Iodine Mediated One-pot Three Component Synthesis of a Novel tricyclic Pyrrolo-1,4-Benzoxazines

A project report submitted

as a part of requirements for the degree of

MASTER OF SCIENCE

By

ARNAB DEY

Roll no. CY12M1006

Under the supervision of

Dr. D. S. Sharada

to the

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY HYDERABAD

INDIA

APRIL, 2014

DECLARATION

I declare that this written submission represents my ideas in my own words, and where others ideas or words have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be a cause for disciplinary action by the institute and can also evoke penal action from the sources that have thus not been properly cited, or from whom proper permission has not been taken when needed.

Dr. D. S. SHARADA
Assistant Professor
Department of Chemistry
Indian Institute of Technology Hyderabad
Ordinance Factory Estate,
Yeddumailaram-502 205, A.P.- India.

(Signature of the Supervisor)

(Student signature)

_____Arnab Dey_____
(Student name)

_____CY12M1006_____
(Roll no.)

2

APPROVAL SHEET

This thesis title **"Iodine Mediated One-pot Three Component Synthesis of a novel tricyclic Pyrrolo-1,4-benzoxazines"** by Arnab Dey is approved for the degree of Master of Science from IIT Hyderabad.

Surendra 11.04.2014

Dr. SURENDRA K. MARTHA
Assistant Professor
Department of Chemistry
Indian Institute of Technology Hyderabad

-Name and affiliation-
Examiner

Dr. G. Satyanarayana
Assistant Professor
Department of Chemistry
Indian Institute of Technology Hyderabad
Ordnance Factory Estate
Yeddumailaram-502 205
Andhra Pradesh, India

G. Satya

-Name and affiliation-
Examiner

Dr. D. S. SHARADA
Assistant Professor
Department of Chemistry
Indian Institute of Technology Hyderabad
Ordinance Factory Estate,
Yeddumailaram-502 205, A.P.- India

-Name and affiliation-
Advisor

-Name and affiliation-
Co-Advisor

-Name and affiliation-
Chairman

3

ACKNOWLEDGEMENTS

I wholeheartedly express my immense respect and deep sense of gratitude to my project supervisor Dr. D. S. Sharada, whose excellent guidance and constant inspiration resulted in this piece of work. I am greatly fortunate to have a teacher like her for the work freedom she has given; helped me to learn a number of new things, which otherwise would have been very difficult for me. I am greatly indebted to her for teaching me and also want to take the opportunity to thank her heartedly for bestowing me of chemistry and moral values of the life.

I also want to take the opportunity to express my hearty thanks to my lab-mates, Mr. Arepally Sagar, Mr. Anand H. Shinde, Mr. Shinde Vidyacharan, M. Srilaxmi and Nagarjuna babu for their help and valuable suggestions throughout my project tenure. I am thankful to Archith, Chaitra, Susanta for a friendly and cordial atmosphere and their time to time assistant in the lab. I specially remember my friends Sayak, Amrita, Captain, Souvik, Arijit, Syantan and Poulam for their love and company which I will never forget throughout my life.

Finally, I express respect to my parents and for their love and encouragement for pursuing something extraordinary in my life.

Arnab Dey

Dedicated

To

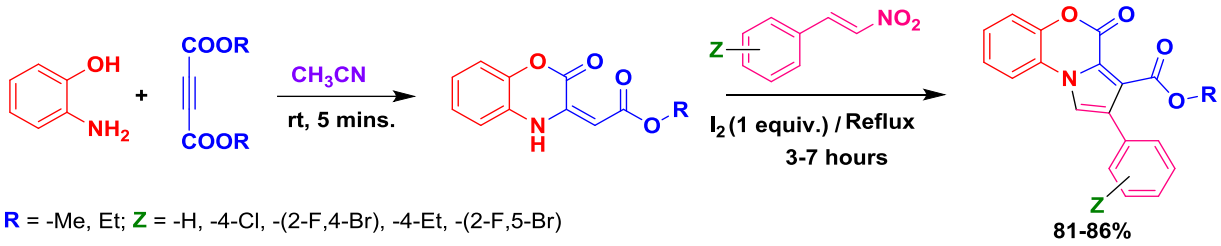
My Parents

ABSTRACT

A simple and efficient synthetic protocol has been developed using iodine, three-component one-pot reaction involving 2-aminophenol, dialkylacetylenedicarboxylate and substituted beta-nitrostyrene. Utilizing this protocol, a variety of novel pyrrolo-1,4-benzoxazine derivatives were synthesized in good to excellent yields.

CONTENTS

Iodine Mediated One-pot Three Component Synthesis of a Novel Tricyclic Pyrrolo-1,4-Benzoxazines



R = -Me, Et; Z = -H, -4-Cl, -(2-F,4-Br), -4-Et, -(2-F,5-Br)

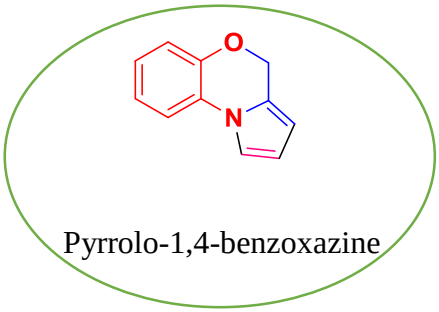
1.1 INTRODUCTION

The preparation of complex molecules by conventional method is not an easy task due to extraction and purification in each step, and time consuming as well as synthetically inefficient as it produces large number of waste. Multicomponent reactions leads to greener synthesis where generally in one pot three different substrates react and join through covalent bond. MCRs offer remarkable advantages like convergence, operational simplicity, facile automation, reduction in number of workup, extraction, purification process and hence minimize waste generation, and rendering the transformations green.[1] One-pot MCRs reduce energy and manpower as it is giving products in short reaction times with higher yields. In drug discovery, organic synthesis and material science MCRs got the highest attraction.[2] Green chemistry strongly influence chemical research and there is an insistence on the use of greener reaction condition.[3]

Iodine is inexpensive, nontoxic, readily available catalyst used for various organic transformatios.[4,5] It has high tolerence in air as well as in moisture and can be easily removed by using reducing agents. Now a days the development of a safe, atom-efficient acid and/or metal-catalyzed organic process is one of the most important challenges in green chemistry. While acid and/or metal catalysis remains the most widely used type of catalysis, the commonly used acid and/or metal catalysts continue to pose serious health and safety problems. Moreover, the mild Lewis acidity of iodine has enhanced its utility for several organic transformations starting from minor catalytic amounts to higher stoichiometric levels.

Many of the iodine-mediated reactions[6] features mild reaction conditions, greater stereo- and regioselectivities, and short reaction times. Most of these reactions are carried out by multicomponent and/or domino reaction sequences. Multicomponent[7,10] and domino[8] reactions allow the creation of several bonds in a single operation and are one of the important synthetic tools for the creation of molecular diversity and complexity.[9] They are also extremely user- and environment-friendly due to the step reduction and high atom-economy associated with their use.

Pyrrolo-1,4-benzoxazine have attracted much more attention. Due to their important biological activity, they are, in recent years broadly investigated and utilized in the pharmaceutical industry.



1.2 BIOLOGICAL & PHARMACEUTICAL ACTIVITY

Pyrrolo-1,4-benzoxazine became highly important heterocyclic molecule as it contains both the highly active heterocyclic moiety pyrrole and benzoxazine. Benzoxazines can be found in drugs[11,12] and natural products[13] such as Cappamensin A extracted from Capparin sikkimensis which has significant in vitro cytotoxicity against various human tumor cell lines. However, the broad potential biological activities for these compounds have not yet been fully explored perhaps due to the lack of general methods for the synthesis of the unique tricyclic core.

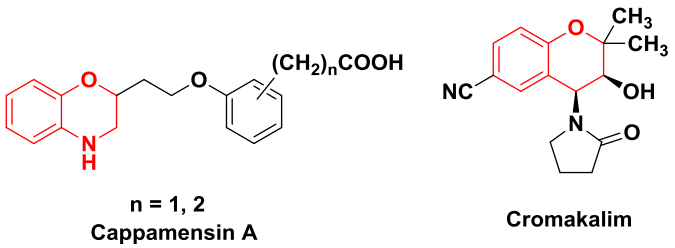
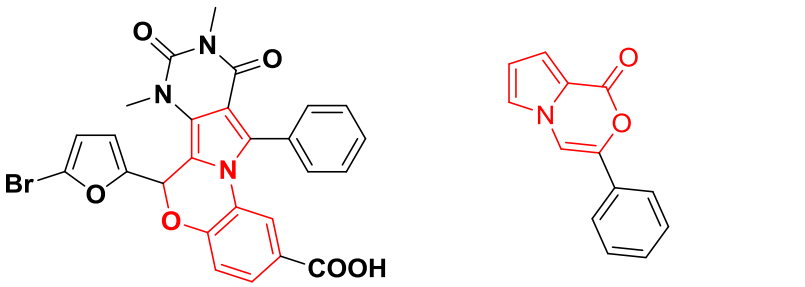


Fig 1. Some benzoxazine derived drugs and natural products.

Pyrrolo-1,4-benzoxzine can be used as a drug[14,15] e.g. benzopyrimidopyrrolo-oxazinedione (BPO) which has a activity of CFTR inhibitors for polycystic kidney diseases. 3-Phenyl-1H-pyrrolo[2,1-c][1,4]oxazin-1-one can be used as a precursor for the synthesis of muscle relaxant agents.



benzopyrimidopyrrolo-oxazinedione (BPO) CFTR inhibitors

3-phenyl-1*H*-pyrrolo [2,1-*c*][1,4]oxazin-1-one

Fig 2. Some pyrrolo-1,4-benzoxazine derived drugs.

1.3 BACKGROUND

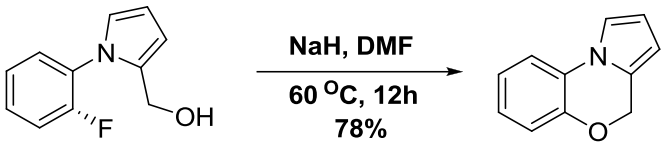
Because of the highly pharmaceutical and biological activity of pyrrolo-1,4-benzoxzine derivatives were synthesized and those are, 1. The synthesis of pyrrolo[2,1-c][1,4]benzoxazines via intramolecular nucleophilic substitution of aromatic fluoride as elegantly demonstrated by Pujol's group (Scheme 1, Eq. 1).[16] 2. Hands et al. who have described the synthesis of 2-substituted-6-azaindoles via condensation of Li_2-(N-Boc)-3-amino-4-picoline with appropriately chosen Weinreb amides(Scheme 2, Eq. 2).[17] 3**.** Based on the above 2 literatures, fused tetracyclic 7-azaindolo[2,1-c][1,4]benzoxazine scaffold has been synthesized (Scheme 3, Eq.3).[18] 4**.** Synthesis of pyrrole and indole quinoxalinone and oxazinone derivatives by intramolecular copper-catalyzed reactions (Scheme 4, Eq.4).[19] 5. $FeCl_3$ catalyzed One-pot multicomponent synthesis of novel tricyclic pyrrolo[2,1-c][1,4]benzoxazines (Scheme 5, Eq.5).[20]

However, most of these methods possess several disadvantages such as low yields of products, long reaction time, harsh reaction conditions,[21] tedious work-ups and large amount of toxic metal waste with solvent,[19] requirement of inert atmosphere and use of stoichiometric or relatively expensive reagents. All these processes contain a high amount of disadvantage as all

the reactions are either metal/acid catalyzed which are highly hazardous and not comes under green protocol.

