Development of New Methods for the Synthesis of Fused-Pyridines and Dihydropyridines

A Thesis

Submitted for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

By

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August 2016

To

My Parents

Naganna & Ashamma

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STATEMENT

I hereby declare that the matter embodied in the thesis is the result of investigation carried out by me in 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 error, is regretted.

Devendram V

Dr. Reddy's Institute of Life Sciences
University of Hyderabad
August 2016

CERTIFICATE

This is to certify that the thesis entitled ***"Development of New Methods for the Synthesis of Fused-Pyridines and Dihydropyridines"*** being submitted by ***Mr. Devendram V*** 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 with that the thesis has reached to the standard fulfilling the requirements of the regulations relating to the nature of the degree.

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(Supervisor)

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Devendram v

Dr. Reddy's Institute of Life Scinecs

August 2016

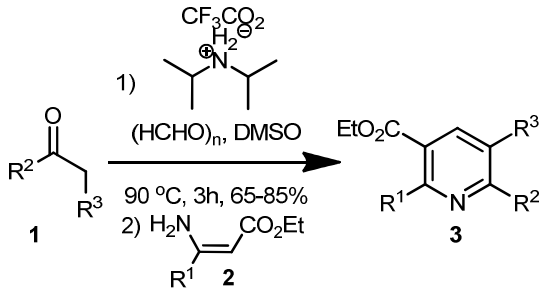
Synopsis

This thesis entitled "Development of New Methods for the Synthesis of Fused-Pyridines and Dihydropyridines" comprises four chapters.

Chapter 1

Salt-mediated oxidative N-annulation for the synthesis of functionalized pyridines

The pyridine moiety is a significant component of various natural products, pharmaceuticals and functional materials. Consequently, the improvement of new synthetic methods for the construction of pyridines is always important. This chapter describes an unprecedented tandem one-pot method for the modular construction of pyridine moieties through the sequential reaction of carbonyl compounds with parafarmaldehyde, ammonium salt reagents (the Mannich reaction) and β-enamino esters. This reaction utilizes commercially available starting materials and operationally simple method for the construction of pyridine ring with controllable substitution patterns. To the best of our knowledge, this new method represents the first use of a parafarmaldehyde and ammonium salts in the construction and derivatization of pyridine (Scheme I). All the compounds synthesized were tested against PDE4B along with a known inhibitor rolipram as a reference compound using an in vitro enzyme assay. Out of 25 synthesized compounds 20 compounds were shown more than 40% of PDE4B inhibitions at 10 μM concentrations.

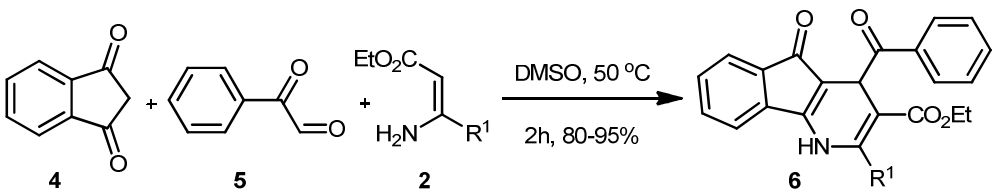


Scheme I Synthesis of substituted pyridines.

Chapter 2

Development of a catalyst-free one-pot domino approach for the synthesis of fused-1,4-dihydropyridines

Multi-component reactions (MCRs) are important in synthesizing small molecule libraries, because of their wide range of applications in the pharmaceutical industry. These reactions allow multi-step syntheses to be conducted in a single-step operation to afford a variety of products. MCRs can dramatically reduce the generation of chemical waste and the costs associated with reactions. In this chapter we describe an efficient synthesis of unsymmetrical fused-1,4-dihydropyridines from 1,3-dicarbonyl compounds, phenylglyoxal and β-enamino esters *via* catalyst free domino strategy. Simple and readily available starting materials, mild reaction conditions, and operational flexibility are advantages of the reaction, which allows a variety of unsymmetrical fused-1,4-dihydropyridines (Scheme II). All the compounds synthesized were tested against PDE4B along with a known inhibitor rolipram as a reference compound using an in vitro enzyme assay. Out of 22 synthesized compounds 15 compounds were shown more than 40% of PDE4B inhibitions at 10 μM concentrations.

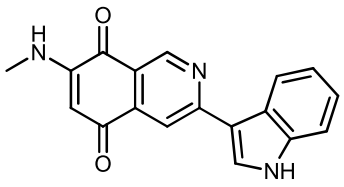


Scheme II Synthesis of fused-dihydropyridines via catalyst-free domino approach.

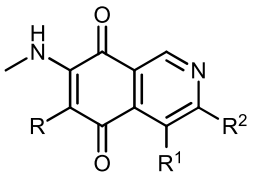
Chapter 3

Novel method for the synthesis of functionalized isoquinolinequinones and its application to the isoquinolinequinone core of Mansouramycin-D

Isoquinoline-5,8-diones have wide range of biological activities such as antitumor, antibacterial, antifungal and antimalarial agents. The isoquinoline-5,8-dione core is an important structural moiety and present in a number of cytotoxic agents, such as Cribrostatins, Renierone and O-demethyl Renierone, and proved their potent cytotoxic activities against the HCT 116 human colon carcinoma cell line with IC_{50} values of 45, 24, and 34 µg/mL respectively. Mansouramycin A-E, a group of isoquinolinequinones were isolated from marine *Streptomyces* spp. in 2009. Mansouramycin D (Fig. 1) showed significant *in vitro* tumor cell selectivity towards ten of the 36 tested tumor cell lines of bladder cancer, glioblastoma, lung cancer, mammary cancer, melanoma, ovarian cancer, renal cancer, and uterus cancer. The antitumor potency of the Mansouramycin molecules differed according to their substitution pattern, variation of the C-8 or C-7 position of the isoquinolinequinone, respectively, strongly influenced cytotoxicity.



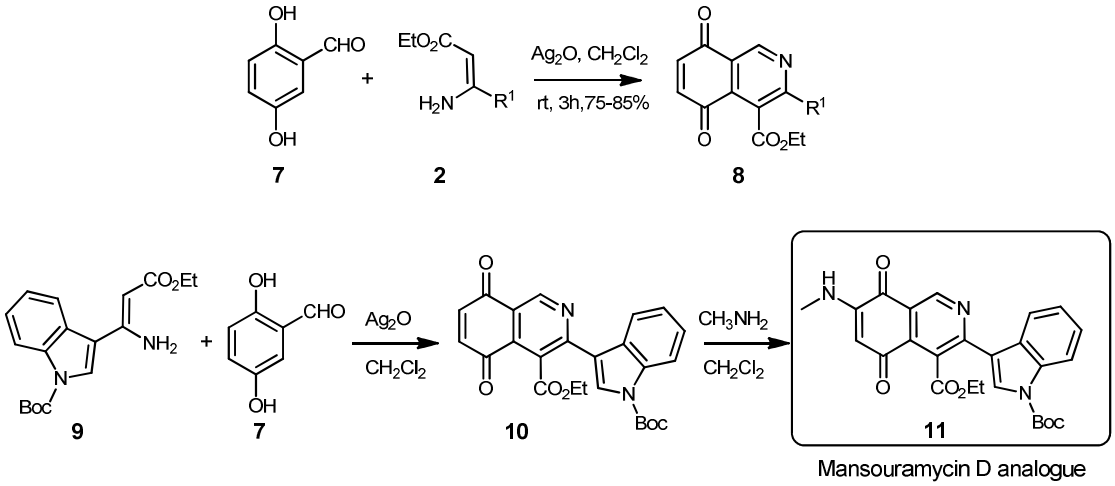
Mansouramycin D



Mansouramycin A. R= H, R^1= CH3, R^2= CH_3
Mansouramycin B. R= Cl, R^1= H, R^2= CH_3
Mansouramycin C. R= H, R^1=H, R^2= COOCH3
Mansouramycin E. R= H, R^1=H, R^2= CH_3

Figure 1. The Mansouramycin family of cytotoxic isoquinolinequinones.

This chapter describes Ag_2O-mediated domino oxidative annulation reaction of 2,5-dihydroxy benzaldehyde **7** and wide range of β-enamino esters **2** to deliver novel 3,4-substituted isoquinoline-5,8-diones **8** with high yield, under mild conditions**.** To further demonstrate the utility of this method, a synthetic approach to the synthesis of Mansouramycin-D analogues was developed (scheme III). The biological evaluation of all these molecules and intermediates obtain in this project is under progress.



Scheme III Synthesis of Mansouramycin D analogue.

Chapter 4

Synthesis of racemic Moxifloxacin intermediate *via* Aza Diels-Alder reaction

Moxifloxacin (Fig. 2) is a broad-spectrum fluoroquinolone antibacterial agent used for treating respiratory infections such as pneumonia, chronic sinusitis, and chronic bronchitis. The market demand of this antibiotic is increasing every year, and developing better and greener technologies for its synthesis is advantageous over current processes. (S,S)-2,8-Diazobicyclo [4.3.0] nonane is a key chiral intermediate of Moxifloxacin, the presence of an azabicyclo group in position 7 improves the activity against Gram-positive bacteria and also brings a marked lipophilicity and half-lives of more than 10h.

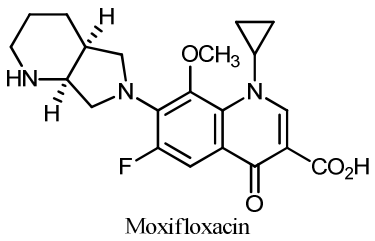
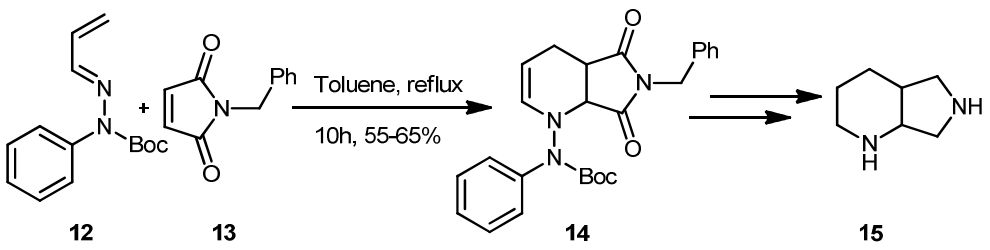


Figure 2. Moxifloxacin

In this chapter we disclose the synthesis of functionalized tetrahydropyridines **14** using 1-Aza Diels-Alder reaction between α,β-unsaturated hydrazone **12** and *N*-benzyl maleimides **13**. Here, the key precursor (*E*)-tert-butyl 2-allylidene-1-phenylhydrazinecarboxylate (diene) **12** was prepared from acrolein, tert-butyl 1-phenylhydrazinecarboxylate and N-benzyl maleimides (dienophile) **13** were prepared

using modified simple reaction procedures. This method provides an effective, general strategy to access valuable Moxifloxacin intermediate i.e 2,8-Diazobicyclo [4.3.0] nonane in large quantities.



Scheme IV Synthesis of Moxifloxacin intermediate

List of Abbreviations

°C	:	degrees Celsius
^{13}C NMR	:	carbon- 13 nuclear magnetic resonance spectroscopy
^{1}H NMR	:	hydrogen- 1 nuclear magnetic resonance spectroscopy
Ac	:	acetyl
Ag_2o	:	Silver oxide
Ar	:	aryl
Aq	:	aqueous
Bn	:	benzyl
Boc	:	tert-butoxycarbonyl
BQ	:	1,4-benzoquinone
BRSM	:	based on recovered starting material
Bu	:	butyl
Bz	:	benzoyl
Calcd	:	calculated
cm^{-1}	:	reciprocal centimeter
CuI	:	copper iodide
Cs_2CO_3	:	cesium carbonate
d	:	doublet
d.r. (dr)	:	diastereomeric ratio
DCM	:	dichloromethane
DIPEA	:	diisopropylethylamine
DMAP	:	4-(dimethylamino)pyridine
DMF	:	N,N-dimethylformamide
DMP	:	Dess-Martin periodinane
DMSO	:	dimethylsulfoxide

Et	:	ethyl
Hz	:	hertz
IBX	:	*o*-iodoxybenzoic acid
IC_{50}	:	inhibitory concentration 50%
g	:	gram
Imid	:	imidazole
J	:	coupling constant in Hertz
K_2CO_3	:	Potsium carbonate
m	:	multiplet
mg	:	milligram
M.S.	:	mass spectrometry
Me	:	methyl
mL	:	milliliter
mmol	:	millimole
Na_2SO_4	:	Sodium sulphate
$NaHCO_3$	:	Sodium bicarbonate
Ph	:	phenyl
Py	:	pyridine
R_f	:	retention factor
rt	:	room temperature
s	:	singlet
t	:	triptet
TBS	:	*tert*-butyl-dimethyl silyl
TEA	:	triethylamine
THF	:	tetrahydrofuran
TMS	:	trimethyl silyl
δ	:	chemical shift in parts per million

CHAPTER 1

SALT-MEDIATED OXIDATIVE N-ANNULATION FOR DIVERSE AND POLY FUNCTIONALIZED PYRIDINES

1.1. Introduction

The substituted pyridine nucleus is a structural component of a huge number of biologically active natural and unnatural compounds. The synthesis and functionalization of pyridines has been the object of research for over the last 100 years.[1] Representative molecules bearing the pyridine skeleton are shown in (Fig. 1.1).

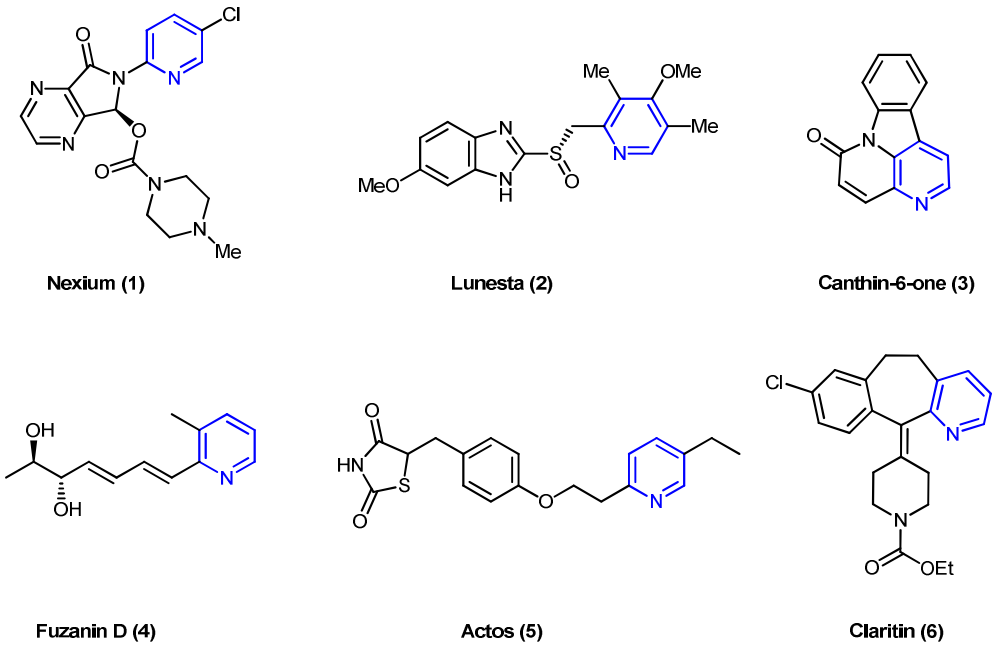


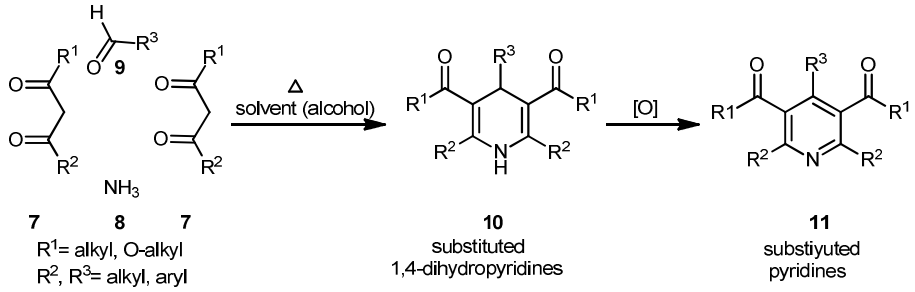
Figure 1. 1. Representative examples of pyridine derivatives

The pyridine core containing drug molecules are very common such as nexium (**1**) (esomeprazole), a novel orally active agent that commonly used to treat acid reflux.[2] Similarly, lunesta (**2**) (eszopiclone) a drug is used to treat insomnia.[3] Canthin-6-one (**3**) is an antibacterial natural product isolated from the roots of *Eurycoma harmandiana* by Haynes in 1952.[4] Fuzanin D (**4**) is a cytotoxic natural compound isolated from the cultural supernatant of *kitasatospora* sp. IFM10917. Fuzanin D showed cytotoxicity against DLD-1 cells (IC_{50} ~ 40 μM) and moderate inhibition of Wnt signal transcription at 25 mM.[5] Actos (**5**) (pioglitazone), is commonly used to treat type II diabetes by selectively stimulates the (PPARγ) nuclear receptor and it is also used decrease the level of triglycerides and increase that of high density lipoproteins (HDL) without changing low-density lipoproteins (LDL).[6] Claritin (**6**) (loratadine) a novel orally active agent and its metabolite desloratadine, which is

largely responsible for the antihistaminergic effects.[7] As a result, there is considerable interest among synthetic chemists to develop several routes for the synthesis of pyridine derivatives. This chapter covers the previous information and our methodology to the substituted pyridine derivatives starting from readily available α-methyl carbonyl compound and β-enamino esters or its analogues.

1.1.1 Precedents on metal free synthesis of substituted pyridines

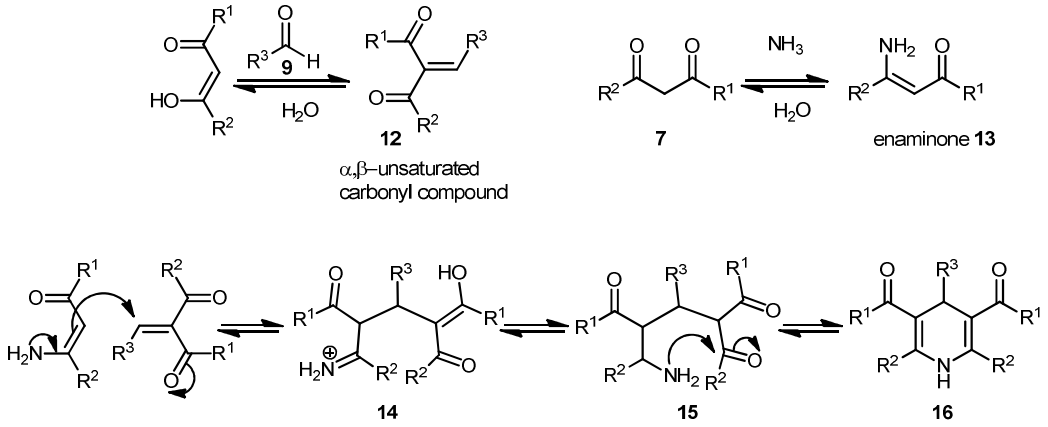
In 1882, Hantzsch reported first synthesis of symmetrical dihydropyridine (Scheme 1.1) by condensing two moles of ethyl acetoacetate with one mole of aldehyde and source of ammonia, and these 1,4 dihydropyridine products are spontaneously oxidized to corresponding substituted pyridines.[8] In the case of stable dihydropyridines, external oxidizing agent [e.g., HNO3, HNO_2, $(NH_4)_2Ce(NO_3)_6$, $Cu(NO_3)_2$, MnO_2] is essential.[9] Unsymmetrical dihydropyridines can be synthesized by using modified methods like 1) α,β-unsaturated carbonyl compound (alkylidene), derived by condensation of one equivalent of β-keto ester with an aldehyde, treating with β-keto ester and a nitrogen source. 2) An α,β-unsaturated carbonyl compound (prepared from the condensation of active methylene compound and aldehyde) is condensed with enamine;[10] (prepared from condensation of ammonia with β-keto ester) and 3) Reaction of substituted 1,5-dicarbonyl compound with a nitrogen source (usually ammonium acetate/acetic acid).[11]



Scheme 1.1 Hantzsch pyridine synthesis.

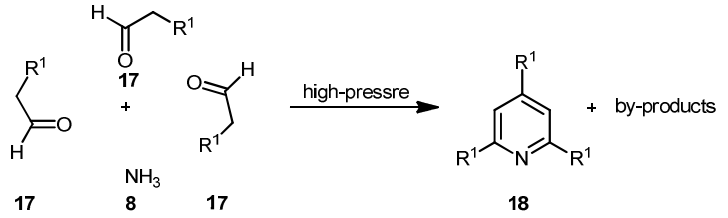
The initial steps of the reaction involve a Knoevenagel condensation of the 1,3-dicarbonyl compound **7** with an aldehyde **9** to give compound **12** and a condensation of ammonia with another equivalent of 1,3-dicarbonyl compound to give on enaminone **13**. The rate determine step is the Michael addition of the enaminone to the α,β-unsaturated carbonyl compound. Subsequently the addition product **14**

undergoes an intramolecular condensation of the amino group and carbonyl group to afford the desired substituted 1,4-dihydropyridine **16** (Scheme 1.2).



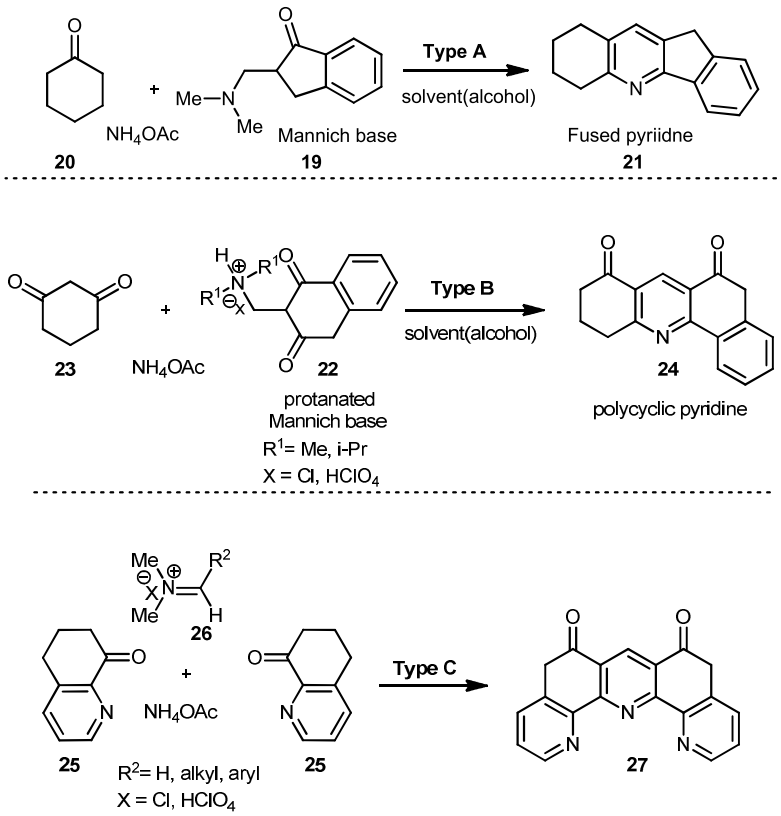
Scheme 1.2 Mechanism of Hantzsch pyridine reaction.

In 1906, Chichibabin has reported pseudo- four component pyridine synthesis from three moles of an enolizable aldehyde **17** treating with one mole of ammonia **8** (Scheme 1.3).[12] The original reaction was done in high-pressure conditions, resulting in the formation of 2,4,6 tri substituted pyridine **18** along with numerous byproducts.



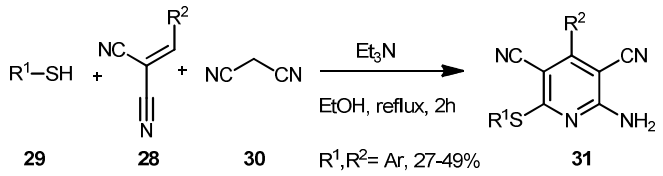
Scheme 1.3 Chichibabin pseudo- four component pyridine synthesis.

In 1990s Risch and co-workers have reported this reaction to the synthesis of pyridines. This methodology was particularly modified to the synthesis of fused pyridines. The approach developed by this group can be divided in three types of reactions (A−C) depending on the substrates used (Scheme 1.4). 1) In type A method previously prepared Mannich base **19** substrate treated with cyclohexanone **20**,[13] 2) In type B method protanated forms of Mannich base substrate **22** treated with 1,3cyclohexanedione **23**,[14] 3) Finally type C method two moles of dihydroquinolinone **25** treated with iminium salt **26**.[15] In all cases, ammonium acetate proved to be the ammonia source of choice.



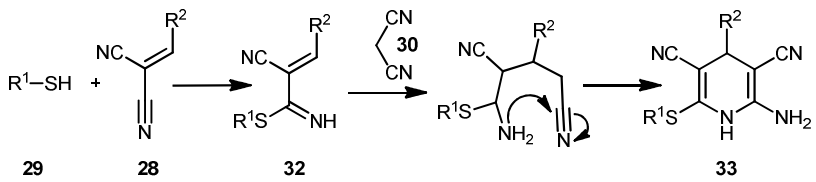
Scheme 1.4 Synthesis of fused pyridines.

In 1981, Kambe and Saito reported a one step synthesis of penta-substituted pyridines using an arylidene malononitrile **28,** a thiol **29**, and malononitrile **30** in presence of catalytic Et_3N, in ethanol (Scheme 1.5).[16]



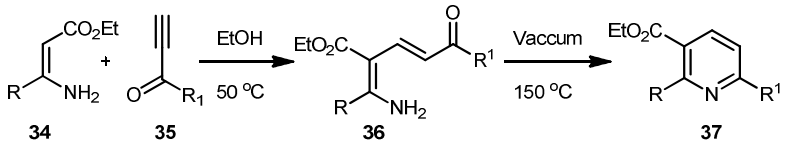
Scheme 1.5 One-step synthesis of substituted pyridines.

The product formation can be explained by nucleophilic addition of thiol **29** to nitrile function of the arylidene malononitrile **28** to give an intermediate **32** that can be under went Michael addition with malononitrile **30** leading to the corresponding 1,4 dihydropyridine **33** after cyclization (Scheme 1.6).



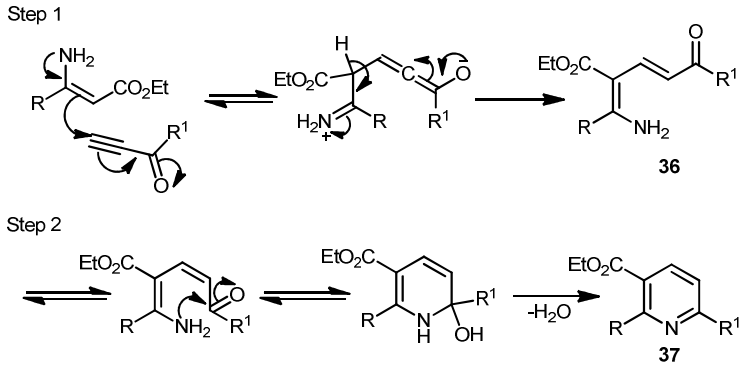
Scheme 1.6 Mechanism of substituted pyridine synthesis.

Bohlmann and Rahtz have developed two step synthesis for trisubstituted pyridines by the reaction of enamine **34** and ethynyl ketone or aldehyde **35** (Scheme 1.7).[17]



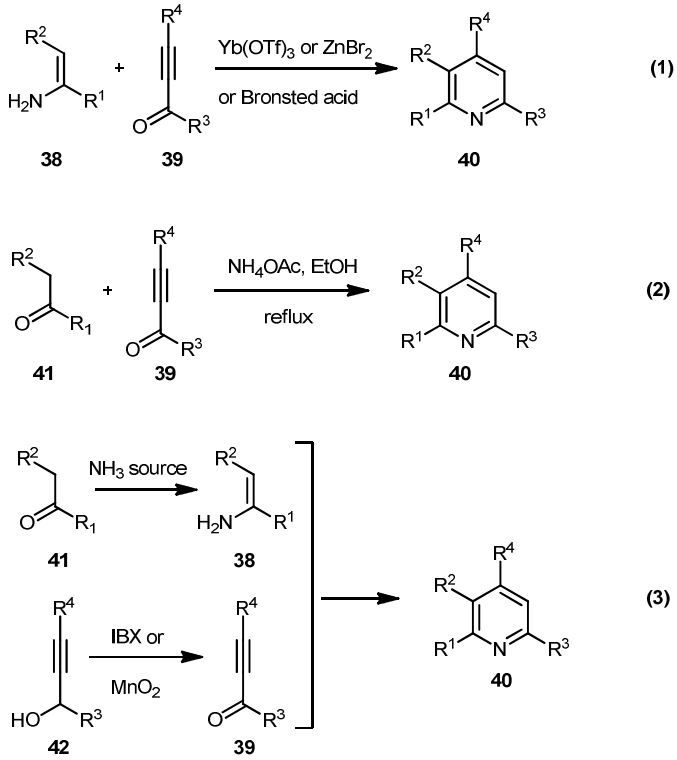
Scheme 1.7 Bohlmann and Rahtz synthesis of pyridines.

The product formation can be explained by Michael addition of enamine **34** to unsaturated ketone or aldehyde **35** to form an intermediate **36** that can be isolated and purified in high yield (Scheme 1.8). Intermediate **36** is kinetically stable and didnot undergo annulation to give products the E-geometry of the enone. However, E/Z isomerisation could be achieved by heating intermediate **36** to high temperature (120-170 ^{o}C) leading to spontaneous cyclodehydration to give 2,3,6-trisubstituted pyridine **37**.



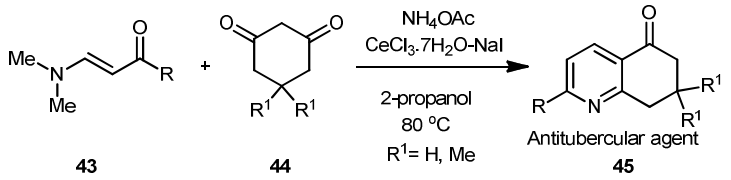
Scheme 1.8 Mechanism of Bohlmann and Rahtz pyridine synthesis.

Bagley and his group have pioneered this reaction for a convenient one-pot method to substituted pyridines (Scheme 1.9).[18] They have achieved a one-pot synthesis of pyridines using Bronsted or Lewis acid promoted conjugate addition followed by double-bond isomerization of aminodiene to give intermediate which undergoes spontaneous cyclodehydration to pyridine (eq. 1). The presence of an acid also enabled the reaction to proceed at a lower temperature, which is substantial improvement over existing methods by involving three component reaction between 1,3-dicarbonyl compound, alkynones and ammonium acetate (eq. 2 of Scheme 1.9). They further improved the method by introducing domino approaches to this reaction *via* in situ preparation of enamines or alkynones (eq. 3).



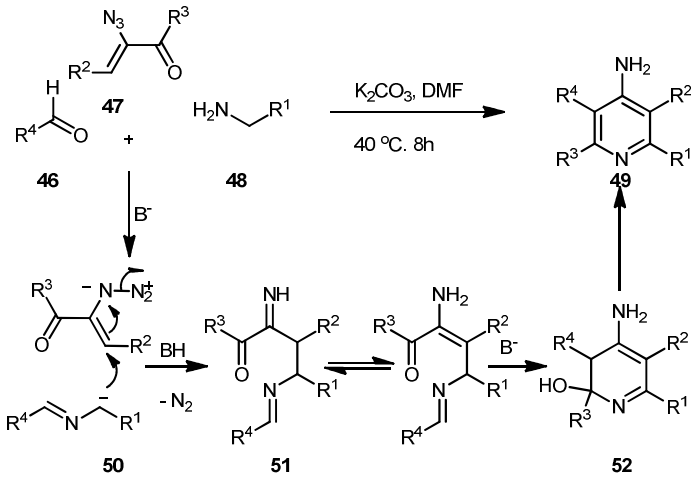
Scheme 1.9 Bronsted or Lewis acid mediated one-pot synthesis of substituted pyridines.

In 2011, Kantaveri and co-workers developed a variant Bohlmann-Rahtz reaction to substituted pyridine synthesis of potent antitubercular agent **45** (Scheme 1.10).[19] By treating of β-N,N-dimethyl vinyl ketone **43**, with 1,3-di carbonyl compound **44** and ammonium acetate in the presence of catalytic $CeCl_3.7H_2O$-NaI, in isopropanol .



Scheme 1.10 Synthesis of antitubercular agent.

In 2012, Shao et al. reported a base catalyzed three component reaction to synthesize the four amino pyridine (Scheme 1.11).[20] Initial steps of the reaction involve an imine **50** formation from amine **48** and aldehyde or ketone **46**. Base promoted 1,4-addition of this imine **50** onto the α-azidovinylketone **47** followed by elimination of molecular nitrogen to form bis-imine intermediate **51**. Equilibration toward the enamino-imine followed by base promoted cyclization and dehydration to give a penta-substituted pyridine.



Scheme 1.11 Base mediated one-pot synthesis of substituted pyridines.

A part from the few known methods for pyridine synthesis most of the methodologies often suffer from drawbacks like longer route, lower yield etc, thus the synthesis of substituted pyridines offers challenges to design and develop simple and efficient strategies. Since the multiple transformations occur under the same conditions in a one-pot, domino, cascade processes avoids the isolation of intermediates and further purification steps. Evidently cascade reactions provide suitable solutions an increase the efficiency of synthetic methods.[21]

1.2 Present Work

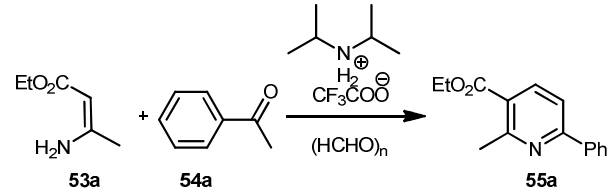
Though several methods have been reported in literature for the synthesis of substituted pyridines, however diversity-oriented synthetic approach for the quick generation of a library of molecules around this class is always desirable. Here, we describe an unprecedented tandem one-pot method for the modular construction of pyridine moieties through the sequential reaction of carbonyl compounds with parafarmaldehyde, ammonium salt reagents (Mannich reaction) and β-enamino esters. This reaction utilizes commercially available starting materials and operationally simple method for the construction of pyridine ring with controllable substitution patterns. To the best of our knowledge, this new method represents the first use of a parafarmaldehyde and ammonium salts in the construction and derivatization of pyridine.

1.3 Results & Discussion

1.3.1. Initial results and optimization of the reaction condition

Ammonium salt (Diisopropylammonium trifluoroacetate), a mild reagent,[22] have found few applications in organic synthesis and was chosen as an oxidizing agent in our study.

Table 1.1. Optimization of reaction conditions



Entry	Solvent	Temp (^oC)	Time (h)	Yield[b] (%)
1	CH_2Cl_2	30	24	-
2	EtOAc	77	24	10
3	THF	66	24	25
4	CH_3CN	80	6	30
5	DMF	100	6	50
6	DMSO	90	3	80
7	DMSO	90	3	0[c]
8	DMSO	90	3	40[d]
9	DMSO	90	3	70[e]
10	DMSO	100	3	75

[a] All reactions were performed using the β-enamino ester **53a** (0.5 mmol), α-methyl carbonyl compound **54a** (0.5 mmol), parafarmaldehyde (1.0 equiv.) and ammoniumsalt (1.2 equiv.) in DMSO (3.0 mL) under open air. [b] Isolated yields. [c] The reaction was performed in the absence of ammonium salt. [d] 0.5 equiv.of ammonium salt. [e] 1.2 equiv. of α-methyl carbonyl compound was used.

In an initial attempt, the reaction of Acetophenone (1.0 equiv.) **54a**, paraformaldehyde (1.0 equiv.) was performed in dichloromethane in the presence of

diisopropylammonium trifluoroacetate salt (1.0 equiv.) at reflux temperature. After two hours another starting material (Z)-ethyl 3-amino-3-methylacrylate (1.0 equiv.) **53a** was added to the reaction mixture as monitored by TLC the reaction could not proceed and a desire compound was not formed though the starting material acetophenone was not consumed after 24h. After assessing various reaction conditions like different solvents and different temperatures (Table 1.1) the best result was achieved by performing the reaction using acetophenone **54a** (0.5 mmol), parafarmaldehyde (0.5 mmol) and ammonium salt (0.6 mmol) in DMSO (3.0 mL) at 90 °C for 1h. Then allowed after that cool it to room temp and added another starting material β-methyl enamino ester **53a** to the reaction mixture and heated at 90 °C for further 2h. The desired ethyl 2-methyl 6-phenylnicotinate (**55a**) was obtained in good yield (entry 6, Table1.1). The reaction did not proceed in the absence of Ammonium salt indicating the key role played by the oxidant (entry 7, Table1.1). The use of lower quantity of ammonium salt (entry 8, Table1.1) or carbonyl compound **54a** (entry 9, Table1.1) decreased the product yield where as enhance in reaction temperature to 100 °C did not improve the yield of **55a** (entry 10, Table1.1).

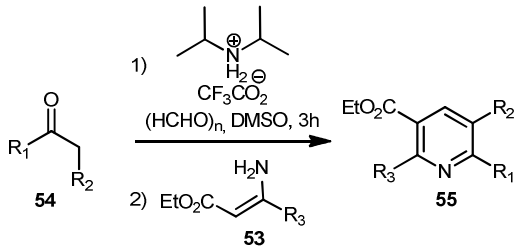
1.3.2. Scope of the reaction

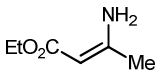
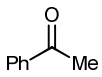
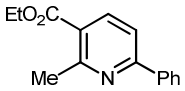
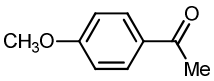
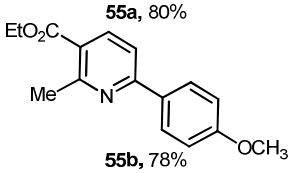
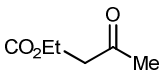
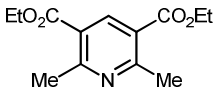
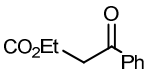
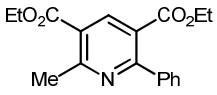
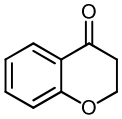
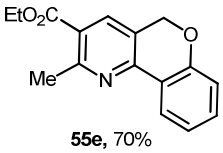
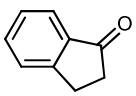
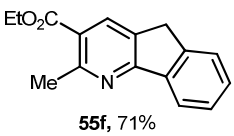
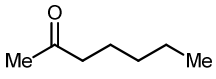
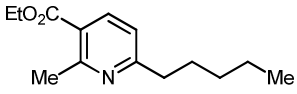
With the optimized reaction conditions in hand we then examined the scope and generality of this method. Thus a range of carbonyl compound (containing aryl/hetero aryl/cinnamyl/aliphatic groups) was reacted with paraformaldehyde, β-enamino ester in the presence of diisopropylammonium trifluoroacetate salt to give various 2,6-disubstituted nicotinic acid derivatives (Table 1.2). All these reactions were performed at 90 °C (entries 1-6, and 23-25, Table 1.2) except for two cases (entry 7, and 8, Table 1.2). Since these reactions do not require the use of any inert (or) anhydrous atmosphere they were performed under open air. Notably, all these derivatives synthesized (**55f, 55j, 55k** Table 1.2) can be converted to azaflurenones in a single step.[23] Azaflurenone, a common skeleton in many natural products and useful agents in medicinal chemistry, are generally accessed *via* multistep sequences using metal-mediated reaction.[24]

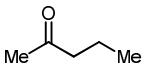
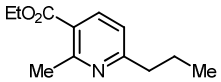
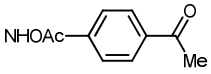
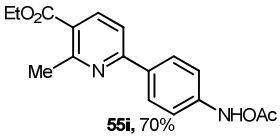
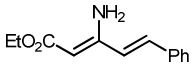
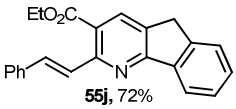
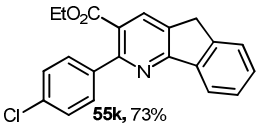
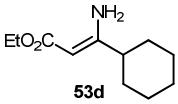
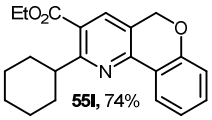
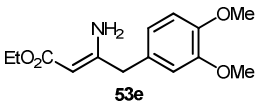
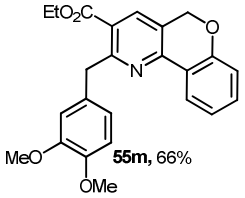
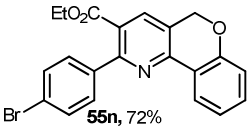
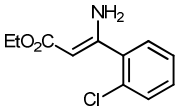
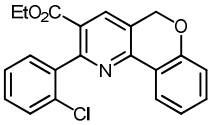
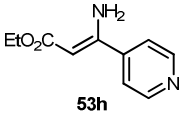
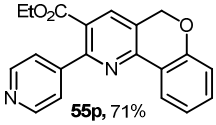
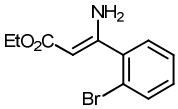
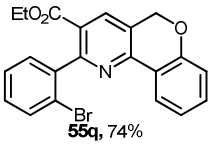
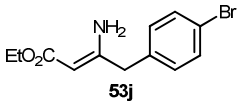
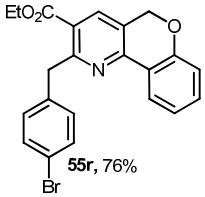
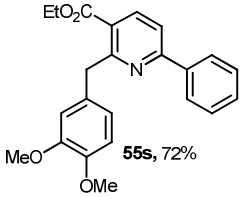
To expand the scope of this reaction we further examined the use of substituted β-enamino ester. Thus various β-enamino esters (containing aromatic/hetero aromatic/cinnamyl/aliphatic groups) were reacted with benzo-fused cyclic carbonyl

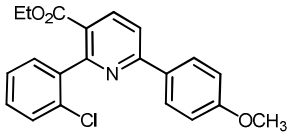
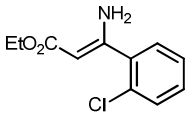
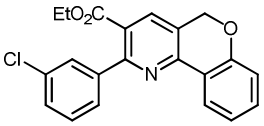
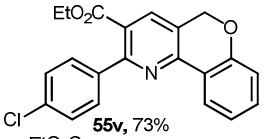
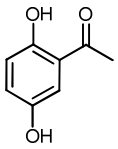
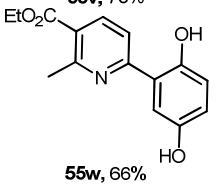
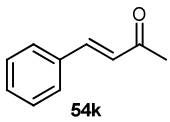
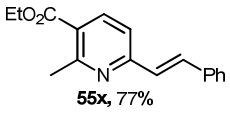
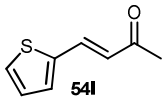
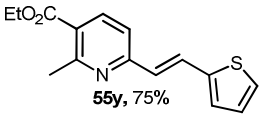
compound (4-chromonone, 1-indanone), paraformaldehyde in the presence of diisopropylammonium trifluoroacetate salt to give the corresponding fused-pyridines in good yields (entries 5, 6, 21, 22 and entries 10-19). And seemed to have advantages over the traditional Hantzsch pyridine synthesis.[8,25] However, the methodology was not successful in the preparation of 4-substituted pyridines from the corresponding carbonyl compound which appeared to be the limitation of this methodology.

Table 1.2. Synthesis of substituted pyridines [a]



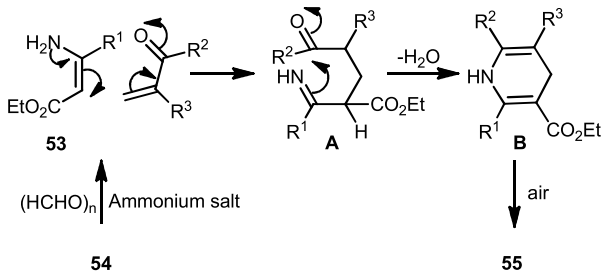
Entry	Enamine	Carbonyl Compound	Product
1	 **53a**	 **54a**	 **55a,** 80%
2	**53a**	 **54b**	 **55b,** 78%
3	**53a**	 **54c**	 **55c,** 73%
4	**53a**	 **54d**	 **55d,** 76%
5	**53a**	 **54e**	 **55e,** 70%
6	**53a**	 **54f**	 **55f,** 71%
7	**53a**	 **54g**	 **55g, 71%**

8	**53a**	 **54h**	 **55h,** 73%
9	**53a**	 **54i**	 **55i,** 70%
10	 **53b**	**54f**	 **55j,** 72%
11	 **53c**	**54f**	 **55k,** 73%
12	 **53d**	**54e**	 **55l,** 74%
13	 **53e**	**54e**	 **55m,** 66%
14	 **53f**	**54e**	 **55n,** 72%
15	 **53g**	**54e**	 **55o,** 74%
16	 **53h**	**54e**	 **55p,** 71%
17	 **54i**	**54e**	 **55q,** 74%
18	 **53j**	**54e**	 **55r,** 76%
19	**53e**	**54a**	 **55s,** 72%

20	**53g**	**54b**	 **55t,** 79%
21	 **53k**	**54e**	 **55u,** 73%
22	**53c**	**54e**	 **55v,** 73%
23	**53a**	 **54j**	 **55w,** 66%
24	**53a**	 **54k**	 **55x,** 77%
25	**53a**	 **54l**	 **55y,** 75%

[a] All reactions were performed using the β-enamino ester **53a** (0.5 mmol), α-methyl carbonyl compound **54a** (0.5 mmol), parafarmaldehyde (0.5 mmol) and ammoniumsalt (0.6 mmol) in DMSO (3.0 mL) under open air. [b] Isolated yields.

These results indicated that this reaction is quite general and has very broad substrate scopes. The Polysubstituted pyridines **55a** to **55y** were fully characterized by ^{1}H NMR, ^{13}C NMR and MS spectra. In ^{1}H NMR spectra the proton at the 4-position of pyridine appears at 8.35 ppm it should be pointed out that all ^{1}H NMR spectra. The formation of the compound **55** can be explained by the reaction sequence in (scheme 1.12).



Scheme 1.12 proposed mechanism

Mechanistically, the reaction seems to proceed (scheme 1.12) *via* (i) ammonium salt mediated conversion of the carbonyl compound (**54**) to corresponding α, β un saturated carbonyl compound which up on (ii) Michael addition with β-enamino ester (**53**) followed by (iii) intra molecular cyclization gives **B** that (iv) aromatizes to **55** in the presence of air.

1.4. Pharmacology

Phosphodiesterase (PDEs) are enzymes that regulate the cellular levels of second messengers like cAMP and cGMP, by controlling their rates of degradation. Among these phosphodiesterases, PDE4 is a cAMP specific PDE present in majority of inflammatory cells. Elevated levels of cAMP trigger a variety of functional response such as suppression of inflammatory mediators which is beneficial in treating inflammatory diseases especially pulmonary diseases including asthma and COPD. A number of PDE4 inhibitors are under development with a wide variety of scaffolds. Some of the new chemical entities containing pyridine ring such as Piclamilast and Roflumilast showed good inhibition of PDE4 (Figure 1.2). As pyridine nucleus fused another heterocycle has found wide application in the design and discovery of novel bioactive molecules and drugs, we focused on chromeno[4,3-b]pyridine, indeno[1,2-b]pyridine scaffolds to explore the potential towards the inhibition of PDE4.

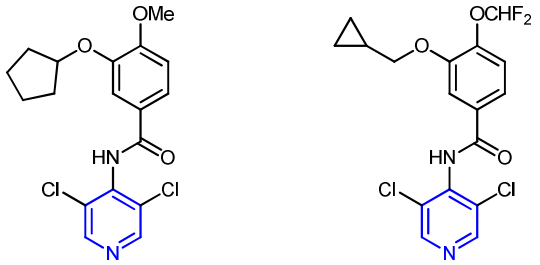


Figure 1.2. Structures of Piclamilast (**a**) and Roflumilast (**b**) compounds.

1.4.1. *In vitro* data

Here, we examined the potential of the previously unexplored pyridine scaffold in developing PDE4B inhibitors. During our investigation to find the potent PDE4B inhibitor, all the compounds synthesized were tested against PDE4B along with a known inhibitor rolipram as a reference compound using an in vitro enzyme assay.[27] some of the compounds were showed good inhibition activity at 10 μM and **55f** being

the best among them. Pyridines, which have shown more than 40% of inhibitions against PDE4B at 10 µM concentrations, are listed in the (Table 1.3.).

Table 1.3. PDE4B inhibition with pyridines.

Entry	Compound 55	% of PDE4B inhibition[a]
1	55a	80.43
2	55b	60.65
3	55f	88.10
4	55i	63.29
5	55j	62.76
6	55k	46.79
7	55l	49.73
8	55m	68.46
9	55o	45.50
10	55q	40.43
11	55r	68.46
12	55s	73.29
13	55v	60.31
14	55w	48.96
15	55x	48.06

[a] All the compounds were tested at a 10µM concentration

In further, the most potent compound **55f** was evaluated for dose response studies shown in Figure 1.3. and their IC_{50} value 1.782µM is noted

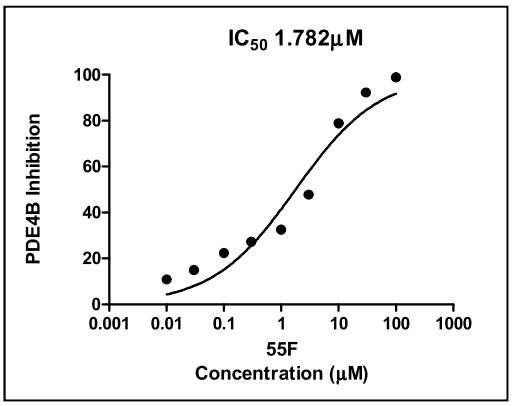
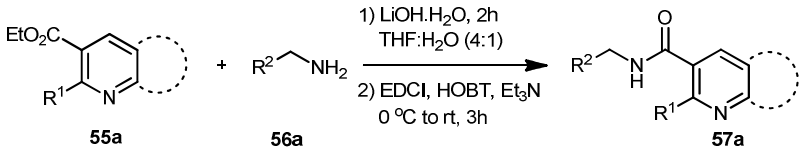


Fig 1.3. Dose dependent inhibition of PDE4B by compound **55f**

To demonstrate the potential of the method the compound fused nicotinate derivatives **(55)** was converted to fused nicotinamide derivatives (**57)** in a single step (Scheme 1.13). Thus, compound **55** was treated with a $Li(OH).H_2O$, participated in ester hydrolysis followed by benzyl amine coupling using coupling reagents afford the compound **57,** details were summarized in the (Table 1.4.).

1.5. Synthesis of fused-nicotinamides

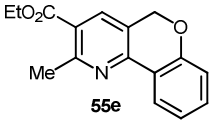
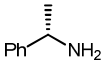
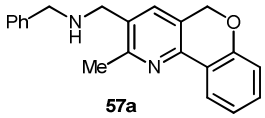
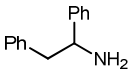
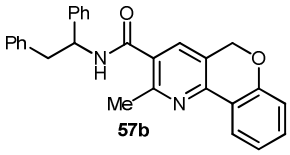
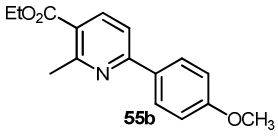
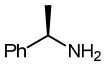
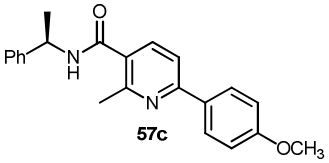
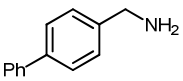
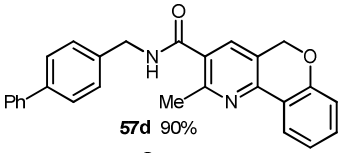
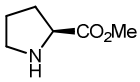
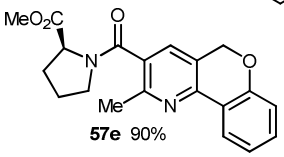
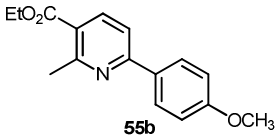
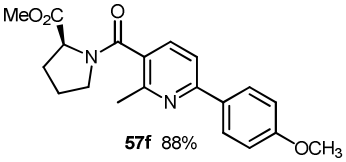
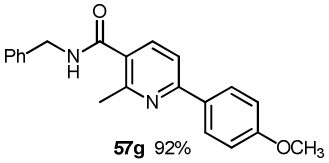
Nicotinic acid derivatives particularly, nicotinamides represent one of the most important families of biologically significant compounds containing a pyridine ring. They are members of the B-vitamin group and play an important role in many essential metabolic processes. The NAD/NADP coenzymes are nicotinamide derivatives, leading to several potential targets for interference with drugs.[28] besides, a number of nicotinamide derivatives have prominent pharmacological activity at other types of targets. Thus, nicorandil is an important drug acting as a selective activator of ATP-dependent potassium channel that is employed in the treatment of cardiac ischemia.[29] Several other pharmacologically relevant nicotinamides have been described, including antiarrythmic compounds acting by inhibition of the sodium-calcium exchanger (NCX),[30] anti-cancer compounds acting by inducing apoptosis [31] or by inhibiting vascular endothelial growth factor (VEGF)-induced angiogenesis,[32] anxiolytic, and antidepressant activity associated to the inhibition of Type 5 metabotropic glutamate receptors (mGluR5) [33] and inhibitors of the gastric H+/K+ ATPase acting as antiulcer agents.[34]

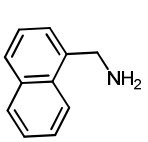
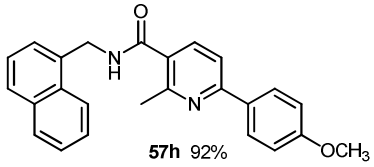
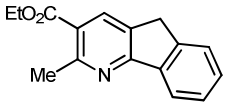
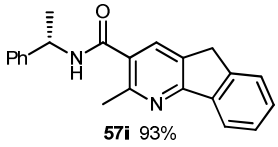
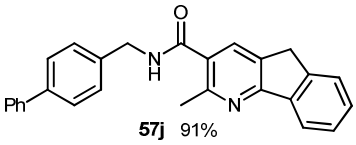
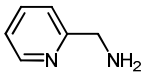
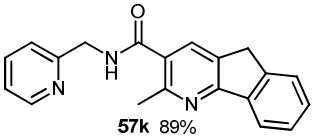
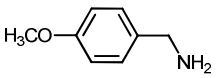
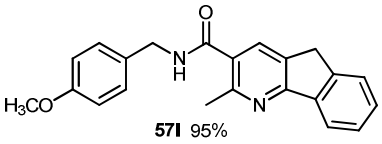
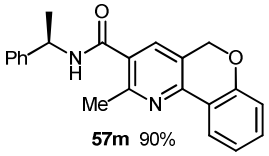
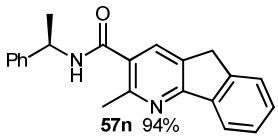


55a 56a 57a

Scheme 1.13 Synthesis of nicotinamide derivatives

Table 1.4. Synthesis of substituted nicotinamide derivatives[a]

Entry	Nicotinate derivative	Benzyl Amine	Product
1	 **55e**	 **56a**	 **57a**
2	**55e**	 **56b**	 **57b**
3	 **55b**	 **56c**	 **57c**
4	**55e**	 **56d**	 **57d** 90%
5	**55e**	 **56e**	 **57e** 90%
6	 **55b**	**56e**	 **57f** 88%
7	**55b**	**56a**	 **57g** 92%

8	**55b**	 **56f**	 **57h** 92%
9	 **55f**	**56a**	 **57i** 93%
10	**55f**	**56d**	 **57j** 91%
11	**55f**	 **56g**	 **57k** 89%
12	**55f**	 **56h**	 **57l** 95%
13	**55e**	**56c**	 **57m** 90%
14	**55f**	**56c**	 **57n** 94%

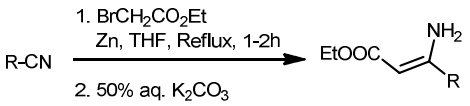
Reaction conditions: nicotinate derivative **55** (0.3 mmol), Li(OH).H_2O (0.36 mmol), benzyl amine **56** (0.3 mmol), EDCI (0.36 mmol), HOBT (0.36 mmol), Et_3N (0.6 mmol) in THF 5 ml at 0 °C to rt, 3h.

1.6. Conclusions

In conclusion, a direct, one-pot and metal-free synthesis of functionalized pyridines have been developed for the first time *via* Ammonium salt mediated reaction of readily available β-enamino esters and α-methelene carbonyl compounds. This tandem method afforded trisubstituted pyridines and unsymmetrical fused-pyridines and precursors of azaflurenones. The limitations and advantages of this methodology have been discussed. The methodology may find wide applications in the construction of pyridine based library of small molecules useful for medicinal uses.

1.7. Experimental section

1.7.1. Materials



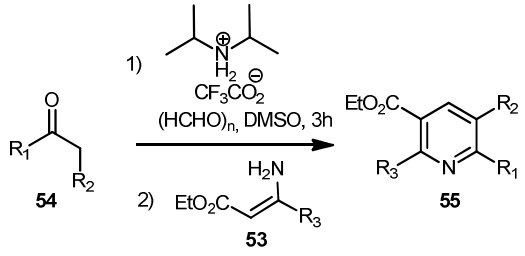
β-enamino esters were synthesized based on the procedure given below:

To the activated Zinc dust (1.31 g, 20.0 mmol) was added trimithylsilylchloride (3.0 drops) in dry THF (10.0 mL) under nitrogen. The mixture was heated to reflux for 10 min and then nitrile (10.0 mmol) was added all at once. While maintaining the refluxing temperature, ethyl bromoacetate (1.65 mL, 15.0 mmol in 5 mL THF) was added to the mixture over a period of 1h, and the reaction mixture was further heated to reflux for 1h. After complete conversion of nitrile, the reaction mixture was cooled to room temperature, quenched with saturated aqueous K_2CO_3 and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to get β-enamino ester.

Ammonium salt was prepared according to the respective literature procedure.[22] Analytical and spectral data of those entire known compound are accurately matching with reported values.

1.7.2. Experimental procedures, spectral and analytical data

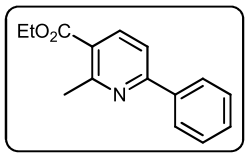
General procedure for synthesis of tri-substituted and fused pyridines 55.



To a mixture of a carbonyl compound (0.5 mmol) and paraformaldehyde (0.5 mmol, 100 mol %) in dry DMSO (3.0 mL) is added the catalyst (0.5 mmol, 100 mol %) and trifluoroacetic acid (0.1 mmol, 20 mol %). The reaction mixture is stirred at 90 °C open to the atmosphere for 1h. The mixture will become clear, then the reaction mixture is cooled down to room temperature and addition of enamine ester (0.5 mmol,

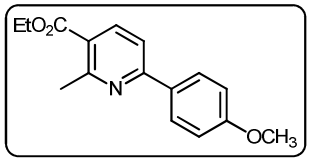
100 mol %) is performed. The reaction mixture is stirred at 90 °C for an additional 2-3h open to the atmosphere (see Table 1.2). The reaction mixture is cooled to room temperature, quenched with sat. NH_4Cl solution (2.0 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and concentrated under vacuum. The crude compound was purified by flash chromatography using 10% (EtOAc–Hexanes) as the eluent.

Ethyl 2-methyl-6-phenylnicotinate (55a):



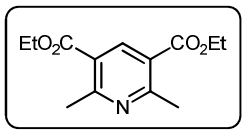
Dark brown liquid, R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.27 (d, *J* = 8.21 Hz, 1H), 8.06 (d, *J* = 7.63 Hz, 2H), 7.63 (d, *J* = 8.14 Hz, 1H), 7.52-7.41 (m, 3H), 4.40 (q, *J* = 7.13 Hz, 2H), 2.91 (s, 3H), 1.42 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 166.5, 159.8, 158.9, 139.2, 138.4, 129.6, 128.7, 127.2, 123.6, 117.2, 61.0, 25.2, 14.2; MS (ESI mass) m/z**:** 242.1[M+1].

Ethyl 6-(4-methoxyphenyl)-2-methylnicotinate (55b):



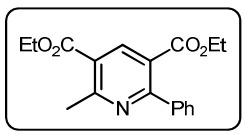
Pale green solid, m.p: 64-66 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.24 (d, *J* = 8.24 Hz, 1H), 8.04 (d, *J* = 8.77 Hz, 2H), 7.57 (d, *J* = 8.24 Hz, 1H), 7.00 (d, *J* = 8.75 Hz, 2H), 4.39 (q, *J* = 7.14 Hz, 2H), 3.87 (s, 3H), 2.91 (s, 3H), 1.41 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 166.5, 161.0, 159.8, 158.5, 139.2, 130.8, 128.6, 122.8, 116.4, 114.1, 61.0, 55.3, 25.1, 14.2; MS (ESI mass) m/z**:** 272.2[M+1].

Diethyl 2, 6-dimethylpyridine-3,5-dicarboxylate (55c):



Pale yellow solid, m.p: 55-57 °C; R_f = 0.3 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.69 (s, 1H), 4.40 (q, *J* = 7.13 Hz, 4H), 2.86 (s, 6H), 1.41 (t, *J* = 7.13 Hz, 6H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 165.7, 162.0, 140.9, 123.1, 61.3, 24.7, 14.2; MS (ESI mass) m/z**:** 252.2[M+1].

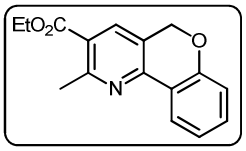
Diethyl 2-methyl-6-phenylpyridine-3,5-dicarboxylate (55d):



Color less thick liquid, R_f = 0.3 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.62 (s, 1H), 7.59-7.53 (m, 2H), 7.43 (m, 3H), 4.42 (q, *J* = 7.13 Hz, 2H), 4.16 (q, *J* = 7.13 Hz, 2H), 2.93 (s, 3H), 1.43 (t, *J* = 7.14 Hz, 3H), 1.06 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100

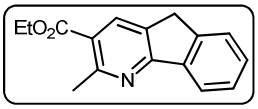
MHz, *CDCl₃*) δ 167.4, 165.7, 161.7, 160.3, 140.5, 139.4, 129.0, 128.6, 128.1, 124.5, 123.4, 61.5, 61.4, 25.0, 14.2, 13.6; MS (ESI mass) m/z**:** 314.2[M+1].

Ethyl 2-methyl-5H-chromeno[4,3-b]pyridine-3-carboxylate (55e):



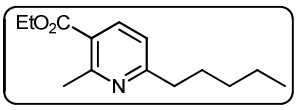
White solid, m.p: 102-104 °C; R_f = 0.45 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.29 (dd, *J* = 7.74, 1.59 Hz, 1H), 7.97 (s, 1H), 7.39-7.32 (m, 1H), 7.12 (dt, *J* = 7.69, 1.10 Hz, 1H), 6.97 (dd, *J* = 8.20, 0.78 Hz, 1H), 5.24 (s, 2H), 4.39 (q, *J* = 7.13 Hz, 2H), 2.90 (s, 3H), 1.43 (t, *J* = 9.38, 4.89 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl₃*) δ 166.3, 159.9, 156.9, 150.3, 134.5, 132.1, 125.3, 122.8, 122.4, 117.0, 67.4, 61.1, 25.1, 14.3; MS (ESI mass) m/z**:** 270.2[m+1].

Ethyl 2-methyl-5H-indeno[1,2-b]pyridine-3-carboxylate (55f):



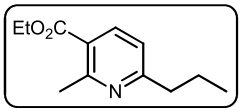
Yellow solid, m.p: 119-121 °C; R_f = 0.45 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.33 (s, 1H), 8.27-8.11 (m, 1H), 7.59 (m, 1H), 7.54-7.42 (m, 2H), 4.40 (q, *J* = 7.12 Hz, 2H), 3.89 (s, 2H), 2.95 (s, 3H), 1.43 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl₃*) δ 166.9, 162.3, 159.3, 145.1, 134.4, 133.6, 129.5, 127.4, 125.2, 122.7, 121.7, 61.0, 34.1, 24.9, 14.2; MS (ESI mass) m/z**:** 254.1[M+1].

Ethyl 2-methyl-6-pentylnicotinate (55g):



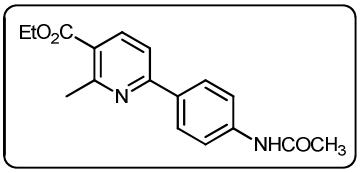
Pale yellow oil; R_f = 0.6 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.09 (d, *J* = 8.03 Hz, 1H), 7.03 (d, *J* = 8.05 Hz, 1H), 4.36 (q, *J* = 7.15 Hz, 2H), 2.81 (s, 3H), 2.80-2.74 (m, 2H), 1.76-1.66 (m, 2H), 1.39 (t, *J* = 7.13 Hz, 3H), 1.36-1.30 (m, 4H), 0.89 (dd, *J* = 9.20, 4.73 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl₃*) δ 166.7, 165.2, 159.2, 138.6, 122.7, 119.6, 60.9, 38.5, 31.5, 29.3, 24.8, 22.4, 14.2, 13.9; MS (ESI mass) m/z**:** 236.2[M+1].

Ethyl 2-methyl-6-propylnicotinate (55h):



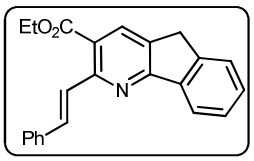
Pale yellow oil; R_f = 0.56 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.10 (d, *J* = 8.03 Hz, 1H), 7.04 (d, *J* = 8.00 Hz, 1H), 4.36 (q, *J* = 7.14 Hz, 2H), 2.81 (s, 3H), 2.79-2.73 (m, 2H), 1.80-1.69 (m, 2H), 1.39 (t, *J* = 7.13 Hz, 3H), 0.97 (t, *J* = 7.36 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl₃*) δ 166.7, 165.0, 159.2, 138.6, 122.8, 119.7, 60.9, 40.4, 24.7, 22.9, 14.2, 13.7; MS (ESI mass) m/z: 208.2[M+1].

Ethyl 6-(4-acetamidophenyl)-2-methylnicotinate (55i):



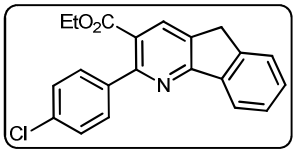
Pale yellow solid; m.p: 145-147 °C; R_f = 0.2 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.24 (dd, *J* = 8.16, 2.71 Hz, 1H), 8.15 (m, 1H), 7.78-7.71 (m, 2H), 7.65-7.56 (m, 1H), 7.39 (m, 1H), 4.39 (q, *J* = 7.13 Hz, 2H), 2.89 (s, 3H), 2.18 (s, 3H), 1.41 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 168.6, 166.3, 159.7, 158.1, 139.6, 138.6, 138.5, 129.4, 123.0, 121.3, 118.7, 117.7, 61.2, 24.8, 24.5, 14.2; MS (ESI mass) m/z: 299.2[M+1].

(E)-Ethyl 2-styryl-5H-indeno [1, 2-b] pyridine-3-carboxylate (55j):



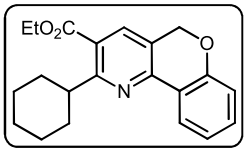
Yellow solid; m.p: 114-116 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.35-8.24 (m, 3H), 8.15 (d, *J* = 15.64 Hz, 1H), 7.69 (d, *J* = 7.24 Hz, 2H), 7.61 (t, *J* = 7.28 Hz, 1H), 7.55-7.46 (m, 2H), 7.40 (t, *J* = 7.47 Hz, 2H), 7.31 (t, *J* = 7.31 Hz, 1H), 4.46 (q, *J* = 7.12 Hz, 2H), 3.94 (s, 2H), 1.47 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 167.1, 162.8, 154.8, 145.2, 140.1, 137.2, 135.3, 134.5, 134.3, 129.7, 128.6, 128.2, 127.5, 127.4, 125.8, 125.2, 122.0; MS (ESI mass) m/z : 342.3[M+1].

Ethyl 2-(4-chlorophenyl)-5H-indeno [1, 2-b] pyridine-3-carboxylate (55k):



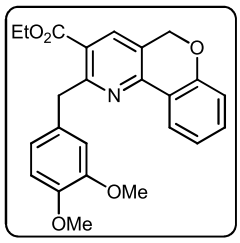
Color less solid; m.p: 150-152 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.25 (s, 1H), 8.18 (dd, *J* = 5.13, 3.41 Hz, 1H), 7.64-7.60 (m, 1H), 7.59-7.54 (m, 2H), 7.50-7.42 (m, 4H), 4.19 (q, *J* = 7.13 Hz, 2H), 3.97 (s, 2H), 1.13 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 168.3, 162.4, 157.4, 144.9, 139.9, 139.4, 137.5, 134.7, 134.0, 130.2, 129.7, 128.2, 127.5, 125.2, 121.9, 61.4, 34.2, 13.7; MS (ESI mass) m/z : 350.2[M+1].

Ethyl 2-cyclohexyl-5H-chromeno [4, 3-b] pyridine-3-carboxylate (55l):



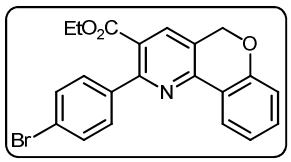
Color less solid; m.p: 114-116 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.34 (dd, *J* = 7.74, 1.59 Hz, 1H), 7.84 (s, 1H), 7.39-7.29 (m, 1H), 7.12 (m, 1H), 6.96 (d, *J* = 8.14 Hz, 1H), 5.23 (s, 2H), 4.39 (q, *J* = 7.12 Hz, 2H), 3.61-3.49 (m, 1H), 1.82 (m, 7H), 1.43 (m, 5H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 166.9, 166.6, 156.9, 149.9, 134.1, 131.9, 125.4, 123.5, 122.8, 122.2, 122.1, 116.9, 67.4, 61.2, 42.9, 32.5, 26.6, 26.2, 14.2; MS (ESI mass) m/z : 338.3[M+1].

Ethyl 2-(3,4-dimethoxybenzyl)-5H-chromeno[4,3-b] pyridine-3-carboxylate (55m):



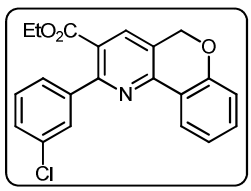
Pale yellow solid, m.p: 141-143 °C; R_f = 0.3 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.29 (s, 1H), 7.91 (d, *J* = 12.37 Hz, 1H), 7.36 (m, 1H), 7.16-7.05 (m, 1H), 6.94 (m, 3H), 6.76 (d, *J* = 8.23 Hz, 1H), 5.23 (s, 2H), 4.57 (s, 2H), 4.39-4.30 (m, 2H), 3.84 (d, *J* = 7.45 Hz, 6H), 1.36 (m, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 166.2, 161.5, 156.9, 150.3, 148.5, 147.3, 134.7, 132.3, 132.2, 125.3, 123.8, 123.1, 122.4, 122.3, 121.0, 117.1, 112.6, 110.9, 67.4, 61.3, 55.8, 55.7, 41.6, 14.2; MS (ESI mass) m/z : 406.3[M+1].

Ethyl 2-(4-bromophenyl)-5H-chromeno [4, 3-b] pyridine-3-carboxylate (3n):



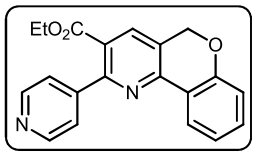
Pale yellow solid, m.p: 108-110 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.29 (dd, *J* = 7.76, 1.57 Hz, 1H), 7.89 (s, 1H), 7.58 (dd, *J* = 8.49, 1.79 Hz, 2H), 7.49 (dd, *J* = 9.00, 2.38 Hz, 2H), 7.39-7.33 (m, 1H), 7.10 (t, *J* = 7.07 Hz, 1H), 6.99 (d, *J* = 8.16 Hz, 1H), 5.30 (s, 2H), 4.20 (q, *J* = 7.13 Hz, 2H), 1.14 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 167.4, 157.7, 156.9, 150.2, 139.2, 134.3, 132.4, 131.1, 130.5, 125.5, 123.9, 122.4, 117.1, 67.3, 61.5, 13.7; MS (ESI mass) m/z : 410.1[M+1].

Ethyl 2-(3-chlorophenyl)-5H-chromeno [4, 3-b] pyridine-3-carboxylate (55o):



Pale yellow solid, m.p: 117-119 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.31 (dd, *J* = 7.77, 1.57 Hz, 1H), 7.90 (s, 1H), 7.61 (t, *J* = 1.59 Hz, 1H), 7.48-7.33 (m, 4H), 7.14-7.07 (m, 1H), 6.99 (d, *J* = 8.22 Hz, 1H), 5.31 (s, 2H), 4.19 (q, *J* = 7.14 Hz, 2H), 1.11 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 167.4, 157.3, 156.9, 150.2, 142.0, 134.4, 132.4, 129.1, 128.9, 128.6, 127.0, 125.5, 124.1, 122.4, 117.1, 67.3, 61.5, 13.7; MS (ESI mass) m/z : 366.2[M+1].

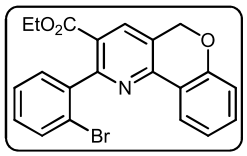
Ethyl 2-(pyridin-4-yl)-5H-chromeno [4, 3-b] pyridine-3-carboxylate (55p):



Pale yellow solid, m.p:119-121 °C; R_f = 0.16 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.71 (d, *J* = 5.87 Hz, 2H), 8.28 (dd, *J* = 7.79, 1.55 Hz, 1H), 7.97 (s, 1H), 7.50 (dd, *J*

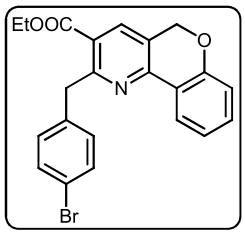
= 4.44, 1.60 Hz, 2H), 7.41-7.34 (m, 1H), 7.11 (m, 1H), 7.02-6.97 (m, 1H), 5.33 (s, 2H), 4.19 (q, *J* = 7.18 Hz, 2H), 1.10 (t, *J* = 7.14 Hz, 4H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 166.7, 157.0, 156.5, 149.3, 148.1, 134.5, 132.6, 125.5, 125.2, 124.8, 123.4, 122.5, 121.9, 117.2, 67.3, 61.7, 14.1**;** MS (ES mass) m/z : 333.2[M+1].

Ethyl 2-(2-bromophenyl)-5H-chromeno [4, 3-b] pyridine-3-carboxylate (55q):



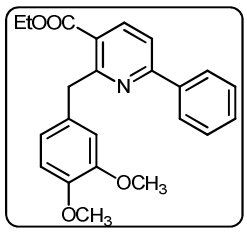
Color less solid, m.p: 172-174 °C; R_f = 0.41 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.25 (dd, *J* = 7.81, 1.58 Hz, 1H), 8.08 (s, 1H), 7.61 (dd, *J* = 11.61, 4.36 Hz, 1H), 7.45-7.28 (m, 4H), 7.11-7.03 (m, 1H), 7.02-6.96 (m, 1H), 5.34 (s, 2H), 4.22-4.12 (m, 2H), 1.04 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 165.7, 158.8, 156.9, 150.6, 142.1, 134.3, 132.3, 132.0, 130.2, 129.3, 127.0, 125.8, 124.6, 122.4, 122.2, 117.0, 67.4, 61.3, 13.5; MS (ESI mass) m/z : 410.0[M+1].

Ethyl 2-(4-bromobenzyl)-5H-chromeno [4, 3-b] pyridine-3-carboxylate (55r):



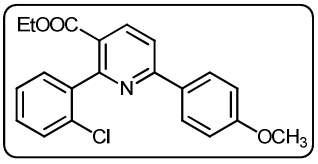
Pale yellow solid, m.p: 142-144 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.30 (dd, *J* = 7.69, 1.44 Hz, 1H), 7.97 (s, 1H), 7.39-7.34 (m, 3H), 7.24 (m, 1H), 7.13 (d, *J* = 7.29 Hz, 1H), 6.97 (d, *J* = 8.15 Hz, 1H), 5.24 (s, 2H), 4.61 (s, 2H), 4.34 (q, *J* = 7.11 Hz, 2H), 1.36 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 167.3, 160.6, 157.0, 141.4, 133.2, 131.3, 131.1, 130.9, 125.6, 125.4, 125.0, 122.5, 117.2, 117.1, 115.0, 67.2, 61.4, 42.1, 14.2; MS (ESI mass) m/z : 424.1[M+1].

Ethyl 2-(3, 4-dimethoxybenzyl)-6-phenylnicotinate (55s):



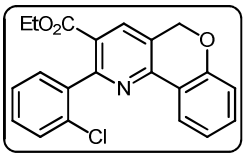
Brown oil, R_f = 0.2 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.26 (d, *J* = 8.24 Hz, 1H), 8.09 (dd, *J* = 8.07, 1.53 Hz, 2H), 7.67 (d, *J* = 8.25 Hz, 1H), 7.52-7.44 (m, 3H), 7.05 (d, *J* = 1.76 Hz, 1H), 6.90 (dd, *J* = 8.24, 1.89 Hz, 1H), 6.77 (d, *J* = 8.24 Hz, 1H), 4.64 (s, 2H), 4.36 (q, *J* = 7.12 Hz, 2H), 3.84 (d, *J* = 7.07 Hz, 6H), 1.38 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 166.3, 161.3, 158.6, 148.5, 147.3, 139.9, 132.3, 129.8, 128.7, 127.3, 123.8, 121.0, 117.6, 112.7, 110.9, 61.2, 55.8, 55.7, 41.4, 14.2; MS (ESI mass) m/z : 378.2[M+1].

Ethyl 2-(2-chlorophenyl)-6-(4-methoxyphenyl) nicotinate (55t):



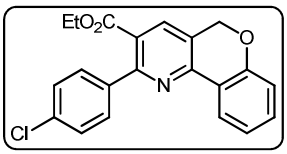
Pale green oil, R_f= 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.35 (d, *J* = 8.29 Hz, 1H), 8.10-8.04 (m, 2H), 7.77 (d, *J* = 8.31 Hz, 1H), 7.47 (m, 1H), 7.46-7.39 (m, 1H), 7.39-7.32 (m, 2H), 7.02-6.96 (m, 2H), 4.19-4.11 (m, 2H), 3.86 (s, 3H), 1.05 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 166.1, 163.4, 161.1, 158.1, 157.2, 140.4, 138.9, 130.5, 130.4, 129.1, 128.8, 126.5, 117.9, 114.1, 113.6, 61.1, 55.5, 13.6; MS (ESI mass) m/z : 368.1[M+1].

Ethyl 2-(2-chlorophenyl)-5H-chromeno [4, 3-b] pyridine-3-carboxylate (55u):



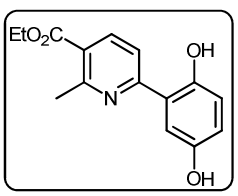
Color less solid, m.p: 154-156 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.27 (dd, *J* = 7.76, 1.49 Hz, 1H), 8.08 (s, 1H), 7.50-7.33 (m, 5H), 7.13-7.04 (m, 1H), 7.00 (d, *J* = 8.06 Hz, 1H), 5.35 (s, 2H), 4.16 (q, *J* = 7.05 Hz, 2H), 1.06 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 165.9, 156.9, 150.7, 140.1, 134.2, 132.3, 130.4, 129.2, 128.8, 126.5, 125.7, 122.4, 117.0, 67.4, 61.2. 13.5; MS (ESI mass) m/z : 366.2[M+1].

Ethyl 2-(4-chlorophenyl)-5H-chromeno [4, 3-b] pyridine-3-carboxylate (55v):



Pale yellow solid, m.p: 105-106 °C; R_f= 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.30 (dd, *J* = 7.77, 1.52 Hz, 1H), 7.90 (s, 1H), 7.56 (dd, *J* = 8.38, 4.04 Hz, 2H), 7.46-7.34 (m, 3H), 7.11 (t, *J* = 7.53 Hz, 1H), 6.99 (d, *J* = 8.15 Hz, 1H), 5.31 (s, 2H), 4.20 (q, *J* = 7.08 Hz, 2H), 1.14 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 167.4, 157.6, 156.9, 150.1, 138.7, 134.7, 134.3, 132.3, 130.2, 130.1, 128.3, 128.1, 125.4, 125.1, 123.8, 122.4, 122.1, 117.0, 67.3, 61.5, 13.7; MS (ESI mass) m/z : 366.2[M+1].

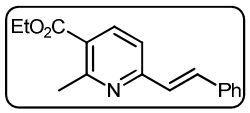
Ethyl 6-(2, 5-dihydroxyphenyl)-2-methylnicotinate (55w):



Pale red solid, m.p: 193-195 °C; R_f = 0.2 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.36 (d, *J* = 8.50 Hz, 1H), 7.71 (d, *J* = 8.58 Hz, 1H), 7.29 (s, 1H), 6.89 (m, 2H), 4.40 (q, *J* = 7.13, 5.71 Hz, 2H), 2.90 (s, 2H), 1.42 (t, *J* = 7.14 Hz,

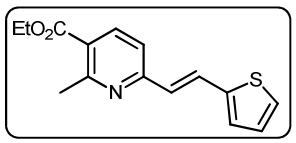
3H); ^{13}C NMR (100 MHz, *CDCl$_3$, DMSO*) δ 165.5, 159.4, 157.2, 153.5, 149.3, 139.8, 122.5, 120.6, 118.9 117.8, 116.1, 112.2, 61.1, 24.4, 14.1; MS (ESI mass) m/z : 274.1[M+1].

(E)-Ethyl 2-methyl-6-styrylnicotinate (55x):



Pale yellow solid, m.p: 59-61 °C; R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.19 (d, *J* = 8.15 Hz, 1H), 7.72 (d, *J* = 16.10 Hz, 1H), 7.60 (d, *J* = 7.35 Hz, 2H), 7.39 (t, *J* = 7.35 Hz, 2H), 7.35-7.28 (m, 2H), 7.18 (d, *J* = 16.08 Hz, 1H), 4.38 (q, *J* = 7.13 Hz, 2H), 2.88 (s, 3H), 1.41 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 166.4, 159.9, 157.4, 139.0, 136.2, 134.9, 128.7, 127.3, 123.4, 118.7, 61.0, 25.1, 14.2; MS (ESI mass) m/z : 268.1[M+1].

(E)-Ethyl 2-methyl-6-(2-(thiophen-2-yl) vinyl) nicotinate (55y):

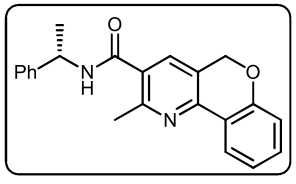


Dark brown thick liquid, R_f = 0.4 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.16 (d, *J* = 8.13 Hz, 1H), 7.87 (d, *J* = 15.73 Hz, 1H), 7.28 (d, *J* = 5.04 Hz, 1H), 7.22-7.19 (m, 2H), 7.04 (dd, *J* = 5.06, 3.60 Hz, 1H), 6.96 (d, *J* = 15.72 Hz, 1H), 4.37 (q, *J* = 7.14 Hz, 2H), 2.85 (d, *J* = 5.56 Hz, 3H), 1.40 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 166.4, 159.9, 157.0, 141.8, 139.0, 128.4, 127.8, 126.4, 126.1, 123.2, 118.7, 61.0, 25.1, 14.2; MS (ESI mass) m/z : 274.0[M+1].

General Procedure for the acid and amine coupling reactions.

A mixture of acid (0.1 mmol) and EDCI (1.2 mmol), HOBt (1.2 mmol) in CH_2Cl_2 (3.0 mL) was stirred at room temperature for 2 min. After addition of amine (1.2 mmol) and Et_3N (2.0 mmol) to the mixture, the whole was stirred for reaction 3h. Ethyl acetate (10.0 mL) was added to the reaction mixture and then the whole was washed with 5% HCl solution (10 mL, 2) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **57a**–**57n** in good yields.

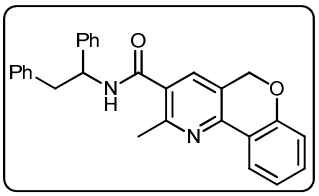
(S)-2-Methyl-N-(1-phenylethyl)-5H-chromeno[4,3-b]pyridine-3-carboxamide (57a):



Pale yellow solid, m.p: 160-162 °C; R_f = 0.2 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.22 (dd, *J* =

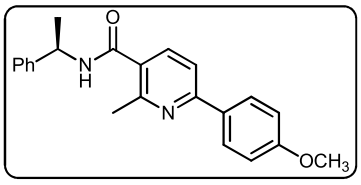
7.76, 1.52 Hz, 1H), 7.39 (dd, *J* = 5.33, 2.55 Hz, 4H), 7.35-7.29 (m, 2H), 7.12-7.06 (m, 1H), 6.95 (d, *J* = 8.13 Hz, 1H), 6.09-6.02 (m, 1H), 5.34 (dd, *J* = 14.42, 7.25 Hz, 1H), 5.16 (s, 2H), 2.67 (s, 3H), 1.63 (d, *J* = 6.90 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 156.4, 155.6, 142.6, 131.6, 130.7, 130.0, 128.7, 128.5, 127.5, 126.2, 124.9, 122.3, 116.9, 67.2, 49.3, 29.6, 21.5; MS (ESI mass) m/z : 345.1[M+1].

N-(1, 2-diphenylethyl)-2-Methyl-5H-chromeno[4,3-b]pyridine-3-carboxamide (57b):



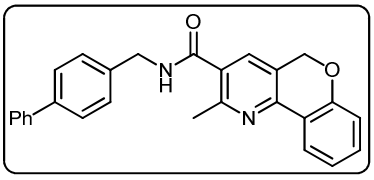
Color less solid, m.p: 189-191 °C; R_f = 0.2 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.74, 1.50 Hz, 1H), 7.40-7.28 (m, 8H), 7.17 (d, *J* = 8.04 Hz, 3H), 7.11-7.05 (m, 1H), 6.95 (d, *J* = 7.46 Hz, 1H), 6.02 (d, *J* = 7.56 Hz, 1H), 5.51 (d, *J* = 6.58 Hz, 1H), 5.13 (s, 2H), 3.30 (dd, *J* = 13.91, 6.39 Hz, 1H), 3.13 (dd, *J* = 14.00, 8.53 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 156.5, 155.8, 141.2, 137.1, 131.6, 130.7, 129.2, 128.7, 128.5, 127.6, 126.8, 126.4, 124.9, 122.7, 122.3, 116.9, 67.3, 54.7, 42.5, 22.8; MS (ESI mass) m/z : 421.2[M+1].

2-Methyl-N-(naphthalen-1-ylmethyl)-5H-chromeno[4,3-b]pyridine-3-carboxamide (57c):



Color less solid, m.p: 175-177 °C; R_f = 0.22 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.85 Hz, 2H), 7.69 (d, *J* = 8.04 Hz, 1H), 7.49 (d, *J* = 8.07 Hz, 1H), 7.42-7.36 (m, 4H), 7.31 (m, 1H), 6.99 (d, *J* = 8.87 Hz, 2H), 6.04 (d, *J* = 7.56 Hz, 1H), 5.37-5.32 (m, 1H), 3.87 (s, 3H), 2.71 (s, 3H), 1.63 (d, *J* = 6.89 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 160.7, 157.4, 155.9, 142.7, 135.4, 131.3, 128.7, 128.3, 127.5, 126.1, 116.4, 114.1, 55.3, 49.3, 23.3, 21.6; MS (ESI mass) m/z : 381.1[M+1].

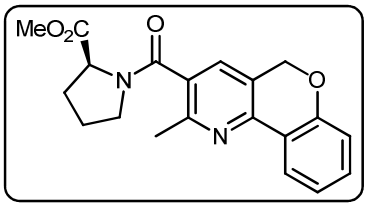
N-(biphenyl-4-ylmethyl)-2-methyl-5H-chromeno[4,3-b]pyridine-3-carboxamide (57d):



Color less solid, m.p: 205-207 °C; R_f = 0.2 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.76 Hz, 1H), 7.60 (t, *J* = 7.82 Hz, 4H), 7.46 (dd, *J* = 9.08, 5.00 Hz, 5H), 7.39-7.30 (m, 2H),

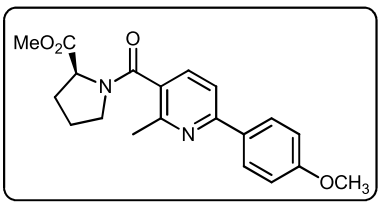
7.09 (t, *J* = 7.29 Hz, 1H), 6.96 (d, *J* = 8.15 Hz, 1H), 6.18 (d, *J* = 5.00 Hz, 1H), 5.17 (s, 2H), 4.68 (d, *J* = 5.71 Hz, 2H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 168.1, 156.5, 155.9, 148.9, 140.7, 140.4, 136.7, 131.7, 130.9, 128.7, 128.3, 127.5, 127.4, 127.0, 124.9, 122.8, 122.3, 116.9, 67.3, 43.8, 23.1; MS (ESI mass) m/z : 407.2[M+1].

(S)-Methyl 1-(2-methyl-5H-chromeno[4,3-b]pyridine-3-carbonyl)pyrrolidine-2 carboxyl ate (57e):



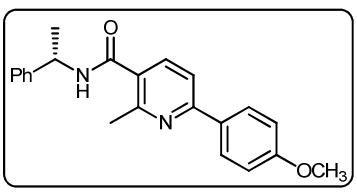
Brown color liquid, R_f = 0.2 (40% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.24 (dd, *J* = 7.71, 1.62 Hz, 1H), 7.35-7.29 (m, 2H), 7.13-7.07 (m, 1H), 6.96 (dd, *J* = 8.16, 0.79 Hz, 1H), 5.19 (s, 2H), 4.70 (dd, *J* = 8.67, 4.52 Hz, 1H), 3.81 (s, 3H), 3.43 (dd, *J* = 6.56, 3.75 Hz, 1H), 3.33-3.25 (m, 1H), 2.65 (s, 3H), 2.37-2.30 (m, 1H), 2.11-1.99 (m, 3H), 1.93 (m, 1H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 172.3, 168.2, 156.4, 154.5, 148.5, 131.5, 129.9, 124.8, 122.9, 122.3, 116.9, 67.4, 58.4, 52.3, 48.6, 29.6, 29.4, 24.7, 22.1; MS (ESI mass) m/z : 353.1[M+1].

(S)-Methyl 1-(6-(4-methoxyphenyl)-2-methylnicotinoyl)pyrrolidine-2-carboxylate (57f):



Color less solid, m.p: 123-125 °C; R_f = 0.2 (40% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.99-7.93 (m, 2H), 7.60 (d, *J* = 8.03 Hz, 1H), 7.50 (dd, *J* = 17.87, 4.94 Hz, 1H), 7.02-6.96 (m, 2H), 4.71 (dd, *J* = 8.69, 4.49 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.43 (dd, *J* = 6.51, 3.70 Hz, 1H), 3.34-3.26 (m, 1H), 2.66 (s, 3H), 2.39-2.29 (m, 1H), 2.13-1.98 (m, 3H), 1.93 (m, 1H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 172.3, 168.7, 160.6, 157.0, 154.5, 134.5, 131.4, 129.4, 128.2, 116.5, 114.0, 58.4, 55.3, 52.3, 48.7, 29.6, 29.4, 24.8, 22.4; MS (ESI mass) m/z : 355.1[M+1].

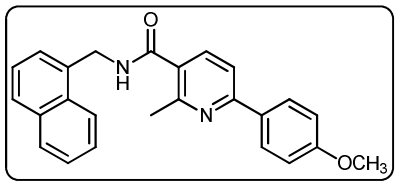
(S)-6-(4-methoxyphenyl)-2-methyl-N-(1-phenylethyl)nicotinamide (57g):



Color less solid, m.p: 127-129 °C; R_f = 0.22 (40% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.99-7.93 (m, 2H), 7.71-7.66 (m, 1H), 7.49 (d, *J* = 8.05 Hz, 1H), 7.42-7.35 (m, 4H), 7.34-7.27 (m, 1H), 6.99 (d, *J* = 8.86 Hz, 2H), 6.02 (d, *J* = 7.71 Hz, 1H), 5.35 (m, *J* = 6.91 Hz, 1H), 3.86 (s,

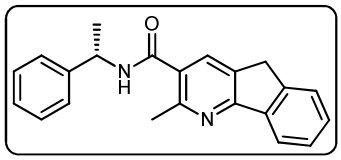
3H), 2.71 (s, 3H), 1.63 (d, *J* = 6.89 Hz, 3H); ^{13}C NMR (100 MHZ, *CDCl$_3$*) δ 167.8, 160.7, 157.4, 155.9, 142.7, 135.4, 131.2, 128.7, 128.3, 127.5, 126.1, 116.4, 114.1, 55.3, 49.3, 23.3, 21.6; MS (ESI mass) m/z : 347.1[M+1].

6-(4-methoxyphenyl)-2-methyl-N-(naphthalen-1-ylmethyl)nicotinamide (57h):



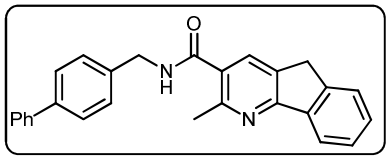
Color less solid, m.p: 134-136 °C; R_f = 0.25 (50 % EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.13 (d, *J* = 8.24 Hz, 1H), 7.92 (t, *J* = 8.45 Hz, 3H), 7.85 (d, *J* = 8.21 Hz, 1H), 7.66-7.50 (m, 4H), 7.45 (dd, *J* = 13.40, 7.80 Hz, 2H), 6.96 (d, *J* = 8.62 Hz, 2H), 6.04 (s, 1H), 5.11 (d, *J* = 5.32 Hz, 2H), 3.85 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (100 MHZ, *CDCl$_3$*) δ 168.3, 160.7, 157.4, 156.1, 135.3, 133.9, 133.1, 131.3, 131.2, 128.8, 128.3, 127.0, 126.7, 126.1, 125.3, 123.4, 116.3, 114.0; MS (ESI mass) m/z : 383.1[M+1].

(S)-2-methyl-N-(1-phenylethyl)-5H-indeno[1,2-b]pyridine-3-carboxamide (57i):



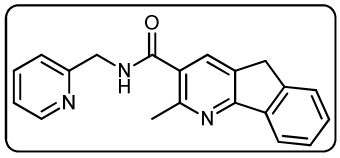
Color less solid, m.p: 173-175 °C; R_f = 0.21 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.08 (d, *J* = 6.42 Hz, 1H), 7.75 (s, 1H), 7.56 (d, *J* = 7.57 Hz, 1H), 7.47-7.36 (m, 6H), 7.31 (t, *J* = 6.86 Hz, 1H), 6.16-6.10 (m, 1H), 5.41-5.33 (m, 1H), 3.80 (s, 2H), 2.73 (s, 3H), 1.65 (d, *J* = 6.89 Hz, 4H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 168.3, 160.8, 154.8, 144.3, 142.7, 140.1, 133.4, 130.8, 129.0, 128.7, 127.5, 127.3, 126.2, 125.1, 121.2, 49.3, 34.0, 23.0, 21.6; MS (ESI mass) m/z : 329.1[M+1].

N-(biphenyl-4-ylmethyl)-2-methyl-5H-indeno[1,2-b]pyridine-3-carboxamide (57j):



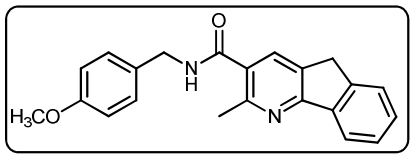
Color less solid, m.p: 174-176 °C; R_f = 0.25 (30 % EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.09 (dd, *J* = 5.97, 2.49 Hz, 1H), 7.78 (s, 1H), 7.61 (t, *J* = 7.12 Hz, 4H), 7.58-7.54 (m, 1H), 7.49-7.43 (m, 6H), 7.37 (t, *J* = 7.33 Hz, 1H), 6.38 (t, *J* = 5.10 Hz, 1H), 4.71 (d, *J* = 5.74 Hz, 2H), 3.78 (s, 2H), 2.78 (s, 3H); **^{13}C NMR** (100 MHz *CDCl$_3$*) δ 169.1, 161.0, 155.0, 144.4, 140.6, 140.5, 140.1, 136.8, 133.5, 131.0, 129.1, 128.7, 128.3, 127.5, 127.4, 127.3, 127.0, 125.1, 121.2, 43.8, 34.1, 23.1; MS (ESI mass) m/z : 391.1[M+1].

2-methyl-N-(pyridin-2-ylmethyl)-5H-indeno[1,2-b]pyridine-3-carboxamide (57k):



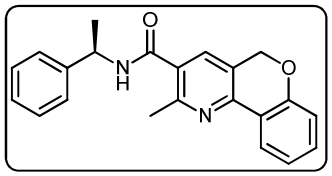
Color less solid, m.p: 165-167 °C; R_f= 0.2 (60% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.57 (d, *J* = 4.88 Hz, 1H), 8.17-8.13 (m, 1H), 7.93 (s, 1H), 7.74 (dt, *J* = 7.68, 1.75 Hz, 1H), 7.60 (d, *J* = 6.59 Hz, 1H), 7.51-7.43 (m, 2H), 7.40-7.33 (m, 2H), 7.27-7.23 (m, 1H), 4.81 (d, *J* = 4.85 Hz, 2H), 3.88 (s, 2H), 2.83 (s, 3H); ^{13}C NMR (100 MHZ, *CDCl$_3$*) δ 148.9, 136.9, 133.6, 131.4, 129.0, 127.3, 125.2, 122.5, 122.2, 121.3, 44.7, 34.2, 23.3; MS (ESI mass) m/z : 316.1[M+1].

N-(4-methoxybenzyl)-2-methyl-5H-indeno[1,2-b]pyridine-3-carboxamide (57l):



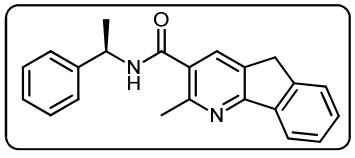
Color less solid, m.p: 163-165 °C; R_f = 0.2 (40% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.14-8.10 (m, 1H), 7.80 (s, 1H), 7.58 (d, *J* = 6.55 Hz, 1H), 7.45 (t, *J* = 5.72 Hz, 2H), 7.40 (d, *J* = 7.38 Hz, 1H), 7.33 (t, *J* = 7.87 Hz, 1H), 7.01-6.91 (m, 2H), 6.38 (d, *J* = 3.95 Hz, 1H), 4.67 (d, *J* = 5.77 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 2H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 168.8, 160.9, 157.5, 154.8, 144.4, 140.2, 133.6, 131.2, 130.1, 129.3, 129.2, 129.0, 127.3, 125.7, 125.2, 121.2, 120.8, 110.3; MS (ESI mass) m/z : 345.1[M+1].

(R)-2-methyl-N-(1-phenylethyl)-5H-chromeno[4,3-b]pyridine-3-carboxamide (57m):



Pale yellow solid, m.p: 160-162 °C; R_f = 0.2 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.22 (dd, *J* = 7.76, 1.52 Hz, 1H), 7.39 (dd, *J* = 5.33, 2.55 Hz, 4H), 7.35-7.29 (m, 2H), 7.12-7.06 (m, 1H), 6.95 (d, *J* = 8.13 Hz, 1H), 6.09-6.02 (m, 1H), 5.34 (dd, *J* = 14.42, 7.25 Hz, 1H), 5.16 (s, 2H), 2.67 (s, 3H), 1.63 (d, *J* = 6.90 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 167.4, 156.4, 155.6, 142.6, 131.6, 130.7, 130.0, 128.7, 128.5, 127.5, 126.2, 124.9, 122.3, 116.9, 67.2, 49.3, 29.6, 21.5; MS (ES mass) m/z : 345.1[M+1].

(R)-2-methyl-N-(1-phenylethyl)-5H-indeno[1,2-b]pyridine-3-carboxamide (57n):



Color less solid, m.p: 173-175 °C; R_f = 0.21 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.08

(d, *J* = 6.42 Hz, 1H), 7.75 (s, 1H), 7.56 (d, *J* = 7.57 Hz, 1H), 7.47-7.36 (m, 6H), 7.31 (t, *J* = 6.86 Hz, 1H), 6.16-6.10 (m, 1H), 5.41-5.33 (m, 1H), 3.80 (s, 2H), 2.73 (s, 3H), 1.65 (d, *J* = 6.89 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 160.8, 154.8, 144.3, 142.7, 140.1, 133.4, 130.8, 129.0, 128.7, 127.5, 127.3, 126.2, 125.1, 121.2, 49.3, 34.0, 23.0, 21.6; MS (ESI mass) m/z**:** 329.1[M+1].

