Design, Synthesis and Bioactivity Evaluation of Novel Dihydropyridines, Pyrrolidinones and their Triazole Derivatives

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DOCTOR OF PHILOSOPHY
In Chemistry

By

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Dedicated to My Parents and Teachers

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Declaration

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

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

V Ratnam Nallamelli
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University of Hyderabad
June 2015

CERTIFICATE

This is certify that the thesis entitled ***''Design, Synthesis and Bioactivity Evaluation of Novel Dihydropyridines, Pyrrolidinones and their Triazole Derivatives''*** being submitted by ***Mr. V Ratnam Nallamelli*** to University of Hyderabad for the award of ***Doctor of Philosophy in Chemistry*** has been carried out by him under my supervision and the same has not been submitted elsewhere for a degree. I am satisfied that the thesis has reached to the standard of fulfilling the requirements of the regulations relating to the nature of the degree.

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Dr. Reddy's Institute of Life Sciences V Ratnam Nallamelli

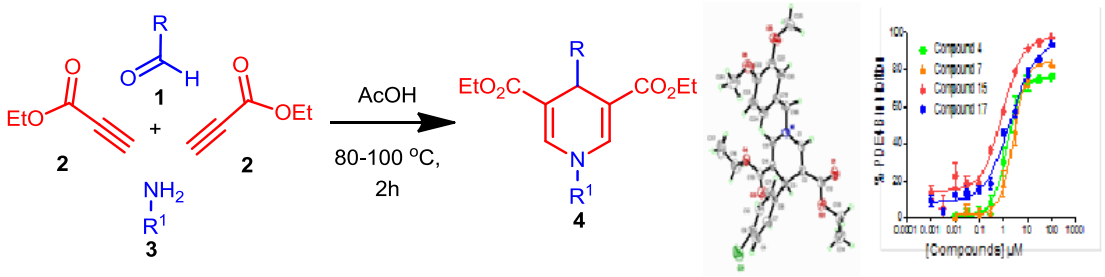
June 2015

Synopsis

The thesis entitled, ‘‘**Design, Synthesis and Bioactivity Evaluation of Novel Dihydropyridines, Pyrrolidinones and their Triazole Derivatives’’** contains four chapters:

Chapter 1: Discovery of novel 1,4-dihydropyridine-based PDE4 inhibitors

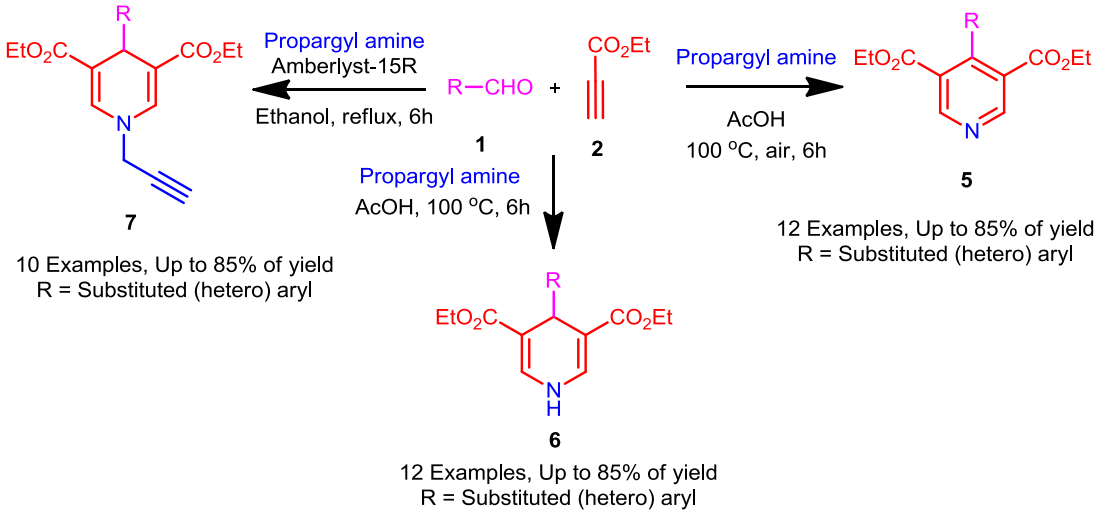
In chapter **1**, we disclose the design, synthesis and *in-vitro* pharmacology of 1,4-dihydropyridines (1,4-DHPs) **4** as novel PDE4 inhibitors. We envisioned to explore the new functional properties of 1,4-DHPs, based on the structure-activity relationship (SAR) studies and inspiring from the unveiled potent pharmaceutical applications such as anti-tumor, anti-diabetic, HIV protease inhibition, Sirtuin modulation, cytochrome P450 inhibition, ACE inhibition, non-diabetic nephropathies, TNF-α inhibition and drugs in the treatment of a number of other diseases. In the present work, we have used modified Hantz reaction one-pot protocol as shown in Scheme **1**, out of thirty synthesized compounds 23 compounds were shown more than 35% of PDE4B inhibitions at 30 µM concentrations and five potent compounds were tested for the dose response studies. One of the most active compounds, which is bearing indole and 3,4-dimethoxy aryl substitutions showed a dose dependent inhibition of PDE4B with an IC_{50} = ~0.54 µM and TNF-α inhibition with an IC_{50} = ~3.20 µM.



Scheme 1. One-pot synthesis of 1,4-dihydropyridine derivatives

Here, we have explored the unexpected drop-off of the propargyl group of 1,4-DHPs, while synthesizing *N*-propargylated 1,4-DHPs in glacial AcOH. Our observations prompted to develop the novel methods to synthesize 1,4-DHPs **7** using amberlyst-15R and other one-pot modifications as shown in Scheme **2**.

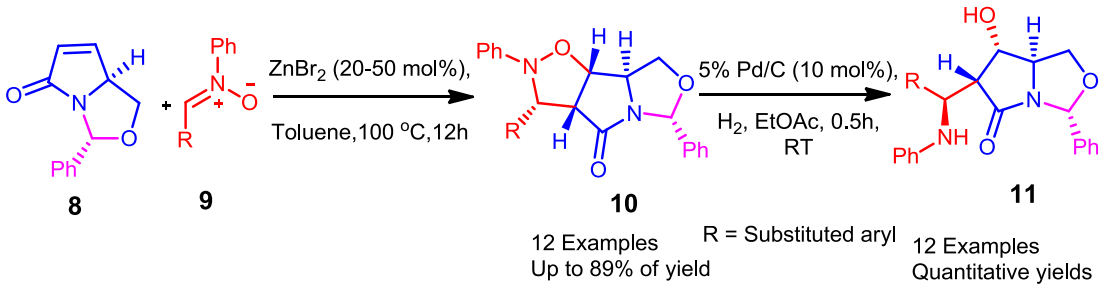
To the best of our knowledge, herein we report first metal free depropargylation one-pot protocol for the synthesis of 1,4-DHPs **6**, and pyridine derivatives **5**.



Scheme 2. Synthesis of functionalized 1,4-DHPs and pyridine derivatives

Chapter 2: $ZnBr_2$-Mediated asymmetric synthesis of functionalized pyrrolidinone and their anti-cancer activities

In chapter **2**, we disclose the $ZnBr_2$-mediated regio and stereo selective synthesis of functionalized pyrrolidinones **10** using 1,3-dipolar cycloaddition reactions between α,β-unsaturated γ-lactam **8** and *N*-phenyl nitrones **9**. Here, the key asymmetric precursor **8** was prepared from the natural chiral synthon (*S*)-pyroglutamic acid **14** and 1,3-dipolar compounds (*N*-phenyl nitrones) **9** were prepared using modified simple reaction procedures. Tricyclic asymmetric pyrrolidinones **10** were further converted to asymmetric bicyclic pyrrolidinone derivatives **11** using catalytic 5% Pd/C in EtOAc, as shown in Scheme **3**. One of the asymmetric 1,3-dipolar adduct **10** was well characterized by using ^1H-^1H COSY and NOESY studies.



Scheme 3. Asymmetric synthesis of functionalized pyrrolidinones

All the synthesized compounds are tested against cal 27 cancer cell lines for their anti-proliferative activities, 12 compounds have shown more than 40 % of inhibition out of 24, at 20 µM concentrations. As well, the more potent compounds are tested for dose response studies, obtained inhibitory constant (IC_{50}) values are 13.84, 1.76, 7.4, 7.06 and 29.03, respectively.

Chapter 3: Design and synthesis of asymmetric pyrrolidinone-based indole derivatives

An extensive literature survey reveals the pharmaceutical importance of indole containing tryptophan derivatives, as well the functionalized indoles. In this **c**hapter, we explore the design and synthesis of asymmetric pyrrolidinone-based indole derivatives **13** from the natural chiral synthon (*S*)-pyroglutamic acid **14** using Sonogashira protocol, as shown in Fig. **1** and Scheme **4**. Designed nucleus may not resemble the exact tryptophan derivative, but its in built functionalities such as indole core and natural amino acid residue may have the potent interactions with the target enzyme or proteins.

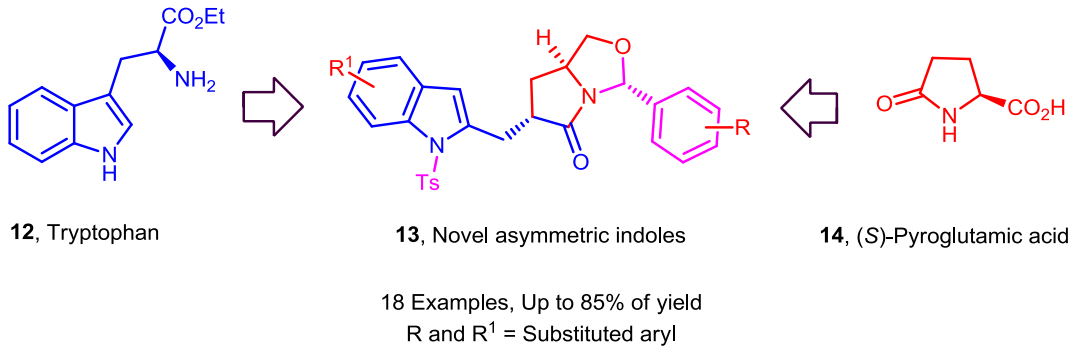
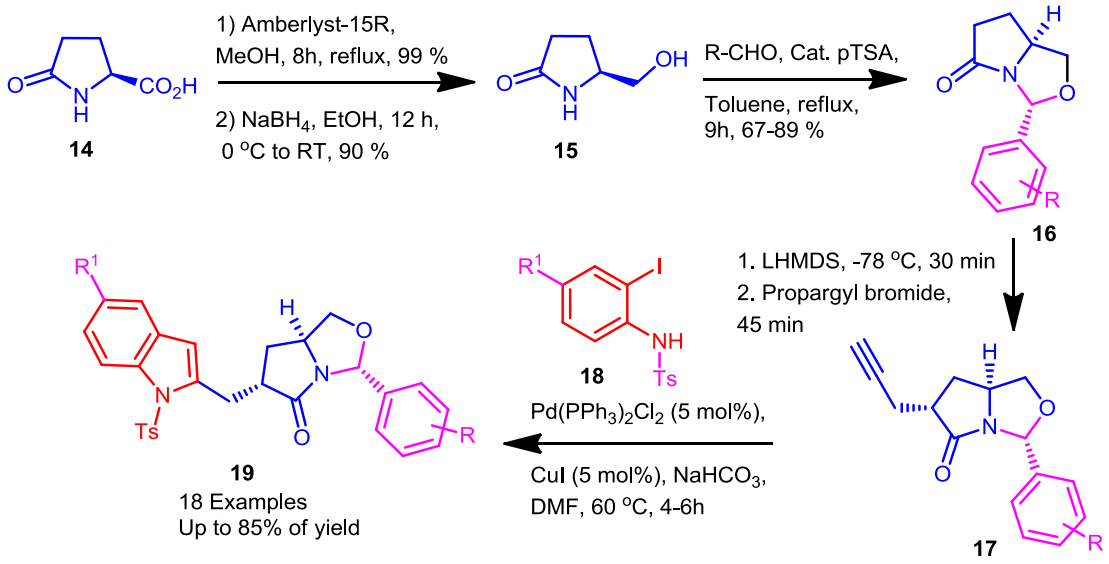


Fig. 1. Design and synthesis of asymmetric pyrrolidinone-based indole derivatives

In the overall synthetic process, the key intermediates **17** and **18** were prepared from simple reaction procedures, while the first key precursor **17** is from (*S*)-pyroglutamic acid **14** and the other substituted 2-iodoanilines **18** from corresponding substituted anilines. The biological evaluations of all these synthesized asymmetric indole derivatives **13** are under progress.



Scheme 4. Synthesis of novel asymmetric pyrrolidinone-based indole derivatives

Chapter 4: Discovery of novel AMPK activators

In this chapter, we have focused on discovering the triazoles-based AMPK activators using CuAAC-click reaction. Here our major focus has been generating the library of 1,4-disubstituted 1,2,3-triazole derivatives (**20**, 2**1** and **22**) from different springs, based on the obtained preliminary results during the course of screening process. We did choose the CuAAC-click reaction to link the innumerable privileged pharmacophores as shown in Fig. **2**. Among the synthesized analogues privileged pharmacophore γ-lactam containing (*S*)-pyroglutamic acid based triazole derivatives have shown the potent AMPK activities, concise results are discussed in the thesis.

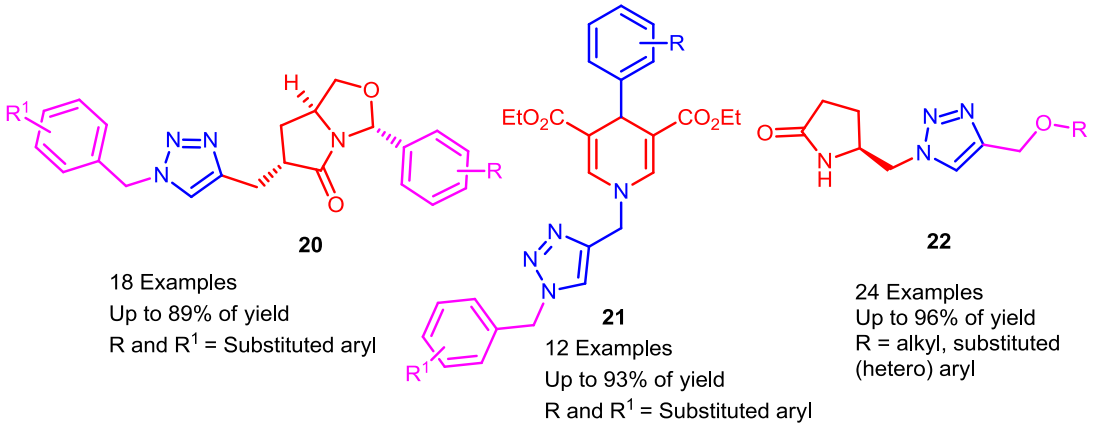


Fig. 2. Synthesis of novel triazole derivatives using CuAAC-click reaction

Abbreviations

^{13}C NMR	:	carbon-13 nuclear magnetic resonance spectroscopy
^{1}H NMR	:	hydrogen-1 nuclear magnetic resonance spectroscopy
AcOH (CH_3CO_2H)	:	acetic acid
Ar	:	aryl
aq	:	aqueous
Br_2	:	bromine
bs	:	broad singlet
cAMP	:	cyclic adenosine mono phosphate
CCDC	:	Cambridge crystallographic data center
$CDCl_3$	:	chloroform-*d*
CH_3CN	:	acetonitrile
COPD	:	chronic obstructive pulmonary disease
COSY	:	correlation spectroscopy
CuBr	:	copper bromide
CuI	:	copper iodide
$Cu(OTf)_2$	:	copper triflates
d	:	doublet
CH_2Cl_2	:	dichloromethane
DMF	:	*N*,*N*-dimethylformamide
DMSO	:	dimethyl sulfoxide
DMSO-d_6	:	dimethyl sulfoxide-d_6
Et	:	ethyl
EtOAc	:	ethyl acetate
EtOH	:	ethanol
h	:	hour (s)
HCl	:	hydrochloric acid
H_2O	:	water
HPLC	:	high performance liquid chromatography

Hz	:	hertz
I_2	:	iodine
IC_{50}	:	half maximal inhibitory concentration
J	:	coupling constant in Hz
K_2CO_3	:	potassium carbonate
$LiAlH_4$	:	lithium aluminiumhydride
m	:	multiplet
MCR	:	multicomponent reaction
Me	:	methyl
MeOH	:	methanol
mg	:	milligram
mL	:	milliliter
mmol	:	mill mole
N_2	:	nitrogen
Na_2CO_3	:	sodium carbonate
NaH	:	sodium hydride
$NaHCO_3$	:	sodium bicarbonate
NaOH	:	sodium hydroxide
Na_2SO_4	:	sodium sulphate
NH_4Cl	:	ammonium chloride
NOE	:	nuclear overhauser effect
Pd/C	:	palladium on carbon
$PdCl_2(PPh_3)_2$	:	bis(triphenylphosphine)palladium(II)dichloride
PDE	:	phosphodiesterase
Ph	:	phenyl
PPh_3	:	triphenyl phosphine
R_f	:	retention factor
RT	:	room temperature
S	:	singlet
t	:	triplet
THF	:	tetrahydrofuran
TNF	:	tumor necrosis factor
UV	:	ultra violet
δ	:	chemical shift in parts per million

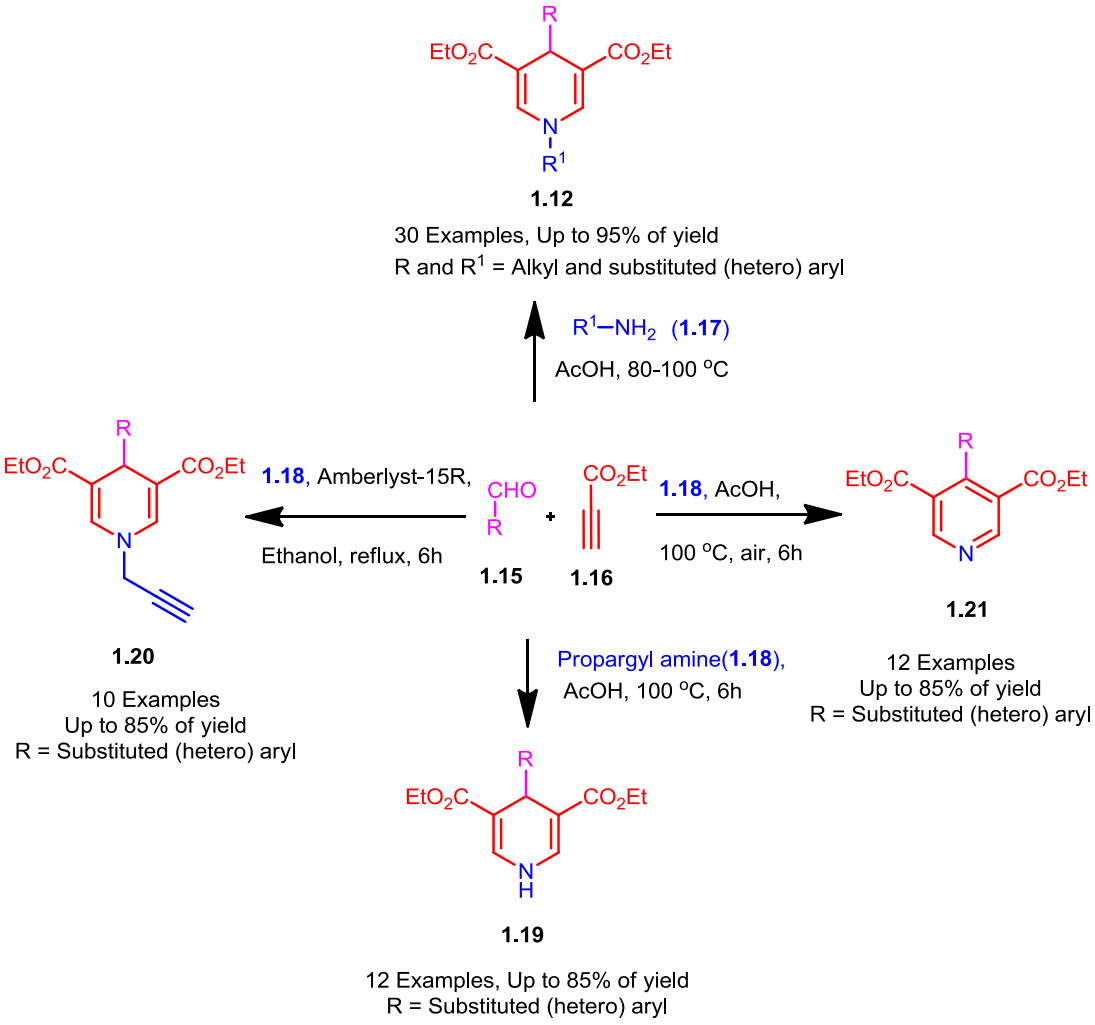
General information

Unless stated otherwise, reagents were obtained commercially and used as supplied without further purification and the solvents were distilled before use. Reactions were monitored by TLC on silica gel plates (60 F254), visualizing with UV light. Flash chromatography was performed on silica gel (230-400 mesh) using *n*-hexane, EtOAc, CH_2Cl_2 and MeOH. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 MHz spectrometer at the frequency indicated. Proton chemical shifts (δ) is relative to tetramethylsilane (TMS, δ = 0.00), as an internal standard and expressed in ppm and the proton chemical shift assignments were made using COSY experiments, and steochemistry assignments were made using NOESY experiments, wherever required. Coupling constants (*J*) are given in hertz; spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) and b (broad). Infrared spectra were recorded on a FT-IR spectrometer. Mass spectra were obtained on a LR-MS mass spectrometer. Melting points were noted from Buchi melting point B-540 instrument and are uncorrected. X-Ray crystal data were recorded by using Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method.

Introduction to the present thesis

Over the last few decades, the major source of drugs for treating various human diseases are *N*-heterocycles, among them nearly 30% were new *N*-heterocycles and 22% were synthetically modified alkaloid derivatives.[1] *N*-heterocycles are one of the most important classes of medicinal compounds, plays a vital role in controlling the metabolism, proliferation and apoptosis of all cells in the human body. Therefore, pharmaceutical industries have a continuous demand of discovering the simple *N*-heterocycles as potent drug candidates in pragmatic ways (*i.e.* mild, efficient, and affordable in terms of cost and eco-friendly synthetic routes). Thus, our attention has been focused on the synthesis of novel and simple *N*-heterocyclic scaffolds through ideal synthesis. Here, the present thesis focuses on the design, synthesis and potent pharmaceutical applications of 1,4-dihydropyridine (pyridine) and asymmetric pyrrolidinone-based *N*-heterocycles. For the convenience, we divided thesis into four chapters, In chapter **1** we disclose the discovery of novel 1,4-dihydropyridine-based PDE4 inhibitors and novel methods for the synthesis of 1,4-DHPs and pyridine derivatives. In chapter **2** we disclose the $ZnBr_2$-mediated asymmetric synthesis of functionalized pyrrolidinones and their anti-cancer activities, In chapter **3** we describe the synthesis of asymmetric oxazolidine-based indole derivatives using Sonogashira protocol and finally, In chapter **4** we discuss the synthetic studies towards the discovery of triazole-based AMPK activators.

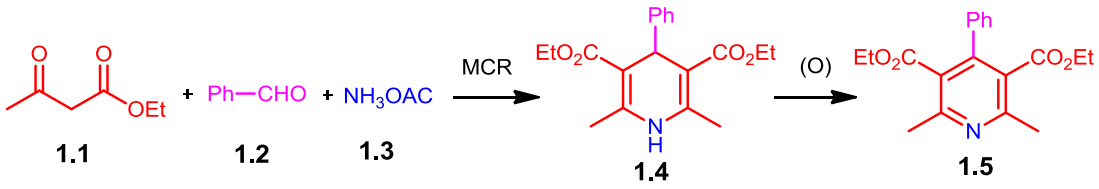
Chapter 1: Discovery of novel 1,4-dihydropyridine-based PDE4 inhibitors



1.1. Introduction:

Enzymes are involved in the multi-step transformations from simple starting materials to complex architectures without isolation of the intermediates. Similarly, synthetic chemists have an endeavor in the discovery of efficient synthetic methods without isolation of intermediates using multi-component reaction (MCR) in one-pot/cascade. MCR have been emerged as a potential tool for generating diverse *N*-heterocyclic scaffolds,[1] which have been extensively used as potential modulators of therapeutic targets and emerged in genomics and proteomics research.[2] For instance, Hantzsch MCR is one of the efficient synthetic method, which allows quick access to bio-active 1,4-dihydropyridine (1,4-DHP) based *N*-heterocycles.

Hantzsch pyridine synthesis was reported by Arthur Rudolf Hantzsch in 1881, which primarily produces 1,4-DHPs,[3] and can be converted into corresponding pyridine derivatives using external oxidizing agents (shown in Scheme **1.1**).[4] Despite the long history, sustaining interest in more advanced synthetic procedures have been triggered by the pharmacological properties embedded in 1,4-DHPs.[5] Recently, many efforts have been expanded in the synthesis of 1,4-DHPs such as using microwave,[6] solvent free,[7] metal triflates,[8] ceric ammonium nitrate,[9] boronic acids,[10] and silica-supported acids.[11]



Scheme 1.1. One-pot method for the synthesis of 1,4-DHPs and pyridine derivatives

1.1.1. Medicinal applications of 1,4-dihydropyridine derivatives:

1,4-DHP nucleus has been recognized as a most versatile pharmacophores in medicinal chemistry (shown in Fig. **1.1**).[12] An extensive literature survey reveals the potent biological applications of 1,4-DHPs, such as antitumor,[17] antidiabetic,[18] HIV protease inhibition,[19] and drugs in the treatment of a number of other diseases.[20] In addition, 1,4-DHPs are known for inhibition and activation of Sirtuins,[21] inhibition of cytochrome P450,[22] ACE inhibition and non-diabetic nephropathies.[23] Representative 1,4-DHP-based drugs **1.6a-1.6f** are shown in Fig. **1.2.**

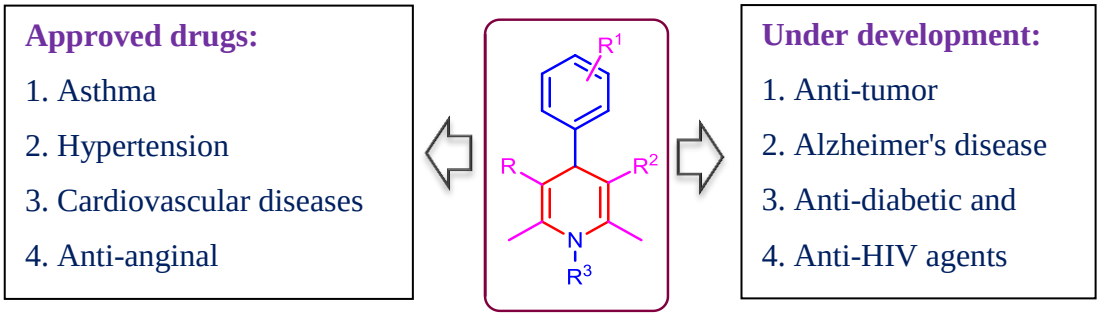


Fig. 1.1. 1,4-Dihydropyridine derivatives in medicinal chemistry

Recently, 1,4-DHPs have been considered as prototypical calcium channel blockers to modulate calcium current at the voltage-dependent calcium channels (VDCCs). Among them nifedipine **1.6a** has been used, in the treatment of angina pectoris and hypertension.[14] Cilnidipine **1.6b** is a potent dual blocker (N/L-type VDCCs) and is currently used for the treatment of hypertension. Felodipine **1.6c**, serving as an anti-hypertensive and anti-anginal drug.[15] Nilvadipine **1.6d** has been employed in the treatment of hypertension and chronic cerebral artery occlusion, it is also exhibiting potent therapeutic potentials for treating Alzheimer's disease.[16] Nimodipine **1.6e** and nicardipine **1.6f** are inhibited the cAMP specific PDE activity of purified PDE in a cell-free preparation.[13]

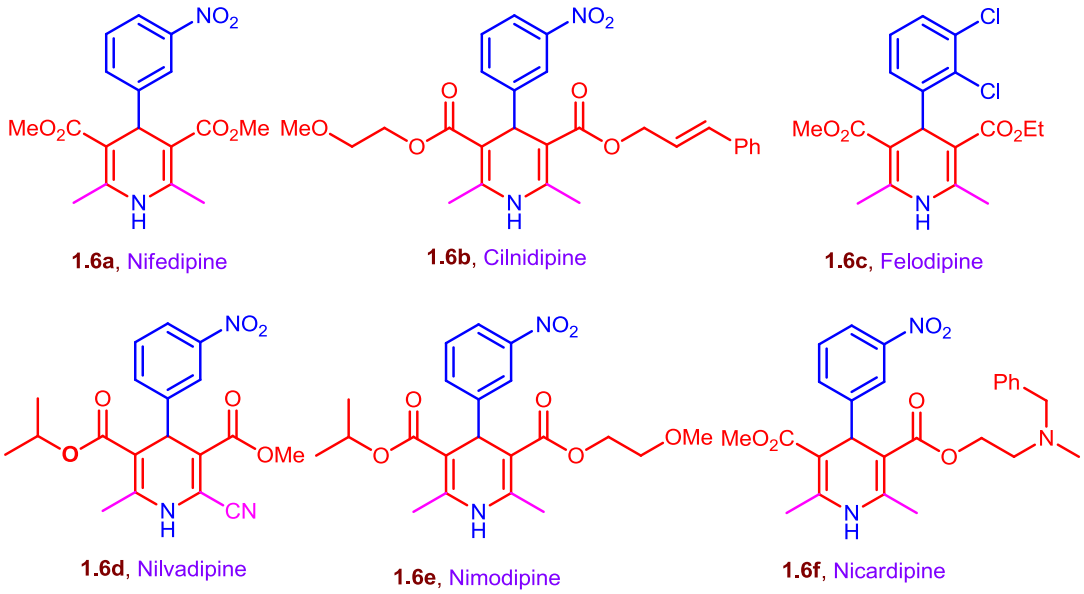


Fig. 1.2. 1,4-DHP-based drugs

1.1.2. PDE4 inhibitors in drug discovery:

Nucleotides are not only central dogma for numerous biological functions, but also it plays a vital role in the control of several metabolic pathways in all living cells. In fact, the origin and fate of the cell lie in nucleic acids such as DNA and RNA, which are comprised of different nucleotide sequences, components of nucleotides adenosine triphosphate (ATP), guanosine triphosphate (GTP), cytidine triphosphate (CTP), 5-methyluridine triphosphate (m^5UTP) and uridine triphosphate (UTP) are responsible for energy source, cellular communication and signal transduction. ATP is a major source of cellular energy and GTP is a very frequent cofactor of enzymes and proteins. In fact, the metabolisms of all living cells are controlled by intracellular cGMP and cAMP levels, which are synthesized by guanylate cyclases (GCs) from GTP and adenylyl cyclases (ACs) from ATP, respectively. These are also responsible for regulation of cell secretion, contraction and other growth factors. PDEs are master switches for controlling the cAMP and cGMP levels, cAMP synthesis and degradations shown in the Fig. **1.3**.

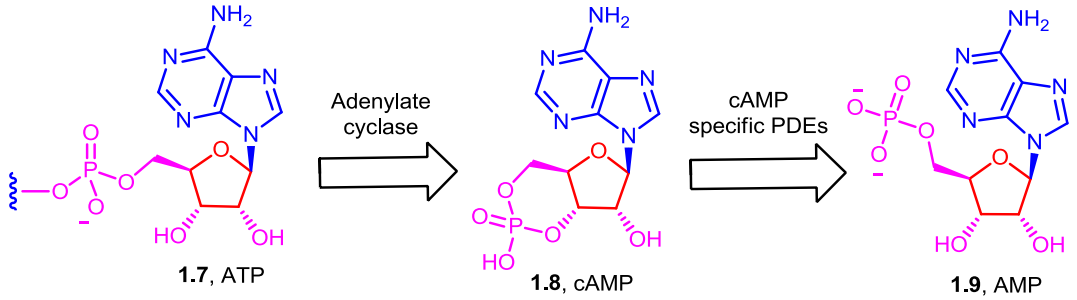


Fig. 1.3. Synthesis of cAMP and its degradation by PDEs

These cAMP and cGMP regulating PDEs enzymes have been identified as 60 isoforms from 21 different genes. PDEs were divided into 11 main classes (*i.e.* PDE1-PDE11) by consideration of their catalytic domains and unique substrate binding specifies. PDEs further classified into three main classes depend on the substrate specificity towards the active forms of cyclic nucleotides, while PDE5-6 and PDE9 are class 1 specific to cGMP; PDE4 and PDE7-8 are class 2 specific to cAMP; and PDE1-3 and PDE10-11 are class 3 dual specific works for both cAMP and cGMP, respectively.[24] The cAMP specific PDE4 enzyme isoforms is encoded by 4 distinct genes represented as PDE4A, PDE4B, PDE4C and PDE4D,[25] therapeutic potencies of novel PDE4 inhibitors in COPD have shown in the Fig. **1.4**.[24]

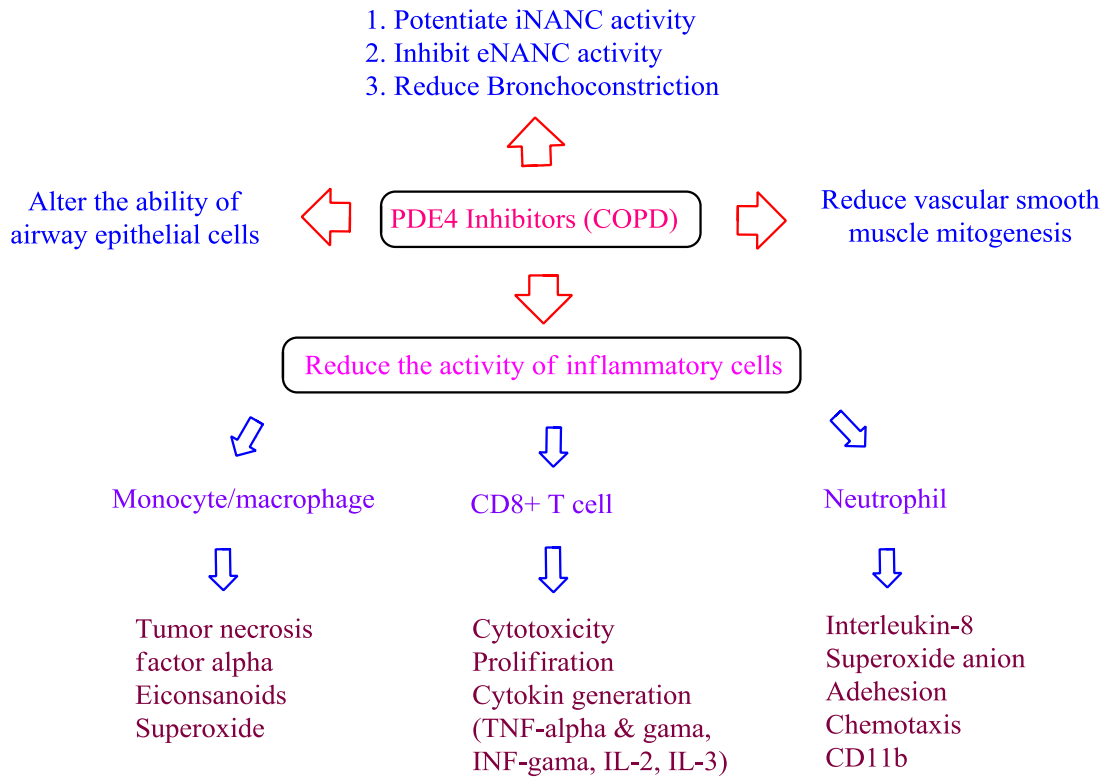
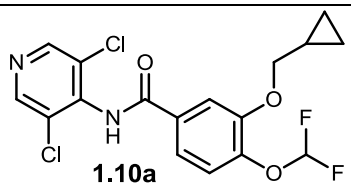
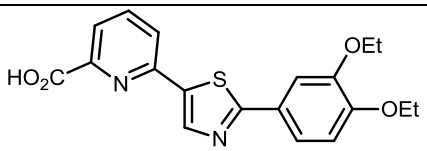
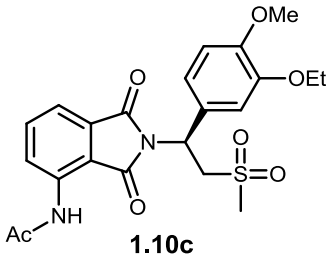
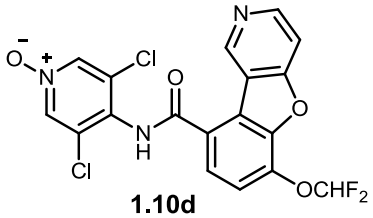
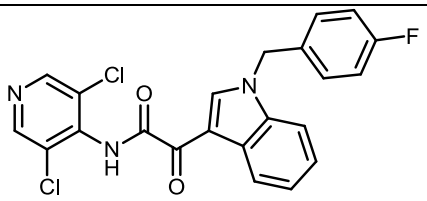
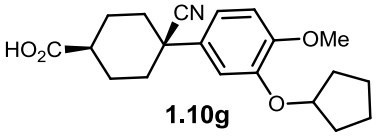
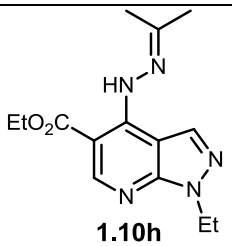
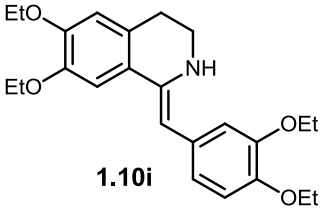
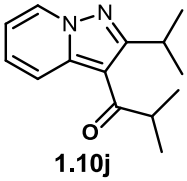


Fig. 1.4. Therapeutic potential of PDE4 inhibitors in COPD

Recently, an extensive effort on selective PDE4 inhibitors discloses the structures of FDA approved drugs roflumilast and apremilast (entry **1** and **3**, Table **1.1**). While the first one for treating inflammatory diseases and other one is for treating psoriatic arthritis. Thus, PDE4 enzyme inhibition has become a potent therapy in the area of respiratory diseases such as asthma and COPD, as well other diseases such as rheumatoid arthritis and Crohn's, *etc*. Therapeutic potential of selective PDE4 inhibitors are given in Table **1.1**.

Table 1.1. Selective PDE4 inhibitors and their therapeutic uses are listed

Entry	Name	Structure	Current status	Therapeutic use
1	Roflumilast	 **1.10a**	FDA approved in March 2011	Inflammatory diseases

2	Tetomilast	 **1.10b**	Phase II	COPD
3	Apremilast	 **1.10c**	FDA approved in March 2014	Rheumatoid arthritis and ankylosing spondylitis
4	Revamilast	 **1.10d**	Phase II	Inflammatory diseases
5	Ronomilast	 **1.10f**	Phase II	Asthma and COPD
6	Cilomilast	 **1.10g**	Drug	Asthma and COPD
7	Etazolate	 **1.10h**	Drug	Anxiolytic and Alzheimer's diseases
8	Drotaverine	 **1.10i**	Drug	Anti-spasmodic disease
9	Ibudilast	 **1.10j**	Drug	Inflammatory diseases

Present work:

1.2. Design of novel PDE4 inhibitors:

An extensive literature survey on selective PDE4 inhibitors reveals the structures of nicotinamide derivatives **1.12**, which may be useful for the treatment of inflammatory diseases such as asthma, COPD, adult respiratory distress syndrome, rheumatoid arthritis and psoriasis and central nervous system disorders such as depression.[26] Thus, we envisioned to design novel 1,4-DHPs **1.14** by keeping R and R^1as diversity points, as shown in Fig. **1.5**.

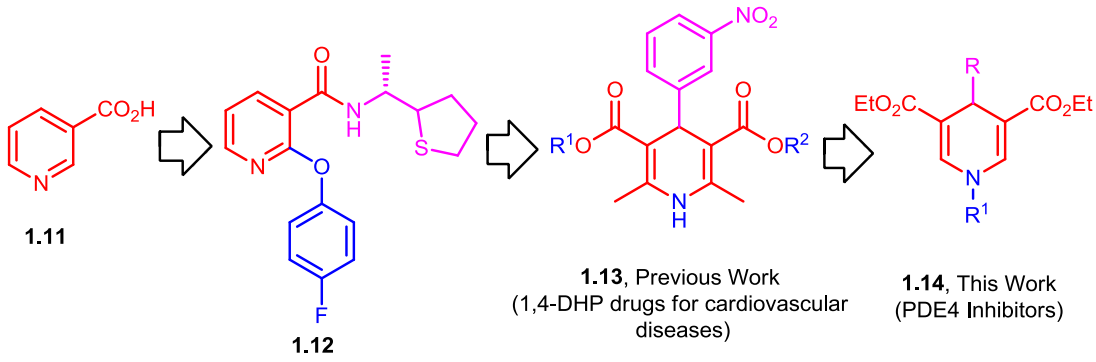
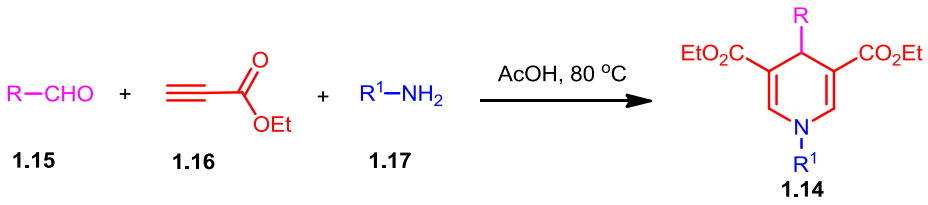


Fig. 1.5. Design and synthesis of 1,4-dihydropyridine derivatives

1.3. Results and discussions:

1.3.1. Synthesis of 1,4-DHPs using modified Hantzsch reaction:

Here, functionalized 1,4-DHPs (**1.14aa-1.14ap**, Table **1.2**) were prepared using Bronsted acid mediated modified Hantzsch reaction protocol, shown in Scheme **1.2**.

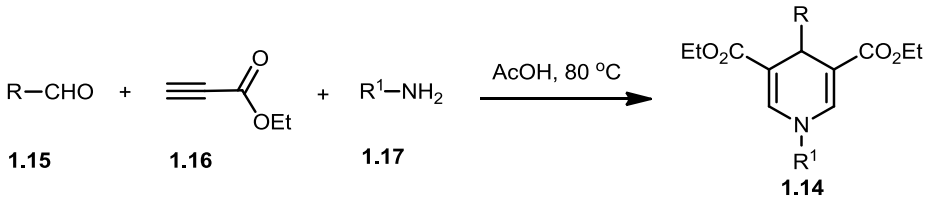


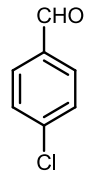
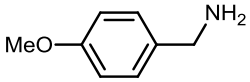
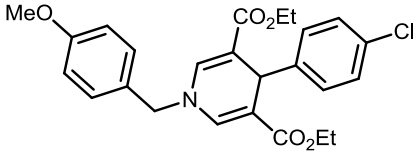
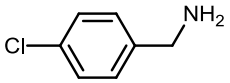
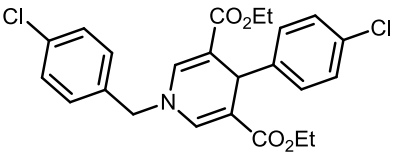
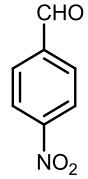
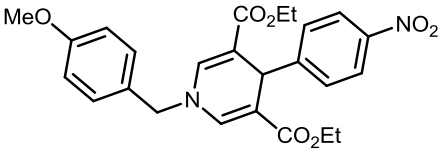
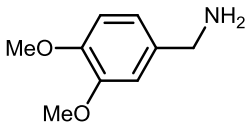
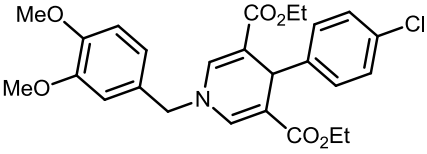
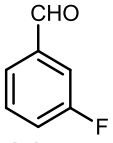
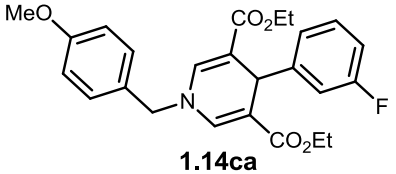
Scheme 1.2. Synthesis of 1,4-DHP derivatives

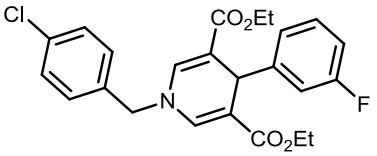
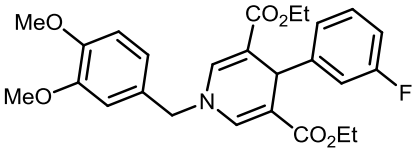
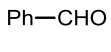
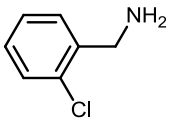
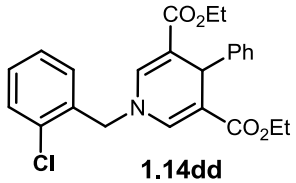
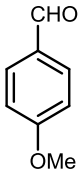
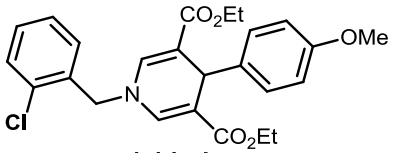
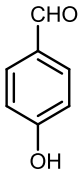
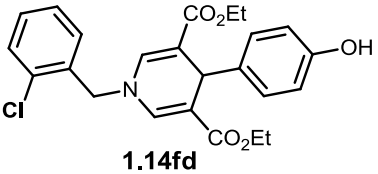
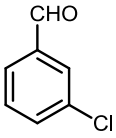
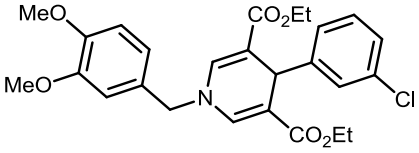
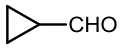
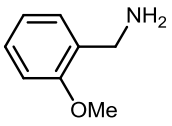
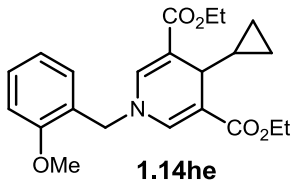
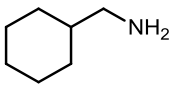
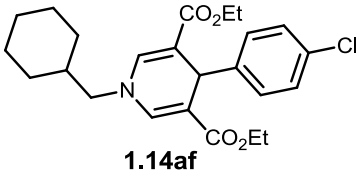
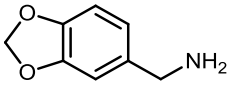
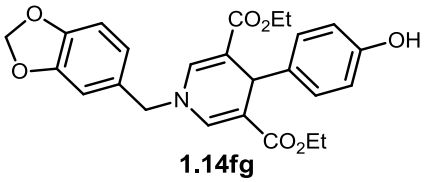
One-pot three component cyclocondensation reactions were performed at 80 ^{o}C in glacial AcOH using substituted aldehyde **1.15**, ethyl propiolate **1.16** and substituted amine **1.17**. Based on the preliminary results obtained during the course of finding

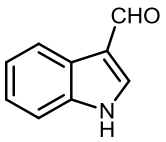
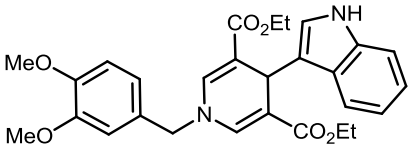
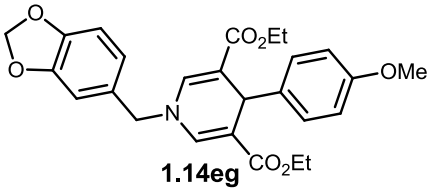
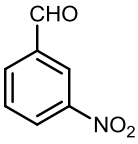
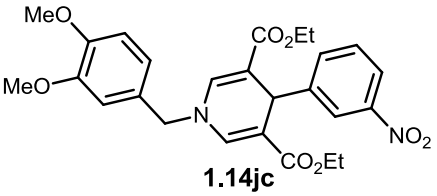
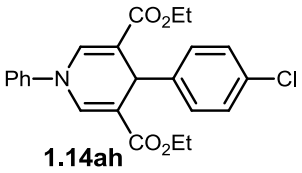
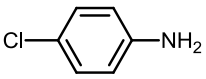
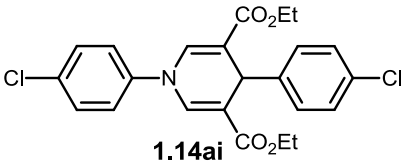
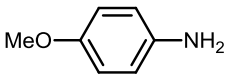
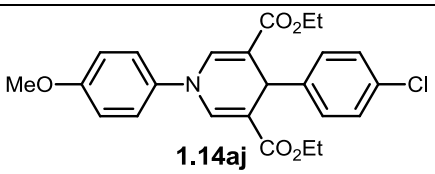
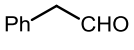
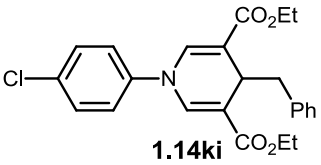
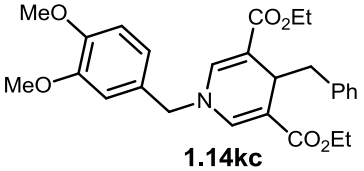
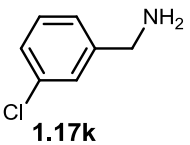
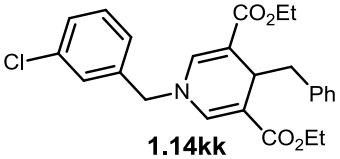
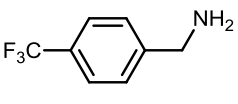
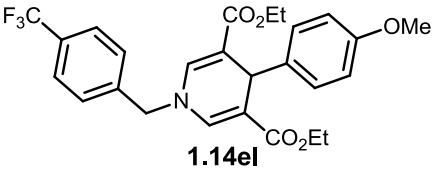
potent PDE4 inhibitor, we have prepared a library of 1,4-DHPs with various substitutions such as OMe, OH, NO_2, Me, Cl, Br, F and CF_3 in good yields (shown in Table **1.2**). It is worth to mention that, 1,4-DHPs contains cyclopropyl **1.14he (**entry **12**, Table **1.2)**, cyclohexyl **1.14af (**entry **13**, Table **1.2**), alkyl (entry **26-37**, Table **1.2**) and allyl **1.14fo-1.14ao (**entry **29-30**, Table **1.2**) were also prepared.

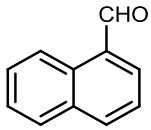
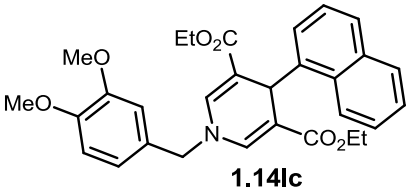
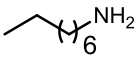
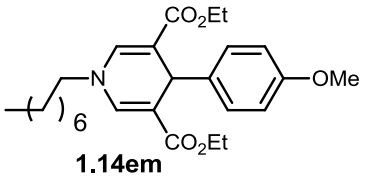
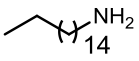
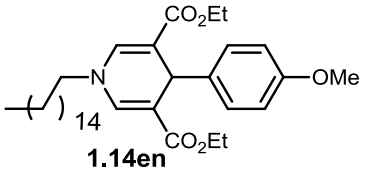
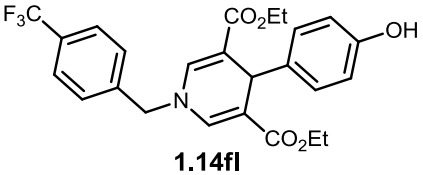
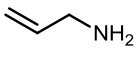
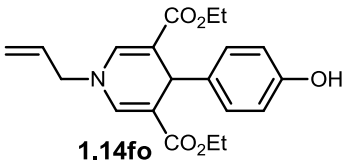
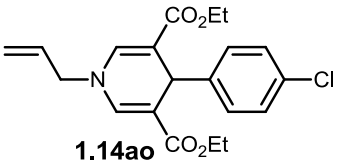
Table 1.2. Library generation of 1,4-DHP derivatives



Entry	R-CHO (**1.15**)	R^1-NH_2 (**1.17**)	Product (**1.14**)	Time (min) / Yield (%)
1	 **1.15a**	 **1.17a**	 **1.14aa**	30/75
2	**1.15a**	 **1.17b**	 **1.14ab**	30/76
3	 **1.15b**	**1.17a**	 **1.14ba**	30/77
4	**1.15a**	 **1.17c**	 **1.14ac**	45/80
5	 **1.15c**	**1.17a**	 **1.14ca**	30/83

6	**1.15c**	**1.17b**	 **1.14cb**	30/84
7	**1.15c**	**1.17c**	 **1.14cc**	45/87
8	 **1.15d**	 **1.17d**	 **1.14dd**	15/75
9	 **1.15e**	**1.17d**	 **1.14ed**	15/80
10	 **1.15f**	**1.17d**	 **1.14fd**	20/79
11	 **1.15g**	**1.17c**	 **1.14gc**	30/71
12	 **1.15h**	 **1.17e**	 **1.14he**	15/69
13	**1.15a**	 **1.17f**	 **1.14af**	15/73
14	**1.15f**	 **1.17g**	 **1.14fg**	30/65

15	 **1.15i**	**1.17c**	 **1.14ic**	120/53
16	**1.15e**	**1.17g**	 **1.14eg**	30/72
17	 **1.15j**	**1.17c**	 **1.14jc**	15/67
18	**1.15a**	 **1.17h**	 **1.14ah**	30/84
19	**1.15a**	 **1.17i**	 **1.14ai**	30/77
20	**1.15a**	 **1.17j**	 **1.14aj**	30/84
21	 **1.15k**	**1.17i**	 **1.14ki**	30/73
22	**1.15k**	**1.17c**	 **1.14kc**	30/73
23	**1.15k**	 **1.17k**	 **1.14kk**	30/71
24	**1.15e**	 **1.17l**	 **1.14el**	15/74

25	 **1.15l**	**1.17c**	 **1.14lc**	15/64
26	**1.15e**	 **1.17m**	 **1.14em**	30/92
27	**1.15e**	 **1.17n**	 **1.14en**	30/89
28	**1.15f**	**1.17l**	 **1.14fl**	15/73
29	**1.15f**	 **1.17o**	 **1.14fo**	30/77
30	**1.15a**	**1.17o**	 **1.14ao**	30/79

Prepared compounds were well characterized using analytical techniques (NMR, LC-Mass and IR), and compound **1.14eg** (entry **16**, Table **1.2**) was unambiguously confirmed by X-ray crystallography, ORTREP diagram (shown in Fig. **1.6**).

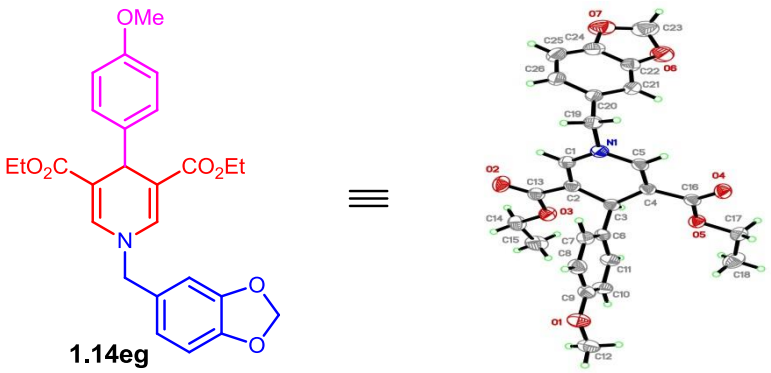


Fig. 1.6. The X-ray crystal structure of compound **1.14eg**

1.3.2. Pharmacology:

PDE4B protein production and purification: PDE4B1 cDNA was sub-cloned into pFAST Bac HTB vector (Invitrogen) and transformed into DH10Bac (Invitrogen) competent cells then recombinant bacmids were tested for integration by PCR analysis. According to the manufacturer's instructions Sf9 cells were transfected with bacmid using lipofectamine 2000 (Invitrogen), then P3 viral titer was amplified, cells were infected and 48h post infected cells, were lysed in lysis buffer (50 mM Tris-HCl pH 8.5, 10 mM 2-Mercaptoethanol, 1% protease inhibitor cocktail (Roche) and 1% NP40). Recombinant His-tagged PDE4B protein was purified, briefly, the lysate was centrifuged at 10,000 rpm for 10 min at 4 ^{o}C and the supernatant was collected, then supernatant was mixed with Ni-NTA resin (GE Life Sciences) in a ratio of 4:1 (v/v) and equilibrated with binding buffer (20 mM Tris-HCl pH 8.0, 5 mM imidazole, 500 mM-KCl, 10% glycerol and 10 mM 2-mercaptoethanol) in a ratio of 2:1 (v/v) and mixed gently on rotary shaker for an hour at 4 ^{o}C. After incubation, lysate-Ni-NTA mixture was centrifuged at 4,500 rpm for 5 min at 4 ^{o}C and the supernatant was collected as the flow-through fraction. The resin was washed twice with wash buffer (20 mM Tris-HCl pH 8.5, 10 mM 2-Mercaptoethanol, 1 M KCl and 10% glycerol). Protein was eluted sequentially twice using elution buffers (Buffer I: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 250 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol, Buffer II: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 500 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol). Eluates were collected in four fractions and analyzed by SDS-PAGE. Eluates containing PDE4B protein was pooled and stored at -80˚C in 50% glycerol until further use.

PDE4 enzymatic assay: As per the manufacturer's instructions inhibition of PDE4 enzyme was measured using PDE light HTS cAMP phosphodiesterase using an assay kit (Lonza). 10 ng of in house purified PDE4B1 or 0.5 ng of commercially procured PDE4D2 enzyme was pre-incubated either with DMSO (vehicle control) or compound for 15 min before incubation with the substrate cAMP (5 µM) for an hour. The reaction was halted with stop solution and the reaction mix was incubated with the detection reagent for 10 minutes in the dark and dose response studies were performed at 13 different concentrations ranging from 200 µM to 0.001 µM. Luminescence values (RLUs) were measured by a multilabel plate reader (Perklin Elmer 1420 Multilabel counter). The percentage of inhibition was calculated using the

following formula and the IC_{50} values was determined by nonlinear regression analysis of the dose response curve using Graph Pad Prism software (San Diego, U.S.A). IC_{50} values are expressed as mean ± SD.[27]

$$\% \text{ inhibition} = \frac{(\text{RLU of vehicle control} - \text{RLU of inhibitior})}{\text{RLU of vehicle control}} \text{X } 100$$

During our investigation to find the potent PDE4 inhibitor, we have initiated screening with in-house compounds, fortunately, compound **1.14ed** (entry **9** Table **1.2**) displayed reasonable 58% of inhibition against PDE4B at 30 µM concentration. This result provoked the use of **1.14ed** as a starting point, as shown in Fig. **1.7.** As described, we have targeted two of the major regions of **1.14ed** for synthetic explorations: (1) the pendant phenyl ring R and (2) the pyridine nitrogen R^1. Accordingly, we prepared a library of 1,4-DHPs **1.14** (entry **1**-**30**, Table **1.2)**.

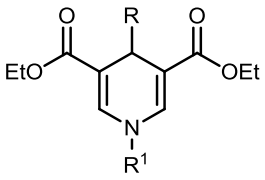


Fig. 1.7. Synthesis of 1,4-DHP derivatives using R and R^1 as diversity points

1,4-DHPs, which have shown more than 40% of inhibitions against PDE4B at 30 µM concentrations are listed in the Table **1.3**.

Table 1.3. PDE4B inhibition with1,4-DHPs

Entry	Compound	PDE4B inhibition (%)
1	**1.14ac**	80
2	**1.14cc**	86
3	**1.14ed**	58
4	**1.14fd**	49
5	**1.14gc**	78
6	**1.14he**	48
7	**1.14fg**	72
8	**1.14ic**	95
9	**1.14eg**	42

10	**1.14jc**	88
11	**1.14ki**	57
12	**1.14kc**	79
13	**1.14lc**	75
14	**1.14fo**	51
15	**1.14ao**	49

In further, the most potent compounds were evaluated for dose response studies shown in Fig. **1.8** and their IC_{50} are noted (entry **1-4**, Table **1.4**), these have shown the similar potencies against PDE4B and PDE4D.

Table 1.4. IC_{50} of selected compounds

Entry	Compound	PDE4B IC_{50} (µM)	PDE4D IC_{50} (µM)
1	**1.14ac**	3.71	2.78
2	**1.14cc**	4.22	3.33
3	**1.14ic**	0.54	0.65
4	**1.14jc**	1.57	2.89

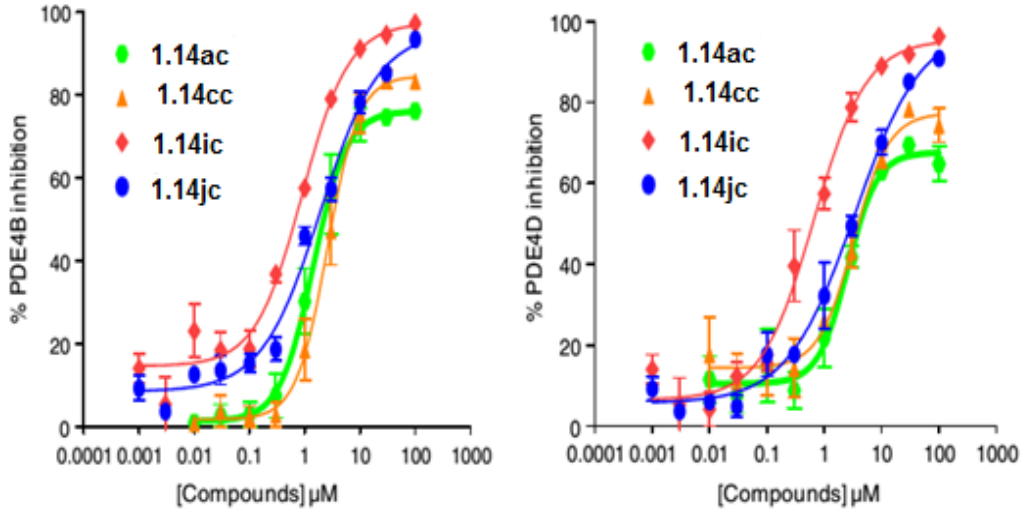


Fig. 1.8. Dose response curves of representative compounds against PDE4B and PDE4D

TNF-α inhibition studies:

TNF-α is produced by activated macrophages and T-cells, which are cytokine with well-established proinflammatory properties.[28] TNF-α inhibiting proteins, such as antibodies and receptor fusion proteins have been considered as remarkable therapeutic potencies in the treatment of Crohn's disease, rheumatoid arthritis and psoriasis.[29] Selective inhibition of TNF-α activity associated with anti-inflammatory effects.[29]

TNF-α production assay: For assaying the effect of compounds on TNF-α production, RAW 264.7 cells were pre-incubated either with DMSO (vehicle control) or compound for 30 minutes and then stimulated with 1 µg/ml of LPS overnight. Dose response studies were carried out at eight different concentrations (30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01 µM), respectively. Post-stimulation and cell supernatants were harvested, centrifuged to clear cell debris, then the amount of TNF-α in the supernatants was measured using mouse TNF-α duo set ELISA kit from R&D systems according to manufacturer's recommendations. Percentage of inhibition was calculated using following formula:

$$\% \text{ inhibition} = 100 - \left[\frac{(\text{LPS stimulated}_{\text{compound}} - \text{unstimulated})}{(\text{LPS stimulated}_{\text{DMSO}} - \text{unstimulated})} \text{ X } 100\right]$$

The IC_{50} values were determined by nonlinear regression analysis of the dose response curve using Graph Pad Prism software (San Diego, U.S.A). Thus, compound **1.14ic** (entry **15**, Table **1.2**) was tested for its ability to blunt LPS-induced TNF-α production and was found to inhibit TNF-α with an IC_{50} of~3.2 µM shown in Fig. **1.9**. IC_{50} values are expressed as mean ± SD.

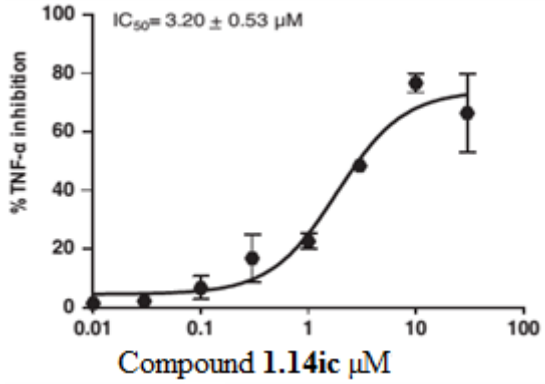


Fig. 1.9. TNF-α inhibition with compound **1.14ic**

1.3.3. *In-silico* studies:

Docking studies were carried out with the help of the glide module Maestro (ver. 9.2), Schrodinger, Inc. 2011 software. For our studies, we used the co-crystal structure of PDE4B with AMP (PDB-ID 1TB5), while the co-crystal structure of PDE4D (PDB-ID 3IAD) with a standard inhibitor (SI-15x). The protein was prepared by giving preliminary treatment like adding missing residues, hydrogen, refining the loop with prime and finally minimized by using OPLS 2005 force fields. The search grid was generated by picking the co-crystal ligand up to 20 Å search area. The hydroxyl groups of the search area were allowed to move. All the molecules were minimized by using macromodule application. We used 1000 iteration for minimization using OPLS 2005 force field and charges were also added from force field only. All the molecules were docked by using glide xp (extra precision) dock application. We performed flexible docking by allowing sample ring conformations and sample nitrogens to move to possible extent in docking. At least 10 conformations of each molecule were generated and consensus docking was utilized then the results are documented and analyzed.[30]

The purpose of the study is not only merely reflecting the correlation of *in-vitro* activities, but also to understand the selectivity profile using docking scores as a measure. As shown in the Fig. **1.10**, both PDE4B and PDE4D enzymes possess similar active sites.

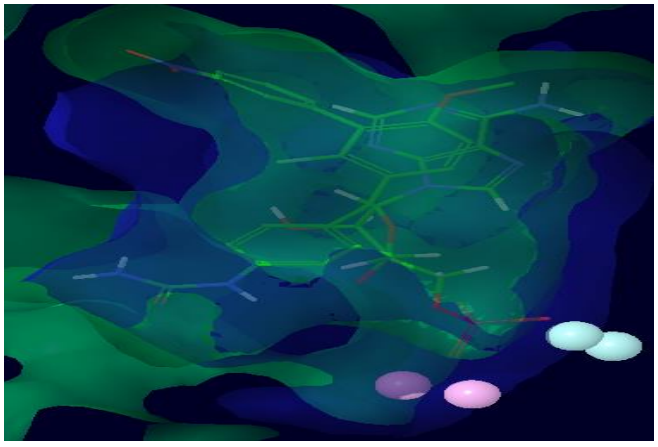


Fig. 1.10. Enzyme active site of PDE4B and PDE4D

Active site volumes of PDE4B (blue) and PDE4D (green), cyan and pink balls represent Zn and Mg atoms (coordination is not displayed for clarity). Two co-crystal ligands (AMP in PDE4B and SI-15x in PDE4D) are shown in capped stick models.

Minor variations within the structural arrangements of residues lie in the active site could lead to differences in activities. Docking of the standard inhibitor SI-15x into PDE4B and PDE4D led to considerably different docking scores, and it is evident from Table **1.5**, docking scores of the SI-15x for PDE4D are higher than PDE4B, indicating that SI-15x should have more inhibitory potency towards PDE4D. AMP was also docked into the PDE4B and PDE4D enzyme crystal structures (not displayed in pictures), whose docking scores were elevated. The conserved with the oxygen atom of the -OMe moiety of SI-15x, while carbonyl oxygen of urea makes strong interactions with the Mg^{2+} atom. It appears that the SI-15x makes use of sufficient space within the active site of PDE4D than in PDE4B although it makes similar interactions within the active site residues of both the enzymes.[31]

The G-scores of AMP in both the enzymes are relatively same (~ -11), while the G-scores of SI-15x are lower for PDE4B (~ -10.6) than for PDE4D (~ -8.2), maintaining similar score for PDE4D as that of AMP, possibly reflecting the activity differences. For most of the synthesized compounds Gln 443 lies within the H-bonding distance.

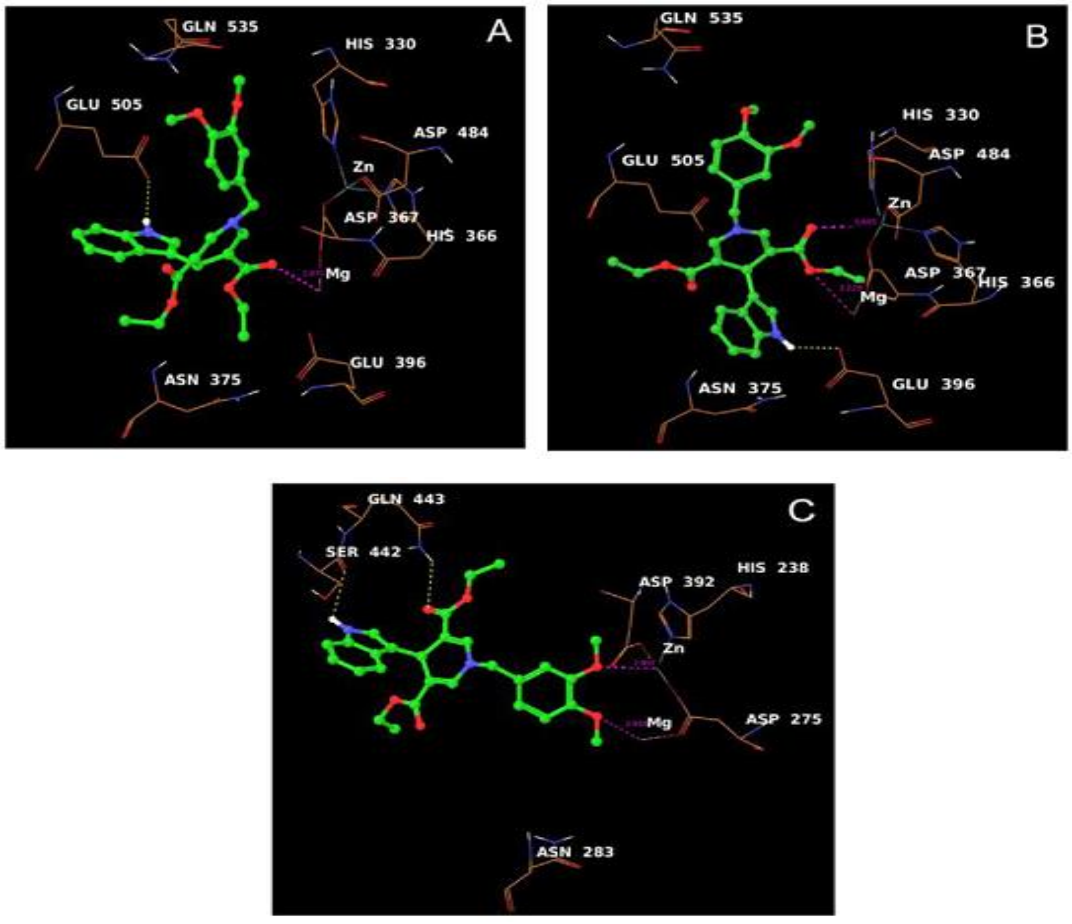


Fig. 1.11. Docking of compound **1.14ic** in PDE4D

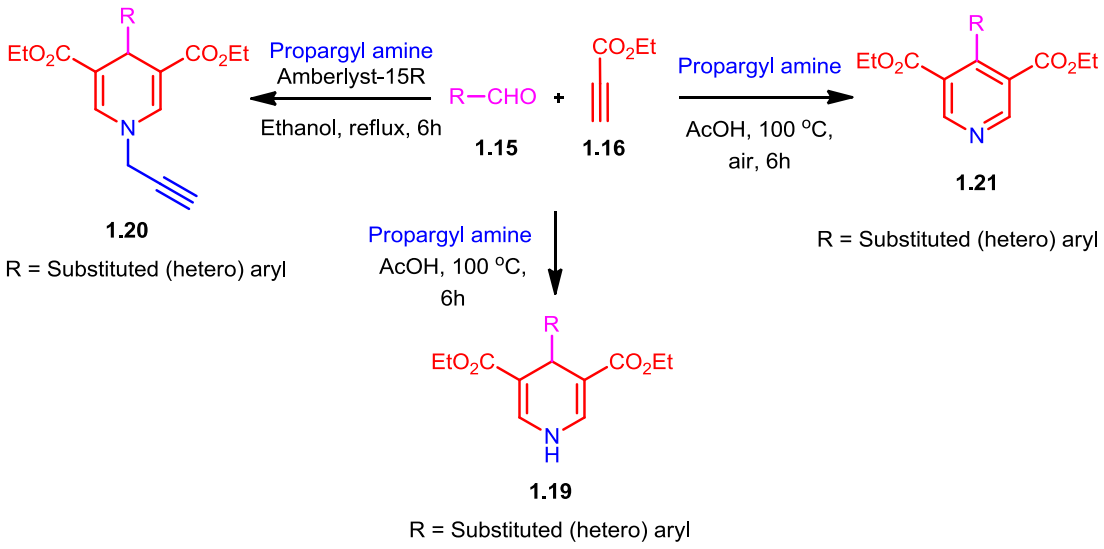
Docking studies of synthesized inhibitors reveal significant understanding, and how they inhibit PDE4B and PDE4D enzymes. Table **1.5** reflects the docking scores of the highest docking pose that has good conformational consensus of AMP, standard inhibitor (SI-15x) and synthesized 1,4-DHPs. Docking scores of most of these molecules fall in a similar range (*i.e.* within 5.7 to 8.2) against PDE4B and PDE4D enzymes. Therefore, these 1,4-DHPs may serve as non-selective PDE inhibitors. As shown Fig. **1.1**, depicts the two possible docked orientations of **1.14ic** in PDE4D (panels A and B), while a single interacting possible orientation in PDE4B (panel C), whereas orientation in PDE4B is completely different from PDE4D.

Dimethoxy group interacts with the metal atoms in PDE4B, while it is supposed to interact with Gln 443. The Gln 535 in PDE4D interacts with the dimethoxy group of **1.14ic**. The indolyl moiety of **1.14ic** forms two possible orientations in PDE4D and in both cases, it makes a strong hydrogen bond with the residues Glu 396 or Glu 505 of PDE4D, while in PDE4B, the same moiety is shown to interact in H-bonded manner with Ser 442 backbone. This additional interaction of indolyl moiety will make it a better inhibitor than the rest of the synthesized inhibitors. Docking scores of **1.14ic** are marginally better (*i.e.* lower) than the rest of the other inhibitors.

Table 1.5. Docking scores of synthesized inhibitors

Entry	Compound	PDE4B	PDE4D
1	**AMP**	-11.4	-11.0
2	**SI-15x**	-10.6	-8.2
3	**1.14ac**	-7.5	-5.7
4	**1.14cc**	-6.9	-6.4
5	**1.14fc**	-6.8	-5.8
6	**1.14ec**	-7.8	-6.8
7	**1.14hc**	-8.1	-7.0
8	**1.14ic**	-7.6	-6.5

In the course of finding potent PDE4 inhibitors, we have also observed PDE4 inhibition profile of *N*-propargylated 1,4-DHP derivatives. While performing the reaction using propargyl amine as an amine source, we have observed the ~1:1 ratio of *N*-propargylated 1,4-DHP **1.20** and the depropargylated 1,4-DHP **1.19**, at 80 ^{o}C in AcOH. This observation has prompted us to develop the novel methods: a) Synthesis of 1,4-DHPs using Bronsted acid mediated *in-situ* depropargylation protocol b) Synthesis of *N*-propargylated 1,4-DHPs using mild acidic resin amberlyst-15R and c) Synthesis of pyridine derivatives using Bronsted acid mediated *in-situ* depropargylation followed by oxidation, shown in Scheme **1.3**.



Scheme 1.3. Novel methods for the synthesis of 1,4-dihydropyridines and pyridines

1.3.4. Synthesis of 1,4-dihydropyridine derivatives using propargyl amine:

As shown in the Fig. **1.12**, 1,4-DHPs (**1.19'**) can be obtained from several approaches in two steps. In our approach, we disclose the Bronsted acid (AcOH) mediated *in-situ* depropargylation one-pot protocol. To the best of our knowledge, this is the first report for the synthesis of 1,4-DHPs **1.19** using *in-situ* depropargylation strategy from simple and commercially available precursors.

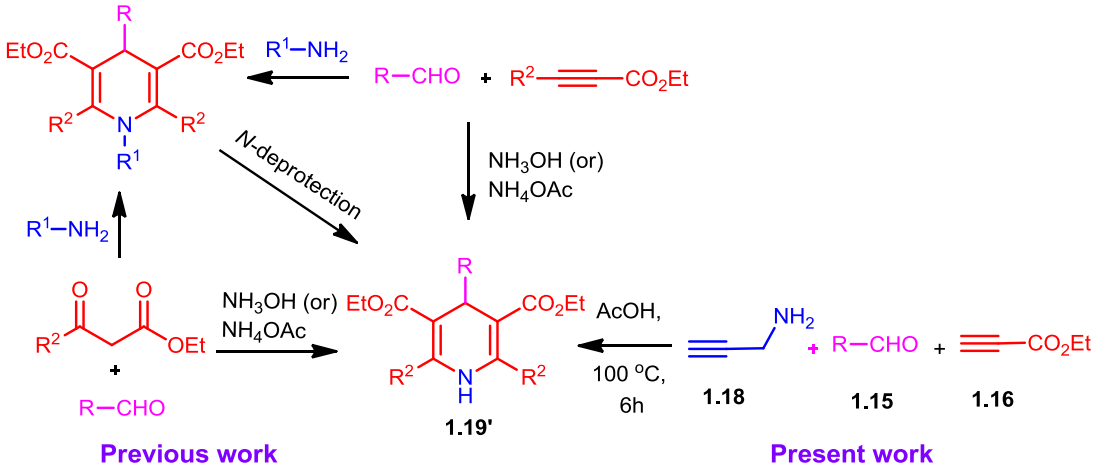
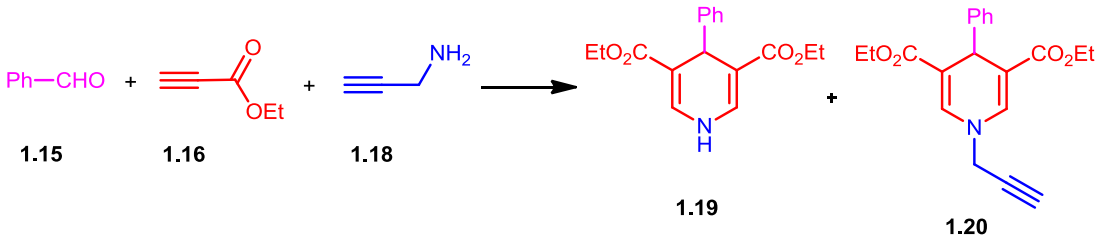


Fig. 1.12. General methods for the synthesis of 1,4-dihydropyridines

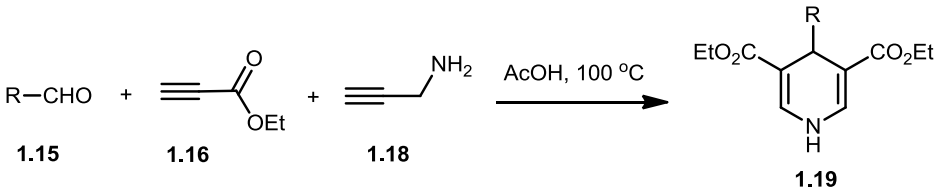
In order to get the optimized reaction condition, we have performed the present reaction in various solvents. While performing the reaction in ethanol we have isolated the exclusively (*E*)-ethyl 3-ethoxyacrylate and 15% of *N*-propargylated 1,4-DHP **1.20** (entry **3**, Table **1.6**), as well as in aprotic polar solvents (DMSO or DMF) not observed 1,4-DHP formations. However, we have optimized the reaction in AcOH at 100 °C (entry **5**, Table **1.6**) for the formation of 1,4-DHP derivative **1.19**. We have generalized the developed protocol with various substituted aldehydes, shown in Table **1.7**.

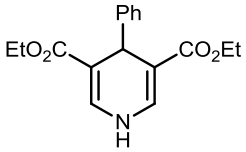
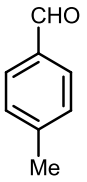
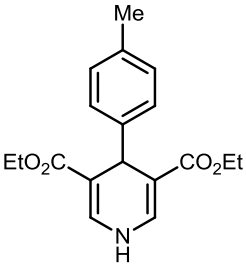
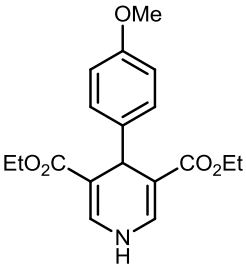
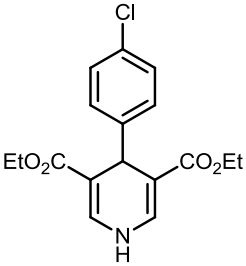
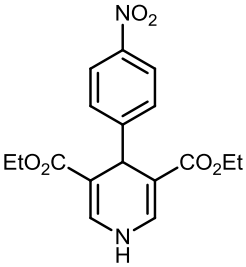
Table 1.6. Optimization studies for the synthesis of 1,4-dihydropyridines

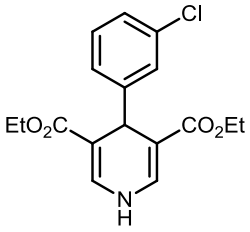
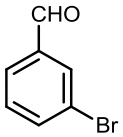
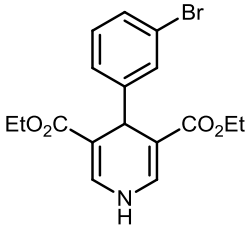
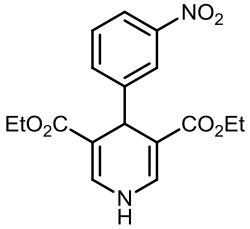
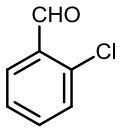
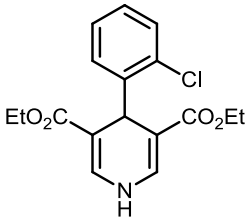
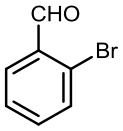
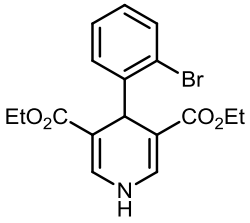


Entry	Solvent	Time (h)	Temp (°C)	**1.19,** Yield (%)	**1.20,** Yield (%)
1	AcOH	0.5	80	35	27
2	AcOH	2	80	45	10
3	EtOH	12	Reflux	ND	15
4	DMSO	12	100	ND	ND
5	AcOH	4	100	76	ND

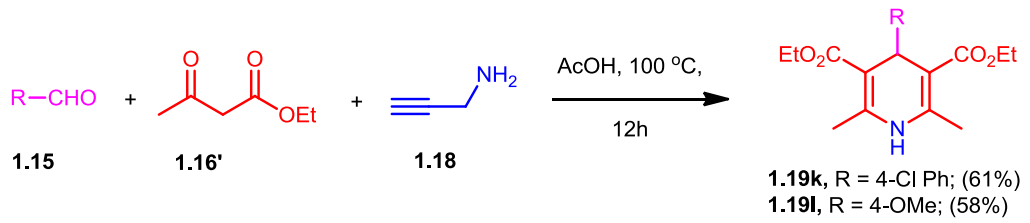
Table 1.7. Synthesis of 1,4-dihydropyridine derivatives



Entry	Aldehyde (**1.15**)	Product (**1.19**)	Time (h)	Yield (%)
1	**1.15d**	 **1.19a**	4	76
2	 **1.15m**	 **1.19b**	4	78
3	**1.15e**	 **1.19c**	6	81
4	**1.15a**	 **1.19d**	2	87
5	**1.15b**	 **1.19e**	2	85

6	**1.15g**	 **1.19f**	2	78
7	 **1.15n**	 **1.19g**	2	83
8	**1.15j**	 **1.19h**	2	79
9	 **1.15o**	 **1.19i**	2	85
10	 **1.15p**	 **1.19j**	2	85

As shown in the Scheme **1.4,** functionalized 1,4-DHP derivatives (**1.19l** and **1.19k**) were synthesized from ethyl 3-oxobutanoate **1.16'**, while the reaction with 4-chloro benzaldehyde **1.15d** and 4-methoxy benzaldehyde **1.15c** in AcOH at 100 ^{o}C, provided 61% and 58% of the yields, respectively.



Scheme 1.4. Synthesis of 1,4-DHP derivatives using ethyl 3-oxobutanoate **1.16'**

Mechanism: We have proposed a mechanism for the formation of depropargylated 1,4-DHP derivative **1.19a**, which involves the Bronsted acid (AcOH) mediated synthetic process as described in Fig. **1.13** and there are two possible ways, in which path 2 is favorable because of in-built enaminone core playing a key hydrogen bonding interaction for accelerating the depropargylation. In addition, we also perform the reaction in the open air to get the pyridine derivative at 100 °C in AcOH.

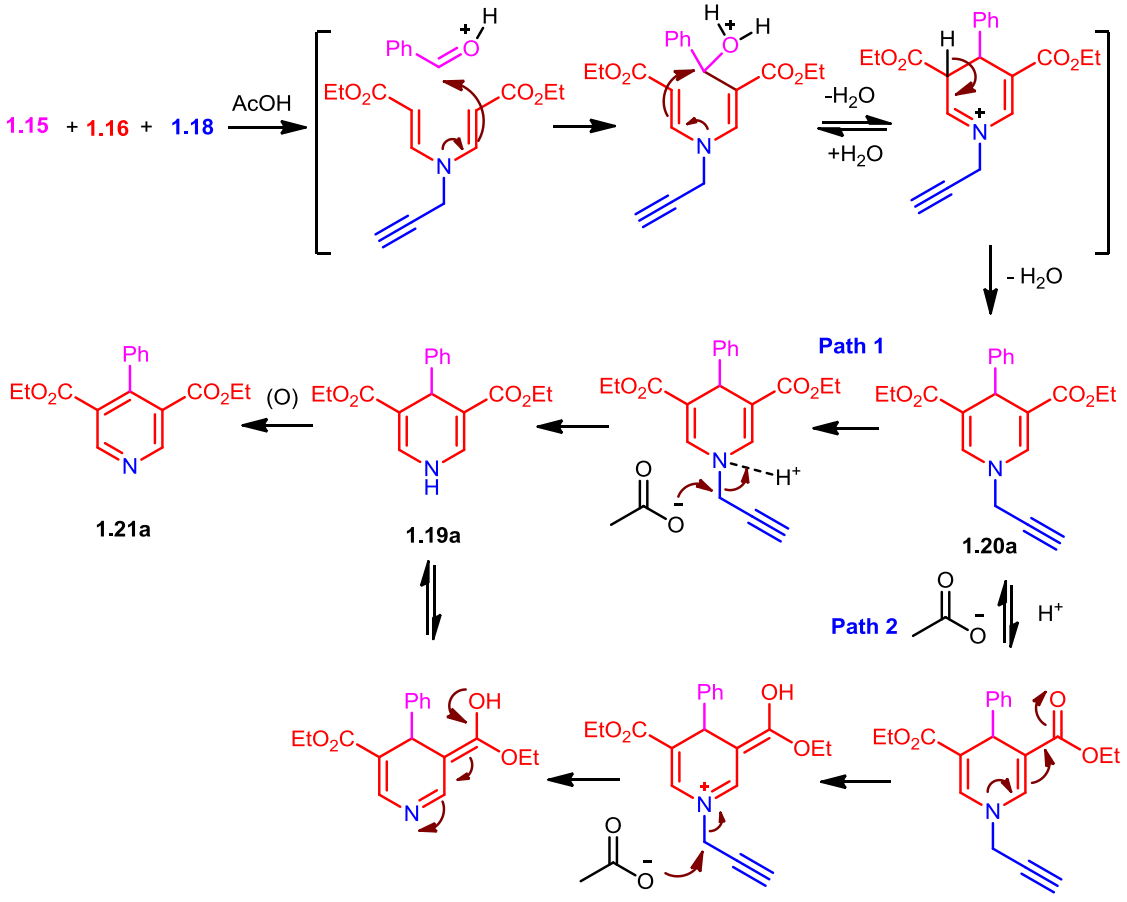
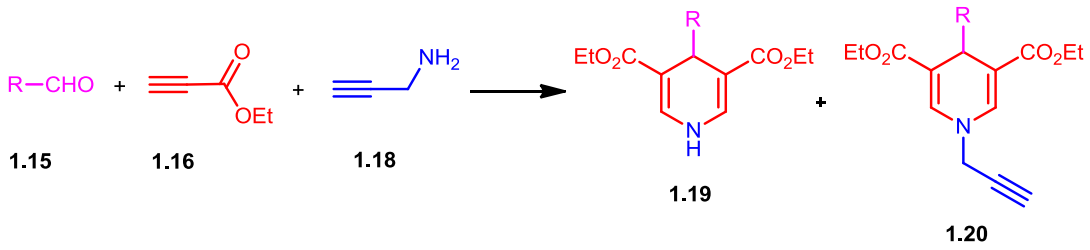


Fig. 1.13. Proposed mechanism for depropargylation on 1,4-dihydropyridines

Synthesis of *N*-propargylated 1,4-dihydropyridine derivatives:

As mentioned, we have observed the slight formation of *N*-propargylated 1,4-DHP **1.20**, as well as (*E*)-ethyl 3-ethoxyacrylate is an exclusive product. In order to avoid the formation of stable (*E*)-ethyl 3-ethoxyacrylate, we performed the reaction in polar aprotic solvents such as DMSO (entry **4**, Table **1.6**), expected product was not formed. As shown in Table **1.8**, we check with Lewis acids to activate the (*E*)-ethyl 3-ethoxyacrylate towards the formation of *N*-propargyl vinyl amines but did not produce any desired results. Later, we demonstrated amberlyst-15R is a mild acid catalyst that has accelerated the reaction effectively (entry **4**, Table **1.8**).

Table 1.8. Optimization studies for the synthesis of *N*-propargyl 1,4-DHPs

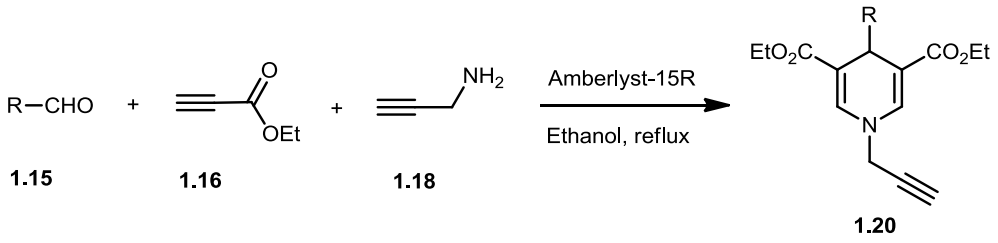


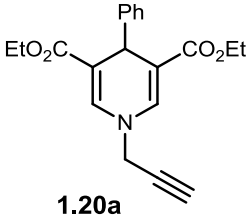
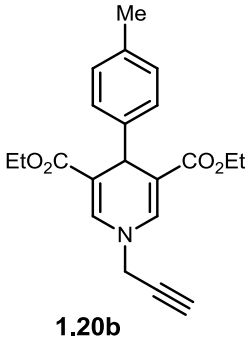
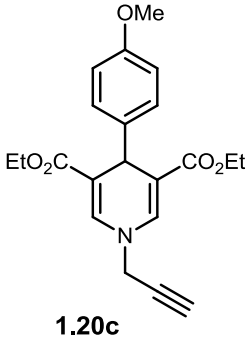
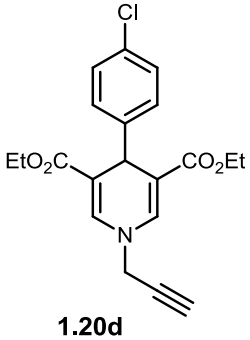
Entry	Solvent	Time (h)	Temp (°C)	**1.19**, Yield (%)	**1.20**, Yield (%)
1	EtOH	12	Reflux	ND	15
2[a]	EtOH	12	RT	ND	ND
3[a]	EtOH	12	Reflux	ND	20
4[b]	EtOH	4	Reflux	ND	79

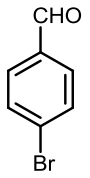
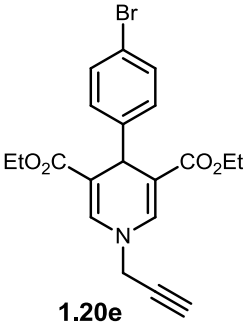
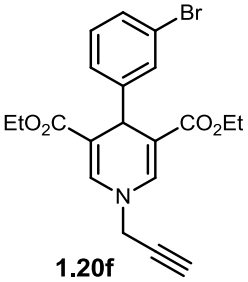
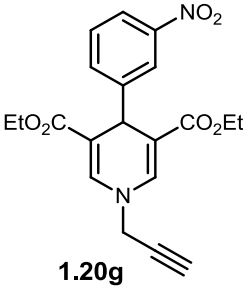
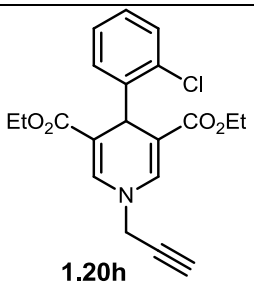
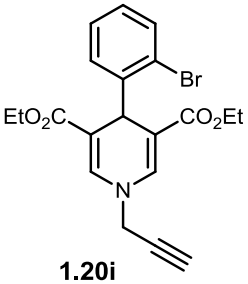
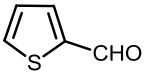
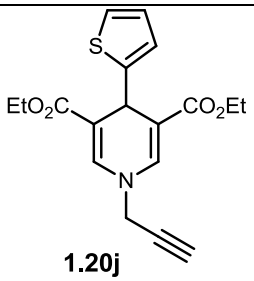
[a]$Sc(OTf)_3$ (or) $Cu(OTf)_2$, [b]Amberlyst-15R

Having the optimized reaction condition (entry **4**, Table **1.8**) in our hand, we moved to generalize with various substituted aldehydes; details are summarized in Table **1.9**.

