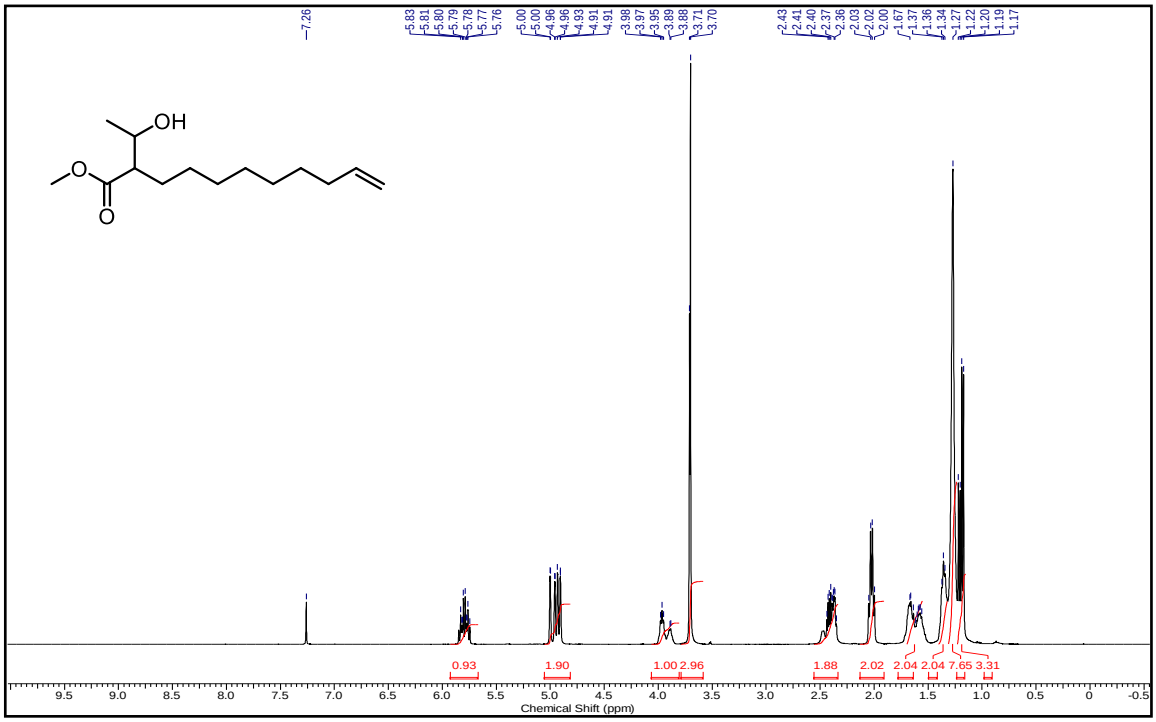
^{1}H NMR (400MHz ,$CDCl_3$) of compound 10c



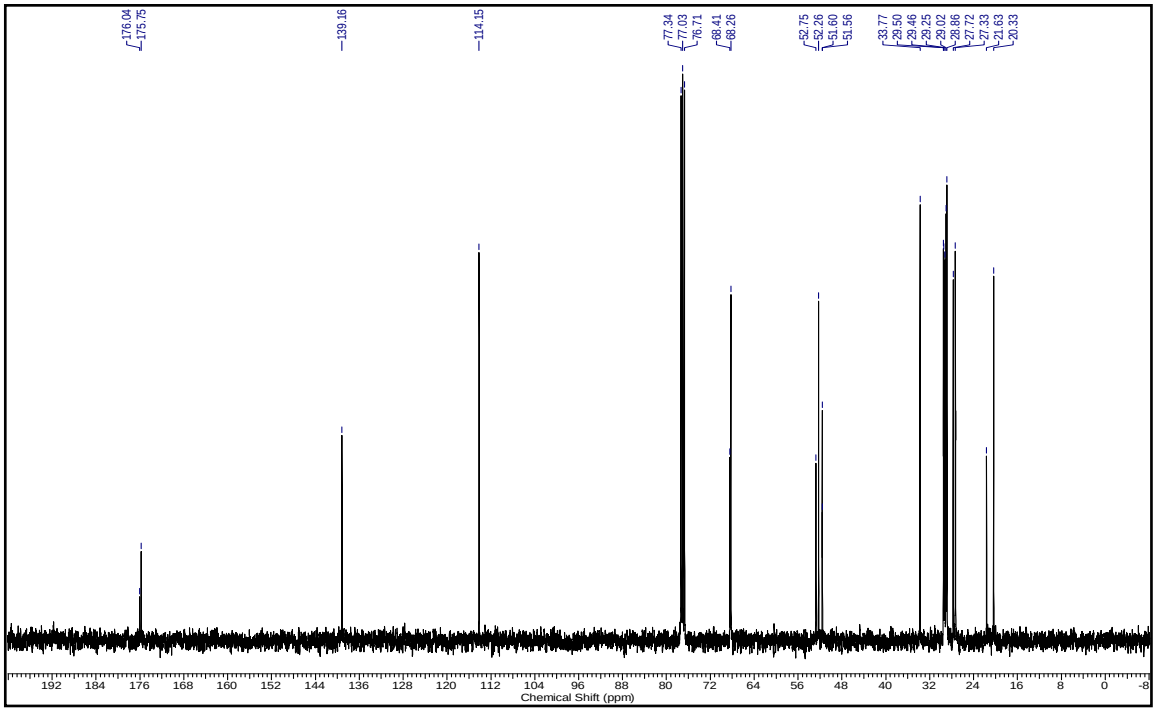
^{13}C NMR (100 MHz, $CDCl_3$) of compound 10c



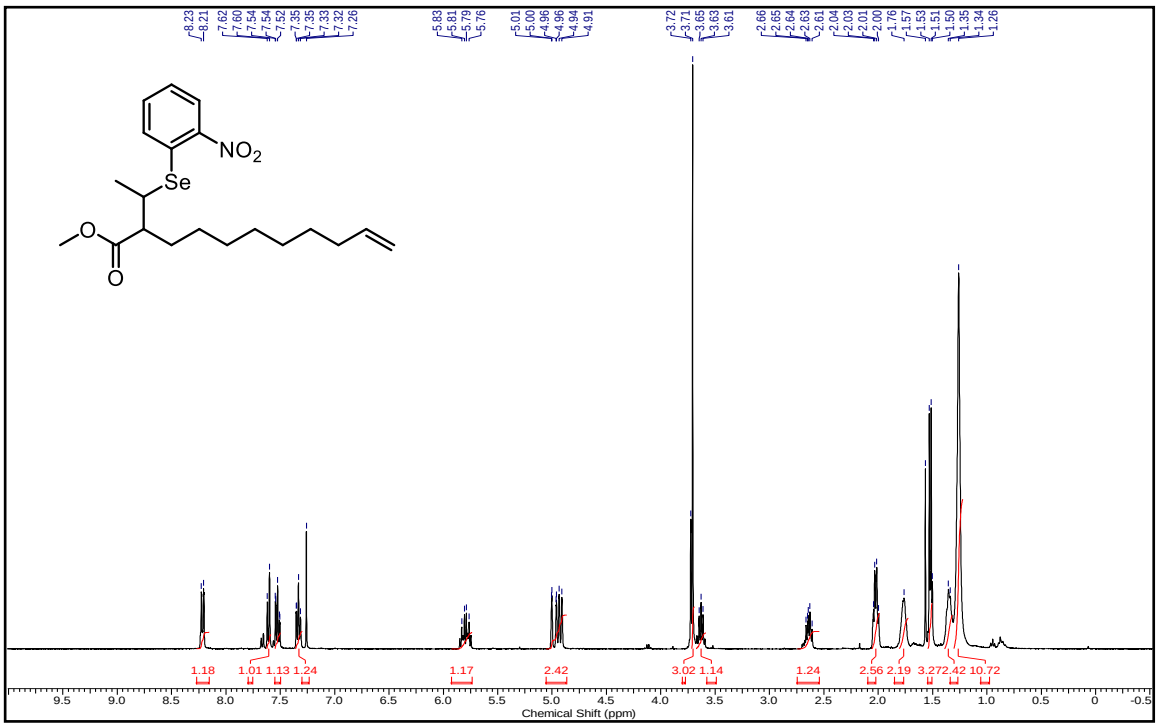
^{1}H NMR (400MHz, $CDCl_3$) of compound 11a



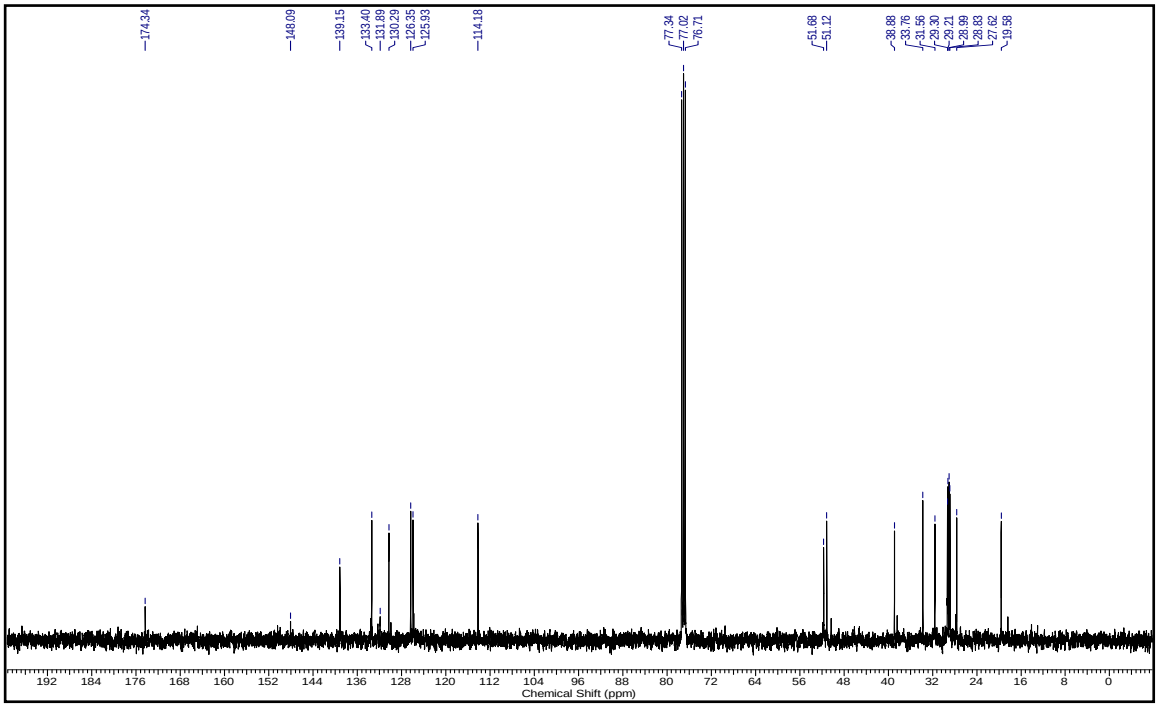
^{13}C NMR (100 MHz, $CDCl_3$) of compound 11a



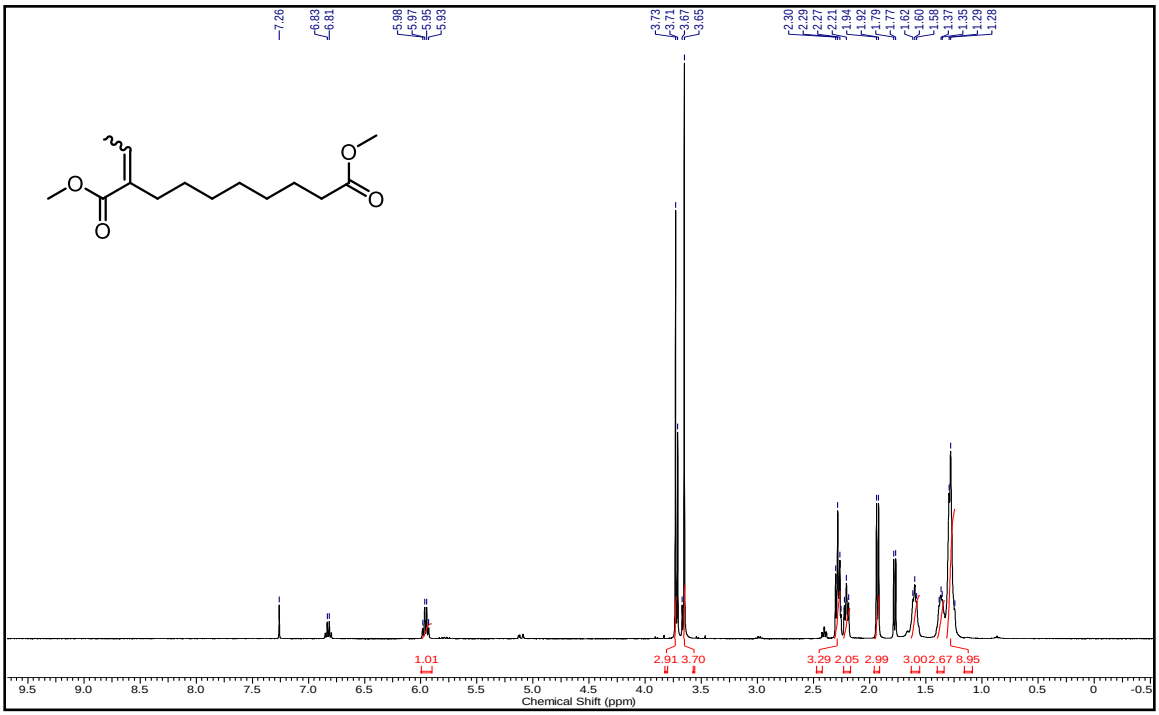
^{1}H NMR (400MHz ,$CDCl_3$) of compound 11b



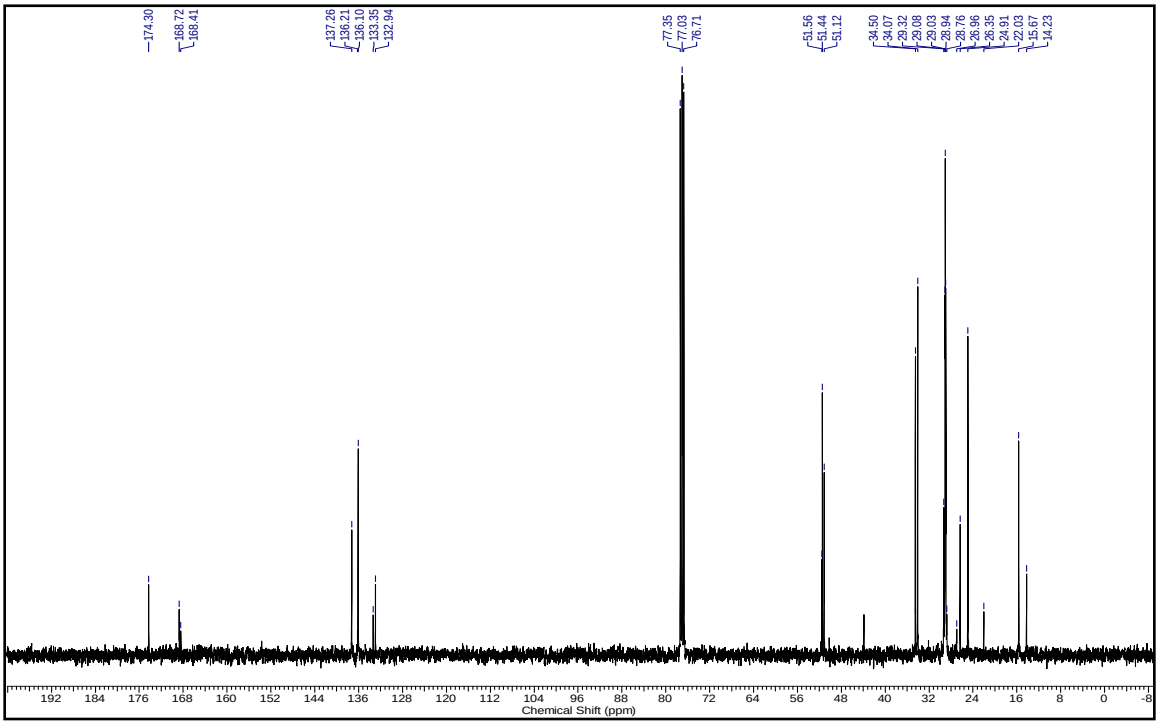
^{13}C NMR (100 MHz, $CDCl_3$) of compound 11b



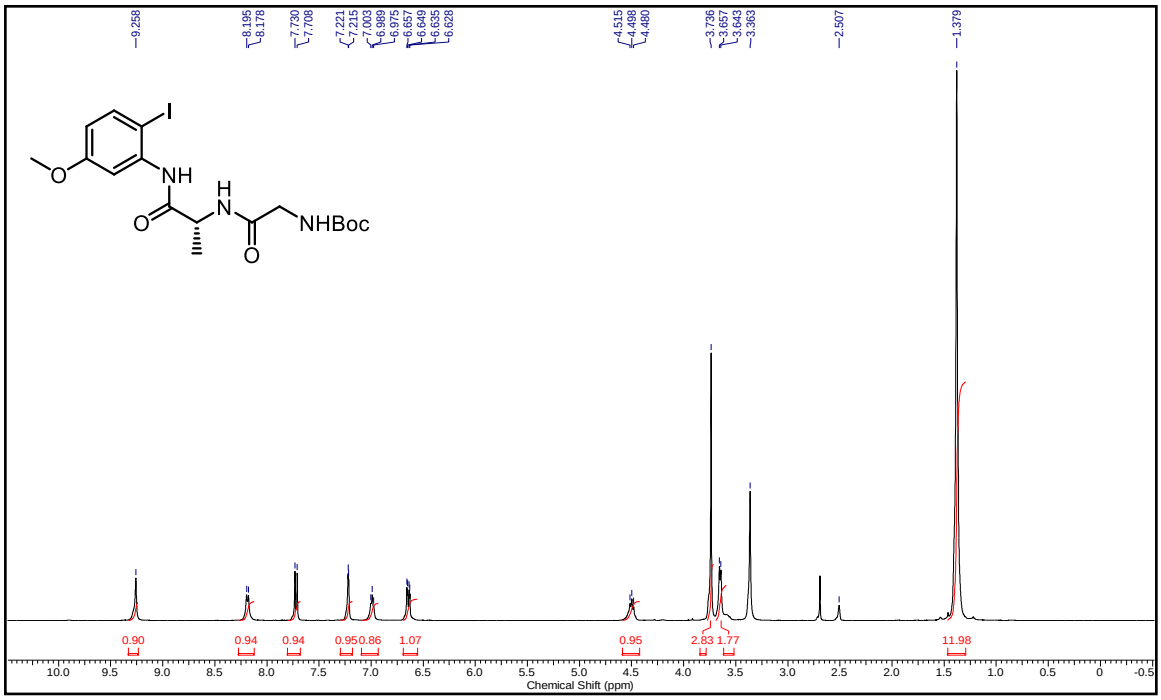
^{1}H NMR (400MHz, $CDCl_3$) of compound 11c



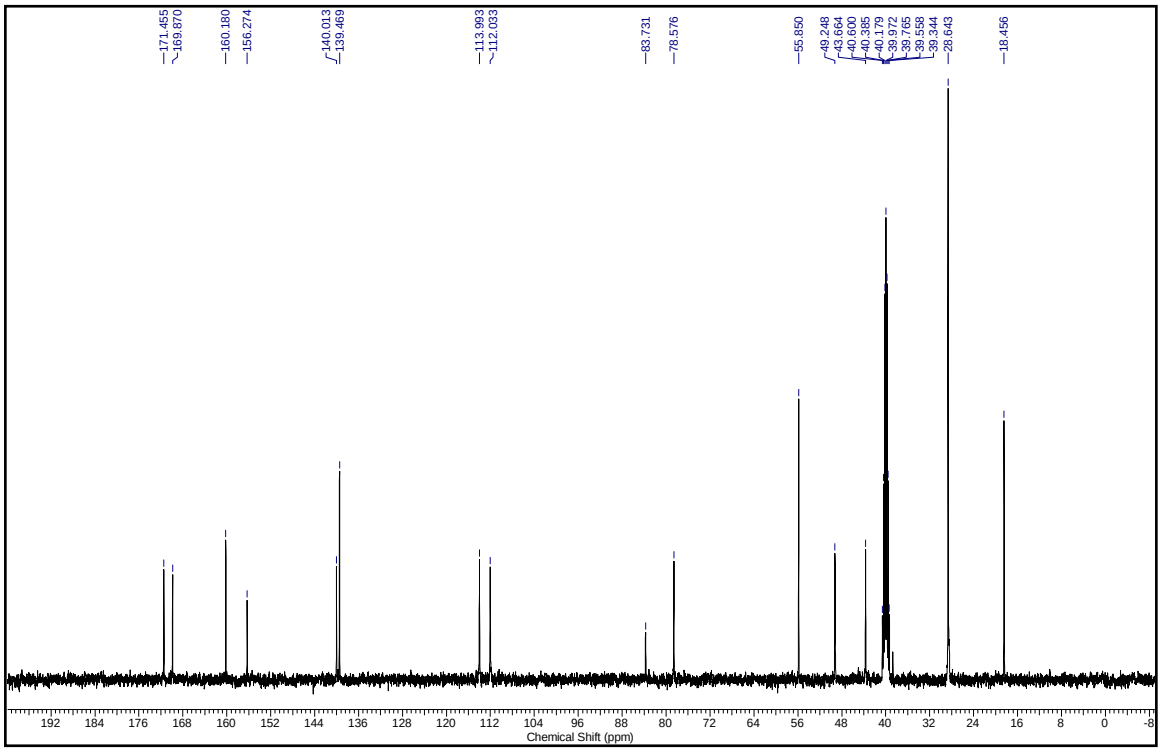
^{13}C NMR (100 MHz, $CDCl_3$) of compound 11c



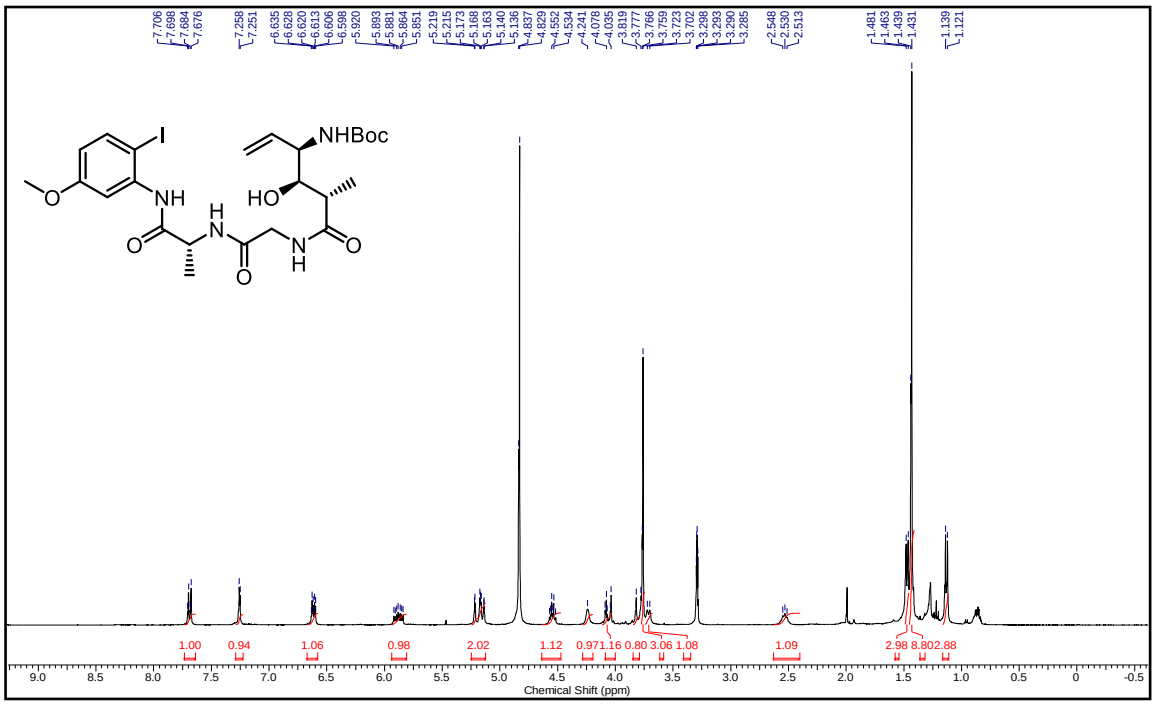
^{1}H NMR (400 MHz, DMSO-d_6) of compound 89



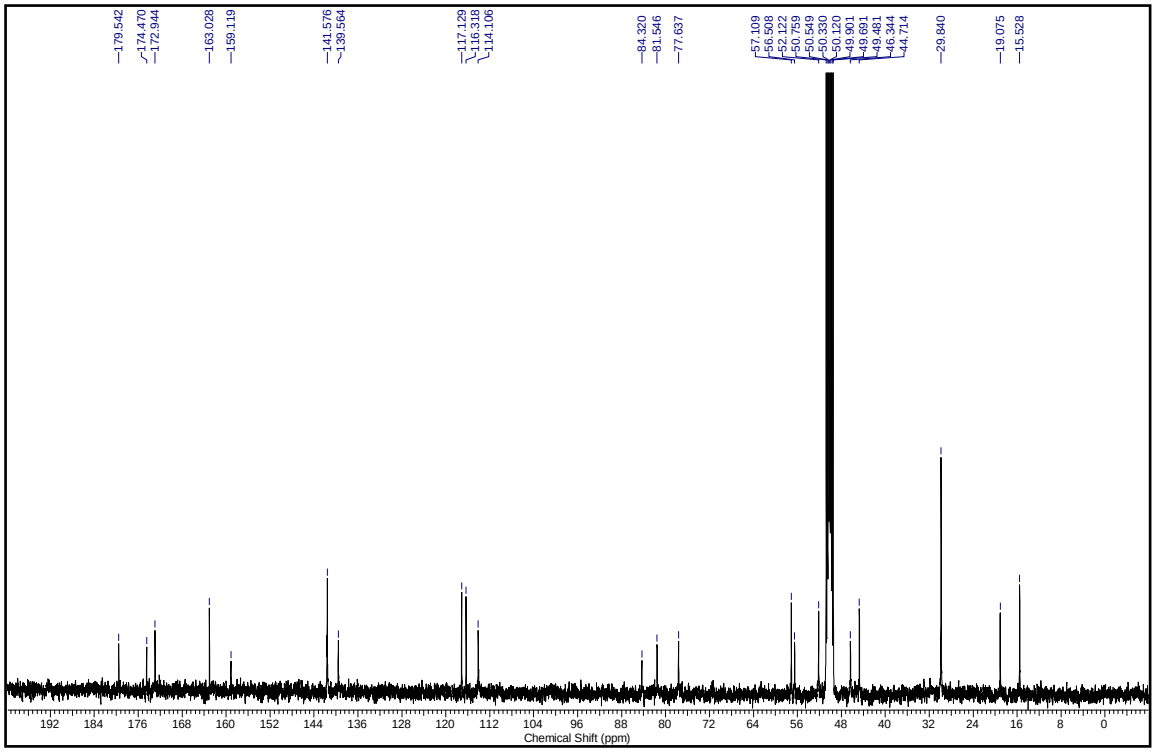
^{13}C NMR (100 MHz, DMSO-d_6) of compound 89



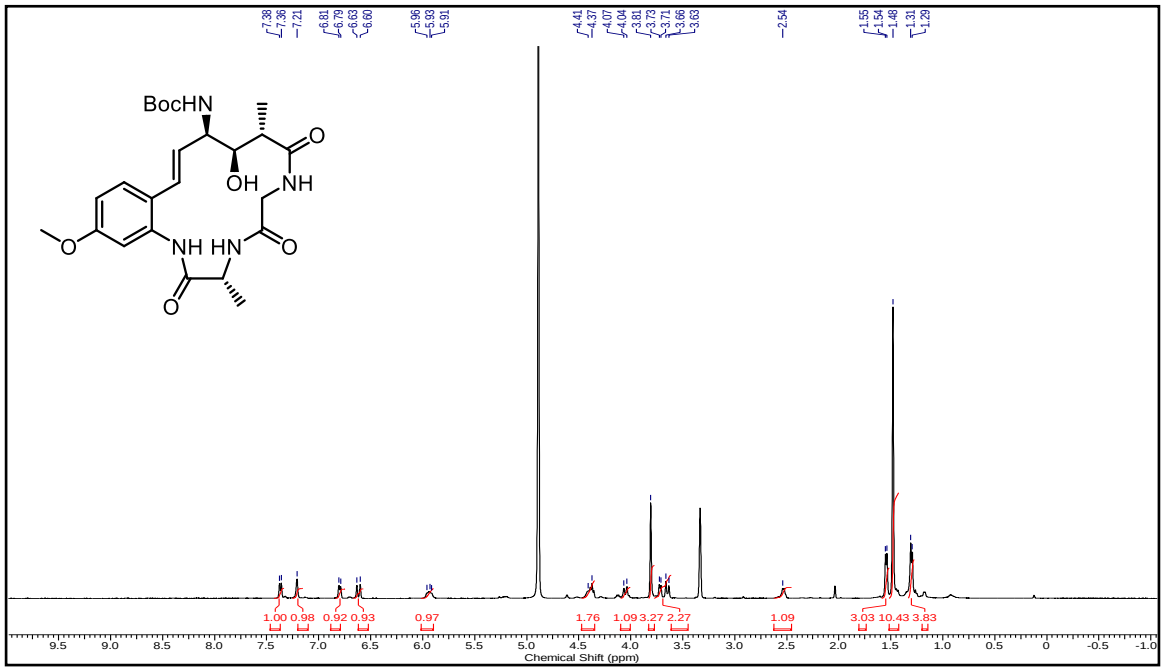
^{1}H NMR (400MHz, CD_3OD) of compound 88



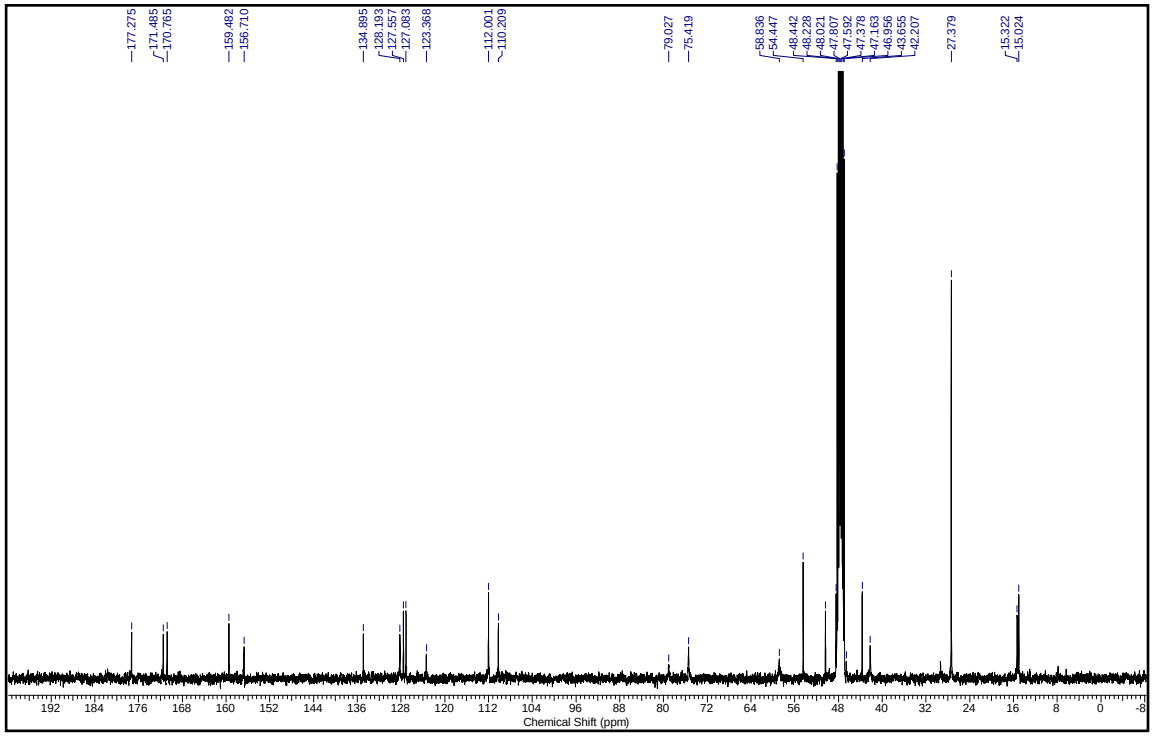
^{13}C NMR (100 MHz, CD_3OD) of compound 88



