SYNTHESIS OF POTENT ORGANIC ASSEMBLIES THROUGH MULTICOMPONENT REACTIONS

Ph.D. THESIS

by

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ROORKEE-247 667 (INDIA)
JUNE, 2019

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A THESIS

Submitted in partial fulfilment of the requirements for the award of the degree

of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

by

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ROORKEE

CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **"SYNTHESIS OF POTENT ORGANIC ASSEMBLIES THROUGH MULTICOMPONENT REACTIONS"** in partial fulfilment of the requirements for the award of the Degree of Doctor of Philosophy and submitted in the Department of Chemistry of the Indian Institute of Technology Roorkee, Roorkee is an authentic record of my own work carried out during a period from July, 2014 to June, 2019 under the supervision of Dr. Anuj Sharma, Associate Professor, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other Institution.

(SOURAV BAGCHI)

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

(Anuj Sharma)
Supervisor

The Ph.D. Viva-Voce Examination of **Mr. Sourav Bagchi**, Research Scholar, has been held on ……..

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Signature of Supervisor **Head of the Department**

Dated: …….


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PARENTS

ABSTRACT OF THE THESIS

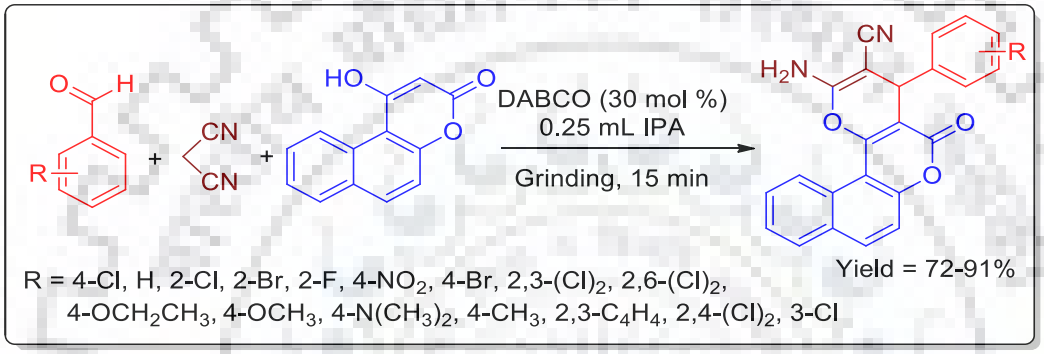
CHAPTER-1

Heterocycles containing N, O and S atoms in the ring, generally show promising biological applications. Synthesis of diversified heterocycles are in high demand due to their wide applications. To fulfill the ongoing demand, the main role of a chemist is to supply novel heterocycles which can be further screened to find out their biological and pharmaceutical applications. Multicomponent reactions (MCRs) are turned up to be an efficient synthetic strategy to deliver such structural diverse scaffolds in time and help building up chemical libraries with larger scope. MCRs are recognized as the chemical transformations of more than two components mainly operated in one-pot to construct the desired products. The MCR strategy has several advantages like operational simplicity, higher atom efficiency and diverse scaffolds generation in short reaction time over single step operation. Several tools and techniques are used to develop a MCR protocol however application of mechanochemical hand-grinding and microwave irradiation in developing new MCRs strategies are presented in this chapter to synthesize functionalized heterocycles. Amongst heterocycles, pyrans and spirooxindoles are worth mentioning due to their wide range of biological and medicinal activities. The chapter also includes a brief description of biological importance and several synthesis procedures of pyrans and spirooxindoles. In short, the background of the present research work is highlighted in this chapter. However, the previous literature survey revealed that there is still scope not only in synthesizing novel biologically relevant heterocycles but also in developing greener and efficient methodologies to access diversified scaffolds. Thus, the presented work is focused on developing efficient green synthetic protocols for synthesis of structurally diverse heterocycles like pyrans, spirooxindoles, bis(benzo[*f*]chromen-3-one), acridione, thioxanthendione, bis(hydroxycyclohex-2-enone), tetrahydroquinazolindione derivatives.

CHAPTER-2

DABCO-Catalysed Green Synthetic Protocol for Novel Pyranochromenone Derivatives

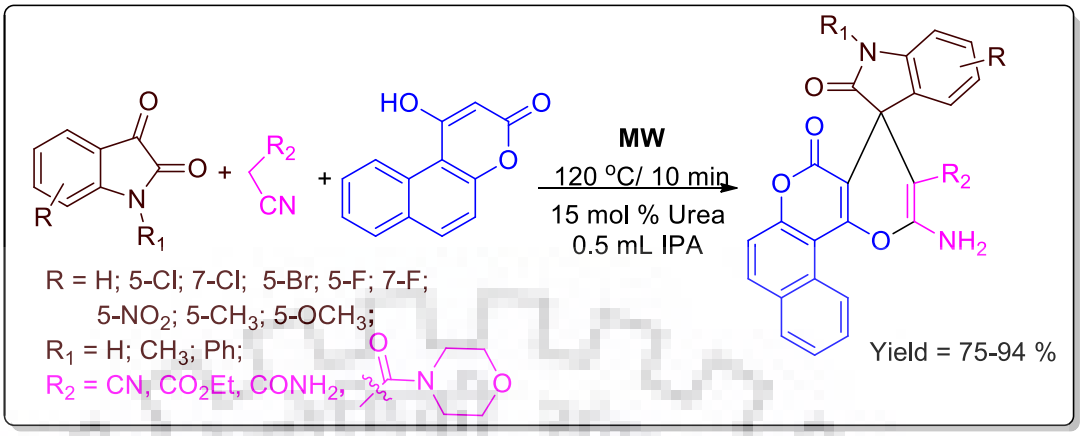
In this chapter, DABCO-catalysed liquid-assisted grinding for the synthesis of novel dihydrobenzo[*f*]pyrano[3,2-*c*]chromenone derivatives has been described. The reported methodology is simple, facile and mild to construct such multicomponent cascade. The benefits of developed one-pot protocol includes diversified scope, excellent yields and high reaction throughput apart from excellent green matrices scores.



CHAPTER-3

Urea-Catalysed Microwave-Assisted Synthesis of Novel Spirooxindole Benzopyrans

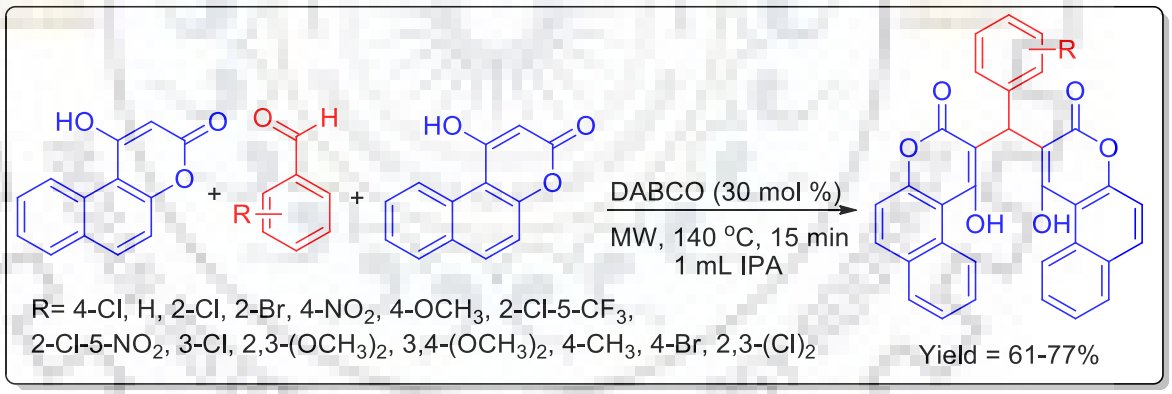
In this chapter, a urea-catalysed easy and facile microwave-assisted protocol is described to construct spiro-benzo[*f*]pyranochromenes in higher yields. The use of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one as a key reactant in such three-component reaction is reported for the first time to provide such novel multicomponent cascade. The superiority of the reported methodology is the operational simplicity, diversified scope and gram scale synthesis along with very good green matrices scores which highlights the synthesis protocol for industry as well.



CHAPTER-4

Diversity Oriented Synthesis of Bis(benzochromenone) Derivatives

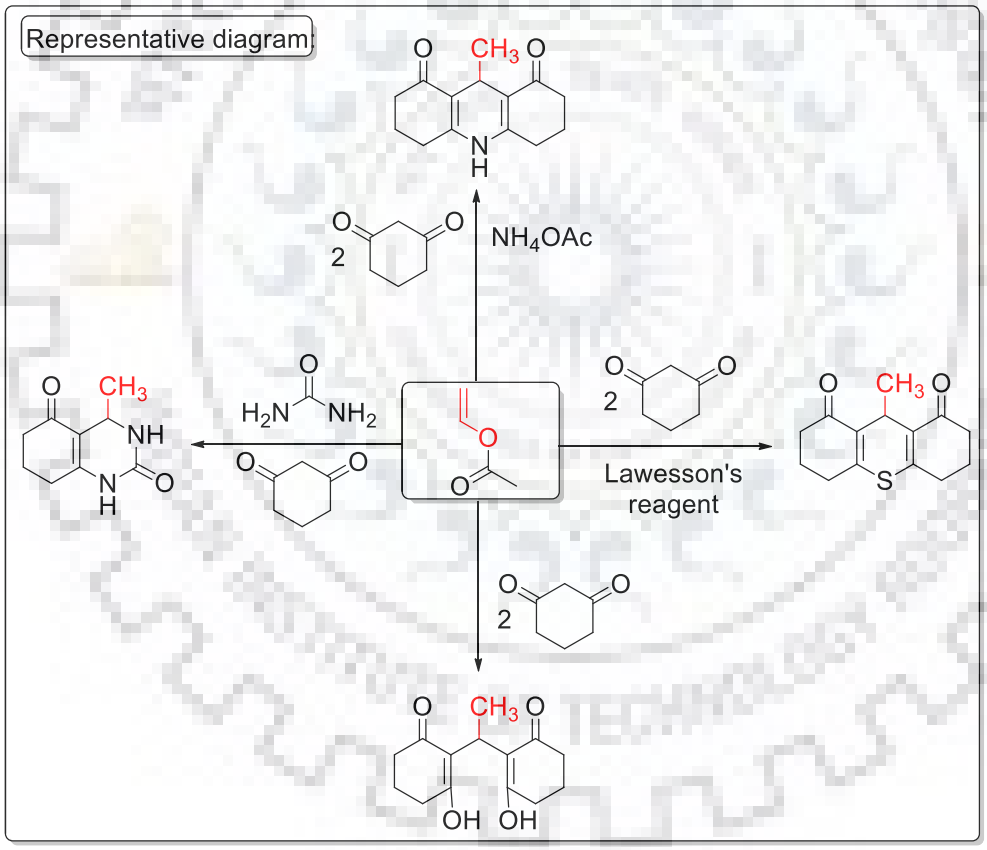
In this chapter, microwave-assisted DABCO-catalysed synthesis of bis(benzo[*f*]chromen-3-one) derivatives are reported. The advantages of the methods is the column free efficient synthesis and mere filtration provides good to excellent yield without using any harsh reagent.



CHAPTER-5

Chemistry of Vinyl Esters as Acetaldehyde Surrogates in Some Common Multicomponent Reactions

In this chapter, the applications of vinyl esters as acetaldehyde surrogates in different well-known multicomponent reaction are reported. Use of acetaldehyde is limited in synthetic chemistry due to self-polymerizations or lower stability. In this report, the effective utilization of vinyl esters as acetaldehyde surrogates in different conditions are explored efficiently to obtain biologically potent scaffolds. The reported methodology is quite successful to formulate different derivatives like acridione, thioxanthendione, bis(hydroxycyclohex-2-enone), tetrahydroquinazolindione in moderate to good yield.



ACKNOWLEDGEMENT

With great pleasure, I would like to convey my sincere gratitude to my research advisor **Dr. Anuj Sharma** (Associate Professor, Department of Chemistry, IIT Roorkee) for his precious suggestions and giving me an opportunity to do research and also providing me valuable guidance during this work. His vision towards solving problems, dynamism, sincerity and motivational words have deeply inspired me. His sincere advice to resolve a problem and scientific approach have helped me to accomplish this task. I am extremely grateful for what he had offered me during my projects and also thankful for always standing by me throughout this period.

In continuation, I would like to express my acknowledgement to my Student Research Committee (SRC) members **Prof. Bina Gupta** and **Dr. M. Sankar**, Department of Chemistry and **Dr. R. Pathania**, Department of Biotechnology, IIT Roorkee for extending me all possible helps and valuable suggestions during the course work.

I owe a deep sense of gratitude to **Prof. K. R. J. Thomas**, Head of the Chemistry Department and Department of Chemistry and also Institute Instrumentation Center (IIC) for providing me necessary facilities to carry out my research work.

I am thankful to Mr. D. C. Meena, Mr. Anuj, Mr. Charan Singh and Mr. Madan Pal for serving with NMR, GC-MS, IR and CHNS and also Mr. S. P. Singh, Mr. Ankur, Mr. Tiwari and other staff members, Department of Chemistry, for giving me a helping hand on all occasions.

I am really grateful to the Editors and Reviewers for their valuable comments/suggestions during publishing manuscripts.

Most importantly, I am gratefully acknowledge to the Ministry of Human Resource Development (**MHRD**), Government of India for providing me financial assistance in the form of junior/senior research scholarship to carry out my research work during this period.

I am heartily thankful to my senior **Dr. Manoj Kumar** for his constant support and help throughout my work. I would like to thank **Dr. T. Kaur**, **Dr. Preeti**, **Dr. D. Saha**, **A. Moonga** and **A. K. S. Hussen** for giving me a chance to work with them during the period. I am also thankful to my other lab-members Dr. Shivani, Amar, Sehdev, Nihal, Anoop, Barkha, Jaya for providing a friendly environment in the lab. I am extending my thanks to **Deeksha** and **Sagar** for working with me during my projects and my friends Pabhel, Ankur, Neetu and Farhan to stay beside me whenever I needed.

I am extremely grateful to my parents **Late Susanta Kumar Bagchi** and **Panchali Bagchi** and my dearest younger brother **Soumendu Bagchi** for their love, prayers, care and sacrifices for educating and preparing me for my future. They are the most important people in my world and I would like to dedicate this thesis to them. I would like to take this opportunity to thank Ms. Susmita Roy for constant support throughout the period.

Finally, I am thankful to almighty GOD, for his mercy and blessing upon me during my education.

Sourav Bagchi

TABLE OF CONTENTS **Page No.**

CHAPTER-3: Urea-catalysed microwave-assisted synthesis of novel spirooxindole benzopyrans

CHAPTER-4: Diversity oriented synthesis of bis(benzochromenone) derivatives

CHAPTER-5: Chemistry of vinyl esters as acetaldehyde surrogates in some common multicomponent reactions

LIST OF FIGURES **Page No.**

CHAPTER-1: Introduction

CHAPTER-2: DABCO-catalysed green synthetic protocol for novel pyranochromenone derivatives

CHAPTER-3: Urea-catalysed microwave-assisted synthesis of novel spirooxindole benzopyrans

CHAPTER-4: Diversity oriented synthesis of bis(benzochromenone) derivatives

CHAPTER-5: Chemistry of vinyl esters as acetaldehyde surrogates in some common multicomponent reactions

LIST OF SCHEMES

CHAPTER-2: DABCO-catalysed green synthetic protocol for novel pyranochromenone derivatives

CHAPTER-3: Urea-catalysed microwave-assisted synthesis of novel spirooxindole benzopyrans

CHAPTER-4: Diversity oriented synthesis of bis(benzochromenone) derivatives

LIST OF TABLES

CHAPTER-1: Introduction

CHAPTER-2: DABCO-catalysed green synthetic protocol for novel pyranochromenone derivatives

CHAPTER-3: Urea-catalysed microwave-assisted synthesis of novel spirooxindole benzopyrans

CHAPTER-4: Diversity oriented synthesis of bis(benzochromenone) derivatives

CHAPTER-5: Chemistry of vinyl esters as acetaldehyde surrogates in some common multicomponent reactions

LIST OF ABBREVIATIONS

DOS	Diversity oriented synthesis
MCR	Multicomponent reaction
3-CR	Three-component reaction
4-CR	Four-component reaction
rt	Room temperature
DABCO	1,4-Diazabicyclo[2.2.2]octane
Et_3N	Triethylamine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
p-TSA	*para*-Toluenesulfonic acid
DCM	Dichloromethane
$CHCl_3$	Chloroform
CH_3OH	Methanol
MeOH	Methanol
IPA	Isopropyl alcohol
EtOH	Ethanol
ACN	Acetonitrile
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
HRMS	High resolution mass spectrometry
NMR	Nuclear magnetic resonance
$CDCl_3$	Deuterated chloroform
TMS	Tetramethylsilane
FTIR	Fourier transform infrared
IR	Infrared
KBr	Potassium bromide
TLC	Thin layer chromatography
MHz	Megahertz
Hz	Hertz
mp	Melting point
equiv.	Equivalent

mmol	Millimole
mg	Milligram
mL	Milliliter
min	Minutes
h	Hour
J	Coupling constant
s	Singlet
d	Doublet
t	Triplet
q	Quartet
dd	Doublet of doublets
brs	Broad singlet
α	Alpha
β	Beta
&	And
®	Registered trademark
Å	Angstrom
EC_{50}	Half maximal effective concentration
IC_{50}	Half maximal effective dose
G10	Glass vial 10
GHz	Gigahertz
MW	Microwave
nd	Not determined

CHAPTER 1

INTRODUCTION

1.1 Background

The ongoing demand to synthesize a library of diversified heterocycles is due to their vast application in biological, pharmaceutical and agrochemical fields. [1-6] A heterocycle moiety contains a heteroatom (N/O/S) in the cyclic ring. [7-12] Various heterocycles have been found as a pharmacophore in several well-known marketed drugs such as penicillin (**I**), cloxacillin (**II**), cephalexin (**III**), Levaquin (**IV**), sulfamethoxazole (**V**) and 5-F uracil (**VI**) etc (**Figure 1.1**). [13-19]

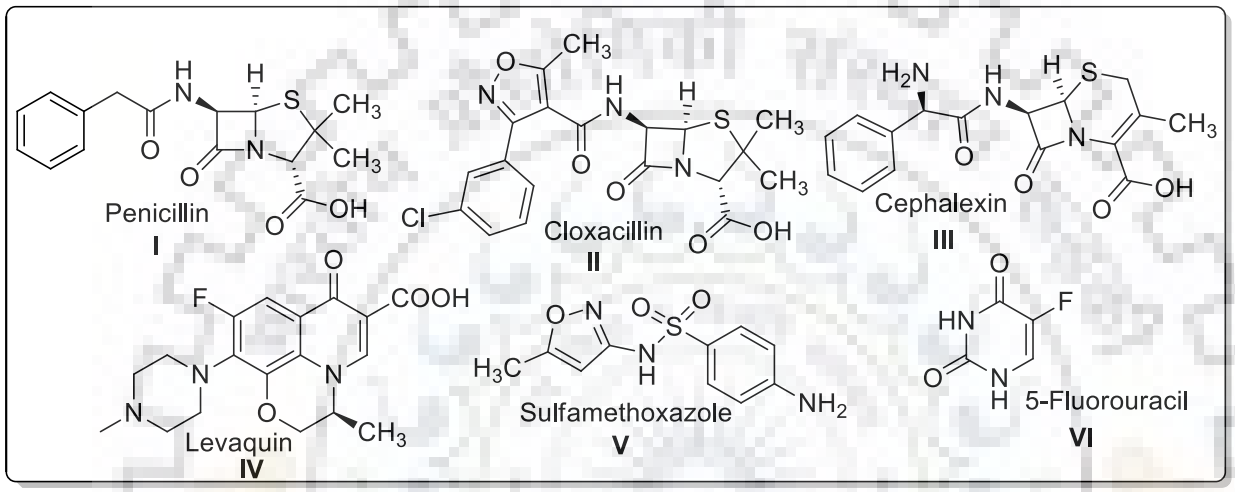


Figure 1.1 Heterocycles as marketed drugs.

Moreover, the ambit of their activities include antibacterial, anticancer, antitumor, antifungal, anti-mycobacterial, anti-tubercular, anti-inflammatory, antidepressant, anti-HIV and insecticidal activities. [20-29] Owing to the pathogenic resistance developed against many of the current drug molecules, a continuous haunt for new molecules remains in focus. [30-31] A good way to find a lead in drug discovery is to keep synthesizing novel heterocycles having potent biological action. Furthermore, heterocycles also act as intermediates for synthesizing various organic molecules. [32-34] Therefore, considering biological and industrial importance of heterocycles, development of simple, fast, effective and atom economical methods for the synthesis of heterocycles is in demand. At the same time, the developed synthetic approach should have advantages like Diversity Oriented Synthesis (DOS), avoiding complex intermediate separation or protection of functional groups, minimum process waste, adopting one-pot methods instead of step-wise synthesis and most importantly environment friendly chemicals and conditions instead of expensive reagents and harsh conditions. [35-39]

Several methodologies *viz.* Solid Phase Organic Synthesis (SPOS), Microwave-Assisted Organic Synthesis (MAOS), use of polymer supported reagents, click reactions and Multicomponent Reactions (MCRs) are some of the smart strategies to construct heterocycles. [40-46] Multicomponent reaction methodologies amongst them, have drawn tremendous attention of chemists over the last few decades for its synthetic efficiency and simple reaction design. [47] The merit of MCRs lie in forging multiple bond formation in a single operation. [48] In the present thesis, all the chapters are designed having a focal theme of developing multicomponent reactions (MCRs) strategies to synthesize diversified heterocycles.

1.2 Multicomponent reactions: a smart and effective route for synthesis

Multicomponent Reactions (MCRs) are a powerful, fast and effective target-guided synthetic approach which have the ability to construct structurally diverse moieties through a single transformation in a short reaction time from readily available starting materials. [49-51] MCRs are defined as a single step one-pot convergent transformation to design the target molecules effectively. A multicomponent reaction, as the name suggests, consists of more than two reactants getting transformed into final product. [52] MCR-chemistry has several advantages like i) operational simplicity, ii) high convergence efficiency, iii) facile automation, iii) one step operation to save time and resources, iv) large number of diversity oriented synthesis in short time, v) low E-factor and high atom economy and most importantly vi) formation of multiple bonds in a single step thus possessing high Bond-Forming-Index (BFI). [49, 53] MCRs show high synthesis impact as it provides higher overall formulated yields in shorter reaction time in comparison to stepwise synthesis and consequently the process reduces costs, time, use of solvents, purification steps, energy and most importantly generation of waste products. [54-56] For all the attributes as manifested above, development of MCRs fall in the realm of "green chemistry". The twelve principles of "Green Chemistry" are sketched in **Figure 1.2**. [57-58] The idea of developing an ideal green synthetic methodology is associated with picking up appropriate reagents and proper selection of solvents and catalysts. [59-63] Development of environment friendly synthetic MCR approaches to construct biologically potent assemblies is the key point of this entire thesis work.

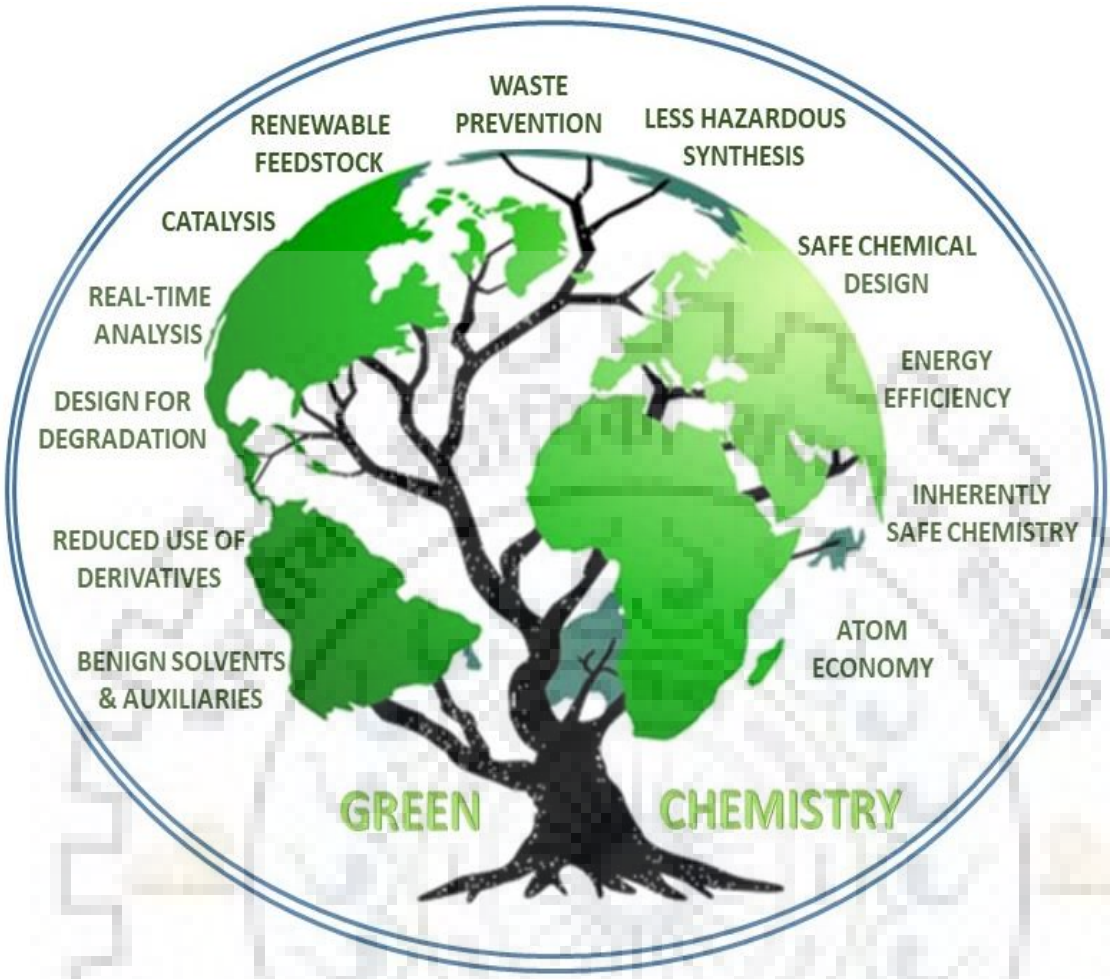


Figure 1.2 Twelve principles of green chemistry.

1.3 Multicomponent reactions: a long journey over the years

In general, multicomponent reactions are mainly classified into two distinct classes; non-isocyanide-based MCRs and isocyanide-based MCRs which is commonly known as IMCRs. The history of development of MCRs is quite vast and may not be fit the proportion of the present work for inclusion. However, a brief chronology of the multicomponent reactions are sketched in **Figure 1.3**. [42, 64-65]

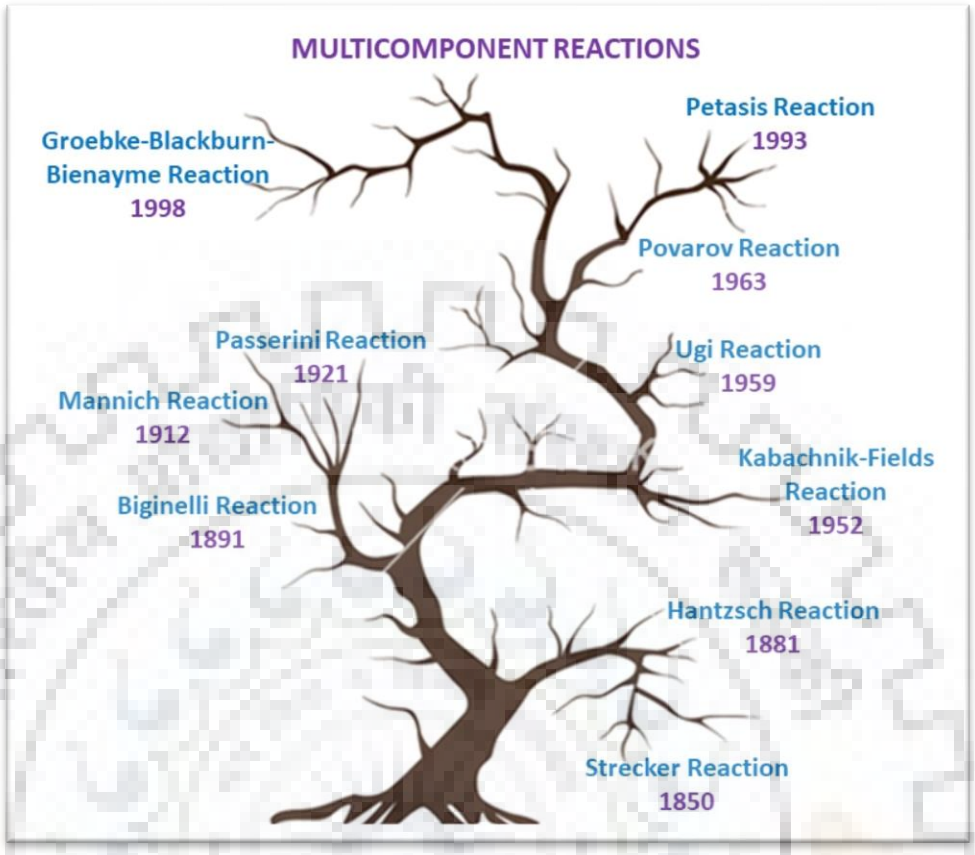


Figure 1.3 Discovery of multicomponent reactions over the years.

Many of the MCRs remained dormant after their discovery and over the last few decades, have gained a tremendous resurgence. Amongst them, Strecker (3-CR, 1850), Hantzsch (4-CR, 1881), Biginelli (3-CR, 1891), Mannich (3-CR, 1912) and Povarov (3-CR, 1963) reactions are non-isocyanide based MCRs whereas Passerini (3-CR, 1921), Ugi (4-CR, 1959) and Groebke-Blackburn-Bienaymé (3-CR, 1998) reactions are popular IMCRs (**Figure 1.4**). [64, 66-68] Later on, several modification and post effect modification have been brought about in some of these reactions by several authors. [69-72]

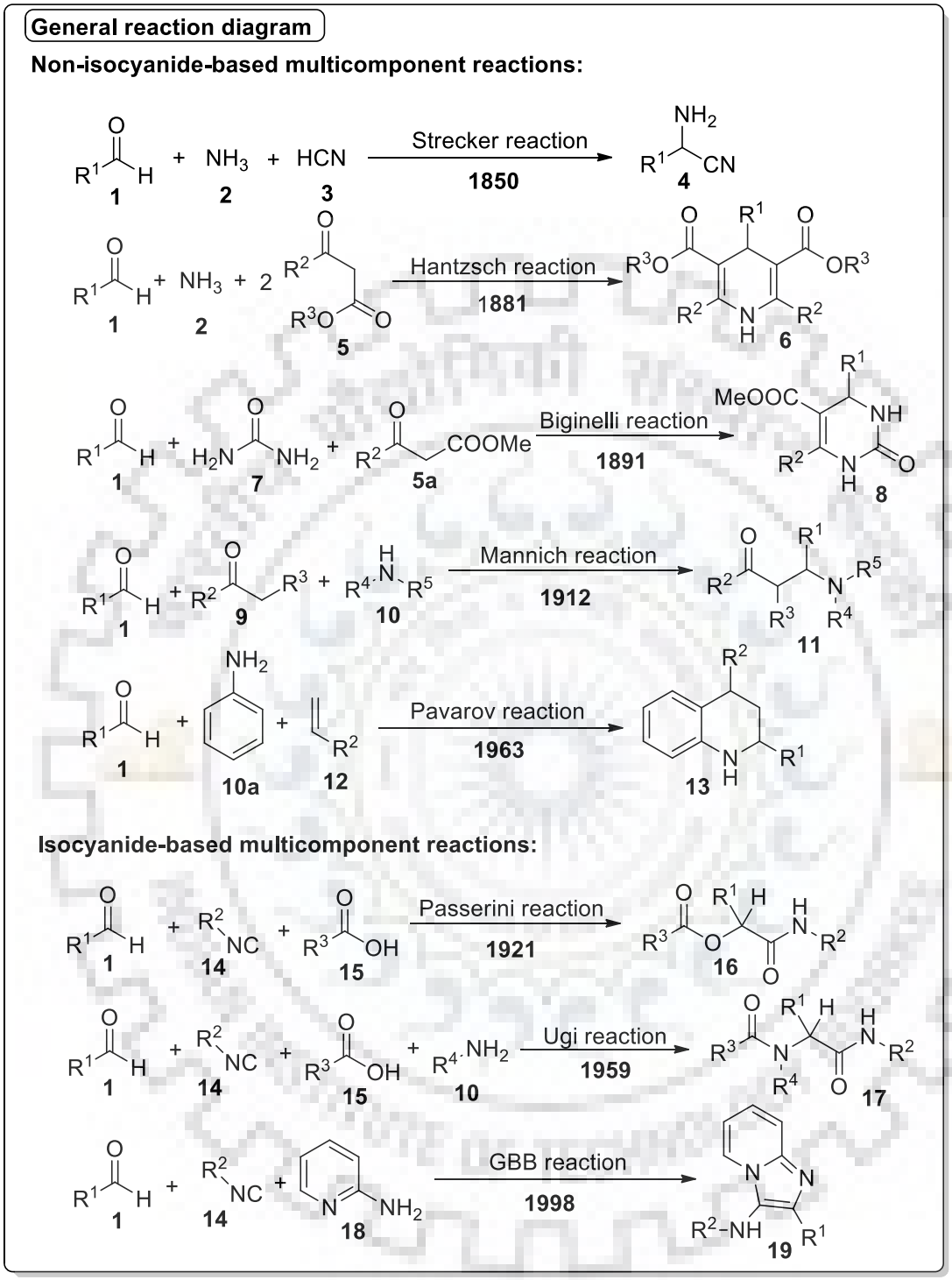


Figure 1.4 Examples of well-known multicomponent name reactions.

1.4 Microwave chemistry: a high rated organic synthesis approach

Microwave-**A**ssisted **O**rganic **S**ynthesis (MAOS) has emerged as an efficient approach to formulate diversified heterocycles in short reaction time. [73-76] The MAOS gained popularity in synthetic community because of its several advantages over conventional methods by overcoming problems like low yields, prolonged reaction time, reproducibility and formation of side products. [74, 77] In general, normally the chemical transformations in conventional methods occur by non-uniform conductive heating of the reaction mixture in which the reaction vessel is heated more than the reaction mixture. Whereas, due to direct electromagnetic in microwave irradiation in MAOS, the reactant molecules and most importantly the solvents are heated directly which result in better outcomes. Most of the microwave ovens operate at 2.45 GHz which is designed in this manner in order not to interfere with the wavelength generally used for telecommunication and radars. [78-79] In MAOS, the choice of solvents is very critical in deciding the fate of the reaction. The important parameters for a solvent to perform effectively in microwave reactors are dielectric constant (ε'), dielectric loss (ε'') and most importantly loss tangent ($\tan\delta$). Notably, the solvent having high loss tangent value can absorbed the microwave radiation more in comparison to lower one (**Table 1.1**). [79]

Table 1.1 Solvents and their loss tangent (tan δ) values.

Solvent	**tan δ**	**Solvent**	**tan δ**
Hexane	0.02	1,2-Dichloroethane	0.127
Toluene	0.04	Dimethylformamide	0.161
Dichloromethane	0.042	Acetic acid	0.174
Tetrahydrofuran	0.047	Methanol	0.659
Acetone	0.054	Isopropyl alcohol	0.799
Acetonitrile	0.062	DMSO	0.825
Chloroform	0.091	Ethanol	0.941
Water	0.123	Ethylene glycol	1.35

Over the years, there are plenty of reports for microwave-assisted synthesis of different classes of heterocycles *viz.* triazoles, tetrazoles, quinolines, oxazines, benzazepines, substituted 2-aminopyridines, spirooxindoles, pyrans and pyrroles etc. [80-85] For example, Van der Eycken and co-workers (2004) reported microwave-assisted synthesis of diversified 1,4-disubstituted-1,2,3-triazoles (**Figure 1.5**). [86] The three-component reaction of sodium azide (**21**), alkyl halides (**20**) and alkynes (**22**) provided the desired product **23** in good to high yields (81-93 %) in microwave heating at 125 ^{o}C (two derivatives at 75 ^{o}C) for 10 to 15 minutes.

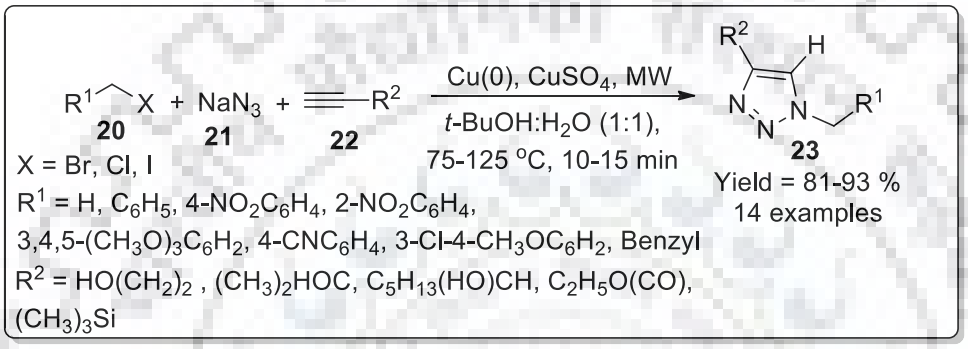


Figure 1.5 Microwave-assisted synthesis of triazoles.

Later on, Chebanov *et al.* (2007) described a one-pot three-component reaction of aromatic aldehydes (**1**), cyclic 1,3-diketones (**25**) and 5-aminopyrazoles (**24**) to synthesize diversified 5*a*-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones (**Figure 1.6**). [87] The microwave-assisted condensation reaction was carried out in a strong basic condition to construct the final product **26** in low to good yields (32-75 %). The reaction proceeded through ring opening of 1,3-diketones (**25**) followed by cyclisation in the presence of a base to provide the desired product **26**.

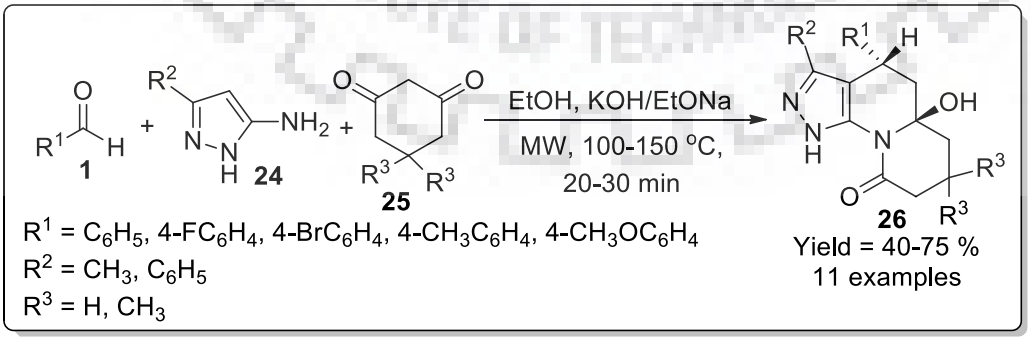


Figure 1.6 Microwave-assisted synthesis of quinolizinones.

Further, Torok *et al.* (2010) reported a microwave-assisted domino reaction in which aldehydes (**1**) and anilines (**10**) reacted first to form imines which further reacted with aryl alkynes to construct substituted 5-aza-7-deaza-adenine (**27**) (**Figure 1.7**). The three-component reaction was performed under microwave irradiation at 100 °C for 10 minutes using montmorillonite K-10 as acid catalyst to provide final product **27** in good to high yields (56-96 %). [88]

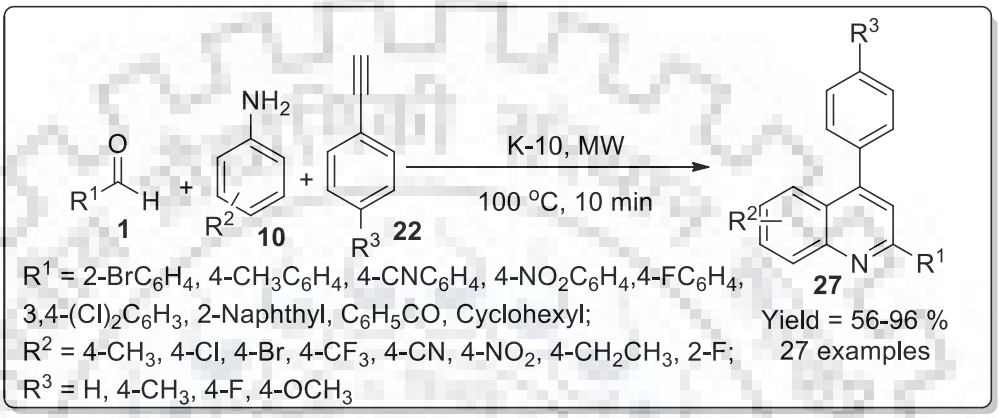


Figure 1.7 Microwave-assisted synthesis of 5-aza-7-deaza-adenine.

In 2017, Dolzhenko and co-worker developed a microwave-assisted three-component reaction of triethyl orthoformate (**29**), 2-aminoimidazoles (**28**) and cyanamide (**30**) to synthesize 4-aminoimidazo[1,2-*a*][1,3,5]triazines (**31**) (**Figure 1.8**). The reaction mixture was microwave irradiated for 20 minutes at 150 °C to give final products in good to high yields (71-92 %). [89]

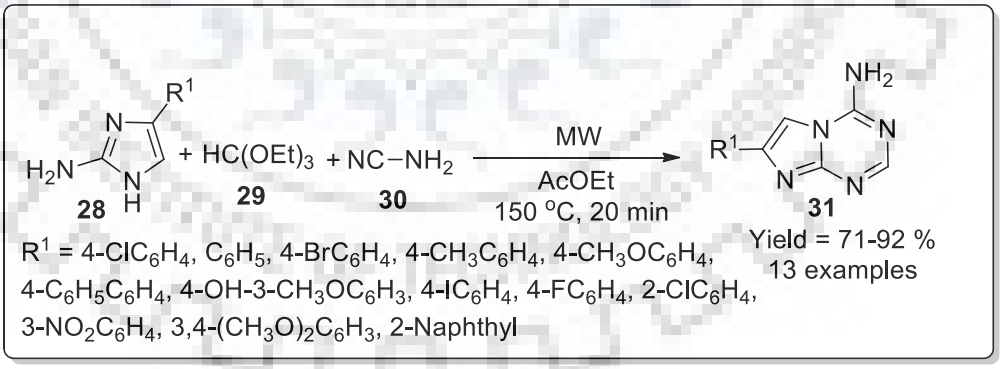


Figure 1.8 Microwave-assisted synthesis of triazines.

1.5 Liquid-assisted grinding: a green approach towards sustainability

In a pursuit towards greenness, mechanochemistry is already recognized by the scientist community as a tool for providing cleaner, less hazardous and sustainable chemical transformations in comparison to conventional synthesis. [90-91] Mechanochemistry entails mechanical energy for transformations via mechanical forces induced in several ways *viz.* impact, stretching, shearing, compression and mostly by grinding or milling processes. [91] The mechanical process can be manual as normally done by mortar and pestle or instrumental by using ball milling. From a reaction point of view, this mechanical friction can grind reactants into small particle sizes, generating a large surface area to force the starting materials come closer to each other, thereby accelerating the contact between reactants. Further, this mechanical transformation can be achieved by "solvent-free" strategy or by adding nominal amount of a solvent as a promoter. The later is known as **L**iquid-**A**ssisted **G**rinding (LAG) in which generally small quantity of liquid is added to improve the synthetic efficiency by minimizing solvent waste leading to better yields. [92] The reason behind the yield enhancement is mainly because of better mixing of reactants leading to higher reaction kinetics. Normally, LAG parameter (η) has been introduced to define a liquid-assisted reaction for which the value lies between 0 to 1. [93]

There are several reports of multicomponent reactions performed under liquid-assisted grinding to furnish diversified scaffolds. For example, Juaristi and co-workers (2016) developed a liquid-assisted high-speed ball milling (HSBM) strategy to formulate Ugi-4CR adduct **17** from the reaction of aromatic aldehydes (**1**), isocyanides (**14**), amines (**10**) and carboxylic acids (**15**) (**Figure 1.9**). The four-component reaction was catalysed by indium(III) chloride (2 mol %) in an agate jar for 45-180 minutes to provide 46-74 % of yields. [94]

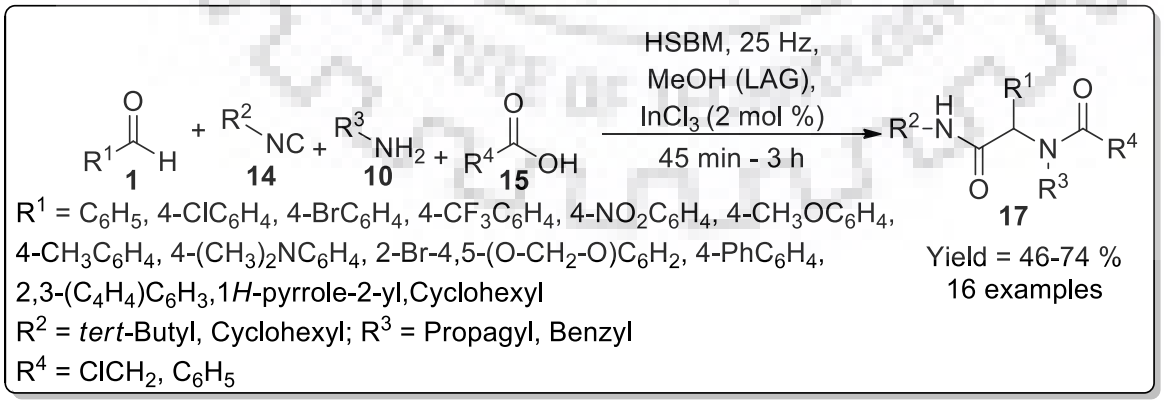


Figure 1.9 Liquid-assisted grinding to synthesize Ugi-4CR products.

Salunkhe *et al.* (2018) reported 2,2,2-trifluoroethanol (TFE) catalysed liquid-assisted mechanochemical transformation to construct diversified chromenes (**Figure 1.10**). [95] The three-component cycloaddition reaction was performed for 11-14 minutes through manual grinding to furnish the final products in good to high yields (80-88 %).

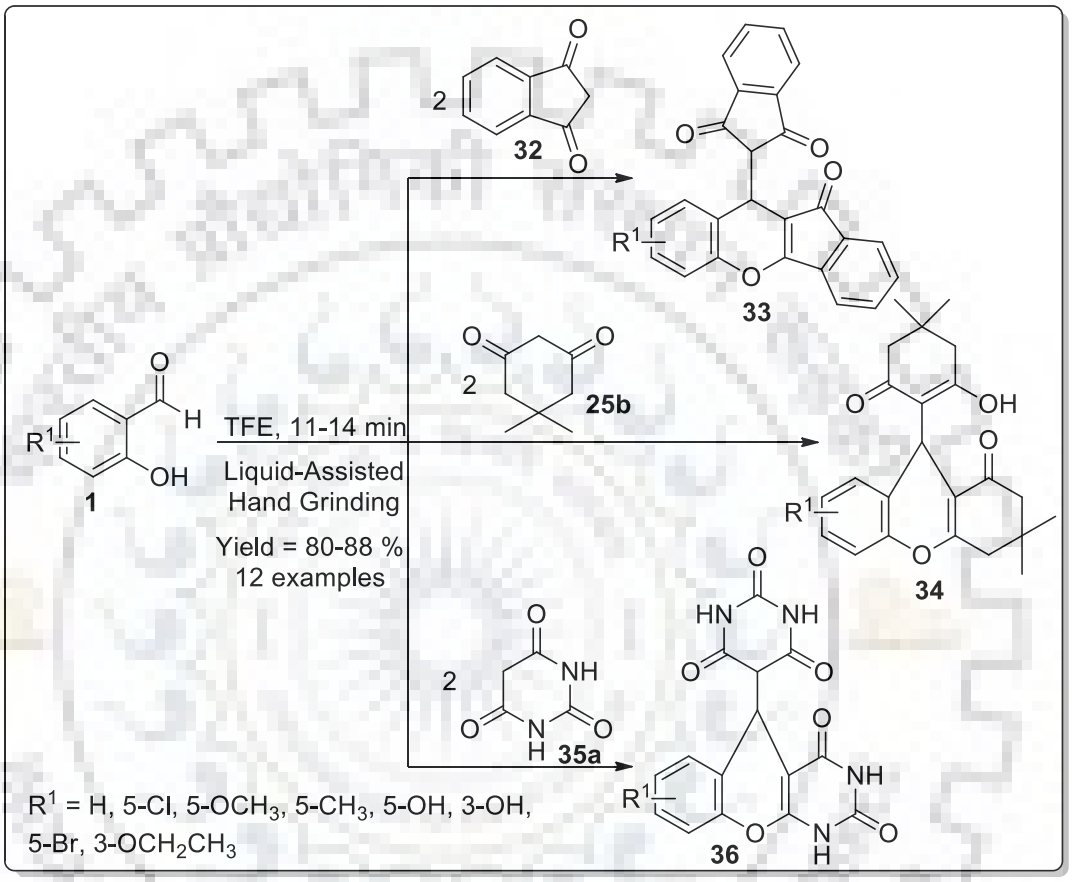


Figure 1.10 Liquid-assisted grinding to synthesize diversified chromenes.

In 2016, Raval *et al.* reported the basic ionic liquid-assisted mechanochemical synthesis of diversified 3,4-dihydropyrano[*c*]chromenes (**Figure 1.11**). The one-pot three-component reaction of 4-hydroxycoumarin (**37**), malononitrile (**38**) and substituted aromatic aldehydes (**1**) provided the desired product **39** in high yields (89-95 %) using hand grinding in catalytic DBU-moderated ionic liquid as a promoter. [96]

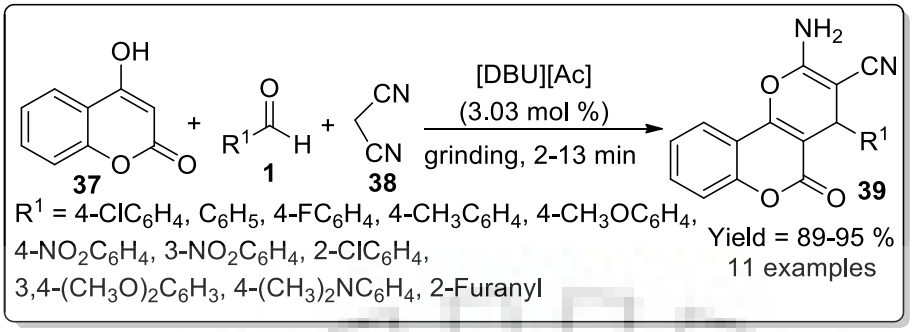


Figure 1.11 Liquid-assisted mechanochemical synthesis of chromene heterocycles.

1.6 Pyran framework: biological importance and synthesis

Pyrans are oxygenated heterocyclic scaffolds which show a wide range of biological and medicinal applications. [97-100] Moreover, pyran framework is the core structure of many well-known molecules *viz*. benzopyran, napthopyran, coumarin, chromone, xanthene, xanthones etc (**Figure 1.12**). [97]

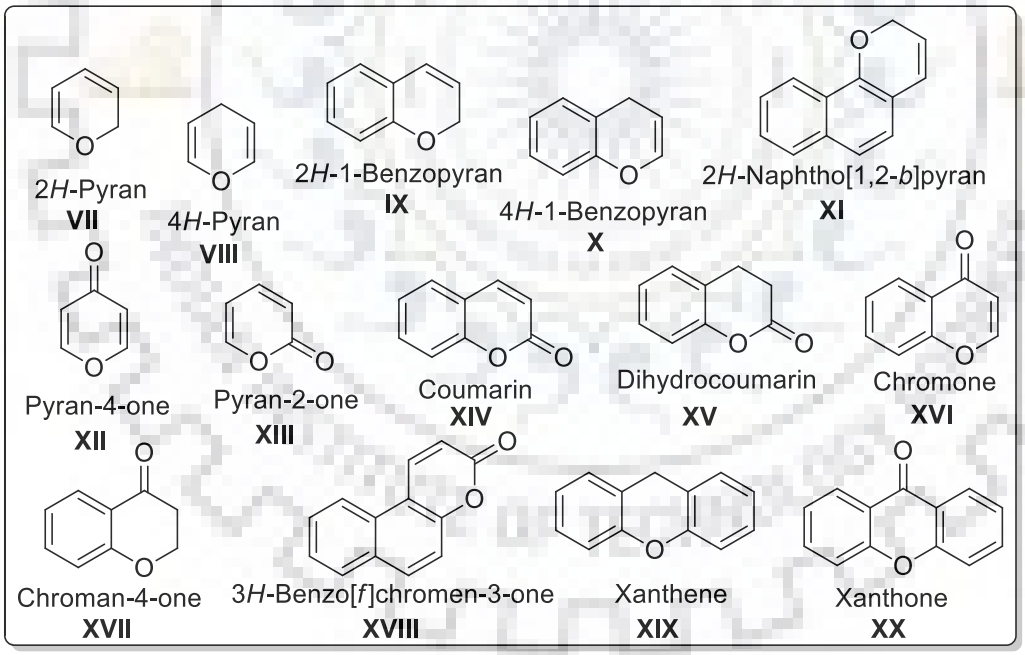


Figure 1.12 Pyran framework in heterocycles.

Most importantly, pyran is the basic unit of many naturally occurring flavonoids with potential biological activities like antioxidant, anti-inflammatory activities (**Figure 1.13**). [101-103]

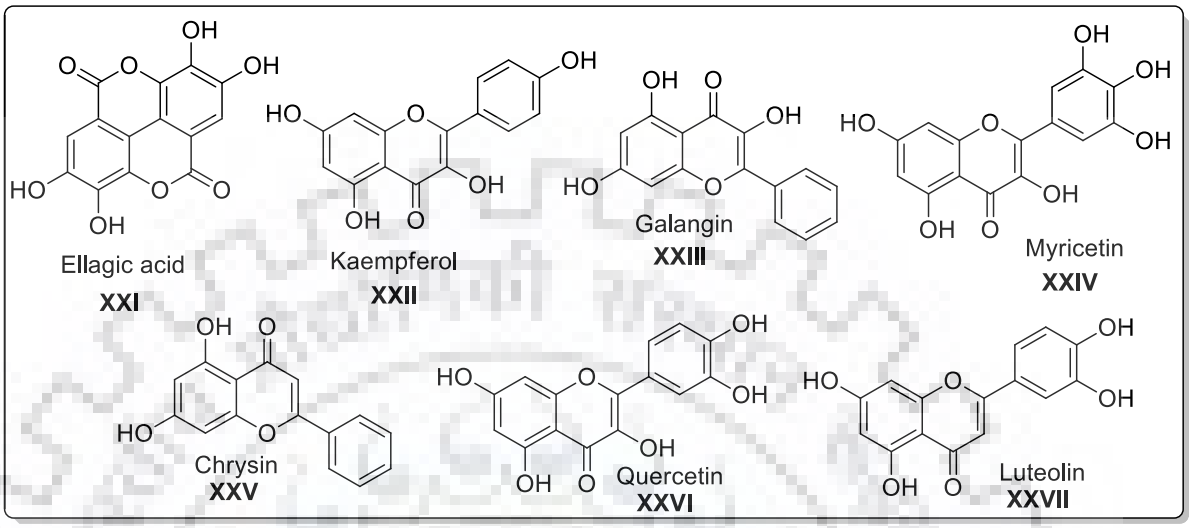


Figure 1.13 Naturally occurring biologically active pyrans.

Similarly, pyrans fused with coumarin or naphthoquinone structures are already recognized as promising chemical class of compounds showing a wide range of biological activities like anticancer, antiviral, antimicrobial, cytotoxic, anti-inflammatory, anti-HIV, antioxidant, antigenotoxic, antibacterial and antirheumatic activities (**Figure 1.14**). [97, 99]

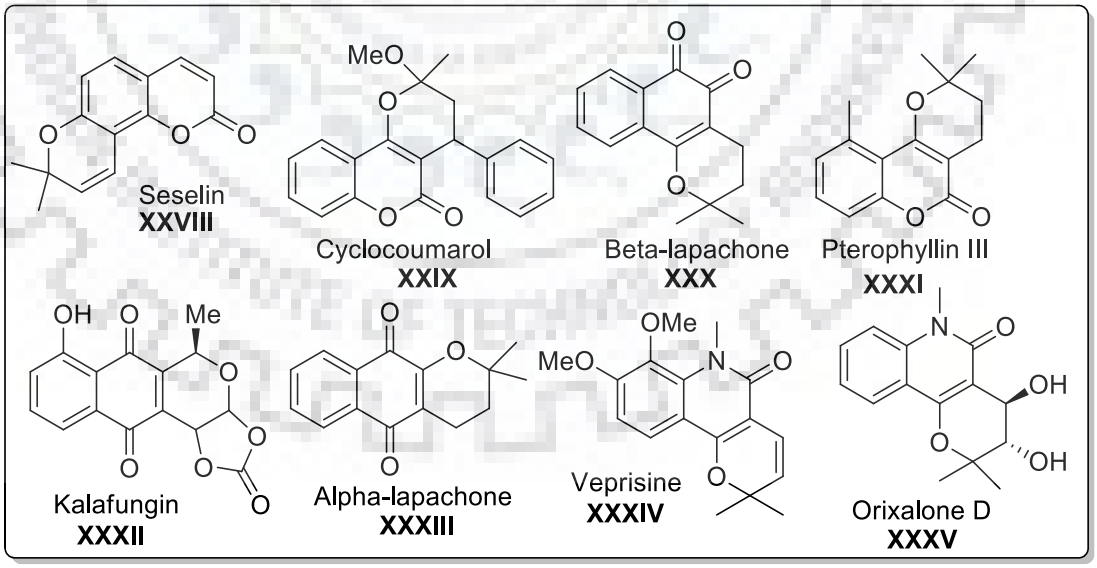


Figure 1.14 Biologically important pyran fused heterocycles.