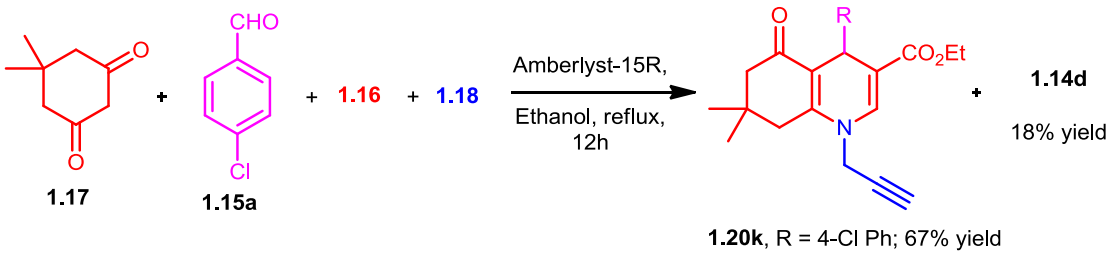
Table 1.9. Reaction optimization with substituted aldehydes



Entry	Aldehyde (**1.15**)	Product (**1.20**)	Time (h)	Yield (%)
1	**1.15d**	 **1.20a**	2	79
2	**1.15m**	 **1.20b**	2	75
3	**1.15e**	 **1.20c**	2	71
4	**1.15a**	 **1.20d**	1	90

5	 **1.15q**	 **1.20e**	1	87
6	**1.15n**	 **1.20f**	1	89
7	**1.15j**	 **1.20g**	1.5	83
8	**1.15o**	 **1.20h**	1	79
9	**1.15p**	 **1.20i**	1	78
10	 **1.15r**	 **1.20j**	4	65

In order to elevate the efficiency of the present MCR method, we perform the present reaction with β-keto carbonyl compound (dimedone) **1.17**, shown in Scheme **1.5**.



Scheme 1.5. Four component synthesis of *N*-propargylated 1,4-DHPs

1.3.5. Synthesis of pyridine derivatives using propargyl amine:

Biological applications of pyridine derivatives: Pyridine is a simple *N*-heterocycle, discovered in 1849 by Anderson, present in numerous biologically important natural products, pharmaceuticals and materials.[32] Pyridine nucleus in the form of NADP presents in living organisms and involve in various oxidation-reduction process, also present in vitamins (niacin, pyridoxine or vitamin B6). Pyridine nucleus is a key pharmacophore in 7000 existing drugs,[32] representative examples have shown in Fig. **1.14**, isoniazide **1.22d** and etoricoxib **1.22e** have been serving as potent pharmaceuticals.

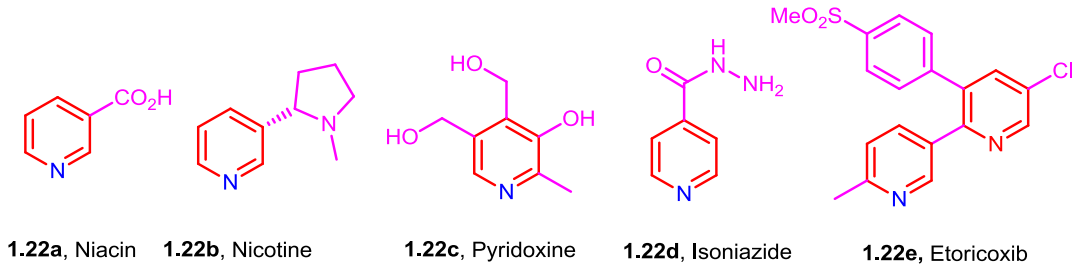


Fig. 1.14. Representative structures of bio-active pyridine derivatives

As shown in Fig. 1.15, pyridine derivatives can be easily adoptable from the 1,4-DHPs, which involves two-step process, often required several oxidizing agents,[4] (includes nitric acid, ceric ammonium nitrate, ferric or cupric nitrates on a solid support, SiO_2/P_2O_5–SeO_2, transition metal catalysts like $RuCl_3$, $Mn(OAc)_3$, $H_2O_2/Co(OAc)_2$, $NaHSO_4/Na_2Cr_2O_7$/wet SiO_2, peroxodisulfate–cobalt(II), $Zr(NO_3)_4$, Dess–Martin reagent, graphite oxide and Pd/C in AcOH).

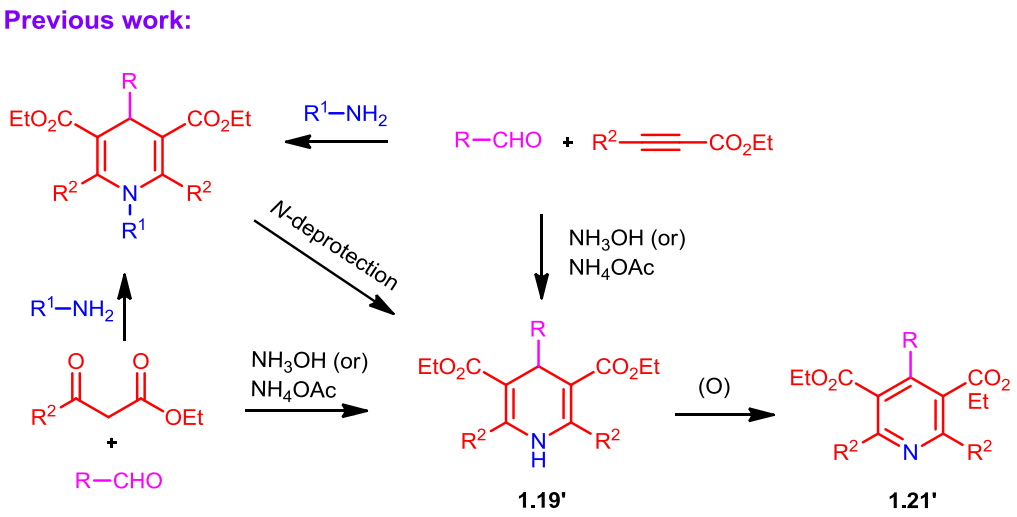
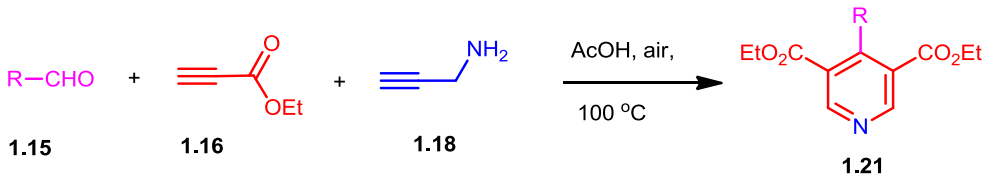
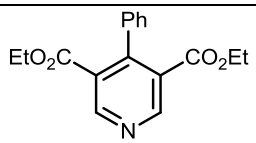
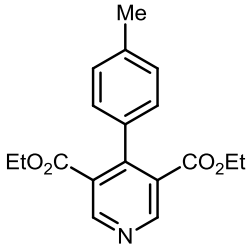


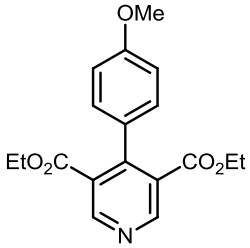
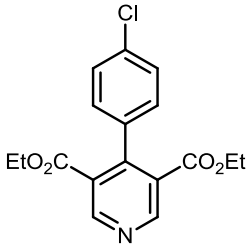
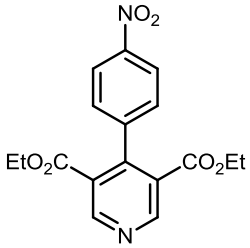
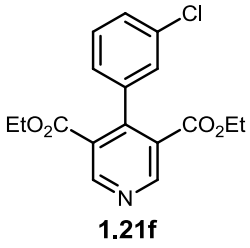
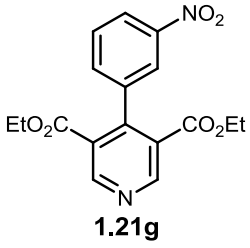
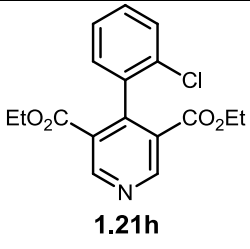
Fig. 1.15. General methods, for accessing the pyridine derivatives from 1,4-DHPs

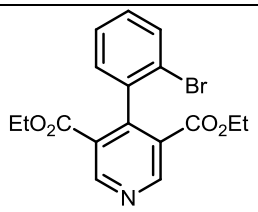
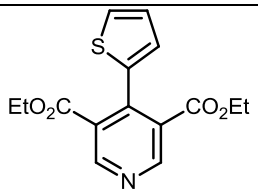
Here, we developed the novel one-pot method for the synthesis of pyridine derivatives, this method involves the metal free depropargylation followed by *in-situ*, oxidation, as shown in Table **1.10**, generalized with substituted aldehydes **1.15**.

Table 1.10. Synthesis of substituted pyridine derivatives

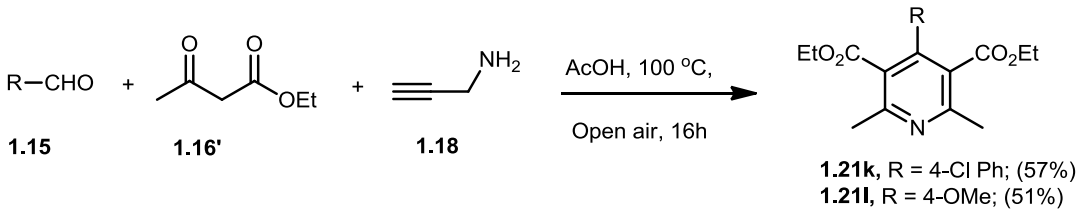


Entry	Aldehyde (**1.15**)	Product (**1.21**)	Time (h)	Yield (%)
1	**1.15d**	 **1.21a**	6	76
2	**1.15m**	 **1.21b**	6	71

3	**1.15e**	 **1.21c**	10	67
4	**1.15a**	 **1.21d**	6	81
5	**1.15b**	 **1.21e**	6	83
6	**1.15g**	 **1.21f**	6	79
7	**1.15j**	 **1.21g**	6	84
8	**1.15o**	 **1.21h**	8	63

9	**1.5p**	 **1.21i**	8	69
10	**1.15r**	 **1.21j**	12	57

In order to synthesize the densely functionalized pyridine derivatives, we expand the developed one-pot protocol using substituted aldehyde **1.15**, ethyl 3-oxobutanoate **1.16'** and propargyl amine **1.18**, shown in the Scheme **1.6,** which have provided the moderate yields, 57% (if R = 4-Cl Ph) and 51% (if R = 4-OMe Ph), respectively.



Scheme 1.6. Synthesis of pyridine derivatives

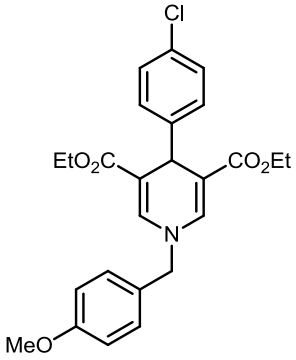
1.4. Conclusions:

In the course of finding potent PDE4 inhibitors, we have used the modified Bronsted acid mediated Hantzsch MCR protocol for the synthesis of 1,4-DHPs. In our bioactive evaluation studies, 1,4-DHPs exerted a new functional properties as inhibitors of PDE4. Here, 1,4-DHPs bearing 3,4-dimehoxy substitutions at R^1 have provided the excellent PDE4 inhibitory profile, as well *in-silico* studies supported the potent binding interactions of 3,4-dimehoxy substitutions in the enzyme active binding site. Unexpected Bronsted acid mediated depropargylation provided insights for the development of new methods for the synthesis of 1,4-DHPs and pyridine derivatives. In which, pyridine synthesis involves the metal free depropargylation followed by *in-situ* oxidation. In addition, we have also demonstrated the amberlyst-15R mediated one-pot protocol for the synthesis of *N*-propargylated 1,4-DHP derivatives.

1.5. Experimental section:

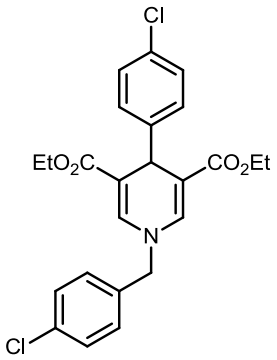
General procedure: Ethylpropiolate (30 mg, 0.3 mmol), 4-chlorobenzaldehyde (10.7 mg, 0.076 mmol) and 4-methoxybenzylamine (10.5 mg, 0.076 mmol) were heated in 0.25 mL of glacial AcOH in preheated oil bath at 80 ^{o}C. Then reaction mixture was poured into ice, from which the product was crystallized on stirring.

Diethyl-4-(4chloropheyl)-1-(4-methoxybenzyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14aa):



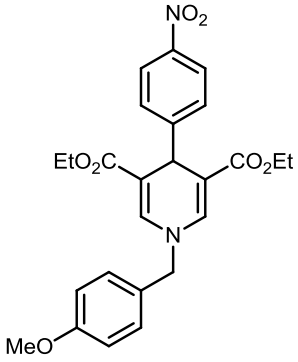
Yield = 74% (25 mg); pale yellow solid; MP: 89-90 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 2H), 7.24-7.14 (m, 6H), 6.93 (m, 2H), 4.87 (s, 1H), 4.51 (s, 2H), 4.14-3.97 (m, 4H), 3.83 (s, 3H), 1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.69, 159.67, 145.15, 137.56, 131.96, 129.57, 128.66, 127.96, 127.89, 114.5, 108.61, 60.07, 57.86, 55.31, 36.96, 14.16, 14.07; ESI-MS (m/z): [M+1] 455.9; FT-IR: 1690, 2856, 2925; and purity in HPLC = 98%.

Diethyl-1-allyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14bb):



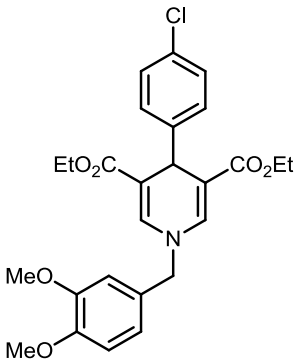
Yield = 76% (26 mg); pale yellow solid; MP: 134-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, 2H), 7.25-7.16 (m, 8H), 4.88 (s, 1H), 4.55 (s, 2H), 4.12-4.01 (m, 4H), 1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.54, 144.91, 137.36, 134.47, 134.42, 132.09, 129.56, 129.35, 128.52, 128.02, 109.01, 60.17, 57.57, 36.10, 14.15, 14.07; ESI-MS (m/z): [M+1] 459.8; FT-IR: 1688, 2857, 2925; and purity in HPLC = 93%.

Diethyl-1-allyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14ba):



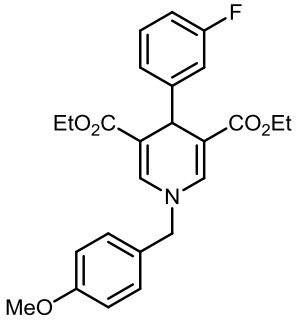
Yield = 76% (72.0 mg); pale yellow solid; MP: 114-115 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2H), 7.30 (d, 2H), 7.25-7.18 (m, 2H), 7.42 (d, 2H), 6.96 (d, 2H), 5.02 (s, 1H), 4.54 (s, 2H), 4.11-4.01 (m, 4H), 3.84 (s, 3H), 1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.32, 159.8, 153.58, 146.46, 138.02, 129.08, 128.69, 127.61, 123.26, 114.59, 107.89, 60.24, 57.97, 55.34, 37.8, 14.16; ESI-MS (m/z): [M+1] 466.9; FT-IR: 1691, 2846, 2938, 2988; and purity in HPLC = 97%.

Diethyl-1-allyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14ac):



Yield = 80% (49 mg); yellow solid; MP: 90-91.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 6H), 6.85 (dd, 2H), 6.75 (d, 1H), 4.88 (s, 1H), 4.51 (s, 2H), 3.90 (d, 6H), 4.14-4.00 (m, 4H), 1.18 (q, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.88, 166.78, 164.56, 158.05, 139.01, 138.08, 137.31, 133.71, 133.31, 131.93, 130.06, 129.68, 129.24, 129.1, 127.46, 127.41, 114.26, 113.23, 109.28, 60.13, 60.01, 55.76, 55.53, 55.09, 36.44, 14.16, 14.11; ESI-MS (m/z): [M+1] 485.9; FT-IR: 1694, 2933; and purity in HPLC = 95%.

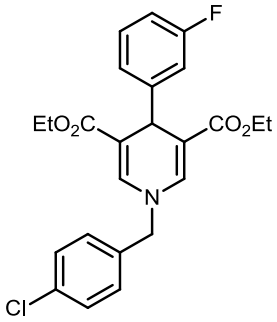
Diethyl-1-allyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14ca):



Yield = 82% (28 mg); yellow solid; Mp: 88-89 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.24-7.11 (m, 3H), 7.06 (d, 1H), 6.94 (m, 3H), 4.90 (s, 1H), 4.52 (s, 2H), 4.07 (m, 4H), 3.83 (s, 3H), 1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.72, 164.0, 161.56, 159.68, 149.1, 149.04, 137.68, 129.11, 129.04, 128.66, 127.87, 123.84, 123.82,

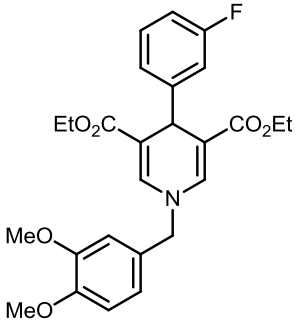
115.19, 114.97, 114.53, 113.28, 113.07, 108.49, 60.09, 57.86, 55.29, 37.26, 14.15; ESI-MS (m/z): [M+1] 439.9; FT-IR: 1694, 2843, 2923,2909; and purity in HPLC = 99%.

Diethyl-1-allyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14cb):



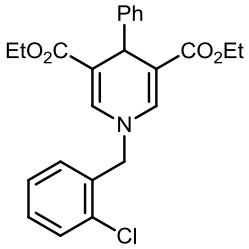
Yield = 83% (29 mg); yellow solid; Mp: 114-116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, 2H), 7.20 (m, 5H), 7.06 (m, 1H), 6.98-6.92 (m, 1H), 6.84 (m, 1H), 4.92 (s, 1H), 4.56 (s, 2H), 4.11-4.03 (m, 4H), 1.20-1.16 (m, 6H); ESI-MS (m/z): [M+1] 443.8 ; FT- IR: 1690, 2905, 2986, 3074; and purity in HPLC = 96%.

Diethyl-1-allyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14cc):



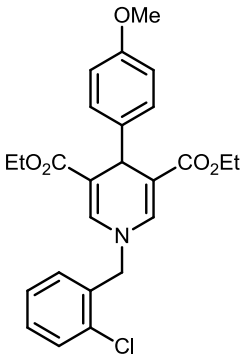
Yield = 86% (51 mg); pale yellow solid; Mp: 82-83 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2H), 7.20-7.06 (m, 2H), 6.96 (d, 1H), 6.85 (td, 3H), 6.76 (d, 2H), 4.92 (s, 1H), 4.08 (m, 4H), 3.90 (d, 6H), 1.18 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 469.9; FT-IR: 1685, 2856, 2928, 3070; and purity in HPLC = 99%.

Diethyl 1-(2-chlorobenzyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1.14dd):



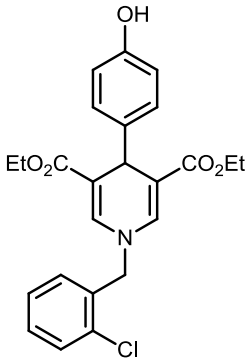
Yield = 75% (42 mg); yellow solid; Mp: 140-142 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 1H), 7.23 (m, 2H), 7.31-7.13 (m, 8H), 4.92 (s, 1H), 4.68 (s, 2H), 4.11-4.01 (m, 4H), 1.16 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.78, 146.38, 137.52, 133.67, 133.33, 130.08, 129.7, 129.09, 128.28, 127.87, 127.41, 126.33, 109.14, 60.12, 60.02, 55.78, 37.36, 14.14; ESI-MS (m/z): [M+1] 426.1; FT-IR: 1692, 2901, 2978; and purity in HPLC = 94%.

Diethyl 1-(2-chlorobenzyl)-4-(4-methoxyphenyl)-1,4-dihyropyridine-3,5-dicarboxylate (1.14ed):



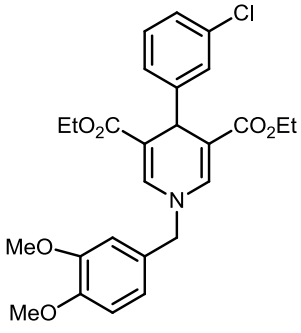
Yield = 80% (46 mg); yellow solid; Mp: 101-103 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 1H), 7.38-7.17 (m, 7H), 6.76 (d, 2H), 4.86 (s, 1H), 4.68 (s, 2H), 4.16-3.94 (m, 4H), 3.77 (s, 3H), 1.24-1.07 (m, 6H); ESI-MS (m/z): [M+1] 456.1; FT-IR: 1698, 2841, 2980; and purity in HPLC = 95%.

Diethyl-1-(2-chlorobenzyl)-4-(4-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14fd):



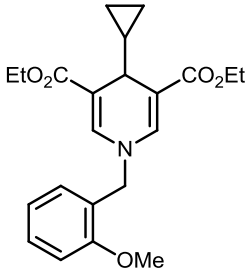
Yield = 79% (44 mg); yellow solid; Mp: 92-93 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 1H), 7.34-7.22 (m, 7H), 7.09 (d, 2H), 5.38 (s, 1H), 4.69 (s, 2H), 4.12-3.98 (m, 4H), 1.15 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 440.1; FT-IR: 1697, 2855, 2929, 3361; and purity in HPLC = 97%.

Diethyl-4-(3-chlorophenyl)-1,3-(3,4-dimethoxybenzyl)-1,4-dihydropyridine-3,5 dicarboxylate (1.14gc):



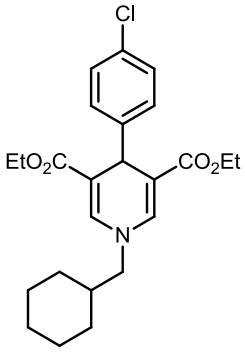
Yield = 70% (43 mg); yellow solid; Mp: 88-90 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, 2H), 7.20-6.87 (m, 6H), 6.76 (s, 1H), 4.89 (s, 1H), 4.52 (s, 2H), 4.14-4.01 (m, 4H), 3.89 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): 486.2; FT-IR: 1695, 2844, 2930; and purity in HPLC = 98%.

Diethyl 4-cyclopropyl-1-(2-methoxybenzyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14hc):



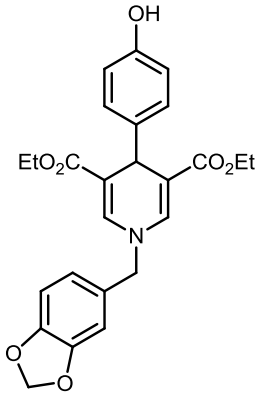
Yield = 68% (4 mg); gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.14 (m, 4H), 6.82 (s, 2H), 4.50 (s, 2H), 4.34-4.01 (m, 4H), 3.82 (s, 3H), 3.66 (d, *J* = 7.1 Hz, 1H), 1.28 (m, *J* = 7.1 Hz, 7H), 0.97-0.75 (m, 2H), 0.23 (m, 2H); ESI-MS (m/z): [M+1] 384.3; FT-IR: 1699, 2855, 2974, 2928; and purity in HPLC = 93%.

Diethyl-4-(4-chlorophenyl)-1-(cyclohexylmethyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14af):



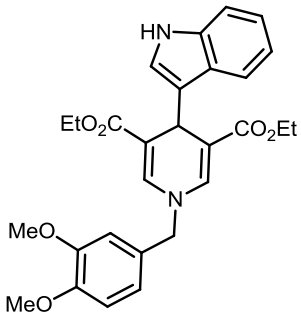
Yield = 73% (39 mg); gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.16 (m, 6H), 4.88 (s, 1H), 4.07 (q, 4H), 3.22 (d, *J* = 6.9 Hz, 2H), 1.18 (m, *J* = 7.1 Hz, 6H), 1.3-1.8 (m, 11H); ESI-MS (m/z): [M+1] 432.3; FT-IR: 1692, 2854, 2925, 2978; and purity in HPLC = 96%.

Diethyl-1-(benzo[d][1,3]dioxol-5-ylmethyl)-4-(4-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14fg):



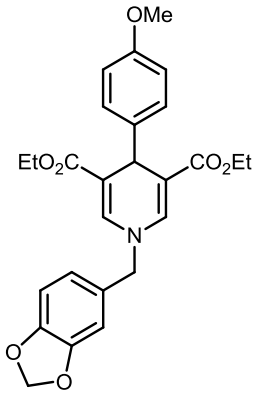
Yield = 64% (22 mg); yellow solid; Mp: 110-112 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.26 (b, 3H), 7.12 (m, 2H), 6.85-6.62 (m, 5H), 5.99 (s, 2H), 4.82 (s, 1H), 4.46 (s, 2H), 4.12-4.01 (m, 4H), 1.18 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 154.51, 148.34, 147.71, 138.64, 137.24, 129.73, 129.28, 120.96, 114.79, 109.25, 108.6, 107.62, 101.3, 60.18, 58.1, 36.41, 14.14; ESI-MS (m/z): [M+1] 452.1; FT-IR: 1673, 2919, 2977, 3399; and purity in HPLC = 97%.

Diethyl-4-(1H-indol-3yl)-1-(4-methoxybenzyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14ic):



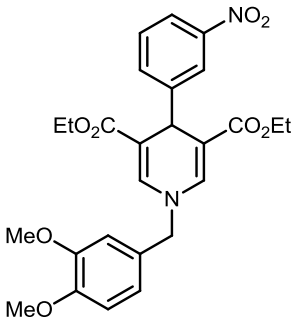
Yield = 52% (19 mg); brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16-8.91 (bs, 1H), 8.32 (d, 1H), 7.84 (d, 1H), 7.47-7.41 (m, 1H), 7.35-7.30 (m, 2H), 6.85 (m, 2H), 6.77 (dd, 2H), 6.70 (bd, 1H), 4.86 (s, 1H), 4.51 (s, 2H), 4.09 (m, 4H), 3.89 (d, 6H), 1.20 (m, *j* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 374.2 [base peak 100%]; FT-IR: 1698, 2836, 2925, 3360; and purity in HPLC = 99%.

Diethyl-1-(benzo[d][1,3]dioxol-5-ylmethyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14eg):



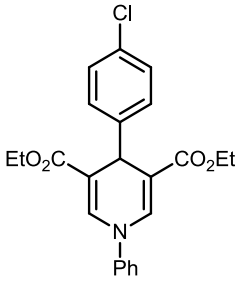
Yield = 72% (25 mg); yellow solid; Mp: 92-94 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-6.82 (m, 3H), 6.76 (m, 4H), 5.99 (s, 2H), 4.83 (s, 1H), 4.46 (s, 2H), 4.07 (m, 4H), 3.75 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 466.1; FT-IR: 1680, 2899, 2982; and HPLC = 96%.

Diethyl-1-(3,4-dimethoxybenzyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14jc):



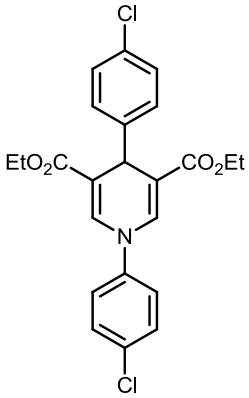
Yield = 66% (25 mg); yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2H), 6.86 (d, 3H), 6.74 (d, 3H), 3.80 (d, 6H), 4.85 (s, 1H), 4.51 (s, 2H), 4.15-4.03 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 6H); ESI-MS (m/z): [M+1] 497.3; FT-IR: 1698, 2850, 2928, 3073; and purity in HPLC = 98%.

Diethyl 4-(4-chlorophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1.14ah):



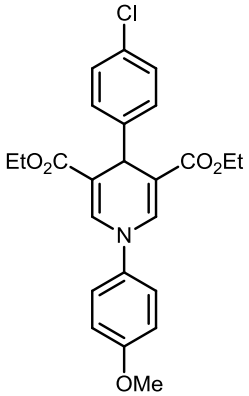
Yield = 84% (87 mg); yellowish semi solid; R_f = 0.67 (25% of EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.43 (m, 2H), 7.35-7.27 (m, 7H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.95 (s, 1H), 4.11 (m, 4H), 1.20 (t, *J* = 7.2 Hz, 6H); ESI-MS (m/z): [M+1] 412.8; FT-IR: 1692, 2976; and purity in HPLC = 99%.

Diethyl 1,4-bis(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14ai):



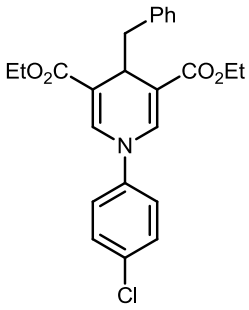
Yield = 76% (87 mg); yellowish semi solid; R_f = 0.59 (25% of EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2H), 7.25 (m, 6H), 7.59 (s, 2H), 4.94 (s, 1H), 4.11 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 447.3; FT-IR: 1697, 2949; and purity in HPLC = 97%.

Diethyl 4-(4-chlorophenyl)-1-(4-methoxyphenyl)-1,4-dihyropyridine-3,5-dicarboxylate (1.14aj):



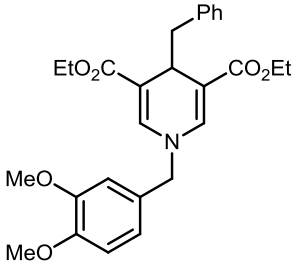
Yield = 84% (94 mg); yellow solid; Mp: 131-133 ^{o}C; R_f = 0.54 (10% of EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 2H), 7.31 (d, 2H), 7.23 (m, 4H), 7.02-6.93 (m, 2H), 4.94 (s, 1H), 3.85 (s, 3H), 4.10 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 442.9; FT-IR: 1698, 2980; and purity in HPLC = 97%.

Diethyl 4-benzyl-1-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14ki):



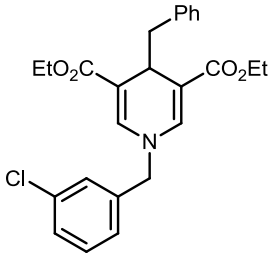
Yield = 73% (39 mg); yellowish gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-7.48 (m, 6H), 6.87-7.05 (m, 5H), 4.17 (m, 4H), 3.96 (dd, 1H), 2.5 (d, 2H), 1.27 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 426.9; FT-IR: 1698, 2982; and purity in HPLC = 94%.

Diethyl 4-benzyl-1-(3,4-dimethoxybenzyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14kc):



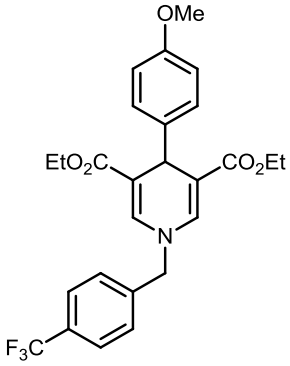
Yield = 73% (43 mg); yellowish gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 6.91-6.69 (m, 5H), 4.43 (s, 2H), 4.17 (m, 4H), 3.96 (dd, 1H), 3.91-3.87 (bs, 6H), 2.50 (d, 2H), 1.27 (m, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 466.54; FT-IR: 1699, 2968; and purity in HPLC = 98%

Diethyl 4-benzy-1-(3-chlorobenzyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14kk):



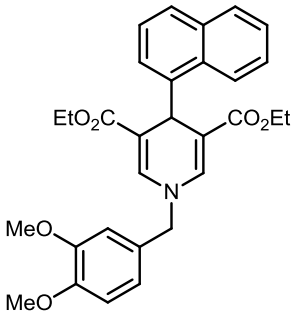
Yield = 70% (39 mg); yellowish gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 10H), 6.96-6.68 (m, 1H), 4.47 (s, 2H), 4.23-4.17 (m, 4H), 3.97 (dd, 1H), 2.53 (d, 2H), 1.20 (m, 6H); ESI-MS (m/z): [M+1] 440.8; FT-IR: 1694, 2925; and purity in HPLC = 96%.

Diethyl-4-(4-methoxyphenyl)-1-(4-(trifluoromethyl)benzyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14el):



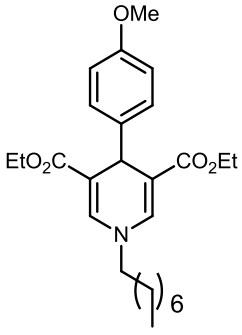
Yield = 73% (27 mg); yellow solid; Mp: 140-142 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68(d, 2H), 7.41 (d, 2H), 7.22 (S, 2H), 7.17 (d, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 4.86 (s, 1H), 4.66 (s, 2H), 4.09 (m, 4H), 3.76 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 490.18; FT-IR: 1682, 2941, 2987, 3071; and purity in HPLC = 97%.

Diethyl-1-(3,4-dimethoxybenzyl)-4-(naphthalen-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14lc):



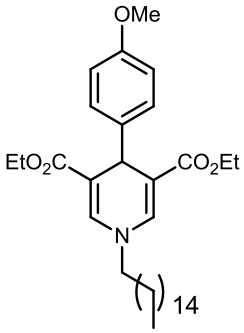
Yield = 63% (65 mg); yellow solid; Mp: 147-153 ^{o}C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.66 (dd, 1H), 7.55-7.28 (m, 6H), 6.91 (d, *J* = 5.8 Hz, 2H), 6.82 (d, 1H), 5.71 (s, 1H), 4.56 (s, 2H), 3.89 (m, 10H), 0.97-0.75 (m, 6H); ESI-MS (m/z): [M+1] 502.1; and purity in HPLC = 99%.

Diethyl-4-(4-methoxyphenyl)-1-octyl-1,4-dihydropyridine-3,5-dicarboxylate (1.14em):



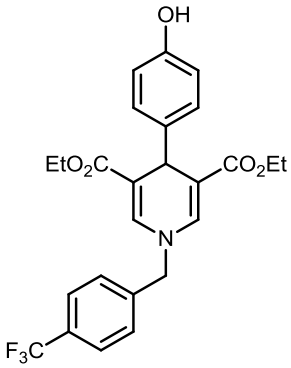
Yield = 91% (31 mg); yellowish gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.17 (m, 4H), 6.77 (d, 2H), 4.10-4.02 (m, 4H), 4.82 (s, 1H), 3.76 (s, 3H), 3.38 (t, *J* = 7.1 Hz, 2H), 0.89 (t, 6H), 1.2-1.3 (m, 22H) 0.9 (t, 3H); ESI-MS (m/z): [M+1] 442.2; FT-IR: 1702, 2854, 2924; and purity in HPLC = 99%.

Diethyl-1-hexadecyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14en):



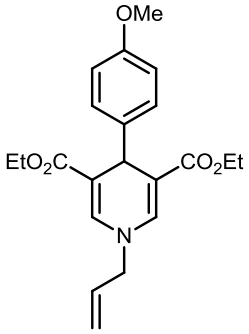
Yield = 88% (35 mg); yellowish gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.15 (m, 4H), 6.77 (d, Hz, 2H), 4.82 (s, 1H), 4.08 (m, 4H) 3.76 (s, 3H), 3.38 (t, *J* = 7.1 Hz, 2H), 0.88 (t, *J* = 6.8 Hz, 3H), 1.2-1.3 (m, 38H), 0.89 (t, 3H); ESI-MS (m/z): [M+1] 554.4; FT-IR: 1702, 2853, 2924; and purity in HPLC = 96%.

Diethyl-4-(4-hydroxyphenyl)-1-(4-(trifluoromethyl)benzyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14fi):



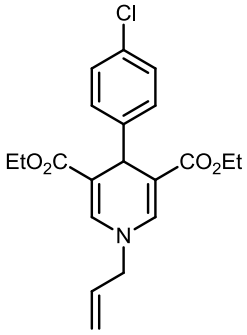
Yield = 72% (26 mg); yellow solid; Mp: 155-157 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 2H), 7.40 (d, 2H), 7.22 (s, 2H) 7.12 (d, 2H), 6.66 (d, 2H), 4.84 (s, 1H), 4.64 (s, 2H), 4.07 (m, 4H), 1.18 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 476.2; FT-IR: 1679, 2920, 2982, 3304; and purity in HPLC = 94%.

Diethyl-1-allyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14fo):



Yield = 76% (21 mg); yellow solid; Mp: 82-84 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, 2H), 7.17 (s, 2H), 6.77 (d, 2H), 6.02-5.77 (m, 1H), 5.3 (m, 2H) 4.83 (s, 1H), 3.75 (s, 3H), 4.00 (d, *J* = 5.5 Hz, 2H), 4.08 (m, 4H), 1.22-1.16 (t, 6H); ESI-MS (m/z): [M+1] 372.2; FT-IR: 1691, 2844, 2926, 2986; and purity in HPLC = 98%.

Diethyl-1-allyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.14ao):



Yield = 78% (22 mg); yellow solid; Mp: 112-114 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.10 (m, 6H), 6.01-5.78 (m, 1H), 5.33 (m, 2H), 4.87 (s, 1H), 4.08 (m, 4H), 4.00 (d, 2H), 1.18 (t, *J* = 7.1 Hz, 6H); ESI-MS (m/z): [M+1] 376.1; FT-IR: 1694, 2855, 2923, 2984; and purity in HPLC = 98%.

X-Ray crystal data: X-ray data of compound **1.14eg** were collected at RT using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames and unit cell dimensions were determined using 5214 reflections for AN22 and 4990 reflections for AM99. Integration and scaling of intensity data were accomplished using the SAINT program.[34] Chemical structures were solved by direct methods using SHELXS972 and refinement was carried out by full-matrix least-squares technique using SHELXL97.[35] Anisotropic displacement parameters were included for all non-hydrogen atoms and for all H atoms positioned geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with $U_{iso}(H) = 1.2U_{eq}$ (C) or $1.5U_{eq}$ for Me atoms.

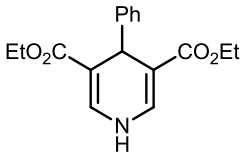
Crystal data for **1.14eg**: $C_{26}H_{27}NO_7$, M = 465.49, colorless block, 0.18 x 0.15 x 0.07 mm^3, triclinic, space group $P\bar{1}$ (No. 2), *a* = 9.5204 (9), *b* = 10.2615 (10), *c* = 13.6412 (13) Å, α = 111.685 (2), β = 97.404 (2),γ = 103.342 (2)°, *V* = 1170.64 (19) $Å^3$, *Z* = 2, D_c = 1.321 g/cm^3, F_{000} = 492, CCD area detector, MoK α radiation, λ = 0.71073 Å, *T* = 294(2)K, $2\theta_{max}$ = 50.0º, 11385 reflections collected, 4124 unique (R_{int} = 0.0217). Final *GooF* = 1.022, *R1* = 0.0407, *wR2* = 0.1114, *R* indices based on 3444 reflections with I > 2σ (I) (refinement on F^2), 310 parameters, μ = 0.096 mm^{-1}. CCDC 882211 data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/ retrieving.html.

Pharmacology cells and reagents: Sf9 cells were obtained from ATCC (Washington D. C., USA) and was routinely maintained in Grace's supplemented medium (Invitrogen) with 10% FBS. RAW 264.7 cells (murine macrophage cell line) were

obtained from ATCC and routinely cultured in RPMI 1640 media with 10% fetal bovine serum (Invitrogen Inc.) and cAMP was purchased from SISCO Research Laboratories (Mumbai, India). PDE light HTS cAMP phosphodiesterase assay kit was procured from Lonza (Basel, Switzerland). PDE4B1 cDNA clone was from OriGene Technologies (Rockville, MD, USA). PDE4D2 enzyme was purchased from BPS Bioscience (San Diego, CA, USA). Lipopolysaccharide (LPS; *Escherichia coli* strain 0127:B8) was obtained from Sigma (St. Louis, MO, USA). Mouse TNF-α ELISA kit was procured from R&D Systems (Minneapolis, USA).

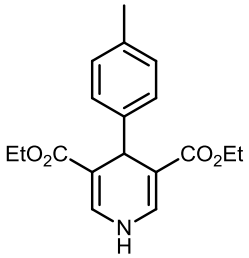
General procedure: Ethyl propiolate (45 mg, 0.46 mmol), benzaldehyde (24.38 mg, 0.23 mmol), and propargylamine (16.4 mg, 0.3 mmol) were dissolved in AcOH and placed in a preheated oil bath at 100 ^{o}C. Then the reaction mixture was poured into ice, from which the product was extracted and purified by flash column chromatography.

Diethyl 4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1.19a):



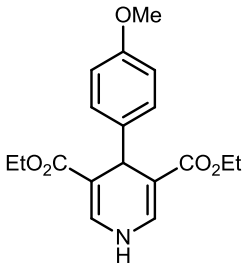
Yield = 76% (41.0 mg); yellow gummy solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 5.8, 3.3 Hz, 4H), 7.24 (s, 2H), 7.17-7.12 (m, 1H), 6.35 (s, 1H), 4.9 (s, 1H), 4.21-4.05 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.02, 146.82, 133.44, 128.51, 128.33, 127.92, 126.38, 108.7, 60.05, 37.58, 14.19; and ESI-MS (m/z): [M+1] 302.5.

Diethyl 4-(p-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19b):



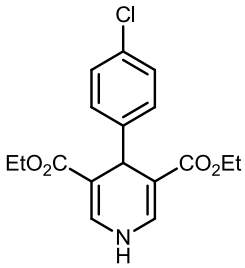
Yield = 78% (44 mg); yellow gummy liquid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.14 (m, 4H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.48 (d, *J* = 4.7 Hz, 1H), 4.85 (s, 1H), 4.07 (m, *J* = 10.8, 7.1 Hz, 4H), 2.28 (m, *J* = 12.3, 9.7 Hz, 3H), 1.22 (t, *J* = 14.2, 5.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 144.09, 135.88, 133.59, 128.69, 128.15, 108.54, 60.04, 37.09, 21.11, 14.23; and ESI-MS (m/z): [M+1] 316.

Diethyl 4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19c):



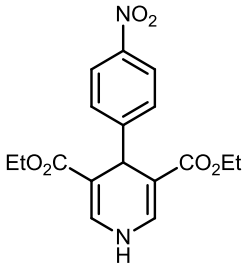
Yield = 81% (48 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, *J* = 11.6, 4.1 Hz, 4H), 6.85-6.69 (m, 2H), 6.57 (t, *J* = 4.8 Hz, 1H), 4.84 (s, 1H), 4.17-4.01 (m, 4H), 3.79-3.72 (m, 3H), 1.19 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 158.04, 139.52, 133.4, 129.27, 113.27, 108.66, 77.36, 77.04, 76.72, 60.03, 55.13, 36.66, 14.23; and ESI-MS (m/z): [M+1] 332.6.

Diethyl 4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19d):



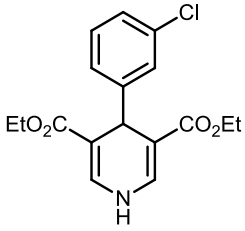
Yield = 87% (52 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, 4H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.58 (s, 1H), 4.88 (s, 1H), 4.12-4.03 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.88, 145.42, 133.68, 132.04, 129.69, 128.04, 108.24, 60.12, 37.18, 1419; and ESI-MS (m/z): [M+1] 336.5.

Diethyl 4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19e):



Yield = 85% (53 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 5.3 Hz, 2H), 7.27 (d, *J* = 6.7 Hz, 2H), 7.2 (t, 2H), 6.31 (s, 1H), 4.88 (s, 1H), 4.14-4.03 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.74, 145.33, 133.47, 132.01, 129.67, 128.01, 108.37, 60.07, 37.13, 14.15; and ESI-MS (m/z): [M+1] 347.1.

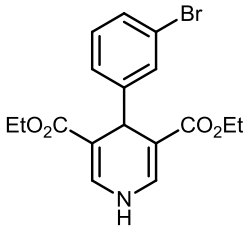
Diethyl 4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19f):



Yield = 78% (47 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 5.33 Hz, 2H), 7.31 (t, *J* = 1.67 Hz, 1H), 7.27 (dd, *J* = 7.46, 1.46 Hz, 1H), 7.22-7.11 (m, 2H), 6.50 (s, 1H), 4.91 (s, 1H), 4.16-4.05 (m, 4H), 1.22 (t, *J* = 7.13 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.77,

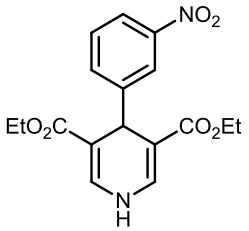
148.73, 133.79, 133.72, 129.04, 128.49, 126.6, 126.56, 108.12, 60.13, 37.52, 14.14; and ESI-MS (m/z): [M+1] 335.9.

Diethyl 4-(3-bromophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19g):



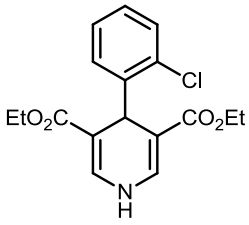
Yield = 83% (57 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, 4H), 7.21 (d, *J* = 8.43 Hz, 2H), 6.58 (s, 1H), 4.88 (s, 1H), 4.12-4.03 (m, 4H), 1.19 (t, *J* = 7.12 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.88, 145.42, 133.68, 132.04, 129.69, 128.04, 108.24, 60.12, 37.18, 14.19; and ESI-MS (m/z): [M+1] 381.4.

Diethyl 4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19h):



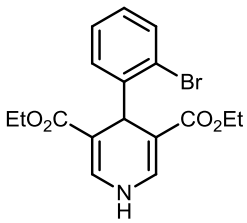
Yield = 79% (49 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 1.89 Hz, 1H), 8.06-7.99 (m, 1H), 7.74 (d, *J* = 7.67 Hz, 1H), 7.42 (dd, *J* = 8.79, 6.68 Hz, 3H), 6.5 (bs, 1H), 5.04 (s, 1H), 4.14-4.0 (m, 4H), 1.19 (t, *J* = 7.13 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.02, 146.82, 133.44, 128.51, 128.33, 127.92, 126.38, 108.7, 60.05, 37.58, 14.19; and ESI-MS (m/z): [M+1] 347.8.

Diethyl 4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19i):



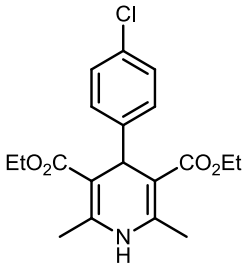
Yield = 68% (41 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.74, 1.60 Hz, 1H), 7.33 (d, *J* = 5.33 Hz, 2H), 7.25 (dd, *J* = 4.94, 2.98 Hz, 1H), 7.18-7.13 (m, 1H), 7.06 (m, *J* = 7.87, 1.68 Hz, 1H), 6.4 (s, 1H), 5.36 (s, 1H), 4.05 (m, *J* = 14.25, 8.98, 5.38 Hz, 4H), 1.16 (t, *J* = 7.13 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.94, 144.75, 133.97, 132.78, 131.57, 129.07, 127.45, 126.73, 108.5, 60.09, 34.9, 14.13; and ESI-MS (m/z): [M+1] 335.9.

Diethyl 4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.19j):



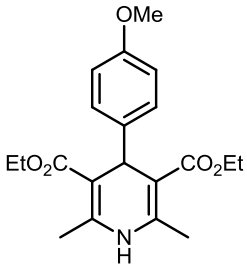
Yield = 71% (49 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.4 Hz, 1H), 7.54 (m, *J* = 7.77, 7.36, 2H), 7.37-7.27 (m, 2H), 7.19-7.14 (m, 1H), 6.08 (dd, *J* = 19.2, 2.67 Hz, 2H), 4.21-4.08 (m, 4H), 1.29 (t, *J* = 7.12 Hz, 3H), 1.21 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.44, 145.77, 140.09, 134.61, 132.95, 129.86, 129.6, 121.75, 111.05, 98.26, 60.31, 59.73, 30.87, 14.48, 14.19; and ESI-MS (m/z): [M+1] 381.4.

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1.19k):



Yield = 61% (40 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, 4H), 5.77 (s, 1H), 4.95 (s, 1H), 4.12-4.04 (m, 4H), 2.31 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.39, 146.28, 143.98, 131.62, 129.35, 127.87, 103.78, 59.76, 39.2, 19.5, 14.21; and ESI-MS (m/z): [M+1] 364.0.

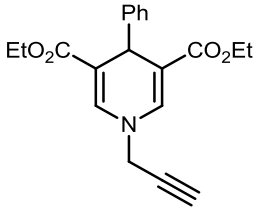
Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1.19l):



Yield = 58% (37 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.65 Hz, 2H), 6.74 (d, *J* = 8.66 Hz, 2H), 5.87 (s, 1H), 4.92 (s, 1H), 4.08 (dq, *J* = 7.07, 3.56 Hz, 4H), 3.75 (d, *J* = 6.33 Hz, 3H), 2.29 (s, 6H), 1.22 (t, *J* = 7.11 Hz, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.71, 157.8, 143.7, 140.33, 128.88, 113.12, 104.19, 59.83, 55.07, 38.68, 29.63, 19.4, 14.22; and ESI-MS (m/z): [M+1] 360.3.

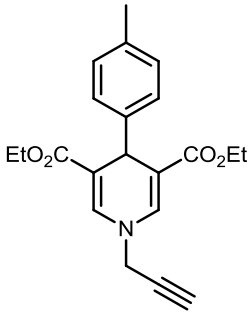
General procedure: Ethyl propiolate (45 mg, 0.46 mmol), benzaldehyde (24.38 mg, 0.23 mmol), propargylamine (16.4 mg, 0.3 mmol) and amberlyst-15R (20 mg) were dissolved in EtOH and placed in a preheated oil bath at reflux temperature, from which the product was extracted and purified by flash column chromatography.

Diethyl 4-phenyl-1-(prop-2-yn-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20a):



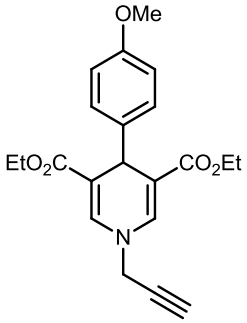
Yield = 79% (48 mg); pale yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 7.17 (m, 2H), 4.88 (s, 1H), 4.19 (t, *J* = 3.8 Hz, 2H), 4.16-4.02 (m, 4H), 2.51 (t, *J* = 2.5 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.66, 146.2, 136.47, 128.32, 127.95, 126.46, 109.93, 75.04, 60.16, 43.66, 37.39, 14.19; and ESI-MS (m/z): [M+1] 340.5.

Diethyl 1-(prop-2-yn-1-yl)-4-(p-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20b):



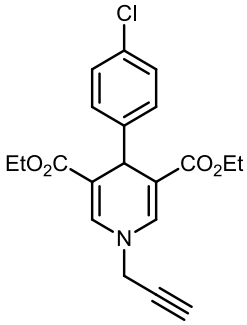
Yield = 75% (24 mg); white solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H), 7.24-7.17 (m, 2H), 7.06 (t, *J* = 8.3 Hz, 2H), 4.84 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 4.14-4.03 (m, 4H), 2.49 (dd, *J* = 6.92, 4.42 Hz, 1H), 2.28 (s, 3H), 1.2 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.69, 143.38, 136.37, 135.94, 128.69, 128.14, 110.03, 74.98, 60.13, 43.64, 36.88, 21.11, 14.22; and ESI-MS (m/z): [M+1] 354.5.

Diethyl 4-(4-methoxyphenyl)-1-(prop-2-yn-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20c):



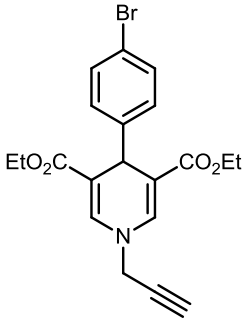
Yield = 71% (47 mg); white solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 4H), 6.86-6.72 (m, 2H), 5.07 Hz, 1H), 4.83 (s, 1H), 4.19 (d, *J* = 2.5 Hz, 2H), 4.09 (m, 10.8, 7.1, 3.7 Hz, 4H), 3.77 (s, 3H), 2.51 (dd, *J* = 7.5, 1.22 (m, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.72, 158.1, 138.82, 136.22, 129.59, 129.28, 113.29, 110.1, 75, 60.13, 55.14, 43.66, 36.47, 14.23; and ESI-MS (m/z): [M+1] 370.3.

Diethyl 4-(4-chlorophenyl)-1-(prop-2-yn-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20d):



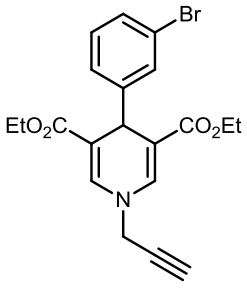
Yield = 90% (30 mg); pale yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2H), 7.2 (dd, 4H), 4.87 (s, 1H), 4.19 (d, *J* = 2.5 Hz, 2H), 4.09 (m, *J* = 7.1, 5.7, 2.8 Hz, 4H), 2.52 (t, *J* = 2.5 Hz, 1H), 1.2 (m, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.43, 144.77, 136.55, 129.69, 128.08, 127.94, 109.62, 75.14, 60.23, 43.69, 36.98, 29.67, 14.18; and ESI-MS (m/z): [M+1] 375.4.

Diethyl 4-(4-bromophenyl)-1-(prop-2-yn-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20e):



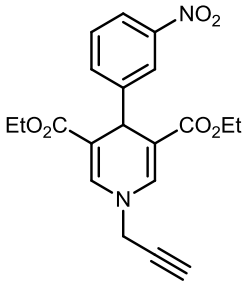
Yield = 87% (33 mg); pale yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.27 (s, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.85 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 4.11-4.04 (m, 4H), 2.51 (t, *J* = 2.4 Hz, 1H), 1.21-1.13 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.69, 148.08, 147.11, 145.28, 127.02, 125.52, 123.66, 120.33, 85.73, 72.48, 56.49, 44.96, 31.51, 14.06; and ESI-MS (m/z): [M+1] 419.3.

Diethyl 4-(3-bromophenyl)-1-(prop-2-yn-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20f):



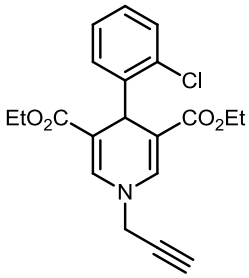
Yield = 87% (33 mg); pale yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2H), 7.2 (m, 4H), 4.87 (s, 1H), 4.19 (d, *J* = 2.5 Hz, 2H), 4.09 (m, *J* = 7.1, 5.7, 2.8 Hz, 4H), 2.52 (t, *J* = 2.5 Hz, 1H), 1.2 (t, *J* = 7.13 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.43, 144.77, 136.55, 129.69, 128.08, 127.94, 109.62, 75.14, 60.23, 43.69, 36.98, 29.67, 14.18; and ESI-MS (m/z): [M+1] 419.3.

Diethyl 4-(3-nitrophenyl)-1-(prop-2-yn-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20g):



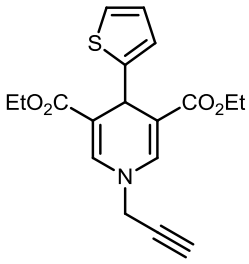
Yield = 83% (26 mg); yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 7.17 (m, 2H), 4.88 (s, 1H), 4.16-4.02 (m, 4H), 4.19 (t, *J* = 3.8 Hz, 2H), 2.51 (t, *J* = 2.5 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.66, 148.2, 136.47, 128.32, 127.95, 126.46, 109.93, 75.04, 60.16, 43.66, 37.39, 14.19; and ESI-MS (m/z): [M+1] 385.1.

Diethyl 4-(2-bromophenyl)-1-(prop-2-yn-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20h):



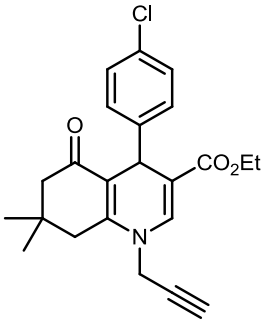
Yield = 79% (53 mg); pale yellow solid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 4H), 7.16 (s, 1H), 7.06 (s, 1H), 5.34 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 4.12-4.02 (m, 4H), 2.51 (t, *J* = 2.4 Hz, 1H), 1.18 (q, *J* = 7.1, 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.56, 144.11, 137.04, 132.98, 131.51, 129.14, 127.52, 126.73, 109.6, 75.07, 60.19, 43.63, 34.73, 14.12; and ESI-MS (m/z): [M+1] 375.

Diethyl 1-(prop-2-yn-1-yl)-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1.20j):



Yield = 65% (20 mg); brown gummy liquid; R_f = 0.57 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.27 (s, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.85 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 4.11-4.04 (m, 4H), 2.51 (t, *J* = 2.4 Hz, 1H), 1.21-1.13 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.41, 150.21, 136.49, 126.52, 124.18, 123.83, 109.2, 75.15, 60.28, 43.69, 31.91, 14.23; and ESI-MS (m/z): [M+1] [M+1]346.3.

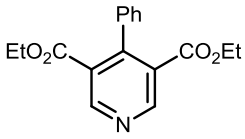
Ethyl 4-(4-chlorophenyl)-6,6-dimethyl-8-oxo-1-(prop-2-yn-1-yl)-1,4,5,6,7,8-hexahydroq-uin-oline-3-carboxylate (1.20k):



Yield = 67% (24 mg); brown solid; R_f = 0.57 (50% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 10.1, 8.6 Hz, 4H), 7.16 (d, *J* = 8.4 Hz, 1H), 4.29 (q, 2H), 4.09 (m, *J* = 6.9, 3.9 Hz, 2H), 2.56-2.50 (m, 3H), 2.19 (q, *J* = 16.1 Hz, 3H), 0.95 (s, 3H), 1.2 (d, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 3.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.53, 166.28, 148.9, 144.41, 138.32, 131.78, 129.46, 128.03, 114.31, 110.76, 74.71, 60.3, 49.89, 40.76, 38.75, 34.9, 32.35, 29.43, 27.21, 14.16; and ESI-MS (m/z): [M+1] [M+1]399.1.

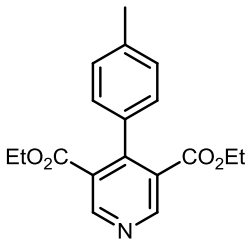
General procedure: Ethyl propiolate (45 mg, 0.46 mmol), benzaldehyde (24.38 mg, 0.23 mmol), and propargylamine (16.4 mg, 0.3 mmol) were dissolved in AcOH and placed in a preheated oil bath at 100 ^{o}C in open air or in presence of oxygen. Then the reaction mixture was poured into ice, from which the product was extracted and purified to afford the title compounds.

Diethyl 4-phenylpyridine-3,5-dicarboxylate (1.21a):



Yield = 76% (82 mg); color less liquid; R_f = 0.74 (20% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 2H), 7.2 (d, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 4H), 1.02 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.07, 152.68, 149.42, 137.14, 134.56, 128.65, 128.11, 109.19, 60.81, 21.47, 13.57; and ESI-MS (m/z): [M+1] 300.1.

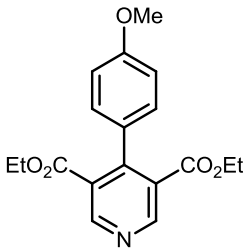
Diethyl 4-(p-tolyl)pyridine-3,5-dicarboxylate (1.21b):



Yield = 71% (40 mg); color less liquid; R_f = 0.75 (20% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 2H), 7.2 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 4H), 2.40 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.05, 151.88, 149.62, 138.11, 133.56, 128.5, 127.61,

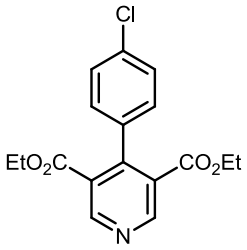
109.19, 61.6, 21.3, 13.61; and ESI-MS (m/z): [M+1] 314.5.

Diethyl 4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (1.21c):



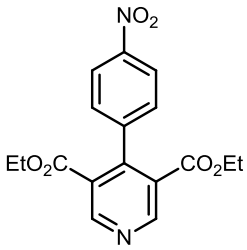
Yield = 67% (40 mg); color less liquid; R_f = 0.62 (20% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 4H), 3.85 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.03, 156.37, 151.77, 141.51, 134.56, 129.13, 113.31, 109.95, 61.58, 55.24, 13.71; and ESI-MS (m/z): [M+1] 330.6.

Diethyl 4-(4-chlorophenyl)pyridine-3,5-dicarboxylate (1.21d):



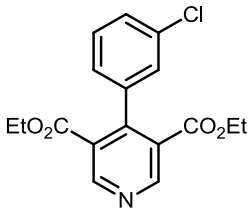
Yield = 81% (49 mg); color less liquid; R_f = 0.79 (20% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 2H), 7.40-7.37 (m, 2H), 7.14 (t, 2H), 4.11 (q, *J* = 7.1 Hz, 4H), 1.05 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.52, 152.46, 135.16, 134.56, 129.14, 127.97, 109.96, 61.72, 13.63; and ESI-MS (m/z): [M+1] 334.5.

Diethyl 4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (1.21e):



Yield = 83% (52 mg); color less liquid; R_f = 0.81 (20% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 4H), 1.04 (t, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.57, 152.54, 148.37, 135.18, 134.34, 129.12, 127.98, 109.34, 61.74, 13.64; and ESI-MS (m/z): [M+1] 345.1.

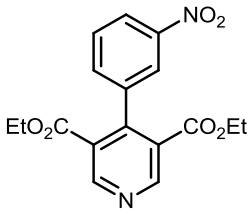
Diethyl 4-(3-chlorophenyl)pyridine-3,5-dicarboxylate (1.21f):



Yield = 79% (47 mg); color less liquid; R_f = 0.83 (20% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 2H), 7.4 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 1.6 Hz, 1H), 7.1-7.06 (m, 1H), 4.12 (t, 4H), 1.03 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.47, 152.66, 147.79, 138.52, 133.72,

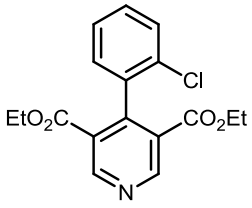
128.96, 128.15, 127.95, 127.75, 126.03, 61.67, 13.59; and ESI-MS (m/z): [M+1] 334.2.

Diethyl 4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (1.21g):



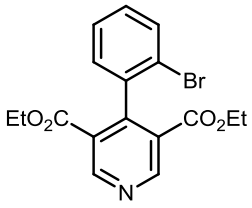
Yield = 84% (52 mg); color less liquid; R_f = 0.67 (20% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27-8.92 (m, 2H), 7.40 (dd, J_1 = 5.1, J_2 =1.9 Hz, 2H), 7.23-7.16 (m, 2H), 4.07 (q, *J* = 7.1 Hz, 4H), 0.97 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.01, 152.15, 149.2, 136.76, 128.13, 127.72, 127.64, 61.52, 13.52; and ESI-MS (m/z): [M+1] 345.4.

Diethyl 4-(2-chlorophenyl)pyridine-3,5-dicarboxylate (1.21h):



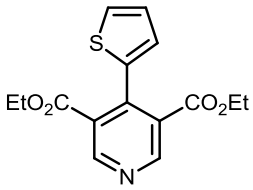
Yield = 63% (38 mg); color less liquid; R_f = 0.7 (25% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.88 (s, 1H), 7.44-7.36 (m, 4H), 4.47 (q, *J* = 7.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.29, 164.32, 160.71, 152.42, 139.19, 132.14, 129.99, 129.82, 129.04, 127.38, 126.77, 125.36, 109.95, 61.81, 61.71, 14.25, 13.56; and ESI-MS (m/z): [M+1] 334.6.

Diethyl 4-(2-bromophenyl)pyridine-3,5-dicarboxylate (1.21i):



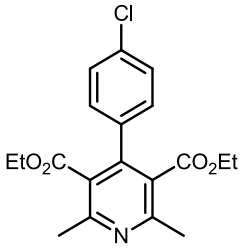
Yield = 69% (47 mg); color less liquid; R_f = 0.68 (25% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.9 (s, 1H), 7.64-7.61 (m, 1H), 7.36 (m, 4H), 4.47 (t, *J* = 5.8 Hz, 2H), 4.2-4.14 (m, 2H), 1.44 (d, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.13, 164.32, 152.41, 139.3, 132.19, 129.84, 129.78, 127.25, 126.11, 125.43, 117.4, 111.93, 61.82, 61.71, 14.25, 13.56 and ESI-MS (m/z): [M+1] 379.0.

Diethyl 4-(thiophen-2-yl)pyridine-3,5-dicarboxylate (1.21j):



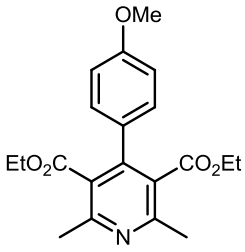
Yield = 57% (31 mg); brown liquid; R_f = 0.5 (30% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 2H), 7.48 (dd, J_1 = 5.1, J_2 = 1.1 Hz, 1H), 7.09 (dd, J = 5.1, 3.5 Hz, 1H), 7.02 (d, J_1 = 3.5, J_2 = 1.1 Hz, 1H), 4.18 (q, J = 7.1 Hz, 4H), 1.12 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.82, 151.77, 141.66, 136.03, 129.39, 127.99, 127.17, 126.82, 61.77, 13.68; and ESI-MS (m/z): [M+1] 306.7.

Diethyl 4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (1.21k):



Yield = 57% (37 mg); color less liquid; R_f = 0.69 (25% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.5 Hz, 2H), 7.22 (t, 2H), 4.06 (q, J = 7.1 Hz, 4H), 2.62 (s, 6H), 1.01 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 155.49, 144.87, 134.82, 134.68, 129.5, 128.27, 126.81, 61.47, 22.79, 13.6; and ESI-MS (m/z): [M+1] 362.9.

Diethyl 4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (1.21l):



Yield = 51% (33 mg); color less liquid; R_f = 0.6 (30% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (q, Hz, 2H), 6.94-6.84 (m, 2H), 4.14-3.99 (m, 4H), 3.84 (s, 3H), 2.60 (s, 6H), 1.01 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.01, 159.74, 155.1, 145.67, 129.36, 128.64, 127.18, 113.5, 61.27, 55.24, 22.8, 13.67; and Mass: ESI (M+1) 358.4.

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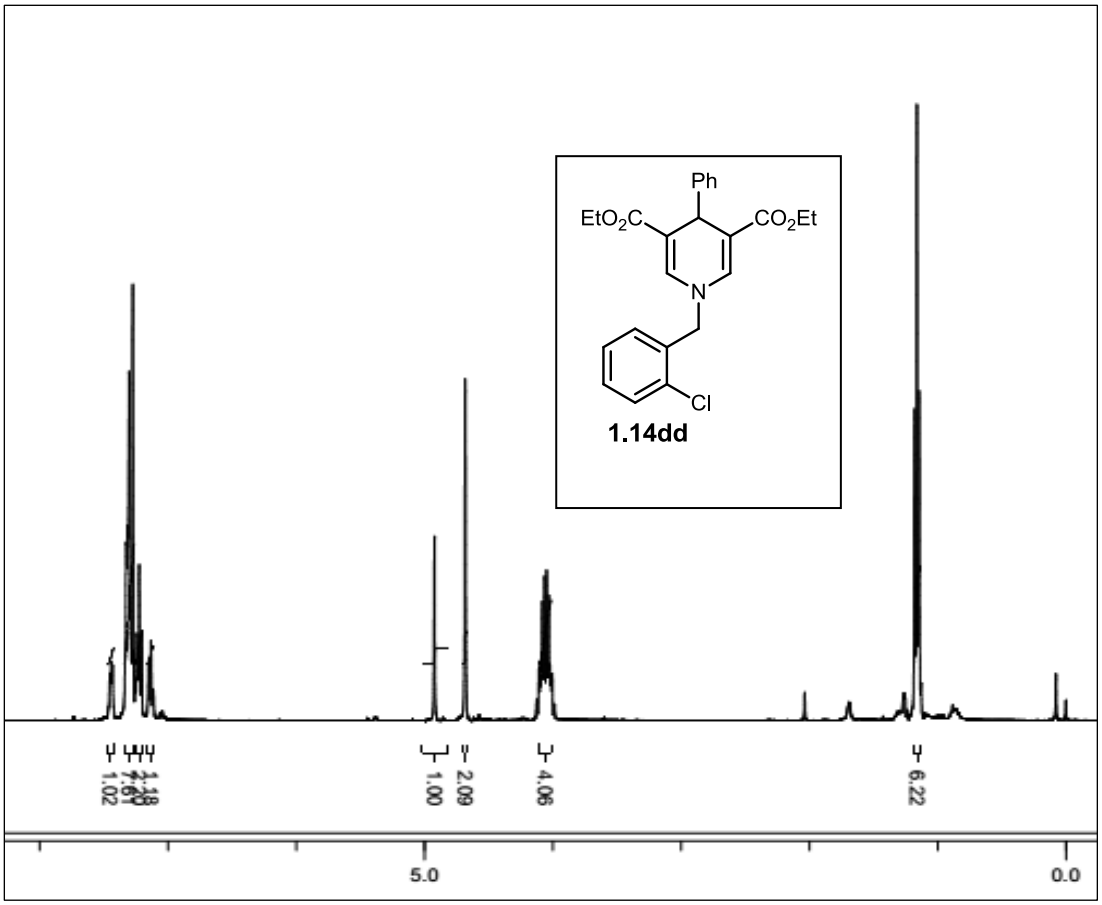
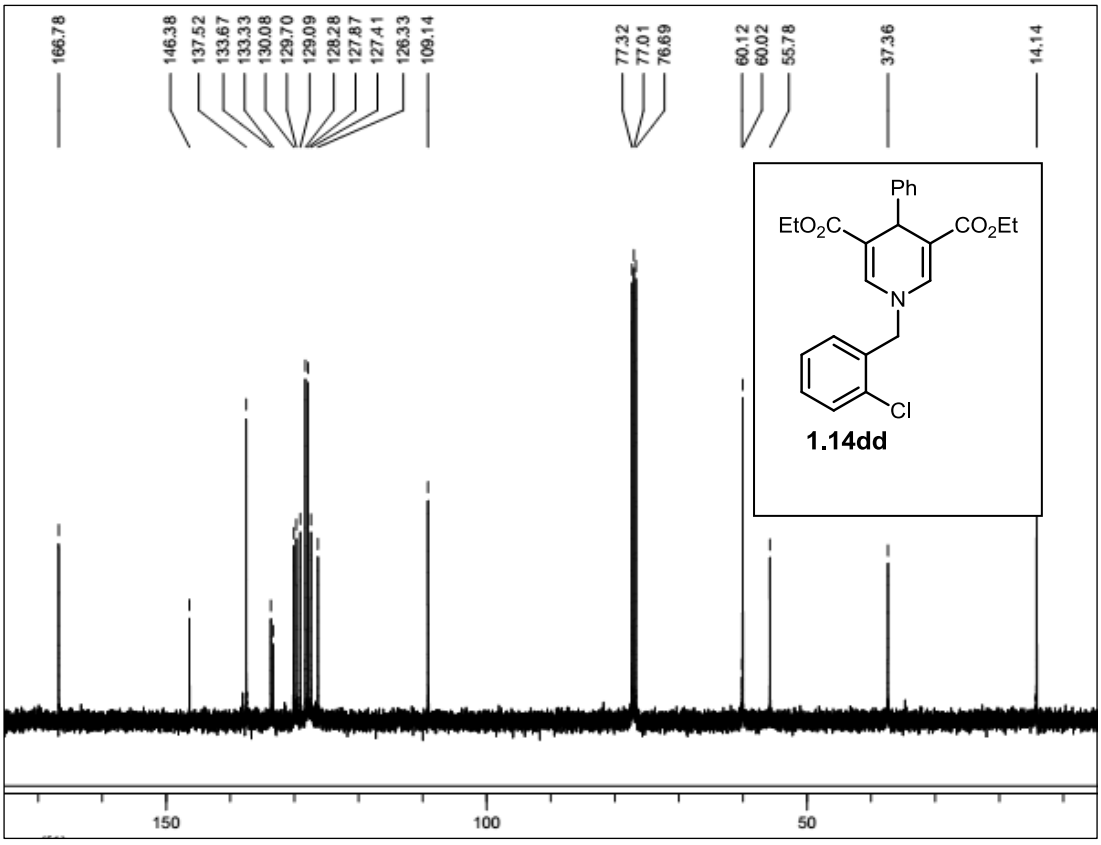
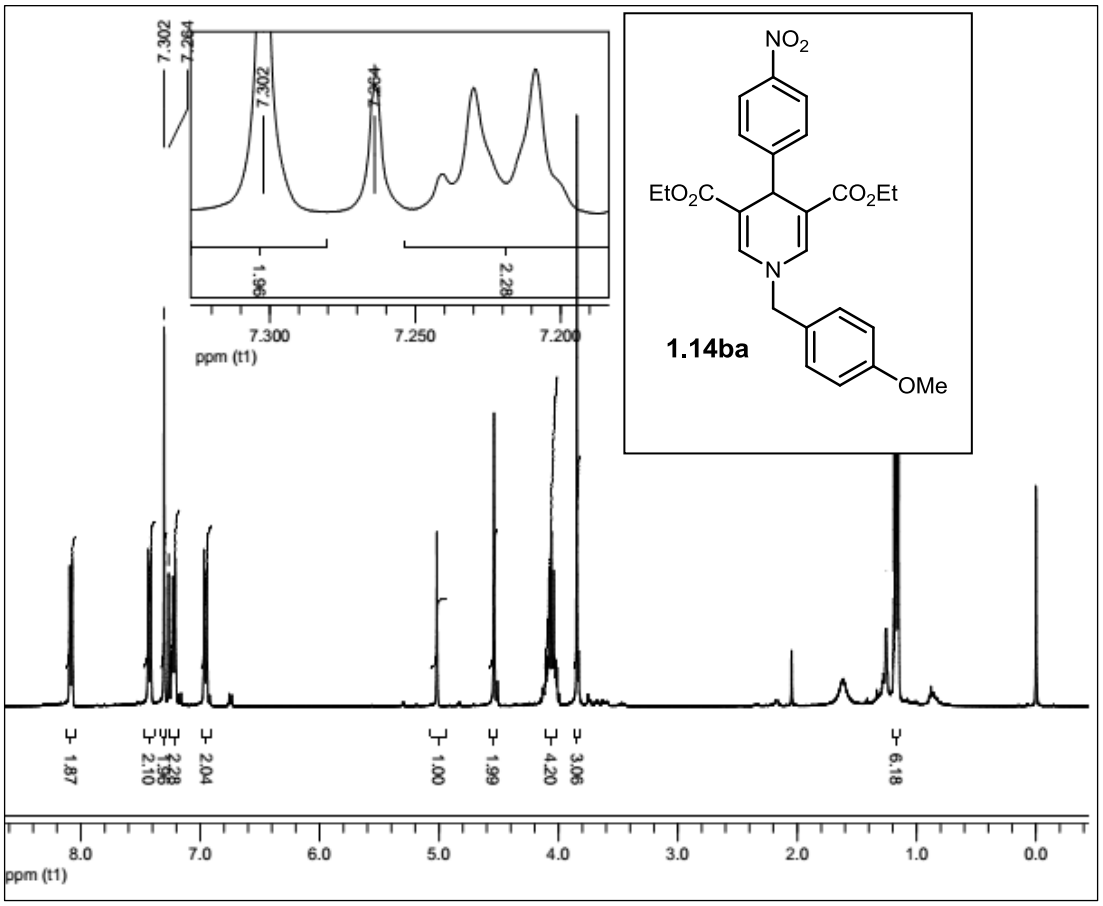
1.7. Appendices:



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1.99
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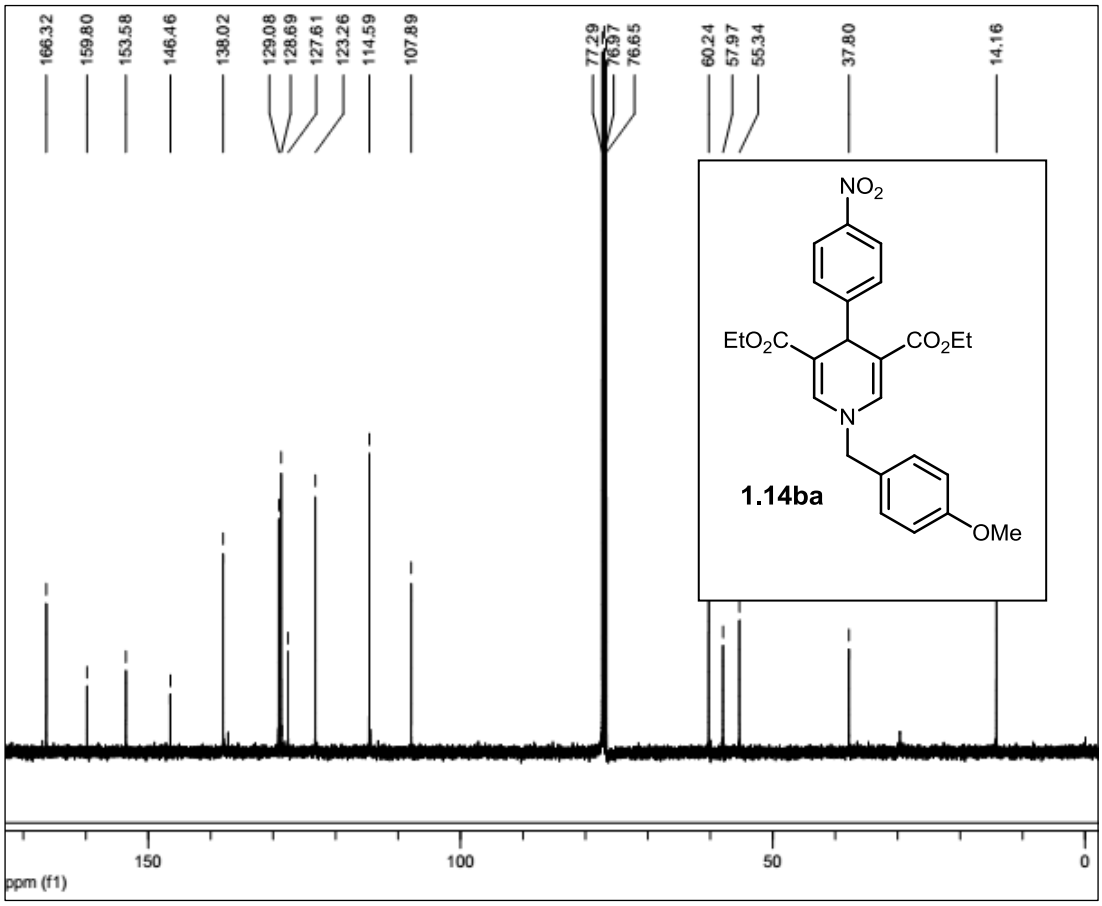
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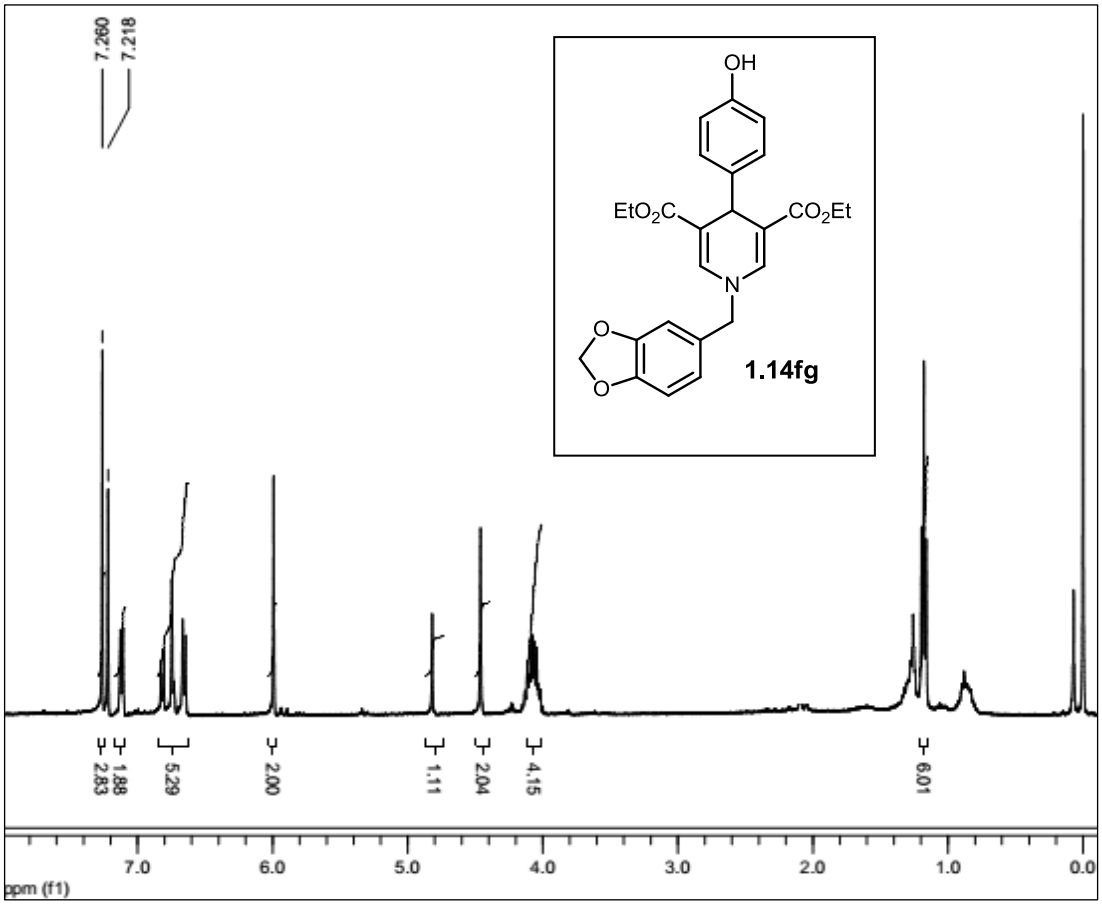
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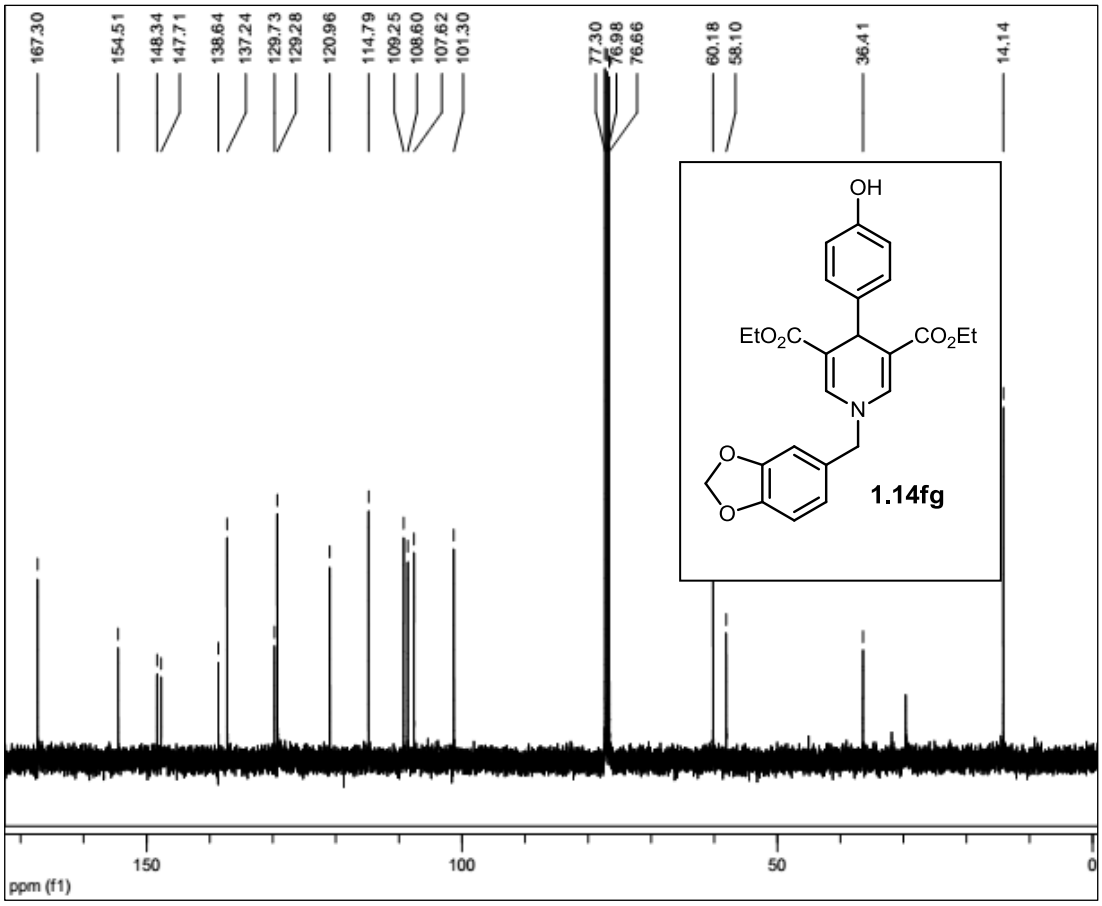
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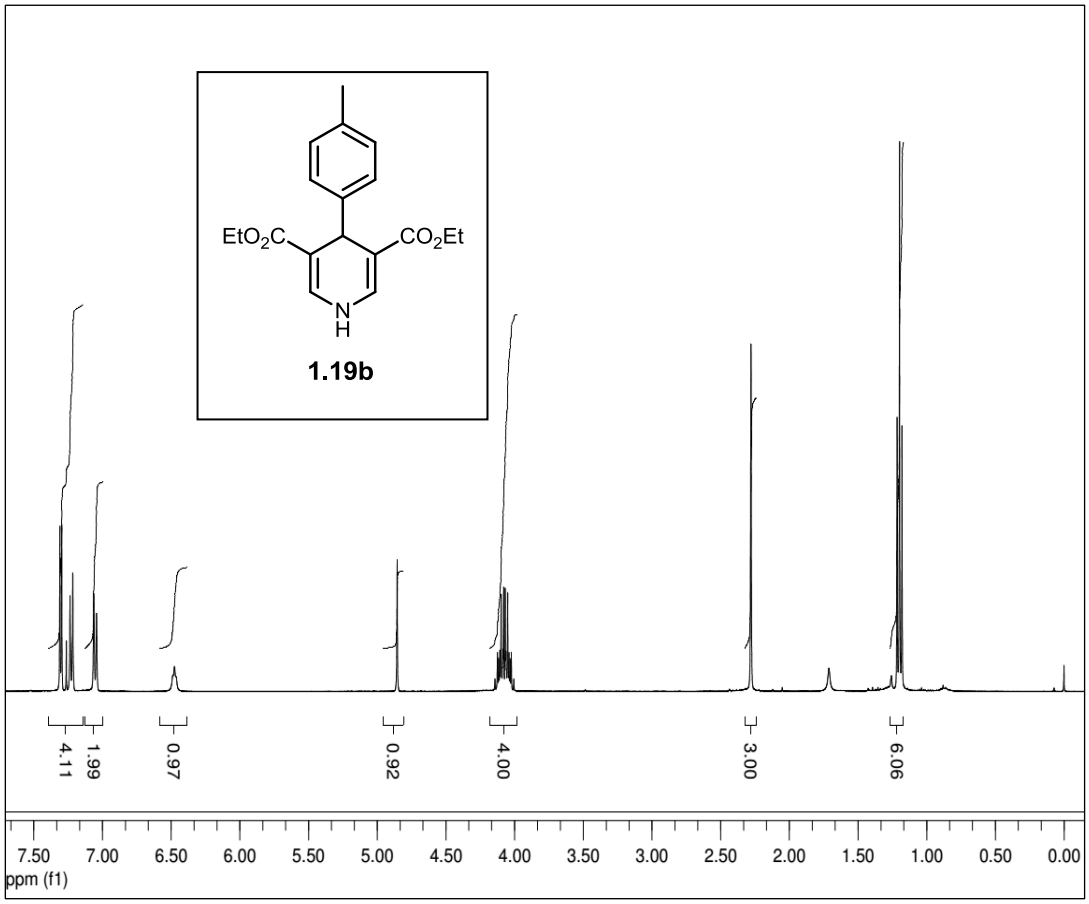
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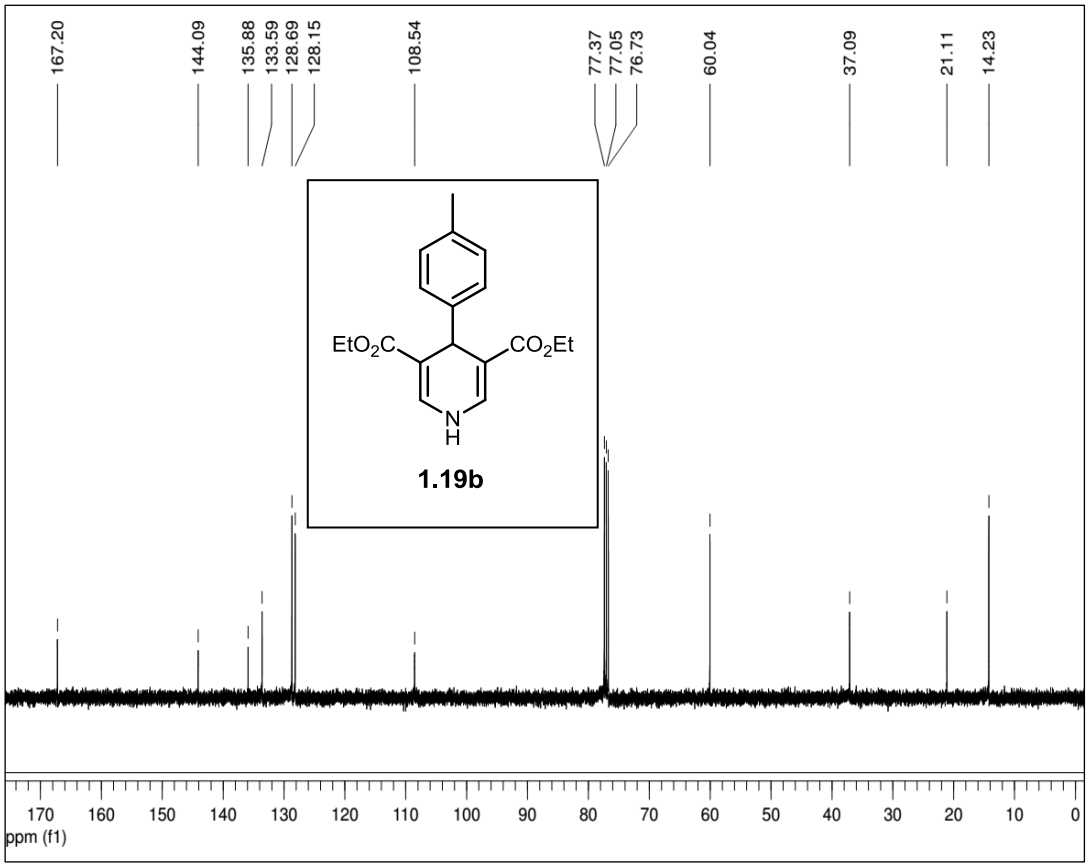
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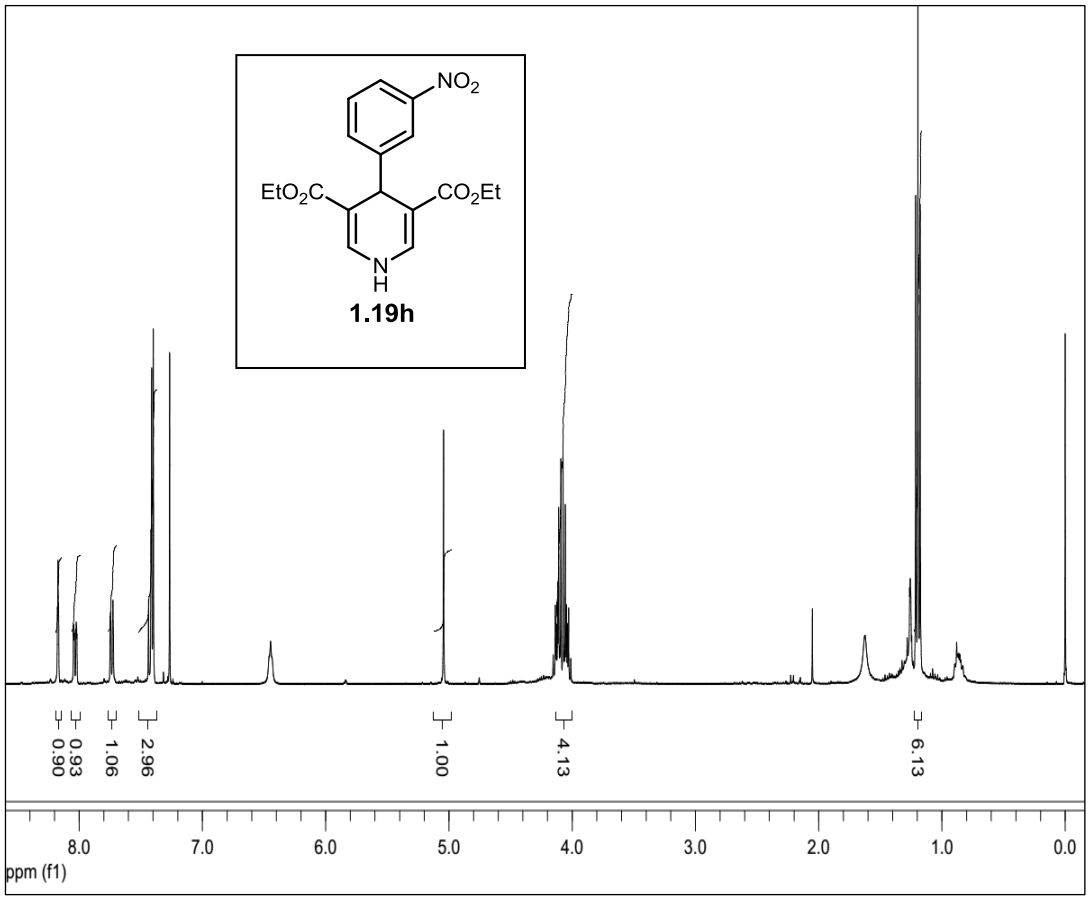
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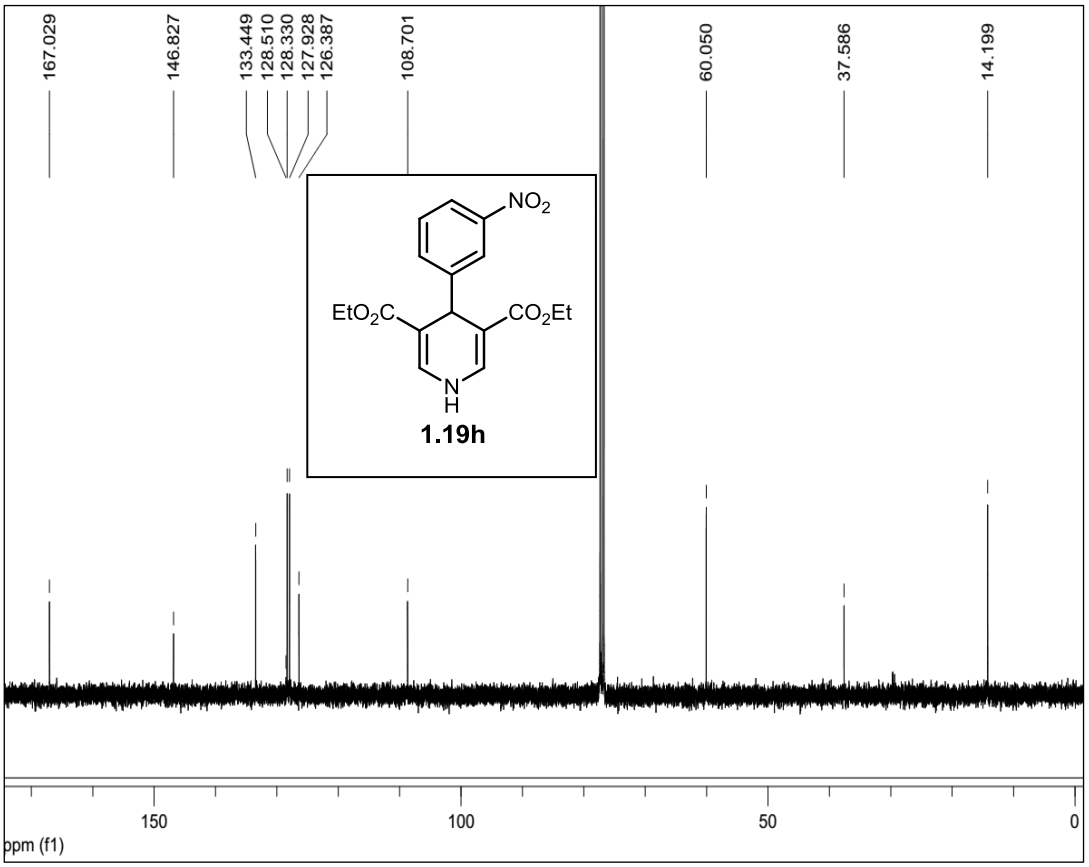
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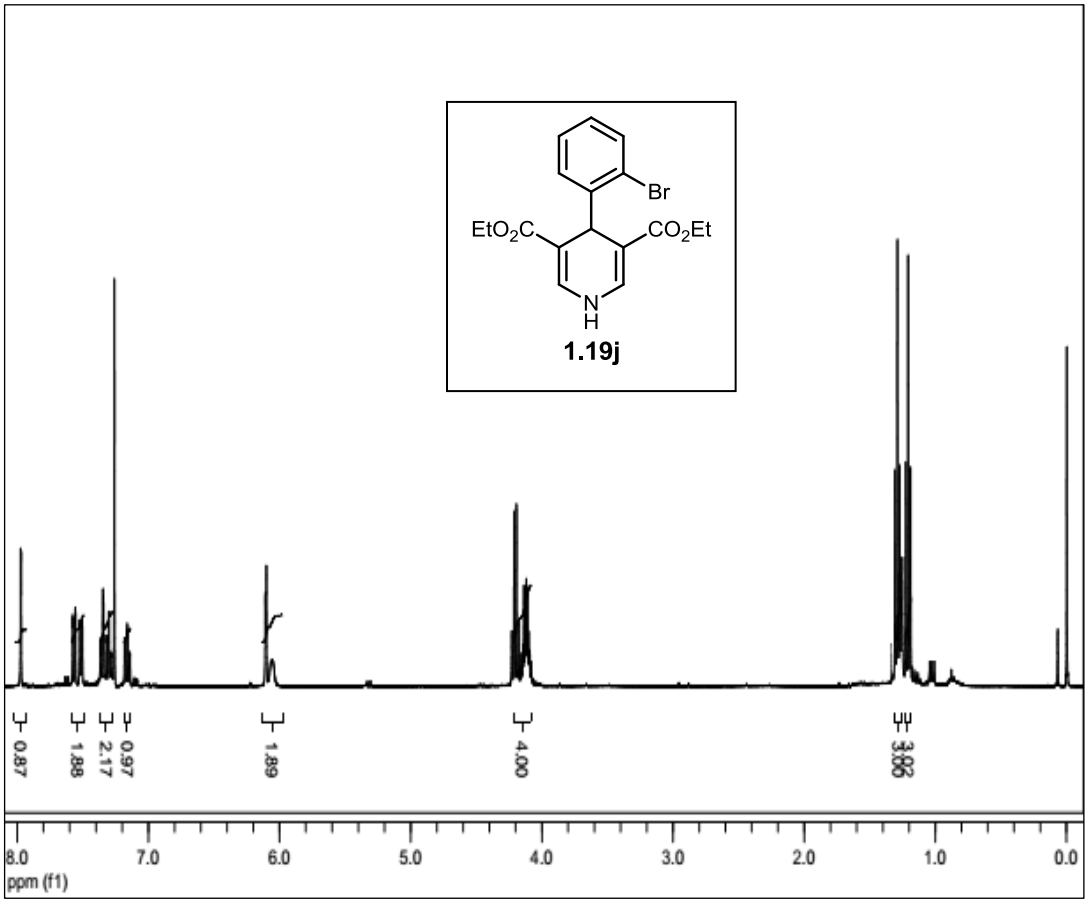
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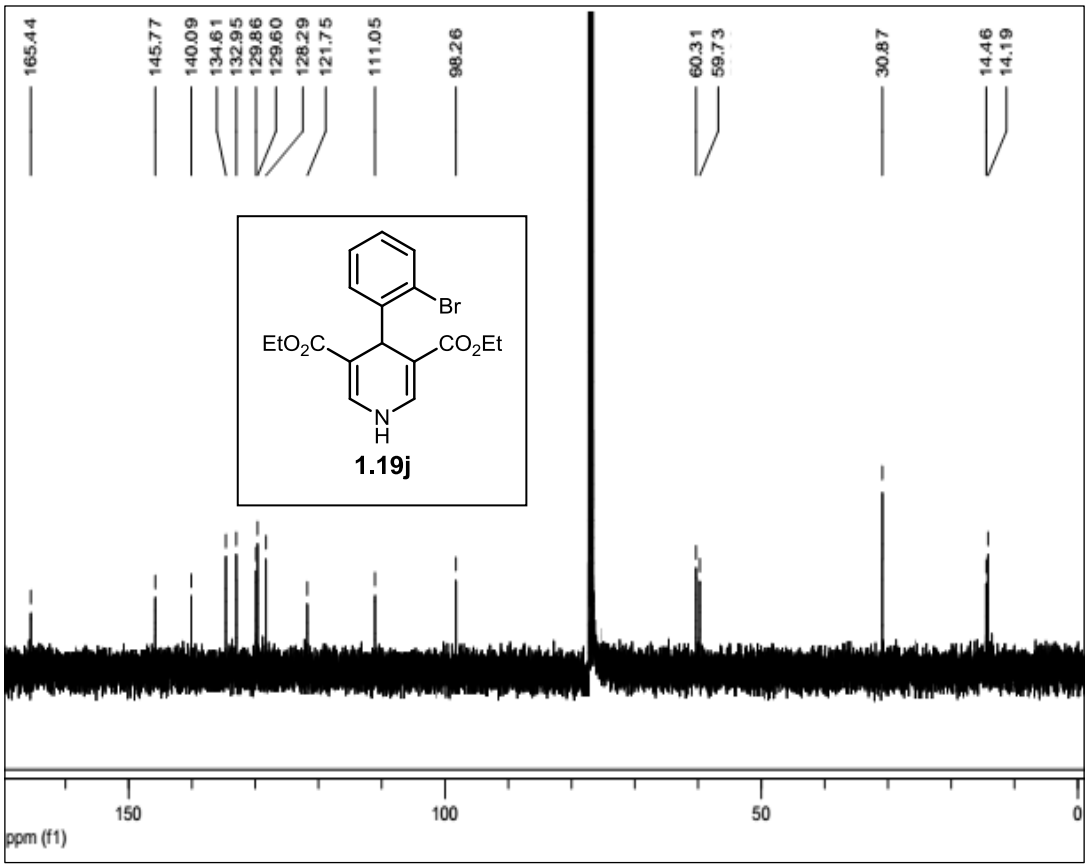
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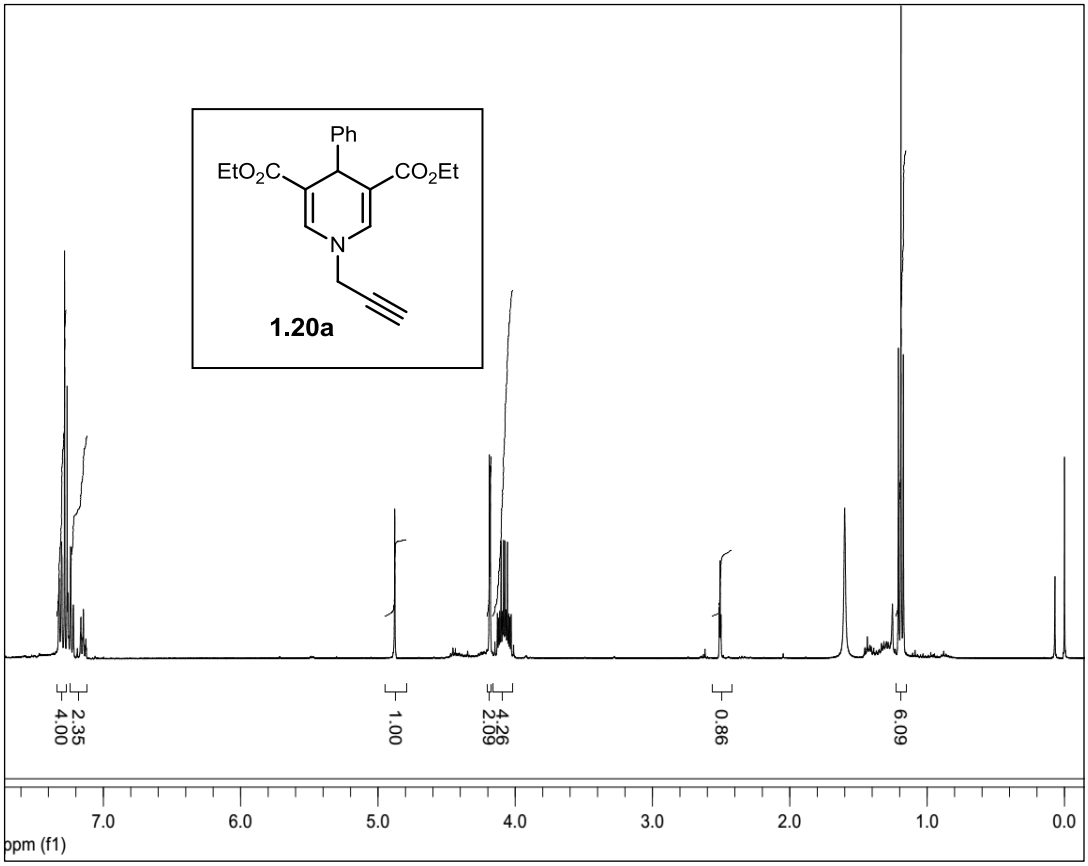
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1.00
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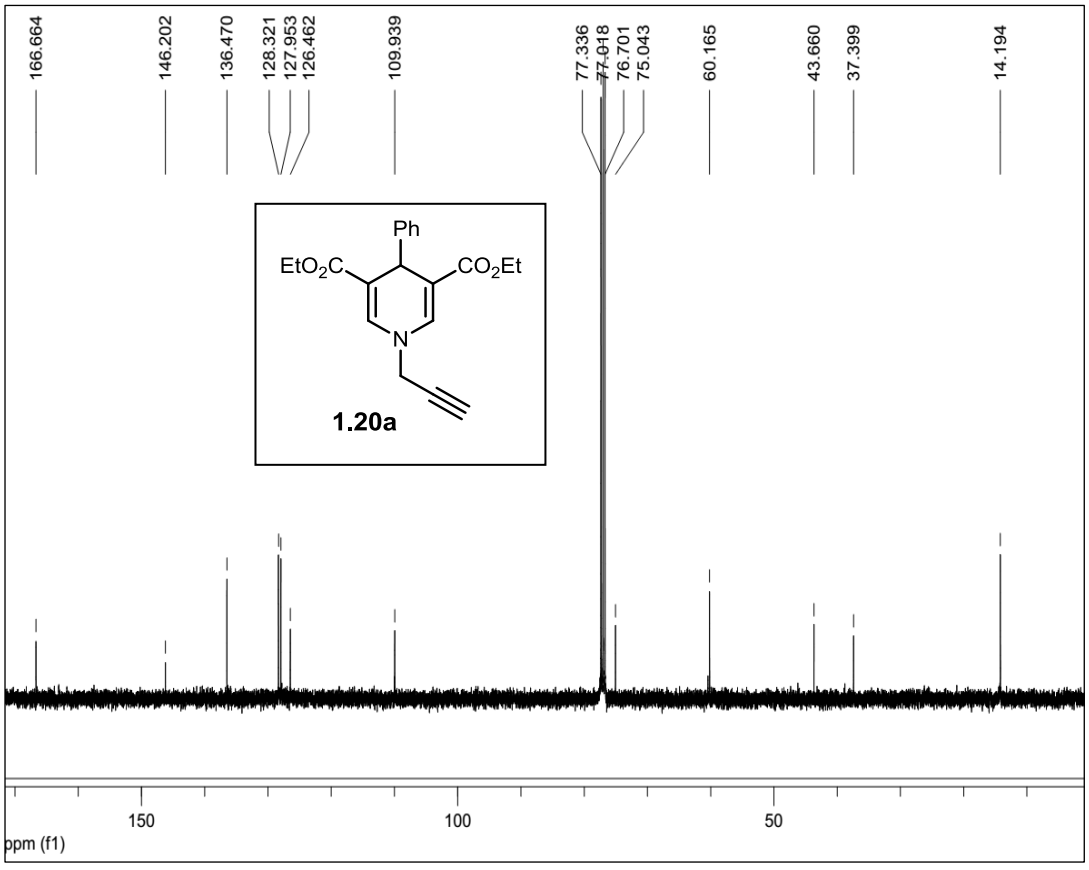
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14.194
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CO2Et
N
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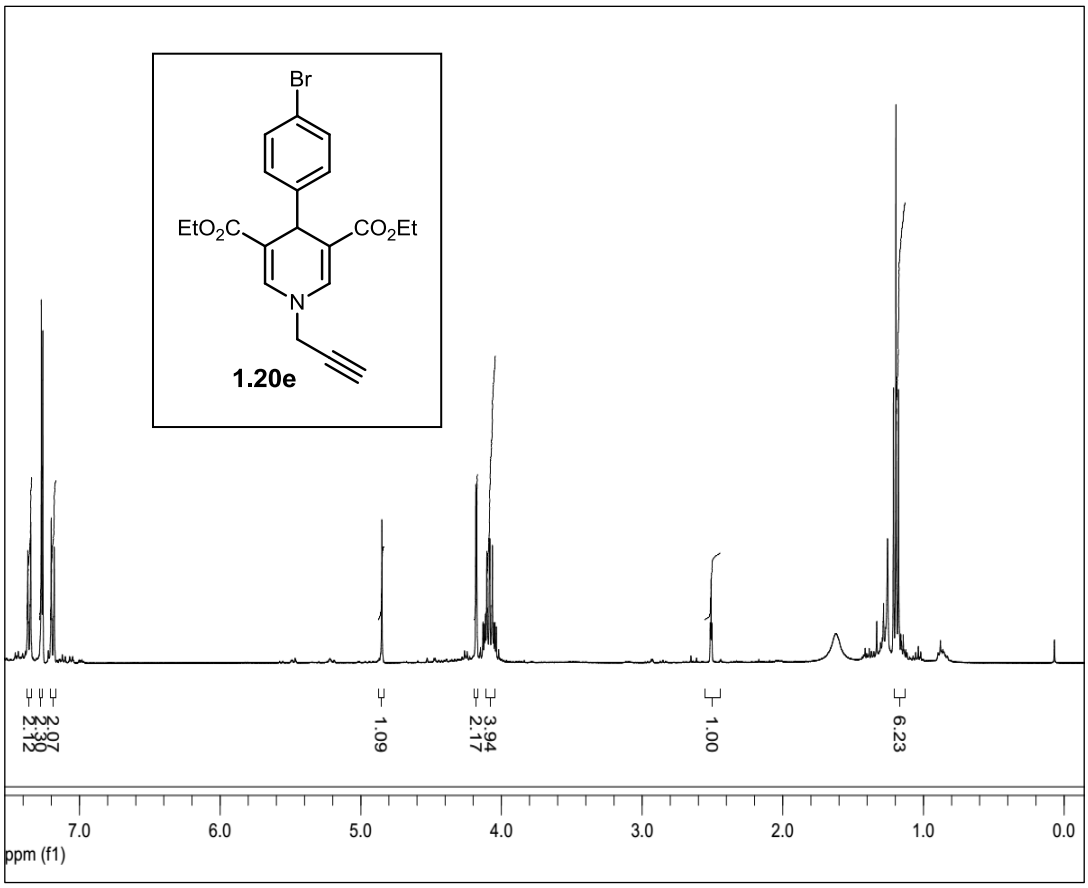
ppm (f1)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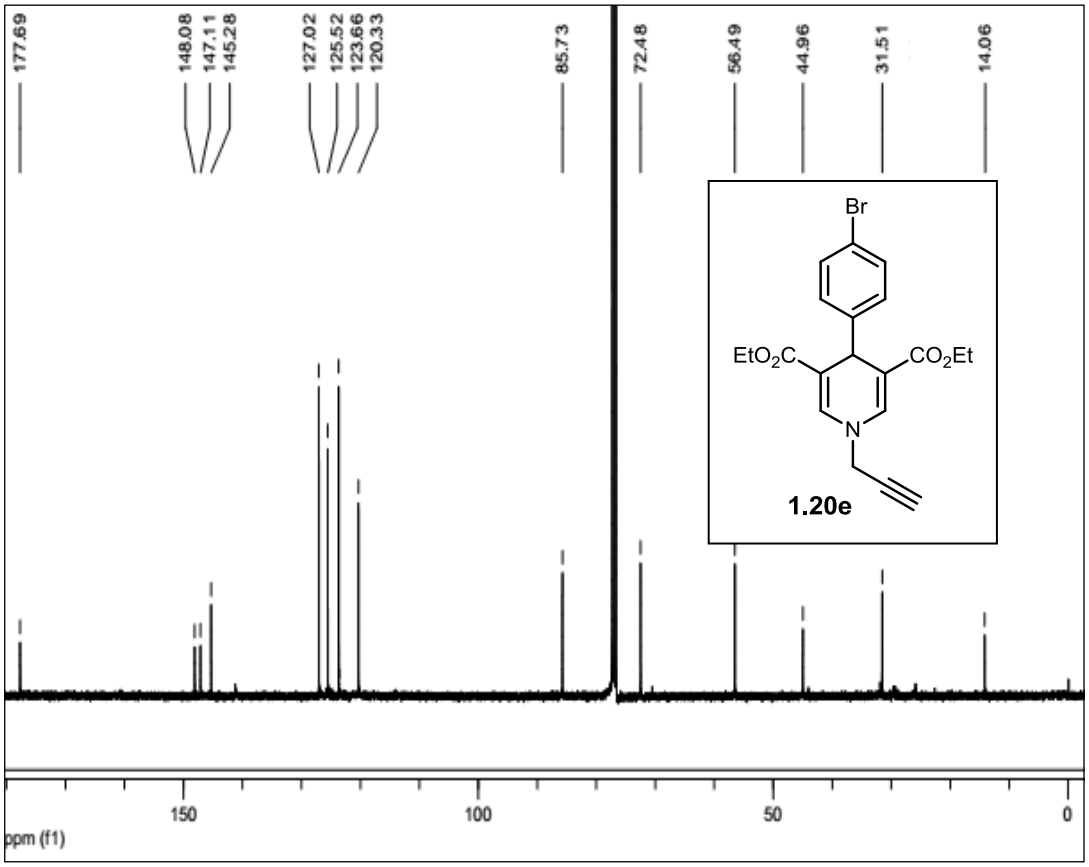
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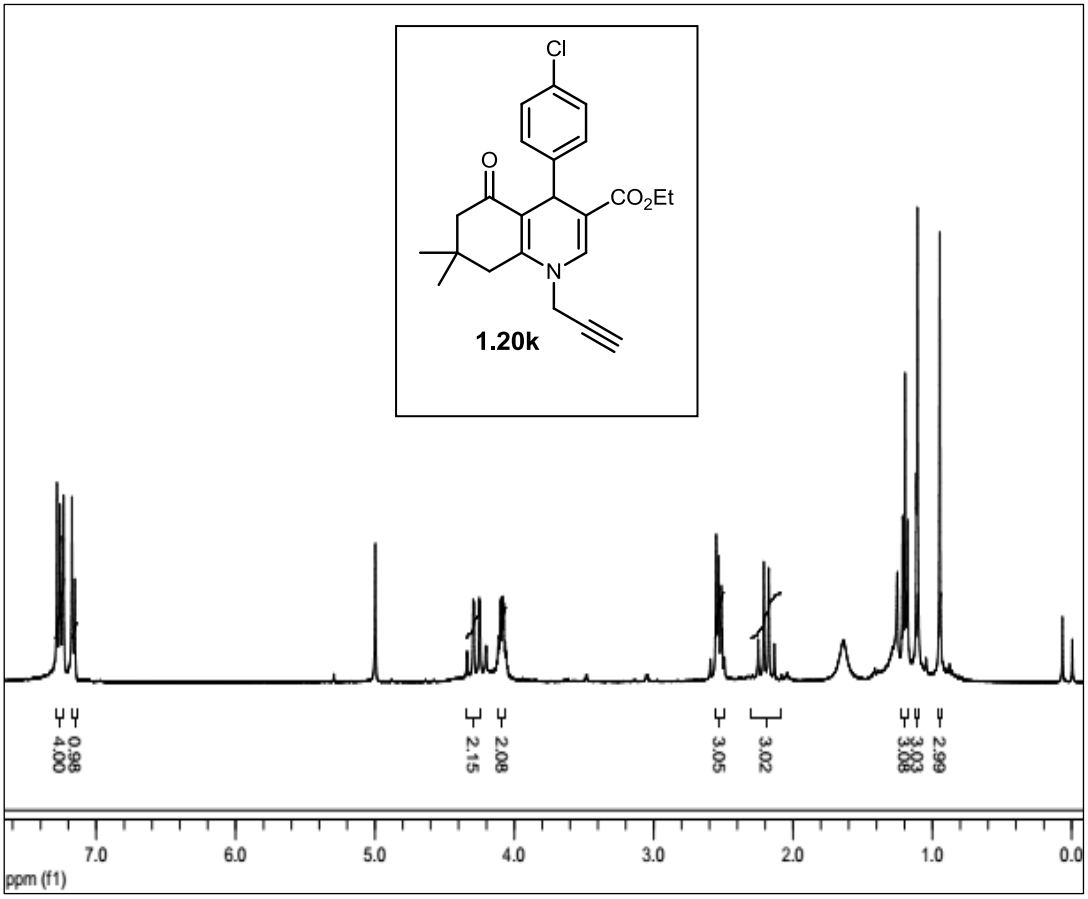
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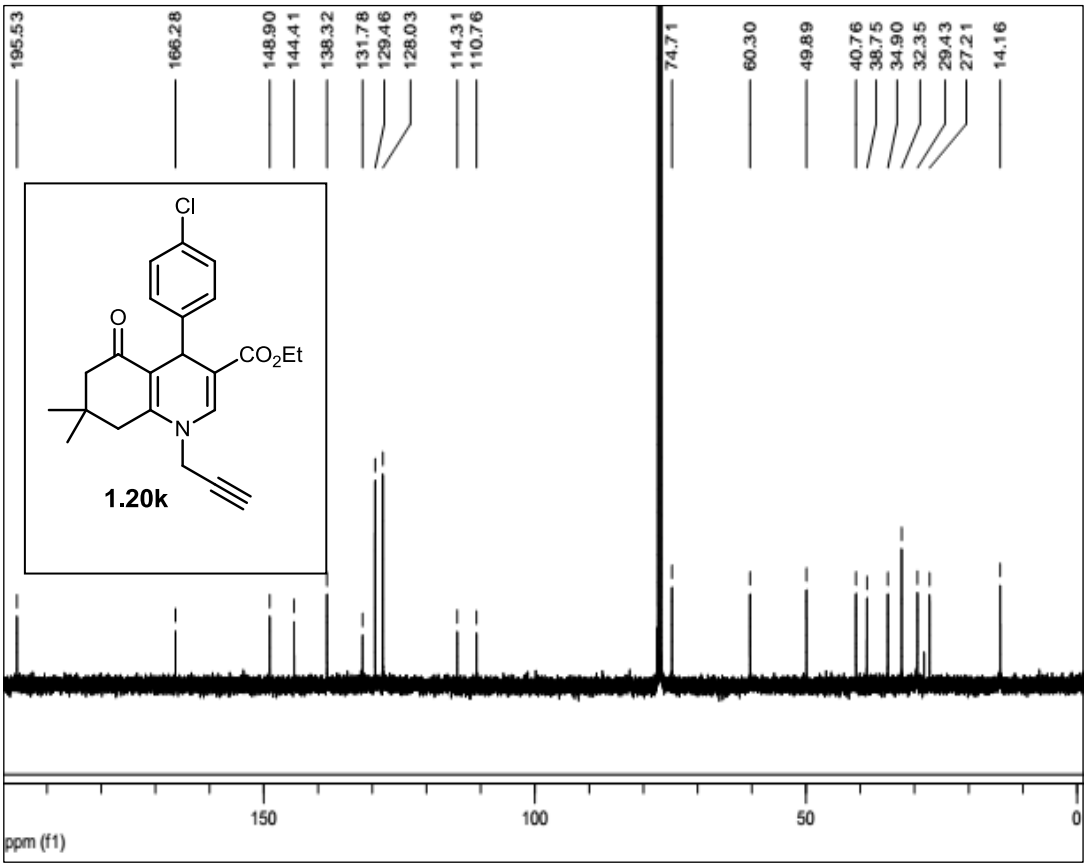
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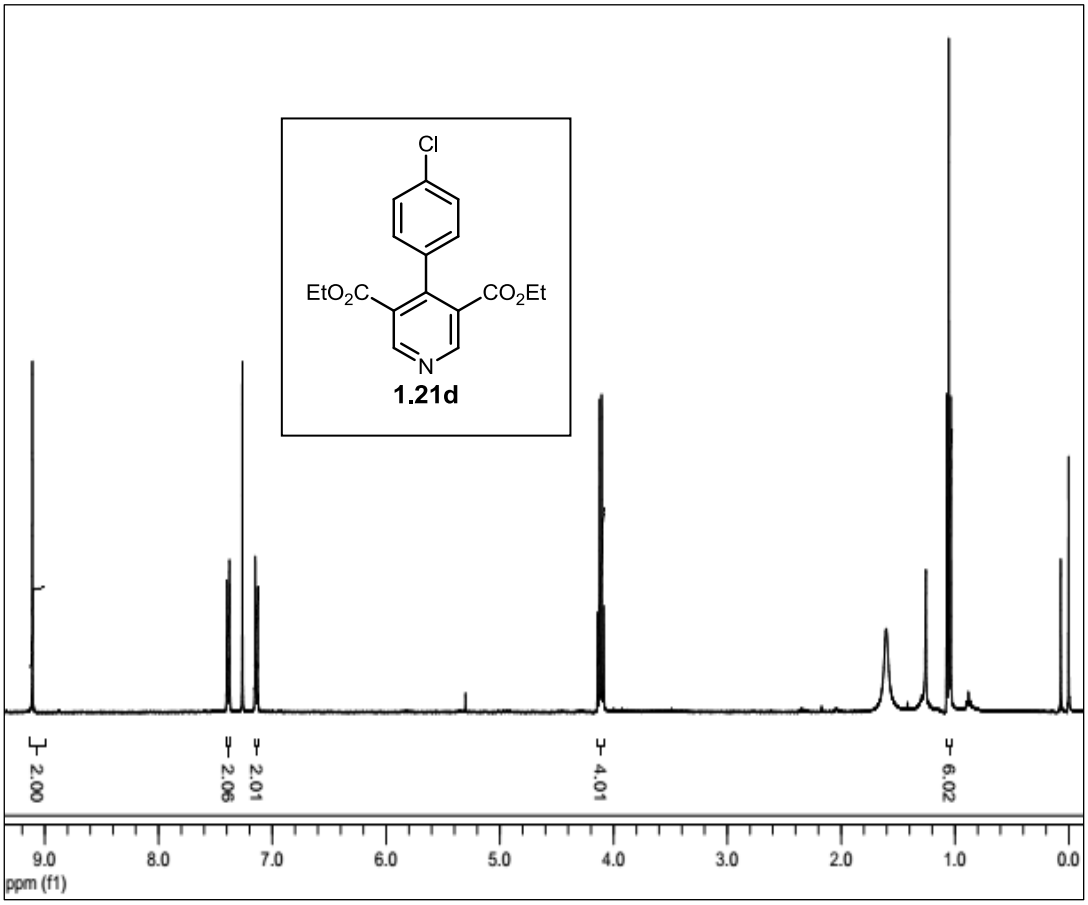
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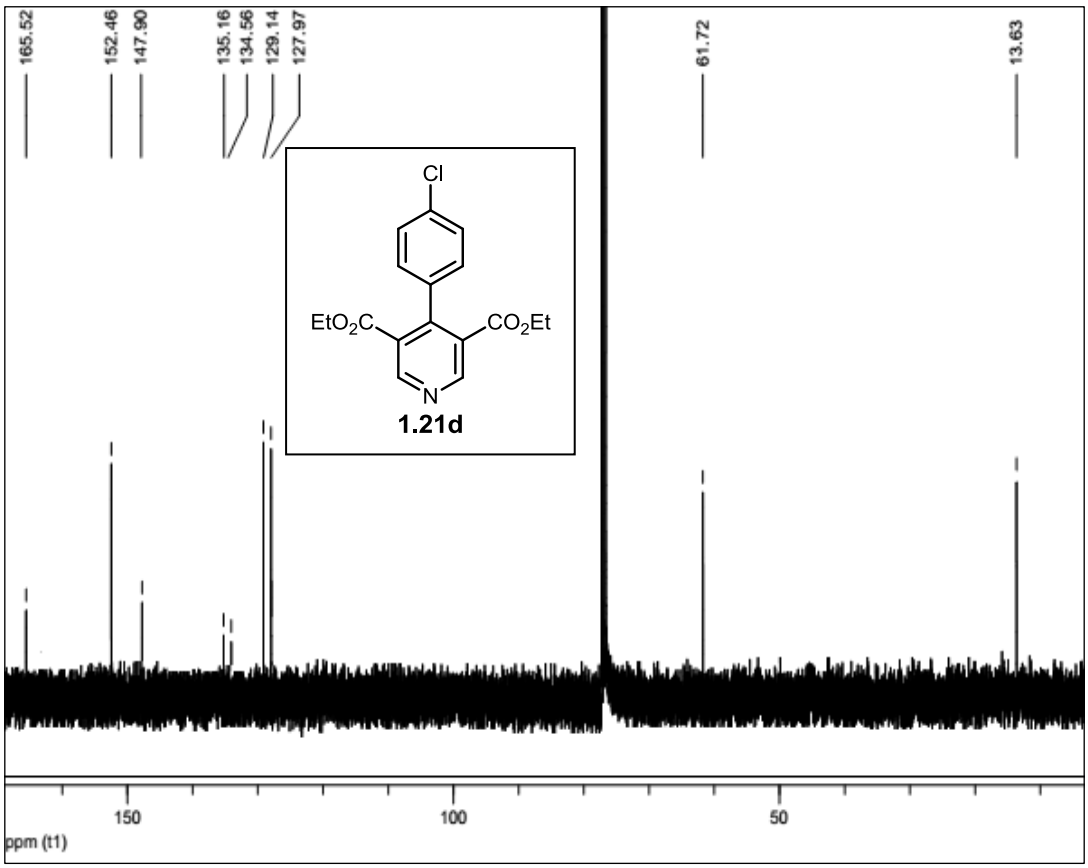
ppm (f1)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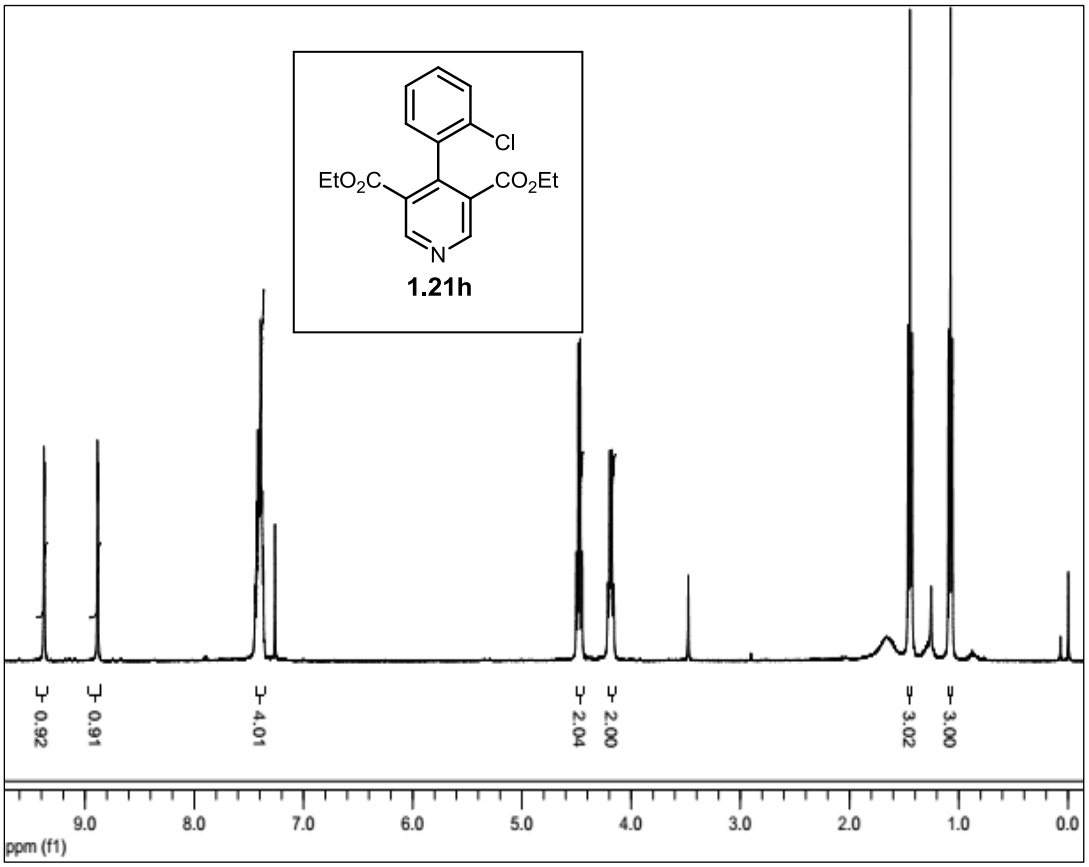
ppm (t1)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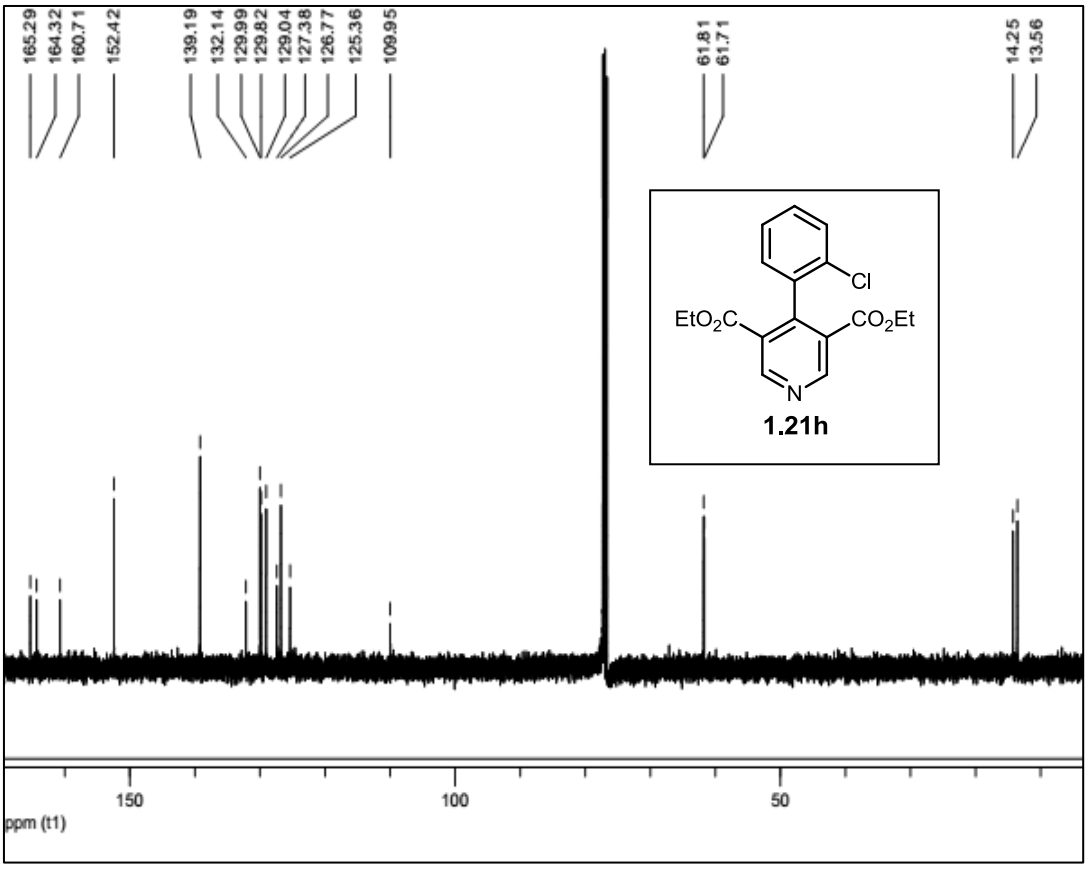
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N
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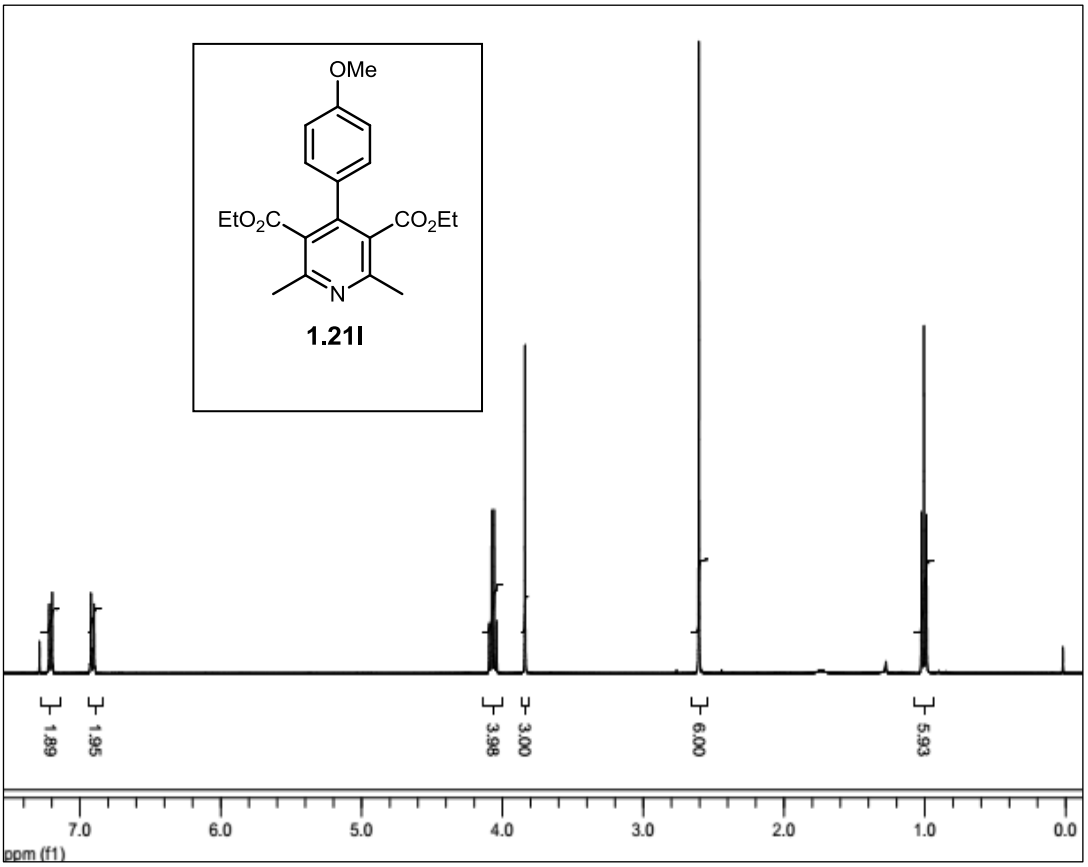
ppm (t1)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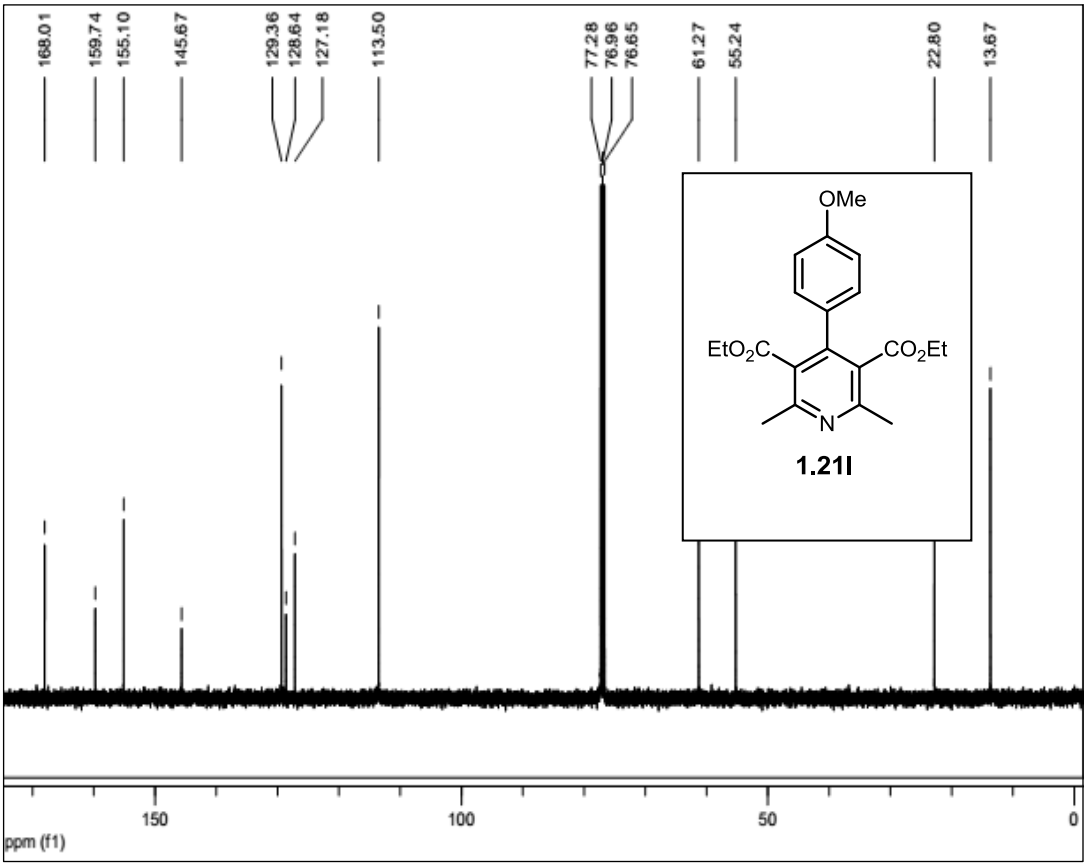
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22.80
13.67
OMe
EtO2C
CO2Et
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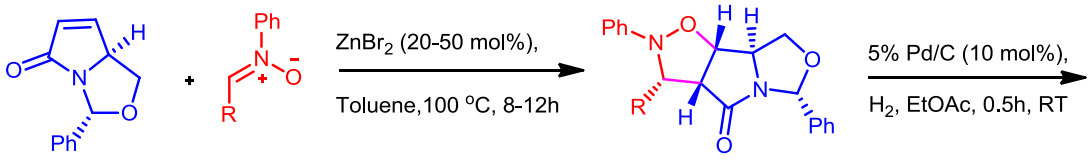
ppm (f1)

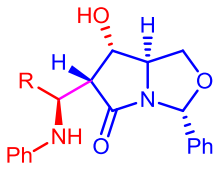
Chapter 2: $ZnBr_2$-Mediated asymmetric synthesis of functionalized pyrrolidinones and their anti-cancer activities



2.7 **2.13** **2.14**

R = Substituted aryl

12 Examples, Up to 89% of yield

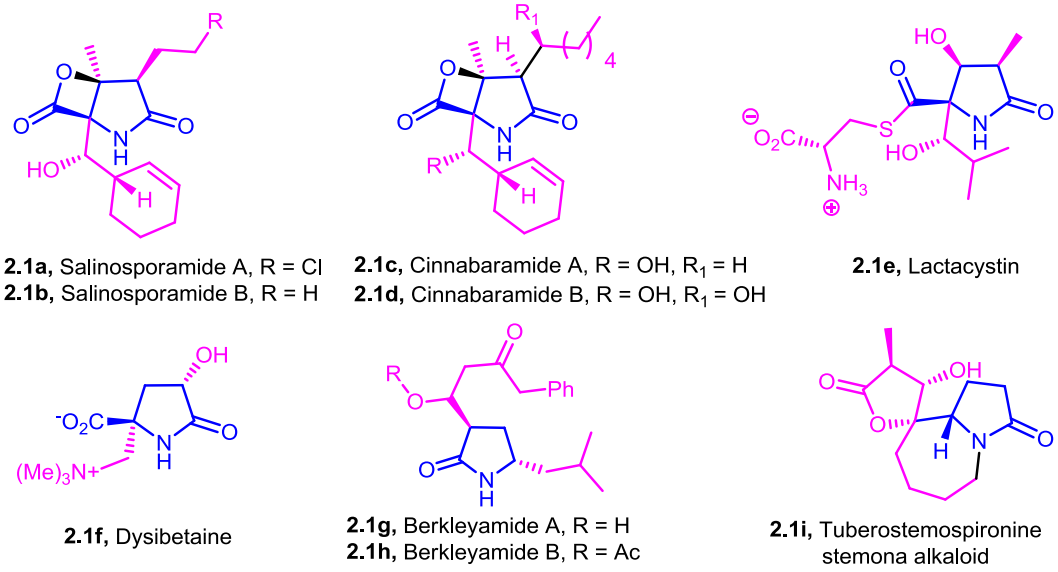


2.15

12 Examples, Quantitative yields

2.1. Introduction:

Lactams are cyclic amides of different ring sizes and are classified as α, β and γ *etc.* γ-lactams contain the pyrrolidinone core, which is a ubiquitous nucleus present in many biologically active alkaloids.[1] In the search of potent anticancer and antimicrobial scaffolds several naturally occurring pyrrolidinone derivatives are isolated, representative bio-active pyrrolidinones are shown in Fig. **2.1**, salinosporamide A and B (**2.1a** and **2.1b)**, cinnabaramide A and B (**2.1c** and **2.1d**), lactacystin (**2.1e**) and dysibetaine (**2.1f**) are proteasome inhibitors,[2] berkleyamide A and B (**2.1g** and **2.1h**) are matrix metalloproteinase and caspase inhibitors,[3] and tuberostemospironine (**2.1i**) has been used as a key precursor in the synthesis of stemona alkaloids, which involves in the treatment of bronchitis, tuberculosis, pertussis and parasitic diseases.[4]



2.1a, Salinosporamide A, R = Cl
2.1b, Salinosporamide B, R = H

2.1c, Cinnabaramide A, R = OH, R_1 = H
2.1d, Cinnabaramide B, R = OH, R_1 = OH

2.1e, Lactacystin

2.1f, Dysibetaine

2.1g, Berkleyamide A, R = H
2.1h, Berkleyamide B, R = Ac

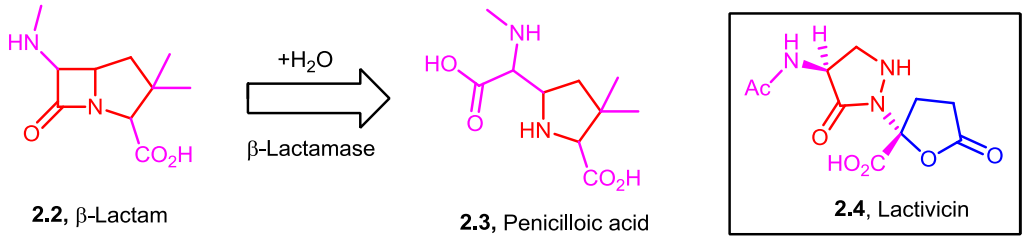
2.1i, Tuberostemospironine
stemona alkaloid

Fig. 2.1. Naturally occurring bio-active pyrrolidinones

2.1.1. Medicinal applications of pyrrolidinone derivatives:

β-Lactam antibiotics have got the extensive attention in the 20th century, soon after disclosing the curative effects of penicillin in various infectious diseases.[5] In fact, these antibiotics inhibit the bacterial cell wall synthesis by arresting the PBPs, penicillins, carbapenems, cephalosporins and penems are β-lactam based anti-infective drugs. However, an increase of various resistant strains produced by β-lactamases (an enzyme produced by bacteria) and mutated PBPs provokes the necessity of discovering the non β-lactam based potent anti-infective drugs. Perhaps,

the active form of the β-lactam antibiotics undergo rapid degradation into inactive penicilloic acid **2.3**, in presence of β-lactamases, as shown in Fig. **2.2**. In order to improve the potential of β-lactam based anti-infective drugs, β-lactamase inhibitors were hosted. Consequently, β-lactam antibiotics have been prescribed in combination with β-lactamase inhibitors, then the situation has become relatively complex as one target and two drug molecules.



2.2, β-Lactam

2.3, Penicilloic acid

2.4, Lactivicin

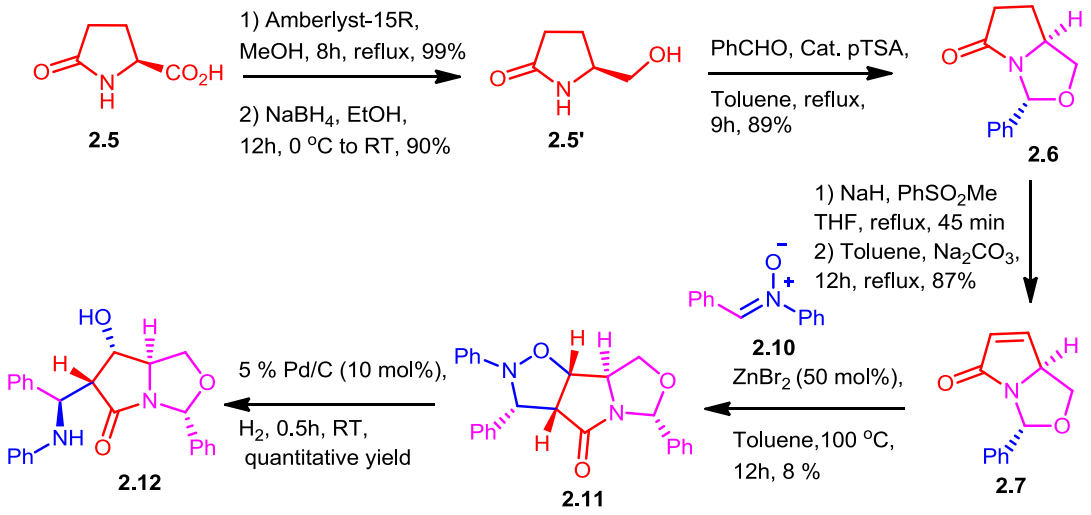
Fig. 2.2. Schematic representation of β-lactam degradation with β-lactamases

For future considerations, researcher envisioned for next generation non β-lactam antibiotics. In those insights Lactivicin (LTV) **2.4** was isolated, which is a first reported natural occurring non β-lactam antibiotic produced by bacteria Empedobacter Lactamgenus.[6] LTV is active against gram positive and gram negative bacteria, also having the similar affinity for PBPs and susceptible to β-lactamases.[6] Thus pyrrolidinone derivatives have been attracted the researcher attention, and recently discovered miscellaneous therapeutic potentials of pyrrolidinone derivatives such as antibacterial,[7,8] cholesterol absorption inhibitors,[10,11] antibiotics,[9] prostate cancer cell growth inhibitors,[12] highly selective EP_2 and EP_4 receptor agonist,[13,14,15] highly potent and selective agonists of α-7-nicotinic acetylcholine receptor,[16,17,18] HDAC inhibitors,[19] TACE inhibitors, PDE4 inhibitors, nootropic and anti-convulsant drugs.[20,21]

Present work:

As mentioned, an extensive literature survey reveals the potent pharmaceutical applications of pyrrolidinone derivatives, has prompted our attention to synthesize novel asymmetric pyrrolidinone derivatives from simple precursors. In the present work, we have chosen the inexpensive chiral precursor (*S*)-pyroglutamic acid, which has privileged functionalities such as differentially activated carbonyls, acid and amine. The major focus is to build a library of pyrrolidinone-based asymmetric *N*-

heterocycles using the privileged precursors derived from (*S*)-pyroglutamic acid. The major focus is to explore facial/substrate induced asymmetric reactions. Among the concerted reactions, 1,3-dipolar cycloaddition reactions between nitrones and respective olefins have been less explored because of uncontrolled regio and stereochemical problems. Here, we have demonstrated the $ZnBr_2$-mediated stereoselective synthesis of pyrrolidinone derivatives using 1,3-dipolar cycloaddition reaction between α,β-unsaturated bicyclic γ-lactam **2.7** and nitrones **2.10**. Synthesized pyrrolidinone-based asymmetric *N*-heterocycles were tested for their anti-proliferative activities against CAL 27 cancer cell lines.



Scheme 2.1. Synthesis of pyrrolidinone-based asymmetric *N*-heterocycles

2.2. Design of novel pyrrolidinone derivatives:

Natural chiral synthons or its derivatives have been widely used in synthesizing several natural products and bio-active *N*-heterocycles. Among them (*S*)-pyroglutamic acid is an efficient chiral synthon, widely used in the synthesis of chiral auxiliaries, organocatalysts (proline derivatives), natural products and bio-active asymmetric *N*-heterocycles.[22,23] (*S*)-Pyroglutamic acid is a physiological molecule present in the human body and plays a key role in structuring the skin, brain and skeletal frame. In addition, it forms salts with related minerals such as calcium, magnesium, zinc, iron, potassium and manganese, these are prescribed as mineral deficient supplements. As shown in Fig. **2.3**, we have used (*S*)-pyroglutamic acid **2.5** as an asymmetric precursor, to synthesize the designed privileged pyrrolidinone derivatives.

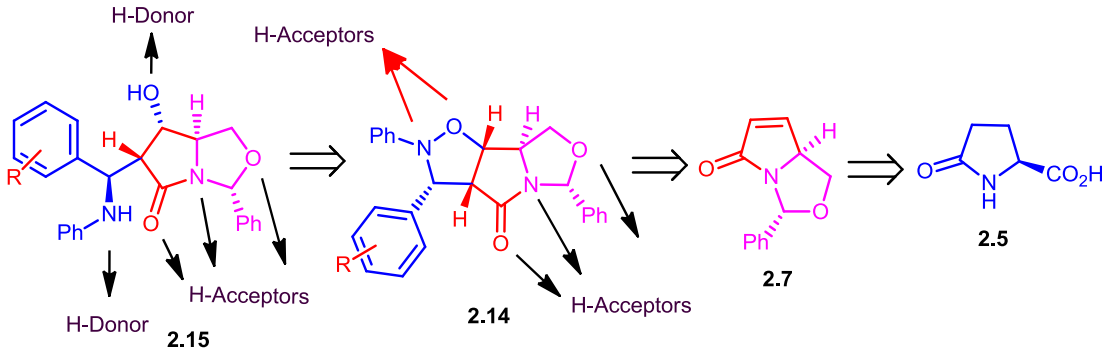
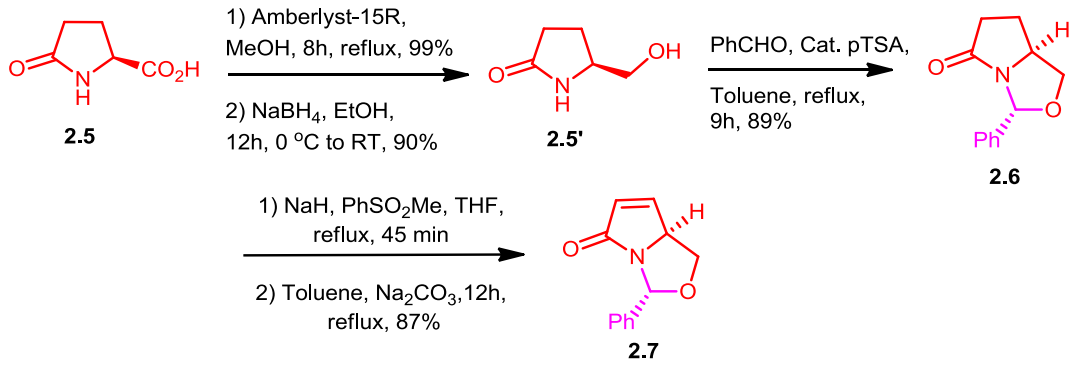


Fig. 2.3. Synthetic route for accessing the novel pyrrolidinone-based *N*-heterocycles

2.3. Results and discussions:

To pursue our investigation, we initiated the synthesis of reactive precursors α,β-unsaturated γ-lactam (**2.7**) and 1,3-dipolar compounds (**2.10)** with the modified reported procedures.

2.3.1. Synthesis of key intermediate α,β-unsaturated γ-lactam (2.7):

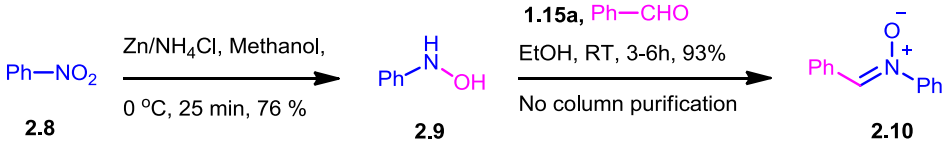


Scheme 2.2. Synthesis of α,β-unsaturated γ-lactam

Pyroglutamic acid **2.5** was converted to pyroglutaminol **2.5'** using mild acidic resin amberlyst-15R followed by reduction with sodium borohydride,[24] using amberlyst-15R having the several advantages: 1) obtaining excellent yield (99%), resin is active for more than 3 cycles (25g scales) and 2) no column purification is required. Pyroglutaminol **2.5'** was protected using benzaldehyde as bicyclic lactam **2.6**, further prepared the key intermediate **2.7** through the enolate chemistry, *i.e.* α-sulfonylation followed by ene-type elimination using Mayer's reagent, shown in scheme **2.10**.[25]

2.3.2. Synthesis of 1,3-dipolar compounds (nitrones):

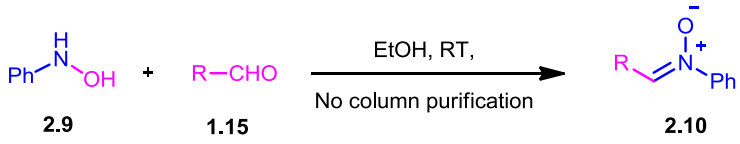
In order to prepare the phenyl hydroxyl amine **2.9**, we initially carried out the reaction in water. Briefly, ammonium chloride dissolved in water and added nitrobenzene, placed the reaction at 0 ºC before attempting the portion wise addition of zinc. After completion of the reaction monitored by TLC, filtered, saturated the crude solution and allowed to keep the crude reaction mixture at 0 ºC overnight, needle type crystals were formed with moderate yield. However, we did the same reaction in methanol at 0 ºC, the reaction was rapid and completed in less than 25 min, and then the crude reaction mixture was filtered and concentrated under reduced pressure, added 100 mL of hexane to obtain crude oil before filtering the white color solid, and was used for further reactions without any purification.



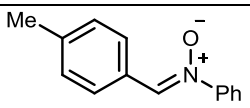
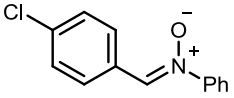
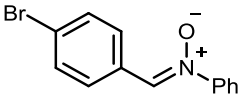
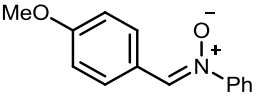
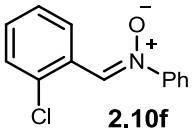
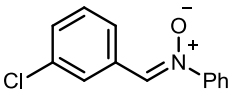
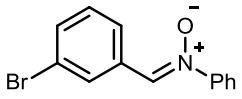
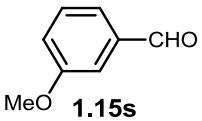
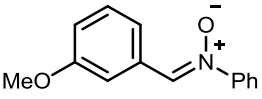
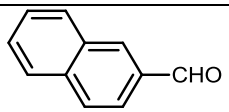
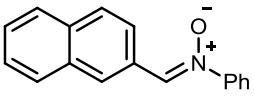
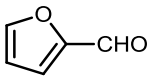
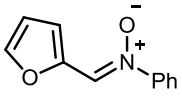
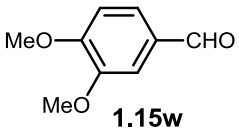
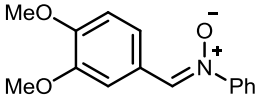
Scheme 2.3. Synthesis of 1,3-dipolar compounds

As shown in Scheme **2.11**, 1,3-dipolar compound or nitrone **2.10** was prepared from condensation of benzaldehydes **1.15** with phenyl hydroxylamine **2.9** in excellent yields.[26] The overall reaction process involves the simple reaction conditions with no column purification. As shown in Table **3.1**, developed method was generalized with various substituted aldehydes **1.15.**

Table 3.1. Synthesis of nitrone derivatives



Entry	Aldehyde (**1.15**)	Product (**2.10**)	Time (h)	Yield (%)
1	**1.15d**	**2.10a**	3	93

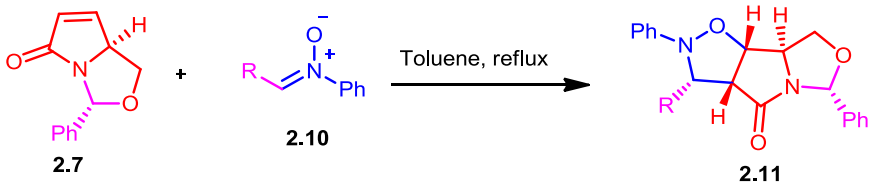
2	**1.15m**	 **2.10b**	3	87
3	**1.15a**	 **2.10c**	3	93
4	**1.15q**	 **2.10d**	3	76
5	**1.15e**	 **2.10e**	3	90
6	**1.15o**	 **2.10f**	6	73
7	**1.15g**	 **2.10g**	3	91
8	**1.15n**	 **2.10h**	3	73
9	 **1.15s**	 **2.10i**	4	78
10	 **1.15q**	 **2.10j**	3	83
11	 **1.15v**	 **2.10k**	6	87
12	 **1.15w**	 **2.10l**	6	77

It is worthy to mention that the synthesized nitrone derivatives have (halo) Cl and Br (entry **3**-**4** and **6**-**8**, Table **3.1**), electron donating Me and OMe (entry **2**, **5**, **9** and **12**, Table **3.1**), napthyl and furan (entry **10**-**11**, Table **3.1**).

2.3.3. Asymmetric synthesis of pyrrolidinone derivatives:

Thermal 1,3-dipolar cycloaddition reaction: Nitrone **2.10a** was treated with 1,3-dipolarophile **2.7** at 100 ^{o}C,[27] for 36h, and obtained moderate yield (56%), a notable amount of unreactive 1,3-dipolarophile **2.7** was recovered. When we perform the same reaction at reflux temperatures, we have observed the slight increase of yield 61% (entry **2**, Table **3.2**) with this reaction condition, we moved to generalize with other nitrones **2.10c-2.10h**, provided good yield as shown in (entry **3-6**, Table **3.2**. Whereas **2.7** was treated with **2.10b** and **2.10l** (entry **7-8**, Table **3.2**) at reflux, in 16h obtained very low yields 35% and 27%, respectively. As well as isolated the notable amount of unreactive **2.7** and observed thermal decomposition of nitrones **2.10** at higher temperatures.

Table 3.2. Thermal 1,3-dipolar cycloaddition reaction



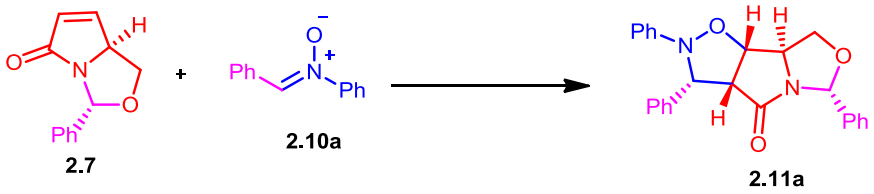
Entry	Nitrone (**2.10**)	Time (h)	Product (**2.11**)	Yield (%)
1	**2.10a**	36	**2.11a**	56[a]
2	**2.10a**	24	**2.11a**	61
3	**2.10c**	16	**2.11c**	67
4	**2.10d**	16	**2.11d**	65
5	**2.10f**	16	**2.11f**	65
6	**2.10h**	16	**2.11h**	63
7	**2.10b**	24	**2.11b**	35
8	**2.10l**	24	**2.11l**	27

All reactions were carried out with 1 mmol of **2.7** and 1.3 mmol of nitrones **2.10**; a = 100 ^{o}C

Thermal decomposition of nitrones **2.10** and recovery unreactive γ-lactam **2.7** has provoked to consider mild and efficient reaction conditions, using Lewis acid catalysts.[28] During our investigation, we performed the reaction using different Lewis acids catalysts such as $Sc(OTf)_3$, $TiCl_4$, and $FeCl_3$, at -78 ^{o}C, no product formation was

observed and recovered the both the reactants**.** Whereas, at room temperature for 12 h, reactant **2.7** was completely consumed within 12h, without formation of adduct. Further insights of the substrate sensitivity,[27] we have performed the reaction with $ZnBr_2$ (inspiring from the pioneering works of Kanemasa et. al.,).[29] In ordered to get the optimized reaction conditions, we used various solvents at reflux temperatures. Reaction with 50 mol% of $ZnBr_2$ in dichloroethane, we observed 10% of yield in 24h (entry **5**, Table **3.3**), in benzene within 12h observed 43% of yield (entry **6**, Table **3.3**), whereas, in xylene reactive precursors was consumed within 8h at 100 ºC and obtained 57% of yield (entry **7**, Table **3.3**). And finally, in toluene 100 ºC obtained 81% of yield (entry **9**, Table **3.3**), as well, obtained the moderate yield (entry **8**, Table **3.3**), with 20 mol% of catalyst at 100 ºC for 16h.

Table 3.3. Optimization of cycloaddition reaction



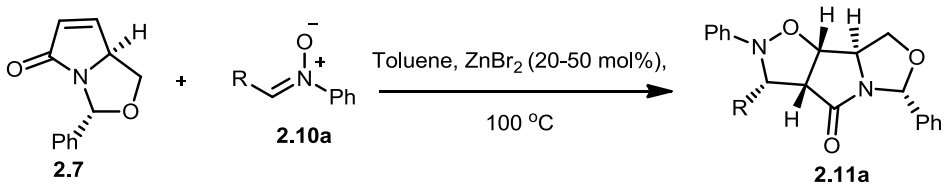
Entry	Solvent	Catalyst (mol %)	Time (h)	Temp (^oC)	Yield (%)
1	CH_2Cl_2/Toluene	$Sc(OTf)_3$	12	-78	ND
2	CH_2Cl_2/Toluene	$TiCl_4$	12	-78	ND
3	CH_2Cl_2	$FeCl_3$	12	-78	ND
4	DCE	$ZnBr_2$ (50)	24	RT	ND
5	DCE	$ZnBr_2$ (50)	24	Reflux	10
6	Benzene	$ZnBr_2$ (50)	12	Reflux	43
7	Xylene	$ZnBr_2$ (50)	8	100	57
8	Toluene	$ZnBr_2$ (20)	16	100	63
9	Toluene	$ZnBr_2$ (50)	12	100	81

All reactions were carried out with 1 mmol of **2.7** and 1.3 mmol of **2.10a**.

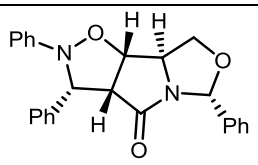
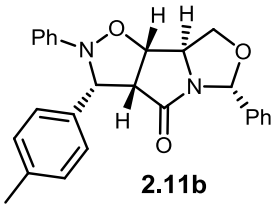
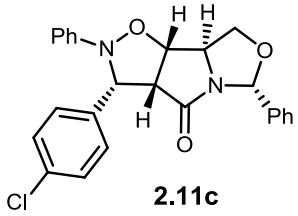
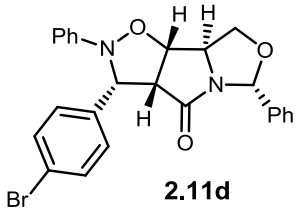
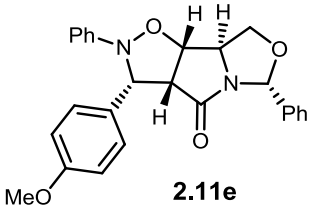
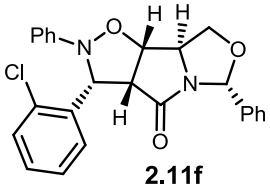
An optimized reaction condition (entry **9**, Table **3.3**) in hand, we moved to generalize with various substituted nitrones. Nitrones having simple phenyl, electron donating groups phenyl (Me and OMe), napthyl and heteroaromatic (furan) were produced, decent yields (entries **1-2**, **5**, **9** and **10-12**, Table **3.4**), also obtained very good yields

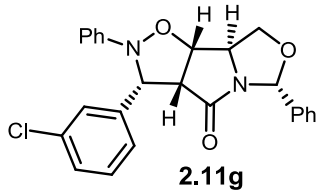
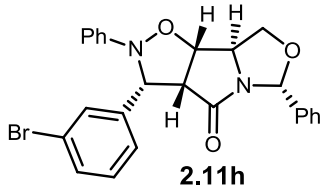
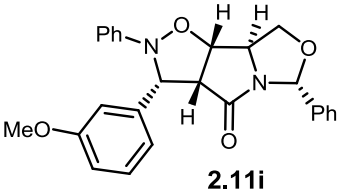
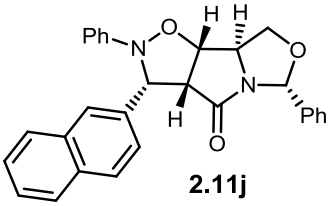
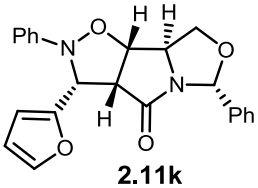
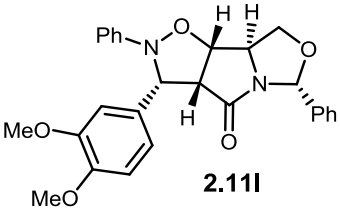
with 20 mol% of $ZnBr_2$, in 8h at 100 ºC for halo (Cl or Br) substituted nitrones (entries **3-4** and **6-8**, Table **3.4**).

Table 3.4. Generalization of $ZnBr_2$ mediated 1,3-dipolar cycloaddition reaction



2.7 + **2.10a** → **2.11a**

Entry	Nitrone (**2.10**)	Product (**2.11**)	Time (h)	Yield (%)
1	**2.10a**	 **2.11a**	12	81
2	**2.10b**	 **2.11b**	12	67
3	**2.10c**	 **2.11c**	8	89
4	**2.10d**	 **2.11d**	8	83
5	**2.10e**	 **2.11e**	12	61
6	**2.10f**	 **2.11f**	8	79

7	**2.10g**	 **2.11g**	8	83
8	**2.10h**	 **2.11h**	8	78
9	**2.10i**	 **2.11i**	12	57
10	**2.10j**	 **2.11j**	12	69
11	**2.10k**	 **2.11k**	12	59
12	**2.10l**	 **2.11l**	16	53

NMR confirmation studies for exo selective adduct 2.11a formation:

Proton chemical shifts assignments of compound **2.11a** were done by using ^{1}H-^{1}H-COSY studies, stereochemical assignments by NOESY studies and coupling constants. In coupling constants at He (J_1 = 8.4 Hz and J_2 = 2.0 Hz); at Hg (J = 9.2 Hz); and at H_f (J_1 = 9.2 Hz, and J_2 = 8.8 Hz), represents H_f cis to H_e and H_g. Whereas, H_e trans to H_d, as shown in Fig. **2.4**, in addition, NOESY spectra provided the cross response 1,3-cis relation of H_a to H_b; H_b to H_e and H_e to H_g, respectively. Related spectra were shown in Fig. **2.5** and Fig. **2.6**.

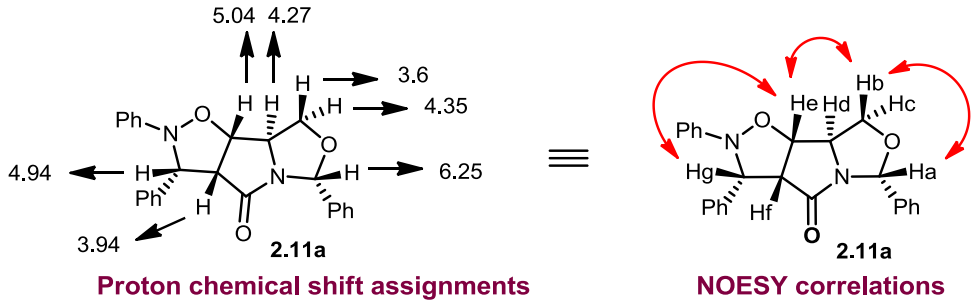


Fig. 2.4. Chemical shifts and NOESY correlations of **2.11a**

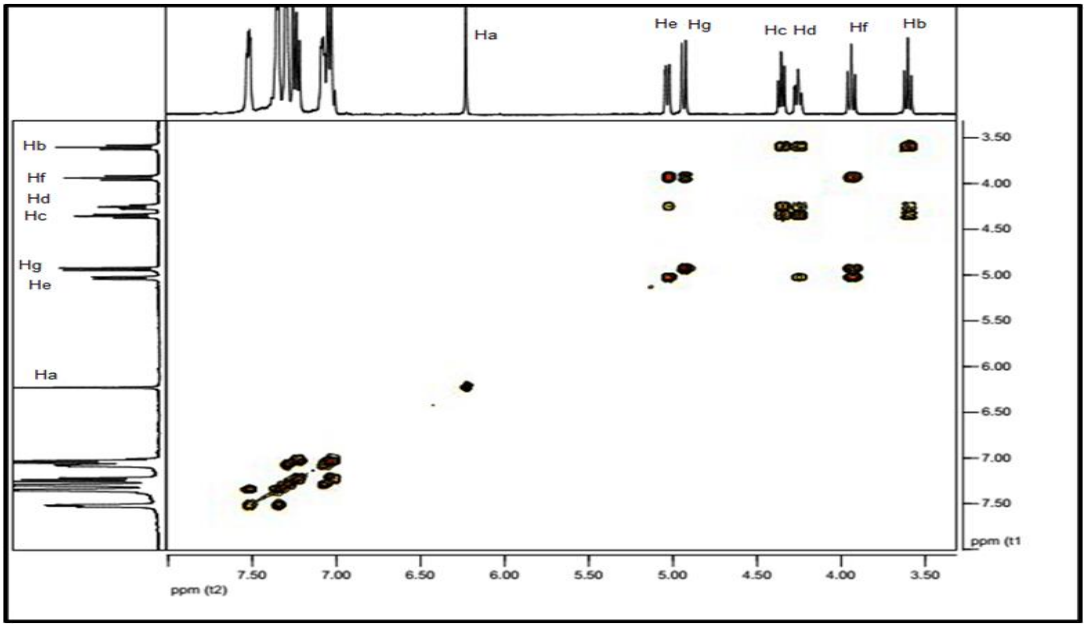
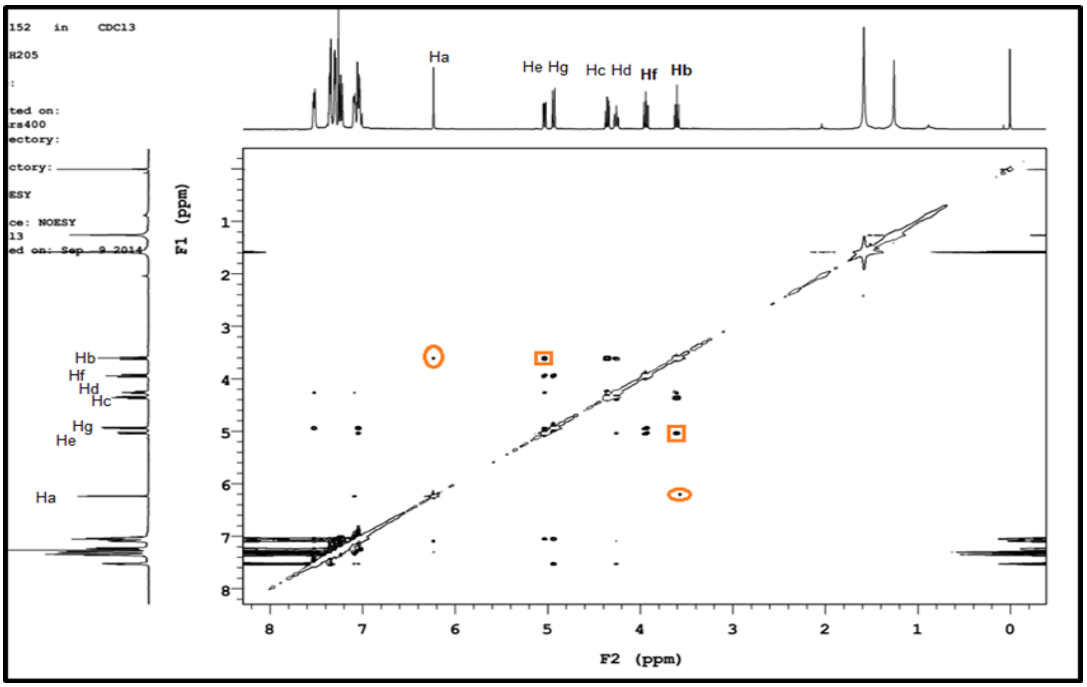


Fig. 2.5. ^{1}H-^{1}H COSY spectra of compound **2.11a**



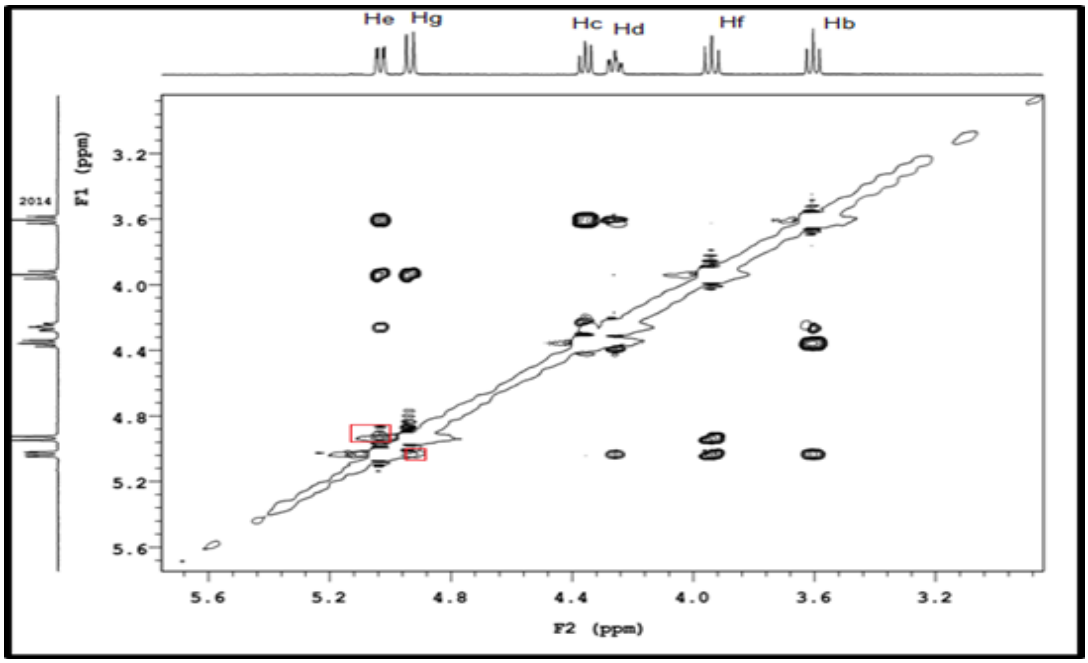


Fig. 2.6. NOESY spectra of 1,3-dipolar adduct **2.11a**

From the above experimental studies, proposed a transition state for favorable *exo* selective 1,3-dipolar adduct formation, whereas *endo* approach is sterically crowded.

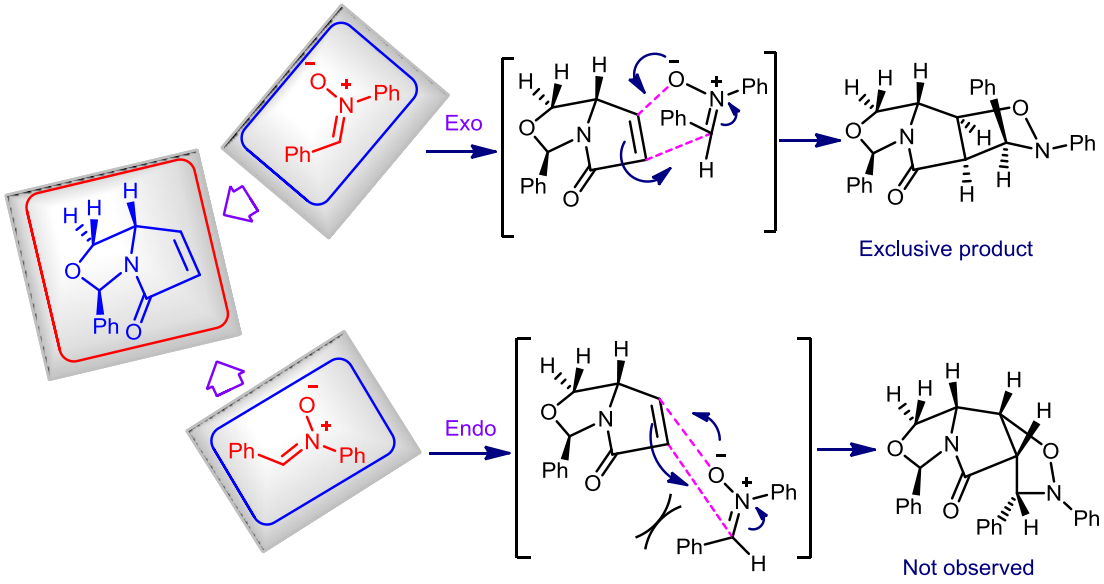
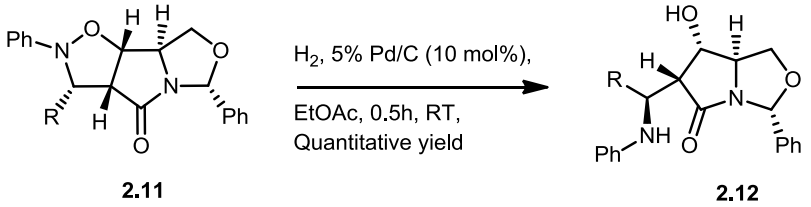
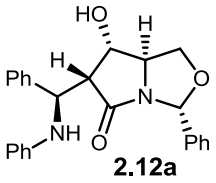
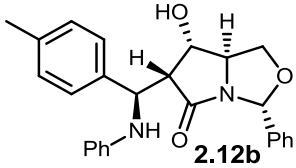
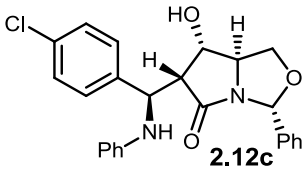
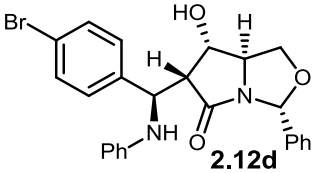
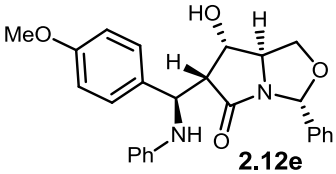
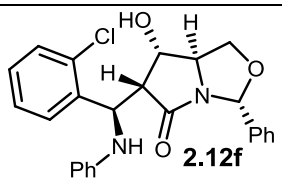
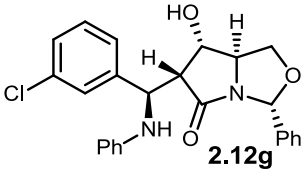


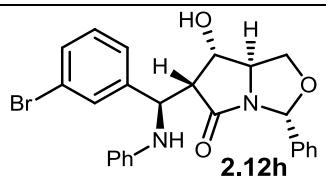
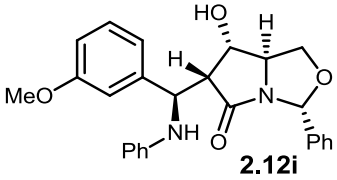
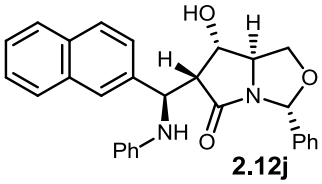
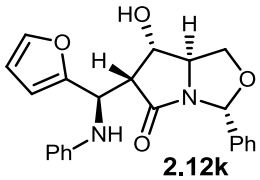
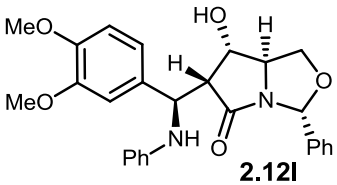
Fig. 2.7. Transition state for the stereo selective 1,3-dipolar cycloaddition reaction

Synthesized tricyclic asymmetric 1,3-dipolar adducts **2.11a-2.11l** was further functionalized to access the bicyclic pyrrolidinone derivatives **2.12a-2.12l** using neutral reaction conditions *i.e.* catalytic atom-economy method 5% Pd/C (10 mol%) in EtOAc, quantitative yields were obtained, details are summarized in Table **3.5**.

Table 3.5. Synthesis of pyrrolidinone-based asymmetric *N*-heterocycles



Entry	Precursor (**2.11**)	Product (**2.12**)	Yield (%)
1	**2.11a**	 **2.12a**	98
2	**2.11b**	 **2.12b**	97
3	**2.11c**	 **2.12c**	96
4	**2.11d**	 **2.12d**	96
5	**2.11e**	 **2.12e**	96
6	**2.11f**	 **2.12f**	95
7	**2.11g**	 **2.12g**	97

8	**2.11h**	 **2.12h**	98
9	**2.11i**	 **2.12i**	97
10	**2.11j**	 **2.12j**	98
11	**2.11k**	 **2.12k**	94
12	**2.11l**	 **2.12l**	98

Compound **2.12e,** is well characterized using ^{1}H-^{1}H COSY and NOESY studies, as described COSY spectra revealed chemical shift values of each proton and NOESY spectra revealed stereochemical assignments such as H_a cis to H_b; and H_b cis to H_e and H_f, as shown in Fig. **2.8**. Related spectra are shown in Fig. **2.9** and Fig. **2.10.**

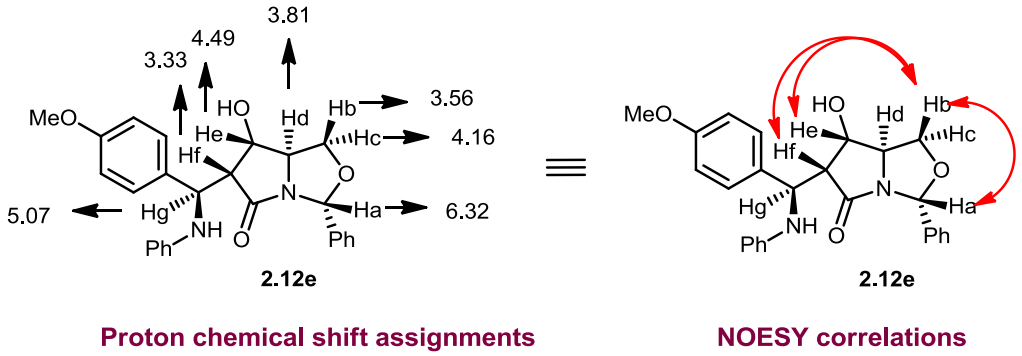


Fig. 2.8. ^{1}H-^{1}H COSY and NOESY details

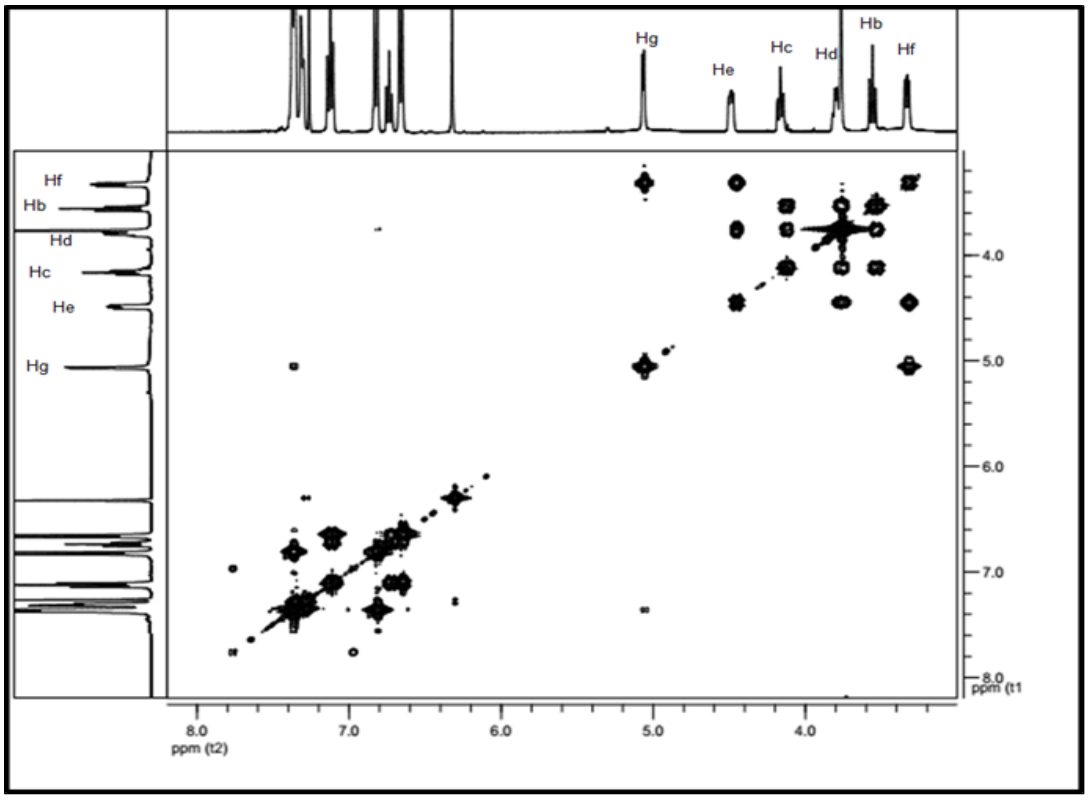


Fig. 2.9. ^{1}H-^{1}H COSY spectra of compound **2.12e**

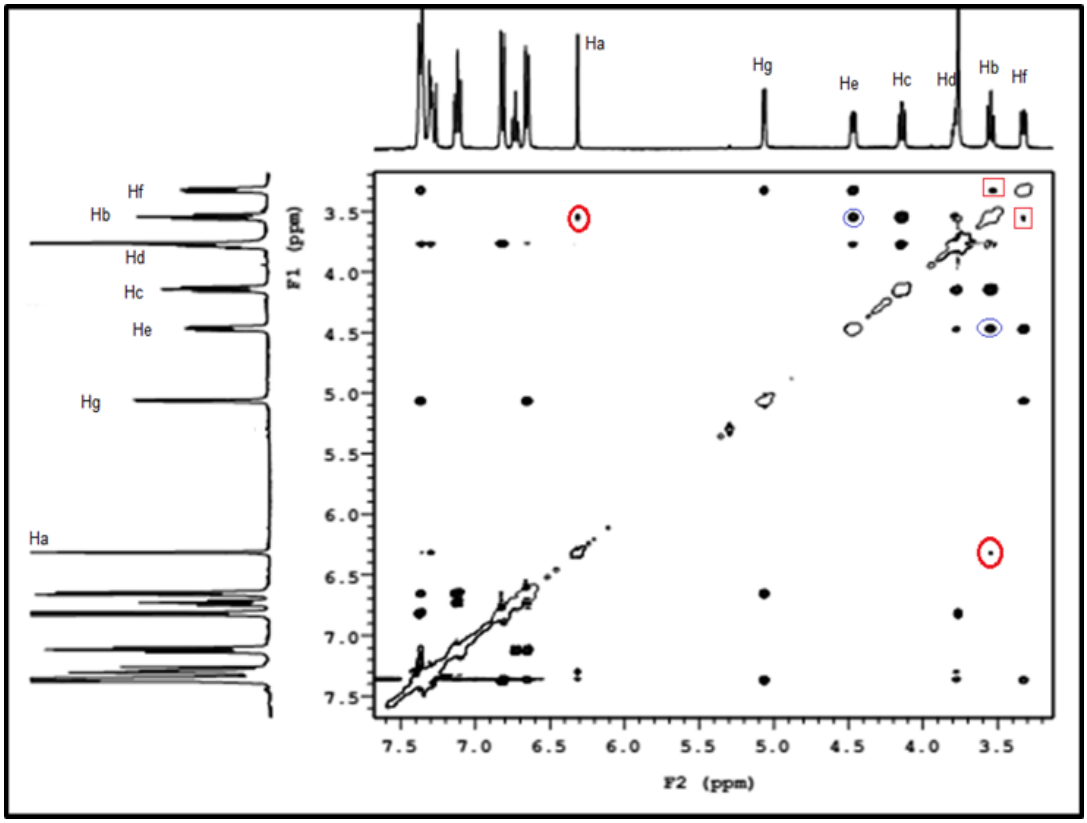


Fig. 2.10. NOESY spectra of compound **2.12e**

2.3.4. Pharmacology:

Cell Proliferation: The anti-proliferative activity of the synthesized compounds on cancer cells was evaluated using the SRB (Sulforhodamine B) cell proliferation assay. This assay was chosen because of its sensitivity, large dynamic range and the ability to measure cell proliferation over three days with normalization to initial cell number and vehicle-treated cells. This assay provides a colorimetric readout, which can be spectrophotometrically measured and does not involve antibodies or toxic reagents, as well as the detection is based on total protein content of cells, which increases or decreases in proportion with cell number. In brief, the assay was performed as follows; cancer cells were seeded in 96-well plates and incubated overnight. We chose the cancerous cell line CAL27 (human tongue adenosquamous carcinoma cells) for the evaluation. The optimum cell numbers to be seeded were determined by a growth curve analysis for each cell line. In the initial (single dose) screen, compounds (dissolved in 100% DMSO to a stock concentration of 100 mM) were added to the adhered cells at a final concentration of 20 μM. After 72 h of treatment, the cells were washed with phosphate-buffered saline and ice-cold 10% trichloroacetic acid added to the cells to precipitate all proteins for an hour at 4 ^{o}C, then cells were washed with water and air-dried followed by cellular proteins stained using 0.4% SRB solution in 1% AcOH for 10 min at RT. Unbound dye was washed away by destaing with 1% AcOH and bound dye solubilized with 10 mM tris solution then absorbance of soluble dye was measured at a wavelength of 590 nM and percentage of growth was determined by the formula [(At-Ao/Ac-Ao)] X 100, where At = absorbance after 72h of test compound treatment, Ao = absorbance at time 0h, Ac = absorbance after 72h without treatment. Compounds which resulted in < 50% growth of cancer cells were considered potentially anti-proliferative. The known cytotoxic agent Gemcitabine was used as a positive control in the assay.[30]

As mentioned, all the synthesized asymmetric pyrrolidinone derivatives were tested for their anti-proliferative activities against CAL27 cancer cell lines and obtained results are summarized in Table **3.6**, in which compound **2.11a** has shown 74% inhibition (entry **1**, Table **3.6**); compound **2.11g** shown 86% inhibition (entry **3**, Table **3.6**); compound **2.11h** shown 99% inhibition (entry **4**, Table **3.6**); compound **2.11c** shown 81% inhibition (entry **9**, Table **3.6**); compound **2.11h** has shown 92% inhibition (entry **11**, Table **3.6**) and **2.11h** shown 95% inhibition at 10μM (entry **12**,

Table **3.6**), then few potent compounds were taken for dose response studies. Dose response curves of corresponding compounds are shown in Fig. **2.11** and their IC_{50} values are noted in (entry **3-4**, **7**, **9** and **11**, Table **3.6**).