1.7.3 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 °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 °C. After incubation, lysate-Ni-NTA mixture was centrifuged at 4,500 rpm for 5 min at 4 °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.[26]

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

1.8. References

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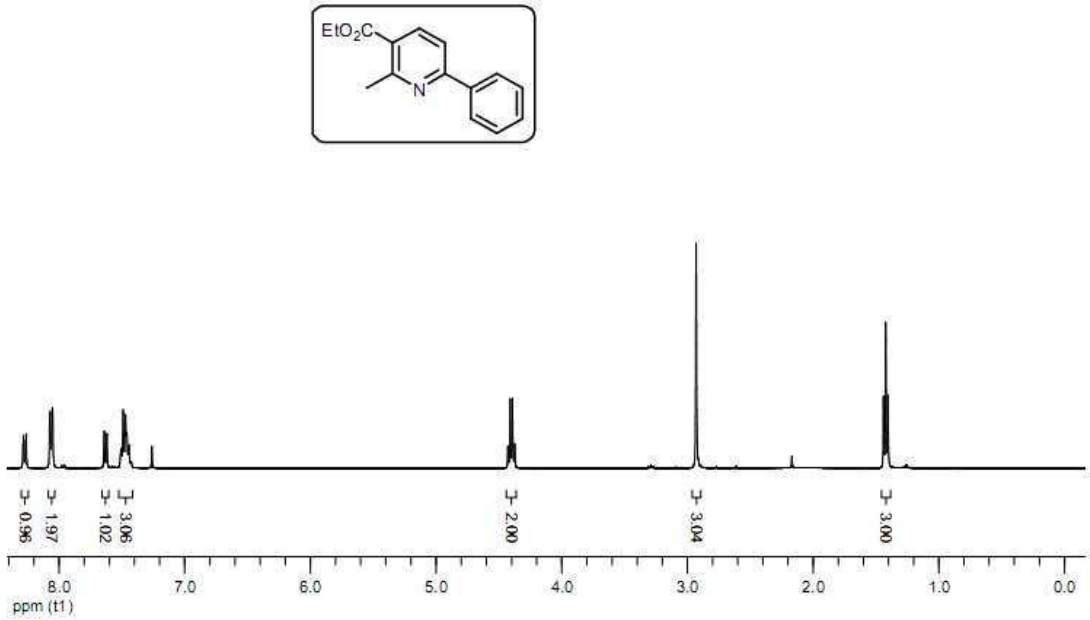
1.9. NMR Spectra

55a ^{1}H NMR ($CDCl_3$, 400 MHz)



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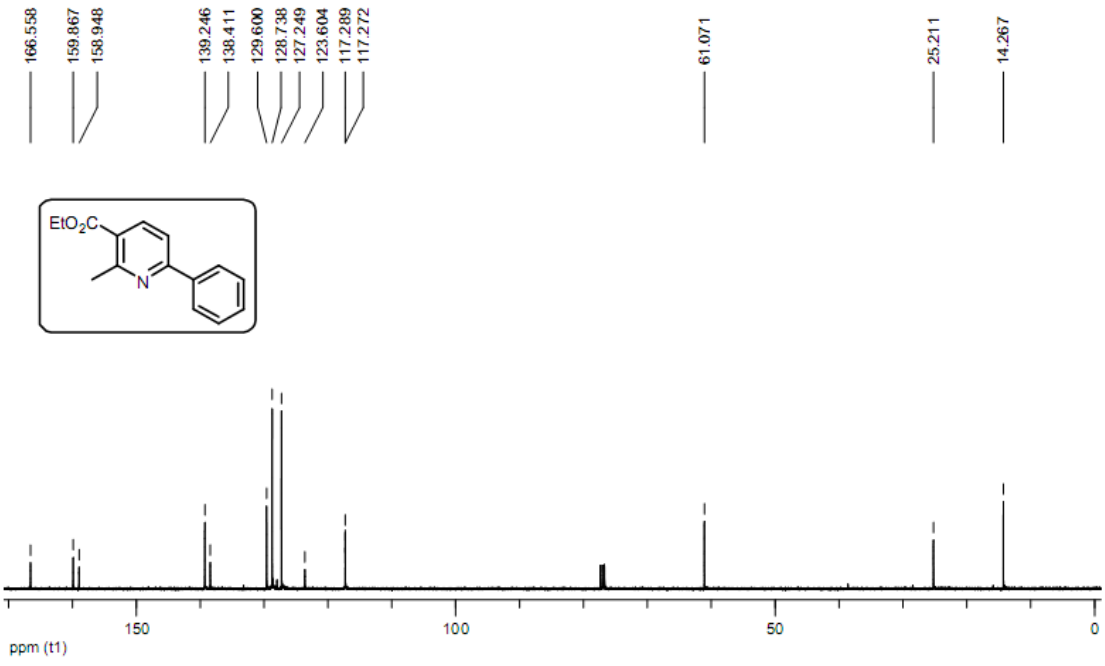

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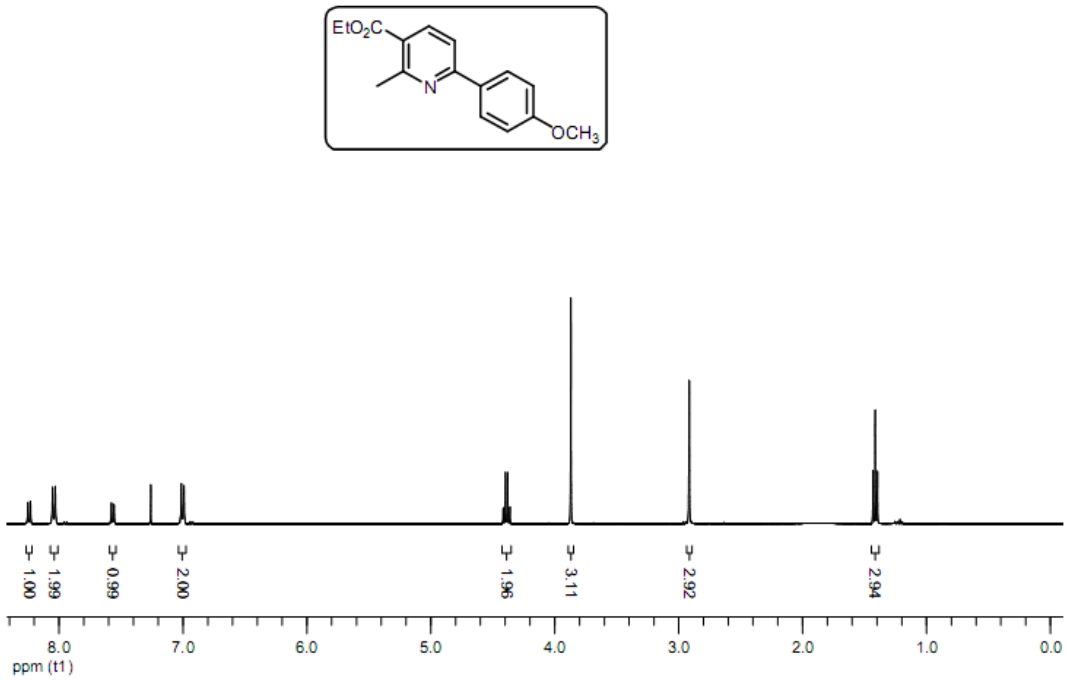

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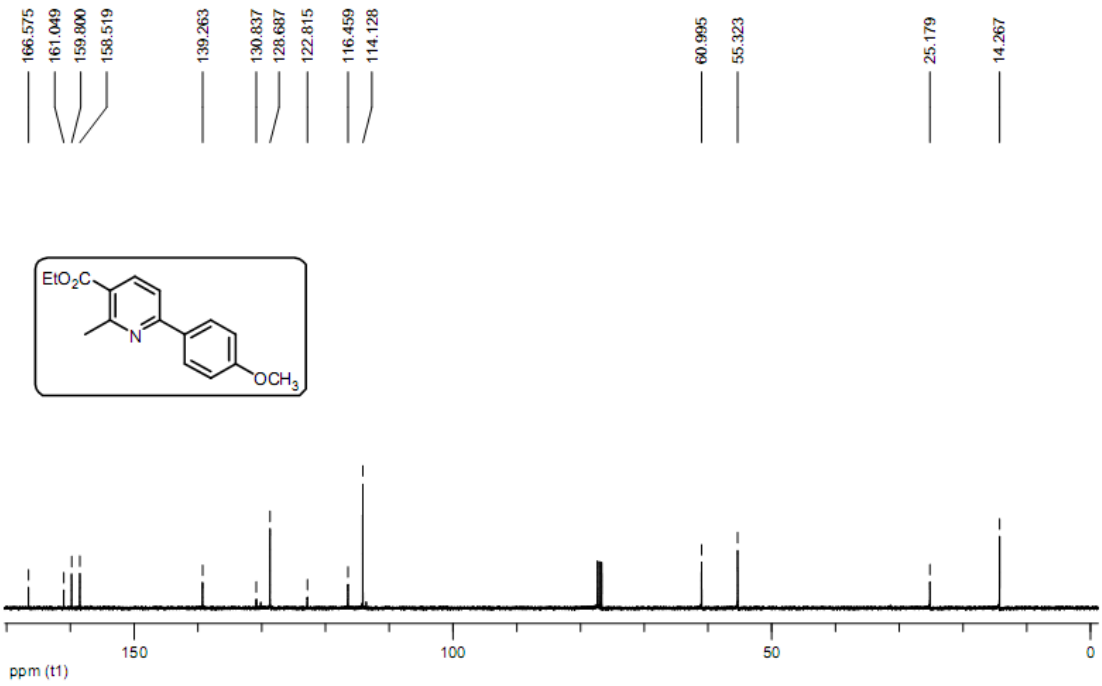

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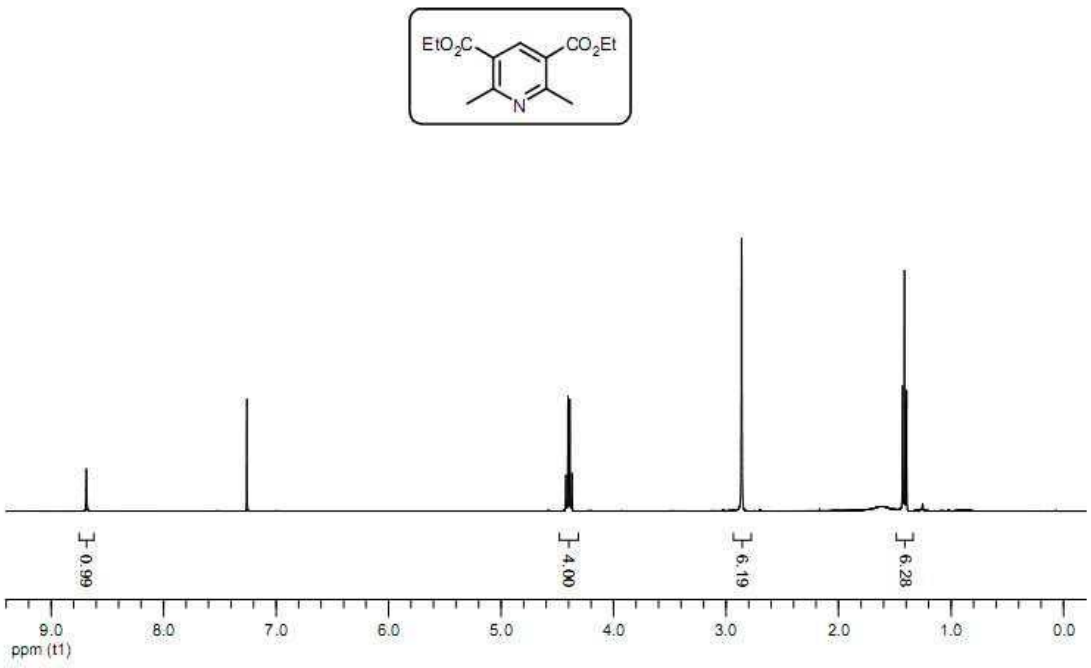

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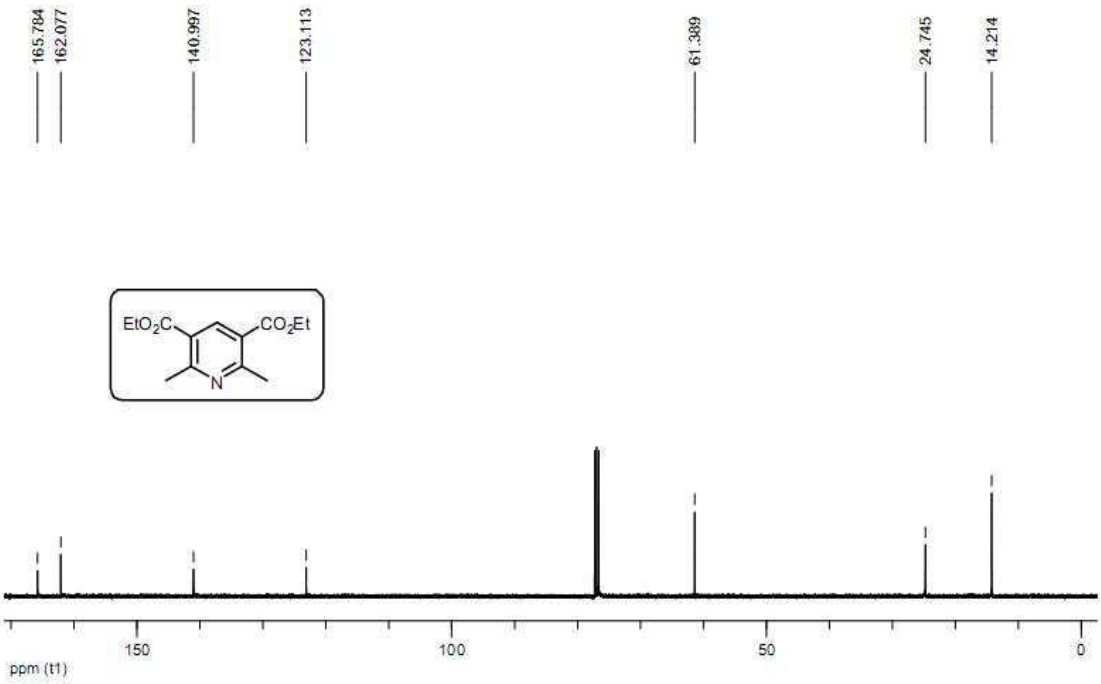

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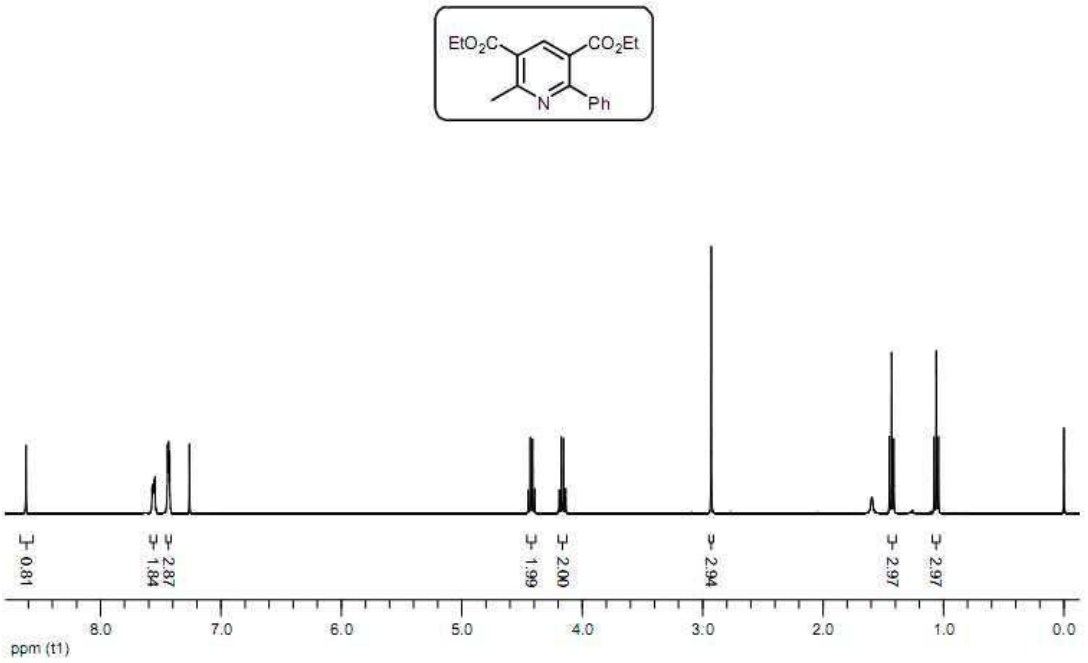

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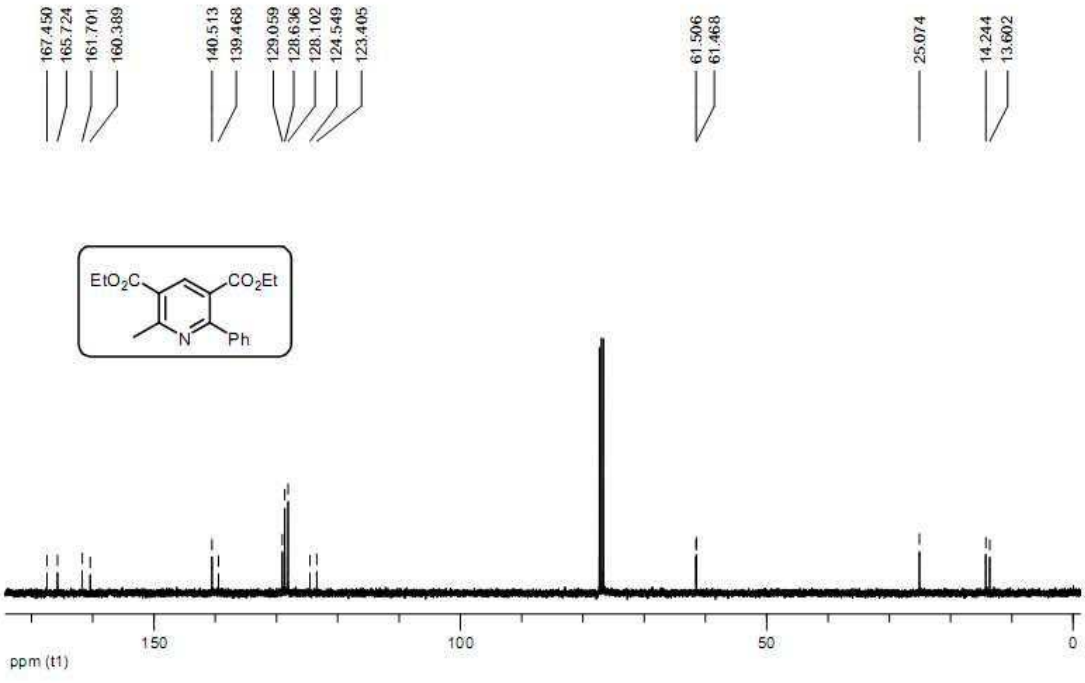

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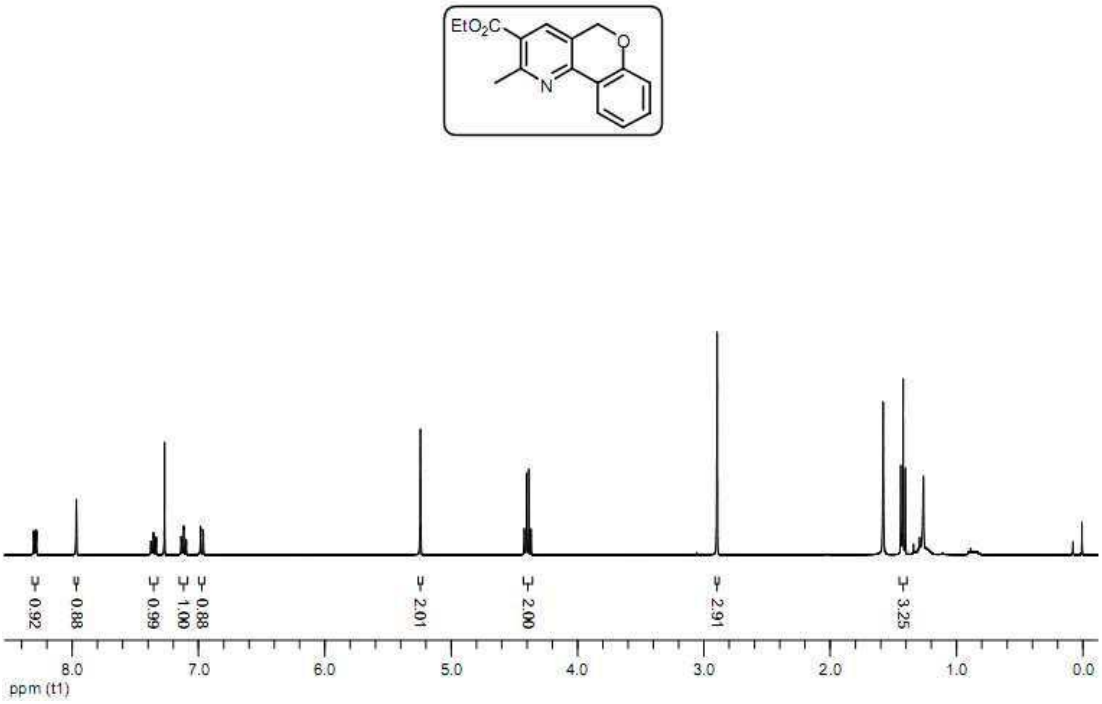

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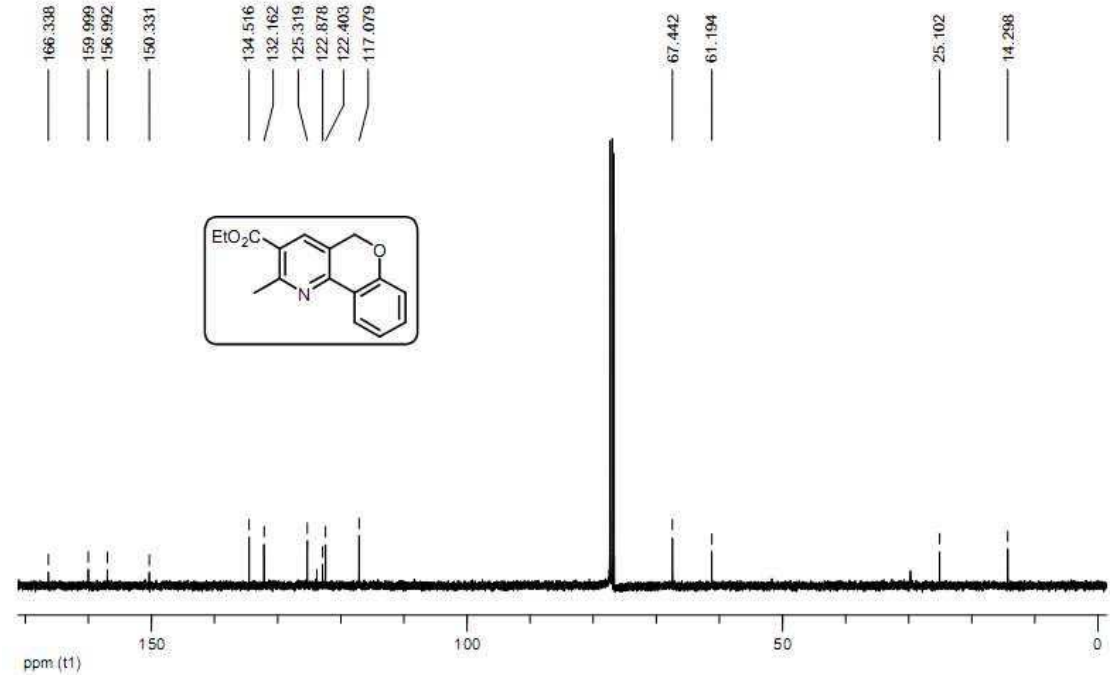

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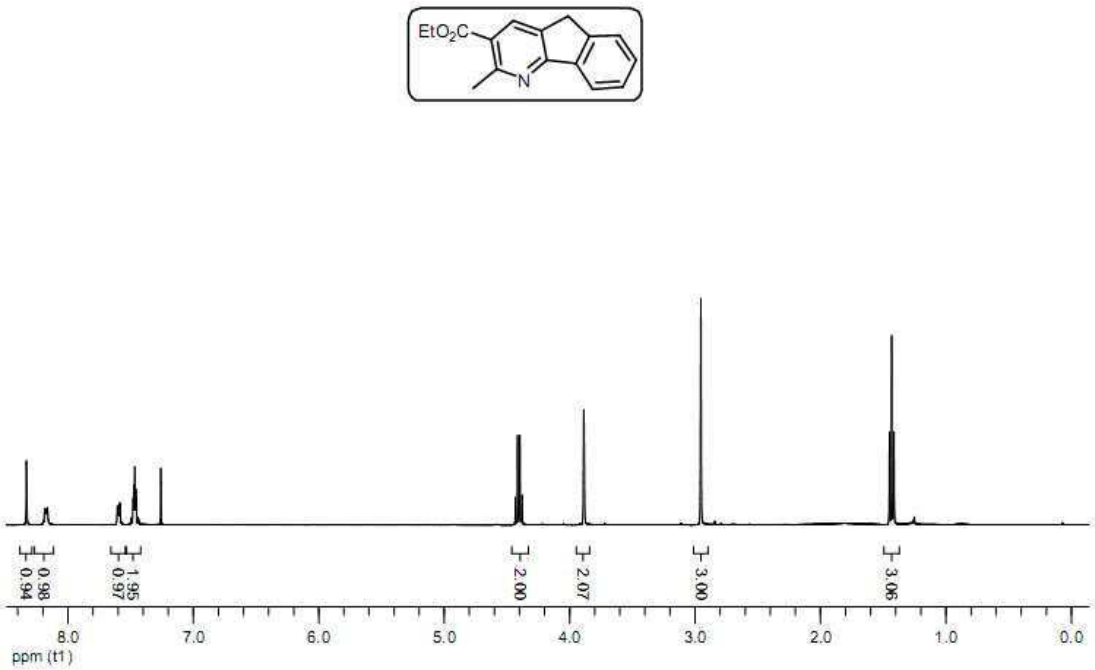

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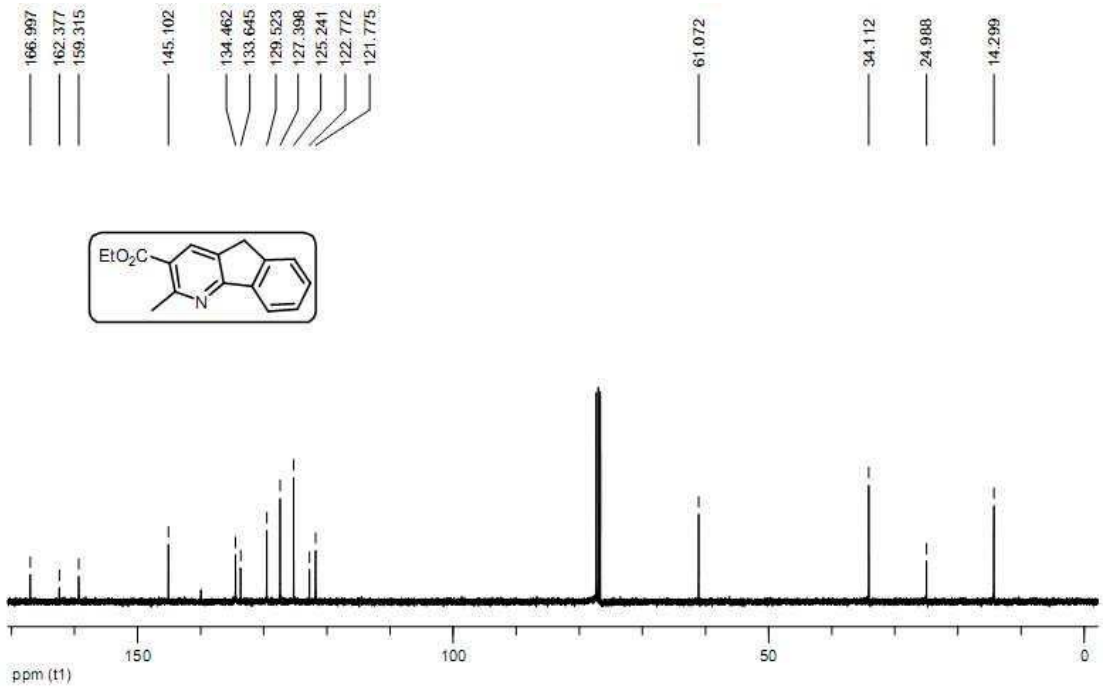

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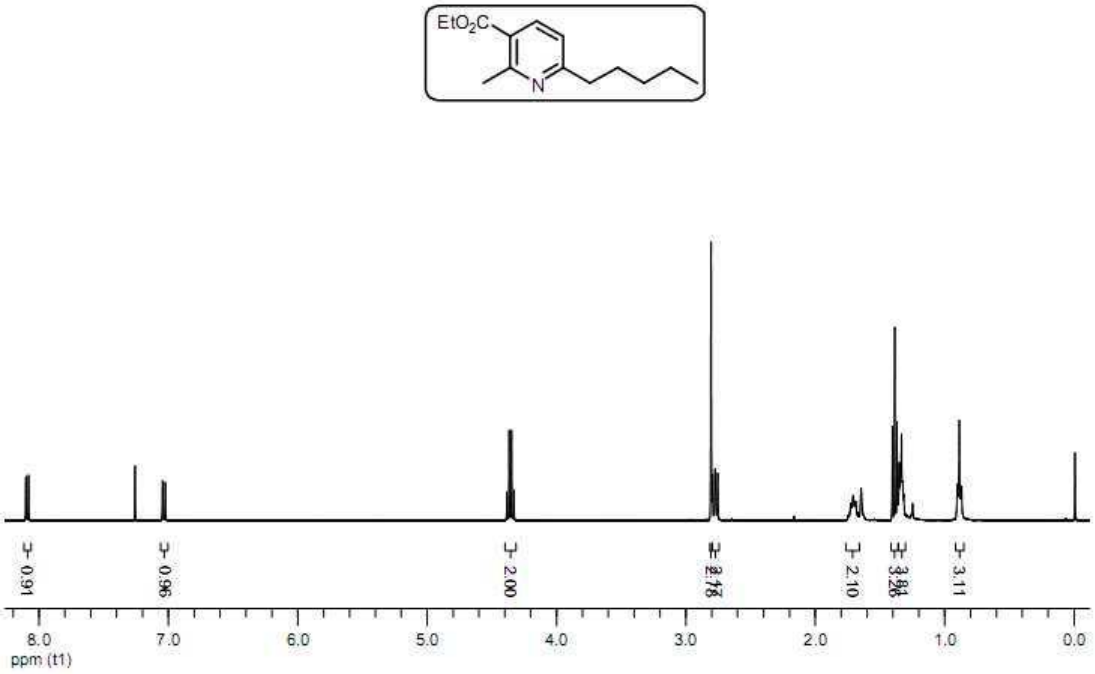

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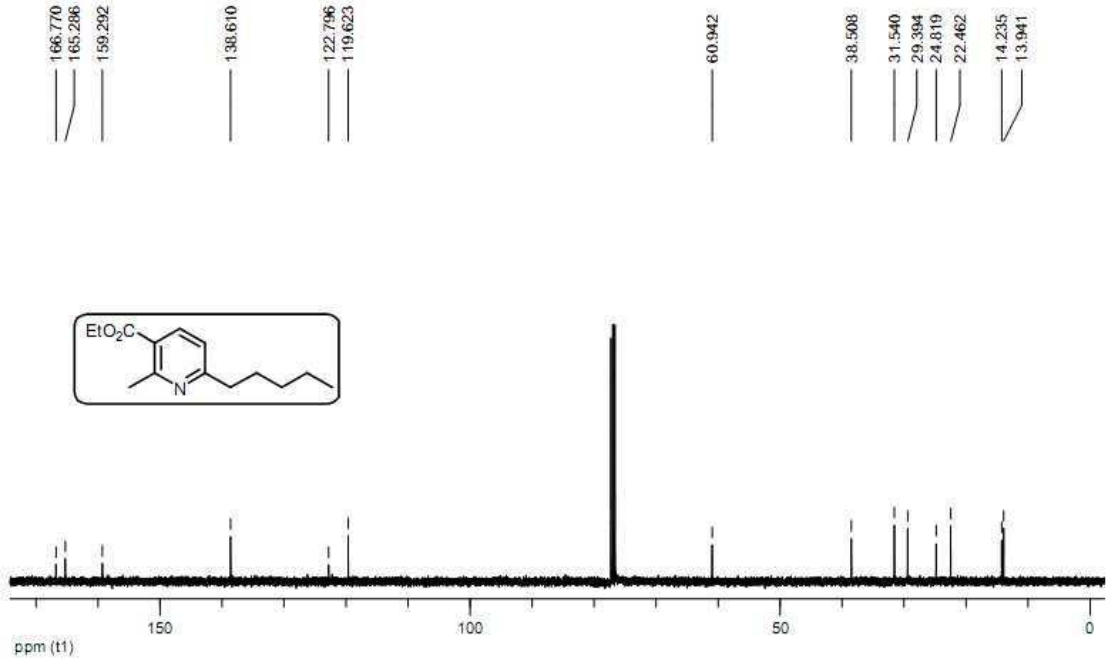

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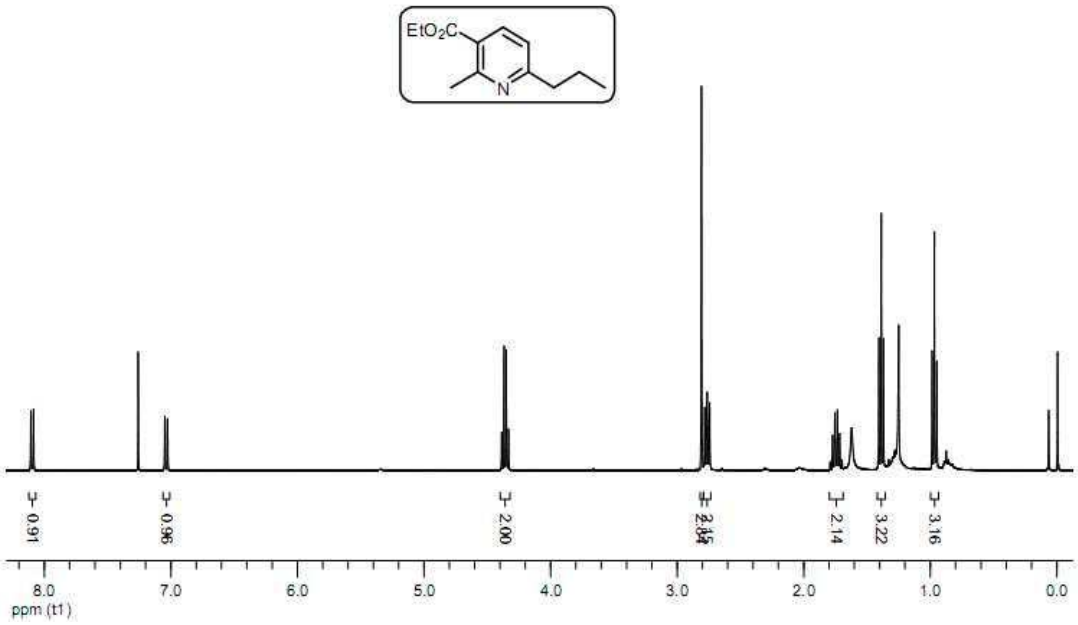

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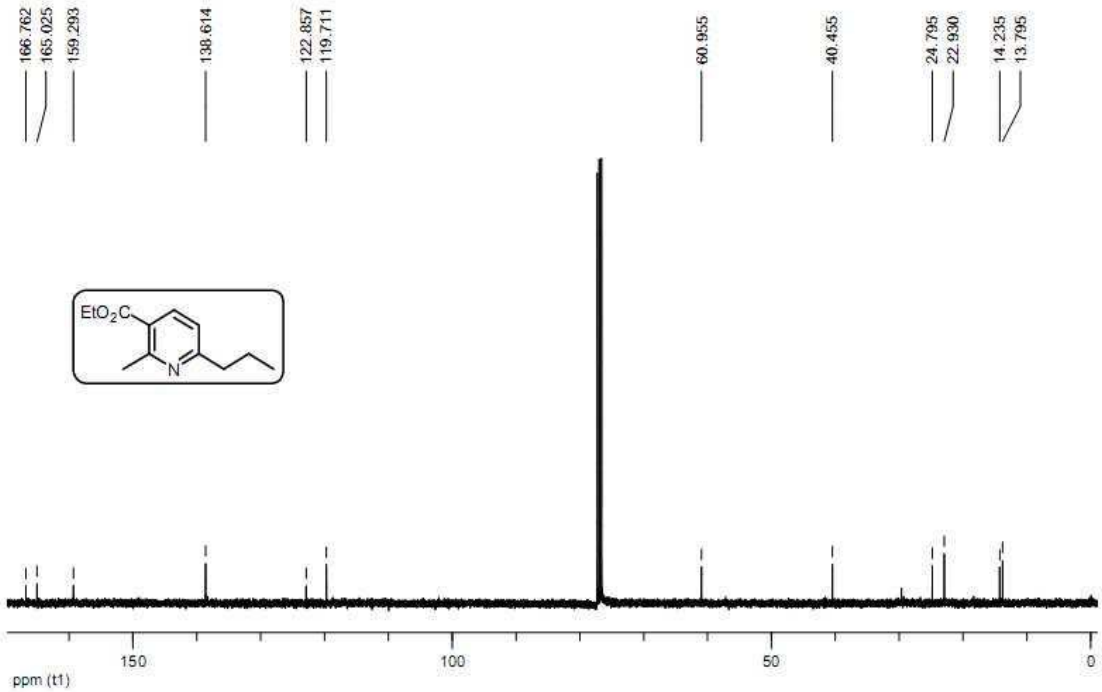

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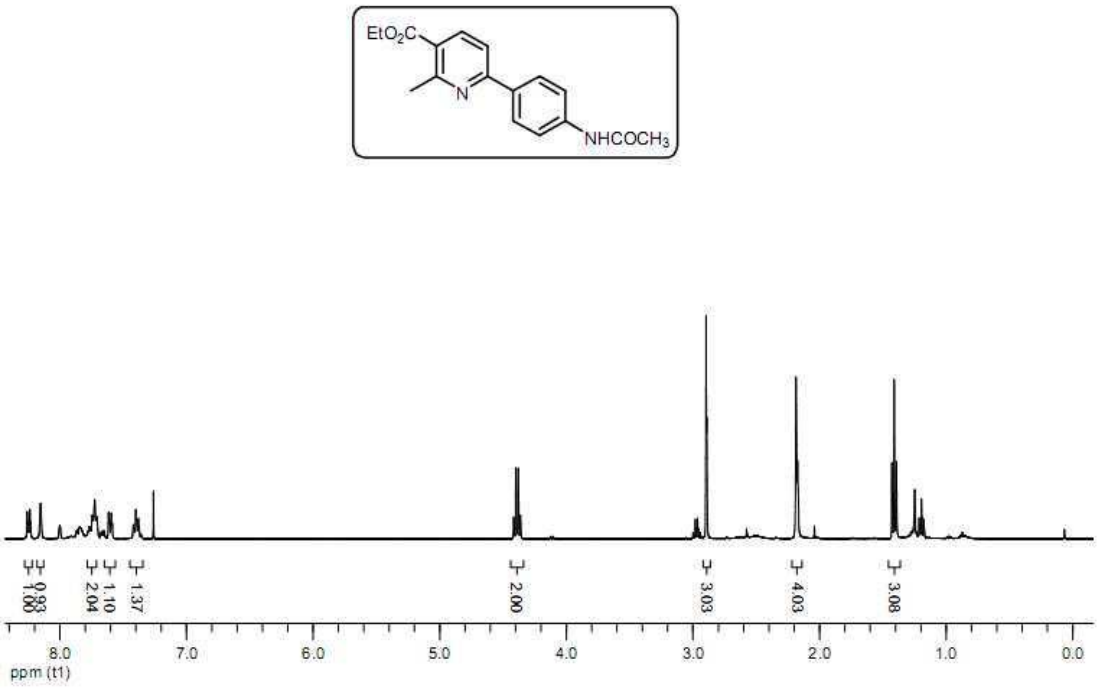

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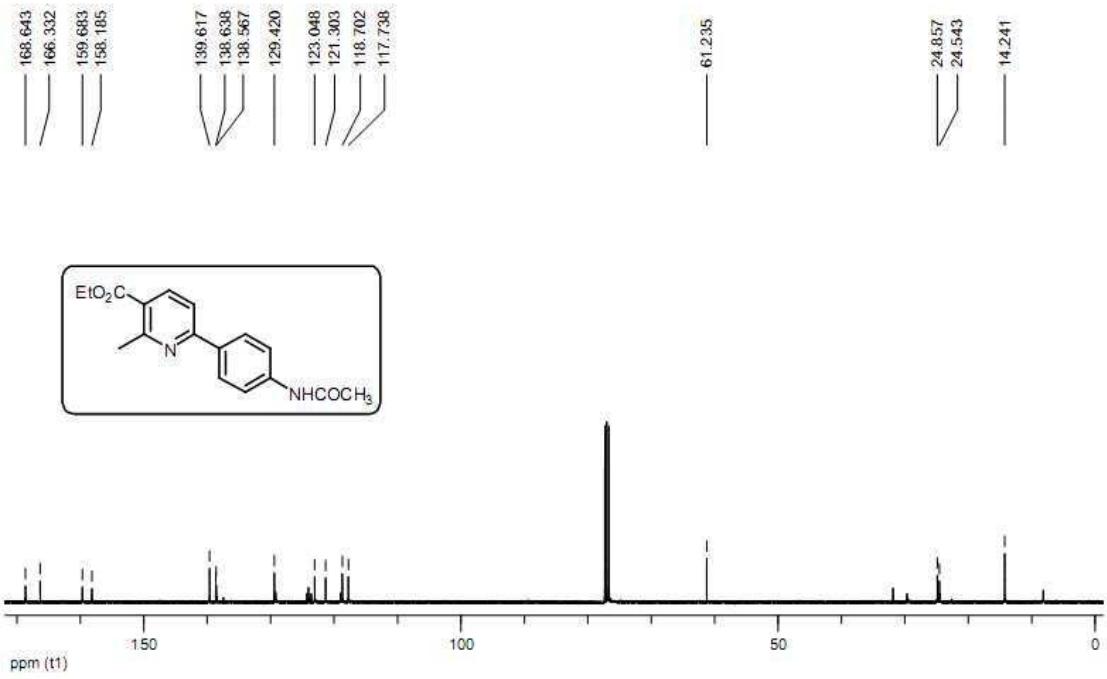

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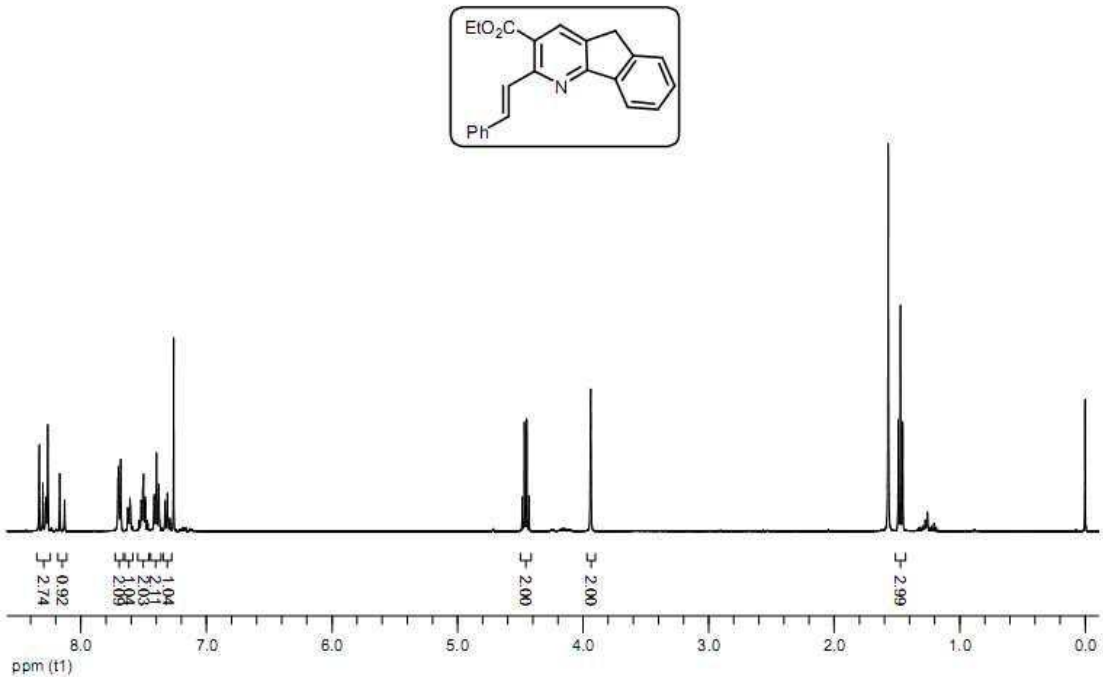

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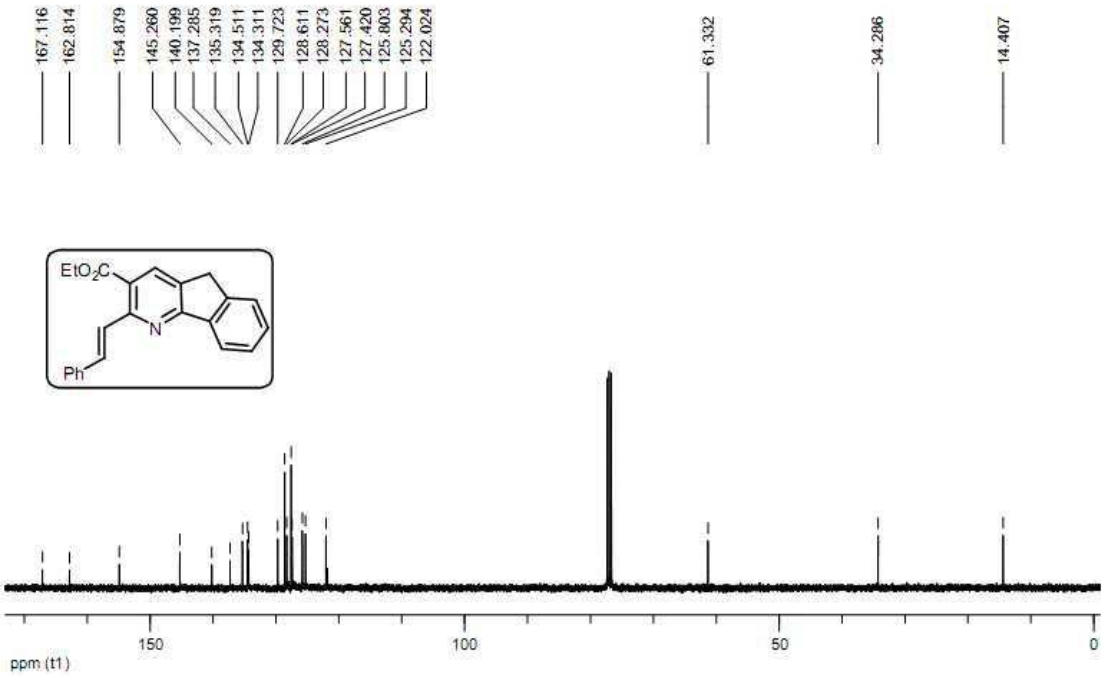

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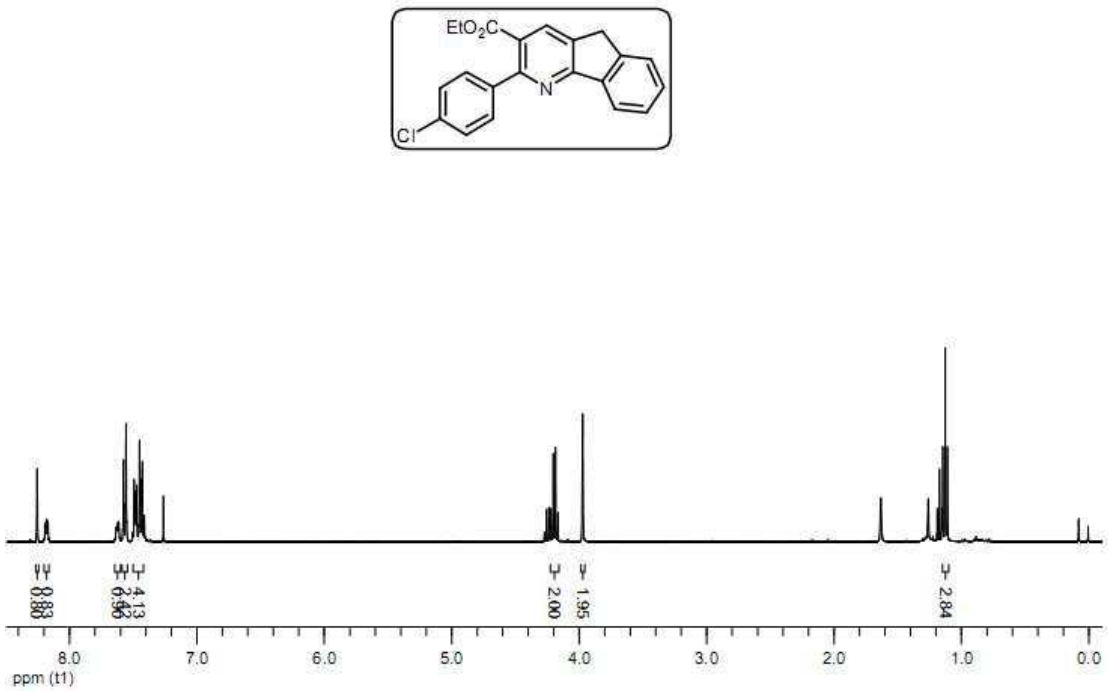
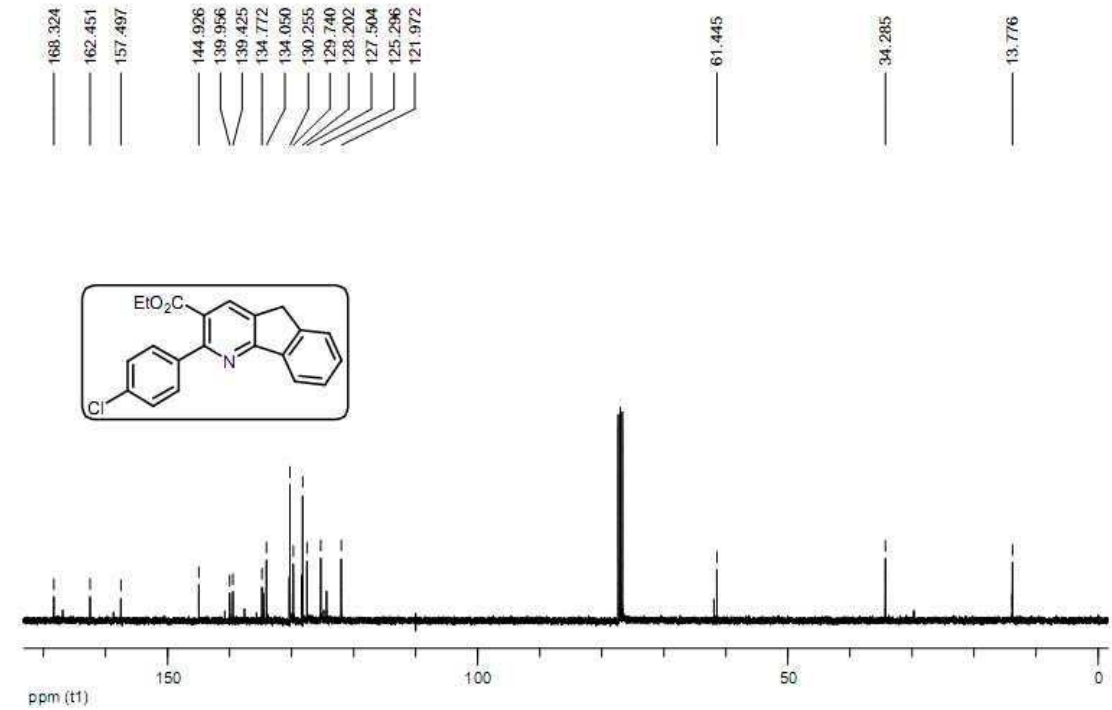


55k ^{13}C NMR ($CDCl_3$, 100 MHz)



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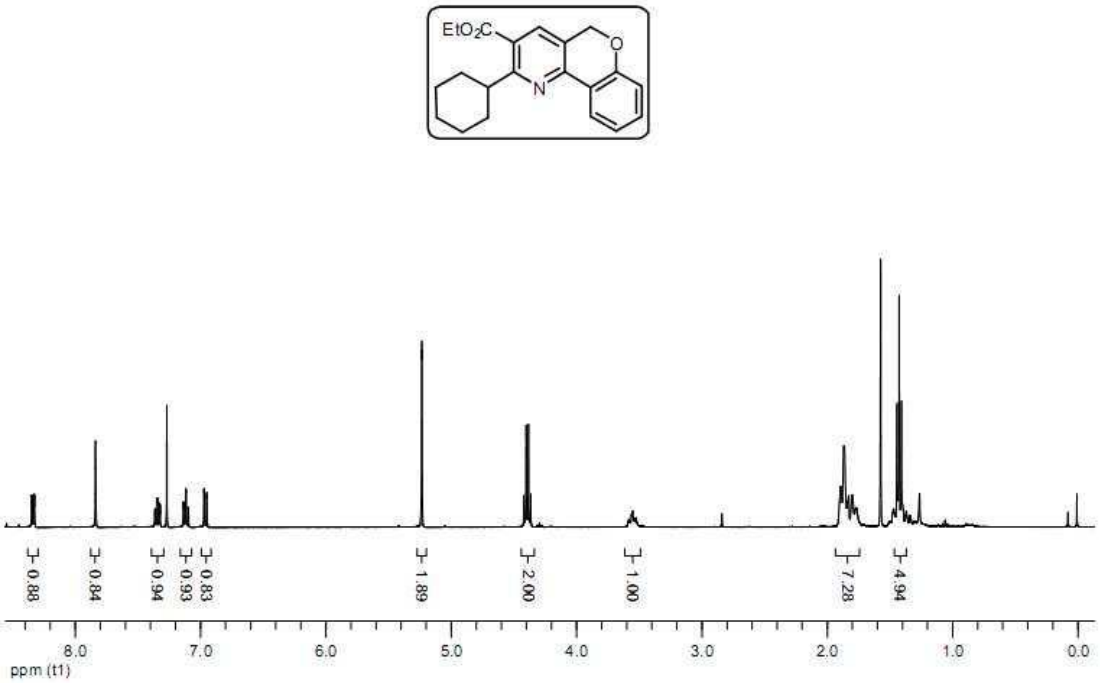

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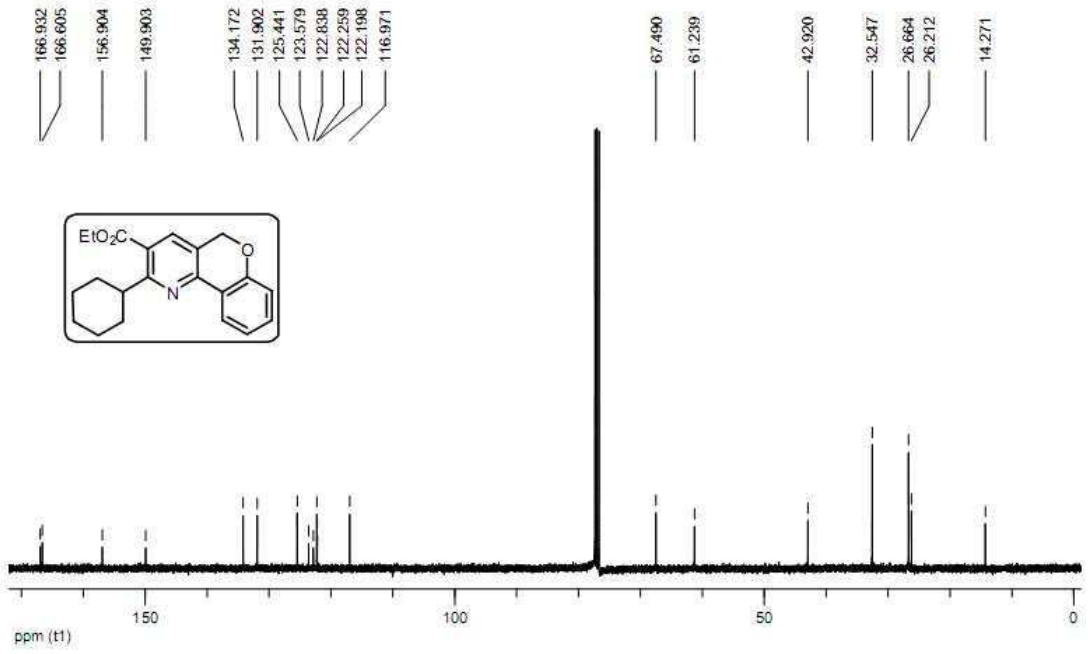
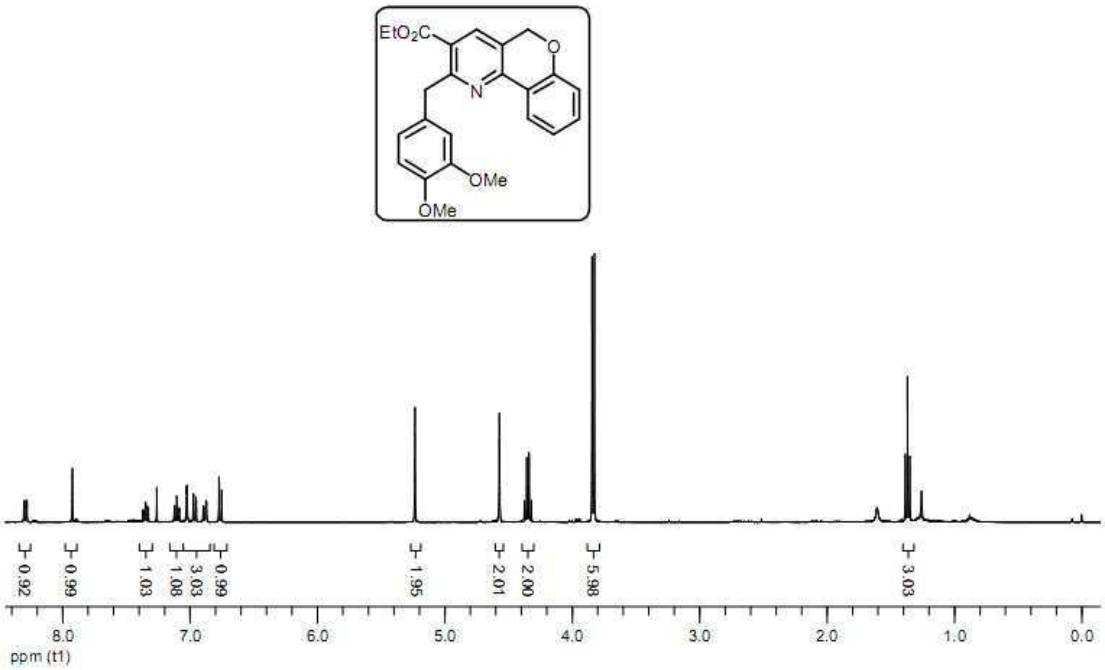


55m ^{1}H NMR ($CDCl_3$, 400 MHz)



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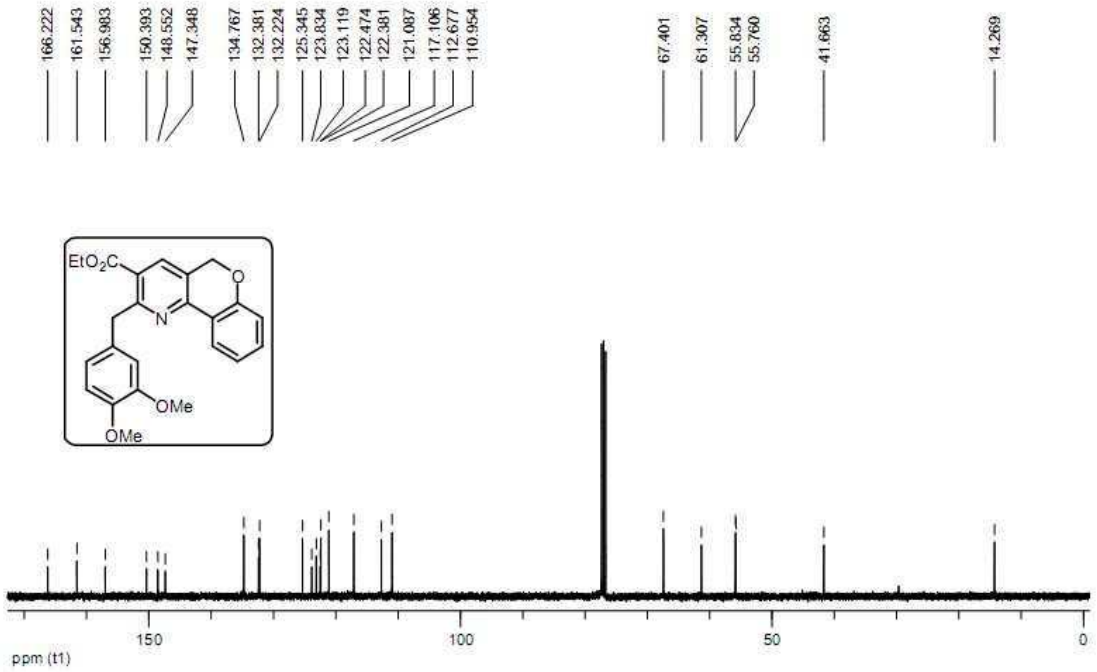
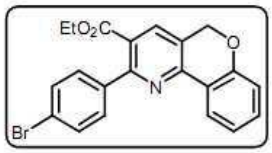
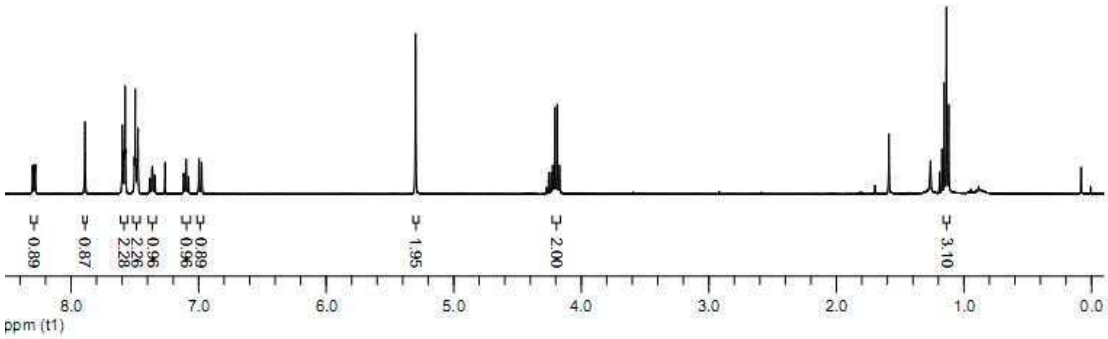


55n ^{1}H NMR ($CDCl_3$, 400 MHz)





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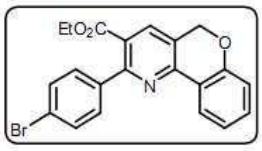

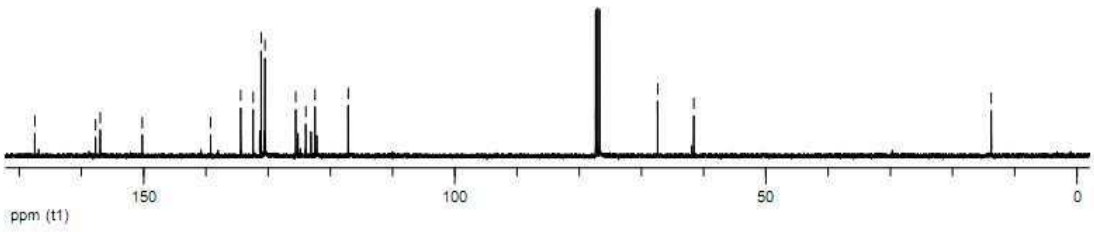

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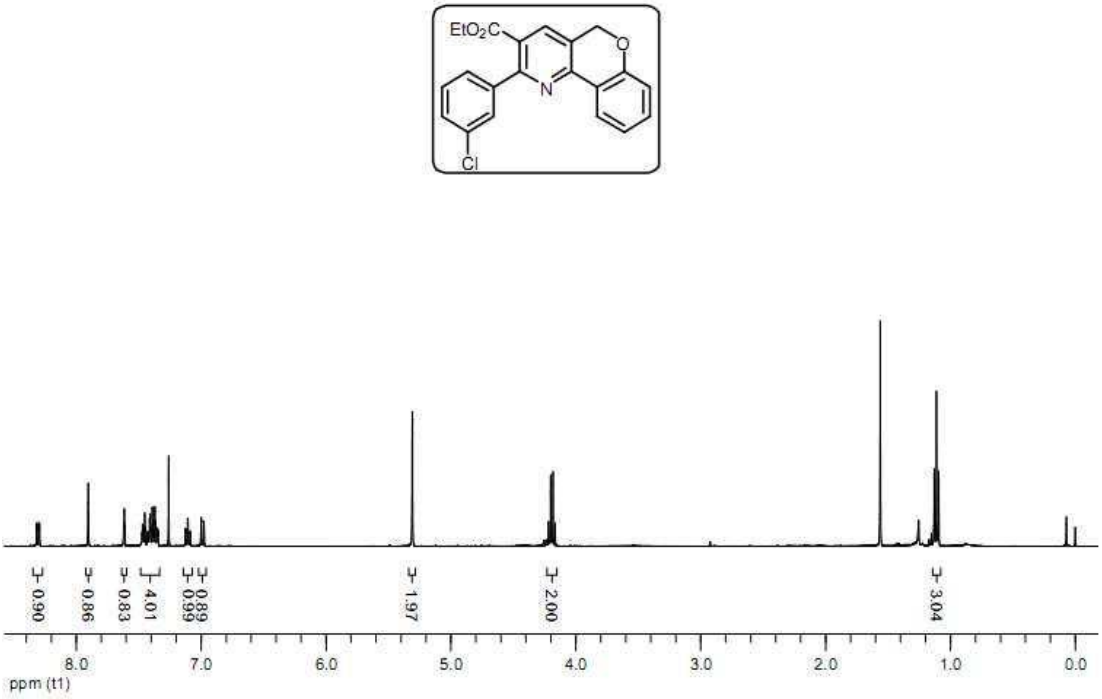

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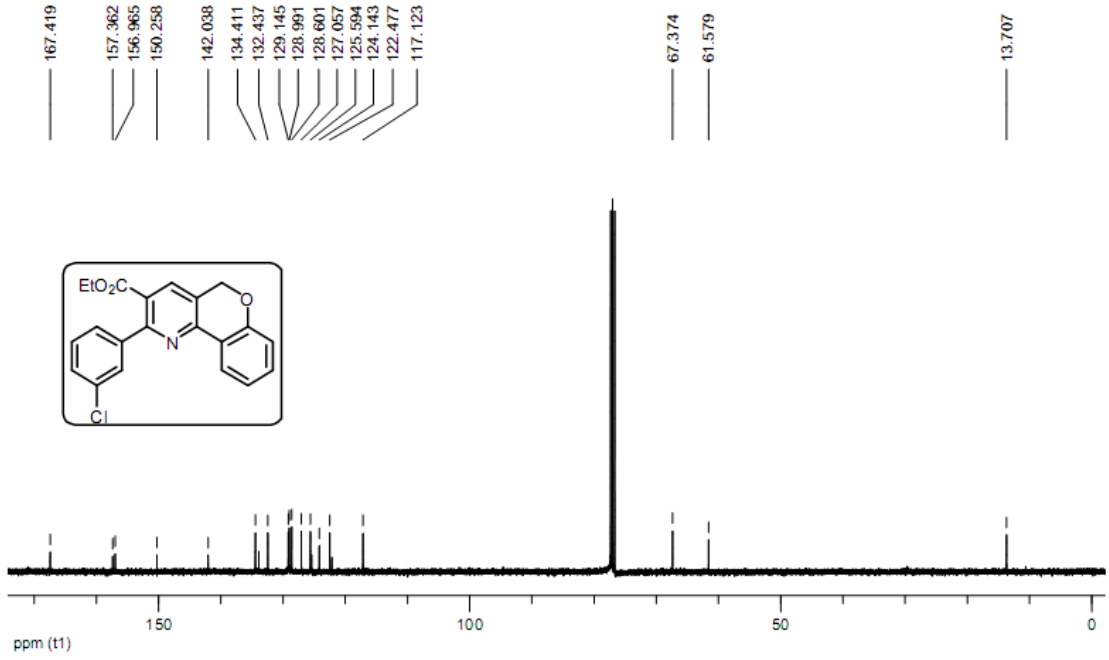

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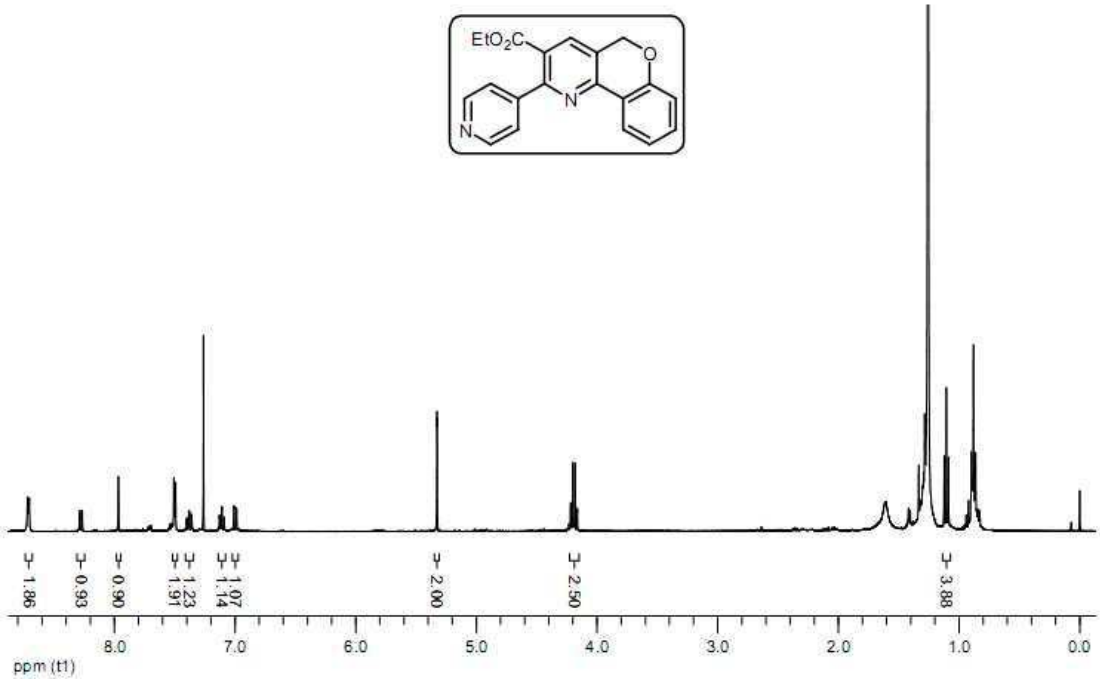

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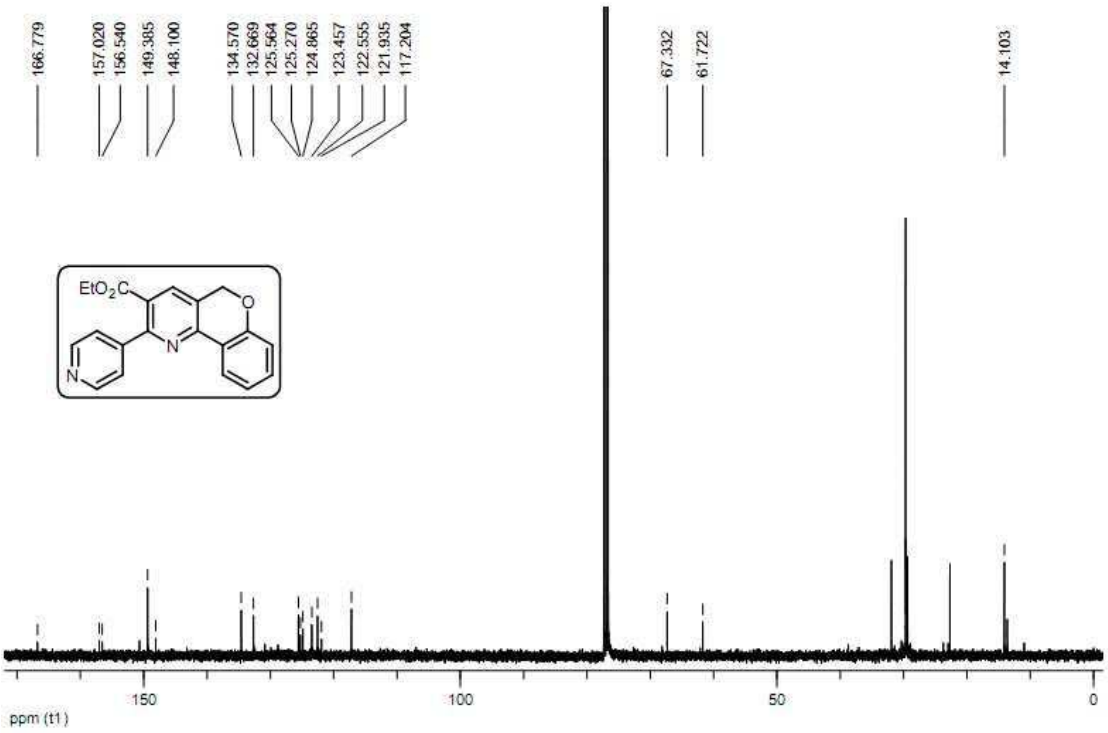

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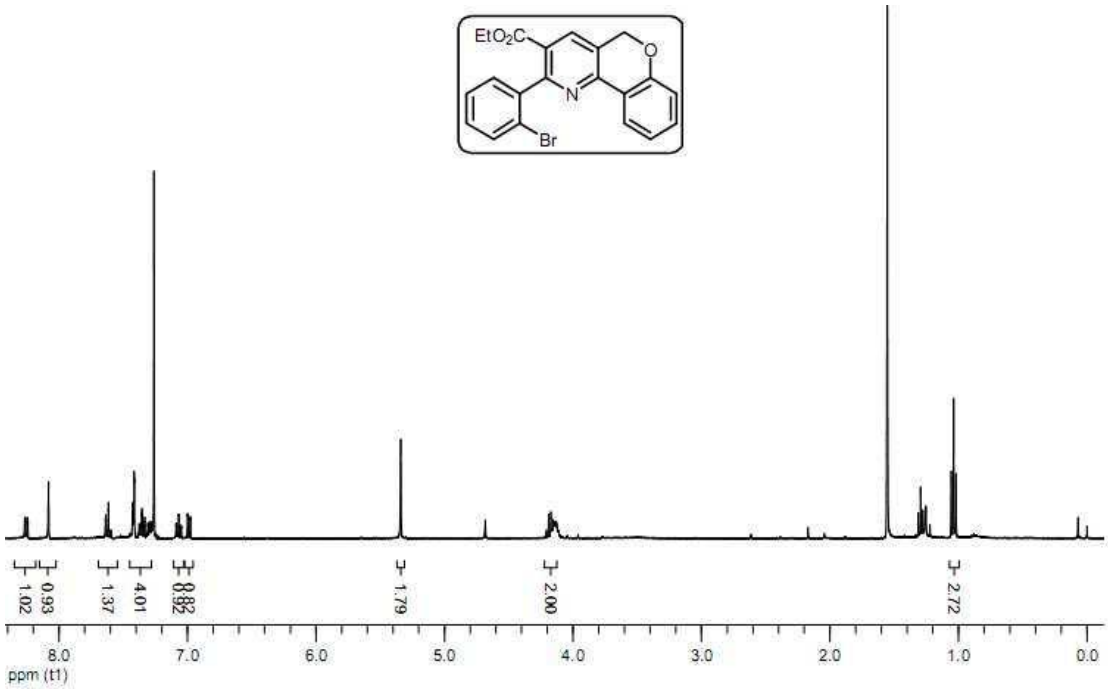

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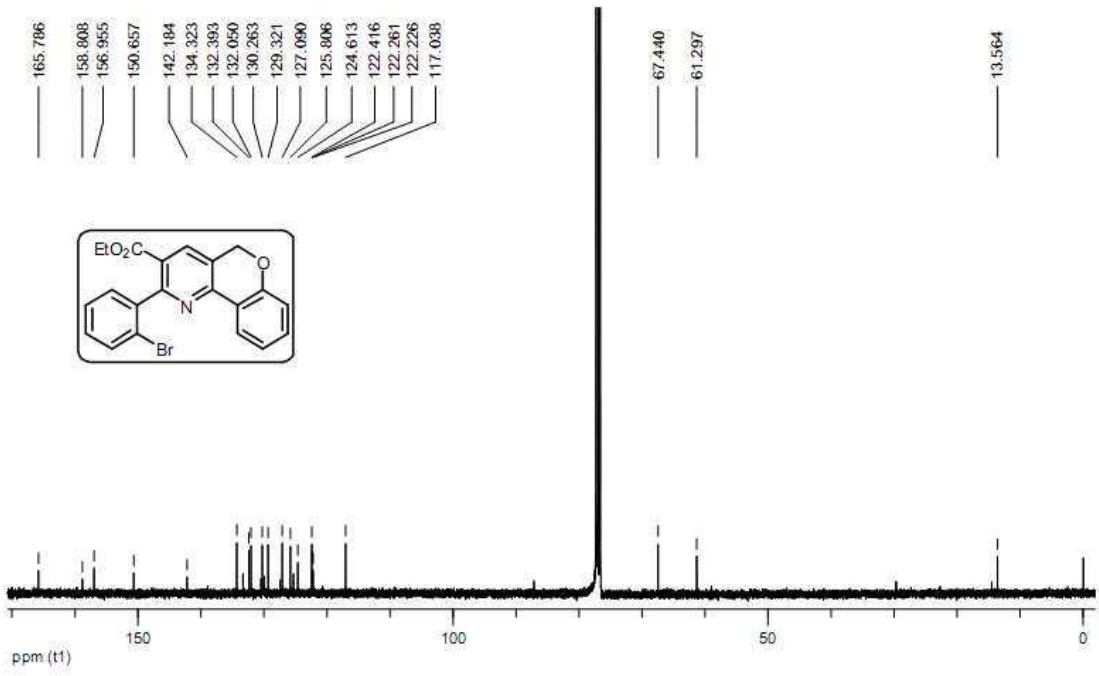

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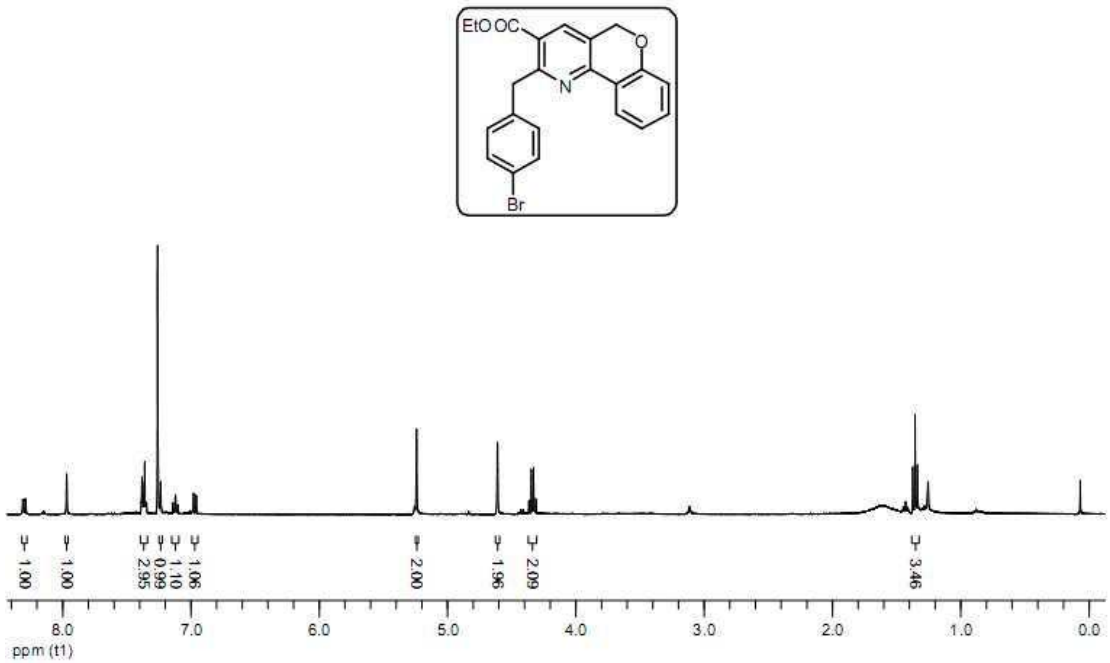

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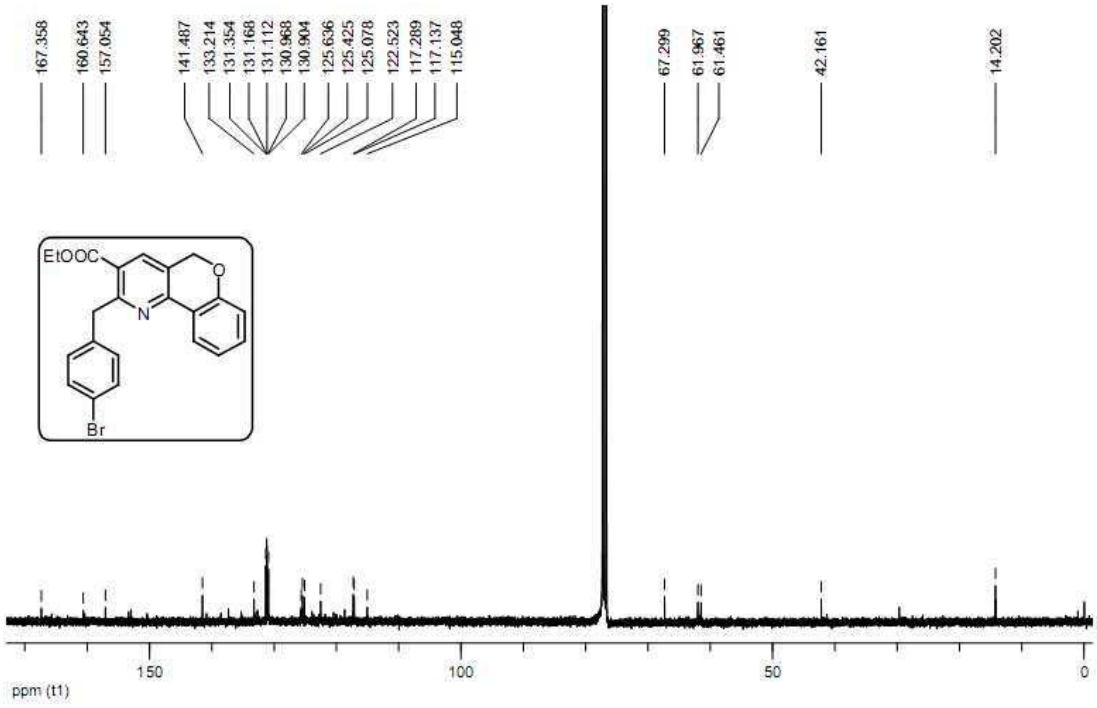

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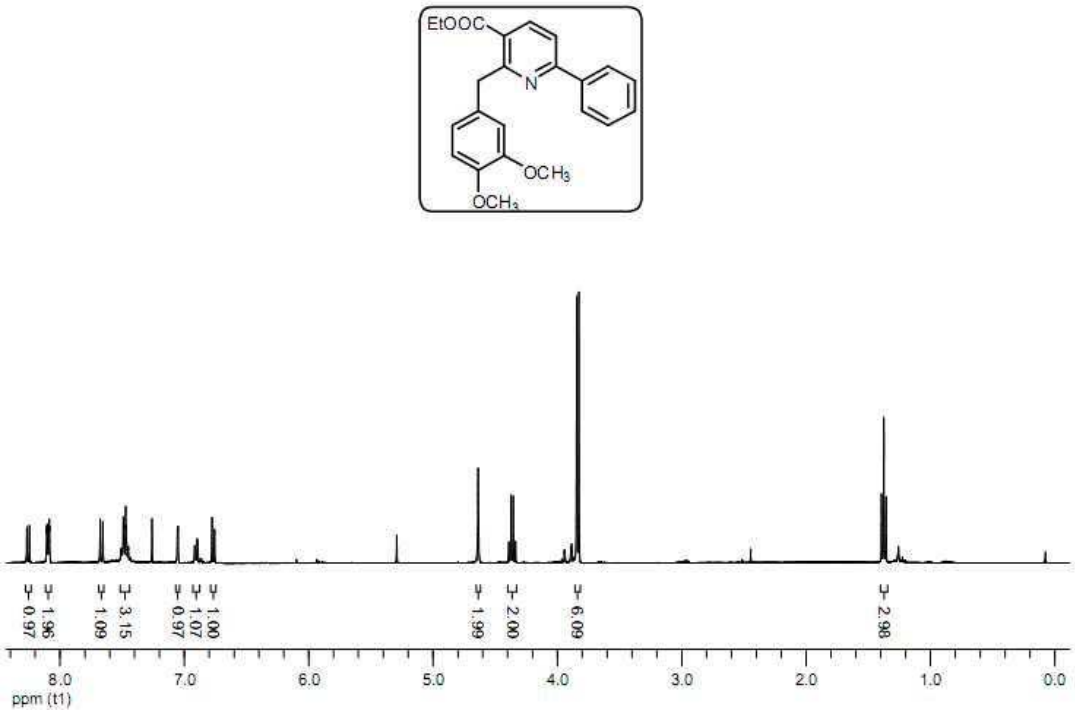

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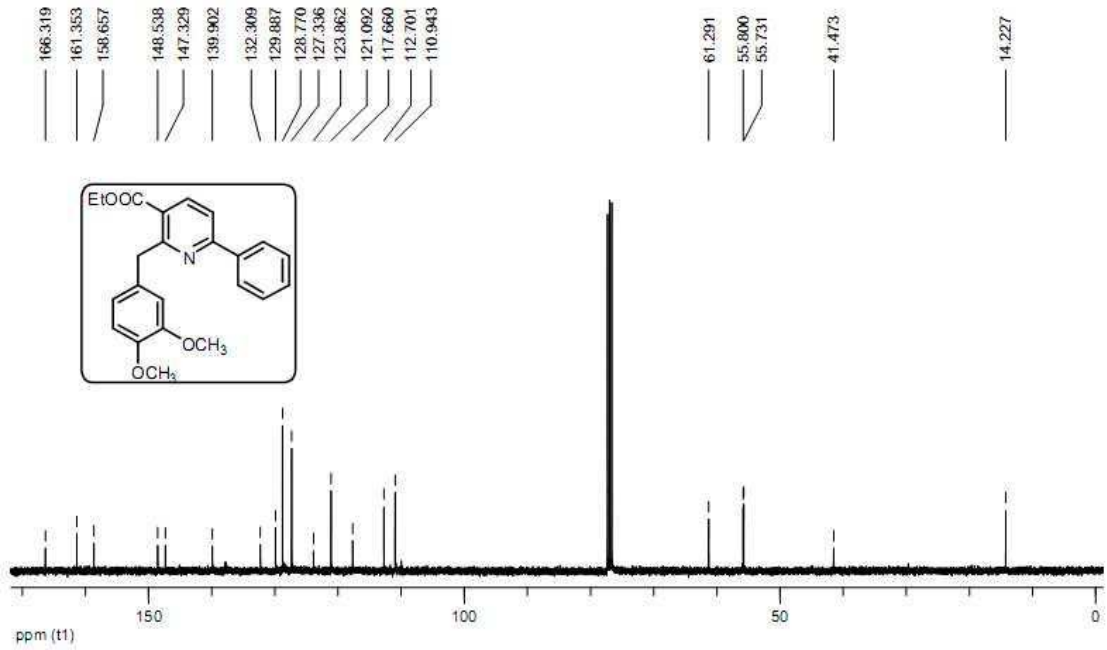

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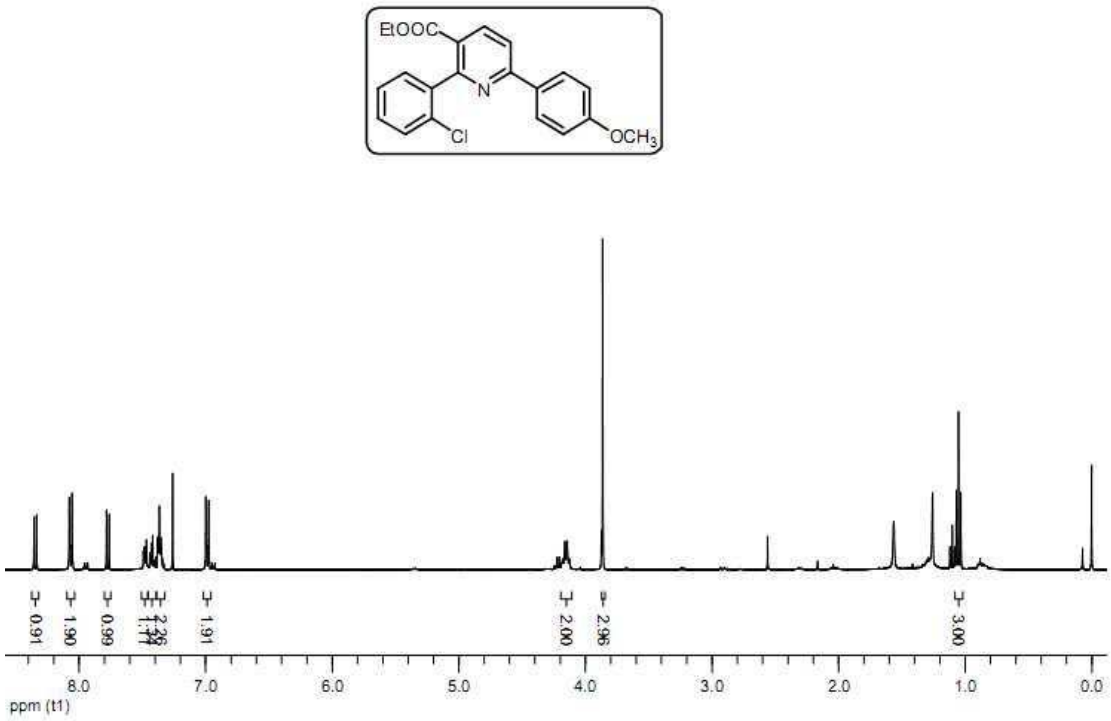

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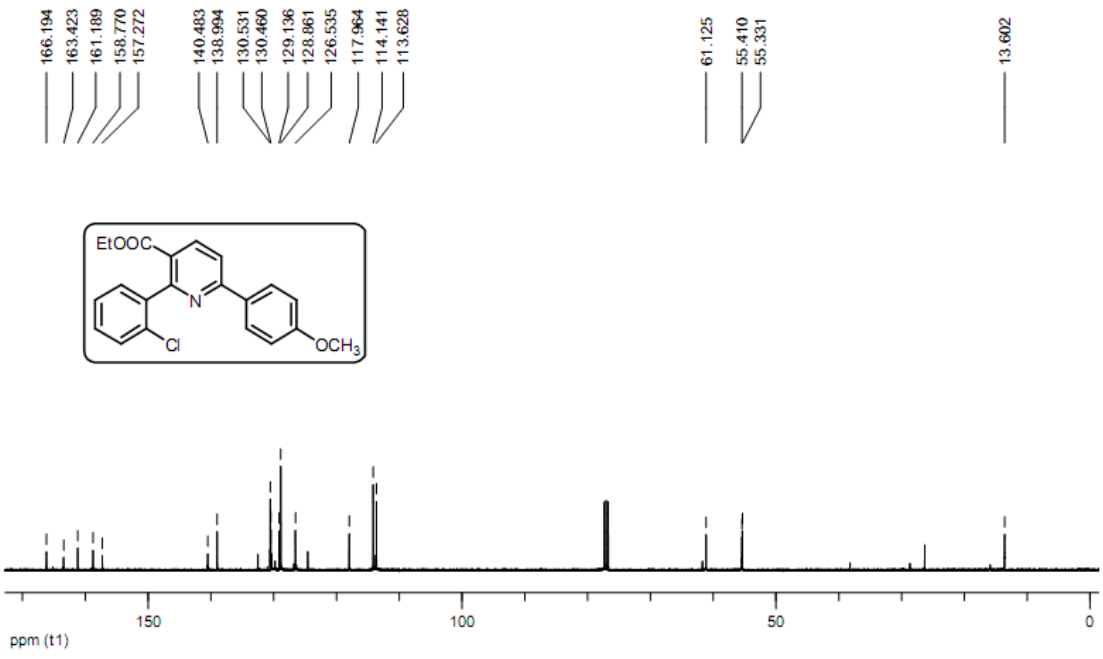

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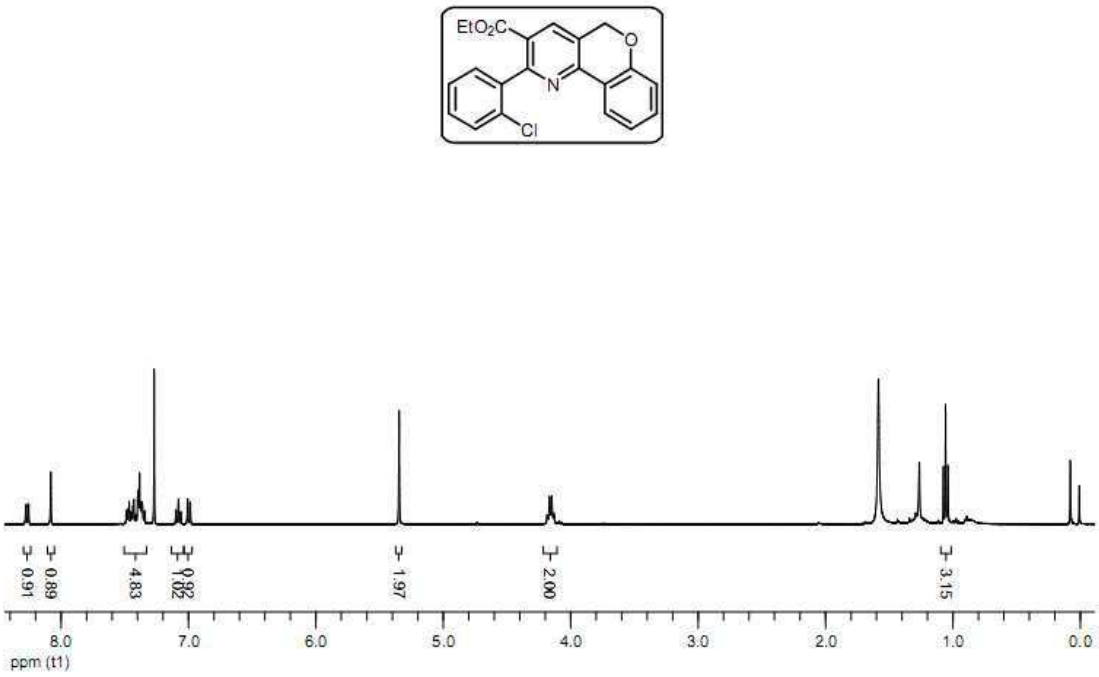

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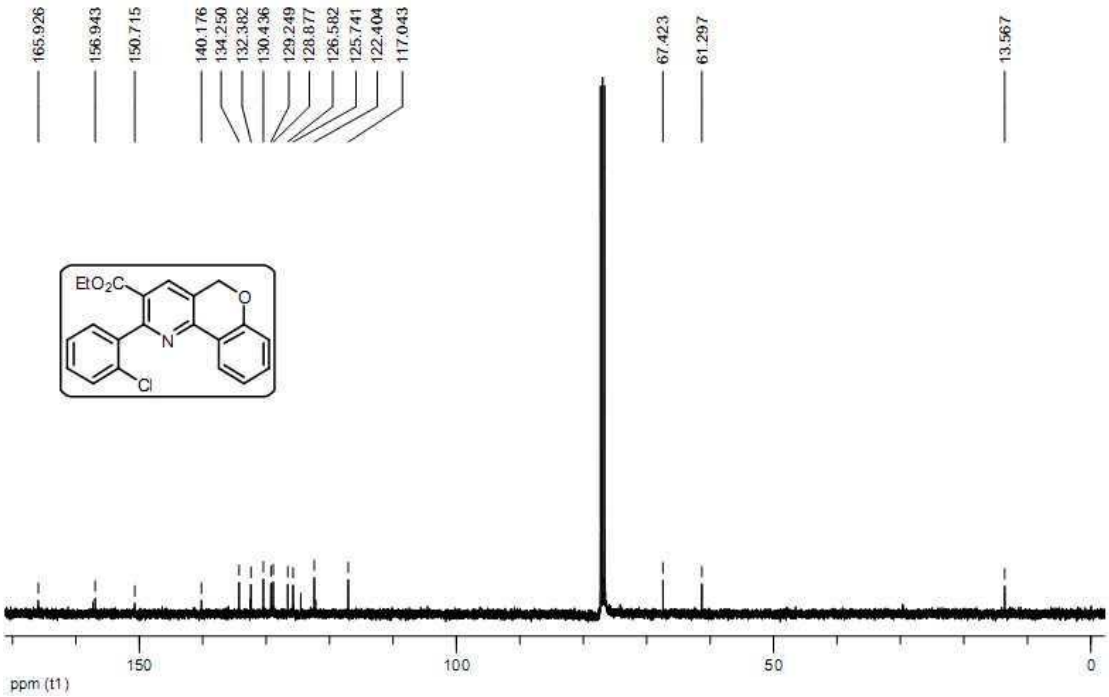

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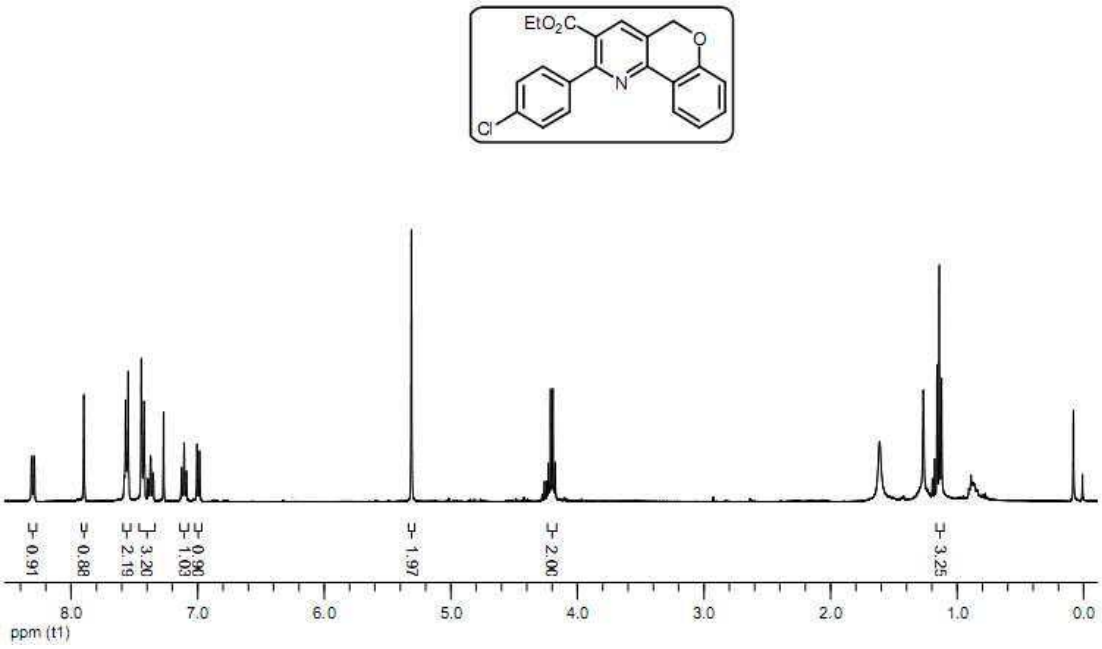

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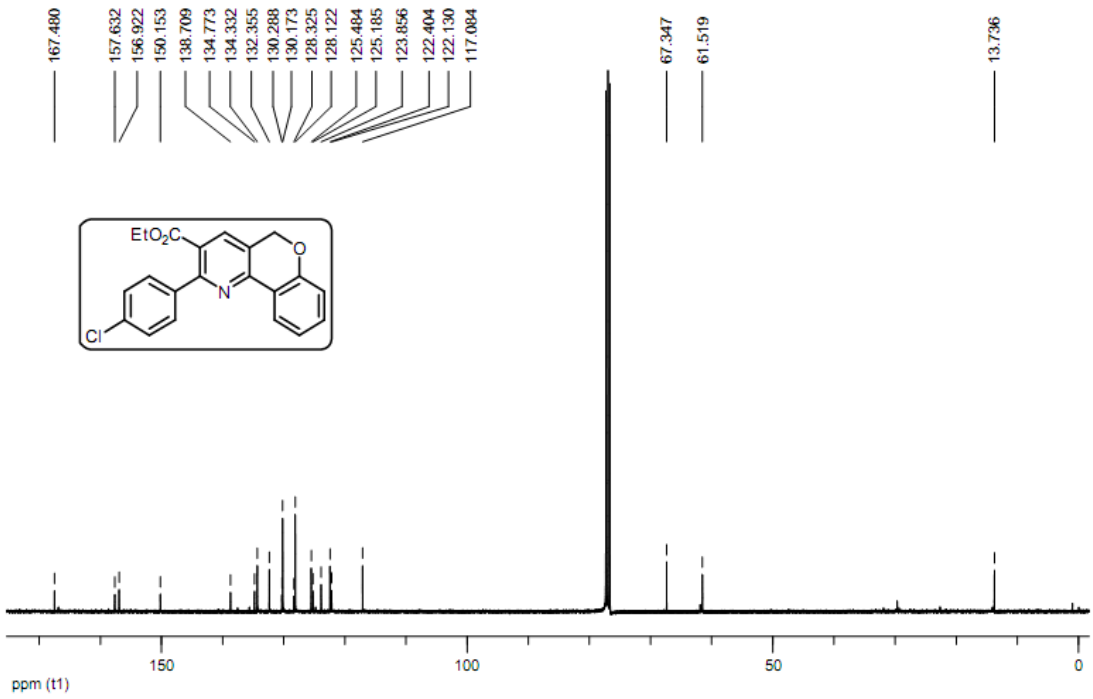

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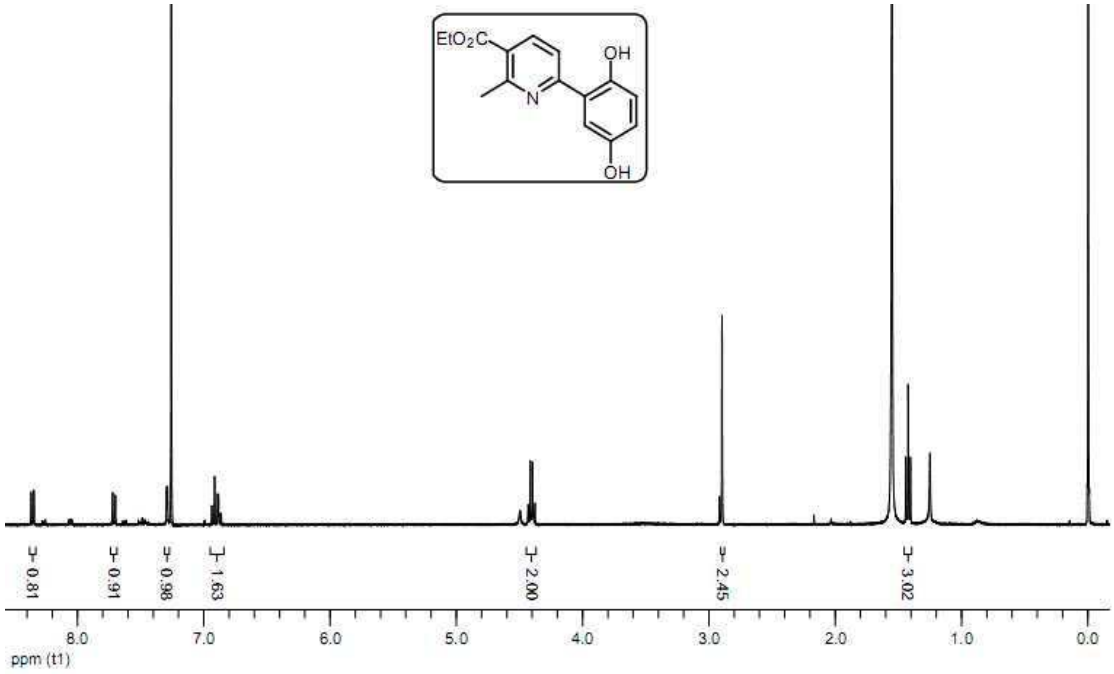
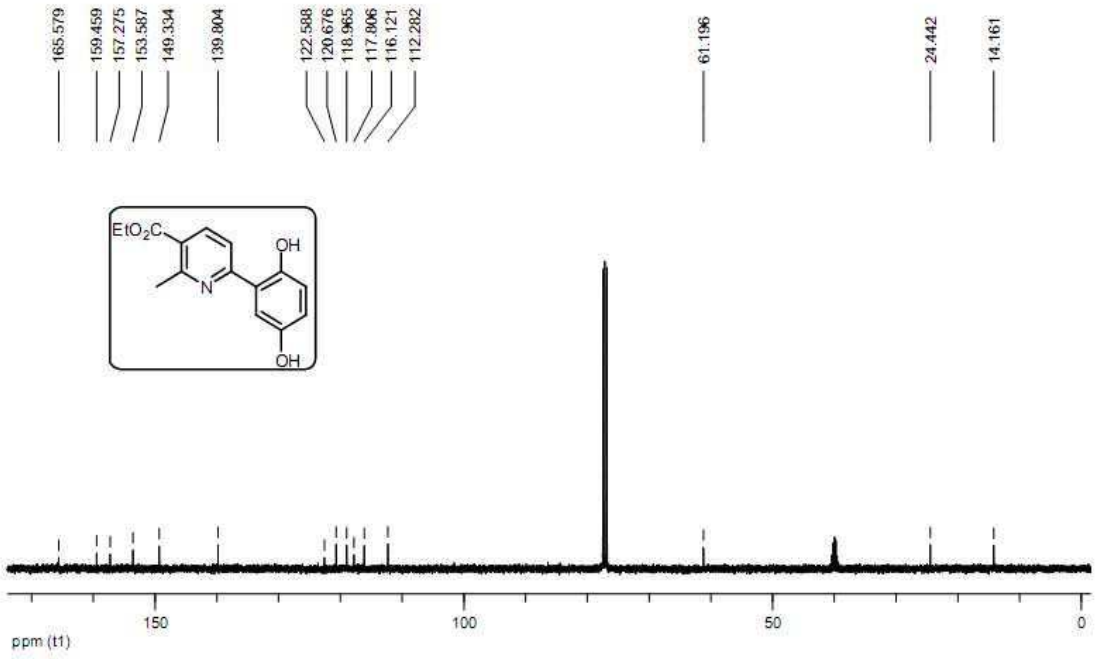
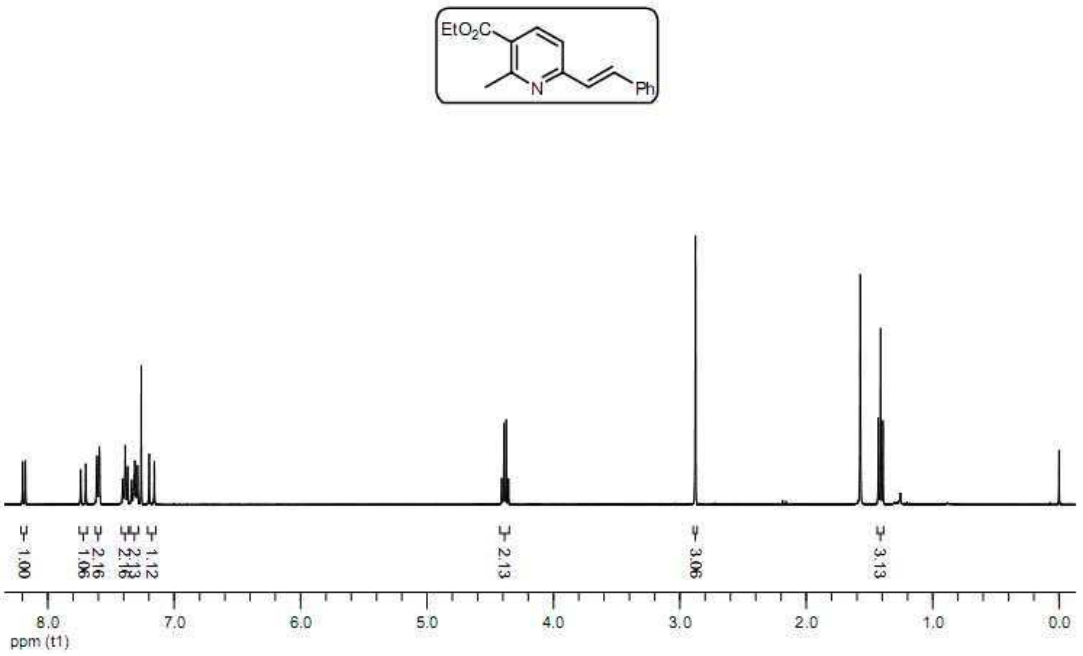


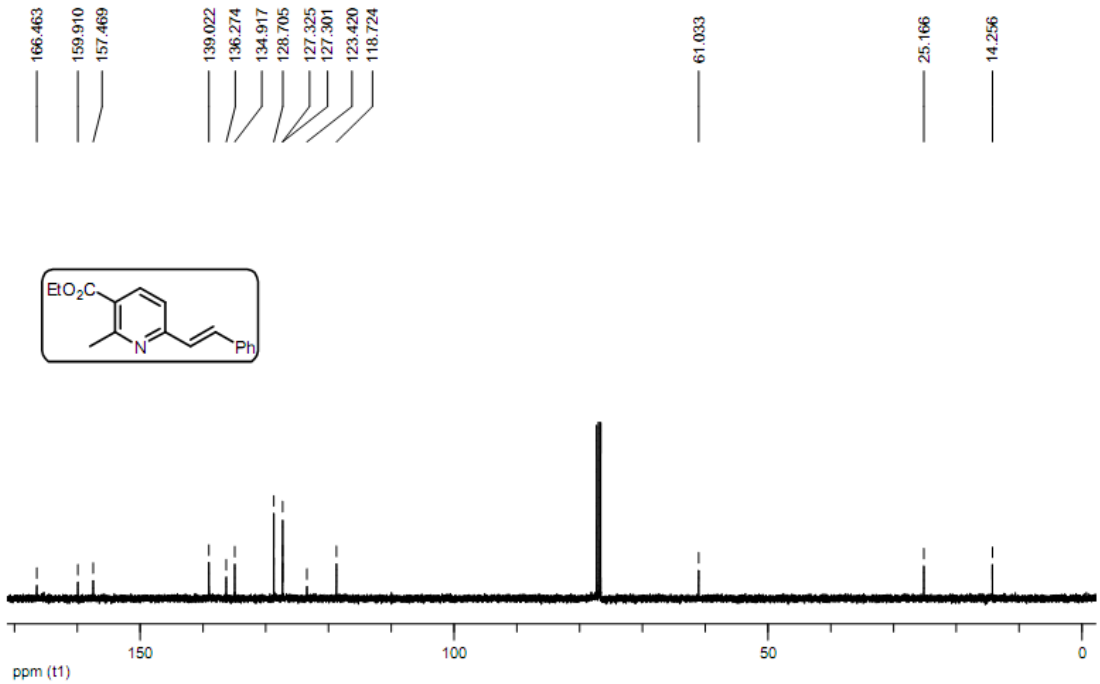
55w ^{13}C NMR ($CDCl_3$, 100 MHz)



55x ^{1}H NMR ($CDCl_3$, 400 MHz)



55x ^{13}C NMR ($CDCl_3$, 100 MHz)



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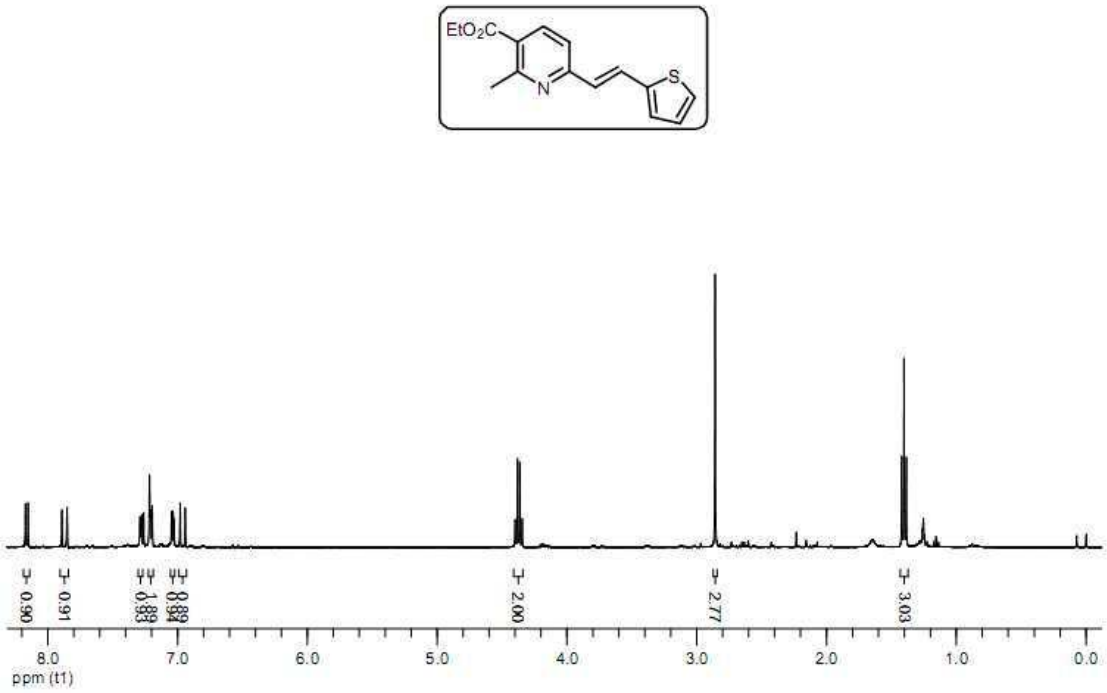
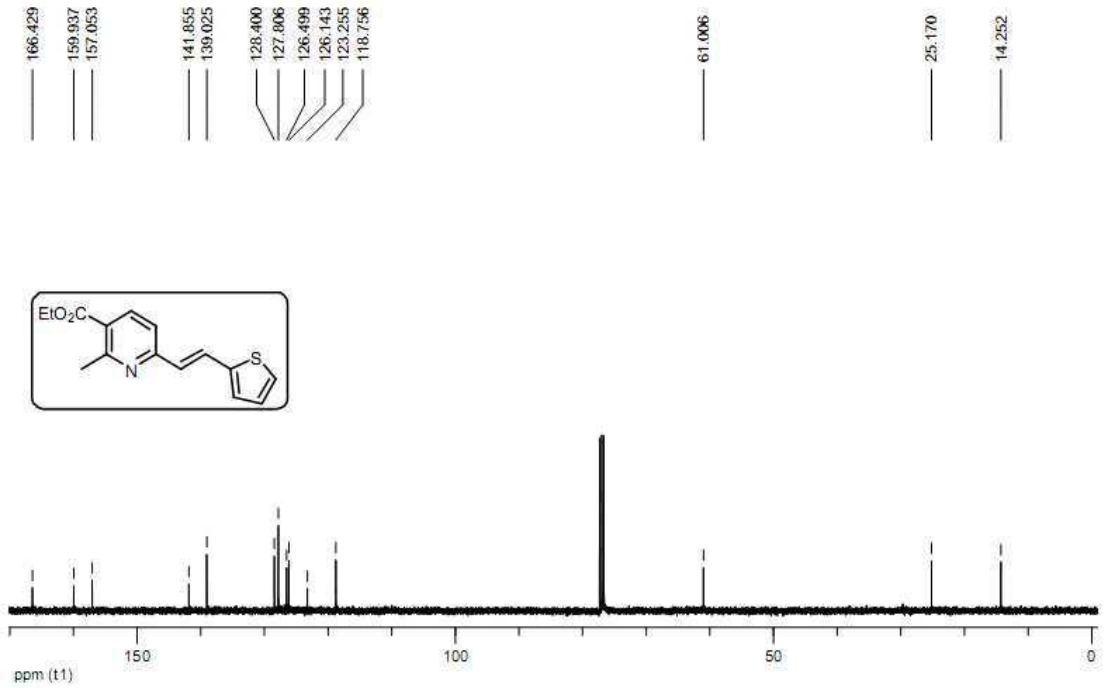
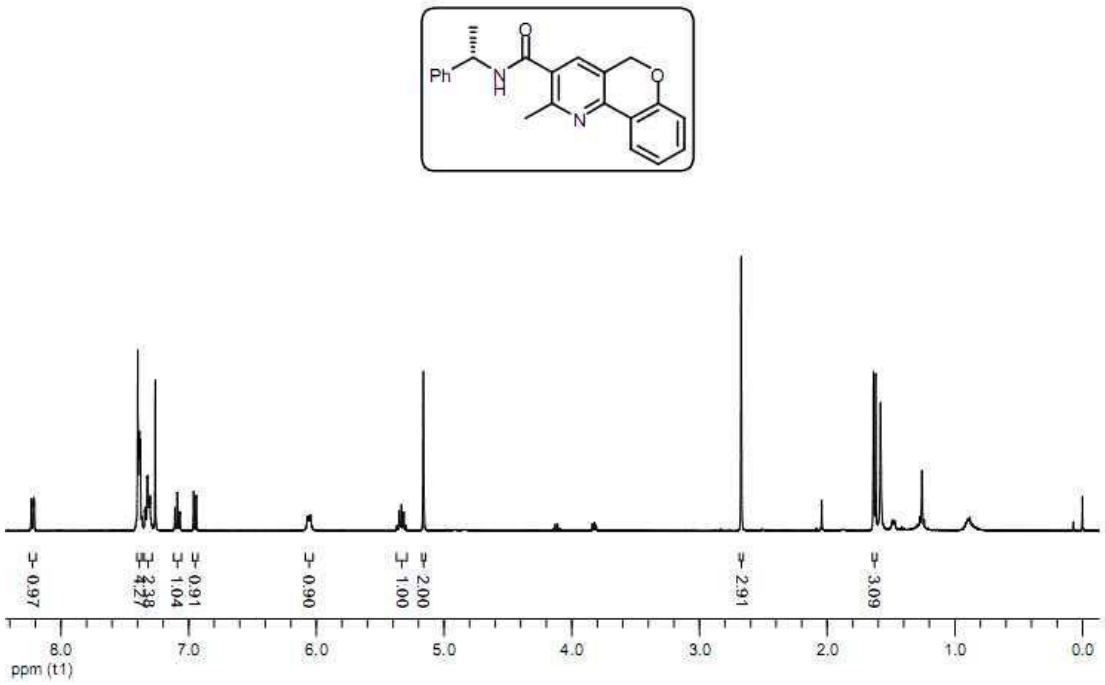