Owing to their widespread biological applications, synthesis of novel fused pyrans or developing greener efficient protocols for their synthesis are in demand. In the literature, several synthetic methodologies have been reported to access the fused pyrans using MCR reaction sequence and some of the noted ones are described below.

Shaabani and co-workers (2009) described a one-pot multicomponent reaction of aldehydes (**1**), malononitrile (**38**) and C-H-activated acids (**40** or **42**) to access diversified 4*H*-benzo[*g*]chromenes (**41**) and dihydropyrano[2,3-*g*]chromenes (**43**) (**Figure 1.15**). The reaction was performed at room temperature for 24 hours using 10 mol % Et_3N to provide functionalized chromenes in good to high yields (60-86 %). [104]

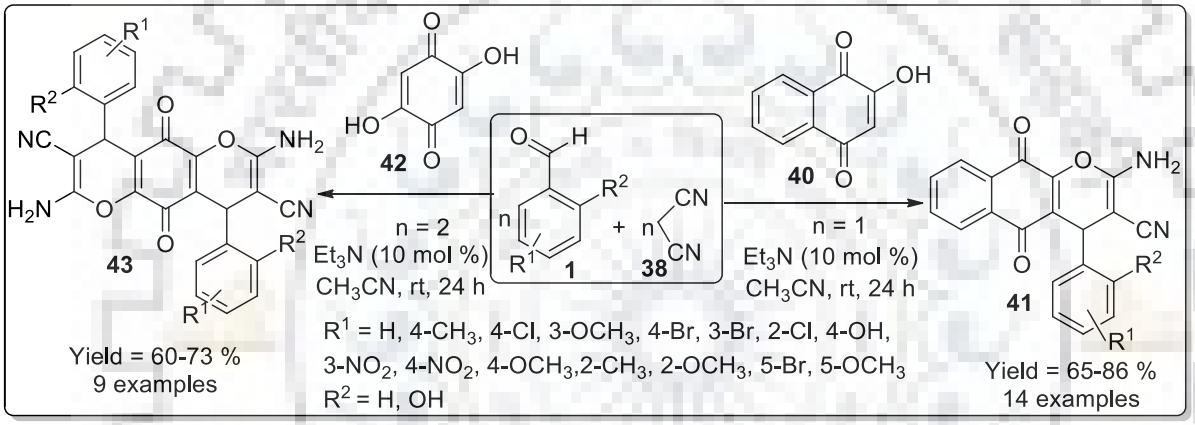


Figure 1.15 Triethylamine-catalysed synthesis of chromenes.

Banerjee *et al.* (2013) reported ZnO nanoparticle catalysed one-pot synthesis of tetrahydrobenzo[*b*]pyrans and dihydropyrimidones (**Figure 1.16**). [105] In this report, the three-component reaction of aromatic aldehydes (**1**), 1,3-diketone (**25b**) and malononitrile (**38**) was performed to formulate 4*H*-pyrans (**44**) at room temperature in excellent yields (94-98 %). On the other hand, the synthesis of dihydropyrimidones from aldehydes (**1**), urea/ thio-urea (**7**) and ethyl acetoacetate (**5b**) was also reported at 70 ºC to give the final product **45** in good to excellent yields (86-95 %).

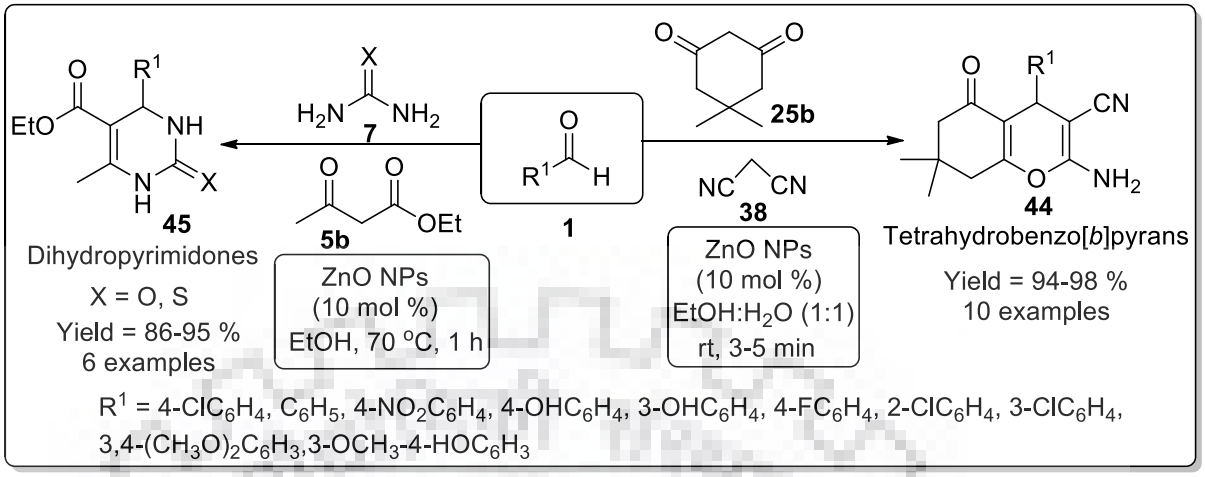


Figure 1.16 ZnO nanoparticles catalysed synthesis of 4*H*-pyrans and dihydropyrimidones.

In 2016, Choudhury and coworkers reported microwave-assisted synthesis of diversified fused 4*H*-pyrans using different 1,3-dicarbonyl variants, arylglyoxals (**46**) and malononitrile (**38**) as substrates (**Figure 1.17**). The reported methodology provided quinolone fused pyrans (**48**) in good to excellent yields (79-93 %) under microwave heating at 110 °C for 10 minutes using ethanol as a solvent. Likewise, the synthesis of pyrans fused with naphthoquinones, coumarins and pyrones was also mentioned in the same report under similar microwave irradiation condition to give the respective final product **50** in good to high yields (70-91 %) (**Figure 1.17**). [99]

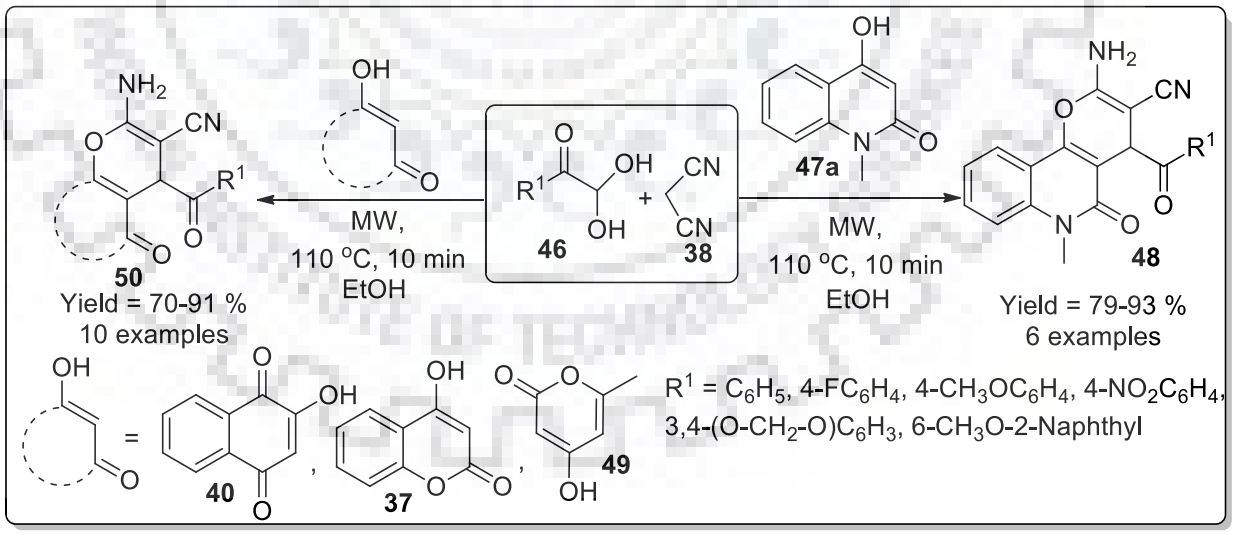


Figure 1.17 Microwave-assisted synthesis of diversified fused 4*H*-pyrans.

Brahmachari *et al.* (2014) described a urea-catalysed one-pot synthesis of pyran annulated heterocycles from reaction of C-H activated acids, aldehydes (**1**) and malononitrile (**38**) (**Figure 1.18**). The reaction was reported at room temperature using catalytic loading of urea (10 mol %) in aqueous ethanol to provide the core structure 2-Amino-3-cyano-4*H*-pyrans (**51/ 53**) in good to excellent yields (80-97 %) and also pyran-fused pyrazoles (**52**) in good yields (84-86 %) (**Figure 1.18**). [106]

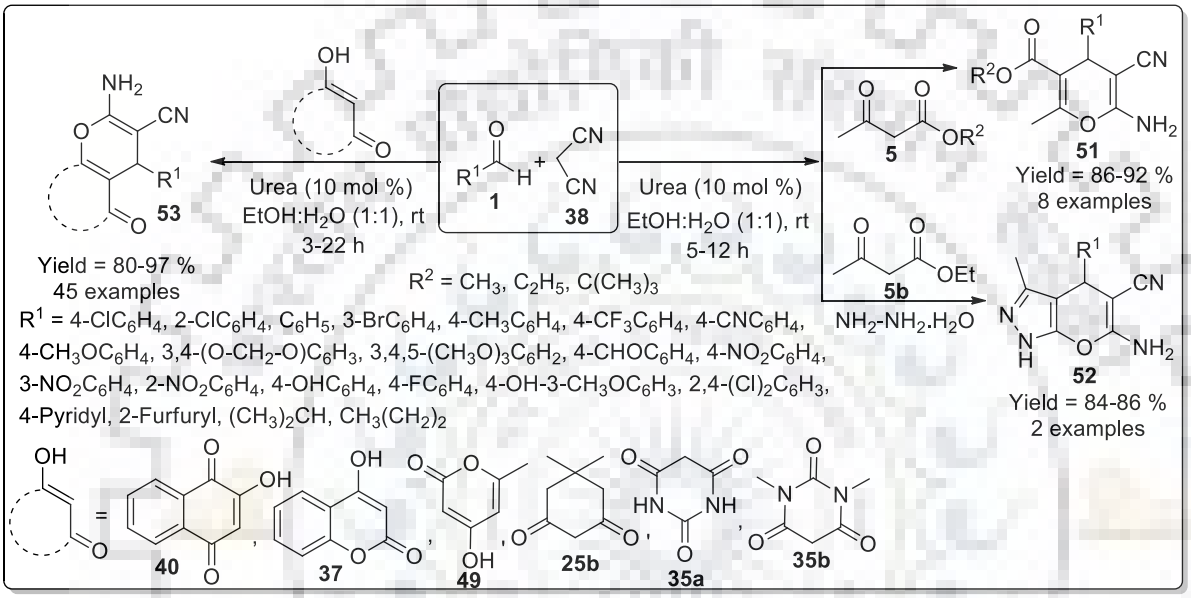


Figure 1.18 Urea-catalysed three-component reaction to access pyrans.

The plausible mechanism for the above mentioned reaction is sketched in **Figure 1.19**. The urea catalysed Knoevenagel condensation reaction of aldehyde (**1**) and malononitrile (**38**) formed the adduct **II** which was further reacted with enolate to form of the C-H-activated acid to give intermediate **III**. The intermediate **III** either in presence of aqueous ethanol cyclised to give the product **53** or else got tautomerised to another intermediate **IV** which provided the final desired product **53** on further cyclisation.

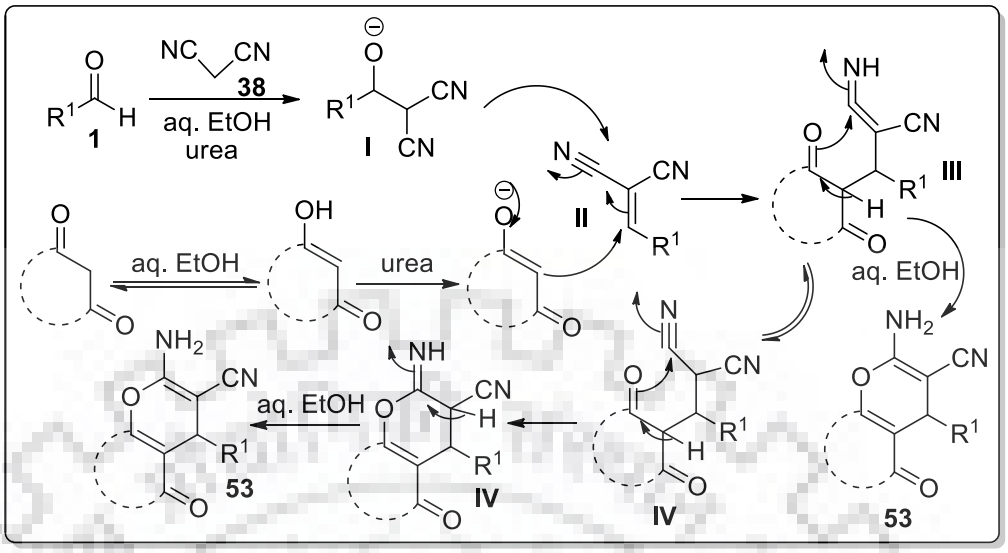


Figure 1.19 Plausible mechanism for the synthesis of 2-Amino-3-cyano-4*H*-pyrans.

Tu and co-workers (2014) presented the three-component reaction of C-H-activated acid, aldehydes (**1**) and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**54**) to furnish fused pyrano[2,3-*b*]pyridine derivatives (**56**) (**Figure 1.20**). The reaction was carried out under microwave irradiation at 80 °C for 16-20 minutes using triethyl amine as a base and ethanol as a solvent to access the final desired pyrano heterocycles **56** in good to excellent yields (74-94 %). [107]

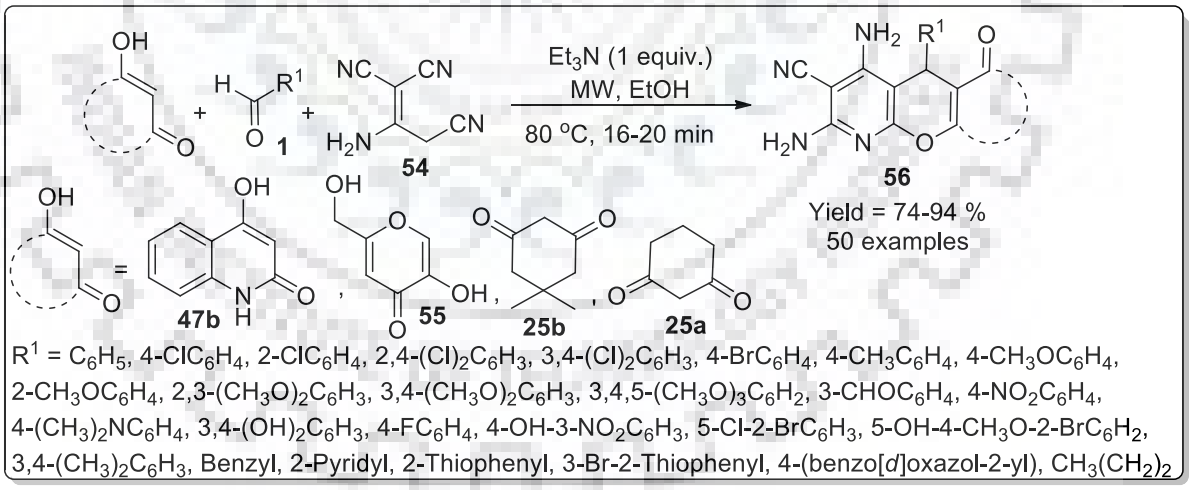


Figure 1.20 Microwave-assisted synthesis of pyrano[2,3-*b*]pyridine derivatives.

The plausible mechanism for the above described three-component reaction is outlined in **Figure 1.21**. The base promoted Knoevenagel condensation reaction of aldehyde (**1**) and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**54**) provided the intermediate **I**. The nucleophilic attack of C-H-activated acid (**55**) to the intermediate **I** formed another intermediate **II** which upon tautomeration followed by intramolecular double cyclisation formed the final pyrano heterocycles **56**.

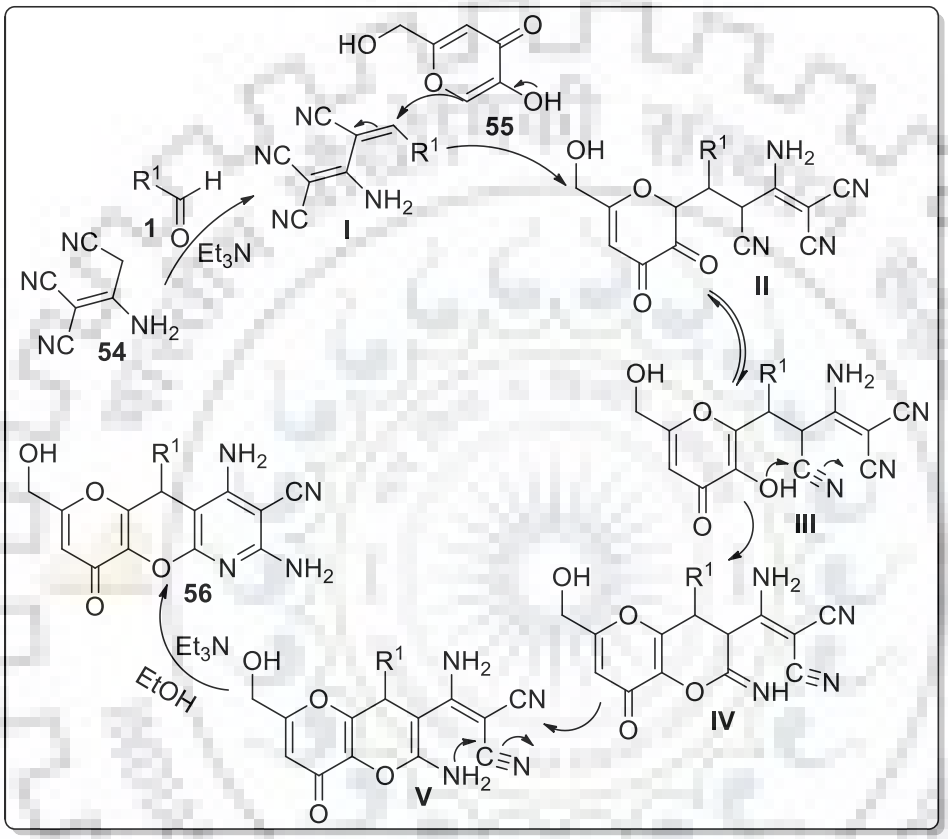


Figure 1.21 Plausible mechanism for the synthesis of pyrano[2,3-*b*]pyridine heterocycles.

1.7 Spirooxindole framework: biological importance and synthesis

Indole is the basic structural unit frequently found in heterocyclic scaffolds. Spirooxindoles are also brought into attention because of their unique fused structure. [108-111] Generally, spiroannulated ring present at the third position of indole is paid a lot of attention due to its virtue of being structurally rigid leading to conformational restrictions of the heterocyclic motifs. [112] Spirooxindoles are found in a number of bioactive natural products showing wide range of biological activities (**Figure 1.22**). [108, 109, 111]

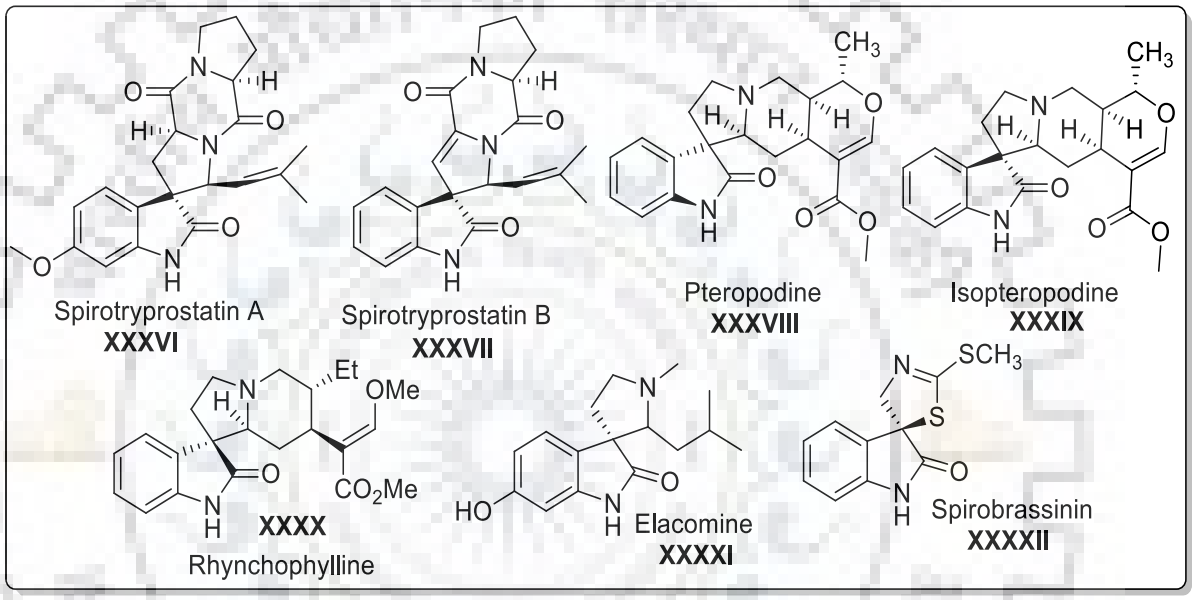


Figure 1.22 Naturally occurring biologically active spirooxindoles.

Synthesis of spirooxindoles also possess a number of biological activities *viz.* antimalarial, antitumor, inhibition activities, anticancer, anti-inflammatory, antimicrobial activities etc. (**Figure 1.23**). [113-117]

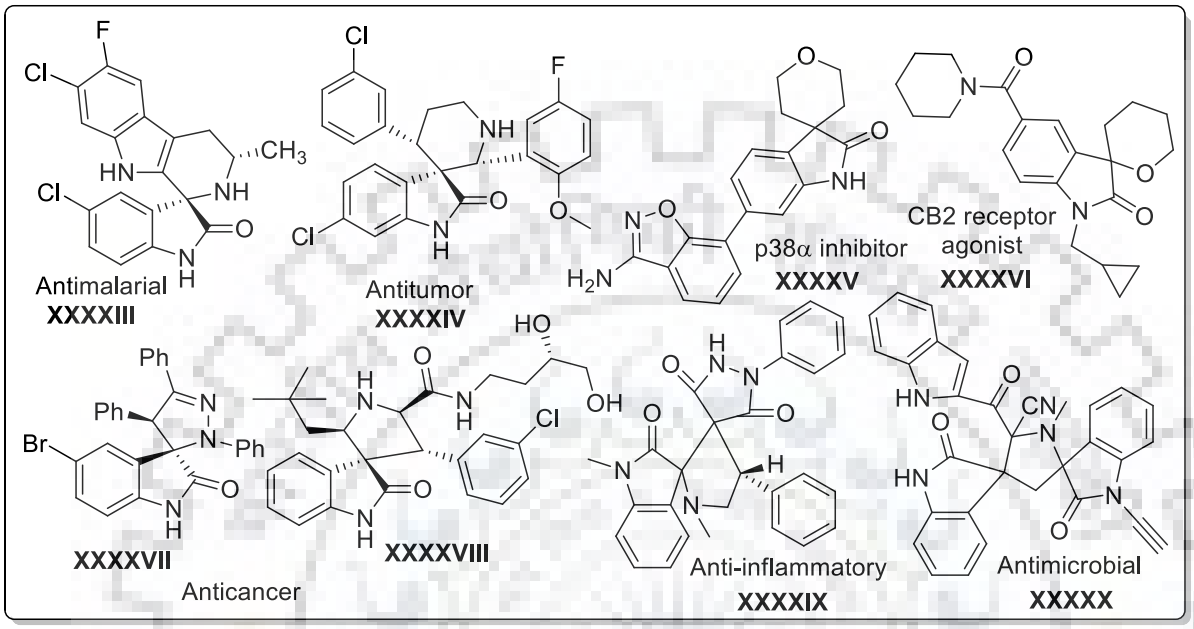


Figure 1.23 Biological applications of spirooxindoles.

Due to their wide range of biological and pharmaceutical applications, the fused spirooxindoles have been recognized as attractive synthetic targets. A number of literature reports can be traced for developing new synthetic routes or constructing novel spiro-fused heterocycles. Some of the noted ones are illustrated below.

Zhang and coworkers (2017) reported a visible light promoted one-pot three-component reaction to access spirooxindole-fused pyrans **58** from the reaction of C-H-activated acid, isatins (**57**) and malononitrile (**38**) (**Figure 1.24**). [118] The reaction was irradiated at room temperature for 4-6 hours under white visible light in water-ethyl lactate solvent mixture to form the final fused spirooxindoles **58** in good to excellent yields (82-96 %) (**Figure 1.24**).

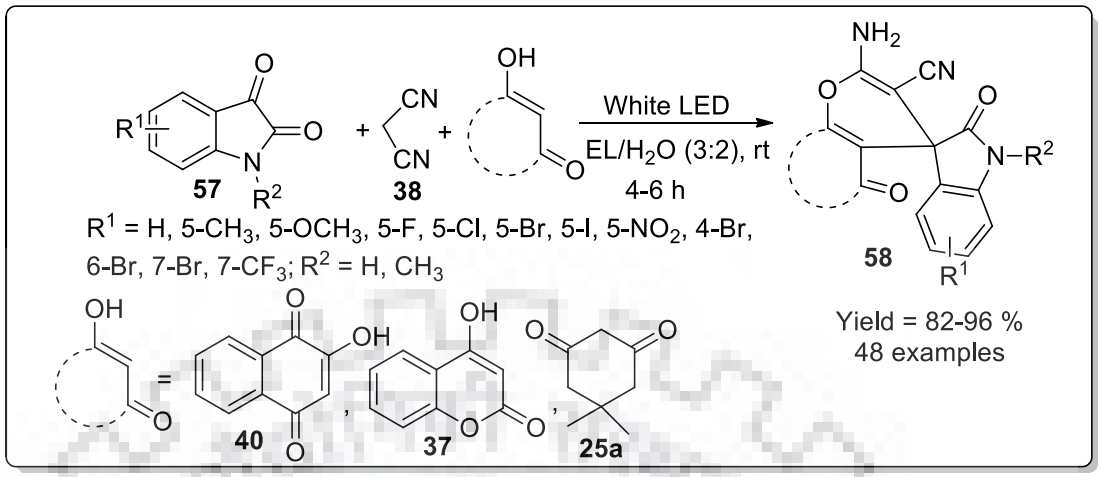


Figure 1.24 Visible-light induced synthesis of spirooxindole fused pyrans.

The plausible mechanism for the three-component reaction is drawn in **Figure 1.25**. The Knoevenagel condensation reaction of isatin (**57**) and malononitrile (**38**) in the presence of visible light provided the intermediate **I**. The intermediate formed another radical intermediate **III** in presence of light which reacted with activated 2-hydroxynaphthalene-1,4-dione to give intermediate **IV**. Later on, the intermediate **IV** provided the final targeted product **58** followed by visible light promoted intramolecular cycloaddition reaction.

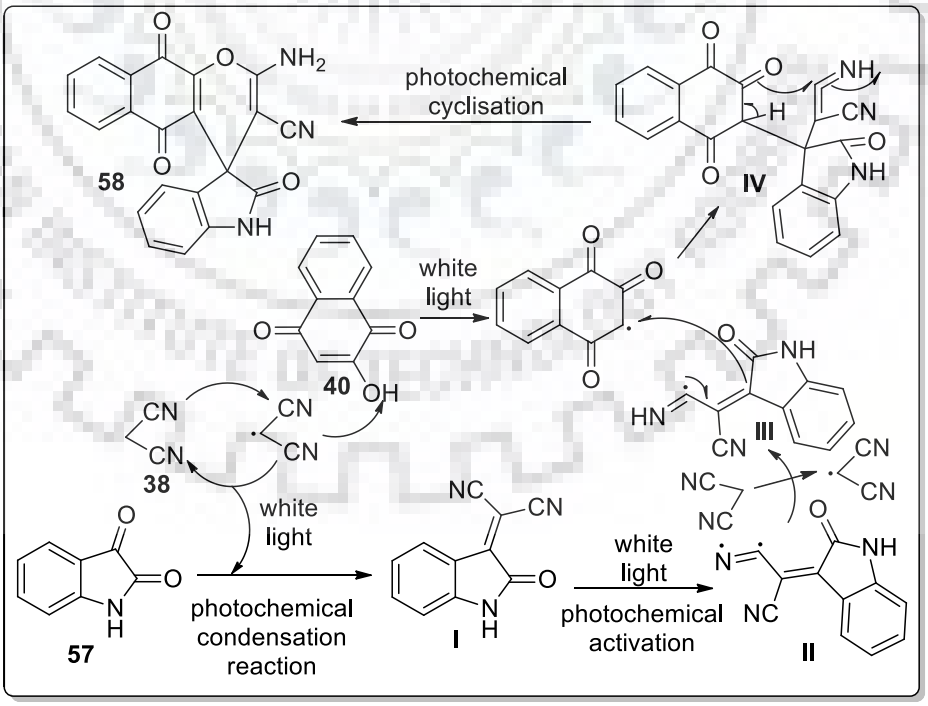


Figure 1.25 Plausible mechanism to access spirooxindole fused pyrans.

Meshram *et al.* (2017) reported the catalyst free microwave-assisted synthesis of diversified spirooxindoles in good to excellent yields (70-93 %) (**Figure 1.26**). The three-component reaction of amino acids (**59**), isatins (**57**) and but-2-ynedioates (**60**) under microwave heating at 80 °C for 10 minutes in aqueous medium provided tetrahydrospiro[indoline-3,3-pyrrolizine]1,2-dicarboxylate (**61**). In addition, formation of *n*-substituted oxindoles **63** was confirmed when the fourth component phenacyl bromide (**62**) was added to the above reaction mixture and irradiated at slightly higher temperature at 100 °C for 15 minutes. [119]

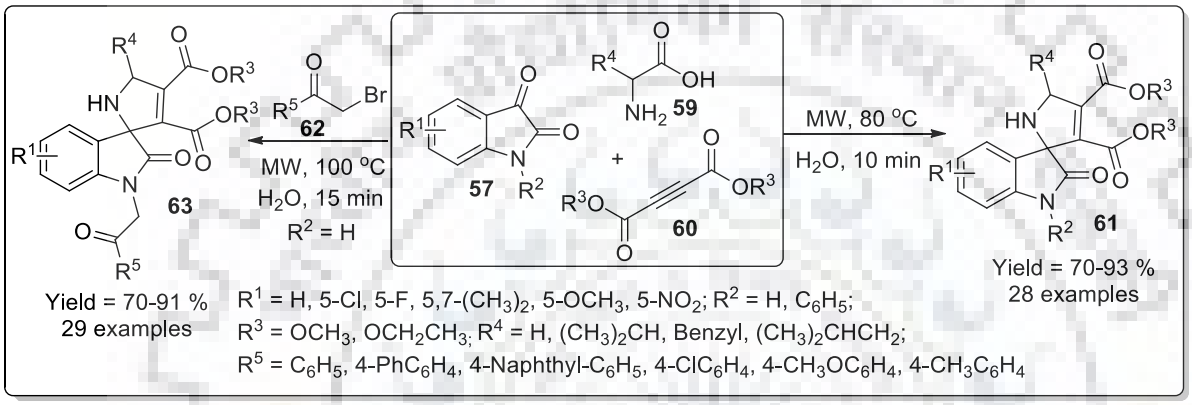


Figure 1.26 Microwave-assisted synthesis of spirooxindoles in aqueous medium.

The mechanism for the above described reaction is sketched in **Figure 1.27**. The condensation by reaction of isatin (**57**) and amino acid (**59**) followed decarboxylation provided the charged imine intermediate **II**. Next, the cycloaddition reaction of intermediate **II** with but-2-ynedioates (**60**) provided the targeted product **61** which on further reaction with phenacyl bromide (**62**) resulted in formation of *n*-substituted oxindoles **63**.

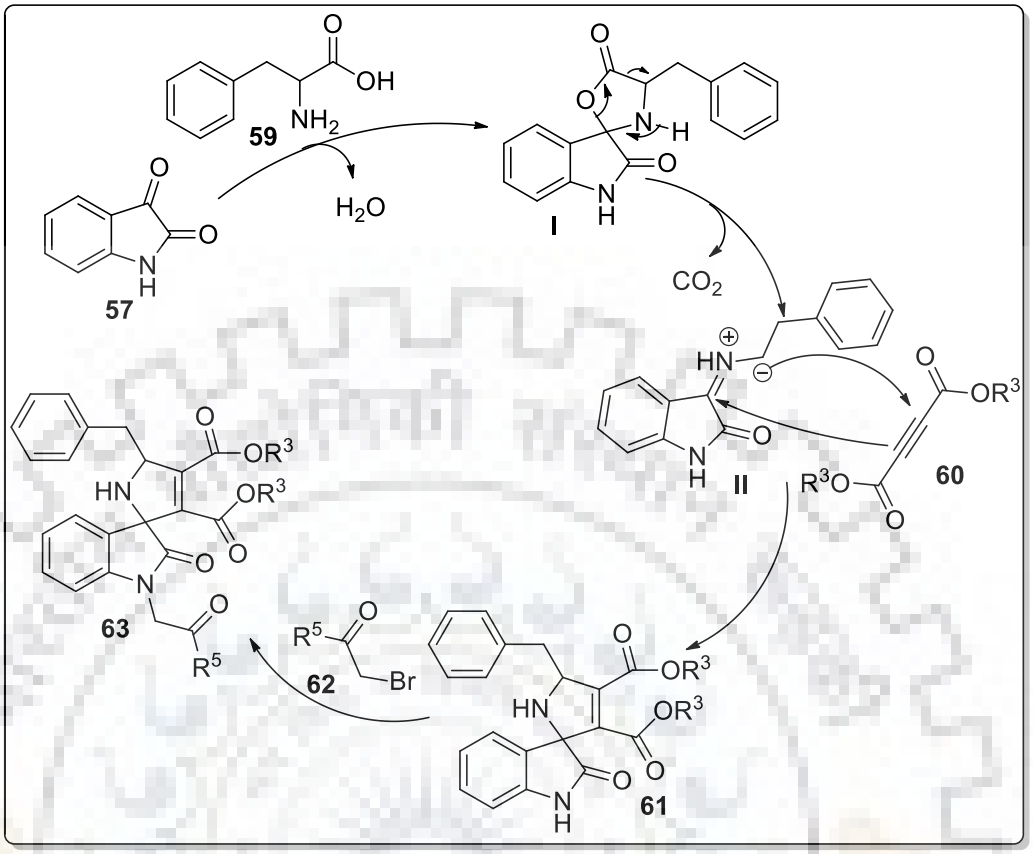


Figure 1.27 Plausible mechanism for the synthesis of spirooxindole moieties.

Esmaeili and co-workers (2018) demonstrated a 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) catalysed domino three-component reaction to access spiro[benzo[4,5]thiazolo[3,2-*a*]chromeno[2,3-*d*]pyrimidine-14,3′-indoline]-1,2′,13(2*H*)-trione (**65**) from isatins (**57**), 1,3-cyclohexanediones (**25**) and 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones (**64**) in good to high yields (60-90 %) (**Figure 1.28**). [120] The condensation reaction was performed for 10-12 hours under reflux using 3 mol % $H_3PW_{12}O_{40}$ and acetonitrile as a solvent.

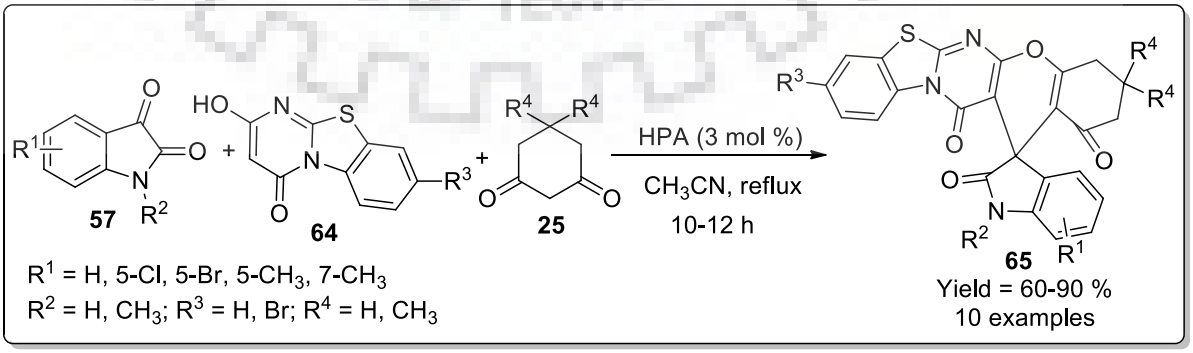


Figure 1.28 $H_3PW_{12}O_{40}$-catalysed access to diversified spirooxindoles.

Choudhury *et al.* (2019) reported the microwave-assisted synthesis of two different class of fused spirooxindoles from similar starting materials *viz.* isatin (**57**), 4-hydroxycoumarins (**37**) and aminopyrazole (**66**) by changing solvent and heating condition (**Figure 1.29**). [114] The synthesis of spirooxindoles fused with pyrazolo-tetrahydropyridinones (**68**) was reported under microwave irradiation of reaction mixture at 85 ºC for 25 minutes in acetonitrile medium by ring opening of 4-hydroxycoumarins (**37**). Whereas, the microwave irradiation of the same reaction mixture at 130 ºC for 25 minutes in acetic acid provided spirooxindole fused coumarin-dihydropyridine-pyrazole/ isooxazole tetracycles (**67**) in good to excellent yields (81- 96 %) (**Figure 1.29**).

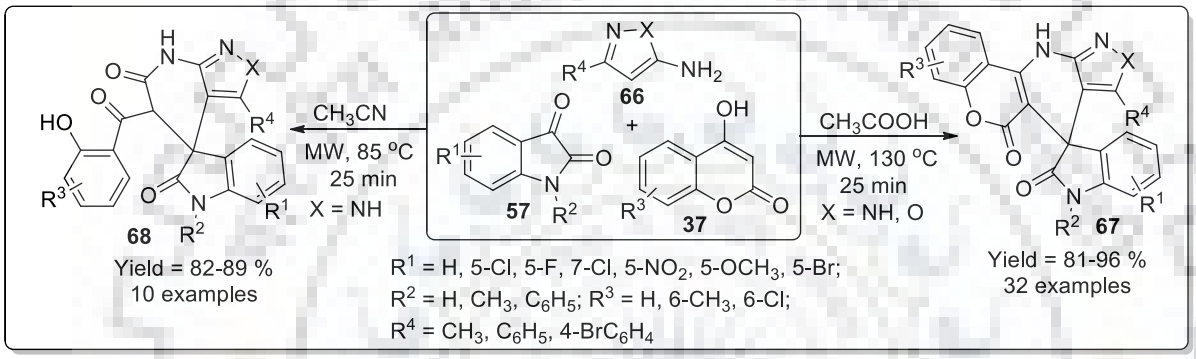


Figure 1.29 Microwave-assisted three-component reaction to access spirooxindoles.

1.8 Abstract and objective of the thesis

Heterocycles containing N, O and S atoms in the ring, generally show promising biological applications. Synthesis of diversified heterocycles are in high demand due to their wide applications. To fulfill the ongoing demand, the main role of a chemist is to supply novel heterocycles which can be further screened to find out their biological and pharmaceutical applications. Multicomponent reactions (MCRs) are turned up to be an efficient synthetic strategy to deliver such structural diverse scaffolds in time and help building up chemical libraries with larger scope. MCRs are recognized as the chemical transformations of more than two components mainly operated in one-pot to construct the desired products. The MCR strategy has several advantages like operational simplicity, higher atom efficiency and diverse scaffolds generation in short reaction time over single step operation. Several tools and techniques are used to develop a MCR protocol however application of mechanochemical hand-grinding and microwave irradiation in developing new MCRs strategies are presented in this chapter to synthesize functionalized heterocycles. Amongst heterocycles, pyrans and spirooxindoles are worth mentioning due to their wide range of biological and medicinal activities. The chapter also includes a brief description of biological importance and several synthesis procedures of pyrans and spirooxindoles. In short, the background of the present research work is highlighted in this chapter. However, the previous literature survey revealed that there is still scope not only in synthesizing novel biologically relevant heterocycles but also in developing greener and efficient methodologies to access diversified scaffolds. Thus, the presented work is focused on developing efficient green synthetic protocols for synthesis of structurally diverse heterocycles like pyrans, spirooxindoles, bis(benzo[*f*]chromen-3-one), acridione, thioxanthendione, bis(hydroxycyclohex-2-enone), tetrahydroquinazolindione derivatives.

In the second chapter, DABCO-catalysed liquid-assisted grinding for the synthesis of novel dihydrobenzo[*f*]pyrano[3,2-*c*]chromenone derivatives has been described. The reported methodology is simple, facile and mild to construct such multicomponent cascade. The benefits of developed one-pot protocol includes diversified scope, excellent yields and high reaction throughput apart from excellent green matrices scores.

In third chapter, a urea-catalysed easy and facile microwave-assisted protocol is described to construct spiro-benzo[*f*]pyranochromenes in higher yields. The use of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one as a key reactant in such three-component reaction is reported for the first

time to provide such novel multicomponent cascade. The superiority of the reported methodology is the operational simplicity, diversified scope and gram scale synthesis along with very good green matrices scores which highlights the synthesis protocol for industry as well.

In fourth chapter, microwave-assisted DABCO-catalysed synthesis of bis(benzo[*f*]chromen-3-one) derivatives are reported. The advantages of the methods is the column free efficient synthesis and mere filtration provides good to excellent yield without using any harsh reagent.

In fifth chapter, the applications of vinyl esters as acetaldehyde surrogates in different well-known multicomponent reaction are reported. Use of acetaldehyde is limited in synthetic chemistry due to self-polymerizations or lower stability. In this report, the effective utilization of vinyl esters as acetaldehyde surrogates in different conditions are explored efficiently to obtain biologically potent scaffolds. The reported methodology is quite successful to formulate different derivatives like acridione, thioxanthendione, bis(hydroxycyclohex-2-enone), tetrahydroquinazolindione in moderate to good yield.

The objective of the present work is highlighted in **Figure 1.30**.

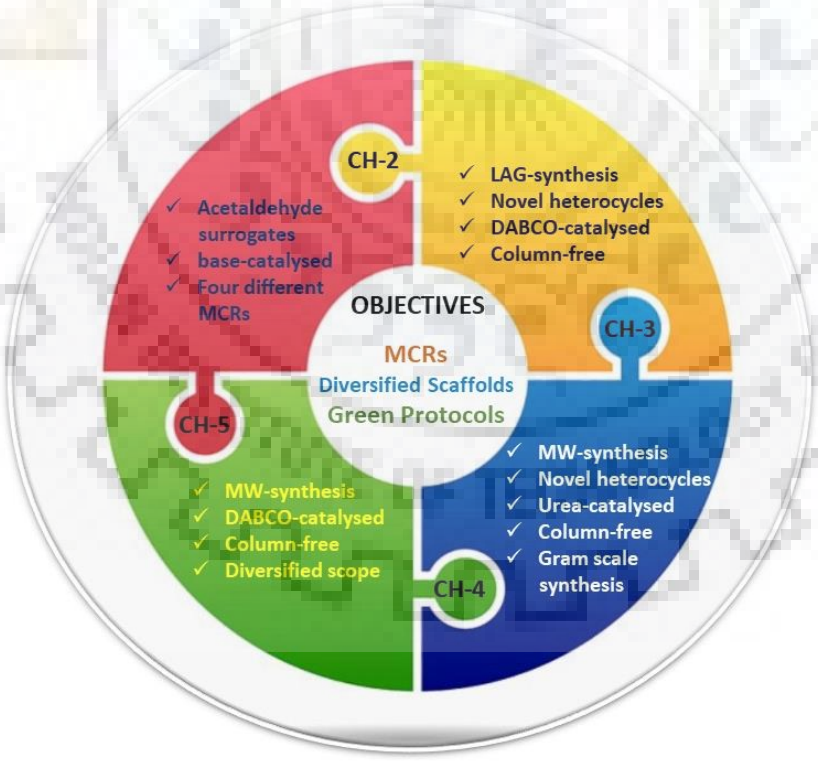


Figure 1.30 Objective of the thesis work.

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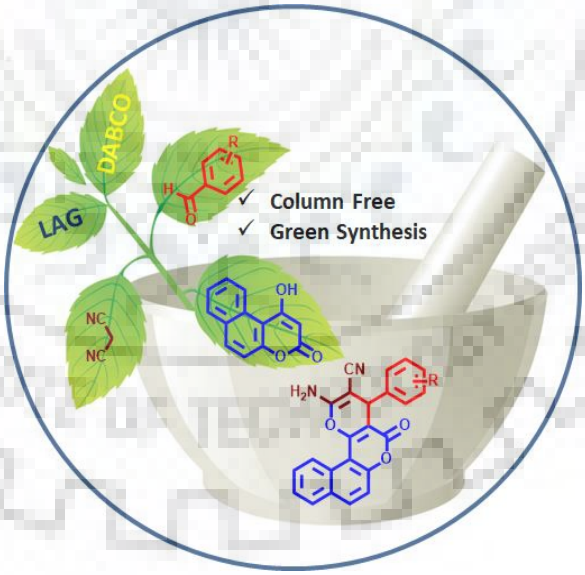
CHAPTER 2

DABCO-Catalysed Green Synthetic Protocol

for

Novel Pyranochromenone Derivatives



2.1 Introduction

Naturally occurring coumarins are known to exhibit various biological activities such as insecticidal, anticoagulant, antihelminthic, antifungal, hypnotic, HIV protease inhibition activities. [1-6] In particular, pyranochromenone is frequently present as a basic skeleton in several naturally occuring molecules like isoethuliacoumarin A (**I**), isoethuliacoumarin B (**II**), ethuliacoumarin A (**III**), pterophyllin III (**IV**), bothrioclinin (**V**) and cyclocoumarol (**VI**) etc. (**Figure 2.1**). [7-9]

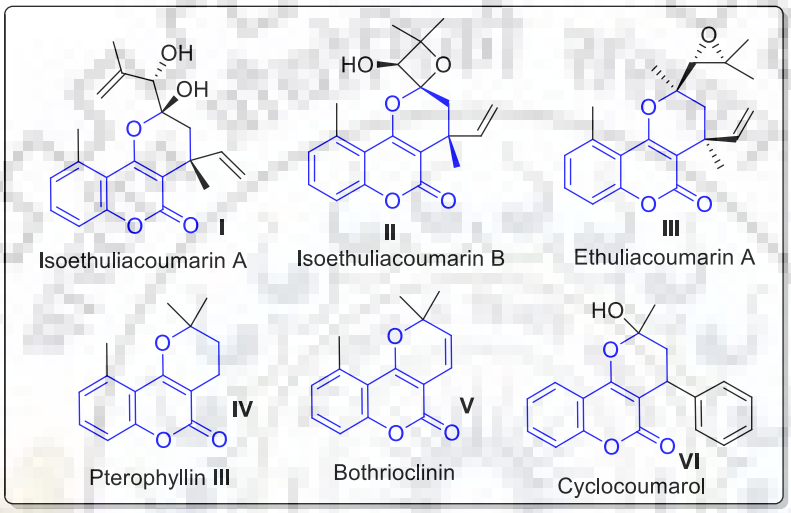


Figure 2.1 Naturally occurring pyranochromenone.

Similarly, pyranochromenones show a wide range of biological activities, for example, anticancer, anti-TB, antifungal, analgesic, anti-HIV, anti-inflammatory and cytotoxic activities (**Figure 2.2**). [10-18]

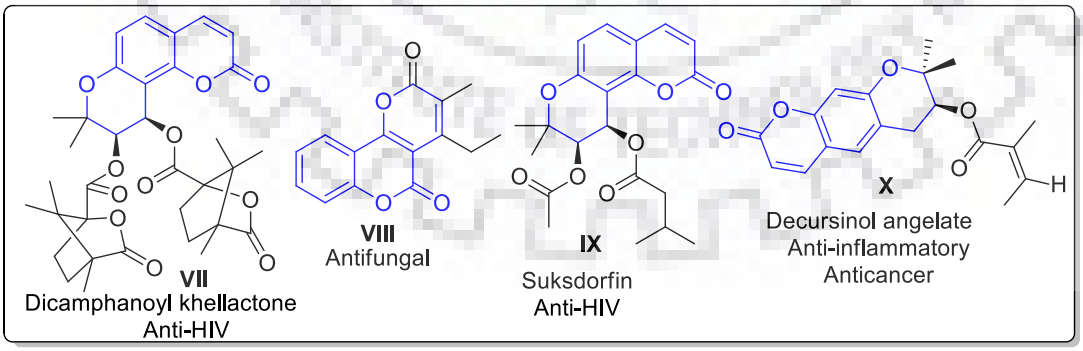


Figure 2.2 Biologically active pyranochromenone.

2.2 Survey of existing methodologies

Many synthetic methodologies have been reported till date in the literature for accessing pyranochromenone compounds which in general, involve Michael addition of 4-hydroxychromenones to a Michael acceptor followed by nucleophilic substitution/cyclisation by the chromene hydroxyl function. Various reagents and substrates have been used using essentially the same strategy.

Khurana *et al.* (2010) attempted the base catalysed protocol using 4-hydroxycoumarin (**3**), aldehydes (**1**) and active methylene compounds like malononitrile (**2a**) /ethyl cyanoacetate (**2b**) to construct pyranochromene derivatives (**4**). The reported reaction provided desired products (**4**) in good to high yields (81-94 %) in water under reflux conditon using 10 mol % DBU as a basic catalyst **(Figure 2.3).** [19]

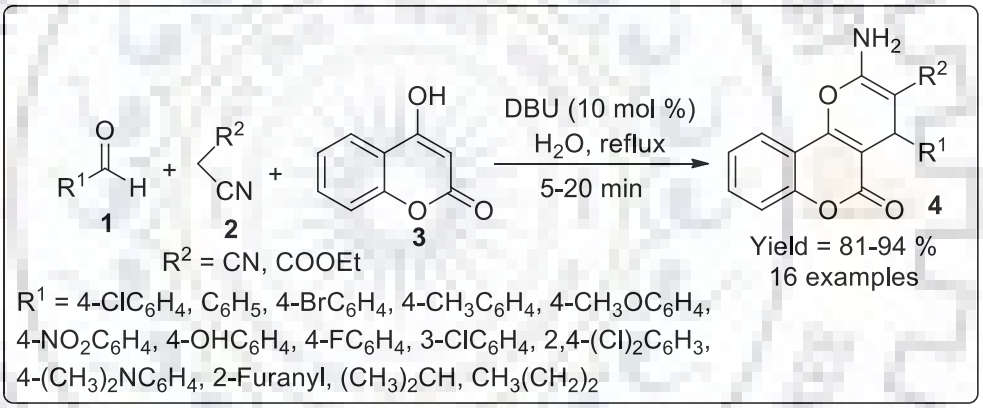


Figure 2.3 DBU-catalysed synthesis of pyranochromene derivatives.

The plausible mechanism of the three-component reaction is depicted in **Figure 2.4**. Mechanistically, the reaction proceeds through a DBU catalysed formation of Knoevenagel adduct **A**. Next, Michael attack of 4-hydroxycoumarin (**3**) to **A** gives intermediate **B** which is further cyclized in the presence of DBU to give the final product **4**.

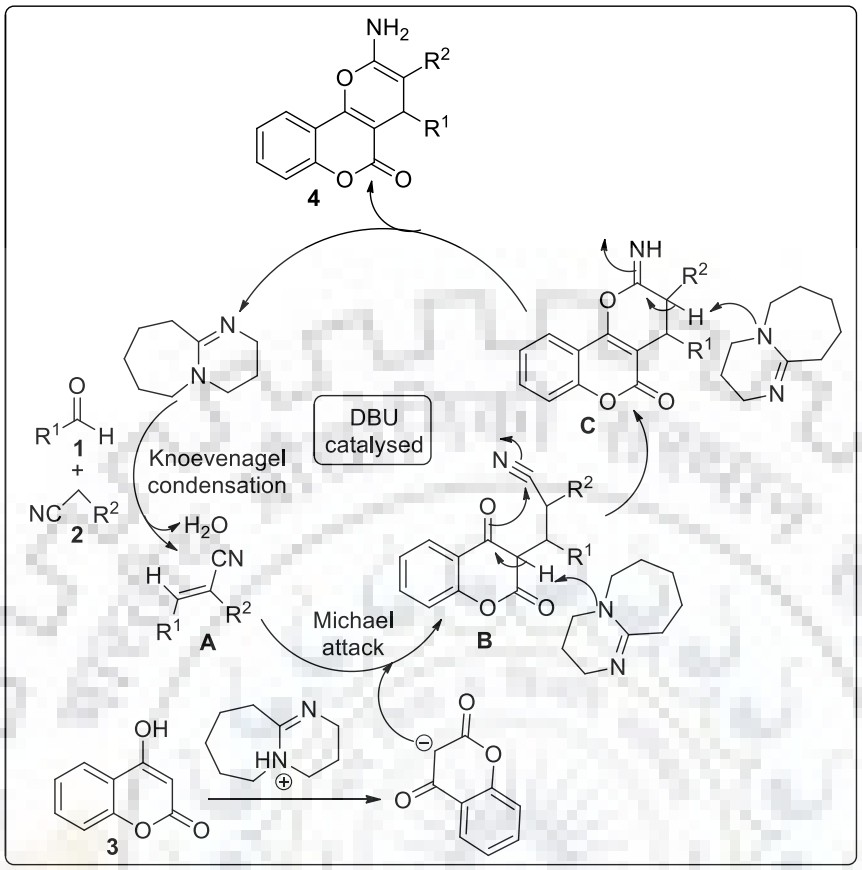


Figure 2.4 Plausible mechanism of DBU-promoted synthesis of pyranochromenes.

On a similar note, in 2013 Dekamin and co-workers synthesized 2-amino-4*H*-chromene derivatives (**4**) using potassium phthalimide-*N*-oxyl (POPINO) as an organocatalyst in aqueous media under reflux conditions (**Figure 2.5**). [20]

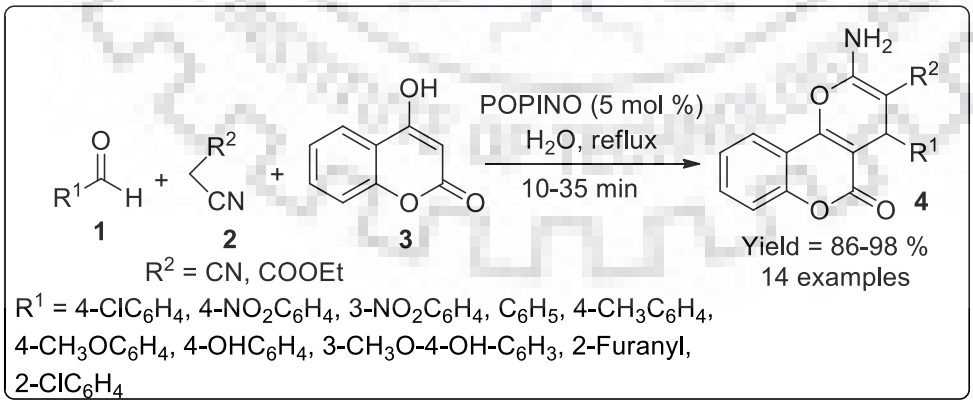


Figure 2.5 Potassium phthalimide-*N*-oxyl (POPINO)-catalysed synthesis of pyranochromene derivatives.

Later on, Karami *et al.* (2015) reported nanosilica molybdic acid (nano-SMA) catalysed one-pot three-component condensation of 4-hydroxycoumarin (**3**), various aldehydes (**1**) and malononitrile (**2a**) to construct various pyrano[2,3-*c*]chromenes (**4**) (**Figure 2.6**) in good to excellent yield (70-96 %). [21]

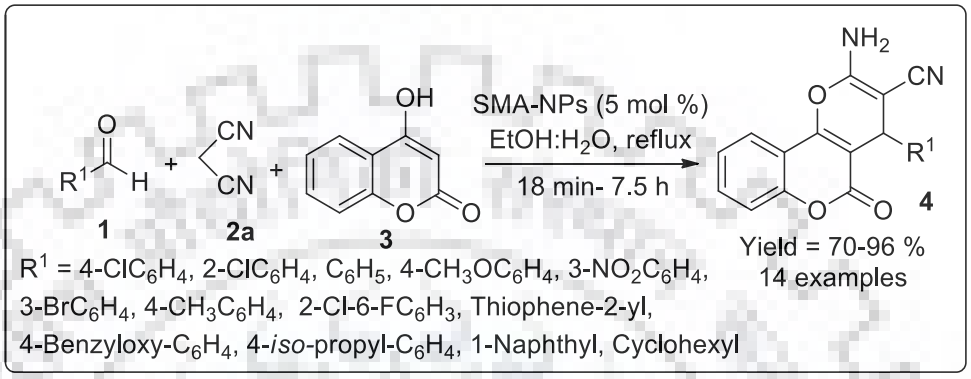


Figure 2.6 Nanosilica molybdic acid catalysed synthesis of pyranochromene derivatives.

