β, γ- Butenolides in Dual Role: As Vinylogous Nucleophile for Michael Initiated Synthesis of Indanol Derivatives and as Organocatalyst for the α-CH_2 Oxygenation of Cyclic Amines/Ethers

by

Siddharth K. Deepake
10CC15J26015

A thesis submitted to the
Academy of Scientific & Innovative Research
for the award of the degree of
DOCTOR OF PHILOSOPHY
in
SCIENCE
Under the supervision of

Dr. Utpal Das

CSIR-National Chemical Laboratory, Pune

Academy of Scientific and Innovative Research
AcSIR Headquarters, CSIR-HRDC campus
Sector 19, Kamla Nehru Nagar,
Ghaziabad, U.P. – 201 002, India

August 2020

Dedicated to

My Parents and Teachers

Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled ,"**β, γ-Butenolides in Dual Role: As Vinylogous Nucleophile for Michael Initiated Synthesis of Indanol Derivatives and as Organocatalyst for the α-CH_2 Oxygenation of Cyclic Amines/Ethers**", submitted by **Mr. Siddharth K. Deepake** to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of **Doctor of Philosophy (Ph.D.)**, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

(Signature of Student)

Siddharth K. Deepake
Date: 24/08/2020

(Signature of Supervisor)

Dr. Utpal Das
Date: 24.08.2020

STATEMENTS OF ACADEMIC INTEGRITY

I **Mr. Siddharth K. Deepake**, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. **10CC15J26015** hereby undertake that, the thesis entitled ,"**β, γ- Butenolides in Dual Role: As Vinylogous Nucleophile for Michael Initiated Synthesis of Indanol Derivatives and as Organocatalyst for the α-CH_2 Oxygenation of Cyclic Amines/Ethers**" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* andthe CSIR Guidelines for "*Ethics in Research and in Governance (2020)*".

Signature of the Student
Date : 24/08/2020
Place : Pune

It is hereby certified that the work done by the student, under my/our supervision, is plagiarism-free in accordance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)*".

Signature of the Co-supervisor (if any)
Name :
Date :
Place :

Signature of the Supervisor
Name : Dr. Utpal Das
Date : 24.08.2020
Place : Pune

DECLARATION

I, **Siddharth K. Deepake**, bearing **AcSIR Registration No. 10CC15J26015** declare:

(a) that the plagiarism detection **software is currently not** available atmy work-place institute.

(b) that my thesis entitled, **"β, γ- Butenolides in Dual Role: As Vinylogous Nucleophile for Michael Initiated Synthesis of Indanol Derivatives and as Organocatalyst for the α-CH_2 Oxygenation of Cyclic Amines/Ethers"** is plagiarism free in accordance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)*".

(c) that I would be solely held responsible if any plagi urised content in my thesis is detected, which is violative of the UGC regulations 2018.

(Signature of the Student)
Date : 24/08/2020
Place : Pune

Acknowledgement

Research is a never-ending process involving a team of persons striving to attain newer horizons in the field of sciences. This thesis would not have been completed without the encouragement and co-operation of my parents, teachers, relatives, friends and all well-wishers. I take this opportunity to express my deep gratitude to one and all.

Firstly, I would like to express my sincere gratitude to my research advisor ***Dr. Utpal Das*** *for the continuous support of my Ph. D. study and related research, for his patience, motivation and immense knowledge. I am very much grateful to him for his valuable guidance and everlasting encouragement throughout my course. I am certain that his ethics and moral values which I learnt from him will go a long way in making me a better human being.*

I would like to thank Dr. S. P. Chavan Head, Division of Organic Chemistry and Dr. Ashwini Nangia Director NCL for providing infrastructure facilities. UGC, New Delhi is acknowledged for financial assistance. I also thank all OCD students and staff members for their timely help throughout. Help rendered by the members of IR, HRMS, HPLC, NMR group, XRD and library staff members is also acknowledged.

I sincerely thank to my AcSIR-DAC members ***Dr. J. Nithyanandhan, Dr. RavindarKontham and Dr. Pradip Maity*** *for time to time evaluation of my work, invaluable suggestions and encouragement.*

I sincerely thanks to ***Mrs. D. Sadafule*** *for HPLC analysis and NMR staff specially Pramod I also acknowledged* ***Dr. S. Borikar*** *for their help in GC-MS.*

I am very much thankful to my M. Sc. Teachers Prof. (Mrs) S. R. Vaidya, Dr. M. G. Shioorkar, Dr. S. A. Jadhav, Dr. KhanduWarad and Sunil Sabhadinde also all the Teachers from chemistry department of Vivekanand Arts, Sardar Dalipsingh Commerce and Science College, Aurangabad for immense support and encouragement during my M. Sc.

I was blessed with an opportunity to work in a most united, homogeneous and clean lab.My special thanks to lab-friend Anil, Someshwar, Atul, pawan, manish, Popat and Imran for their helpful discussion, co-operation and maintaining amazing atmosphere with humour in the lab. The warm memories of my days in Lab-180 will haunt me forever. I would like to extend my thanks to my dearest friends Dr. Prashishkumar, Dr. Amar Yeware, Dr. PrabhanjanGiram, Dr. Venkatesh Mullapudi, Dr. Goudappa Patil, Ravi Mule, Digambar, Rahul, Amol, Vivek, Mahesh, Tony, Sagar, Madhukar, Nilesh, Sunil, Rohit, Datta, Someshwar, Milind, Pankaj, Virat and my all other friends for making me very happy every time.

Acknowledgement

No word would suffice to express my gratitude and love to my family members Aai-Baba (mother-father), My wife Vaishali, my little ***Pari (Shreya)****, Gautam (brother), Komal (Vahini), my sister Sanghmitra, Sanjay (bhauji) and my little champs Khushi, Prerana and Prathmeshfor their continuous showering of boundless affection on me and supporting me in whatever I chose or did. It is my parent's constant struggle and relentless hard work to overcome the odds of life, which has inspired me to pursue life with a greater optimism. The warmth and moral value of my parents have stood me in good stead throughout my life and I would always look up to them for strength no matter what I have to go through. This Ph. D. thesis is a result of the extraordinary will, efforts and sacrifices of my parents. My all successes are dedicated to them now and always.*

Finally, my acknowledgement would not be completed without thanking the Buddha and Dr. B. R. Ambedkar for giving me the strength and the determination to overcome the hardships faced in my life.

Thank you.

…Siddharth

Content

Content

BHT	2,6-Di-tert-butyl-p-cresol
Boc_2O	Di-*tert*-butyl dicarbonate
CH_3CN	Acetonitrile
$CHCl_3$	Chloroform
CuI	Copper (I) iodide
$CuCl_2$	Copper (II) chloride
DBU	1,8-Diazabicyclo [5.4.0] undec-7-ene
DABCO	1,4-Diazabicyclo [2.2.2] octane
DCM	Dichloromethane
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulphoxide
DMF	*N*, *N*-Dimethylformamide
DMAP	*N*, *N*-Dimethyl-4-aminopyridine
DIPEA	*N*, *N*-Diisopropylethylamine
dr	Diastereomeric ratio
ee	Enantiomeric excess
Me	Methyl
EtOH	Ethanol
EtOAc	Ethyl acetate
Et_3N	Triethylamine
g	Grams
h	Hours
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HCl	Hydrochloric acid
K_2CO_3	Potassium carbonate
M+	Molecular ion
MeOH	Methanol
MEMCl	2-Methoxyethoxymethyl chloride
min	Minute
mg	Miligram
mL	Milliliter
MS	Mass spectrum
NaOH	Sodium hydroxide
NMR	Nuclear magnetic resonance
Pd/C	Palladium on activated charcoal
Ph	Phenyl
PPh_3	Triphenylphosphine
Rf	Retention factor
p-TSA	*p*-Toluenesulfonic acid
THF	Tetrahydrofuran
2Me-THF	2-Methyl Tetrahydrofuran
TLC	Thin layer chromatography
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

GENERAL REMARKS

1. All solvents were distilled and dried before use
2. Petroleum ether refers to the fraction collected in the boiling range 60–80 °C
3. Organic layers after every extraction were dried over anhydrous sodium sulfate
4. Column Chromatographic purifications were performed over silica gel (60–120 & 230–400 mesh) and alumina (neutral)
5. TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol), $KMnO_4$ (in ethanol) and ninhydrin (in ethanol)
6. Chemical nomenclature (IUPAC) and structures were generated using ChemDraw Professional 14.
7. ^{1}H and ^{13}C NMR and DEPT spectra were recorded on Brucker Avance 400 MHz, 500 MHz and JEOL ECX 400 instruments using TMS or solvent residue as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, td = triplet of doublet, dt = doublet of triplet, dq = doublet of quartet and app = apparent
8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light
9. Enantiomeric excess was determined on Agilent HPLC instrument equipped with a chiral column
10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump
11. The compounds, scheme and reference numbers given in each chapter/section refers to that particular chapter/section only
12. Reaction were carried out in oven dried glassware. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa.
13. Any reagents, starting material, and solvents were obtained from commercial suppliers and used without further purification.

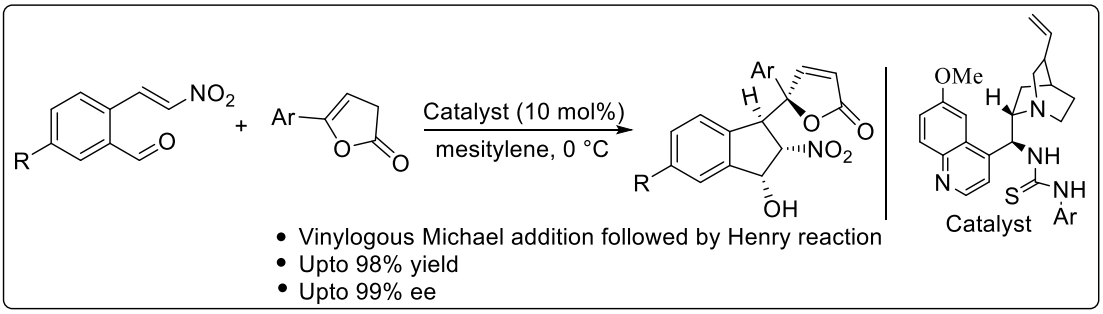
	Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry
Name of the Candidate	**Siddharth K. Deepake**
AcSIR Enrolment No. & Date	**Ph. D in Chemical Sciences (10CC15J26015); January 2015**
Title of the Thesis	**β, γ- Butenolides in Dual Role: As Vinylogous Nucleophile for Michael Initiated Synthesis of Indanol Derivatives and as Organocatalyst for the α-CH_2 Oxygenation of Cyclic Amines/Ethers.**
Research Supervisor	**Dr. Utpal Das**

Keywords: *Organocatalyst, Michael Reaction, Oxidation, α-Angelica Lactone*.

Abstract: β, γ-Unsaturated γ-lactones constitutes structural core of numerous natural products and are well-known as multi-centered nucleophile. The present thesis demonstrates application of these lactones not only as nucleophile (γ-regioselective) but also as (hitherto unexplored) organocatalyst for α-CH_2 oxygenation of cyclic amines and ethers. The thesis comprises of three chapters. The first chapter presents application of γ-lactones as nucleophile for enantioselective synthesis of indanol derivatives. The second chapter is about application of γ-lactones as catalyst for oxidation of benzylic sp3 C−H bonds of tetrahydroisoquinolines, isoindolines, isochromans and phthalans. The third chapter deals with α-oxygenation of cyclic amines using γ-lactones as catalyst.

Chapter I: **Asymmetric Cascade Reaction of γ-Substituted Deconjugated Butenolides with *o*-Formyl-β-nitrostyrene**

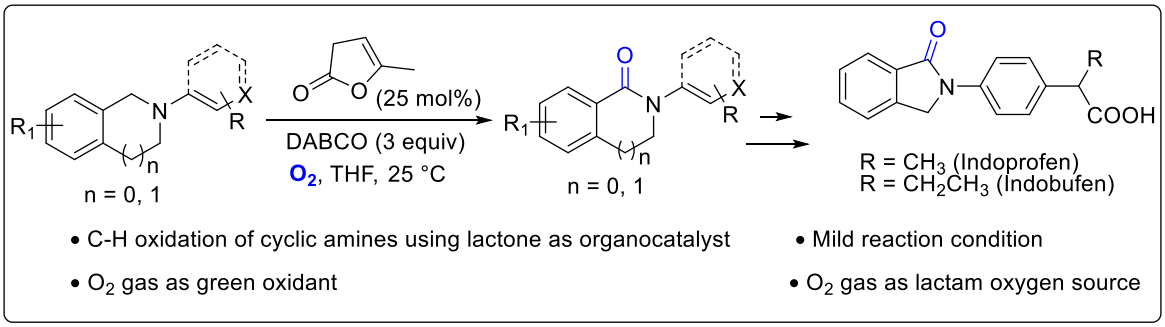
An efficient chemo-, diastereo- and enantio-selective cascade synthesis of functionalized indanols bearing four contiguous stereogenic centres has been developed via reaction of β, γ-butanolides with *o*-formyl-β-nitrostyrenes in the presence of quinine derived bi-functional hydrogen-bonding catalyst. Indanol derivatives containing γ, γ-disubstituted butenolides were obtained in good yields.



Chapter II: Organocatalytic Benzylic Oxidation of Cyclic Amines/Ethers Using α-Angelica Lactone as a Catalyst

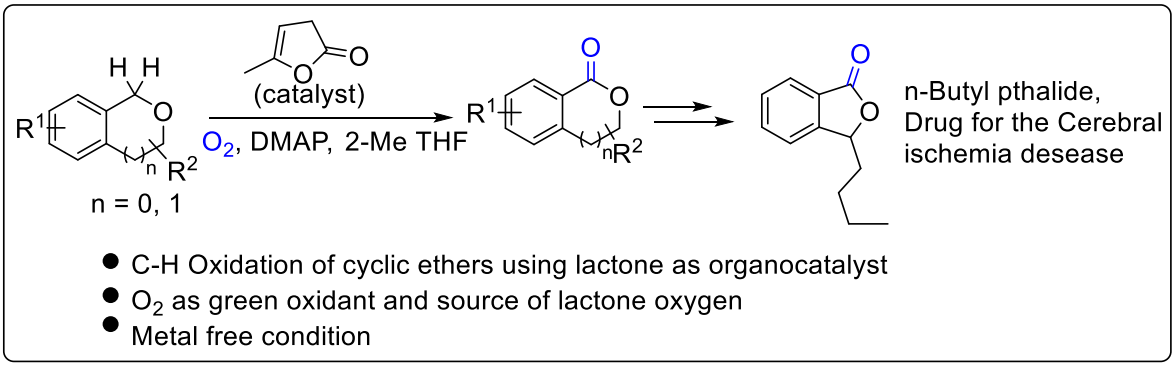
<u>Section A</u>: Metal-Free Organocatalytic Oxidation of Benzylic sp3 C−H Bonds of Tetrahydroisoquinoline and Isoindoline

A new method for the direct oxidation of various *N*-aryl tetrahydroisoquinolines and isoindolines to the corresponding lactams using α-angelica lactone as a catalyst was developed. The utility of the method was further demonstrated by synthesis of indoprofen and indobufen.



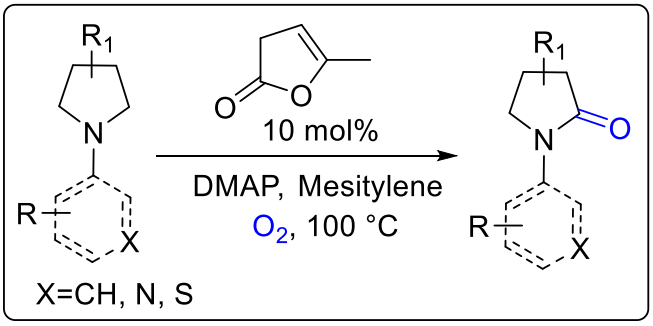
<u>Section B</u>: Metal-Free Organocatalytic Oxidation of Benzylic sp3 C−H Bonds of Isochromans and Phthalans

A metal-free organocatalytic system has been developed for highly efficient benzylic C–H oxygenations of isochromans and phthalans using oxygen as an oxidant. This oxidation reaction utilizes α-angelica lactone as a low cost catalyst. Benign reaction conditions allow the synthesis of valued isocoumarins and phthalides from readily available precursors in good yields. Mechanistic studies indicate that the reaction pathway likely involves a radical process via a peroxide intermediates.



Chapter III: **Oxidation of Pyrrolidine Derivatives to Corresponding Lactams by using α-Angelica Lactone as a Organocatalyst**

Highly efficient method for the synthesis of lactams by the α-oxygenation of amines employing α-angelica lactone as a organocatalyst and O_2 as green oxidant was developed. A library of lactams were obtained in good chemical yields.



Noteworthy Findings:

- Organocatalytic distereo- and enantio- selective approach for synthesis of Indanol derivatives with the 4 stereocenters including one quarternary center.
- Organocatalytic approach for the direct oxidation of benzylic sp3 C–H bonds of amines and ethers.
- Oxidation of *N*-aryl pyrrolidines to the corresponding lactams using α- angelica lactone as the catalyst.

References:

1) "Organocatalytic Asymmetric Cascade Reaction of γ-Substituted Deconjugated Butenolides with *o*-Formyl-β-nitrostyrene". **Siddharth K. Deepake**, Atul B. Lanjewar, Thanusha Thatikonda, Rajesh G. Gonnade and Utpal Das* *ChemistrySelect* **2018**, *3*, 8189-8192.

2) "α-Angelica Lactone in a New Role: Facile Access to N-Aryl Tetrahydroisoquinolinones and Isoindolinones via Organocatalytic α-CH_2 Oxygenation". Thanusha Thatikonda, **Siddharth K. Deepake** and Utpal Das* *Org. Lett.* **2019**, *21*, 2532-2535.

3) "α-Angelica Lactone Catalyzed Oxidation of Benzylic sp^3 C−H Bonds of Isochromans and Phthalans". Thanusha Thatikonda[#], **Siddharth K. Deepake[#]**, Pawan Kumar and Utpal Das* *Org. Biomol. Chem.* **2020**, *18*, 4046-4050. ([#]Equal Contribution).

4) "Oxidation of Pyrrolidine Derivatives to Corresponding Lactams by Using α-Angelica Lactone as an Organocatalyst". **Siddharth K. Deepake**, Manish Kumar and Utpal Das* (*Manuscript under preparation).*

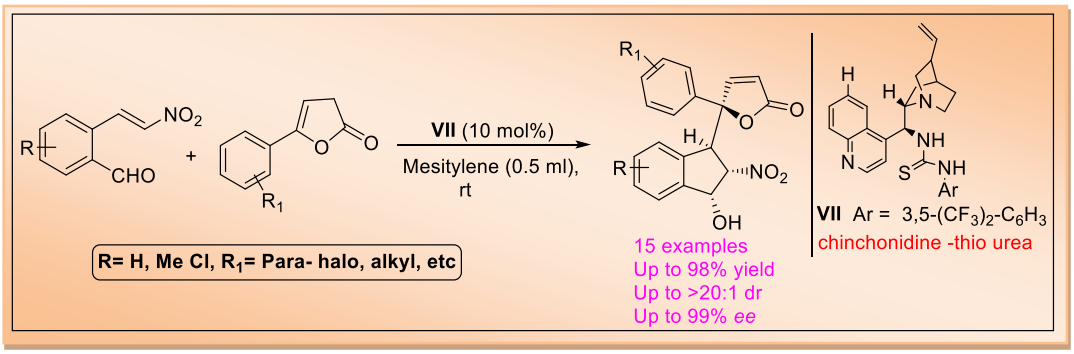
CHAPTER I

Asymmetric Cascade Reaction of γ-Substituted Deconjugated Butenolides with *o*-Formyl-β- nitrostyrene

Chapter I

Asymmetric Cascade Reaction of γ-Substituted Deconjugated Butenolides with *o*-Formyl-β-nitrostyrene

In this chapter, efficient chemo-, diastereo- and enantio-selective organocatalytic cascade reaction of various γ-substituted deconjugated butenolides with *o*-formyl-β-nitrostyrenes to furnish functionally rich chiral indanol derivatives bearing four contiguous stereogenic centers in the presence of bi-functional hydrogen-bonding catalyst are described. The indanol derivatives were obtained with good yields and moderate to high enantioselectivities.



ChemistrySelect **2018**, *3*, 8189-8192.

1.1 Introduction

About 10% of total natural products contain butenolide and lactone framework thus making it an attractive target to the synthetic community.[1] MacMillan and co-workers in 2003[2] reported the use of preformed silyloxyfurans for the synthesis of butenolides using catalytic asymmetric Mukaiyama type aldol & Michael reactions.[3,4] Afterwards, this preformed silyloxyfurans was a preferred choice by many research groups. γ-Substituted butenolides, however, got much late attention although they possess a nucleophilic center at its γ-position and can deliver a quaternary stereogenic center *via* vinylogous Michael addition. The reason could be additional steric bulk of γ-substituted butenolides and the challenges associated with the enantioselective synthesis of quaternary stereogenic center.[5] γ-Substituted butenolides are well known for the synthesis of γ, γ-disubstituted butenolides via vinylogous Michael and related reactions.[6] Here, we demonstrate the unprecedented use of γ-substituted butenolides for a cascade reaction leading to the synthesis of (nitro) indanol derivatives. It is mention-worthy that indanol core is found in many chiral catalysts, such as Rovis-NHC,[7] Ricci's chiral thiourea,[8] Seidel's thioamide,[9] oxazaborolidines[10], bis(oxazoline) ligands[11] etc.[12] and also as drug molecules[13] (Figure 1).

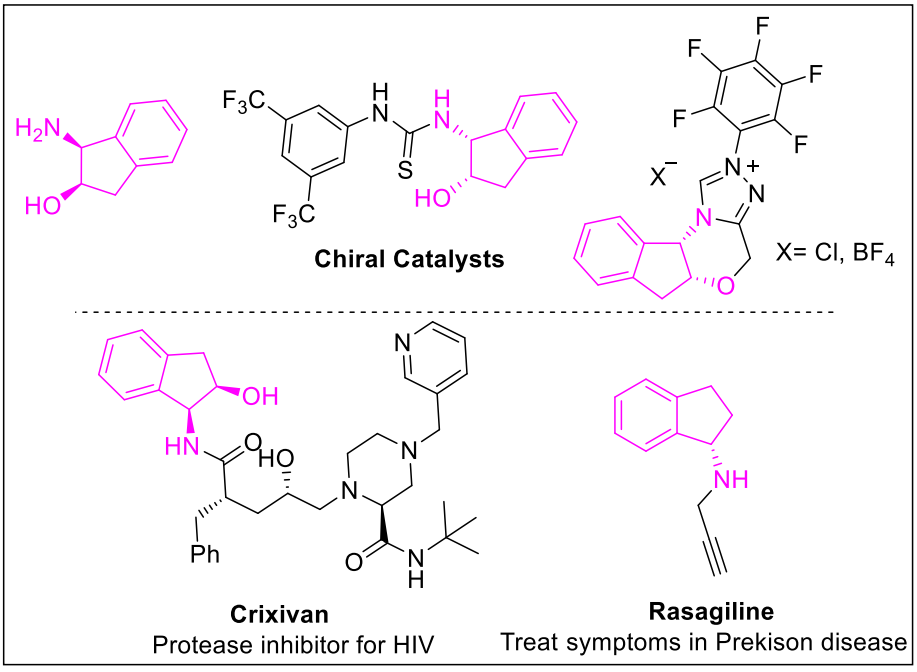
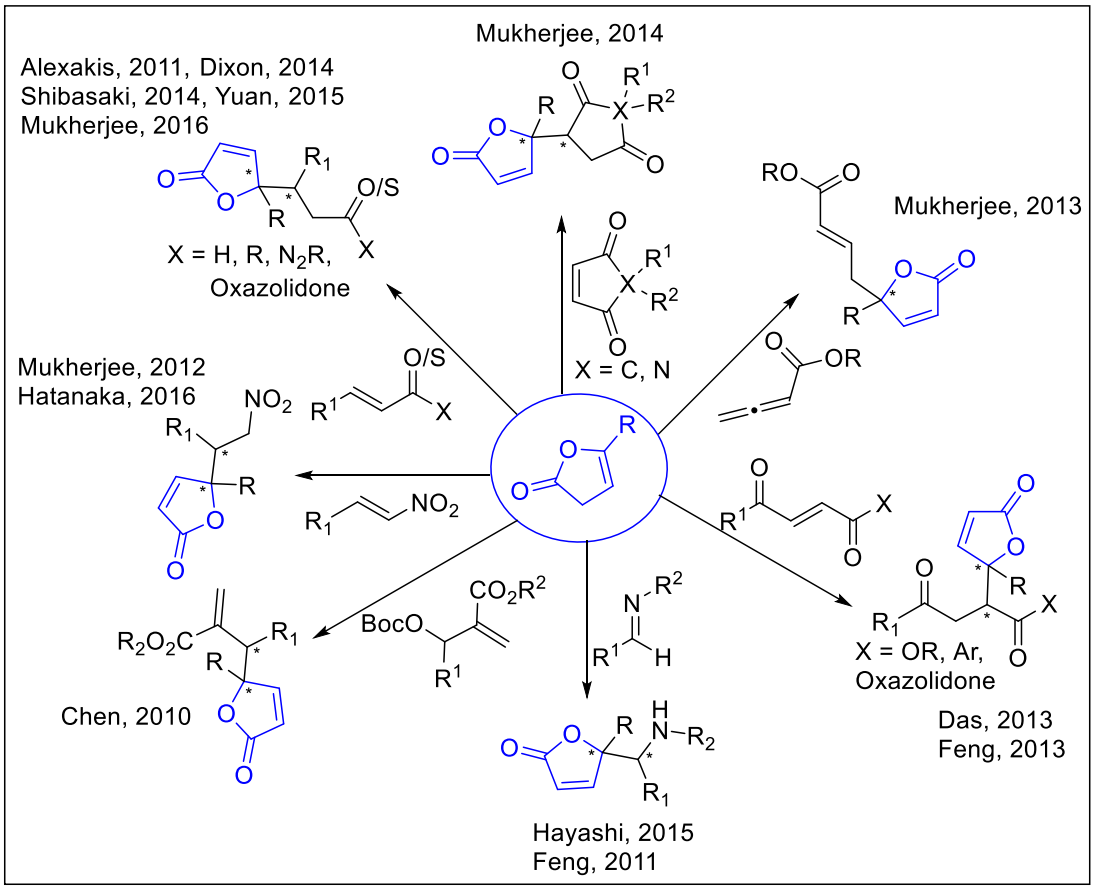


Figure 1. Indanol containing chiral catalysts and drugs

1.2 Literature review:

Chen *et al.* in 2010 reported for the first time the use of γ-substituted butenolides for direct asymmetric allylic alkylation reaction with Morita−Baylis−Hillman carbonate.[14] Afterwards, many research groups reported the application of γ-substituted butenolides for the synthesis of butenolide derivatives (Scheme 1). Alexakis *et al.* in 2011 reported the direct vinylogous Michael addition (DVMA) of γ-substituted butenolides with enals in presence of aminal-pyrrolidine as a catalyst with high stereoselectivity (>95% *ee*).[15]



Scheme 1: Cursory of literature using γ-substituted butenolides

After this, many research groups reported the DVMA reactions with the oxazolidone, keto, amide, thio-keto, etc.[16] In the same year, Feng *et al.* and Hayashi *et al.* in 2015 also reported the asymmetric vinylogous Mannich-type (AVM) reaction with aldimines/ketimines with use of Lewis acid and *N*, *N*-dioxide ligand or cinchona-derived catalyst.[17] Whereas, Mukherjee *et al.* in 2012[18] and Hatanaka *et al.* in 2016[19] reported separately the asymmetric nitro-Michael reaction with nitroolefins in quinine-derived catalysts. Next, the DVMA proved to be one of

the best choice for the conversion of α, β-unsaturated γ-keto esters, chalcones, and oxazolidone derivatives to different value-added products.[20] Moreover, Mukherjee's group has developed several methods by employing γ-substituted butenolides in presence of bifunctional-thiourea's as a catalyst with different electrophiles such as allenoates, succinimides.[21]

1.3 Origin of present work:

From the above paragraph, it is evident that direct vinylogous Michael and related addition reactions occupy a major section of the literature reports. But γ-substituted butenolides have never been explored for cascade reactions.[6] Hence, the development of new approaches utilizing these γ-substituted butenolides is highly desirable. Another limitation to the known protocols is that they are limited to the formation of only one C-C bond and a maximum three stereogenic center.

1.4 Objective:

As mentioned earlier, both indanol and β, γ-butenolides system is a representative carbo/hetero-cycle whose derivatives display diverse biological activities. Additionally, the combination of *o*-formyl-*β*-nitrostyrene and *γ*-substituted *β, γ*-butenolide (henceforth *γ*-butenolide) remains an unprecedented cascade protocol. These inspired us to develop a cascade reaction employing *o*-formyl-*β*-nitrostyrenes and *γ*-butenolide as the reaction partners. We anticipated that base mediated deprotonation of an acidic proton from *γ*-butenolide will lead to a dienolate which will add to β-carbon of *o*-formyl-*β*-nitrostyrenes to provide vinylogous Michael addition product **A**. In the presence of a base, further deprotonation will lead to form nitronate which will participate in a Henry reaction with the formyl functional group to furnish a (nitro) indanol derivative **3** (Figure 2a) along with the formation of two new C-C bonds and four stereogenic centers. However, there are challenges that need to be addressed, especially when developing the protocol in an asymmetric fashion, such as control of enantio- and diastereoselectivity of the product. Another challenge was the issue of regioselectivity. The substrate, *o*-formyl-*β*-nitrostyrenes has two competing acceptor sites (nitroolefin and aldehyde).[22] Hence, an aldol addition of *γ*-butenolide to *o*-formyl-*β*-nitrostyrenes, followed by an intramolecular oxa-Michael reaction to furnish benzo-furan derivative (**3′**) is also a possibility (Figure 2b).

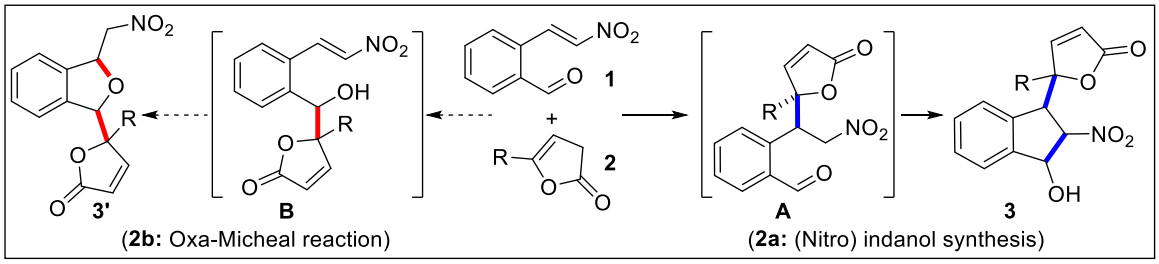


Figure 2: Regioselective addition of *γ*-butenolide to *o*-formyl-*β*-nitrostyrenes

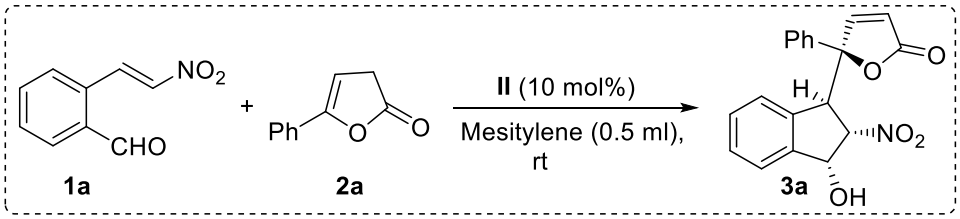
To overcome these difficulties, we decided to use bi-functional hydrogen-bonding catalysts (**II-VII**) because they are known to act as a base to convert *γ*-butenolide into dienolate by deprotonating the acidic α-proton of a butenolide using tertiary N of quinuclidine and thiourea part is known to activate β- carbon of nitrostyrene by forming hydrogen bonds with the nitro group.

1.5 Results and discussion

Our survey started with *o*-formyl-*β*-nitrostyrene (**1a**) and *β, γ*-butenolide (**2a**) as model substrates. The protocol was first evaluated using DABCO (10 mol%) as the base and Schreiner's catalyst **I** as a promoter. After 48 h, the product **3a** was isolated in 63% yield with a 3:1 diastereomeric ratio. In the absence of either **I** or DABCO, only a trace amount of product was observed (Table 1, entry 1). In presence of cinchonidine derived bifunctional catalyst **II**, product **3a** was obtained in 72% enantiomeric excess along with 18:1 dr and 82% yield (Table 1, entry 2) within a short reaction time (3 h). Next, we have performed solvent screening using bifunctional catalysts **II.** While using chlorinated solvents like chloroform, dichloromethane, and chlorobenzene, the corresponding product was obtained in excellent yields with good to excellent dr in short reaction time. However, in all the cases the product was obtained in low enantiomeric excess. Since we obtained good yields in chlorinated solvent and good enantiomeric excess in toluene; we performed the reaction in a mixture of solvent. Accordingly, we performed a reaction using 5 mol% catalyst and 4:1 ratio of toluene and dichloromethane solvents. However, the reaction took relatively more time for completion and the yield was dropped to 63%. The product was also obtained in moderate dr and enantiomeric excess (Table 1, entry 5). Next, the reaction was performed in the presence of ethereal solvents like MIBK and tetrahydrofuran. The corresponding cascade product was

obtained with good yields however enantiomeric excess remained low (Table 1, entries 7 & 8).

Table 1: Optimization studies [a]



Entry	Cat.	Solvent	Time	Yield%[b]	dr[c]	ee[d]
1	I+B	Toluene	48 h	63	3:1	±
2	II	Toluene	3 h	82	18:1	72
3	II	$CHCl_3$	2 h	96	>20:1	5
4	II	DCM	3 h	89	-	10
5[e]	II	PhMe+DCM(4:1)	18 h	63	10:1	62
6	II	PhCl	3 h	86	9:1	16
7	II	MIBK	3 h	69	-	34
8	II	THF	18 h	87	>20:1	32
9	II	Xylene	3 h	80	>20:1	62
10	**II**	**Mesitylene**	**3 h**	**93**	**>20:1**	**80**

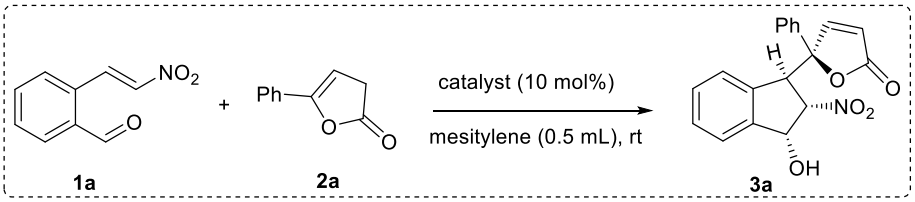
[a] **1a** (0.1mmol), **2a** (0.1 mmol) and cat. (10 mol %) were used in 0.5 mL solvent. [b] Isolated yield. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Enantiomeric excess was determined by HPLC analysis. [e] 5 mol% catalyst was used. DABCO (B) =1,4-diaza- bicyclo [2.2.2] octane

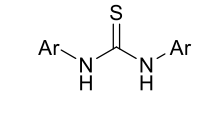
Further, when xylene was used as solvent at rt, the product **3a** was obtained in 80% yield with excellent dr (>20:1) and 62% enantiomeric excess (Table 1, entry 9). Gratifyingly, while using mesitylene as solvent at rt, the product was obtained in 93% yield with excellent dr (>20:1) and 80% enantiomeric excess in 3 h (Table 1, entry 10).

Having the best solvent condition in hand, the reaction was further optimized with different bifunctional catalysts. By using phenyl substituted urea catalyst **III** product **3a** was obtained in 57% yield with 6:1 dr and 36% *ee* (Table 2, entry 1). When compared between thiourea and urea derivatives of bifunctional catalysts, it is generally observed that thiourea derivatives offer better results than their urea counterparts and this trend was also observed in the present case. While using the catalyst **IV** the product was obtained in good yield (73%) with moderate *ee* i.e. 53% (Table 2, entry 2). Interestingly, further investigation in the presence of catalyst

II shows that temperature plays a key role in this cascade reaction to form the corresponding product **3a**.

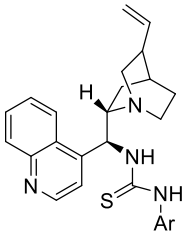
Table 2: Optimization of Catalysts [a]



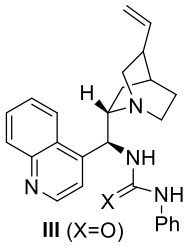


I

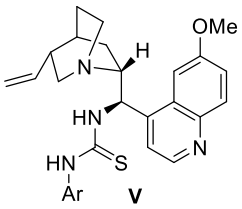
Ar = 3,5-$(CF_3)_2$-C_6H_3



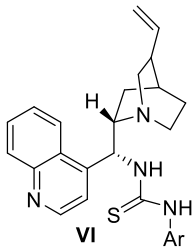
II



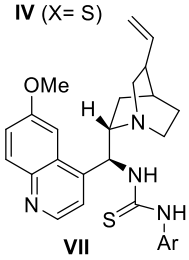
III (X=O)
IV (X= S)



V



VI



VII

Entry	Cat	T (h)	3a (%)[b]	dr[c]	ee[d]
1	III	3	73	6:1	53
2	IV	3	57	6:1	36
3[e]	II	23	78	>20:1	94
4[f]	II	45	79	>20:1	92
5[g]	II	40	87	>20:1	91
6[h]	II	48	95	>20:1	92
7[e]	V	48	48	>20:1	-70
8[e]	VI	23	97	>20:1	-89
9[e]	**VII**	**19**	**97**	**>20:1**	**97**
10[i]	VII	66	90	>15:1	71

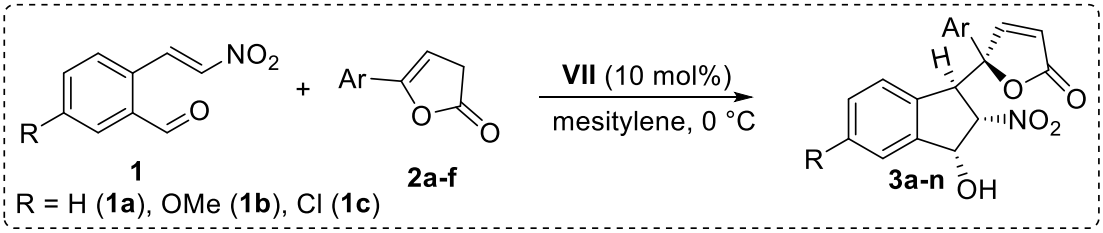
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), **Cat.** (10 mol%) in 0.5 mL mesitylene at room temperature. [b] Isolated yield. [c] Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Enantiomeric excess was determined by HPLC analysis. [e] The reaction was performed at 0 °C. [f] at −20 °C. [g] 0.25 mL mesitylene was used. [h] 1.0 mL mesitylene was used. [i] 5 mol % **VII** was used.

When the reaction was performed at 0 °C, the reaction took a long time for completion but both diastereo- and enantio-selectivities were enhanced to >20:1 and 94% respectively (Table 2, entry 3). On the other hand, when the reaction temperature was further decreased to -20 °C, the reaction took much longer reaction time (45 h) and also slightly reduced the enantioselectivity of product **3a** (92% *ee*) was observed (Table 2, entry 4). We also found that solvent concentration does not have much effect as by using either 0.25 mL or 1.0 mL of mesitylene, the product was obtained in very similar enantioselectivity. However, the chemical yield of the product improved up to 95% while performing the reaction under high dilution (Table 2, entries 5 & 6). To further improve the stereoselectivity of the product, bifunctional catalysts **V–VI** were evaluated at 0 °C. Quinidine derived bifunctional catalyst **V** provided the enantiomer of product **3a** with moderate yield (48%) and enantioselectivity (70%) but with good diastereoselectivity (>20:1) (Table 2, entry 7). In contrast, cinchonine derived bifunctional thiourea catalyst **VI** afforded enantiomer of product **3a** in high diastereo- and enantio-selectivities with excellent chemical yield (97%) (Table 2, entry 8). Best optimal condition was obtained by employing quinine derived thiourea **VII** as a catalyst. The desired product (nitro) indanol **3a** was obtained in 97% yield, >20:1 dr, and 97% *ee* (Table 2, entry 9). However, when the same reaction condition (entry 9) was performed using 5 mol% of catalyst loading, the product was obtained in reduced enantio- and diastereo-selectivity (Table 2, entry 10).

With the best optimal condition in hand, the scope of this cascade reaction was explored by using *o*-formyl-β-nitrostyrenes **1a-c** and aryl-substituted β, γ-butenolides **2a-f** and the results are summarized in Table 3. The corresponding cascade products **3a–m** containing four stereocenters along with one quaternary stereogenic centers were obtained in good to excellent enantioselectivities and high diastereoselectivities with high chemical yields. The reaction of *para*- halo aryl substituents of β, γ-butenolides **2b-d** with *o*-formyl-β-nitrostyrenes **1a** delivered the corresponding products **3b-d** in good chemical yields (78-90%) along with good enantioselectivities (70-79%) and high diastereomeric ratios (>10:1) (Table 3, entries 2-4). Whereas β, γ-butenolides **2e-f** substituted with *para*-Methyl and *para*-phenyl were equally well tolerated with **1a** (98 and 56% yield) and (nitro) indanol product **3e** and **3f** were obtained in 70 and 72% *ee* respectively (Table 3, entries 5 & 6). While the reaction of **1a** with

bulky group substituent 2-naphthyl *β, γ*-butenolides **2g** gave the corresponding product **3g** in low dr and moderate yield with good enantioselectivity (65%).

Table 3: Substrate scope for the cascade reaction [a]



Entry	R	Ar	t (h)	**3**[b] (%)	dr[c]	*ee*[d] (%)
1	H	C_6H_5, **2a**	19	**3a**, 97	>20:1	97
2	H	4-FC_6H_4, **2b**	50	**3b**, 90	>20:1	79
3	H	4-BrC_6H_4, **2c**	27	**3c**, 78	13:1	70
4	H	4-ClC_6H_4, **2d**	27	**3d**, 87	>10:1	76
5	H	4-MeC_6H_4, **2e**	36	**3e**, 98	>20:1	70
6	H	4-$C_6H_5C_6H_4$, **2f**	88	**3f**, 56	>20:1	72
7	H	2-Naphthyl, **2 g**	38	**3g**, 40	4:1	65
8	OMe	C_6H_5, **2a**	67	**3h**, 94	13:1	99
9	OMe	4-FC_6H_4, **2b**	72	**3i**, 97	>20:1	97
10	OMe	4-BrC_6H_4, **2c**	72	**3j**, 94	>20:1	79
11	OMe	4-ClC_6H_4, **2d**	67	**3k**, 92	>20:1	95
12	OMe	4-MeC_6H_4, **2e**	40	**3l**, 58	>20:1	98
13	OMe	4-$C_6H_5C_6H_4$, **2f**	94	**3m**, 53	>20:1	84
14	OMe	2-Naphthyl, **2 g**	38	**3n**, 35	12:1	96
15	Cl	C_6H_5, **2a**	33	**3o**, 63	>20:1	62

[a]Reaction conditions: **1a-c** (0.1 mmol), **2a-f** (1 equiv.), **VII** (10 mol%) in 0.5 mL mesitylene. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] *ee* for the major isomer.

Next, β, γ-butenolides **2a-g** was examined with *o*-formyl-β-nitrostyrenes **1b** containing electron releasing group –OMe. The reaction was well tolerated in all the cases and the corresponding products **3h-n** were afforded in excellent enantioselectivities (79-99%) and diastereomeric ratios (up to >20:1) as well as good to excellent chemical yields (35-97%) (Table 3, entries 8-14). The substrate scope was further extended by employing *para*- chloro aryl substituent of **1c** with **2a**. The product **3m** was obtained in high diastereomeric ratios (>20:1) with good yields but with a moderate enantiomeric excess (Table 3, entry 15). The requirement of γ-aryl-substituted deconjugated butenolides **2** as a reaction partner is a limitation for this developed protocol. Very trace amount of product (<10%) formation was observed with methyl or benzyl substituted **2**. The reason might be the higher reactivity of alkyl-substituted butenolides. As a result, several non-separable products were noticed in thin layer chromatography. To determine the absolute configuration, a single-crystal for compound **3c** was developed and it was analyzed by single-crystal X-ray data. The absolute configuration of product **3c** is presented in figure 3 and that of others was assigned analogously.

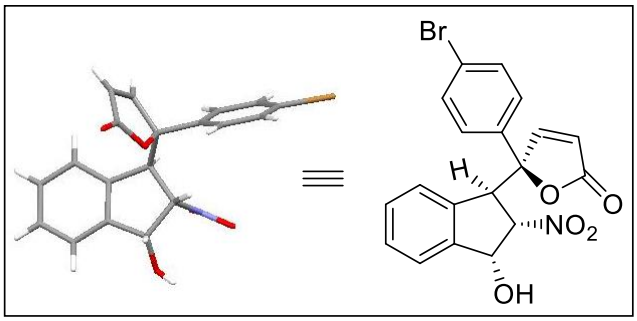


Figure 2. Single crystal X-ray structure of **3c**

A plausible mechanism for this transformation has been depicted in figure 4. The reaction proceeds *via* vinylogous Michael reaction followed by Henry reaction to furnish the final cascade adduct **3** in the presence of the catalytic amount of bifunctional catalyst. The reaction begins by deprotonation of α-acidic proton of butenolide by the tertiary N of quinuclidine to form a dienolate. At the same time, the nitro group of **1** was also tethered by thiourea. This tethered binding of the bifunctional catalyst makes nitrostyrene more electrophilic and the addition of dienolate from the γ- position *via* vinylogous Michael addition occurs. The formed intermediate **B** was also stabilized by the bifunctional catalyst via H-bond formation.

Formation of nitro-enolate and subsequent Henry reaction on the aldehyde group gave final cascade product **3**.

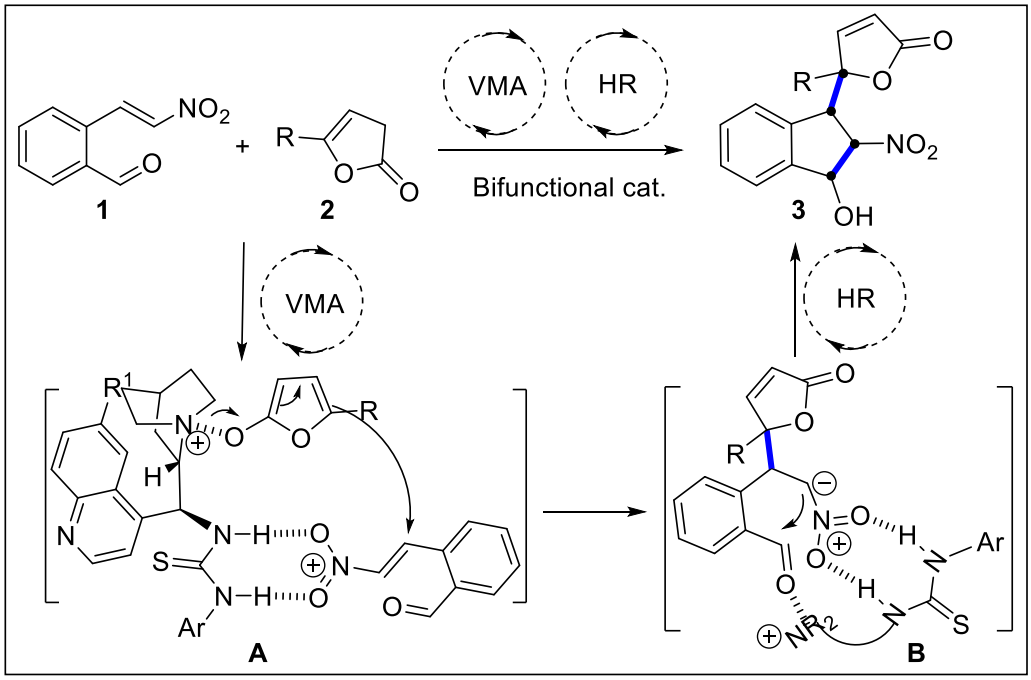


Figure 3: Plausible mechanism for the cascade reaction

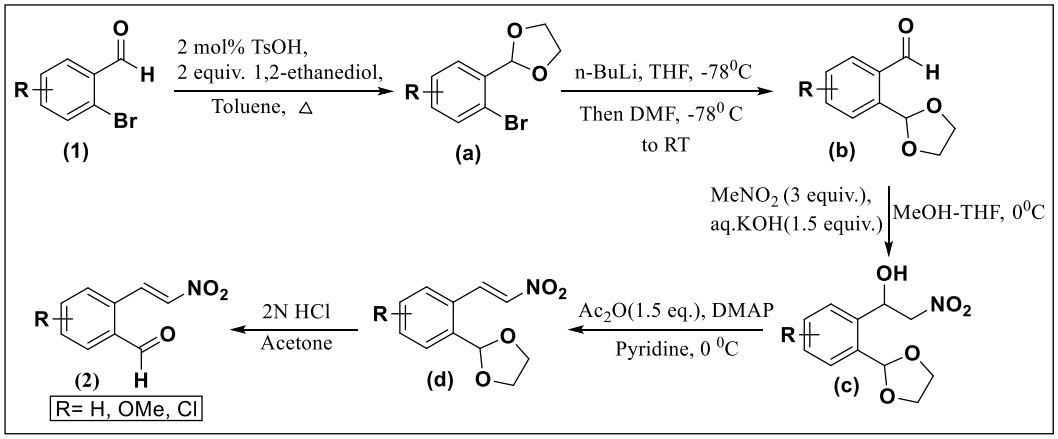
1.6 Conclusion

In conclusion, we have developed a highly enantio-, diastereo, and chemo-selective procedure for the synthesis of nitro-indnol derivatives starting from β, γ-butenolides, and *o*-formyl-β-nitrostyrenes as the reactive partners. The reaction was catalyzed by cinchona alkaloid derived bifunctional catalysts and the corresponding products were obtained in good yields. The nitro-indanol products were obtained with four contiguous (one quaternary and three tertiary) stereogenic centers. This protocol is the first example where β, γ-butenolides were employed for cascade reaction.

1.7 Experimental Section

A) General procedure for the synthesis of *o*-formyl-β-nitrostyrenes derivatives:

Step 1[23]: 2-Bromobenzaldehyde (37.2 mmol, 1 equiv.), *p*-TsOH.H_2O (2 mol%) and 1,2-ethandiol (2 equiv.) were heated to reflux under Dean-Stark condition for overnight in toluene (80 mL). After completion of the reaction, the reaction mixture was cooled to rt. Saturated aq. $NaHCO_3$ solution was added and extracted with EtOAc (2×20 mL), washed with



brine (20 mL) and dried over Na_2SO_4 and filter. After evaporation in *vacuo,* the residue was purified by column chromatography (20% ethyl acetate/pet ether) to afford acetal **a** in quantitative yield.

Step 2[23]: To a stirred solution of acetal **a** (19.29 mmol, 1 equiv.) in dry THF (100 mL) at -78 °C was added *n*-BuLi (1.6 M in THF, 2 equiv.). The reaction mixture stir for 1 h at this temperature then distilled DMF (1.5 equiv.) was added in one portion. The reaction mixture was allowed come to rt and was quenched by adding saturated aq. NH_4Cl solution and extracted with EtOAc (2×20 mL), washed with brine (20 mL) and dried over Na_2SO_4 and filter. After evaporating solvents, residue was purified by column chromatography (20% ethyl acetate/pet ether) to afford aldehyde **b** in 57% yield.

Step 3[24]: To a solution of aldehyde **b** (11.04 mmol, 1 equiv.) in THF (33 mL) and nitromethane (3 equiv.) in MeOH (16 mL) was added KOH (1.5 equiv. in 7 mL H_2O) at 0 °C and the resulting mixture was stirred for 15 min. Saturated aq. NH_4Cl solution was added and extracted with EtOAc (2×20 mL), subsequently wash with brine (20 mL) and dried over Na_2SO_4 and filter. After evaporating solvents, residue was purified by column chromatography (10% ethyl acetate/pet ether) to obtain nitroethanol intermediate **c** in an 85% yield in colourless oil.

Step 4[24]: To a solution of nitroethanol intermediate **c** (9.28 mmol, 1 equiv.) in pyridine (22 mL) was added acetic anhydride (1.5 equiv.) and DMAP (0.2 equiv.) in pyridine (7 mL) at 0 °C and the resulting mixture stirred for 30 min. Saturated aq. $NaHCO_3$ solution was added and extracted with DCM (2×10 mL), wash with water (10 mL) and brine (10 mL) and dried. After evaporating solvents, residue was purified by column chromatography (10% ethyl acetate/pet ether) to obtain nitrostyrene **d** in 71% yield as yellow solid.

Step 5[25]: To a solution of nitrostyrene **d** (6.65 mmol, 1 equiv.) in acetone (30 mL) was added 2N HCl (4 equiv.) and the reaction mixture stirred at rt for 3 h. After completion of the reaction, excess distilled water was added and formed precipitated was filter and wash several times with pentane and dried under high vacuum to obtain yellow solid in 65% yield. (E)-4-methoxy-2-(2-nitrovinyl) benzaldehyde (**2b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.94 – 8.88 (m, 1H), 7.64 – 7.59 (m, 1H), 7.52 – 7.46 (m, 1H), 7.44 – 7.40 (m, 1H), 7.21 – 7.15 (m, 1H), 3.95 (s, 3H).

B) General procedure for the synthesis of γ-substituted butenolides derivatives[26]

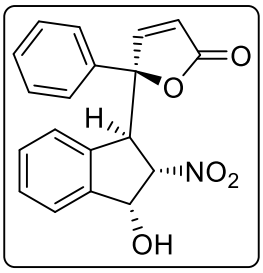
γ-substituted butenolides synthesized by applying Yuan *et al* procedure with modification as, 3-benzoyl propionic acid (2.6 mmol, 500 mg) was added in a stirred solution of acetic anhydride (0.5 mL) and acetic acid (0.3 mL) containing a catalytic amount of *p*-TsOH.H_2O (9.89 mg). This mixture was stirred for 2 h at rt. Then the mixture was diluted with distilled water (5 mL) and stirred for another 30 min. Reaction mixture was dumped on crushed ice and filtered. Then was added Na_2SO_4 and filter again and washed with EtOAc (5 mL). The residue was purified by the column chromatography (10% ethyl acetate/pet ether) immediately to obtain a yellow solid. 5-(p-tolyl) furan-2(3H)-one (90% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 – 7.46 (m, 2H), 7.23 – 7.18 (m, 1H), 5.72 (t, *J* = 2.7 Hz, 1H), 3.40 (d, *J* = 2.8 Hz, 2H), 2.38 (s, 3H).

C) General procedure for the synthesis of indanol derivatives:

An oven-dried glass vial with a magnetic stir bar was charged with **1a-c** (0.1 mmol), **2a-g** (0.1 mmol) in mesitylene (0.5 mL), and catalyst **VII** (10 mol%). The reaction mixture was stirred at 0 °C for the indicated time and was monitored by TLC. The products were directly purified by flash column chromatography on silica gel (petroleum ether: ethyl acetate = 7:3) to afford the desired product **3a-o**.

1.8 Characterization data of compounds

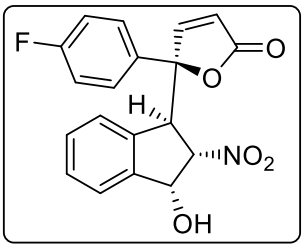
S)-5-((1R,2S,3R)-3-hydroxy-2-nitro-2,3-dihydro-1H-inden-1-yl)-5-phenylfuran-2(5H)-one (3a):



Yield: 97%; d.r.: >20:1; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 8.41 (d, *J* = 5.6 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.53-7.45 (m, 2H), 7.44-7.39 (m, 1H), 7.37-7.26 (m, 3H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.44 (d, *J* = 6.3 Hz, 1H), 6.21 (d, *J* = 5.6 Hz, 1H), 5.56-5.45 (m, 1H), 5.10 (d, *J* = 7.1 Hz, 1H), 4.83 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d$_6$)** δ 170.93, 159.68, 143.31, 137.53, 136.00, 129.23, 128.73, 128.56, 127.73, 126.41, 125.05, 124.52, 119.91, 91.16, 91.12, 74.24, 55.33. **HRMS (ESI)** $C_{19}H_{15}NNaO_5$, $[M+Na]^+$ (360.0950) found: 360.0842.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 16.22 min; t_R (minor) =21.01 min.] *ee* = 97%.

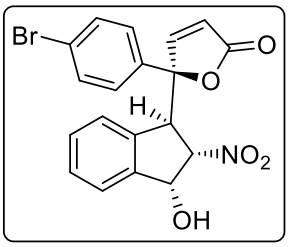
(S)-5-(4-fluorophenyl)-5-((1R,2S,3R)-3-hydroxy-2-nitro-2,3-dihydro-1H-inden-1-yl) furan-2(5H)-one (3b):



Yield: 90%; d.r.: >20:1; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.63 (d, *J* = 5.6 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.25-7.21 (m, 1H), 7.08 (m, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.97 (d, *J* = 5.6 Hz, 1H), 5.62 (s, 1H), 5.17 (dd, *J* = 6.9, 1.8 Hz, 1H), 4.60 (s, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 170.24, 156.64, 142.31, 135.03, 129.75, 128.92, 127.08, 127.02, 126.31, 125.17, 121.47, 116.77, 116.60, 90.84, 90.60, 75.07, 56.45. **HRMS (ESI)** $C_{19}H_{14}FNNaO_5$, $[M+Na]^+$ (378.0754) found: 378.0748.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 17.30 min; t_R (minor) = 27.20 min] *ee* = 79%.

(S)-5-(4-bromophenyl)-5-((1R,2S,3R)-3-hydroxy-2-nitro-2,3-dihydro-1H-inden-1-yl) furan-2(5H)-one (3c):



Yield: 78%; d.r.: 13:1; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.62 (d, *J* = 5.6 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.33-7.29 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 3H), 6.93 (d, *J* = 7.7 Hz, 1H), 5.95 (d, *J* = 5.6 Hz, 1H), 5.61 (d, *J* = 6.7 Hz, 1H), 5.15 (dd, *J* = 6.9, 1.6 Hz, 1H), 4.59 (s, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 170.31,

156.55, 142.25, 135.57, 134.91, 132.74, 129.71, 128.86, 126.73, 126.30, 125.16, 123.59, 121.50, 90.91, 90.59, 75.05, 56.11. **HRMS (ESI)** $C_{19}H_{14}BrNNaO_5$, $[M+Na]^+$ (437.9953) found: 437.9948.

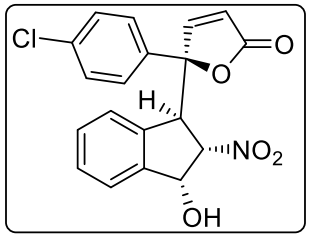
The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 18.03 min; t_R (minor) = 24.02 min] *ee* = 70%.

X-ray data of compound 3C: X-ray intensity data measurements of compound **3c** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Mo micro-focus sealed tube diffraction source (MoK_α= 0.71073 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω and φ scan width of 0.5° at different settings of φ, ω and 2θ with a frame time of 15 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by the APEX3 program (Bruker, 2016). All the data were corrected for Lorentzian, polarization, and absorption effects using SAINT and SADABS programs (Bruker, 2016). ShelX-97 was used for structure solution and full-matrix least-squares refinement on F^2. All the hydrogen atoms were placed in a geometrically idealized position and constrained to ride on its parent atoms. An *ORTEP* III view of the compound was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. The absolute configuration was established by anomalous dispersion effect (Flack parameter, 0.014(3)) in X-ray diffraction measurements carried out with Mo radiation. The single-crystal X-ray diffraction data analysis clearly established that the synthesized compound has *R*, *R*, *S*, and *R* configurations at C1, C11 (C11'), C12 (C12') and C13(C13') positions respectively.

Crystal data of **3c** ($C_{19}H_{14}BrNO_5$), 0.5(C_7H_8), M=462.29, colourless needle, 0.19 x 0.11 x 0.06 mm^3, orthorhombic, chiral space group $P2_12_12_1$, a =12.8818(5)Å, b=15.2182(6)Å, c=20.8840(8)Å, V = 4094.1(3)$Å^3$, Z = 8, T = 100(2) K, $2\theta_{max}$= 57.4°, D_{calc} (g cm^{-3}) = 1.500, $F(000)$ = 1880, μ (mm^{-1}) = 2.042, 49710 reflections collected, 10536 unique reflections (R_{int}=0.0501 and R_{sig}=0.0561), 8612 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.698, T_{max} = 0.887, 499 refined parameters, Good of Fit = S = 1.027,

*R*1=0.0389, *wR*2=0.0887 (all data *R* = 0.0557, *wR*2 = 0.0949), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.602, $\Delta\rho_{min}$= -0.865 (eÅ^{-3}).

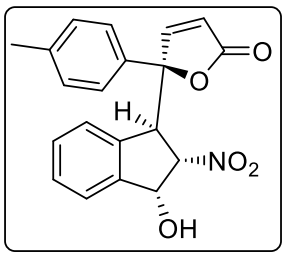
(S)-5-(4-chlorophenyl)-5-((1R,2S,3R)-3-hydroxy-2-nitro-2,3-dihydro-1H-inden-1-yl) furan-2(5H)-one (3d):



Yield: 87%; d.r.: >10:1; **^{1}H NMR {400 MHz, CDCl$_3$+DMSO-d$_6$ [84:16] }** δ 7.87 (d, *J* = 5.5 Hz, 1H), 7.34 – 7.24 (m, 4H), 7.17 (d, *J* = 6.9 Hz, 3H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.04 (d, *J* = 6.4 Hz, 1H), 5.92 (d, *J* = 5.6 Hz, 1H), 5.61-5.51 (m, 1H), 5.09 (d, *J* = 7.1 Hz, 1H), 4.69 (s, 1H). **^{13}C NMR (101 MHz, CDCl$_3$+DMSO-d$_6$ [84:16])** δ 170.43, 157.64, 142.66, 138.32, 135.26, 133.38, 129.44, 128.34, 127.54, 125.76, 124.59, 124.53, 120.11, 90.99, 90.66, 74.18, 55.23. **HRMS (ESI)** $C_{19}H_{14}ClNNaO_5$, $[M+Na]^+$ (394.0458) found: 394.0453.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 19.86 min; t_R (minor) = 26.76 min] *ee* = 76%.

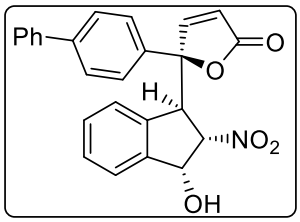
(S)-5-((1R,2S,3R)-3-hydroxy-2-nitro-2,3-dihydro-1H-inden-1-yl)-5-(p-tolyl)furan-2(5H)-one (3e):



Yield: 98%; d.r.: >20:1; **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ 8.37 (d, *J* = 5.6 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.31 (dd, *J* = 25.5, 7.7 Hz, 5H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.43 (d, *J* = 11.1 Hz, 1H), 6.18 (d, *J* = 5.5 Hz, 1H), 5.52 (d, *J* = 6.6 Hz, 1H), 5.11 (d, *J* = 6.8 Hz, 1H), 4.81 (s, 1H), 2.33 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d$_6$)** δ 170.98, 159.74, 143.28, 138.11, 136.06, 134.55, 129.72, 128.50, 127.70, 126.40, 124.97, 124.49, 119.70, 91.17, 74.24, 55.29, 20.60. **HRMS (ESI)** $C_{20}H_{17}NNaO_5$, $[M+Na]^+$ (374.1004) found: 374.0999.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 48.50 min; t_R (minor) = 60.36 min] *ee* = 70%.

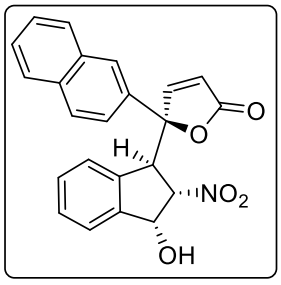
(S)-5-([1,1'-biphenyl]-4-yl)-5-((1R,2S,3R)-3-hydroxy-2-nitro-2,3-dihydro-1H-inden-1-yl) furan-2(5H)-one (3f):



Yield: 56%; d.r.: >20:1; **^{1}H NMR {400 MHz, $CDCl_3$+DMSO-d_6 [84:16] }** δ 7.92 (d, *J* = 5.1 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.41-7.36 (m, 3H), 7.32 (d, *J* = 3.5 Hz, 1H), 7.29 (d, *J* = 5.5 Hz, 1H), 7.20-7.15 (m 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.05 (dd, *J* = 15.1, 4.8 Hz, 1H), 5.95 (dd, *J* = 5.5, 2.5 Hz, 1H), 5.64 – 5.58 (m, 1H), 5.17-5.13 (m, 1H), 4.76 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6 [84:16])** δ 170.32, 157.47, 142.69, 141.09, 139.12, 135.51, 135.14, 128.40, 127.57, 127.29, 126.45, 125.80, 125.22, 124.59, 120.30, 120.26, 90.90, 90.68, 74.25, 55.20. **HRMS (ESI)** $C_{25}H_{19}NNaO_5$, $[M+Na]^+$ (436.1161) found: 436.1155.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 17.83 min; t_R (minor) = 19.76 min] *ee* = 72%.

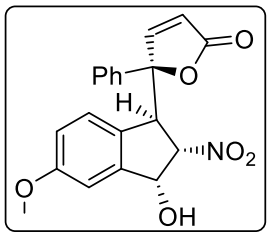
(S)-5-((1R,2S,3R)-3-hydroxy-2-nitro-2,3-dihydro-1H-inden-1-yl)-5-(naphthalen-2-yl) furan-2(5H)-one (3g):



Yield: 40%; d.r. 4:1; **^{1}H NMR (500 MHz, DMSO-d_6)** δ 8.52 (d, *J* = 5.7 Hz, 1H), 8.10 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 8.01 (dd, *J* = 6.0, 3.4 Hz, 1H), 7.98 (dd, *J* = 5.9, 3.3 Hz, 1H), 7.80 (d, *J* = 9.9 Hz, 1H), 7.60 (dd, *J* = 6.2, 3.2 Hz, 3H), 7.37 – 7.34 (m, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 6.47 (d, *J* = 6.6 Hz, 1H), 6.26 (d, *J* = 5.6 Hz, 1H), 5.57 (t, *J* = 6.7 Hz, 1H), 5.18 (dd, *J* = 7.2, 1.6 Hz, 1H), 4.97 (s, 1H). **^{13}C NMR (126 MHz, DMSO-d_6)** δ 171.46, 160.02, 143.84, 136.50, 135.51, 133.18, 133.01, 129.56, 129.09, 128.76, 128.27, 128.13, 127.45, 127.42, 126.97, 125.06, 124.39, 123.35, 120.60, 91.85, 91.66, 79.64, 74.79, 55.67. **HRMS (ESI)** $C_{23}H_{17}NNaO_5$, $[M+Na]^+$ (410.1107) found: 410.0999.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, n-Hexane: IPA= 80:20, Flow rate: 1ml/min, t_R (major) = 67.03 min; t_R (minor) = 81.90 min] *ee* = 65%.

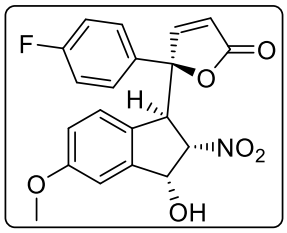
(S)-5-((1R,2S,3R)-3-hydroxy-5-methoxy-2-nitro-2,3-dihydro-1H-inden-1-yl)-5-phenylfuran-2(5H)-one (3h):



Yield: 94%; d.r.: 13:1;**^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.90 (d, J = 5.1 Hz, 1H), 7.52 (s, 1H), 7.44 (d, J = 7.7 Hz, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.06 (s, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 9.7 Hz, 1H), 6.13 (d, J = 5.3 Hz, 1H), 5.89 (d, J = 5.8 Hz, 1H), 5.76 (d, J = 5.6 Hz, 1H), 5.31 (d, J = 6.7 Hz, 1H), 4.76 (s, 1H), 3.92 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$+DMSO-d$_6$ [84:16])** δ 170.20, 159.76, 158.17, 144.65, 136.33, 131.73, 127.03, 126.93, 126.81, 122.12, 119.96, 114.10, 108.72, 91.09, 90.69, 74.06, 54.80, 54.55. **HRMS (ESI)** $C_{20}H_{17}NNaO_6$, $[M+Na]^+$ (390.0954) found: 390.0948.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol =80:20, flow rate: 1.0 mL/min, t_R (major) =19.39 min; t_R (minor) =22.57 min] *ee* = 99%.

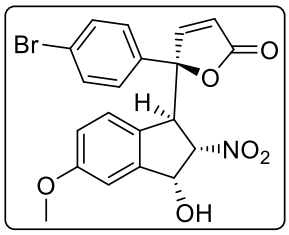
(S)-5-(4-fluorophenyl)-5-((1R,2S,3R)-3-hydroxy-5-methoxy-2-nitro-2,3-dihydro-1H-inden-1-yl) furan-2(5H)-one (3i):



Yield: 97%; d.r.: >20:1; **^{1}H NMR {500 MHz, CDCl$_3$+DMSO-d$_6$ [84:16] }** δ 8.03 (d, *J* = 5.6 Hz, 1H), 7.48 (dd, *J* = 8.4, 5.1 Hz, 2H), 7.11-7.06 (m, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.82 (s, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.16 (d, *J* = 6.2 Hz, 1H), 5.95 (d, *J* = 5.6 Hz, 1H), 5.53-5.46 (m, 1H), 5.05 (d, *J* = 7.1 Hz, 1H), 4.63 (s, 1H), 3.72 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$+DMSO-d$_6$ [84:16])** δ 170.24, 159.78, 157.97, 144.48, 132.89, 126.96, 126.89, 126.83, 126.75, 120.02, 115.70, 115.53, 114.22, 108.71, 91.02, 90.66, 74.01, 54.77. **HRMS (ESI)** $C_{20}H_{16}FNNaO_5$, $[M+Na]^+$ (408.0859) found: 408.0854.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 17.05 min; t_R (minor) = 25.65 min] *ee* = 97%.

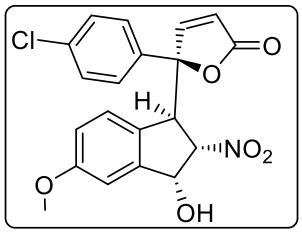
(S)-5-(4-bromophenyl)-5-((1R,2S,3R)-3-hydroxy-5-methoxy-2-nitro-2,3-dihydro-1H-inden-1-yl)furan-2(5H)-one (3j):



Yield: 94%; d.r.: >20:1; **^{1}H NMR {400 MHz, $CDCl_3$+DMSO-d_6 [84:16] }** δ 8.19 (d, *J* = 5.4 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.30 (d, *J* = 6.4 Hz, 1H), 6.03 (d, *J* = 5.5 Hz, 1H), 5.57-5.52(m, 1H), 5.10 (d, *J* = 7.0 Hz, 1H), 4.71 (s, 1H), 3.79 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6 [84:16])** δ 170.20, 159.76, 158.17, 144.65, 136.33, 131.73, 127.03, 126.93, 126.81, 122.12, 119.96, 114.10, 108.72, 91.09, 90.69, 74.06, 54.80, 54.55. **HRMS (ESI)** $C_{20}H_{16}BrNNaO_6$, $[M+Na]^+$ (468.0058) found: 468.0053.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 18.86 min; t_R (minor) = 27.11 min] *ee* = 79%.

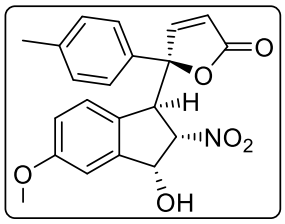
(S)-5-(4-chlorophenyl)-5-((1R,2S,3R)-3-hydroxy-5-methoxy-2-nitro-2,3-dihydro-1H-inden-1-yl) furan-2(5H)-one (3k):



Yield: 92%; d.r.: >20:1; **^{1}H NMR {500 MHz, $CDCl_3$+DMSO-d_6 [84:16] }** δ 7.94 (d, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.84 (s, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.10 (d, *J* = 6.3 Hz, 1H), 5.95 (d, *J* = 5.5 Hz, 1H), 5.55-5.49 (m, 1H), 5.06 (d, *J* = 6.9 Hz, 1H), 4.61 (s, 1H), 3.72 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$+DMSO-d_6 [84:16])** δ 170.13, 159.87, 157.45, 144.39, 135.42, 134.10, 128.82, 126.69, 126.66, 126.28, 120.26, 114.37, 108.73, 90.97, 90.59, 74.05, 54.77, 54.59. **HRMS (ESI)** $C_{20}H_{16}ClNNaO_6$, $[M+Na]^+$ (424.0564) found: 424.0558.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 18.02 min; t_R (minor) = 25.77 min] *ee* = 95%.

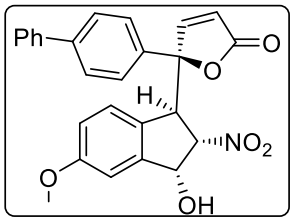
(S)-5-((1R,2S,3R)-3-hydroxy-5-methoxy-2-nitro-2,3-dihydro-1H-inden-1-yl)-5-(p-tolyl)furan-2(5H)-one (3l):



Yield: 58%; d.r.: >20:1; **^{1}H NMR {400 MHz, $CDCl_3$+DMSO-d_6 [84:16] }** δ 7.87 (d, *J* = 5.3 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 6.89 – 6.80 (m, 2H), 6.69 (dd, *J* = 9.9, 3.1 Hz, 1H), 6.06 (d, *J* = 5.9 Hz, 1H), 5.92 (d, *J* = 5.6 Hz, 1H), 5.55-5.49 (m, 1H), 5.08 (d, *J* = 7.1 Hz, 1H), 4.59 (s, 1H), 3.72 (s, 3H), 2.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6 [84:16])** δ 170.49, 159.80, 157.74, 144.37, 138.19, 133.64, 129.38, 126.97, 126.61, 125.69, 124.54, 120.03, 114.34, 108.71, 91.11, 54.77, 54.68, 20.52. **HRMS (ESI)** $C_{21}H_{19}NNaO_6$, $[M+Na]^+$ (404.1110) found: 404.1105.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 15.67 min; t_R (minor) = 25.29 min] *ee* = 98%.

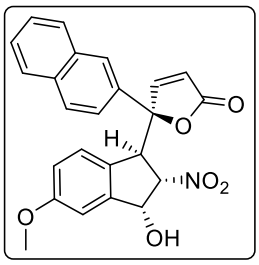
(S)-5-([1,1'-biphenyl]-4-yl)-5-((1R,2S,3R)-3-hydroxy-5-methoxy-2-nitro-2,3-dihydro-1H-inden-1-yl)furan-2(5H)-one (3m):



Yield: 53%; d.r.: >20:1; **^{1}H NMR {400 MHz, $CDCl_3$+DMSO-d_6 [84:16] }** δ 7.84 (d, *J* = 5.6 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.43 – 7.34 (m, 3H), 7.33-7.27 (m, 1H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.02-5.87 (m, 2H), 5.562-5.54 (m, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 4.65 (s, 1H), 3.72 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6 [84:16])** δ 170.80, 160.37, 157.69, 144.76, 141.53, 139.57, 135.87, 128.79, 127.71, 127.17, 127.00, 126.87, 125.58, 120.79, 114.99, 109.18, 91.52, 91.45, 74.60, 55.22, 55.12, 29.45. **HRMS (ESI)** $C_{26}H_{21}NNaO_6$, $[M+Na]^+$ (466.1267) found: 466.1261.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 18.02 min; t_R (minor) = 20.61 min] *ee* = 84%.

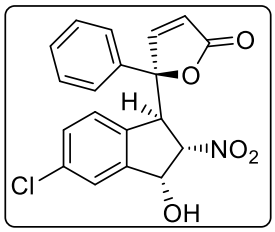
(S)-5-((1R,2S,3R)-3-hydroxy-5-methoxy-2-nitro-2,3-dihydro-1H-inden-1-yl)-5-(naphthalen-2-yl)furan-2(5H)-one (3n):



Yield: 35%; d.r.: 12:1; **^{1}H NMR (500 MHz, DMSO-d$_6$)** δ 8.49 (d, *J* = 5.7 Hz, 1H), 8.09 (s, 1H), 8.05 (d, *J* = 8.7 Hz, 1H), 8.01 (dd, *J* = 6.1, 3.4 Hz, 1H), 7.97 (dd, *J* = 6.1, 3.4 Hz, 1H), 7.78 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.87 (dd, *J* = 11.2, 2.9 Hz, 2H), 6.45 (d, *J* = 6.4 Hz, 1H), 6.26 (d, *J* = 5.6 Hz, 1H), 5.52 (t, *J* = 6.7 Hz, 1H), 5.15 (dd, *J* = 7.1, 1.6 Hz, 1H), 4.86 (s, 1H), 3.77 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d$_6$)** δ 171.55, 160.32, 160.04, 145.58, 135.56, 133.18, 132.99, 129.53, 128.74, 128.16, 128.13, 127.86, 127.43, 124.35, 123.34, 120.60, 114.80, 109.45, 92.06, 91.99, 74.69, 55.68, 55.11, 21.52. **HRMS (ESI)** $C_{24}H_{19}NNaO_6$, [M+Na]$^+$ (440.1212) found: 440.1105.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, n-Hexane: IPA = 80:20, Flow rate: 1ml/min, t_R (major) = 21.20 min; t_R (minor) = 27.19 min] *ee* = 96%.

(S)-5-((1R,2S,3R)-5-chloro-3-hydroxy-2-nitro-2,3-dihydro-1H-inden-1-yl)-5-phenylfuran-2(5H)-one (3o):

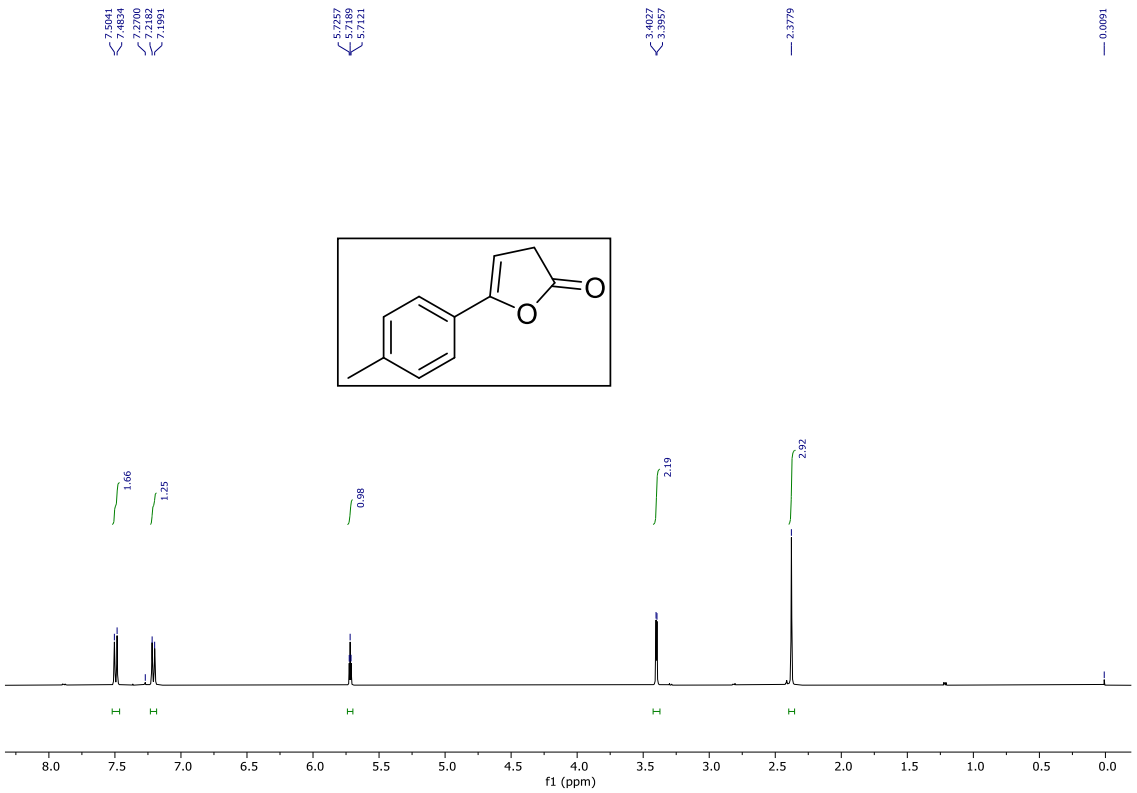


Yield: 63%; d.r.: >20:1; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 8.39 (d, *J* = 5.6 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.52-7.46 (m, 2H), 7.45 – 7.37 (m, 2H), 7.33 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 6.3 Hz, 1H), 6.23 (d, *J* = 5.7 Hz, 1H), 5.52 (t, *J* = 6.6 Hz, 1H), 5.11 (dd, *J* = 7.2, 1.2 Hz, 1H), 4.84 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d$_6$)** δ 171.32, 159.95, 146.33, 137.68, 135.55, 133.72, 129.73, 129.27, 128.65, 128.37, 125.47, 124.85, 120.48, 91.72, 91.42, 74.39, 55.41. **HRMS (ESI)** $C_{19}H_{14}ClNNaO_5$, [M+Na]$^+$ (394.0458) found: 394.0453.

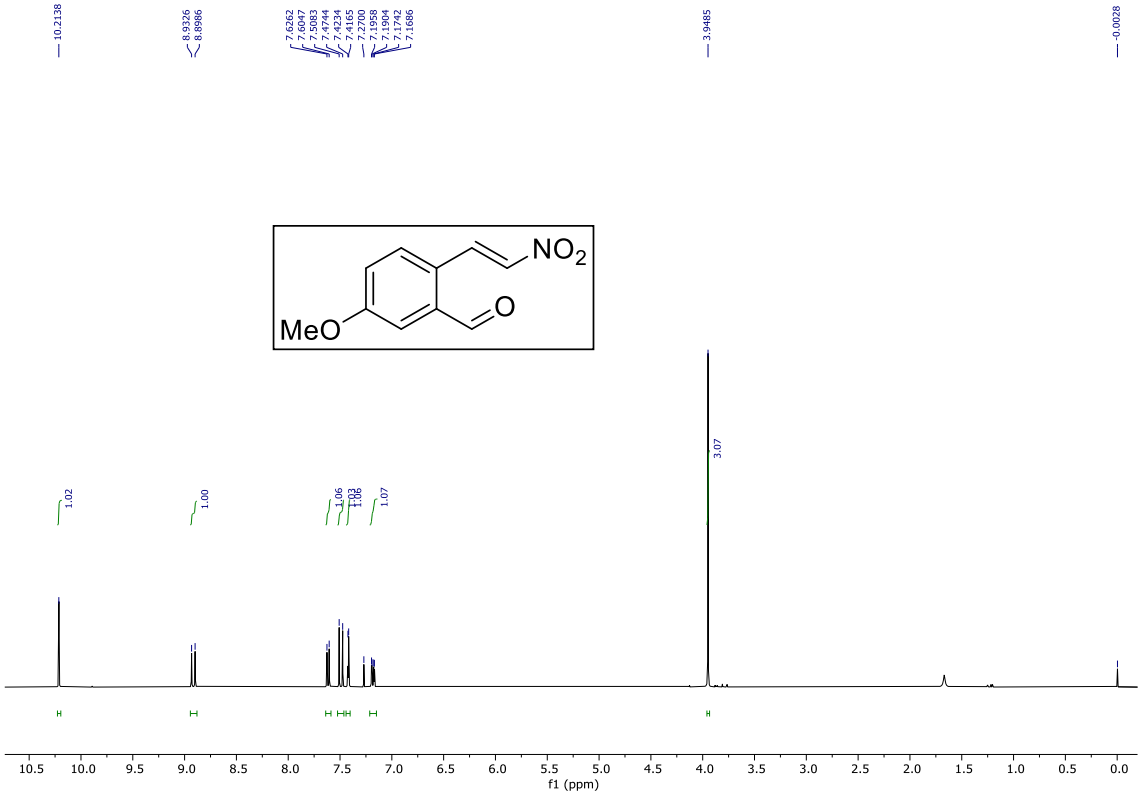
The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 254 nm, *n*-Hexane: 2-propanol = 80:20, flow rate: 1.0 mL/min, t_R (major) = 11.76 min; t_R (minor) = 25.45 min] *ee* = 62%.

1.9 Spectral data

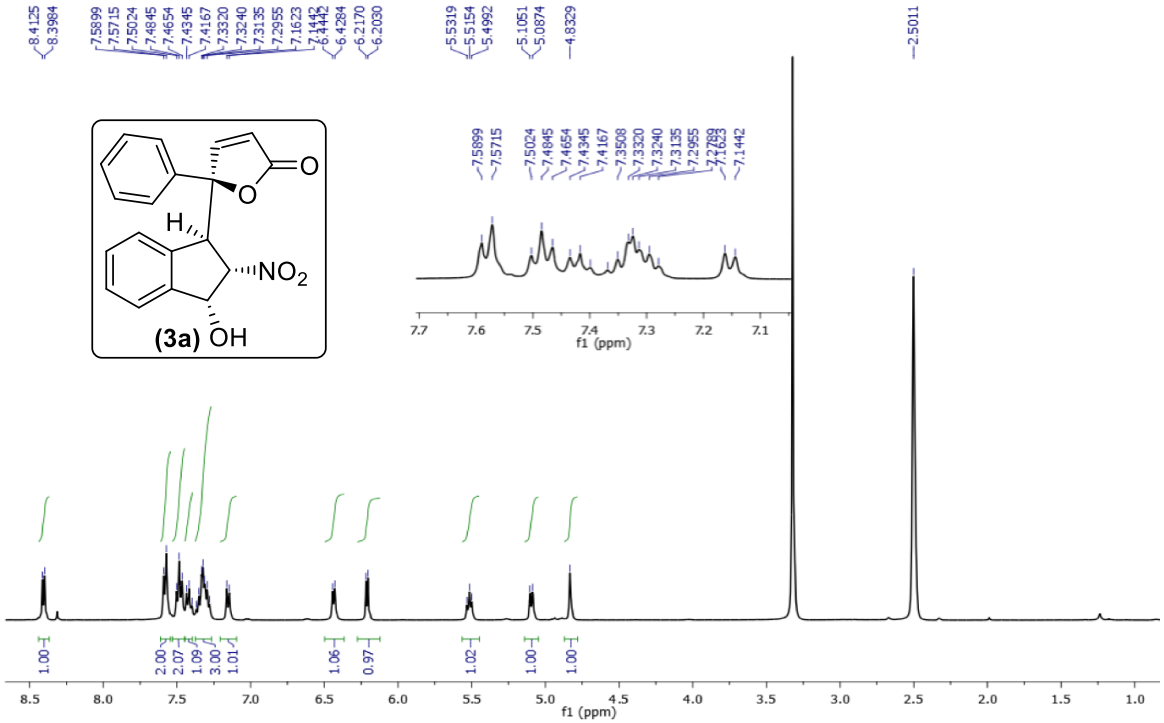
^{1}H NMR of **(1e)** in $CDCl_3$



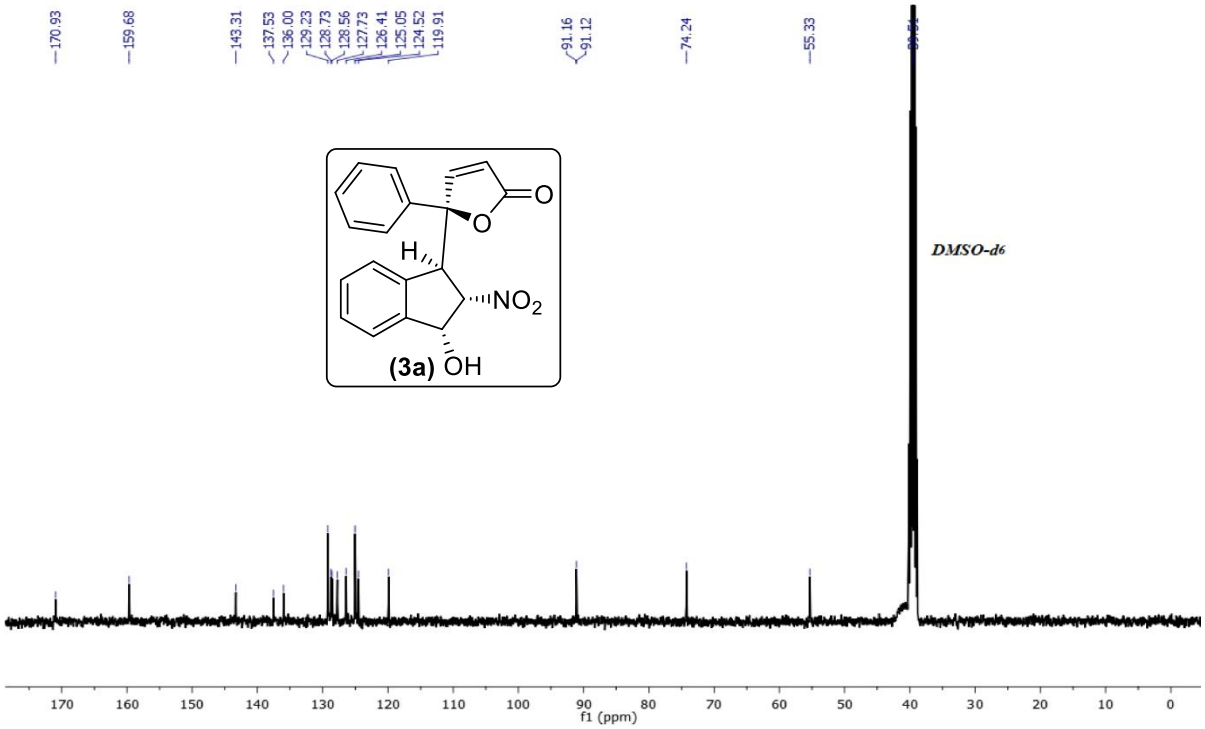
^{1}H NMR of **(2b)** in $CDCl_3$



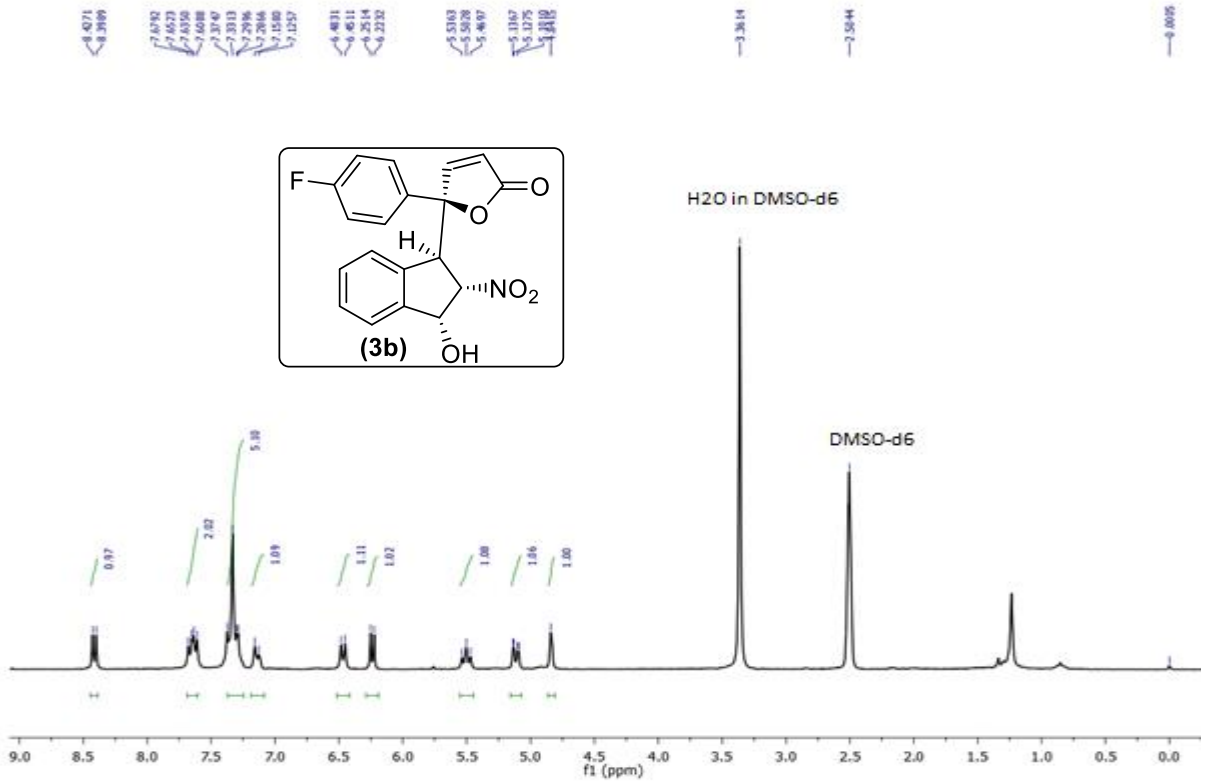
^{1}H NMR of **(3a)** in DMSO-d$_6$



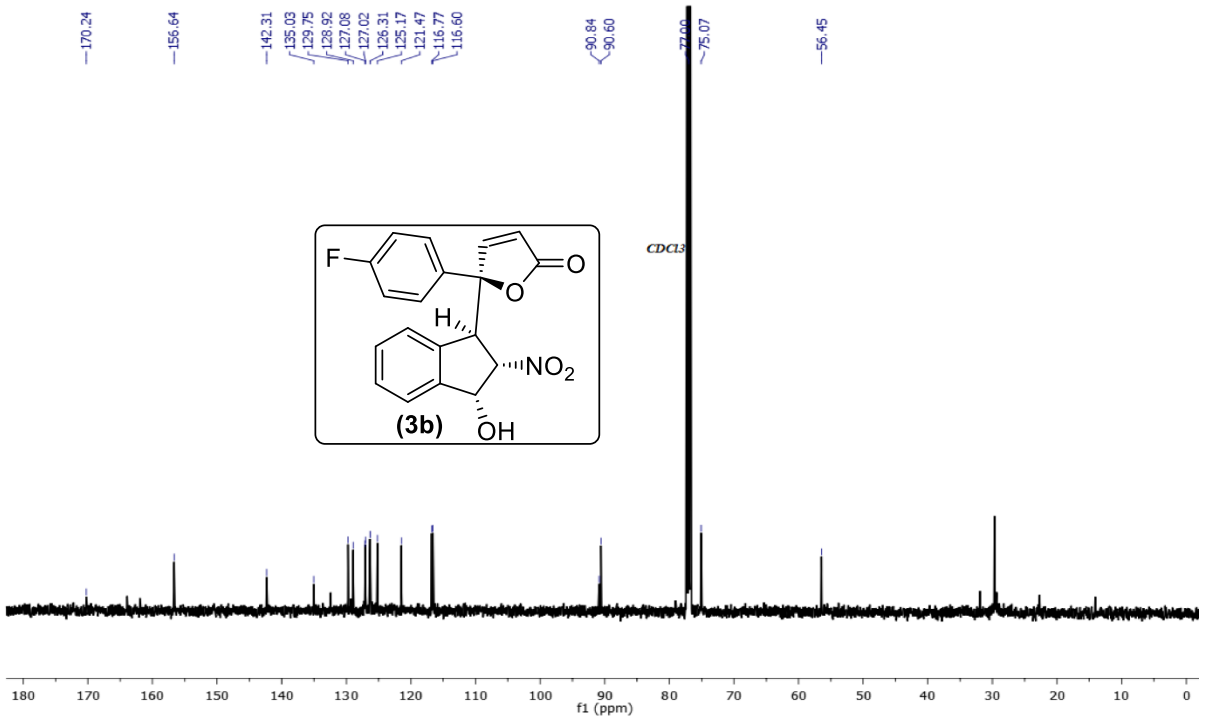
^{13}C NMR of **(3a)** in DMSO-d$_6$



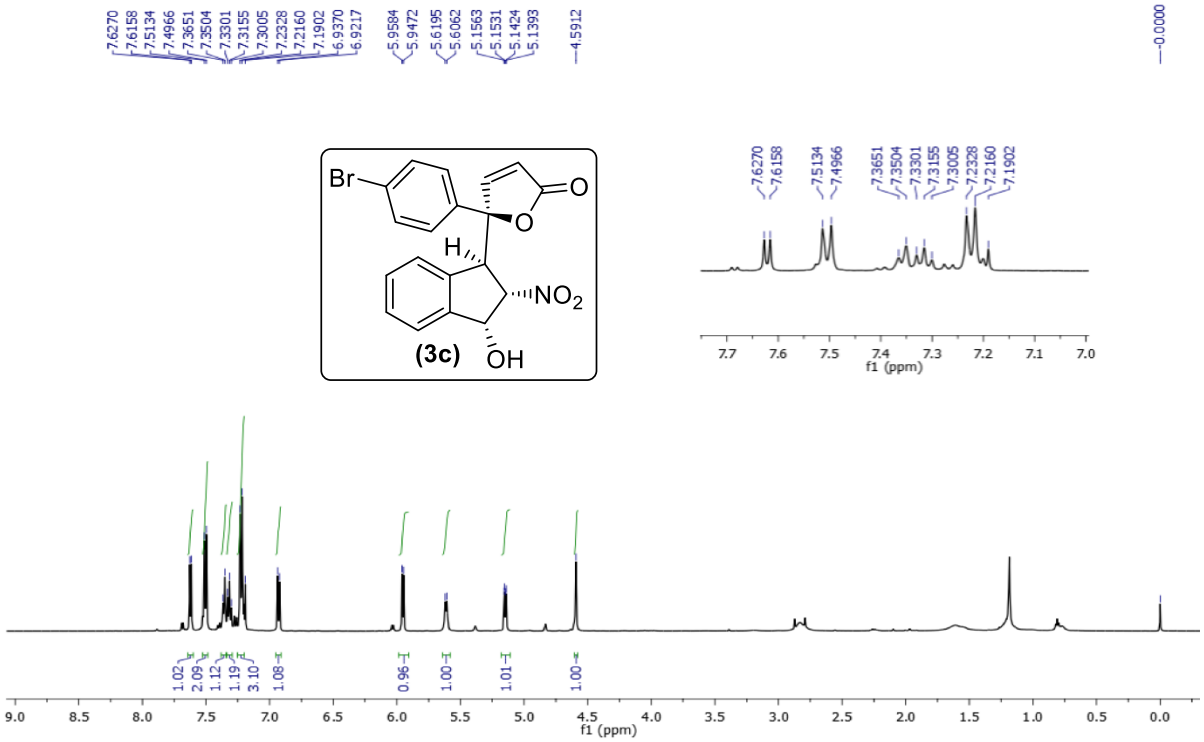
^{1}H NMR of **(3b)** in DMSO-d_6



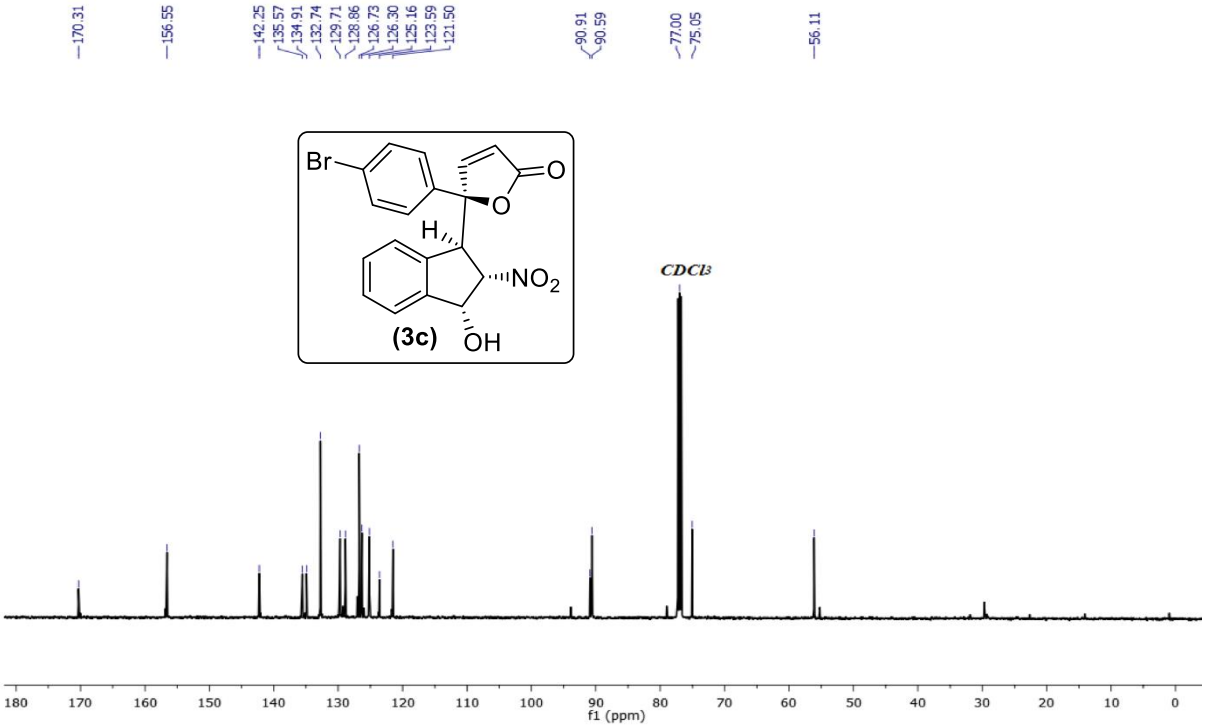
^{13}C NMR of **(3b)** in DMSO-d_6



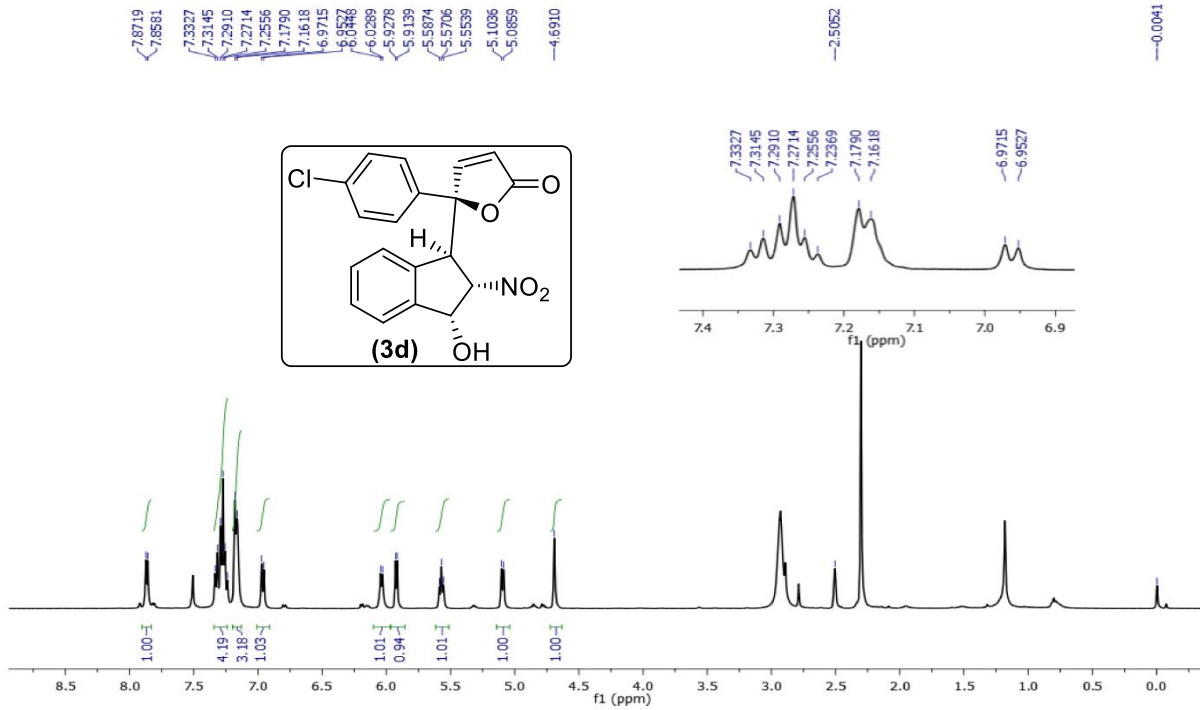
^{1}H NMR of **(3c)** in $CDCl_3$



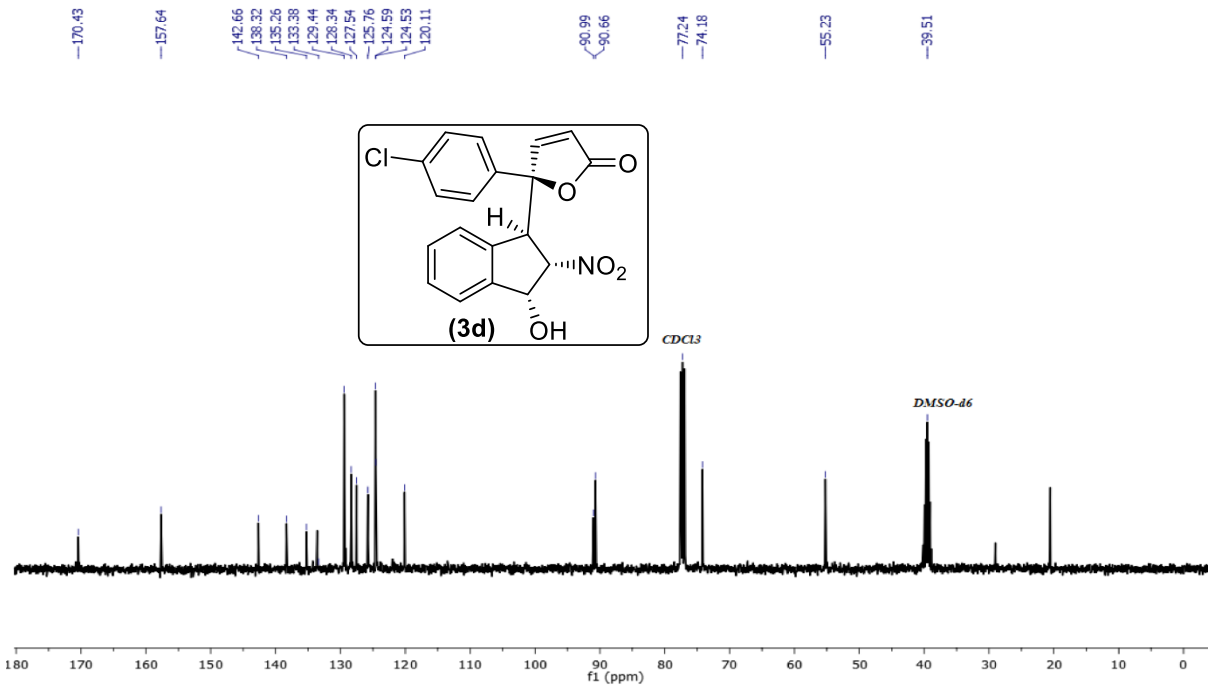
^{13}C NMR of **(3c)** in $CDCl_3$



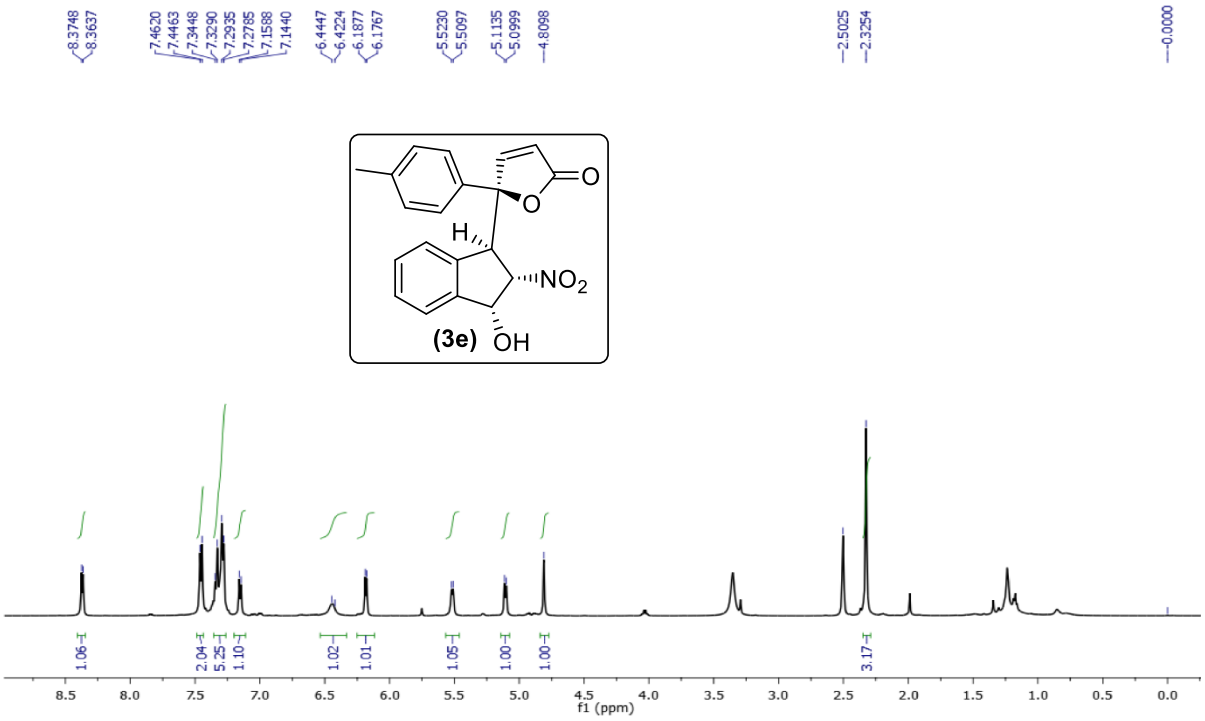
^{1}H NMR of **(3d)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



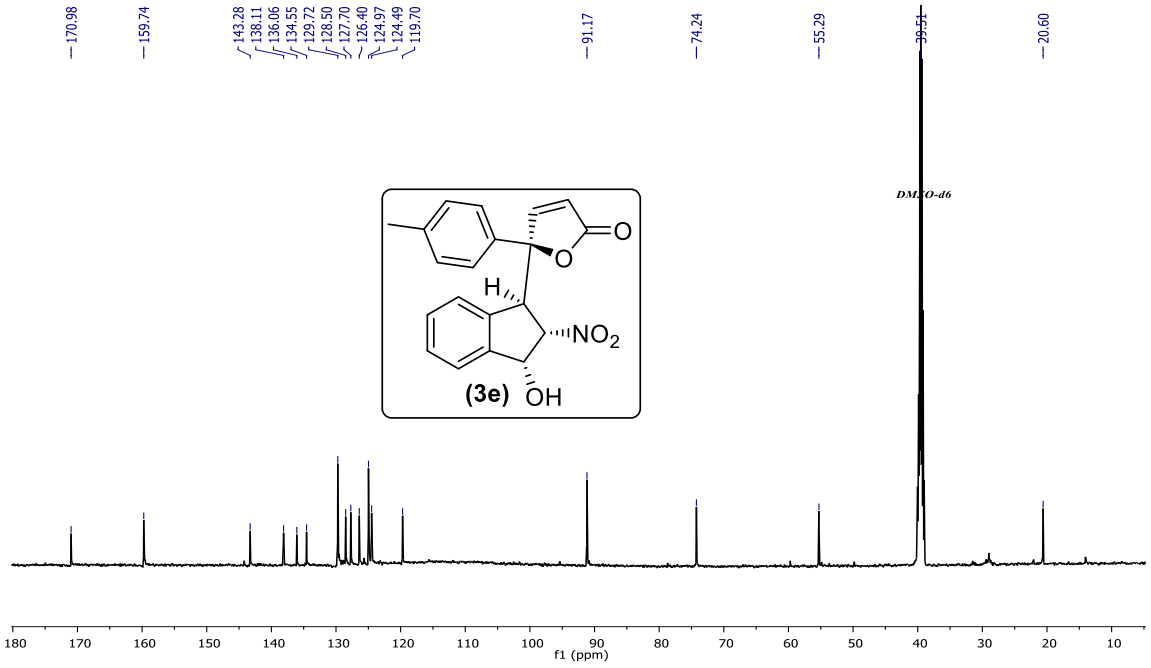
^{13}C NMR of **(3d)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