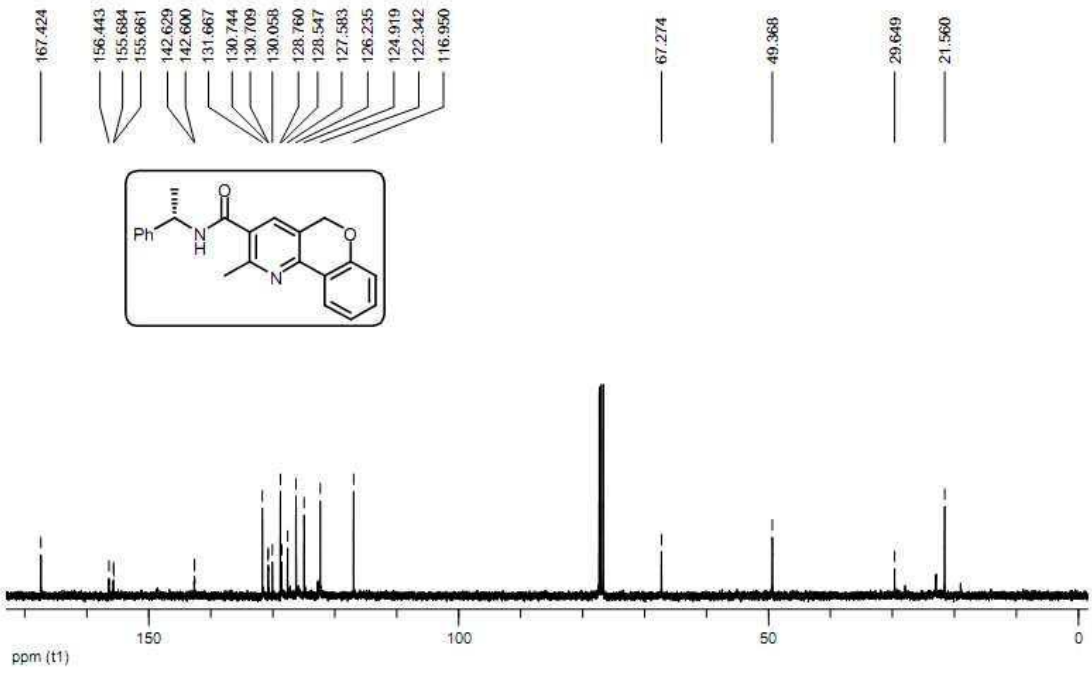
55y ^{13}C NMR ($CDCl_3$, 100 MHz)



57a ^{1}H NMR ($CDCl_3$, 400 MHz)



57a ^{13}C NMR ($CDCl_3$, 100 MHz)



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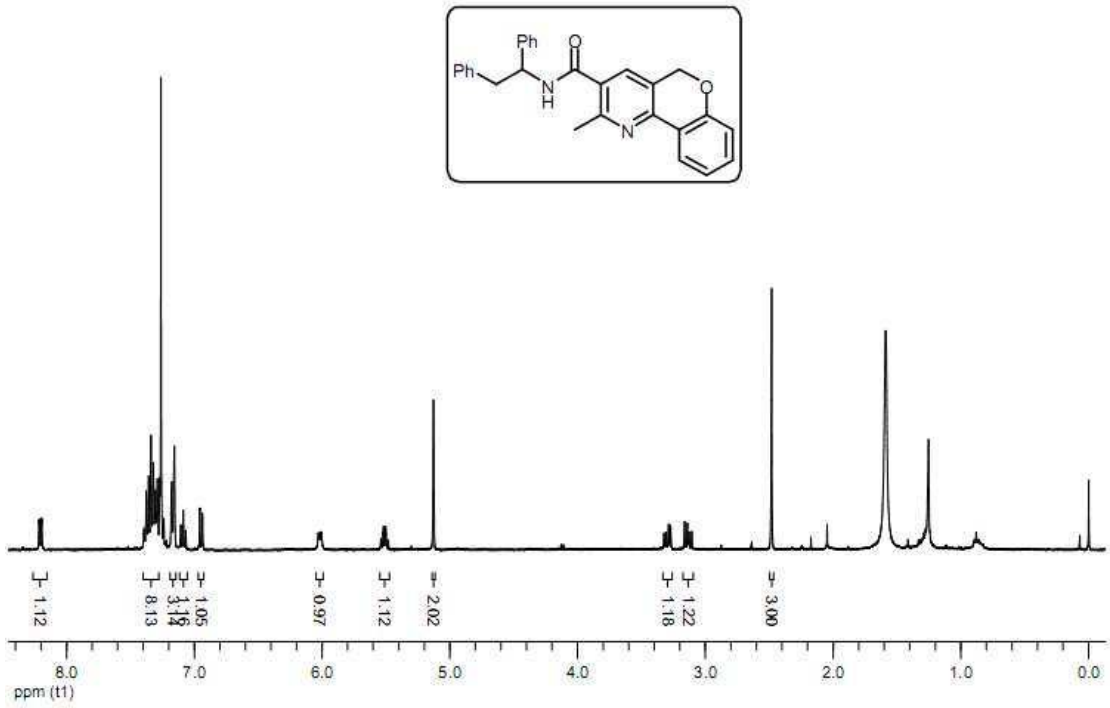
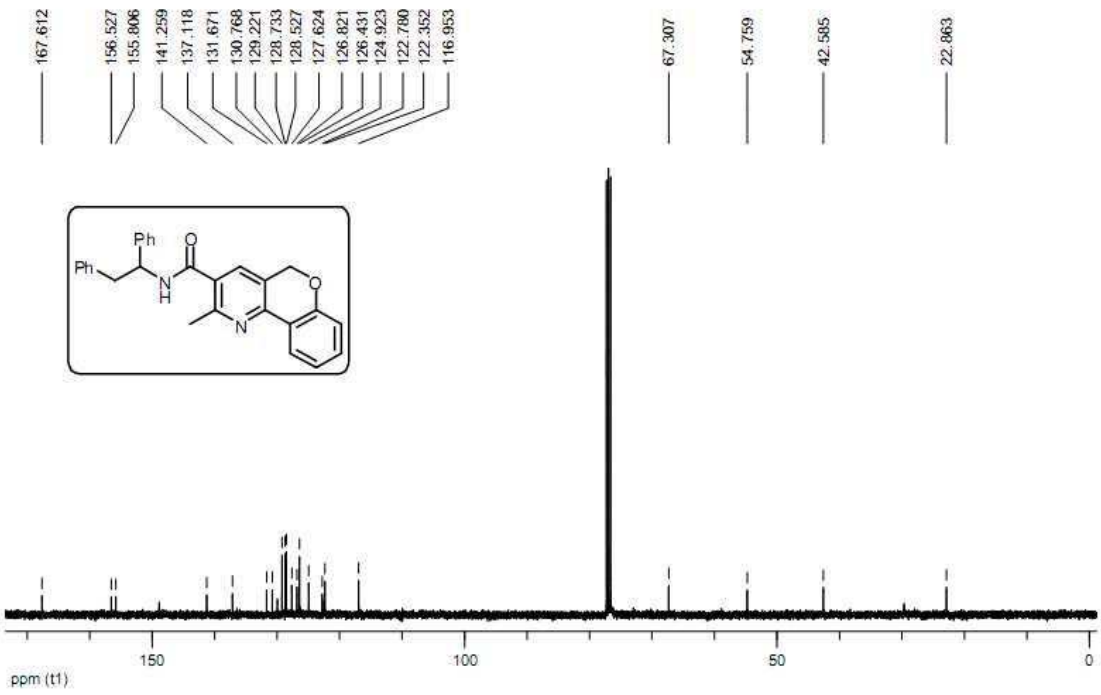


57b ^{13}C NMR ($CDCl_3$, 100 MHz



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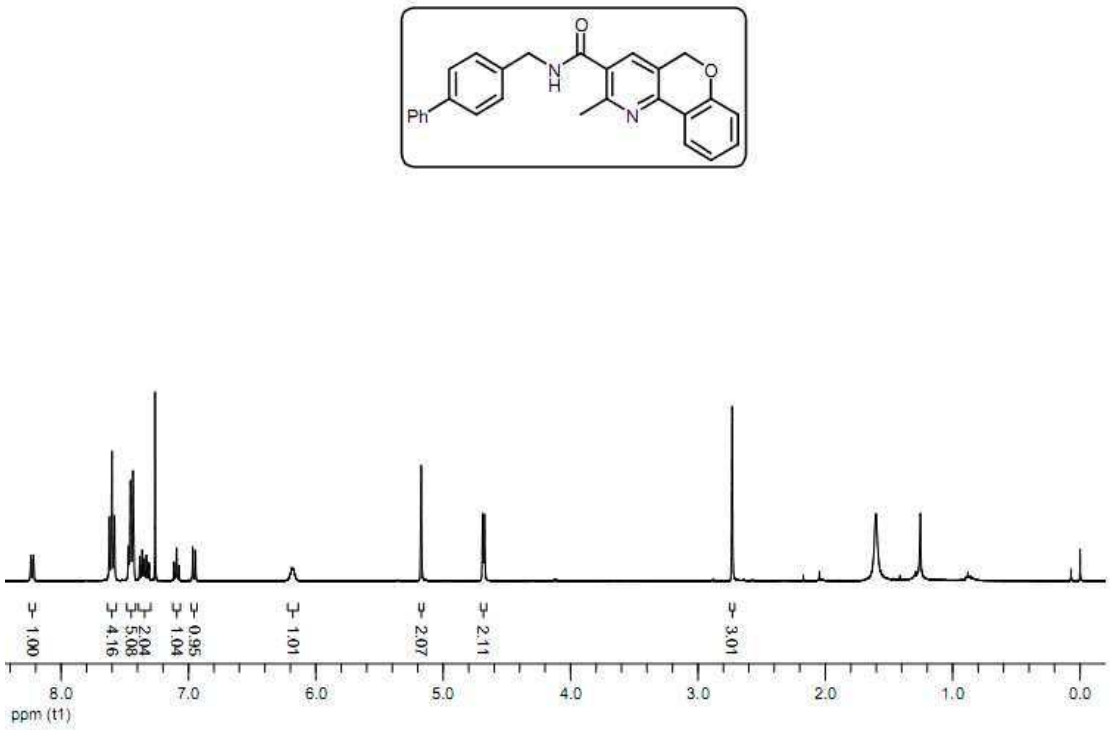

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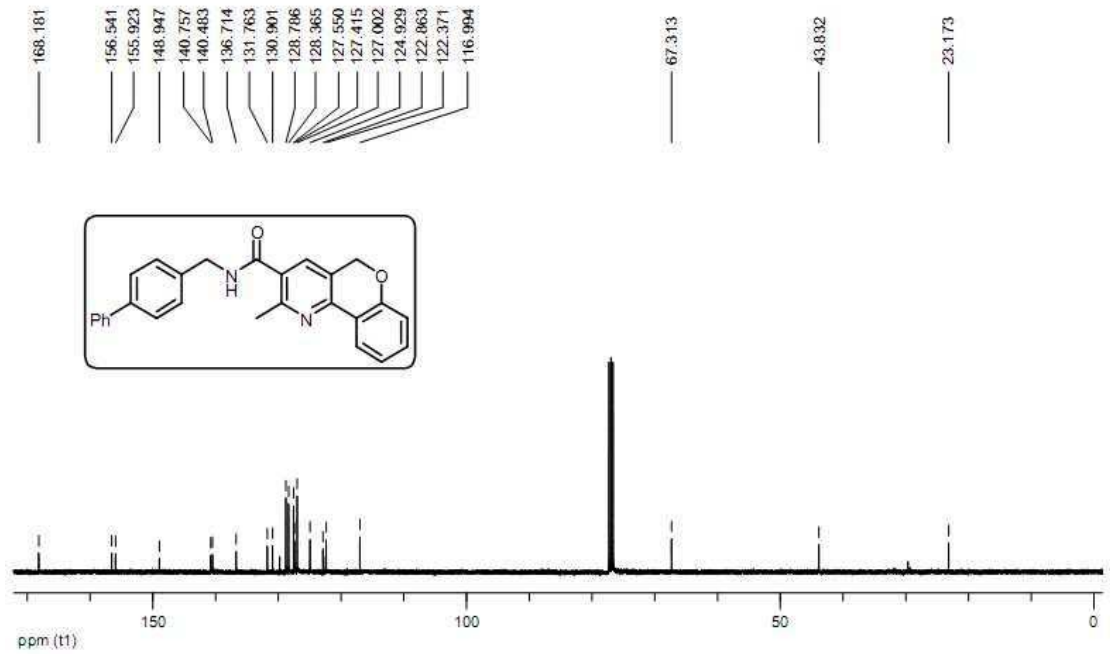

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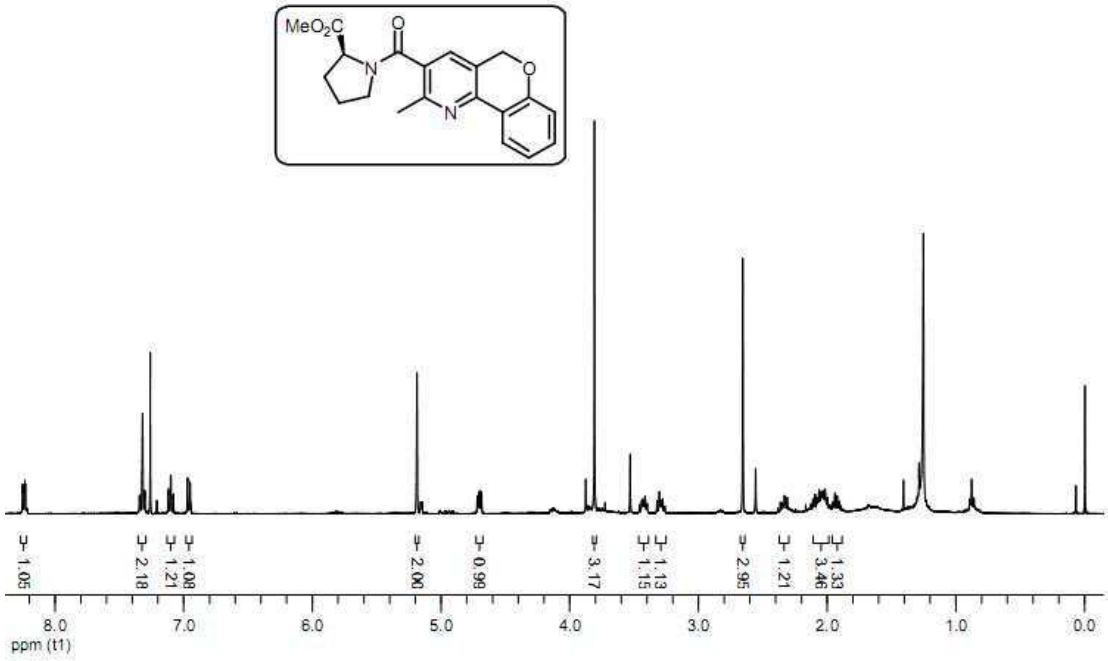
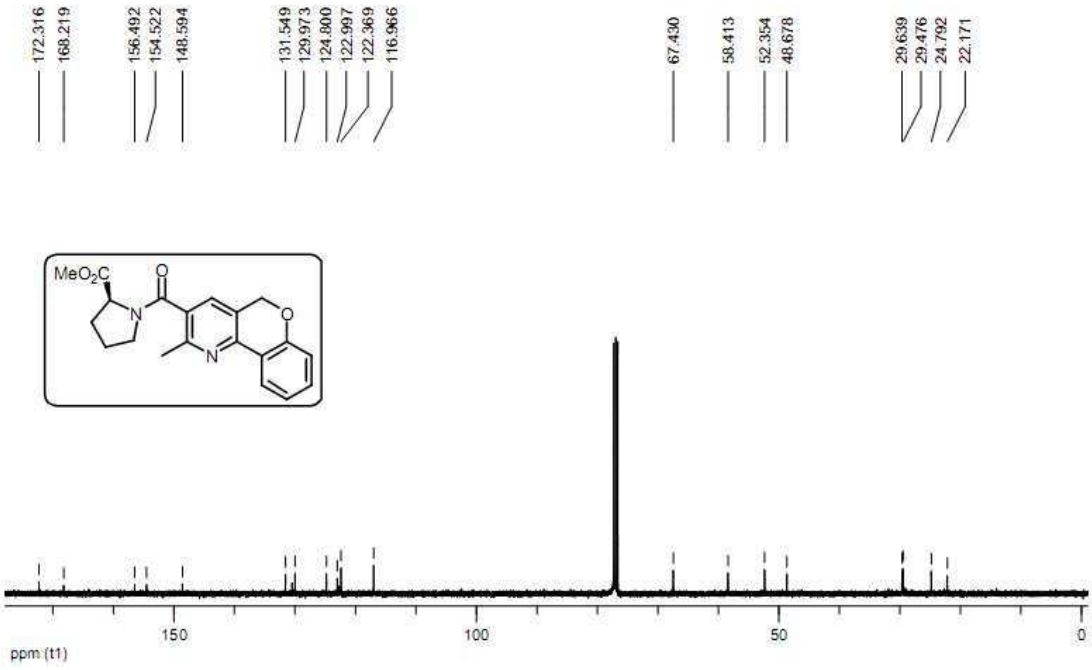


57e ^{13}C NMR ($CDCl_3$, 100 MHz)



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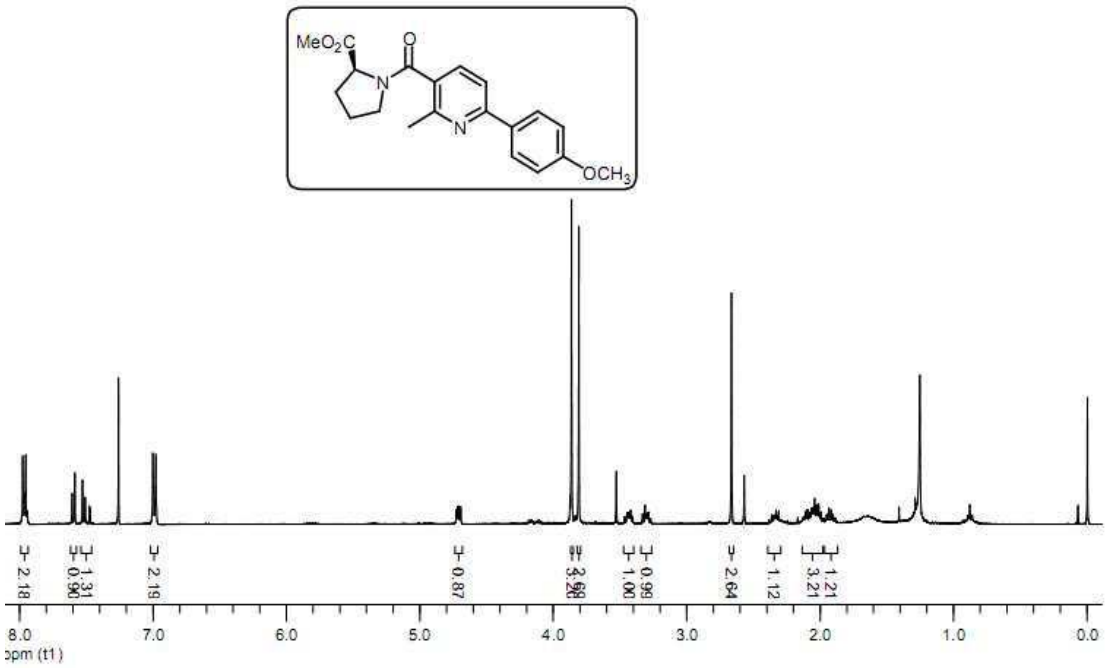
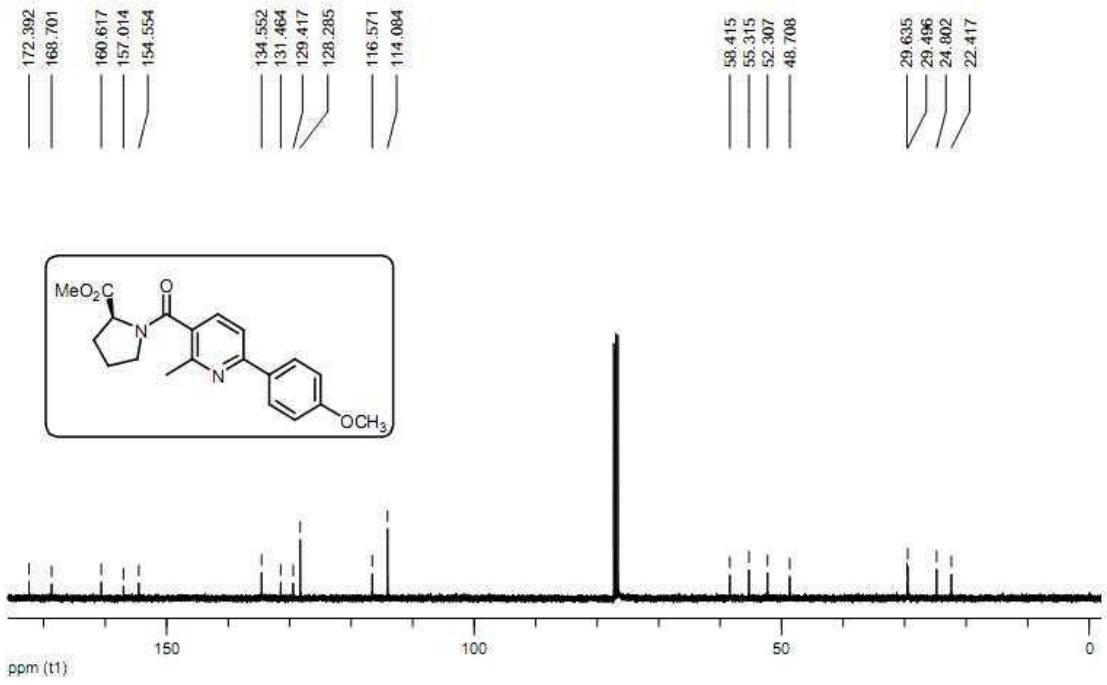


57f ^{13}C NMR ($CDCl_3$, 100 MHz)



CHAPTER 2

DEVELOPMENT OF A CATALYST-FREE ONE-POT DOMINO APPROACH FOR THE SYNTHESIS OF FUSED-1,4-DIHYDROPYRIDINES

2.1. Introduction

The dihydropyridines (DHPs), a class of drugs,[1] have a broad range of pharmacological and biological activities; DHPs are calcium channel antagonists with extensive use in the treatment of cardiovascular diseases.[2-6] They have attracted significant interest from scientific community over the last century. A few representative molecules bearing the dihydropyridine skeleton are shown in (Fig. 2.1).

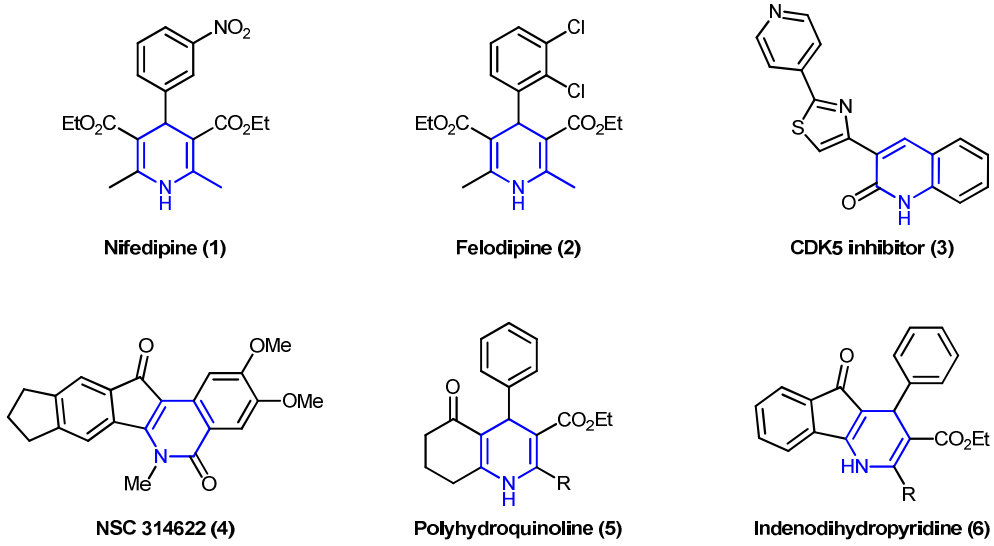
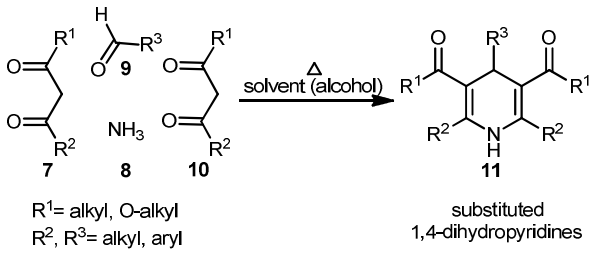


Figure 2.1. Representative examples of dihydropyridine derivatives

The DHP moiety containing drug molecules are very common such as Nifedipine **(1)** orally active agent that selectively antagonist calcium channel.[7] similarly, Felodipine **(2)** orally active agent used to control hypertension.[8] CDK5 inhibitor **(3)** quinilon-2H-ones (IC_{50}= 54 nM) as potent CDK5 inhibitors.[9] NSC 314622 **(4)** is a novel topoisomerase 1-targated drug with a unique chemical structure,[10] it has antitumour activity and toxicity in nude mice bearing human A253 and FaDu head and neck xenografts.[11] Poly hydroquinoline **(5),** Indeno dihydropyridines **(6)** are biologically active molecules showed calcium-antagonistic effects on smooth muscle and positive inotropic activity on electrically stimulated guinea pigs, atria.[12] As a result, there is considerable interest among synthetic chemist to develop several routes for the synthesis of dihydropyridine derivatives. This chapter covers the earlier reports and our approach to the substituted, fused monocyclic and polycyclic dihydropyridine derivatives starting from readily available starting materials such as 1,3 dicarbonyl compound, phenylgyloxal and β-enamino esters.

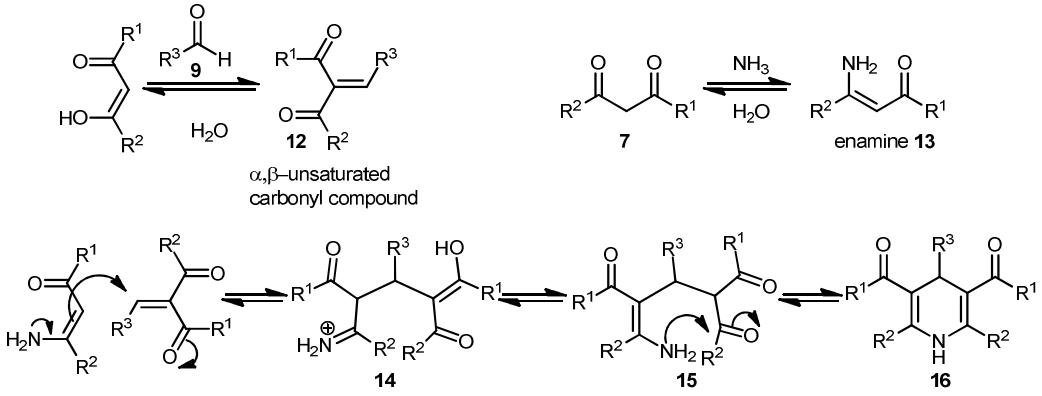
2.1.1. Precedents on synthesis of substituted monocyclic, polycyclic dihydropyridines

In 1882, Hantzsch reported an efficient and practical synthesis of symmetrical dihydropyridine (Scheme 2.1) *via* the four component reaction, two moles of ethyl acetoacetate, one mole of aldehyde and source of ammonia to synthesize 1,4-dihydropyridine (1,4-DHP).[13] Unsymmetrical dihydropyridines can be synthesized by using modified methods like 1) α,β-unsaturated carbonyl compound (alkylidene), derived by condensation of one equivalent of β-keto ester with an aldehyde, treating with β-keto ester and a nitrogen source. 2) an α,β-unsaturated carbonyl compound (prepared from the condensation of active methylene compound and aldehyde) is condensed with enamine;[14] (prepared from condensation of ammonia with β-keto ester) and 3) reaction of substituted 1,5-dicarbonyl compound with a nitrogen source.[15]



Scheme 2.1 Hantzsch 1,4-dihydropyridine synthesis.

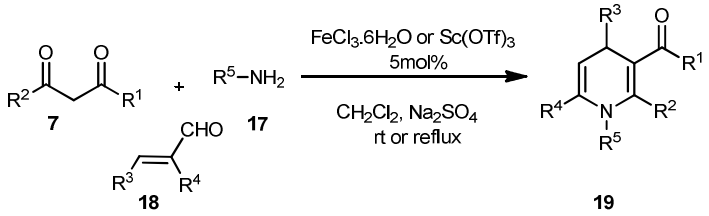
To explain the mechanism of this multi-component reaction involve a Knoevenagel condensation of the 1,3-dicarbonyl compound **7** with an aldehyde **9** to give compound **12.** Condensation of ammonia with another equivalent of 1,3-dicarbonyl compound to give on enamine **13**.



Scheme 2.2 Mechanism of Hantzsch 1,4-dihydropyridine synthesis.

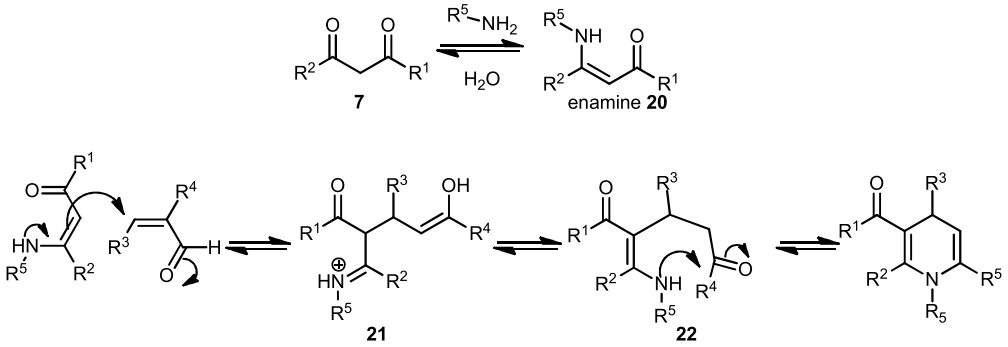
Michael addition of the enamine **13** to α,β-unsaturated carbonyl compound **12,** which was then transformed to intermediate **15** through the migration of hydrogen atom. An intramolecular addition of the amine group to the C-O double bond of intermediate **15,** gave the desired substituted 1,4-dihydropyridine **16** (Scheme 2.2).

In 2006, Renaud and co-workers have reported the one-pot three component reaction to substituted 1,4-DHPs by using 1,3-dicarbonyl compound **7**, amine **17** and α,β-unsaturated aldehyde or ketone **18** in the presence of catalytic Lewis acid by stepwise manner in dichloromethane (Scheme 2.3).[16]



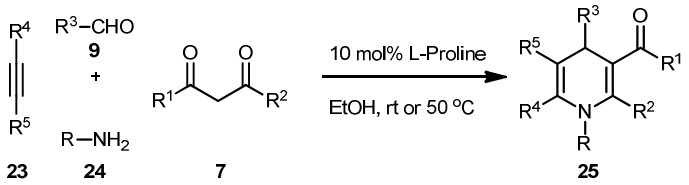
Scheme 2.3 Lewis acid catalyzed dihydropyridine synthesis.

The *in situ* generated β-enamino esters **20** from starting aromatic amine **17** and 1,3-dicarbonyl compound **7,** efficiently reacted with α,β-unsaturated carbonyl compound in the manner of Michael addition to provide compound **21** in the presence of $Sc(OTf)_3$. Subsequently the addition product **21** undergoes an intramolecular condensation of the amino group and carbonyl group to afford the desired substituted 1,4-DHP **19** (Scheme 2.4).



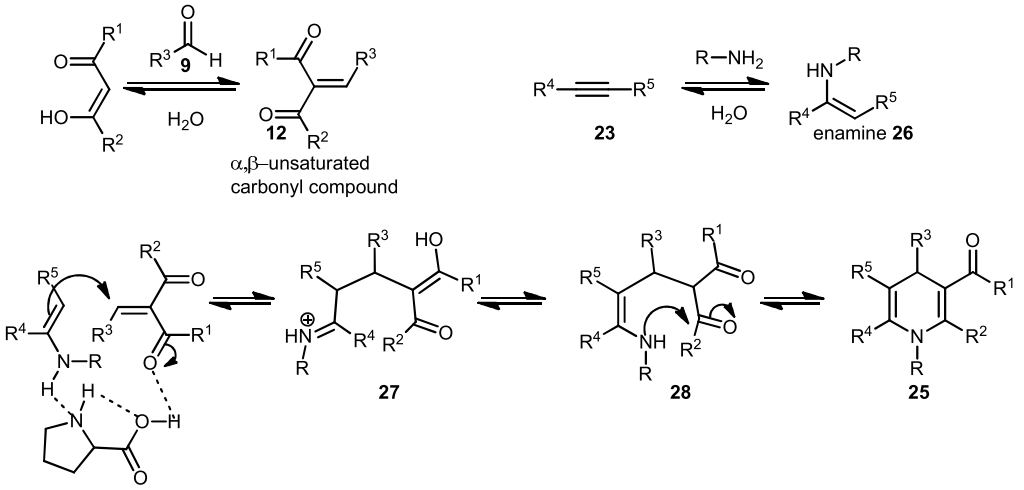
Scheme 2.4 Mechanism of Lewis acid-catalyzed dihydropyridine synthesis.

In 2009 Jiang and his group reported the L-proline catalyzed Multi-Component Reaction for the synthesis of substituted 1,4-DHPs using acetylenedicarboxylates, amines, aldehydes and 1,3-dicarbonyl compound in ethanol (Scheme 2.5).[17]



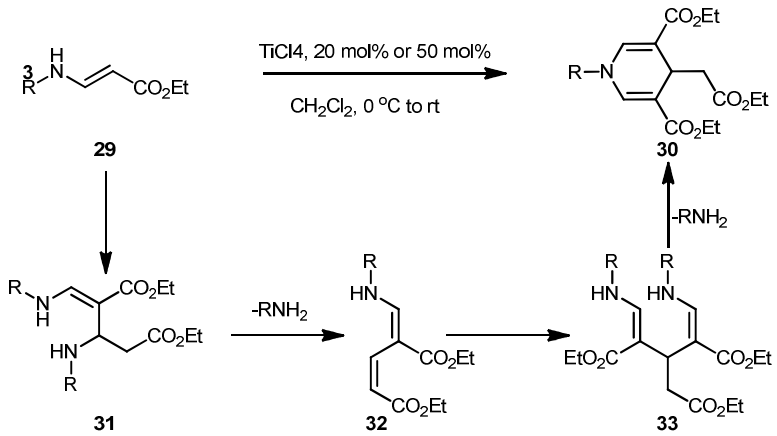
Scheme 2.5 Proline-catalyzed dihydropyridine synthesis

Knoevenagel condensation of the 1,3-dicarbonyl compound **7** with an aldehyde **9** takes place with the elimination of water and formation of corresponding α,β-unsaturated carbonyl compound **12.** Alkyl amine added to substituted acetylene to give the enamine **26**. Subsequent Michael addition of the enamine **26** to the electron-deficient α,β-unsaturated carbonyl compound **12** in the presence of proline**,** followed by cyclization to afford the desired substituted 1,4-DHPs **25** (Scheme 2.6).



Scheme 2.6 Mechanism of Proline-catalyzed dihydropyridine synthesis.

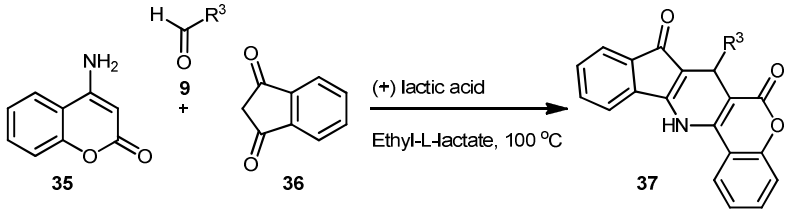
In 2010, Ajavakom and co-workers reported a Lewis acid $TiCl_4$ catalyzed conversion of N-alkyl enaminones **29** to substituted 1,4dihydropyridines **30** in one step (Scheme 2.7).[18]



Scheme 2.7 $TiCl_4$ catalyzed dihydropyridine synthesis.

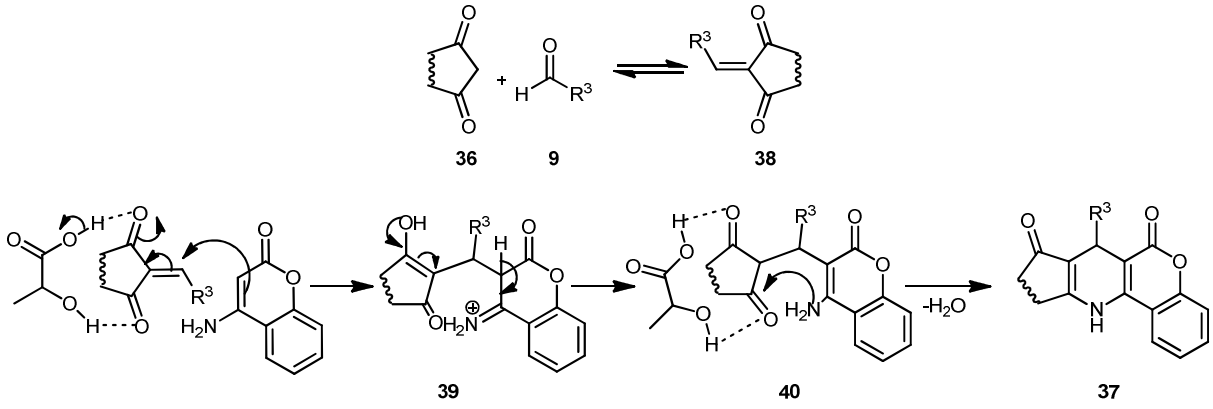
The dihydropyridine ring formation from **29** can be explained by Michael addition of one mole of N-alkyl enaminones with second mole of N-alkyl enaminones to give intermediate **31** and subsequent elimination of amine on **31** new Michael acceptors **32** were generated. The Michael addition of third mole of **29** on **32** led to formation of intermediates **33**, which on subsequent intramolecular elimination cyclization affords 1,4 dihydropyridine derivative **30**.

In 2012, Das and his group reported a lactic acid-catalyzed reaction of 1,3 di-carbonyl compound, aromatic aldehyde with cyclic enamino ester to synthesize highly decorated indenodihydropyridine derivatives (Scheme 2.8).[19]



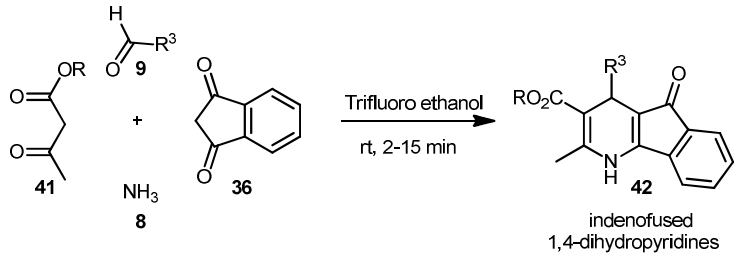
Scheme 2.8 Lactic acid-catalyzed dihydropyridine synthesis.

Mechanism of the reaction which involves mild organic acid-catalyzed Knoevenagel condensation of the 1,3-dicarbonyl compound **36** with an aldehyde **9** to give arylidene 1,3-indanedione **38.** Then, Michael addition of the cyclic enamino ester **35** to the α,β-unsaturated carbonyl compound **38** gave intermediate **39** in the presence of lactic acid. Subsequently the addition product **39** undergoes tautomerization to gave intermediate **40,** which undergoes an intramolecular condensation of the amino group and carbonyl group to afford the highly decorated desired 1,4-dihydropyridine **37** (Scheme 2.9).



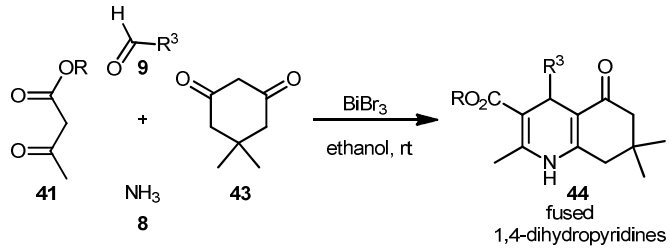
Scheme 2.9 Mechanism of Lactic acid-catalyzed dihydropyridine synthesis.

In 2014, Samad khaksar and his group reported a new convenient method for indenofused dihydropyridine derivatives by one-pot four component cyclocondensation of 1,3-indanedione, aldehyde, alkyl acetoacetate and ammonium acetate in trifluroethanol (Scheme 2.10).[20]



Scheme 2.10 Synthesis of indenofused 1,4 dihydropyridines

In 2015, Mohan and his group has used similar strategy to construct fused dihydropyridine ring in the presence of $BiBr_3$ catalyst (Scheme 2.11) by one-pot four component cyclocondensation of dimedone, aldehyde, alkyl acetoacetate and ammonium acetate in alcohol.[21]



Scheme 2.11 $BiBr_3$ catalyzed synthesis of fused 1,4 dihydropyridines.

With the exception of few known methods in which for 1,4-dihydropyridine synthesis most of the methodologies typically suffer from drawbacks like longer route, lower yield etc, that the synthesis of substituted dihydropyridines offers challenges to design and develop easy and economical strategies. In organic synthesis, the cascade reactions are used to reduce waste, avoid isolating intermediates and improve the reaction efficiency.

2.2. Present Work

Earlier from our group, we identified 1,4-dihydropyridine scaffold as PDE4B/ TNF-α inhibitors. In continuation of this work we became interested in the synthesis of fused 1,4-dihydropyridine scaffold.[22] Multi-component reactions (MCRs) are important in synthesizing small molecule libraries, because of their wide range of applications in the pharmaceutical industry. These reactions allow multi-step syntheses to be conducted in a single-step operation to afford a variety of products. MCRs can dramatically reduce the generation of chemical waste and the costs associated with reactions. In this chapter we describe an efficient synthesis of unsymmetrical fused-1,4-dihydropyridines from 1,3-dicarbonyl compounds, phenylglyoxal and β-enamino esters *via* catalyst free domino strategy. Simple and readily available starting materials, mild reaction conditions, and operational flexibility are advantages of the reaction, which allows a variety of unsymmetrical fused-1,4-dihydropyridines

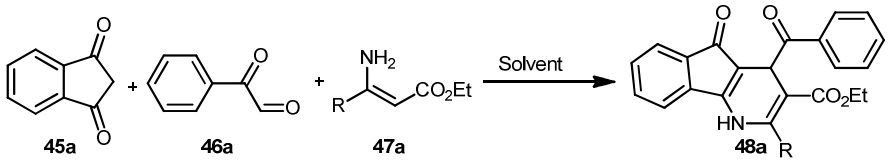
2.3. Results & Discussion

2.3.1. Initial results and optimization of reaction condition

We initially evaluated the three-component reaction of the1,3-indandione **45a**, phenylglyoxal **46a** and (Z)-ethyl 3-amino-3-phenylacrylate **47a.** The reaction mixture, which was composed of a 1:1:1 mixture of **45a, 46a,** and **47a** was tested under a variety of different conditions. The effects of solvent and temperature were evaluated for this reaction, and the results are summarized in below (Table 2.1). It was found that when the reaction was carried out in water without any catalyst the yield of the product **48a was** very low (entry 1, Table 2.1). DMSO provided higher yields than those using other organic solvents (entry 7,vs entry 2-6, Table 2.1), so DMSO was chosen as the solvent for all further reactions.

To identify the optimum reaction temperature, the reaction was carried out at room temperature, 30 °C, 50 °C and 70 °C, providing the desired product ethyl 4-benzoyl-5-oxo-2-phenyl-4,5-dihydro-1H-indeno[1,2-b]pyridine-3-carboxylate **48a** in yields of 20%, 40%, 90%, 70% (entries 7-10, Table 2.1) respectively. After assessing various reaction conditions (Table 2.1) it was observed that the best result is obtained when the reaction is performed at 50 °C in DMSO. Scope of this reaction was next assessed with a representative selection of 1,3-dicarbonyl compound, phenylglyoxal, and β-enaminoesters.

Table 2.1. Optimization of reaction conditions[a]



Entry	Solvent	Temp (^{O}C)	Time (h)	Yield [b] (%)
1	H_2O	50	10	20
2	THF	60	6	20
3	CH_3OH	60	6	10
4	CH_3CN	70	5	30
5	EtOAc	70	5	30
6	DMF	90	5	50
7	DMSO	rt	5	20
8	DMSO	30	4	40
9	DMSO	50	2	90
10	DMSO	70	4	80

[a] All reactions were performed using the β-enamino ester **47a** (0.3mmol), 1,3dicarbonyl compound **45a** (0.3 mmol), phenylglyoxal **46a** (0.3 mmol) in DMSO (3.0 mL) under open air. [b] Isolated yields.

2.3.2. Scope of the reaction

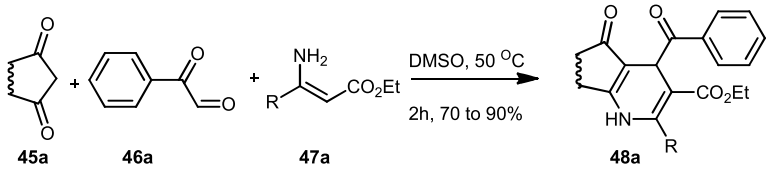
As shown in Table 2.2, at first variety of 1,3-dicarbonyl compound (1,3-indandione, dimedone, Ethyl acetoacetate) were employed, and the reaction proceeded very well to give corresponding simple and fused Polysubstituted 1,4-dihydropyridines **48a-48e** in 70-95% yields. All these reactions were performed at 50 °C (entries 1, 3, and 5, Table 2.2). Except one case (entry 4, Table 2.2) in this case we used ethyl glyoxalate instead of phenylglyoxal since these reactions do not require the use of any inert (or) anhydrous atmosphere they were performed under open air.

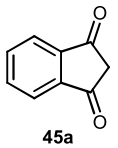
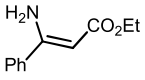
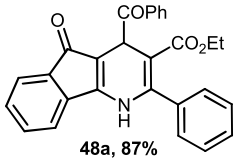
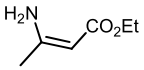
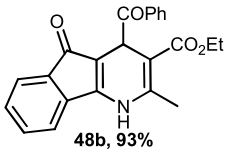
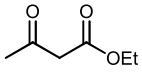
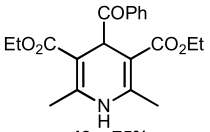
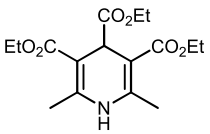
To expand the scope of this reaction we further examine the use of substituted β-enaminoesters. Thus various β-enaminoesters (containing aromatic/heteroaromatic/Cinnamyl/ aliphatic groups) was reacted with phenylglyoxal and simple, benzo-fused cyclic 1,3-dicarbonyl compound like (dimedone, 1,3-indandione) in DMSO to give the corresponding fused 1,4-dihydro pyridines in good

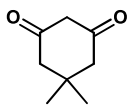
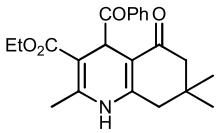
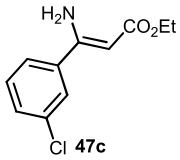
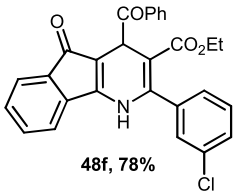
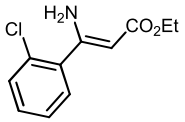
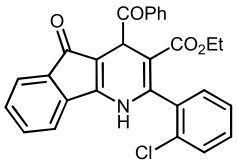
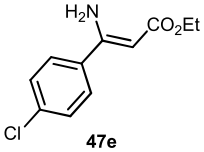
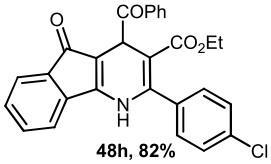
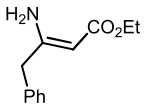
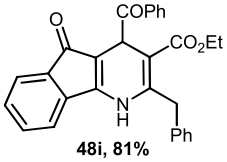
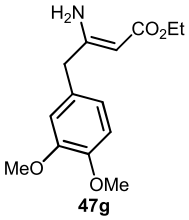
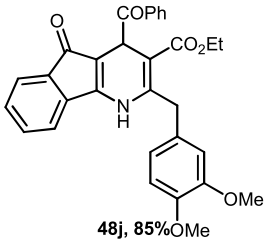
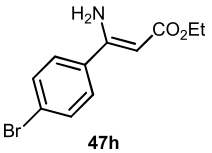
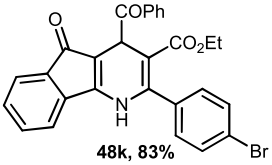
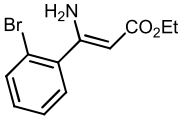
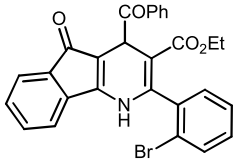
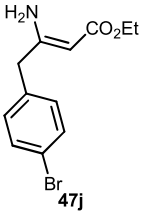
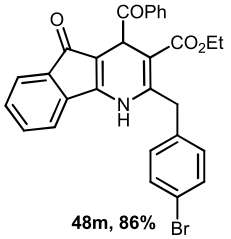
yields (entries 5-22, Table 2.2). β-enaminoesters with both stronger electron-donating (-OMe, -Me) and electron-withdrawing (-Cl,-Br) substituents all afford the desired products in very satisfactory yields (entry 6-8, entry 11-13, entry 10, Table 2.2). Notably, all the indeno fused dihydropyridine derivatives synthesized (entries 1, 2, 22 and entries 6-17, Table 2.2) can be converted easily to azafluorenones in a single step.[23] Azafluorenones, common skeletons in many natural products and useful agents in medicinal chemistry, are generally accessed via multistep sequences using metal mediated reactions.[24]

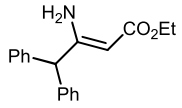
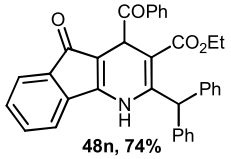
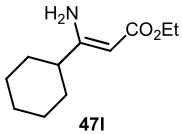
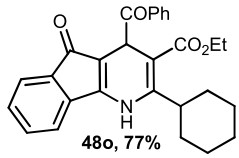
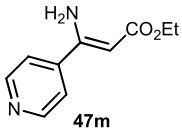
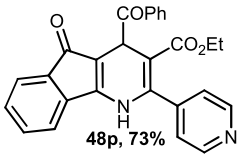
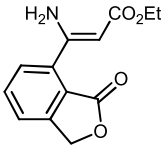
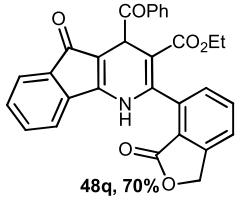
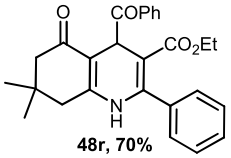
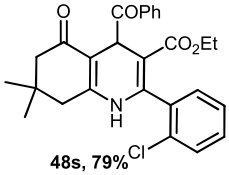
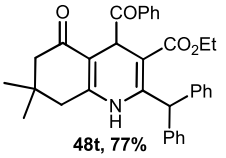
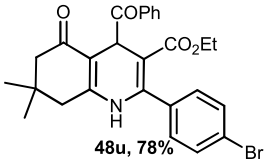
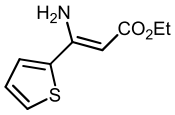
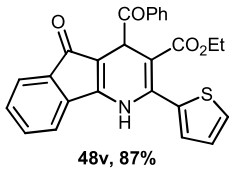
These results indicated that this three-component reaction is quite general and has very broad substrate scopes. The Polysubstituted dihydropyridines **48a** to **48v** were fully characterized by ^{1}H NMR, ^{13}C NMR and MS spectra. In ^{1}H NMR spectra the proton at the 4-position of Dihydropyridines appears at 4.53 ppm.

Table 2.2 Catalyst free synthesis of simple and fused dihydropyridines.

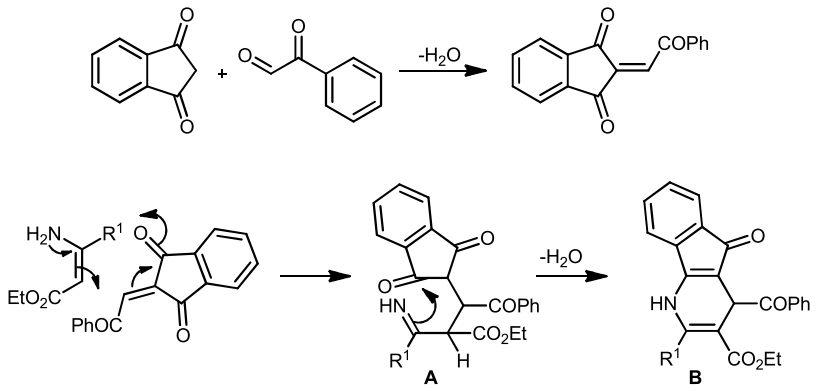


entry	1,3-dicarbonylcompound	enamine	product
1	 **45a**	 **47a**	 **48a, 87%**
2	**45a**	 **47b**	 **48b, 93%**
3	 **45b**	**47b**	 **48c, 75%**
4	**45b**	**47b**	 **48d, 88%**

5	 **45c**	**47b**	 **48e, 77%**
6	**45a**	 **47c**	 **48f, 78%**
7	**45a**	 **47d**	 **48g, 80%**
8	**45a**	 **47e**	 **48h, 82%**
9	**45a**	 **47f**	 **48i, 81%**
10	**45a**	 **47g**	 **48j, 85%**
11	**45a**	 **47h**	 **48k, 83%**
12	**45a**	 **47i**	 **48l, 82%**
13	**45a**	 **47j**	 **48m, 86%**

14	**45a**	 **47k**	 **48n, 74%**
15	**45a**	 **47l**	 **48o, 77%**
16	**45a**	 **47m**	 **48p, 73%**
17	**45a**	 **47n**	 **48q, 70%**
18	**45c**	**47a**	 **48r, 70%**
19	**45c**	**47d**	 **48s, 79%**
20	**45c**	**47k**	 **48t, 77%**
21	**45c**	**47h**	 **48u, 78%**
22	**45a**	 **47o**	 **48v, 87%**

[a] All reactions were performed using the β-enamino ester **47** (0.3mmol),1,3 dicarbonyl compound **45** (0.3mmol), and phenylglyoxal **46** (0.3mmol) in DMSO (3.0 mL) under open air. [b] Isolated yields.



Scheme 2.12 Proposed mechanism for fused dihydropyridines

Mechanistically, the reaction seems to proceed (scheme 2.12) *via* (i) Knoevenagel condensation[21] of the phenylglyoxal with the 1,3-dicarbonyl compound with the elimination of water and formation of the corresponding α,β-unsaturated carbonyl compound, then followed by (ii) Michael addition with β-enamino ester (**47**) and (iii) intra molecular cyclization gives **B**.[25]

2.4. Pharmacology

2.4.1. *In vitro* data

All the compounds synthesized were tested against PDE4B along with a known inhibitor rolipram as a reference compound using an in vitro enzyme assay.[26] some of the compounds were showed moderate inhibition activity at 10 μM and **48k** being the best among them. Fused dihydropyridines, which have shown more than 30% of inhibitions against PDE4B at 10 μM concentrations, are listed in table 2.3.

Table 2.3. PDE4B inhibition with fused-DHPs

Entry	Compound 4	% of PDE4B inhibition [a]
1	**48a**	42.71
2	**48b**	50.71
3	**48f**	47.48

4	**48g**	41.00
5	**48h**	53.90
6	**48i**	54.77
7	**48j**	48.88
8	**48k**	58.03
9	**48l**	50.10
10	**48m**	55.11
11	**48n**	50.98
12	**48o**	35.48
13	**48p**	39.3
14	**48q**	39.33
15	**48r**	30.11
16	**48s**	38.96
17	**28t**	32.88
18	**48v**	51.94

[a] All the compounds were tested at a 10 μM concentrations.

Since COPD and asthma are major health burden worldwide hence the present class of new chemical entities is of further interest. Dose response studies of most potent compounds 48k, 48m, and 48a are under progress.

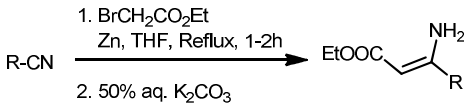
2.5. Conclusions

In conclusion, a direct, one-pot and catalyst free synthesis of functionalized dihydropyridines have been developed from readily available β-enamino esters and 1,3-dicarbonyl compounds, phenylglyoxal. This domino method afforded highly

substituted dihydropyridines and unsymmetrical fused dihydropyridines and precursors of azaflurenones. This methodology may find wide applications for the construction of dihydropyridine-based libraries , eventually useful for medicinal uses or natural product synthesis.

2.6. Experimental section

2.6.1. Materials

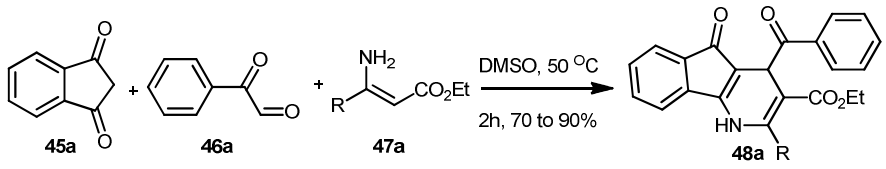


β-enamino esters were synthesized based on the procedure given below: [27,28]

To the activated zinc dust (1.31 g, 20 mmol) was added trimithylsilylchloride (3.0 drops) in dry THF (10 mL) under nitrogen. The mixture was heated to reflux for 10 min and then nitrile (10 mmol) was added all at once. While maintaining the refluxing temperature, ethyl bromoacetate (1.65 mL, 15 mmol in 5.0 mL THF) was added to the mixture over a period of 1h, and the reaction mixture was further heated to reflux for 1h. After complete conversion of nitrile, the reaction mixture was cooled to room temperature, quenched with saturated aqueous K_2CO_3 and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to get β-enamino ester.

2.6.2. Experimental procedure, spectral and analytical data

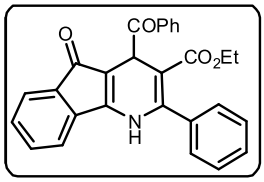
General Procedure for Synthesis of substituted simple and fused-dihydropyridines.



A mixture of β-enamino ester **47** (0.3 mmol), Phenylglyoxal **46**, (0.3 mmol) and 1,3-dicarbonyl compound **45** (0.3mmol) in DMSO (3.0 mL) was stirred at 50 °C for 1.5 to 2h (see Table 2.2). After completion of the reaction (monitored by TLC), the reaction mixture was quenched with sat. $NaHCO_3$ solution (1.5 mL) and extracted with EtOAc

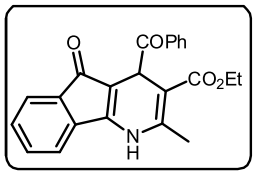
(3 x 4 mL).The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The crude compound was purified by using flash chromatography (EtOAc/Hexane).

Ethyl 4-benzoyl-5-oxo-2-phenyl-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48a):



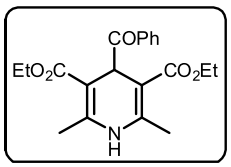
Pale red color solid, m.p: 238-240 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.51 (s, 1H), 8.03 (dd, *J* = 4.85, 2.49 Hz, 2H), 7.88-7.82 (m, 2H), 7.56 (td, *J* = 4.29, 2.80 Hz, 4H), 7.40 (m, 6H), 4.53 (s, 1H), 3.65 (q, *J* = 7.01 Hz, 2H), 0.76 (t, *J* = 7.07 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 198.9, 164.0, 141.7, 138.0, 135.2, 135.0, 132.1, 130.9, 129.5, 129.0, 128.3, 128.2, 127.8, 123.0, 112.8, 59.4, 54.7, 13.7; MS (ESI mass) m/z: 434.2[M-1].

Ethyl 4-benzoyl-2-methyl-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48b):



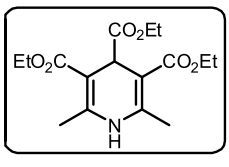
Pale yellow color solid, m.p: 224-226 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.40 (s, 1H), 8.02 (dd, *J* = 5.35, 3.03 Hz, 2H), 7.83 (dd, *J* = 5.49, 3.03 Hz, 2H), 7.48 (d, *J* = 7.38 Hz, 2H), 7.39 (t, *J* = 7.44 Hz, 2H), 7.32 (t, *J* = 7.27 Hz, 1H), 4.48 (s, 1H), 3.71 (q, *J* = 7.11 Hz, 2H), 2.52 (s, 3H), 0.88 (t, *J* = 7.09 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 199.2, 164,6, 141.6, 136.8, 135.0, 133.3, 131.1, 128.9, 127.9, 127.8, 122.9, 111.3, 109.9, 59.0, 54.7, 14.0; MS (ESI mass) m/z: 372.2[M-1].

Diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (48c):



Pale yellow color solid, m.p: 99-101 °C; R_f = 0.3 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.13 (d, *J* = 8.06 Hz, 2H), 7.52 (dd, *J* = 10.67, 3.98 Hz, 1H), 7.43 (t, *J* = 7.66 Hz, 2H), 5.70 (s, 1H), 4.04-3.91 (m, 4H), 2.32 (s, 6H), 1.04 (t, *J* = 7.08 Hz, 6H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 166.8, 146.8, 136.9, 132.6, 129.5, 127.8, 99.6, 59.8, 41.6, 19.3. 14.0; MS (ESI mass) m/z: 356.2[M-1].

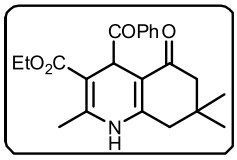
Triethyl 2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (48d):



Pale yellow color solid, m.p: 104-106 °C; R_f = 0.3 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 4.83 (s, 1H), 4.19 (m,

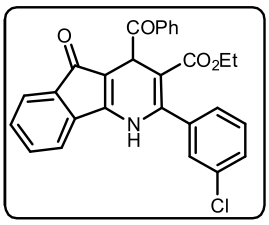
4H), 4.07 (q, *J* = 7.12 Hz, 2H), 2.29 (s, 6H), 1.28 (t, *J* = 7.12 Hz, 6H), 1.20 (t, *J* = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 174.4, 167.2, 145.6, 98.4, 60.6, 59.8, 40.5, 18.9, 14.3. 14.0; MS (ESI mass) m/z: 324.3[M-1].

Ethyl 4-benzoyl-2,7,7-trimethyl-5-oxo-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxylate (48e):



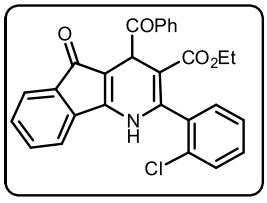
Pale yellow colored solid, m.p: 183-185 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.98 (s, 1H), 7.24-7.16 (m, 4H), 5.82 (s, 1H), 4.22-4.12 (m, 2H), 2.52-2.48 (m, 1H), 2.45 (s, 4H), 2.38-2.24 (m, 2H), 1.27 (dt, *J* = 7.11, 6.78, 3.82 Hz, 4H), 1.19 (d, *J* = 10.23 Hz, 3H), 1.09 (d, *J* = 8.97 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.0, 164.7, 137.7, 131.3, 130.0, 128.5, 127.2, 126.1, 112.6, 111.2, 109.1, 59.1, 50.9, 41.3, 31.7, 29.5, 27.6, 14.5, 14.0; MS (ESI mass) m/z: 366.3[M-1].

Ethyl 4-benzoyl-2-(3-chlorophenyl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48f):



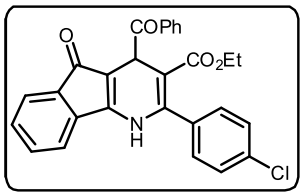
Pale red color solid, m.p: 260-262 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.58 (s, 1H), 8.02 (dd, *J* = 5.27, 2.93 Hz, 2H), 7.85 (dd, *J* = 5.40, 3.01 Hz, 2H), 7.55 (s, 3H), 7.38 (m, 7H), 4.52 (s, 1H), 3.69 (d, *J* = 6.95 Hz, 2H), 0.81 (t, *J* = 7.03 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.7, 141.6, 135.0, 133.7, 129.6, 129.1, 128.5, 128.4, 128.3, 127.6, 123.0, 59.6, 54.6, 13.7; MS (ESI mass) m/z: 468.1[M-1].

Ethyl 4-benzoyl-2-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48g):



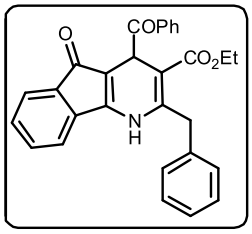
Pale yellow color solid, m.p: 258-260 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.60 (s, 1H), 8.02 (dd, *J* = 5.49, 3.08 Hz, 2H), 7.86-7.81 (m, 2H), 7.59 (d, *J* = 7.34 Hz, 2H), 7.49 (dd, *J* = 7.27, 2.00 Hz, 1H), 7.45-7.35 (m, 4H), 7.30 (m, 2H), 4.54 (s, 1H), 3.63 (q, *J* = 7.02 Hz, 2H), 0.68 (t, *J* = 7.09 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.7, 141.7, 134.9, 134.0, 132.5, 129.8, 129.4, 129.0, 128.3, 126.1, 123.0, 59.4, 54.4, 13.5; MS (ESI mass) m/z: 468.1[M-1].

Ethyl 4-benzoyl-2-(4-chlorophenyl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48h):



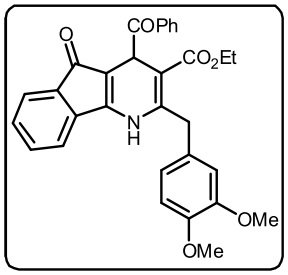
Pale red color solid, m.p: 199-201 °C; R_f = 0.25 (30% EtOAc in Hexane): ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.76 (s, 1H), 8.00 (dd, *J* = 5.48, 3.03 Hz, 2H), 7.84 (dd, *J* = 5.58, 3.08 Hz, 2H), 7.53 (d, *J* = 7.00 Hz, 2H), 7.45-7.34 (m, 5H), 7.30 (d, *J* = 8.52 Hz, 2H), 4.48 (s, 1H), 3.62 (dd, *J* = 13.89, 6.88 Hz, 2H), 0.76 (t, *J* = 7.02 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.8, 163.9, 141.6, 135.1, 134.3, 130.8, 130.7129.1, 128.4, 128.3, 128.0, 123.0, 112.9, 110.7. 109.9, 59.9, 54.7, 13.7; MS (ES mass) m/z: 468.1[M-1].

Ethyl 4-benzoyl-2-benzyl-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48i):



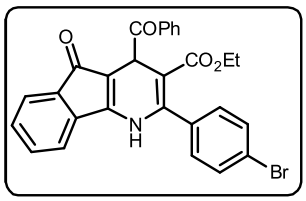
Pale red color solid, m.p: 188-190 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.41 (s, 1H), 7.99 (dd, *J* = 5.53, 3.07 Hz, 2H), 7.82 (dd, *J* = 5.56, 3.08 Hz, 2H), 7.40 (d, *J* = 6.87 Hz, 2H), 7.34-7.23 (m, 8H), 4.47 (s, 1H), 4.32 (s, 2H), 3.69 (q, *J* = 7.07 Hz, 2H), 0.86 (t, *J* = 7.10 Hz, 4H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 199.1, 164.5, 141.7, 138.6, 137.3, 135.0, 133.9, 131.1, 129.2, 128.9, 128.2, 128.0, 126.9, 123.0, 111.8, 109.9, 59.2, 54.7, 33.9, 14.0; MS (ESI mass) m/z: 448.2[M-1].

Ethyl 4-benzoyl-2-(3,4-dimethoxybenzyl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48j):



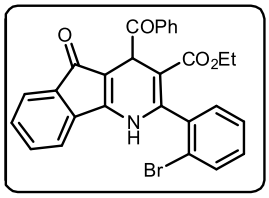
Dark brown color semi solid, R_f = 0.23 (40% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.07-7.99 (m, 3H), 7.87 (m, 3H), 7.42-7.28 (m, 5H), 6.84 (t, *J* = 8.65 Hz, 3H), 4.46 (s, 1H), 4.29 (s, 2H), 3.87 (s, 6H), 3.72 (q, *J* = 7.15 Hz, 2H), 0.88 (dd, *J* = 9.14, 5.01 Hz, 4H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 199.0, 164.4, 149.2, 148.0. 141.7, 139.1, 135.0, 133.6, 131.1, 129.0, 128.9, 128.2, 128.1, 123.0, 121.5, 112.5, 111.9, 111.5, 109.6, 59.2, 55.8, 54.7, 33.9, 14.1; MS (ESI mass) m/z: 508.2[M-1].

Ethyl 4-benzoyl-2-(4-bromophenyl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridine-3-carboxylate (48k):



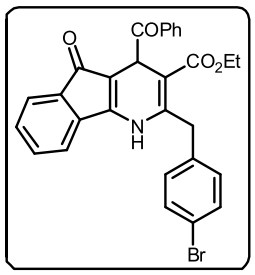
Pale yellow color solid, m.p: 219-221 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.05 (s, 1H), 7.96 (dd, *J* = 5.56, 3.07 Hz, 2H), 7.86-7.80 (m, 2H), 7.50 (d, *J* = 6.97 Hz, 2H), 7.42-7.28 (m, 8H), 4.44 (s, 1H), 3.61 (q, *J* = 6.97 Hz, 2H), 0.75 (t, *J* = 7.06 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 199.0, 171.3, 163.9, 141,6, 136.6, 135.1, 131.1, 130.9, 130.7, 129.0, 128.4, 128.3, 123.0, 122.5, 112.9, 110.6, 59.5, 54.7, 13.8; MS (ESI mass) m/z: 512.1[M-1].

Ethyl 4-benzoyl-2-(2-bromophenyl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48l):



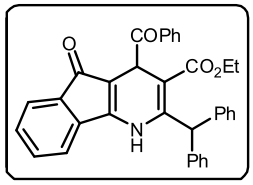
Pale yellow color solid, m.p: 260-262 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.55 (s, 1H), 8.02 (dd, *J* = 5.43, 3.08 Hz, 2H), 7.84 (dd, *J* = 5.58, 3.09 Hz, 2H), 7.64-7.56 (m, 3H), 7.49-7.30 (m, 5H), 7.22 (dd, *J* = 7.66, 1.61 Hz, 1H), 4.54 (s, 1H), 3.62 (q, *J* = 6.98 Hz, 2H), 0.67 (t, *J* = 7.10 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.7, 163.8, 141.7, 134.9, 133.7, 132.5, 130.9, 130.0, 129.0, 128.3, 128.2, 126.6, 124.2, 123.0, 112.2, 109.9, 59.3, 54.3, 13.5; MS (ESI mass) m/z: 512.1[M-1].

Ethyl 4-benzoyl-2-(4-bromobenzyl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48m):



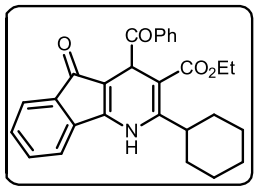
Pale yellow color solid, m.p: 229-231 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.11 (s, 1H), 8.02 (dd, *J* = 5.43, 3.07 Hz, 2H), 7.84 (dd, *J* = 5.48, 3.03 Hz, 2H), 7.46 (d, *J* = 8.20 Hz, 2H), 7.43-7.30 (m, 5H), 7.16 (d, *J* = 8.16 Hz, 2H), 4.46 (s, 1H), 4.31 (s, 2H), 3.70 (q, *J* = 7.06 Hz, 2H), 0.85 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.9, 164.2, 141.7, 137.7, 136.2, 135.0, 134.1, 132.0, 130.9, 129.0, 128.2, 123.0, 120.9, 111.9, 59.3, 54.6, 33.4, 14.0; MS (ESI mass) m/z: 526.1[M-1].

Ethyl 2-benzhydryl-4-benzoyl-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridine-3 carboxylate (48n) :



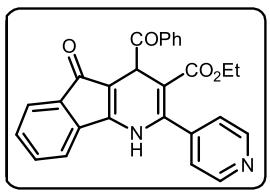
Color less solid, m.p: 239-241 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.03-7.98 (m, 2H), 7.94 (s, 1H), 7.82 (dd, *J* = 5.59, 3.06 Hz, 2H), 7.36 (m, 11H), 7.27-7.21 (m, 3H), 7.14 (d, *J* = 7.30 Hz, 4H), 6.29 (s, 1H), 4.48 (s, 1H), 3.60 (q, *J* = 7.11 Hz, 2H), 0.71 (t, *J* = 7.11 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.8, 163.9, 141.9, 141.7, 139.5, 134.9, 133.9, 131.1, 129.0, 128.9, 128.7, 128.2, 128.1, 127.3, 126.8, 123.1, 122.9, 112.7, 110.7, 59.2, 54.5, 49.3, 13.8; MS (ESI mass) m/z: 524.1[M-1].

Ethyl 4-benzoyl-2-cyclohexyl-5-oxo-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48o):



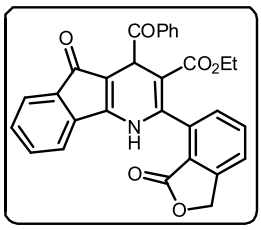
Yellow color solid, m.p: 228-230 °C; R_f = 0.25 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.38 (s, 1H), 8.00 (dd, *J* = 5.52, 3.06 Hz, 2H), 7.83 (dd, *J* = 5.56, 3.09 Hz, 2H), 7.50 (d, *J* = 7.15 Hz, 2H), 7.39 (t, *J* = 7.32 Hz, 2H), 7.32 (t, *J* = 7.31 Hz, 1H), 4.45 (s, 1H), 3.67 (q, *J* = 7.08 Hz, 2H), 3.47-3.38 (m, 1H), 2.10-2.02 (m, 2H), 1.84 (d, *J* = 12.89 Hz, 2H), 1.75 (d, *J* = 12.89 Hz, 1H), 1.61 (d, *J* = 4.49 Hz, 1H), 1.48-1.31 (m, 5H), 0.87 (t, *J* = 7.09 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 199.0, 164.3, 145.4, 141.7, 134.9, 133.1, 131.4, 128.9, 128.2, 128.0, 123.0, 111.5, 108.8, 59.0, 54.7, 36.3, 32.4, 26,5, 26.1, 14.0; MS (ESI mass) m/z: 440.1[M-1].

Ethyl 4-benzoyl-5-oxo-2-(pyridin-4-yl)-4,5-dihydro-1H-indeno[1,2-b] pyridine-3-carboxylate (48p):



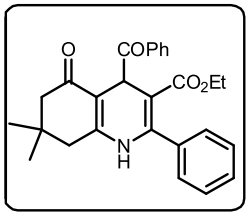
Color less solid, m.p: 274-276 °C; R_f = 0.15 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.25 (s, 2H), 7.99 (d, *J* = 3.22 Hz, 2H), 7.84 (dd, *J* = 5.39, 3.13 Hz, 2H), 7.56 (d, *J* = 6.59 Hz, 2H), 7.43 (d, *J* = 4.71 Hz, 2H), 7.35 (d, *J* = 8.41 Hz, 3H), 4.52 (s, 1H), 3.69-3.58 (m, 2H), 0.75 (t, *J* = 6.93 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.8, 163.8, 148.3, 141.6, 140.4, 135.1, 134.3, 130.7, 128.9, 128.6, 128.5, 124.3, 123.1, 113.6. 111.8, 59.7, 54.7, 13.7; MS (ESI mass) m/z: 437.0[M+1].

Ethyl 4-benzoyl-5-oxo-2-(3-oxo-1,3-dihydroisobenzofuran-4-yl)-4,5-dihydro-1H-indeno [1,2-b] pyridine-3-carboxylate (48q):



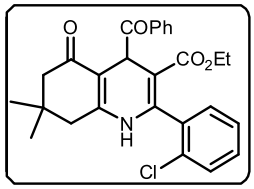
Red colored semi solid, R_f = 0.15 (30 % EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 9.51 (s, 1H), 7.98 (dd, *J* = 5.55, 3.08 Hz, 2H), 7.87-7.81 (m, 2H), 7.75-7.70 (m, 1H), 7.64 (dd, *J* = 9.61, 6.16 Hz, 3H), 7.55 (d, *J* = 10.91 Hz, 3H), 7.42-7.31 (m, 3H), 5.21 (s, 2H), 4.53 (s, 1H), 3.59 (dd, *J* = 13.83, 6.80 Hz, 2H), 0.71 (t, *J* = 7.03 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 198.8, 172.1, 171.0, 163.7, 146.1, 145.6, 141.5, 138.0, 135.2, 131.8, 130.5, 129.0, 128.5, 128.3, 127.1, 124.8, 123.2, 123.1, 113.3, 111.6, 109.9, 69.7, 59.6, 54.7, 13.7; MS (ES mass) m/z: 490.1[M-1].

Ethyl 4-benzoyl-7,7-dimethyl-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (48r):



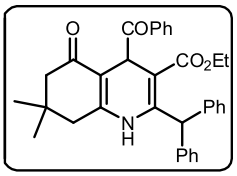
Color less solid, m.p: 199-201 °C; R_f = 0.22 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) 8.71 (s, 1H), 7.56 (d, *J* = 6.88 Hz, 2H), 7.32 (m, 8H), 6.01 (s, 1H), 4.13-4.02 (m, 2H), 2.53-2.38 (m, 2H), 2.34-2.26 (m, 2H), 1.18 (s, 3H), 1.08 (m, 6H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 197.5, 169.6, 164.3, 138.3, 132.0, 131.2, 129.1, 128.8, 128.4, 128.0, 127.9, 126.7, 113.7, 110.8, 110.7, 59.6, 50.9, 41.5, 31.7, 29.5, 27.6, 14.1; MS (ESI mass) m/z: 430.1[M+1].

Ethyl 4-benzoyl-2-(2-chlorophenyl)-7, 7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (48s):



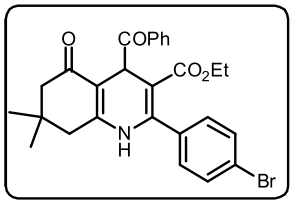
Pale yellow color solid, m.p: 198-200 °C; R_f = 0.21(30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.81 (s, 1H), 7.51 (dd, *J* = 7.15, 2.14 Hz, 1H), 7.46 (dd, *J* = 7.55, 1.55 Hz, 1H), 7.40-7.27 (m, 7H), 6.02 (s, 1H), 4.01 (q, *J* = 7.11 Hz, 2H), 2.55-2.41 (m, 2H), 2.36-2.26 (m, 2H), 1.19 (s, 3H), 1.10 (s, 3H), 0.97 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 197.3, 169.7, 163.9, 134.6, 133.8, 132.3, 132.1, 131.5, 131.1, 129.8, 129.4, 128.8, 127.9, 126.6, 126.3, 115.5, 110.5, 110.0, 59.6, 50.9, 41.5, 31.7, 29.3, 27.8, 13.8; MS (ESI mass) m/z: 464.0[M+1].

Ethyl 2-benzhydryl-4-benzoyl-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (48t):



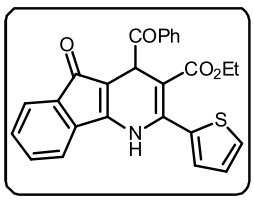
Pale yellow color solid, m.p: 192-194 °C; R_f= 0.2 (30 % EtOAc in Hexane. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.04 (s, 1H), 7.36-7.29 (m, 4H), 7.25 (dd, *J* = 12.10, 7.91 Hz, 5H), 7.21-7.16 (m, 4H), 7.13 (d, *J* = 7.11 Hz, 2H), 6.34 (s, 1H), 5.80 (s, 1H), 4.07-3.97 (m, 2H), 2.50-2.40 (m, 2H), 2.33-2.26 (m, 2H), 1.18 (s, 3H), 1.08 (s, 3H), 1.04 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 197.2, 168.9, 164.0, 142.3, 140.4, 130.6, 129.0, 128.8, 128.7, 128.6, 127.7, 127.1, 126.8, 126.5, 110.9, 110.5, 59.4, 51.0, 49.5, 41.4, 31.7, 29.5, 14.2; MS (ESI mass) m/z: 520.1[M+1].

Ethyl 4-benzoyl-2-(4-bromophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7 8-hexahydroquinoline-3-carboxylate (48u):



Color less solid, m.p: 259-261 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.81 (s, 1H), 7.51 (dd, *J* = 7.15, 2.14 Hz, 1H), 7.46 (dd, *J* = 7.55, 1.55 Hz, 1H), 7.40-7.27 (m, 7H), 6.02 (s, 1H), 4.01 (q, *J* = 7.11 Hz, 2H), 2.55-2.41 (m, 2H), 2.36-2.28 (m, 2H), 1.19 (s, 3H), 1.10 (s, 3H), 0.97 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 197.3, 169.7, 163.9, 134.6, 133.8, 132.3, 132.1, 131.5, 131.1, 129.8, 129.4, 128.8, 127.9, 126.6, 126.3, 115.5, 110.5, 110.0, 59.6, 50.9, 41.5, 31.7, 29.3, 27.8, 13.8; MS (ESI mass) m/z: 510.0[M+2].

Ethyl 4-benzoyl-5-oxo-2-(thiophen-2-yl)-4,5-dihydro-1H-indeno[1,2-b]pyridine-3-carboxylate (48v):



Brown color solid, m.p: 264-266 °C; R_f = 0.2 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.78 (s, 1H), 8.00 (dd, *J* = 5.60, 3.08 Hz, 2H), 7.85-7.81 (m, 2H), 7.54 (d, *J* = 7.08 Hz, 2H), 7.43-7.31 (m, 5H), 7.02 (dd, *J* = 5.10, 3.67 Hz, 1H), 4.49 (s, 1H), 3.66 (q, *J* = 6.85 Hz, 2H), 0.81 (t, *J* = 7.07 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 198.7, 171.1, 163.7, 141.6, 135.0, 132.7, 130.9, 130.6, 129.0, 128.5, 128.4, 128.2, 126.8, 126.5, 123.0, 113.1, 59.5, 54.7, 21.0, 13.8; MS (ESI mass) m/z: 440.1[M-1].

2.7. References

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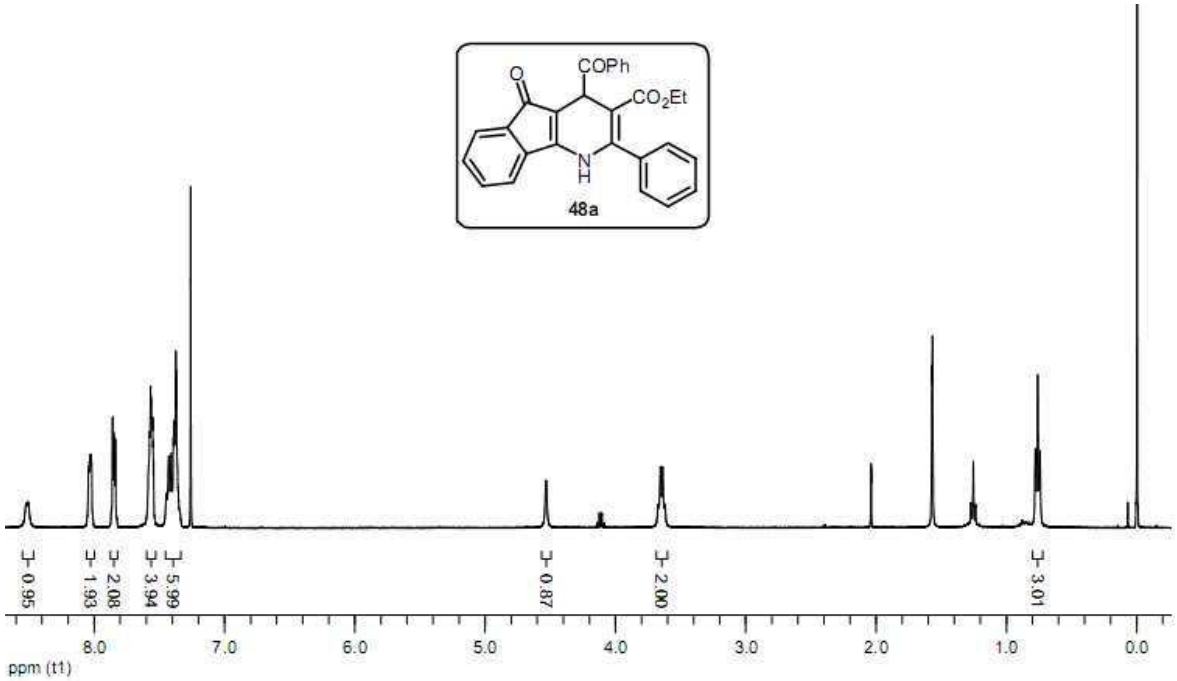
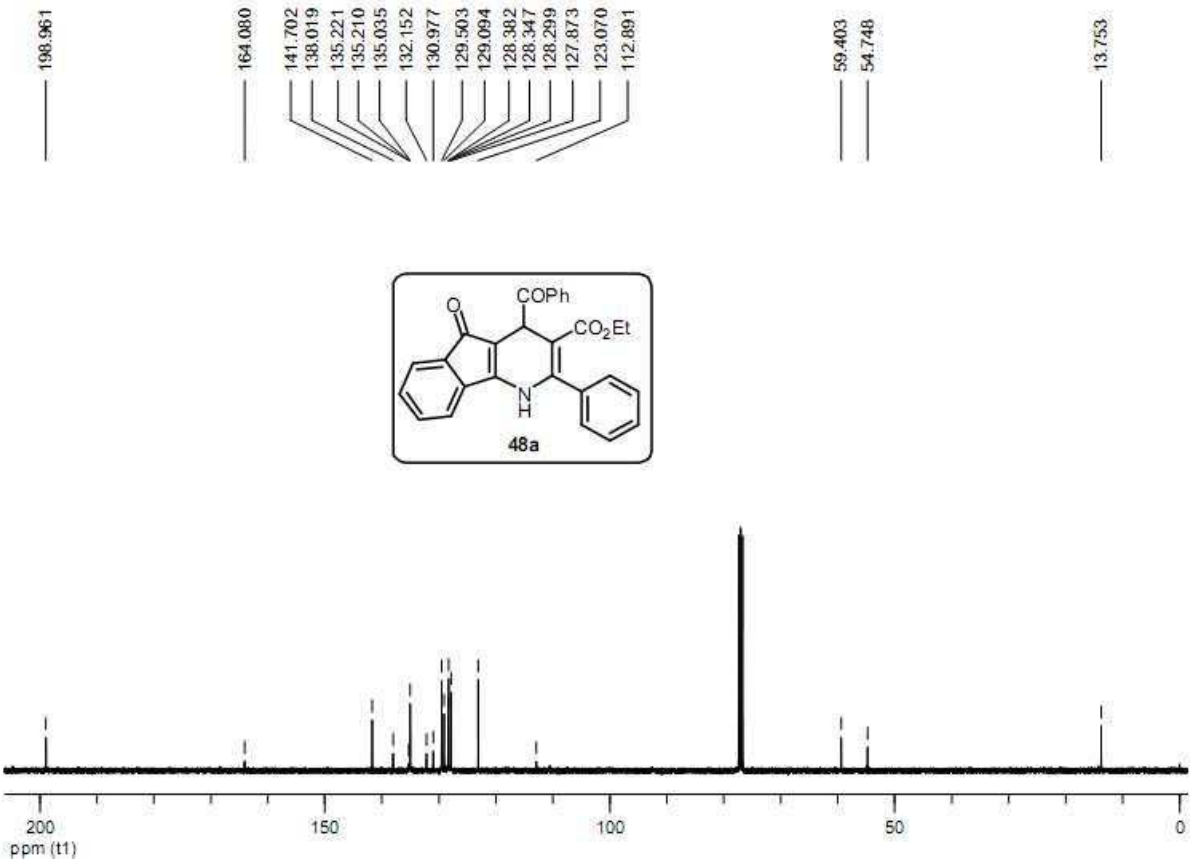
2.8. NMR Spectra

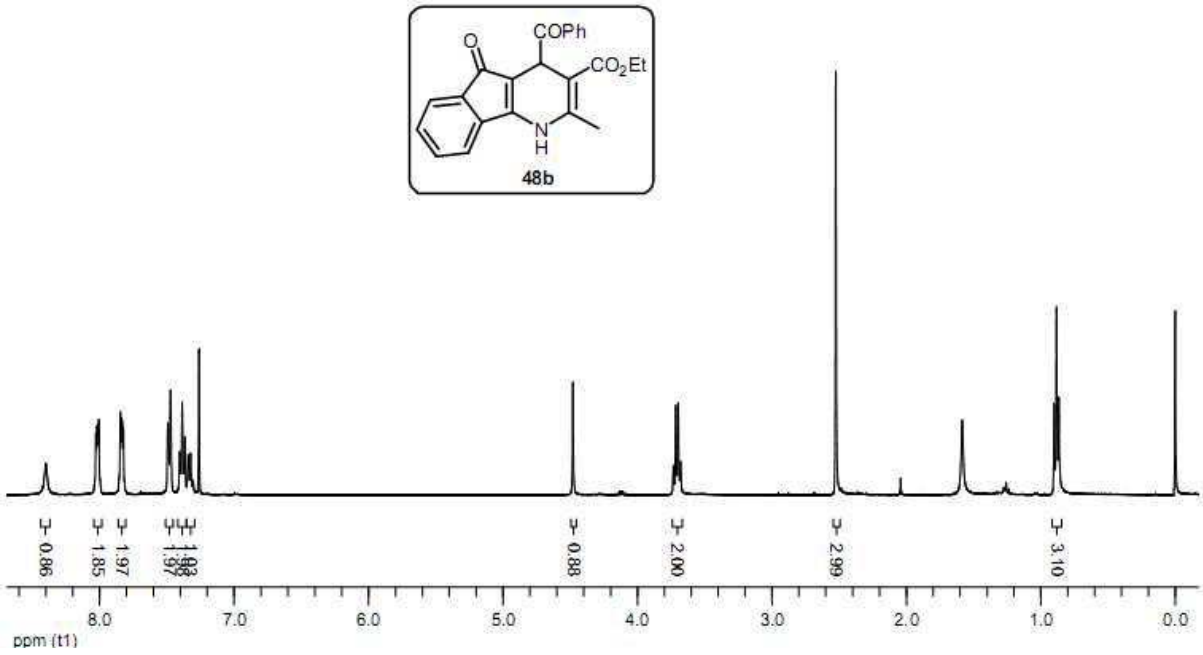
48a ^{1}H NMR ($CDCl_3$, 400 MHz)



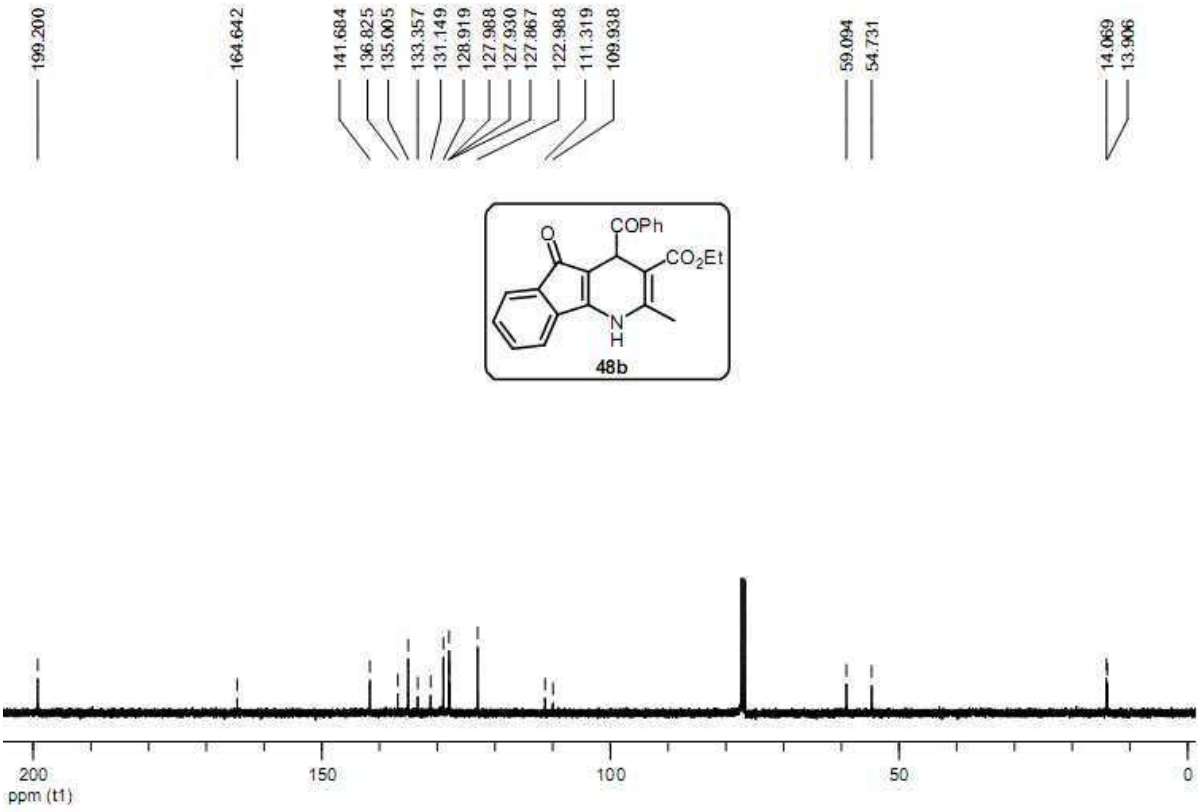
48a ^{13}C NMR ($CDCl_3$, 100 MHz)



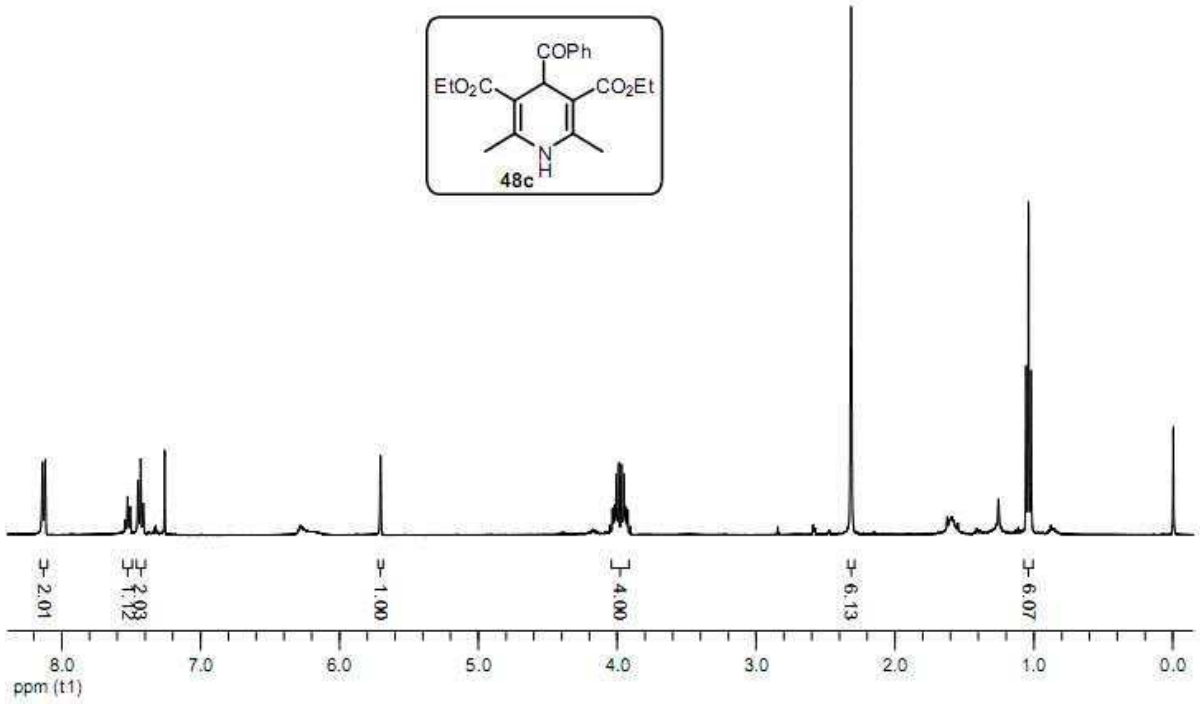
48b ^{1}H NMR ($CDCl_3$, 400 MHz)



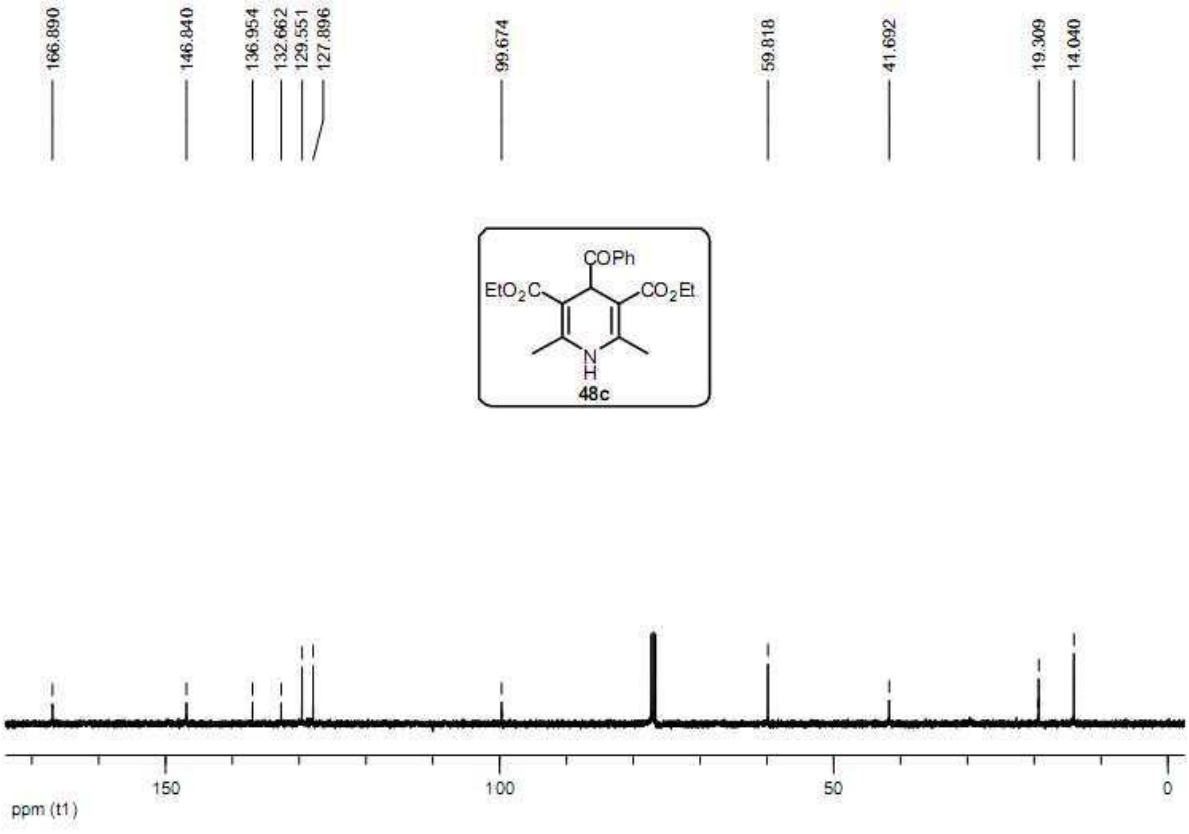
48b ^{13}C NMR ($CDCl_3$, 100 MHz)



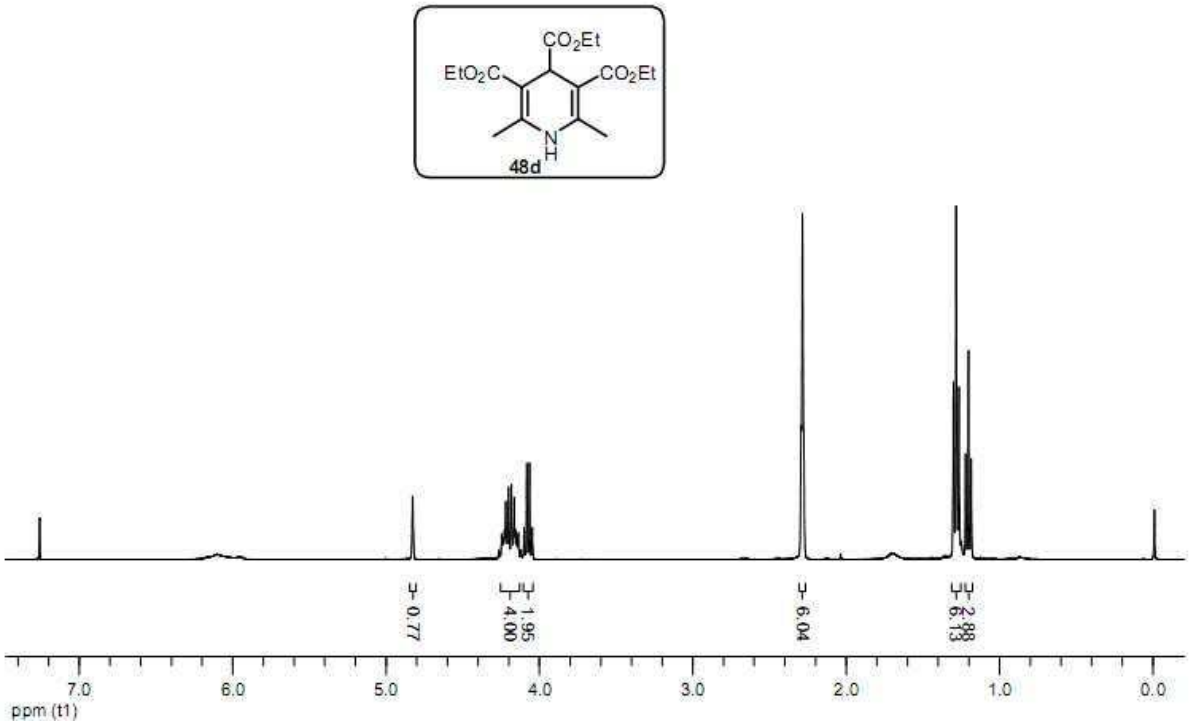
48c ^{1}H NMR ($CDCl_3$, 400 MHz)



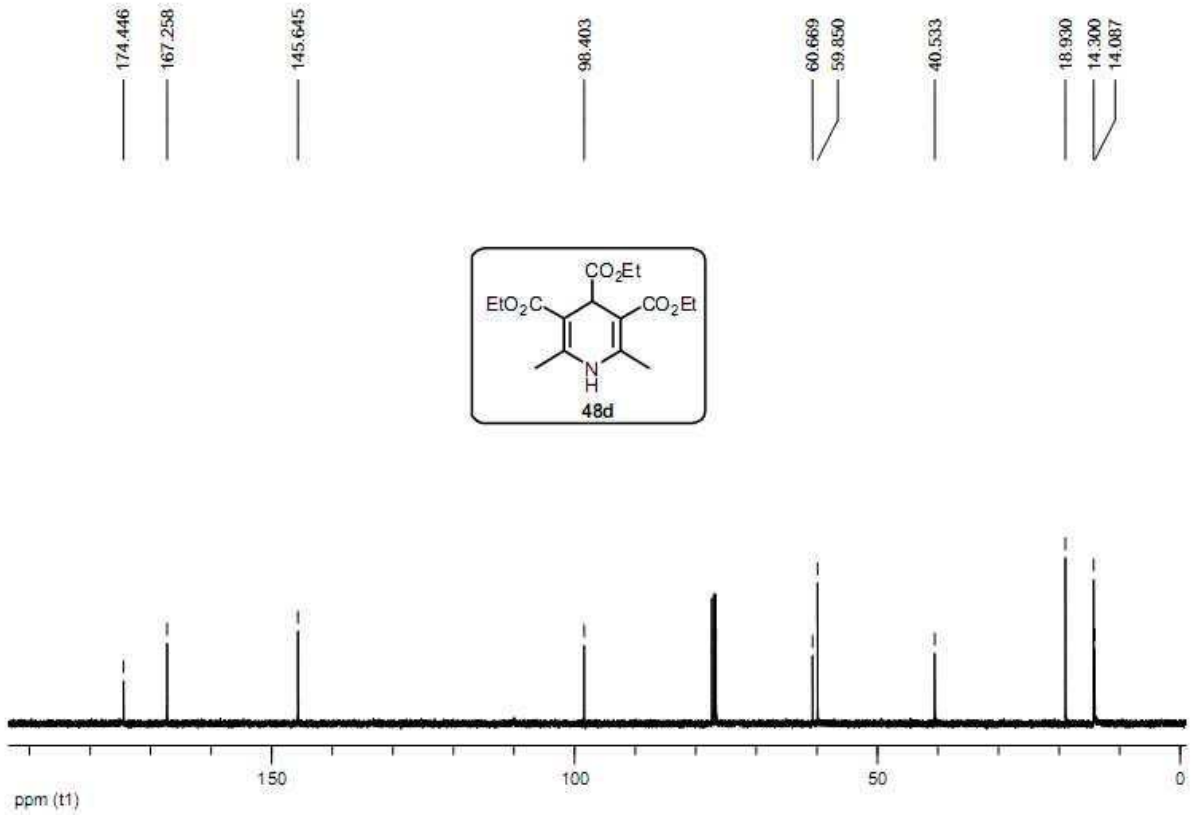
48c ^{13}C NMR ($CDCl_3$, 100 MHz)



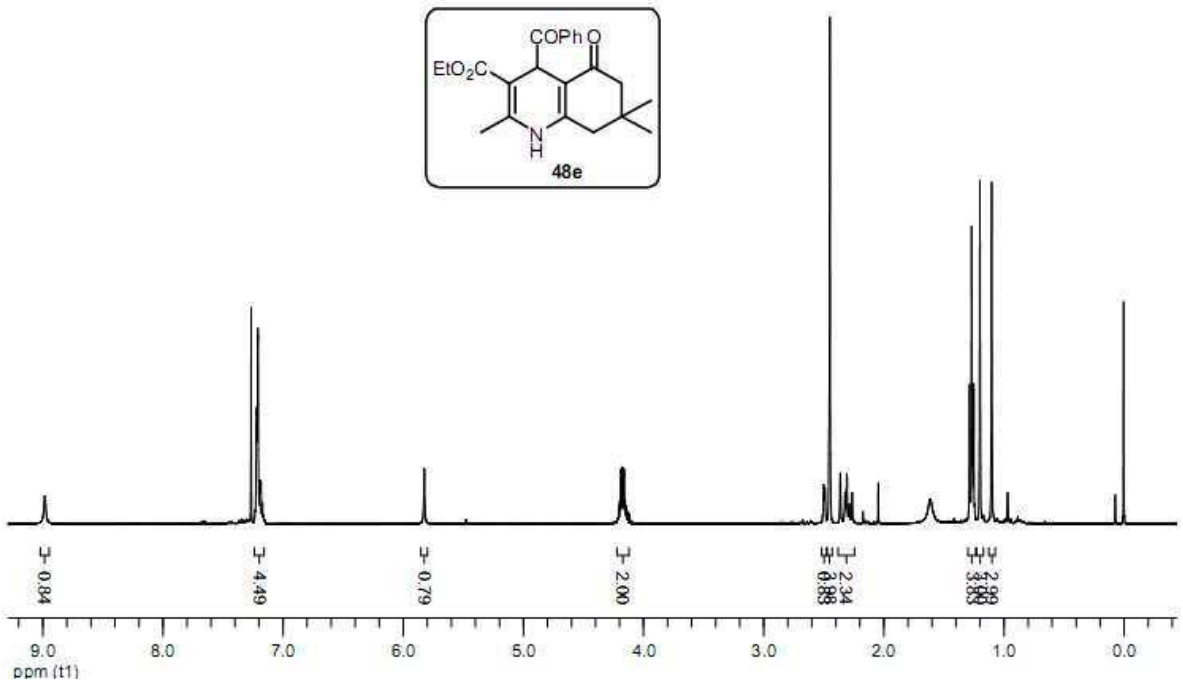
48d ^{1}H NMR ($CDCl_3$, 400 MHz)



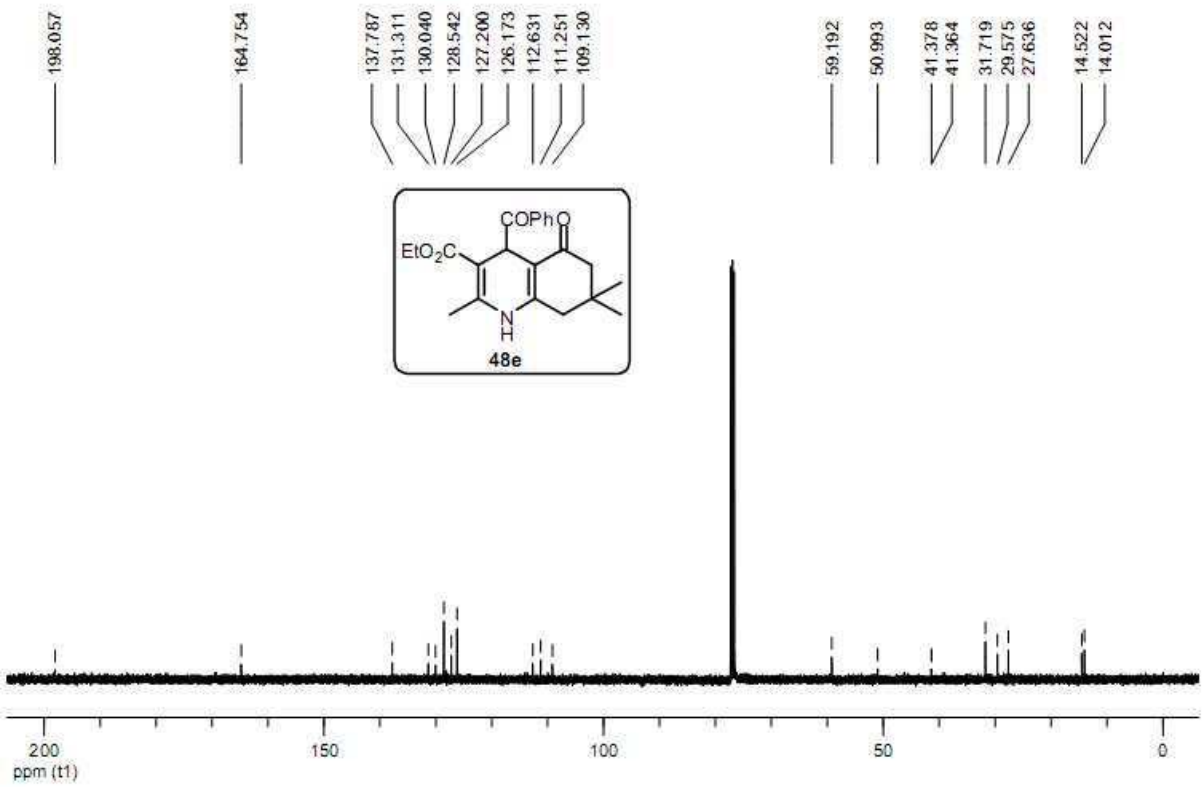
48d ^{13}C NMR ($CDCl_3$, 100 MHz)