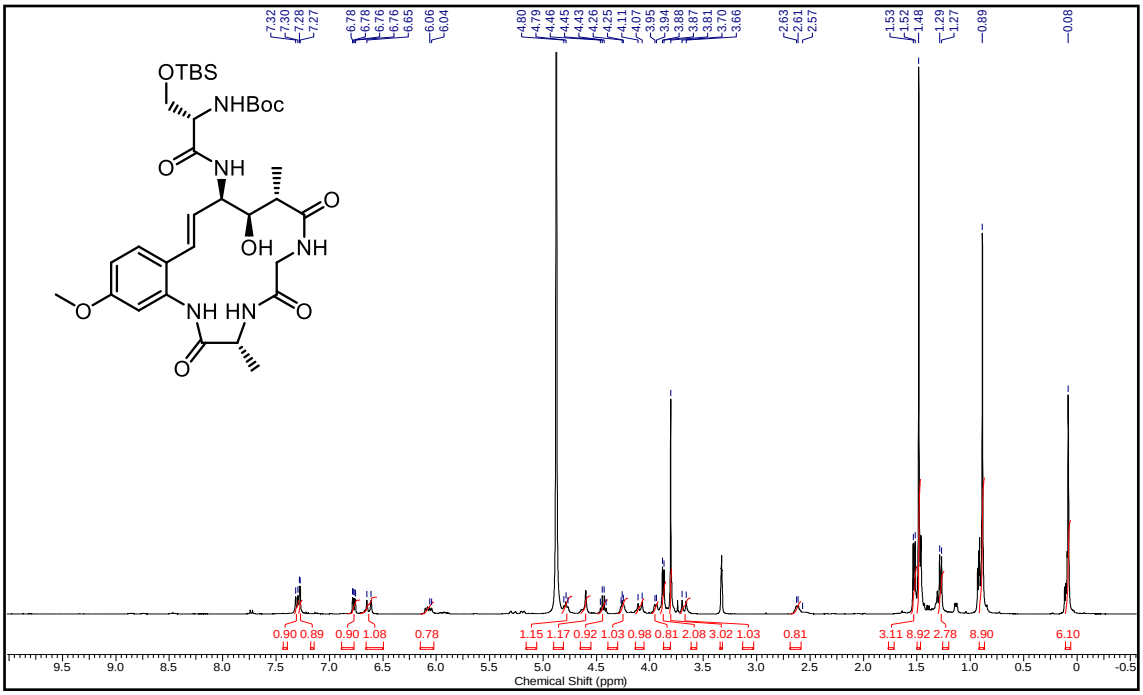
^{1}H NMR (400MHz, CD_3OD) of compound 87



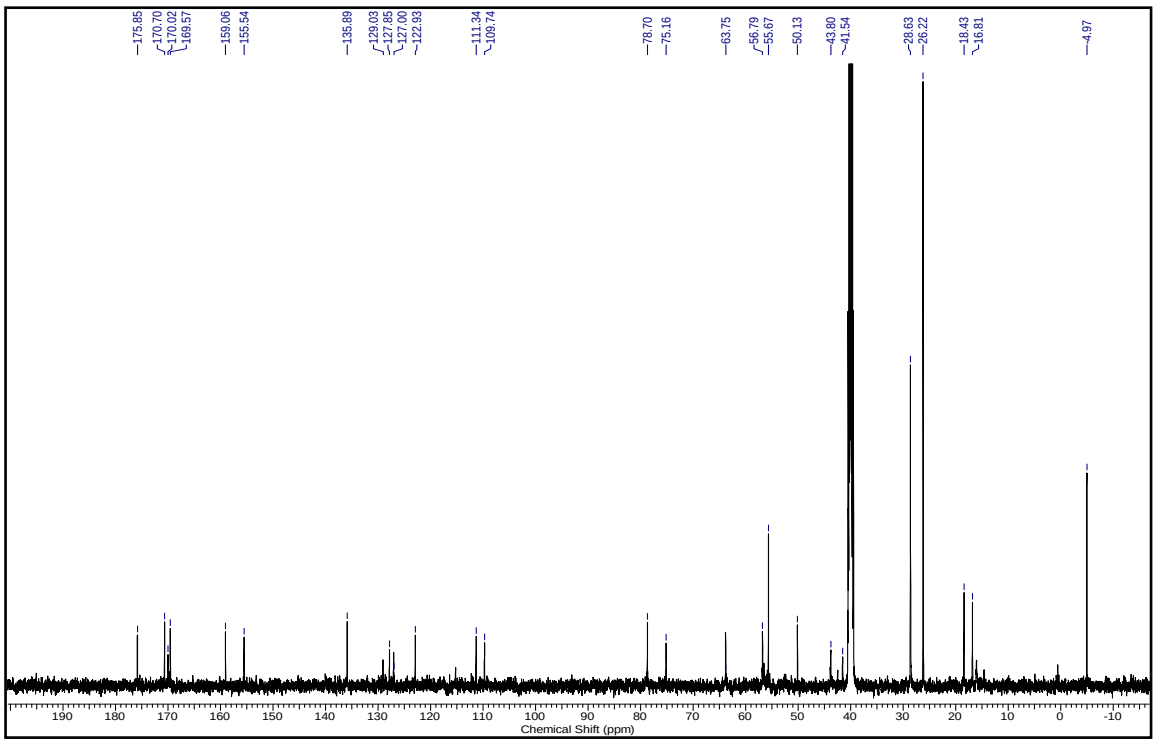
^{13}C NMR (100 MHz, CD_3OD) of compound 87



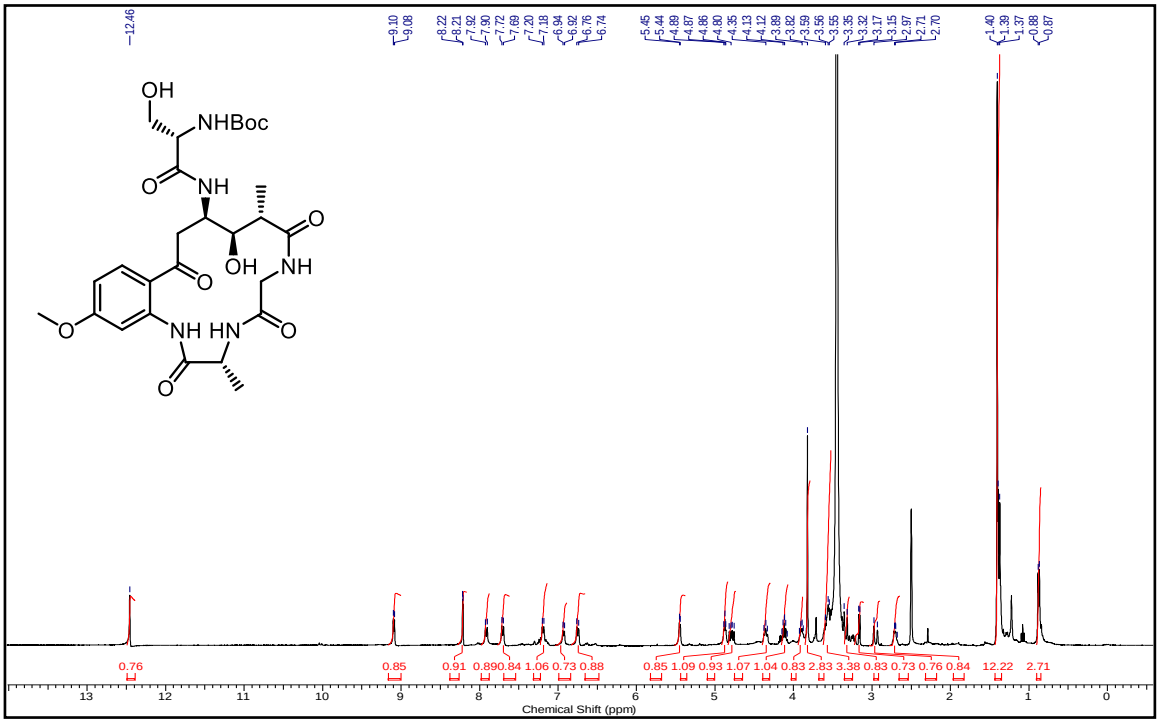
^{1}H NMR (400MHz, CD_3OD) of compound 100



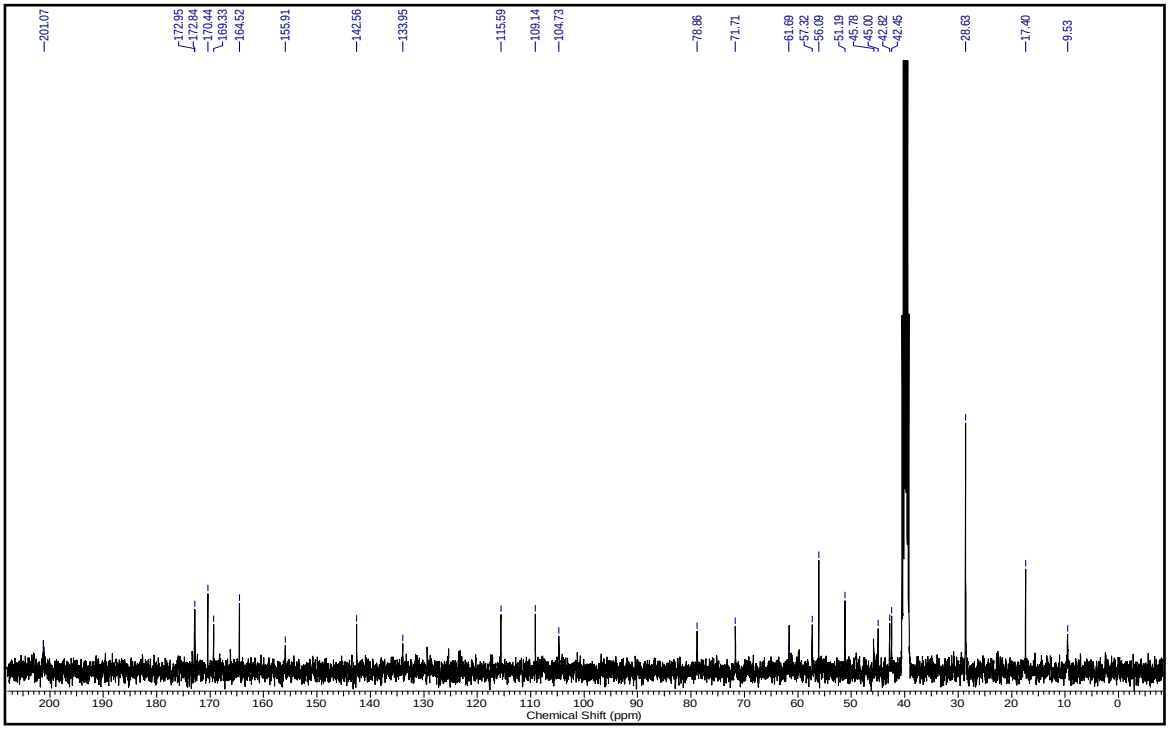
^{13}C NMR (125 MHz, DMSO-d_6) of compound 100



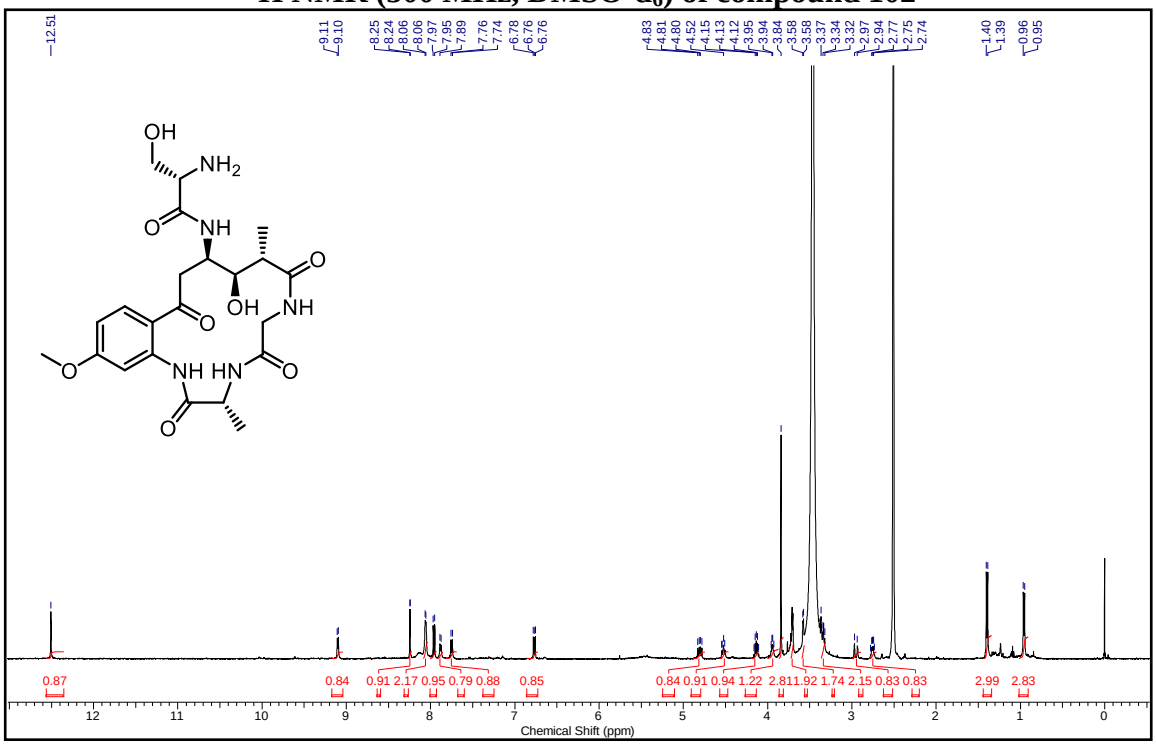
^{1}H NMR (400 MHz, DMSO-d_6) of compound 101



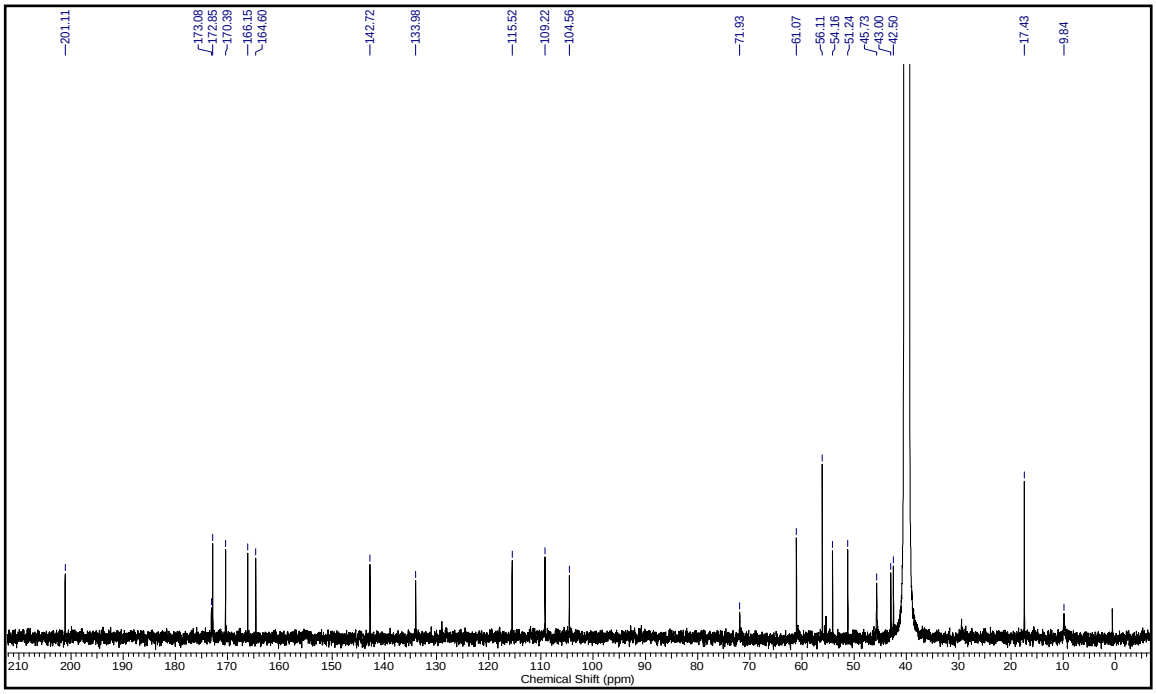
^{13}C NMR (100 MHz, DMSO-d_6) of compound 101



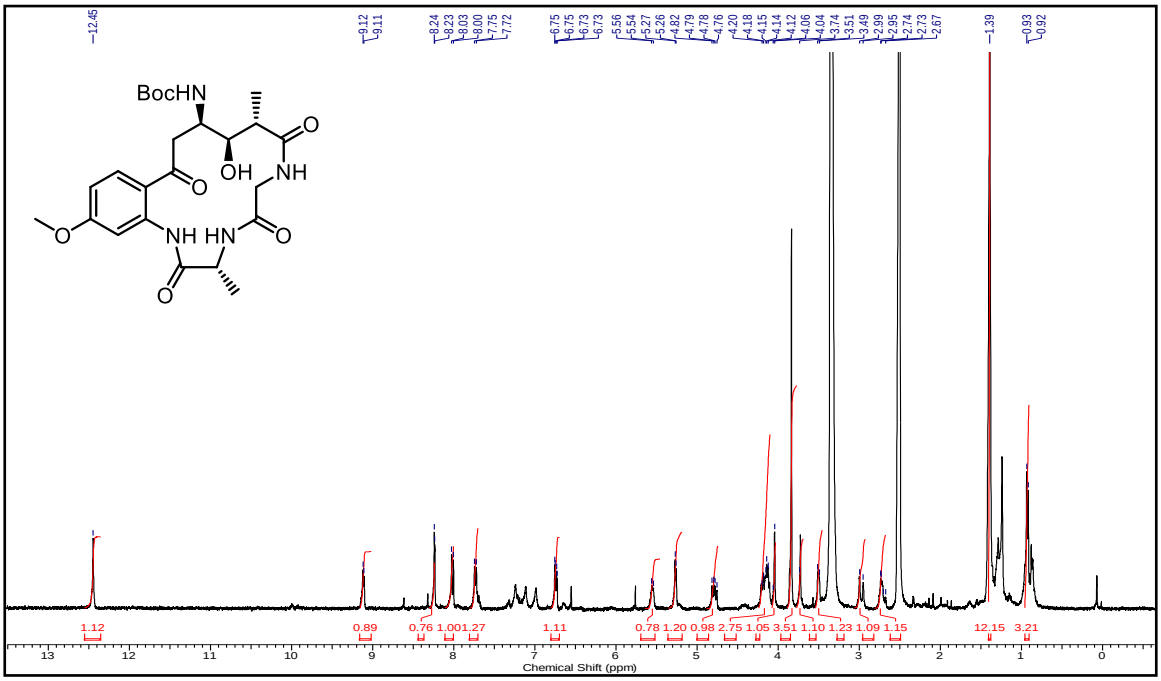
^{1}H NMR (500 MHz, DMSO-d_6) of compound 102



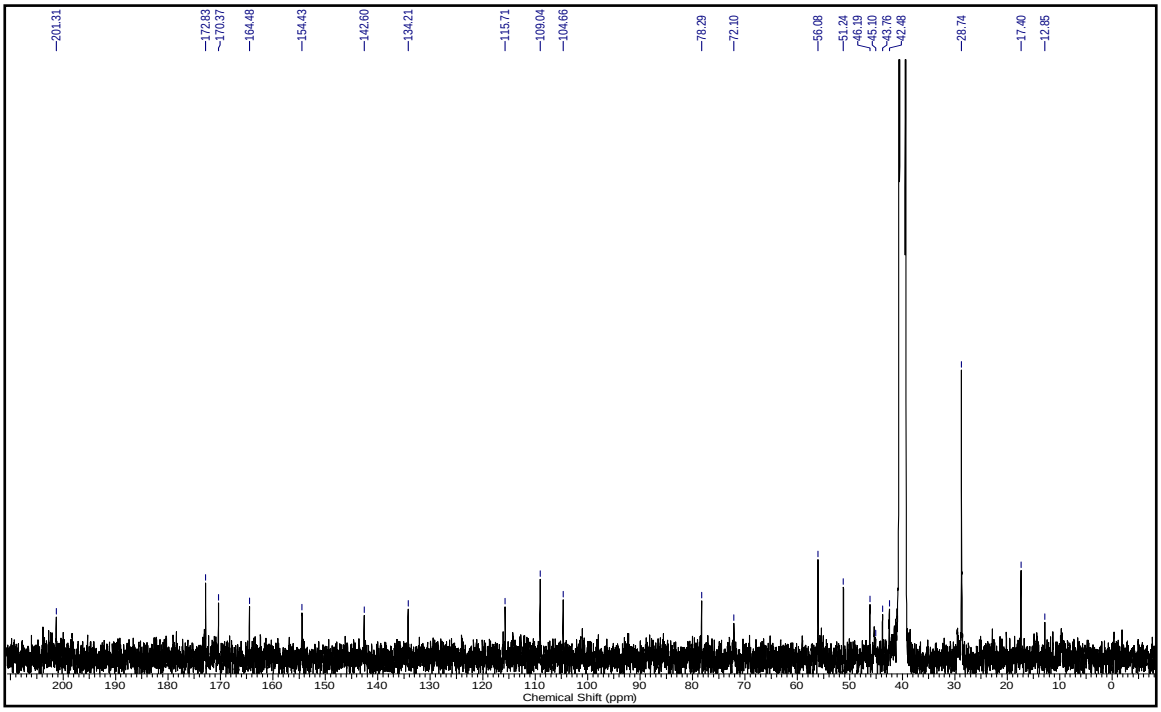
^{13}C NMR (100 MHz, DMSO-d_6) of compound 102



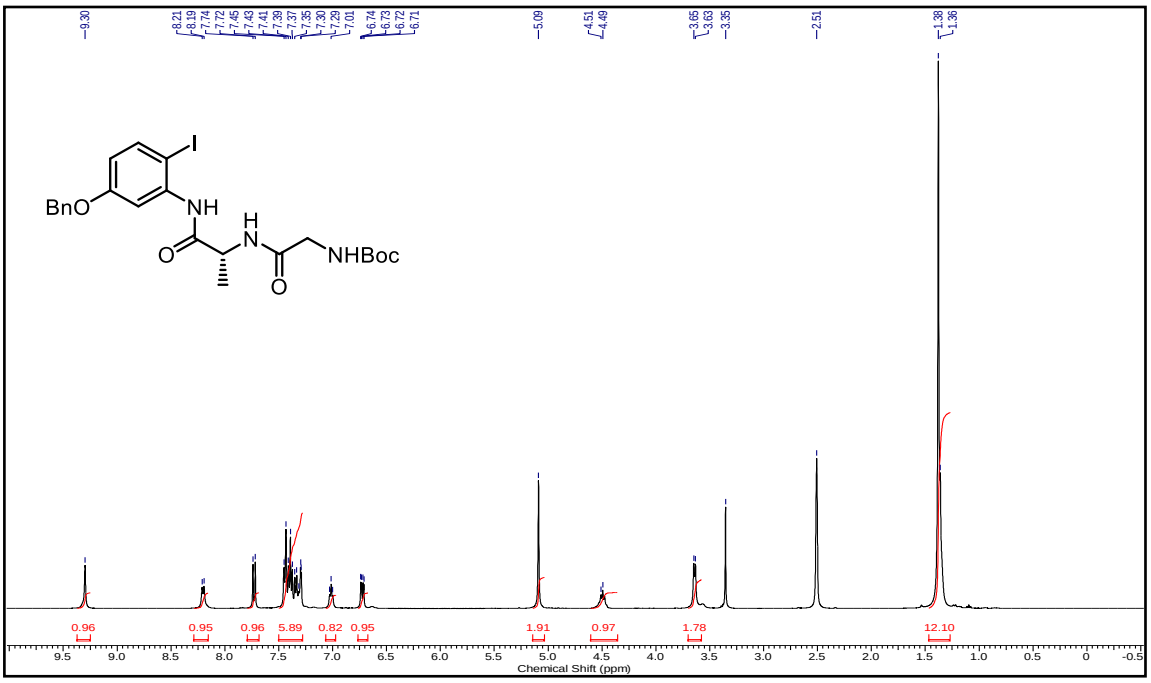
^{1}H NMR (400 MHz, DMSO-d_6) of compound 103



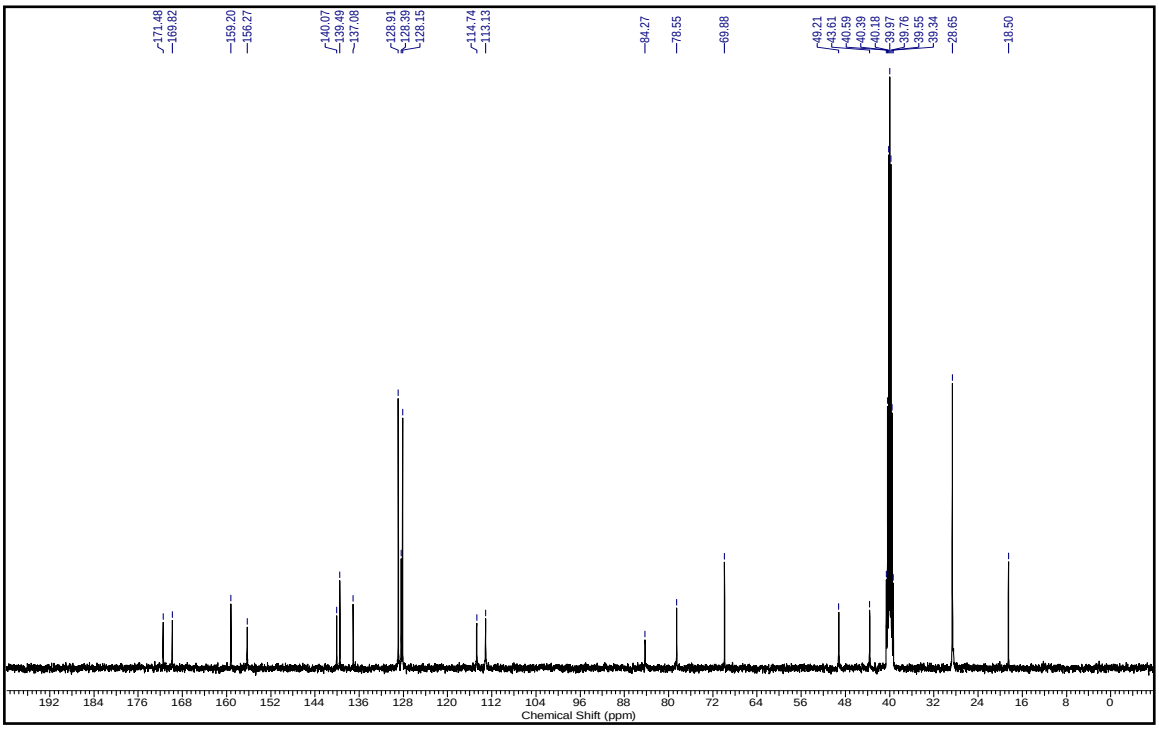
^{13}C NMR (100 MHz, DMSO-d_6) of compound 103



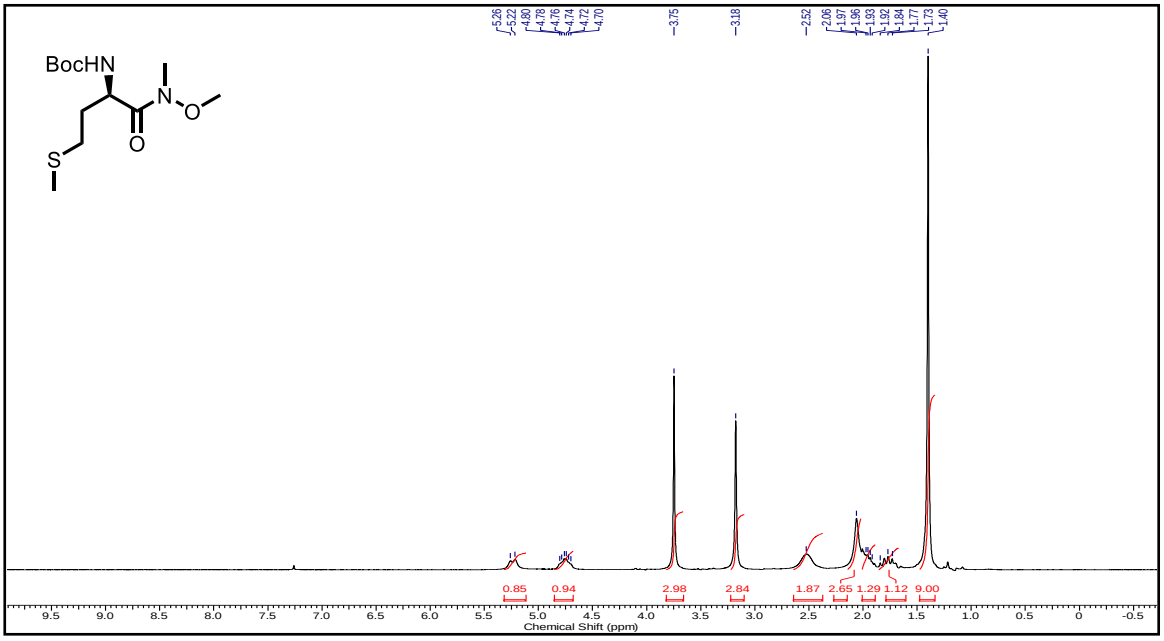
^{1}H NMR (400 MHz, DMSO-d_6) of compound 115



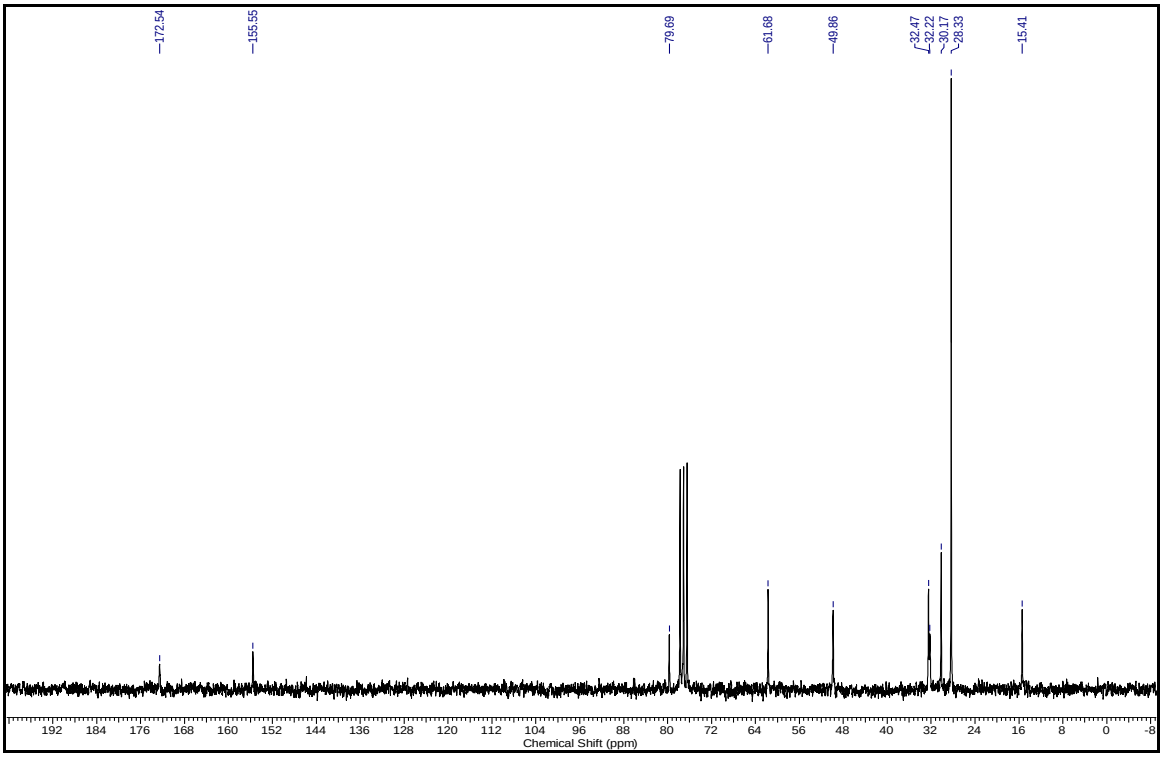
^{13}C NMR (100 MHz, DMSO-d_6) of compound 115