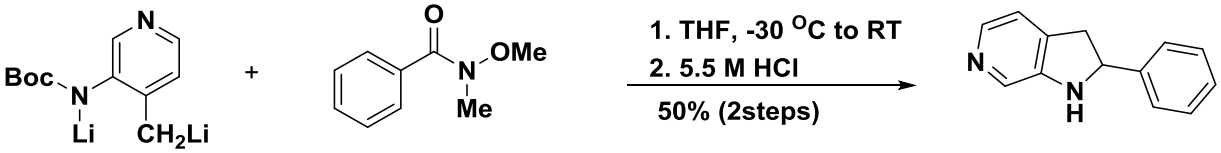
As part of our current studies[22] on the development of new greener methodologies for the synthesis of heterocyclic systems, herein we propose to iodine for the synthesis of pyrrolo -1,4-benzoxazines. Iodine can activate (i) carbon-carbon double bond (ii) carbon-carbon triple bond (iii) enamine, thioamide, and hydrazine (iv) carbonyl and imine (v) orthoformate. Because of its non-combustible, inexpensive, non-toxic, and ready availability, high tolerance to air and moisture and can be easily removable from reaction mixture using reducible agent, it is highly used in organic transformations starting from minor catalytic amount to stoichiometric amount. Recently it is used hugely in heterocyclic synthesis. Based on these results, we aimed to investigate if it would be possible to develop an iodine mediated[21] one pot protocol to synthesize pyrrolo-1,4-benzoxazines. So far to the best of our knowledge, there are no reports on iodine mediated synthesis of pyrrolo-1,4-benzoxazine derivatives. Details of this investigation are described in the following chapter.

Scheme 1: A Convenient Synthesis of Pyrrolo[2,1-c][1,4] benzoxazines



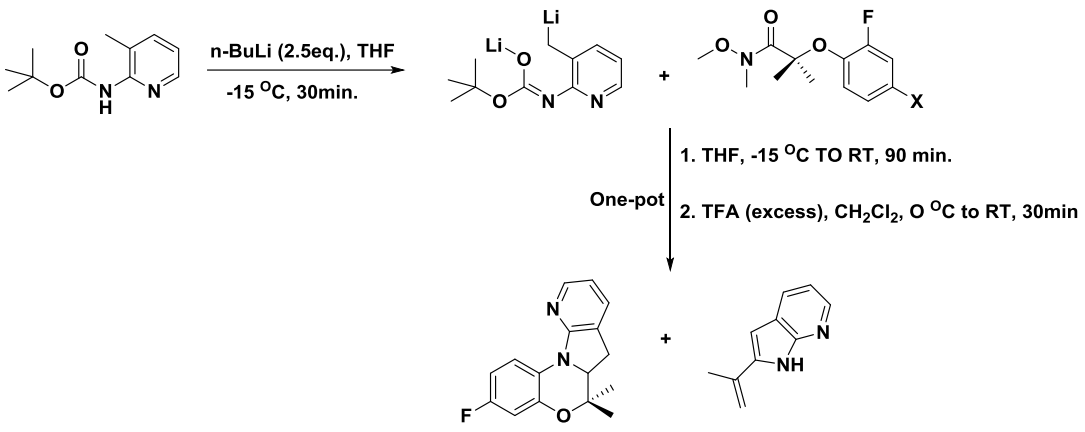
Eq 1. Intramolecular aromatic nucleophilic substitution.

Scheme 2:



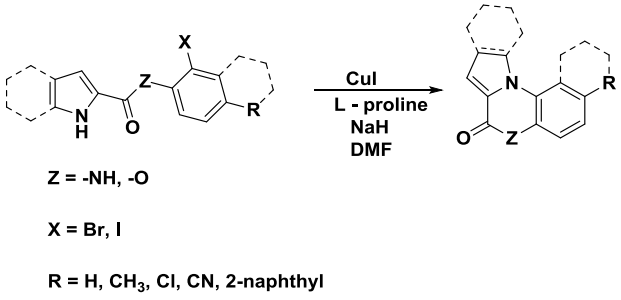
Eq 2. Pyrrole ring construction

Scheme 3: Synthesis of a novel tetracyclic azaindolo[2,1-c][1,4]benzoxazine ring system



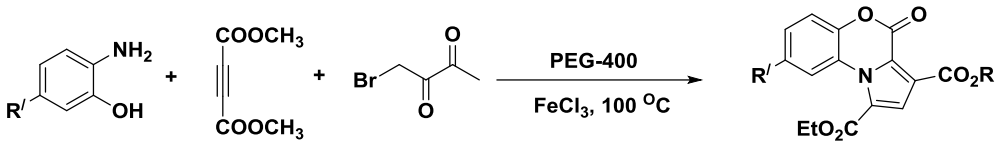
Eq 3. Synthesis of 7-azaindolo[2,1-c][1,4]benzoxazine

Scheme 4: Synthesis of pyrrole and indole quinoxalinone and oxazinone derivatives by intramolecular copper-catalyzed reactions



Eq 4. Cu- catalyzed intramolecular N-arylation.

Scheme 5: One-pot multicomponent synthesis of novel tricyclic 4 pyrrolo[2,1-c][1,4]benzoxazines

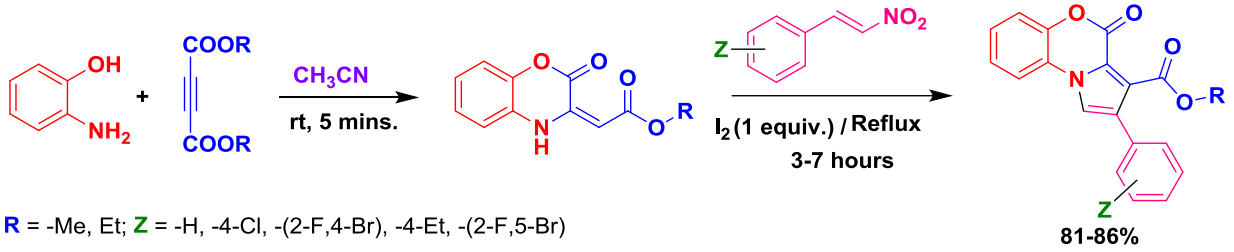


R = Me, Et, t-Bu

R/ = H, Me, Cl

Eq 5. Synthesis of pyrrolo[2,1-c][1,4]benoxazine derivative

Our method:

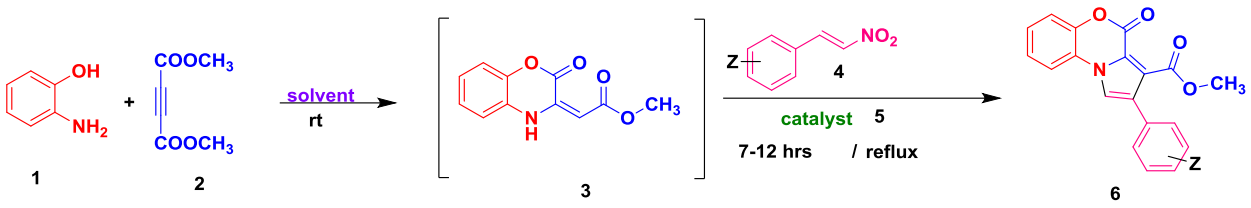


R = -Me, Et; Z = -H, -4-Cl, -(2-F,4-Br), -4-Et, -(2-F,5-Br)

1.4 RESULT AND DISCUSSION

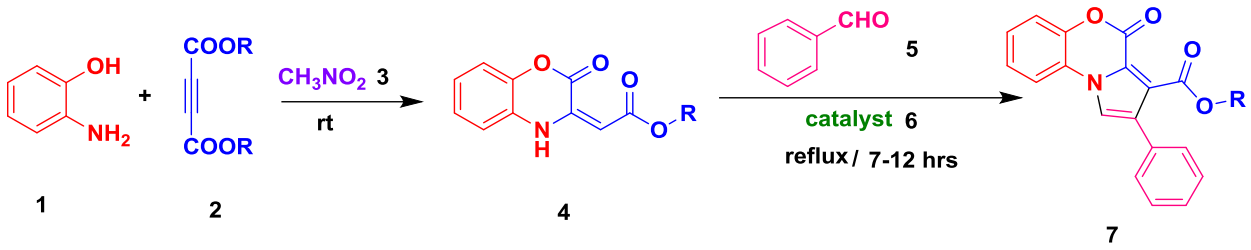
In our investigation initially we have selected 2-amino phenol, dimethylacetylenedicarboxylate and beta-nitrostyrene as a test reaction and the reaction conditions like temperature, catalyst (iodine) 1equiv., solvent and time were varied (Table 1). we screened a series of Brønsted acids and lewies acids for this reaction, such as HOAc, $MeSO_3H$, CF_3SO_3H, TFA, PTSA , but the desired product was obtained in a low yield. When we performed the reaction in the presence of iodine at low temparature observed the desired product with low yield. The best result was observed temperature at 82 ^{O}C. After several optimization processes we found that the mixture of equimolar amount of 2-aminophenol, DMAD and beta-nitrostyrene in presence of 1eq. iodine in acetonitrile solvent at 82 ^{O}C resulted in 85% isolated yield of methyl 4-oxo-2-phenyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate. We tried to investigate in situ generation of nitrostyrene from aromatic aldehyde and nitromethane as four component reaction which gave low yield. Hence, we focused the three component one pot synthesis by using beta- nitrostyrenes which was made by reported method.[23,24] Optimization table for three component (Table 1) and four component (Table 2) is given below.

Table1. One- pot three component synthesis of methyl 4-oxo-2-phenyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylate (**6)** from 2-aminophenol (**1)**, dimethylacetylene dicarboxylate (**2)**, and beta-nitrostyrene (**4).**



Entry	Solvent	Catalyst	Time(hours.)	Yield(%)
1	DCM	Acetic acid (1 equiv.)	12	-
2	Toluene	Acetic acid (1 equiv.)	12	35
3	Toluene	Acetic acid (1.5 equiv.	12	35
4	Toluene	Acetic acid (2 equiv.)	12	35
5	Toluene	TFA (1 equiv.)	12	43
6	Toluene	p-TSA (0.2 equiv.)	12	32
7	Toluene	NEt_3 (0.5 equiv.)	12	10
8	Ethanol	Acetic acid (1 equiv.)	12	30
9	Water	TBAI (1 equiv.)	12	21
10	PEG 400	Acetic acid (1 equiv.)	12	45
11	PEG 400	$FeCl_3$ (0.1 equiv.)	12	66
12	Acetic acid	Acetic acid (1 ml.)	12	60
13	Acetonitrile	$FeCl_3$ (0.1equiv)	12	15
14	Acetonitrile	L-proline (1 equiv.)	12	12
15	**Acetonitrile**	**I_2 (1 equiv.)**	**7**	**85**
16	Acetonitrile	$FeCl_3$ (0.1 equiv.)	7	73
17	Acetonitrile	$FeCl_3$ (0.1 equiv.) piperidine (0.5 equiv.)	7	13

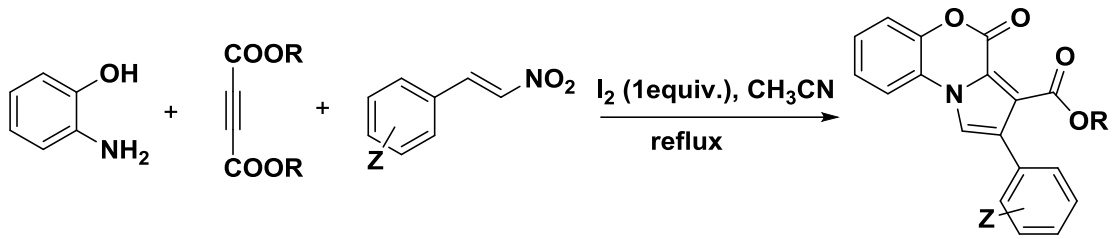
Table 2. One-pot four component synthesis of methyl 4-oxo-2-phenyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (**7)** from 2-aminophenol (**1)**, dimethyl acetylene dicarboxylate (**2)**, nitromethane (**3)**, and benzaldehyde (**5)**.