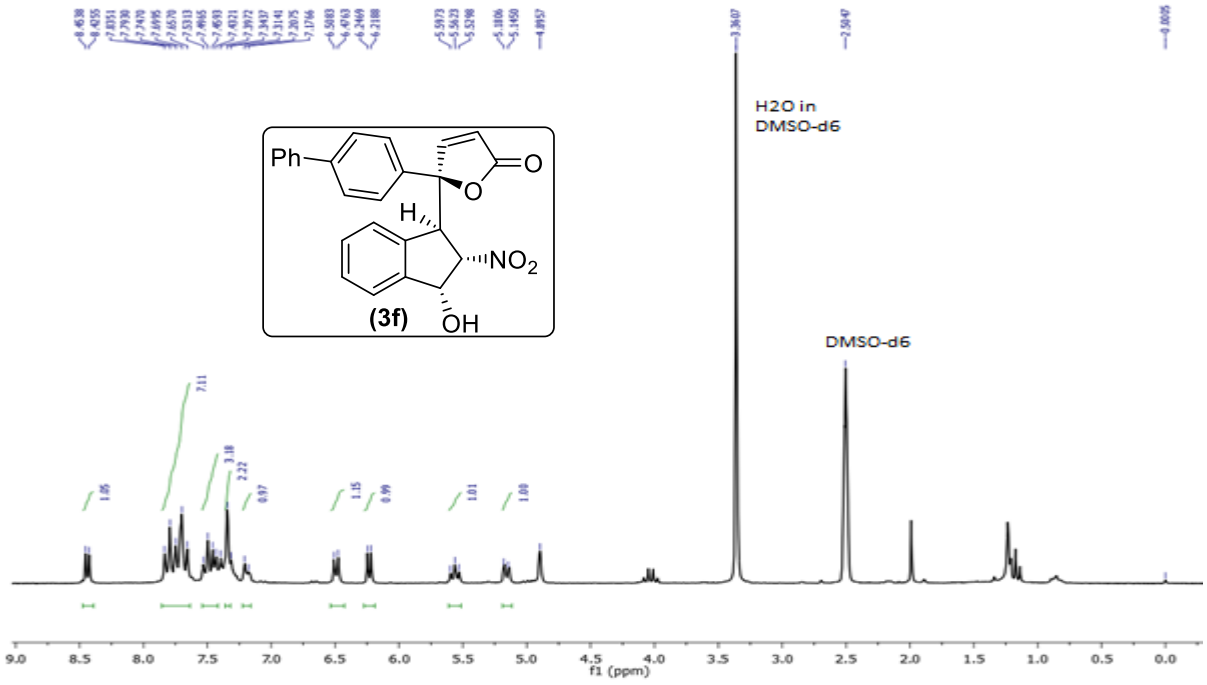
^{1}H NMR of **(3e)** in DMSO-d$_6$



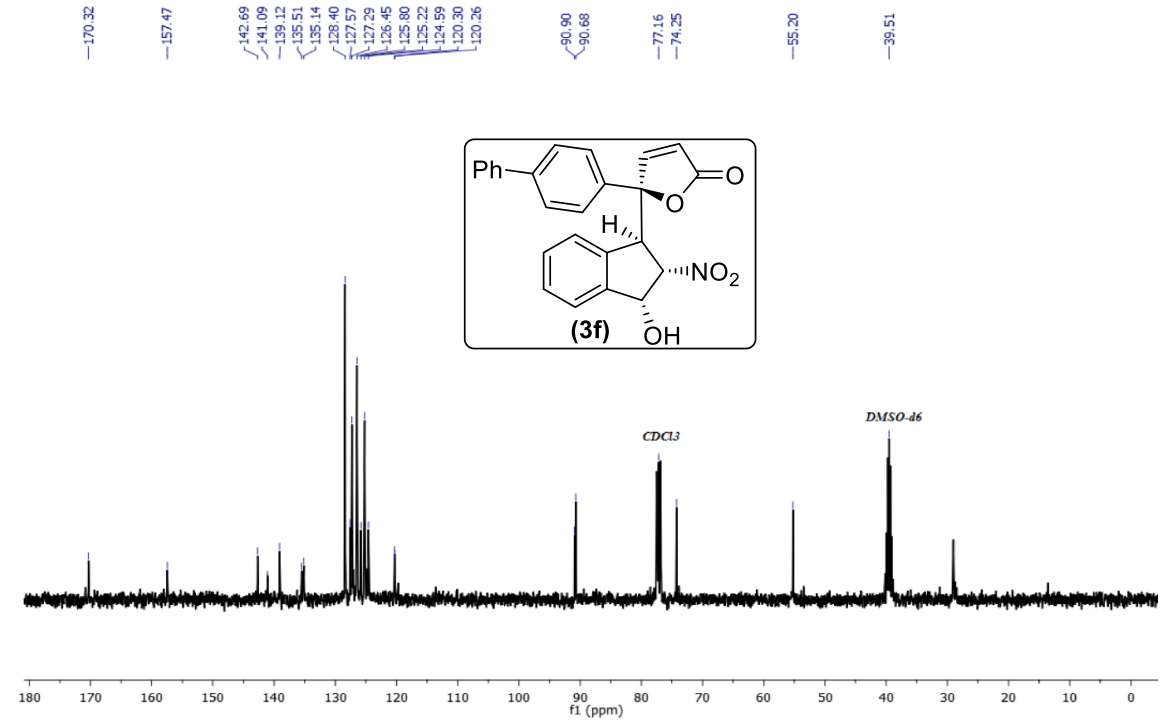
^{13}C NMR of **(3e)** in DMSO-d$_6$



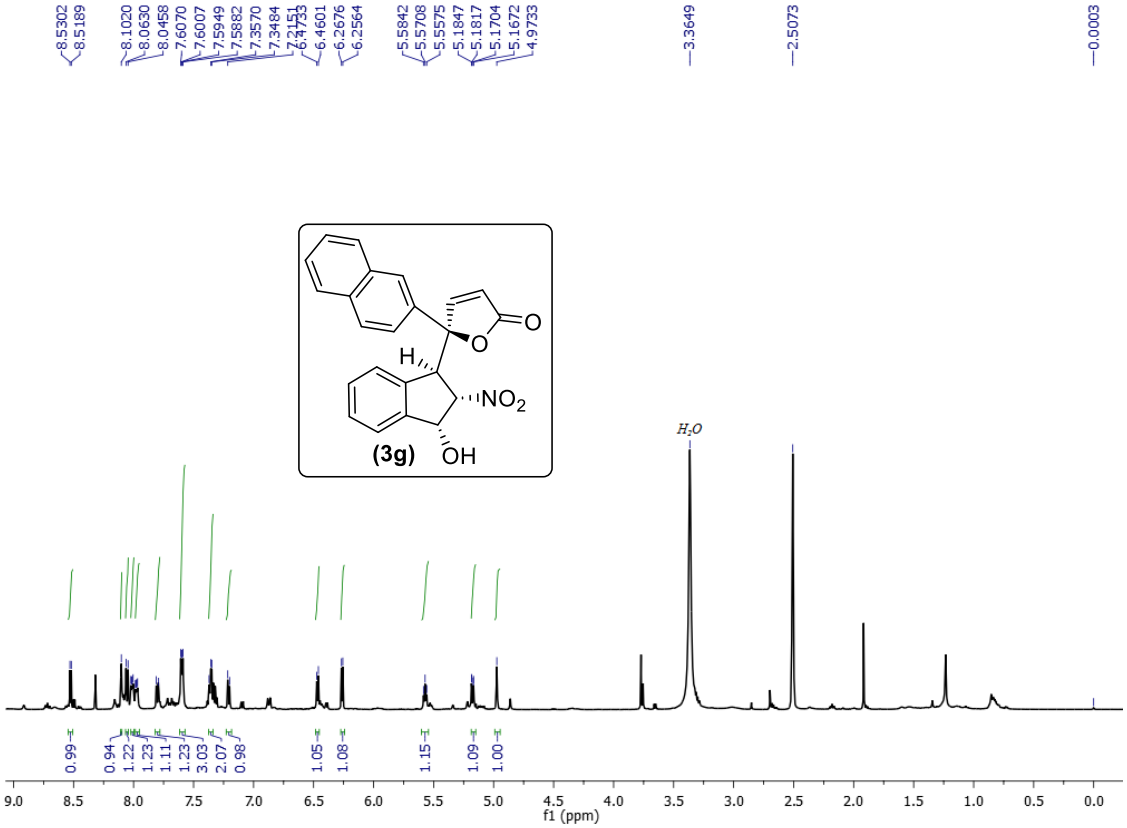
^{1}H NMR of **(3f)** in DMSO-d$_6$



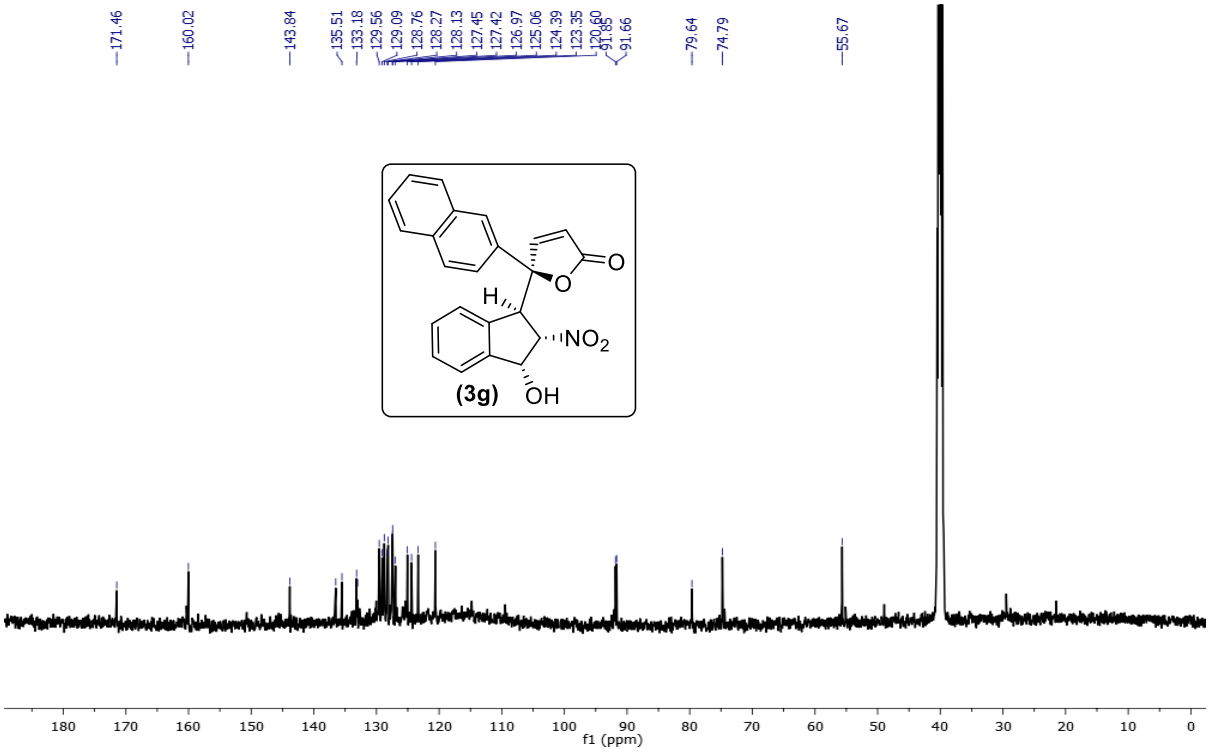
^{13}C NMR of **(3f)** in DMSO-d$_6$



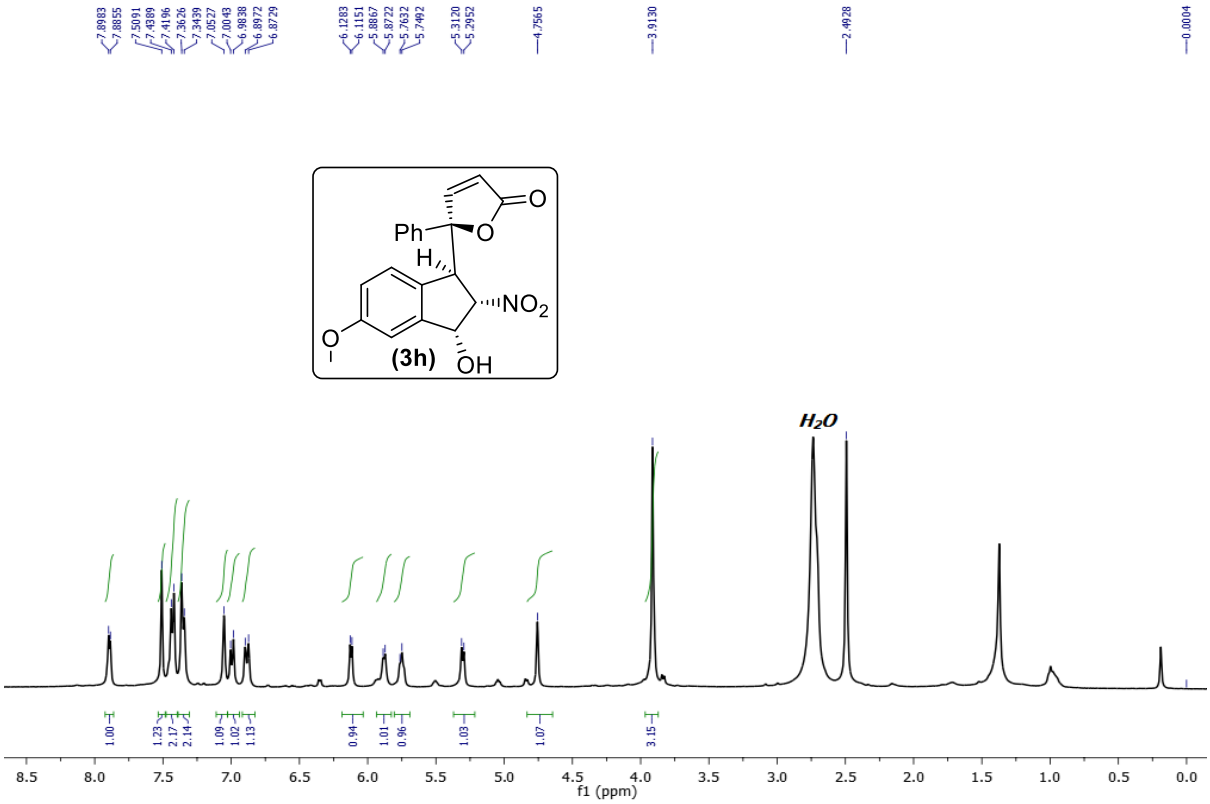
^{1}H NMR of **(3g)** in DMSO-d$_6$



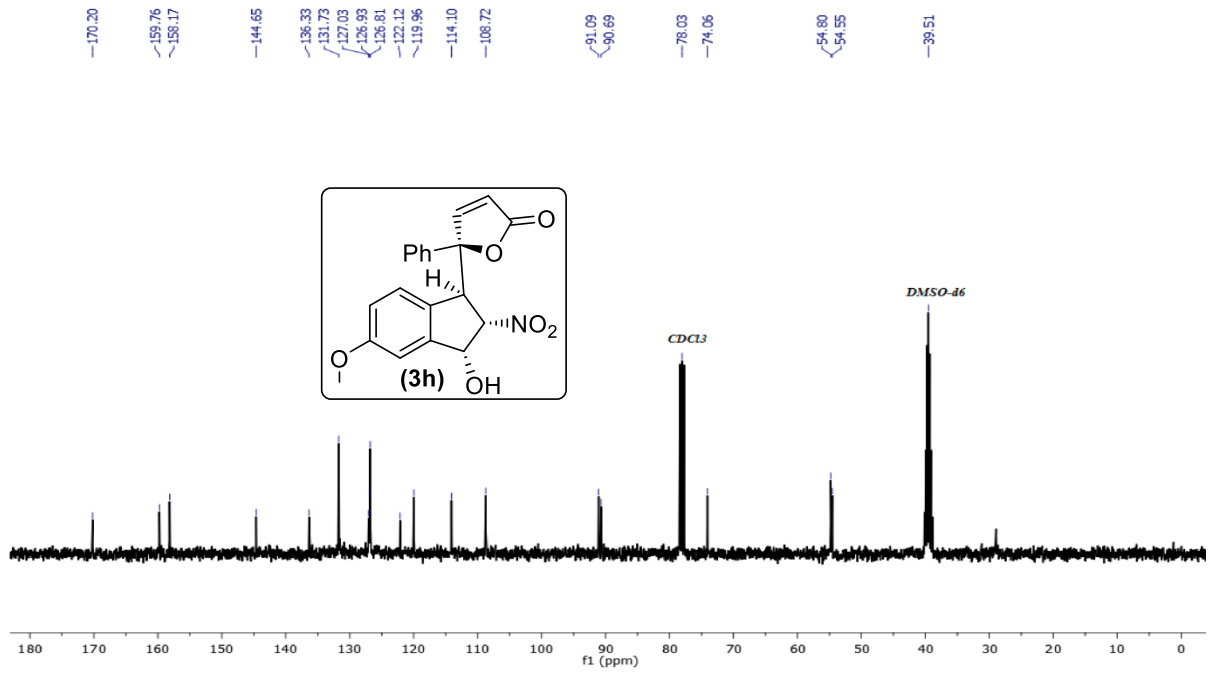
^{13}C NMR of **(3g)** in DMSO-d$_6$



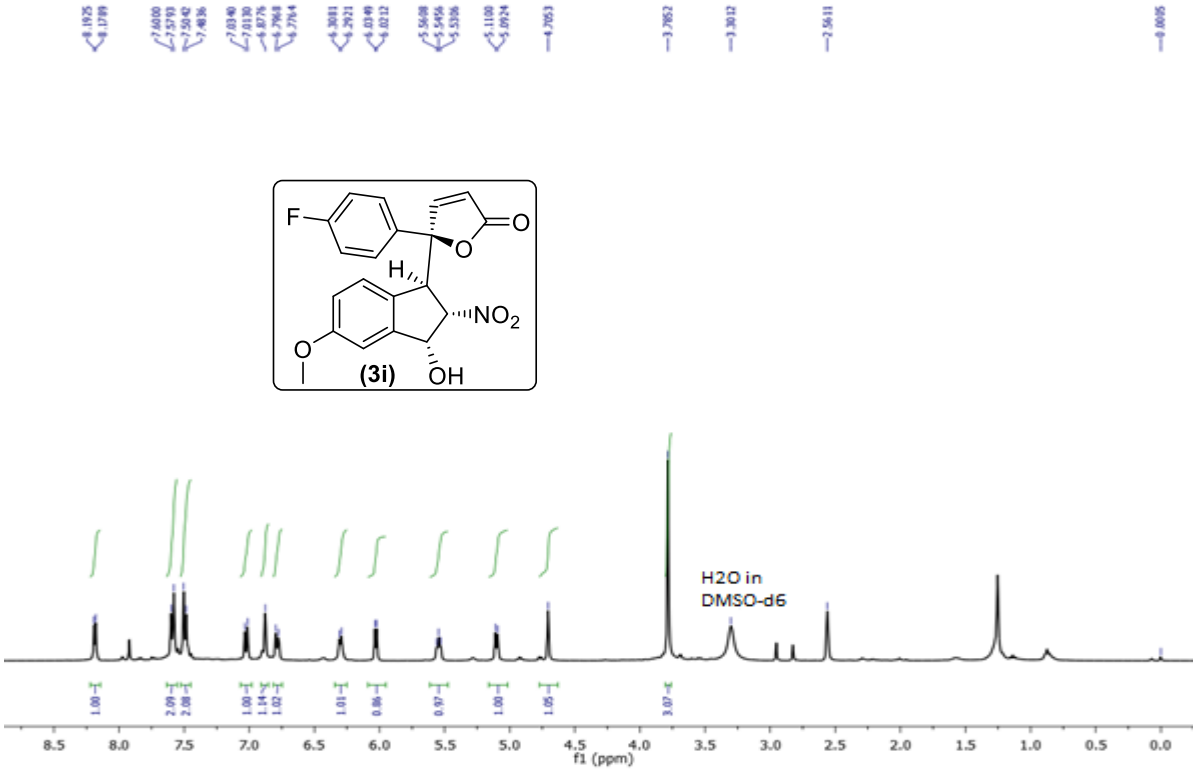
^{1}H NMR of **(3h)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



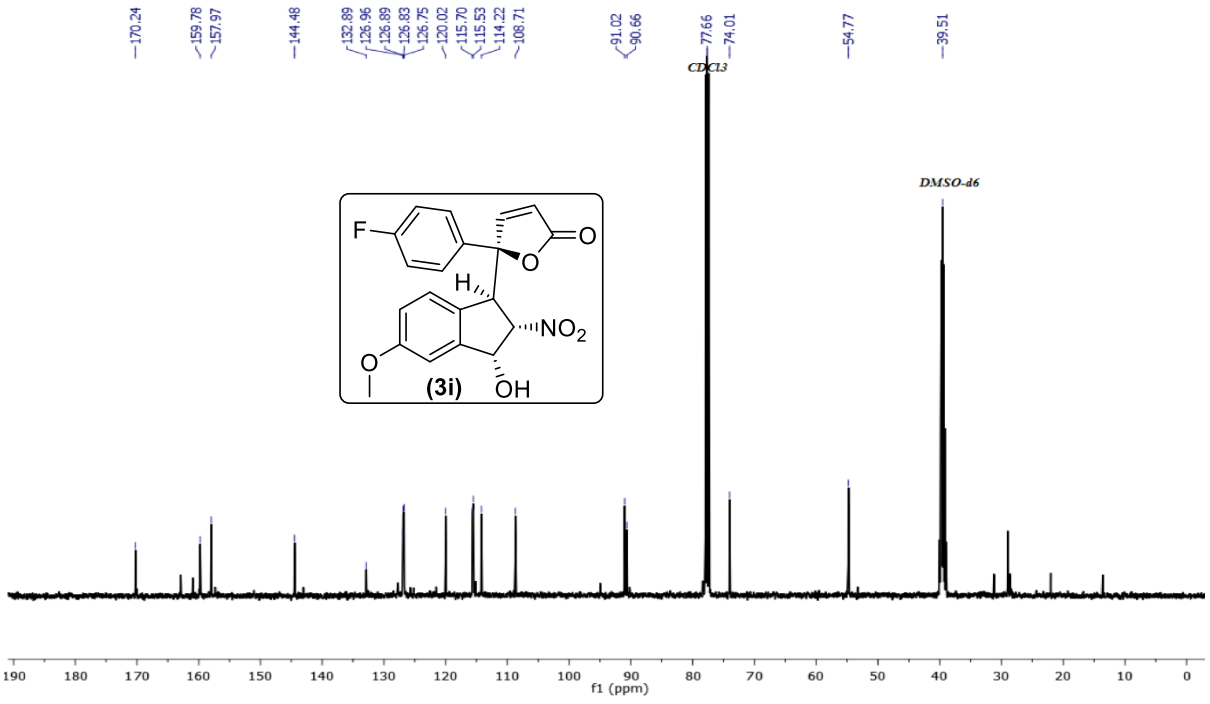
^{13}C NMR of (**3h)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



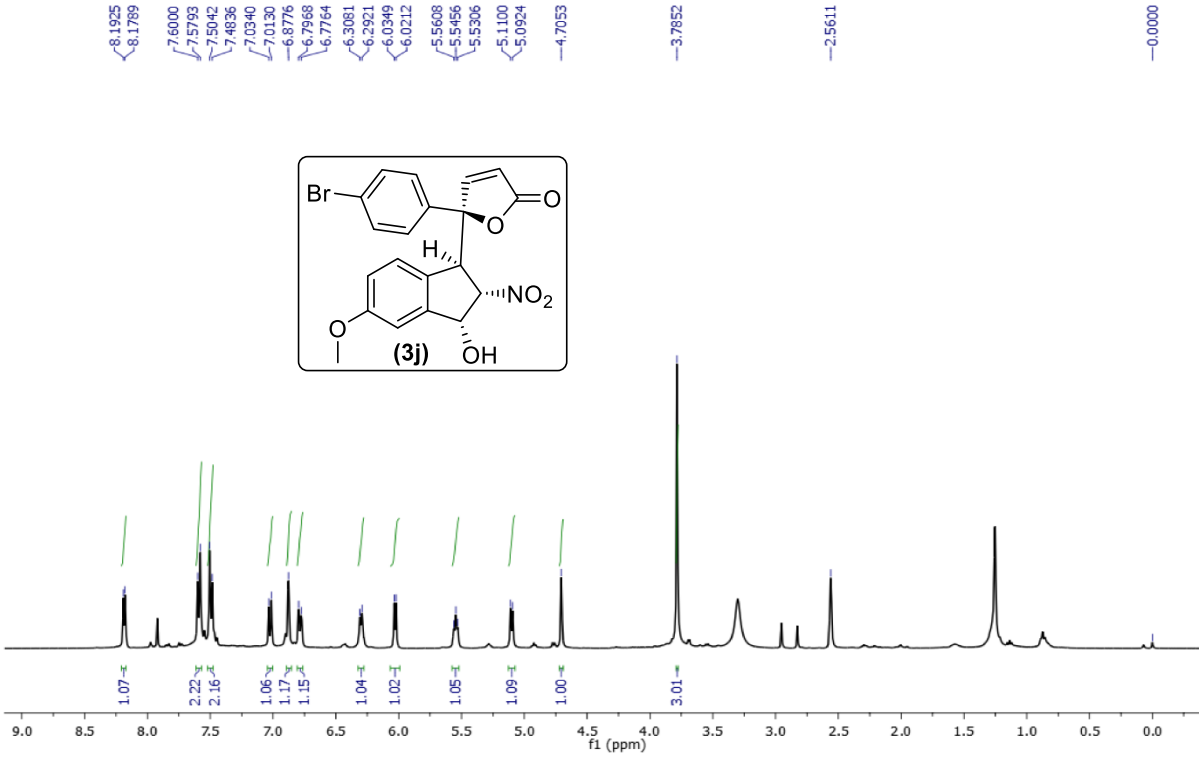
^{1}H NMR of **(3i)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



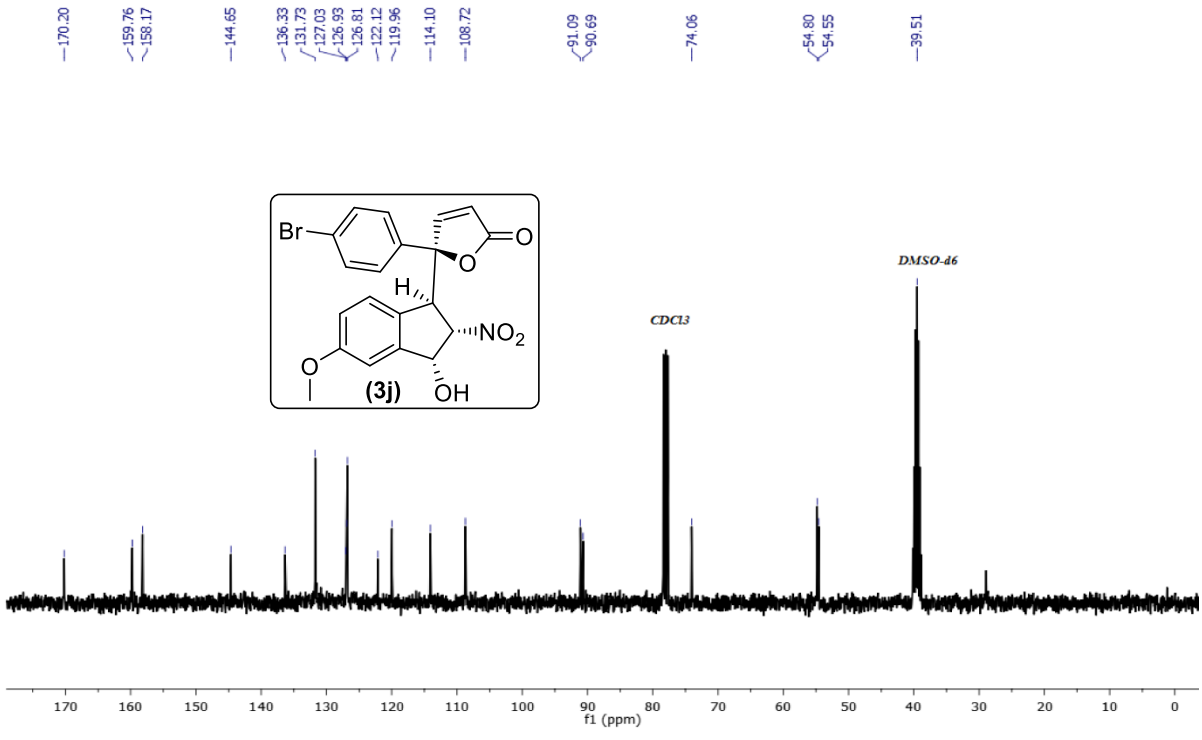
^{13}C NMR of **(3i)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



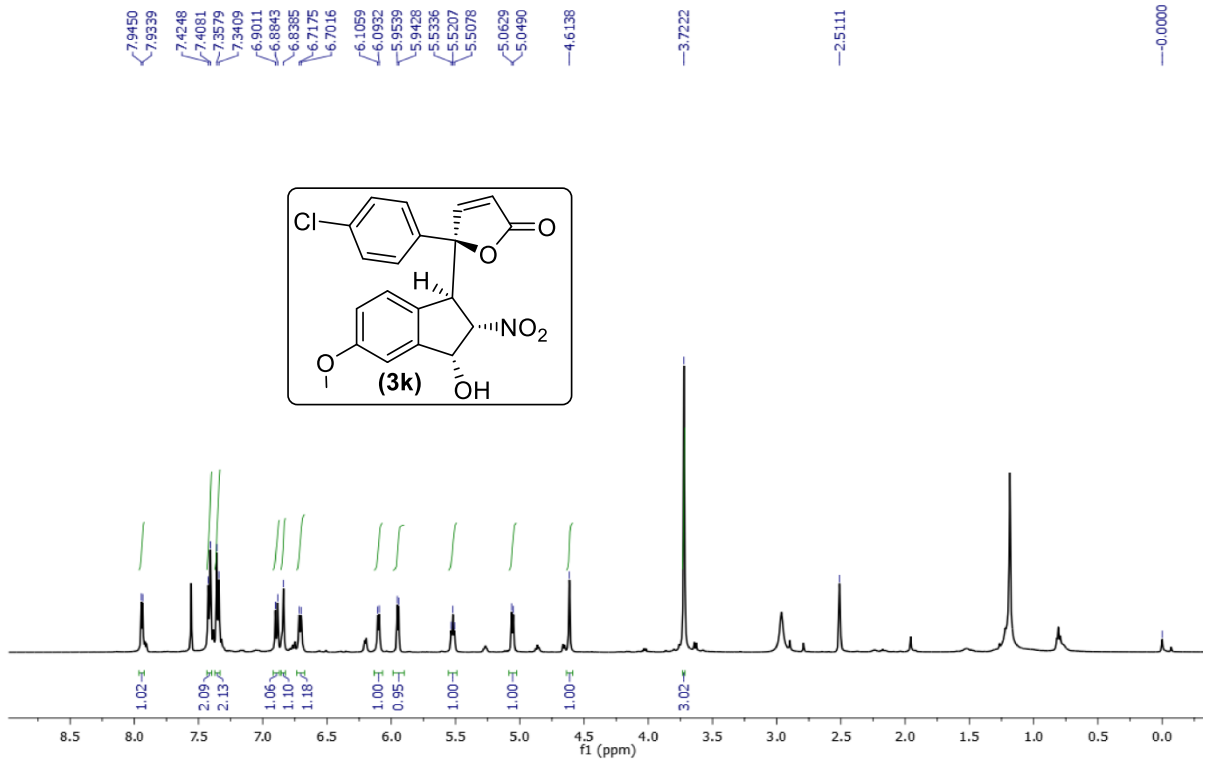
^{1}H NMR of **(3j)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



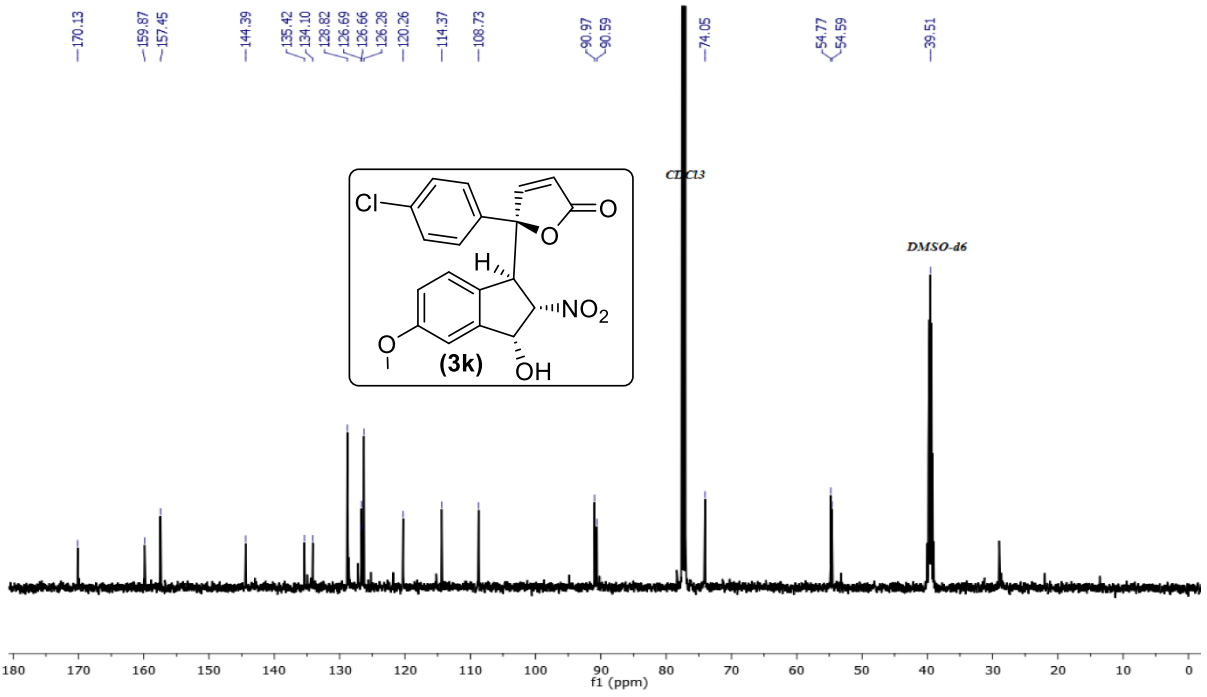
^{13}C NMR of **(3j)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



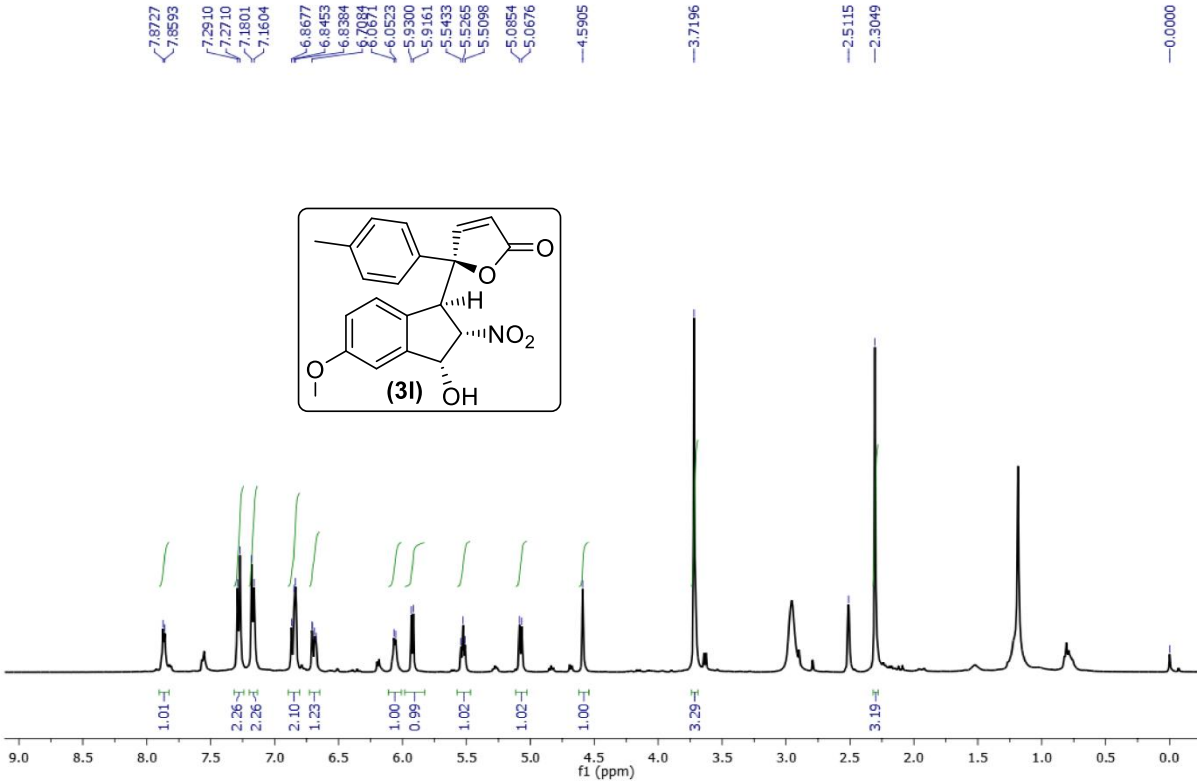
^{1}H NMR of **(3k)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



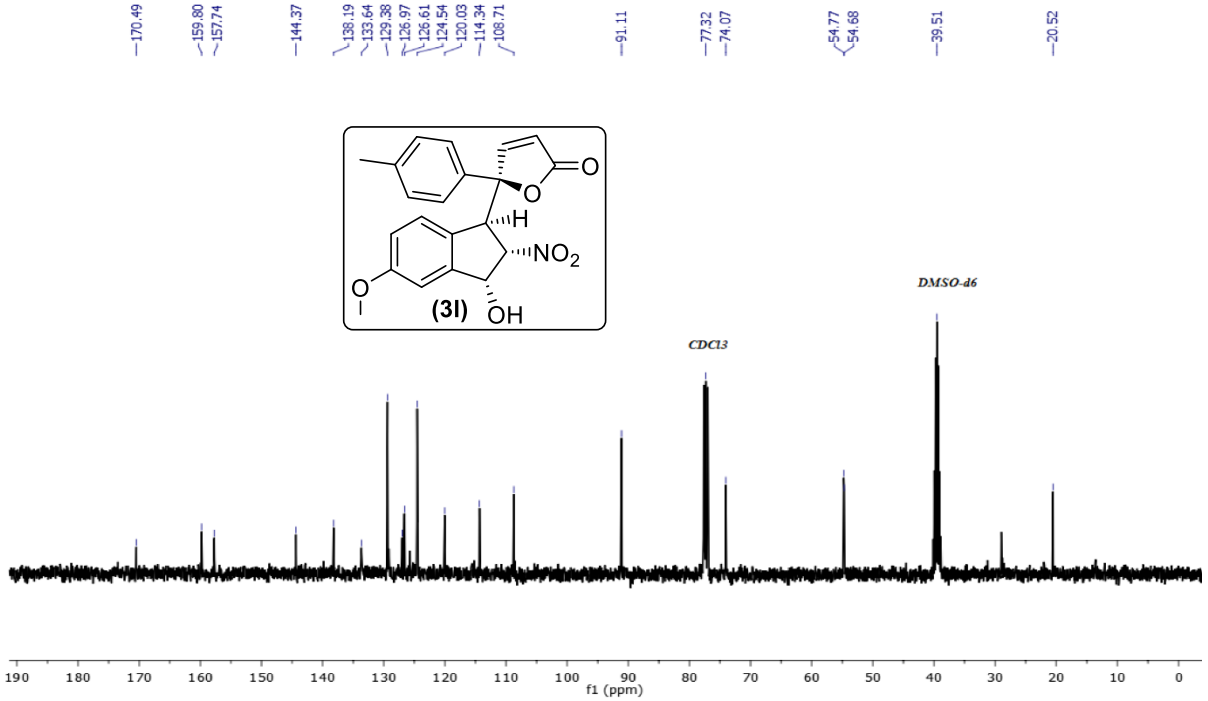
^{13}C NMR of **(3k)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



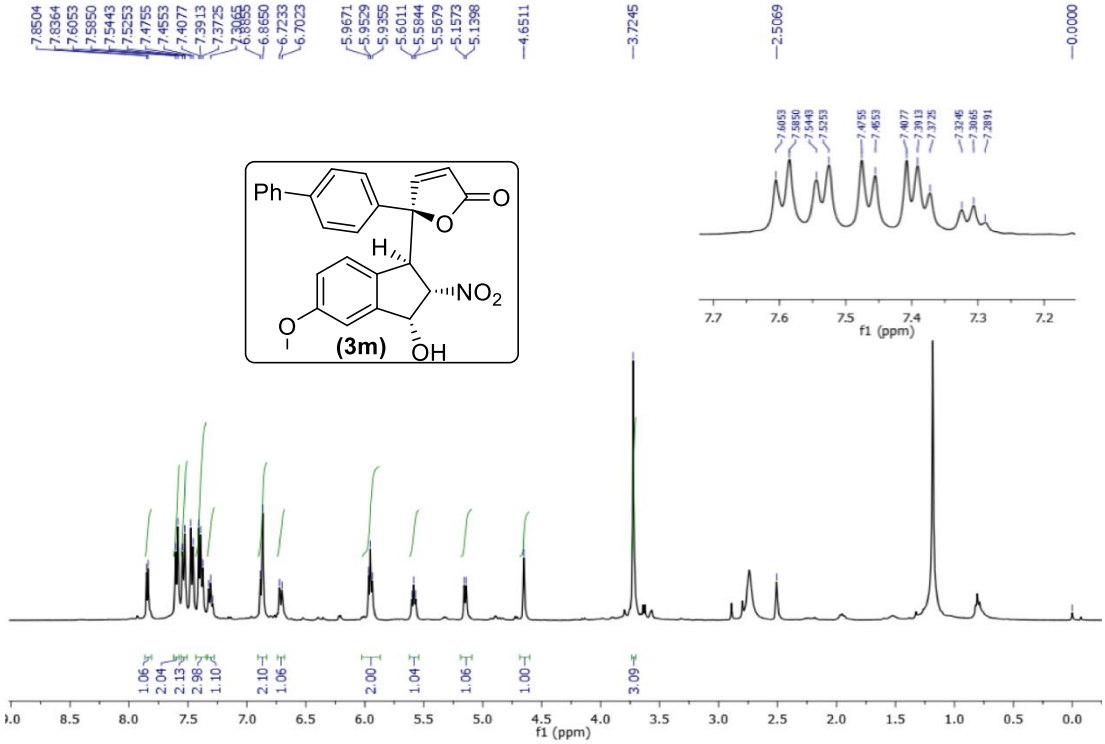
^{1}H NMR of **(3l)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



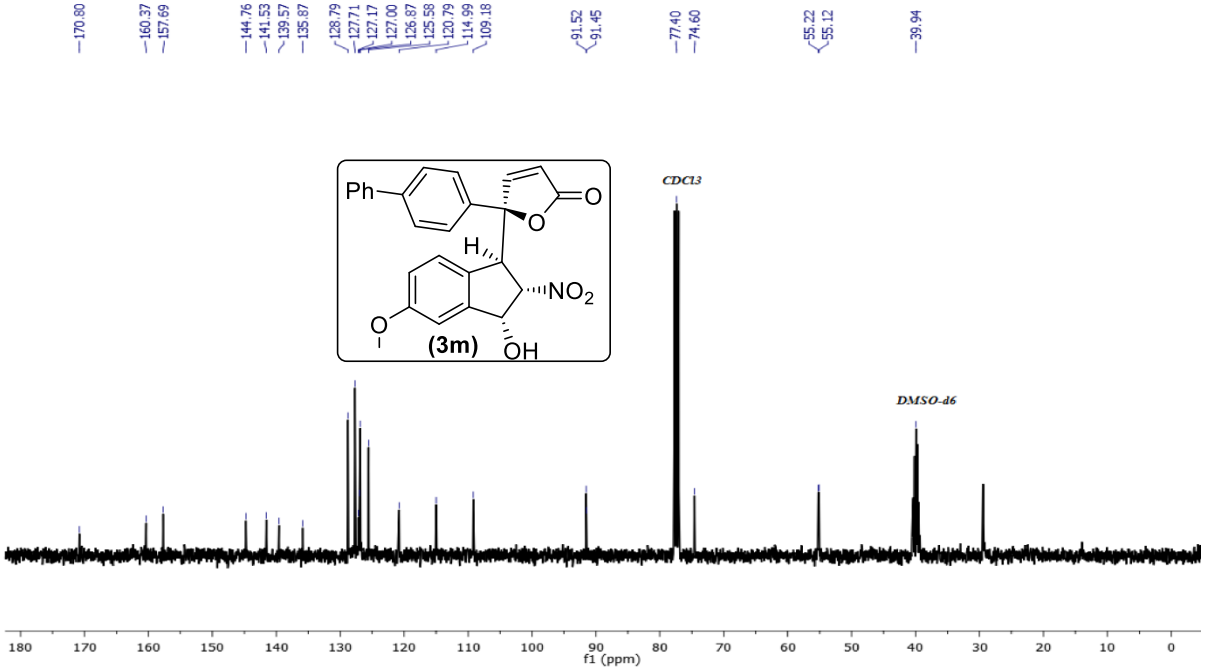
^{13}C NMR of **(3l)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



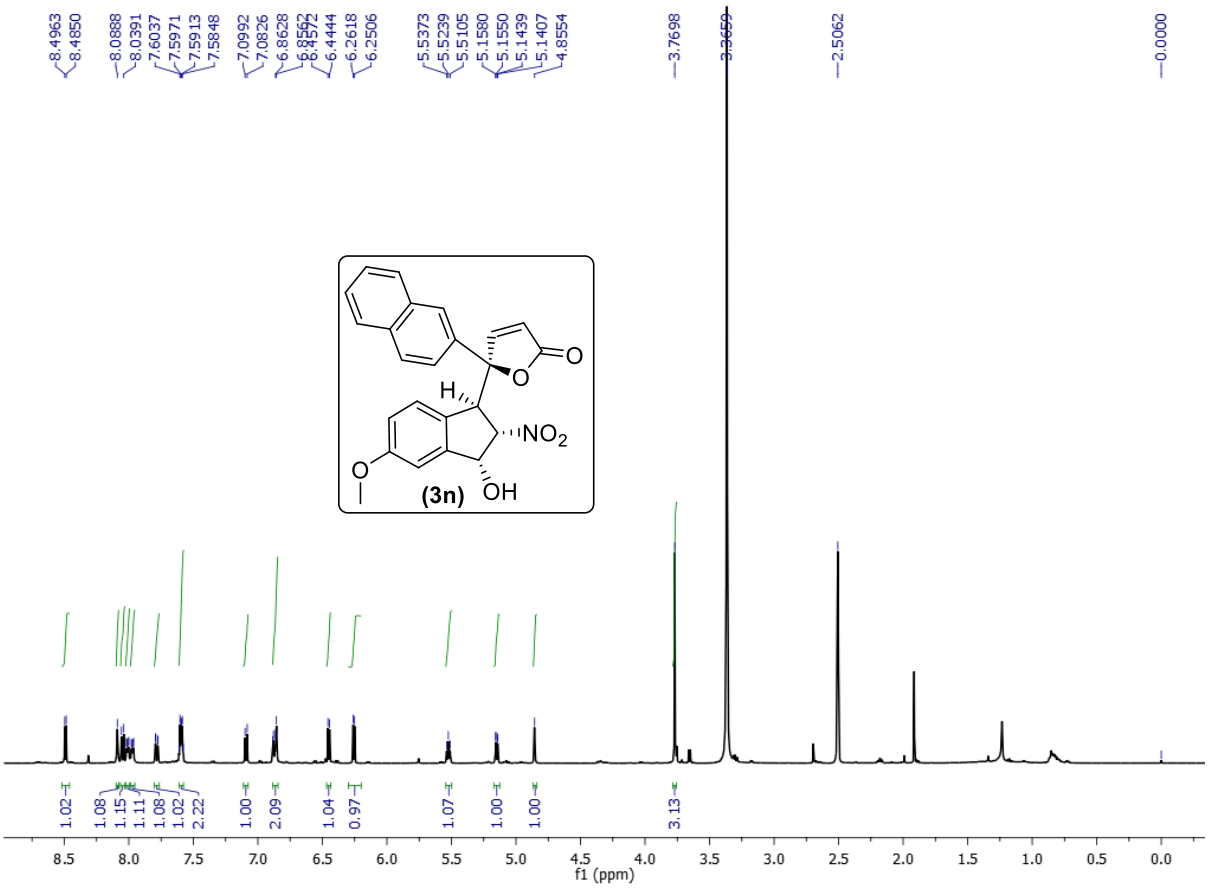
^{1}H NMR of **(3m)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



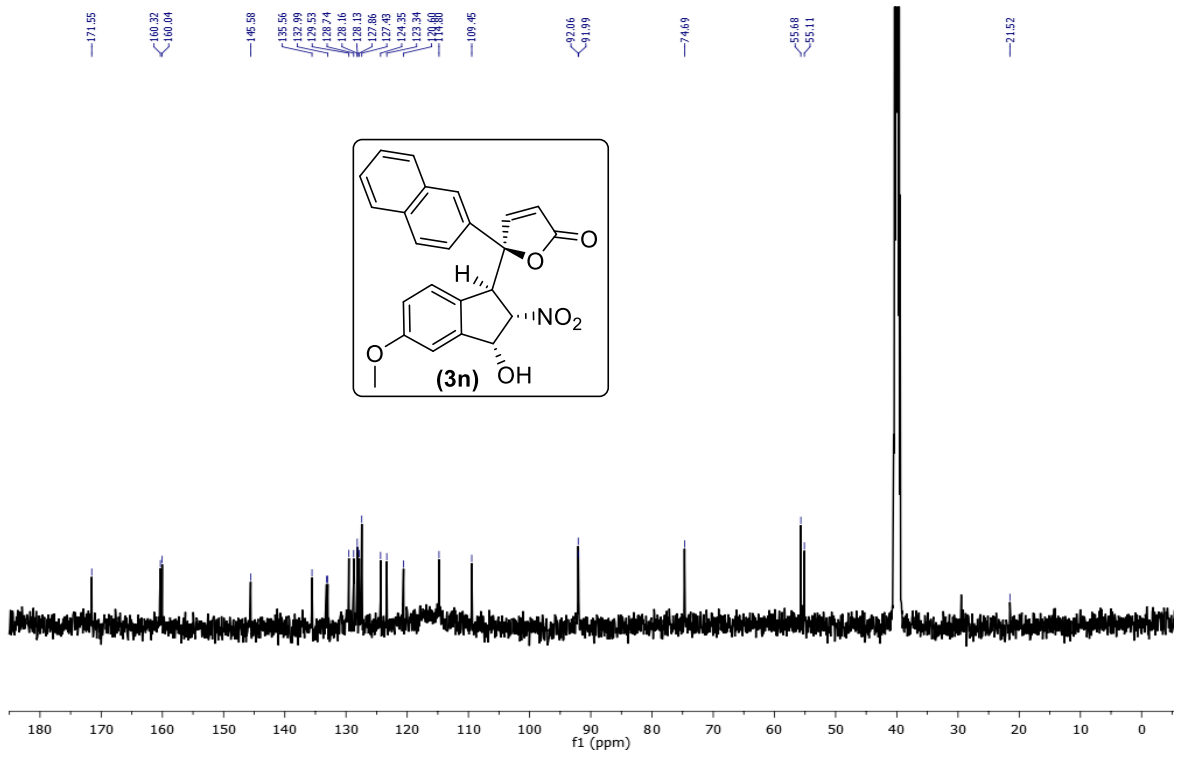
^{13}C NMR of **(3m)** in mixture of $CDCl_3$ and DMSO-d_6 (84:16)



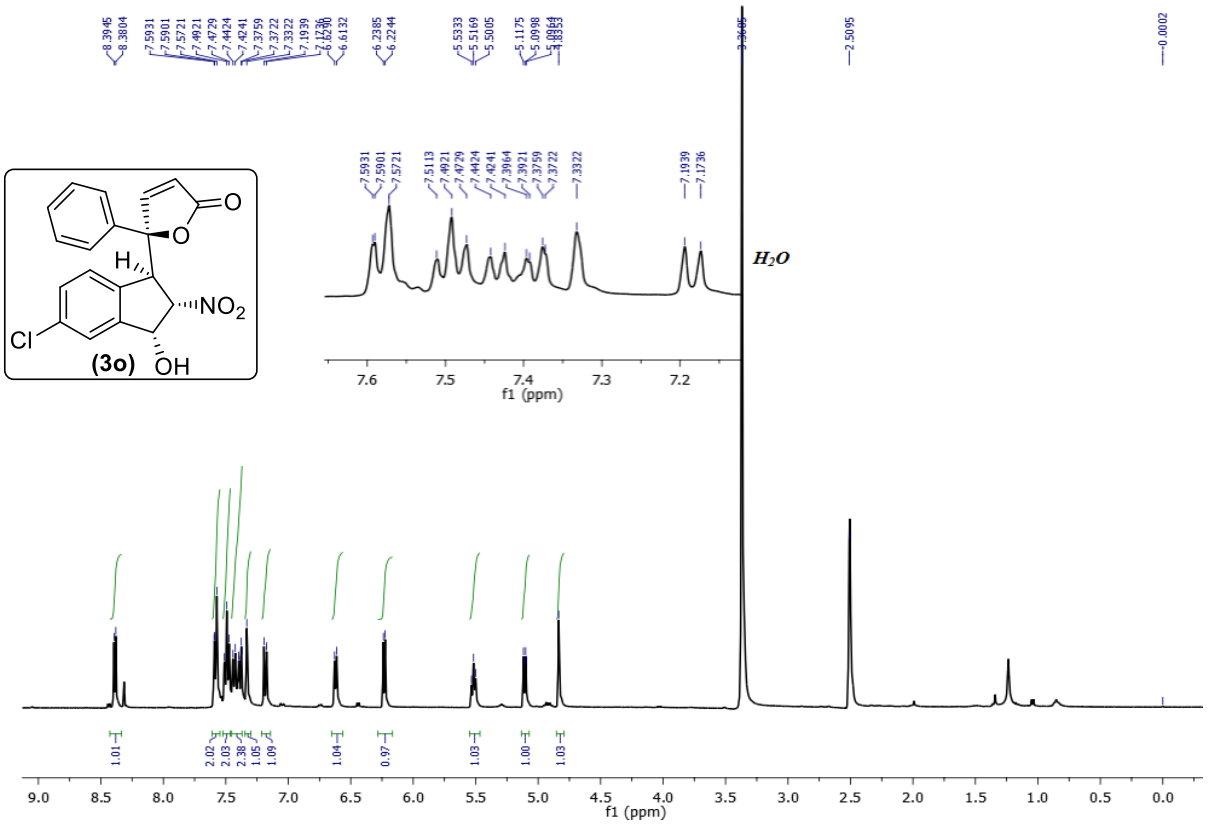
^{1}H NMR of **(3n)** in DMSO-d$_6$



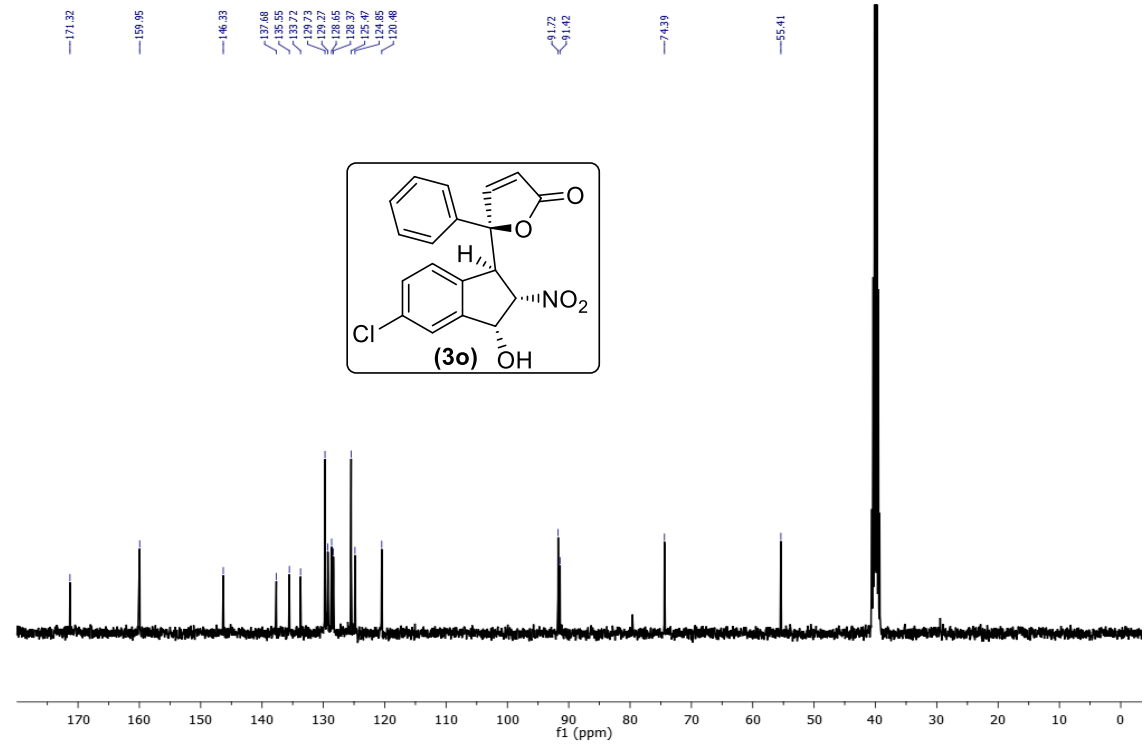
^{13}C NMR of **(3n)** in DMSO-d$_6$



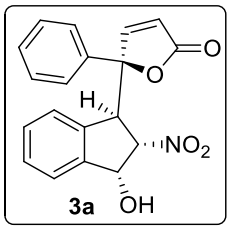
^{1}H NMR of **(3o)** in DMSO-d$_6$



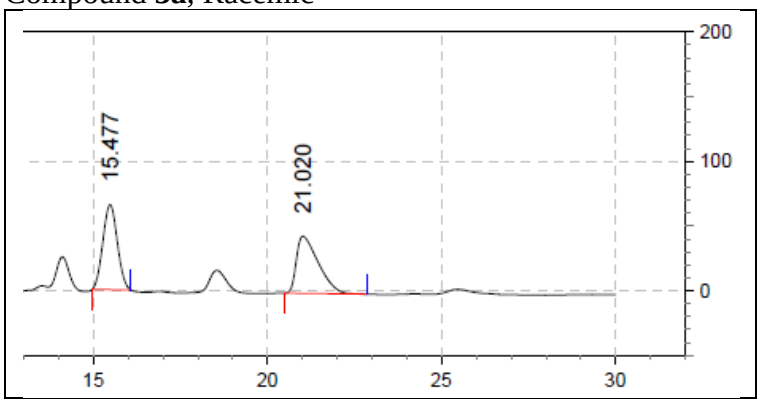
^{13}C NMR of **(3o)** in DMSO-d$_6$



HPLC spectra of **(3a)**

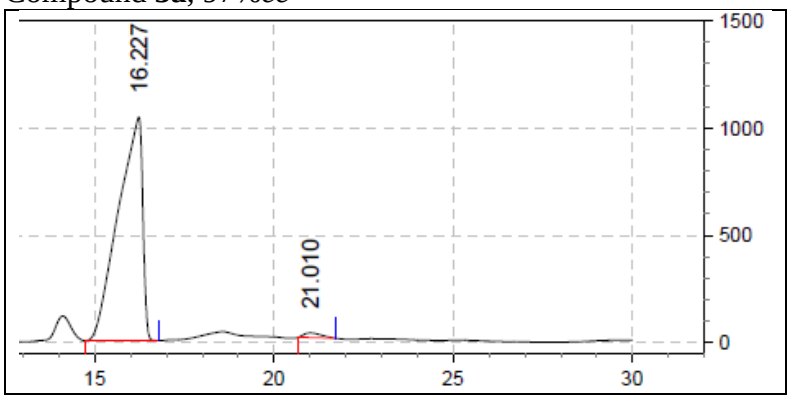


Compound **3a**, Racemic



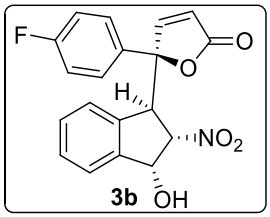
Retention Time(min)	Area(mv.sec)	Area (%)
15.47	31775021	49.66
21.02	32208462	50.34

Compound **3a**, 97%*ee*

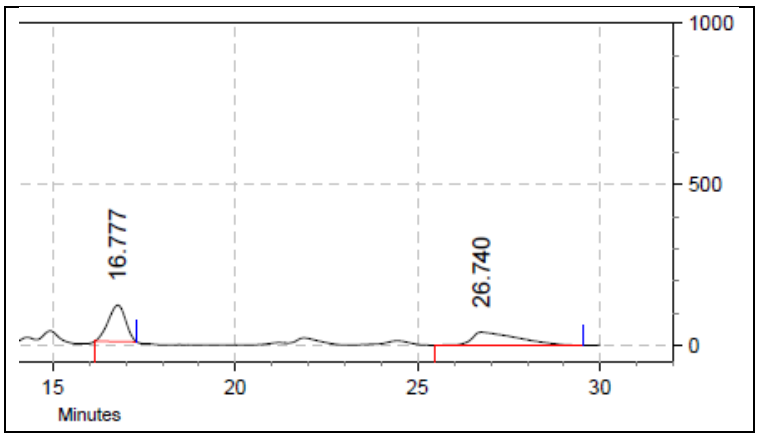


Retention Time(min)	Area(mv.sec)	Area (%)
16.22	828179781	98.53
21.01	12339250	1.47

HPLC spectra of **(3b)**

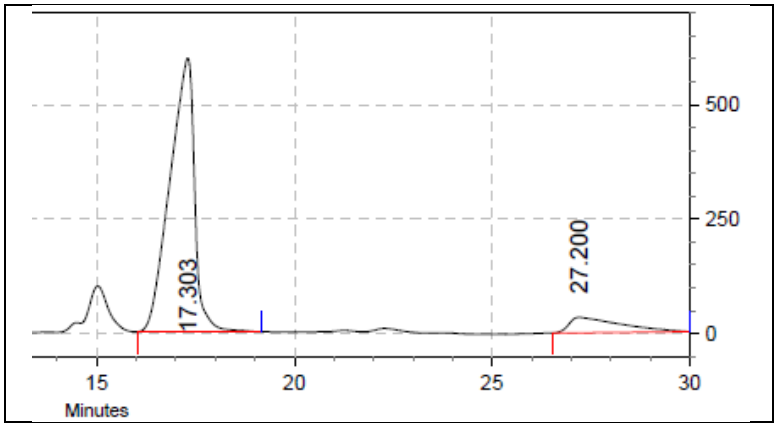


Compound **3b**, Racemic



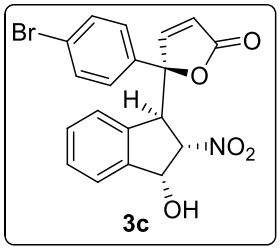
Retention Time(min)	Area(mv.sec)	Area (%)
16.77	62574068	50.72
26.74	60788789	49.28

Compound **3b**, 79% *ee*

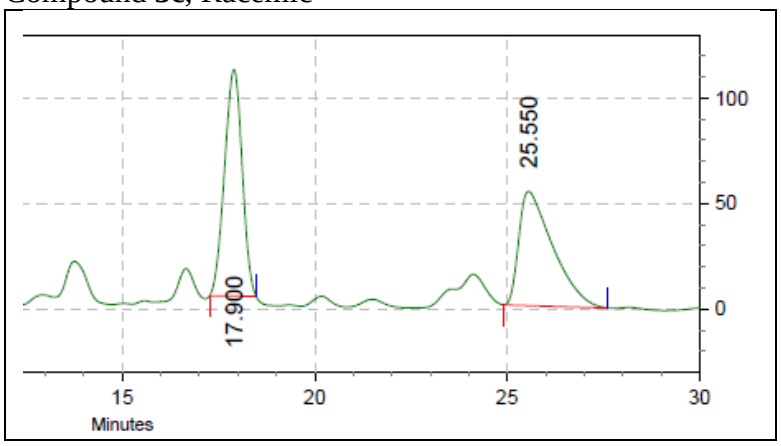


Retention Time(min)	Area(mv.sec)	Area (%)
17.30	436332762	89.45
27.20	51470948	10.55

HPLC spectra of **(3c)**

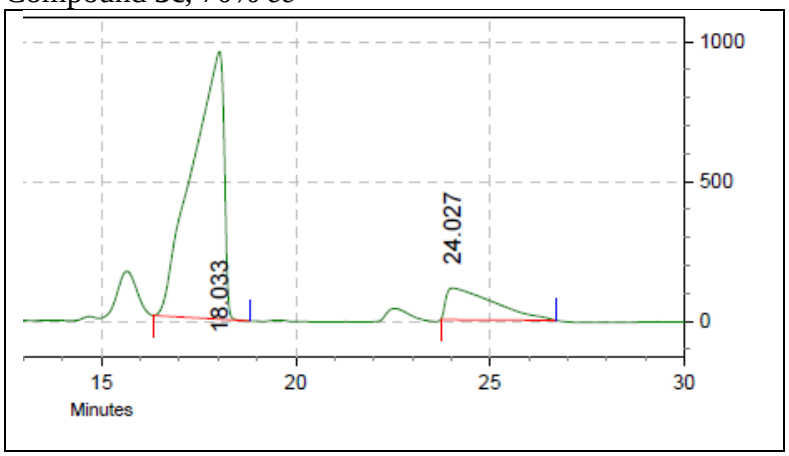


Compound **3c**, Racemic



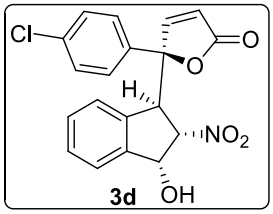
Retention Time(min)	Area(mv.sec)	Area (%)
17.90	57182864	50.74
25.55	55507028	49.26

Compound **3c**, 70% *ee*

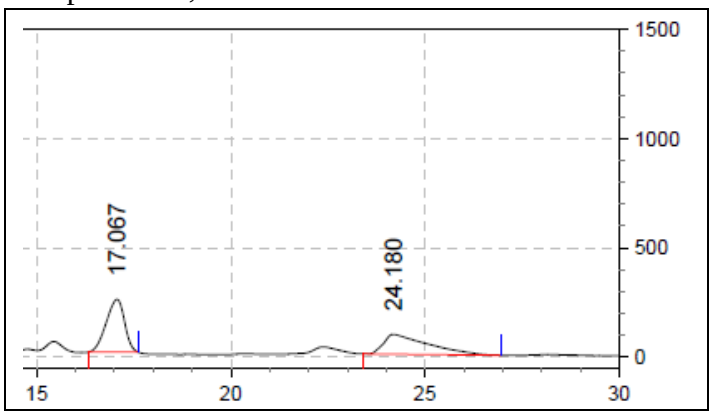


Retention Time(min)	Area(mv.sec)	Area (%)
18.03	909184116	84.93
24.02	161318321	15.07

HPLC spectra of **(3d)**

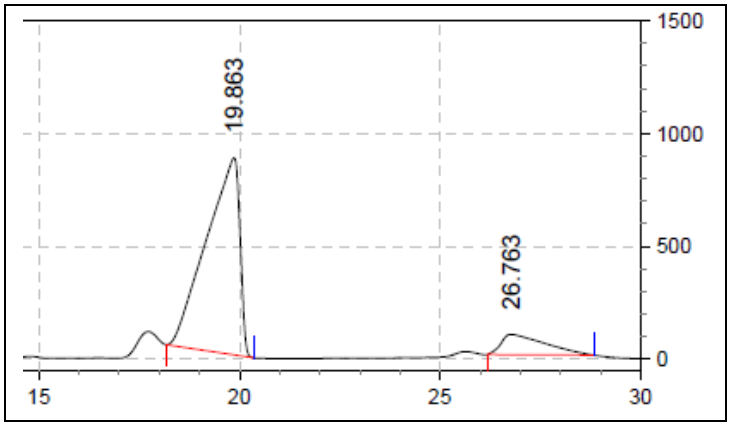


Compound **3d**, Racemic



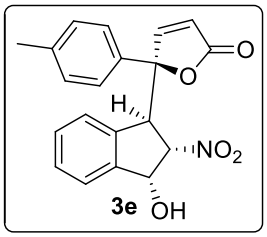
Retention Time(min)	Area(mv.sec)	Area (%)
17.06	131989868	52.34
24.18	120205095	47.66

Compound **3d**, 76% *ee*

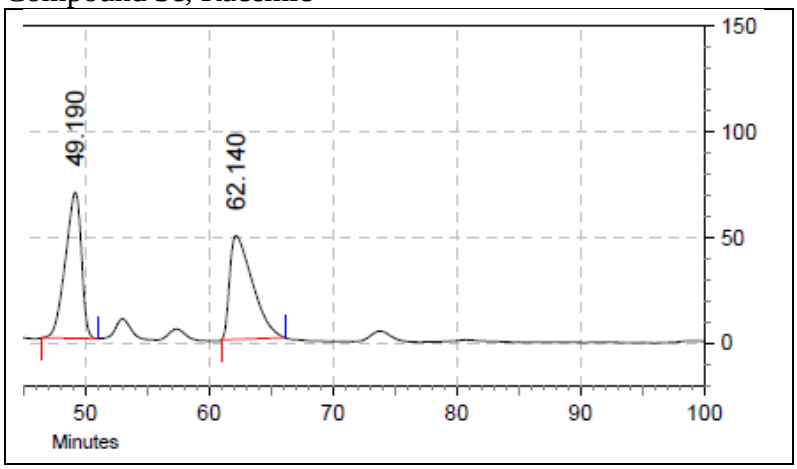


Retention Time(min)	Area(mv.sec)	Area (%)
19.86	845873404	87.98
26.76	115558840	12.02

HPLC spectra of **(3e)**

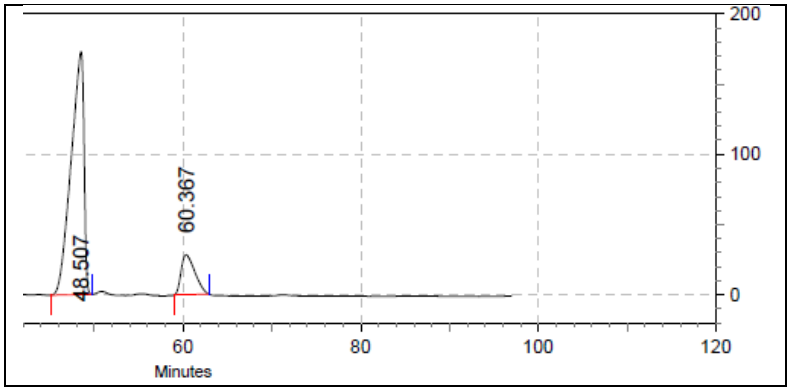


Compound **3e**, Racemic



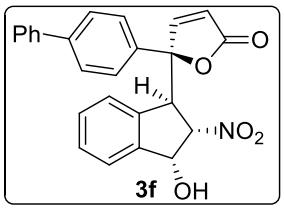
Retention Time(min)	Area(mv.sec)	Area (%)
49.19	103848593	49.63
62.14	105386594	50.37

Compound **3e**, 70% *ee*

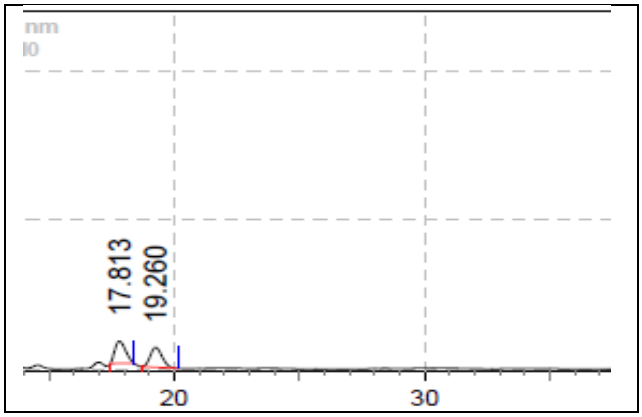


Retention Time(min)	Area(mv.sec)	Area (%)
48.50	292849878	85.10
60.36	51291221	14.90

HPLC spectra of **(3f)**

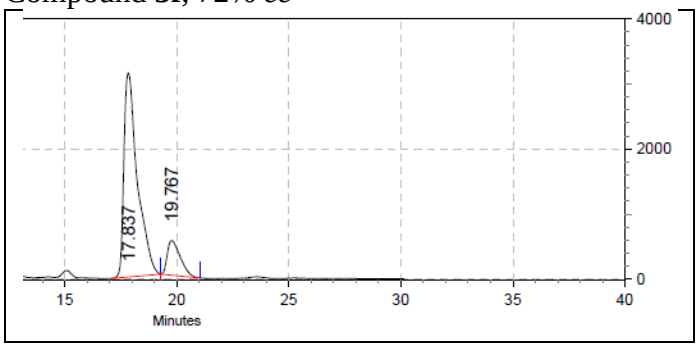


Compound **3f**, Racemic



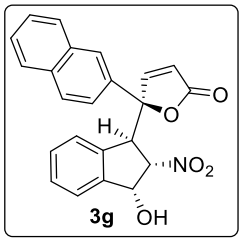
Retention Time(min)	Area(mv.sec)	Area (%)
17.81	37451718	50.54
19.26	36646031	49.46

Compound **3f**, 72% *ee*

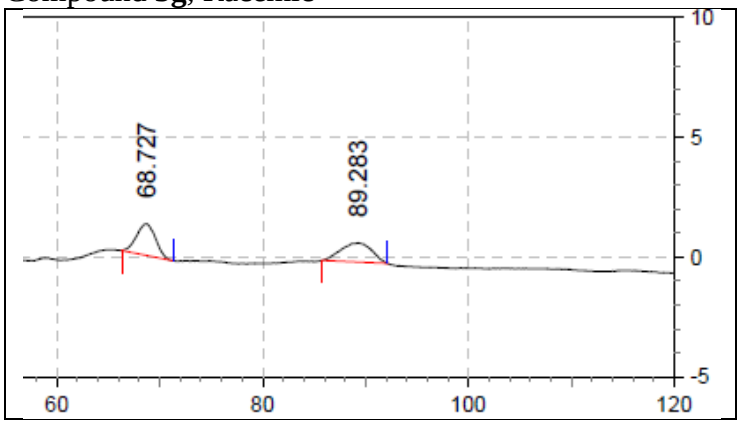


Retention Time(min)	Area(mv.sec)	Area (%)
17.83	2191530288	85.83
19.76	361663223	14.17

HPLC spectra of **(3g)**

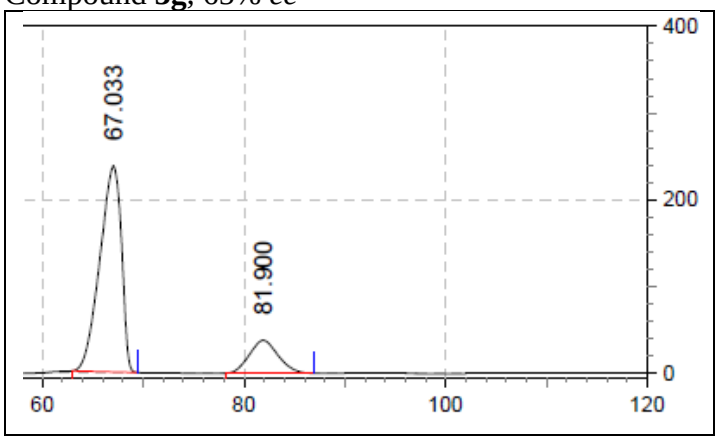


Compound **3g**, Racemic



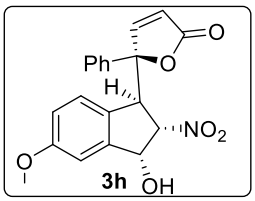
Retention Time(min)	Area(mv.sec)	Area (%)
68.72	2846497	50.39
89.28	2802880	49.61

Compound **3g**, 65% *ee*

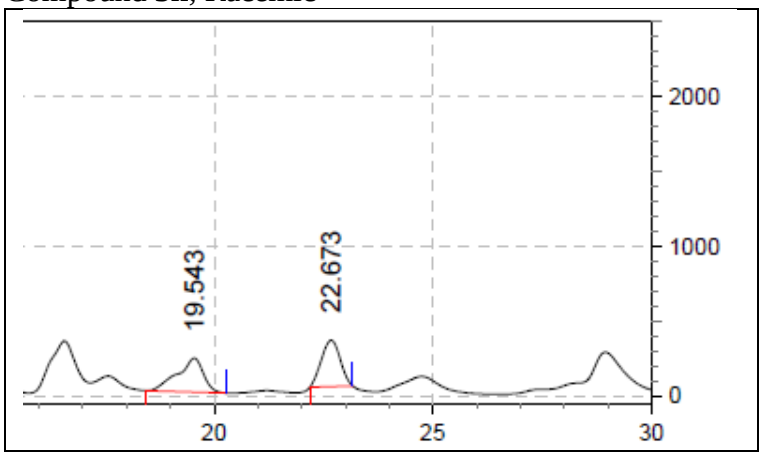


Retention Time(min)	Area(mv.sec)	Area (%)
67.03	590797588	82.36
81.90	126558137	17.64

HPLC spectra of **(3h)**

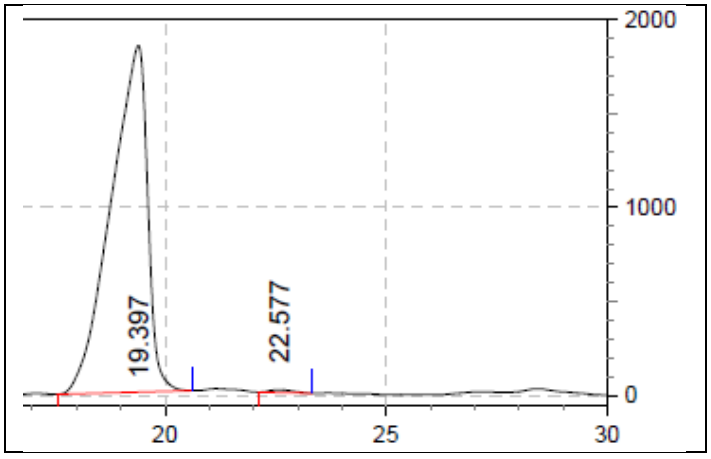


Compound **3h**, Racemic



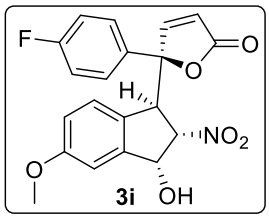
Retention Time(min)	Area(mv.sec)	Area (%)
19.54	157254426	50.40
22.67	154784772	49.60

Compound **3h**, 99% *ee*

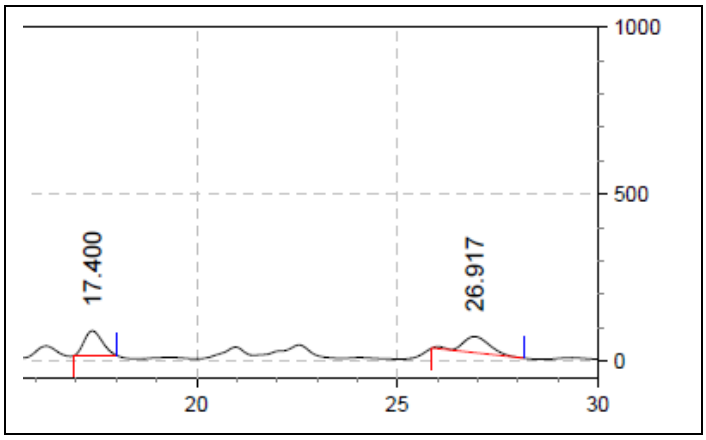


Retention Time(min)	Area(mv.sec)	Area (%)
19.39	1776850607	99.49
22.57	9060053	0.51

HPLC spectra of **(3i)**

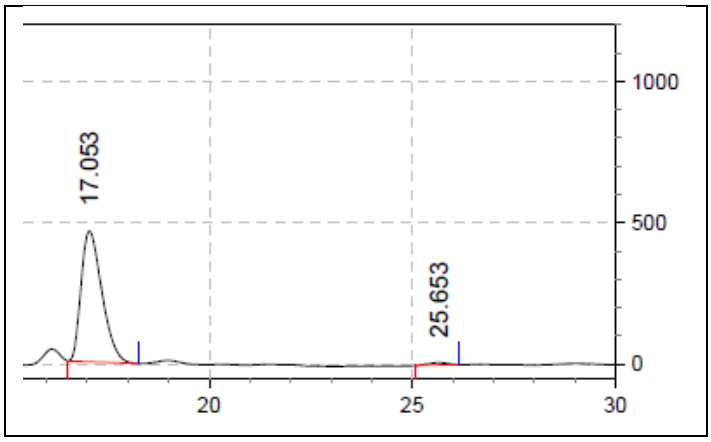


Compound **3i**, Racemic



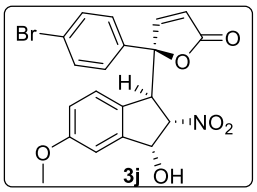
Retention Time(min)	Area(mv.sec)	Area (%)
17.40	38627012	50.19
26.91	38188281	49.71

Compound **3i**, 97% *ee*

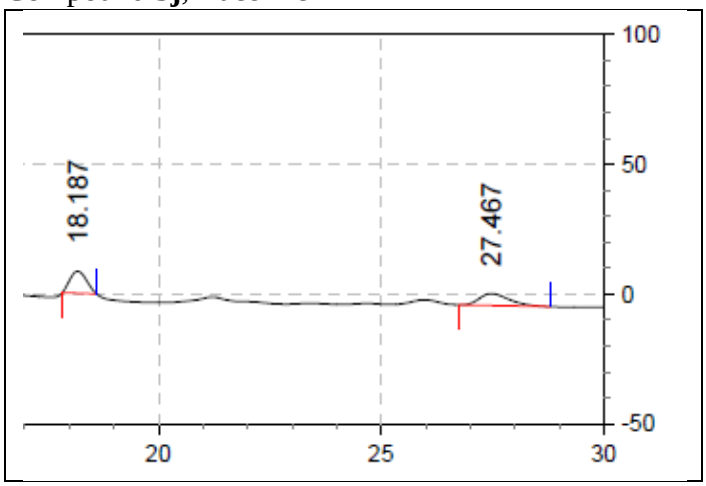


Retention Time(min)	Area(mv.sec)	Area (%)
17.05	276128187	98.33
25.65	4699061	1.67

HPLC spectra of **(3j)**

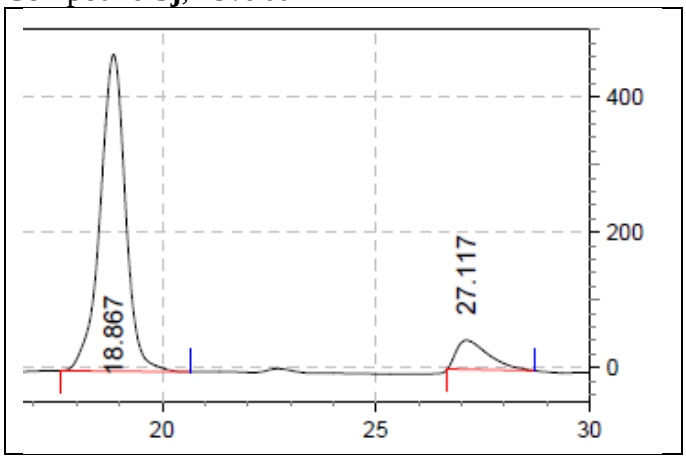


Compound **3j**, Racemic



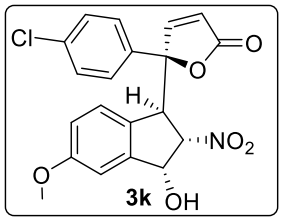
Retention Time(min)	Area(mv.sec)	Area (%)
18.18	3624409	50.11
27.46	3608483	49.89

Compound **3j**, 79% *ee*

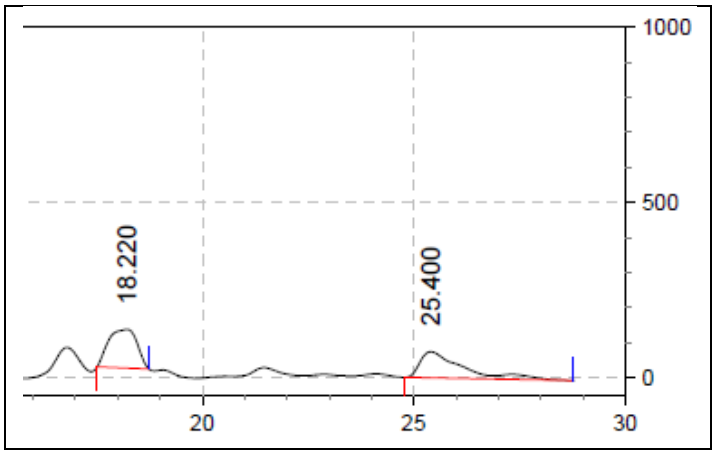


Retention Time(min)	Area(mv.sec)	Area (%)
18.86	324196886	89.52
27.11	37970894	10.48

HPLC spectra of **(3k)**

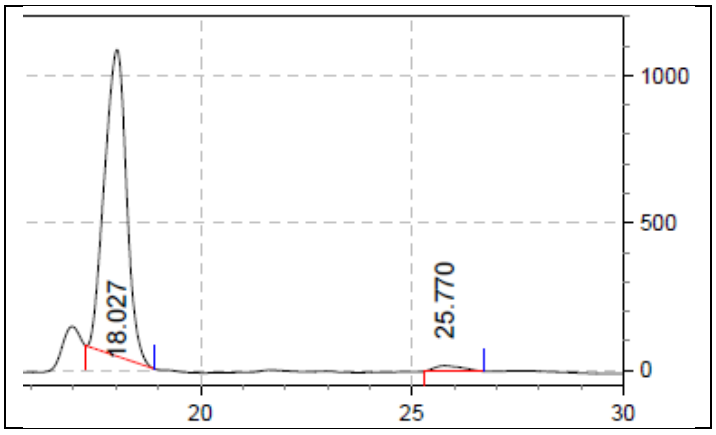


Compound **3k**, Racemic



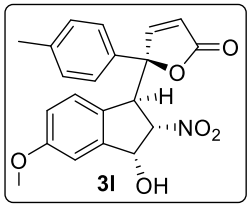
Retention Time(min)	Area(mv.sec)	Area (%)
18.22	86778500	49.52
25.40	88445406	50.48

Compound **3k**, 95% *ee*

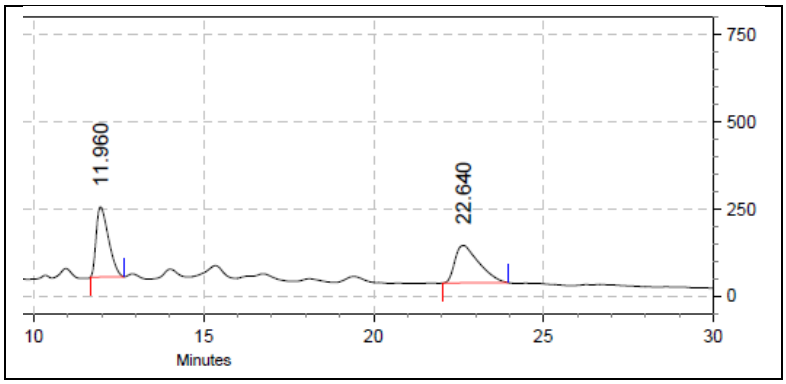


Retention Time(min)	Area(mv.sec)	Area (%)
18.02	630079494	97.71
25.77	14796344	2.29

HPLC spectra of **(3l)**

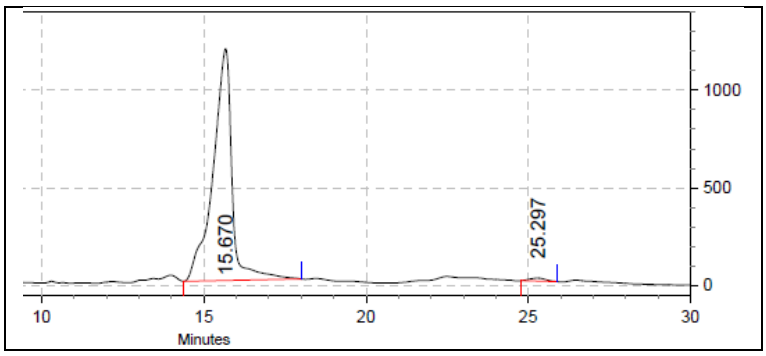


Compound **3l**, Racemic



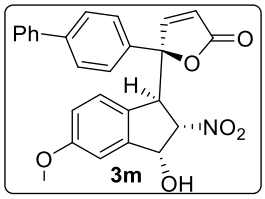
Retention Time(min)	Area(mv.sec)	Area (%)
11.96	84904236	49.08
22.64	88092896	50.92

Compound **3l**, 98% *ee*

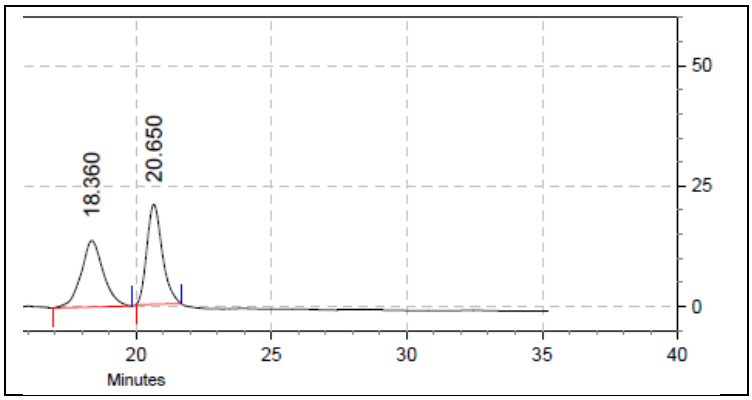


Retention Time(min)	Area(mv.sec)	Area (%)
15.67	814746713	98.92
25.29	8887419	1.08

HPLC spectra of **(3m)**

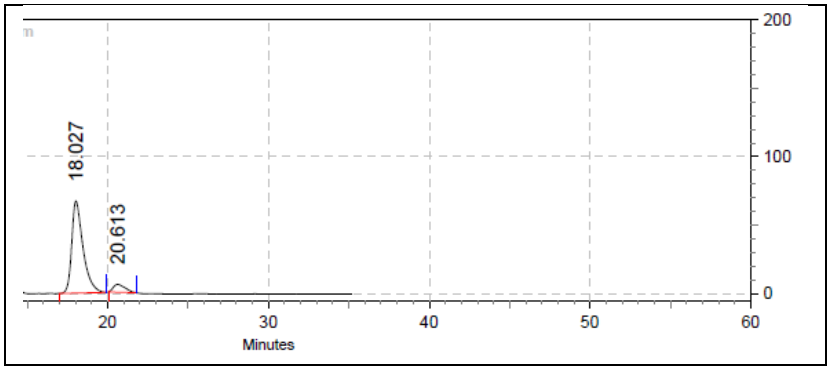


Compound **3m**, Racemic



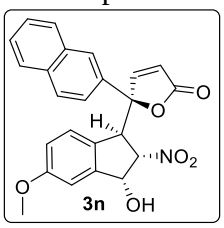
Retention Time(min)	Area(mv.sec)	Area (%)
18.36	13222626	48.95
20.65	13792139	51.05

Compound **3m**, 84% *ee*

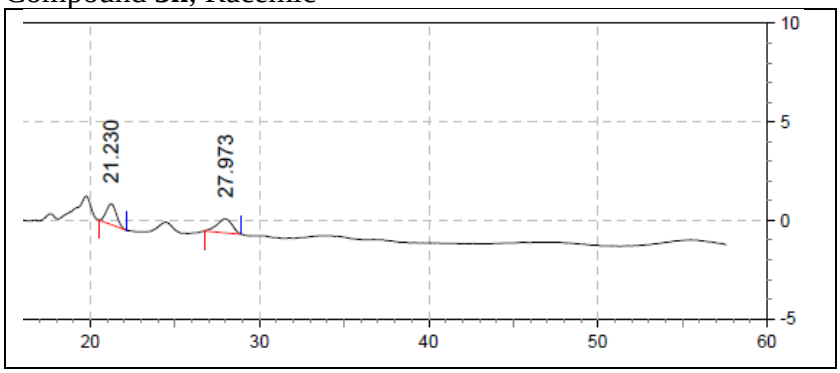


Retention Time(min)	Area(mv.sec)	Area (%)
18.02	55018721	91.80
20.61	4912001	8.20

HPLC spectra of **(3n)**

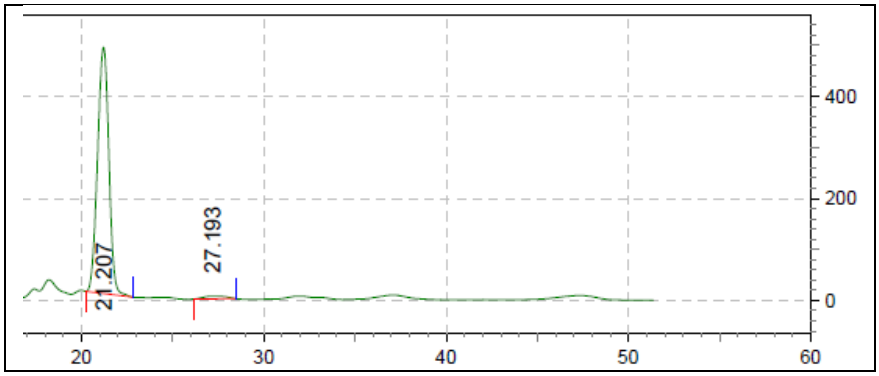


Compound **3n**, Racemic



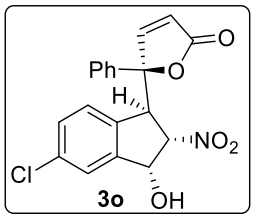
Retention Time(min)	Area(mv.sec)	Area (%)
21.23	743484	50.12
27.97	739921	49.88

Compound **3n**, 96% *ee*

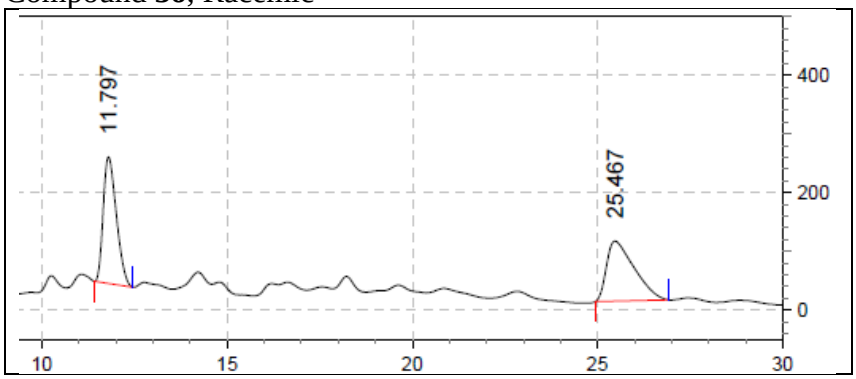


Retention Time(min)	Area(mv.sec)	Area (%)
21.20	349533539	97.93
27.19	7382935	2.07

HPLC spectra of **(3o)**

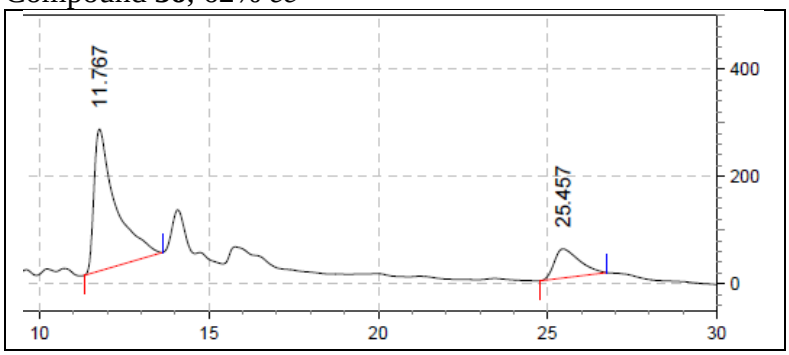


Compound **3o**, Racemic



Retention Time(min)	Area(mv.sec)	Area (%)
11.79	89235697	50.15
25.46	88699441	49.85

Compound **3o**, 62% *ee*



Retention Time(min)	Area(mv.sec)	Area (%)
11.76	198628160	81.05
25.45	46448407	18.95

1.10 References

1. Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285; For reviews on natural products having butenolides, see: a) Bermejo, A.; Figadere, B.; Zafra-Polo, M.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269. b) Sellars, J. D.; Steel, P. G. *Eur. J. Org. Chem.* **2007**, 3815. c) Prassas, I.; Diamandis, E. P. *Nat. Rev. Drug Discovery* **2008**, *7*, 926. d) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298.
2. Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.
3. For reviews, see a) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525; b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*,3076. c) Pansare, S. V.; Paul, E. K. *Chem. Eur. J.* **2011**, *17*, 8770. d) Zhang, Q.; Liu, X.; Feng, X. *Curr. Org. Synth.* **2013**, *10*, 764. e) Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595. f) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531. g) Mao, B.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Rev.* **2017**, *117*, 10502.
4. For recent examples using 2-siloxyfurans as pre-activated butenolides, see a) Jadhav, A. P.; Rao, V. U. B.; Singh, P.; Gonnade, R. G.; Singh, R. P. *Chem. Commun.* **2015**, *51*, 13941. b) Li, J.; Huang, R.; Xing, Y- K.; Qiu, G.; Tao, H.-Y.; Wang, C.-J. *J. Am. Chem. Soc.* **2015**, *137*, 10124. c) Liu, J.; Li, Z.; Tong, P.; Xie, Z.; Zhang, Y.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1632. d) Steinkamp, A.-D.; Frings, M.; Thom, I.; Schiffers, I.; Bolm, C. *Chem. Eur. J.* **2015**, *21*, 7705. e) Liu, K.; Chang, X.; Wang, C.-J. *Org. Lett.* **2016**, *18*, 6288.
5. For a selected review on quaternary stereocenters, see: a) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. b) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. c) Chen, L.; Yin, X.-P.; Wang, C.-H.; Zhou, J. *Org. Biomol. Chem.* **2014**, *12*, 6033. d) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, 516, 181. e) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740. f) Ling, T.; Rivas, F. *Tetrahedron* **2016**, *72*, 6729. g) for a book, see: Quaternary Stereocenters (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**.
6. For selected reviews on organocatalysed cascade reactions, see: a) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. b) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. c) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. d) Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. e) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. f) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem. Int. Ed.* **2010**, 49, 846. g) Ramachary, D. B.;

Jain, S. *Org. Biomol. Chem.* **2011**, *9*, 1277. h) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278. i) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. j) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253.

7. Kerr, M. S.; deAlaniz, J. R.; Rovis, T. *J. Am. Chem.Soc.* **2002**, *124*, 10298.

8. Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.

9. Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464.

10. Didier, E.; Loubinoux, B.; Ramos Tombo, G. M.; Rihs, G. *Tetrahedron* **1991**, *47*, 4941.

11. Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753.

12. For reviews, see: a) Gallou, I.; Senanayake, C. H. *Chem. Rev.* **2006**, *106*, 2843. b) Borie, C.; Ackermann, L.; Nechab, M. *Chem. Soc. Rev.* **2016**, *45*, 1368. c) Gabriele, B.; Mancuso, R.; Veltri, L. *Chem. Eur. J.* **2016**, *22*, 5056.

13. Merck researchers used indanol building block for HIV protease inhibitor Crixivan, a leading drugs for AIDS treatment, a) Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.- W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4096. b) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443. c) Rasagiline derivatives having anti-Parkinson activity, González-Díaz, H.; Prado-Prado, F.; García-Mera, X.; Alonso, N.; Abeijo'n, P.; Caamaño, O.; Yáñez, M.; Munteanu, C. R.; Pazos, A.; Dea- Ayuela, M. A.; Gómez-Muñoz, M. T.; Garijo, M. M.; Sansano, J.; Ubeira, F. M. *J. Proteome Res.* **2011**, *10*, 1698.

14. a) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720. Also, see b) Huang, X.; Peng, J.; Dong, L.; Chen, Y.-C. *Chem. Commun.* **2012**, *48*, 2439.

15. Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540.

16. a) Li, X.; Lu, M.; Dong, Y.; Wu, W.; Qian, Q.-Q.; Ye, J.-X.; Dixon, D. *Nat. Commun.* **2014**, *5*, 4479. b) Yin, L.; Takada, H.; Lin, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem.*

Int. Ed. **2014**, *53*, 5327. c) Wang, Z.-H.; Wu, Z- J.; Huang, X.-Q.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51*, 15835. d) Manna, M. S.; Sarkar, R.; Mukherjee, S. *Chem. Eur. J.* **2016**, *22*, 14912. e) Simlandy, A. K.; Mukherjee, S. *Org. Biomol. Chem.* **2016**, *14*, 5659. f) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 10069. g) Yang, D.; Wang, L.; Zhao, D.; Han, F.; Zhang, B.; Wang, R. *Chem. Eur. J.* **2013**, *19*, 4691. h) M. Zhang, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2016**, *22*, 5525. i) Tang, Q.; Lin, L.; Ji, J.; Hu, H.; Liu, X.; Feng, X. *Chem. Eur. J.* **2017**, *23*, 16447.

17. a) Zhou, L.; Lin, L. L.; Ji, J.; Xie, M.-S.; Liu, X.-H.; Feng, X.-M. *Org. Lett.* **2011**, *13*, 3056. b) Nakamura, S.; Yamaji, R.; Hayashi, M. *Chem. Eur. J.* **2015**, *21*, 9615.
18. Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193.
19. Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2016**, *18*, 646.
20. a) Ji, J.; Lin, L.-L.; Zhou, L.; Zhang, Y.-H.; Liu, Y.-B.; Liu, X.-H.; Feng, X.-M.; *Adv. Synth. Catal.* **2013**, *355*, 2764. b) Das, U.; Chen, Y.-R.; Tsai, Y.-L.; Lin, W. *Chem. Eur. J.* **2013**, *19*, 7713.
21. a) Kumar, V.; Ray, B.; Rathi, P.; Mukherjee, S. *Synthesis* **2013**, *45*, 1641. b) Kumar, V.; Mukherjee, S. *Chem. Commun.* **2013**, *49*, 11203. c) Manna, M. S.; Mukherjee, S. *Chem. Sci.* **2014**, *5*, 1627. d) Manna, M. S.; Mukherjee, S. *Chem. Eur. J.* **2012**, *18*, 15277.
22. For selected examples initiated by an aldol followed by an intramolecular Michael reaction on similar types of substrates, see: a) Sanchez-Larios, E.; Homes, J. M.; Daschner, C. L.; Gravel, M. *Org. Lett.* **2010**, *12*, 5772. b) Luzzio, F. A.; Okoromoba, O. E. *Tetrahedron Lett.* **2011**, *52*, 6530.
23. Nakano Y.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 3135.
24. Asami, M.; Taketoshi, A.; Hoshino K. M. H.; Sakakibara, K. *ChemistryLetters* **2007**, *36*, 64.
25. Loh, C. C. J.; Hack, D.; Enders, D. *Chem. Comm.* **2013**, *49*, 10230.
26. a) Wang, Z.-H.; Wu, Z.-J.; Huang, X.-Q.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun*. **2015**, *51*, 15835. b) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.

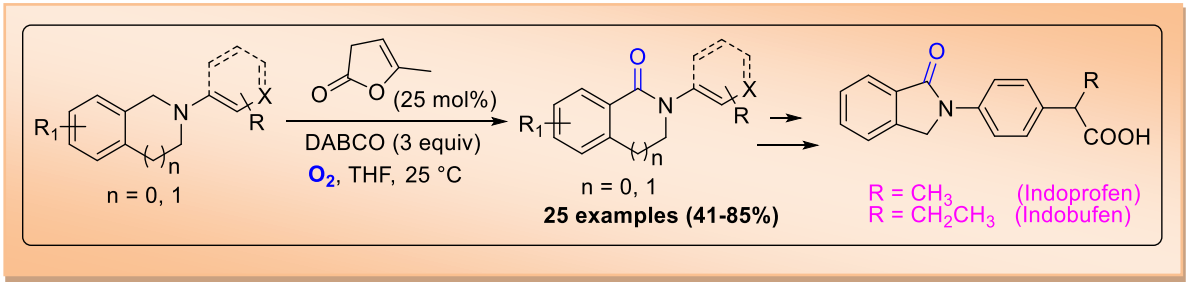
CHAPTER II

Organocatalytic Benzylic Oxidation of Cyclic Amines/Ethers Using α-Angelica Lactone as a Catalyst

Chapter II: Section A

Metal-Free Organocatalytic Oxidation of Benzylic sp3 C−H Bonds of Tetrahydroisoquinoline and Isoindoline

This section includes the development of a new method for the direct oxidation of various *N*-aryl tetrahydroisoquinolines and isoindolines to the corresponding lactams employing α-angelica lactone as a catalyst. The utility of this protocol was also further extended by the synthesis of indoprofen and indobufen.



Org. Lett. **2019**, *21*, 2532-2535.

2.1.1 Introduction

Over the years, lactam moiety has attracted the chemical community because of its presence in a myriad of natural products and various clinically approved medicinal agents.[1] Consequently, direct and straightforward methods for the α-oxidation of amines to corresponding lactams is an attractive transformation for the synthetic chemists.[2] Several natural products containing iso-quinolinone/indolinone scaffold with biological and pharmaceutical activities are known in the literature (Figure 1). Selective oxidation of the α-methylene group of amines to amides is challenging because the reactivity of amines is higher than that of α-methylene carbon.[3] ACS GCI pharmaceutical roundtable has enlisted "amide formation avoiding poor atom economy reagents" as one of the desired research areas in green chemistry and organocatalysis as one of the "more aspirational reactions".[4] In general, a stoichiometric amount of oxidants including organic or metal peroxides along with transition-metal based catalyst are used for α-oxygenation of amines.[5] Here, we demonstrate the *α*-CH_2-oxygenation of *N*-aryl tetrahydroisoquinolines and isoindolines by employing commercially available α-angelica lactone as an organocatalyst in the presence of base like 1,4-diazabicyclo [2.2.2]octane (DABCO) under the oxygen atmosphere. In this manner, it mirrors nature's oxidant combination O_2/NAD(P)H oxidation path. It should be noted that α-angelica lactone is a well-known vinylogous nucleophile and it has never been used as a catalyst for any type of reaction.[6]

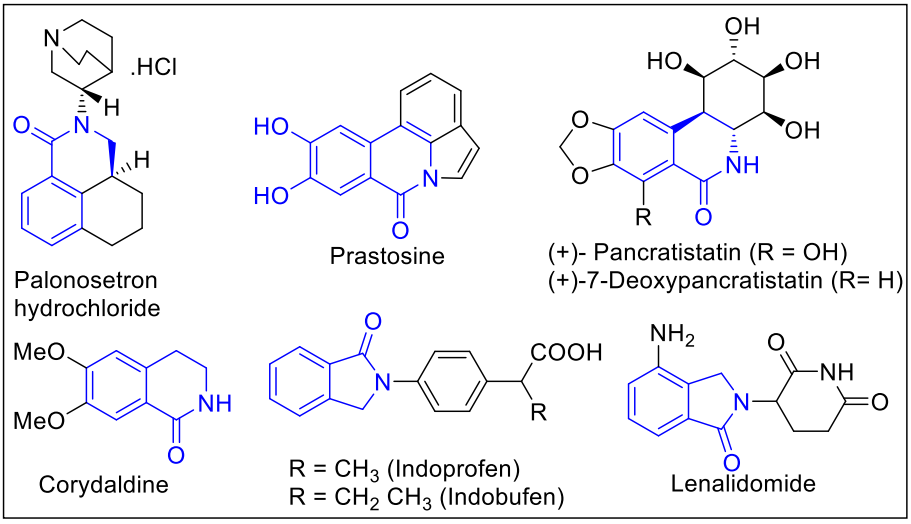
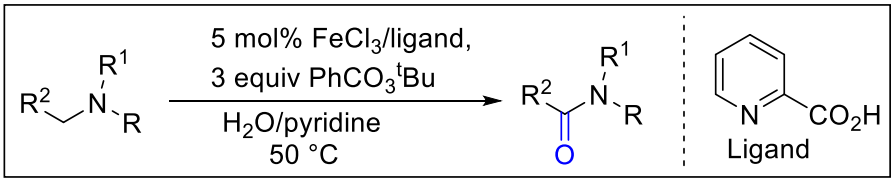


Figure 1. Bioactive natural products and pharmaceuticals containing iso-quinolinone/indolinone scaffold.

2.1.2 Literature Review

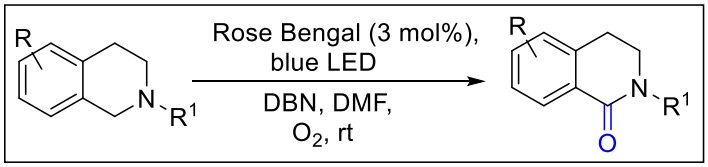
I. Fe-catalyzed C-H functionalization[7]

Emmert *et al.* in 2015 reported Fe-catalyzed C-H oxygenation of aliphatic amines to amides in presence of *tert*-butyl benzoperoxoate with a ligand such as picolinic acid. The amide products were obtained in low to good yields. Further, the protocol was used for the synthesis of drug Lidocaine.



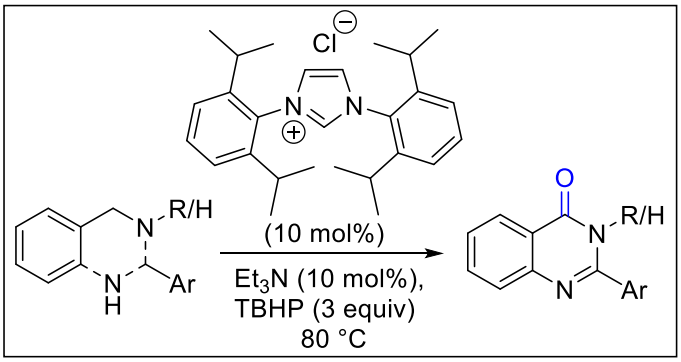
II. Visible-light mediated[8]

Das *et al.* in 2018 has reported a metal-free condition for direct α-oxygenation of secondary and tertiary amines to corresponding amides in presence of Rose Bengal as photocatalyst and by employing oxygen as an oxidant in presence of visible light. Here, water was the only by-product. The oxidation products are obtained in good yields. Mechanistic studies show the pivotal role of photocatalyst, base, and oxygen.



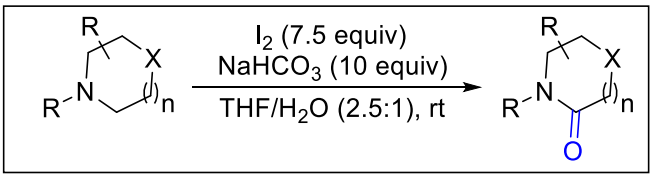
III. NHC-catalyzed in presence[9]

Maheswari *et al.* in 2016 reported an NHC-catalyzed benzylic C-H bond oxidation of *N*-benzylamines. The present organocatalyzed transformation affords the corresponding amide/lactam products in moderate to good yields. The developed protocol was also extended for the synthesis of 3*H*-quinazolin-4-ones in good yields.



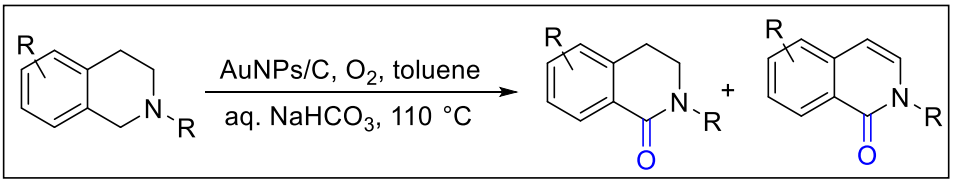
IV. I_2 Catalyzed[10]

Talbot *et al.* in 2017 reported a metal-free procedure by using iodine as an oxidant in stoichiometric amount and corresponding lactams were obtained in moderate to excellent yields. The authors also executed this methodology for late-stage chemoselective oxidation for the synthesis of industrially relevant drug scaffolds.



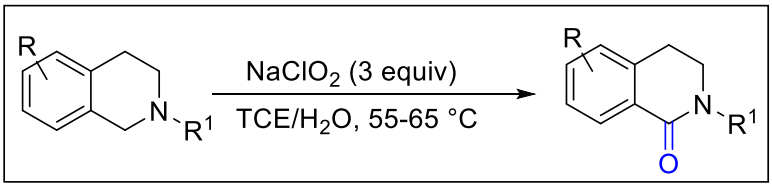
V. Graphite-supported gold nanoparticles[11]

Selective oxidation of cyclic and acyclic benzylic amines to corresponding lactam/amides by employing the graphite-supported gold nanoparticles (AuNPs/C) with O_2 as terminal oxidant was developed by Che *et al.* in 2009. The amide products were obtained in good yields and good selectivity. AuNPs/C catalyst can be reused for up to ten cycles without any loss of catalytic activity and selectivity.



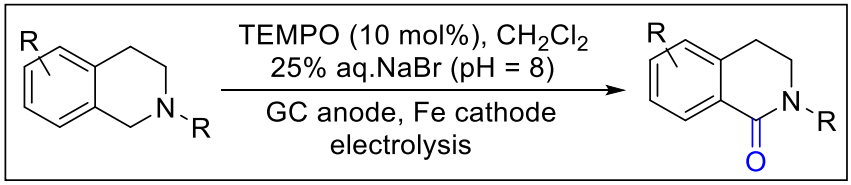
VI. By using sodium chlorite[12]

Zhang *et al.* in 2012 reported noncatalytic benzylic oxidation of cyclic ethers and *N*-protected cyclic amines to corresponding benzolactams in high to excellent yields. They used sodium chlorite as a catalyst as well as sole oxidant.



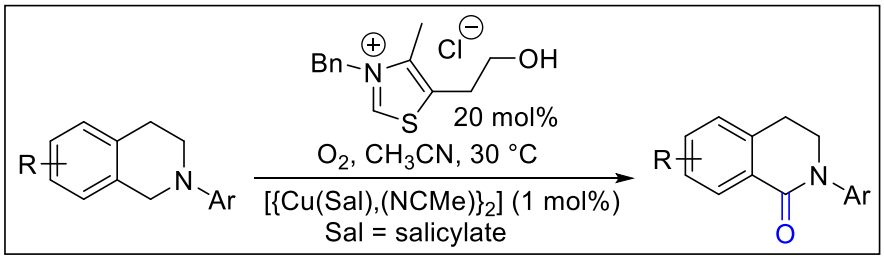
VII. Electrochemically induced[13]

Little *et al.* in 2013 successfully demonstrated the first electrochemical oxidation of benzylic C-H bonds of *N*-protected tetrahydroisoquinolines. The corresponding lactams were obtained in moderate to good yields. They utilized dual redox catalytic system like bromide ion and TEMPO in a two-phase electrolytic medium.



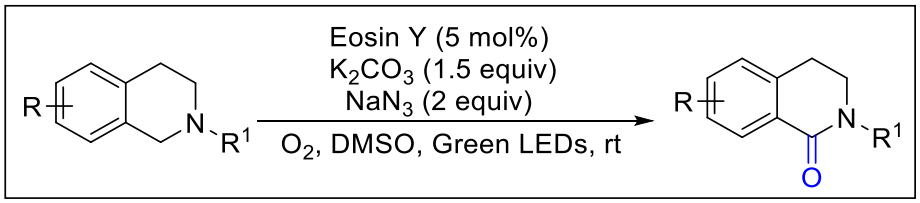
VIII. By using Cu^{II}– salicylate complex[14]

Xiao *et al.* in 2017 developed a protocol by using a binuclear copper-complex with vitamin B1 analog as a relay or cooperative catalysis in the presence of oxygen as oxidant. The corresponding products dihydroisoquinolines were obtained in good to excellent yields. From the mechanistic study, it was shown that Cu catalyst delivers the iminium intermediate from amine which on oxygenation by employing vitamin B1 analog deliver target oxidation products.



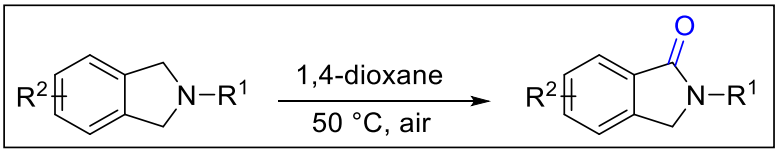
IX. Visible-light mediated[15]

Lee *et al.* in 2019 reported a metal-free α-oxygenation of *N*-substituted tetrahydroisoquinolines to corresponding lactams under visible light irradiation with eosin Y as photocatalyst and oxygen as oxidant. The desired target products were obtained in good to excellent yields at rt.