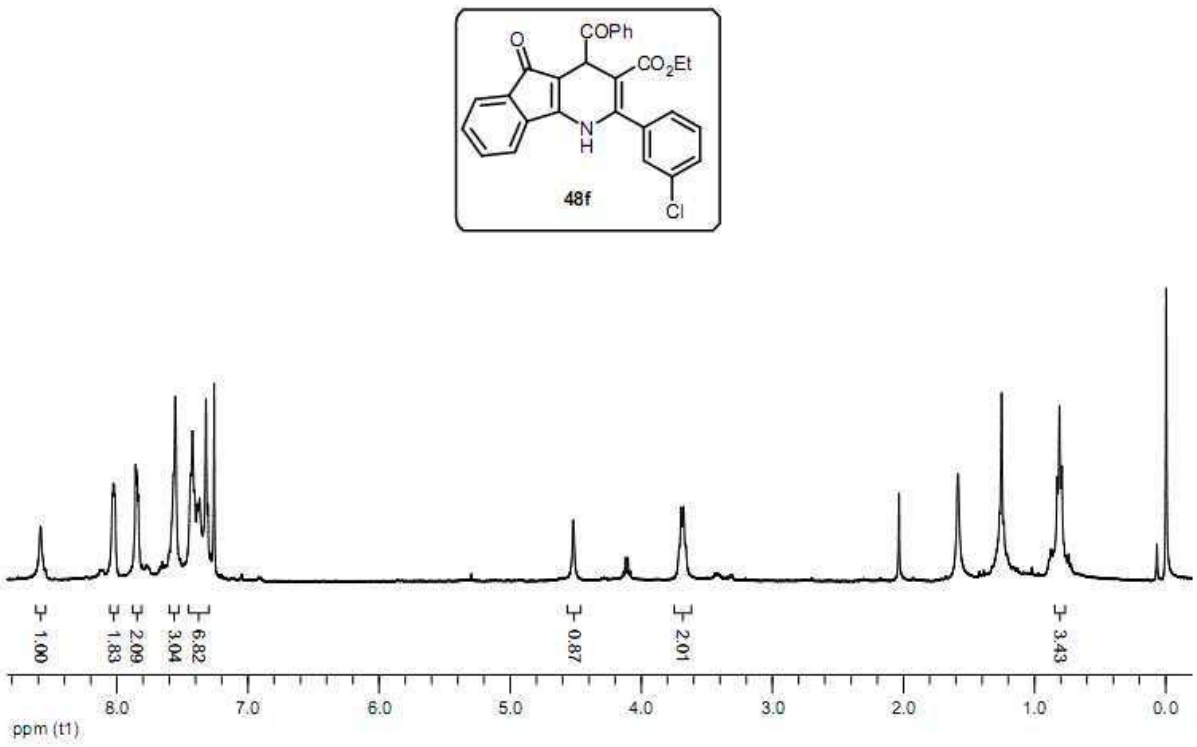
48e ^{1}H NMR ($CDCl_3$, 400 MHz)



48e ^{13}C NMR ($CDCl_3$, 100 MHz)



48f ^{1}H NMR ($CDCl_3$, 400 MHz)



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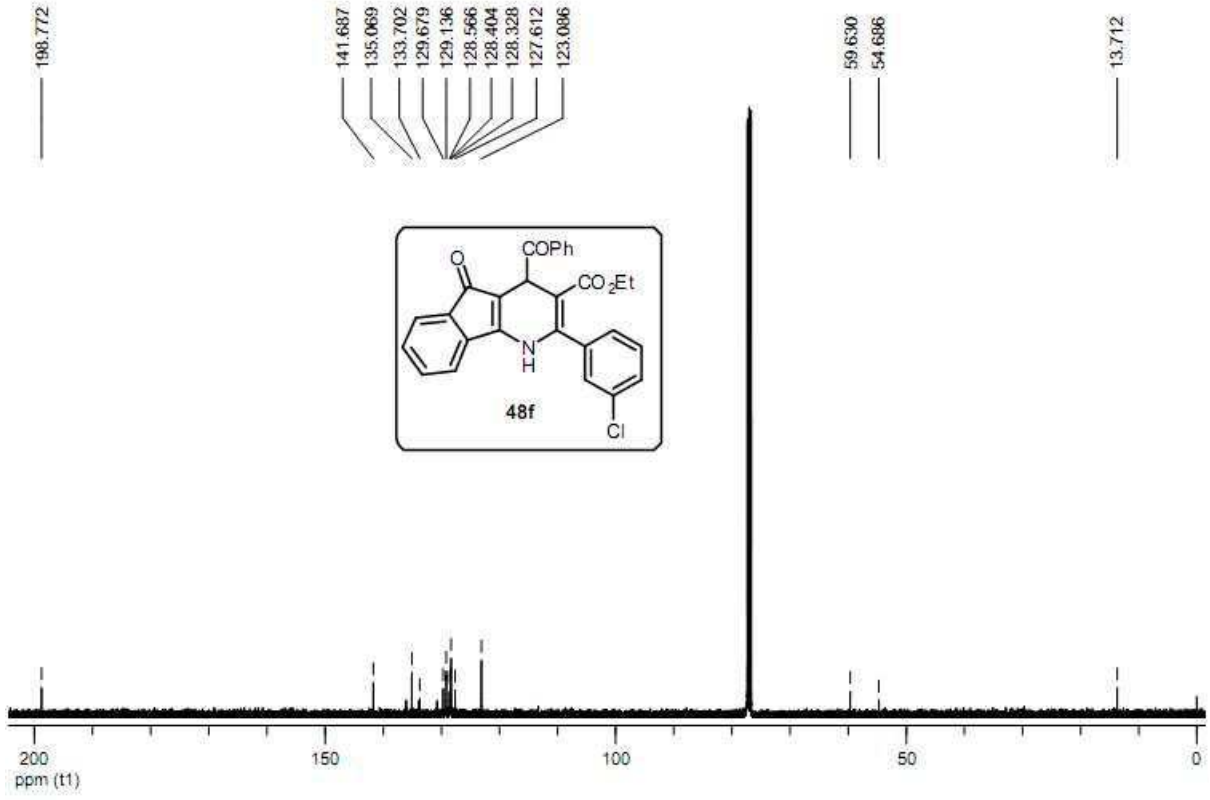

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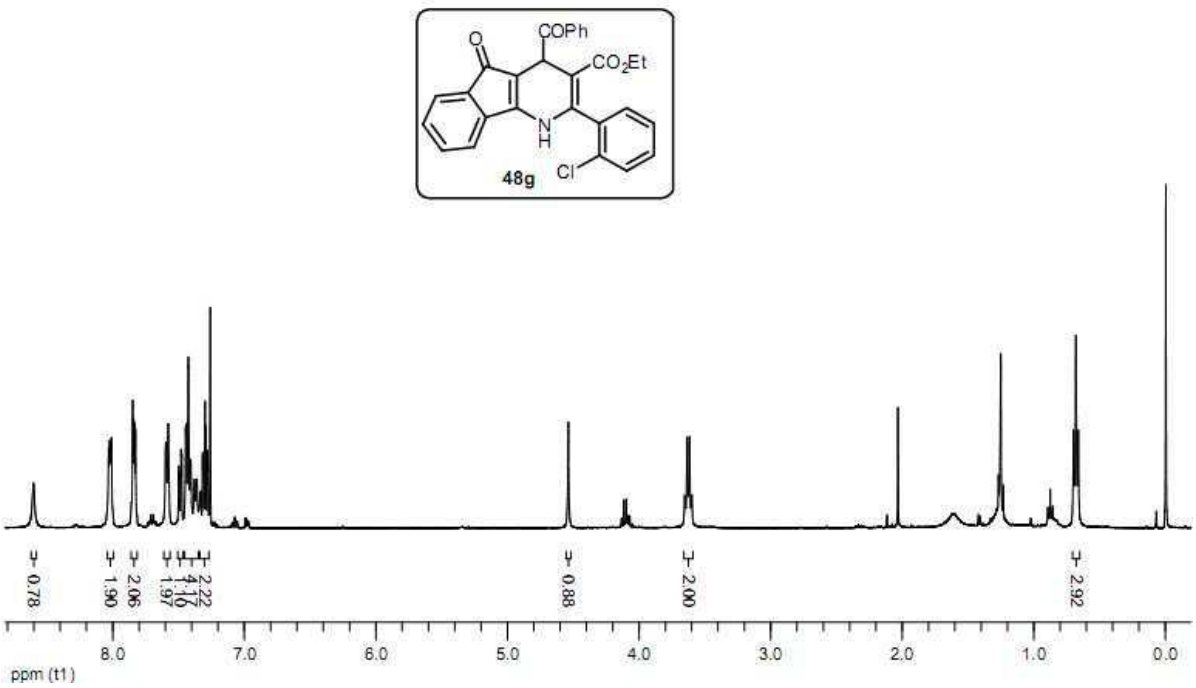

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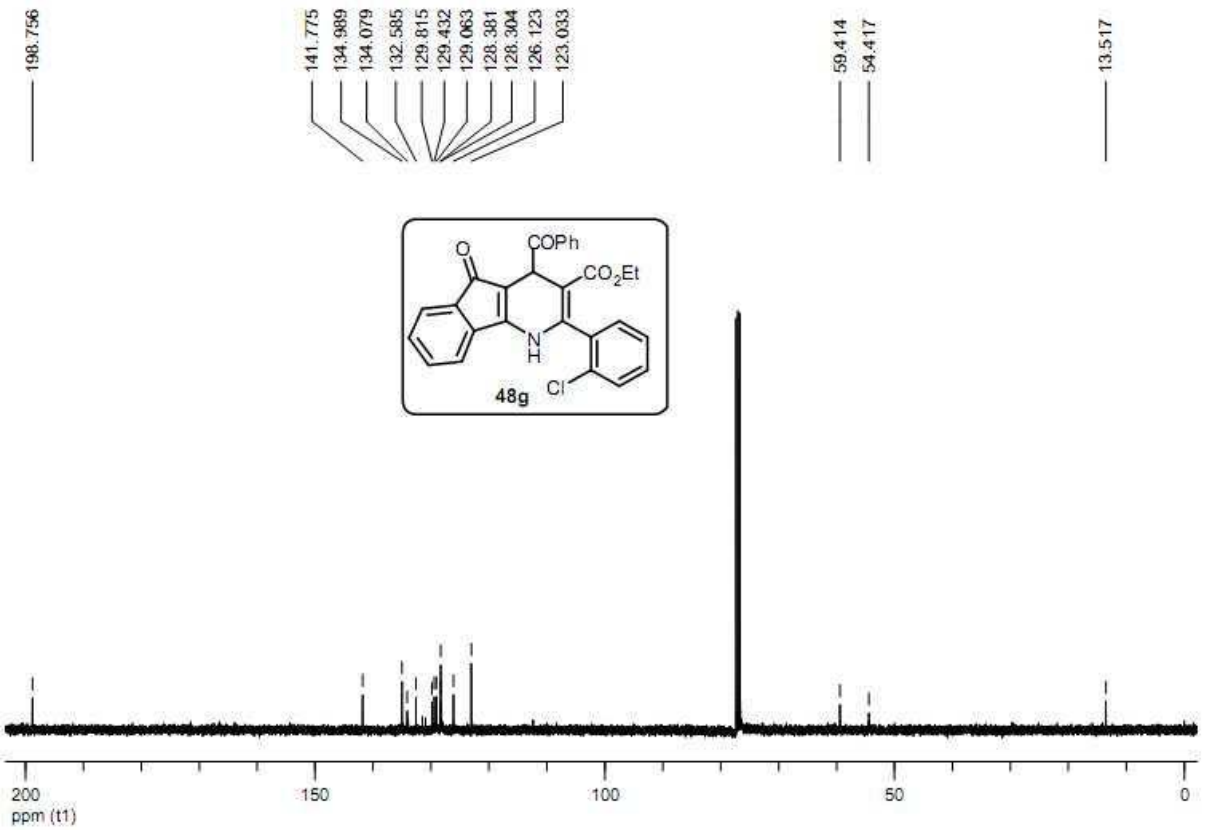

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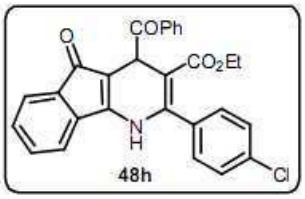

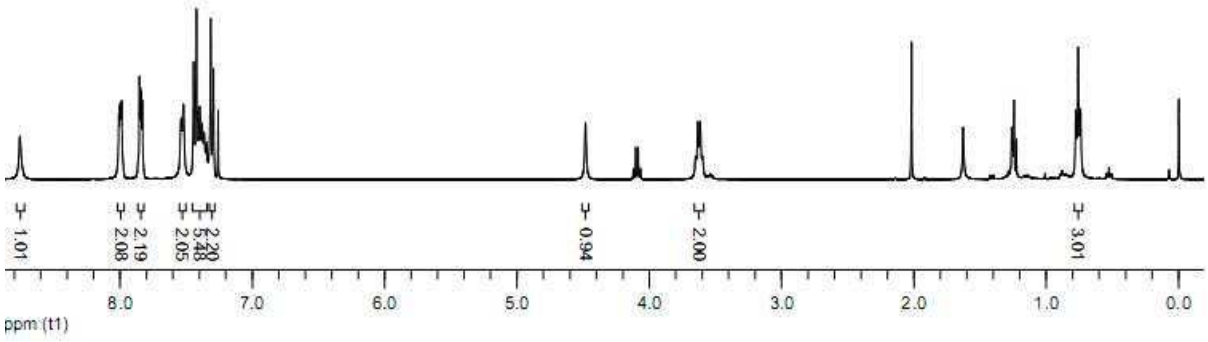

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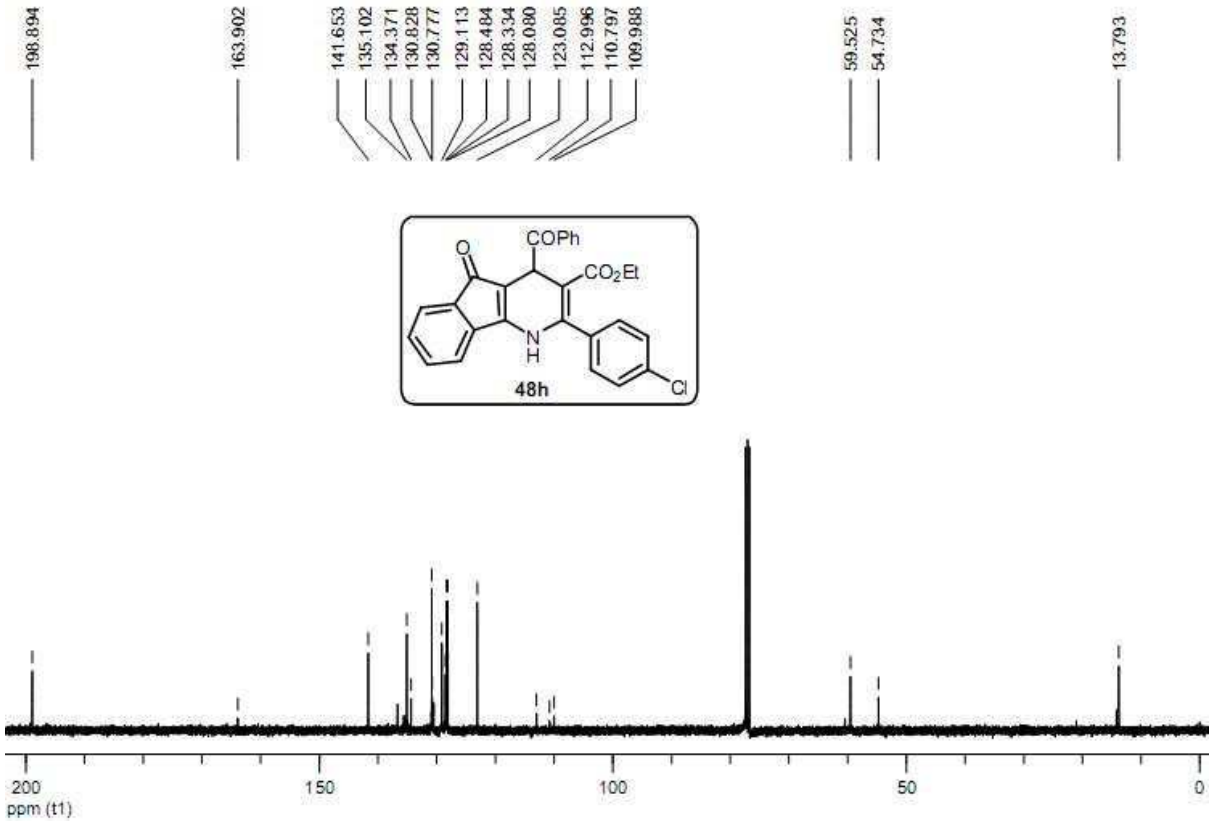

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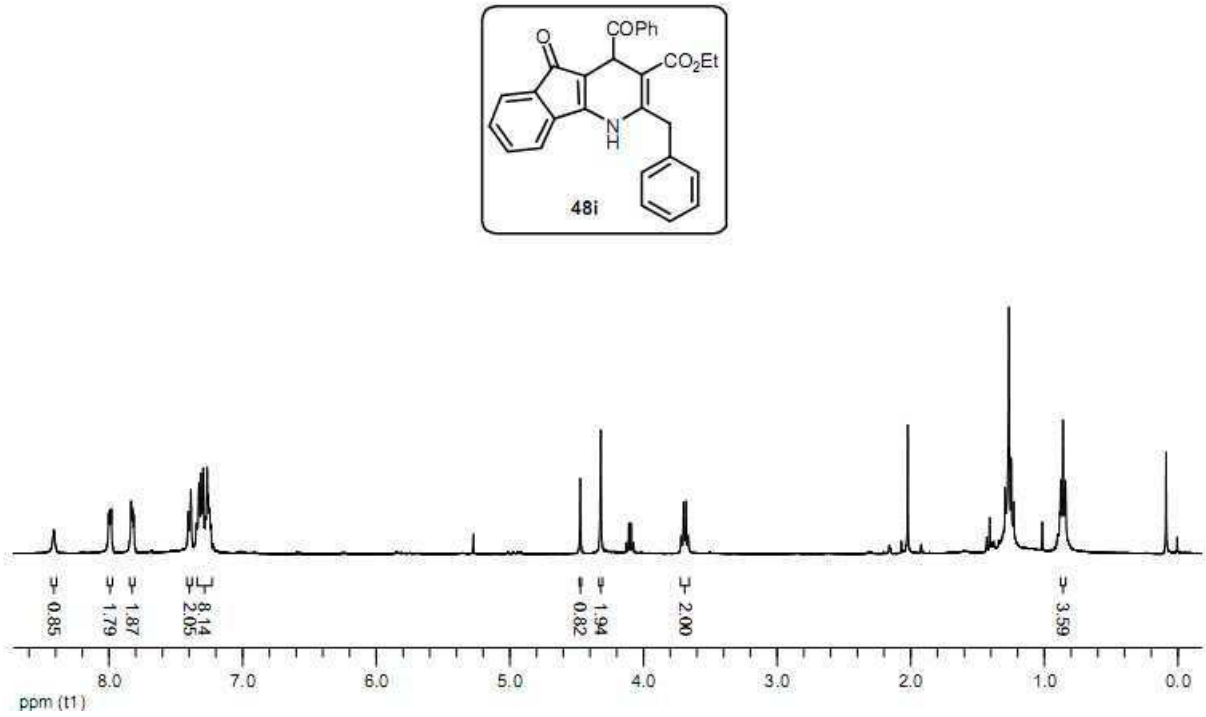

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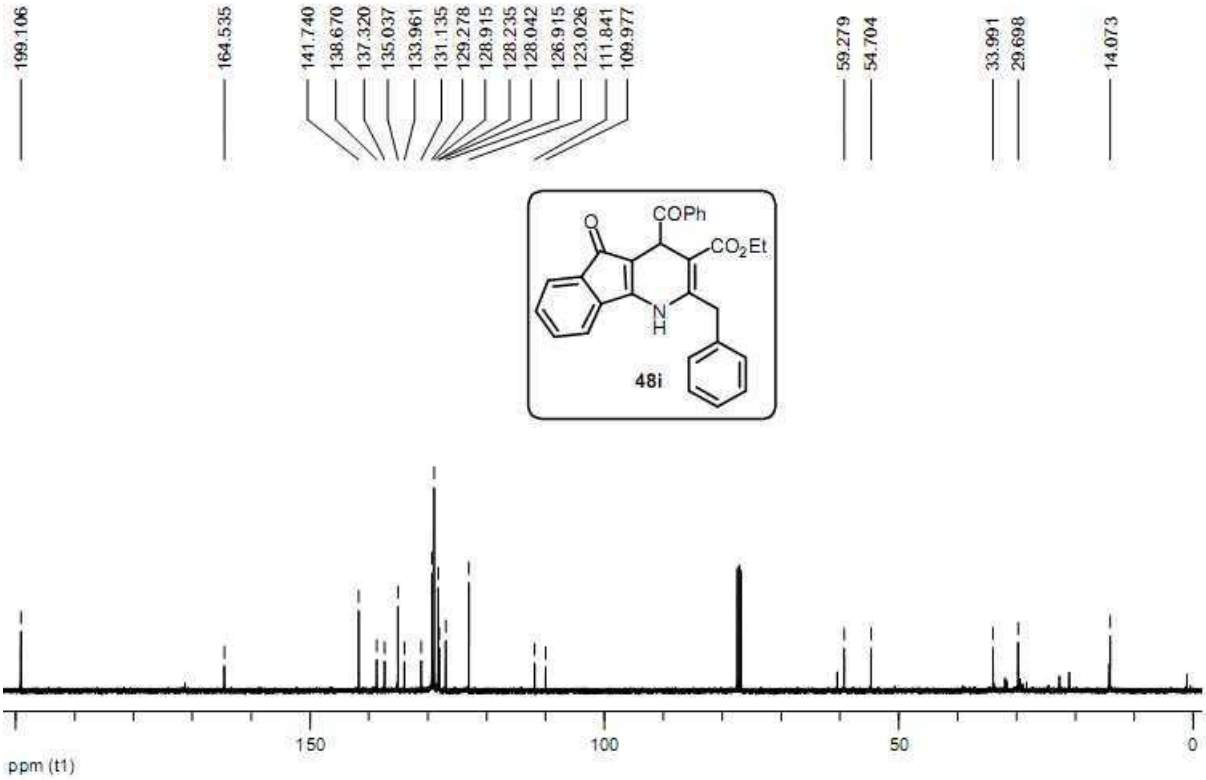

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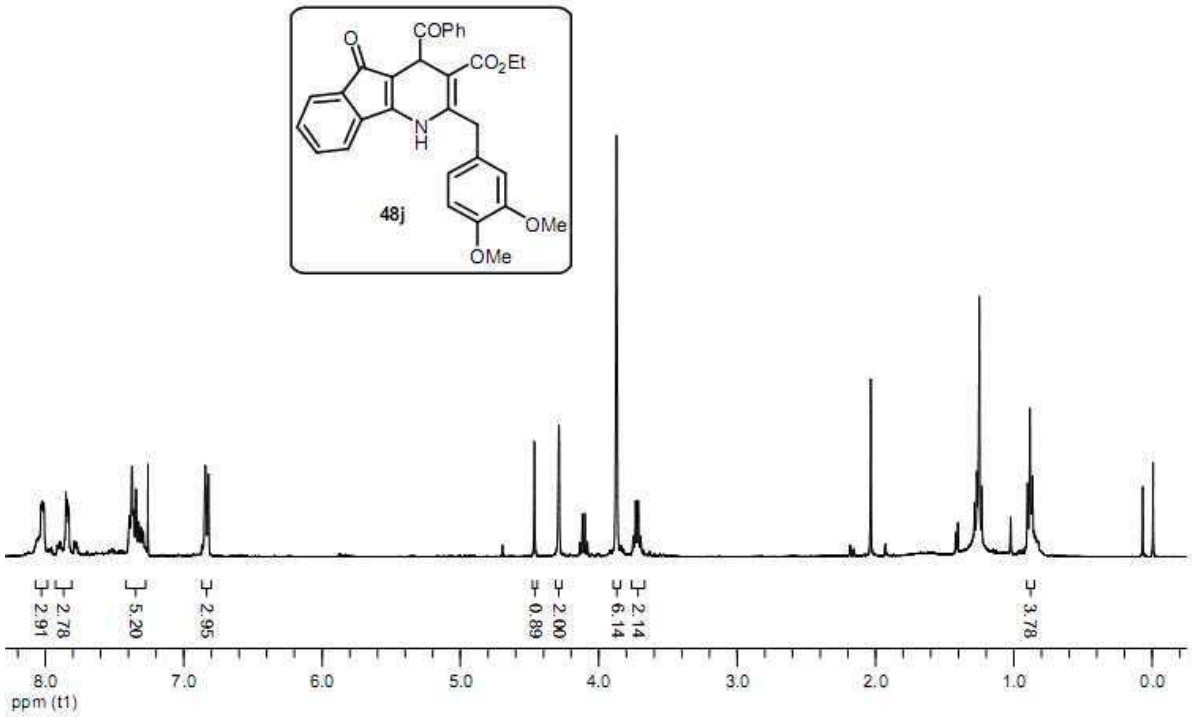

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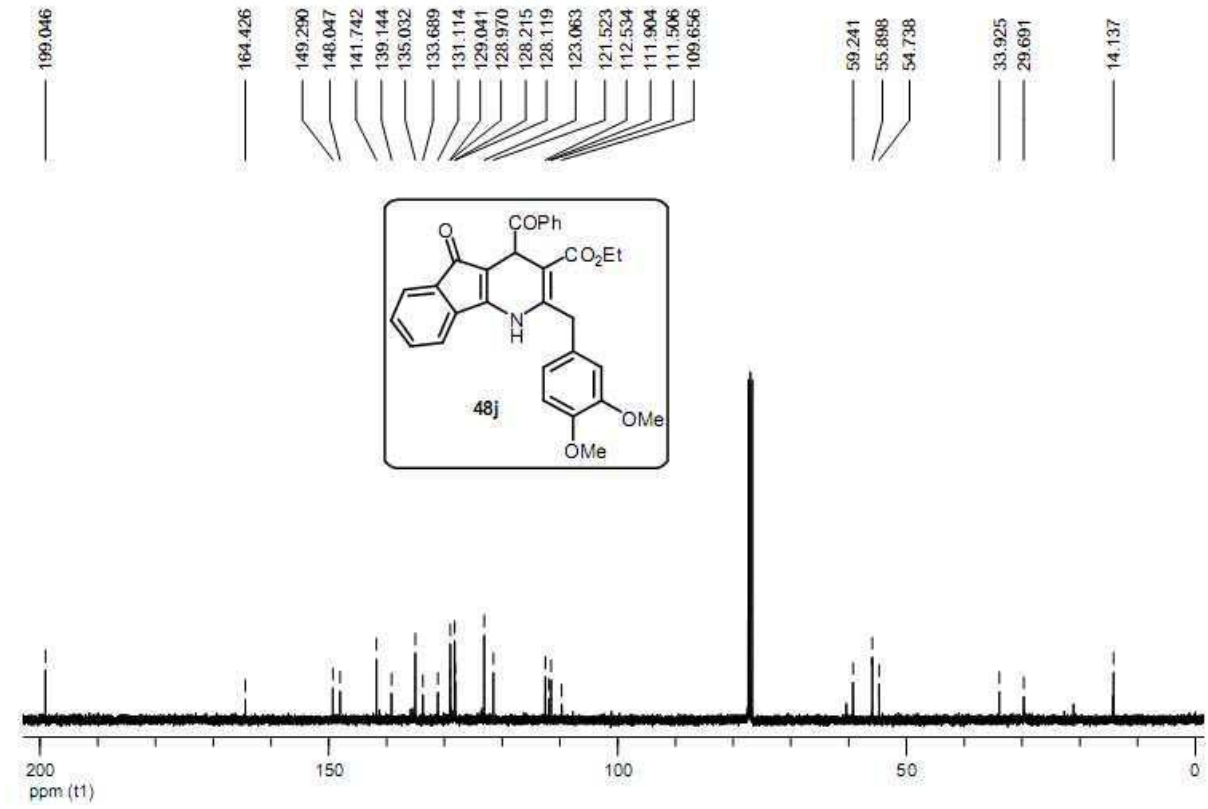

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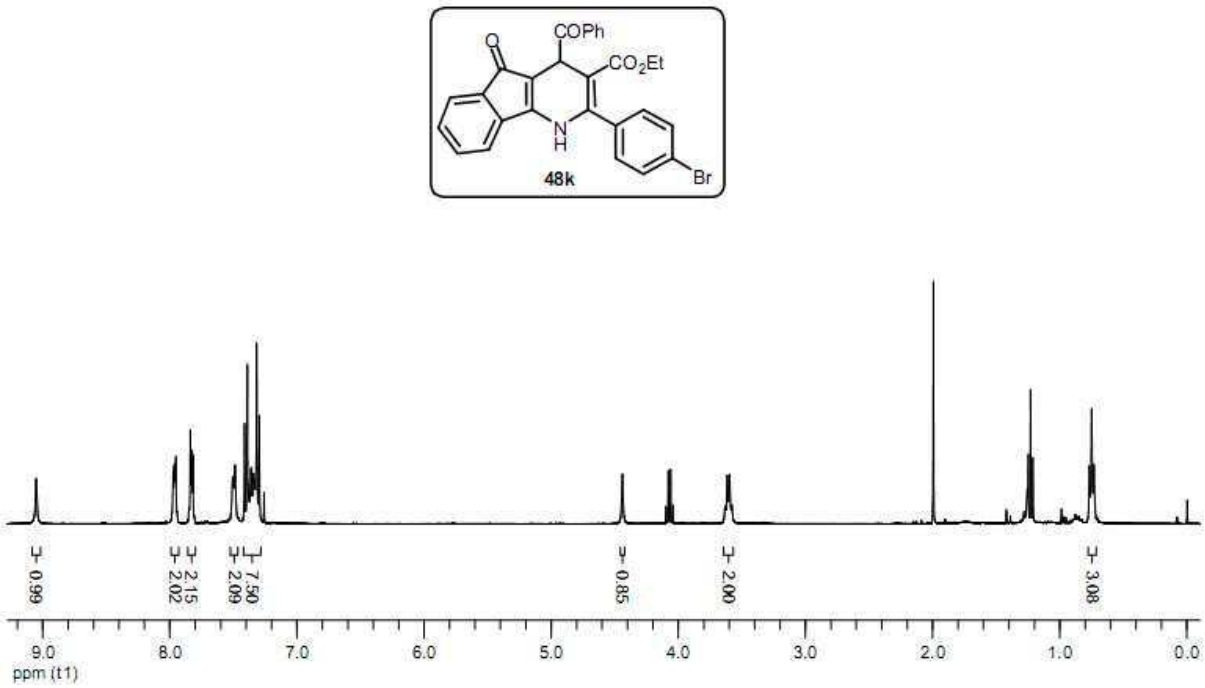

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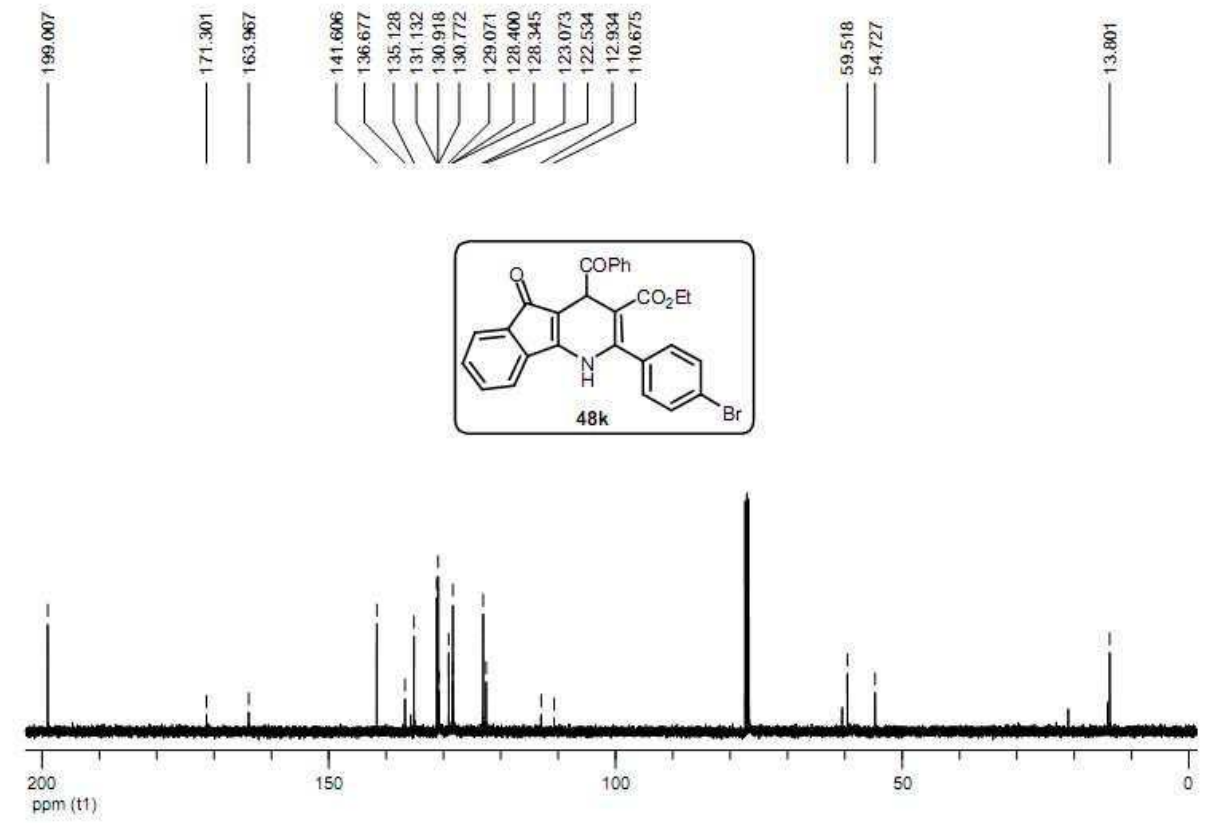

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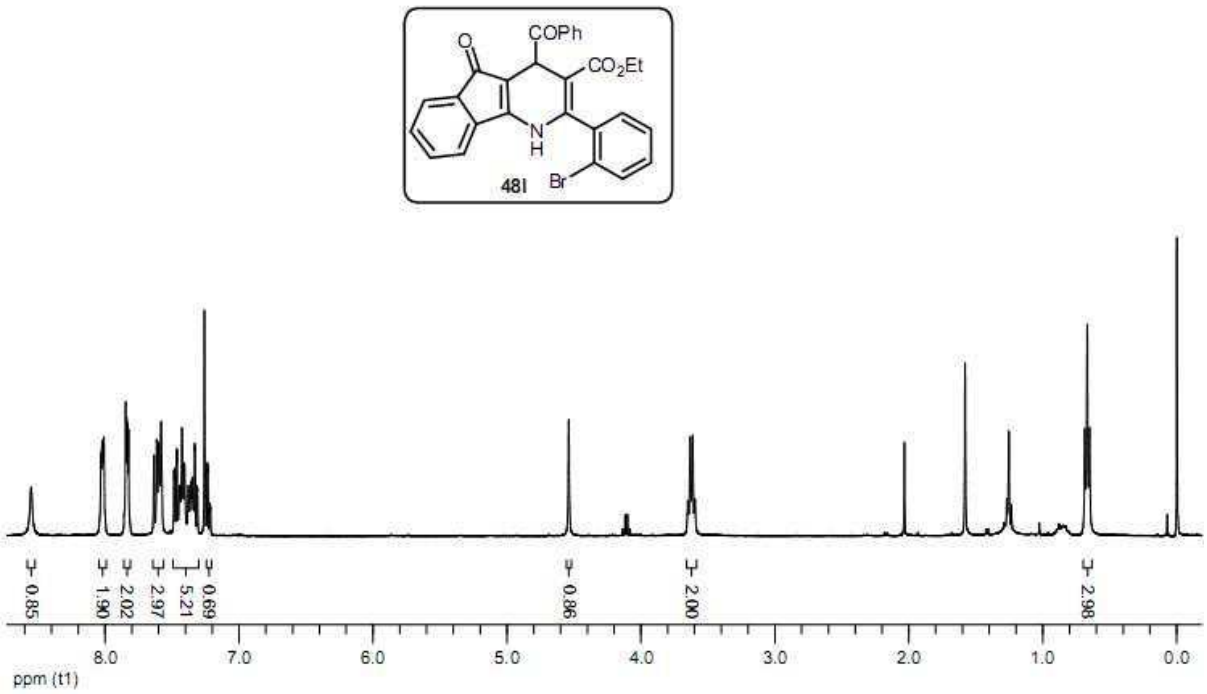

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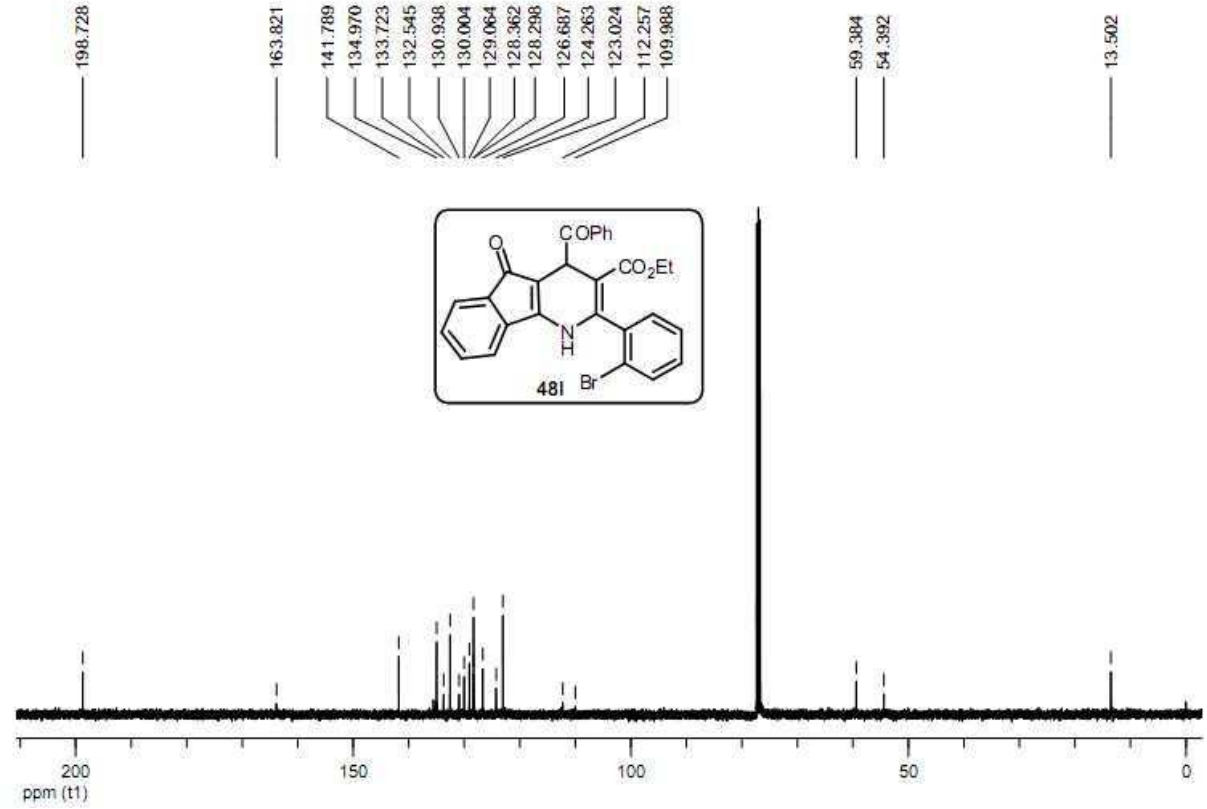

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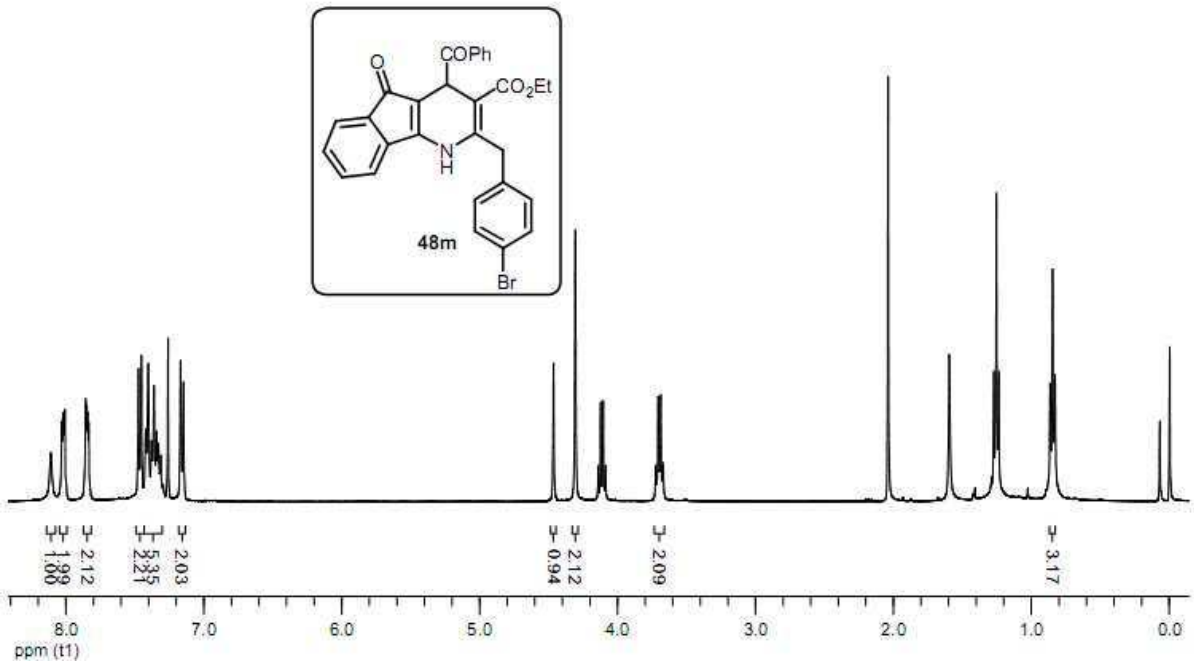

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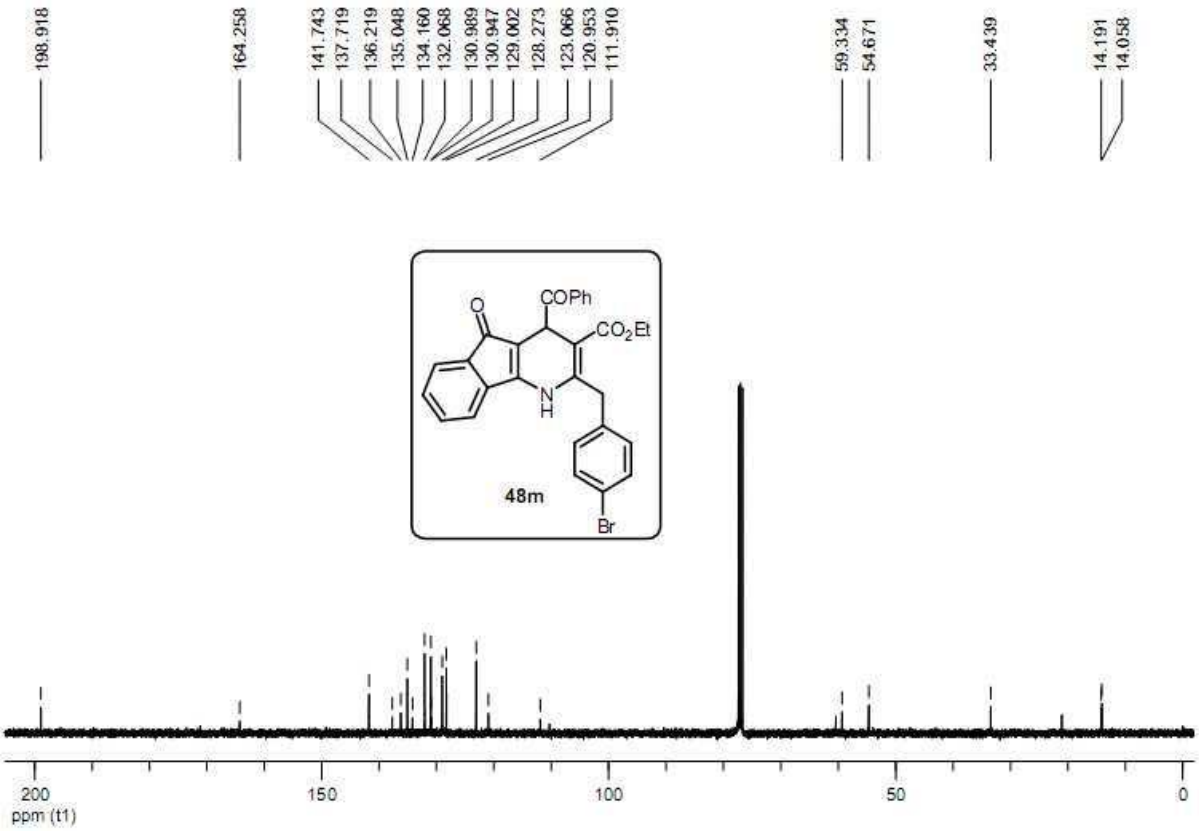

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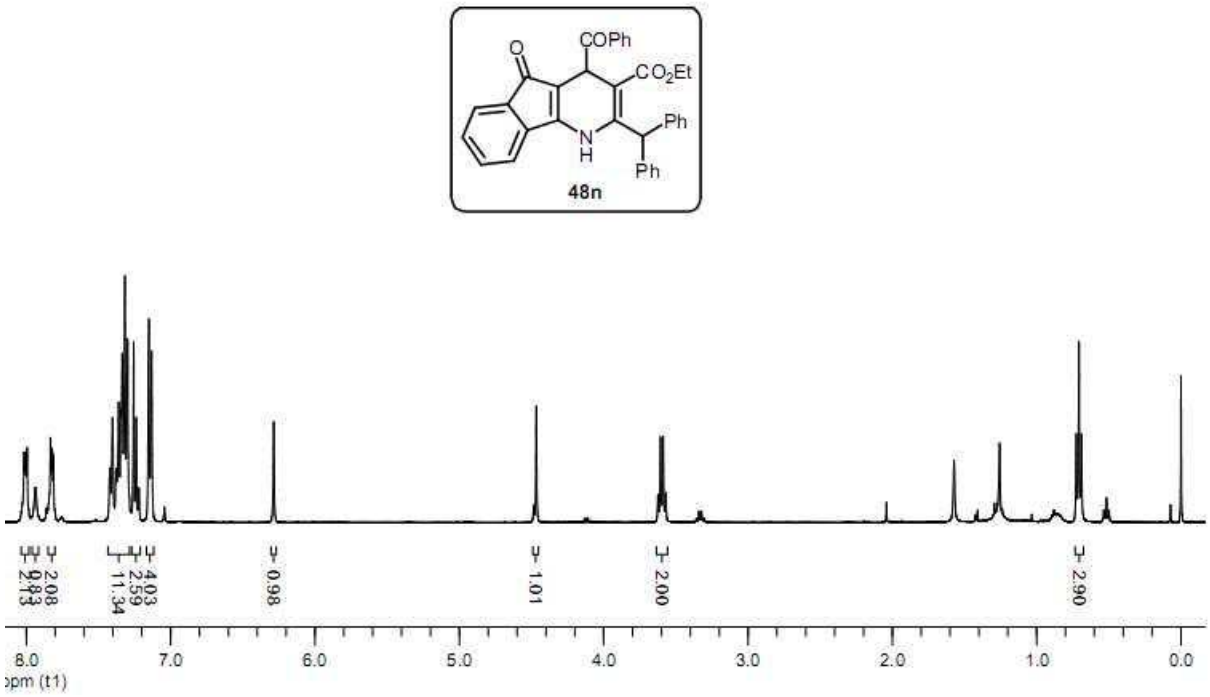

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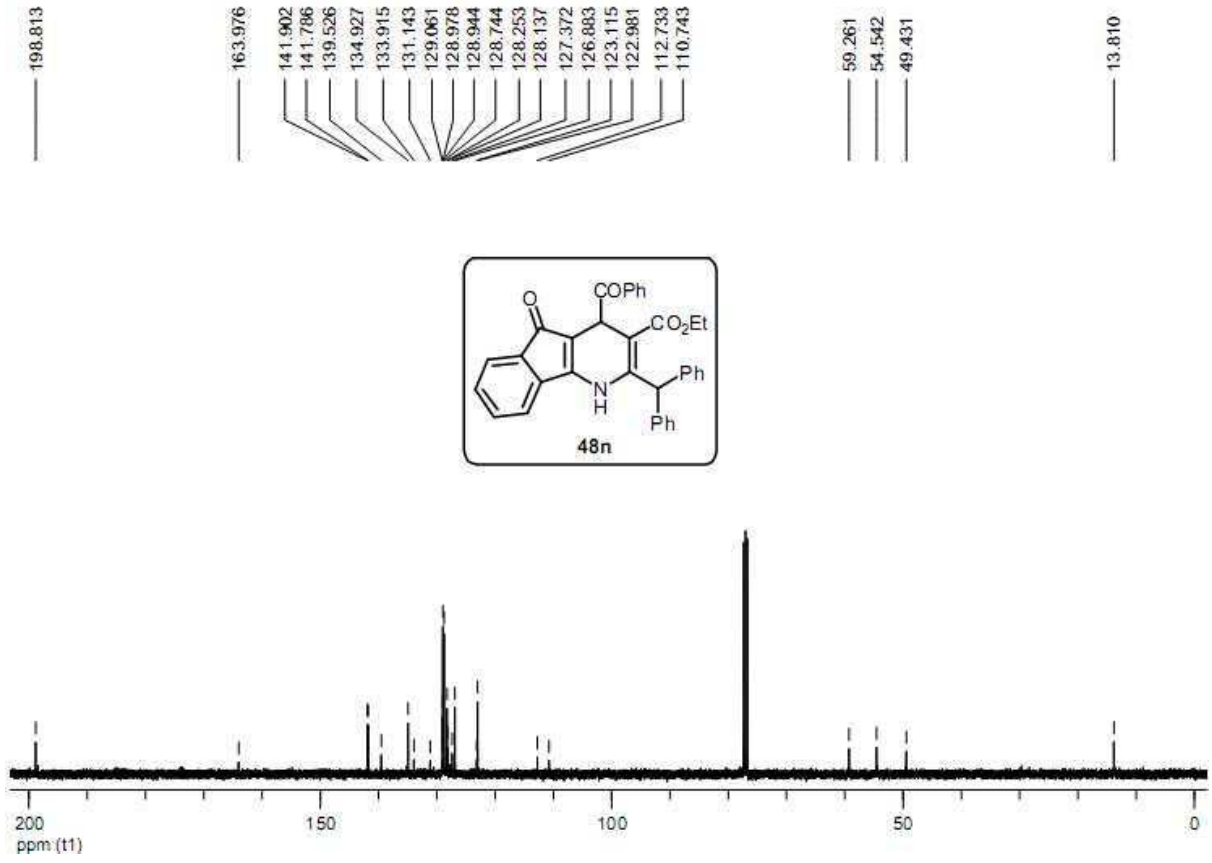

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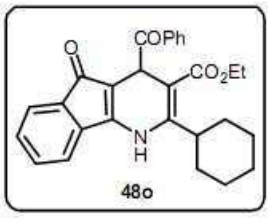

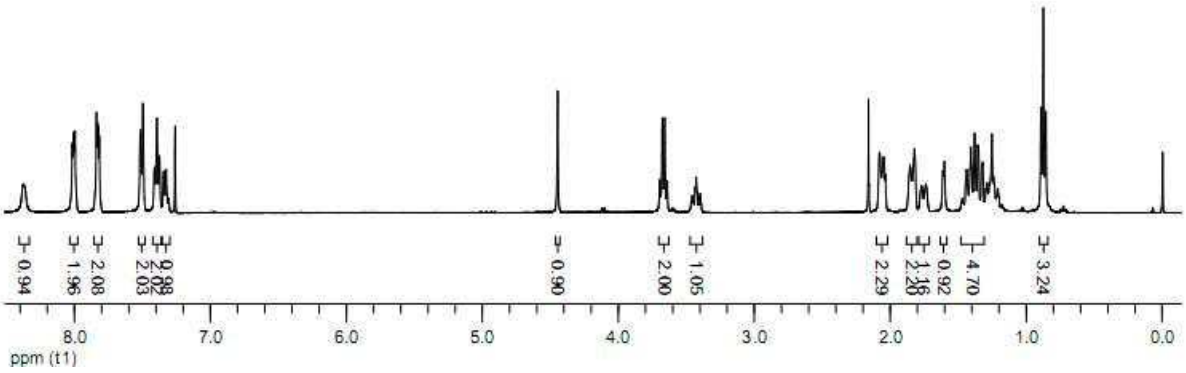

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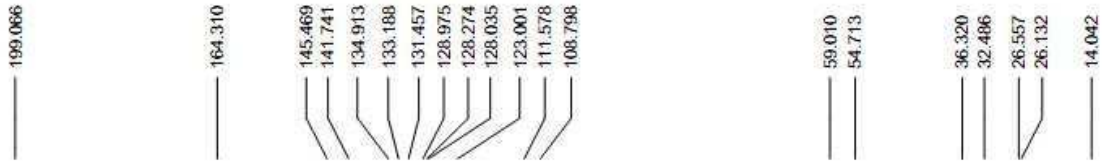
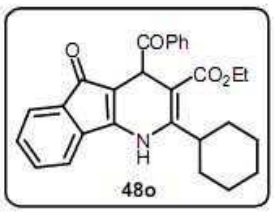
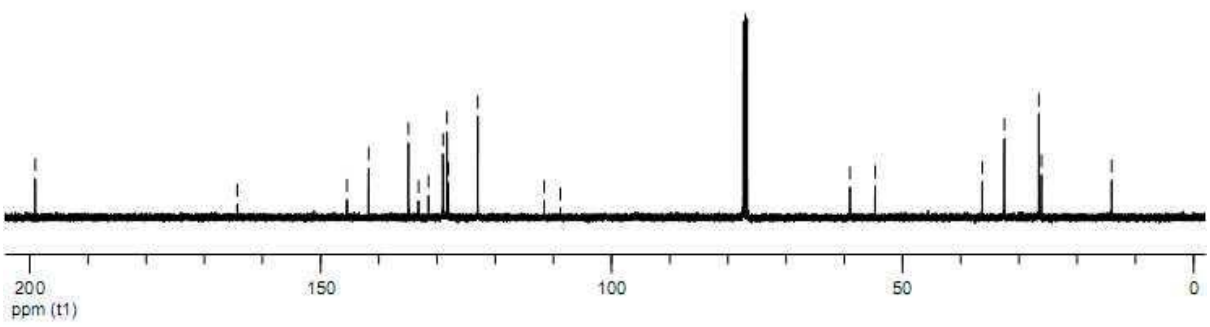
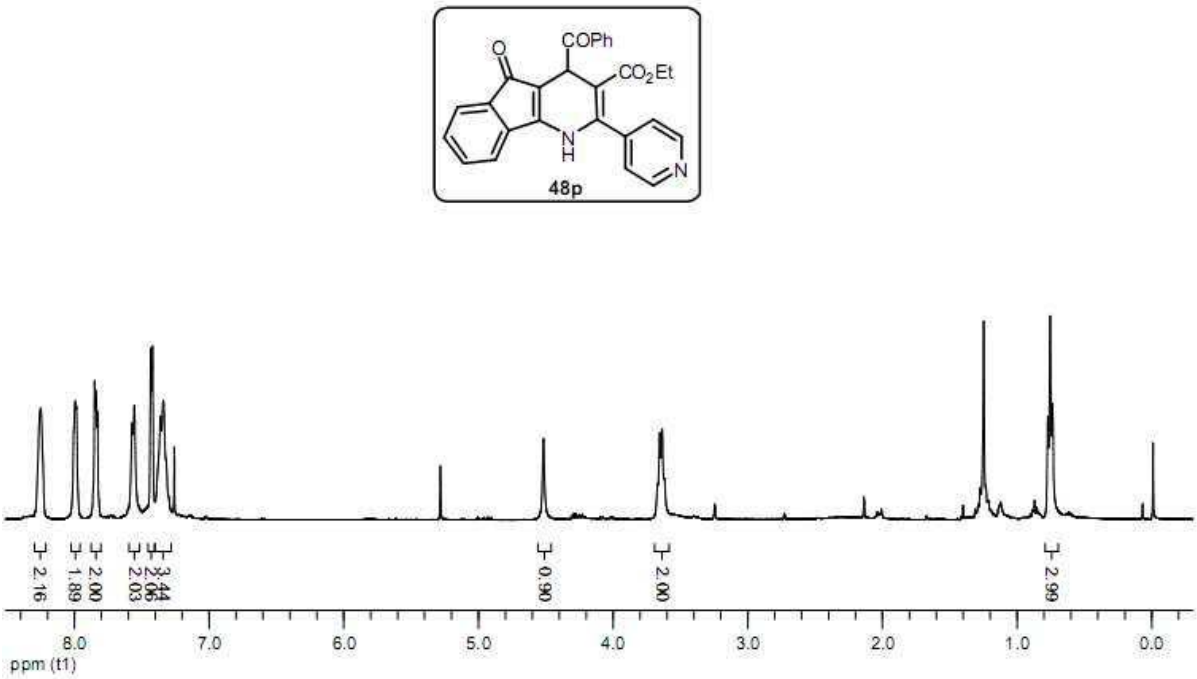


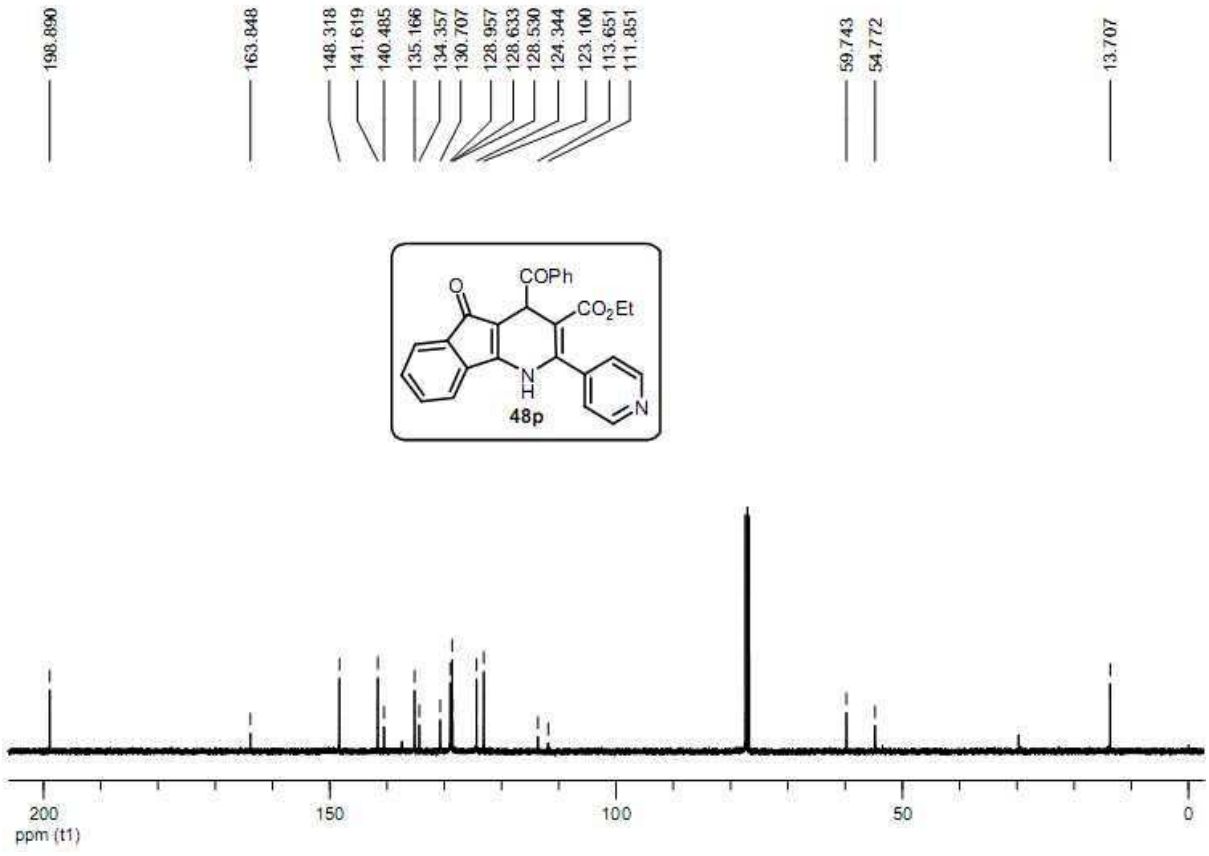




48p ^{1}H NMR ($CDCl_3$, 400 MHz)



48p ^{13}C NMR ($CDCl_3$, 100 MHz



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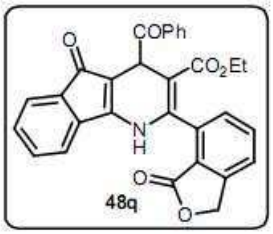

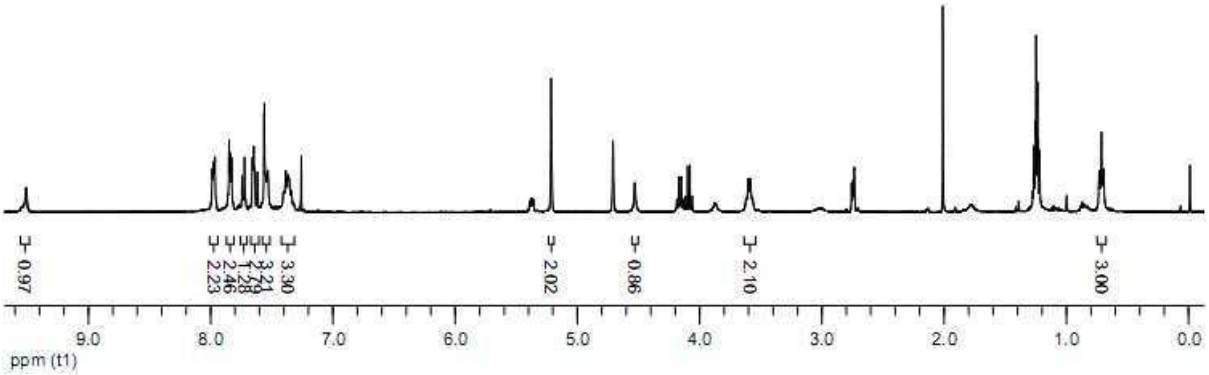

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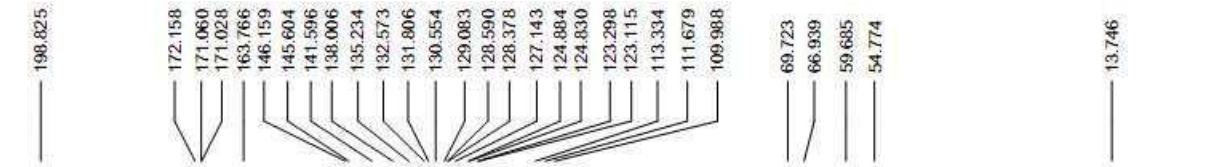
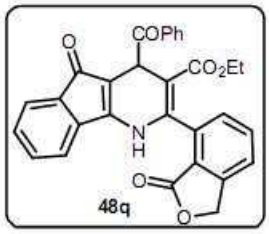
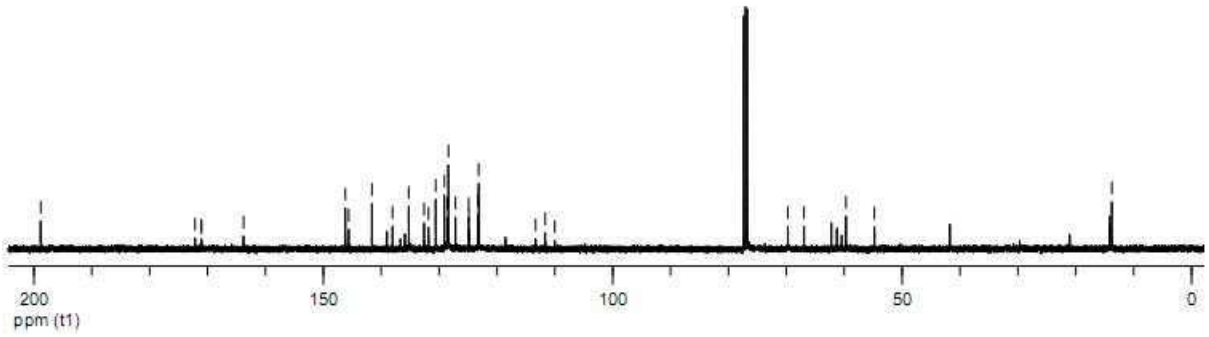
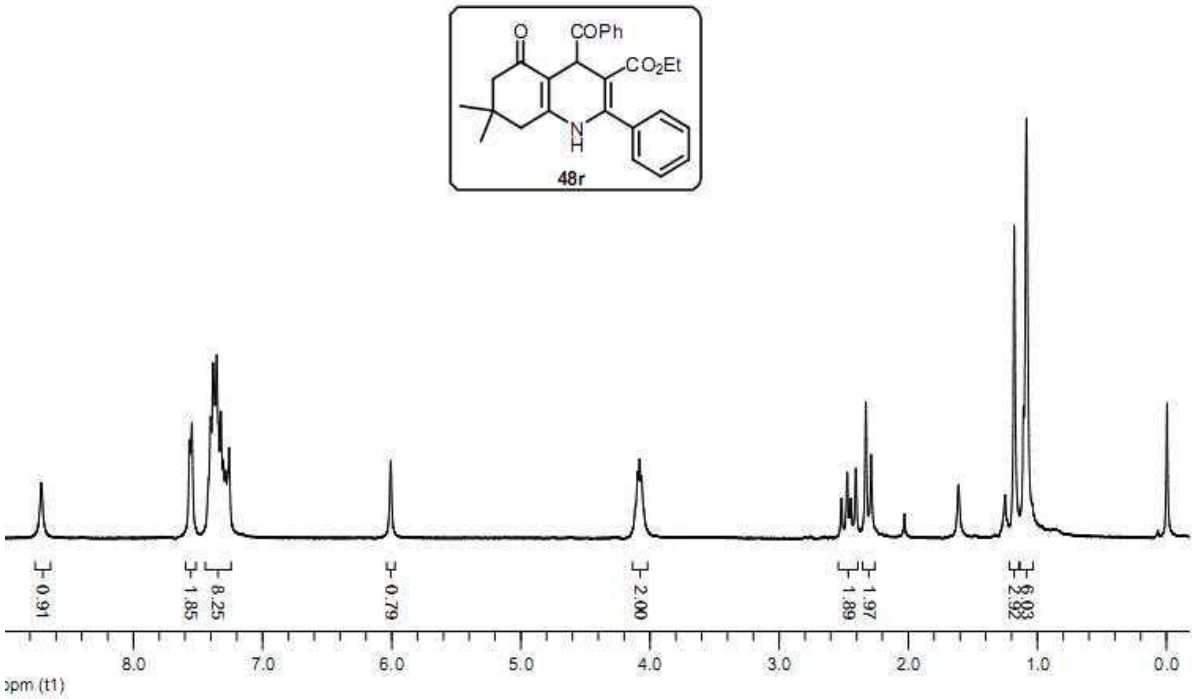


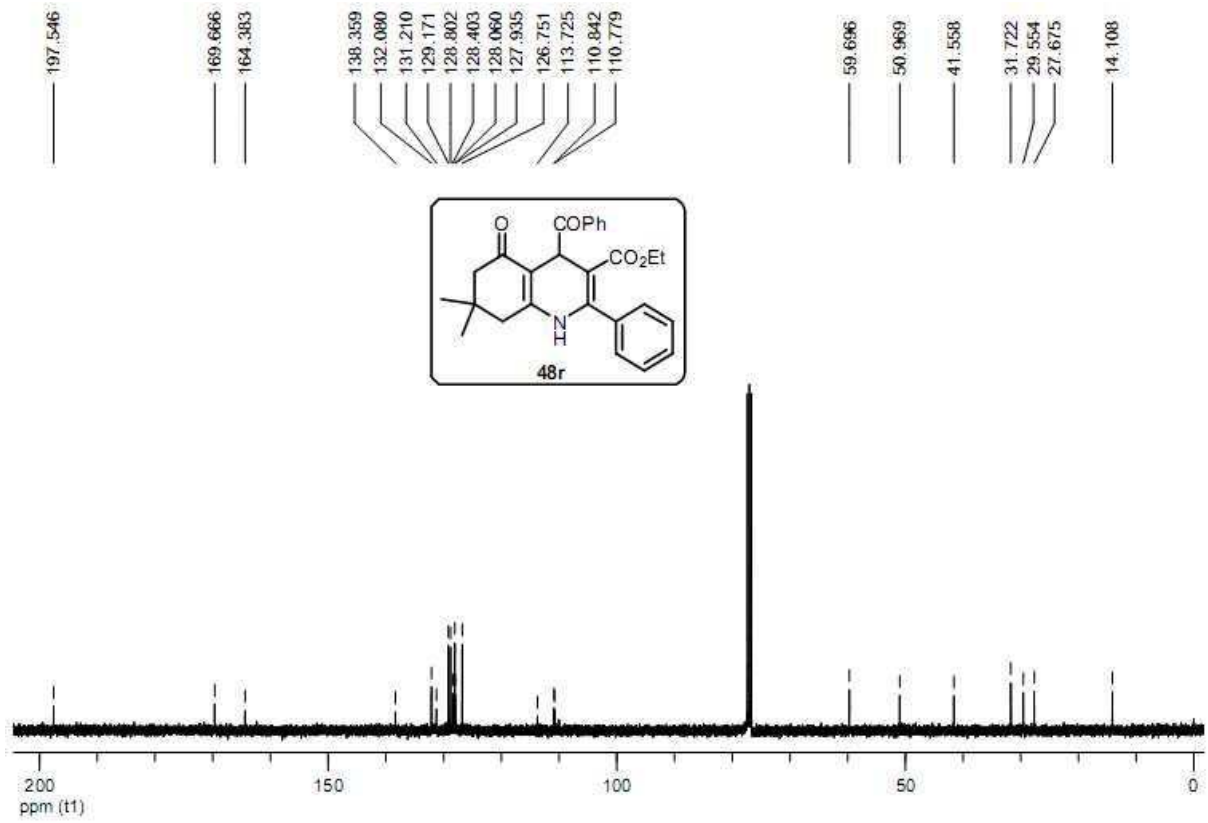




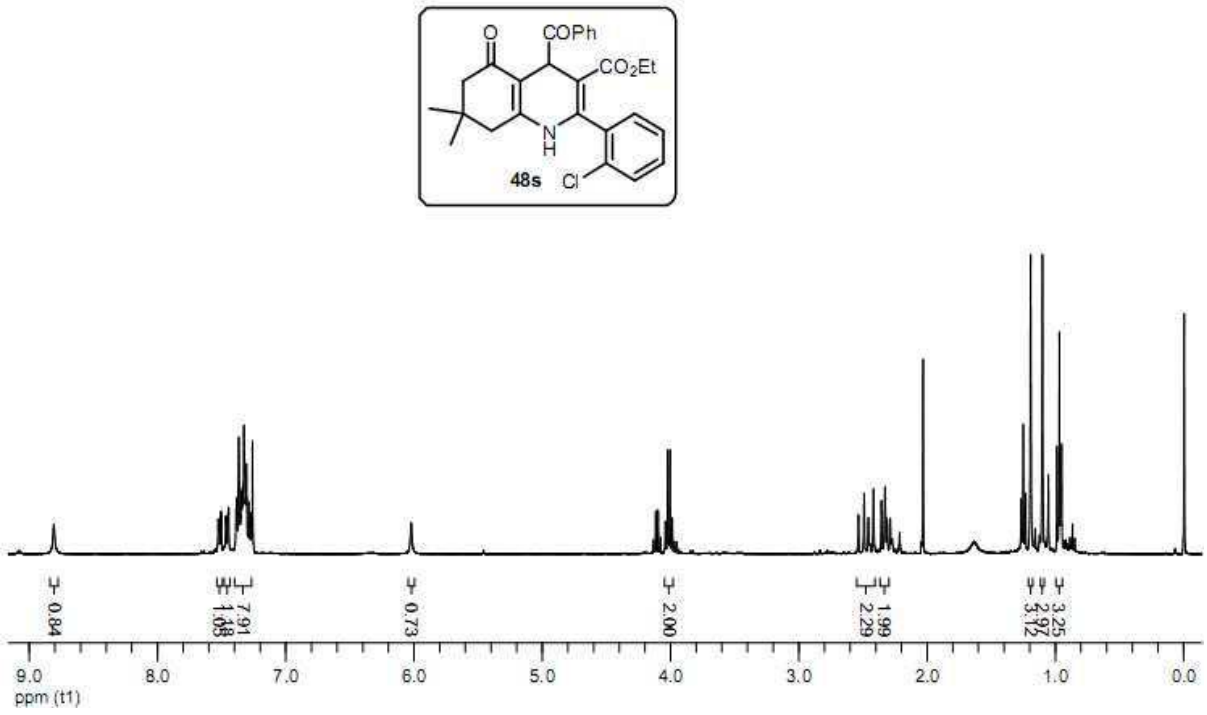
48r ^{1}H NMR ($CDCl_3$, 400 MHz)



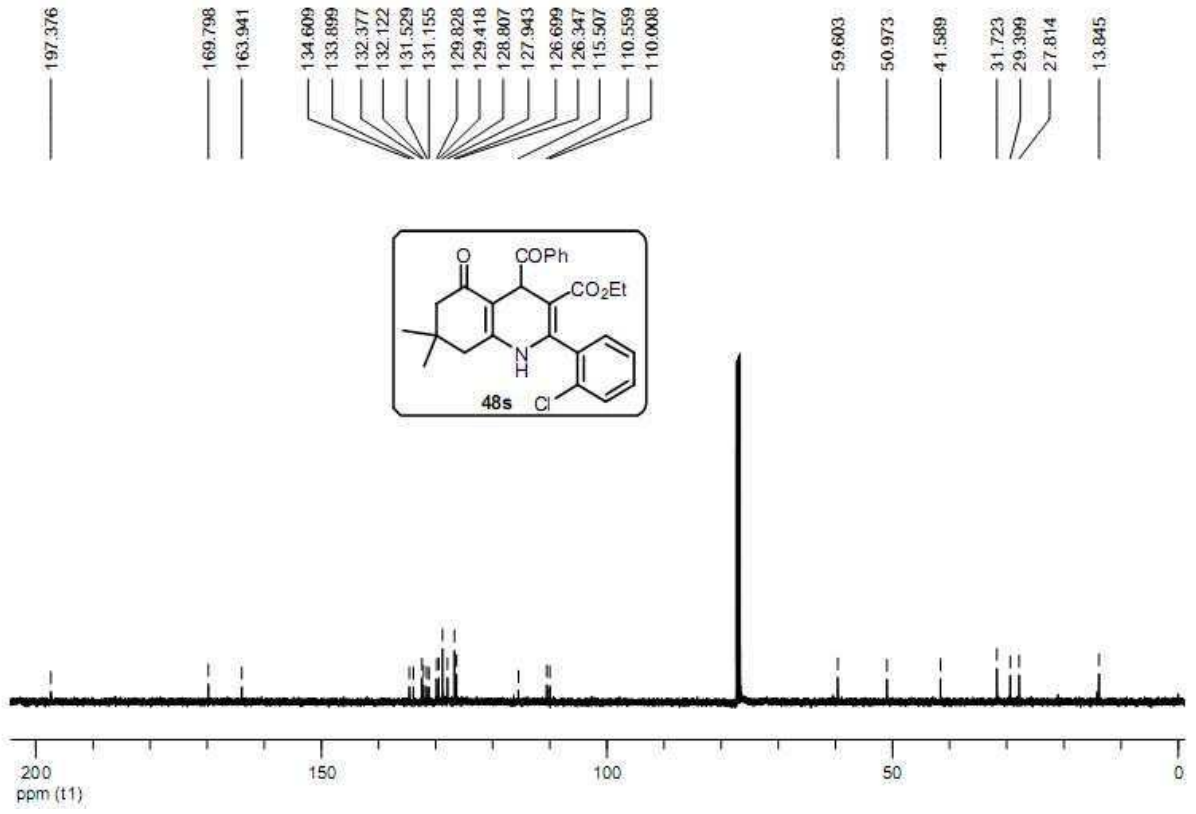
48r ^{13}C NMR ($CDCl_3$, 100 MHz



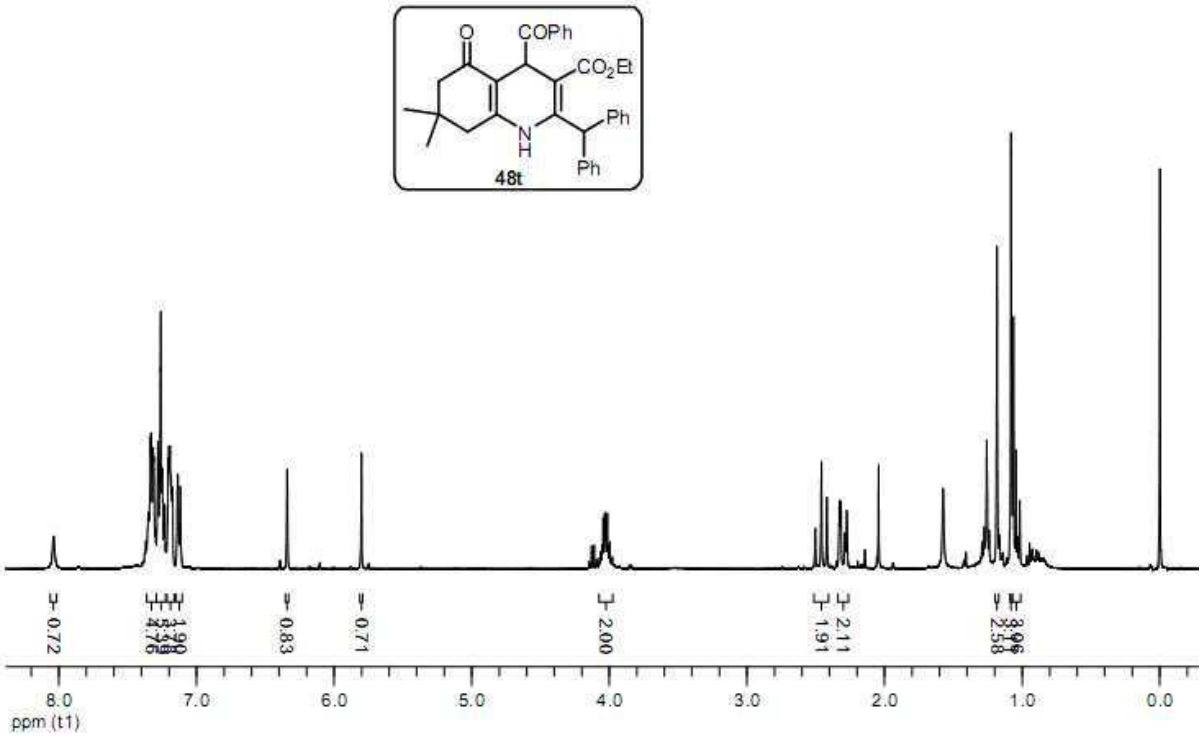
48s ^{1}H NMR ($CDCl_3$, 400 MHz)



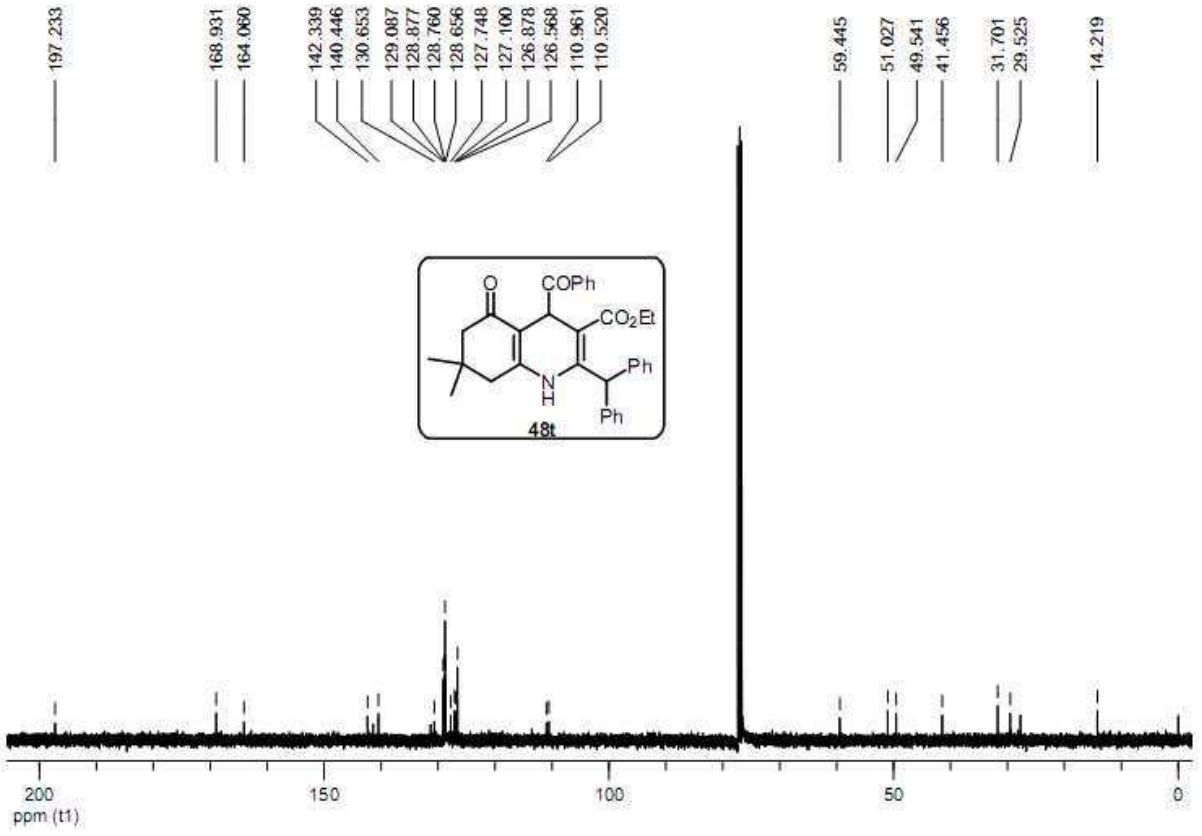
48s ^{13}C NMR ($CDCl_3$, 100 MHz



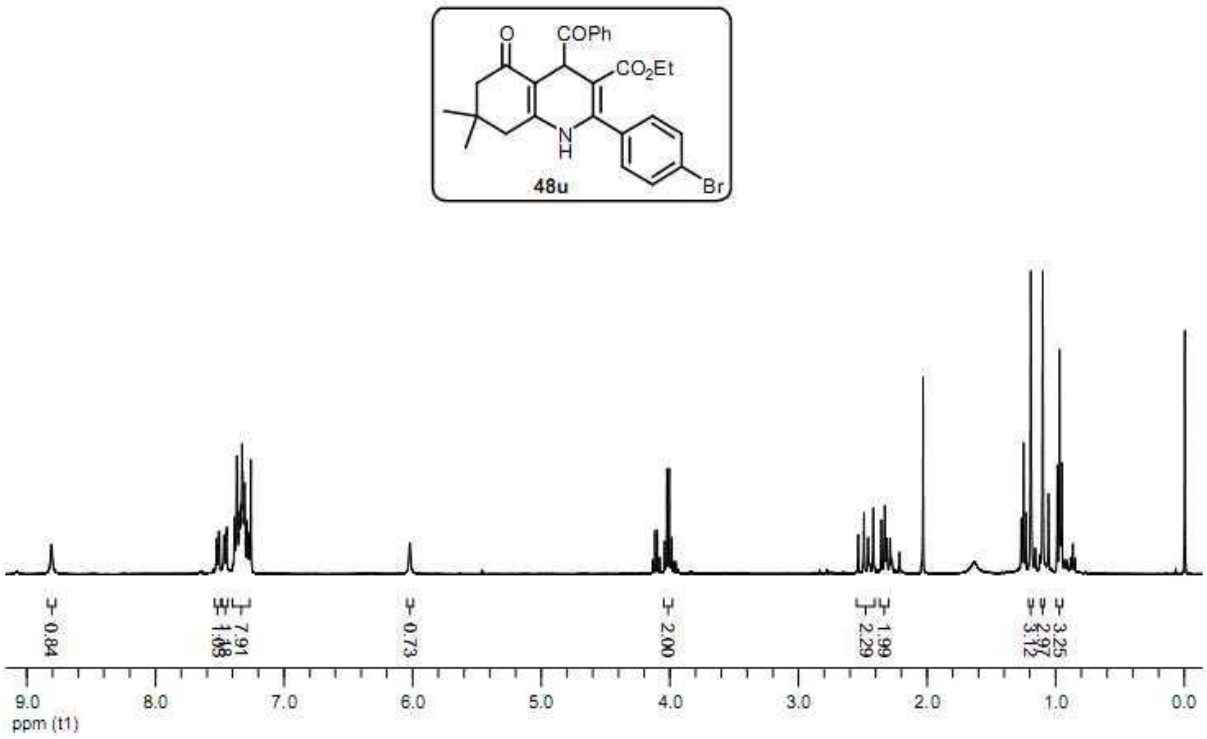
48t ^{1}H NMR ($CDCl_3$, 400 MHz)



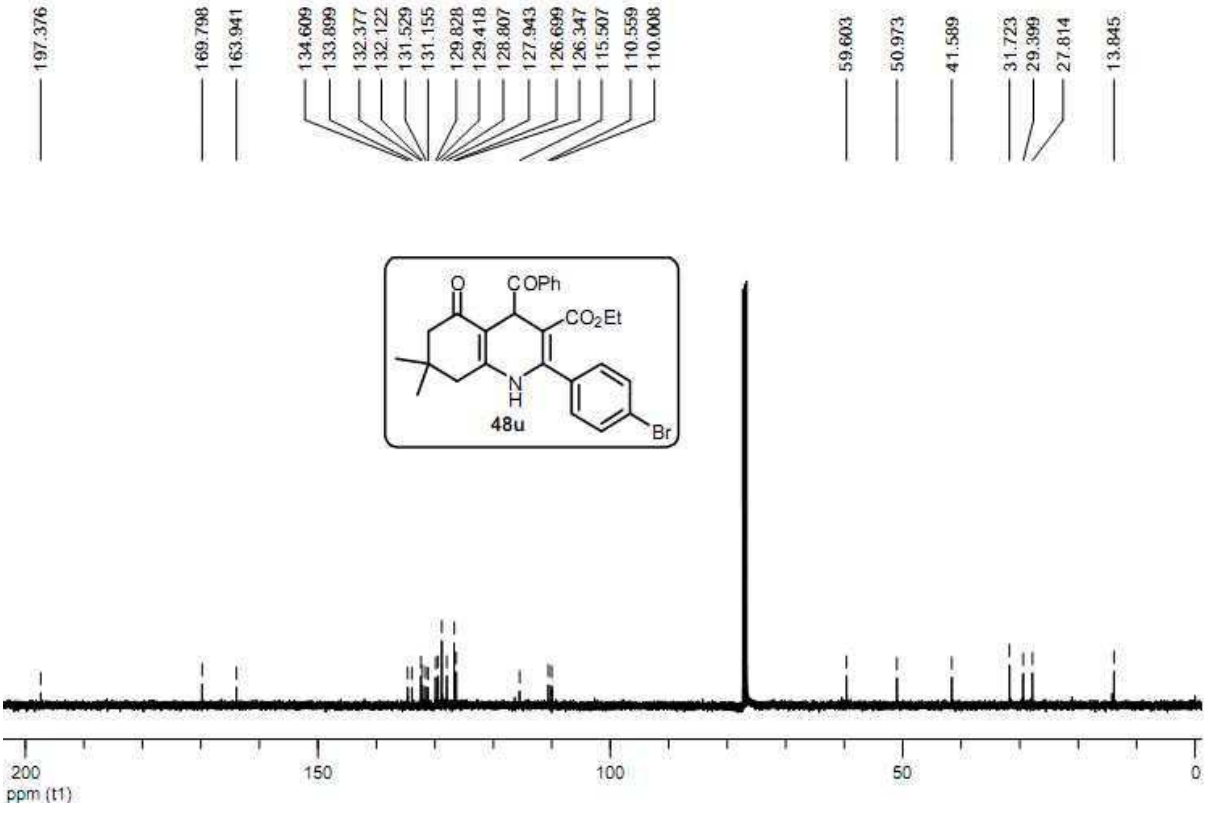
48t ^{13}C NMR ($CDCl_3$, 100 MHz



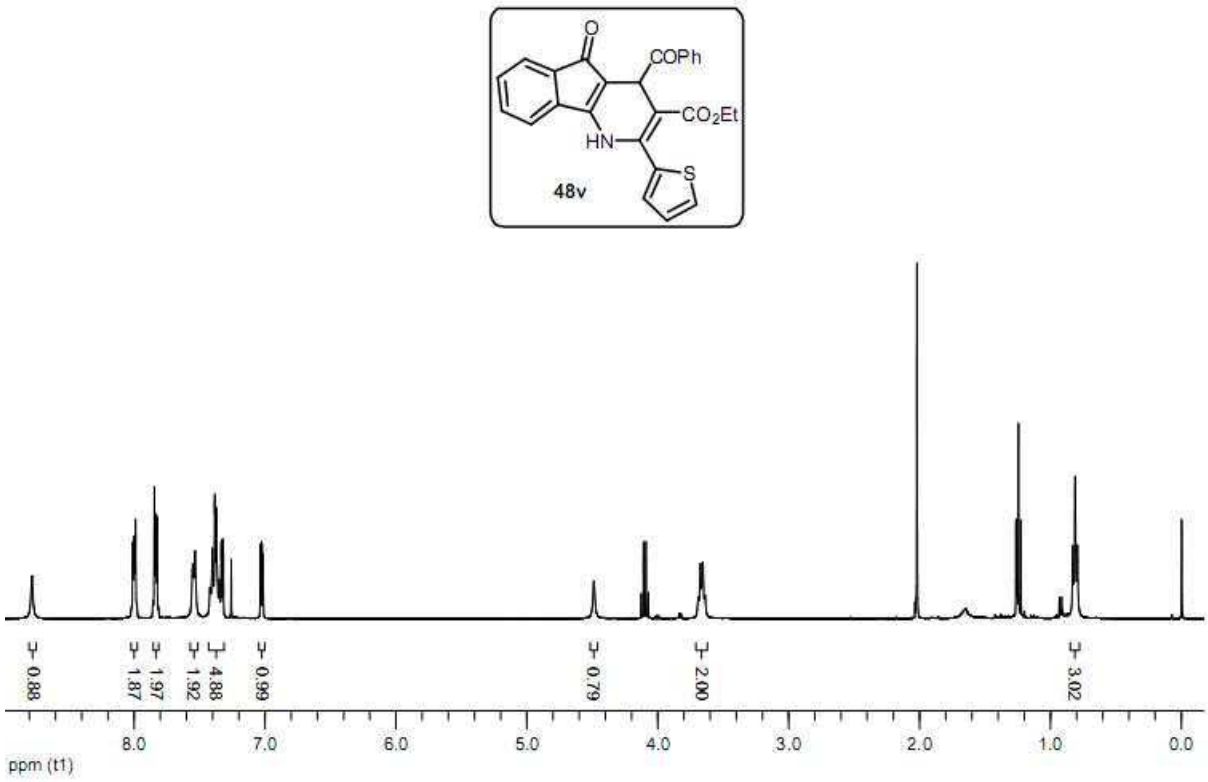
48u ^{1}H NMR ($CDCl_3$, 400 MHz)



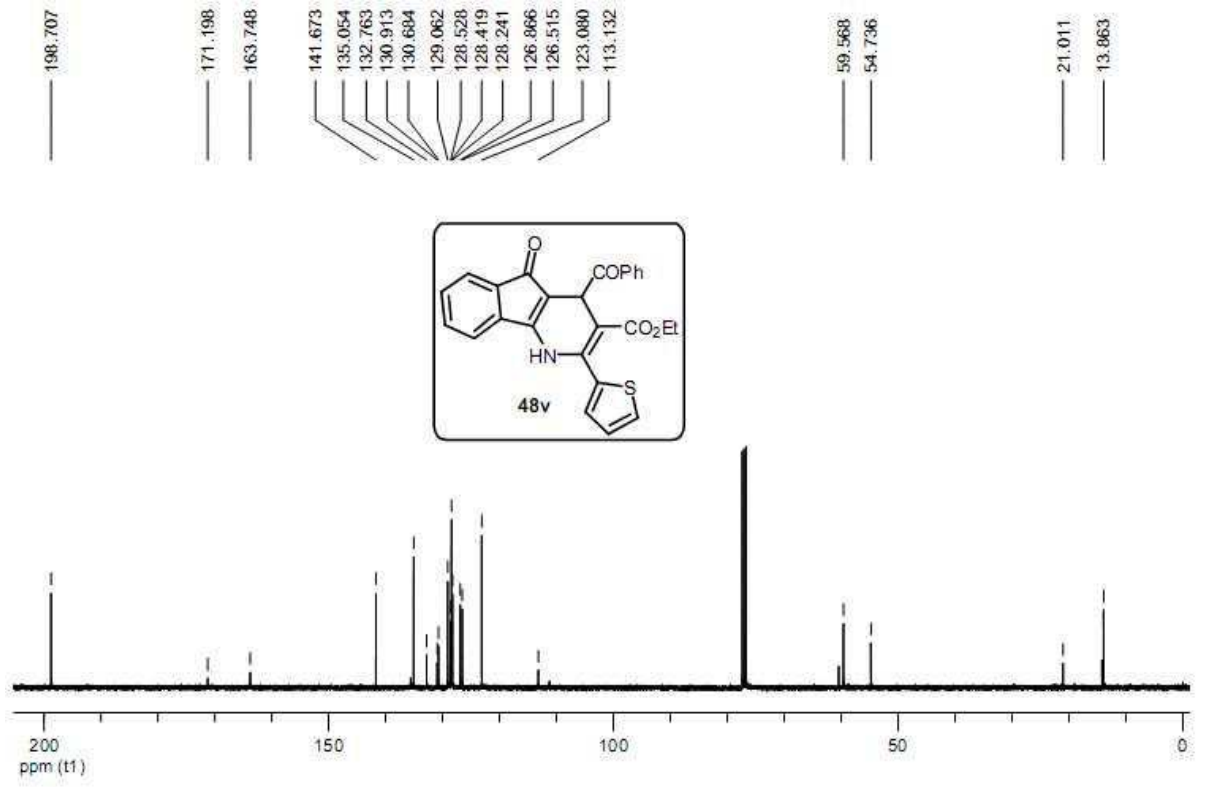
48u ^{13}C NMR ($CDCl_3$, 100 MHz



48v ^{1}H NMR ($CDCl_3$, 400 MHz)



48v ^{13}C NMR ($CDCl_3$, 100 MHz



CHAPTER 3

NOVEL METHOD FOR THE SYNTHESIS OF FUNCTIONALIZED ISOQUINOLINEQUINONES AND ITS APPLICATION TO THE ISOQUINOLINEQUINONE CORE OF MANSOURAMYCIN-D

3.1. Introduction

The substituted quinone moiety is a structural component of a large number of biologically active natural and unnatural compounds such as antitumor,[1-5] antimalarial, antifungal, and antibacterial agents.[6-10] The synthesis and functionalization of quinone has been the object of research for over the last decade.[11] A few representative molecules bearing the quinone skeleton are shown in (Fig. 3.1).

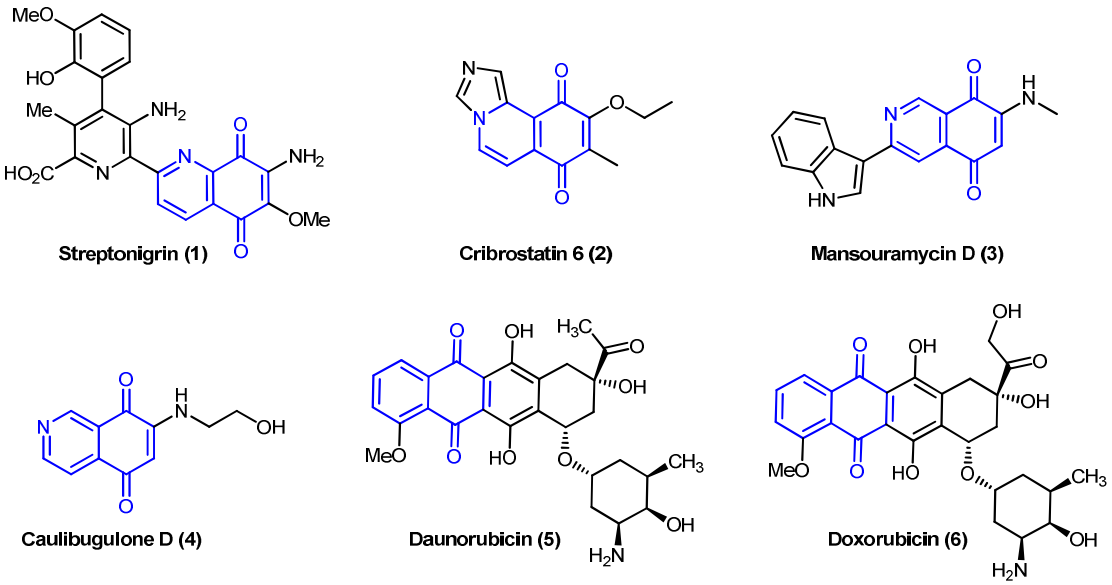


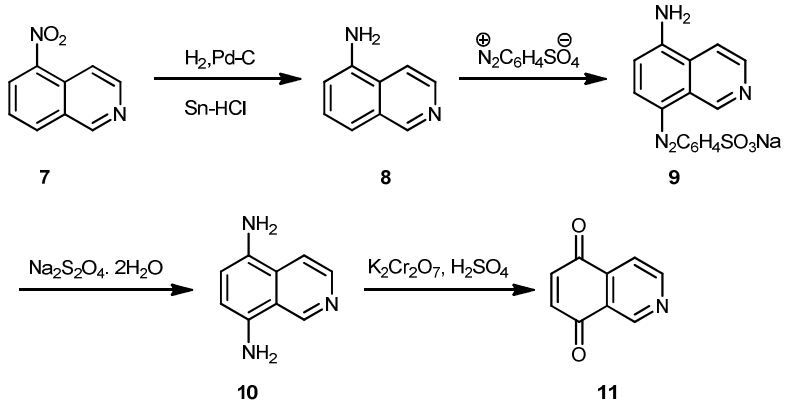
Figure 3.1. Representative examples of quinone derivatives

The quinone moiety containing drug molecules are very common such as Streptonigrin **(1)** is an aminoquinone antitumor antibiotic natural product isolated from cultures of *Streptomyces flocculus* in 1959 by Rao and Cullen, causes DNA breakage in E. coli.[12] Similarly, Cribrostatin 6 **(2)** is a cytotoxic natural product isolated in 2003 from the blue colored marine sponge *Cribrochalina* sp., Cribrostatin 6 showed antimicrobial activity, as well as antineoplastic activity against murine and human cancer cell lines at micromolar concentrations (P388 ED_{50} 0.3 μg/mL).[13] Mansouramycin D **(3)** is a cytotoxic alkaloid isolated from a marine *Streptomyces sp.* In 2009 by Laatsch et al. It showed high cytotoxicity against many human cancer cell lines with an IC_{50} value up to 0.089 micromolar specifically for lung cancer.[14] Caulibugulone D **(4)** is cytotoxic isoquinoline quinone and isolated from marine bryozoans *Caulibugula intermis* and it showed antitumor activity against the murine IC-2^{WT} cell line.[15] Daunorubicin **(5)** is an active antitumor compound used in the treatment of some neoplastic diseases.[16] Doxorubicin **(6)** is an anti-cancer chemotherapy drug. It slows down or stops the growth of cancer cells by blocking the

topoisomerase 2 enzyme.[17] As a result of desired biological activities; there is considerable interest among synthetic chemists to develop novel routes for the synthesis of quinine derivatives. This chapter covers the literature precedents and also our methodology for the substituted quinone derivatives starting from readily available 2,5-dihydroxy benzaldehyde and β-enamino esters or its analogues.

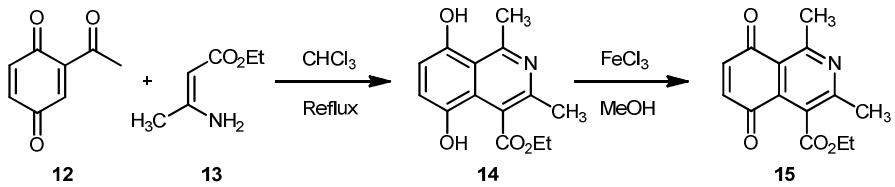
3.1.1. Precedents on synthesis of substituted quinones

In 1964, Joseph and Joullie reported the synthesis of isoquinolinoquinone in four steps (Scheme 3.1),[18] and obtained quinone compound **11** by the reduction of 5-nirto isoquinoline **7** with Sn/HCl reduction to give the corresponding amine **8**. 5-amino isoquinoline **8** was converted to 5,8-di amino isoquinoline **10** *via* the diazonium coupling product. The compound 5,8-diamino isoquinoline **10** was oxidized with potassium dichromate to form the isoquinolinquinone **11**.



Scheme 3.1 Synthesis of isoquinolinquinone.

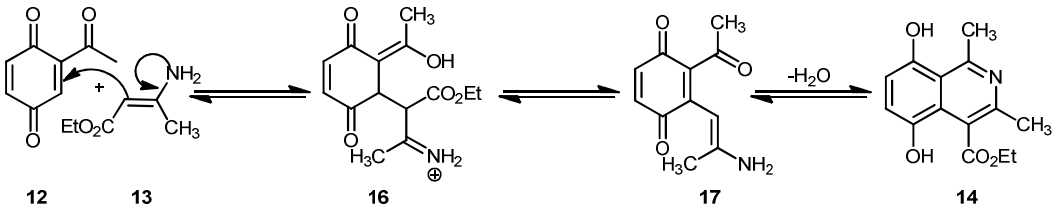
In 1967, Weiss and coworkers have reported the two-step synthesis of substituted isoquinolinequinone by the reaction of 2-acetyle-1,4-benzoquinone **12** and enamine **13** (Scheme 3.2).[19]



Scheme 3.2 Synthesis of isoquinolinquinone.

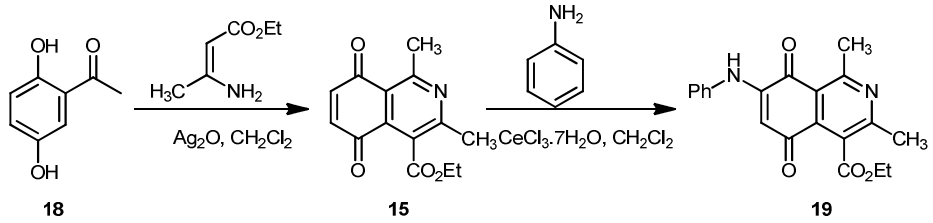
The product formation can be explained by Michael addition of enamine **13** to unsaturated ketone **12** to form an intermediate **16.** Subsequently the addition product

16 undergoes an intramolecular condensation of the amino group and carbonyl group to afford the desired substituted isoquinoline **14** (Scheme 3.3).



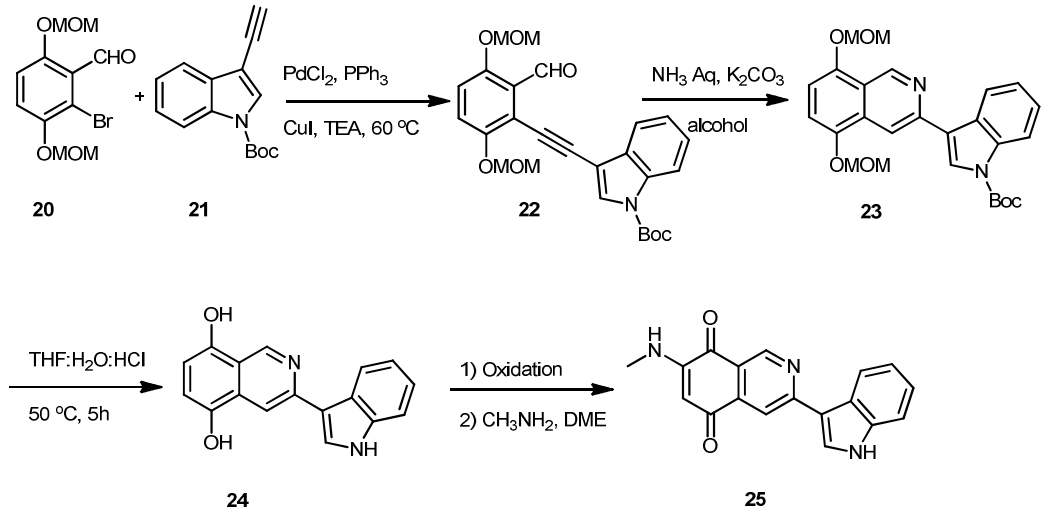
Scheme 3.3 Mechanism of Weiss's synthesis of isoquinolinquinone reactions.

In 2009, Valderrama and co-workers have used similar strategy to construct isoquinolinequinone ring in the synthesis of antitumor agents (Scheme 3.4) by treating of 2,5-dihydroxyacetophenone **18** with methyl 3-aminocrotonate **13** in presence of Ag_2O in dichloromethane.[20]



Scheme 3.4 Valderrama's synthesis of isoquinolinquinone.

In 2014, Nagarajan and Prakash reported the first synthesis of Mansouramycin D, **25** in a total of 4 steps with an overall yield 54.5% to 60.9% (Scheme 3.5).[14b]



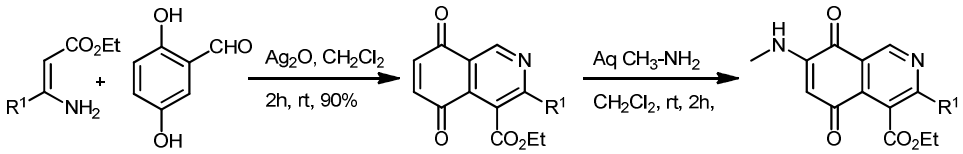
Scheme 3.5 First total synthesis of Mansouramycin D.

They synthesized compound **25** by Sonagashira coupling of MOM ether of 2-bromo -3,6-dihydroxybenzaldehyde **20,**[21] and *N*-Boc protected 3-ethynyl-1*H*-indole in the presence of $PdCl_2$ to give the compound **22**. The compound **22** undergoes

intramolecular iminoannulation in the presence of aqueous ammonia to give the isoquinoline core **23**. Compound **23** was underwent deprotection of MOM with HCl, leading to spontaneous oxidation and amino oxidation with methyl amine to get Mansouramycin D **25**.

3.2. Present work

Among the plethora of heterocycles, isoquinolinoquinone gained prior importance because of its abundance in bioactive compounds and emerged as privileged structure. In addition, by virtue of their multifunctional composition, isoquinolinoquinone could serve as versatile precursors for heterocycles synthesis, Diels-Alder cycloaddition, Michael addition, and in many other useful synthetic transformations. On the other hand 7-amino isoquinolinoquinone is one of the key structural frameworks found in many naturally occurring alkaloids, bioactive compounds and drugs. Though several methods have been reported in literature for the synthesis of substituted isoquinolinequinone, however diversity-oriented synthetic approach for the quick generation of a library of molecules around this class is always desirable. To the best of our knowledge the use of our strategy leading to indole substituted isoquinolinquinone core of Mansouramycin D is unprecedented. Herein we report Ag_2O mediated Michael addition of (E)-ethyl 3-amino-3-(1H-indol-3-yl)acrylate with 2,5-dihydroxy benzaldehyde leading to substituted isoquinolinoquinone. The present protocol features advantages including atom economy, environmentally friendly oxidant, and nonhazardous byproduct (water), and more importantly offers great flexibility in the construction of isoquinolinequinones under open air with readily available starting materials.



Scheme 3.6 Synthesis of 7-amino isoquinolinequinone

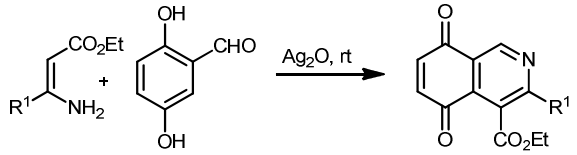
3.3. Results & Discussion

3.3.1. Initial results and optimization of the reaction condition

Ag_2O is a mild oxidizing agent,[22] with wide applications in organic synthesis, and was chosen as an oxidizing agent in our study. In our initial investigation, β-enaminoester

26a and 2,5-dihydroxybenazaldehyde **27a** were used as substrates to verify the above hypothesis. To our delight, the desired product ethyl 3-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate **28a** was isolated in 79% yield when the mixture of (E)-ethyl 3-aminobut-2-enoate **26a,** 2,5-dihydroxybenzaldehyde **27a** in CH_3CN at room temperature was treated with Ag_2O for 2h. The structure was determined by ^1H NMR studies. Acceptable yields were achieved in other solvents such as methanol, THF, CH_2Cl_2, toluene and DMSO. Dichloromethane gave the best result, affording **28a** in 93% yield. Substituted isoquinolinequinones were selected as suitable precursors of 7-amino isoquinolinequinone.

Table 3.1. Optimization of reaction conditions



26a **27a** **28a**

Entry	Solvent	Yield[b] (%)
1	CH_3CN	79
2	MeOH	70
3	THF	75
4	CH_2Cl_2	93
5	Toluene	77
6	DMSO	75

[a] All reactions were performed using the β-enamino ester **26a** (0.5 mmol), 2,5 di hydroxy benzaldehyde **27a** (0.5 mmol), silver oxide (2.0 equiv.)