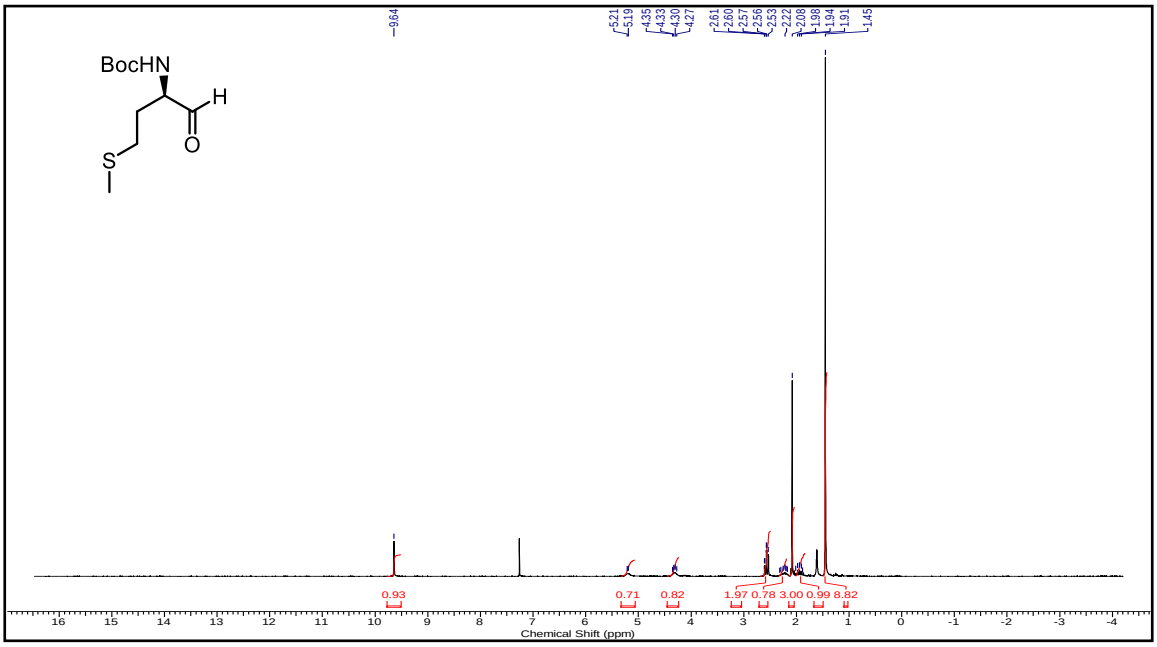
^{1}H NMR (200 MHz, $CDCl_3$) of compound 117



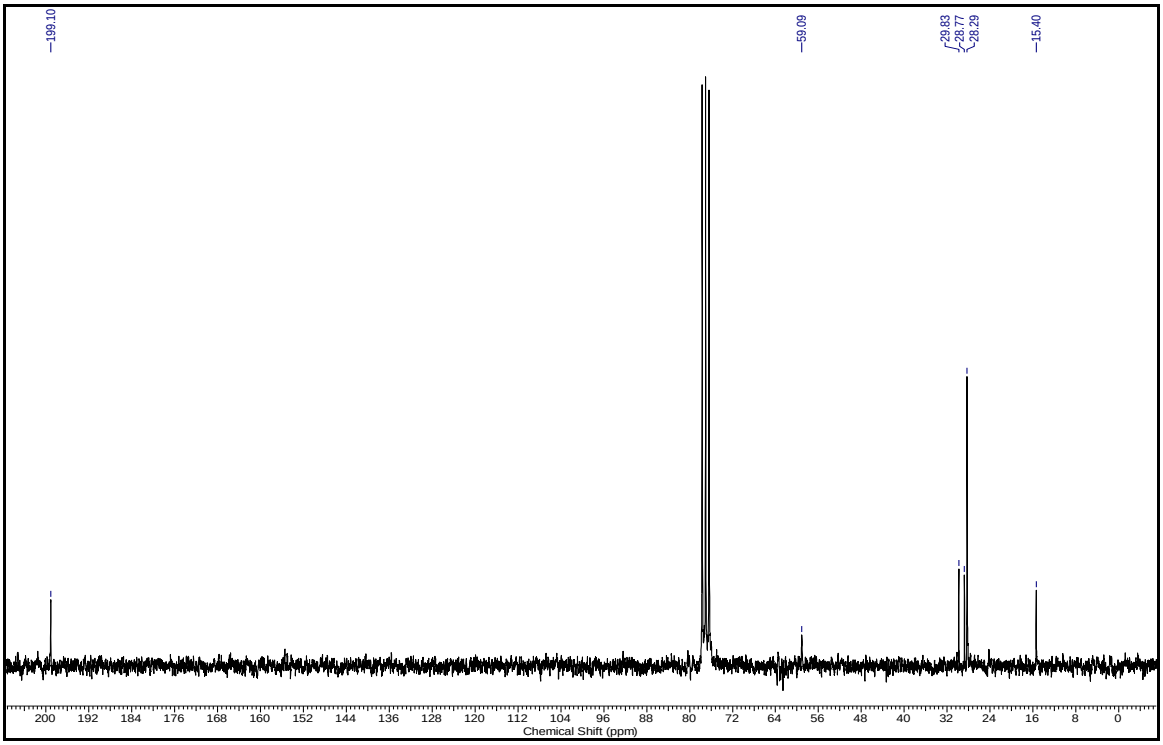
^{13}C NMR (50 MHz, $CDCl_3$) of compound 117



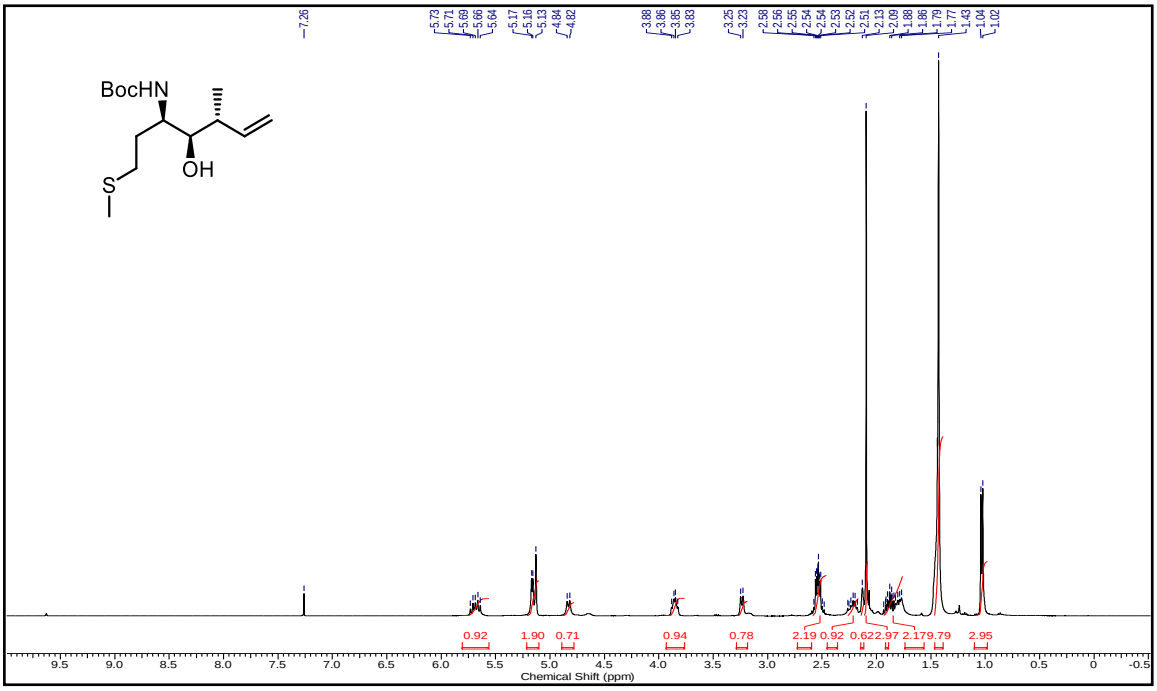
^{1}H NMR (200 MHz, $CDCl_3$) of compound 118



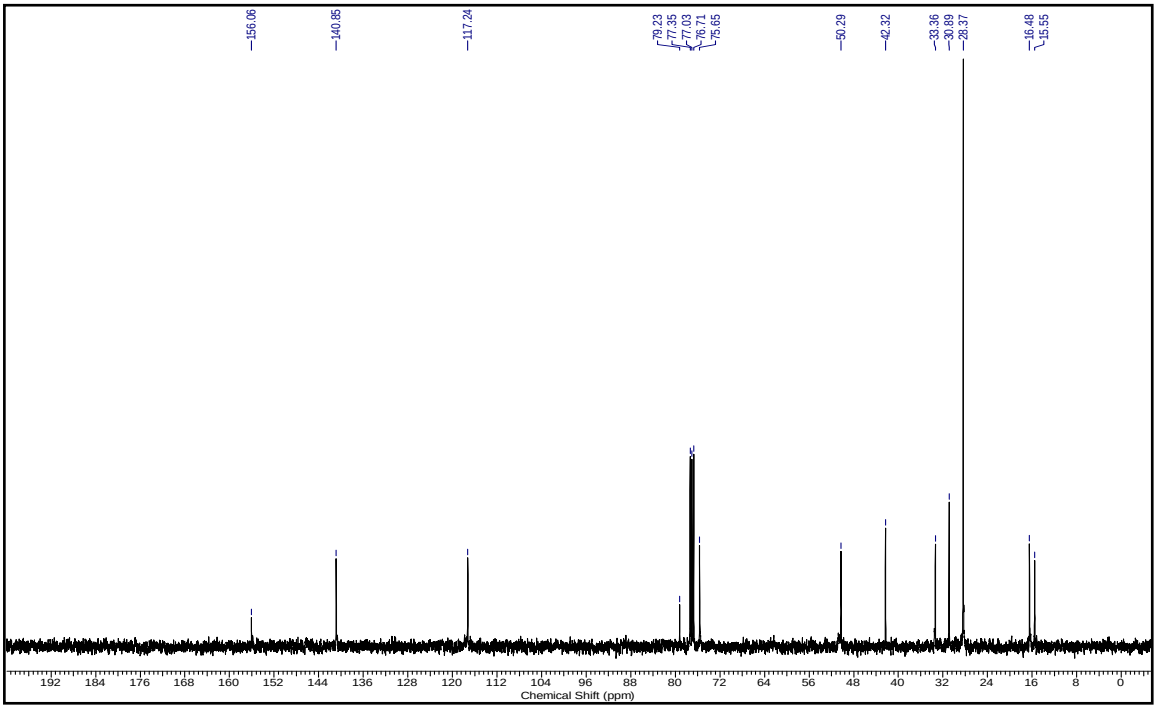
^{13}C NMR (50 MHz, $CDCl_3$) of compound 118



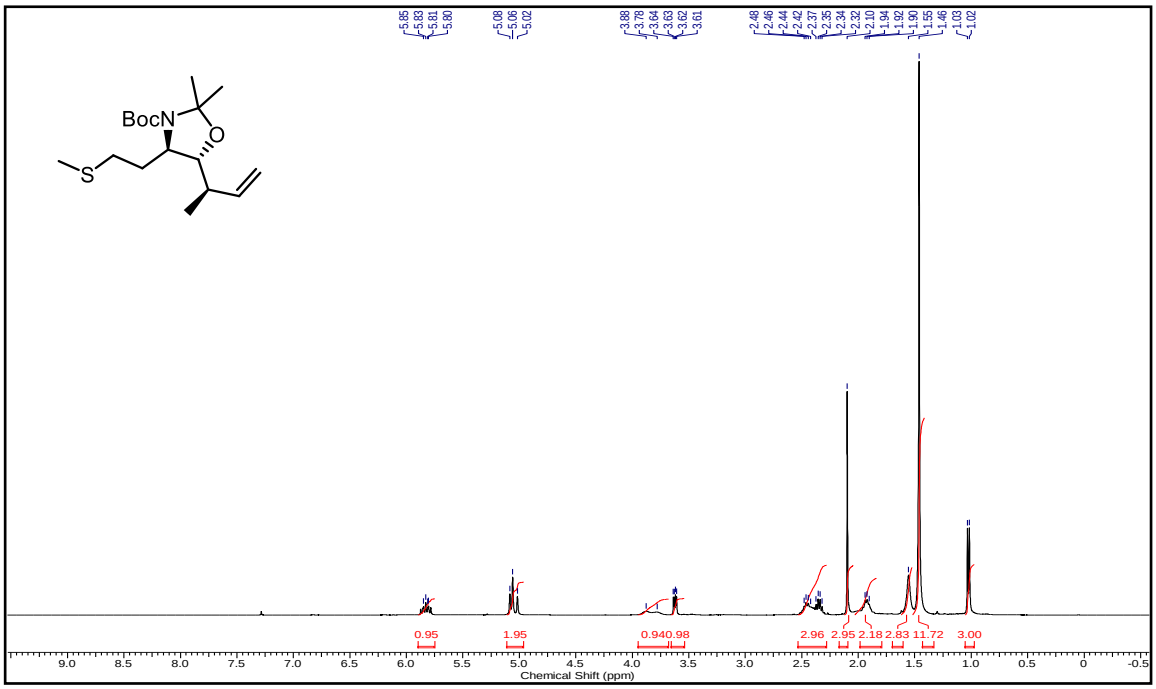
^{1}H NMR (400 MHz, $CDCl_3$) of compound 119



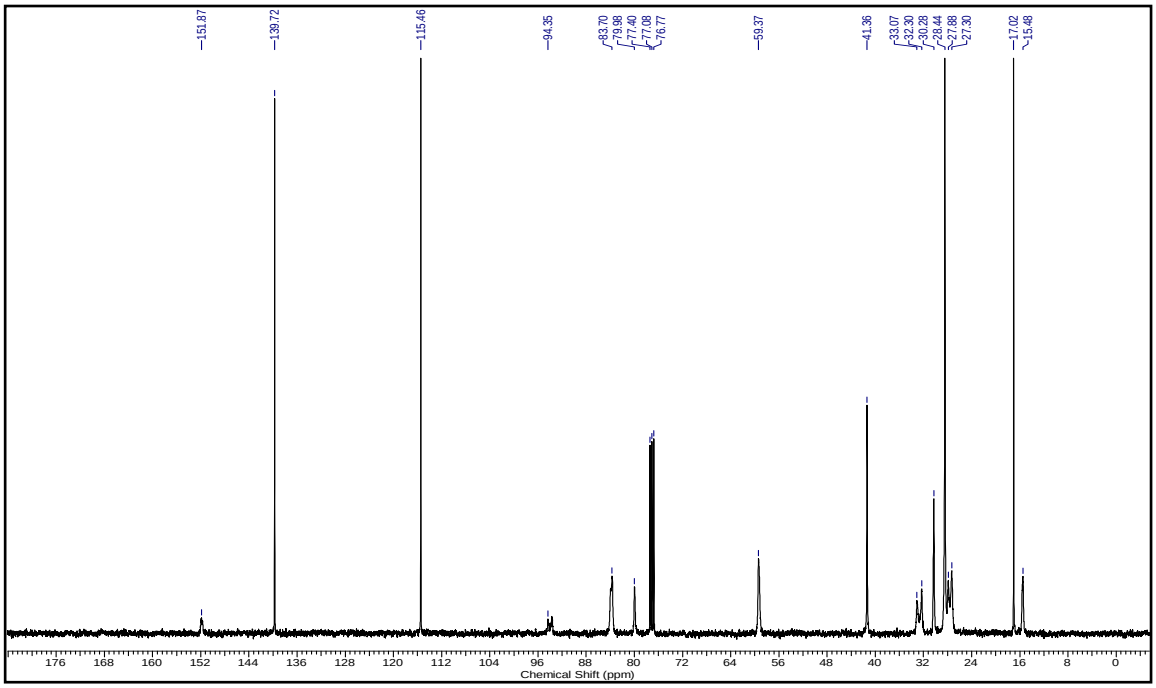
^{13}C NMR (100 MHz, $CDCl_3$) of compound 119



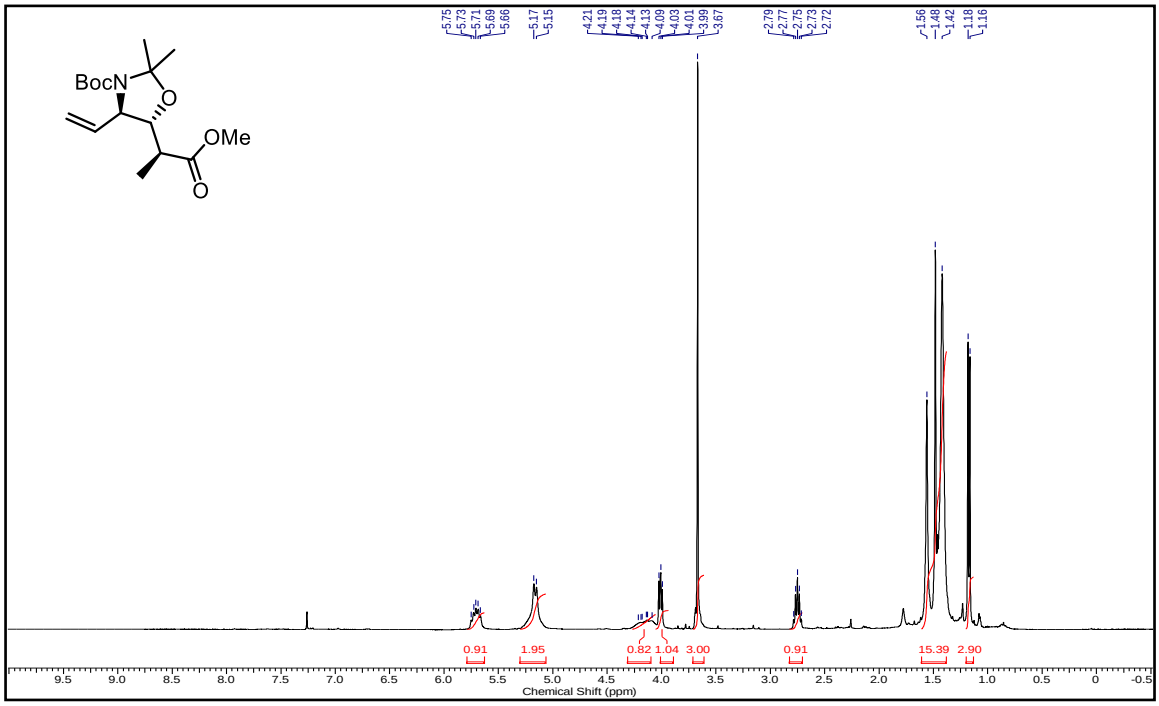
^{1}H NMR (400 MHz, $CDCl_3$) of compound 120



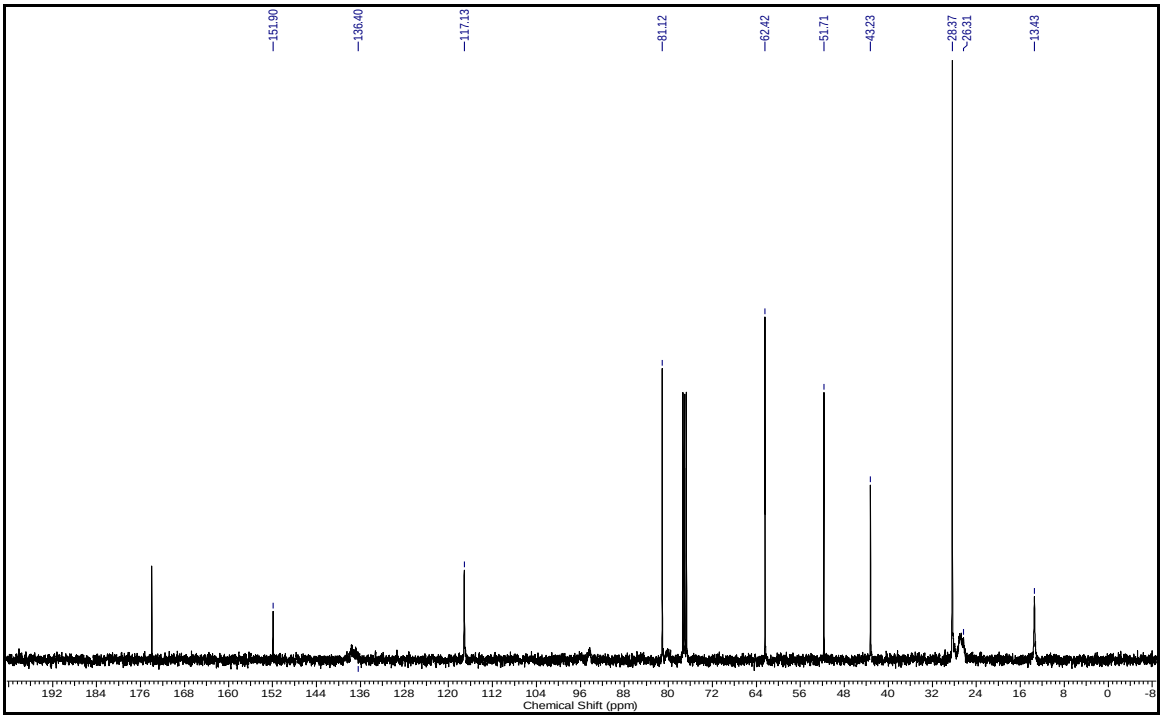
^{13}C NMR (100 MHz, $CDCl_3$) of compound xx



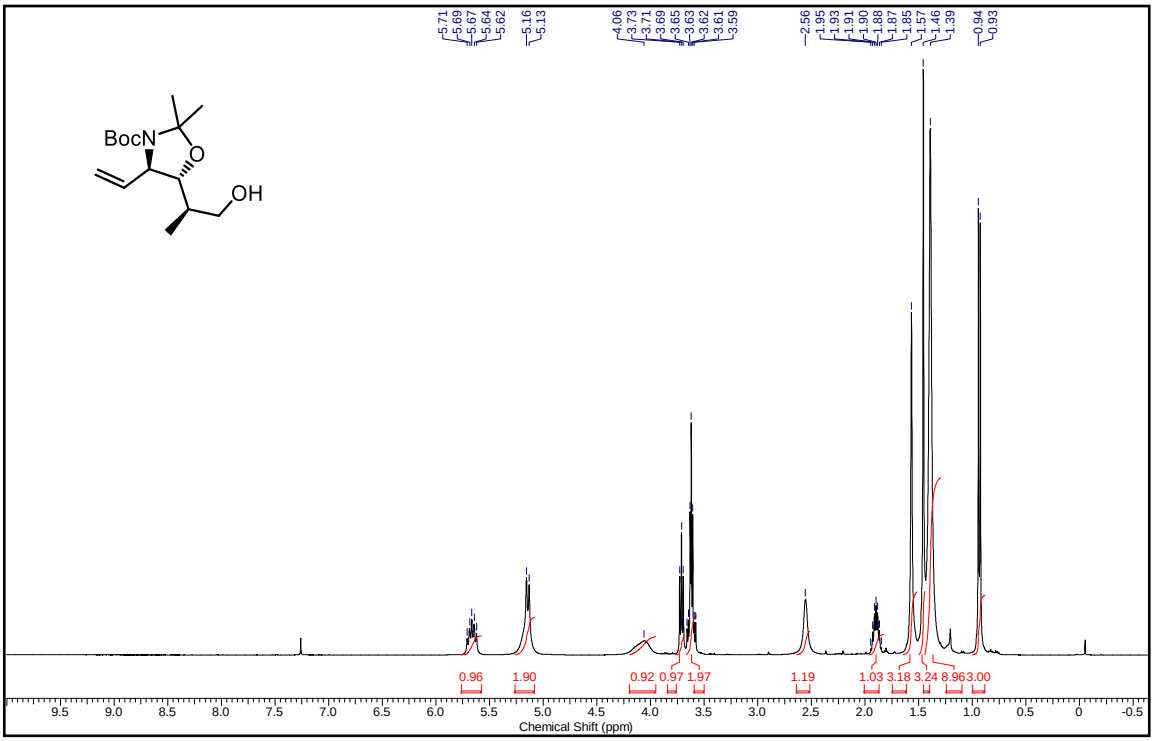
^{1}H NMR (400 MHz, $CDCl_3$) of compound 121



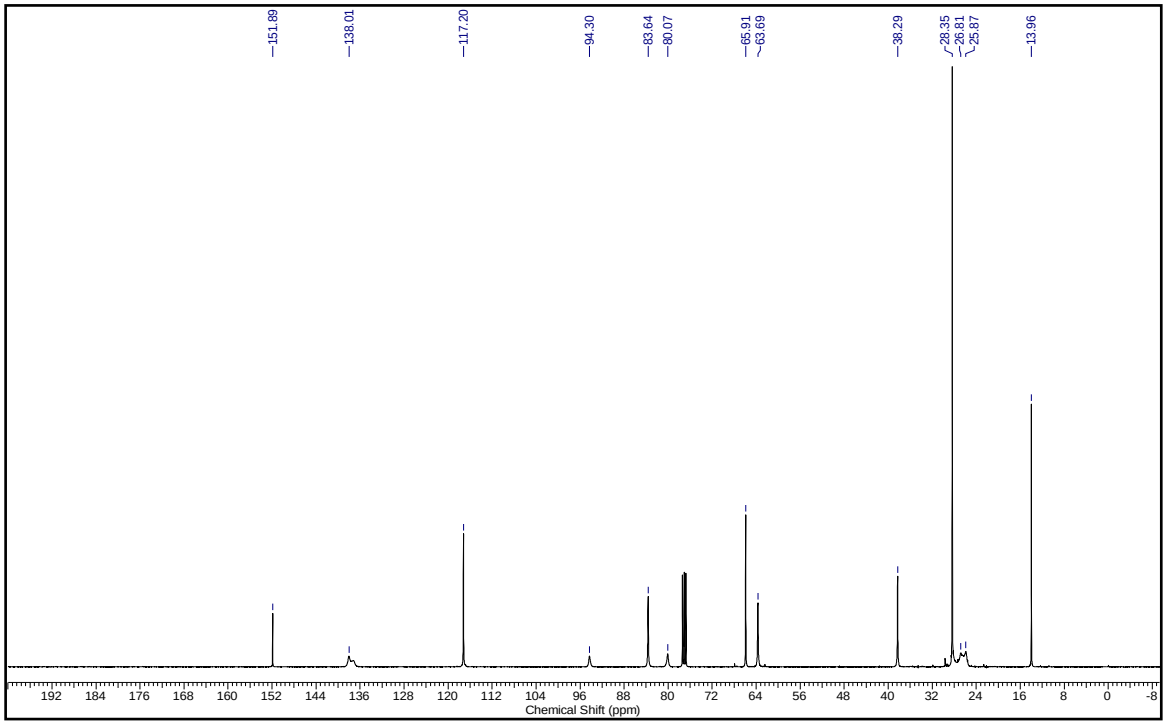
^{13}C NMR (100 MHz, $CDCl_3$) of compound 121



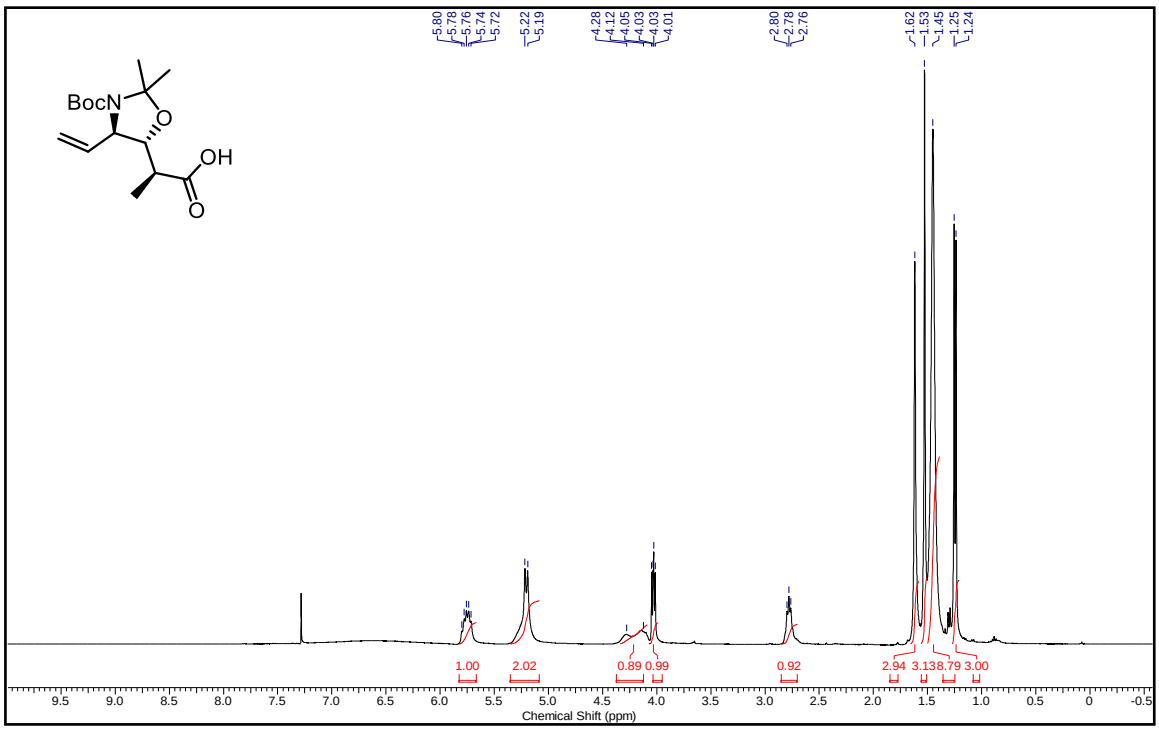
^{1}H NMR (400 MHz, $CDCl_3$) of compound 122



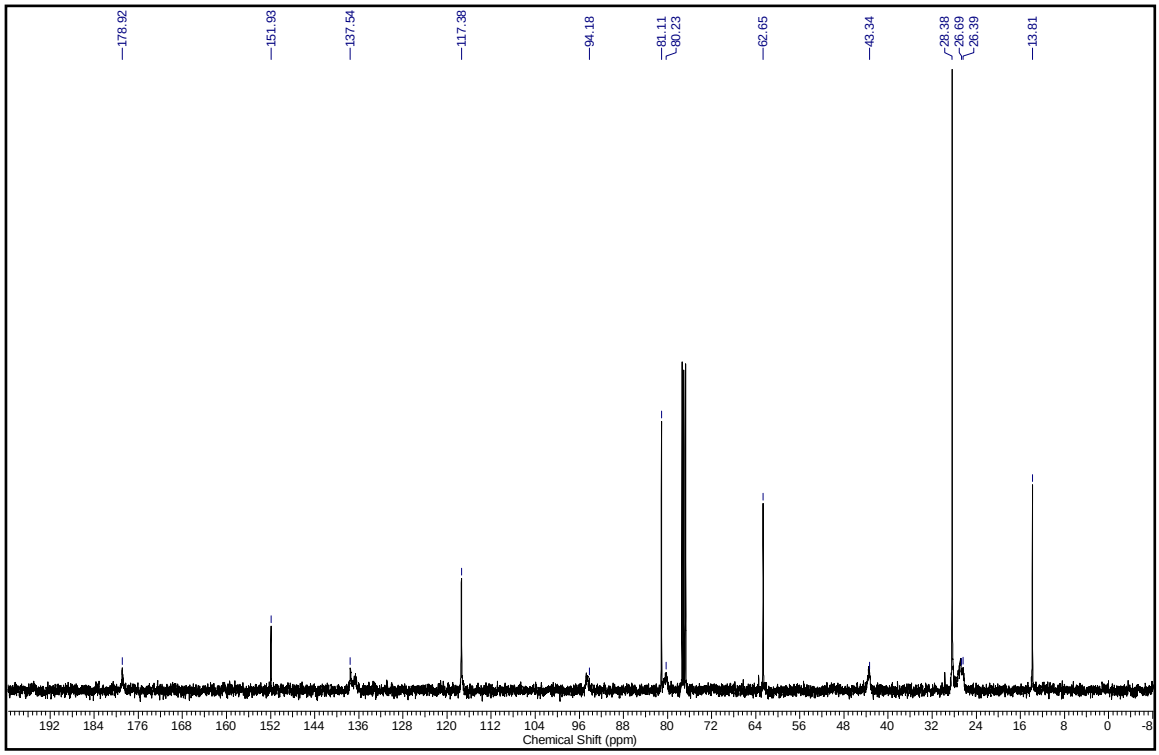
^{13}C NMR (100 MHz, $CDCl_3$) of compound 122