Entry	Solvent	Catalyst	Time(hours)	Yield (%)
1	**CH_3NO_2 (2 ml)**	**I_2 (1 equiv.)**	**7**	**30**
2	CH_3NO_2 (2 ml)	I_2 (0.2 equiv.)	7	10[a]
3	CH_3NO_2 (2 ml)	I_2 (0.2 equiv.)	7	-
4	CH_3NO_2 (2 ml)	I_2 (0.5 equiv.)	7	-
5	CH_3NO_2 (2 ml)	I_2 (0.2 equiv.) & acetic acid (1 equiv.)	7	-
6	CH_3NO_2(2 ml)	I_2 (0.2 equiv.) & acetic acid (5 equiv.)	7	-
7	CH_3NO_2 (2 ml)	I_2 (0.2 equiv.) & triflic acid (1equiv.)	12	12
8	CH_3NO_2 (2 ml)	I_2 (0.2equiv) & triflic acid (5 equiv.)	12	15
9	[bmIm]Br	[bmIm]Br (3 equiv.)	7	26
10	CH_3NO_2 (0.5 ml)	$FeCl_3$ (0.1equiv.)	7	10

[a] microwave(250Watt, 100 ^{O}C, 250psi).

Table 3. The scope of 2-aminophenol, acetylenic esters and substituted beta-nitrostyrenes.



1 2 3 4

Entry	R	Z	Product	Time (hours)	Yield(%)
1	Me	H **(3a)**	**4a**	6.5	85
2	Et	H (**3a**)	**4b**	7	83
3	Me	4-Cl **(3b)**	**4c**	4	86
4	Et	4-Cl (**3b**)	**4d**	4.25	82
5	Me	2-F,4-Br **(3c**)	**4e**	4	82
6	Et	2-F,4-Br (**3c**)	**4f**	4.5	81
7	Me	4-Et **(3d)**	**4g**	4	82
8	Et	4-Et (**3d**)	**4h**	4.2	84

After successful accomplishment of this method we turned to the illustration of the reaction mechanism **(Figure 3).** Based on the above result a plausible mechanism for the formation of pyrrolo-1,4-benzoxazine has been proposed. The reaction between 2-aminophenol and dialkylacetylenedicarboxylate affords benzoxazine intermediate, The resulting intermediate reacts with nitrostyrene in the presence of iodine followed by formation of iminium ion which then undergoes a series of cyclisation and elimination reaction to generate our desired product.

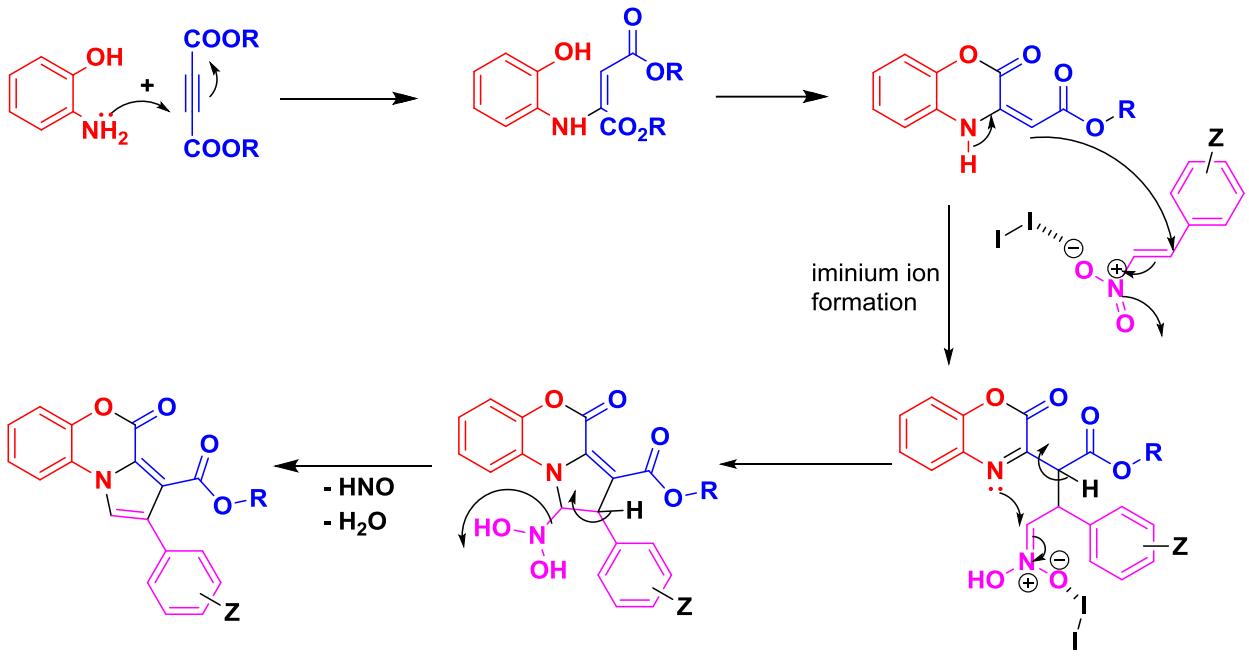


Figure 3. Plausible reaction mechanism

1.5 CONCLUSION

In summary, we have successfully developed I_2 mediated novel, simple, economic, environmental friendly one pot three component reaction to synthesize medicinally and biologically important pyrrolo-1,4-benzoxazine. There are several advantages associated with this method (i) easy accessibility of pyrrolo-1,4-benzoxazine by mixing all three starting material without inert atmosphere, (ii) easy work-ups, (iii) metal, acid and base free synthesis and (iv) non moisture sensitive. This methodology might be the best alternative for existing literature methods.

1.6 EXPERIMENTAL SECTION

General information

In this section the preparation of all the compounds that have been made in the course of synthesis of substituted pyrroles and the optimization process is discussed. For experiment all the starting material and reagents are purchased from standard commercial source or were prepared in laboratory. All the glasswares were cleaned with soap water followed by acetone and dried in hot air oven at 100 ^{O}C for 2 hrs. Solvent were distilled prior to use; petroleum ether with a boiling point range 40-60 ^{O}C was used.

IR spectra were recorded on the Bruker Tensor 37(FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295K in $CDCl_3$; chemical shifts value (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.26ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at 298K in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [(δ_C=77.00ppm) central line of triplet]. In ^{13}C NMR the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT-135 spectra. In ^{1}H NMR, the following abbreviations were used throughout the thesis; s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br.s = broad singlet. The assignment of the signals was confirmed by ^{1}H, ^{13}C and DEPT spectra. Reactions were monitored by TLC on silica gel (254 mesh) using a combination of petroleum ether and ethyl acetate as eluents.

Representative experimental procedure for the synthesis of methyl 4-oxo-2-phenyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (Table 2, 4a). To a mixture of 2-aminophenol (100mg, 0.92mmol), dimethyl acetylene dicarboxylate (130.7mg, 0.92mmol) in acetonitrile stirred for 15mins under rt. After formation of the intermediate conforming by TLC beta-nitrostyrene (137.2mg, 0.92 mmol), Iodine (233.7mg, 1eq.) was added and the resulting mixture was refluxed for 6.5hrs. The reaction completion was monitored by TLC with pet ether-ethyl acetate as eluent. After completion of the reaction, reaction mixture was extracted using ethyl acetate and the extract was washed with 20% aqueous $Na_2S_2O_3$ solution to remove excess iodine, dried over anhydrous

Na_2SO_4 and concentrated under reduced pressure. The crude extract was purified by filtration through a silica gel (100-200 mesh) column using pet ether/ EtOAc (80 : 20) to yield the desired product **4a** as white solid (85% yield) and spectroscopic data matching with the reported literature data.

All reaction for the synthesis of pyrrolo 1,4-benzoxazines were carried out following this representative procedure.

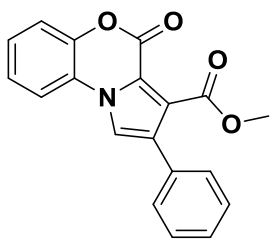
Representative experimental procedure for the synthesis of substituted beta-nitrostyrenes (3a, 3c, 3d, 3e):

A solution of 1 equiv. substituted benzaldehyde and 1 equiv. of nitromethane in 4 ml. of methanol was cooled to 5 ^{O}C in an ice-bath. 5ml of ice-cold aqueous solution of sodium hydroxide, containing 690mg of NaOH, was added dropwise with stirring at such a rate that the temperature was maintained between 10 to 15 ^{O}C. A white precipitate occurred which upon addition of about two-thirds of the NaOH solution became too thick for efficient stirring. An additional 2 ml. of methanol was added and stirring continued for 15 min. after all the NaOH solution had been added. A water-ice mixture (12 ml.) was added and the resulting solution was slowly added with stirring to a mixture of 3.1 ml. of concentrated hydrochloric acid and 5.9 ml. of water. The resulting precipitate was washed to free of chloride, giving of dry crude product. Recrystallization have done from 95% ethanol.

Representative experimental procedure for the synthesis of substituted beta-nitrostyrene (3b):

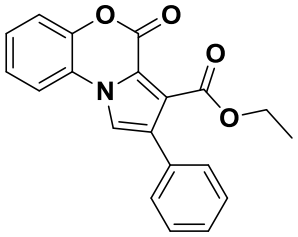
1.1 equiv. of nitromethane and 1 equiv. of substituted benzaldehyde, 0.5 equiv. ammonium acetate in 2 ml. of glacial acetic acid was heated under reflux for 1hours. The hot mixture was poured into 30 ml. of ice- water mixture. The resulting precipitate was washed with water and recrystallized from a mixture of 95% ethanol and acetone(2:1).

1.7 SPECTRAL DATA



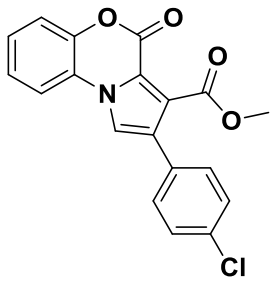
4a

Methyl 4-oxo-2-phenyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (4a): pale yellow powder (85%); mp 185-187 ^{O}C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 3.92 (s, 3H, CH_3), 7.3-7.43 (m, 6H, ArH), 7.45-7.51 (m, 2H, ArH), 7.61-7.67 (m, 1H, ArH), 7.69 (s, 1H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 100MHz): δ = 165.47, 152.36, 143.41, 132.33, 129.79, 129.11, 128.28, 128.07, 127.53, 125.399, 122.40, 121.91, 118.75, 116.14, 115.97, 114.75, 53.16 ppm.