X. Solvent-mediated method[16]

Isoindolinones were prepared by dioxane-mediated oxidation of corresponding isoindolines in a catalyst-free environment with air/oxygen as oxidant. This chemoselective reaction was reported by the Foss Jr. *et al.* in 2019. No over oxidation products were observed as reported by the authors. This strategy was also utilized for late-stage oxidation in the synthesis of methyl indoprofen.



2.1.3 Origin of the present work:

Selective oxidation of benzylic C-H bond of cyclic amines is an important area in organic chemistry as the corresponding products, the lactams serve as the important building block and also an important core structure in many drug molecules. Many efficient methods are known for the synthesis of lactams but these reactions suffer huge drawbacks such as harsh conditions, use of metal-based catalysts, need of stoichiometric amounts of catalyst or oxidants, and produces large amounts of by-product.[17] Hence, a catalytic system utilizing oxygen as a terminal oxidant along with the use of an organocatalyst was much anticipated in the context of green chemistry.

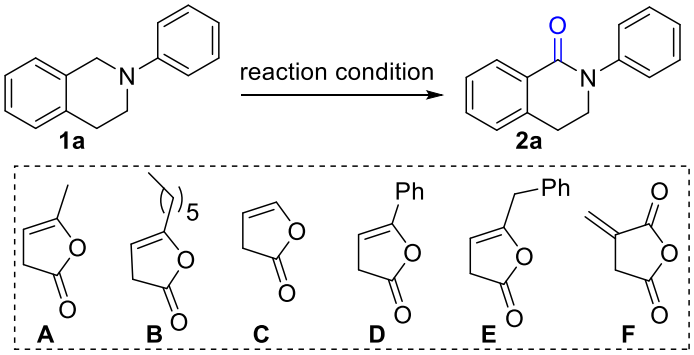
2.1.4 Objectives:

In nature, oxidative reactions play a vital important role and are also used in the fundamental transformations in chemical synthesis. Also, amine to lactam is an attractive synthetic target with a detailed account of the widest appearance in natural products and biologically active molecules.[18] Lactams are also used as one of the useful synthons in organic synthesis. There are many methods in literature by employing molecular oxygen as an oxidant but mainly with metal reagents/catalysts.[19,20] These inspire us, to design an efficient, green, and atom economical oxidative reactions by applying O_2. In our previous chapter I, we have discussed the use of α-angelica lactone as a vinylogous nucleophile. Here, for the first time, we demonstrate the use of α-angelica lactone as an organocatalyst. To validate our proposal, we have chosen *α*-CH_2-oxygenation of *N*-aryl tetrahydroisoquinolines to the corresponding lactams. However, some challenges need to be addressed. For example, α-angelica lactone has never been employed as an organocatalyst. Another issue was the reactivity of the benzylic position of amines. In general, the nitrogen center is more reactive than carbon. Also, after the formation of iminium intermediate, there is a possibility for the formation of the undesired product like oxidative Mannich-type reaction as reported by Doyle and others.[21] Finally, controlling the chemoselectivity and over oxidation of tetrahydroisoquinolines was also a matter of concern.

2.1.5 Results and discussion

We started the optimization of reaction conditions by choosing *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** as a model substrate. Initially, the reaction was carried out with **1a** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in tetrahydrofuran (THF) and α-angelica lactone (25 mol%) (**A**) as a catalyst. The reaction was performed at room temperature under an oxygen atmosphere. After a period of 36 h, the corresponding benzolactam product **2a** was obtained in 41% yield when 0.1 mmol of DABCO was used (Table 1, entry 1). Increasing the DABCO quantity to 2 and 3 equivalents did affect the yield. The yield was improved to 58 and 81% respectively (Table 1, entries 2 & 3). A substantial decrease in chemical yield (49%) was observed by using 10 mol% catalyst (Table 1, entry 4). While only a slight increase in yield was noted when 50 mol% of **A** was used (Table 1, entry 5). Next, lactones **B-E** were investigated as potential catalysts for this transformation. The corresponding product was obtained in all the cases but in lower yields as compared to catalyst **A** (Table 1, entries 6-9). However, by using itaconic anhydride **F** as a catalyst, we didn't observe any oxidation product (Table 1, entry 10). Next, the effect of different solvents and bases on this reaction was studied. In the case of toluene, the product **2a** was obtained in 76% yield (Table 1, entry 11). The reaction worked very sluggishly in case of using protic solvents, such as CH_3CN, DMF, DMSO, and MeOH. Product **2a** was obtained in either trace or very poor yields (Table 1, entries 12-15). Moderate yield of *N*-phenyl tetrahydroisoquinolinone was obtained when the reaction was conducted in acyclic ethers such as Et_2O and MTBE (Table 1, entries 16-17). The product was obtained in 56 and 45% respectively. Switching to bases like NEt_3, NMM, and pyridine to carry out the reaction proved to be less efficient in respect of time and yield. Inorganic base Na_2CO_3 was totally inactive under this reaction condition (Table 1, entries 18–21). Hence for the benzylic oxidation of *N*-phenyl tetrahydroisoquinoline (**1a**) to *N*-phenyl tetrahydroisoquinolinone (**2a**) in the presence of 25 mol% of angelica lactone (**A**) in THF (0.5 mL) at room temperature turned out to be the optimum reaction condition.

Table 1: Optimization studies [a]

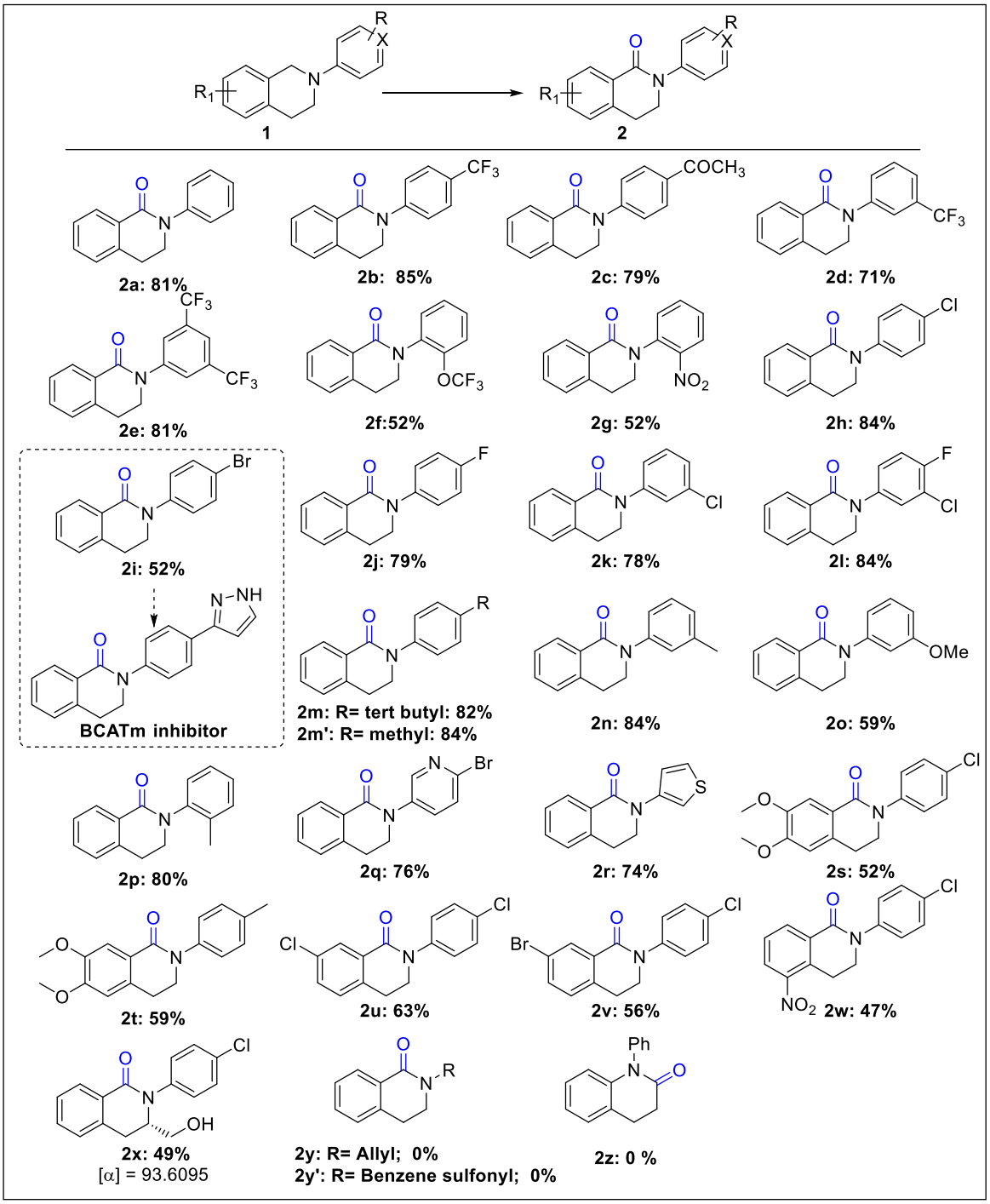


Entry	Base	Solvent	Catalyst	Yield [%][b]
1[c]	DABCO	THF	A	41
2[d]	DABCO	THF	A	58
3	**DABCO**	**THF**	**A**	**81**
4[e]	DABCO	THF	A	49
5[f]	DABCO	THF	A	85
6	DABCO	THF	B	72
7	DABCO	THF	C	67
8	DABCO	THF	D	63
9	DABCO	THF	E	54
10	DABCO	THF	F	ND
11	DABCO	Toluene	A	76
12	DABCO	CH_3CN	A	Trace
13	DABCO	DMF	A	<10
14	DABCO	DMSO	A	11
15	DABCO	MeOH	A	13
16	DABCO	Et_2O	A	56
17	DABCO	MTBE	A	45
18	Et_3N	THF	A	44
19	NMM	THF	A	40
20	Pyridine	THF	A	18
21	Na_2CO_3	THF	A	trace

[a] Reaction condition: **1a** (0.1 mmol), DABCO (0.3 mmol), catalyst **A** (25 mol %), in solvent (0.5 mL), at room temperature for 36 h under O_2 (balloon) atmosphere. [b] Isolated yield (%). [c] 0.1 mmol of DABCO was used. [d] 0.2 mmol of DABCO was used. [e] 10 mol% of **A** was used. [f] 50 mol% of **A** was used. N.D. = not determined.

By employing this optimized reaction condition, the substrate scope for the oxidation reaction of different tetrahydroisoquinoline derivatives was investigated and the results are summarized in table 2. A number of reactions were carried out using various *N*-aryl/heteroaryl tetrahydroisoquinolines **1a-x** and the corresponding tetrahydroisoquinolinones **2a-x** were obtained in good to excellent chemical yields. The reaction tolerated various electron-withdrawing groups such as $–CF_3$, $–COCH_3$ at the *para* and *meta*-position of *N*-phenyl ring of tetrahydroisoquinoline. The corresponding oxidation products **2b-2e** were obtained in good to excellent yields (71-85%). The product **2c** which was obtained in 79% yield is mention-worthy because of the presence of additional keto functional group which can be used for further transformation. Next, the role of an electron-donating ($-OCF_3$) and withdrawing group ($-NO_2$) substitution at the *ortho*-position on the *N*-phenyl ring of tetrahydroisoquinolines was tested. We observed corresponding products **2f-2g** in moderate yields (52% each). The decrease in yield was plausibly because of the steric hindrance of substitution on the *N*-phenyl ring at *ortho*-position. Likewise, halo groups substituted onthe *N*-phenyl ring of tetrahydroisoquinolines was also evaluated. The corresponding oxidation products **2h-2l** were obtained in moderate to good yields (52-84%). The product **2i** where a new carbon-bromine bond was created was obtained in 52% yield is a known precursor for the synthesis of BCATm inhibitor.[22] The presence of electron-donating groups such as *tert*-butyl, methyl, and methoxy at *para*, *meta*, and *ortho*-positions of the *N*-phenyl ring of tetrahydroisoquinolines was also evaluated. The corresponding oxidation products **2m-2p** were obtained in 59-84% yields. The present protocol was also extended to heteroaryl groups substituents at *N*-center. The corresponding oxidation products **2q** and **2r** were obtained in 76 and 74% yields respectively. Further, a substrate with substitution on the attached aryl ring of tetrahydroisoquinoline moiety, 6, 7- dimethoxy *N*-4-chlorophenyl and *N*-4-methyl phenyl- 1, 2, 3, 4-tetrahydroisoquinolines was also performed. The corresponding lactams **2s** and **2t** were obtained in 52% and 59% yields. Likewise, 7-chloro *N*-4-chlorophenyl, 7-bromo *N*-4-chlorophenyl, and 5-nitro *N*-4-chlorophenyl-1, 2, 3, 4-tetrahydroisoquinolines gave corresponding lactams **2u**, **2v** and **2w** in 63, 56 and 47% yields, respectively. Similarly, our protocol was also suitable for chiral molecules, such as (*S*)-1,2,3,4-tetrahydro-3-isoquinolinemethanol substituted with *N*-4-Chlorophenyl to give the corresponding lactam **2x** in 49% yield. Here we observed that the optical activity retained as such and the methylene hydroxy group also remained untouched in **1x**.

Table 2: Substrate scope [a,b]

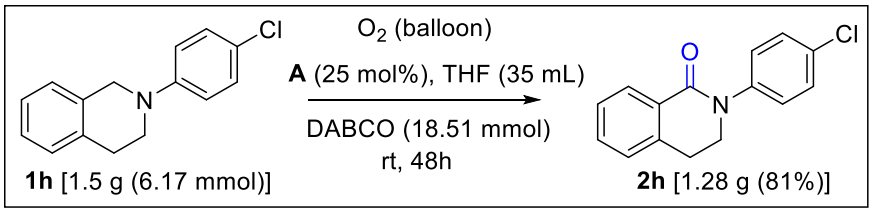


[a] Reaction conditions: **1** (0.1 mmol), DABCO (0.3 mmol), **A** (25 mol %), THF (0.5 mL), room temperature for 36 h under O_2 atmosphere (balloon). [b] Isolated yields.

However, substrates like *N*-allyl and *N*-phenyl sulfonyl-protected compound **1y** and **1y′** remained unreactive under this condition. Also, our present protocol was not compatible with

N-phenyl tetrahydroquinoline and it failed to give product **2z**. Next, to check the feasibility of this developed protocol in preparative synthesis, the reaction was examined in a gram scale synthesis. Accordingly, when 1.5 g of **1h** was treated under the optimized reaction condition, the corresponding product **2h** was obtained in 81% isolated yield (Scheme 2).

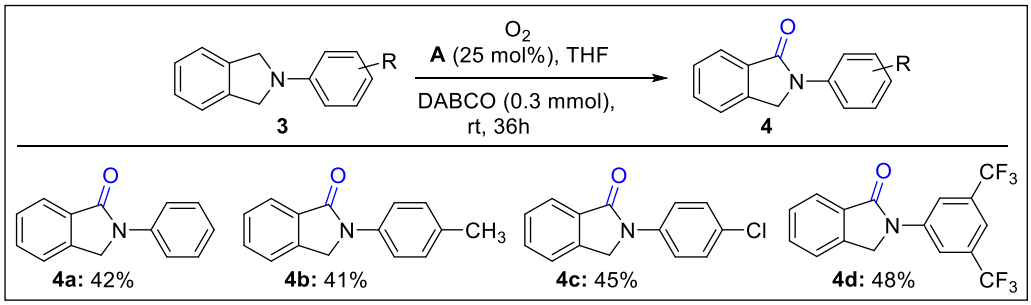
Scheme 2: Scale-up synthesis of 2h



To further extend the scope of this benzylic oxidation protocol, next we focused our attention on the α-oxygenation of isoindolines **3** to the corresponding oxidation products isoindolinones **4**. To our delight, product **4a-d** were obtained 41-48% yield by using the same optimized reaction condition which was used in the case of isoquinolines (Table 3). Another notable point of this protocol is excellent chemoselectivity. In all the cases, no over oxidation product like *N*-phenyl phthalimide was detected by GC-MS and NMR studies.

It is mention-worthy that isoindolinone core is present in many bioactive molecules such as indoprofen[23] and indobufen.[24] These are mainly known for anti-inflammatory drug and platelet aggregation inhibitors. Indobufen is at present in phase 4 clinical trial.[25]

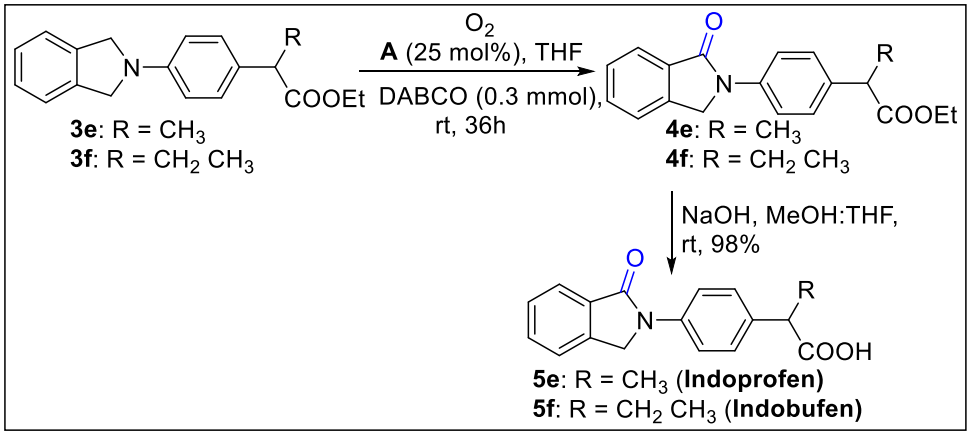
Table 3: α-Oxygenation of isoindolinones [a,b]



[a] Reaction conditions: As in Table 2. [b] Isolated yields.

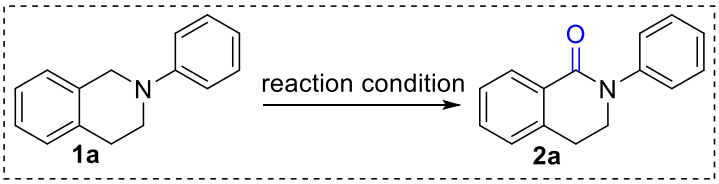
Applying the present optimized reaction condition on compound **3e-f**, the corresponding lactams **4e** and **4f** were obtained in 44% and 38% yields, respectively. Hydrolysis of **4e** and **4f** under basic condition provided indoprofen (**5e**) and Indobufen (**5f**) (Scheme 3).

Scheme 3: Application in the synthesis of Indoprofen and Indobufen



To understand the reaction mechanism, we have performed some control experiments which are summarised in table 4. Presence of base and catalyst **A** is a must for the progress of the reaction. In the absence of base/catalyst, the starting material remained as it was (Table 4, entry 1). Similar observation, i.e. absence of any conversion of starting material (**1a**) was also noted when the reaction was performed under an inert atmosphere such as N_2 or argon. These experiments clearly indicate that the oxygen atom source in lactam moiety might be coming from either air or moisture (Table 4, entry 2). To confirm the source of lactam oxygen, the reaction was performed in water as a solvent. But due to poor solubility of the reactants in water, no product formation was observed (Table 4, entry 3). Hence, we performed the reaction in the presence of 4 equivalents of H_2O^{18} in THF. Still, we didn't observe O-18 labeled product in the mass spectrum (m/z for $C_{15}H_{13}N$ (^{18}O) = 225) (Table 4, entry 4). This experiment gives a clear idea that the source of oxygen in lactam is from molecular O_2. To check the reaction pathway is whether ionic or radical, we performed reactions in the presence of radical scavenger. Thus, when stoichiometric amounts of either TEMPO or BHT was used, yields of the product dropped to <10%. These results clearly indicate that our reaction pathway includes radical intermediates (Table 4, entry 5). Moreover, when the reaction was performed in the presence of $CuCl_2$, a trace amount of product was detected. This result indicates that there is the involvement of single-electron processes (Table 4, entry 6).

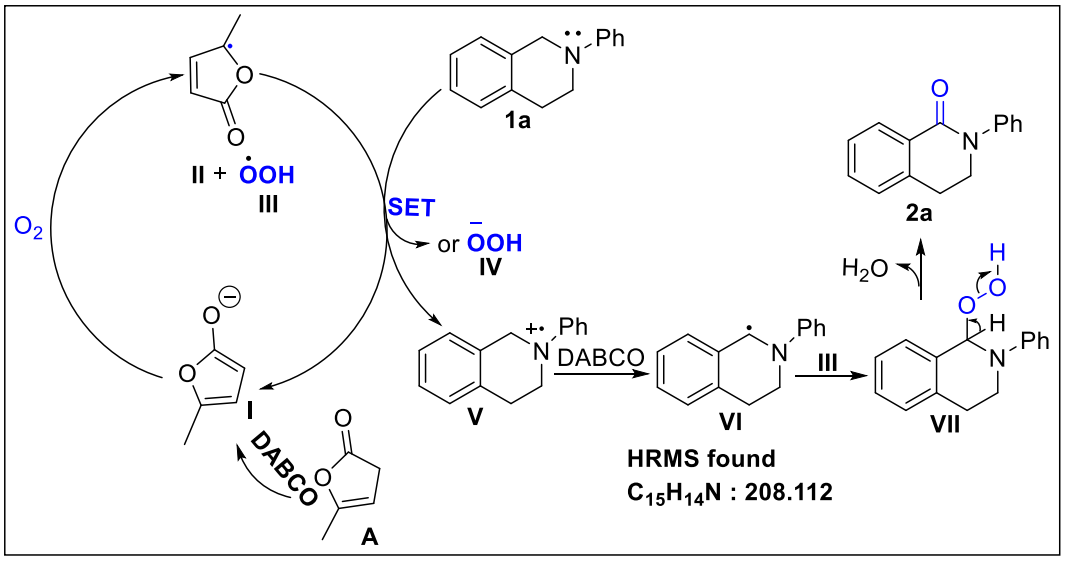
Table 4: Mechanistic investigations



Entry	Condition	Result	Conclusion
1	No base/No Cat. **A**	No reaction	Base and Cat. **A** required
2	N_2 or Ar atm.	No reaction	Oxygen source needed
3	H_2O as solvent	No reaction	H_2O is not the source
4	THF:H_2O^{18} (4 equiv; 492 µL:8 µL)	>98% unlabeled **2a**	No O^{18} labeled
5	TEMPO or BHT (1 equiv)	<10% of **2a**	Presence of radical species
6	$CuCl_2$ (1 equiv)	Trace of **2a**	Single-electron

Based on the results obtained from the control experiments and previous reports,[8,26] a plausible mechanism for this transformation is proposed in scheme 4. Firstly, deprotonation of lactone **A** by DABCO gives dienolates species **I**.

Scheme 4: Proposed mechanism



This dienolate reacts with triplet oxygen[27] to form radical intermediate **II** and peroxy intermediate **III**. In the next step, a single electron transfer (SET) from tetrahydroisoquinoline **1a** to radical intermediates **II** or **III** gives radical cation **V**[8,28] and **I** or **IV**. Deprotonation from this radical cation **V** by DABCO leads to a more stable radical **VI**. The presence of radical

VI in the reaction was confirmed by HRMS analysis of the crude reaction mixture. Radical **VI** further reacts with peroxy radical **III** to provide the intermediate **VII**. Deprotonation by base and elimination of water from the intermediate **VII** furnished the final product **2a**.

2.1.6 Conclusion

We have demonstrated here for the first time that α-angelica lactone is an efficient catalyst for the direct oxidation of various *N*-aryl tetrahydroisoquinolines and isoindolines to corresponding lactams. The reaction proceeds with the very mild condition along with good chemical yields by employing molecular oxygen as oxidant. Also, the source of oxygen in lactam is from molecular oxygen. From the mechanistic study, it is evident that the present reaction follows the radical pathway which involves a peroxide species as intermediates. The present protocol was also successfully applied towards the direct synthesis of bioactive molecules like indoprofen and indobufen.

2.1.7 Experimental Section

A) General procedure for the synthesis of *N*-aryl/heteroaryl tetrahydroisoquinolines and isoindolines[29]

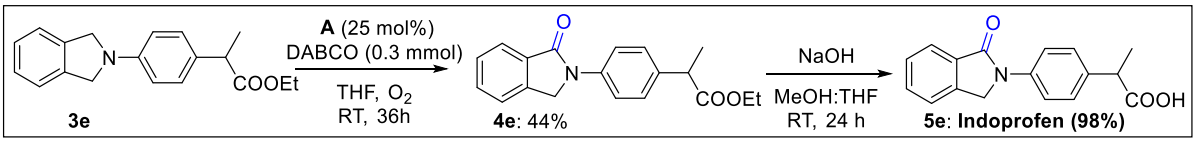
N-aryl/heteroaryl tetrahydroisoquinolines or *N*-aryl isoindolines were prepared by the following method.

To a solution of iodobenzene (10 mmol), 1,2,3,4-tetrahydroisoquinoline (15 mmol) and ethylene glycol (20 mmol) in *i*-PrOH (10 mL) was added CuI (1 mmol) and K_3PO_4 (20 mmol) sequentially under N_2 atmosphere. The reaction mixture was heated at 85 °C in an oil bath for 24 h and starting material consumption was monitored by TLC. After completion, the reaction mixture was cooled to rt, water (10 mL) was added followed by extraction with EtOAc (3×10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in *vacuo* to obtain a residue. The crude product was purified by flash column chromatography (10% Ethyl acetate/pet ether) to afford the product as solid. 2-(3-chloro-4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**(1i)** White solid (1.33 g, 23%); **^{1}H NMR (400 MHz, CDCl3)** δ 7.25 – 7.13 (m, 4H), 7.09 – 7.03 (m, 1H), 6.99 – 6.94 (m, 1H), 6.84 – 6.78 (m, 1H), 4.35 (s, 2H), 3.50 (t, J = 5.9 Hz, 2H), 3.00 (t, J = 5.8 Hz, 2H).

B) General procedure for the oxidation of *N*-aryl/heteroaryl tetrahydroisoquinolines and isoindolines

To a solution of *N*-aryl/heteroaryl tetrahydroisoquinolines or *N*-aryl isoindolines (0.1 mmol) and DABCO (0.3 mmol) in THF (0.5 mL) was added α-angelica lactone (25 mol%, 2.3 µL) at room temperature. The vial was equipped with a balloon containing O_2 gas and the reaction mixture was stirred at room temperature for 36 h. The progress of the reaction was monitored by TLC. When no further progress was noticed, the reaction mixture was diluted with dichloromethane (2 mL) and washed with water (2 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The products were purified on a silica gel column using 20% pet ether/EtOAc.

C) General procedure for the synthesis of Indoprofen (3e-5e)



a) Synthesis of ethyl 2-(4-(isoindolin-2-yl) phenyl) propanoate (3e)[30]

An oven-dried 10 mL two neck round bottom flask equipped with a magnetic stir bar was charged with (±)-BINAP (5 mol %) and purged with argon. Anhydrous toluene (2 mL) was added and the mixture was heated to 100 °C with vigorous stirring until a homogenous solution was obtained. The solution was cooled to room temperature, $Pd(OAc)_2$ (5 mol%) was added and the mixture was stirred vigorously for 1 min. Ethyl 2-(4-bromophenyl)propanoate (0.25 mmol), isoindoline (0.3 mmol) and potassium *tert*-butoxide (0.35 mmol) were added sequentially and the mixture was heated at 100 °C. After 30 min, the mixture was cooled to room temperature, diluted with EtOAc (2 mL), and filtered through Celite and this crude reaction mixture was purified by flash chromatography using 20% pet ether/EtOAc to give compound **3e**.

(b) Synthesis of ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) propanoate (4e)

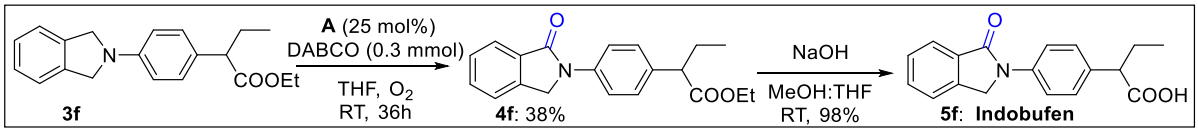
To a solution of ethyl 2-(4-(isoindolin-2-yl) phenyl) propanoate **3e** (0.1 mmol) and DABCO (0.3 mmol) in THF (0.5 mL) was added the α-angelica lactone (25 mol%, 2.3 µL) at room temperature. The vial was equipped with a balloon containing O_2 gas and the reaction was stirred at room temperature for 36 h. The resulting reaction mixture was monitored by TLC. Then the reaction mixture was diluted with dichloromethane (2 mL) and washed with water

(2 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using 20% pet ether/EtOAc which afforded compound **4e** in 44% yield.

(c) Synthesis of Indoprofen (5e)

Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) propanoate **4e** (9 mg, 0.03 mmol) was dissolved in MeOH (1 mL) and 2M NaOH (aq.) (1 mL) was added. THF was added until the reaction mixture was clear. The reaction mixture was stirred at rt and monitored by TLC. After the reaction was completed (24 h), the mixture was acidified using 3M HCl (5 mL). The product was extracted with ethylacetate (3×5 mL) and the combined EtOAc fractions were washed with brine and dried over $MgSO_4$. The solvent was removed and 8 mg of yellow solid of **5e** was obtained.

D) General procedure for the synthesis of Indobufen[30,31] (3f-5f)



The synthesis of indobufen was performed in a similar method as described above for Indoprofen.

E) Gram scale reaction procedure

To a solution of 2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (1.5 g, 6.17 mmol) and DABCO (2.0 g, 18.51 mmol) in THF (35 mL) was added α-angelica lactone (25 mol%, 139 µL) at room temperature. The round bottom flask was equipped with a balloon containing O_2 gas and the reaction mixture was stirred at room temperature for 48 h. The resulting reaction mixture was monitored by TLC. Then the reaction mixture was diluted with dichloromethane (5 mL) and washed with water (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL).The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified on a silica gel column using 10% EtOAc/pet ether in 81% (1.28 g) yield.

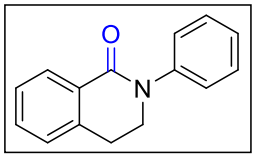
F) H_2O^{18} experiment procedure

H_2O^{18} was purchased from Sigma Aldrich (catalog no: 329878-250 mg) with 97% isotopic purity. The experiment was carried out according to the procedure reported for the oxidation of **1a** to **2a** using 4 equiv of H_2O^{18} and 492 µL THF. The percentage of ^{18}O enrichment was examined by GC-MS spectrometry as shown in the following spectra below. The calculated data showed no enrichment of ^{18}O.

Reaction condition: 2-Phenyl-1, 2,3,4-tetrahydroisoquinoline (0.1 mmol), DABCO (0.3 mmol), α-angelica lactone (25 mol%, 2.3 µL) and THF (492 µL) and H_2O^{18} (8 µL) were added in a Schlenk tube inside the glove box. The reaction mixture was stirred under O_2 (1 atm) at 25 °C for 36 h. No isotopic enrichment in product **2a** was determined by GC-MS.

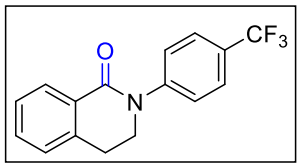
2.1.8 Characterization data of compounds

2-Phenyl-3,4-dihydroisoquinolin-1(2H)-one (2a):



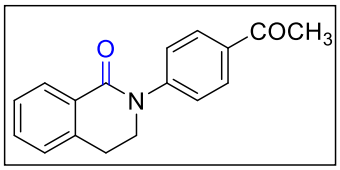
White solid (18.0 mg, 81%); TLC R_f = 0.5 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 7.5 Hz, 1H), 7.48-7.45 (m, 1H), 7.42-7.36 (m, 5H), 7.24 (d, *J* = 7.5 Hz, 2H), 4.00 (t, *J* = 6.1 Hz, 2H), 3.15 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.24, 143.15, 138.34, 132.06, 129.75, 128.94, 128.78, 127.22, 126.97, 126.28, 125.36, 49.45, 28.65. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{14}NO$ [M+H] 224.1075 found 224.1070.

2-(4-(Trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2b):



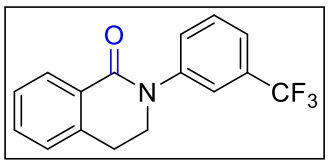
White solid (24.7 mg, 85%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.34-7.30 (m, 1H), 7.20-7.18 (m, 1H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.09 (t, *J* = 6.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.24, 146.08, 138.26, 132.47, 129.26, 128.90, 128.02, 127.39, 127.08, 125.955 (q, *J* = 6.3 Hz), 125.12, 124.011 (q, *J* = 271.69 Hz), 49.10, 28.51. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{13}F_3NO$ [M+H] 292.0949 found 292.0944.

2-(4-Acetylphenyl)-3,4-dihydroisoquinolin-1(2H)-one (2c):



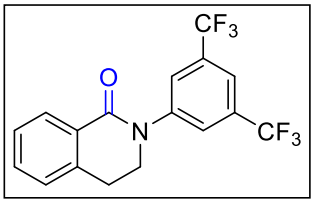
Yellow solid (20.9 mg, 79%); TLC R_f = 0.4 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.50 (dd, *J* = 18.9, 7.9 Hz, 3H), 7.41-7.38 (m, 1H), 7.26 (d, *J* = 6.8 Hz, 1H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.17 (t, *J* = 6.2 Hz, 2H), 2.61 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 197.16, 164.16, 147.25, 138.28, 134.36, 132.45, 129.35, 129.08, 128.91, 127.36, 127.06, 124.60, 49.02, 28.50, 26.61. **HRMS (ESI+) (*m/z*)** calcd for $C_{17}H_{16}NO_2$ [M+H] 266.1181 found 266.1176.

2-(3-(Trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2d):



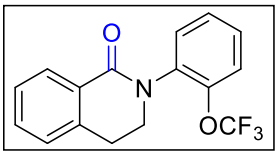
Yellow oil (20.6 mg, 71%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 7.6 Hz, 1H), 7.67 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.40-7.37 (m, 1H), 7.27 – 7.24 (m, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.16 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.29, 143.53, 138.30, 132.43, 131.29 (q, *J* = 32.4 Hz), 129.35, 129.25, 128.81, 128.65, 127.35, 127.11, 124.95, 122.78, 121.98, 49.21, 28.51. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{13}F_3NO$ [M+H] 292.0949 found 292.0944.

2-(3,5-bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2e):



Colorless oil (29.0 mg, 81%); TLC R_f = 0.7 (10% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 7.6 Hz, 1H), 7.90 (s, 2H), 7.74 (s, 1H), 7.54-7.50 (m, 1H), 7.42-7.39 (m, 1H), 7.31 – 7.24 (m, 1H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.20 (t, *J* = 6.1 Hz, 2H). **^{13}C NMR (101MHz, $CDCl_3$)** δ 164.38, 144.28, 138.23, 132.87, 132.05 (q, *J* = 33 Hz), 128.90, 128.68, 127.53, 127.23, 125.09, 124.46, 121.75, 119.39, 119.03, 49.01, 28.36. **HRMS (ESI+) (*m/z*)** calcd for $C_{17}H_{12}F_6NO$ [M+H] 360.0823 found 360.0818.

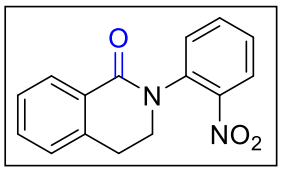
2-(2-(Trifluoromethoxy) phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2f):



Yellow oil (15.9 mg, 52%); TLC R_f = 0.5 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 7.7 Hz, 1H), 7.50-7.46 (m, 1H), 7.44 – 7.33 (m, 5H), 7.25 (d, *J* = 7.4 Hz, 1H), 3.88 (t, *J* = 6.0 Hz, 2H), 3.15 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.15, 144.80, 138.63, 135.37, 132.29,

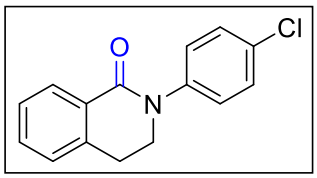
129.43, 129.10, 128.79, 128.68, 127.52, 127.23, 127.13, 121.69, 49.38, 28.52. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{13}F_3NO_2$ [M+H] 308.0898 found 308.0893.

2-(2-Nitrophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2g):



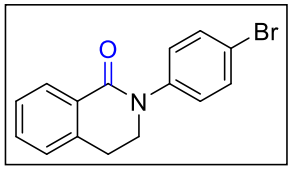
Yellow solid (13.9 mg, 52%); TLC R_f = 0.4 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (t, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.51-7.47 (m, 1H), 7.44-7.41 (m, 1H), 7.33-7.30 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 3.99 (t, *J* = 6.4 Hz, 2H), 3.12 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.33, 148.48, 144.00, 138.28, 132.68, 131.42, 129.42, 128.90, 127.44, 127.19, 120.70, 119.72, 49.08, 28.44. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{13}N_2O_3$ [M+H] 269.0926 found 269.0921 and calcd for $C_{15}H_{12}N_2O_3$ [M+Na] 291.0746 found 291.0740.

2-(4-Chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2h):



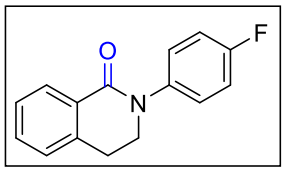
White solid (21.5 mg, 84%); TLC R_f = 0.6 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.49-7.46 (m, 1H), 7.39 – 7.31 (m, 5H), 7.24 (d, *J* = 7.5 Hz, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.14 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.22, 141.59, 138.26, 132.25, 131.57, 129.44, 128.99, 128.78, 127.29, 127.03, 126.57, 49.33, 28.55. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{13}ClNO$ [M+H] 258.0686 found 258.0680.

2-(4-Bromophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2i):



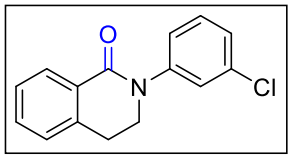
White solid (15.6 mg, 52%);TLC R_f = 0.6 (10% EtOAc/Hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.39-7.36 (m, 1H), 7.26 (dd, *J* = 14.5, 8.1 Hz, 3H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.14 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.16, 142.09, 138.25, 132.28, 131.94, 129.41, 128.78, 127.30, 127.05, 126.89, 119.43, 49.26, 28.54. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{13}BrNO$ [M+H] 302.0181 found 302.0175.

2-(4-Fluorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2j):



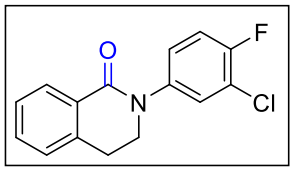
White solid (19.0 mg, 79%); TLC R_f = 0.6 (10% EtOAc/Hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.50-7.46 (m, 1H), 7.43 – 7.32 (m, 3H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.13 – 7.07 (m, 2H), 3.98 – 3.94 (m, 2H), 3.15 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.47, 162.01, 159.57, 139.11, 138.33, 132.25, 129.56, 128.82, 127.36, 127.23, 127.14, 127.09, 115.96, 115.73, 49.65, 28.67. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{13}FNO$ [M+H] 241.0981 found 242.0976 and calcd for $C_{15}H_{12}FNO$ [M+Na] 264.0801 found 264.0795.

2-(3-Chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2k):



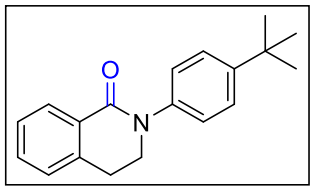
White solid (20.0 mg, 78%); TLC R_f = 0.6 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 7.7 Hz, 1H), 7.49-7.46 (m, 1H), 7.41 (s, 1H), 7.39-7.36 (m, 1H), 7.34 – 7.28 (m, 2H), 7.23 (dd, *J* = 11.1, 7.9 Hz, 2H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.14 (t, *J* = 6.4 Hz, 2H. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.19, 144.18, 138.28, 134.35, 132.33, 129.82, 129.38, 128.82, 127.31, 127.06, 126.33, 125.57, 123.50, 49.30, 28.54. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{13}ClNO$ [M+H] 258.0686 found 258.0680.

2-(3-Chloro-4-fluorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2l):



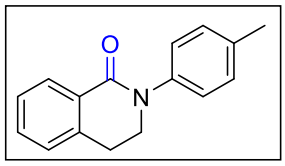
White solid (23.1 mg, 84%); TLC R_f = 0.8 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.50-7.46 (m, 2H), 7.40-7.37 (m, 1H), 7.28-7.24 (m, 2H), 7.19-7.16 (m, 1H), 3.96 (t, *J* = 6.3 Hz, 2H), 3.15 (t, *J* = 6.1 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.33, 155.18 (d, *J* = 249.4 Hz), 139.57, 138.21, 132.40, 129.19, 128.80, 127.75, 127.35, 127.09, 125.27 (d, *J* = 7.0 Hz), 121.05 (d, *J* = 18.7 Hz), 116.57 (d, *J* = 22.1 Hz), 49.46, 28.52. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{12}ONClF$ [M+H] 276.0592 found 276.0586.

2-(4-(*tert*-butyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one (2m):



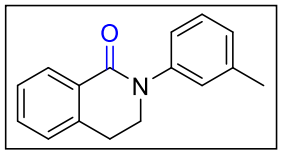
White solid (22.8 mg, 82%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.08 (d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 17.7, 7.5 Hz, 3H), 7.30-7.27 (m, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.17 – 7.14 (m, 1H), 3.90 (t, *J* = 6.5 Hz, 2H), 3.05 (t, *J* = 6.4 Hz, 2H), 1.25 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.34, 149.16, 140.50, 138.41, 132.05, 129.90, 128.81, 127.25, 127.02, 125.94, 124.82, 49.51, 34.63, 31.46, 28.71. **HRMS (ESI+) (*m/z*)** calcd for $C_{19}H_{22}NO$ [M+H] 280.1701 found 280.1696 and calcd for $C_{19}H_{21}NONa$ [M+Na] 302.1521 found 302.1515.

2-(*p*-tolyl)-3,4-dihydroisoquinolin-1(2H)-one (2m'):



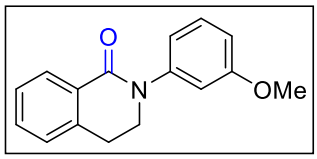
Yellow oil (19.9 mg, 84%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.39-7.35 (m, 1H), 7.30-7.27 (m, 1H), 7. 20 – 7.12 (m, 5H), 3.90 – 3.86 (m, 2H), 3.05 (t, *J* = 6.5 Hz, 2H), 2.28 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.36, 140.64, 138.40, 136.16, 132.04, 129.87, 129.64, 128.80, 127.25, 127.03, 125.30, 49.61, 28.72, 21.16. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{16}NO$ [M+H] 238.1232 found 238.1226.

2-(*m*-tolyl)-3,4-dihydroisoquinolin-1(2H)-one (2n):



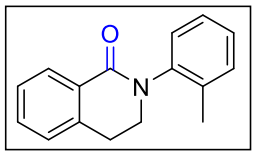
Yellow oil (19.9 mg, 84%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.40-7.36 (m, 1H), 7.31-7.27 (m, 1H), 7. 24-7.20 (m, 1H), 7.17 – 7.12 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 3.91 – 3.86 (m, 2H), 3.05 (t, *J* = 6.5 Hz, 2H), 2.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.33, 143.14, 138.91, 138.41, 132.09, 129.85, 128.90, 128.81, 127.27, 127.04, 126.30, 122.41, 49.60, 28.72, 21.53. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{16}NO$ [M+H] 238.1232 found 238.1226.

2-(3-Methoxyphenyl)-3,4-dihydroisoquinolin-1(2H)-one (2o):



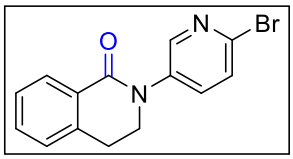
Yellow oil (14.9 mg, 59%); TLC R_f = 0.5 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 7.7 Hz, 1H), 7.47-7.44 (m, 1H), 7.38-7.35 (m, 1H), 7.32-7.29 (m, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.80 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.81 (s, 3H), 3.12 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.22, 160.00, 144.31, 138.33, 132.08, 129.73, 129.61, 128.75, 127.21, 126.99, 117.50, 112.18, 111.43, 55.40, 49.51, 28.63. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{16}NO2$ [M+H] 254.1181 found 254.1176.

2-(*o*-tolyl)-3,4-dihydroisoquinolin-1(2H)-one (2p):



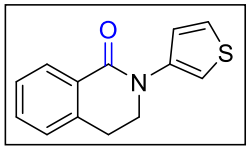
Yellow oil (18.9 mg, 80%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.32 – 7.29 (m, 1H), 7.28 – 7.23 (m, 3H), 7.23 – 7.19 (m, 1H), 4.00 – 3.93 (m, 1H), 3.78 – 3.70 (m, 1H), 3.29 – 3.21 (m, 1H), 3.14 – 3.06 (m, 1H), 2.29 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.87, 142.15, 138.39, 135.38, 131.99, 131.05, 129.66, 128.70, 127.69, 127.21, 127.07, 127.02, 126.70, 49.38, 28.80, 18.17. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{16}NO$ [M+H] 238.1232 found 238.1226.

2-(6-Bromopyridin-3-yl)-3,4-dihydroisoquinolin-1(2H)-one (2q):



White solid (22.9 mg, 76%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.42 (d, *J* = 2.7 Hz, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 7.71 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.41-7.37 (m, 1H), 7.28 – 7.25 (m, 1H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.18 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.35, 145.99, 139.14, 138.31, 138.15, 135.41, 132.79, 128.92, 128.84, 127.85, 127.54, 127.28, 49.03, 28.45. **HRMS (ESI+) (*m/z*)** calcd for $C_{14}H_{12}BrN_2O$ [M+H] 303.0133 found 303.0128.

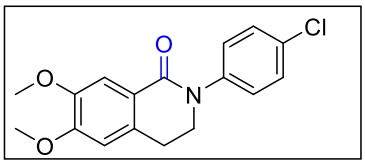
2-(Thiophen-3-yl)-3,4-dihydroisoquinolin-1(2H)-one (2r):



White solid (16.9 mg, 74%); TLC R_f = 0.6 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.47-7.44 (m, 1H), 7.38 (d, *J* = 6.6 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.23 (d, *J* = 7.4 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.12 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.53, 141.23, 137.99, 132.10,

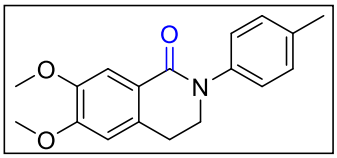
129.68, 128.70, 127.27, 126.90, 124.15, 123.87, 113.96, 48.98, 28.30. **HRMS (ESI+) (*m/z*)** calcd for $C_{13}H_{12}NOS$ [M+H] 230.0640 found 230.0634.

2-(4-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (2s):



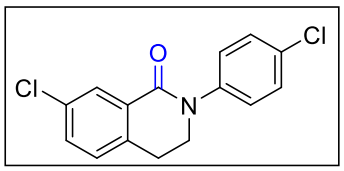
White solid (16.4 mg, 52%); TLC R_f = 0.4 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.64 (s, 1H), 7.34 (dd, *J* = 19.1, 8.6 Hz, 4H), 6.69 (s, 1H), 3.94 (d, *J* = 8.0 Hz, 8H), 3.07 (t, *J* = 6.2 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.23, 152.32, 148.17, 141.76, 132.10, 131.34, 128.91, 126.50, 121.87, 110.81, 109.23, 56.11, 49.52, 28.19. **HRMS (ESI+) (*m/z*)** calcd for $C_{17}H_{16}ClNO_3$ [M+H] 318.0897 found 318.0891.

6,7-dimethoxy-2-(*p*-tolyl)-3,4-dihydroisoquinolin-1(2H)-one (2t):



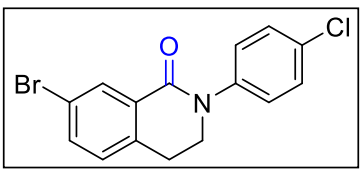
Yellow solid (17.5 mg, 59%); TLC R_f = 0.5 (40% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 (s, 2H), 7.23 (dd, *J* = 18.6, 7.8 Hz, 9H), 6.69 (s, 2H), 3.94 (d, *J* = 6.8 Hz, 16H), 3.06 (t, *J* = 6.5 Hz, 4H), 2.36 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.27, 152.07, 148.09, 140.77, 135.87, 132.05, 129.49, 125.20, 122.33, 110.90, 109.21, 56.09, 49.74, 28.29, 21.04. **HRMS (ESI+) (*m/z*)** calcd for $C_{18}H_{20}NO_3$ [M+H] 298.1443 found 298.1438.

7-chloro-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2u):



White solid (18.3 mg, 63%); TLC R_f = 0.5 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.11 (s, 1H), 7.41 (dd, *J* = 20.4, 7.1 Hz, 3H), 7.33 (s, 2H), 7.20 (d, *J* = 7.5 Hz, 1H), 3.97 (s, 2H), 3.12 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.04, 141.23, 136.47, 133.42, 132.20, 131.92, 130.99, 129.13, 128.73 128.52, 126.58, 49.27, 28.05. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{12}ONCl_2$ [M+H] 292.0296 found 292.0290.

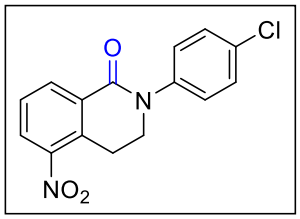
7-Bromo-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (2v):



White solid (18.7 mg, 56%); TLC R_f = 0.6 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.26 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.6 Hz,

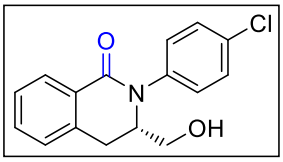
2H), 3.95 (t, *J* = 5.8 Hz, 2H), 3.09 (t, *J* = 5.9 Hz, 2H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 141.22, 136.99, 135.09, 131.89, 131.65, 131.19, 129.11, 128.80, 126.55, 121.15, 49.17, 28.07. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{12}ON^{79}BrCl$ [M+H] 335.9791 found 335.9785 and calcd for $C_{15}H_{12}ON^{81}BrCl$ [M+H] 337.9770 found 337.9765.

2-(4-chlorophenyl)-8-nitro-3,4-dihydroisoquinolin-1(2H)-one (2w):



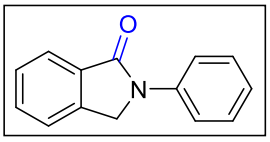
White solid (14.2 mg, 52%); TLC R_f = 0.4 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.48 (d, *J* = 7.7 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 162.19, 147.51, 140.61, 134.00, 133.60, 132.15, 129.76, 129.22, 128.05, 127.73, 126.30, 48.17, 25.81. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{12}O_3N_2Cl$ [M+H] 303.0536 found 303.0531.

(S)-2-(4-Chlorophenyl)-3-(hydroxymethyl)-3,4-dihydroisoquinolin-1(2H)-one (2x):



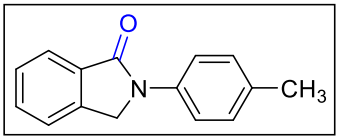
White solid (14.0 mg, 49%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 7.7 Hz, 1H), 7.48-7.45 (m, 1H), 7.35 (d, *J* = 8.7 Hz, 3H), 7.30 – 7.26 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 4.06 – 4.01 (m, 1H), 3.67 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.47 (ddd, *J* = 22.0, 13.3, 7.2 Hz, 2H), 3.19 (dd, *J* = 16.2, 1.9 Hz, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 163.87, 140.58, 136.17, 132.56, 129.41, 129.29, 128.83, 128.69, 128.51, 128.03, 127.28, 61.54, 60.47, 29.55. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{14}ClNO_2$ [M+H] 288.0791 found 288.0786.

2-Phenylisoindolin-1-one (4a):



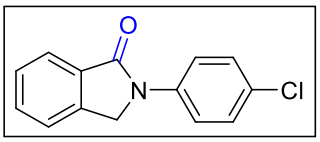
Yellow solid (8.7 mg, 42%); TLC R_f = 0.5 (25% EtOAc/Pet ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.55-7.52 (m, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.39-7.35 (m, 2H), 7.19-7.10 (m, 1H), 4.81 (s, 2H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 167.65, 140.19, 139.95, 139.56, 133.31, 132.18, 129.27, 128.49, 124.61, 124.28, 122.71, 119.61, 50.85. **HRMS (ESI+) (*m/z*)** calcd for $C_{14}H_{12}NO$ [M+H] 210.0919 found 210.0913 and $C_{14}H_{11}NO$ [M+H] 210.0738 found 232.0733.

2-(*p*-tolyl) isoindolin-1-one (4b):



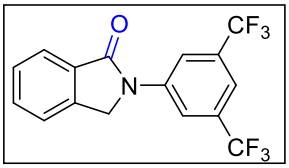
White solid (9.1 mg, 41%); TLC R_f = 0.5 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.63-7.59 (m, 1H), 7.53 (d, *J* = 7.1 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 4.86 (s, 2H), 2.38 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.40, 140.15, 136.97, 134.24, 133.36, 131.78, 129.69, 128.34, 124.11, 122.57, 119.68, 50.90, 20.87. **HRMS (ESI+) (*m/z*)** calcd for $C_{15}H_{14}NO$ [M+H] 224.1075 found 224.1070 and calcd for $C_{15}H_{13}NO$ [M+Na] 246.0895 found 246.0889.

2-(4-Chlorophenyl) isoindolin-1-one (4c):



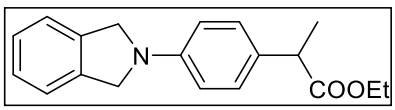
White solid (10.9 mg, 45%); TLC R_f = 0.5 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.86 (d, *J* = 8.1 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.54 (dd, *J* = 11.0, 4.4 Hz, 1H), 7.46 (d, *J* = 6.7 Hz, 2H), 7.37 – 7.28 (m, 2H), 4.78 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.63, 139.96, 138.18, 133.02, 132.41, 129.65, 129.26, 128.63, 124.34, 122.73, 120.55, 50.75. **HRMS (ESI+) (*m/z*)** calcd for $C_{14}H_{11}ClNO$ [M+H] 244.0529 found 244.0524.

2-(3,5-bis(trifluoromethyl) phenyl) isoindolin-1-one (4d):



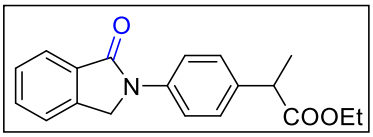
White solid (16.5 mg, 48%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.43 (s, 2H), 7.96 (d, *J* = 7.0 Hz, 1H), 7.72 – 7.51 (m, 4H), 4.95 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.93, 140.97, 139.62, 133.09, 132.71, 132.21, 128.92, 124.60, 122.84, 118.35, 117.31, 50.46. **HRMS (ESI+) (*m/z*)** calcd for $C_{16}H_{10}F_6NO$ [M+H] 346.0667 found 346.0661.

Ethyl 2-(4-(isoindolin-2-yl) phenyl) propanoate (3e):



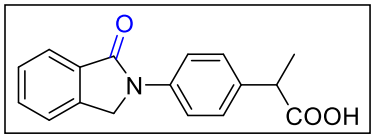
Yellow solid (57 mg, 64%); TLC R_f = 0.8 (20% EtOAc/Pet ether); **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.40 – 7.12 (m, 6H), 6.78 – 6.46 (m, 2H), 4.64 (s, 4H), 4.24 – 3.96 (m, 2H), 3.64 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). **HRMS (ESI+) (*m/z*)** calcd for $C_{19}H_{22}NO_2$ [M+H] 296.1651 found 296.1645.

Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) propanoate (4e):



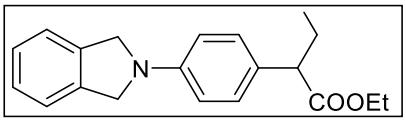
Yellow solid (13.6 mg, 44%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 7.3 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 6.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 4.86 (s, 2H), 4.17 – 4.11 (m, 2H), 3.72 (d, *J* = 7.2 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.60, 167.59, 140.17, 138.48, 136.87, 133.25, 132.18, 128.50, 128.33, 128.21, 128.06, 124.27, 122.72, 119.75, 60.91, 50.83, 45.09, 18.65, 14.22. **HRMS (ESI+) (*m/z*)** calcd for $C_{19}H_{20}NO_3$ [M+H] 310.1443 found 310.1438.

Indoprofen (5e):[32]



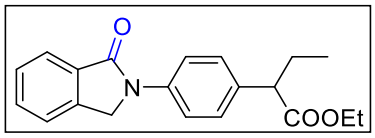
Yellow solid (12.0 mg, 98%); TLC R_f = 0.5 (10% DCM/MeOH); **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.33 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.58 – 7.53 (m, 1H), 7.35 (dd, *J* = 9.0, 2.1 Hz, 2H), 5.02 (s, 2H), 3.71 (d, *J* = 7.1 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H). **HRMS (ESI+) (*m/z*)** calcd for $C_{17}H_{16}NO_3$ [M+H] 282.1130 found 282.1125.

Ethyl 2-(4-(isoindolin-2-yl) phenyl) butanoate (3f):



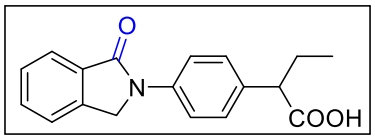
Yellow solid (47 mg, 61%); TLC R_f = 0.7 (20% EtOAc/Pet ether); **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.32 (d, *J* = 2.8 Hz, 4H), 7.26 (s, 1H), 7.20 (s, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 4.64 (s, 4H), 4.14 (dd, *J* = 14.2, 7.1 Hz, 3H), 3.54 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 6H). **HRMS (ESI+) (*m/z*)** calcd for $C_{20}H_{24}NO_2$ [M+H] 310.1807 found 310.1802.

Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) propanoate (4f):



Yellow solid (12.2 mg, 38%); TLC R_f = 0.5 (25% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 – 7.90 (m, 1H), 7.86 – 7.81 (m, 2H), 7.64 – 7.58 (m, 1H), 7.54 – 7.49 (m, 2H), 7.35 (dd, *J* = 8.9, 2.3 Hz, 2H), 4.87 (s, 2H), 4.16 (dd, *J* = 14.4, 6.9 Hz, 3H), 3.63 (s, 2H), 1.27 (t, *J* = 6.9 Hz, 6H). **HRMS (ESI+) (*m/z*)** calcd for $C_{20}H_{21}NO_3$ [M+Na] 346.1419 found 346.1414.

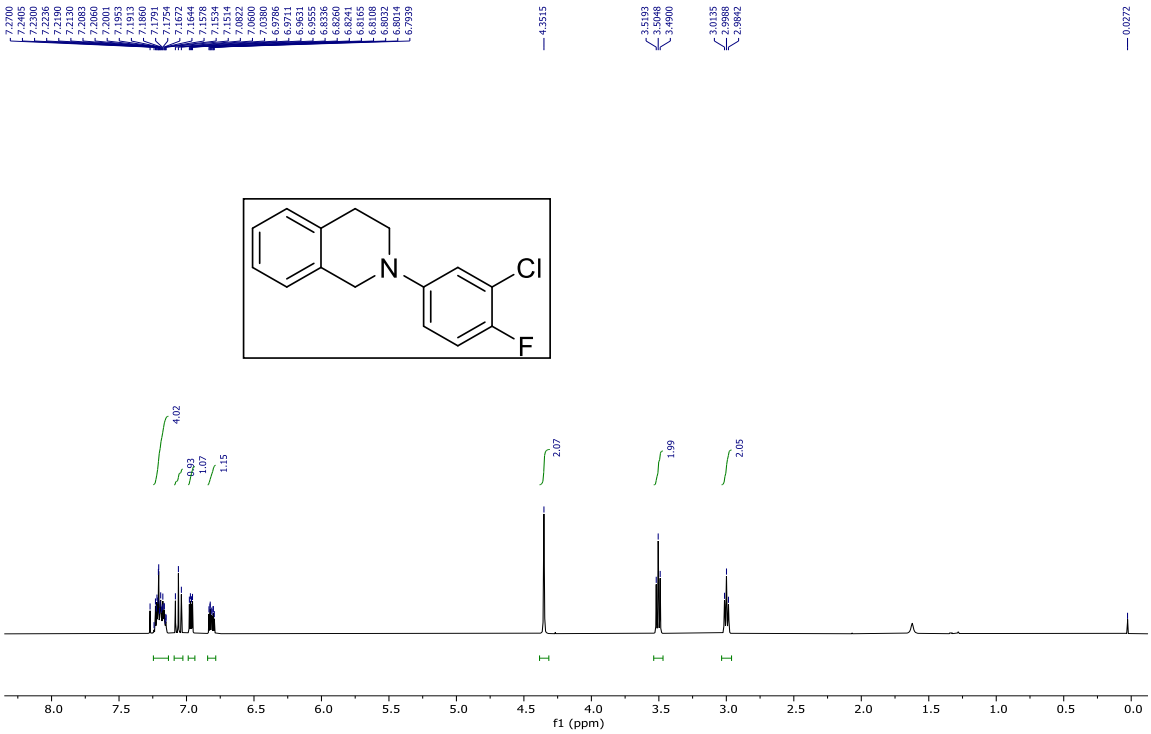
Indobufen (5f):[33]



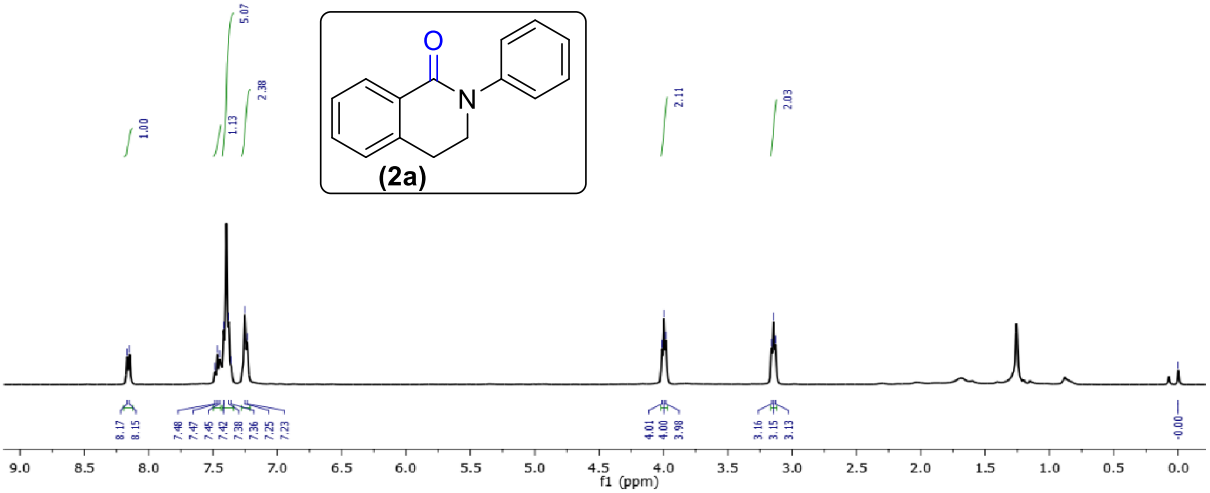
Yellow solid **(**10.9 mg, 98%); TLC R_f = 0.5 (10% DCM/MeOH); **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.80 (dd, *J* = 13.4, 8.1 Hz, 3H), 7.69 – 7.65 (m, 2H), 7.55 (s, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 5.02 (s, 2H), 3.50 (d, *J* = 5.5 Hz, 3H), 1.23 (s, 3H).**HRMS (ESI+) (*m/z*)** calcd for $C_{18}H_{18}NO_3$ [M+H] 296.1287 found 296.1281 and calcd for $C_{18}H_{17}NO_3$ [M+Na] 318.1106 found 318.1101.

2.1.9 Spectral data

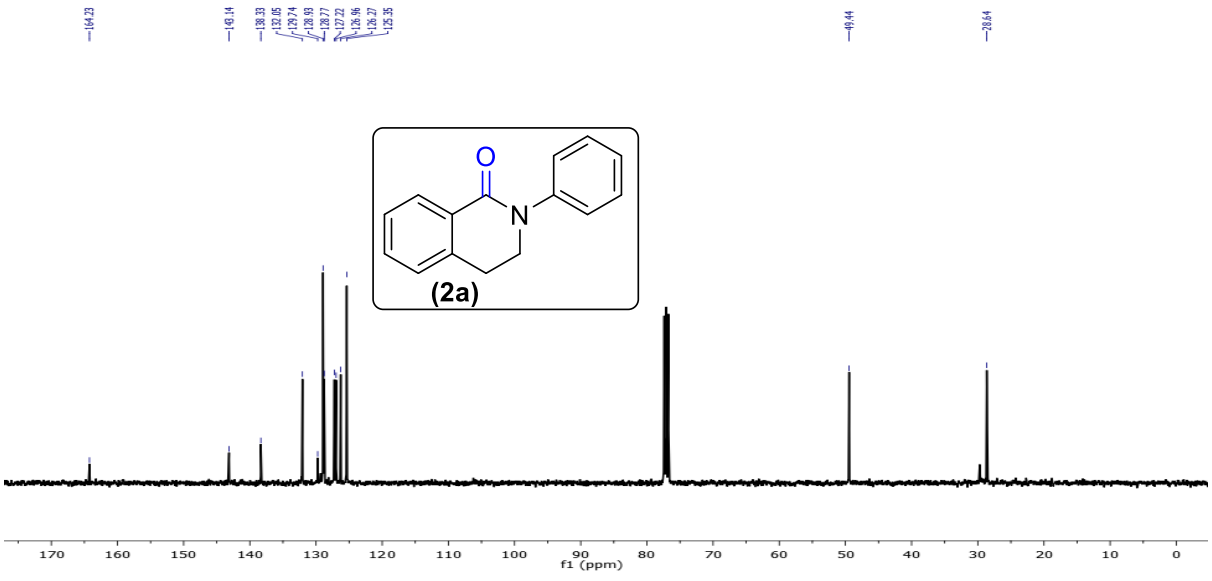
^{1}H NMR of 2-(3-chloro-4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline **(1i)** in $CDCl_3$



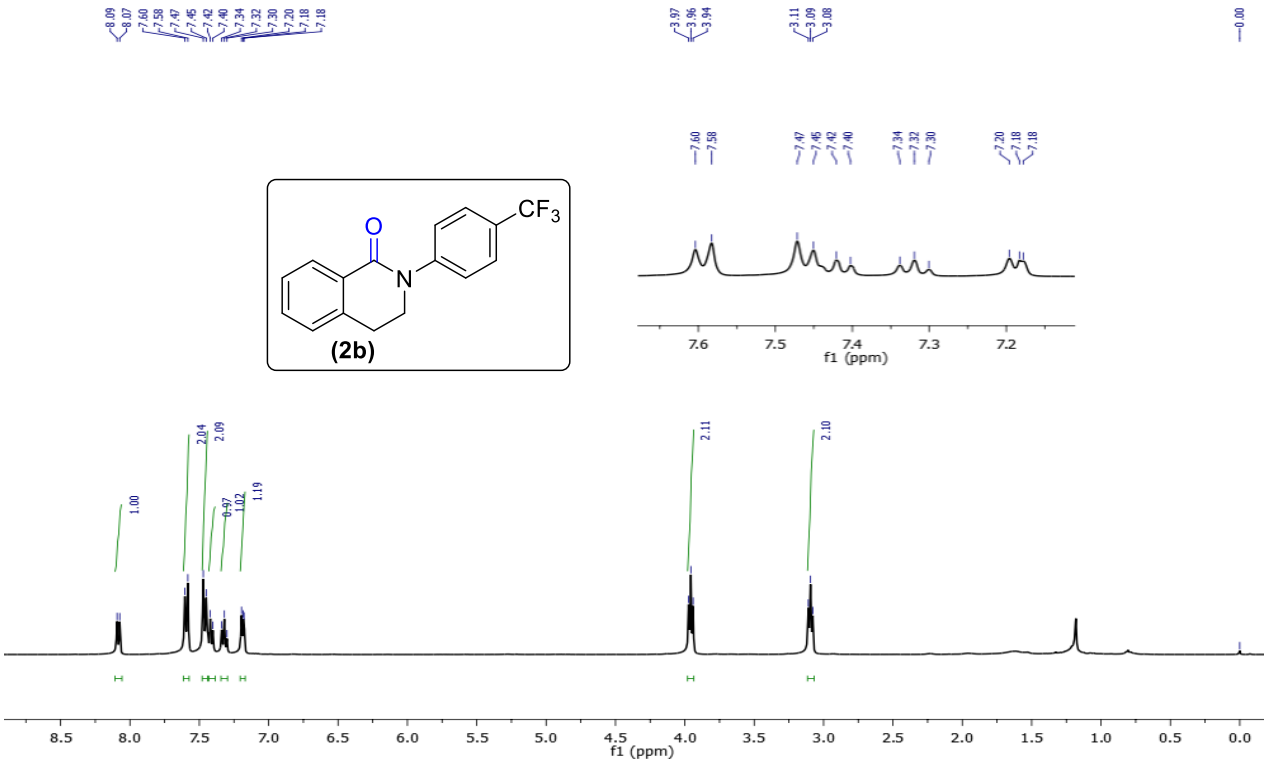
^{1}H NMR of 2-phenyl-3, 4-dihydroisoquinolin-1(2H)-one **(2a)** in $CDCl_3$



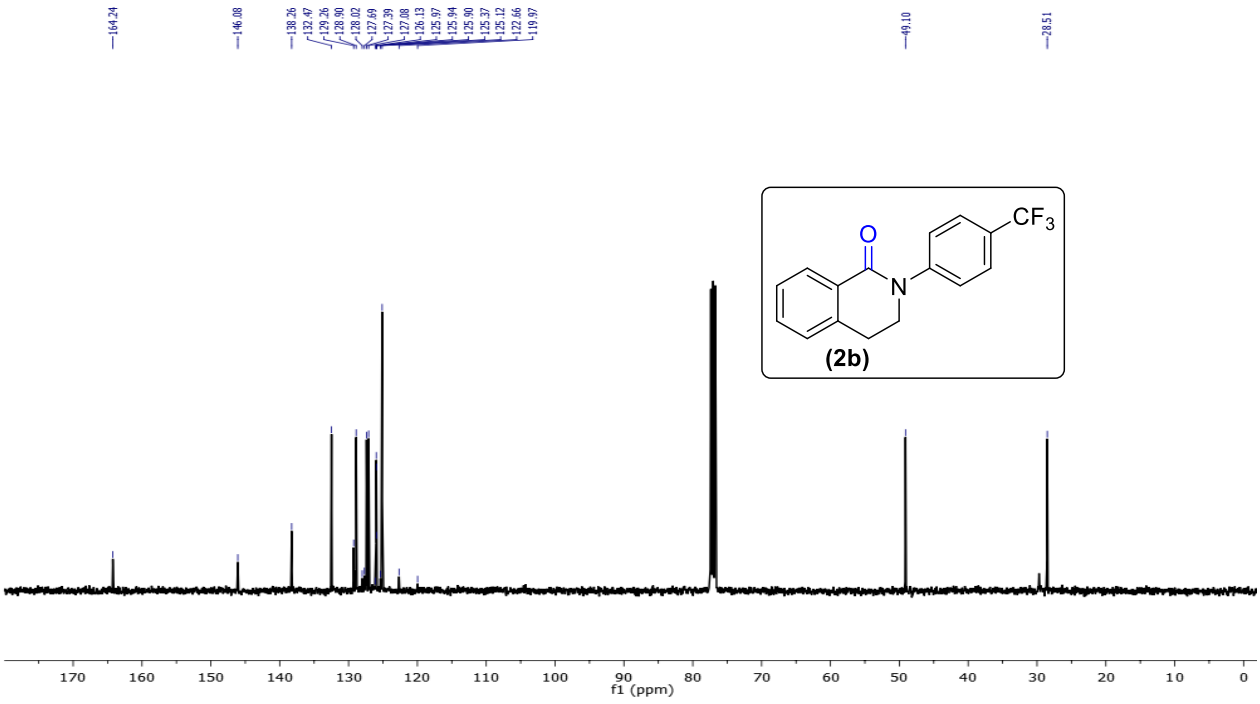
^{13}C NMR of 2-phenyl-3, 4-dihydroisoquinolin-1(2H)-one **(2a)** in $CDCl_3$



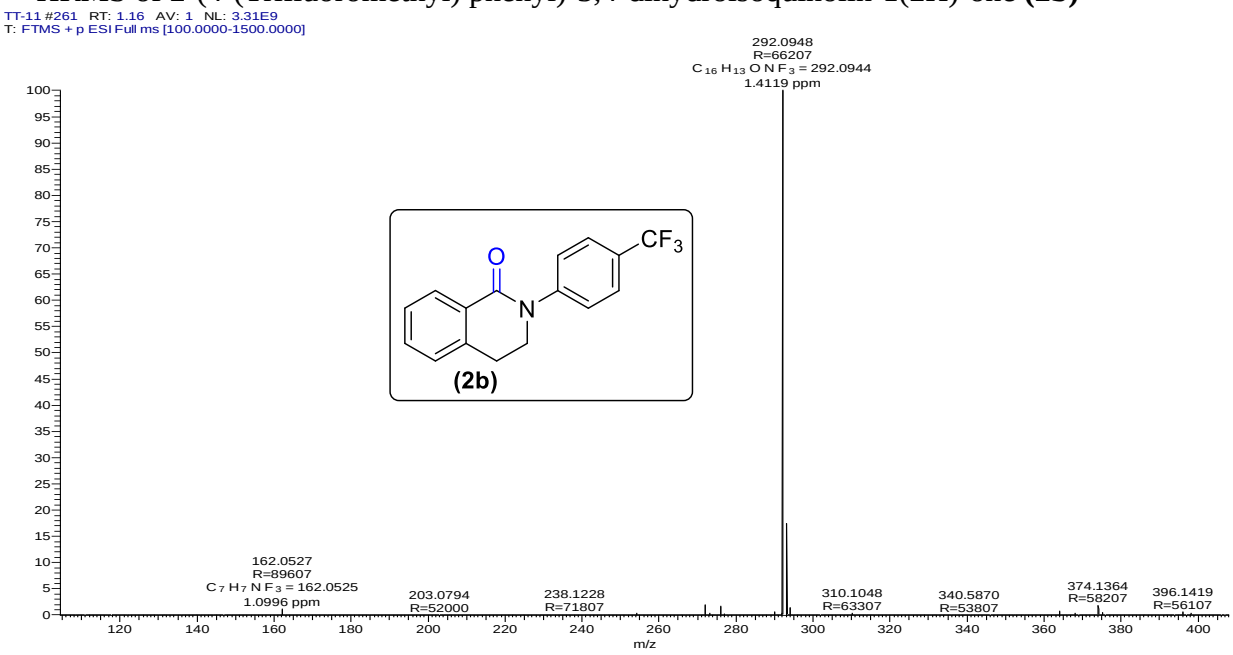
^{1}H NMR of 2-(4-(Trifluoromethyl) phenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2b)** in $CDCl_3$



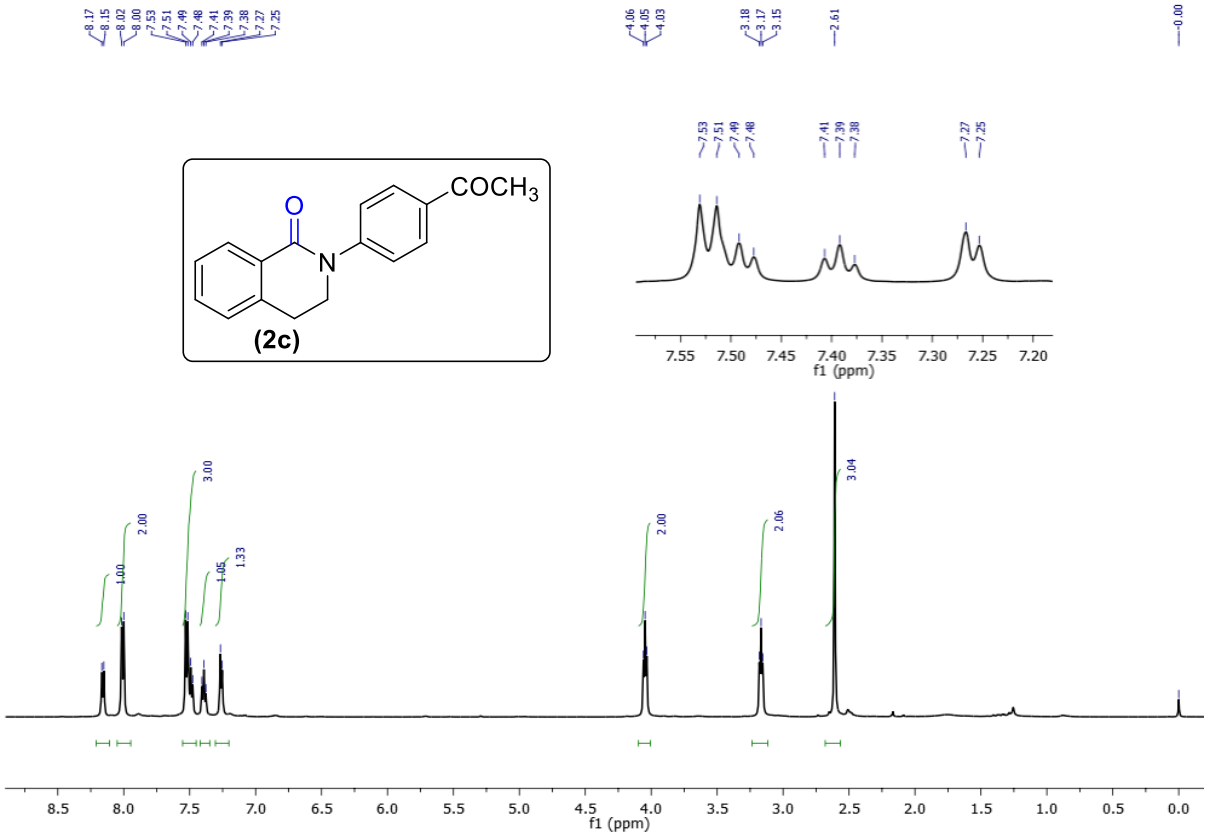
^{13}C NMR of 2-(4-(Trifluoromethyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2b)** in$CDCl_3$



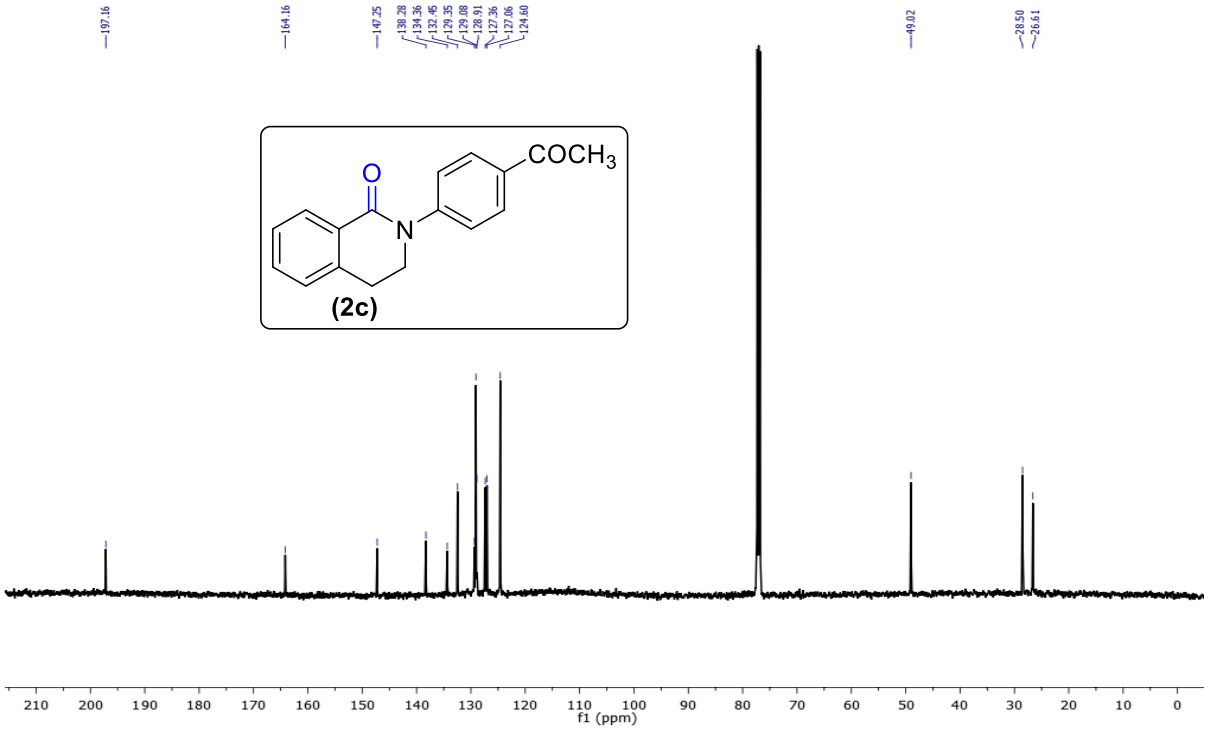
HRMS of 2-(4-(Trifluoromethyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2b)**



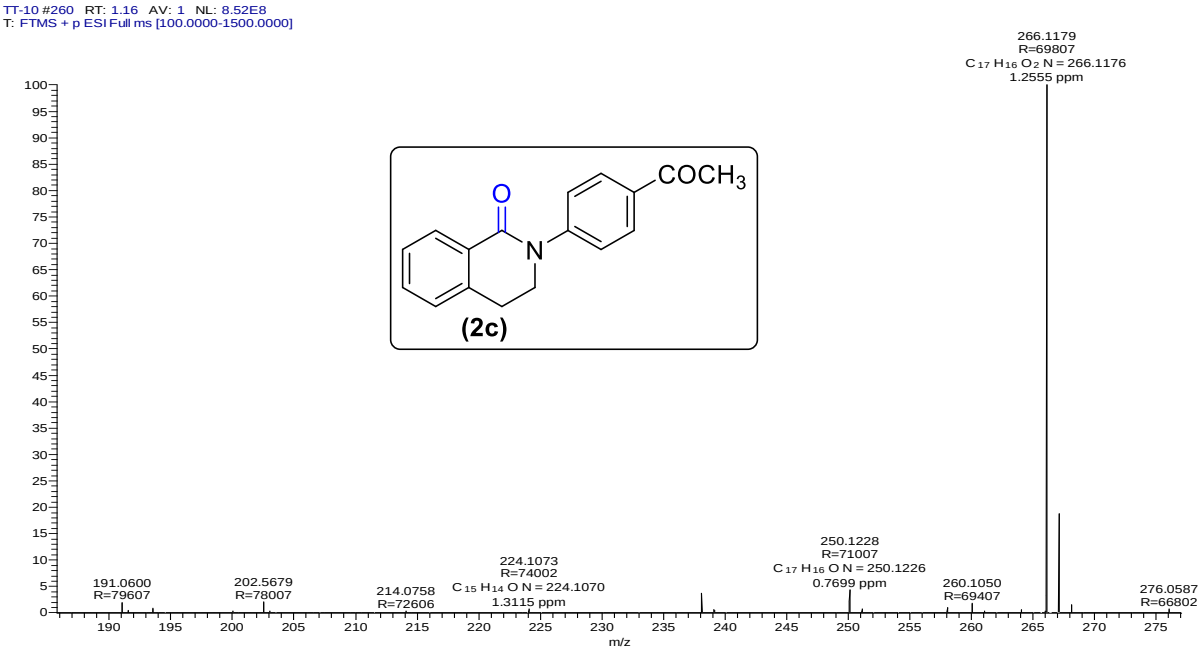
^{1}H NMR of 2-(4-Acetylphenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2c)** in $CDCl_3$



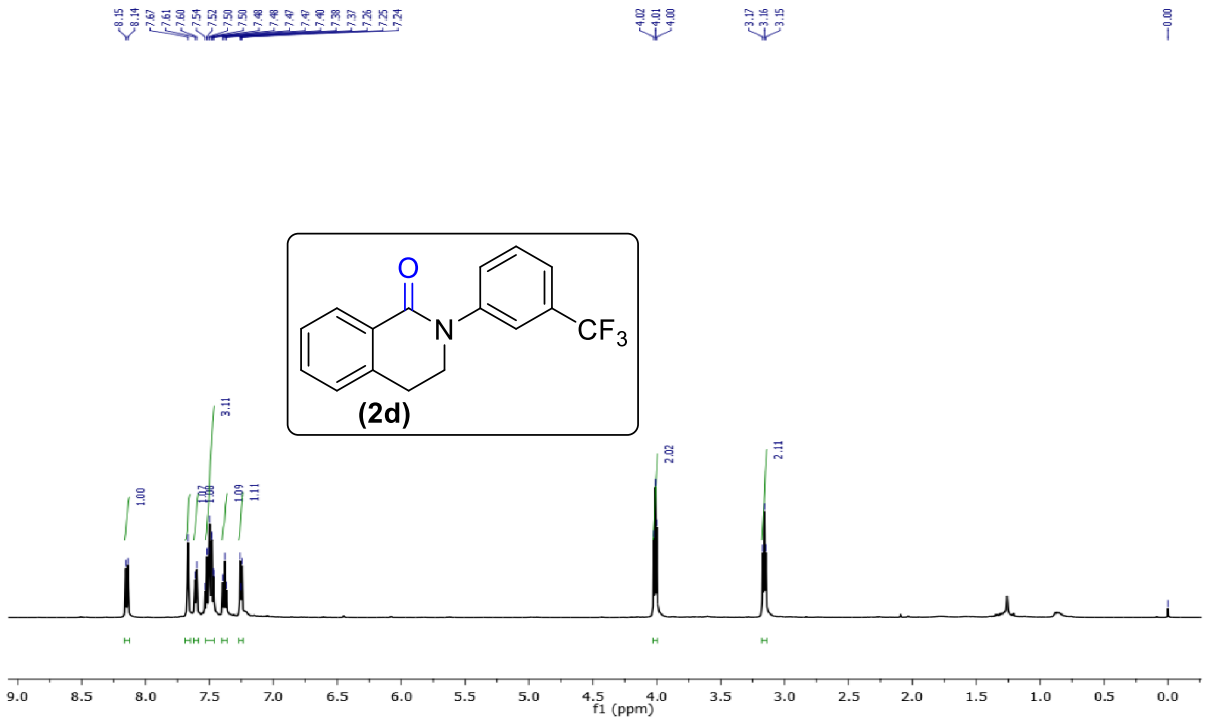
^{13}C NMR of 2-(4-Acetylphenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2c)** in $CDCl_3$



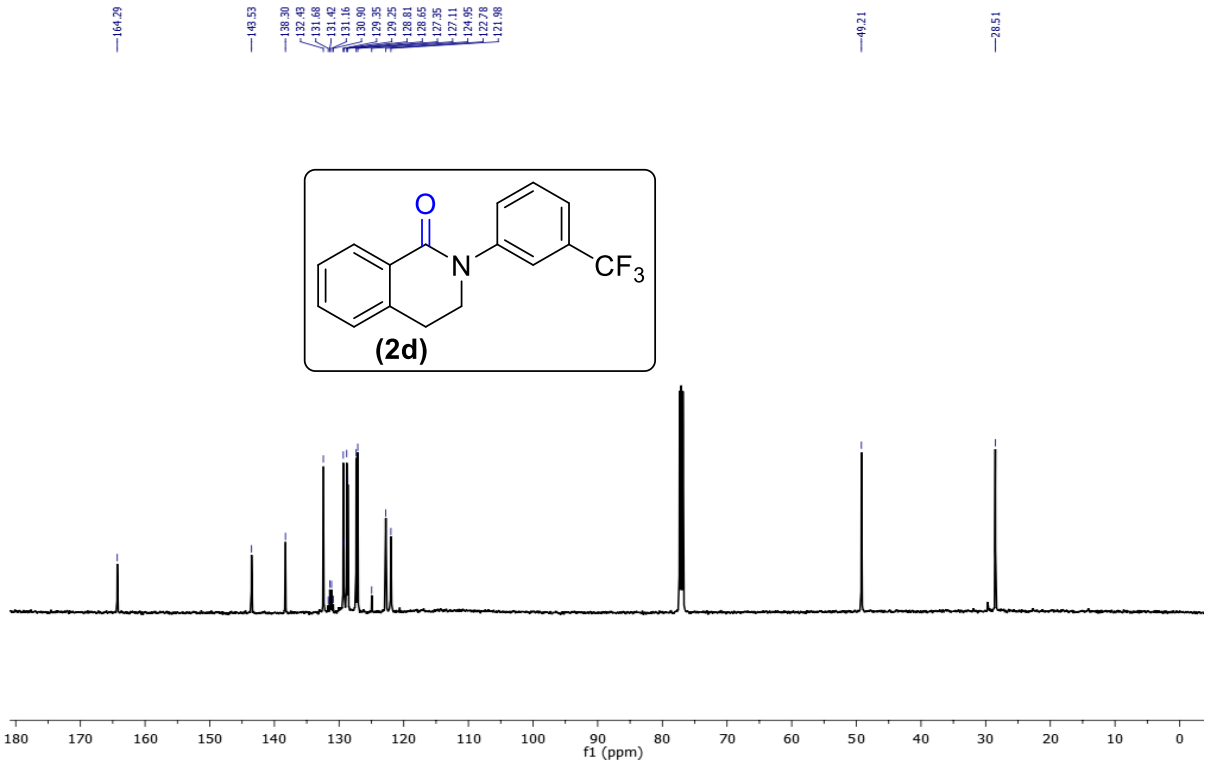
HRMS of 2-(4-Acetylphenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2c)**



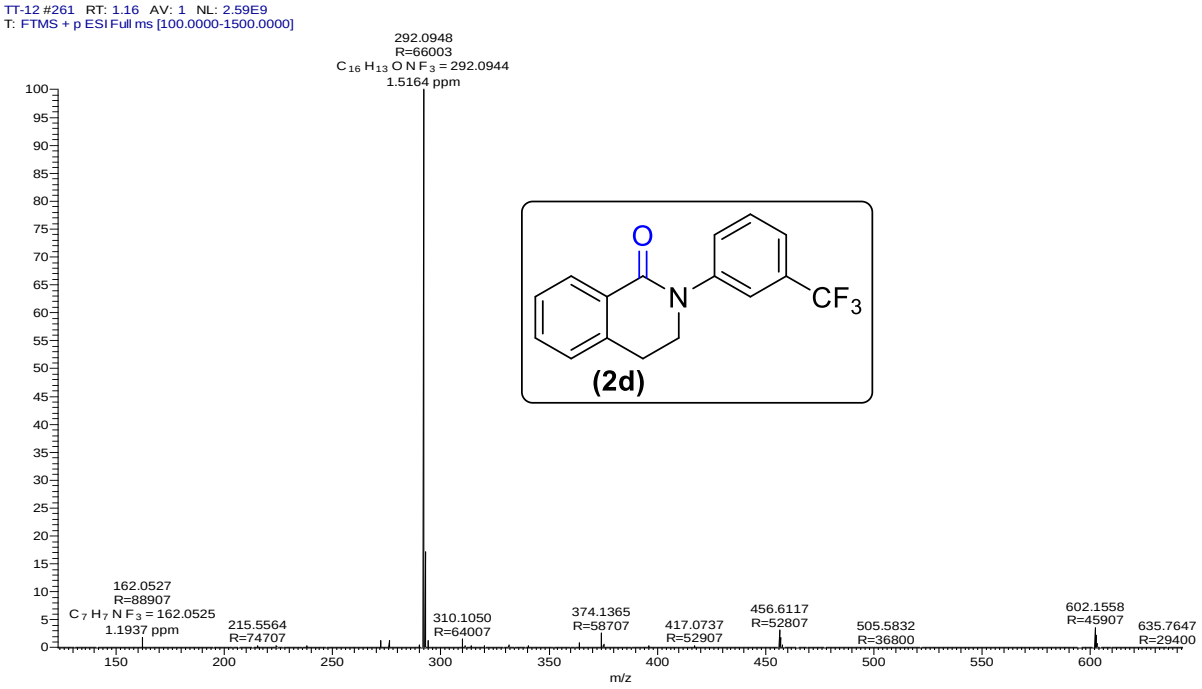
^{1}H NMR of 2-(3-(Trifluoromethyl) phenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2d)** in $CDCl_3$



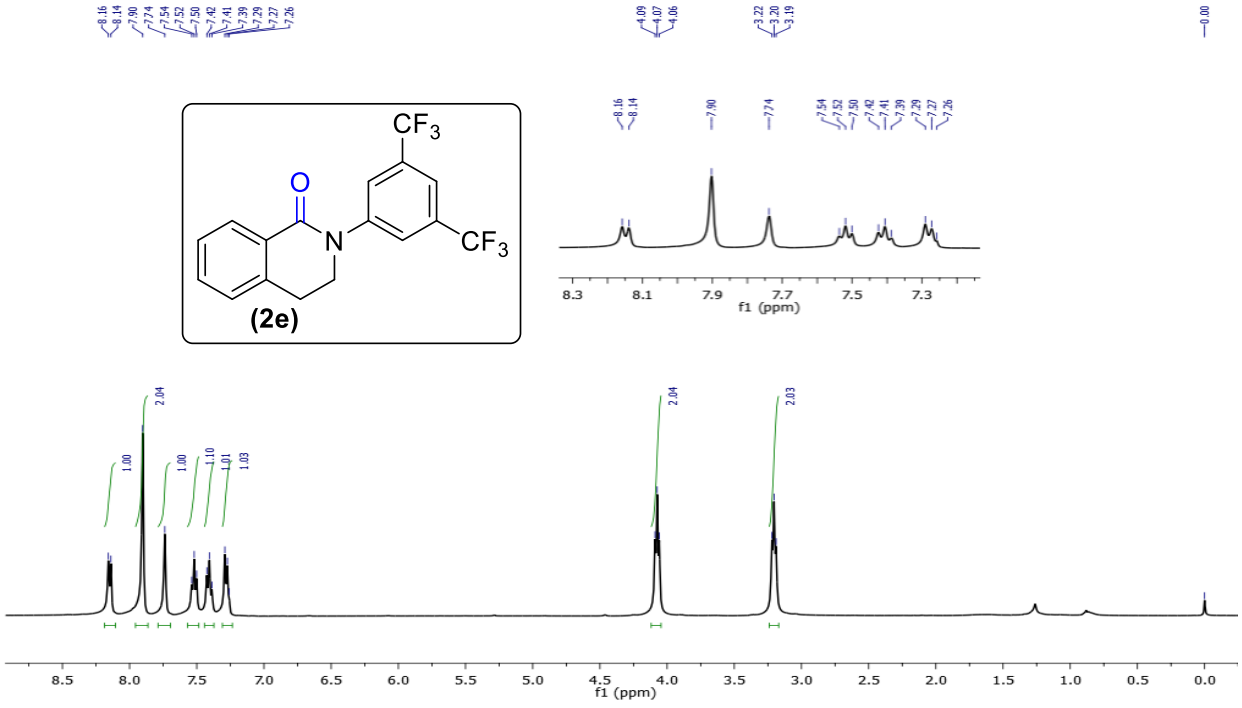
^{13}C NMR of 2-(3-(Trifluoromethyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2d)** in $CDCl_3$



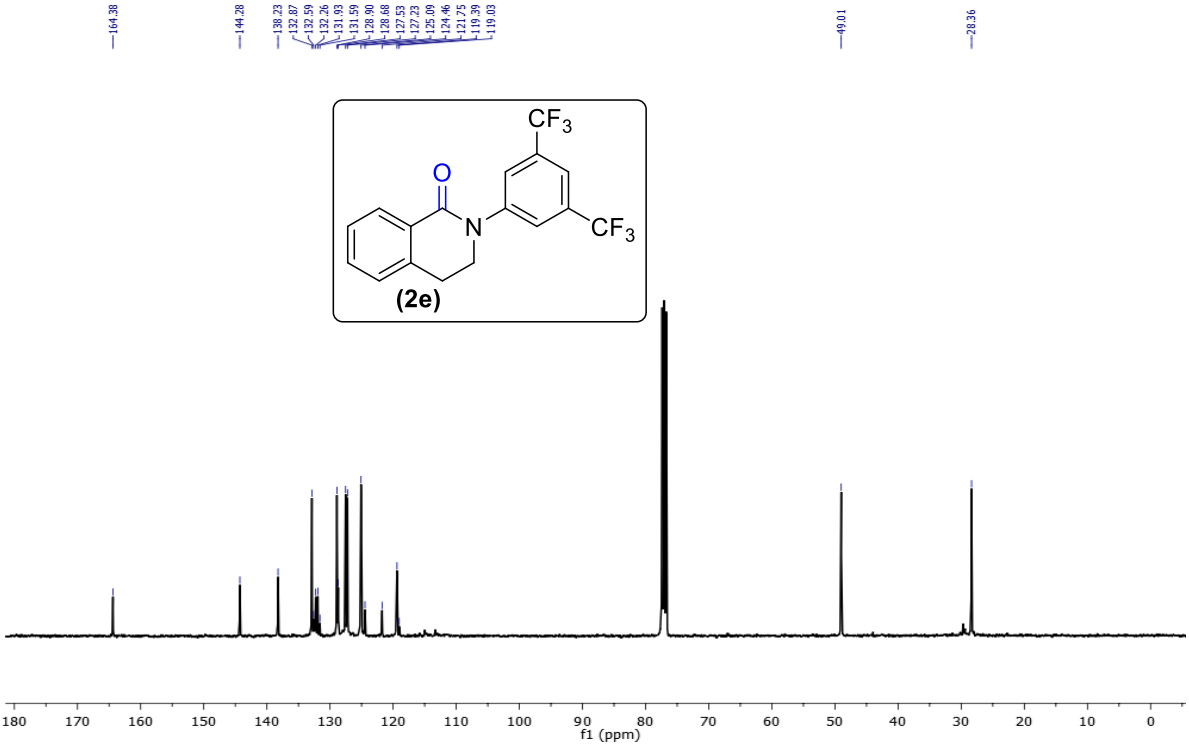
HRMS of 2-(3-(Trifluoromethyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2d)**



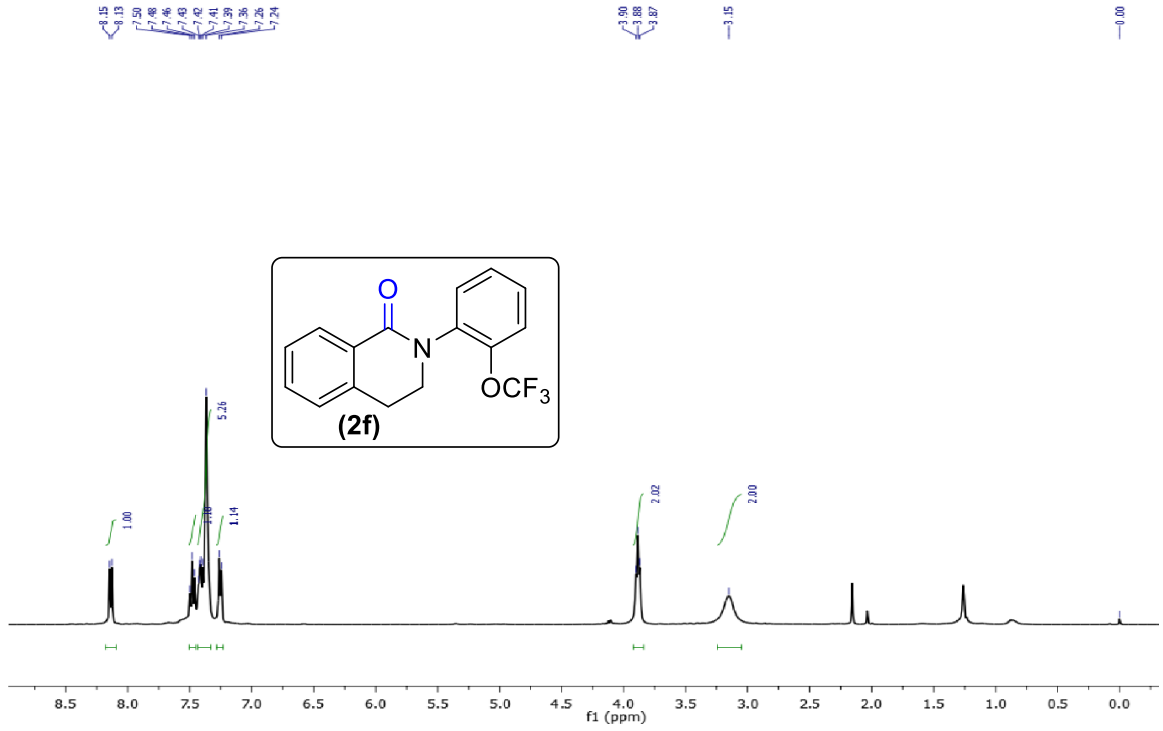
^{1}H NMR of 2-(3,5-bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2e)** in $CDCl_3$



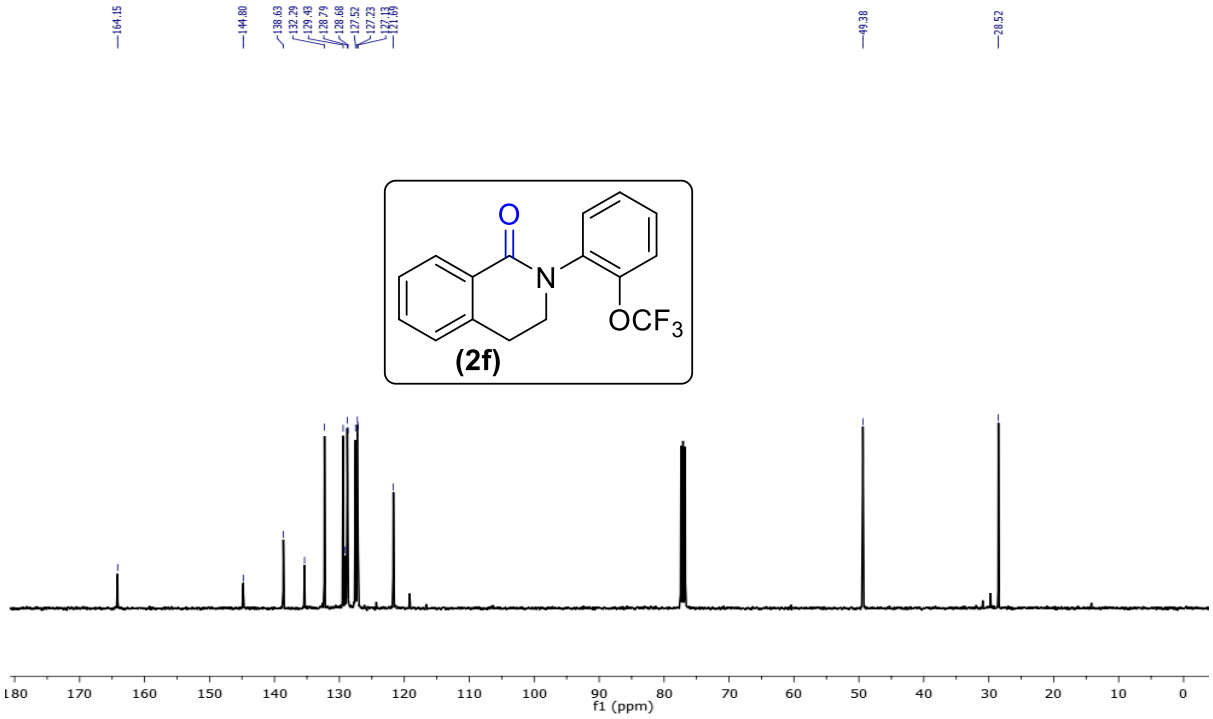
^{13}C NMR of 2-(3, 5-bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2e)** in $CDCl_3$



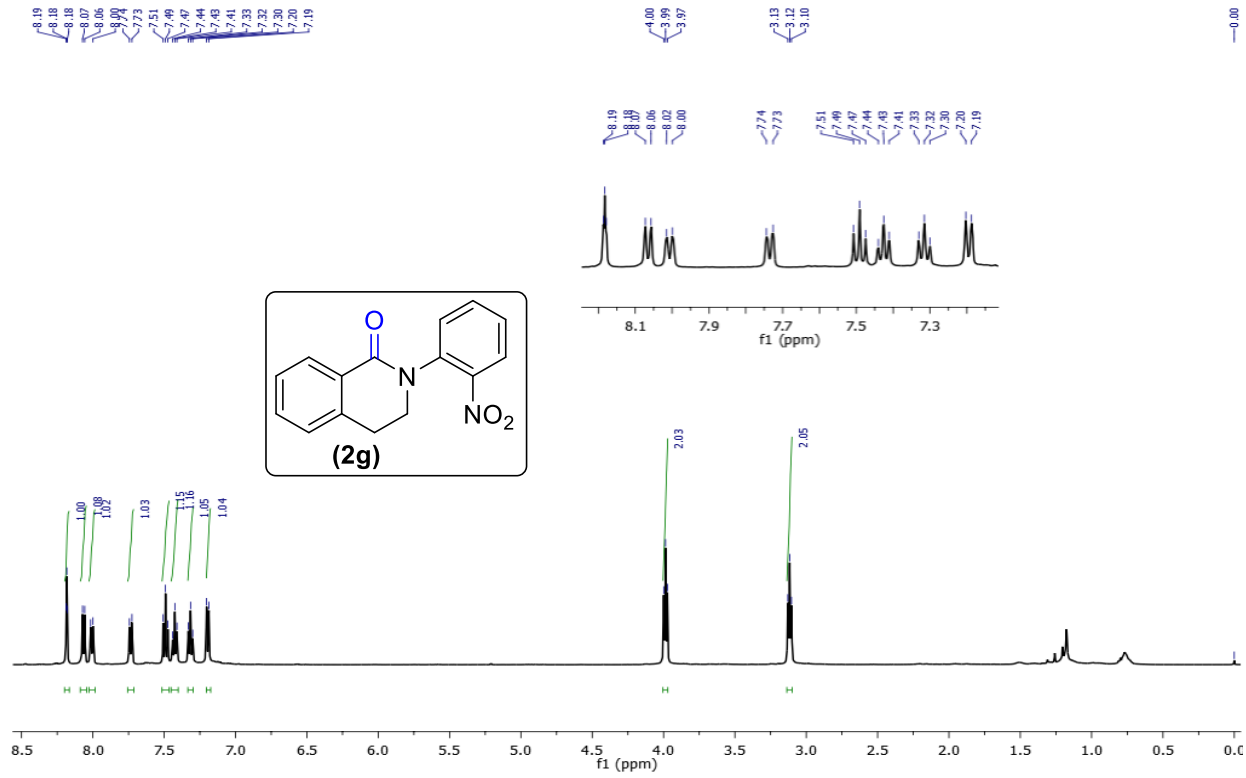
^{1}H NMR of 2-(2-(Trifluoromethoxy) phenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2f)** in $CDCl_3$



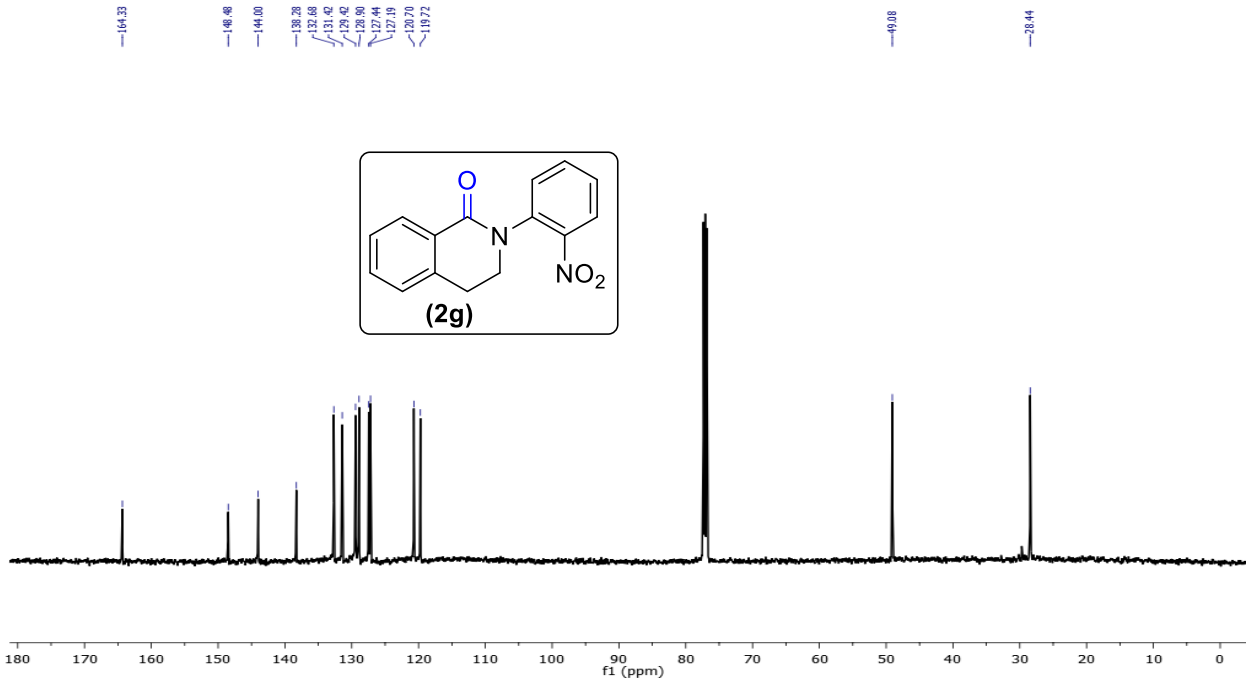
^{13}C NMR of 2-(2-(Trifluoromethoxy) phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2f)** in $CDCl_3$



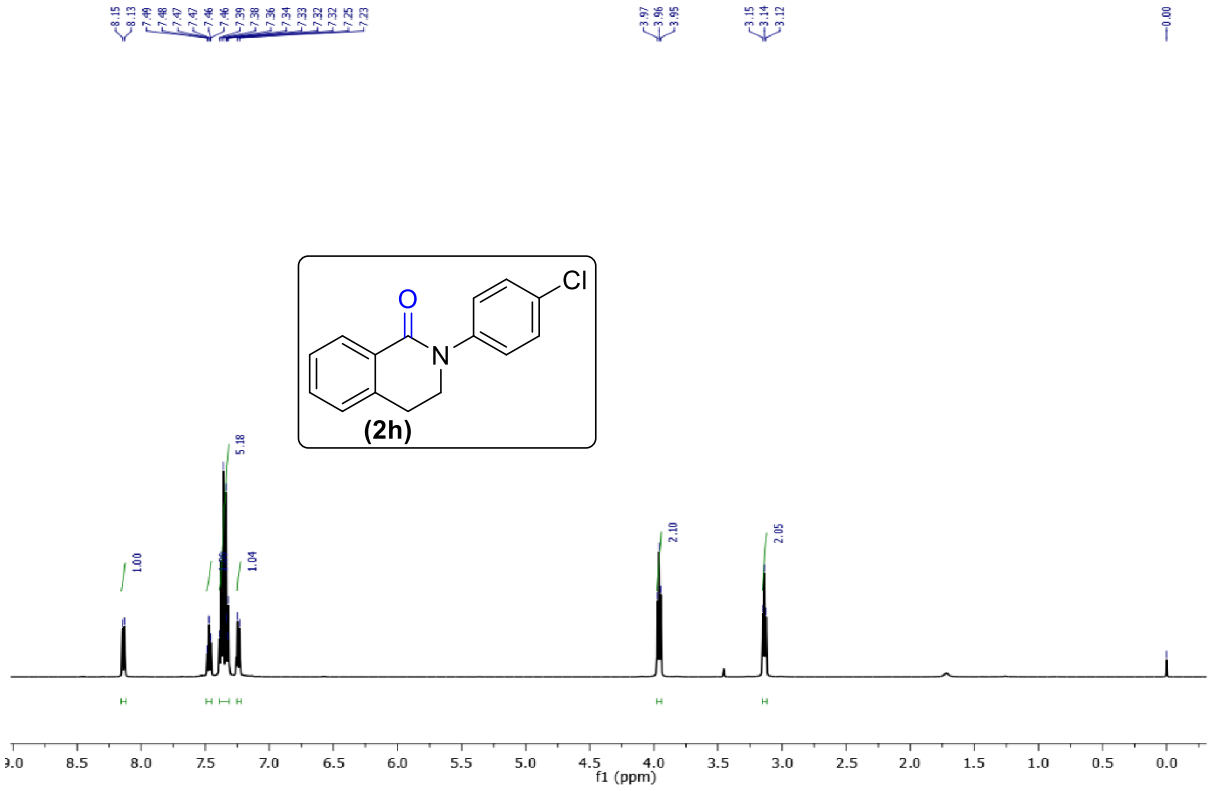
^{1}H NMR of 2-(2-Nitrophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2g)** in $CDCl_3$



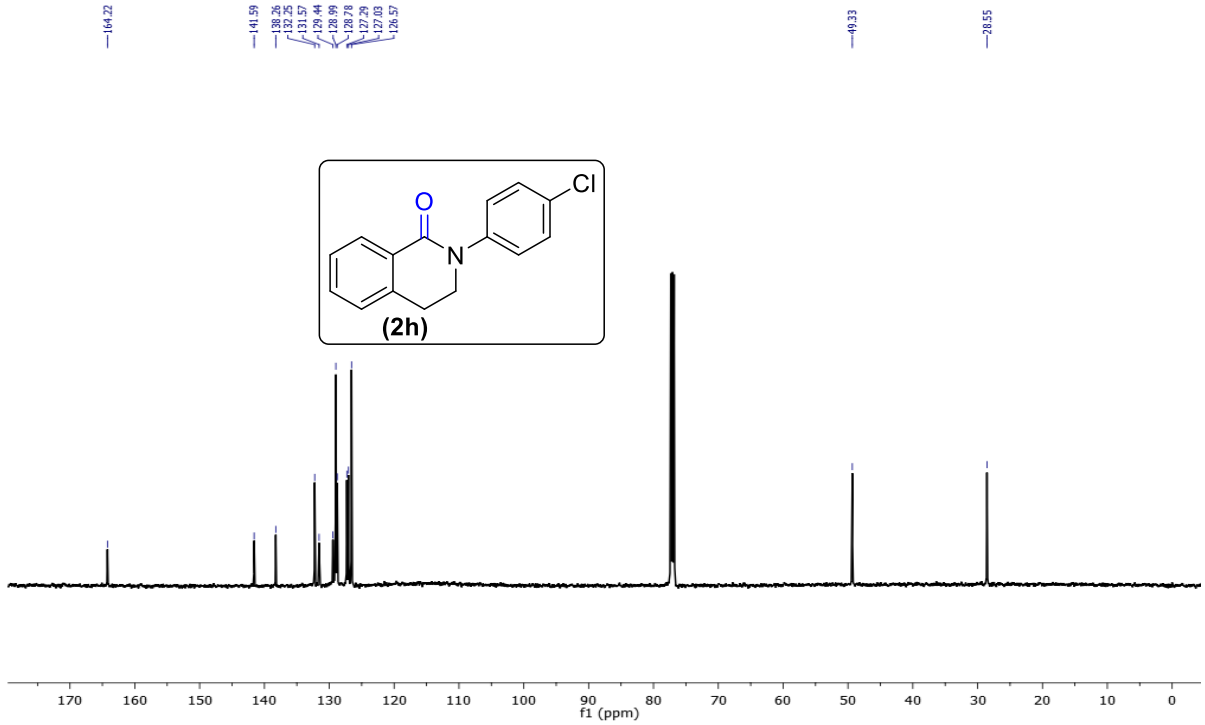
^{13}C NMR of 2-(2-Nitrophenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2g)** in $CDCl_3$