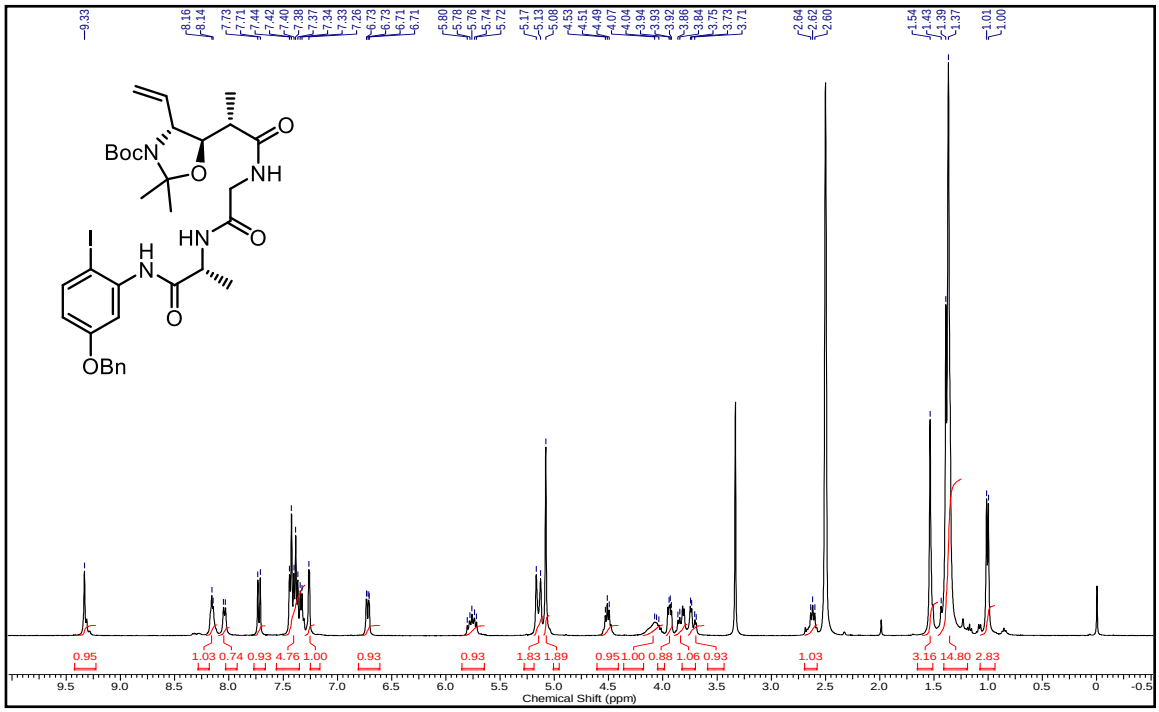
^{1}H NMR (400 MHz, $CDCl_3$) of compound 123



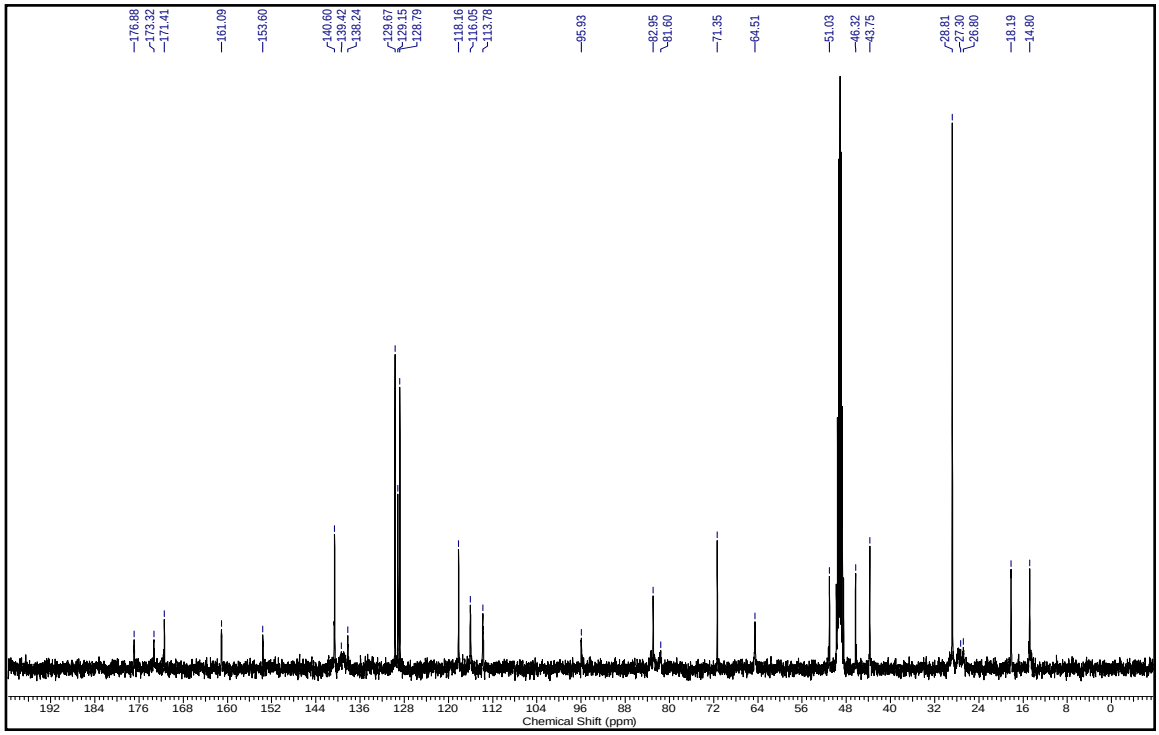
^{13}C NMR (100 MHz, $CDCl_3$) of compound 123



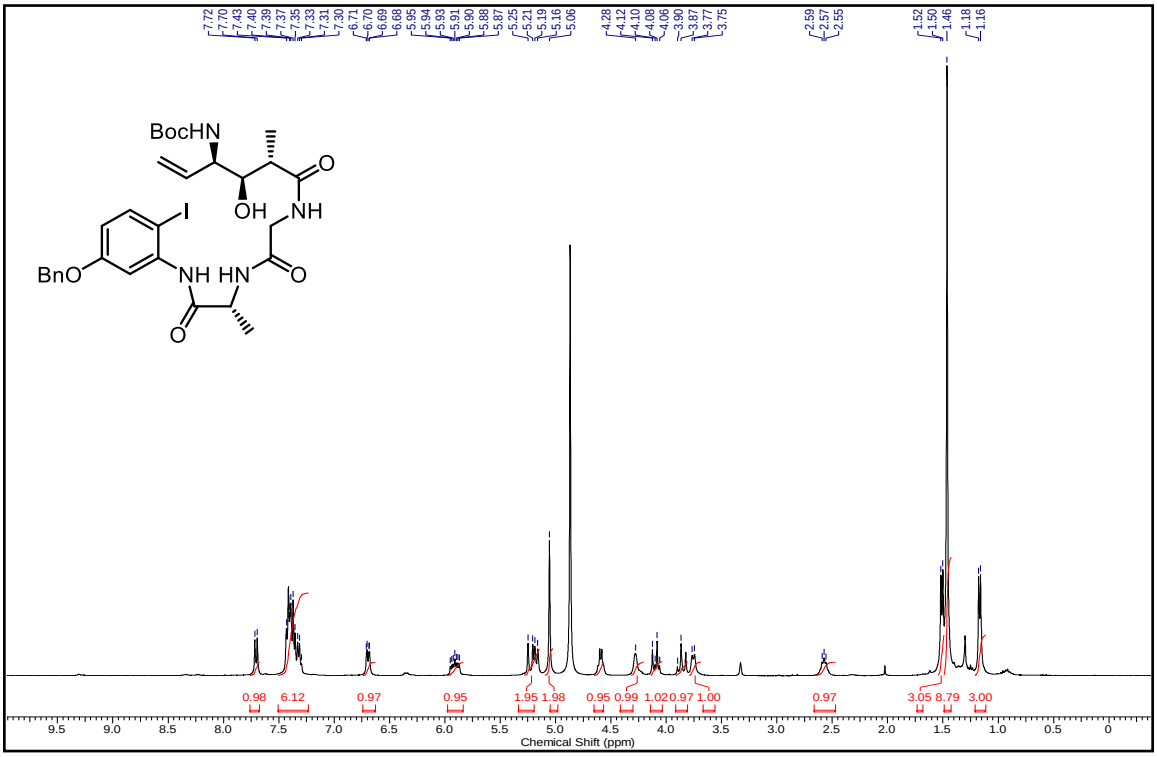
^{1}H NMR (400 MHz, DMSO-d_6) of compound 124



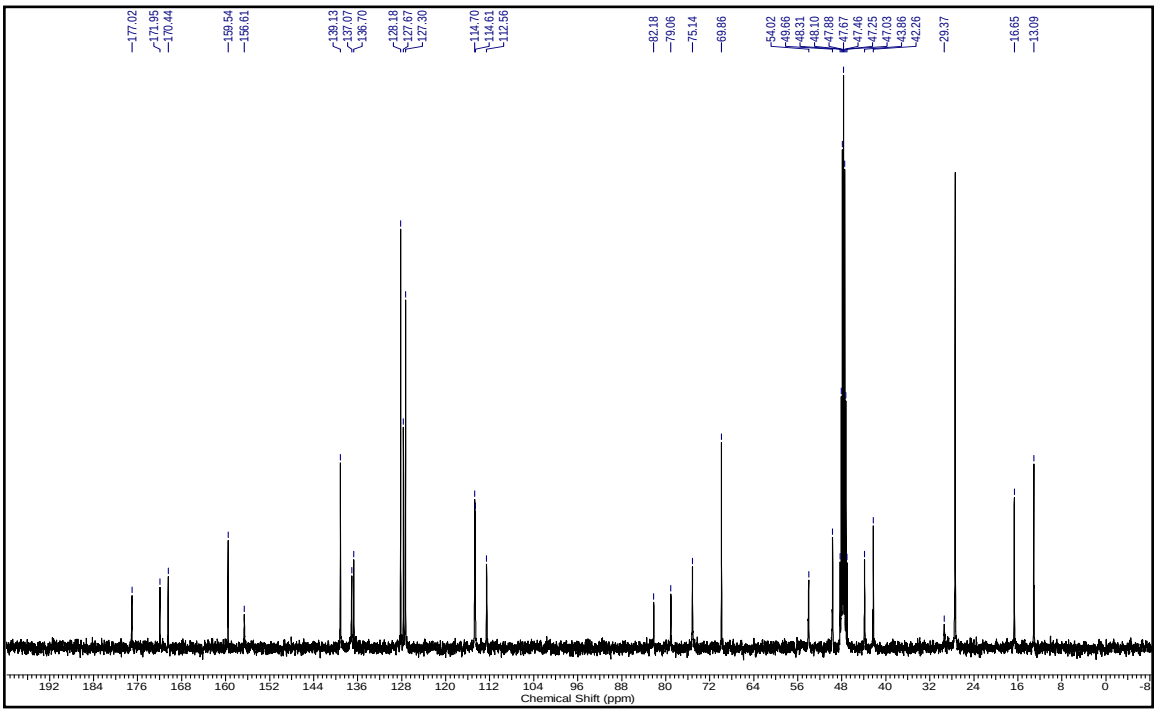
^{13}C NMR (100 MHz, CD_3OD) of compound 124



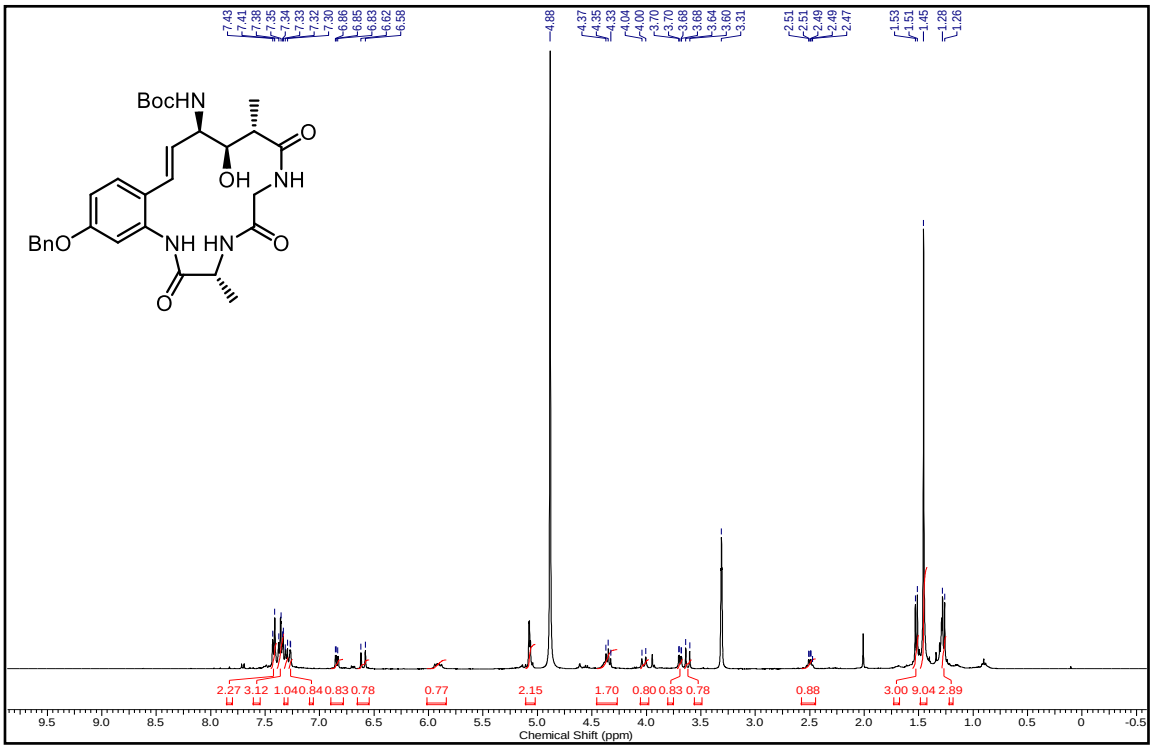
^{1}H NMR (400MHz, CD_3OD) of compound 125



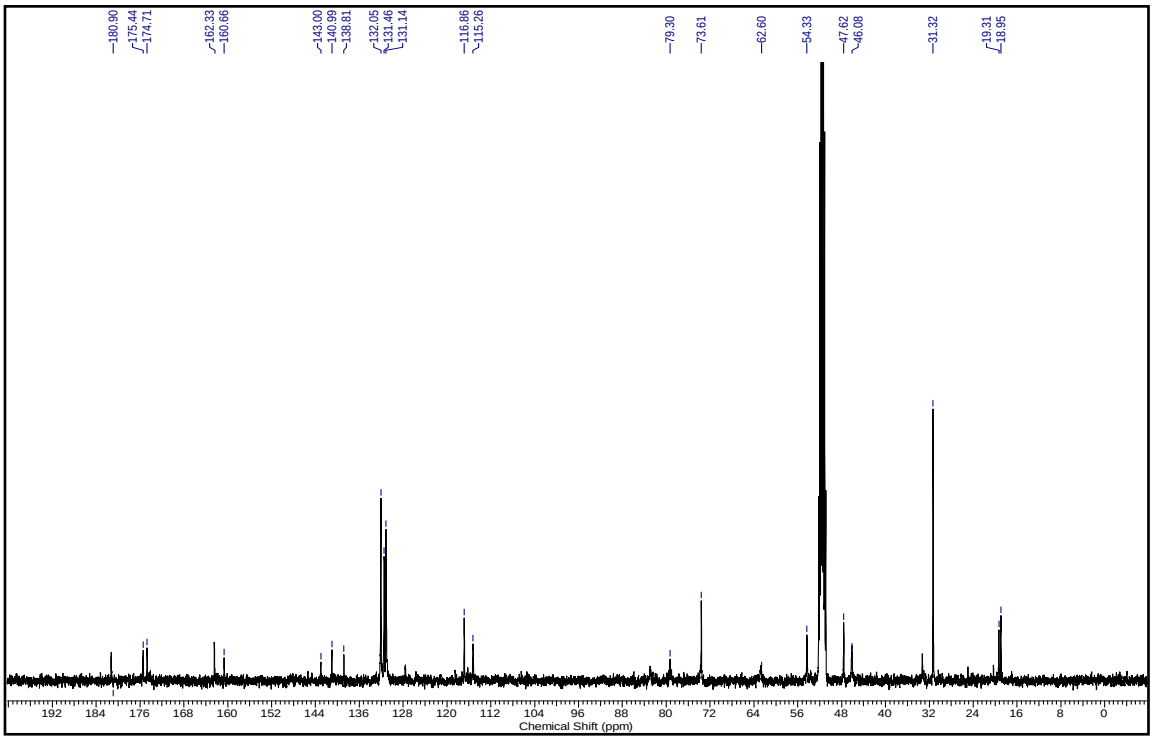
^{13}C NMR (100 MHz, CD_3OD) of compound 125



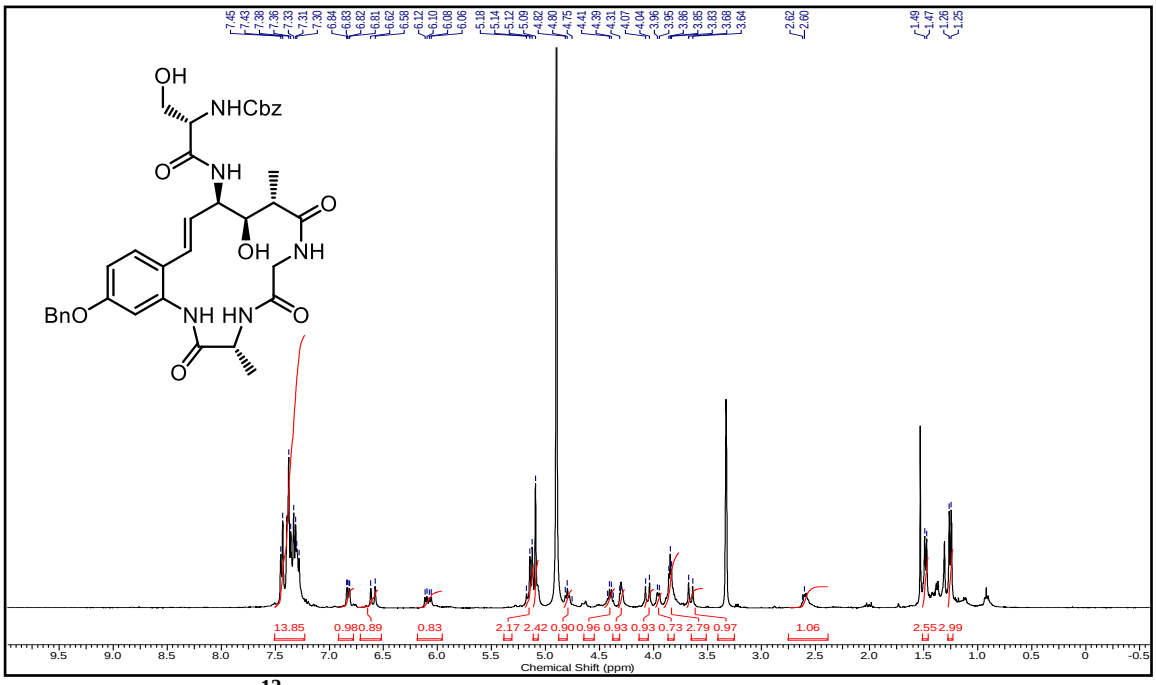
^{1}H NMR (400MHz, CD_3OD) of compound 106



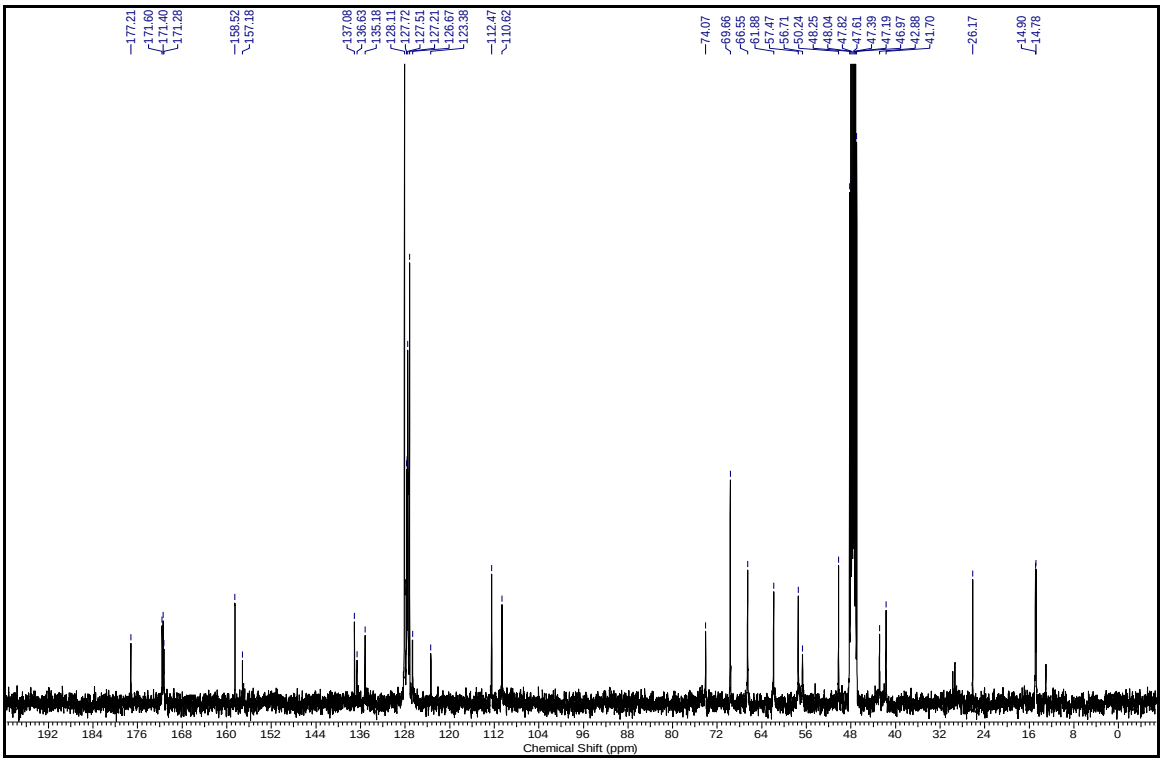
^{13}C NMR (100 MHz, CD_3OD) of compound 106



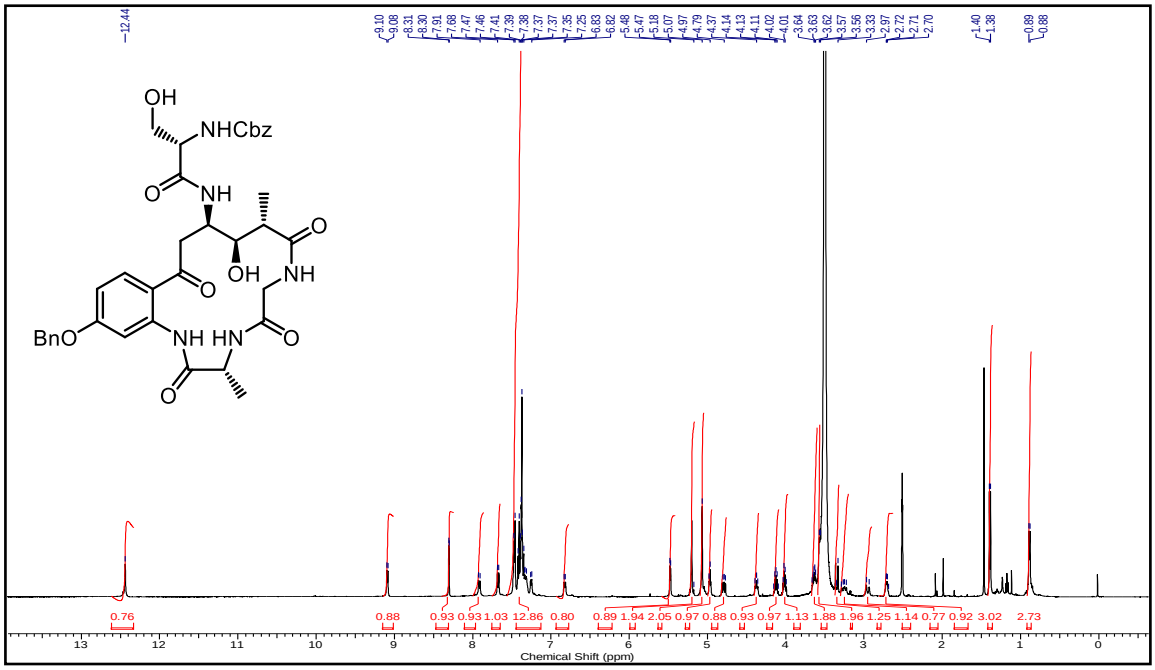
^{1}H NMR (400MHz, CD_3OD) of compound 127



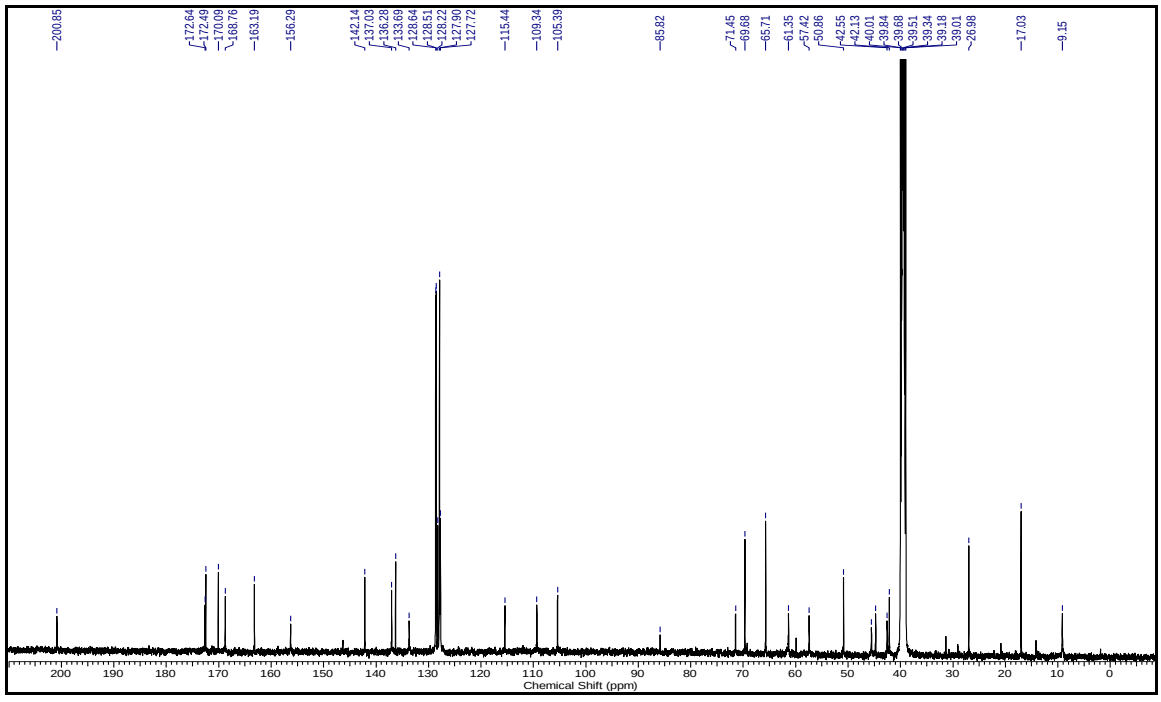
^{13}C NMR (100 MHz, CD_3OD) of compound 127



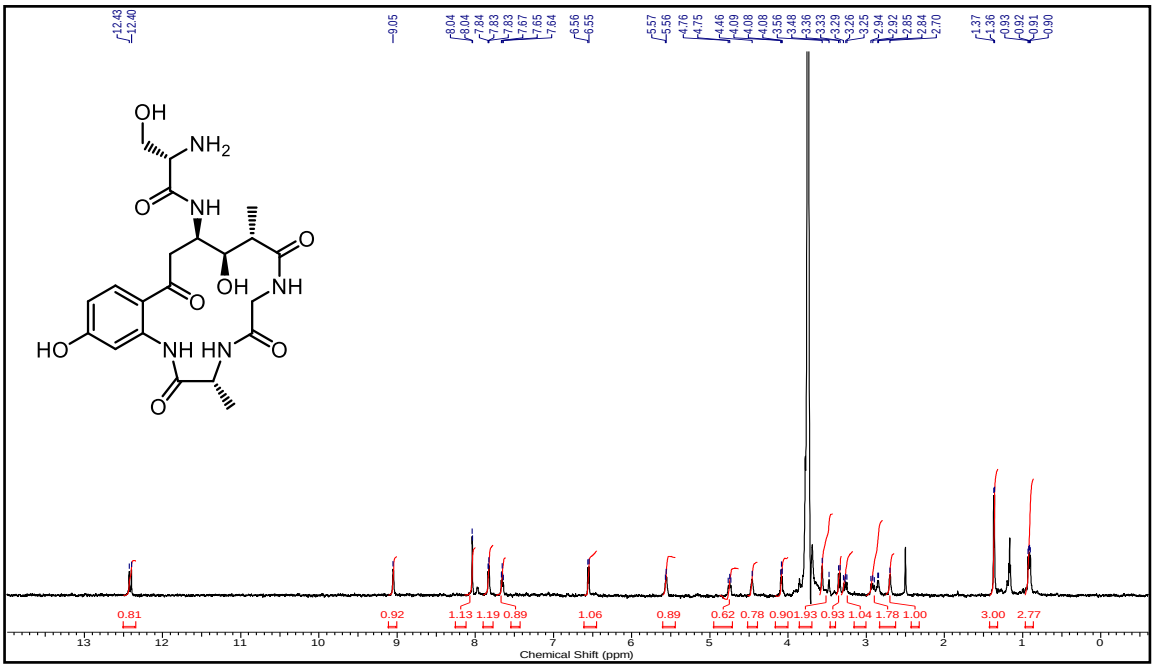
^{1}H NMR (500 MHz, DMSO-d_6) of compound 128



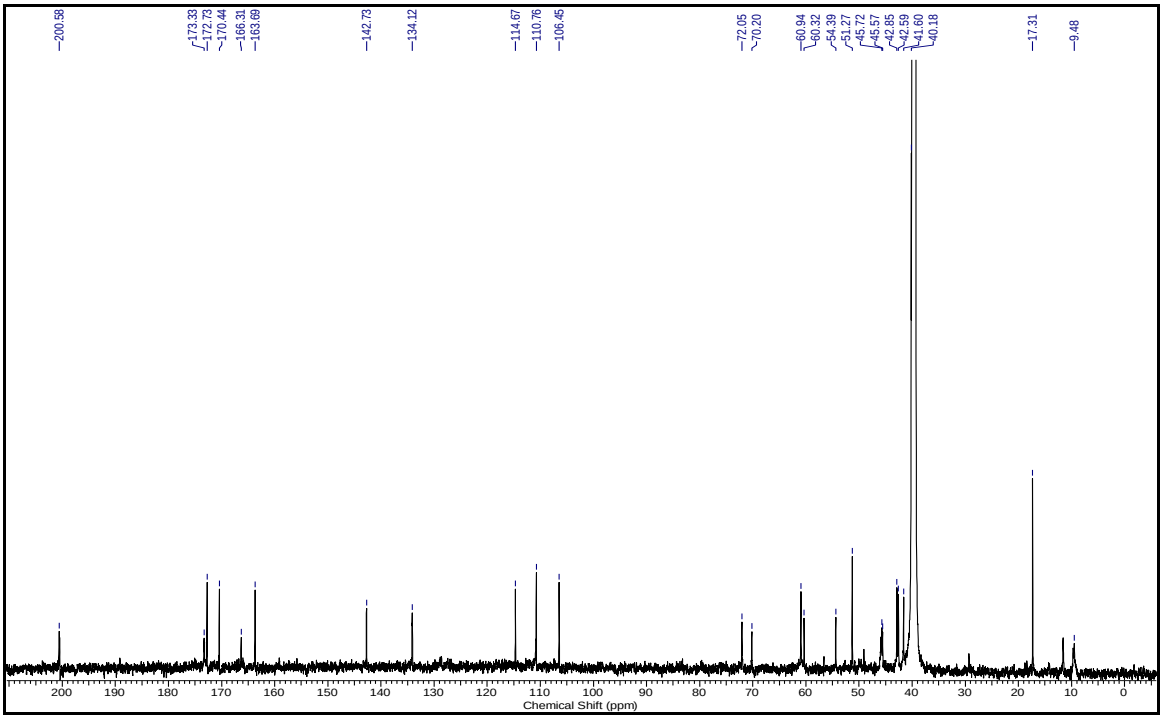
^{13}C NMR (1725 MHz, DMSO-d_6) of compound 128