Table 3.6. Potent cytotoxic compounds are listed

Entry	Compound	Inhibition (%) (20 µM)	Inhibitory constant IC_{50} (µM)
1	**2.11a**	74.1	ND
2	**2.11c**	45.6	ND
3	**2.11g**	86.4	13.84
4	**2.11h**	99.3	1.769
5	**2.11i**	49.3	ND
6	**2.11j**	74.4	ND
7	**2.11e**	62.6	7.473
8	**2.11i**	42.7	ND
9	**2.12c**	81.3	7.064
10	**2.12g**	64.2	ND
11	**2.12h**	92.2	29.03
12	**2.11h**	95.3[a]	ND
13	Gemcitabine	102.1	-

[a] at 10 µM; Compounds which has shown more than 40% inhibition are noted in the table

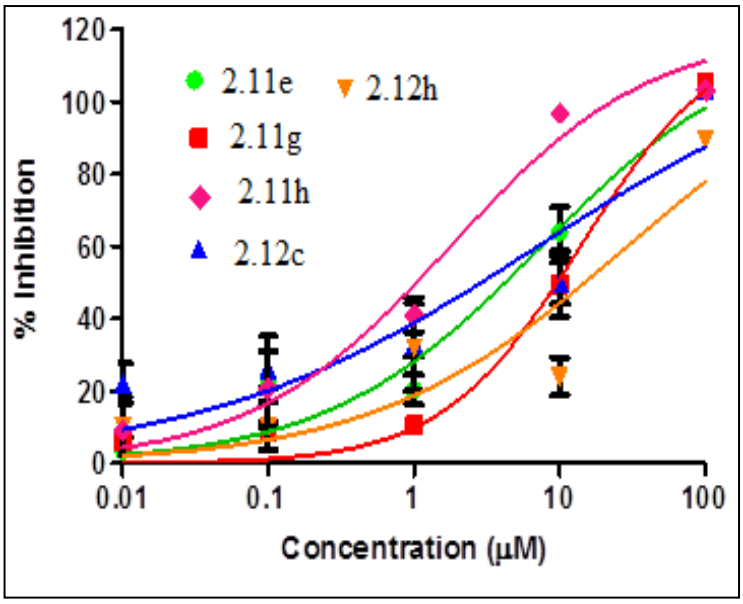


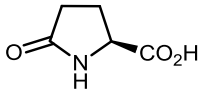
Fig. 2.11. Dose response curves of compound **2.11** and **2.12.**

2.4. Conclusions:

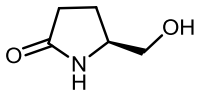
We have demonstrated the efficient $ZnBr_2$-mediated 1,3-dipolar cycloaddition reaction between α,β-unsaturated γ-lactam **2.7** and 1,3-dipolar compounds **2.10a**, for the synthesis of functionalized pyrrolidinone derivatives. One of the pyrrolidinone derivatives was well characterized using COSY and NOESY studies, based on the experimental studies proposed transition state for *exo*-selective adduct formation, through regio and stereo-controlled fashion. The key precursor α,β-unsaturated γ-lactam **2.7** was prepared from natural chiral synthon (*S*)-pyroglutamic acid using adopted efficient synthetic protocols and 1,3-dipolar compounds were prepared using modified simple reaction procedures. Most of the synthesized asymmetric functionalized pyrrolidinone derivatives were shown potent anti-proliferative activities against cal 27 cancer cell lines.

2.5. Experimental section:

(S)-5-(hydroxymethyl)pyrrolidin-2-one (2.5'): Methyl pyroglutamate was synthesized using the reported procedure,[9a] then reduction of methyl pyroglutamate (20 g, 139.86 mmol) with sodium tetraborohydride (10.58 g, 279.72 mmol) in 125 ml of EtOH at (0 ^oC to RT) for 12h. Reaction completion was monitored by TLC (on charring 10% H_2SO_4: MeOH) 4% methanol in CH_2Cl_2 as eluent, after completion of the reaction quenched with 10% HCl allowed to stir for 10 to 15 minutes. The crude reaction mixture was neutralized with aq. $NaHCO_3$ and removed water azeotropically under reduced pressure, then the crude white salt was dissolved in 2×150 mL of 20% methanol in CH_2Cl_2 and allowed to pass on Buchner funnel with a filter paper, filtrates were combined and concentrated under reduced pressure, further purified by flash column chromatography.

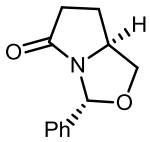


Yield = 99.9% (27.7 g); color less liquid; R_f = 0.6 (5% methanol in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 6.85-6.53 (b, 1H), 4.27 (dd, J_1 = 8.7 Hz, J_2 = 5.1 Hz, 1H), 3.78 (s, 3H), 2.54-2.33 (m, 3H), 2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.33, 172.55, 55.44, 52.52, 29.26, 24.72; ESI-MS (m/z): [M+1] 143.8.



Yield = 91% (14.7 g); white solid; MP: 69-73 ^{o}C; R_f = 0.6 (10% methanol in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (b, 1H), 4.64-4.32 (m, 1H), 3.87-3.74 (m, 1H), 3.67 (dd, J_1 = 11.4 Hz, J_2 = 3.1 Hz, 1H), 3.45 (dd, J_1 = 11.4, J_2 = 3.1 Hz, 1H), 2.45-2.24 (m, 2H), 2.24-2.07 (m, 1H), 1.79 (m, J_1= 9.5 Hz, J_2 = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.59, 65.64, 56.57, 30.34, 22.25; ESI-MS (m/z): [M+1] 115.8.

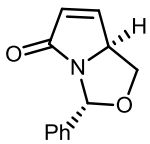
(3R,7aS)-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.6):



A mixture of (5.0 g, 43.42 mmol) of pyroglutaminol **2.5'** (5.07 g, 47.77 mmol) of benzaldehyde **1.15d** and catalytic amount (33.6 mg, 0.2 mmol) of *p*- toluene sulfonic acid in toluene (60 mL) was refluxed under a Dean-stark water separator with vigorous stirring, after 9 h the collection of water was stopped and reaction completion was monitored by TLC (on charring with 2,4-DNP), then solvent was removed under reduced pressure before washing with 5% $NaHCO_3$ (2 × 50 mL) and brine (1 × 50 mL). The organic layer (EtOAc) was dried over anhydrous Na_2SO_4 and concentrated to afford oil and the further purification was done by flash column chromatography (45% EtOAc in *n*-Hexane).

Yield = 89% (7.8 g); color less liquid (solidified at lower temperature); MP: 33-37 ^{o} C; R_f = 0.49 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, Hz, 5H), 6.32 (s, 1H), 4.17 (m, J_1 = 14.1 Hz, J_2 = 6.8 Hz, 2H), 3.48 (t, J = 8.1 Hz, 1H), 2.87-2.75 (m, 1H), 2.55 (m, 1H), 2.42-2.33 (m, 1H), 1.92 (m, J_1 = 14.5 Hz, J_2 = 9.3 Hz, J_3 = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.15, 138.79, 128.54, 128.42, 125.91, 87.02, 71.64, 58.79, 33.45, 23.05; ESI-MS (m/z): [M+1] 203.9 and $[\alpha]_D^{¼}$ = +247.5 (c 0.32, $CHCl_3$)

(3R,7aS)-3-phenyl-1,7a-dihydropyrrolo[1,2-c]oxazol-5(3H)-one (2.7):



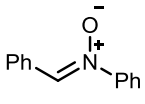
At 0 ^{o}C, oil-free NaH (1.31g, 54.66 mmol) was dissolved in dry.THF, bicyclic γ-lactam **2.6** (5.0 g, 24.85 mmol) was slowly added and allowed to stir for 30 minutes then pre-prepared Mayer's reagent (3.87g, 24.85 mmol) was added carefully, then reaction mixture was shifted 0 ^{o}C to reflux temperature, after 20 minutes there was a formation of white color precipitate indicating the completion of α-phenyl sulfonylation. Then the crude reaction mixture

was quenched with 10 % dil. phosphoric acid (10 mL), organic solvent was removed under reduced pressure followed by extracted with EtOAc (3×100 mL) and extracted solvents are combined and concentrated in vacuo. The crude product was dissolved in toluene and added 75 mmoles of Na_2CO_3 and allowed to reflux for 8h, then the reaction completion was monitored by TLC on charring with 2,4-DNP and potassium permanganate stains. After completion of the reaction filtered through a pad of celite, concentrated and crude product was further purified by flash chromatography.

Yield = 89% (4.4 g); MP: 85-87 ^{o}C; R_f = 0.47 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.3 Hz, 2H), 7.46-7.33 (m, 3H), 7.29 (d, *J* = 5.9 Hz, 1H), 6.4-5.96 (m, 2H), 4.64 (t, *J* = 7.3 Hz, 1H), 4.29 (t, *J* = 6.9 Hz, 1H), 3.45 (m, J_1 = 8.3, J_2 =1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.97, 147.83, 138.57, 129.27, 128.68, 128.49, 126.19, 87.43, 68.13, 65.16; ESI-MS (m/z): [M+1] 201.9 and $[\alpha]_D^{¼}$ = +201.69 (c 0.32, $CHCl_3$).

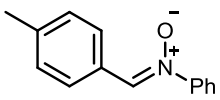
Synthesis of Phenyl hydroxyl amine (2.9): Nitrobenzene **2.8** (10 g, 81.26 mmol), ammonium chloride (5.2 g, 97.5 mmol) was dissolved in 150 mL methanol, then zinc (10.6 g, 162.52 mmol) was added portion wise at 0 ^{o}C. After 15 to 20 minutes of vigorous stirring, formation of heat was observed and the reaction completion was monitored by TLC. Then the crude reaction mixture was passed on celite pad (2×100 ml of methanol), all filtrates were combined and concentrated in vacuo to get the crude oil, added 100 mL of hexane to the crude oil and allowed to stir for few minutes colorless solid formation was observed, solid was washed thoroughly and directly used for further reactions.

(Z)-*N*-benzylideneaniline oxide (2.10a): Phenyl hydroxyl amine **2.9** (500 mg, 4.6 mmol) and benzaldehyde **1.15d** (488.15 mg, 4.6 mmol) was dissolved in 10 mL of ethanol, allowed to stir until the reaction was completed monitored by TLC. After completion of reaction added 2-4 mL of hexane and allowed to stir for few minutes then condensed nitrone adducts were solidified. The product was filtered and washed with 10 ml of cold (1:1) ethanol and *n*-hexane.



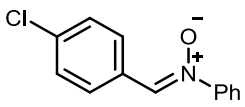
Yield = 93% (840 mg); brown solid; MP: 110-114 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48-8.33 (m, 2H), 7.93 (s, 1H), 7.8-7.7 (m, 2H), 7.49 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.94, 130.66, 129.92, 129.16, 129.03, 128.65, 121.77; ESI-MS (m/z): [M+1] 197.9.

(Z)-N-(4-methylbenzylidene)aniline oxide (2.10b):



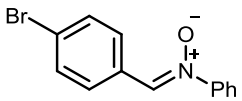
Yield = 87% (841 mg); brown solid; MP: 74-77 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.2 Hz, 2H), 7.88 (s, 1H) 7.84-7.72 (m, 2H), 7.54-7.37 (m, 3H), 7.37-7.25 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.92, 141.51, 134.62, 129.7, 129.3, 129.05, 129.03, 127.93, 121.62, 21.72; ESI-MS (m/z): [M+1] 211.9.

(Z)-N-(4-chlorobenzylidene)aniline oxide (2.10c):



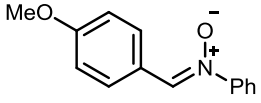
Yield = 93% (986 mg); brown solid; MP: 147-150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.6 Hz, 2H), 7.91 (s, 1H), 7.82-7.70 (d, 2H), 7.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.91, 136.33, 133.34, 130.14, 130.09, 129.2, 129.15, 128.91, 121.67; ESI-MS (m/z): [M+1] 231.8.

(Z)-N-(4-bromobenzylidene)aniline oxide (2.10d):



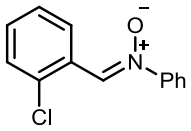
Yield = 76% (961 mg); brown solid; MP: 145-148 ^{o}C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.5 Hz, 2H), 7.90 (s, 1H), 7.77 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.50 (dd, J_1 = 5.1, J_2 = 1.8 Hz, 3H); ESI-MS (m/z): [M+1] 277.8.

(Z)-N-(4-methoxybenzylidene)aniline oxide (2.10e):



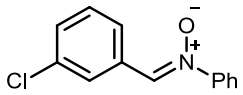
Yield = 90% (936 mg); brown solid; MP: 109-112 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.8 Hz, 2H), 7.90-7.82 (s, 1H), 7.83-7.71 (d, 2H), 7.53-7.40 (m, 3H), 6.99 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.45, 148.83, 134.21, 131.14, 129.57, 129.06, 123.66, 121.58, 113.96, 55.36; ESI-MS (m/z): [M+1] 227.9.

(Z)-N-(2-chlorobenzylidene)aniline oxide (2.10f): Compound was purified by column chromatography (20% EtOAc in *n*-Hexane)



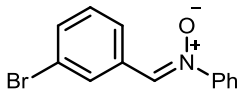
Yield = 73% (774 mg); brown gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.7, 1H), 8.43 (s, 1H), 7.79 (m, *J* = 5.3, 3.6 Hz, 2H), 7.44 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ149.40, 133.64, 131.55, 130.58, 130.2, 129.54, 129.24, 129.21, 128.28, 127.21, 121.82; ESI-MS (m/z): [M+1] 231.8.

(Z)-N-(3-chlorobenzylidene)aniline oxide (2.10g):



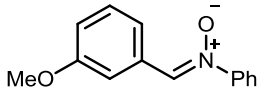
Yield = 91% (965 mg); brown solid; MP: 101-103 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.17 (d, *J* = 7.2 Hz, 1H), 7.91 (s, 1H), 7.78-7.74 (m, 2H), 7.52-7.48 (m, 3H), 7.43 (m, Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.93, 137.31, 133.33, 130.21, 130.1, 129.5, 129.15, 128.91, 122.13; ESI-MS (m/z): [M+1] 231.8.

(Z)-N-(3-bromobenzylidene)aniline oxide (2.10h):



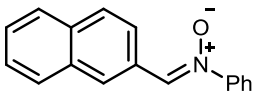
Yield = 73% (923 mg); brown solid; MP: 93-95 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.91 (s, 1H), 7.77 (dd, J_1 = 6.6, J_2 = 3.1 Hz, 2H), 7.65-7.58 (m, 1H), 7.51 (dd, J_1 = 5.1, J_2 = 1.7 Hz, 3H), 7.37 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.84, 133.74, 133.23, 132.37, 131.35, 130.25, 130.08, 129.25, 122.76, 121.70, 12.47; ESI-MS (m/z): [M+1] 275.5.

(Z)-N-(3-methoxybenzylidene)aniline oxide (2.10i):



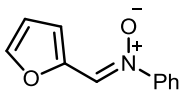
Yield = 78% (811 mg); brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.93 (s, 1H), 7.79 (dd, *J* = 7.6, 2H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.56-7.45 (m, 3H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.06 (dd, J_1 = 8.2, J_2 = 1.9 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.57, 149.01, 134.82, 131.8, 130.0, 129.47, 127.19, 122.28, 121.73, 118.05, 112.56, 55.37; ESI-MS (m/z): [M+1] 227.9.

(Z)-N-(naphthalen-2-ylmethylene)aniline oxide (2.10J):



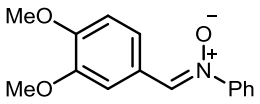
Yield = 83% (940 mg); brown solid; MP: 130-133 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.08 (s, 1H), 8.0 (m, *J* = 7.1, 3.5 Hz, 2H), 7.85 (m, 4H), 7.53 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.04, 134.67, 134.35, 133.13, 129.96, 129.45, 129.4, 129.2, 129.16, 128.11, 127.81, 127.64, 127.55, 126.61, 126.17, 121.72; ESI-MS (m/z): [M+1] 247.9.

(Z)-N-(furan-2-ylmethylene)aniline oxide (2.10k):



Yield = 87% (745 mg); brown solid; MP: 87-90 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.0 (d, *J* = 3.5 Hz, 1H), 7.84-7.72 (m, 2H), 7.57 (s, 1H), 7.54-7.41 (m, 3H), 6.64 (dd, J_1 = 3.1, J_2 = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.45, 147.21, 144.63, 129.92, 129.15, 124.3, 121.0, 116.5, 112.68; ESI-MS (m/z): [M+1] 187.9.

(Z)-N-(3,4-dimethoxybenzylidene)aniline oxide (2.10l):



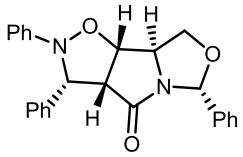
Yield = 77% (907 mg); brown solid; MP: 132-137 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.89-7.88 (m, 1H), 7.82-7.74 (m, 2H), 7.53-7.40 (m, 3H), 7.64 (dd, *J* = 8.4, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.97 (ss, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.17, 148.77, 148.47, 134.64, 129.69, 129.11, 124.03, 123.95, 121.55, 111.05, 110.6, 55.91, 55.89; ESI-MS (m/z): [M+1] 257.9.

1,3-dipolar cycloaddition reaction (thermal atom-economy) procedure: α,β-unsaturated bicyclic γ-lactam **2.7** (100 mg, 0.497 mmol) and *N*-phenyl nitrone **2.10a** (128.2 mg, 0.65 mmol) were dissolved in 5 ml of toluene and allowed to stir at reflux temperatures, once the reaction is completed monitored by TLC, extracted with EtOAc, concentrated under reduced pressure followed by purified using flash column chromatography.

$ZnBr_2$ catalyzed procedure: α,β-unsaturated bicyclic γ-lactam **2.7** (100 mg, 0.497 mmol), *N*-phenyl nitrone **2.10a** (128.2 mg, 0.65 mmol) and $ZnBr_2$ (50 mol%) were dissolved in 5 ml of toluene and allowed to heat 12h at 100 ^{o}C. After completion of reaction monitored by TLC, reaction mixture was diluted with 50 ml of EtOAc and

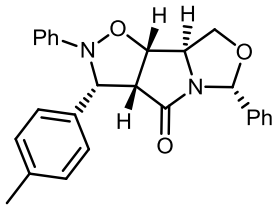
filtered on celite pad then the crude nitrone adduct was concentrated under reduced pressure followed by purified using flash column chromatography.

(3R,3aR,6R,8aR,8bS)-2,3,6-triphenylhexahydrooxazolo[3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11a):



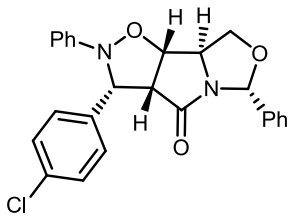
Yield = 81% (160 mg); white solid; MP: 76-80 ^{o}C; R_f = 0.6 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J_1 = 6.4 Hz, J_2 = 2.7 Hz, 2H), 7.32 (m, 8H), 7.06 (m, 5H) 6.23 (s, 1H), 5.03 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 4.94 (d, J = 9.2 Hz, 1H), 4.36 (t, J = 7.5 Hz, 1H), 4.37-4.33 (m, 1H), 3.94 (t, J_1 = 9.2 Hz, J = 8.8 Hz, 1H), 3.60 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.87, 148.62, 137.84, 135.73, 128.84, 128.89, 128.4, 128.24, 127.63, 125.58, 123.7, 117.05, 86.66, 79.49, 71.44, 69.32, 64.6, 61.16; ESI-MS (m/z): [M+1] 398.6; and purity in HPLC = 97%.

(3R,3aR,6R,8aR,8bS)-2,6-diphenyl-3-(p-tolyl)hexahydrooxazolo[3',4':1,5]pyrrolo [3,4-d]isoxazol-4(2H)-one (2.11b):



Yield = 67% (157 mg); white solid; MP: 157-160 ^{o}C; R_f = 0.6 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4 (d, J = 7.9 Hz, 2H), 7.33-7.29 (m, 3H), 7.12 (m, 9H), 6.25 (s, 1H), 5.03 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 4.90 (d, J = 9.2 Hz, 1H), 4.37-4.34 (m, 2H), 3.92 (t, J_1 = 9.2 Hz, J_2 = 8.8 Hz, 1H), 3.62 (d, J = 8.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.01, 148.69, 137.92, 137.9, 132.6, 129.3, 128.8, 128.4, 128.2, 127.5, 125.65, 123.66, 117.14, 86.7, 79.45, 71.36, 69.35, 64.69, 61.19, 21.26; ESI-MS (m/z): [M+1] 412.8; HRMS (ESI-MS) Calcd for $C_{26}H_{24}N_2O_3$ $[M+H]^+$ 413.1860, found 413.1868; purity in HPLC = 96% and $[\alpha]_D^{¼}$ = +351.66 (c 0.32, $CHCl_3$).

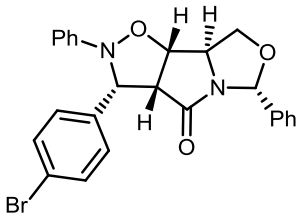
(3R,3aR,6R,8aR,8bS)-3-(4-chlorophenyl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11c):



Yield = 89% (191 mg); yellow solid; MP: 174-177 ^{o}C; R_f = 0.6 (30% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2H), 7.22-7.16 (m, 4H), 7.27 (m, 3H),

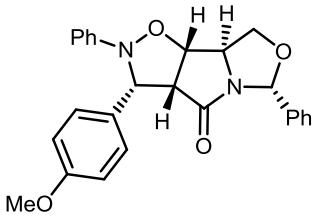
6.97 (m, J_1 = 9.4 Hz, J_2 = 6.7 Hz, 5H), 6.15 (s, 1H), 5.04 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 4.94 (d, J = 9.2, 1H), 4.4-4.20 (m, 2H), 4.19-4.06 (m, 1H), 3.94 (t, J_1 = 9.2 Hz, J_2 = 8.8 Hz, 1H), 3.52 (t, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.53, 148.46, 137.78, 134.36, 134.13, 129.09, 128.98, 128.78, 128.56, 128.35, 125.49, 123.95, 116.94, 86.69, 79.54, 70.85, 69.31, 64.51, 61.06; ESI-MS (m/z): [M+1] 433.8; and purity in HPLC = 99%.

(3R,3aR,6R,8aR,8bS)-3-(4-bromophenyl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11d):



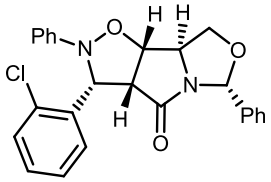
Yield = 83% (196 mg); yellow solid; MP: 157-160 ^{o}C and R_f = 0.6 (30% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 9H), 7.13-6.95 (m, 5H), 6.23 (s, 1H), 5.04 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 4.94 (d, J = 9.2 Hz, 1H), 4.37-4.33 (m, 1H), 4.2 (t, 1H), 3.94 (dd, J_1 = 9.2 Hz, J_2 = 8.8 Hz, 1H), 3.52 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.57, 148.45, 137.72, 134.91, 131.74, 129.41, 129.02, 128.6, 128.41, 125.49, 123.96, 122.31, 116.87, 88.66, 76.71, 70.87, 69.3, 64.5, 61.01; ESI-MS (m/z): [M+1] 478.9; HRMS (ESI-MS) calcd for $C_{25}H_{21}BrN_2O_3$ $[M+H]^{2+}$ 479.0715, found 479.0796; purity in HPLC = 96%; and $[\alpha]_D^{¼}$ = +272.4 (c 0.32, $CHCl_3$).

(3R,3aR,6R,8aR,8bS)-3-(4-methoxyphenyl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11e):



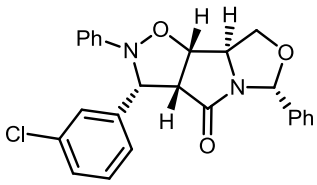
Yield = 61% (129 mg); brown solid; MP: 126-131 ^{o}C; R_f = 0.6 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.6 Hz, 2H), 7.33-7.29 (m, 3H), 7.25-7.20 (m, 2H), 7.12 (dd, J_1 = 6.1 Hz, J_2 = 2.9 Hz, 2H), 7.03 (d, J = 8.1 Hz, 3H), 6.87 (d, J = 8.6 Hz, 2H), 6.25 (s, 1H), 5.02 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 4.88 (d, J = 9.2 Hz, 1H), 4.37 (t, J = 7.5 Hz, 1H), 4.26 (dd, J_1 = 11.3, J_2 = 4.4 Hz, 1H), 3.90 (dd, J_1 = 9.2 Hz, J_2 = 8.8 Hz, 1H), 3.81 (s, 3H), 3.60 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.01, 159.46, 148.71, 137.96, 128.84, 128.48, 128.26, 127.60, 128.68, 123.73, 117.18, 113.95, 86.7, 79.43, 71.18, 69.41, 64.73, 61.21, 55.15; ESI-MS (m/z): [M+1] 429.0; HPLC = 98%; and $[\alpha]_D^{¼}$ = +286.31 (c 0.32, $CHCl_3$).

(3R,3aR,6R,8aR,8bS)-3-(2-chlorophenyl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11f):



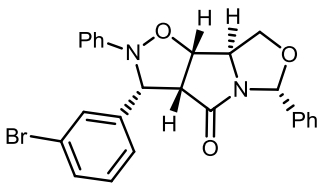
Yield = 79% (169 mg); yellow solid; MP: 127-130 ^{o}C; R_f = 0.6 (30% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 1H), 7.52 (dd, *J* = 8.1 Hz, 1H), 7.42-7.37 (m, 2H), 7.31-7.23 (m, 6H), 7.13-7.02 (m, 4H), 6.30 (s, 1H), 5.32 (d, *J* = 9.2 Hz, 1H), 5.05 (d, J_1 = 8.1 Hz, J_2 = 2.0 Hz, 1H), 4.43-4.40 (m, 2H), 4.18 (t, *J* = 8.8 Hz, 1H), 3.65 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.95, 147.72, 133.59, 129.56, 129.37, 128.85, 128.58, 128.44, 128.26, 126.98, 125.66, 124.1, 118.19, 114.9, 86.94, 78.61, 69.26, 67.29, 64.69, 58.88; ESI-MS (m/z): [M+1] 432.9 and purity in HPLC = 99%.

(3R,3aR,6R,8aR,8bS)-3-(3-chlorophenyl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11g):



Yield = 83% (178 mg); yellow solid; R_f = 0.6 (30% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.40-7.28 (m, 6H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.20-7.14 (m, 2H), 7.06 (dd, J_1 = 9.8 Hz, J_2 = 8.9 Hz, 3H), 6.27 (s, 1H), 5.04 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 4.93 (d, *J* = 9.2 Hz, 1H), 4.40-4.30 (m, J_1 = 11.9 Hz, J_2 = 4.5 Hz, 2H), 4.28-4.26 (m, J_1 = 7.2 Hz, J_2 = 8.8 Hz, 1H) 3.95 (t, J_1 = 9.2 Hz, J_2 = 8.8 Hz, 1H), 3.63 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.78, 148.18, 137.86, 137.7, 134.74, 129.82, 129.93, 128.58, 128.48, 128.44, 127.46, 126.1, 125.5, 124.02, 117.25, 86.79, 79.39, 70.88, 69.24, 64.52, 61.0; ESI-MS (m/z): [M+1] 432.9 and purity in HPLC = 96%.

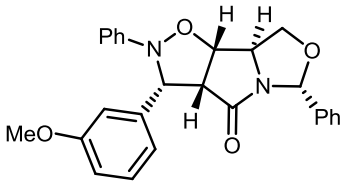
(3R,3aR,6R,8aR,8bS)-3-(3-bromophenyl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11h):



Yield = 78% (185 mg); brown solid; MP: 72-75 ^{o}C; R_f = 0.6 (30% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.47 (dd, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.35 (dd, *J* = 4.5 Hz, 3H), 7.08-6.99 (m, 3H), 7.16

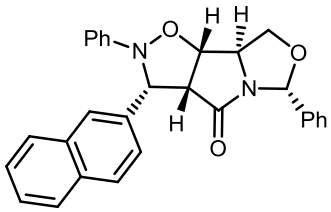
(d, J = 6.7 Hz, 2H), 7.26-7.18 (m, 3H), 6.26 (s, 1H), 5.03 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 4.88 (d, J = 9.2 Hz, 1H), 4.35 (t, J = 7.5 Hz, 1H), 4.28-4.24 (m, 1H), 3.96 (t, J_1 =9.2 Hz, J_2 = 8.8 Hz, 1H), 3.61 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.88, 148.24, 138.15, 137.72, 131.53, 130.34, 130.13, 128.98, 128.53, 128.49, 126.62, 125.56, 124.07, 122.97, 117.26, 86.89, 79.48, 70.88, 69.25, 64.55, 61.03; ESI-MS (m/z): [M+1] 478.9; and purity in HPLC = 95%.

(3R,3aR,6R,8aR,8bS)-3-(3-methoxyphenyl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11i):



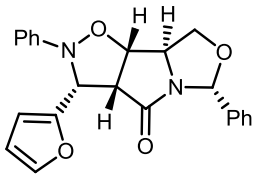
Yield = 57% (121 mg); brown solid; MP: 134-135 ^{o}C; R_f = 0.6 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 8H), 7.11-7.02 (m, 4H), 6.97 (t, J = 7.3 Hz, 1H), 6.83 (dd, J_1 = 8.1 Hz, J_2 = 2.2 Hz, 1H), 6.34 (s, 1H), 5.24 (s, 1H), 4.96 (d, J = 8 Hz, 1H), 4.35-4.31 (m, J_1 = 16.3 Hz, J_2 =7.1 Hz, 1H), 4.28-4.24 (m, 1H), 3.85 (m, 4H), 3.44-3.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.03, 159.87, 148.22, 140.72, 137.78, 129.87, 128.8, 128.56, 128.38, 125.69, 122.45, 119.19, 115.83, 113.41, 112.36, 87.93, 77.44, 69.61, 67.99, 64.49, 62.02, 55.26; ESI-MS (m/z): [M+1] 429.0 and purity in HPLC = 95%.

(3R,3aR,6R,8aR,8bS)-3-(naphthalen-2-yl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11J):



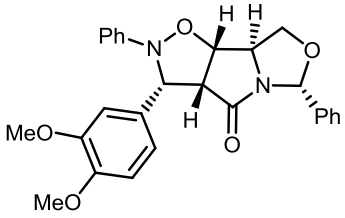
Yield = 69% (153 mg); brown solid; MP: 76-79 ^{o}C; R_f = 0.6 (50% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.85 (dd, J_1 = 10.1 Hz, J_2 = 5.1 Hz, 2H), 7.78-7.73 (m, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.52-7.47 (m, 2H), 7.24-7.18 (m, 3H), 7.10-7.0 (m, 5H), 6.91 (d, J = 7.6 Hz, 2H), 6.18 (s, 1H), 5.07 (t, 2H), 4.38-4.14 (t, J = 8.8 Hz, 2H), 4.02 (t, J = 8.8 Hz, 1H), 3.63 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.74, 148.69, 137.73, 133.33, 128.91, 128.38, 128.34, 128.26, 128.22, 127.82, 126.72, 126.22, 126.2, 125.46, 123.77, 117.11, 86.61, 79.67, 71.66, 69.43, 64.73, 61.37. ESI-MS (m/z): [M+1] 448.9; and purity in HPLC = 97%.

(3R,3aR,6R,8aR,8bS)-3-(furan-2-yl)-2,6-diphenylhexahydrooxazolo[3',4':1,5] pyrrolo [3,4-d]isoxazol-4(2H)-one (2.11k):



Yield = 59% (114 mg); brown solid; R_f = 0.6 (50% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.31 (m, 6H), 7.29-7.22 (m, 3H), 7.11-6.99 (m, 3H), 6.39 (dd, *J* = 7.3 Hz, 2H), 5.02 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 2H), 4.96 (dd, J_1 = 9.2 Hz, J_2 = 8.8 Hz, 1H), 4.39-4.27 (m, 2H), 3.91 (t, J_1 = 9.2 Hz, J_2 = 8.8 Hz, 1H), 3.60 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.83, 148.58, 148.14, 142.89, 138.01, 128.92, 128.57, 125.79, 124.23, 117.23, 110.67, 109.61, 87.08, 79.28, 69.22, 66.33, 64.58, 59.27; ESI-MS (m/z): [M+1] 389.0 and purity in HPLC = 97%.

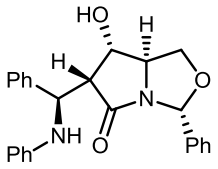
(3R,3aR,6R,8aR,8bS)-3-(3,4-dimethoxyphenyl)-2,6-diphenylhexahydrooxazolo [3',4':1,5]pyrrolo[3,4-d]isoxazol-4(2H)-one (2.11l):



Yield = 53% (120 mg); brown solid; MP: 139-142 ^{o}C; R_f = 0.6 (60% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 3H), 7.21 (m, 4H), 7.02 (m, 5H), 6.81 (d, 1H), 6.22 (s, 1H), 5.02 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 4.81 (d, *J* = 9.2 Hz, 1H), 4.43-4.29 (m, 2H), 3.92 (dd, J_1 = 9.2 Hz, J_2 = 8.8 Hz, 4H), 3.67-3.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.09, 149.01, 148.86, 148.71, 138.13, 128.83, 128.66, 128.39, 127.83, 125.76, 123.84, 120.3, 117.26, 110.35, 110.32, 87.07, 79.12, 71.76, 69.5, 65.01, 61.25, 55.71, 55.65; ESI-MS (m/z): [M+1] 459.0 and purity in HPLC = 92%.

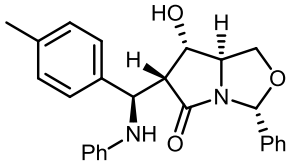
General procedure for catalytic hetero bond cleavage: Nitrone adduct **2.11a** (25 mg, 0.063 mmol) was dissolved in 10 ml of EtOAc and added dry. 5% Pd/C (10 mol %), then allowed to stir for 30 mins under 1 atm H_2. After completion of the reaction monitored by TLC, crude reaction was passed over the celite pad before removing the solvent under reduced pressure.

(3R,6R,7S,7aR)-7-hydroxy-3-phenyl-6-((R)-phenyl(phenylamino)methyl) tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12a):



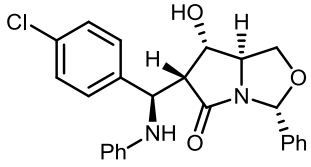
Yield = 98% (24 mg); brown solid; MP: 186-189 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 10H), 7.12 (t, *J* = 7.9 Hz, 2H), 6.80-6.56 (m, 3H), 6.33 (s, 1H), 5.12 (d, *J* = 4.8 Hz, 1H), 4.49 (dd, J_1 = 8.1 Hz, J_2 = 4.2 Hz, 1H), 4.19-4.14 (m, 1H), 3.82 (dt, J_1 = 7.0 Hz, J_2 = 4.4 Hz, 1H), 3.56 (t, *J* = 8.1 Hz, 1H), 3.35 (dd, J_1 = 8.1 Hz, J_2 = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.87, 145.95, 139.98, 137.72, 129.26, 128.77, 128.66, 128.50, 127.66, 127.40, 125.98, 119.09, 114.90, 87.63, 72.15, 68.93, 66.18, 55.77, 55.20; ESI-MS (m/z): [M+1] 401.1; HRMS (ESI-MS) Calcd for $C_{25}H_{24}N_2O_3$ $[M+H]^+$ 401.1820; found 401.1865; purity in HPLC = 95%; and $[\alpha]_D$ ¼ = +132.85 (c 0.32, $CHCl_3$).

(3R,6R,7S,7aR)-7-hydroxy-3-phenyl-6-((R)-(phenylamino)(p-tolyl)methyl) tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12b):



Yield = 97% (24 mg); brown solid; MP: 165-167 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 7H), 7.11 (dd, *J* = 12.1, 5.6 Hz, 4H), 6.74-6.70 (m, 3H), 6.31 (s, 1H), 5.08 (dd, *J* = 4.8 Hz, 1H), 4.48 (dd, J_1= 8.1 Hz, J_2 = 4.3 Hz, 1H), 4.17-4.13 (m, 1H), 3.81 (dd, J_1 = 11.3 Hz, J_2 = 6.9 Hz, 1H), 3.54 (t, *J* = 8.1 Hz, 1H), 3.33 (dd, J_1 = 8.1 Hz, J_2 = 4.9 Hz, 1H), 2.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ175.83, 146.06, 137.72, 137.29, 136.83, 129.33, 129.23, 128.74, 128.44, 127.31, 126.02, 118.98, 114.89, 87.52, 72.41, 69.02, 66.08, 60.44, 55.71, 21.07; ESI-MS (m/z): [M+1] 415.0; HRMS (ESI-MS) Calcd for $C_{26}H_{26}N_2O_3$ $[M+H]^+$ 415.1977; found 415.2025; purity in HPLC = 97%; and $[\alpha]_D$ ¼ = +130 (c 0.32, $CHCl_3$).

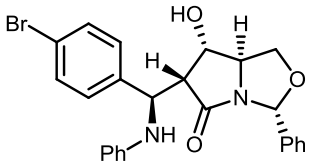
(3R,6R,7S,7aR)-6-((R)-(4-chlorophenyl)(phenylamino)methyl)-7-hydroxy-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12c):



Yield = 96% (24 mg); brown solid; MP: 180-184 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 5H), 7.29-7.23 (m, 3H), 7.12 (dd, J_1 = 8.1 Hz, J_2 = 7.6 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.6 (d, *J* = 7.7 Hz, 2H), 6.28 (s, 1H), 5.07 (d, *J* = 4.3 Hz, 1H), 4.44 (dd, J_1 = 7.8

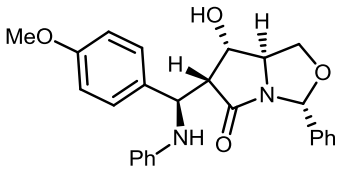
Hz, J_2 = 4.6 Hz, 1H), 4.11 (dd, J_1= 8.3 Hz, J_2 = 6.8 Hz, 1H), 3.73 (dd, J_1 = 11.7 Hz, J_2 = 6.9 Hz, 1H), 3.51 (dd, J_1 = 10.2 Hz, J_2 = 5.7 Hz, 2H), 3.31 (dd, J_1 = 8.1 Hz, J_2 = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.30, 145.78, 138.54, 137.48, 133.35, 129.33, 129.03, 128.95, 128.71, 128.58, 125.97, 119.06, 114.67, 87.45, 72.38, 69.13, 66.01, 55.50, 55.46. ESI-MS (m/z): [M+1] 434.9; and purity in HPLC = 95%; $[\alpha]_D^{¼}$ = +134.78 (c 0.32, $CHCl_3$).

(3R,6R,7S,7aR)-6-((R)-(4-bromophenyl)(phenylamino)methyl)-7-hydroxy-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12d):



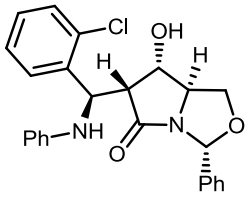
Yield = 96% (24 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.30 (m, 9H), 7.13 (t, J = 7.7 Hz, 2H), 6.75 (s, 1H), 6.62 (d, J = 7.9 Hz, 2H), 6.33 (d, J = 8.5 Hz, 1H), 5.08 (dd, J = 4.2 Hz, 1H), 4.52 (dd, J = 3.6 Hz, 1H), 4.18 (t, J = 7.4 Hz, 1H), 3.81 (t, J = 4.9 Hz, 1H), 3.58 (t, J = 8.1 Hz, 1H), 3.33 (t, J = 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ175.3, 145.8, 138.5, 137.5, 133.3, 129.3, 129.0, 128.9, 128.7, 126.0, 119.1, 114.7, 87.5, 72.4, 69.1, 66.0, 550.5, 55.55; ESI-MS (m/z): [M+1] 480.9 and purity in HPLC = 96%.

(3R,6R,7S,7aR)-7-hydroxy-6-((R)-(4-methoxyphenyl)(phenylamino)methyl)-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12e):



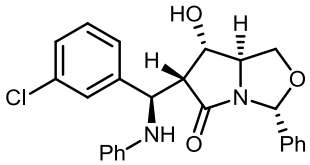
Yield = 96% (24 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.23 (m, 7H), 7.12 (m, J = 7.8 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.74 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 7.9 Hz, 2H), 6.32 (s, 1H), 5.06 (dd, J = 4.8 Hz, 1H), 4.48 (dd, J = 8.0 Hz, J_2 = 4.4 Hz, 1H), 4.16 (t, J = 7.5 Hz, 1H), 3.79-3.76 (m, 4H), 3.56 (t, J = 8.1 Hz, 1H), 3.34 (dd, J = 8.1 Hz, J_2 = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ175.81, 158.98, 146.08, 137.73, 131.81, 129.24, 128.76, 128.59, 128.46, 126.01, 119.01, 114.93, 113.96, 87.5, 72.5, 72.47, 69.07, 66.06, 55.59, 55.18; ESI-MS (m/z): [M+1] 430.9 and purity in HPLC = 96%.

(3R,6R,7S,7aR)-6-((R)-(2-chlorophenyl)(phenylamino)methyl)-7-hydroxy-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12f):



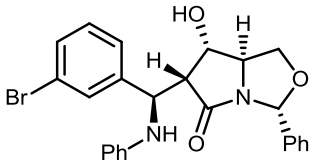
Yield = 95% (23 mg); brown solid; MP: 124-127 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.33 (m, 7H), 7.18 (m, 6.70 Hz, 4H), 6.78-6.75 (t, *J* = 7.3 Hz, 1H), 6.65-6.32 (d, *J* = 7.8 Hz, 2H), 6.33 (s, 1H), 5.57 (s, 1H), 4.62 (d, 1H), 4.34-4.30 (m, 1H), 4.12-4.10 (m, 1H), 3.56 (t, *J* = 8.4 Hz, 1H), 3.34 (dd, J_1 = 8.1 Hz, J_2 = 2.7 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ176.37, 144.69, 138.22, 136.48, 132.7, 129.63, 129.42, 128.86, 128.82, 128.64, 128.44, 126.96, 125.92, 119.99, 115.2, 86.04, 70.54, 68.72, 67.27, 52.7, 50.58.ESI-MS (m/z): [M+1] 435.0; and purity in HPLC = 95%.

(3R,6R,7S,7aR)-6-((R)-(3-chlorophenyl)(phenylamino)methyl)-7-hydroxy-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12g):



Yield = 97% (24 mg); brown solid; MP: 173-176 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.47-7.25 (m, 7H), 7.23 (m, J_1 = 11.6 Hz, J_2 = 8.5 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 2H), 6.63 (d, *J* = 7.8 Hz, 2H), 6.34 (s, 1H), 5.04 (d, 1H), 4.44 (dd, *J* = 7.9 Hz, 1H), 4.23-4.11 (m, 1H), 3.90-3.71 (m, 1H), 3.57 (t, *J* = 8.1 Hz, 1H), 3.31 (dd, J_1 = 7.9 Hz, J_2 = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.72, 145.64, 142.48, 137.55, 134.45, 129.80, 129.29, 128.77, 128.53, 127.83, 127.64, 125.87, 125.62, 119.13, 114.67, 87.7, 71.83, 68.72, 66.11, 55.19, 55.01; ESI-MS (m/z): [M+1] 435.0; and purity in HPLC = 96%.

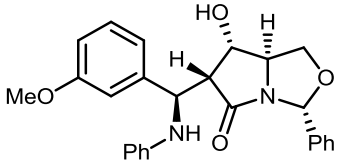
(3R,6R,7S,7aR)-6-((R)-(3-bromophenyl)(phenylamino)methyl)-7-hydroxy-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (3.12h):



Yield = 98% (24 mg); brown solid; MP: 179-181 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.42-7.26 (m, 7H), 7.14 (dd, J_1 = 16.8 Hz, J_2 = 8.2 Hz, 3H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 2H), 6.34 (s, 1H), 5.07 (d, *J* = 4.7 Hz, 1H), 4.49 (dd, J_1 = 7.7 Hz, J_2 = 3.9 Hz, 1H), 4.17 (dd, J_1 = 8.3 Hz, J_2 = 6.8 Hz, 1H), 3.82 (dt, J_1 = 7.6 Hz, J_2 = 4.2 Hz, 1H), 3.56 (t, *J* = 8.1 Hz, 1H), 3.30 (dd, J_1 = 8.0, J_2 = 4.80 Hz, 1H);

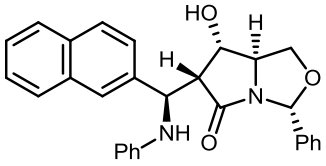
^{13}C NMR (100 MHz, $CDCl_3$) δ175.78, 145.71, 142.91, 137.62, 130.79, 130.58, 130.13, 129.32, 128.8, 128.58, 126.12, 125.91, 122.75, 119.18, 109.99, 87.77, 71.82, 68.73, 68.16, 55.21, 55.06; ESI-MS (m/z): [M+1] 480.9 and purity in HPLC = 98%.

(3R,6R,7S,7aR)-7-hydroxy-6-((R)-(3-methoxyphenyl)(phenylamino)methyl)-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12i):



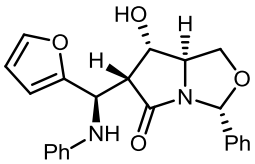
Yield = 97% (24 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 5.1, 1.6 Hz, 3H), 7.25-7.06 (m, 5H), 7.0 (m, 7.9 Hz, 5H), 6.81 (dd, J_1 = 8.3 Hz, 1.8 Hz, 1H), 6.32 (s, 1H), 5.22 (d, *J* = 2.4 Hz, 1H), 4.94 (d, *J* = 7.6 Hz, 1H), 4.35-4.24 (m, 2H), 3.78 (m, *J* = 5.7 Hz, 4H), 3.40 (dd, J_1 = 9.2 Hz, J_2 = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.78, 148.18, 137.86, 137.7, 134.74, 129.82, 128.93, 128.56, 128.48, 128.44, 127.46, 126.1, 125.5, 124.02, 117.25, 86.79, 79.39, 76.65, 70.86, 69.24, 64.52, 61.0; ESI-MS (m/z): [M+1] 430.9 and purity in HPLC = 97%.

(3R,6R,7S,7aR)-7-hydroxy-6-((R)-naphthalen-2-yl(phenylamino)methyl)-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12J):



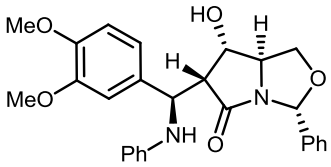
Yield = 98% (24 mg); brown solid; MP: 185-187 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.79 (dd, J_1 = 8.8 Hz, J_2 = 5.8 Hz, 3H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.47 (m, J_1 = 5.3 Hz, J_2 = 4.1 Hz, 2H), 7.31-7.16 (m, 5H), 7.10 (t, *J* = 7.8 Hz, 2H), 6.70 (t, *J* = 7.2 Hz, 3H), 6.31 (s, 1H), 5.27 (d, 1H), 4.51 (dd, J_1 = 8.1 Hz, J_2 = 4.46 Hz, 1H), 4.17 (dd, J_1 = 8.3 Hz, J_2 = 6.9 Hz, 1H), 3.78 (dd, J_1 = 6.9 Hz, J_2 = 4.6 Hz, 1H), 3.46-3.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.89, 146.07, 137.63, 137.48, 133.23, 132.95, 129.26, 128.70, 128.54, 128.45, 128.04, 127.67, 126.65, 126.25, 126.06, 125.90, 125.18, 119.01, 114.83, 87.61, 72.44, 68.81, 66.03, 56.23, 55.29; ESI-MS (m/z): [M+1] 451.1; and purity in HPLC = 97%.

(3R,6R,7S,7aR)-6-((R)-furan-2-yl(phenylamino)methyl)-7-hydroxy-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12k):



Yield = 94% (23 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 12.5 Hz, 6H), 7.18 (t, *J* = 7.9 Hz, 2H), 6.87-6.62 (m, 3H), 6.34-6.25 (m, 3H), 5.20 (d, *J* = 4.7 Hz, 1H), 4.55 (dd, J_1 = 8.1 Hz, J_2 = 4.2 Hz, 1H), 4.23 (d, *J* = 7.1 Hz, 1H), 3.84- 3.80 (m, J_1 = 7.1 Hz, J_2 = 4.4 Hz, 1H), 3.61-3.57 (m, 1H), 3.59-3.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 153.09, 145.98, 141.88, 137.78, 129.35, 128.74, 128.48, 125.96, 119.45, 114.67, 110.82, 108.03, 87.52, 71.63, 69.08, 66.18, 53.32, 50.39; ESI-MS (m/z): [M+1] 391.0 and purity in HPLC = 97%.

(3R,6R,7S,7aR)-6-((R)-(3,4-dimethoxyphenyl)(phenylamino)methyl)-7-hydroxy-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (2.12l):



Yield = 98% (24 mg); brown solid; MP: 146-149 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 7.20-6.90 (m, 4H), 6.77-6.71 (m, 4H), 6.28 (s, 1H), 5.04 (d, *J* = 4.9 Hz, 1H), 4.47 (dd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, 1H), 4.10-4.08 (m, 1H), 3.83-3.82 (m, 7H), 3.59 (dd, J_1 = 14.1 Hz, J_2 = 5.9 Hz, 1H), 3.33 (dd, J_1 = 8.1 Hz, J_2 = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.76, 148.86, 148.3, 146.24, 137.56, 132.48, 129.21, 128.82, 128.49, 126.02, 125.96, 119.69, 118.81, 114.74, 110.88, 110.72, 87.46, 72.60, 69.06, 65.89, 56.11, 55.78, 55.48.ESI-MS (m/z): [M+1] 460.9; and purity in HPLC = 99%.

2.6. References:

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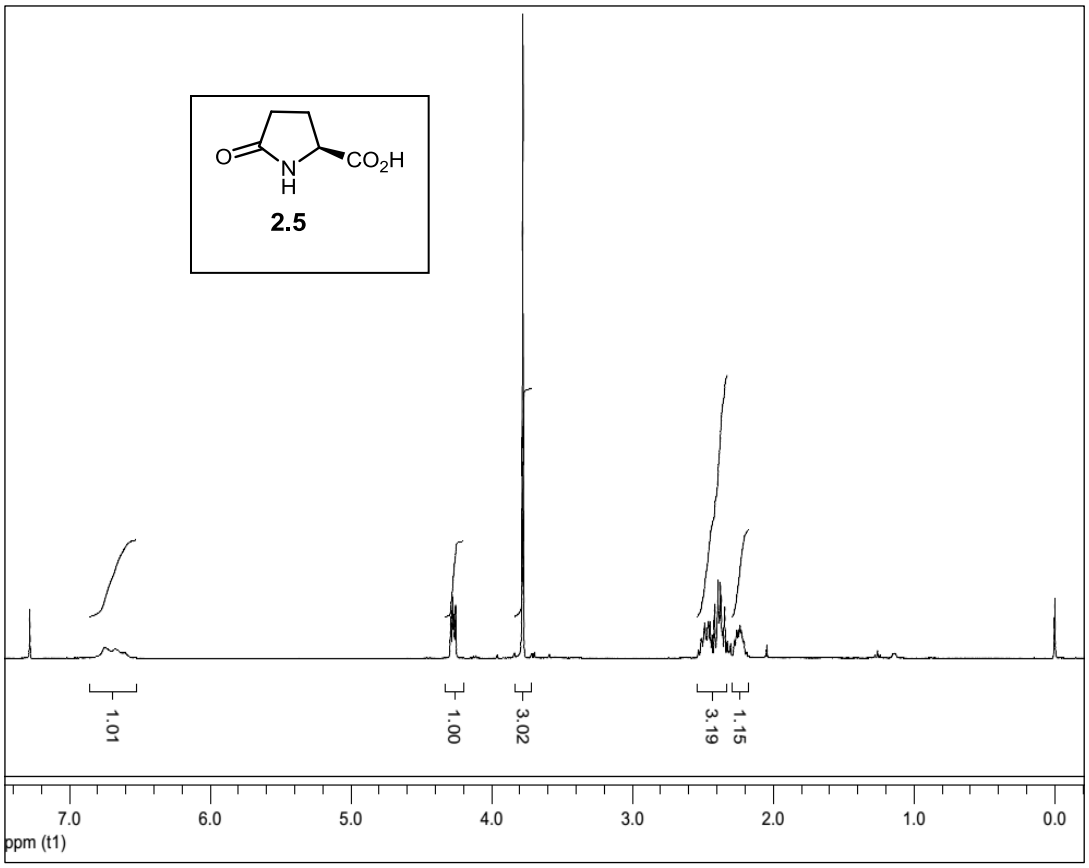
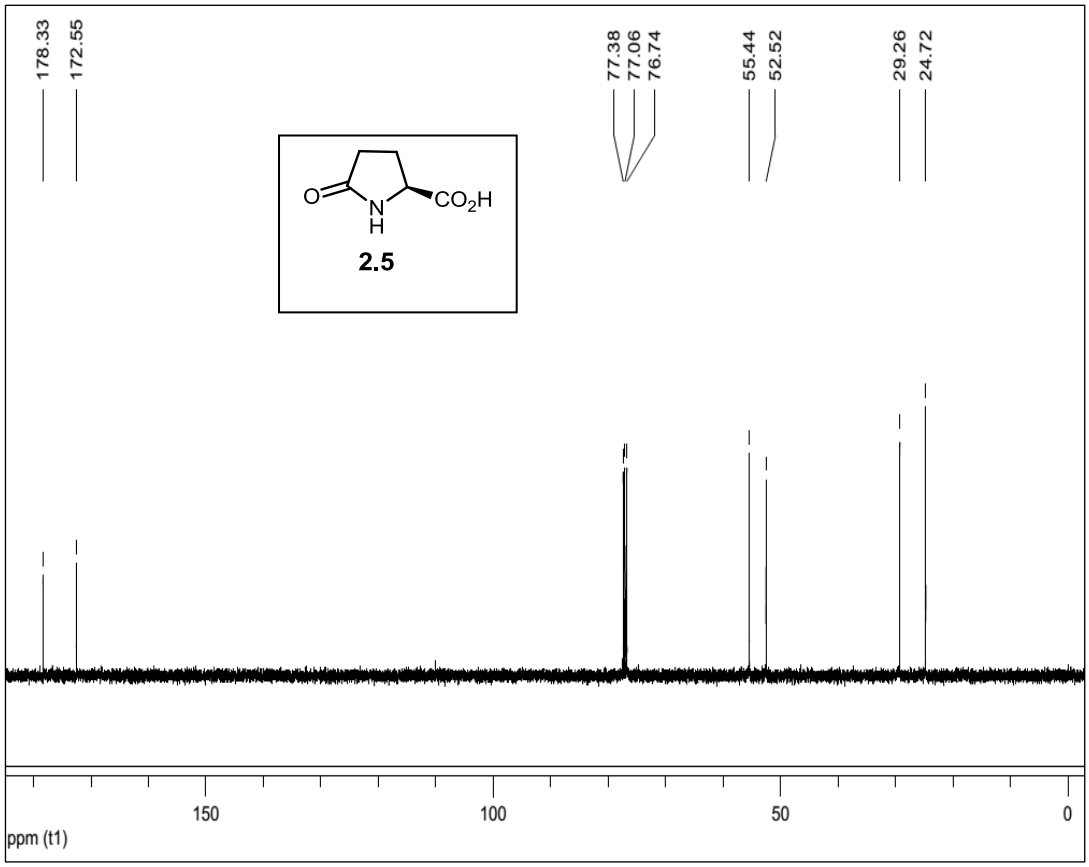
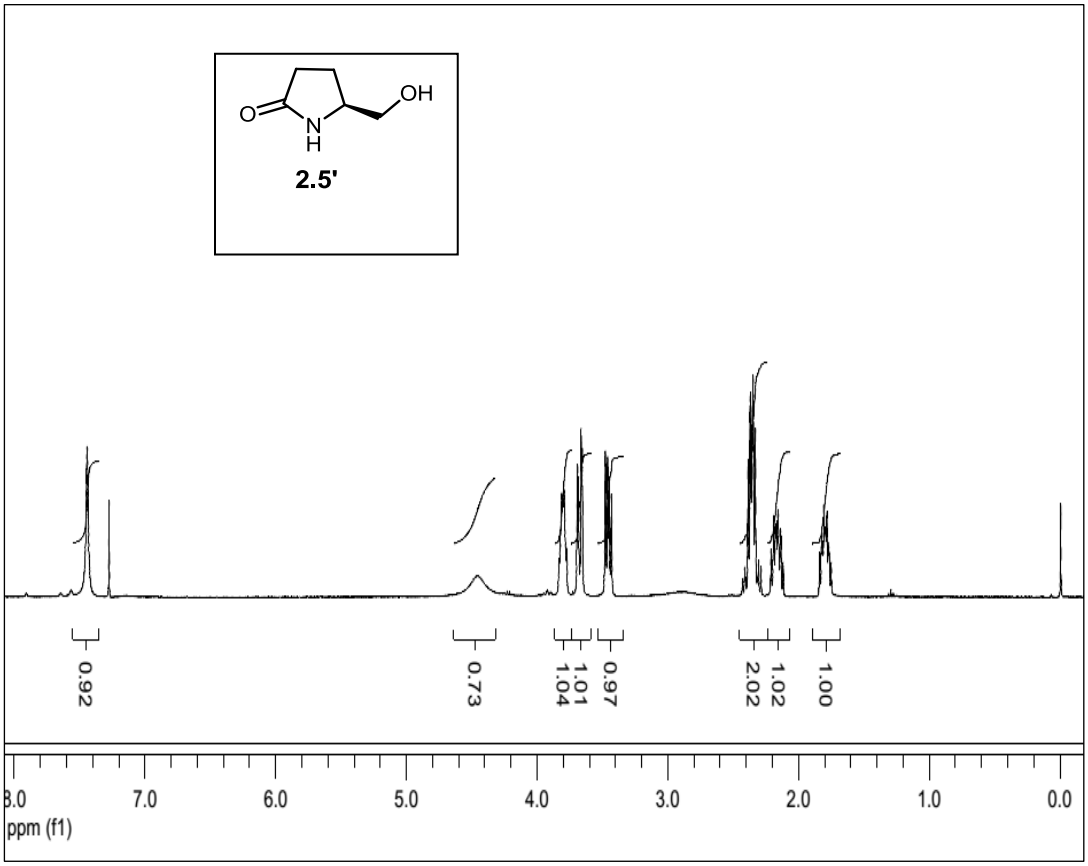
2.7. Appendices:



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O
N
H
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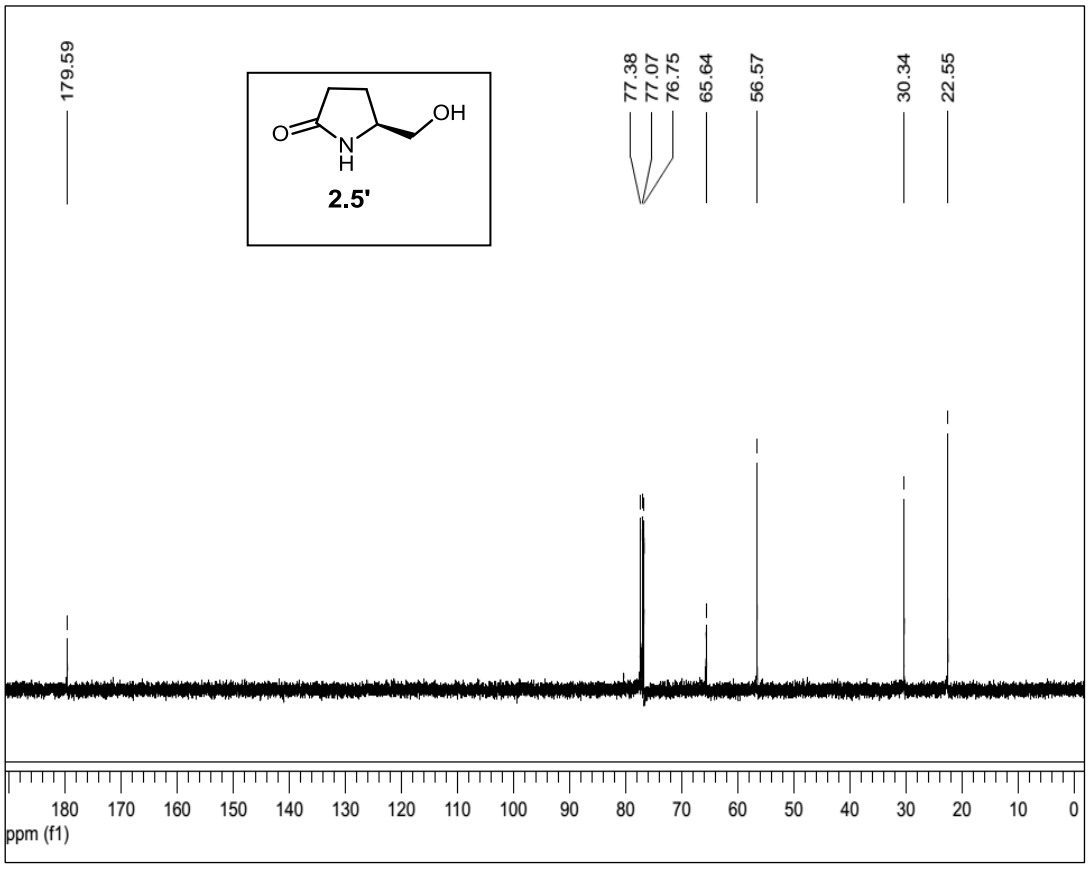
0.92
0.73
1.01
1.04
0.97
2.02
1.02
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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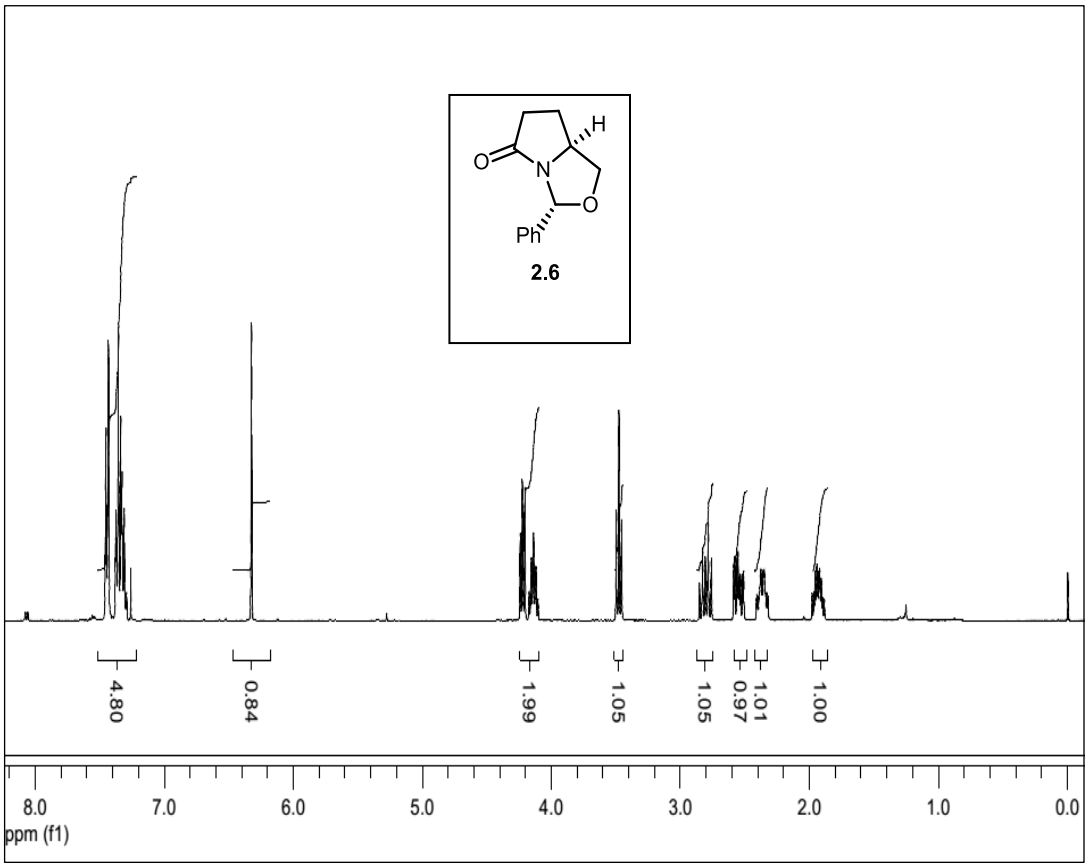
77.38
77.07
76.75
65.64
56.57
30.34
22.55
OH
O
N
H
2.5'
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)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O
N
O
Ph
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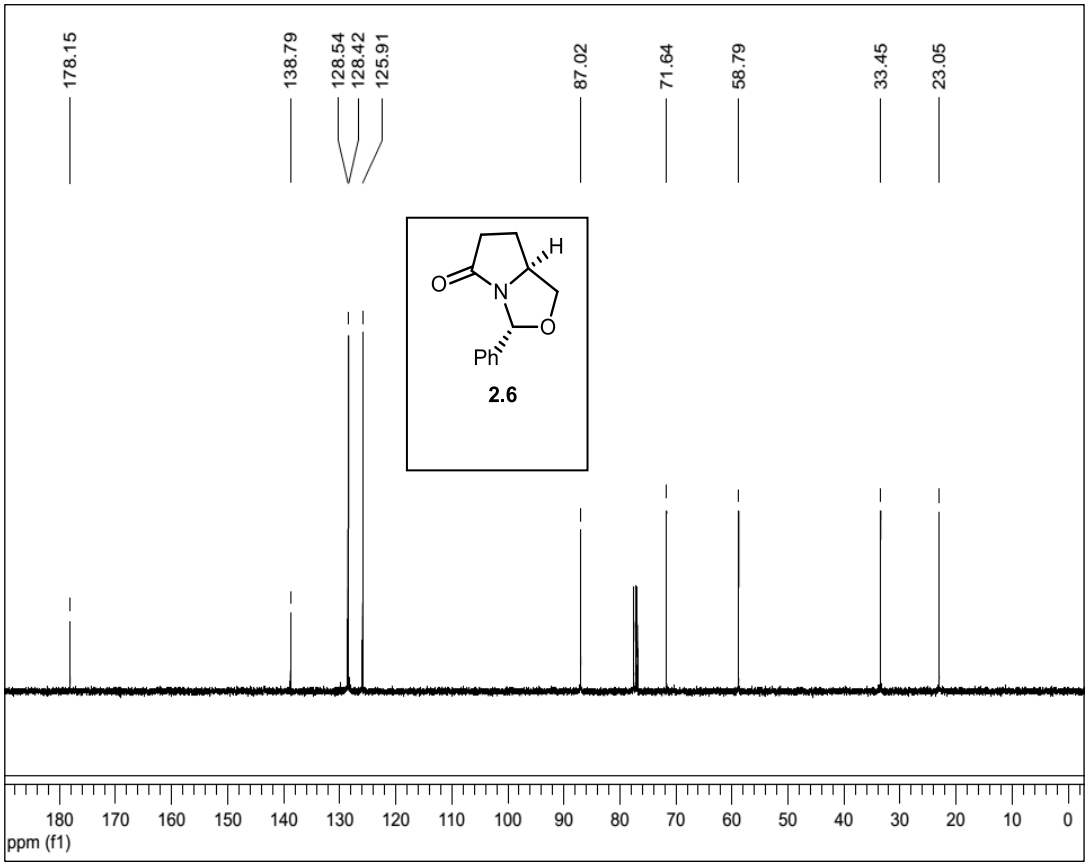
4.80
0.84
1.99
1.05
1.05
0.97
1.01
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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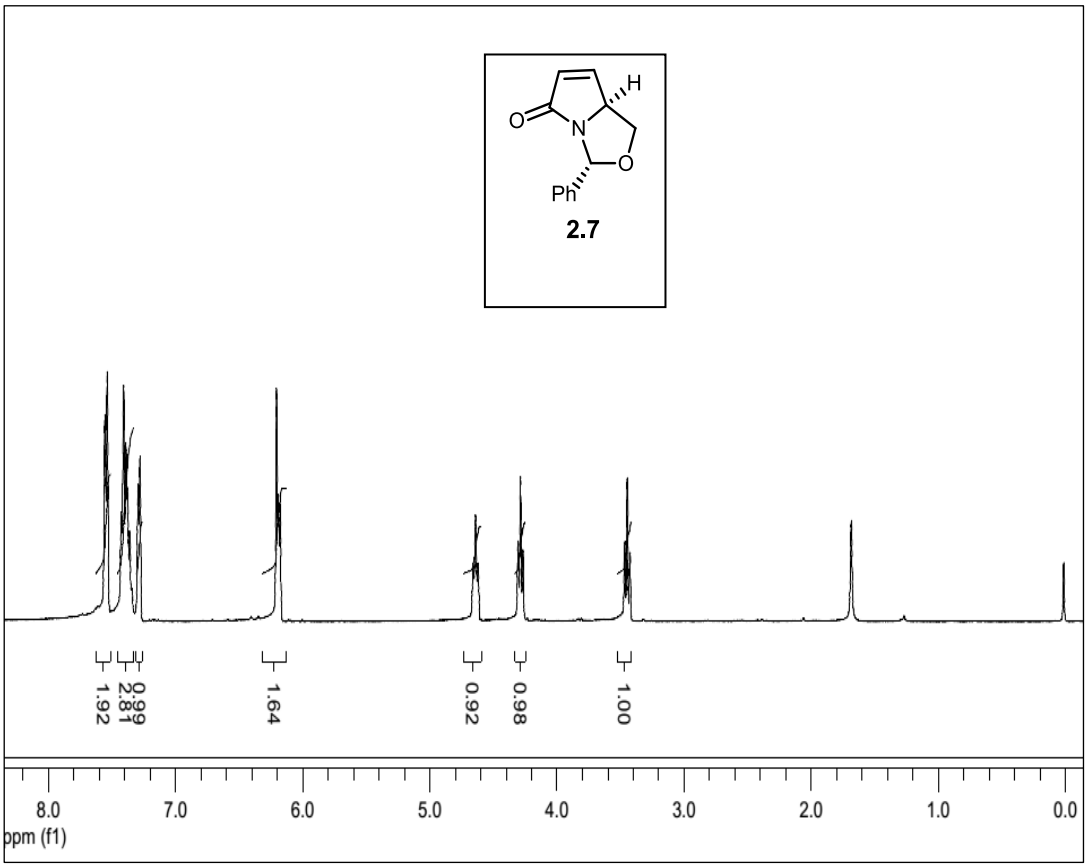
138.79
128.54
128.42
125.91
87.02
71.64
58.79
33.45
23.05
H
O
N
O
Ph
2.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)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N
H
O
Ph
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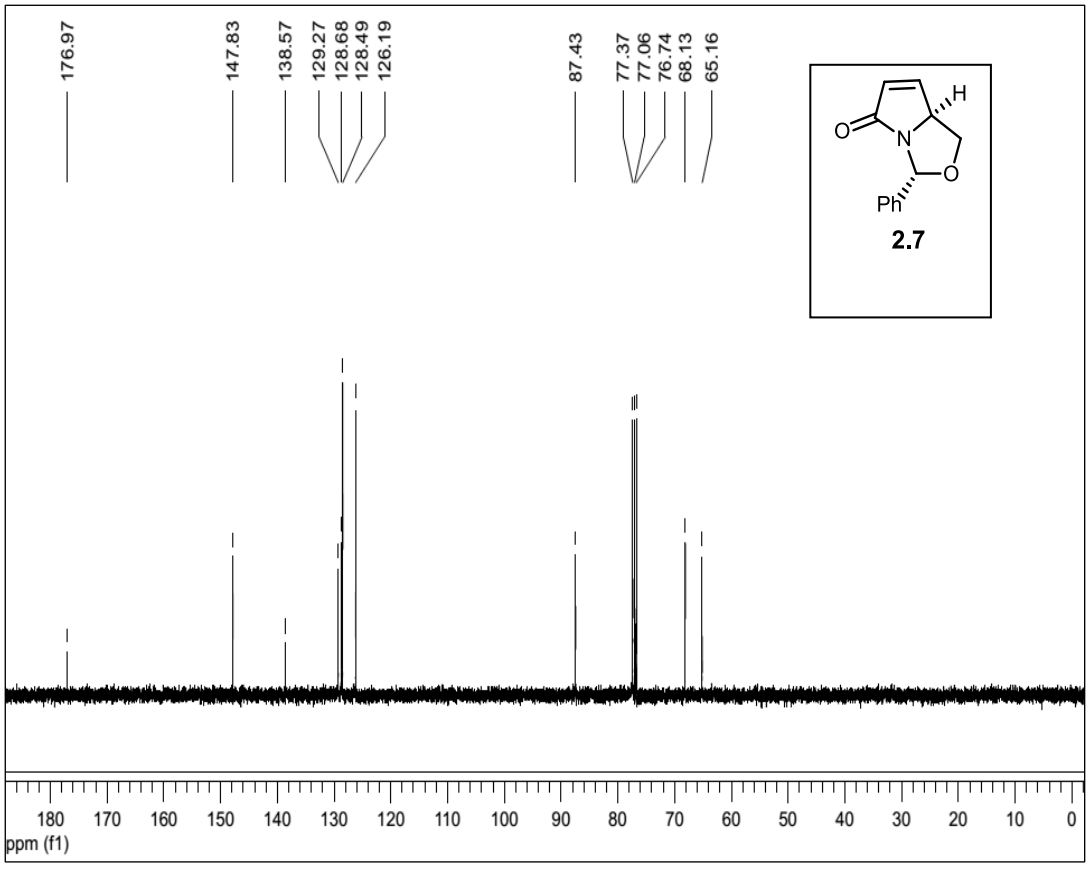
1.92
2.81
0.99
1.64
0.92
0.98
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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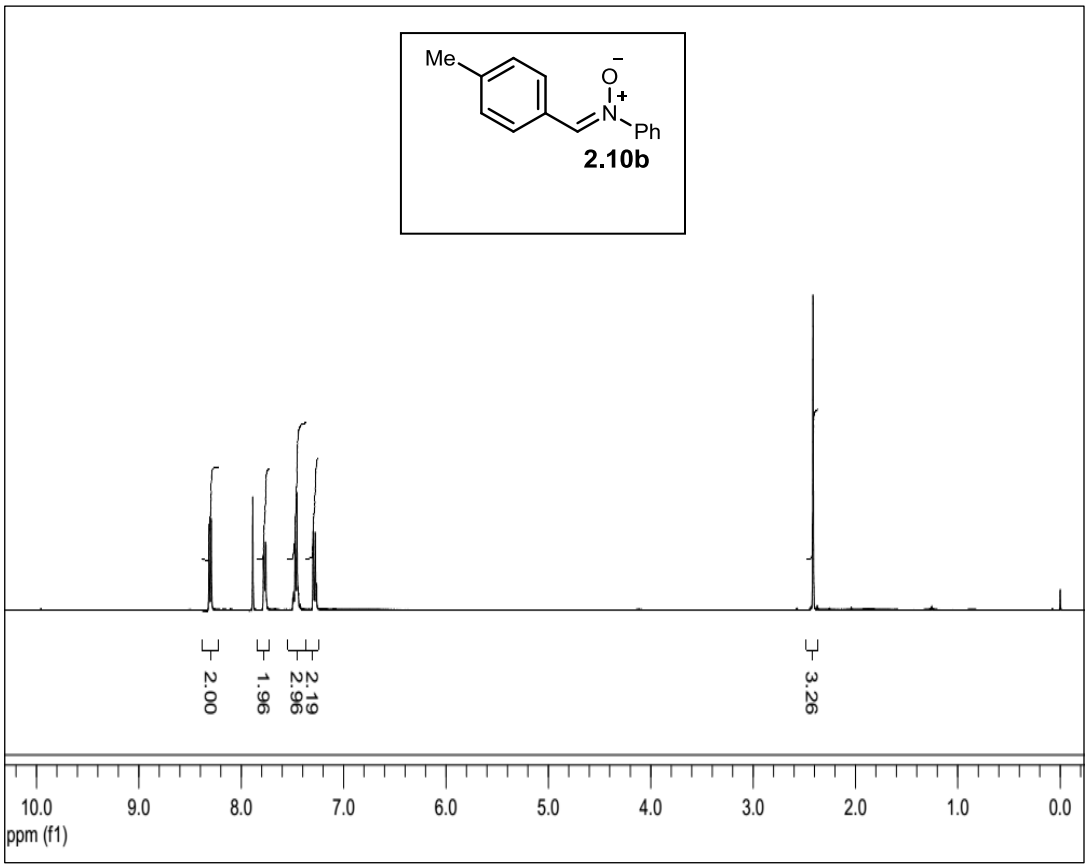
129.27
128.68
128.49
126.19
87.43
77.37
77.06
76.74
68.13
65.16
O
N
H
O
Ph
2.7
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)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O
N
Ph
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2.00
1.96
2.96
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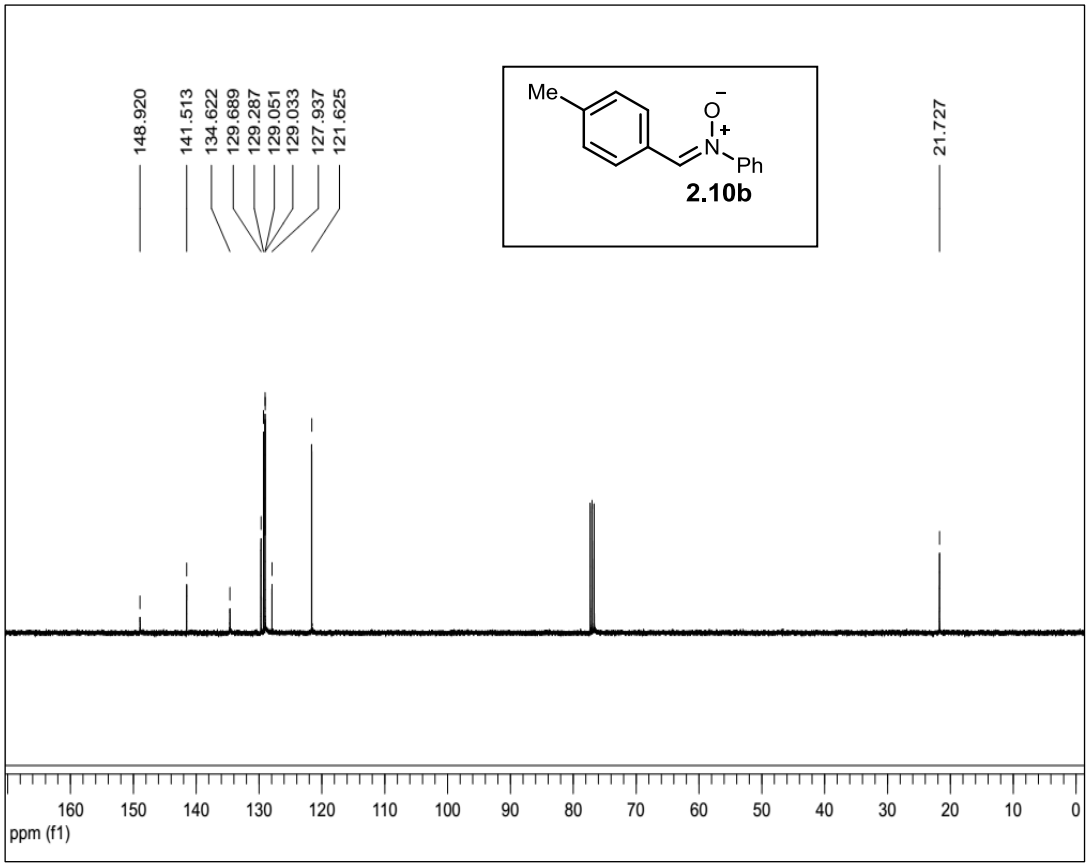
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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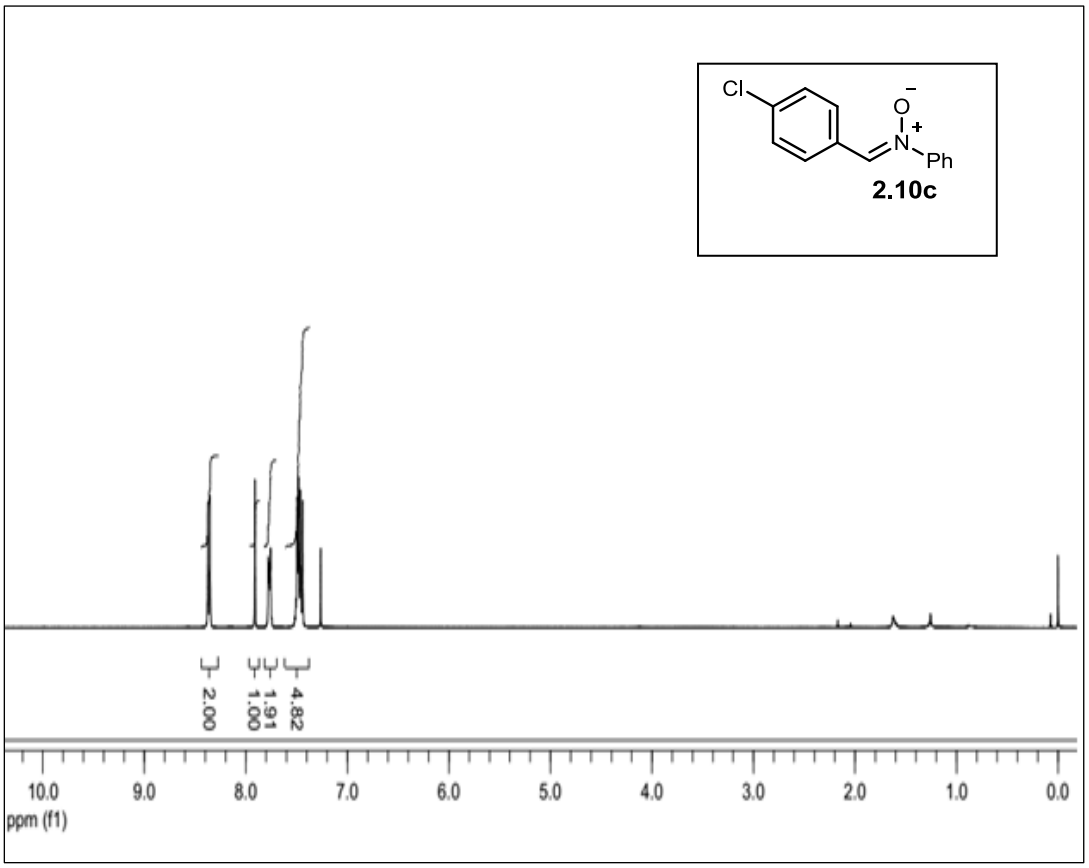
129.689
129.287
129.051
129.033
127.937
121.625
Me
O
N
Ph
2.10b
21.727
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)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N
Ph
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1.00
1.91
4.82
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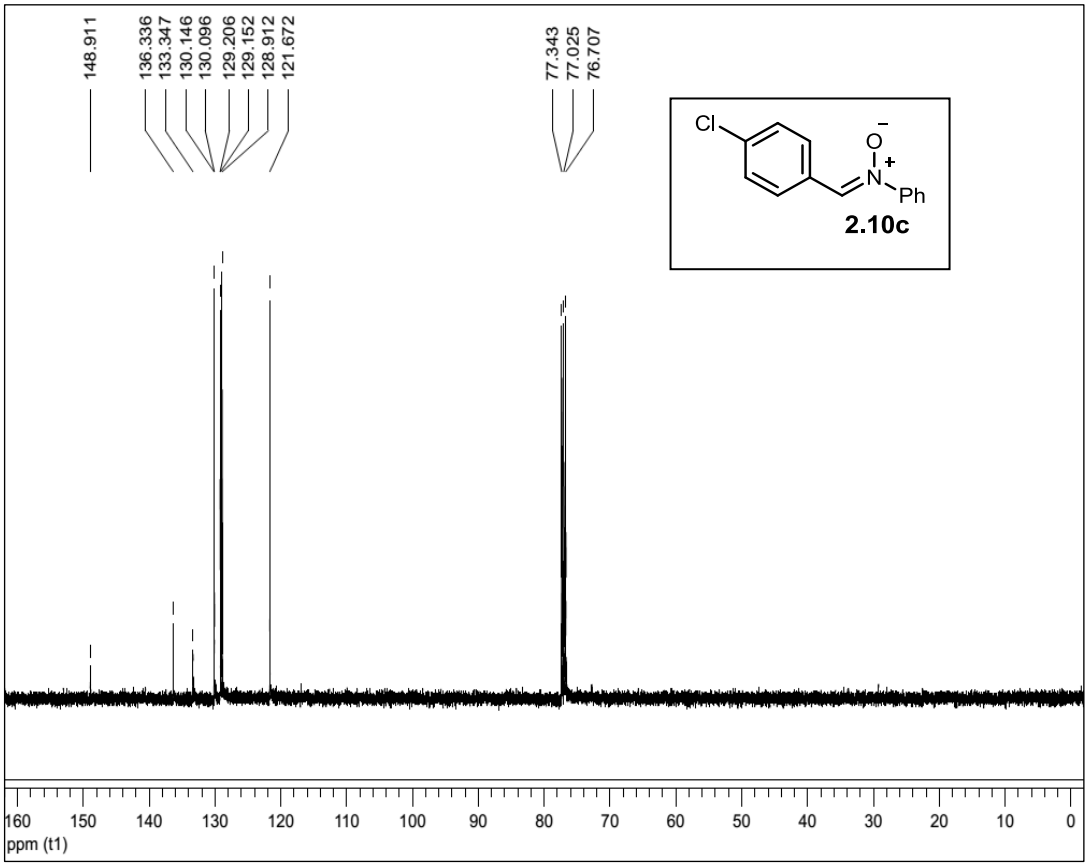
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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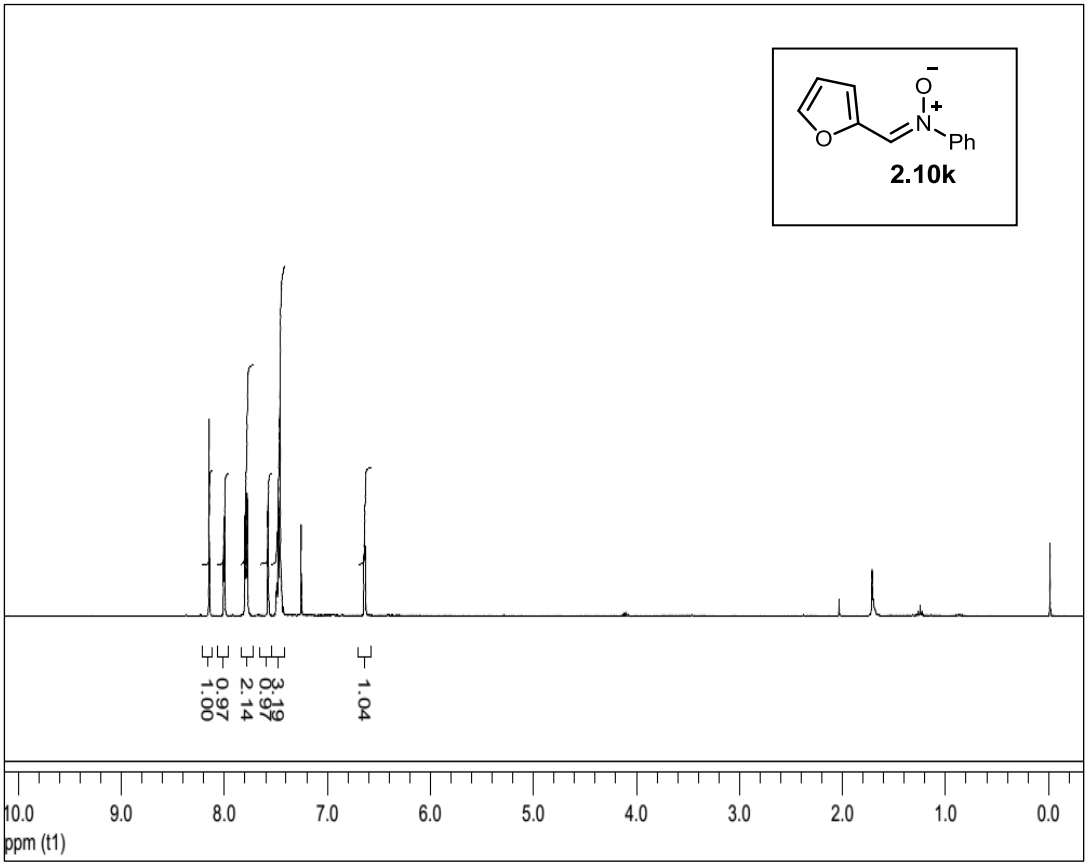
129.206
129.152
128.912
121.672
77.343
77.025
76.707
Cl
O
N
Ph
2.10c
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (t1)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0.97
1.04
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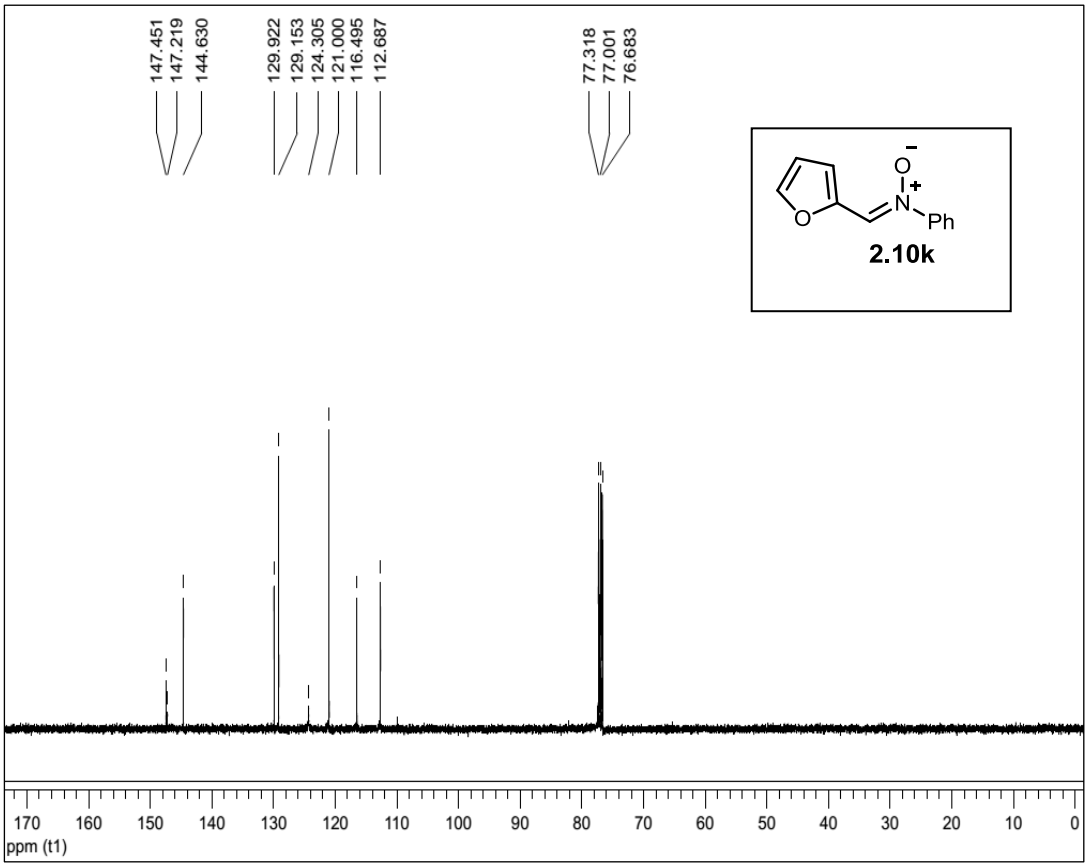
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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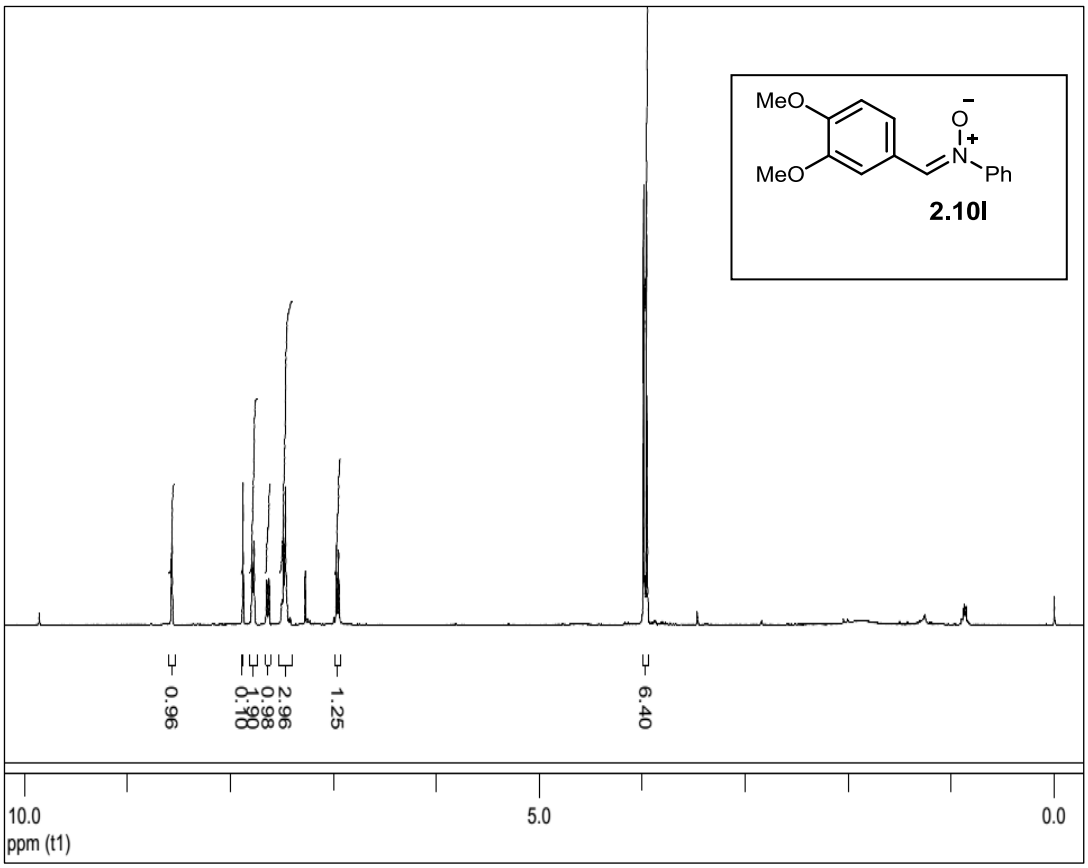
129.153
124.305
121.000
116.495
112.687
77.318
77.001
76.683
2.10k
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (t1)