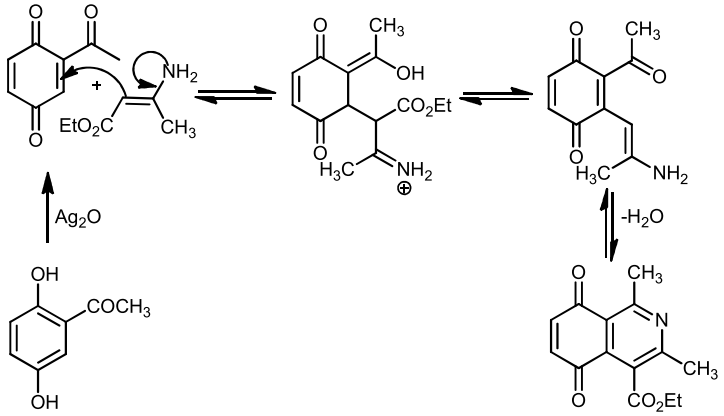
3.3.2. Scope of the reaction

With the optimal reaction conditions established, we then examined the scope and generality of this two compound cyclization reaction of β-enamino ester **26** with 2,5-dihydoxycarbonyl compound **27** in the presence of Ag_2O in dichlromethane. The results are summarized in table 3.2.

Optimized the best reaction condition (DCM, Ag_2O) by using β-enamino ester (26) and 2,5-dihydroxycarbonyl compound (27) as substrates. After having the well optimized reaction condition in hand, then I decided to validate the substrate scope. For that a wide range of β-enamino esters are used. Firstly aromatic β-enamino esters, which having both electron withdrawing (-Cl, -Br) and electron donating groups (-OMe) on it. Observed lower yields and slower reaction rates in which starting material containing EWG. And in the case of EDG containing β-enamino esters gave higher yields with less reaction time.

In addition to that I have used different hetero aromatic β-enamino esters like thiophene, indole and pyridine. In which thiophene and indole reactions were fast and gave higher yields compare to pyridine β-enamino ester. The same time I tested some aliphatic β-enamino esters such as methyl and cyclohexyl β-enamino esters. Reactions of aliphatic substrates fast and higher yields. From this data it clearly states that substituent's ion the aromatic ring of enamimo ester is influencing on the yield and reaction rates.

The aromatic β-enaminoesters with electron-withdrawing groups such has chloro and bromo groups (entries 5-8 and entry 10, Table 3.2) reacted slower and gave lower yields then those elecron-donating group such as methoxy group (entry 9, Table 3.2). Hetero aromatic β-enaminoesters thiophene and indole (entry 12 and 22, Table 3.2) and aliphatic β-enaminoesters such as methyl and cyclohexyl (entry 1-3, Table 3.2) gave highier yields and needed lower reaction time.



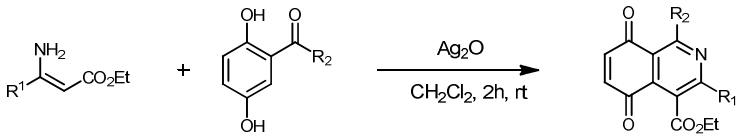
Scheme 3.7 Proposed mechanism for isoquinolinoquinones

These results indicated that this reaction is quite general and has very broad substrate scope. The structures of isoquinoline quinone **28a-v** were characterized by ^{1}H NMR,

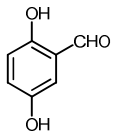
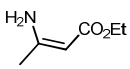
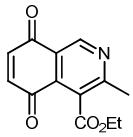
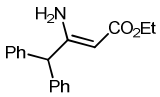
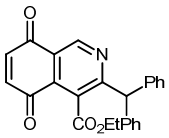
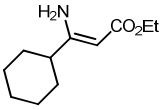
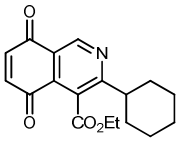
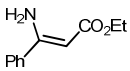
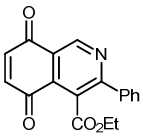
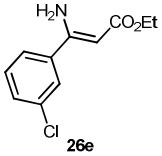
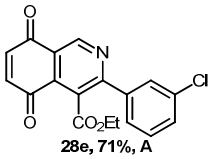
^{13}C NMR and Mass spectra. In ^{1}H NMR spectra proton at the 1-positon of isoquinolinquinone appears at 9.38 ppm and protons at 7,8-positions of isoquinolinequinone appears at 7.02 ppm it should be pointed out in all ^{1}H NMR spectra.

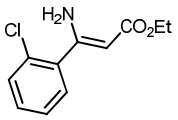
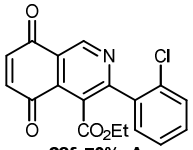
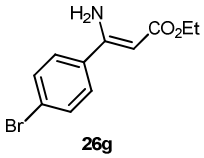
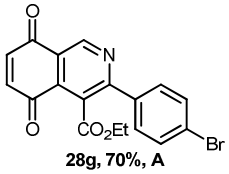
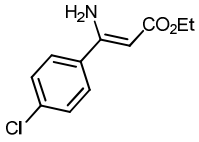
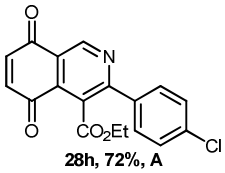
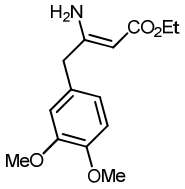
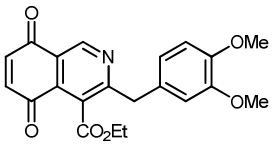
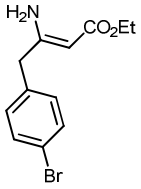
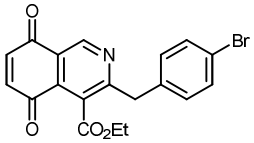
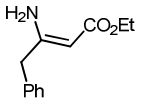
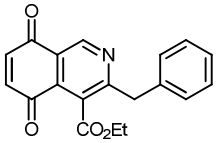
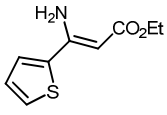
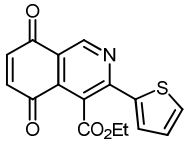
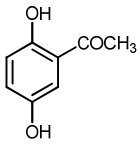
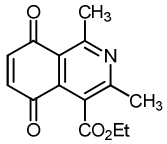
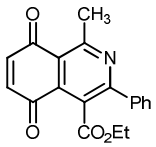
Mechanistically, the reaction seems to proceed *via* (i) Ag_2O mediated conversion of the 2,5-dihydroxycarbonyl compound to corresponding 3,6-dioxocyclohexa-1,4-dienecarbaldehyde which up on (ii) Michael addition with β-enamino ester followed by (iii) intra molecular cyclization and aromatization to get the final product isoquinolinequinone **28** in the presence of air.

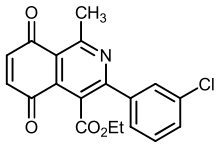
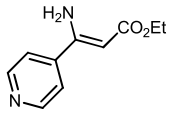
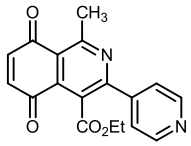
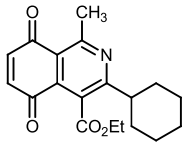
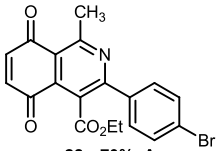
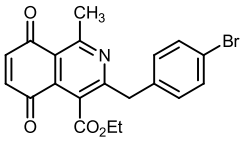
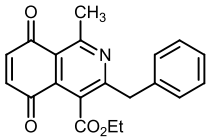
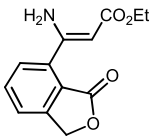
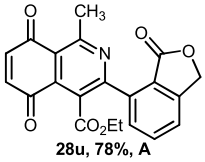
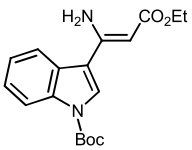
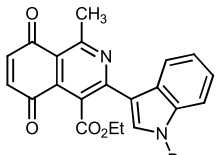
Table 3.2. Synthesis of 3-substituted isoquinolinoquinone



26 **27** **28**

entry	carbonylcompound	enamine	product
1	 **27a**	 **26a**	 **28a, 87%, B**
2	**27a**	 **26b**	 **28b, 93%, A**
3	**27a**	 **26c**	 **28c, 75%, A**
4	**27a**	 **26d**	 **28d, 88%, A**
5	**27a**	 **26e**	 **28e, 71%, A**

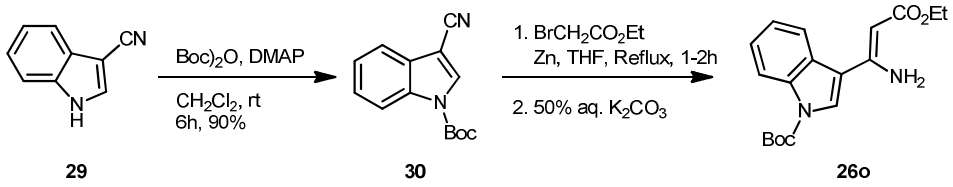
6	**27a**	 **26f**	 **28f, 70%, A**
7	**27a**	 **26g**	 **28g, 70%, A**
8	**27a**	 **26h**	 **28h, 72%, A**
9	**27a**	 **26i**	 **28i, 85%, A**
10	**27a**	 **26j**	 **28j, 75%, A**
11	**27a**	 **26k**	 **28k, 83%, A**
12	**27a**	 **26l**	 **28l, 82%, A**
13	 **27b**	**26a**	 **28m, 86%, B**
14	**27b**	**26d**	 **28n, 74%, A**

15	**27b**	**26e**	 **28o, 70%, A**
16	**27b**	 **26m**	 **28p, 73%, A**
17	**27b**	**26c**	 **28q, 85%, A**
18	**27b**	**26g**	 **28r, 70%, A**
19	**27b**	**26j**	 **28s, 73%, A**
20	**27b**	**26j**	 **28t, 83%, A**
21	**27b**	 **26n**	 **28u, 78%, A**
22	**27b**	 **26o**	 **28v, 87%, B**

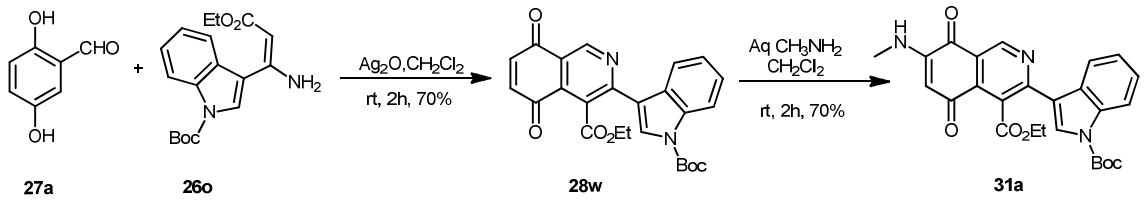
[a] Reaction conditions A: enamine (0.3 mmol), aldehyde or ketone (0.3 mmol), Ag_2O (2 equiv.) in 3 mL CH_2Cl_2 at room temp; conditions B: enamine (2 mmol), aldehyde or ketone (2 mmol), Ag_2O (2 equiv.) in 3 mL CH_2Cl_2 at room temp.

3.4. Synthesis of Mansouramycin D analogue:

The potential of our methodology was demonstrated in the synthesis of Mansouramycin D analogues. Mansouramycin D is one of structually distinct marine alkaloid isoquinolinequinone strong antimicrobial activity, specifically high cytotoxicity was shown against human lung cancer cells with an IC_{50} values up to 0.089 μmol/L.[14b] Many marine alkaloids such as caulibugulones A-D and mansouramycins A-D contains the isoquinolinequinone core and several groups have developed different synthetic routes to this moiety.[18] Our strategy was mainly based on bringing the corresponding indole enaminoester **26o** and 2,5-dihydroxy bezadehyde **27a** togather by applying the developed methodology to give the compound **28w**, and we used the compound **28w** without purification. Finally, the amino methylation was acomplished using an aqueous solution of methyl amine (33 wt %) in dichloromethane at 0 °C. It is noteworthy to mention that the reaction proceeded in a regieo selective manner and gave only the compound **31a**. Thus, the required indole enamine **26o** was prepared from 3-cyano indole in 2 steps (Scheme 3.8).



Scheme 3.8 Synthesis of indole enamino ester.

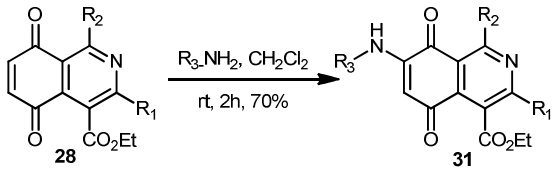


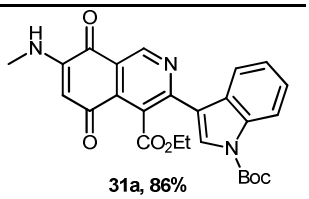
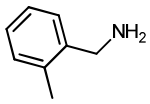
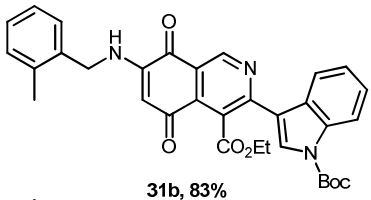
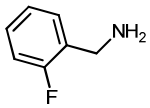
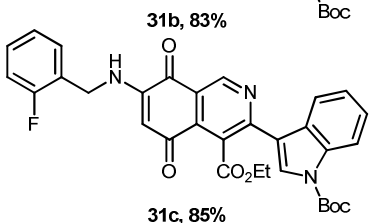
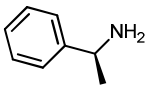
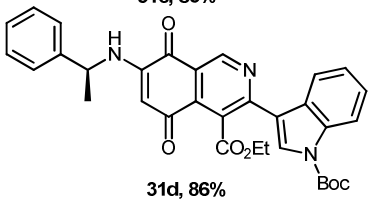
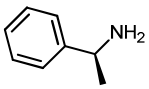
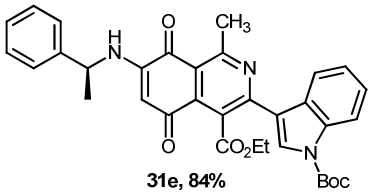
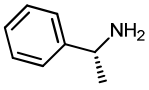
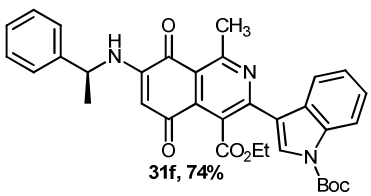
Scheme 3.9 Synthesis of Mansouramycin-D analogue.

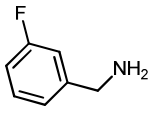
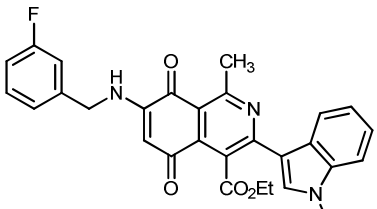
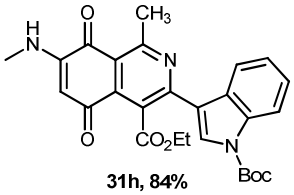
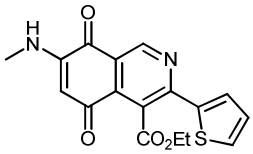
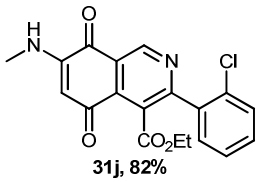
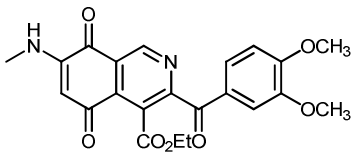
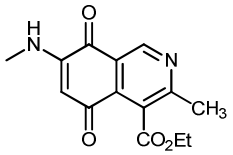
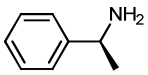
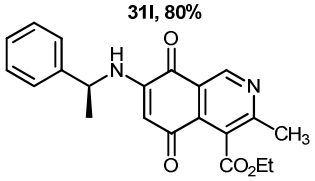
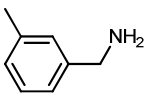
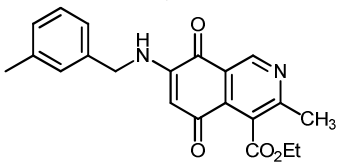
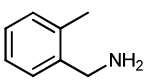
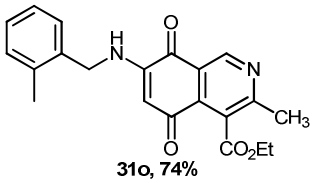
Initially, we explored the reaction of isoquinolinequinone **28** with aqueous methyl amine. After considerable experimentation in different solvents (ethanol, acetonitrile and dichloromethane), the reaction was performed by treating 1.0 equiv of **28** with 2.0 equiv of amine in dichloromethane for 2h at room temperature. Under these conditions amino quinone **31** was isolated in 80% yield (Scheme 3.9).The structures of amino isoquinoline quinone **31a-v** were characterized by ^{1}H NMR, ^{13}C NMR, 2D-NMR, and Mass spectra. In ^{1}H NMR spectra proton at the 6-positon of amino isoquinolinquinone appears at 5.8 ppm and proton at -NH of amino

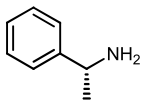
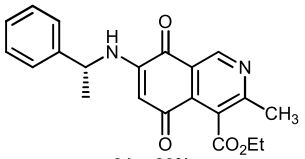
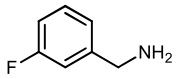
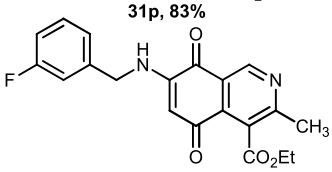
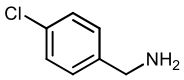
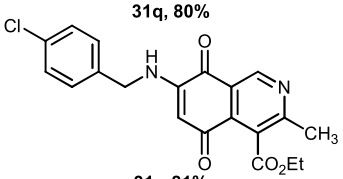
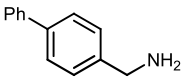
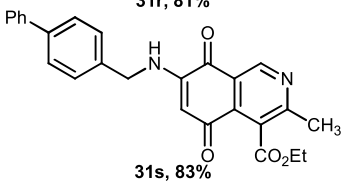
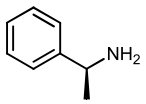
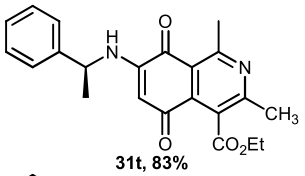
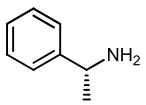
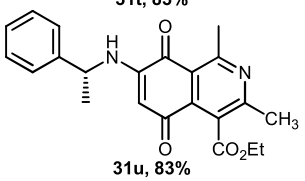
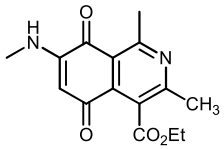
isoquinolinquinone appears at 6.2 ppm it should be pointed out in all ^{1}H NMR spectra.

Table 3.3s. Synthesis of 7-amino isoquinolinequinone



entry	isoquinolinoquinone	amine	product
1	28w	Aq CH_3NH_2	 **31a, 86%**
2	28w		 **31b, 83%**
3	28w		 **31c, 85%**
4	28w		 **31d, 86%**
5	28v		 **31e, 84%**
6	28v		 **31f, 74%**

7	**28v**		 **31g, 82%**
8	**28v**	Aq CH_3NH_2	 **31h, 84%**
9	**28l**	Aq CH_3NH_2	 **31i, 84%**
10	**28f**	Aq CH_3NH_2	 **31j, 82%**
11	**28i**	Aq CH_3NH_2	 **31k, 85%**
12	**28a**	Aq CH_3NH_2	 **31l, 80%**
13	**28a**		 **31m, 77%**
14	**28a**		 **31n, 84%**
15	**28a**		 **31o, 74%**

16	**28a**		 **31p, 83%**
17	**28a**		 **31q, 80%**
18	**28a**		 **31r, 81%**
19	**28a**		 **31s, 83%**
20	**28m**		 **31t, 83%**
21	**28m**		 **31u, 83%**
22	**28m**	Aq CH_3NH_2	 **31v, 83%**

[a] Reaction conditions: isoquinolinequinone (0.2 mmol), amine (0.4 mmol), in 3 mL CH_2Cl_2 at room temp;

The position of the nitrogen substituent in these aminoisoquinolinequinones was determined by means of HMBC experiments. For example, the location of the nitrogen group at C-7 in compound **31l** was deduced by the $^{3}J_{C,H}$ couplings between the carbon at C-8 (δ 180.07) with the protons at C-1 (δ 9.12), at C-6 (δ 5.71) and that of the NH group (δ 6.13) and $^{3}J_{C,H}$ couplings between the carbon at C-4 (δ 136.0) with the protons at C-1 (δ 9.12), at (δ 5.17) can be observed (Figure 2).

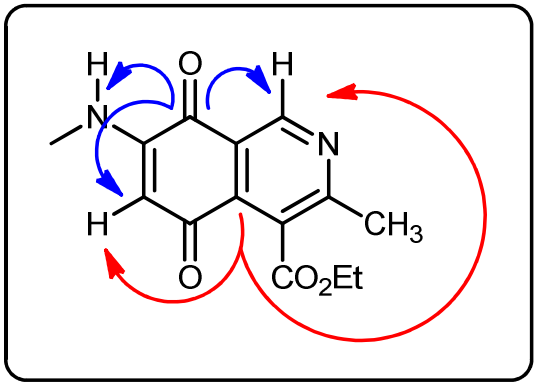
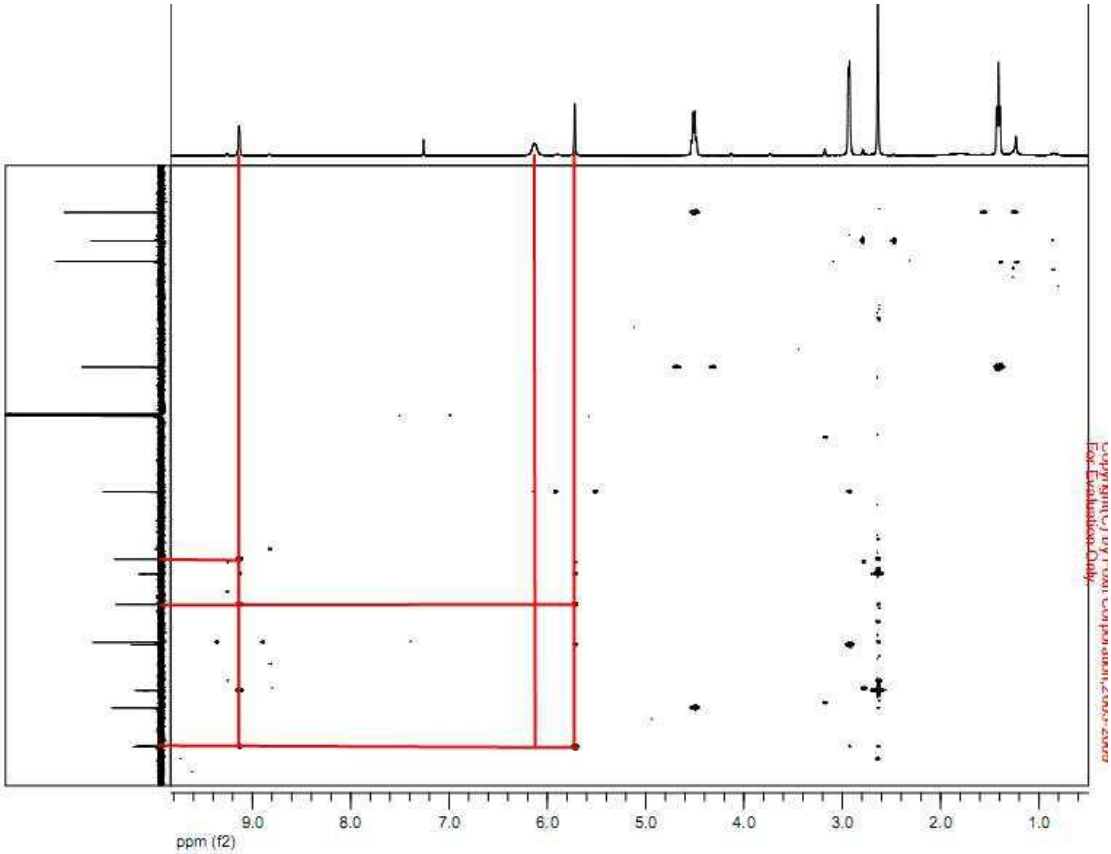


Figure 3.2. HMBC correlation of regio isomer **31l**



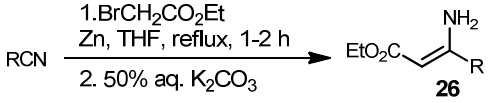
HMBC correlation spectra of 31l

3.5. Conclusions

In conclusion, a direct, one-pot synthesis of functionalized isoquinolinoquinones have been developed *via* the Ag_2O mediated reaction of readily available *β*-enamino esters and 2,5-dihydroxy benzaldehyde (or) Acetophenone. This tandem method afforded 3,4-substituted isoquinolinoquinones, 7-amino substituted isoquinolinoquinone and analoges of Mansouramycins-D.The limitations and advantages of this methdology has been discussed. The methodology may find wide applications in the construction of 7-amino isoquinolinoquinone based library of small molecules useful for medicinal uses or natural product synthesis.

3.6. Experimental section

3.6.1. Materials

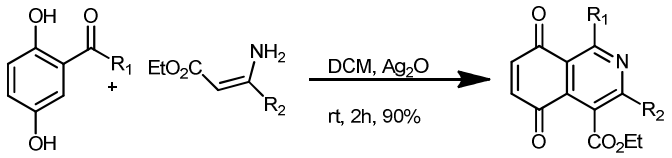


β-enamino esters 26 were synthesized based on the procedure given below:

To activated zinc dust (1.31 g, 20 mmol) was added trimithylsilylchloride (3 drops) in anhydrous THF (10 mL). After 10 min of reflux, nitrile (10 mmol) was added all at once. While maintaining reflux temperature, ethyl bromoacetate (1.65 mL, 15 mmol in 5 mL THF) was added over 1h using addition funnel, and the reaction mixture was further heated at reflux for 1h. After complete conversion of nitrile, the reaction mixture was cooled to room temperature and quenched with saturated aqueous K_2CO_3 at room temperature and extracted with ethyl acetate (3 x 30 mL). The combined organic layers was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to get *β*-enamino ester.

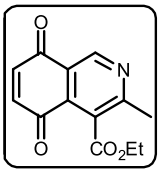
3.6.2. Experimental procedures, spectral and analytical data.

General procedure for the synthesis of substituted isoqinolinoquinone from substituted 2,5-dihydroxy benzaldehyde or acetophenone.



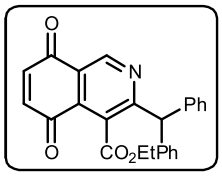
A suspension of 2,5-dihydroxybenzaldehyde or Acetophenone (0.5 mmol), silver(II) oxide (1 mmol), and β-enamino ester (0.mmol in dichloromethane (5 mL) was stirred for 1 h. Silver(II) oxide (1 mmol) was added to the mixture and the stirring was continued for 90 min. The mixture was filtered and the solvent was removed under reduced pressure to yield crude quinone **28** (94%). The residue was chromatographed on silica gel (9:1 hexane–ethyl acetate) to yield pure quinone **28** (86%).

Ethyl 3-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28a):



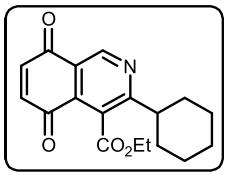
Color less solid, m.p:55-57 °C; R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.28 (s, 1H), 7.02 (s, 2H), 4.55 (q, *J* = 7.15 Hz, 2H), 2.70 (s, 3H), 1.44 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ ppm 183.5, 183.4, 167.2, 161.9, 148.5, 138.5, 138.4, 133.2, 125.6, 122.1, 62.3, 22.7, 13.8; MS (ESI mass) m/z : 246.2[M+1].

Ethyl 3-benzhydryl-5, 8-dioxo-5, 8-dihydroisoquinoline-4-carboxylate (28b):



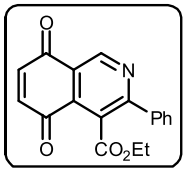
Color less solid, m.p:129-131 °C; R_f = 0.2 (10 % EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.40 (s, 1H), 7.34-7.24 (m, 11H), 7.02 (s, 2H), 5.84 (s, 1H), 4.46 (q, *J* = 7.14 Hz, 2H), 1.30 (t, *J* = 7.17 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.5, 183.4, 167.2, 165.6, 148.9, 140.6, 138.5, 138.4, 133.8, 129.3, 128.3, 126.9, 126.0, 122.1, 62.4, 55.4, 13.6; MS (ESI mass) m/z : 398.2[M+1].

Ethyl 3-cyclohexyl-5, 8-dioxo-5, 8-dihydroisoquinoline-4-carboxylate (28c):



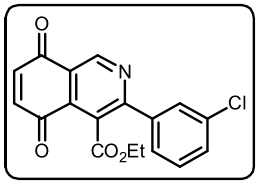
Color less semi soild, R_f= 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.33 (s, 1H), 7.01 (s, 2H), 4.56 (q, *J* = 7.10 Hz, 2H), 2.86-2.77 (m, 1H), 1.94-1.65 (m, 10H), 1.45 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.8, 183.6, 169.3, 167.4, 148.8, 138.4, 133.3, 124.7, 122.0, 62.2, 44.4, 31.9, 26.1, 25.6, 13.9; MS (ESI mass) m/z : 314.2[M+1].

Ethyl 5, 8-dioxo-3-phenyl-5, 8-dihydroisoquinoline-4-carboxylate (28d):



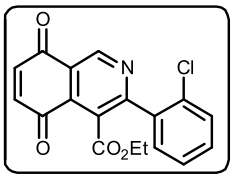
Color less liquid, R_f = 0.22 (10 % EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.46 (s, 1H), 7.71-7.67 (m, 2H), 7.50-7.45 (m, 3H), 7.06 (s, 2H), 4.35 (q, *J* = 7.16 Hz, 2H), 1.22 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.5, 167.0, 161.8, 148.9, 138.8, 138.4, 137.8, 134.3, 130.0, 128.6, 128.5, 125.5, 122.6, 62.3, 13.6, MS (ESI mass) m/z : 308.2[M+1].

Ethyl 3-(3-chlorophenyl)-5, 8-dioxo-5, 8-dihydroisoquinoline-4-carboxylate (28e):



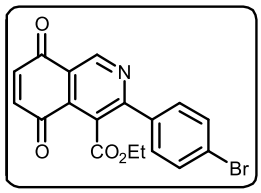
Color less liquid, R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.46 (d, *J* = 0.78 Hz, 1H), 7.72 (s, 1H), 7.60 (d, *J* = 7.60 Hz, 1H), 7.48 (d, *J* = 8.06 Hz, 1H), 7.41 (t, *J* = 7.83 Hz, 1H), 7.08 (s, 2H), 4.40 (q, *J* = 7.15 Hz, 2H), 1.27 (d, *J* = 9.46 Hz, 3H) ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.3, 166.7, 160.0, 149.0, 139.3, 138.8, 138.4, 134.5, 134.4, 130.1, 129.8, 128.8, 126.9, 125.6, 122.9, 62.5, 13.7**;** MS (ESI mass) m/z : 342.2[M+1].

Ethyl 3-(2-chlorophenyl)-5, 8-dioxo-5, 8-dihydroisoquinoline-4-carboxylate (28f):



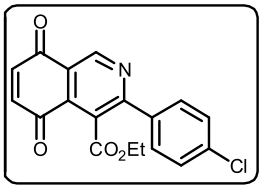
Color less liquid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.48 (s, 1H), 7.50 (d, *J* = 7.94 Hz, 1H), 7.45-7.38 (m, 1H), 7.37-7.32 (m, 2H), 7.09 (s, 2H), 4.20 (q, *J* = 7.14 Hz, 2H), 1.09 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.3, 183.2, 165.8, 160.6, 148.6, 138.7, 138.5, 135.9, 134.0, 132.9, 130.7, 130.2, 129.8, 126.6, 126.3, 123.3, MS (ESI mass) m/z : 342.2[M+1].

Ethyl 3-(4-bromophenyl)-5, 8-dioxo-5, 8-dihydroisoquinoline-4-carboxylate (28g):



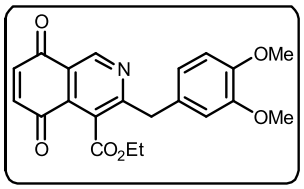
Color less liquid, R_f = 0.22 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.44 (s, 1H), 7.60 (d, *J* = 2.21 Hz, 3H), 7.07 (s, 2H), 4.38 (q, *J* = 7.16 Hz, 2H), 1.28 (t, *J* = 7.26 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.2, 166.7, 160.1, 148.8, 138.6, 138.3, 136.5, 134.3, 131.6, 130.2, 125.2, 124.7, 122.6, 62.4, 13.5; MS (ESI mass) m/z : 386.2[M+2].

Ethyl 3-(4-chlorophenyl)-5, 8-dioxo-5, 8-dihydroisoquinoline-4-carboxylate (28h):



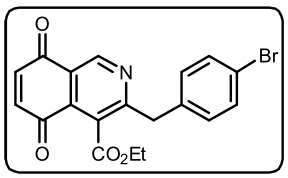
Color less liquid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.44 (s, 1H), 7.66 (d, *J* = 8.50 Hz, 2H), 7.45 (d, *J* = 8.49 Hz, 2H), 7.07 (s, 2H), 4.38 (q, *J* = 7.16 Hz, 2H), 1.28 (d, *J* = 7.16 Hz, 3H): ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.2, 166.8, 160.2, 148.8, 138.7, 138.3, 136.3, 136.0, 134.3, 130.0, 128.6, 125.2, 122.6, 62.4, 13.5, MS (ESI mass) m/z : 342.2[M+1].

Ethyl 3-(3, 4-dimethoxybenzyl)-5, 8-dioxo-5, 8-dihydroisoquinoline-4-carboxylate (28i):



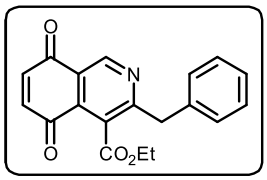
Color less liquid, R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.33 (s, 1H), 7.00 (d, *J* = 10.68 Hz, 2H), 6.85 (s, 1H), 6.80 (dd, *J* = 7.32, 5.74 Hz, 2H), 4.48 (q, *J* = 7.15 Hz, 2H), 4.21 (s, 2H), 3.84 (t, *J* = 6.25 Hz, 6H), 1.36 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 183.4, 167.2, 163.9, 149.0, 148.9, 147.9, 138.5, 133.9, 129.7, 125.3, 122.4, 121.3, 112.3, 111.1, 62.4, 55.8, 41.7, 13.7; MS (ESI mass) m/z : 382.2[M+1].

Ethyl 3-(4-bromobenzyl)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28j):



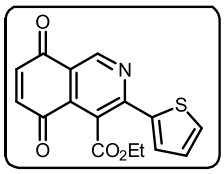
Color less solid, m.p:145-147 °C; R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.32 (s, 1H), 7.42-7.38 (m, 2H), 7.15 (d, *J* = 8.49 Hz, 2H), 7.02 (s, 2H), 4.46 (q, *J* = 7.16 Hz, 2H), 4.22 (s, 2H), 1.35 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.4, 183.3, 167.1, 163.0, 149.0, 138.5, 138.4, 136.1, 134.0, 131.5, 130.9, 125.5, 122.5, 120.9, 62.5, 41.4, 13.7; MS (ESI mass) m/z : 401.2[M+2].

Ethyl 3-benzyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28k):



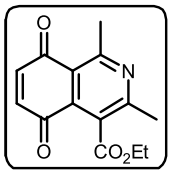
Colorless solid, m.p:129-131 °C; R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.33 (s, 1H), 7.30-7.20 (m, 5H), 7.01 (d, *J* = 2.76 Hz, 2H), 4.44 (q, *J* = 7.15 Hz, 2H), 4.29 (s, 2H), 1.32 (t, *J* = 7.17 Hz, 3H); ^{13}C NMR (100 MHZ, *CDCl$_3$*) δ 183.5, 183.4, 167.1, 163.7, 148.9, 138.5, 138.4, 137.2, 133.9, 129.1, 128.5, 126.8, 125.5, 122.4, 62.4, 42.1. 13.6; MS (ESI mass) m/z **:** 322.1[M+1].

Ethyl 5,8-dioxo-3-(thiophen-2-yl)-5,8-dihydroisoquinoline-4-carboxylate (28l):



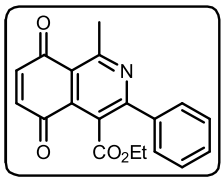
Color less semi solid, R_f = 0.19 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.31 (s, 1H), 7.63 (d, *J* = 3.06 Hz, 1H), 7.59 (d, *J* = 5.06 Hz, 1H), 7.15-7.11 (m, 1H), 7.03 (s, 2H), 4.61-4.52 (m, 2H), 1.41 (t, *J* = 7.18 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.5, 183.0, 167.4, 153.8, 148.9, 141.7, 138.6, 134.5, 131.8, 129.0, 128.7, 122.1, 122.0, 62.7, 29.6, 13.7; MS (ESI mass) m/z: 314.0[M+1].

Ethyl 1,3-dimethyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28m):



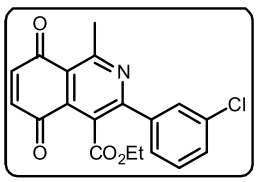
Color less solid, m.p:55-57 °C; R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 6.96 (s, 2H), 4.52 (q, *J* = 7.17 Hz, 2H), 2.98 (s, 3H), 2.64 (s, 3H), 1.42 (t, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 185.0, 184.0, 167.8, 160.9,160.0, 140.2, 136.5, 135.2, 124.7, 120.5, 62.1, 25.6, 22.7, 13.8; MS (ESI mass) m/z : 260.2[M+1].

Ethyl 1-methyl-5,8-dioxo-3-phenyl-5,8-dihydroisoquinoline-4-carboxylate (28n):



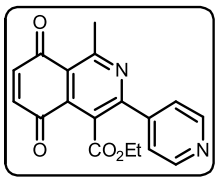
Color less liquid, R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.68 (td, *J* = 8.39, 3.63 Hz, 2H), 7.49-7.44 (m, 3H), 6.99 (s, 2H), 4.32 (q, *J* = 7.16 Hz, 2H), 3.06 (s, 3H), 1.20 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 185.1, 184.1, 167.5, 161.3, 160.0, 140.1, 137.9, 137.0, 136.3, 129.8, 128.6, 128.4, 124.6, 121.1, 62.0, 26.0, 13.6; MS (ESI mass) m/z : 322.2[M+1].

Ethyl 3-(3-chlorophenyl)-1-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28o):



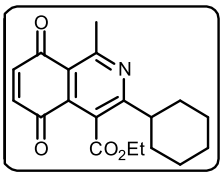
Color less liquid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.71 (s, 1H), 7.59 (d, *J* = 7.58 Hz, 1H), 7.45 (d, *J* = 8.08 Hz, 1H), 7.39 (t, *J* = 7.81 Hz, 1H), 7.01 (s, 2H), 4.36 (q, *J* = 7.16 Hz, 2H), 3.06 (s, 3H), 1.27 (t, *J* = 7.15 Hz, 3H): ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 185.0, 183.8, 167.2, 161.4, 158.2, 140.1, 139.5, 137.0, 136.4, 134.4, 129.9, 129.7, 128.8, 126.8, 124.6, 121.5, 62.2, 25.9, 13.7; MS (ESI mass) m/z : 356.2[M+1].

Ethyl 1-methyl-5,8-dioxo-3-(pyridin-4-yl)-5,8-dihydroisoquinoline-4-carboxylate (28p):



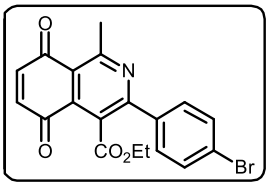
Color less liquid, R_f = 0.15 (10 % EtOAc in Hexane). ^{1}H NMR (400 *CDCl$_3$*) δ 8.74 (dd, *J* = 4.50, 1.59 Hz, 2H), 7.60 (dd, *J* = 4.47, 1.61 Hz, 2H), 7.03 (s, 2H), 4.34 (q, *J* = 7.15 Hz, 2H), 3.08 (s, 3H), 1.23 (t, *J* = 7.19 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 184.9, 183.6, 166.9, 161.7, 156.9, 150.0, 149.9, 149.8, 145.3, 140.1, 137.0, 136.6, 124.8, 123.0, 122.9, 122.1, 62.4, 25.9, 13.6; MS (ESI mass) m/z : 323.2[M+1].

Ethyl 3-cyclohexyl-1-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28q):



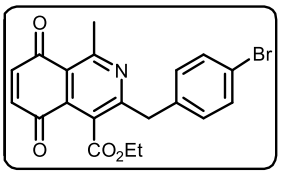
Color less liquid, R_f= 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 6.93 (s, 2H), 4.53 (q, *J* = 7.10 Hz, 2H), 2.97 (s, 3H), 2.82-2.72 (m, 1H), 1.78 (ddd, *J* = 23.86, 14.04, 6.81 Hz, 9H), 1.43 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 185.3, 184.4, 168.1, 167.4, 161.1, 140.1, 136.6, 135.2, 123.8, 120.3, 62.0, 44.2, 31.8, 26.2, 26.0, 25.6, 14.0; MS (ESI mass) m/z : 328.2[M+1].

Ethyl 3-(4-bromophenyl)-1-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28r):



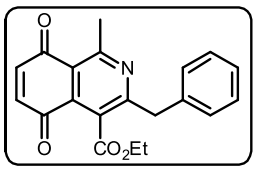
Color less liquid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.62-7.56 (m, 4H), 7.00 (s, 2H), 4.35 (q, *J* = 7.15 Hz, 2H), 3.04 (d, *J* = 11.04 Hz, 3H), 1.25 (m, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 185.0, 183.9, 167.4, 161.4, 158.5, 140.1, 136.9, 136.8, 136.5, 131.6, 130.3, 124.6, 124.4, 121.3, 62.2, 26.0, 13.7; MS (ESI mass) m/z : 401.2[M+2].

Ethyl 3-(4-bromobenzyl)-1-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28s):



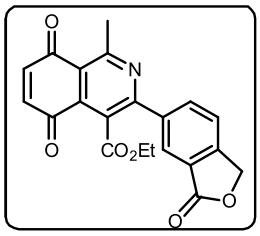
Color less solid, m.p:126-128 °C; R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 6.35, 4.54 Hz, 2H), 7.17 (d, *J* = 8.44 Hz, 2H), 6.95 (s, 2H), 4.42 (q, *J* = 7.15 Hz, 2H), 4.16 (s, 2H), 2.97 (s, 3H), 1.32 (t, *J* = 7.19 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 185.0, 183.9, 167.6, 161.5, 161.0, 140.1, 136.6, 136.3, 136.0, 131.4, 130.9, 124.5, 120.7, 62.2, 41.4, 25.9, 13.6; MS (ESI mass) m/z : 415.2[M+2].

Ethyl 3-benzyl-1-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28t):



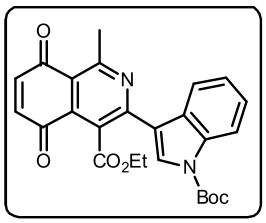
Color less solid, m.p:104-106 °C; R_f = 0.21(10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.30-7.18 (m, 5H), 6.94 (s, 2H), 4.39 (q, *J* = 7.14 Hz, 2H), 4.24 (s, 2H), 2.98 (s, 3H), 1.28 (t, *J* = 7.18 Hz, 4H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 185.1, 184.0, 167.6, 161.7, 161.3, 140.0, 137.4, 136.6, 135.9, 129.1, 128.3, 126.6, 124.6, 120.8, 62.1, 42.1, 25.9, 13.6; MS (ESI mass) m/z: 336.1[M+1].

Ethyl 1-methyl-5,8-dioxo-3-(3-oxo-1,3-dihydroisobenzofuran-5-yl)-5,8-dihydroisoquinoline-4-carboxylate (28u):



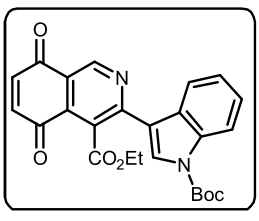
Color less solid, m.p:55-57 °C; R_f = 0.18 (10% EtOAc in Hexane): ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.02 (d, *J* = 7.89 Hz, 1H), 7.88-7.82 (m, 2H), 7.05 (s, 2H), 5.40 (s, 2H), 4.34 (q, *J* = 7.16 Hz, 2H), 3.09 (s, 3H), 1.24 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 183.6, 170.3, 167.1, 161.6, 158.0, 146.5, 143.5, 140.1, 137.0, 136.6, 129.6, 126.6, 125.7, 122.8, 121.9; MS (ESI mass) m/z **:** 378.1[M+1].

Ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-6-yl)-1-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28v):



Color less solid, m.p:164-166 °C; R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.30 (d, *J* = 7.82 Hz, 1H), 8.21 (d, *J* = 8.07 Hz, 1H), 8.15 (s, 1H), 7.38 (m, 2H), 6.98 (d, *J* = 10.43 Hz, 2H), 4.52 (q, *J* = 7.14 Hz, 2H), 3.10 (d, *J* = 11.47 Hz, 3H), 1.71 (s, 10H), 1.41 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 185.0, 184.1, 168.1, 161.2, 154.0, 149.1, 140.2, 136.8, 136.2, 135.5, 128.7, 127.5, 125.3, 123.8, 123.7, 122.1, 120.1, 117.8, 115.0, 84.6, 62.3, 28.1, 26.0, 13.7; MS (ESI mass) m/z : 461.2[M+1].

Ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (28w):



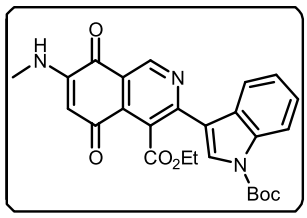
Pale yellow colored solid, m.p:173-174 °C; R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.52 (s, 1H), 8.22 (dd, *J* = 7.68, 4.82 Hz, 2H), 8.15 (s, 1H), 7.43-7.32 (m, 2H), 7.06 (s, 2H), 4.54 (q, *J* = 7.17 Hz, 2H), 1.71 (s, 9H), 1.42 (t, *J* = 7.17 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.6, 183.3, 167.5, 155.9,

148.8, 138.6, 135.4, 134.1, 128.6, 127.4, 125.3, 124.7, 123.7, 121.9, 121.6, 118.0, 115.0, 84.7, 62.5, 28.1, 13.7; MS (ESI mass) m/z : 447.1[M+1].

Genaral procedure for the synthesis of 7-amino isoquinolino quinone

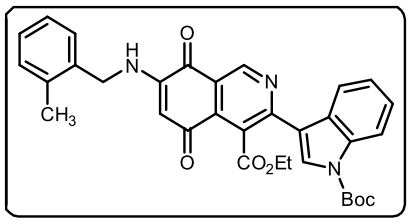
A suspension of quinone **28** (0.3 mmol), methylamine hydrochloride (0.6 mmol) or benzylamine in dichloromethane (5 mL) was stirred at rt for 1.5 h. The solvent was removed under reduced pressure to give an exciusively one regieo isomer **31** (74%) in 80:20 proportion. The regioisomer **31** was isolated by column chromatography over silica gel (70:30 Hexane/AcOEt).

Ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-7-(methylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31a):



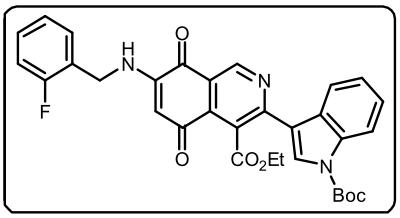
Pale yellow color semi solid, R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.41 (s, 1H), 8.22 (t, *J* = 7.13 Hz, 2H), 8.17 (s, 1H), 7.41-7.30 (m, 2H), 6.09 (d, *J* = 5.15 Hz, 1H), 5.79 (s, 1H), 4.51 (dd, *J* = 6.48, 5.16 Hz, 2H), 2.97 (t, *J* = 4.78 Hz, 3H), 1.70 (s, 9H), 1.41 (dd, *J* = 8.67, 5.68 Hz, 4H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.2, 180.1, 168.3, 156.6, 148.1, 136.9, 128.7, 127.5, 125.2, 123.6, 122.0, 121.3, 118.2, 115.0, 109.9, 101.1, 84.5, 62.1, 29.6, 28.1, 13.7; MS (ESI mass) m/z : 476.2[M+1].

Ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-7-(2-methylbenzylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31b):



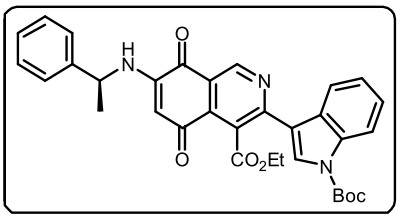
Pale yellow color semi solid, R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.40 (s, 1H), 8.22 (dd, *J* = 9.75, 8.89 Hz, 2H), 8.17 (d, *J* = 3.41 Hz, 1H), 7.37 (m, 2H), 7.26-7.19 (m, 4H), 6.21 (s, 1H), 5.84 (s, 1H), 4.56-4.44 (m, 2H), 4.34 (t, *J* = 5.54 Hz, 2H), 2.33 (s, 3H), 1.70 (s, 9H), 1.41 (dd, *J* = 9.57, 4.76 Hz, 3H); ^{13}C NMR(100 MHz, *CDCl$_3$*) δ 180.4, 180.2, 168.4, 156.6, 149.1, 148.2, 147.3, 136.7, 136.3, 133.0, 130.9, 128.5, 128.3, 127.5, 126.5, 125.3, 123.7, 122.1, 121.3, 118.2, 115.0, 102.0, 84.6, 62.2, 45.0, 28.1, 19.0, 13.8; MS (ESI mass) m/z : 566.2[M+1].

Ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-7-(2-fluorobenzylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31c):



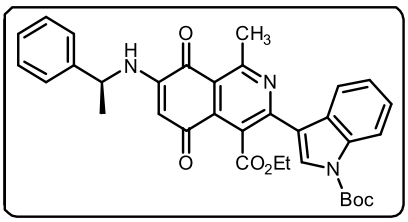
Pale yellow color solid, m.p:119-121 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.38 (s, 1H), 8.21 (dd, *J* = 12.54, 7.99 Hz, 2H), 8.16 (s, 1H), 7.42-7.23 (m, 5H), 7.14-7.05 (m, 2H), 6.44 (t, *J* = 5.47 Hz, 1H), 5.83 (s, 1H), 4.56-4.47 (m, 2H), 4.45 (t, *J* = 6.68 Hz, 2H), 1.68 (s, 9H), 1.40 (t, *J* = 7.02 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.4, 180.1, 168.4, 162.0, 159.5, 156.5, 148.2, 147.3, 136.6, 135.5, 130.2, 130.1, 129.5, 129.4, 128.7, 127.5, 125.3, 123.7, 122.1, 121.3, 118.2, 115.0, 102.1, 84.7, 62.2, 40.7, 28.1, 13.8; MS (ESI mass) m/z : 570.3[M+1].

(S)-ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-5,8-dioxo-7-(1-phenylethylamino)-5,8-dihydroisoquinoline-4-carboxylate (31d):



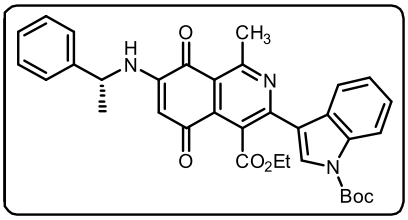
Pale yellow color solid, m.p:123-125 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.41 (s, 1H), 8.64 (s, 1H), 8.43-8.38 (m, 1H), 7.85 (d, *J* = 2.65 Hz, 1H), 7.37 (m, 6H), 6.34 (d, *J* = 6.25 Hz, 1H), 5.62 (d, *J* = 6.27 Hz, 1H), 4.63-4.37 (m, 3H), 1.68 (s, 9H), 1.29 (t, *J* = 7.11 Hz, 4H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.8, 180.2, 172.1, 169.3, 148.3, 146.6, 139.6, 136.4, 129.0, 127.8, 126.5, 125.6, 123.1, 122.2, 121.6, 115.5, 62.1, 52.8, 23.5, 13.7; MS (ESI mass) m/z : 566.2[M+1].

(S)-ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-1-methyl-5,8-dioxo-7-(1-phenylethylamino)-5,8-dihydroisoquinoline-4-carboxylate (31e):



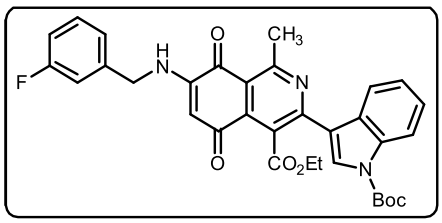
Pale yellow color solid, m.p:111-113 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.30 (d, *J* = 7.61 Hz, 1H), 8.20 (d, *J* = 8.11 Hz, 1H), 8.15 (s, 1H), 7.36 (ddd, *J* = 9.83, 9.34, 6.47 Hz, 4H), 7.29-7.23 (m, 3H), 6.41 (d, *J* = 6.34 Hz, 1H), 5.59 (s, 1H), 4.56-4.40 (m, 3H), 3.08 (s, 3H), 1.68 (s, 9H), 1.64 (d, *J* = 6.77 Hz, 4H), 1.35 (dd, *J* = 12.76, 5.77 Hz, 3H); ^{13}C NMR (100 MHz *CDCl$_3$*) δ 181.4, 180.4, 168.8, 160.6, 154.7, 149.1, 147.1, 138.8, 135.6, 129.1, 125.6, 123.6, 122.2, 118.0, 115.0, 102.1, 84.5, 62.0, 52.9, 29.7, 28.1, 26.3, 13.8; MS (ESI mass) m/z : 580.3[M+1].

(R)-ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-1-methyl-5,8-dioxo-7-(1-phenylethylamino)-5,8-dihydroisoquinoline-4-carboxylate (31f):



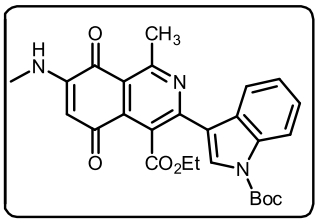
Pale yellow color solid, m.p:109-111 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.31 (d, *J* = 7.72 Hz, 1H), 8.20 (d, *J* = 8.07 Hz, 1H), 8.15 (s, 1H), 7.41-7.32 (m, 4H), 7.28 (ddd, *J* = 8.90, 6.93, 4.73 Hz, 3H), 6.42 (d, *J* = 6.36 Hz, 1H), 5.59 (s, 1H), 4.55-4.40 (m, 3H), 3.08 (s, 3H), 1.69 (s, 9H), 1.64 (d, *J* = 6.77 Hz, 3H), 1.36 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 181.4, 180.4, 168.8, 160.6, 154.7, 149.1, 147.1, 138.8, 135.5, 129.1, 125.6, 123.6, 122.2, 118.0, 115.0, 102.1, 84.5, 62.0, 52.9, 29.7, 28.1, 26.3, 13.8; MS (ESI mass) m/z : 580.3[M+1].

Ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-7-(3-fluorobenzylamino)-1-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31g):



Pale yellow color solid, m.p:108-110 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.31 (d, *J* = 7.55 Hz, 1H), 8.20 (d, *J* = 8.12 Hz, 1H), 8.17 (s, 1H), 7.41-7.30 (m, 3H), 7.09-6.96 (m, 3H), 6.48 (t, *J* = 5.69 Hz, 1H), 5.74 (s, 1H), 4.48 (dd, *J* = 13.55, 6.55 Hz, 2H), 4.39 (d, *J* = 5.88 Hz, 2H), 3.07 (s, 3H), 1.69 (s, 9H), 1.38 (t, *J* = 7.17 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 181.0, 180.6, 168.2, 164.3, 161.8, 160.8, 154.8, 149.1, 148.0, 138.7, 135.6, 130.7, 130.6, 128.8, 127.7, 125.2, 123.6, 119.5, 118.0, 115.2, 115.0, 114.4, 114.2, 101.2, 84.6, 62.0, 46.2, 28.1, 26.3, 13.8; MS (ESI mass) m/z : 584.3[M+1].

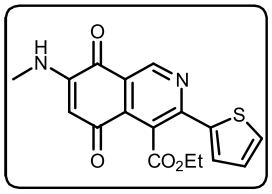
Ethyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-1-methyl-7-(methylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31h):



Pale yellow color solid, m.p:175-177 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.30 (d, *J* = 7.12 Hz, 1H), 8.20 (d, *J* = 8.16 Hz, 1H), 8.17 (s, 1H), 7.41-7.30 (m, 2H), 6.17 (d, *J* = 5.30 Hz, 1H), 5.74 (s, 1H), 4.50 (d, *J* = 6.65 Hz, 2H), 3.06 (s, 3H), 2.95 (d, *J* = 5.33 Hz, 3H), 1.69 (s, 9H), 1.39 (t, *J* = 7.18 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 181.1, 180.2, 168.9, 160.7, 154.7, 149.3, 139.1, 135.6, 128.9, 127.6, 125.2, 123.6,

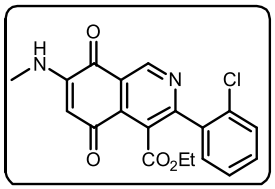
122.2, 119.6, 118.1, 115.0, 99.8, 84.5, 62.0, 29.2, 28.1, 26.3, 13.8; MS (ESI mass) m/z : 490.2[M+1].

Ethyl 1-methyl-7-(methylamino)-5,8-dioxo-3-(thiophen-2-yl)-5,8-dihydroisoquinoline-4-carboxylate (31i):



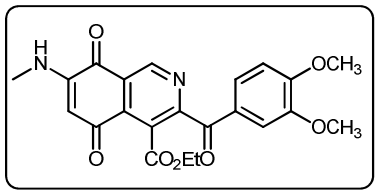
Pale yellow color solid, m.p: 232-234 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.28 (s, 1H), 7.67 (d, *J* = 3.52 Hz, 1H), 7.56 (dd, *J* = 11.52, 4.92 Hz, 1H), 7.12 (d, *J* = 9.08, Hz, 1H), 6.08 (d, *J* = 4.23 Hz, 1H), 5.76 (d, *J* = 3.51 Hz, 1H), 4.57 (q, *J* = 13.65, 10.87, 5.14 Hz, 2H), 2.95 (d, *J* = 5.28 Hz, 3H), 1.40 (dt, *J* = 7.13, 4.29 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.0, 179.9, 168.2, 154.4, 148.2, 142.1, 137.3, 131.6, 129.1, 128.7, 123.0, 121.7, 101.2, 62.4, 29.2, 13.7; MS (ESI mass) m/z : 343.0[M+1].

Ethyl 3-(2-chlorophenyl)-7-(methylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31j):



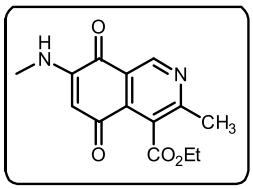
Pale yellow color semi solid, R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.37 (s, 1H), 7.43 (m, 4H), 6.23-6.06 (m, 1H), 5.81 (s, 1H), 4.18 (s, 2H), 2.96 (s, 3H), 1.16 (d, *J* = 75.29 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.4, 179.6, 166.6, 161.3, 148.5, 147.7, 136.2, 132.9, 130.5, 130.3, 130.2, 129.7, 127.3, 126.2, 123.1, 101.3, 61.7, 29.2, 13.5; MS (ESI mass) m/z : 371.0[M+1].

Ethyl 3-(3,4-dimethoxybenzoyl)-7-(methylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31k):



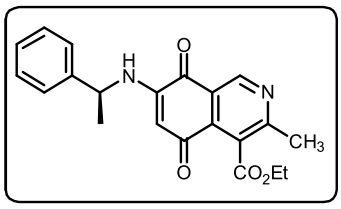
Pale yellow color solid, m.p:142-144 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.31 (s, 1H), 7.59 (s, 1H), 7.44 (d, *J* = 8.39 Hz, 1H), 6.87 (d, *J* = 8.47 Hz, 1H), 6.06 (d, *J* = 4.78 Hz, 1H), 5.84 (s, 1H), 4.45 (q, *J* = 7.14 Hz, 2H), 3.94 (d, *J* = 8.11 Hz, 6H), 2.98 (d, *J* = 5.39 Hz, 3H), 1.35 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 190.3, 180.1, 179.1, 166.5, 159.2, 154.2, 149.1, 148.2, 147.0, 137.8, 127.9, 127.0, 124.6, 111.8, 109.9, 101.8, 62.3, 56.1, 29.2, 13.7; MS (ESI mass) m/z : 423.1[M-1].

Ethyl 3-methyl-7-(methylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31l):



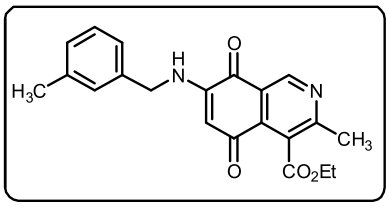
Pale yellow color solid, m.p:189-191 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.12 (d, *J* = 3.83 Hz, 1H), 6.13 (s, 1H), 5.71 (s, 1H), 4.50 (q, *J* = 7.11, 2.34 Hz, 2H), 2.92 (dd, *J* = 5.39, 1.79 Hz, 3H), 2.63 (d, *J* = 2.40 Hz, 3H), 1.41 (t, *J* = 7.16, 2.16 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.3, 180.0, 168.2, 162.7, 148.6, 147.7, 136.0, 126.5, 121.9, 100.9, 62.1, 29.2, 22.8, 13.9; MS (ESI mass) m/z : 275.1[M+1].

(S)-ethyl 3-methyl-5,8-dioxo-7-(1-phenylethylamino)-5,8-dihydroisoquinoline-4-carboxylate (31m):



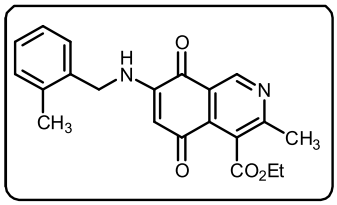
Pale yellow color semi solid, R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.17 (s, 1H), 7.37-7.31 (m, 3H), 7.31-7.27 (m, 1H), 7.23 (s, 1H), 6.27 (d, *J* = 6.16 Hz, 1H), 5.59 (s, 1H), 4.53-4.44 (m, 3H), 2.64 (d, *J* = 3.73 Hz, 3H), 1.63 (d, *J* = 6.80 Hz, 3H), 1.39 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.7, 180.2, 168.1, 162.8, 147.8, 146.4, 141.1, 135.7, 129.1, 128.0, 126.4, 125.6, 121.9, 103.2, 62.1, 52.9, 23.4, 22.8, 13.9; MS (ESI mass) m/z : 365.2[M+1].

Ethyl 3-methyl-7-(3-methylbenzylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31n):



Pale yellow color semi solid, R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.17 (s, 1H), 7.28-7.23 (m, 1H), 7.14 (d, *J* = 7.47 Hz, 1H), 7.08 (d, *J* = 7.37 Hz, 2H), 6.32 (t, *J* = 4.98 Hz, 1H), 5.80 (s, 1H), 4.51 (q, *J* = 7.15 Hz, 2H), 4.34 (d, *J* = 5.84 Hz, 2H), 2.66 (s, 3H), 2.35 (s, 3H), 1.42 (m, 3H); ^{13}C MMR (100 MHz, *CDCl$_3$*) δ 180.5, 180.3, 168.2, 162.8, 147.8, 147.3, 138.9, 135.8, 135.1, 129.0, 128.9, 128.3, 124.6, 121.9, 102.0, 62.1, 46.8, 29.6, 22.8, 21.3, 13.9; MS (ESI mass) m/z : 365.2[M+1].

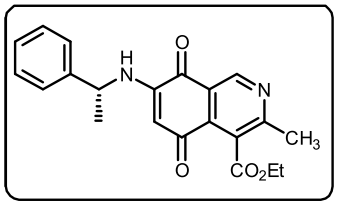
Ethyl 3-methyl-7-(2-methylbenzylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31o):



Pale yellow color semi solid, R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.17 (s, 1H),

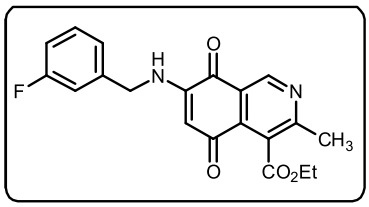
7.32-7.16 (m, 5H), 6.13 (d, *J* = 4.39 Hz, 1H), 5.82 (s, 1H), 4.52 (q, *J* = 7.10 Hz, 2H), 4.32 (t, *J* = 6.36 Hz, 2H), 2.66 (s, 3H), 2.33 (s, 3H), 1.42 (t, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ ppm 180.4, 180.3, 168.1, 162.8, 147.8, 147.3, 136.3, 135.8, 132.9, 130.9, 129.3, 128.6, 128.4, 126.5, 121.9, 101.9, 62.1, 45.1, 22.8, 18.9, 13.9; MS (ESI mass) m/z : 365.1[M+1].

(R)-ethyl 3-methyl-5,8-dioxo-7-(1-phenylethylamino)-5,8-dihydroisoquinoline-4-carboxylate (31p):



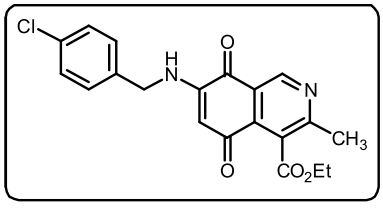
Pale yellow color solid, m.p:55-57 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.18 (s, 1H), 7.35 (dd, *J* = 9.86, 4.55 Hz, 2H), 7.30-7.22 (m, 4H), 6.27 (d, *J* = 6.13 Hz, 1H), 5.59 (s, 1H), 4.53-4.44 (m, 3H), 2.64 (d, *J* = 3.70 Hz, 3H), 1.64 (d, *J* = 6.79 Hz, 4H), 1.39 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.6, 180.2, 168.1, 162.8, 147.8, 146.3, 141.1, 135.6, 129.1, 128.0, 126.4, 125.6, 121.8, 103.2, 62.1, 52.9, 29.6, 22.8, 13.9; MS (ESI mass) m/z : 365.1[M+1].

Ethyl 7-(3-fluorobenzylamino)-3-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31q):



Pale yellow color solid, m.p:55-57 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.18 (s, 1H), 7.33 (t, *J* = 12.28, 6.13 Hz, 1H), 7.08-6.94 (m, 4H), 6.38 (t, *J* = 5.33 Hz, 1H), 5.74 (s, 1H), 4.50 (q, *J* = 7.13 Hz, 2H), 4.39 (d, *J* = 6.07 Hz, 2H), 2.65 (s, 3H), 1.41 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.4, 180.4, 168.0, 164.3, 162.9, 147.8, 147.2, 137.8, 137.7, 135.6, 130.7, 130.6, 126.4, 122.9, 121.8, 115.3, 115.1, 114.4, 114.2, 102.4, 62.1, 46.2, 29.6, 22.8, 13.9; MS (ESI mass) m/z : 369.1[M+1].

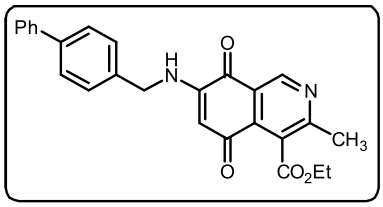
Ethyl 7-(4-chlorobenzylamino)-3-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31r):



Pale yellow color semi solid, R_f= 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.16 (s, 1H),

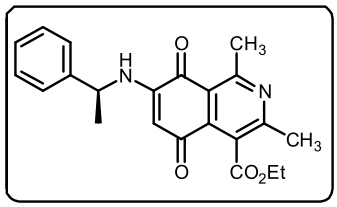
7.33 (t, *J* = 6.57 Hz, 2H), 7.23 (dd, *J* = 13.73, 7.97 Hz, 2H), 6.34 (t, *J* = 5.04 Hz, 1H), 5.74 (s, 1H), 4.50 (q, *J* = 11.19, 5.14 Hz, 2H), 4.36 (d, *J* = 5.98 Hz, 2H), 2.65 (s, 3H), 1.41 (t, *J* = 7.11 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.4, 180.3, 168.0, 162.9, 147.8, 147.2, 135.6, 134.2, 133.7, 129.2, 128.8, 126.4, 121.8, 102.3, 62.1, 46.1, 29.6, 22.8, 13.9; MS (ESI mass) m/z : 385.1[M+1].

Ethyl 7-(biphenyl-4-ylmethylamino)-3-methyl-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31s):



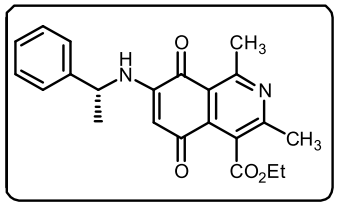
Pale yellow color solid, m.p:119-121 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 9.18 (s, 1H), 7.59 (dd, *J* = 11.17, 4.61 Hz, 5H), 7.44 (dt, *J* = 7.74, 7.49, 2.86 Hz, 2H), 7.37-7.33 (m, 2H), 6.38 (t, *J* = 5.60 Hz, 1H), 5.83 (s, 1H), 4.55-4.48 (m, 2H), 4.41 (d, *J* = 6.34 Hz, 2H), 2.66 (s, 3H), 1.42 (t, *J* = 10.02, 4.28 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 180.5, 180.3, 168.1, 162.8, 148.5, 147.8, 147.3, 141.3, 140.3, 135.7, 134.1, 128.8, 128.0, 127.8, 127.5, 127.0, 126.5, 121.9, 102.2, 62.1, 46.5, 22.8, 13.9. MS (ESI mass) m/z: 427.2[M+1].

(S)-ethyl 1,3-dimethyl-5,8-dioxo-7-(1-phenylethylamino)-5,8-dihydroisoquinoline-4-carboxylate (31t):



Pale yellow color semi solid, R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.36-7.29 (m, 2H), 7.29-7.21 (m, 3H), 6.36 (d, *J* = 6.23 Hz, 1H), 5.55 (s, 1H), 4.53-4.40 (m, 3H), 2.94 (s, 3H), 2.58 (s, 3H), 1.63 (t, *J* = 7.45 Hz, 3H): ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 181.6, 180.3, 168.6, 160.9, 160.4, 147.1, 141.3, 137.8, 129.0, 127.9, 125.6, 120.0, 101.9, 61.8, 52.9, 25.9, 23.4, 22.7, 13.9; MS (ESI mass) m/z : 379[M+1].

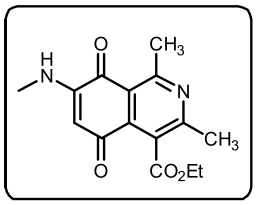
(R)-ethyl 1,3-dimethyl-5,8-dioxo-7-(1-phenylethylamino)-5,8-dihydroisoquinoline-4-carboxylate (31u):



Pale yellow color semi solid, 55-57 °C; R_f = 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.33-7.30 (m, 2H), 7.29-7.22 (m, 3H), 6.37 (d, *J* = 6.19 Hz, 1H), 5.56 (s, 1H), 4.53-4.42 (m, 3H), 2.95 (s, 3H), 2.58 (s,

3H), 1.62 (d, *J* = 6.79 Hz, 3H), 1.39 (d, *J* = 6.74 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ ppm 181.6, 180.3, 168.6, 160.9, 160.4, 147.7, 147.1, 141.3, 137.7, 129.0, 128.4, 127.9, 126.7, 125.6, 125.5, 120.0, 101.9, 61.8, 52.9, 51.3, 25.9, 22.7, 13.9; MS (ESI mass) m/z : 379.2[M+1].

Ethyl 1,3-dimethyl-7-(methylamino)-5,8-dioxo-5,8-dihydroisoquinoline-4-carboxylate (31v):



Pale yellow color solid, m.p:184-186 °C; R_f= 0.21 (30% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 6.14 (d, *J* = 1.74 Hz, 1H), 5.70 (s, 1H), 4.50 (q, *J* = 7.14 Hz, 2H), 2.93 (d, *J* = 4.70 Hz, 6H), 2.60 (s, 3H), 1.42 (t, *J* = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 181.3, 180.1, 168.7, 160.9, 160.5, 149.3, 138.1, 125.6, 120.0, 99.6, 61.8, 29.2, 25.9, 22.7, 13.9; MS (ESI mass) m/z : 289.2[M+1].

3.7. References

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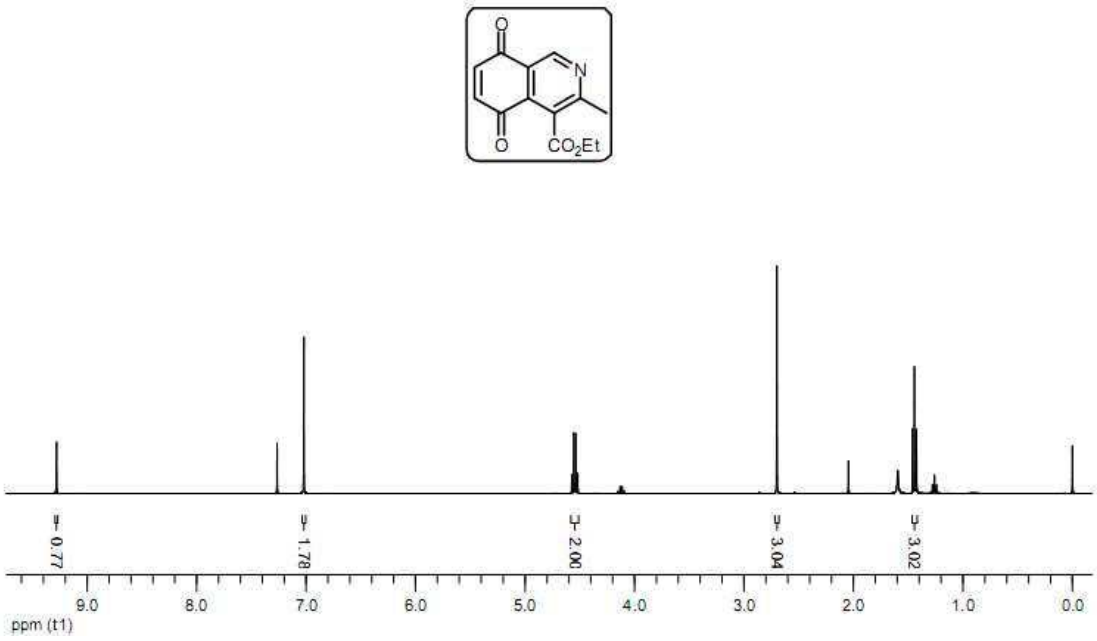
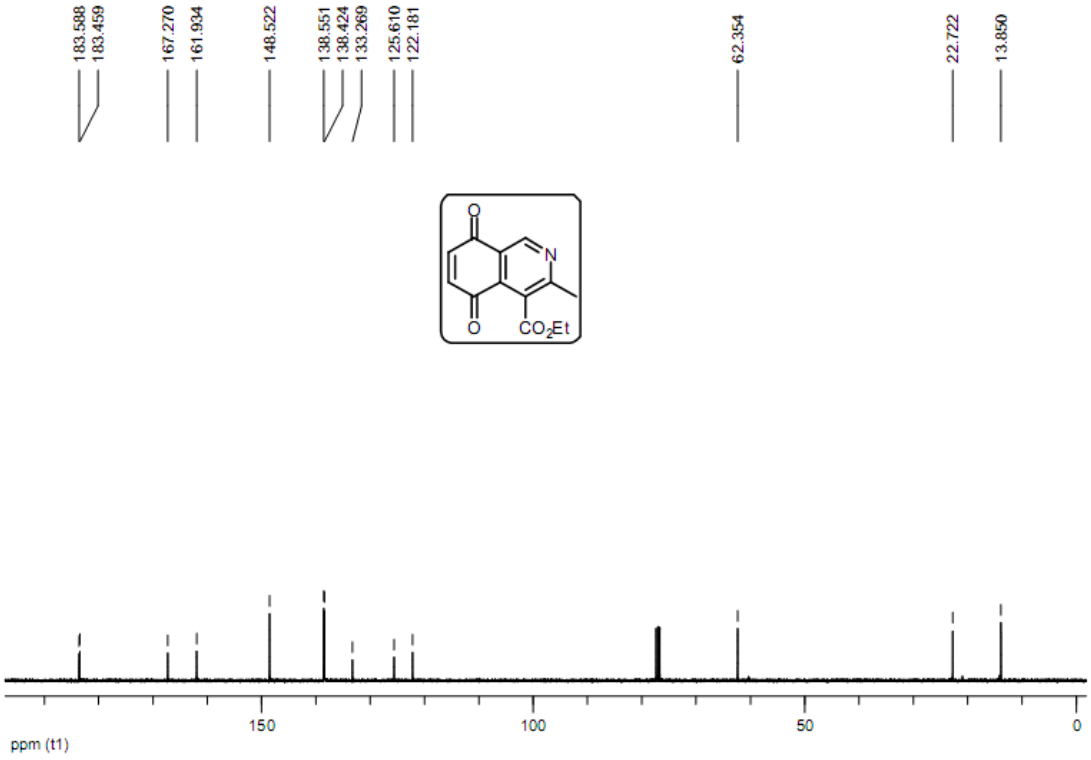
3.8. NMR Spectra

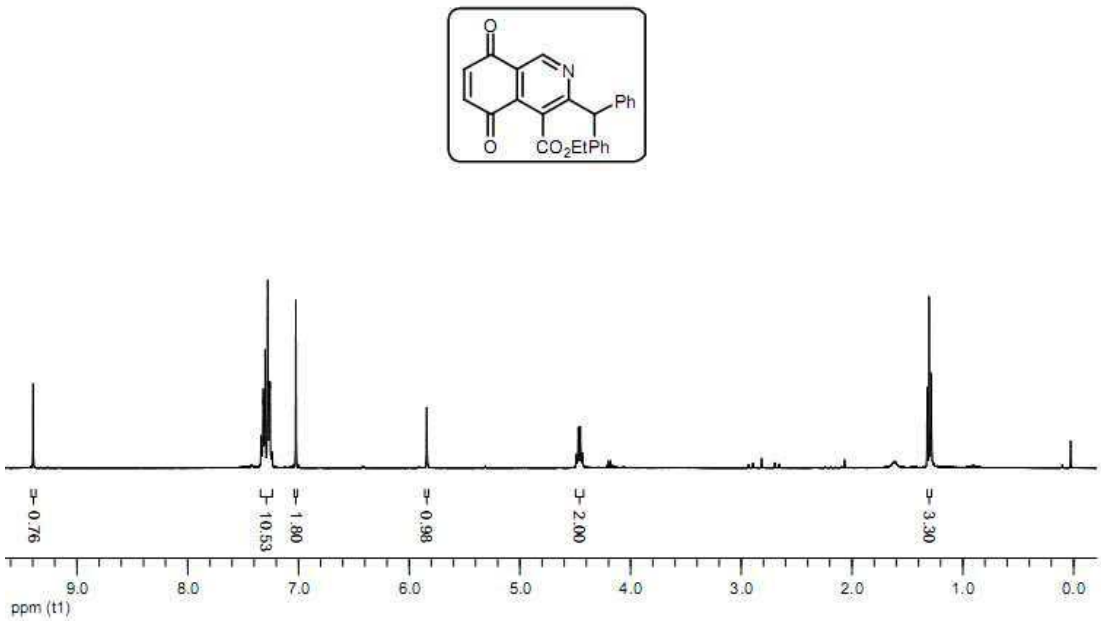
28a ^{1}H NMR ($CDCl_3$, 400 MHz)



28a ^{13}C NMR ($CDCl_3$, 100 MHz)



28b ^{1}H NMR ($CDCl_3$, 400 MHz)



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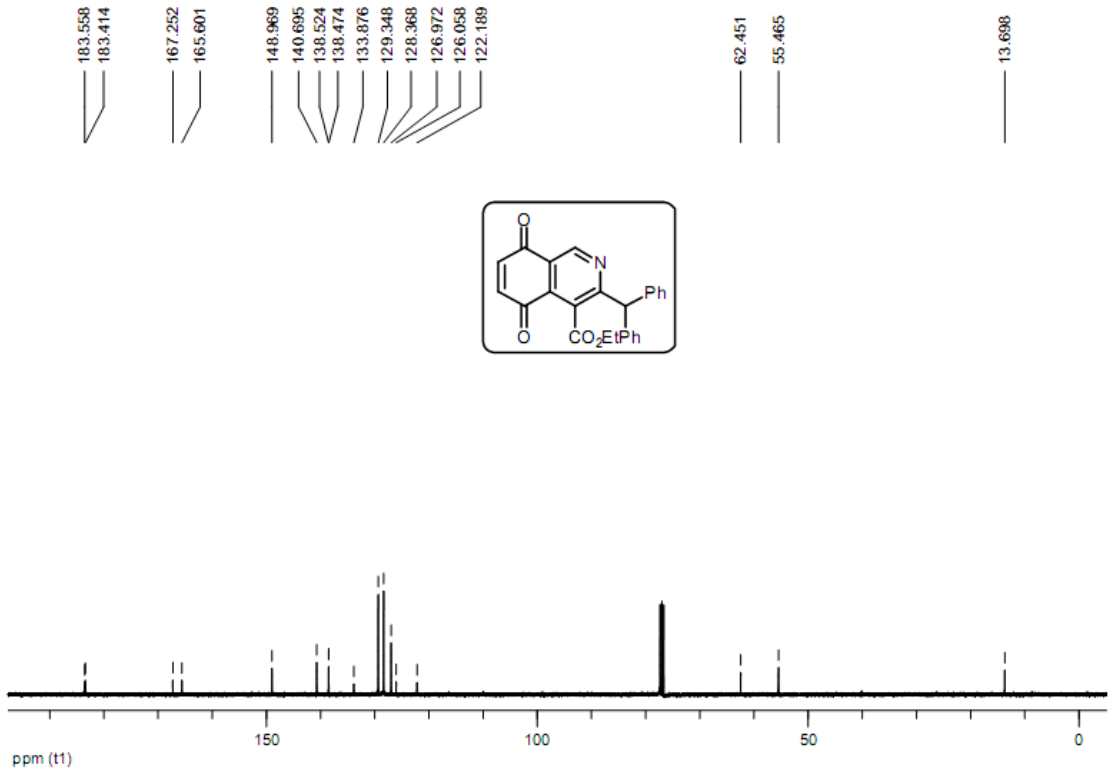
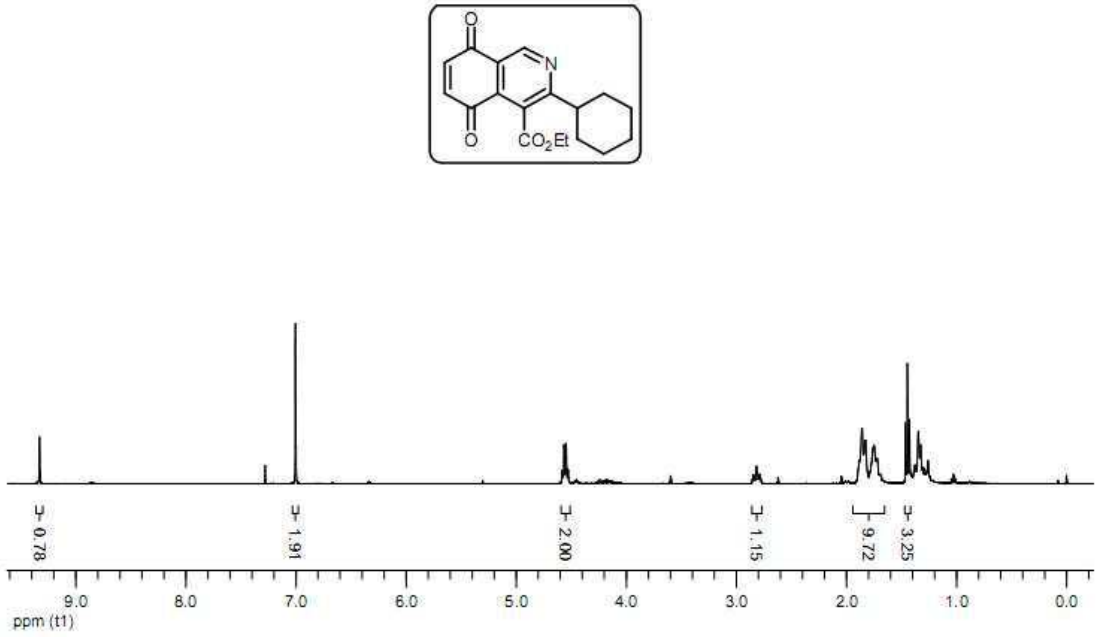
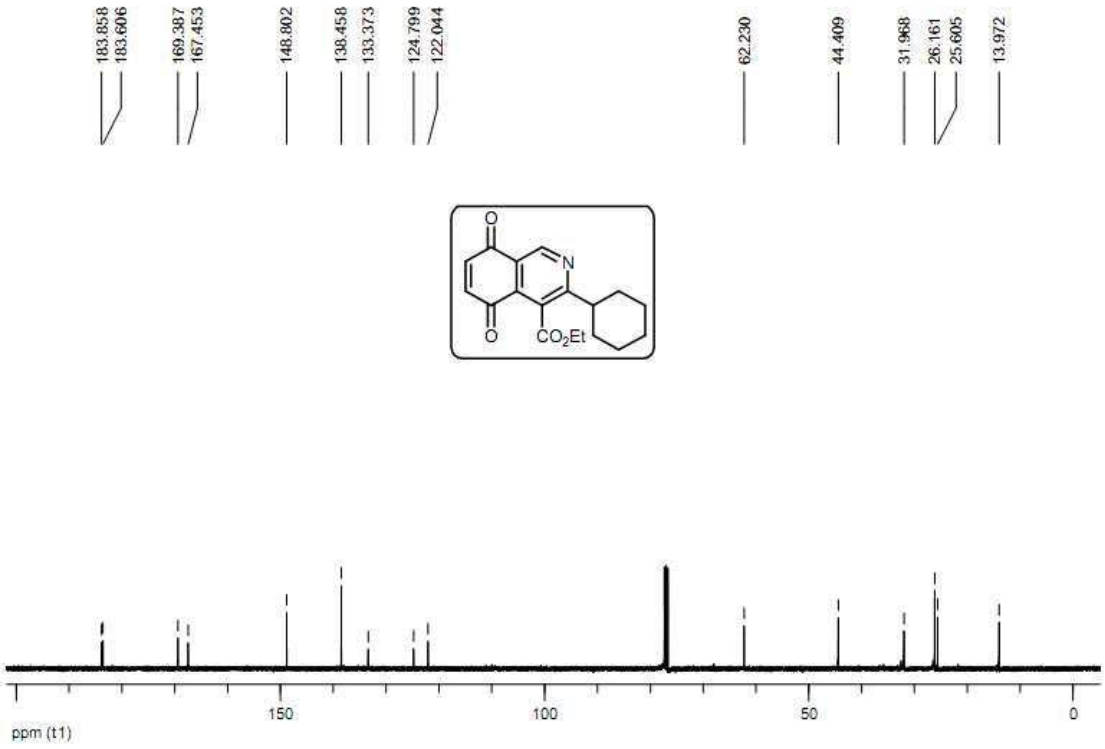


28c ^{1}H NMR ($CDCl_3$, 400 MHz)



28c ^{13}C NMR ($CDCl_3$, 100 MHz)



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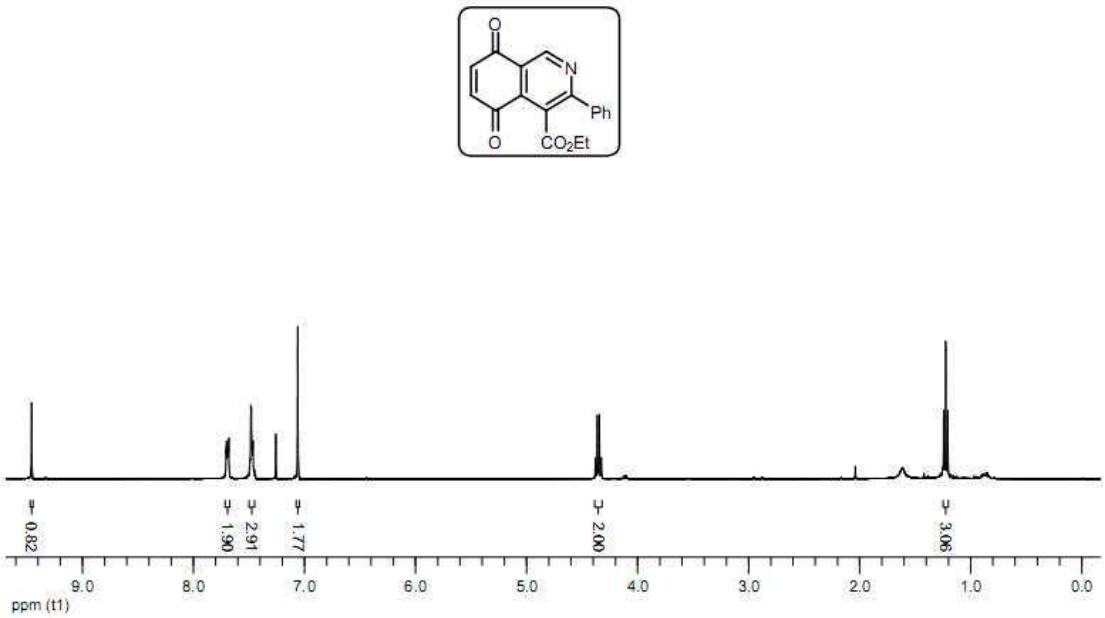
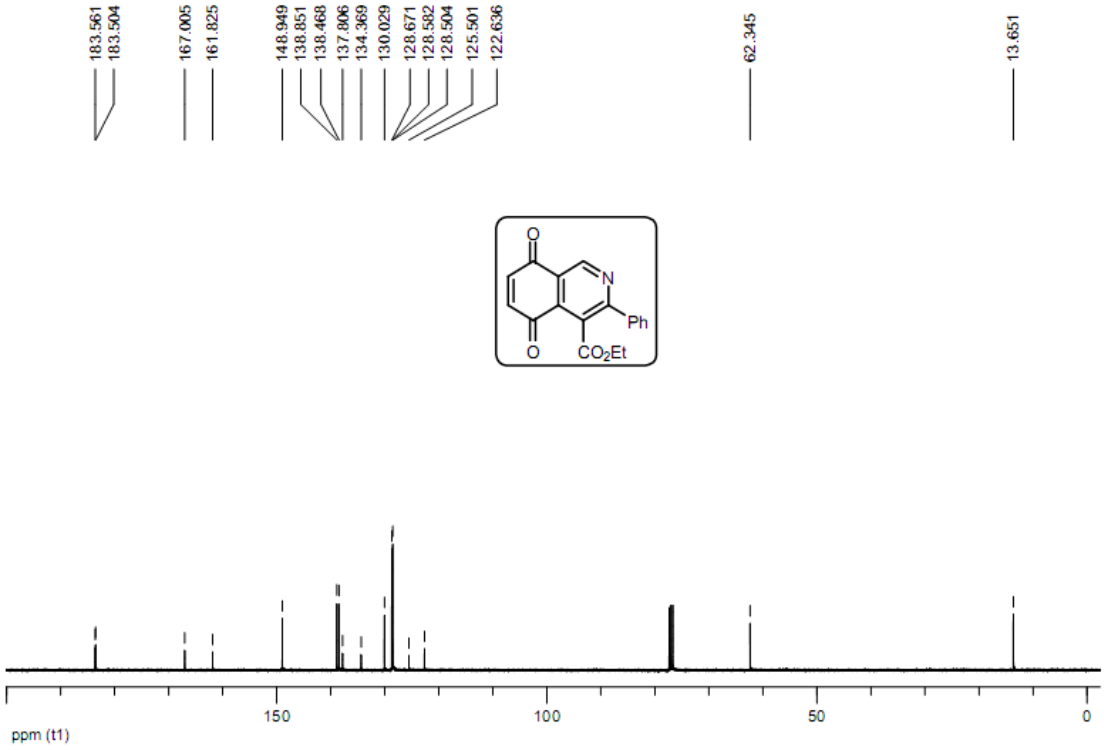
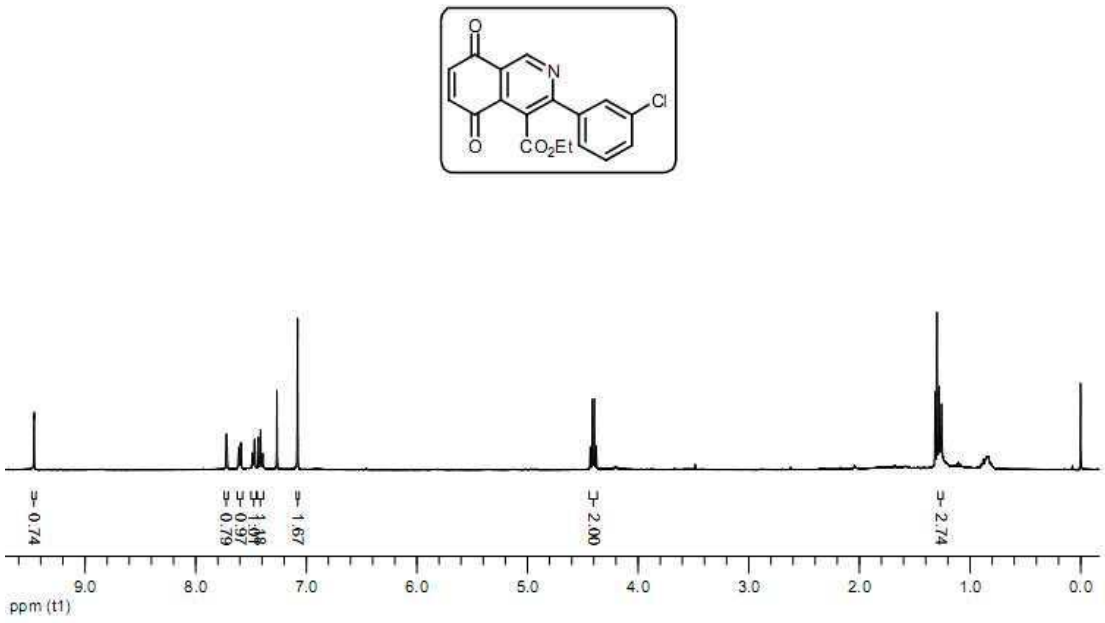


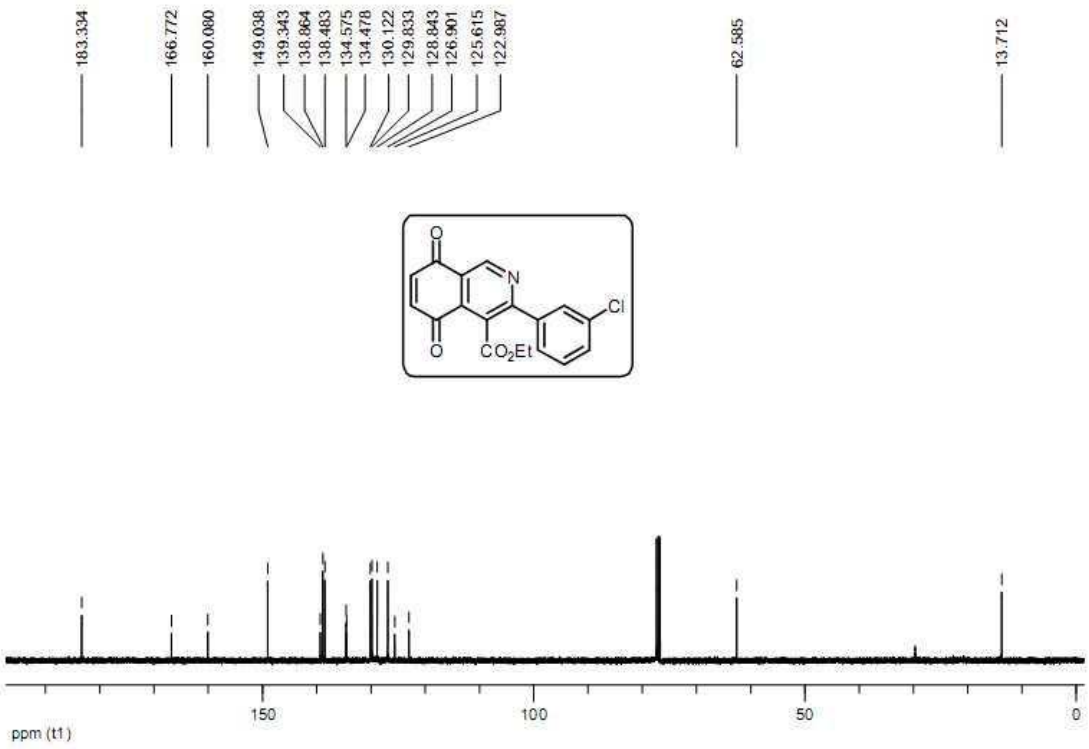
28d ^{13}C NMR ($CDCl_3$, 100 MHz)



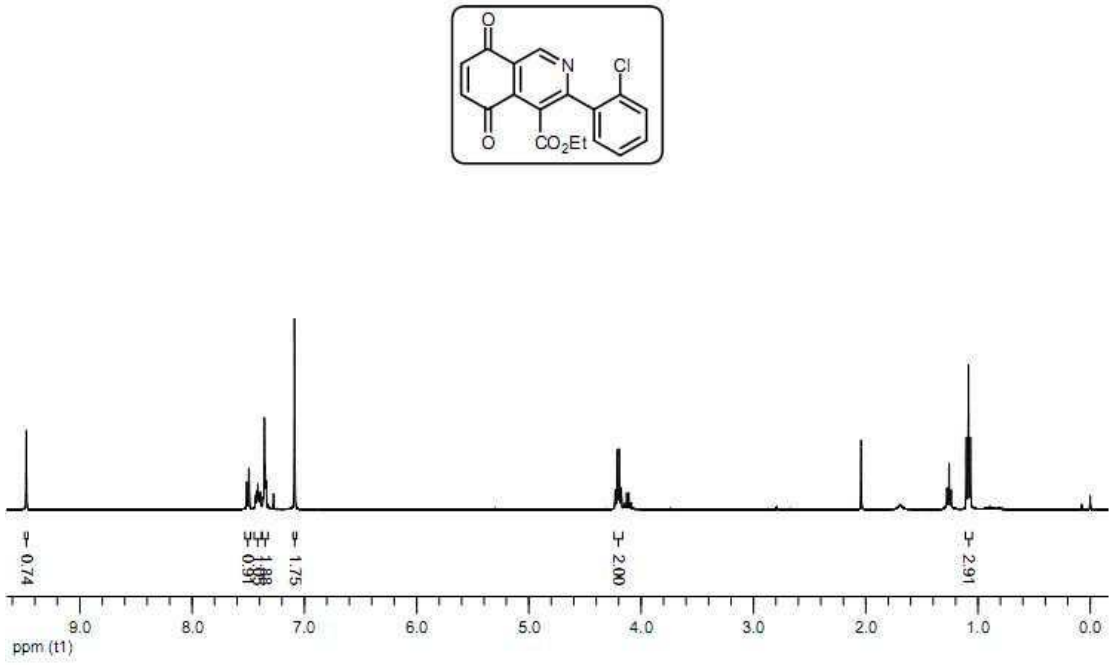
28e ^{1}H NMR ($CDCl_3$, 400 MHz)



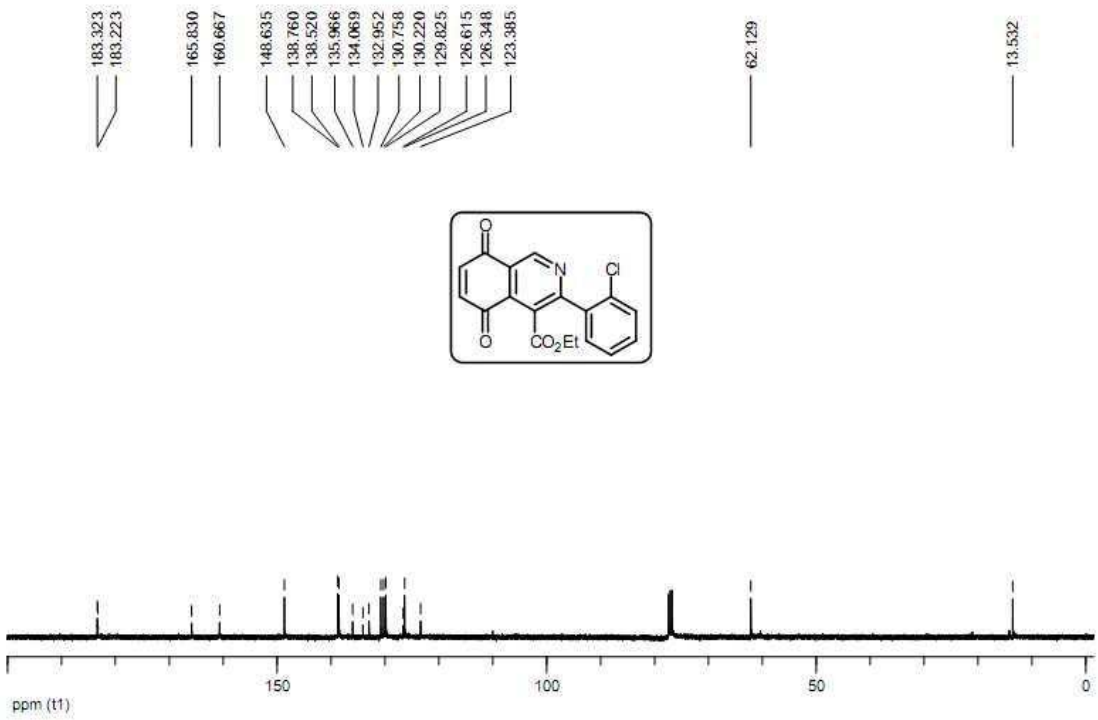
28e ^{13}C NMR ($CDCl_3$, 100 MHz)



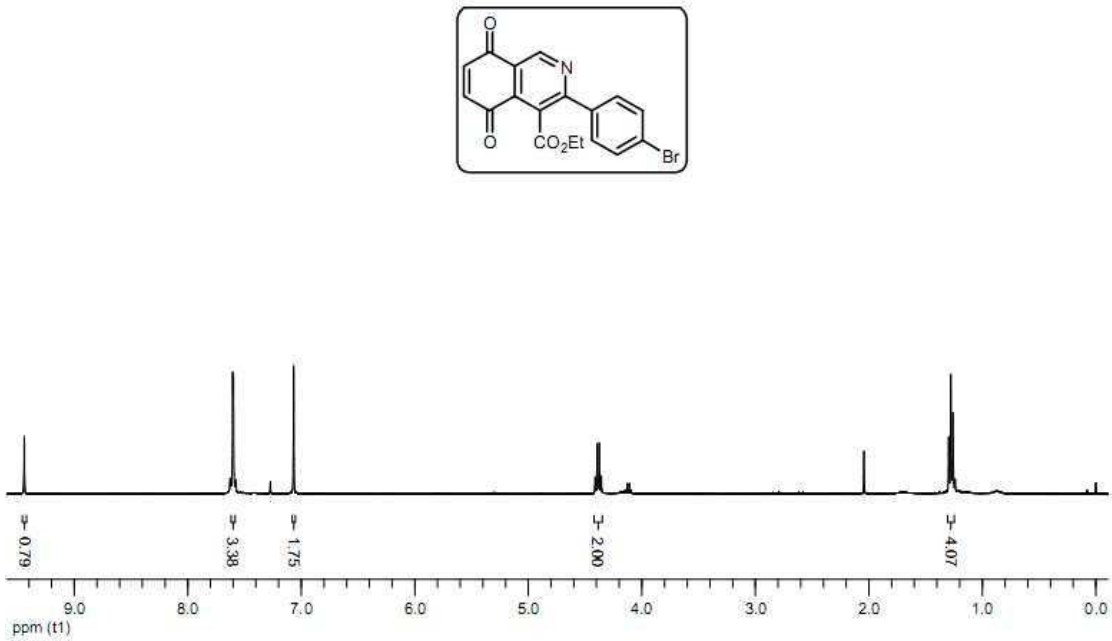
28f ^{1}H NMR ($CDCl_3$, 400 MHz)



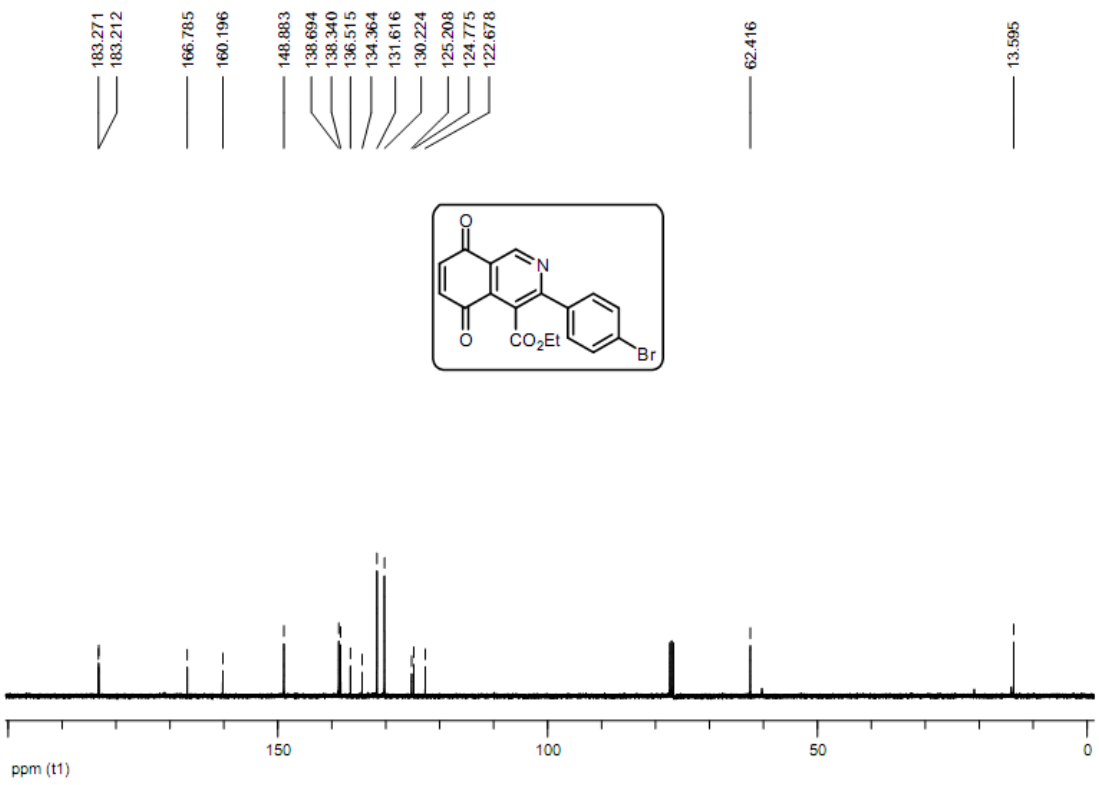
28f ^{13}C NMR ($CDCl_3$, 100 MHz)



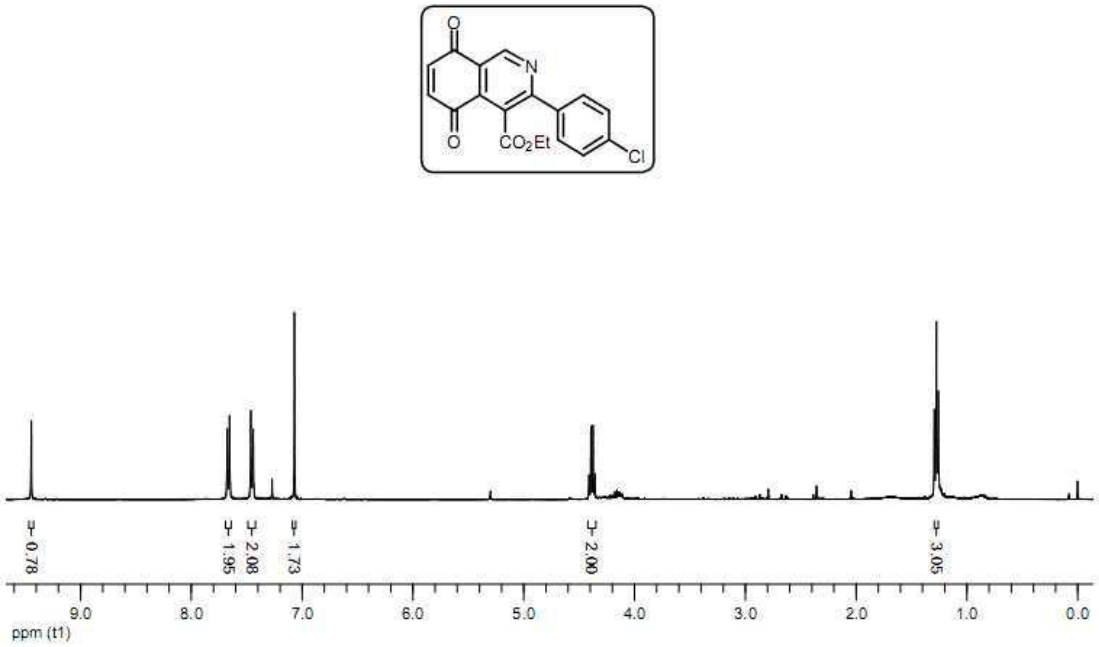
28g ^{1}H NMR ($CDCl_3$, 400 MHz)



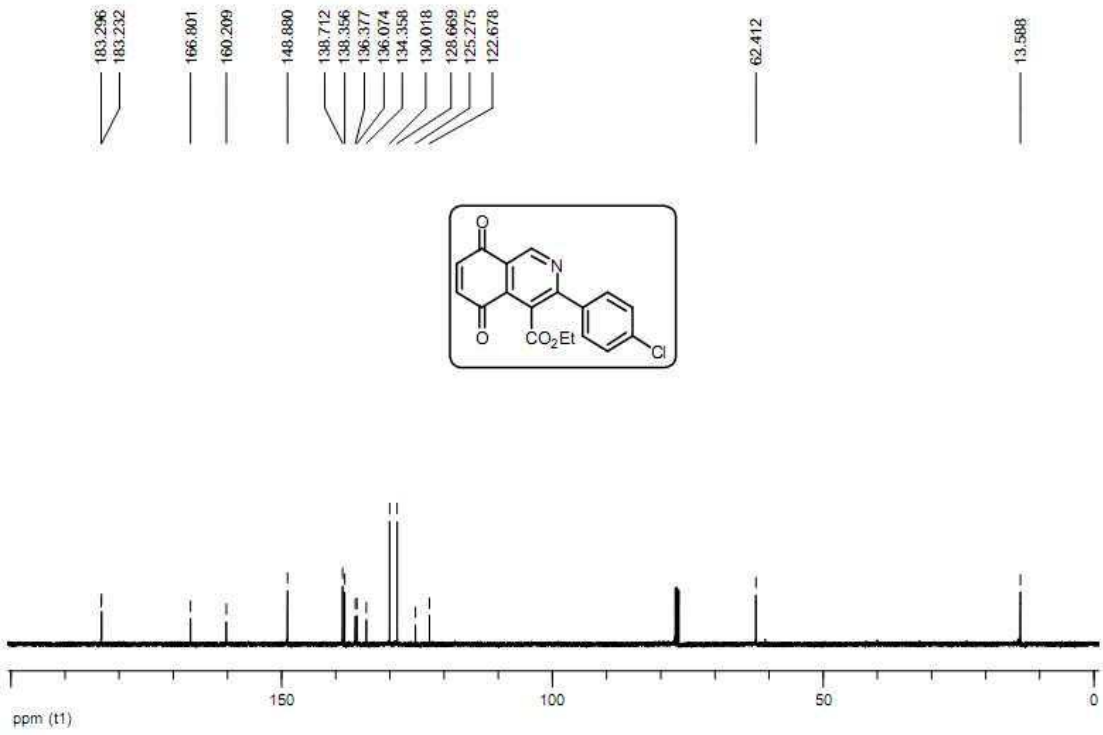
28g ^{13}C NMR ($CDCl_3$, 100 MHz)