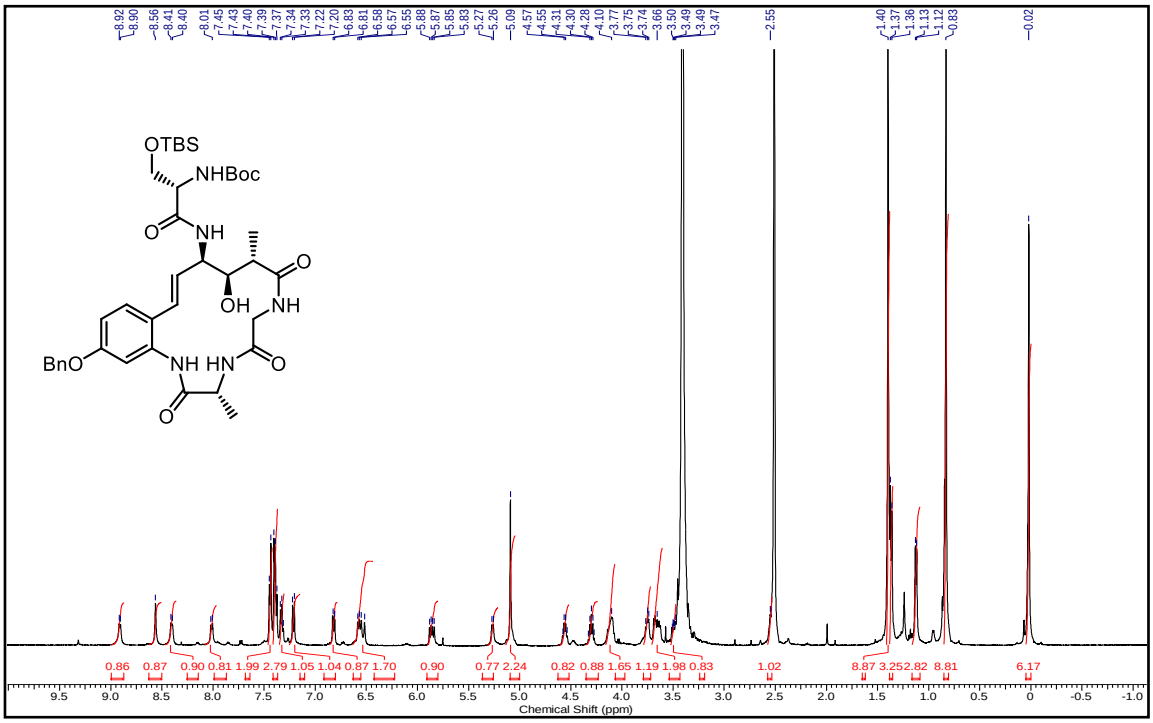
^{1}H NMR (700 MHz, DMSO-d_6) of compound 10'



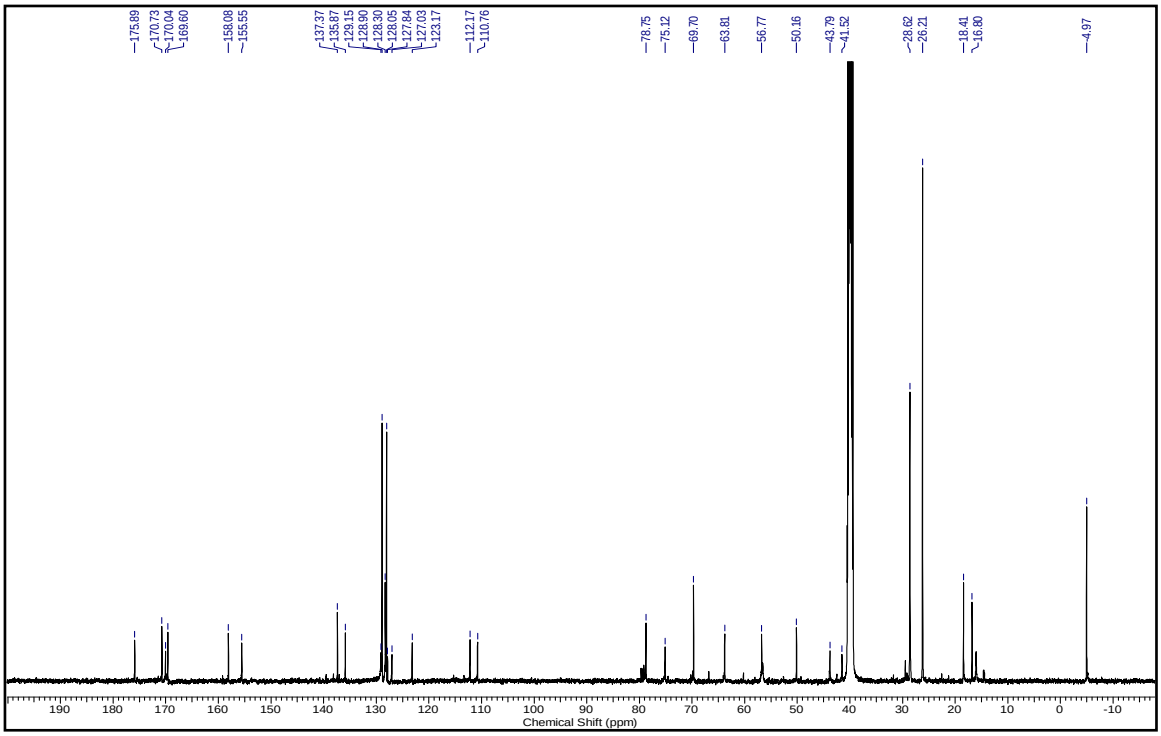
^{13}C NMR (175 MHz, DMSO-d_6) of compound 10'



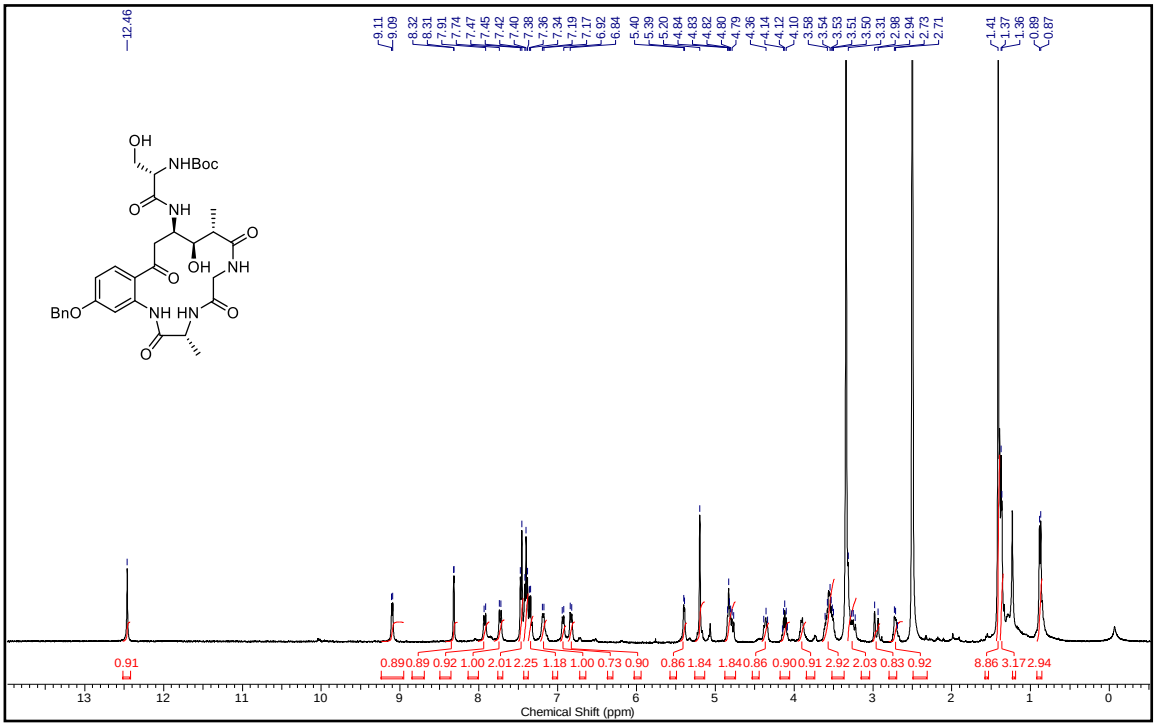
^{1}H NMR (500 MHz, DMSO-d_6) of compound 104



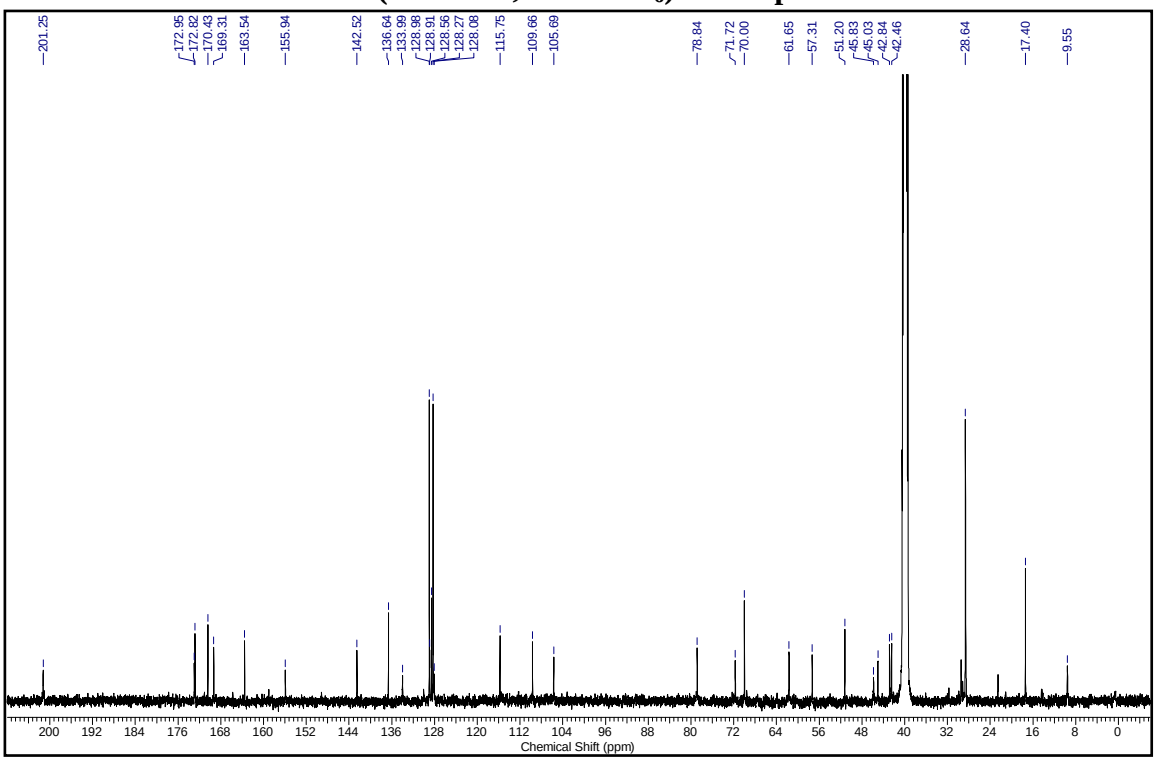
^{13}C NMR (125 MHz, DMSO-d_6) of compound 104



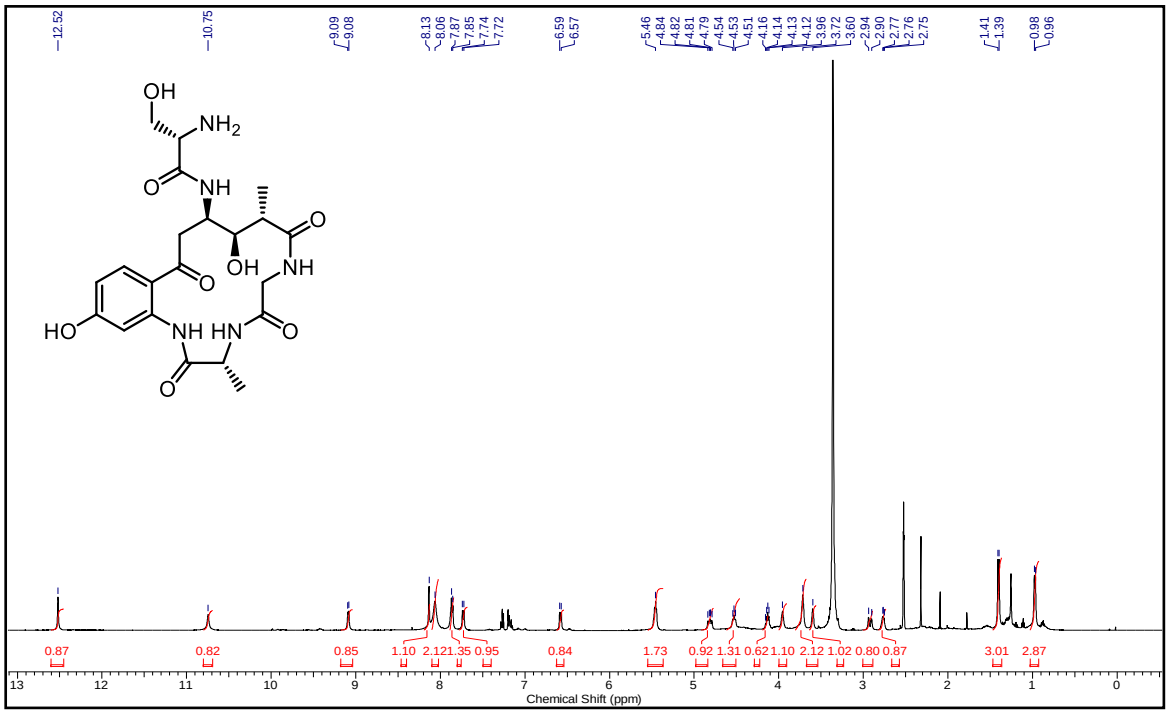
^{1}H NMR (500 MHz, DMSO-d_6) of compound 105



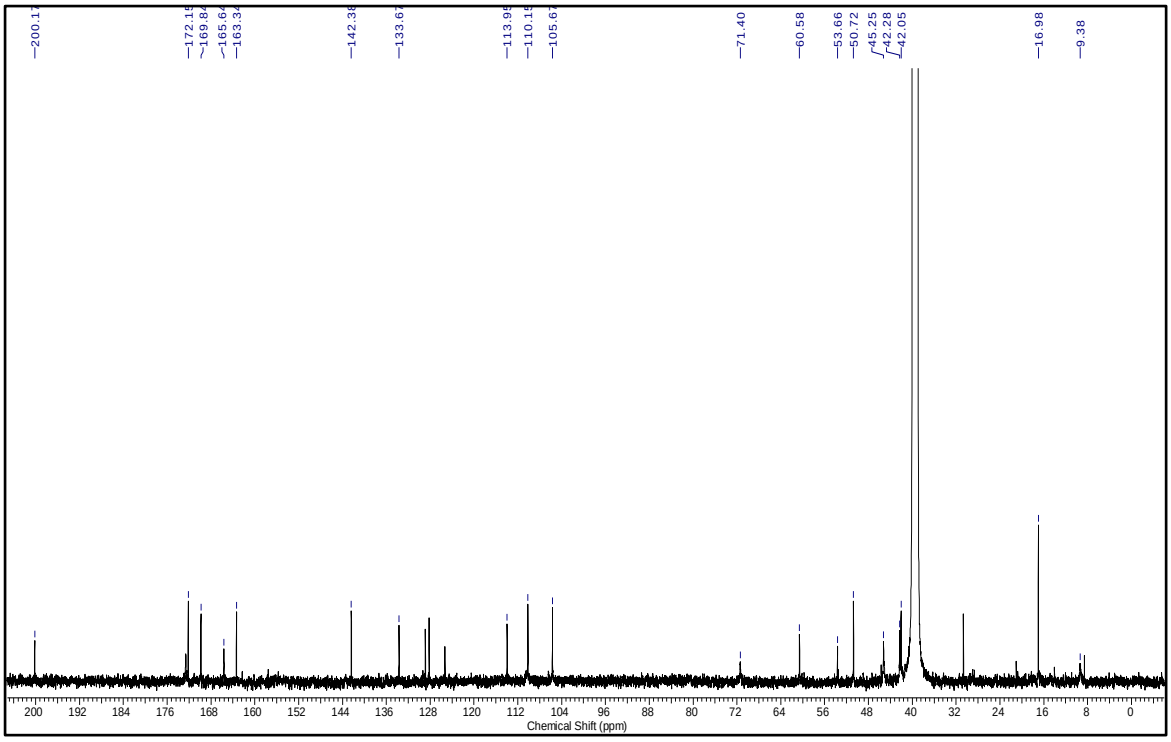
^{13}C NMR (125 MHz, DMSO-d_6) of compound 105



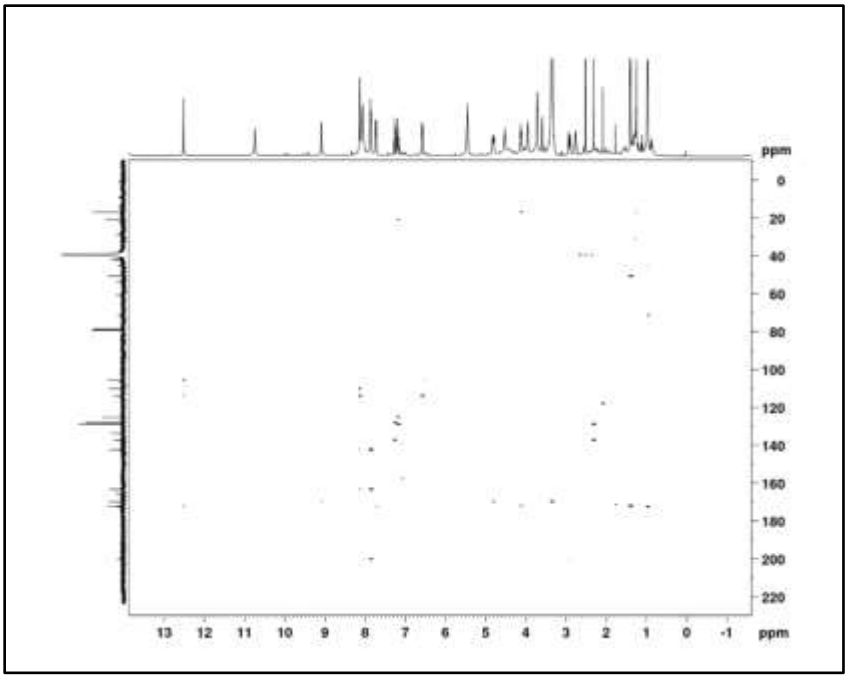
^{1}H NMR (500 MHz, DMSO-d_6) of compound 10



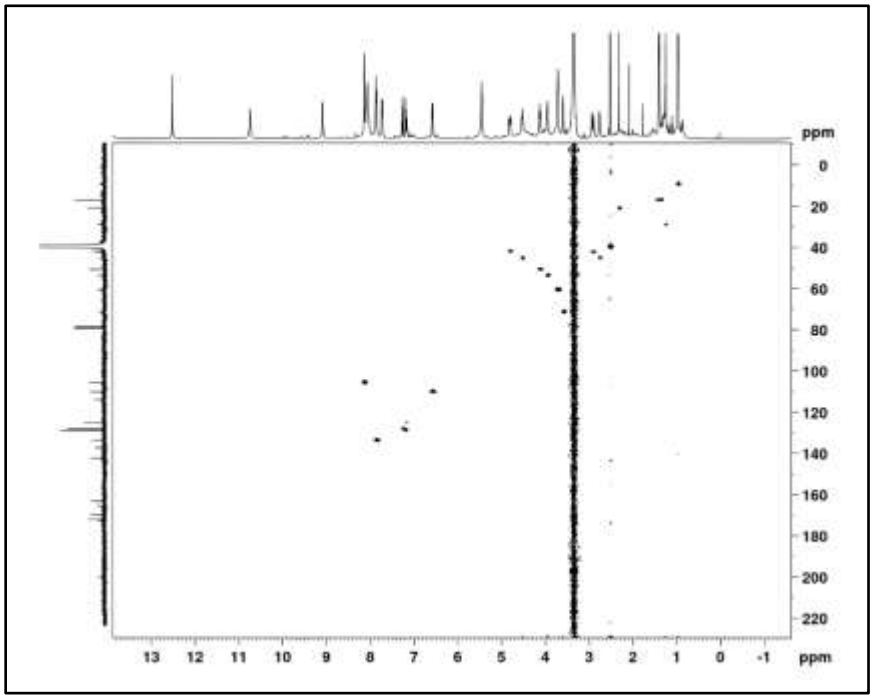
^{13}C NMR (125 MHz, DMSO-d_6) of compound 10



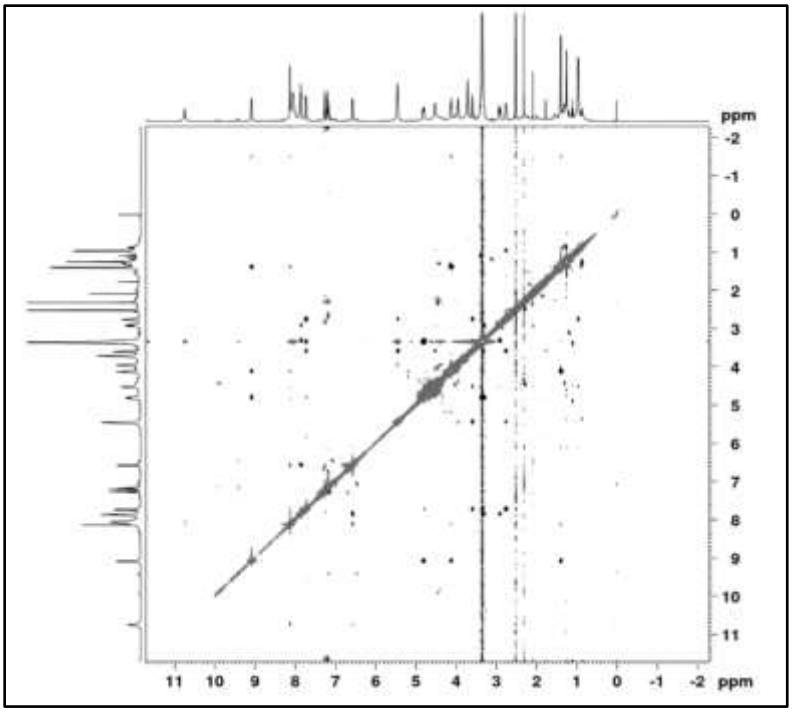
HMBC spectrum (500 MHz, DMSO-d_6) of compound 10



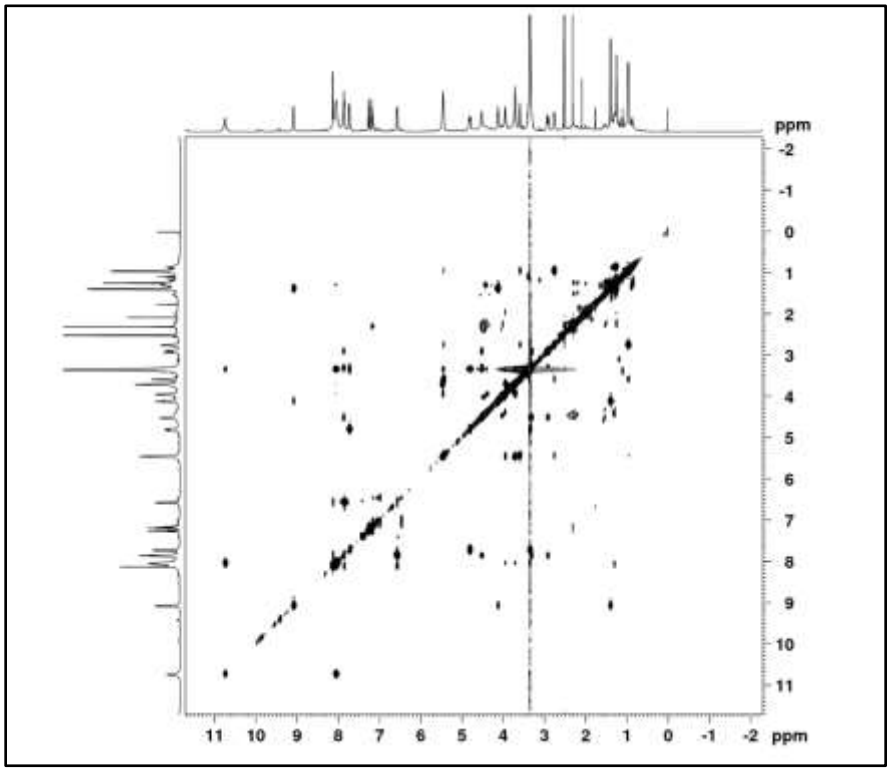
HSQC spectrum (500 MHz, DMSO-d_6) of compound 10



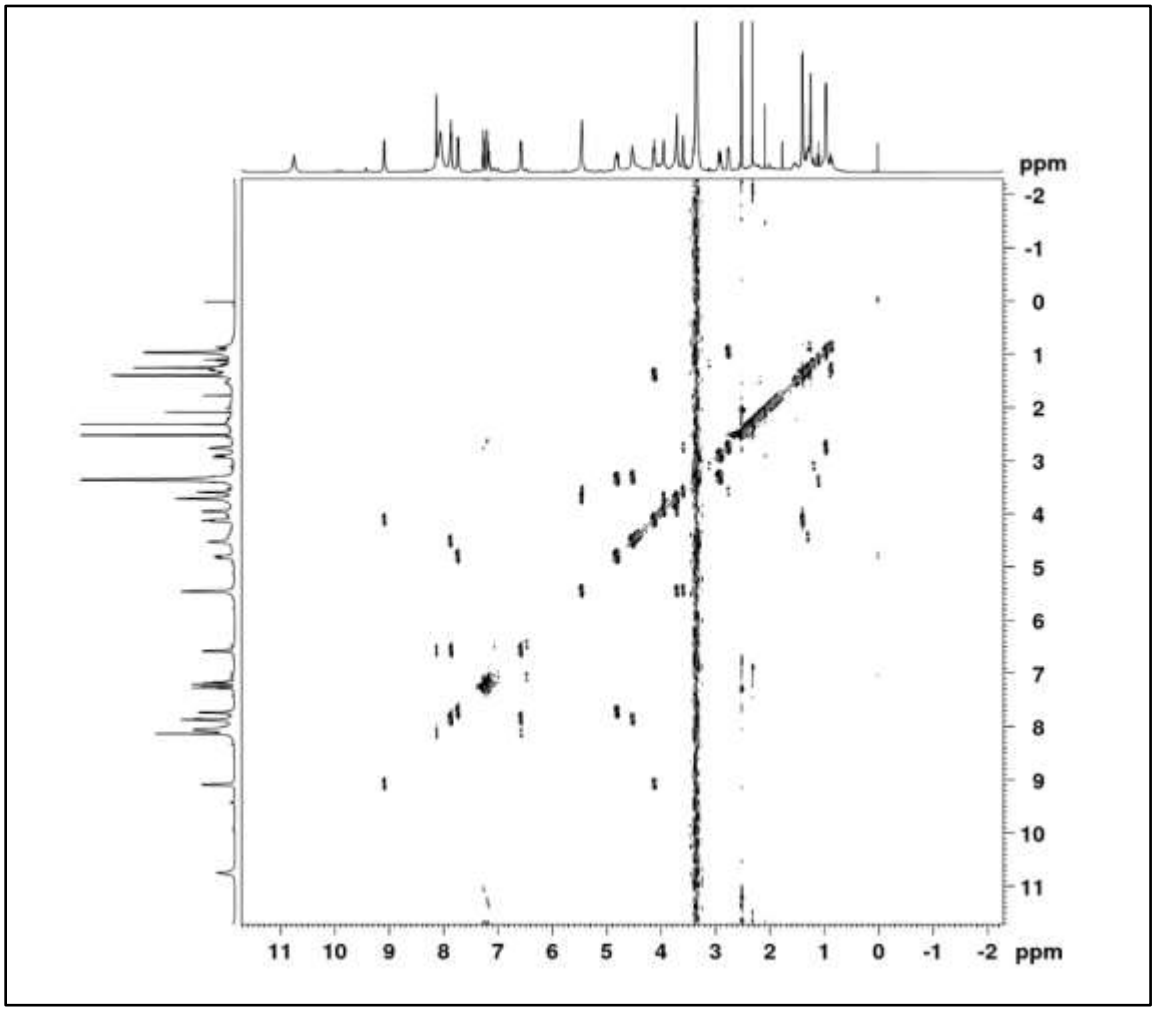
ROESY spectrum (500 MHz, DMSO-d_6) of compound 10



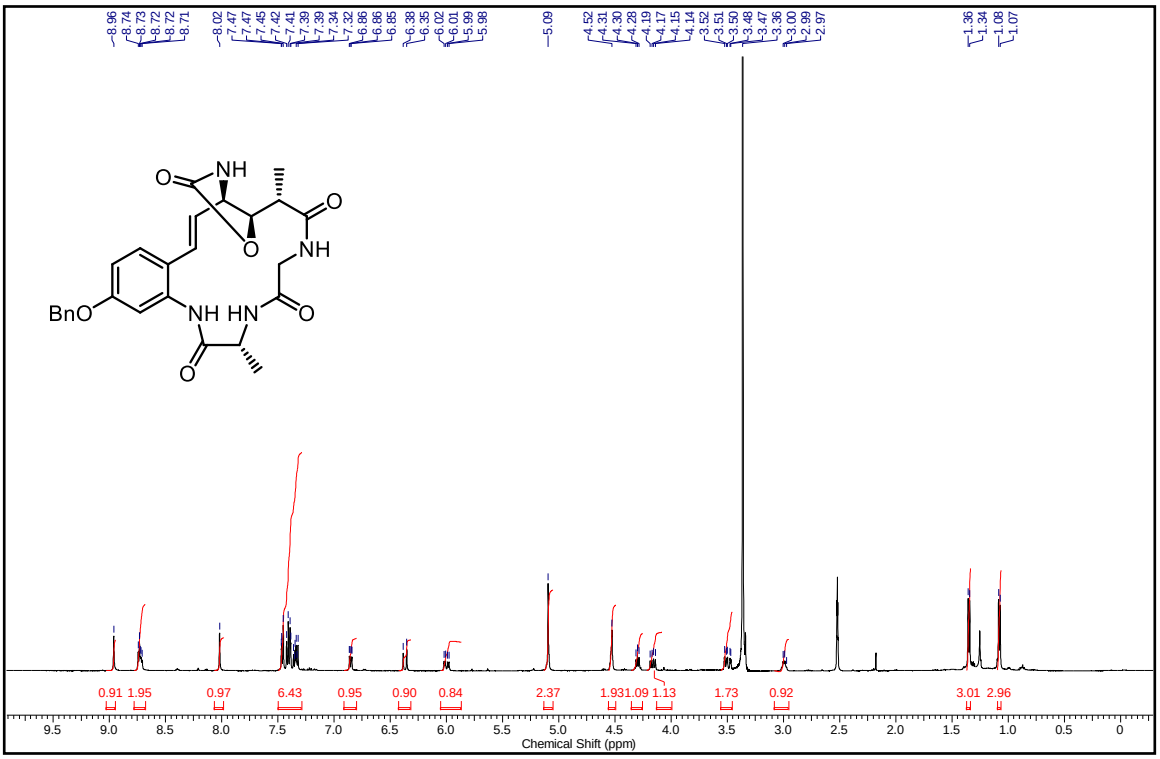
TOCSY spectrum (500 MHz, DMSO-d_6) of compound 10