Bhosle and co-workers (2018) reported *β*-cyclodextrin promoted synthesis of diversified dihydropyranochromenes (**4**) in aqueous media in moderate to high yields (63-93 %) (**Figure 2.7**). [22]

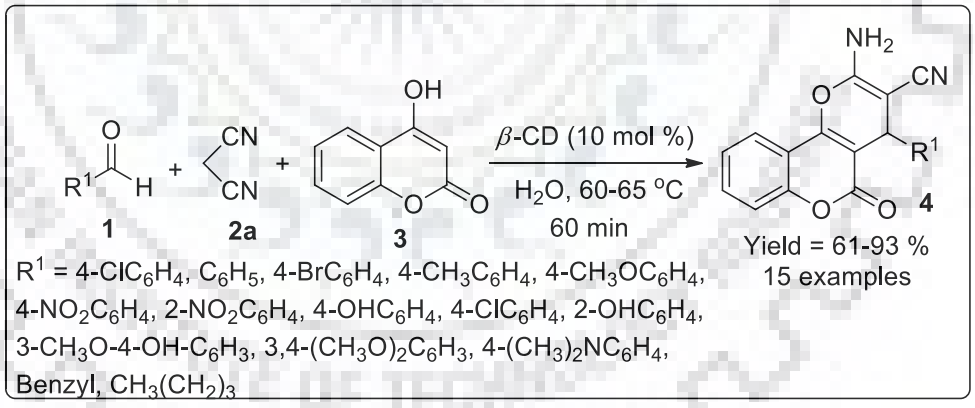


Figure 2.7 *β*-Cyclodextrin promoted synthesis of diversified dihydropyranochromenes.

In continuation, Shirini and co-workers (2018) reported the synthesis of functionalized 2-amino-3-cyano-4*H*-pyrans (**4**) in water using piperazine as an efficient basic catalyst. Interestingly, the authors found that a smaller amount of catalyst (22 mol %) was required in heating of the reaction mixture (method A) whereas a little larger amount of catalyst (58 mol %) ensured that the reaction went well at room temperature (method B) (**Figure 2.8**). [23] Moreover, the reaction provided

competitively higher yields under heating (97-99 %) than stirring at room temperature (92-98 %) for a longer time.

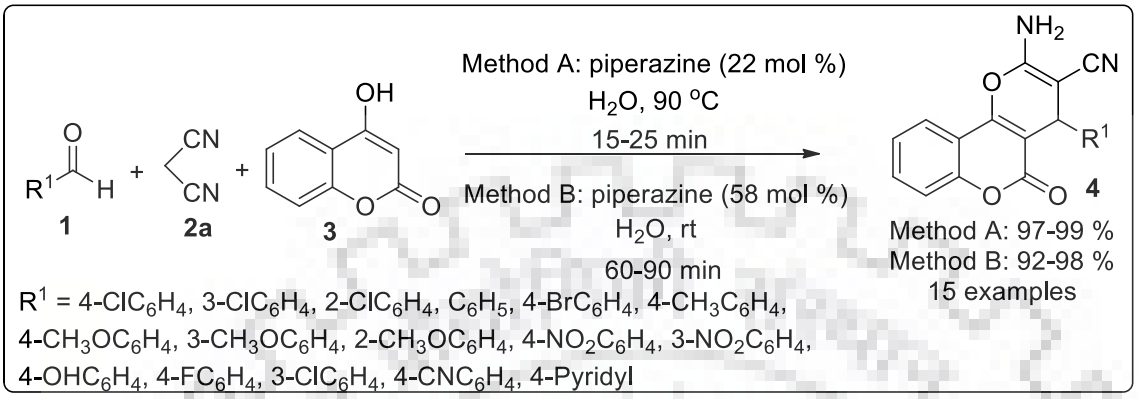


Figure 2.8 Piperazine-catalysed synthesis of functionalized 2-amino-3-cyano-4*H*-pyrans.

In addition to the above, there are several other important methods reported using the above mentioned substrates. A variety of reagents have been used in these transformations, namely, urea [24], $Bi(OTf)_3$ [25], $Cu(OTf)_2$ [26], $Ca(OTf)_2$ [27], ionic liquid-coated carbon nanotubes [28] and $(CTA)_3[SiW_{12}]$-Li^+-MMT [29] amongst others.

Unfortunately, there are limited reports with 4-hydroxy-2H-benzo[*h*]chromen-2-one (**5**) istead of 4-hydroxycoumarin in the above mentioned three-component reaction. This included a report in 2014, wherein Zeeb and co-workers synthesized dihyrobenzo[*h*]pyrano[3,2-*c*]chromenes (**6**) at room temperature using triethylamine as a base using aromatic aldehydes (**1**), malononitrile (**2a**) and 4-hydroxy-2*H*-benzo[*h*]chromen-2-one (**5**) as substrates in moderate to good yields (69-85 %) in 5-8 hours (**Figure 2.9**). [30]

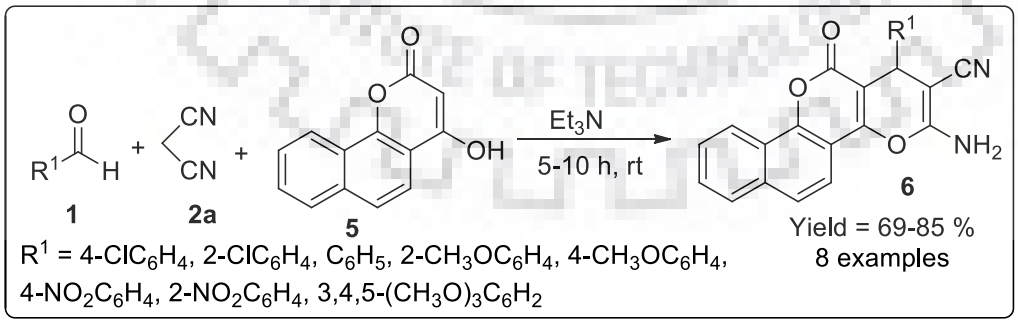


Figure 2.9 Triethylamine-catalysed synthesis of dihydrobenzo[*h*]pyrano[3,2-*c*]chromenes.

Later, Foroumadi *et al.* (2015) modified this reaction by using catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) in ethanol at room temperature for 8-12 hours to construct diversified benzopyranochromenes (**6**) (**Figure 2.10**) in comparatively higher yields (70-90 %). [31]

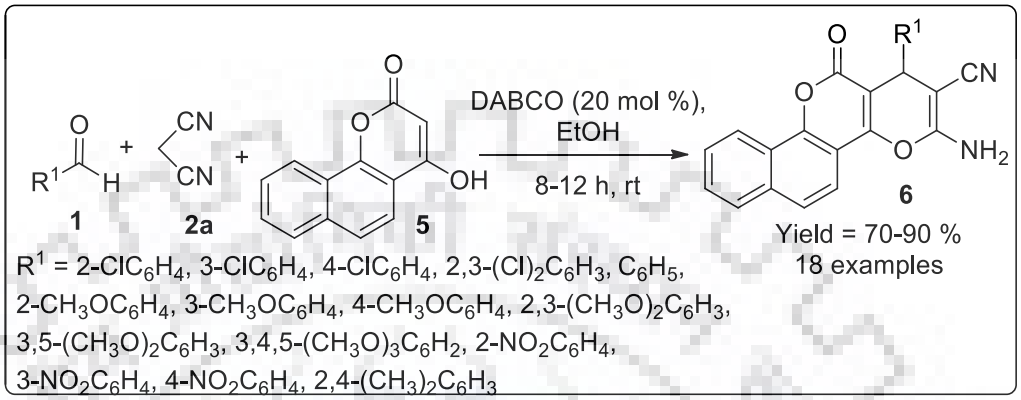


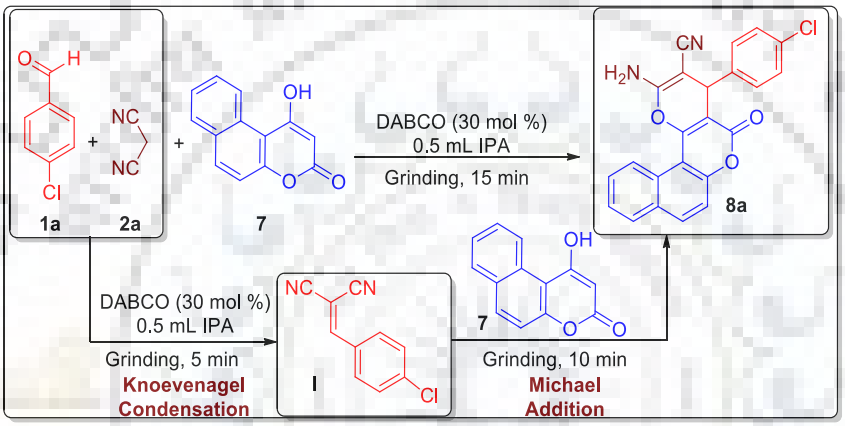
Figure 2.10 DABCO-catalysed synthesis of diversified benzopyranochromenes.

Although the reported reactions are meritorious in their own right, nevertheless most of them suffer from drawbacks such as pre-functionalised substrates, use of expensive ionic liquids, metal catalysts, chiral organocatalysts, nanoparticles, nanotubes, long reaction time and formation of large chemical waste. Therefore, a mild, greener and more effective alternative to target novel diversified pyranochromenone motifs is required.

Hence, in an extension to our ongoing interest to develop sustainable methodologies for diversified heterocyclic compounds [32-35], a liquid-assisted grinding, one-pot domino synthesis of novel dihydrobenzo[*f*]pyrano[3,2-*c*]chromenones is presented using catalytic amount of DABCO for effective transformation of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one as a substrate. Notably, the merits of the developed protocol presented in this chapter are (i) operational simplicity; (ii) reaction in few minutes; (iii) non-tedious work up and (iv) excellent green matrices score.

2.3 Results and discussion

In order to develop a green methodology, initially in a sequential reaction, 4-chlorobenzaldehyde **1a** (1.0 equiv.) and malononitrile **2a** (1.0 equiv.) were mixed together by manual grinding for 5 minutes followed by the addition of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one **7** (1.0 equiv.) and continued grinding for another 10 minutes in an agate-mortar and pestle (**Scheme 2.1**). Unfortunately, the anticipated product 2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile **8a** was not formed even after extended time of grinding (**Table 2.1**, entry 1).

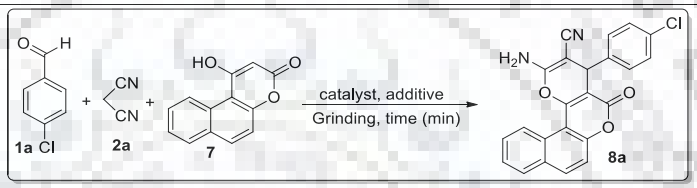


Scheme 2.1 Sequential three-component reaction for the synthesis of benzo[*f*]pyrano[3,2-*c*]chromenes.

In continuation, anticipating base catalysed acceleration in the Knoevenagel condensation and subsequent Michael addition as shown in **Scheme 2.1**, the starting substrates **1a** and **2a** were mixed and ground for 5 minutes followed by addition of **7** and ground for another 10 minutes using 20 mol % DABCO. Fortunately, the desired product **8a** was obtained in 57 % yield along with unreacted starting materials (**Table 2.1**, entry 2). Further, addition of 0.25 mL IPA as a promoter effectively increase the yield of **8a** upto 73 % (**Table 2.1**, entry 3). In the resulted product, three new bonds were simultaneously formed in a sequential reaction via liquid-assisted grinding. Next, the efficiency of different bases like DBU, Et_3N, K_2CO_3 and piperidine were examined in the above conversion but there was no further enhancement in product yield in any case (**Table 2.1**, entries 4-7). In continuation, 30 mol % DABCO turned out to be the optimized amount of catalyst for this transformation (**Table 2.1**, entries 8-10). Later, this reaction was screened for different grinding time (**Table 2.1**, entries 11-12) and with different promoters like ACN and EtOH (**Table 2.1**, entries 13-

14). From these sets of reactions, it was clearly noted that 15 minutes of grinding in the presence of IPA as a polar protic promoter is ideal for the desired transformation. Hence, the optimum condition for this sequential three-component reaction was manual grinding for 15 minutes in an agate-mortar and pestle of each substrates benzaldehydes (**1**, 1.0 mmol), malononitrile (**2a**, 1.0 mmol) and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**7**, 1.0 mmol), in 30 mol % DABCO using 0.25 mL IPA as a promoter. The final pure product **8a** was obtained just by mere filtration and washing with IPA: water (1:2) solvent mixture and no further purification process was required.

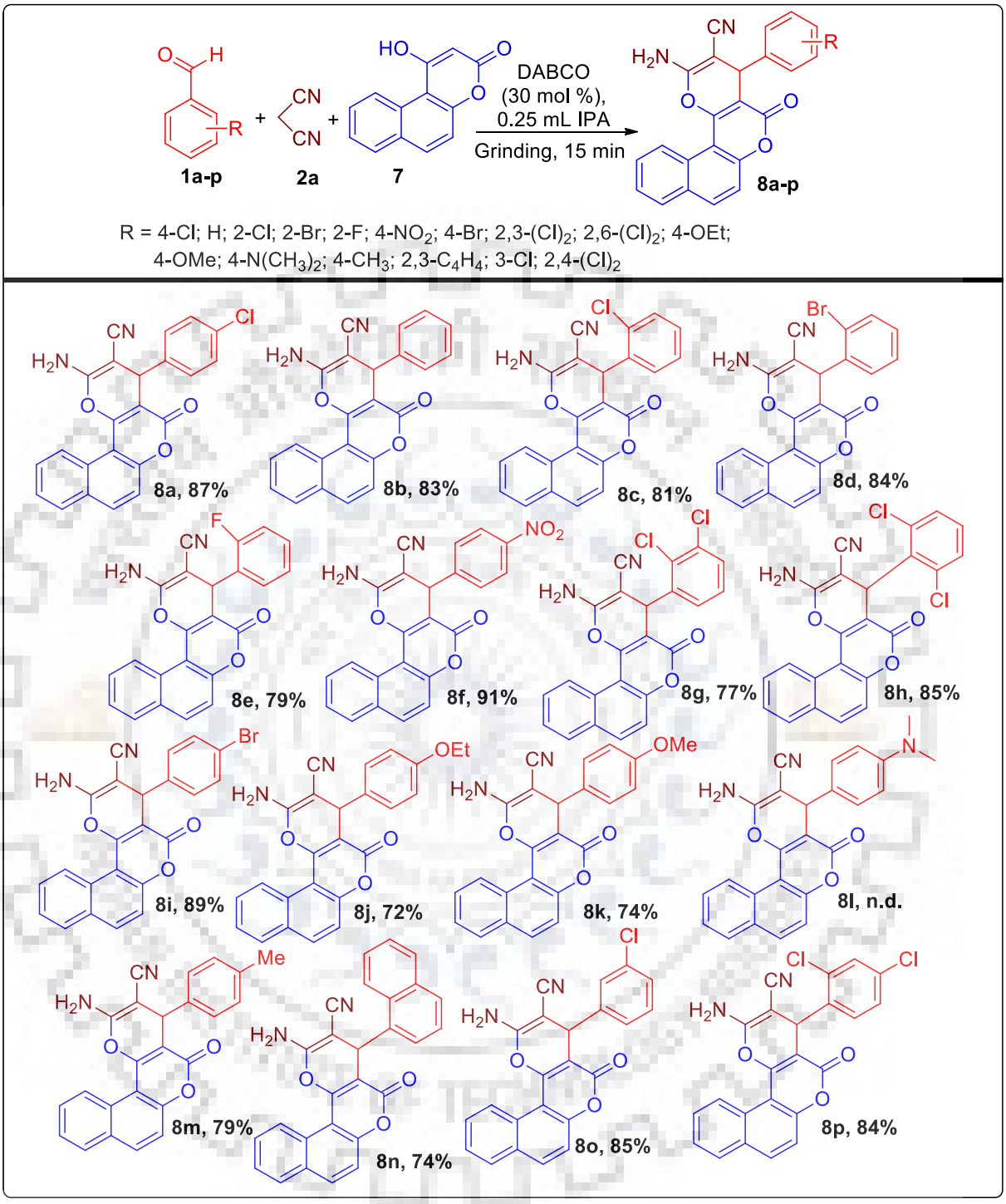
Table 2.1 Optimization of the domino reaction between 4-chlorobenzaldehyde (**1a**), malononitrile (**2a**) and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**7**)[a].



Entry	Catalyst (mol %)	Promoter (0.25 mL)	Condition	Time (min)	Yield (%)[b]
1	-	-	Grinding	15	-
2	DABCO (20 mol %)	-	Grinding	15	57
3	DABCO (20 mol %)	IPA	Grinding	15	73
4	DBU (20 mol %)	IPA	Grinding	15	nd
5	Et_3N (20 mol %)	IPA	Grinding	15	59
6	K_2CO_3 (20 mol %)	H_2O	Grinding	15	37
7	Piperidine (20 mol %)	IPA	Grinding	15	nd
8	DABCO (10 mol %)	IPA	Grinding	15	69
9	**DABCO (30 mol %)**	**IPA**	**Grinding**	**15**	**87**
10	DABCO (40 mol %)	IPA	Grinding	15	84
11	DABCO (30 mol %)	IPA	Grinding	10	67
12	DABCO (30 mol %)	IPA	Grinding	20	88
13	DABCO (30 mol %)	ACN	Grinding	15	55
14	DABCO (30 mol %)	EtOH	Grinding	15	76

[a]Reaction conditions: Grinding in agate-mortar and pestle, **1a** (1.0 equiv.), **2a** (1.0 equiv.), **7** (1.0 equiv.); Knoevenagel condensation : 5 min; Final conditions: (5+10) min sequential addition; nd: not determined; [b]Isolated yields.

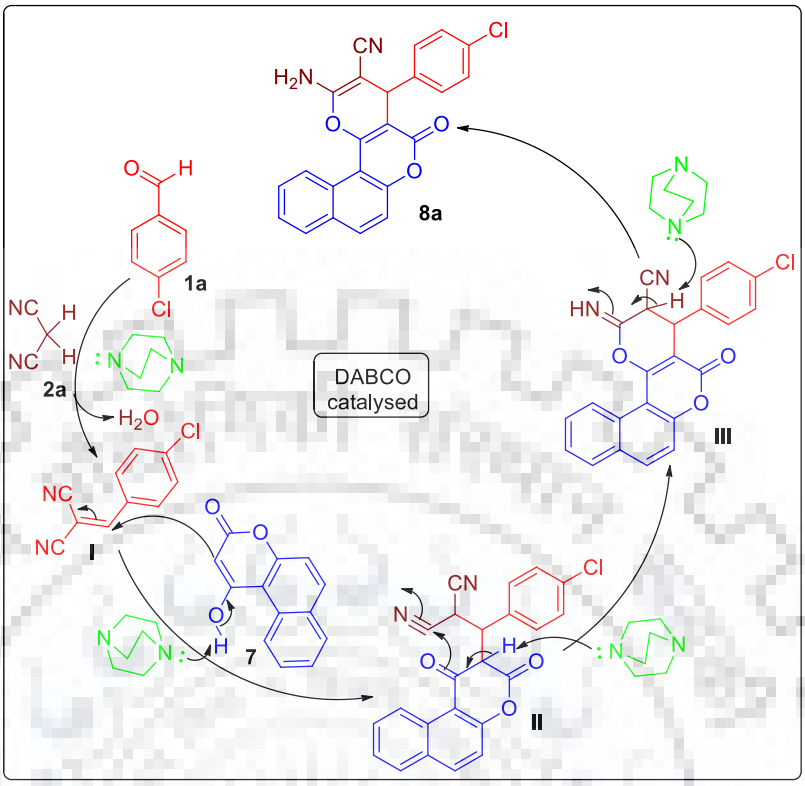
With optimized conditions for the domino reaction in hand, next set of reactions are focused on finding its scope and limitations using substituted aldehydes and the corresponding results are presented in **Scheme 2.2**. All the electron-withdrawing and electron-donating substituted aromatic aldehydes were reacted to synthesize respective desired products **8a-p** in good to high yields (72-91 %). However, it was worth noting that product yields were higher in case of unsubstituted (83 %, **8b**) and electron deficient benzaldehydes (4-Cl (87 %, **8a**); 2-Cl (81 %, **8c**); 2-Br (84 %, **8d**); 2-F (79 %, **8e**); 4-NO_2 (91 %, **8f**); 2,3-$(Cl)_2$ (77 %, **8g**); 2,6-$(Cl)_2$ (85 %, **8h**); 4-Br (89 %, **8i**); 3-Cl (85 %, **8o**) and 2,4-$(Cl)_2$ (84 %, **8p**)) as compared to other electron rich benzaldehydes (4-OEt (72 %, **8j**); 4-OMe (74 %, **8k**) and 4-Me (79 %, **8m**)). Unfortunately, 4-*N*,*N*-dimethyl benzaldehyde did not provide the requisite product **8l** and the starting material **7** remained unreacted in the reaction mixture. Moreover, the reaction went smoothly with 1-napthaldehyde to provide **8n** in good yield (74 %). However, the role of steric influence on the reaction outcome was also observed while *ortho*-substituted aldehydes provided lower yield of the corresponding products (2-Cl (81 %, **8c**); 2-Br (84 %, **8d**)) as compared to *para*-substituted (4-Cl (87 %, **8a**); 4-Br (89 %, **8i**)). Unfortunately, the multicomponent transformation did not go well with ethyl cyanoacetate and ended up with multiple spots on TLC. This observation may be a consequence of more reactivity and lower pKa value of malononitrile than ethyl cyanoacetate. [36]



Scheme 2.2 Domino reaction between aromatic aldehydes (**1**), malononitrile (**2a**) and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**7**). [a]Reaction conditions: Grinding in agate-mortar and pestle: **1** (1.0 mmol), **2a** (1.0 mmol), **7** (1.0 mmol), DABCO (0.30 mmol), IPA (0.25 mL), 15 min.

The plausible mechanism for the synthesis of 2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (**8a**) is outlined in **Scheme 2.3**. In the first step, DABCO-catalysed Knoevenagel condensation between 4-chlorobenzaldehyde (**1a**) and malononitrile (**2a**) yields intermediate **I**. In the following step, Michael attack of **7** on intermediate **I** provides another intermediate **II**. In the subsequent step, the intermediate **III** is formed by DABCO-assisted intramolecular cyclisation of intermediate **II** and finally the desired product 2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (**8a**) is resulted due to subsequent proton shift in intermediate **III**.

To find out the effective "greenness" of the reported methodology, the reaction was carried out to calculate different green matrices for the synthesis of novel 2-amino-5-oxo-4-phenyl-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (**8a**). The aim of this experiment was focused on calculating atom efficiency (AE), carbon efficiency (CE), reaction mass efficiency (RME), Sheldon environmental impact factor (E-factor) and process mass intensity (PMI) of the reaction protocol. Fortunately, the reaction scored well in all these green calculations with high atom efficiency (95.70 %), 100 % carbon efficiency, 83.10 % of RME and low E-factor (0.82) and 1.82 PMI (**Figure 2.11**). Hence, the reaction methodology presented in this chapter is green based on rational yardsticks for greenness.



Scheme 2.3 Plausible mechanism for the synthesis of 2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (**8a**).

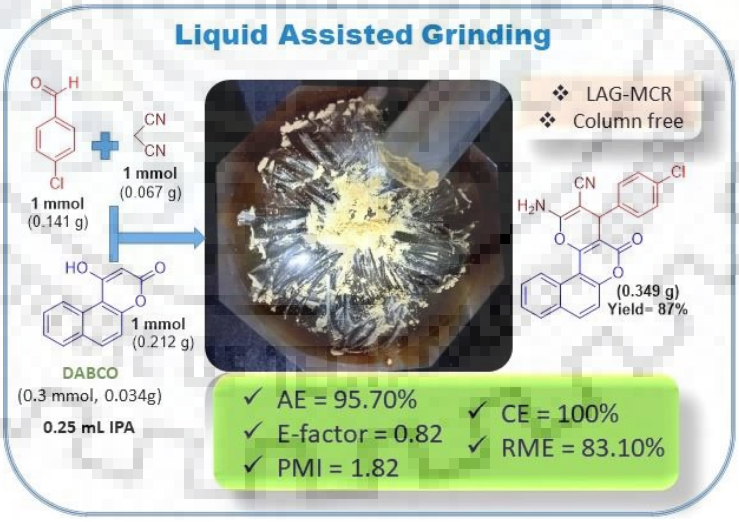


Figure 2.11 Green matrices calculation for the synthesis of **8a**.

2.4 Conclusions

In short, a domino liquid-assisted hand grinding DABCO-catalysed protocol for the synthesis of novel dihydrobenzo[*f*]pyrano[3,2-*c*]chromenone using aromatic aldehydes, malononitrile and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one as key reactants was developed effectively. The reported methodology is highly efficient, atom-economical and have effective green matrices scores. Most interestingly, all the synthesized products were obtained by filtration only. The reaction condition tolerated various functional groups to derive the final pyranochromenones in good to high yields.

2.5 Experimental section

2.5.1 General information

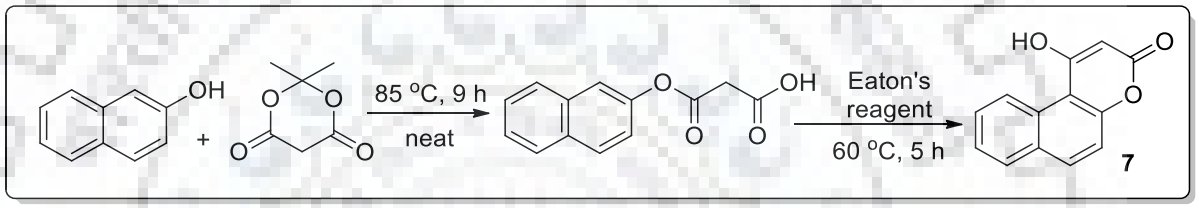
Except 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**7**), which was prepared in accordance with the reported literature [36], all other substrates, reagents and solvents were purchased commercially. ^{1}H NMR spectra were taken by JEOL Resonance® ECX-400II (400 MHz) and Bruker Avance® III (500 MHz), ^{13}C NMR spectra were respectively recorded at 100 and 125 MHz. Deuterated DMSO (DMSO-d_6) with TMS as internal standard was used as a solvent for taking NMR analyses. In the evaluation of ^{1}H NMR spectra, chemical shift has been assigned in units of parts per million (ppm), wherein,"s" stands for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "dd" for doublet of doublet", "brs" for broad singlet and "m" for multiplet. The units of coupling constant (*J*) has been assigned in Hz. The High Resolution Mass Spectra (HRMS) of three representative compounds **8a**, **8m** and **8n** were recorded on Bruker daltronics microTOF-QII® spectrometer using ESI ionization. Functional groups were detected by Perkin Elmer® FT-IR spectrometer-Spectrum two. Elemental analyses were carried out on vario MICRO cube Elementar®. Melting points were obtained on Optimelt® automated melting point system. Analyses of reactions were done using thin layer chromatography (TLC), which was performed on silica gel TLC plates.

The synthesis of pyranochromenones **8** were achieved on agate-mortar and pestle.

2.5.2 General procedure

Synthesis of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (7) [36]:

The mixture of 2-naphthol (2 mmol) and meldrum's acid (2 mmol) was stirred at 85 °C for 9 h (**Scheme 2.4**). After that, the reaction mixture was cooled to room temperature and extracted with ethyl acetate followed by saturated $NaHCO_3$ solution. The collected water extract was acidified with conc. HCl and further extracted with methylene dichloride (DCM) to yield the crude intermediate after evaporating the organic solvent. This crude intermediate (1 mmol) in 1.5 mL Eaton's reagent was stirred at 60 °C for 5 h. To this resultant mixture, water was added while vigorous stirring. The precipitate thus obtained was filtered by suction and dried to get final product **7**.



Scheme 2.4 Synthesis of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one.

[36] Park, S.-J.; Lee, J.-C.; Lee, K.-I.; A Facile Synthesis of 4-Hydroxycoumarin and 4-Hydroxy-2-quinolone Derivatives. *Bull. Korean Chem. Soc.* **2007**, *28*, 1203-1205.

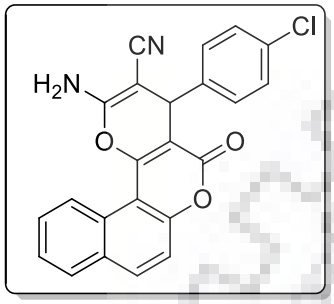
Synthesis of benzo[*f*]pyrano[3,2-*c*]chromenes derivatives (8a-8p):

In an agate- mortar and pestle, 1 mmol each of aromatic aldehydes (**1**), malononitrile (**2a**) were ground for 5 minutes in 30 mol % DABCO and 0.25 mL IPA. To the Knoevenagel product thus formed, 1 mmol of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**7**) was added and the resulting mixture was further ground for next 10 minutes. The solid hence obtained was filtered off and washed with isopropanol: water (1:4) to yield the desired products **8**.

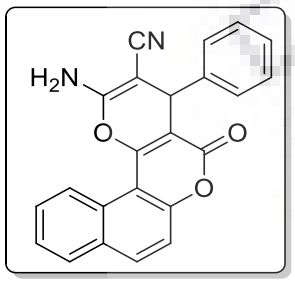
2.5.3 Characterization of the synthesized molecules

All the products were characterized via techniques of ^{1}H NMR, ^{13}C NMR Spectra, FT-IR and elemental analyses. Further, selected HRMS of **8a**, **8m** and **8n** compounds are reported to confirm the products.

Analytical information for the synthesized molecules is given below:

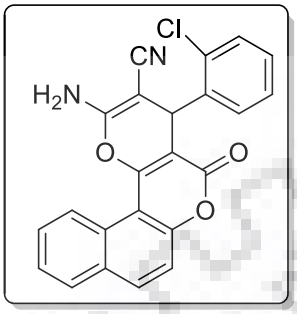


2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8a): Yellow solid (87 %); mp: 288-290 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.20 (d, 1H, *J* = 8.8 Hz), 8.21 (d, 1H, *J* = 8.8 Hz), 8.05 (d, 1H, *J* = 7.6 Hz), 7.78-7.61 (m, 4H), 7.52 (d, 1H, *J* = 8.8 Hz), 7.45-7.30 (m, 4H), 4.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.9, 158.4, 157.4, 153.8, 143.2, 135.2, 132.2, 131.1, 130.1, 129.7, 129.6, 129.0, 128.2, 127.2, 126.7, 119.6, 117.4, 106.9, 104.1, 57.9, 36.9; IR (KBr) υ_{max}/cm^{-1}: 3434, 2192, 1707, 1668, 1564, 1379; Elem. Anal. For $C_{23}H_{13}ClN_2O_3$: calcd.: C: 68.92; H: 3.27; N: 6.99 %; found: C: 69.12; H: 3.15; N: 6.81 %; HRMS (ESI) m/z calcd. for $C_{23}H_{13}ClN_2O_3$ $[M+Na]^+$: 423.0506, found: 423.0503.

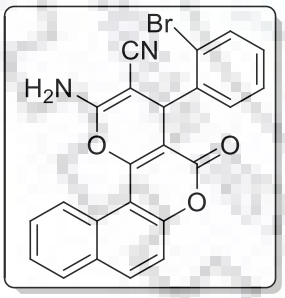


2-amino-5-oxo-4-phenyl-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8b): Pale yellow solid (83 %); mp: 291-292 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.25 (d, 1H, *J* = 8.4 Hz), 8.25 (d, 1H, *J* = 8.8 Hz), 8.08 (d, 1H, *J* = 9.2 Hz), 7.73 (t, 1H, *J* = 6.8 Hz), 7.67 (t, 1H, *J* = 6.8 Hz), 7.62 (brs, 2H), 7.56 (d, 1H, *J* = 8.8 Hz), 7.35-7.28 (m, 4H), 7.27-7.21 (m, 1H), 4.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.9, 158.5, 157.3, 153.8, 144.2, 135.1, 131.1, 129.7,

129.6, 129.1, 128.2, 128.1, 127.6, 127.2, 126.6, 119.8, 117.4, 107.0, 104.7, 58.5, 37.4; IR (KBr) υ_{max}/cm^{-1}: 3565, 2209, 1673, 1520, 1382; Elem. Anal. For $C_{23}H_{14}N_2O_3$: calcd.: C: 75.40; H: 3.85; N: 7.65 %; found: C: 75.05; H: 3.93; N: 6.85 %.

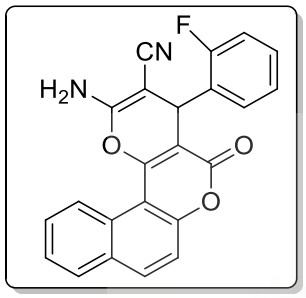


2-amino-4-(2-chlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8c): Yellow solid (81 %); mp: 268-270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.25 (d, 1H, *J* = 8.4 Hz), 8.25 (d, 1H, *J* = 9.2 Hz), 8.08 (d, 1H, *J* = 7.2 Hz), 7.74 (t, 1H, *J* = 6.8 Hz), 7.67 (t, 1H, *J* = 6.8 Hz), 7.61 (brs, 2H), 7.56 (d, 1H, *J* = 8.8 Hz), 7.44-7.39 (m, 1H), 7.38-7.33 (m, 1H), 7.30-7.23 (m, 2H), 5.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.7, 158.5, 157.9, 153.9, 141.2, 135.3, 132.9, 131.2, 131.1, 130.1, 129.7, 129.6, 129.3, 128.3, 128.2, 127.2, 126.7, 119.4, 118.6, 117.4, 106.8, 103.5, 56.9, 34.8; IR (KBr) υ_{max}/cm^{-1}: 3435, 2200, 1638, 1402; Elem. Anal. For $C_{23}H_{13}ClN_2O_3$: calcd.: C: 68.92; H: 3.27; N: 6.99 %; found: C: 68.72; H: 3.43; N: 7.28 %.

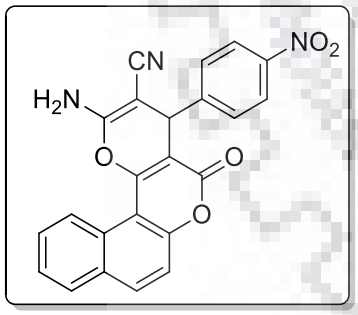


2-amino-4-(2-bromophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8d): Pale yellow solid (84 %); mp: 268-270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.25 (d, 1H, *J* = 8.8 Hz), 8.25 (d, 1H, *J* = 9.2 Hz), 8.08 (d, 1H, *J* = 8.0 Hz), 7.74 (t, 1H, *J* = 6.8 Hz), 7.67 (t, 1H, *J* = 7.6 Hz), 7.60 (brs, 2H), 7.59-7.54 (m, 2H), 7.36-7.28 (m, 2H), 7.18 (t, 1H, *J* = 6.8 Hz), 5.05 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.7, 158.4, 157.9, 153.9, 142.9, 135.2, 133.3, 131.1, 129.7, 129.6, 129.5, 128.9, 128.2, 127.3, 126.6, 123.4, 119.3, 118.6, 117.4, 106.8, 103.8, 57.2,

37.0; IR (KBr) υ_{max}/cm^{-1}: 3434, 2200, 1638, 1402; Elem. Anal. For $C_{23}H_{13}BrN_2O_3$: calcd.: C: 62.04; H: 2.94; N: 6.29 %; found: C: 62.27; H: 3.23; N: 7.28 %.

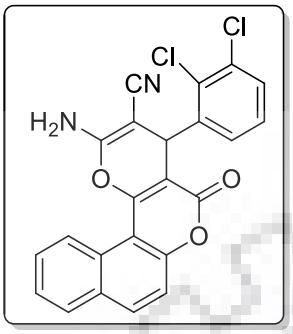


2-amino-4-(2-fluorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8e): Dark yellowish solid (79 %); mp: 276-277 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.22 (d, 1H, *J* = 8.4 Hz), 8.23 (d, 1H, *J* = 8.8 Hz), 8.07 (d, 1H, *J* = 8.0 Hz), 7.72 (t, 1H, *J* = 7.2 Hz), 7.70-7.63 (m, 3H), 7.52 (d, 1H, *J* = 8.8 Hz), 7.34 (t, 1H, *J* = 8.0 Hz), 7.29 (t, 1H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 4.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 162.0, 159.8, 159.5, 158.7, 157.8, 153.9, 135.3, 131.1, 130.8, 130.8, 130.7, 129.8, 129.7, 129.6, 128.2, 127.2, 126.7, 125.3, 125.2, 119.6, 117.4, 116.2, 116.0, 106.9, 103.3, 56.8, 31.9; IR (KBr) υ_{max}/cm^{-1}: 3426, 2204, 1710, 1638, 1402; Elem. Anal. For $C_{23}H_{13}FN_2O_3$: calcd.: C: 71.87; H: 3.41; N: 7.29 %; found: C: 71.63; H: 3.33; N: 7.03 %.

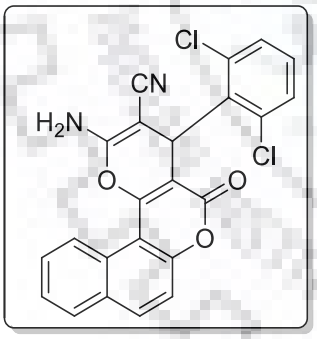


2-amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8f): Light brownish solid (91 %); mp: 274-276 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.24 (d, 1H, *J* = 8.4 Hz), 8.26 (d, 1H, *J* = 9.2 Hz), 8.18 (d, 2H, *J* = 8.8 Hz), 8.09 (d, 1H, *J* = 6.8 Hz), 7.76 (brs, 2H), 7.73 (d, 1H, *J* = 6.8 Hz), 7.67 (t, 1H, *J* = 8.0 Hz), 7.63 (d, 2H, *J* = 8.8 Hz), 7.57 (d, 1H, *J* = 8.8 Hz), 4.73 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.9, 158.5, 157.9, 154.0, 151.6, 147.1, 135.5, 131.2, 129.8, 129.7, 128.3, 127.3, 126.7, 124.3, 119.4, 117.4, 107.0, 103.5, 57.2, 37.3;

IR (KBr) υ_{max}/cm^{-1}: 3460, 2209, 1705, 1640, 1402; Elem. Anal. For $C_{23}H_{13}N_3O_5$: calcd.: C: 67.15; H: 3.19; N: 10.21 %; found: C: 67.31; H: 3.02; N: 9.88 %.

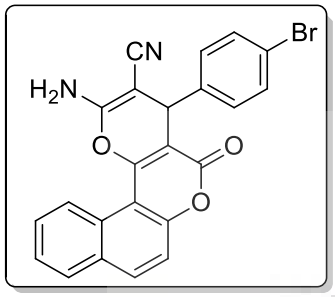


2-amino-4-(2,3-dichlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8g): Pale yellow solid (77 %); mp: 286-288 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.26 (d, 1H, *J* = 8.4 Hz), 8.28 (d, 1H, *J* = 9.2 Hz), 8.10 (d, 1H, *J* = 8.0 Hz), 7.77-7.66 (m, 4H), 7.60 (d, 1H, *J* = 8.4 Hz), 7.55 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.39 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.30 (t, 1H, *J* = 8.08 Hz), 5.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.7, 158.5, 158.0, 153.9, 144.0, 135.4, 132.4, 131.1, 131.0, 129.8, 129.7, 129.6, 129.1, 128.2, 127.2, 126.7, 119.2, 117.4, 106.8, 103.3, 56.5, 35.5; IR (KBr) υ_{max}/cm^{-1}: 3464, 2194, 1714, 1664, 1591, 1399; Elem. Anal. For $C_{23}H_{12}Cl_2N_2O_3$: calcd.: C: 63.47; H: 2.78; N: 6.44 %; found: C: 63.17; H: 3.03; N: 6.88 %.

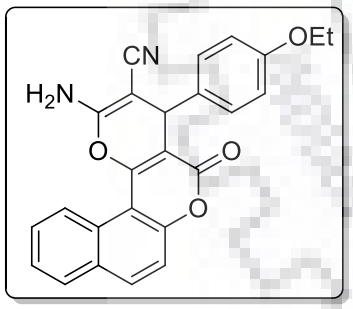


2-amino-4-(2,6-dichlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8h): Yellow solid (85 %); mp: 302-304 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.22 (d, 1H, *J* = 8.8 Hz), 8.24 (d, 1H, *J* = 9.2 Hz), 8.07 (d, 1H, *J* = 8.8 Hz), 7.75-7.69 (m, 3H), 7.66 (t, 1H, *J* = 6.8 Hz), 7.54 (t, 2H, *J* = 6.8 Hz), 7.37 (d, 1H, *J* = 6.8 Hz), 7.31 (t, 1H, *J* = 8.0 Hz), 5.56 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.5, 159.2, 158.4, 154.0, 136.5, 136.0, 135.5, 134.8, 131.2, 130.9, 130.2, 129.8, 129.8, 129.2, 128.2, 127.1, 126.8, 119.1, 117.4, 106.4, 101.8, 53.7,

33.9; IR (KBr) υ_{max}/cm^{-1}: 3437, 2201, 1639, 1402; Elem. Anal. For $C_{23}H_{12}Cl_2N_2O_3$: calcd.: C: 63.47; H: 2.78; N: 6.44 %; found: C: 63.17; H: 3.03; N: 6.88 %.

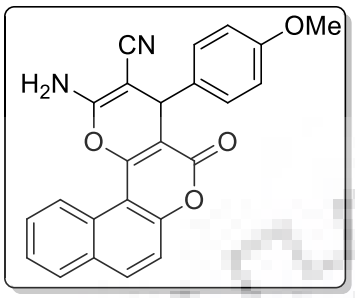


2-amino-4-(4-bromophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8i): Yellow solid (89 %); mp: 292-294 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.23 (d, 1H, *J* = 8.4 Hz), 8.25 (d, 1H, *J* = 8.8 Hz), 8.08 (d, 1H, *J* = 6.8 Hz), 7.73 (t, 1H, *J* = 6.8 Hz), 7.69-7.63 (m, 3H), 7.56 (d, 1H, *J* = 8.8 Hz), 7.50 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 4.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.8, 158.4, 157.4, 153.8, 143.6, 135.2, 131.9, 131.1, 130.5, 129.7, 129.6, 128.2, 127.2, 126.6, 120.7, 119.6, 117.4, 106.9, 104.0, 57.9, 37.0; IR (KBr) υ_{max}/cm^{-1}: 3429, 2193, 1706, 1667, 1565, 1380; Elem. Anal. For $C_{23}H_{13}BrN_2O_3$: calcd.: C: 62.04; H: 2.94; N: 6.29 %; found: C: 62.47; H: 3.15; N: 6.88 %.

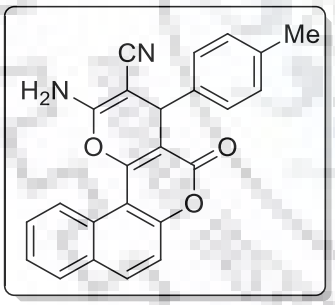


2-amino-4-(4-ethoxyphenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8j): Pale yellow solid (72 %); mp: 242-244 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.25 (d, 1H, *J* = 8.8 Hz), 8.25 (d, 1H, *J* = 9.2 Hz), 8.08 (d, 1H, *J* = 8.0 Hz), 7.73 (t, 1H, *J* = 6.8 Hz), 7.67 (t, 1H, *J* = 6.8 Hz), 7.65-7.54 (m, 3H), 7.20 (d, 2H, *J* = 8.8 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 4.46 (s, 1H), 3.97 (q, 2H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.9, 158.4, 158.1, 157.0, 153.7, 136.1, 135.1, 131.1, 129.7, 129.6, 129.2, 128.2, 127.2, 126.7, 119.9, 117.4, 114.8, 107.0, 105.0, 63.5, 58.6, 36.6, 15.2; IR (KBr) υ_{max}/cm^{-1}: 3417, 2199, 1717, 1670, 1587,

1402; Elem. Anal. For $C_{25}H_{18}N_2O_4$: calcd.: C: 73.16; H: 4.42; N: 6.83 %; found: C: 73.63; H: 4.67; N: 7.29 %.

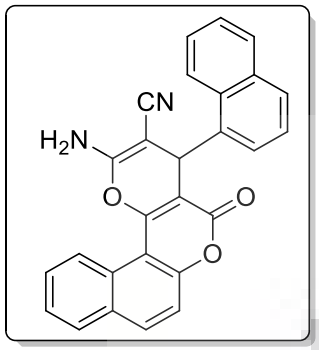


2-amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8k): Dark yellow solid (74 %); mp: 260-261 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.25 (d, 1H, *J* = 8.4 Hz), 8.24 (d, 1H, *J* = 9.2 Hz), 8.08 (d, 1H, *J* = 8.0 Hz), 7.74 (t, 1H, *J* = 7.2 Hz), 7.67 (t, 1H, *J* = 7.2 Hz), 7.60-7.55 (m, 3H), 7.22 (d, 2H, *J* = 8.8 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 4.47 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 159.9, 158.8, 158.4, 157.0, 153.7, 136.3, 135.1, 131.1, 129.7, 129.6, 129.3, 128.2, 127.2, 126.6, 119.9, 117.4, 114.4, 107.0, 105.0, 58.6, 55.6, 36.6; IR (KBr) υ_{max}/cm^{-1}: 3420, 2202, 1716, 1673, 1568; Elem. Anal. For $C_{24}H_{16}N_2O_4$: calcd.: C: 72.72; H: 4.07; N: 7.07 %; found: C: 72.41; H: 3.87; N: 7.54 %.

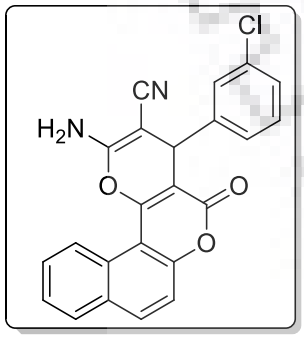


2-amino-5-oxo-4-(*p*-tolyl)-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8m): Pale yellow solid (79 %); mp: 264 ^oC; ^1H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 9.24 (d, 1H, *J* = 9.0 Hz), 8.24 (d, 1H, *J* = 8.5 Hz), 8.08 (d, 1H, *J* = 8.0 Hz), 7.73 (t, 1H, *J* = 8.5 Hz), 7.67 (t, 1H, *J* = 7.5 Hz), 7.59 (brs, 2H), 7.56 (d, 1H, *J* = 9.0 Hz), 7.21-7.08 (m, 4H), 4.47 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 159.8, 158.4, 157.1, 153.7, 141.2, 136.7, 135.0, 131.1, 129.6, 129.6, 129.5, 128.2, 127.9, 127.1, 126.6, 119.7, 117.3, 106.9, 104.8, 58.6, 37.0, 21.1; IR (KBr) υ_{max}/cm^{-1}: 3424, 2194, 1709, 1670, 1566, 1380; Elem. Anal. for $C_{24}H_{16}N_2O_3$: calcd.: C: 75.78; H:

4.24; N: 7.36 %; found: C: 75.43; H: 4.27; N: 7.53 %; HRMS (ESI) m/z calcd. for $C_{24}H_{16}N_2O_3$ $[M+Na]^+$: 403.1053, found: 403.1047.

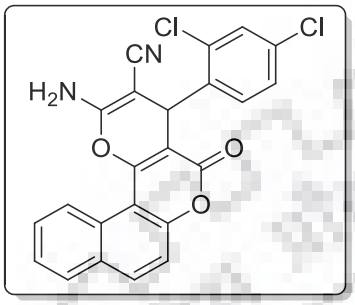


2-amino-4-(naphthalen-1-yl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8n): Yellow solid (74 %); mp: 270 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 9.32 (d, 1H, *J* = 8.5 Hz), 8.49 (d, 1H, *J* = 8.0 Hz), 8.27 (d, 1H, *J* = 9.0 Hz), 8.11 (d, 1H, *J* = 8.0 Hz), 7.96 (d, 1H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 7.5 Hz), 7.77 (t, 1H, *J* = 8.5 Hz), 7.70 (t, 1H, *J* = 7.5 Hz), 7.65-7.52 (m, 5H), 7.45-7.35 (m, 2H), 5.54 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 159.8, 158.3, 157.7, 153.7, 141.6, 135.1, 133.8, 131.4, 131.2, 129.7, 129.6, 129.0, 128.2, 127.9, 127.2, 126.6, 126.4, 126.3, 124.0, 119.6, 117.4, 115.0, 107.0, 105.3, 59.1, 26.0; IR (KBr) υ_{max}/cm^{-1}: 3441, 2197, 1707, 1669, 1566, 1376; Elem. Anal. for $C_{27}H_{16}N_2O_3$: calcd.: C: 77.87; H: 3.87; N: 6.73 %; found: C: 77.91; H: 3.96; N: 6.90 %; HRMS (ESI) m/z calcd. for $C_{27}H_{16}N_2O_3$ $[M+Na]^+$: 439.1053, found: 439.1037.



2-amino-4-(3-chlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8o): Light brownish solid (85 %); mp: 280 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 9.25 (d, 1H, *J* = 8.5 Hz), 8.26 (d, 1H, *J* = 9.0 Hz), 8.09 (d, 1H, *J* = 8.0 Hz), 7.74 (t, 1H, *J* = 8.0 Hz), 7.70-7.63 (m, 3H), 7.70-7.63 (m, 3H), 7.58 (d, 1H, *J* = 8.5 Hz), 7.40 (s, 1H), 7.38-7.28 (m, 3H), 4.58 (s,

1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 159.8, 158.4, 157.6, 153.8, 146.6, 135.2, 133.6, 131.1, 130.9, 129.6, 129.5, 128.2, 128.0, 127.6, 127.2, 127.0, 126.6, 119.5, 117.3, 107.0, 103.8, 57.8, 37.2; IR (KBr) υ_{max}/cm^{-1}: 3402, 2199, 1714, 1668, 1567, 1383; Elem. Anal. for $C_{23}H_{13}ClN_2O_3$: calcd.: C: 68.92; H: 3.27; N: 6.99 %; found: C: 68.53; H: 3.24; N: 6.95 %.



2-amino-4-(2,4-dichlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile (8p): Orange solid (84 %); mp: 256 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 9.24 (d, 1H, *J* = 8.5 Hz), 8.26 (d, 1H, *J* = 9.0 Hz), 8.09 (d, 1H, *J* = 8.0 Hz), 7.73 (t, 1H, *J* = 8.5 Hz), 7.71-7.64 (m, 3H), 7.62-7.55 (m, 2H), 7.47-7.30 (m, 2H), 5.03 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 159.6, 158.5, 158.0, 153.9, 140.3, 135.3, 133.8, 132.8, 132.6, 131.1, 129.7, 129.6, 129.3, 128.4, 128.2, 127.2, 126.6, 119.1, 117.3, 106.8, 103.1, 56.5, 34.4; IR (KBr) υ_{max}/cm^{-1}: 3419, 2197, 1706, 1670, 1563, 1381; Elem. Anal. for $C_{23}H_{12}Cl_2N_2O_3$: calcd.: C: 63.47; H: 2.78; N: 6.44 %; found: C: 63.17; H: 2.97; N: 6.57 %.

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CHAPTER 3

Urea-Catalysed Microwave-Assisted Synthesis of Novel Spirooxindole Benzopyrans

3.1 Introduction

Spirooxindoles are nitrogen containing fused heterocycles which are well-known for their wide biological and medicinal applications. [1-4] Spirooxindole moieties have been commonly found in natural products like Spirotryprostatin A (**I**) and Spirotryprostatin B (**II**) which usually occur in *Aspergillus fumigatus* and act as muscarinic serotonin receptors modulators (**Figure 3.1**). [5-7] Mitraphylline (**III**), another natural spirooxindole shows anti-tumor activity and is isolated from *Uncaria tomentosa*. Naturally occurring Horsfiline (**IV**) and Elacomine (**V**) act as indigenous medicines and are isolated from *Eleagnus commutate* (**Figure 3.1**). [5-10]

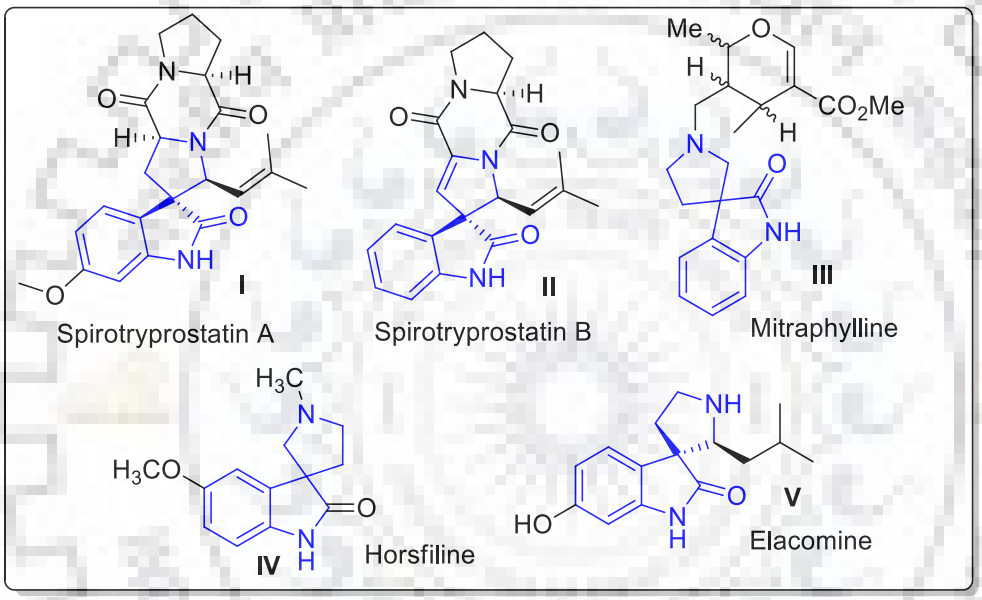


Figure 3.1 Some naturally occurring spirooxindoles.

Other than that, biological applications of spirooxindole are extensive and they have been found active as anticancer, antimicrobial, antitumor, antiviral and anti-inflammatory agents. [11, 12] Moreover, some fused oxindoles act as laser dyes, pigments, optical brighteners and fluorescence markers (**Figure 3.2**). [13, 14]

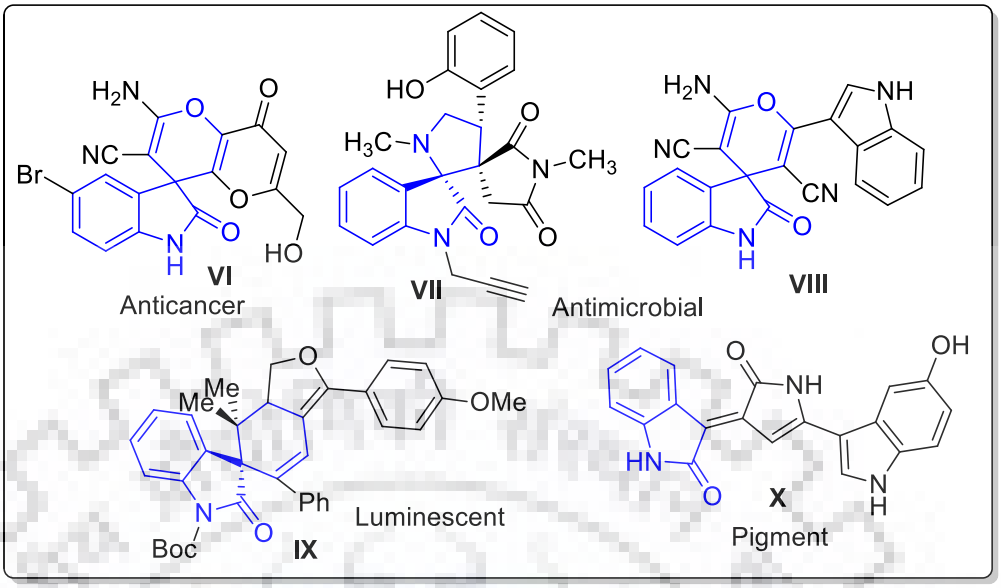


Figure 3.2 Applications of spirooxindole in different perspectives.

Likewise, benzochromenone containing heterocycles exhibit several biological applications. One of the most promising scaffolds of this class is furo-benzochromenone which possesses broad spectrum of biological activities, *e.g.* antibacterial, antitumor, antifungal, antioxidant, anti-trypanosomal and insecticidal. [15-19] Naturally occurring furo-benzochromenones *viz.* tanshinones (**XIII**) [20, 21], tanshinlactone (**XII**) [22] and neo-tanshinlactone (**XI**) [22, 23], extracted from *Salvia miltiorrhiza* are well-known anticancerous agents (**Figure 3.3**).

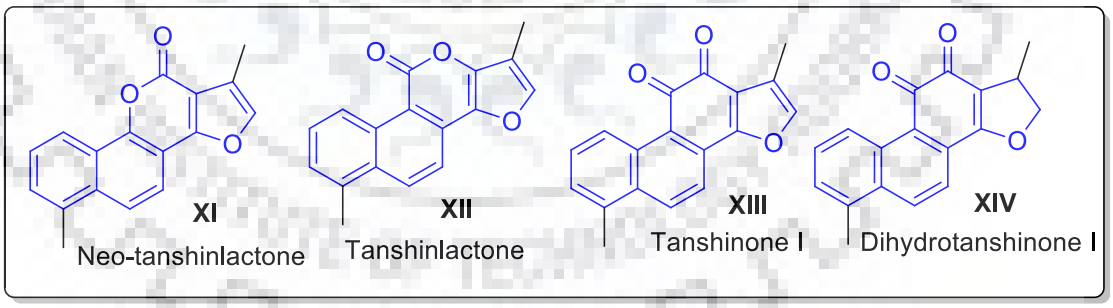


Figure 3.3 Naturally occurring benzochromenones.