MeO
MeO
O
N
Ph
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0.98
2.96
1.25
9.40
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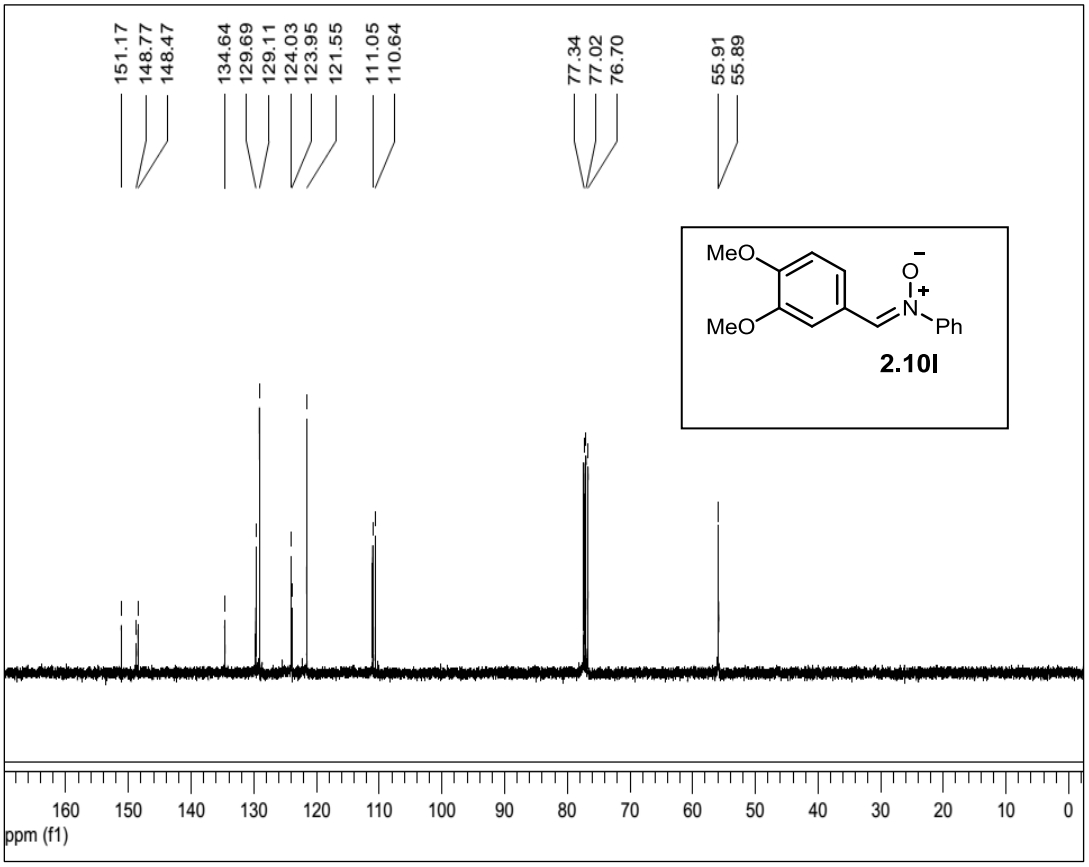
5.0
0.0
ppm (t1)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134.64
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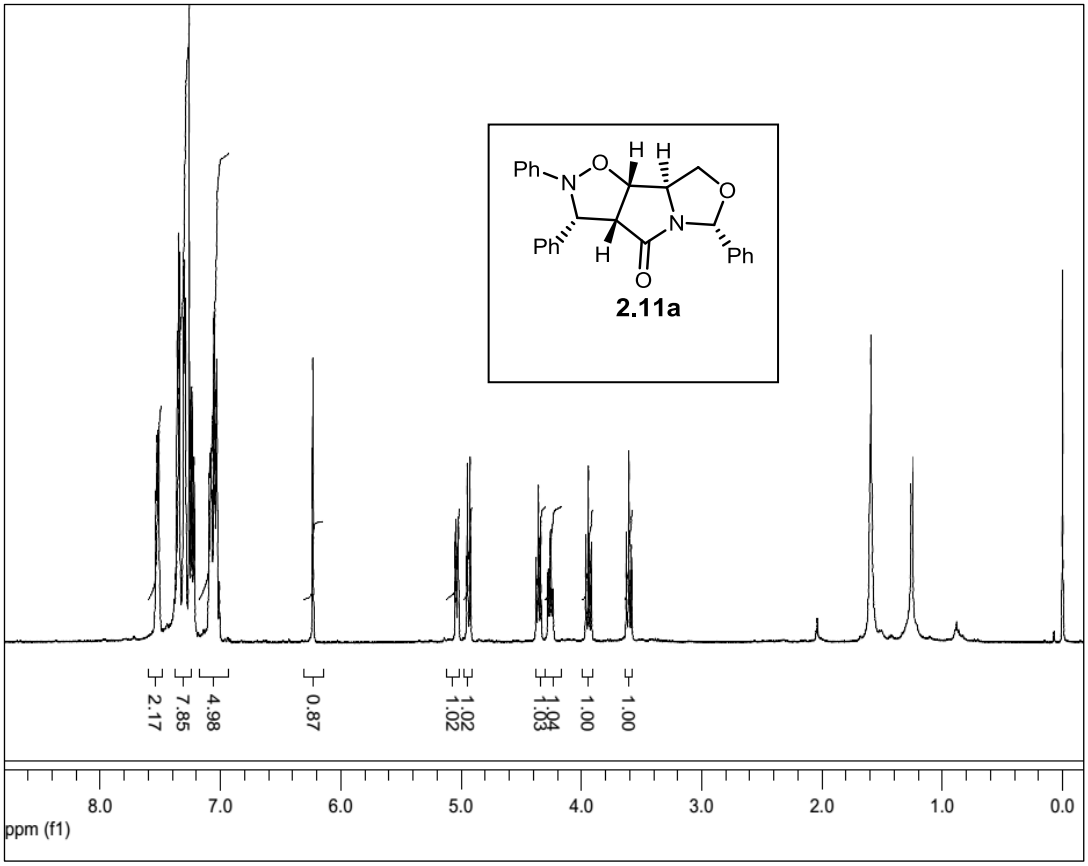
124.03
123.95
121.55
111.05
110.64
77.34
77.02
76.70
55.91
55.89
MeO
MeO
O
N
Ph
2.10l
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)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H
H
O
N
Ph
Ph
H
O
Ph
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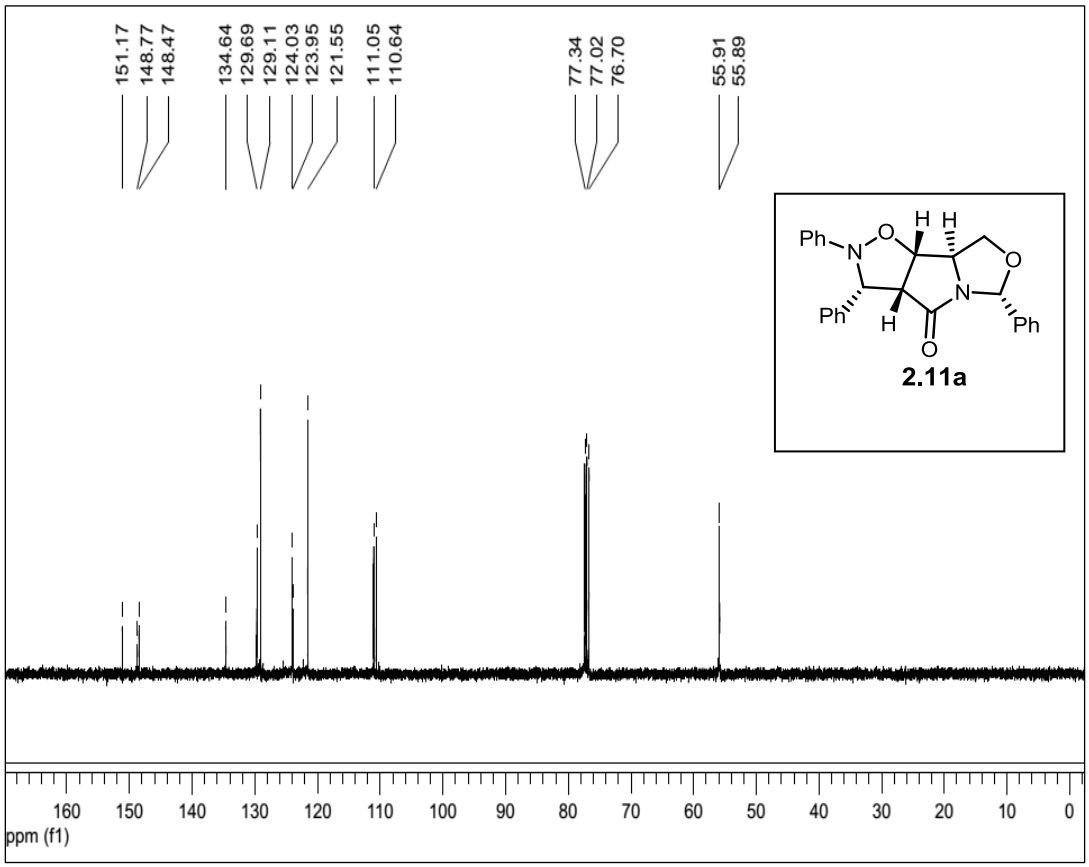
2.17
7.85
4.98
0.87
1.02
1.03
1.04
1.00
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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148.77
148.47
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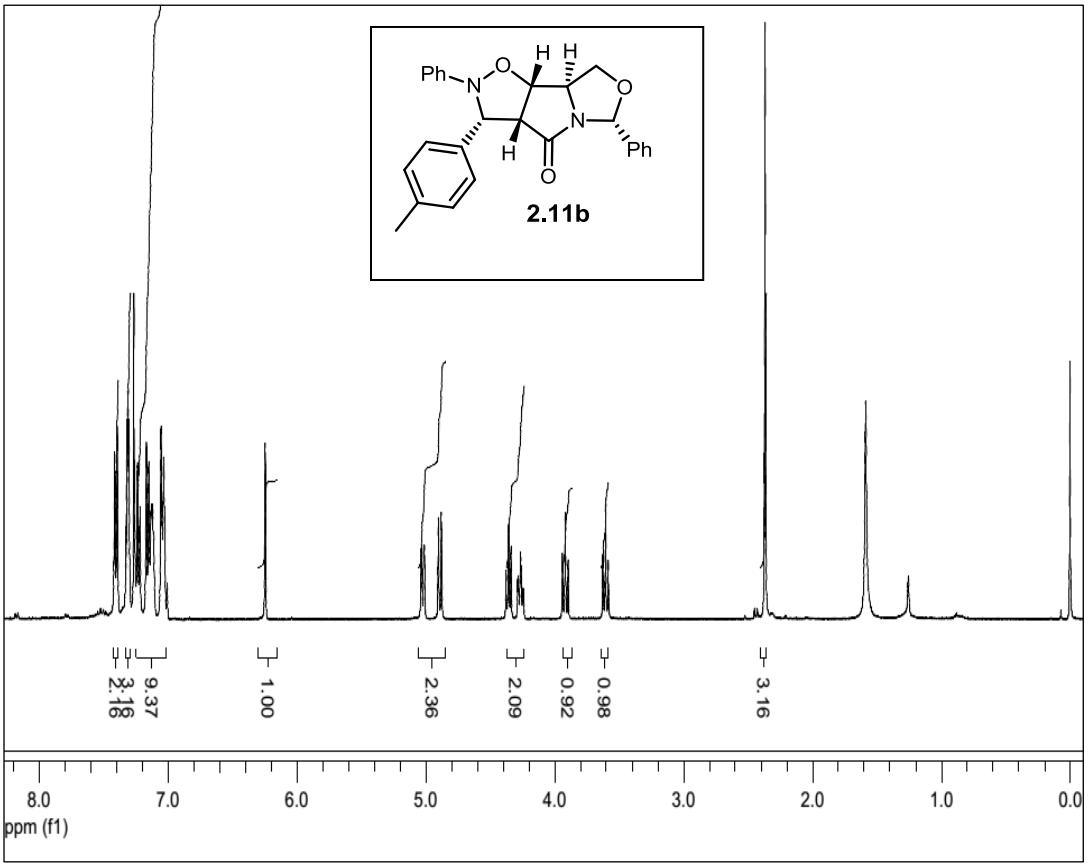
111.05
110.64
77.34
77.02
76.70
55.91
55.89
Ph
N
O
H
H
O
N
Ph
Ph
H
O
Ph
2.11a
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)


Ph
N
O
H
H
O
N
Ph
H
O
2.11b
2.16
3.16
9.37
1.00
2.36
2.09
0.92
0.98
3.16
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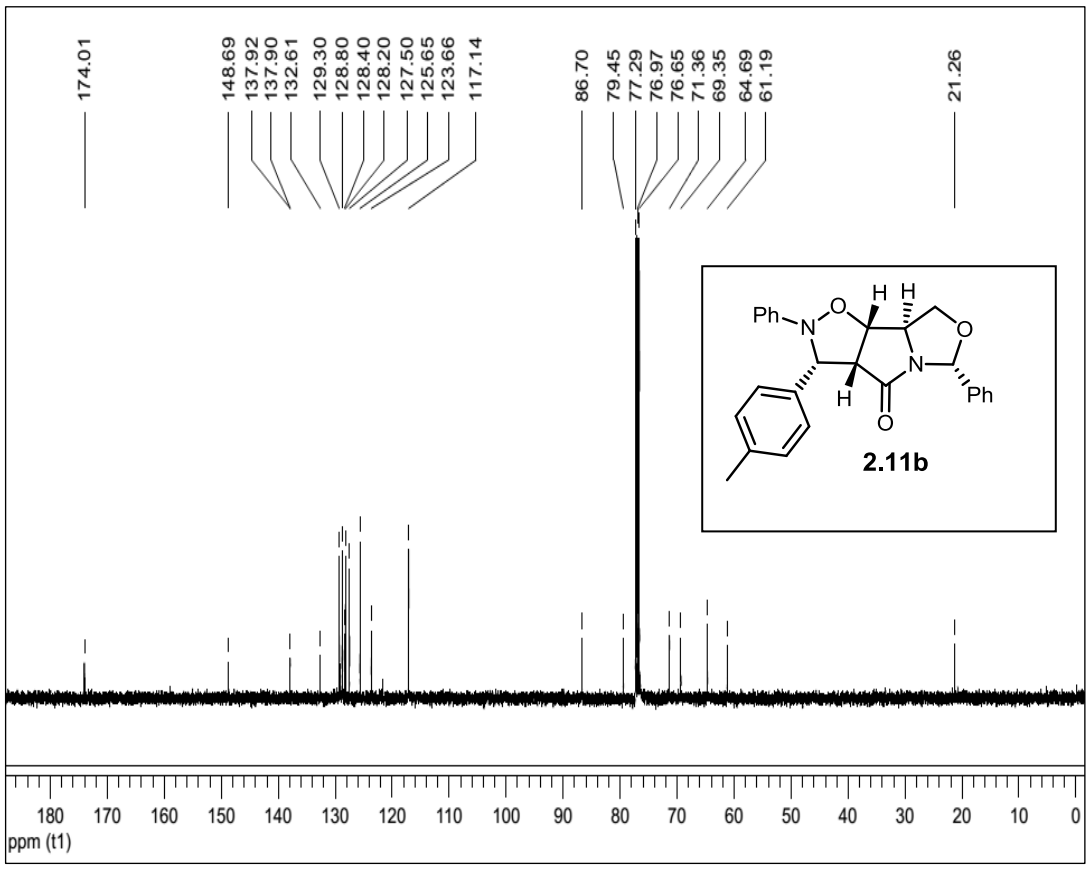
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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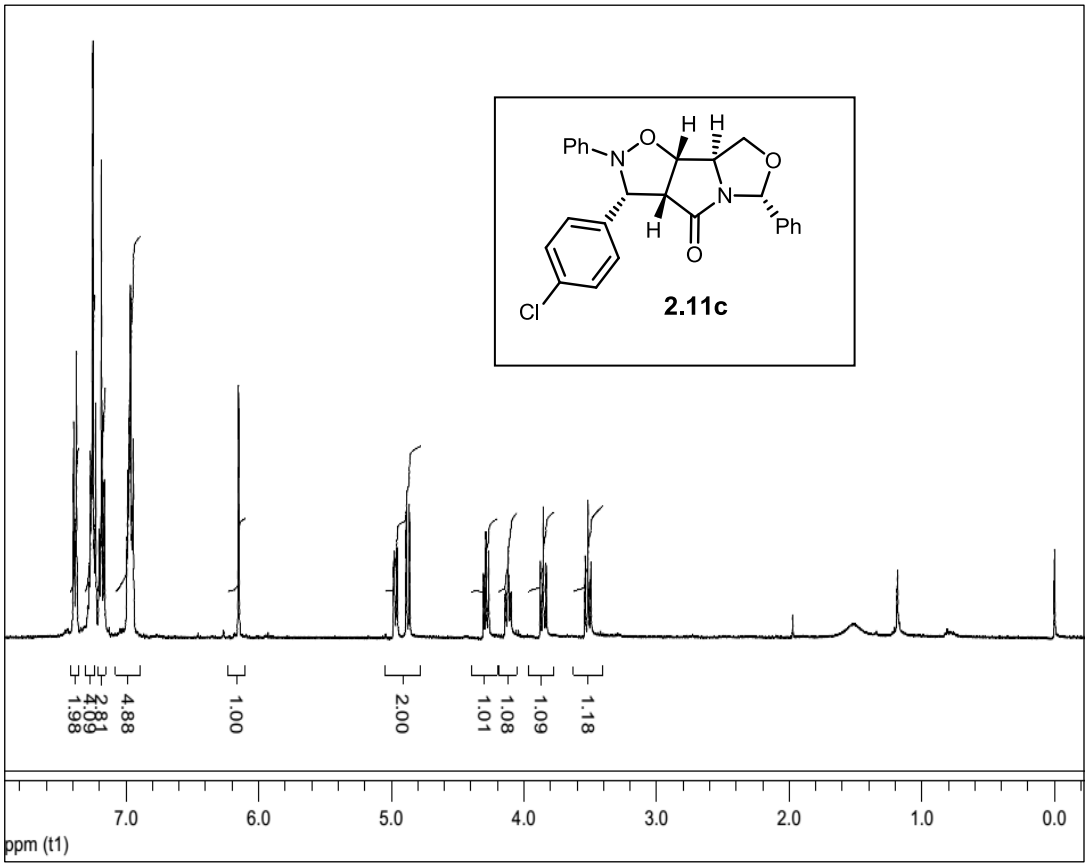
137.92
137.90
132.61
129.30
128.80
128.40
128.20
127.50
125.65
123.66
117.14
86.70
79.45
77.29
76.97
76.65
71.36
69.35
64.69
61.19
21.26
Ph
N
O
H
H
O
N
Ph
H
O
2.11b
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (t1)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H
H
O
N
Ph
H
O
Cl
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1.98
2.81
4.09
4.88
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2.00
1.01
1.08
1.09
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7.0
6.0
5.0
4.0
3.0
2.0
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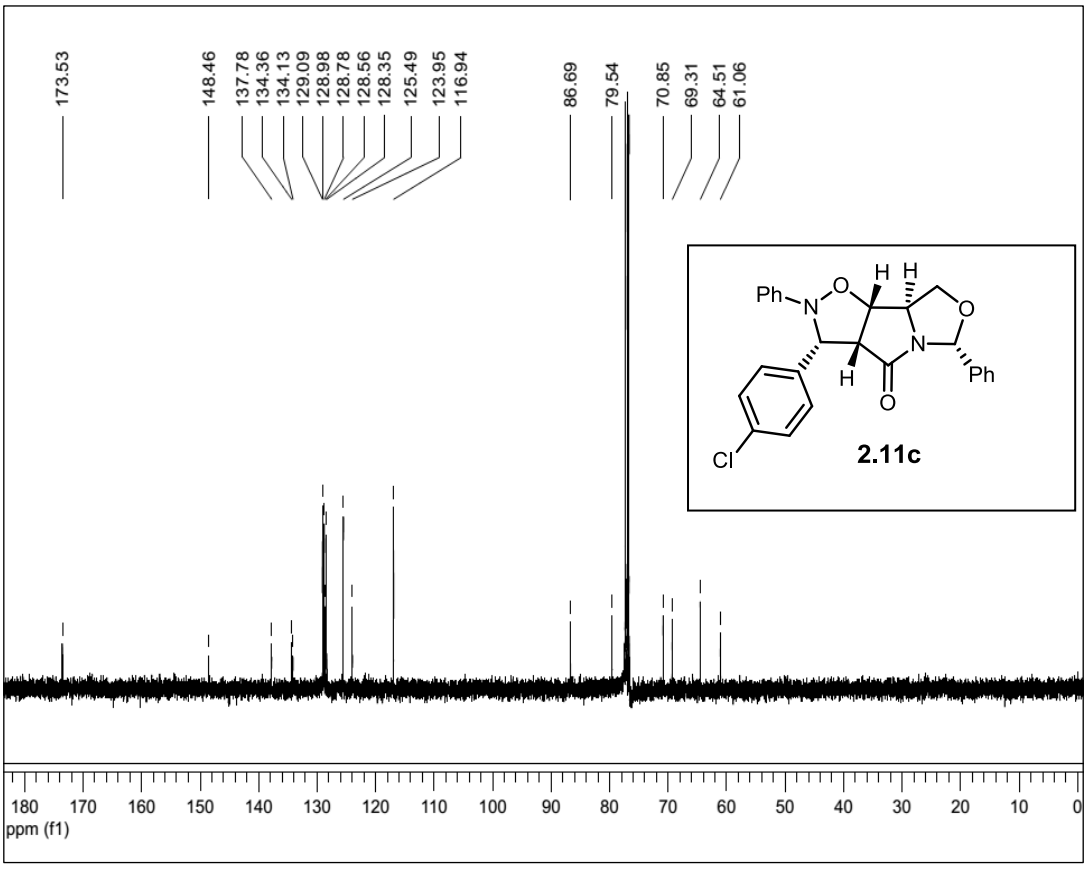
0.0
ppm (t1)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128.78
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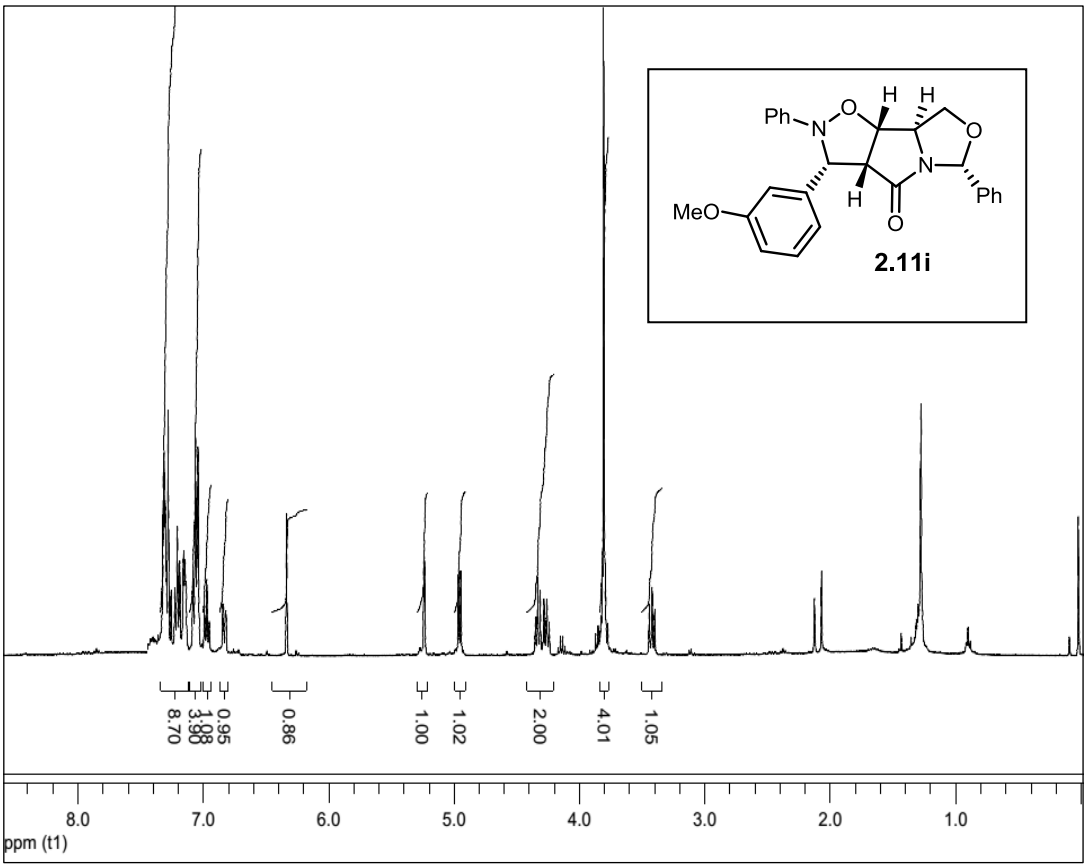
128.35
125.49
123.95
116.94
86.69
79.54
70.85
69.31
64.51
61.06
Ph
N
O
H
H
O
N
Ph
H
O
Cl
2.11c
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)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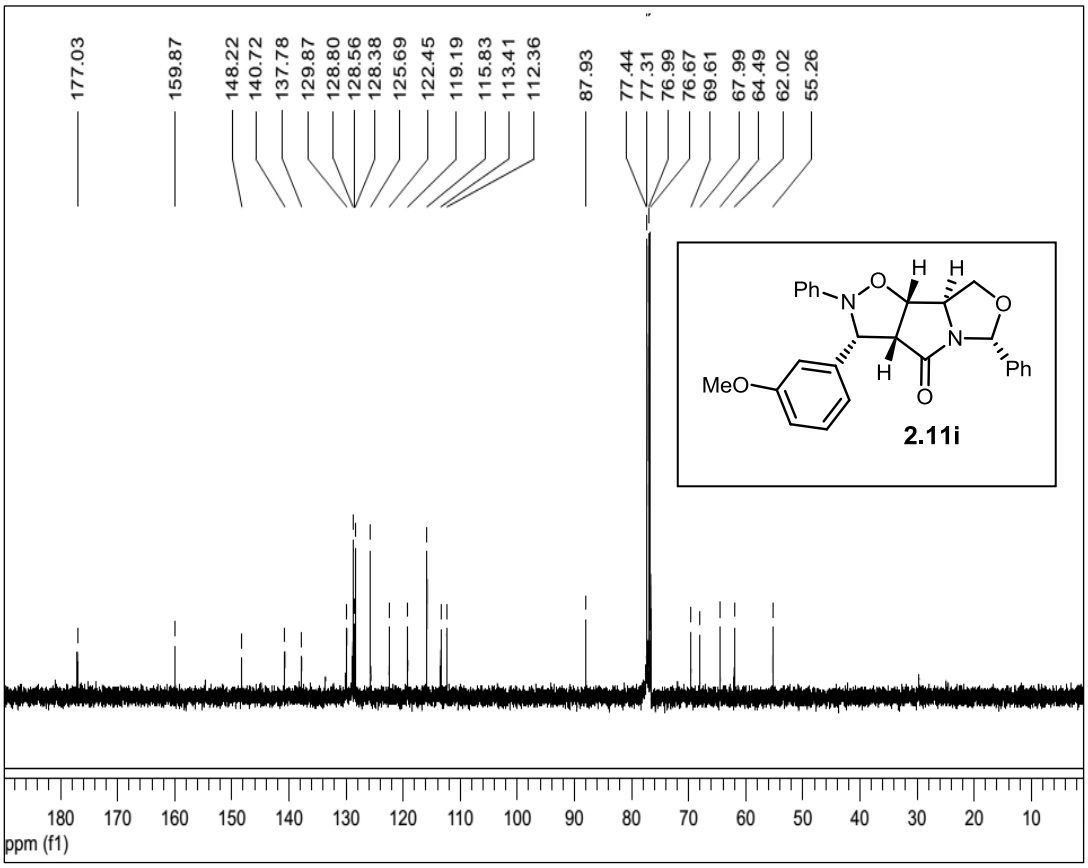
O
H
H
O
N
Ph
H
O
MeO
2.11i
8.70
3.88
3.86
3.83
3.80
0.95
0.86
1.00
1.02
2.00
4.01
1.05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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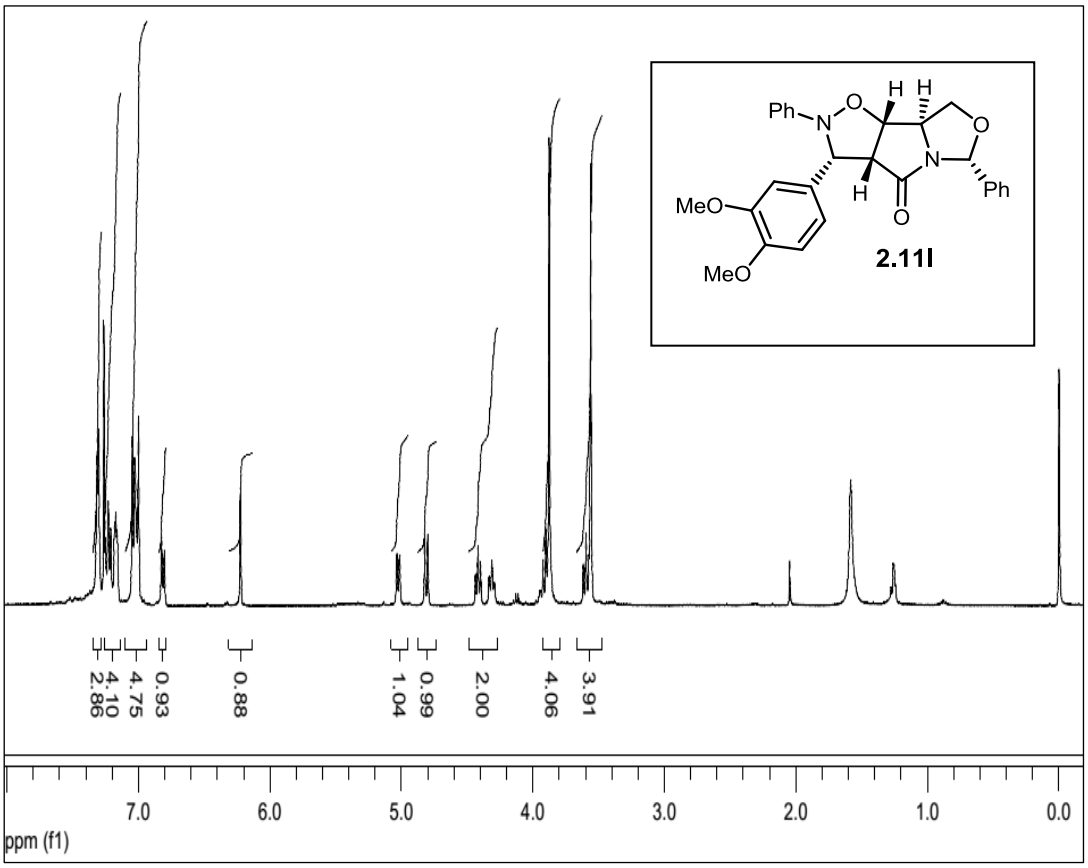
148.22
140.72
137.78
129.87
128.80
128.56
128.38
125.69
122.45
119.19
115.83
113.41
112.36
87.93
77.44
77.31
76.99
76.67
69.61
67.99
64.49
62.02
55.26
Ph
N
O
H
H
O
N
Ph
H
O
MeO
2.11i
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (f1)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O
H
H
O
N
Ph
H
O
MeO
MeO
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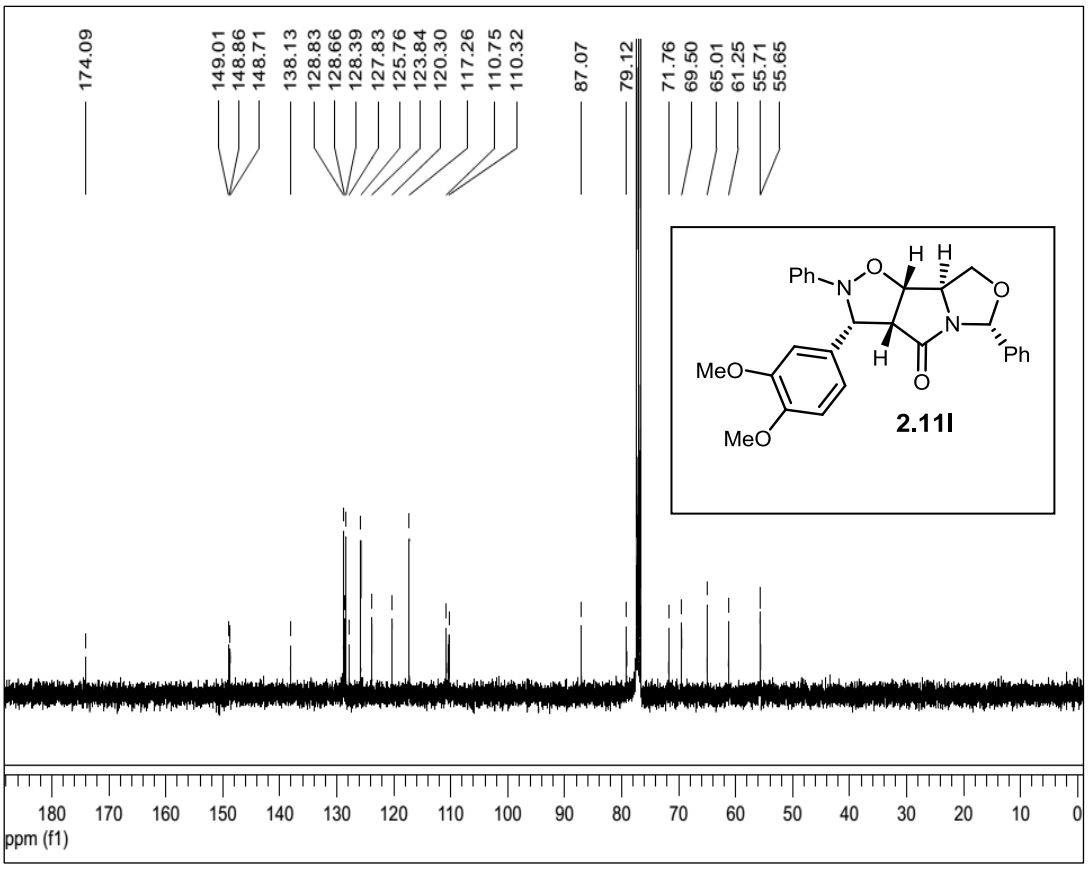
2.86
4.10
4.75
0.63
0.88
1.04
0.69
2.00
4.06
3.91
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


174.09
149.01
148.86
148.71
138.13
128.83
128.66
128.39
127.83
125.76
123.84
120.30
117.26
110.75
110.32
87.07
79.12
71.76
69.50
65.01
61.25
55.71
55.65
Ph
N
O
H
H
O
N
Ph
H
O
MeO
MeO
2.11l
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100
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50
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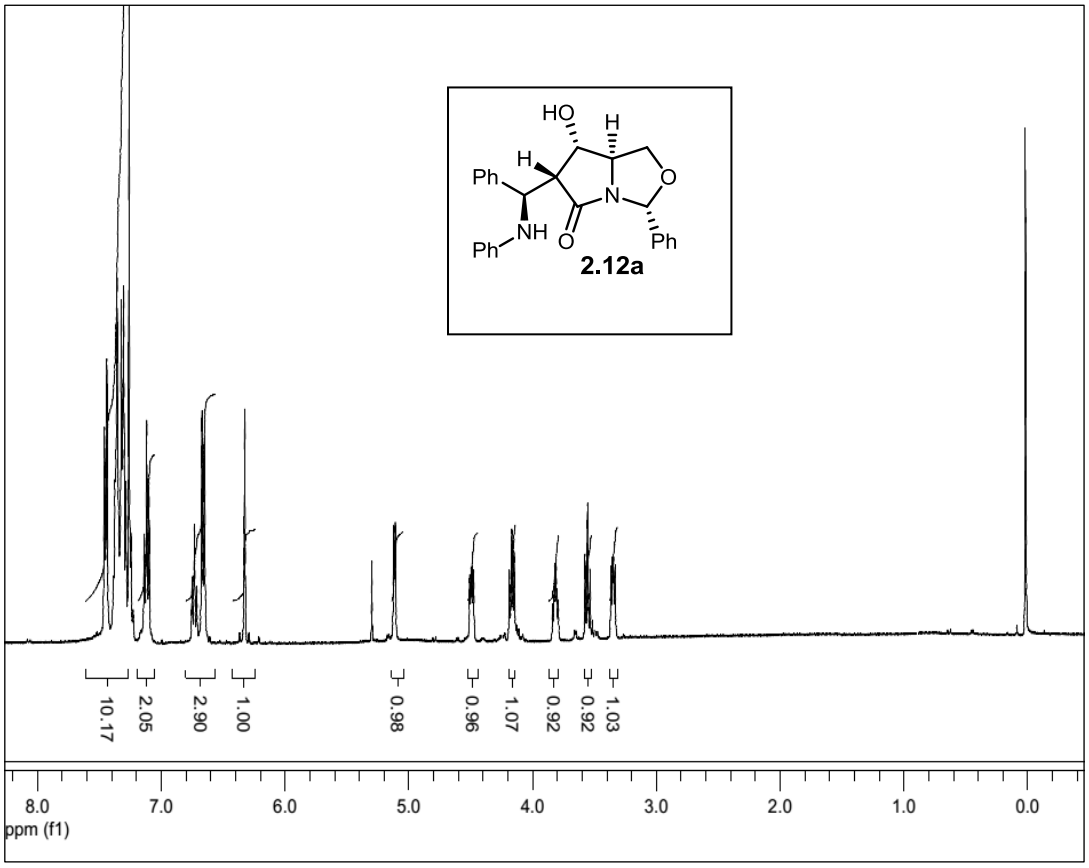
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1.07
0.92
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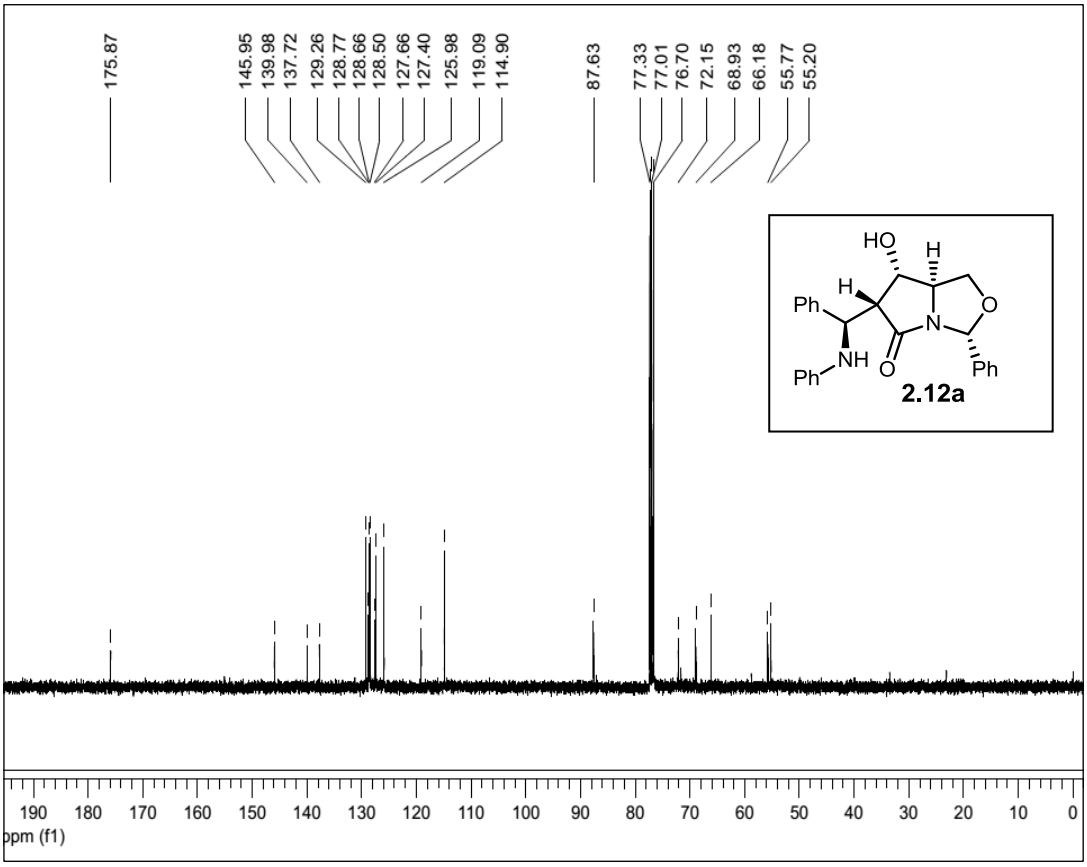
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87.63
77.33
77.01
76.70
72.15
68.93
66.18
55.77
55.20
HO
H
H
Ph
O
N
NH
O
Ph
Ph
2.12a
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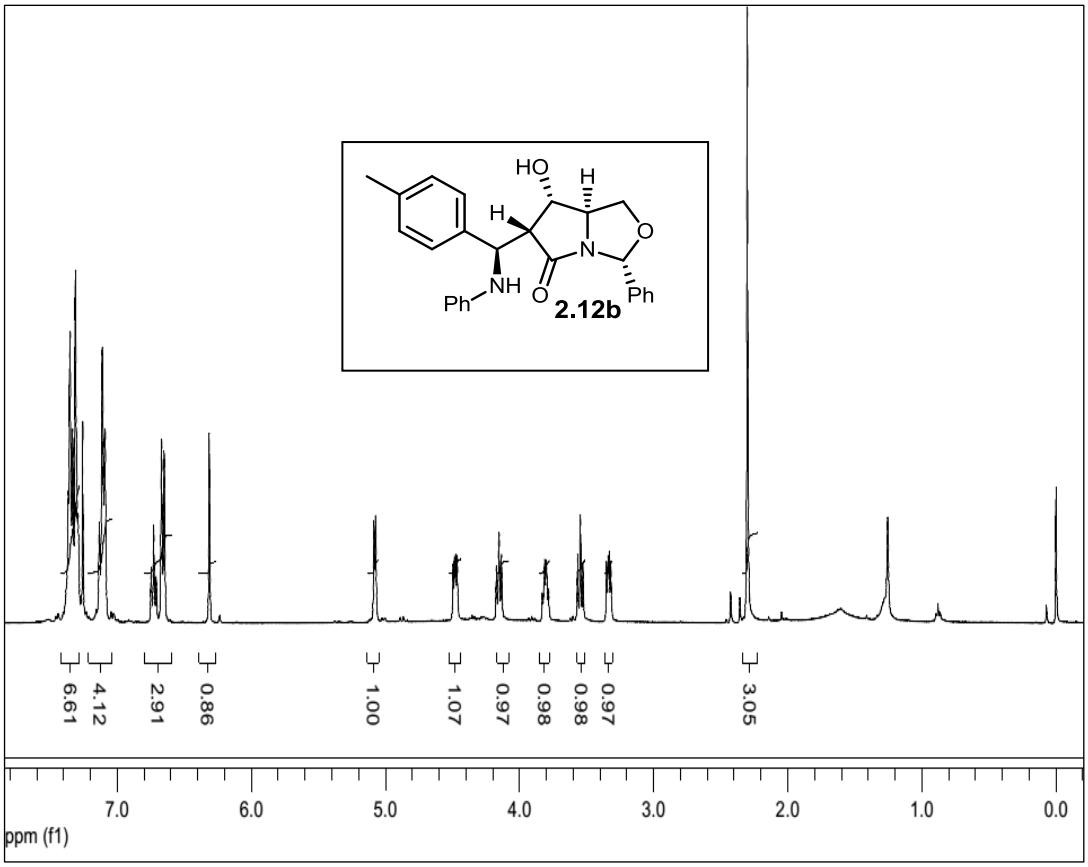
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0.98
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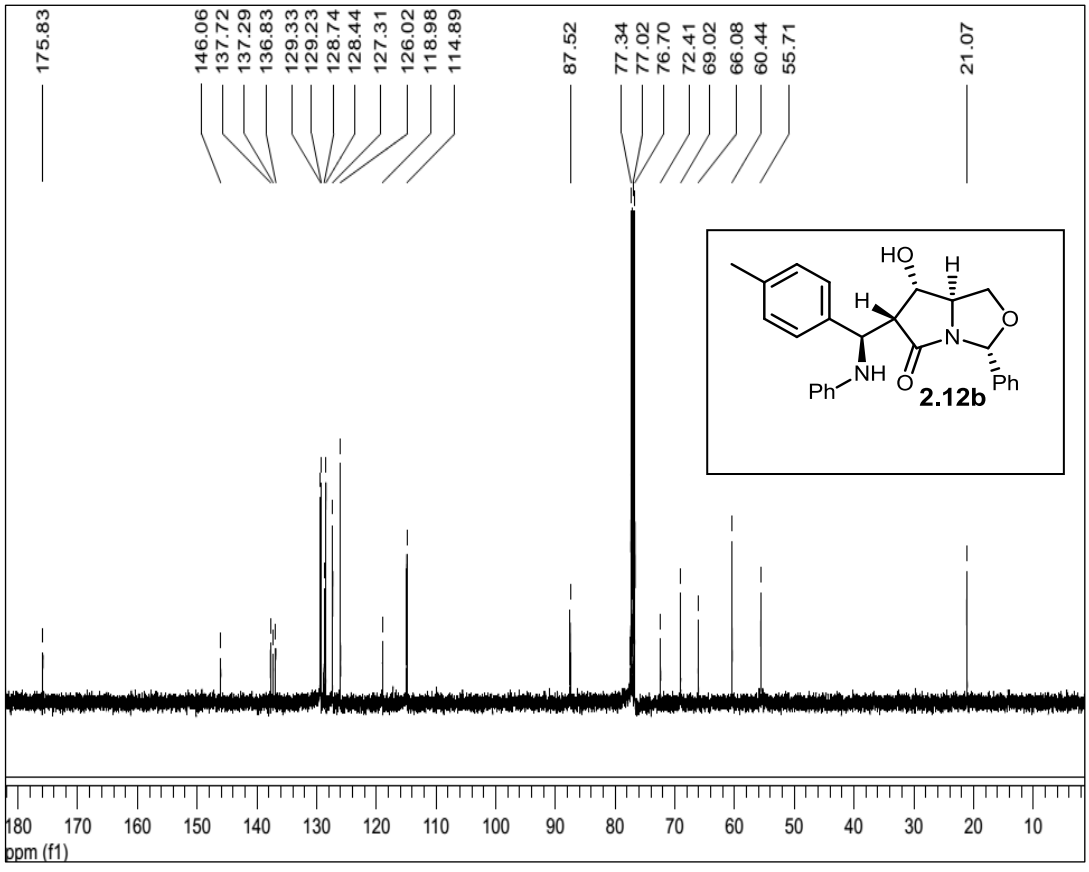
ppm (f1)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114.89
87.52
77.34
77.02
76.70
72.41
69.02
66.08
60.44
55.71
21.07
HO
H
H
O
N
NH
Ph
O
Ph
2.12b
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130
120
110
100
90
80
70
60
50
40
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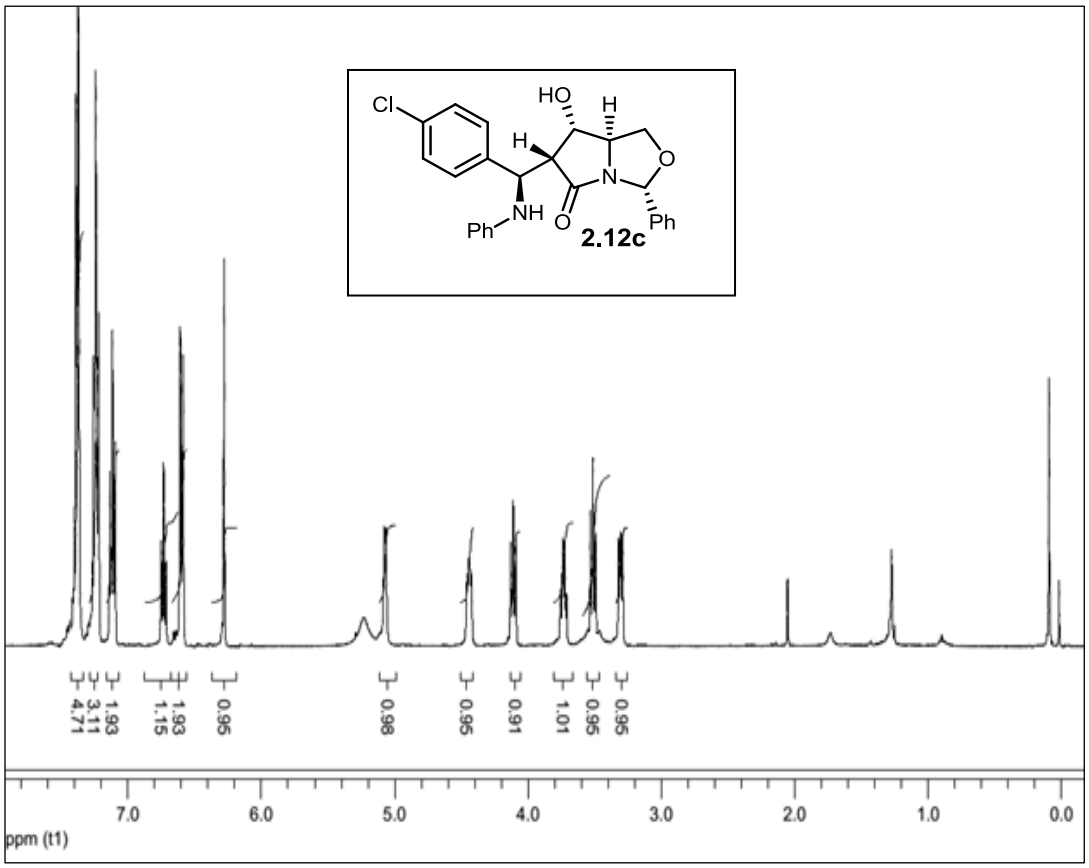
20
10
ppm (f1)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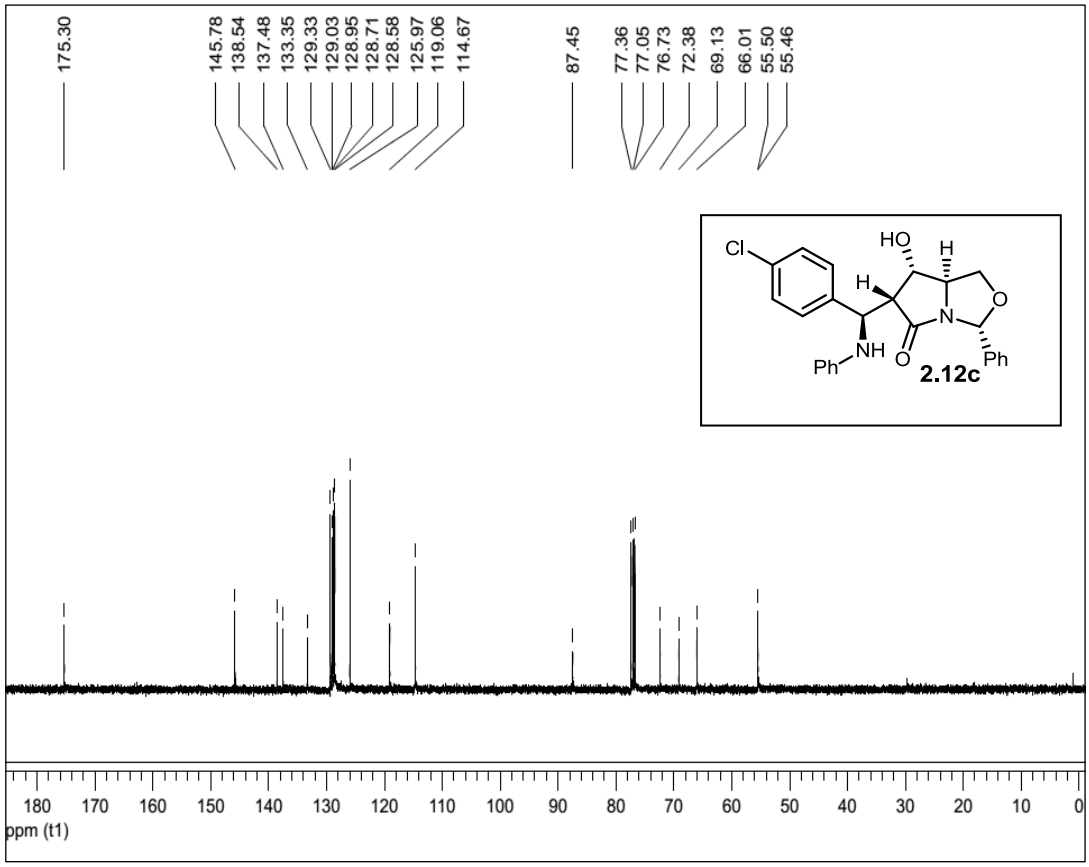
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72.38
69.13
66.01
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HO
H
H
O
N
NH
Ph
O
Ph
2.12c
180
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110
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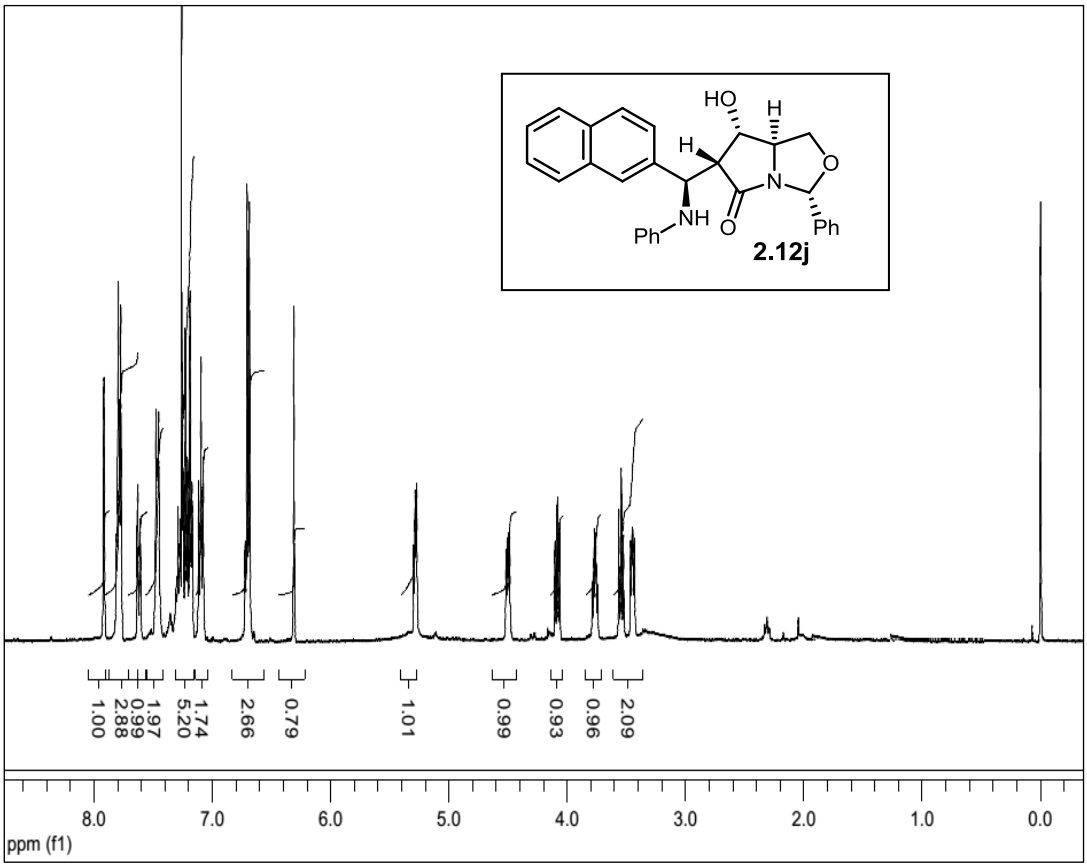
ppm (t1)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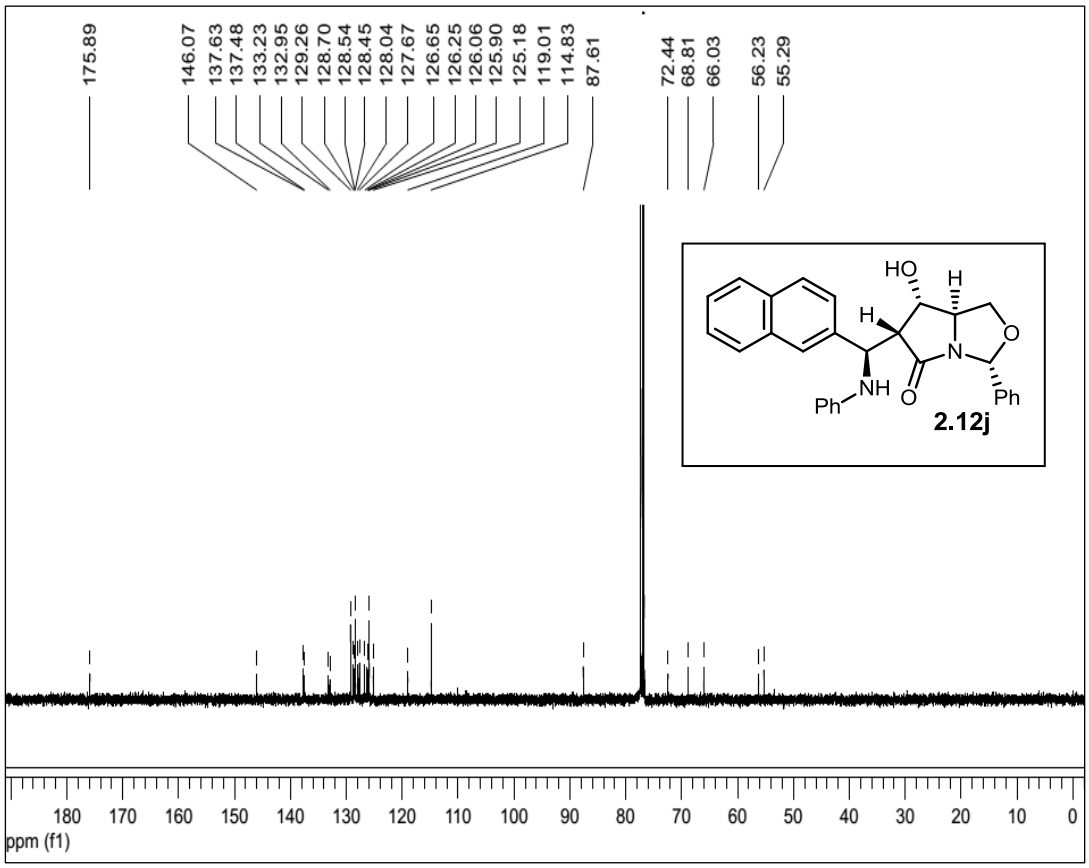
ppm (f1)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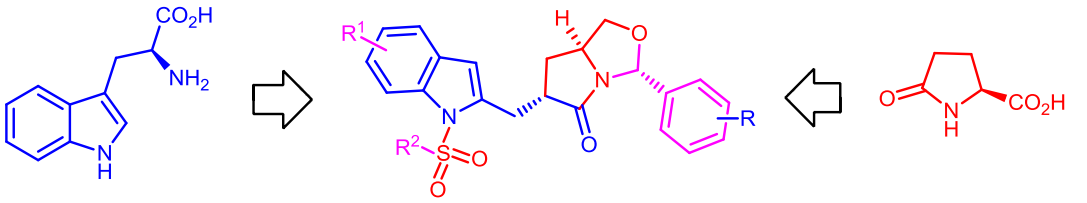
126.65
126.25
126.06
125.90
125.18
119.01
114.83
87.61
72.44
68.81
66.03
56.23
55.29
HO
H
H
O
N
NH
O
Ph
Ph
2.12j
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)

Chapter 3: Synthesis of asymmetric pyrrolidinone-based indole derivatives



3.1, Tryptophan

3.5

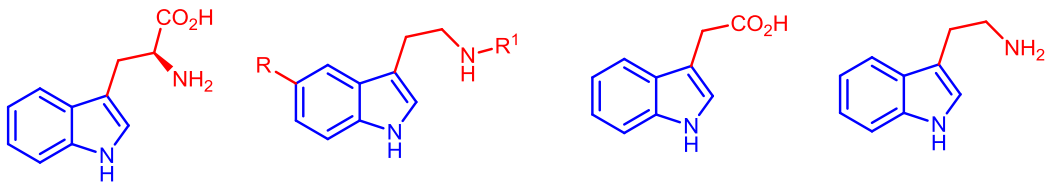
2.5, (*S*)-Pyroglutamic acid

18 Examples, Up to 85 % of yield

R and R^1 = Substituted aryl; R^2 = Me and Tolyl

3.1. Introduction:

Indole is a versatile nucleus present in several bio-active alkaloid marine natural products and potent pharmaceuticals,[1] which includes miscellaneous physiological functions such as anticancer,[2] antihypertensive,[3] antidiabetic,[1] antiHIV,[3,4] antituberculosis,[5] antiinflammatory,[6] antiviral,[7] anticonvulsants and antidepressants,[1,7] *etc.* Among the indole derivatives naturally occurring essential amino acid tryptophan and its derivatives occupied ubiquitous role in medicinal chemistry. In *Escherichia coli*, the enzyme tryptophanase (TnaA) produces indole from tryptophan in the mammalian and regulates diverse microbial processes such as biofilm formation, bacterial motility, antibiotic resistance and host cell invasion.[8] Tryptophan is also a key precursor for proteins, hormones (serotonin and melatonin), neurotransmitters, alkaloids and pigments.[9,10] Therapeutically, tryptophan **3.1a** has been used as a food supplement for treating epilepsy, insomnia, sleep apnea, depression, anxiety, facial pain, smoking cessation, attention deficient hyperactivity disorders, tourette syndrome and grinding teeth during sleep (bruxism). Representative naturally occurring tryptophan derived indole derivatives are shown in Fig. **3.1**, which includes hormones serotonine **3.1b** plays a key role in feeling of well-being and happiness, melatonin **3.1c** is a food supplement for sleeping disorders and heteroauxin **3.1d** produced by higher plants.[11] And neurotransmitter tryptamine **3.1e** controls the significant functions such as intestinal movement regulation and having the control on central nervous system functions like mood, appetite, sleep and other cognitive functions including memory and learning; synthetic analogues of tryptamine used as drugs in the treatment of migraine headaches, called as triptans.[12]



3.1a, Tryptophan

3.1b, R = OH, R^1 = H, Serotonin
3.1c, R = OMe, R^1 = Ac, Melatonin

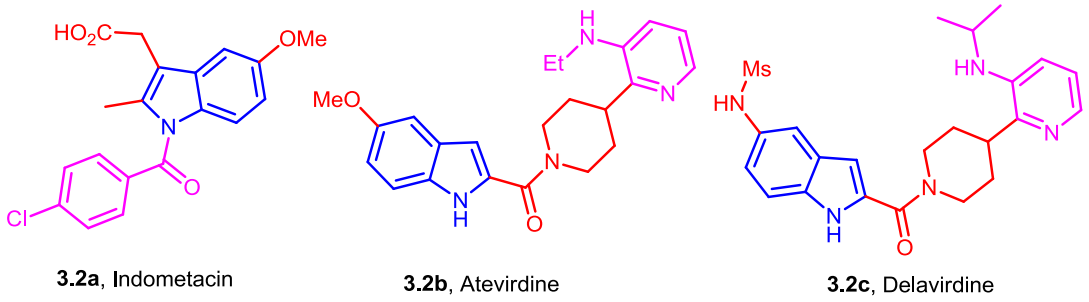
3.1d, Indole-3-acetic acid

3.1e, Tryptamine

Fig. 3.1. Representative naturally occurring indole derivatives

Representative indole based drugs are shown in Fig. **3.2.** Indomethacin **3.2a** is a non-steroidal anti-inflammatory drug commonly prescribed medication to reduce fever, swelling, pain and stiffness.[13] Ateviridine **3.2b** is a non-nucleoside reverse

transcriptase inhibitor, used as a drug in the treatment of HIV1.[14] Delavirdine **3.2c** is a drug used in the treatment of HIV1, through inhibition of cytochrome P450 isozyme CYP3A4.[15]

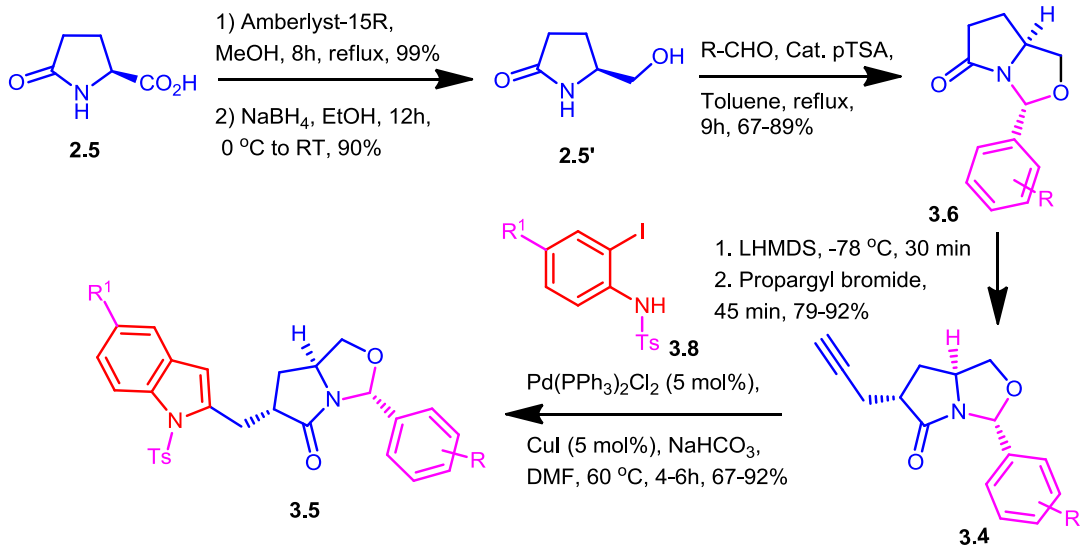


3.2a, Indometacin **3.2b**, Atevirdine **3.2c**, Delavirdine

Fig. 3.2. Representative examples of functionalized indoles as drugs

Present work:

We envisioned that asymmetric oxazolidine containing pyrrolidinone-based indole derivatives may have potential pharmaceutical applications. We have continuous interest in developing new synthetic methods and also generating novel heterocycles for drug discovery programs. Accordingly, we have adopted the Sonogashira protocol for *in-situ* generation of indole derivatives. As shown in Scheme **3.1**, asymmetric precursor oxazolidine containing pyrrolidinone-based terminal alkynes **3.4** were prepared from (*S*)-pyroglutamic acid **2.5** and substituted 2-iodoanilines **3.8** were prepared from corresponding 4-substituted anilines.



Scheme 3.1. Synthesis of asymmetric 2-substituted indole derivatives

3.2. Design of novel pyrrolidinone-based indole derivatives:

An extensive literature survey reveals the pharmaceutical importance of indole containing tryptophan derivatives, as well as functionalized asymmetric indole derivatives. Here, we envisioned to design and synthesize the pyrrolidinone-based asymmetric indole derivatives **3.5** from (*S*)-pyroglutamic acid, as shown in Fig.**3.3**. Designed nucleus may not resemble the exact tryptophan derivative, however it has in built functionalities *i.e.* indole core and natural amino acid residue taken from the (*S*)-pyroglutamic acid **2.5** may have interactions with the targeted enzymes or proteins. As discussed in the chapter 2 (*S*)-pyroglutamic acid is a privileged asymmetric precursor for the synthesis of pyrrolidinone-based asymmetric *N*-heterocycle.[16] Designed scaffold **3.5** also having the privileged oxazolidine nucleus, which is an important class of heterocyclic core with a broad spectrum of biological activities such as antibacterial, antitumor, mono-amine oxidase inhibition and neuroleptics and antihyperglycemic.[17]

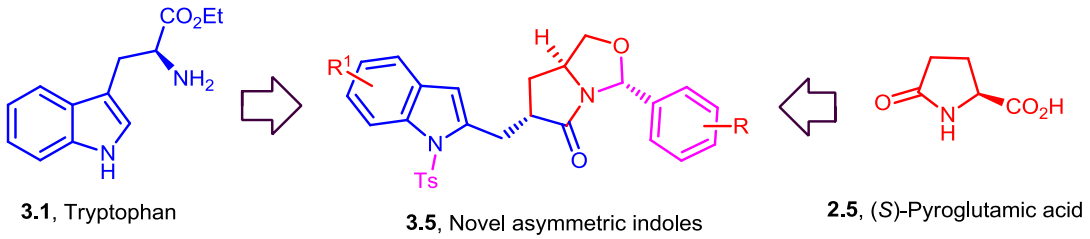


Fig. 3.3. Design of pyrrolidinone-based asymmetric indole derivatives

3.3. Results and discussions:

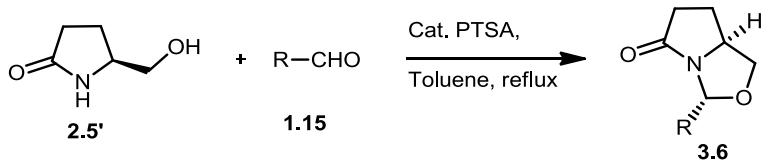
To pursue our investigation, towards the synthesis of pyrrolidinone-based asymmetric indole derivatives, synthesized reactive precursors of α-propargylated asymmetric pyrrolidinones **3.4a-3.4f** and 4-substituted *N*-protected 2-iodoanilines **3.8a-38h**, details are as follows.

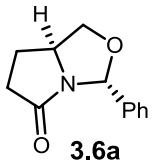
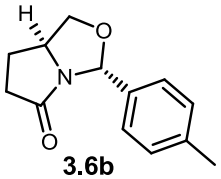
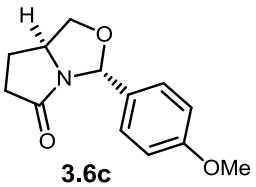
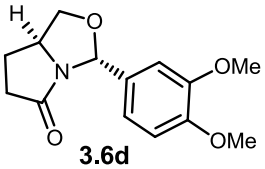
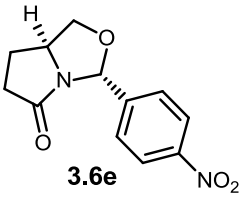
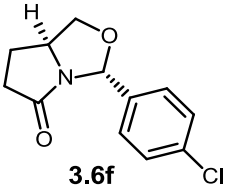
Synthesis of asymmetric bicyclic lactam derivatives:

In order to access the asymmetric alkyne precursors **3.4**, we have prepared the asymmetric bicyclic lactams **3.6** through condensation of substituted benzaldehydes

2.9 with (*S*)-pyroglutaminol **2.5'** in the presence of Bronsted acid (p-toluene sulfonic acid) under azeotropic conditions,[16] details are shown in Table **3.1**.

Table 3.1. Synthesis of asymmetric bicyclic lactam derivatives

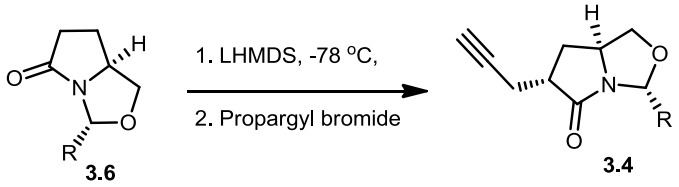


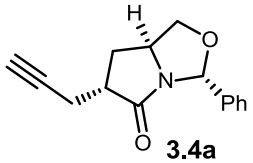
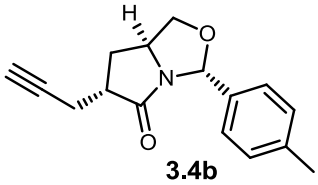
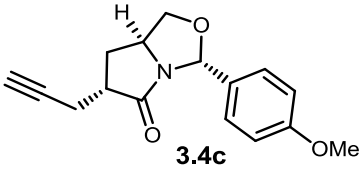
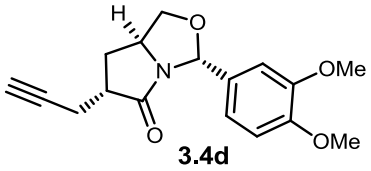
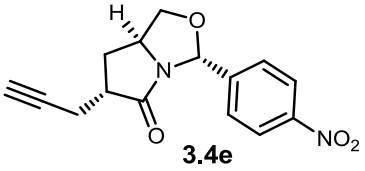
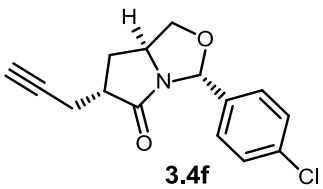
Entry	Aldehyde (**1.15**)	Product (**3.6**)	Time (h)	Yield (%)
1	**1.15d**	 **3.6a**	9	89
2	**1.15m**	 **3.6b**	9	80
3	**1.15e**	 **3.6c**	11	75
4	**1.15w**	 **3.6d**	16	67
5	**1.15b**	 **3.6e**	8	85
6	**1.15a**	 **3.6f**	8	83

3.3.1. Synthesis of α-propargylated asymmetric pyrrolidinones:

Asymmetric α-propargylation was performed on bicyclic lactams **3.6** using LHMDS at -78 ^{o}C followed by addition of propargyl bromide. All the synthesized compounds are shown in Table **3.2**.

Table 3.2. Synthesis of asymmetric pyrrolidinone-based alkyne precursors



Entry	Precursors (**3.6**)	Product (**3.4**)	Time (h)	Yield (%)
1	**3.6a**	 **3.4a**	1.15	92
2	**3.6b**	 **3.4b**	1.5	89
3	**3.6c**	 **3.4c**	1.5	87
4	**3.6d**	 **3.4d**	3	79
5	**3.6e**	 **3.4e**	1	85
6	**3.36f**	 **3.4f**	1	93

COSY and NOESY experiments of compound 3.4e:

Based on ^{1}H-^{1}H COSY studies, we have confirmed the chemical shift values of each proton of compound **3.4e**, shown in Fig. **3.4**, further the stereochemical assignments were done by NOESY studies.

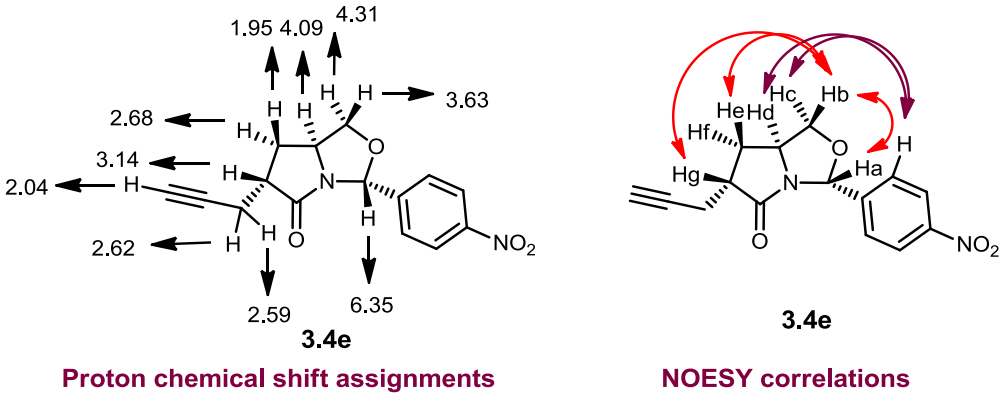


Fig. 3.4. NMR studies

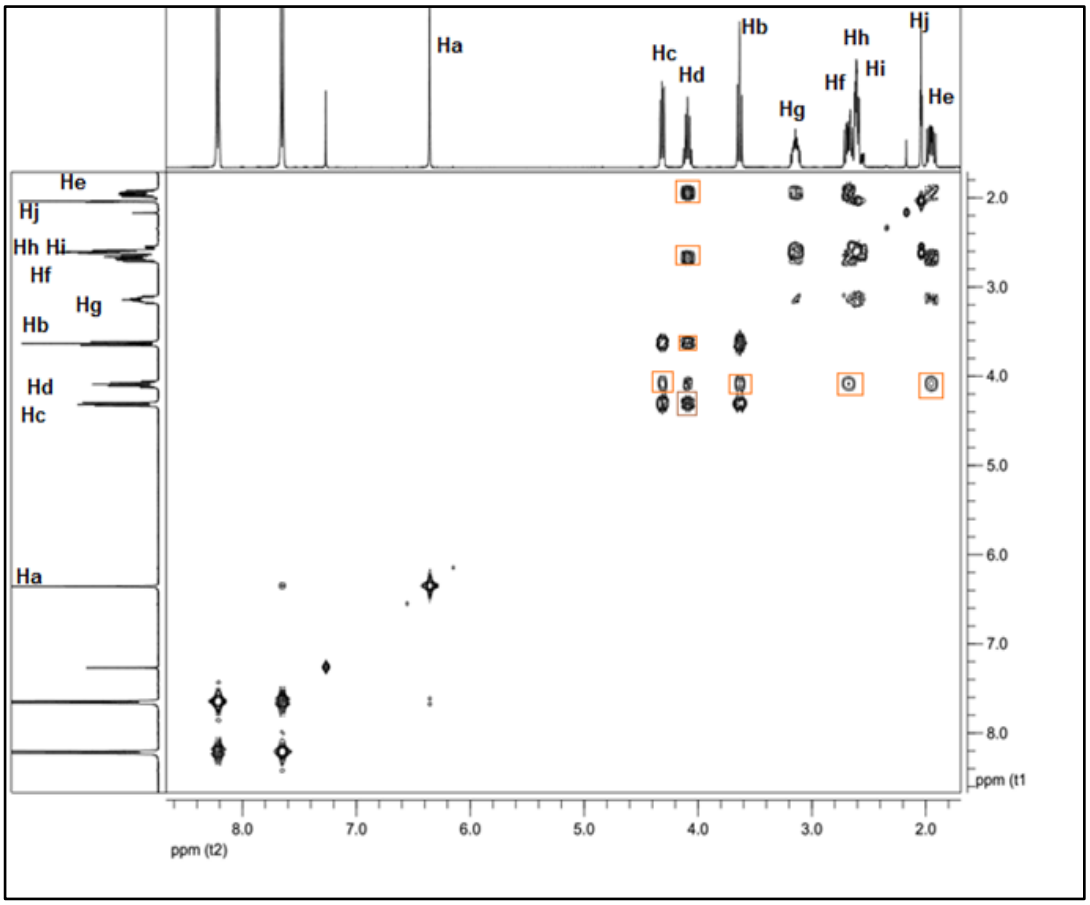


Fig. 3.5. ^{1}H-^{1}H COSY spectra of **3.4e**

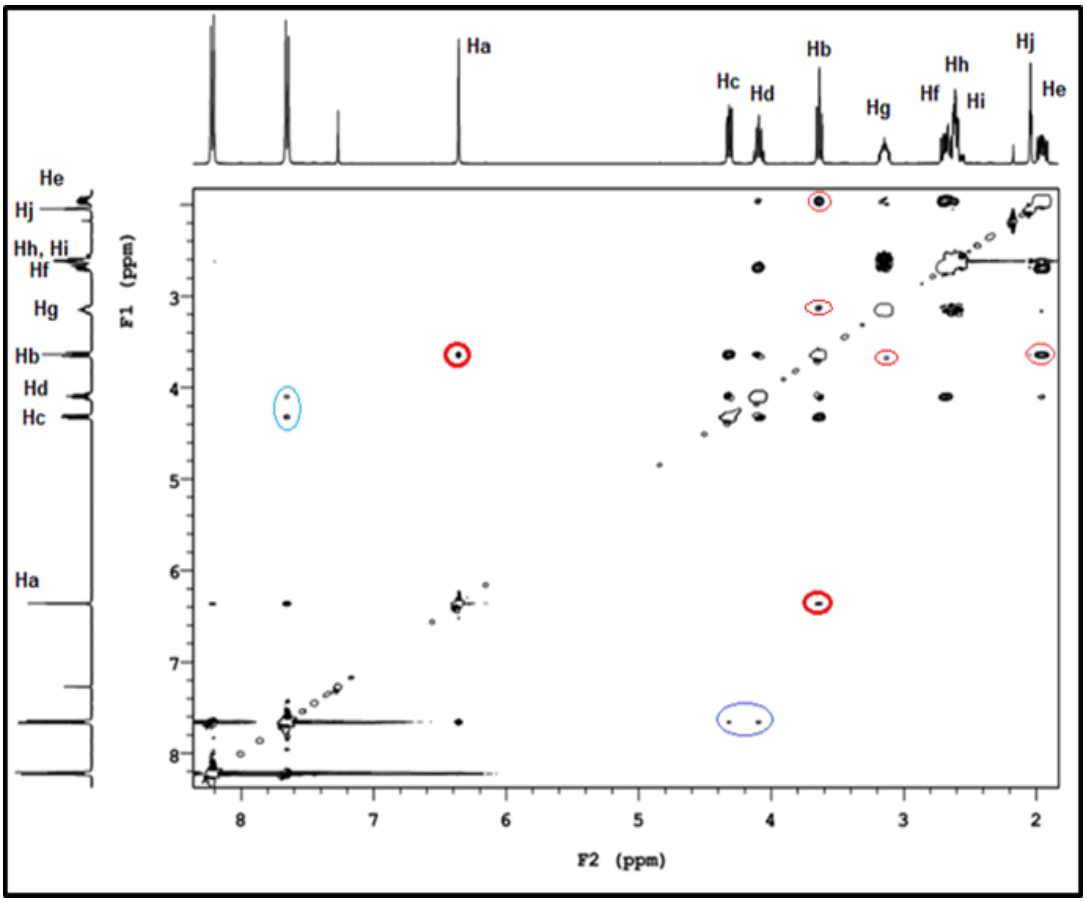
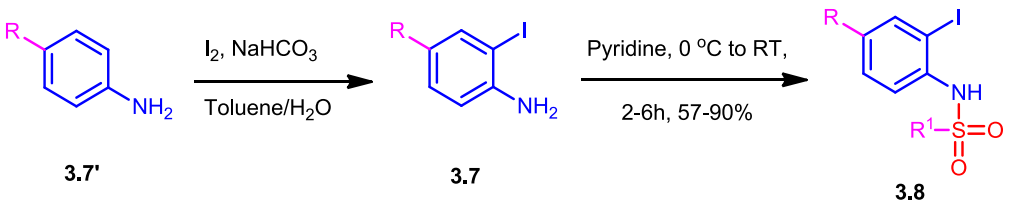


Fig. 3.6. NOESY spectra of **3.4e**

3.3.3. Preparation of *N*-protected 2-iodoanilines:

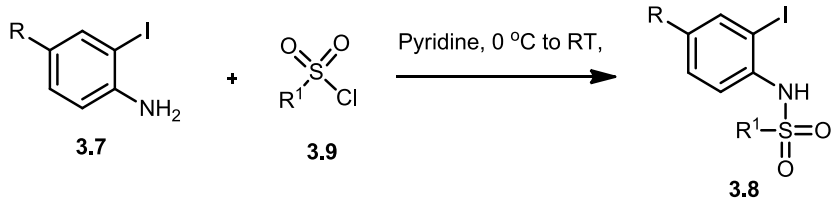
4-substituted *N*-protected 2-iodo anilines **3.8** were prepared from the corresponding 4-substituted anilines **3.7'** using iodination followed by *N*-mesylation/ tosylation procedures,[19] details are shown in Scheme **3.2**, and prepared compounds are listed in Table **3.3**.

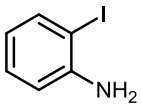
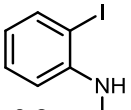
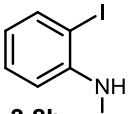
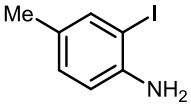
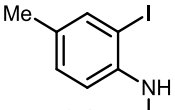
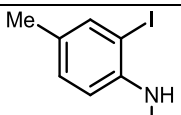
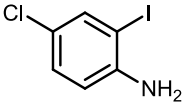
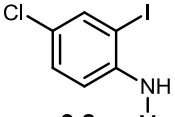
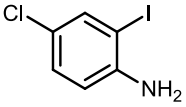
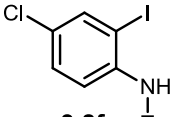
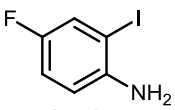
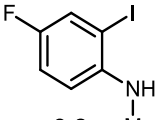
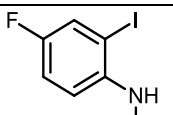


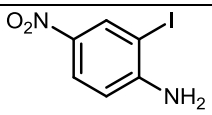
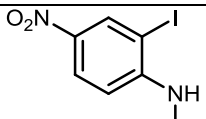
3.7' **3.7** **3.8**

Scheme 3.2. Preparation of *N*-protected 4-substituted 2-iodoanilines

Table 3.3 Preparation of *N*-(2-iodophenyl)methane/p-tolyl sulfonamides



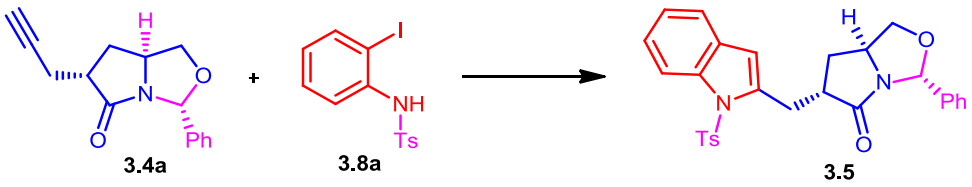
Entry	Precursor (**3.7**)	Precursor (**3.9**)	Product (**3.8**)	Time (h)	Yield (%)
1	 **3.7a**	Methane sulfonyl chloride **3.9a**	 **3.8a**	4	87
2	**3.7a**	p-Toluene sulfonyl chloride **3.9b**	 **3.8b**	4	90
3	 **3.7b**	**3.9a**	 **3.8c**	6	85
4	**3.7b**	**3.9b**	 **3.8d**	6	87
5	 **3.7c**	**3.9a**	 **3.8e**	6	83
5	 **3.7c**	**3.9b**	 **3.8f**	6	83
6	 **3.7d**	**3.9a**	 **3.8g**	6	77
7	**3.7d**	**3.9b**	 **3.8h**	6	79

8	 3.7e	**3.9a**	 3.8i	2	57

3.3.3. Synthesis of pyrrolidinone-based asymmetric indole derivatives:

Reaction optimization: Here, the synthesis of asymmetric pyrrolidinone-based 2-substituted indole derivatives **3.5** has disclosed using Sonogashira protocol, initially we performed the reaction between **3.4a** (1 mmol) and **3.8a** (1 mmol), using 5 mol% of CuI, 10 mol of 5% Pd/C, 0.0088 mmol of PPh_3 and potassium carbonate as a base in ethanol (entry **1**, Table **3.4**), we did not isolate the desired product. However, same reaction proceeds in polar aprotic solvents such as in DMSO obtained ~10% of yield (entry **2**, Table **3.4**). In order to get the efficient reaction conditions, we perform the present reaction with 5 mol% of $Pd(PPh_3)_2Cl_2$, 5 mol% of CuI and 1.2 mmol of $NaHCO_3$ in DMF (entry **4**, Table **3.4**), provided decent yield (85%).

Table 3.4. Reaction optimization for asymmetric indole synthesis



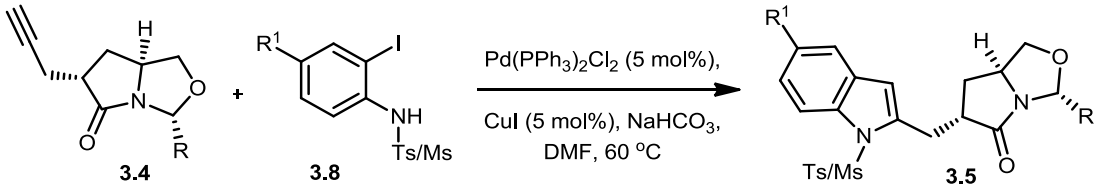
Entry	Catalyst	Base	Solvent	Temp (^oC)	Time (h)	Yield (%)
1	5% Pd/C	K_2CO_3	Ethanol	70	12	ND
2	10% Pd/C	K_2CO_3	DMSO	70	12	10
3	$Pd(PPh_3)_2Cl_2$	$NaHCO_3$	DMSO	70	6	83
4	$Pd(PPh_3)_2Cl_2$	$NaHCO_3$	DMF	60	4	85

0.1 mmol of **3.4a** and **3.8a**; 5 mol% of CuI used in all the cases; [a]Pd/C (10 mol%); and [b] $Pd(PPh_3)_2Cl_2$ (5 mol%)

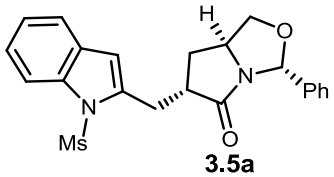
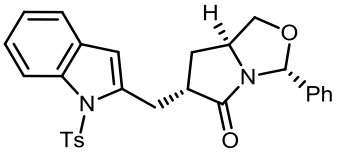
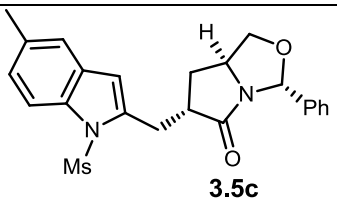
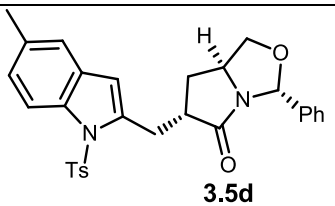
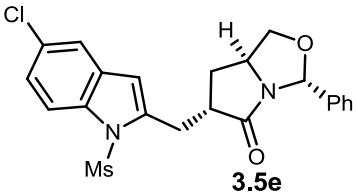
Having the optimized reaction condition (entry **4**, Table **3.4**) in our hand, we moved to generalize the reaction with various asymmetric alkynes **3.4** and 4-substituted 2-

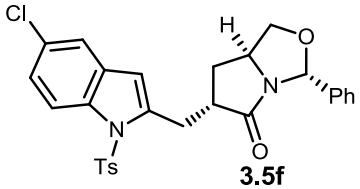
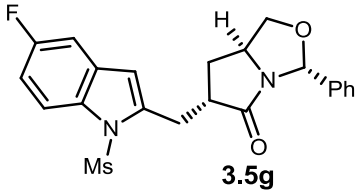
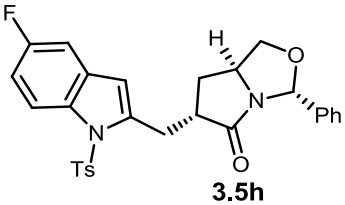
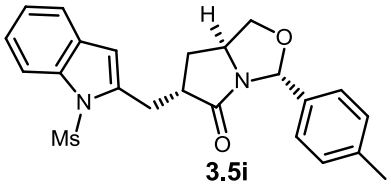
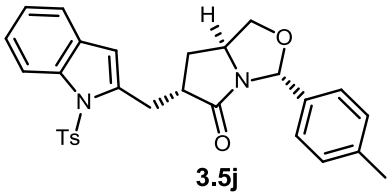
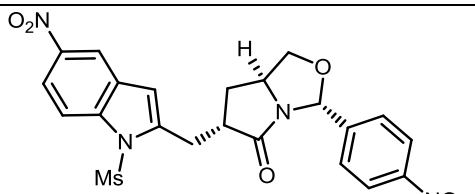
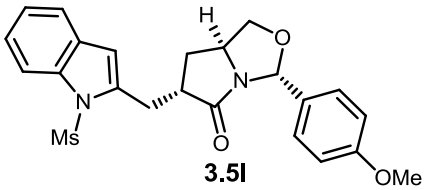
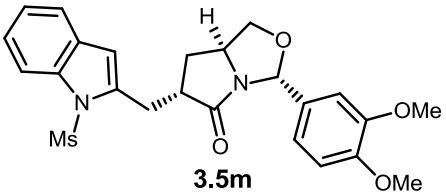
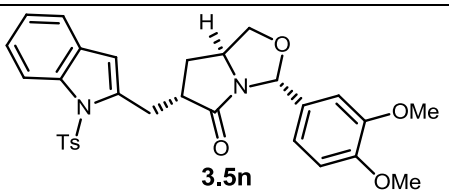
iodo anilines **3.8**, results are summarized in Table **3.5**. *N*-mesyl or *N*-tosyl 2-iodoanilines such as 4-methyl, 4-chloro, 4-nitro and 4-fluro group afforded good yields of the desired products, on the other side, reactive substituted asymmetric precursors **3.4** such as 4-methyl, 4-chloro, 4-methoxy, 3,4-dimethoxy and 4-nitro groups were used.