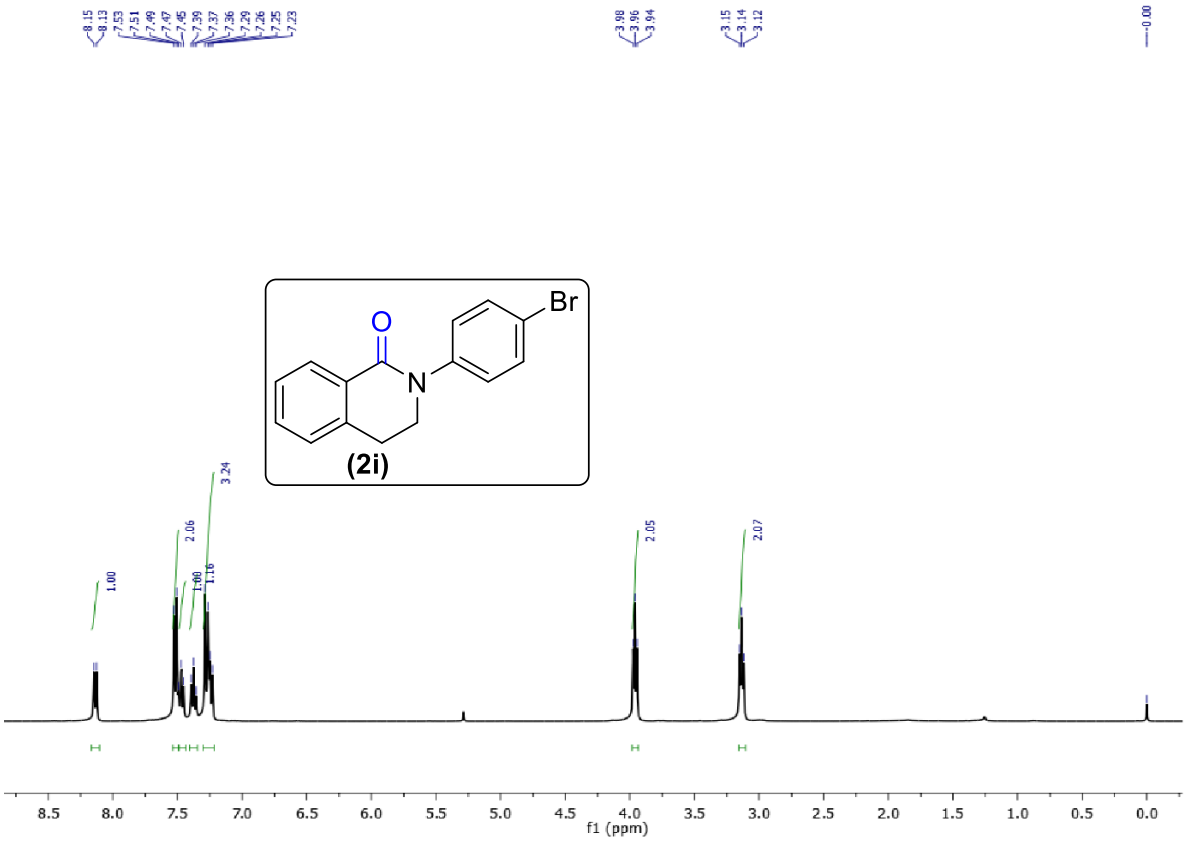
^{1}H NMR of 2-(4-Chlorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2h)** in $CDCl_3$



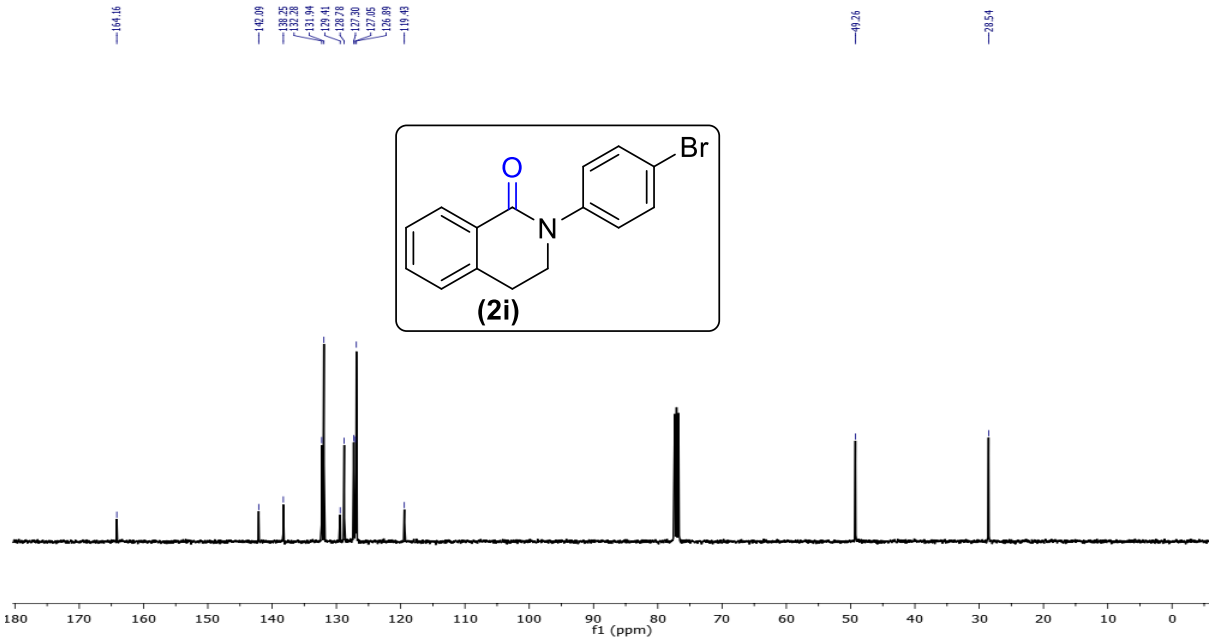
^{13}C NMR of 2-(4-Chlorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2h)** in $CDCl_3$



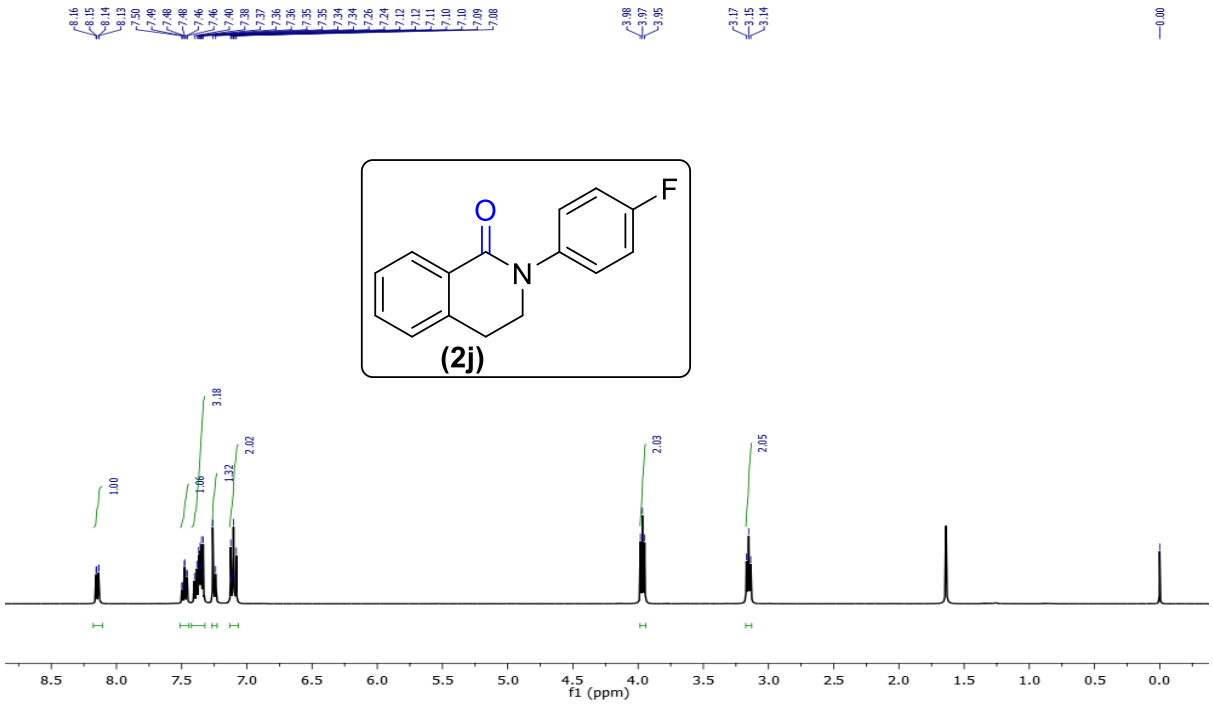
^{1}H NMR 2-(4-Bromophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2i)** in $CDCl_3$



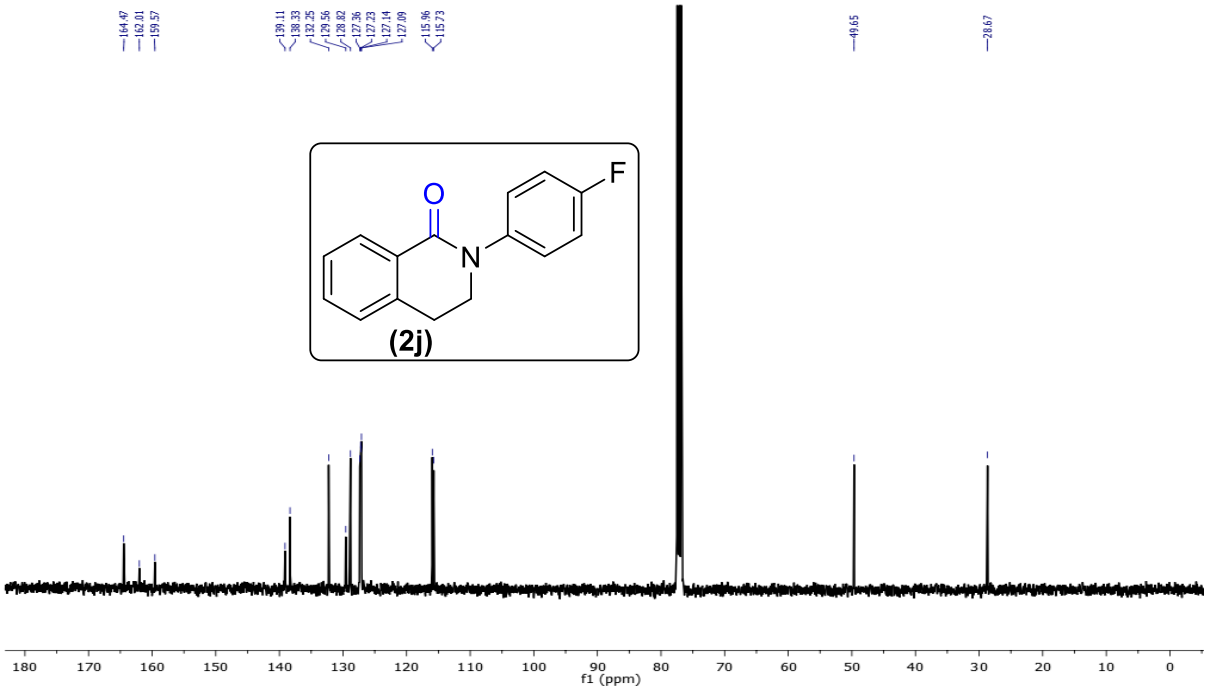
^{13}C NMR of 2-(4-Bromophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2i)** in $CDCl_3$



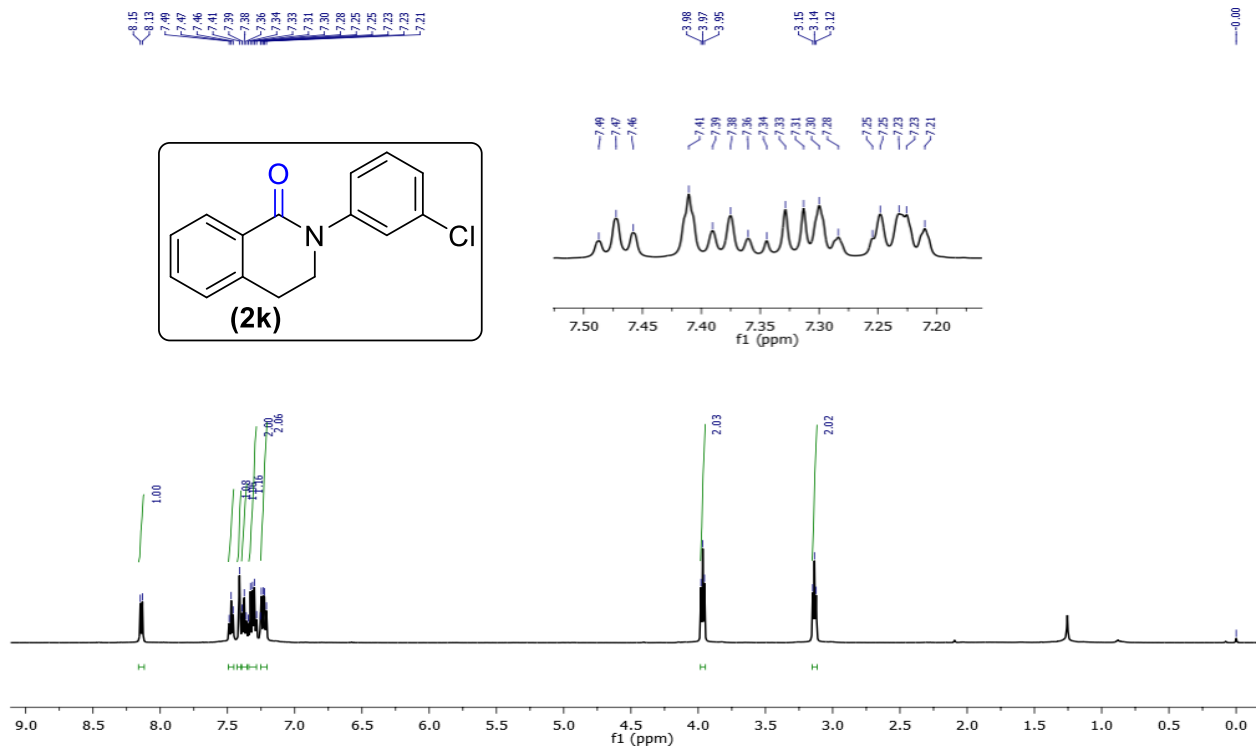
^{1}H NMR of 2-(4-Fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2j)** in $CDCl_3$



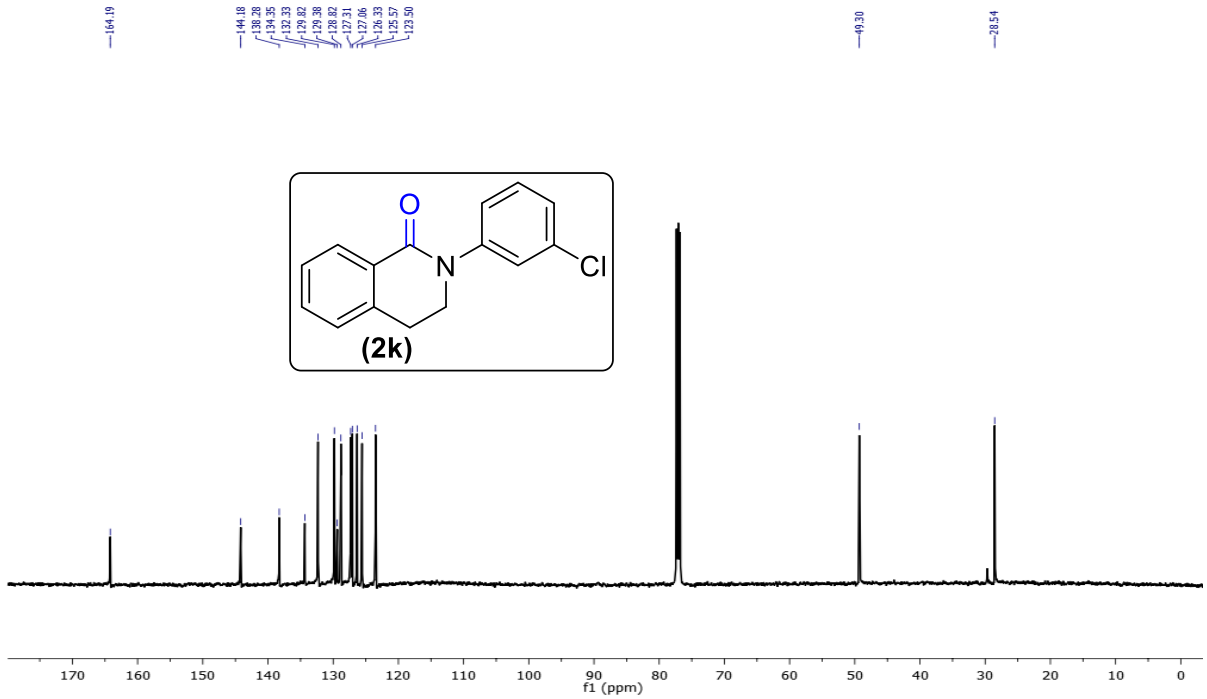
^{13}C NMR of 2-(4-Fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2j)** in $CDCl_3$



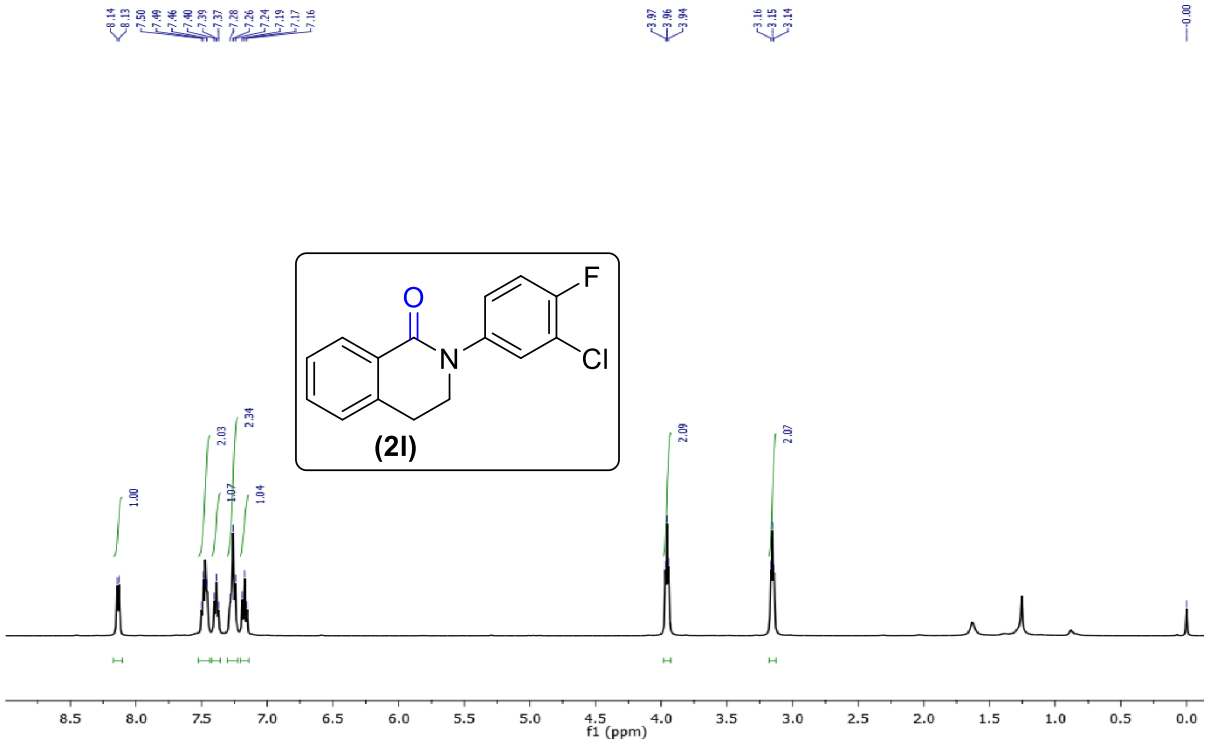
^{1}H NMR of 2-(3-Chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2k)** in $CDCl_3$



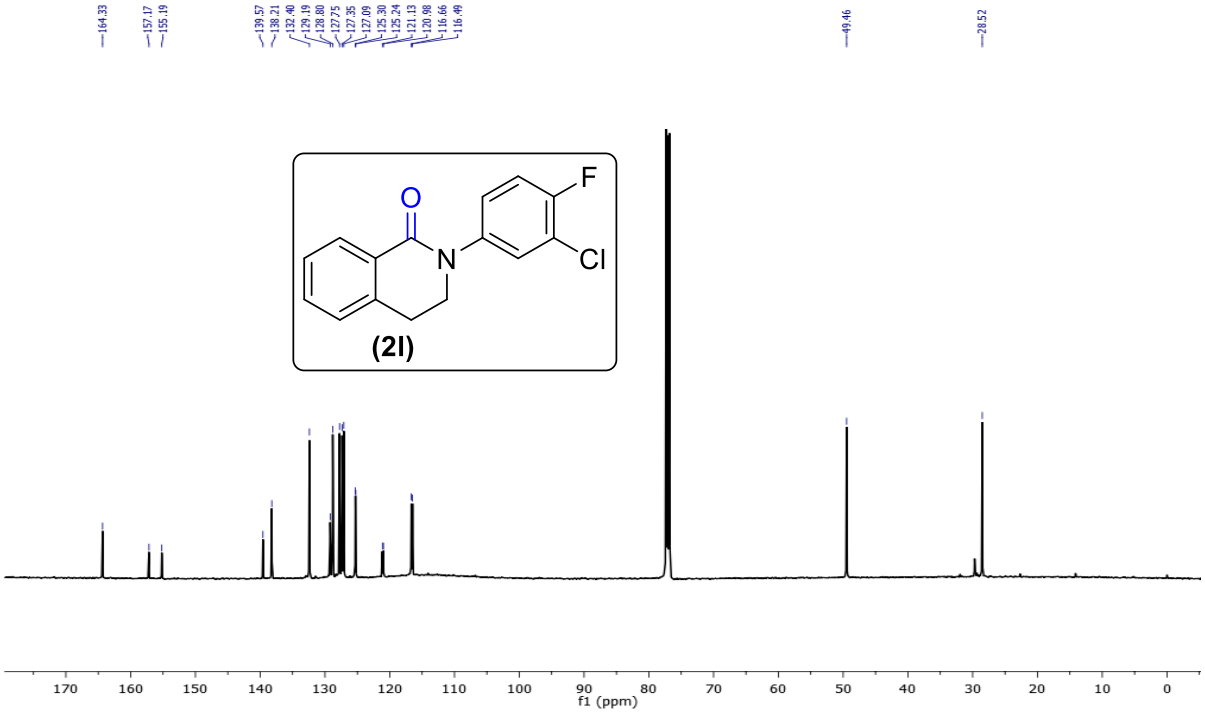
^{13}C NMR of 2-(3-Chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2k)** in $CDCl_3$



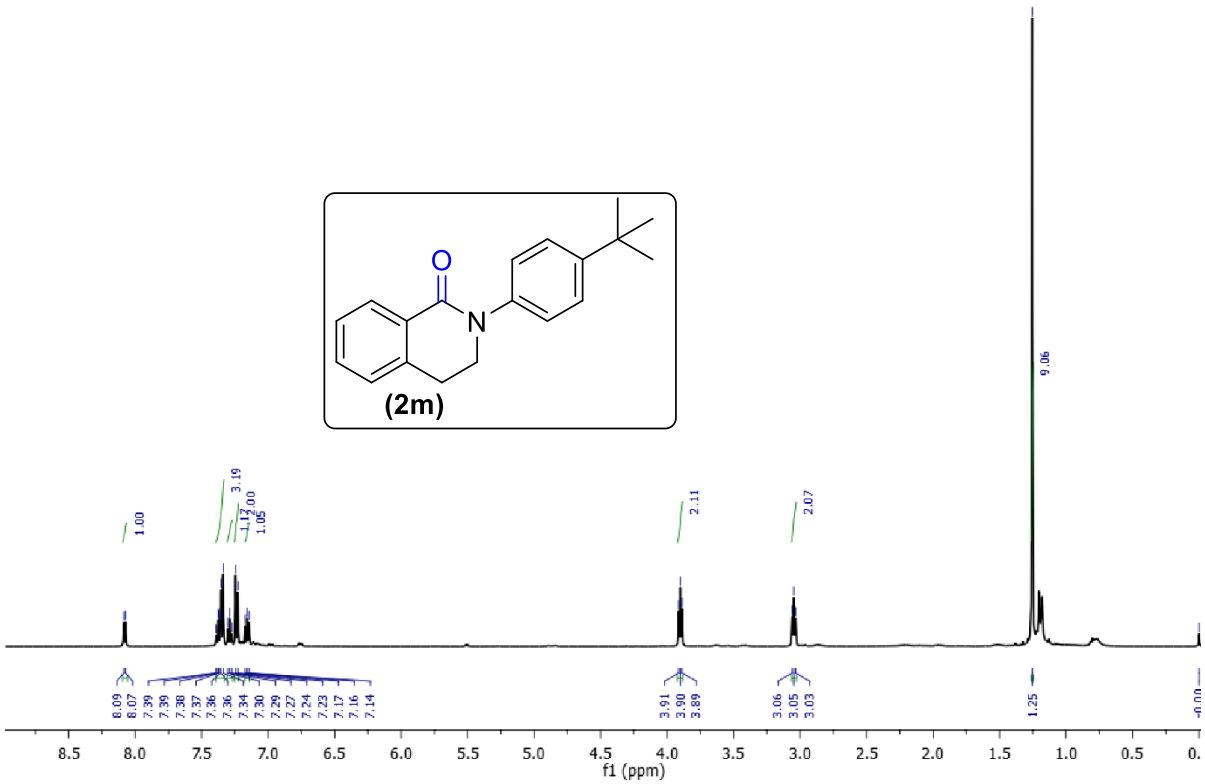
^{1}H NMR of 2-(3-Chloro-4-fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2l)** in $CDCl_3$



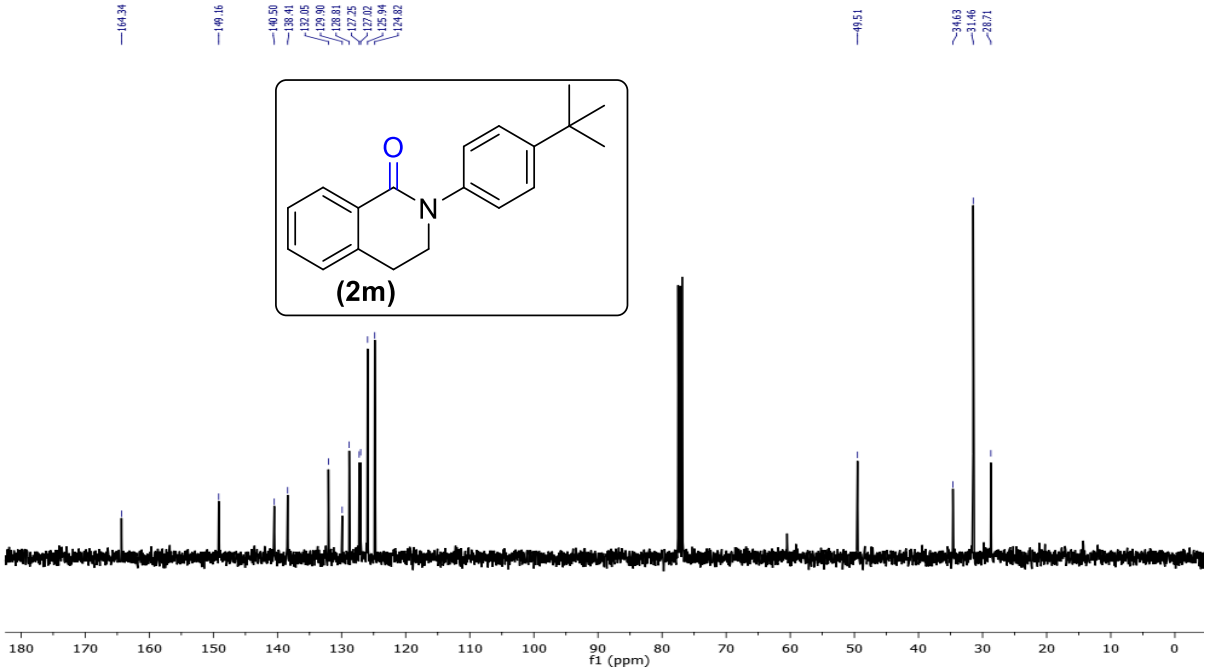
^{13}C NMR of 2-(3-Chloro-4-fluorophenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2l)** in $CDCl_3$



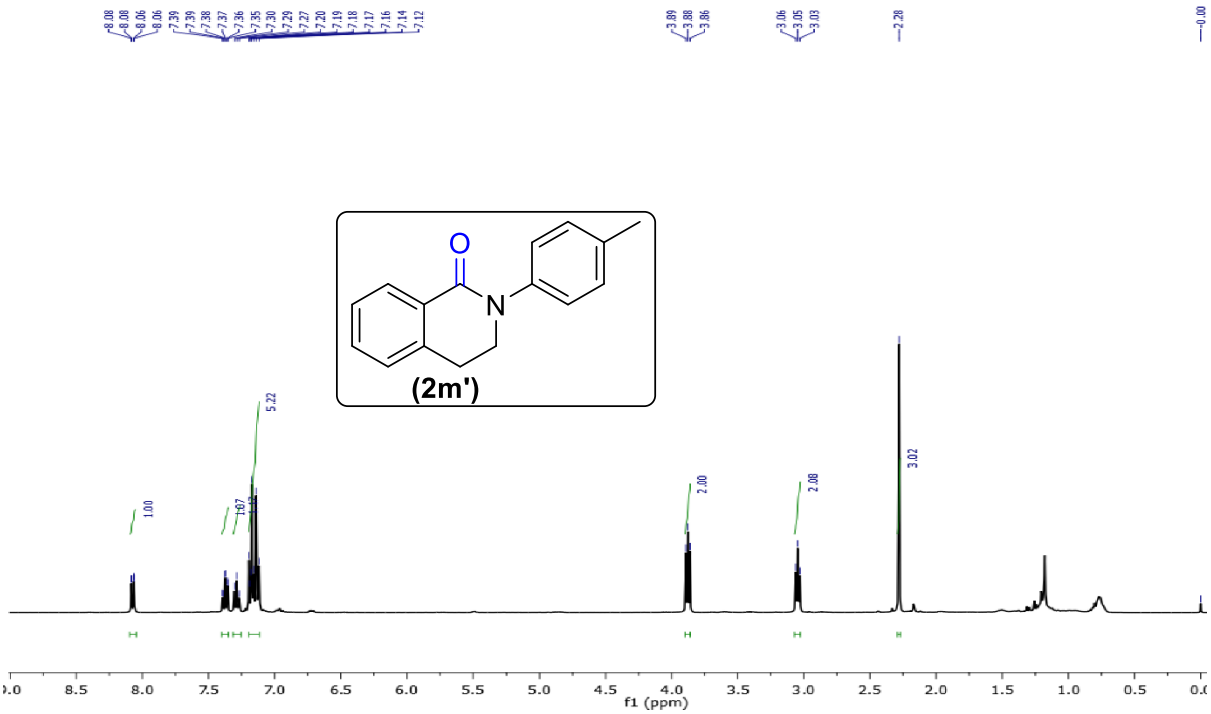
^{1}H NMR of 2-(4-(*tert*-butyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2m)** in $CDCl_3$



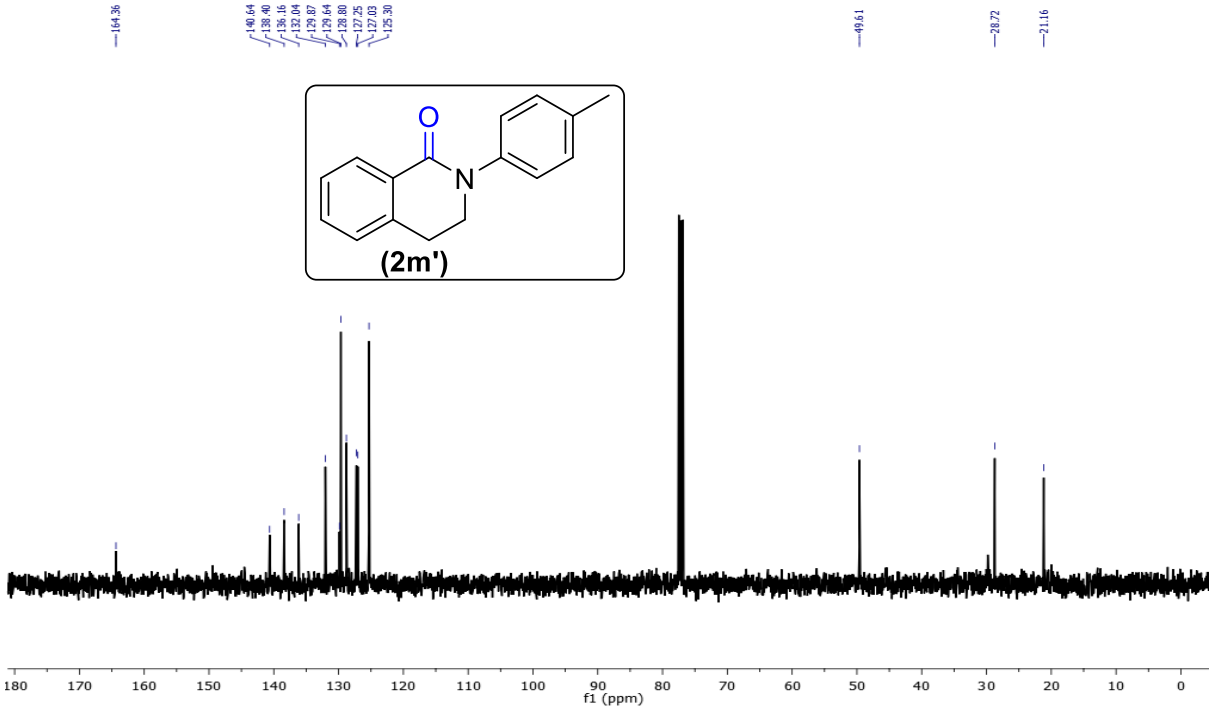
^{13}C NMR of 2-(4-(*tert*-butyl) phenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2m)** in $CDCl_3$



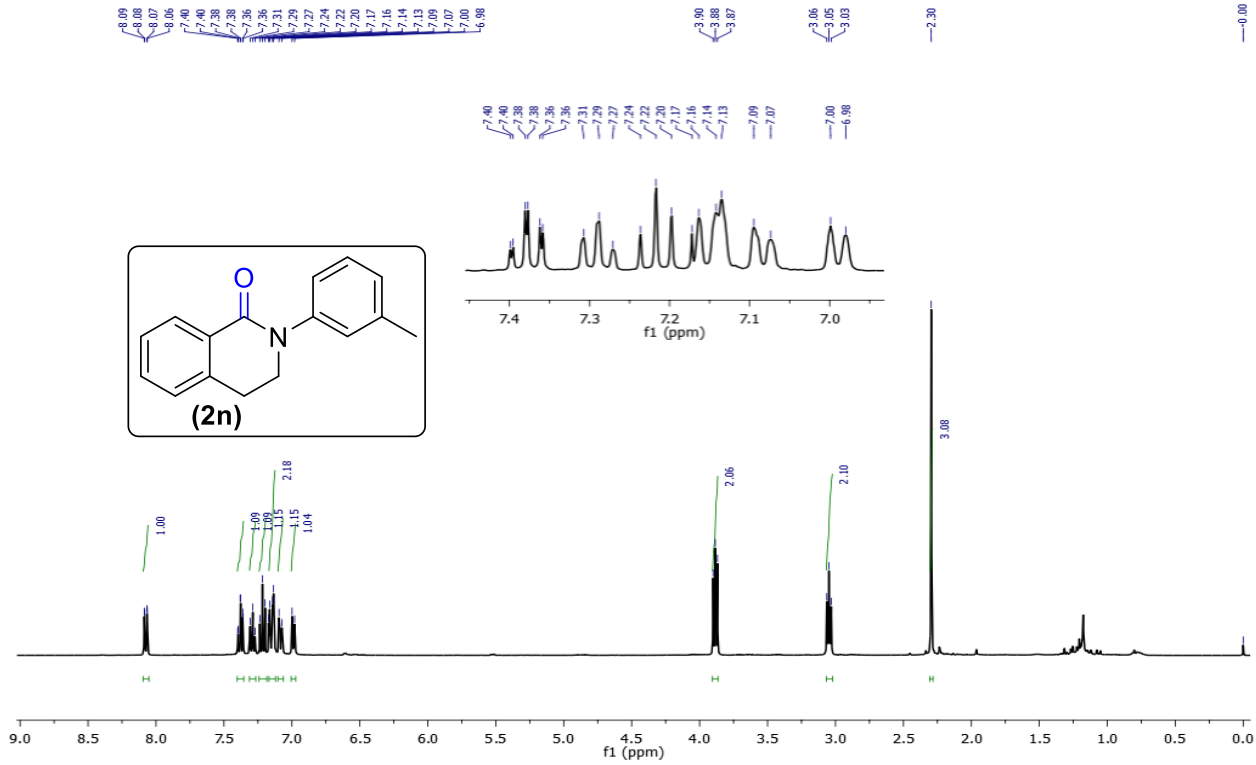
^{1}H NMR of 2-(*p*-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2m')** in $CDCl_3$



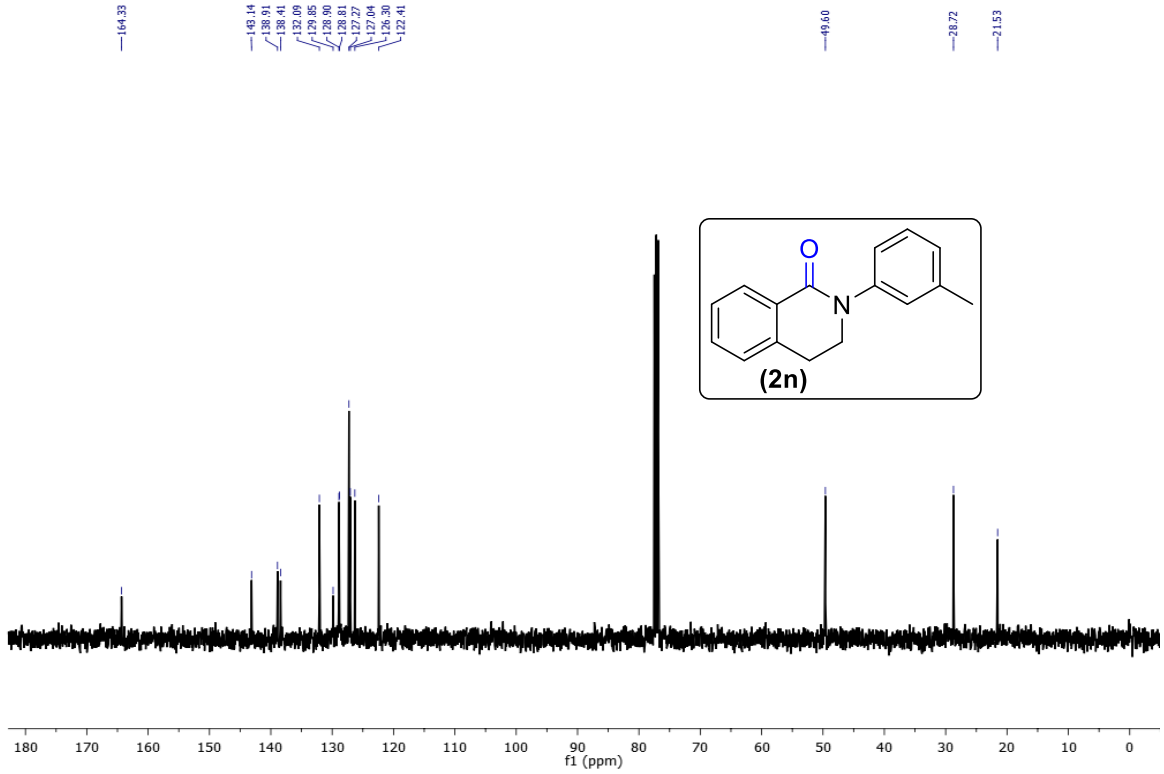
^{13}C NMR of 2-(*p*-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2m')** in $CDCl_3$



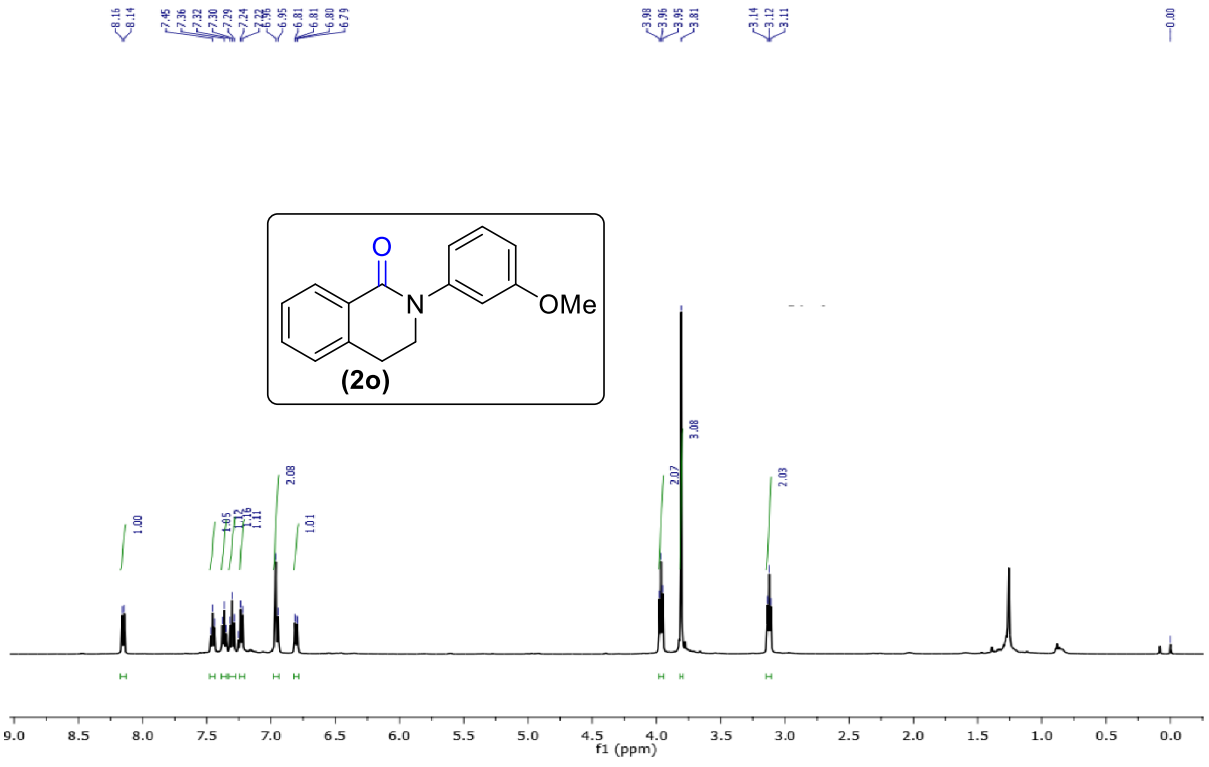
^{1}H NMR of 2-(*m*-tolyl)-3,4-dihydroisoquinolin-1(2H)-one **(2n)** in $CDCl_3$



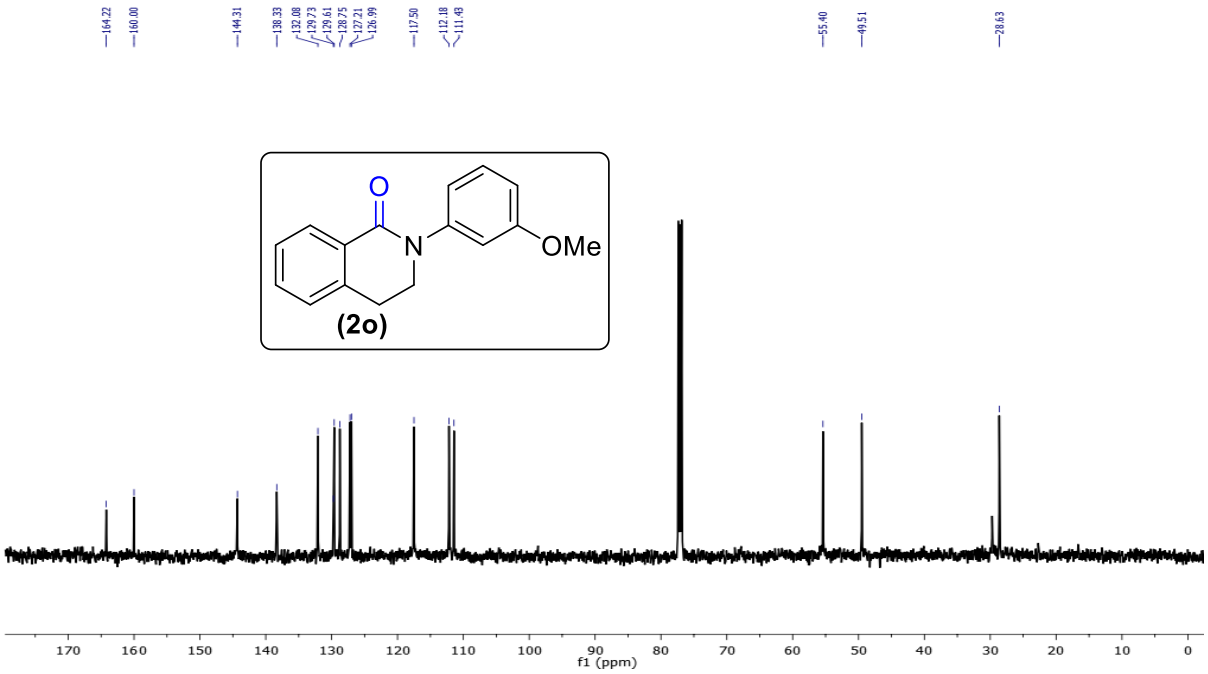
^{13}C NMR of 2-(*m*-tolyl)-3,4-dihydroisoquinolin-1(2H)-one **(2n)** in $CDCl_3$



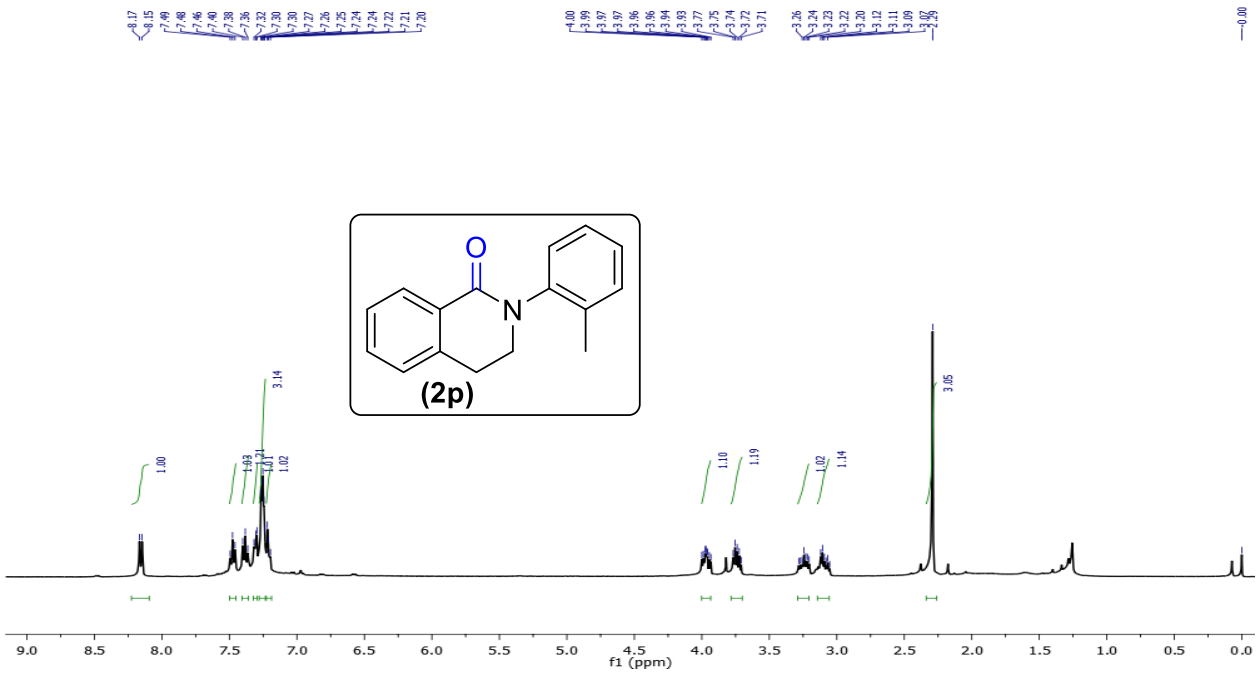
^{1}H NMR of 2-(3-Methoxyphenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2o)** in $CDCl_3$



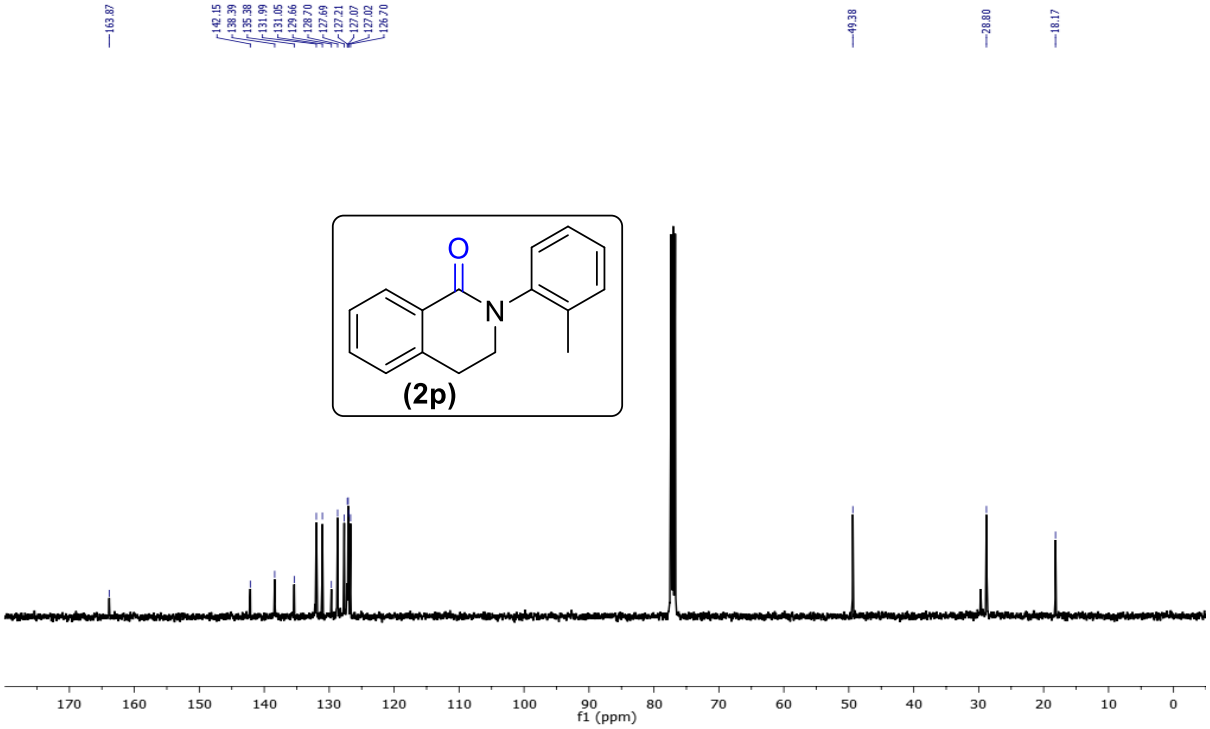
^{13}CNMR of 2-(3-Methoxyphenyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2o)** in $CDCl_3$



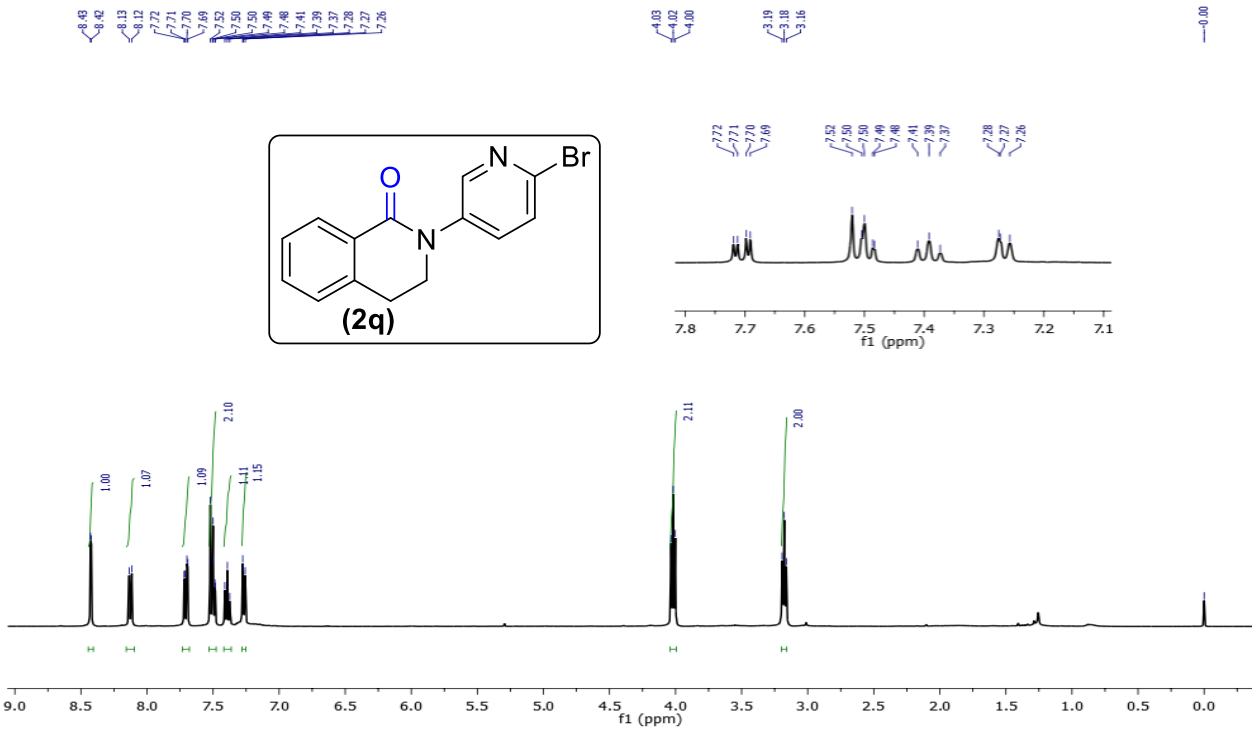
^{1}H NMR of 2-(*o*-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2p)** in $CDCl_3$



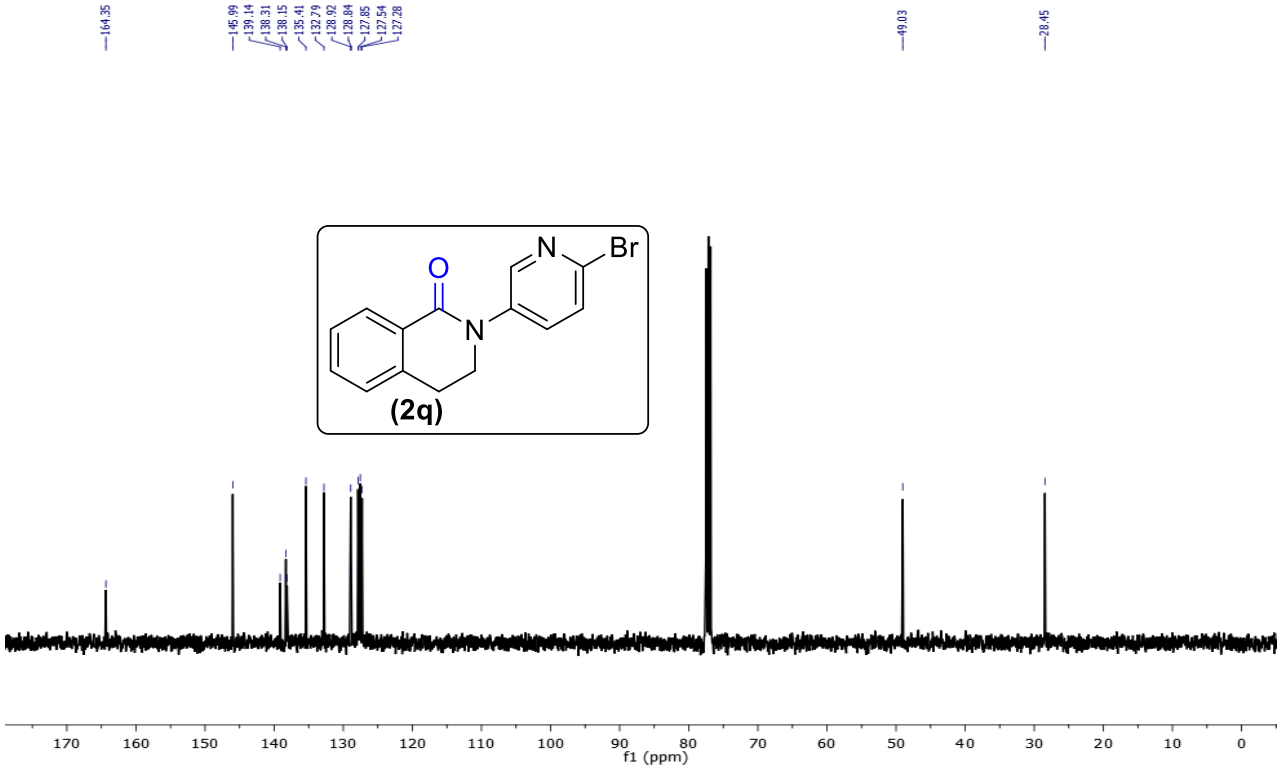
^{13}C NMR of 2-(*o*-tolyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2p)** in $CDCl_3$



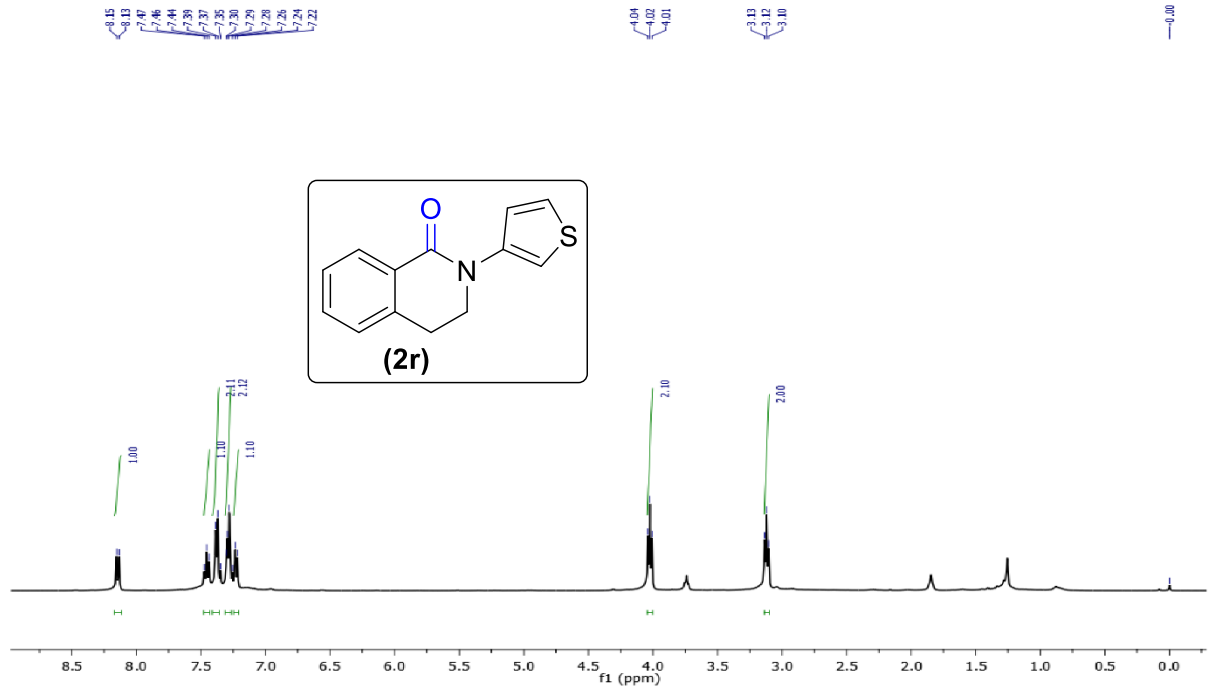
^{1}H NMR of 2-(6-Bromopyridin-3-yl)-3,4-dihydroisoquinolin-1(2H)-one **(2q)** in $CDCl_3$



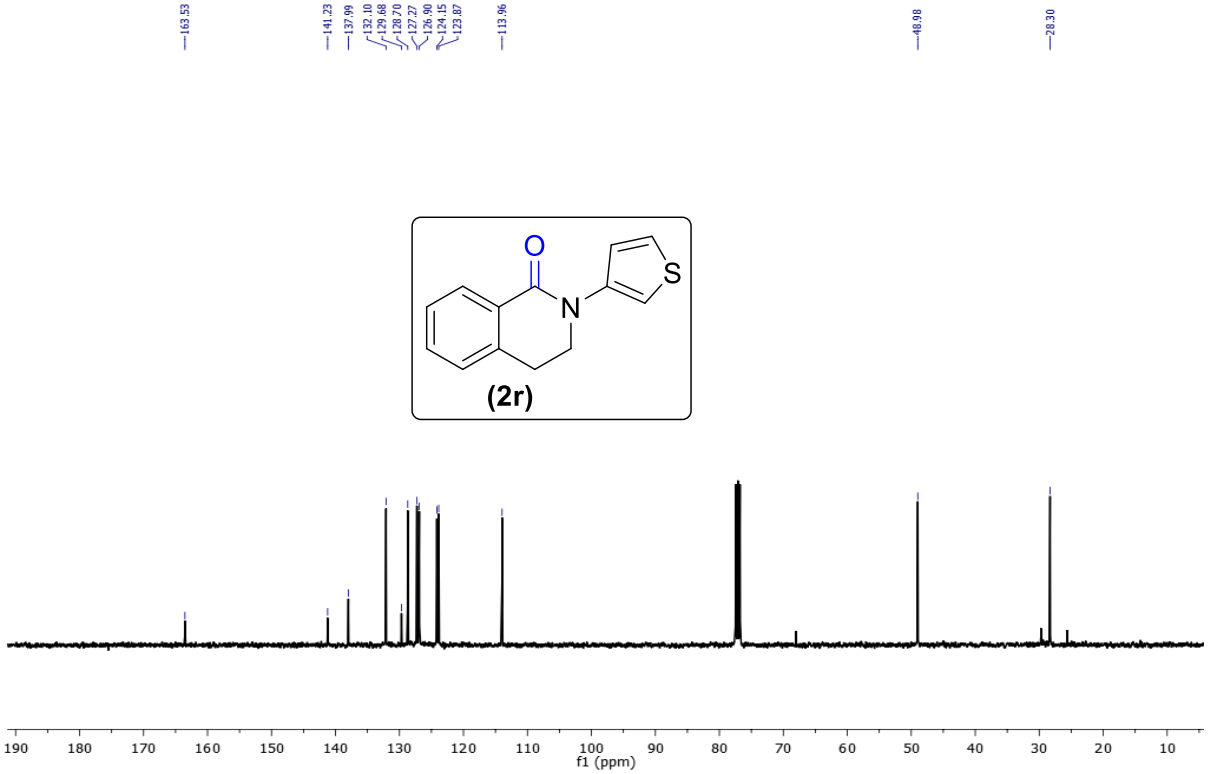
^{13}C NMR of 2-(6-Bromopyridin-3-yl)-3,4-dihydroisoquinolin-1(2H)-one **(2q)** in $CDCl_3$



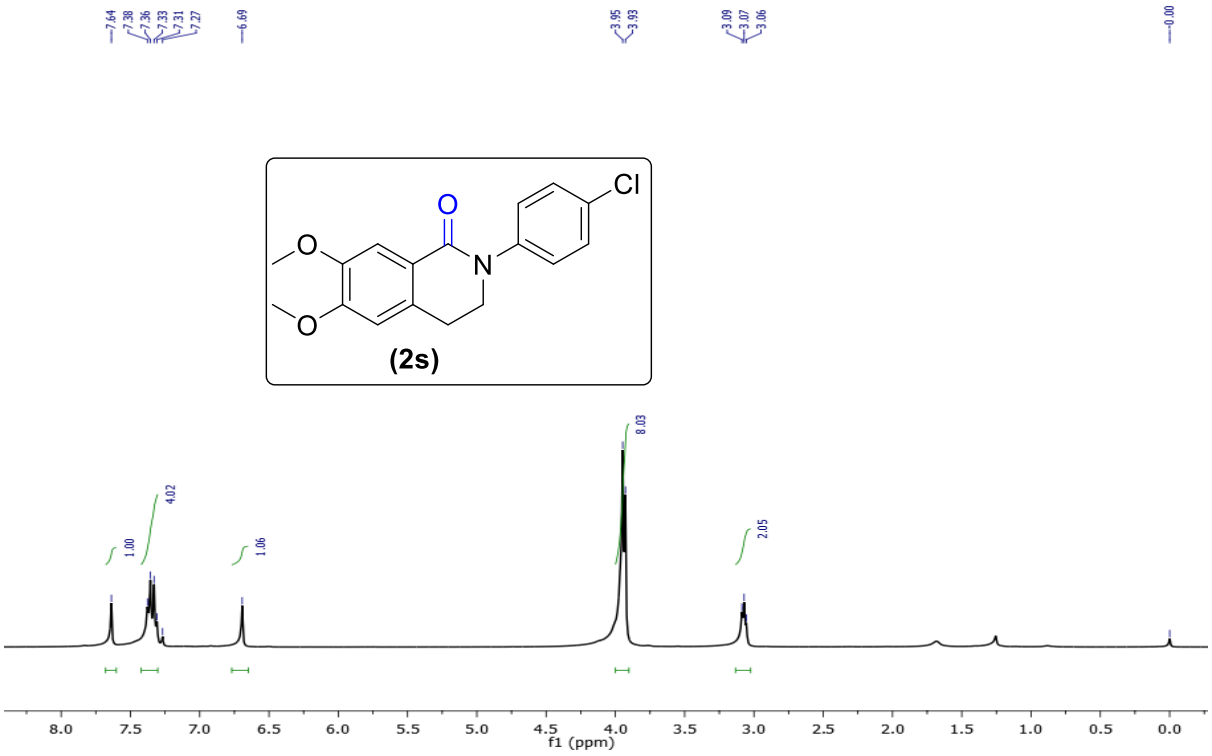
^{1}H NMR of 2-(Thiophen-3-yl)-3, 4-dihydroisoquinolin-1(2H)-one **(2r)** in $CDCl_3$



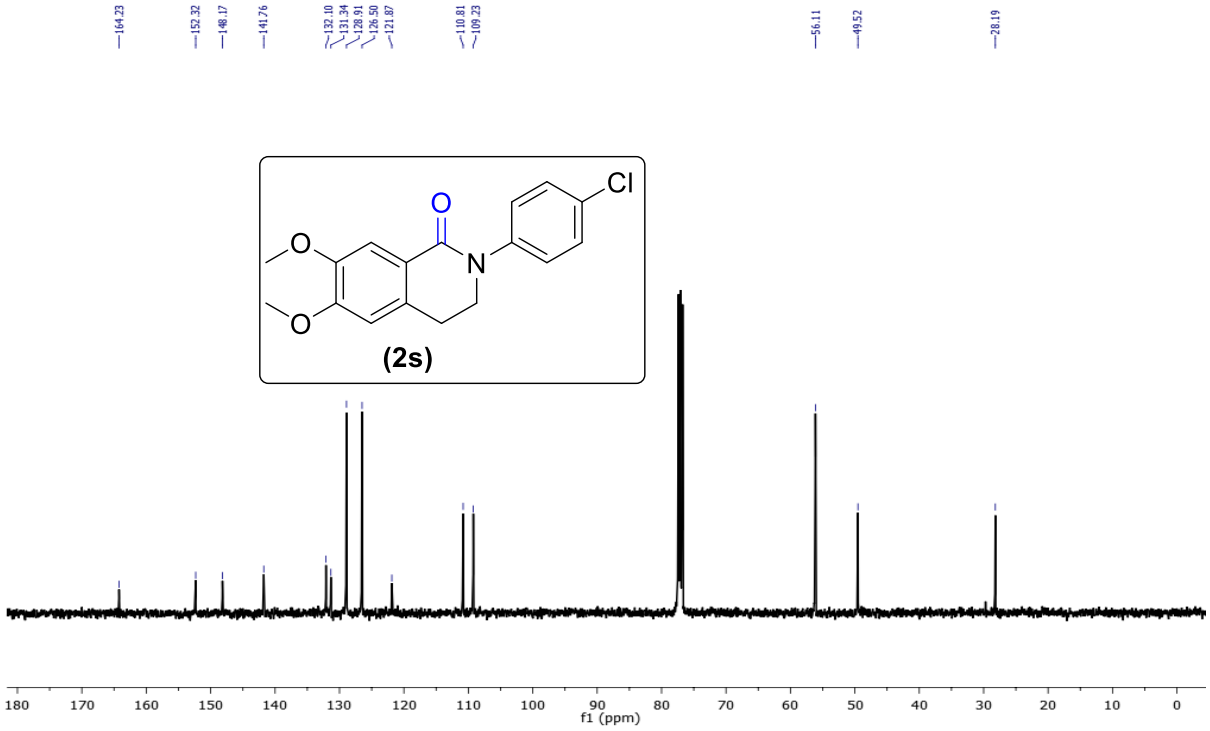
^{13}C NMR of 2-(Thiophen-3-yl)-3, 4-dihydroisoquinolin-1(2H)-one **(2r)** in $CDCl_3$



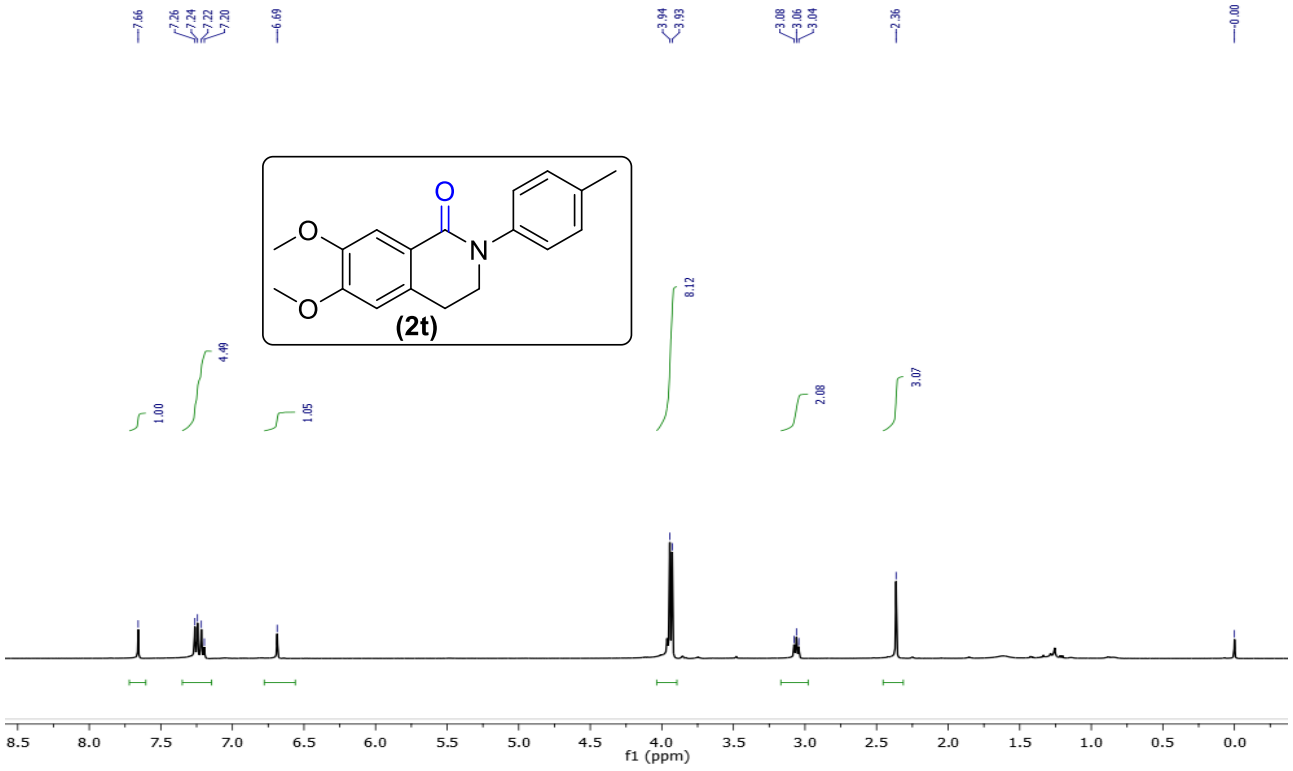
^{1}H NMR of 2-(4-Chlorophenyl)-6, 7-dimethoxy-3, 4-dihydroisoquinolin-1(2H)-one **(2s)** in $CDCl_3$



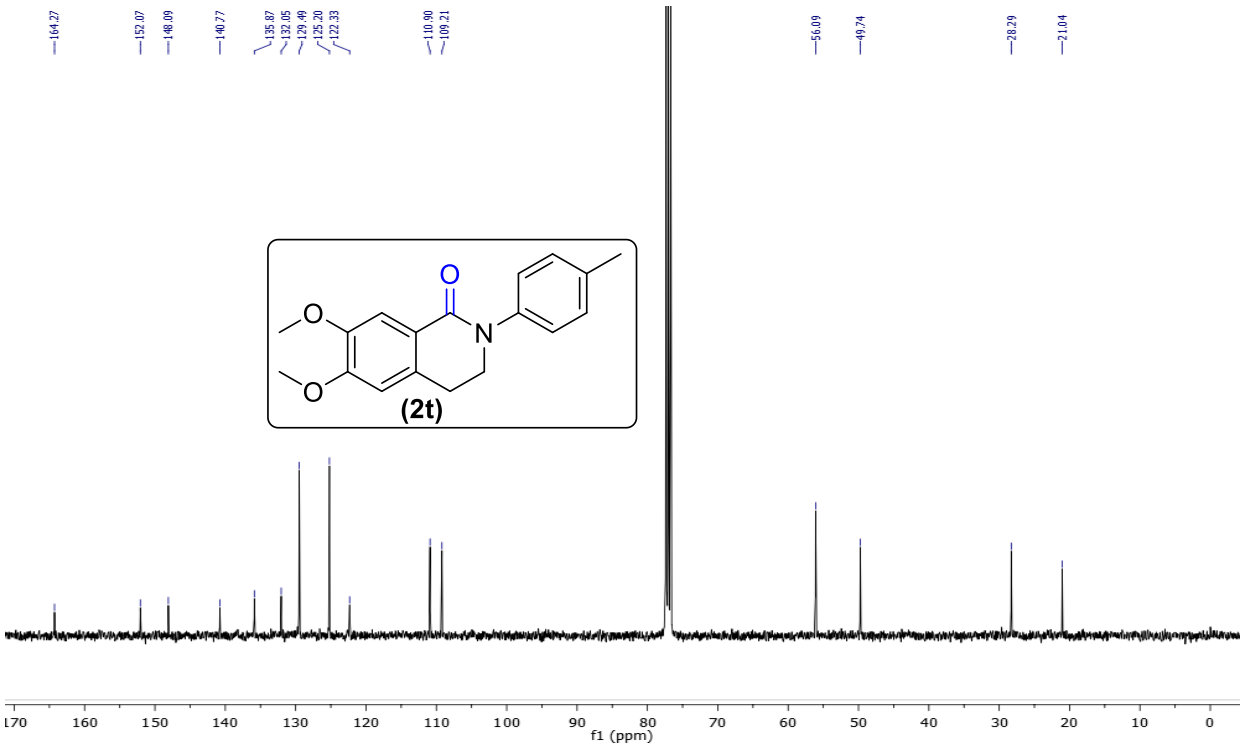
^{13}C NMR of 2-(4-Chlorophenyl)-6, 7-dimethoxy-3, 4-dihydroisoquinolin-1(2H)-one **(2s)** in $CDCl_3$



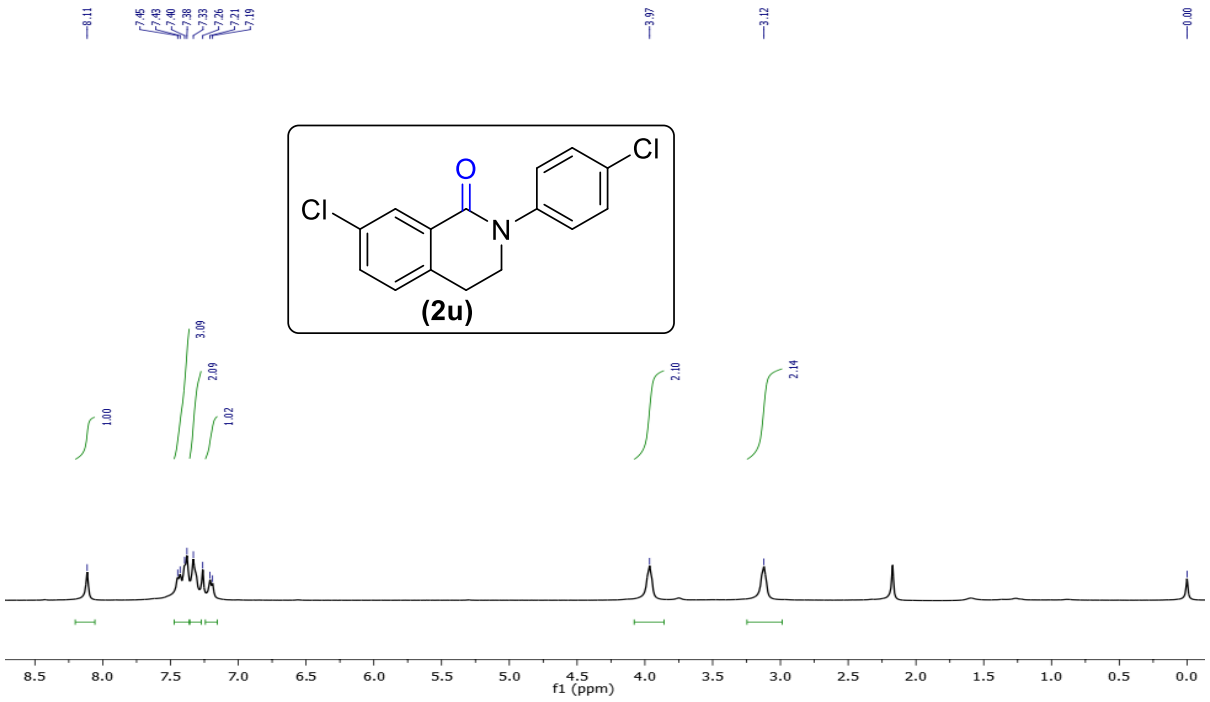
^{1}H NMR of 6,7-dimethoxy-2-(*p*-tolyl)-3,4-dihydroisoquinolin-1(2H)-one **(2t)** in $CDCl_3$



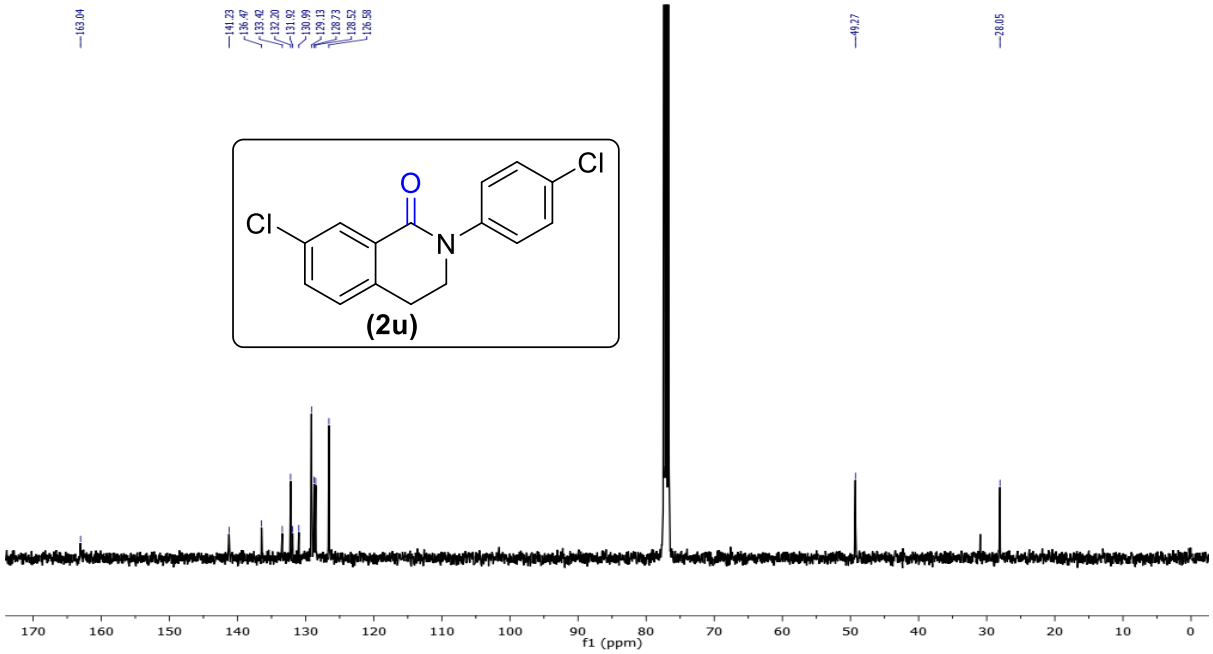
^{13}C NMR of 6,7-dimethoxy-2-(*p*-tolyl)-3,4-dihydroisoquinolin-1(2H)-one **(2t)** in $CDCl_3$



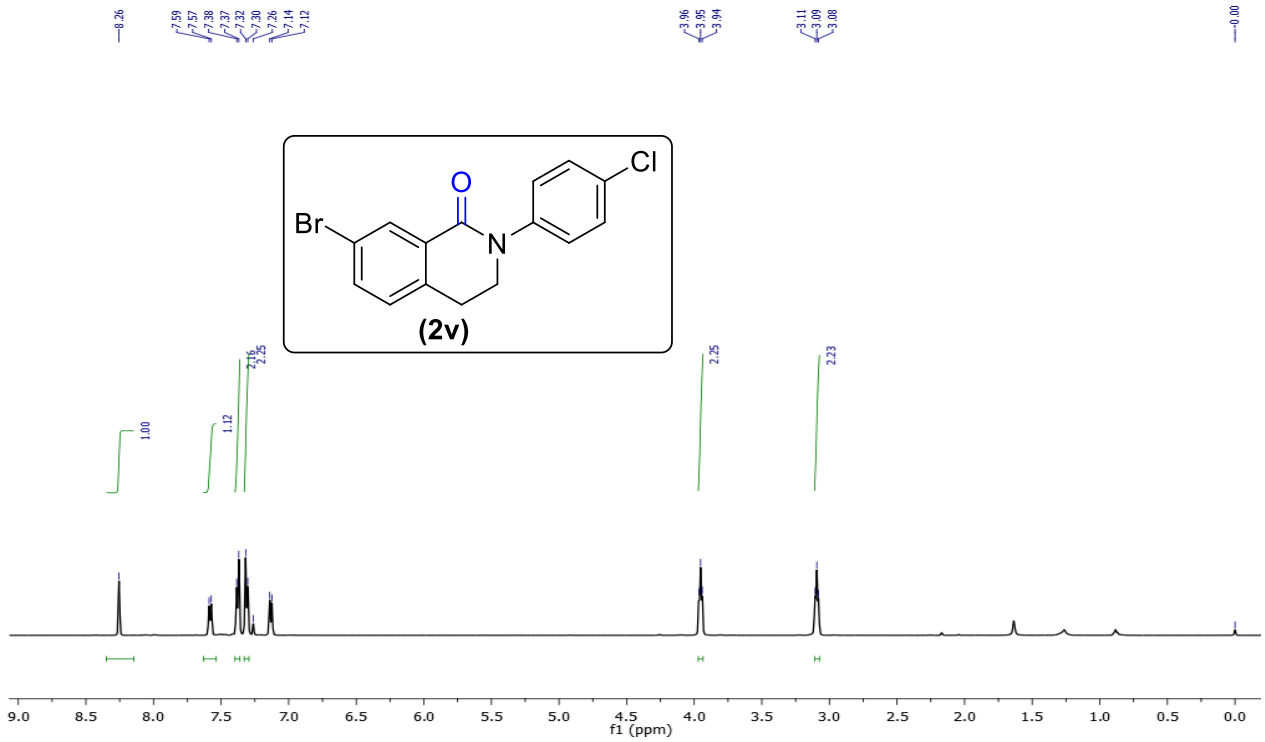
^{1}H NMR of 7-chloro-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2u)** in $CDCl_3$



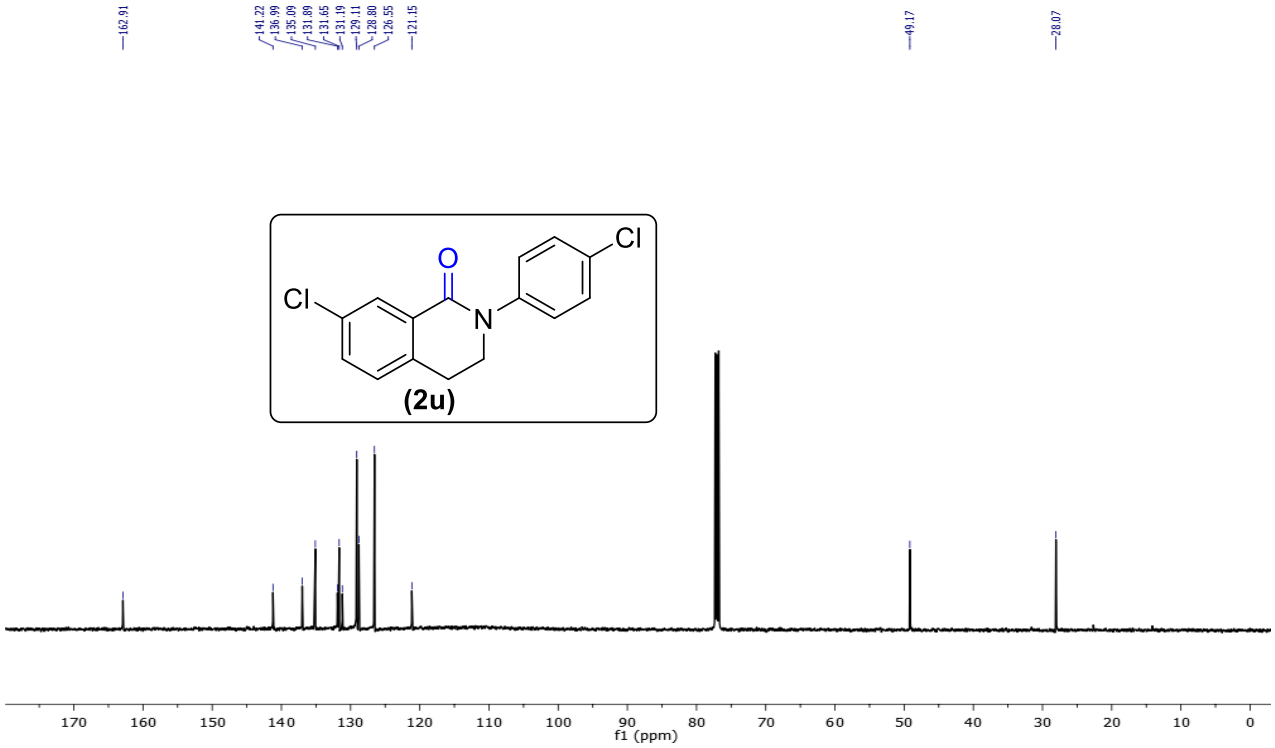
^{13}C NMR of 7-chloro-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2u)** in $CDCl_3$



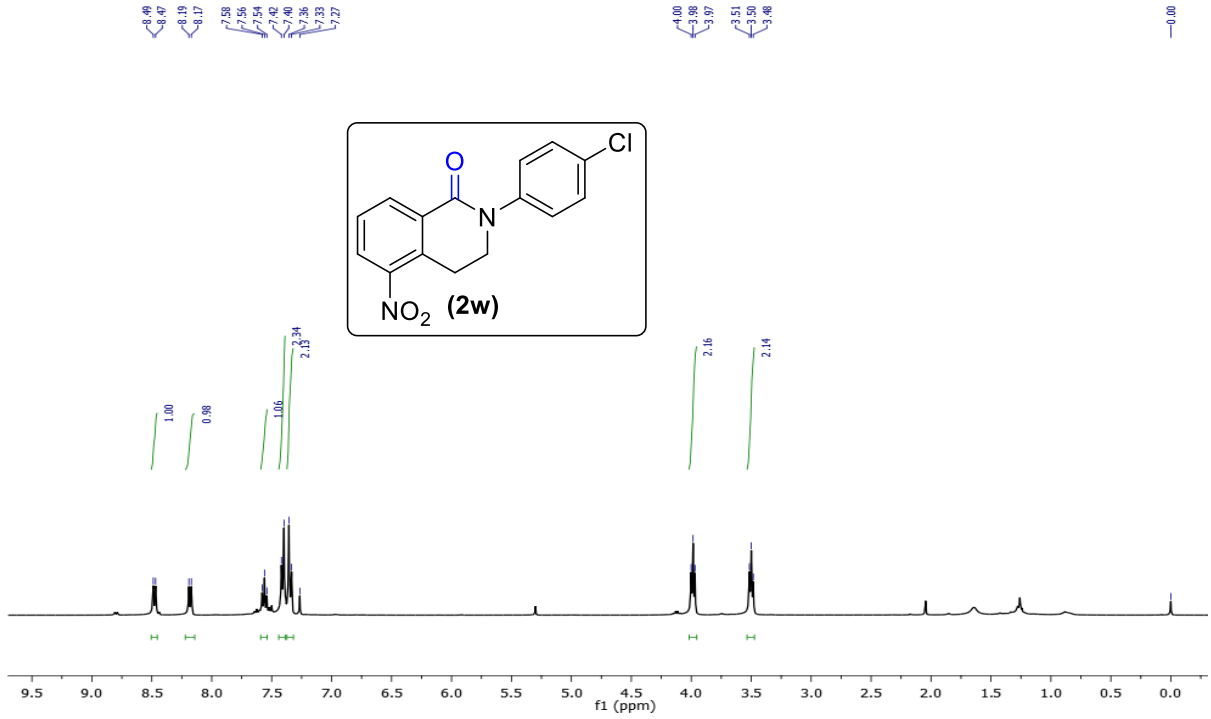
^{1}H NMR of 7-Bromo-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2v)** in $CDCl_3$



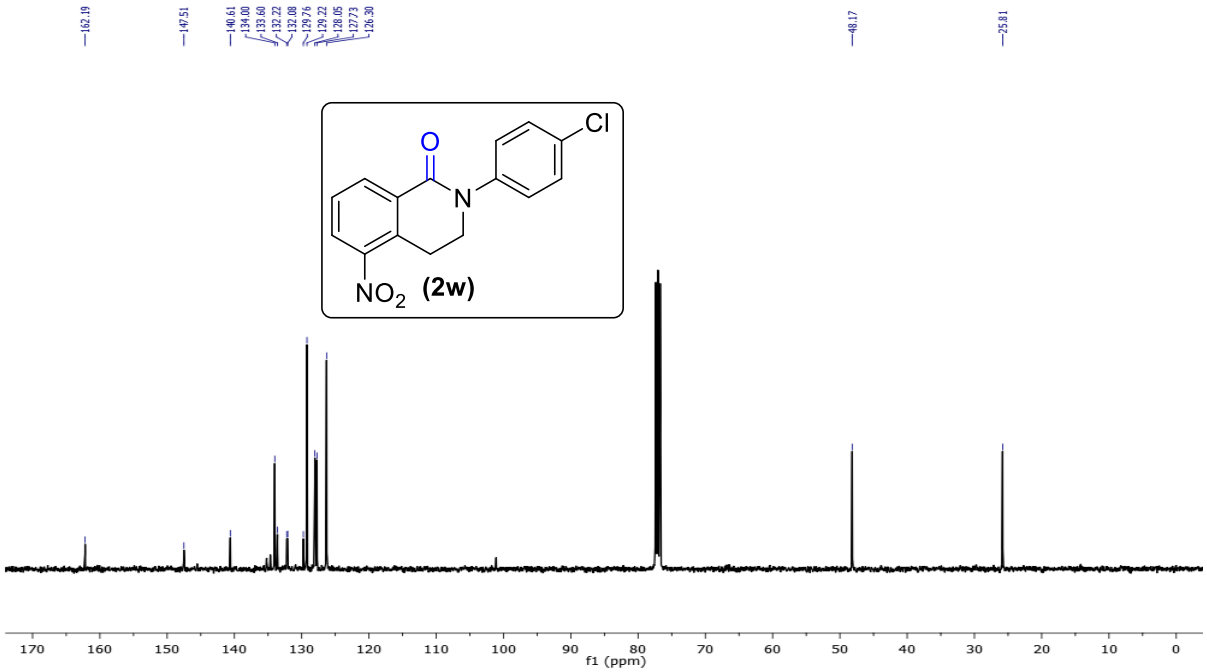
^{13}C NMR of 7-Bromo-2-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one **(2v)** in $CDCl_3$



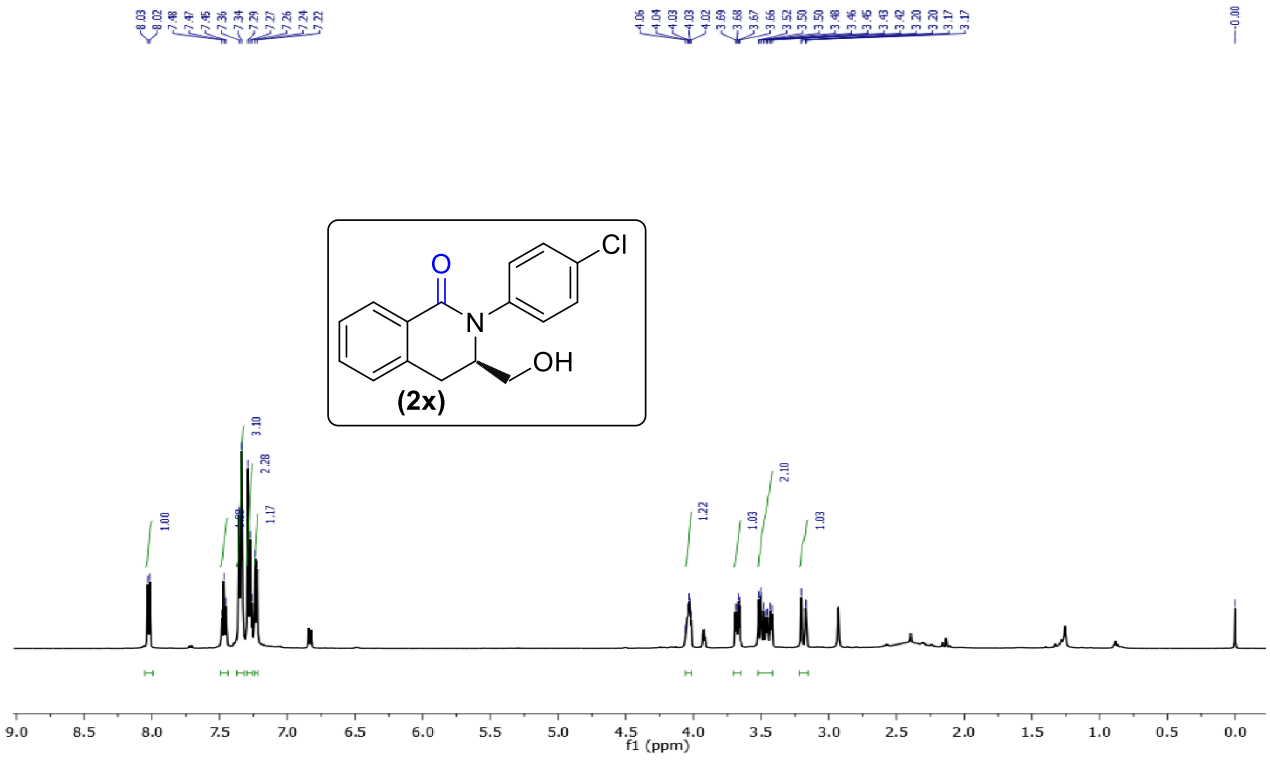
^{1}H NMR of 2-(4-chlorophenyl)-8-nitro-3,4-dihydroisoquinolin-1(2H)-one **(2w)** in $CDCl_3$



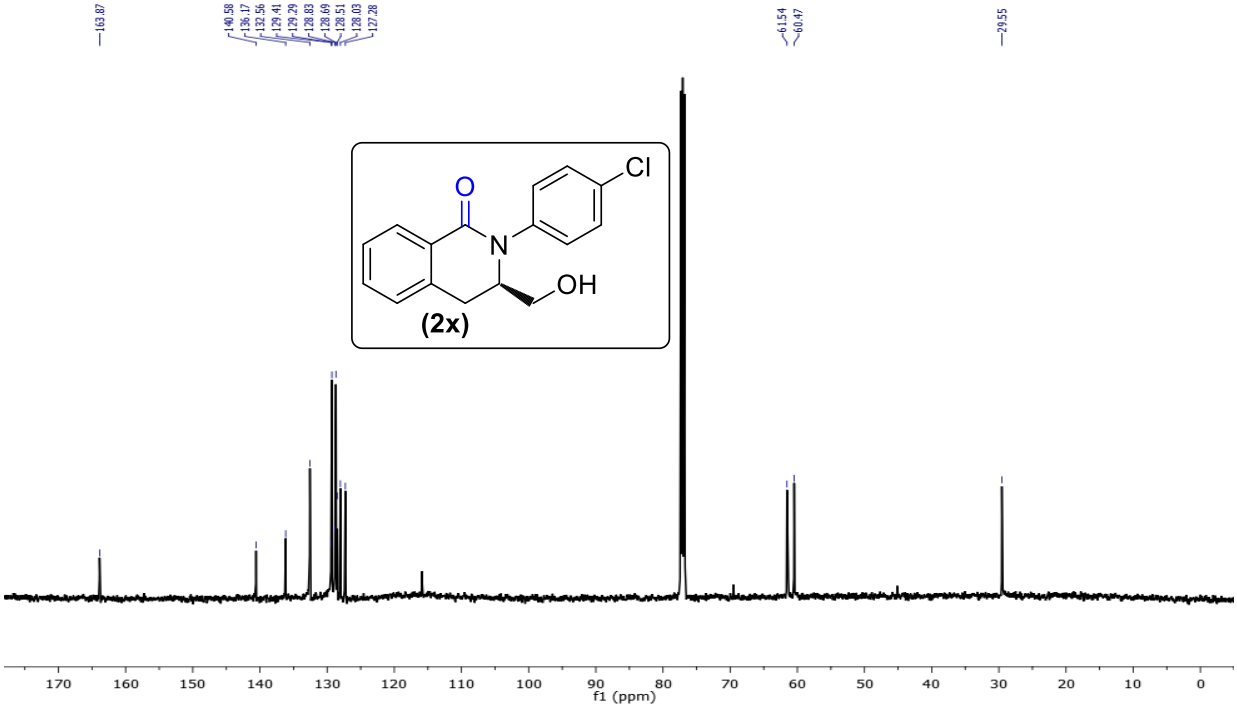
^{13}C NMR of 2-(4-chlorophenyl)-8-nitro-3,4-dihydroisoquinolin-1(2H)-one **(2w)** in $CDCl_3$



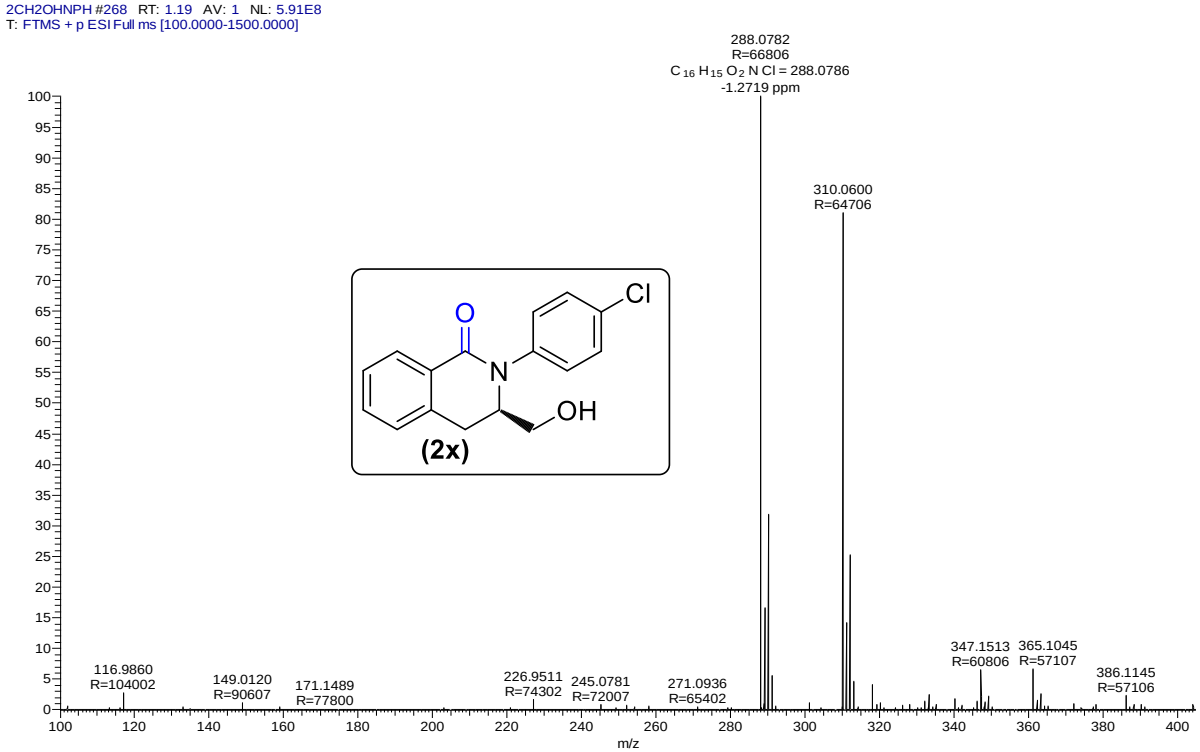
^{1}H NMR of (S)-2-(4-Chlorophenyl)-3-(hydroxymethyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2x)** in $CDCl_3$



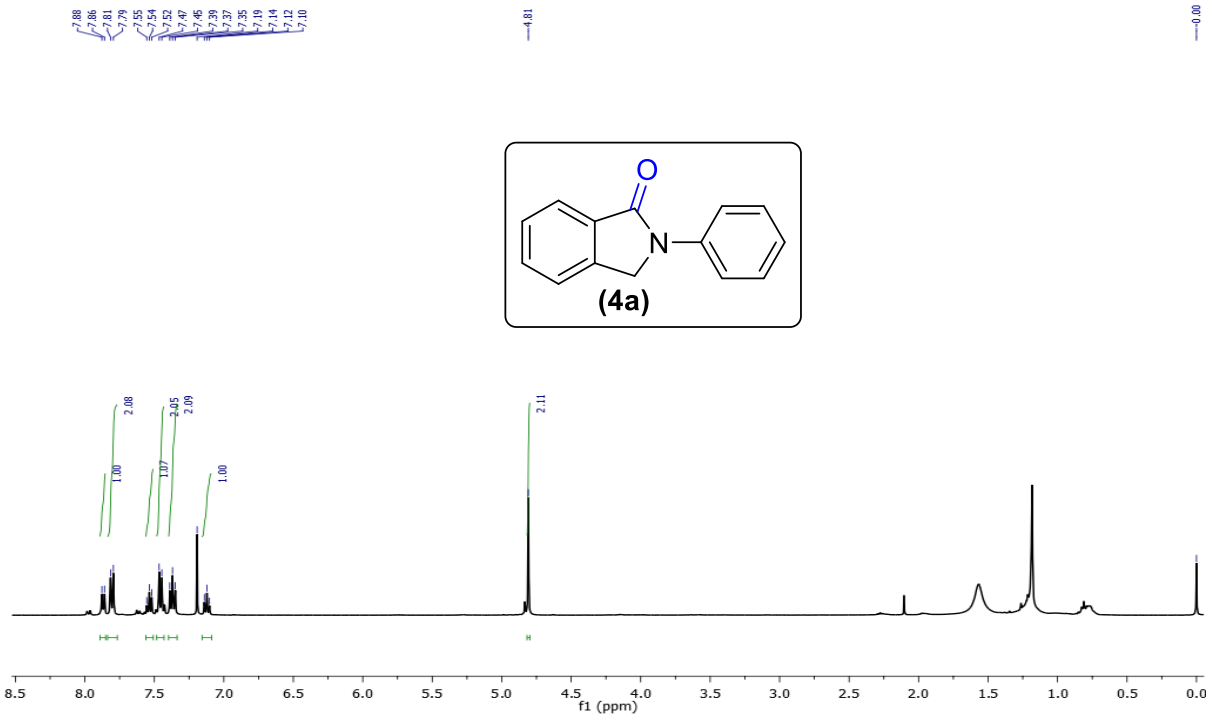
^{13}C NMR of (S)-2-(4-Chlorophenyl)-3-(hydroxymethyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2x)** in $CDCl_3$



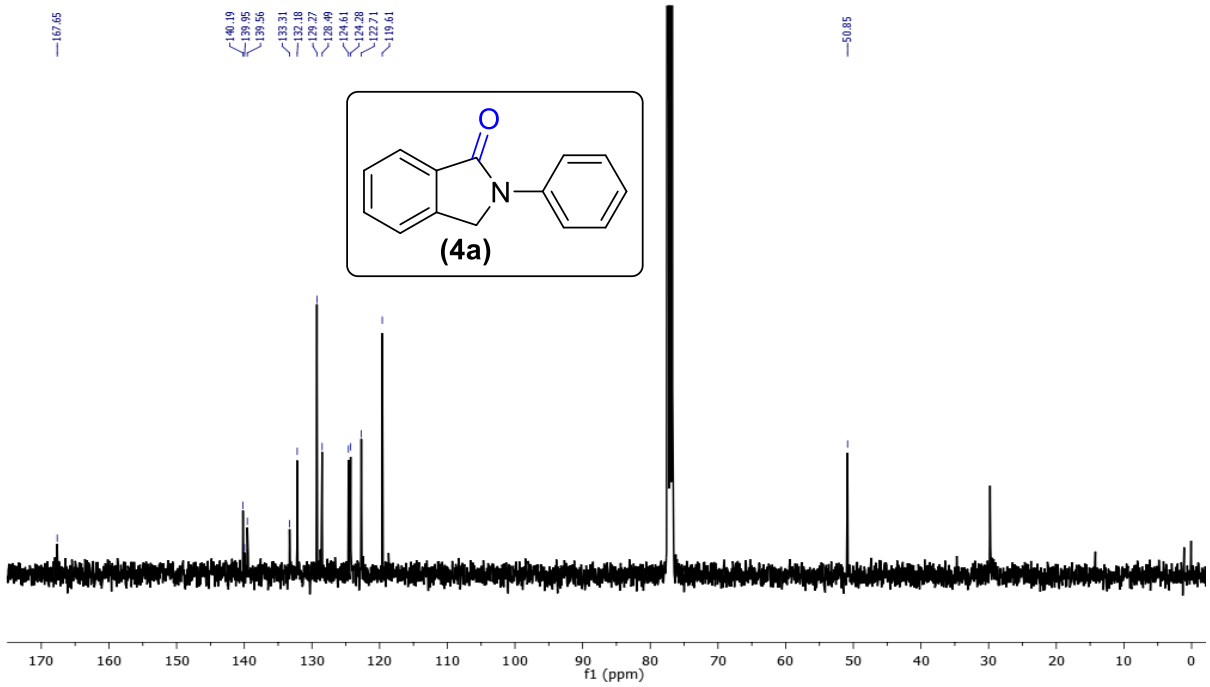
HRMS of (S)-2-(4-Chlorophenyl)-3-(hydroxymethyl)-3, 4-dihydroisoquinolin-1(2H)-one **(2x)**



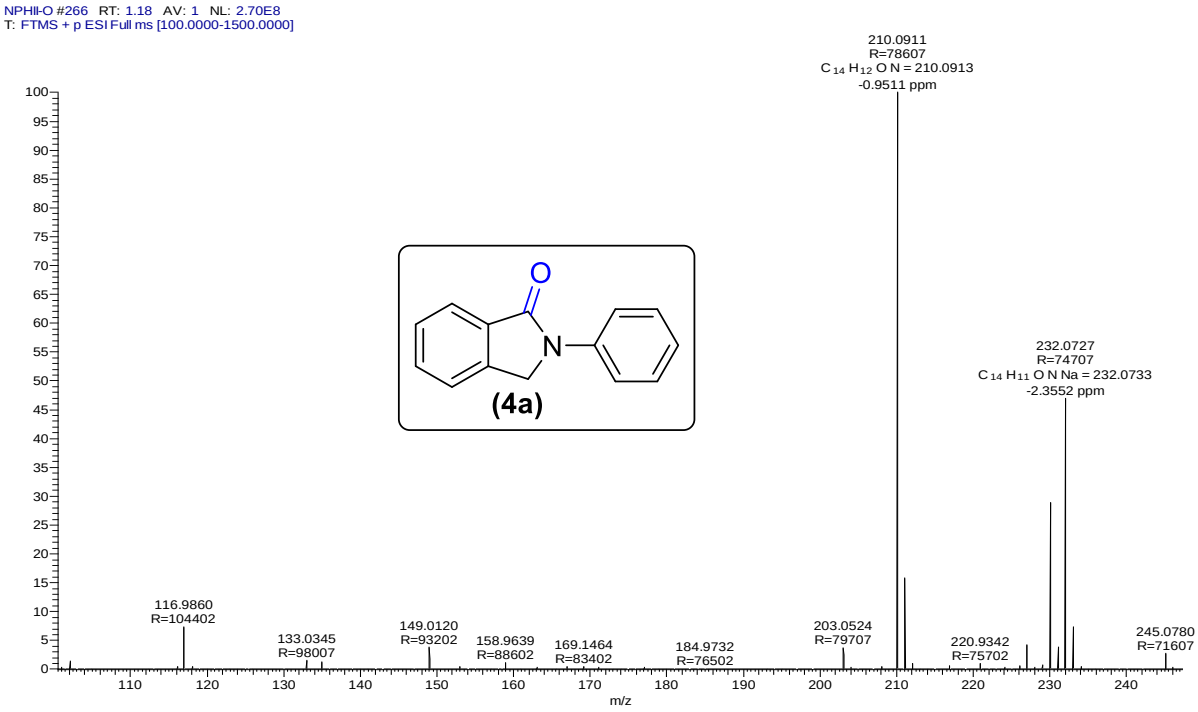
^{1}H NMR of 2-Phenylisoindolin-1-one **(4a)** in $CDCl_3$



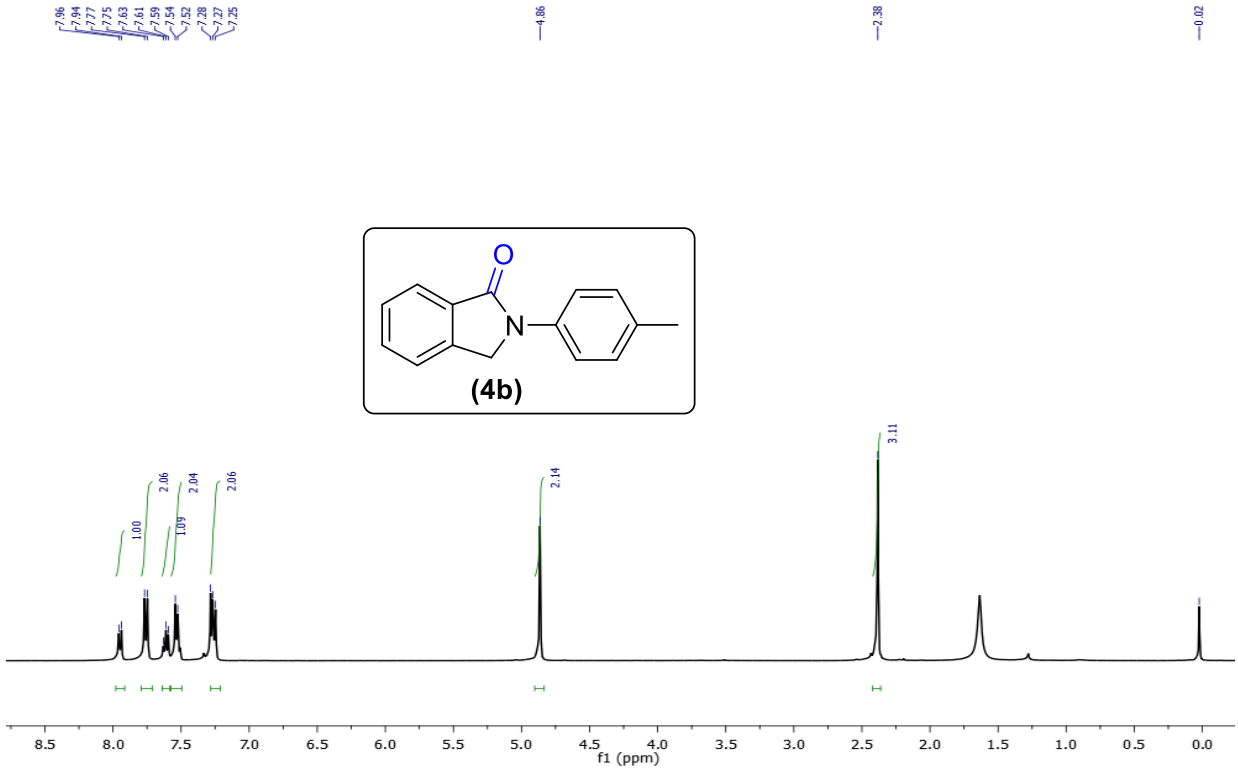
^{13}C NMR of 2-Phenylisoindolin-1-one **(4a)** in $CDCl_3$