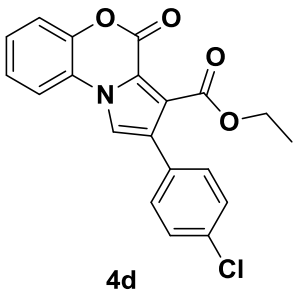
4b

Ethyl 4-oxo-2-phenyl-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (4b) : pale yellow powder (83%); mp 170-172 ^{O}C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.31 (t, 3H, *J*=7.09Hz, CH_3), 4.41 (q, 2H, *J*=7.01Hz, CH_2), 7.28-7.42 (m, 6H, Ar*H*), 7.44-7.51 (m, 2H, Ar*H*), 7.59-7.66 (m, 1H, Ar*H*), 7.68 (s, 1H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 100MHz): δ = 164.71, 152.06, 143.09, 132.10, 129.30, 128.74, 127.93, 127.85, 127.18, 125.09, 122.58, 121.63, 118.39, 115.70, 114.47, 61.98, 13.95 ppm.



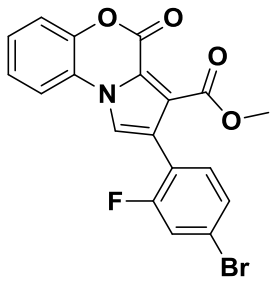
4c

Methyl 2-(4-chlorophenyl)-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (4c): pale yellow powder (86%); mp 186-188 ^{O}C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 3.93 (s, 3H, C*H*$_3$), 7.32-7.46 (m, 7H, Ar*H*), 7.61-7.74 (m, 2H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 100MHz): δ = 164.76,158.53, 151.97, 143.18, 134.14, 130.06, 129.22, 129.06, 128.34, 127.45, 125.19, 122.03, 121.55, 116.10, 115.66, 114.48, 52.88 ppm.



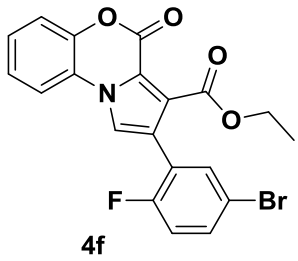
4d

Ethyl 2-(4-chlorophenyl)-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (4d): pale yellow powder (82%); mp 170-172 ^{O}C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.32 (t, J=7.09 Hz, 3 H, C*H*$_3$), 4.41 (q, J=7.34 Hz, 2 H, C*H*$_2$) 7.30 - 7.44 (m, 7 H, Ar*H*), 7.64 (dd, J=7.82, 1.96 Hz, 1 H, Ar*H*), 7.66 - 7.69 (m, 1 H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 100MHz): δ = 164.47, 151.94, 143.14, 134.04, 130.63, 129.22, 128.96, 128.47, 128.16, 127.37, 125.15, 122.47, 121.53, 118.53, 115.97, 115.62, 114.45, 13.97 ppm.



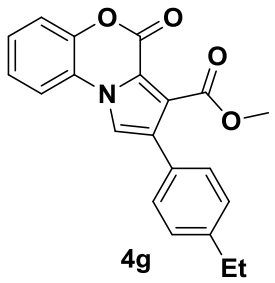
4e

Methyl 2-(4-bromo-2-fluorophenyl)-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (4e): pale yellow powder (82%); mp 192-194 ^{O}C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 3.92 (s, 3H, C*H*$_3$), 7.31-7.44 (m, 6H, Ar*H*), 7.66 (dd, 1H, *J*=8.07, 1.71 Hz, Ar*H*), 7.77 (d, 1H, *J*=1.47 Hz, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 100MHz): δ = 164.57, 158.15, 151.69, 143.18, 131.28, 127.84, 127.61, 125.19, 121.98, 121.42, 119.79, 119.28, 118.55, 117.19, 114.58, 52.86 ppm.

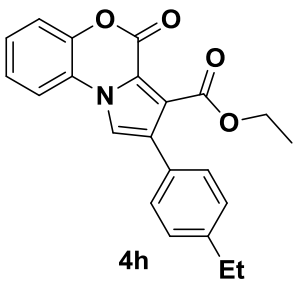


4f

Ethyl 2-(4-bromo-2-fluorophenyl)-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (4f): pale yellow powder (81%); mp 184-186 $^{\circ}$C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.30 (t, J=7.34 Hz, 3 H, C*H*$_3$) 4.39 (q, J=7.34 Hz, 2 H, C*H*$_2$) 7.29 - 7.39 (m, 6 H, Ar*H*) 7.61 - 7.67 (m, 1 H, Ar*H*) 7.75 (d, J=0.98 Hz, 1 H, Ar*H*)ppm. ^{13}C NMR ($CDCl_3$, 100MHz): δ = 163.86, 158.13, 151.63, 143.09, 131.38, 127.76, 127072, 127.53, 125.16, 121.84, 121.36, 1199.66, 119.43, 118.41, 117.23, 114.58, 61.94, 13.92 ppm.



Methyl 2-(4-ethylphenyl)-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (4g): pale yellow powder (82%); mp 166-168 ^{O}C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.25 (t, J=7.58 Hz, 3 H, CH_3), 2.66 (q, J=7.50 Hz, 2 H, CH_2) 3.93 (s, 3 H, CH_3) 7.20 - 7.40 (m, 7 H, Ar*H*) 7.60 - 7.63 (m, 1 H, Ar*H*) 7.66 (s, 1 H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 100MHz): δ = 165.40, 152.13, 144.16, 143.06, 129.36, 129.28, 128.35, 127.64, 127.14, 125.20, 121.96, 121.62, 118.388, 115.73, 115.60, 114.48, 52.90, 28.58, 15.43 ppm.



Ethyl 2-(4-ethylphenyl)-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylate (4h): pale yellow powder (84%); mp 162-164 °C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 1.22 - 1.27 (m, 3 H) 1.33 (t, J=7.09 Hz, 3 H) 2.65 (q, J=7.34 Hz, 2 H) 4.42 (q, J=7.17 Hz, 2 H) 7.19 (m, J=8.31 Hz, 2 H) 7.27 - 7.35 (m, 3 H) 7.36 - 7.40 (m, 2 H) 7.57 - 7.62 (m, 1 H) 7.65 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100MHz): δ = 164.92, 152.11, 144.10, 143.02, 129.32, 129.23, 128.25, 127.69, 127.09, 125.07, 122.42, 121.61, 118.30, 115.60, 114.48, 61.98, 28.57, 15.47, 13.99 ppm.

1.7 REFERENCES

1. Toure B.R. and Hall G.D., *Chem. Rev*., **2009**, *19*, 4439-4486.
2. Orru A.V.R. and Greef D. M., *Synthesis*, **2003**, 1471-1499.
3. Alfonsi K., Colberg J., Dunn J. P., Ferig T., Jennings S., Johnson A. T., Kleine P. H., Knight C., Naggy A. M., Pery A. D. and Stefanik M., *Green Chem.*, **2008**, *10*, 3.
4. Togo H., Iida S., *Synlett*, **2006**, 2159 – 2175.
5. Banerjee K. A., Vera W., Mora H., Laya S. M., Bedoya L., Cabrera V. E., *J. Sci. Ind. Res*., **2006**, *65*, 299 – 308.
6. Stavber S., Jereb M., Zupan M., *Synthesis*, **2008**, 1487 – 1513.
7. (a) Marek I., *Tetrahedron*, **2005**, *61*, 11309 – 11310; (b) Domling A., *Chem. Rev.*, **2006**, *106*, 17 – 89.
8. Tietze F. L.,*Chem. Rev*., **1996**, *96*, 115 – 136;
9. Rodriguez J., *Synlett*, **1999**, 505 – 518.
10. Pellissier H., *Tetrahedron*, **2006**, *62*, 1619 – 1665.
11. Caliendo G., Grieco P., Perissutti E., Santagada V., Santini A., Albrizio S., Fattorusso C., PintoA., Sorrentino. R, *Eur. J. Med. Chem.*, **1998**, *33*, 957-967.
12. Rybczynski J. P., Zeck E.R., Combs W.D., Turchi I., Burris P.T., Xu Z. J., Yang M. and Demarest T. K., *Bioorg. Med. Chem. Lett.,* **2003**, *13*, 2359–2362.
13. Wu H. J., Chang R. F., Hayashi K., Shiraki H., Liaw C.C., Nakanishi Y., Bastow F. K., Yu D., Chen S. I. and Lee H. K., *Bioorg. Med. Chem. Lett.,* **2003**, *13*, 2223–2225.
14. Khan S.T., P. Yu, Chantrapromma S., Y. E. Guo and N. Afza, *Acta Cryst***., 2010**. *E66*, o1469.
15. Snyder S. D., Tradtrantip L., Yao C., Kurth J. M. and Verkman S. A., *J. Med. Chem.*, **2011**, *54*, 5468–5477.
16. Sánchez, I.; Pujol, M. D., *Tetrahedron*, **1999**, *55*, 5593–5598.
17. Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B., *Synthesis,* **1996**, 877–882.
18. Kurhade S., Kaduskar D.R., Dave B., Ramaiah A. P., Palle P. V., Bhuniya D., *Tertahedron Lett*., **2011**, *52*, 1874-1877.
19. Vaillard A. V., Rossi A. R. and Martin E. S., *Org. Biomol. Chem*., **2011**, *9*, 4927–4935.
20. Piltan M., Moradib L., Zarei A. S., Rostami H., *Chinese Chemical Lett.*,**2013**.
21. Vidyacharan S., Shinde H. A., Satpathi B., Sharada S. D., *Green Chem.*, DOI: 10.1039/C3GC42130A
22. Parvatkar T.P., Parameswaran S. P., and G. Tilve G. S., *Chem. Eur. J*., **2012**, *18*, 5460 – 5489.
23. "Organic Syntheses," Coll., *John Wiley and Sons, Inc*., **1941**, *Vol. I*, 413.
24. Gairaud B.C.and Lappin R.G., *J. Org. Chem*., **1953,** *18***,** 1**.**

1.8 SUPPORTING INFORMATION

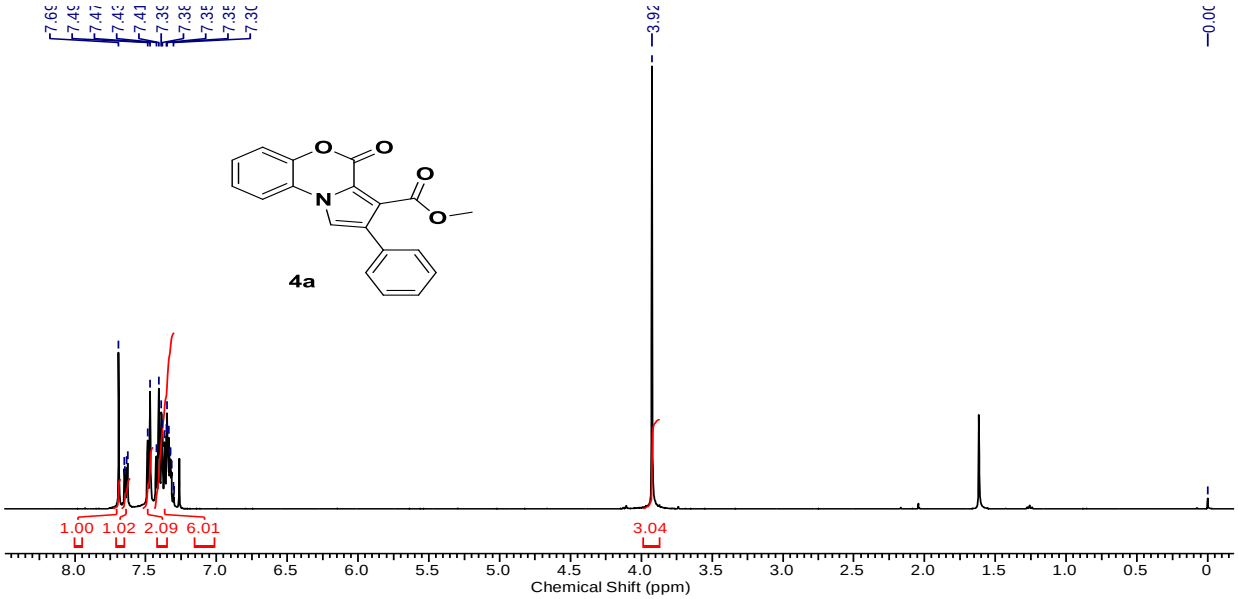


Figure 4. ^{1}H NMR (400MHz) spectrum of compound **4a** in $CDCl_3$.