Inspecting biological applications of spirooxindoles on one hand and benzochromenones on the other, the spirooxindole fused benzochromenones molecules might be effective from therapeutic point of view. Nevertheless, based on the literature reports, such hybrid molecules have not been studied. However, there are reports of preparation of spirooxindoles-pyran derivatives obtained by fusion of isatins with 4-hydroxycoumarin which can be a good starting point for the present study.

3.2 Survey of existing methodologies

As mentioned, there are several literature reports for the synthesis of spirooxindole-pyran derivatives. The most common pathway involves Knoevenagel reaction of isatins and malononitrile followed by Michael addition of 4-hydroxycoumarin and cyclisation to synthesize this hybrid scaffold.

For example, Kidwai *et al.* (2012) reported the synthesis of functionalized spirochromenes from the reaction of isatins (**1**) with malononitrile (**2a**)/ ethylcyanoacetate (**2b**) and 4-hydroxycoumarin (**3**) (**Figure 3.4**). [24] The reaction was carried out using catalytic amount of Gold (III) chloride ($HAuCl_4 \cdot 3H_2O$) in PEG-400 at 70 ºC to provide desired hybrid molecules (**4**) in 84-94 % yields.

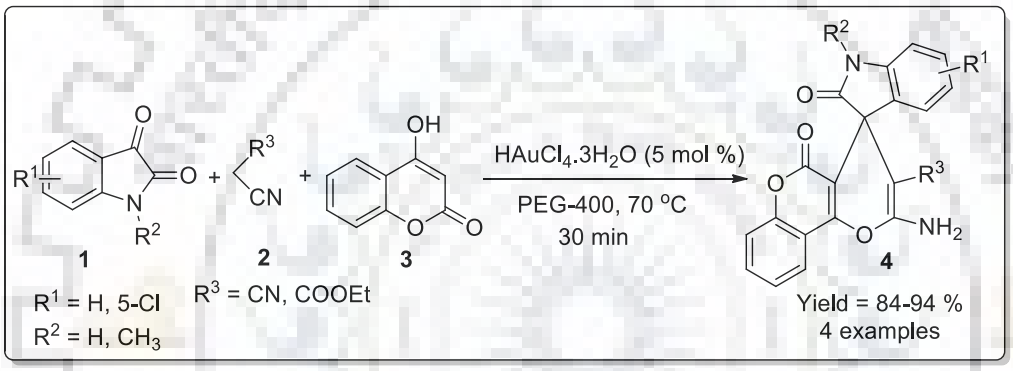


Figure 3.4 Gold(III) chloride-catalysed synthesis sprirooxindole fused pyrans.

On a similar note, Khurana and co-workers (2013) developed a one pot methodology for the above mentioned three-component reaction to synthesize spiropyrans (**4**) using 10 mol % DBU as a catalyst in water under reflux conditions (**Figure 3.5**). [25]

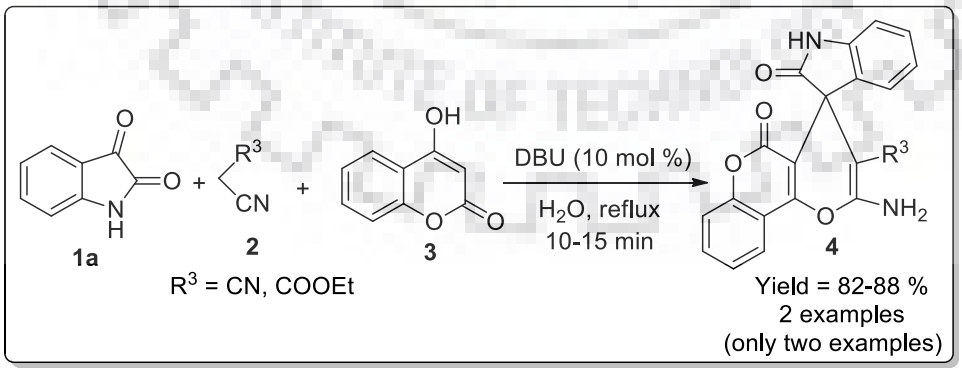


Figure 3.5 DBU-catalysed synthesis of spiropyrans.

Later on, in 2013, Zhang and co-workers reported a meglumine catalysed one pot methodology to furnish 2'-amino-2,5'-dioxo-5'*H*-spiro[indoline-3,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile (**4**) using the substrates isatin (**1a**), malononitrile (**2a**) and 4-hydroxycoumarin (**3**) at room temperature (**Figure 3.6**). [26]

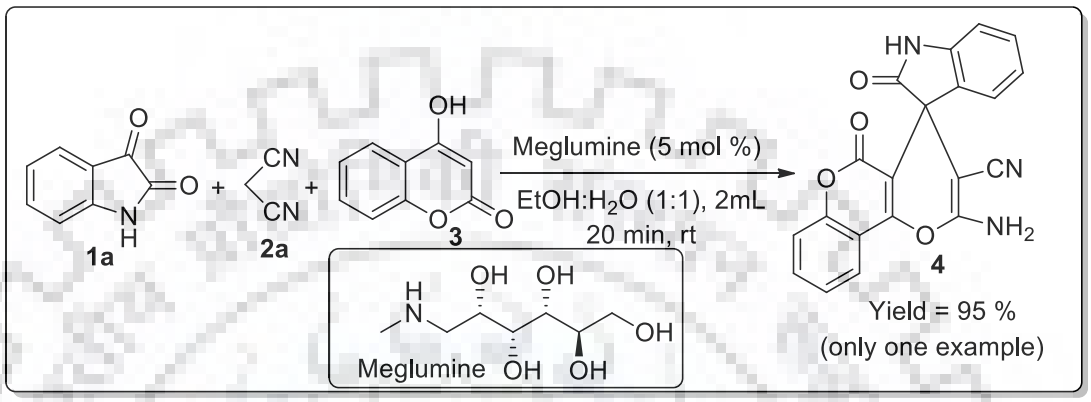


Figure 3.6 Meglumine-catalysed synthesis of spiropyranochromene.

Later, Hasaninejad *et al.* in 2017 discovered a DABCO-catalysed three-component reaction to synthesize spirooxindole fused pyrans (**4**) in good to high yield (84-98 %) under reflux conditions (**Figure 3.7**). [27]

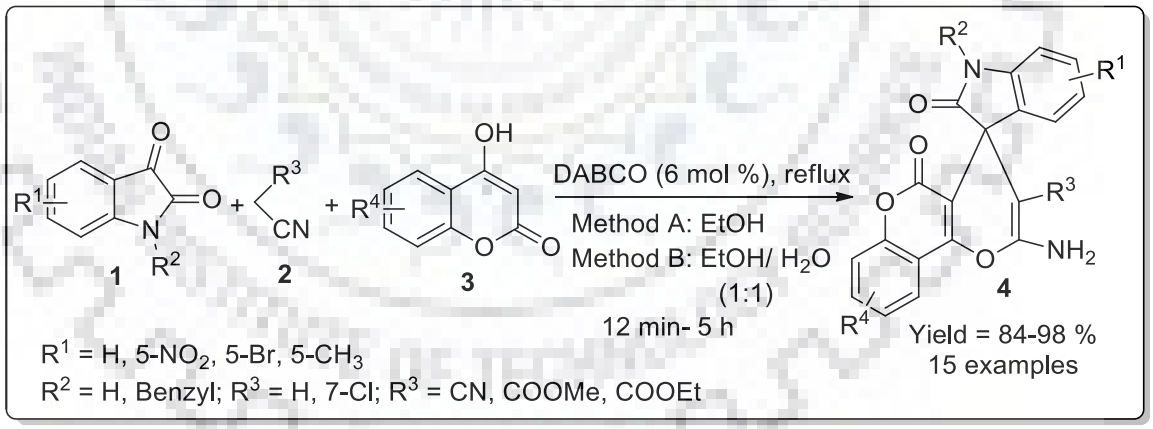


Figure 3.7 DABCO-catalysed synthesis of spirooxindole fused pyrans.

Next, Xu and co-workers (2018) developed a DABCO-based ionic liquid-catalysed synthesis of spiro[2-amino-4*H*-pyrans] (**4**) from isatin (**1a**), malononitrile (**2a**) and 4-hydroxycoumarin (**3**). [28] The described transformation was performed using 10 mol % of [DABCO-H]Cl as a catalyst in acetonitrile at 50 ^{o}C to give 95 % of the final product (**Figure 3.8**).

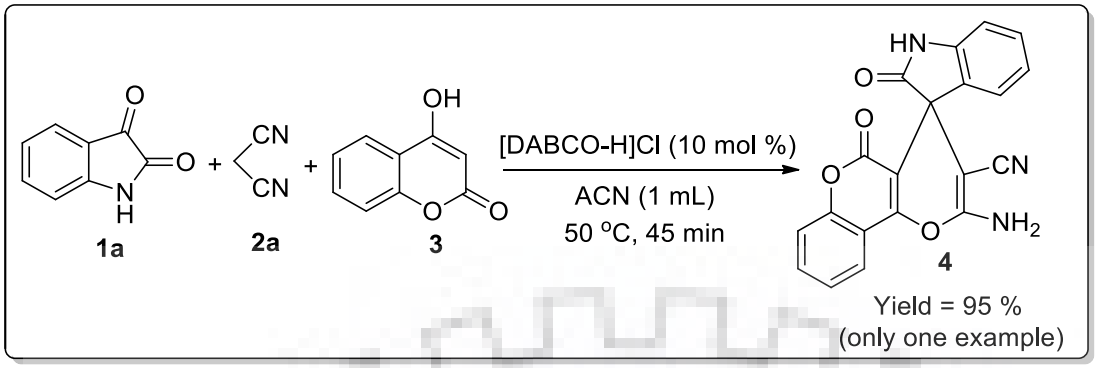


Figure 3.8 Ionic liquid-promoted synthesis of spiro[2-amino-4*H*-pyrans].

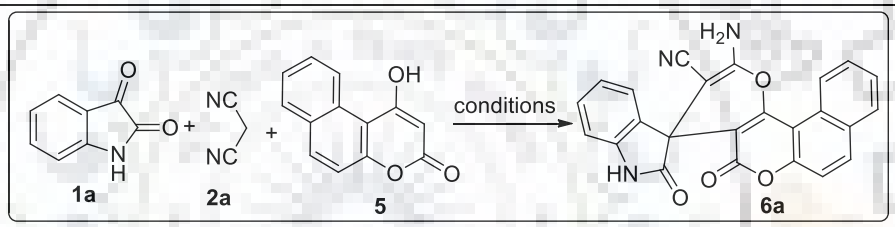
Apart from these reports, use of other reagents like nano-crystalline MgO (2012, Banerji *et al.*) [29], *N*,2-dibromo-6-chloro-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide (DCDBTSD) (2015, Khazaei *et al.*) [30], Copper (II) acetate monohydrate (2016, Maghsoodlou *et al.*) [31] and nano-sized copper ferrite (2016, Khodabakhshi *et al.*) [32] are also reported for the above described three-component reaction to formulate diversified spiro-pyrans.

Unfortunately, most of these methods suffer from drawbacks like expensive reagents, pre-functionalized catalysts, long reaction time, limited diversity and complicated purification process. Moreover, there is no report of the three-component reaction with 1-hydroxy-3*H*-benzo[*f*]chromen-3-one. Therefore, in continuation with the aim to develop greener and efficient methodology, a urea-catalysed microwave irradiated synthesis of novel fused heterocycles, namely, spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile and spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate derivatives, is presented in this chapter. The reported protocol has advantages like minutes synthesis, no tedious work up, column-free purification and more importantly, easy scale up process.

3.3 Results and discussion

According to the preliminary hypothesis based on similar reactivity of 4-hydroxycoumarin and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one, the early investigations were directed towards formation of 2-amino-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (**6a**) from standard three-component reaction of isatin (**1a,** 0.5 mmol), malononitrile (**2a,** 0.5 mmol) and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**5,** 0.5 mmol) using similar conditions which were previously reported for pyranochromenones synthesis. [25-27] Unfortunately, the desired product **6a** was either not obtained or was formed in very low yields (**Table 3.1**, entries 1-3). The results pointed out that the reactivity difference may be due to an additional fused aromatic ring and decresed solubility of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one.

Table 3.1. Exploring the reaction conditions for the synthesis of **6a**[a].



Entry	Catalyst	Solvent	Reaction Conditions[a]	Yield (%)[b]
1	Meglumine (5 mol %)[26]	2 mL EtOH:H_2O	rt, 30 min	nd
2	DABCO (6 mol %)[27]	5 mL EtOH	reflux, 30 min	47
3	DBU (10 mol %)[25]	5 mL H_2O	reflux, 30 min	nd
4	DABCO (10 mol%)	0.5 mL EtOH	MW/ 130 °C/ 15 min	55

[a]Reaction conditions: catalyst amount, solvent and condition as per reports; nd: not determined; [b]Isolated yields.

With the reported protocols not working, it was decided to use a one-pot microwave irradiation of 0.5 mmol each of **1a**, **2a** and **5** using 10 mol % DABCO at 130 °C for 15 minutes in 0.5 mL EtOH to form the desired product **6a**. Fortunately, the microwave-assisted protocol was found suitable as it provided 55 % yield of the targeted product **6a** (**Table 3.1**, entry 4). Having these sets of results in hand and also from the past experience on similar substrate **5** in the three-component reaction [33], a sequential approach was adopted to construct final product **6a** as shown in the **Figure 3.9**.

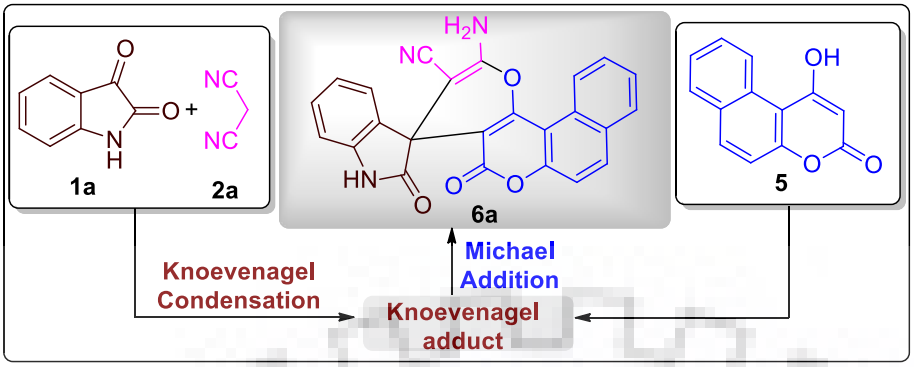
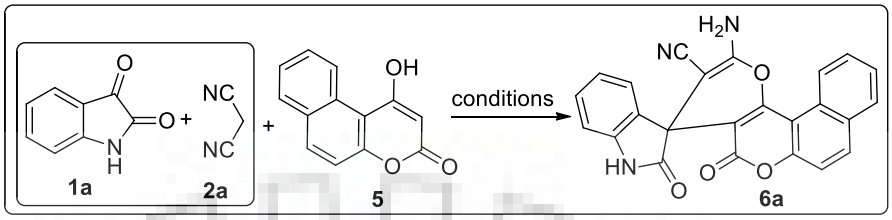


Figure 3.9 Reaction outline for sequential pathway.

Gratifyingly, when 0.5 mmol each of **1a** and **2a** were irradiated under microwave using catalytic amount of DABCO (10 mol %) at 130 °C for 5 minutes in 0.5 mL EtOH followed by addition of **5** (0.5 mmol) and the resulting mixture was further irradiated at 130 °C for another 10 minutes, it resulted in 77 % yield of the desired product **6a** (**Table 3.2**, entry 1). Later on, DABCO in the above reaction was replaced with different bases like DBU, Et_3N and urea (**Table 3.2**, entries 2-4). Fortunately, the reaction provided maximum yield with economical and abundantly available urea in which 82 % of **6a** was obtained. The acidic condition (*p*-TSA) in this reaction was not found suitable for the desired conversion (**Table 3.2**, entry 5). Thereafter, the reaction condition was optimized with respect to time and temperature and it was observed that Knoevenagel condensation of **1a** and **2a** for 2 minutes at 120 °C followed by Michael addition of **5** for 8 minutes at 120 °C was optimum for the desired transformation to **6a** (**Table 3.2**, entries 6-10). In next set of reactions, 15 mol % urea was found optimal for the transformation, providing 86 % of the product **6a** (**Table 3.2**, entries 9, 11 & 12). At last, to find out the effect of solvents, the reaction was carried out in different solvents in which IPA was found most effective for the above mentioned convertion (92 %, **6a**) (**Table 3.2**, entries 13-15). Henceforth, the final optimum condition for the one-pot sequential three-component reaction was the irradition of **1a** (0.5 mmol) and **2a** (0.5 mmol) for 2 minutes followed by its reaction with **5** (0.5 mmol) at 120 °C for another 8 minutes using 15 mol % urea in 0.5 mL IPA under microwave irradiation. It is worth mentioning that in all the cases pure solid products were obtained just by fitration and washing with IPA: H_2O (1:2) solvent mixture and no further purification proceess was required.

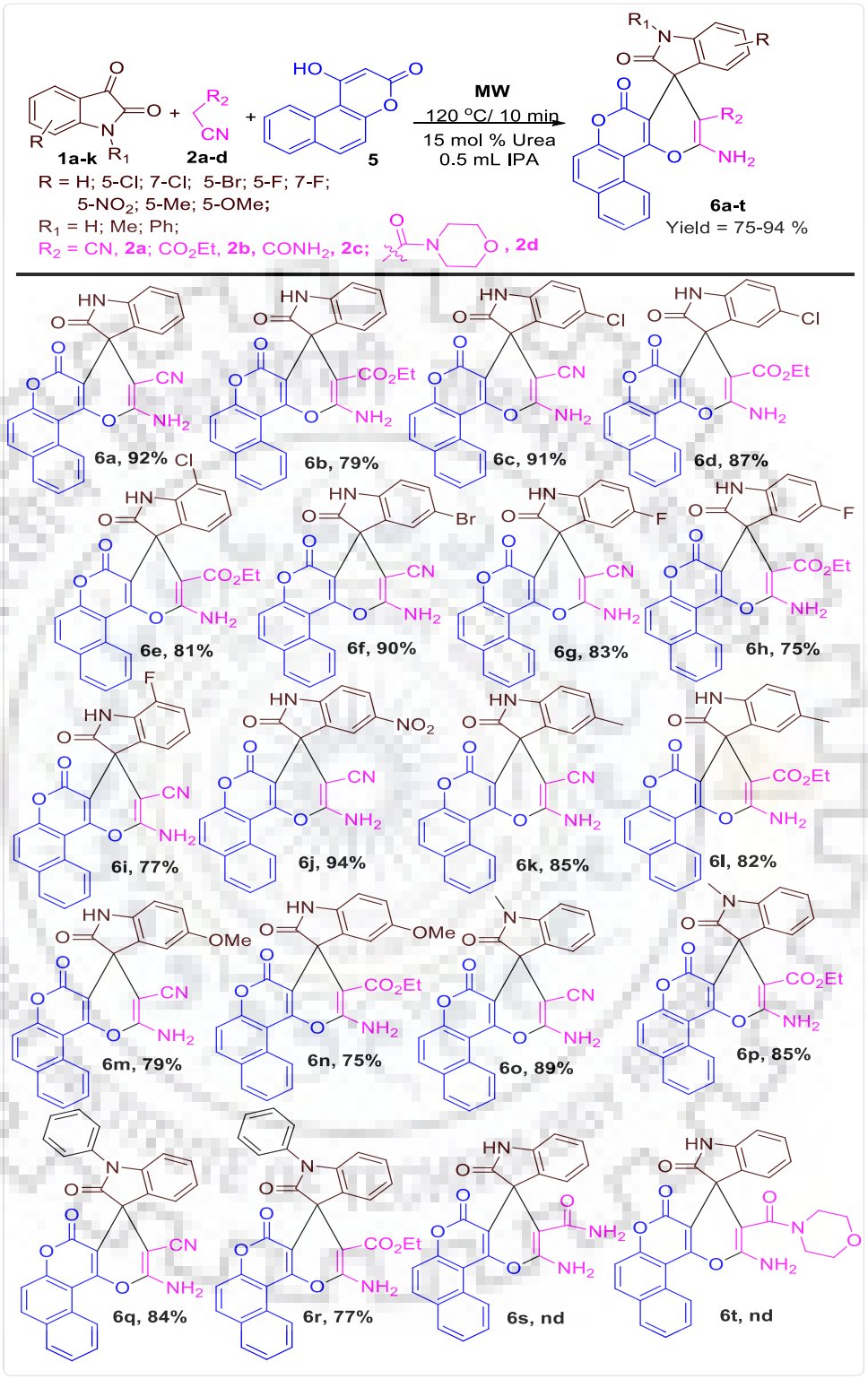
Table 3.2 Optimization reaction condition for the domino reaction between isatin (**1a**), malononitrile (**2a**) and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**5**)[a].



Entry	Catalyst	Solvent	Reaction Conditions	Yield (%)[b]
1	DABCO (10 mol %)	EtOH	MW (130 °C, 15 min)	77
2	DBU (10 mol %)	EtOH	MW (130 °C, 15 min)	73
3	Et_3N (10 mol %)	EtOH	MW (130 °C, 15 min)	71
4	Urea (10 mol %)	EtOH	MW (130 °C, 15 min)	82
5	*p*-TSA (10 mol %)	EtOH	MW (130 °C, 15 min)	-
6	Urea (10 mol %)	EtOH	MW (120 °C, 15 min)	81
7	Urea (10 mol %)	EtOH	MW (140 °C, 15 min)	83
8	Urea (10 mol %)	EtOH	MW (100 °C, 15 min)	66
9	Urea (10 mol %)	EtOH	MW (120 °C, 10 min)	82
10	Urea (10 mol %)	EtOH	MW (120 °C, 8 min)	74
11	Urea (15 mol %)	EtOH	MW (120 °C, 10 min)	86
12	Urea (20 mol %)	EtOH	MW (120 °C, 10 min)	87
13	Urea (15 mol %)	H_2O	MW (120 °C, 10 min)	nd
14	**Urea (15 mol %)**	**IPA**	**MW (120 °C, 10 min)**	**92**
15	Urea (15 mol %)	ACN	MW (120 °C, 10 min)	nd

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **5** (0.5 mmol), solvent: 0.5 mL; Anton Paar Monowave 300 reactor; initial conditions: 1 min 60 °C; nd: not determined; Time for Knoevenagel condensation: 5 min for entries 1-8 and 2 min for entries 9-15; Final conditions: (2+8) min sequential addition at 120 °C. [b]Isolated yields.

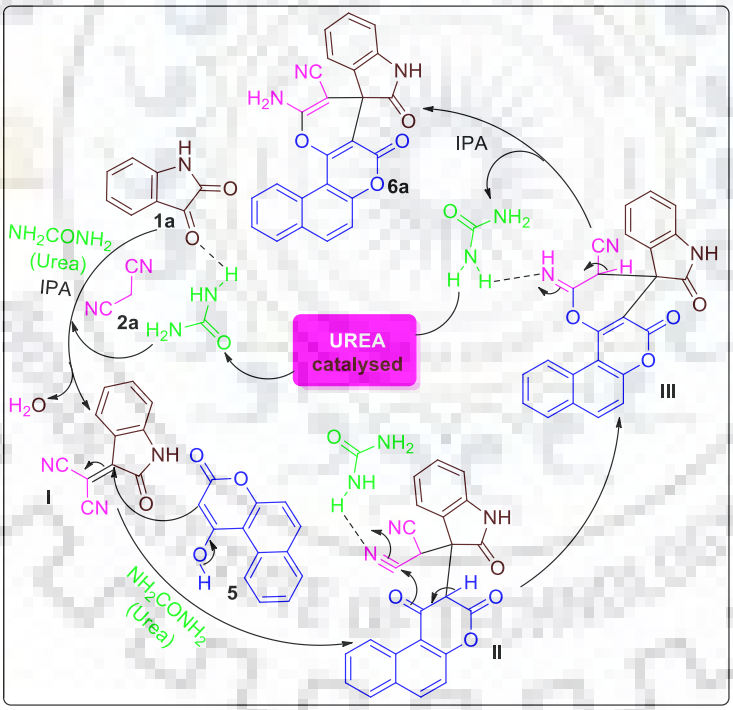
Having established the optimized condition, the reaction was extensively explored to find out its scope and limitations (**Scheme 3.1**). It was found that the reaction worked equally well with both electron donating and electron withdrawing groups substituted on isatins (**1a-k**). The reaction also worked well with both malononitrile **2a** and ethyl cyanoacetate **2b** substrates. However minor improvement of yield was observed with electron withdrawing isatin moieties (5-Cl (91 %, **6c**; 87 %, **6d**); 7-Cl (81 %, **6e**); 5-Br (90 %, **6f**); 5-F (83 %, **6g**; 75 % **6h**); 7-F (77 % **6i**); 5-NO_2 (94 %, **6j**)) in comparison to electron donating substrates (5-Me (85 %, **6k**; 82 %, **6l**); 5-OMe (79 %, **6m**; 75 %, **6n**)). Moreover, malonitrile **2a** provided higher yield in most of the cases (92 %, **6a**; 91 %, **6c**; 90 %, **6f**; 83 %, **6g**; 77 %, **6i**; 94 %, **6j**; 85 %, **6k**; 79 %, **6m**; 89 %, **6o**; 84 %, **6q**) as compared to ethyl cyanoacetate **2b** (79 %, **6b**; 87 %, **6d**; 81 %, **6e**; 75 %, **6h**; 82 %, **6l**; 75 %, **6n**; 85 %, **6p**; 77 %, **6r**). Moreover, 5-substituted isatins provided comparitively higher yields (91 %, **6c**; 87 %, **6d**; 90 %, **6f**; 83 %, **6g**; 75 %, **6h**; 94 %, **6j**) as compared to 7-substituted isatins (81 %, **6e**; 77 %, **6i**). Overall, the electronics of the substrates had little influence on the reaction outcome as the reaction in general provided excellent yield with majority of the substrates. Notably, 5-nitro substituted isatin produced highest yield of the corresponding product (94 %, **6j)**. On the other hand, *N*-substituted isatins also resulted in good yield of the products under given conditions (77-89 %, **6o-6r**). In continuation, the reaction was also performed with cyanoacetamide (**2c**) and 4-cyanoacetylmorpholine (**2d**). Unfortunately, it resulted in unidentifiable products and the respective products **6s** and **6t** were not obtained. In nutshell, the developed methodology provided an easy access to diversified spiro-benzopyranochromenes in good to high yield (75-94 %, **6a-r**).



Scheme 3.1 Scope of the reported domino multicomponent reaction. [a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **5** (0.5 mmol), urea (15 mol %), IPA (0.5 mL), 120 °C for (2+8) min sequential addition in Anton Paar Monowave 300 reactor; initial conditions: 1 min 60 °C.

Later on, the reaction condition was reexamined to evaluate "greenness" of this method by estimating carbon efficiency (CE), atom economy (AE), reaction mass efficiency (RME), process mass intensity (PMI) and most importantly, Sheldon environmental impact factor (E-factor) in a "gram scale reaction" to construct the target molecule **6a** (reaction in 5 mmol scale). Fortunately, the desired transformation worked effortlessly to give 84 % yield (1.710 gm) of product **6a**. Furthermore, the high AE (95.77 %), RME (80.39 %) and CE (100 %) and low E-factor (1.19) and PMI (2.19) proved that the reported protocol is suitable for an up scale synthesis.

The mechanism of this three-component reaction is sketched in **Scheme 3.2**. In this case, urea catalysed Knoevenagel condensation reaction of isatin (**1a**) and malanonitrile (**2a**) provides intermediate **I**. [34-35] Then, Michael attack of **5** on intermediate **I** forms intermediate **II**. Next, urea catalysed intramolecular cyclisation followed by proton shift in intermediate **III** provides the final desired product **6a**.



Scheme 3.2 Plausible mechanism for the synthesis of 2-amino-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (**6a**).

3.4 Conclusions

In conclusion, urea-catalysed mild and efficient methodology was developed to synthesized novel spiro-benzo[*f*]chromene derivatives under microwave irradiation. The optimised condition was suitable for a wide range of electronically diversified isatins to generate diversified novel scaffolds in good to high yields. The advantage of the present protocol includes low catalyst loading, shorter reaction time, no tedious work up and ease of scalibility. Overall, an ecofriendly urea-catalysed three-component reaction strategy is developed in this chapter.

3.5 Experimental section

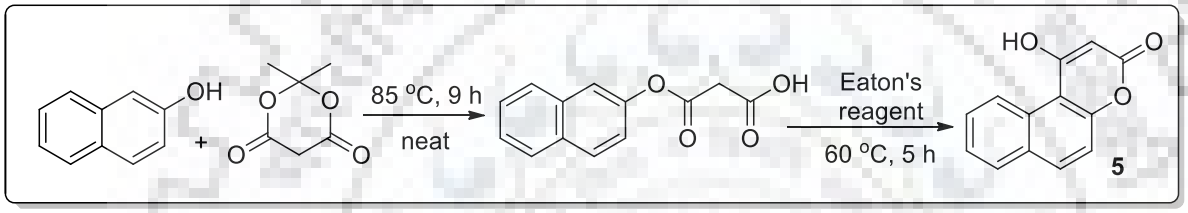
3.5.1 General information

All the substrates except 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**5**), reagents and solvents were purchased commercially. The synthesis of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**5**) was achieved in lab as directed in the literature [34]. All ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were taken in deuterated DMSO (DMSO-d_6) with TMS as internal standard and analyzed by JEOL Resonance® ECX-400II. ^{13}C NMR (125 MHz) of compounds **6m** and **6p** spectra were recorded on a Bruker Advance® 500 (500 MHz), ^{13}C NMR of compound **6k** could not recorded even after high number of scans due to lower solubility in NMR solvent. In the evaluation of ^{1}H NMR spectra, the unit parts per million (ppm) denotes the chemical shift, wherein "s" stands for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "dd" for doublet of doublet", "brs" for broad singlet and "m" for multiplet. The units of coupling constant (*J*) is in Hz. The High-resolution mass spectra (HRMS) of four representative compounds **6b**, **6g**, **6k** and **6p** were recorded on Bruker daltronics microTOF-QII® spectrometer using ESI ionization. Perkin Elmer® FT-IR spectrometer-Spectrum two has been used to detect the functional groups and vario MICRO cube Elementar® for elemental analyses. Optimelt® automated melting point system helped to get the melting points of the synthesized compounds. Silica gel TLC (thin layer chromatography) plates were used to analysis the progress of the reactions.

The microwave-assisted synthesis of the compounds was performed in Anton Paar® Monowave reactor which has an operating frequency of 2.455 GHz with continuous irradiation power of 0 to 300 W. The reactants were taken in a G-10 glass vial capped with Teflon septum and was exposed to microwave irradiation.

3.5.2 General procedures

Synthesis of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (5) [34]: The mixture of 2-naphthol (5 mmol) and meldrum's acid (5 mmol) was heated at 90 °C for 9-10 h. After that, the reaction mixture was cooled to room temperature and first extracted with ethyl acetate and then with saturated $NaHCO_3$ solution. The collected water extract was acidified with conc. HCl and additionally extracted with methylene dichloride (DCM) which provided the crude intermediate after evaporation of the organic solvent. The solid intermediate (2 mmol) in 2 mL Eaton's reagent was stirred at 60 °C for 5 h. After that, cold water was added to this resultant mixture while vigorous stirring. The solid product **5** was obtained by filtration and dried overnight to use in the reported reaction.



Scheme 3.3 Synthesis of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one.

[34] Park, S.-J.; Lee, J.-C.; Lee, K.-I.; A Facile Synthesis of 4-Hydroxycoumarin and 4-Hydroxy-2-quinolone Derivatives. *Bull. Korean Chem. Soc.* **2007**, *28*, 1203-1205.

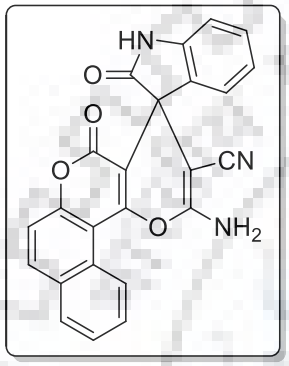
General synthesis procedure for microwave-assisted three-component reaction (6a-6r):

In a G-10 microwave vial, 15 mol % urea in 0.5 mL IPA were added to a mixture of isatins (**1**, 0.5 mmol) and malononitrile (**2a**) or ethylcyanoacetate (**2b**) (0.5 mmol) and subjected to microwave irradiation at 120 ºC for 2 minutes. Furthermore, 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**5**) was added to the reaction vial and again the mixture was irradiated for 8 minutes at 120 ºC**.** The solid product was obtained in the reaction vial after cooling down to room temperature, which was then filtered off and washed with washed with isopropanol: water (1:2) to get the pure final desired products **6**.

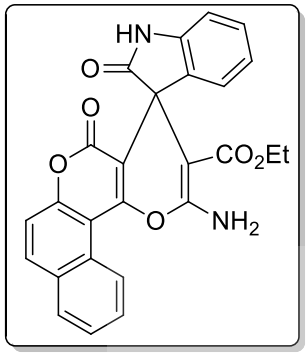
3.5.3 Characterization of the synthesized molecules

All the products were characterized via techniques of ^{1}H NMR, ^{13}C NMR Spectra, FT-IR and elemental analyses. Further, selected HRMS of **6b**, **6g**, **6k** and **6p** compounds are reported to confirm the products.

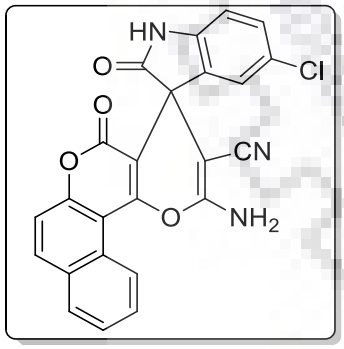
Analytical information for the synthesized molecules is given below:



2-amino-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6a): Pale brown solid (92 %); mp: 314 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.66 (s, 1H), 9.21 (d, 1H, *J* = 8.8 Hz), 8.27 (d, 1H, *J* = 8.8 Hz), 8.07 (d, 1H, *J* = 8.0 Hz), 7.84 (brs, 2H), 7.72 (t, 1H, *J* = 7.2 Hz), 7.65 (t, 1H, *J* = 7.2 Hz), 7.55 (d, 1H, *J* = 8.8 Hz), 7.23-7.15 (m, 2H), 6.90 (t, 1H, *J* = 7.6 Hz), 6.83 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 178.0, 159.0, 158.7, 158.6, 154.0, 142.7, 136.1, 134.1, 131.2, 129.9, 129.4, 128.1, 127.2, 126.8, 124.7, 122.6, 117.5, 117.3, 110.0, 106.5, 102.0, 57.6, 48.3; IR (KBr) υ_{max}/cm^{-1}: 2206, 1723, 1699, 1673,1631 1563, 1340, 1239; Elem. Anal. for $C_{24}H_{13}N_3O_4$: calcd.: C: 70.76; H: 3.22; N: 10.31 %; found: C: 69.60; H: 3.18; N: 10.15 %.

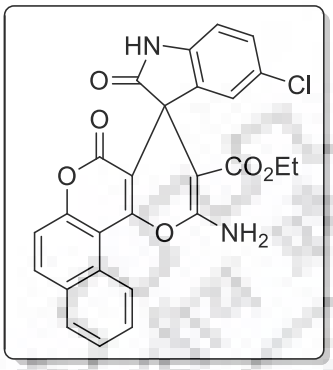


ethyl 2-amino-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate (6b): Pale yellow solid (79 %); mp: 263 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.40 (s, 1H), 9.27 (d, 1H, *J* = 8.8 Hz), 8.34 (brs, 2H), 8.23 (d, 1H, *J* = 8.8 Hz), 8.06 (d, 1H, *J* = 6.8 Hz), 7.75 (t, 1H, *J* = 8.8 Hz), 7.65 (t, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 9.2 Hz), 7.09 (t, 1H, *J* = 7.6 Hz), 7.03 (d, 1H, *J* = 7.2 Hz), 6.77 (t, 1H, *J* = 7.6 Hz), 6.72 (d, 1H, *J* = 7.6Hz), 3.82-3.71 (m, 2H), 0.82 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 179.7, 167.8, 158.9, 158.1, 157.7, 153.7, 144.7, 135.8, 135.5, 131.2, 129.9, 129.8, 128.4, 128.2, 127.2, 126.7, 123.8, 121.5, 117.2, 108.9, 106.4, 104.6, 75.94, 59.8, 47.9, 13.7; IR (KBr) υ_{max}/cm^{-1}: 1725, 1698, 1647, 1568, 1404, 1335, 1240; Elem. Anal. for $C_{26}H_{18}N_2O_6$: calcd.: C: 68.72; H: 3.99; N: 6.16 %; found: C: 68.44; H: 3.99; N: 6.12 %; HRMS (ESI) m/z calcd. for $C_{26}H_{18}N_2O_6$ $[M+Na]^+$: 477.1057; found: 477.1059.

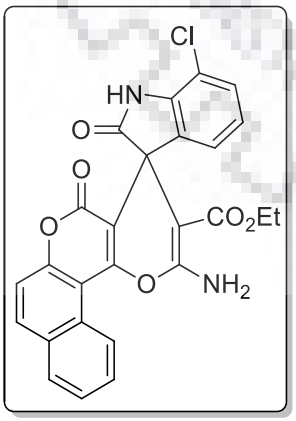


2-amino-5'-chloro-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6c): Brown solid (91 %); mp: 314 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.83 (s, 1H), 9.25 (d, 1H, *J* = 8.4 Hz), 8.31 (d, 1H, *J* = 9.2 Hz), 8.11 (d, 1H, *J* = 8.0 Hz), 7.93 (brs, 2H), 7.76 (t, 1H, *J* = 8.8 Hz), 7.69 (t, 1H, *J* = 8.0 Hz), 7.59 (d, 1H, *J* = 8.8 Hz), 7.49 (d, 1H, *J* = 2.4 Hz), 7.27 (dd, 1H, *J* = 8.0 & 2.4 Hz), 6.88 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm)

177.8, 159.3, 158.8, 158.8, 154.1, 141.6, 136.1, 131.2, 129.9, 129.3, 128.2, 127.3, 126.8, 126.6, 125.1, 125.1, 117.5, 117.3, 111.4, 106.7, 101.3, 56.9, 48.5; IR (KBr) υ_{max}/cm^{-1}: 2195, 1707, 1663, 1615, 1565, 1337, 1238; Elem. Anal. for $C_{24}H_{12}ClN_3O_4$: calcd.: C: 65.24; H: 2.74; N: 9.51 %; found: C: 65.55; H: 2.97; N: 9.72 %.

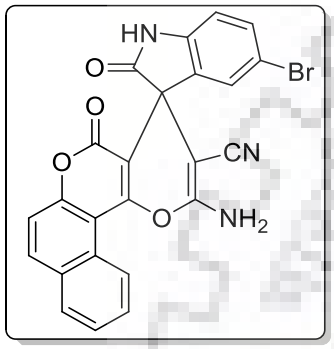


ethyl 2-amino-5'-chloro-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate (6d): Gray solid (87 %); mp: 298 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.54 (s, 1H), 9.28 (d, 1H, *J* = 8.8 Hz), 8.40 (brs, 2H), 8.25 (d, 1H, *J* = 8.8 Hz), 8.07 (d, 1H, *J* = 8.4 Hz), 7.75 (t, 1H, *J* = 8.4 Hz), 7.66 (t, 1H, *J* = 9.2 Hz), 7.52 (d, 1H, *J* = 9.2 Hz), 7.22 (d, 1H, *J* = 2.0 Hz), 7.13 (dd, 1H, *J* = 8.4 & 2.4 Hz), 6.72 (d, 1H, *J* = 8.4 Hz), 3.84-3.74 (m, 2H), 0.85 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 179.5, 167.7, 159.1, 158.2, 158.1, 153.8, 143.8, 137.5, 135.9, 131.2, 129.9, 129.8, 128.3, 127.3, 126.7, 125.4, 123.2, 110.1, 106.6, 103.8, 75.4, 59.9, 48.2, 13.7; IR (KBr) υ_{max}/cm^{-1}: 1731, 1710, 1639, 1568, 1402, 1334, 1240; Elem. Anal. for $C_{26}H_{17}ClN_2O_6$: calcd.: C: 63.88; H: 3.50; N: 5.73 %; found: C: 63.83; H: 3.57; N: 5.66 %.

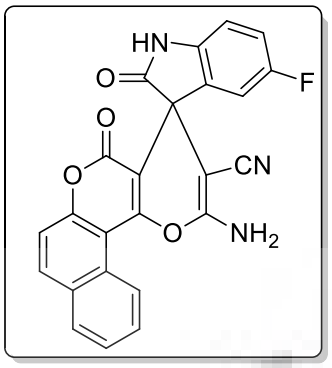


ethyl 2-amino-7'-chloro-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate (6e): Pale brown solid (81 %); mp: 284 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm)

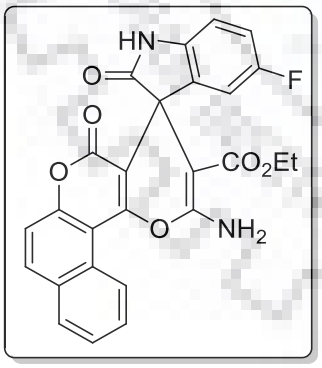
10.87 (s, 1H), 9.30 (d, 1H, *J* = 8.8 Hz), 8.45 (brs, 2H), 8.28 (d, 1H, *J* = 9.2 Hz), 8.10 (d, 1H, *J* = 8.0 Hz), 7.78 (t, 1H, *J* = 8.4 Hz), 7.69 (t, 1H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 8.8 Hz), 7.19 (dd, 1H, *J* = 8.4 & 1.2 Hz), 7.09 (d, 1H, *J* = 7.2 Hz), 6.84 (dd, 1H, *J* = 8 & 7.6 Hz), 3.88-3.74 (m, 2H), 0.89 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ_C (ppm) 179.7, 167.7, 159.0, 158.2, 157.9, 153.8, 142.4, 137.3, 136.0, 131.2, 129.9, 129.8, 128.4, 128.2, 127.2, 126.8, 122.8, 122.5, 117.2, 113.5, 106.4, 104.0, 75.6, 59.9, 48.8, 13.5; IR (KBr) υ_{max}/cm^{-1}: 1717, 1696, 1621, 1570, 1406, 1238; Elem. Anal. for $C_{26}H_{17}ClN_2O_6$: calcd.: C: 63.88; H: 3.50; N: 5.73 %; found: C: 63.28; H: 3.34; N: 5.87 %.



2-amino-5'-bromo-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6f): Dark brown solid (90 %); mp: 320 ^{o}C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ_H (ppm) 10.83 (s, 1H), 9.26 (d, 1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 8.8 Hz), 8.12 (d, 1H, *J* = 7.12 Hz), 7.94 (brs, 2H), 7.77 (t, 1H, *J* = 8.8 Hz), 7.70 (t, 1H, *J* = 7.6 Hz), 7.63-7.58 (m, 2H), 7.40 (dd, 1H, *J* = 8.4 & 2.0 Hz), 6.83 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ_C (ppm) 177.7, 159.3, 158.8, 158.8, 154.1, 142.0, 136.4, 136.1, 132.1, 131.2, 129.9, 128.2, 127.8, 127.3, 126.9, 117.5, 117.4, 114.3, 111.9, 106.7, 101.3, 56.9, 48.5; IR (KBr) υ_{max}/cm^{-1}: 2198, 1732, 1709, 1656, 1564, 1338, 1234; Elem. Anal. for $C_{24}H_{12}BrN_3O_4$: calcd.: C: 59.28; H: 2.49; N: 8.64 %; found: C: 59.29; H: 2.69; N: 8.67 %.

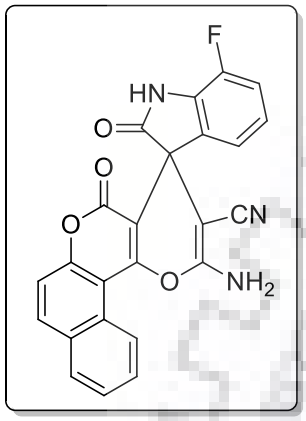


2-amino-5'-fluoro-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6g): Brown solid (83 %); mp: 318 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.66 (s, 1H), 9.22 (d, 1H, *J* = 8.8 Hz), 8.28 (d, 1H, *J* = 9.2 Hz), 8.08 (d, 1H, *J* = 8.0 Hz), 7.87 (brs, 2H), 7.73 (t, 1H, *J* = 8.8 Hz), 7.66 (t, 1H, *J* = 7.6 Hz), 7.56 (d, 1H, *J* = 9.2 Hz), 7.26 (dd, 1H, *J* = 8.4 & 2.4 Hz), 7.05-6.97 (m, 1H), 6.82 (dd, 1H, *J* = 11.6 &4.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 178.1, 159.2, 158.8 (d, *J* = 8.0 Hz), 157.7, 154.1, 138.9 (d, *J* = 2.0 Hz), 136.1, 135.8, 135.7, 131.2, 129.9, 128.2, 127.3, 126.9, 117.4 (d, *J* = 11.0 Hz), 115.8, 115.5, 112.8, 112.6, 110.7, 106.6, 101.4, 57.0, 48.7; IR (KBr) υ_{max}/cm^{-1}: 2199, 1697, 1667, 1630, 1403, 1338, 1239; Elem. Anal. for $C_{24}H_{12}FN_3O_4$: calcd.: C: 67.77; H: 2.84; N: 9.88 %; found: C: 67.39; H: 2.99; N: 9.83 %; HRMS (ESI) m/z calcd. for $C_{24}H_{12}FN_3O_4$ [M+Na]$^+$: 448.0704; found: 448.0685.

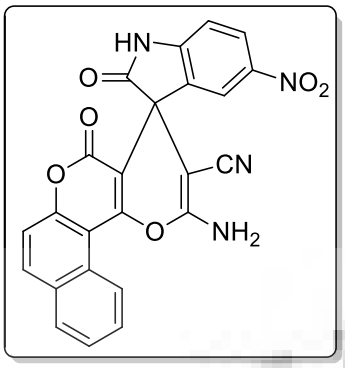


ethyl 2-amino-5'-fluoro-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate (6h): Pale brown solid (75 %); mp: 284 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.44 (s, 1H), 9.26 (d, 1H, *J* = 8.8 Hz), 8.39 (brs, 2H), 8.24 (d, 1H, *J* = 6.8 Hz), 8.06 (d, 1H, *J* = 6.8 Hz), 7.75 (t, 1H, *J* = 8.4 Hz), 7.65 (t, 1H, *J* = 8.0 Hz), 7.51 (d, 1H, *J* = 8.8 Hz), 7.05 (dd, 1H, *J* = 8.4 & 2.8 Hz), 6.95-6.87 (m, 1H), 6.69 (dd, 1H, *J* = 9.2 & 4.4 Hz), 3.84-3.71 (m, 2H), 0.83 (t, 3H, *J* =

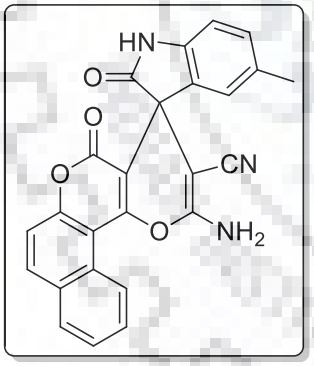
7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 179.7, 167.7, 159.0, 158.1 (d, J = 10.0 Hz), 157.3, 153.8, 141.1 (d, J = 2.0 Hz), 137.2, 137.1, 135.9, 131.2, 129.9, 129.8, 128.2, 127.3, 126.7, 117.2, 114.5, 112.0, 109.2 (d, J = 8.0 Hz), 106.5, 104.0, 75.6, 59.8, 48.5, 13.7; IR (KBr) υ_{max}/cm^{-1}: 1731, 1693, 1633, 1568, 1403, 1335, 1240; Elem. Anal. for $C_{26}H_{17}FN_2O_6$: calcd.: C: 66.10; H: 3.63; N: 5.93 %; found: C: 66.23; H: 3.59; N: 5.87 %.



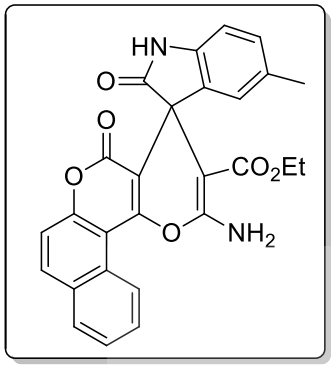
2-amino-7'-fluoro-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6i): Pale brown solid (77 %); mp: 322 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 11.18 (s, 1H), 9.21 (d, 1H, J = 8.8 Hz), 8.28 (d, 1H, J = 9.2 Hz), 8.08 (d, 1H, J = 8.0 Hz), 7.90 (brs, 2H), 7.73 (t, 1H, J = 8.8 Hz), 7.66 (t, 1H, J = 7.6 Hz), 7.56 (d, 1H, J = 8.8 Hz), 7.16-7.07 (m, 2H), 6.97-6.87 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 177.8, 159.1, 158.8 (d, J = 1.0 Hz), 154.1, 145.5, 136.8, 136.8, 136.2, 131.3, 129.9 (d, J = 3.0 Hz), 129.8, 129.7, 128.1, 127.2, 126.9, 123.5, 123.4, 120.9, 117.4 (d, J = 8.0 Hz), 116.5, 106.5, 101.5, 56.9, 48.6; IR (KBr) υ_{max}/cm^{-1}: 2197, 1709, 1666, 1645, 1591, 1403, 1340, 1239; Elem. Anal. for $C_{24}H_{12}FN_3O_4$: calcd.: C: 67.77; H: 2.84; N: 9.88 %; found: C: 67.84; H: 3.01; N: 9.97 %.



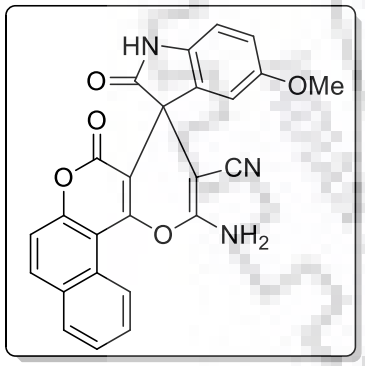
2-amino-5'-nitro-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6j): Brown solid (94 %); mp: 308 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 11.44 (s, 1H), 9.26 (d, 1H, *J* = 8.8 Hz), 8.41 (d, 1H, *J* = 2.4 Hz), 8.32 (d, 1H, *J* = 9.2 Hz), 8.22 (dd, 1H, *J* = 8.0 & 2.4 Hz), 8.11 (d, 1H, *J* = 8.4 Hz), 8.03 (brs, 2H), 7.77 (t, 1H, *J* = 8.8 Hz), 7.70 (t, 1H, *J* = 8.0 Hz), 7.59 (d, 1H, *J* = 8.8 Hz), 7.10 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 178.7, 159.7, 159.1, 159.0, 154.1, 149.1, 143.3, 135.0, 131.2, 129.9, 128.2, 127.3, 126.9, 126.9, 120.9, 117.4, 110.3, 110.1, 106.8, 100.8, 56.1, 48.5; IR (KBr) υ_{max}/cm^{-1}: 2201, 1722, 1663, 1625, 1401, 1340, 1238; Elem. Anal. for $C_{24}H_{12}N_4O_6$: calcd.: C: 63.72; H: 2.67; N: 12.39 %; found: C: 63.53; H: 2.84; N: 12.51 %.



2-amino-5'-methyl-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6k): Whitish solid (85 %); mp: 305 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.57 (s, 1H), 9.26 (d, 1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 8.8 Hz), 8.12 (d, 1H, *J* = 8.0 Hz), 7.84 (brs, 2H), 7.77 (t, 1H, *J* = 8.8 Hz), 7.70 (t, 1H, *J* = 7.6 Hz), 7.59 (d, 1H, *J* = 9.2 Hz), 7.08 (s, 1H), 7.02 (d, 1H, *J* = 8.0 Hz), 6.75 (d, 1H, *J* = 8.0 Hz), 2.19 (s, 3H); IR (KBr) υ_{max}/cm^{-1}: 2200, 1706, 1670, 1567, 1340, 1238; Elem. Anal. for $C_{25}H_{15}N_3O_4$: calcd.: C: 71.25; H: 3.59; N: 9.97 %; found: C: 71.12; H: 3.85; N: 9.57 %; HRMS (ESI) m/z calcd. for $C_{25}H_{15}N_3O_4$ $[M+Na]^+$: 444.0954; found: 444.0918.

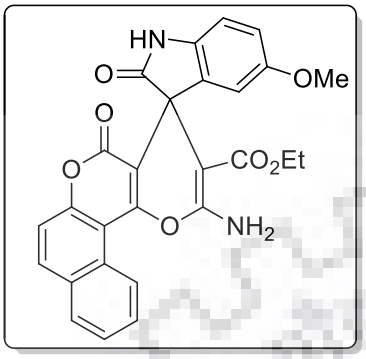


ethyl 2-amino-5'-methyl-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate (6l): Pale yellow solid (82 %); mp: 281 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.33 (s, 1H), 9.31 (d, 1H, *J* = 8.8 Hz), 8.37 (brs, 2H), 8.28 (d, 1H, *J* = 8.8 Hz), 8.10 (d, 1H, *J* = 8.0 Hz), 7.79 (t, 1H, *J* = 8.8 Hz), 7.69 (t, 1H, *J* = 8.0 Hz), 7.54 (d, 1H, *J* = 8.8 Hz), 6.92 (d, 1H, *J* = 7.6 Hz), 6.89 (s, 1H), 6.64 (d, 1H, *J* = 7.6 Hz), 3.81 (q, 2H, *J* = 6.8 Hz), 2.14 (s, 3H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 179.6, 167.9, 158.9, 158.0, 157.7, 153.7, 142.3, 135.5, 131.2, 130.2, 129.9, 129.8, 128.2, 127.2, 126.7, 124.6, 117.2, 108.6, 106.4, 104.8, 76.1, 59.8, 48.0, 29.8, 21.1, 13.7; IR (KBr) υ_{max}/cm^{-1}: 1710, 1691, 1637, 1567, 1331, 1238; Elem. Anal. for $C_{27}H_{20}N_2O_6$: calcd.: C: 69.22; H: 4.30; N: 5.98 %; found: C: 69.32; H: 4.29; N: 5.75 %.

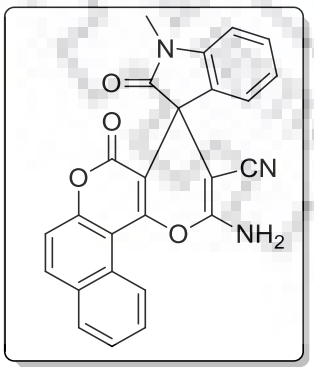


2-amino-5'-methoxy-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6m): Green solid (79 %); mp: 293 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.49 (s, 1H), 9.27 (d, 1H, *J* = 8.8 Hz), 8.31 (d, 1H, *J* = 8.8 Hz), 8.11 (d, 1H, *J* = 8.0 Hz), 7.84 (brs, 2H), 7.76 (t, 1H, *J* = 8.8 Hz), 7.70 (t, 1H, *J* = 8.0 Hz), 7.60 (d, 1H, *J* = 8.8 Hz), 6.96 (s, 1H), 6.79-6.76 (m, 2H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 177.3, 158.4, 158.1, 158.0, 155.2, 153.4, 135.4, 135.3, 134.7, 130.6, 129.2, 127.6, 126.7, 126.2, 116.9, 116.7, 114.5, 113.7, 110.8, 109.8, 106.1, 101.4, 57.2, 55.4, 48.2; IR (KBr) υ_{max}/cm^{-1}: 2203, 1721, 1705, 1658, 1631, 1566,

1404, 1338; Elem. Anal. for $C_{25}H_{15}N_3O_5$: calcd.: C: 68.65; H: 3.46; N: 9.61 %; found: C: 68.36; H: 3.52; N: 9.49 %.

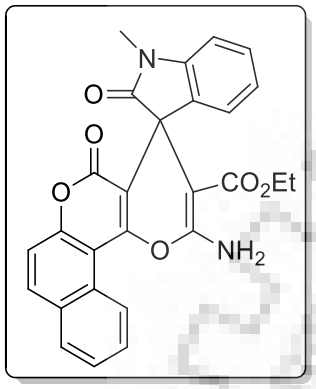


ethyl 2-amino-5'-methoxy-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate (6n): Pale yellow solid (75 %); mp: 269 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.26 (s, 1H), 9.31 (d, 1H, *J* = 8.8 Hz), 8.38 (brs, 2H), 8.27 (d, 1H, *J* = 8.8 Hz), 8.10 (d, 1H, *J* = 7.2 Hz), 7.78 (t, 1H, *J* = 8.4 Hz), 7.69 (t, 1H, *J* = 7.6 Hz), 7.55 (d, 1H, *J* = 8.8 Hz), 6.75 (d, 1H, *J* = 2.4 Hz), 6.72-6.63 (m, 2H), 3.81 (q, 2H, *J* = 6.8 Hz), 3.60 (s, 3H), 0.88 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 179.5, 167.9, 158.9, 158.0, 157.8, 155.1, 153.7, 138.3, 136.7, 135.8, 131.2, 129.9, 129.7, 128.3, 127.3, 126.7, 112.9, 111.1, 109.0, 106.5, 104.5, 76.0, 59.8, 55.9, 48.5, 13.7; IR (KBr) υ_{max}/cm^{-1}: 1731, 1693, 1633, 1568, 1403, 1335, 1240; Elem. Anal. for $C_{27}H_{20}N_2O_7$: calcd.: C: 66.94; H: 4.16; N: 5.78 %; found: C: 66.87; H: 4.17; N: 5.67 %.