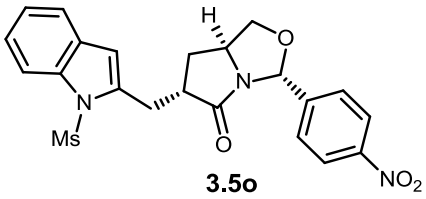
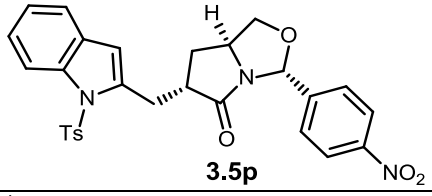
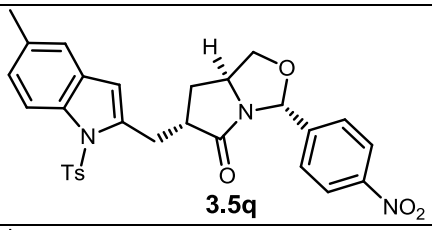
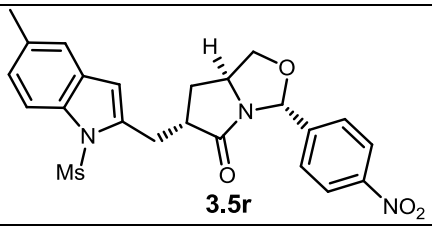
Table 3.5. Synthesis of asymmetric indole derivatives



3.4 **3.8** **3.5**

Entry	Precursor (**3.8**)	Precursor (**3.4**)	Product (**3.5**)	Time (h)	Yield (%)
1	**3.8a**	**3.4a**	 **3.5a**	4	92
2	**3.8b**	**3.4a**	 **3.5b**	4	85
3	**3.8c**	**3.4a**	 **3.5c**	4	89
4	**3.8d**	**3.4a**	 **3.5d**	4	87
5	**3.8e**	**3.4a**	 **3.5e**	4	77

6	**3.8f**	**3.4a**	 **3.5f**	4	79
7	**3.8f**	**3.4a**	 **3.5g**	4	79
8	**3.8g**	**3.4a**	 **3.5h**	4	85
9	**3.8a**	**3.4b**	 **3.5i**	4	91
10	**3.8b**	**3.4b**	 **3.5j**	4	88
11	**3.8h**	**3.4e**	 **3.5k**	4	79
12	**3.8a**	**3.4c**	 **3.5l**	4.5	75
13	**3.8a**	**3.4d**	 **3.5m**	6	67
14	**3.8a**	**3.4d**	 **3.5n**	6	69

15	**3.8a**	**3.4e**	 **3.5o**	4	79
16	**3.8b**	**3.4e**	 **3.5p**	4	81
17	**3.8d**	**3.4e**	 **3.5q**	4	83
18	**3.8c**	**3.4e**	 **3.5r**	4	83

One of the compounds **3.5o** is well characterized by using ^{1}H-^{1}H COSY and NOESY studies. Here, proton chemical shifts assignments by ^{1}H-^{1}H COSY studies, and the stereochemical assignments were done by NOESY studies *i.e.* H_a cis to H_b; H_b cis to H_f and H_g, as shown in Fig. **3.7.** Related spectra are shown in Fig. **3.8** and Fig. **3.9.**

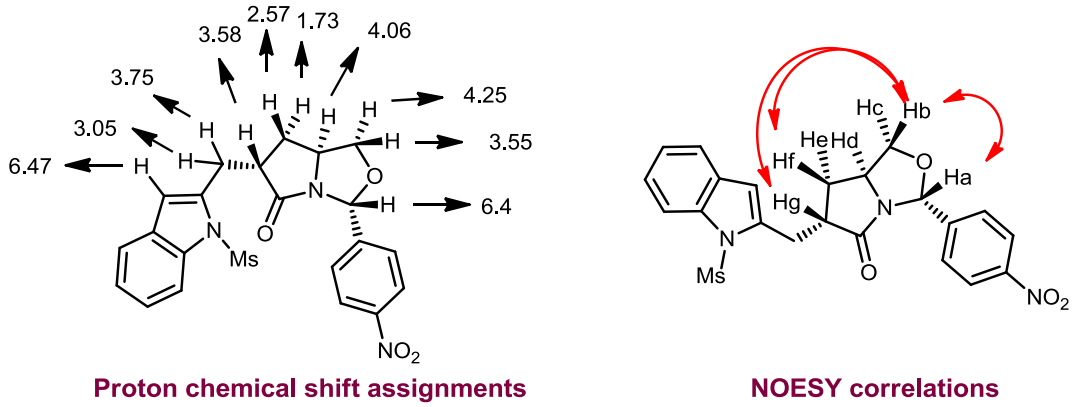


Fig. 3.7. ^{1}H-^{1}H COSY and NOESY representation of compound **3.5o**

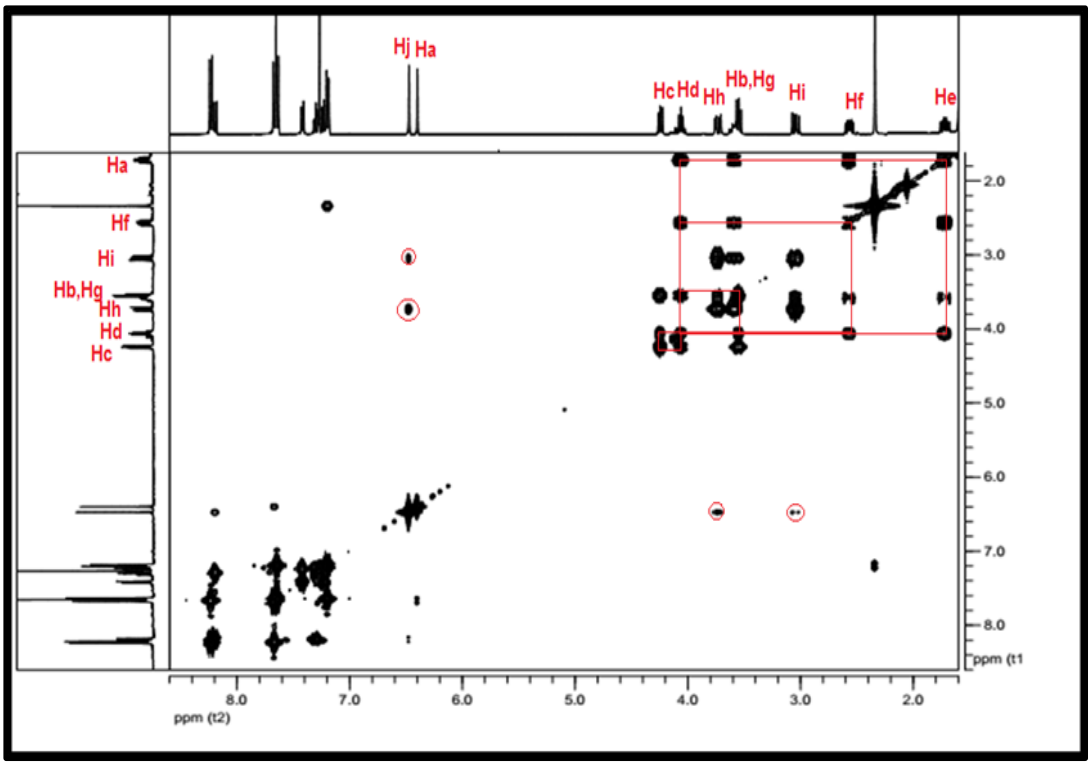


Fig. 3.8. ^{1}H-^{1}H COSY spectra of compound **3.5o**

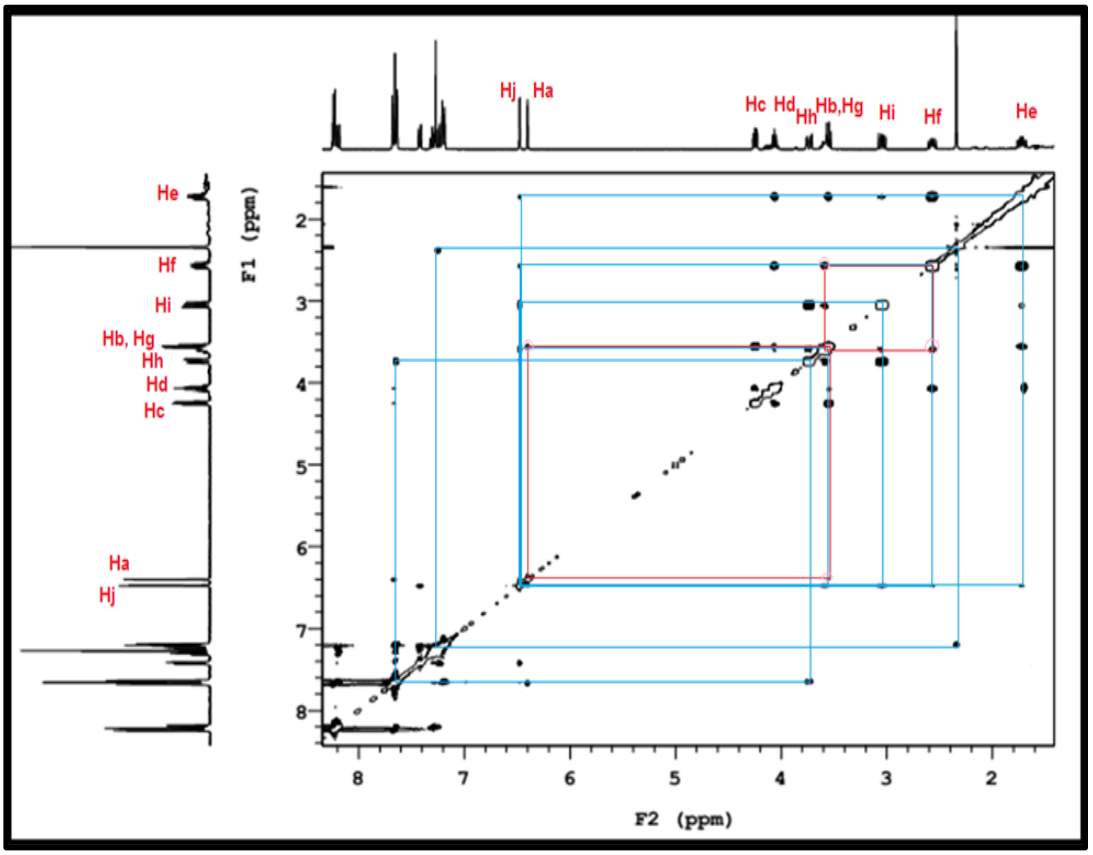


Fig. 3.9. NOESY spectra of compound **3.5o**

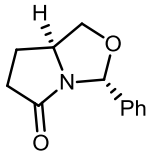
3.4. Conclusions:

We have demonstrated the efficient synthetic method for the synthesis of pyrrolidinone-based asymmetric indole derivatives, which involve the Sonogashira reaction followed by *in-situ* cyclization. Synthesized asymmetric α-propargylated precursors and pyrrolidinone-based asymmetric indole derivatives were well characterized using COSY and NOESY studies. These novel asymmetric indole derivatives are under biological screening.

3.5. Experimental section:

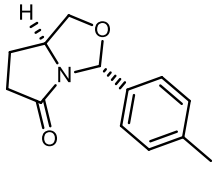
O,N-acetal protection: A mixture of (5.0 g, 43.42 mmol) of pyroglutaminol **2.5'**, (5.07 g, 47.77 mmol) of benzaldehyde **1.15d** and catalytic amount (60 mg, 0.35 mmol) of *p*- toluene sulfonic acid in toluene (60 mL) was refluxed under a Dean-Stark water separator with vigorous stirring in an oil bath. After 9h collection of water was stopped, once the reaction completion was monitored by TLC (on charring with 2,4-DNP) then the solvent was removed under reduced pressure before washing with 5% aq $NaHCO_3$ (2x50 mL) and brine (1×50 mL). The organic layer (EtOAc) was dried over anhydrous Na_2SO_4 and concentrated before purified by flash column chromatography.

(3R,7aS)-3-phenyltetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.6a):



Yield = 81% (1.1 g); Colorless liquid; R_f = 0.53 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.35 (m, Hz, 5H), 6.32 (s, 1H), 4.17 (m, 6.88 Hz, 2H),3.48 (t, *J* = 8.1 Hz, 1H), 2.87-2.75 (m, 1H), 2.55 (m, J_1 = 10.0 Hz, J_2 = 3.7 Hz, 1H), 2.42-2.33 (m, 1H), 1.92 (m, J_1 = 14.5 Hz, J_2 = 9.3 Hz, J_3 = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.15, 138.79, 128.54, 128.42, 125.91, 87.02, 71.64, 58.79, 33.45, 23.05; ESI-MS (m/z): [M+1] 203.9; MP: 33 ^{o}C-37 ^{o}C and Yield = 89.3%; $[\alpha]_D^{¼}$= +247.5 (c 0.32, $CHCl_3$).

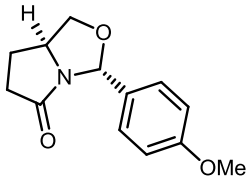
(3R,7aS)-3-(p-tolyl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.6b):



Yield = 80% (1.1 g); Colorless liquid; R_f = 0.5 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.2 Hz, 2H),

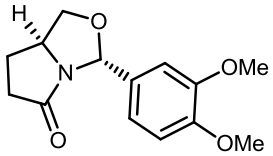
7.25-7.11 (dd, 2H), 6.32 (s, 1H), 4.29-4.12 (m, 2H), 3.47 (t, J = 7.9 Hz, 1H), 2.86-2.74 (m, 1H), 2.64-2.51 (m, 1H), 2.34 (s, 3H), 1.97-1.90 (m, 1H), 2.39 (ddd, J_1 = 9.8 Hz, J_2 = 7.6, J_3 = 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.95, 138.31, 135.83, 129.06, 125.81, 87.03, 71.57, 58.79, 33.46, 23.11, 21.15; ESI-MS (m/z): [M+1] 278.1; $[\alpha]_D^{¼}$= +178.57 (c 0.32, $CHCl_3$).

(3R,7aS)-3-(4-methoxyphenyl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.6c):



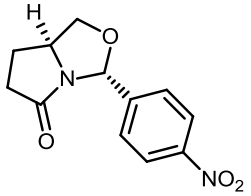
Yield = 75% (1.1 g); colorless liquid; R_f = 0.48 (10% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.47 Hz, 2H), 6.90-6.87 (m, 2H), 6.28 (s, 1H), 4.24-4.15 (m, 2H), 3.80 (s, 3H), 3.47 (t, J = 7.87 Hz, 1H), 2.84-2.76 (m, 1H), 2.58-2.50 (m, 1H), 2.38 (ddd, J_1 = 9.6 Hz, J_2 = 6.5 Hz, J_3 = 3.6 Hz, 1H), 1.94 (q, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.88, 159.77, 131.95, 127.22, 113.77, 86.94, 71.6, 55.56, 55.28, 33.54, 23.12; ESI-MS (m/z): [M+1] 233.9.

(3R,7aS)-3-(3,4-dimethoxyphenyl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.6d):



Yield = 67% (1.15 g); Colorless semisolid; R_f = 0.53 (60% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-6.93 (d, 2H), 6.84 (s, 1H), 6.28 (s, 1H), 4.31-4.11 (m, 2H), 3.96 (d, J = 9.62 Hz, 1H), 3.88 (ss, 6H), 3.48 (t, J = 8.1 Hz, 1H), 2.83 (td, J_1 = 17.4 Hz, J_2 = 9.67 Hz, 1H), 2.56 (m, J_1 = 17.2, J_2 = 10.1, J_2 = 3.69 Hz, 1H), 2.45-2.36 (m, 1H), 1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.88, 126.85, 118.08, 110.82, 110.35, 109.06, 108.92, 86.98, 71.62, 86.18, 56.16, 55.99, 33.48, 22.69; ESI-MS (m/z): [M+1] 263.9.

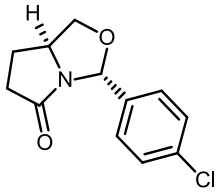
(3R,7aS)-3-(4-nitrophenyl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.6e):



Yield = 85% (1.3g); Yellow color liquid; R_f = 0.6 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.16 (m, 2H), 7.65 (d, J = 8.34 Hz, 2H), 6.36 (s, 1H), 4.27 (dd, J_1 = 8.14 Hz, J_2 = 6.33 Hz, 1H), 4.10 (m, J_1 = 7.9 Hz, J_2 = 5.8 Hz, 1H), 3.53 (t, J = 8.3 Hz, 1H), 2.84 (ddd, J_1 = 17.6 Hz, J_2 = 10.1 Hz, J_3 = 9.1 Hz, 1H), 2.67-2.56 (m,

1H), 2.44-2.36 (m, 1H), 2.00 (ddd, J_1 = 17.6, J_2 = 8.9 Hz, J_3 = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.41, 148.01, 145.86, 127.00, 123.60, 86.09, 71.90, 58.58, 33.11, 22.82; Mass: ESI (M+1) 249.5; $[\alpha]_D^{¼}$= +283.07 (c 0.32, $CHCl_3$).

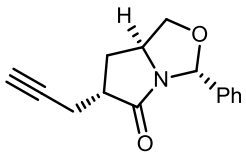
(3R,7aS)-3-(4-chlorophenyl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.6f):



Yield = 83% (1.2 g); Colorless liquid; R_f = 0.58 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (s, 1H), 3.48 (t, J = 8.1 Hz, 1H), 2.81 (td, J_1 = 17.6 Hz, J_2 = 9.6 Hz, 1H), 2.59-2.51 (m, 1H), 2.38 (ddd, J_1 = 13.7 Hz, J_2 = 6.4, J_3 = 3.7 Hz, 1H), 1.94 (ddd, J_1 = 13.4 Hz, J_2 = 9.3 Hz, J_3 = 4.1 Hz, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.22 (dd, J_1 = 7.9 Hz, J_2 = 6.4 Hz, 1H), 4.11 (ddd, J_1 = 13.8 Hz, J_2 = 7.7 Hz, J_3 = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.16, 137.36, 134.35, 128.54, 127.38, 86.45, 71.68, 58.68, 33.34, 23.03; ESI-MS (m/z): [M+1] 238.1; $[\alpha]_D^{¼}$= +240 (c 0.32, $CHCl_3$).

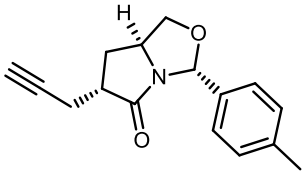
General procedure for synthesis of α-propargylated bicyclic lactams: Bicyclic lactam **3.6a** (400 mg, 1.97 mmol) was dissolved in dry. THF to this added LHMDS (361 mg, 2.16 mmol) at -78 ^oC. After 30 mins of vigorous stirring added propargyl bromide (200 mg, 11.0 mmol) and allowed to stir for 45 min, once the reaction completion was monitored by TLC reaction was quenched with aq. NH_4Cl followed by extracted with EtOAc. Further, crude product was purified by flash column chromatography.

(3R,6R,7aS)-3-phenyl-6-(prop-2-yn-1-yl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.4a):



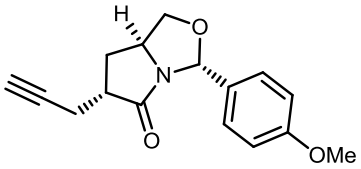
Yield = 92% (546 mg); MP: 109-115 ^oC; R_f = 0.46 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 5H), 6.34 (d, J = 6.38 Hz, 1H), 4.29 (dd, J_1 = 8.1 Hz, J_2 = 6.2 Hz, 1H), 4.18-4.10 (m, 1H), 3.61 (t, J = 7.8 Hz, 1H), 3.18-3.10 (m, 1H), 2.66 (m, 2H), 2.58-2.52 (m, 1H), 2.05 (dd, J_1 = 7.1 Hz, J_2 = 4.4 Hz, 1H),1.93-1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.15, 138.79, 128.54, 128.42, 125.91, 87.02, 71.64, 58.79, 33.45, 23.05; ESI-MS (m/z): [M+1] 241.9.

(3R,6R,7aS)-6-(prop-2-yn-1-yl)-3-(p-tolyl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.4b):



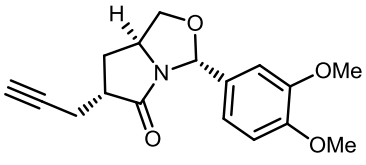
Yield = 89% (523 mg); MP: 120-125 ^{o}C; R_f = 0.43 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 6.30 (s, 1H), 4.26 (dd, J_1 = 8.8 Hz, J_2 = 6.3 Hz, 1H), 4.11 (dd, J_1 = 13.7, J_2 = 7.5 Hz, 1H), 3.57 (t, *J* = 7.8 Hz, 1H), 3.15-3.05 (m, 1H), 2.69-2.62 (m, 2H), 2.57-2.50 (m, 1H), 2.34 (s, 3H), 2.02 (t, *J* = 2.62 Hz, 1H), 1.93-1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.16, 138.43, 135.54, 129.08, 125.88, 86.74, 81.17, 72.19, 70.24, 56.47, 44.21, 30.7, 21.15, 19.76; ESI-MS (m/z): [M+1] 256.5; $[\alpha]_D$ ^{¼}= +244.62 (c 0.32, $CHCl_3$).

(3R,6R,7aS)-3-(4-methoxyphenyl)-6-(prop-2-yn-1-yl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.4c):



Yield = 87% (505 mg); MP: 121-125 ^{o}C; R_f = 0.48 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.28 (s, 1H), 4.27 (dd, J_1 = 7.9 Hz, J_2 = 6.38 Hz, 1H), 4.12 (dd, J_1 = 13.8 Hz, 7.1 Hz, 1H), 3.80 (s, 3H), 3.56 (t, *J* = 7.9 Hz, 1H), 3.15-3.02 (m, 1H), 2.66-2.45 (m, 3H), 2.03 (dd, J_1 = 7.8, J_2 = 5.2 Hz, 1H), 1.88 (ddd, J_1 = 12.8 Hz, J_2 =10.9 Hz, J_3 = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.12, 159.84, 130.66, 127.30, 113.79, 86.66, 81.17, 72.2, 70.26, 56.56, 55.28, 44.25, 30.63, 19.75; ESI-MS (m/z): [M+1] 272.5.

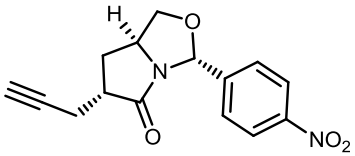
(3R,6R,7aS)-3-(3,4-dimethoxyphenyl)-6-(prop-2-yn-1-yl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.4d):



Yield = 79% (451 mg); MP: 131-135 ^{o}C; R_f = 0.5 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04-6.96 (m, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.27 (s, 1H), 4.28 (dd, *J* = 8.1 Hz, 6.2 Hz, 1H), 4.19-4.07 (m, 1H), 3.88 (d, *J* = 6.1 Hz, 6H), 3.57 (t, *J* = 7.9 Hz, 1H), 3.22-3.04 (m, 1H), 2.70-2.51 (m, 3H), 2.06-1.99 (m, 1H), 1.89 (ddd, *J* = 12.9 Hz, 10.8 Hz, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.26,

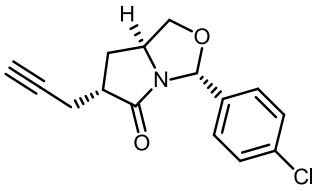
149.24, 149, 131.04, 118.15, 110.83, 109.12, 86.67, 81.13, 72.25, 70.28, 56.51, 55.92, 55.88, 44.24, 30.6, 19.74; ESI-MS (m/z): [M+1] 302.5.

(3R,6R,7aS)-3-(4-nitrophenyl)-6-(prop-2-yn-1-yl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.4e):



Yield = 85% (489 mg); MP: 127-131 ^{o}C; R_f = 0.54 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.14 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 6.35 (s, 1H), 4.31 (dd, J_1 = 8.2 Hz, J_2 = 6.27 Hz, 1H), 4.09 (dd, J_1 = 14.2 Hz, 7.0 Hz, 1H), 3.63 (t, *J* = 8.4 Hz, 1H), 3.19-3.10 (m, 1H), 2.69-2.55 (m, 3H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.97-1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.71, 148.05, 145.54, 127.06, 123.63, 85.76, 80.86, 72.6, 70.51, 56.31, 44.04, 30.24, 19.68; ESI-MS (m/z): [M+1] 287.9; $[\alpha]_D$ ¼= +266 (c 0.32, $CHCl_3$).

(3R,6R,7aS)-3-(4-chlorophenyl)-6-(prop-2-yn-1-yl)tetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one (3.4f):



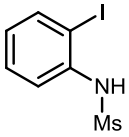
Yield = 93% (539 mg); MP: 119-122 ^{o}C; R_f = 0.52 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-2.70-2.62 (m, 2H), 7.33 (m, 4H), 6.29 (d, *J* = 5.6 Hz, 1H), 4.28 (dd, J_1 = 8.2 Hz, J_2 = 6.2 Hz, 1H), 4.20-4.03 (m, 1H), 3.60 (dd, J_1 = 10.1 Hz, J_2 = 5.8 Hz, 1H), 3.22-3.05 (m, 1H), 2.04 (t, *J* = 2.6 Hz, 1H), 2.58 (q, 1H),1.92 (ddd, J_1 = 12.9 Hz, J_2 = 10.8 Hz, J_3 = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 137.07, 134.45, 128.57, 127.44, 86.17, 81.03, 72.32, 70.36, 56.38, 44.13, 30.51, 19.7; ESI-MS (m/z): [M+1] 276.9; $[\alpha]_D$ ¼= +226.51 (c 0.32, $CHCl_3$).

General procedure: Step 1: *p*-Toluidine **3.7** (1g, 9.34 mmol) and iodine (2.36g, 9.3 mmol) was added in aqueous solution (40.0 mL) of $NaHCO_3$ (1.17g, 14.01 mmol), at 0 °C, then the reaction mixture was allowed to stir for 6h, at ambient temperature. After completion, reaction mixture was quenched with aqueous sodium thiosulphate followed by extracted with EtOAc and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

Step 2: 2-Iodo 4-methyl aniline **3.7b** (232.9 mg, 1 mmol) and *p*-toluene sulfonyl

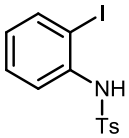
chloride **3.9b** (190.6mg. 1.0 mmol) was mixed at 0 °C in pyridine, then the reaction mixture was allowed to stir for 3h at ambient temperature. After completion of the reaction monitored by TLC, added 10 % CH_2Cl_2 in *n*-hexane (100 mL) and allowed to stir for 0.5h, before filtering the desired product, filtered crude solid was washed using 2N HCl solution (2×20 mL), and the crude product was used for further reactions without any purification.

N-(2-iodophenyl)methanesulfonamide (3.8a):



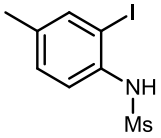
Yield = 75% (600 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.3 Hz, 1H), 7.57-7.39 (m, 2H), 7.25-7.12 (m, 1H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.57, 137.77, 135.82, 130.45, 123.02, 92.27, 39.94; and ESI-MS (m/z): [M+1] 298.1.

N-(2-iodophenyl)-4-methylbenzenesulfonamide (3.8b):



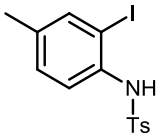
Yield = 78% (500 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 3H), 7.35-7.19 (m, 3H), 6.89-6.77 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.18, 139.05, 137.44, 135.84, 129.59, 129.45, 127.4, 126.8, 122.42, 92.28, 21.55; and ESI-MS (m/z): [M+1] 374.1.

N-(2-iodo-4-methylphenyl)methanesulfonamide (3.8c):



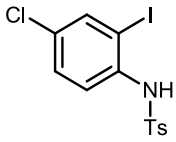
Yield = 87% (300 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, Hz, 1H), 7.61-7.43 (m, 1H), 7.2 (dd, *J* = 8.4, 1H), 6.52 (s, 1H), 3.0 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.56, 137.78, 134.97, 130.58, 123.02, 92.72, 39.92, 20.26; and ESI-MS (m/z): [M+1] 312.5.

N-(2-iodo-4-methylphenyl)-4-methylbenzenesulfonamide (3.8d):



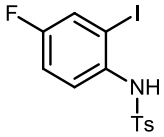
Yield = 78% (300 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.57-7.53 (m, 1H), 7.48 (d, *J* = 1.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.17-7.09 (m, 1H), 6.68 (s, 1H), 2.4 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.01, 139.25, 137.14, 135.91, 134.86, 130.2, 129.53, 127.42, 122.83, 92.75, 21.54, 20.23; and ESI-MS (m/z): [M+1] 387.9.

N-(4-chloro-2-iodophenyl)-4-methylbenzenesulfonamide (3.8f):



Yield = 77% (200 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.58 (m, 4H), 7.29 (q, 3H), 6.76 (s, 1H), 2.41 (s, 3H); and ESI-MS (m/z): [M+1] 408.2.

N-(4-fluoro-2-iodophenyl)-4-methylbenzenesulfonamide (3.8h):

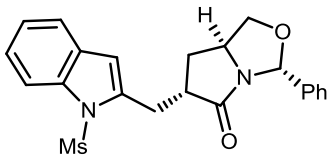


Yield = 67% (100 mg); brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.56 (m, 3H), 7.39 (dd, J_1 = 7.6, J_2 = 2.8 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.09 (m, J_1 = 7.8, J_2 = 2.8 Hz, 1H), 6.63 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 135.64, 133.97, 133.94, 129.63, 127.42, 125.78, 125.54, 124.54, 124.45, 116.56, 116.34, 109.95, 92.73, 21.53; and ESI-MS (m/z): [M+1] 392.3.

General procedure for the synthesis of 2-substituted asymmetric indoles:

Precursor substrate **3.4a** (24 mg, 0.1 mmol) and tosyl 2-iodo aniline **3.8a** (37 mg, 0.1 mmol) was dissolved in 3 ml of DMF, to this reaction mixture added Na_2HCO_3 (12.5 mg, 0.12 mmol), 5 mol % CuI (1.0 mg, 0.005 mmol) followed by 5 mol % $Pd(PPh_3)_2Cl_2$ (1.5 mg, 0.005 mmol) and allowed to stir at 60 ^{o}C for 3h. Completion of the reaction was monitored by TLC, in ordered to obtain the pure title compound, crude reaction mixture was extracted with EtOAc (2×25 mL) followed by flash column chromatography (25% EtOAc in *n*-hexane).

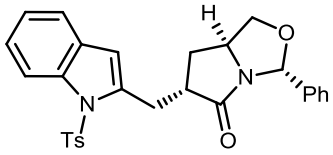
(3R,6S,7aS)-6-((1-(methylsulfonyl)-1H-indol-2-yl)methyl)-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (3.5a):



Yield = 84% (41 mg); White solid; MP: 103-109 ^{o}C; R_f = 0.48 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.8 Hz, 1H), 7.55-7.49 (m, 1H), 7.45 (d, J = 6.8 Hz, 2H), 7.40-7.27 (m, 5H), 6.57 (s, 1H), 6.36 (s, 1H), 4.20 (dd, J_1 = 8.1 Hz, J_2 = 6.5 Hz, 1H), 3.06-2.96 (m, 4H), 2.58-2.49 (m, 1H), 4.13-4.05 (m, 1H), 3.67 (dd, J_1 = 15.5 Hz, 5.0 Hz, 1H), 3.50 (td, J_1 = 8.6 Hz, J_2 = 5.7 Hz, 2H), 1.68 (q, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.16, 138.88, 138.31, 137.02, 129.62, 128.61, 128.44,

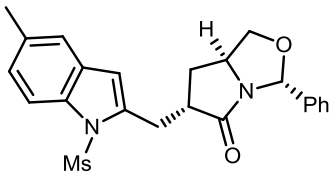
126.02, 124.52, 123.96, 120.57, 114.38, 110.69, 86.81, 72.22, 56.63, 45.16, 40.36, 33.02, 29.78; ESI-MS (m/z): [M+1] 410.9; and purity in HPLC = 98%.

(3R,6S,7aS)-3-phenyl-6-((1-tosyl-1H-indol-2-yl)methyl)tetrahydropyrrolo [1,2-c]oxazol-5(3H)-one (3.5b):



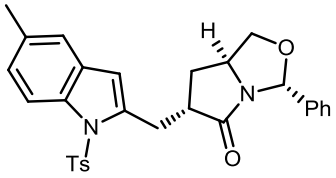
Yield = 85% (41 mg); White solid; R_f = 0.55 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.26-7.14 (m, 3H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.35 (m, J_1 = 15.8 Hz, J_2 = 9.2, J_1 = 4.4 Hz, 5H), 6.46 (s, 1H), 6.37 (s, 1H), 4.21 (dd, *J* = 8.1 Hz, J_2 = 6.4 Hz, 1H), 4.12-4.03 (m, 1H), 3.71 (dd, J_1 = 15.5 Hz, J_2 = 4.4 Hz, 1H), 3.53 (ddd, J_1 = 15.2 Hz, J_2 = 6.1 Hz, J_3 = 4.8 Hz, 2H), 3.03 (dd, J_1 = 15.4 Hz, J_2 = 9.4 Hz, 1H), 2.54 (ddd, J_1 = 12.8 Hz, J_2 = 8.4 Hz, J_3 = 6.8 Hz, 1H), 2.32 (d, *J* = 8.1 Hz, 3H), 1.71-1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.22, 144.88, 138.85, 138.38, 137.39, 129.83, 129.62, 128.57, 128.41, 126.32, 126.30, 126.07, 126.00, 124.27, 123.71, 120.28, 115.04, 111.00, 109.99, 86.80, 72.23, 56.64, 45.34, 32.87, 30.05, 29.66, 21.52; ESI-MS (m/z): [M+1] 487.7; and purity in HPLC = 97%.

(3R,6S,7aS)-6-((5-methyl-1-tosyl-1H-indol-2-yl)methyl)-3-phenyltetrahydropy-rrolo[1,2-c]oxazol-5(3H)-one (3.5c):



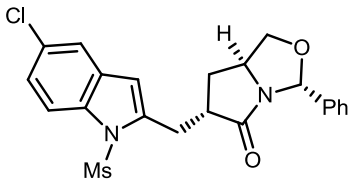
Yield = 89% (38 mg); White solid; R_f = 0.54 (35% Ethyl acetate in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 6.6 Hz, 2H), 7.40-7.27 (m, 5H), 7.12 (d, *J* = 8.9 Hz, 1H), 6.50 (s, 1H), 6.35 (s, 1H), 4.20 (dd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, 1H), 4.12-4.05 (m, 1H), 3.67-3.60 (m, 1H), 3.53-3.45 (m, 2H), 3.06-2.99 (m, 1H), 3.01-2.94 (m, 4H), 2.56-2.48 (m, 1H), 2.43 (s, 3H), 1.75-1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.17, 138.94, 138.34, 135.29, 133.65, 129.89, 128.57, 128.40, 126.00, 125.82, 120.48, 114.10, 110.67, 86.79, 72.20, 56.61, 45.18, 40.03, 32.86, 29.73, 21.17; ESI-MS (m/z): [M+1] 425.5; and purity in HPLC = 98%.

(3R,6S,7aS)-6-((5-methyl-1-tosyl-1H-indol-2-yl)methyl)-3-phenyltetrahydropy-rrolo[1,2-c]oxazol-5(3H)-one (3.5d):



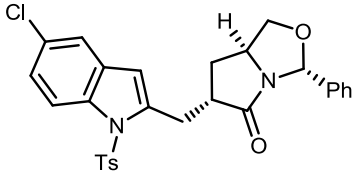
Yield = 87% (43 mg); White solid; R_f = 0.43 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 6.9 Hz, 2H), 7.39-7.31 (m, 3H), 7.17 (d, *J* = 8.7 Hz, 3H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.38 (s, 1H), 6.36 (s, 1H), 4.20 (s, 1H), 4.09 (d, *J* = 7.1 Hz, 1H), 3.68 (d, *J* = 15.2 Hz, 1H), 3.50 (d, *J* = 7.4 Hz, 2H), 3.02 (d, *J* = 9.7 Hz, 1H), 2.55-2.48 (m, 1H), 2.39 (s, 3H), 2.27 (d, *J* = 3.3 Hz, 1H), 2.32 (d, *J* = 5.2 Hz, 3H), 1.69-1.63 (m, 1H); ^{13}C NMR (100 $CDCl_3$) MHz, δ 177.12, 144.87, 138.88, 138.39, 137.39, 135.60, 135.43, 129.83, 129.63, 129.08, 126.32, 125.93, 124.25, 123.70, 120.27, 115.03, 110.97, 86.78, 72.15, 56.65, 45.35, 32.87, 30.05, 21.52, 21.15; ESI-MS (m/z): [M+1] 501.6; and purity in HPLC = 96%.

(3R,6S,7aS)-6-((5-chloro-1-(methylsulfonyl)-1H-indol-2-yl)methyl)-3-phenylte-trahydro pyr-rolo[1,2-c]oxazol-5(3H)-one (3.5e):



Yield = 77% (34 mg); White solid; R_f = 0.48 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9 Hz, 1H), 7.46 (dd, J_1 = 16.2 Hz, J_2 = 4.3 Hz, 3H), 7.40-7.31 (m, 3H), 7.26 (dd, 2H), 6.52 (s, 1H), 6.35 (s, 1H), 2.63-2.48 (m, 1H), 3.54-3.40 (m, 2H), 3.64 (dd, J_1 = 15.6 Hz, J_2 = 5.3 Hz, 1H), 4.09 (dd, J_1 = 13.7 Hz, J_1 = 6.8 Hz, 1H), 4.21 (dd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, 1H), 3.10-2.91 (m, 4H), 1.71-1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.93, 140.42, 138.23, 135.29, 130.81, 129.74, 128.62, 128.43, 125.99, 124.6, 120.12, 115.4, 109.82, 86.83, 72.18, 56.6, 45.06, 40.63, 33.06, 29.67; ESI-MS (m/z): [M+1] 445.9; and purity in HPLC = 94%.

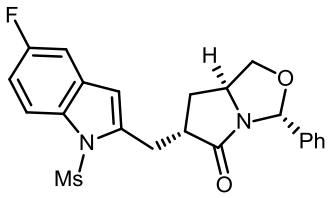
(3R,6S,7aS)-6-((5-chloro-1-tosyl-1H-indol-2-yl)methyl)-3-phenyltetrahydropy-rrolo[1,2-c]oxazol-5(3H)-one (3.5f):



Yield = 79% (41 mg); White solid; R_f = 0.5 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ

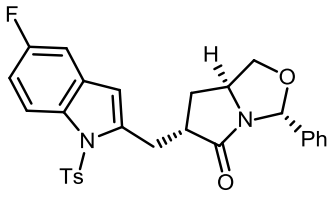
8.16-8.08 (m, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 6.6 Hz, 2H), 7.55 (d, J = 8.3 Hz, 1H), 7.41-7.27 (m, 6H), 7.22 (dd, J_1 = 9.1 Hz, J_2 = 5.1 Hz, 2H), 6.41 (s, 1H), 6.36 (s, 1H), 4.21 (dd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, 1H), 4.10 (dd, J_1 = 14.3 Hz, J_2 = 7.2 Hz, 1H), 3.68 (dd, J_1 = 15.4 Hz, J_2 = 4.3 Hz, 1H), 3.52 (ddd, J_1 = 15.2 Hz, J_2 = 8.5, J_3 = 7.1 Hz, 2H), 3.02 (dd, J_1 = 15.5 Hz, J_2 = 9.2 Hz, 1H), 2.54 (ddd, J_1 = 12.7 Hz, J_2 = 8.3, J_3 = 6.8 Hz, 1H), 2.34 (d, J = 7.1 Hz, 3H), 1.71-1.61 (m, 1H); ESI-MS (m/z): [M+1] 521.9; and purity in HPLC = 99%.

(3R,6S,7aS)-6-((5-fluoro-1-(methylsulfonyl)-1H-indol-2-yl)methyl)-3-phenyltetrahydro pyrrolo[1,2-c]oxazol-5(3H)-one (3.5g):



Yield = 79% (34 mg); White solid; R_f = 0.5 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.9 Hz, 1H), 7.48 (dd, J_1 = 16.4 Hz, J_2 = 4.2 Hz, 3H), 7.41-7.31 (m, 3H), 6.54 (s, 1H), 6.38 (s, 1H), 4.23 (dd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, 1H), 4.13 (dd, J_1 = 13.1 Hz, J_2 = 6.1 Hz, 1H), 3.66 (dd, J_1 = 15.6 Hz, J_2 = 5.2 Hz, 1H), 3.56-3.46 (m, 2H), 3.08-2.97 (m, 4H), 2.58 (ddd, J_1 = 12.7 Hz, J_2 = 8.3 Hz, J_3 = 6.7 Hz, 1H), 1.74-1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.94, 140.42, 138.23, 135.29, 130.81, 129.74, 128.62, 128.43, 125.99, 124.6, 120.12, 115.4, 109.82, 86.83, 72.18, 56.6, 45.06, 40.63, 33.06, 29.67; ESI-MS (m/z): [M+1] 428.9; and purity in HPLC = 97%.

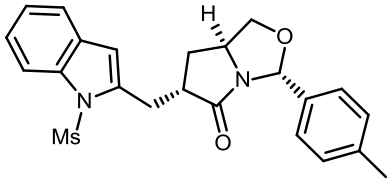
(3R,6S,7aS)-6-((5-fluoro-1-tosyl-1H-indol-2-yl)methyl)-3-phenyltetrahydro-pyrrolo[1,2-c]oxazol-5(3H)-one (3.5h):



Yield = 85% (42 mg); White solid; R_f = 0.47 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J_1 = 9.1 Hz, J_2 = 4.4 Hz, 1H), 7.63 (d, J_1 = 8.3 Hz, 2H), 7.47 (d, J = 7.1 Hz, 2H), 7.38 (ddd, J_1 = 9.8 Hz, J_2 = 5.2 Hz, J_2 = 2.3 Hz, 4H), 7.21 (d, J = 8.1 Hz, 2H), 7.08-6.99 (m, 2H), 6.44 (s, 1H), 6.38 (s, 1H), 4.22 (dd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, 1H), 4.14-4.08 (m, 1H), 3.70 (dd, J_1 = 15.2 Hz, J_2 = 4.7 Hz, 1H), 3.56-3.49 (m, 2H), 3.03 (dd, J_1 = 15.4 Hz, J_2 = 9.2 Hz, 1H), 2.55 (ddd, J_1 = 12.7 Hz, J_2 = 8.3 Hz, J_3 = 6.8 Hz, 1H), 2.36 (s, 3H), 1.72-1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.08, 158.61, 145.13, 140.73, 138.33, 135.34, 133.64, 129.92, 128.61, 128.44, 126.31, 126.01, 116.08, 112.17, 111.92, 110.83, 110.79,

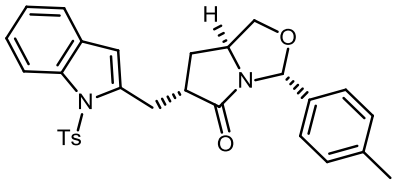
106.0, 105.77, 86.83, 72.22, 56.64, 45.33, 32.94, 30.11, 21.56; ESI-MS (m/z): [M+1] 505.3; and purity in HPLC = 96%.

(3R,6S,7aS)-6-((1-(methylsulfonyl)-1H-indol-2-yl)methyl)-3-(p-tolyl)tetrahydro-pyrrolo[1,2-c]oxazol-5(3H)-one (3.5i):



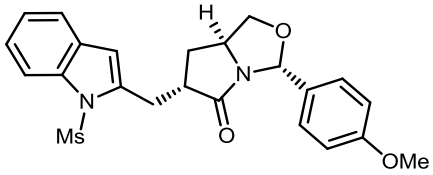
Yield = 91% (38 mg); White solid; R_f = 0.46 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.44-7.38 (m, 2H), 7.21 (t, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.47 (s, 1H), 6.33 (s, 1H), 4.24-4.18 (m, 1H), 4.14-4.08 (m, 1H), 3.81 (d, *J* = 7.0 Hz, 3H), 3.72 (dd, J_1 = 15.3 Hz, J_2 = 4.6 Hz, 1H), 3.58-3.46 (m, 2H), 3.03 (dd, J_1 = 15.4 Hz, J_2 = 9.5 Hz, 1H), 2.59-2.49 (m, 1H), 2.34 (s, 3H), 1.67 (dd, J_1 = 12.1 Hz, J_2 = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.08, 159.84, 144.88, 138.89, 137.4, 135.61, 130.58, 129.84, 129.64, 127.36, 126.33, 124.27, 123.72, 120.28, 115.05, 113.81, 110.99, 86.71, 72.19, 56.74, 55.3, 45.43, 32.85, 30.06, 21.53; ESI-MS (m/z): [M+1] 425.1; and purity in HPLC = 95%.

(3R,6S,7aS)-3-(p-tolyl)-6-((1-tosyl-1H-indol-2-yl)methyl)tetrahydropyrr-olo[1,2-c] oxazol-5(3H)-one (3.5j):



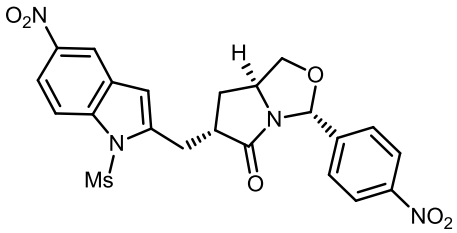
Yield = 88% (44 mg); White solid; R_f = 0.5 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 7.1 Hz, 1H), 7.36-7.27 (m, 3H), 6.46 (s, 1H), 6.34 (s, 1H), 4.23-4.09 (m, 2H), 3.70 (dd, J_1 = 15.4 Hz, J_2 = 4.6 Hz, 1H), 3.50 (dd, J_1 = 9.2 Hz, J_2 = 2.2 Hz, 2H), 3.02 (dd, J_1 = 15.4 Hz, J_2 = 9.5 Hz, 1H), 2.52 (ddd, J_1 = 12.7 Hz, J_2 = 8.4 Hz, J_3 = 6.8 Hz, 1H), 2.34 (d, *J* = 7.7 Hz, 6H), 1.66 (dd, J_1 = 12.1 Hz, J_2 = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.12, 144.87, 138.88, 138.39, 137.39, 135.6, 135.43, 129.83, 129.63, 129.08, 126.32, 125.83, 124.25, 123.7, 120.27, 115.03, 110.97, 86.78, 72.15, 58.85, 32.87, 30.05, 21.52, 21.15; ESI-MS (m/z): [M+1] 501.9; and purity in HPLC = 95%.

(3R,6S,7aS)-3-(4-methoxyphenyl)-6-((1-(methylsulfonyl)-1H-indol-2-yl)methyl)tetrahydro pyrrolo[1,2-c]oxazol-5(3H)-one (3.5k):



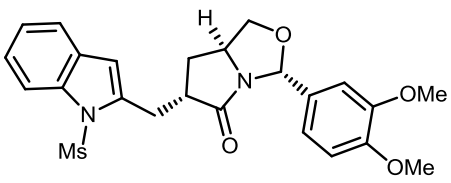
Yield = 80% (36 mg); white solid; R_f = 0.5 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.98 (m, 1H), 7.53-7.49 (m, 1H), 7.38-7.35 (m, 2H), 7.29 (dd, J_1 = 7.6 Hz, J_2 = 6.3 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.56 (s, 1H), 6.30 (s, 1H), 4.18 (m, 1H), 4.11 (m, 1H), 3.80 (d, *J* = 1.9 Hz, 3H), 3.69-3.60 (m, 1H), 3.50 (d, *J* = 8.6 Hz, 2H), 3.01 (s, 3H), 2.60-2.48 (m, 2H), 1.67-1.63 (m, 1H); ESI-MS (m/z): [M+1] 441.5; and purity in HPLC = 97%.

(3R,6S,7aS)-6-((1-(methylsulfonyl)-5-nitro-1H-indol-2-yl)methyl)-3-(4-nitrophenyl) tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (3.5l):



Yield = 79% (39 mg); white solid; R_f = 0.46 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.1 Hz, 1H), 8.24-8.19 (m, 3H), 8.15 (d, *J* = 9.1 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 6.72 (s, 1H), 6.39 (s, 1H), 4.27 (s, 1H), 4.13-4.07 (m, 1H), 3.72-3.66 (m, 1H), 3.62-3.50 (m, 3H), 3.17 (s, 3H), 3.12-3.07 (m, 1H), 2.67-2.61 (m, 1H), 1.75-1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.06, 148.13, 145.16, 141.89, 139.68, 129.27, 127.07, 127.03, 123.67, 123.64, 119.6, 116.61, 114.44, 110.31, 85.86, 72.59, 56.44, 44.88, 43.99, 41.61, 30.5, 20.59; ESI-MS (m/z): [M+1] 501.9; and purity in HPLC = 98%.

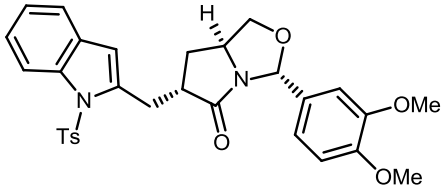
(3R,6S,7aS)-3-(3,4-dimethoxyphenyl)-6-((1-(methylsulfonyl)-1H-indol-2-yl)methyl)tetrahy dropyrrolo[1,2-c]oxazol-5(3H)-one (3.5m):



Yield = 67% (37 mg); white solid; R_f = 0.4 (65% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.61 Hz, 1H), 7.51 (dd, *J* = 6.5, 1.9 Hz, 1H), 7.02-6.95 (m, 2H), 6.86-6.82 (m, 1H), 6.57 (s, 1H), 6.31 (s, 1H), 3.88 (d, *J* = 7.5 Hz, 7H), 3.66 (dd, *J* = 15.6, 5.04 Hz, 1H), 3.50 (ddd, *J* = 8.6, 6.9, 4.1 Hz, 2H), 3.06-2.97 (m, 4H), 2.57-2.49 (m, 1H), 1.70-1.64

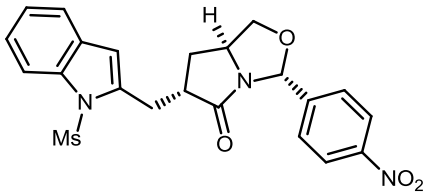
(m, 1H), 7.33-7.27 (m, 2H), 4.20 (dd, *J* = 8.1, 6.39 Hz, 1H), 4.09 (t, 1H); ESI-MS (m/z): [M+1] 571.5; and HPLC = 97%.

(3R,6S,7aS)-3-(3,4-dimethoxyphenyl)-6-((1-tosyl-1H-indol-2-yl)methyl)tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (3.5n):



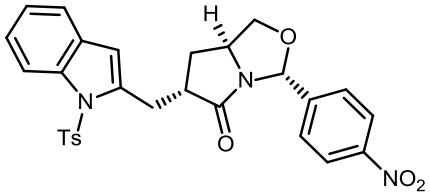
Yield = 69%; white solid; R_f = 0.4 (65% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 3H), 7.41 (d, *J* = 7.1 Hz, 1H), 7.23-7.18 (m, 2H), 7.30 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.02-6.95 (m, 2H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.46 (s, 1H), 6.32 (s, 1H), 4.20 (dd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, 1H), 4.12-4.06 (m, 1H), 3.89 (d, *J* = 8.7 Hz, 6H), 3.74-3.68 (m, 1H), 3.58-3.48 (m, 2H), 3.02 (dd, J_1 = 15.4 Hz, J_2 = 9.5 Hz, 1H), 2.56-2.48 (m, 1H), 2.33 (s, 3H), 1.66 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.31, 149.24, 149.03, 144.9, 138.85, 137.4, 135.57, 130.93, 129.85, 129.64, 126.33, 124.3, 123.74, 120.29, 118.27, 115.06, 111.07, 110.84, 109.12, 86.74, 72.2, 56.71, 55.92, 45.39, 32.88, 31.91, 22.67, 21.54, 14.1; ESI-MS (m/z): [M+1] 547.8; and HPLC = 95%.

(3R,6S,7aS)-6-((1-(methylsulfonyl)-1H-indol-2-yl)methyl)-3-(4-nitrophenyl)tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (3.5o):



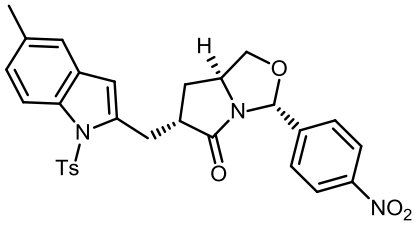
Yield = 79% (36 mg); white solid; R_f = 0.48 (35% Ethyl acetate in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-7.98 (m, 1H), 7.51 (dd, J_1 = 6.4 Hz, J_2 =1.9 Hz, 1H), 7.46-7.43 (m, 2H), 7.32 (m, 4H), 6.57 (s, 1H), 6.36 (s, 1H), 4.20 (dd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, 1H), 4.12-4.06 (m, 1H), 3.67 (dd, J_1 = 15.1 Hz, J_2 = 4.7 Hz, 1H), 3.53-3.45 (m, 2H), 3.04-2.97 (m, 4H), 2.57-2.48 (m, 1H), 1.68 (dd, J_1 = 12.1 Hz, J_2 = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.14, 138.88, 138.32, 137.02, 129.61, 126.58, 128.41, 126.0, 124.5, 123.94, 120.55, 114.36, 110.67, 86.81, 72.2, 56.62, 45.15, 40.33, 32.97, 29.75; ESI-MS (m/z): [M+1] 455.9; and purity in HPLC = 95%.

(3R,6S,7aS)-3-(4-nitrophenyl)-6-((1-tosyl-1H-indol-2-yl)methyl)tetrahydro-pyrrolo[1,2-c]oxazol-5(3H)-one (3.5p):



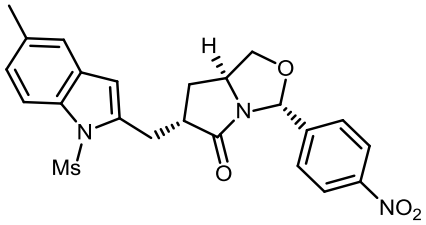
Yield = 81% (43 mg); white solid; R_f = 0.46 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J_1 = 15.6 Hz, J_2 = 8.3 Hz, 3H), 7.66 (t, J = 8.7 Hz, 4H), 7.42 (d, J = 7.1 Hz, 1H), 7.32-7.27 (m, 1H), 7.25-7.17 (m, 3H), 6.47 (s, 1H), 6.40 (s, 1H), 4.24 (dd, J_1 = 8.3 Hz, J_2 = 6.4 Hz, 1H), 4.08-4.02 (m, 1H), 3.73 (dd, J_1 = 15.3 Hz, J_2 = 4.2 Hz, 1H), 3.61-3.52 (m, 2H), 3.04 (dd, J_1 = 15.3 Hz, J_2 = 9.3 Hz, 1H), 2.60-2.50 (m, 1H), 2.34 (s, 3H), 2.18 (s, 1H), 1.72 (dd, J_1 = 12.2 Hz, J_2 = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 148.05, 145.48, 144.94, 138.51, 137.37, 135.47, 129.83, 129.55, 127.09, 126.28, 124.37, 123.77, 123.63, 120.29, 115.04, 111.17, 85.79, 72.62, 56.49, 45.32, 32.64, 29.98, 21.51; ESI-MS (m/z): [M+1] 532; and purity in HPLC = 97%.

(3R,6S,7aS)-6-((5-methyl-1-tosyl-1H-indol-2-yl)methyl)-3-(4-nitrophenyl) tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (3.5q):



Yield = 83% (45 mg); white solid; R_f = 0.47 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.21 (m, 2H), 8.05 (d, J = 8.5 Hz, 1H), 7.64 (dd, J_1 = 15.2 Hz, J_2 = 8.4 Hz, 4H), 7.18 (d, J = 8.1 Hz, 3H), 7.10 (dd, J_1 = 8.5 Hz, J_2 = 1.2 Hz, 1H), 6.39 (s, 2H), 4.23 (dd, J_1 = 8.3 Hz, J_2 = 6.4 Hz, 1H), 4.08-4.01 (m, 1H), 3.70 (dd, J_1 = 15.3 Hz, J_2 = 4.6 Hz, 1H), 3.58-3.49 (m, 2H), 3.01 (dd, J_1 = 15.2 Hz, J_2 = 9.3 Hz, 1H), 2.57-2.50 (m, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 2.17 (dd, J_1 = 7.3 Hz, J_2 = 5.2 Hz, 1H), 1.70 (dd, J_1 = 11.7 Hz, J_2 = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.64, 145.5, 144.81, 138.53, 135.6, 135.46, 133.43, 129.81, 129.79, 127.09, 126.25, 125.72, 123.63, 120.24, 114.76, 111.14, 85.78, 72.61, 56.48, 45.36, 32.52, 29.95, 21.5, 21.15; ESI-MS (m/z): [M+1] 546.7; and purity in HPLC = 98%.

(3R,6S,7aS)-6-((5-methyl-1-(methylsulfonyl)-1H-indol-2-yl)methyl)-3-(4-nitrophenyl) tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (3.5r):



Yield = 83% (38 mg); white solid; R_f = 0.4 (35% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.31 (s, 1H), 7.14 (dd, *J* = 8.5 Hz, J_2 = 1.2 Hz, 1H), 6.51 (s, 1H), 6.39 (s, 1H), 4.24 (dd, J_1 = 8.3 Hz, J_1 = 6.3 Hz, 1H), 4.07-4.03 (m, 1H), 3.67 (dd, J_1 = 15.1 Hz, J_1 = 4.8 Hz, 1H), 3.56-3.50 (m, 2H), 3.03-2.98 (m, 4H), 2.59-2.53 (m, 1H), 1.70 (dd, J_1 = 10.0 Hz, J_2 = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.53, 148.04, 145.45, 138.6, 135.28, 133.73, 129.82, 127.09, 125.93, 123.62, 120.49, 114.1, 110.81, 85.78, 72.59, 56.48, 45.15, 39.99, 32.63, 29.68, 21.15; ESI-MS (m/z): [M+1] 470.1; and purity in HPLC = 97%.

3.6. References:

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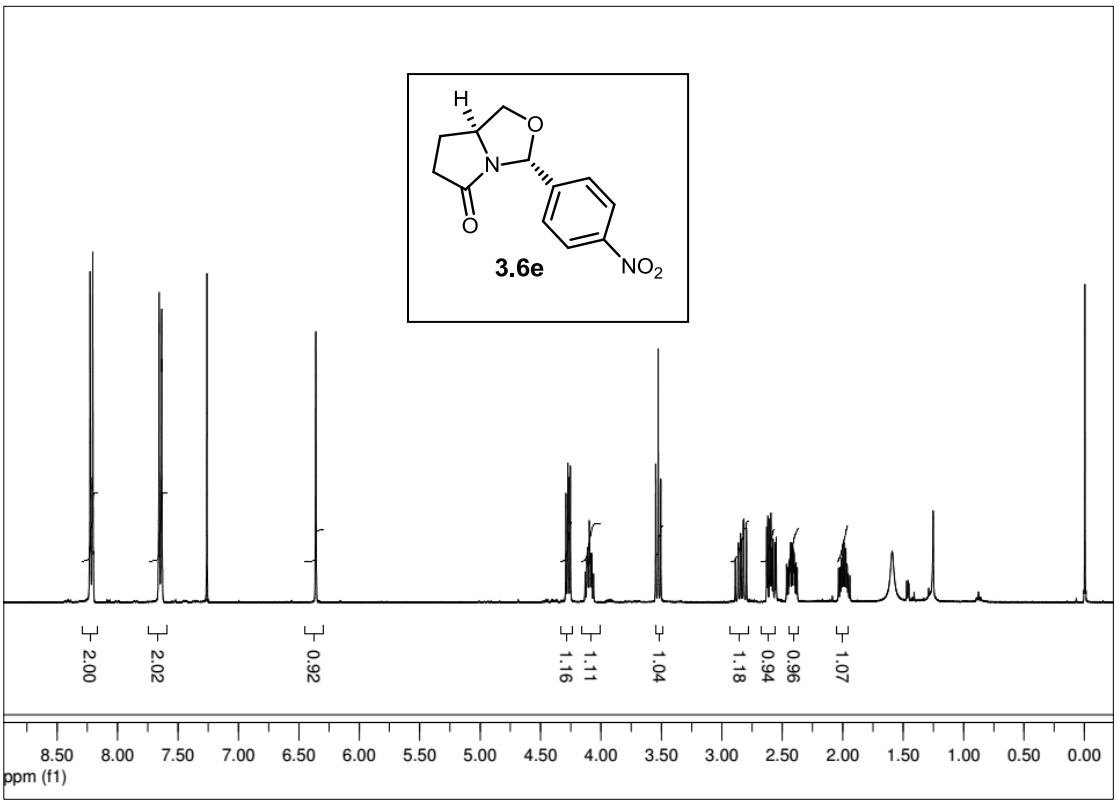
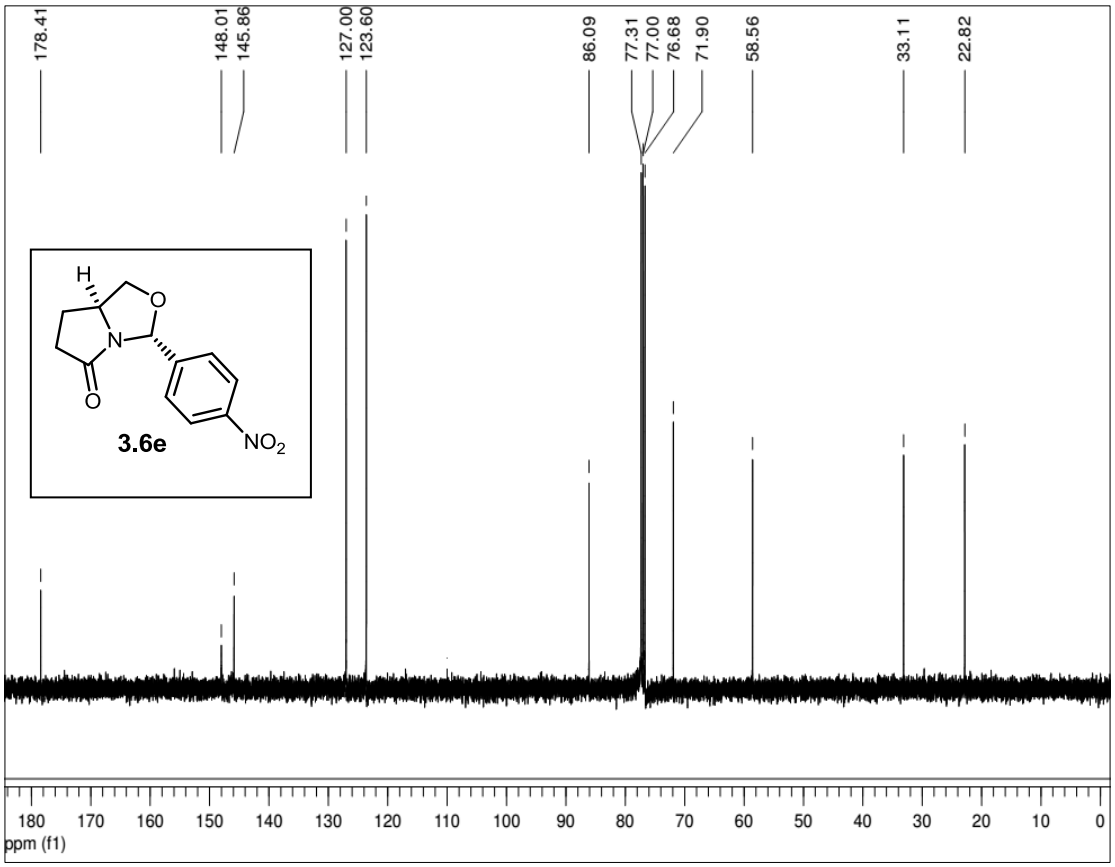
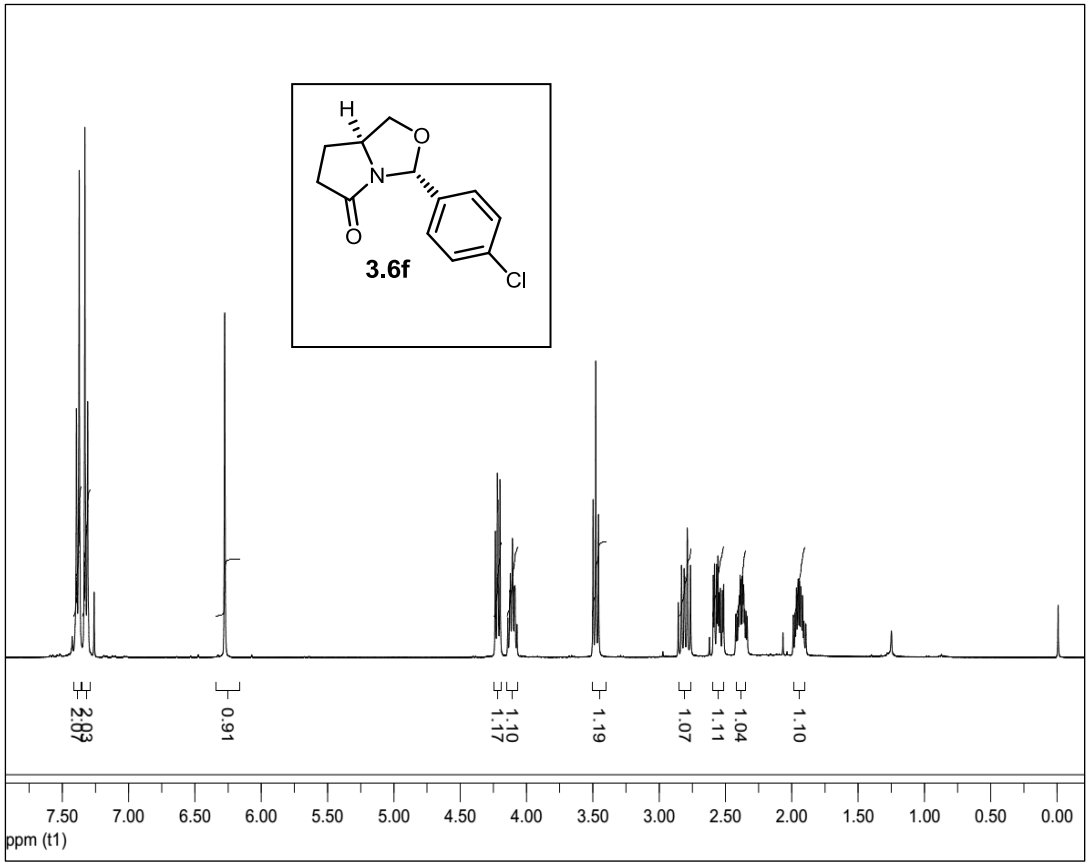
3.7. Appendices:



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1.04
1.10
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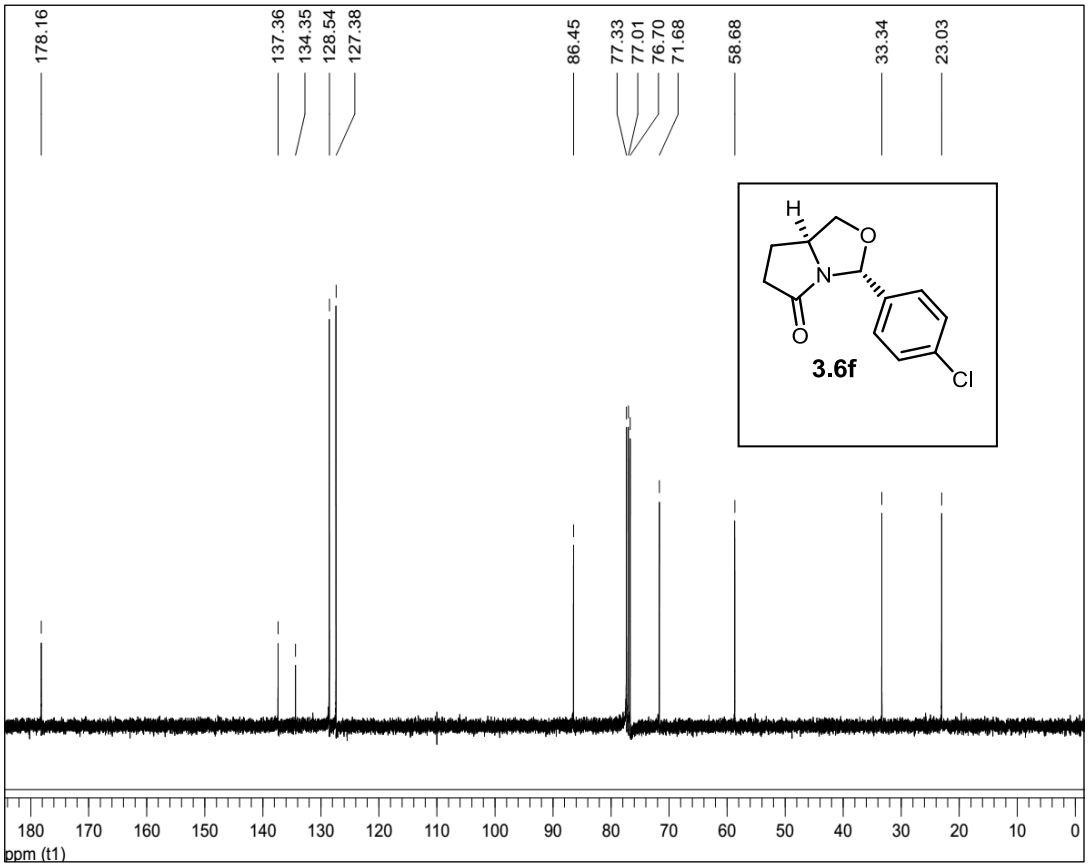
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O
N
O
Cl
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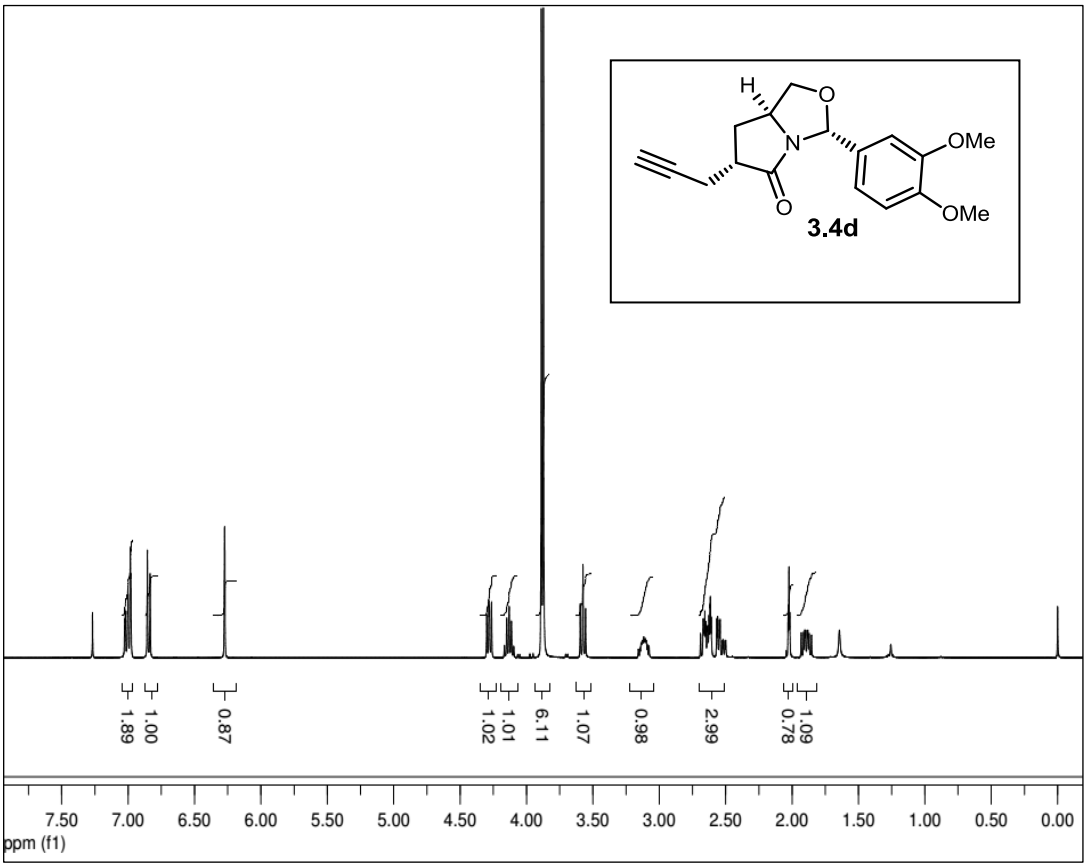
ppm (t1)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1.01
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1.07
0.98
2.99
0.78
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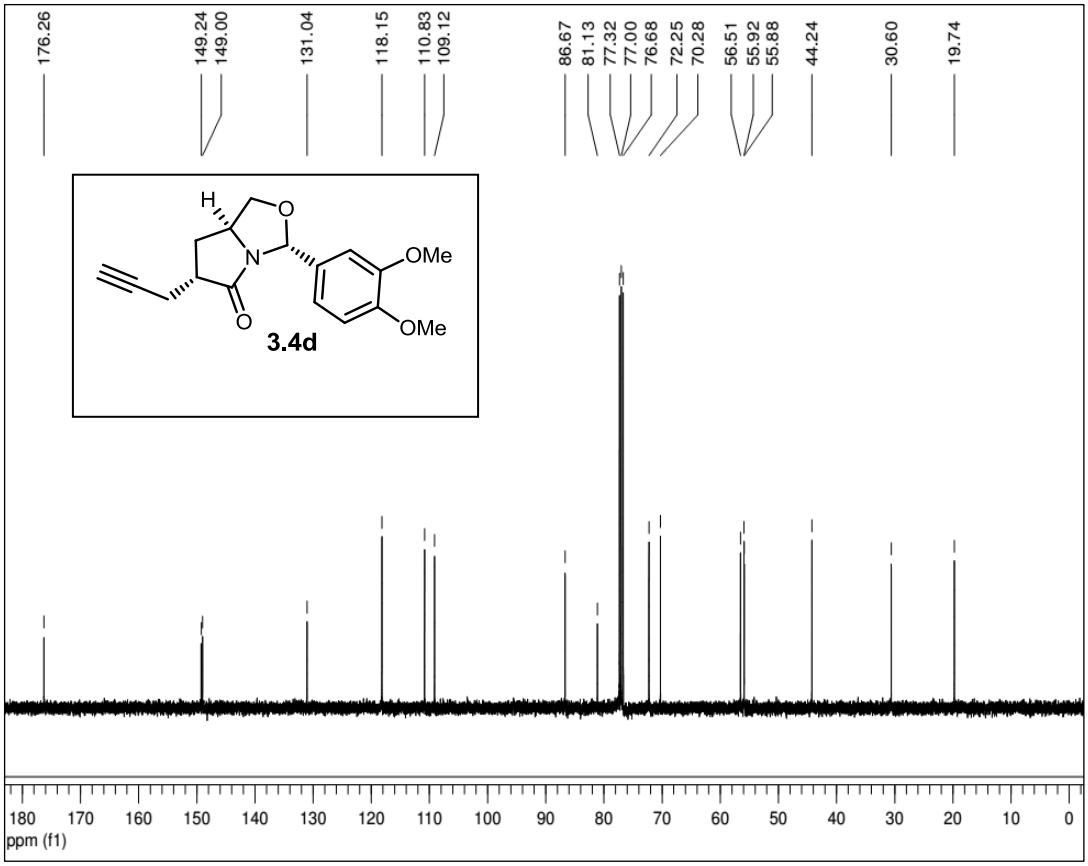
ppm (f1)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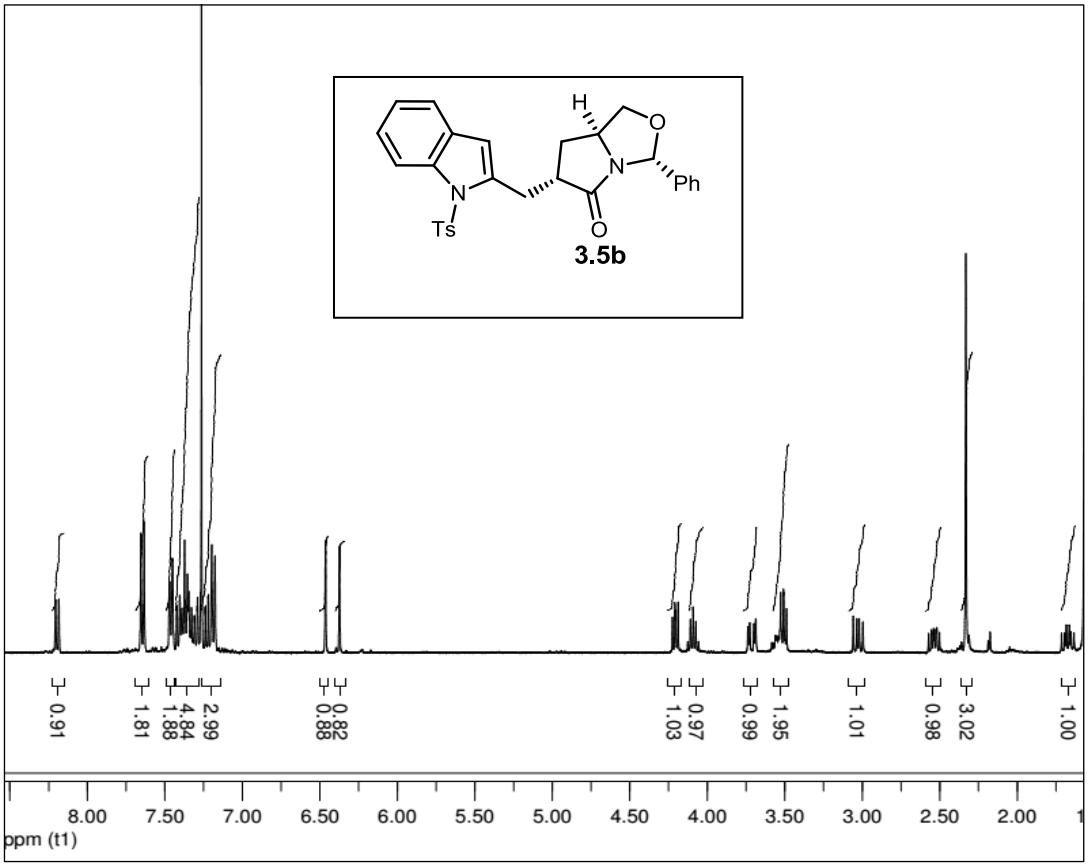
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0.99
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1.00
8.00
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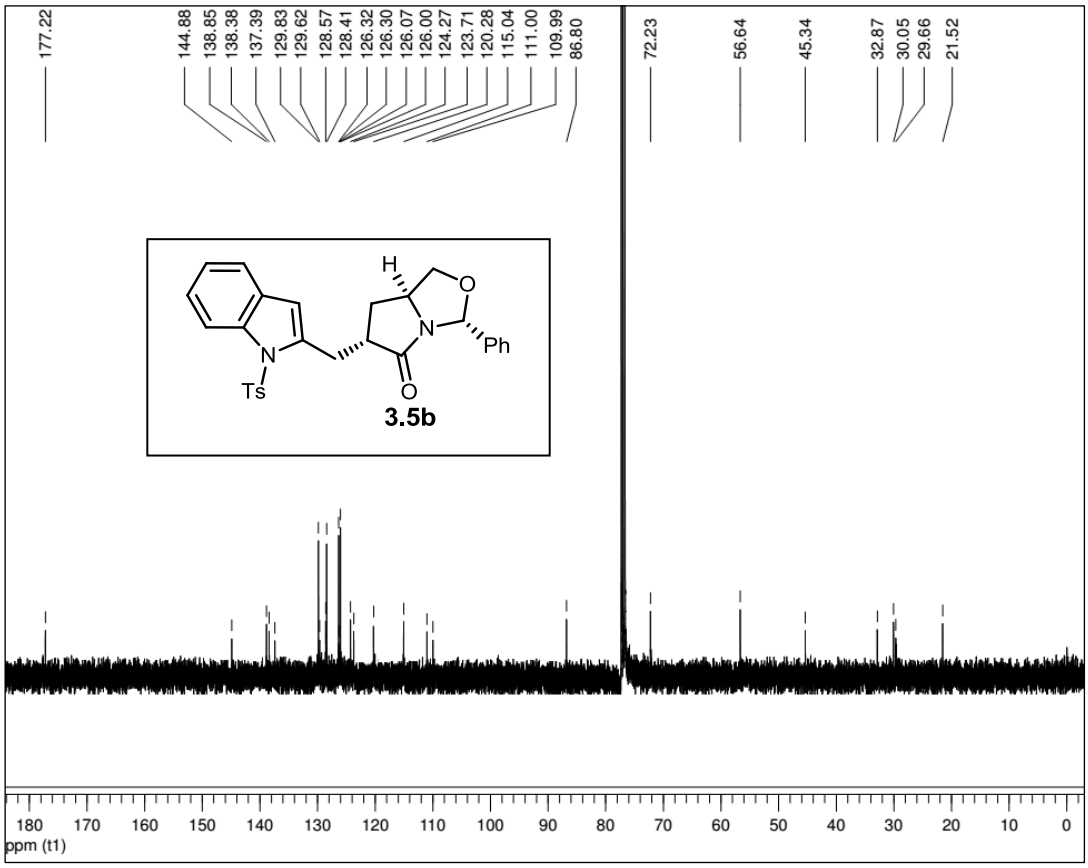
ppm (t1)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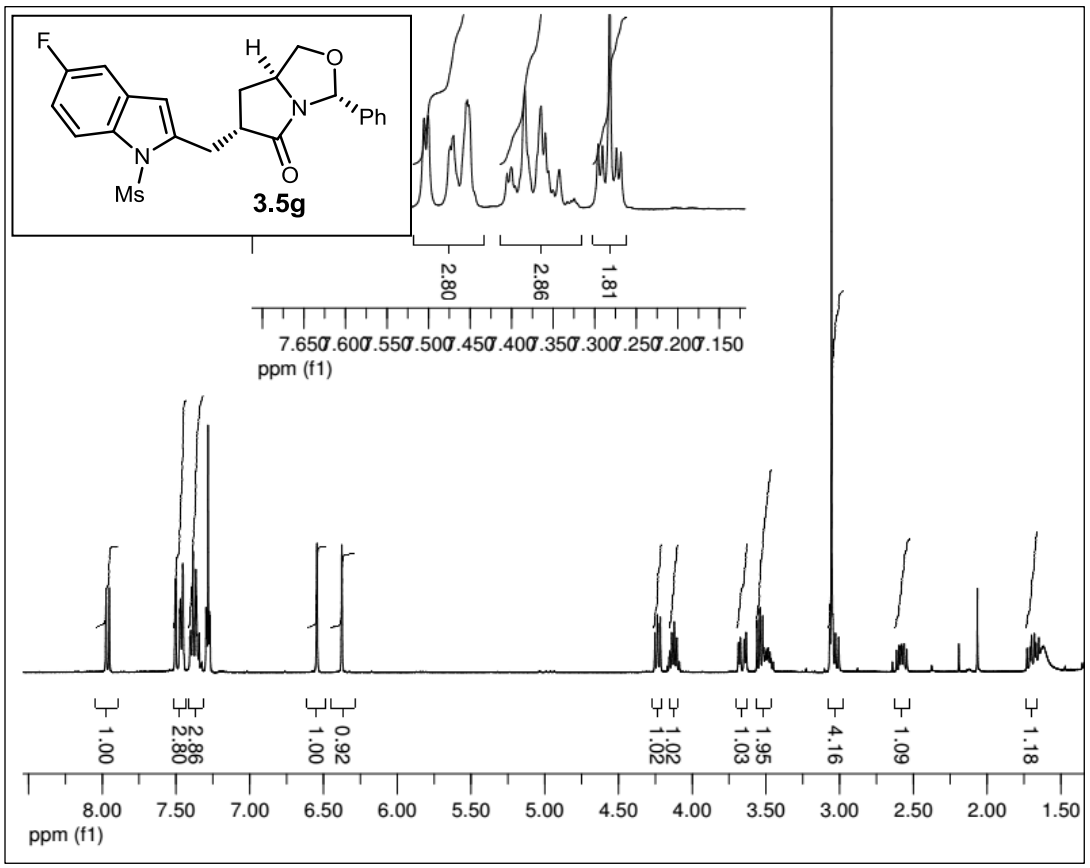
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ppm (f1)
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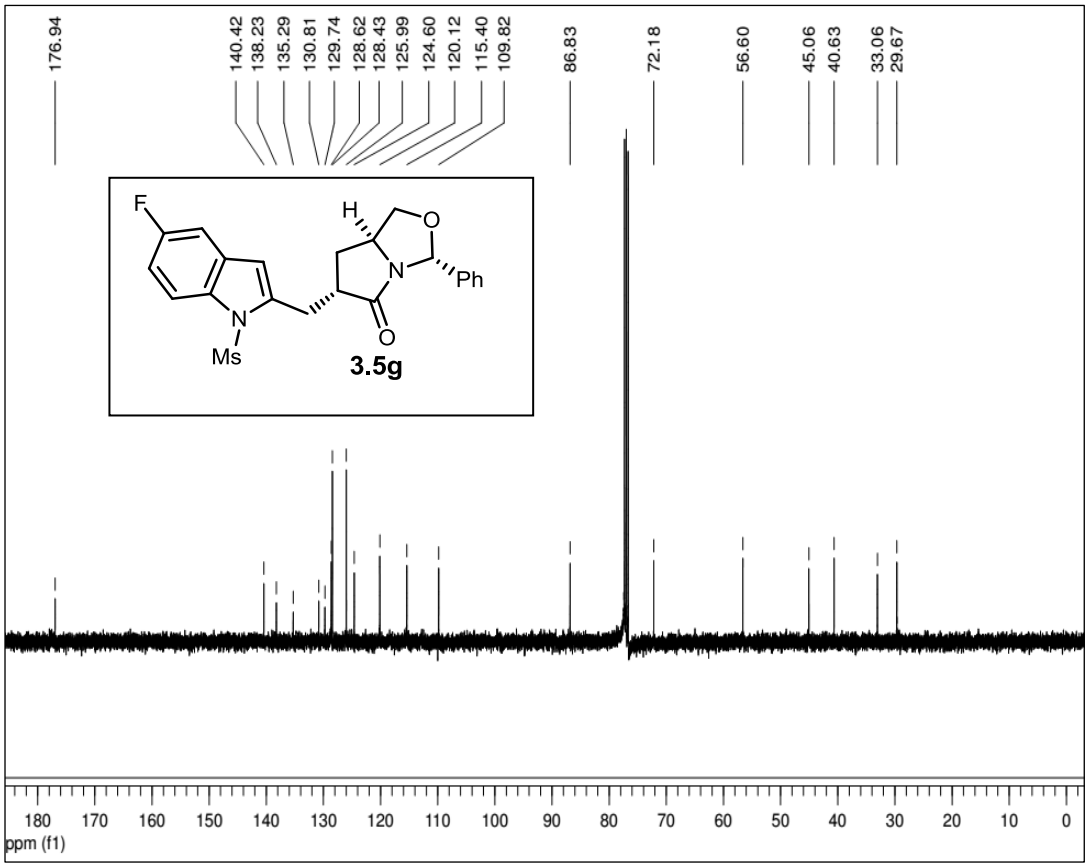
2.86
1.00
0.92
1.02
1.02
1.03
1.95
4.16
1.09
1.18
8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50
ppm (f1)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45.06
40.63
33.06
29.67
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N
Ph
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O
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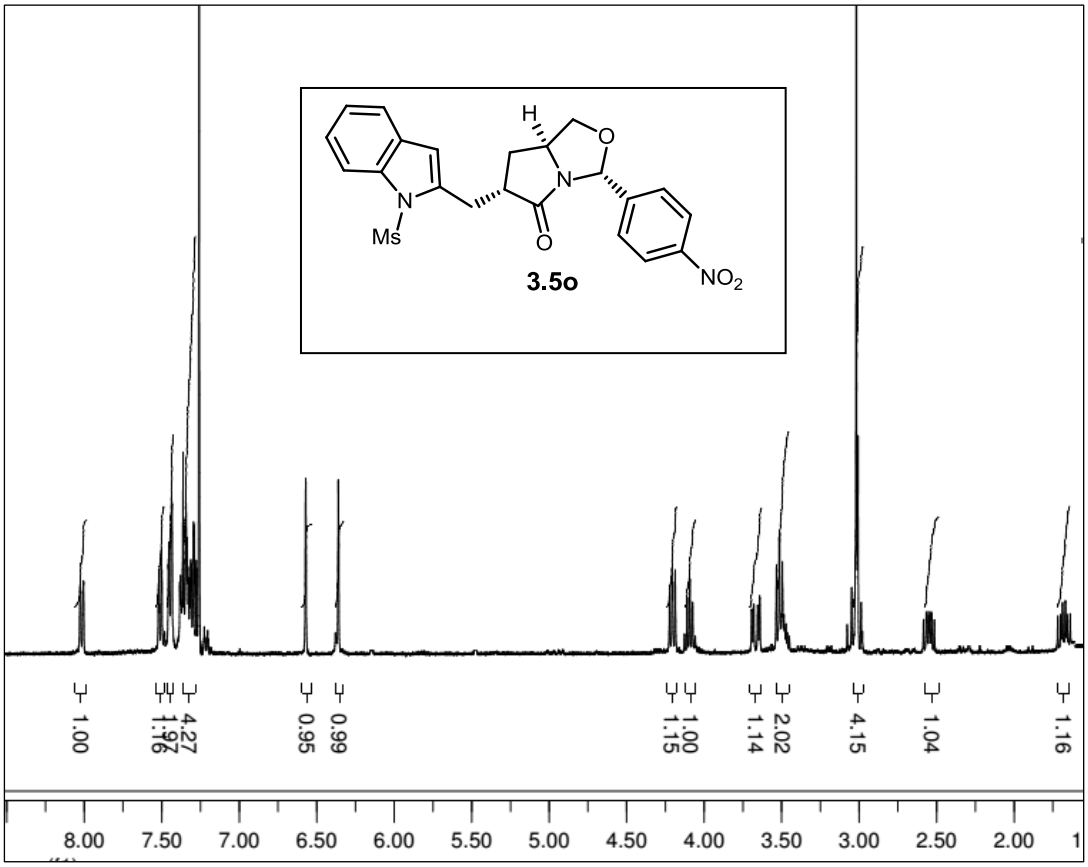
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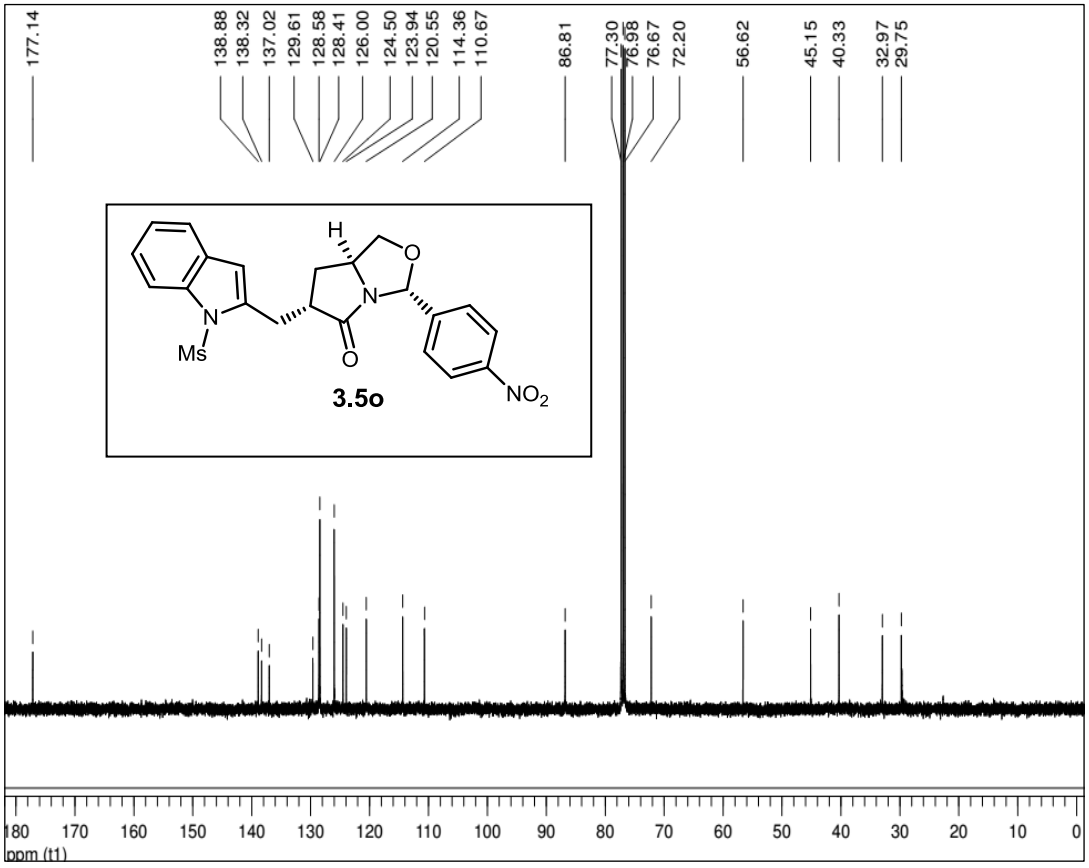
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123.94
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76.67
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45.15
40.33
32.97
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170
160
150
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130
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110
100
90
80
70
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50
40
30
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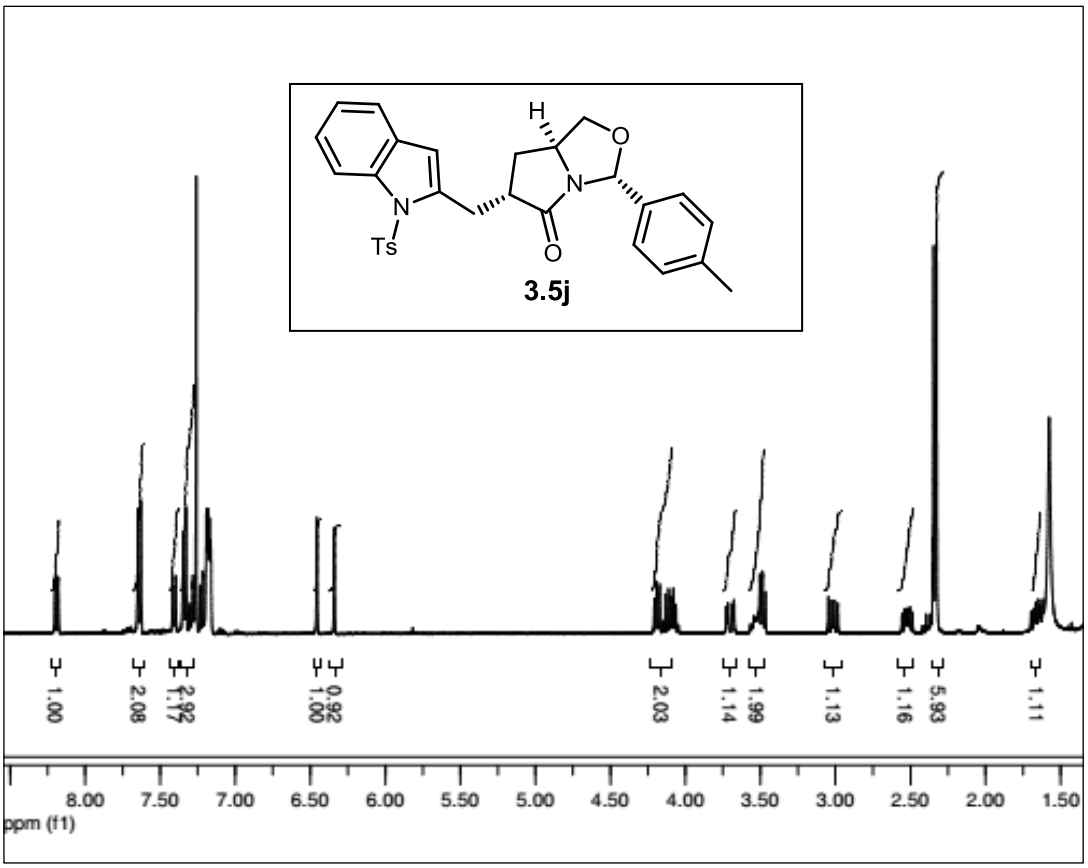
ppm (t1)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N
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1.16
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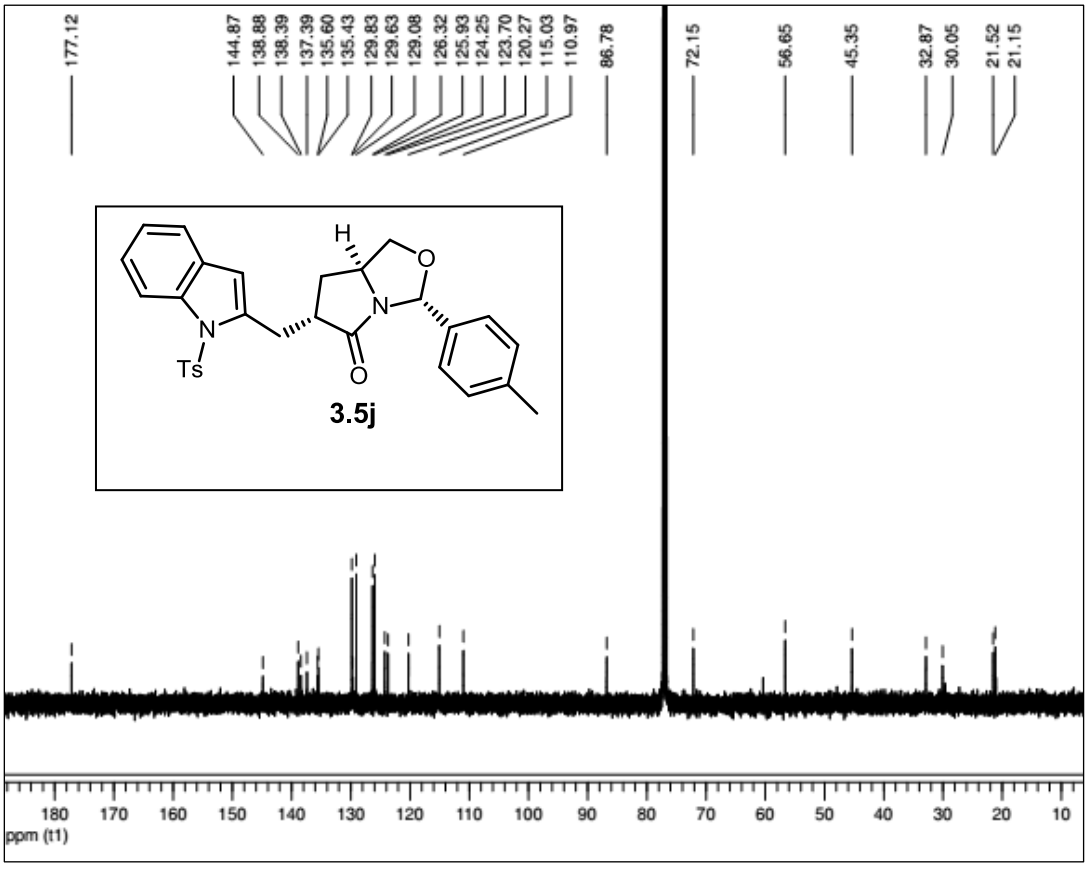
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H
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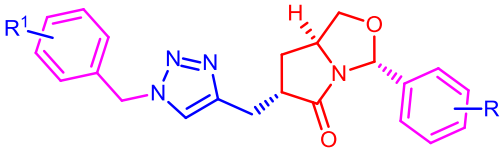
ppm (t1)

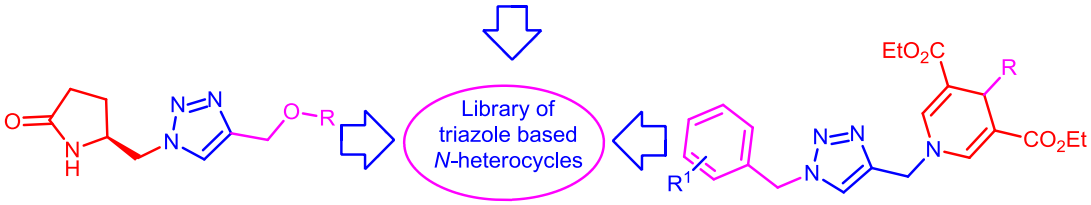
Chapter 4: Discovery of novel AMPK activators



4.12

18 Examples, Up to 89 % of yield

R and R^1 = alkyl and substituted (hetero) aryl



4.10

24 Examples, Up to 96 % of yield

R = alkyl, substituted (hetero) aryl

4.13

12 Examples, Up to 93 % of yield

R and R^1 = alkyl and substituted (hetero) aryl

4.1. Introduction:

Huisgen 1,3-dipolar cycloaddition reaction (1,3-DCR) between organic azides (R-N_3) with alkynes (R_1-C≡CH) is an efficient synthetic tool for generating the diverse bio-active triazoles.[1] Huisgen1,3-DCR often requires elevated temperatures and produces mixtures of an equimolar ratio of regio-isomers (1,4- and 1,5-disubstituted 1,2,3-triazoles). Sharpless and Meldal, independently discovered the Cu(I)-catalyzed protocol for the synthesis of regio-selective 1,4-disubstituted 1,2,3-triazole derivatives.[2] Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has shown the dramatic rate enhancement (up to 10^7-fold) at ambient temperature. Although, thermal 1,3-DCRs have been experiencing for several years, the most applicative azide-alkyne 1,3-DCRs were established in the 20th century, since the disclosure of CuAAC reaction utilities by Sharpless. These reactions are modular, high yielding, wide in scope, no byproducts, operates easily removable solvents, product purification follows the non-chromatographic methods and precursors are readily accessible. CuAAC reaction represented as CuAAC-click reaction, soon after displayed the stringent criteria of a click-reaction.[3] Later, Sharpless developed the Ru-catalyzed [Cp*RuCl(PPh_3)$_2$] protocol for the synthesis of 1,5-disubstituted-1,2,3-triazole derivatives.[4]

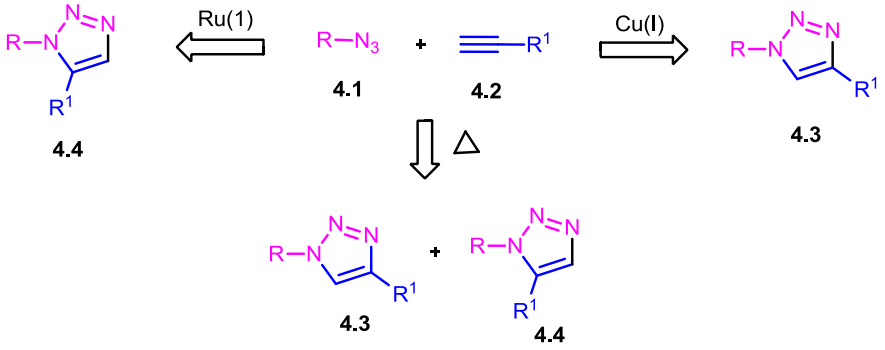


Fig. 4.1. General methods for the synthesis of triazole derivatives

4.1.1. Medicinal applications of triazole derivatives:

Apart from the transition metal mediated regio-controlled synthetic endowers; the CuAAC-click reaction adducts such as 1,4-disubstituted 1,2,3-triazole based *N*-heterocycles have been considered as corner stone of medicinal chemistry due to their potent biological applications.[5,6,7] Fragment based drug discovery is an effective

strategy in medicinal chemistry research for linking the selective fragments. Although several methods have been well known, CuAAC-click reaction has been using as a common conjugation method in medicinal and materials research, because of its selectivity, robust, and tolerate to the changes in pH and temperature. CuAAC-click reaction also allows the access for diverse novel *N*-heterocycles for controlling the chronic, metabolic and neurodegenerative disorders, *etc*.[5,6] Bioisosterism is one of the factor often associate with the drug discovery research, bioisosteres are acquired for discovering the potent drug candidates, which mainly useful for reducing the toxicity or modifying the activity or alter the metabolism of the lead compound.[8] In fact, the triazole nucleus is stable in acidic, basic as well as the oxidative and reductive conditions and serves as a bio-isostere to esters, amides and isoxazoles, *etc*.[8] In addition, novel *N*-heterocycles having triazole as a privileged nucleus provides the additional hydrogen bonding interactions because of high dipole moment as well the hydrophobic interactions, which improves their solubility and bio-availabity.[6]

4.1.2 AMPK activators in drug discovery:

Metabolic disorders such as diabetes, hypertension, dyslipidemia and obesity, *etc* are well recognized as factors increasing the cardiovascular risk. For example, type 2 diabetes (T2D) is a complex metabolic disorder with many risk factors and implications. T2D patients with atherogenic dyslipidemia, includes low HDL, elevated plasma triglycerides and preponderance small dense LDL particles, which are having a higher risk of atherosclerosis.[11,12,13] Therefore, treatment of T2D should address both hyperglycemia to prevent microvascular disease and atherogenic dyslipidemia to prevent macro vascular complications. This currently requires multiple medications, including anti-diabetic, lipid-lowering agents and antihypertensive agents, to sufficiently manage all aspects of the pathology of this disease.