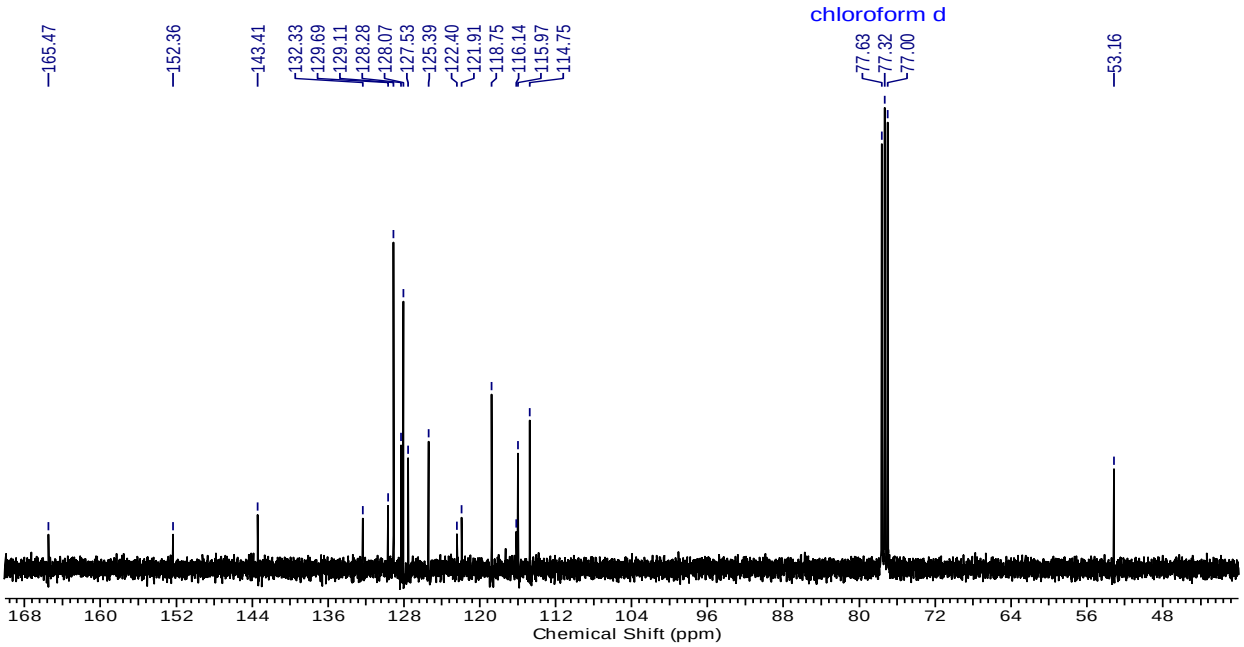


Figure 5. ^{13}C NMR (100MHz) spectrum of compound **4a** in $CDCl_3$.

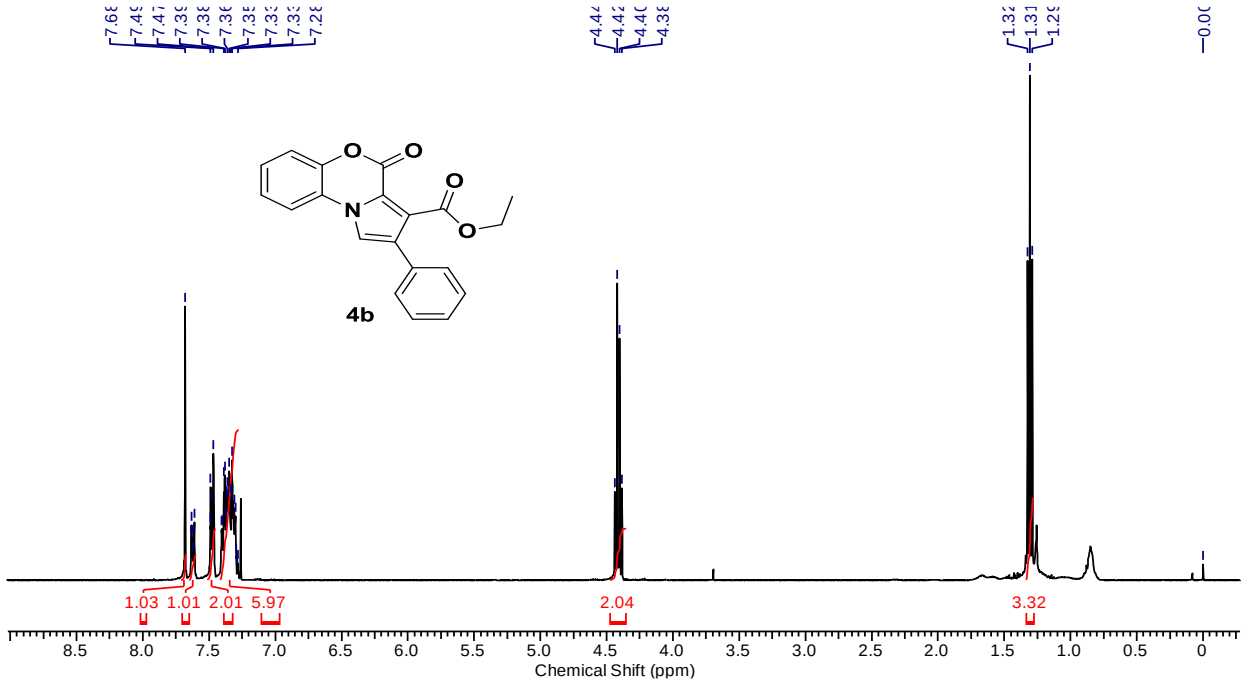
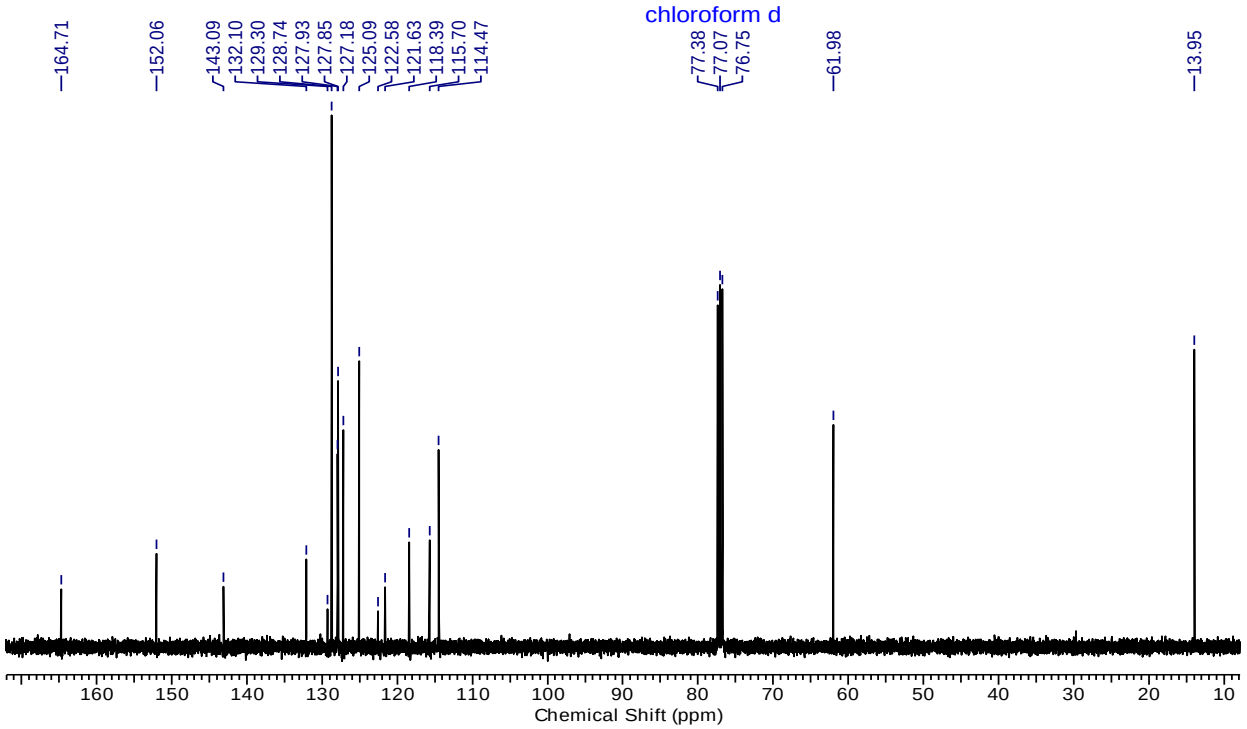


Figure 6. ^{1}H NMR (400MHz) spectrum of compound **4b** in $CDCl_3$.



. **Figure 7.** ^{13}C NMR (100MHz) spectrum of compound **4b** in $CDCl_3$.