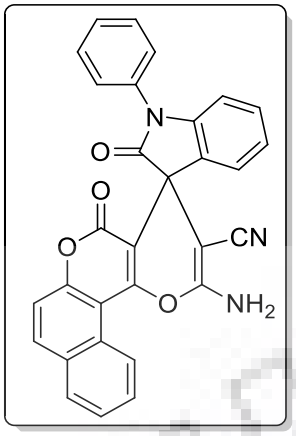


2-amino-1'-methyl-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6o): Pale yellow solid (89 %); mp: 316 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.22 (d, 1H, *J* = 8.4 Hz), 8.28 (d, 1H, *J* = 8.8 Hz), 8.08 (d, 1H, *J* = 6.8 Hz), 7.86 (brs, 2H), 7.73 (t,

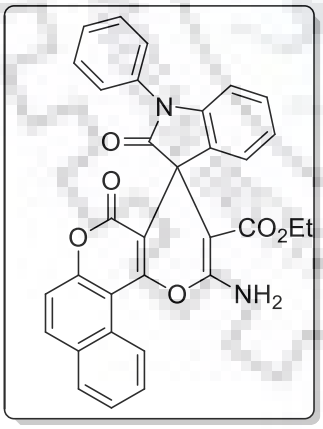
1H, *J* = 8.8 Hz), 7.66 (t, 1H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 9.2 Hz), 7.33-7.25 (m, 2H), 7.05 (d, 1H, *J* = 8.0 Hz), 6.99 (t, 1H, *J* = 7.6 Hz), 3.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 176.5, 159.0, 158.8, 158.6, 154.0, 144.2, 136.1, 133.2, 131.2, 129.9, 129.6, 128.1, 127.2, 126.9, 124.4, 123.3, 117.4, 117.3, 109.0, 106.5, 101.8, 57.2, 47.9, 27.1; Elem. Anal. for $C_{25}H_{15}N_3O_4$: calcd.: C: 71.25; H: 3.59; N: 9.97 %; found: C: 71.37; H: 3.66; N: 10.14 %.



ethyl 2-amino-1'-methyl-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate (6p): Pinkish white solid (85 %); mp: 294 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 9.32 (d, 1H, *J* = 8.4 Hz), 8.44 (brs, 2H), 8.29 (d, 1H, *J* = 9.2 Hz), 8.11 (d, 1H, *J* = 8.0 Hz), 7.80 (t, 1H, *J* = 7.2 Hz), 7.70 (t, 1H, *J* = 6.8 Hz), 7.54 (d, 1H, *J* = 9.2 Hz), 7.24 (t, 1H, *J* = 7.6 Hz), 7.14 (d, 1H, *J* = 7.2 Hz), 6.95 (d, 1H, *J* = 7.6 Hz), 6.89 (t, 1H, *J* = 7.2 Hz), 3.82-3.70 (m, 2H), 3.18 (s, 3H), 0.79 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 177.8, 158.8, 158.6, 158.5, 153.9, 140.2, 135.9, 134.1, 131.4, 131.2, 129.8, 129.6, 128.1, 127.1, 126.8, 125.1, 117.5, 117.2, 109.7, 106.5, 102.1, 62.5, 57.8, 48.3, 26.0, 21.0; IR (KBr) υ_{max}/cm^{-1}: 1734, 1697, 1640, 1569, 1402, 1333, 1240; Elem. Anal. for $C_{27}H_{20}N_2O_6$: calcd.: C: 69.22; H: 4.30; N: 5.98 %; found: C: 69.37; H: 4.25; N: 5.92 %; HRMS (ESI) m/z calcd. for $C_{27}H_{20}N_2O_6$ $[M+Na]^+$: 491.1213; found: 491.1229.



2-amino-2',5-dioxo-1'-phenyl-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (6q): Pale yellow solid (84 %); mp: 308 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ_H (ppm) 9.28 (d, 1H, *J* = 8.8 Hz), 8.33 (d, 1H, *J* = 9.2 Hz), 8.13 (d, 1H, *J* = 8.4 Hz),8.01 (brs, 2H), 7.78 (t, 1H, *J* = 8.4 Hz), 7.71 (t, 1H, *J* = 7.6 Hz), 7.68-7.58 (m, 3H), 7.52 (t, 1H, *J* = 7.6 Hz), 7.48-7.40 (m, 3H), 7.27 (t, 1H, *J* = 7.6 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.73 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ_C (ppm) 176.1, 159.2, 158.9, 158.8, 154.2, 143.9, 136.2, 135.0, 132.9, 131.3, 130.4, 129.9, 129.9, 129.7, 128.9, 128.2, 127.3, 127.2, 126.9, 125.1, 124.0, 117.4, 117.4, 109.3, 106.6, 101.8, 57.2, 48.1; IR (KBr) υ_{max}/cm^{-1}: 2200, 1711, 1669, 1598, 1377, 1340, 1237; Elem. Anal. for $C_{30}H_{17}N_3O_4$: calcd.: C: 74.53; H: 3.54; N: 8.69 %; found: C: 74.51; H: 3.35; N: 8.62 %.



ethyl 2-amino-2',5-dioxo-1'-phenyl-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carboxylate (6r): Pale yellow solid (77 %); mp: 271-272 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ_H (ppm) 9.35 (d, 1H, *J* = 8.8 Hz), 8.50 (brs, 2H), 8.30 (d, 1H, *J* = 9.2 Hz), 8.12 (d, 1H, *J* = 8.0 Hz), 7.81 (t, 1H, *J* = 7.2 Hz), 7.71 (t, 1H, *J* = 7.2 Hz), 7.65-7.57 (m, 2H), 7.55 (d, 1H, *J* = 8.8 Hz), 7.53-7.48 (m, 2H), 7.46 (t, 1H, *J* = 7.2 Hz), 7.26 (d, 1H, *J* = 7.2 Hz), 7.19 (t, 1H, *J* = 7.6 Hz), 6.96 (t, 1H,

J = 7.6 Hz), 6.75 (d, 1H, *J* = 8.0 Hz), 4.06-3.80 (m, 2H), 0.75 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 177.6, 167.6, 159.2, 158.5, 157.9, 153.8, 145.3, 136.0, 135.7, 134.3, 131.3, 130.0, 129.9, 129.9, 128.6, 128.2, 128.1, 127.3, 126.8, 126.6, 117.2, 108.3, 106.4, 104.5, 75.7, 59.7, 47.7, 14.4; IR (KBr) υ_{max}/cm^{-1}: 1726, 1698, 1639, 1568, 1374, 1332, 1239; Elem. Anal. for $C_{32}H_{22}N_2O_6$: calcd.: C: 72.45; H: 4.18; N: 5.28 %; found: C: 72.17; H: 4.04; N: 5.24 %.

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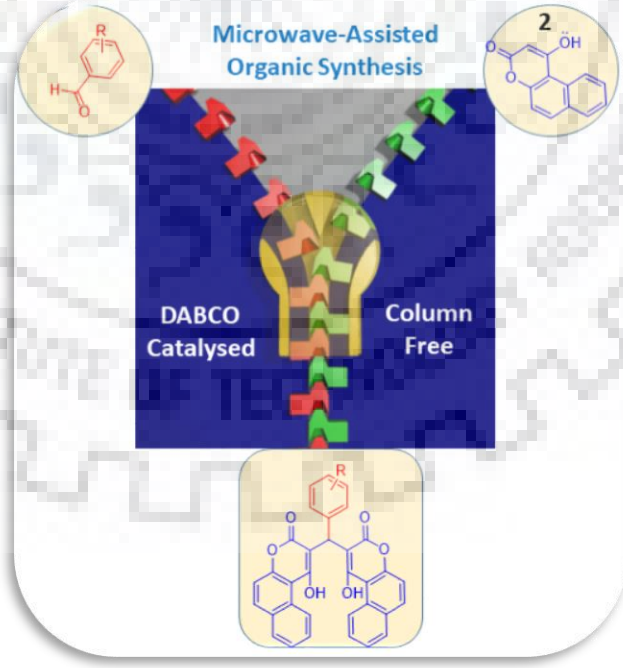
CHAPTER 4

Diversity Oriented Synthesis

of

Bis(benzochromenone) Derivatives



4.1 Introduction

Six membered oxygenated heterocycles are well recognized scaffolds for their bioorganic, medicinal, agricultural, pharmaceutical and industrial applications. [1] Among them, biscoumarin derivatives are of particular interest because of their wide range of activities and applications. [2, 3] Till now, there are several reports of naturally occurring compounds containing basic bicoumarin units like Dicoumarol (**I**), Gerberinol (**II**), Ismailin (**III**), Bisosthenon (**IV**) etc (**Figure 4.1**). [4-5] Above all, Dicoumarol (**I**) is a well-established anticoagulant drug which operates as a vitamin K antagonist. [4] It is also worth mentioning that in 2004 Cullen *et al.* reported beneficial effects of Dicoumarol (**I**) on cancer pancreatic cells. [4]

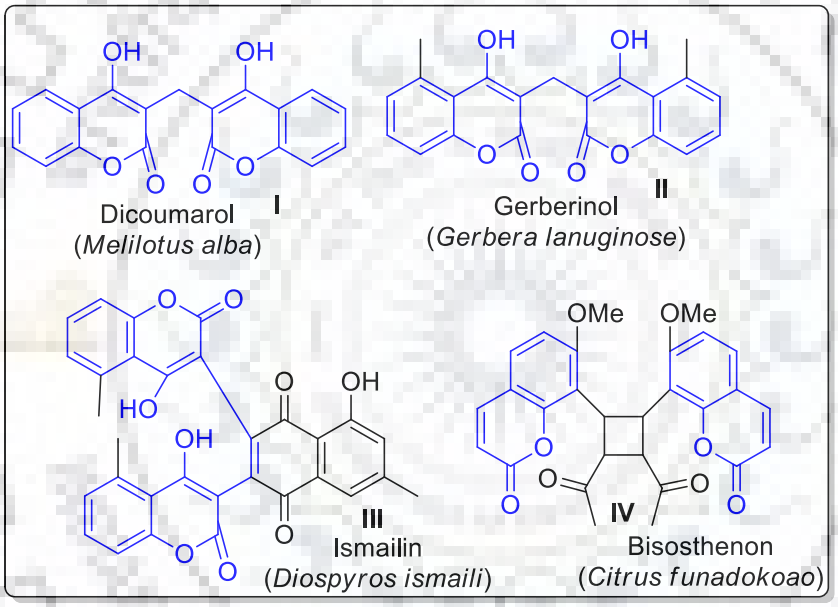


Figure 4.1 Naturally occurring biscoumarin.

After the recognition of biscoumarin as a biological important class of compounds, scientists found out various activities associated with these molecules such as anticoagulant, antibacterial, urease inhibition activities, anti-oxidant, anti-HIV, anti-cancer, anti-bacterial and anti-coagulant activities (**Figure 4.2**). [6-10] Interestingly, despite having structural similarity with biscoumarin, the activity profile of bis(benzochromenone) is not well documented till now. However, in 2009, Bryce *et al.* reported the inhibition activity of such bis(benzochromenone) (**VIII**) against human NAD(P)H: quinone oxidoreductase-1 (NQO1) enzyme (**Figure 4.2**). [11, 12] This study raised the scope for exploration of bis(benzochromenone) further into the domain of medicinal chemistry.

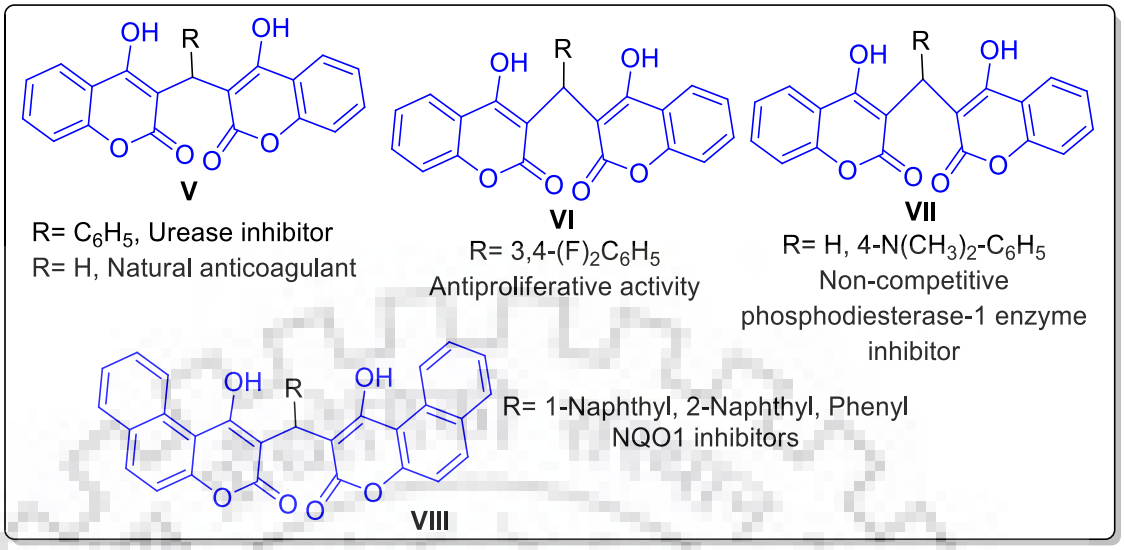


Figure 4.2 Biological activities of some synthesized biscoumarin.

4.2 Survey of existing methodologies

Most of the synthetic methodologies can be traced back in the scientific reports for the synthesis of biscoumarin using 4-hydroxycoumarin and aldehyde as starting materials. To start with, in 2007 Kidwai and co-workers reported the synthesis of 3,3′-arylmethylenebis-(4-hydroxycoumarin) (**3**) using molecular iodine in catalytic amount in aqueous media. The reaction involved Michael reaction of various substituted aldehydes (**1**) with 4-hydroxycoumarin (**2**) which resulted in diversified biscoumarin products (**3**) in good to excellent yields (91-99 %) (**Figure 4.3**). [13]

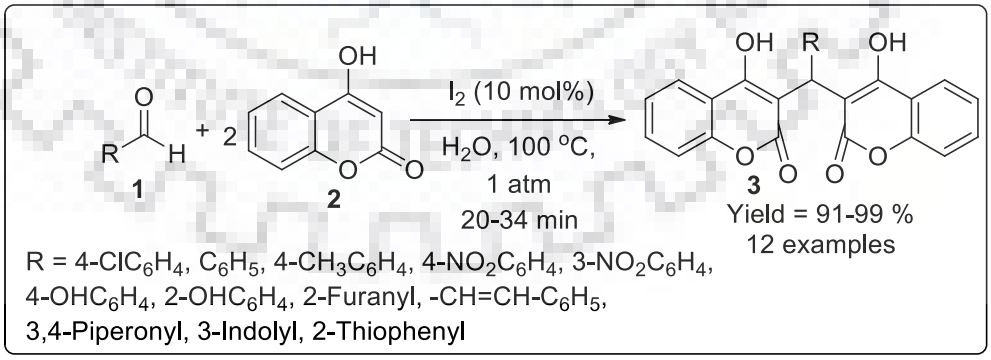


Figure 4.3 Iodine-catalysed synthesis of 3,3′-arylmethylenebiscoumarins.

In continuation, Khurana *et al.* (2009) came out with tetrabutylammonium bromide catalysed Michael reaction of 4-hydroxycoumarin (**2**) and aldehydes (**1**) to construct biscoumarins (**3**) using water as solvent at 100 °C. The same reaction could also be performed successfully under neat condition at a slightly higher temperature (120 °C) (**Figure 4.4**). [14]

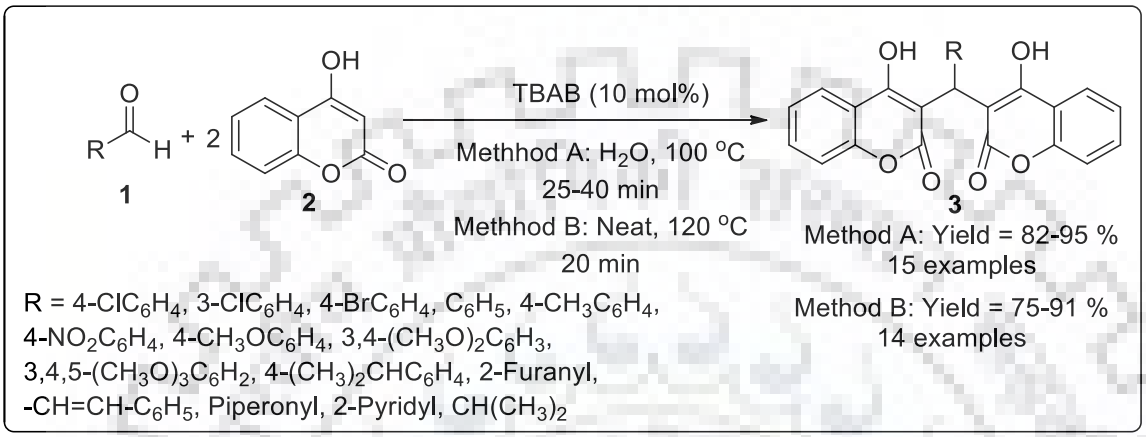


Figure 4.4 Tetrabutylammonium bromide-catalysed synthesis of biscoumarins.

Similarly, Shinde and his group in 2009 reported another one-pot reaction using manganese (II) chloride tetrahydrate as an efficient catalyst for the above mentioned conversion to yield bis-(4-hydroxycoumarin)methanes (**3**, 93-99 % yield) in aqueous medium (**Figure 4.5**). [15]

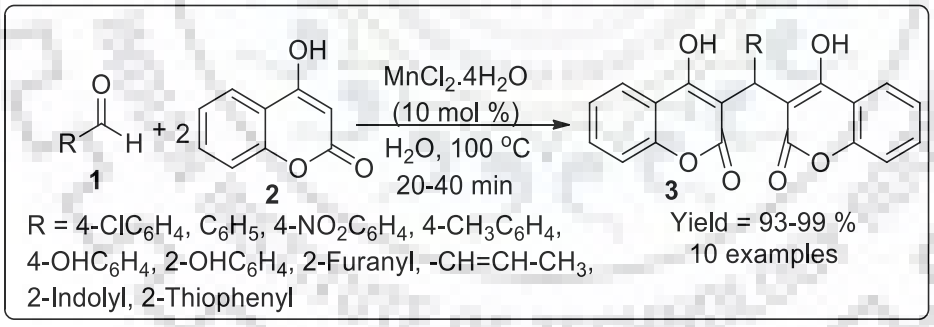


Figure 4.5 Manganese chloride-catalysed synthesis of bis-(4-hydroxycoumarin)methanes.

Later on, in 2015 Wang and co-workers devised an ionic liquid tetramethylguanidium acetate ([TMG][Ac]) assisted domino reaction of 4-hydroxycoumarin (**2**) with various aromatic and hetero-aromatic aldehydes (**1**) to furnish biscoumarins (**3**, 84-99 % yield) at room temperature (**Figure 4.6**). [16]

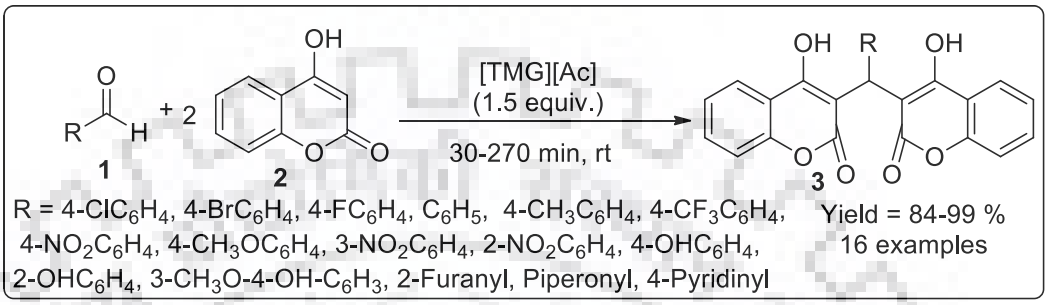


Figure 4.6 Ionic liquid-assisted synthesis of biscoumarins.

On a similar line, Xu *et al.* (2016), prepared a wide variety of biscoumarin derivatives (**3**) using catalytic amount of 1,4-diazabicyclo[2.2.2]octane [DABCO]-based ionic liquid in water at 80 ^{o}C to get comparatively higher yields (96-99 %) of the targeted molecules (**Scheme 4.7**). [17]

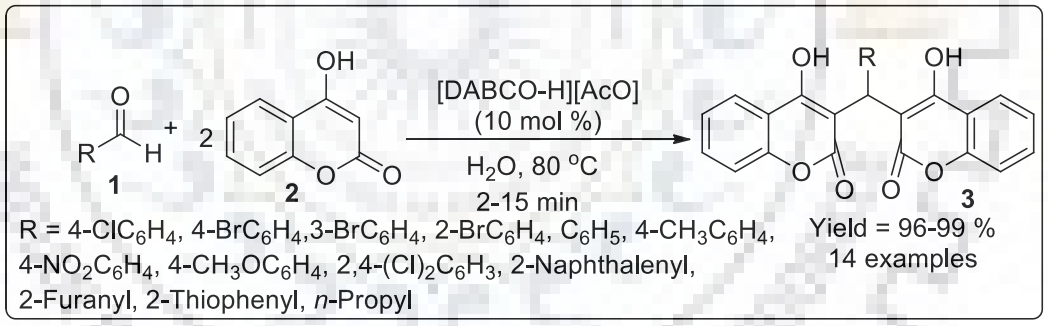


Figure 4.7 DABCO-based ionic liquid-assisted synthesis of biscoumarins.

Recently, Azizi *et al.* (2018) reported a domino Knoevenagel Michael addition reaction of 4-hydroxycoumarin (**2**) and various aldehydes (**1**) using thiamine tagged Ni^{2+} immobilized on $Fe_3O_4@SiO_2$ nanocomposite ($Fe_3O_4@SiO_2@VB_1$-Ni^{2+}) to furnish biscoumarins (**3**, 65-98 % yield). The reaction was performed for 30-50 minutes under solvent free condition at 110 ^oC (**Figure 4.8**). [18]

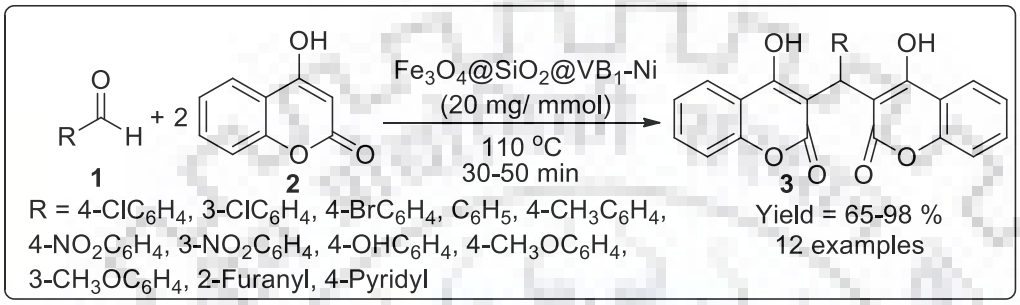


Figure 4.8 $Fe_3O_4@SiO_2$ nanocomposite catalysed synthesis of biscoumarins.

Likewise, in 2018 Myrboh and co-workers synthesized biscoumarin derivatives at room temperature using nickel nanoparticles in aqueous medium (**Figure 4.9**). The designed protocol involved a three-component condensation reaction between two equivalent of 4-hydroxycoumarin (**2**) and one equivalent of aldehydes (**1**) to provide the final product (**3**) in good to excellent yield (86-94%). [19]

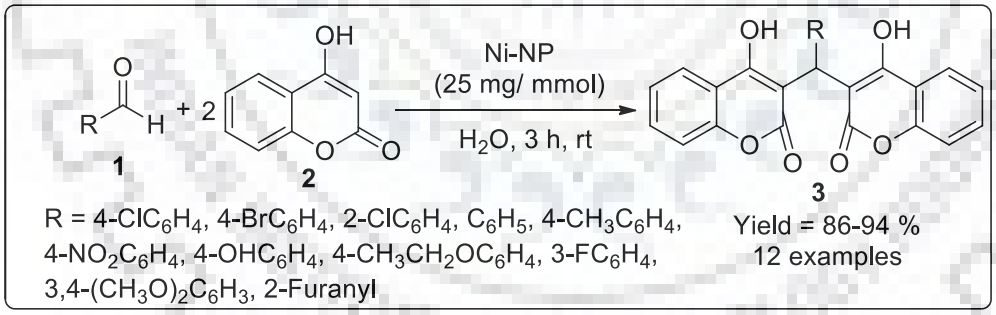


Figure 4.9 Nickel nanoparticles catalysed synthesis of diversified biscoumarins.

Apart from these, the synthesis of biscoumarins from 4-hydroxycoumarin is also reported using several other reagents like phosphotungstic acid (Chandra *et al.*, 2010) [20], choline hydroxide (Wang *et al.*, 2015) [21], pre-functionalised nanoparticles (Karimi *et al.*, 2014) [22], ionic liquids [23, 24] and nanocrystalline MgO (Banerji *et al.*, 2012) [25] using essentially the same strategy.

As mentioned previously, reports for the synthesis of bis(benzochromenone) are scarce. To the best of our knowledge, there is only one report in which 1-Hydroxy-3*H*-benzo[*f*]chromen-3-one (**4**) is used to construct bis-benzocoumarin scaffolds. Bryce and co-workers (2009) reported the synthesis of bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) derivatives (**5**) using ethanol as a solvent under reflux (**Figure 4.10**). [11] However, only three examples of bis-benzocoumarin moieties were reported by the author.

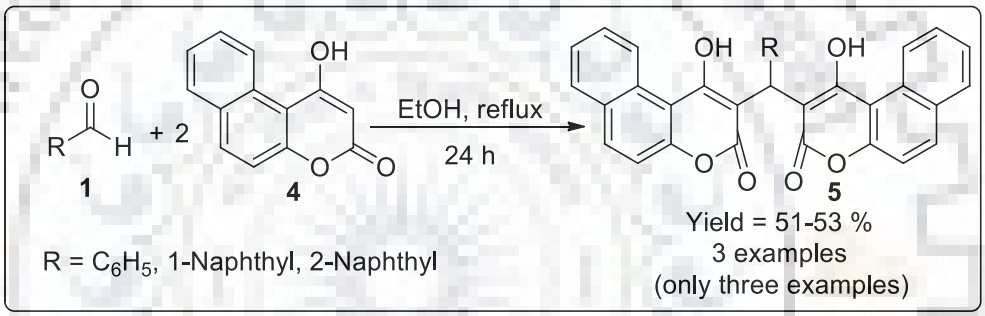


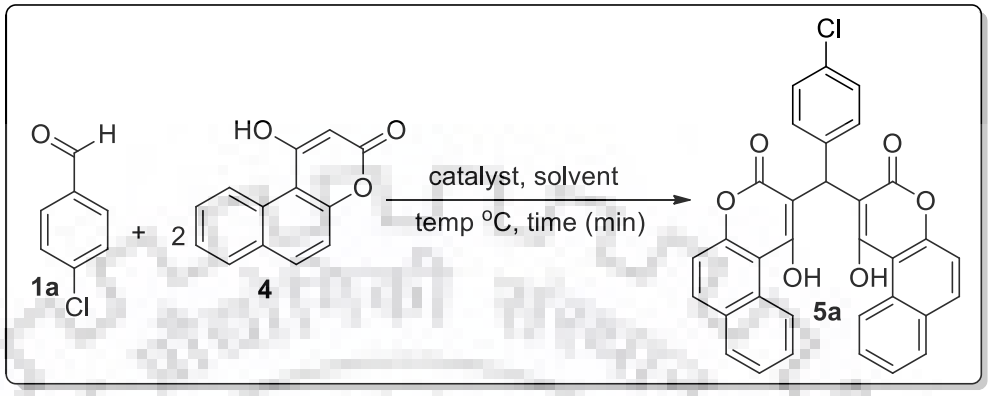
Figure 4.10 Synthesis of bis-benzocoumarins under reflux condition.

From the above described literature reports, it is clear that most of the described methodologies suffer from one or the other drawback like use of pre-functionalized and expensive catalysts, long reaction times, limited substrate scope, tedious work-up and purification processes. Having a focus on adopting efficient greener methodology for the synthesis of biologically relevant molecules, [26-28] the aim of this chapter is to develop an effective methodology to construct such biologically important bis-benzocoumarin derivatives from 1-hydroxy-3*H*-benzo[*f*]chromen-3-one.

4.3 Results and discussion

In a prototypical reaction, a liquid-assisted grinding was tried to afford 2,2'-((4-chlorophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (**5a**) from the reaction of 4-chlorobenzaldehyde (**1a**, 1.0 mmol) and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**4**, 2.0 mmol) using IPA as a promoter in the presence of base as a catalyst. Unfortunately, the desired product **5a** was not observed in the presence of either DABCO (30 mol %) or Et_3N (30 mol %) (**Table 4.1**, entries 1 and 2). Then, the same reaction mixture was irradiated under microwave at 130 ^oC for 15 minutes using 30 mol % of DABCO in IPA which favored the reaction to provide the desired product **5a** in 67 % yield (**Table 4.1**, entry 3). Next, the reaction was studied with other bases like Et_3N and DBU (**Table 4.1**, entries 4, 5) but the conditions failed to give better yield of the desired product **5a**. Later on, the reaction was further screened for optimum catalytic loading of DABCO as well as optimum microwave heating temperature and time (**Table 4.1**, entries 6-10). From this set of experiments, it was ascertained that 30 mol % DABCO at 140 ^oC for 15 minutes provided highest yield of **5a** as 74 % (**Table 4.1**, entry 6). Next, in order to examine the solvent effect on the reaction mixture, different solvents were explored in this reaction and IPA came out as an ideal solvent for the desired conversion (**Table 4.1**, entries 6, 11-12). After having all these experiments, the maximum yield (74 %) of **5a** was obtained under microwave irradiation of a reaction mixture of chlorobenzaldehyde (**1a**, 1 mmol) and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**4**, 2 mmol) for 15 minutes at 140 ^oC using 30 mol % DABCO in 1 mL IPA (**Table 4.1**, entry 6). It is worth noting that mere filtration of the crude product and washing with IPA (2 mL) followed by water (3 mL) provided the pure solid products for further data analysis.

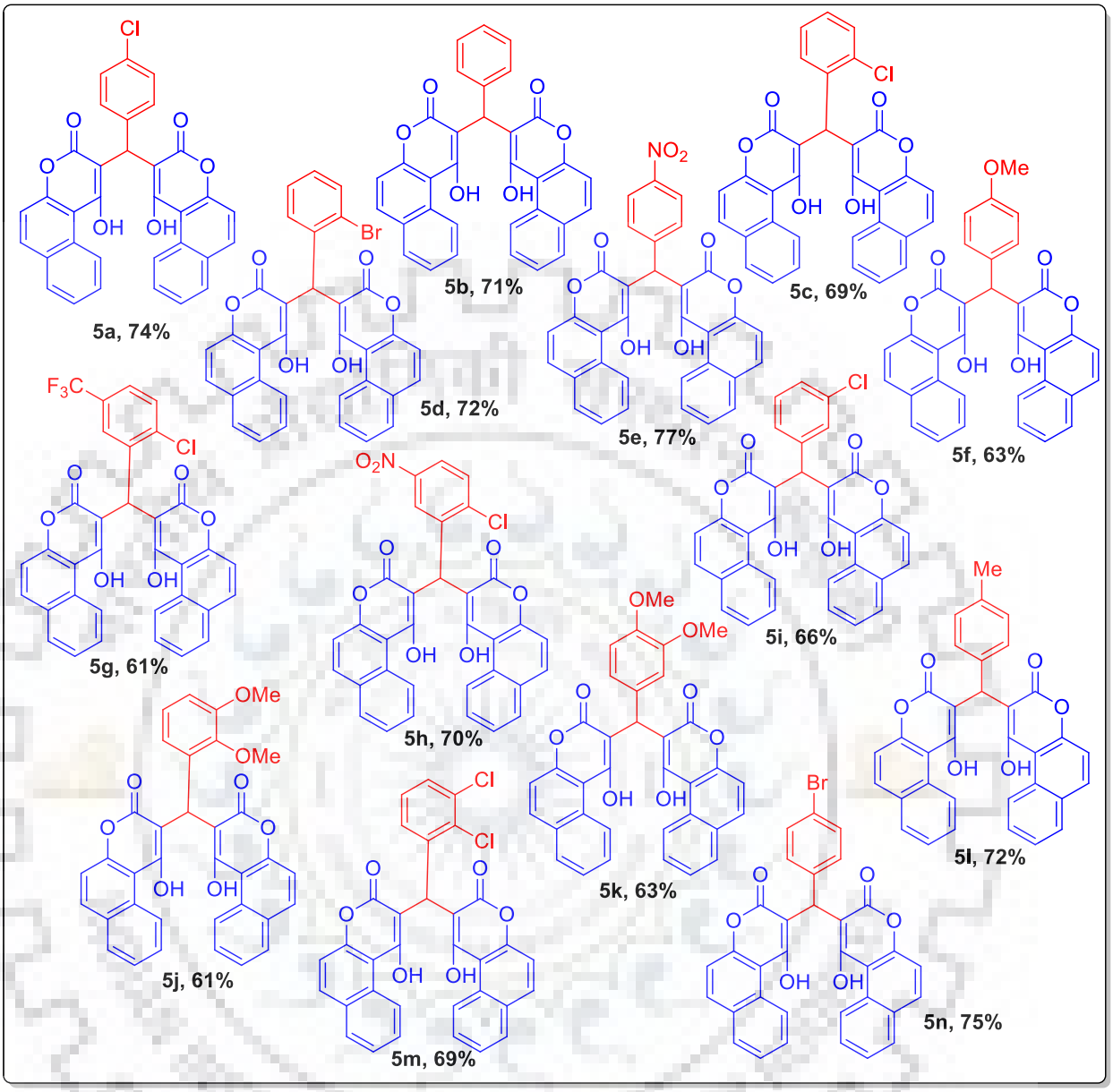
Table 4.1 Optimization of the reaction between 4-chlorobenzaldehyde (**1a**) and 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**4**) under microwave condition[a].



Entry	Catalyst (mol %)	Solvent* (mL)	Condition	Yield (%)[b]
1	DABCO (30 mol %)	IPA	Grinding[c]	-
2	Et_3N (30 mol %)	IPA	Grinding[c]	nd
3	DABCO (30 mol %)	IPA	MW (130 °C for 15 min)	67
4	Et_3N (30 mol %)	IPA	MW (130 °C for 15 min)	61
5	DBU (30 mol %)	IPA	MW (130 °C for 15 min)	63
6	**DABCO (30 mol %)**	**IPA**	**MW (140 °C for 15 min)**	**74**
7	DABCO (30 mol %)	IPA	MW (150 °C for 15 min)	73
8	DABCO (30 mol %)	IPA	MW (140 °C for 12 min)	72
9	DABCO (30 mol %)	IPA	MW (140 °C for 20 min)	75
10	DABCO (20 mol %)	IPA	MW (140 °C for 15 min)	65
11	DABCO (30 mol %)	ACN	MW (140 °C for 15 min)	41
12	DABCO (30 mol %)	EtOH	MW (140 °C for 15 min)	63

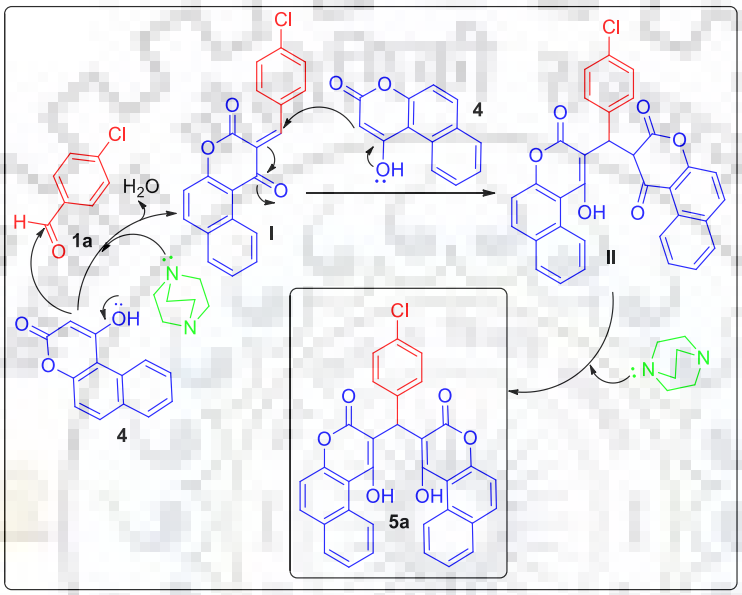
[a]Reaction conditions: **1a** (1.0 equiv.), **4** (2.0 equiv.), catalyst, solvent, Anton Paar Monowave 300 reactor; initial conditions: 1 min 60 °C; final conditions 15 min 140 °C; nd: not determined; [b]Isolated yields; [c]Hand grinding in agate- mortar and pestle; *0.25 mL IPA (entry 1-2); 1 mL of solvent (entries 3-12).

Having optimum conditions for the synthesis of bis(benzochromenone) **5** in hand, the reaction was further explored to examine the substrate scope. Most interestingly, the use of different substituted benzaldehydes did not affect the reaction outcomes. Notably, aromatic aldehydes having electron-withdrawing (4-Cl; 2-Cl; 3-Cl; 4-NO_2; 2-Cl-5-NO_2; 2-Br; 2-Cl-5-CF_3; 2,3-$(Cl)_2$; 4-Br) and electron-donating groups (4-Me; 4-OMe; 3,4-$(OMe)_2$; 2,3-$(OMe)_2$) were proved equally effective in providing corresponding bisbenzochromenones in good to high yields (61-77 %, **5a**-**5n**) as shown in **Scheme 4.1**. Nevertheless, the desired transformation was better in case of unsubstituted (71 %, **5b**) and electron deficient benzaldehydes (4-Cl (74 %, **5a**); 2-Cl (69 %, **5c**); 2-Br (72 %, **5d**); 4-NO_2 (77 %, **5e**); 2-Cl-5-CF_3 (61 %, **5g**); 2-Cl-5-NO_2 (70 %, **5h**); 3-Cl (66 %, **5i**); 2,3-$(Cl)_2$ (69 %, **5m**); 4-Br (75 %, **5n**)) in comparison to electron rich benzaldehydes (4-OMe (63 %, **5f**); 2,3-$(OMe)_2$ (61 %, **5j**); 3,4-$(OMe)_2$ (63 %, **5k**); 4-Me (72 %, **5l**)). In the above conversion, 4-nitro benzaldehyde provided the highest yield of the product **5e** (77 %).



Scheme 4.1 Reaction between 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**4**) and benzaldehydes (**1**). [a]Reaction conditions: **1** (1.0 equiv.), **4** (2.0 equiv.), DABCO (30 mol %), IPA (1 mL), 140 °C for 15 min in Anton Paar Monowave 300 reactor; initial conditions: 1 min 60 °C.

The plausible mechanism for the synthesis of 2,2'-((4-chlorophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (**5a**) is illustrated in **Scheme 4.2**. In the reaction, the base catalysed reaction of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**4**) and 4-chlorobenzaldehyde (**1a**) provided intermediate **I**. The Michael addition of **4** to the intermediate **I** leads to intermediate **II**. Finally, base promoted proton shift provided the final desired product, 2,2'-((4-chlorophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (**5a**).



Scheme 4.2 Mechanism for the synthesis of 2,2'-((4-chlorophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (**5a**).

4.4 Conclusions

In summary, the chapter illustrated a green and efficient synthesis of bis(benzo[*f*]chromen-3-one) derivatives from 1-hydroxy-3*H*-benzo[*f*]chromen-3-one and benzaldehydes under microwave irradiation using DABCO as organocatalyst. The key advantages of the developed strategies are minutes synthesis and diversified substrates. Most importantly, all the synthesized products were obtained by filtration only. Moreover, the column-free procedure provided diversified biologically relevant molecules in good to high yield which is beneficial for their future biological studies.

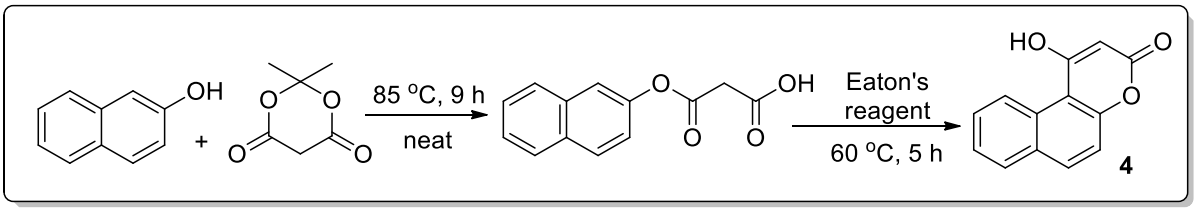
4.5 Experimental details

4.5.1 General information

Except 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**4**), which was prepared in accordance with the reported literature [29], all other substrates, reagents and solvents were purchased commercially. ^{1}H NMR spectra were taken by Bruker Avance® III (500 MHz), ^{13}C NMR spectra were respectively recorded at 125 MHz. Deuterated DMSO (DMSO-d_6) with TMS as internal standard was used as a solvent for taking NMR analyses, ^{13}C NMR of compound **5m** could not recorded even after high number of scans due to lower solubility in NMR solvent. In the evaluation of ^{1}H NMR spectra, chemical shift has been assigned in units of parts per million (ppm), wherein, "s" stands for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "dd" for doublet of doublet", "brs" for broad singlet and "m" for multiplet. The units of coupling constant (*J*) has been assigned in Hz. Functional groups were detected by Perkin Elmer® FT-IR spectrometer- Spectrum two. The High-resolution mass spectra (HRMS) of representative compounds **5b**, **5k**, **5l** and **5m** were recorded on Bruker daltronics microTOF-QII® spectrometer using ESI ionization. Elemental analyses were carried out on vario MICRO® cube Elementar. Melting points were obtained on Optimelt® automated melting point system. Analyses of reactions were done using thin layer chromatography (TLC), which was performed on silica gel TLC plates. The microwave-assisted synthesis of the compounds was performed in Anton Paar® Monowave reactor which has an operating frequency of 2.455 GHz with continuous irradiation power of 0 to 300 W. The reactants were taken in a G-10 glass vial capped with Teflon septum and was exposed to microwave irradiation.

4.5.2 General procedure

Preparation of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (4) [29]: The mixture of 2-naphthol (2 mmol) and meldrum's acid (2 mmol) was stirred at 85 °C for 9 h (**Scheme 4.3**). After that, the reaction mixture was cooled to room temperature and extracted with ethyl acetate followed by saturated $NaHCO_3$ solution. The collected water extract was acidified with conc. HCl and further extracted with methylene dichloride (DCM) to yield the crude intermediate after evaporating the organic solvent. This crude intermediate (1 mmol) in 1.5 mL Eaton's reagent was stirred at 60 °C for 5 h. To this resultant mixture, water was added while vigorous stirring. The precipitate thus obtained was filtered by suction and dried to get final product **4**.



Scheme 4.3 Synthesis of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one.

[29] Park, S.-J.; Lee, J.-C.; Lee, K.-I.; A Facile Synthesis of 4-Hydroxycoumarin and 4-Hydroxy-2-quinolone Derivatives. *Bull. Korean Chem. Soc.* **2007**, *28*, 1203-1205.

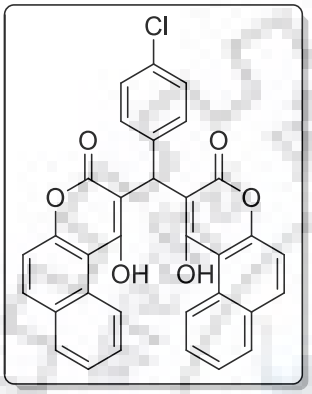
Synthesize of bis(1-hydroxy-3*H*-benzo[*f*]chromenones (5a-5n):

In a G-10 microwave vial, 2 equiv. of 1-hydroxy-3*H*-benzo[*f*]chromen-3-one (**4**) and 1 equiv. of aromatic aldehydes (**1**) were added. To this 30 mol % DABCO and 1 mL IPA were added in succession. This G-10 microwave vial was then subjected to microwave irradiation at 140 °C for 15 minutes. The solid hence obtained was filtered off and washed with IPA followed by water to yield the desired pure products **5**.

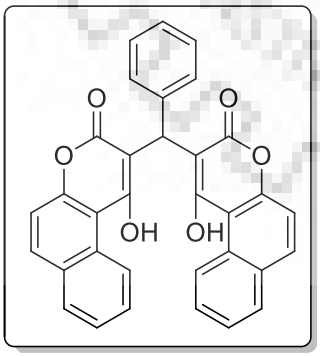
4.5.3 Characterization of the synthesized molecules

All the products were characterized via techniques of ^{1}H NMR, ^{13}C NMR Spectra, FT-IR and elemental analyses. Further, selected HRMS of **5b**, **5k**, **5l** and **5m** compounds are reported to confirm the products.

Analytical Information for the synthesized molecules is given below:

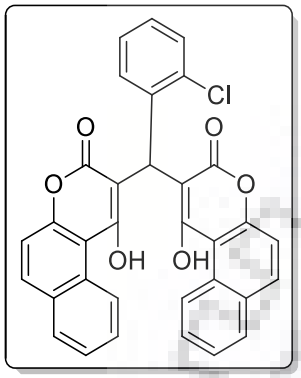


2,2'-((4-chlorophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5a): White solid (74 %); mp: 292-293 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 17.96 (s, 1H), 9.72 (d, 2H, J = 8.5 Hz), 8.07 (d, 2H, J = 9.0 Hz), 7.96 (d, 2H, J = 7.5 Hz), 7.60 (t, 2H, J = 7.0 Hz), 7.51 (t, 2H, J = 7.0 Hz), 7.48 (d, 2H, J = 8.5 Hz), 7.26-7.20 (m, 4H), 6.35 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 172.2, 164.1, 153.3, 141.8, 132.8, 130.5, 130.5, 129.7, 128.9, 128.8, 128.0, 127.8, 127.0, 125.2, 117.4, 112.2, 104.3, 44.4; IR (KBr) υ_{max}/cm^{-1}: 3434, 1677, 1626, 1584, 1404, 1385; Elem. Anal. For $C_{33}H_{19}ClO_6$: calcd.: C: 72.47; H: 3.50 %; found: C: 72.13; H: 3.67 %.

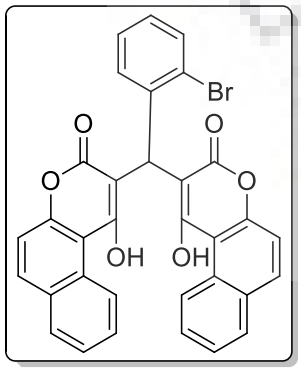


2,2'-(phenylmethylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5b): Pale yellow solid (71 %); mp: 284-286 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 18.04 (s, 1H), 9.74 (d, 2H, J = 8.5 Hz), 8.07 (d, 2H, J = 9.0 Hz), 7.96 (d, 2H, J = 8.0 Hz), 7.59 (t, 2H, J = 8.5 Hz), 7.54-7.46 (m, 4H),

7.24-7.17 (m, 4H), 7.10 (t, 1H, *J* = 7.0 Hz), 6.39 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ_C (ppm) 172.3, 164.3, 153.4, 142.8, 132.7, 130.7, 130.6, 128.9, 128.2, 127.8, 127.2, 127.1, 125.3, 117.5, 112.4, 104.7, 44.5; IR (KBr) υ_{max}/cm^{-1}: 3435, 1634, 1456; Elem. Anal. For $C_{33}H_{20}O_6$: calcd.: C: 77.34; H: 3.93 %; found: C: 77.09; H: 3.59 %; HRMS (ESI) m/z calcd. for $C_{33}H_{20}O_6$ $[M+Na]^+$: 535.1152, found: 535.1176.

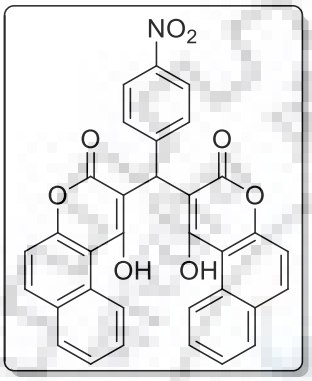


2,2'-((2-chlorophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5c): Yellow solid (69 %); mp: 256-257 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ_H (ppm) 17.69 (s, 1H), 9.73 (d, 2H, *J* = 9.0 Hz), 8.06 (d, 2H, *J* = 9.0 Hz), 7.96 (d, 2H, *J* = 8.0 Hz), 7.59 (t, 2H, *J* = 7.0 Hz), 7.54 (d, 1H, *J* = 7.5 Hz), 7.51 (t, 2H, *J* = 7.0 Hz), 7.54 (d, 2H, *J* = 9.0 Hz), 7.26-7.21 (m, 2H), 7.16 (t, 1H, *J* = 7.5 Hz), 6.27 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ_C (ppm) 172.2, 163.7, 153.2, 141.0, 133.1, 132.7, 131.1, 130.7, 130.5, 129.8, 128.9, 127.9, 127.5, 127.1, 126.6, 125.3, 117.5, 115.0, 112.4, 104.4, 44.5; IR (KBr) υ_{max}/cm^{-1}: 3441, 1689, 1616, 1444; Elem. Anal. For $C_{33}H_{19}ClO_6$: calcd.: C: 72.47; H: 3.50 %; found: C: 72.63; H: 3.69 %.

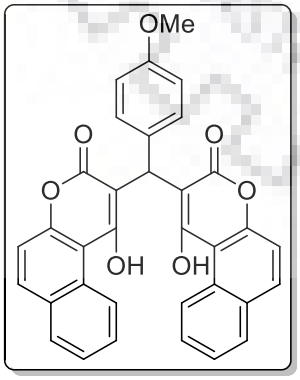


2,2'-((2-bromophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5d): Yellow solid (72 %); mp: 251 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ_H (ppm) 17.59 (s, 1H), 9.72 (d, 2H, *J* =

8.5 Hz), 8.06 (d, 2H, *J* = 9.0 Hz), 7.96 (d, 2H, *J* = 8.0 Hz), 7.59 (t, 2H, *J* = 7.0 Hz), 7.55 (d, 1H, *J* = 7.5 Hz), 7.51 (t, 2H, *J* = 7.0 Hz), 7.47 (d, 2H, *J* = 9.0 Hz), 7.44 (d, 1H, *J* = 9.0 Hz), 7.29 (t, 1H, *J* = 8.0 Hz), 7.09 (t, 1H, *J* = 7.5 Hz), 6.15 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 172.2, 163.7, 153.2, 142.5, 133.3, 132.6, 131.2, 130.7, 130.5, 128.9, 127.8, 127.1, 125.3, 123.6, 117.5, 115.0, 112.4, 104.5, 44.5; IR (KBr) υ_{max}/cm^{-1}: 3428, 1688, 1622, 1452; Elem. Anal. For $C_{33}H_{19}BrO_6$: calcd.: C: 67.02; H: 3.24 %; found: C: 67.45; H: 3.07 %.

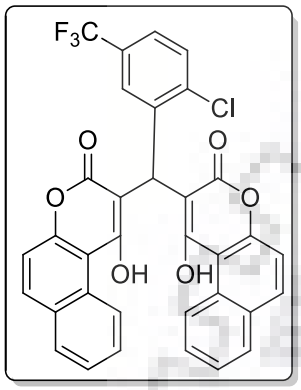


2,2'-((4-nitrophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5e): Dark yellow solid (77 %); mp: 265-267 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 17.86 (s, 1H), 9.70 (d, 2H, *J* = 8.5 Hz), 8.18-8.07 (m, 4H), 7.97 (d, 2H, *J* = 8.0 Hz), 7.60 (t, 2H, *J* = 7.0 Hz), 7.55-7.46 (m, 6H, *J* = 7.2 Hz), 6.47 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 172.2, 163.8, 153.2, 151.8, 145.5, 132.7, 130.3, 130.2, 128.6, 128.0, 127.7, 126.7, 125.1, 123.3, 117.2, 114.7, 111.9, 103.7, 44.2; IR (KBr) υ_{max}/cm^{-1}: 3435, 1643, 1406; Elem. Anal. For $C_{33}H_{19}NO_8$: calcd.: C: 71.09; H: 3.44 %; found: C: 71.37; H: 3.27 %.

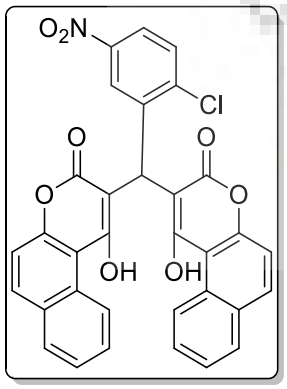


2,2'-((4-methoxyphenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5f): Yellow solid (63 %); mp: 262-263 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 18.05 (s, 1H), 9.75 (d, 2H,

J = 9.0 Hz), 8.06 (d, 2H, *J* = 9.0 Hz), 7.96 (d, 2H, *J* = 9.0 Hz), 7.60 (t, 2H, *J* = 7.0 Hz), 7.51 (t, 2H, *J* = 6.5 Hz), 7.47 (d, 2H, *J* = 9.0 Hz), 7.11 (d, 2H, *J* = 9.0 Hz), 6.76 (d, 2H, *J* = 9.0 Hz), 6.31 (s, 1H), 3.69 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 172.2, 164.3, 153.3, 142.2, 132.7, 130.7, 128.9, 128.1, 127.8, 127.2, 126.9, 125.3, 117.5, 115.0, 113.6, 105.0, 55.3, 44.5; IR (KBr) υ_{max}/cm^{-1}: 3435, 1641, 1507, 1403; Elem. Anal. For $C_{34}H_{22}O_7$: calcd.: C: 75.27; H: 4.09 %; found: C: 75.23; H: 4.01 %.

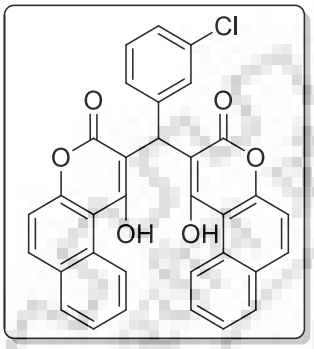


2,2'-((2-chloro-5-(trifluoromethyl)phenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5g): Pale yellow solid (61 %); mp: 269-270 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 17.66 (s, 1H), 9.69 (d, 2H, *J* = 9.0 Hz), 8.08 (d, 2H, *J* = 9.0 Hz),7.97 (d, 2H, *J* = 7.5 Hz),7.81 (s, 1H), 7.61 (t, 2H, *J* = 7.0 Hz), 7.58-7.50 (m, 4H), 7.48 (d, 2H, *J* = 9.0 Hz), 6.34 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 172.1, 163.3, 153.0, 142.3, 132.6, 130.7, 130.3, 130.1, 128.6, 127.7, 126.7, 125.1, 117.1, 114.7, 111.9, 103.4, 44.1; IR (KBr) υ_{max}/cm^{-1}: 3442, 1666, 1556, 1406; Elem. Anal. For $C_{34}H_{18}ClF_3O_6$: calcd.: C: 66.41; H: 2.95 %; found: C: 66.53; H: 2.81 %.

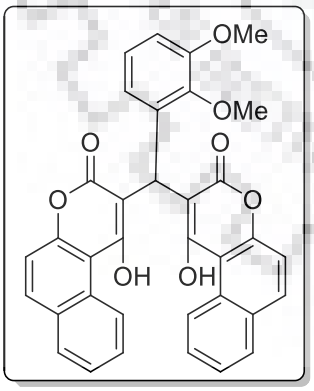


2,2'-((2-chloro-5-nitrophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5h): Dark yellow solid (70 %); mp: 264-265 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 17.68 (s, 1H),

9.69 (d, 2H, *J* = 8.4 Hz), 8.37 (d, 1H, *J* = 2.5 Hz), 8.12-8.06 (m, 3H), 7.98 (d, 2H, *J* = 7.5 Hz), 7.64-7.58 (m, 3H), 7.53 (t, 2H, *J* = 7.0 Hz), 7.49 (d, 2H, *J* = 9.0 Hz), 6.38 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ_C (ppm) 171.9, 163.1, 152.8, 145.8, 142.9, 139.6, 132.5, 130.8, 130.2, 129.9, 128.4, 127.5, 126.5, 125.0, 122.2, 116.9, 111.6, 102.9, 44.0; IR (KBr) υ_{max}/cm^{-1}: 3423, 1670, 1457; Elem. Anal. For $C_{33}H_{18}ClNO_8$: calcd.: C: 66.96; H: 3.06 %; found: C: 66.57; H: 3.39 %.

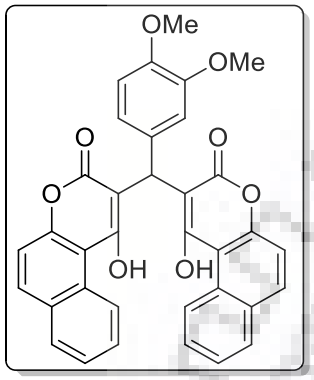


2,2'-((3-chlorophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5i): Pale yellow solid (66 %); mp: 282 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ_H (ppm) 17.95 (s, 1H), 9.72 (d, 2H, *J* = 8.5 Hz), 8.08 (d, 2H, *J* = 9.0 Hz), 7.97 (d, 2H, *J* = 8.0 Hz), 7.61 (t, 2H, *J* = 7.5 Hz), 7.54-7.47 (m, 4H), 7.24 (t, 1H, *J* = 6.5 Hz), 7.21-7.16 (m, 3H), 6.38 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ_C (ppm) 171.6, 163.5, 152.7, 145.0, 132.3, 132.2, 129.9, 129.8, 129.4, 128.2, 127.2, 126.3, 126.0, 125.2, 124.7, 124.6, 116.7, 111.5, 103.4, 43.8; IR (KBr) υ_{max}/cm^{-1}: 3437, 1624, 1405; Elem. Anal. For $C_{33}H_{19}ClO_6$: calcd.: C: 72.47; H: 3.50 %; found: C: 72.42; H: 3.58 %.