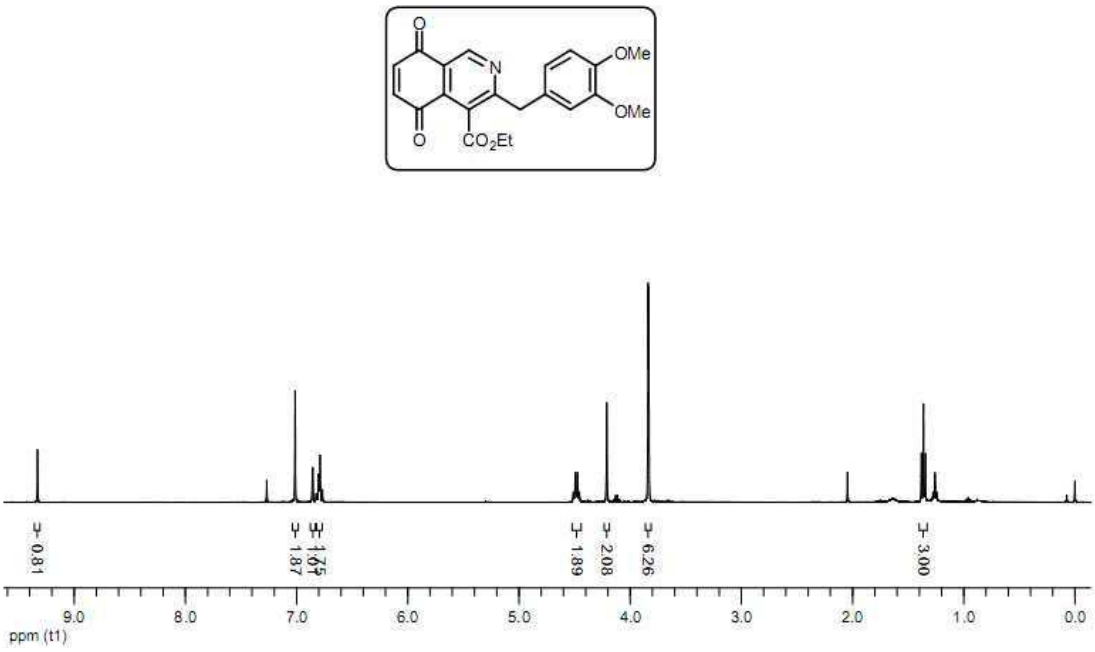
28h ^{1}H NMR ($CDCl_3$, 400 MHz)



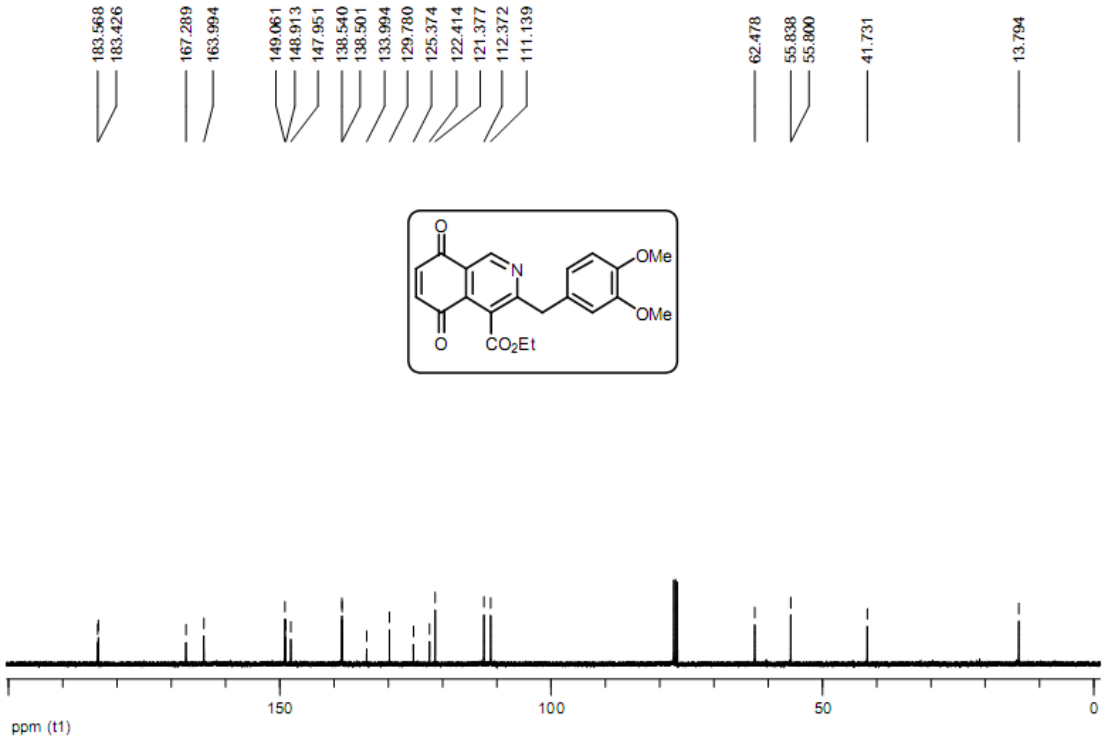
28h ^{13}C NMR ($CDCl_3$, 100 MHz)



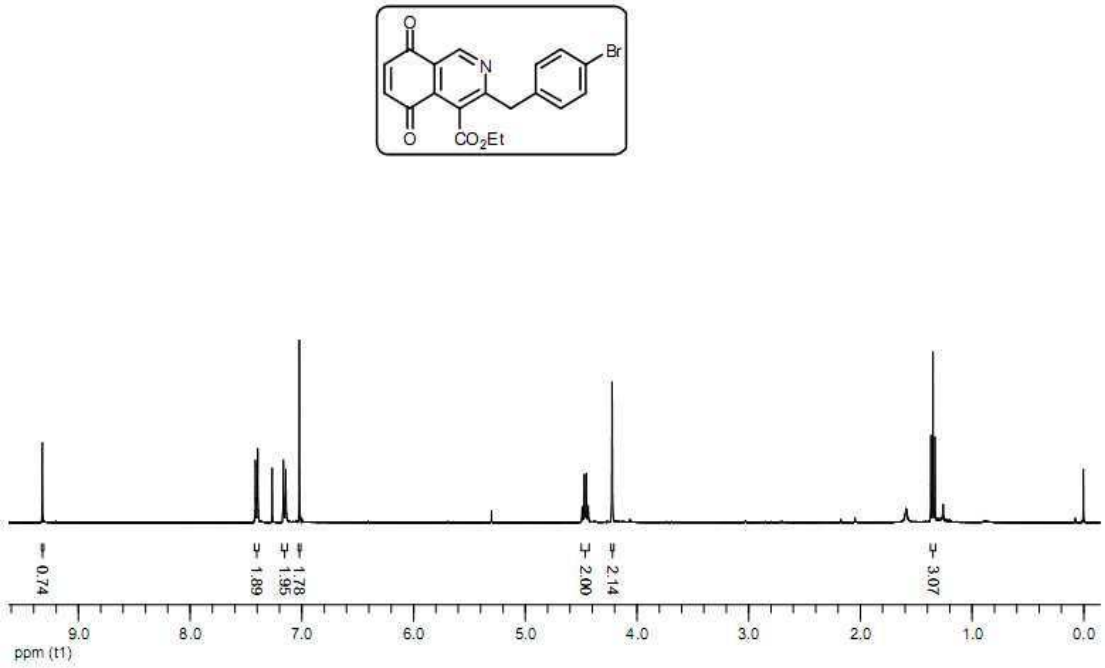
28i ^{1}H NMR ($CDCl_3$, 400 MHz)



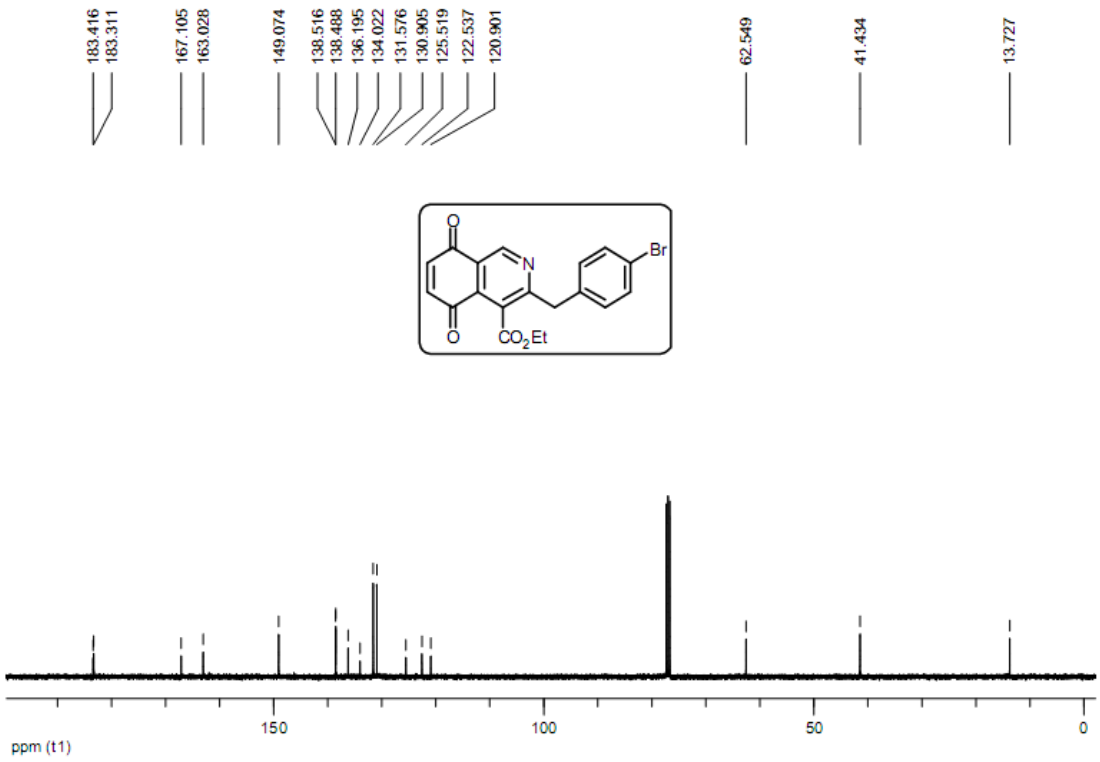
28i ^{13}C NMR ($CDCl_3$, 100 MHz)



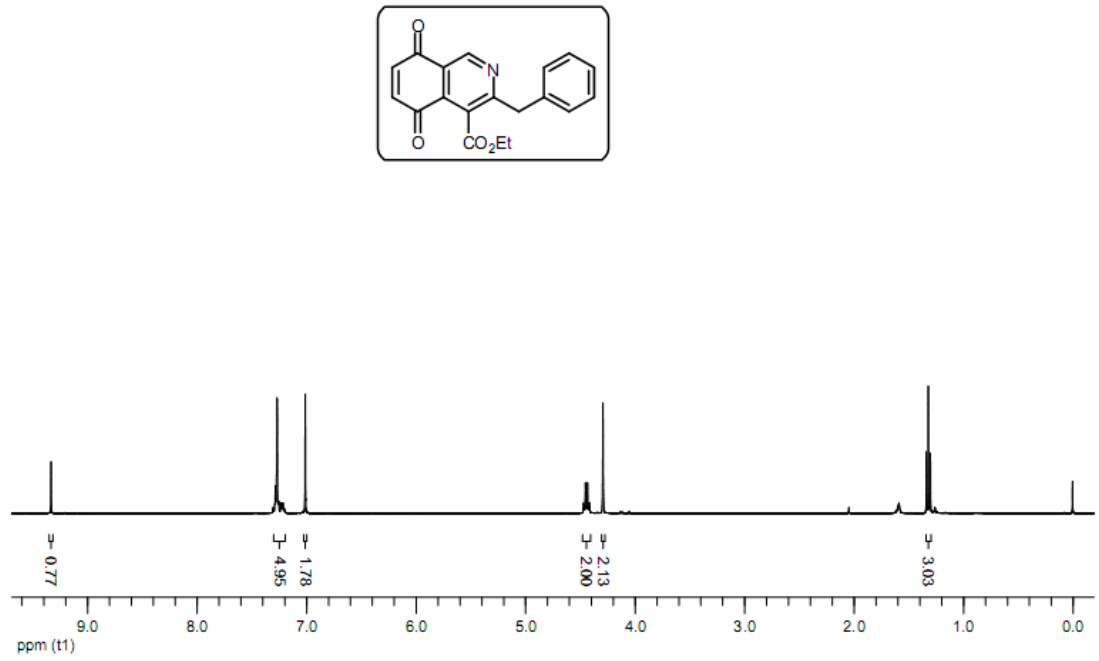
28j ^{1}H NMR ($CDCl_3$, 400 MHz)



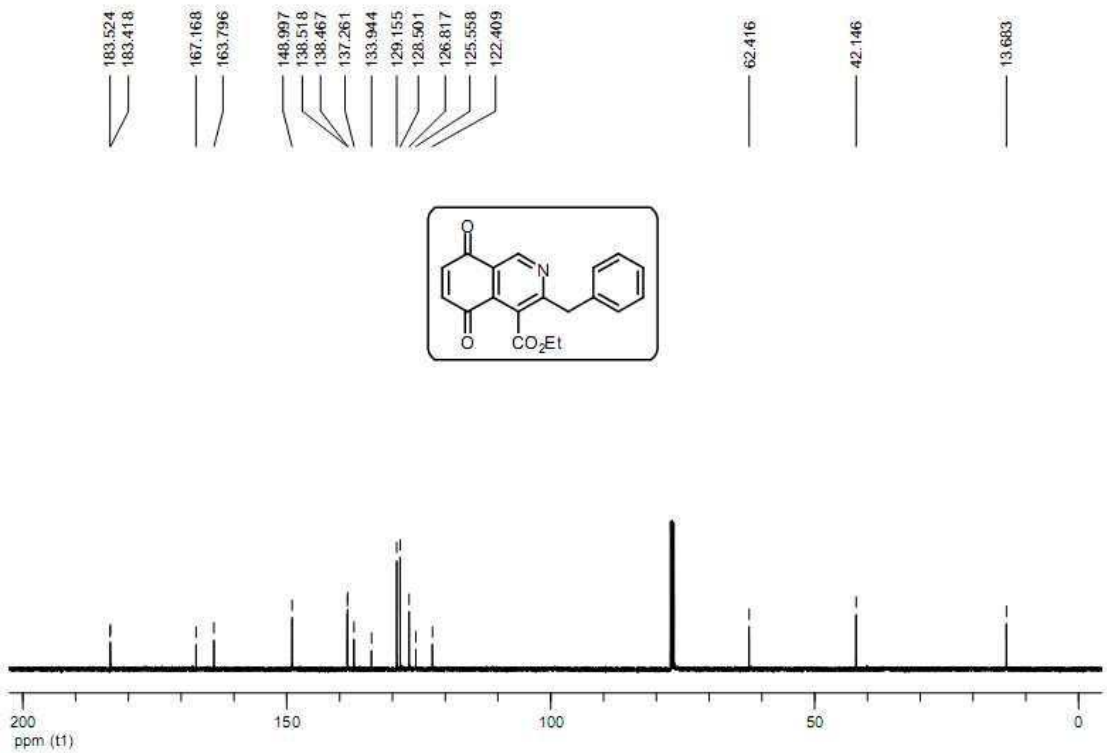
28j ^{13}C NMR ($CDCl_3$, 100 MHz)



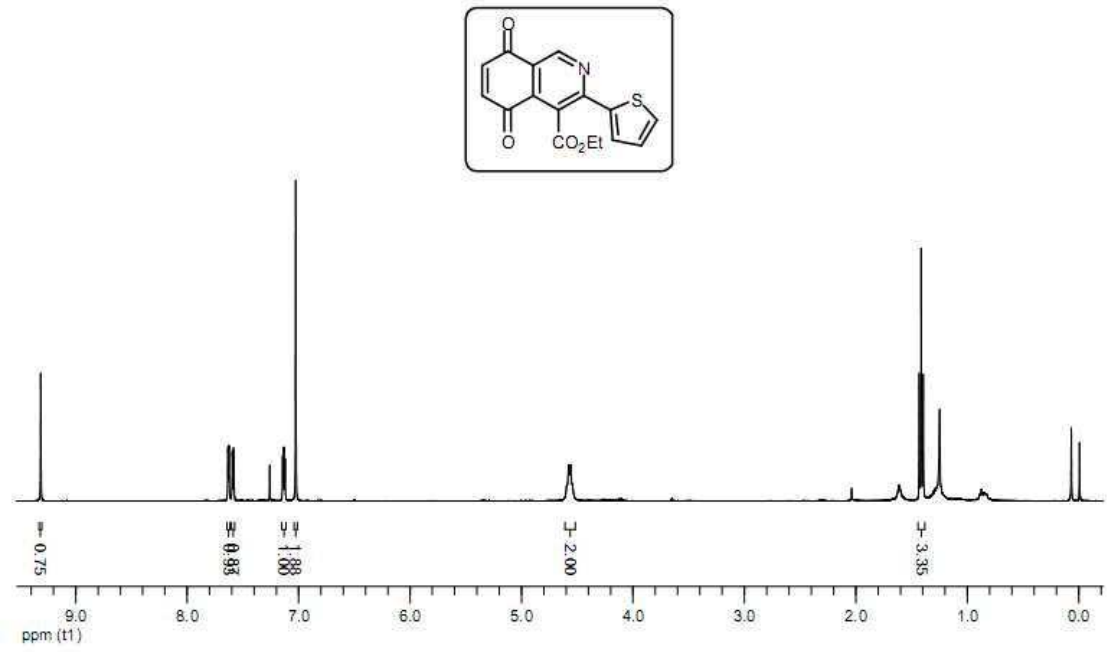
28k ^{1}H NMR ($CDCl_3$, 400 MHz)



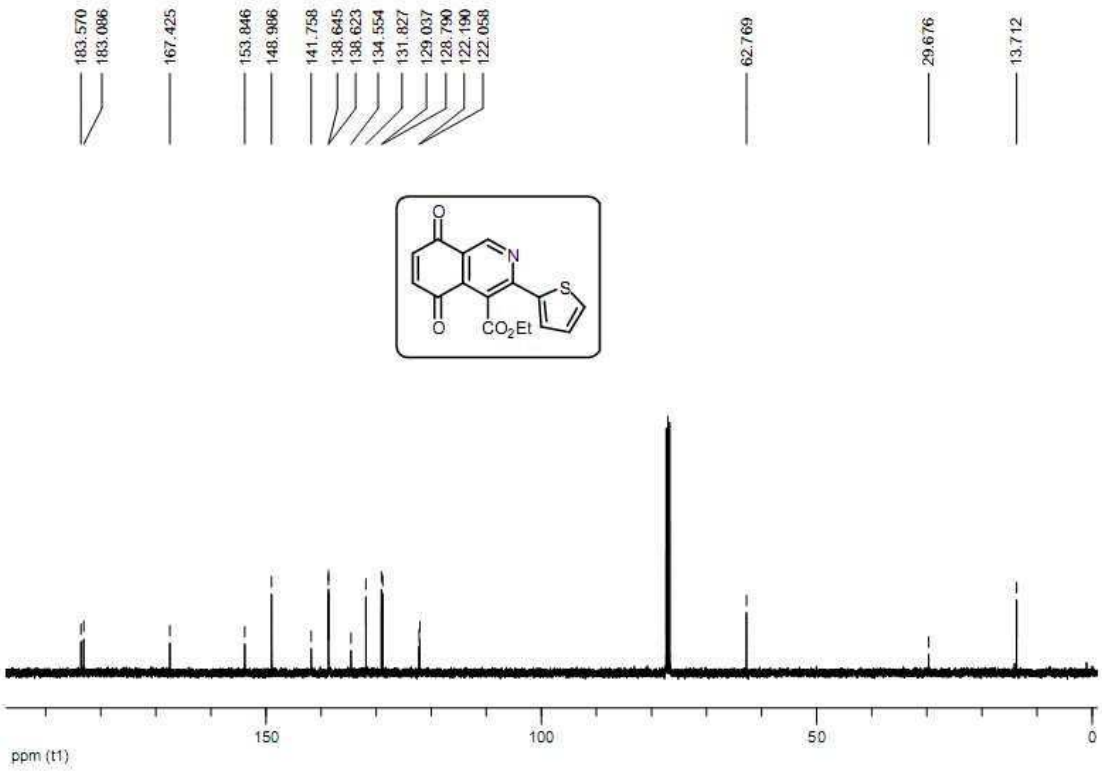
28k ^{13}C NMR ($CDCl_3$, 100 MHz)



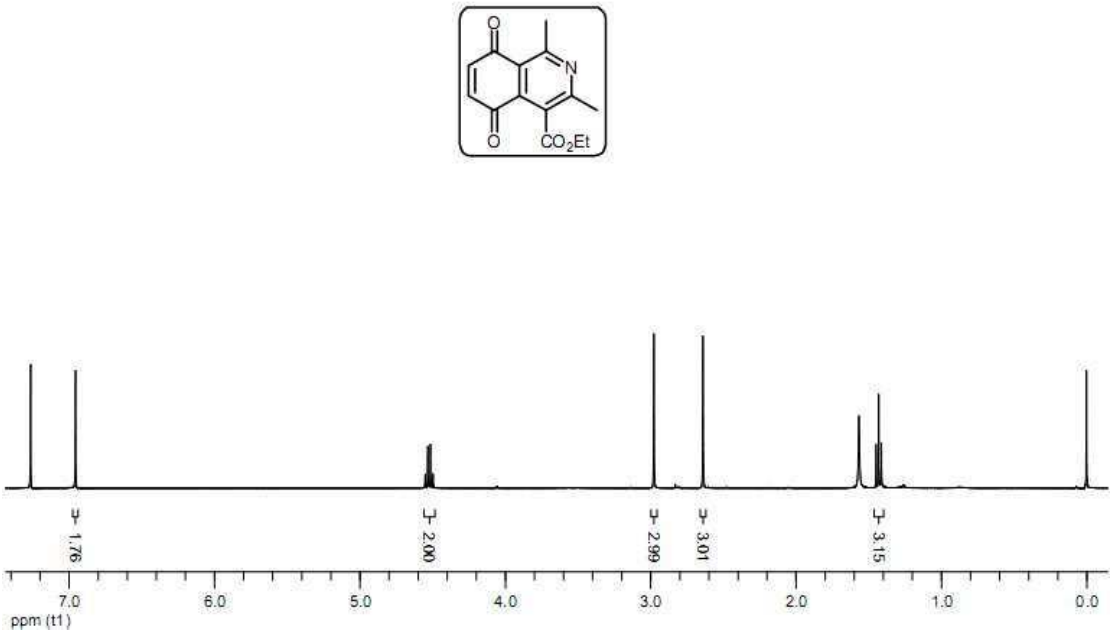
28l ^{1}H NMR ($CDCl_3$, 400 MHz)



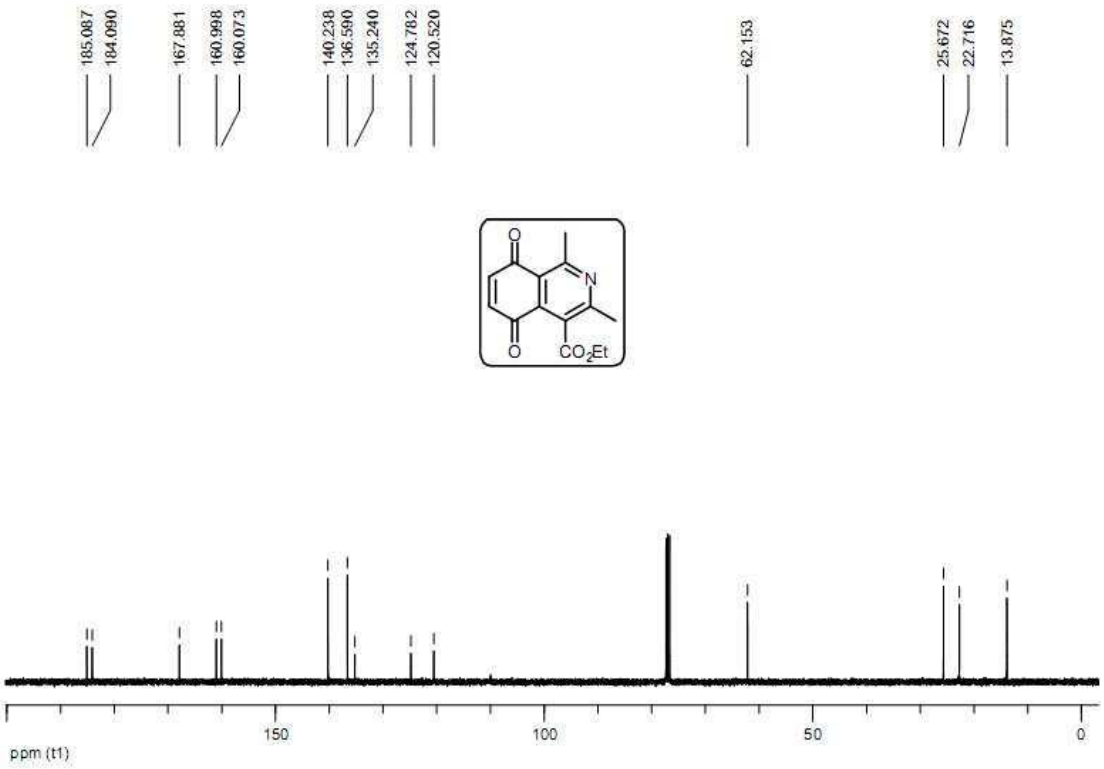
28l ^{13}C NMR ($CDCl_3$, 100 MHz)



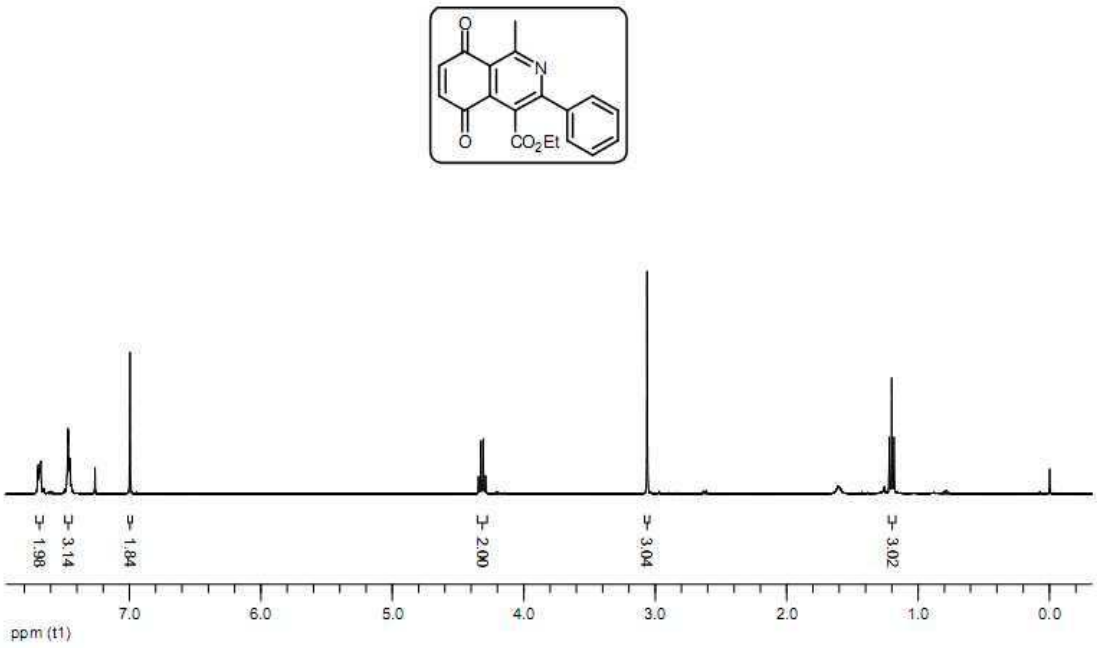
28m ^{1}H NMR ($CDCl_3$, 400 MHz)



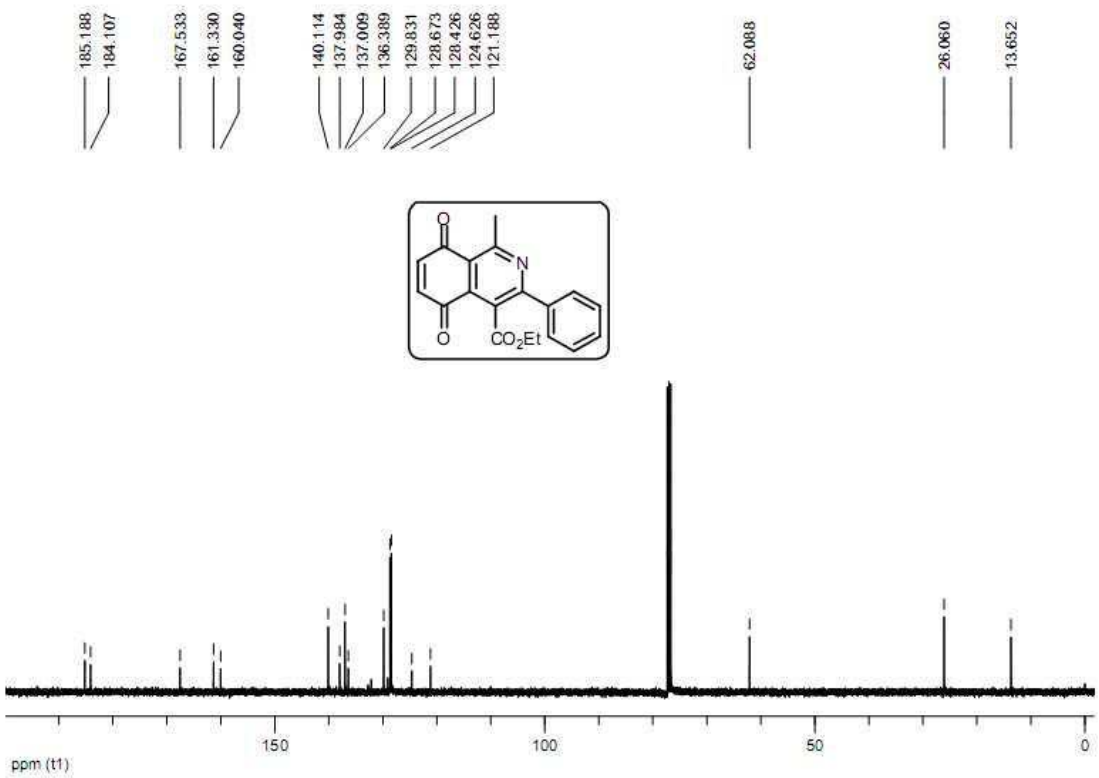
28m ^{13}C NMR ($CDCl_3$, 100 MHz)



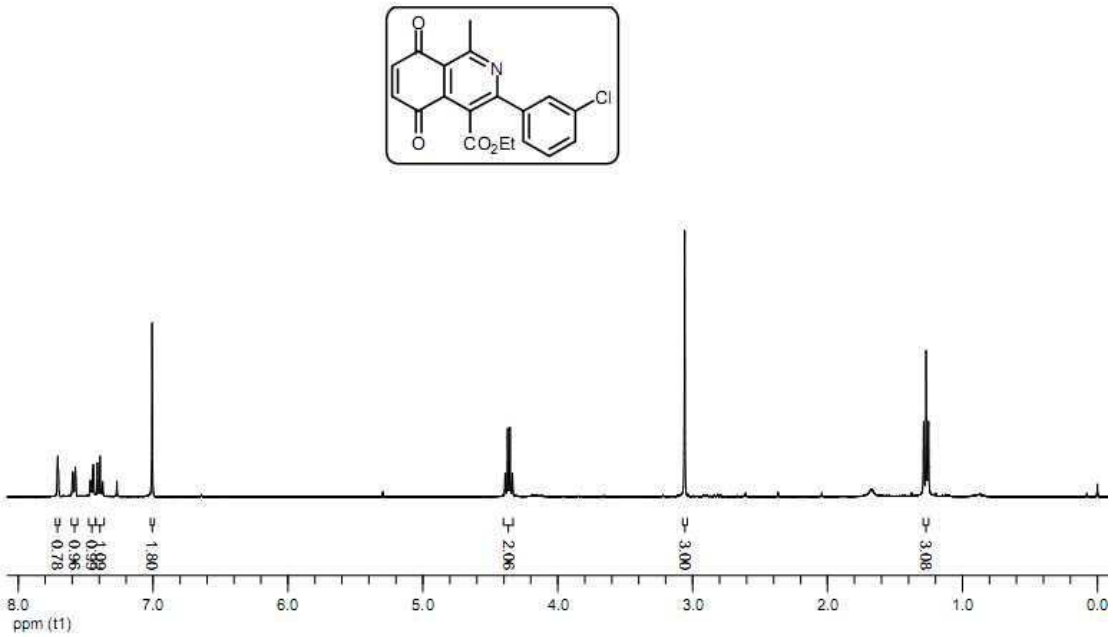
28n ^{1}H NMR ($CDCl_3$, 400 MHz)



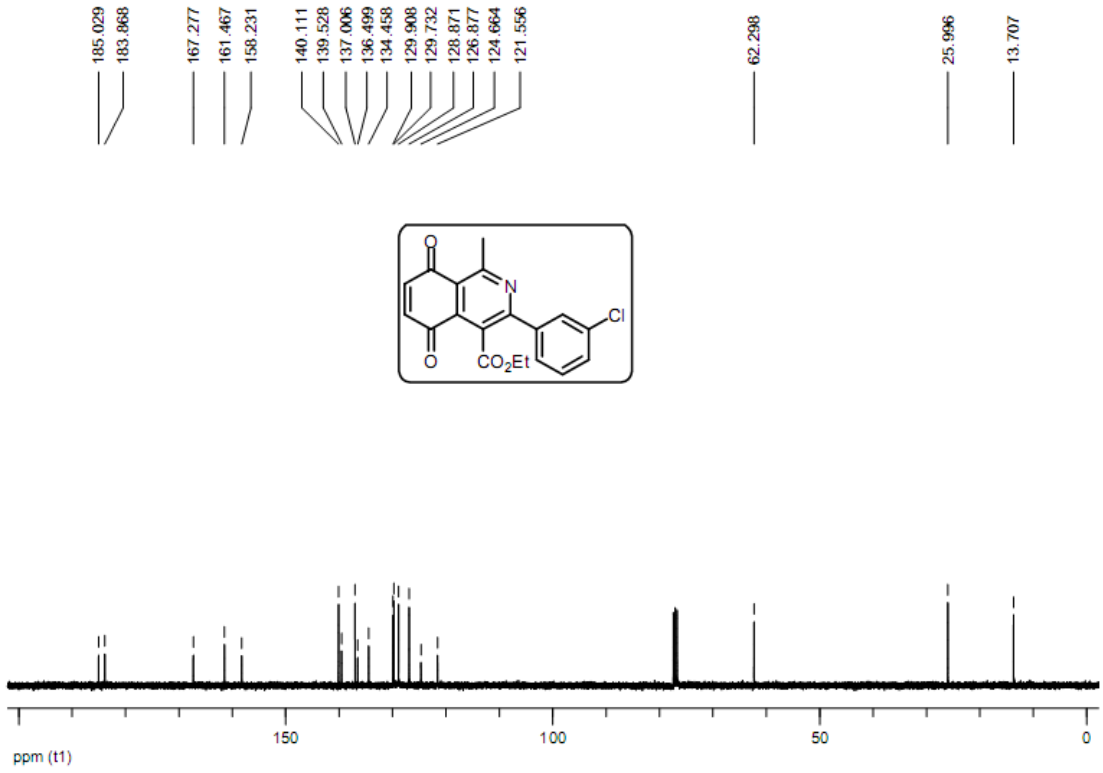
28n ^{13}C NMR ($CDCl_3$, 100 MHz)



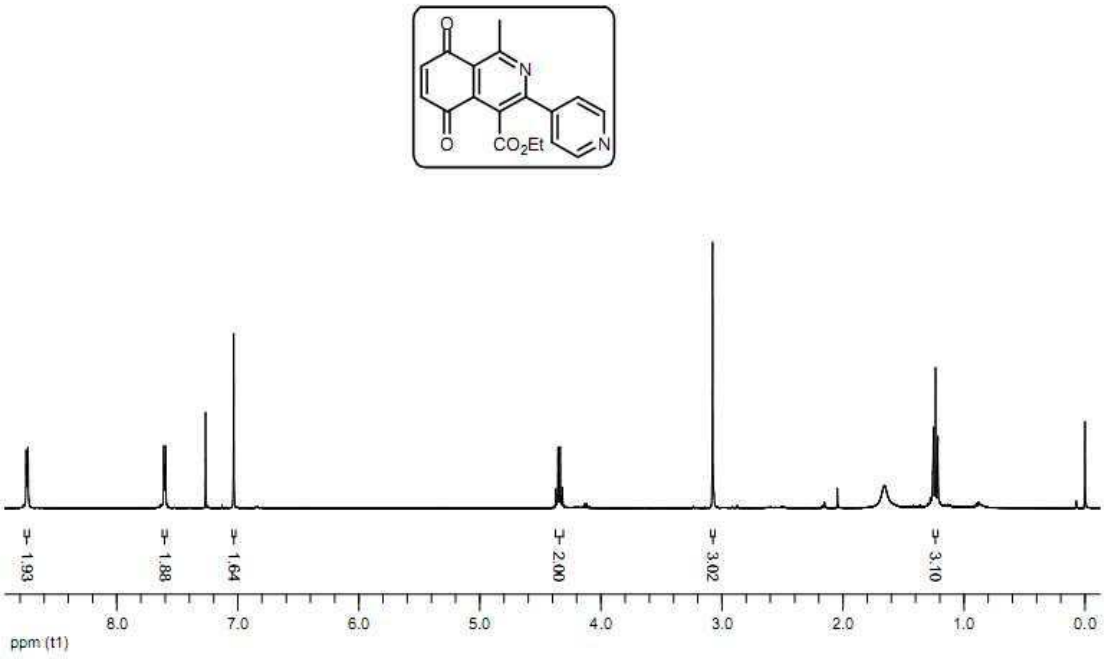
28o ^{1}H NMR ($CDCl_3$, 400 MHz)



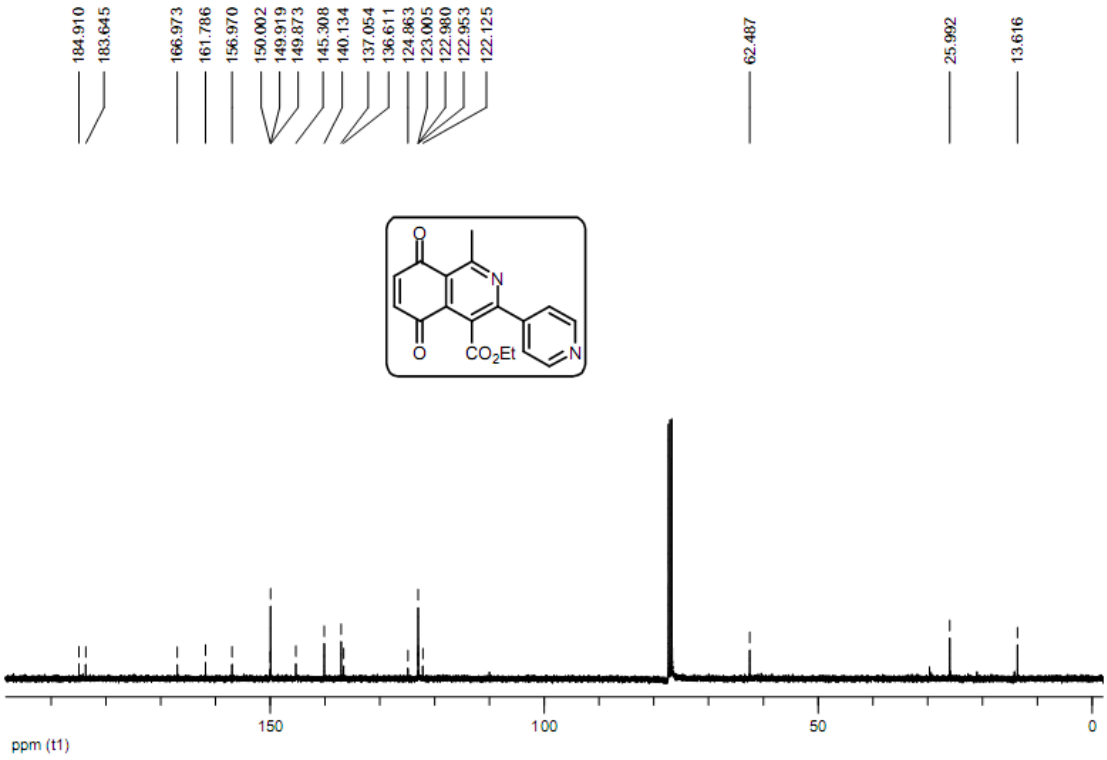
28o ^{13}C NMR ($CDCl_3$, 100 MHz)



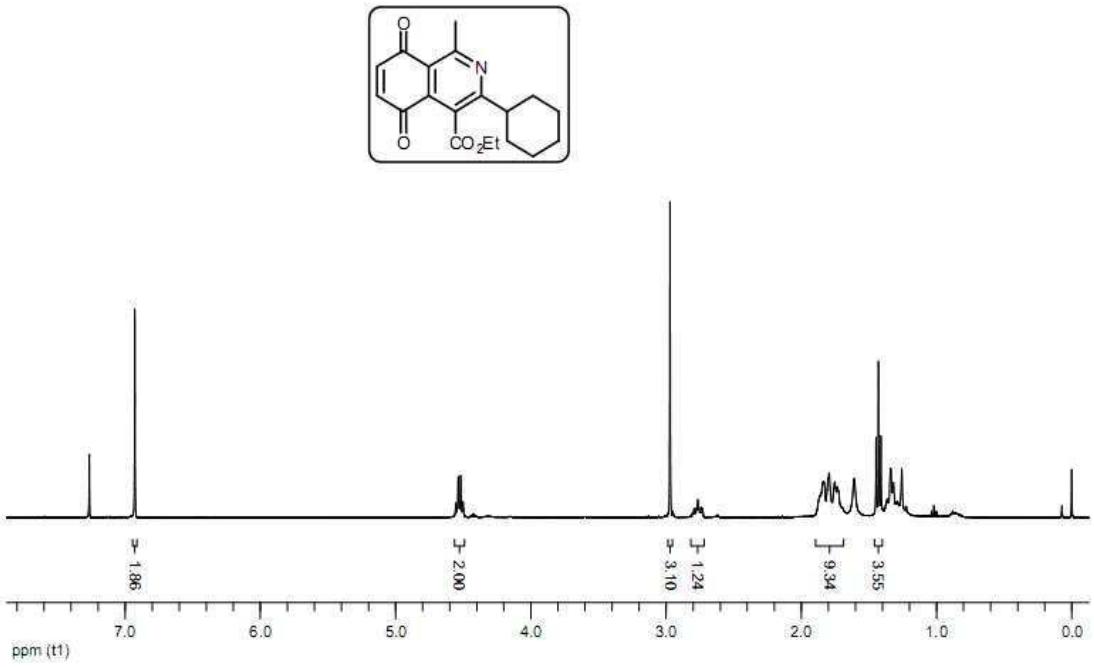
28p ^{1}H NMR ($CDCl_3$, 400 MHz)



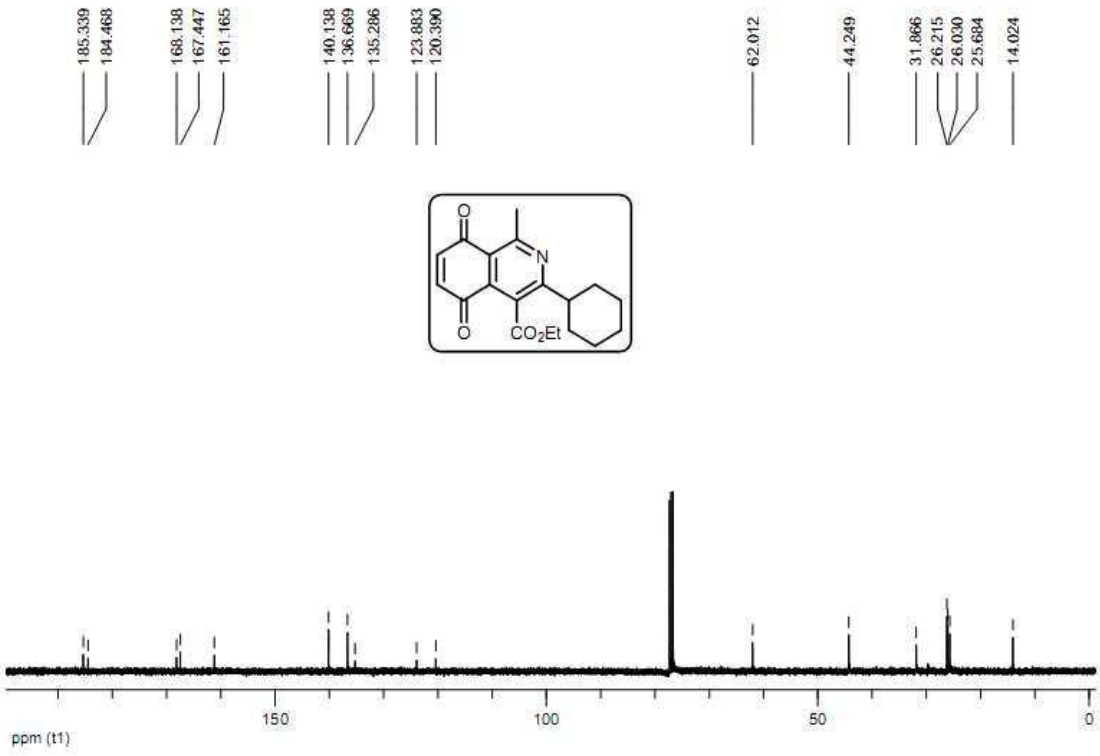
28p ^{13}C NMR ($CDCl_3$, 100 MHz)



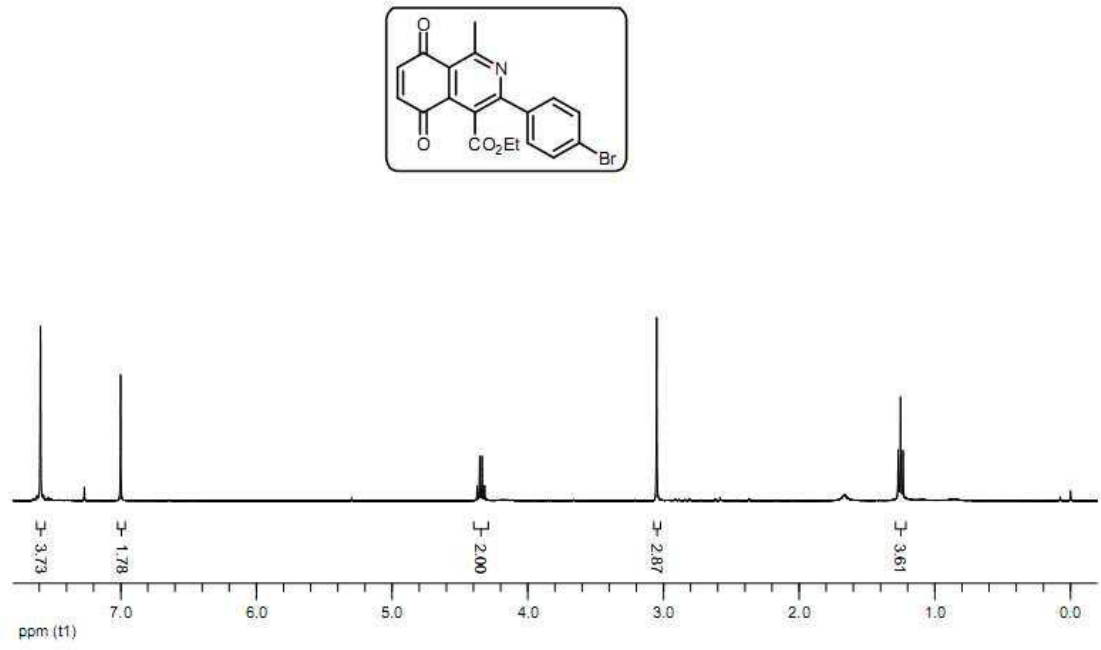
28q ^{1}H NMR ($CDCl_3$, 400 MHz)



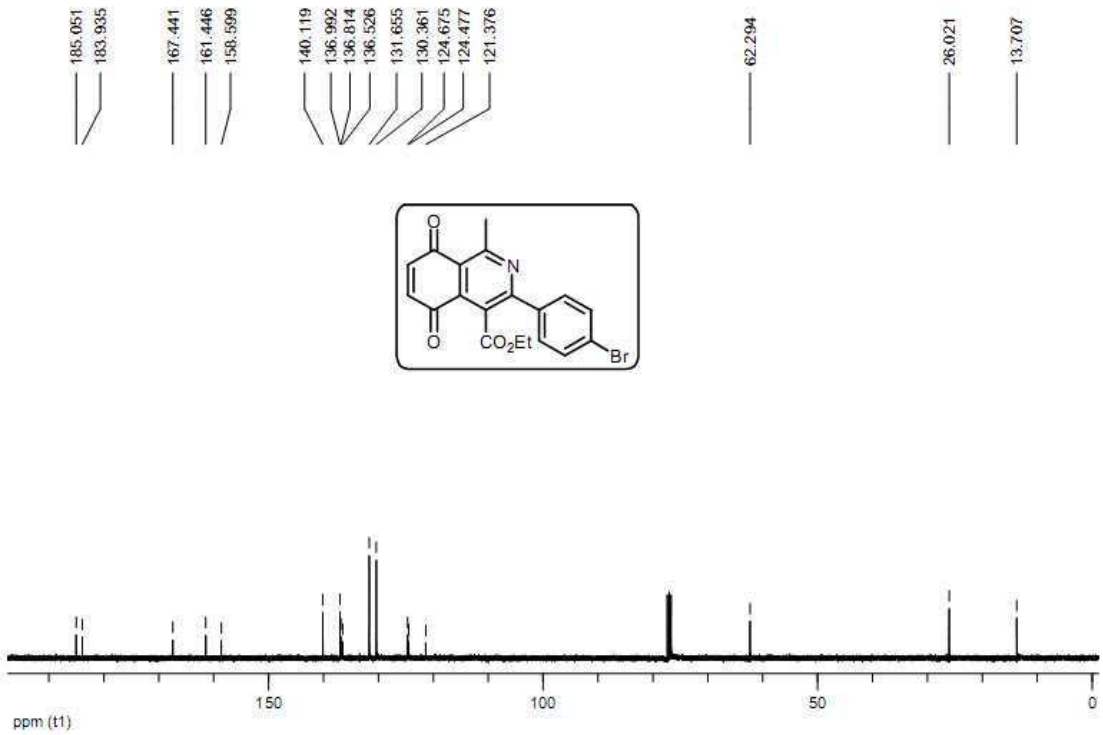
28q ^{13}C NMR ($CDCl_3$, 100 MHz)



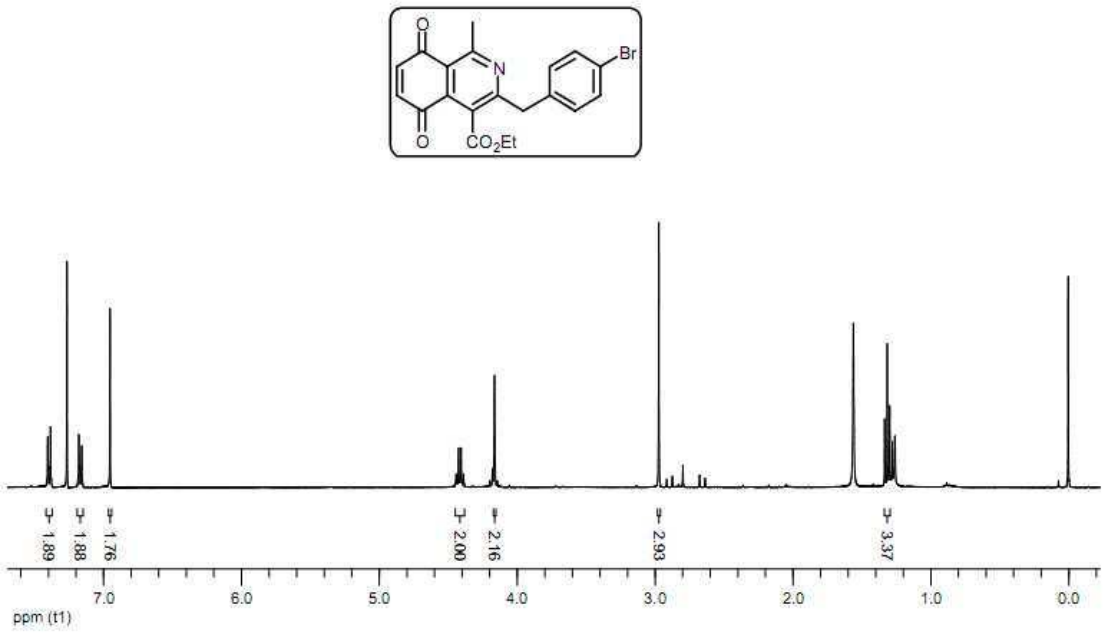
28r ^{1}H NMR ($CDCl_3$, 400 MHz)



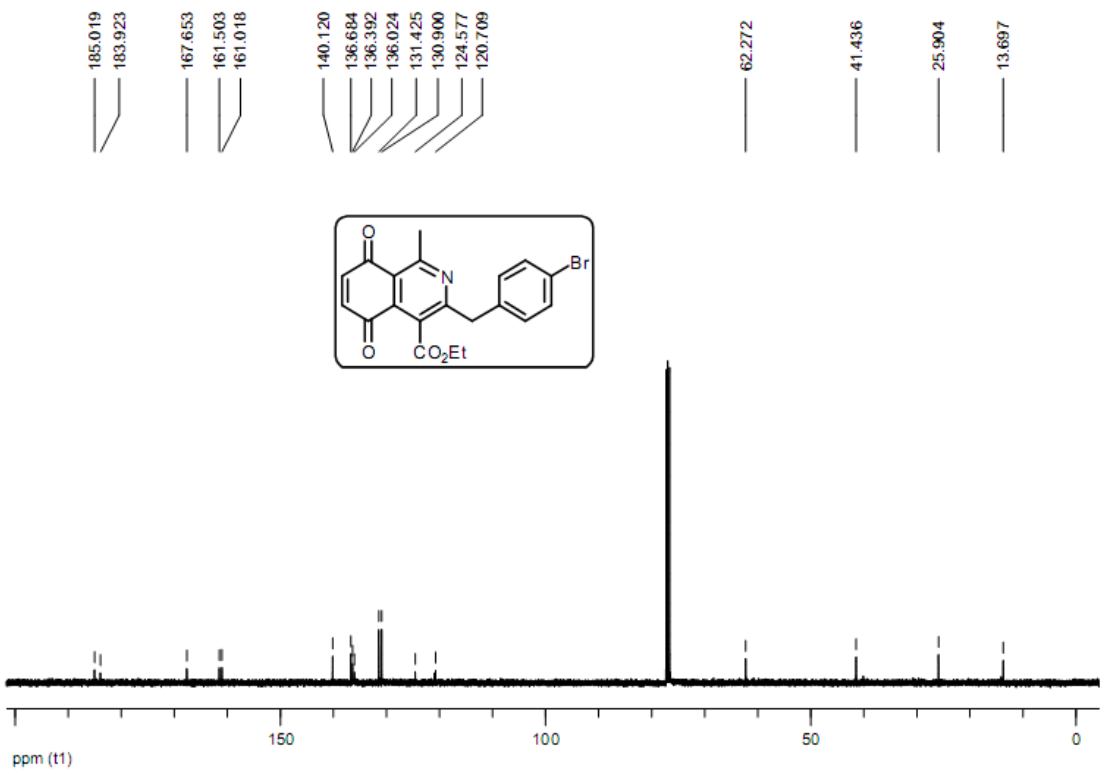
28r ^{13}C NMR ($CDCl_3$, 100 MHz)



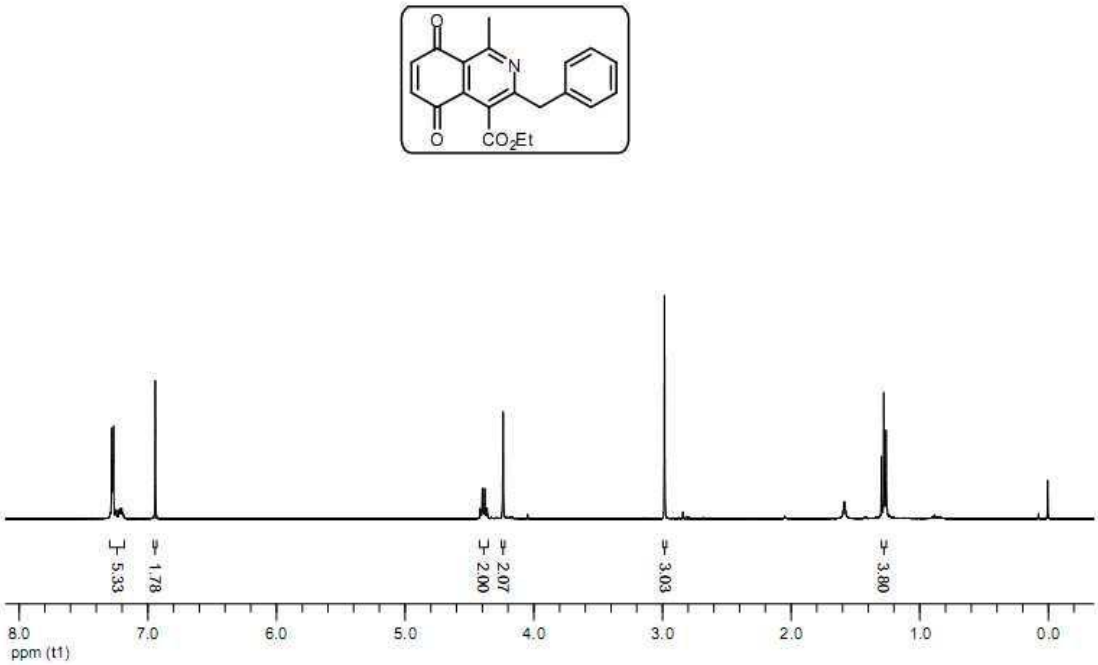
28s ^{1}H NMR ($CDCl_3$, 400 MHz)



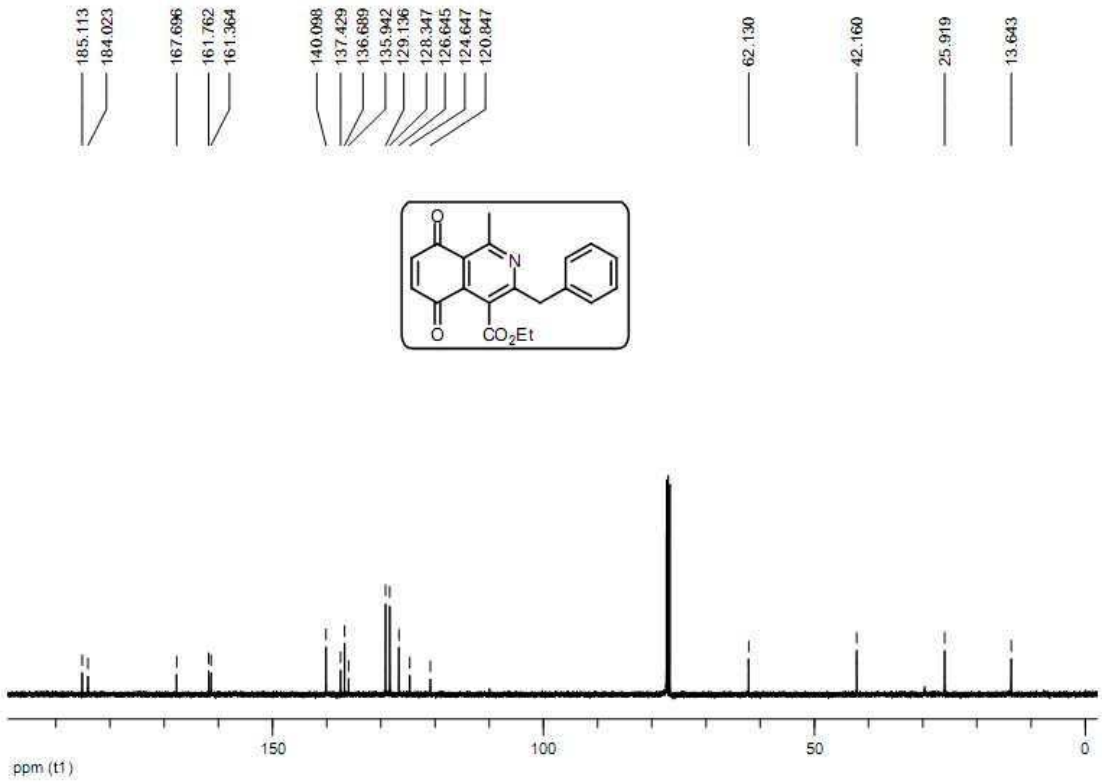
28s ^{13}C NMR ($CDCl_3$, 100 MHz)



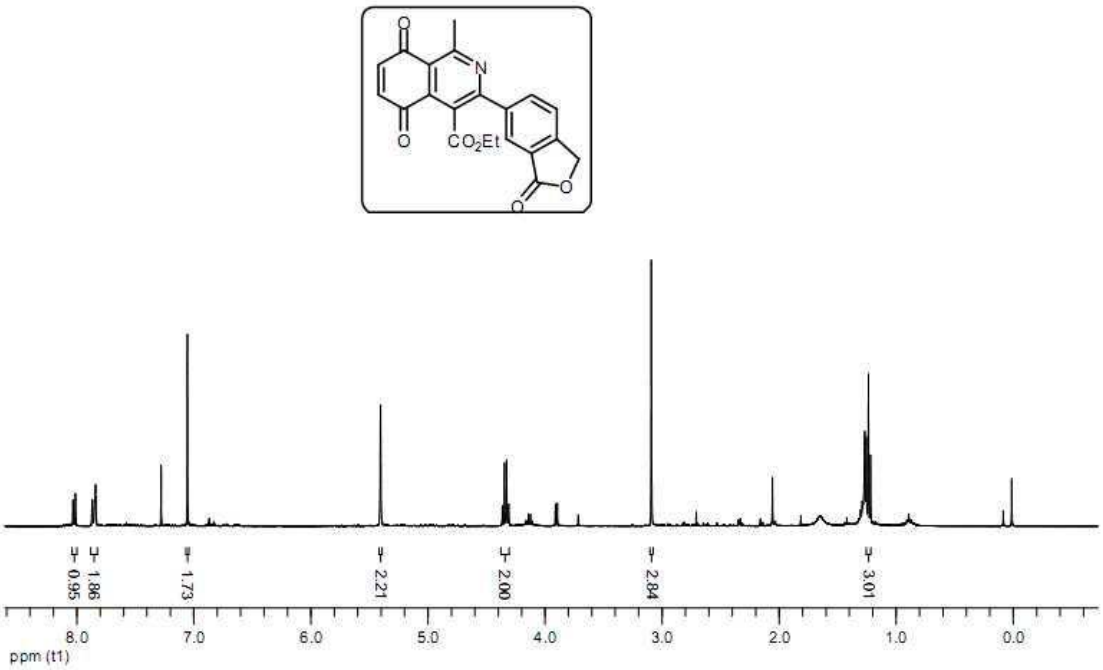
28t ^{1}H NMR ($CDCl_3$, 400 MHz)



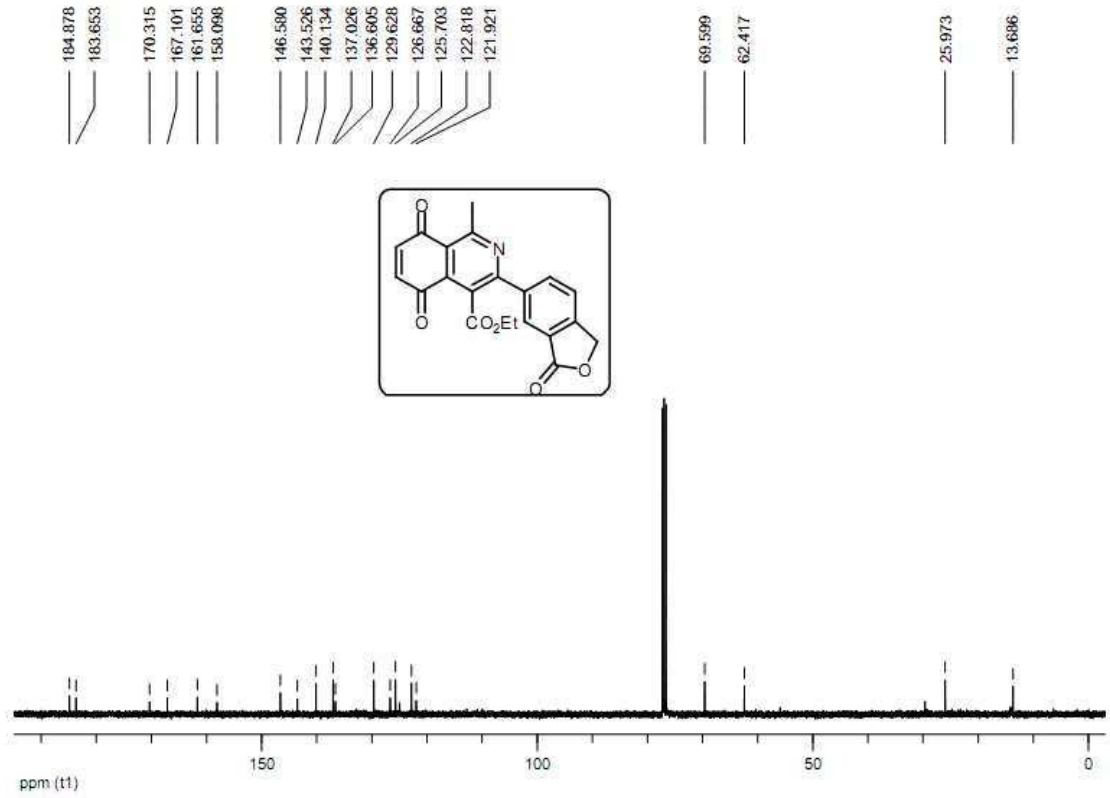
28t ^{13}C NMR ($CDCl_3$, 100 MHz)



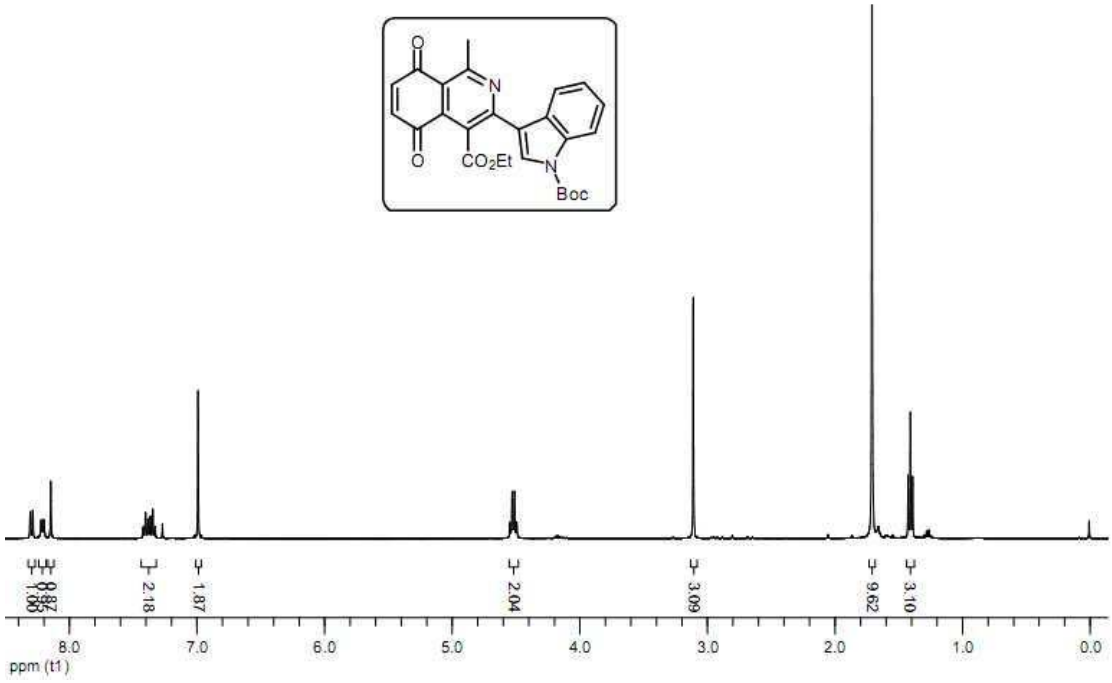
28u ^{1}H NMR ($CDCl_3$, 400 MHz)



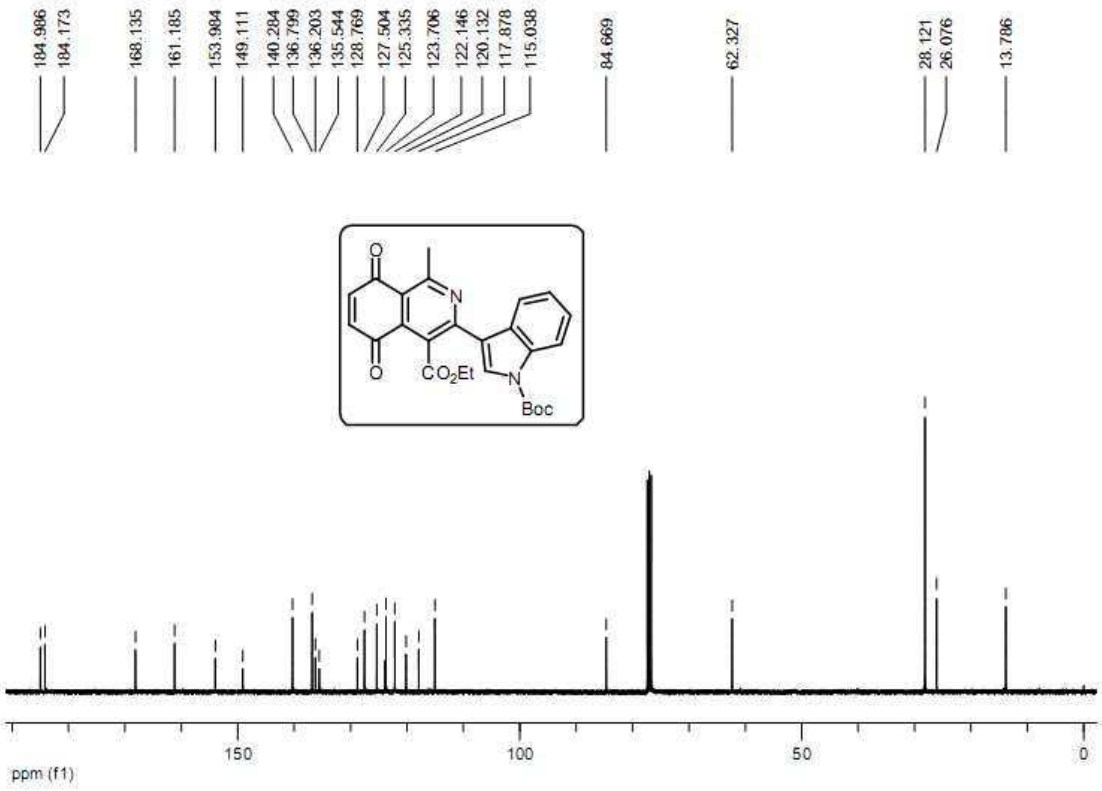
28u ^{13}C NMR ($CDCl_3$, 100 MHz)



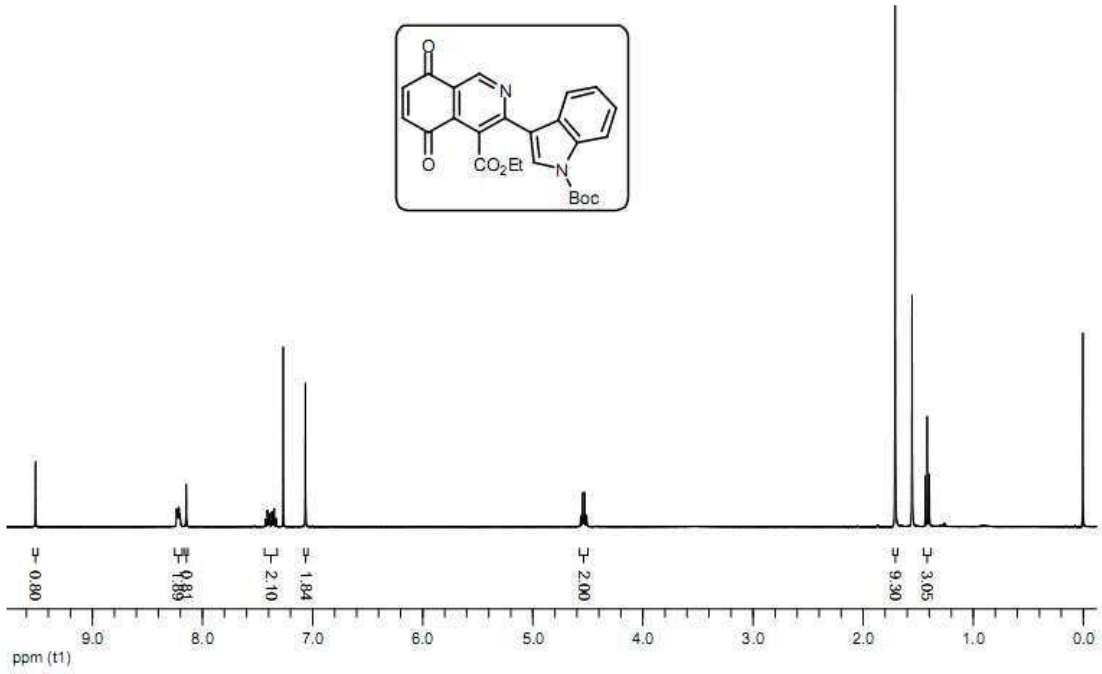
28v ^{1}H NMR ($CDCl_3$, 400 MHz)



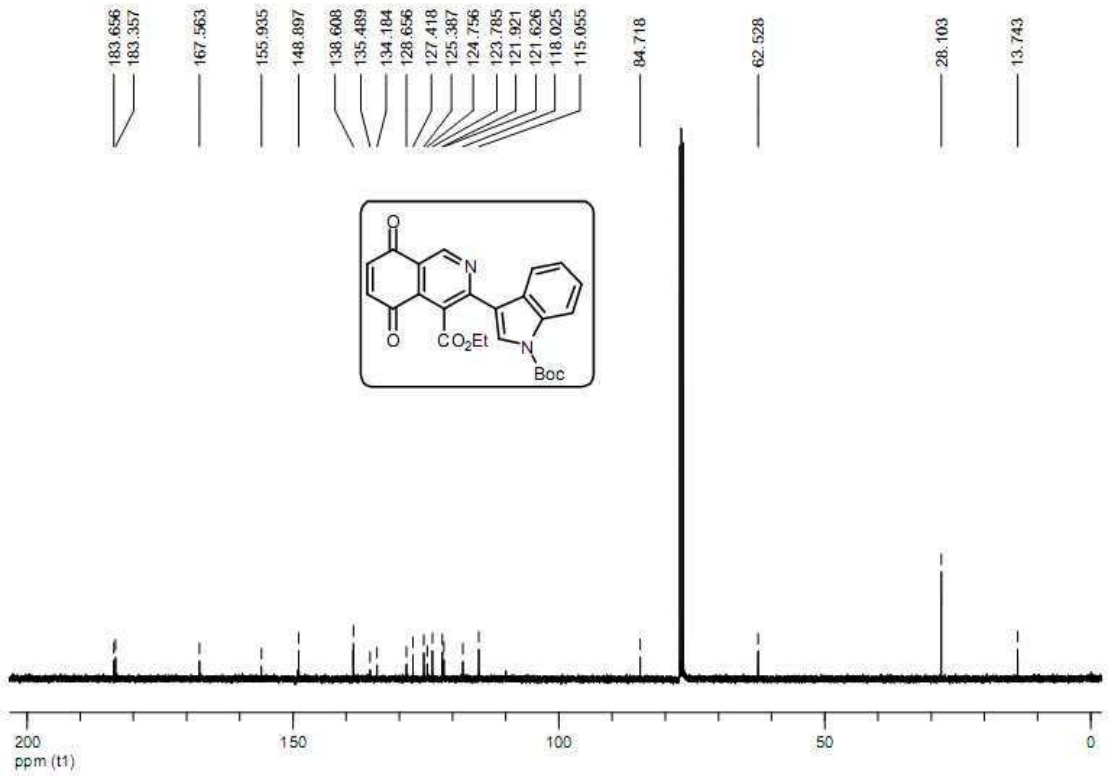
28v ^{13}C NMR ($CDCl_3$, 100 MHz)



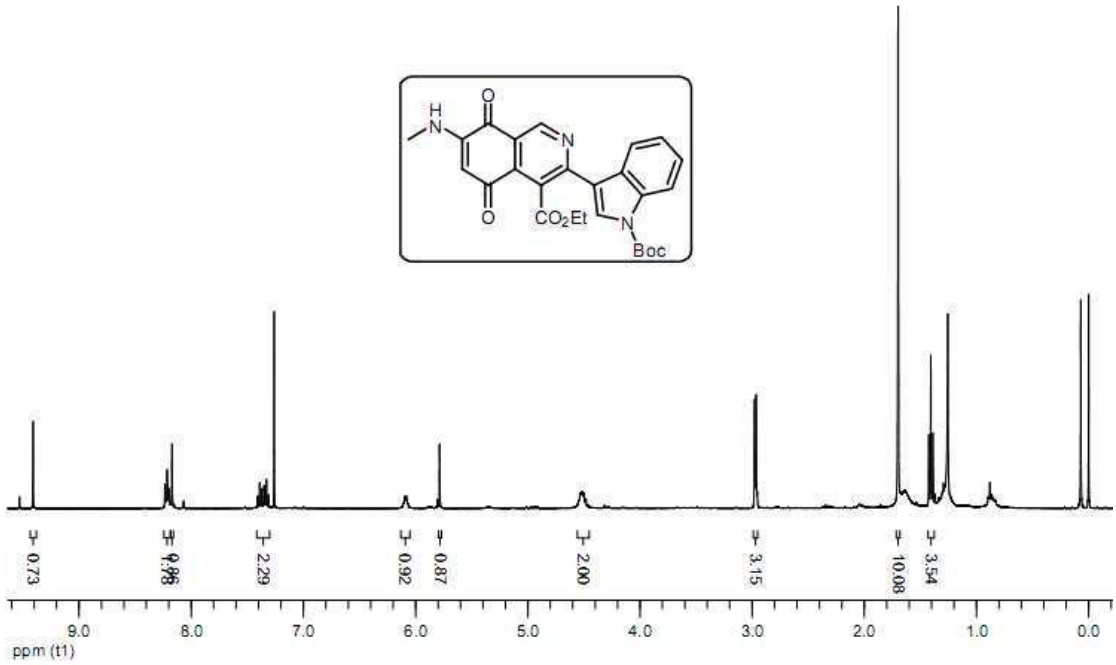
28w ^{1}H NMR ($CDCl_3$, 400 MHz)



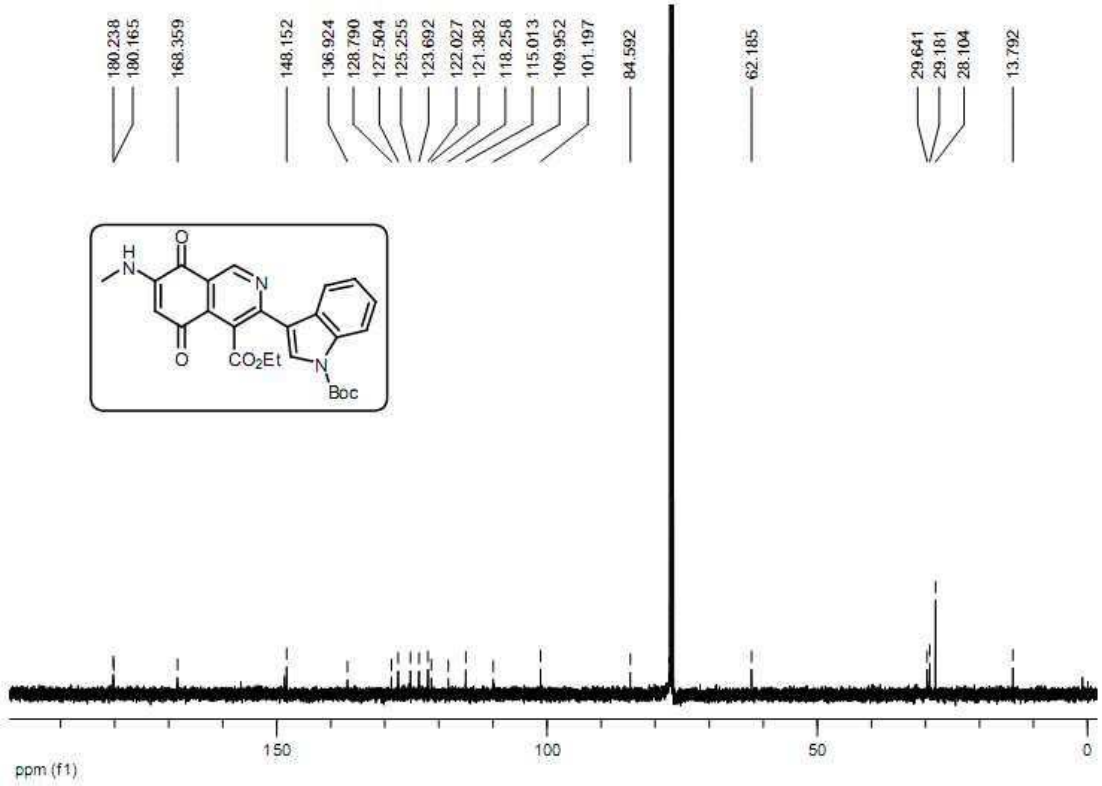
28w ^{13}C NMR ($CDCl_3$, 100 MHz)



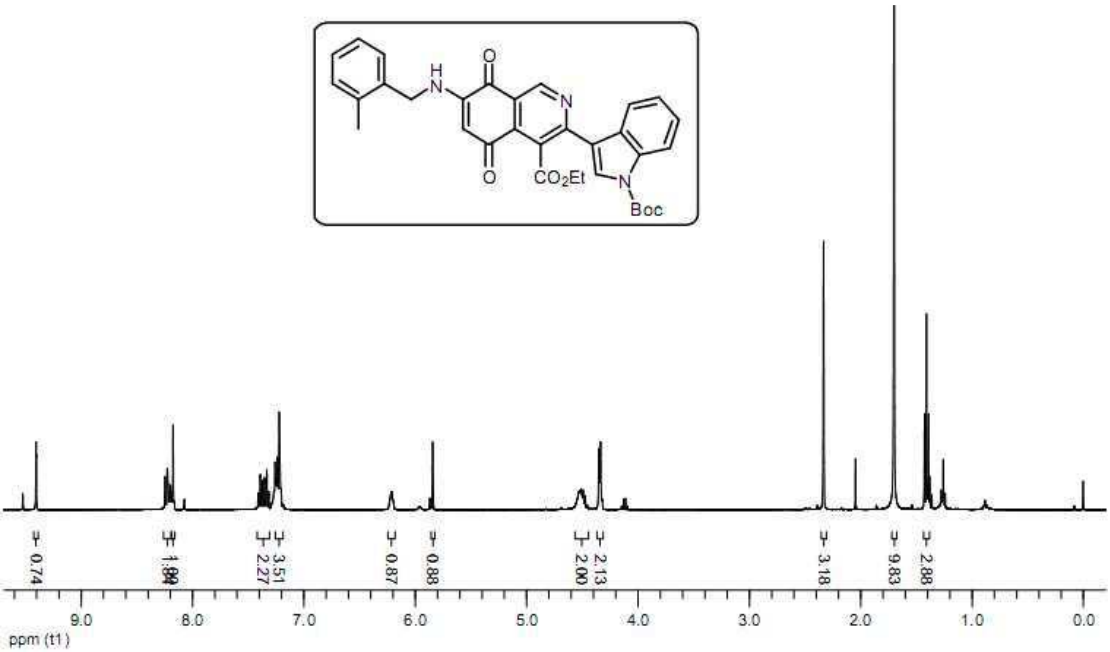
31a ^{1}H NMR ($CDCl_3$, 400 MHz)



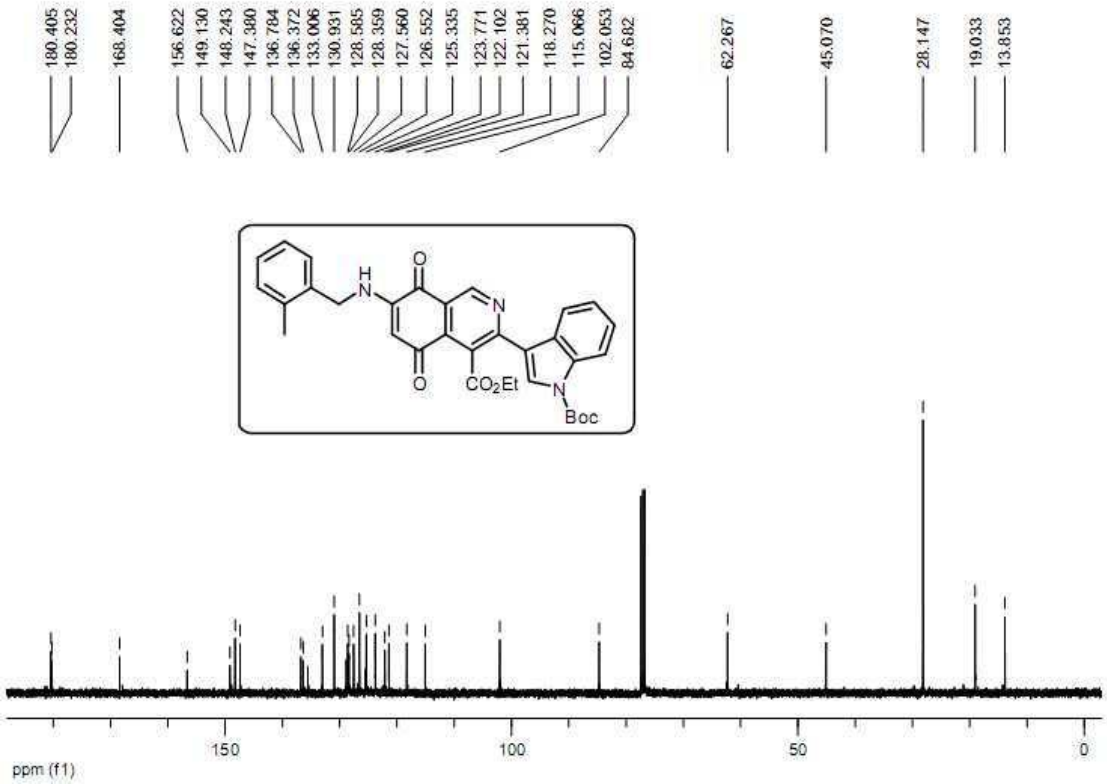
31a ^{13}C NMR ($CDCl_3$, 100 MHz)



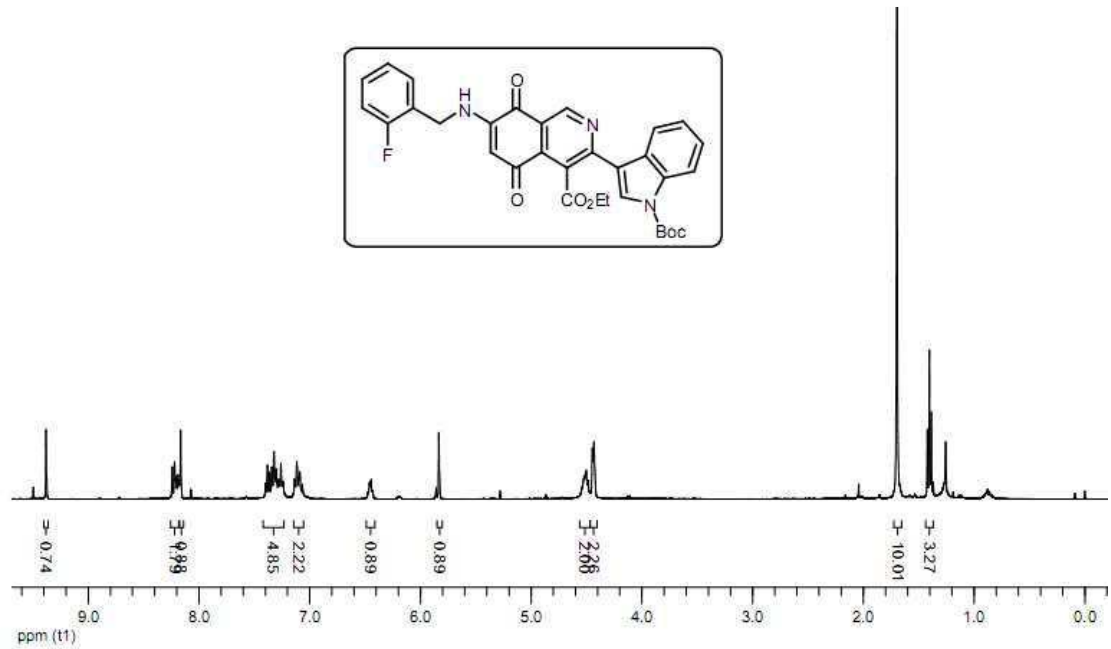
31b ^{1}H NMR ($CDCl_3$, 400 MHz)



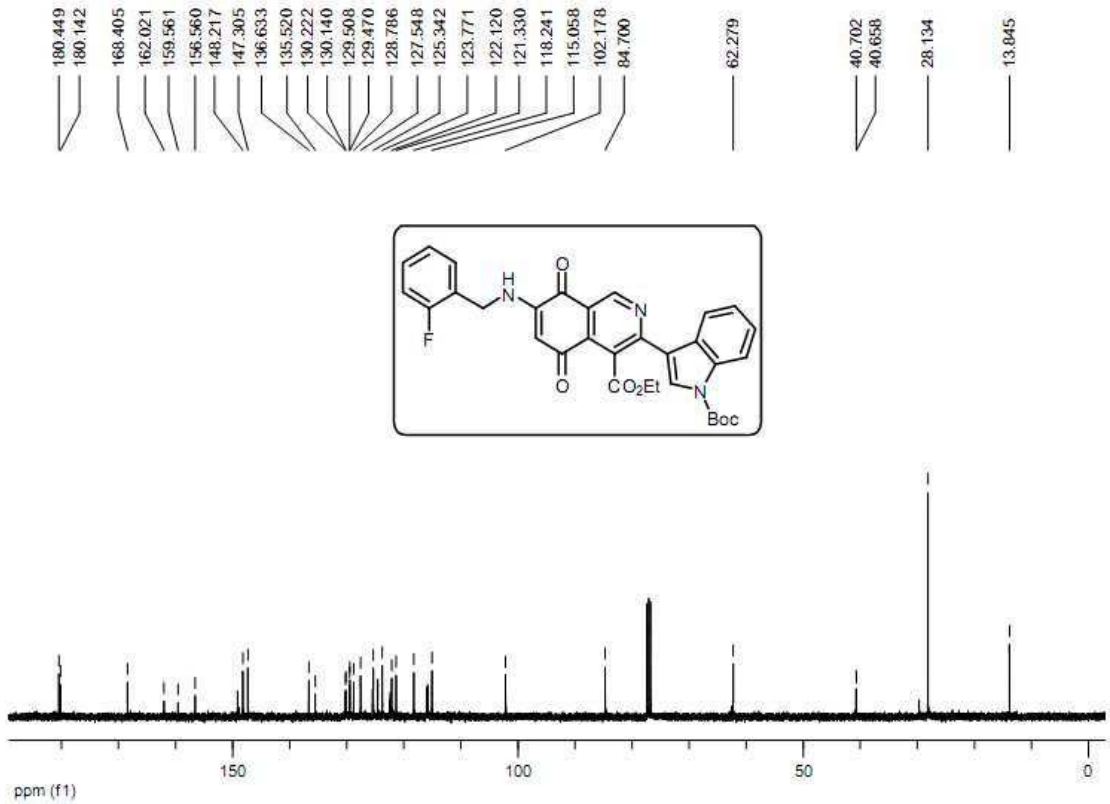
31b ^{13}C NMR ($CDCl_3$, 100 MHz)



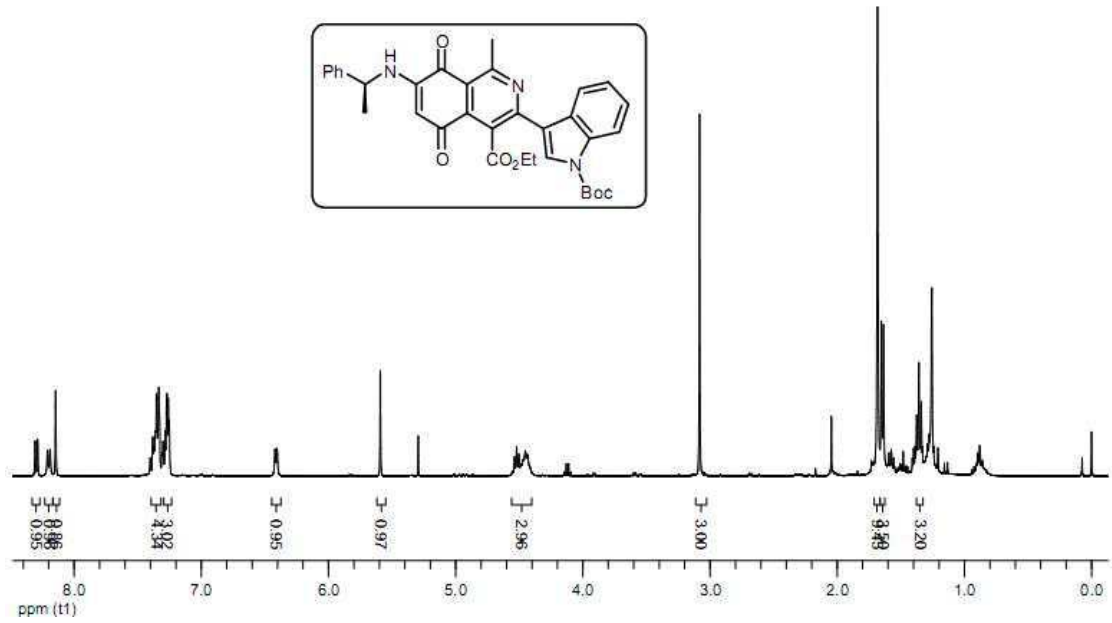
31c ^{1}H NMR ($CDCl_3$, 400 MHz)



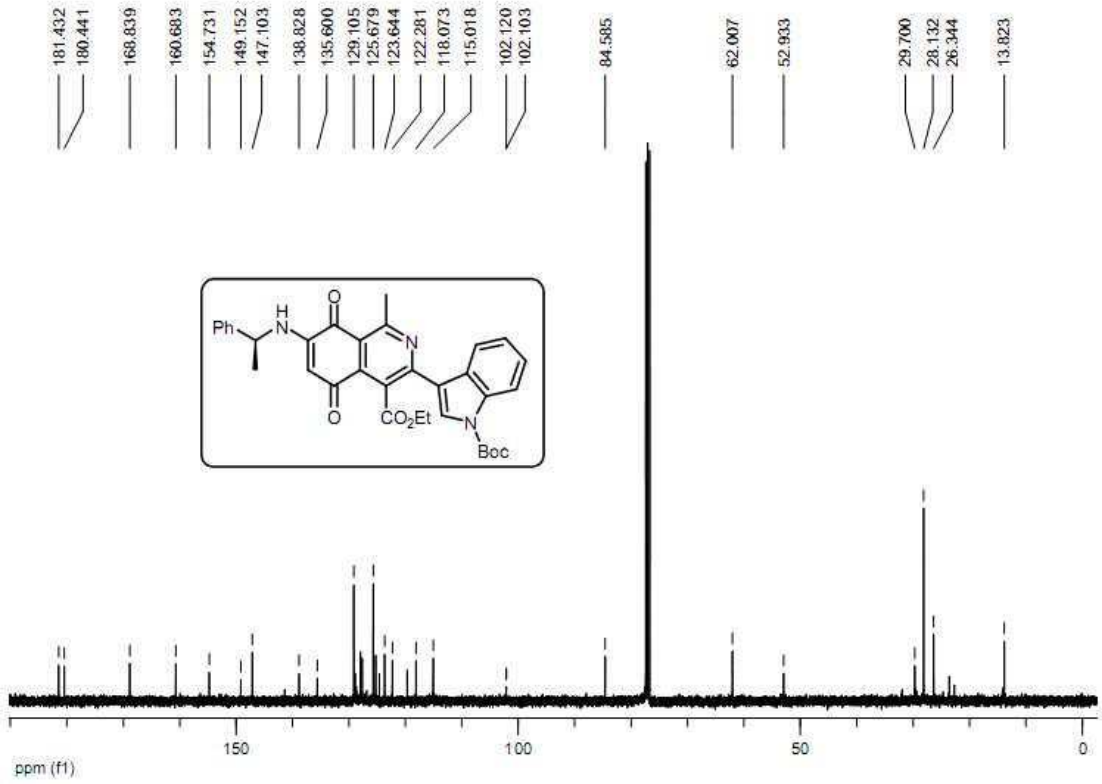
31c ^{13}C NMR ($CDCl_3$, 100 MHz)



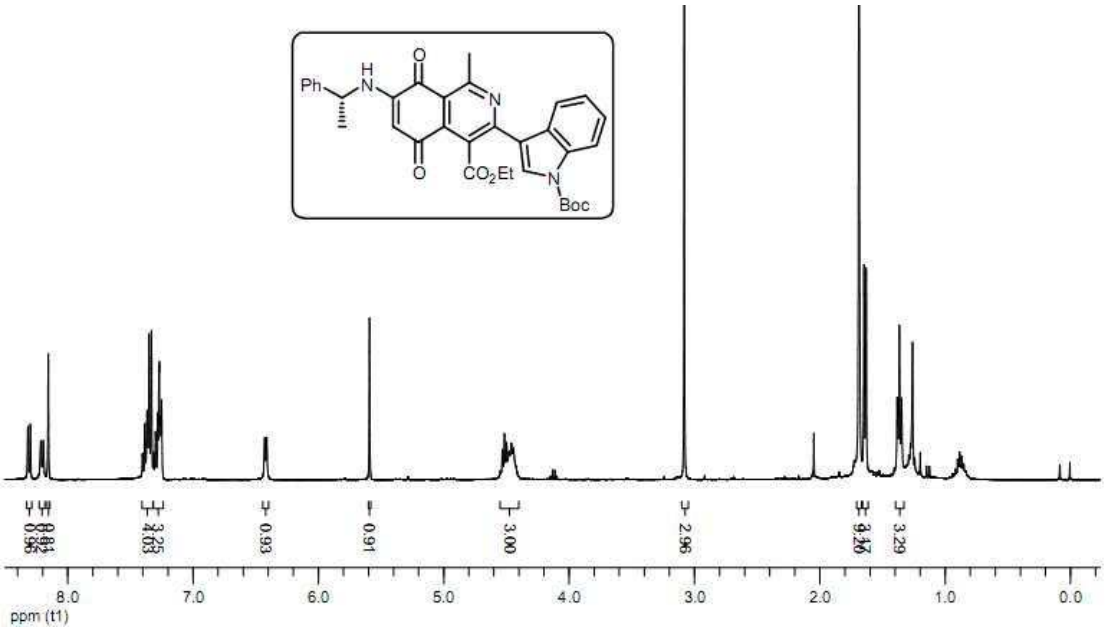
31e ^{1}H NMR ($CDCl_3$, 400 MHz)



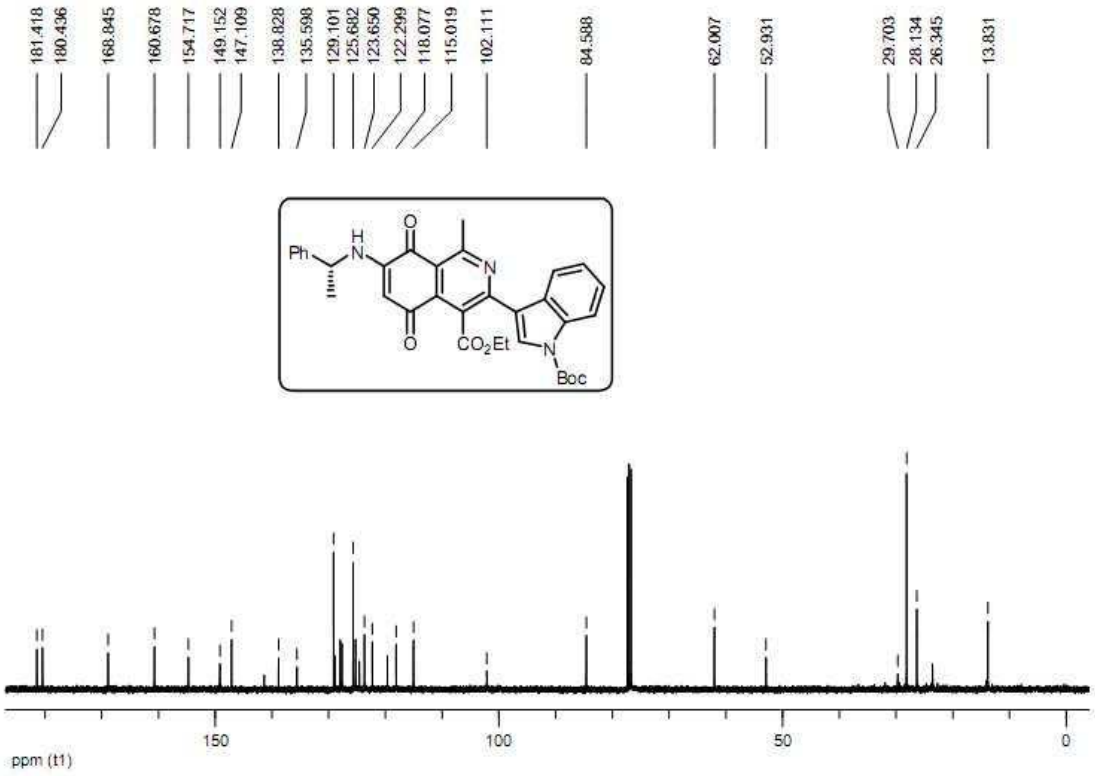
31e ^{13}C NMR ($CDCl_3$, 100 MHz)



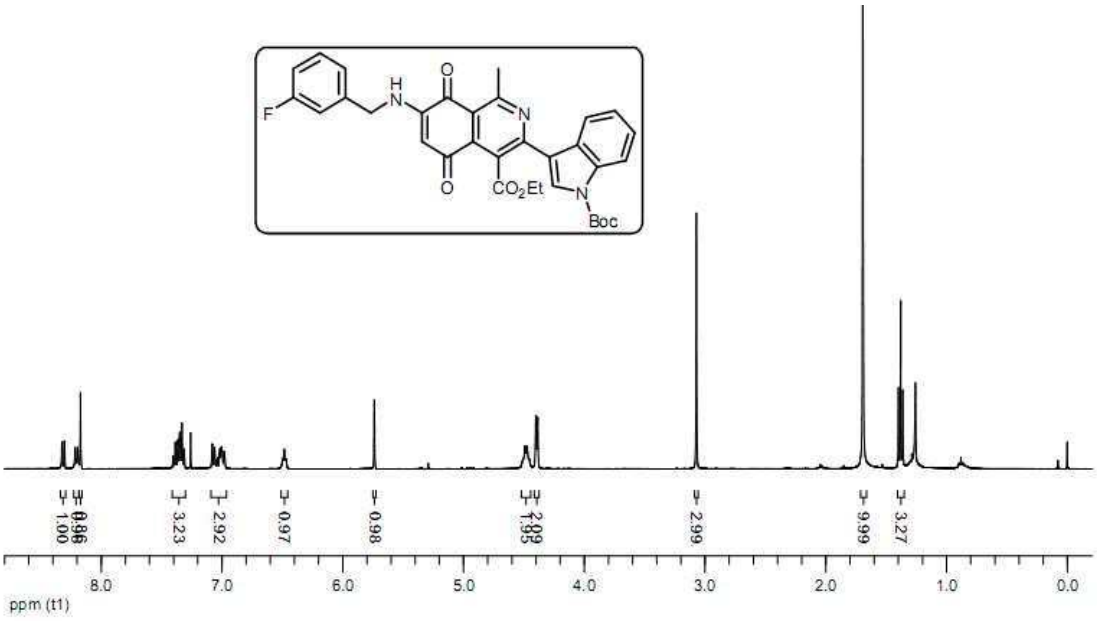
31f ^{1}H NMR ($CDCl_3$, 400 MHz)



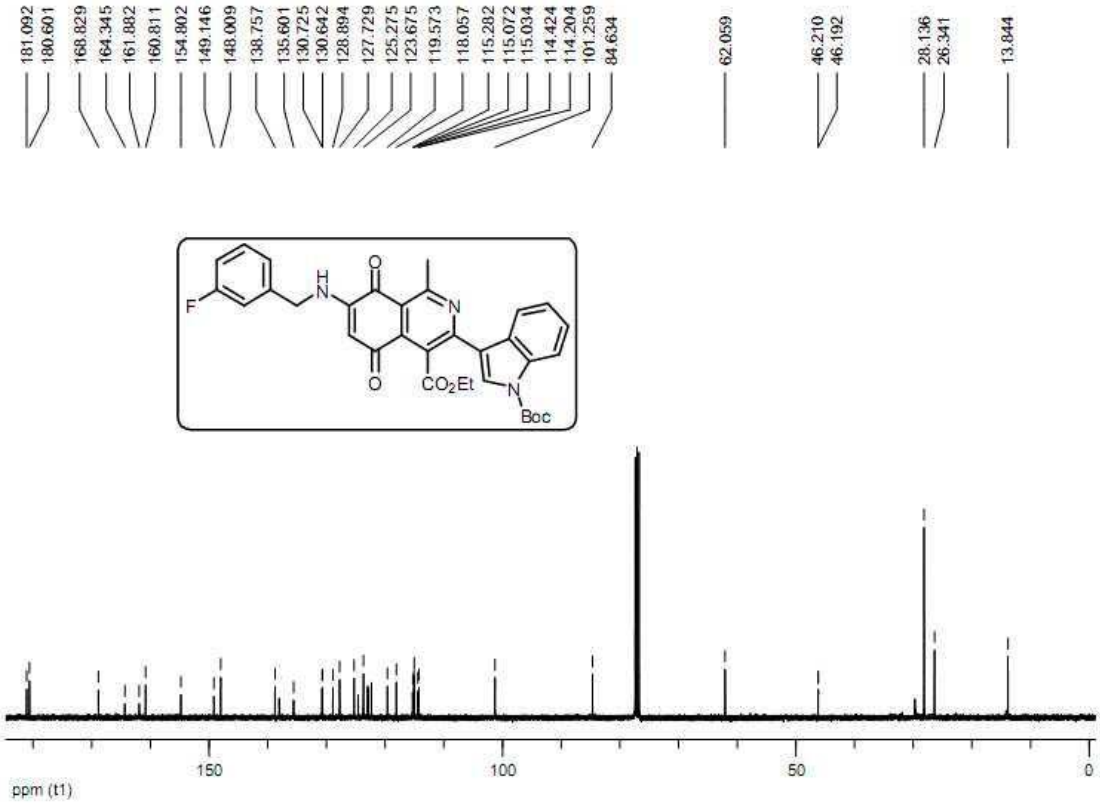
31f ^{13}C NMR ($CDCl_3$, 100 MHz)



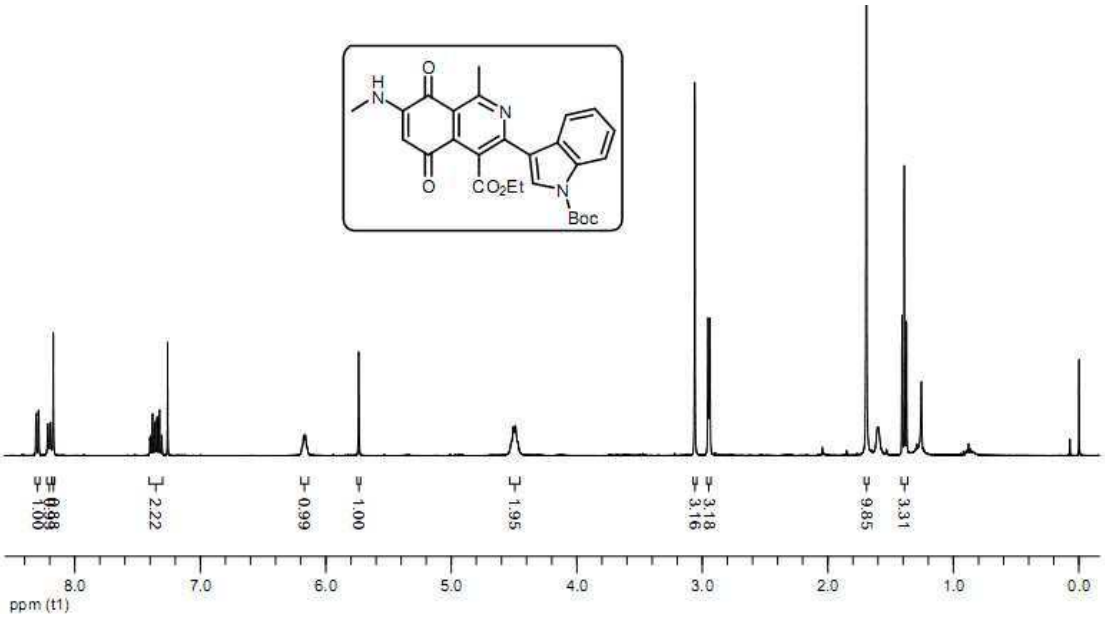
31g ^{1}H NMR ($CDCl_3$, 400 MHz)