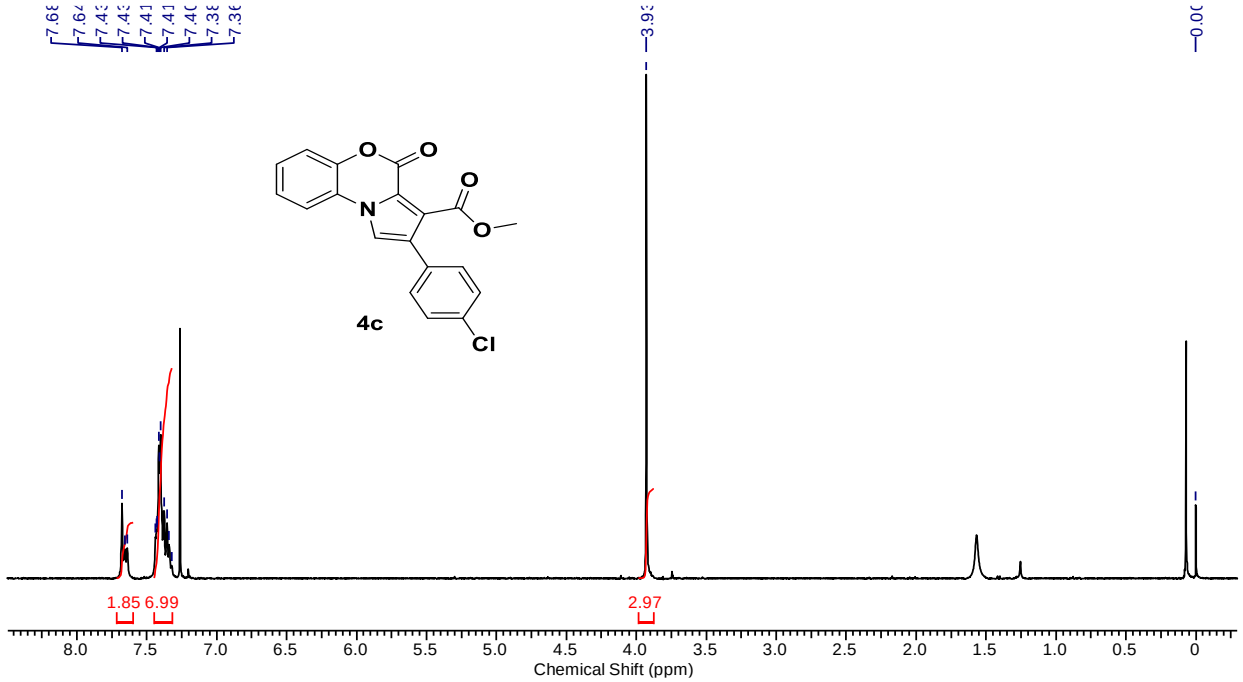


Figure 8. ^{1}H NMR (400MHz) spectrum of compound **4c** in $CDCl_3$.

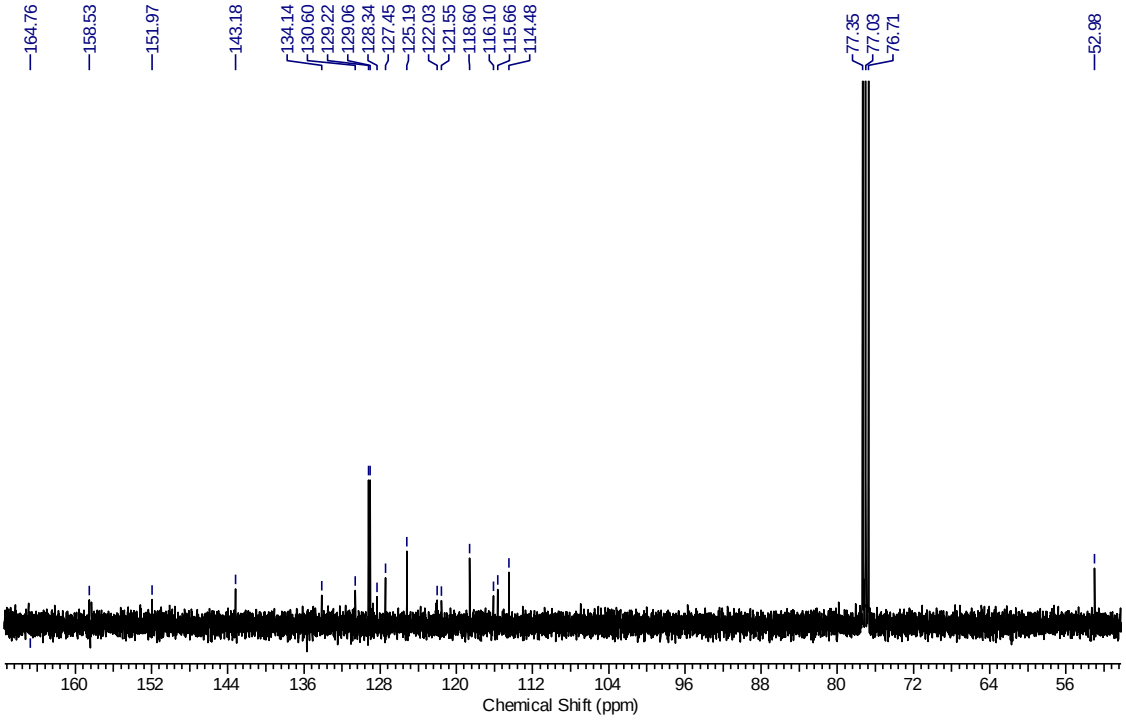


Figure 9 . ^{13}C NMR (100MHz) spectrum of compound **4c** in $CDCl_3$.

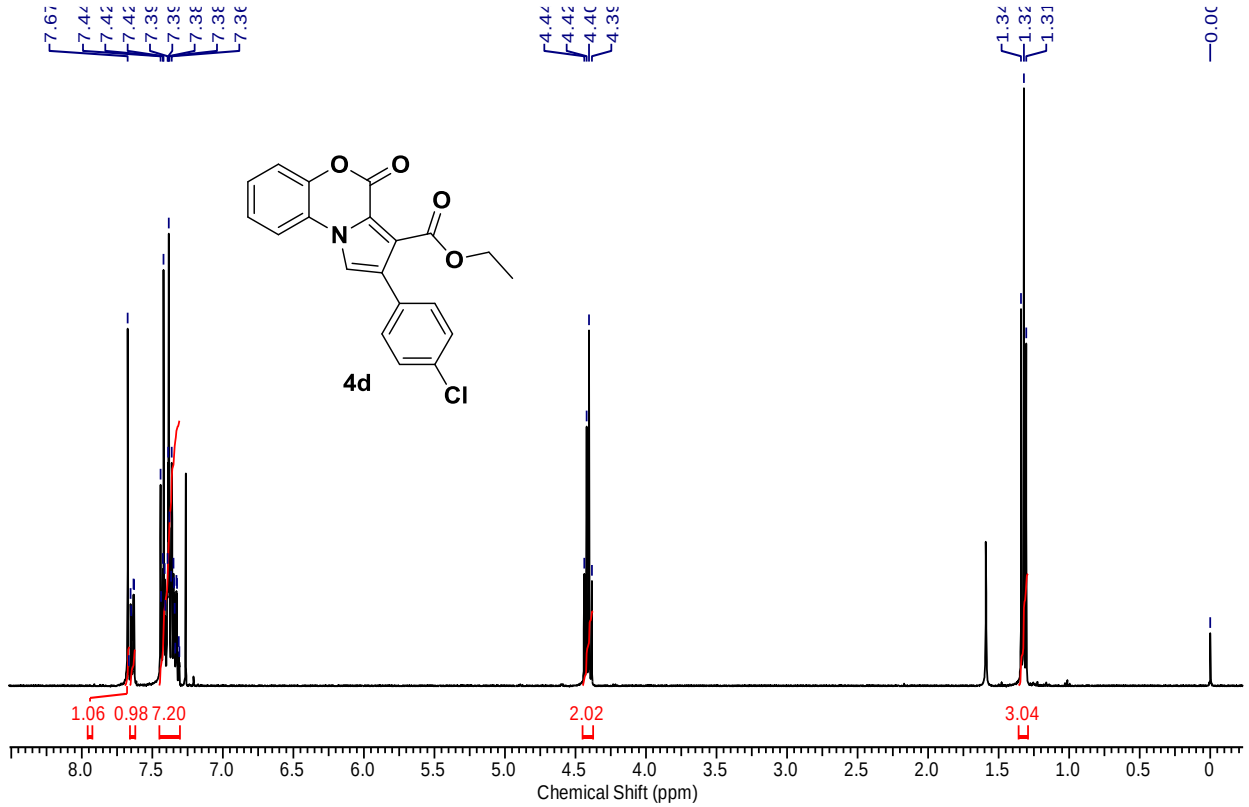


Figure 10. ^{1}H NMR (400MHz) spectrum of compound **4d** in $CDCl_3$.

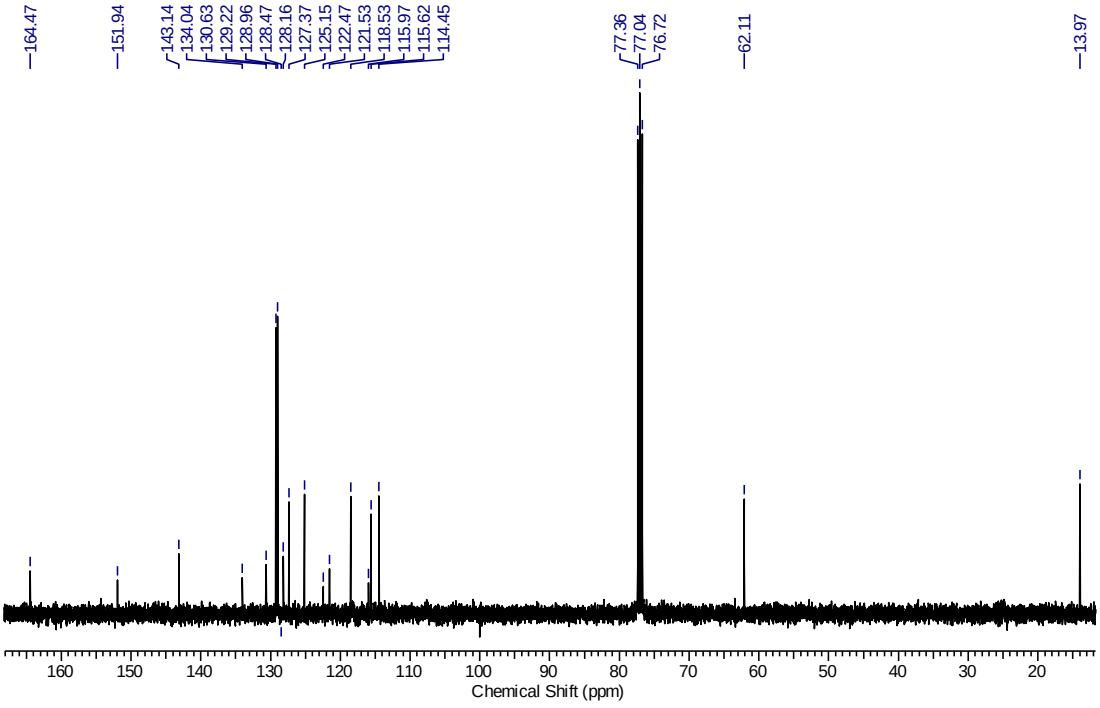


Figure 11. ^{13}C NMR (100MHz) spectrum of compound **4d** in $CDCl_3$.