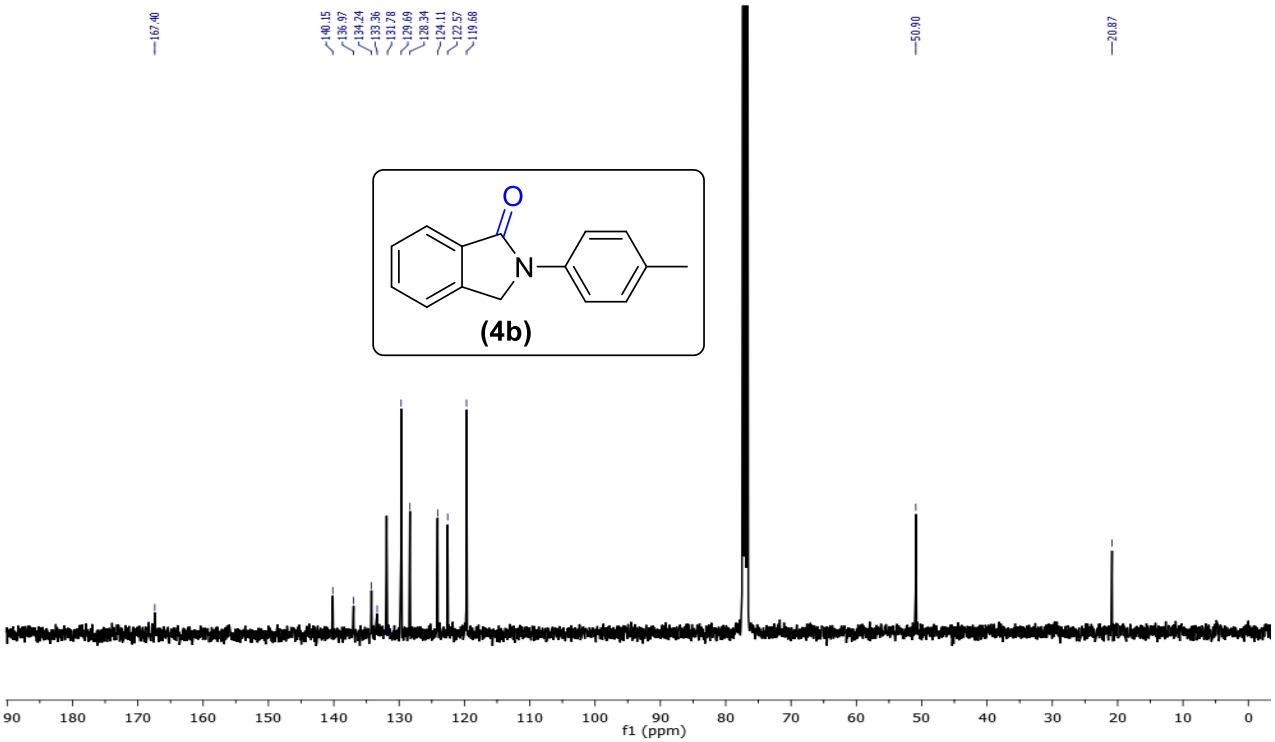
HRMS of 2-Phenylisoindolin-1-one **(4a)**



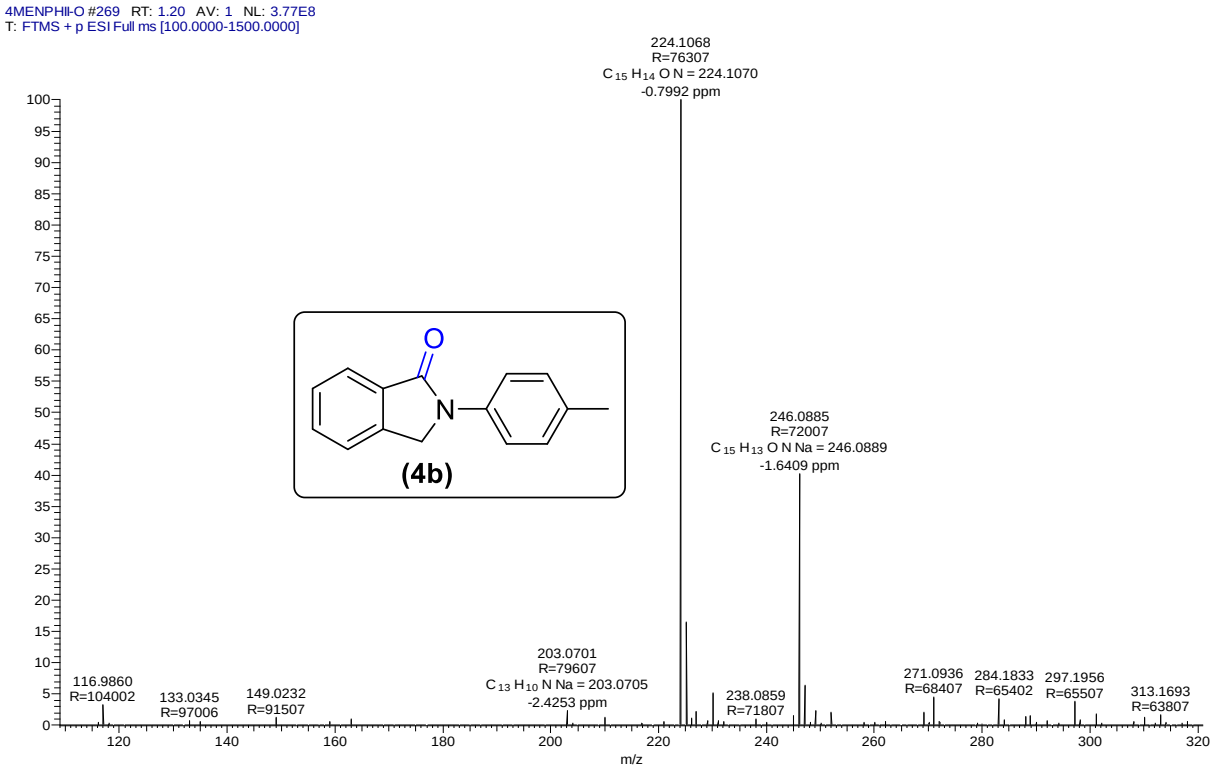
^{1}H NMR of 2-(*p*-tolyl)isoindolin-1-one **(4b)** in $CDCl_3$



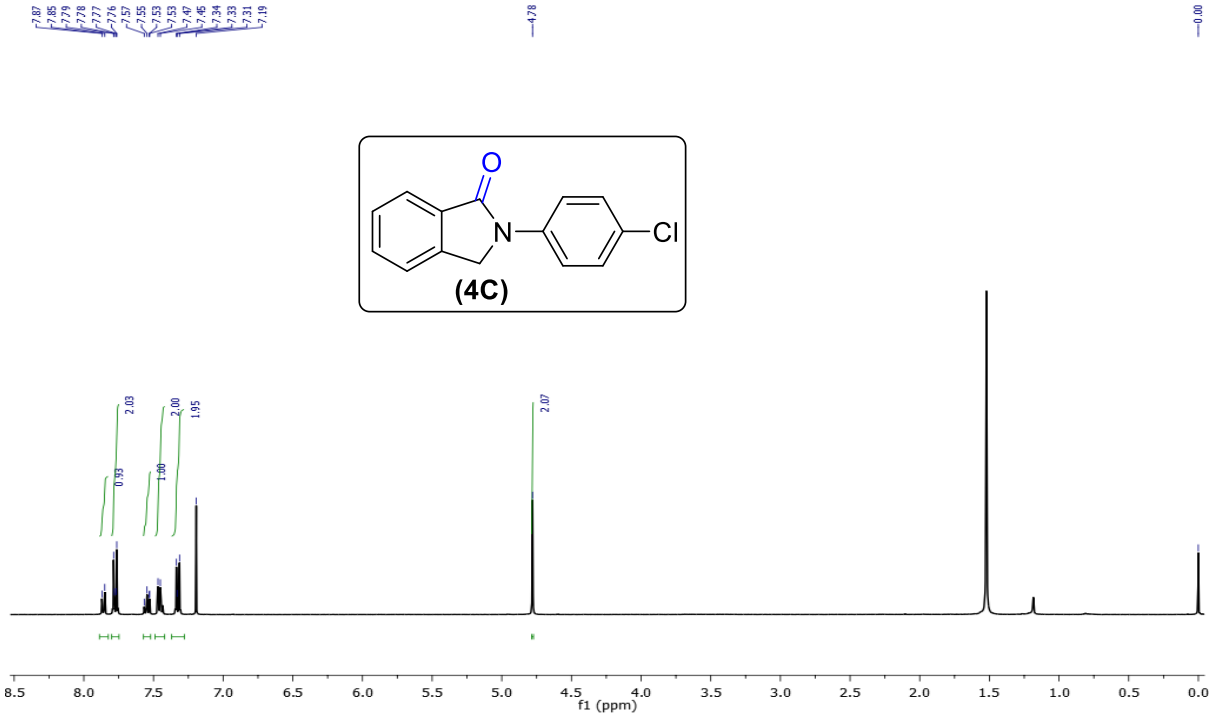
^{13}C NMR of 2-(*p*-tolyl)isoindolin-1-one **(4b)** in $CDCl_3$



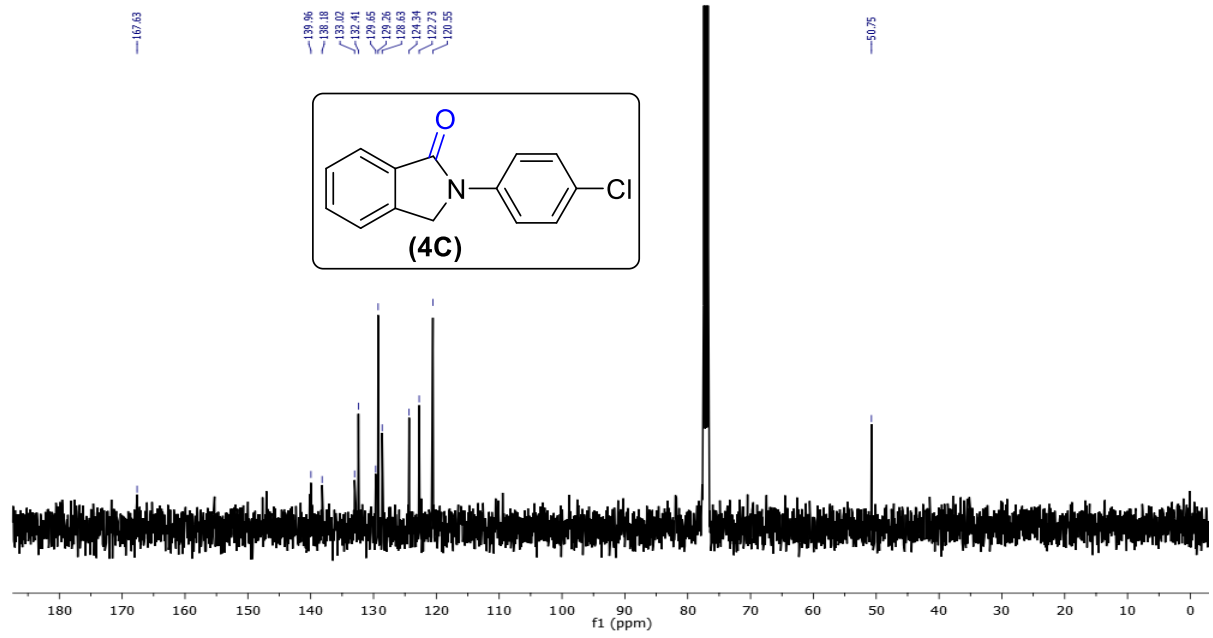
HRMS of 2-(*p*-tolyl)isoindolin-1-one **(4b)**



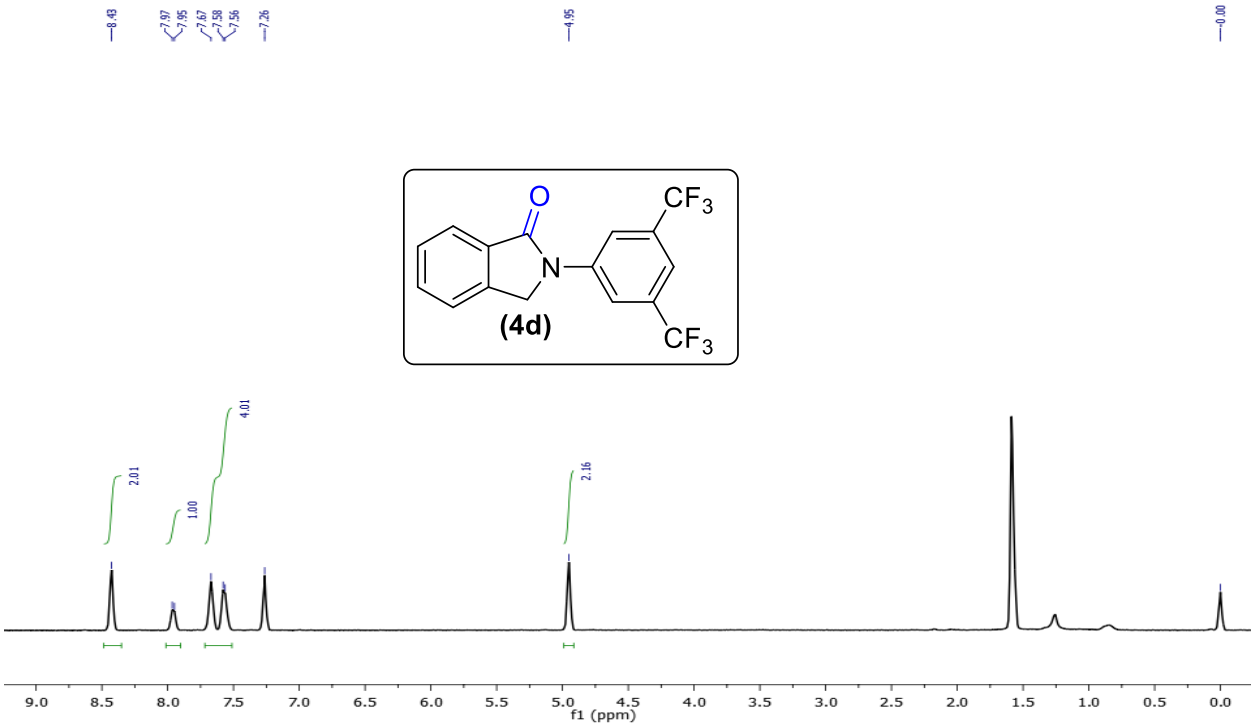
^{1}H NMR of 2-(4-Chlorophenyl)isoindolin-1-one **(4c)** in $CDCl_3$



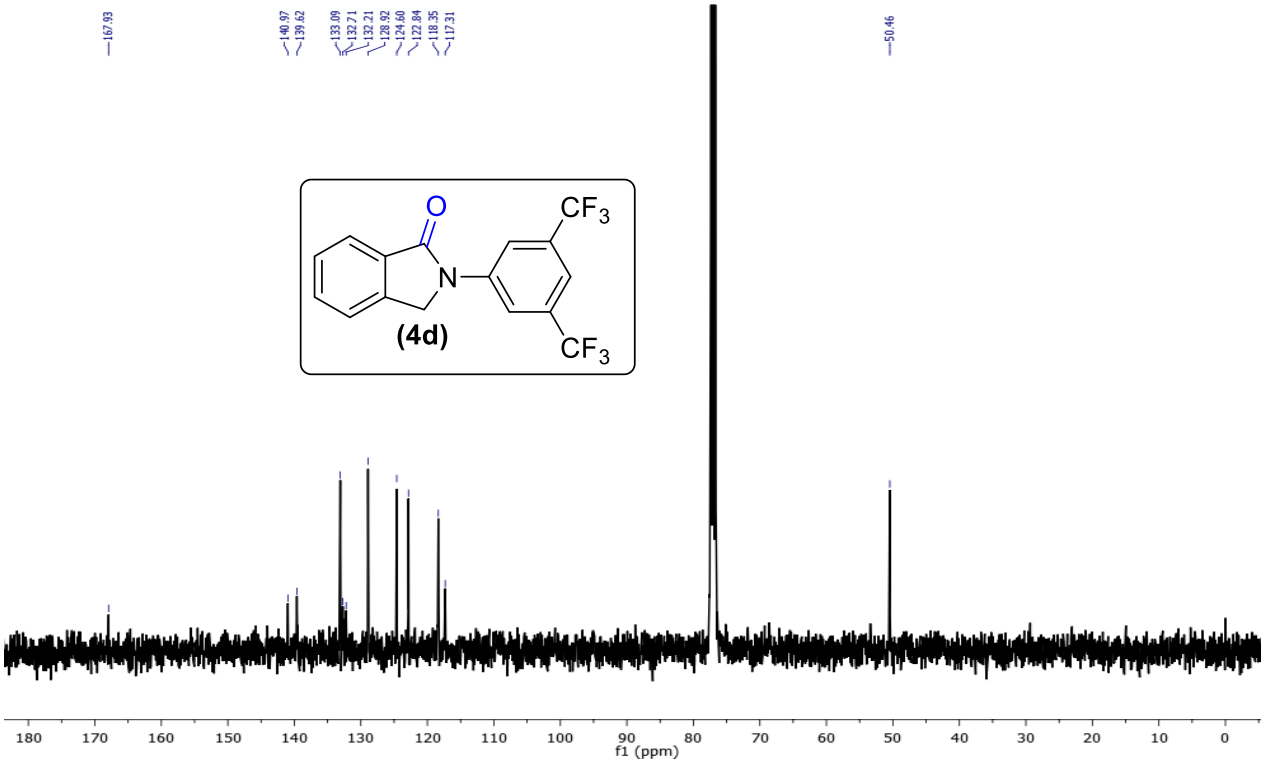
^{13}C NMR of2-(4-Chlorophenyl)isoindolin-1-one **(4c)** in $CDCl_3$



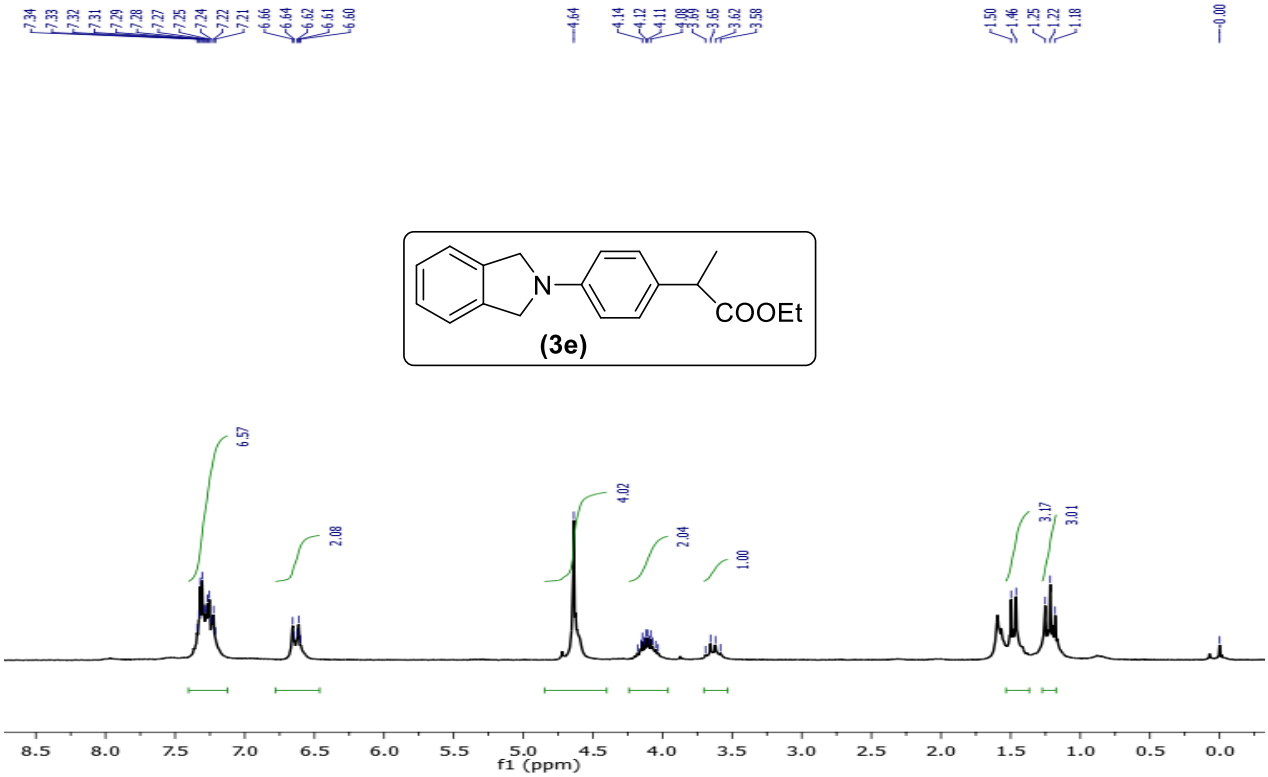
^{1}H NMR of 2-(3,5-bis(trifluoromethyl)phenyl)isoindolin-1-one **(4d)** in $CDCl_3$



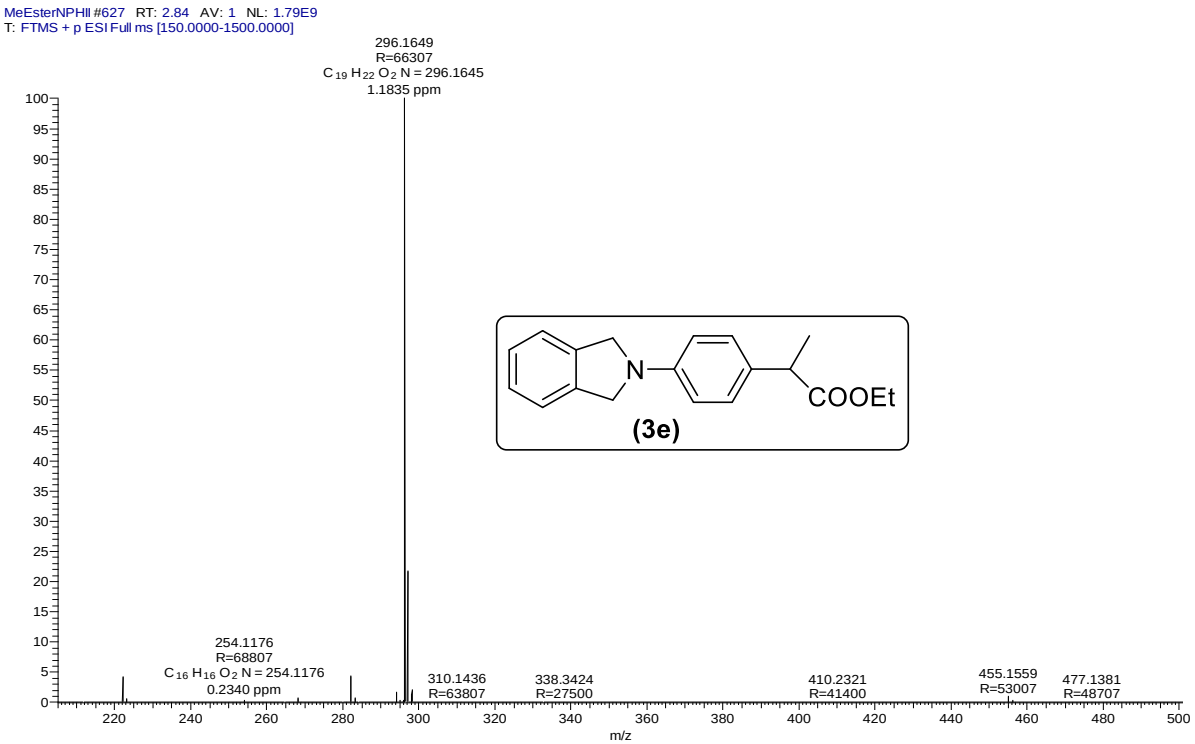
^{13}C NMR of 2-(3,5-bis(trifluoromethyl)phenyl)isoindolin-1-one **(4d)** in $CDCl_3$



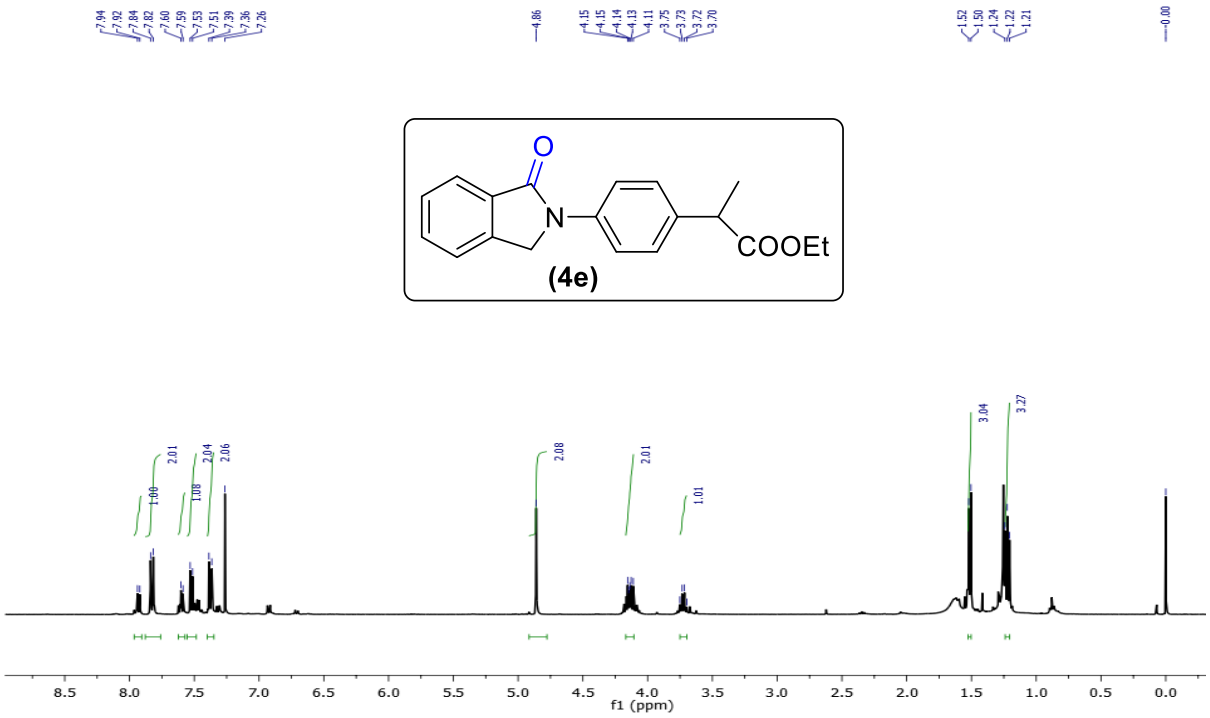
^{1}H NMR of Ethyl 2-(4-(isoindolin-2-yl) phenyl) propanoate **(3e)** in $CDCl_3$



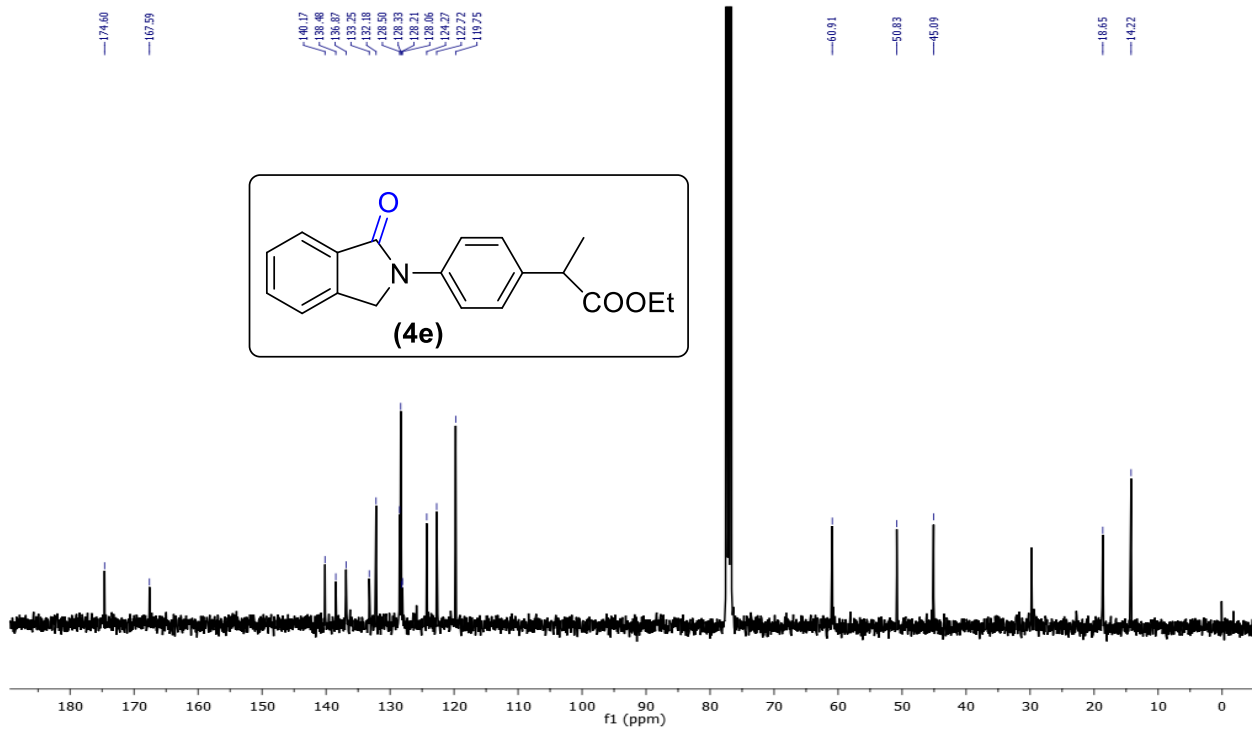
HRMS of Ethyl 2-(4-(isoindolin-2-yl) phenyl) propanoate **(3e)**



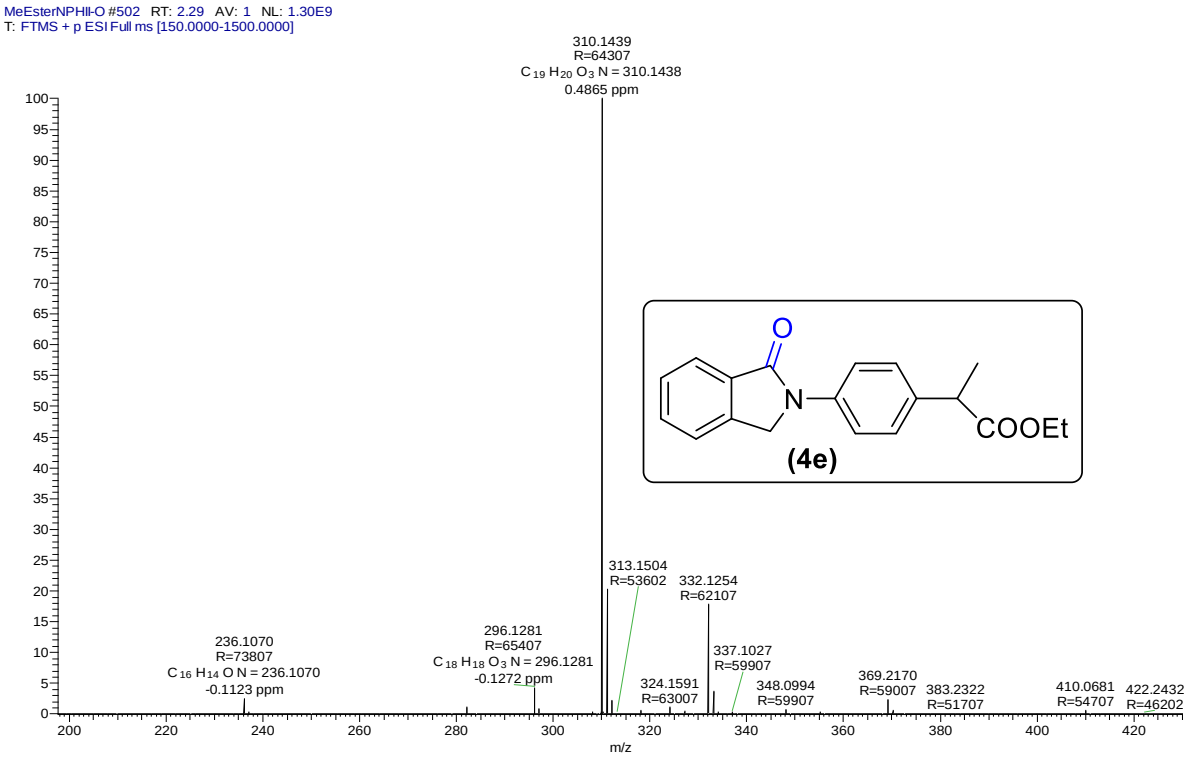
^{1}H NMR of Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) propanoate **(4e)** in $CDCl_3$



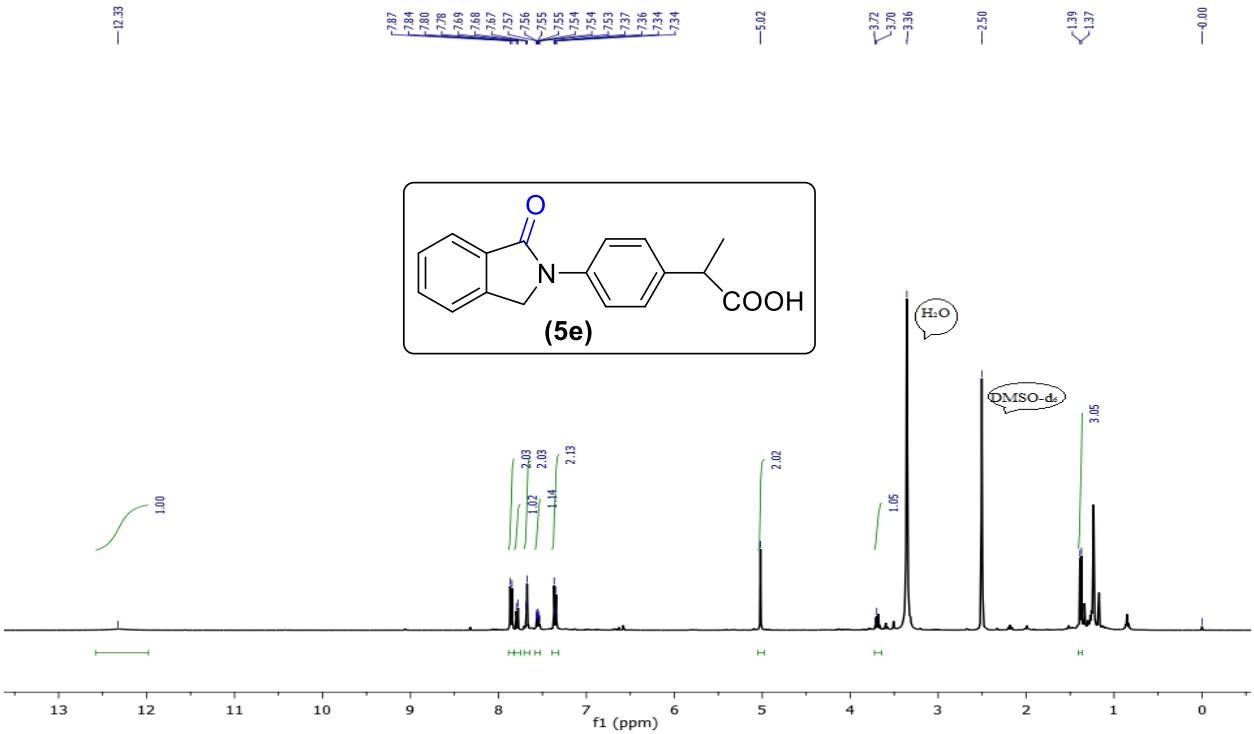
^{13}C NMR of Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) propanoate **(4e)** in $CDCl_3$



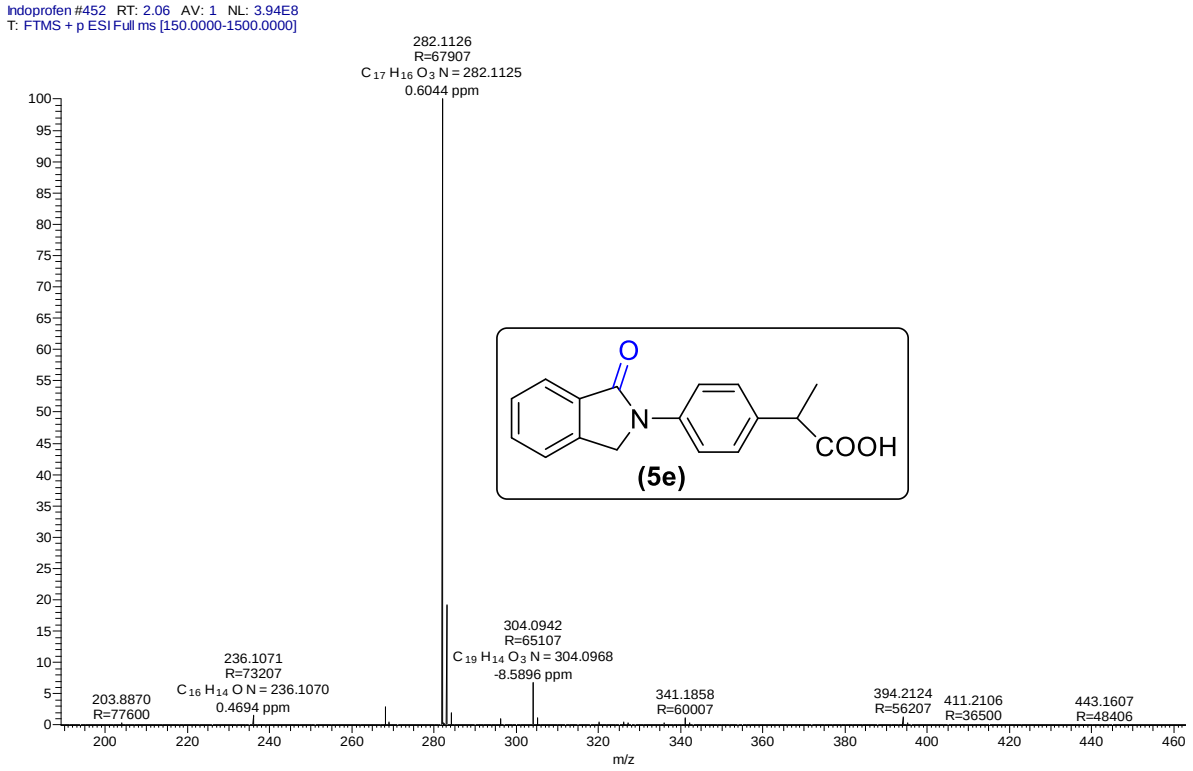
HRMS of Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) propanoate **(4e)**



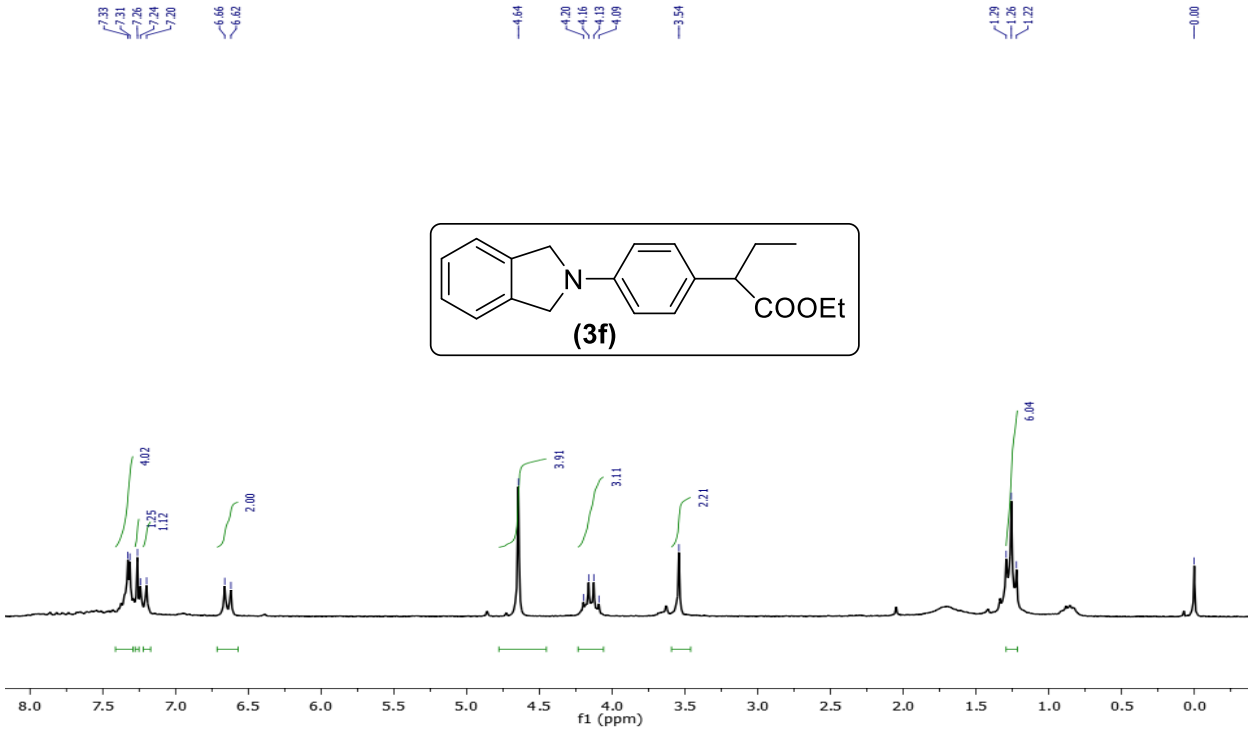
^{1}H NMR of Indoprofen **(5e)** in DMSO-d_6



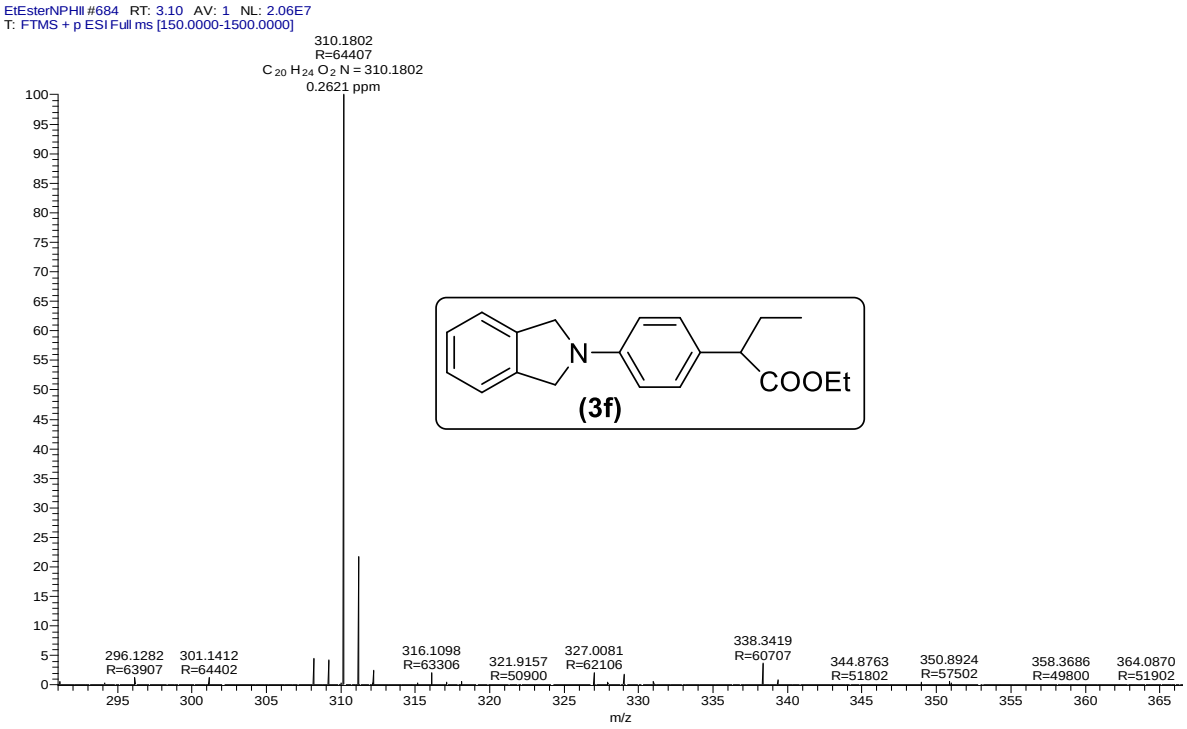
HRMS of Indoprofen **(5e)**



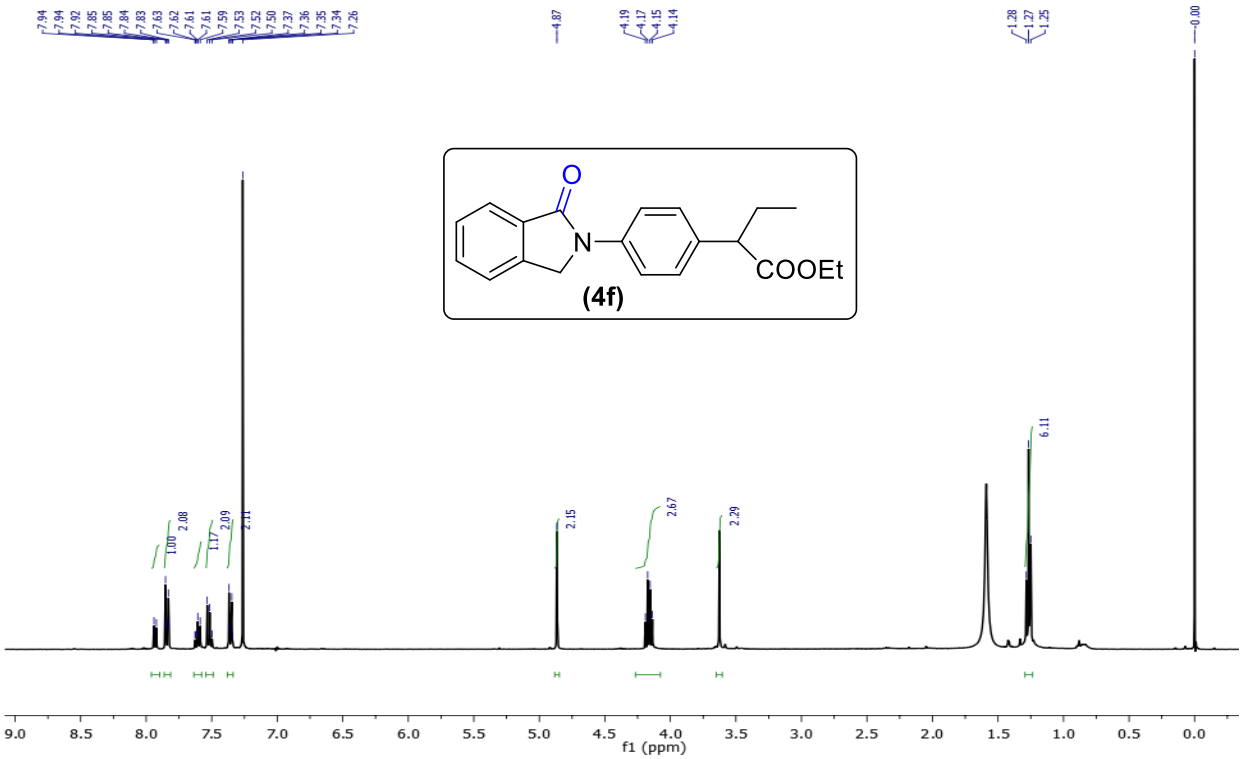
^{1}H NMR of Ethyl 2-(4-(isoindolin-2-yl) phenyl) butanoate **(3f)** in $CDCl_3$



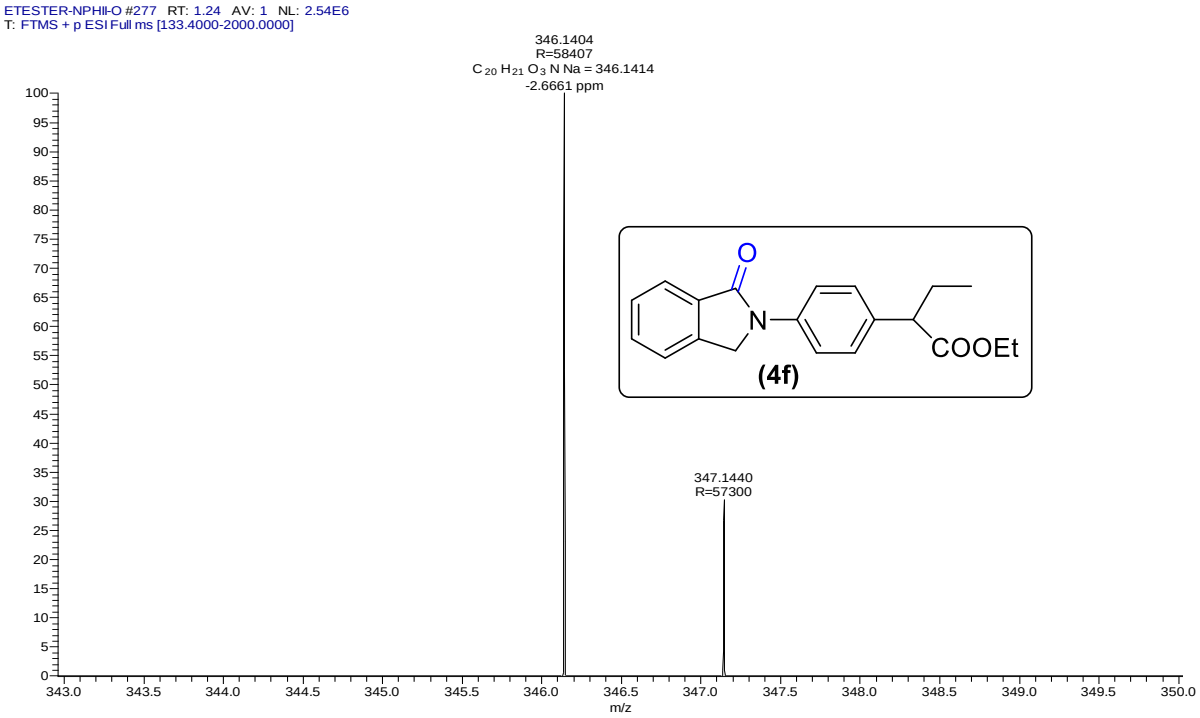
HRMS of Ethyl 2-(4-(isoindolin-2-yl) phenyl) butanoate **(3f)**



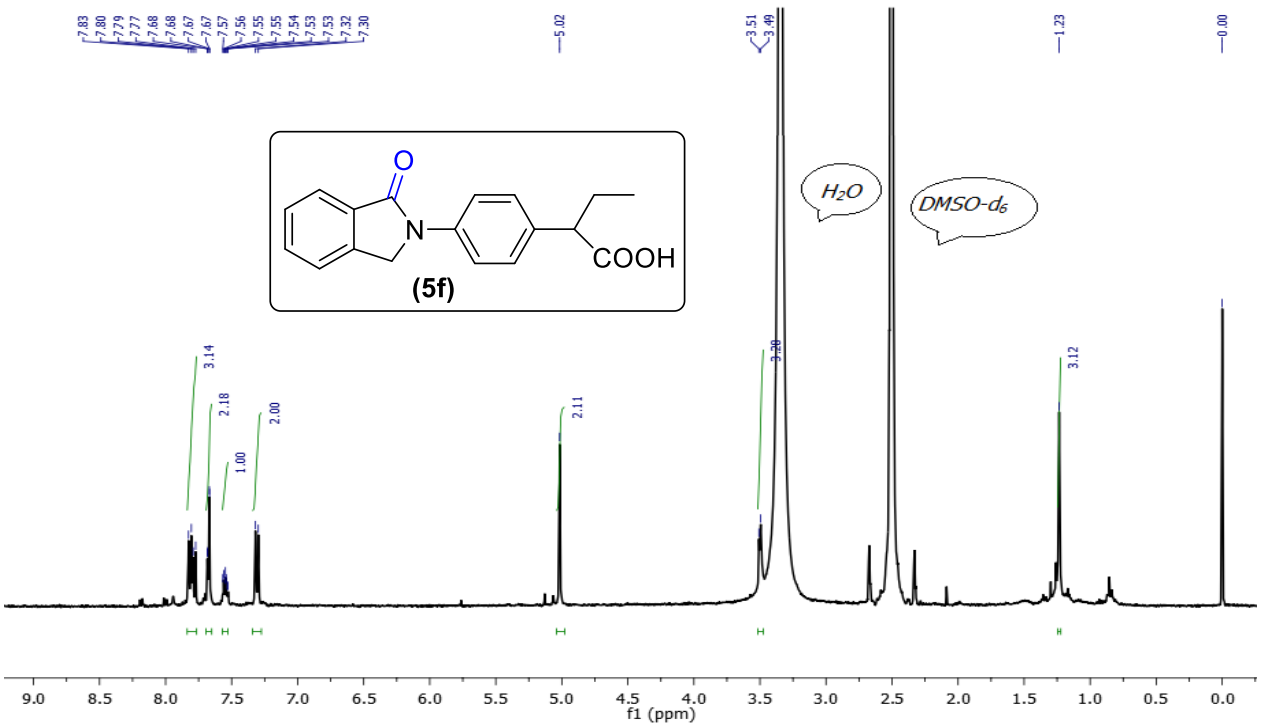
^{1}H NMR Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) butanoate **(4f)** in $CDCl_3$



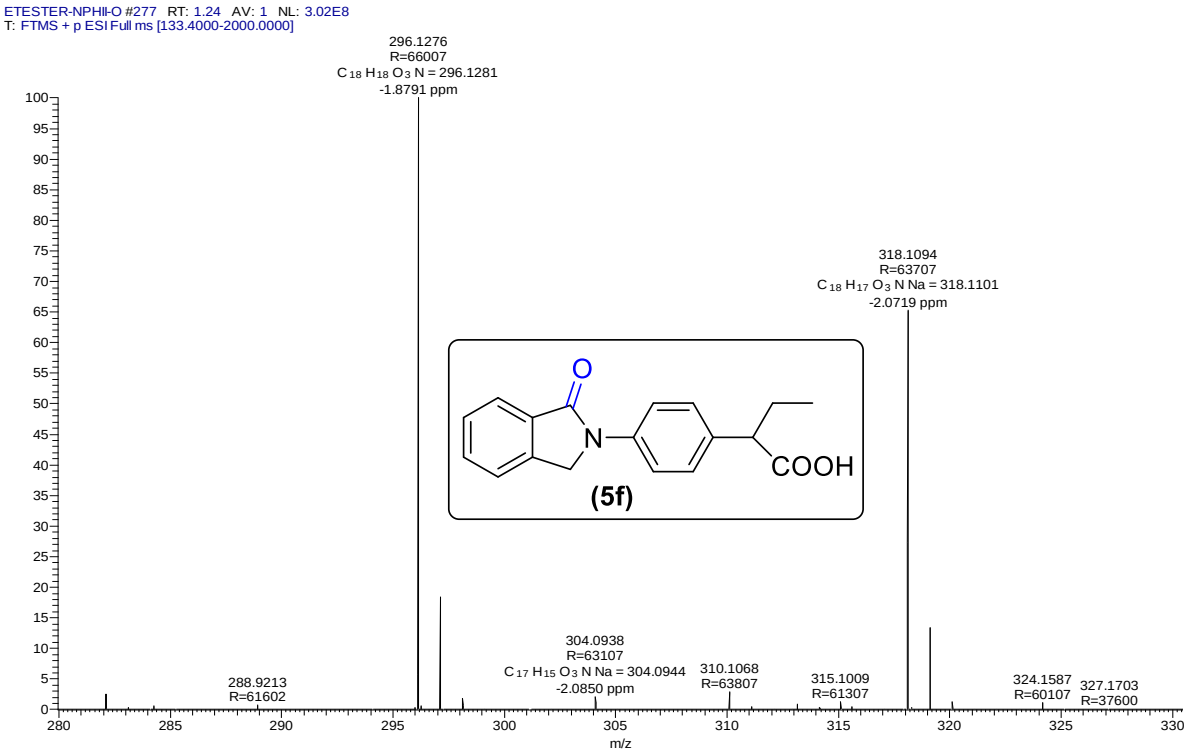
HRMS of Ethyl 2-(4-(1-oxoisoindolin-2-yl) phenyl) butanoate **(4f)** in $CDCl_3$



^{1}H NMR of Indobufen **(5f)** in DMSO-d_6

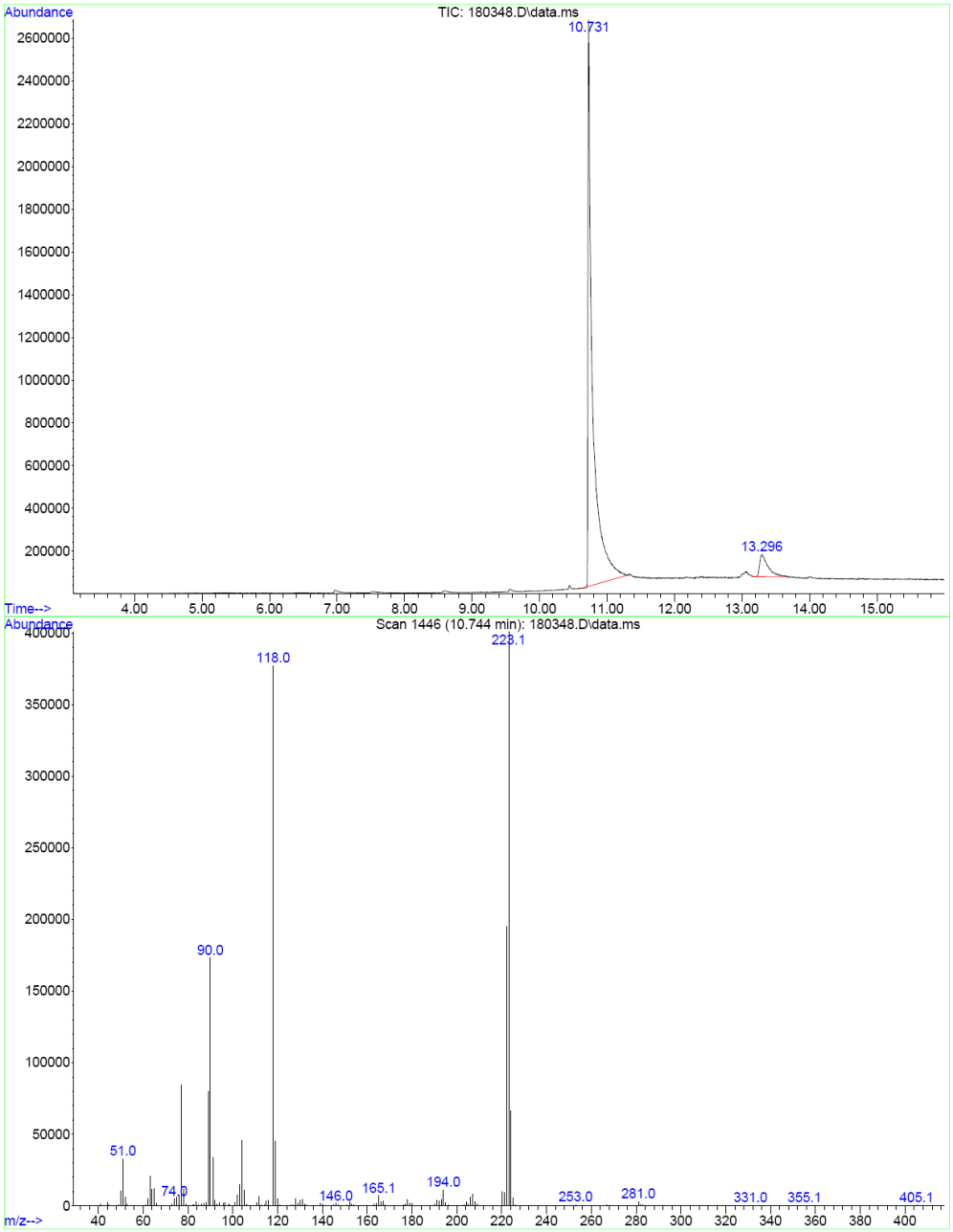


HRMS of Indobufen **(5f)**



2.2.10 GC-MS spectrum of the reaction of *N*-phenyl tetrahydroisoquinoline in the presence of H_2O^{18}

```
File       :D:\NCL\DATA\OCD\Year_2018\180348.D
Operator   : Dr. Borikar
Acquired   : 20 Apr 2018  12:29     using AcqMethod OCD_Common.M
Instrument :    GCMSD
Sample Name:
Misc Info  : O18-4
Vial Number: 0
```



2.1.11 References

1. (a) Toyooka, N.; Nemoto, H. In Studies in Natural Products Chemistry; Atta-ur-Rahman, Ed.; Elsevier B. V. **2003**; p 419. (b) Guntern, A.; Ioset, J.-R.; Queiroz, E. F.; Sándor, P.; Foggin, C. M.; Hostettmann, K. *J. Nat. Prod.* **2003**, *66*, 1550. (c) Drawz, S. M.; Bonomo, R. A. *Clin. Microbiol. Rev.* **2010**, *23*, 160. (d) Kazmierski, W. M.; Andrews, W.; Furfine, E.; Spaltenstein, A.; Wright, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689. (e) Enz, A.; Feuerbach, D.; Frederiksen, M. U.; Gentsch, C.; Hurth, K.; Müller, W.; Nozulak, J.; Roy, B. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1287. (f) Shorvon, S. *Lancet* **2001**, *358*, 1885.
2. Finney, L. C.; Mitchell, L. J.; Moody, C. J. *Green Chem.* **2018**, *20*, 2242.
3. Howell, J. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. *J. Am. Chem. Soc.* **2015**, 137, 14590.
4. Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
5. (a) Sheehan, J. C.; Tulis, R. W. *J. Org. Chem.* **1974**, *39*, 2264. (b) Wenkert, E.; Angell, E. C. *Synth. Commun.* **1988**, *18*, 1331. (c) Tanaka, K.-I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3125. (d) Al-Subu, M. M.; Jondi, W. J.; Amer, A. A.; Hannoun, M.; Musmar, M. *Chem. Heterocycl. Compd.* **2003**, 39, 478. (e) Wei, Y.; Ding, H.; Lin, S.; Liang, F. *Org. Lett.* **2011**, *13*, 1674. (f) Yan, X.; Fang, K.; Liu, H.; Xi, C. *Chem. Commun.* **2013**, *49*, 10650. (g) Rao, G.; Periasamy, M. *Synlett* **2015**, *26*, 2231. (h) Breault, G.; Eyermann, C. J.; Geng, B.; Morningstar, M.; Reck, F. Compounds for the Treatment of Multi-Drug Resistant Bacterial Infections. Patent Appl. WO2006134378 (A1), **2006**.
6. Mao, B.; Fananas-Mastral, M.; Feringa, B. L. *Chem. Rev.* **2017**, *117*, 10502.
7. Legacy, C. J.; Wang, A.; OÏDay, B. J.; Emmert, M. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 14907.
8. Zhang, Y.; Riemer, D.; Schilling, W.; Kollmann, J.; Das, S. *ACS Catal.* **2018**, *8*, 6659.
9. Alanthadka, A.; Devi, E. S.; Nagarajan, S.; Sridharan, V.; Suvitha, A.; Maheswari, C. U. *Eur. J. Org. Chem.* **2016**, 4872.
10. Griffiths, R. J.; Burley, G. A.; Talbot, E. P. A. *Org. Lett.* **2017**, *19*, 870.
11. So, M.-H.; Liu, Y.; Ho, C.-M.; Che, C.-M. *Chem. Asian J.* **2009**, *4*, 1551.
12. Song, A.-R.; Yu, J.; Zhang, C. *Synthesis* **2012**, *44*, 2903.

13. Lia, C.; Zenga, C.-C.; Hua, L.-M.; Yangb, F.-L.; Yood, S. J.; Little, R. D. *Electrochimica Acta* **2013**, *114*, 560.

14. Liu, Y.; Wang, C.; Xue, D.; Xiao, M.; Liu, J.; Li, C.; Xiao, J. *Chem. Eur. J.* **2017**, *23*, 3062.

15. Aganda, K. C. C.; Hong, B.; Lee, A. *Adv. Synth. Catal.* **2019**, *361*, 1124.

16. Thapa, P.; Corral, E.; Sardar, S.; Pierce, B. S.; Foss, Jr., F. W. *J. Org. Chem.* **2019**, *84*, 1025.

17. (a) Ratnikov, M. O.; Xu, X.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 9475. (b) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092. (c) Patil, M. R.; Dedhia, N. P.; Kapdi, A. R.; Kumar, A. V. *J. Org. Chem.* **2018**, *83*, 4477.

18. Jin, X.; Kataoka, K.; Yatabe, T.; Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 7212.

19. (a)So, M.-H.; Liu, Y.; Ho, C.-M.; Che, C.-M. *Chem. -Asian J.* **2009**, *4*, 1551. (b)Liu, Y.;Wang,C.; Xue,D.; Xiao, M.;Liu, J.; Li, C.; Xiao, J. *Chem.- Eur. J.* **2017**, *23*, 3062. (c) Also see: Periasamy, M.; Shanmugaraja, M.; Reddy, P. O.; Ramusagar, M.; Ananda Rao, G. *J. Org. Chem.* **2017**, *82*, 4944.

20. (a) Klobukowski, E. R.; Mueller, M. L.; Angelici, R. J.; Woo, L. K. *ACS Catal.* **2011**, *1*, 703. (b) Xu, W.; Jiang, Y.; Fu, H. *Synlett* **2012**, *23*, 801. (c) Xu, M.; Zhang, X.-H.; Shao, Y.-L.; Han, J.-S.; Zhong, P. *Adv. Synth. Catal.* **2012**, *354*, 2665. For metal-free multistep reaction, see: (d) Nishinaga, A.; Shimizu, T.; Matsuura, T. J. J. Chem. Soc., *Chem. Commun.* **1979**, *21*, 970. (e) Rong, H.-J.; Cheng, Y. F.; Liu, F.-F.; Ren, S.-J.; Qu, J. *J. Org. Chem.* **2017**, *82*, 532.

21. Bakac, A. *Inorg. Chem.* **2010**, *49*, 3584.

22. Borthwick, J. A.; Ancellin, N.; Bertrand, S. M.; Bingham, R. P.; Carter, P. S.; Chung, C.; Churcher, I.; Dodic, N.; Fournier, C.; Francis, P. L.; Hobbs, A.; Jamieson, C.; Pickett, S. D.; Smith, S. E.; Somers, D. O.; Spitzfaden, C.; Suckling, C.J.; Young, R. J. *J. Med. Chem.* **2016**, *59*, 2452.

23. (a) Lawrence, N. J.; Liddle, J.; Bushell, S. M.; Jackson, D. A. *J. Org. Chem.* **2002**, *67*, 457. (b) Ogiwara, Y.; Uchiyama, T.; Sakai, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 1864.

24. (a) Xue-Min, G.; Yue-Xuana, C.; Wei-Xing, C. *Chin. J. Pharma.* **1989**, 486. (b) Eligini, S.; Violi, F.; Banfi, C.; Barbieri, S. S.; Brambilla, M.; Saliola, M.; Tremoli, E.; Colli, S. *Cardiovasc. Res.* **2006**, *69*, 218.

25. https://clinicaltrials.gov/ct2/show /record/NCT03230851.

26. (a) Chu, L.; Qing, F. L. *Chem. Commun.* **2010**, *46*, 6285. (b) Qu, C.; Xu, P.; Ma, W.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2015**, *51*, 13508.

27. For reaction of dienolate species with molecular oxygen, see: (a) Peixoto, P. A.; Jean, A.; Maddaluno, J.; De Paolis, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6971. (b) Peixoto, P. A.; Cormier, M.; EkossoEpane, J.; Jean, A.; Maddaluno, J.; De Paolis, M. *Org. Chem. Front.* **2014**, *1*, 748. (c) Gersmann, H. R.; Nieuwenhuis, H. J. W.; Bickel, A. F. *Tetrahedron Lett.* **1963**, *4*, 1383. (d) Becker, H.D.; Sanchez, D. *Tetrahedron Lett.* **1975**, *16*, 3745.

28. For references of electron transfer from amine to radical, see: Ratnikov, M. O.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 1549.

29. (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (b) Arokianathar, J. N.; Frost, A. B.; Slawin, A. M. Z.; Stead, D.; Smith, A. D. *ACS Catal.* **2018**, *8*, 1153. (c) Henrich, M.; Weil, T.; Muller, S.; Kauss, V.; Erdmare, E.; Zemribo, R. 6-halo-pyrazolo [1, 5-a] pyridines, a process for their preparation and their use as metabotropic glutamate receptor (mglur) modulators. WO 2009095253 (A1), **2009**.

30. Brzozowski, M.; Forni, J. A.; Savage, G. P.; Polyzos, A. *Chem. Commun.* **2015**, *51*, 334.

31. Kuuloja, N.; Kylmala, T.; Xu, Y.; Franzen, R. Cent. *Eur. J. Chem.* **2008**, *6*, 390.

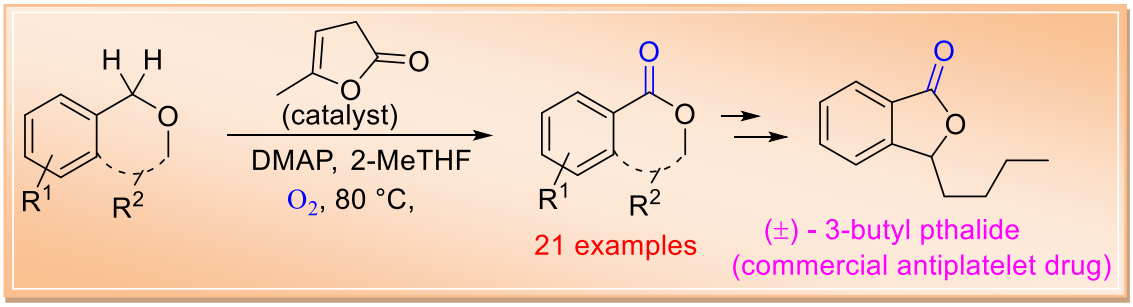
32. Verma, A.; Patel, S.; Meenakshi; Kumar, A.; Yadav, A.; Kumar, S.; Jana, S.; Sharma, S.; Prasada, C. D.; Kumar, S. *Chem. Commun.* **2015**, *51*, 1371.

33. Xue-Min, G.; Yue-Xuana, C.; Wei-Xing, C. *Chin. J. Pharma.* **1989**, 486.

Chapter II: Section B

Metal-Free Organocatalytic Oxidation of Benzylic sp3 C−H Bonds of Isochromans and Phthalans

We present here a metal-free organocatalytic system for the development of highly efficient benzylic C–H oxygenation of isochromans and phthalans by employing a kinetically poor but environmentally benign oxidant such as oxygen. It is worth noting that, this persuasive reaction utilizes a low cost and low molecular weight α-angelica lactone as a catalyst. This system allows the synthesis of valued isocoumarins and phthalides from the easily available precursors under 'easy to perform' reaction conditions in good yields. Mechanistic studies indicate that the reaction follows a radical pathway and involves peroxide intermediate.



Org. Biomol. Chem. **2020**, *18*, 4046-4050

2.2.1 Introduction

Oxidation is a versatile tool for the synthesis of valuable oxyfuctionalized building blocks from the raw materials.[1] Oxygen-containing heterocycles are of ample presence in the natural products and biologically active molecules, so they are the attractive synthetic targets for the synthetic organic chemists.[2] Additionally, they are also used as a useful synthon in the organic synthesis. In this perspective, selective, direct, and straightforward oxidation of benzylic sp3 C-H bonds of cyclic ethers is described. In other words, the highly cogent and direct oxidation of benzylic sp3 C-H bonds of isochroman and phthalans to give corresponding isocoumarins and phthalides is of high importance because of its relatively high step economy and synthetic efficiency. Synthetic efficiency is an important parameter in the discovery of active pharmaceutical ingredients, agrochemicals and even in the synthesis of new materials.[3]

Isocoumarin and phthalide scaffold are widely present in many natural products and drug molecules which show a broad range of biological activities. Some examples are depicted in figure 1.

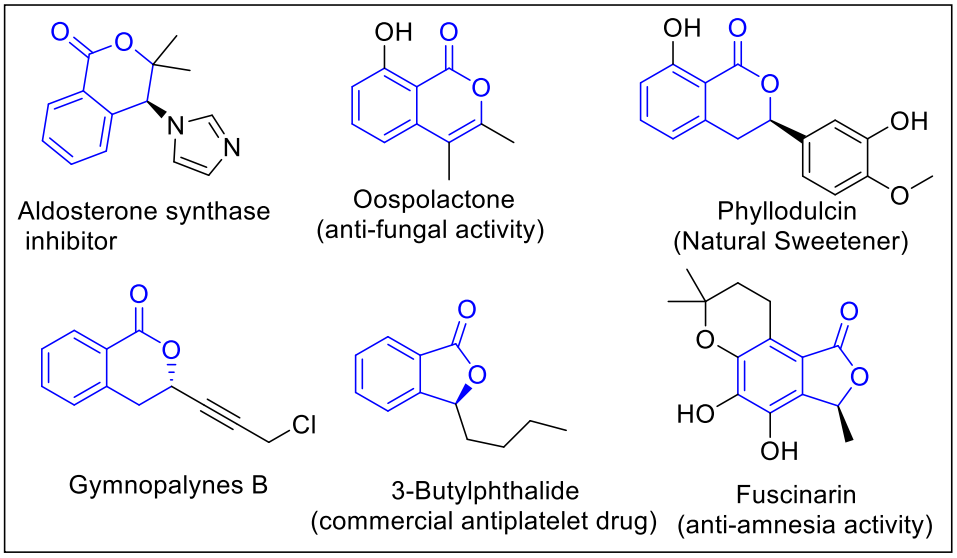


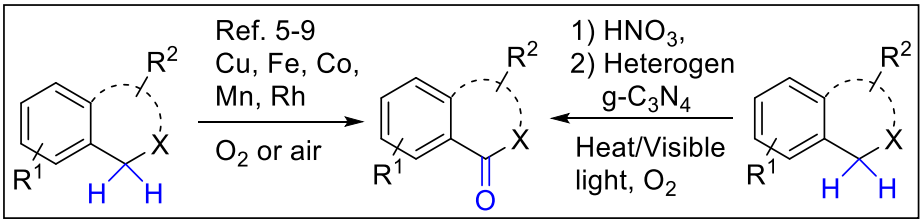
Figure 1. Selected examples of natural products and drugs containing the isocoumarins and phthalide core structure**.**

2.2.2 Literature Review

The studies in the field of direct oxidation of benzylic sp^3 C−H bonds of isochromans and phthalans have been well-reviewed from the past several years. Traditionally, metal oxides of chromium[4] are employed for the oxidation of benzylic sp3 C-H bonds. But the toxicity of

chromium gives ample space for the development of transition-metal based catalysts with oxygen or peroxides as oxidant. The example includes cobalt[5], copper[6], rhodium[7], manganese[8], and iron[9].

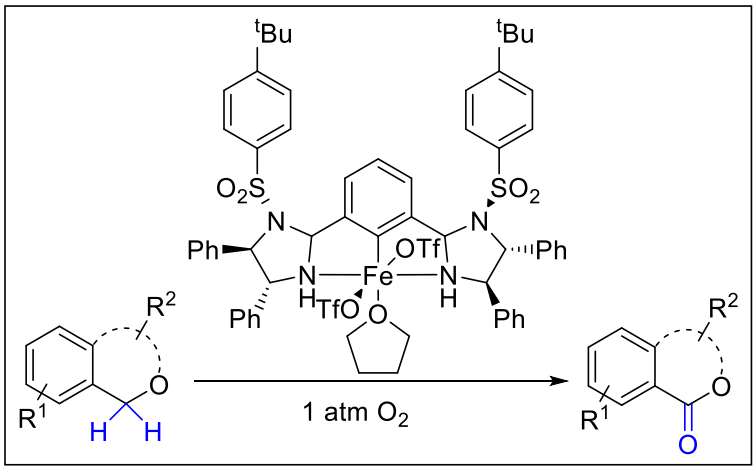
Benzylic oxidation is also known by the use of 'non-metal' reagents. For example, Wang *et al*. in 2018 reported HNO_3 mediated benzylic oxidation of ethers at very high temperatures.[10] Again, Hu *et al*. in 2019 reported visible-light catalyzed heterogeneous graphene carbon nitride (g-C_3N_4) as a catalyst for the same purpose. Because of the heterogeneous nature of the catalyst, it was easy to recycle and reuse without any loss of activity.[11]



Recent advances in the chemistry of oxidation of benzylic sp3 C-H of acyclic and cyclic ethers are well documented in the literature. Apart from metal-based catalysts, strong acids, and nano-materials, organic molecules are also known to catalyze the oxidation of cyclic/acyclic ethers to the corresponding lactone/ester. Selected methods from literature where an organic molecule has been used as a catalyst and oxygen gas/air as oxidant are presented below.

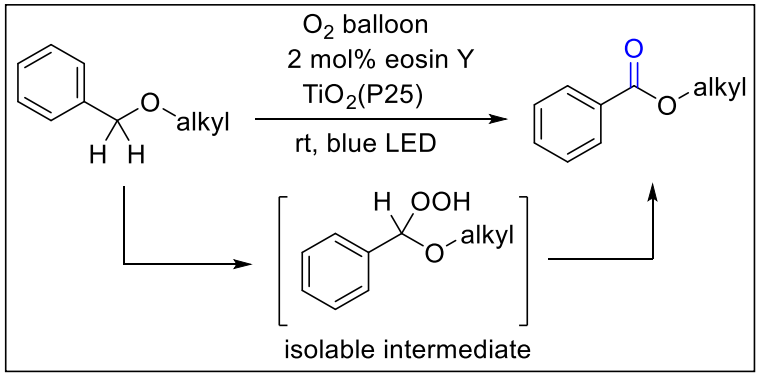
I. Iron-catalysed[12]

Xiao *et al*. in 2014 reported the application of an iron catalyst containing a chiral pyridine bissulfonylimidazole was ligand for chemoselective α-oxidation of ethers using oxygen as an oxidant in additive-free condition with high turnover numbers but low conversion. This catalytic system produced H_2 as a sole by-product. This method is a milestone for the designing and understanding of biomimetic catalysts for C-H oxidation.



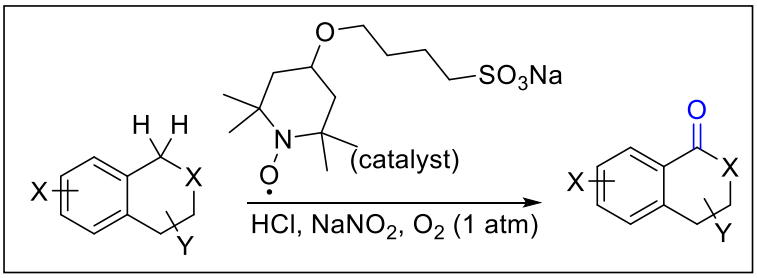
II. Visible-light induced[13]

Catalytic eosin Y-sensitized titanium dioxide (dye-sensitized semiconductor) catalysts were also reported as photocatalyst for the oxidation of benzyl ethers. This method was developed by Cong *et al*. in 2017. The reaction proceeds via isolable peroxide intermediates which were converted to the benzoate product by radical chain process. The products were obtained in good to excellent yields.



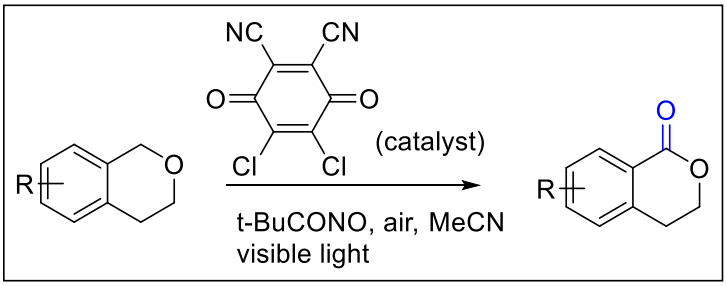
IV. Organocatalytic aerobic oxidation[14]

Wang *et al*. in 2015 reported a TEMPO derived sulfonic salt as a catalyst in the presence of O_2 and combination with mineral acids like $NaNO_2$ and HCl as co-catalyst. The recyclable catalyst provided the corresponding products in moderate to excellent yields.

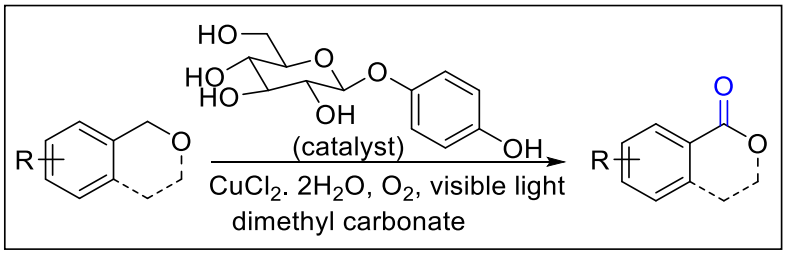


V. Organocatalytic visible-light catalysed[15]

Visible-light induced photocatalytic benzylic sp3 C-H oxidation of aromatic hydrocarbons with DDQ as a catalyst and tert-butyl nitrile as co-catalyst was reported by Brasholz *et al*. in 2016. They compared the thermal and photochemical reaction conditions. Here, the authors observed that high product yields with photochemical reactions. But DDQ is toxic and in contact with water, it releases HCN.



A biorenewable glucoside such as arbutin acts as a source of 1,4-hydroquinone under visible-light condition to convert the C-H bonds of benzylic ethers to benzoate esters in moderate to good yields. This protocol was developed by Moody *et al*. in 2018.[16] Here copper (II) chloride dihydrate was used as an electron-transfer mediator in the presence of oxygen gas as the terminal oxidant in dimethyl carbonate as a solvent.



2.2.3 Origin of the present work:

Although the aforementioned reports gave good results as well as selectivity but these methods also have some significant shortcomings. In many reported methods,metal-based

catalysts or additives were used, in some examples, sacrificial oxidant was employed. Additionally, the formation of by-products or over-oxidation products is also encountered in some cases. Hence developments of new efficient methods for the benzylic oxidation of cyclic ethers to the corresponding lactones are always sought after.

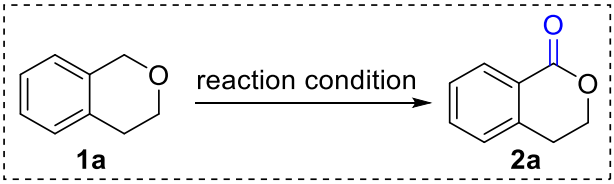
2.2.4 Objectives:

Very recently, we have demonstrated an efficient method for the benzylic C−H oxidations of *N*-aryl tetrahydroisoquinolines and isoindolines to the corresponding lactams using α-angelica lactone as an organocatalyst.[17] The reaction was performed at room temperature in the presence of a base under the oxygen atmosphere and the lactams were obtained in good yields. This was an unprecedented result as lactones were never used as a catalyst for any reaction. Inspired by this finding, we thought of evaluating a similar catalytic system for the benzylic sp3 C−H bond oxidation of isochromans and phthalans to the corresponding lactone (isocoumarin and phthalide respectively) derivatives. In the 10th anniversary report by the ACS Green Chemistry Institute® Pharmaceutical Roundtable pointed that "*Aliphatic and aromatic C–H activation, using green oxidants and giving predictable site selectivities*" is one of the top 10 research areas.[18] Our present research objective is in line with the ACS-GCI research topic.

2.2.5 Results and discussion

The optimization study started with the selection of isochroman **1a** as a model substrate. Initially, we have carried out the reaction as in our previous optimized reaction condition which was used in the case of *N*-aryl tetrahydroisoquinolines. Thus, oxidation of isochroman **1a** was performed in presence of α-angelica lactone **A** (25 mol%) as organocatalyst, DABCO (3 equiv.) as base and oxygen gas as an oxidant in THF at 25 °C (Table 1, entry 1). After 36 h, the product isocoumarin **2a** was isolated in a 27% yield. A small increment in yield to 34% (Table 1, entry 2) was observed when the base was changed from DABCO to 4-dimethylaminopyridine (DMAP, 3 equiv.). These results inspired us for further optimization with various solvents and bases. When the reaction was conducted in acyclic ethers (diethyl ether & MTBE),

Table 1: Solvent and base optimization[a]



Entry	Base	Solvent	Catalyst	Time	Temp.	Yield (%)[b]
1	DABCO	THF	A	36 h	rt	27
2	DMAP	THF	A	36 h	rt	34
3	DMAP	DEE	A	36 h	rt	27
4	DMAP	MTBE	A	36 h	rt	30
5	DMAP	MeOH	A	36 h	rt	N. D.
6	DMAP	DMF	A	36 h	rt	N. D.
7	DMAP	DMSO	A	36 h	rt	N. D.
8	DMAP	ACN	A	36 h	rt	47
9	DMAP	Toluene	A	36 h	rt	41
10	DMAP	Toluene	A	24 h	80 °C	47
11	DMAP	ACN	A	24 h	80 °C	68
12	DMAP	2-MeTHF	A	24 h	80 °C	81
13[c]	DMAP	2-MeTHF	A	24 h	80 °C	71
14[d]	DMAP	2-MeTHF	A	24 h	80 °C	62
15	PPh_3	2-MeTHF	A	24 h	80 °C	N. D.
16	Pyridine	2-MeTHF	A	24 h	80 °C	18
17	2,6-Lutidine	2-MeTHF	A	24 h	80 °C	Trace
18	*N*-Methyl Morpholine	2-MeTHF	A	24 h	80 °C	27
19	DIPEA	2-MeTHF	A	24 h	80 °C	Trace
20	Na_2CO_3	2-MeTHF	A	24 h	80 °C	N. D.
21	Cs_2CO_3	2-MeTHF	A	24 h	80 °C	N. D.

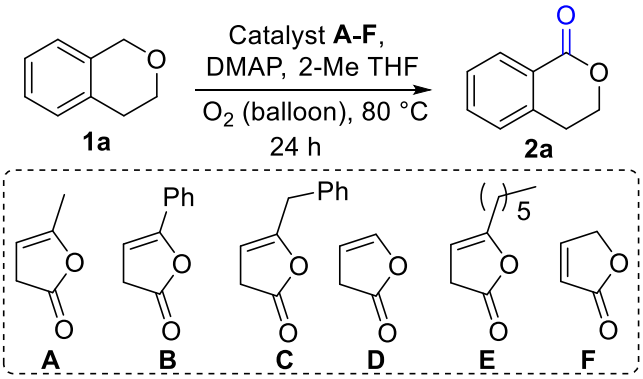
[a] Reaction condition: **1a** (0.1 mmol), DMAP (0.3 mmol), catalyst **A** (25 mol %) in 2-Me THF (0.5 mL) at 80 °C for 36 h under O_2 (balloon) atmosphere. [b] Isolated yields. [c] 1 ml 2-MeTHF. [d] 2 ml 2-MeTHF.

the product was obtained with almost similar yield (27% & 30%) as compared with THF (Table 1, entries 3, 4). No oxidation product (**2a**) was observed after 36 h at rt when MeOH, DMF, and DMSO were used as solvents (Table 1, entries 5-7). Acetonitrile (ACN) and toluene showed improvement in yields (47% & 41% respectively, Table 1, entries 8, 9). To our delight, when the reaction condition of entry 9 was performed at 80 °C, an increment of

6% yield was observed (Table 1, entry 10). However, significant improvement in yield (68%) was observed when the reaction was performed in ACN as solvent at 80 °C (Table 1, entry 11). The best optimization condition was obtained when 2-methyltetrahydrofuran (2-Me THF) was employed at 80 °C. The product **2a** was obtained in 81% yield (Table 1, entry 12). A diminished yield was obtained when a lower or higher concentration of 2-Me THF was used (Table 1, entries 13, 14). Further optimization with different organic and inorganic bases was also performed but no improvement in chemical yields was noted (Table 1, entries 15-21).

Next, the reaction was evaluated with various lactones as catalysts (**B**-**F**). The results are presented in Table-2.

Table 2: Catalyst optimization [a]



Entry	Catalyst	Solvent	Yield (%) [b]
1	B	2-Me THF	46
2	C	2-Me THF	26
3	D	2-Me THF	34
4	E	2-Me THF	71
5	F	2-Me THF	24
6[c]	A	2-Me THF	54
7[d]	A	2-Me THF	83

[a] Reaction condition: **1a** (0.1 mmol), DMAP (0.3 mmol), catalyst **A** (25 mol %), in 2-Me THF (0.5 mL) at 80 °C for 24 h under O_2 (balloon) atmosphere. [b] Isolated yields. [c] with 10 mol% catalyst **A**. [d] with 30 mol% catalyst **A**.

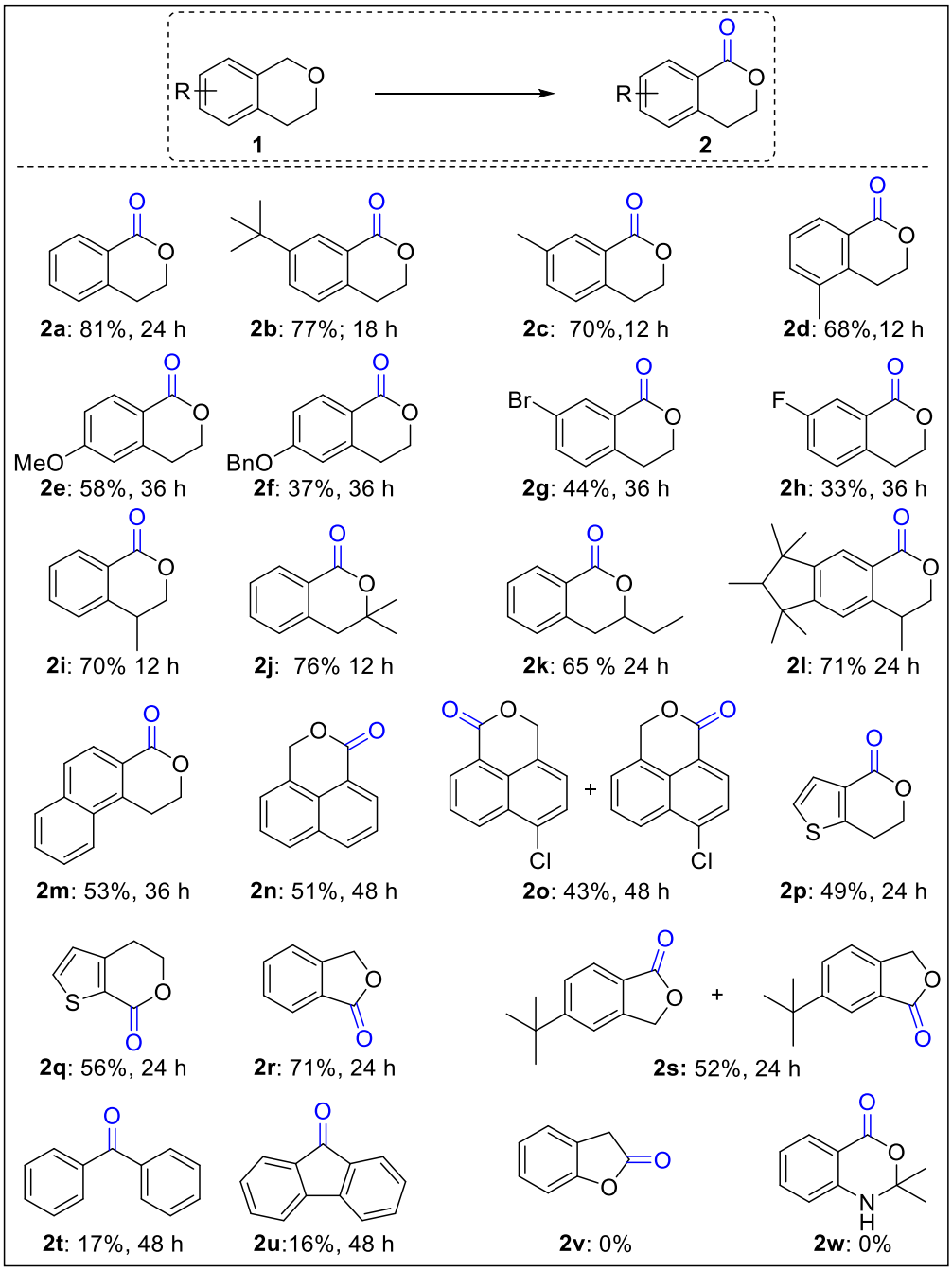
The desired product **2a** was obtained in 71% isolated yield with catalyst **E** (Table 2, entry 4). For remaining catalysts, only moderate to low yield was observed. Further, the reaction was also performed with a reduced and increased catalytic quantity of catalyst loading. Thus,

when 10 mol% catalyst **A** was used, the yield was only 54% (Table 2, entry 6). A nominal improvement in the chemical yield was observed when with 30 mol%catalyst **A** was used. The isolated yield was 83% (Table 2, entry 7).

After the optimization of various solvents, bases, and catalysts and having the best condition in hand we moved to explore the substrate scope for different isochromans and phthalans. The results are summarized in table 3. No over oxidation product was observed as confirmed by GC-MS and NMR studies of the reaction mixture.And the reason could be the deactivation of the ring after the first oxidation. The optimized reaction condition was applied successively to the substituted isochromans **1a-1q** and the oxidized products **2a-2q** wereobtained in moderate to excellent chemical yields (33-81%). The presence of electron-donating groups on the aromatic ring of isochroman are well tolerated and the oxidized products **2b-2f** were isolated in 37-77% chemical yields. Isochroman with halogen atom substituents such as -Br, -F are also compatible with our protocol, and respective oxidized products **2g** and **2h** were obtained in 44 and 33% yields. Even substitutions on the saturated ring of isochroman with alkyl (methyl, dimethyl, and ethyl) groups were also well tolerated. The corresponding target products (**2i-k**) were isolated in 70%, 76%, and 65% yields. Oxidation of musk chemical Galoxolide **1l** (hexamethylisochroman) was also carried out and the product **2l** was isolated in 71% yield. The derivatives of benzo-isochromans were also proved to be suitable substrates to our protocol and the corresponding lactones **2m-o**were obtained in 43-53% chemical yields. Regioisomeric mixtures of isocoumarins with 60:40 ratios were observed in the case of product **2o** as it has two benzylic positions available for oxidation. The less hindered product was obtained as a major isomer. We believe that due to steric reason 6-chloro isomer was obtained as the major isomer. Heteroaromatic isochromans such as **1p-q** are also found to be compatible reaction partners and the corresponding products **2p-2q** were obtained in 49 and 56% yields.

To further explore the substrate scope of this method, α-oxygenation of phthalans were investigated. The targeted phthalides were isolated in good yields. Phthalide **2r** was obtained in 71% isolated yield. Notably, in the case of compound **2s**, regioisomeric mixtures (77:23 ratios) of phthalides were obtained. The ratio is in favor of the para oxidation product which is probably controlled by the electronic effects.

Table 3: Substrate scope [a, b]

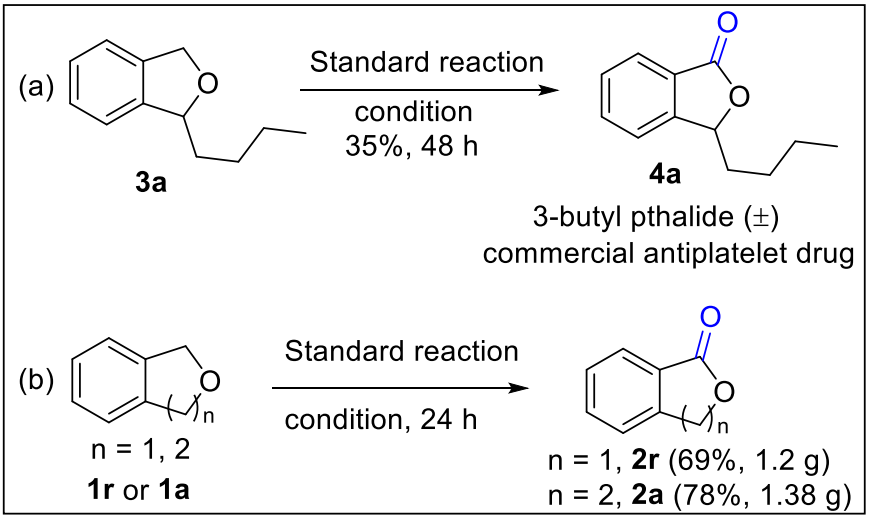


[a] Reaction condition: **1a** (0.1 mmol), DMAP (0.3 mmol), catalyst **A** (25 mol %) in 2-Me THF (0.5 mL) at 80 °C for stated time under O_2 (balloon) atmosphere. [b] Isolated yields.

Benzylic C-H oxidation of alkylarenes is more challenging than that of cyclic ethers due to the higher bond dissociation energy (benzylic C-H) of alkylarenes.[19] Hence, a slight modification in the reaction condition (toluene at 100 °C) was necessary to obtain satisfactory results. The corresponding oxidized products benzophenone (**2t**) and 9H-fluorene (**2u**) were

isolated in low yields (17 and 16% respectively). The developed protocol has some limitations. For example, in the case of compound 2,3-dihydrobenzofuran, we didn't observe oxidation product **2v** due to the absence of an O-benzyl (activated) position. Benzoxazine derivative **1w** was also found to be inactive to our developed protocol. This is possibly because of the existence of another heteroatom (N).

Next, we demonstrated the potential application of our developed catalytic system for synthesizing racemic 3-butylphthalide (**4a**) which is a commercial antiplatelet drug.[20] By utilizing a standard reaction condition, the targeted oxidation product was obtained in a 35% isolated yield (Scheme 1a). Our optimized reaction condition is also reproducible in gram-scale synthesis (Scheme 1b). Products **2r** (1.2 g, 69%) and **2a** (1.38 g, 78%) were obtained in similar chemical yields as in the case of the milligram reaction scale.

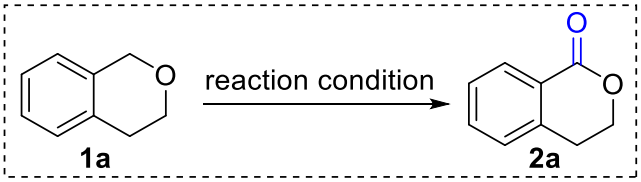


Scheme 1: Synthetic utility and gram-scale reaction

To interpret the reaction mechanism, we have performed some control experiments and the results are summarized in Table 4. Firstly, the reaction was not working whenever there is no base and catalyst **A**. From these results, we conclude that base and catalyst **A** is required for the reaction (Table 4, entry 1 & 2). In the presence of an inert atmosphere (nitrogen or argon), the reaction was also not operational which indicated that the oxygen source is from moisture or air (Table 4, entry 3). However, when the reaction was performed in H_2O^{18} and 2-Me-THF (980 µL:20 µL), we didn't observe the O-18 product by GC-MS study (Table 4, entry 4). This indicates that the source of oxygen is from O_2 in corresponding products. To understand the reaction pathway, a stoichiometric amount of TEMPO or BHT (radical scavengers) were

used. In both the experiments, product **2a** was isolated in a <10% yield. These results indicated that reaction proceeds *via* a radical intermediate pathway (Table 4, entry 5). On addition stoichiometric amount of $CuCl_2$, only a trace amount of product formation was observed. This experiment indicates the possible participation of a single electron transfer process (Table 4, entry 6).[21] Next, the reaction was performed in the presence of H_2O_2 scavengers such as catalase enzymes using the optimized reaction condition. However, only a trace amount (13%) of the oxidized product was observed (Table 4, entry 7).[22]

Table 4: Mechanistic investigation



Entry	Condition	Result	Conclusion
1	No base	No reaction	Base required
2	No Catalyst **A**	No reaction	Catalyst **A** required
3	N_2 or Argon atm.	No reaction	Oxygen source needed
4	2Me-THF:H_2O^{18} (10 equiv.; 980 µL:20 µL)	>98% unlabeled	Molecular O_2 needed
5	TEMPO or BHT (1 equiv)	<10%	Presence of radical species
6	$CuCl_2$ (1 equiv)	No reaction	Single-electron
7	Catalase (70 mg)	13%	Peroxide species
8[b]	Catalase (70 mg)	8%	Peroxide species
9	$^{18}O_2$ atm.	82% ^{18}O incorporation	From molecular oxygen

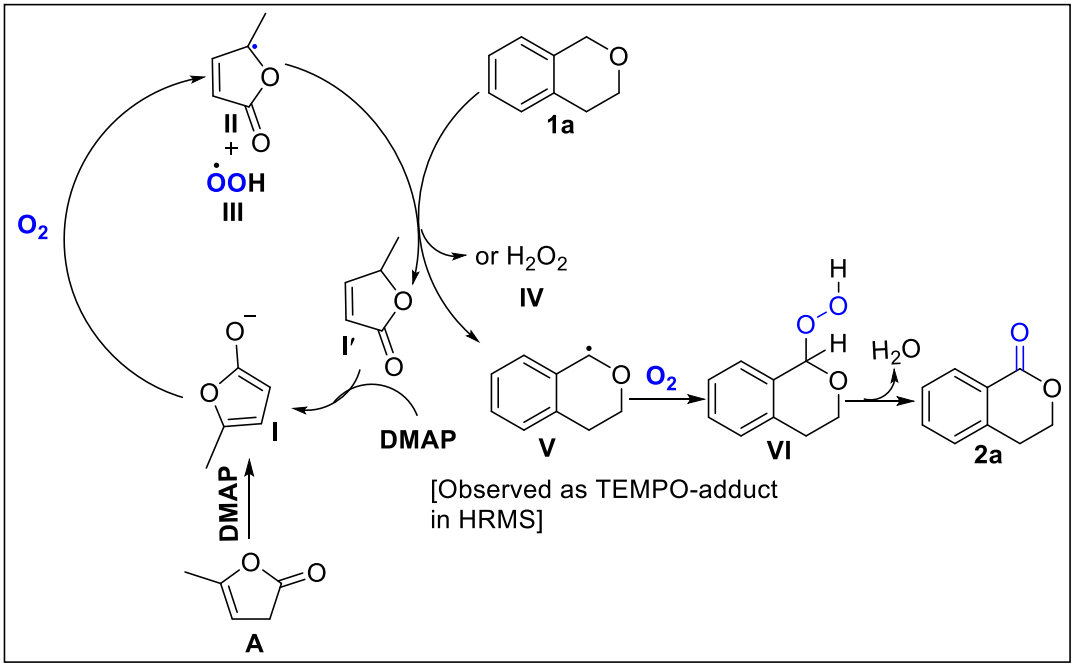
[a] Reaction condition: **1a** (0.1 mmol), DMAP (0.3 mmol), catalyst **A** (25 mol %) in 2-Me THF (0.5 mL) at 80 °C for 24 h under O_2 (balloon) atmosphere. [b] Reaction performed at 40 °C.

The optimal performance of the catalase enzyme is reported at 40 °C.[23] Hence, the same experiment was also performed at 40 °C, but again trace amount (8%) of product formation was observed. These observations point towards the presence of peroxide species in the reaction system (Table 4, entries 7 and 8). To further prove our hypothesis that the source of oxygen in the product is from molecular oxygen and also give support to the mechanism pathway, we performed the isotope labeling experiment with ^{18}O labeled oxygen gas. The GC-mass spectrum of the product **2a** (m/z = 150) was found two mass units higher compared

to m/z = 148 in **2a**. From this result, it is clear that the incorporation of oxygen in lactone products is from molecular oxygen (Table 4, entry 9).

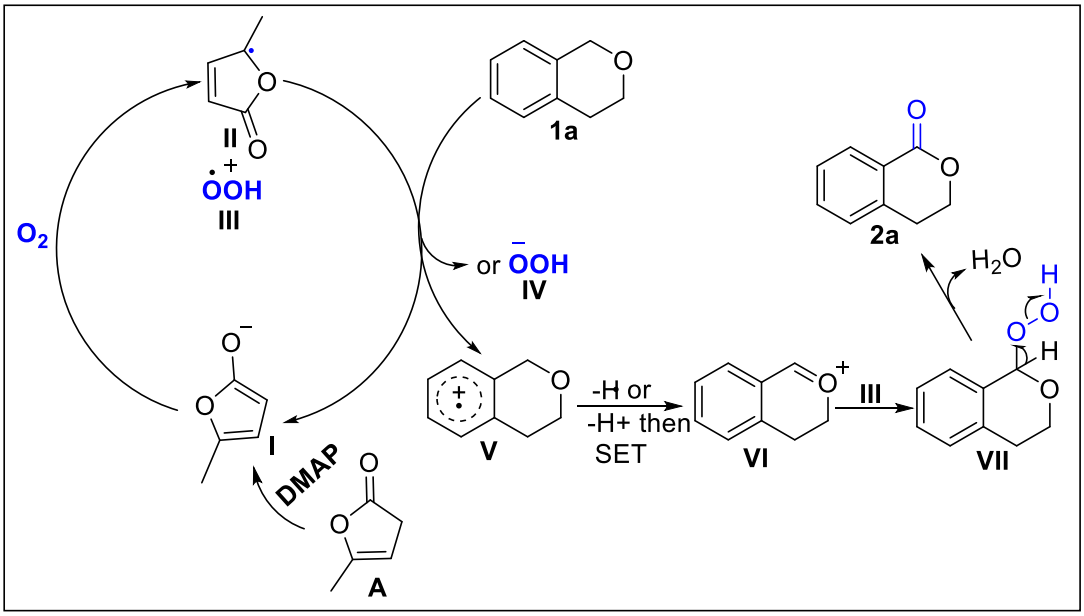
A plausible mechanism was proposed based on literature precedents[15,16,17] and the above-mentioned experimental data (Scheme 2). Firstly, DMAP abstract acidic proton from catalyst **A** which leads to the formation of dienolate species **I**. This dienolate **I** react with triplet oxygen to form peroxide species.[24]

Scheme 2: Proposed mechanism



Then by homolytic cleavage, it breaks into radical species **II** and **III**. Next, radical species **V** forms by H-abstraction from **1a** either by alkoxy radical **II** or peroxy radical **III**. Formation of radical species **V** was detected by HRMS analysis of the reaction mass. We were able to confirm the presence of species **V** by trapping it with radical quencher TEMPO. Radical species **V** on reaction with triplet oxygen gives hydroperoxide intermediate **VI**. Removal of a hydrogen atom from **VI** by base DMAP provides the final product **2a**. An alternative mechanism for the formation of product **2a** is given in scheme 3. A single electron transfer from substrate **1a** by either radical **II** or **III** may give a radical cation **V**. This radical cationcan undergo H-atom transfer to give an oxonium ion **VI**. A combination of oxonium ion **VI** and radical **III** may lead to the formation of hydroperoxide species **VII**. The next step was the removal of H-atom by base followed by the elimination of water to afford product **2a**.

Scheme 3: Alternative Plausible Mechanism



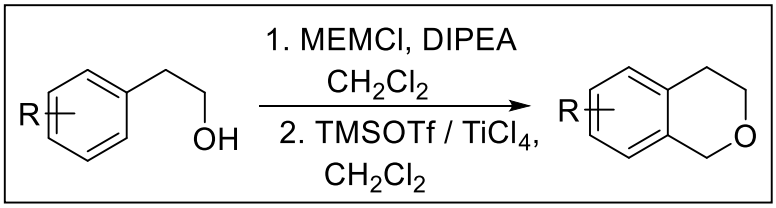
2.2.6 Conclusion

In summary, we have successfully developed a protocol for the direct oxidation of isochromans and phthalans to the corresponding lactones by employing α-angelica lactone as a catalyst. α- Angelica lactone is a very cheap and low molecular weight catalyst. This is the first report where α-angelica lactone has been used as a catalyst for oxidation of isochromans and phthalans. The reaction condition is mild in nature and is compatible with a wide number of isochromans and phthalans. This protocol makes use of molecular oxygen as the green oxidant and also serves as a source of the oxygen atom in lactones. From the control experiments, it is proved that this catalytic system follows a radical pathway involving peroxide species as intermediates. We are also successful inthe synthesis of 3-butylphthalide which is a bioactive drug molecule by using this methodology.

2.2.7 Experimental Section

A) General procedure for the synthesis of isochromans and phthalans

Reported reaction procedure[25, 26] was applied with some modification as:



In a dry round bottom flask substituted phenylethyl alcohol (1.0 equiv.), (2-methoxyethoxy) methyl (MEM) chloride (1.5 equiv.), and 1.5 equiv of *N, N*-diisopropylethylamine in anhydrous dichloromethane was stirred at rt for 2.5 h. Then the solvent was evaporated in *vacuo*. The obtained residue was purified by flash chromatography to give the desired MEM acetal. TMSOTf (0.1 equiv) or titanium tetrachloride (1.5 equiv) was added dropwise to the solution of MEM acetal (1.0 equiv) in dichloromethane at 0 °C. After stirring overnight at rt, the reaction was quenched by adding saturated aq. $NaHCO_3$. The organic extract was washed with brine, dried over Na_2SO_4, and then concentrated in *vacuo* to give the crude product. The crude reaction mixture was purified by flash chromatography to obtain the corresponding isochroman derivatives. 1,4-dihydro-2H-benzo[f]isochromene (**1m**, 67%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 – 7.90 (m, 1H), 7.86 – 7.82 (m, 1H), 7.72 – 7.68 (m, 1H), 7.61 – 7.40 (m, 3H), 7.15 – 7.09 (m, 1H), 4.92 (s, 2H), 4.16 (t, *J* = 5.8 Hz, 2H), 3.18 (t, *J* = 5.6 Hz, 2H). Other substituted isochroman derivatives were synthesized by the above general method.

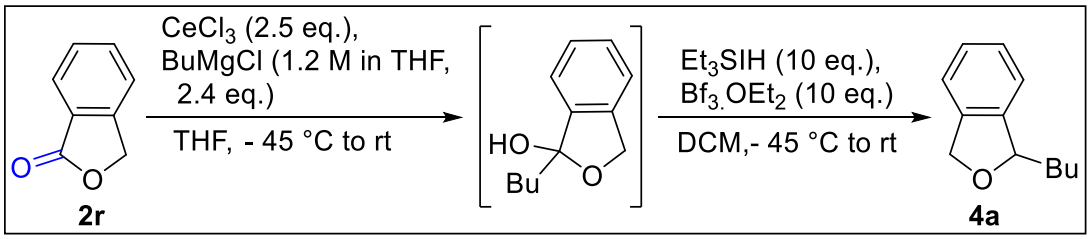
B) General procedure for the oxidation of isochromans and phthalans

To a solution of isochromans or phthalans (0.1 mmol) and DMAP (0.3 mmol) in 2-Me-THF (0.5 mL) was added α-angelica lactone (25 mol%, 2.3 µL) at room temperature. The round bottom flask was equipped with a balloon containing O_2 gas and the reaction mixture was stirred at a preheated oil bath at 80˚C for 12 h to 48 h. The progress of the reaction was monitored by TLC. After cooling to rt, the reaction mixture was diluted with dichloromethane (2 mL) and washed with water (2 mL). The layers were separated and the aqueous layer was re-extracted with dichloromethane (3 ×5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a neutral alumina column using 20% pet ether/EtOAc.

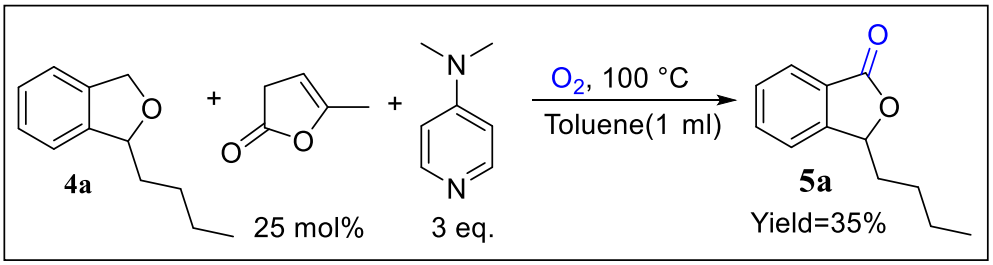
C) General procedure for the synthesis of natural product 3-butylphthalide (5a)

a) Synthesis of 1-butyl-1,3-dihydroisobenzofuran (4a)[27]

To a solution of $CeCl_3$ (2.5 equiv.) in anhydrous THF (10 mL) in a round bottom flask was added solution of phthalide (3.73 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred at rt for 1 h under N_2 atmosphere. Then the reaction mixture was allowed to cool to -45 °C and was added Grignard reagent (1.2 M in THF, 2.4 equiv., 1.2 mL) dropwise. The reaction mixture was stirred at the same temperature for 1 h and then left overnight at rt. Then the reaction was quenched by the addition of water (5 mL) and filtered through a pad of Celite and extracted by ether (3 ×15 mL). Dried over Na_2SO_4 and concentrated to obtain oil of crude hemiketal. Et_3SiH (10 equiv., 5.4 mL) was slowly added to the solution of hemiketal in DCM (15 mL) at -45 °C. After stirring the reaction mixture at the same temperature for 2 h, it was quenched by adding a saturated solution of aq. $NaHCO_3$ (5 mL). Then the mixture was extracted with DCM, dried over Na_2SO_4, and thus obtained residue was purified by column chromatography (EA+ Pet ether = 1:20) to give 352 mg product as a colourless oil.



b) Synthesis of 3-butylphthalide:



To a solution of n-butyl phthalan (0.3 mmol) and DMAP (3 equiv.) in toluene (1 mL) was added the α-angelica lactone (25 mol %) at room temperature. The round bottom flask was equipped with a balloon containing O_2 gas and the reaction mixture was stirred at a preheated 100˚C temperature oil bath for 48 h. The progress of the reaction was monitored by TLC. After cooling to rt, the reaction mixture was diluted with dichloromethane (5 mL) and washed with water (2 mL). The layers were separated and the aqueous layer was again extracted with dichloromethane (3 ×5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a flash silica gel column using 20% pet ether/EtOAc to give a colourless oil in 19.9 mg (35% yield). **^{1}H NMR**

(400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.69-7.64 (m, 1H), 7.54-7.49 (m, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 5.48 (dd, *J* = 7.9, 4.1 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.82 – 1.71 (m, 1H), 1.47 – 1.34 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.79, 150.22, 134.01, 129.10, 126.26, 125.80, 121.79, 81.53, 34.53, 26.96, 22.52, 13.94. HRMS (ESI+) (*m/z*) calcd for $C_{12}H_{15}O_2$ [M+H] 191.1027 found 191.1067.