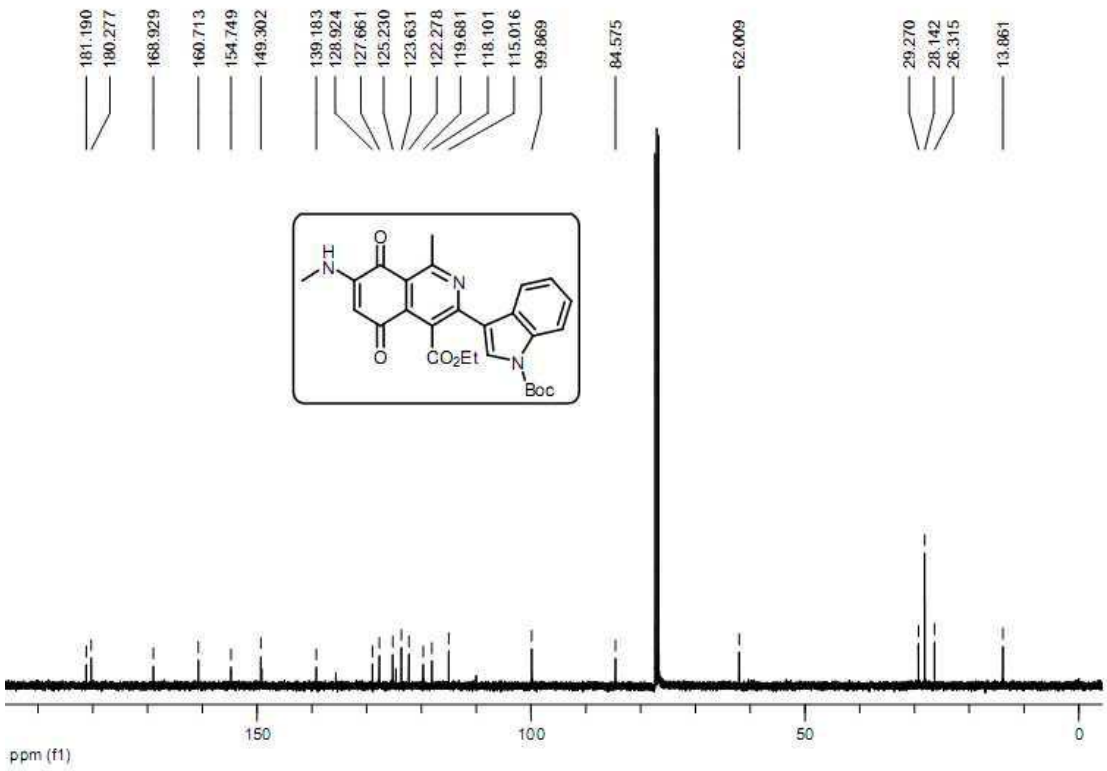
31g ^{13}C NMR ($CDCl_3$, 100 MHz)



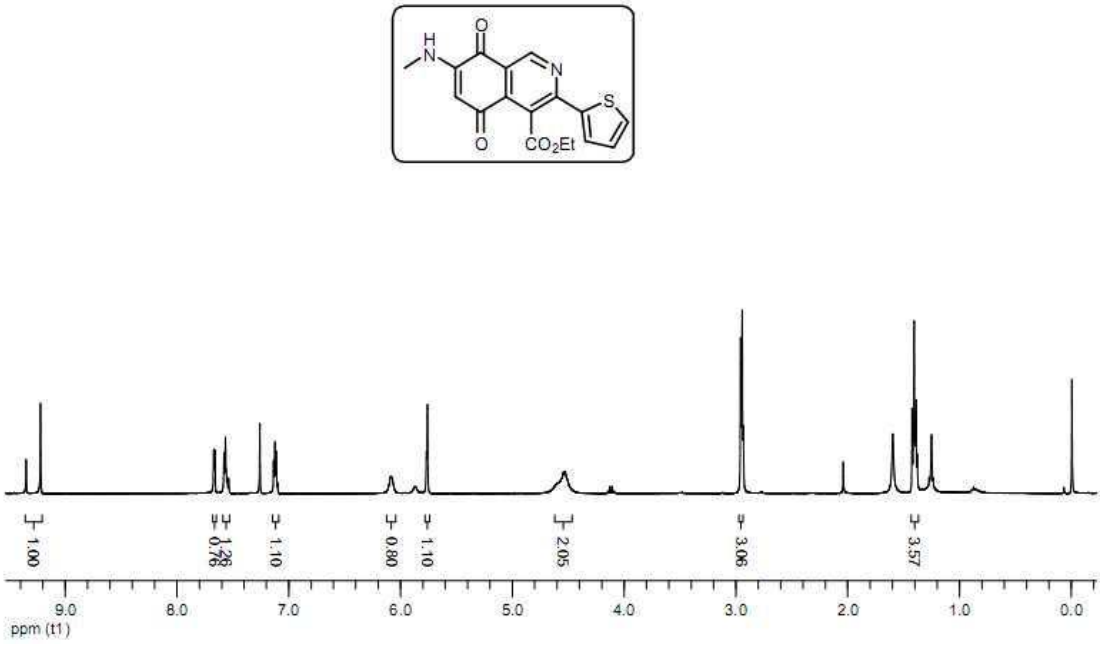
31h ^{1}H NMR ($CDCl_3$, 400 MHz)



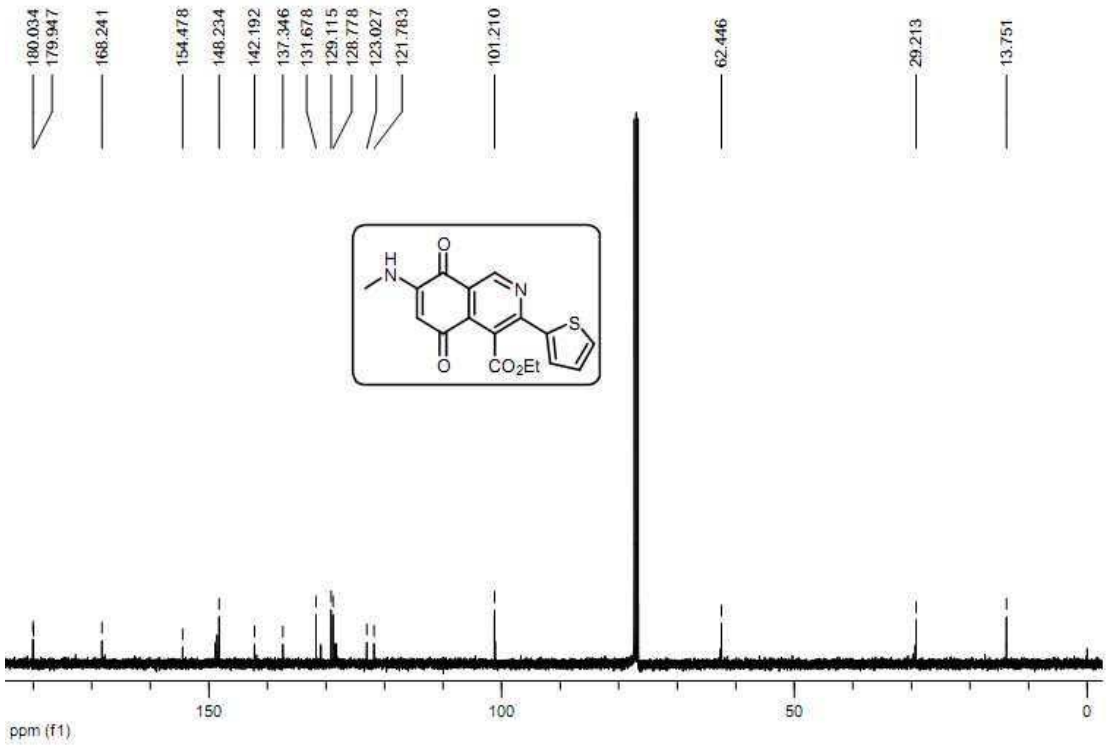
31h ^{13}C NMR ($CDCl_3$, 100 MHz)



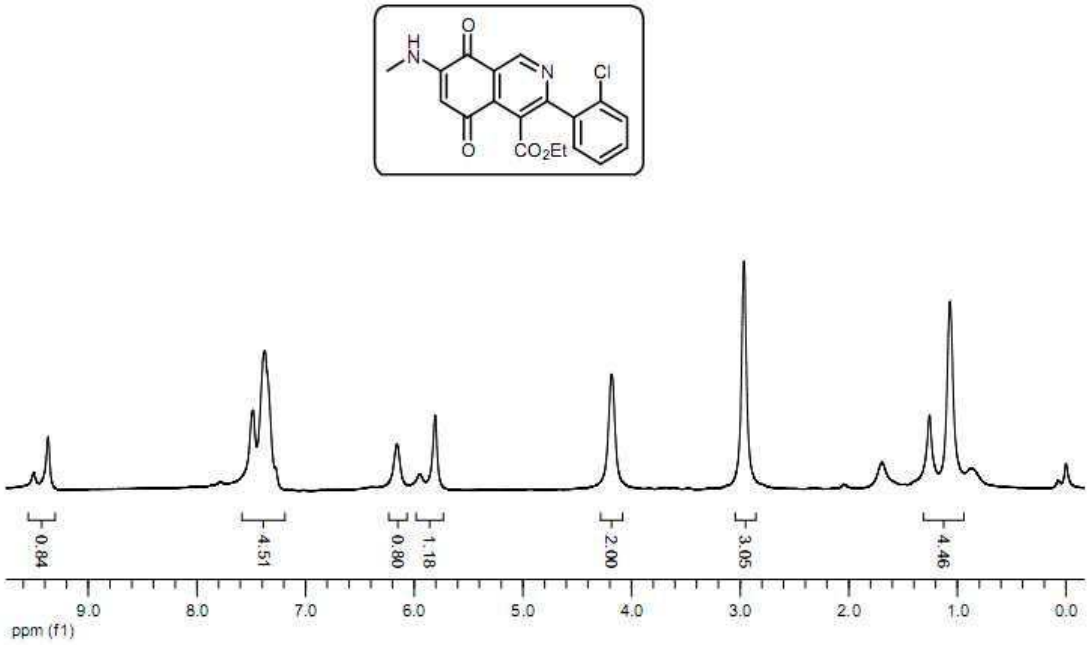
31i ^{1}H NMR ($CDCl_3$, 400 MHz)



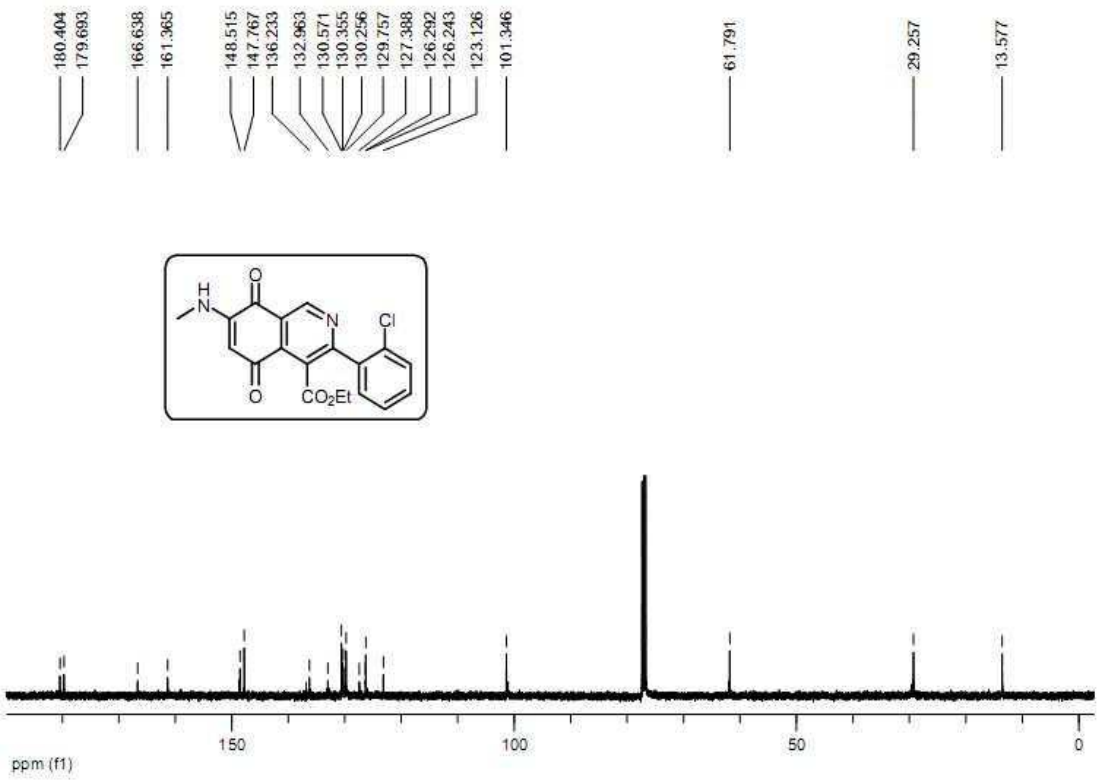
31i ^{13}C NMR ($CDCl_3$, 100 MHz)



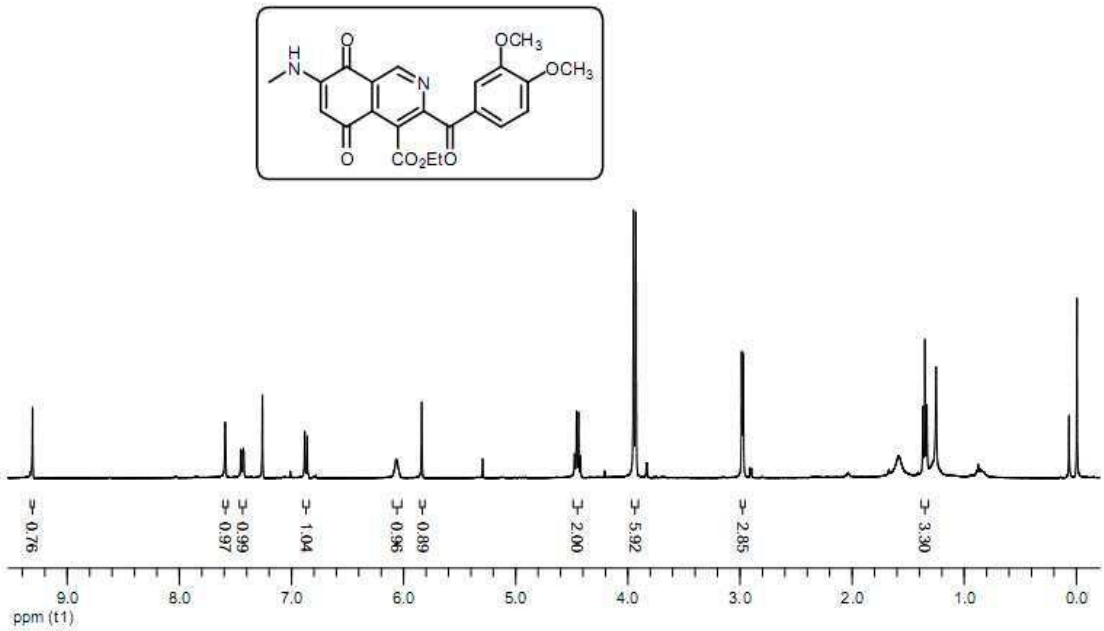
31j ^{1}H NMR ($CDCl_3$, 400 MHz)



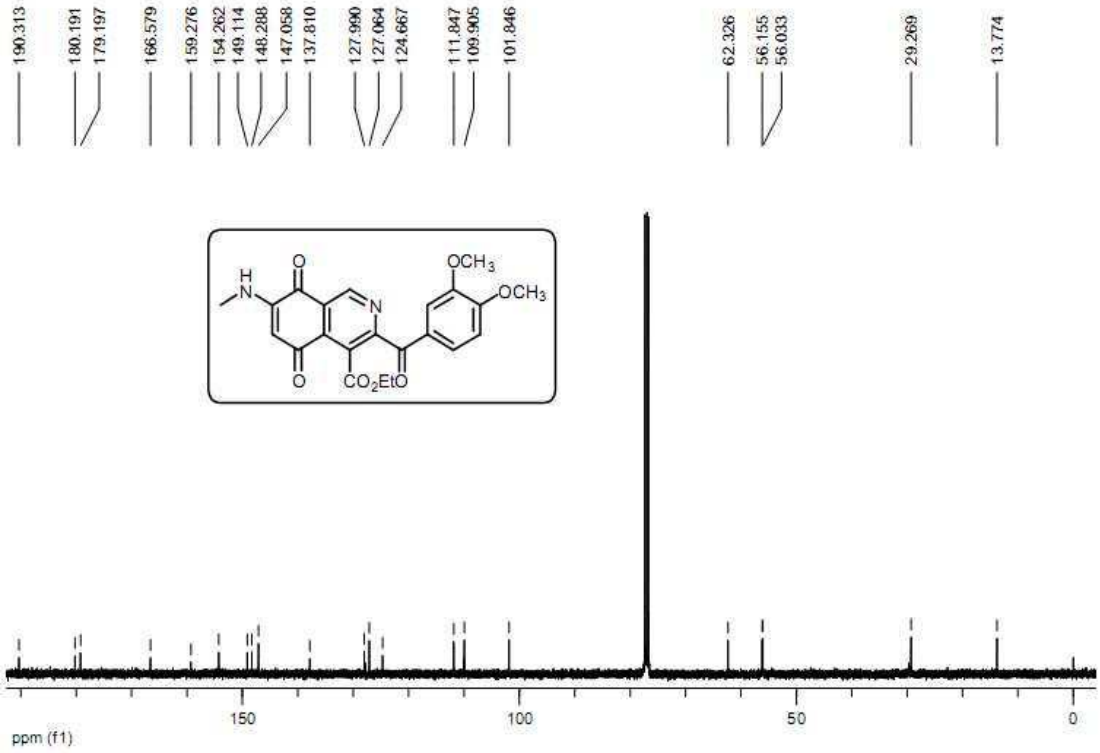
31j ^{13}C NMR ($CDCl_3$, 100 MHz)



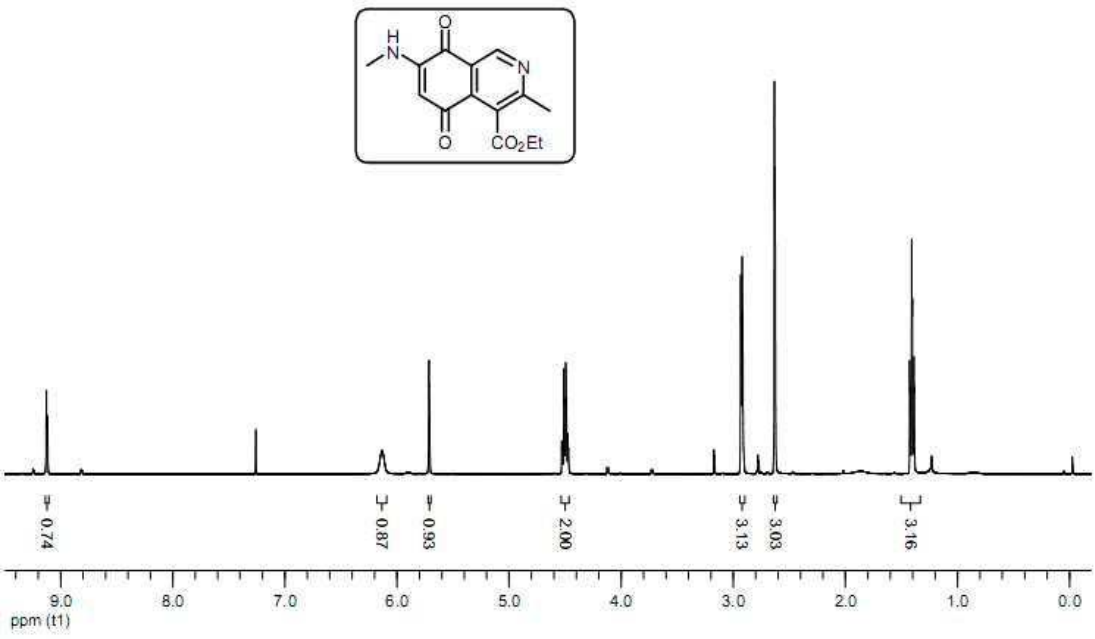
31k ^{1}H NMR ($CDCl_3$, 400 MHz)



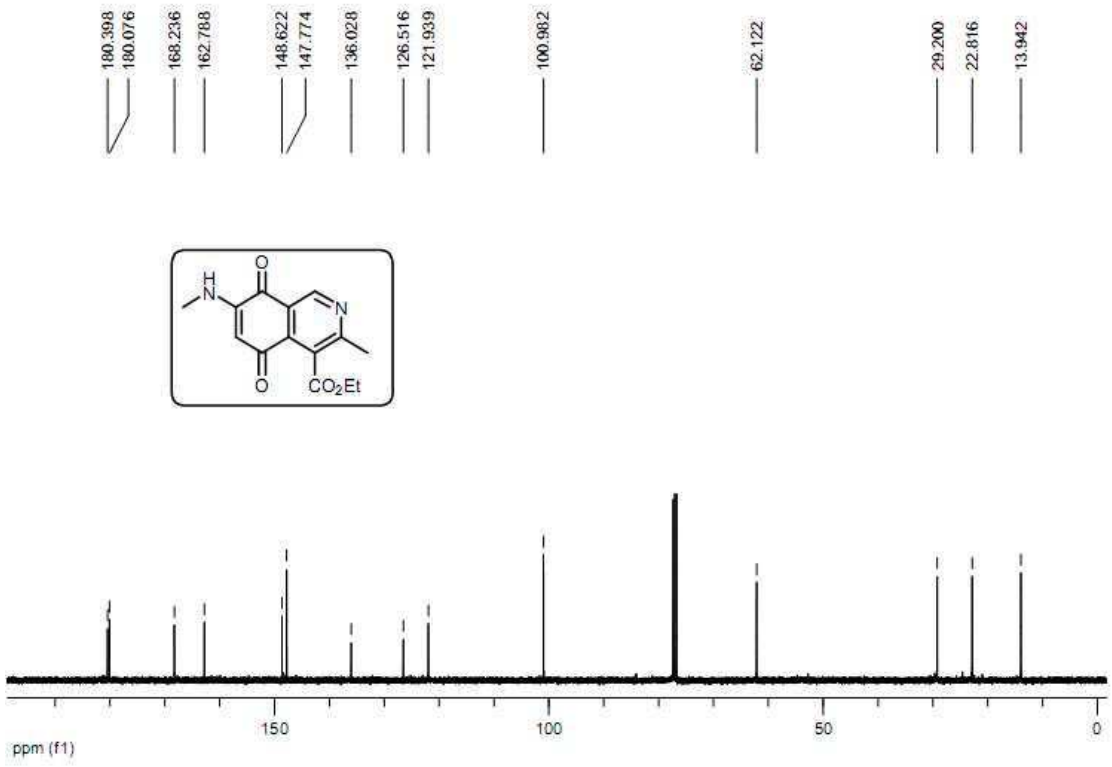
31k ^{13}C NMR ($CDCl_3$, 100 MHz)



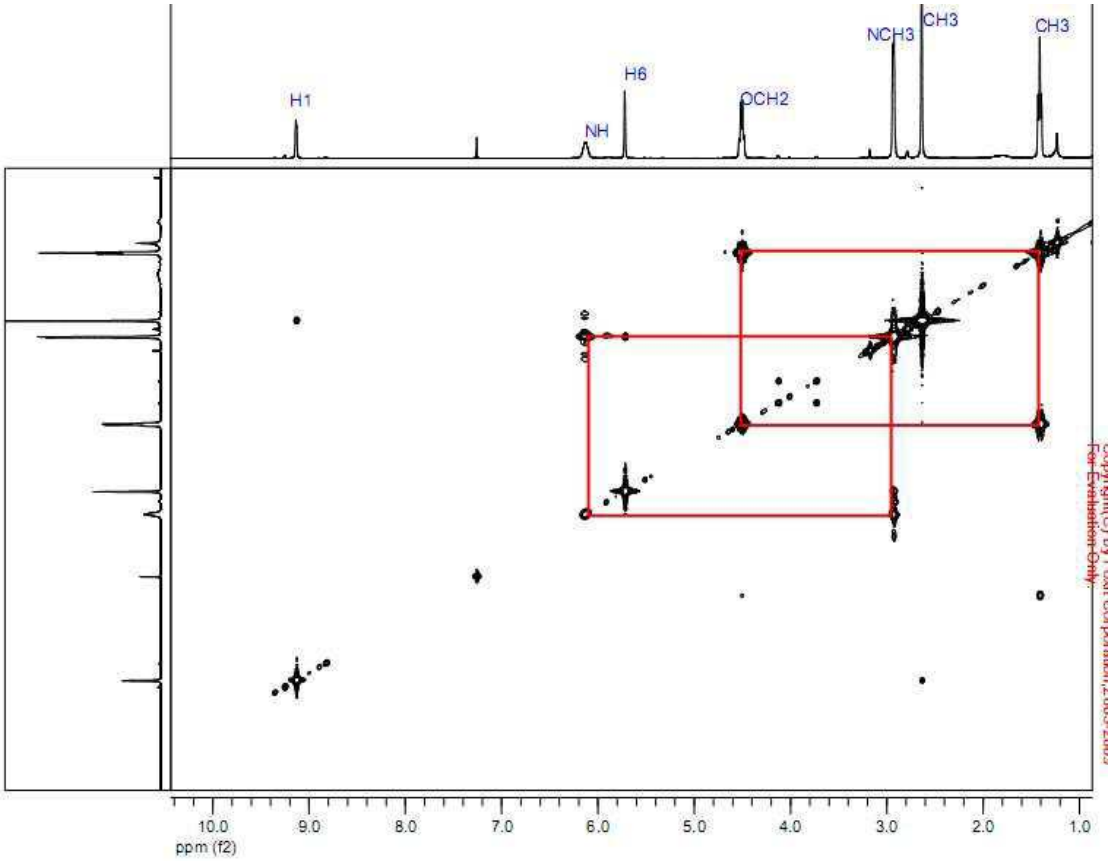
31l ^{1}H NMR ($CDCl_3$, 400 MHz)



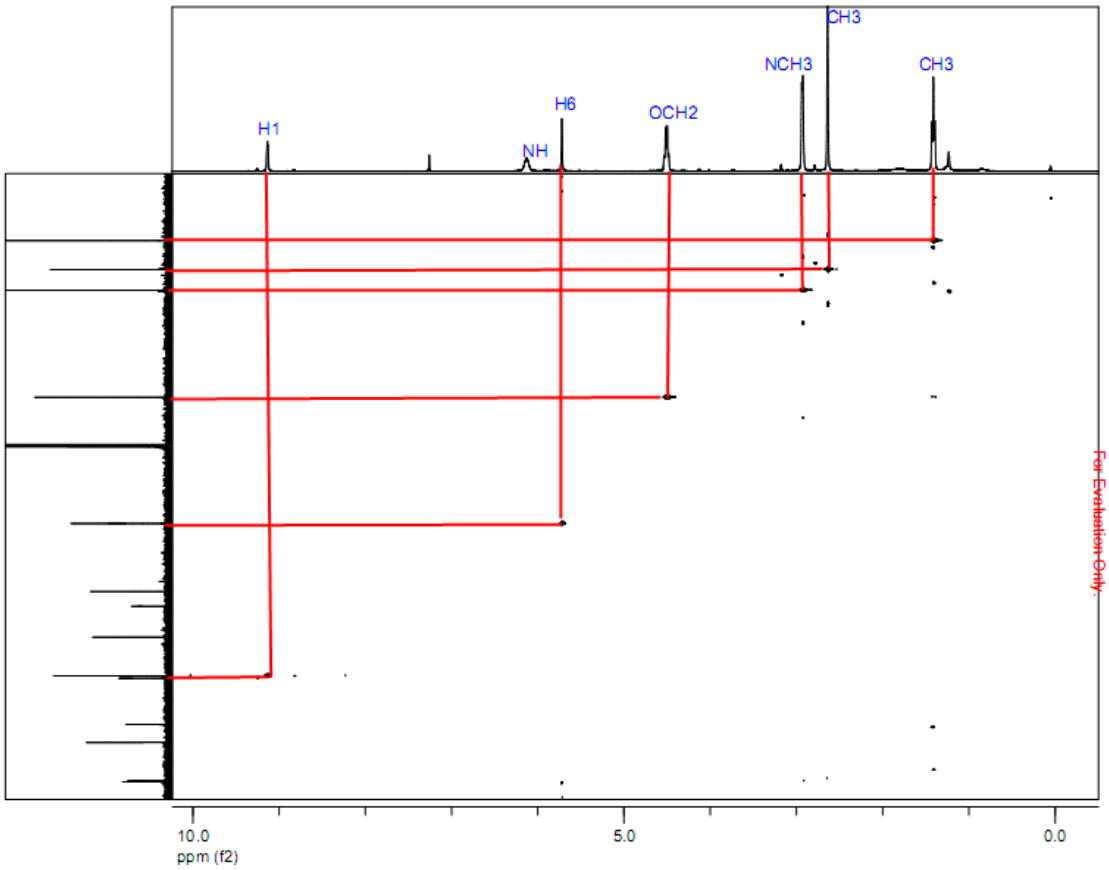
31l ^{13}C NMR ($CDCl_3$, 100 MHz)



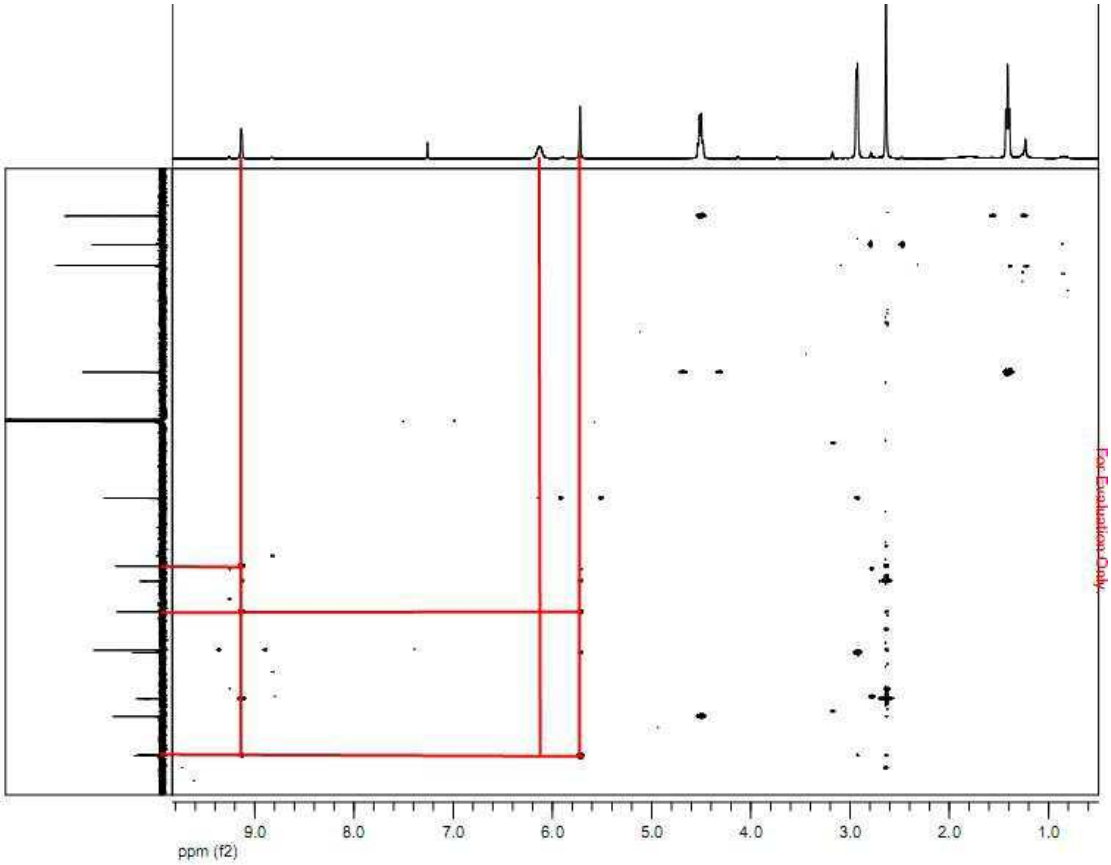
31l COSY ($CDCl_3$, 400 MHz)



31l HSQC ($CDCl_3$, 400 MHz)



31l HMBC ($CDCl_3$, 400 MHz)



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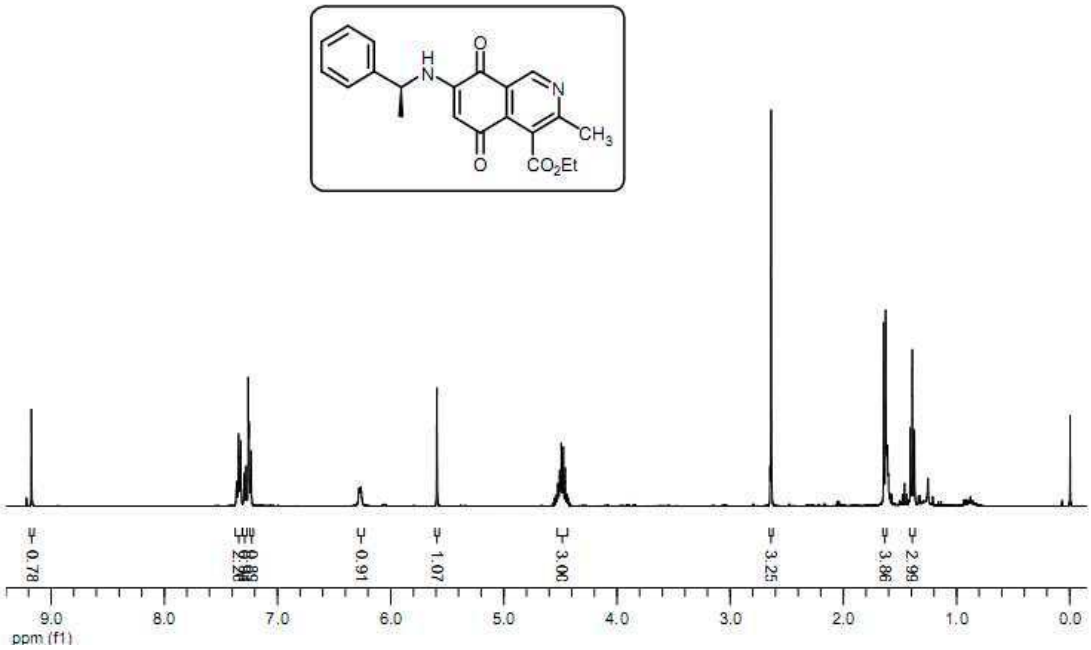
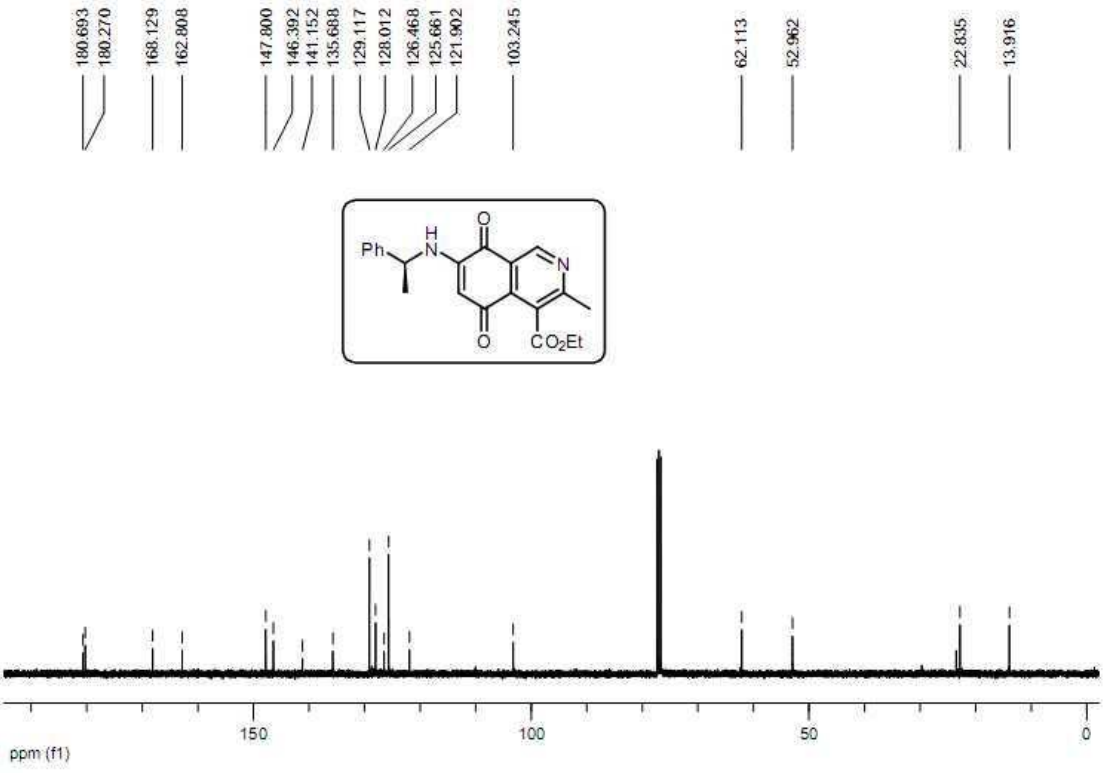
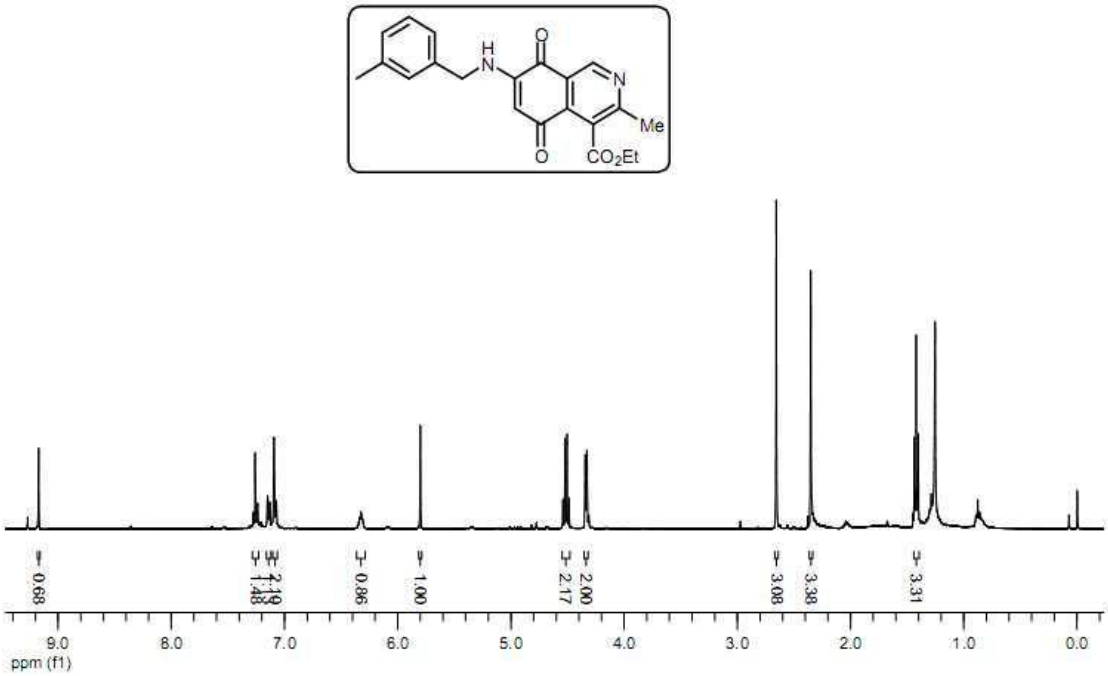


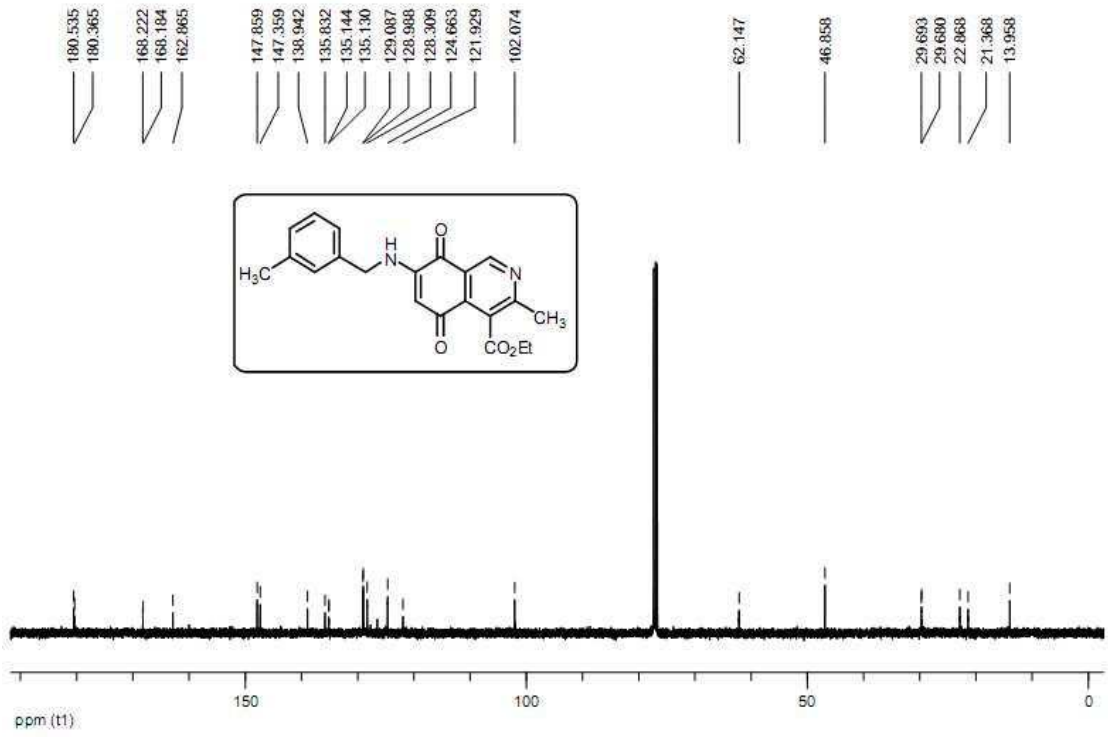
31m ^{13}C NMR ($CDCl_3$, 100 MHz)



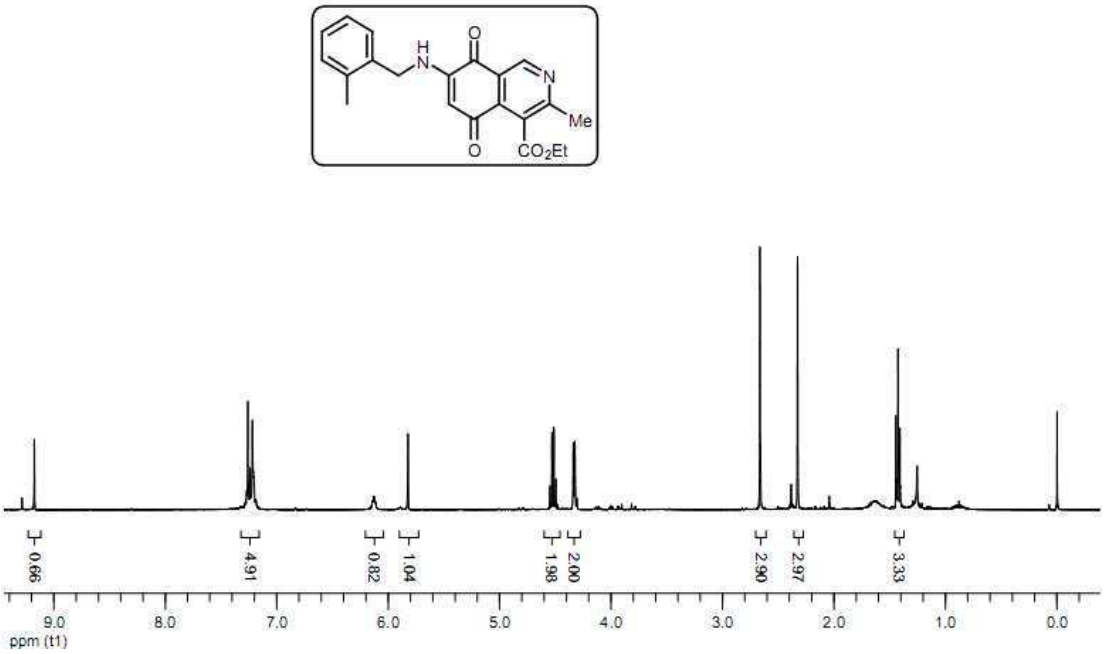
31n ^{1}H NMR ($CDCl_3$, 400 MHz)



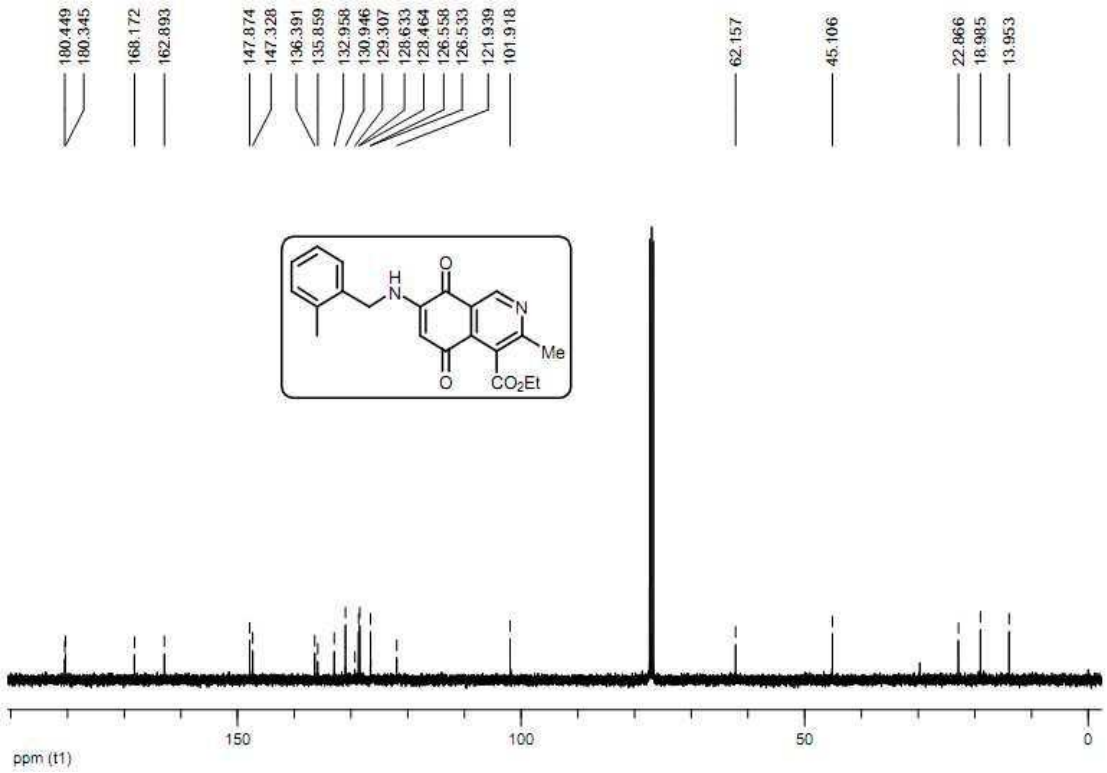
31n ^{13}C NMR ($CDCl_3$, 100 MHz)



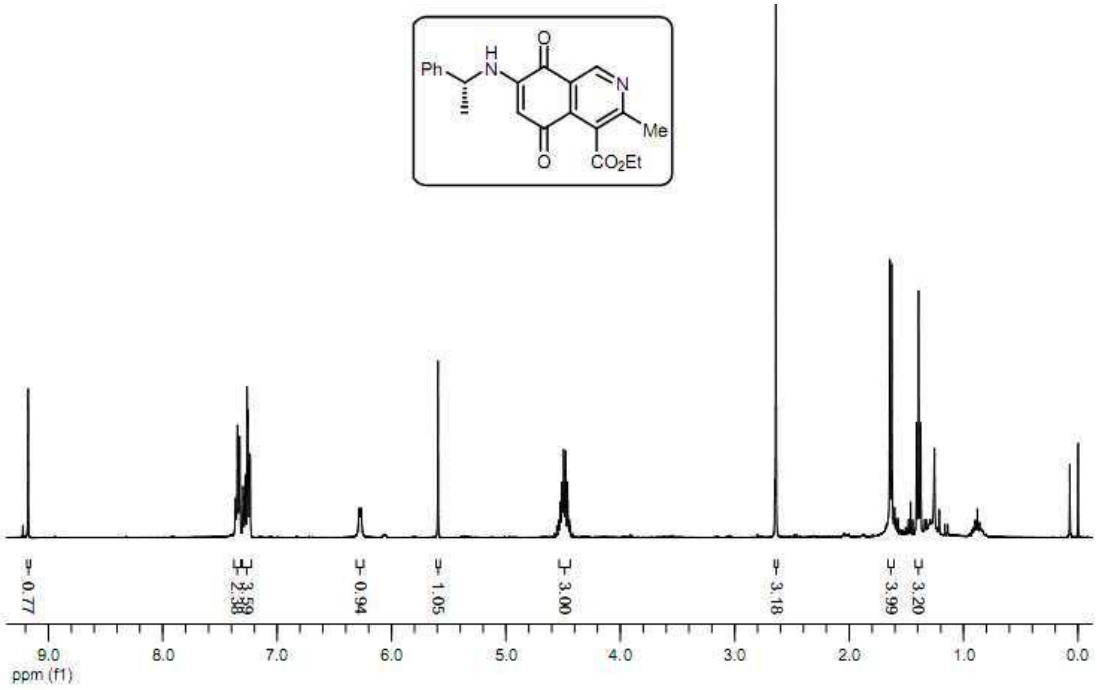
31o ^{1}H NMR ($CDCl_3$, 400 MHz)



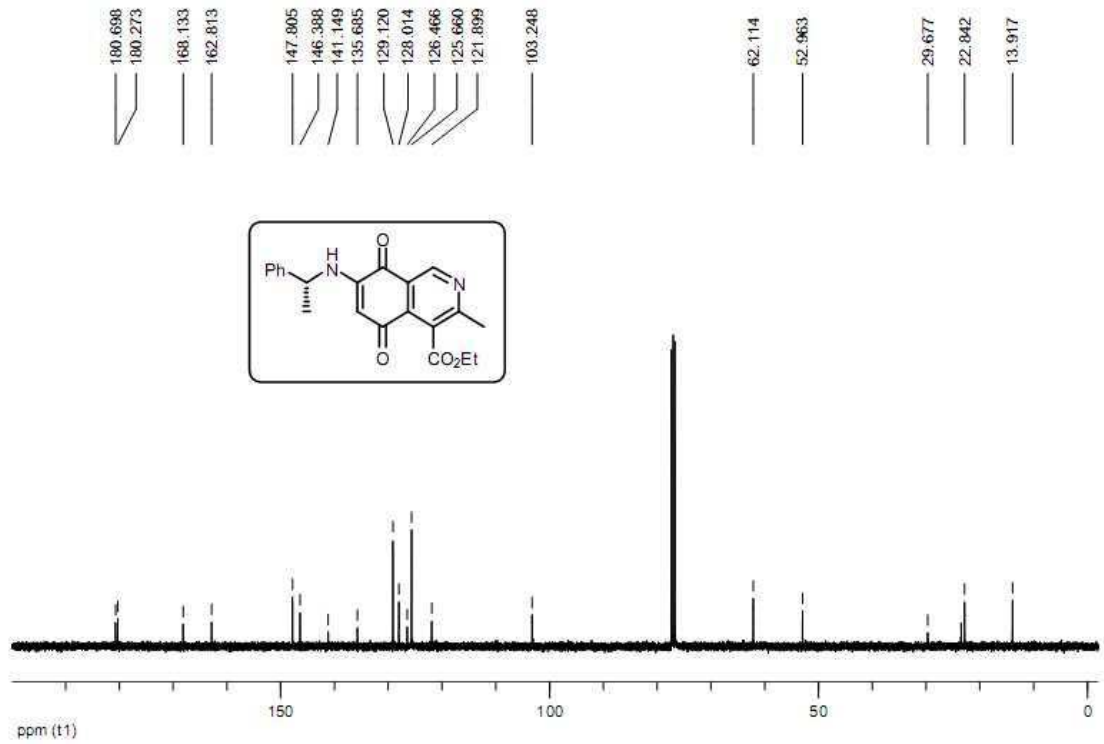
31o ^{13}C NMR ($CDCl_3$, 100 MHz)



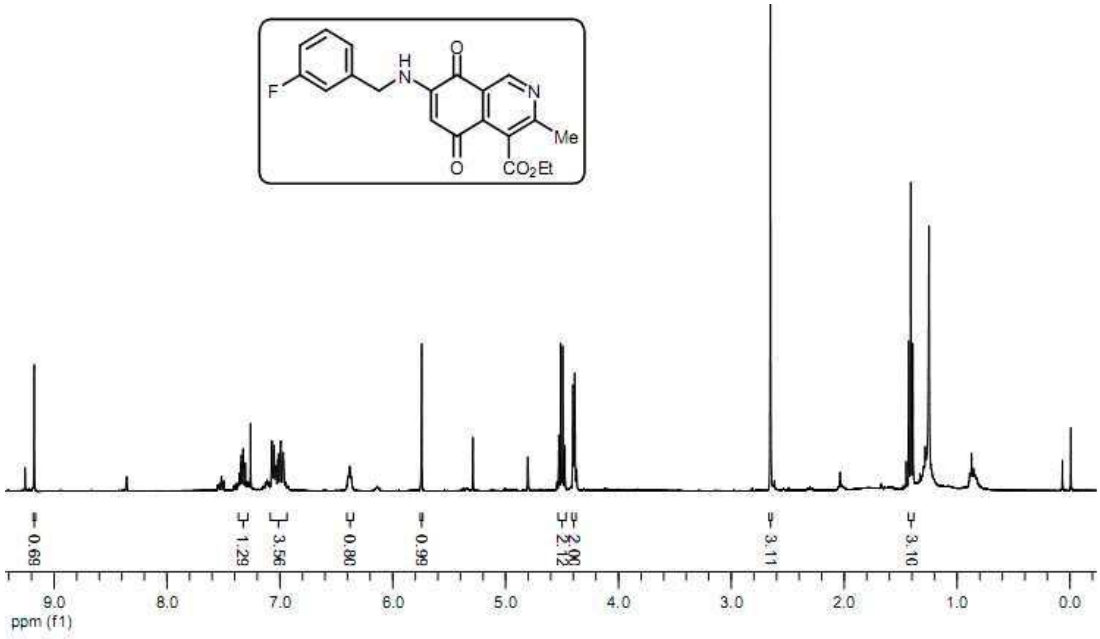
31p ^{1}H NMR ($CDCl_3$, 400 MHz)



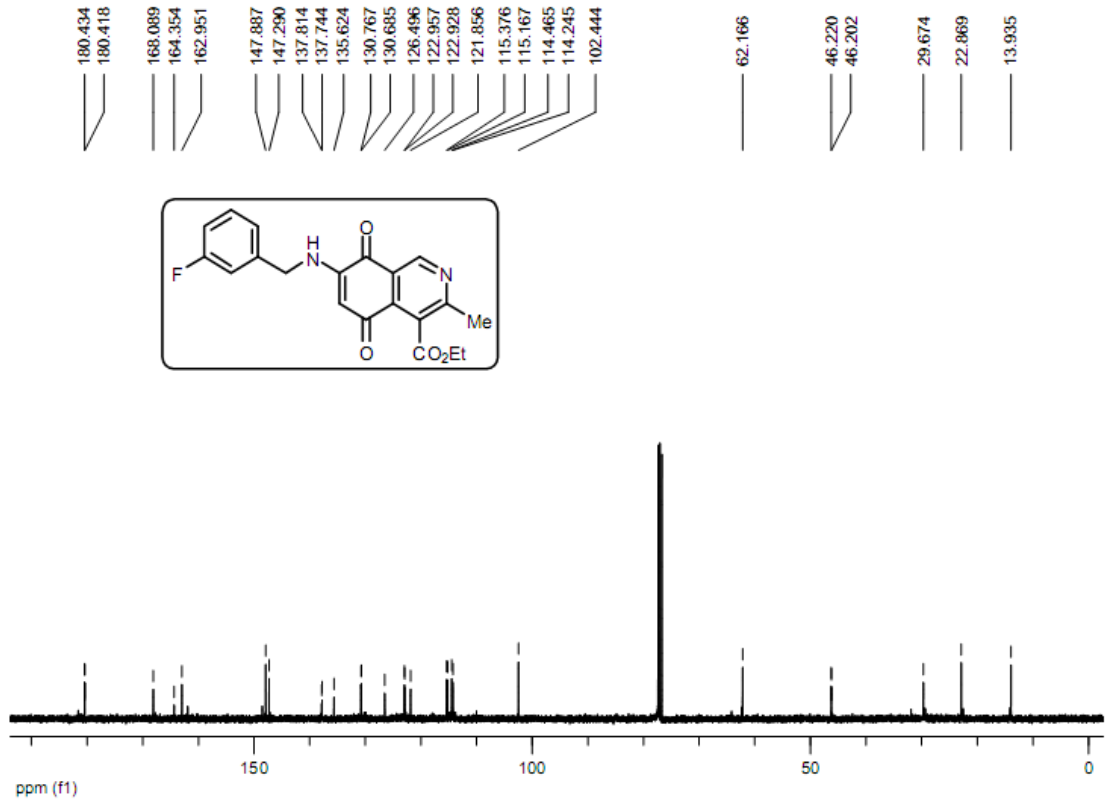
31p ^{13}C NMR ($CDCl_3$, 100 MHz)



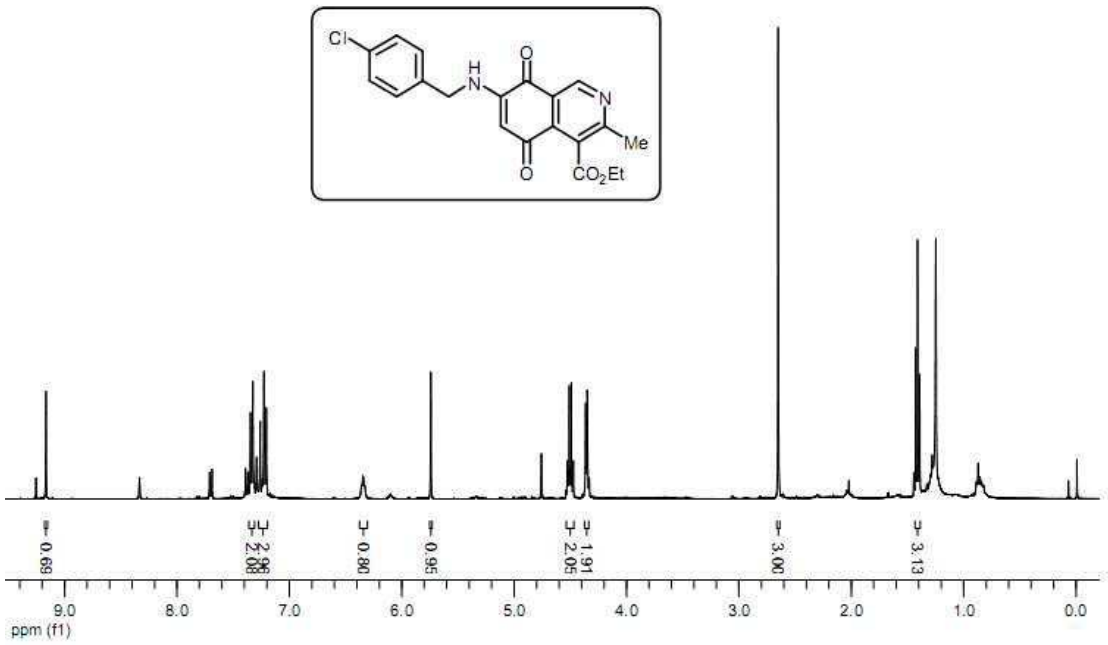
31q ^{1}H NMR ($CDCl_3$, 400 MHz)



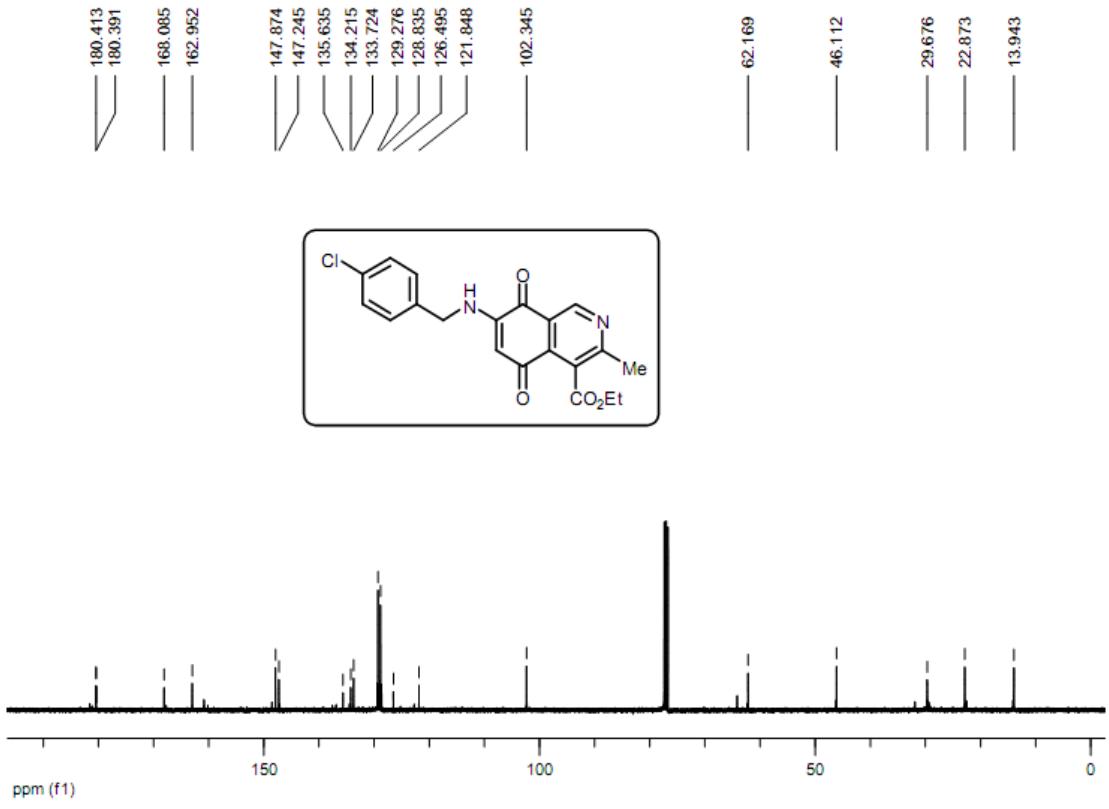
31q ^{13}C NMR ($CDCl_3$, 100 MHz)



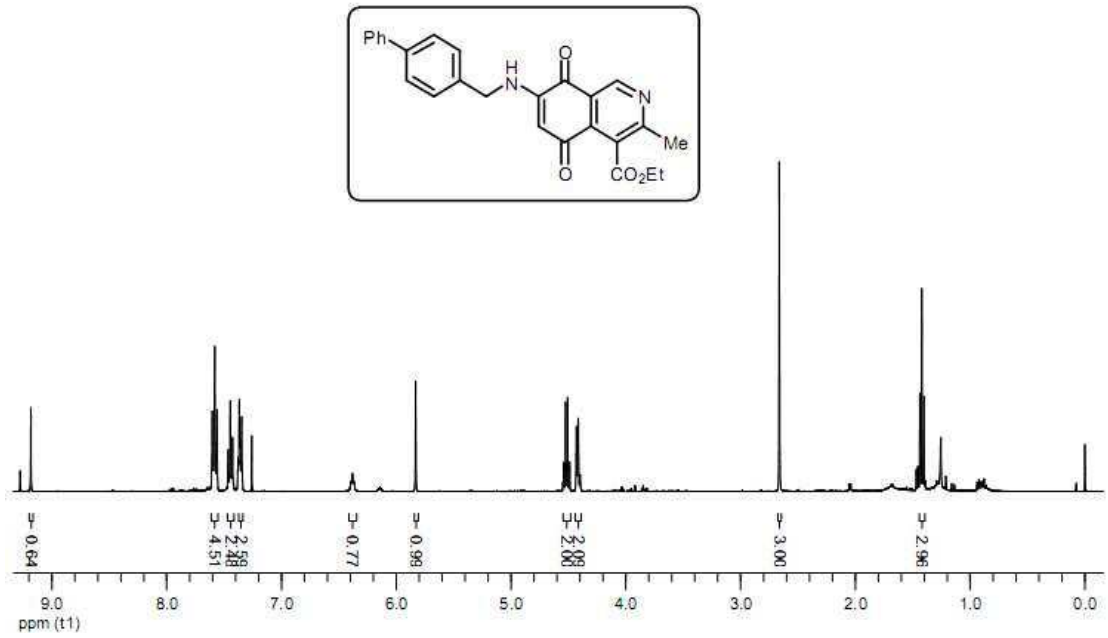
31r ^{1}H NMR ($CDCl_3$, 400 MHz)



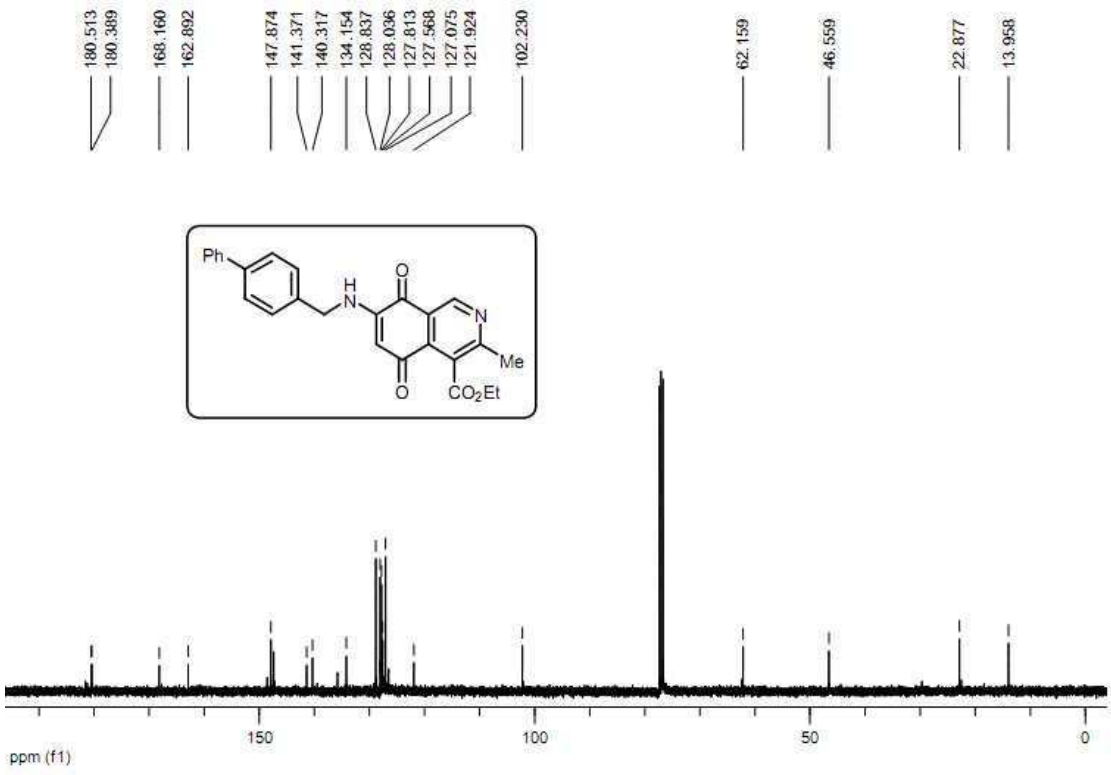
31r ^{13}C NMR ($CDCl_3$, 100 MHz)



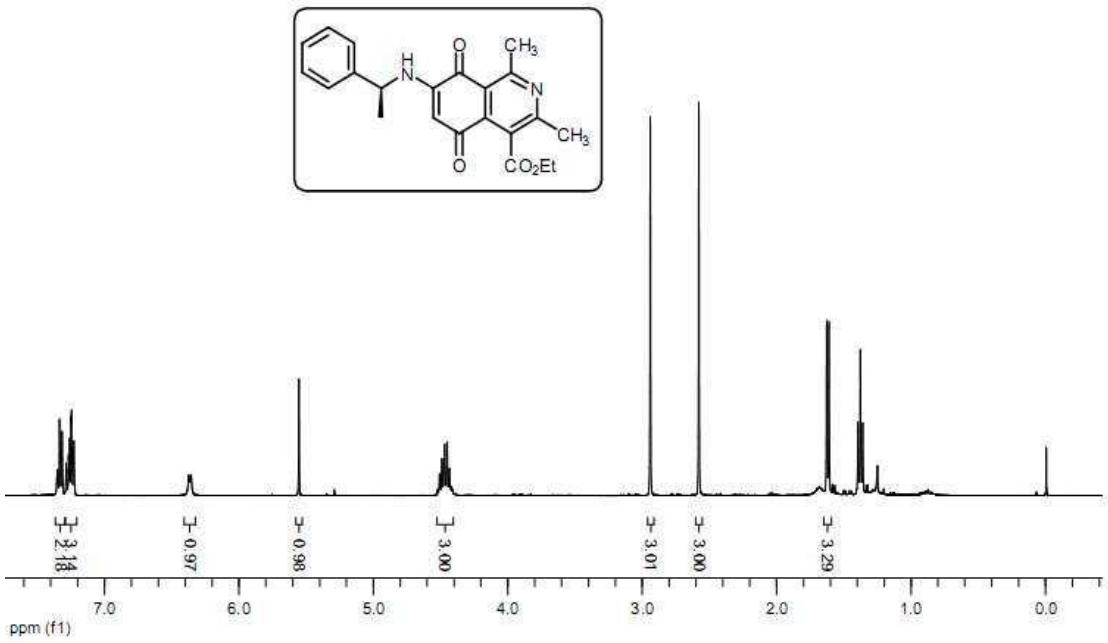
31s ^{1}H NMR ($CDCl_3$, 400 MHz)



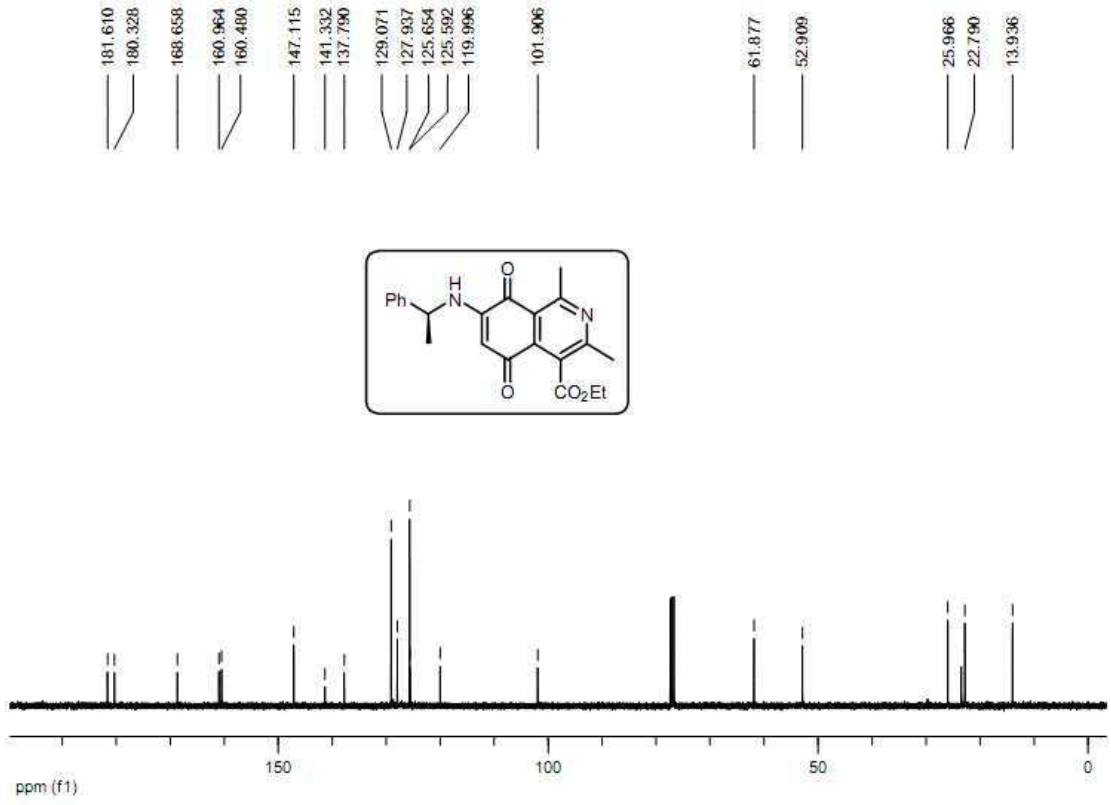
31s ^{13}C NMR ($CDCl_3$, 100 MHz)



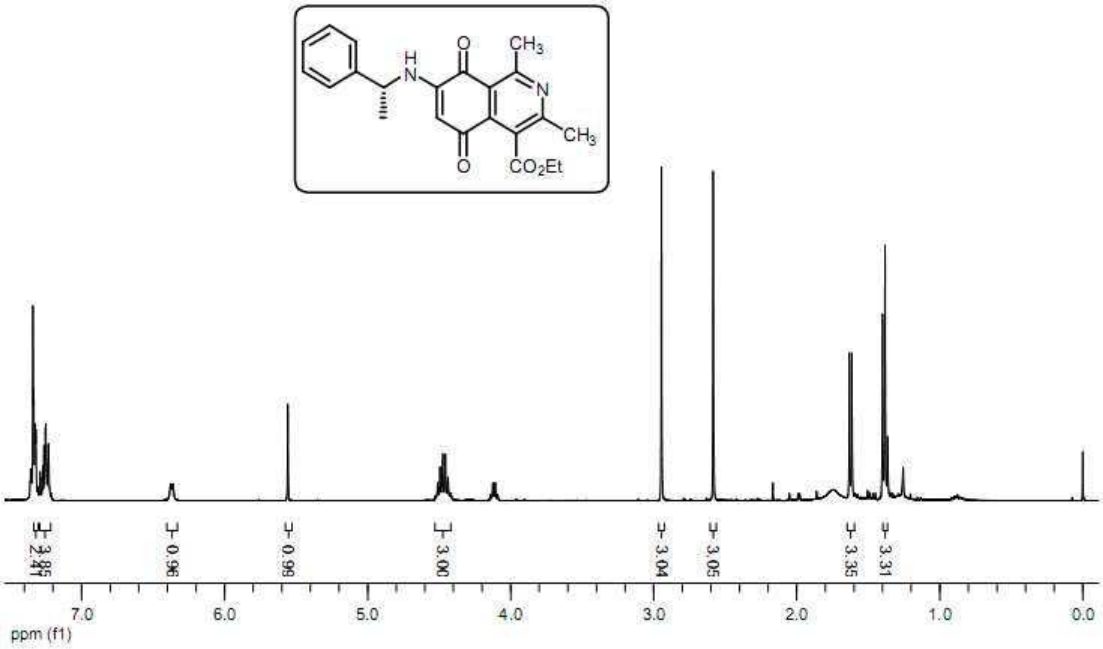
31t ^{1}H NMR ($CDCl_3$, 400 MHz)



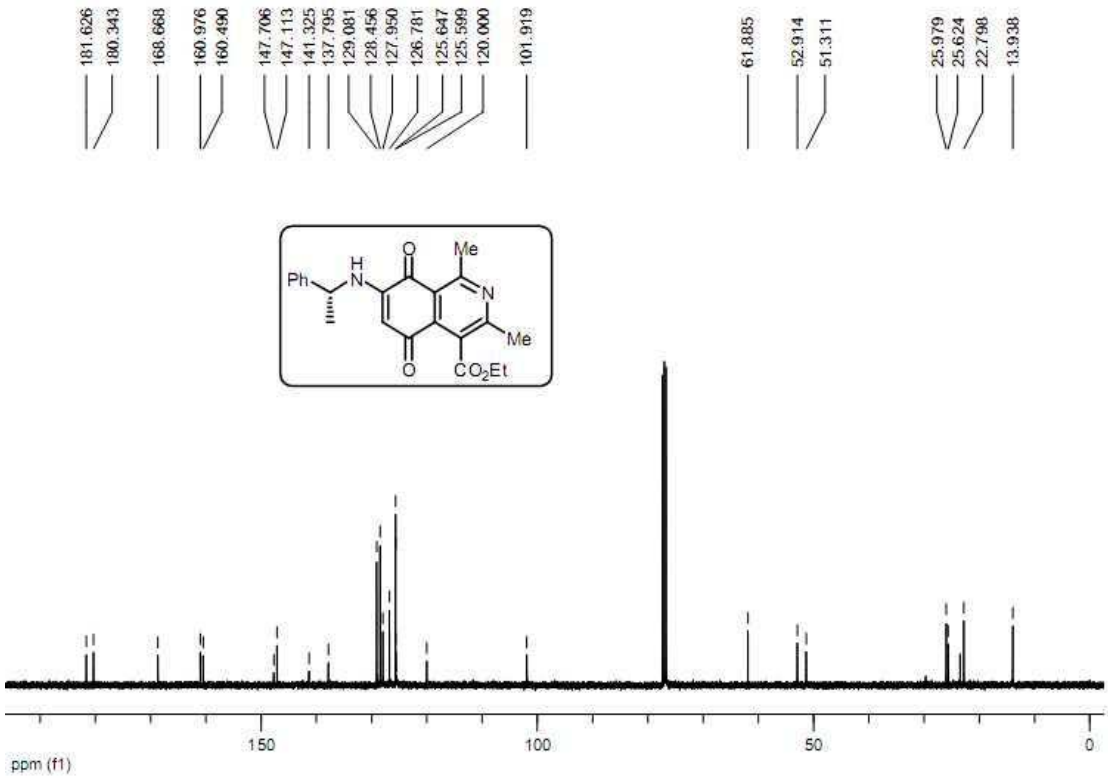
31t ^{13}C NMR ($CDCl_3$, 100 MHz)



31u ^{1}H NMR ($CDCl_3$, 400 MHz)



31u ^{13}C NMR ($CDCl_3$, 100 MHz)



CHAPTER 4

SYNTHESIS OF RACEMIC MOXIFLOXACIN INTERMEDIATE *VIA* AZA DIELS-ALDER REACTION

4.1. Introduction

Six-membered nitrogen-containing heterocyclic compounds, such as piperidines have been recognized as a class of highly important molecular skeletons which are abundant in natural products, pharmaceuticals, agrochemicals, functionalmaterials[1] and as key intermediates in the preparation of nitrogen-containing alkaloids.[2] A few representative molecules bearing the piperidine skeleton are shown in (Fig. 4.1).

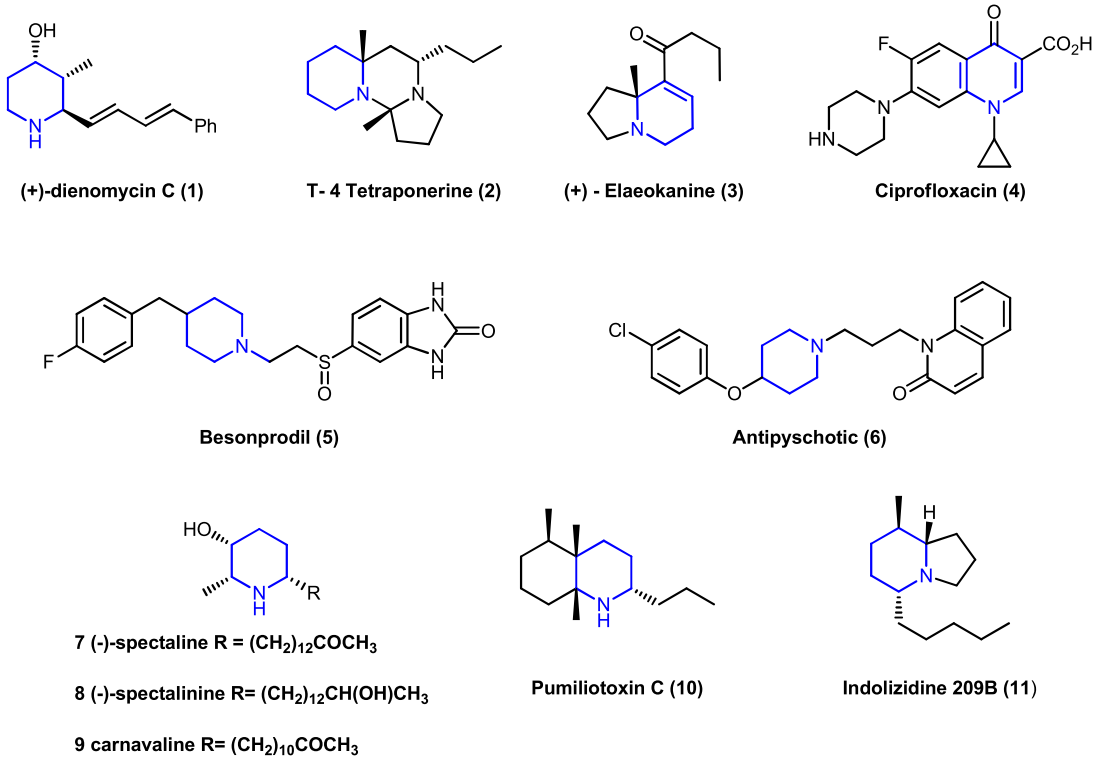


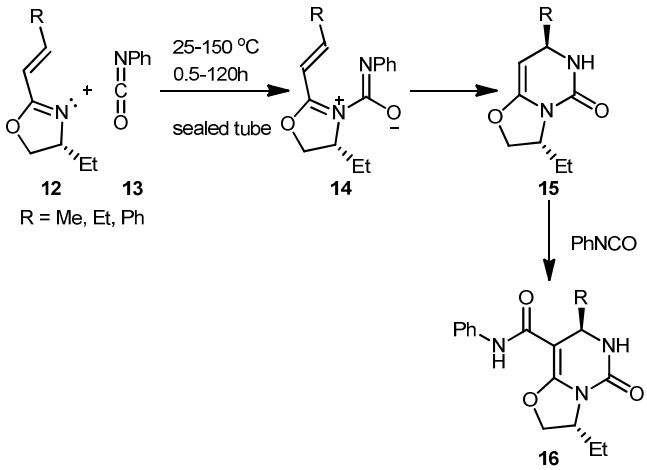
Figure 4.1. Representative examples of piperidine derivatives

The piperidine moiety containing drug molecules are very common such as (+)-Dienomycin C **(1),** is an antibacterial natural product isolated from the culture filtrate of the *Streptomyces* strain MC67-C1 by Umezawa in 1970.[3] (+)-Dienomycin C showed antibacterial activity against some strains of Mycobacterium tuberculosis. Similarly, T-4 Tetraponerine **(2)** is cytotoxic natural product isolated from the venom of the New Guinean ant *Tetraponera sp.*by braekman in 1987.[4] (+)-Elaeokanine A **(3)** was isolated from *Ekaeocarous kaniensis Schltr.,* a large rain-forest tree in New Guinea.[5] Ciprofloxacin **(4)** is an antibiotic, orally active agent that treat a variety of bacterial infections.[6] Besonprodil **(5)** is a antiparkinson's agent which act as an NMDA(N-methyl-D-aspartate receptor) antagonist, selectively NR2B subunit.[7] Antipyschotic **(6),** an important molecule for dopamine D_4 antagonist.[8] The first

natural piperidine alkaloids (-)-Spectaline **(7)**, (+)-Spectalinine **(8)**, and Carnavaline **(9)** with DNA-altering properties were reported by Kingston *et al*[9] and isolated from the Brazilian legume Cassia leptophylla. A yeast bioassay was used to find DNA-modifying agents for potential anti-cancer drugs, and the results showed that (-)-Spectaline and (+)-Spectalinine were cytotoxic in Vero monkey and Chinese hamster ovary cell assays. Piperidine rings can also be found embedded in multi-cyclic systems such as indolizidine and quinoline alkaloids. Pumiliotoxin C **(10)** was isolated from the neotropical frogs *Dendrobates pumilio* and *D. auratus*, while indolizidine 209B **(11)** was isolated from *D. pumilio* and *D. histrionicus*. These derivatives have been the focus of much synthetic interest,[10,11] as indolizidine alkaloids shown to act as non-competitive blockers of the passage of sodium ions through nicotinic acetylcholine receptor channels.[12] As a result, there is considerable interest among synthetic chemist to develop several routes for the synthesis of substituted piperidine derivatives. This chapter covers the earlier reports and our approach to the substituted piperidine derivatives starting from 1-azadienes or its analogues.

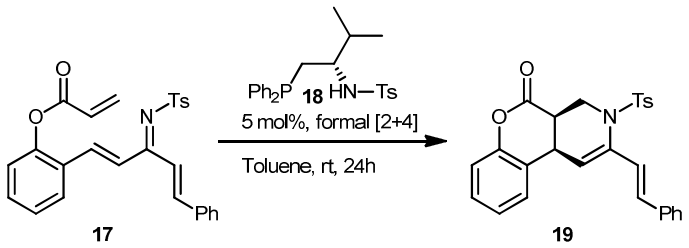
4.1.1. Precedents on 1-Aza- Diels-Alder (ADA) reactions

In 2001, Elliot and co-workers applied this strategy to synthesize total synthesis of batzelladine A, **16** (scheme 4.1).[13] Initially diastereomeric oxazolo[3,2-c]pyrimidine ring **15** was prepared by ADA reaction between 2-alkenyle-2-oxazolines **12** (as the 1-azadiene) and isocyanate **13**. This presumably occurs by addition of a second equivalent of isocyanate to compound **15.**



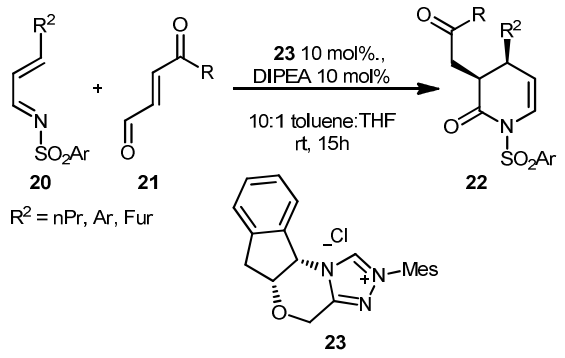
Scheme 4.1 Total synthesis of batzelladiene.

In 2012, Robin Chi and co-workers reported a first chiral phosphine **18** -catalyzed activation of electron-deficient alkenes for intramolecular formal [2+4] reactions with α,β-unsaturated imines **17** to form the bicyclic N,O-containing compound **19** (Scheme 4.2).[14]



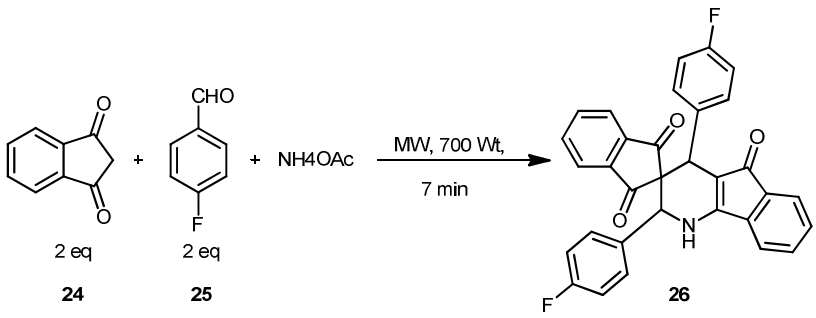
Scheme 4.2 Intramolecular Aza Diels-Alder reaction.

In 2006, Bode and co-workers reported a first example of NHC-catalyzed generation of highly reactive dienophile (Breslow intermediate) that participates in LUMO (diene)-controlled ADA cyclization with α,β-unsaturated imine **20** under mild conditions to afford a new class of substituted a dihydropyridinone **22** (Scheme 4.3).[15]



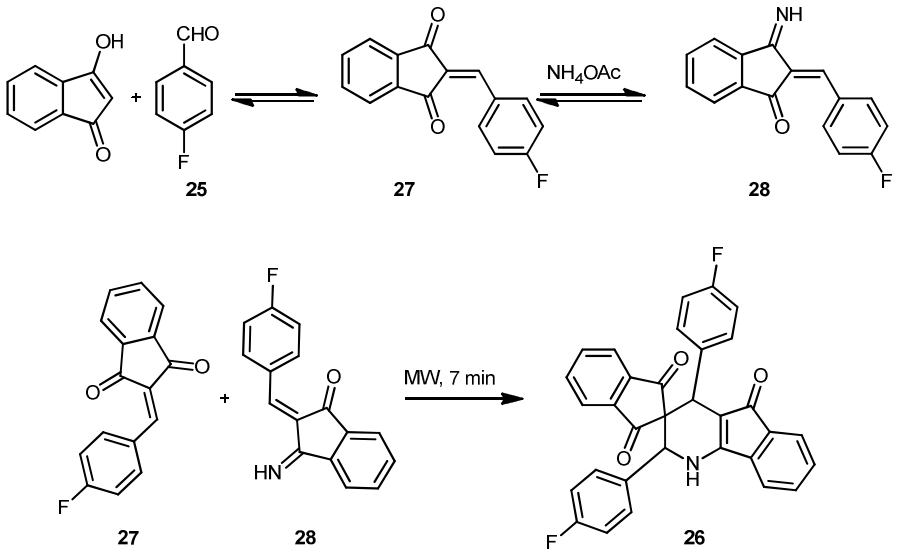
Scheme 4.3 NHC- Catalyzed Aza Diels-Alder reaction.

In 2014, Prajapati *et al*. reported a microwave-assisted solvent and catalyst free green procedure for the synthesis of complex novel spiroindenopyridines (Scheme 4.4).[16]



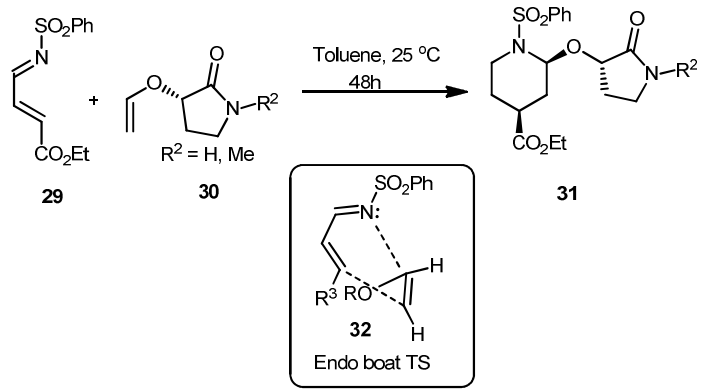
Scheme 4.4 Microwave-assisted solvent and catalyst free Aza Diels-Alder reactions.

The initial steps of the reaction involve a Knoevenagel condensation of the 1,3-dicarbonyl compound **24** with an aldehyde **25** to give compound **27** and a condensation of ammonia acetate with α,β-unsaturated carbonyl compound **27** to give on 1-azadiene **28**. The rate determine step is the ADA reaction of the 1-azadiene to the α,β-unsaturated carbonyl compound to afford an spiroindenopyridine **26** (Scheme 4.5).



Scheme 4.5 Mechanism of microwave-assisted Aza Diels-Alder reactions.

In 2006, Boger and co-workers reported a diastereoselective, auxiliary-assisted, Aza-Diels-Alder reaction by treating sulfonyl-1-azadiene **29** with optically active enol ether **30** leading to the cycloadducts **31** are obtained with high diastereoselectivity (Scheme 4.6).[17]



Scheme 4.6 Auxiliary-assisted, Aza Diels-Alder reaction.

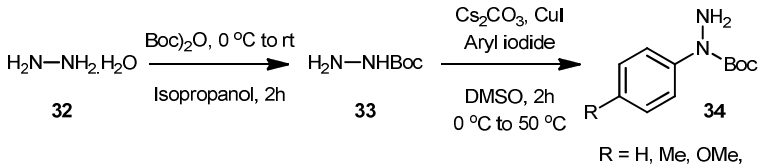
1-Aza Diels-Alder reactions have made large impact on synthetic chemistry. However this class of reactions suffers from many limitations. Often times, toxic and expensive

metals are used along with high molecular weight and expensive chiral ligands, lower yields etc. Thus the synthesis of substituted piperidine offers challenges to design and develop simple and efficient strategies. Since 1-aza-Diels-Alder reactions are one of the most efficient ways to access these important heterocycles. As a result, efforts to develop 1-Aza Diels-Alder reactions to efficiently access these substructures have increased.[18]

4.2. Results & Discussion

4.2.1. Preparation of starting materials

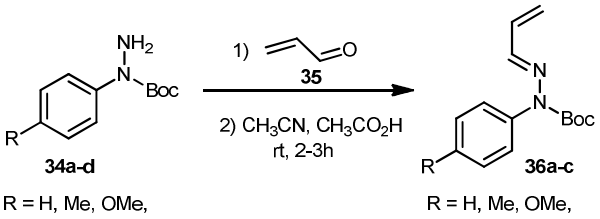
The key starting material (*E*)-tert-butyl-2-alkylidene-1-phenylhydrazinecarboxylate (1-azadiene) **36** was synthesized from tert-butyl-2-allylidene-1-phenylhydrazinecarboxylate **34.** This condensation reaction with acrolein was carried out in presence of catalytic amount of aceticacid in acetonitrile at rt. Compound **34** was obtained from hydrazine **32** via Boc protection[19] (33) and N-arylation (34) (by using aryliodide, Cs_2CO_3, CuI in DMSO).[20]

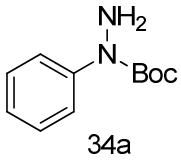
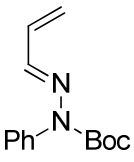
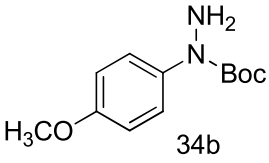
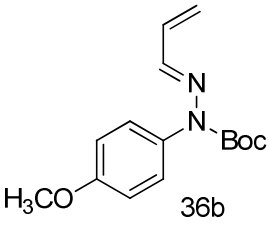
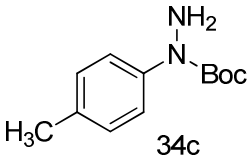
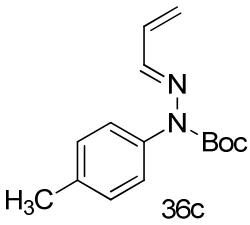
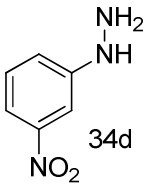
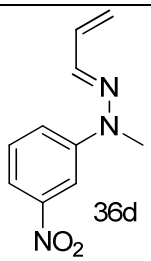
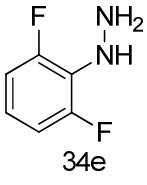
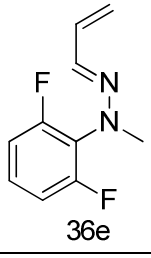


Scheme 4.7 Synthesis of tert-butyl 1-phenylhydrazinecarboxylate

The synthesis of 1-azadiene **36** was carried out using tert-butyl 1-phenylhydrazinecarboxylate **34** condensation reactions with acrolein **35** in the presence of catalytic amount of aceticacid,[21] we performed condensation reaction between tert-butyl 1-phenylhydrazinecarboxylate **34** with acrolein **35** in the presence of catalytic amount of acetic acid in acetonitrile at room temperature to afford a variety of 1-azadienes **36a-c** in high yields (**36a-36c**, Table 4.1). The synthesis of 1-azadienes **36d, 36e** is different from **36a-36c**, this synthesis can be explained by corresponding phenylhydrazine condensed with acrolein in EtOH to gave the imine intermediates.[22] This imines undergo alkylation with methyl iodide in the presence of sodium hydride in THF to form the 1-azadienes **36d, 36e** as shown (Entry 4, and Entry 5, Table 4.1).

Table 4.1. Synthesis of 1-azadienes[a]



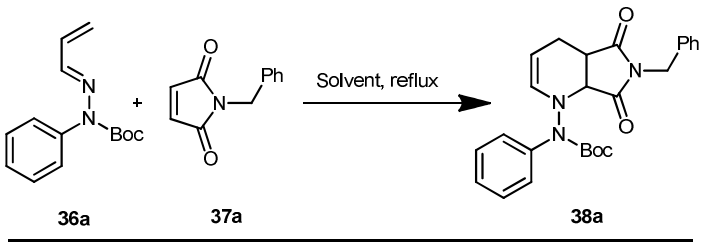
Entry	N,N- disubstituted hydrazine **(34)**	1-Azadienes **(36)**	Time /h	Yield [b] (%)
1	 34a	 36a	3	73, A
2	 34b	 36b	3	68, A
3	 34c	 36c	3	66, A
4	 34d	 36d	5	75, B
5	 34e	 36e	5	70, B

[a] Reaction conditions A: 0 °C to 50 °C, 3h, conditions B: 0 °C to 30 °C, 5 h. [b] isolated yields.

4.2.2. Initial results and optimization of reaction condition

In an initial attempt, the reaction of benzyl maleimide **37a** (0.5 mmol) and tert-butyl 2-allylidene-1-phenylhydrazinecarboxylate **36a** (0.5 mmol) was performed in CH_2Cl_2 at 30 °C. After two hours the reaction mixture was monitored by TLC the reaction could not proceed and desire compound was not formed though the starting materials benzyl maleimide **37a**, tert-butyl 2-allylidene-1-phenylhydrazinecarboxylate **36a** were not consumed after 24h.

Table 4.2. Optimization of reaction conditions[a]



36a **37a** **38a**

Entry	Solvent	Temp (^{O}C)	Time (h)	Yield [b] (%)
1	CH_2Cl_2	30	24	0
2	THF	60	24	0
3	CH_3OH	60	24	0
4	CH_3CN	70	24	5
5	EtOAc	70	20	0
6	Toluene	110	10	65
7	DMF	130	5	15
8	Toluene	70	10	0
9	Toluene	110	20	50
10	DMSO	150	20	20
11	Toluene	110	10	10[c]

[a] All reactions were performed using the 1-Azadiene 36a (0.5 mmol) and benzyl maleimide 37a (0.5 mmol), in toluene (5 mL) under open air, [b] Isolated yields, [c] the reaction was performed in the presence of Lewis acid catalysts

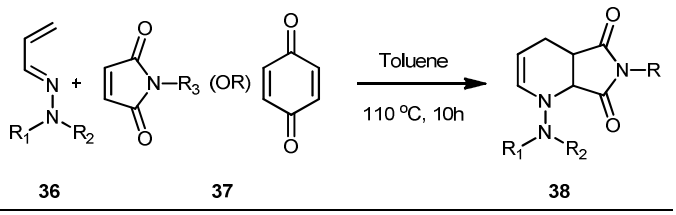
To screen different set of reaction conditions, I choose Benzylmaleimide (37a) and tert-butyl-2-allylidene-1-phenylhydrazinecarboxylate (36a) as starting substrates. To get the best set of conditions, I screened various solvents (like DMSO, DMF, Toluene) at different temperatures (Table 4.2). After screening a series of reaction conditions, I found that 1:1 ratio of both starting materials and toluene (as solvent) at 110 ^{o}C is the best condition which given moderate yield. After having this in hand further screened different Lewis acids ($InCl_3$, $Cu(OTf)_2$, $Yb(OTf)_3$) to see whether there is any improvement in the yield. But none of them gave better result. After that I decided heating toluene at 110 ^{o}C is the better condition for ADA reactions.

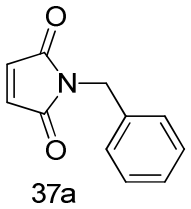
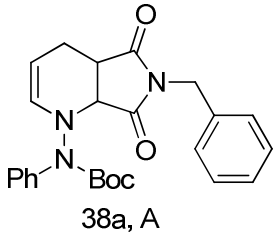
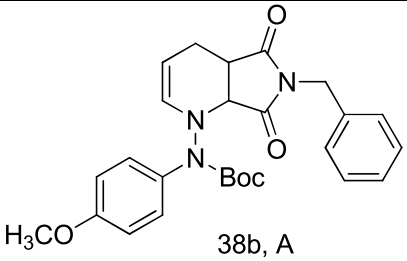
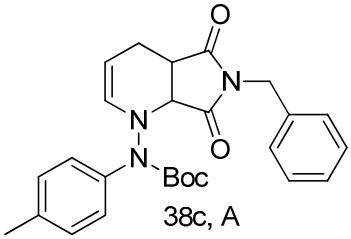
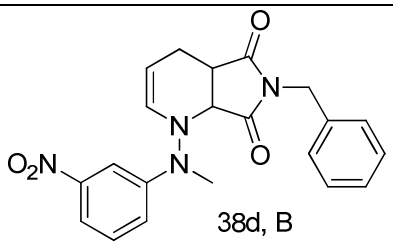
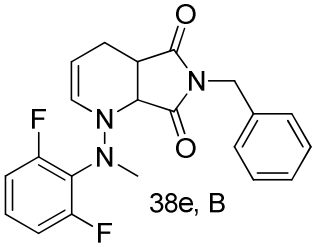
4.2.3. Scope of the reaction

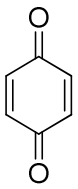
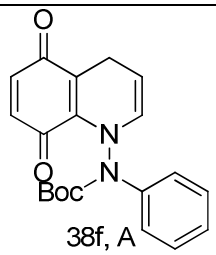
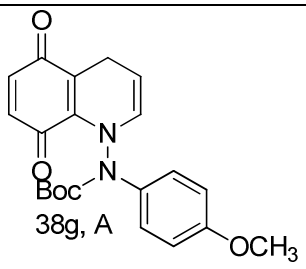
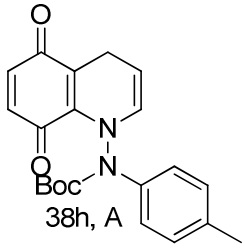
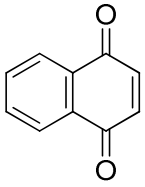
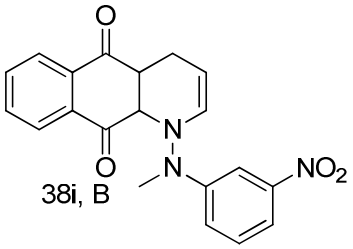
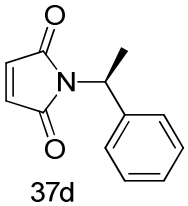
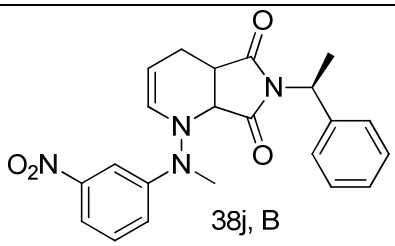
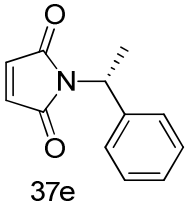
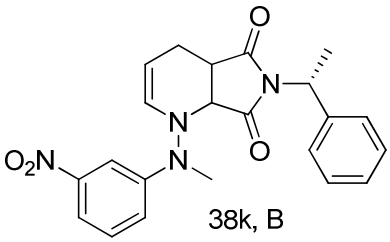
Having established optimal conditions, the scope and generality of the reaction were examined (Table 4.3). A variety of 1-azadienes (**36a-36e**) were reacted with benzyl maleimides to give various bicyclic fused-piperidines (Table 4.3). Maleimides were chosen as electron-poor dienophiles since they are known to afford complete *endo*-selectivity in their cycloaddition reactions and also direct construction of the pyrrolidine ring in this case. All these reactions were performed at 110 ^{O}C (entry 1-3, entry 6-8, entry 14, Table 4.3). Since these reactions do not require the use of any inert (or) anhydrous atmosphere they were performed under open air.

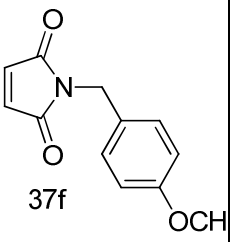
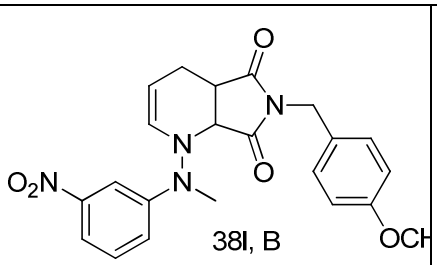
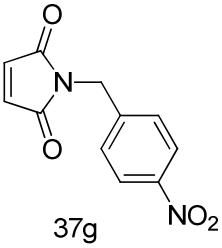
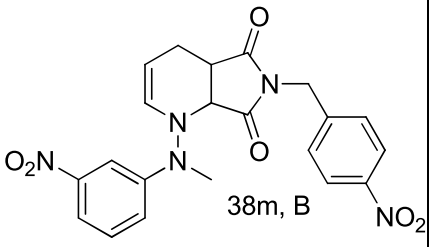
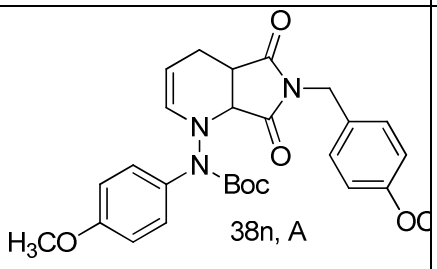
To expand the scope of this reaction we further examine the use of electron deficient dienophiles like Benzoquinone, Napthaquinone and various N-benzyl maleimides (containing H/-OMe/-NO_2) was reacted with 1-azadienes in toluene thus providing bicyclic derivatives in good yield. All these reactions were performed at 90 ^{O}C (Entry 4, 5, Entry 9-13, Table 4.3). The methodology was not successful in the preparation of 4-substituted fused piperidines from the corresponding 1-azadiene which appeared to be the limitation of this methodology.

Table 4.3. Synthesis of Bicyclic derivatives[a]



Entry	Diene (36)	Dienophile (37)	Product (38)	Yield[b] (%)
1	**36a**	 37a	 38a, A	63
2	**36b**	**37a**	 38b, A	62
3	**36c**	**37a**	 38c, A	60
4	**36d**	**37a**	 38d, B	66
5	**36e**	**37a**	 38e, B	64

6	**36a**	 37b	 38f, A	60
7	**36b**	**37b**	 38g, A	61
8	**36c**	**37b**	 38h, A	62
9	**36d**	 37c	 38i, B	65
10	**36d**	 37d	 38j, B	61
11	**36d**	 37e	 38k, B	61

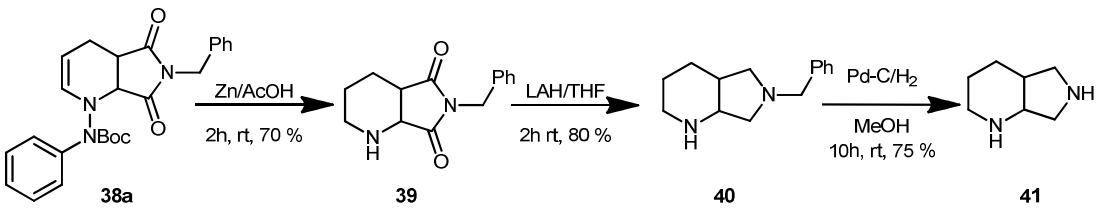
12	**36d**	 37f	 38l, B	63
13	**36d**	 37g	 38m, B	62
14	**36b**	**37f**	 38n, A	60

[a] Reaction conditions A: 1-Azadiene (0.5 mmol), dienophile (0.5 mmol) in 5 mL toluene at 110 °C; conditions B: 1-Azadiene (0.5 mmol), dienophile (0.5 mmol) in 5 mL toluene at 90 °C.

4.3. Application to 2,8-diazobicyclo [4.3.0] nonane core of Moxifloxacine

The potential of this methodology was demonstrated in the synthesis of 2,8-diazobicyclo [4.3.0] nonane, which is a core moiety of Moxifloxacine.[23] Moxifloxacin is a broad-spectrum fluoroquinolone antibacterial agent used for treating respiratory infections such as pneumonia, chronic sinusitis, and chronic bronchitis. The market demand of this antibiotic is increasing every year, and developing better and greener technologies for its synthesis is advantageous over current processes. (S,S)-2,8-diazobicyclo [4.3.0] nonane is a key chiral intermediate of Moxifloxacin,[24] the presence of an azabicyclo group in position 7 improves the activity against Gram-positive bacteria and also brings a marked lipophilicity and half-lives of more than 10h.

Several groups have developed different synthetic routes to this moiety.[25] Our strategy was mainly based on the bicyclic adducts were obtained in ADA reaction was subjected to Zn/AcOH conditions, required to hydrolyze the hydrazine and flash chromatographic purification. Interestingly, we were able to cleave hydrazine and reduction of double bond in one-step operation.[26] Then the reduction of amide with LAH,[27] followed by debenzylation protocol gave us the target Moxifloxacin intermediate in good yields (Scheme 4.8).[28]



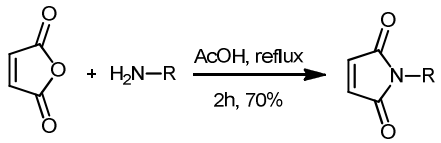
Scheme 4.8 Synthesis of 2,8-diazobicyclo [4.3.0] nonane core of Moxifloxacine

4.4. Conclusions

In summary, we have explored a new approach for the construction of biclyclic core intermediate, involving an ADA reaction under extremely mild condition. This unprecedented procedure enabled the construction of fused piperidines through ADA reaction, with one C-C bond one C-N bond formation. Various 1-azadienes and benzyl maleimides were well tolerated with the reaction condition. The use of a ADA adduct afforded the racemic 2,8-diazobicyclo [4.3.0] nonane core of Moxifloxacine by simple transformations. The methodology may find wide applications in the construction of fused piperidines and their small molecule libraries for medicinal uses or natural product synthesis.