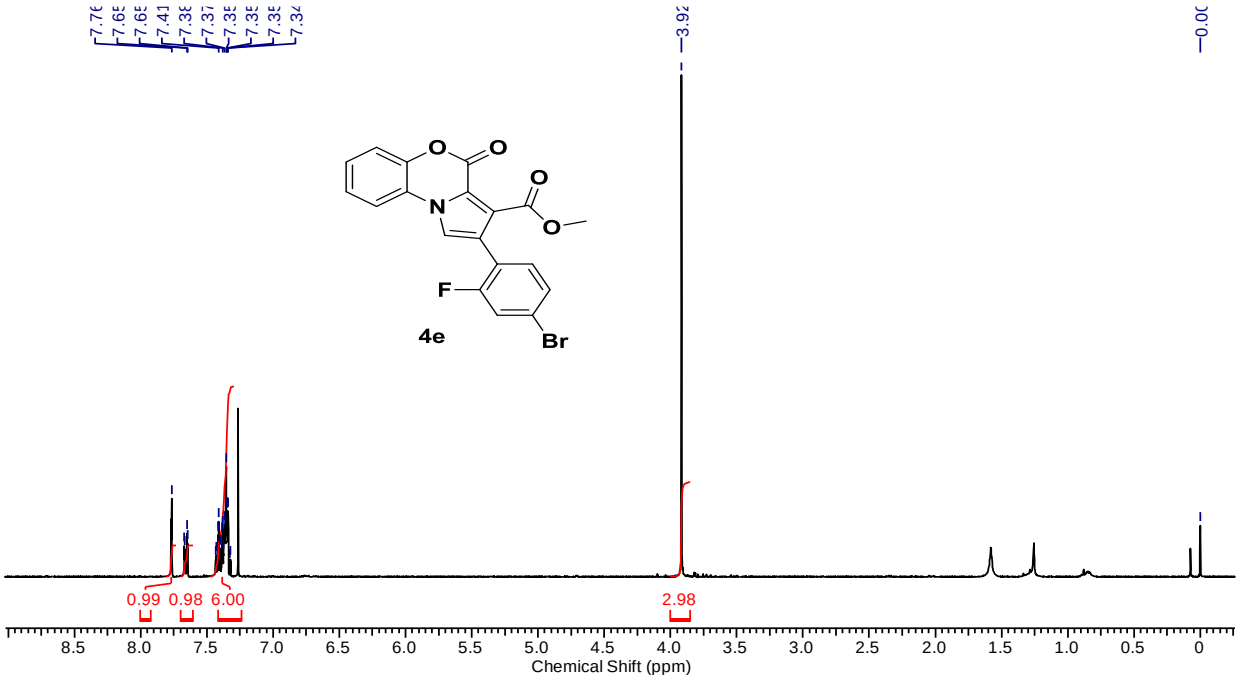


Figure 12. ^{1}H NMR (400MHz) spectrum of compound **4e** in $CDCl_3$

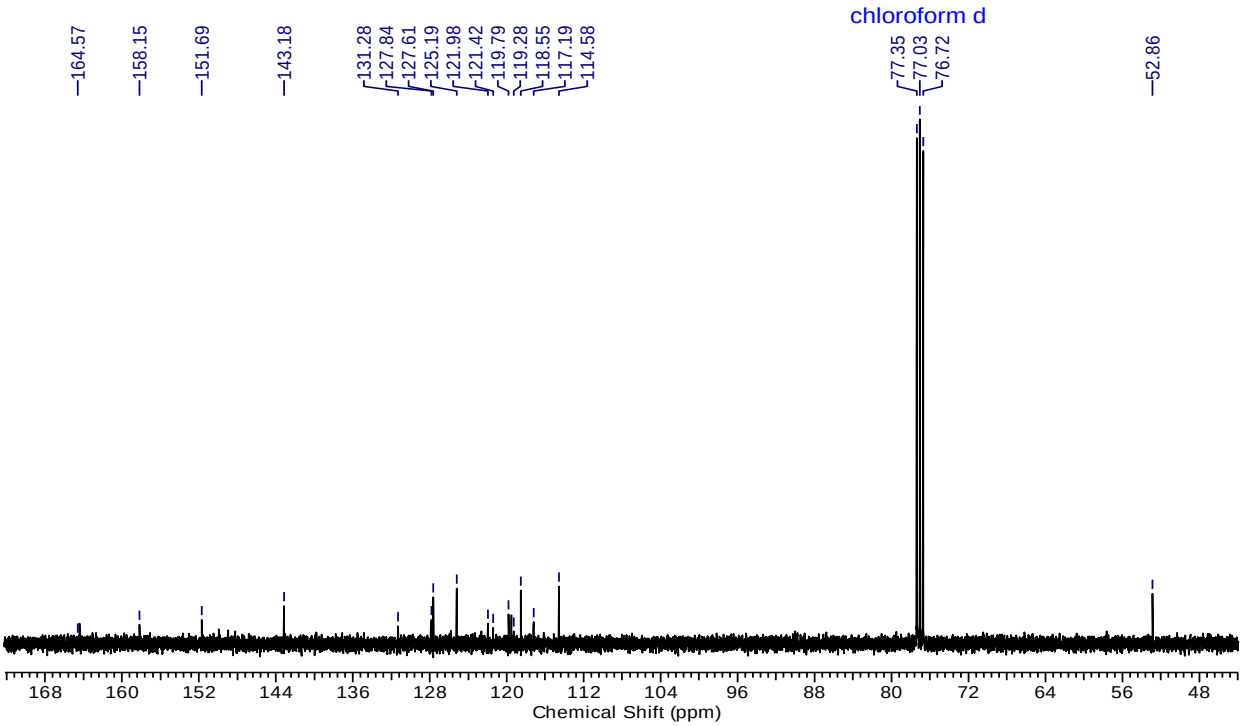


Figure 13. ^{13}C NMR (100MHz) spectrum of compound **4e** in $CDCl_3$.

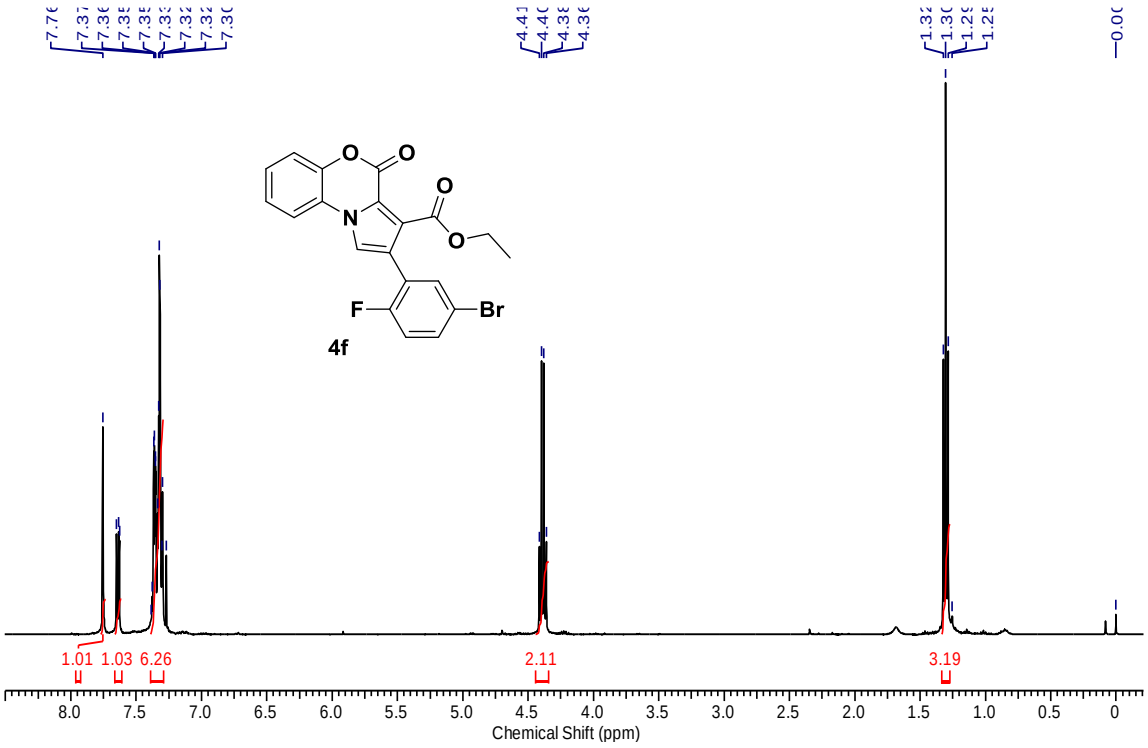


Figure 14. ^{1}H NMR (400MHz) spectrum of compound **4f** in $CDCl_3$.

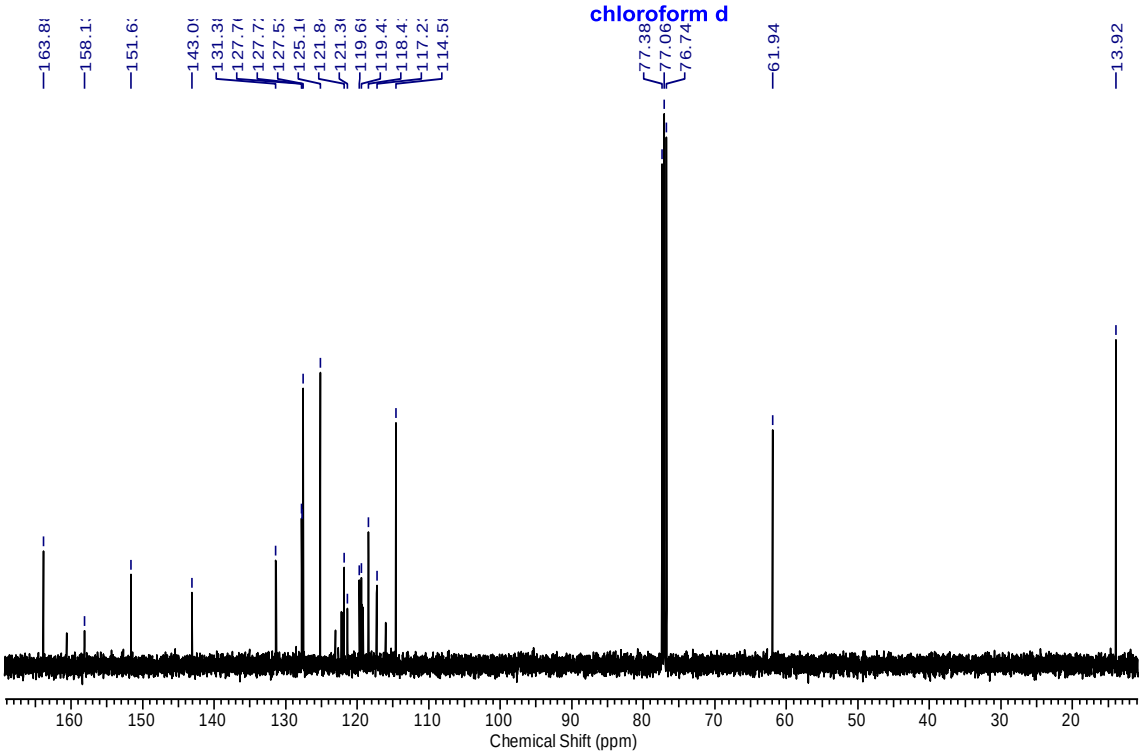


Figure 15. ^{13}C NMR (100MHz) spectrum of compound **4f** in $CDCl_3$.