The AMPK acts as an intracellular metabolic sensor in a variety of cell types, where it monitors and responds to variations in the AMP/ATP ratio. AMPK is switched on by any cellular stress that causes a rise in the AMP/ATP ratio, either by interfering with ATP production or increasing ATP consumption. Besides its function as a sensor of cellular energy status, which is also plays a critical role in the energy balance of the whole organism. For instance, AMPK is triggered by hormones and cytokines,

including leptin and adiponectin, which increase AMPK signaling. All those properties combine to make activation of AMPK a target of choice for the treatment of metabolic disorders.

There is currently hardly any drug available that is active on more than one factors of the cardiovascular risk. Therefore, in view of decreasing the need for multiple medications to treat a single patient, remains a need for a drug that acts on more than one factors of the cardiovascular risk in patients with metabolic disorders. AMPK activation improves the metabolic health as well, maintains the glucose homeostasis by enhancing insulin sensitivity. AMPK activation has been a therapeutic target for treating T2D. Diabetes is a chronic metabolic disorder associated with insulin resistance, β-cell dysfunction and abnormal regulation of hepatic glucose production. [11,12,13] Representative potent AMPK activators has mentioned in Fig. **4.2.**

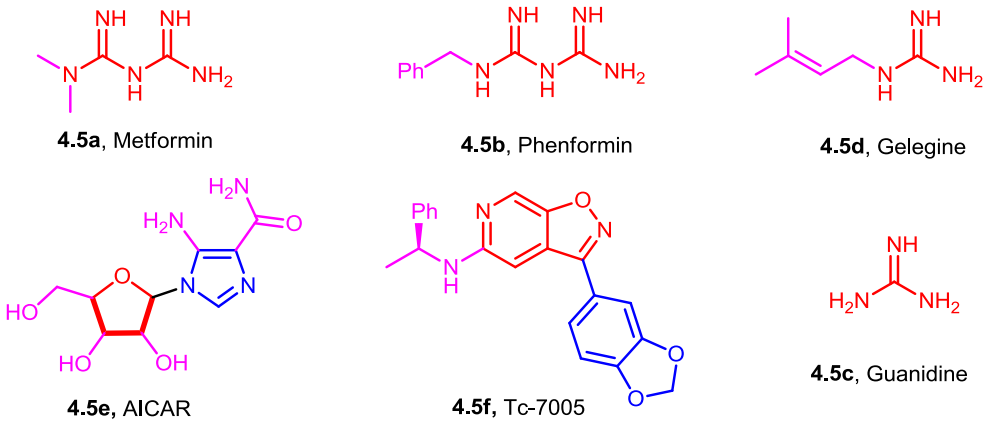


Fig. 4.2. Representative structures of AMPK activators

Present work:

4.2. Design of novel triazole derivatives:

Triazole nucleus stability and its physiochemical favorability provoked our attention to design the new pharmacophores enclosing triazole framework. As shown in Fig. **4.3**, asymmetric pyrrolidinone (γ-lactam) based triazole derivatives, pyrrolidinone-based oxazolidine nucleus containing triazole derivatives and 1,4-DHP-based triazole derivatives are designed. In fact, initial screening with in-house compounds against AMPK activation has been encouraged to design the new class of triazole-based *N*-

heterocycles. Here, CuAAC-click reaction was used to synthesize novel 1,4-disubstituted 1,2,3-triazole derivatives from diverse springs.

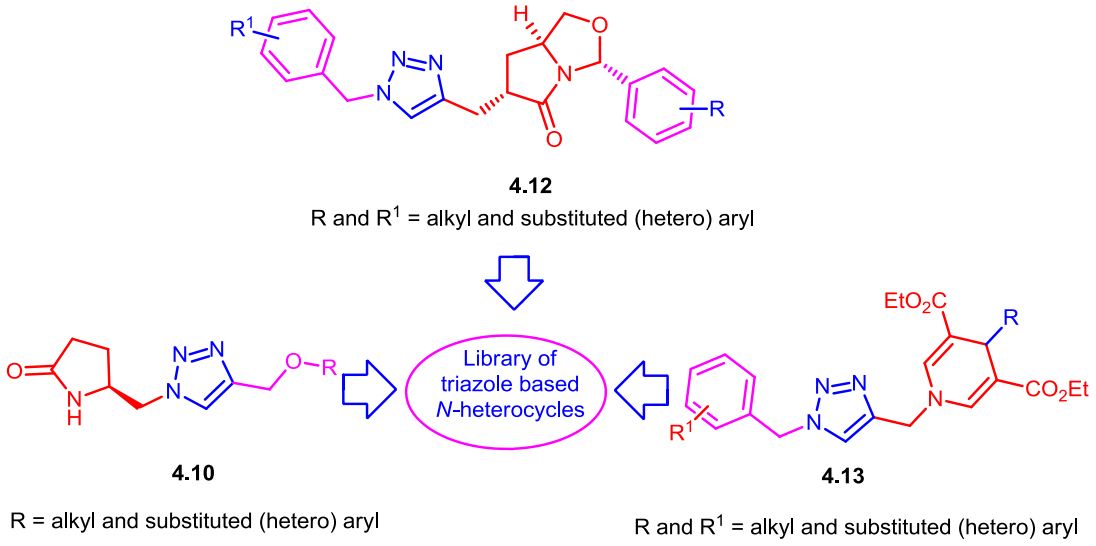


Fig. 4.3. Synthesis of triazole derivatives from diverse springs

In the present work, we disclose the synthesis of asymmetric pyrrolidinone-based novel 1,4-disubstituted 1,2,3-triazole derivatives. Here, present strategy concerns selective fragments linking as shown in Fig. **4.4**, using CuAAC-click reaction. Here, the key intermediate **4.6** was synthesized from the (*S*)-pyroglutamic acid **2.5**.

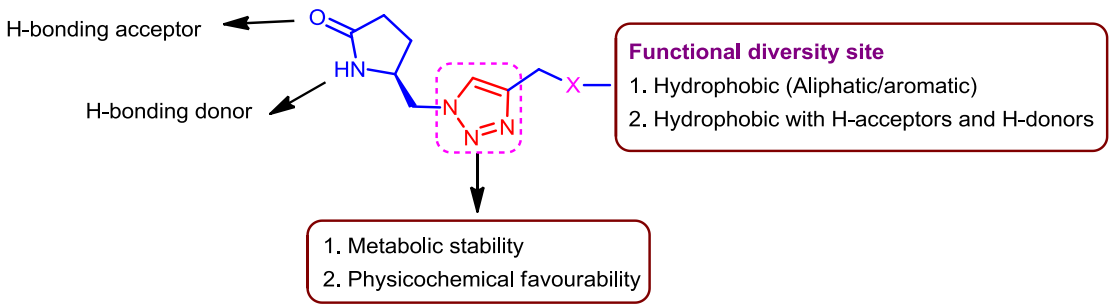
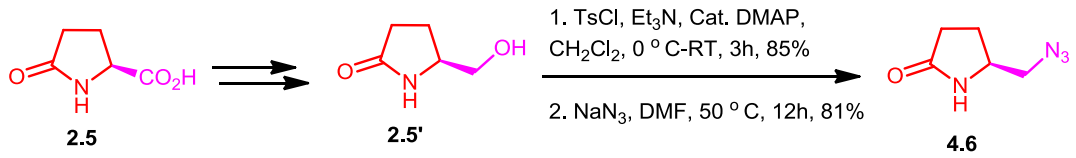


Fig. 4.4. Designed (*S*)-pyroglutamic acid based triazole derivatives

4.3. Results and discussions:

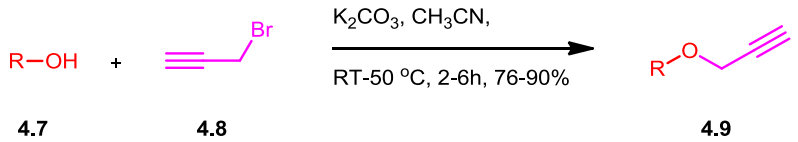
4.3.1. Synthesis of pyrrolidinone-based asymmetric triazole derivatives:

Reactive precursor asymmetric azide **4.6** was synthesized from (*S*)-pyroglutamic acid as shown in Scheme **4.1**, as well as other reactive precursors terminal alkynes **4.9** were prepared by using propargylation on corresponding substituted alcohols.



Scheme 4.1. Synthesis of (S)-(azidomethyl)pyrrolidin-2-one

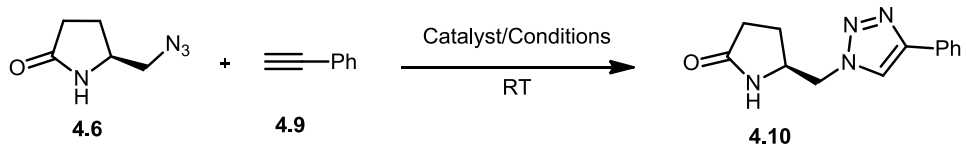
Here, the propargylation protocol involves the 1 mmol of substituted phenol **4.7** and 1 mmol of propargyl bromide **4.8** is stirred at RT for 2h, whereas in the case of substituted benzyl alcohols, 1.1 mmol of **4.8** and 1 mmol of **4.7** was used at 50 ºC, after completion of the reaction (monitored by TLC) filtered to remove the inorganic salt, and the crude propargylated compounds were used for CuAAC-click reactions without any further purification.



Scheme 4.2. Preparation of propargyl containing ethers

In order to get the optimized reaction condition, we perform the present reaction using various copper(I) catalysts, while the reaction with $CuSO_4.5H_2O$, obtained 47% of yield in 45min (entry **1**, Table **4.1**), with CuBr and K_2CO_3 (entry **2**, Table **4.1**) isolated the phenyl acetylene dimer as a major product, with CuI in DMF and K_2CO_3 obtained the decent yields 87%, as well 85% in DMSO (entry **3** and **4**, Table **4.1**), respectively. In further, we performed the present reaction in the absence of base provided the decent yield 85% (entry **5**, Table **4.1**), either in DMF or DMSO often requires work up and extraction process, by performing the present reaction in easily removable solvent green solvent such as CH_3CN avoided laborious work up and extraction procedures. Once the reaction was completed (monitored by TLC) removed acetonitrile under reduced pressure, followed by washed with 10% *n*-hexane in EtOAc solution, then the crude solid was dissolved in CH_2Cl_2 and passed over the celite pad, after removal of solvent under reduced pressure 87% of yield was obtained.

Table 4.1. Optimization studies of CuAAC-click reaction



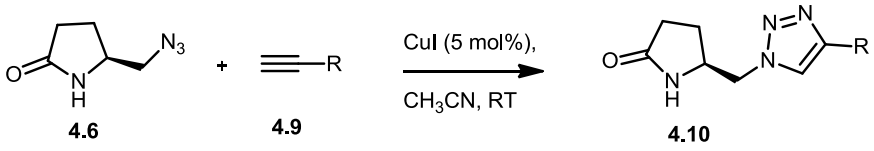
4.6 **4.9** **4.10**

Entry	Catalyst (5 mol%)	Conditions	Time (min)	Yield (%)
1	$CuSO_4.5H_2O$	Sodium ascorbate tBuOH:H_2O (1:1)	45	47
2	CuBr	K_2CO_3/DMF	45	10[a]
3	CuI	K_2CO_3/DMF	30	87
4	CuI	K_2CO_3/DMSO	30	85
5	CuI	DMSO	30	85
6	CuI	CH_3CN	20	87

0.1 mmol of **4.6**, and **4.9** was used, [a]Dimer of phenyl acetylene isolated

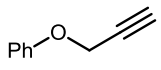
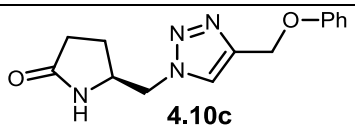
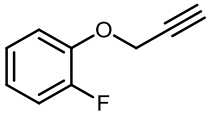
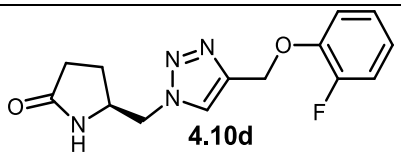
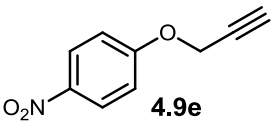
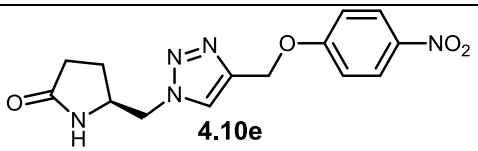
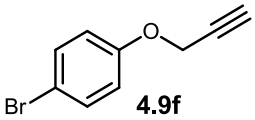
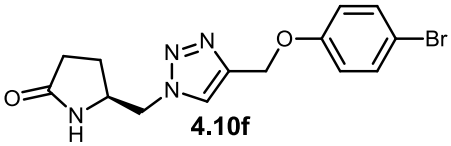
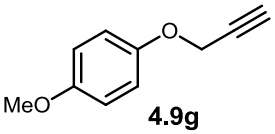
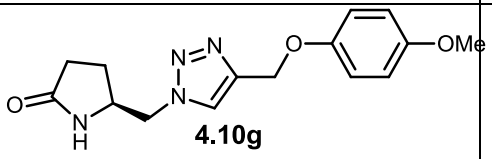
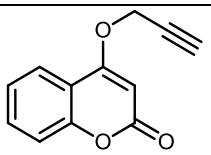
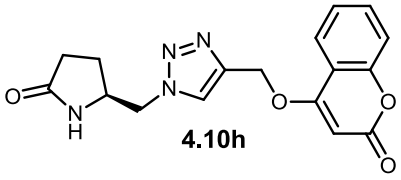
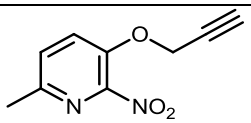
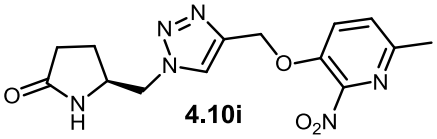
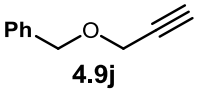
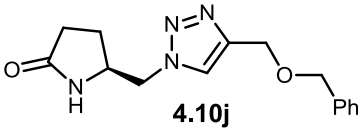
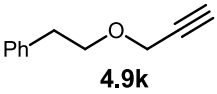
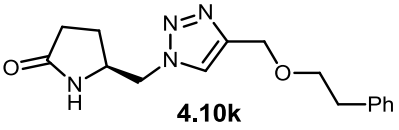
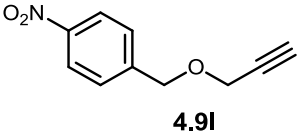
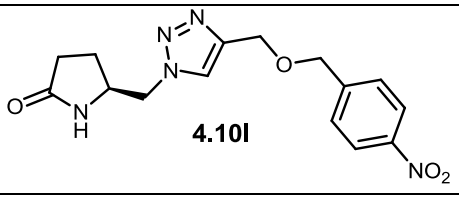
Optimized reaction condition in our hand (entry **6**, Table **4.1**), we generalized with various substituted terminal alkynes **4.9**, which includes substituted phenyl ethers and benzyl ethers. Details are summarized in Table **4.2**. It is worth to mention that coumarin **4.9h** (entry **8**, Table **4.2**) and pyridine **4.9i** and **4.9x** (entry **9** and **24**, Table **4.2**) based on 1,4-disubstituted 1,2,3-triazole also synthesized using present reaction.

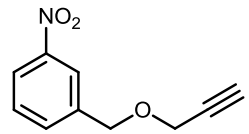
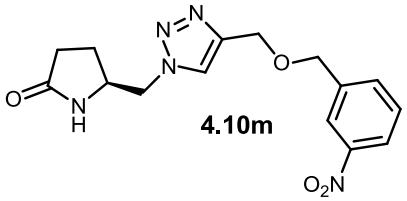
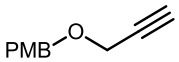
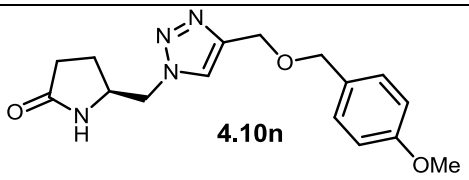
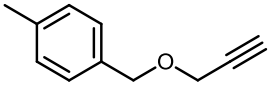
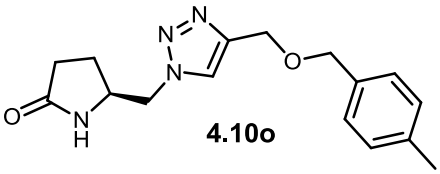
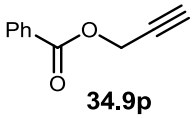
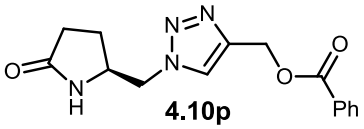
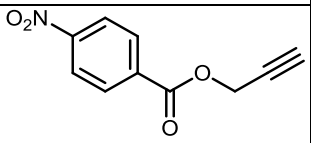
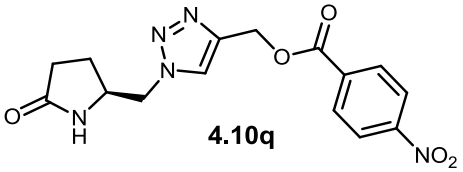
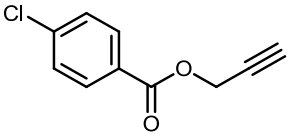
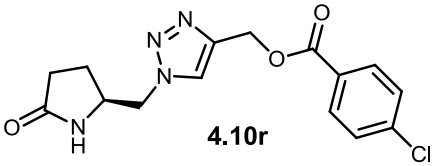
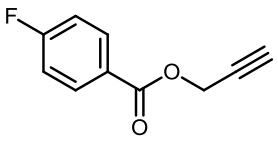
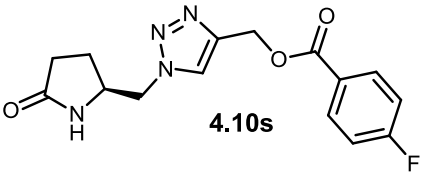
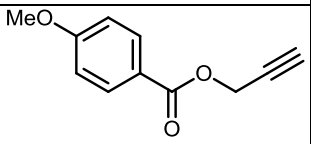
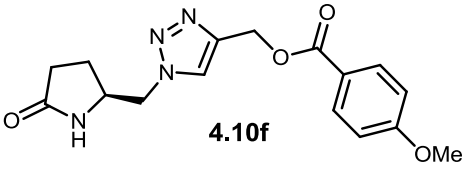
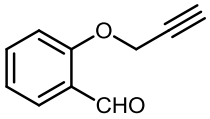
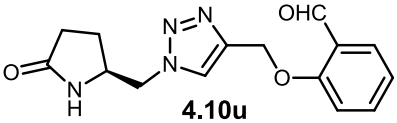
Table 4.2. Generalization of developed protocol

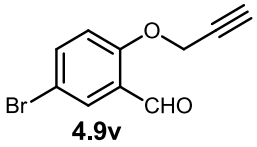
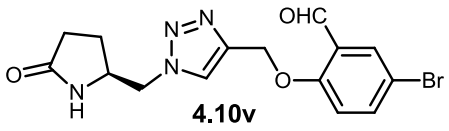
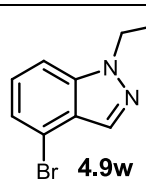
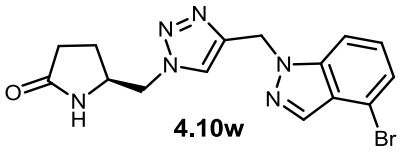
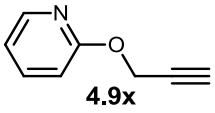
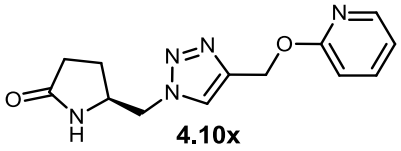


4.6 **4.9** **4.10**

Entry	R (**4.9**)	Product (**4.10**)	Time (min)	Yield (%)
1	Ph— **4.9a**	**4.10a**	15	96
2	6 **4.9b**	6 **4.10b**	15	91

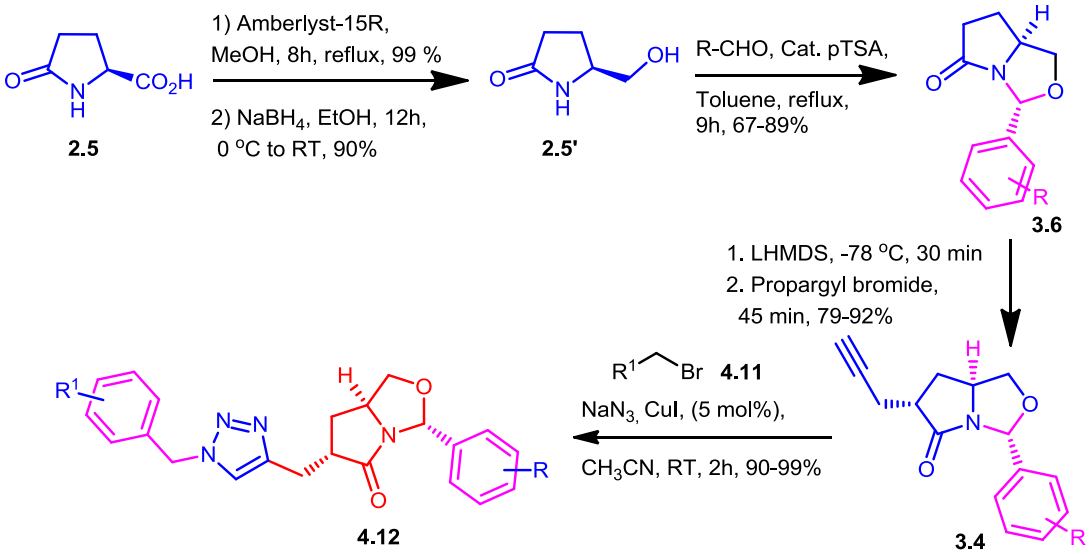
3	 **4.9c**	 **4.10c**	20	84
4	 **4.9d**	 **4.10d**	20	73
5	 **4.9e**	 **4.10e**	20	79
6	 **4.9f**	 **4.10f**	20	75
7	 **4.9g**	 **4.10g**	20	83
8	 **4.9h**	 **4.10h**	20	76
9	 **4.9i**	 **4.10i**	20	79
10	 **4.9j**	 **4.10j**	20	75
11	 **4.9k**	 **4.10k**	20	76
12	 **4.9l**	 **4.10l**	20	80

13	 **4.9m**	 **4.10m**	20	81
14	 **4.9n**	 **4.10n**	20	83
15	 **4.9o**	 **4.10o**	20	81
16	 **34.9p**	 **4.10p**	25	89
17	 **4.9q**	 **4.10q**	25	93
18	 **4.9r**	 **4.10r**	25	92
19	 **4.9s**	 **4.10s**	25	91
20	 **4.9t**	 **4.10f**	25	90
21	 **4.9u**	 **4.10u**	45	71

22	 4.9v	 4.10v	45	67
23	 4.9w	 4.10w	15	73
24	 4.9x	 4.10x	15	79

4.3.2. Synthesis of oxazolidinone-based asymmetric triazole derivatives:

In this part of the chapter, we disclose the design and synthesis of asymmetric pyrrolidinone-based triazole derivatives, using CuAAC-click reaction. Here the pyrrolidinone-based asymmetric oxazolidine core linked to diverse scaffolds, shown in Scheme **4.3**. In fact oxazolidine nucleus containing heterocyclic scaffolds known for various potent biological activities such as antibacterial, antitumor, mono-amine oxidase inhibition and neuroleptics and antihyperglycemic.[10]

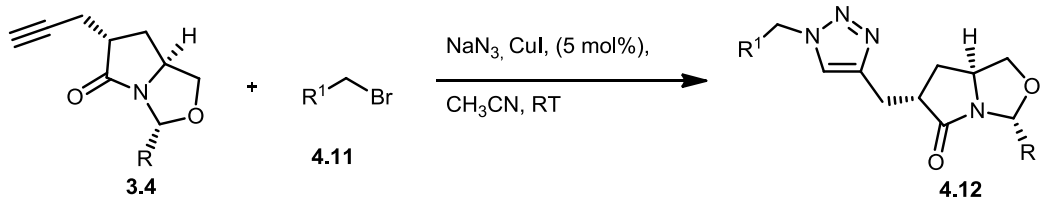


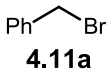
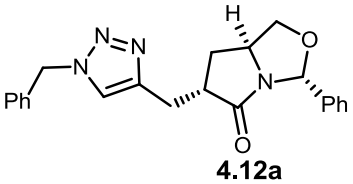
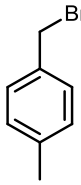
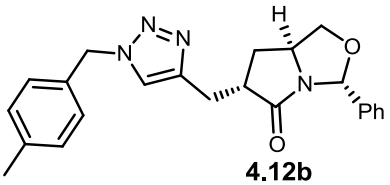
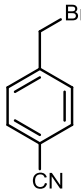
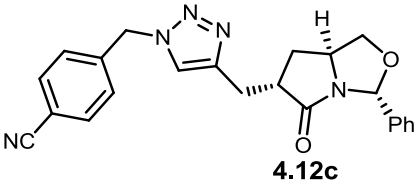
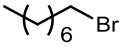
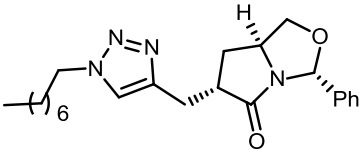
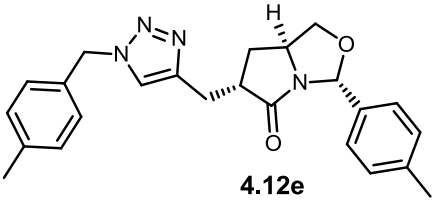
Scheme 4.3. Synthesis of pyrrolidinone-based asymmetric triazole derivatives

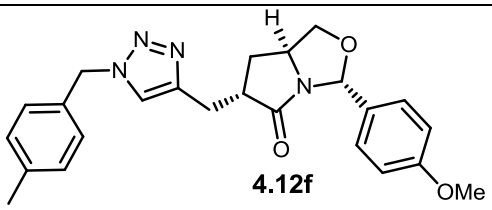
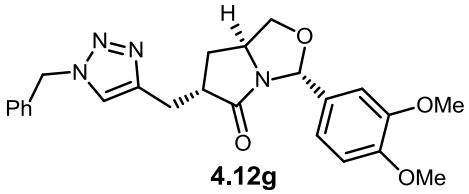
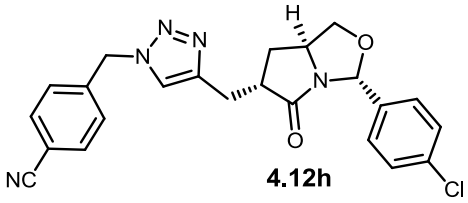
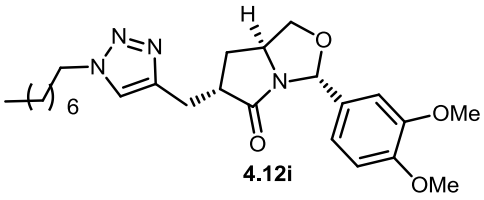
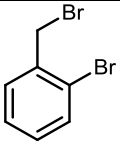
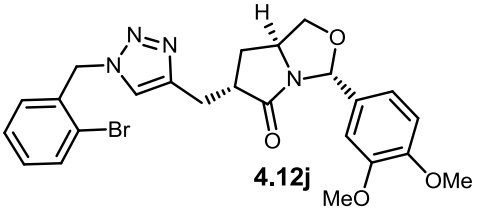
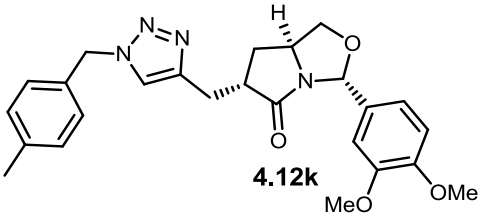
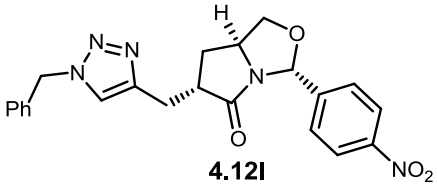
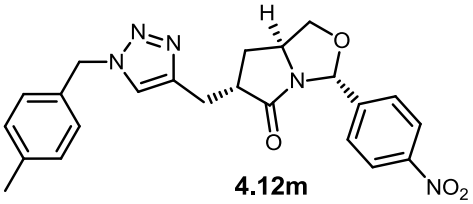
Optimized reaction condition in our hand (entry **6**, Table **4.1**), we generalize with various asymmetric oxazolidine nucleus containing terminal alkynes **3.4** and *in-situ*

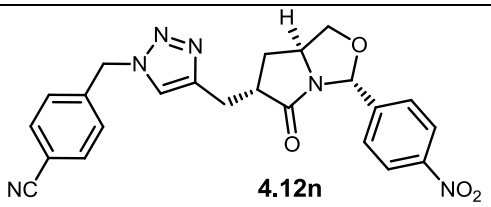
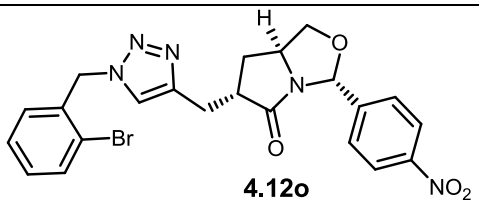
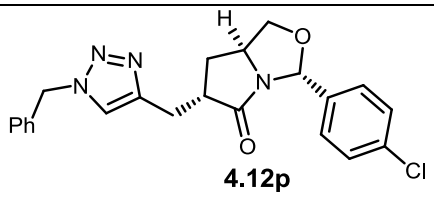
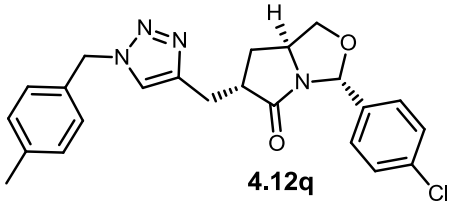
generated azides from the corresponding alkyl or aryl bromides **4.11**. α-Propargylated asymmetric alkyne derivatives were prepared, as mentioned in Table **3.1** and Table **3.2**, of chapter **3.**

Table 4.3. Synthesis pyrrolidinone-based asymmetric triazole derivatives



Entry	Reactant (**3.4**)	Reactant (**4.11**)	Product (**4.12**)	Time (min)	Yield (%)
1	**3.4a**	 **4.11a**	 **4.12a**	50	89
2	**3.4a**	 **4.11b**	 **4.12b**	60	83
3	**3.4a**	 **4.11c**	 **4.12c**	60	77
4	**3.4a**	 **4.11d**	 **4.12d**	45	69
5	**3.4b**	**4.11b**	 **4.12e**	60	77

6	**3.4c**	**4.11b**	 **4.12f**	60	85
7	**3.4d**	**4.11a**	 **4.12g**	75	81
8	**3.4f**	**4.11c**	 **4.12h**	60	77
9	**3.4d**	**4.11d**	 **4.12i**	75	63
10	**3.4d**	 **4.11e**	 **4.12j**	75	
11	**3.4d**	**4.11b**	 **4.12k**	75	78
12	**3.4e**	**4.11a**	 **4.12l**	60	81
13	**3.4e**	**4.11b**	 **4.12m**	60	77

14	**3.4e**	**4.11c**	 **4.12n**	60	72
15	**3.4e**	**4.11e**	 **4.12o**	60	84
16	**3.4f**	**4.11a**	 **4.12p**	60	87
17	**3.4f**	**4.11b**	 **4.12q**	60	81

COSY and NOESY studies of compound 4.12l: Chemical shift values of each proton of compound **4.12l** were confirmed by ^{1}H-^{1}H COSY studies. And NOESY studies provided stereochemical information *i.e.* H_a cis to H_b; and H_b cis to H_e and H_g, shown in Fig. **4.5**.

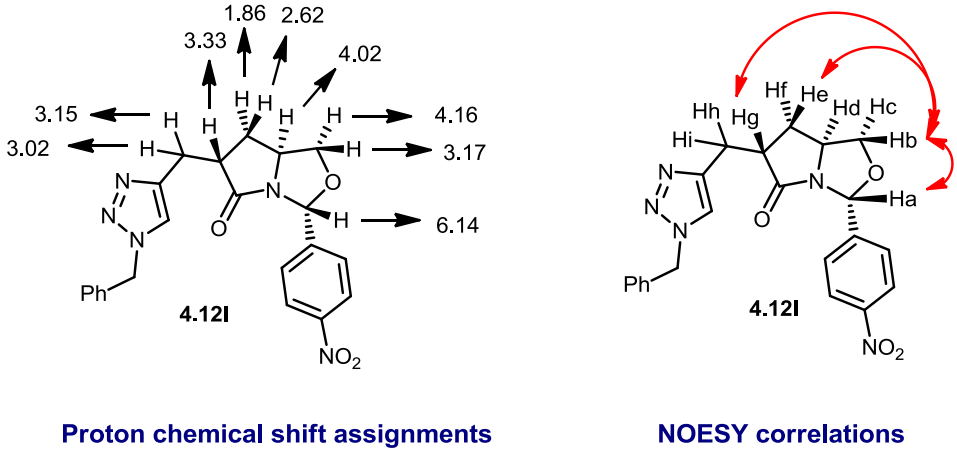


Fig. 4.5. COSY and NOESY studies representations of **4.12l**

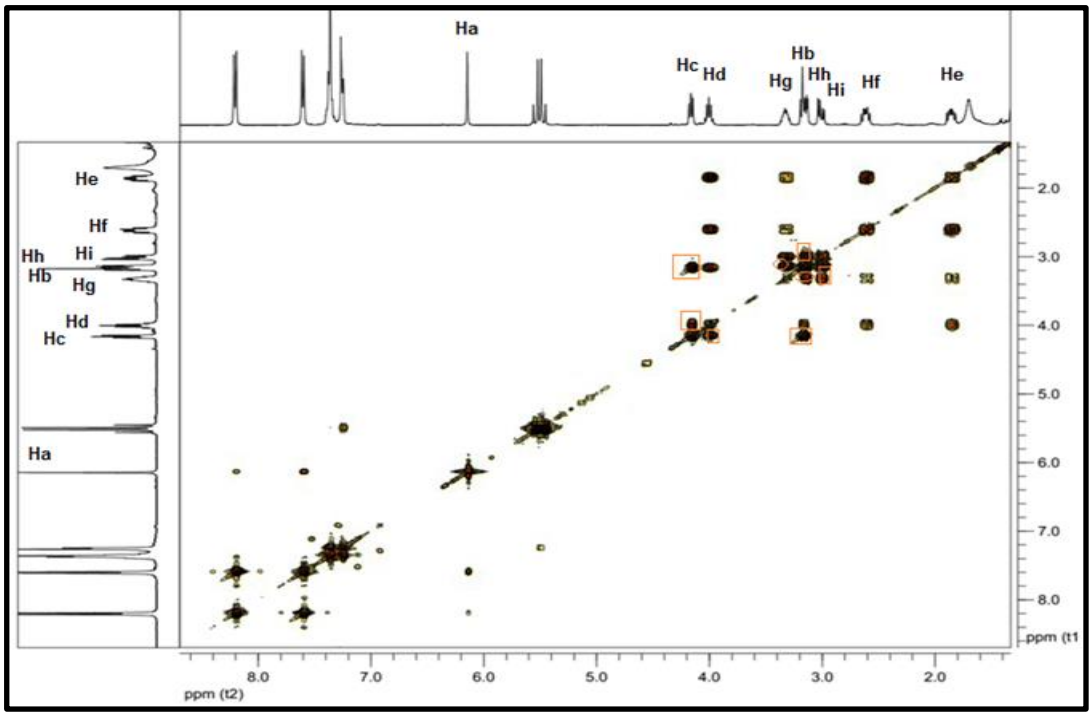


Fig. 4.6. ^{1}H-^{1}H COSY spectra of compound **4.12l**

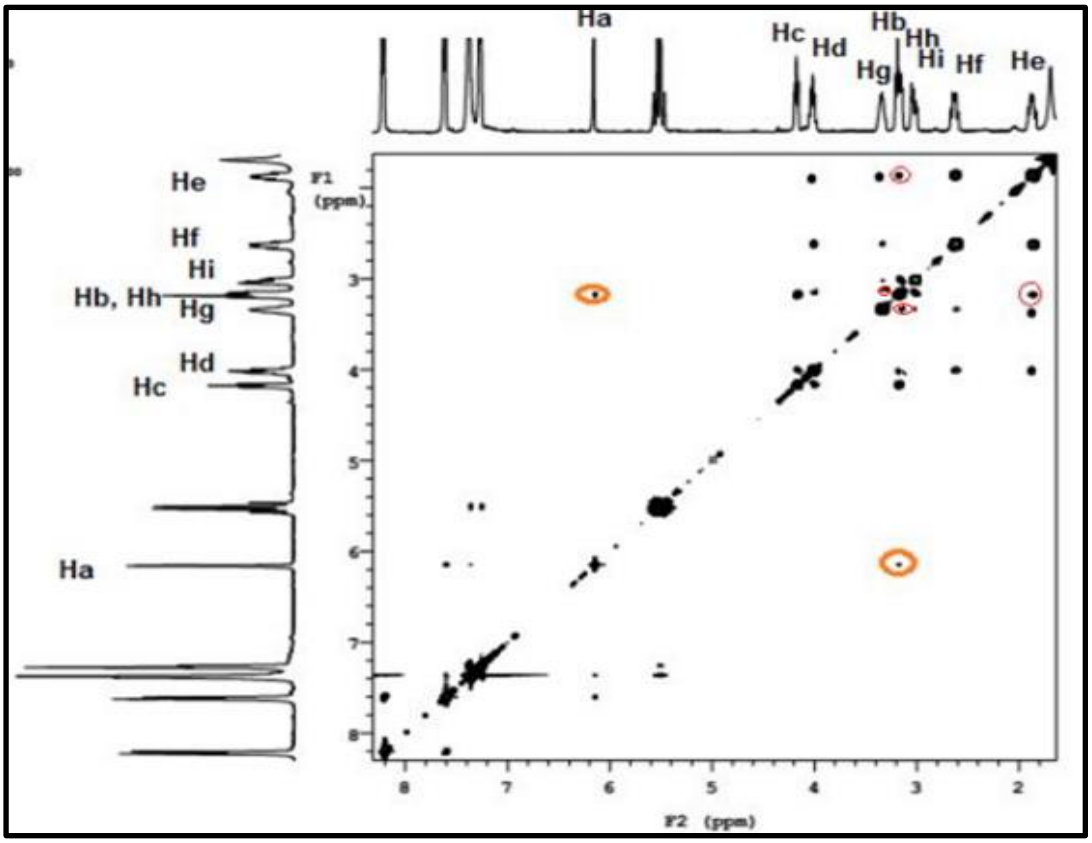
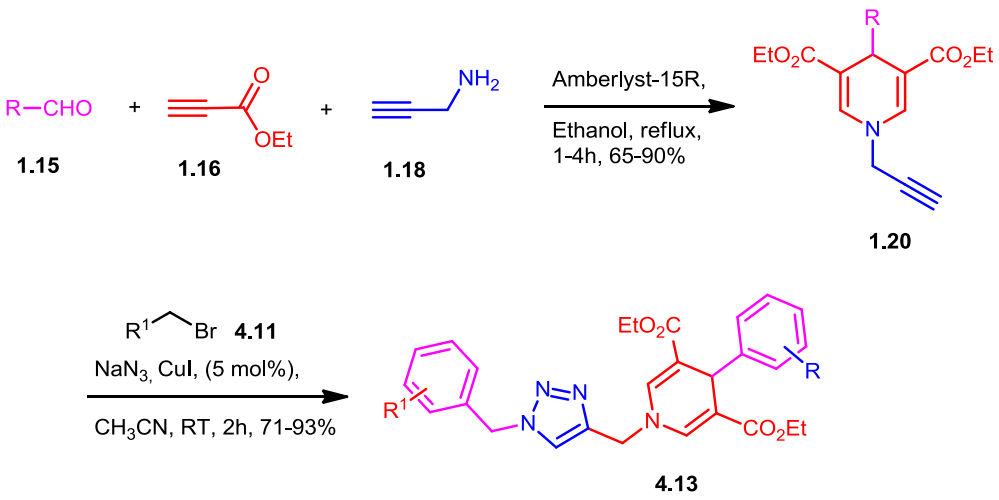


Fig. 4.7. NOESY spectra of compound **4.12l**

4.3.3. Synthesis of 1,4-dihydropyridine-based triazole derivatives:

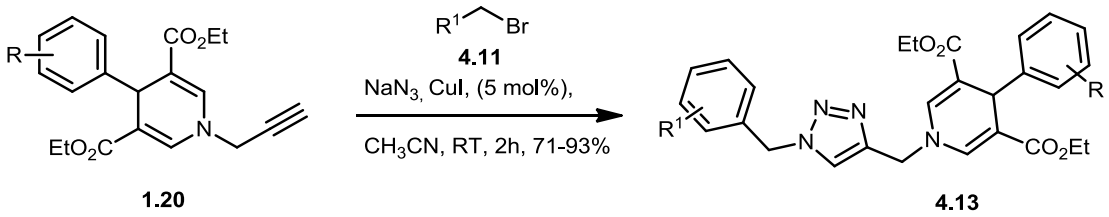
In continuation of chapter **1** work, here we disclose the synthesis of novel 1,4-DHP based-triazole derivatives using CuAAC-click reaction. As described in chapter **1**, 1,4-DHP nucleus is a privileged motif in the medicinal chemistry, thus we designed novel 1,4-DHP-based triazole derivatives using selective fragment linking from diverse springs. Overall synthetic route is given in the Scheme **4.4.**

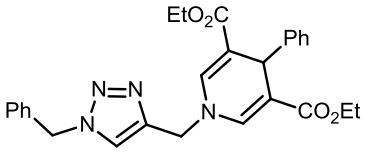
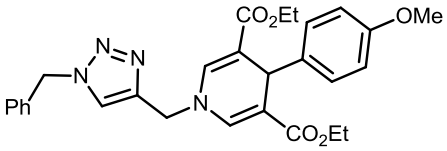
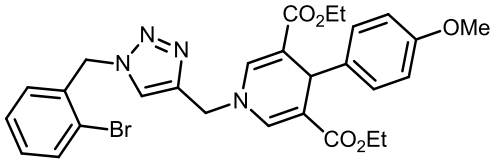
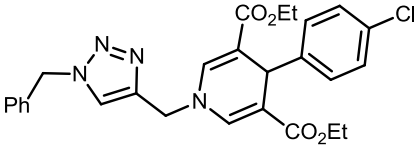
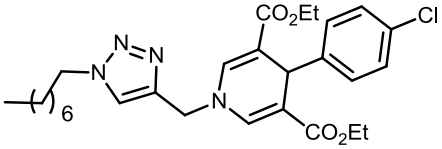
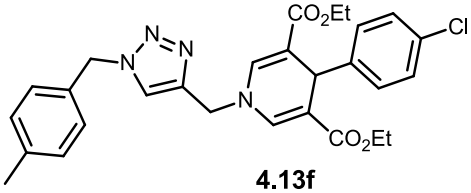


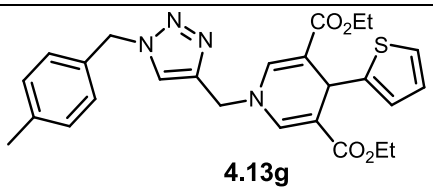
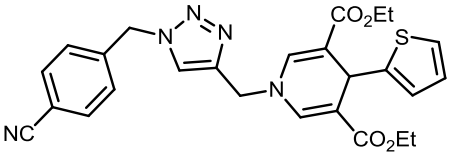
Scheme 4.4. Synthesis of 1,4-DHP based-triazoles using CuAAC-click reaction

Here, precursors terminal alkynes such as substituted 1,4-DHPs were prepared from Amberlyst-15R mediated MCR protocol and substituted azides were generated from corresponding benzyl bromides**4.11**. In order to get the optimized reaction condition, we performed the reaction in various condition and finally synthesized 1,4-DHP-based triazole derivatives **4.13a-4.13i,** details are shown in (entry **1-9**, Table **4.4**).

Table 4.4. Generalization of the developed protocol

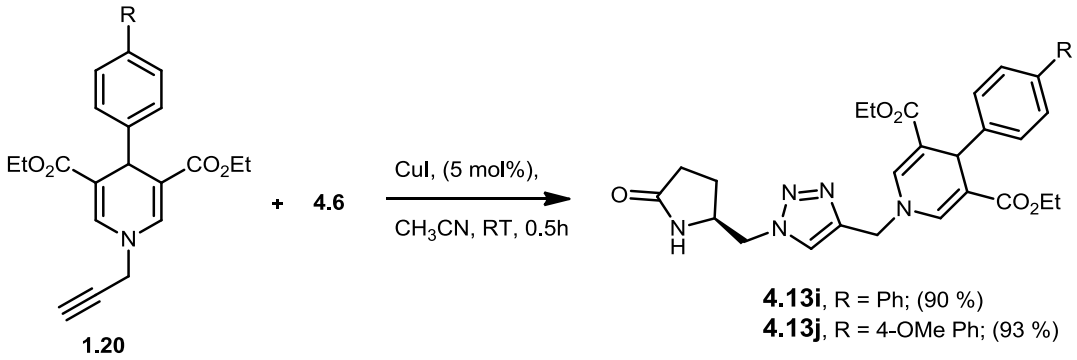


Entry	Precursor (**1.20**)	Precursor (**4.11**)	Product (**4.13**)	Yield (%)
1	**1.20a**	**4.11a**	 **4.13a**	87
2	**1.20c**	**4.11a**	 **4.13b**	87
3	**1.20c**	**4.11e**	 **4.13c**	84
4	**1.20d**	**4.11a**	 **4.13d**	88
5	**1.20d**	**4.11d**	 **4.13e**	79
6		**4.11b**	 **4.13f**	

7	**1.20k**	**4.11b**	 **4.13g**	71
8	**1.20k**	**4.11c**	 **4.13h**	75

Synthesis of 1,4-DHP and asymmetric pyrrolidinone-based triazole derivatives:

We also expanded developed protocol for the synthesis of pyrrolidinone and 1,4-DHP-based triazole derivatives (shown in Scheme **4.5**), for our biological interest.



Scheme 4.5. Synthesis of novel triazole derivatives using CuAAC-click reaction

4.3.4. Pharmacology:

Cell Based pAMPK Assays: AMPK activation potential of the triazoles derivatives was evaluated using a cell based ELISA approach. Skeletal muscle (L6 - derived from rat skeletal muscle) and hepatoma liver cells (HepG2 - human hepatoma cell lines) were cultured for 48 hours prior to compound addition at various concentrations, 24 hours later, the cells were fixed and the ELISA plate developed following standard protocol using pAMPK specific antibody. Liver and skeletal muscle is two major sites for whole body glucose homeostasis and insulin sensitization. AMPK activation potential of the NCEs was evaluated in vitro using a cell based ELISA approach in HepG2 and L6. The cells were treated with 1μM and 30 nM NCEs or 2 mM metformin for 24h. Activation of AMPK was detected by primary pAMPK α (Thr^{172})

antibody and secondary antibody (anti-rabbit IgG, horseradish peroxidase (HRP) linked whole antibody). AMPK activity at 2 mM metformin was considered 108%.

Table **4.5**. Contains the compounds, which have shown AMPK activation against HepG2 (Liver) and L6 (Mucle) cell lines, among the synthesized triazole derivatives, pyrrolidinone-based triazole derivatives **4.10,** shown the potent activation with respect to the reference compound metformin, AICAR and **7005.**

Table 4.5. AMPK activation (%) at 1 μM and 30 nM as measured by cell based pAMPK estimation

Entry	Conc.	Activity (%)	
		HepG2 (Liver)	L6 (Muscle)
DMSO	0.1%	100	100
Metformin	2mM	108	112
AICAR	250μM	105	ND
7005	1μM	ND	100
4.10a	1μM	103	121
4.10b		166	108
4.10e		96	108
4.10g		98	109
4.10h		99	102
4.10i		103	115
4.10f		140	117
4.10f	30nM	120	ND
4.10c		120	ND
4.10d		115	ND
4.10k		127	ND
4.10l		118	ND
4.10m		123	ND
4.10n		117	ND
4.10o		110	ND
4.10p		103	ND
4.10q		102	ND

4.10r		115	ND
4.10s		106	ND
4.10f		105	ND
4.10u		111	ND
4.10v		97	ND

ND = Not determined

Compound **4.10f,** was taken for dose response studies, shown in Fig. **4.8.**

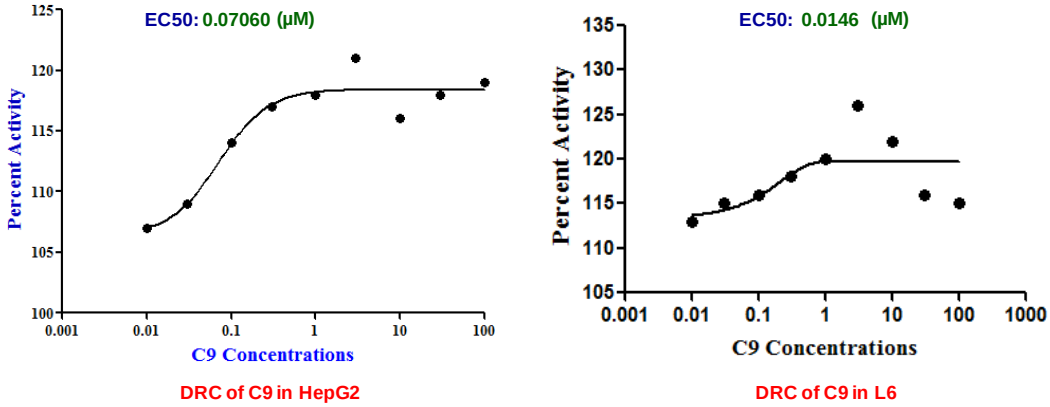


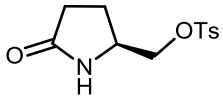
Fig. 4.8. Dose response studies of compound **4.10f,** against HepG2 and L6

4.4. Conclusions:

We have developed a base free Cu(I)-catalyzed efficient synthetic method for the synthesis of functionalized asymmetric pyrrolidinone and 1,4-DHP based-triazole derivatives. CuAAC-click reaction, involves the linking of various potent pharmacophores from diverse springs. Synthesized novel *N*-heterocycles, contains the pyrrolidinone or γ-lactam, asymmetric oxazolidinone, and 1,4-DHP, *etc*. Among them, triazole containing pyrrolidinone derivatives identified as novel potent AMPK activators. And synthesized 1,4-DHP based-triazole derivatives are under biological evaluation.

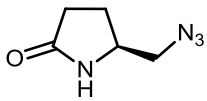
4.5. Experimental section:

(S)-(5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate:



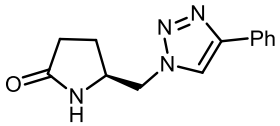
Yield = 90% (5.0 gms); white solid; MP: 127-132 ^{o}C; R_f = 0.45 (10% methanol in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 4.05 (dd, J_1 = 9.6 Hz, J_2 = 3.5 Hz, 1H), 6.01 (q, 1H), 3.99-3.82 (m, 2H), 2.47 (s, 3H), 2.37-2.18 (m, 3H), 1.77 (m, J_1 = 9.3 Hz, J_2 = 8.1 Hz, J_3 = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.05, 145.29, 132.26, 130.02, 127.87, 77.40, 77.08, 76.76, 71.92, 52.57, 29.29, 22.73, 21.64; ESI-MS (m/z): [M+1] 270.

(S)-5-(azidomethyl)pyrrolidin-2-one (4.6):



Yield = 87% (2.9 gms); color less liquid; R_f = 0.6 (10% methanol in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83-3.70 (m, 1H), 3.40 (dd, *J* = 12.2, 4.3 Hz, 1H), 3.23 (dd, *J* = 12.2, 6.6 Hz, 1H), 2.42-2.13 (m, 3H), 1.84-1.70 (m, 1H), 7.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.05, 77.49, 77.17, 76.85, 55.74, 53.40, 29.68, 23.90; ESI-MS (m/z): [M+1] 141.3.

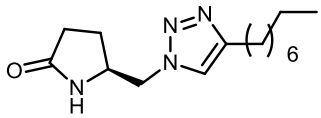
(S)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10a):



Azide **4.6** (20 mg, 0.1427 mmol) and phenyl acetylene **4.9a** (14 mg, 0.1427 mmol) was dissolved in CH_3CN which contains 5 mol% of CuI (2.71 mg, 0.01427 mmol) then the reaction mixture was allowed to stir for 15 min, then reaction completion was monitored by TLC, using 8% methanol in CH_2Cl_2 as eluent.

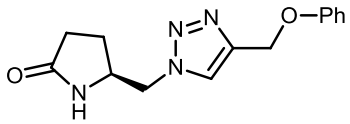
Yield = 96% (23 mg); MP: 185-190 ^{o}C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 6.0 Hz, J_2 = 2.4 Hz, 3H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.38-7.32 (m, 1H), 6.51 (s, 1H), 4.5-4.35 (m, 2H), 4.24 (dd, J_1 = 11.1 Hz, J_2 = 5.7 Hz, 1H), 2.39-2.23 (m, 3H), 1.98 (q, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.76, 130.09, 128.89, 128.42, 125.74, 120.46, 109.98, 54.92, 53.75, 29.67, 24.28; ESI-MS (m/z): [M+1] 143.8; and purity in HPLC = 97%.

Synthesis of (S)-5-((4-octyl-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10b):



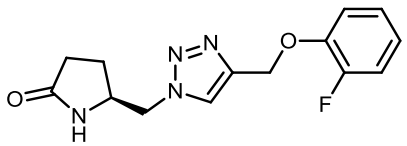
Yield = 91% (22 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.77 (s, 1H), 4.44 (m, J_1 = 13.8 Hz, J_2 = 5.3 Hz, 2H), 4.2 (d, J = 4.9 Hz, 1H), 2.76 (t, J = 7.6 Hz, 2H), 2.38-2.26 (m, 2H), 1.99-1.85 (m, 2H), 1.65 (dd, J_1 = 14.4 Hz, J_2 = 7.18 Hz, 2H), 0.89 (d, J = 6.4 Hz, 3H), 1.27 (d, J = 11.4 Hz, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ 177.85, 136.06, 121.87, 54.74, 53.78, 31.90, 31.53, 29.67, 29.63, 29.35, 28.89, 25.64, 24.17, 22.66, 22.53; ESI-MS (m/z): [M+1] 143.8; purity in HPLC = 96%.

Synthesis of (S)-5-((4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10c):



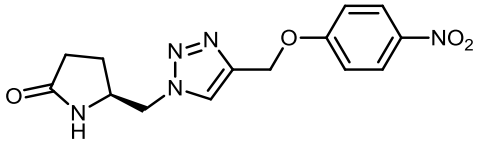
Yield = 84% (23 mg); MP: 134-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.3 (t, J = 7.8 Hz, 2H), 6.97 (d, J = 8.3 Hz, 3H), 6.51 (s, 1H), 5.21 (s, 2H), 4.41 (m, J_1 = 13.9 Hz, J_2 = 5.6 Hz, 2H), 4.25-4.14 (m, 1H), 2.3 (m, J_1 = 16.8 Hz, J_2 = 10.9 Hz, 3H), 1.98-1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.76, 158.03, 144.63, 129.58, 123.58, 121.37, 114.71, 61.81, 54.88, 53.69, 29.29, 24.21; ESI-MS (m/z): [M+1] 143.8; purity in HPLC = 98%.

(S)-5-((4-((2-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (4.10d):



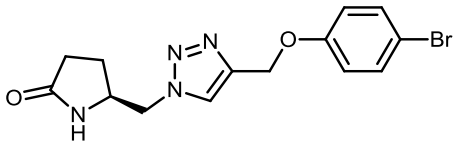
Yield = 73% (18 mg); MP: 134-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.25-6.96 (m, 4H), 6.91 (d, J = 12.4 1H), 5.24 (s, 2H), 4.51-4.33 (m, 2H), 4.22-4.09 (m, 1H), 2.32-2.09 (m, 3H), 1.89 (m, J_1 = 19.2 Hz, J_2 = 9.8 Hz, J_3 = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 153.97, 151.53, 146.11, 146.01, 143.96, 124.46, 124.43, 124.11, 121.99, 121.92, 116.38, 116.2, 115.8, 63.23, 54.55, 53.81, 29.36, 24.0; ESI-MS (m/z): [M+1] 143.8; and purity in HPLC = 97%.

Synthesis of (S)-5-((4-((4-nitrophenoxy) methyl-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10e):



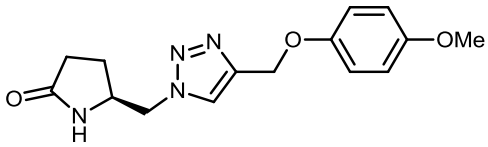
Yield = 79% (25 mg); MP: 151-155 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.2, 2H), 7.76 (s, 1H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.91 (s, 1H), 5.29 (s, 2H), 4.51-4.4 (m, 2H), 4.19 (t, *J* = 8.6 Hz, 1H), 2.43-2.23 (m, 3H), 1.97 (m, J_1 = 15.9 Hz, J_2 = 7.7 Hz, J_3 = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.67, 147.45, 145.30, 144.91, 127.9, 123.65, 123.57, 71.16, 63.95, 54.91, 53.62, 29.21, 24.22; ESI-MS (m/z): [M+1] 318.4; and purity in HPLC = 99%.

Synthesis of (S)-5-((4-((4-bromophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10f):



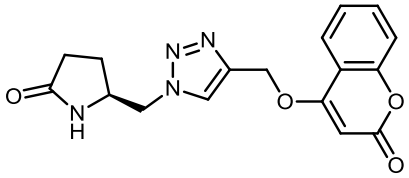
Yield = 75% (26 mg); MP: 174-180 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (s, 1H), 7.4-7.29 (d, *J* = 9.2, 2H), 6.89-6.87 (m, *J* = 9.1, 2H) 5.3-5.2 (d, 2H) 4.48-4.41(m, 2H), 2.3-2.22 (s, 1H) 2.4-2.4 (d, 3H), 1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.31, 157.14, 144.19, 132.37, 123.37, 123.47, 116.59, 113.62, 62.03, 55.05, 53.49, 29.11, 24.27; ESI-MS (m/z): [M+1] 351.9; and purity in HPLC = 99%.

Synthesis of (S)-5-((4-((4-methoxyphenoxy)mmmethyl)-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10g):



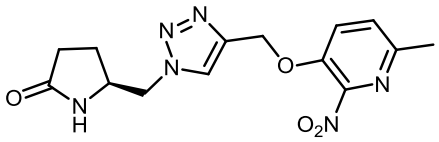
Yield = 83% (25 mg); MP: 134-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-7.92 (d, 2H), 7.76 (s, 1H), 6.91 (d, 2H), 6.31 (s, 1H), 5.47 (d, *J* = 13.1 Hz, 2H), 4.41 (m, J_1 = 13.8 Hz, J_2 = 5.8 Hz, 2H), 4.27-4.15 (m, 1H), 3.87 (s, 3H), 2.43-2.27 (m, 3H), 1.95 (m, J_1 = 12.5 Hz, J_2 = 7.1, J_1 = 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.19, 163.60, 143.52, 131.80, 124.90, 121.96, 113.66, 57.64, 55.43, 54.87, 53.64, 29.25, 24.26; ESI-MS (m/z): [M+1] 303.4; purity in HPLC = 98%.

Synthesis of (S)-5-((4-((2-oxo-2H-chromen-4-yloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10h):



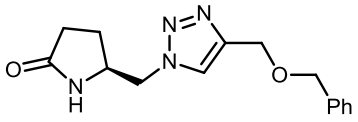
Yield = 76% (25 mg); MP: 180-183 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.77 (m, 2H), 7.58-7.50 (m, 1H), 7.32 (d, *J* = 8.23 Hz, 1H), 7.25 (t, 1H), 6.39 (d, 1H), 5.88 (s, 1H), 5.37 (s, 2H), 4.48 (m, *J* = 13.9 Hz, J_2 = 5.6 Hz, 2H), 4.26 (dd, J_1 = 7.4 Hz, J_2 = 4.0 Hz, 1H), 2.51-2.12 (m, 3H), 2.03-1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 164.92, 162.68, 153.28, 141.74, 132.62, 124.53, 123.98, 123.14, 116.75, 115.36, 91.19, 62.42, 54.98, 53.56, 29.69, 24.15;ESI-MS (m/z): [M+1] 341.1; purity in HPLC = 99%.

Synthesis of (S)-5-((4-((6-methyl-2-nitropyridin-3-yloxy)methyl)-1H-1,2,3-triazol-1-1yl)methyl) pyrrolidin-2-one (4.10i):



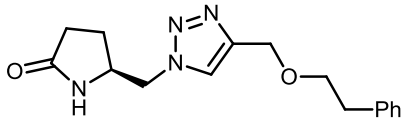
Yield = 79% (26 mg); MP: 134-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.95-6.79 (m, 1H), 5.37 (s, 2H), 4.46 (t, *J* = 6.0 Hz, 2H), 4.23-4.14 (m, 1H), 2.53 (d, *J* = 8.4 Hz, 3H), 2.36-2.26 (m, 2H), 2.23-2.12 (m, 1H), 1.95 (dd, J_1 = 10.9 Hz, J_2 = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.97, 149.97, 148.29, 144.06, 128.45, 125.75, 124.54, 63.7, 54.81, 53.69, 29.34, 24.08, 22.67; ESI-MS (m/z): [M+1] 333.6; purity in HPLC = 99%.

(S)-5-((4-((benzyloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (4.10j):



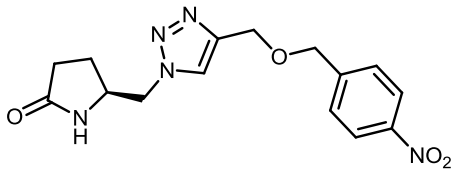
Yield = 75% (21 mg); MP: 128-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.3 (t, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 3H), 6.51 (s, 1H), 5.21 (s, 2H), 4.41 (m, J_1 = 13.9 Hz, J_2 = 5.6 Hz, 2H), 4.25-4.14 (m, 1H), 2.30 (m, J_1 = 16.8 Hz, J_2 = 10.9 Hz, 3H), 1.98-1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.96, 137.67, 128.44, 127.94, 127.84, 72.67, 63.60, 54.69, 53.74, 29.33, 24.15; ESI-MS (m/z): [M+1] 143.8; purity in HPLC = 97%.

(S)-5-((4-(phenethoxymethyl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (4.10k):



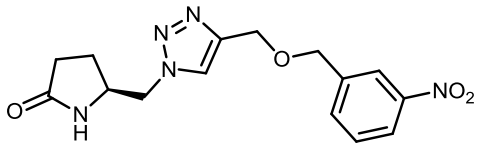
Yield = 76% (22 mg); MP: 137-141 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.3-7.22 (q, 5H), 4.63 (d, *J* = 9.9 Hz, 2H), 4.41-4.0 (m, 4H), 3.74 (m, *J* = 7.0, 4.0 Hz, 2H), 2.94-2.87 (m, 2H), 2.32 (m, *J* = 14.4, 8.5, 5.5 Hz, 3H), 2.0-1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.43, 138.80, 128.97, 128.88, 128.85, 128.35, 128.33, 126.23, 64.33, 54.88, 53.61, 36.22, 36.09, 29.24, 24.28; ESI-MS (m/z): [M+1] 300.9; and purity in HPLC = 94%.

(S)-5-((4-(((4-nitrobenzyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyrolidin-2-one (4.10l):



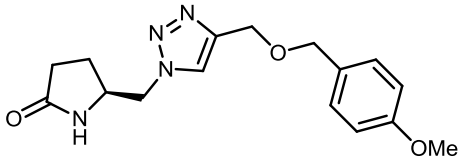
Yield = 80% (26 mg); MP: 126-130 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.62 (s, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 6.07 (s, 1H), 4.73 (d, *J* = 11.6 Hz, 4H), 4.49-4.37 (m, 2H), 4.27-4.15 (m, 1H), 2.42-2.23 (m, 3H), 1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.67, 147.45, 145.3, 144.91, 127.9, 123.65, 123.57, 71.16, 63.95, 54.91, 53.62, 29.21, 24.22; ESI-MS (m/z): [M+1] 331.9; and purity in HPLC = 98%.

(S)-5-((4-(((3-nitrobenzyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10m):



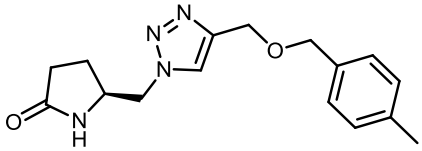
Yield = 81% (27 mg); MP: 129-134 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 4.76 (s, 2H), 4.71 (s, 2H), 7.69 (d, *J* = 11.2 Hz, 2H), 6.47 (s, 1H), 4.44 (m, *J* = 13.8 Hz, J_2 = 5.6 Hz, 3H), 4.22 (dd, J_1 = 7.2 Hz, J_2 = 3.4 Hz, 1H), 2.37-2.21 (m, 3H), 1.99 (m, *J* = 12.1 Hz, J_2 = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.69, 148.31, 144.92, 139.99, 133.53, 129.42, 123.63, 122.74, 122.37, 71.13, 63.93, 54.89, 53.65, 29.26, 24.23; ESI-MS (m/z): [M+1] 331.9; and purity in HPLC = 96%.

(S)-5-((4-(((4-methoxybenzyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.10n):



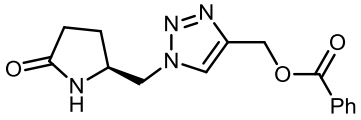
Yield = 83% (26 mg); MP: 134-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.34-7.29 (m, 2H), 6.90 (s, 2H),6.23-6.13 (m, 1H), 4.58-4.53 (m, 4H), 4.42-4.36 (m, 2H), 3.81 (s, 3H), 2.32 (dd, J = 8.4 Hz, J_2 = 4.6 Hz, 3H), 1.97-1.91 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 177.56, 159.35, 129.64, 129.60, 123.34, 113.85, 113.81, 72.38, 63.25, 55.28, 54.85, 53.66, 29.23, 24.45; ESI-MS (m/z): [M+1] 317.1; and purity in HPLC = 99%.

(S)-5-((4-(((4-methylbenzyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyrro-lidin-2-one (4.10o):



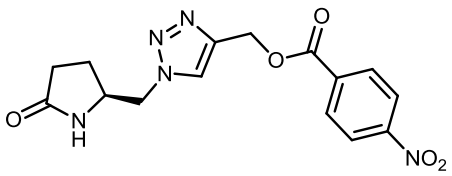
Yield = 81% (26 mg); MP: 134-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.27 (d, J = 7.7 Hz, 2H), 7.17 (d, J = 7.7 Hz, 2H), 6.51 (s, 1H), 4.67 (s, 2H), 4.57 (s, 2H), 4.46-4.34 (m, 2H), 4.19-4.13 (m, 1H), 2.28 (m, 6H),1.97-1.9 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.80, 145.66, 137.59, 134.59, 129.11, 128.07, 123.41, 72.57, 63.43, 54.72, 53.71, 29.28, 24.19, 21.15; ESI-MS (m/z): [M+1] 300.9; purity in HPLC = 94%.

(S)-(1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl benzoate (4.10p):



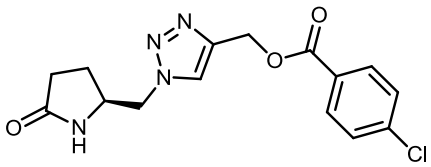
Yield = 89% (26 mg); MP: 131-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.42 Hz, 2H), 7.8 (s, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 6.87 (s, 1H), 5.54-5.38 (m, 2H), 4.54-4.31 (m, 2H), 4.23-4.11 (m, 1H), 2.28 (m, 3H), 2.02-1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.93, 166.45, 143.23, 133.25, 129.7, 129.61, 128.39, 125.01, 57.92, 54.73, 53.73, 29.3, 24.17; ESI-MS (m/z): [M+1] 301.3; and purity in HPLC = 99%.

(S)-(1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl-4-nitrobenzoate (4.10q):



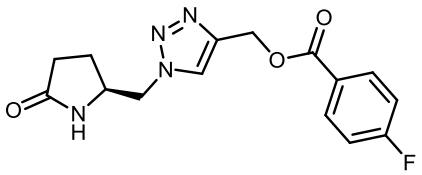
Yield = 93% (32 mg); MP: 135-140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (q, 4H), 7.8 (s, 1H), 6.51 (s, 1H), 5.52 (s, 2H), 4.51-4.4 (m, 2H), 4.33-4.2 (m, 1H), 2.44-2.21 (m, 3H), 2.0-1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.84, 164.56, 150.67, 134.98, 130.94, 130.89, 123.61, 123.55, 58.58, 54.88, 53.62, 29.33, 24.16; ESI-MS (m/z): [M+1] 346.1; purity in HPLC = 99%.

(S)-(1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl-4-chlorobenzoate (4.10r):



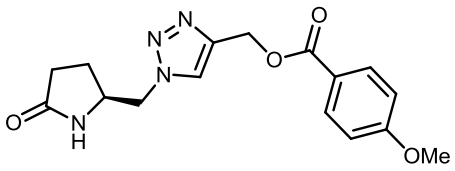
Yield = 92% (30 mg); MP: 132-137 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz, 2H), 7.76 (s, 1H), 7.13-7.03 (m, 2H), 6.49 (s, 1H), 5.45 (s, 2H), 4.41 (m, J_1 = 13.9 Hz, J_2 = 5.7 Hz, 2H), 4.19 (dd, J_1 = 11.1 Hz, J_2 = 6.2 Hz, 1H), 2.29 (m, 3H), 1.95 (m, J_1 = 8.6 Hz, J_2 = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.69, 165.48, 132.37, 132.27, 124.98, 115.7, 115.48, 109.99, 57.96, 54.88, 53.63, 29.24, 24.23; ESI-MS (m/z): [M+1] 334.9; purity in HPLC = 98%.

(S)-(1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl-4-fluorobenzoate (4.10s):



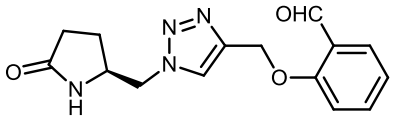
Yield = 91% (28 mg); MP: 128-133 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 2H), 7.77 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 6.67 (s, 1H), 5.47 (d, J = 12.9 Hz, 2H), 4.53-4.35 (m, 2H), 4.22-4.06 (m, 1H), 2.44-2.2 (m, 3H), 1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.82, 165.6, 143.0, 139.77, 131.11, 128.76, 128.05, 125.03, 58.05, 54.82, 53.66, 29.26, 24.19; ESI-MS (m/z): [M+1] 319.8; and purity in HPLC = 95%.

(S)-(1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl 4-methoxy benzoate (4.10t):



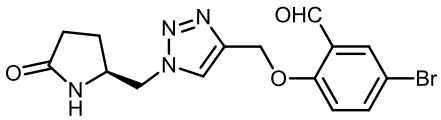
Yield = 90% (29 mg); MP: 148-152 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-7.92 (m, 2H), 7.76 (s, 1H), 6.91 (t, *J* = 5.8 Hz, 2H), 6.31 (s, 1H), 5.47 (d, *J* = 13.1 Hz, 2H), 4.41 (m, *J* = 13.8 Hz, J_2 = 5.8 Hz, 2H), 4.27-4.15 (m, 1H), 3.87 (s, 3H), 2.43-2.27 (m, 3H), 1.95 (m, J_1 = 12.5 Hz, J_2 = 7.1 Hz, J_3 = 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.64, 166.19, 163.6, 143.52, 131.8, 124.90, 121.96, 113.66, 57.64, 55.43, 54.87, 53.64, 29.25, 24.26; ESI-MS (m/z): [M+1] 331.0; and purity in HPLC = 97%.

(S)-2-((1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy) benzaldehyde (4.10u):



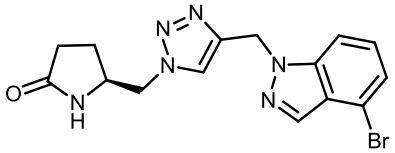
Yield = 71% (21 mg); MP: 137-140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.91-7.79 (m, 2H), 7.61 (t, *J* = 9.1 Hz, J_2 = 7.3 Hz, J_2 = 1.8 Hz, 1H), 7.21-6.94 (m, 3H), 5.38 (s, 2H), 4.62-4.48 (m, 2H), 4.33-4.19 (m, 1H), 2.42-2.3 (m, 2H), 2.25-2.16 (m, 1H), 2.0 (m, J_1 = 9.2 Hz, J_2 = 8.7 Hz, J_2 = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.71, 178.28, 160.28, 143.72, 136.07, 128.87, 125.04, 124.0, 121.42, 112.97, 62.47, 54.7, 53.8, 29.69, 24.07; ESI-MS (m/z): [M+1] 300.8; and purity in HPLC = 95%.

(S)-5-bromo-2-((1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)metho xy)benzaldehyde (4.10v):



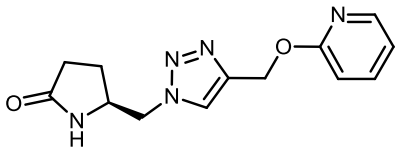
Yield = 67% (25 mg); MP: 145-150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.91 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.1 (d, *J* = 8.8 Hz, 1H), 6.63 (s, 1H), 7.80 (s, 1H), 5.31 (d, *J* = 10.4 Hz, 2H), 4.47 (dd, *J* = 13.6 Hz, J_2 = 9.1 Hz, 2H), 4.30-4.16 (m, 1H), 2.48-2.11 (m, 3H), 1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.22, 159.2, 138.35, 131.29, 126.37, 115.18, 114.24, 62.69, 54.77, 53.73, 29.67, 24.08; ESI-MS (m/z): [M+1] 380.7; and purity in HPLC = 94%.

(S)-5-((4-((4-bromo-1H-indazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-pyrrolidin-2-one (4.10w):



Yield = 73% (27 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.26 (t, *J* = 15.7 Hz, J_2 = 7.1 Hz, 3H), 6.62 (s, 1H), 5.69 (s, 2H), 4.38-4.3 (m, 2H), 4.13 (m, J_1 = 11.1 Hz, J_2 = 5.7 Hz, 1H), 2.31-2.15 (m, 3H), 1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.81, 133.93, 133.89, 127.65, 123.88, 123.44, 114.62, 114.05, 108.66, 54.86, 53.63, 44.89, 29.69, 24.15; ESI-MS (m/z): [M+1] 376.1; purity in HPLC = 99%.

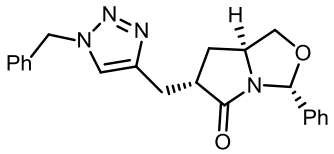
(S)-5-((4-((pyridin-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (4.10x):



Yield = 85% (23 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.78 (m, 2H), 7.58-7.53 (m, 1H), 32 (d, *J* = 8.3 Hz, 1H), 7.28-7.23 (m, 1H), 7 2.49-2.33 (m, 2H), 6.46 (s, 1H), 5.89 (s, 1H), 5.38 (s, 2H), 4.49 (dd, J_1 = 13.1 Hz, J_2 = 5.5 Hz, 2H), 4.33-4.23 (m, 1H), 2.25 (t, 1H), 1.99 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.93, 149.97, 147.27, 144.0, 129.05, 124.7, 124.54, 63.7, 54.85, 53.91, 29.34, 24.18; ESI-MS (m/z): [M+1] 273.29; purity in HPLC = 99%.

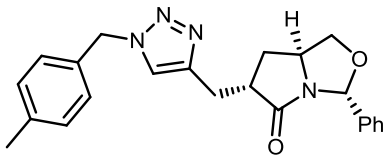
General procedure: Benzyl bromide **4.11** (20 mg, 0.117 mmol) was treated with sodium azide (15 mg, 0.234 mmol) in 2 mL of acetonitrile for 30 min, then the crude reaction mixture was filtered to get the azide. Phenyl acetylene (22 mg, 0.094 mmol) and 5 mol% of CuI(1.2 mg, 0.006 mmol) was added to the crude reaction mixture then allowed to stir for 15 min, once the reaction completed (monitored by TLC) removed acetonitrile under reduced pressure, then added 20% *n*-hexane in EtOAc solution to the crude product and filtered or decant the solvent. The crude solid was dissolved in CH_2Cl_2 and passed over the celite pad, after removal of solvent under reduced pressure obtained the desired product **4.12a**.

(3R,6S,7aS)-6-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-phenyltetrahydropyrrolo-[1,2-c]oxazol-5(3H)-one (4.12a):



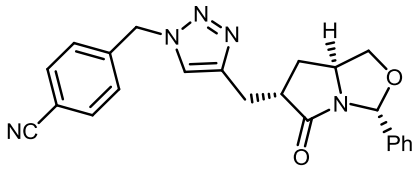
Yield = 89% (33 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.30 (m, 12H), 6.13 (s, 1H), 5.57-5.45 (m, 2H), 4.13 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.05 (t, 1H), 3.32 (s, 1H), 3.13 (dd, *J* = 20.1 Hz, J_2 = 12.2 Hz, 3H), 2.61 (dd, J_1 = 7.1 Hz, J_2 = 4.7 Hz, 1H), 1.80 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.61, 138.46, 134.59, 129.11, 128.74, 128.6, 128.46, 128.42, 127.96, 125.95, 125.85, 86.65, 72.13, 56.65, 54.30, 45.33, 30.71, 22.67; ESI-MS (m/z): [M+1] 375.3; and purity in HPLC = 91%.

(3R,6S,7aS)-6-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-3-phenyltetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12b):



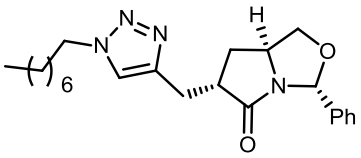
Yield = 83% (16 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.30 (m, 12H), 6.13 (s, 1H), 5.57-5.45 (m, 2H), 4.13 (dd, J_1 = 8.8 Hz, J_2 = 5.4 Hz, 1H), 4.05 (t, 1H), 3.32 (s, 1H), 3.13 (dd, J_1 = 20.1 Hz, 12.2 Hz, 3H), 2.61 (dd, J_1 = 7.1 Hz, J_2 = 4.7 Hz, 1H), 1.80 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.61, 138.46, 134.59, 129.11, 128.74, 128.6, 128.46, 128.42, 127.96, 125.95, 125.85, 86.65, 72.13, 56.65, 54.30, 45.33, 30.71, 22.67, 21.13; ESI-MS (m/z): [M+1] 389.5; and purity in HPLC = 95%.

4-((4-(((3R,6S,7aS)-5-oxo-3-phenylhexahydropyrrolo[1,2-c]oxazol-6-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzonitrile (4.12c):



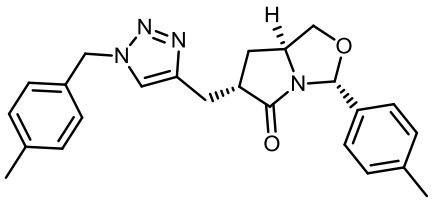
Yield = 77% (15 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.49 (s, 1H), 7.43-7.32 (m, 7H), 6.19 (s, 1H), 5.60 (t, *J* = 11.1 Hz, 2H), 4.11 (td, J_1 = 13.6 Hz, J_2 = 6.6 Hz, 2H), 3.33 (s, 1H), 3.20-3.05 (m, 3H), 2.62 (dd, J_1 = 6.4 Hz, J_2 = 2.2 Hz, 1H), 1.82 (dd, J_1 = 6.7 Hz, J_2 = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.66, 145.66, 139.93, 138.24, 132.88, 128.67, 128.47, 128.23, 125.88, 122.96, 118.11, 112.75, 86.66, 72.02, 56.51, 53.35, 45.21, 31.91, 22.67; ESI-MS (m/z): [M+1] 400.1; and purity in HPLC = 96%.

(S)-5-((4-octyl-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.12d):



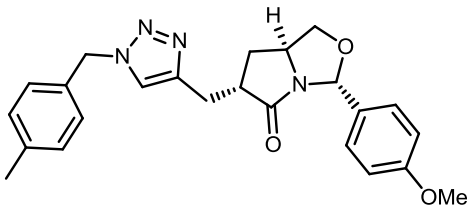
Yield = 69% (27 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.45-7.30 (m, 5H), 6.24 (s, 1H), 4.41 (dt, J_1 = 14.0 Hz, J_2 = 6.6 Hz, 2H), 4.19-3.98 (m, 2H), 3.36 (s, 1H), 3.27-3.22 (m, 2H), 1.93-1.85 (m, 2H), 2.75-2.63 (m, 1H), 1.26 (d, J = 11.1 Hz, 8H), 1.82-1.73 (m, 1H), 0.86 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.87, 138.4, 128.6, 128.42, 125.97, 86.65, 72.18, 56.73, 45.36, 31.69, 30.21, 29.67, 29.05, 28.96, 26.46, 22.57, 14.08, 14.05; ESI-MS (m/z): [M+1] 397.2; and HPLC = 97%.

Benzyl(3R,6S,7aS)-6-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(p-tolyl)tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12e):



Yield = 77% (27 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.28 (t, J = 8.7 Hz, 2H), 7.19-7.12 (m, 6H), 6.09 (s, 1H), 5.45 (q, J = 14.7 Hz, 2H), 4.29 (s, 2H), 4.14-3.96 (m, 2H), 3.34-3.18 (m, 1H), 3.07 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H), 1.83-1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.46, 159.81, 138.71, 130.62, 129.75, 129.44, 128.21, 128.13, 127.28, 113.77, 86.52, 72.07, 56.77, 55.26, 45.39, 30.84, 26.09, 21.11; ESI-MS (m/z): [M+1] 403.2; and purity in HPLC = 97%.

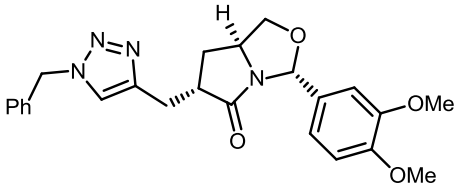
(3R,6S,7aS)-3-(4-methoxyphenyl)-6-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12f):



Yield = 85% (27 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.3 (d, J = 8.6 Hz, 2H), 7.27-7.16 (m, 4H), 6.86 (d, J = 8.6 Hz, 2H), 6.02 (s, 1H), 5.55 (d, J = 14.6 Hz, 1H), 5.43 (d, J = 14.7 Hz, 1H), 4.28 (s, 1H), 4.06 (td, J_1 = 13.4 Hz, J_2 = 6.45 Hz, 2H), 3.78 (s, 3H), 3.3 (s, 1H), 3.11 (t, J = 7.65 Hz, 2H), 2.32 (s, 3H), 1.74 (d, J = 6.37 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.45, 159.81, 138.7, 130.64, 129.75, 128.94, 128.3,

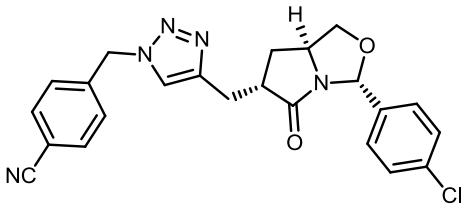
128.23, 127.11, 113.61, 86.5, 72.17, 56.78, 56.7, 55.6, 45.37, 30.48, 26.1, 21.11; ESI-MS (m/z): [M+1] 419.5; and purity in HPLC = 98%.

(3R,6S,7aS)-6-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-(3,4-dimethoxyphe-nyl)tetr-ahydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12g):



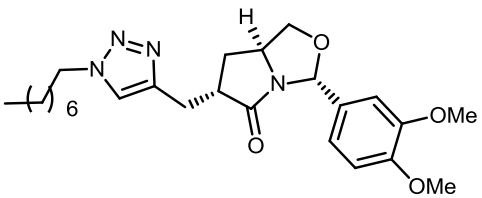
Yield = 81% (18 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 3H), 7.26 (dd, *J* = 6.2, 4.26 Hz, 3H), 6.97-6.90 (m, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.07 (s, 1H), 5.51 (q, *J* = 14.8 Hz, 2H), 4.17-4.04 (m, 2H), 3.87 (d, *J* = 5.2 Hz, 6H), 3.35-3.27 (m, 1H), 3.18-2.99 (m, 3H), 2.59 (q, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.42, 149.25, 149.02, 131.02, 129.09, 127.92, 118.2, 110.84, 110.38, 109.07, 86.57, 72.13, 56.17, 56, 55.93, 55.89, 31.9, 30.56, 22.67; ESI-MS (m/z): [M+1] 435.9; and purity in HPLC = 97%.

4-((4-(((3R,6S,7aS)-3-(4-chlorophenyl)-5-oxohexahydropyrrolo[1,2-c]oxazol-6-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzonitrile (4.12h):



Yield = 77% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 2H), 7.33 (d, *J* = 2.39 Hz, 4H), 6.13 (s, 1H), 5.64-5.51 (m, 2H), 4.45 (s, 3H), 4.14-3.98 (m, 2H), 3.32 (s, 1H), 3.25-3.00 (m, 3H), 2.62 (dd, *J* = 7.31, 3.75 Hz, 1H), 1.81 (d, *J* = 7.16 Hz, 1H), 7.65 (s, 1H), 7.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 140.73, 139.87, 136.83, 134.53, 132.62, 128.24, 127.38, 118.43, 118.12, 112.72, 112.13, 72.11, 56.47, 54.01, 45.08, 30.83, 22.68; ESI-MS (m/z): [M+1] 434; and purity in HPLC = 98%.

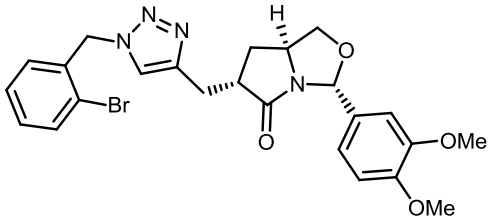
(3R,6S,7aS)-3-(3,4-dimethoxyphenyl)-6-((1-octyl-1H-1,2,3-triazol-4-yl)met-hyl)tetra-hydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12i):



Yield = 63% (28 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.04-6.90 (m, 2H), 6.84 (d, *J* = 8.27 Hz, 1H), 6.20 (s, 1H), 4.34 (dt, J_1 = 6.9 Hz, J_2 = 1.2 Hz, 2H), 4.19-4.05 (m, 2H), 3.88 (d, J_1 = 5.8 Hz, 6H), 3.33 (dd, J_1 = 9.6 Hz, J_2 = 4.8 Hz, 1H), 3.24-3.15 (m, 2H),

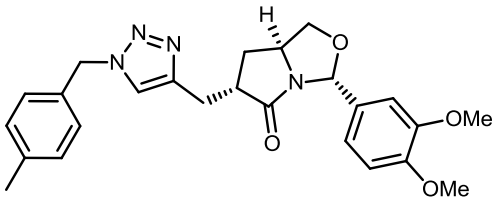
3.08 (dd, J_1 = 14.9 Hz, J_2 = 6.4 Hz, 1H), 2.67-2.60 (m, 1H), 1.94-1.73 (m, 3H), 1.26 (s, 10H), 0.87 (dd, J_1 = 6.9 Hz, J_2 = 3.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 149.25, 149.03, 139.46, 131.02, 118.18, 116.02, 110.84, 109.06, 86.58, 72.13, 58.67, 55.93, 55.89, 50.37, 45.43, 31.69, 30.27, 29.68, 28.94, 26.47, 22.57, 14.04; ESI-MS (m/z): [M+1] 458.5; and purity in HPLC = 98%.