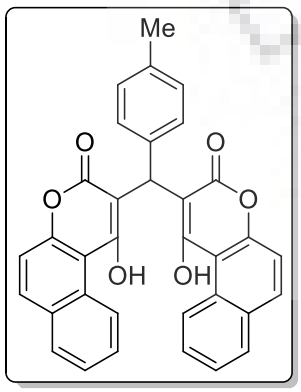


2,2'-((2,3-dimethoxyphenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5j): Pale yellow solid (61 %); mp: 260-261 ^{o}C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ_H (ppm) 17.99 (s, 1H), 9.73 (d, 2H, *J* = 8.5 Hz), 8.05 (d, 2H, *J* = 9.0 Hz), 7.95 (d, 2H, *J* = 7.5 Hz), 7.59 (t, 2H, *J* = 7.0 Hz), 7.50

(t, 2H, *J* = 7.0 Hz), 7.46 (d, 2H, *J* = 9.0 Hz), 6.78 (d, 2H, *J* = 8.5 Hz), 6.74 (d, 1H, *J* = 8.0 Hz), 6.30 (s, 1H), 3.69 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ_C (ppm) 172.3, 164.3, 153.3, 148.7, 147.0, 132.6, 130.7, 128.9, 127.8, 127.1, 125.3, 119.3, 117.5, 115.0, 112.5, 112.0, 111.9, 105.0, 55.9, 44.5; Elem. Anal. For $C_{35}H_{24}O_8$: calcd.: C: 73.42; H: 4.22 %; found: C: 73.53; H: 3.93 %.

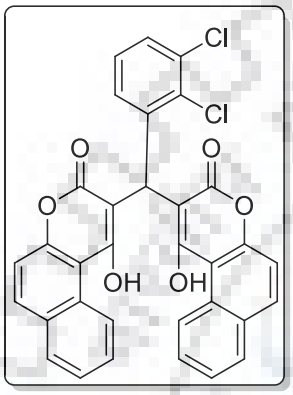


2,2'-((3,4-dimethoxyphenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5k): Yellow solid (63 %); mp: 248-250 ºC; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ_H (ppm) 17.99 (s, 1H), 9.73 (d, 2H, *J* = 8.5 Hz), 8.05 (d, 2H, *J* = 9.0 Hz), 7.95 (d, 2H, *J* = 8.0 Hz), 7.59 (t, 2H, *J* = 8.0 Hz), 7.53-7.43 (m, 4H), 6.81-6.70 (m, 3H), 6.29 (s, 1H), 3.69 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ_C (ppm) 172.3, 164.4, 153.3, 148.8, 147.1, 135.2, 132.7, 130.7, 130.7, 128.9, 127.8, 125.3, 119.4, 117.5, 112.5, 112.1, 112.0, 105.0, 56.0, 44.5; IR (KBr) υ_{max}/cm^{-1}: 3433, 1655, 1555, 1455; Elem. Anal. For $C_{35}H_{24}O_8$: calcd.: C: 73.42; H: 4.22 %; found: C: 73.31; H: 4.17 %; HRMS (ESI) m/z calcd. for $C_{35}H_{24}O_8$ $[M+Na]^+$: 595.1363, found: 595.1399.

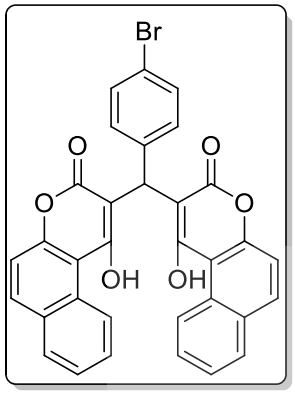


2,2'-(p-tolylmethylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5l): Pale yellow solid (72 %); mp: 286-287 ºC; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ_H (ppm) 9.72 (d, 2H, *J* = 9.0 Hz), 8.06 (d,

2H, *J* = 9.0 Hz), 7.96 (d, 2H, *J* = 8.0 Hz), 7.59 (t, 2H, *J* = 8.0 Hz), 7.54-7.43 (m, 4H), 7.11-6.95 (m, 4H), 6.33 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 172.4, 164.5, 153.4, 139.5, 134.0, 132.7, 130.7, 130.7, 128.9, 128.9, 127.8, 127.2, 127.1, 125.3, 117.5, 112.5, 104.9, 44.0, 21.0; IR (KBr) υ_{max}/cm^{-1}: 3437, 1661, 1557, 1404; Elem. Anal. For $C_{34}H_{22}O_6$: calcd.: C: 77.56; H: 4.21 %; found: C: 77.37; H: 3.99 %; HRMS (ESI) m/z calcd. for $C_{34}H_{22}O_6$ $[M+Na]^+$: 549.1308, found: 549.1308.



2,2'-((2,3-dichlorophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5m): Pale yellow solid (69 %); mp: 282-284 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 17.61 (s, 1H), 9.71 (d, 2H, *J* = 9.0 Hz), 8.06 (d, 2H, *J* = 9.0 Hz), 7.96 (d, 2H, *J* = 8.0 Hz), 7.59 (t, 2H, *J* = 8.5 Hz), 7.53-7.39 (m, 6H), 7.27 (d, 1H, *J* = 8.0 Hz), 6.28 (s, 1H); IR (KBr) υ_{max}/cm^{-1}: 3439, 1659, 1556, 1458, 1402; Elem. Anal. For $C_{33}H_{18}Cl_2O_6$: calcd.: C: 68.17; H: 3.12 %; found: C: 68.03; H: 2.93 %; HRMS (ESI) m/z calcd. for $C_{33}H_{18}Cl_2O_6$ $[M+Na]^+$: 603.0372, found: 603.0398.



2,2'-((4-bromophenyl)methylene)bis(1-hydroxy-3*H*-benzo[*f*]chromen-3-one) (5n): Pale yellow solid (75 %); mp: 277-278 ºC; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 17.98 (s, 1H), 9.79 (d, 2H, *J* = 9.0 Hz), 8.06 (d, 2H, *J* = 9.0 Hz), 7.95 (d, 2H, *J* = 7.5 Hz), 7.60 (t, 2H, *J* = 8.5 Hz), 7.53-7.45 (m, 4H), 7.38 (d, 2H, *J* = 8.5 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 6.36 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C (ppm) 172.4, 164.3, 153.4, 142.4, 132.9, 131.1, 130.7, 130.6, 129.5, 128.9, 127.9, 127.1, 125.4, 118.3, 117.5, 112.4, 104.4, 44.3; IR (KBr) υ_{max}/cm^{-1}: 3442, 1648, 1549, 1412; Elem. Anal. For $C_{33}H_{19}BrO_6$: calcd.: C: 67.02; H: 3.24 %; found: C: 66.89; H: 3.63 %.

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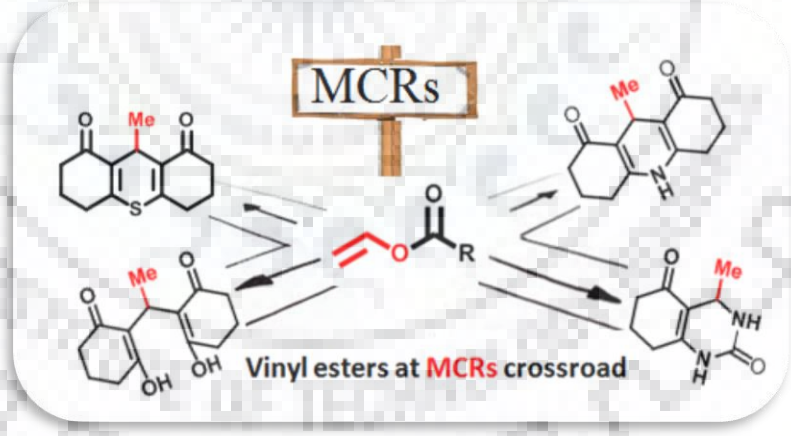
CHAPTER 5

Chemistry of Vinyl Esters as Acetaldehyde Surrogates

in

Some Common Multicomponent Reactions



5.1 Introduction

Introduction of methyl group in a scaffold may significantly causes alteration of its biological activity mainly target selectivity, binding, metabolism and half-life (**Figure 5.1**). [1-7] In 2010, Njardarson *et al.* reported that around 67 % among the top selling marketed drugs containing methyl fragment in their scaffolds. [2] In short, monovalent methyl group is proven to be an important carbon fragment in the biological framework. [1] There are numerous reports in which replacement of C-H by C-Me group results in significant changes in the activity profile of drug (**Figure 5.1**).

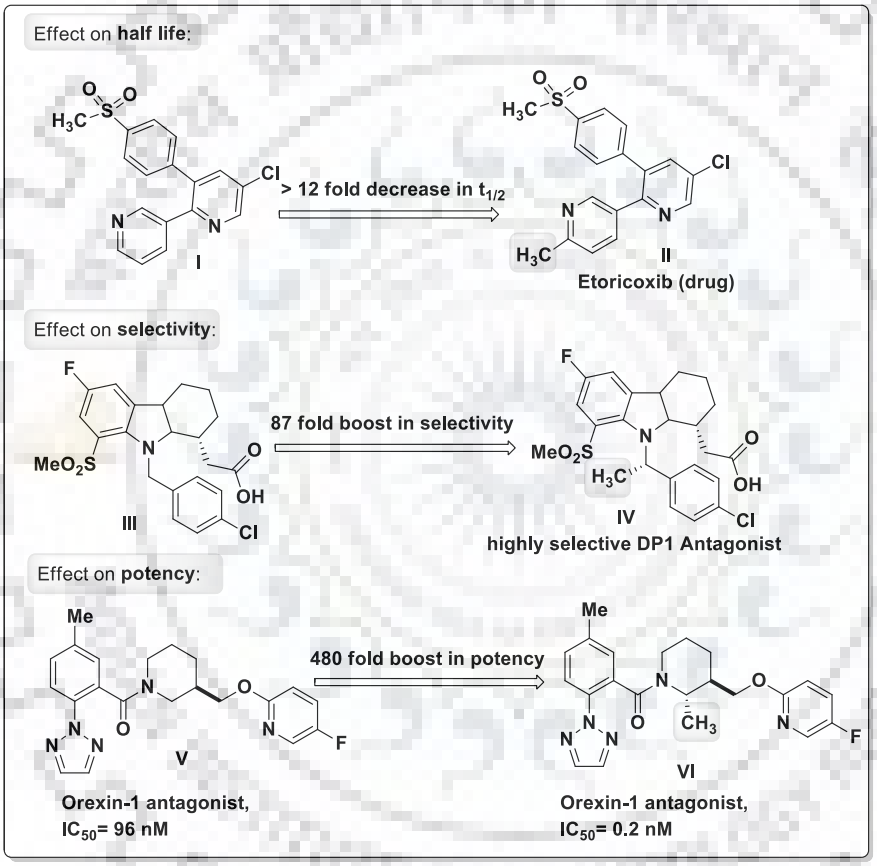


Figure 5.1 Effect of methyl group on drug molecules.

For example, the Structure-Activity Relationship (SAR) studies of 2-phenylaminopyrimidines (PAPs) exhibit an interesting result of "flag methyl" group effect. [5] The conclusion of the report is that methyl substituted phenyl ring (**VIII**) was showing better selectivity of PAPs toward Platelet-derived growth factor-receptor (PDGF-R) than a non-substituted one (**VII**) (**Figure 5.2**).

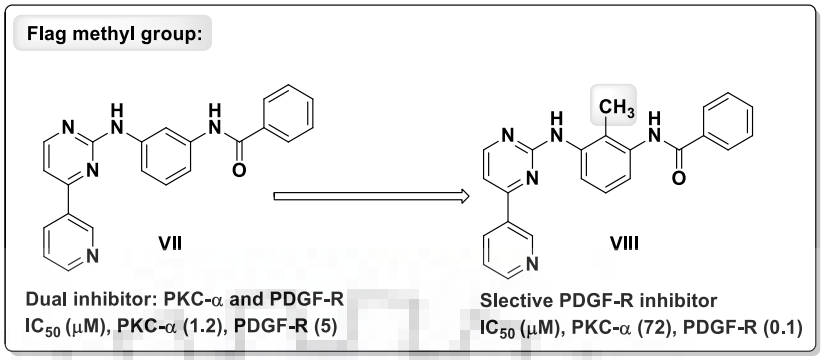


Figure 5.2 Flag methyl effect in molecular selectivity.

The molecular behaviour of compound as agonist and antagonist can also be effected by the addition or removal of methyl groups depending upon their particular position replacement. [6, 7] As a case in point, Abel and co-workers in 2013 reported that double methylation of **MRZ-3573** caused molecular switch to NAM (negative allosteric modulation) (**X**) from PAM (positive allosteric modulator) (**IX**) on glutamate receptor (mGLuR5) (**Figure 5.3**). [6] Similarly, double methylation on 7,8-dihydroquinazoline-5-one (**XI**) effected to change it to PAM (**XII**) (**Figure 5.3**). [6]

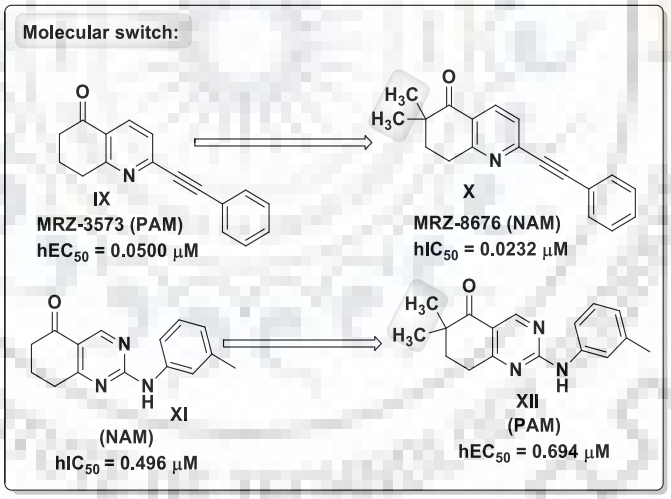


Figure 5.3 Molecular switch due to methyl group effect.

In 2008, from the Quorum Sensing (QS) studies of Janda and co-workers, (*S*)-4,5-dihydroxy-2,3-pentanedione (DPD) derivatives (**XIV-XV**) on methylation showed potential antagonist property (**Figure 5.4**). [7]

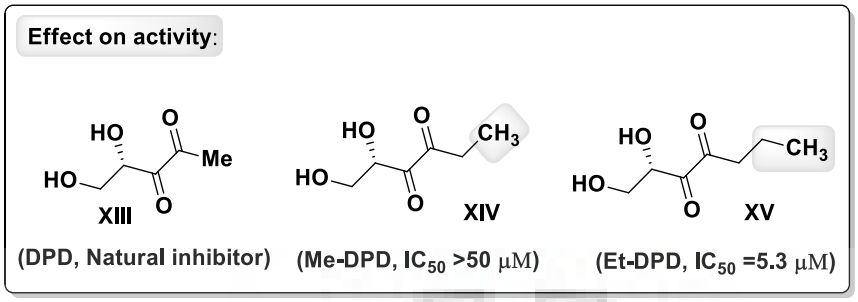


Figure 5.4 Methyl group effect on molecular activity.

The above detailed observations reflects the effect of methyl group on the biologically active scaffolds. In drug discovery, this effect due to introduction of methyl group is known as "magic methyl effect".

In addition to this, scaffolds like acridione, thioxanthendione, bis(hydroxycyclohex-2-enone), tetrahydroquinazolindione exhibits broad spectrum of biological activities like anti-tumor, anti-viral, anti-cancer and anti-alzheimer activity. (**Figure 5.5**). [8-12] It might therefore, be equally interesting to observe "magic methyl effect" in these scaffolds by synthesizing scaffolds having methyl group.

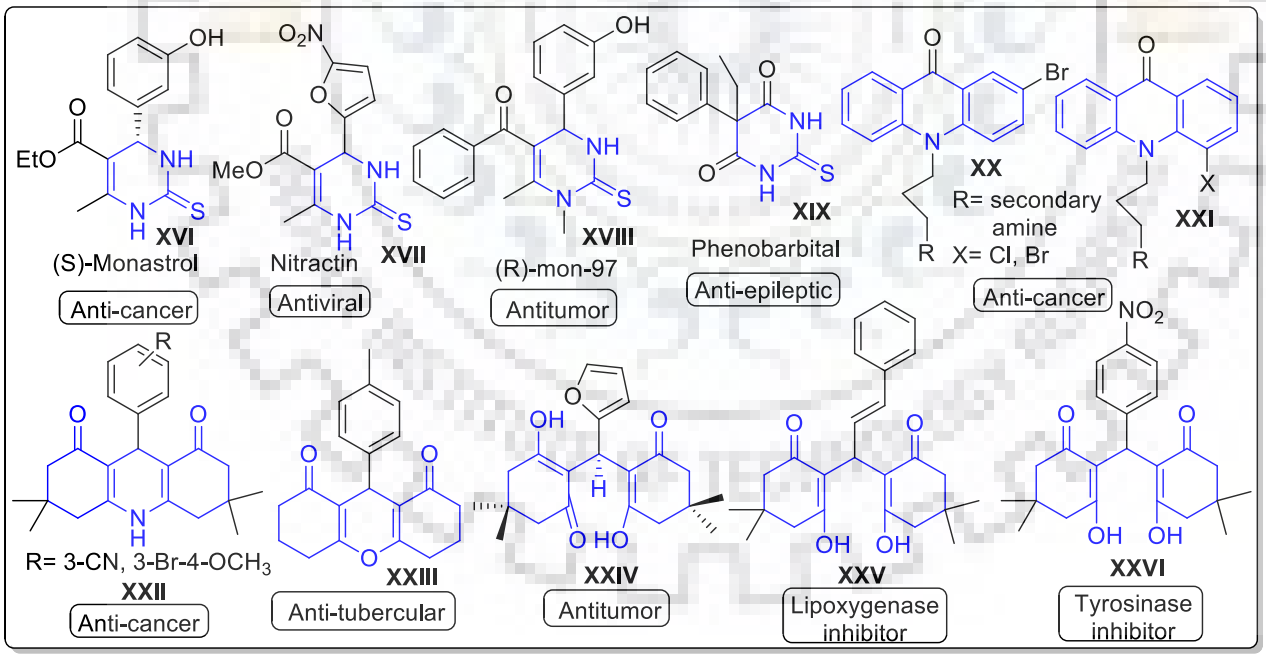


Figure 5.5 Biological activities of diversified reported scaffolds.

From the above discussion, having medicinal importance of methyl group on one hand and biological activities of acridione, thioxanthendione, bis(hydroxycyclohex-2-enone), tetrahydroquinazolindione on another, the initial aim is to develop a method to incorporate methyl group in such biologically active scaffolds.

5.2 Survey of existing methodologies

From the synthesis point of view, methyl group introduction can be achieved by methylation or non-methylation reactions. In the recent past, multicomponent reaction sequences have proven to be an effective tool for the synthesis of diversified scaffolds. Most commonly, acetaldehyde and other aliphatic aldehydes are used for methyl or other alkyl fragments introduction in a multicomponent reaction.

The direct application of acetaldehyde or other aliphatic aldehydes in many MCRs is not always as fruitful as that of aromatic aldehydes. There are numerous MCR reports where direct use of acetaldehyde/aliphatic aldehydes provided lower yield of products or ended up in failure. [13-24] The outcomes of these results conclude that this failure may be a result of high reactivity, low stability and high sensitivity towards self-polymerization of the aliphatic aldehydes.

To counter these problems, use of acetaldehyde/alkyaldehyde surrogates seems to be an impressive alternative to get success in MCR sequences. A detailed survey of previous reports revealed that the application of dihydrofuran (DHF) and other vinyl ethers [25-30], *N*-vinyl amides in the presence of water [31] and (*Z*)-2-(trimethylsiloxy)vinyllithium (by hydrolysis) [32] are the common acetaldehyde or alkyl aldehyde surrogates largely explored by synthetic community (**Figure 5.6**).

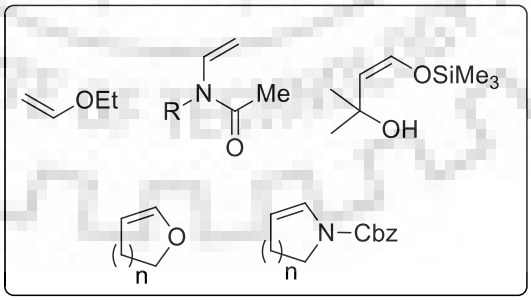


Figure 5.6 Common aldehyde surrogates.

For example, in 2001, Batey and co-workers reported dysprosium(III)-catalysed access of substituted hexahydrofuro[3,2-*c*]quinolones (**3**) by simple Diels-Alder reaction using anilines (**1**) and dihydrofuran (**2**) as an alkylaldehyde surrogate (**Figure 5.7)**. [33] The reaction proceeded through *in situ* generation of 2-azadiene which was formed in reaction between substituted amines (**1**) and one equivalent of dihydrofuran (**2**).

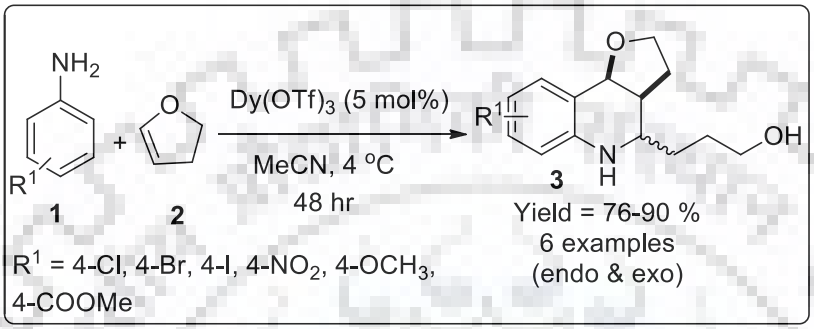


Figure 5.7 Dysprosium(III)-catalysed reaction of dihydrofuran with substituted anilines.

Likewise, in 2004, Prashad *et al.* designed a methodology in which the use of *N*-vinylacetamides (**5**) or ethyl vinyl ether (**6a**) are described as acetaldehyde anion equivalents (**Figure 5.8)**. [34] The described method was developed for an efficient synthesis of xanthene, thioxanthene and acridine carboxaldehyde derivaties (**7**) using xanthydrol, thioxanthydrol, and 9,10-dihydro-10-methyl-9-acridinol (**4**) as starting materials.

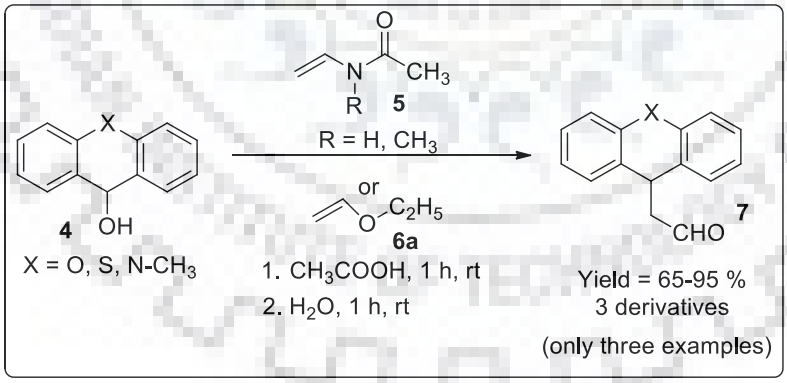


Figure 5.8 Use of *N*-vinylacetamides and ethyl vinyl ether as acetaldehyde anion equivalents.

The mechanism of the reaction is sketched in **Figure 5.9**. The cationic intermediate **A** is formed due to dehydration of starting material in presence of acid. The nucleophilic attacked by *N*-acyliminium (**5**) to intermediate **A** led to intermediate ion **B** which provided **C** in presence of water which further got hydrolyzed to give final aldehyde (**7**).

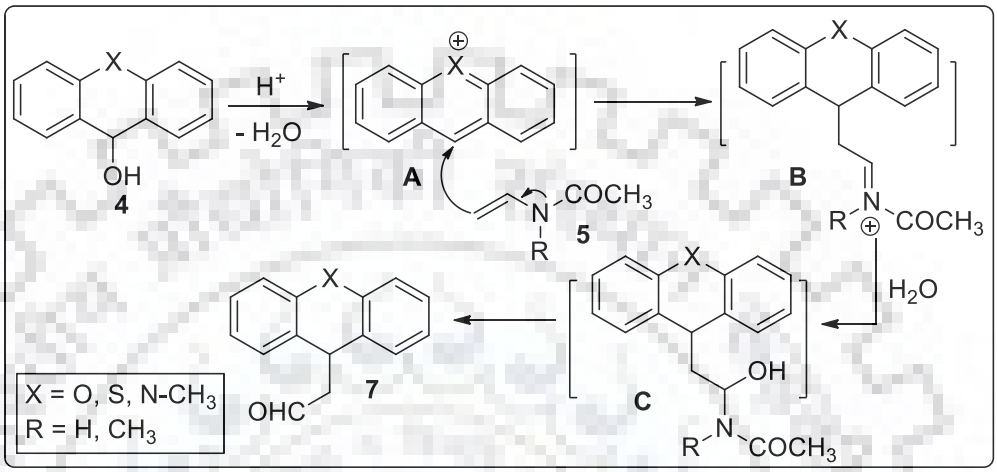


Figure 5.9 Mechanism for *N*-vinylacetamides acting as acetaldehyde equivalents.

Similarly, Jia *et al.* (2010) investigated the stable radical cation salt tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\cdot}$) mediated synthesis of 2-methyl-4-anilino-1,2,3,4-tetrahydroquinolines (**8**) using diversified *N*-vinyllactams (**5**) as an acetaldehyde surrogates **(Figure 5.10)**. [35]

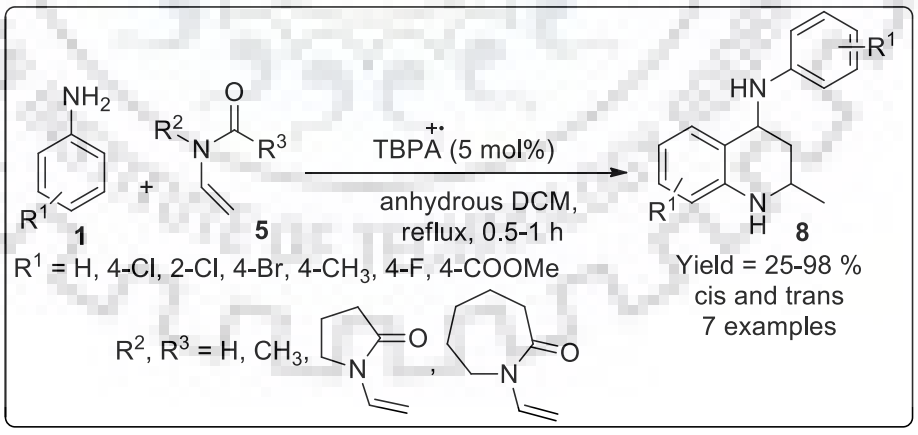


Figure 5.10 A tandem cyclisation reaction of amines with *N*-vinyllactams.

The proposed mechanism is illustrated in **Figure 5.11**. *N*-vinylamides (**5**) formed intermediate cation **A** after forming an adduct with radical cation TBPA. Later, aniline (**1**) reacted with the intermediate **A** to give **B** which provided enamine **D** after rearrangement. The enamine **D** tautomerised to **E** which was oxidized to radical cation intermediate **F** which further reacted with another enamine **D** to give intermediate **G**. The intermediate **G** after intramolecular cyclisation in presence of acid provided final desired product **8**.

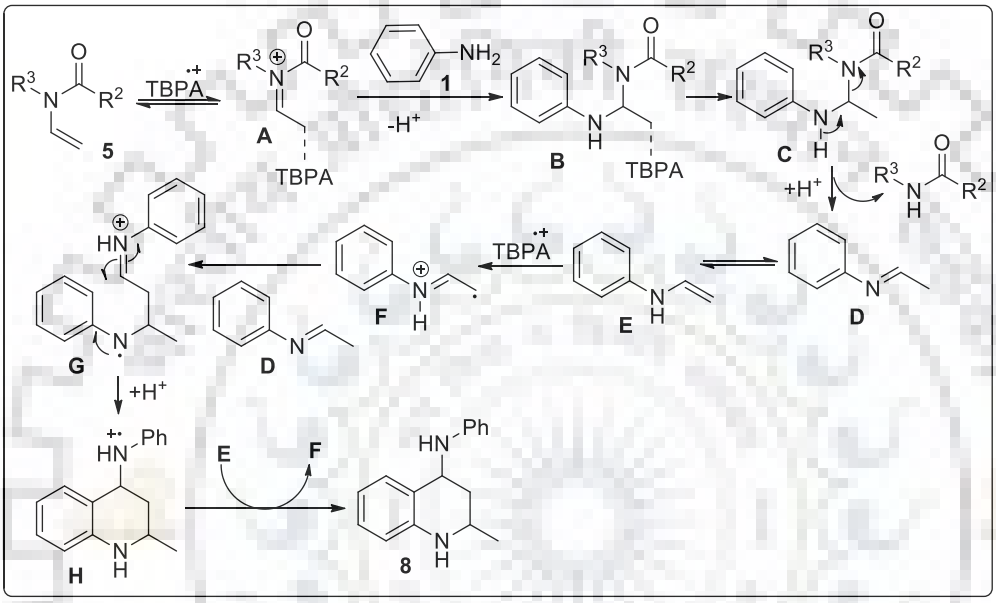


Figure 5.11 *N*-vinyllactams promoted synthesis of 2-methyl-4-anilino-1,2,3,4-tetrahydroquinolines.

Next, Matsubara *et al.* (2011) demonstrated an efficient strategy for $PdCl_2$ mediated synthesis of quinolines (**9**, **10**) using alkenyl ethers (**6**) as an efficient aldehyde surrogates while reaction with anilines (**1**) (**Figure 5.12).** [36]

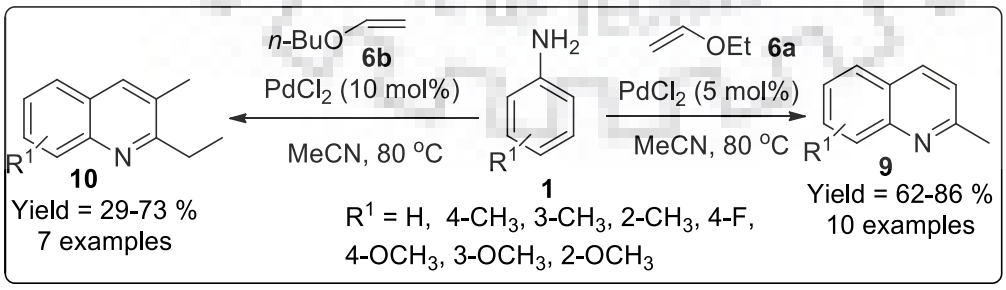


Figure 5.12 Palladium-catalysed synthesis of substituted methylquinolines.

The plausible mechanism for the reaction of aniline (**1**) with vinyl ether (**6a**) is outlined in **Figure 5.13**. Firstly, the reaction of aniline (**1**) with vinyl ether (**6a**) in presence of palladium ion (II) formed intermediate cation **A** which further reacted with **6a** and **1** to provide intermediate **B**. Later on, palladium (II) catalysed aromatization of **B** formed the final product methylquinoline (**9**).

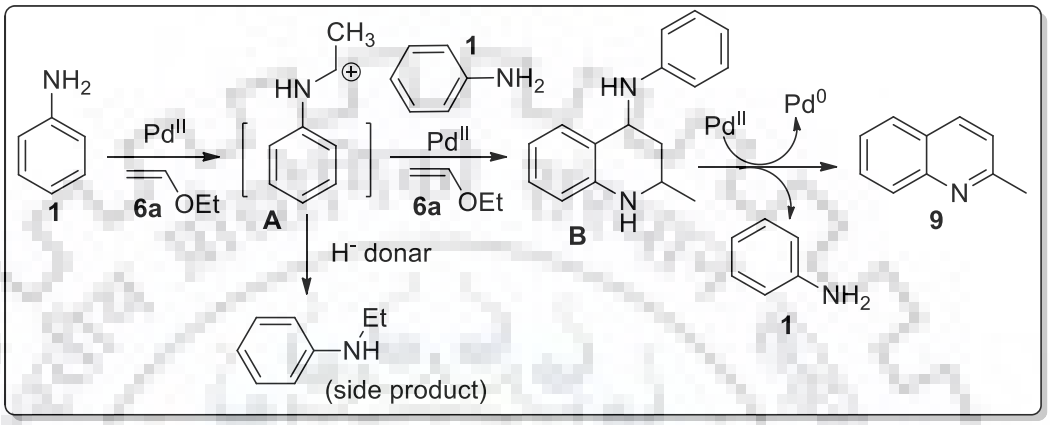


Figure 5.13 Plausible mechanism for synthesis of methylquinoline using vinyl ether.

Similarly, Litinas and co-workers (in 2013) reported a Povarov-type three-component reaction of aminocoumarins (**11**) with two equivalents of *n*-butyl vinyl ether (**6b**) for the synthesis of pyridocoumarin derivatives (**12**) using molecular iodine as a catalyst (**Figure 5.14).** [37]

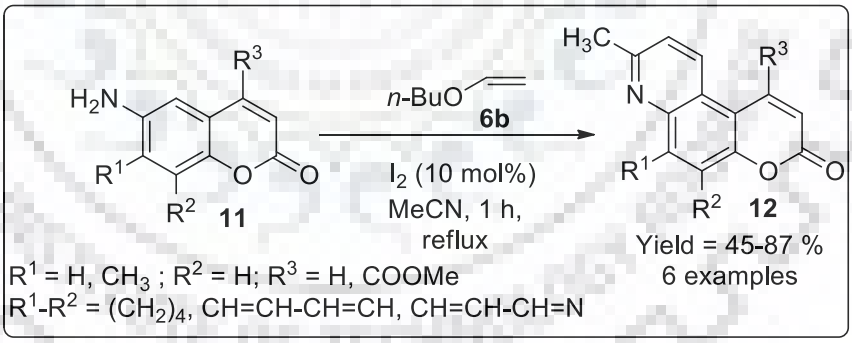


Figure 5.14 Iodine-catalysed reaction of aminocoumarins with *n*-butyl vinyl ether.

Likewise, Sharma *et al.* (2015) developed a DABCO-catalysed three-component synthesis to construct annulated furans (**16**) using vinyl esters (**14**) as acetaldehyde surrogates. The isocyanide based multicomponent reaction (IMCR) was performed under microwave irradiation (typical time 10 minutes at 120 ^{o}C) and afforded moderate to good yield of annulated furanones (**16**, 62-85 %) (**Figure 5.15**). [38]

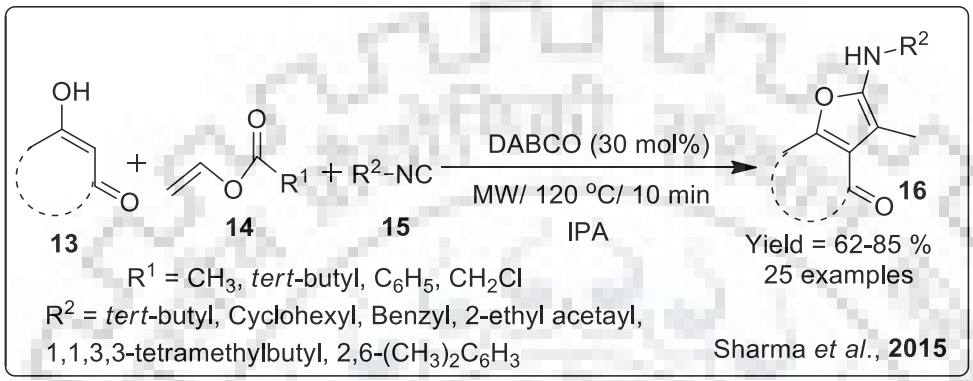


Figure 5.15 DABCO-catalysed synthesis of diversified methyl substituted furans.

The plausible mechanism of the above described IMCR reaction is sketched in **Figure 5.16**. The nucleophilic attack of DABCO to vinyl ester (**14**) provided intermediate acylate ion **A** and enolate ion **B**. The acetaldehyde was formed followed by conversion of enolate **B** into enol **C**. Later on, the acetaldehyde reacted with corresponding 1,3-dicarbonyl systems (**13**) to give enone **D** which further reacted with isocyanides (**15**) in [4+1] cycloaddition fashion to give final desired products **16**.

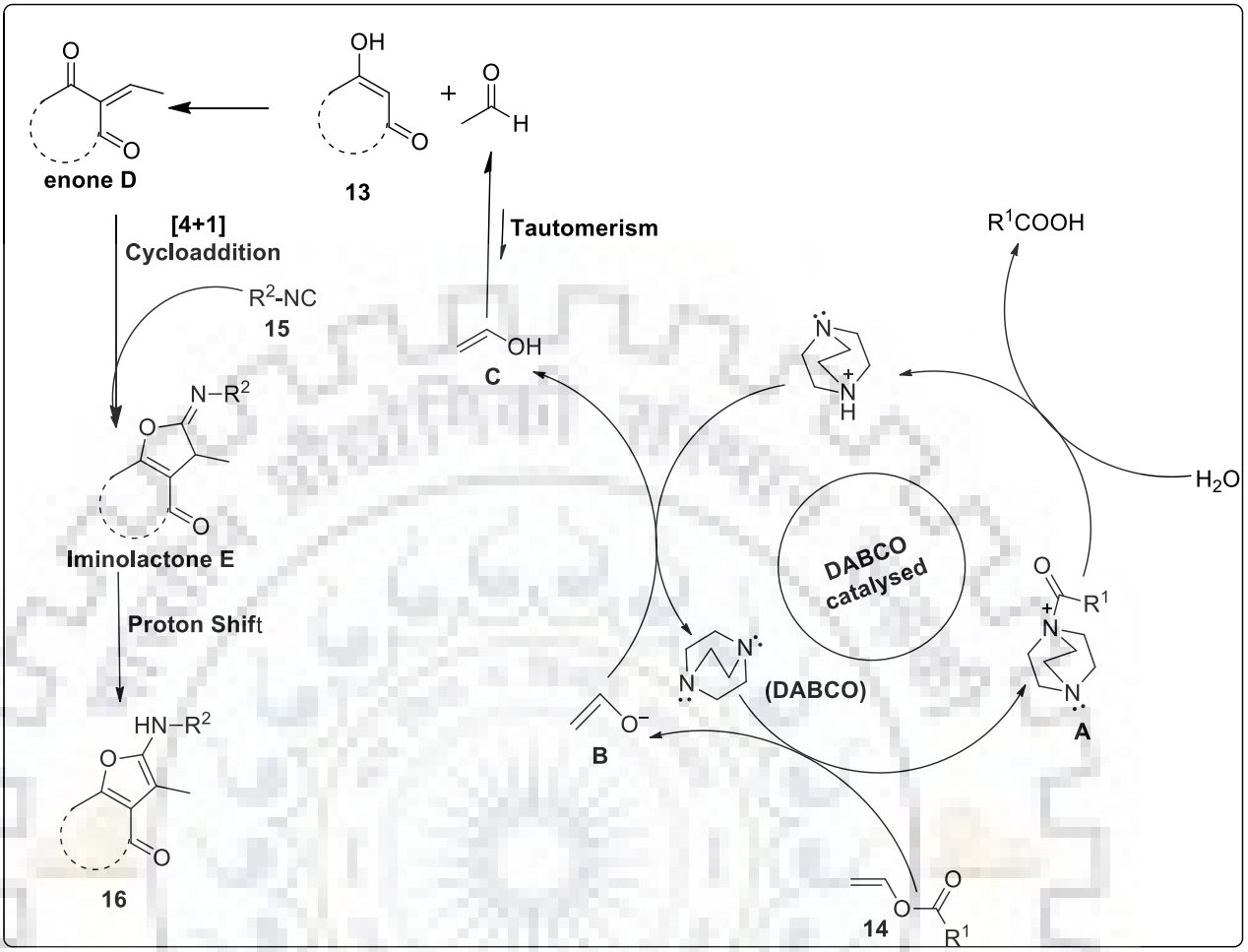


Figure 5.16 Mechanism of DABCO-catalysed vinyl ester mediated IMCR reaction.

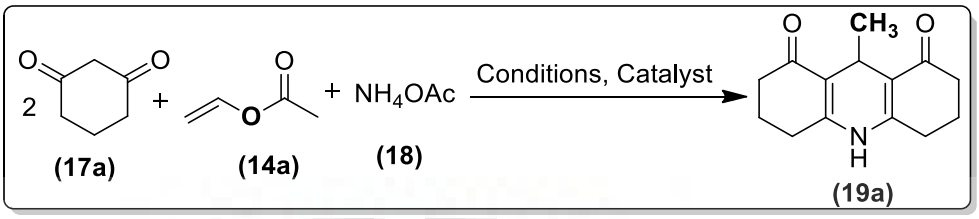
In short, there are plenty of reports in which chemists already explored acetaldehyde/alkyaldehyde surrogates to overcome the problems associated with aldehydes themselves in MCR reactions. In comparison to other aldehyde surrogates, vinyl esters have remained relatively less explored as acetaldehyde surrogates. The reasons behind choosing vinyl esters as acetaldehyde surrogates are because it is cheap, readily available and already explored in some common MCR sequence like Aldol type condensation [39], [4+1] cycloaddition and acylation reactions. [38, 40] Along with these advantages, they have a long shelf life and do not require pre-conditioning. The primary aim of this chapter is to develop methods to incorporate methyl group employing vinyl esters as acetaldehyde surrogates to build up a library of diversified methyl substituted molecules. More precisely, this work highlights the use of vinyl esters in some common multicomponent reactions to synthesize the scaffolds like acridione, thioxanthendione, bis(hydroxycyclohex-2-enone) and tetrahydroquinazolindione derivatives.

5.3 Results and discussion

5.3.1 Synthesis of methyl substituted hexahydroacridine-1,8(2*H*,5*H*)-dione

In a prototype reaction, cyclohexane-1,3-dione (**17a**, 2 mmol), vinyl acetate (**14a**, 1.5 mmol) and NH_4OAc (**18**, 1 mmol) reacted together as standard substrates in presence of 30 % of catalytic DABCO in IPA for the synthesis of 9-methyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**19a**) under microwave irradiation for 10 minutes at 120 ^oC which resulted in 85 % yield of the desired product **19a** (**Table 5.1**, entry 1). In order to optimize the reaction, it was initially decided to try different bases like piperidine, morpholine, DBU, DMAP and NaOH. However none of these bases were able to form the product in good yields (**Table 5.1**, entries 2-7). Later, the reaction was tried in various solvents like MeOH, ACN and tolulene (**Table 5.1**, entries 8-10), which unfortunately provided relatively lower yield of the desired product (**19a**). Next, the temperature and time of the reaction mixture under microwave irradiation was varied (**Table 5.1**, entries 11-12). It was observed that lowering the time to 5 minutes brought down the yield of **19a** to 79 % (**Table 5.1**, entry 12). However increasing the reaction time to 20 minutes brought about a very slight improvement in the yield of **19a** upto to 87 % (**Table 5.1**, entry 13). Lastly, the catalytic loading of DABCO was varied in the above reaction, and 30 mol % catalytic loading of DABCO was found to provide maximum yield of **19a** (**Table 5.1**, entries 13-15). So, the final optimized condition for the desired conversion to result in **19a** was microwave radiation of the reaction mixture at 120 ^oC for 10 minutes using 30 % catalytic DABCO in IPA.

Table 5.1 Optimization of reaction conditions (synthesis of acridine-1,8(2*H*,5*H*)-dione)[a]



Entry	Catalyst (mol %)	Solvent	Conditions	Yield (%)[b]
1	**DABCO (30)**	**IPA**	**MW (120 ^{O}C, 10 min)**	**85**
2	Piperidine (30)	IPA	MW (120 ^{O}C, 10 min)	57
3	Morpholine (30)	IPA	MW (120 ^{O}C, 10 min)	59
4	DBU (30)	IPA	MW (120 ^{O}C, 10 min)	68
5	DMAP (30)	IPA	MW (120 ^{O}C, 10 min)	71
6	NaOH (30)	MeOH	MW (120 ^{o}C, 10 min)	52
7	NaOH (30)	Water	MW (120 ^{o}C, 10 min)	57
8	DABCO (30)	ACN	MW (120 ^{O}C, 10 min)	81
9	DABCO (30)	Toluene	MW (120 ^{O}C, 10 min)	78
10	DABCO (30)	MeOH	MW (120 ^{O}C, 10 min)	83
11	DABCO (30)	IPA	MW (160 ^{O}C, 10 min)	90
12	DABCO (30)	IPA	MW (120 ^{O}C, 5 min)	79
13	DABCO (30)	IPA	MW (120 ^{O}C, 20 min)	87
14	DABCO (10)	IPA	MW (120 ^{O}C, 10 min)	71
15	DABCO (50)	IPA	MW (120 ^{O}C, 10 min)	87

[a]General condition: **17a** (2.0 mmol), **14a** (1.5 mmol), **18** (1.0 mmol); Anton Paar Monowave 300 Microwave reactor, irradiation power: 850 W, ramp time: 1min at 60 °C, [b]Isolated yield.

In order to compare, the same optimized reaction was performed with acetaldehyde in place of vinyl acetate to synthesize respective acridine (**19a**). Unfortunately, the reaction profile was not clean and finally the chromatographic separation only resulted in 57 % yield of **19a**. This is in contrast to the optimized protocol wherein a column-free pure solid product is obtained with 85 % yield of **19a**. The outcome of the reactions clearly manifested the advantage of using vinyl esters over acetaldehyde in this MCR sequence (**Figure 5.17**).

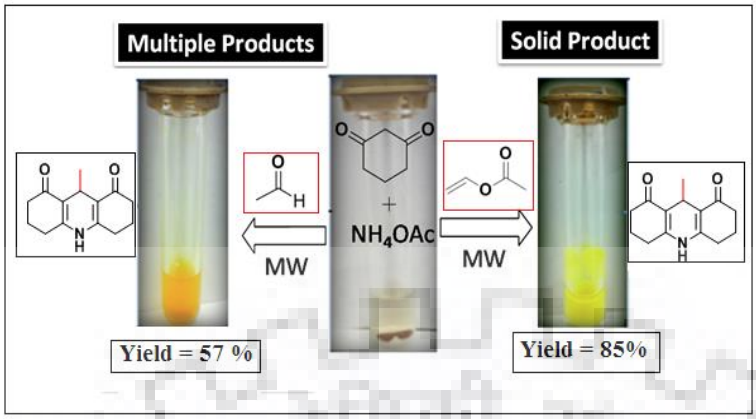
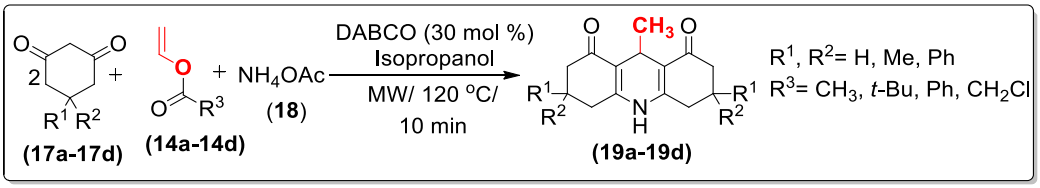
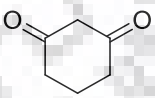
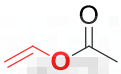
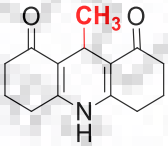
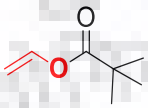
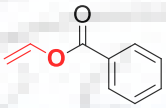
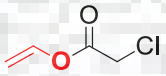
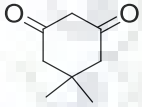
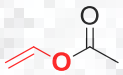
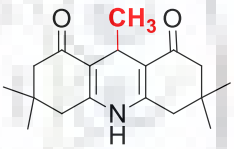
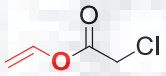
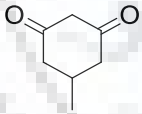
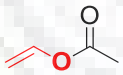
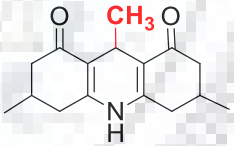
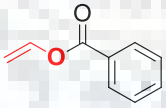
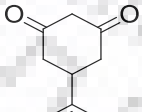
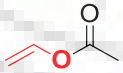
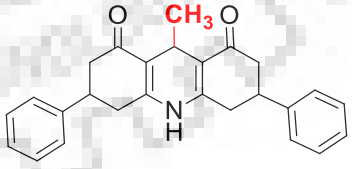
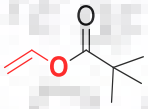


Figure 5.17 Comparison of vinyl ester and acetaldehyde in four-component condensation.

Having optimized condition in hand, the reaction was explored in terms of the substrate scope and limitations. All the substrates such as cyclohexane-1,3-dione (**17a**), 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**17b**), 5-methylcyclohexane-1,3-dione (**17c**) and 5-phenylcyclohexane-1,3-dione (**17d**) resulted in good to high yield of the respective methyl substituted acridines (**19a-19d**) (**Table 5.2**). The reported methodology seemed to be well tolerant to various substituted vinyl esters. Especially, the results were better in case of vinyl acetate (**14a**) and vinyl chloroacetate (**14d**) as compared to vinyl pivalate (**14b**) and vinyl benzoates (**14c**) (**Table 5.2**).

Table 5.2 Scope of four-component reaction (synthesis of acridine-1,8(2*H*,5*H*)-dione)[a]



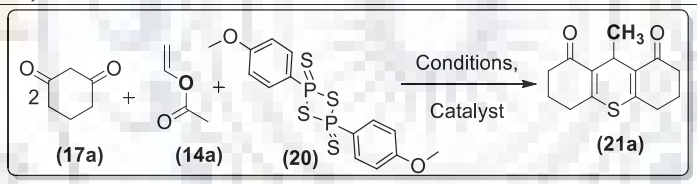
Entry	C-H acid	Enol ester	Product	Yield (%)[b]
1	 (17a)	 (14a)	 (19a)	85
2		 (14b)		83
3		 (14c)		83
4		 (14d)		91
5	 (17b)	 (14a)	 (19b)	81
6		 (14d)		88
7	 (17c)	 (14a)	 (19c)	78
8		 (14c)		79
9	 (17d)	 (14a)	 (19d)	79
10		 (14b)		76

[a]General condition: **17** (2.0 mmol), **14** (1.5 mmol), **18** (1.0 mmol); Anton Paar Monowave 300 Microwave reactor, irradiation power: 850 W, ramp time: 1 min at 60 °C. [b] Isolated yield.

5.3.2 Synthesis of methyl substituted thioxanthene-1,8(2*H*)-dione

After having optimized condition to synthesize 9-methyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**19a**) under microwave irradiation, a similar condition was set to construct 9-methyl-3,4,5,6,7,9-hexahydro-1*H*-thioxanthene-1,8(2*H*)-dione (**21a**) using substrates cyclohexane-1,3-dione (**17a**, 2 mmol), vinyl acetate (**14a**, 1.5 mmol) and Lawesson's reagent (**20**, 0.5 mmol). The reaction provided 65 % yield of **21a** using 30 mol % DABCO as a catalyst in IPA (**Table 5.3**, entry 1). To enhance the yield of the desired product, a number of conditions again examined by changing catalyst (**Table 5.3**, entries 1-3), catalyst loading (**Table 5.3**, entries 4-5) and solvents (**Table 5.3**, entries 8-9) as well. However, there were no significant enhancement in the yield was observed while increasing the microwave irradiation time and temperature (**Table 5.3**, entries 6-7). After all the screening experiments, the optimized condition was found out to be loading of 30 mol % DABCO as a catalyst in IPA and microwave irradiation at 120 ^{o}C for 10 minutes which provided optimum yield of **21a**.

Table 5.3 Optimization of reaction conditions (synthesis of thioxanthene-1,8(2*H*)-dione)[a]

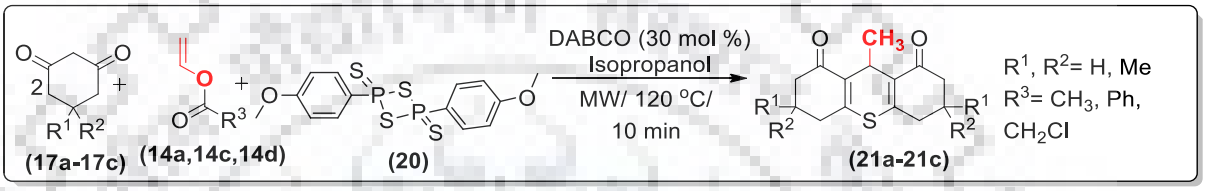


Entry	Catalyst (mol %)	Solvent	Conditions	Yield (%)[b]
1	**DABCO (30)**	**IPA**	**MW (120 ^{O}C, 10 min)**	**65**
2	Morpholine (30)	IPA	MW (120 ^{O}C, 10 min)	59
3	NaOH (30)	MeOH	MW (120 ^{o}C, 10 min)	nd
4	DABCO (10)	IPA	MW (120 ^{O}C, 10 min)	53
5	DABCO (40)	IPA	MW (120 ^{O}C, 10 min)	66
6	DABCO (30)	IPA	MW (120 ^{O}C, 15 min)	67
7	DABCO (30)	IPA	MW (150 ^{O}C, 10 min)	67
8	DABCO (30)	ACN	MW (120 ^{O}C, 10 min)	61
9	DABCO (30)	Toluene	MW (120 ^{O}C, 10 min)	56

[a]General condition: **17a** (2.0 mmol), **14a** (1.5 mmol), **20** (0.5 mmol); Anton Paar Monowave 300 Microwave reactor, irradiation power: 850 W, ramp time: 1 min at 60 ^{o}C. nd = not determined. [b] Isolated yield.

In order to find out the substrate scopes of the reaction, the 1,3-carbonyl compound variants *viz.* cyclohexane-1,3-dione (**17a**), 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**17b**) and 5-methylcyclohexane-1,3-dione (**17c**) were reacted with three different vinyl esters, vinyl acetate (**14a**), vinyl chloroacetate (**14d**) and vinyl benzoates (**14c**) to get the desired thioxanthenediones derivatives (**21a-21c**) in moderate yield (**Table 5.4**, entries 1-5).

Table 5.4 Scope of four-component reaction (synthesis of thioxanthene-1,8(2*H*)-dione)[a]



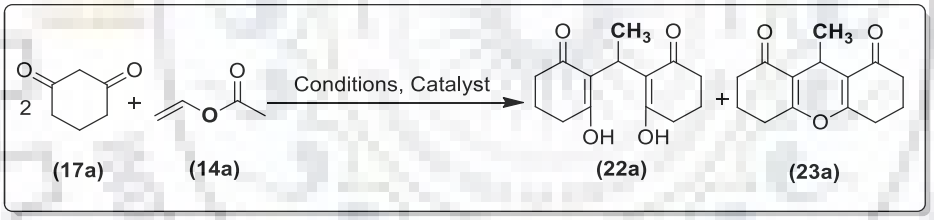
Entry	C-H acid	Enol ester	Product	Yield (%)[b]
1	(17a)	(14a)	(21a)	65
2		(14d)		67
3	(17b)	(14a)	(21b)	61
4	(17c)	(14a)	(21c)	68
5		(14c)		57

[a]General condition: **17** (2.0 mmol), **14** (1.5 mmol), **20** (0.5 mmol); Anton Paar Monowave 300 Microwave reactor, irradiation power: 850 W, ramp time: 1 min at 60 °C. [b] Isolated yield.

5.3.3 Synthesis of methyl substituted bis(3-hydroxycyclohex-2-enone)

Again a similar organocatalytic condition was investigated to synthesize 2,2'-(ethane-1,1-diyl)bis(3-hydroxycyclohex-2-enone) (**22a**) using cyclohexane-1,3-dione (**17a**, 2 mmol) and vinyl acetate (**14a**, 1.5 mmol) under microwave irradiation at 120 ^{o}C for 10 minutes (**Table 5.5**, entry 1). The desired product **22a** was formed in 61 % yield whereas 9-methyl-3,4,5,6,7,8a,9,10a-octahydro-1*H*-xanthene-1,8(2*H*)-dione (**23a**) was also formed as a side product. To improve the reaction outcome, the above reaction was tried under reflux (**Table 5.5**, entry 2) as well as under room temperature (**Table 5.5**, entry 3) and the reaction under room temperature provided better yield (63 %) of **22a**. Therefore, the reaction was further investigated under room temperature using different bases (**Table 5.5**, entries 4-5). Fortunately, application of potassium *tert*-butoxide in MeOH helped to increase the yield (79 %) of **22a** with better reaction profile (**Table 5.5**, entries 6-11). Therefore, the optimized condition for this transformation is room temperature stirring of the reaction mixture for six hours using 10 mol % potassium *tert*-butoxide in MeOH to get the final product **22a**.