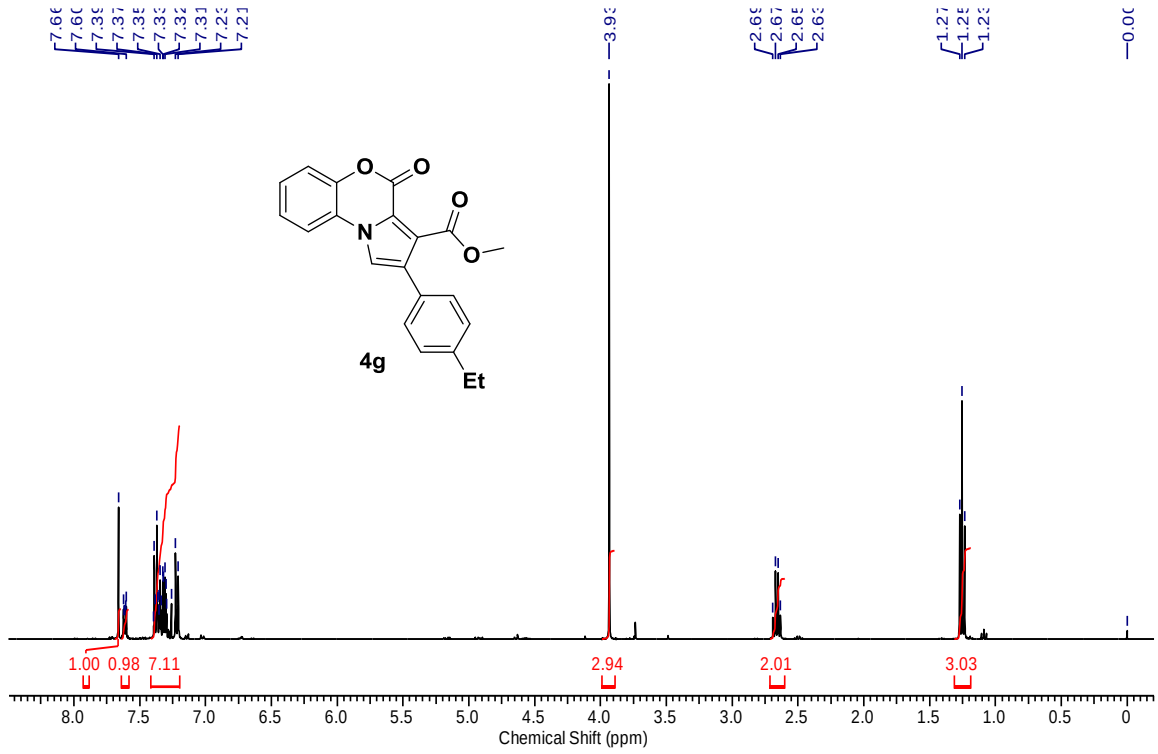


Figure 16. ^{1}H NMR (400MHz) spectrum of compound **4g** in $CDCl_3$.

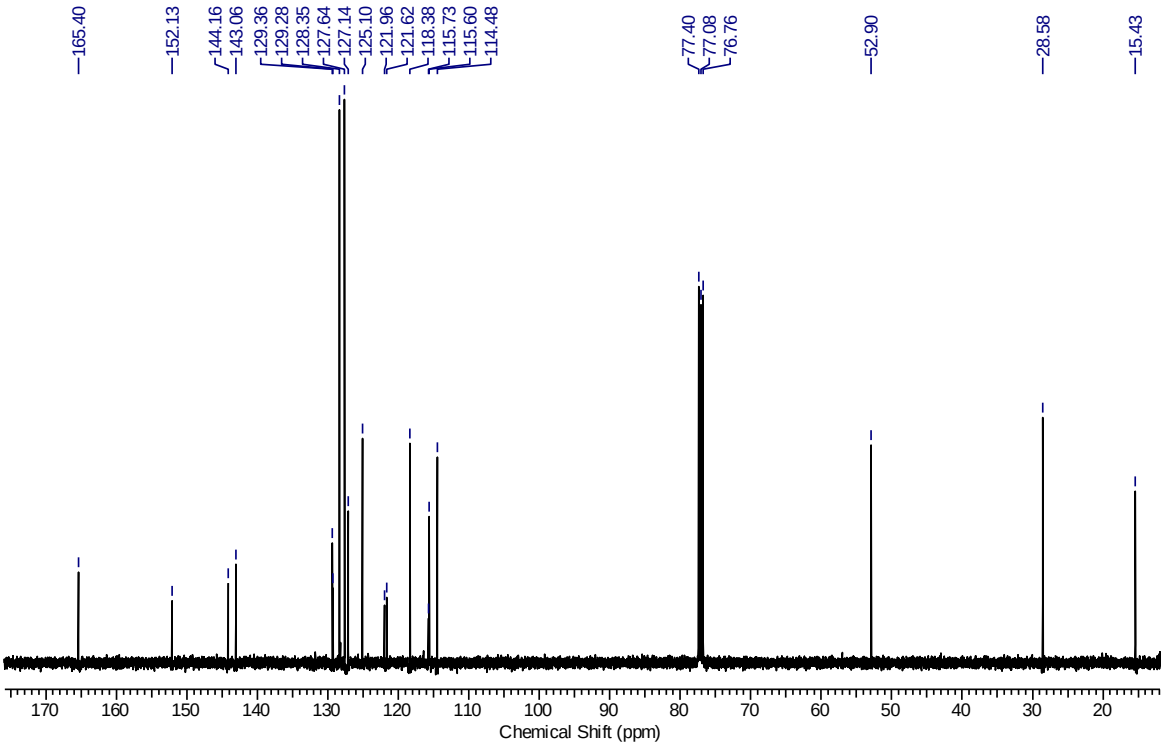


Figure 17. ^{13}C NMR (100MHz) spectrum of compound **4g** in $CDCl_3$.

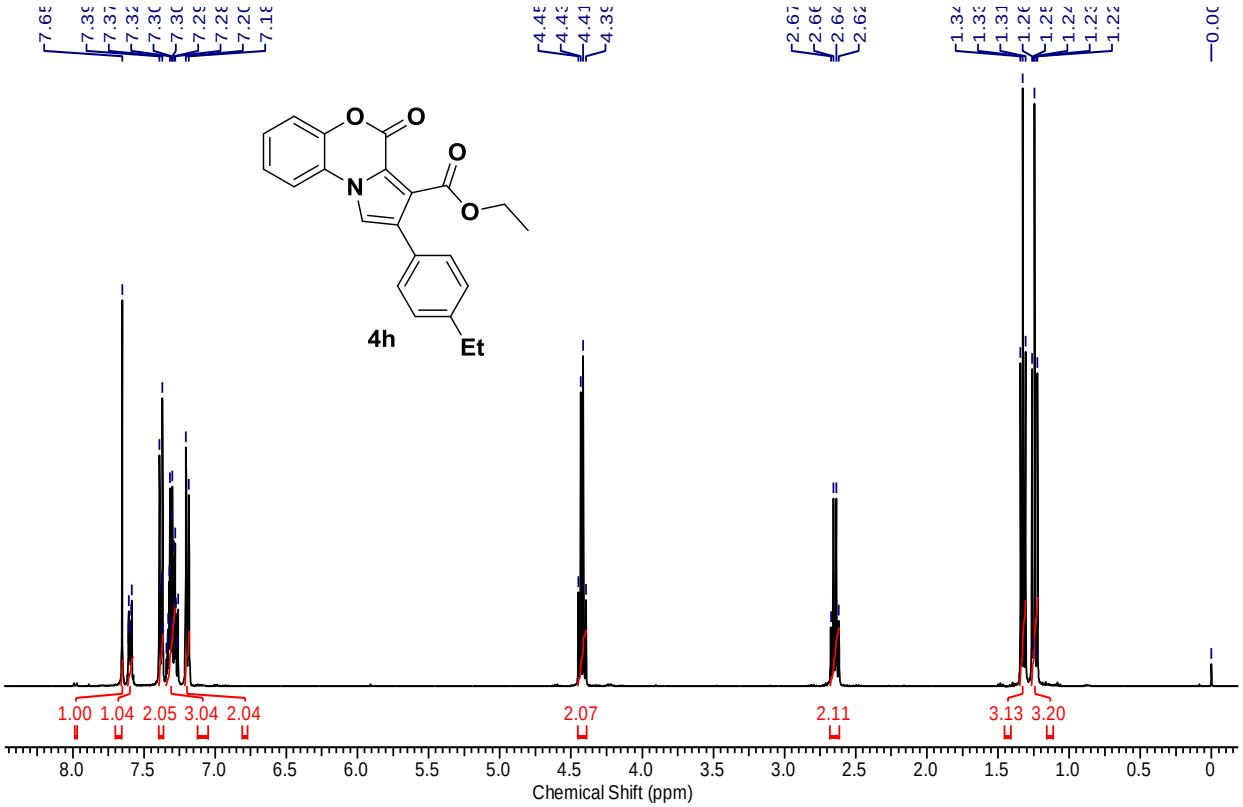


Figure 18. ^{1}H NMR (400MHz) spectrum of compound **4h** in $CDCl_3$.

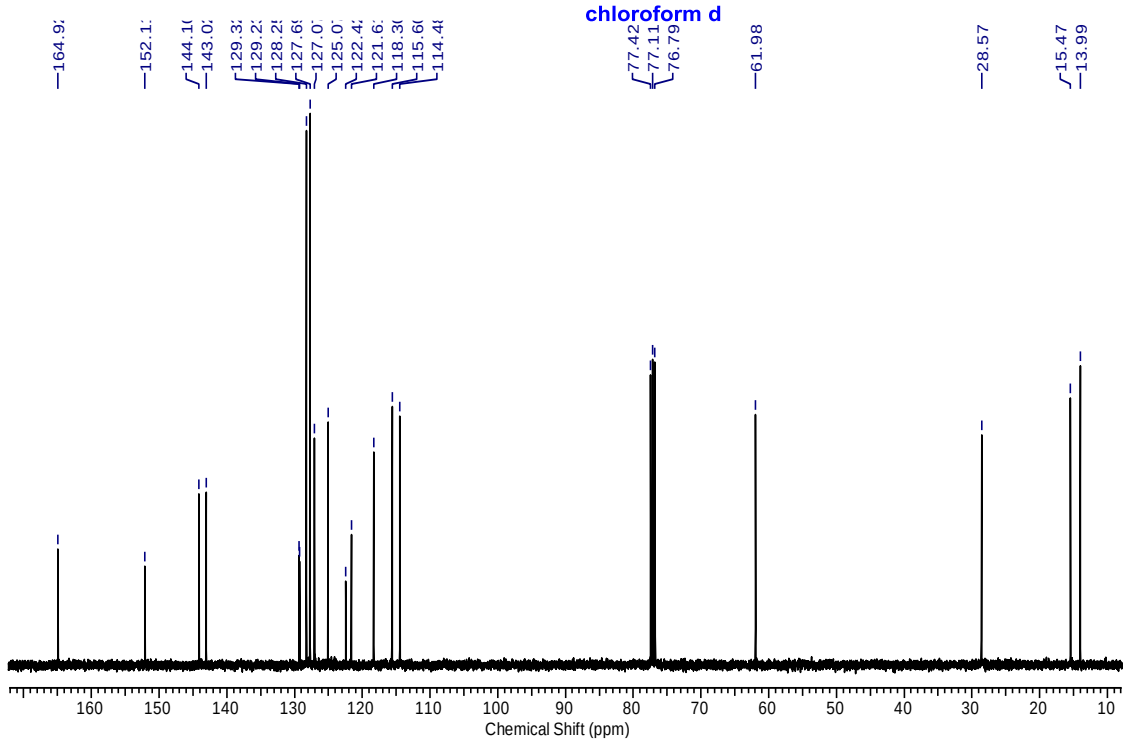


Figure 19. ^{13}C NMR (100MHz) spectrum of compound **4h** in $CDCl_3$.