D) Gram scale reaction procedure

In a solution of isochromans (12 mmol, 1.6 g) or phthalans (13 mmol, 1.55g) and DMAP (36 mmol, 4.4 g) in 2-Me-THF (20 mL) was added the α-angelica lactone (25 mol%, 270 µL) at 80˚C. The round bottom flask was equipped with a balloon containing O_2 gas and the reaction was stirred at a preheated oil bath at 80˚C for 24 h. The progress of the reaction was monitored by TLC. After cooling to rt, the reaction mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL). The layers were separated and the aqueous layer was extracted again with dichloromethane (3×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a neutral alumina column using 20% pet ether/EtOAc in 1.38 g (78%) of **2a** and 1.2 g (69% yield) of **2r**.

E) Experiment procedure of reaction isochroman 1a in the presence of H_2O^{18}

H_2O^{18} was purchased with 97% isotopic purity from Sigma Aldrich (catalog no: 329878-250 mg). According to the general procedure for the oxidation of **1a** to **2a** under 10 equiv of H_2O^{18} and 980 µL of the 2-Me-THFexperiment was carried out. The percentage of ^{18}O enrichment was examined by mass spectrometry. No enrichment of ^{18}O was observed by the calculated data.

Reaction condition: Inside the glove box was added isochroman **1a** (0.1 mmol), DMAP (0.3 mmol), α-angelica lactone (25 mol%), 2-Me-THF (980 µL) and H_2O^{18} (20 µL) in a Schlenk tube. The reaction mixture was stirred at 25 °C under the O_2 (balloon) atmosphere for 24 h. GC-MS and ESI-MS studies of product **2a** show that there is no isotopic enrichment.

F) Experiment procedure for the reaction of isochroman 1a in the presence of catalase enzyme

The powder form of the Catalase enzyme was purchased from Sigma Aldrich (catalog no:C1345-1 g). The experiment was carried out according to the general procedure for the oxidation of **1a** to **2a** with 70 mg of the Catalase enzyme.

Reaction condition: Isochroman (0.1 mmol), DMAP (0.3 mmol), α-angelica lactone (25 mol%, 2-Me-THF (1 mL) and 70 mg of catalase enzyme were taken in a glass vial. The reaction mixture stirred under O_2 (balloon) at 80 °C for 24 h. After completion of reaction time, product **2a** was obtained in 13% yield.

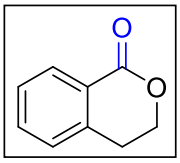
G) Experiment procedure of reaction isochroman 1a in the presence of $^{18}O_2$

$^{18}O_2$was purchased from icon isotopes (catalog no: IO 6393) with 98% isotopic purity.The experiment was carried out according to the general procedure for the oxidation of **1a** to **2a** under $^{18}O_2$ atmosphere. The percentage of ^{18}O enrichment was examined by mass spectrometry. The calculated data showed 82% of ^{18}O.

Reaction condition: Inside glove boxwere added isochroman (0.1 mmol), DMAP (0.3 mmol), α-angelica lactone (25 mol%), 2-Me-THF (1 mL) in a Schlenk tube. The tube was filled with $^{18}O_2$ gas and the mixture was stirred at 80 °C for 24 h. 82% of ^{18}O isotopic enrichment in product **2a** was indicated by GCMS.

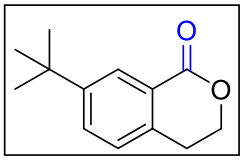
2.2.8 Characterization data of compounds

Isochroman-1-one (2a):



Colourless oil (12 mg, 81%); TLC R_f = 0.5 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.57-7.51 (m, 1H), 7.43-7.37 (m, 1H), 7.29 – 7.25 (m, 1H), 4.55 (t, *J* = 6.2 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.25, 139.63, 133.77, 130.51, 127.79, 127.32, 125.40, 67.40, 27.92. **HRMS (ESI+) (*m/z*)** calcd for $C_9H_9O_2$ [M+H] 149.0602 found 149.0597.

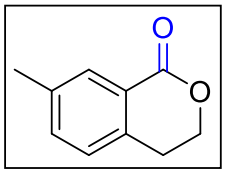
7-(*tert-butyl*)isochroman-1-one (2b):



Colourless oil (15.7 mg, 77%); TLC R_f = 0.6 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 (d, *J* = 2.3 Hz, 1H), 7.60-7.56 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 4.52 (t, *J* = 6.0 Hz, 2H), 3.02 (t, *J* = 6.0 Hz, 2H), 1.34 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.70, 151.08, 136.71, 131.09, 127.16,

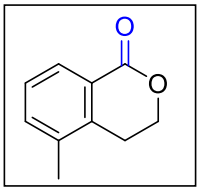
127.10, 124.91, 67.47, 34.84, 31.27, 27.50. **HRMS (ESI+) (*m/z*)** calcd for $C_{13}H_{17}O_2$ [M+H] 205.1229 found 205.1223.

7-Methylisochroman-1-one (2c):



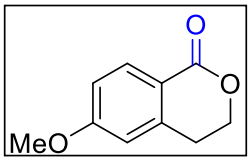
Yellow oil (11.3 mg, 70%); TLC R_f = 0.6 (20% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.92 (s, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 4.52 (t, *J* = 6.7 Hz, 2H), 3.02 (t, *J* = 6.2 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.77, 137.67, 136.67, 134.65, 130.72, 127.21, 125.12,68.20, 27.55, 21.11. **HRMS (ESI+) (*m/z*)** calcd for $C_{10}H_{11}O_2$ [M+H] 163.0759 found 163.0754.

5-Methylisochroman-1-one (2d):



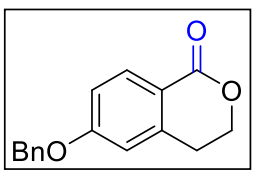
Yellow oil (11 mg, 68%); TLC R_f = 0.6 (20% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.99 (d, *J* = 9.4 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 1H), 7.32-7.27 (m, 1H), 4.54 (t, *J* = 6.2 Hz, 2H), 2.99 (t, *J* = 6.1 Hz, 2H), 2.34 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.64, 138.26, 135.09, 128.34, 127.22, 125.40, 66.78, 25.01, 18.97. **HRMS (ESI+) (*m/z*)** calcd for $C_{10}H_{11}O_2$ [M+H] 163.0759 found 163.0754.

6-methoxyisochroman-1-one (2e):



Yellow oil (10.3 mg, 58%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 2.7 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.11 (dd, *J* = 8.3, 2.7 Hz, 1H), 4.55 (t, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 3.00 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.37, 159.08, 131.92, 128.50, 126.14, 121.77, 113.05, 67.74, 55.71, 27.09. **HRMS (ESI+) (*m/z*)** calcd for $C_{10}H_{11}O_3$ [M+H] 179.0708 found 179.0703.

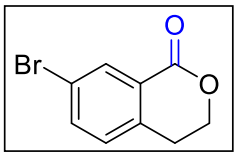
6-(benzyloxy)isochroman-1-one (2f):



Yellow oil (9.4 mg, 37%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 (s, 1H), 7.46-7.32 (m, 5H), 7.18 (s, 2H), 5.10 (s, 2H), 4.52 (t, *J* = 6.0 Hz, 2H), 2.99 (t, *J* = 6.0 Hz, 2H). **^{13}C**

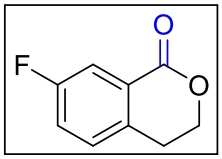
NMR (101 MHz, $CDCl_3$) δ 165.26, 158.21, 136.43, 132.19, 128.74, 128.57, 128.25, 127.65, 126.19, 122.36, 114.25, 70.38, 67.70, 27.12. **HRMS (ESI+) (*m/z*)** calcd for $C_{10}H_{11}O_3$ [M+H] 255.1021 found 255.1016.

7-Bromoisochroman-1-one (2g):



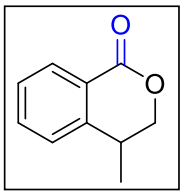
Yellow solid (9.9 mg, 44%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.24 (d, *J* = 2.0 Hz, 1H), 7.66 (dd, *J* = 7.7, 2.2 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 4.54 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.86, 138.31, 136.68, 133.26, 129.05, 127.07, 121.46, 67.30, 27.44. **HRMS (ESI+) (*m/z*)** calcd for $C_9H_8O_2Br$ [M+H] 226.9708 found 226.9702 and calcd for $C_9H_7O_2BrNa$ [M+Na] 248.9527 found 248.9522.

7-Fluoroisochroman-1-one (2h):



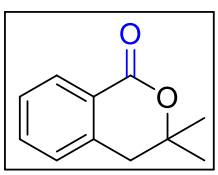
White solid (5.5 mg, 33%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.79 (d, *J* = 10.0 Hz, 1H), 7.28 – 7.25 (m, 2H), 4.55 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 5.9 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.18, 163.18, 160.72, 135.35, 129.18 (d, *J* = 28 Hz), 127.07 (d, *J* = 32 Hz), 121.19 (*J* = 88 Hz), 116.90 (d, *J* = 96 Hz), 67.56, 27.23. **HRMS (ESI+) (*m/z*)** calcd for $C_9H_8O_2F$ [M+H] 167.0508 found 167.0503.

4-Methylisochroman-1-one (2i):



Colourless oil (11.4 mg, 70%); TLC R_f = 0.7 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.60-7.55 (m, 1H), 7.43-7.37 (m, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 4.53 (dd, *J* = 11.0, 4.1 Hz, 1H), 4.25 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.21-3.12 (m, 1H), 1.38 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.27, 144.64, 134.01, 130.56, 127.63, 125.78, 124.45, 72.55, 31.82, 16.78. **HRMS (ESI+) (*m/z*)** calcd for $C_{10}H_{11}O_2$ [M+H] 163.0759 found 163.0754.

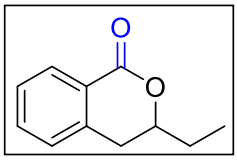
3,3-dimethylisochroman-1-one (2j):



Colorless oil (13.4 mg, 76%); TLC R_f = 0.7 (30% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.56-7.51 (m, 1H), 7.40-7.36 (m, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 3.03 (s, 2H), 1.46 (s, 6H). **^{13}C**

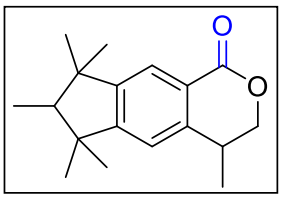
NMR (126 MHz, $CDCl_3$) δ 165.18, 138.15, 133.85, 130.12, 128.02, 127.60, 124.88, 80.76, 39.54, 27.63. **HRMS (ESI+) (*m/z*)** calcd for $C_{11}H_{13}O_2$ [M+H] 177.0916 found 177.0910.

3-Ethylisochroman-1-one (2k):



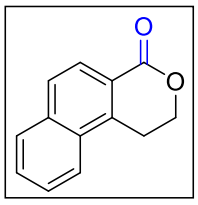
Yellow oil (11.4 mg, 65%); TLC R_f = 0.7 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.59-7.53 (m, 1H), 7.43-7.37 (m, 1H), 7.26 (d, *J* = 4.8 Hz, 1H), 4.55 (dd, *J* = 11.2, 3.2 Hz, 1H), 4.47 (dd, *J* = 11.2, 2.9 Hz, 1H), 2.81-2.74 (m, 1H), 1.82-1.71 (m, 2H), 1.04 – 1.00 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.24, 143.79, 133.65, 130.57, 127.72, 127.08, 124.58, 70.41, 39.12, 25.76, 11.85. **HRMS (ESI+) (*m/z*)** calcd for $C_{11}H_{13}O_2$ [M+H] 177.0916 found 177.0910.

4,6,6,7,8,8-hexamethyl-3,4,7,8-tetrahydrocyclopenta[g]isochromen-1(6H)-one (2l):



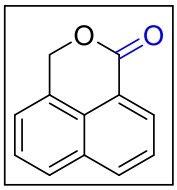
White solid (19.3 mg, 71%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.90 (s, 1H), 7.04 (s, 1H), 4.52 – 4.45 (m, 1H), 4.25 – 4.18 (m, 1H), 3.17-3.09 (m, 1H), 1.92-1.84 (m, 1H), 1.38 – 1.35 (m, 3H), 1.31 – 1.29 (m, 6H), 1.09 (t, *J* = 4.5 Hz, 6H), 1.01 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.97, 158.46, 151.25, 143.62, 125.13, 123.02, 119.90, 72.58, 54.18, 45.32, 44.69, 32.12, 29.13, 28.79, 25.86, 25.77, 17.03, 8.53. **HRMS (ESI+) (*m/z*)** calcd for $C_{18}H_{25}O_2$ [M+H] 273.1855 found 273.1849.

1H-benzo[f]isochromen-4(2H)-one (2m):



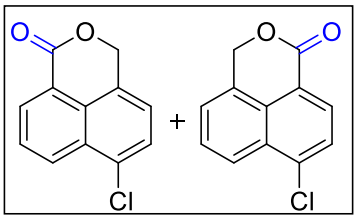
White solid (10.5 mg, 53%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.11 (d, *J* = 8.6 Hz, 1H), 8.02 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.92 – 7.88 (m, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.67 – 7.59 (m, 2H), 4.66 (t, *J* = 6.1 Hz, 2H), 3.43 (t, *J* = 6.1 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.54, 138.59, 135.65, 130.72, 128.93, 128.73, 127.80, 127.27, 125.22, 124.44, 122.49, 66.73, 24.22. **HRMS (ESI+) (*m/z*)** calcd for $C_{13}H_{11}O_2$ [M+H] 199.0759 found 199.0754.

Benzo[de]isochromen-1(3H)-one (2n):



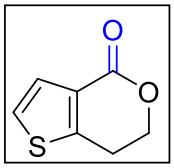
White solid (9.4 mg, 51%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.40 (d, *J* = 7.0 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.58 – 7.52 (m, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 5.83 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.33, 133.66, 132.15, 129.31, 128.50, 127.31, 126.87, 126.68, 126.65, 121.64, 120.31, 70.18. **HRMS (ESI+) (*m/z*)** calcd for $C_{12}H_9O_2$ [M+H] 185.0603 found 185.0597.

7-Chlorobenzo[de]isochromen-1(3H)-one (2o) (major regio-isomer is mentioned):



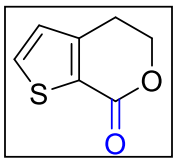
White solid (9.4 mg, 43%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.52 (d, *J* = 8.5 Hz, 1H), 8.33 (d, *J* = 7.7 Hz, 1H), 7.77 (dd, *J* = 18.2, 7.8 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 1H), 5.84 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.76, 138.37, 130.46, 129.79, 129.53, 127.65, 127.11, 126.40, 123.88, 122.64, 70.04, 66.21. **HRMS (ESI+) (*m/z*)** calcd for $C_{12}H_8ClO_2$ [M+H] 219.0213 found 219.0207.

6,7-dihydro-4H-thieno[3,2-c]pyran-4-one (2p):



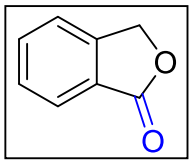
White solid (7.6 mg, 49%); TLC R_f = 0.5 (30% EtOAc/Pet ether);**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (d, *J* = 5.2 Hz, 1H), 7.17 (d, *J* = 5.3 Hz, 1H), 4.60 (t, *J* = 6.1 Hz, 2H), 3.16 (t, *J* = 6.1 Hz, 2H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.35, 149.01, 128.22, 127.03, 124.08, 67.79, 24.70. **HRMS (ESI+) (*m/z*)** calcd for $C_7H_7O_2S$ [M+H] 155.0167 found 155.0161.

4H-thieno[2,3-c]pyran-7(5H)-one (2q):



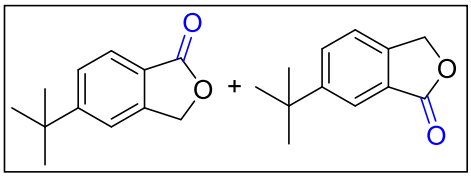
White solid (8.6 mg, 56%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 (d, *J* = 5.2 Hz, 1H), 7.01 (d, *J* = 4.7 Hz, 1H), 4.59 (t, *J* = 6.2 Hz, 2H), 3.02 (t, *J* = 6.1 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.29, 147.55, 134.52, 126.80, 126.64, 68.46, 25.18. **HRMS (ESI+) (*m/z*)** calcd for $C_7H_7O_2S$ [M+H] 155.0167 found 155.0161.

Isobenzofuran-1(3H)-one(2r):



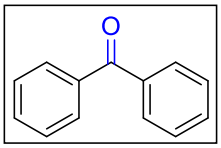
White solid (9.5 mg, 71%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.72-7.67 (m, 1H), 7.57 – 7.49 (m, 2H), 5.34 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.23, 146.61, 134.11, 129.14, 125.87, 122.19, 69.76. **HRMS (ESI+) (*m/z*)** calcd for $C_8H_7O_2$ [M+H] 135.0446 found 135.0441.

5-(*tert*-butyl)isobenzofuran-1(3H)-one (major regio-isomer is mentioned)(2s):



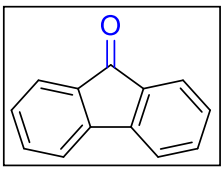
Yellow oil (9.8 mg, 52%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.49 (s, 1H), 5.30 (s, 2H), 1.38 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.30, 158.53, 147.03, 126.84, 125.41, 122.29, 118.75, 69.77, 35.67, 31.33. **HRMS (ESI+) (*m/z*)** calcd for $C_{12}H_{15}O_2$ [M+H] 191.1072 found 191.1067.

Benzophenone (2t):



Yellow solid (3 mg, 17%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 7.5 Hz, 4H), 7.62-7.55 (m, 2H), 7.50-7.44 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.83, 137.66, 132.49, 130.13, 128.35. **HRMS (ESI+) (*m/z*)** calcd for $C_{13}H_{10}O$ [M+H] 183.0765 found 183.0804.

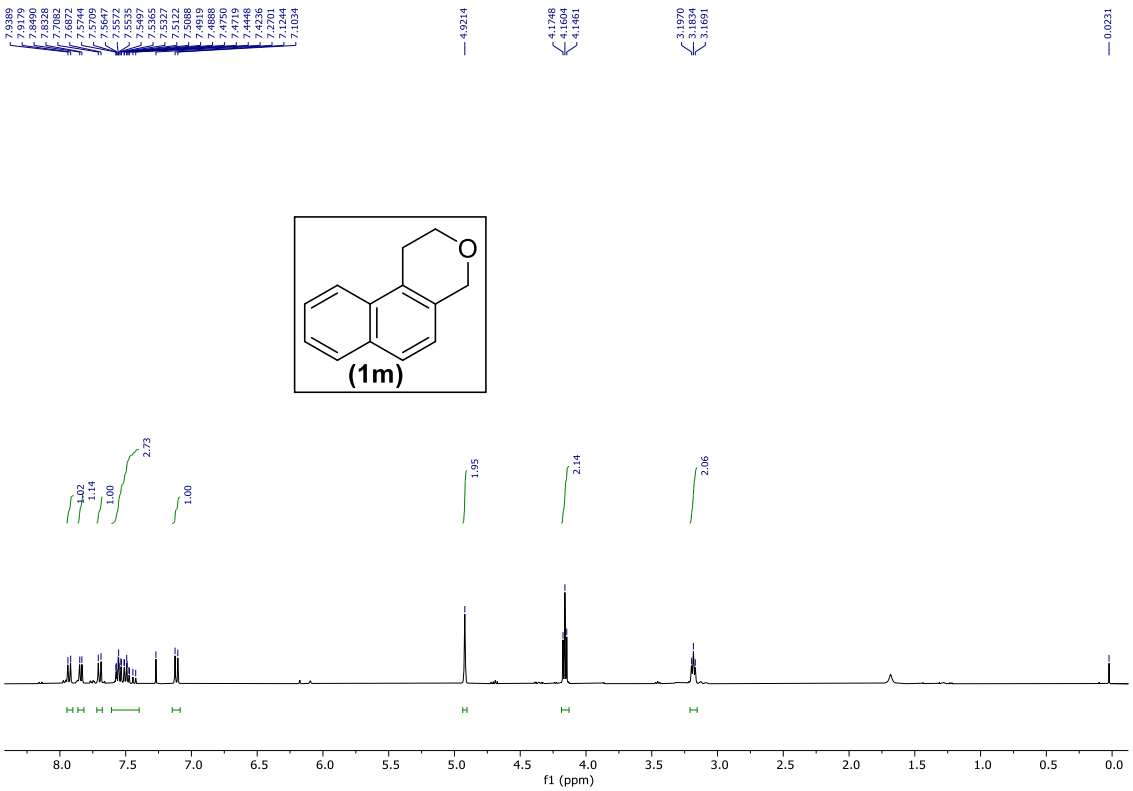
9H-fluoren-9-one (2u):



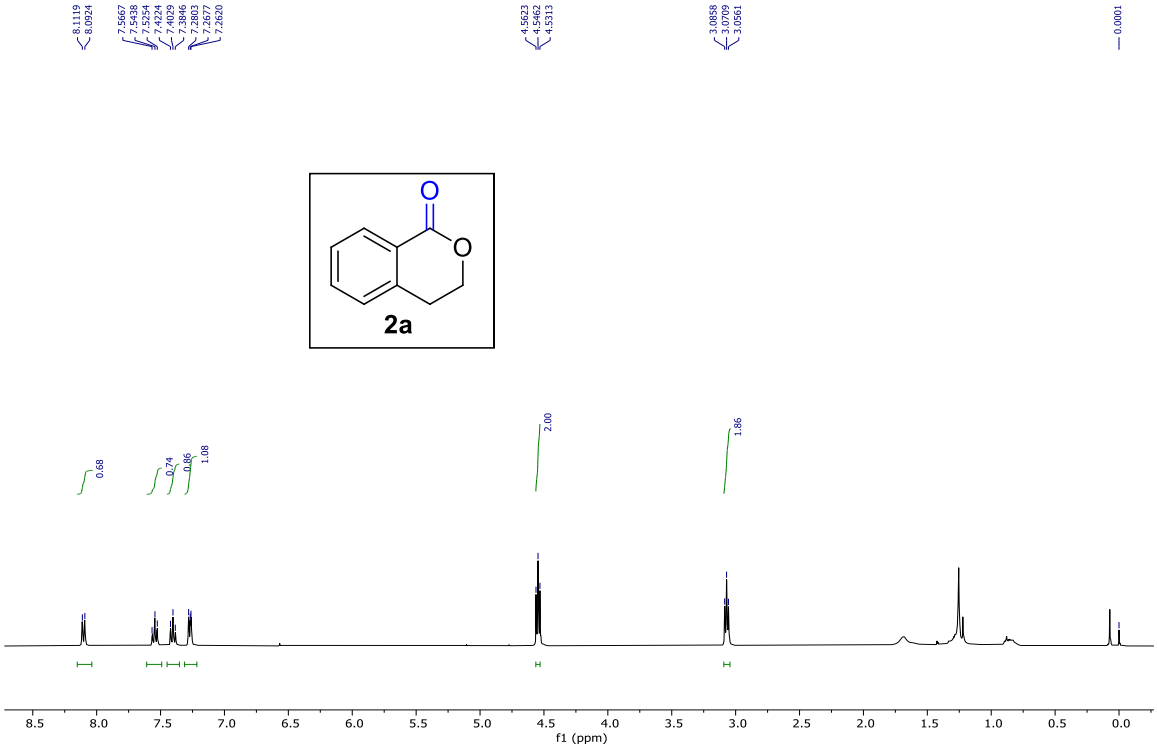
Yellow solid (2.92 mg, 16%); TLC R_f = 0.5 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.65 (d, *J* = 7.4 Hz, 2H), 7.52 – 7.45 (m, 4H), 7.30 – 7.26 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 194.01, 144.50, 134.76, 134.22, 129.15, 124.38, 120.38. **HRMS (ESI+) (*m/z*)** calcd for $C_{13}H_8O$ [M+H] 181.0609 found 181.0648.

2.2.9 Spectral data

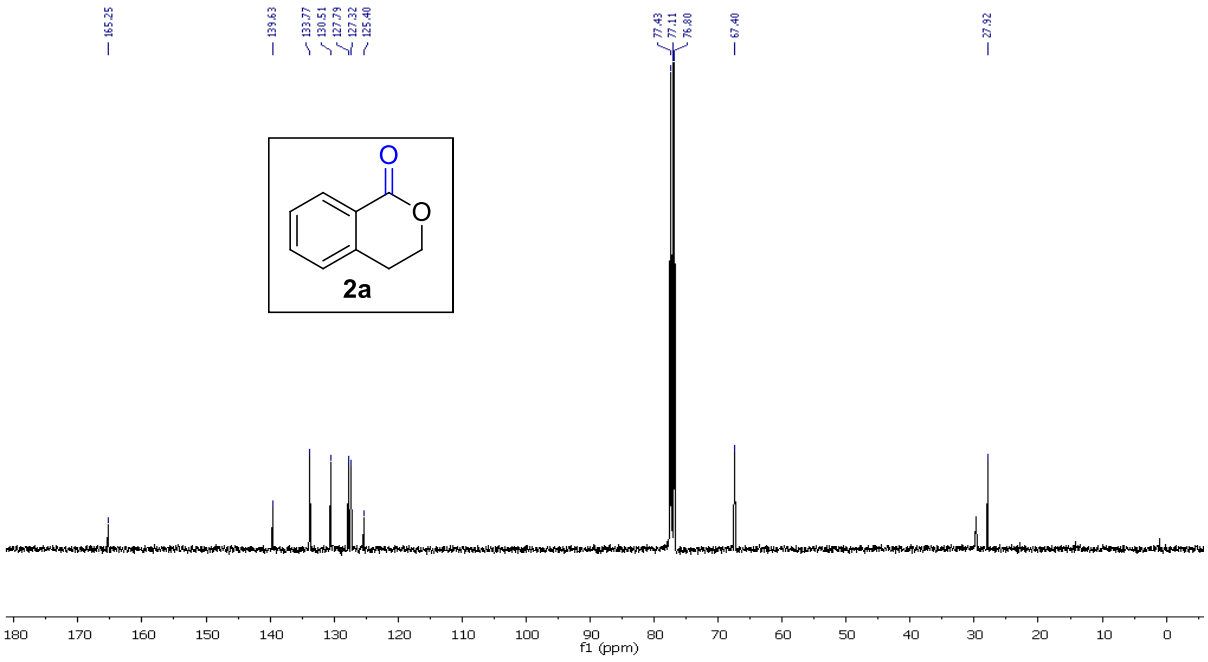
^{1}H NMR of compound **(1m)** in $CDCl_3$



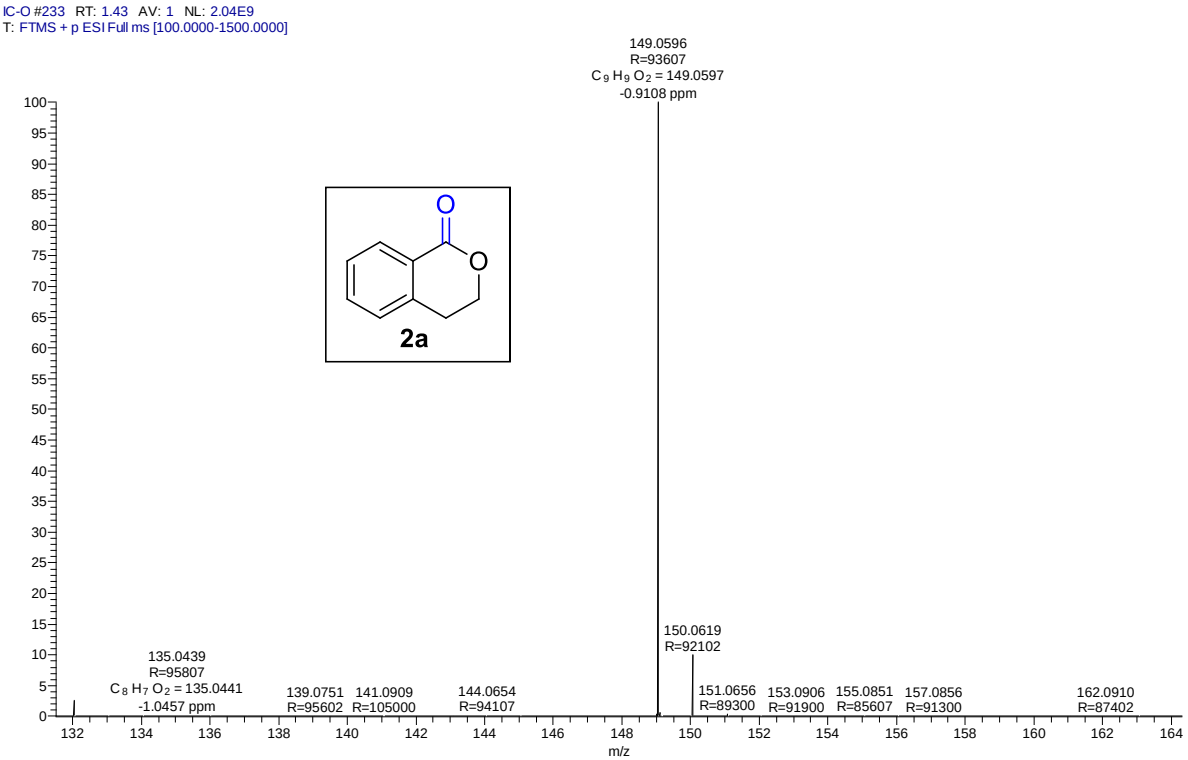
^{1}H NMR of compound **(2a)** in $CDCl_3$



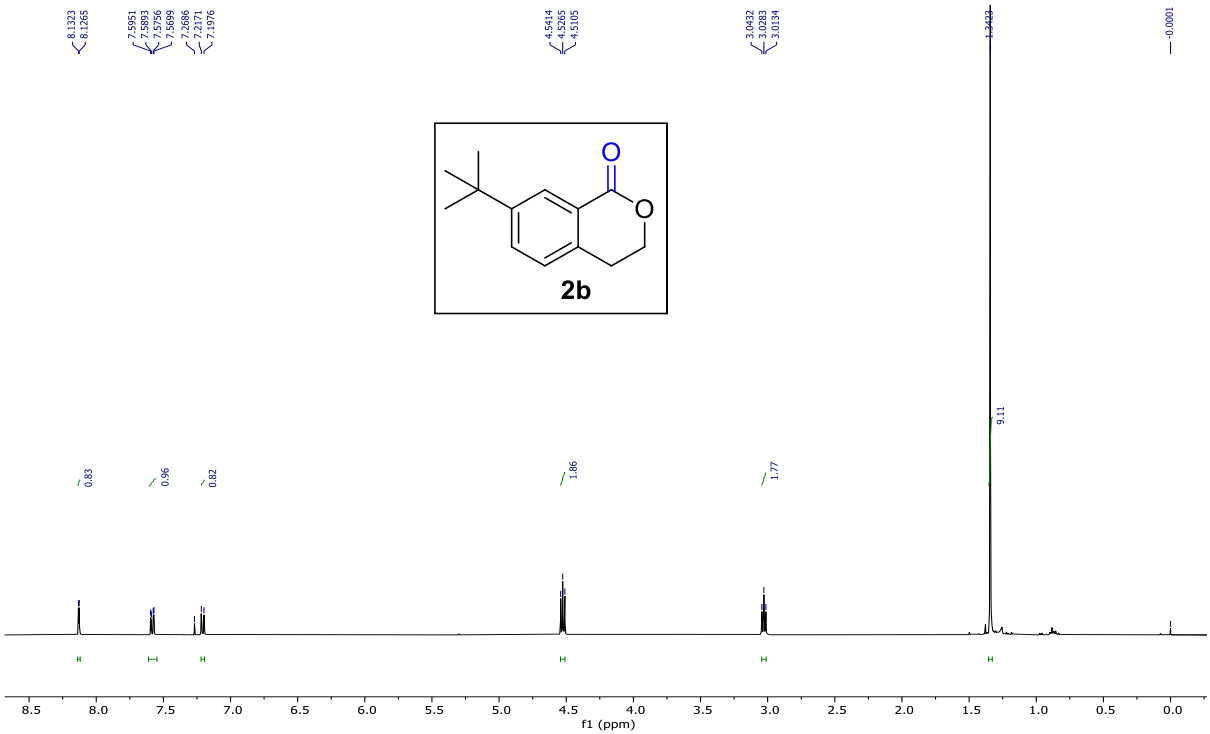
^{13}C NMR of compound **(2a)** in $CDCl_3$



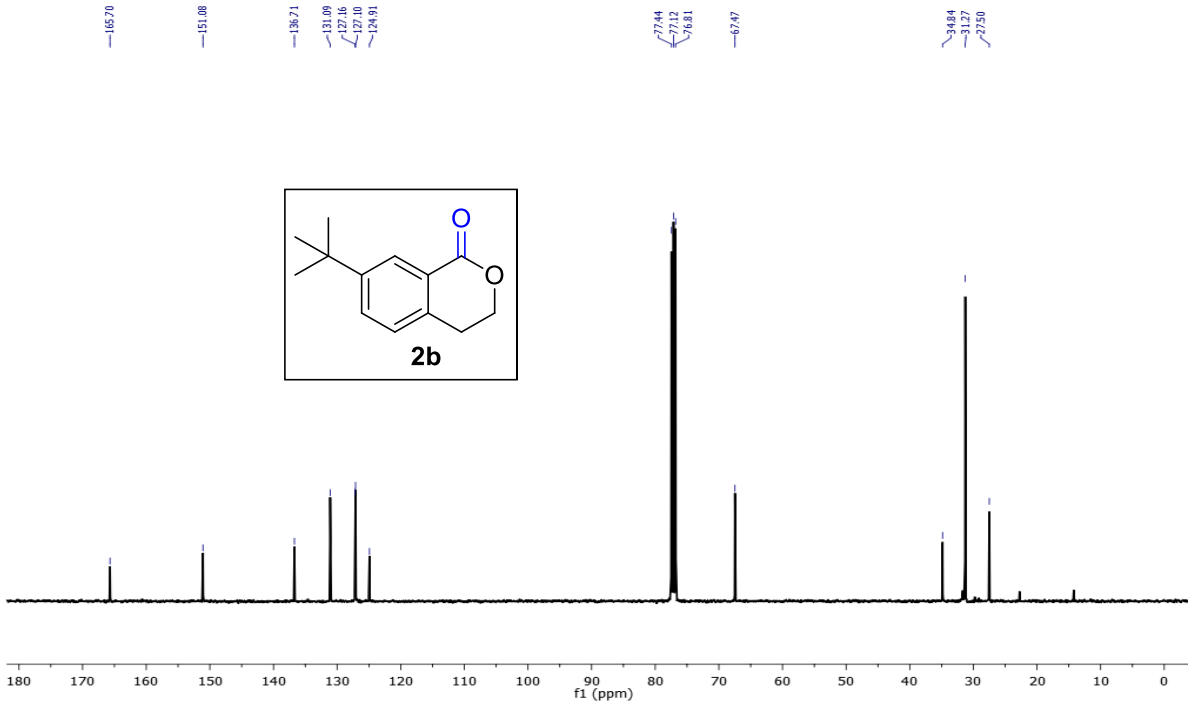
HRMS of compound **(2a)**



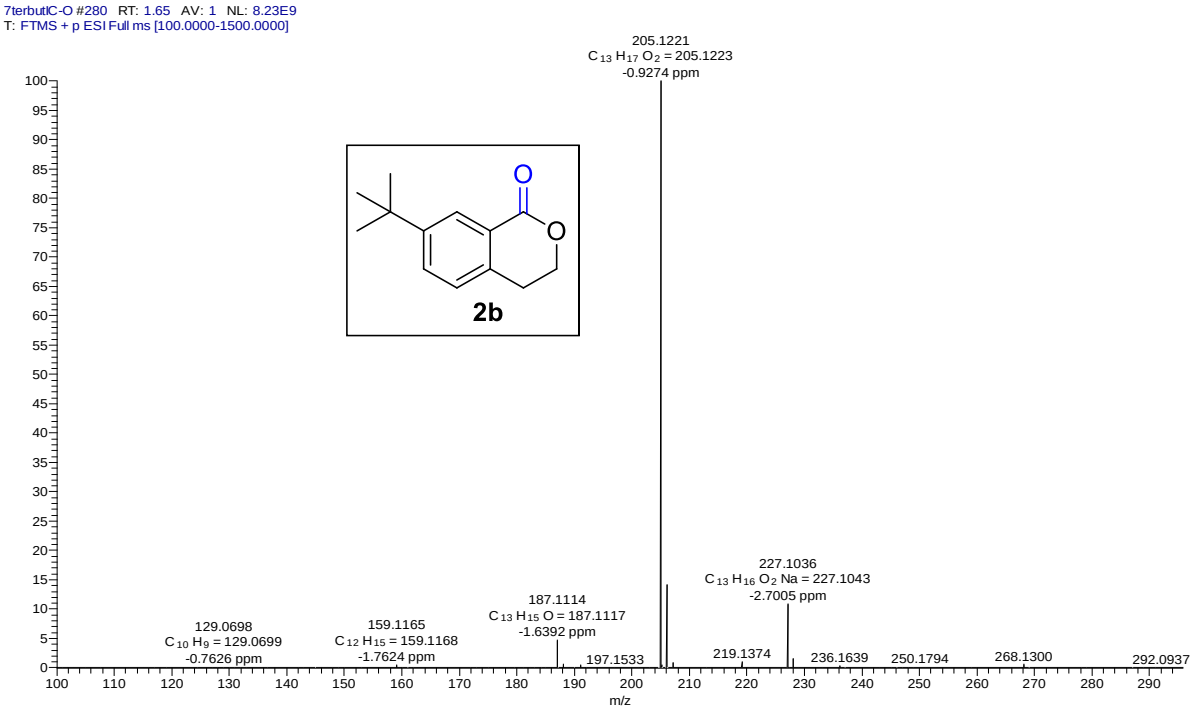
^{1}H NMR of compound **(2b)** in $CDCl_3$



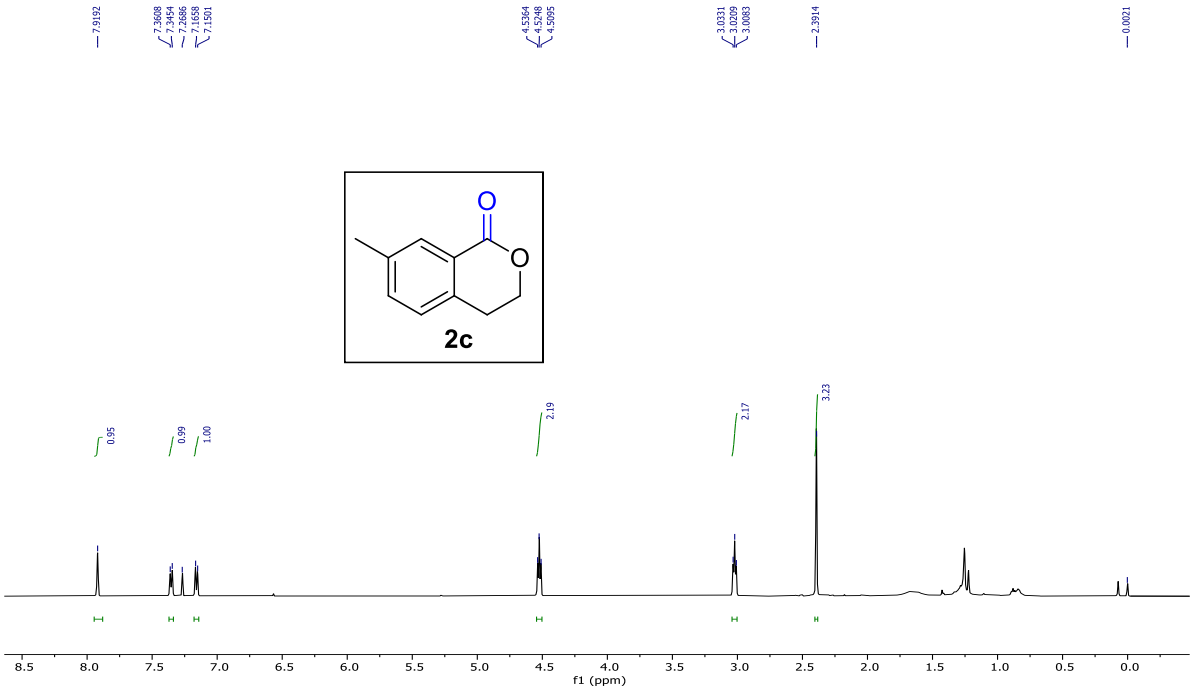
^{13}C NMR of compound **(2b)** in $CDCl_3$



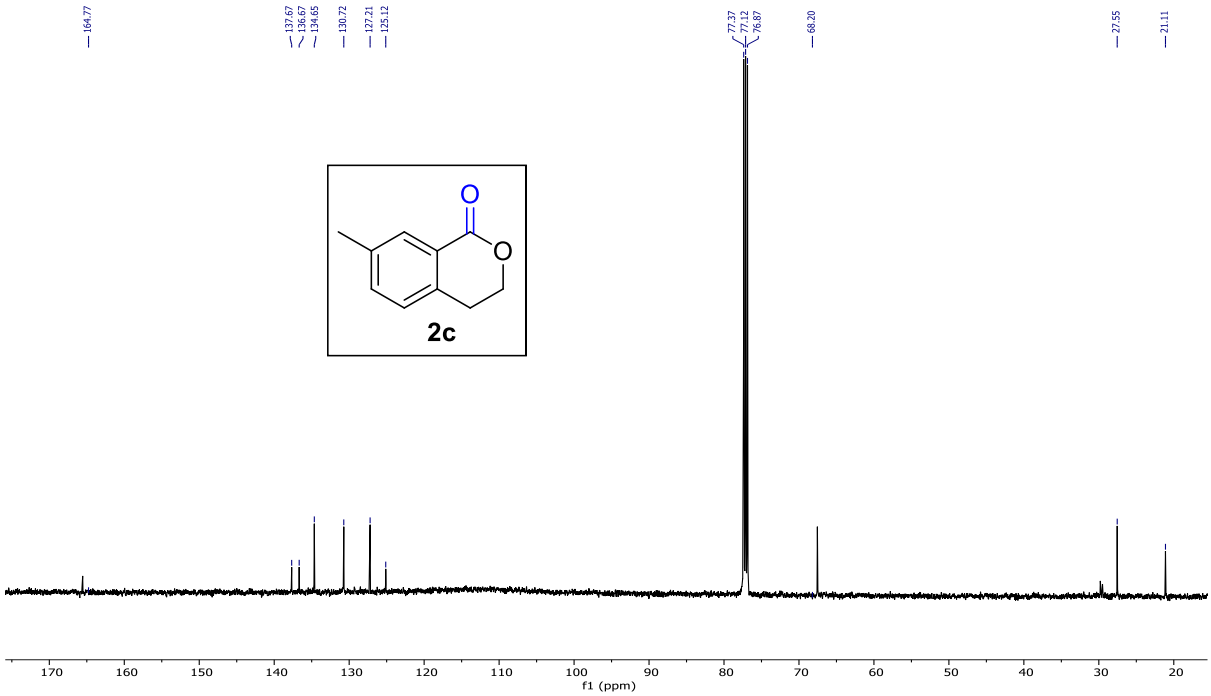
HRMS of compound **(2b)**



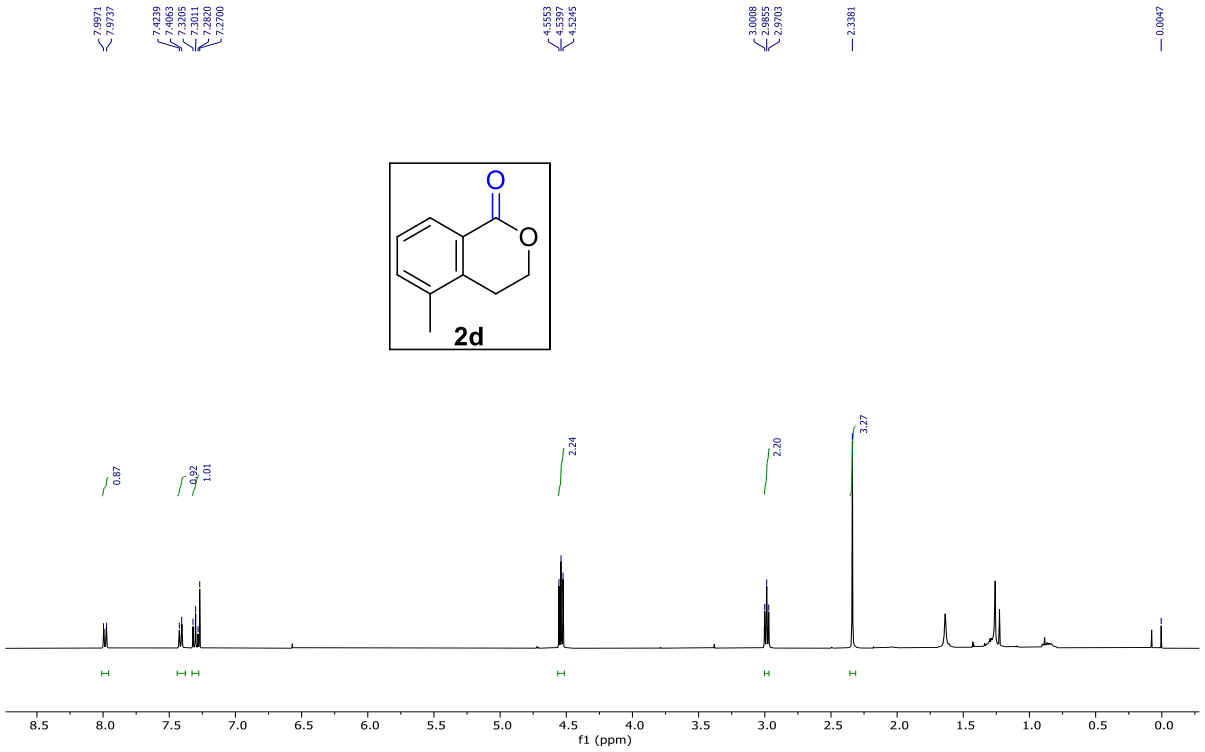
^{1}H NMR of compound **(2c)** in $CDCl_3$



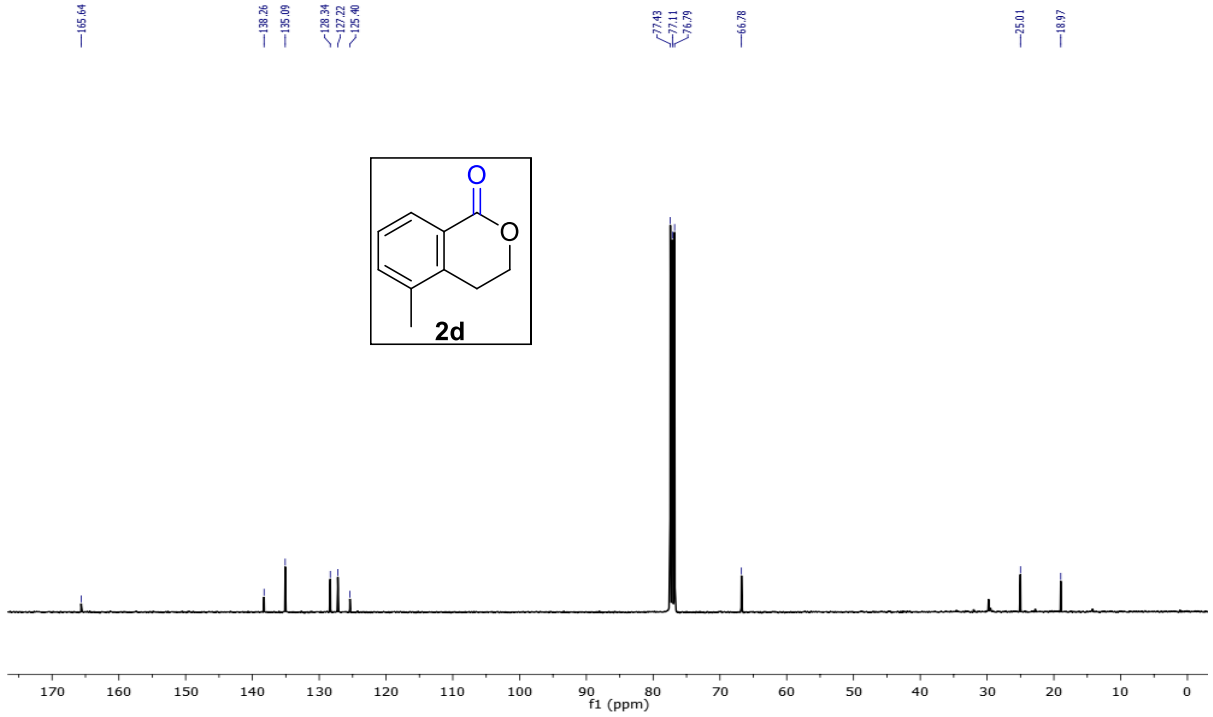
^{13}C NMR of compound **(2c)** in $CDCl_3$



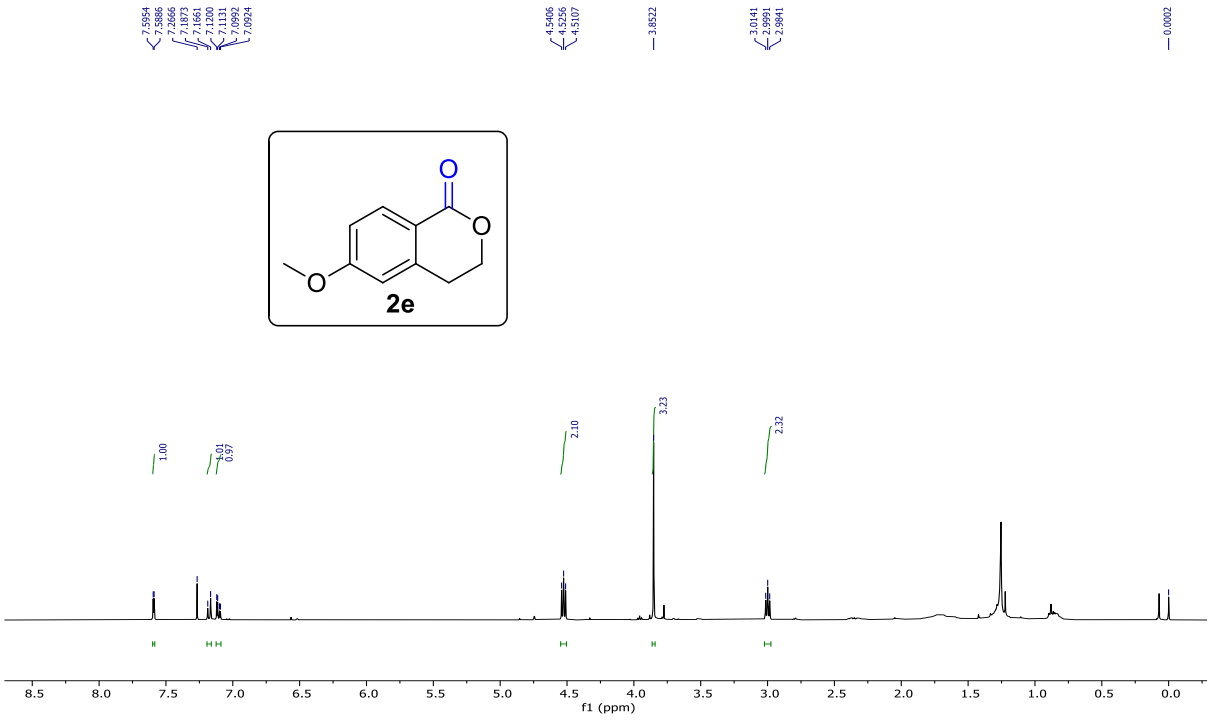
^{1}H NMR of compound **(2d)** in $CDCl_3$



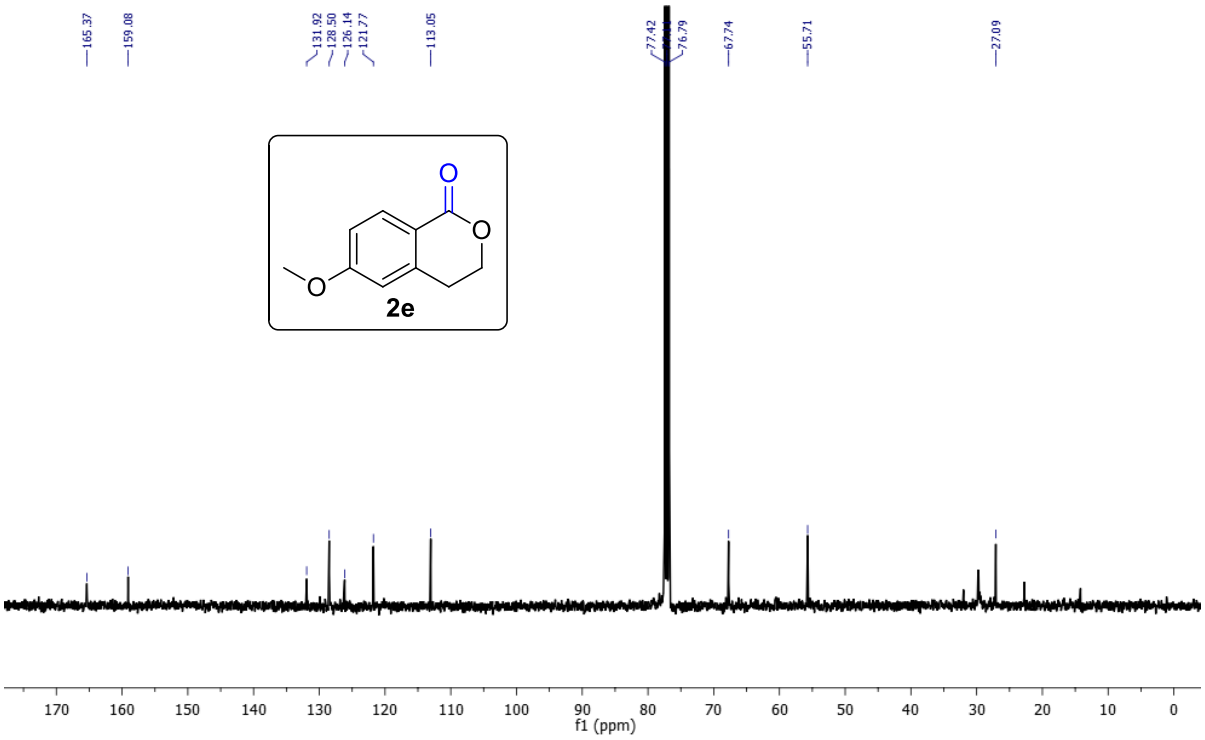
^{13}C NMR of compound **(2d)** in $CDCl_3$



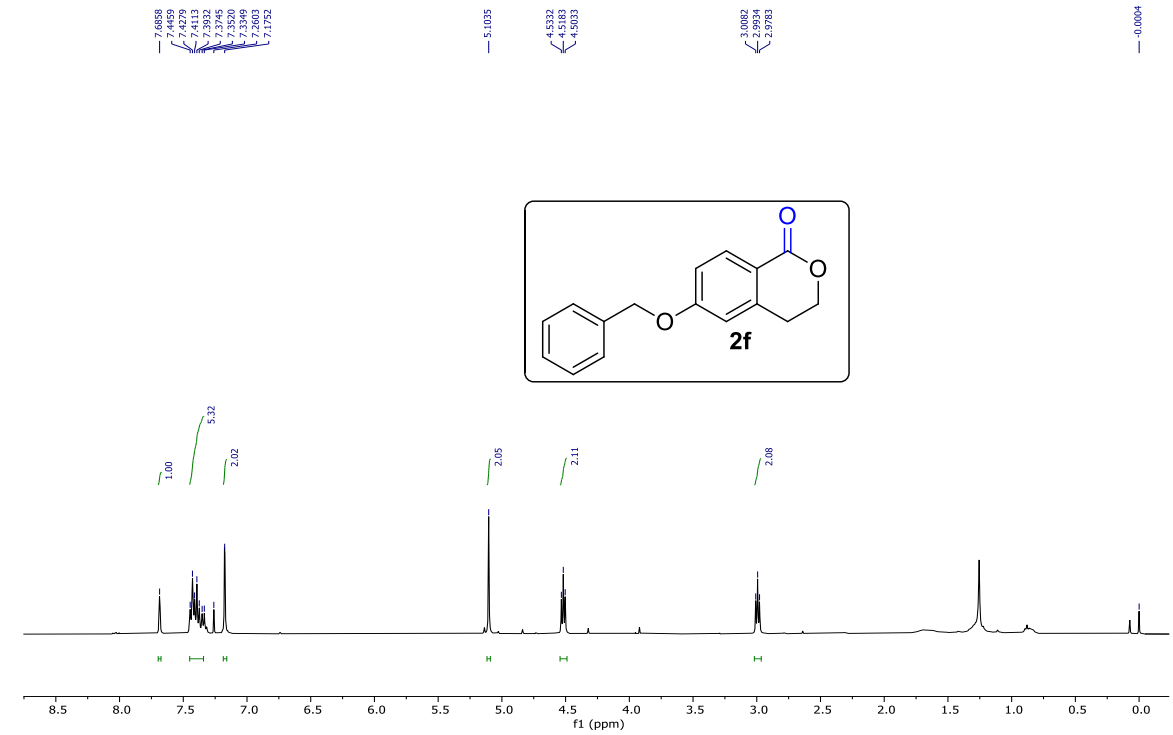
^{1}H NMR of compound **(2e)** in $CDCl_3$



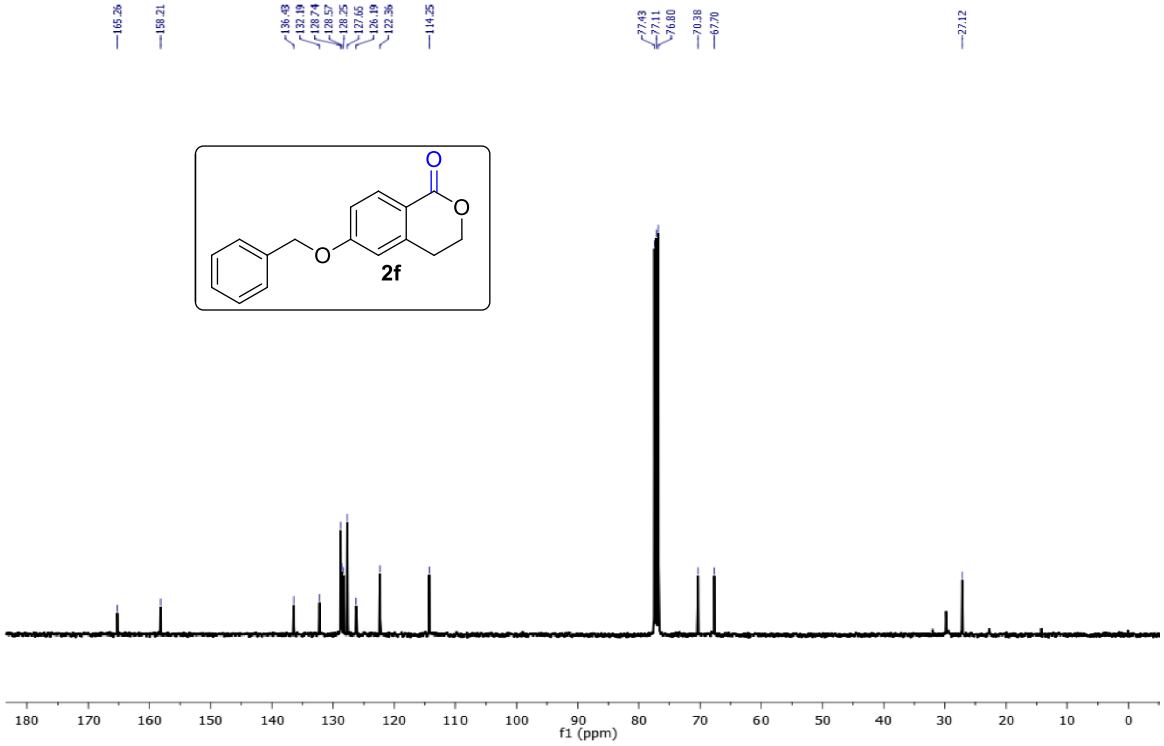
^{13}C NMR of compound **(2e)** in $CDCl_3$



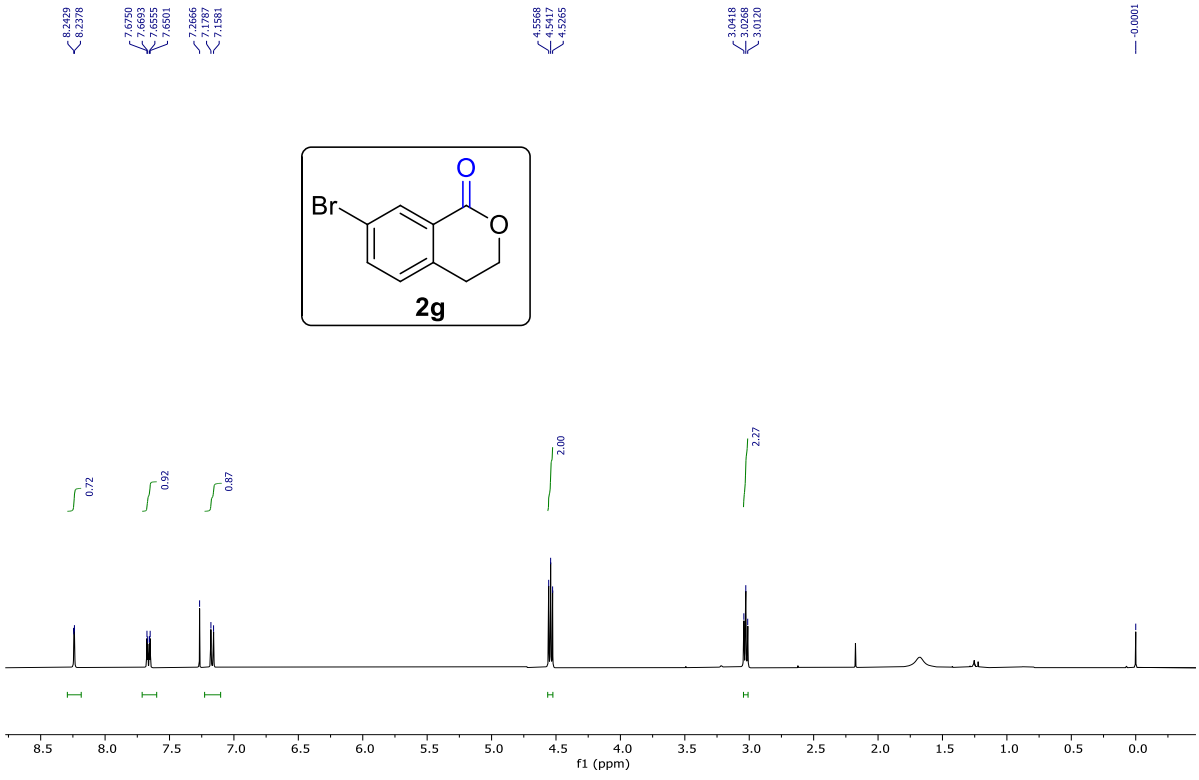
^{1}H NMR of compound **(2f)** in $CDCl_3$



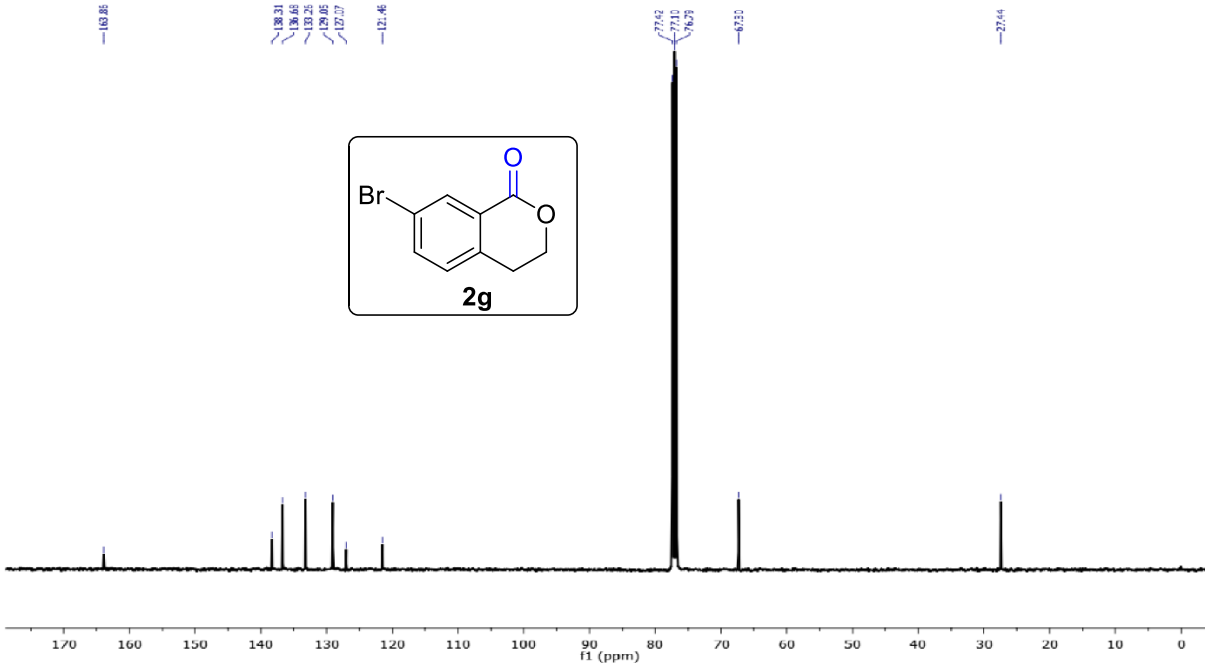
^{13}C NMR of compound **(2f)** in $CDCl_3$



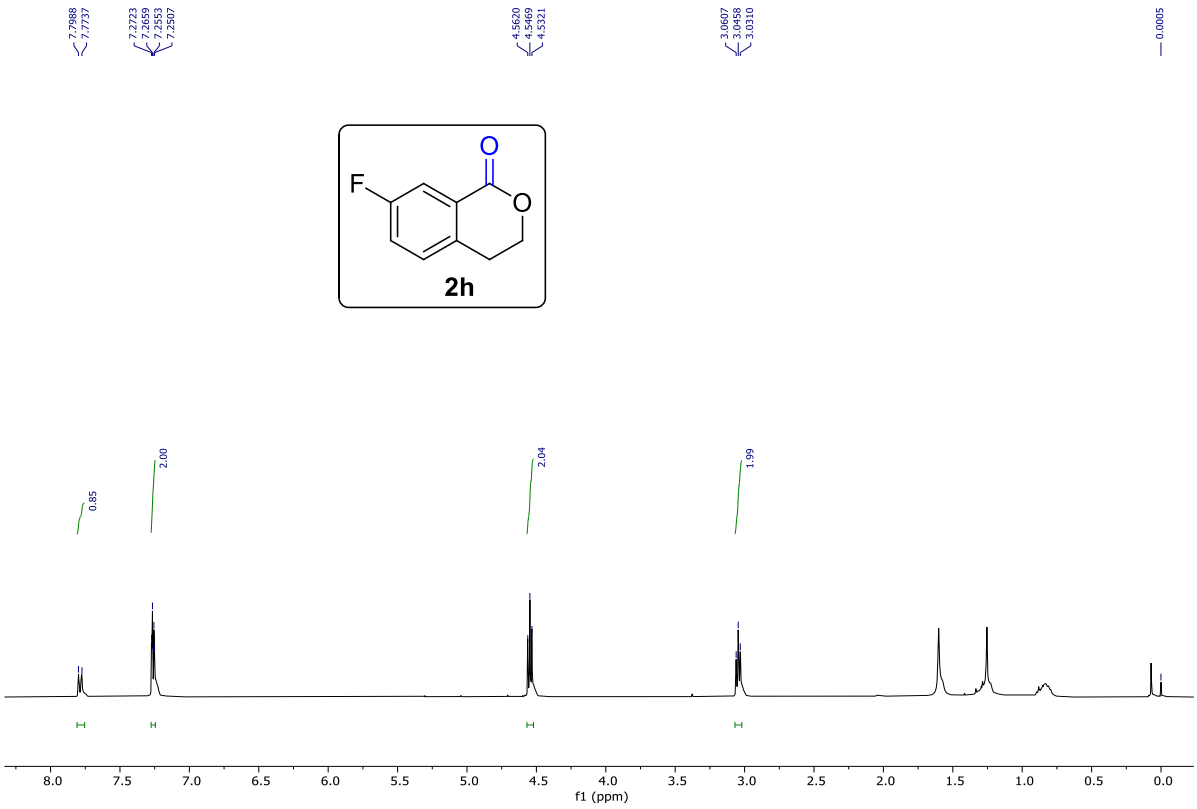
^{1}H NMR of compound **(2g)** in $CDCl_3$



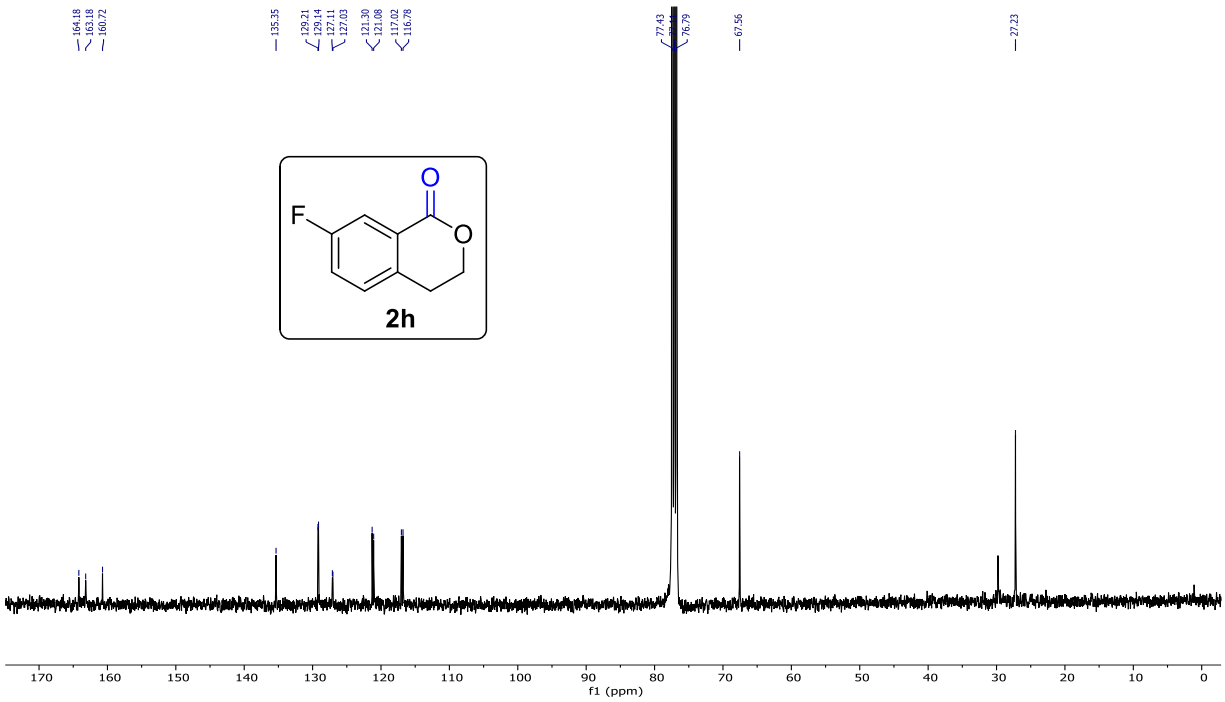
^{13}C NMR of compound **(2g)** in $CDCl_3$



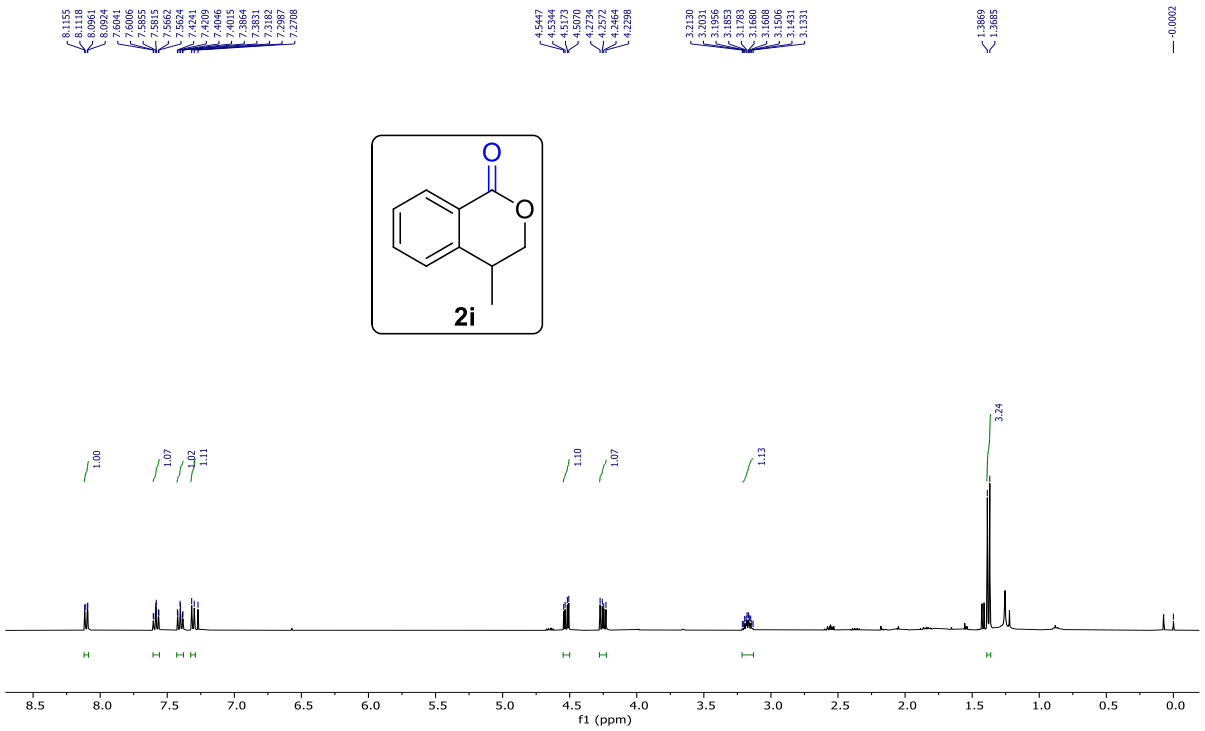
^{1}H NMR of compound **(2h)** in $CDCl_3$



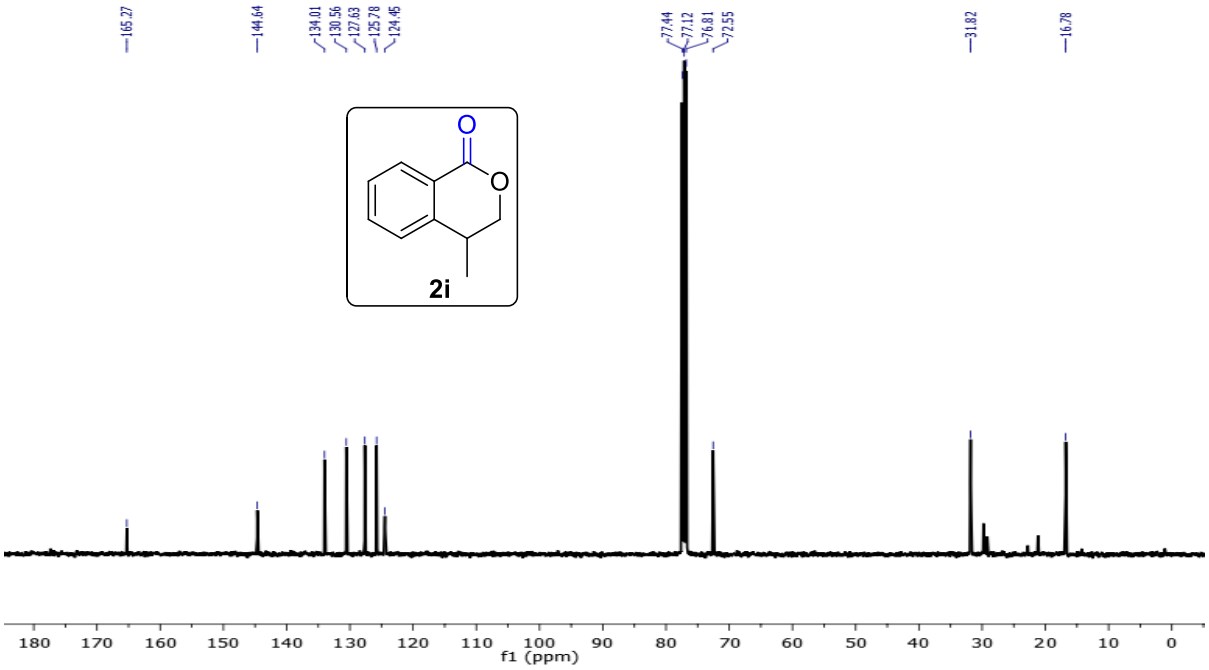
^{13}C NMR of compound **(2h)** in $CDCl_3$



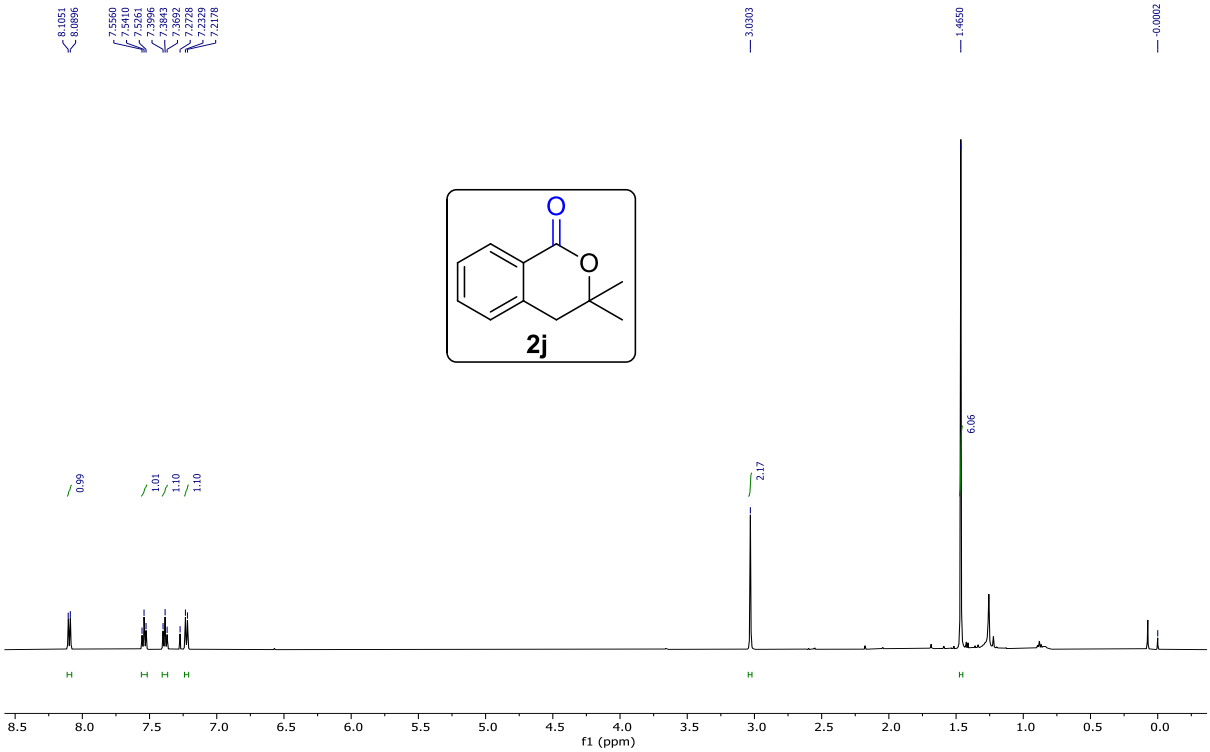
^{1}H NMR of compound **(2i)** in $CDCl_3$



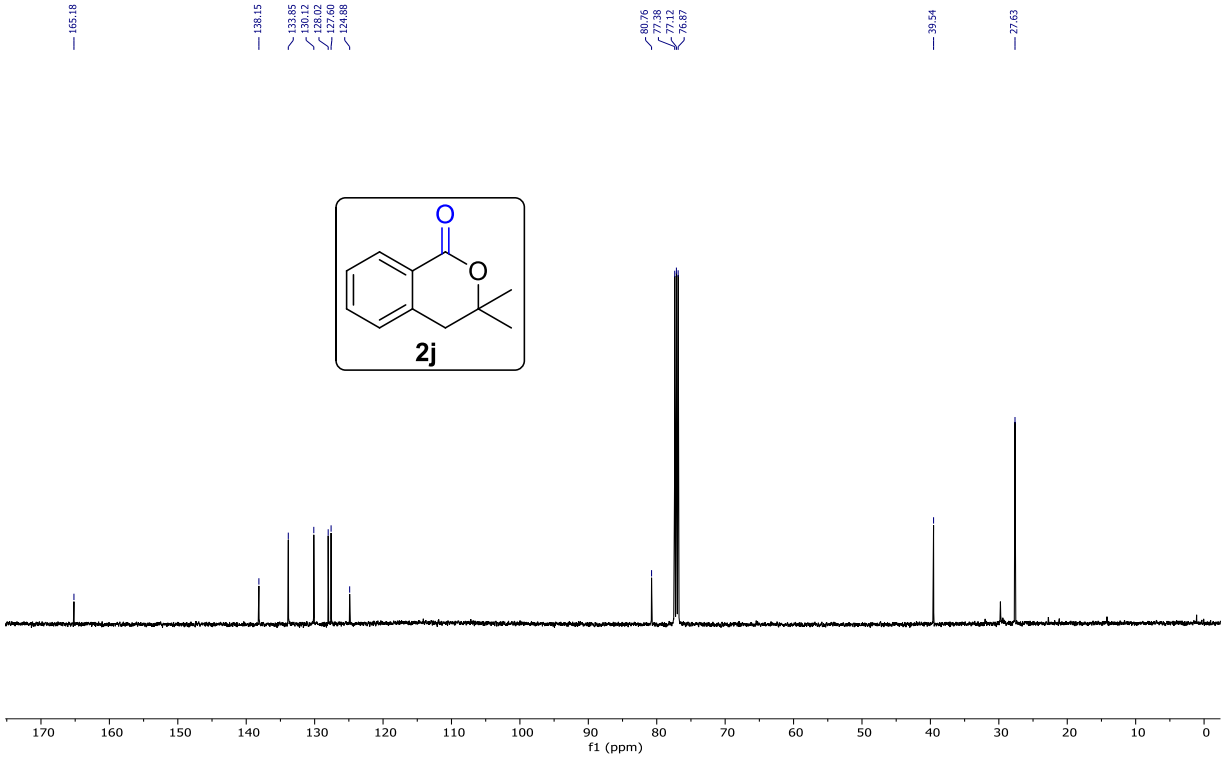
^{13}C NMR of compound **(2i)** in $CDCl_3$



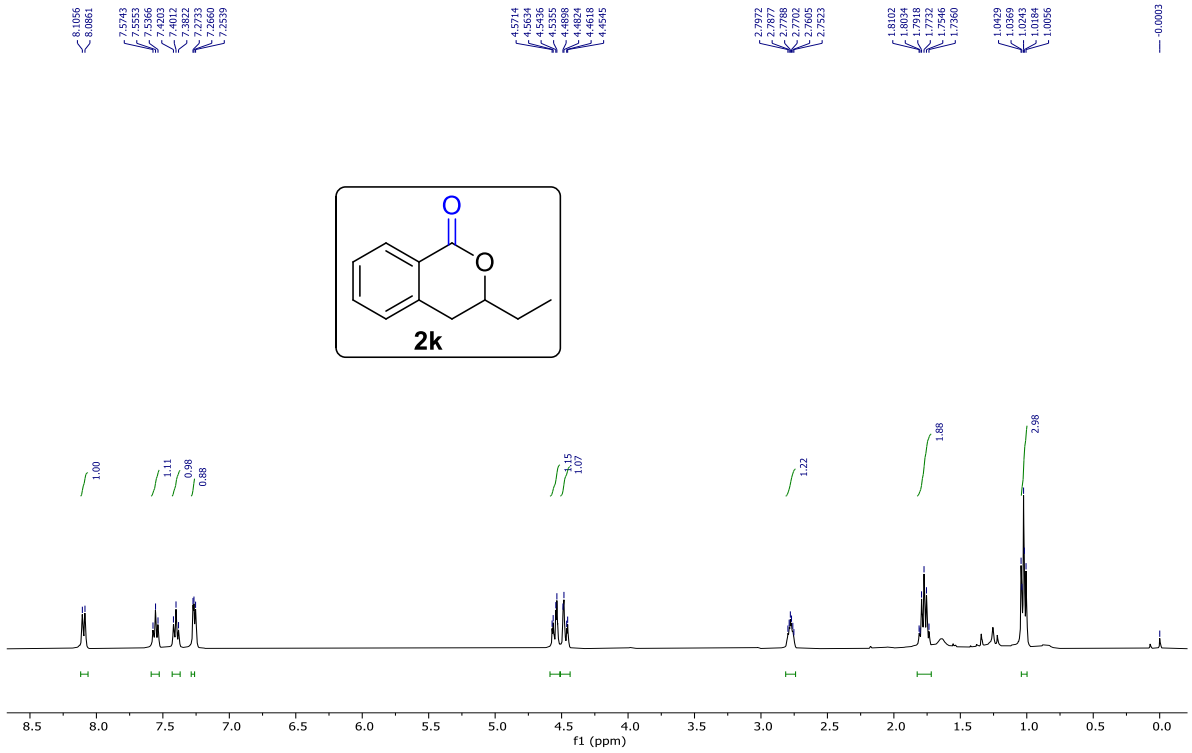
^{1}H NMR of compound **(2j)** in $CDCl_3$



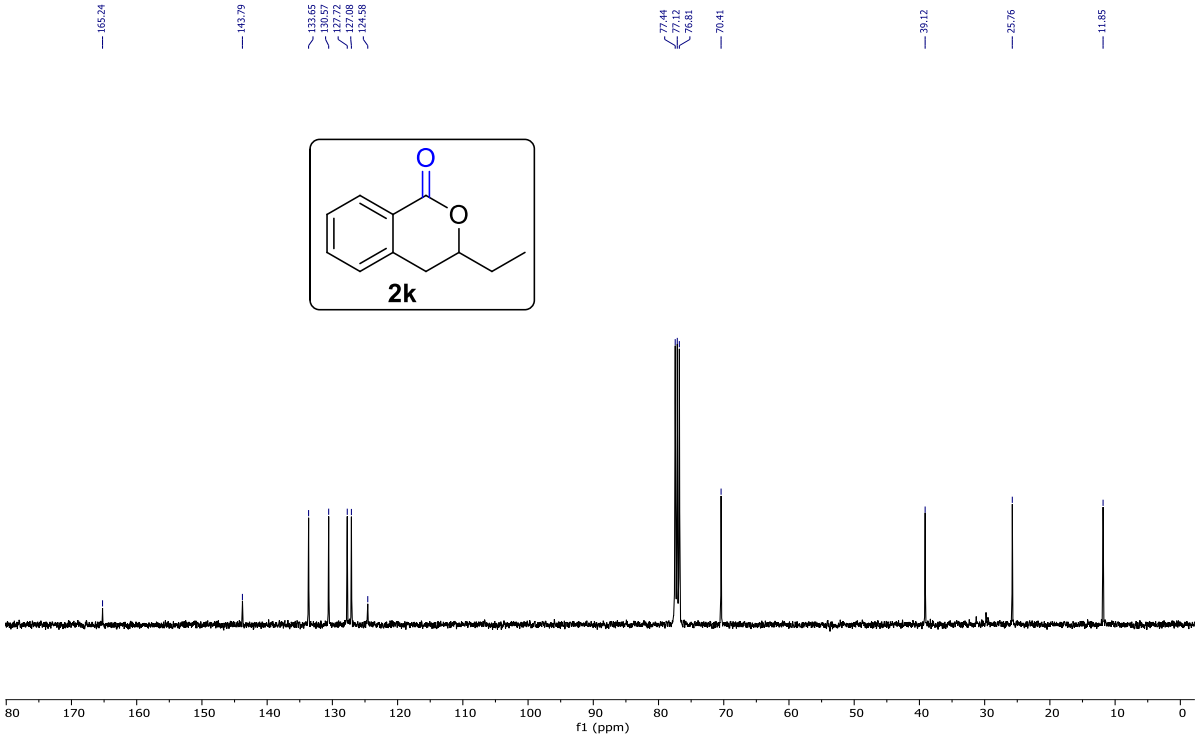
^{13}C NMR of compound **(2j)** in $CDCl_3$



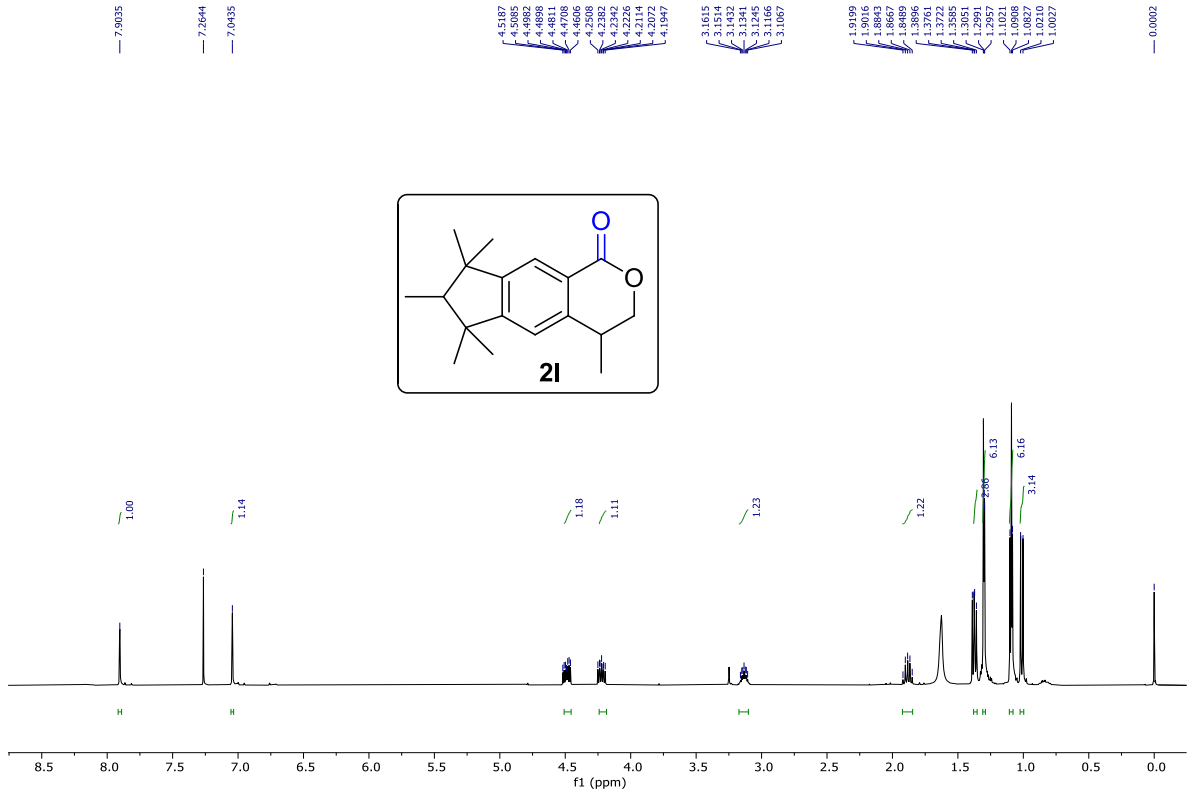
^{1}H NMR of compound **(2k)** in $CDCl_3$



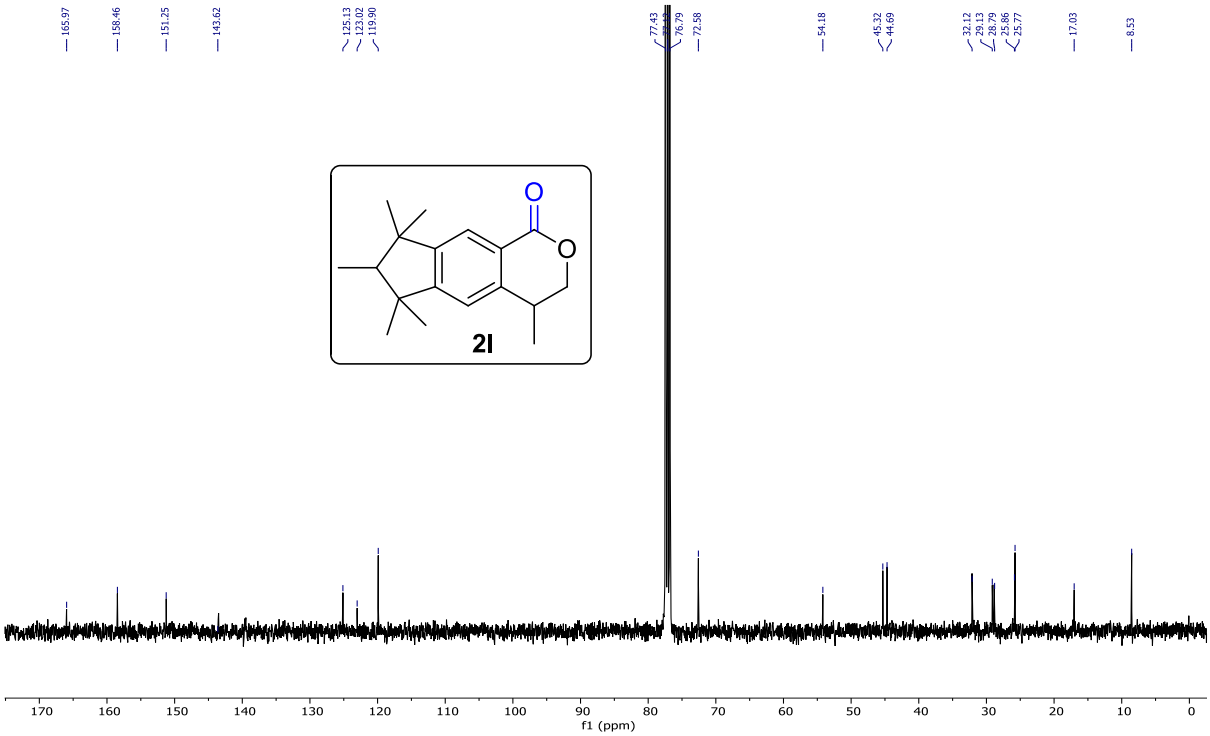
^{13}C NMR of compound **(2k)** in $CDCl_3$



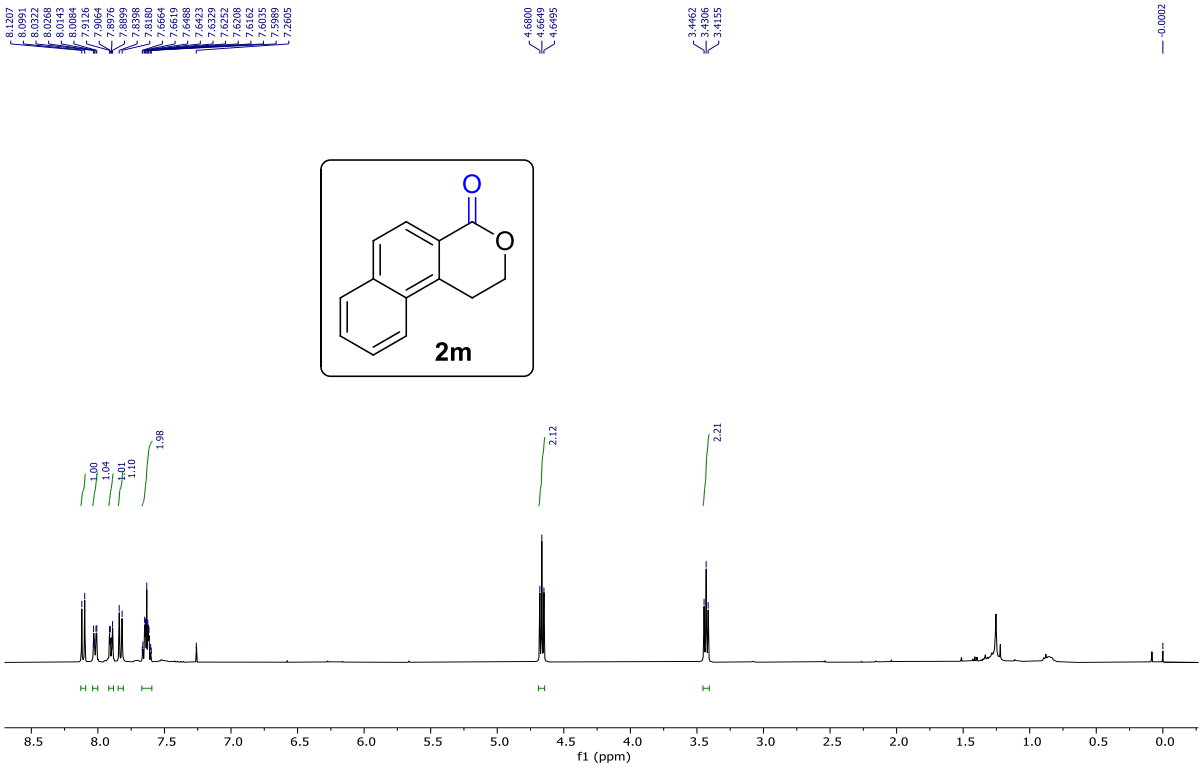
^{1}H NMR of compound **(2l)** in $CDCl_3$



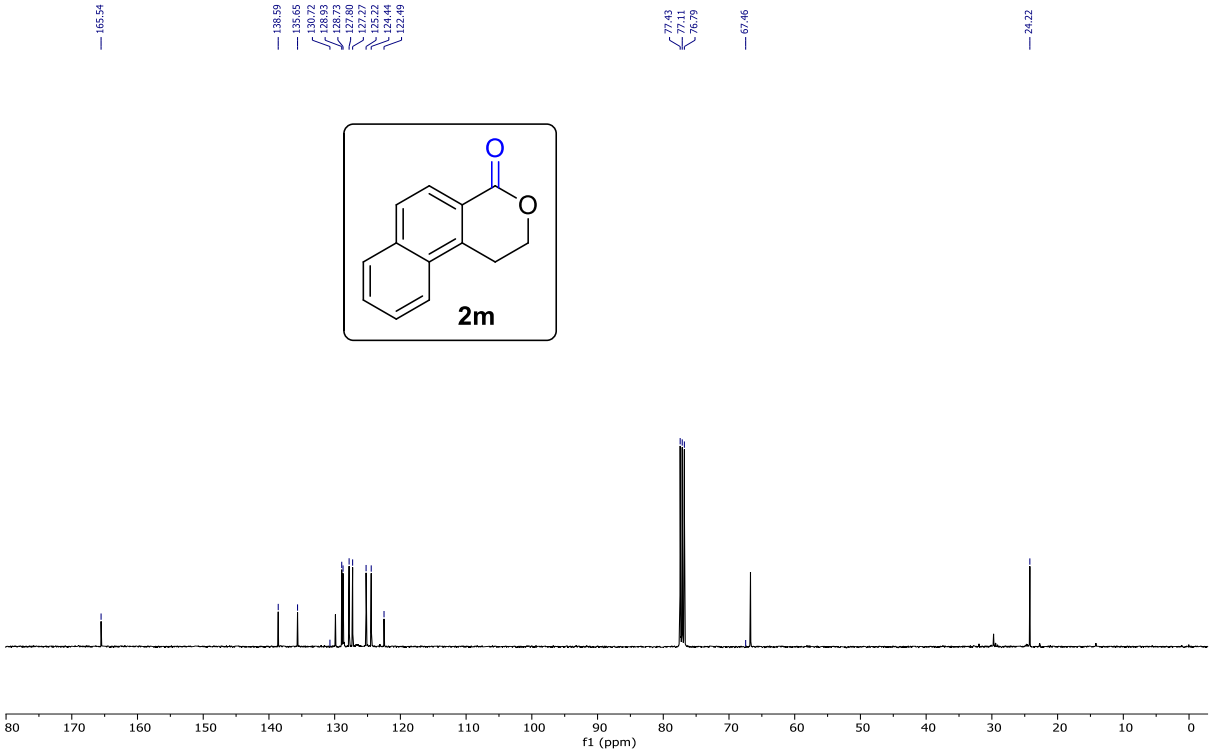
^{13}C NMR of compound **(2l)** in $CDCl_3$



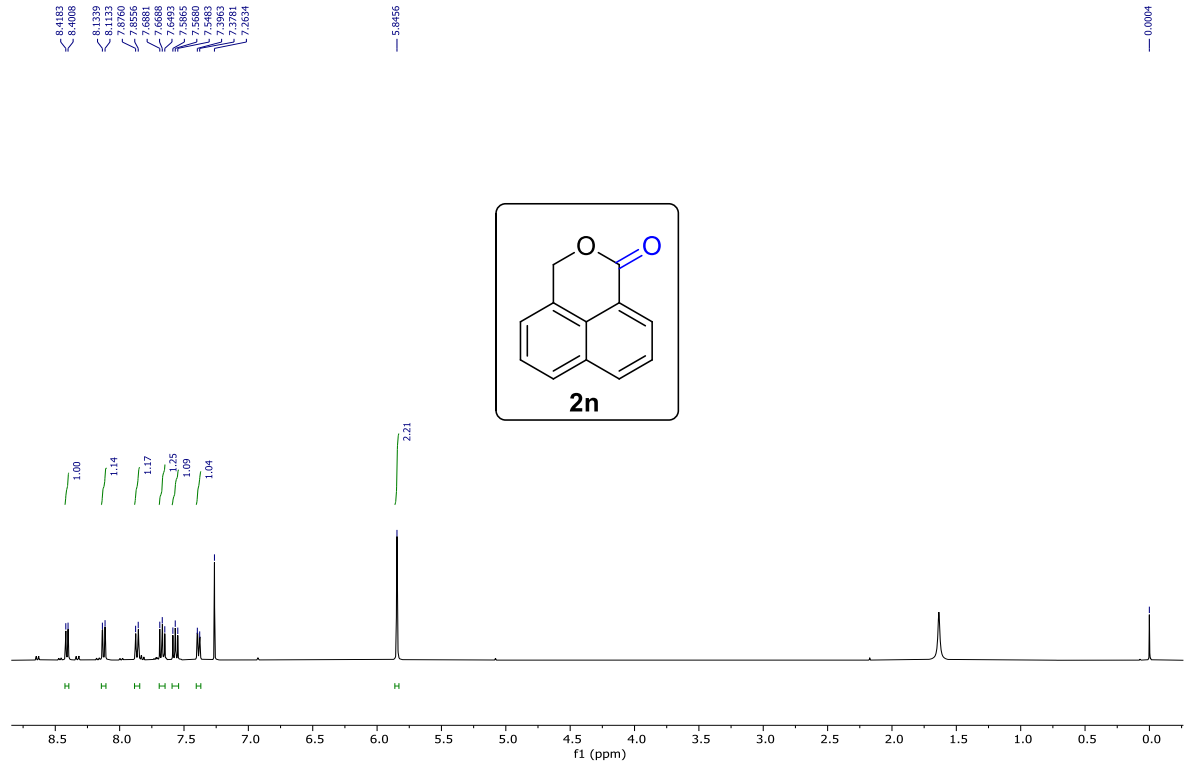
^{1}H NMR of compound **(2m)** in $CDCl_3$



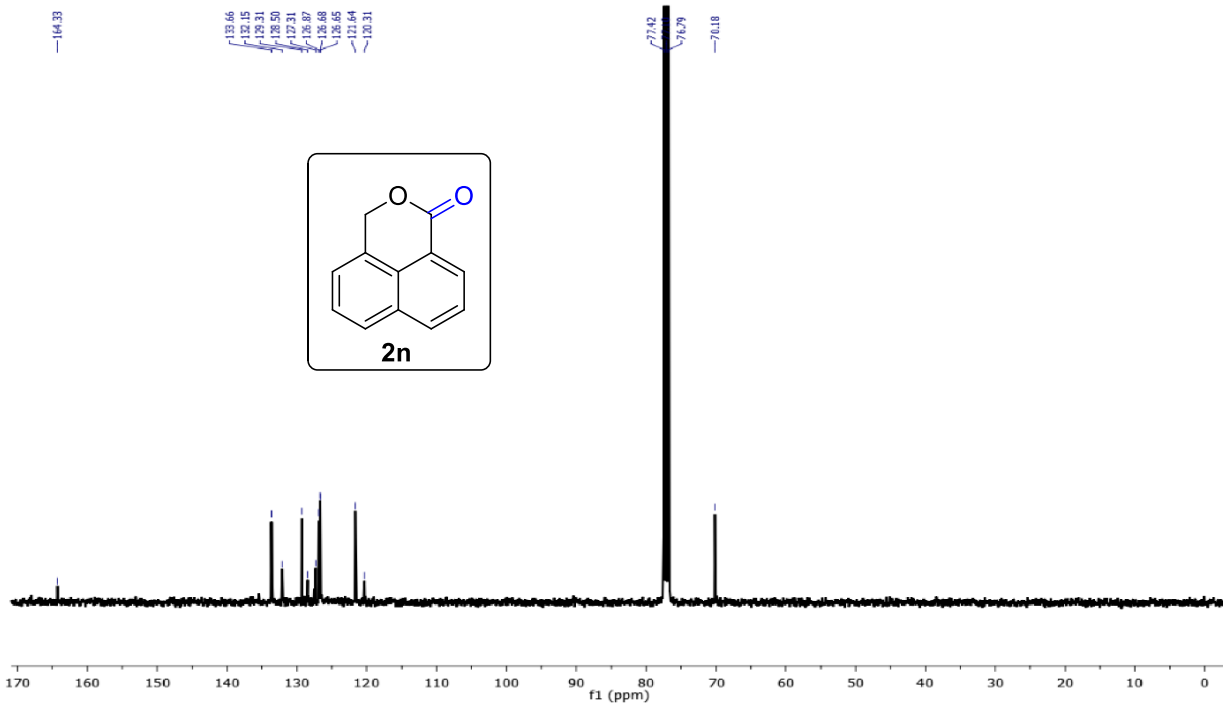
^{13}C NMR of compound **(2m)** in $CDCl_3$



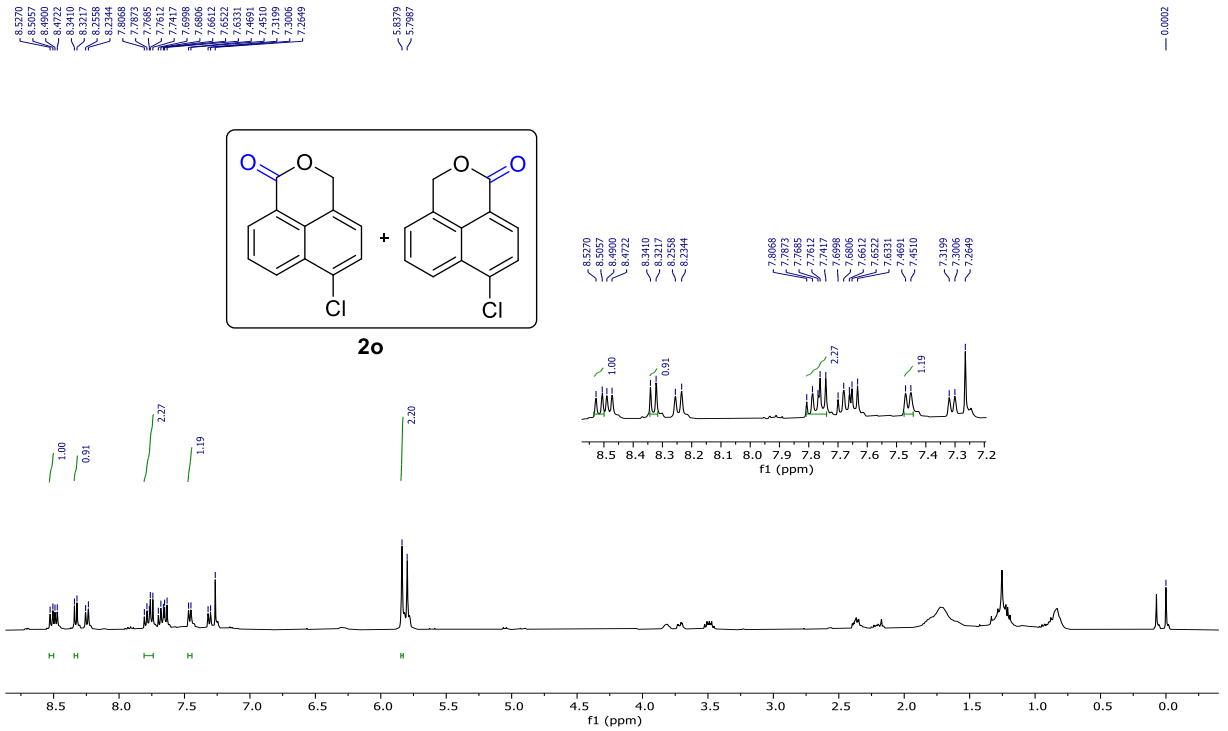
^{1}H NMR of compound **(2n)** in $CDCl_3$



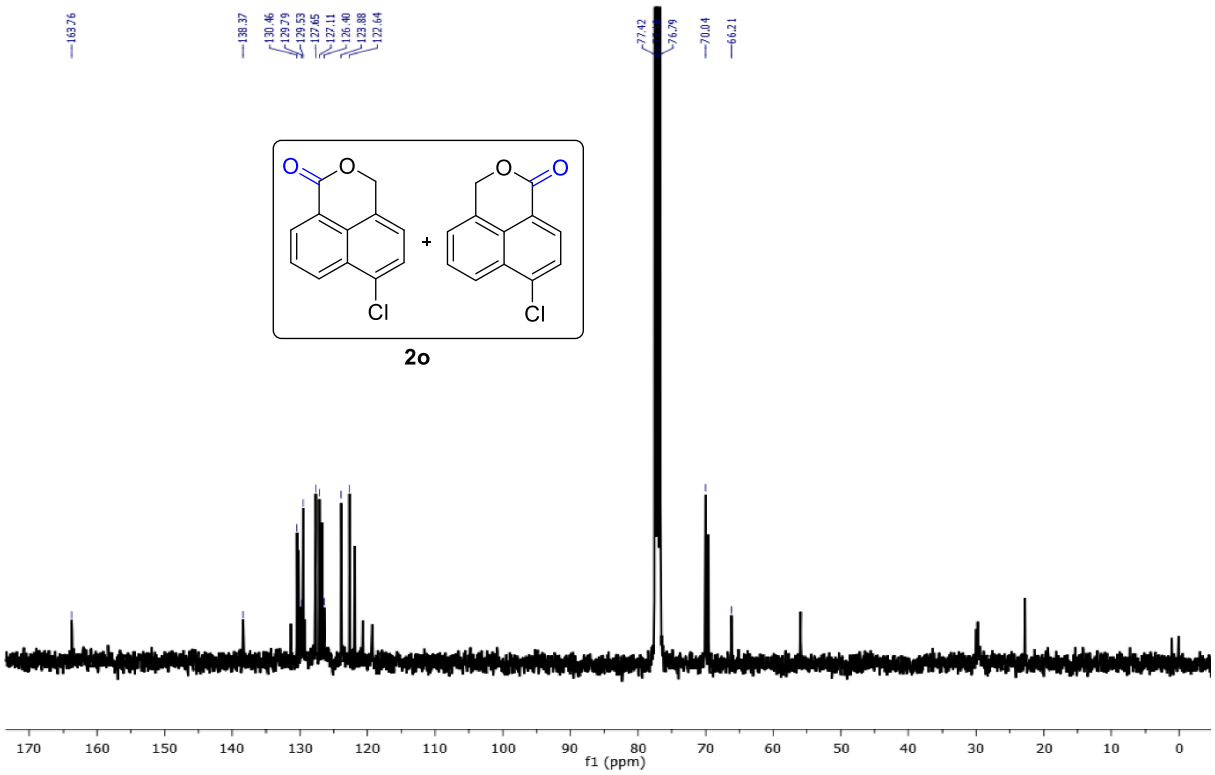
^{13}C NMR of compound **(2n)** in $CDCl_3$