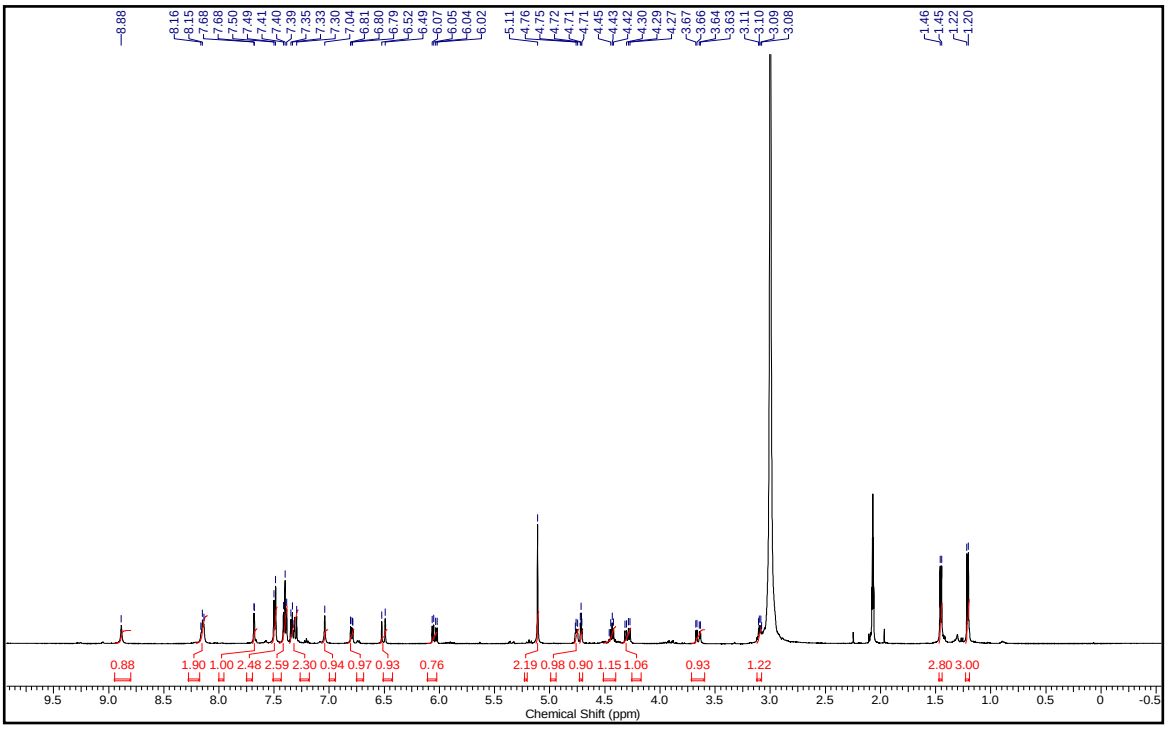
DQF-COSY spectrum (500 MHz, DMSO-d_6) of compound 10



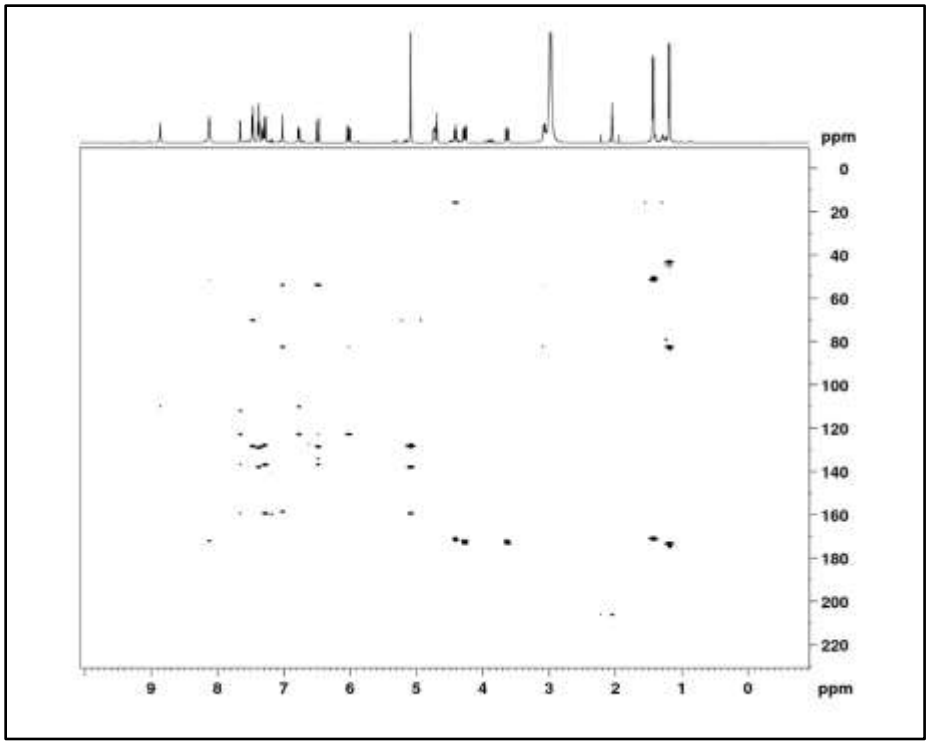
^{1}H NMR (500 MHz, DMSO-d_6) of compound 129



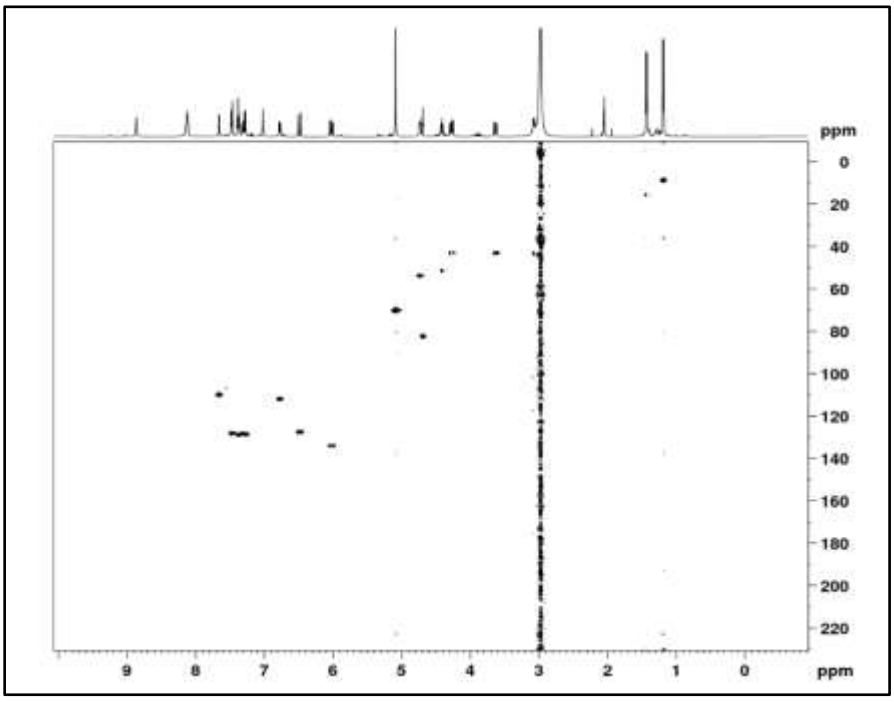
^{1}H NMR (500 MHz, Acetone-d_6) of compound 129



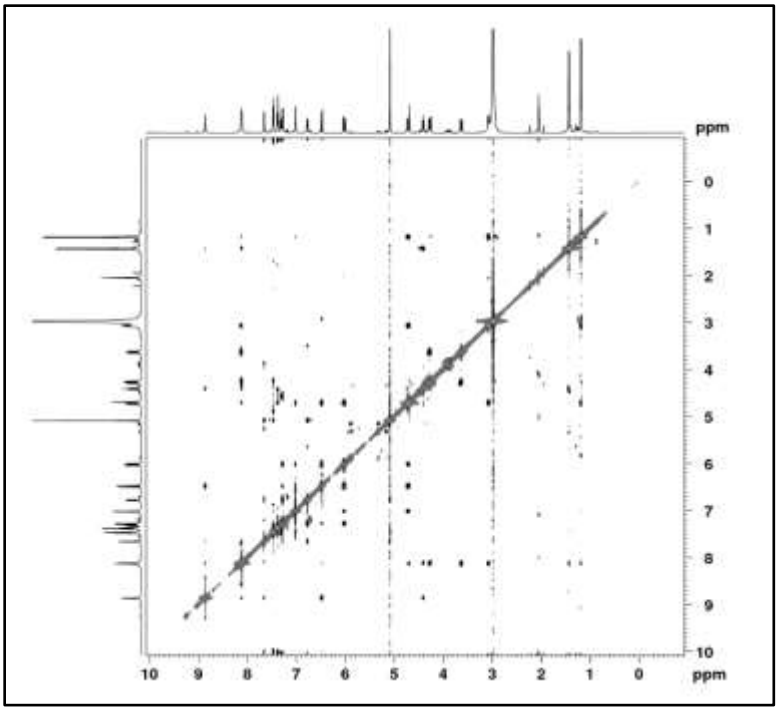
HMBC spectrum (500 MHz, Acetone-d_6) of compound 129



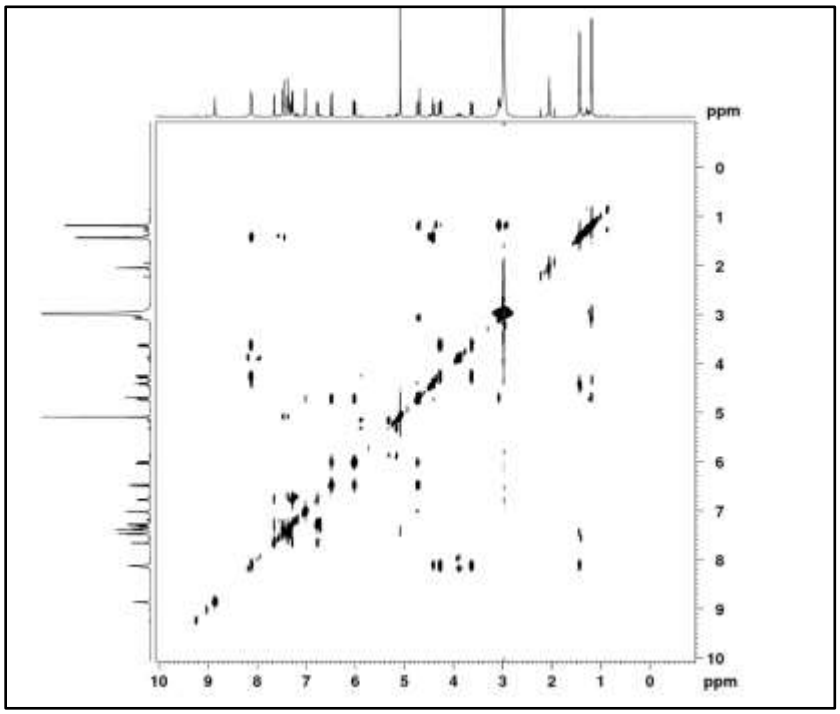
HSQC spectrum (500 MHz, Acetone-d_6) of compound 129



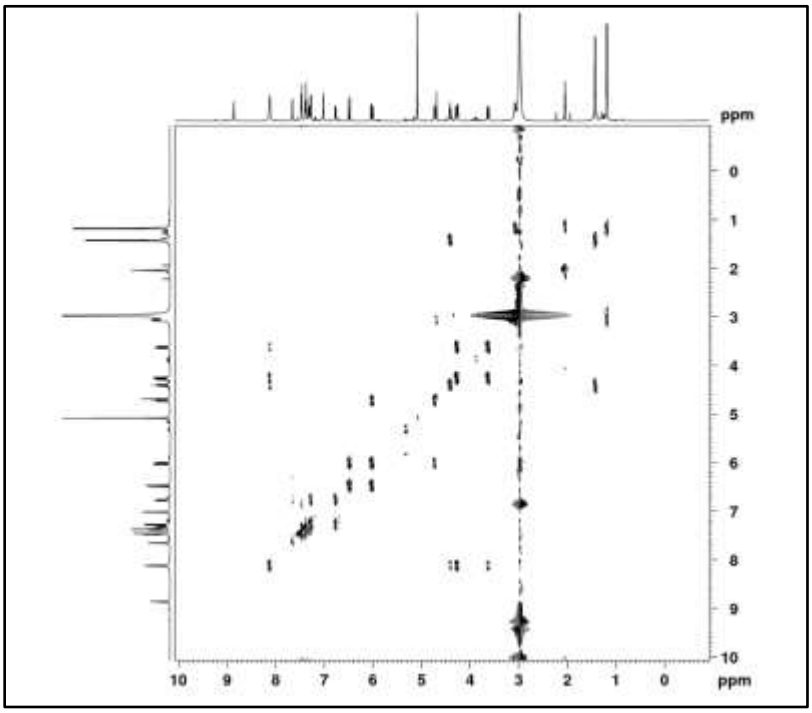
ROESY spectrum (500 MHz, Acetone-d_6) of compound 129



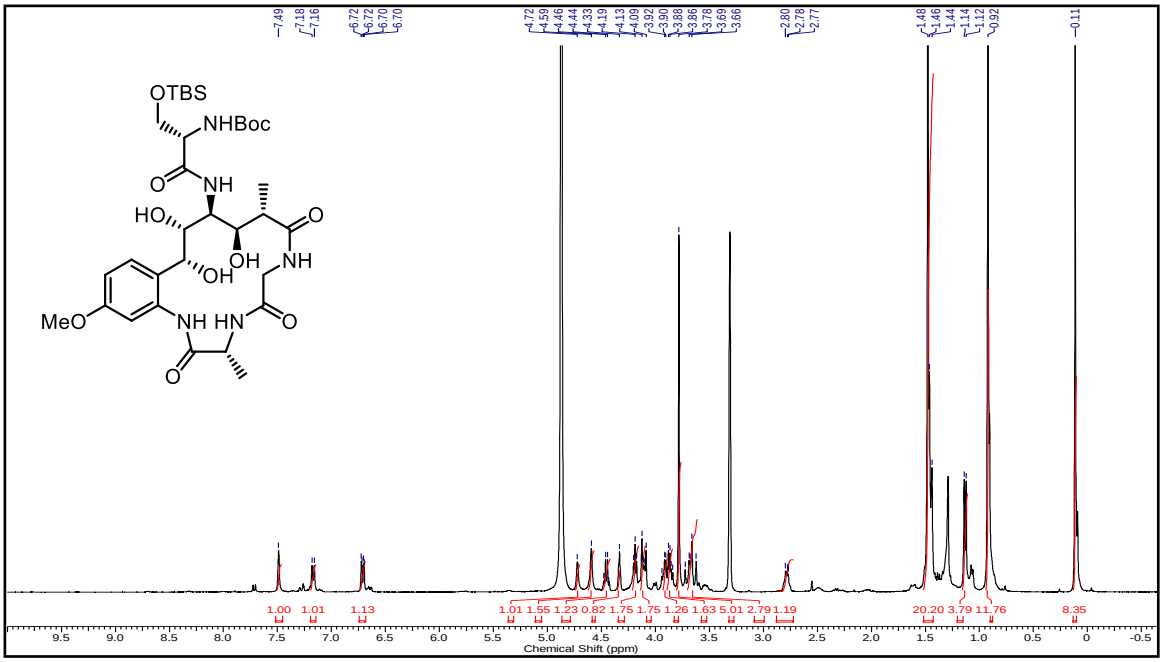
TOCSY spectrum (500 MHz, Acetone-d_6) of compound 129



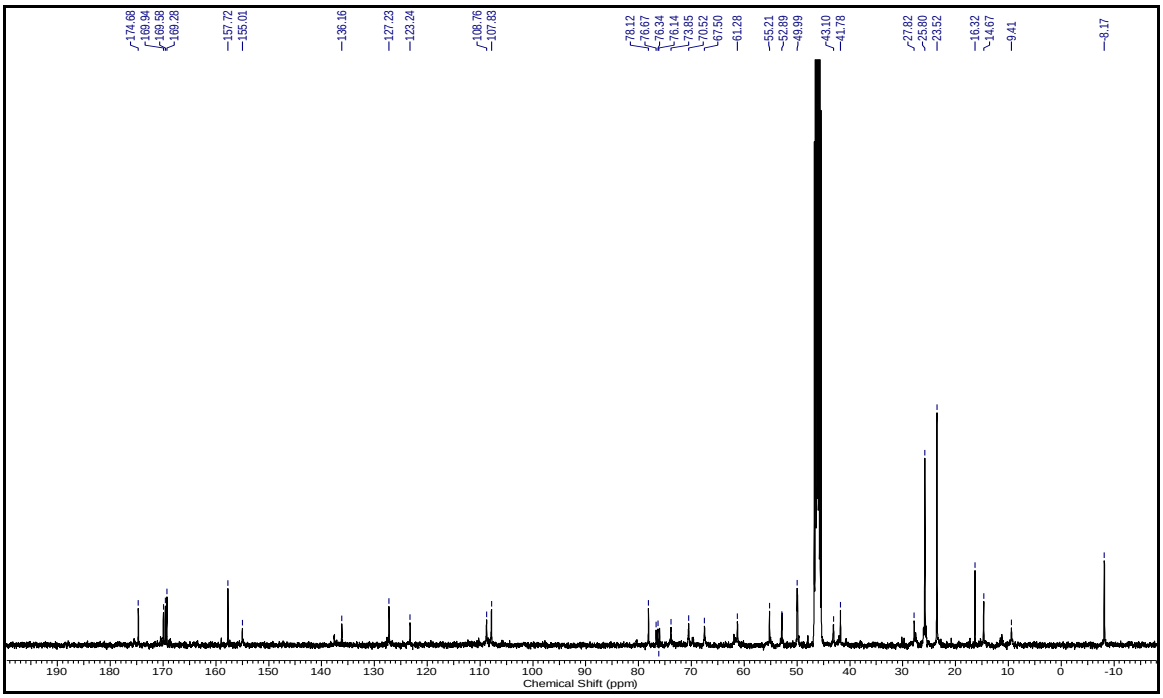
DQF-COSY spectrum (500 MHz, Acetone-d_6) of compound 129



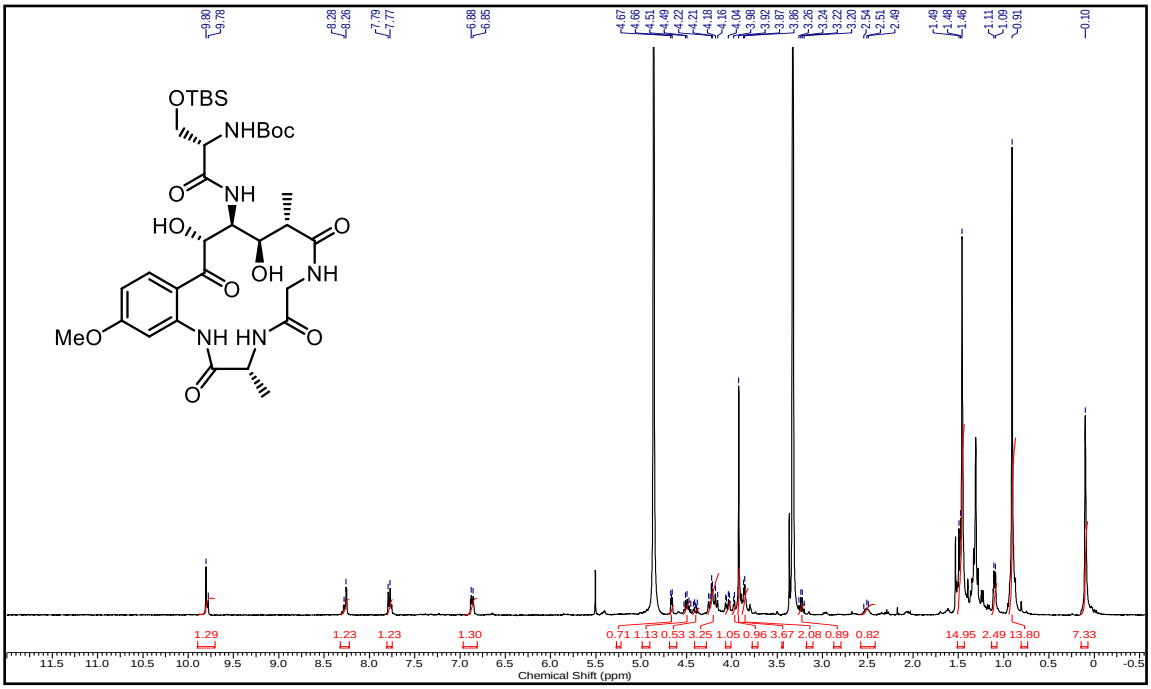
^{1}H NMR (400MHz, CD_3OD) of compound 130



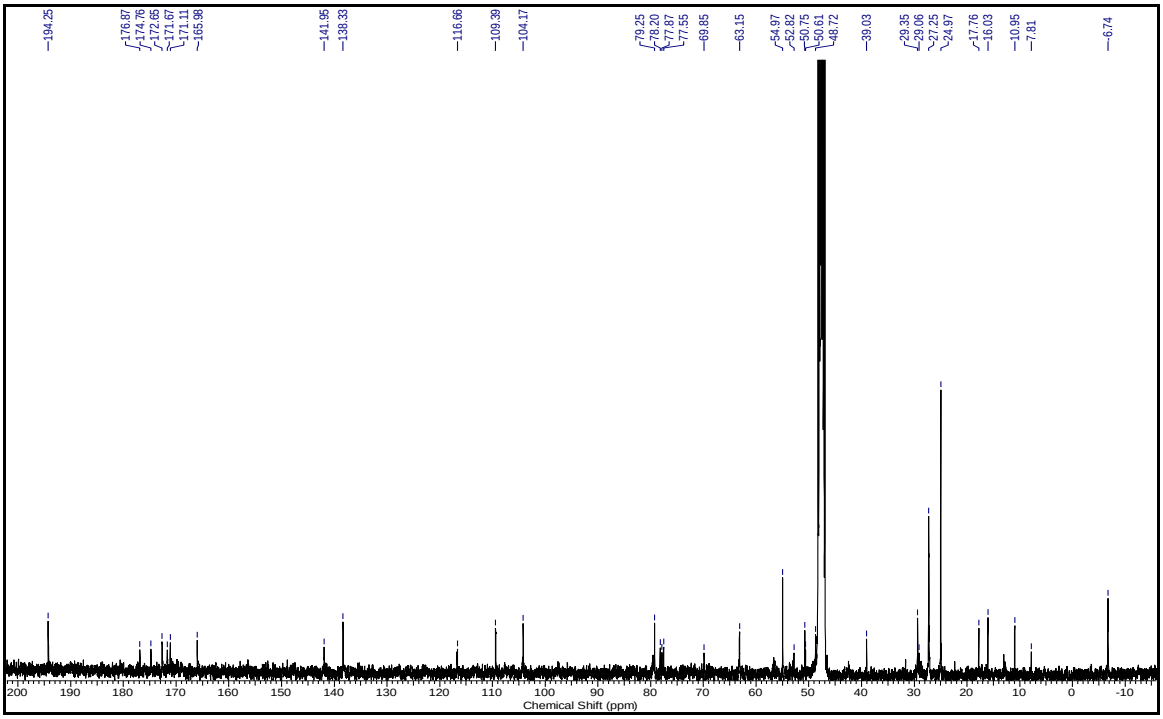
^{13}C NMR (100 MHz, CD_3OD) of compound 130



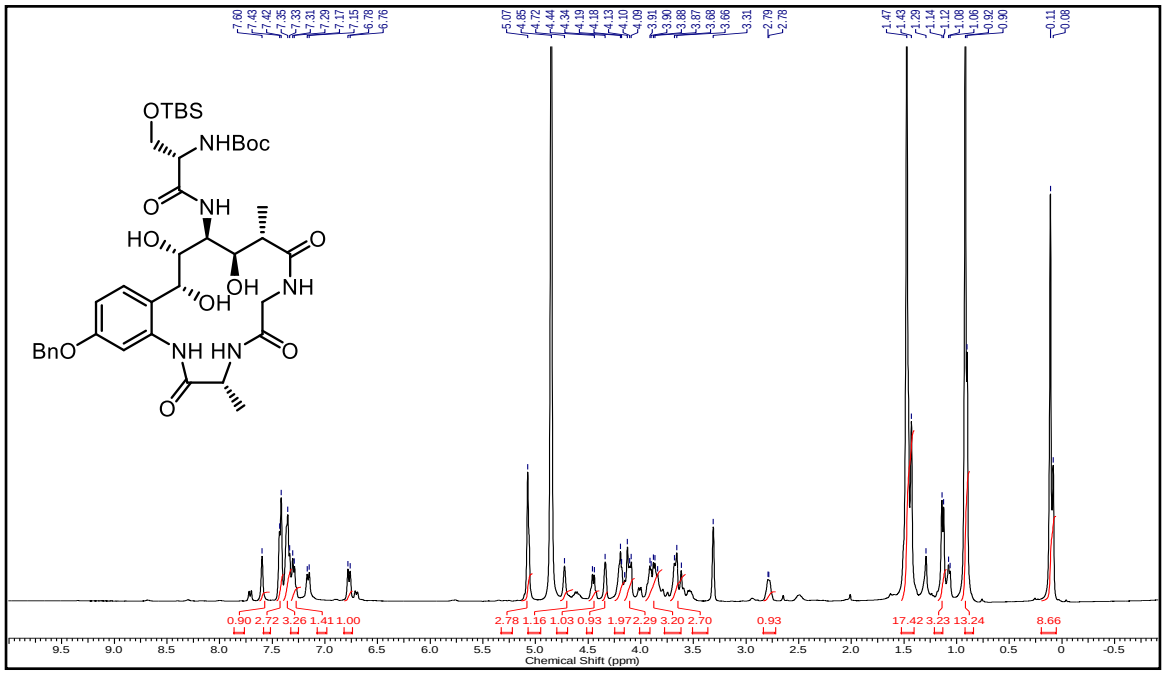
^{1}H NMR (400MHz, CD_3OD) of compound 131



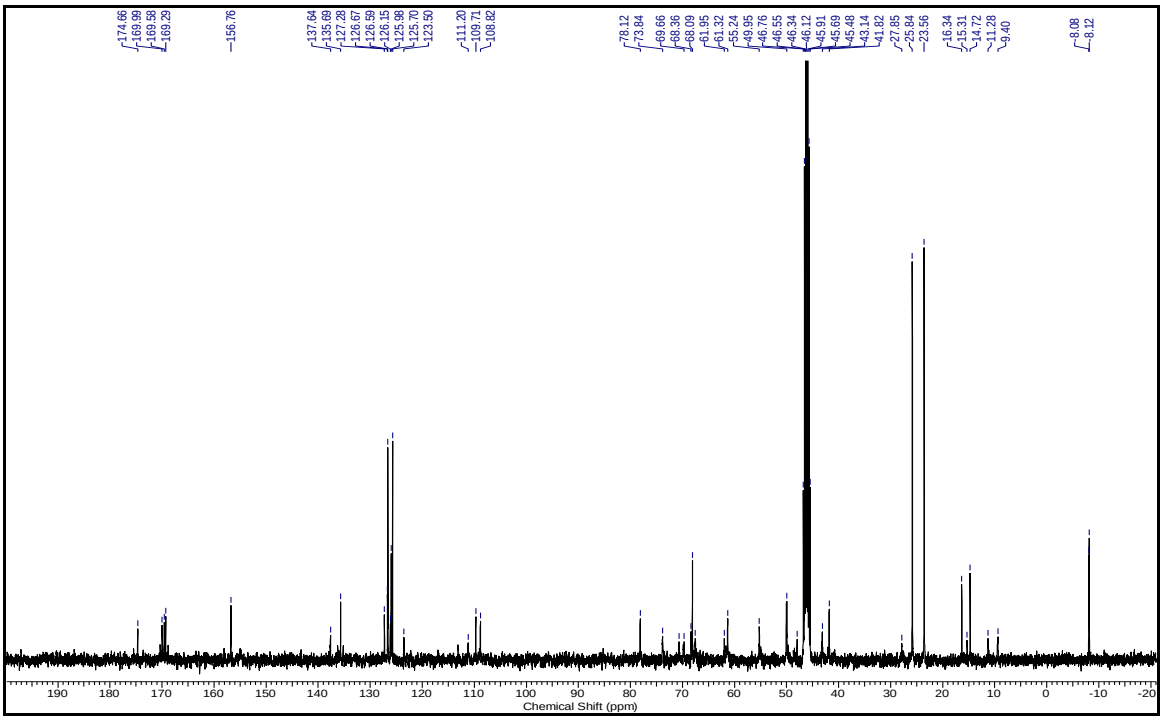
^{13}C NMR (100MHz, CD_3OD) of compound 131



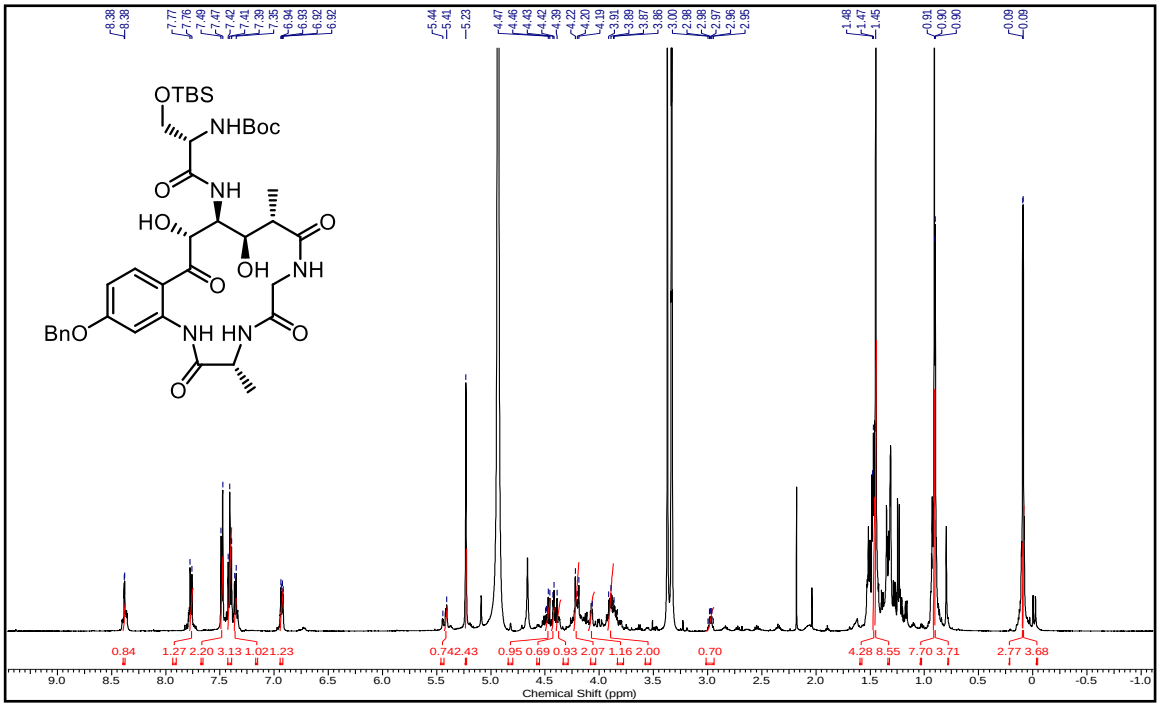
^{1}H NMR (400MHz, CD_3OD) of compound 132