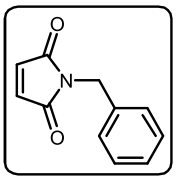
4.5. Experimental sections

4.5.1. Materials



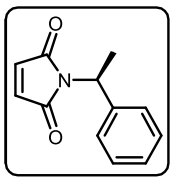
Benzyl maleimides were synthesized base on the procedure given below.[29, 30]
Benzyl amines (10.0 mmol) and maleic anhydride (11.0 mmol) were dissolved in AcOH (20.0 rnL) and the reaction mixture was reflux for 2 hours. After complete conversion of maleic anhydride, the reaction mixture was cooled to room temperature. The AcOH was removed under reduced pressure, the crude solid was purified by column chromatography (eluting with 2:8 ethyl acetate/petroleum ether) afford the corresponding benzyl maleimide.

Benzyl maleimide (37a):



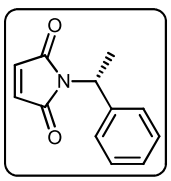
Colorless solid, m.p: 95-96 °C; R_f = 0.22 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.30 (m, 5H), 6.71 (d, *J* = 4.30 Hz, 2H), 4.68 (s, 2H), MS: m/z 187.9 (M+1); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 170.7, 170.5, 136.2, 134.2, 128.7, 128.4, 127.9, 41.4; MS (ESI mass) m/z: 187.9 [M+1].

(S)-1-(1-phenylethyl)-1H-pyrrole-2,5-dione (37d):



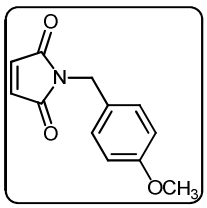
Color less liquid, R_f = 0.21 (20% EtOAc in Hexane)**.** ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.56-7.19 (m, 5H), 6.65 (s, 2H), 5.37 (q, *J* = 7.33 Hz, 1H), 1.84 (d, *J* = 7.37 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 170.7, 170.5, 140.0, 135.8, 128.5, 126.9, 126.7, 42.4, 17.7; MS (ESI mass) m/z: 201.8[M+1].

(R)-1-(1-phenylethyl)-1H-pyrrole-2,5-dione (37e):



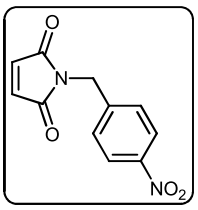
Color less liquid, R_f = 0.21 (20% EtOAc in Hexane)**.** ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.56-7.19 (m, 5H), 6.65 (s, 2H), 5.37 (q, *J* = 7.33 Hz, 1H), 1.84 (d, *J* = 7.37 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 170.7,170.5, 140.0, 135.8, 128.5, 126.9, 126.7, 42.4, 17.7; MS (ESI mass) m/z: 201.8[M+1].

4-Methoxy benzyl maleimide (37f):



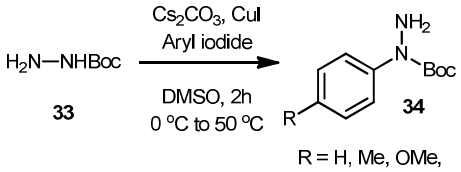
Colorless solid, m.p: 101-103 °C; R_f = 0.2 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.28 (dd, *J* = 9.57, 6.69 Hz, 2H), 6.88-6.80 (m, 2H), 4.61 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 170.8, 170.6, 158.6, 140.0, 135.8, 130.5, 124.1, 55.8, 41.7; MS (ESI mass) m/z: 217.9[M+1].

4-Nitro benzyl maleimide (37g):



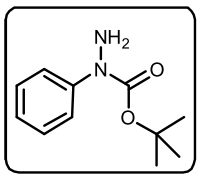
Colorless solid, m.p: 143-145 °C; R_f = 0.18 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.18 (d, J = 8.9 Hz, 2H), 7.52 (d, J = 8.9 Hz, 2H), 6.78 (s, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 170.8, 170.6, 145.9, 142.6, 135.8, 127.8, 123.7, 41.5; MS (ESI mass) m/z: 232.9[M+1].

Synthesis of N-aryl hydrazides



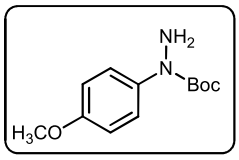
A mixture of aryl iodide (3.0 mmol), N-Boc hydrazine (3.6 mmol), Cs_2CO_3 (4.5 mmol), and CuI (0.15 mmol) in 5.0 mL of DMSO was heated at 50 °C until the iodide disappeared monitored by TLC. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified *via* chromatography (eluting with 1:8 to 1:2 ethylacetate/hexane) to afford the corresponding N-aryl hydrazide.

tert-butyl 1-phenylhydrazinecarboxylate (36a):



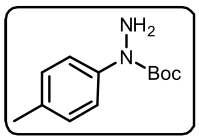
Color less liquid, R_f = 0.21 (20% EtOAc in Hexane).^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.53-7.05 (m, 5H), 4.45 (br s, 2H), 1.55-1.42 (s, 9H); ^{13}C NMR (100 Hz, *CDCl$_3$*) δ 155.9, 136.5, 129.2, 123.9, 122.8, 79.5, 28.1; MS (ESI mass) m/z: 208.8[M+1].

tert-butyl 1-(4-methoxyphenyl)hydrazinecarboxylate (36b):



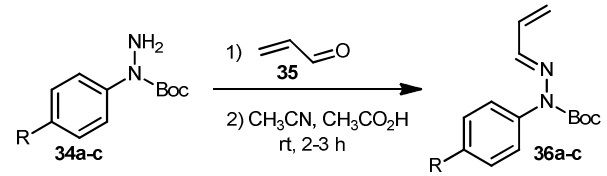
Color less liquid, R_f = 0.21 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.28 (dd, *J* = 9.57, 6.69 Hz, 2H), 6.88-6.80 (m, 2H), 4.45 (br s, 2H), 1.55-1.48 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 158.6, 153.7, 138.1, 127.2, 125.5, 124.1, 79.5, 55.8, 28.1; MS (ESI mass) m/z: 238.9[M+1].

tert-butyl 1-p-tolylhydrazinecarboxylate (36c):



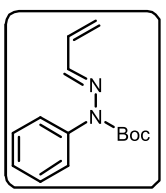
Color less liquid, R_f = 0.21 (20% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.27-7.15 (m, 3H), 6.92 (d, *J* = 6.9Hz, 1H), 4.45 (br s, 2H), 2.30 (s, 3H), 1.47(s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 155.4, 143.3, 138.1, 128.2, 125.7, 124.4, 120.9, 81.8, 28.4, 21.7; MS (ESI mass) m/z: 222.8[M+1].

Synthesis of 1-Azadiene



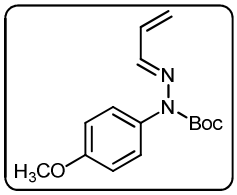
A mixture of N-aryl hydrazide (3.0 mmol), Acrolein (3.6 mmol) were dissolved in 10.0 mL of CH_3CN and than stirred in the presence of aceticacid (0.1 mmol) at room temperature until the hydrazide disappeared monitored by TLC. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethylacetate.The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified via chromatography (eluting with 1:9 ethyl acetate/hexane) to afford the corresponding 1-azadiene.

(E)-tert-butyl 2-allylidene-1-phenylhydrazinecarboxylate (36a):



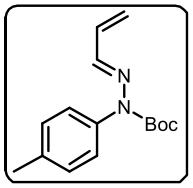
Color less liquid, R_f = 0.2 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.37-7.22 (m, 5H), 6.92 (m, 1H), 6.64 (m, 1H), 5.38 (dd, *J* = 23.03, 13.86 Hz, 2H), 1.42 (s, 3H), ^{13}C NMR (100 MHz, *CDCl$_3$*) δ ppm 159.4, 142.7, 142.2, 135.8, 133.9, 133.0, 130.2, 129.6, 81.5, 28.3; MS (ESI mass) m/z: 246.8[M+1].

(E)-tert-butyl 2-allylidene-1-(4-methoxyphenyl)hydrazinecarboxylate (36b):



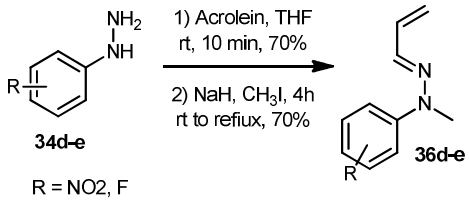
Color less liquid, R_f = 0.1.8 (10% EtOAc in Hexane)**.** ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.26 (s, 1H), 7.18 (d, *J* = 9.06 Hz, 2H), 6.87 (t, *J* = 6.30 Hz, 2H), 6.70-6.53 (m, 1H), 5.33 (dd, *J* = 24.30, 13.87 Hz, 2H), 3.77 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 159.4, 153.8, 135.7, 133.8, 133.0, 128.5, 126.7, 81.3, 28.3; MS (ESI mass) m/z: 276.8[M+1].

(E)-tert-butyl 2-allylidene-1-p-tolylhydrazinecarboxylate (36c):



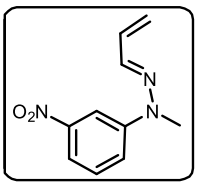
Color less liquid, R_f = 0.21 (10% EtOAc in Hexane)**.** ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.26 (s, 1H), 7.18 (d, *J* = 9.06 Hz, 2H), 7.08 (t, *J* = 6.30 Hz, 2H), 6.70-6.53 (m, 1H), 5.33 (dd, *J* = 24.30, 13.87 Hz, 2H), 2.47 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 159.4, 142.7, 142.2, 135.8, 133.9, 133.0, 130.2, 129.6, 81.5, 28.3, 14.1; MS (ESI mass) m/z: 260.8[M+1].

Synthesis of N-methyl, N-aryl hydrazones



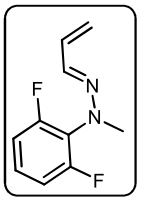
A mixture of phenyl hydrazine (5.0 mmol), Acrolein (6.0 mmol), were dissolved in THF, the reaction mixture was cooled to 0 °C for two min and then NaH (10.0 mmol), was added to all at once. While maintaining room temperature, methyl iodide (15 mmol in 5.0 mL THF) was added to the mixture over a period of 1h, and the reaction mixture was further heated to reflux for 2 h. After complete conversion of methyl iodide, the reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to get N-methyl, N-aryl hydrazones.

(E)-2-allylidene-1-methyl-1-(3-nitrophenyl)hydrazine (36d):



Red Color solid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 8.06 (d, *J* = 2.18 Hz, 1H), 7.78-7.51 (m, 2H), 7.37 (m, 2H), 6.76-6.52 (m, 1H), 5.47 (t, *J* = 14.04 Hz, 2H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 148.7, 144.7, 137.2, 130.8, 130.4, 125.2, 122.8, 112.3, 106.4, 34.6; MS (ESI mass) m/z: 205.9[M+1].

(E)-2-allylidene-1-(2,6-difluorophenyl)-1-methylhydrazine (36e):

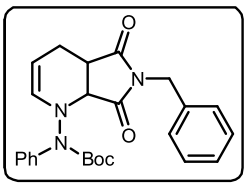


Color less liquid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 7.39-7.22 (m, 3H), 7.05 (dd, *J* = 8.54, 2.49 Hz, 1H), 6.58 (m, 1H), 5.43 (t, *J* = 14.36 Hz, 2H), 3.25 (s, 3H), ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 156.3, 155.7, 137.2, 130.8, 125.2, 118.3, 117.5, 112.9, 111.9, 34.4; MS (ESI mass) m/z: 196.9[M+1].

General Procedure for Aza Diels-Alder reaction:

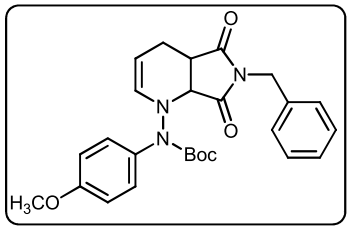
A mixture of Benzyl maleimide (or) benzoquinone (0.5 mmol), Azadiene (0.5 mmol), in 5.0 mL of Toluene was stirred at 110 °C temperature 10h. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethylacetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified via chromatography (eluting with 1:9 ethyl acetate/petroleum ether) to afford the corresponding Diels-alder adduct.

tert-butyl 6-benzyl-5,7-dioxo-4,4a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-1-yl(phenyl)carbamate (38a):



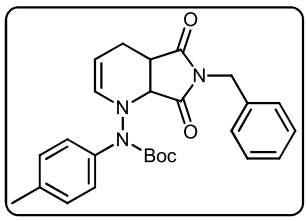
Color less solid, m.p:173-175 °C; R_f = 0.23 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ 7.40-7.22 (m, 5H), 7.20 (dd, *J* = 25.44, 6.80 Hz, 3H), 6.99 (t, *J* = 7.41 Hz, 1H), 5.69-5.41 (m, 1H), 4.63 (s, 2H), 3.80 (d, *J* = 9.95 Hz, 1H), 3.62 (d, *J* = 8.20 Hz, 1H), 2.60-2.43 (m, 1H), 2.33 (s, 1H), 2.11 (dd, *J* = 10.87, 6.43 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, *CDCl*$_3$) δ 178.6, 176.9, 135.4, 128.9, 128.7, 128.6, 128.5, 128.4, 127.9, 127.8, 122.9, 114.3, 72.2, 48.5, 42.2, 37.0, 28.4, 28.3, 23.6; MS (ESI mass) m/z: 333.9[M-Boc+1].

tert-butyl 6-benzyl-5,7-dioxo-4,4a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-1-yl(4-methoxyphenyl)carbamate (38b):



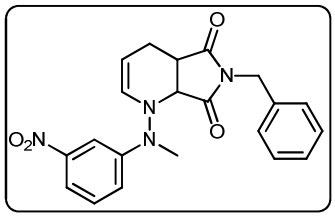
Color less solid, m.p:153-155 °C; R_f = 0.20 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.44-7.14 (m, 6H), 6.73 (m, 2H), 5.68-5.39 (m, 1H), 4.64 (s, 2H), 3.76 (d, *J* = 7.82 Hz, 4H), 3.63 (d, *J* = 8.18 Hz, 1H), 2.54 (s, 1H), 2.31 (d, *J* = 0.89 Hz, 1H), 2.10 (dt, *J* = 13.53, 13.16, 3.99 Hz, 1H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 178.7, 177.0, 155.9, 135.4, 128.6, 128.4, 114.9, 113.3, 113.2, 110.1, 106.0, 81.5, 72.3, 55.6, 48.6, 48.4, 42.2, 36.9, 28.5; MS (ESI mass) m/z: 464.0[M+1].

tert-butyl 6-benzyl-5,7-dioxo-4,4a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-1-yl(p-tolyl)carbamate (38c):



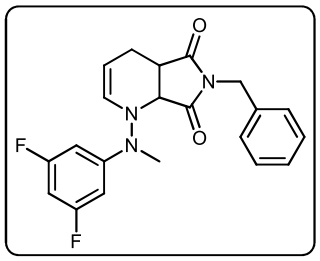
Color less solid, m.p:169-171 °C; R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.31 (m, 7H), 7.00 (s, 2H), 5.66-5.47 (m, 1H), 4.66 (s, 2H), 3.83-3.72 (m, 1H), 3.64 (d, *J* = 8.12 Hz, 1H), 2.63-2.49 (m, 1H), 2.42-2.33 (m, 2H), 2.31 (s, 3H), 2.19-2.06 (m, 1H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 178.8, 177.0, 153.1, 135.4, 128.5, 128.5, 128.4, 128.3, 127.9, 114.0, 72.3, 42.2, 37.0, 31.9, 28.5, 22.6; MS (ESI mass) m/z: 447.7[M+1].

6-benzyl-1-(methyl (3-nitrophenyl) amino)-4, 4a-dihydro-1H-pyrrolo [3, 4-b] pyridine-5, 7(6H, 7aH)-dione (38d):



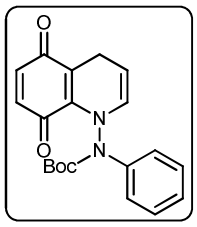
Pale red color solid, m.p:168-170 °C; R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.44 (d, *J* = 8.33 Hz, 1H), 7.35-7.27 (m, 5H), 7.23 (t, *J* = 8.04 Hz, 1H), 6.57 (d, *J* = 7.83 Hz, 1H), 4.91 (d, *J* = 9.57 Hz, 1H), 4.66 (s, 2H), 4.25 (s, 1H), 3.85 (d, *J* = 8.31 Hz, 1H), 2.80 (s, 3H), 2.68 (s, 1H), 2.24 (m, 1H), 2.04 (q, *J* = 6.93, 6.66 Hz, 1H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 177.9, 177.6, 153.3, 145.8, 135.4, 129.8, 128.7, 128.4, 128.0, 125.3, 112.9, 110.4, 49.3, 42.2, 38.5, 37.4, 31.5, 23.7; MS (ESI mass) m/z: 392.8[M+1].

6-benzyl-1-((3,5-difluorophenyl)(methyl)amino)-4,4a-dihydro-1H-pyrrolo[3,4-b]pyridine-5,7(6H,7aH)-dione (38e):



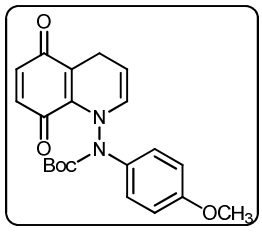
Color less semi solid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.36-7.20 (m, 6H), 6.72 (s, 1H), 6.03 (m, 1H), 5.84 (dd, *J* = 9.60, 1.82 Hz, 1H), 4.86 (d, *J* = 9.55 Hz, 2H), 4.63 (d, *J* = 13.49 Hz, 2H), 3.73 (d, *J* = 8.29 Hz, 1H), 2.76 (s, 3H), 2.74-2.66 (m, 1H), 2.37 (dd, *J* = 13.27, 5.62, Hz, 1H), 1.92 (m, 1H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 177.9, 177.6, 153.3, 145.3, 135.0, 129.3, 128.2, 128.0, 127.0, 126.8, 111.9, 110.0, 49.3, 42.2, 38.5, 37.4, 31.5, 23.7; MS (ESI mass) m/z: 383.8[M+1].

tert-butyl 5, 8-dioxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl(phenyl)carbamate(38f):



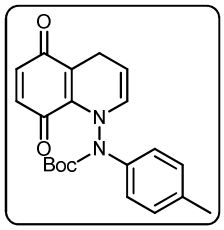
Color less solid, m.p:157-159 °C; R_f = 0.20 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.3 (m, 2H), 7.18 (dd, *J* = 12.77, 7.51 Hz, 2H), 7.00 (dt, *J* = 7.47, 0.85 Hz, 1H), 6.56 (d, *J* = 10.12 Hz, 1H), 6.48 (d, *J* = 10.12 Hz, 1H), 5.77-5.67 (m, 1H), 3.81 (d, *J* = 1.70 Hz, 1H), 3.03 (dd, *J* = 17.26, 3.73 Hz, 1H), 2.80 (dd, *J* = 17.35, 6.63 Hz, 1H), 7.26 (s, 2H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.7, 182.1, 142.0, 139.1, 133.0, 131.7, 129.4, 128.7, 128.6, 123.9, 114.5, 68.7, 28.4, 19.2; MS (ESI mass) m/z: 352.8[M+1].

tert-butyl 5, 8-dioxo-5, 6, 7, 8-tetrahydroquinolin-1(4H)-yl (4-methoxyphenyl) carbamate (38g):



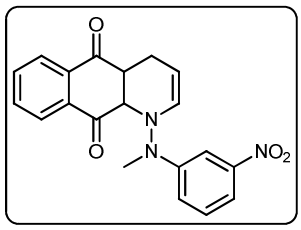
Color less solid, m.p:167-169 °C; R_f = 0.20 (10% EtOAc in Hexane).^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.26 (s, 2H), 6.71 (d, *J* = 8.54 Hz, 2H), 6.57 (d, *J* = 10.11 Hz, 1H), 6.48 (d, *J* = 10.09 Hz, 1H), 5.80-5.63 (m, 1H), 3.79 (dd, *J* = 3.51, 2.14 Hz, 1H), 3.76 (s, 3H), 3.00 (dd, *J* = 17.48, 3.24 Hz, 1H), 2.78 (dd, *J* = 17.43, 6.52 Hz, 1H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.6, 182.1, 159.4, 148.2, 139.1, 133.0, 131.7, 115.5, 112.9, 109.5, 100.6, 68.8, 55.7, 28.4, 19.3; MS (ESI mass) m/z: 382.8[M+1].

tert-butyl 5, 8-dioxo-5, 6, 7, 8-tetrahydroquinolin-1(4H)-yl (p-tolyl) carbamate (38h):



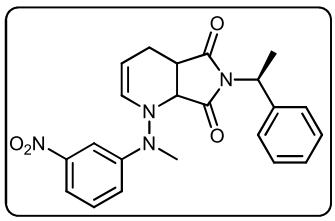
Color less solid, m.p:183-185 °C; R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.26 (s, 1H), 6.98 (d, *J* = 10.32 Hz, 3H), 6.57 (d, *J* = 10.11 Hz, 1H), 6.47 (d, *J* = 10.12 Hz, 1H), 5.81-5.60 (m, 1H), 3.79 (s, 1H), 3.04 (dd, *J* = 17.42, 3.27 Hz, 1H), 2.77 (dd, *J* = 17.40, 6.57 Hz, 1H), 2.28 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 183.7, 182.1, 142.0, 139.1, 133.0, 131.7, 129.4, 128.7, 128.6, 123.9, 114.5, 68.7, 28.4, 20.9, 19.2; MS (ESI mass) m/z: 366.8[M+1].

1-(methyl (3-nitrophenyl) amino)-1, 4, 4a, 10a-tetrahydrobenzo[g]quinoline-5, 10-dione (38i):



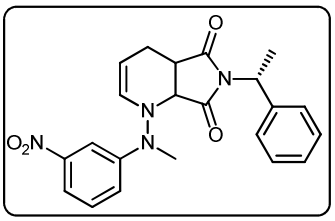
Pale yellow color solid, m.p:148-150 °C; R_f = 0.19 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.19 (d, *J* = 7.84 Hz, 1H), 7.75 (t, *J* = 7.39 Hz, 1H), 7.58-7.48 (m, 2H), 7.41 (d, *J* = 8.26 Hz, 1H), 7.18 (s, 1H), 7.01 (t, *J* = 8.16 Hz, 1H), 6.71 (d, *J* = 7.92 Hz, 1H), 5.86 (d, *J* = 7.91 Hz, 1H), 5.00 (s, 1H), 4.45 (s, 1H), 3.59 (s, 1H), 3.10 (s, 3H), 2.96-2.86 (m, 1H), 2.32 (m, 1H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 194.3, 193.8, 149.4, 148.6, 134.6, 134.2, 133.7, 129.0, 127.0, 118.0, 113.1, 107.5, 104.8, 66.2, 47.4, 33.0, 30.9, 20.7; MS (ESI mass) m/z: 363.8[M+1].

1-(methyl (3-nitrophenyl) amino)-6-((S)-1-phenylethyl)-4, 4a-dihydro-1H-pyrrolo [3, 4-b] pyridine-5, 7(6H, 7aH)-dione (38j):



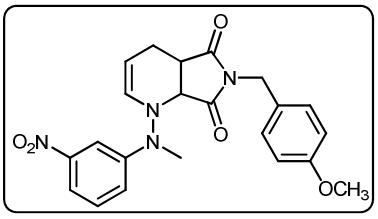
Pale red Color semi solid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.28 (dd, *J* = 13.22, 8.01 Hz, 4H), 7.20-7.13 (m, 3H), 7.08 (t, *J* = 8.10 Hz, 1H), 6.42 (d, *J* = 7.85 Hz, 1H), 5.26 (q, *J* = 7.26, 3.64 Hz, 1H), 4.76 (dd, *J* = 9.40, 8.05 Hz, 1H), 4.10 (dd, *J* = 5.68, 3.88 Hz, 1H), 3.65 (dd, *J* = 16.74, 8.37 Hz, 1H), 2.64 (s, 3H), 2.53-2.45 (m, 1H), 2.09-2.01 (m, 1H), 1.66 (d, *J* = 2.85 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 178.0, 177.8, 153.3, 145.8, 139.3, 129.8, 128.4, 127.2, 112.9, 110.4, 110.3, 53.4, 50.1, 38.5, 31.5, 23.8, 16.5; MS (ESI mass) m/z**:** 406.8[M+1].

1-(methyl (3-nitrophenyl) amino)-6-((R)-1-phenylethyl)-4, 4a-dihydro-1H-pyrrolo [3, 4-b] pyridine-5, 7(6H, 7aH)-dione (38k):



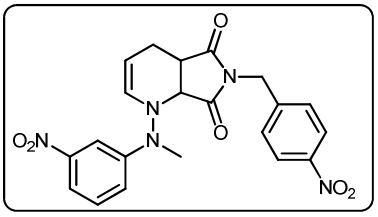
Pale red Color semi solid, R_f = 0.21 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.49 (s, 1H), 7.41 (dd, *J* = 13.64, 7.98 Hz, 3H), 7.31 (t, *J* = 7.22 Hz, 3H), 7.22 (t, *J* = 8.09 Hz, 1H), 6.56 (d, *J* = 7.87 Hz, 1H), 5.39 (dd, *J* = 7.26, 3.73 Hz, 1H), 4.90 (dd, *J* = 9.48, 7.71 Hz, 1H), 4.23 (d, *J* = 1.80 Hz, 1H), 3.78 (dd, *J* = 16.23, 8.36 Hz, 1H), 2.78 (d, *J* = 2.68 Hz, 3H), 2.63 (d, *J* = 1.26 Hz, 1H), 2.21 (dd, *J* = 5.20, 1.81 Hz, 1H), 1.80 (d, *J* = 4.81 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 178.0, 177.8, 153.3, 145.8, 139.3, 129.8, 128.4, 127.2, 112.9, 110.4, 110.3, 53.4, 50.1, 38.5, 31.5, 23.8, 16.5; MS (ESI mass) m/z**:** 406.8[M+1].

6-(4-methoxybenzyl)-1-(methyl (3-nitrophenyl) amino)-4, 4a-dihydro-1H-pyrrolo [3, 4-b] pyridine-5, 7(6H, 7aH)-dione (38l):



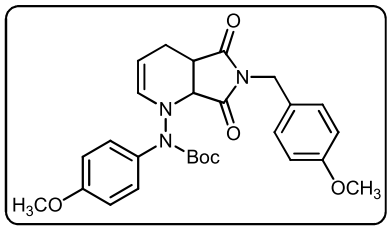
Pale red color solid, m.p: 133-135 °C; R_f = 0.19 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) 7.67-7.33 (m, 4H), 7.15-7.00 (m, 1H), 6.82 (td, *J* = 6.57, 5.85 Hz, 4H), 6.57 (d, *J* = 7.79 Hz, 1H), 4.59 (s, 3H), 4.24 (d, *J* = 2.03 Hz, 1H), 3.77 (s, 4H), 2.79 (s, 3H), 2.65 (s, 1H), 2.25-2.19 (m, 1H), 2.01 (dd, *J* = 13.60, 6.71 Hz, 1H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 177.9, 177.6, 153.3, 145.8, 135.4, 129.8, 128.7, 128.4, 128.0, 125.3, 112.9, 110.4, 55.5, 49.3, 42.2, 38.5, 37.4, 31.5, 23.7; MS (ESI mass) m/z: 422.8[M+1].

1-(methyl (3-nitrophenyl) amino)-6-(4-nitrobenzyl)-4, 4a-dihydro-1H-pyrrolo [3, 4-b] pyridine-5, 7(6H, 7aH)-dione (38m):



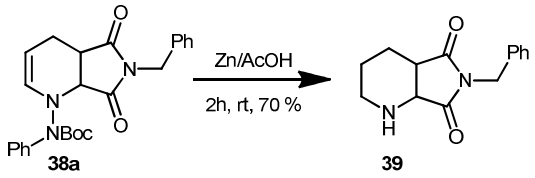
Pale red Color semi solid, R_f = 0.18 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.19 (m, 3H), 7.63-7.43 (m, 6H), 6.60 (d, *J* = 7.79 Hz, 1H), 4.75 (s, 3H), 4.32-4.24 (m, 1H), 3.91 (d, *J* = 8.26 Hz, 1H), 3.78 (d, *J* = 8.01 Hz, 1H), 2.83 (s, 3H), 2.75-2.67 (m, 1H), 2.26 (m, 1H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 177.9, 177.6, 153.3, 149.8, 139.4, 133.8, 132.7, 131.4, 130.0, 129.3, 112.9, 110.4, 49.3, 42.2, 38.5, 37.4, 31.5, 23.7; MS (ESI mass) m/z: 437.8[M+1].

tert-butyl 6-(4-methoxybenzyl)-5,7-dioxo-4,4a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-1-yl(4-methoxyphenyl)carbamate (38n):



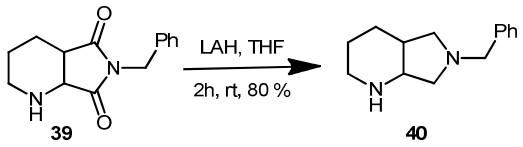
Pale red Color semi solid, R_f = 0.18 (10% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.39-7.18 (m, 4H), 6.84-6.70 (m, 4H), 5.63-5.42 (m, 1H), 4.57 (d, *J* = 1.33 Hz, 2H), 3.77 (d, *J* = 4.64 Hz, 6H), 3.61 (d, *J* = 8.09 Hz, 1H), 2.60-2.43 (m, 1H), 2.37-2.23 (m, 1H), 2.16-2.02 (m, 1H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 178.7, 177.0, 159.2, 130.0, 127.7, 114.9, 113.9, 113.8, 113.3, 110.1, 109.9, 81.5, 72.3, 55.6, 55.2, 48.4, 41.7, 36.9, 28.3, 23.5; MS (ESI mass) m/z: 493.8[M+1].

6-benzyltetrahydro-1H-pyrrolo[3,4-b]pyridine-5,7(6H,7aH)-dione (39):



To a stirred solution of tert-butyl6-benzyl-5,7-dioxo-4,4a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-1-yl(phenyl)carbamate (110 mg, 0.25 mmol) in acetic acid (3.0 mL) was added to Zn (165 mg, 2.5 mmol) under nitrogen, the reaction mixture was stirred at room temperature. After completion the reaction, the residue was dissolved in EtOAc (5.0 mL) and washed with saturated $NaHCO_3$ solution. The aqueous layer was further extracted with EtOAc (3 x 3 ml). The combined organic layers were collected, washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under *vacuo*. The residue was purified by flash chromatography using 50% EtOAc in Hexane to give desire compound **39** (45 mg, 75% yield) as a color less liquid, R_f = 0.15 (50% EtOAc in Hexane). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.40-7.23 (m, 5H), 4.67 (d, *J* = 8.56 Hz, 2H), 3.85 (d, *J* = 7.06 Hz, 1H), 2.87 (q, *J* = 7.16 Hz, 1H), 2.80 (td, *J* = 10.68, 5.24 Hz, 1H), 2.67 (td, *J* = 11.72, 5.90 Hz, 1H), 1.98 (td, *J* = 13.07, 6.25 Hz, 2H), 1.65 (dt, *J* = 13.73, 6.93 Hz, 1H), 1.51 (m, 2H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 177.9, 177.7, 135.7, 128.6, 128.4, 127.8, 55.3, 42.3, 42.1, 39.2, 23.0, 22.3. MS (ESI mass) m/z: 244.7[M+1].

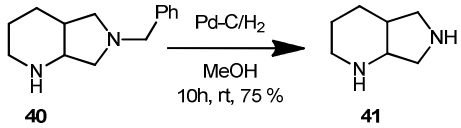
6-benzyloctahydro-1H-pyrrolo[3,4-b]pyridine (40):



39 40

To a stirred solution of 6-benzyltetrahydro-1H-pyrrolo[3,4-b]pyridine-5,7(6H,7aH)-dione **39** (36 mg, 0.15 mmol) in dry THF (5.0 mL) was added to LAH (25 mg, 0.6 mmol) under nitrogen at 0 °C. The reaction mixture was heated to 40 °C stirred at same temperature. After completion the reaction the mixture was cooled to room temperature and quenched with 5ml ethyl acetate. The residue passed through celite pad and the resulting solution was evaporated under reduced pressure will get desire compound **40** (25 mg, 70% yield) as colorless liquid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.39-7.28 (m, 5H), 3.76 (dd, *J* = 37.10, 13.04 Hz, 2H), 3.27 (dd, *J* = 4.89, 3.68 Hz, 1H), 3.05-2.93 (m, 4H), 2.86 (dd, *J* = 10.12, 4.88 Hz, 1H), 2.78 (t, *J* = 8.99 Hz, 1H), 2.68 (dd, *J* = 14.41, 5.27 Hz, 2H), 2.25 (td, *J* = 13.07, 4.13 Hz, 1H), 1.68 (td, *J* = 9.66, 4.55 Hz, 2H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 139.6, 128.5, 128.1, 126,7, 60.8, 60.6, 56.5, 55.3, 44.4, 36.5, 29.6, 24.1, 22.1; MS (ESI mass) m/z : 216.7[M+1].

Octahydro-1H-pyrrolo[3,4-b]pyridine (41):



40 41

To a stirred solution of 6-benzyloctahydro-1H-pyrrolo[3,4-b]pyridine **40** (20 mg, 0.1 mmol) in dry MeOH (5.0 mL) was added to Pd/C (20 mg,) under hydrogen. The reaction mixture was heated to 70 °C stirred at same temperature for 5 to 7 hours. After completion the reaction the mixture was cooled to room temperature and the residue passed through sintered funnel and the resulting solution was evaporated under reduced pressure will get desire compound **41** (10 mg, 80% yield) as colorless liquid.

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 3.75 (m, 1H), 3.55-3.45 (m, 1H), 3.19-3.05 (m, 1H), 2.86 (m, 2H), 2.24 (s, 1H), 2.07 (d, *J* = 13.26 Hz, 4H), 2.62 (d, *J* = 23.27 Hz, 2H), 1.73 (m, 2H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 64.2, 58.1, 55.8, 43.3, 43.1, 38.0, 21.6, 20.7 MS (ESI mass) m/z : 126.7[M+1].

4.6. References

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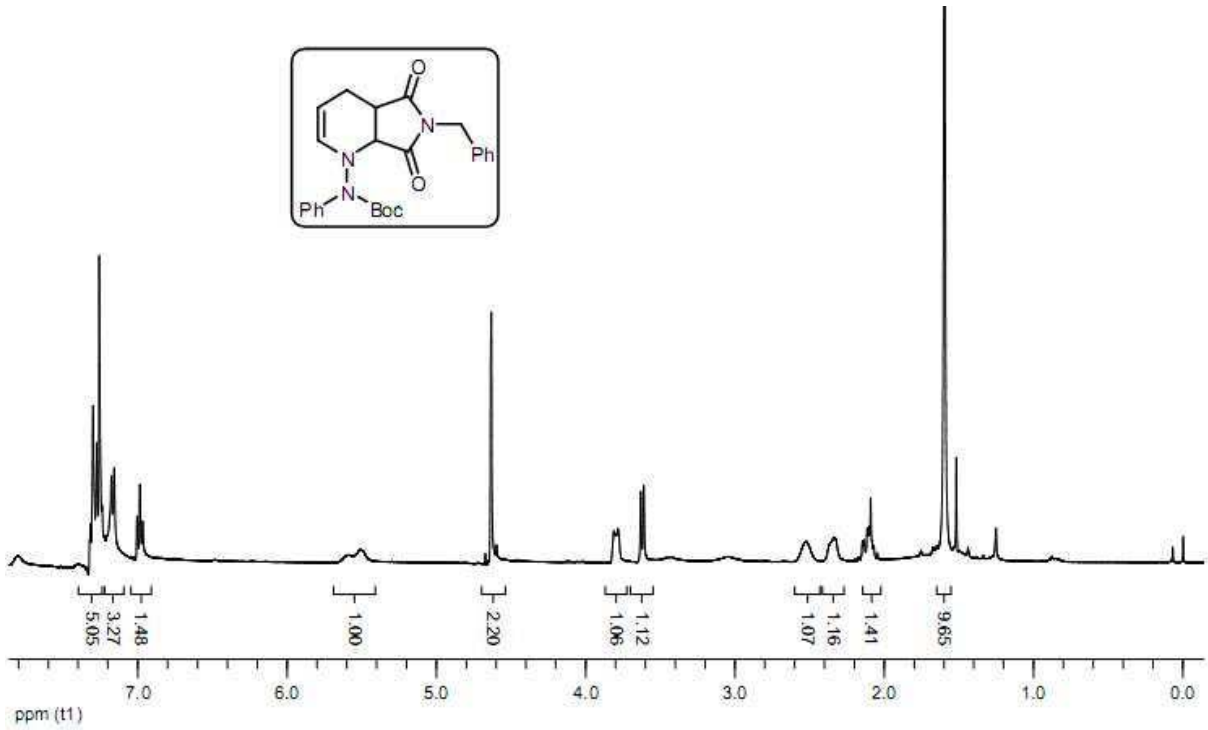
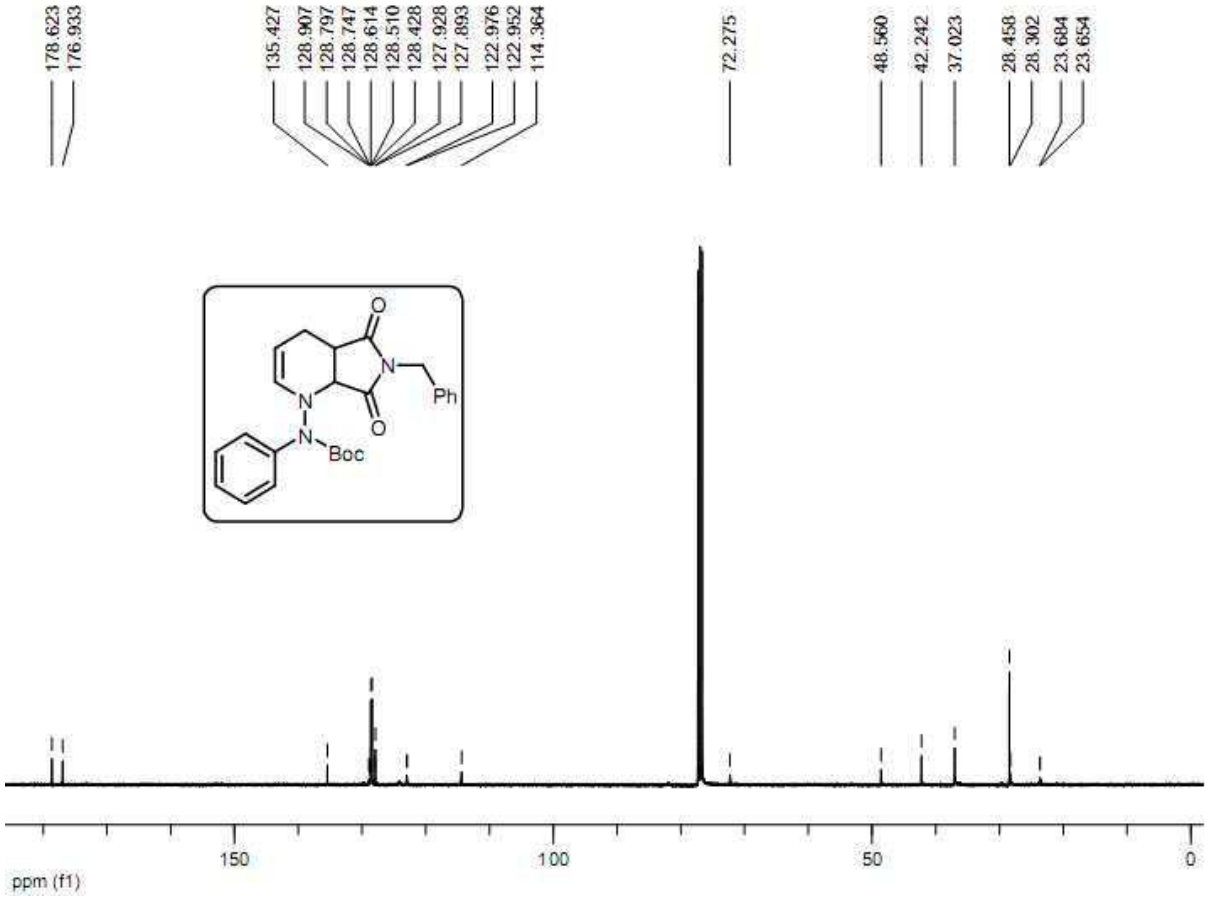
4.7. NMR Spectra

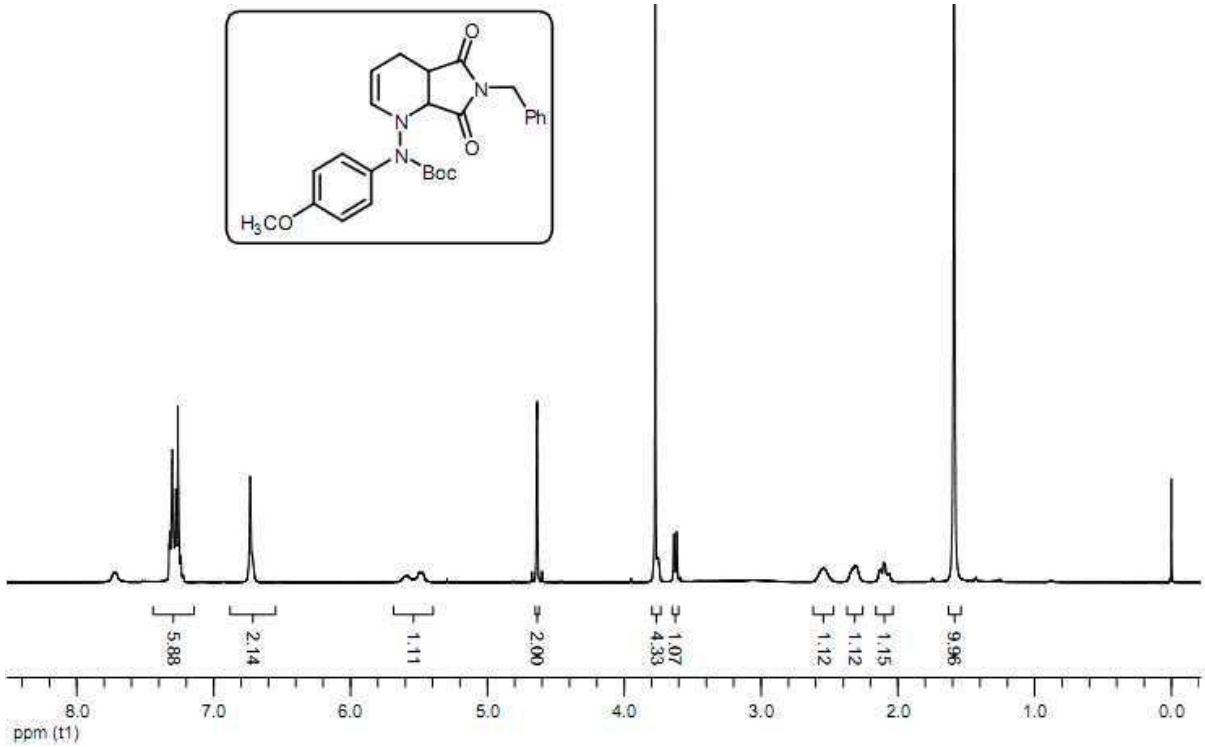
38a ^{1}H NMR ($CDCl_3$, 400 MHz)



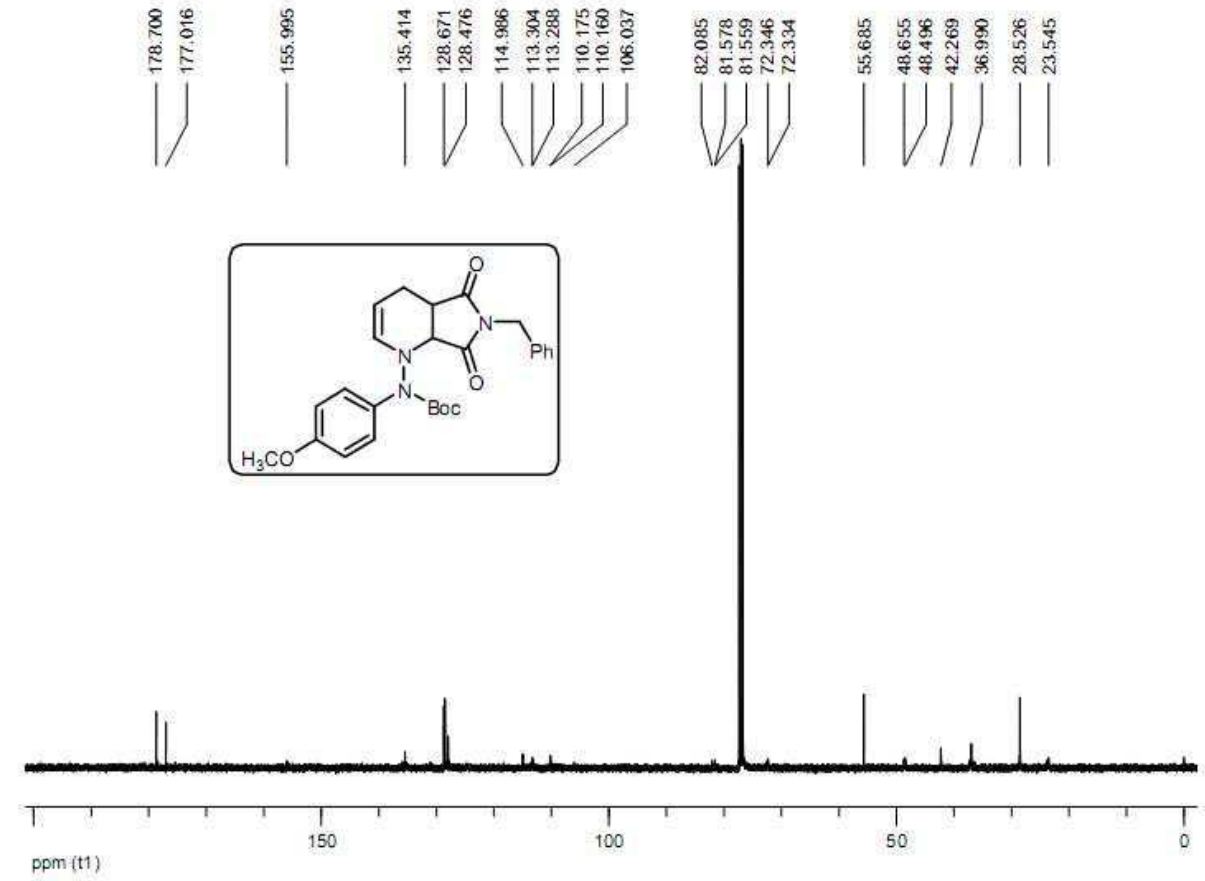
38a ^{13}C NMR ($CDCl_3$, 100 MHz



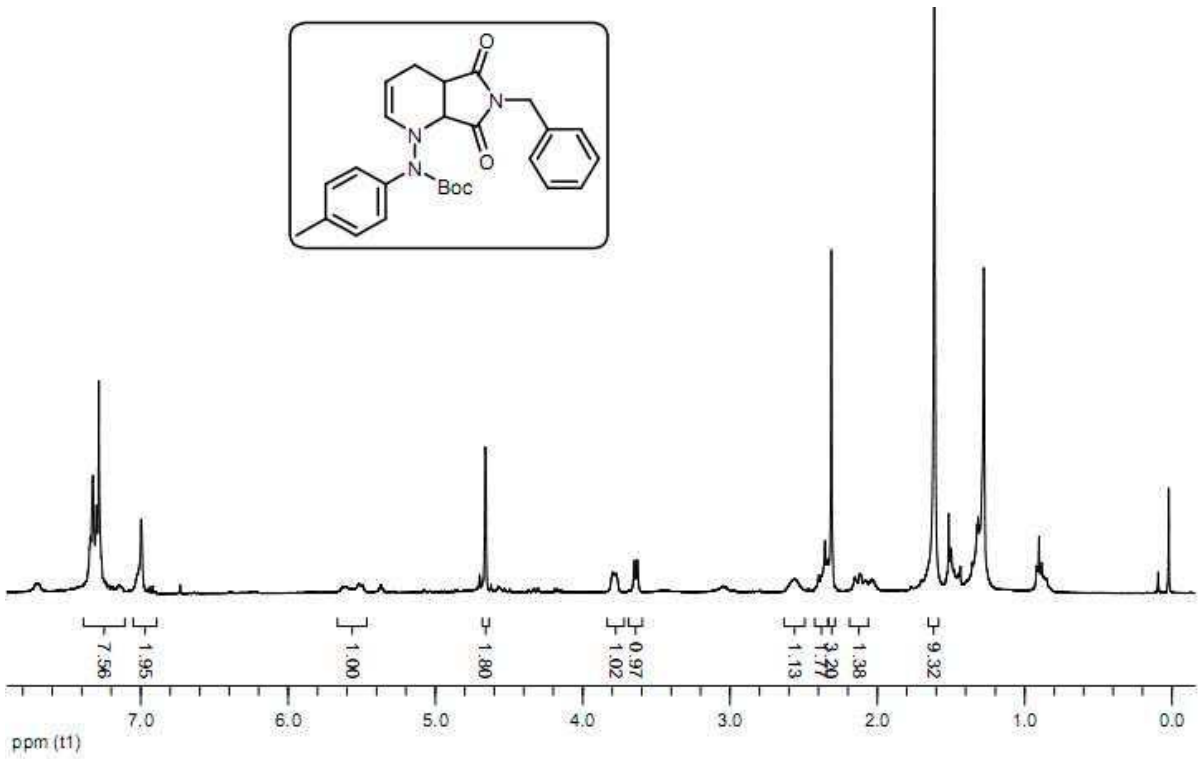
38b ^{1}H NMR ($CDCl_3$, 400 MHz)



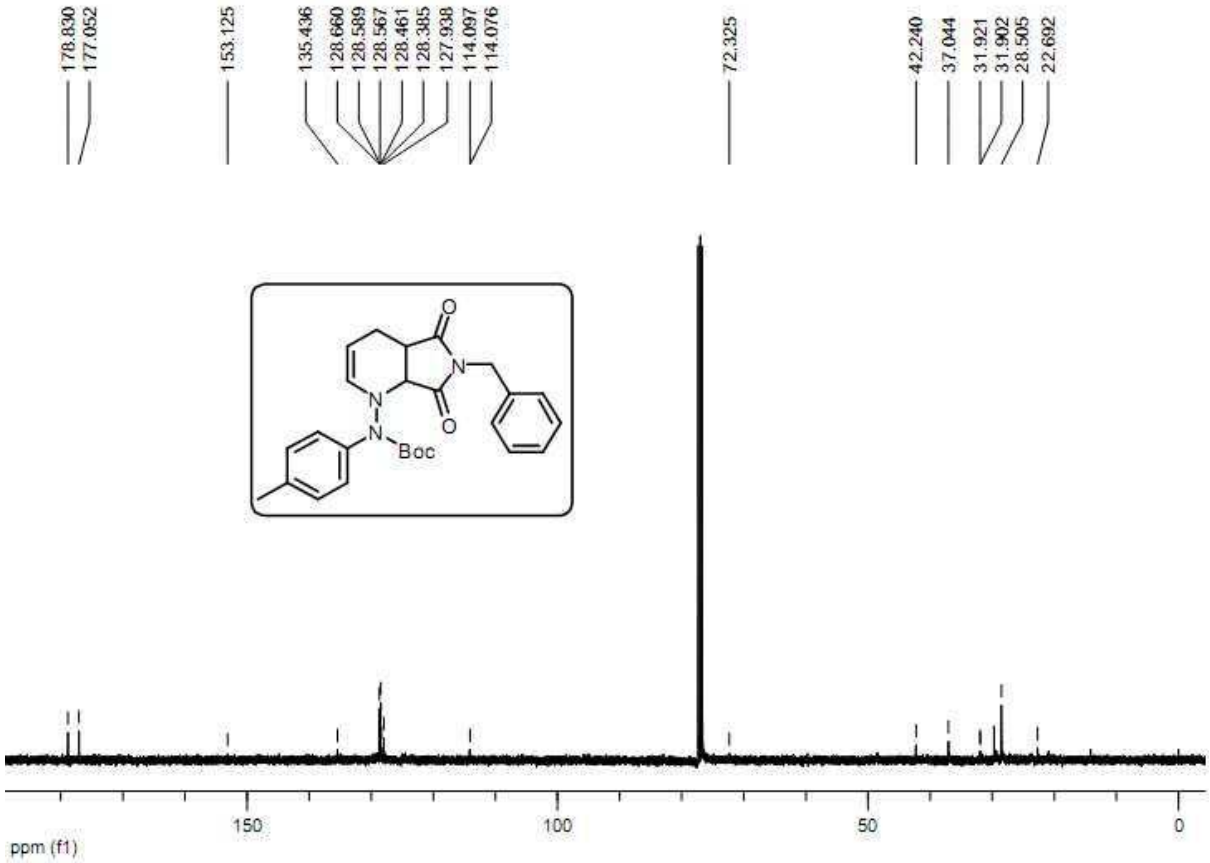
38b ^{13}C NMR ($CDCl_3$, 100 MHz



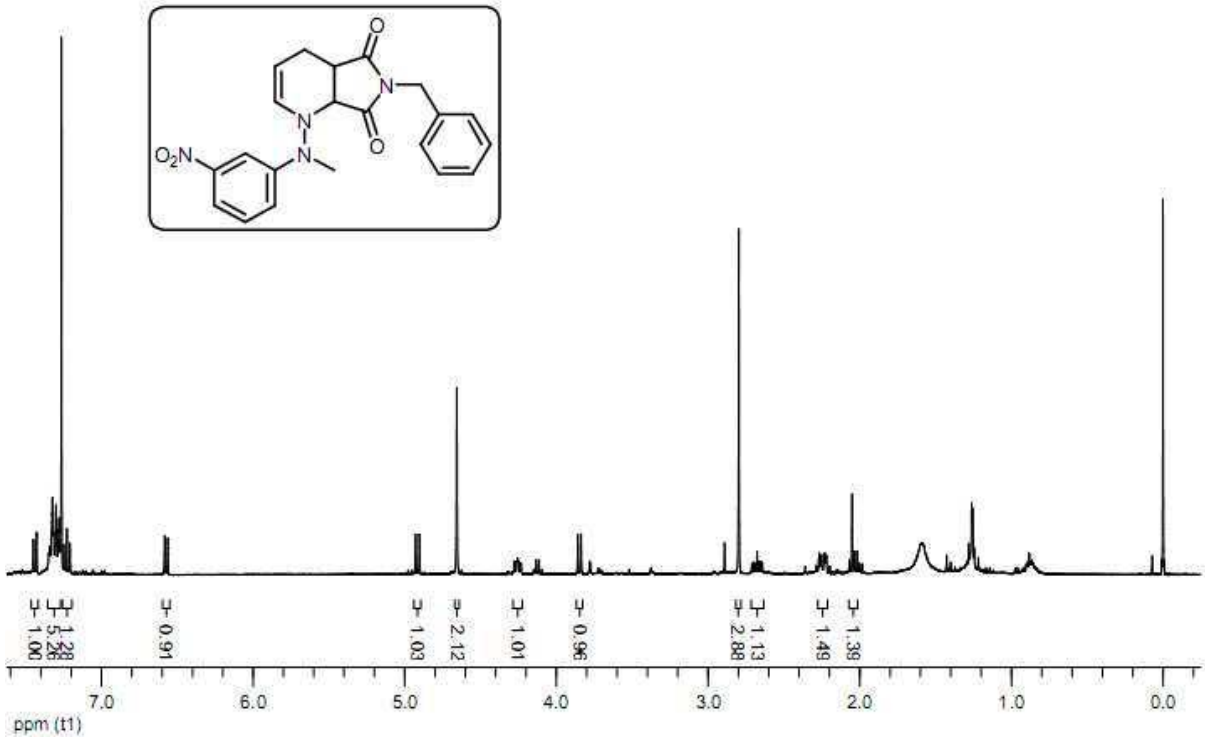
38c ^{1}H NMR ($CDCl_3$, 400 MHz)



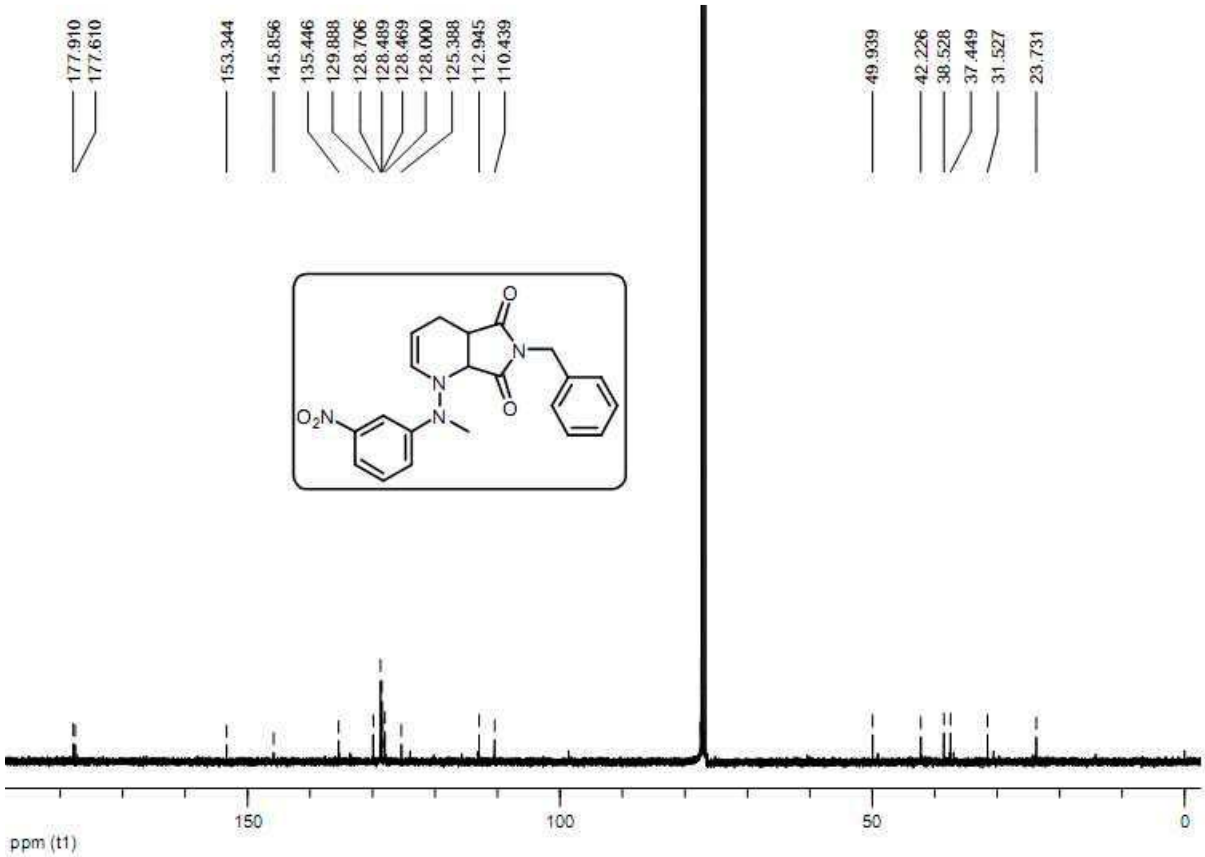
38c ^{13}C NMR ($CDCl_3$, 100 MHz)



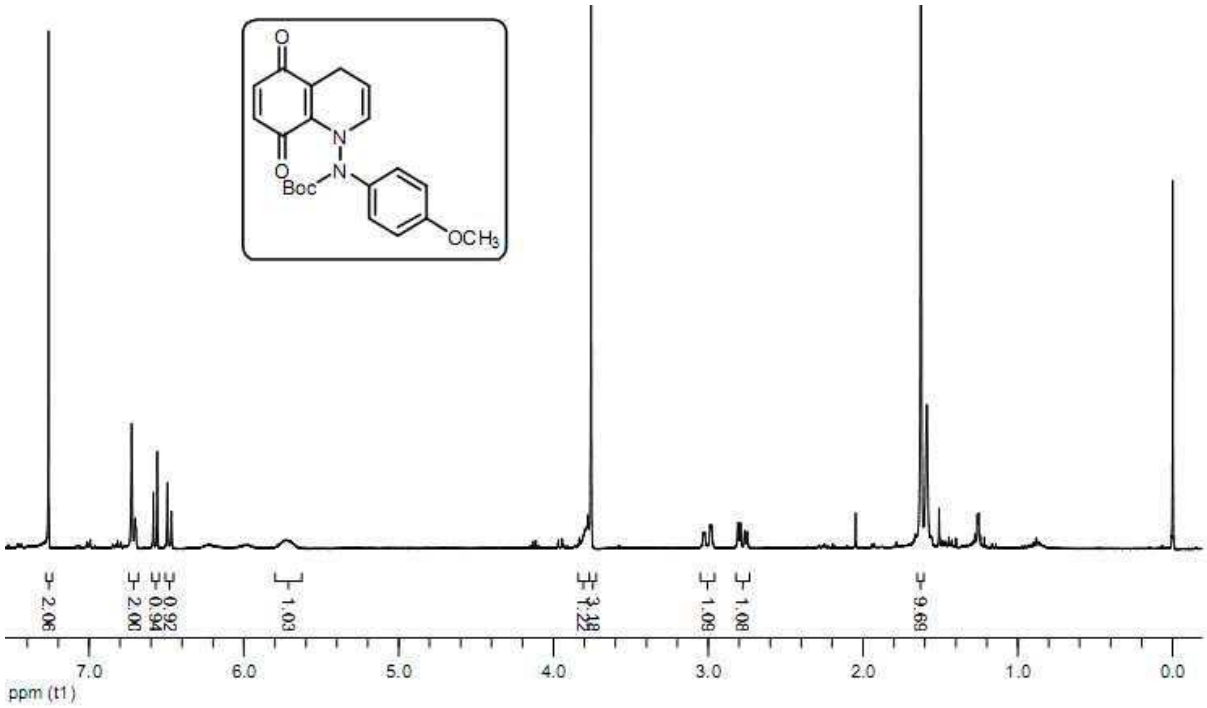
38d ^{1}H NMR ($CDCl_3$, 400 MHz)



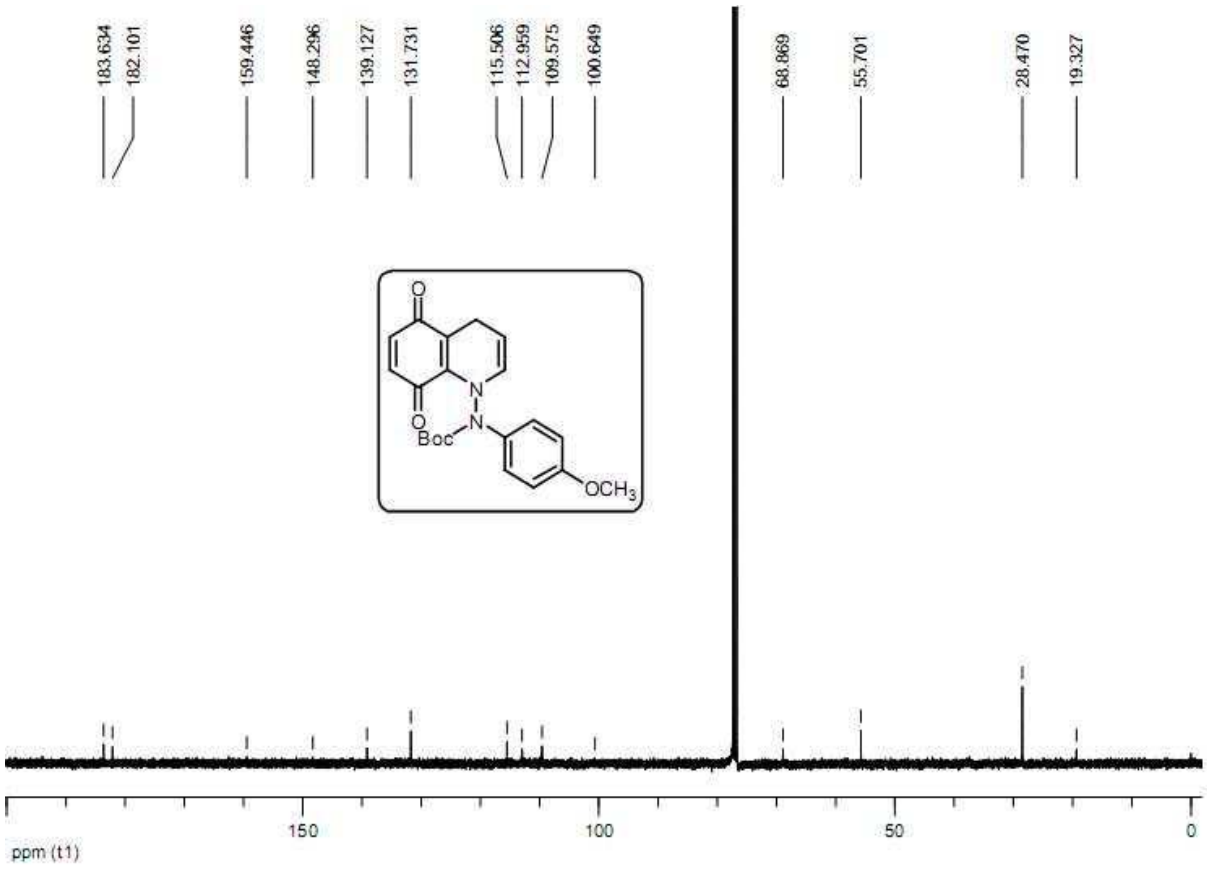
38d ^{13}C NMR ($CDCl_3$, 100 MHz)



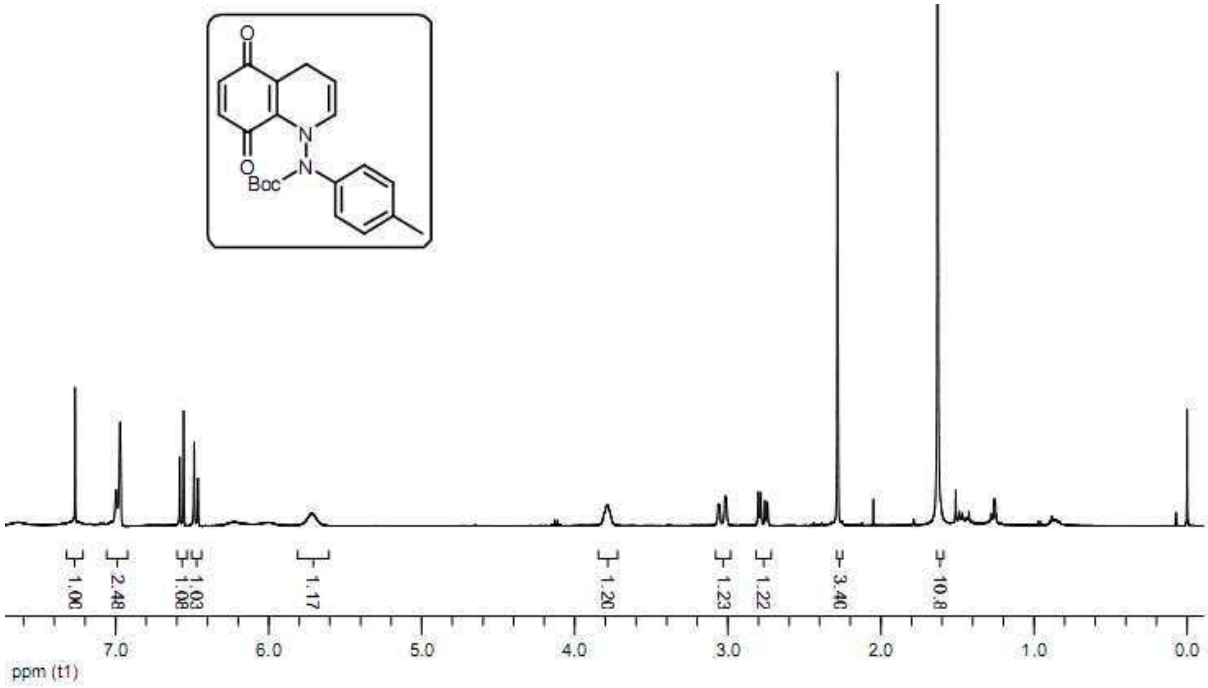
38g ^{1}H NMR ($CDCl_3$, 400 MHz)



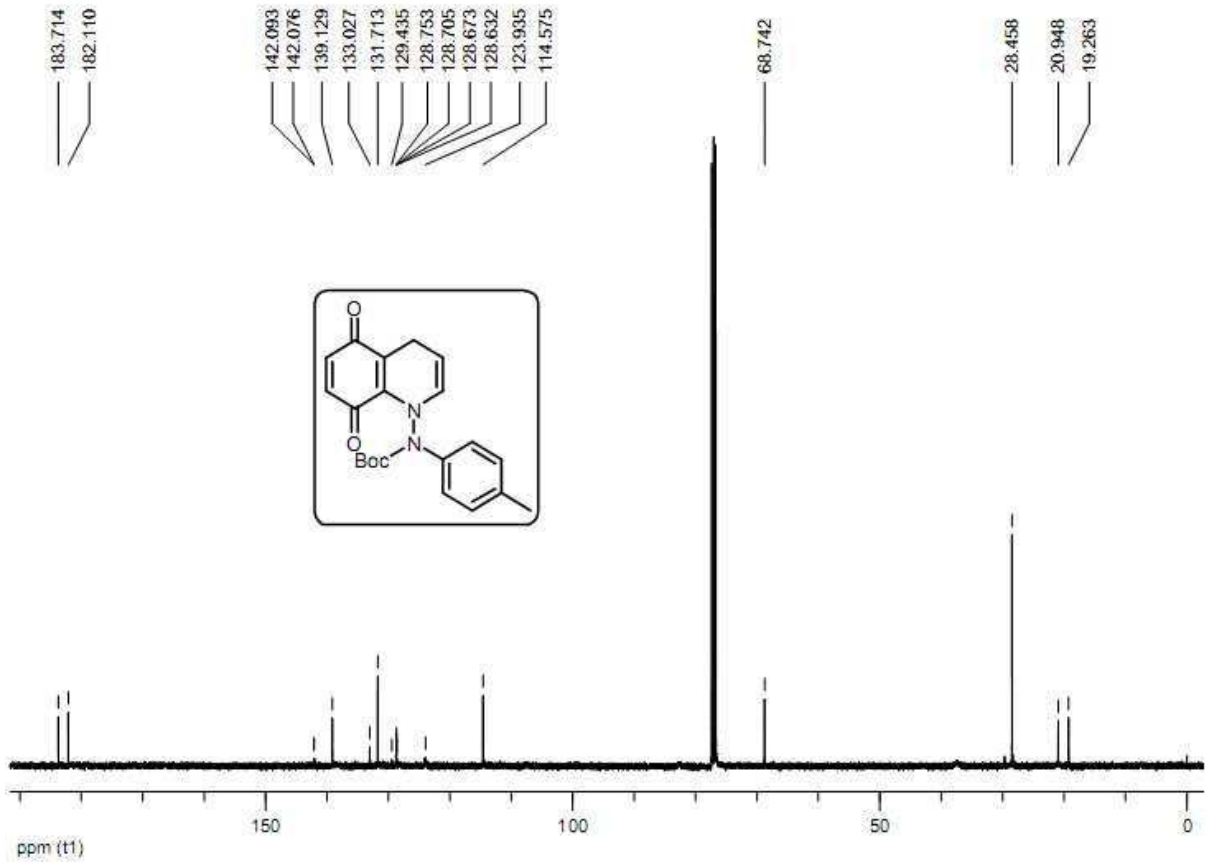
38g ^{13}C NMR ($CDCl_3$, 100 MHz)



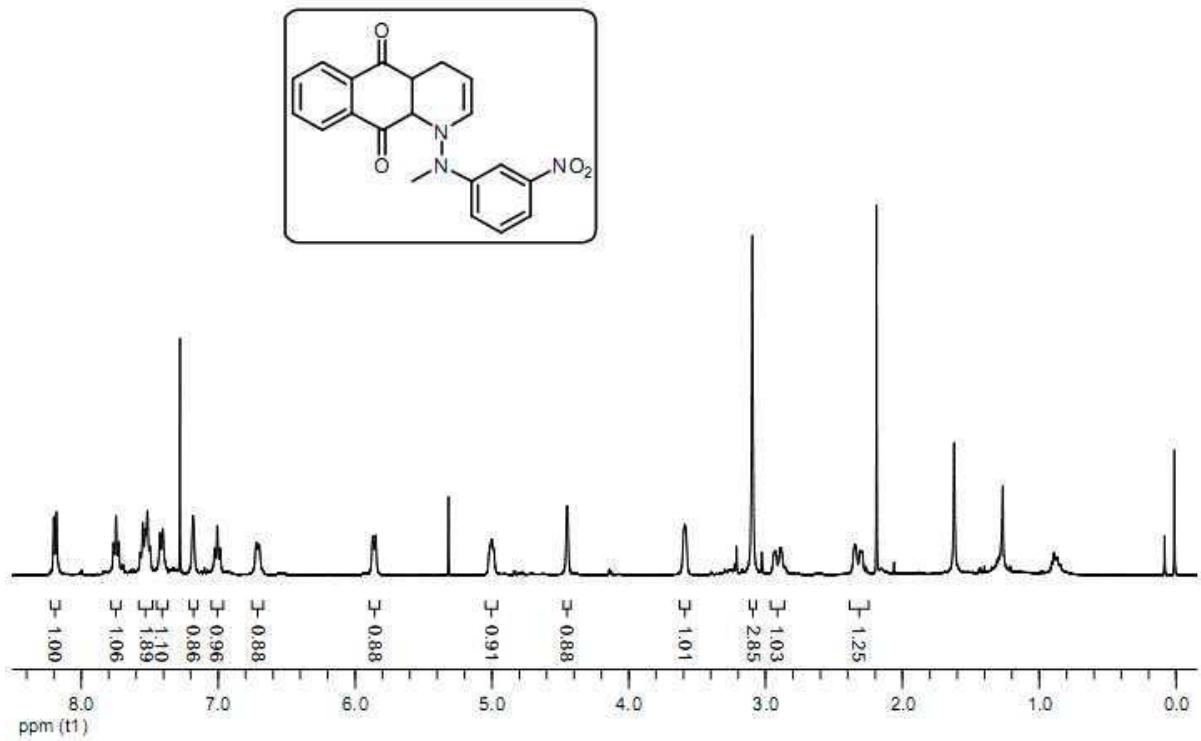
38h ^{1}H NMR ($CDCl_3$, 400 MHz)



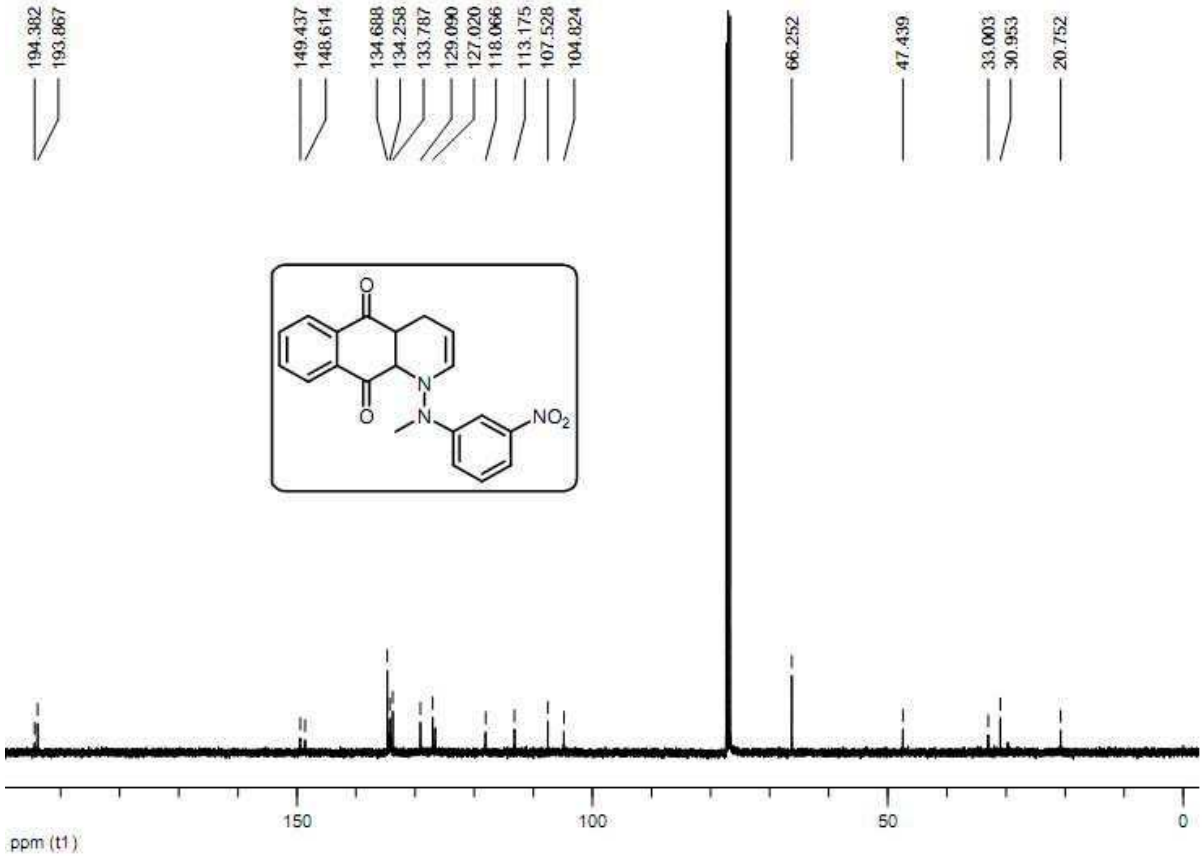
38h ^{13}C NMR ($CDCl_3$, 100 MHz)



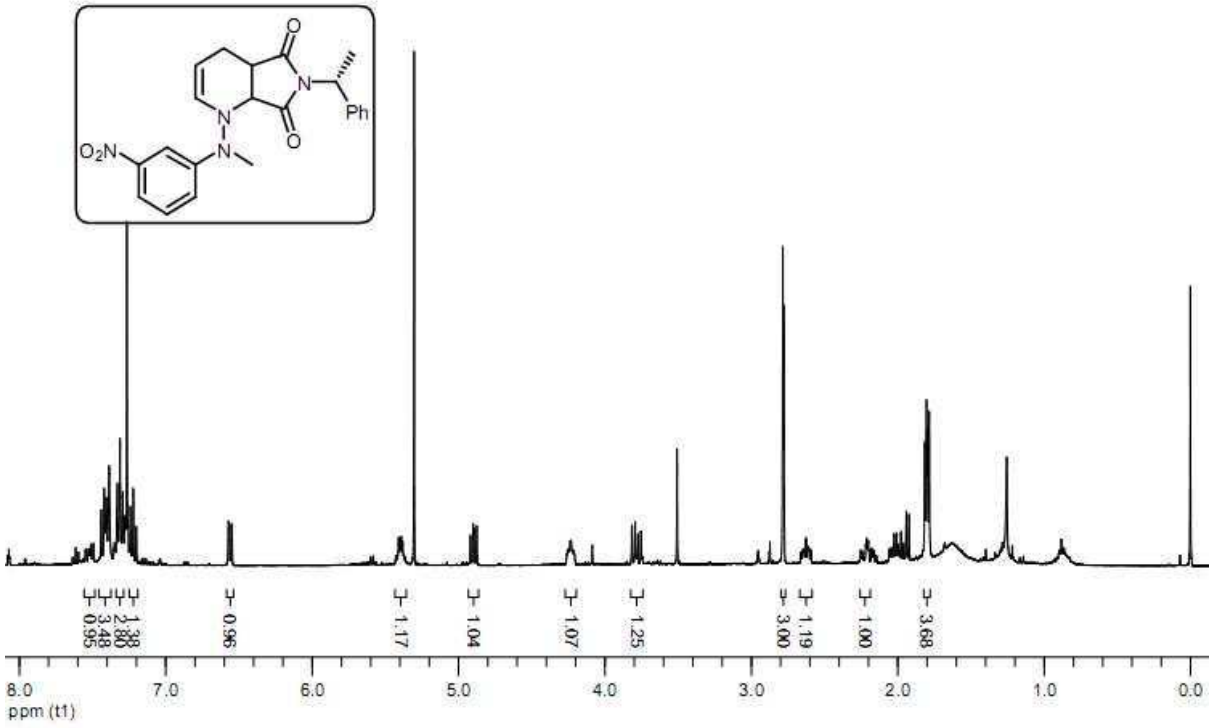
38i ^{1}H NMR ($CDCl_3$, 400 MHz)



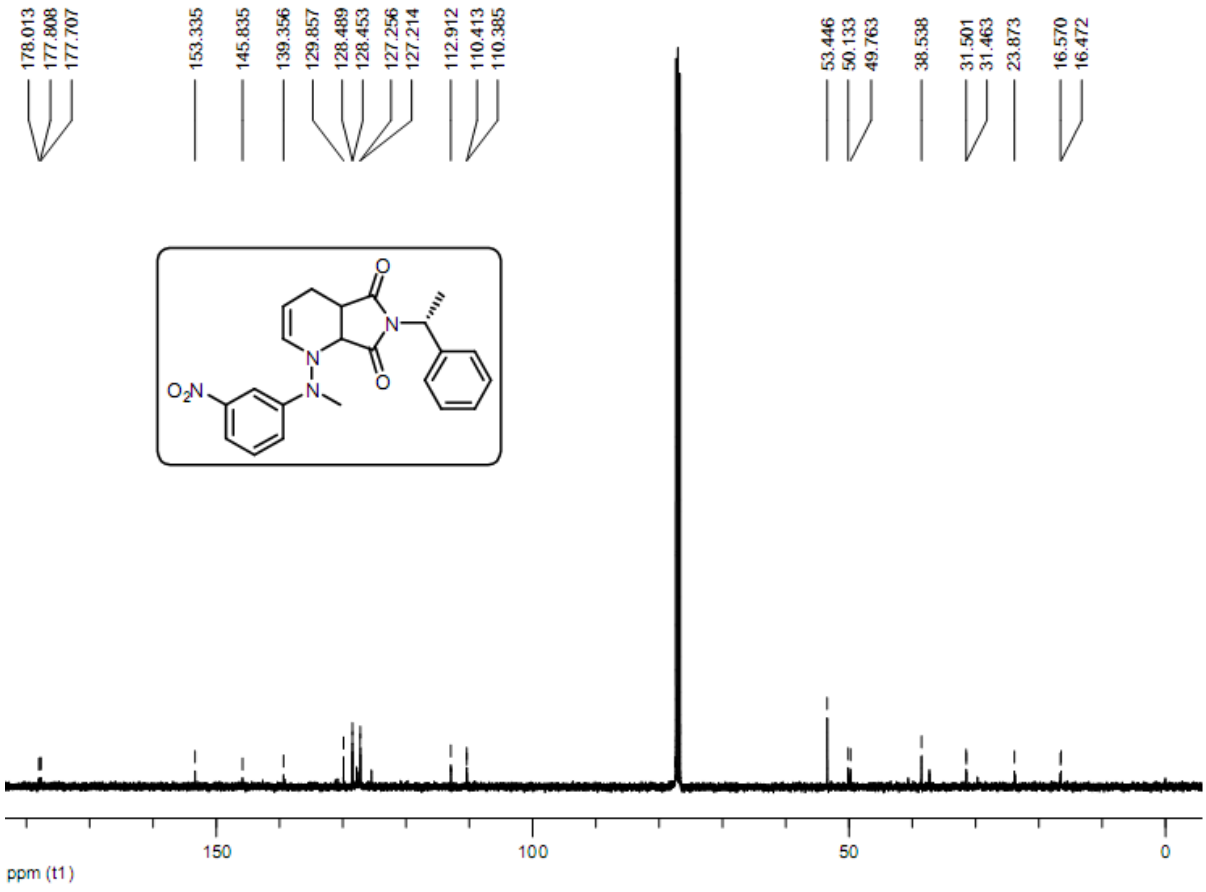
38i ^{13}C NMR ($CDCl_3$, 100 MHz)



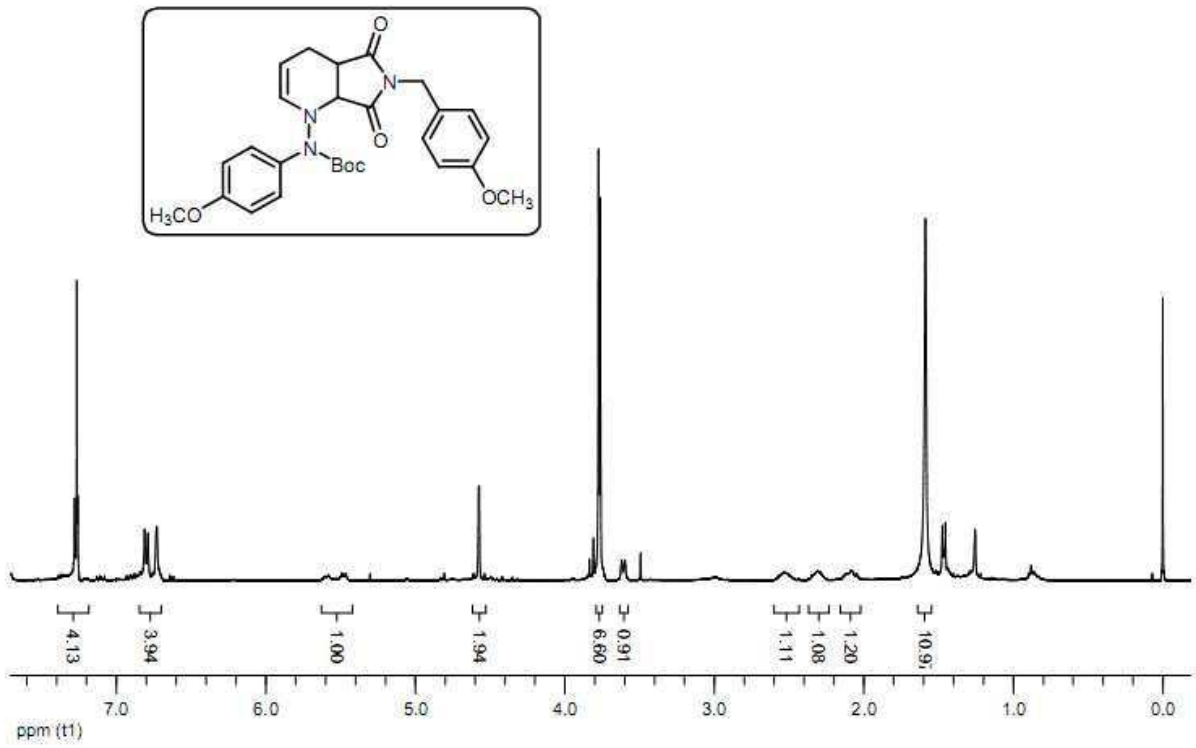
38k ^{1}H NMR ($CDCl_3$, 400 MHz)



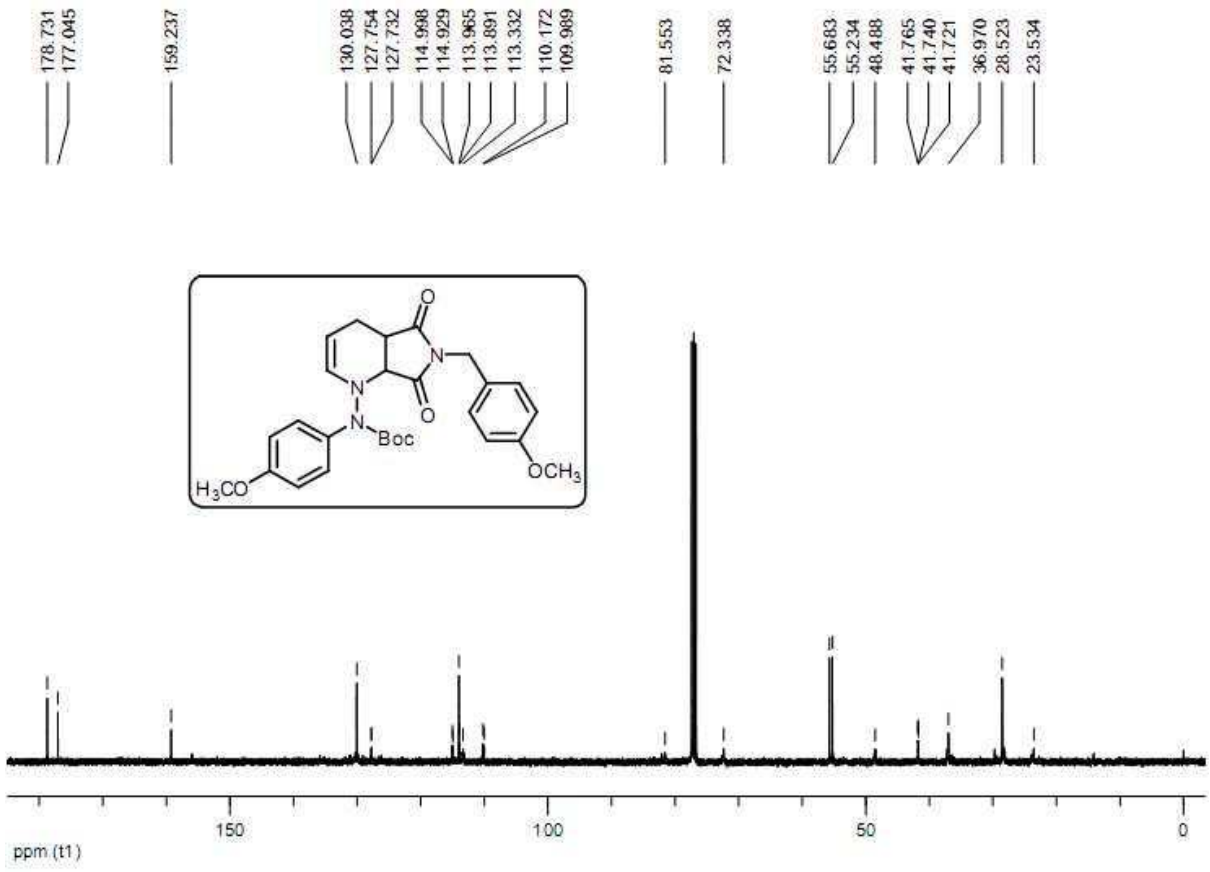
38k ^{13}C NMR ($CDCl_3$, 100 MHz)



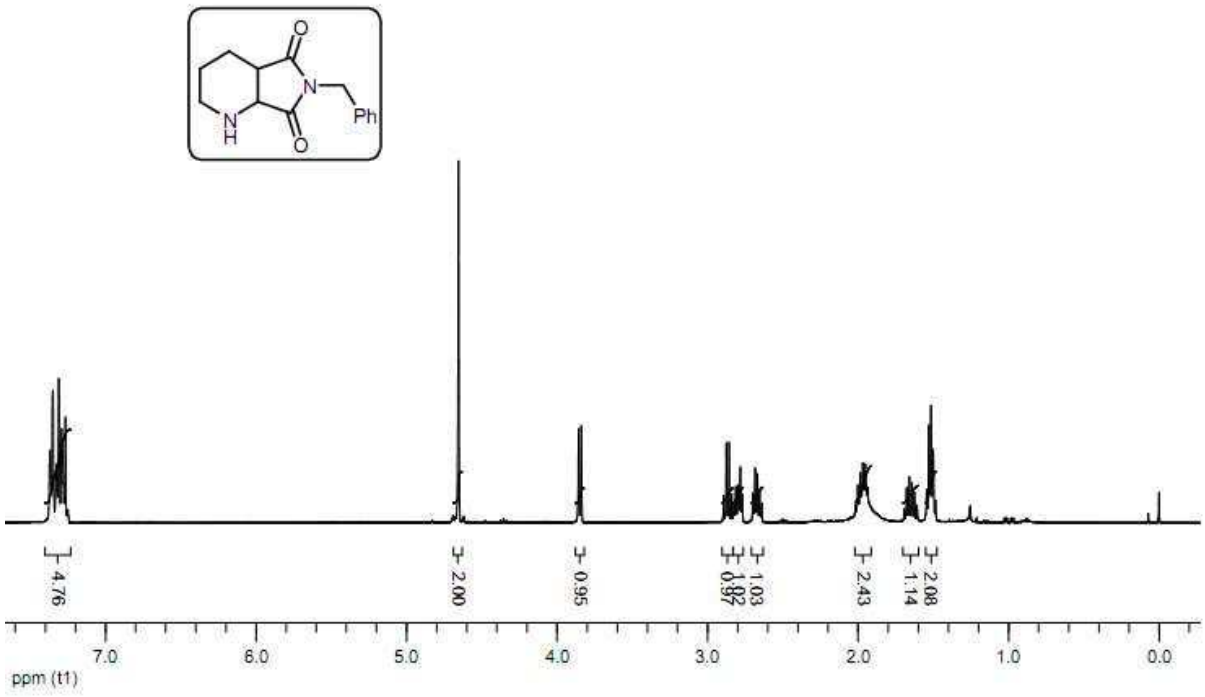
38n ^{1}H NMR ($CDCl_3$, 400 MHz)



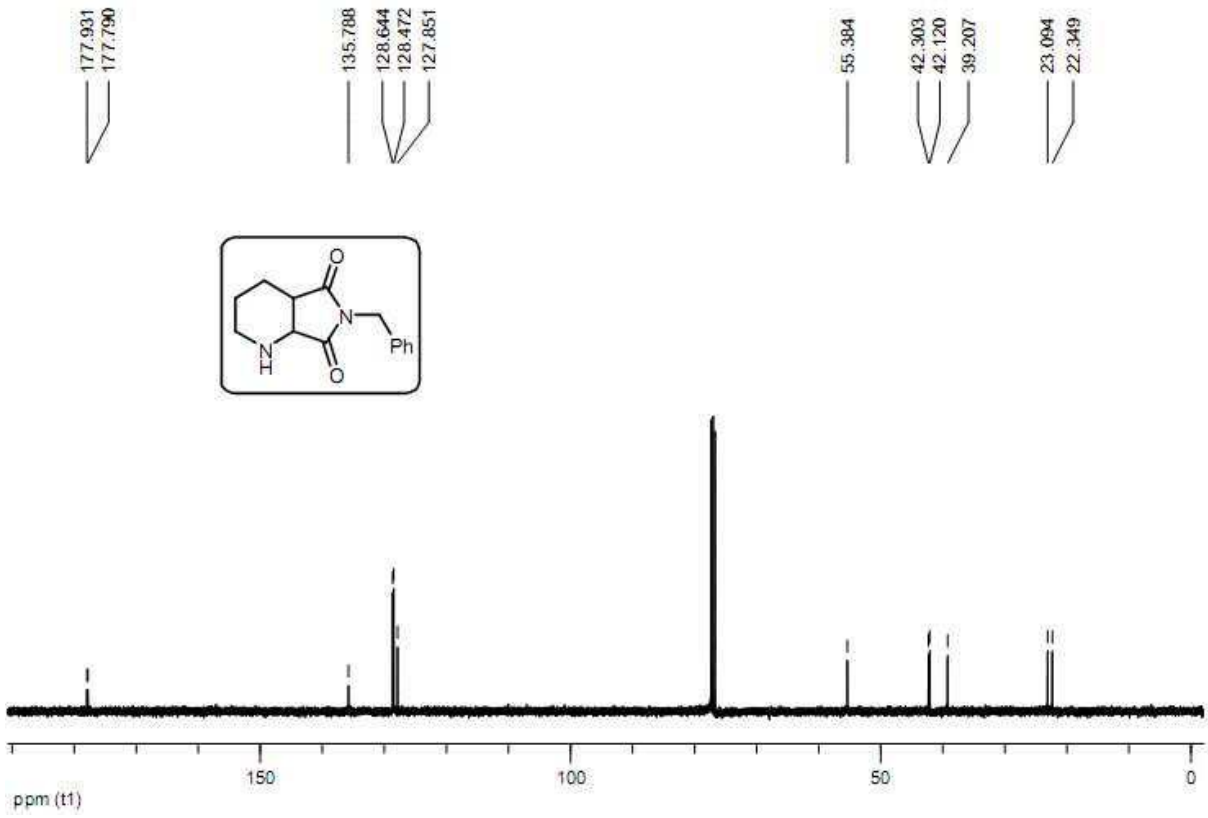
38n ^{13}C NMR ($CDCl_3$, 100 MHz)



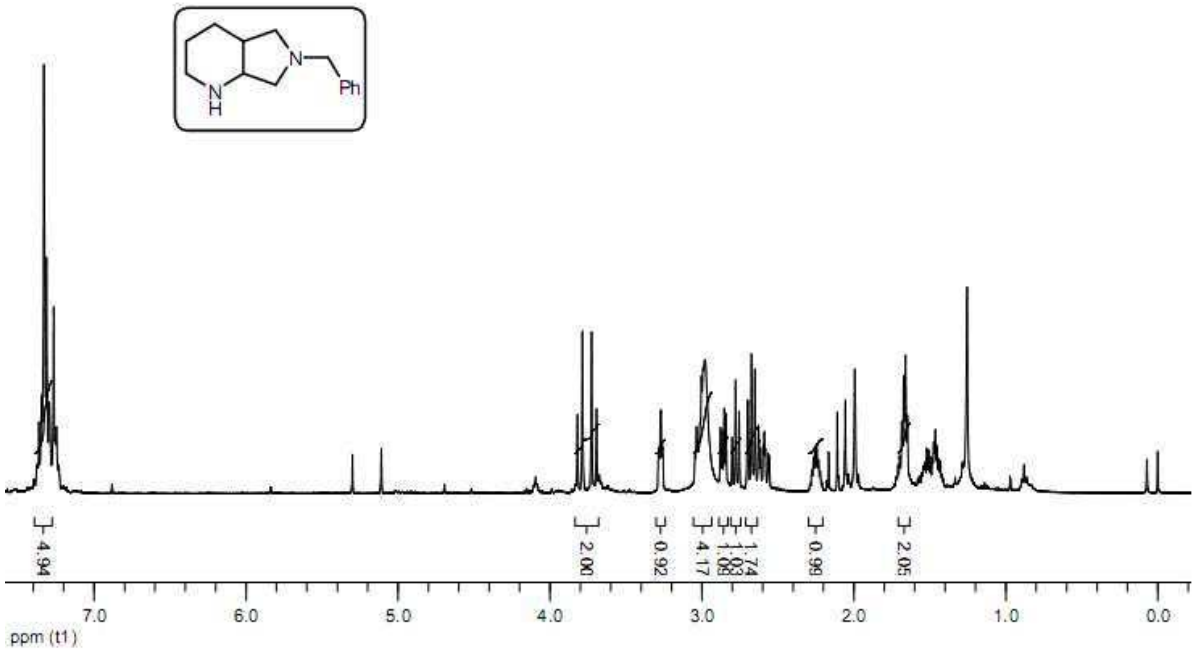
39 ^{1}H NMR ($CDCl_3$, 400 MHz)



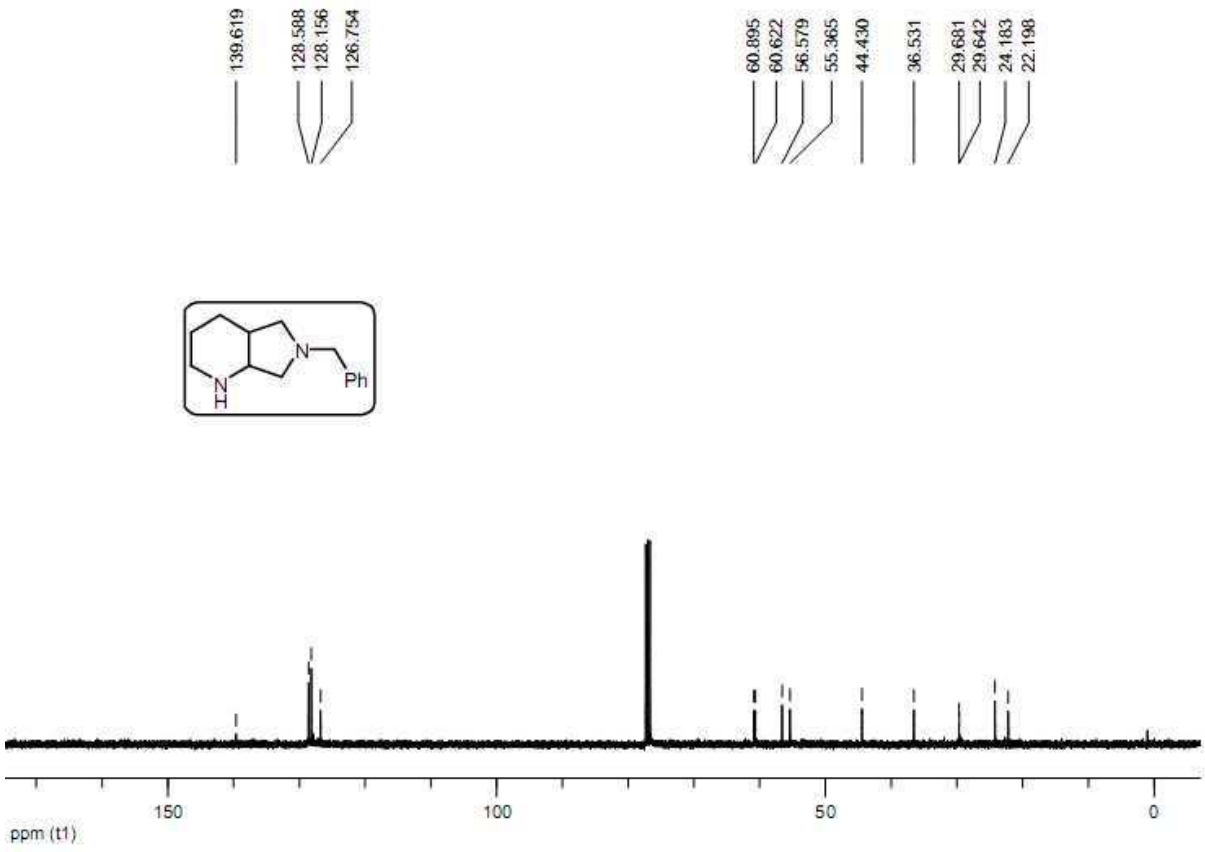
39 ^{13}C NMR ($CDCl_3$, 100 MHz)



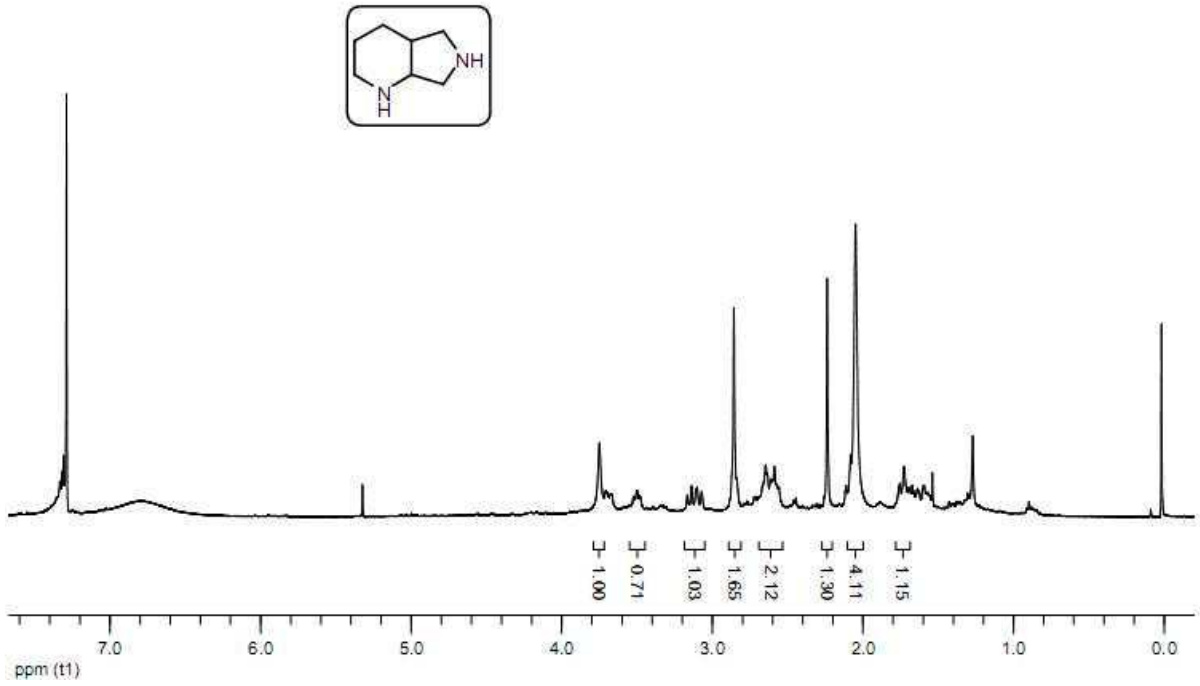
40 ^{1}H NMR ($CDCl_3$, 400 MHz)



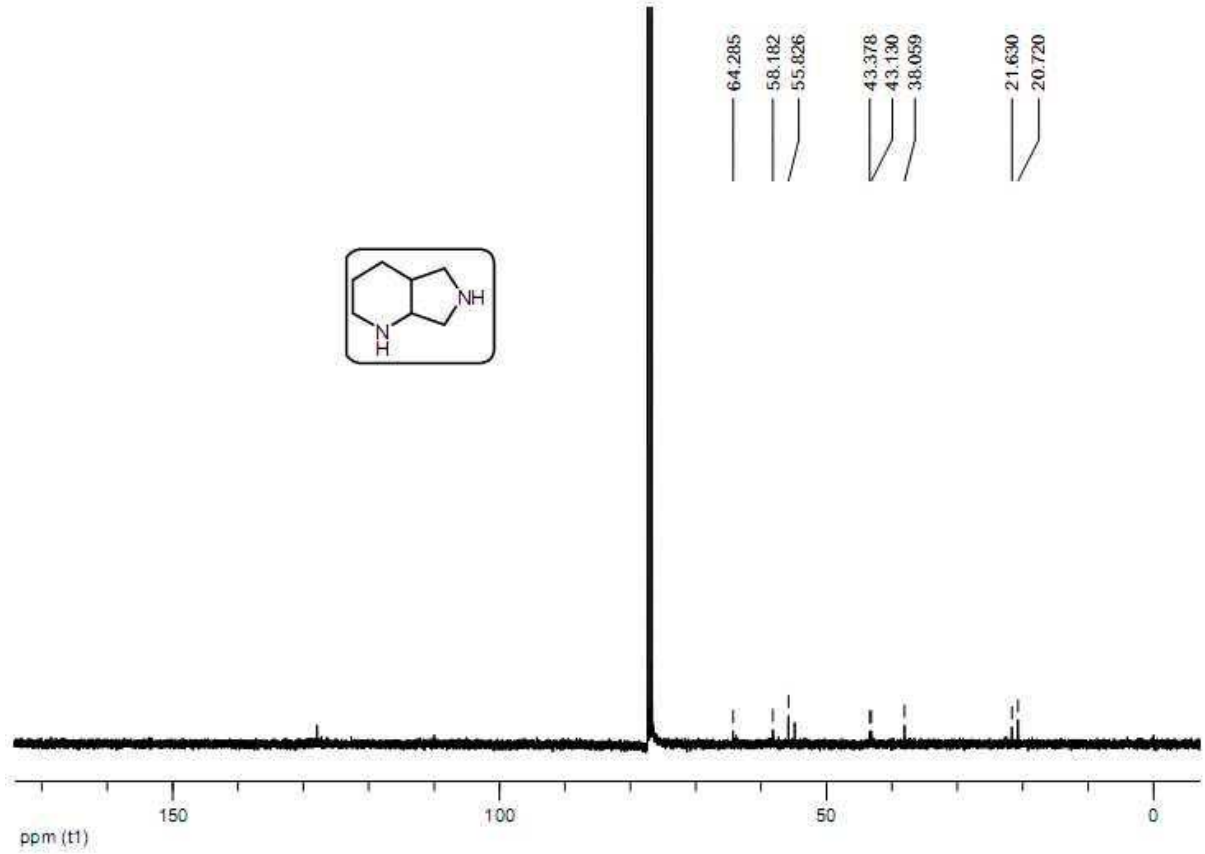
40 ^{13}C NMR ($CDCl_3$, 100 MHz)



41 ^{1}H NMR ($CDCl_3$, 400 MHz)



41 ^{13}C NMR ($CDCl_3$, 100 MHz)



Research Publications

1. Salt-mediated oxidative *N*-annulation for diverse and functionalized pyridines. V. **Devendram,** Rajamohan R Poondra*. *Manuscript in preparation.*
2. Development of a one-pot catalyst free Domino approach to functionalized 1,4-Dihydropyridines. V. **Devendram,** Rajamohan R Poondra*. *Manuscript in preparation*
3. New method for the synthesis of functionalized isoquinolinequinones and its application to the isoquinolinequinone core of Mansouramycin-D. **V Devendram** and Rajamohan R Poondra*. *Manuscript in preparation*
4. Synthesis of Moxifloxacin intermediate by using 1-AzaDiels-Alder reaction. **V Devendram** and Rajamohan R Poondra*. *Manuscript in preparation*
5. IBX mediated reaction of *β*-enamino esters with allylic alcohols: A one pot metal free domino approach to functionalized pyridines. Narendar Reddy Gade**, V. Devendram**, Manojit Pal*, Javed Iqbal*. *Chem. Commun.* **2013,** *49*, 7926.

Poster Presentations in Conferences and Symposiums

- **Devendram V**, Rajamohan R Poondra*, Synthesis of racemic moxifloxacine intermediate by AzaDiels-Alder reaction
- Presented a poster at "**Dr. Kallam Anji Reddy Memorial Symposium"** organized by Dr. Reddy's ILS, on 21st Sep-2013.
- **Devendram. V,** Rajamohan R Poondra*. Development of a one-pot catalyst free Domino approach to functionalized 1,4-Dihydropyridines
- Presented a poster at "**Young Scholar's Science Cafe Meet**" organized by Dr. Reddy's ILS, on 10th August-2015.
- **Devendram V**, Rajamohan R Poondra* Salt-mediated oxidative N-annulation for diverse and functionalized pyridines
- Presented a poster at international Conference on "**Trend Setting Innovations in Chemical Science & Technology Applications in Pharmaceutical Industry**" held at JNTUH, Hyderabad, India on December 2015.