Table 5.5 Optimization of reaction conditions [synthesis of bis(3-hydroxycyclohex-2-enone)][a]

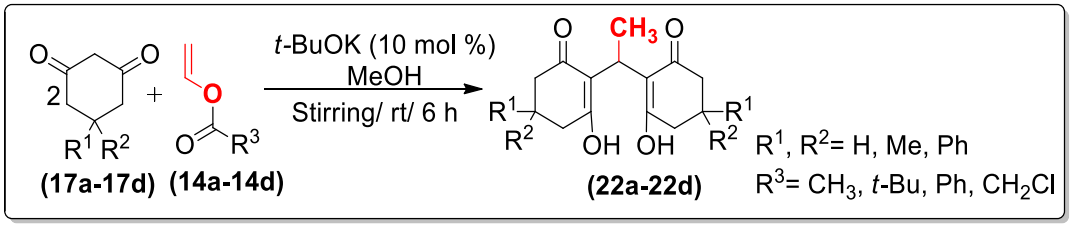


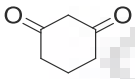
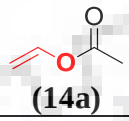
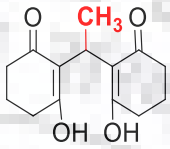
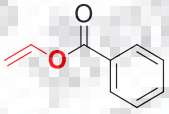
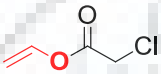
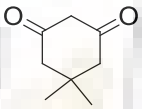
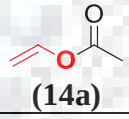
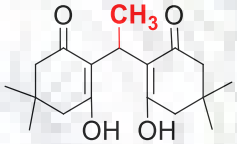
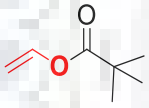
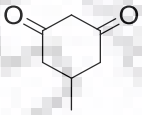
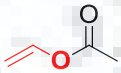
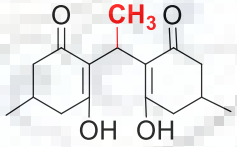
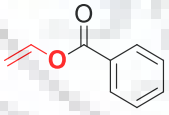
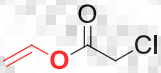
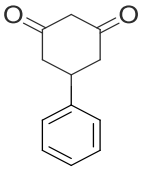
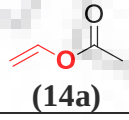
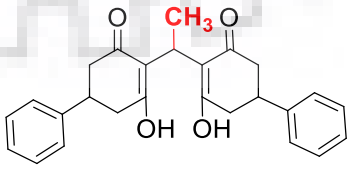
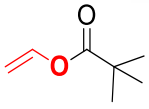
Entry	Catalyst (mol %)	Solvent	Conditions	Yield (%) **(22a)**	**(23a)**
1	DABCO (30)	IPA	MW (120 ^{O}C, 10 min)	61	27
2	DABCO (30)	IPA	Reflux (2 h)	59	23
3	DABCO (30)	IPA	Stirring (6h)	63	23
4	Piperidine (30)	IPA	Stirring (6h)	48	31
5	DBU (30)	IPA	Stirring (6h)	59	24
6	NaOH (10)	MeOH	Stirring (6h)	71	-
7	NaOH (10)	MeOH	Stirring (10h)	70	-
8	NaOH	H_2O	Stirring (6h)	68	-
9	NaOMe (10)	MeOH	Stirring (6h)	73	-
10	***t*-BuOK (10)**	**MeOH**	**Stirring (6h)**	**79**	**-**
11	*t*-BuOK (20)	MeOH	Stirring (6h)	81	-

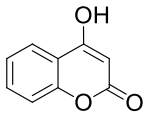
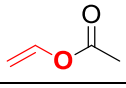
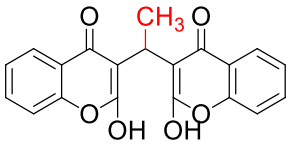
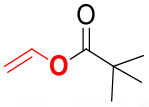
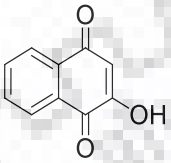
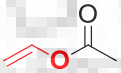
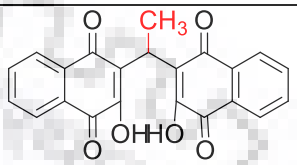
[a]General condition: **17a** (2.0 mmol), **14a** (1.5 mmol); Anton Paar Monowave 300 Microwave reactor, irradiation power: 850 W, ramp time: 1 min at 60 ^{o}C.

With the optimized condition in hand, the substrates like cyclohexane-1,3-dione (**17a**), 5,5-dimethylcyclohexane-1,3-dione (**17b**), 5-methylcyclohexane-1,3-dione (**17c**) and 5-phenylcyclohexane-1,3-dione (**17d**) were reacted with different vinyl esters. In all the cases, the desired products were obtained in good yields (67-87 %). In general, reactions seemed to be working well with vinyl chloroacetate (**Table 5.6**, entries 3 and 8). Unfortunately, substrates 4-hydroxycoumarine (**17e**) and Lawsone (**17f**) failed to provide the respective products (**Table 5.6**, entries 11-13**)**.

Table 5.6 Scope of three-component reaction [synthesis of bis(3-hydroxycyclohex-2-enone)][a]



Entry	C-H acid	Enol ester	Product	Yield (%)[b]
1	 (17a)	 (14a)	 (22a)	79
2		 (14c)		75
3		 (14d)		87
4	 (17b)	 (14a)	 (22b)	81
5		 (14b)		79
6	 (17c)	 (14a)	 (22c)	77
7		 (14c)		71
8		 (14d)		81
9	 (17d)	 (14a)	 (22d)	67
10		 (14b)		68

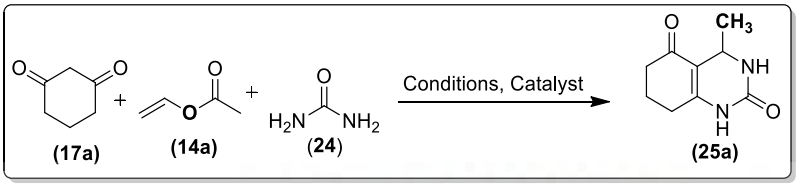
11	 **(17e)**	 **(14a)**	 **(22e)**	nd
12		 **(14b)**		nd
13	 **(17f)**	 **(14a)**	 **(22f)**	nd

[a]General condition: **17** (2.0 mmol), **14** (1.5 mmol); Anton Paar Monowave 300 Microwave reactor, irradiation power: 850 W, ramp time: 1 min at 60 °C. [b] Isolated yield, nd = not determined. [b] Isolated yield.

5.3.4 Synthesis of methyl substituted tetrahydroquinazoline-2,5(1*H*,6*H*)-dione

To extend the work, a similar three-component condensation reaction was investigated to synthesize 3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (**25a**) using DABCO as an organocatalyst (30 mol %) and cyclohexane-1,3-dione (**17a**, 1 mmol), vinyl acetate (**14a**, 1.5 mmol) and urea (**24**, 1 mmol) as starting materials which provided 73 % of conversion to **25a** in IPA at 120 °C for 10 minutes under microwave irradiation (**Table 5.7**, entry 1). In order to optimize, different bases were explored in the above reaction which did not improve yield of the desired product **25a** (**Table 5.7**, entries 2-4). Next, the reaction was analyzed with respect to temperature (**Table 5.7**, entry 5) and solvents (**Table 5.7**, entries 7-8) but no fruitful outcomes were obtained. Reaction did not work at room temperature (**Table 5.7**, entry 6) and only starting materials were recovered unreacted. Fortunately, the reaction provided better yield (82 %) of the desired product **25a** when the mixture was irradiated in neat condition at 120 °C for 10 minutes using 30 mol % DABCO as a basic catalyst (**Table 5.7**, entries 9-12) and this was established as the optimized condition for the desired transformation.

Table 5.7 Optimization of reaction conditions (synthesis of tetrahydroquinazoline-2,5(1*H*,6*H*)-dione)[a]

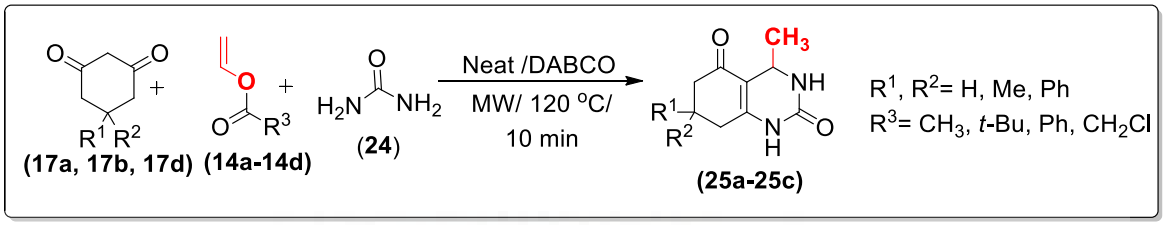


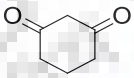
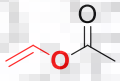
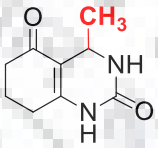
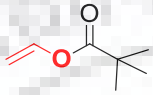
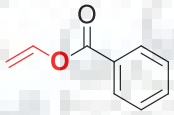
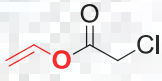
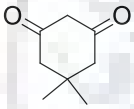
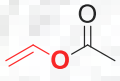
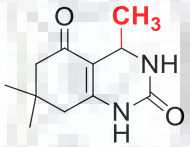
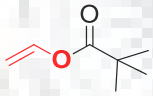
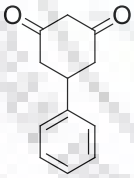
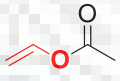
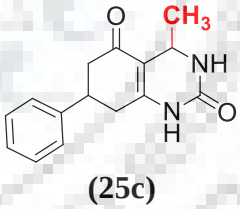
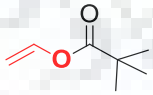
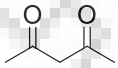
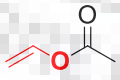
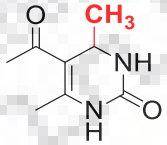
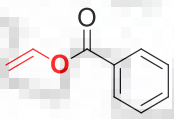
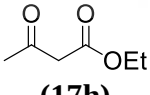
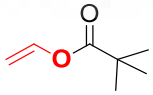
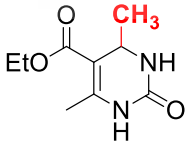
Entry	Catalyst (mol %)	Solvent	Conditions	Yield (%)[b]
1	DABCO (30)	IPA	MW (120 ^{O}C, 10 min)	73
2	DBU (30)	IPA	MW (120 ^{O}C, 10 min)	69
3	Piperidine (30)	IPA	MW (120 ^{O}C, 10 min)	59
4	NaOH (30)	MeOH	MW (120 ^{O}C, 10 min)	61
5	DABCO (30)	IPA	MW (160 ^{O}C , 10 min)	74
6	DABCO (30)	IPA	Stirring (RT)	-
7	DABCO (30)	ACN	MW (120 ^{O}C, 10 min)	76
8	DABCO (30)	Toluene	MW (120 ^{O}C, 10 min)	61
9	**DABCO (30)**	**Neat**	**MW (120 ^{O}C, 10 min)**	**82**
10	DABCO (20)	Neat	MW (120 ^{O}C, 10 min)	72
11	DABCO (40)	Neat	MW (120 ^{O}C, 10 min)	84
12	DABCO (30)	Neat	MW (120 ^{O}C, 15 min)	83

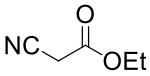
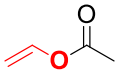
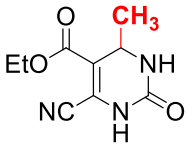
[a]General condition: **17a** (1.0 mmol), **14a** (1.5 mmol), **24** (1.0 mmol); Anton Paar Monowave 300 Microwave reactor, irradiation power: 850 W, ramp time: 1 min at 60 ^{o}C. [b] Isolated yield.

Having optimized the synthesis of desired quinazolines, the reaction was analyzed for its scope using cyclohexane-1,3-dione (**17a**), 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**17b**) and 5-phenylcyclohexane-1,3-dione (**17d**) to get the corresponding products (**Table 5.8**, entries 1-8). The stable conformer of the synthesized compound **25c** is explained later on with respect to computational study. Unfortunately, the acyclic diketones like acetyl acetone (**17g**), ethyl acetoacetate (**17h**) and ethyl cynoacetate (**17i**) did not provide the desired products at all (**Table 5.8**, entries 9-12).

Table 5.8 Scope of three-component reaction (synthesis of tetrahydroquinazoline-2,5(1*H*,6*H*)-dione)[a]



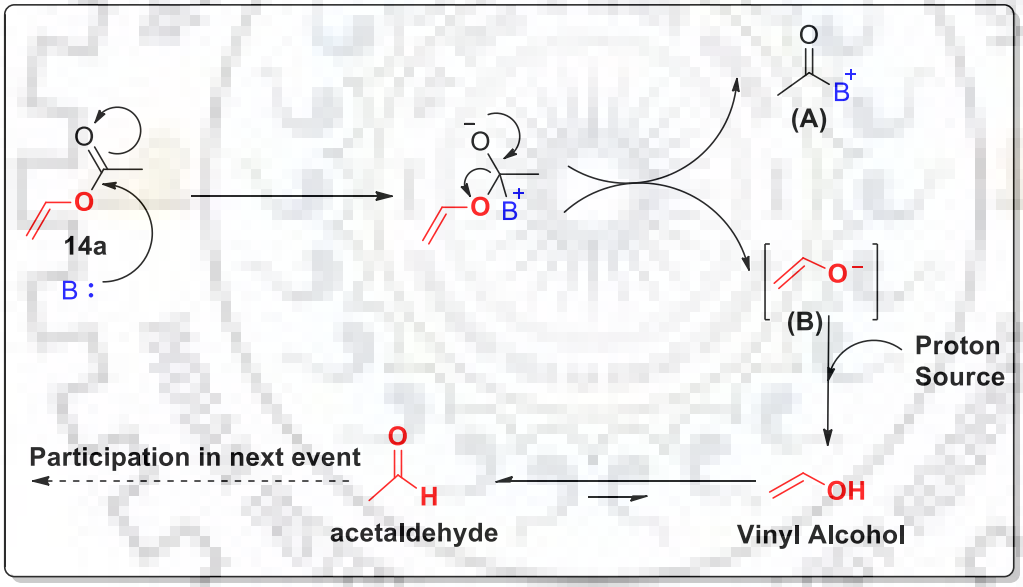
Entry	C-H acid	Enol ester	Product	Yield (%)[b]
1	 (17a)	 (14a)	 (25a)	82
2		 (14b)		81
3		 (14c)		79
4		 (14d)		87
5	 (17b)	 (14a)	 (25b)	77
6		 (14b)		74
7	 (17d)	 (14a)	 (25c)	65
8		 (14b)		67
9	 (17g)	 (14a)	 (25d)	nd
10		 (14c)		nd
11	 (17h)	 (14b)	 (25e)	nd

12	 **(17i)**	 **(14a)**	 **(25f)**	nd

[a]General condition: **17** (1.0 mmol), **14** (1.5 mmol), **24** (1.0 mmol); Anton Paar Monowave 300 Microwave reactor, irradiation power: 850 W, ramp time: 1 min at 60 °C. [b] Isolated yield, nd =not determined. [b] Isolated yield.

5.3.5 Mechanistic study for formation of acetaldehyde from vinyl esters

The mechanistic study of vinyl esters as acetaldehyde equivalent is sketched in **Scheme 5.1**. Initial nucleophilic attack of a base on vinyl acetate leads to the cleavage of vinyl acetate (**14a**) into two parts where in one out as acylating half **A** and the other part becomes enolate **B**. After proton abstraction, the enolate **B** tautomerize to acetaldehyde and undergoes a subsequent multicomponent cascade (**Scheme 5.1**).



Scheme 5.1 Plausible mechanism for the generation of acetaldehyde from vinyl esters.

5.4 Conclusions

In summary, the effective use of vinyl esters as acetaldehyde surrogates have been explored on mainly cyclic 1,3-diketone as a substrate in different multicomponent synthesis to develop medicinally relevant diversified scaffolds like methyl substituted hexahydroacridione, thioxanthendione, bis(hydroxycyclohex-2-enone), tetrahydroquinazolindione derivatives. In the present report, vinyl esters provided better results compared to the acetaldehyde in terms of reaction profile and yield. In short, the reaction of vinyl esters as acetaldehyde surrogates worked well with cyclic 1,3-diketone in four different sets of MCR sequences.

5.5 Experimental section

5.5.1 General information

NMR spectra were recorded on a Jeol Resonance® ECX-400II. Chemical shifts are reported in parts per million and are referenced to TMS. Mass spectrometry (HRMS) was performed using a Bruker daltronics micro TOF-QII® spectrometer using ESI ionization. Analytical Thin layer chromatography (TLC) was performed on a silica gel plate (Merck® $60F_{254}$). Melting points were performed with Ambassador® and Digital Melting point apparatus (Nutronics), Popular India. All chemicals were purchased from sigma-Aldrich® and were used without further purification.

Microwave Irradiation Experiment

All microwave experiments were carried out in a dedicated Anton Paar® Monowave 300 reactor, operating at a frequency of 2.455 GHz with continuous irradiation power of 0 to 300 W. The reactions were performed in a G10 Borosilicate glass vial sealed with Teflon septum and placed in a microwave cavity. Initially, microwave of required power was used and temperature was being ramped from room temperature to a desired temperature. Once this temperature was attained, the process vial was held at this temperature for required time. The reactions were continuously stirred. Temperature was measured by an IR sensor. After the experiments a cooling jet cooled the reaction vessel to ambient temperature.

5.5.2 General procedures

General procedure for the synthesis of 19(a-d): C-H acid (2.0 mmol), vinyl ester (1.5 mmol), ammonium acetate (1.0 mmol) DABCO (30 mol %) in isopropanol was taken in G10 process vial capped with Teflon septum. After a pre-stirring of 1 or 2 minutes, the vial was subjected to microwave irradiation with the initial ramp time of 1 minute at 60 °C. The temperature was then raised to 120 °C with the holding time of 10 minutes. The reaction mixture was cooled down to 0-5 °C by a cooling air jet.

For compound **19a** and **19b** products directly got crystallized in the reaction vial, which was then filtered off and washed with ether.

For compound **19c** and **19d** direct crystallization was not observed. Solvent was removed in vacuum and crude mixture was dissolved in DCM and washed with water and dilute acid two times. This extract was purified by column chromatography using DCM + Methanol.

General procedure for the synthesis of 21(a-c): C-H acid (2.0 mmol), vinyl ester (1.5 mmol), lawesson's reagent (0.5 mmol) DABCO (30 mol %) in isopropanol was taken in G10 process vial capped with Teflon septum. After a pre-stirring of 1 or 2 minutes, the vial was subjected to microwave irradiation with the initial ramp time of 1 minute at 60 °C. The temperature was then raised to 120 °C with the holding time of 10 minutes. The reaction mixture was cooled down to 0-5 °C by a cooling air jet. Solvent was removed in vacuum and crude mixture was dissolved in DCM and washed with water and dilute acid two times. This extract was purified by silica column using DCM + Methanol as an eluant to get the final desired products.

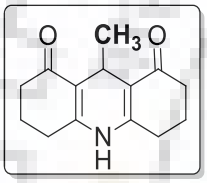
General procedure for the synthesis of 22(a-d): C-H acid (2.0 mmol), vinyl ester (1.5 mmol), *t*-BuOK (10 mol %) in MeOH was stirred at room temperature for about 6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction MeOH was removed in vacuum, and residue was dissolved in ethyl acetate and washed with water. This aqueous layer was neutralised by HCl solution and again washed with DCM. Removal of this organic layer under vacuum provided spectrally pure products **22(a-d)**.

General procedure for the synthesis of 25(a-c): C-H acid (1.0 mmol), vinyl ester (1.5 mmol), urea (1.0 mmol) DABCO (30 mol %) was taken in G10 process vial capped with Teflon septum. After a pre-stirring of 1 or 2 minutes, the vial was subjected to microwave irradiation with the initial ramp time of 1 minute at 60 ℃. The temperature was then raised to 120 ℃ with the holding time of 10 minutes. The crude mixture was dissolved in DCM and washed with brine and dilute acid solution 2-3 times. The organic layer was removed in vacuum and subjected to column chromatography using DCM + Methanol as eluants to get the final desired products.

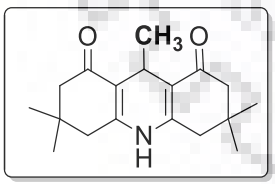
5.5.3 Characterization of the synthesized molecules

All the products were characterized via techniques of ^{1}H NMR, ^{13}C NMR Spectra and HRMS.

Analytical information for the synthesized molecules is given below:

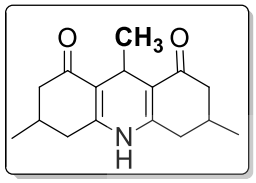


9-methyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (**19a**): Yield: 85 % (using vinyl acetate), 83 % (using vinyl pivalate), 83 % (using vinyl benzoate), 91% (using vinyl chloroacetate); greenish yellow solid; mp: 298-299 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.17 (s, 1H), 3.71 (q, 1H, J = 6.5 Hz), 2.34-2.45 (m, 4H), 2.12-2.28 (m, 4H), 1.75-1.94 (m, 4H), 0.76 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.5, 151.8, 114.1, 37.3, 26.7, 22.8, 22.3, 21.5; HRMS (ESI) m/z calcd. for $C_{14}H_{17}NO_2$ $[M+Na]^+$: 254.1157, found: 254.1149.

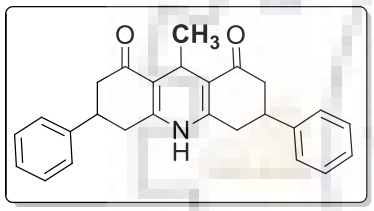


3,3,6,6,9-pentamethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (**19b**)**:** Yield: 81 % (using vinyl acetate), 88 % (using vinyl chloroacetate); greenish yellow solid; mp: 269-271 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.06 (s, 1H), 3.68 (q, 1H, J = 6.4 Hz), 2.34 (d, 2H, J = 17.0 Hz), 2.14-2.25 (m, 4H), 2.06 (d, 2H, J = 15.9 Hz), 1.00 (s, 6H), 0.98 (s, 6H), 0.78 (d, 3H, J = 6.4

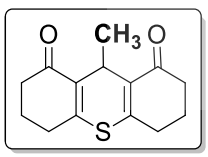
Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.0, 150.3, 112.5, 50.6, 32.6, 29.6, 26.9, 22.3, 22.0; HRMS (ESI) m/z calcd. for $C_{18}H_{25}NO_2$ $[M+Na]^+$: 310.1783, found: 310.1779.



3,6,9-trimethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (19c): Yield: 78 % (using vinyl acetate), 79 % (using vinyl benzoate); greenish yellow solid; mp: 268-270 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 3.39 (q, 1H, *J* = 5.1 Hz), 2.88 (dd, 2H, *J* = 9.9 & 6.4 Hz), 2.39 (dd, 2H, *J* = 10.0 & 6.4 Hz), 2.24 (q, 2H, *J* = 3.8 Hz), 1.97-2.09 (m, 4H), 1.47 (d, 3H, *J* = 5.1 Hz), 1.35 (d, 6H, *J* = 4.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.1, 153.8, 114.5, 52.8, 45.3, 33.5, 29.6, 24.2, 21.1; HRMS (ESI) m/z calcd. for $C_{16}H_{21}NO_2$ $[M+Na]^+$: 282.1470, found: 282.1467.

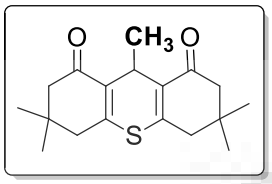


9-methyl-3,6-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione (19d): Yield: 79 % (using vinyl acetate), 76 % (using vinyl pivalate); greenish yellow solid; mp: 328-329 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 7.30-7.38 (m, 8H), 7.23-7.28 (m, 2H), 3.48 (quin, 2H, *J* = 2.8 Hz), 3.34 (q, 1H, *J* = 5.1 Hz), 3.30 (dd, 2H, *J* = 10.0 & 3.3 Hz), 3.00 (dd, 2H, *J* = 9.9 & 2.6 Hz), 2.69 (dd, 2H, *J* = 10.0 & 3.2 Hz), 2.52 (dd, 2H, *J* = 9.9 & 3.4 Hz), 1.46 (d, 3H, *J* = 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 201.3, 156.1, 149.0, 133.3, 133.0, 132.5, 121.5, 57.4, 48.1, 43.8, 39.1, 28.9; HRMS (ESI) m/z calcd. for $C_{26}H_{25}NO_2$ $[M+Na]^+$: 406.1783, found: 406.1769.

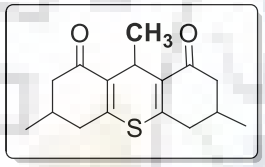


9-methyl-3,4,6,7,9-hexahydro-1*H*-thioxanthene-1,8-(2*H*)-dione (21a): Yield: 65 % (using vinyl acetate), 67 % (using vinyl chloroacetate); yellow solid; mp: 246-248 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.71 (q, 1H, *J* = 5.4 Hz), 2.43 (t, 4H, *J* = 5.4 Hz), 2.00 (t, 4H, *J* = 4.7 Hz), 1.43

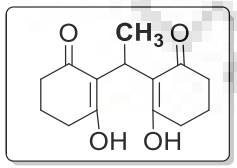
(quin, 4H, *J* = 5.0 Hz), 0.87 (d, 3H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 192.2, 133.3, 129.6, 54.1, 36.2, 28.2, 23.0, 22.1; HRMS (ESI) m/z calcd. for $C_{14}H_{16}O_2S$ $[M+Na]^+$: 271.3304, found: 271.3302.



3,3,6,6,9-pentamethyl-3,4,5,6,7,9-hexahydro-1*H*-thioxanthene-1,8-(2*H*)-dione (21b): Yield: 61 % (using vinyl acetate); yellow solid; mp: 272 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.69 (q, 1H, *J* = 5.1 Hz), 1.98 (s, 4H), 1.81 (s, 4H), 1.14 (d, 3H, *J* = 5.1 Hz), 0.86 (s, 12H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.0, 141.2, 133.2, 58.0, 54.3, 39.6, 35.4, 31.6, 26.9; HRMS (ESI) m/z calcd. for $C_{18}H_{24}O_2S$ $[M+Na]^+$: 327.4368, found: 327.4358.

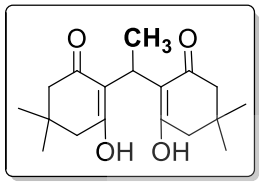


3,6,9-trimethyl-3,4,5,6,7,9-hexahydro-1*H*-thioxanthene-1,8-(2*H*)-dione (21c): Yield: 68 % (using vinyl acetate), 57 % (using vinyl benzoate); yellow solid; mp: 249-250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.94 (q, 1H, *J* = 5.1 Hz), 2.74-2.81 (m, 2H), 2.27-2.34 (m, 2H), 2.20-2.27 (m, 2H), 1.90-2.04 (m, 4H), 1.33 (d, 3H, *J* = 5.1 Hz), 1.21 (d, 6H, *J* = 4.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.9, 138.8, 136.4, 55.2, 45.1, 35.8, 29.8, 24.1, 21.0; HRMS (ESI) m/z calcd. for $C_{16}H_{20}O_2S$ $[M+Na]^+$: 299.1082, found: 299.1076.

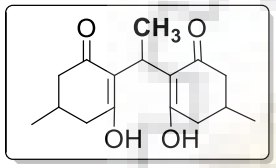


2,2'-(ethane-1,1-diyl)bis(3-hydroxycyclohex-2-enone) (22a): Yield: 79 % (using vinyl acetate), 75 % (using vinyl benzoate), 87% (using vinyl chloroacetate); white solid; mp: 128-129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.97 (brs, 1H), 13.08 (brs, 1H), 3.10 (q, 1H, *J* = 5.2 Hz), 3.02 (t, 4H, *J* = 4.4 Hz), 2.32 (t, 4H, *J* = 4.8 Hz), 1.75 (quin, 4H, *J* = 4.8 Hz), 1.39 (d, 3H, *J* = 5.3 Hz); ^{13}C

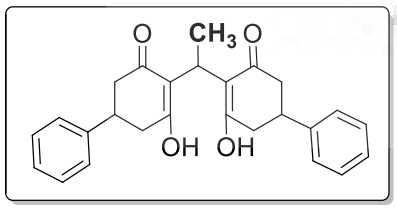
NMR (100 MHz, DMSO-d_6) δ 196.4, 180.6, 117.6, 38.5, 34.4, 30.4, 26.0, 21.2; HRMS (ESI) m/z calcd. for $C_{18}H_{14}O_4$ $[M+Na]^+$: 273.1103, found: 273.1096.



2,2'-(ethane-1,1-diyl)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (22b): Yield: 81 % (using vinyl acetate), 79 % (using vinyl pivalate); white-brown solid; mp: 127-129 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.95 (brs, 1H), 13.12 (brs, 1H), 3.1 (q, 1H, J = 5.1 Hz), 2.65 (s, 4H), 2.11 (s, 4H), 1.40 (d, 3H, J = 5.1 Hz), 1.01 (s, 12H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 192.7, 185.2, 116.9, 51.5, 45.0, 33.4, 33.2, 28.8, 24.7; HRMS (ESI) m/z calcd. for $C_{18}H_{26}O_4$ $[M+Na]^+$: 329.1729, found: 329.1723.

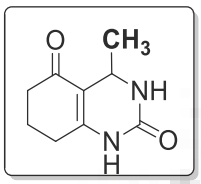


2,2'-(ethane-1,1-diyl)bis(3-hydroxy-5-methylcyclohex-2-enone) (22c): Yield: 77 % (using vinyl acetate), 71 % (using vinyl benzoate), 81 % (using vinyl chloroacetate); grey solid; mp: 111-112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.98 (brs, 1H), 13.05 (brs, 1H), 3.22 (q, 1H, J = 5.2 Hz), 2.92 (dd, 2H, J = 10.0 & 6.1 Hz), 2.44 (dd, 2H, J = 9.9 & 6.2 Hz), 2.25-2.32 (m, 2H), 1.87-2.01 (m, 4H), 1.55 (d, 3H, J = 5.2 Hz), 1.26 (d, 6H, J = 4.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.7, 177.0, 115.4, 45.1, 35.5, 33.2, 30.3, 24.7, 21.0; HRMS (ESI) m/z calcd. for $C_{16}H_{22}O_4$ $[M+Na]^+$: 301.1416, found: 301.1411.

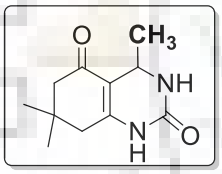


4,4'-(ethane-1,1-diyl)bis(5-hydroxy-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one) (22d): Yield: 67 % (using vinyl acetate), 68 % (using vinyl pivalate); white solid; mp: 168-170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.91 (brs, 1H), 13.03 (brs, 1H), 7.23-7.29 (m, 8H), 7.13-7.20 (m, 2H), 3.36-3.47 (m,

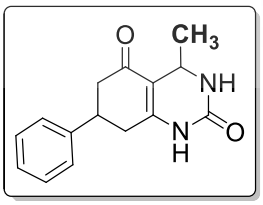
2H), 3.17 (dd, 2H, *J* = 12.0 & 5.8 Hz), 3.10 (q, 1H, *J* = 5.2 Hz), 2.73 (dd, 2H, *J* = 8.0 & 5.7 Hz), 2.58 (dd, 2H, *J* = 8.0 & 4.0 Hz), 2.31 (dd, 2H, *J* = 8.0 & 4.0 Hz), 1.44 (d, 3H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.0, 177.3, 144.2, 128.5, 128.2, 127.6, 115.6, 43.3, 36.4, 36.1, 33.2, 24.7; HRMS (ESI) m/z calcd. for $C_{25}H_{26}O_4$ $[M+Na]^+$: 425.1729, found: 425.1719.



4-methyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (25a): Yield: 82 % (using vinyl acetate), 81% (using vinyl pivalate), 79 % (using vinyl benzoate), 87 % (using vinyl chloroacetate); white solid; mp: 148-150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.62 (s, 1H), 4.38 (q, 1H, *J* = 4.8 Hz), 2.76 (t, 2H, *J* = 4.8 Hz), 2.66 (t, 2H, *J* = 4.5 Hz), 1.84 (quin, 2H, *J* = 4.7 Hz), 1.45 (d, 3H, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.6, 155.4, 151.4, 112.9, 47.8, 37.3, 28.5, 20.6, 19.7; HRMS (ESI) m/z calcd. for $C_9H_{12}N_2O_2$ $[M+Na]^+$: 203.0799, found: 203.0794.



4,7,7-trimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (25b): Yield: 77 % (using vinyl acetate), 74 % (using vinyl pivalate); white solid; mp: 168-169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.60 (s, 1H), 4.35 (q, 1H, *J* = 4.8 Hz), 2.67 (s, 2H), 2.39 (s, 2H), 1.38 (d, 3H, *J* = 4.8 Hz), 1.08 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.2, 156.5, 153.1, 122.8, 52.6, 48.9, 37.5, 33.9, 30.0, 20.9; HRMS (ESI) m/z calcd. for $C_{11}H_{16}N_2O_2$ $[M+Na]^+$: 231.1110, found: 231.1107.



4-methyl-7-phenyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (25c): Yield: 65 % (using vinyl acetate), 67 % (using vinyl pivalate); white solid; mp: 172-174 °C; ^{1}H NMR (400 MHz,

DMSO-d_6) δ 9.80 (s, 1H), 8.66 (s, 1H), 7.24-7.32 (m, 4H), 7.14-7.21 (m, 1H), 4.38 (q, 1H, J = 4.8 Hz), 3.20-3.28 (m, 2H), 2.80-2.92 (m, 2H), 1.45-1.48 (m, 1H), 1.47 (d, 3H, J = 4.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.5, 155.4, 148.0, 144.2, 128.5, 128.2, 127.6, 112.7, 47.8, 43.3, 38.9, 34.2, 19.7; HRMS (ESI) m/z calcd. for $C_{15}H_{16}N_2O_2$ $[M+Na]^+$: 279.1110, found: 279.1108.

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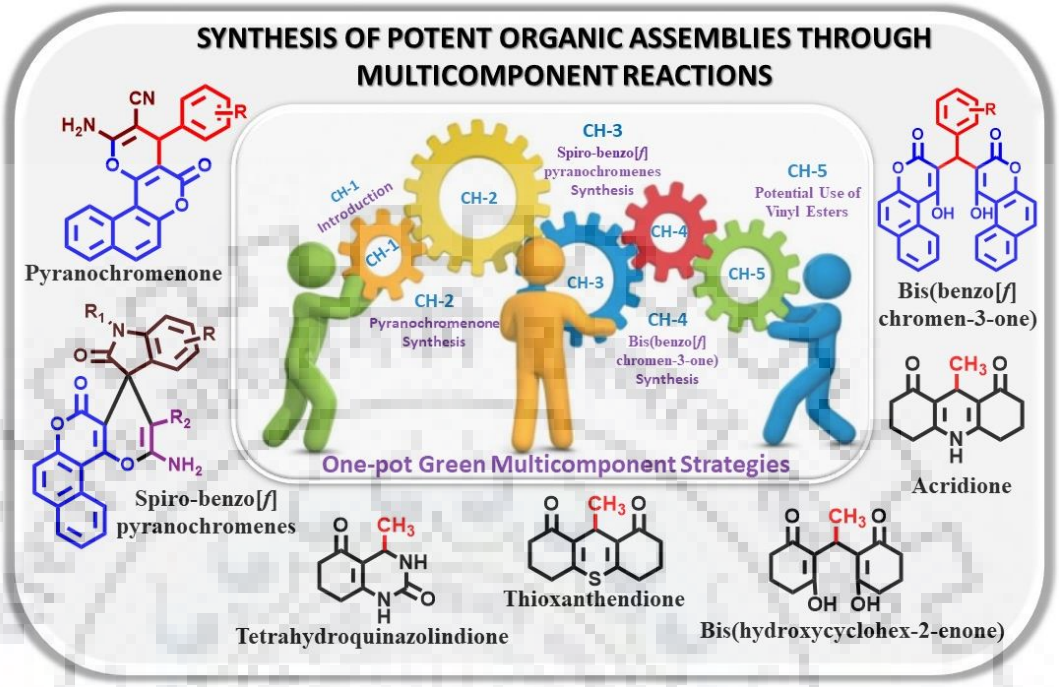
CONCLUSIONS & PERSPECTIVES



In summary, this work is focused on developing greener and efficient methodologies to access diversified heterocycles through multicomponent reactions. In this work, one-pot multicomponent approaches have been developed using different organocatalysts like DABCO and urea to construct desired scaffolds. In all the chapters certain limitations of existing reports are highlighted along with advantages of the developed methodologies. Primarily, the present work focuses on development of green and efficient multicomponent approaches to synthesize scaffolds like pyranochromenone, bis(benzo[*f*]chromen-3-one), spiro-benzo[*f*]pyranochromenes, acridione, bis(hydroxycyclohex-2-enone), thioxanthendione, tetrahydroquinazolindione derivatives under mild condition using microwave irradiation and mechanochemistry as efficient synthetic tools. In most of the cases, mere filtration and washing with organic solvents provided good to excellent yields of the targeted molecules. Additionally, the liquid-assisted synthesis protocol for accessing pyranochromenone and microwave-assisted synthesis for spiro-benzo[*f*]pyranochromenes have been accessed for green matrices parameters and the results proved that these methods are quite environment friendly. Moreover, some novel biologically relevant heterocycles are synthesized which may be potent biological leads.

LIST OF PUBLICATIONS

Thesis related publications:

[1] Bagchi, S.; Shube Hussen, A.; Deeksha; Sharma, A. Urea-Catalysed Access to Novel Spirooxindole Benzopyrans via Domino Multicomponent Cascade: Approach Towards Sustainability. *ChemistrySelect* **2019**, *4*, 6593–6597. (**Chapter 3**)

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[3] Kumar, M.; Bagchi, S.; Sharma, A. Vinyl Esters as Acetaldehyde Surrogates: Potential Utility in Some Common Multicomponent Sequences. *ChemistrySelect* **2016**, *1*, 4672–4681. (Co-first author in the paper) (**Chapter 5**)

Additional publications:

[4] Monga, A.; Bagchi, S.; Sharma, A. DABCO-Catalysed Amidation under Assistance of Aerial Oxidation: Access to *α*-Ketoamides. *ChemistrySelect* **2018**, *3*, 9617–9621.

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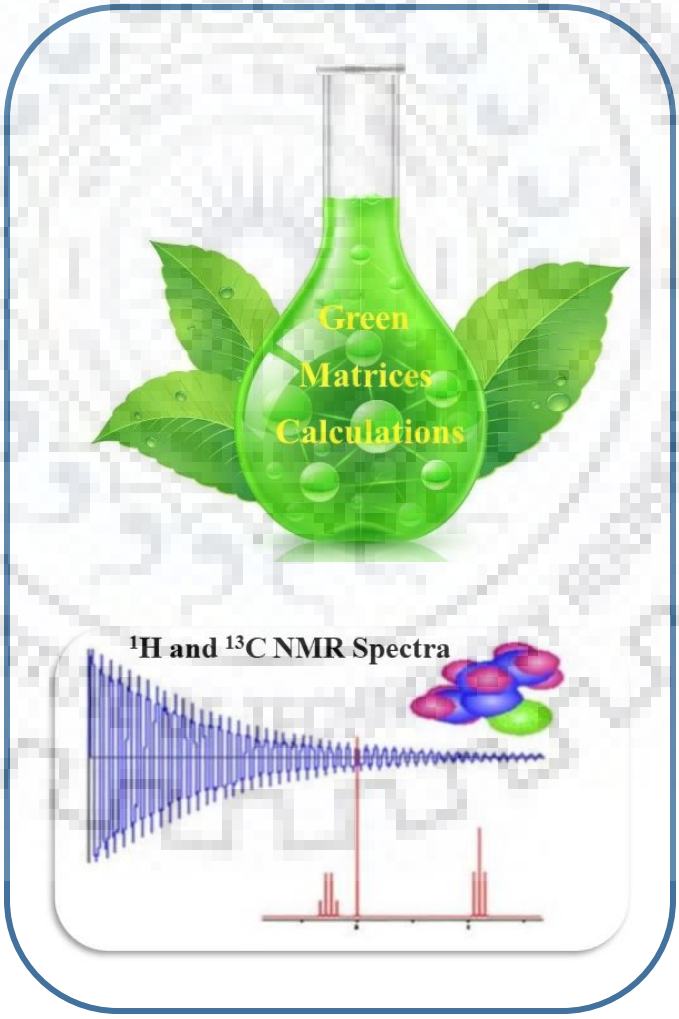
GREEN MATRICES CALCULATIONS

&

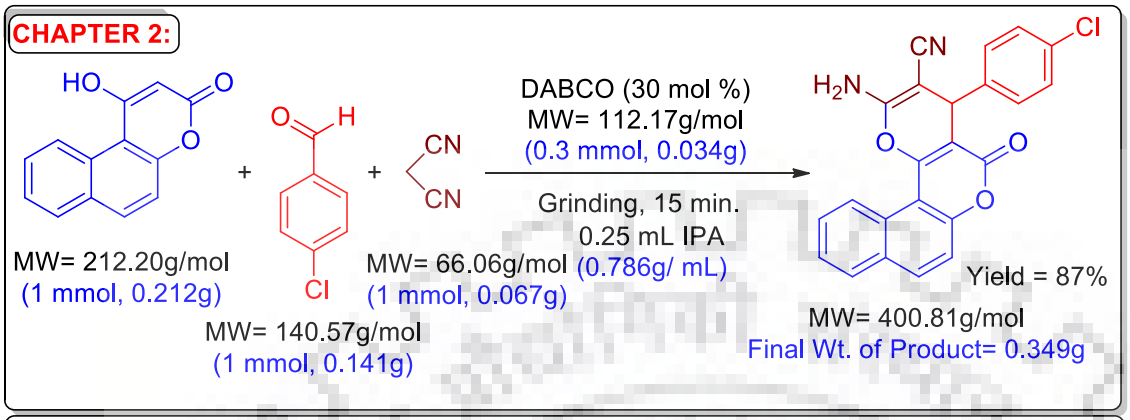
COMPUTATIONAL RESULTS

&

^{1}H & ^{13}C SPECTRA



Chapter 2: Green matrices calculation for 2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydrobenzo[*f*]pyrano[3,2-*c*]chromene-3-carbonitrile



Green Matrices Calculation

$$\text{\% Atom Efficency} = \frac{\text{(Mol Wt. of desired product)}}{\Sigma\ \text{(Mol Wt. of all reagents)}} \times 100 = \mathbf{95.70\%}$$

$$\text{\% Carbon Efficency} = \frac{\text{(Mass of carbon in desired product)}}{\text{(Total mass of carbon in key reactants)}} \times 100 = \mathbf{100\%}$$

$$\text{\% Reaction Mass Efficency} = \frac{\text{(Mass of Isolated product)}}{\text{(Total mass of reactants used in the reaction)}} \times 100$$

$$= \mathbf{83.10\%}$$

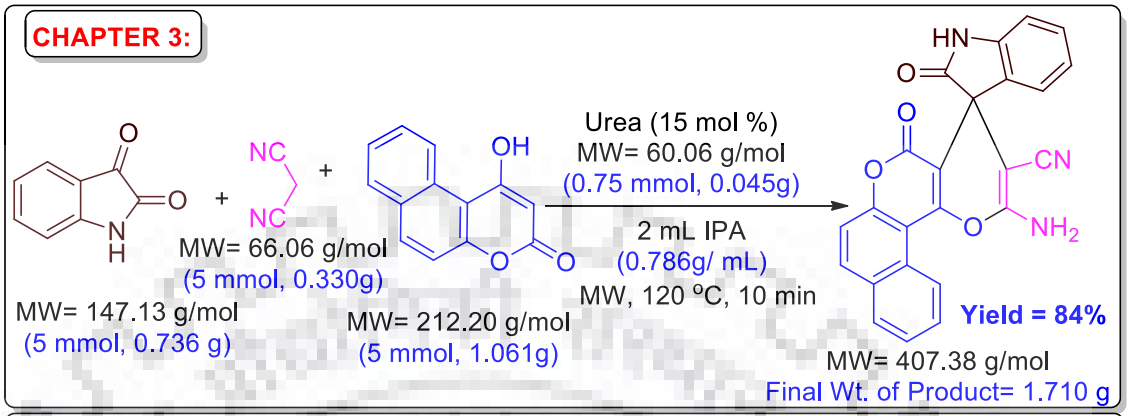
$$\text{E-Factor} = \frac{\text{(Mass of total waste)}}{\text{(Mass of crude product)}} = \mathbf{0.82}$$

$$\text{Process Mass Intensity (PMI)} = \frac{\text{(Total mass used in the process)}}{\text{(Mass of product)}} = \mathbf{1.82}$$

Comparison of green matrices calculation (Previous vs. Present Report)

Entry	Mass of Product	Total mass of all reactants	AE (%)	CE (%)	RME (%)	PMI	E-factor	Work details (1 mmol scale)
DABCO[31] (81 % Yield)	0.325 g	0.419 g	95.70	100	77.56	13.50	12.50	Foroumadi *et al.* ***2015***
DABCO (87 % Yield)	0.349 g	0.419 g	95.70	100	83.10	1.82	0.82	Present work

Chapter 3: Green matrices calculation for 2-amino-2',5-dioxo-5*H*-spiro[benzo[*f*]pyrano[3,2-*c*]chromene-4,3'-indoline]-3-carbonitrile (Gram scale synthesis)



Green Matrices Calculation

$$\textbf{\% Atom Efficency} = \frac{\text{(Mol Wt. of desired product)}}{\Sigma\ \text{(Mol Wt. of all reactants)}} \times 100 = \textbf{95.77\%}$$

$$\textbf{\% Carbon Efficency} = \frac{\text{(Mass of carbon in desired product)}}{\text{(Total mass of carbon in key reactants)}} \times 100 = \textbf{100\%}$$

$$\textbf{\% Reaction Mass Efficency} = \frac{\text{(Mass of Isolated product)}}{\text{(Total mass of reactants used in the reaction)}} \times 100 = \textbf{80.39\%}$$

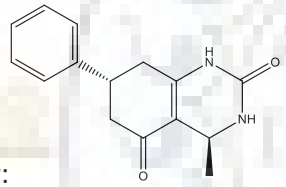
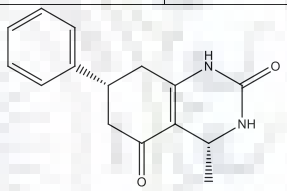
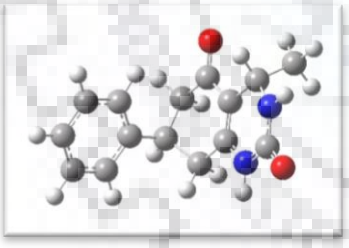
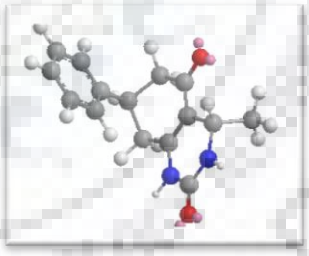
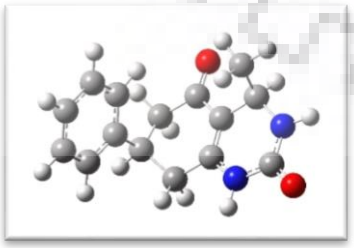
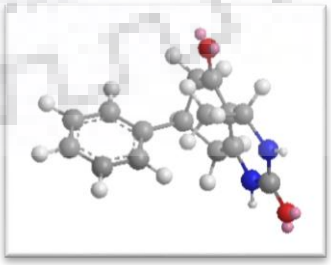
$$\textbf{E-Factor} = \frac{\text{(Mass of total waste)}}{\text{(Mass of crude product)}} = \textbf{1.19}$$

$$\textbf{Process Mass Intensity (PMI)} = \frac{\text{(Total mass used in the process)}}{\text{(Mass of product)}} = \textbf{2.19}$$

Comparison of green matrices calculation (Previous vs. Present Report)

Entry	Mass of Product	Total mass of all reactants	AE (%)	CE (%)	RME (%)	PMI	E-factor	Work details (1 mmol scale)
DABCO[27] (98 % Yield)	0.350 g	0.375 g	95.20	100	93.33	12.36	11.36	Hasaninejad *et al.* ***2017***
Urea (91 % Yield)	0.371 g	0.425 g	95.77	100	87.29	2.23	1.23	Present work

Chapter 5: Computational study for preferred conformation of 4-methyl-7-phenyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (25c)

Software Name	Parameters	Energy minimized conformer	Software Name	Parameters	Energy minimized conformer
Avogadro	Steepest Descent of MMFF94s force field (1000 runs) + Conjugate gradient of MMFF94s (1000 runs)	Anti-isomer : -234.34 KJ/ mol Syn-isomer : -236.56 KJ/ mol	Chem Draw 3D Pro Version 12.0.2	MM2	Anti-isomer : -2.6957 Kcal/ mol Syn-isomer : -3.1204 Kcal/ mol
Anti-isomer: 			Syn-isomer: 		
Results from Avogadro Anti 			Results from Chem Draw 3D Pro Anti 		
Syn 			Syn 		

Based upon the energy minimizations studies, it was found that syn-isomer of 4-methyl-7-phenyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**25c**) is more stable than the anti-isomer. Moreover, the role of amide in formation of hydrogen bonding is well established in literatures [1, 2] and this would reinforce the syn product. However, the final determination of the structure and further mechanistic studies are currently underway in the laboratory.