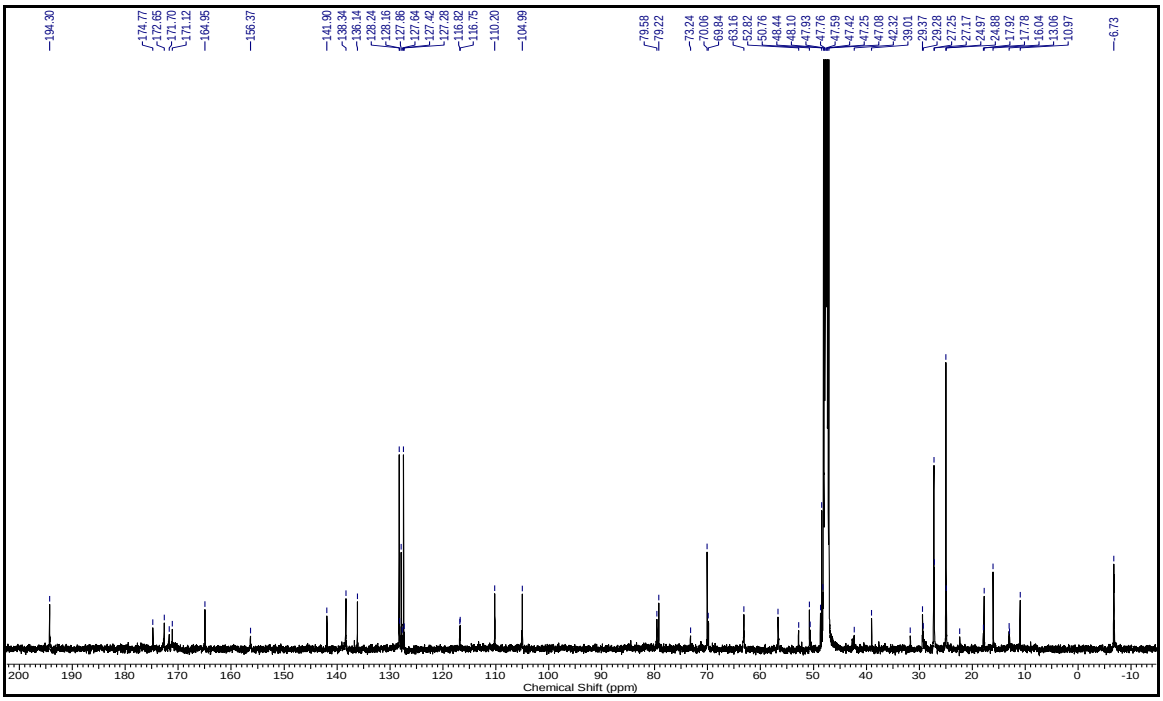
^{13}C NMR (100 MHz, CD_3OD) of compound 132



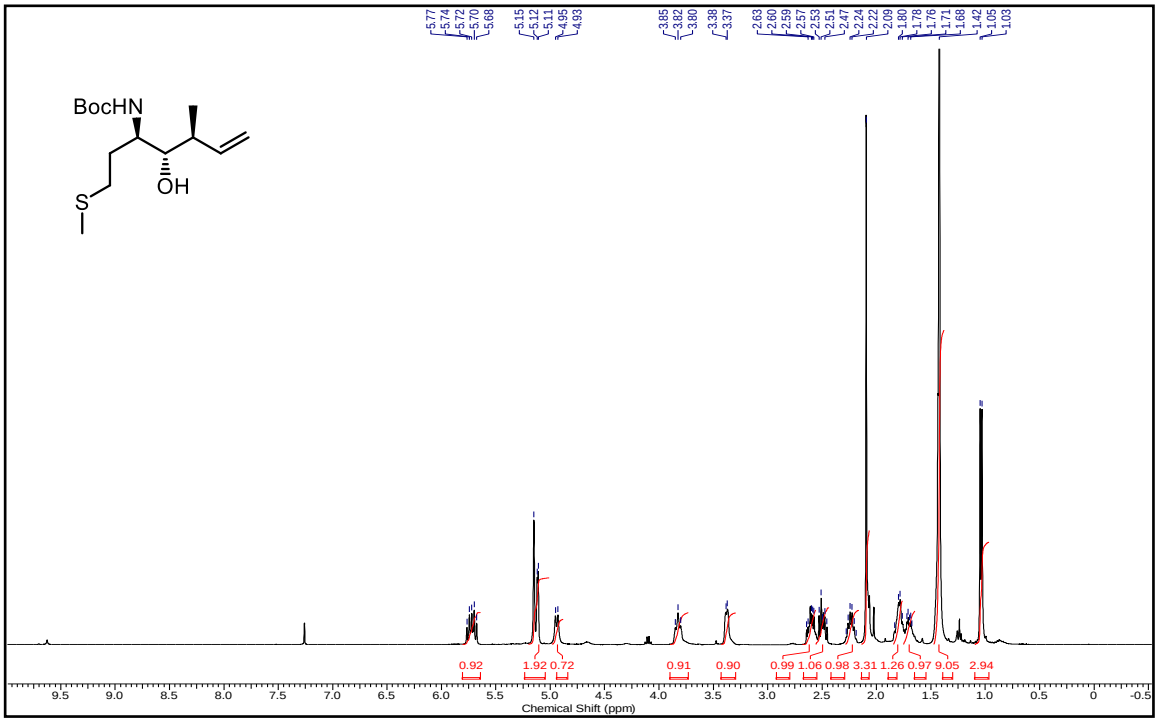
^{1}H NMR (400MHz, CD_3OD) of compound 133



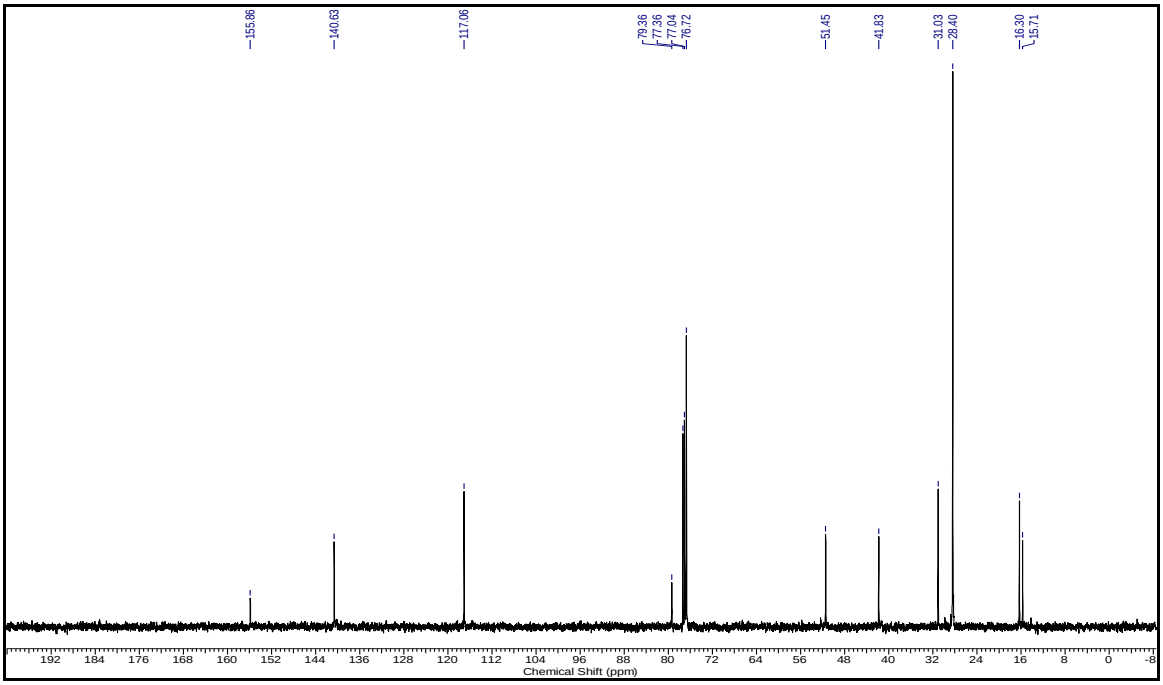
^{13}C NMR (100 MHz, CD_3OD) of compound 133



^{1}H NMR (400 MHz, $CDCl_3$) of compound 135

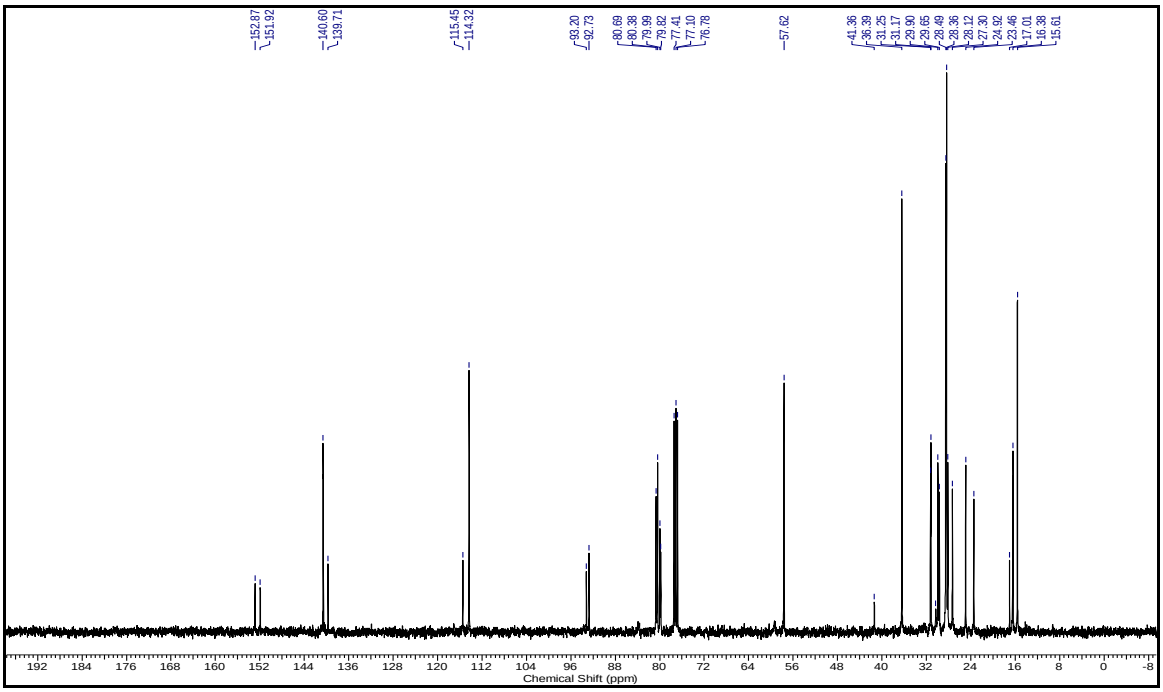


^{13}C NMR (100 MHz, $CDCl_3$) of compound 135

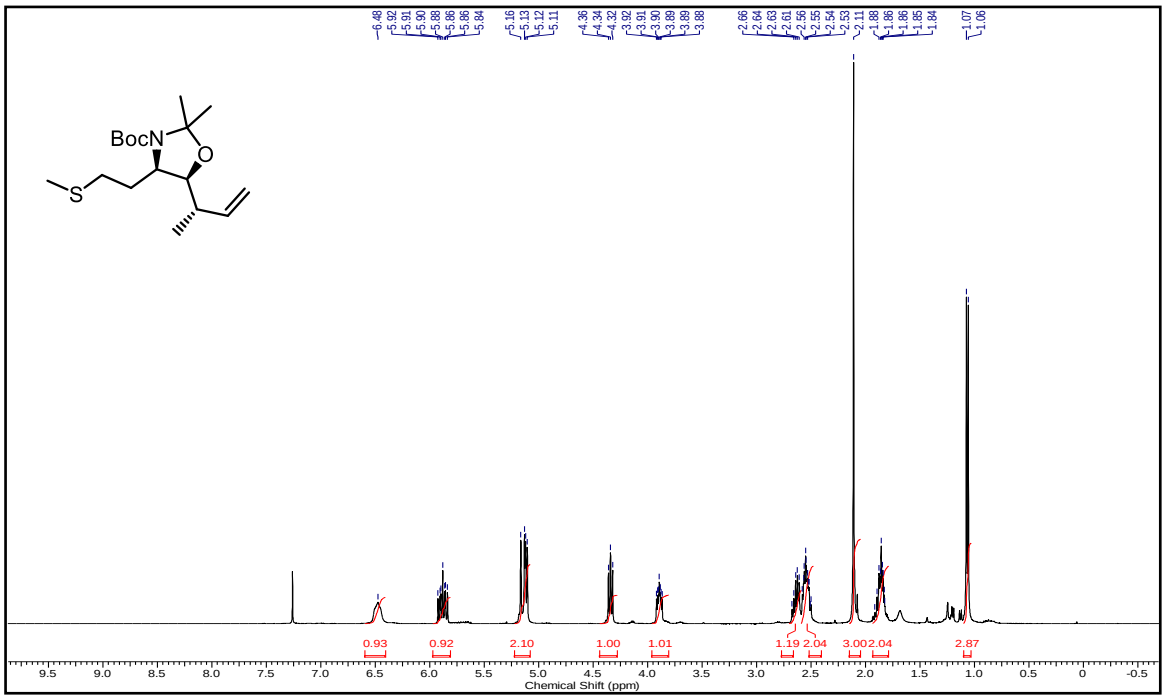


^{1}H NMR (400 MHz, $CDCl_3$) of compound 136

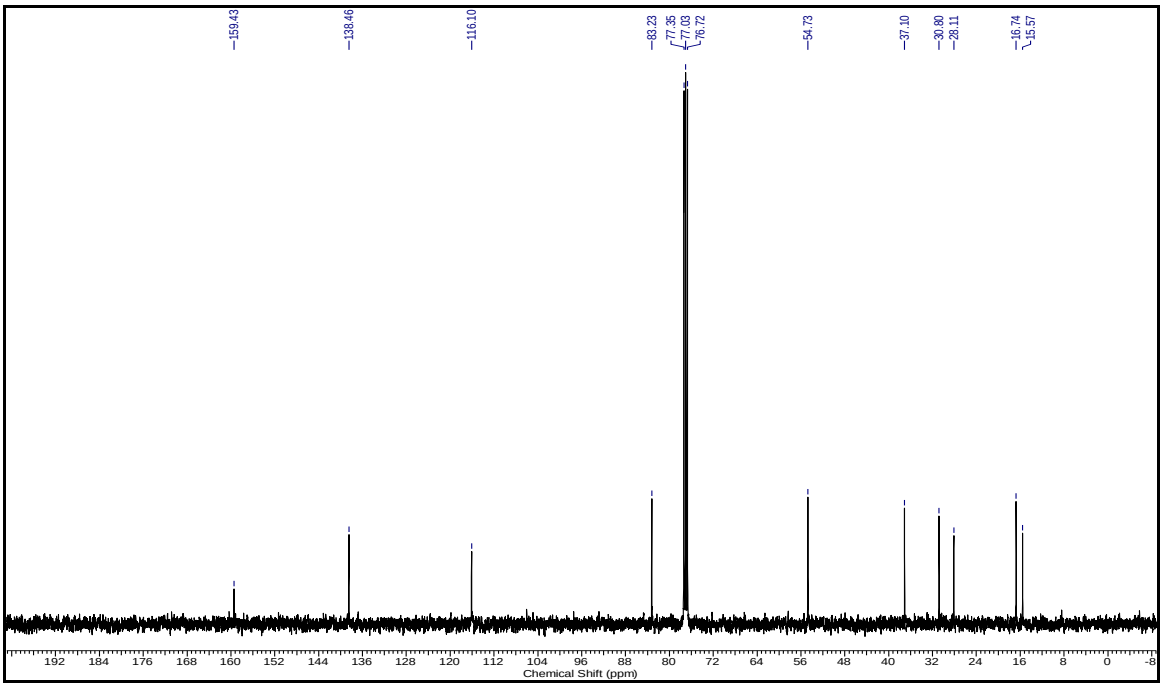
^{13}C NMR (100 MHz, $CDCl_3$) of compound 136



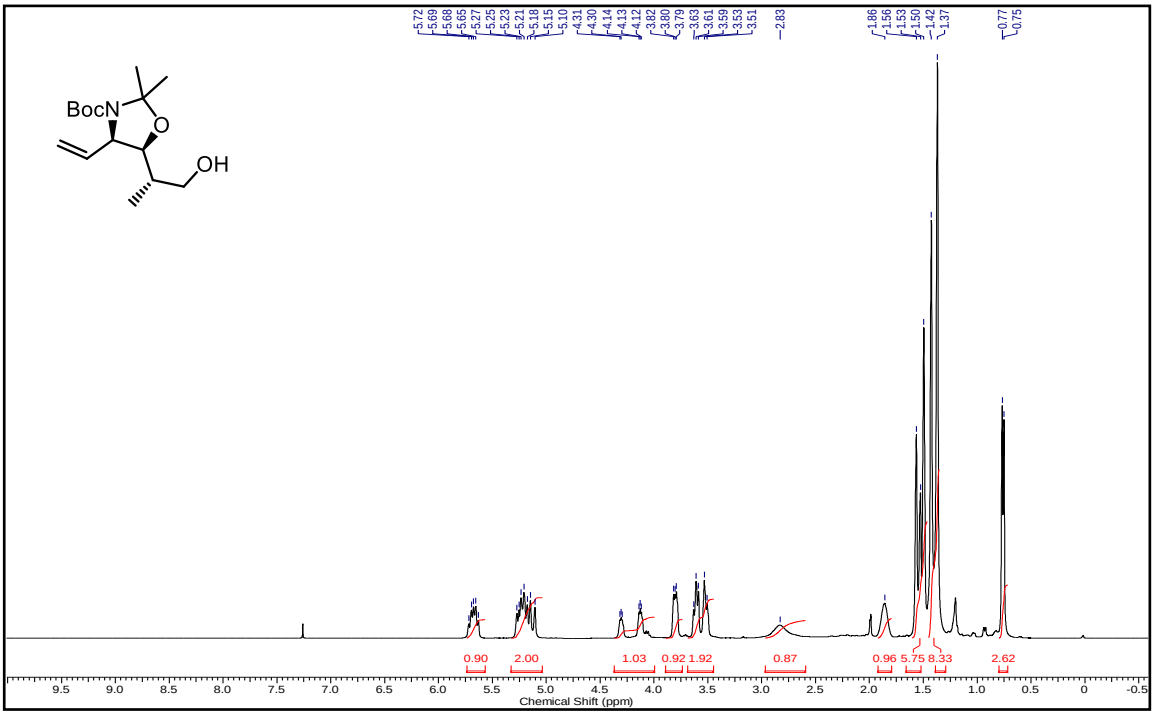
^{1}H NMR (400 MHz, $CDCl_3$) of compound 137



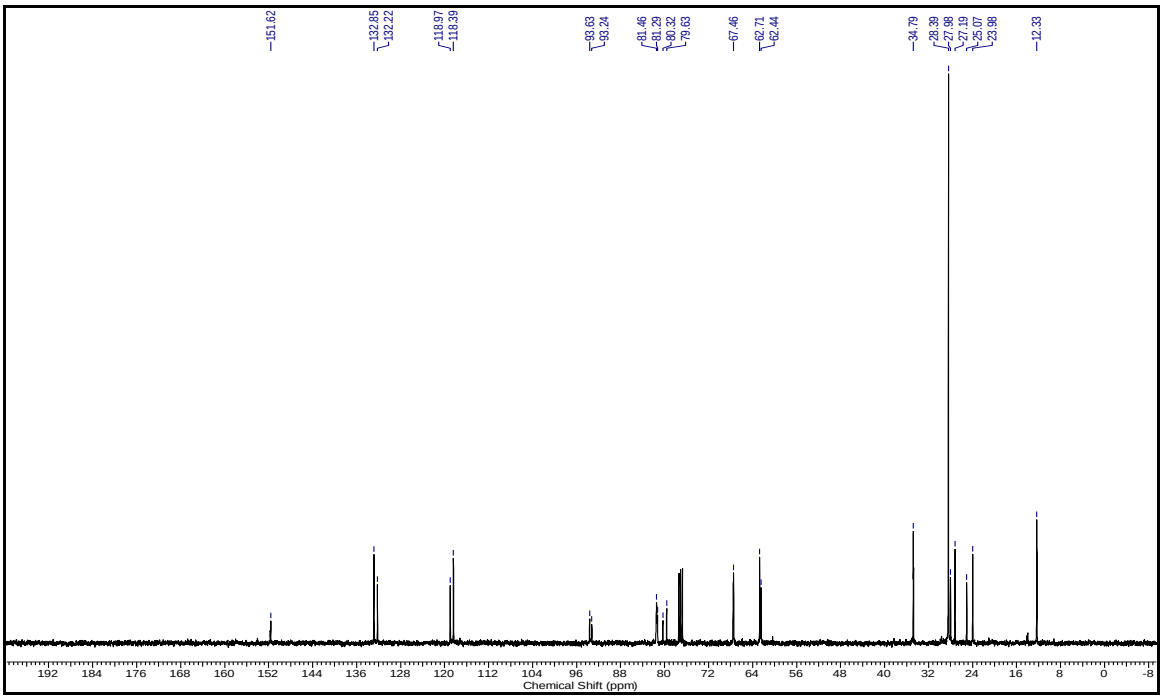
^{13}C NMR (100 MHz, $CDCl_3$) of compound 137



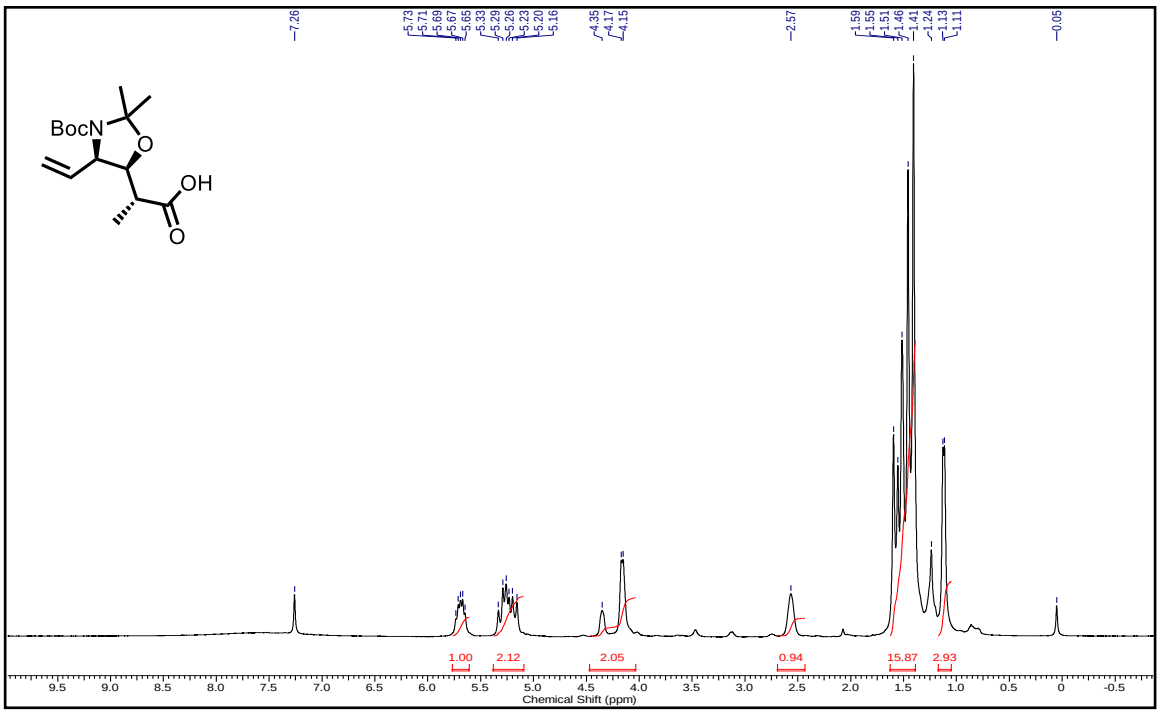
^{1}H NMR (400 MHz, $CDCl_3$) of compound 138



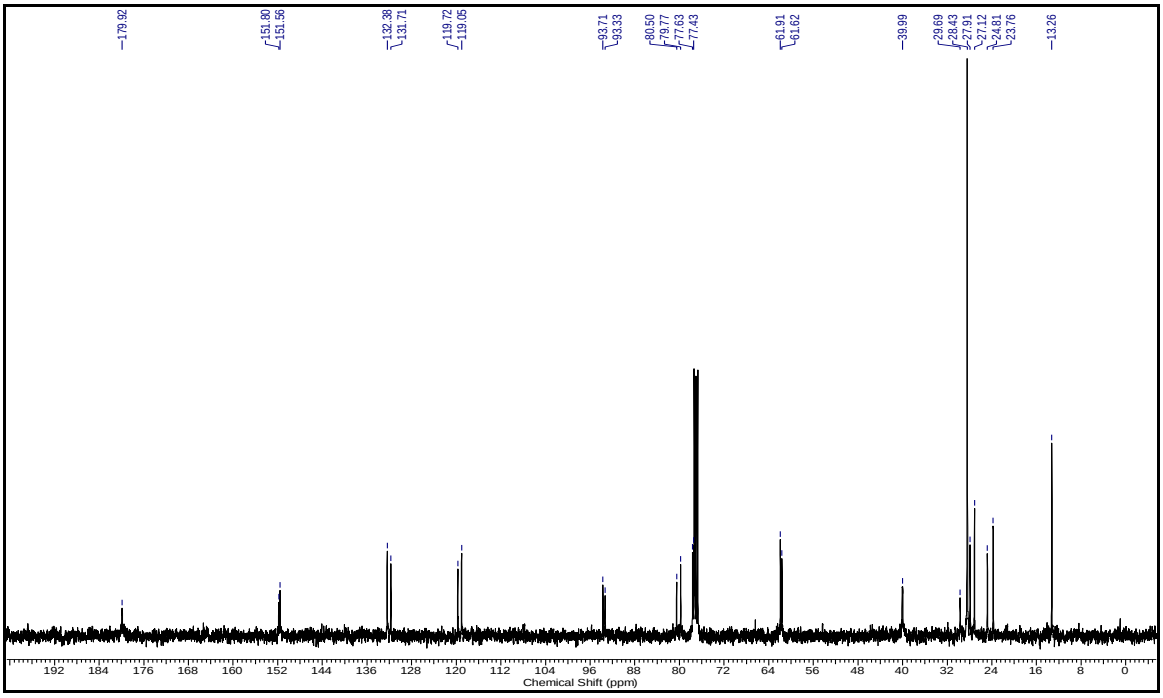
^{13}C NMR (100 MHz, $CDCl_3$) of compound 138



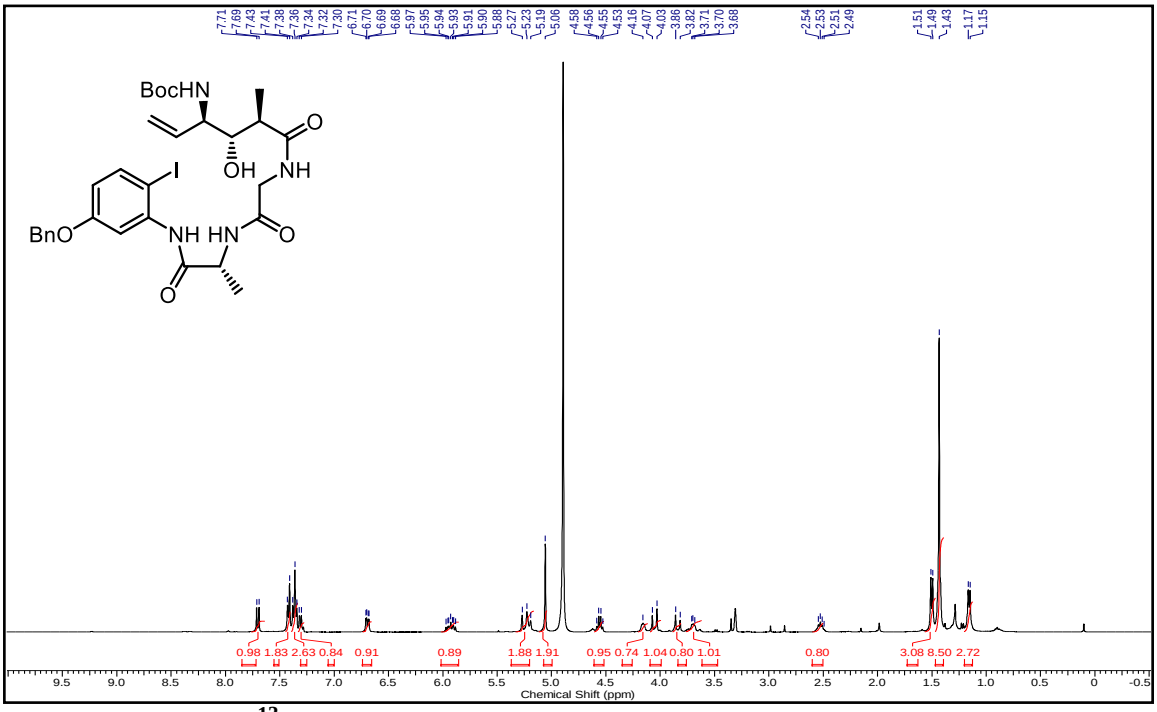
^{1}H NMR (400 MHz, $CDCl_3$) of compound 139



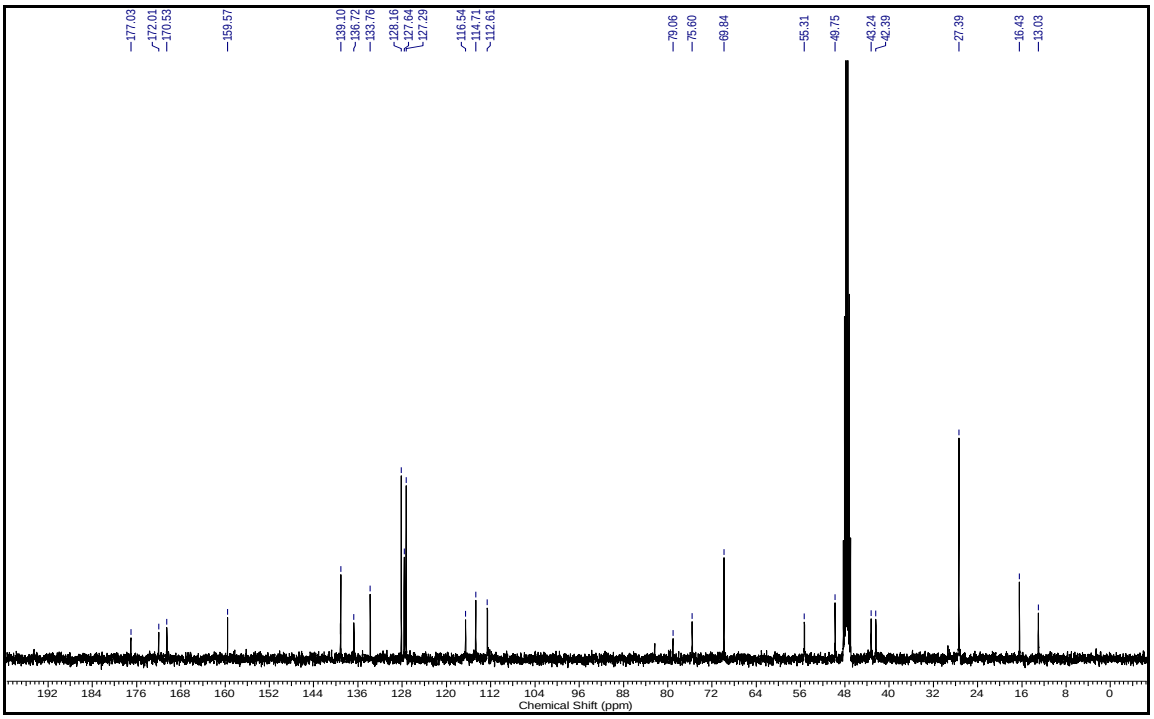
^{13}C NMR (100 MHz, $CDCl_3$) of compound 139