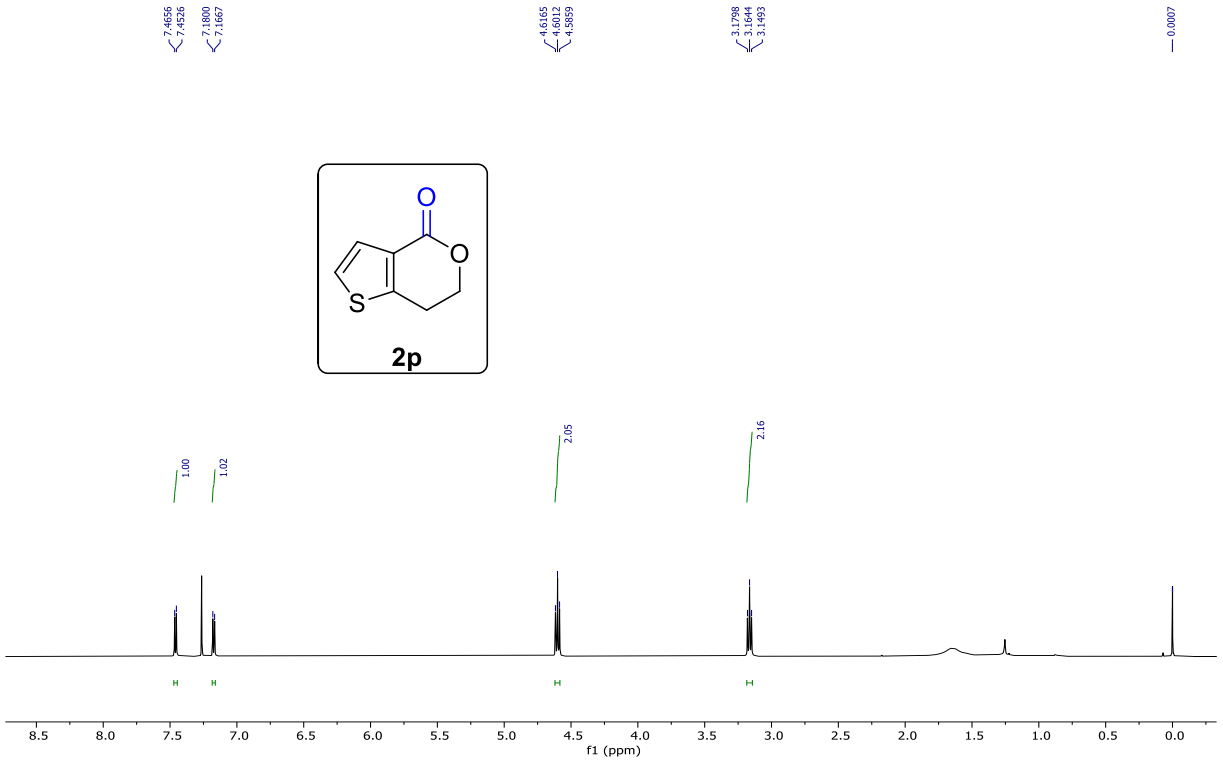
^{1}H NMR of compound **(2o)** in $CDCl_3$



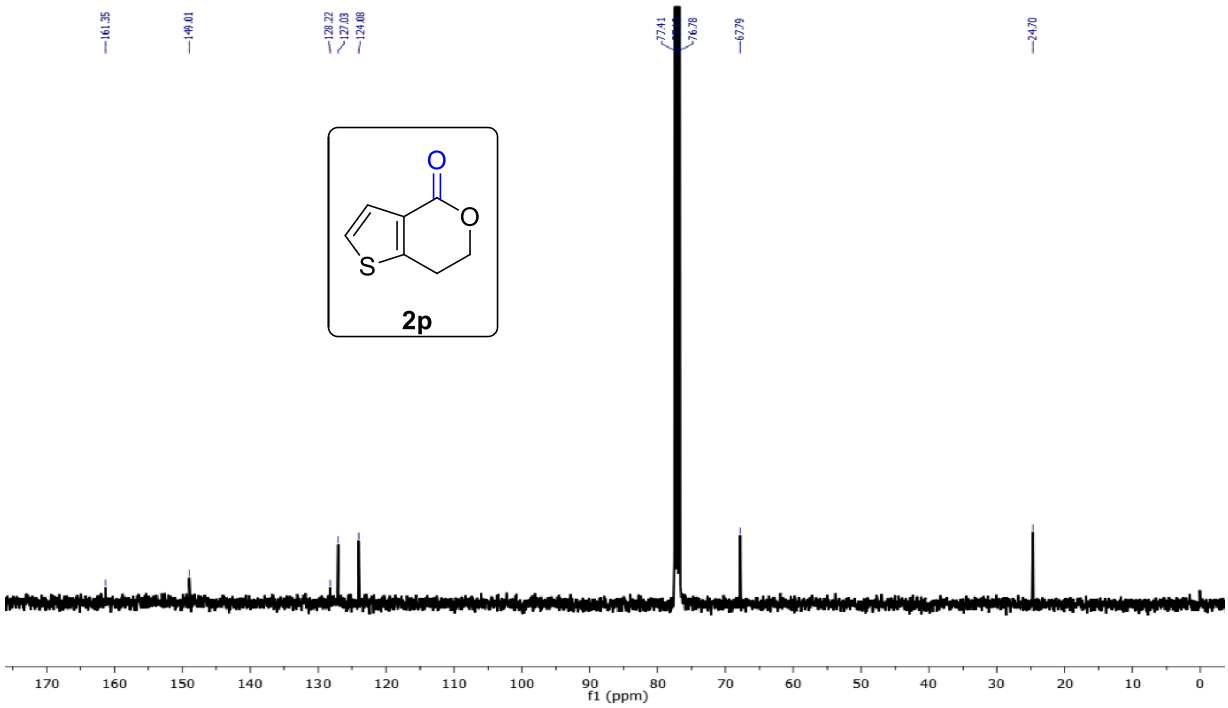
^{13}C NMR of compound **(2o)** in $CDCl_3$



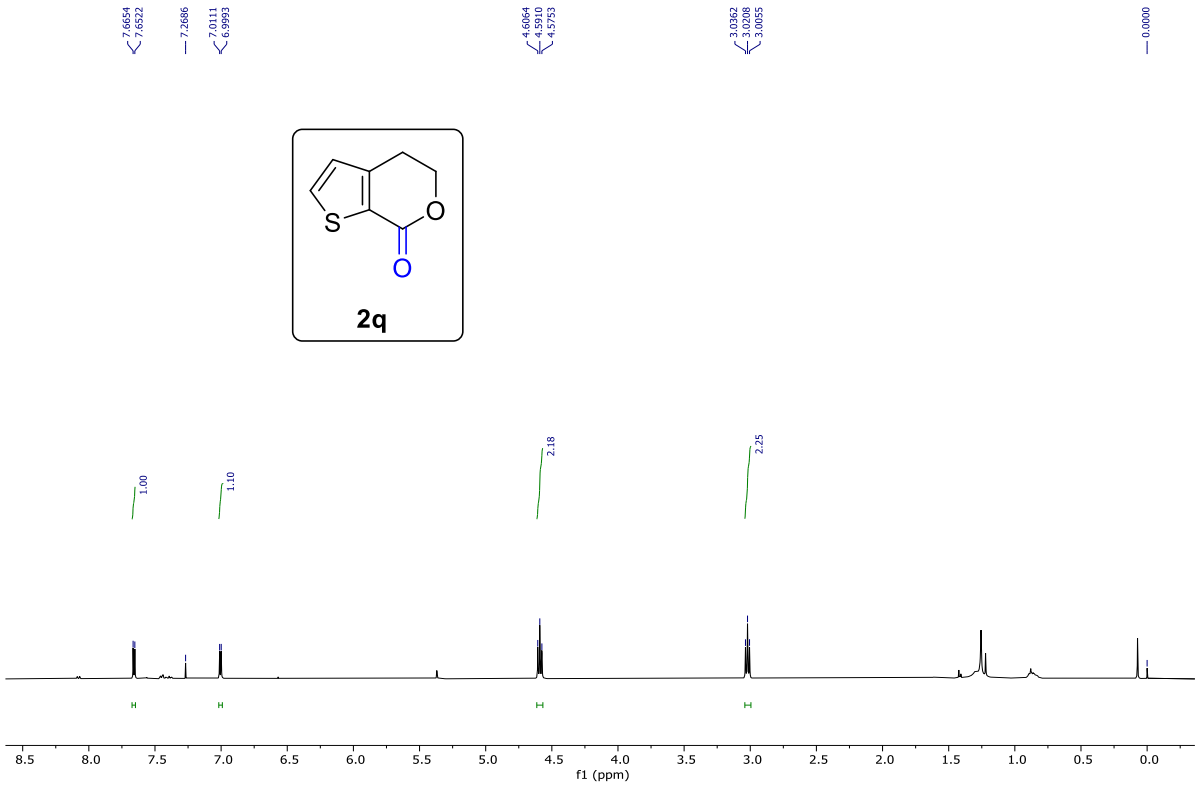
^{1}H NMR of compound **(2p)** in $CDCl_3$



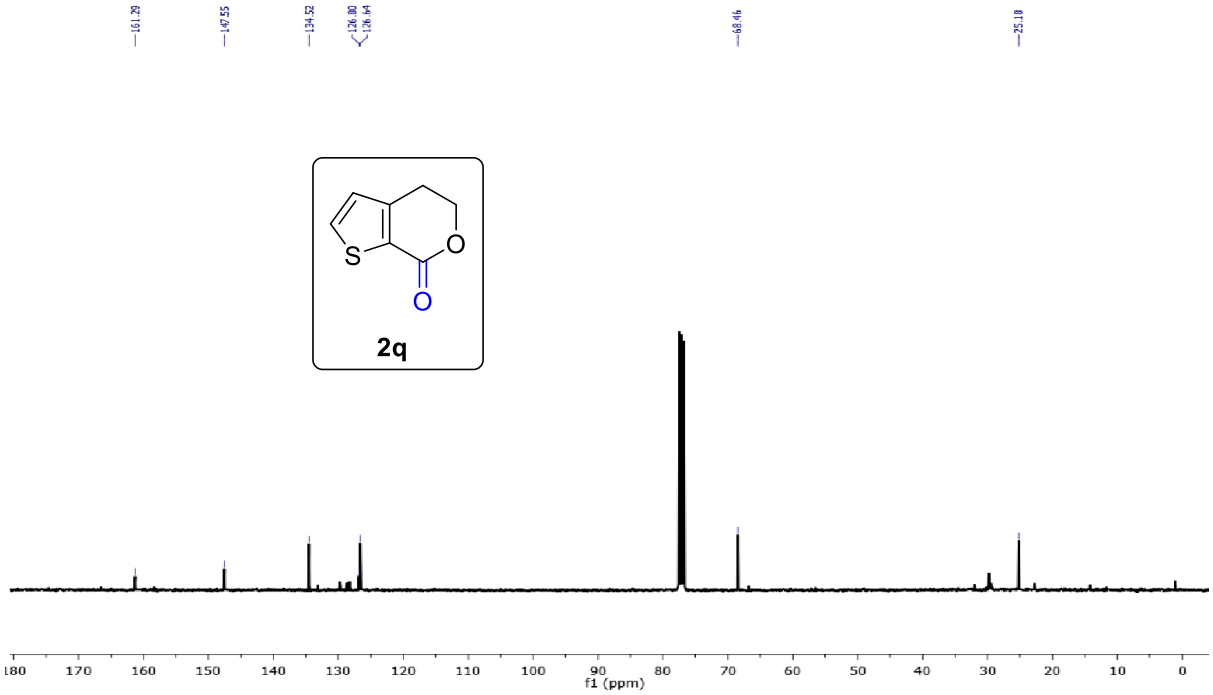
^{13}C NMR of compound **(2p)** in $CDCl_3$



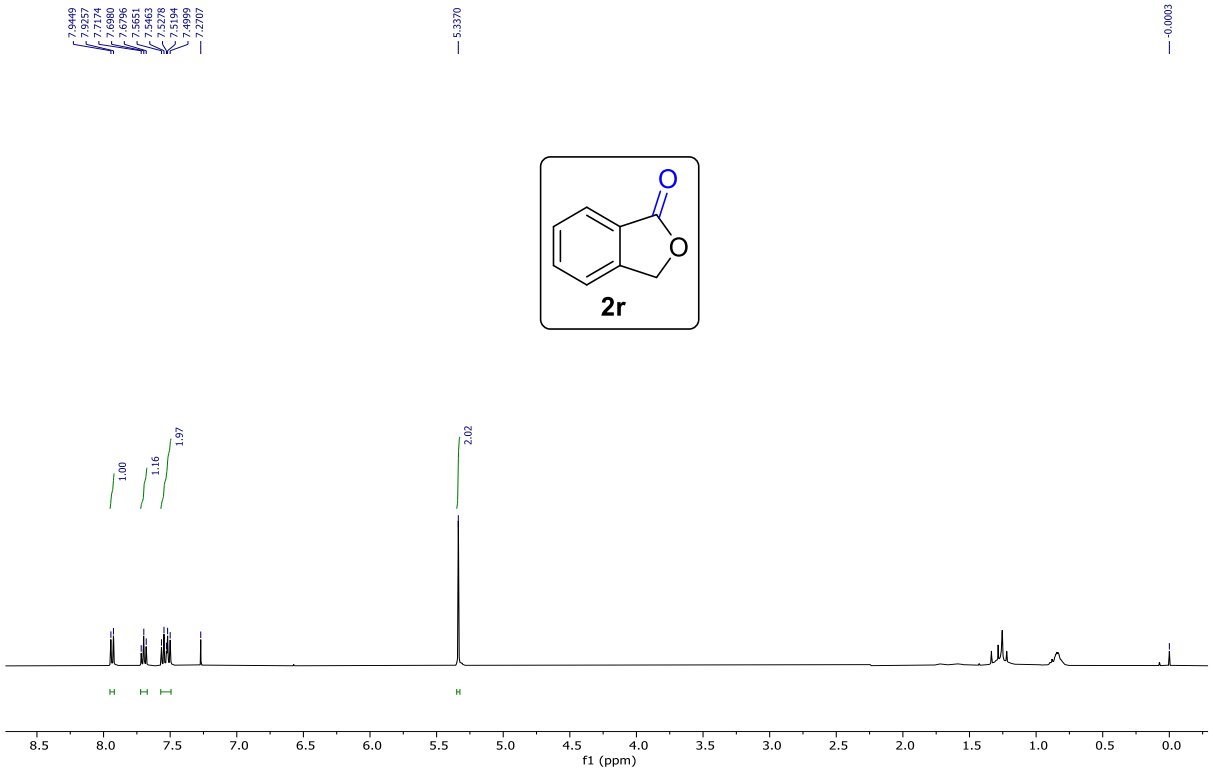
^{1}H NMR of compound **(2q)** in $CDCl_3$



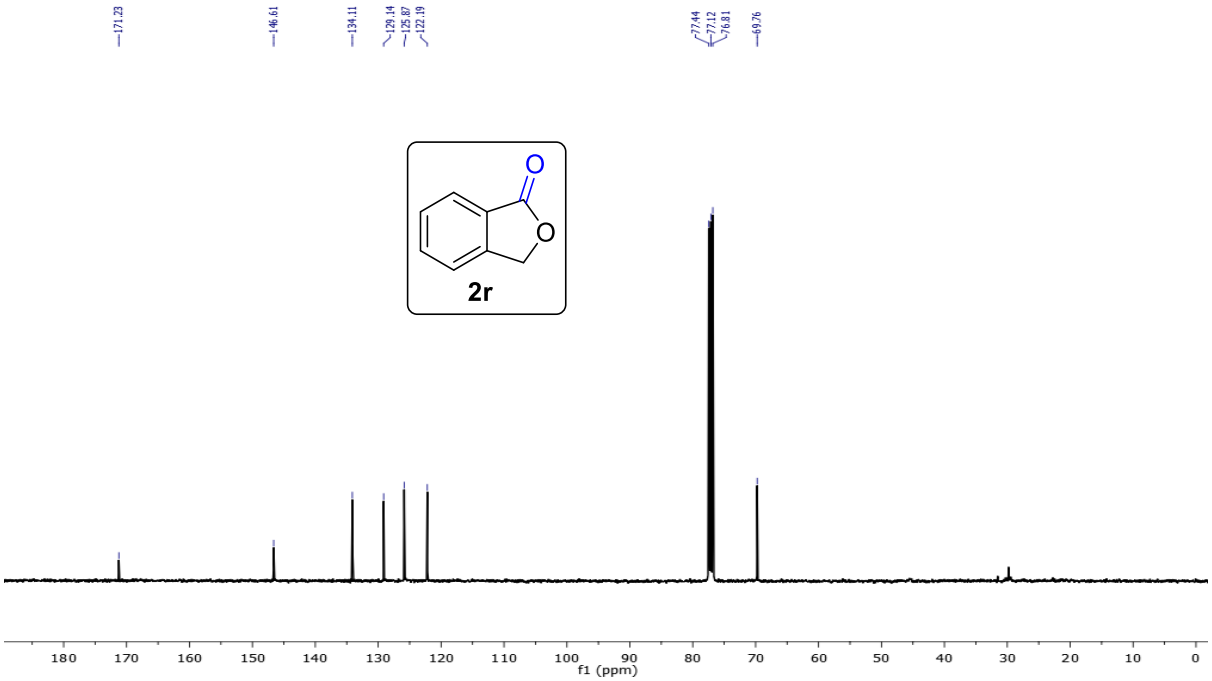
^{13}C NMR of compound **(2q)** in $CDCl_3$



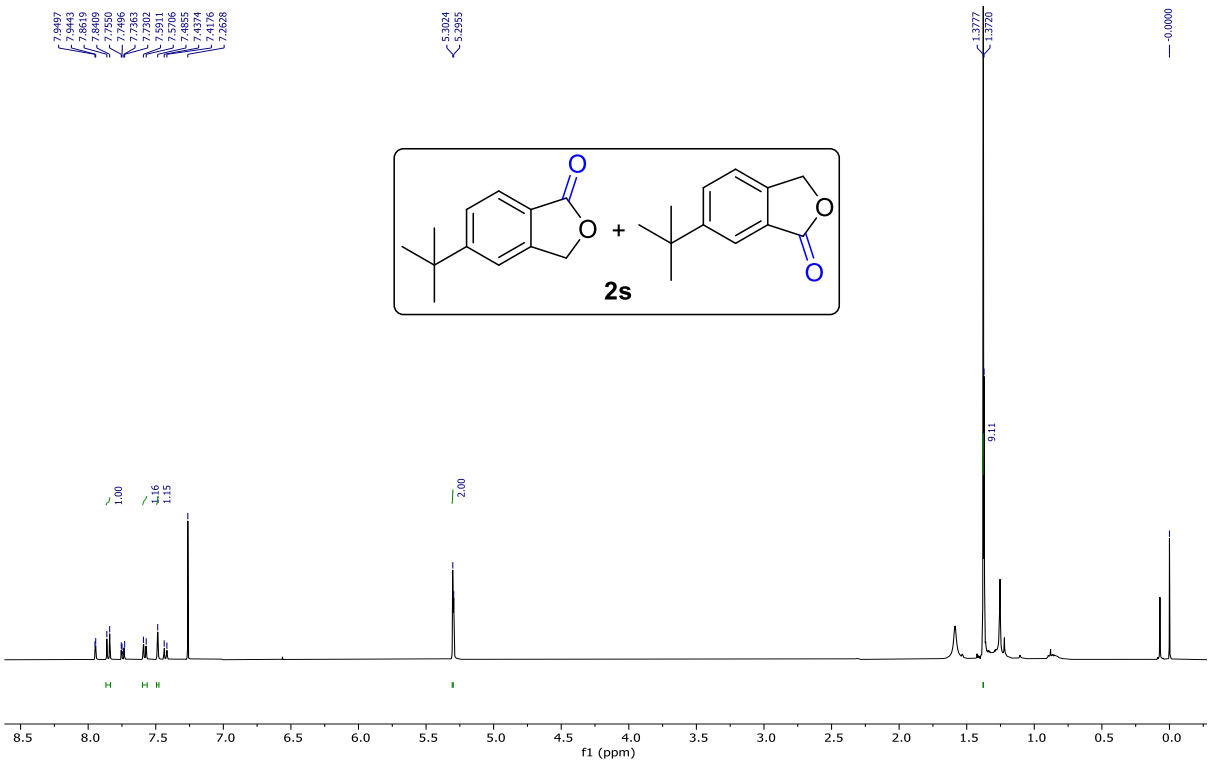
^{1}H NMR of compound **(2r)** in $CDCl_3$



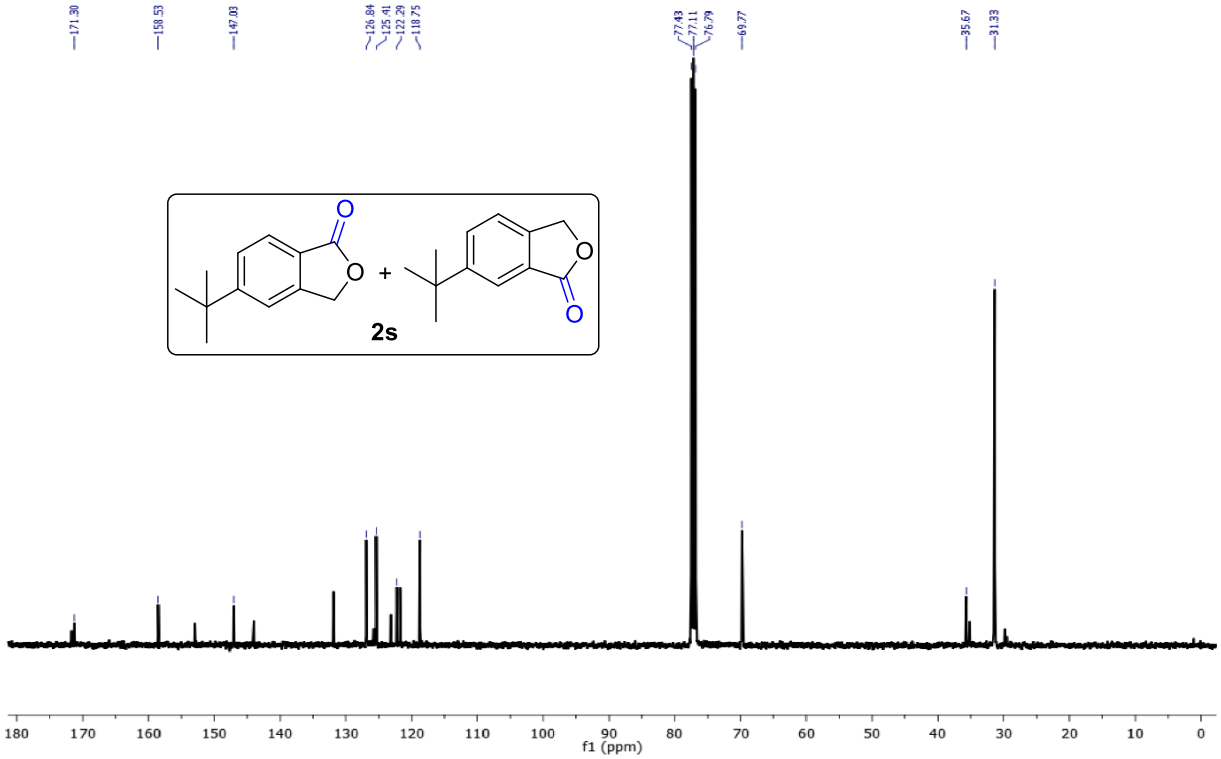
^{13}C NMR of compound **(2r)** in $CDCl_3$



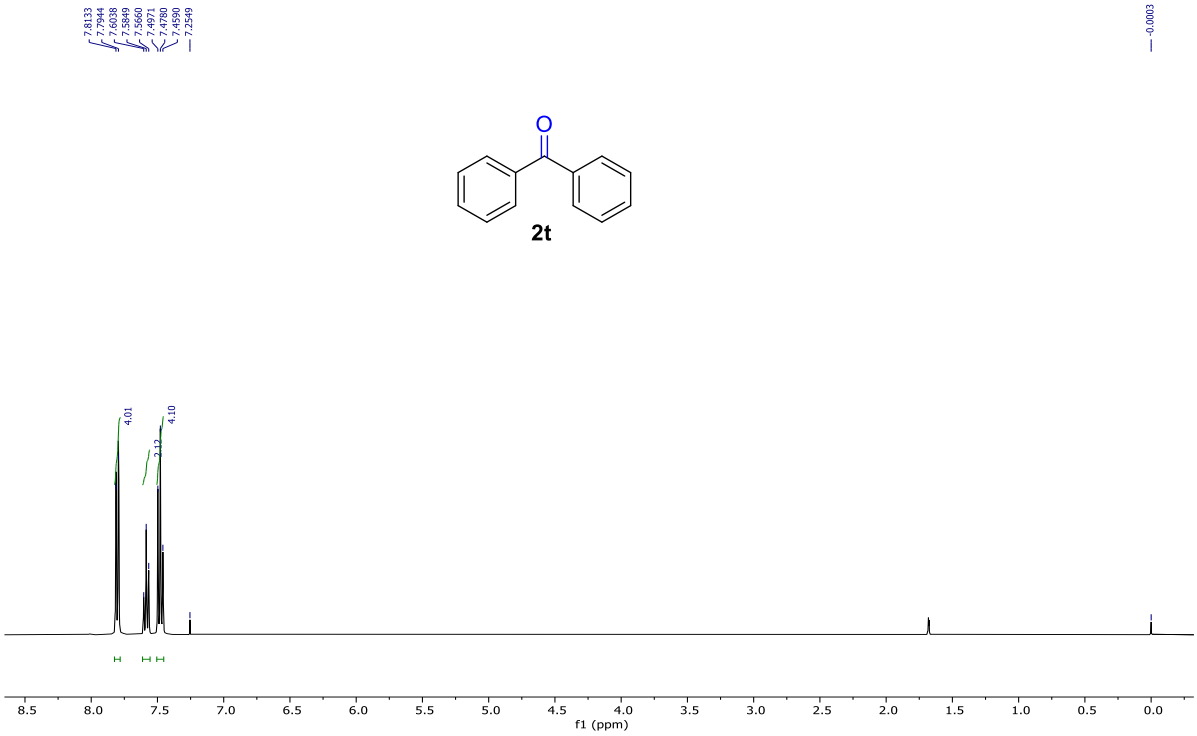
^{1}H NMR of compound **(2s)** in $CDCl_3$



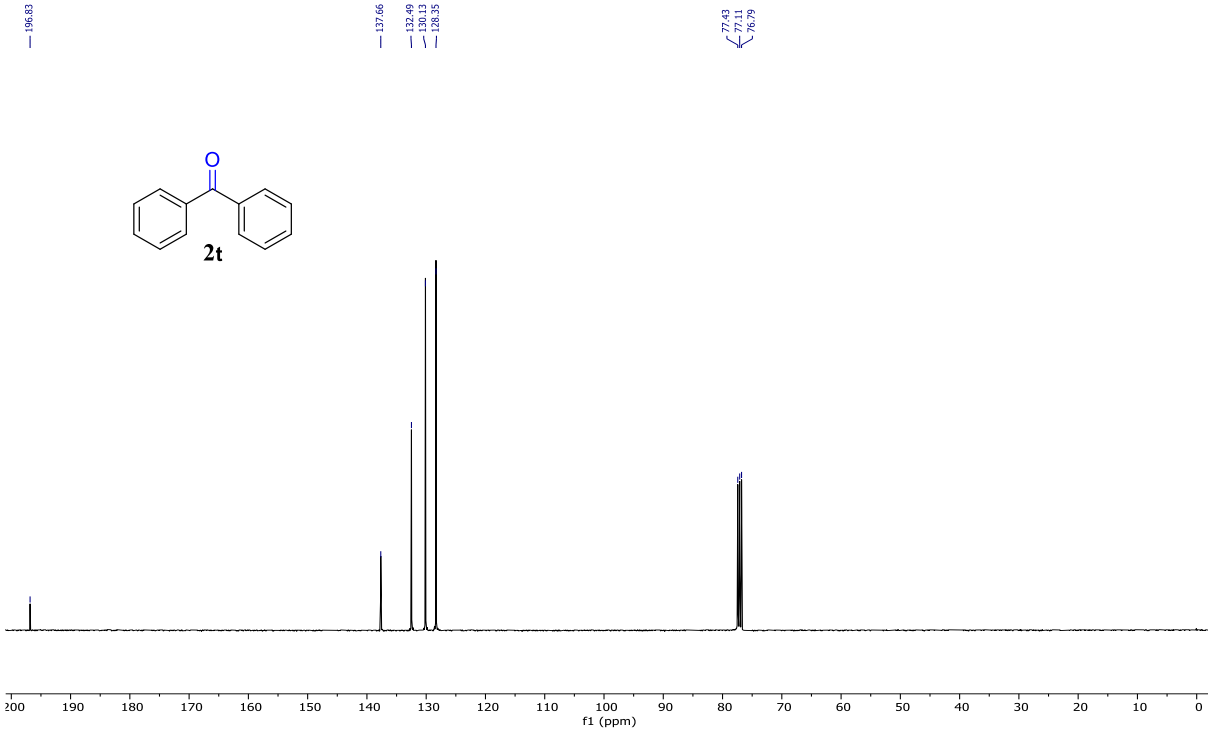
^{13}C NMR of compound **(2s)** in $CDCl_3$



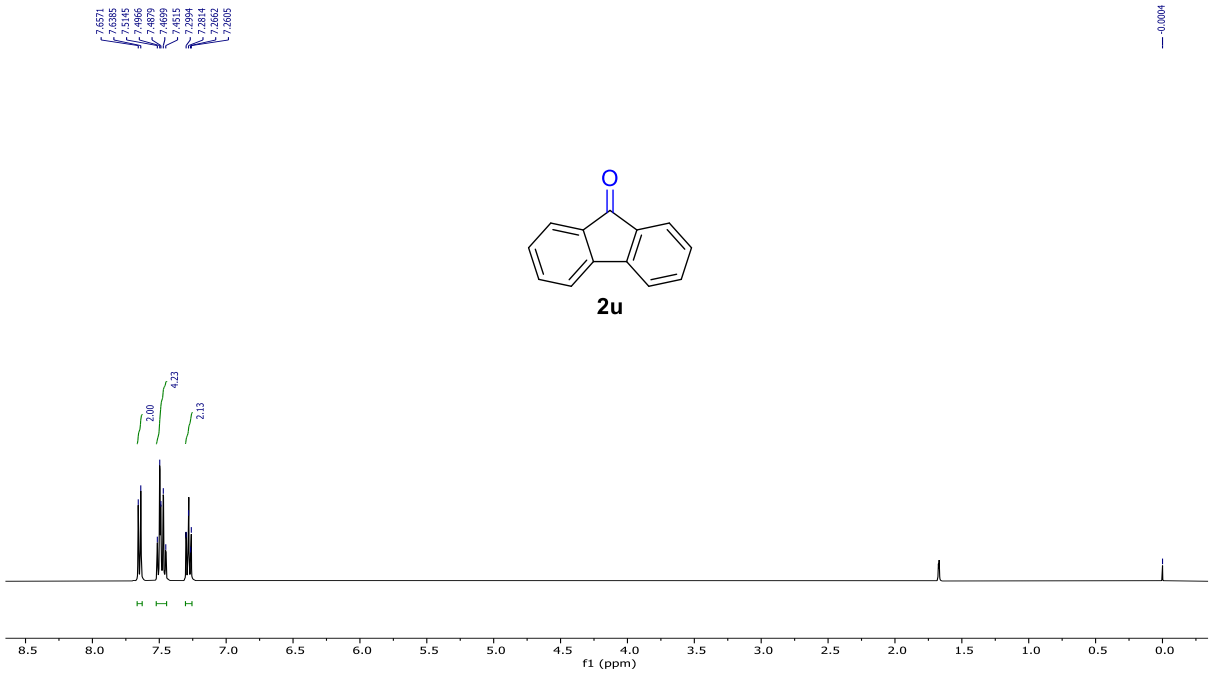
^{1}H NMR of compound **(2t)** in $CDCl_3$



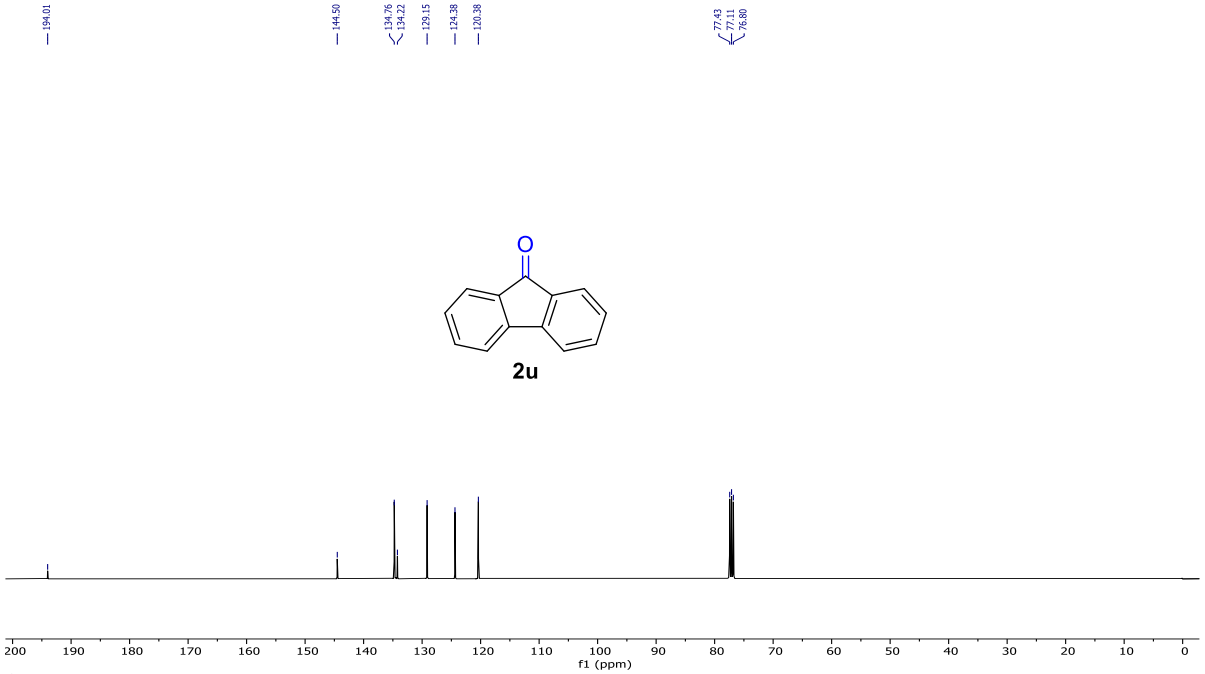
^{13}C NMR of compound **(2t)** in $CDCl_3$



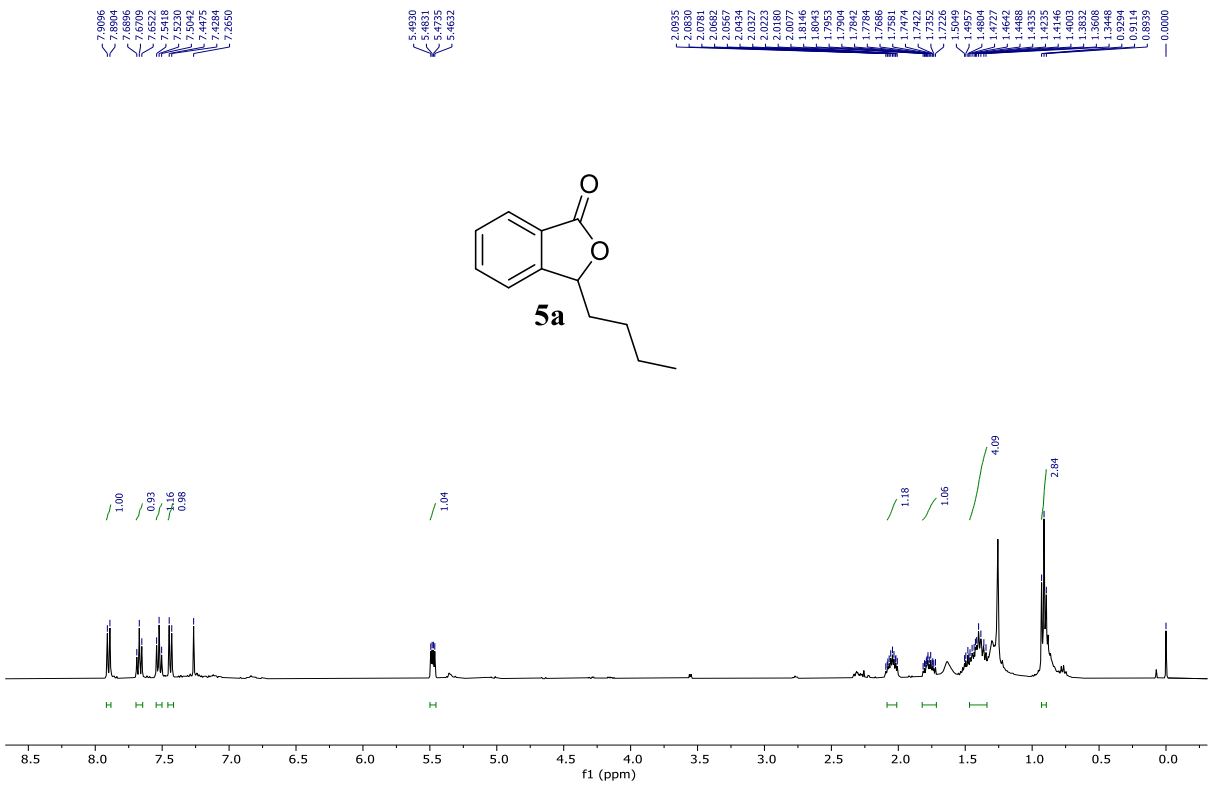
^{1}H NMR of compound **(2u)** in $CDCl_3$



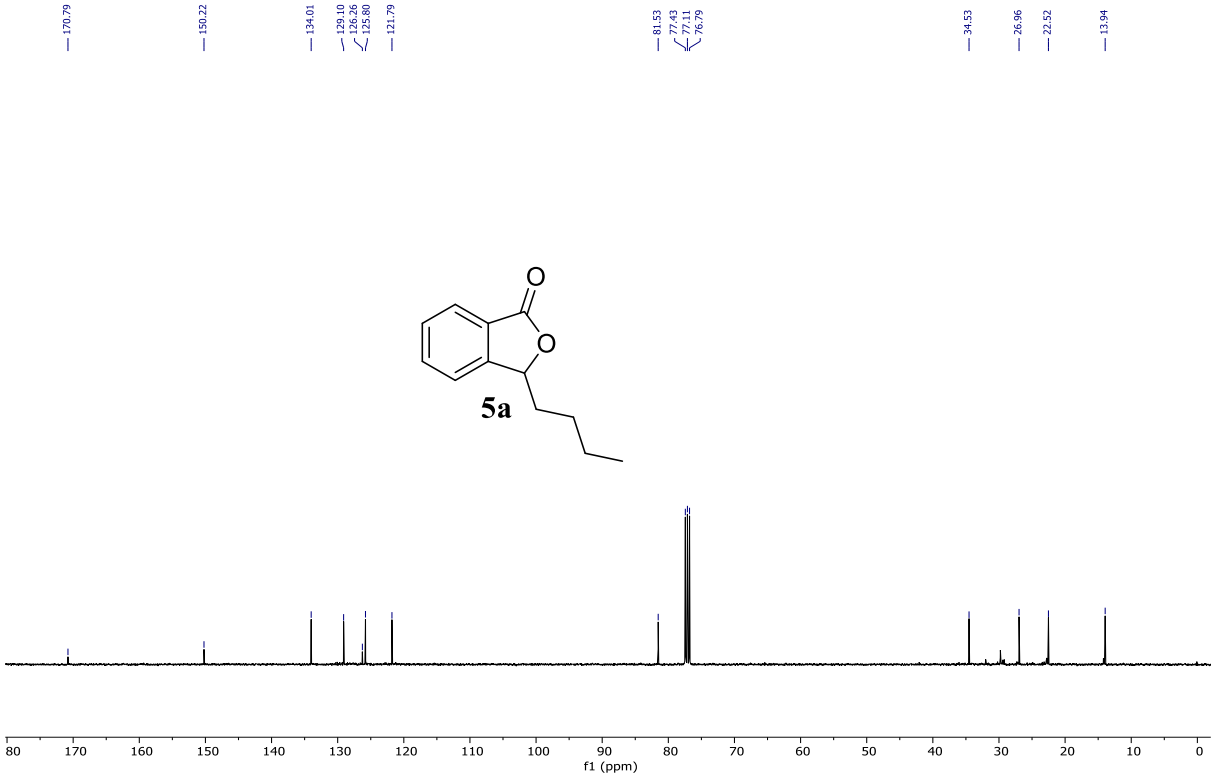
^{13}C NMR of compound **(2u)** in $CDCl_3$



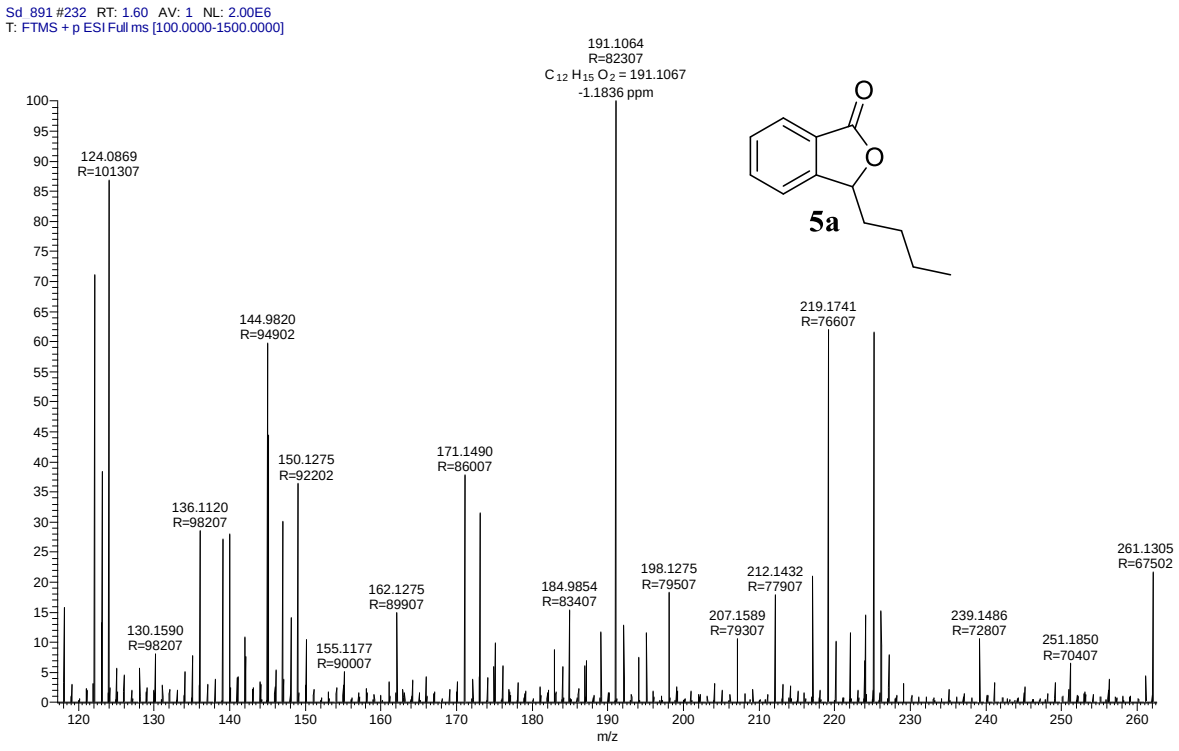
^{1}H NMR of compound **(5a)** in $CDCl_3$



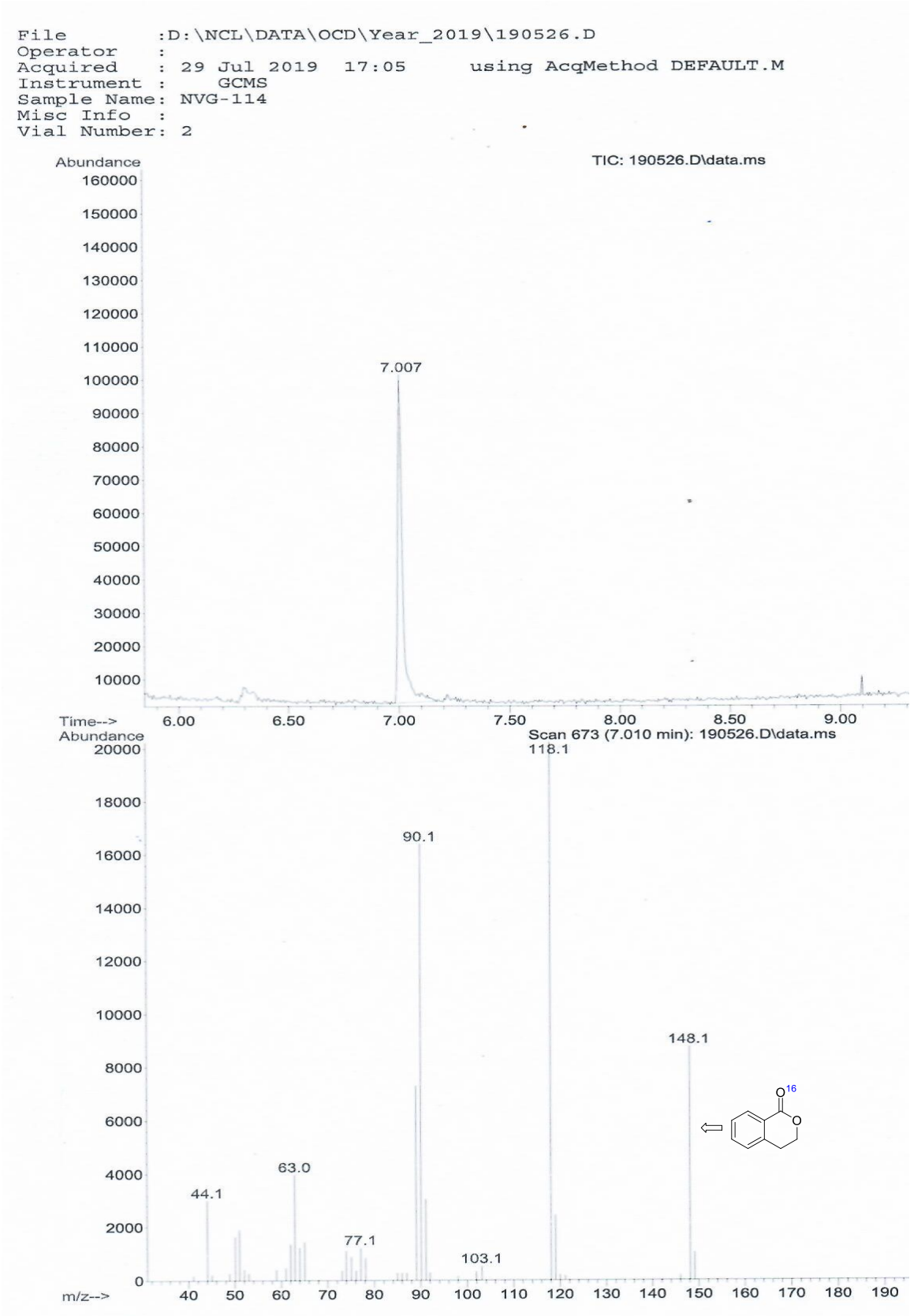
^{13}C NMR of compound **(5a)** in $CDCl_3$



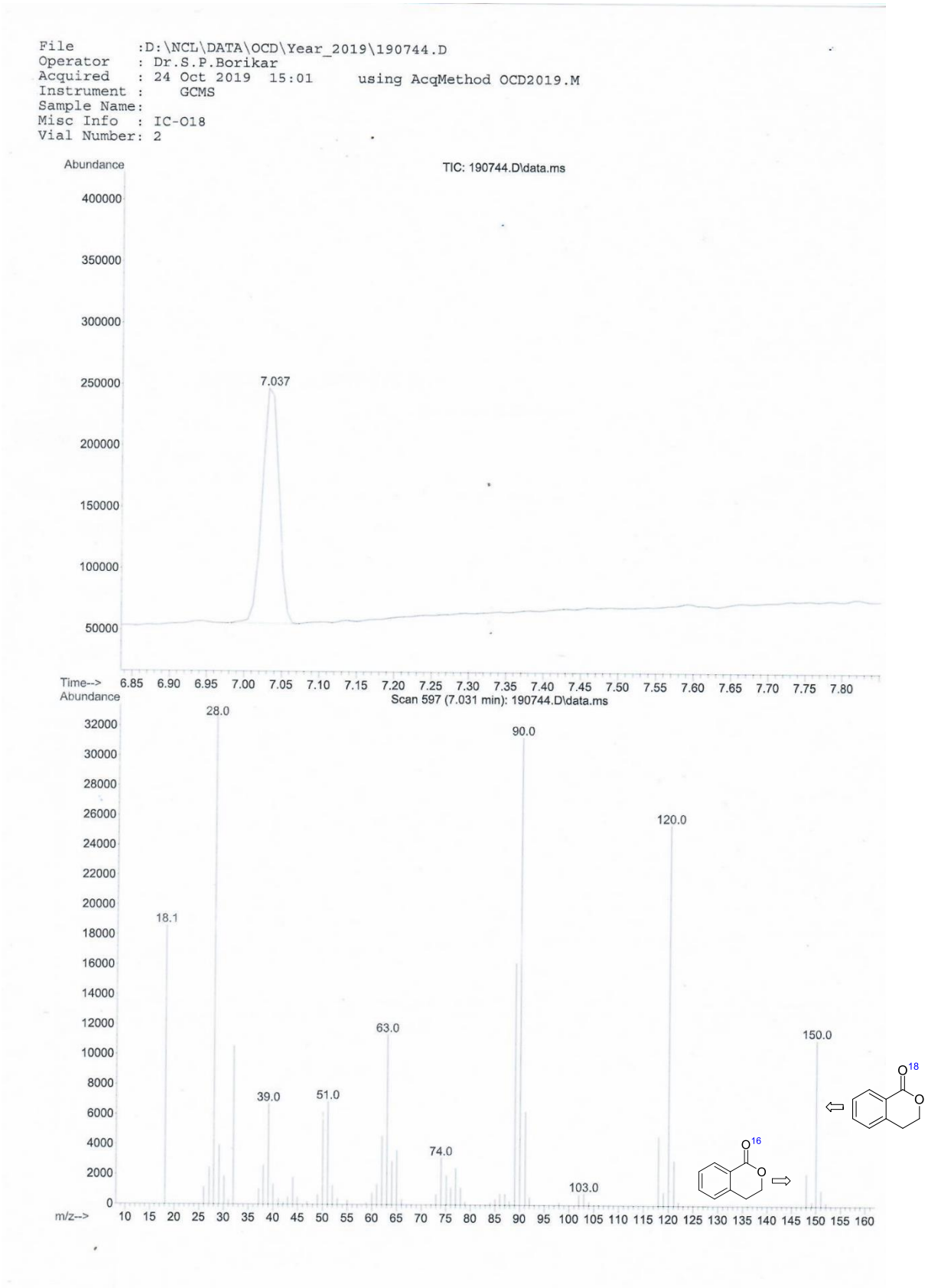
HRMS of compound **(5a)**



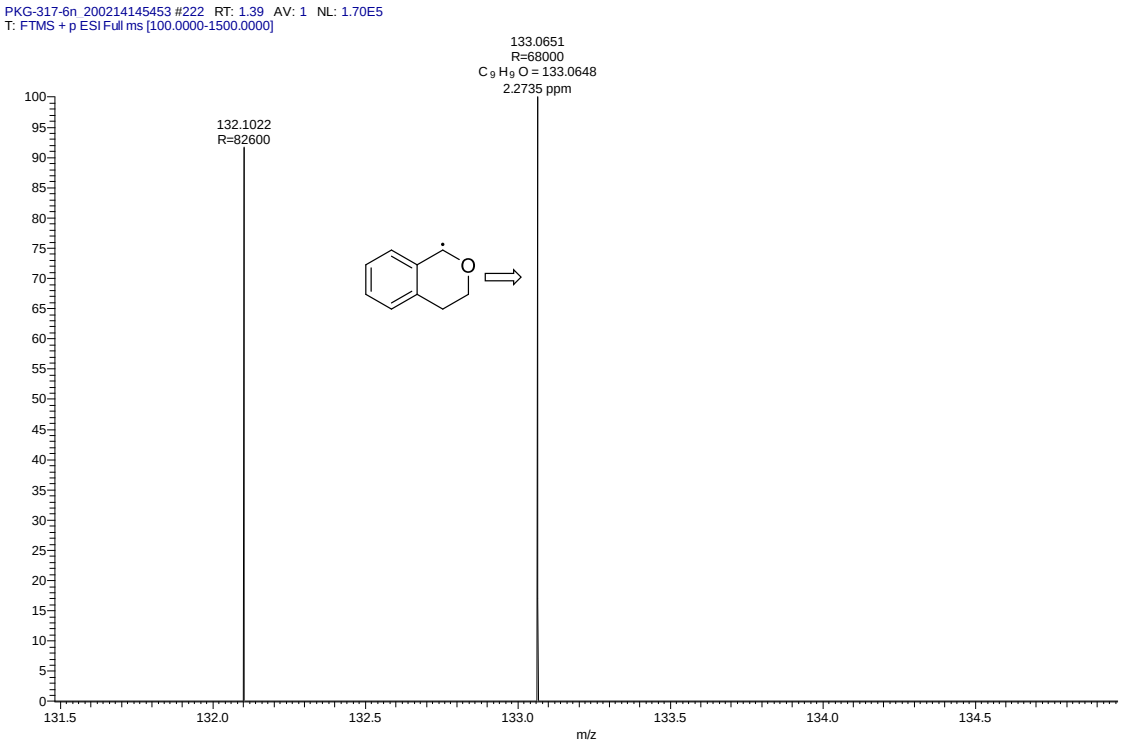
2.2.10 GC-MS spectrum of the reaction of isochroman 1a in the presence of H_2O^{18}



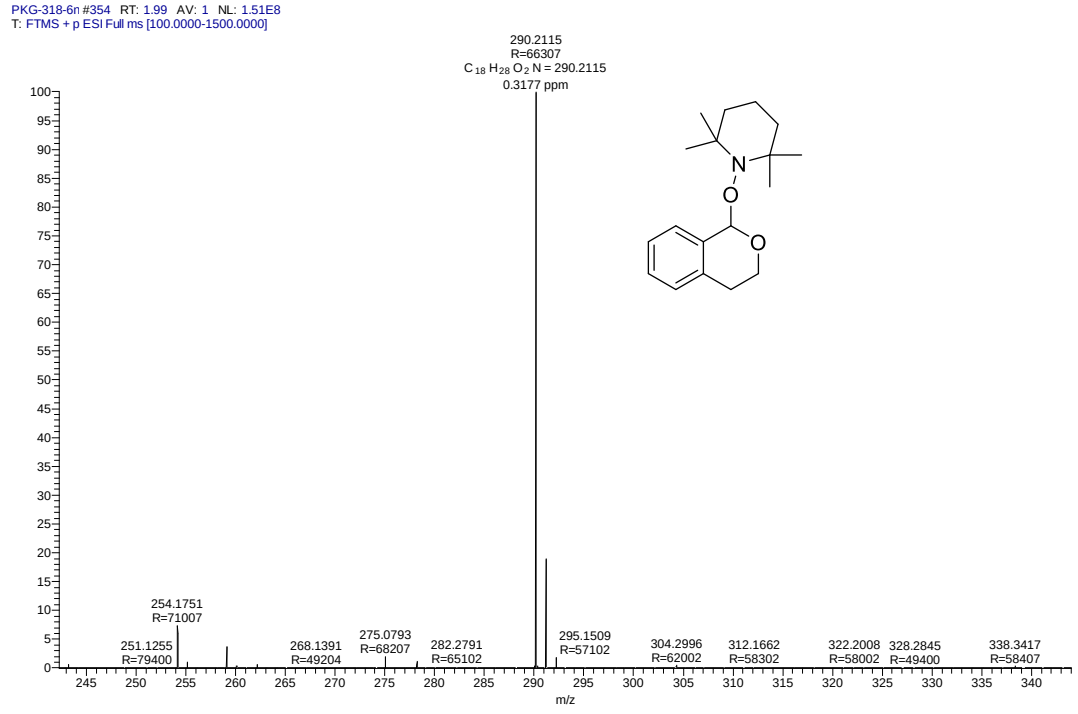
2.2.11 GC-MS spectrum of the reaction of isochroman 1a in the presence of $^{18}O_2$



2.2.12 HRMS spectrum for the detection of intermediate VI



2.2.13 HRMS spectrum for the detection of intermediate VI trapped by TEMPO



2.2.14 References

1. Liang, Y.-F.; Jiao, N. *Acc. Chem. Res.* **2017**, *50*, 1640.
2. a) Miyafuji, A.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10339. b) Zhou, J.; Fu, C. L.; Ma, S. M. *Nat. Commun.* **2018**, *9*, 1654. c) Zhang, X. Y.; Fevre, M.; Jones, G. O.; Waymouth, R. M. *Chem. Rev.* **2018**, *118*, 839.
3. Hartwig, J. F.; Larsen, M. A. *ACS Cent. Sci.* **2016**, *2*, 281.
4. (a) J. Muzart, *Tetrahedron Lett.* **1987**, *28*, 2131. (b) S. Yamazaki, *Org. Lett.* **1999**, *1*, 2129.
5. (a) Modica, E.; Bombieri, G.; Colombo, D.; Marchini, N.; Ronchetti, F.; Scala, A.; Toma, L. *Eur. J. Org. Chem.* **2003**, 2964. (b) Yang, Y.; Ma, H. *Tetrahedron Lett.* **2016**, *57*, 5278.
6. (a) Komiya, N.; Naota, T.; Murahashi, S. I. *Tetrahedron Lett.* **1996**, *37*, 1633. (b) Wang, F.; Yang, G. Y.; Zhang, W.; Wu, W. H.; Xu, J. *Chem. Commun.* **2003**, 1172. (c) Tanaka, H.; Oisaki, K.; Kanai, M. *Synlett* **2017**, *28*, 1576.
7. (a) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167. (b) Wang, Y.; Kuang, Y.; Wang, Y. *Chem. Commun.* **2015**, *51*, 5852.
8. (a) Murahashi, S. I.; Naota, T.; Komiya, N. *Tetrahedron Lett.* **1995**, *36*, 8059; (b) Blay, G.; Fernández, I.; Giménez, T.; Pedro, J. R.; Ruiz, R.; Pardo, E.; Lloret, F.; Munoz, M. C. *Chem. Commun.* **2001**, 2102.
9. (a) Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170. (b) Nakanishi, M.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 861. (c) Gonzalez-de-Castro, A.; Robertson, C. M.; Xiao, J. *J. Am. Chem. Soc.* **2014**, *136*, 8350. (d) Hong, C.; Ma, J.; Li, M.; Jin, L.; Hu, X.; Mo, W.; Hu, B.; Sun, N.; Shen, Z. *Tetrahedron* **2017**, *73*, 3002.
10. Tian, X.; Ren, F.; Zhao, B.; Ren, Y.-L.; Zhao, S.; Wang, J. *Catal. Commun.* **2018**, *106*, 44.
11. Geng, P.; Tang, Y.; Pan, G.; Wang, W.; Hu, J.; Cai, Y. *Green Chem.* **2019**, *21*, 6116.
12. Ren, L.; Yang, M.-M.; Tung, C.-H.; Wu, L.-Z.; Cong, H. *ACS Catal.* **2017**, *7*, 8134.
13. Gonzalez-de-Castro, A.; Robertson, C. M.; Xiao, J. *J. Am. Chem. Soc.* **2014**, *136*, 8350.
14. (a) Zhang, Z.; Gao, Y.; Liu, Y.; Li, J.; Xie, H.; Li, H.; Wang, W. *Org. Lett.* **2015**, *17*, 5492. Also see, (b) Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. *J. Org. Chem.* **2009**, *74*, 9524.
15. Rusch, F.; Schober, J. C.; Brasholz, M. *ChemCatChem* **2016**, *8*, 2881. Also see (b) Wendlandt, A. E.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2015**, *54*, 14638.

16. Finney, L. C.; Mitchell, L. J.; Moody, C. J. *Green Chem.* **2018**, *20*, 2242.

17. Thatikonda, T.; Deepake, S. K.; Das, U. *Org. Lett.* **2019**, *21*, 2532.

18. Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Weiberth, F. J. *Green Chem.* **2018**, *20*, 5082.

19. (a) Sterckx, H.; De Houwer, J.; Mensch, C.; Herrebout, W.; Tehrani, K. A.; Maes, B. U. W. *Beilstein J. Org. Chem.* **2016**, *12*, 144. (b) Wang, H.; Wang, Z.; Huang, H.; Tan, J.; Xu, K. *Org. Lett.* **2016**, *18*, 5680. (c) Li, J.-S.; Yang, F.; Yang, Q.; Li, Z.-W.; Chen, G.-Q.; Da, Y.-D.; Huang, P.-M.; Chen, C.; Zhang, Y.; Huang, L.-Z. *Synlett* **2017**, *28*, 994; for catalyst-free aerobic oxidation under 0.5 MPa oxygen, see (d) Tian, X.; Cheng, X.; Yang, X.; Ren, Y.-L.; Yao, K.; Wang, H.; Wang, J. *Org. Chem. Front.* **2019**, *6*, 952.

20. Wang, X.; Wang, L.; Sheng, X.; Huang, Z.; Li, T.; Zhang, M.; Xu, J.; Ji, H.; Yin, J.; Zhang, Y.; *Org. Biomol. Chem.* **2014**, *12*, 5995. b) Jian, Y.; Ji, J.; Huang, Z.; Gao, Y.; Sheng, X.; Yin, W.; Zhang, D.; Ji, H.; Zhang, Y. *RSC Adv.* **2016**, *6*, 36888.

21. Huang, W.; Ma, B.-C.; Lu, H.; Li, R.; Wang, L.; Landfester, K.; Zhang, K. A. I. *ACS Catal.* **2017**, *7*, 5438.

22. For the capture of molecular oxygen by dienolate species (a) Peixoto, P. A.; Jean, A.; Maddaluno, J.; De Paolis, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6971. (b) Peixoto, P. A.; Cormier, M.; Epane, J. E.; Jean, A.; Maddaluno, J.; De Paolis, M. *Org. Chem. Front.* **2014**, *1*, 748; For conversion of β-angelica lactone (I') to dienolate (I) in presence of base, (c) Wang, X.-J.; Hong, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 2664.

23. a) Nichols, P.; Fita, I.; Loewen, P. C. Enzymology and structure of catalases. In Advances in Inorganic Chemistry Sykes, A. G.; Mauk, G. Eds.; Academic Press: New York, **2001**; pp 51-106. b) Deisseroth, A.; Dounce, A. L. *Physiol. Rev.* **1970**, *50*, 319. c) Arica, M.Y.; Denizli, A.; Salih, B.; Piskin, E.; Hasirci, V. *J. Membr. Sci.* **1997**, *129*, 65.

24. Rioz-Martínez, A.; de Gonzalo, G.; Pazmiño, D. E. T.; Fraaije, M. W.; Gotor, V. *J. Org. Chem.* **2010**, 75, 2073.

25. Xiang, M.; Meng, Q. Y.; Li, J. X.; Zheng, Y. W.; Ye, C.; Li, Z. J.; Chen, B.; Tung, C. H.; Wu, L. Z. *Chem. Eur. J.* **2015**, *21*, 18080.

26. a) Xia, Q.; Wang, Q.; Yan, C.; Dong, J.; Song, H.; Li, L.; Liu, Y.; Wang, Q.; Liu, X.; Song, A.H. *Chem. Eur. J.* **2017**, *23*, 10871. (b) Favor, D. A.; Johnson, D. S.; Powers, J. J.; Li, T.; Madabattula, A. R. *Tetrahedron Lett.* **2007**, *48*, 3039.

27. Takabe, K.; Mizutani, M.; Yoda, H. *Heterocycles* **1998**, *48*, 679.

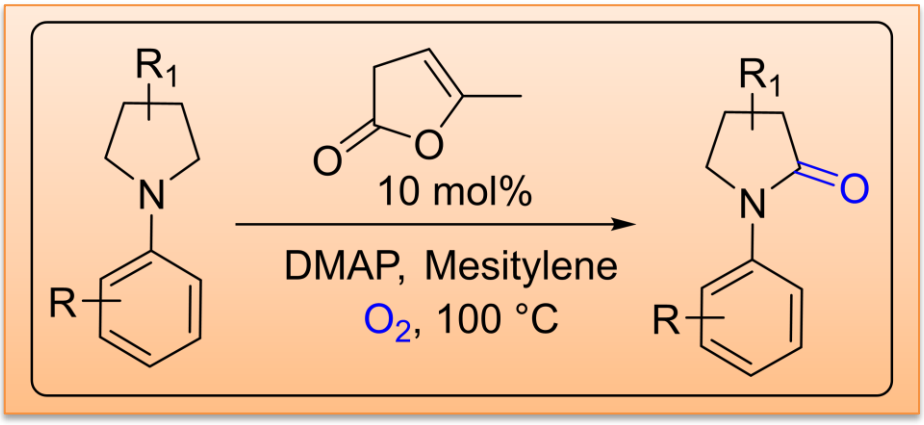
CHAPTER III

Oxidation of Pyrrolidine Derivatives to Corresponding Lactams by using α-Angelica Lactone as an Organocatalyst

Chapter III

Oxidation of Pyrrolidine Derivatives to Corresponding Lactams by using α-Angelica Lactone as an Organocatalyst

α- Angelica lactone was employed as an organocatalyst for the development of a highly efficient method for the α-CH_2 oxygenation of *N*-aryl pyrrolidines to the corresponding γ-lactams in presence of O_2 as a green oxidant. This catalytic system allows the synthesis of a library of valued γ-lactams in good to excellent chemical yields.



Manuscript under preparation

3.1 Introduction

The presence of nitrogen-containing heterocycles is ubiquitous in natural products and drug templates. For instance, more than half of the small molecule drugs approved by the US FDA contain at least one nitrogen heterocycles.[1] Among these, the most predominant is the five-membered nitrogen-containing heterocycles such as 2-pyrrolidinones or γ-lactams.[2] For example, γ-lactams containing compounds play the major role in the treatment of HIV[3], epilepsy[4], neurodegenerative diseases and depression.[5,6] Few important examples of γ-lactams containing molecules which possess biological and pharmaceutical activity are depicted in figure 1.

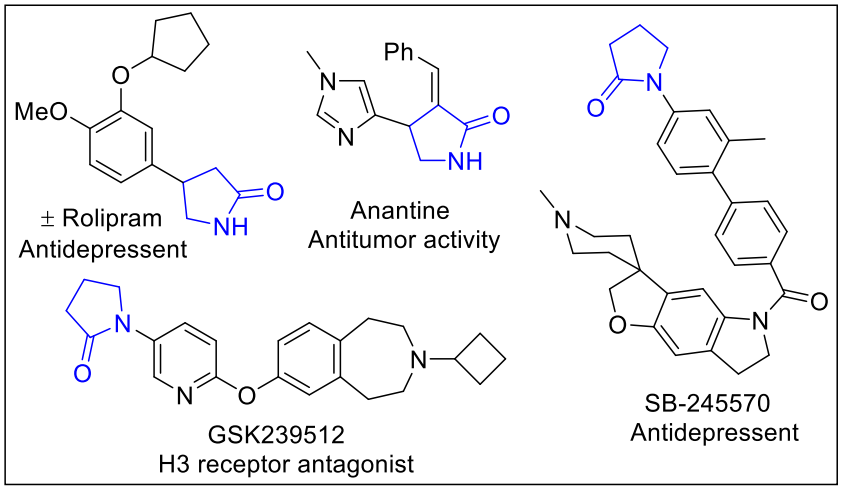


Figure 1: Selective examples of γ-lactam containing drug molecules.

Nature has mastered for the selective oxidation of C-H bond employing enzymes that generally consist of transition metals.[7] Given the significance of γ-lactams, for the synthetic community it is a challenge to develop highly efficient, and chemoselective methods for the construction of γ-lactams by employing the new catalytic methods from the simple precursors. There are many approaches to the preparation of γ-lactams. The most commonly used is the cyclization of carboxylic acids and amines.[8] Other than this, cycloaddition or annulation reactions[9], multi-component or cascade reactions[10] are among the commonly employed methods which lead to γ-lactams.

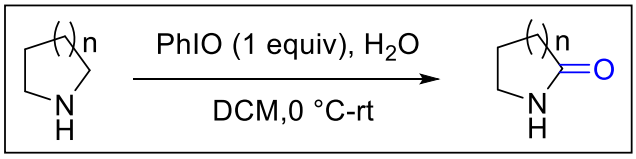
In the previous chapters (chapter II: section A and B) we have performed oxidations of sp3 C-H benzylic bonds of isoquinolines and isochromans to corresponding lactams or lactones. In continuation of our work for the oxidation of sp3 C-H bonds of various moieties, we were

eager to know if our developed protocol will work for the oxidation of *N*-aryl pyrrolidines to the corresponding γ-lactams. In recent years, there are plenty of oxidation reactions for the synthesis of amides[11], although the surge for the environmentally "green" and high atom economical methods are rare. The basic requirement for "green oxidation chemistry" includes the use of molecular oxygen as oxidant and employing organic molecules as catalysts. In this chapter, we describe the use of α-angelica lactone as a catalyst for α-CH_2 oxygenation of *N*-aryl pyrrolidines to the corresponding γ-lactams along with O_2 as an oxidant. O_2 also serves as the source of lactam oxygen.

3.2 Literature review:

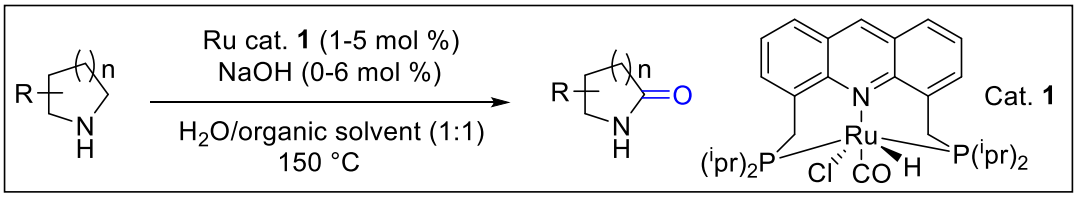
I. Iodosobenzene/water[12]

Moriarty *et al.* in 1988 performed the oxidation of cyclic amines such as pyrrolidines and piperidines to corresponding lactams in the presence of iodosobenzene in water. The products were obtained in good yields when less reactive iodosobenzene was used in dichloromethane as solvent.



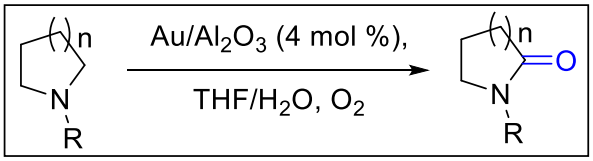
II. Ru-catalysed[13]

An oxidant free condition for the formation of lactams from cyclic amines in water with the liberation of H_2 gas was developed by Milstein *et al.* in 2014. Modest yields were obtained but this reaction was unique in nature and it also opens the door for the development of new methods for catalytic oxidation of cyclic amines to the corresponding lactams.



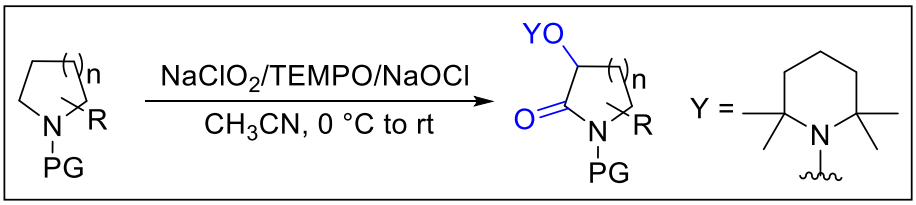
III. Au-nanoparticles supported on alumina (Al_2O_3)[14]

Mizuno *et al.* in 2016 developed a heterogeneous Au-nanoparticle supported alumina catalyst for the α-oxygenation of amines to corresponding amides in water as a source of oxygen and O_2 as the terminal oxidant. The corresponding amide products were obtained in moderate to high yields. While reusing the heterogeneous catalyst, a decrease in yield was noted after repeated use.



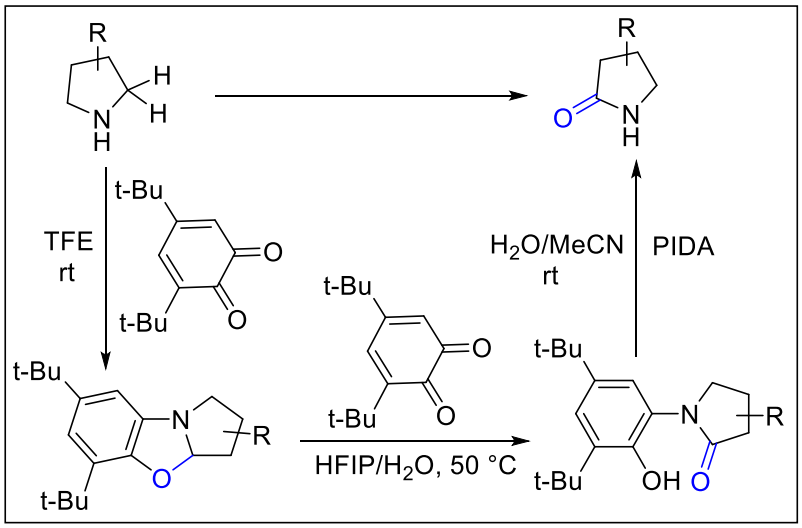
V. Dual sp3 C-H functionalization[15]

A selective and dual sp3 C-H functionalization at α- and β-positions of cyclic tertiary amines to the corresponding 3-alkoxyamine lactams was developed by Sartillo-Piscil*et al.* in 2016. Here, by employing $NaClO_2$/TEMPO/NaClO system and the corresponding lactam products was obtained in low to good chemical yields.



VI. o-Benzoquinone-induced[16]

Qu *et al.* in 2017 reported a late-stage functionalization and direct oxidation of *N*-heterocycles such as pyrrolidines to pyrrolidinone with o-benzoquinone followed by PIDA to obtained target products in moderate to excellent yields. Firstly, direct oxidation with o-benzoquinone gives *N, O*-acetal which was further oxidized with o-benzoquinone to obtain pyrrolidinones. The synthetic utility of this transformation was further demonstrated by the synthesis of (S)-vigabatrin and their analogs.



3.3 Origin of the present work

It is evident from the above-mentioned literature that the synthesis of γ-lactams/amides from the corresponding amines requires the presence of metal catalysts and the use of a stoichiometric amount of oxidant. In many cases, the multi-step synthesis was required for the catalyst itself. Late-stage oxidation of α-CH_2 bond of pyrrolidines is known but the direct oxidation of *N*-aryl pyrrolidines to pyrrolidinone are not much explored. Also, it is desirable to develop a green and environmentally safe method with high atom economy methods without using any peroxides as the terminal oxidants but make use of molecular oxygen as the greenest possible oxidant. As discussed in our previous chapters also, the major challenge is, there is a possibility of the formation of oxidative Mannich-type reaction with the nucleophilic organocatalysts. Other challenge includes control of chemoselectivity or over oxidation.

3.4 Objectives

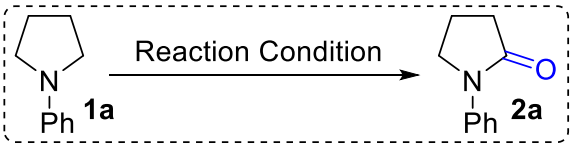
Encouraged by the recent development in the α-CH_2 oxidation of *N*-substituted pyrrolidines to pyrrolidinones, we desired for the development of a highly efficient, chemoselective and metal-free protocol for the synthesis of 2-pyrrolidinones or γ-lactams. It is mention-worthy that γ-lactams have a wide presence in the small drug molecules as a core unit. While in terms of medicinal chemistry, they are known to reduce the hydrophilicity in the ammonium species (secondary and tertiary) and also can enhance the drug efficacy and reduce the toxicity of

drugs.[17] Previously, we have reported the regioselective α-oxygenation of tetrahydroisoquinoline derivatives using α-angelica lactone as a catalyst. However, mono-oxidation of *N*-aryl pyrrolidines is difficult as it has two α-methylene groups with same bond dissociation energies. Again, BDE of C-H in α-methylene group of pyrrolidine is higher in comparison to benzylic C-H.

3.5 Results and discussion

We started our optimization by choosing *N*-phenyl pyrrolidine **1a** as a model substrate. Thus, **1a** was treated with 25 mol% α-angelica lactone as organocatalyst in the presence of 4-dimethylaminopyridine (DMAP, 3 equiv.) in 2-methyl tetrahydrofuran (2-MeTHF, 1 mL). The reaction was performed under an oxygen atmosphere using an O_2 balloon (Table 1, entry 1). The product **2a** was obtained in low chemical yield (12%). The reason could be the low reactivity of *N*- phenyl pyrrolidine and this compels us to do the reaction at a higher temperature. When the same reaction was performed at 80 °C with the aforementioned condition, we observed an increment of yield to 55% (Table 1, entry 2). Next, we studied the effect of various solvents and bases. In the case of using toluene, γ-lactams **2a** was obtained in 47% yield (Table 1, entry 3) but a slight decrease in yield (43%) was observed when trifluoro toluene was used (Table 1, entry 4). When the reaction was performed in DMSO and DMF, the yields obtained are 33 and 30% (Table 1, entries 5, 6). In chlorinated solvent such as 1,2-dichloroethane, the product **2a** was obtained in 31% yield (Table 1, entry 7). A small increment in yield (56%) was observed when the reaction was performed in mesitylene (Table 1, entry 8). While using xylene and its derivatives as a solvent, the product was obtained in low yields (Table 1, entries 9-11). Optimization concerning different bases such as DABCO, DBU, Et_3N, pyridine, Na_2CO_3, DIPEA were also performed and we obtained moderate or trace amount of yields (Table 1, entries 12-17). Further optimization of the reaction condition was performed by investigating the required quantity of the base, solvent, and catalyst. Firstly, by reducing the amount of DMAP from 3 equiv. to 1 and 2 equiv., a moderate yield (43 % & 47%) was obtained, respectively (Table 1, entries 18 & 19). A significant improvement in yield (72 %) was observed in the case of using 10 mol% catalyst (Table 1, entry 20).

Table 1: Solvent and base optimization [a]



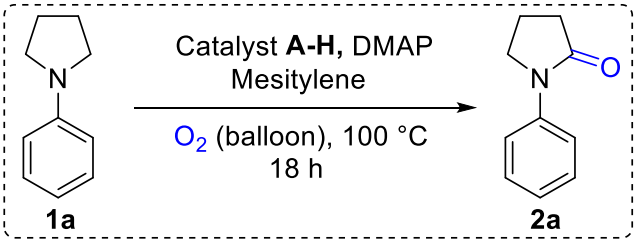
Entry	Base	Solvent	Time	Temp.	Yield% [b]
1	DMAP	2-MeTHF	48 h	rt	12
2	DMAP	2-MeTHF	18 h	80 °C	55
3	DMAP	Toluene	18 h	80 °C	47
4	DMAP	TFT	18 h	80 °C	43
5	DMAP	DMSO	18 h	80 °C	33
6	DMAP	DMF	18 h	80 °C	30
7	DMAP	DCE	18 h	80 °C	31
8	DMAP	Mesitylene	18 h	80 °C	56
9	DMAP	Xylene	18 h	80 °C	34
10	DMAP	m-Xylene	18 h	80 °C	51
11	DMAP	p-Xylene	18 h	80 °C	38
12	DABCO	Mesitylene	18 h	80 °C	39
13	DBU	Mesitylene	18 h	80 °C	31
14	Et_3N	Mesitylene	18 h	80 °C	17
15	Pyridine	Mesitylene	18 h	80 °C	33
16	Na_2CO_3	Mesitylene	18 h	80 °C	Trace
17	DIPEA	Mesitylene	18 h	80 °C	Trace
18[c]	DMAP	Mesitylene	18 h	80 °C	43
19[d]	DMAP	Mesitylene	18 h	80 °C	47
20[e]	DMAP	Mesitylene	18 h	80 °C	72
21[f]	DMAP	Mesitylene	18 h	80 °C	69
22[e]	DMAP	Mesitylene	18 h	60 °C	44
23[e]	**DMAP**	**Mesitylene**	**18 h**	**100 °C**	**80**
24[e,g]	DMAP	Mesitylene	18 h	100 °C	70
25[e,h]	DMAP	Mesitylene	18 h	100 °C	55

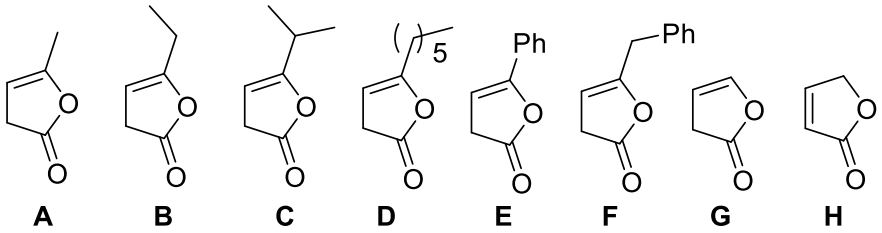
[a] Reaction condition:**1a** (0.2 mmol), DMAP (0.3 mmol), catalyst **A-H** (25 mol %), in mesitylene (1 mL) at 100 °C for 18 h under O_2 (balloon) atmosphere. [b] Isolated yields. [c] DMAP (1 equiv). [d] DMAP (2 equiv). [e] Catalyst **A** (10 mol%). [f] Catalyst **A** (50 mol%). [g] 0.5 mL mesitylene. [h] 2 mL mesitylene.

When the catalyst loading was changed from 25 mol% to 50 mol%, the corresponding γ-lactam **2a** was obtained in 69 % yield (Table 1, entry 21). Having this condition in hand, next we moved towards the temperature study. The reaction was performed with **1a** in DMAP (3 equiv.), 10 mol% catalyst **A** in mesitylene at 60 °C and 100 °C.

Further optimization was performed with various catalysts **B-H**. We found these catalysts are not efficient enough as no further improvement in chemical yield was observed. Moderate yield was noted only in case of using catalyst **B** and **D** which gives 40 and 35% chemical yield (Table 2, entries 1 and 3).

Table 2: Catalyst optimization [a]





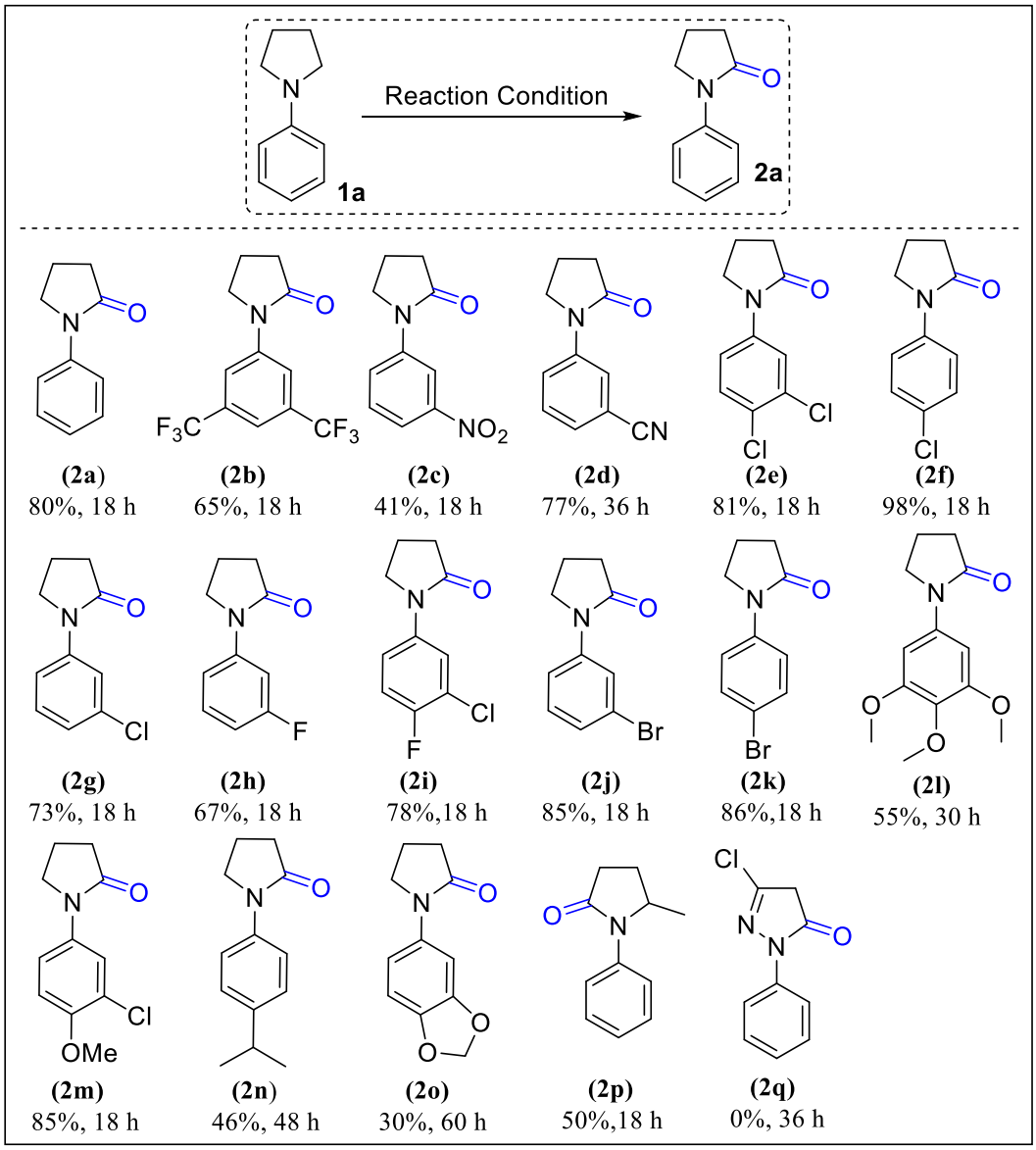
Entry	Catalyst	Yield (%) [b]
1	B	40
2	C	15
3	D	35
4	E	19
5	F	30
6	G	19
7	H	23

[a] Reaction condition: **1a** (0.2 mmol), DMAP (0.3 mmol), catalyst **A-H** (25 mol %), in mesitylene (1 mL) at 100 °C for 18 h under O_2 (balloon) atmosphere. [b] Isolated yields.

Having the best optimization in hand (entry 23, Table 1), we moved towards exploring the substrate scope using different *N*-aryl pyrrolidines and results are summarized in table 3. No over oxidation products were observed and we confirmed this by GC-MS and NMR studies.

This could be because, after the first oxidation the newly introduced carbonyl group deactivate the ring and chances of further oxidation lapses.

Table 3: Substrate scope [a, b]



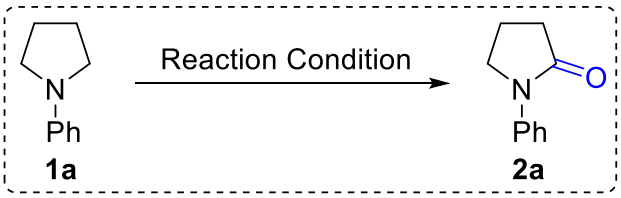
[a] Reaction condition: **1a** (0.2 mmol), DMAP (0.3 mmol), catalyst **A** (10 mol %), in mesitylene (1 mL) at 100 °C for mentioned time under O_2 (balloon) atmosphere. [b] Isolated yields.

Next, this optimized condition was applied to a number of the substituted *N*-aryl pyrrolidines (**1a-1q**) and the corresponding γ-lactams (**2a-2q**) were obtained in moderate to excellent yields (30-98%). Presence of a strong electron-withdrawing group in the aromatic ring of *N*-aryl pyrrolidines was well tolerated. The corresponding oxidized products **2b-2d** was isolated

in 41-77% chemical yields. Halogen substitution on the aromatic ring of *N*-aryl pyrrolidines was also well-tolerated and the corresponding γ-lactams **2e-2k** were obtained in excellent (67-98%) chemical yields. When the aromatic ring was substituted by electron-donating groups such as trimethoxy and 3-chloro-4-methoxy, the reaction worked well and the corresponding products **2l** and **2m** were isolated in 55% and 85% respectively. *para*-Isopropyl group on the aromatic ring of *N*-aryl pyrrolidine provided the corresponding product **2n** in moderate yield. Benzo[d][1,3]-dioxole is also a good reaction partner for this oxidation and the product **2o** was isolated in 30% chemical yield. Even substitution on the pyrrolidine ring was also well-tolerated and γ-lactam **2p** was obtained in 50% isolated yield. When there is another heteroatom in unsaturated ring such as nitrogen, no product observed (**2q)**.

To understand the reaction mechanism, several control experiments were conducted. No product formation was observed when the reaction was performed in the absence of DMAP.

Table 4: Mechanistic investigation



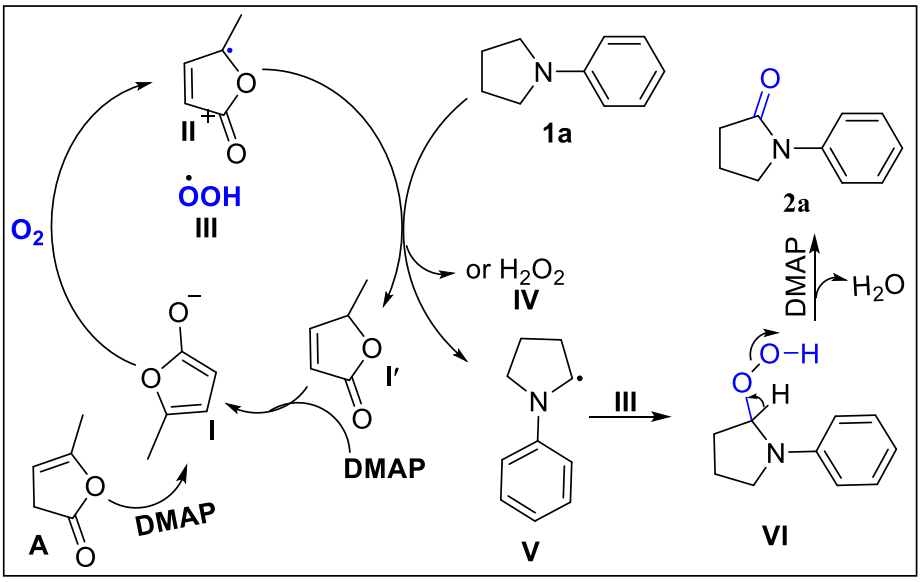
Entry	Condition	Result	Conclusion
1	No base	No reaction	Base required
2	No Catalyst **A**	No reaction	Catalyst **A** required
3	N_2 or Argon atm.	No reaction	Oxygen source needed
4	H_2O^{18}	No ^{18}O labeled product	Source of oxygen is not moisture
5	TEMPO (1 equiv)	15%	Presence of radical
6	BHT (1 equiv)	17%	Presence of radical
7	$CuCl_2$ (1 equiv)	20%	Single-electron

Similar observation was also noted in the absence of catalyst **A**. This concludes that both base and catalyst **A** is essential for the reaction (Table 4, entries 1 & 2). Next, the reaction was performed in the inert atmosphere, no reaction was observed (Table 4, entry 3). Again, when the reaction was performed in the presence of 2 equivalent of H_2O^{18} as co-solvent, no ^{18}O-

labelled product was obtained. This experiment confirms that the source of oxygen in the product is not from moisture in the reaction flask (Table 4, entry 4). In addition, this oxidation was almost completely inhibited by the addition of a radical scavenger such as TEMPO or BHT, suggesting that a radical process might be involved (Table 4, entries 5 & 6). Also, by addition of a stoichiometric amount of $CuCl_2$ substantial decrease in yield was observed. This result indicates the probable participation of a single electron transfer process (Table 4, entry 7).[18]

Based on these control experiments and previous literature precedents,[19-21] a plausible reaction mechanism is proposed in scheme 2. Dienolate species **I** was formed by abstracting the acidic proton from catalyst **A** by DMAP. The dienolate species **I** react with O_2 to give transient peroxide intermediate which breaks into radical species **II** and **III** by homolytic cleavage.[22] Next, H-abstraction from **1a** either by alkoxy radical **II** or peroxy radical **III** gives intermediate **V** along with the formation of **I'** or H_2O_2. Radical species **V** reacts with peroxy radical **III** to give hydroperoxide intermediate **VI**. Finally, the removal of a hydrogen atom by DMAP and elimination of H_2O from **VI** furnishes the final product **2a**.

Scheme 2: Plausible mechanism



3.6 Conclusion

In conclusion, α-angelica lactone was proved to be an efficient catalyst for direct oxidation of *N*-aryl pyrrolidines to the corresponding pyrrolidinones. The reaction set-up is very simple and good to excellent chemical yields were observed by employing molecular oxygen as oxidant. Molecular oxygen also served as the source of the oxygen atom in lactam moiety. Control experiments indicate that this catalytic system follows the radical pathway and the presence of a single-electron transfer process. Exploring for the substrate scope and application of this catalytic system for direct synthesis of the bioactive molecule is underway.

3.7 Experimental Section

A) General procedure for the synthesis of *N*-aryl pyrrolidines[23]

MacMillan procedure was applied with modification, substituted aniline (1 equiv) was added to the suspension of K_2CO_3 (1.1 equiv) in DMF (10 mL). Then 1, 4- dibromo butane (1.1 equiv) was added at once and the reaction mixture was stirred at 80 °C for overnight and the progress of the reaction was monitored by TLC. The mixture was allowed to cool to rt and then it was diluted with EtOAc (10 mL) and ice-cooled H_2O (100 mL). The solvent layer was separated and the organic layer was re-extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (10 mL), dried over Na_2SO_4, and purified by flash column chromatography to obtain a yellow oil. 1-phenylpyrrolidine **(1a)**, 87%; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26 – 7.18 (m, 2H), 6.68 – 6.62 (m, 1H), 6.59 – 6.53 (m, 2H), 3.31 – 3.24 (m, 4H), 2.04 – 1.94 (m, 4H).

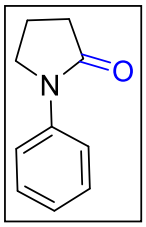
Other derivatives of pyrrolidines were synthesized by the above general method.

B) General procedure for the oxidation of *N*-aryl/heteroaryl pyrrolidines

To a solution of *N*-aryl/heteroaryl pyrrolidines (1 equiv, 0.2 mmol), DMAP (3 equiv) in mesitylene (1 mL) was added α-angelica lactone (10 mol%) with O_2 balloon in dry PYREX^{TM} glass tubes with a septum at rt. The resulting reaction mixture was heated at 100 °C for 12 h to 60 h and the progress of the reaction was monitor by TLC. After cooling to rt it was diluted by dichloromethane (2 mL) and washed with water (2 mL). The combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified over flash column chromatography (30% EtOAc/Pet ether).

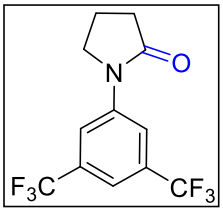
3.8 Characterization data of compounds

1-phenylpyrrolidin-2-one (2a):



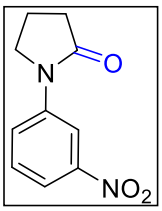
Yellow liquid (26.1 mg, 80%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.64 – 7.56 (m, 2H), 7.41 – 7.32 (m, 2H), 7.18 – 7.11 (m, 1H), 3.92 – 3.81 (m, 2H), 2.61 (t, *J* = 8.1 Hz, 2H), 2.16 (p, *J* = 7.5 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.38, 139.48, 128.92, 124.63, 120.10, 48.91, 32.86, 18.13.

1-(3,5-bis(trifluoromethyl) phenyl) pyrrolidin-2-one (2b):



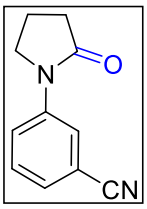
Yellow liquid (38.3 mg, 65%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18-8.12 (m, 2H), 7.66 – 7.60 (m, 1H), 3.93 (t, *J* = 7.0 Hz,2), 2.68 (t, *J* = 8.1 Hz, 2H), 2.30 – 2.20 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.89, 140.90, 132.26 (q, *J* = 33.4 Hz), 124.68, 121.96, 119.04 (d, *J* = 4.2 Hz), 117.48 (p, *J* = 3.8 Hz), 48.51, 32.73, 17.87.

1-(3-nitrophenyl) pyrrolidin-2-one (2c):



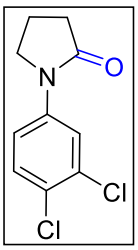
Yellow solid (16.8 mg, 41%); TLC R_f = 0.6 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.38 (m, 1H), 8.20 (m, 1H), 7.99-7.96 (m, 1H), 7.55-7.50 (m, 1H), 3.94 (t, J = 7.0 Hz, 2H), 2.67 (t, J = 8.1 Hz, 2H), 2.24 (p, J = 7.9, 7.5 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.80, 148.57, 140.56, 129.75, 125.47, 118.90, 113.87, 48.61, 32.76, 17.91.

3-(2-oxopyrrolidin-1-yl) benzonitrile (2d):



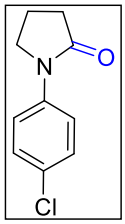
Yellow solid (28.8 mg, 78%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.98 – 7.88 (m, 2H), 7.50 – 7.44 (m, 1H), 7.43-7.39 (m, 1H), 3.87 (t, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 8.1 Hz, 2H), 2.26-2.16 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.75, 140.26, 129.84, 127.70, 123.66, 122.62, 118.73, 112.97, 48.45, 32.75, 17.95.

1-(3,4-dichlorophenyl) pyrrolidin-2-one (2e):



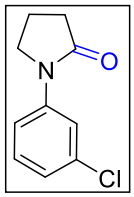
Yellow solid (37.2 mg, 81%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80-7.78 (m, 1H), 7.55-7.51 (m, 1H), 7.41-7.38 (m, 1H), 3.82 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 8.1 Hz, 2H), 2.23-2.12 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.50, 138.99, 132.72, 130.41, 127.66, 121.26, 118.87, 48.60, 32.75, 17.87.

1-(4-chlorophenyl) pyrrolidin-2-one (2f):



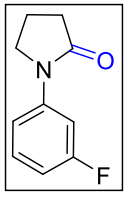
Yellow solid (38.7 mg, 98%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ7.58-7.54 (m, 2H), 7.32-7.28 (m, 2H), 3.80 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 8.1 Hz, 2H), 2.15 (p, *J* = 7.6 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.33, 138.05, 129.49, 128.83, 120.98, 48.69, 32.70, 17.90.

1-(3-chlorophenyl) pyrrolidin-2-one (2g):



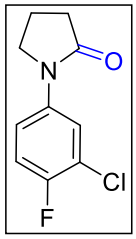
Yellow solid (28.6 mg, 73%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ7.70-7.66 (m, 1H), 7.56-7.53 (m, 1H), 7.31-7.27 (m, 1H),7.14 – 7.10 (m, 1H), 3.85 (t, *J* = 7.0 Hz, 2H), 2.63 (t, *J* = 8.1 Hz, 2H), 2.18 (p, *J* = 7.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.48, 140.68, 134.64, 129.93, 124.51, 119.87, 117.81, 48.74, 32.87, 18.03.

1-(3-fluorophenyl) pyrrolidin-2-one (2h):



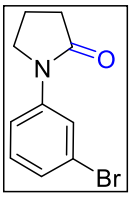
Yellow solid (24.0 mg, 67%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.55-7.50 (m, 1H), 7.35 – 7.27 (m, 2H), 6.87 – 6.79 (m, 1H), 3.83 (t, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 8.2 Hz, 2H), 2.16 (p, *J* = 7.6 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.53, 164.15, 161.72, 140.98 (d, *J* = 40 Hz), 129.97 (d, *J* = 36 Hz), 114.84 (d, *J* = 12 Hz), 111.12 (d, *J* = 84 Hz), 107.22(d, *J* = 104 Hz), 48.74, 32.88, 17.90.

1-(3-chloro-4-fluorophenyl) pyrrolidin-2-one(2i):



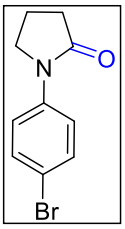
Yellow solid (33.2 mg, 78%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.76 – 7.70 (m, 1H), 7.53 – 7.46 (m, 1H), 7.16 – 7.07 (m, 1H), 3.82 (t, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 8.1 Hz, 2H), 2.18 (p, *J* = 7.5 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.39, 154.91 (d, *J* = 246.5 Hz), 136.21 (d, *J* = 3.3 Hz), 122.02, 121.09 (d, *J* = 18.4 Hz), 119.51 (d, *J* = 6.8 Hz), 116.53 (d, *J* = 21.8 Hz), 48.90, 32.61, 17.93.

1-(3-bromophenyl) pyrrolidin-2-one (2j):



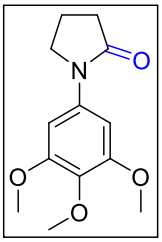
Yellow solid (41.0 mg, 85%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.60-7.56 (m, 2H), 7.35-7.30 (m, 2H), 3.85 (t, *J* = 7.02 Hz, 2H), 2.63 (t, *J* = 8.1 Hz, 2H), 2.23 – 2.18 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.44, 138.09, 129.68, 128.96, 121.10, 48.81, 32.79, 18.03.

1-(4-bromophenyl) pyrrolidin-2-one (2k):



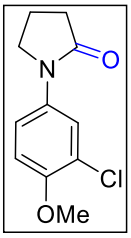
Yellow solid (41.3 mg, 86%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.55-7.51 (m, 2H), 7.49-7.45 (m, 2H), 3.84 (t, *J* = 7.0 Hz,2H), 2.62 (t, *J* = 8.1 Hz, 2H), 2.21-2.13 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)**δ 174.44, 138.60, 131.91, 121.41, 117.39, 48.73, 32.81, 18.01.

1-(3,4,5-trimethoxyphenyl) pyrrolidin-2-one (2m):



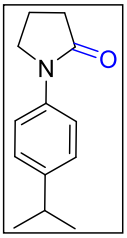
Brown solid (27.5 mg, 55%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.88 (s, 2H), 3.90-3.77 (m, 11H), 2.61 (t, *J* = 8.1 Hz, 2H), 2.16 (p, *J* = 7.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.34, 153.23, 135.54, 135.25, 98.41, 61.00, 56.29, 49.38, 32.86, 18.00.

1-(3-chloro-4-methoxyphenyl) pyrrolidin-2-one (2n):



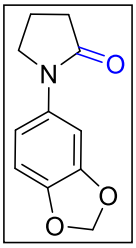
Yellow solid (38.5 mg, 85%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63-7.60 (m, 1H), 7.53-7.48 (m, 1H), 6.93-6.88 (m, 1H), 3.88 (s, 3H), 3.81 (t, *J* = 7.1 Hz, 2H), 2.58 (t, *J* = 8.2 Hz, 2H), 2.19-2.11 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.18, 152.06, 133.19, 122.50, 122.32, 119.77, 112.16, 56.47, 49.04, 32.55, 18.00.

1-(4-isopropylphenyl) pyrrolidin-2-one (2o):



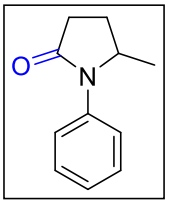
Yellow liquid (18.7 mg, 46%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52-7.47 (m, 2H), 7.23-7.20 (m, 2H), 3.85 (t, *J* = 7.0 Hz, 2H), 2.89 (hept, *J* = 6.8 Hz, 1H), 2.60 (t, *J* = 8.1 Hz, 2H), 2.17 – 2.13 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.25, 145.44, 137.24, 126.90, 120.38, 49.10, 33.76, 32.80, 24.14, 18.25.

1-(benzo[d][1,3]dioxol-5-yl)pyrrolidin-2-one (2p):



Brown liquid (12.3 mg, 30%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.30-7.28 (m,1H),6.88-6.83 (m, 1H), 6.80-6.75 (m, 1H), 5.96 (s, 2H),3.80 (t, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 8.1 Hz, 2H), 2.15 (p, *J* = 7.5 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.15, 147.90, 144.66, 129.10, 113.46, 108.01, 103.16, 101.40, 49.67, 32.63, 18.11.

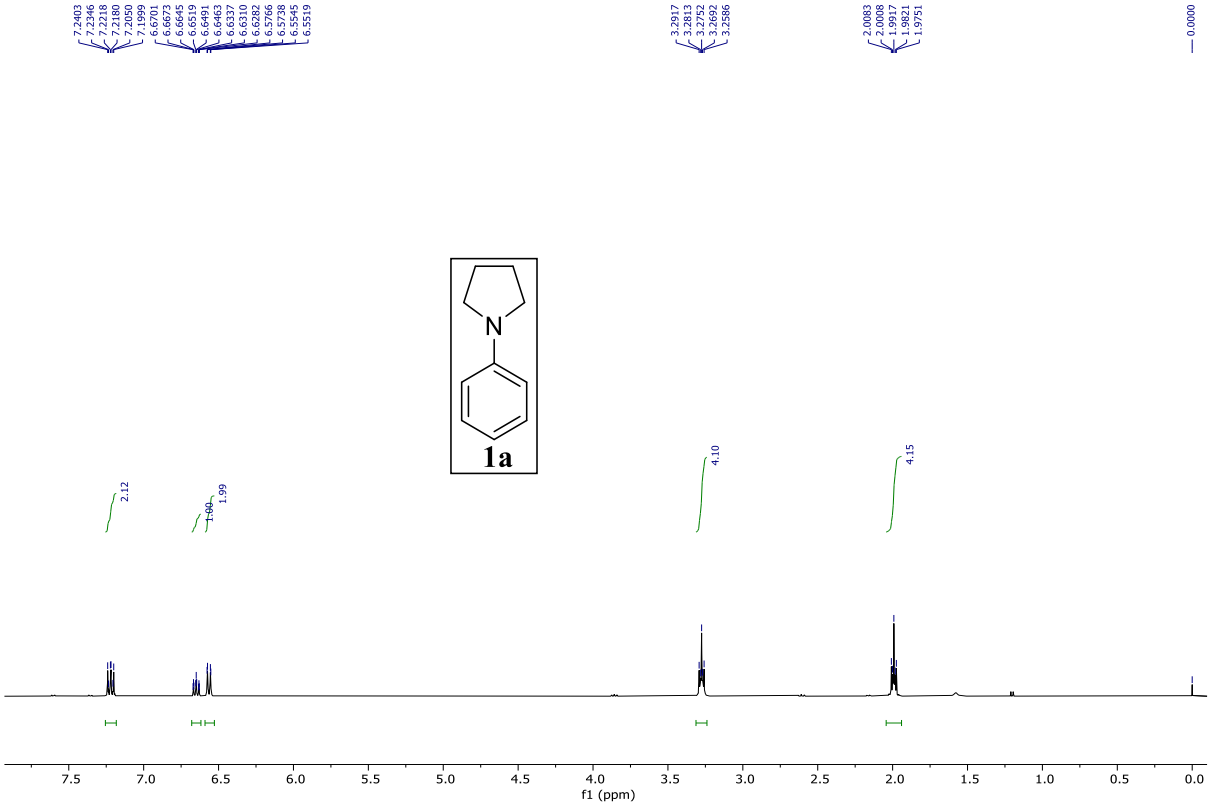
5-methyl-1-phenylpyrrolidin-2-one (2q):



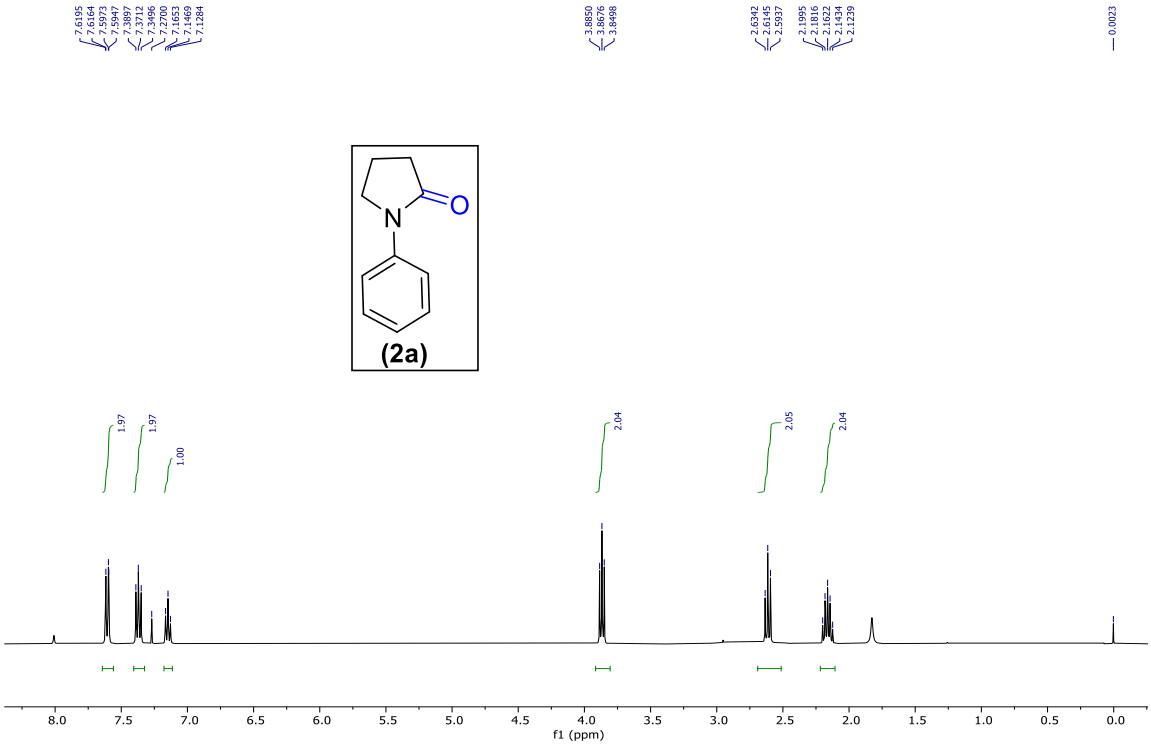
Yellow solid (17.5 mg, 50%); TLC R_f = 0.8 (30% EtOAc/Pet ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 – 7.34 (m, 4H), 7.23 – 7.19 (m, 1H), 4.35 – 4.26 (m, 1H), 2.68 – 2.50 (m, 2H), 2.43 – 2.32 (m, 1H), 1.81 – 1.71 (m, 1H), 1.21 (d, *J* = 7.9 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.38, 137.68, 129.11, 125.90, 124.21, 55.77, 31.46, 26.87, 20.29.