(3R,6S,7aS)-6-((1-(2-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(3,4-dimethoxy phenyl)tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12j):



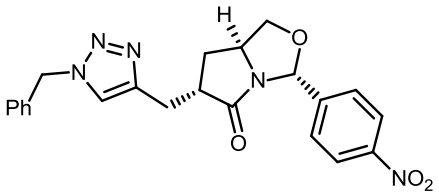
Yield = 79% (20 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.94, 0.95 Hz, 1H), 7.48 (s, 1H), 6.84 (d, J = 8.2 Hz, 1H), 7.01-6.90 (m, 2H), 7.12 (dd, J_1 = 7.6, J_2 = 1.3 Hz, 1H), 7.23 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.32 (dt, J_1 = 7.5 Hz, J_2 =1.05 Hz, 1H), 6.12 (s, 1H), 5.70-5.57 (m, 2H), 4.18-4.05 (m, 2H), 3.88 (d, J = 5.58 Hz, 6H), 3.41-3.26 (m, 1H), 3.17 (dt, J_1 = 7.9 Hz, J_2 = 4.4 Hz, 2H), 3.03 (dd, J_1 = 14.9 Hz, J_2 = 6.8 Hz, 1H), 2.63-2.56 (m, 1H), 1.79 (q, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.79, 154.48, 149.62, 133.95, 133.08, 130.46, 130.12, 128.18, 128.13, 126.87, 110.38, 108.94, 86.59, 72.16, 56.17, 56, 54.59, 54.38, 45.75, 31.9, 22.67; ESI-MS (m/z): [M+1] 414.9; and purity in HPLC = 94%.

(3R,6S,7aS)-3-(3,4-dimethoxyphenyl)-6-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12k):



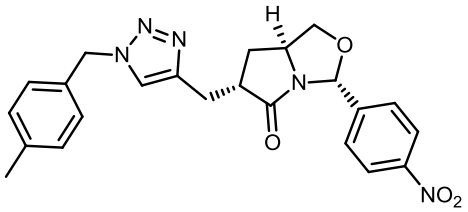
Yield = 85% (19 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.26 (s, 1H), 7.17 (t, J = 5.8 Hz, 3H), 7.01-6.90 (m, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.06 (s, 1H), 5.45 (q, J = 14.7 Hz, 2H), 4.09 (td, J_1 = 13.5 Hz, J_2 = 6.5 Hz, 2H), 3.87 (d, J = 5.2 Hz, 6H), 3.38-3.23 (m, 1H), 3.12 (t, J = 7.7 Hz, 2H), 3.01 (d, J = 5.3 Hz, 1H), 2.58 (dd, J_1 = 7.5 Hz, J_2 = 4.9 Hz, 1H), 2.33 (s, 3H), 1.78 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.55, 149.24, 149.02, 138.63, 131.72, 131.06, 129.74, 127.96, 118.19, 110.83, 110, 109.05, 86.58, 72.12, 56.69, 55.93, 55.88, 53.95, 45.4, 30.49, 26.08, 21.14. ESI-MS (m/z): [M+1] 448.9; and purity in HPLC = 96%.

(S)-5-((4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (4.12l):



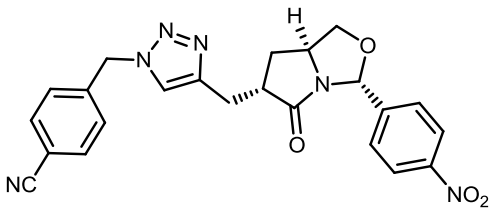
Yield = 81% (17 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.44-7.31 (m, 4H), 7.26 (d, *J* = 8.1 Hz, 2H), 6.15 (s, 1H), 5.51 (q, *J* = 14.8 Hz, 2H), 4.19-4.14 (m, 1H), 4.03-3.97 (m, 1H), 3.38-3.28 (m, 1H), 3.20-3.12 (m, 2H), 3.01 (dd, J_1 = 14.9 Hz, J_2 = 6.8 Hz, 1H), 2.64-2.58 (m, 1H), 1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.03, 148.05, 145.56, 134.75, 129.11, 128.72, 127.91, 127.04, 123.64, 122.32, 85.68, 72.48, 56.49, 54.14, 45.18, 30.3, 25.98; ESI-MS (m/z): [M+1] 420.4; and purity in HPLC = 97%.

(S)-5-((4-(2-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (4.12m):



Yield = 77% (16 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.51 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.48-7.35 (m, 1H), 7.28 (s, 2H), 6.15 (s, 1H), 7.19 (s, 4H), 5.50 (d, *J* = 14.7 Hz, 2H), 4.17 (d, *J* = 7.8 Hz, 1H), 4.08-3.93 (m, 1H), 3.42-3.30 (m, 1H), 3.19 (t, *J* = 7.9 Hz, 2H), 2.70-2.59 (m, 1H), 2.35 (s, 3H), 3.14-2.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ESI-MS (m/z): [M+1] 434.5; and purity in HPLC = 93%.

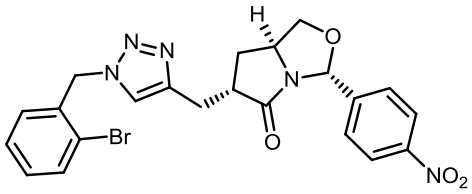
(S)-5-((4-((4-methoxyphenoxy)mmmethyl)-1H-1,2,3-triazol-1-yl)methyl) pyrrolidin-2-one (4.12n):



Yield = 72% (31 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.44 (s, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 6.19 (s, 1H), 5.58 (t, *J* = 10.9 Hz, 2H), 4.16 (dd, J_1 = 8.2, J_2 = 6.4 Hz, 1H), 4.00 (dd, J_1 = 13.9 Hz, J_2 = 7.2 Hz, 1H), 3.47-3.28 (m, 1H), 3.24-3.12 (m, 2H), 3.03 (dd, J_1 = 14.8 Hz, J_1 = 6.4 Hz, 1H), 2.64 (ddd, J_1 = 13.2 Hz, J_2 = 9.2 Hz, J_2 = 7.4 Hz, 1H), 1.86 (ddd, J_1 = 13.2 Hz, J_2 = 10.8 Hz, J_3 = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.03,

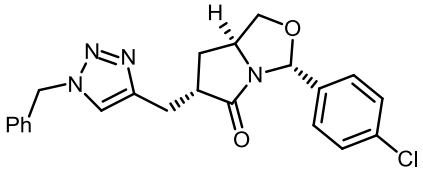
148.09, 145.42, 145.36, 139.93, 132.87, 128.24, 127, 123.68, 122.7, 118.06, 112.78, 85.68, 72.4, 56.38, 53.33, 45.03, 30.65, 25.88; ESI-MS (m/z): [M+1] 444.9; and purity in HPLC = 97%.

(3R,6S,7aS)-6-((1-(2-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(4-nitrophenyl) tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12o):



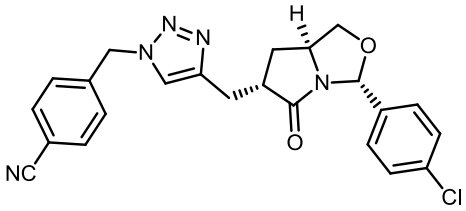
Yield = 84% (20 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.78 Hz, 2H), 7.65-7.52 (m, 3H), 7.46 (s, 1H), 7.32 (dt, J_1 = 7.4 Hz, 1.2 Hz, 1H), 7.23 (dt, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1H), 7.14 (dd, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1H),6.19 (s, 1H), 5.70-5.55 (m, 2H), 4.16 (dd, *J* = 8.2 Hz, J_2 = 6.4 Hz, 1H), 4.04-3.95 (m, 1H), 3.40-3.30 (m, 1H), 3.18 (m, 2H), 3.04 (dd, J_1 = 14.2 Hz, J_2 = 6.8 Hz, 1H), 2.65-2.57 (m, 1H), 1.90-1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.97, 145.58, 134.17, 133.26, 130.4, 130.25, 128.19, 127.05, 123.65, 123.45, 109.99, 85.71, 72.49, 56.48, 53.83, 45.17, 25.94, 22.67; ESI-MS (m/z): [M+1] 499.5; and purity in HPLC = 97%.

(3R,6S,7aS)-6-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-(4-chlorophenyl) tetrahyd-ropyrrolo[1,2-c]oxazol-5(3H)-one (4.12p):



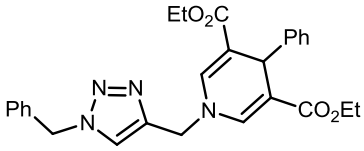
Yield = 87% (18 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.38-7.28 (m, 9H), 7.25 (d, *J* = 8.37 Hz, 1H), 6.07 (s, 1H), 5.60-5.47 (m, 2H), 4.17-4.00 (m, 2H), 3.37-3.28 (m, 1H), 3.14 (t, *J* = 7.8 Hz, 3H), 2.61 (s, 1H), 1.81-1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.75, 137.04, 134.53, 134.47, 129.11, 128.77, 128.61, 128.59, 128, 127.44, 127.31, 86.07, 56.59, 54.44, 45.22, 31.91, 22.67, 14.1; ESI-MS (m/z): [M+1] 408.1; and purity in HPLC = 97%.

(3R,6S,7aS)-3-(4-chlorophenyl)-6-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl) tetrahydropyrrolo[1,2-c]oxazol-5(3H)-one (4.12q):



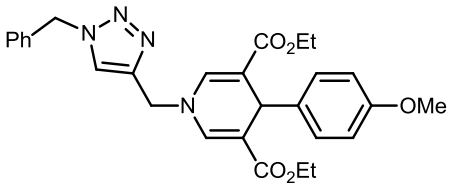
Yield = 81% (16 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 7.17 (t, *J* = 5.2 Hz, 4H), 6.05 (s, 1H), 5.46 (d, *J* = 15.7 Hz, 2H), 4.11 (d, *J* = 8.2 Hz, 1H), 3.34-3.21 (m, 1H), 3.12 (t, *J* = 7.8 Hz, 2H), 3.02 (s, 1H), 2.62-2.55 (m, 1H), 1.83-1.76 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.75, 138.71, 137.06, 134.46, 131.5, 129.84, 129.77, 128.58, 128.06, 127.43, 127.29, 86.08, 72.19, 56.61, 54.16, 45.3, 31.9, 22.67, 21.13; ESI-MS (m/z): [M+1] 422.9; and purity in HPLC = 97%.

Diethyl 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4.13a):



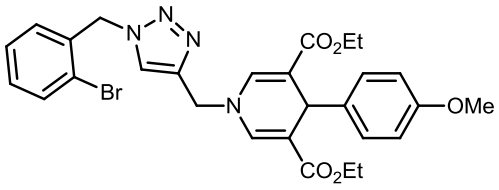
Yield = 87% (18 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.38 (m, 4H), 7.31 (t, 2H), 7.19-7.14 (m, 2H), 6.75-6.71 (m, 2H), 5.57 (s, 2H), 4.82 (s, 1H), 4.68 (s, 2H), 4.07 (ddt, *J* = 10.8 Hz, J_2 = 6.8 Hz, J_3 = 3.6 Hz, 4H), 3.77 (d, *J* = 3.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ESI-MS (m/z): [M+1] 473; and purity in HPLC = 99%.

Diethyl 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4.13b):



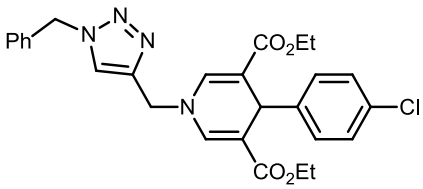
Yield = 87% (18 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.38 (m, 4H), 7.31 (t, 2H), 7.19-7.14 (m, 2H), 6.75-6.71 (m, 2H), 5.57 (s, 2H), 4.82 (s, 1H), 4.68 (s, 2H), 4.07 (ddt, J_1 = 10.8 Hz, J_2 = 6.8 Hz, J_3 = 3.6 Hz, 4H), 3.77 (d, 3H), 1.20 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ESI-MS (m/z): [M+1] 473; and purity in HPLC = 99%.

Diethyl 1-((1-(2-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4.13c):



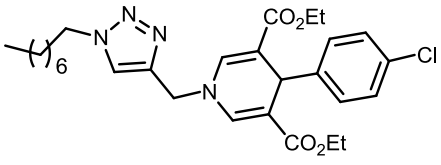
Yield = 84% (19 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.56 (s, 1H), 7.35 (dt, J = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.28 (s, 3H), 7.25-7.21 (m, 1H), 7.19-7.13 (m, 2H), 6.73 (dd, J = 9.1 Hz, J_2 = 2.4 Hz, 2H), 5.69 (s, 2H), 4.81 (s, 1H), 4.68 (s, 2H), 4.14-3.98 (m, 4H), 3.75 (s, 3H), 1.25-1.13 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.78, 158.05, 143.65, 138.96, 136.77, 133.7, 133.34, 130.65, 130.55, 129.13, 128.33, 122.06, 113.28, 109.63, 60.04, 55.12, 54.07, 49.78, 36.36, 14.2; ESI-MS (m/z): [M+1] 582.9; and purity in HPLC = 98%.

Diethyl 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4.13d):



Yield = 88% (17 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 2H), 7.48 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.28 (q, 5H), 5.61 (s, 2H), 7.12 (d, J = 8.4 Hz, 2H), 4.83 (s, 1H), 4.69 (s, 2H), 4.16-4.01 (m, 4H), 1.17 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 145.32, 139.22, 137.11, 133.02, 130.09, 129.95, 128.48, 121.9, 121.88, 120.33, 117.94, 109.23, 60.26, 53.64, 49.67, 36.89, 14.19; ESI-MS (m/z): [M+1] 407.5; and purity in HPLC = 95%.

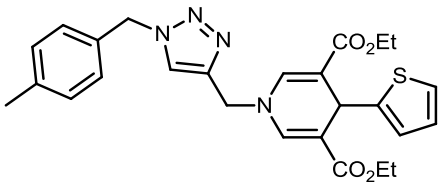
Diethyl 4-(4-chlorophenyl)-1-((1-octyl-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate (4.13e):



Yield = 69% (14 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.33 (t, 4H), 7.15 (d, J = 8.2 Hz, 2H), 4.85 (s, 1H), 4.70 (s, 2H), 4.37 (t, J = 7.4 Hz, 2H), 4.14-3.99 (m, 4H), 1.97-1.88 (m, 2H), 1.31 (d, J = 12.2 Hz, 10H), 1.22-1.17 (m, 6H), 0.89 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.54, 145.46, 143.1, 137.21, 130.98, 130.0, 121.48, 120.29, 109.05, 60.19, 50.65, 49.82,

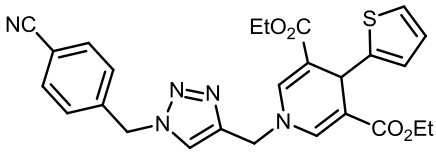
36.96, 31.67, 30.26, 29.67, 28.92, 26.49, 22.56, 14.2; ESI-MS (m/z): [M+1] 529.9; and purity in HPLC = 98%.

Diethyl 1-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4.13g):



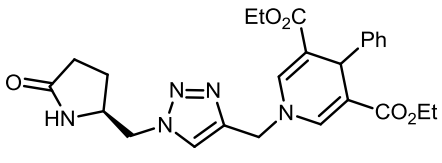
Yield = 71% (15 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.18-7.03 (m, 6H), 6.96 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H), 6.77-6.72 (m, 2H), 5.40 (d, J = 6.2 Hz, 2H), 5.14 (s, 1H), 4.61 (s, 2H), 4.13-4.03 (m, 4H), 2.29 (s, 3H), 1.18-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.46, 150.65, 138.88, 137.1, 131.04, 129.84, 129.76, 128.2, 126.57, 123.98, 123.62, 118.16, 108.73, 60.23, 54.24, 50.16, 31.83, 21.14, 14.22; ESI-MS (m/z): [M+1] 492.9; and purity in HPLC = 94%.

Diethyl 1-((1-(4-cyanobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4.13h):



Yield = 65% (17 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 8H), 7.45 (s, 4H), 7.35 (d, J = 7.8 Hz, 2H), 7.03 (t, 1H), 6.83 (d, J = 3.4 Hz, 2H), 5.61 (s, 3H), 5.22 (s, 1H), 4.45 (s, 7H), 4.21-4.12 (m, 4H), 1.29-1.26 (m, 6H); ESI-MS (m/z): [M+1] 5.4.3; and purity in HPLC = 97%.

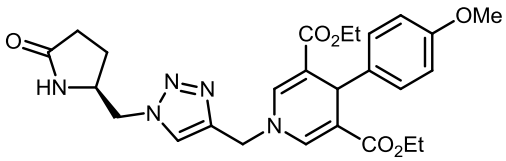
(S)-diethyl 1-((1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4.13i)



Yield = 90% (30 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.4 Hz, 1H), 7.34 (s, 2H), 7.27 (t, J = 3.4 Hz, 3H), 7.22 (t, J = 7.4 Hz, 2H), 7.14 (dd, J_1 = 11.4 Hz, J_2 = 4.2 Hz, 1H), 7.01 (s, 1H), 4.87 (s, 1H), 4.71 (s, 2H), 4.49-4.39 (m, 2H), 4.20-4.14 (m, 1H), 4.13-3.98 (m, 4H), 2.38-2.11 (m, 4H), 2.04-1.79 (m, 2H), 1.18 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.15, 166.86, 146.41, 143.67, 137.2, 137.18, 128.25, 127.94, 126.45, 123.17, 109.48, 60.18, 54.79, 53.74,

49.51, 37.31, 29.35, 24.05, 14.19; ESI-MS (m/z): [M+1] 480.3; and purity in HPLC = 99%.

(S)-diethyl 4-(4-methoxyphenyl)-1-((1-((5-oxopyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate (4.13j):



Yield = 93% (33 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.31 (s, 2H), 7.17 (d, J_1 = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 4.80 (s, 1H), 4.70 (s, 2H), 4.47 (dd, J_1 = 18.9 Hz, J_2 = 5.22 Hz, 2H), 4.21 (d, J = 1.54 Hz, 1H), 4.13-3.97 (m, 4H), 3.75 (s, 3H), 2.31 (s, 2H) 2.05 (s, 1H), 1.99-1.90 (m, 1H), 1.74-1.63 (m, 2H), 1.18 (t, J = 7.11 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.98, 167.01, 166.98, 158.1, 143.67, 138.99, 136.96, 136.94, 129.21, 123.31, 113.28, 109.75, 109.68, 60.17, 55.16, 54.76, 53.62, 49.49, 36.38, 29.26, 24.0, 14.21; ESI-MS (m/z): [M+1] 509.9; and purity in HPLC = 97%.

4.6. References:

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Silverman, S. M.; Lindstron, W.; Olson, A. J. *Angew Chem. Int. Ed.* **2006,** *45*, 1435; (c) Horne, W. S.; Yadav, M. K.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soci.* **2004**, *126*, 15366.

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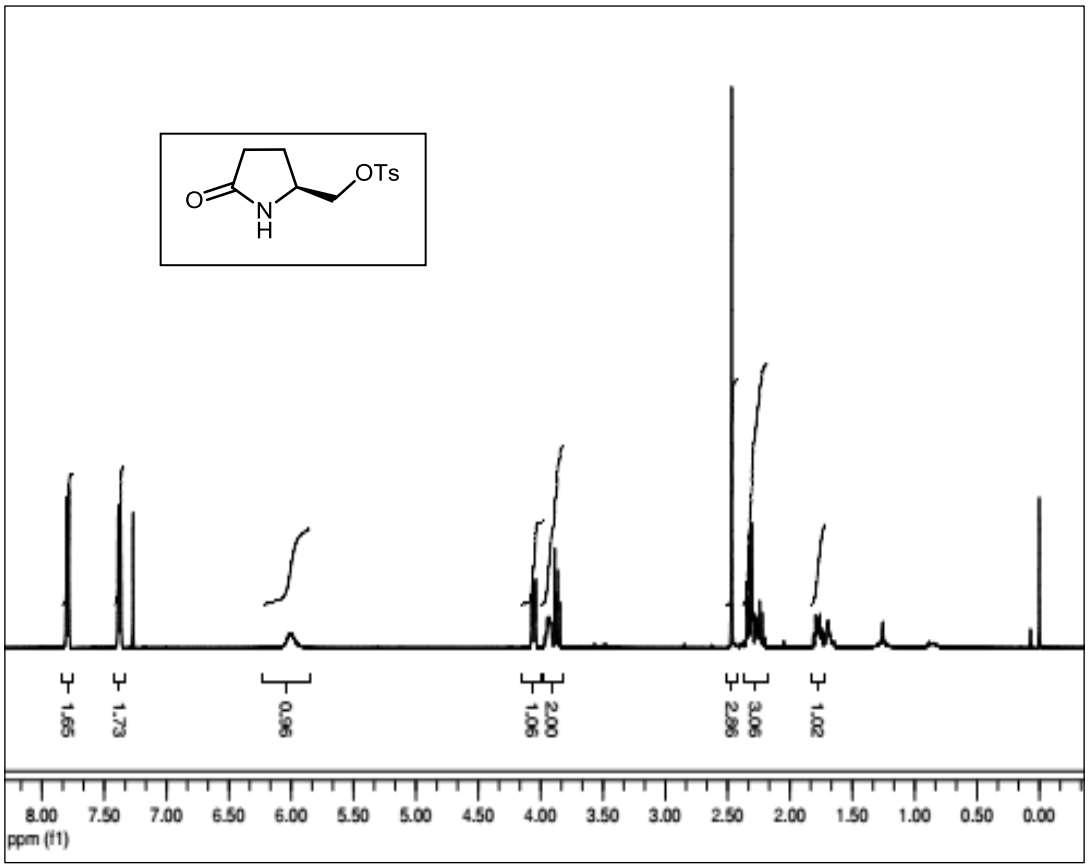
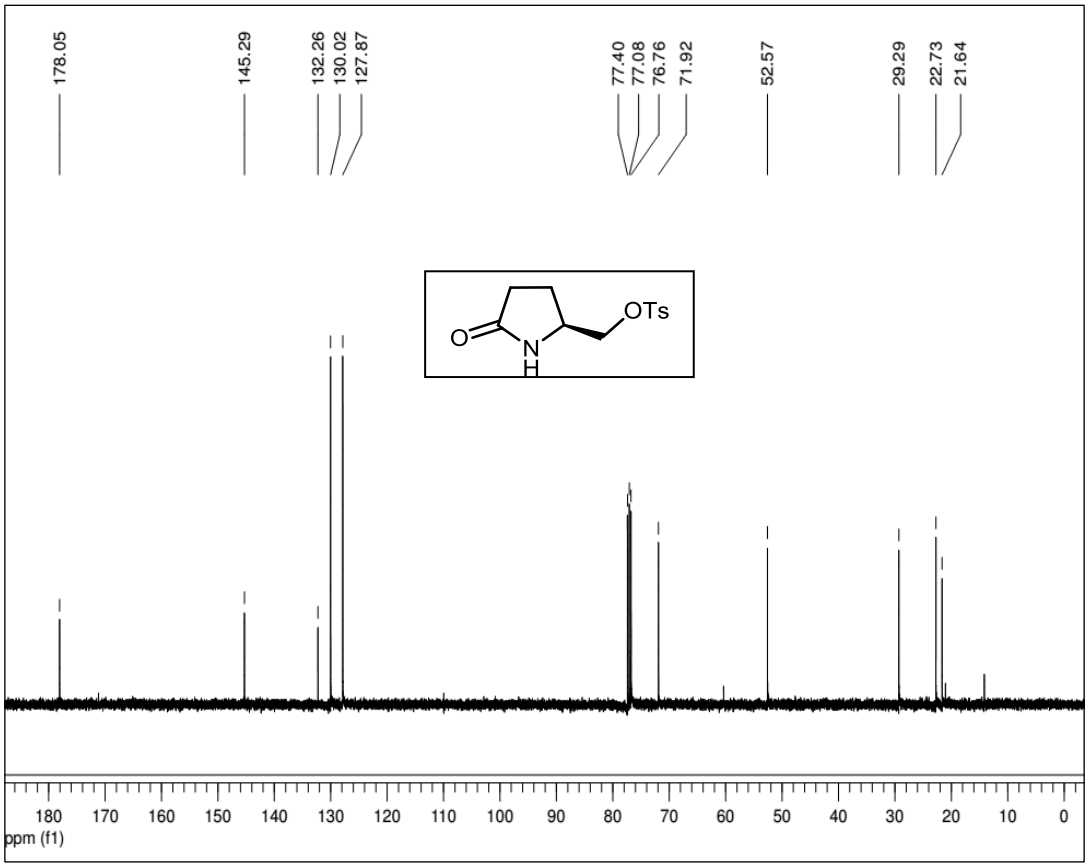
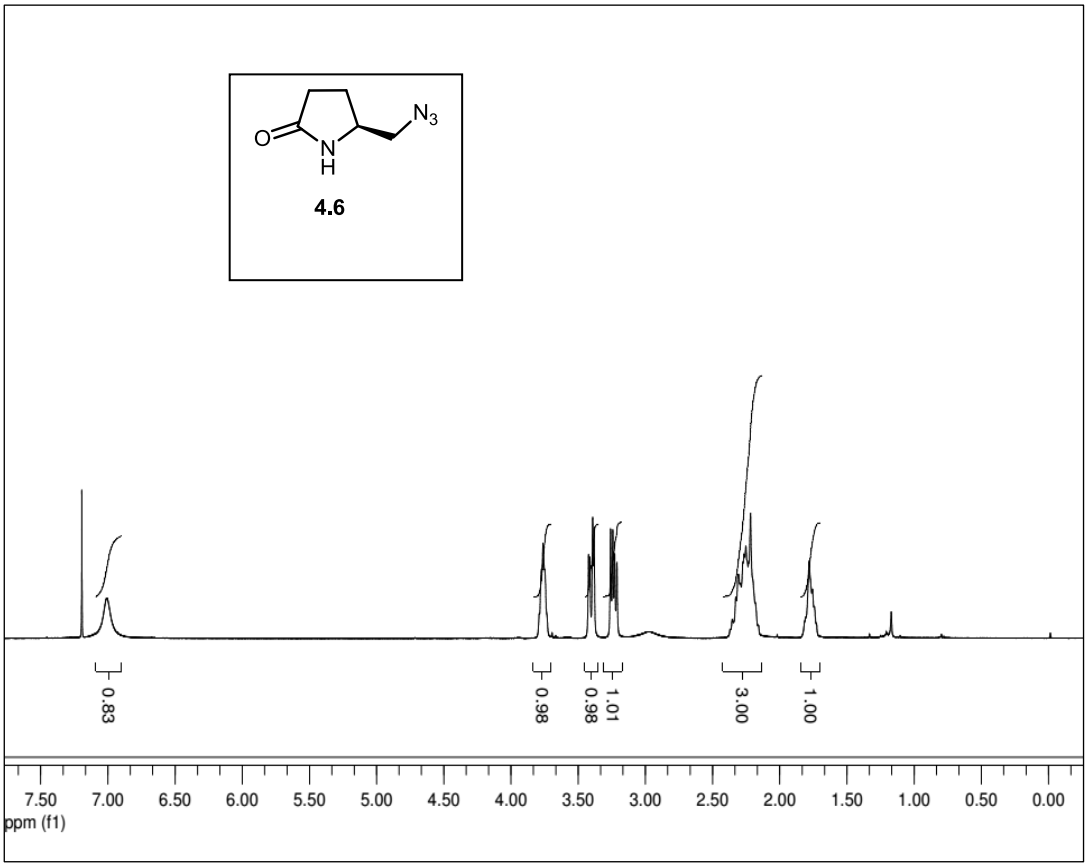
4.7. Appendices:



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0.98
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1.00
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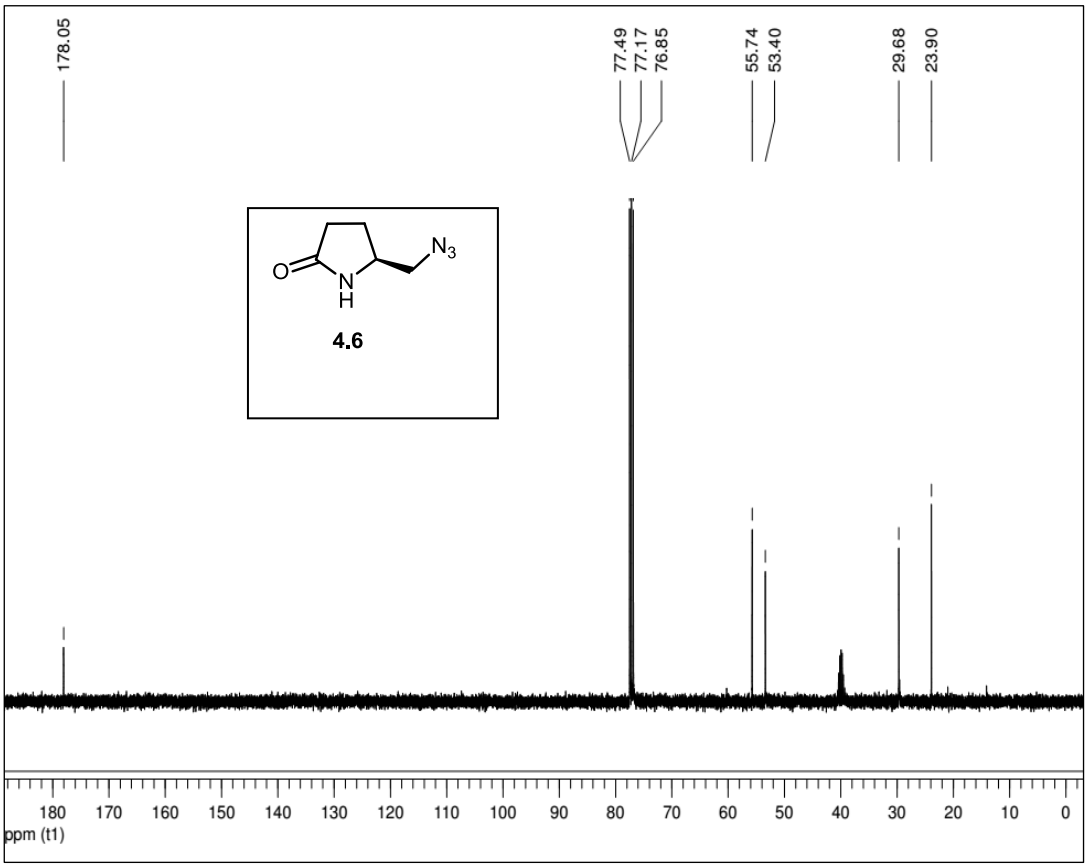
ppm (f1)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N
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N3
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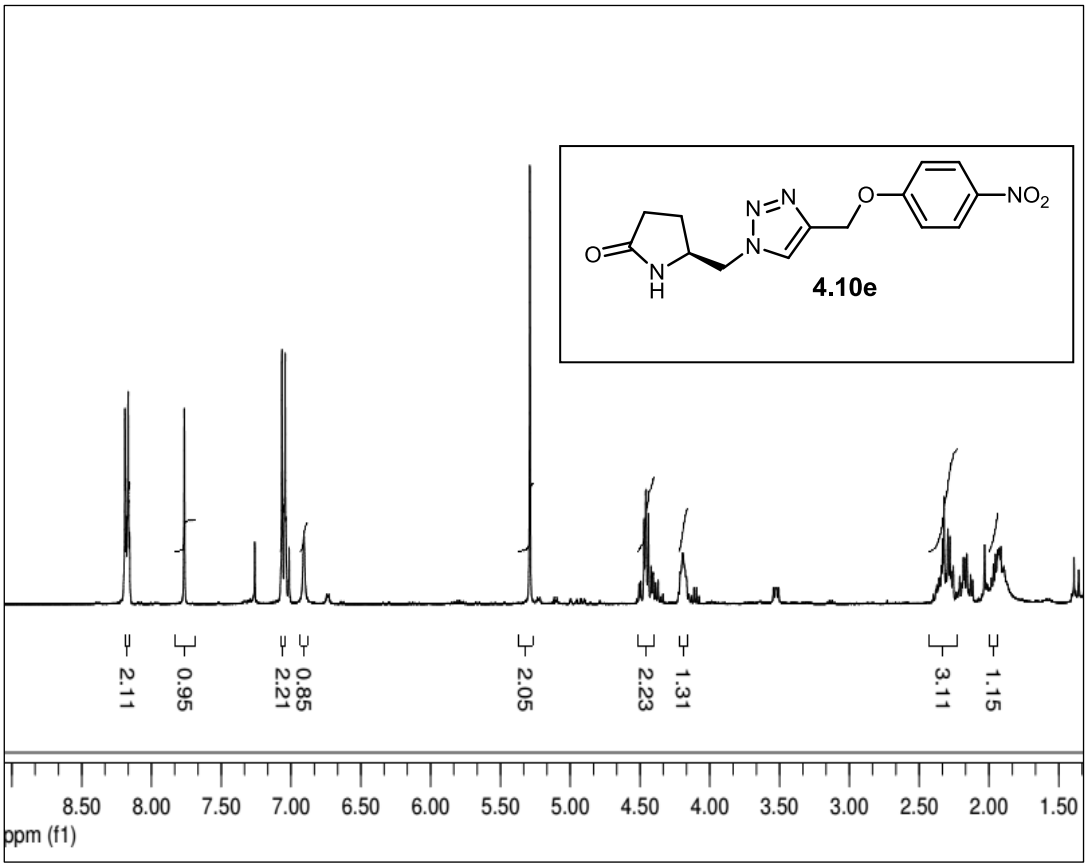
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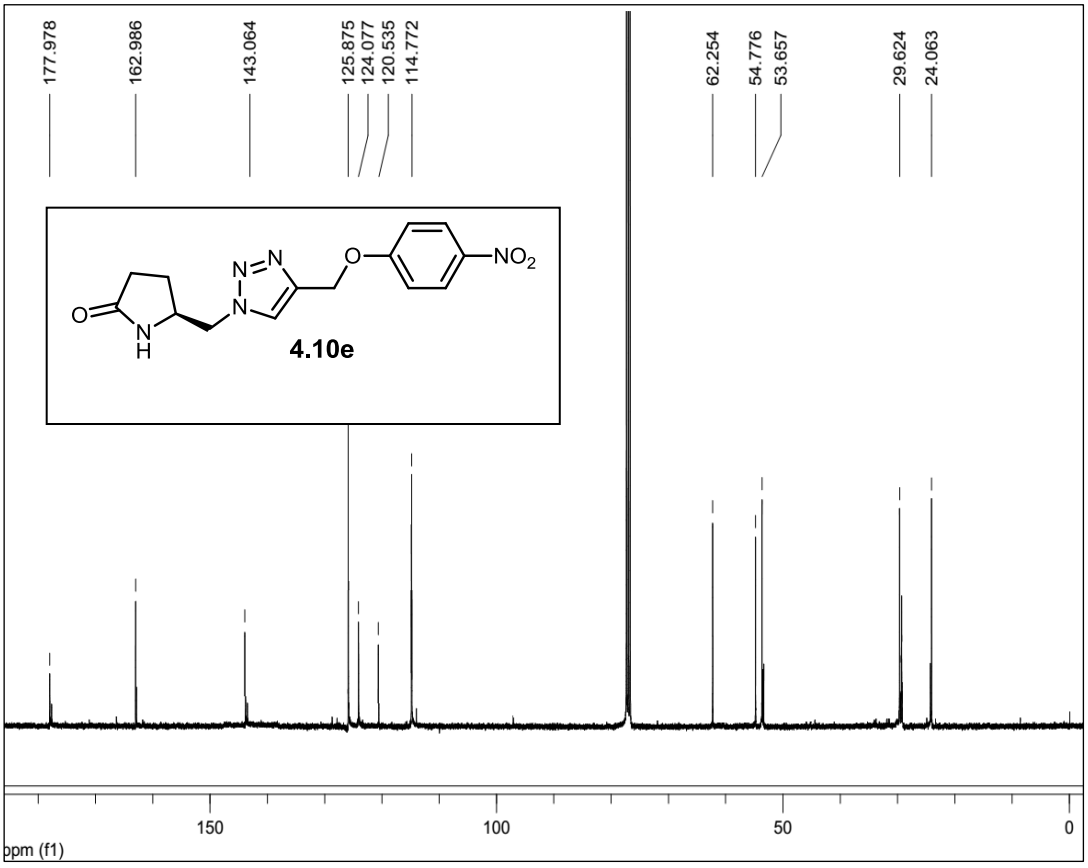
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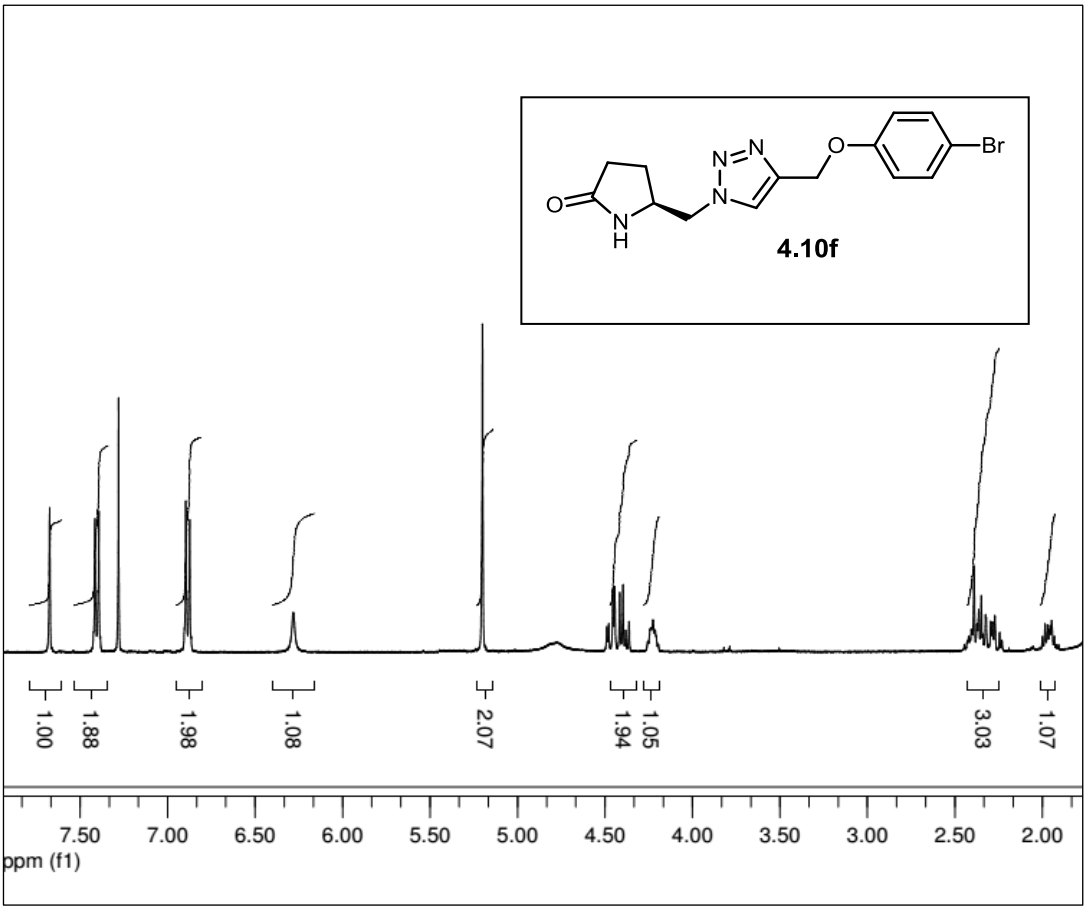
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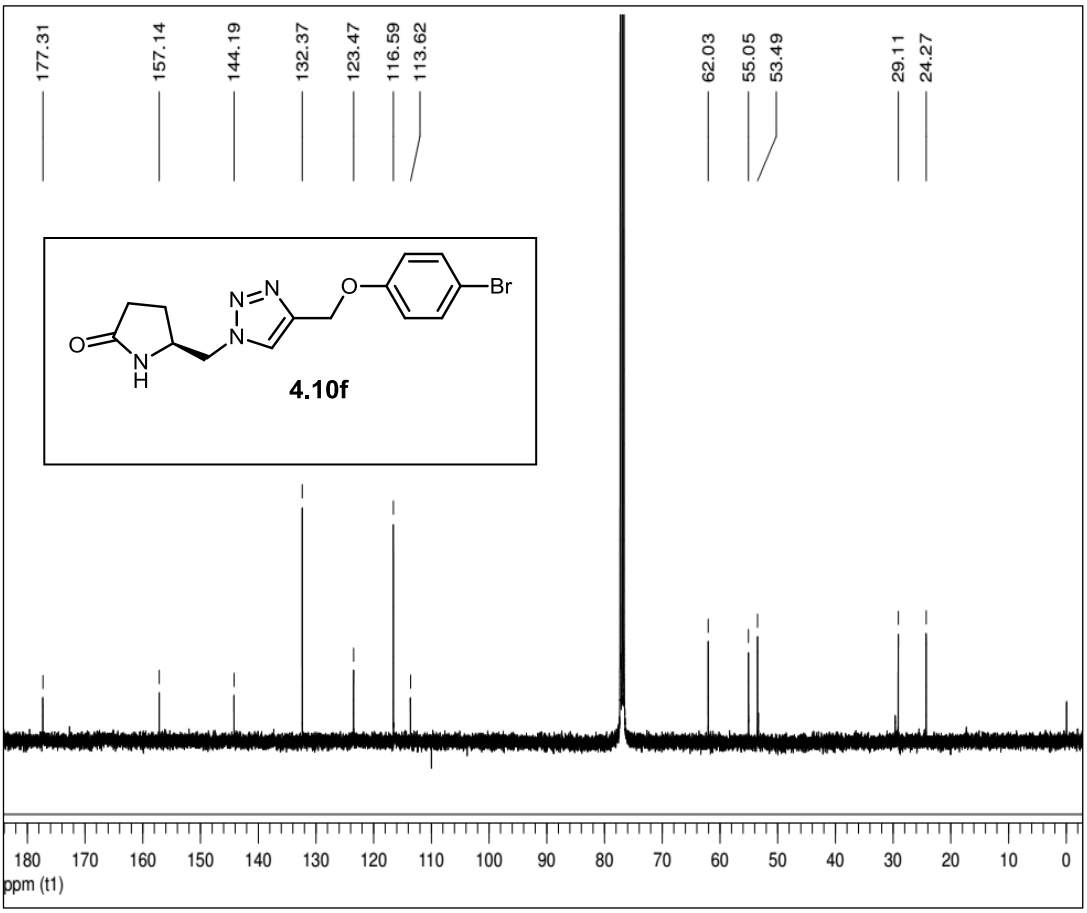
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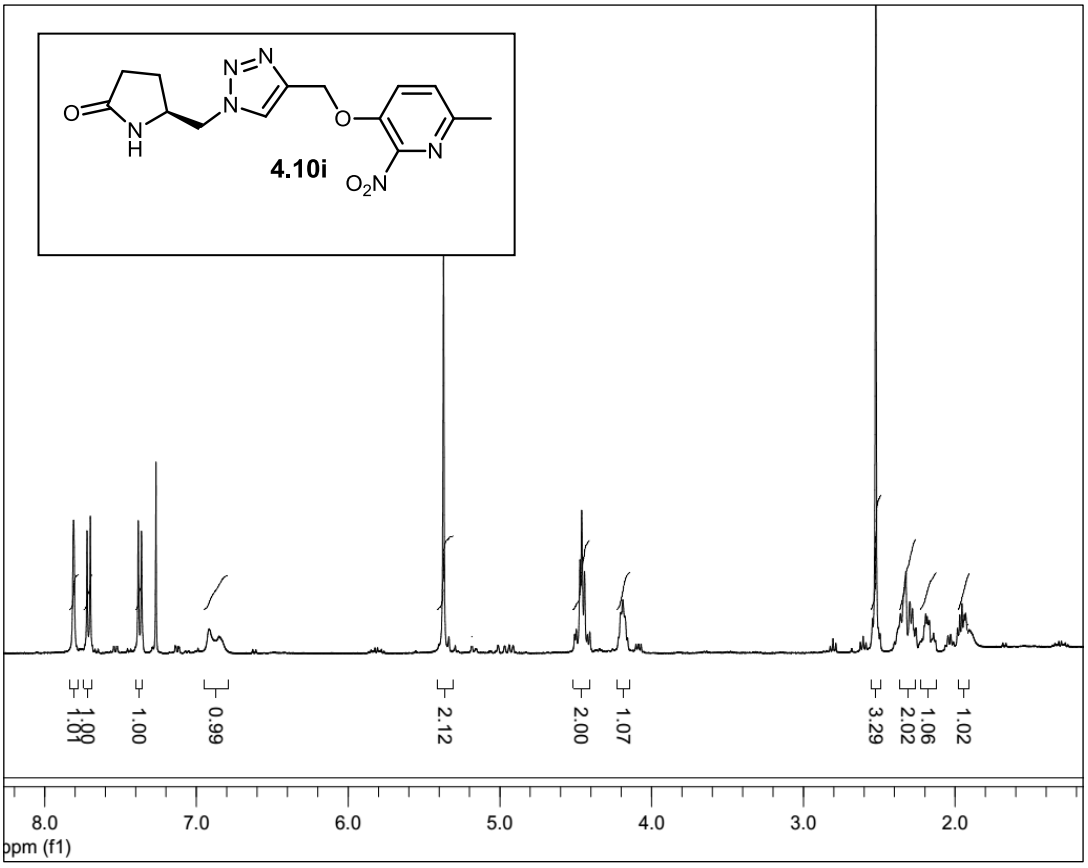
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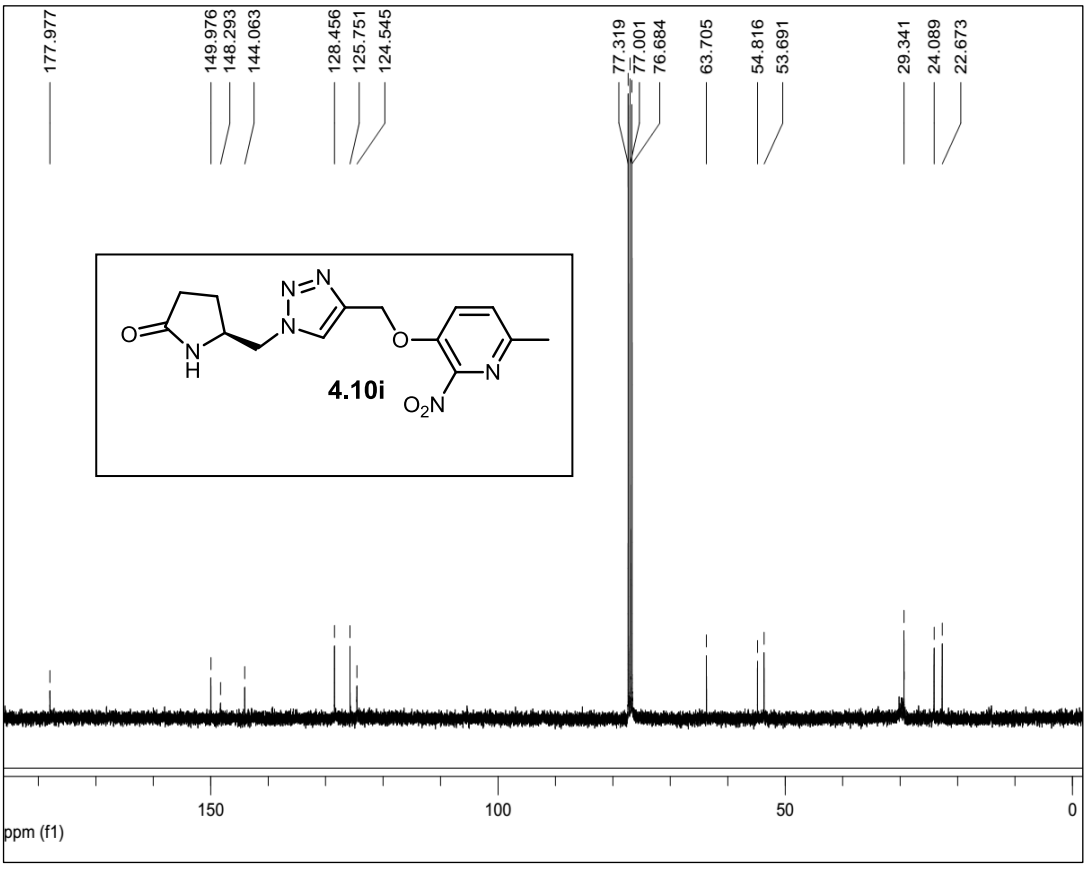
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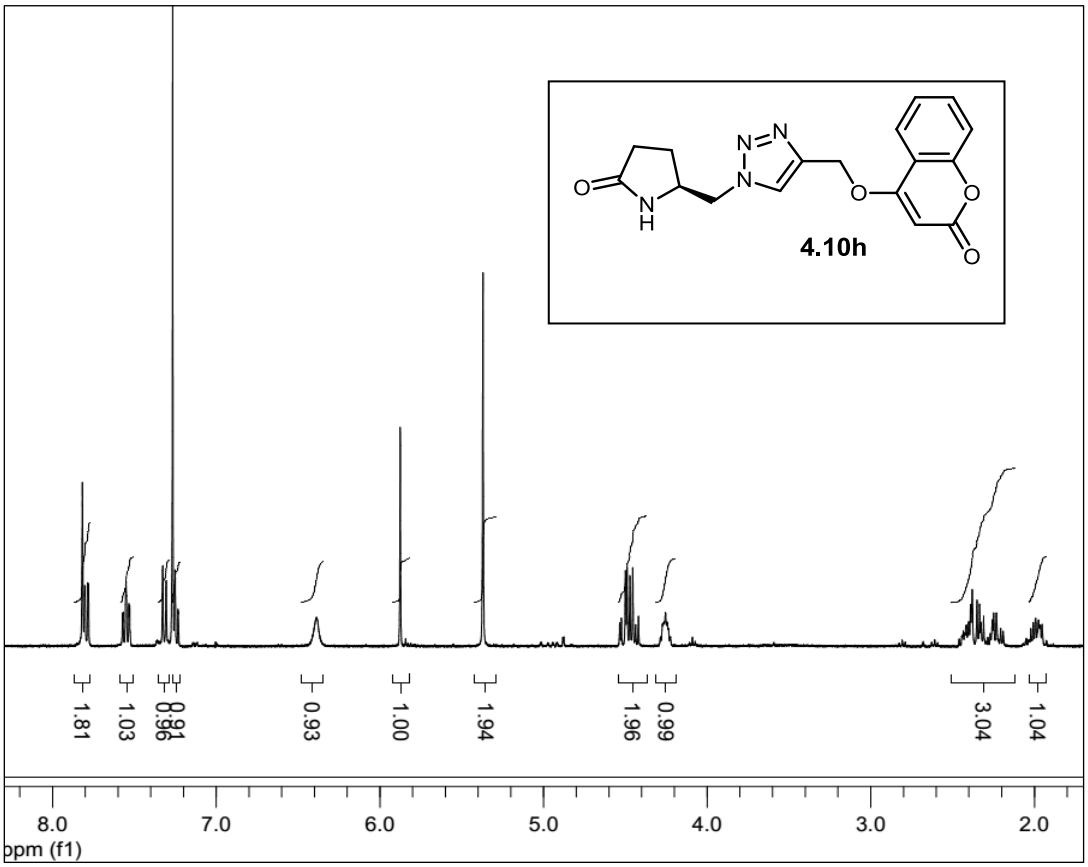
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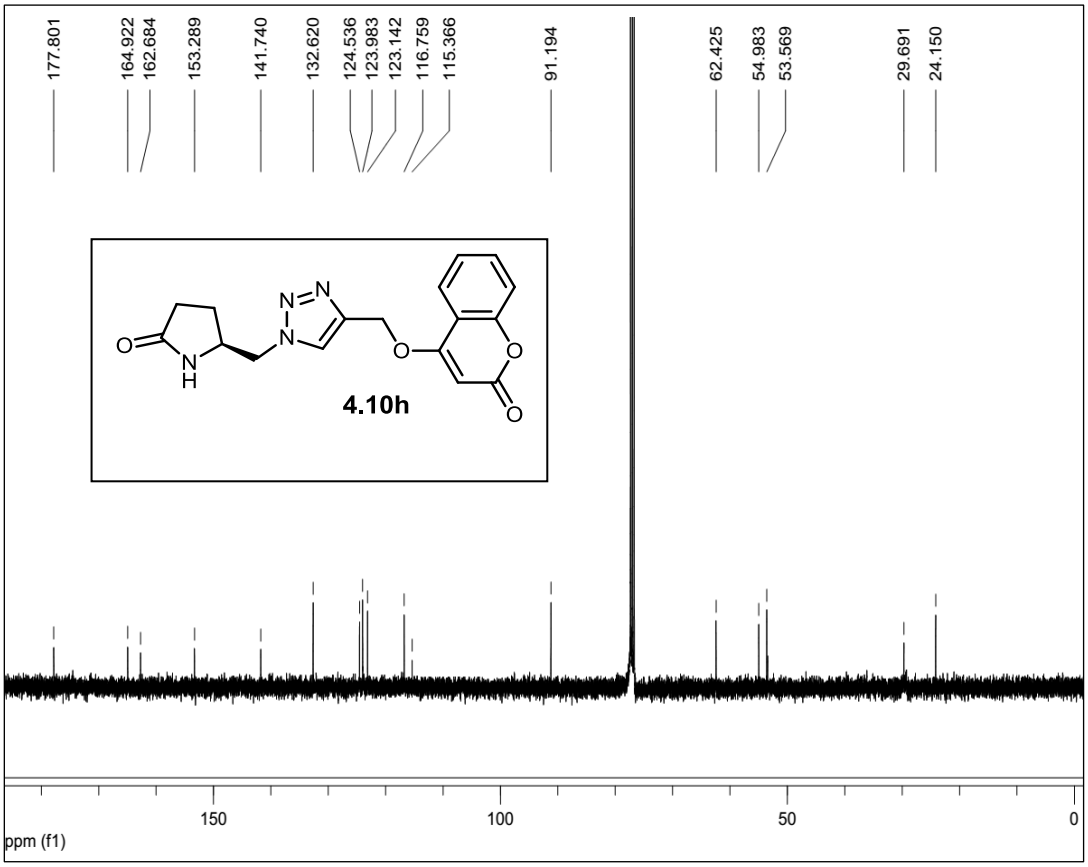
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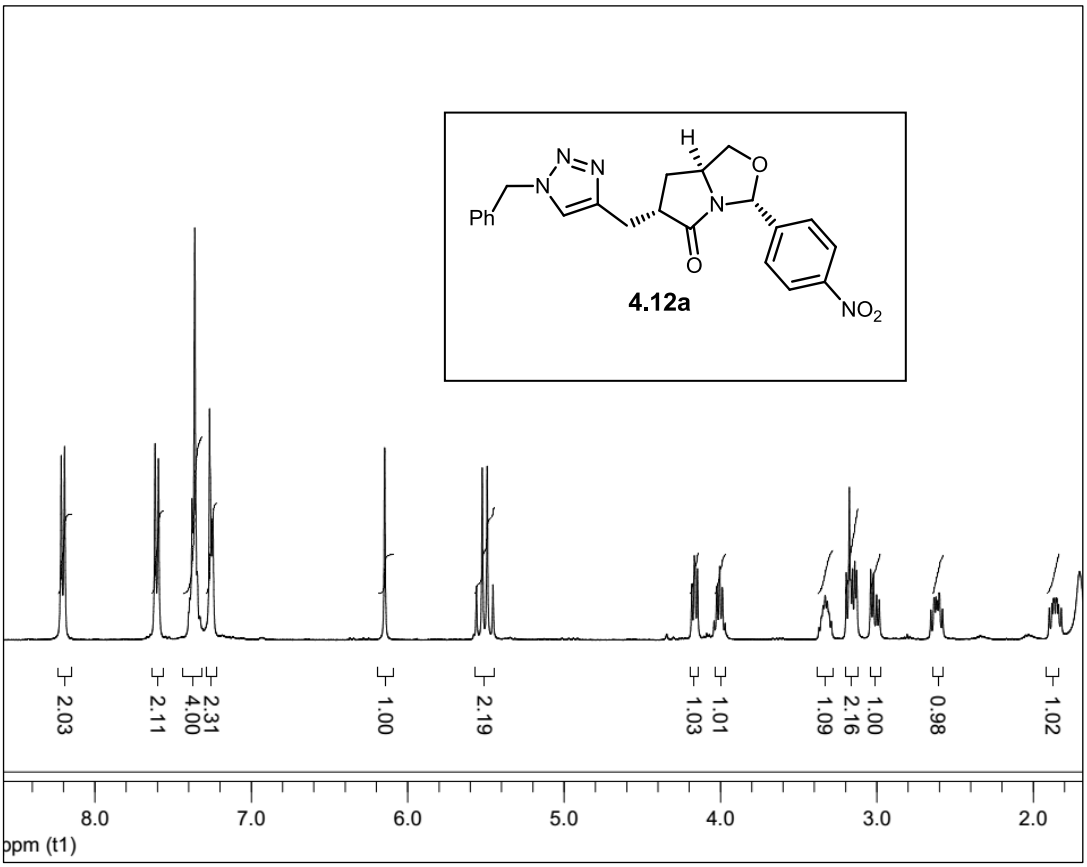
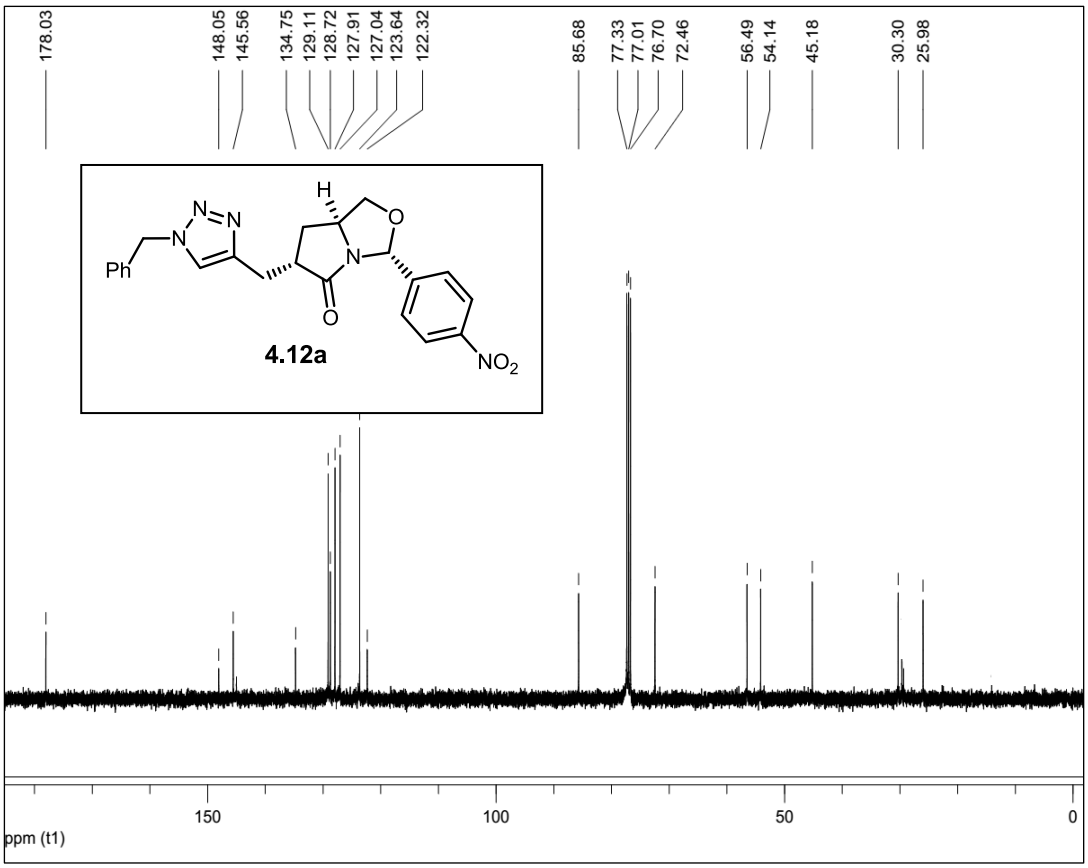
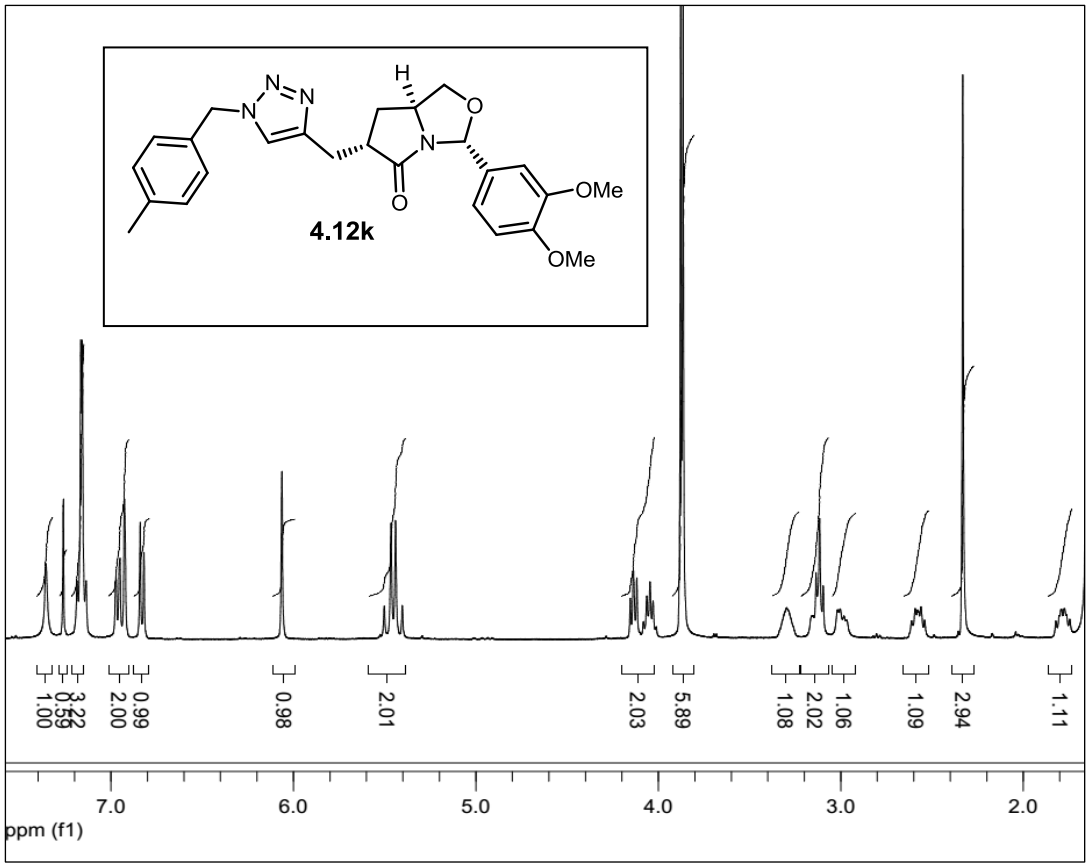
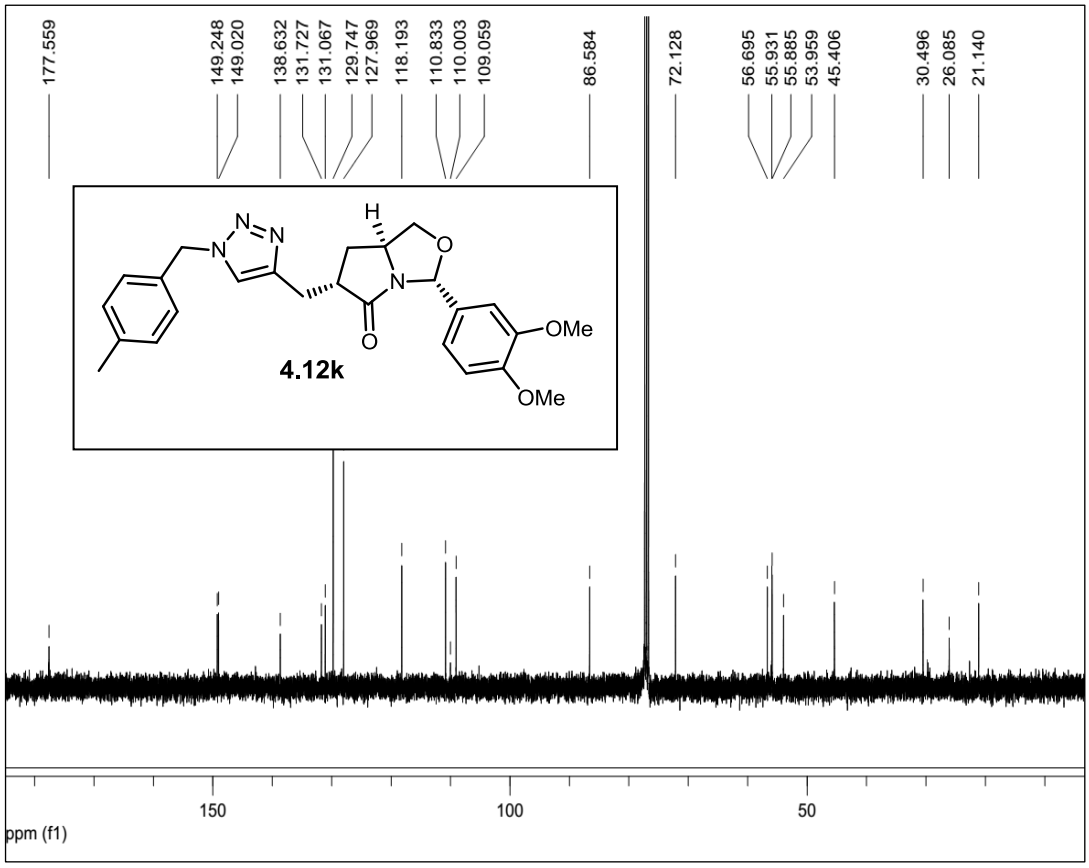
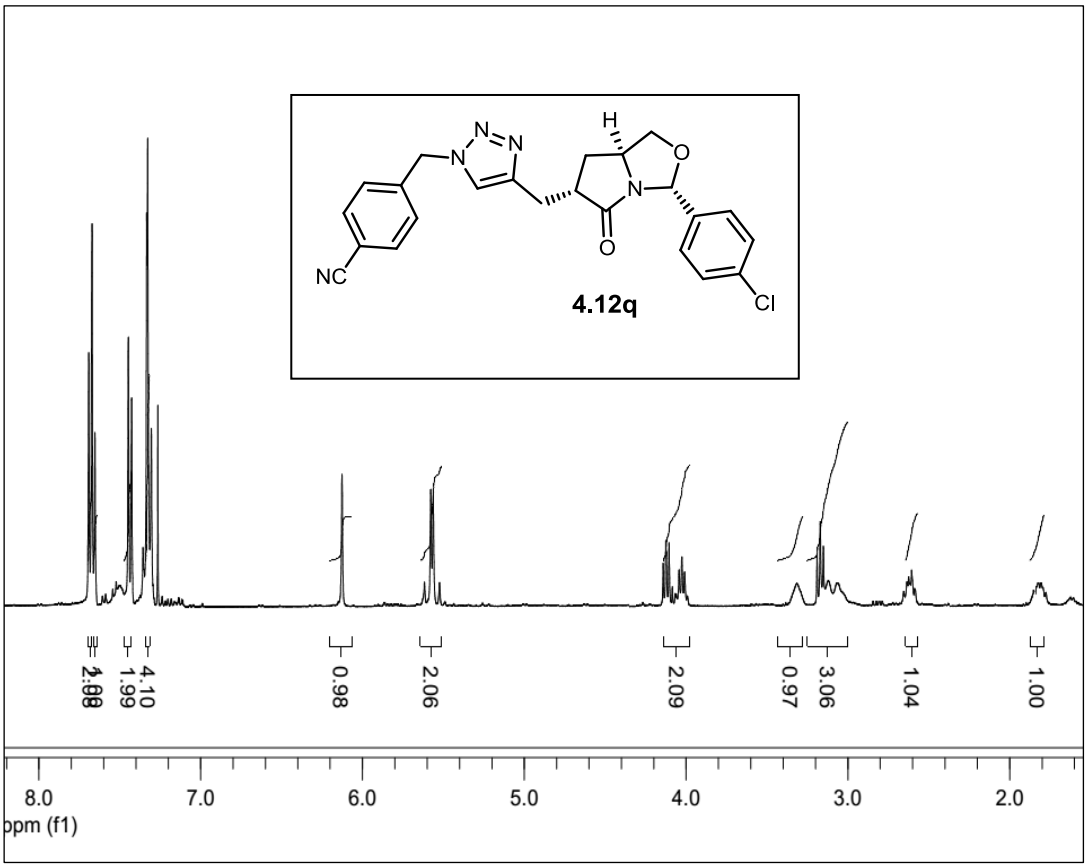
123.983
123.142
116.759
115.366
91.194
62.425
54.983
53.569
29.691
24.150
4.10h
150
100
50
0
ppm (f1)

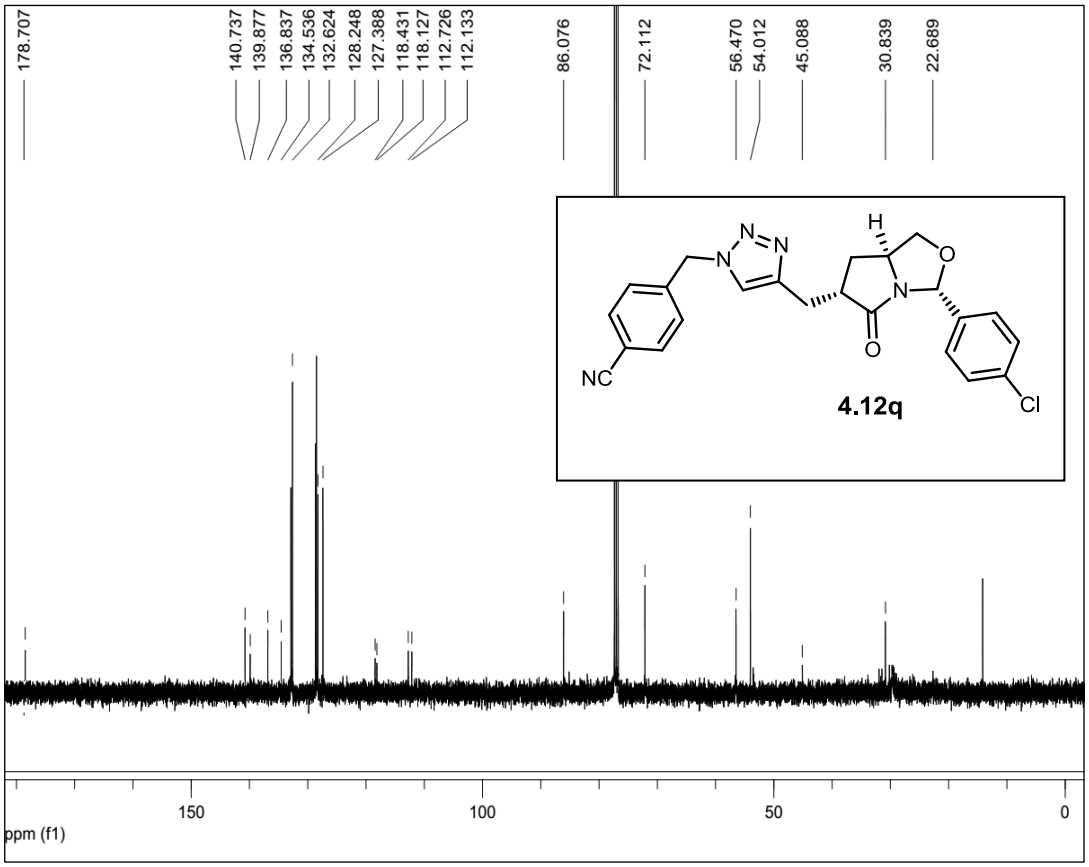

4.12a
2.03
2.11
4.00
2.31
1.00
2.19
1.03
1.01
1.09
2.16
1.00
0.98
1.02
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)

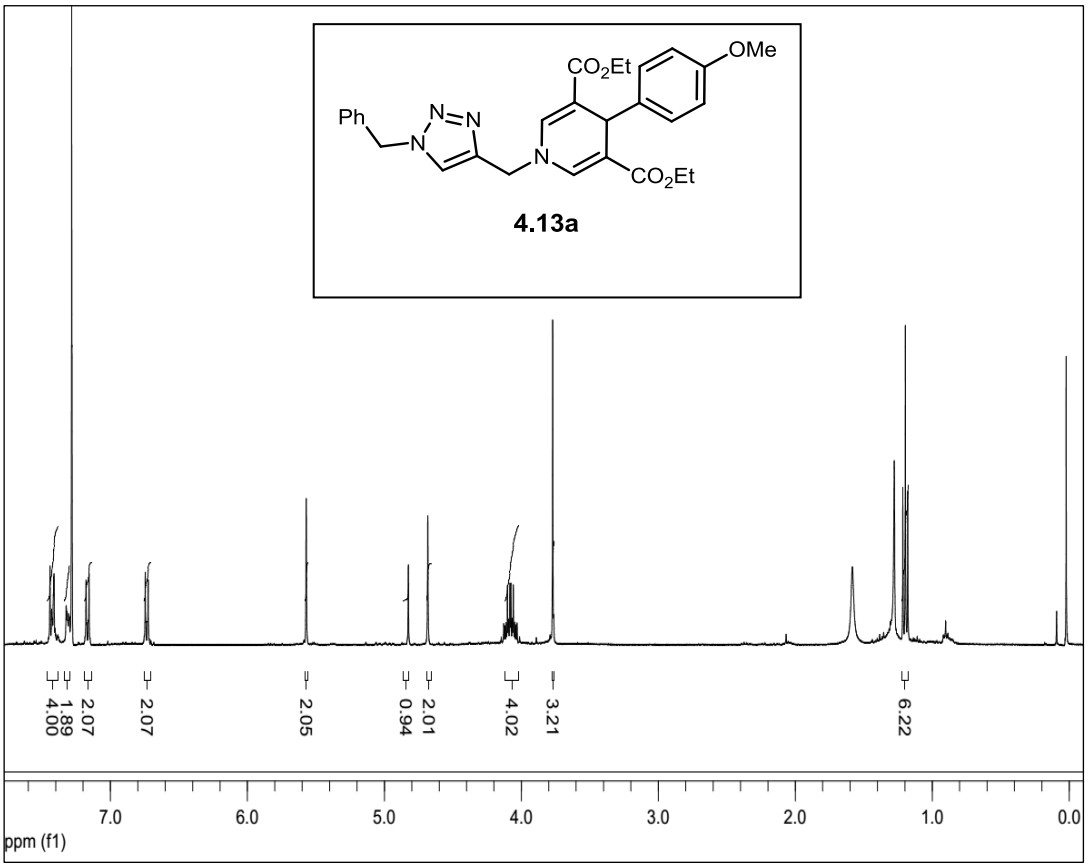

178.03
148.05
145.56
134.75
129.11
128.72
127.91
127.04
123.64
122.32
85.68
77.33
77.01
76.70
72.46
56.49
54.14
45.18
30.30
25.98
4.12a
150
100
50
0
ppm (t1)

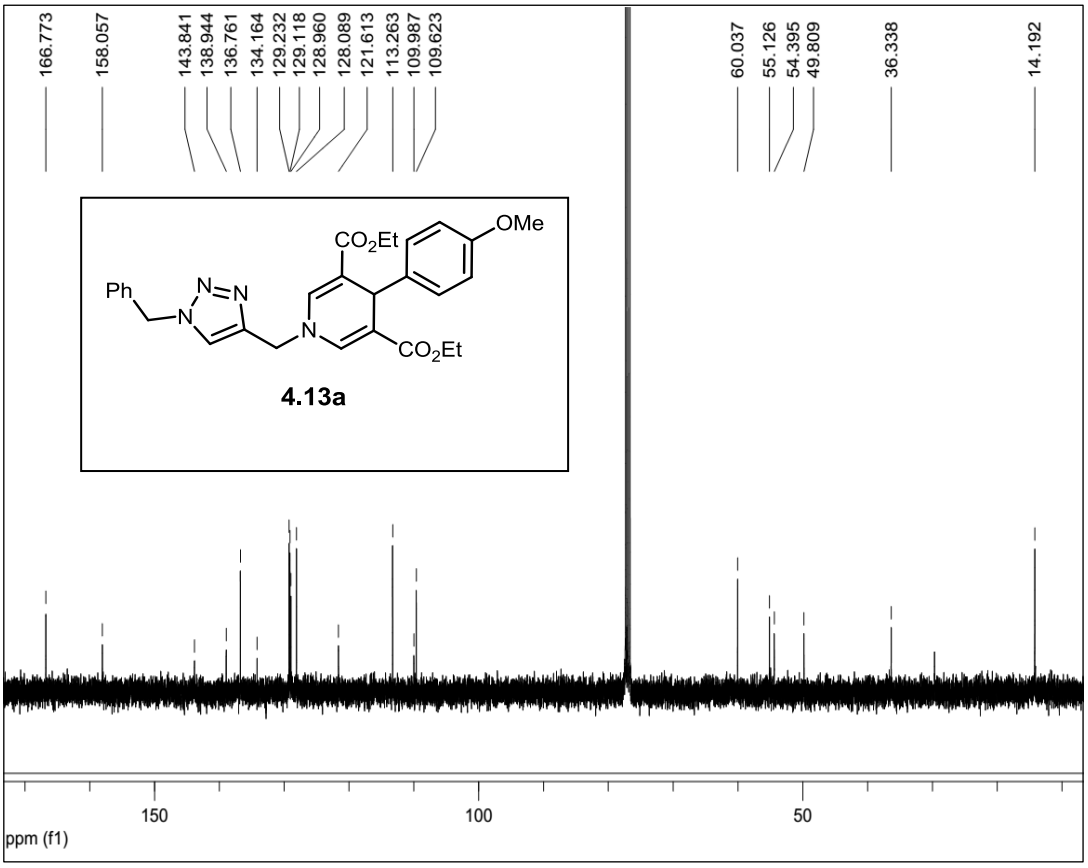

4.12k
OMe
OMe
1.00
3.22
2.00
0.99
0.98
2.01
2.03
5.89
1.08
2.02
1.06
1.09
2.94
1.11
7.0
6.0
5.0
4.0
3.0
2.0
ppm (f1)

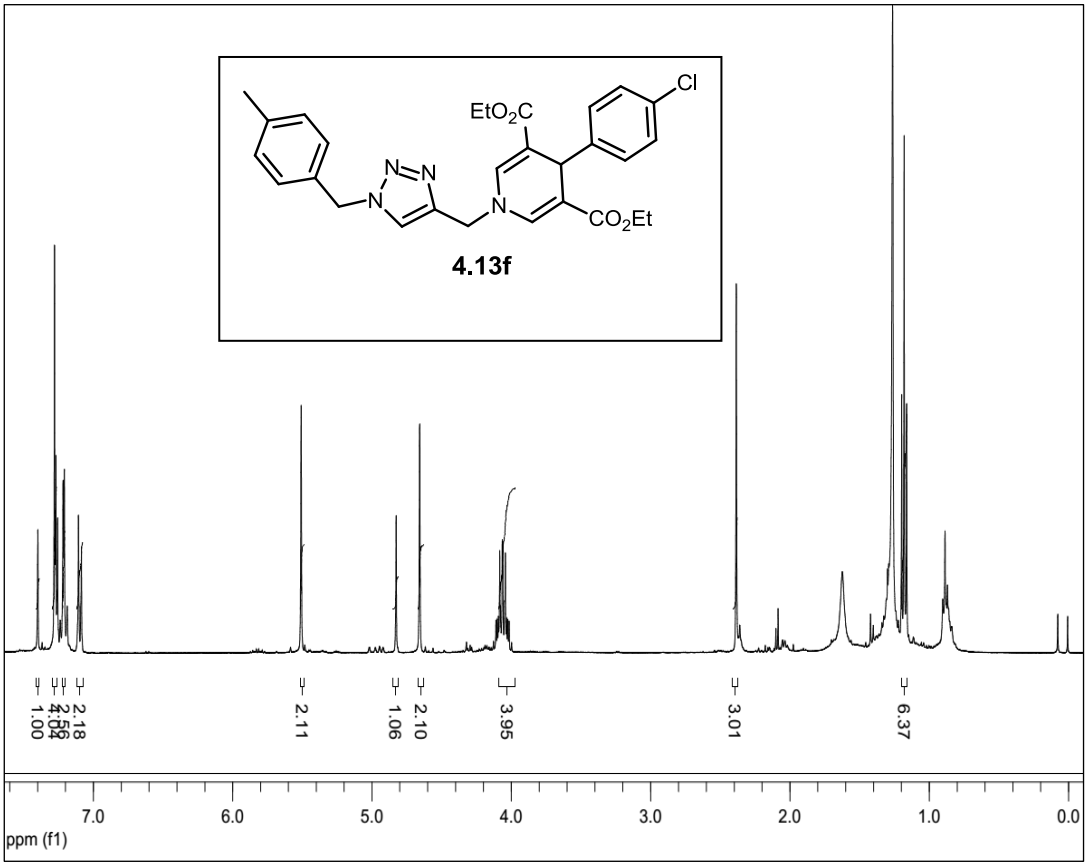

177.559
149.248
149.020
138.632
131.727
131.067
129.747
127.969
118.193
110.833
110.003
109.059
86.584
72.128
56.695
55.931
55.885
53.959
45.406
30.496
26.085
21.140
4.12k
OMe
OMe
150
100
50
ppm (f1)

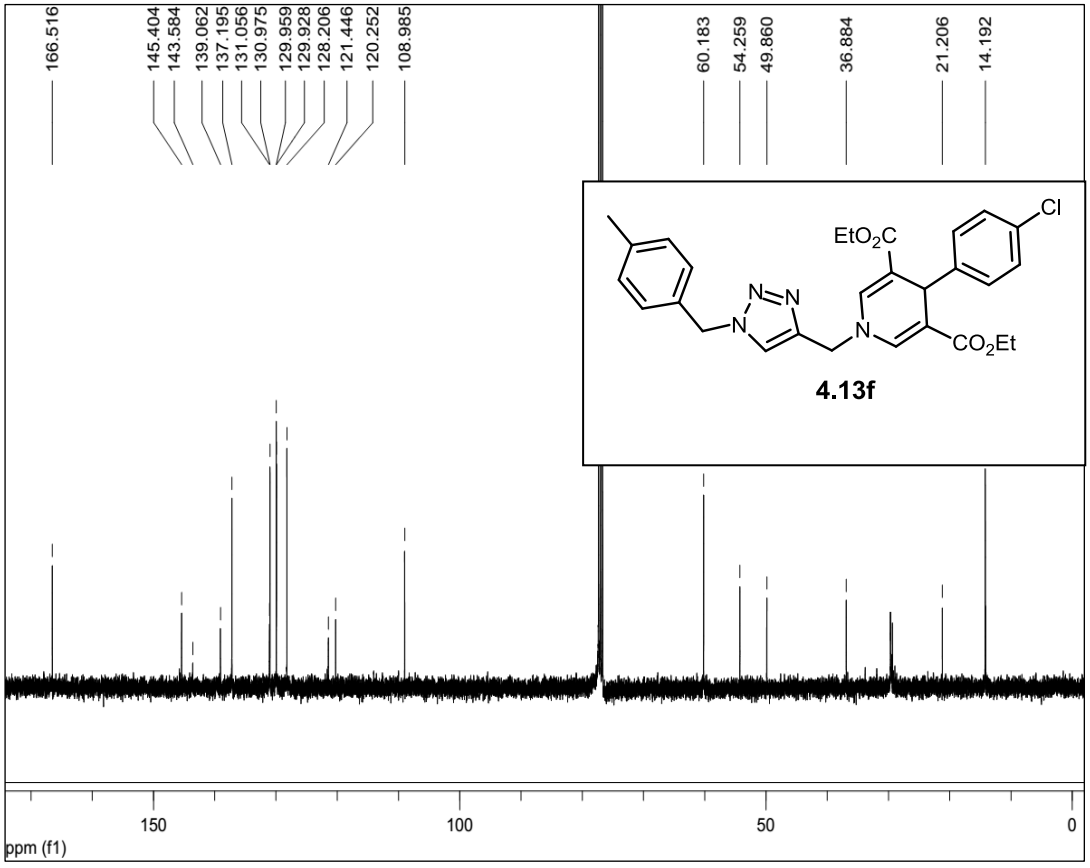

4.12q
NC
Cl
1.00
1.99
4.10
0.98
2.06
2.09
0.97
3.06
1.04
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (f1)

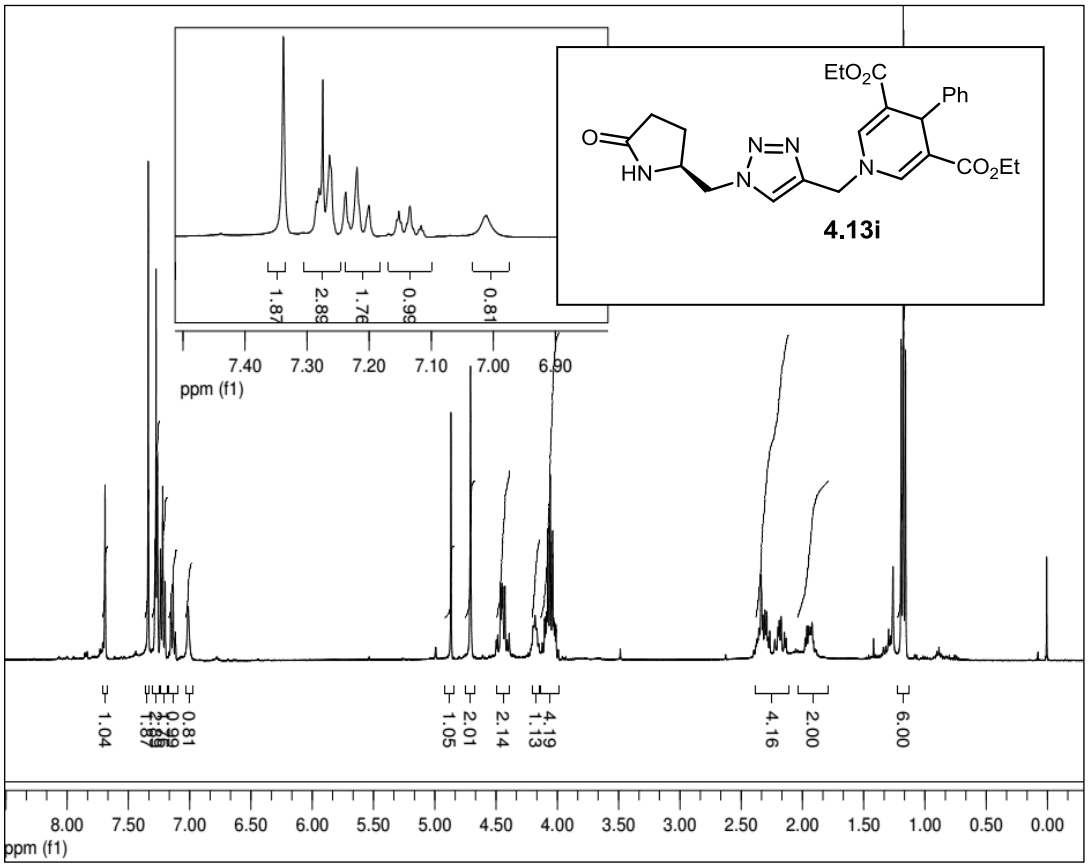

178.707
140.737
139.877
136.837
134.536
132.624
128.248
127.388
118.431
118.127
112.726
112.133
86.076
72.112
56.470
54.012
45.088
30.839
22.689
4.12q
NC
Cl
150
100
50
0
ppm (f1)

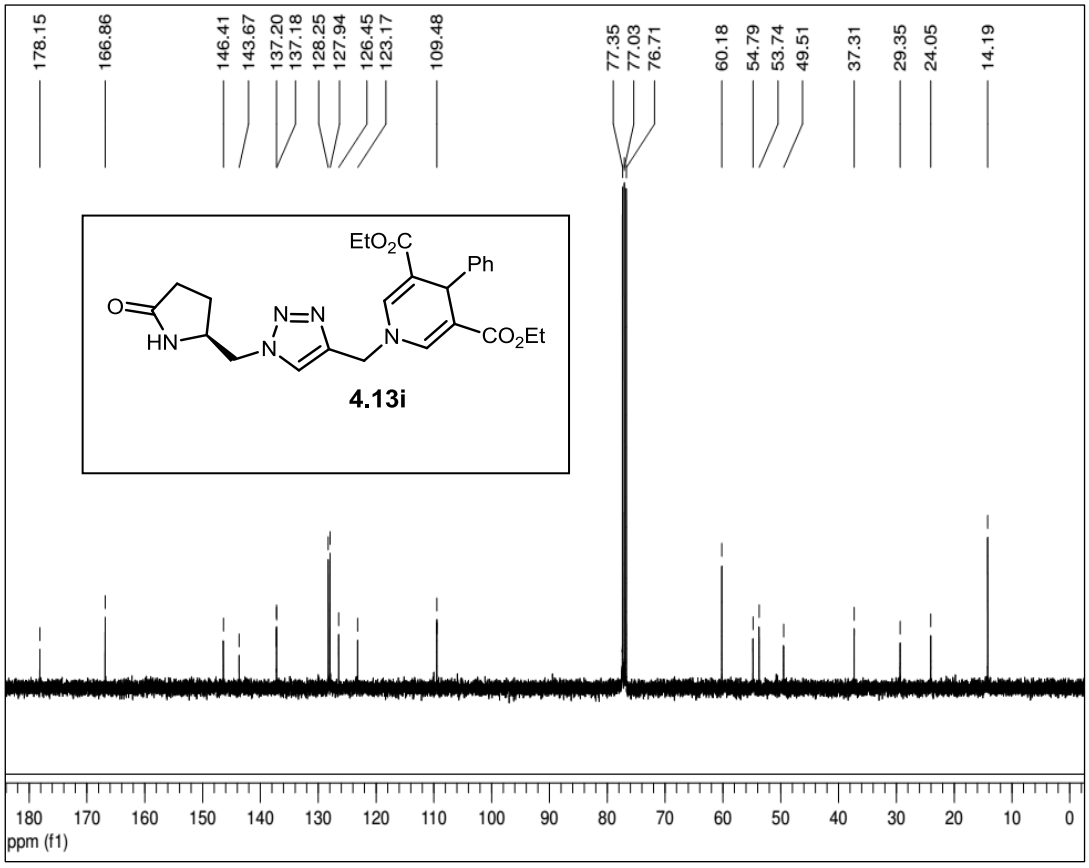

CO2Et
OMe
Ph
N
N
N
N
CO2Et
4.13a
4.00
1.89
2.07
2.07
2.05
0.94
2.01
4.02
3.21
6.22
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


166.773
158.057
143.841
138.944
136.761
134.164
129.232
129.118
128.960
128.089
121.613
113.263
109.987
109.623
60.037
55.126
54.395
49.809
36.338
14.192
CO2Et
OMe
Ph
N
N
N
N
CO2Et
4.13a
150
100
50
ppm (f1)


Cl
EtO2C
CO2Et
4.13f
1.00
4.04
4.56
2.18
2.11
1.06
2.10
3.95
3.01
6.37
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


166.516
145.404
143.584
139.062
137.195
131.056
130.975
129.959
129.928
128.206
121.446
120.252
108.985
60.183
54.259
49.860
36.884
21.206
14.192
Cl
EtO2C
CO2Et
4.13f
150
100
50
0
ppm (f1)


EtO2C
Ph
O
HN
N=N
N
N
CO2Et
4.13i
7.40
7.30
7.20
7.10
7.00
6.90
ppm (f1)
1.04
0.81
1.05
2.01
2.14
1.13
4.16
2.00
9.00
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
ppm (f1)


178.15
166.86
146.41
143.67
137.20
137.18
128.25
127.94
126.45
123.17
109.48
77.35
77.03
76.71
60.18
54.79
53.74
49.51
37.31
29.35
24.05
14.19
EtO2C
Ph
O
HN
N=N
N
N
CO2Et
4.13i
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)

Seminars/Conferences/Workshops Attended:

2014 Participated and presented a poster at the International Conference on Chemical Biology Disease Mechanisms and Therapeutics (ICCB-2014) organized by **IICT-Hyderabad,** on 6-8th Feb-2014.

2013 Participated and presented a poster at the National Conference on Advances in Anti-Cancer Drug Discovery and Development *organized by* the Department of Chemistry, **IIT-Madras,** on 25-26th Oct-2013.

2013 Participated and presented a poster at Dr. Kallam Anji Reddy Memorial *Symposium* on Insulin Resistance and type 2 diabetes: An Indian Epidemic organized by **Dr. Reddy's ILS,** on 21st Sep-2013

2013 Participated in Dr. Reddy's annual conclave journey towards sustainability (Catalyst 2013) organized by **Dr Reddy's Laboratories**, on 9-10th Jan-2013.

2012 Participated and presented a poster at the I*nternational Symposium* (CCBNP-2012) organized by **IICT-Hyderabad,** on **2-4th Aug-2012.**

List of Publications:

1) $ZnBr_2$-Mediated stereoselective synthesis of functionalized pyrrolidinones. **Nallamelli**, **R. V**.; Krishna, I. V.; Chatti. K.; Poondra, R. R.* (Manuscript under preparation).
2) Effect of Bronsted acid in the synthesis of 1,4-dihydropyridine and pyridine derivatives. **Nallamelli**, **R. V**.; Poondra, R. R.* (Manuscript under preparation).
3) (*S*)-Pyroglutamic acid triazole derivatives as AMPK activators. Rajamohan Reddy Poondra; Parimal Misra; **Venkata Ratnam Nallamelli**. *Indian Patent Office*, 1761/CHE/**2015**.
4) Discovery of novel 1,4-dihydropyridine-based PDE4 inhibitors. Poondra, R. R.; **Nallamelli**, **R. V**.; Meda, C. L. T.; Srinivas, B. N. V.; Grover, A.; Muttabathula, J.; Voleti, S. R.; Sridhar, B.; Pal, M.; Parsa, K. V. L. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1104-1109.