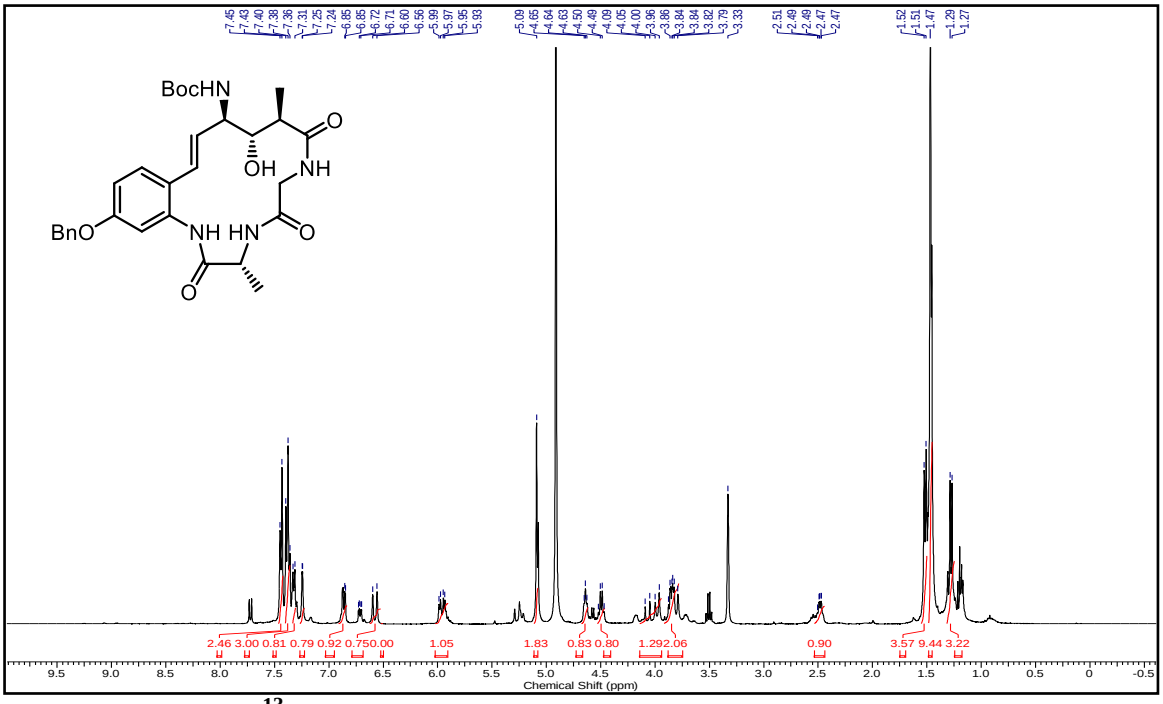
^{1}H NMR (400MHz, CD_3OD) of compound 140



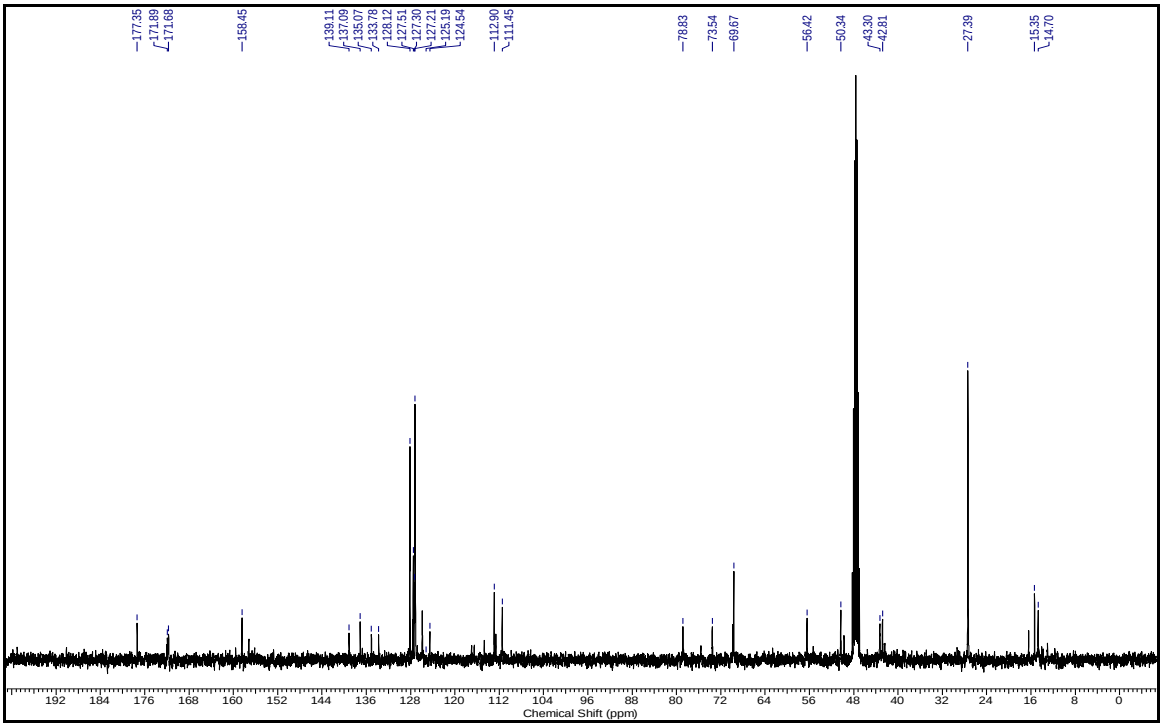
^{13}C NMR (100MHz, CD_3OD) of compound 140



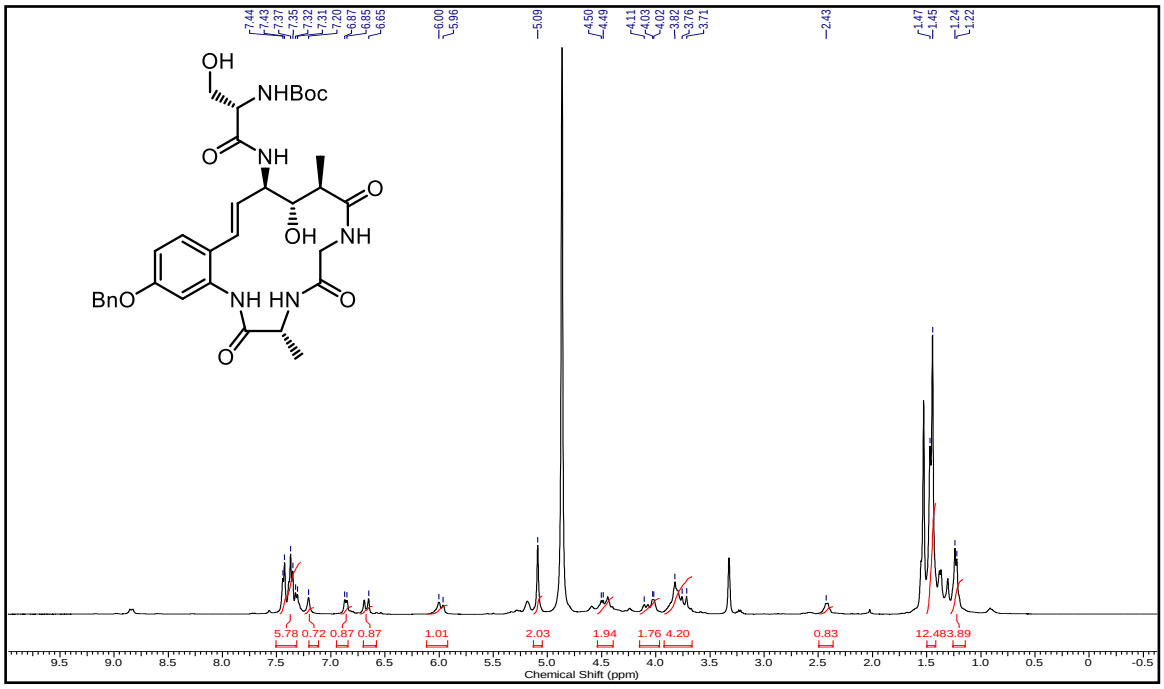
^{1}H NMR (400MHz, CD_3OD) of compound 141



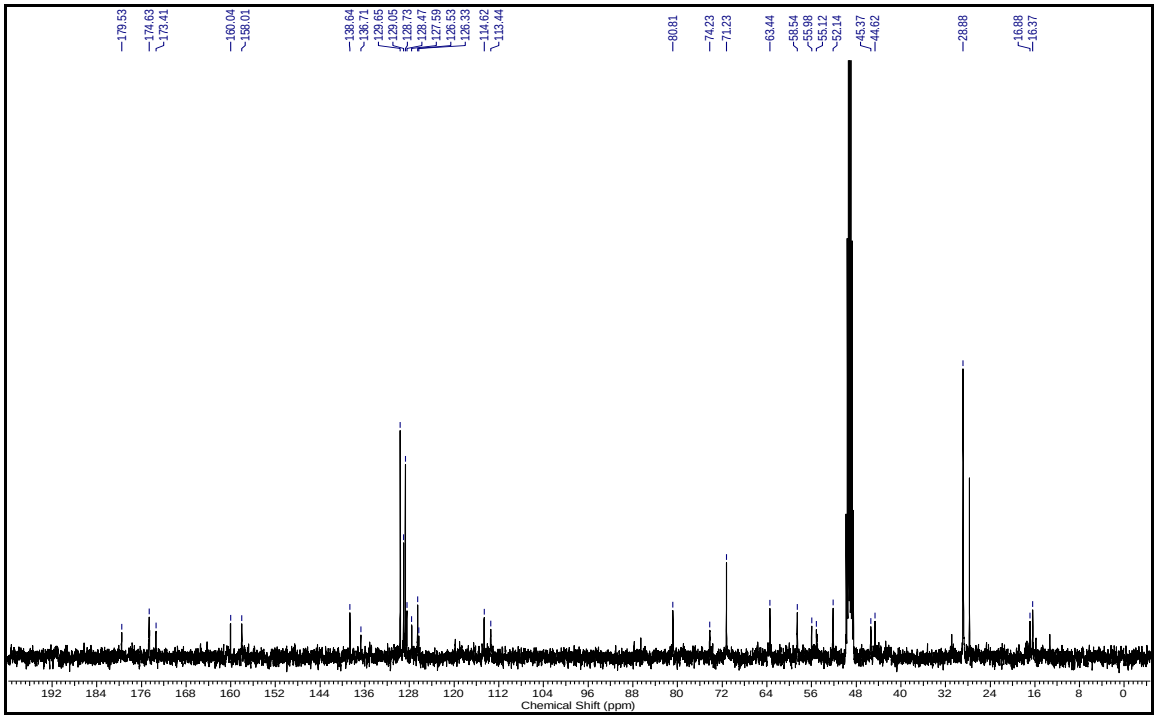
^{13}C NMR (100MHz, CD_3OD) of compound 141



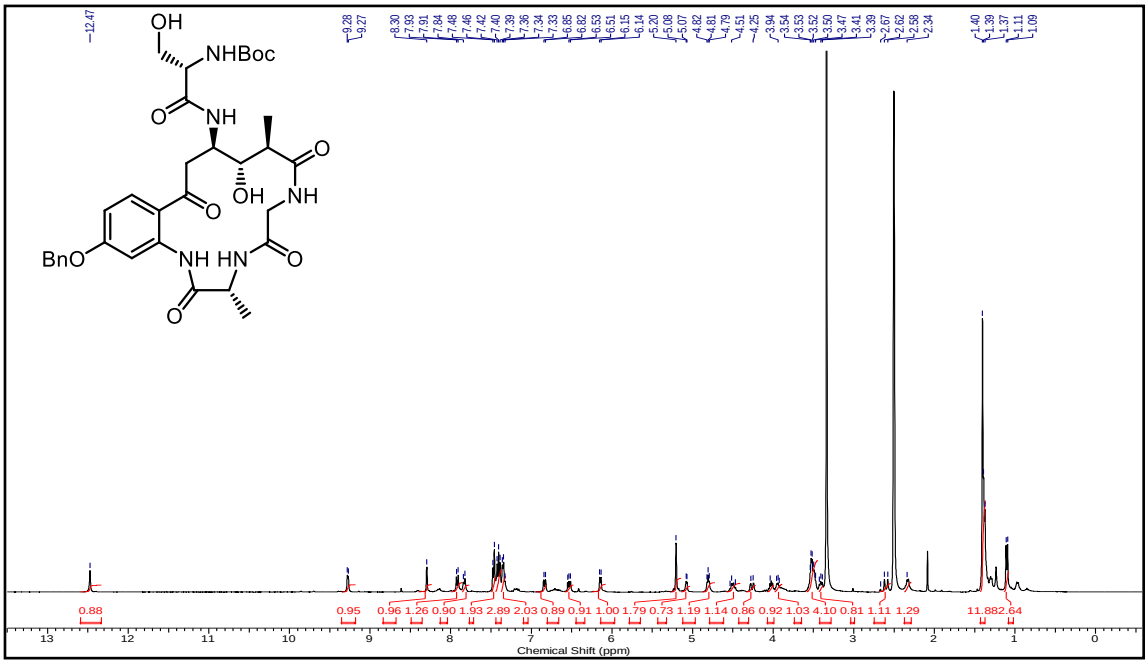
^{1}H NMR (400MHz, CD_3OD) of compound 142



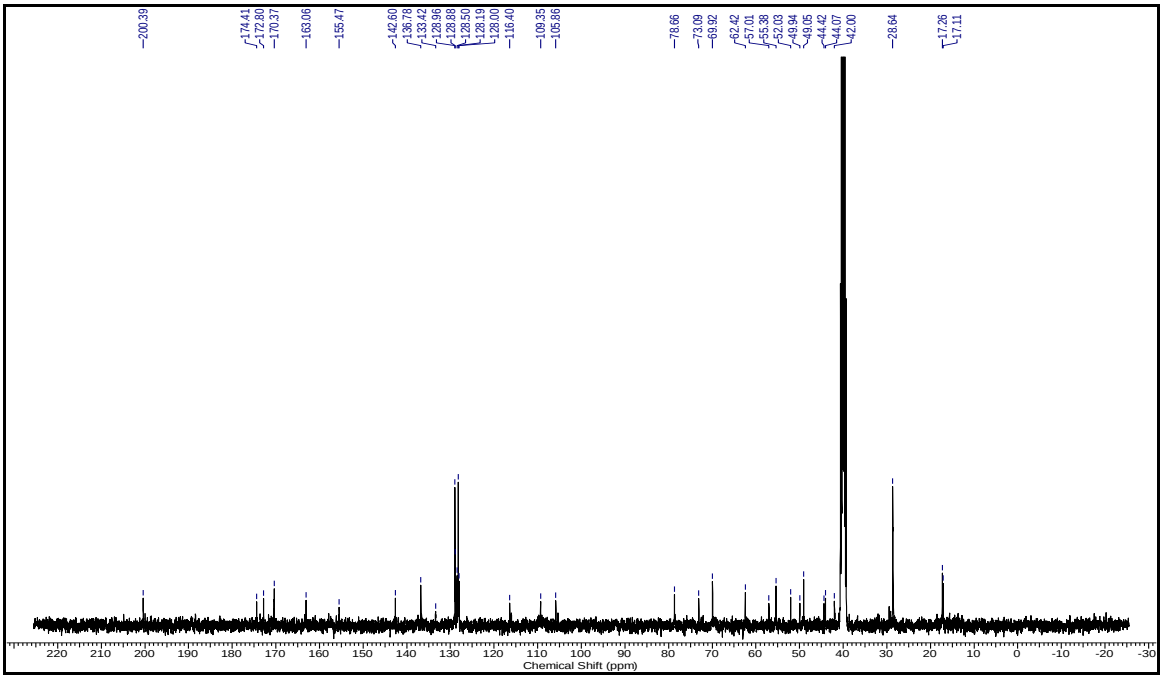
^{13}C NMR (100MHz, CD_3OD) of compound 142



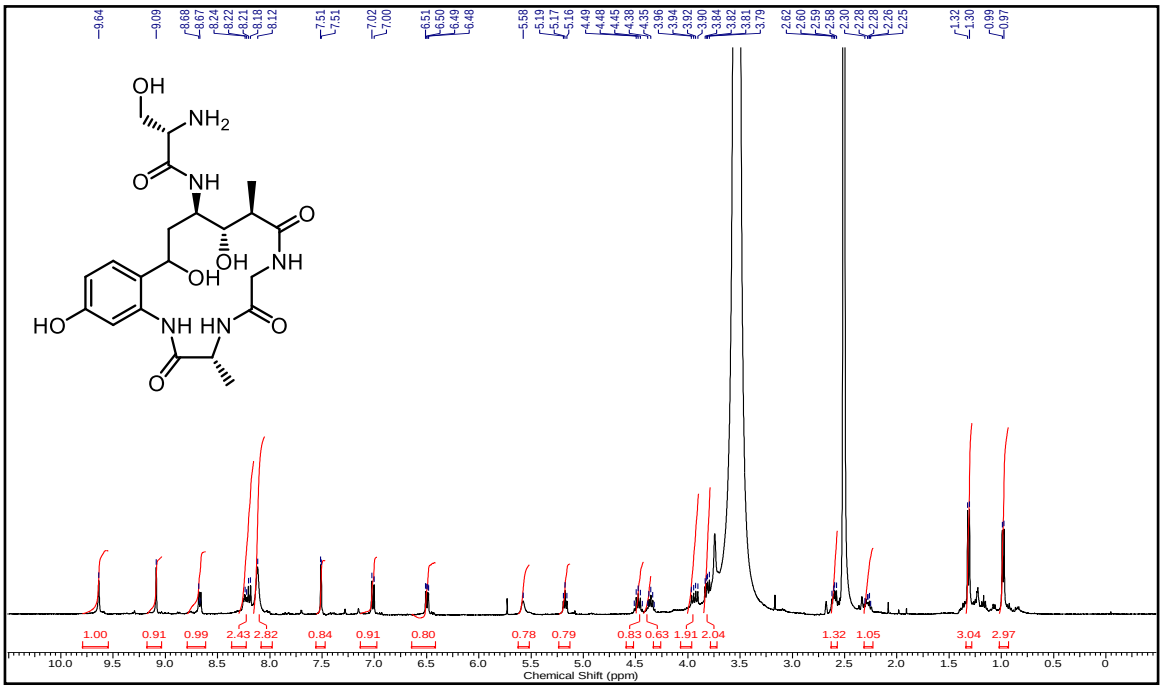
^{1}H NMR (400 MHz, DMSO-d_6) of compound 143



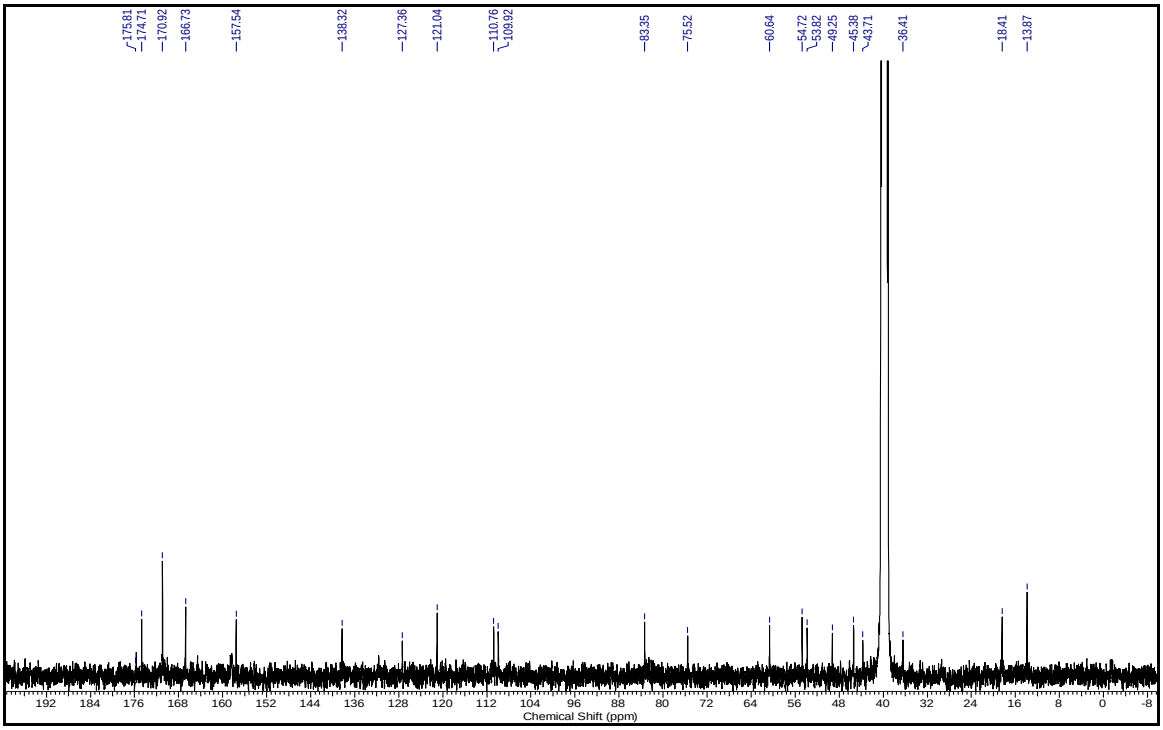
^{13}C NMR (100 MHz, DMSO-d_6) of compound 143



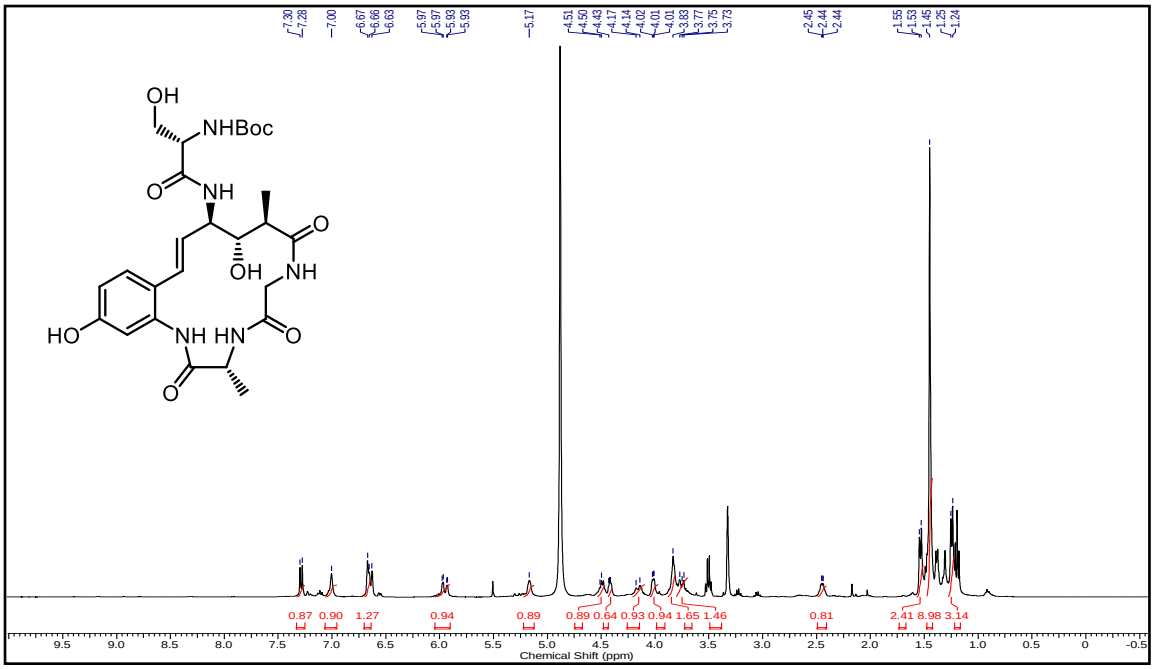
^{1}H NMR (400 MHz, DMSO-d_6) of compound 144



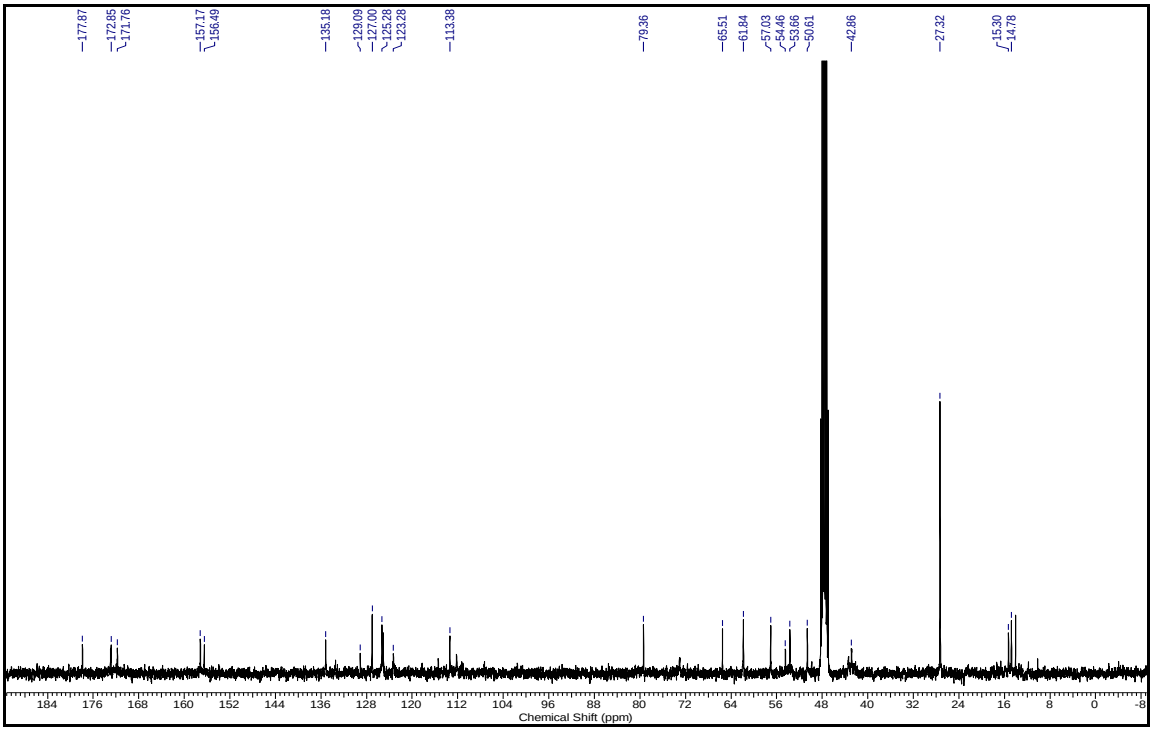
^{13}C NMR (100 MHz, DMSO-d_6) of compound 144



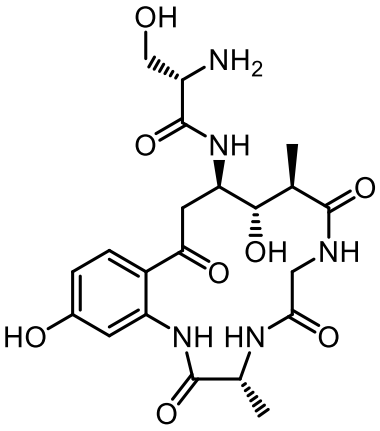
^{1}H NMR (400MHz, CD_3OD) of compound 145

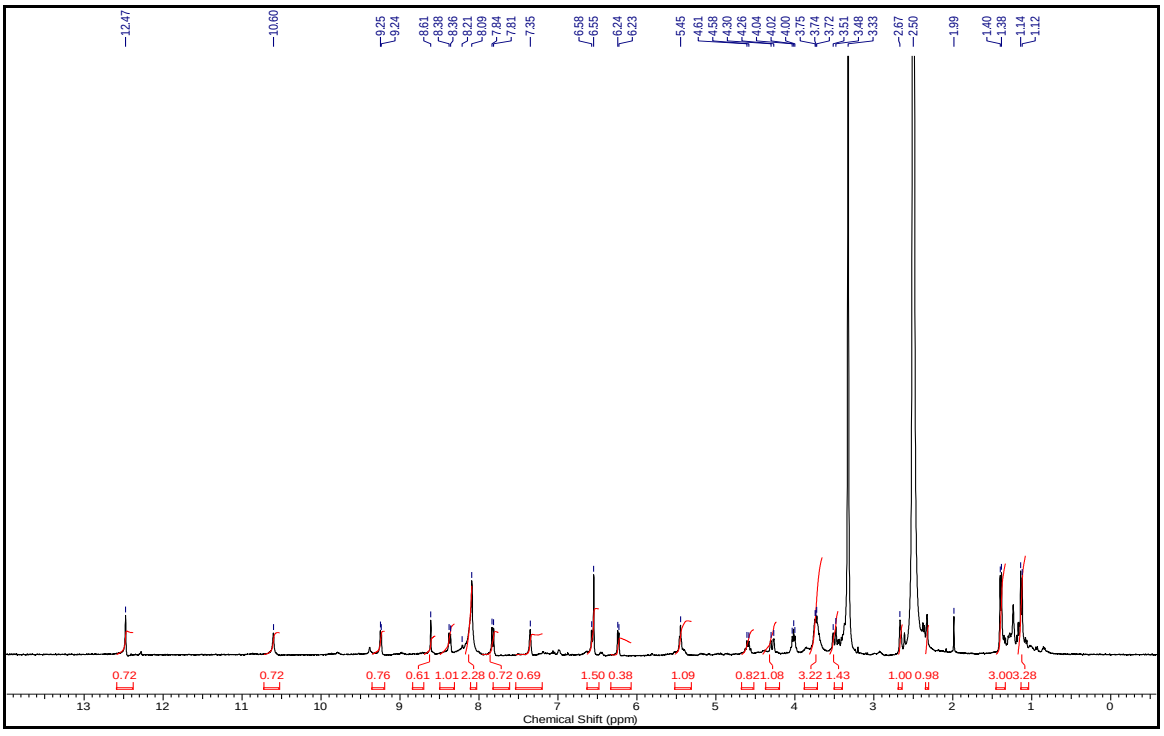


^{13}C NMR (100MHz, CD_3OD) of compound 145



^{1}H NMR (400 MHz, DMSO-d_6) of compound 146





List of Publications

1. A green synthetic route to antimalarial and antibacterial agent CJ-15,801 and its isomer *cis*-CJ-15,801, **K. Kashinath**, Pandrangi Siva Swaroop and D. Srinivasa Reddy. ***RSC Adv.***, **2012**, *2*, 3596.
2. Studies toward the Synthesis of Potent Anti-inflammatory Peptides Solomonamides A and B: Synthesis of a Macrocyclic Skeleton and Key Fragment 4-Amino-6-(20 amino-40-hydroxyphenyl)-3- hydroxy-2-methyl-6-oxohexanoic Acid (AHMOA), **K. Kashinath**, N. Vasudevan, and D. Srinivasa Reddy. ***Org. Lett.***, **2012**, 14, 6222.
3. Total synthesis of an anticancer norsesquiterpene alkaloid isolated from the fungus *Flammulina velutipes*, **K. Kashinath**, P. D. Jadhav, and D. Srinivasa Reddy ***Org. Biomol. Chem.***, **2014**, *12*, 4098.
4. Total Synthesis of Deoxy-solomonamide B by Mimicking Biogenesis, N. Vasudevan, **K. Kashinath**, and D. Srinivasa Reddy ***Org. Lett.*** **2014**, *16*, 6148.
5. One-pot quadruple/triple reaction sequence: A useful tool for the synthesis of natural products, **K. Kashinath** and D. Srinivasa Reddy ***Org. Biomol. Chem.***, **2015**, *13*, 970.
6. Breaking and Making of Olefins Simultaneously Using Ozonolysis: Application to the Synthesis of Useful Building Blocks and Macrocyclic Core of Solomonamides, **K. Kashinath**, S. Dhara, and D. Srinivasa Reddy ***Org. Lett.***, **2015**, 17, 2090.
7. Enantiospecific Formal Synthesis of Inthomycin C, P. R. Athawale, **K. Kashinath**, and D. Srinivasa Reddy *ChemistrySelect* **2016**, 3, 495.
8. Molecules with *O*-acetyl, not *N*-acetyl group, protect protein glycation by acetylating lysine residues, Garikapati Vannuru swamy, Mashanipalya G. Jagadeeshaprasad, **K. Kashinath**, Suresh K Kesavan, Shweta Bhat, Arvind M. Korwar, Ashok D. Chougale, Ramanamurthy Boppanna, D.Srinivasa Reddy, and Mahesh J. Kulkarni (**manuscript submitted**).
9. Total synthesis of the marine natural product solomonamide B necessitates its structural revision, **K. Kashinath**, Gorakhnath R. Jachak, Paresh R. Athawale,

Udaya Kiran Marelli, Rajesh G. Gonnade and D. Srinivasa Reddy (**manuscript under preparation)**

Patents:

1. Process for the preparation of aminoacrylic acid derivatives, Dumbala Srinivasa Reddy, **Kashinath Komirishetty**, Siva Swaroop Pandrangi **US20140256976 A1**; **EP2766340A1**; **WO2013054366A1**
2. A process for the preparation of solomonamide analogues Dumabala Srinivasa Reddy, **Kashinath Komirishetty**, Vasudevan Natarajan **WO2014083578 A1**
3. Novel indazole compound: preaparation and uses there of Dumabala Srinivasa Reddy, Chaitanya saxena, **Kashinath Komirishetty**, **WO2015015519A1**
4. Novel tricyclic compounds and preparation thereof Dumabala Srinivasa Reddy, **Kashinath Komirishetty**, Prakash Jadhav, **WO 2015121876 A1**