3.9 Spectral data

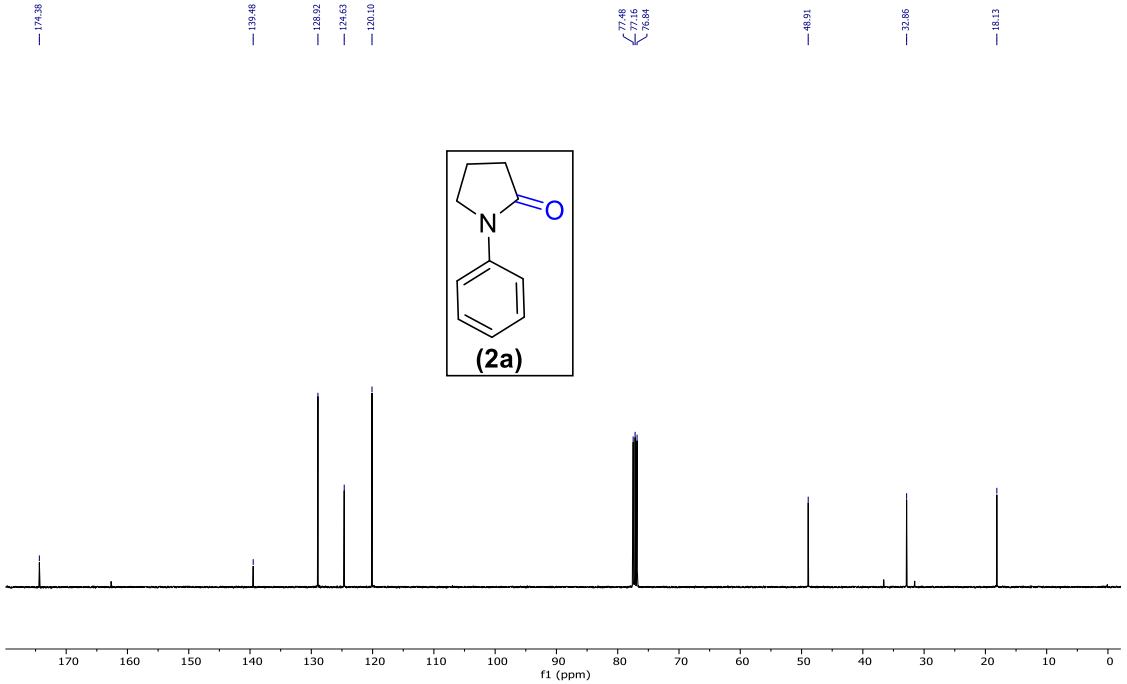
^{1}H NMR of 1-phenylpyrrolidine **(1a)** in $CDCl_3$



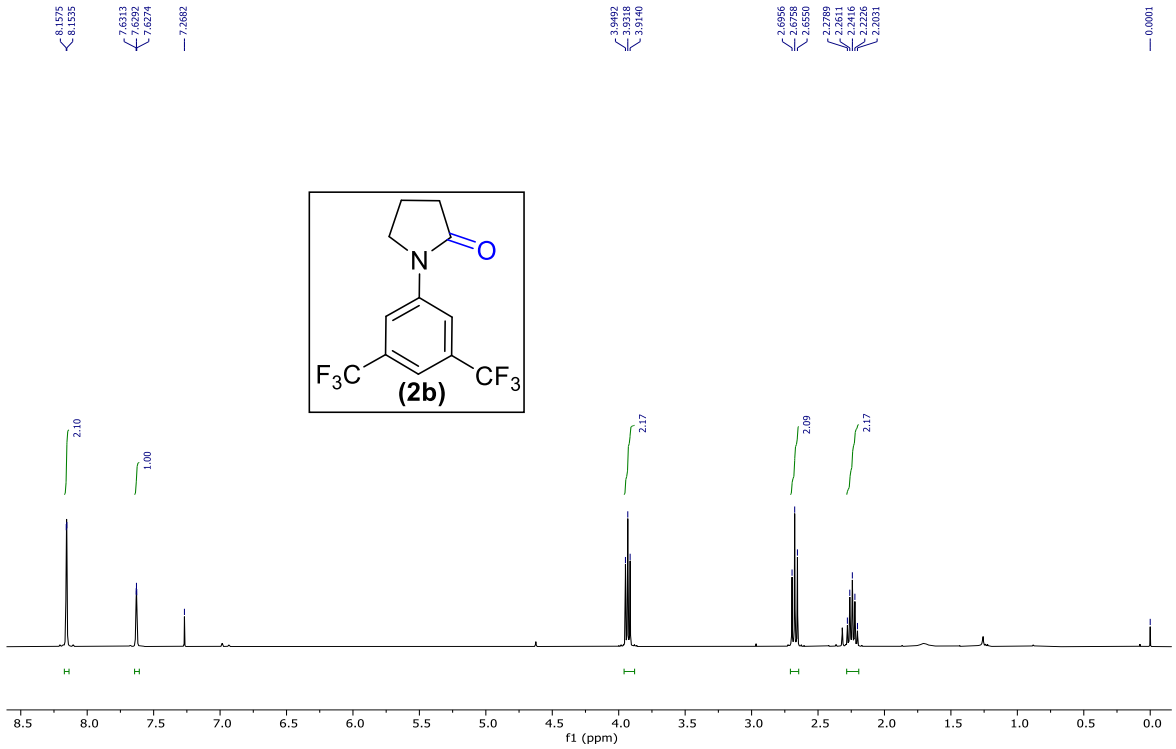
^{1}H NMR of 1-phenylpyrrolidin-2-one **(2a)** in $CDCl_3$



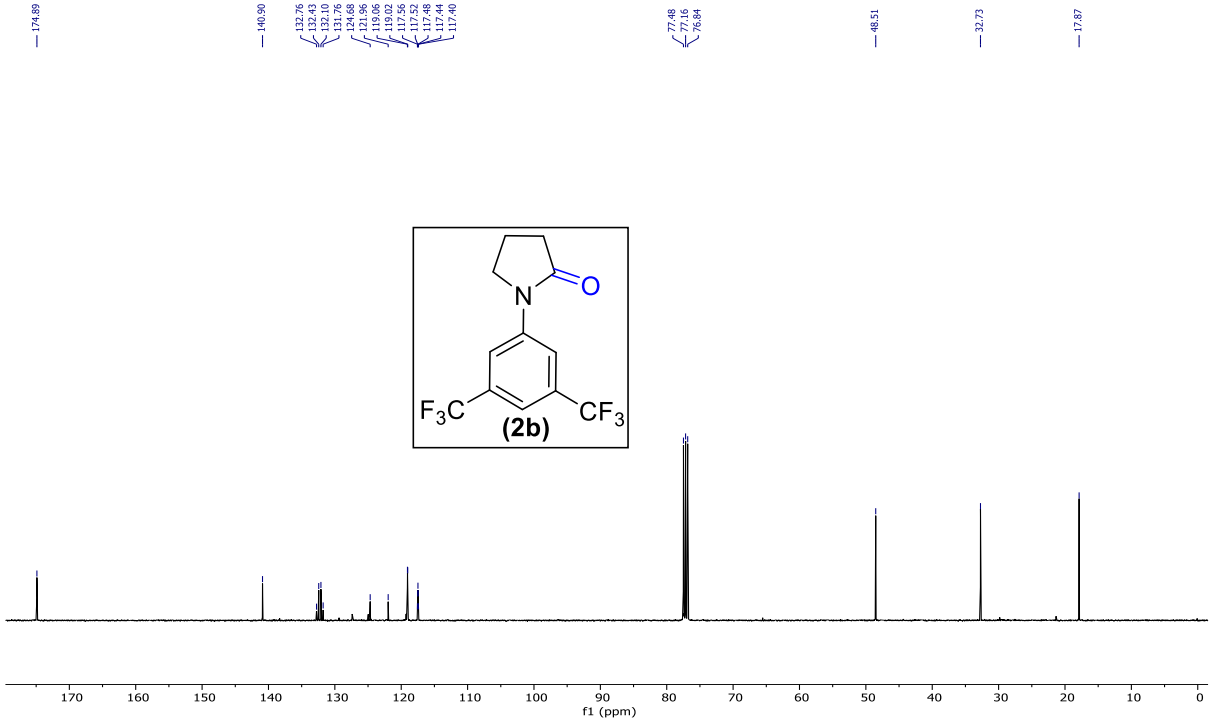
^{13}C NMR of 1-phenylpyrrolidin-2-one **(2a)** in $CDCl_3$



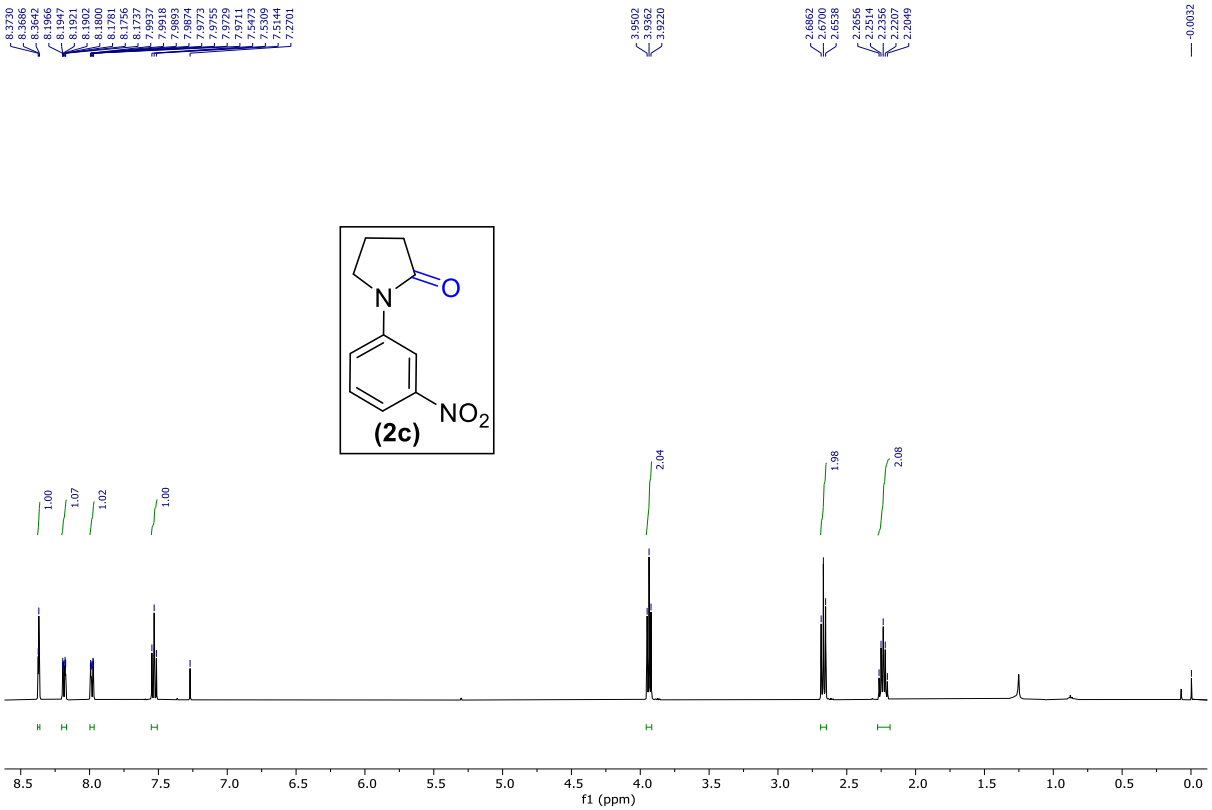
^{1}H NMR of 1-(3,5-bis(trifluoromethyl)phenyl) pyrrolidin-2-one **(2b)** in $CDCl_3$



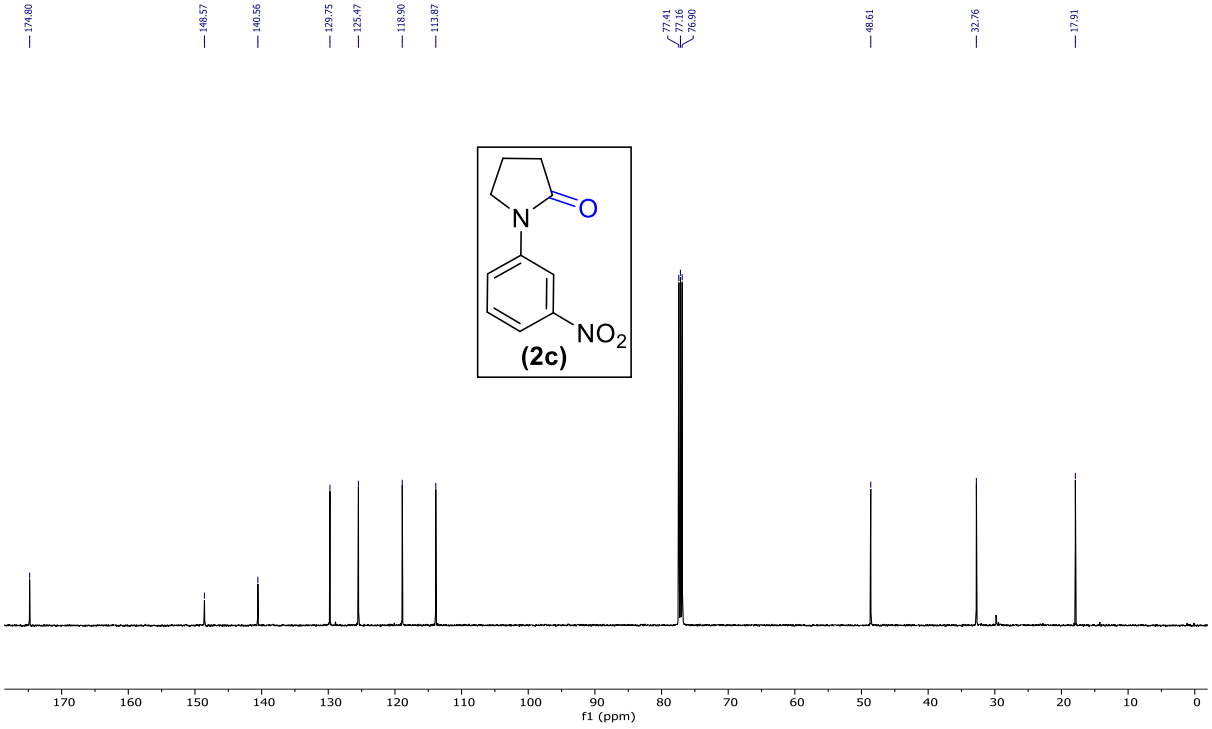
^{13}C NMR of 1-(3,5-bis(trifluoromethyl)phenyl) pyrrolidin-2-one **(2b)** in $CDCl_3$



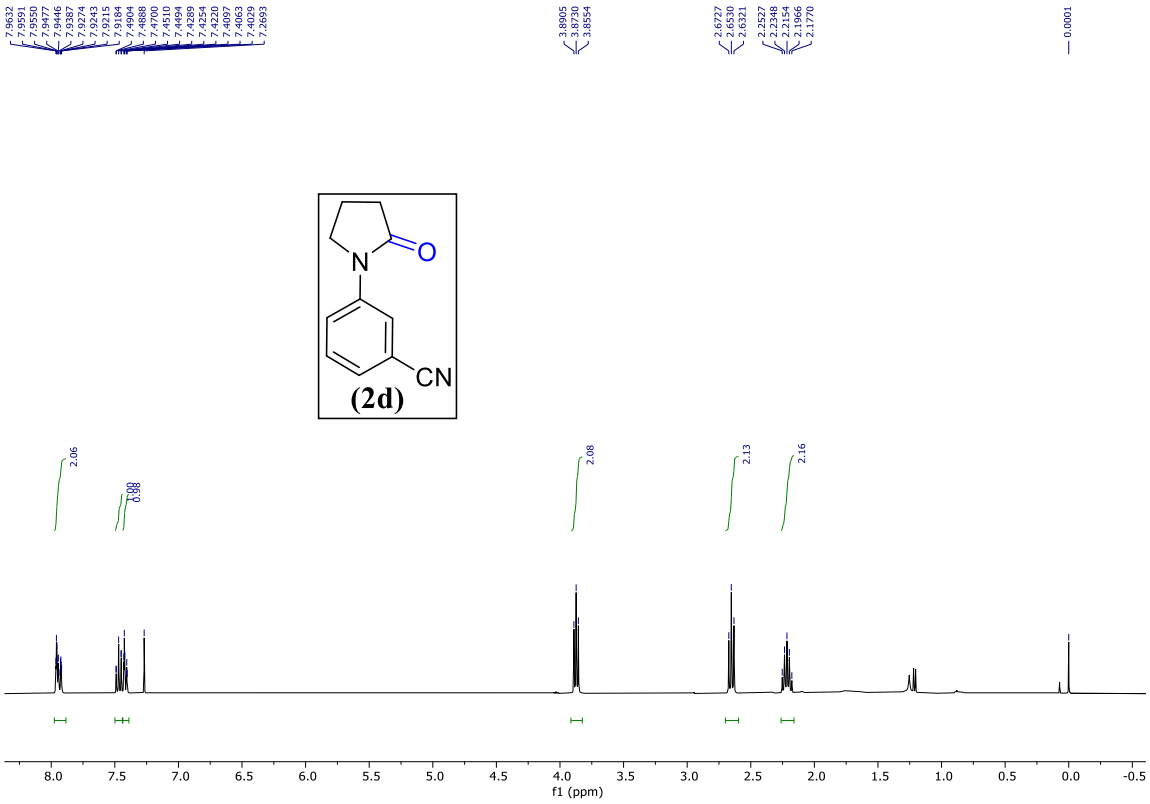
^{1}H NMR of 1-(3-nitrophenyl) pyrrolidin-2-one **(2c)** in $CDCl_3$



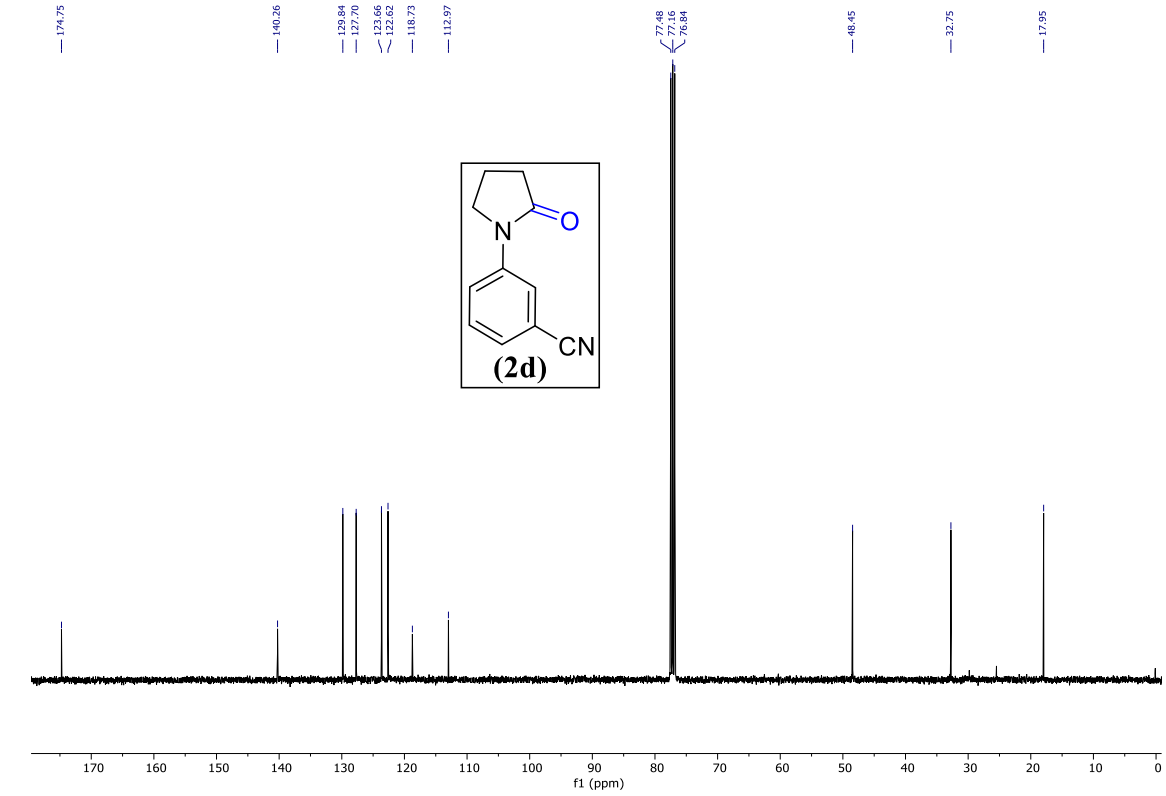
^{13}C NMR of 1-(3-nitrophenyl) pyrrolidin-2-one **(2c)** in $CDCl_3$



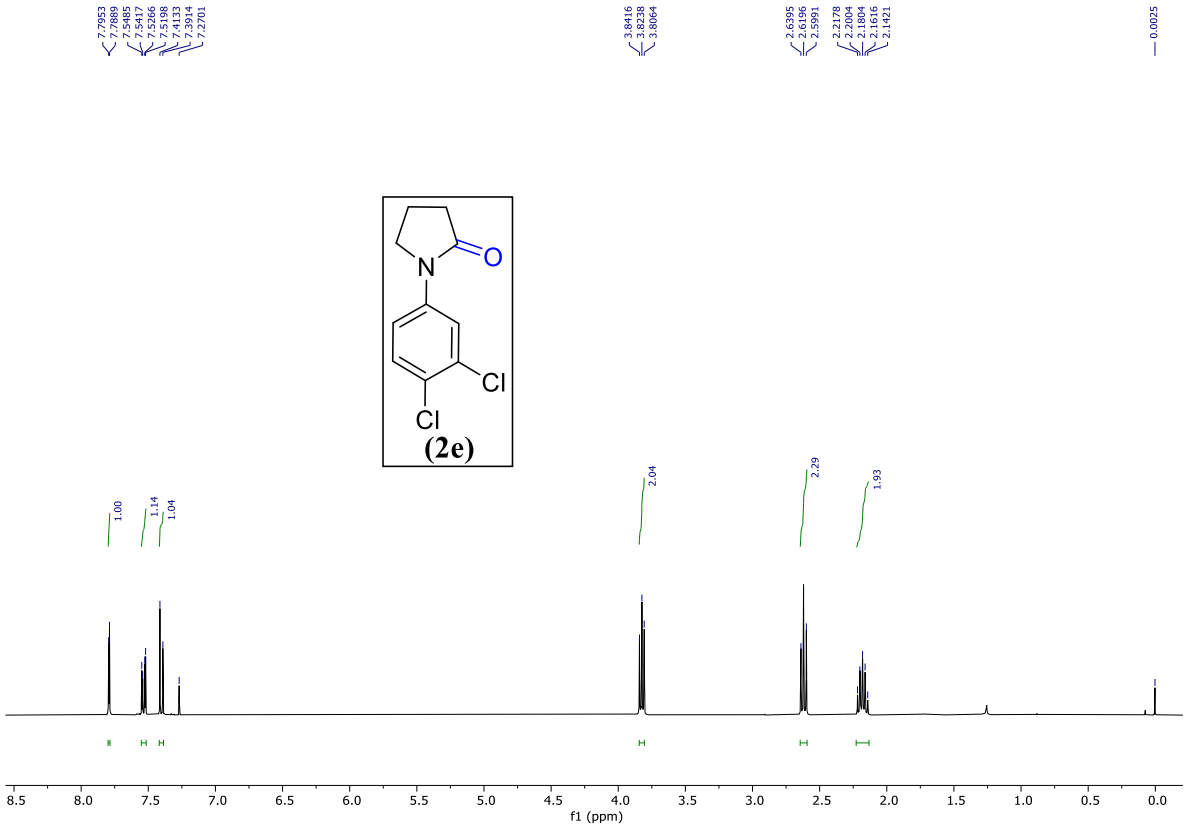
^{1}H NMR of 3-(2-oxopyrrolidin-1-yl) benzonitrile (**2d**) in $CDCl_3$



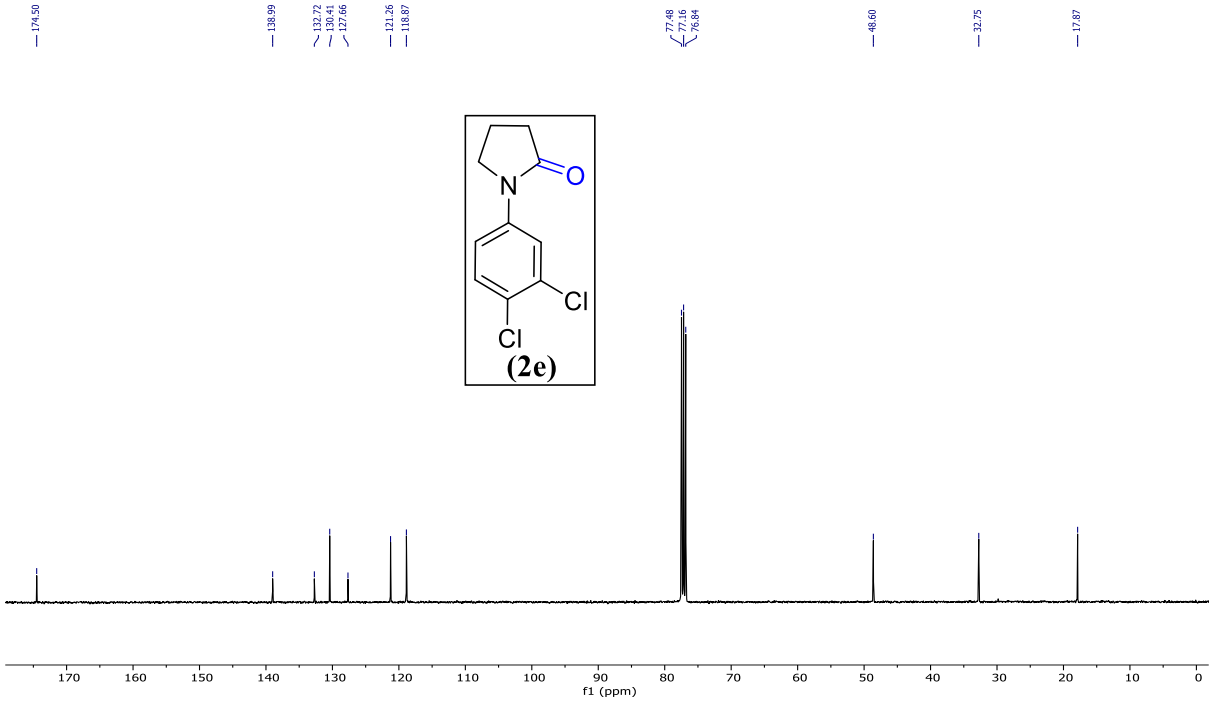
^{13}C NMR of 3-(2-oxopyrrolidin-1-yl) benzonitrile (**2d**) in $CDCl_3$



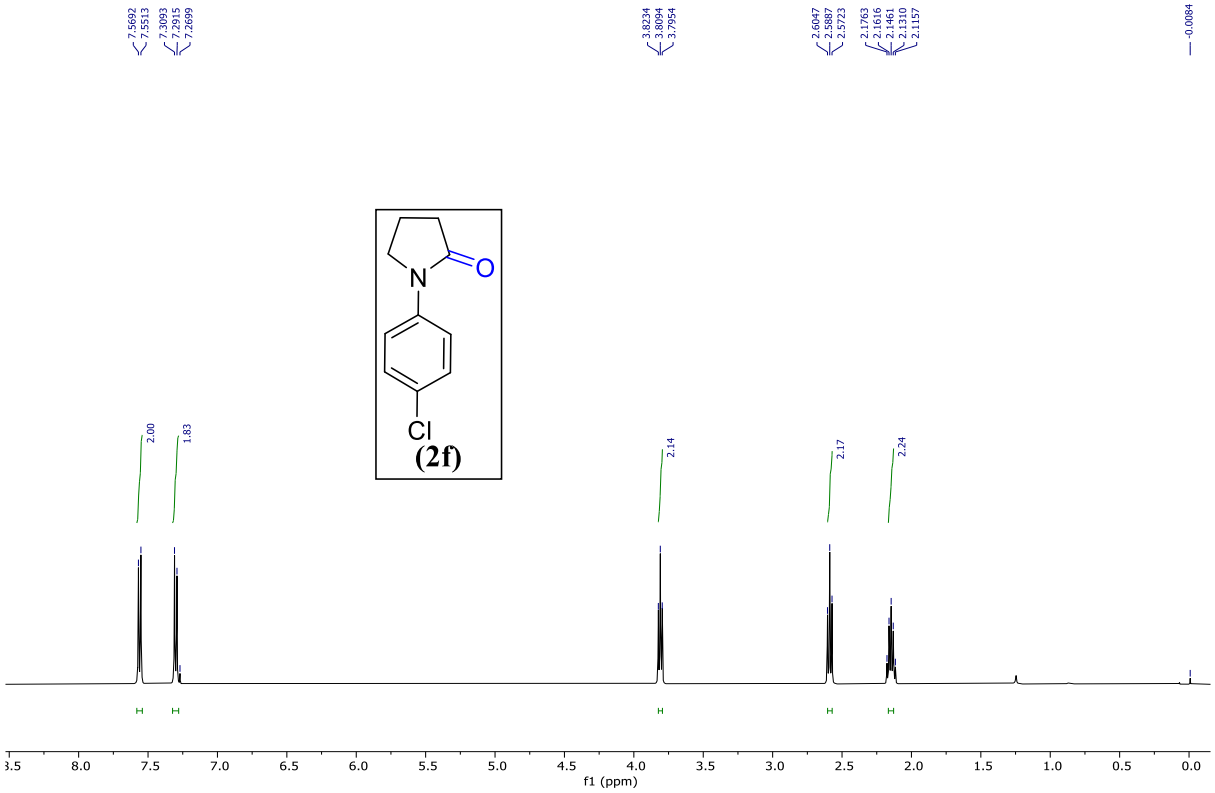
^{1}H NMR of 1-(3,4-dichlorophenyl) pyrrolidin-2-one **(2e)** in $CDCl_3$



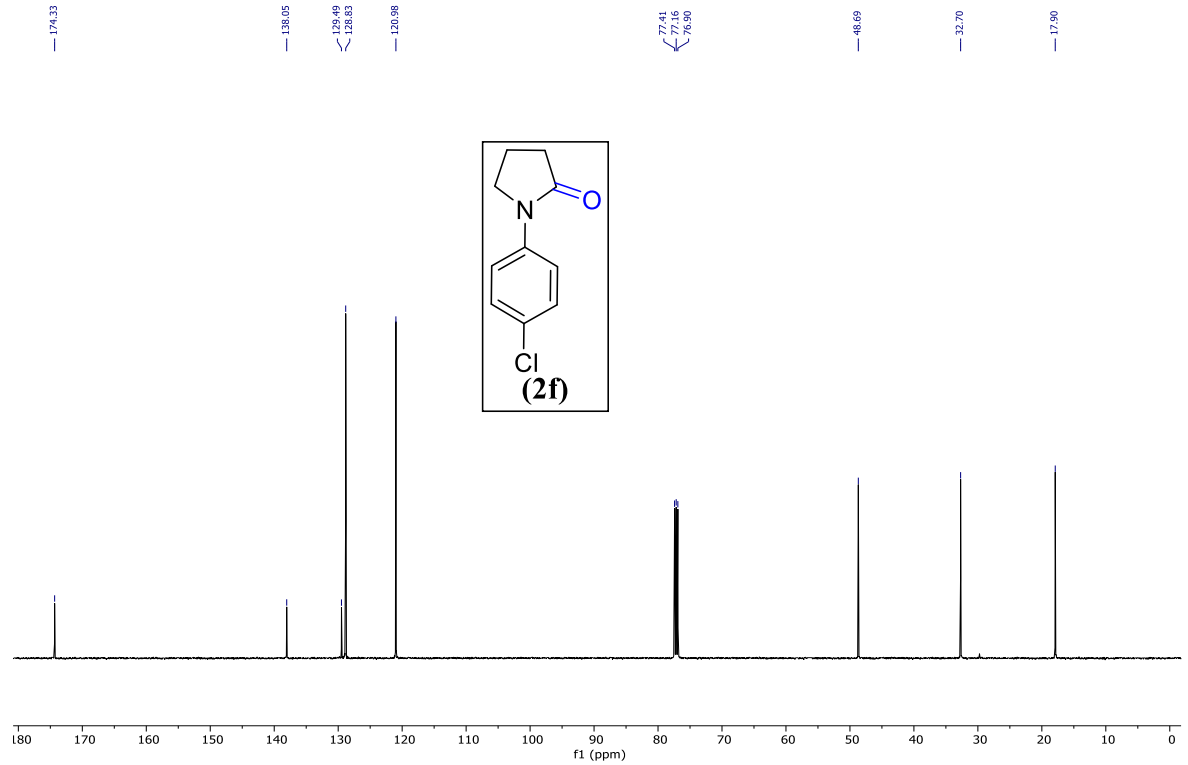
^{13}C NMR of 1-(3,4-dichlorophenyl) pyrrolidin-2-one **(2e)** in $CDCl_3$



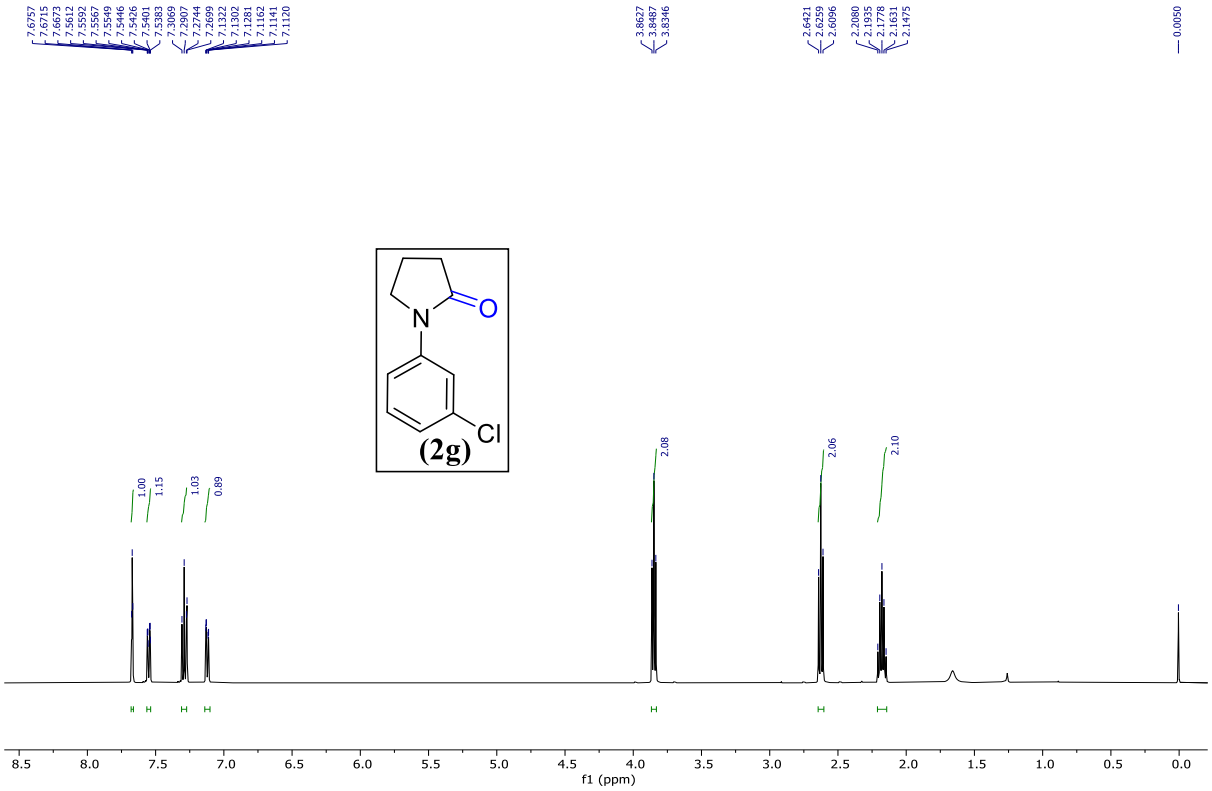
^{1}H NMR of 1-(4-chlorophenyl) pyrrolidin-2-one **(2f)** in $CDCl_3$



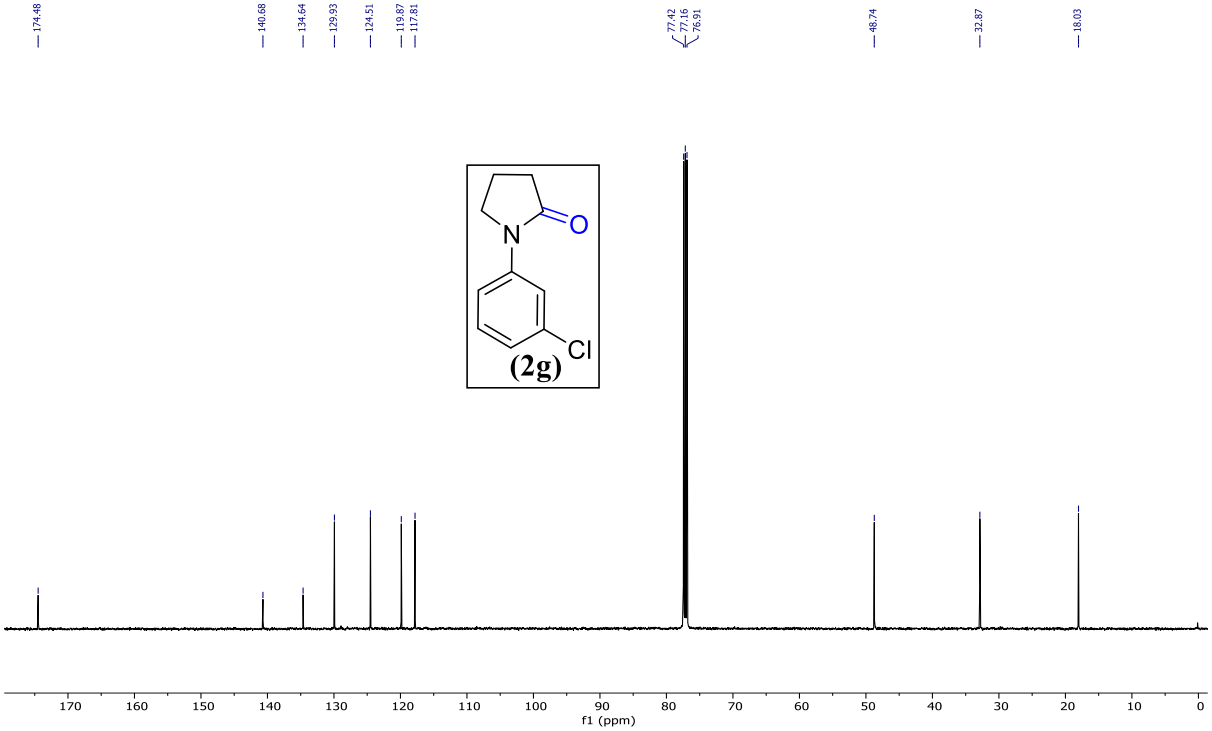
^{13}C NMR of 1-(4-chlorophenyl) pyrrolidin-2-one **(2f)** in $CDCl_3$



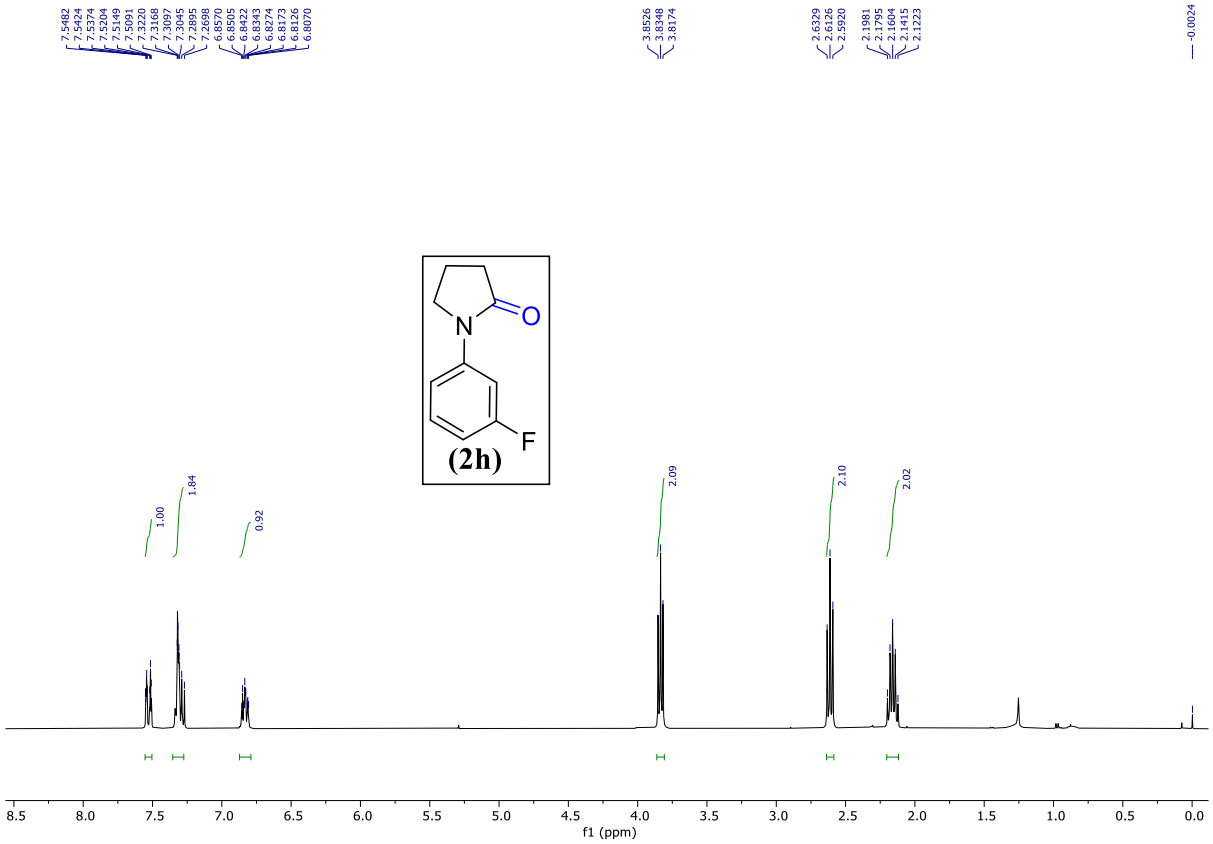
^{1}H NMR of 1-(3-chlorophenyl) pyrrolidin-2-one **(2g)** in $CDCl_3$



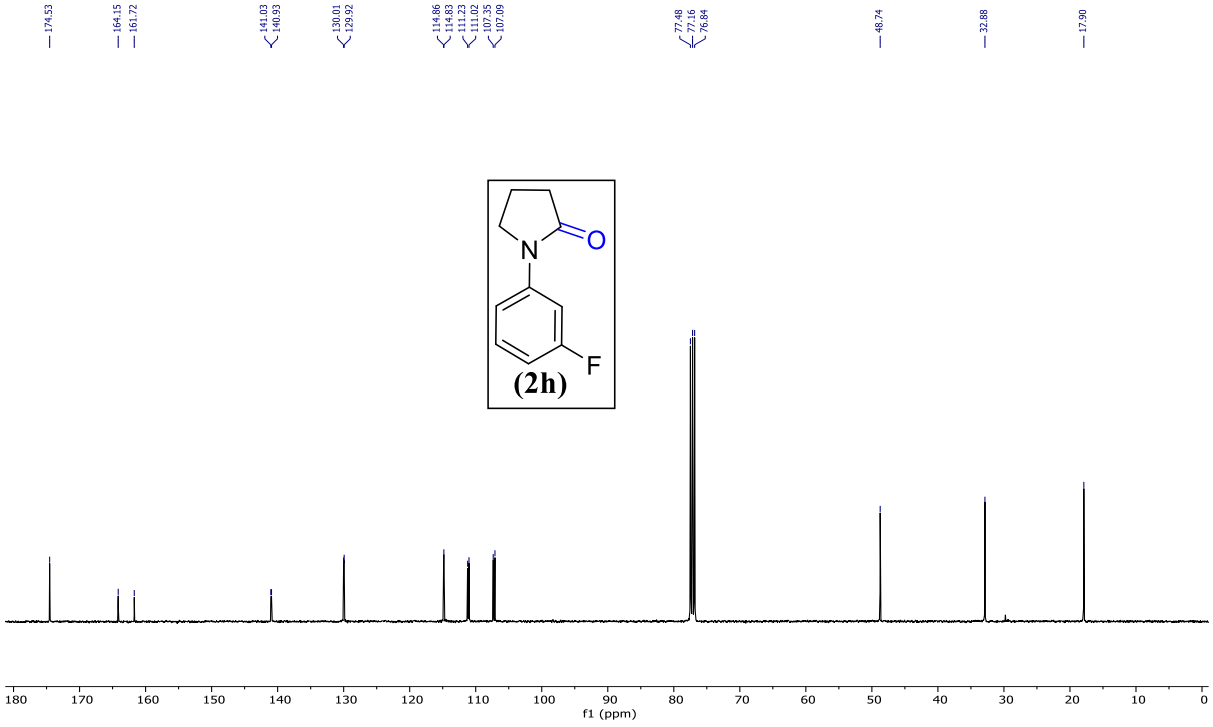
^{13}C NMR of 1-(3-chlorophenyl) pyrrolidin-2-one **(2g)** in $CDCl_3$



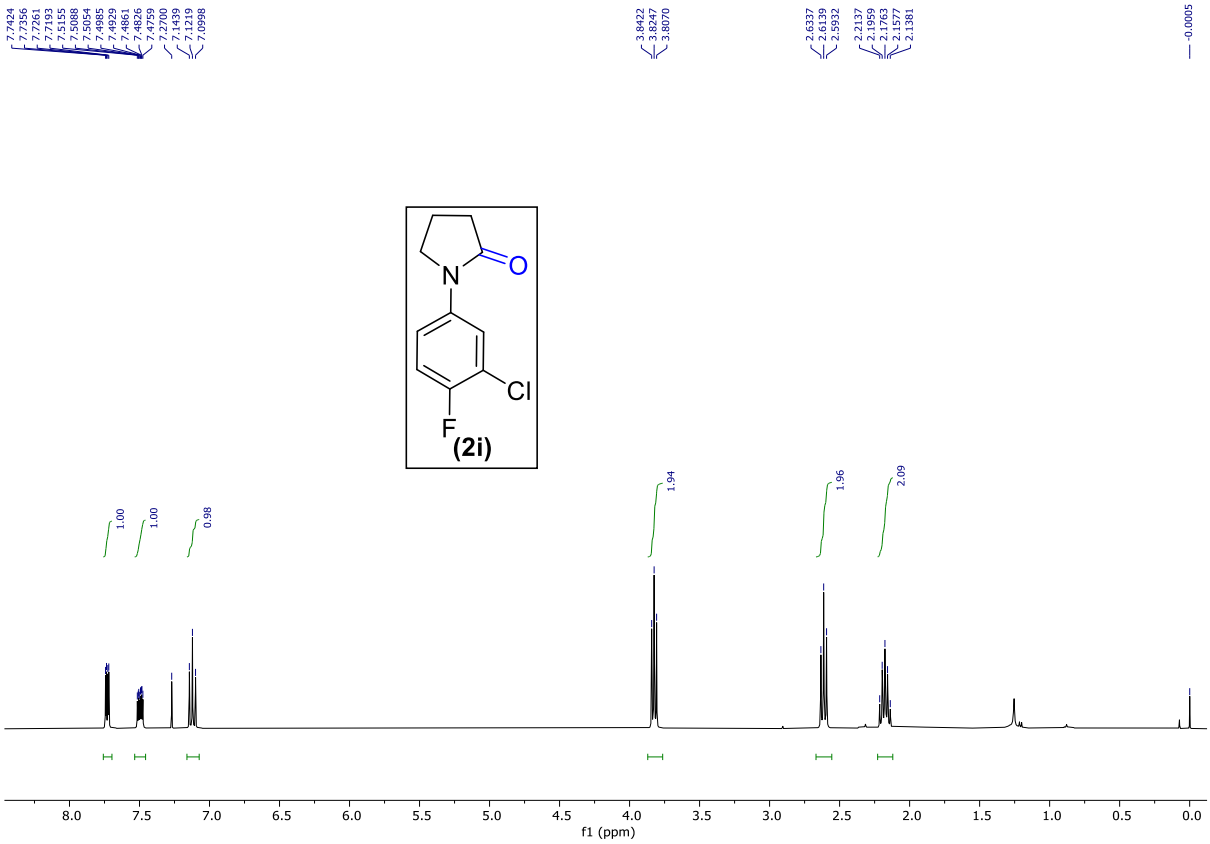
^{1}H NMR of 1-(3-fluorophenyl) pyrrolidin-2-one **(2h)** in $CDCl_3$



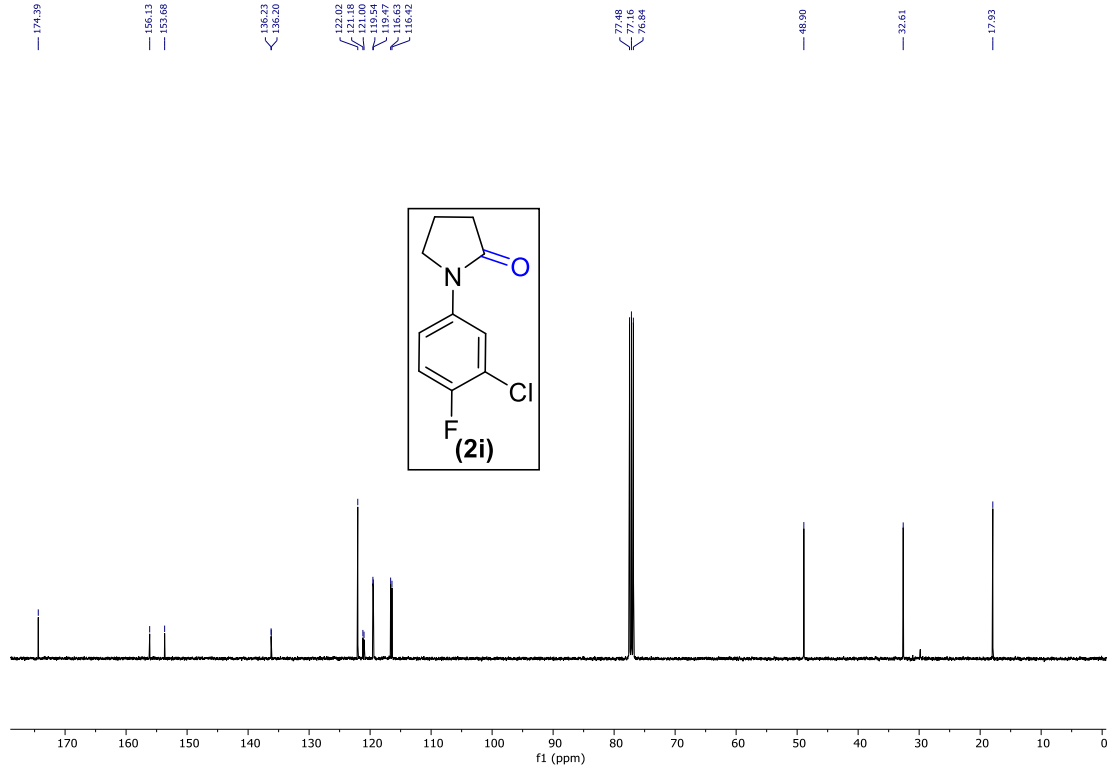
^{13}C NMR of 1-(3-fluorophenyl) pyrrolidin-2-one **(2h)** in $CDCl_3$



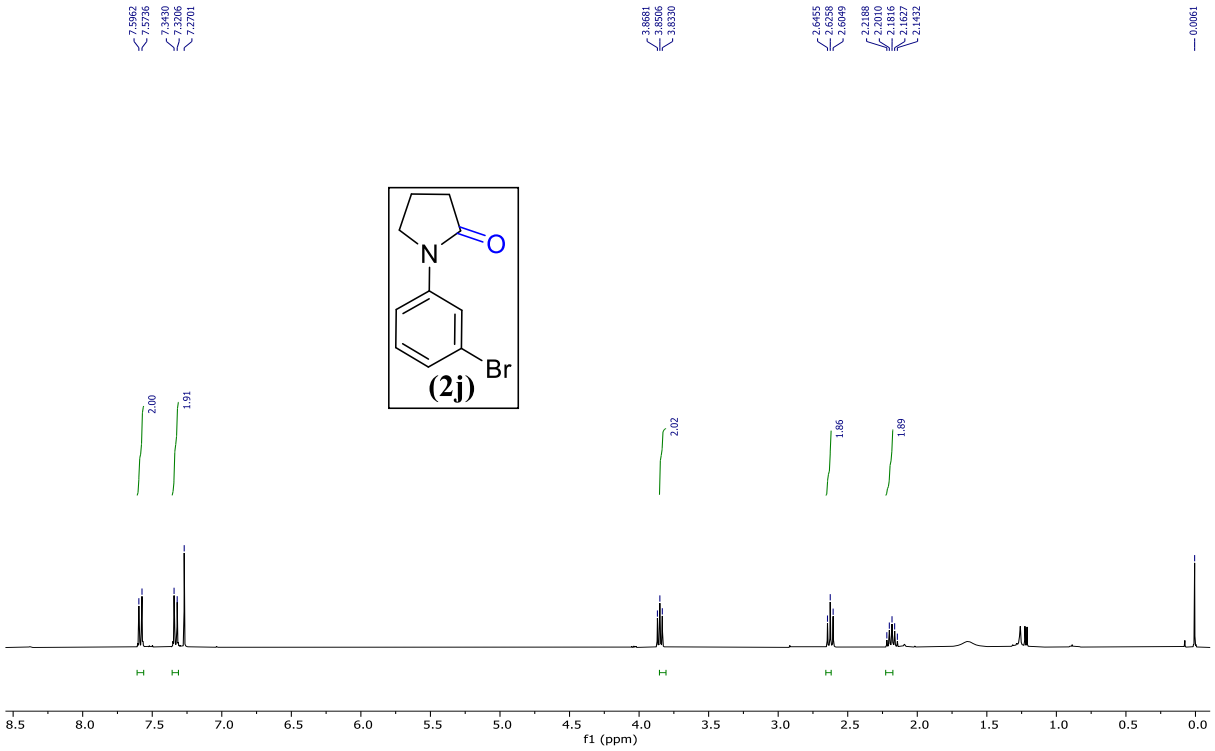
^{1}H NMR of1-(3-chloro-4-fluorophenyl) pyrrolidin-2-one **(2i)** in $CDCl_3$



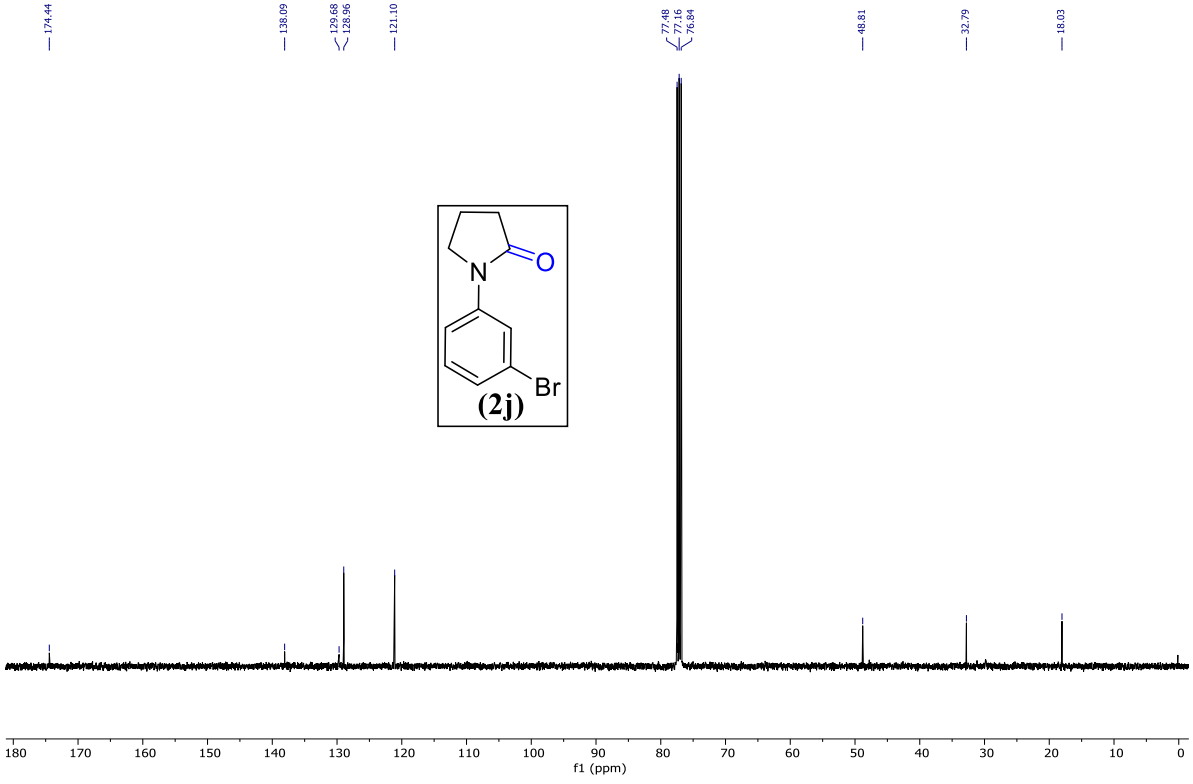
^{13}C NMR of 1-(3-chloro-4-fluorophenyl) pyrrolidin-2-one **(2i)** in $CDCl_3$



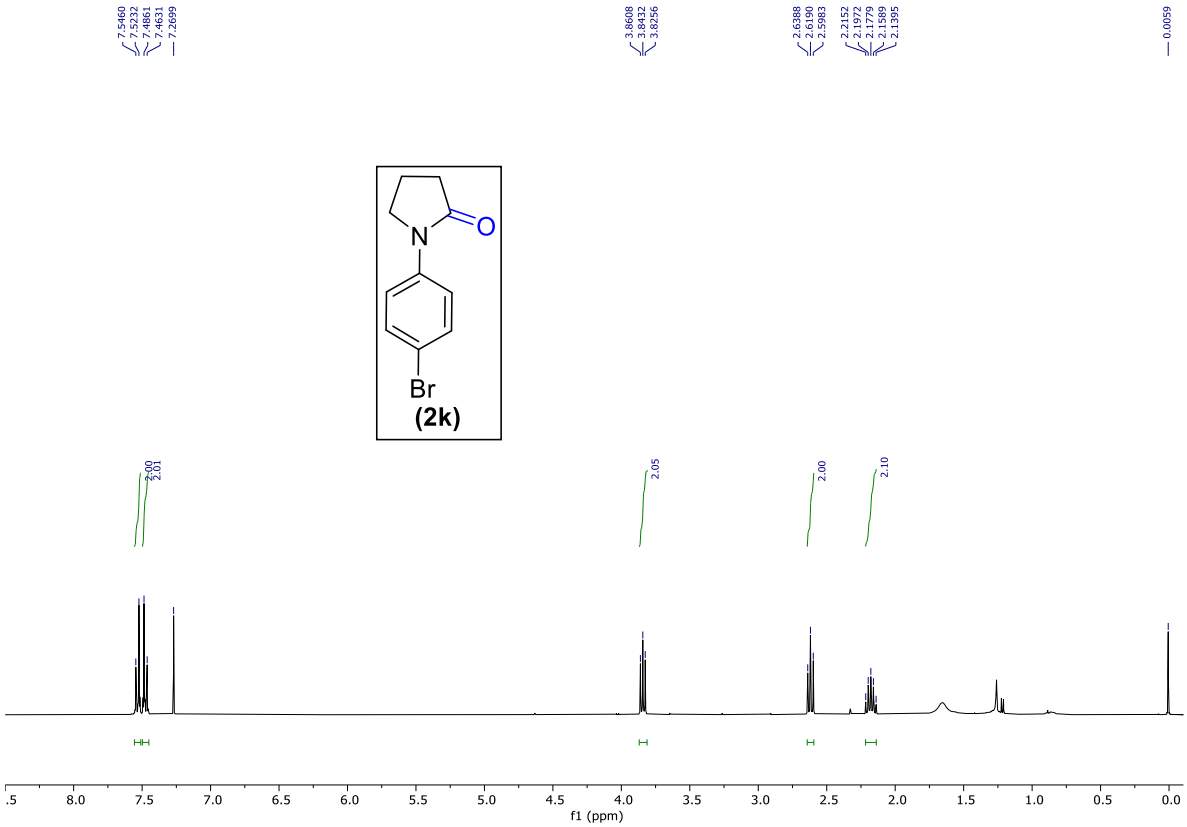
^{1}H NMR of 1-(3-bromophenyl) pyrrolidin-2-one **(2j)** in $CDCl_3$



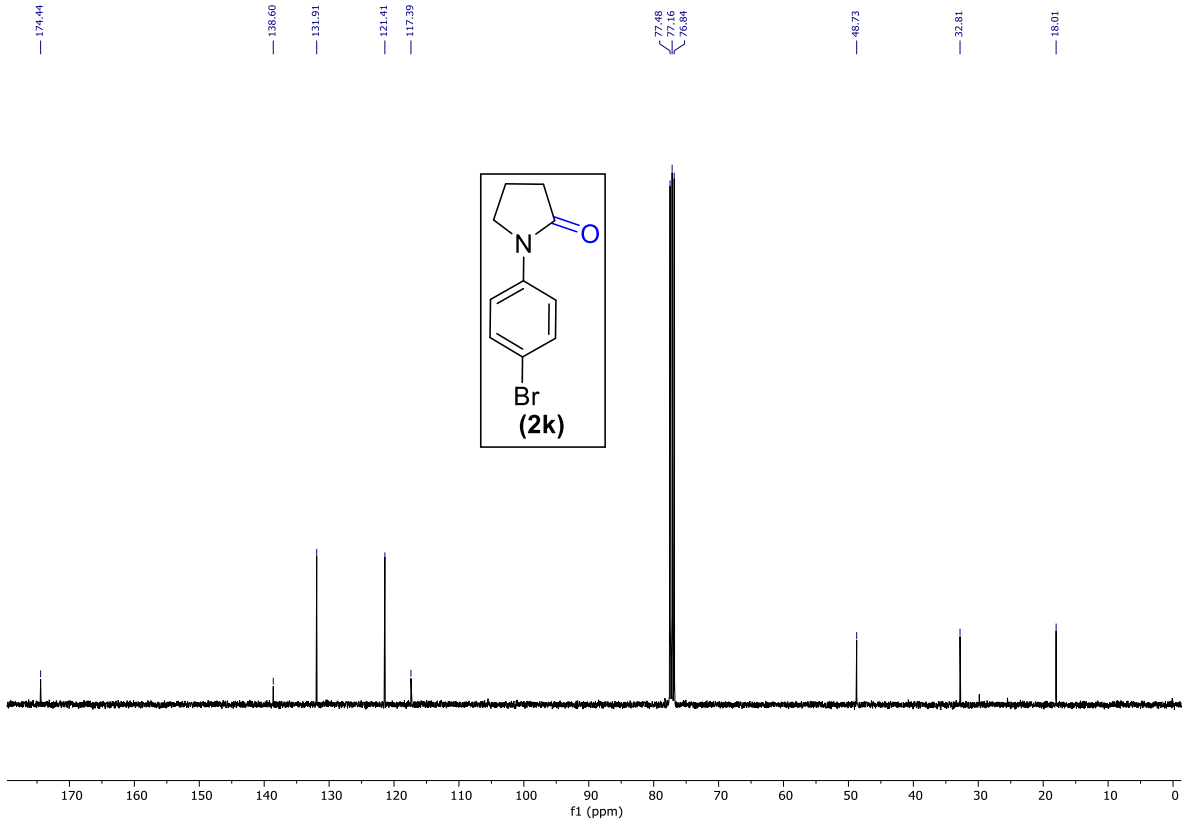
^{13}C NMR of 1-(3-bromophenyl) pyrrolidin-2-one **(2j)** in $CDCl_3$



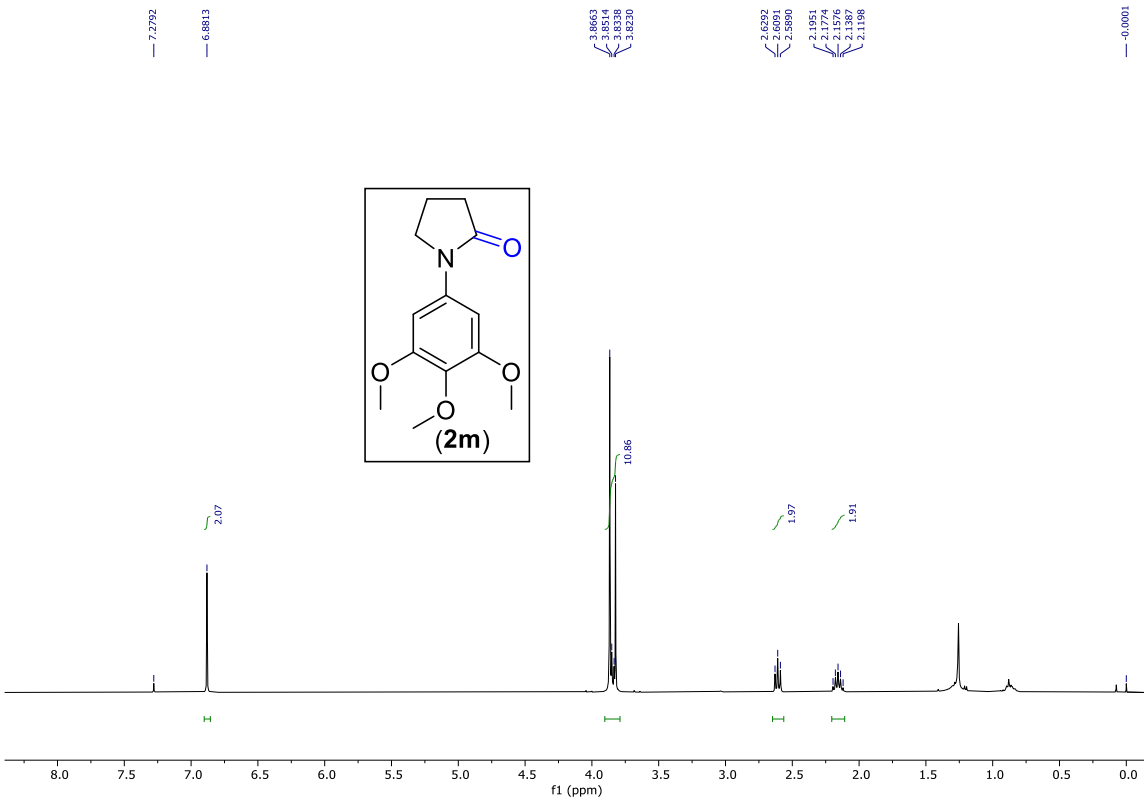
^{1}H NMR of 1-(4-bromophenyl) pyrrolidin-2-one **(2k)** in $CDCl_3$



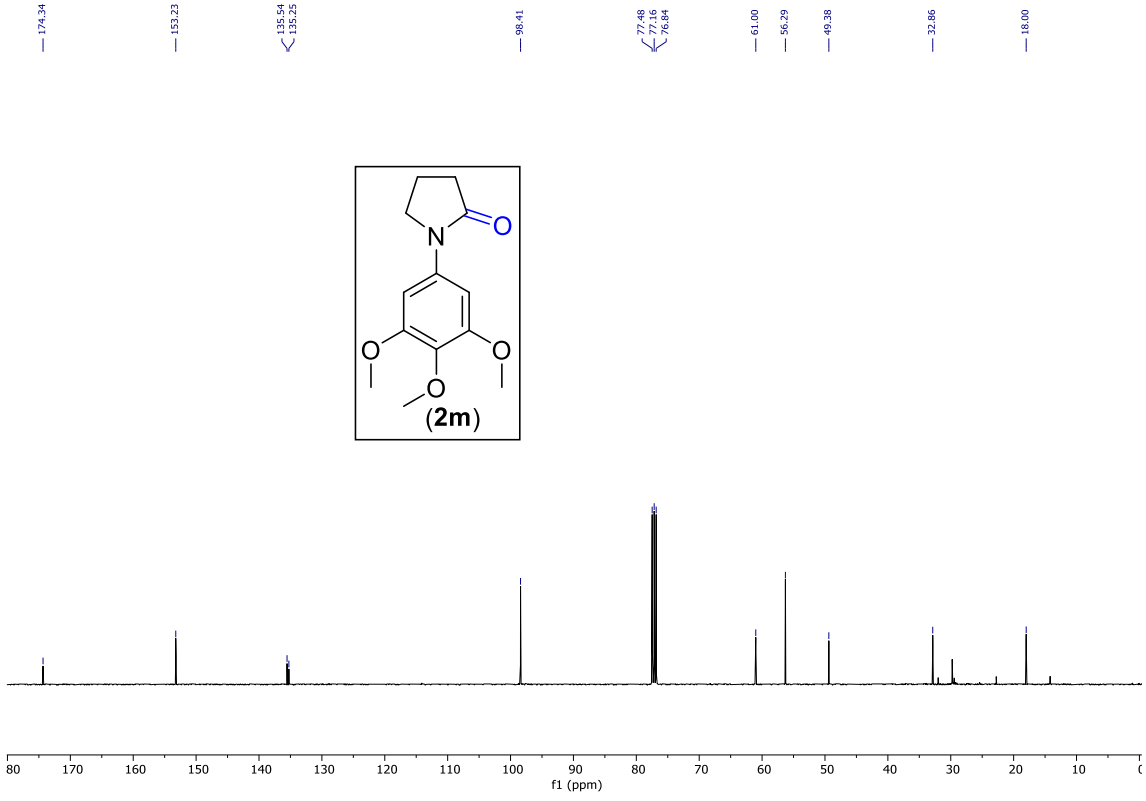
^{13}C NMR of 1-(4-bromophenyl) pyrrolidin-2-one **(2k)** in $CDCl_3$



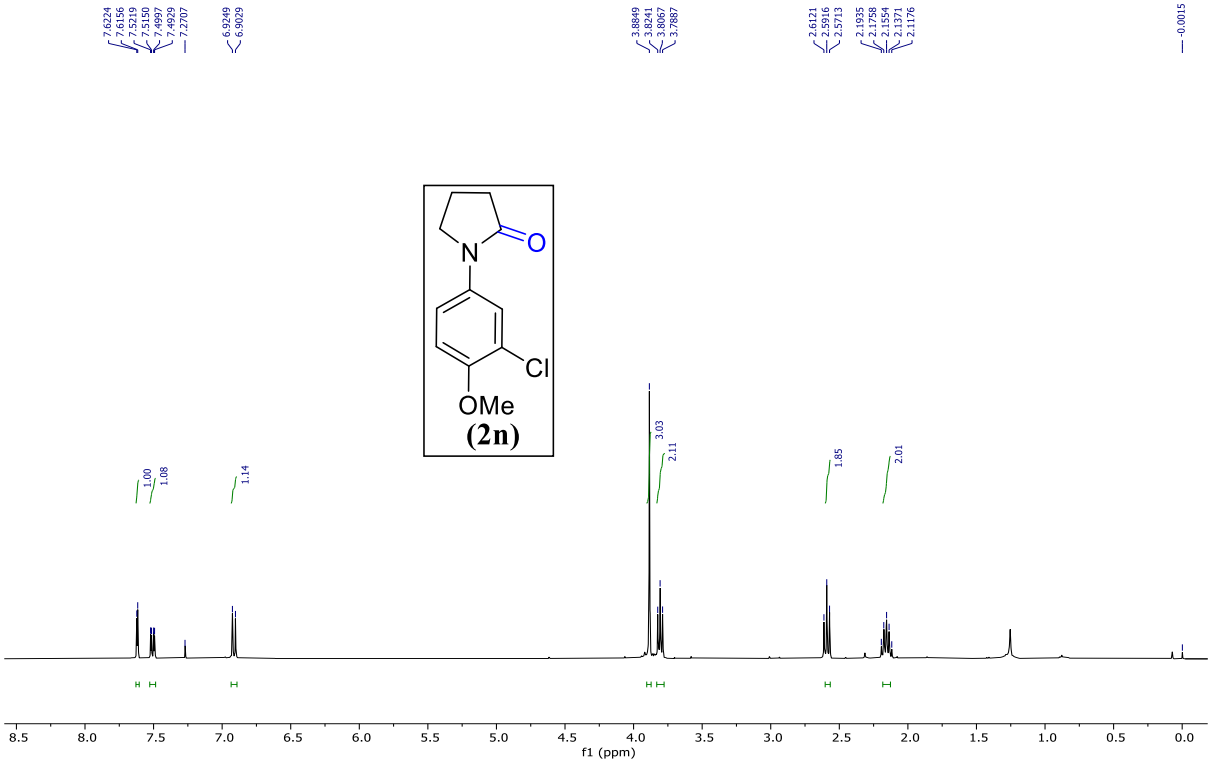
^{1}H NMR of 1-(3,4,5-trimethoxyphenyl) pyrrolidin-2-one **(2m)** in $CDCl_3$



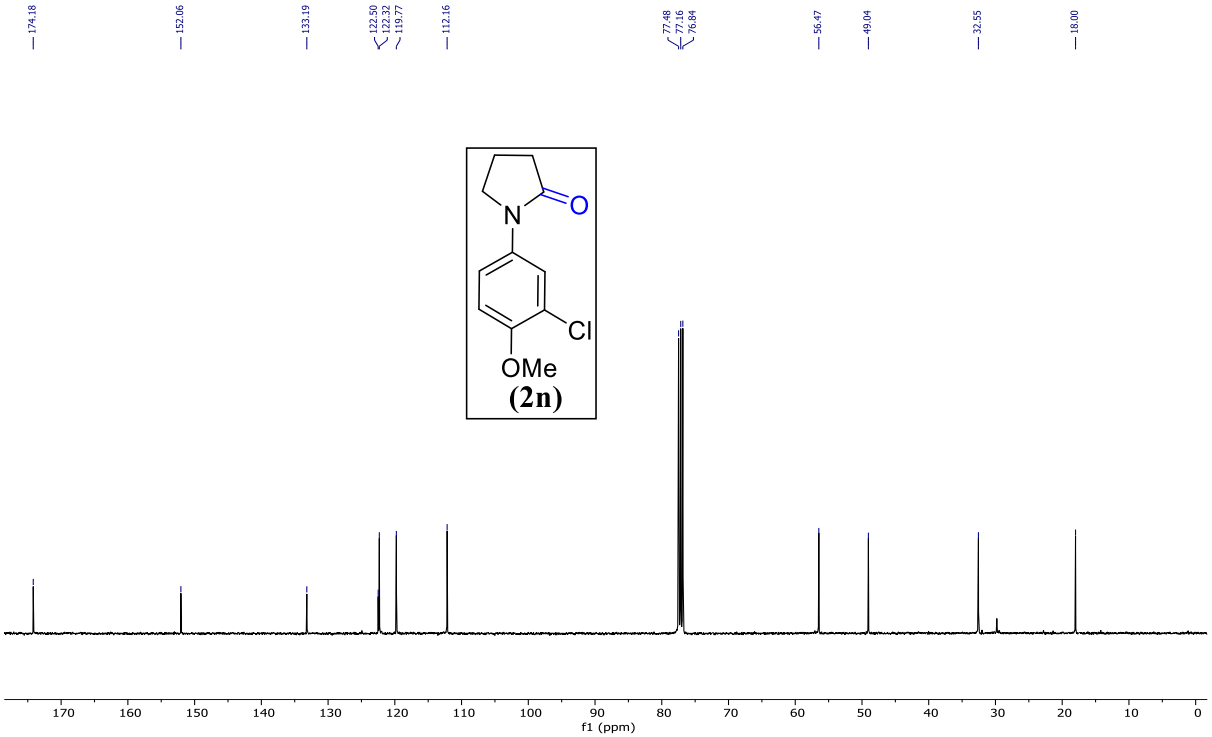
^{13}C NMR of 1-(3,4,5-trimethoxyphenyl) pyrrolidin-2-one **(2m)** in $CDCl_3$



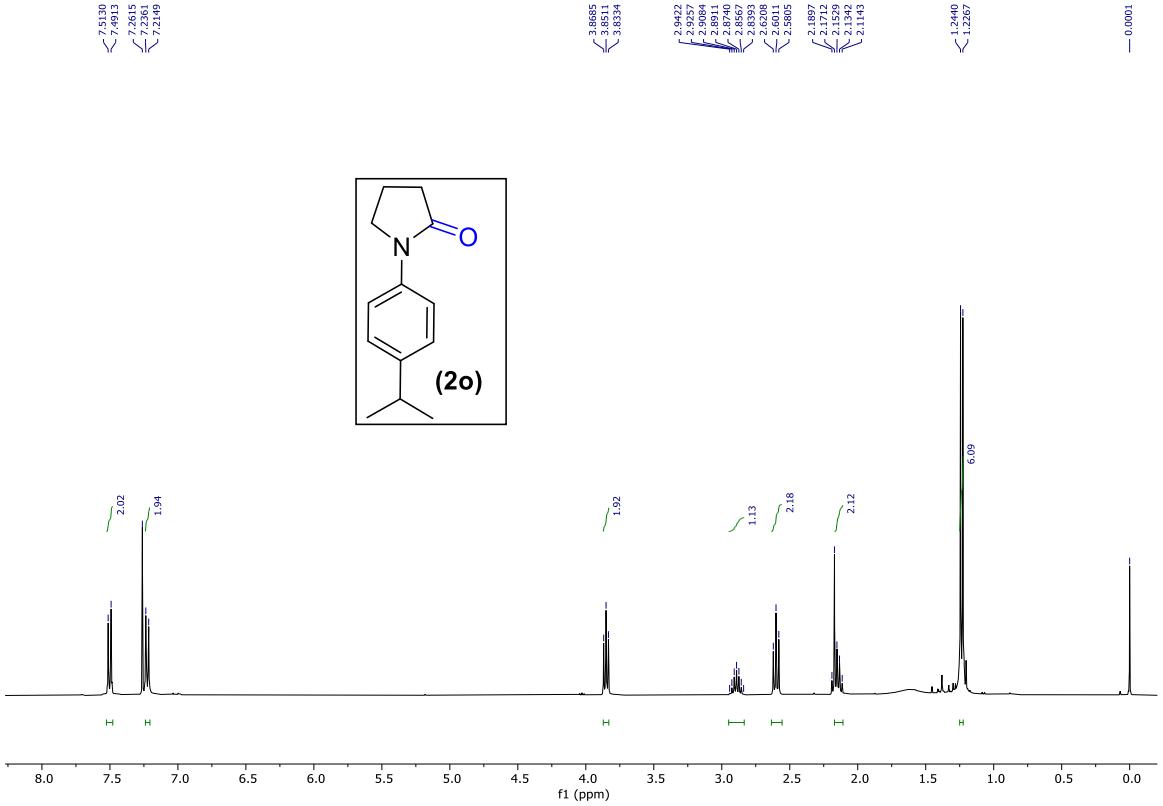
^{1}H NMR of 1-(3-chloro-4-methoxyphenyl) pyrrolidin-2-one **(2n)** in $CDCl_3$



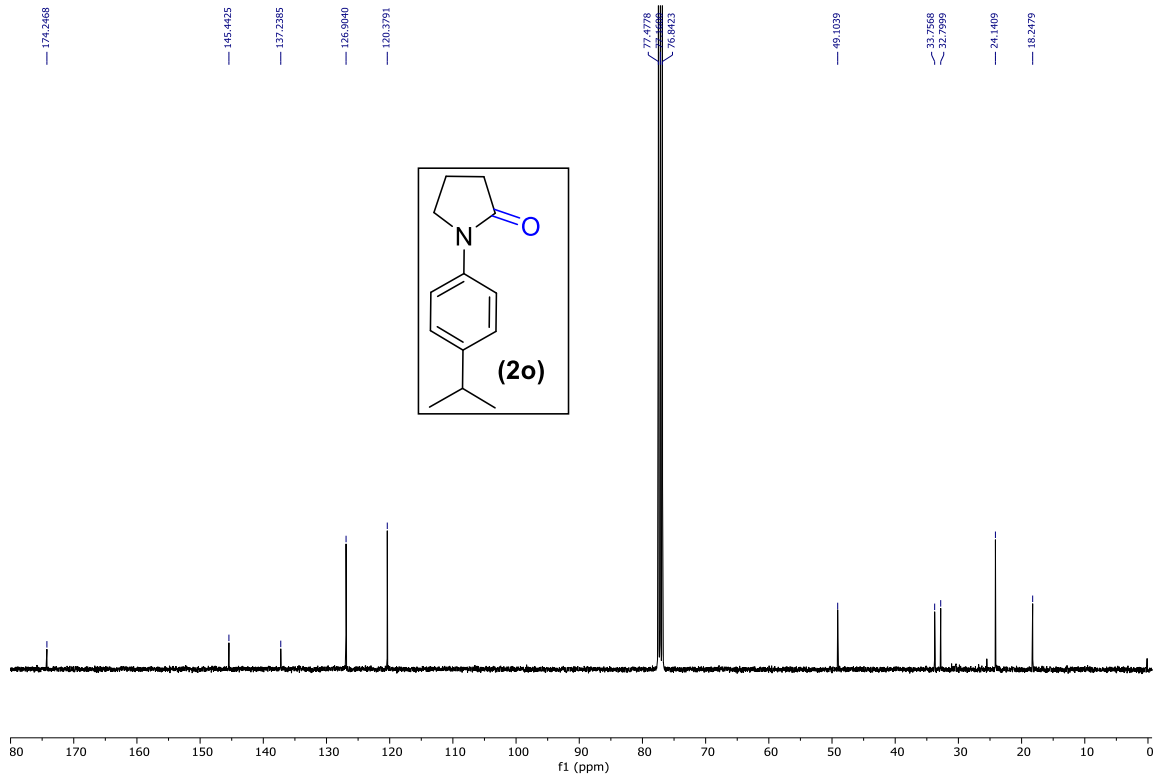
^{13}C NMR of 1-(3-chloro-4-methoxyphenyl) pyrrolidin-2-one **(2n)** in $CDCl_3$



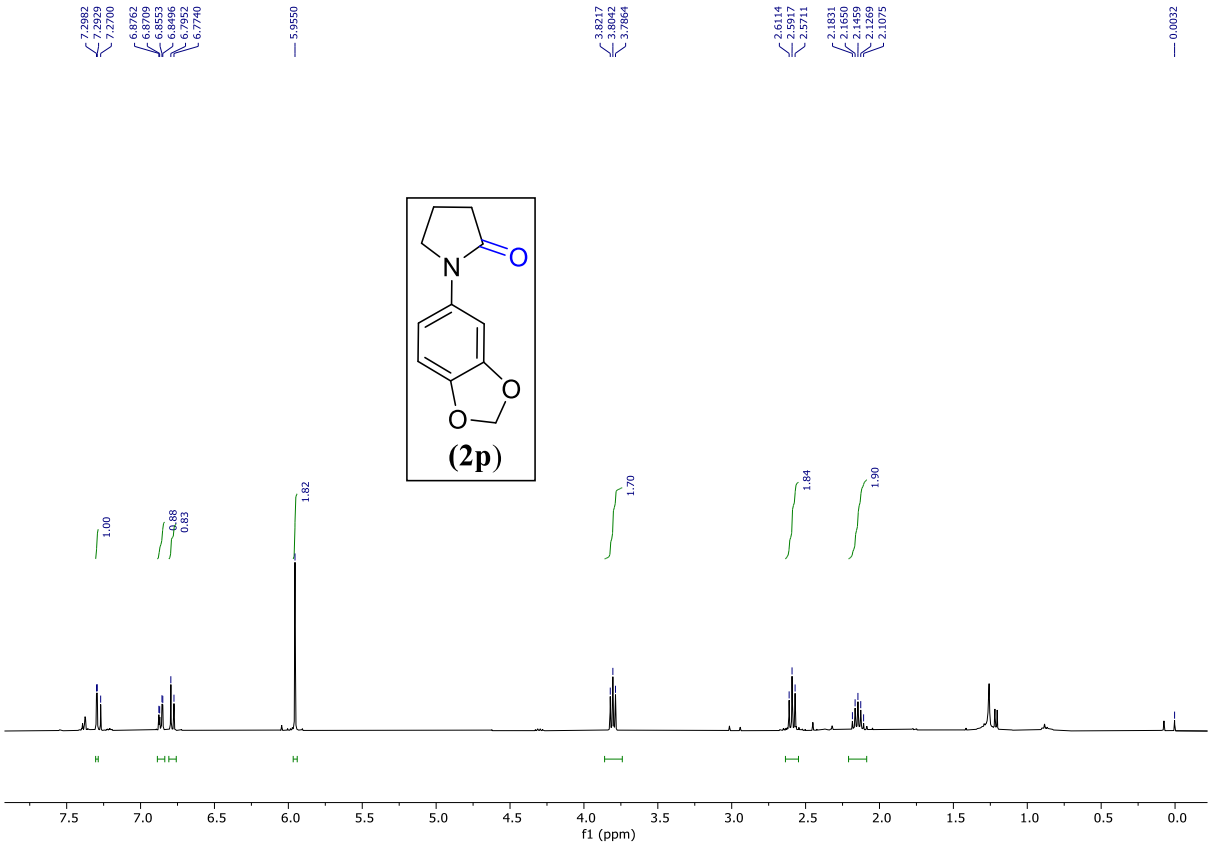
^{1}H NMR of 1-(4-isopropylphenyl) pyrrolidin-2-one **(2o)** in $CDCl_3$



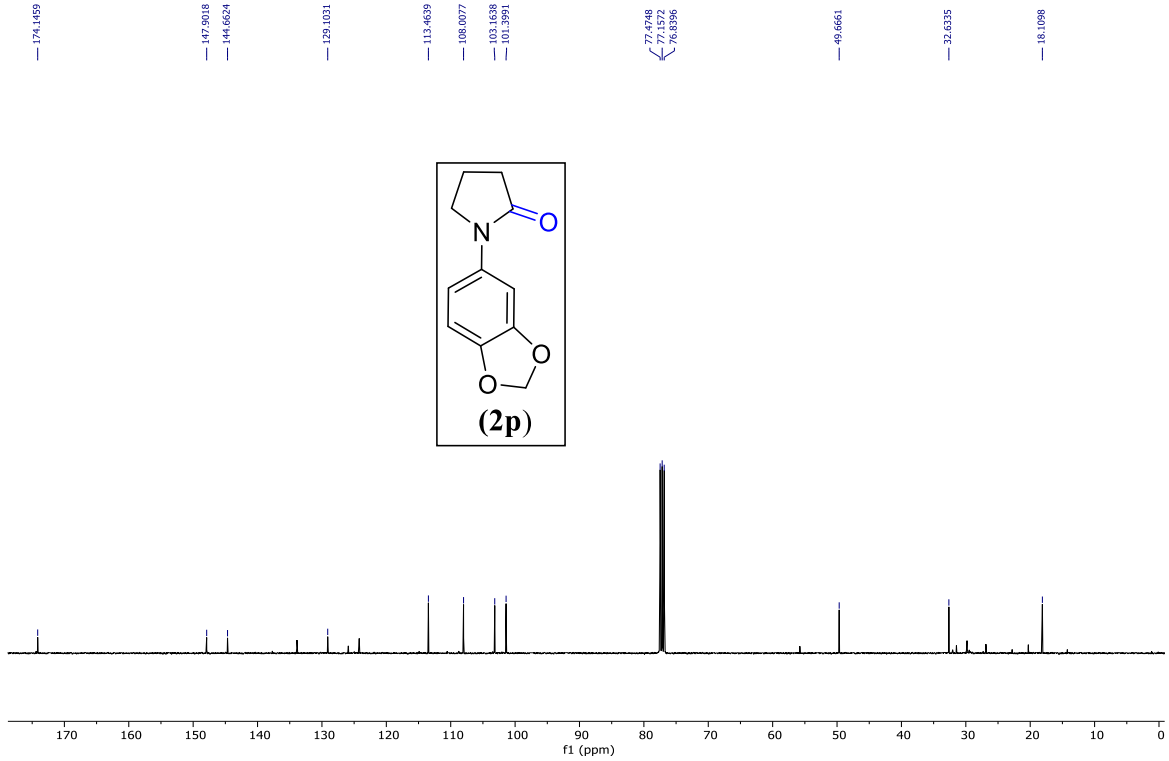
^{13}C NMR of 1-(4-isopropylphenyl) pyrrolidin-2-one **(2o)** in $CDCl_3$



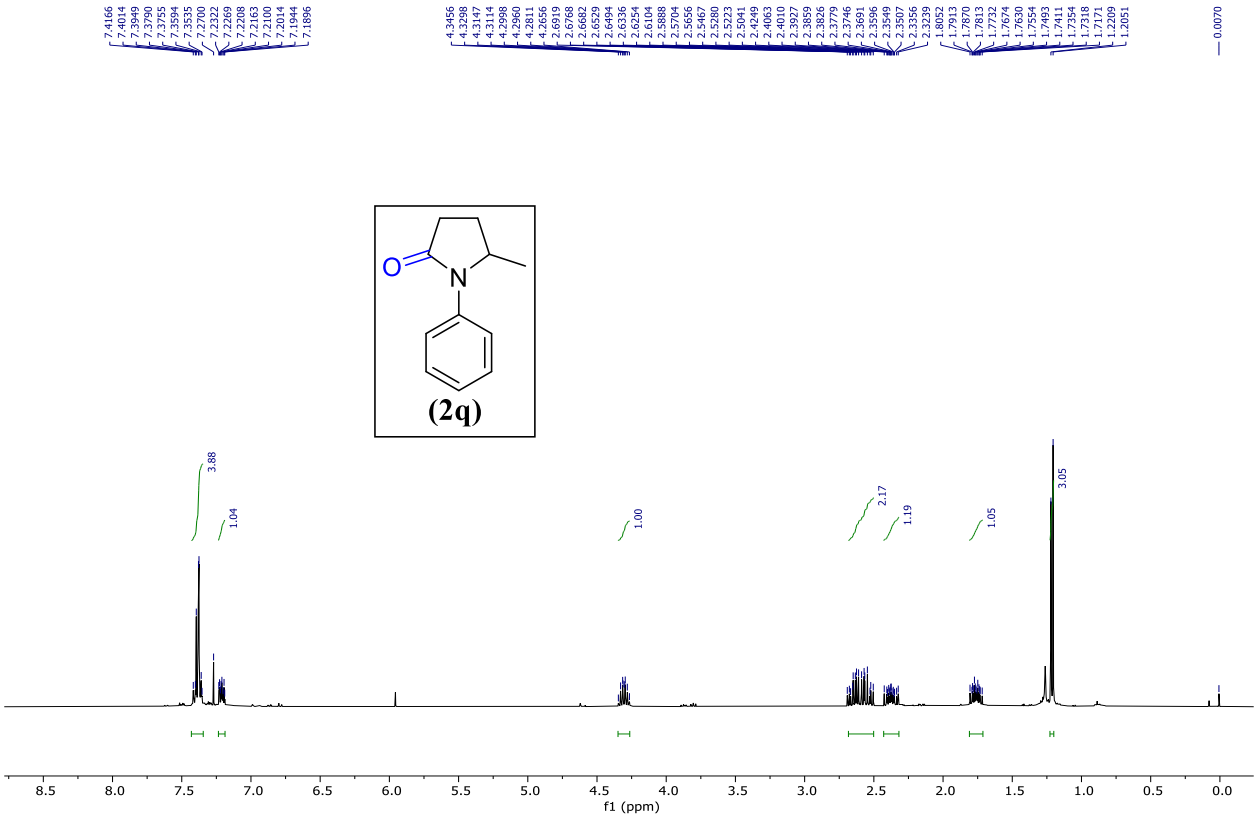
^{1}H NMR of 1-(benzo[d] [1,3] dioxol-5-yl) pyrrolidin-2-one **(2p)** in $CDCl_3$



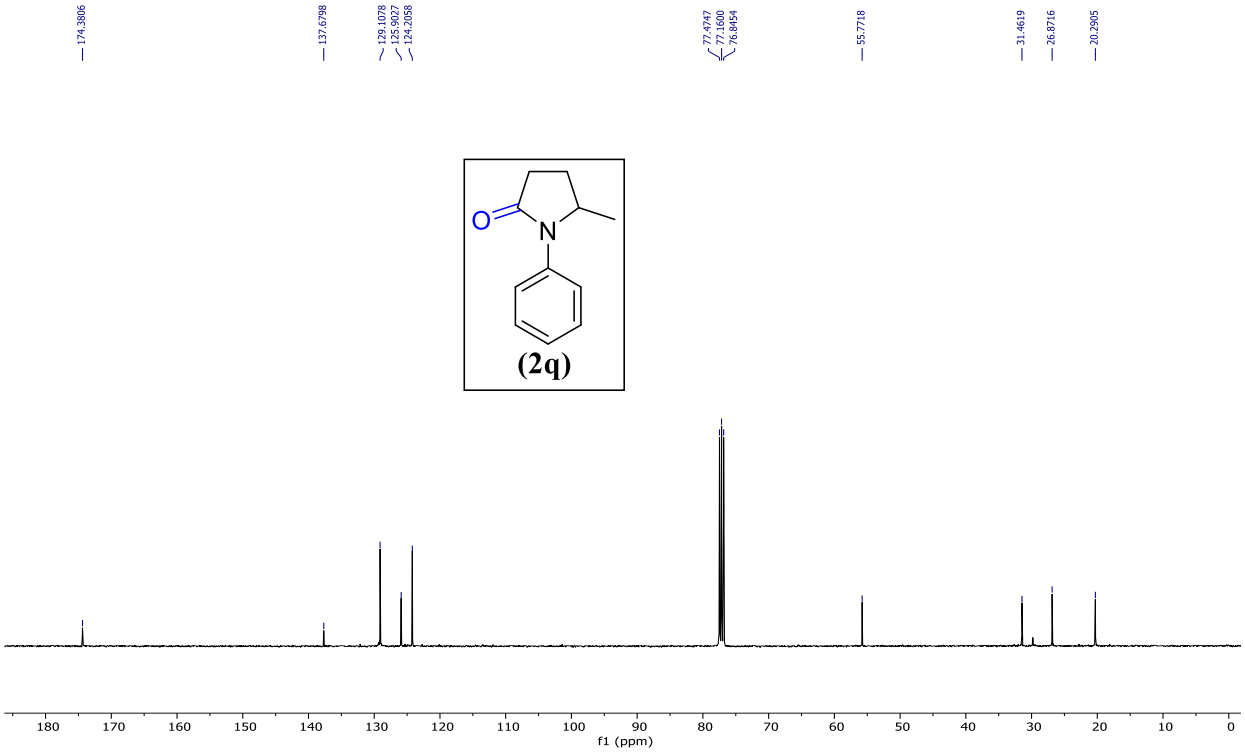
^{13}C NMR of 1-(benzo[d] [1,3] dioxol-5-yl) pyrrolidin-2-one **(2p)** in $CDCl_3$



^{1}H NMR of 5-methyl-1-phenylpyrrolidin-2-one **(2q)** in $CDCl_3$



^{13}C NMR of 5-methyl-1-phenylpyrrolidin-2-one **(2q)** in $CDCl_3$



3.10 References

1. Vitaku, E.; Smith, D.T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.
2. Caruano, J.; Mucciolib, G. G.;Robiette, R. *Org. Biomol. Chem.* **2016**, *14*, 10134.
3. Reddy, P. A.; Hsiang, B. C. H.; Latifi, T. N.; Hill, M. W.; Woodward, K. E.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem.* **1996**, *39*, 1898.
4. Kazmierski, W. M.; Andrews, W.; Furfine, E.; Spaltenstein, A.; Wright, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689.
5. Tang, K.; Zhang, J. T. *Neurol. Res.* **2002**, *24*, 473.
6. Barnes, D. M.; Wittenberger, S. J.; Zhang, J.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M. *J. Am. Chem. Soc.* **2002**, *124*, 13097.
7. Sterckx, H.; Morel, B.; Maes, B. U. W. *Angew. Chem. Int. Ed.* **2019**, *58*, 7946.
8. a) Goodreid, J. D.; Duspara, P. A.; Bosch, C.; Batey, R. A. *J. Org. Chem.* **2014**, *79*, 943. b) Chung, S.-W.; Uccello, D. P.; Choi, H.; Montgomery, J. I.; Chen, J. *Synlett* **2011**, *14*, 2072. c) Maehara, T.; Kanno, R.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2012**, *14*, 1946. d) Lanigan, R. M.; Starkov, P.; Sheppard, T. M. *J. Org. Chem.* **2013**, *78*, 4512. For reviews see, e) Lanigan, R. M.; Sheppard, T. M. *Eur. J. Org. Chem.* **2013**, *33*, 7453. f) Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. *Chem. Soc. Rev.* **2014**, *43*, 2714.
9. Riether, D.; Zindell, R.; Wu, L.; Betageri, R.; Jenkins, J. E.; Khor, S.; Berry, A. K.; Hickey, E. R.; Ermann, M.; Albrecht, C. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 581.
10. a) Scansetti, M.; Hu, X.; Mcdermott, B. P.; Lam, H. W. *Org. Lett.* **2007**, *9*, 2159. b) Isaacson, J.; Gilley, C. B.; Kobayashi, Y. *J. Org. Chem.* **2007**, *72*, 3913.
11. Vijayakumar, V.; Nagaraaj, P. *Org. Chem. Front.* **2019**, *6*, 2570.
12. Vaid, R. K.; Duncan, M. P.; Moriarty, R. M. *Tetrahedron Lett*. **1988**, *29*, 6913.
13. Khusnutdinova, J. R.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2014**, *136*, 2998.
14. Jin, X.; Kataoka, K.; Yatabe, T.; Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 7212.
15. Osorio-Nieto, U.; Chamorro-Arenas, D.; Quintero, L.; Hopfl, H.; Sartillo-Piscil, F. *J. Org. Chem.* **2016**, *81*, 8625.
16. Rong, H.-J.; Cheng, Y.-F.; Liu, F.-F.; Ren, S.-J.; Qu, J. *J. Org. Chem.* **2017**, *82*, 532.
17. Griffiths, R. J.; Burley, G. A.; Talbot, E. P. A. *Org. Lett.* **2017**, *19*, 870.
18. Huang, W.; Ma, B.-C.; Lu, H.; Li, R.; Wang, L.; Landfester, K.; Zhang, K. A. I. *ACS Catal*. **2017**, *7*, 5438.

19. Thatikonda, T.; Deepake, S. K.; Das, U. *Org. Lett.* **2019**, *21*, 2532.

20. Thatikonda, T.; Deepake, S. K.; Kumar, P.; Das, U. *Org. Biomol. Chem.* **2020**, *18*, 4046.

21. a) Finney, L. C.; Mitchell, L. J.; Moody, C. J. *Green Chem*. **2018**, *20*, 2242. b) Huang, W.; Ma, B.-C.; Lu, H.; Li, R.; Wang, L.; Landfester, K.; Zhang, K. A. I. *ACS Catal*. **2017**, *7*, 5438.

22. For the capture of molecular oxygen by dienolate species (a) Peixoto, P. A.; Jean, A.; Maddaluno, J.; De Paolis, M. *Angew. Chem. Int. Ed*. **2013**, *52*, 6971. (b) Peixoto, P. A.; Cormier, M.; Epane, J. E.; Jean, A.; Maddaluno, J.; De Paolis, M. *Org. Chem. Front.* **2014**, *1*, 748; For conversion of β-angelica lactone (**I'**) to dienolate (**I**) in presence of base, (c) Wang, X.-J.; Hong, M. *Angew. Chem. Int. Ed*. **2020**, *59*, 2664.

23. Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 11602.

ABSTRACT

Name of the Student: Mr. Siddharth K. Deepake **Registration No.: 10CC15J26015**
Faculty of Study: Chemical Science **Year of Submission: August 2020**
AcSIR CSIR Lab: CSIR-NCL **Name of the Supervisor(s): Dr. Utpal Das**

Title of the thesis: β, γ- Butenolides in Dual Role: As Vinylogous Nucleophile for Michael Initiated Synthesis of Indanol Derivatives and as Organocatalyst for the α-CH_2 Oxygenation of Cyclic Amines/Ethers

- **Chapter I:** In this chapter, efficient chemo-, diastereo- and enantio-selective organocatalytic cascade reaction of various γ-substituted deconjugated butenolides with *o*-formyl-β-nitrostyrene to furnish functionally rich chiral indanol derivatives bearing four contiguous stereogenic centers in the presence of bi-functional hydrogen-bonding catalyst are described. The indanol derivatives were obtained with good yields and moderate to high enantioselectivities.

- **Chapter II: Section A:** This section includes the development of a new method for the direct oxidation of various *N*-aryl tetrahydroisoquinolines and isoindolines to the corresponding lactams employing α-angelica lactone as a catalyst. The utility of this protocol was also further extended by the synthesis of indoprofen and indobufen.

- **Chapter II: Section B:** We present here a metal-free organocatalytic system for the development of highly efficient benzylic C–H oxygenation of isochromans and phthalans by employing a kinetically poor but environmentally benign oxidant such as oxygen. It is worth noting that, this persuasive reaction utilizes a low cost and low molecular weight α-angelica lactone as a catalyst. This system allows the synthesis of valued isocoumarins and phthalides from the easily available precursors under 'easy to perform' reaction conditions in good yields. Mechanistic studies indicate that the reaction follows a radical pathway and involves peroxide intermediate.

- **Chapter III:** α- Angelica lactone was employed as an organocatalyst for the development of a highly efficient method for the α-CH_2 oxygenation of *N*-aryl pyrrolidines to the corresponding γ-lactams in presence of O_2 as a green oxidant. This catalytic system allows the synthesis of a library of valued γ-lactams in good to excellent chemical yields.

List of Publication

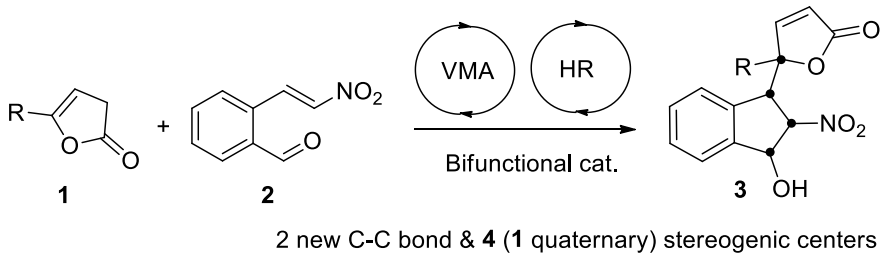
1) "Organocatalytic Asymmetric Cascade Reaction of γ-Substituted Deconjugated Butenolides with *o*-Formyl-β-nitrostyrene". **Siddharth K. Deepake**, Atul B. Lanjewar, Thanusha Thatikonda, Rajesh G. Gonnade and Utpal Das* *ChemistrySelect* **2018**, *3*, 8189-8192.

2) "α-Angelica Lactone in a New Role: Facile Access to *N*-Aryl Tetrahydroisoquinolinones and Isoindolinones via Organocatalytic α-CH_2 Oxygenation". Thanusha Thatikonda, **Siddharth K. Deepake** and Utpal Das* *Org. Lett.* **2019**, *21*, 2532-2535.

3) "α-Angelica Lactone Catalyzed Oxidation of Benzylic sp^3 C−H Bonds of Isochromans and Phthalans". Thanusha Thatikonda[#], **Siddharth K. Deepake[#]**, Pawan Kumar and Utpal Das* *Org. Biomol. Chem.* **2020**, *18*, 4046-4050. ([#]Equal contribution).

4) "Oxidation of Pyrrolidine Derivatives to Corresponding Lactams by Using α-Angelica Lactone as an Organocatalyst". **Siddharth K. Deepake**, Manish Kumar and Utpal Das* (Manuscript under preparation).

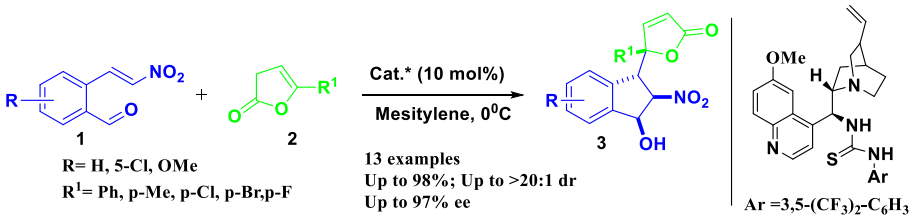
- Participated and poster presentation at "Contemporary Facts in Organic Synthesis" held at IIT Roorkee, during December 22-24, 2017.
  Title: **Regioselective Addition of Deconjugated β, γ-Butenolides to O-Benzaldehyde Nitroolefins**



Abstract: "Catalytic enantioselective synthesis of indanol derivatives bearing four continuous stereocenters along with one quaternary stereocenter using Quinine derived thio-urea catalyst (10 mol%) is described. The corresponding products were obtained in good yield (upto 98%), diastereoselectivity (upto 20:1) and enantioselectivity (upto 97%)."

- Participated and oral presentation at "Annual Student Conference" held at NCL-RF, CSIR-NCL, Pune during November 29-30, 2018.

Title: **Organocatalytic asymmetric cascade reaction of γ-substituted deconjugated butenolides with *o*-formyl-β-nitrostyrene**



Abstract: "An efficient chemo-, diastereo- and enantio-selective cascade synthesis of functionalized indanols bearing four continuous stereogenic centers has been developed via reaction of β, γ-butenolides with o-formyl-β-nitrostyrenes in the presence of bi-functional hydrogen-bonding catalyst. Indanol derivatives containing γ, γ-disubstituted butenolides were obtained in good yields."

Published paper: "Organocatalytic Asymmetric Cascade Reaction of **γ**-Substituted Deconjugated Butenolides with *o*-Formyl-β-nitrostyrene". **Siddharth K. Deepake**, Atul B. Lanjewar, Thanusha Thatikonda, Rajesh G. Gonnade and Utpal Das* *ChemistrySelect* **2018**, *3*, 8189-8192.

ChemPubSoc Europe

DOI: 10.1002/slct.201801467

Chemistry SELECT Communications

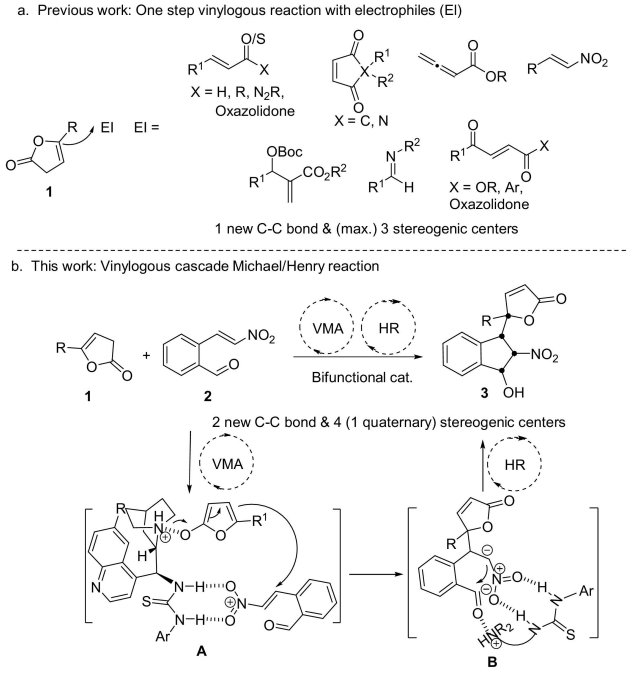
Organic & Supramolecular Chemistry

Organocatalytic Asymmetric Cascade Reaction of γ-Substituted Deconjugated Butenolides with *o*-Formyl-β-nitrostyrene

Siddharth K. Deepake,[a, b] Atul B. Lanjewar,[a] Thanusha Thatikonda,[a] Rajesh G. Gonnade,[b, c] and Utpal Das*[a, b]

An efficient chemo-, diastereo- and enantio-selective cascade synthesis of functionalized indanols bearing four contiguous stereogenic centres has been developed *via* the reaction of β,γ-butenolides with *o*-formyl-β-nitrostyrenes in the presence of bi-functional hydrogen-bonding catalyst. Indanol derivatives containing γ,γ-disubstituted butenolides were obtained in good yields and with moderate to high enantioselectivities/ diastereoselectivities.

Widespread presence of butenolides and lactones in organic compounds (~10% of natural products)[1] has attracted considerable attention from the synthetic community for the synthesis of these structural units, especially by employing environmentally benign asymmetric catalysis.[2] In this regard much attention has been paid for the preformed silyloxyfurans after MacMillan and co-workers report in 2003[3] *via* catalytic asymmetric Mukaiyama type aldol & Michael reactions.[2,4] Surprisingly, the use of γ-substituted butenolides as pronucleophiles for functionalization at the γ-position *via* vinylogous Michael addition has received relatively late attention although it can deliver a quaternary stereogenic center with step- and atom-economy. The reason could be its less reactivity imposed by additional steric bulk and challenges associated with enantioselective creation of quaternary stereogenic center.[5] The first breakthrough came in 2010 by Chen and co-workersfor direct asymmetric allylic alkylation of deconjugated γ-substituted butenolides with Morita – Baylis – Hillman carbonates.[6] Afterwards, several asymmetric Michael- and Mannich-type reactions with γ-substituted deconjugated butenolides have been well documented.[7] Direct vinylogous Michael and related addition reactions occupy a significant proportion of the literature reports (Scheme 1a). But γ-substituted butenolides have never been employed towards cascade reactions[8]



Scheme 1. Vinylogous addition of γ-substituted butenolides.

which is triggered by a γ-regioselective vinylogous Michael reaction. Hence, development of an efficient protocol for this transformation is highly desirable.

Herein, we describe a chemoselective cascade approach to build (nitro)indanol scaffold using vinylogous Michael addition of γ-substituted deconjugated butenolides to *o*-formyl-β-nitrostyrenes. It is mention worthy, that indanol is a valuable backbone in many chiral catalysts and also used as a building block (such as Crixivan and rasagiline derivatives).[9,10]

We envisaged that combination of γ-substituted butenolides and *o*-formyl-β-nitrostyrenes will constitute an unprecedented cascade protocol. Racemic synthesis of indane derivatives *via* cascade reactions are documented in the literature.[11] Again, dealing with two competing acceptor sites (nitroolefin and aldehyde)[12] in a compound (**2**) is another challenging

[a] *S. K. Deepake, A. B. Lanjewar, Dr. T. Thatikonda, Prof. U. Das*
Division of Organic Chemistry, CSIR – National Chemical Laboratory, Pune 411008, India
E-mail: u.das@ncl.res.in
[b] *S. K. Deepake, Prof. R. G. Gonnade, Prof. U. Das*
Academy of Scientific and Innovative Research (AcSIR), New Delhi 110020, India
[c] *Prof. R. G. Gonnade*
Centre for Materials Characterization, CSIR – National Chemical Laboratory

Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.201801467

OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 2532−2535

pubs.acs.org/OrgLett

α-Angelica Lactone in a New Role: Facile Access to *N*-Aryl Tetrahydroisoquinolinones and Isoindolinones via Organocatalytic α-CH_2 Oxygenation

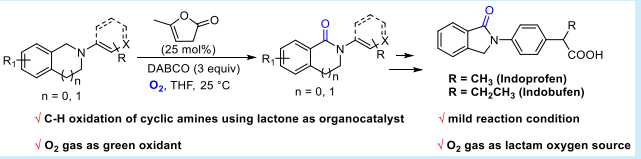
Thanusha Thatikonda,[†] Siddharth K. Deepake,[†,‡] and Utpal Das*[,†,‡]

[†]Division of Organic Chemistry, CSIR − National Chemical Laboratory, Pune 411008, India

[‡]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India

Supporting Information

ABSTRACT: A method for the direct oxidation of various *N*-aryl tetrahydroisoquinolines and isoindolines to the corresponding lactams using α-angelica lactone as a catalyst was developed. The utility of the method was further demonstrated by synthesis of indoprofen and indobufen.



The lactam moiety has attracted particular interest in the chemical community because it is present in a myriad of natural products and clinically approved medicinal agents.[1] A number of natural products with biological activities and synthetic pharmaceutical compounds containing an isoquinolinone/isoindolinone scaffold are known (Figure 1).

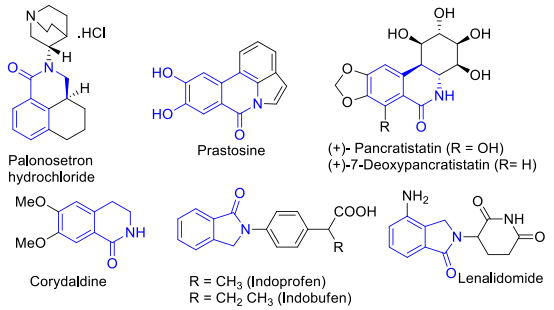
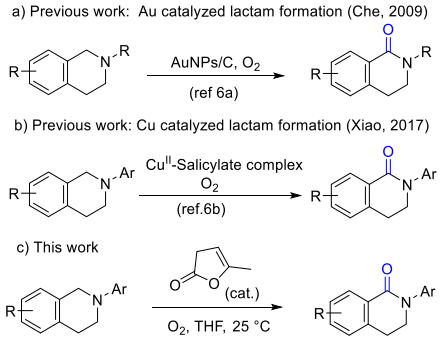


Figure 1. Bioactive natural products and pharmaceuticals containing an isoquinolinone and isoindolinone scaffold.

Consequently, development of an efficient catalytic method to synthesize compounds containing a isoquinolinone or isoindolinone core in a direct and cost-effective manner is of huge importance. A straightforward method for the synthesis of the isoquinolinone/isoindolinone core would be direct oxygenation of the α-methylene group of isoquinoline/isoindoline derivatives. However, selective oxidations of the α-methylene group of amines to amides are notoriously challenging because of the higher reactivity of the amines in comparison to that of the α-methylene carbon.[2] In general, α-oxygenation of amines requires a stoichiometric amount of organic or metal peroxides as oxidant and use of transition-metal-based catalysts.[3] Recently, gold nanoparticles supported on alumina (Au/Al_2O_3) were developed for the catalytic oxidation of cyclic and acyclic amines to the corresponding lactams and amides.[4] However, the reaction requires use of an air-sensitive catalyst, multistep synthesis of catalysts, high reaction temperature, and longer reaction periods. Formations of dihydroisoquinolinone via cross-dehydrogenative coupling reactions are well-known but only as a byproduct.[5] Very recently, oxidation of *N*-alkyl tetrahydroisoquinolines to the corresponding lactams using gold nanoparticles (Scheme 1a) and

Scheme 1. Lactam Formation via C−H Oxidation of Cyclic Amines



a copper−salicylate complex (Scheme 1b) as catalyst in the presence of either *t*-BuOOH or oxygen as oxidant was reported.[6] This process looks attractive, but in many cases, the reaction requires higher temperature and longer reaction periods. 9*H*-Fluoren-9-imine offers an alternative to metal catalysts; however, the substrate scope is limited by the requirement of a stoichiometric amount of fluorenimine along with reflux temperature.[7a] During the preparation of this paper, Das group reported α-oxygenation of tertiary and secondary amines by visible light using Rose Bengal as catalyst.[7b] Consequently, the ACS GCI pharmaceutical roundtable identified "amide formation avoiding poor atom economy reagents" as the most desired green chemistry research area and organocatalysis as one of the "more

Received: January 21, 2019
Published: April 2, 2019

DOI: 10.1021/acs.orglett.9b00224
Org. Lett. 2019, 21, 2532−2535

Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2020, **18**, 4046

α-Angelica lactone catalyzed oxidation of benzylic sp^3 C–H bonds of isochromans and phthalans†

Thanusha Thatikonda,‡[a] Siddharth K. Deepake,‡[a,b] Pawan Kumar[a,b] and Utpal Das *[a,b]

Received 7th April 2020,
Accepted 9th May 2020

DOI: 10.1039/d0ob00729c

rsc.li/obc

A metal-free organocatalytic system has been developed for highly efficient benzylic C–H oxygenations of cyclic ethers using oxygen as an oxidant. This oxidation reaction utilizes α-angelica lactone as a low cost/low molecular weight catalyst. The optimized reaction conditions allow the synthesis of valued isocoumarins and phthalides from readily available precursors in good yields. Mechanistic studies indicate that the reaction pathway likely involves a radical process *via* a peroxide intermediate.

Introduction

Isocoumarin and phthalide derived scaffolds are frequently encountered in many natural products and drug molecules that possess a broad range of biological activities (Fig. 1).[1] Given the immense applications and significance of these compounds, a challenging study of interest is the development of a concise and efficient method to synthesize these oxygen-containing heterocyclic compounds. Direct oxidation of benzylic sp^3 C–H bonds of isochromans and phthalans is one of the most effective means to enable expeditious synthesis due to the high step economy and synthetic efficiency. Traditionally, oxidation of benzylic sp^3 C–H bonds is performed by using metal oxides of chromium.[2] Since chromium is toxic in nature, transition-metal catalysts using oxygen or peroxides as the oxidant were developed. The metal catalysts for the oxidation of the benzylic sp^3 C–H bond include copper,[3] cobalt,[4] rhodium,[5] manganese[6] and iron.[7] Among them, an iron catalyst containing a chiral pyridine bissulfonylimidazole ligand is worthy of mention although it experiences low conversion.[7c] The use of photoredox methods[8] and a strong base in the presence of oxygen is also known for benzylic oxidation which avoid metals.[9] Recently, the application of a TEMPO derived sulfonic salt catalyst and mineral acids for the aerobic oxidation of benzylic sp^3 C–H bonds of ethers and alkylarenes (Scheme 1a) has been reported.[10] DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as a catalyst in the

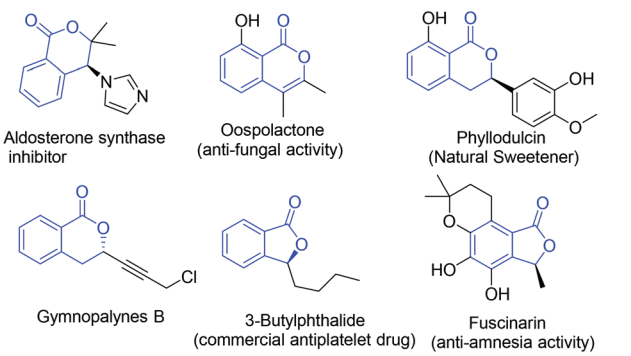
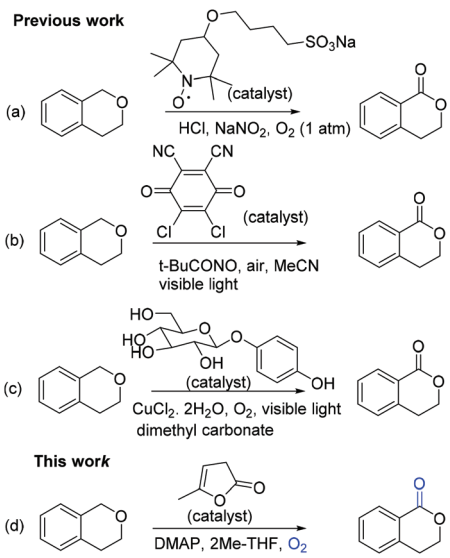


Fig. 1 Selected examples of natural products and drugs containing an isocoumarin and phthalide core structure.



Scheme 1 C–H oxidation of isochromans.

[a]*Division of Organic Chemistry, CSIR – National Chemical Laboratory, Pune 411008, India. E-mail: u.das@ncl.res.in*
[b]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*
†Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ob00729c
‡These authors contributed equally.

Erratum