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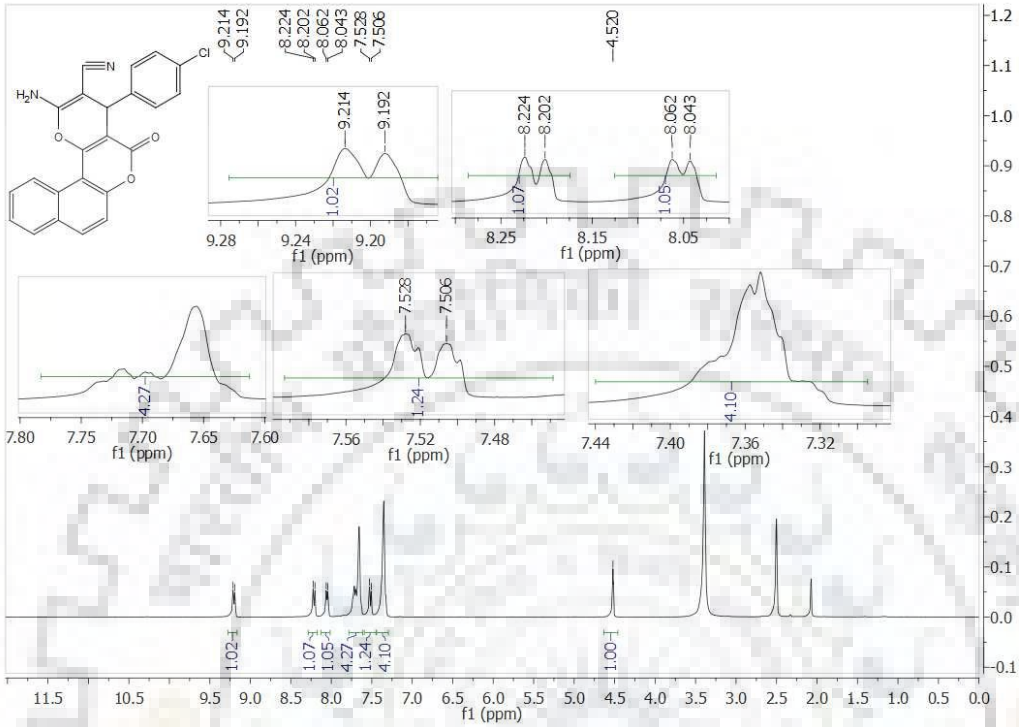
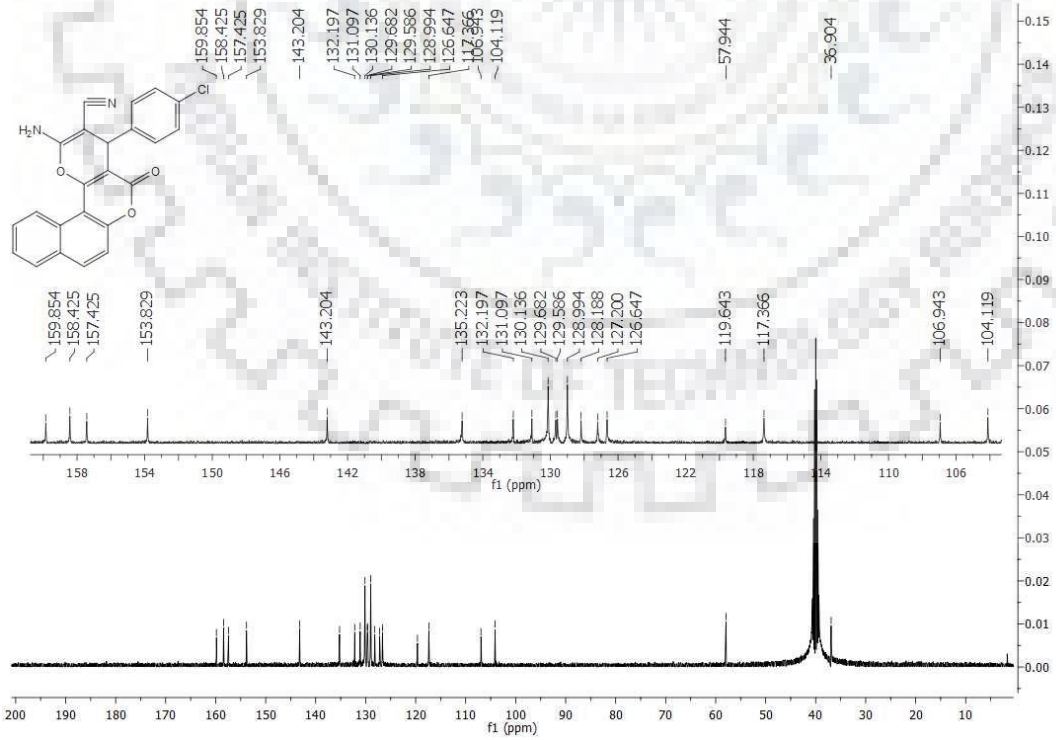
Chapter 2: Spectral information for benzo[*f*]pyrano[3,2-*c*]chromenes derivatives 8 (a-k, n-p)

^{1}H NMR of 8a



^{13}C NMR of 8a



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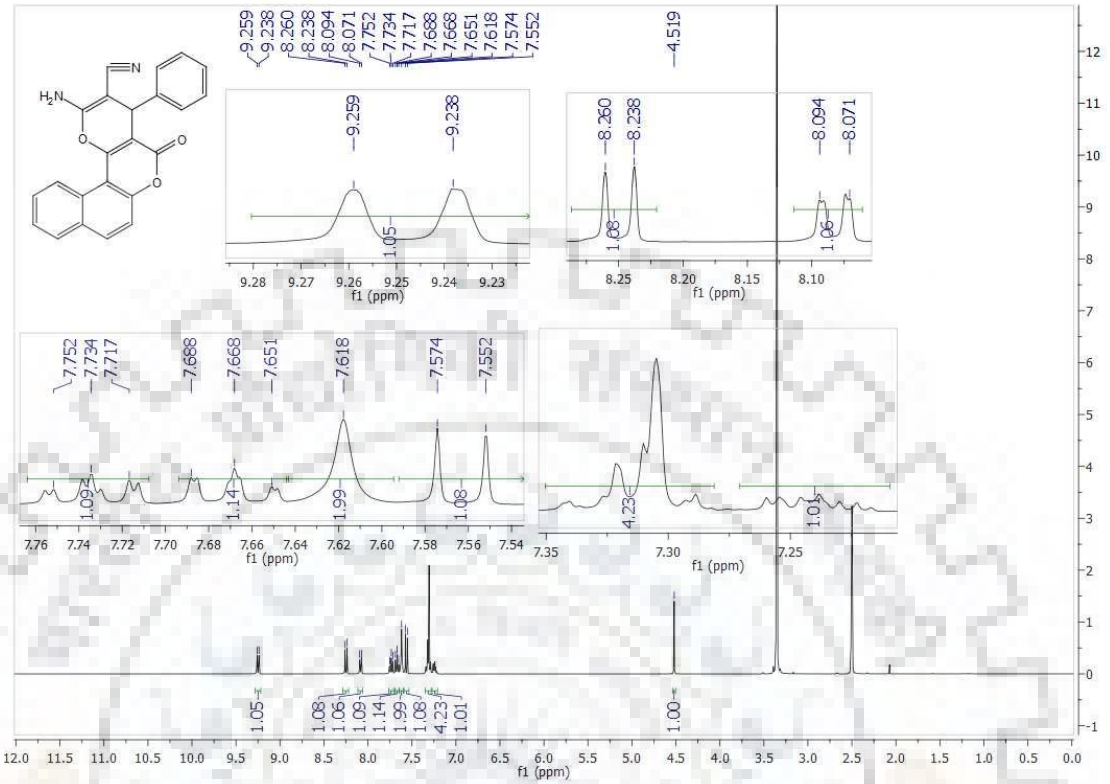

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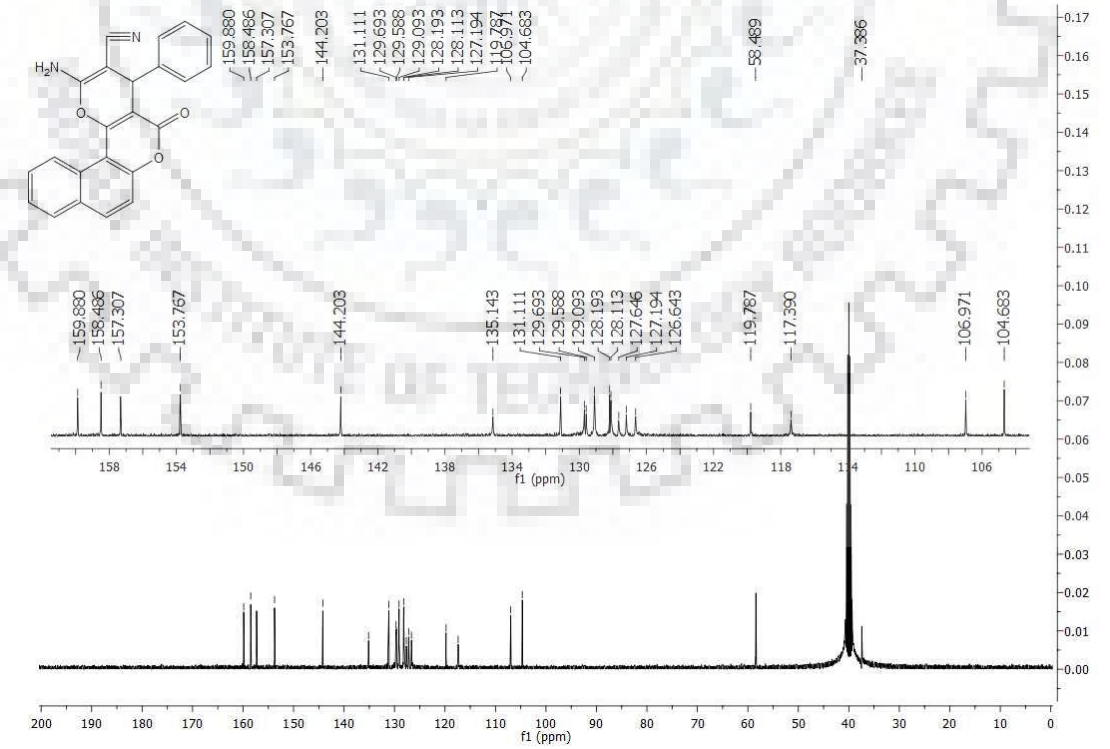
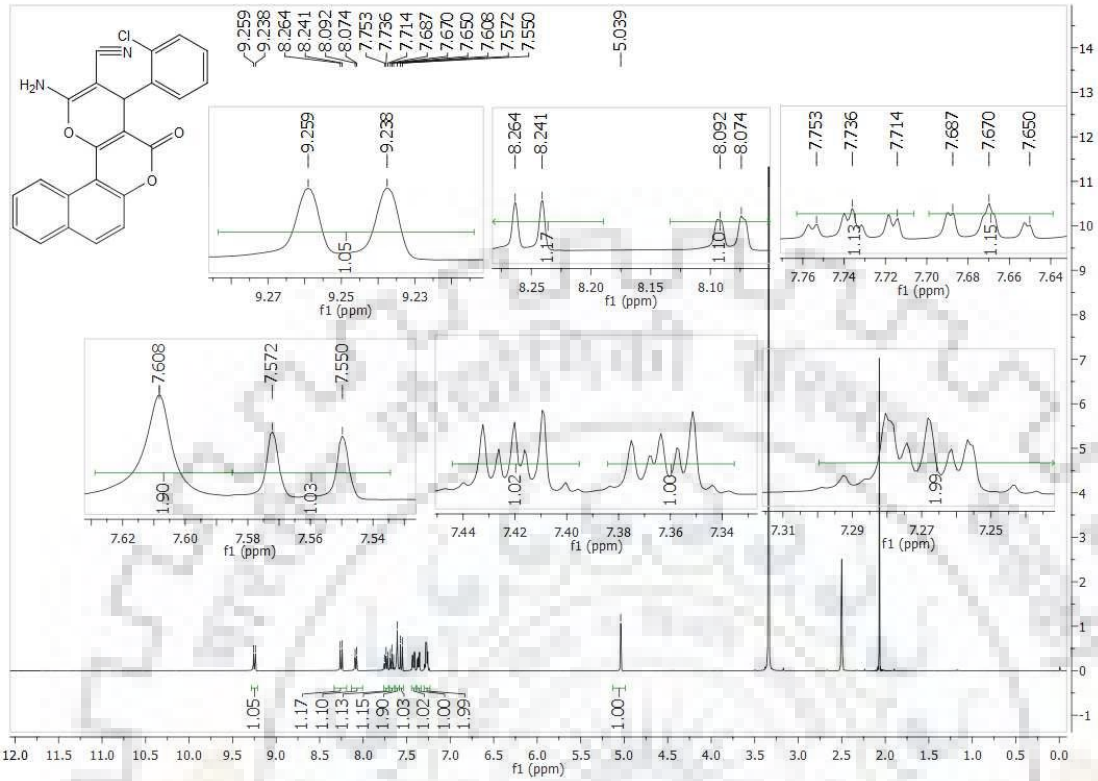


^{1}H NMR of 8c



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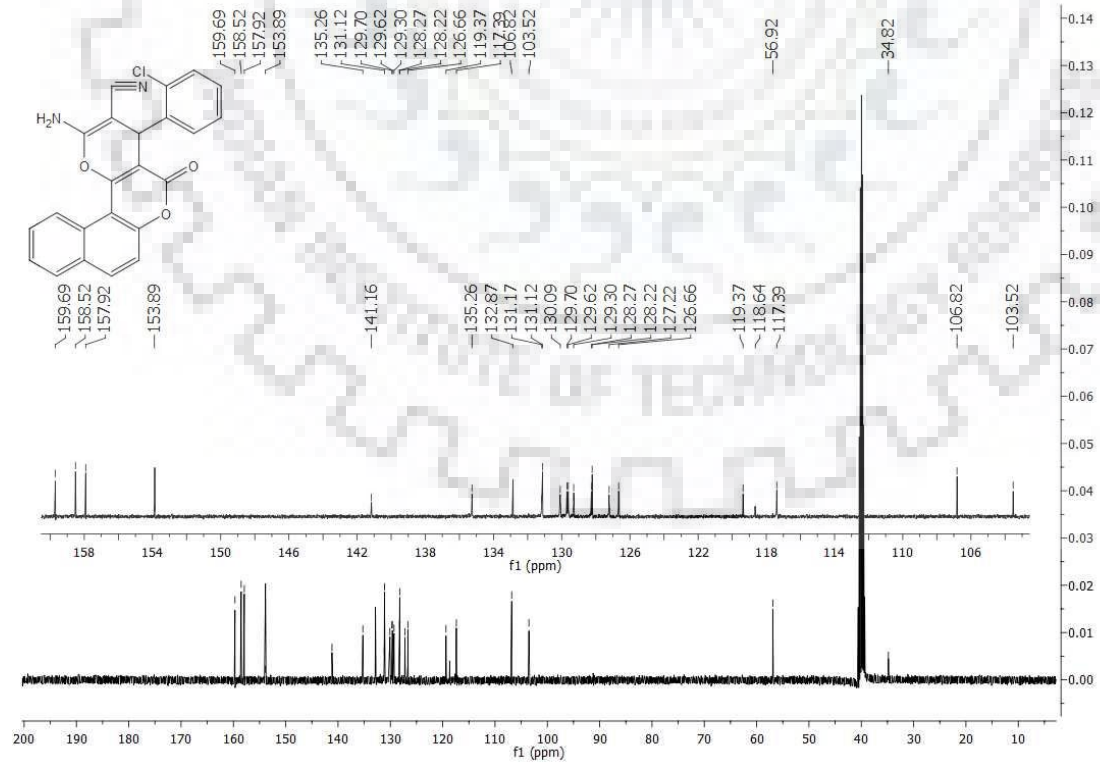
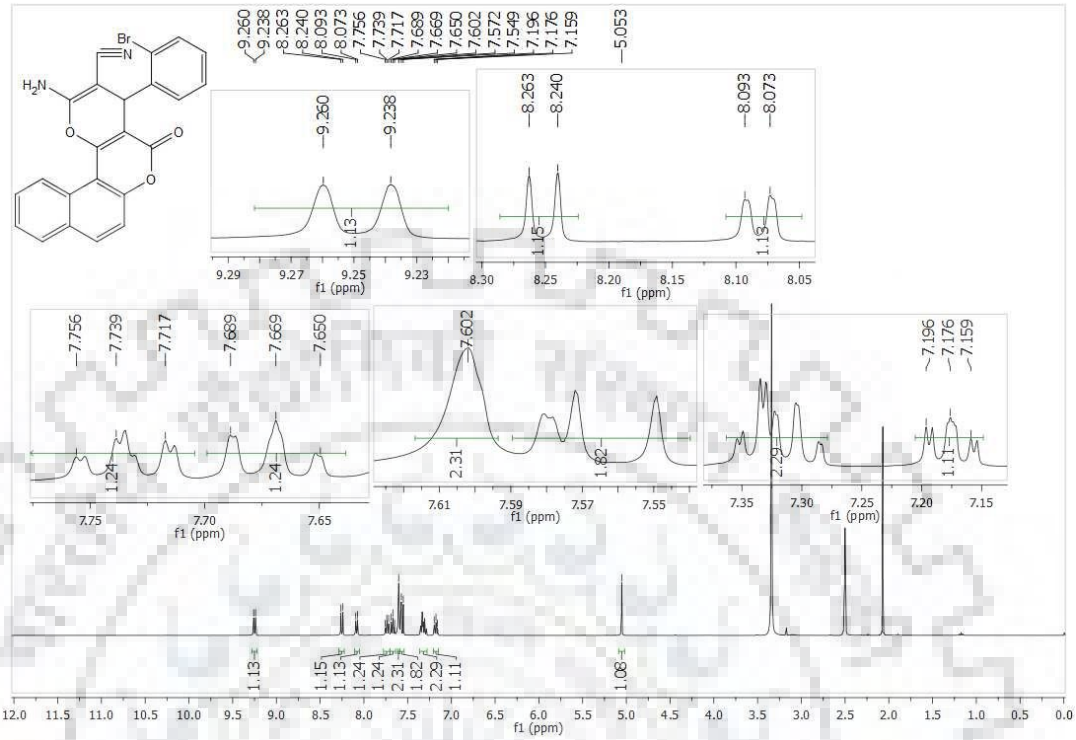
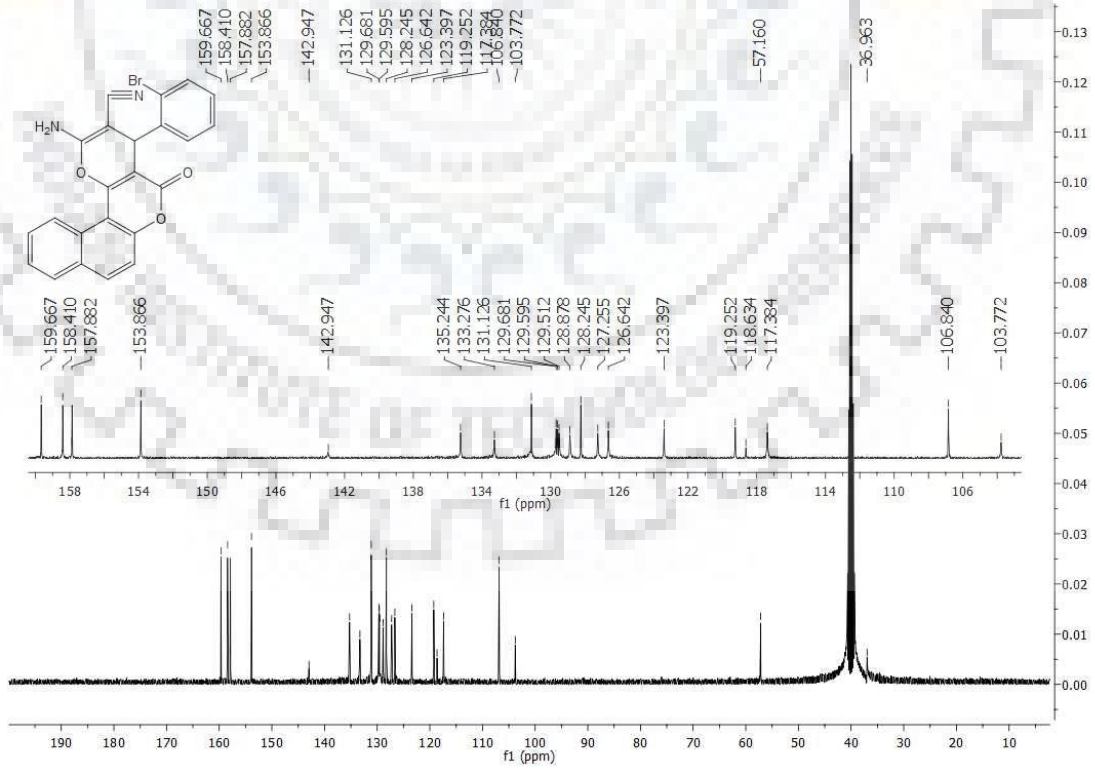


^{1}H NMR of 8d



^{13}C NMR of 8d



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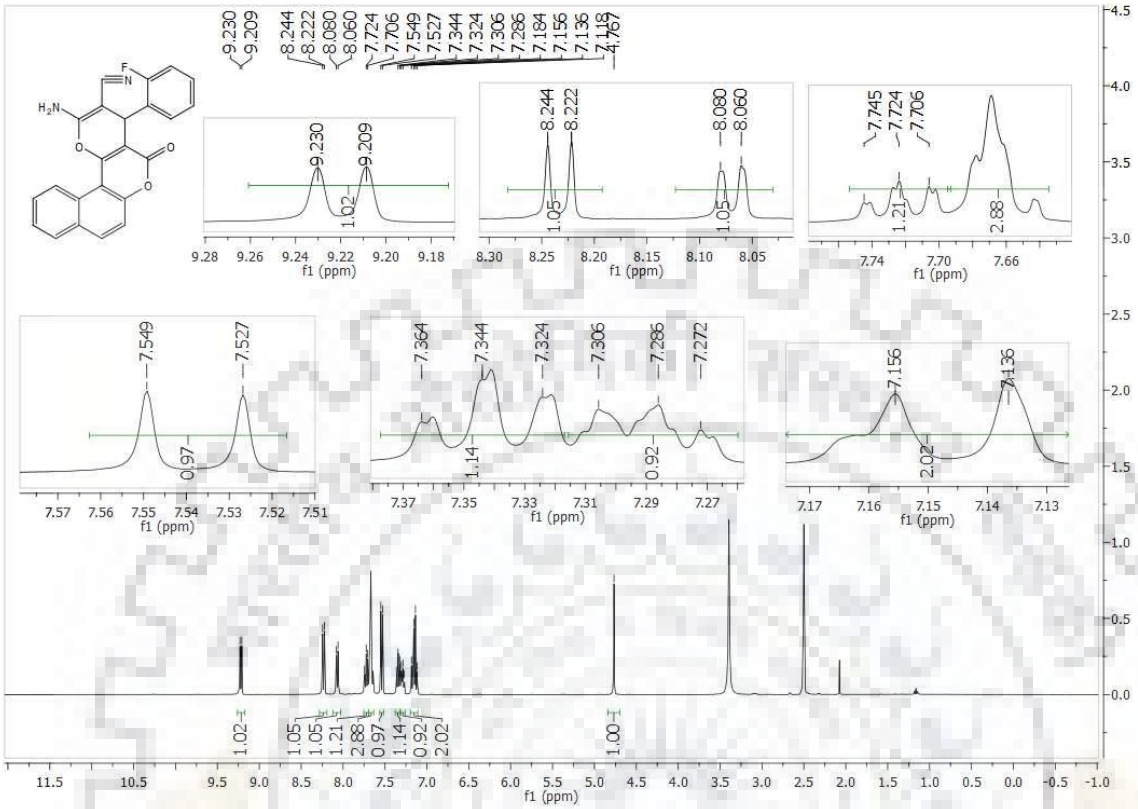

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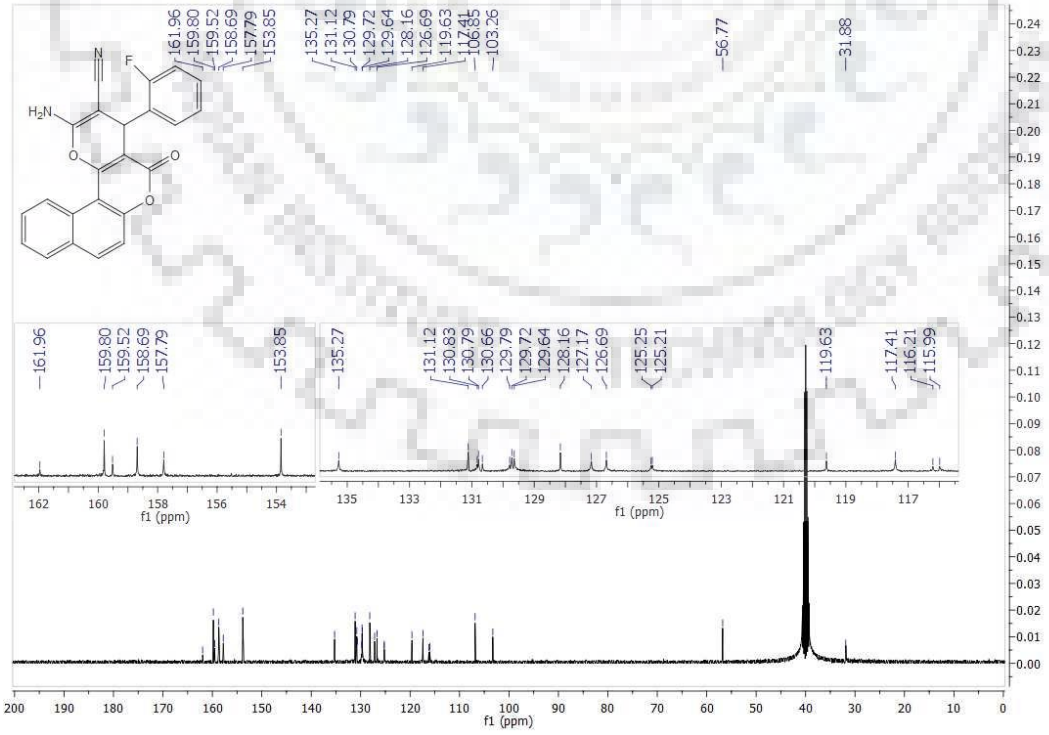

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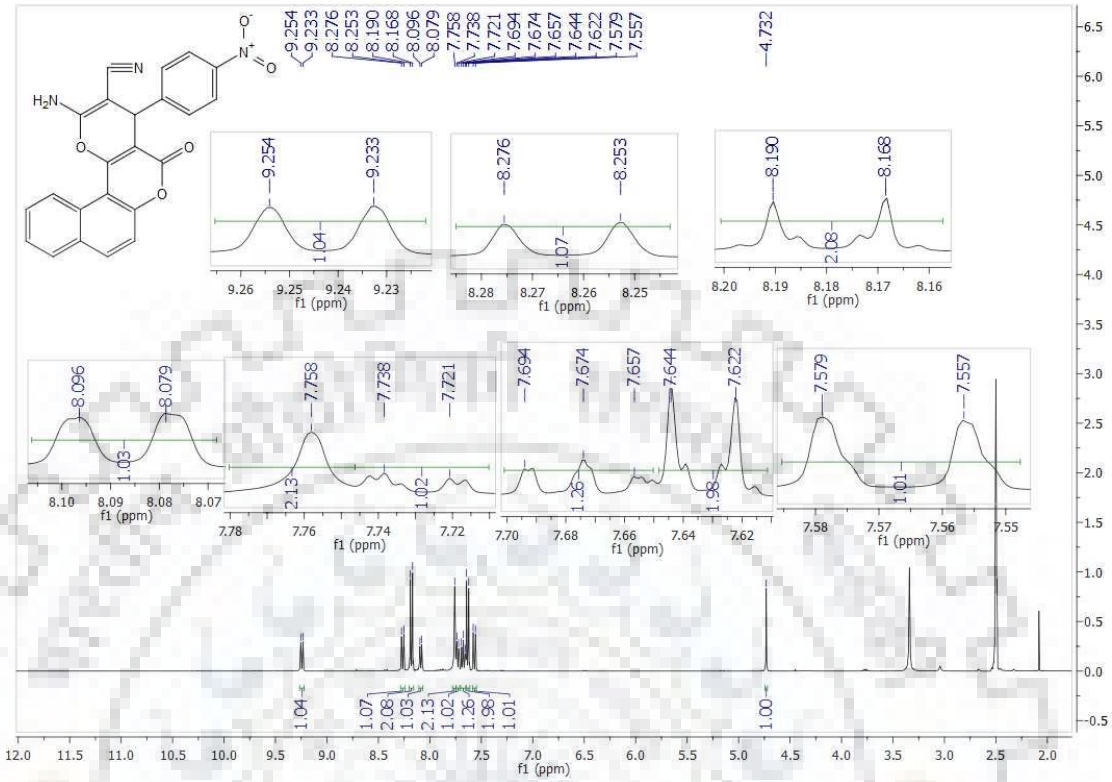

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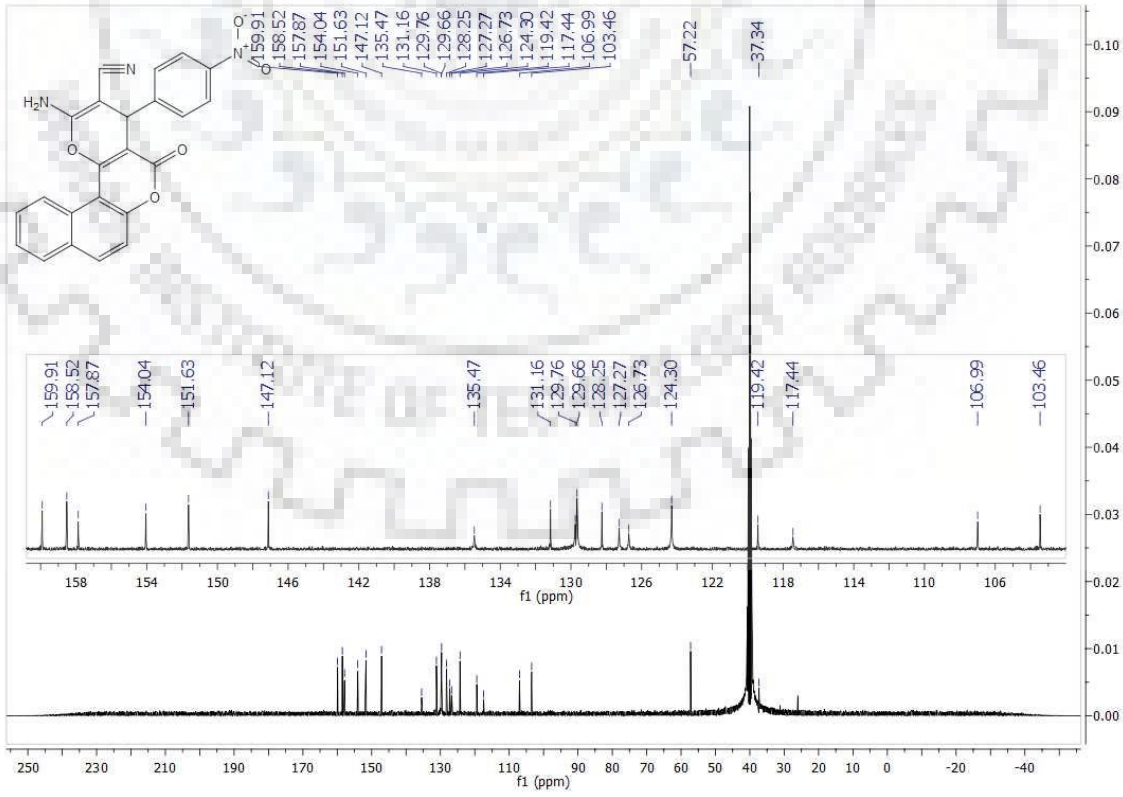

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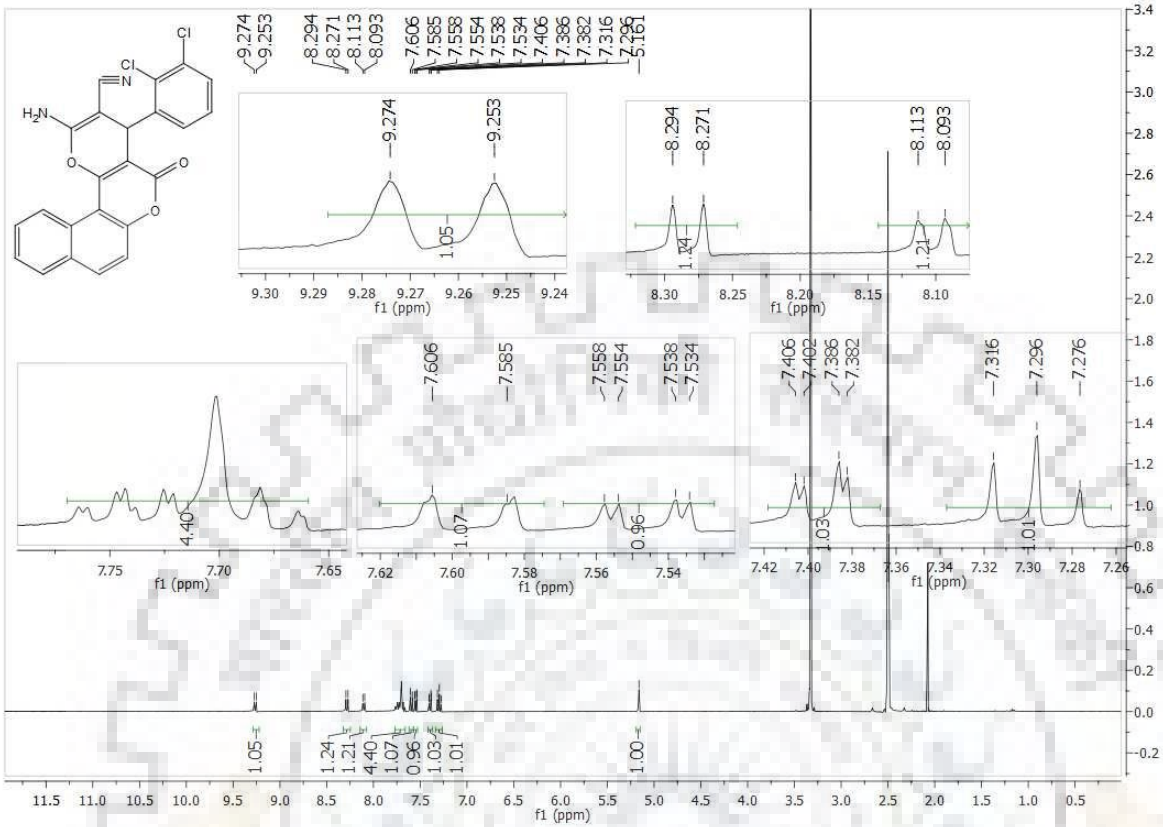
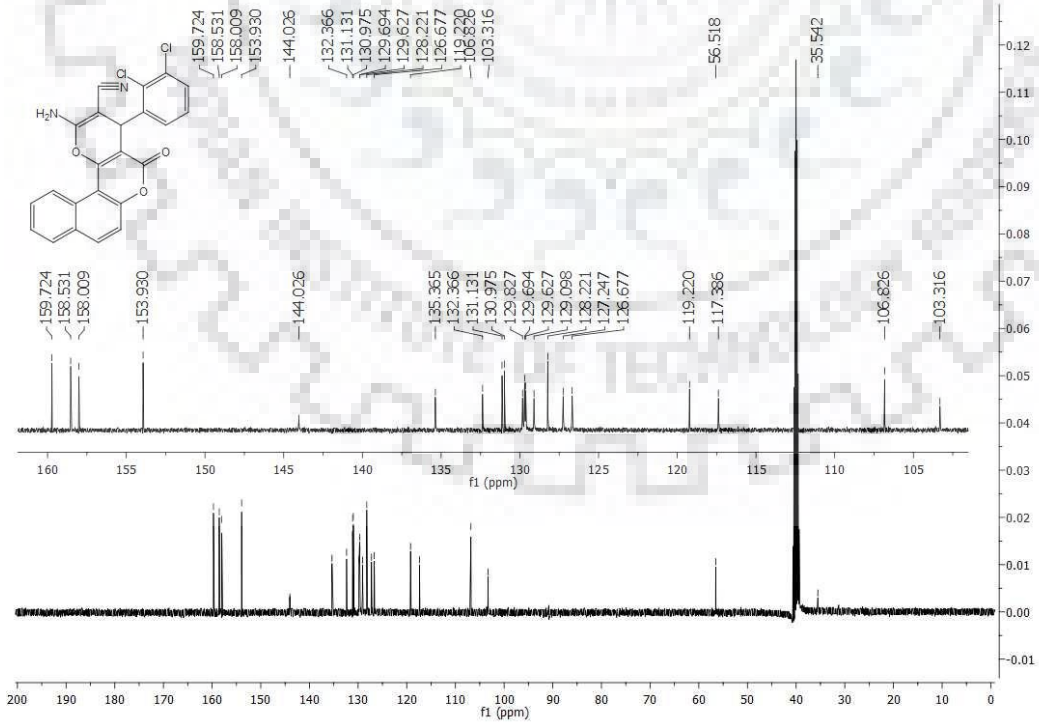
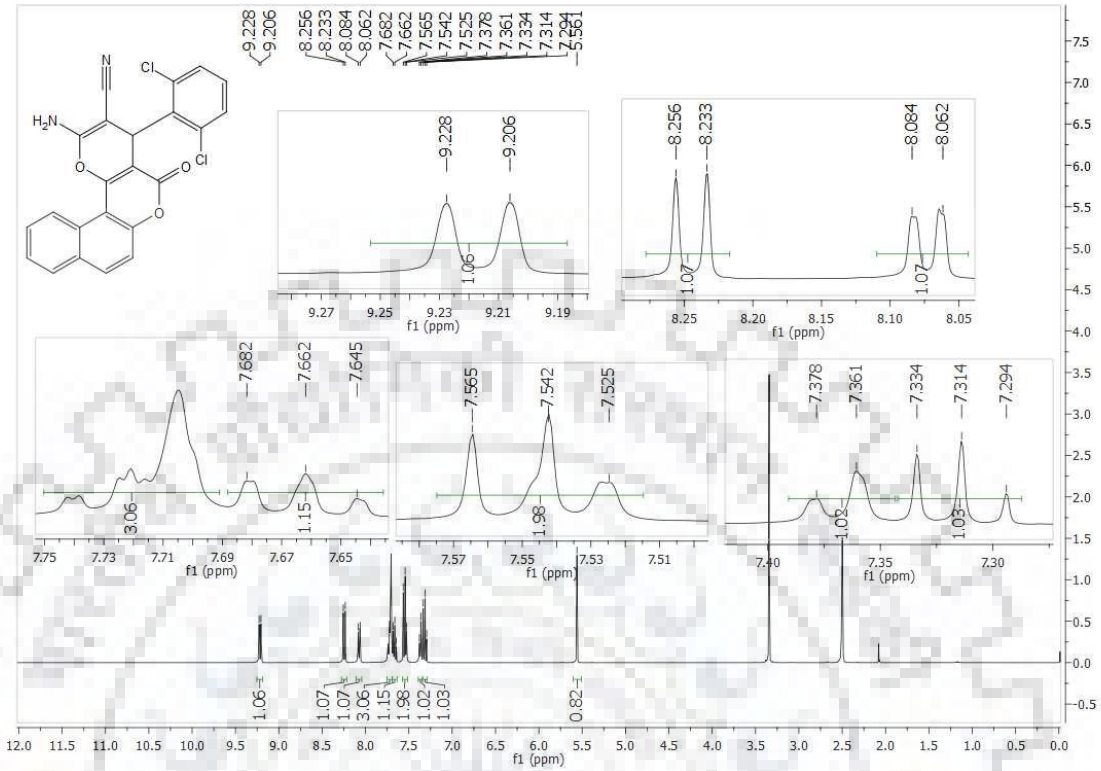


^{13}C NMR of 8g



^{1}H NMR of 8h



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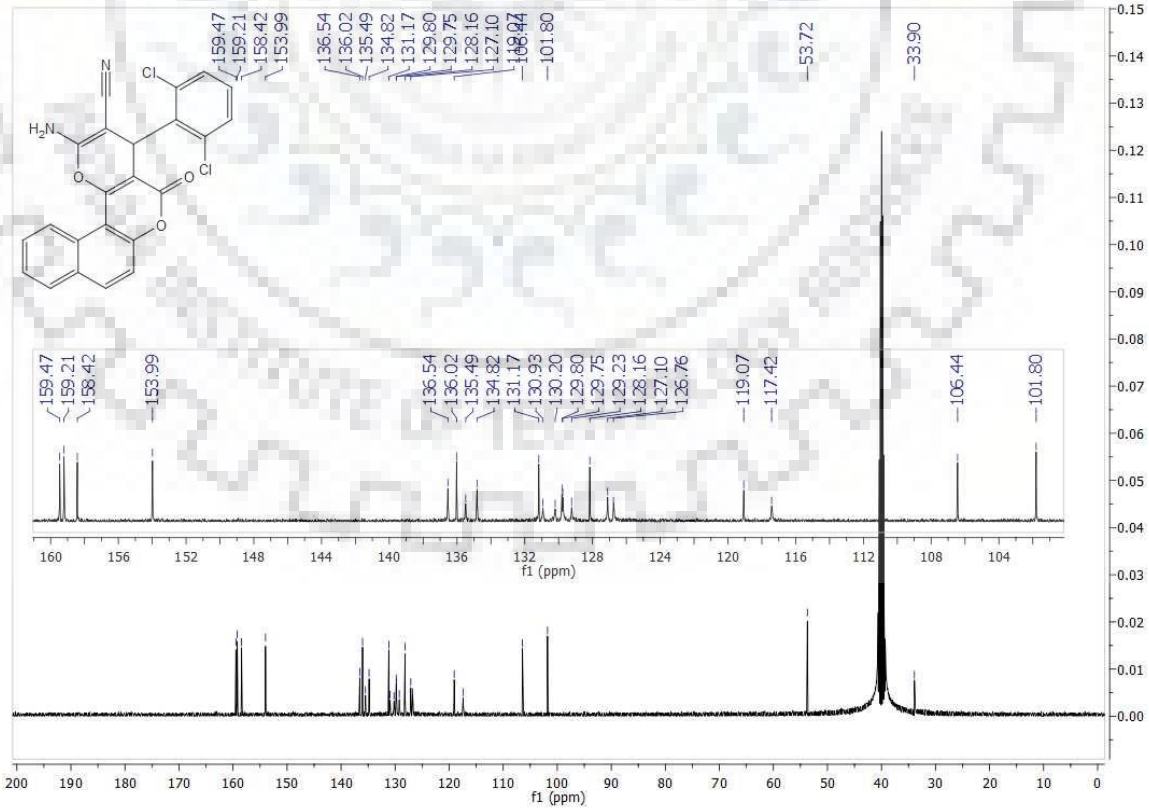

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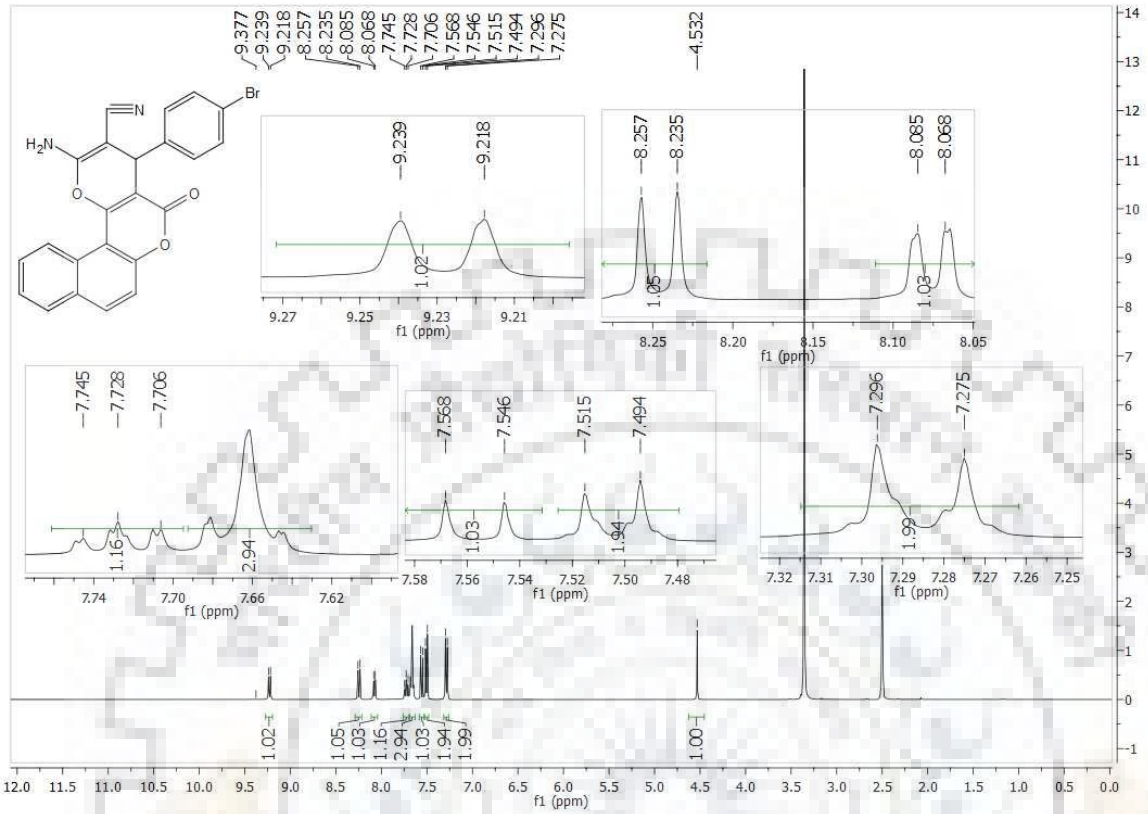

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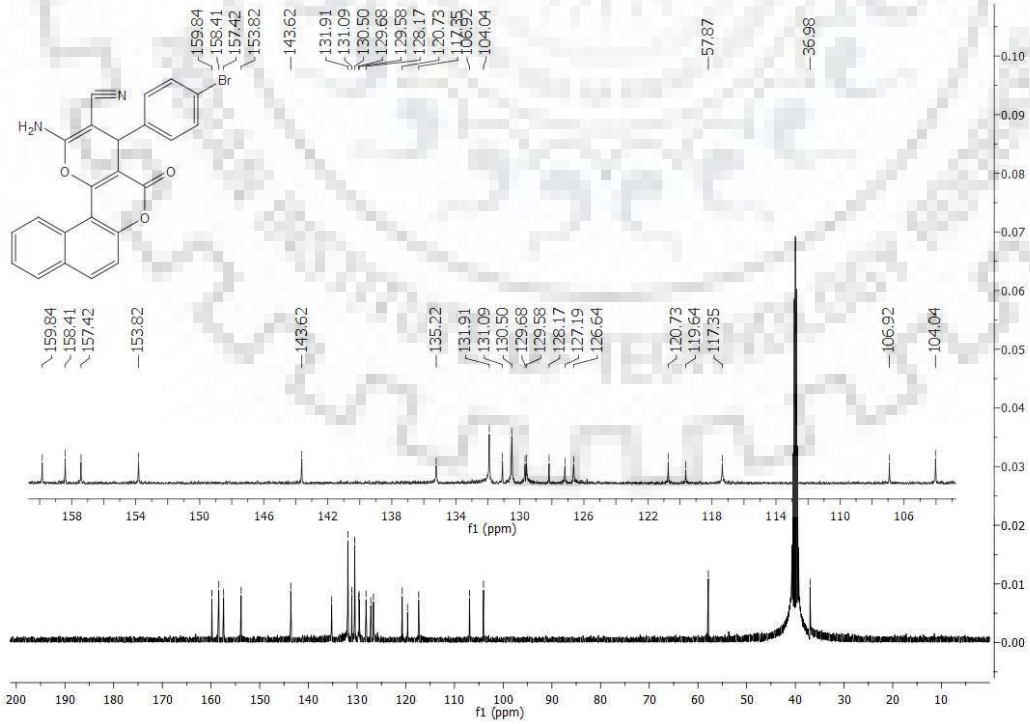

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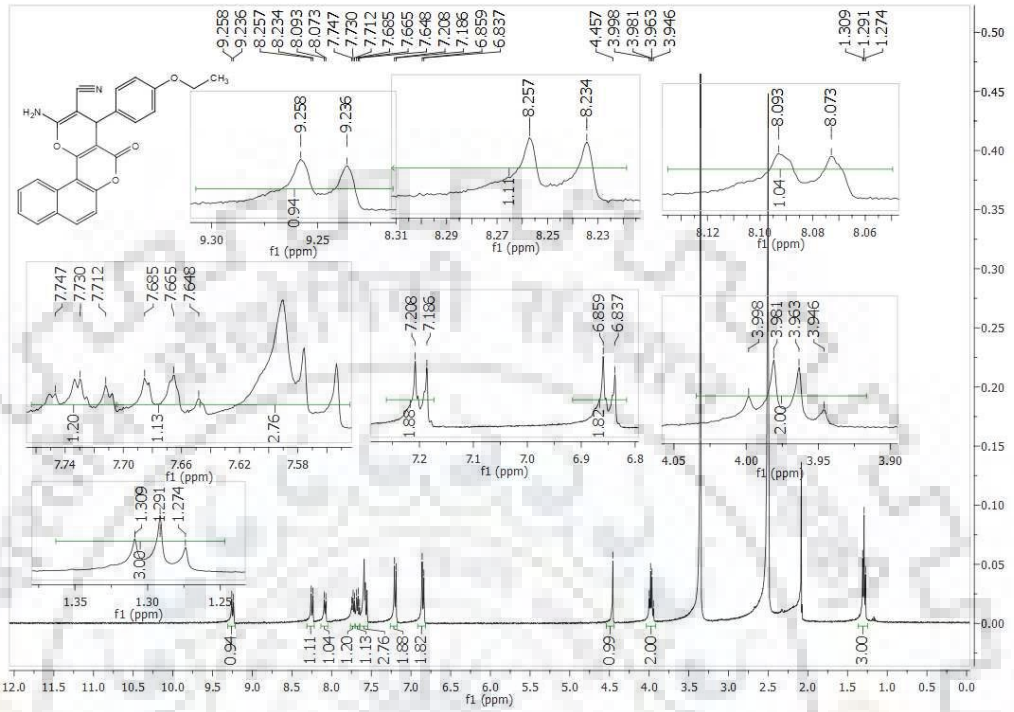

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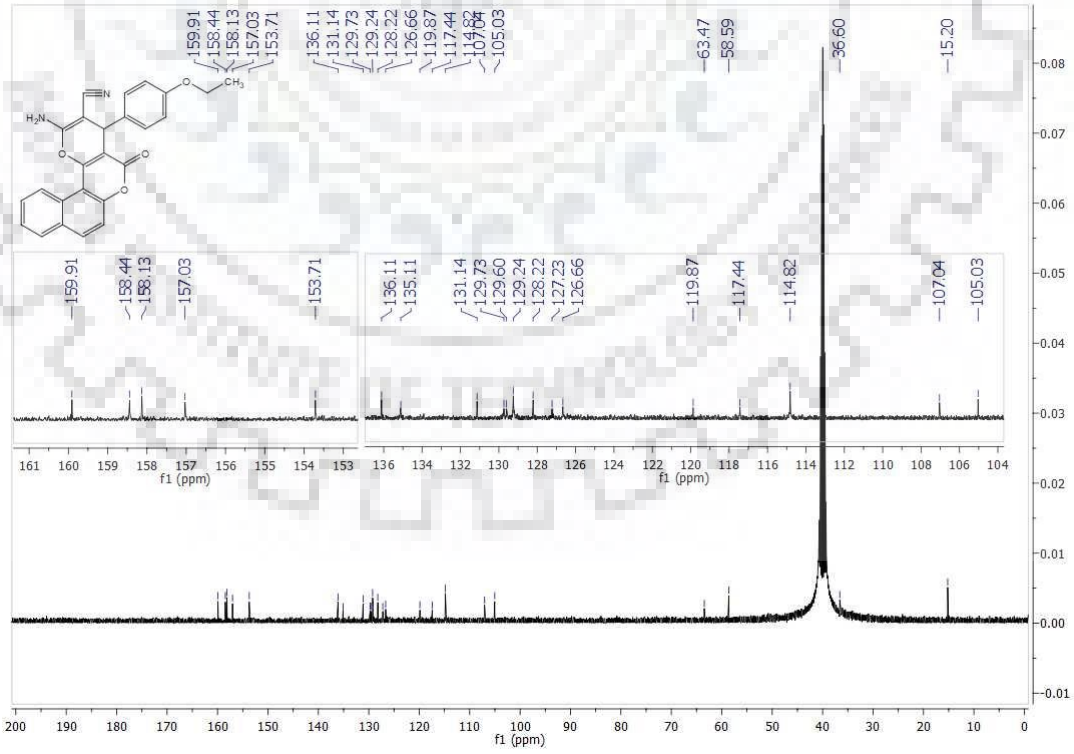
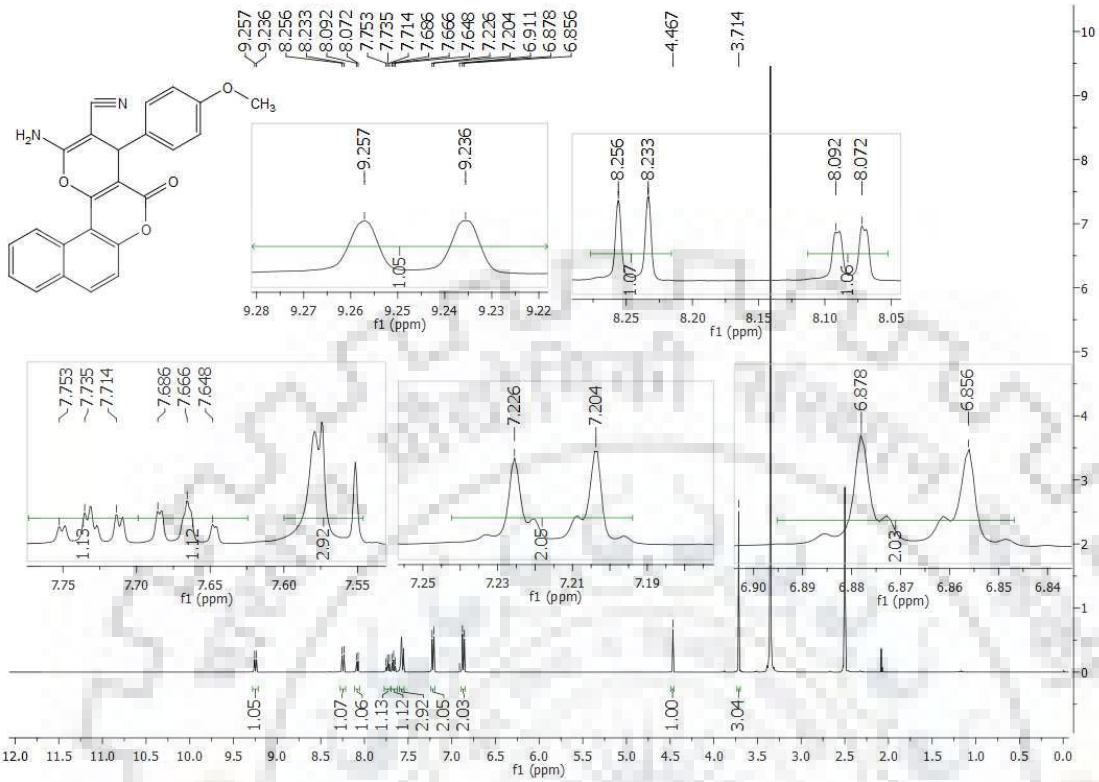


^{1}H NMR of 8k



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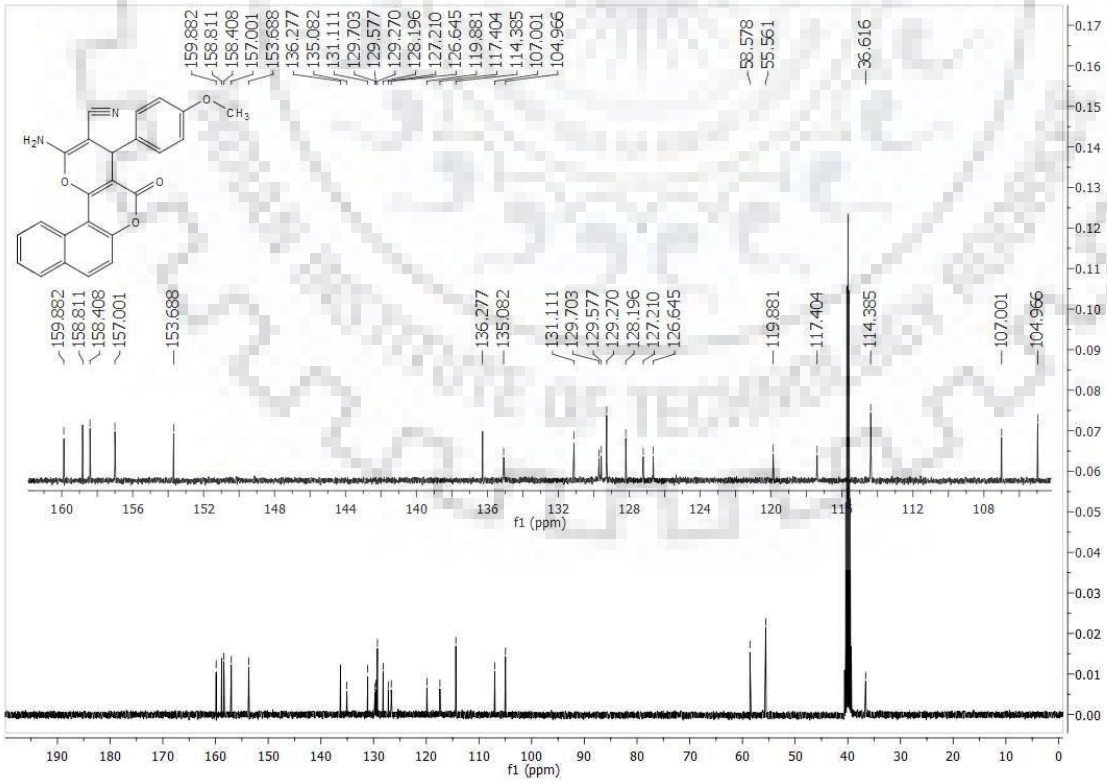
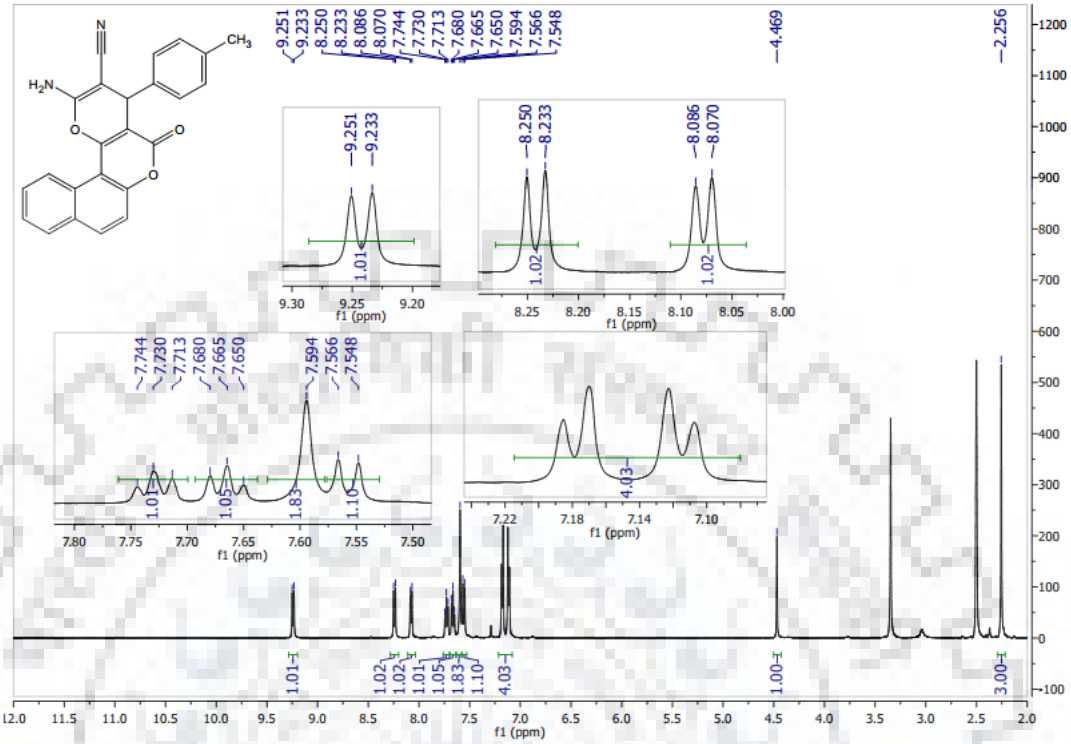


^{1}H NMR of 8m



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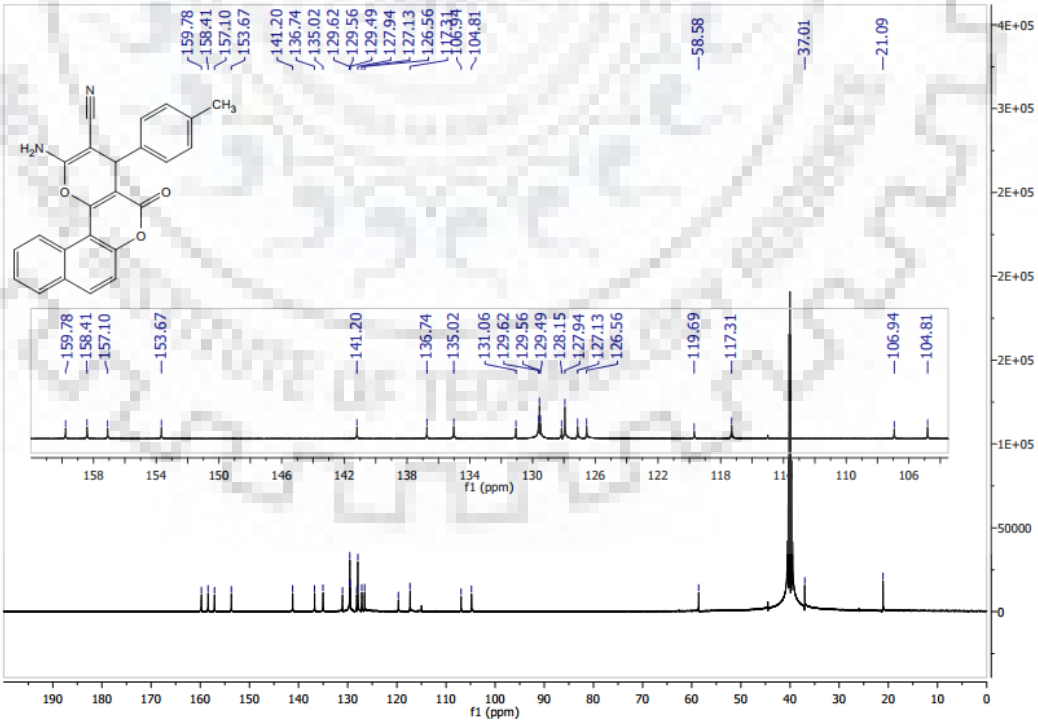

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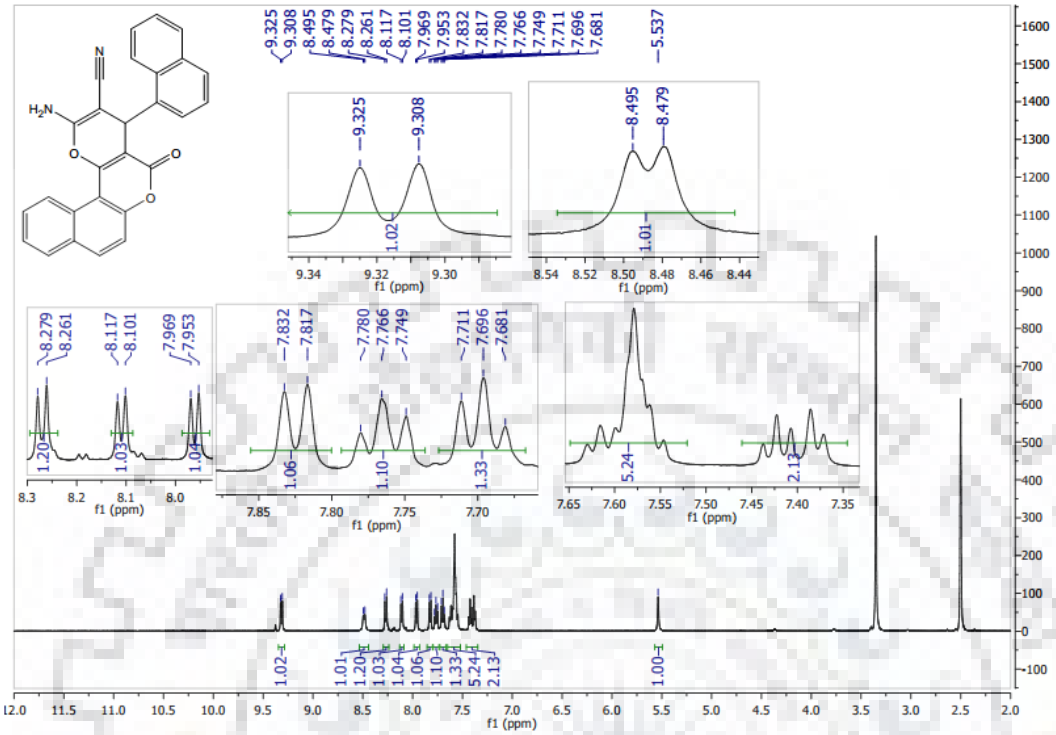
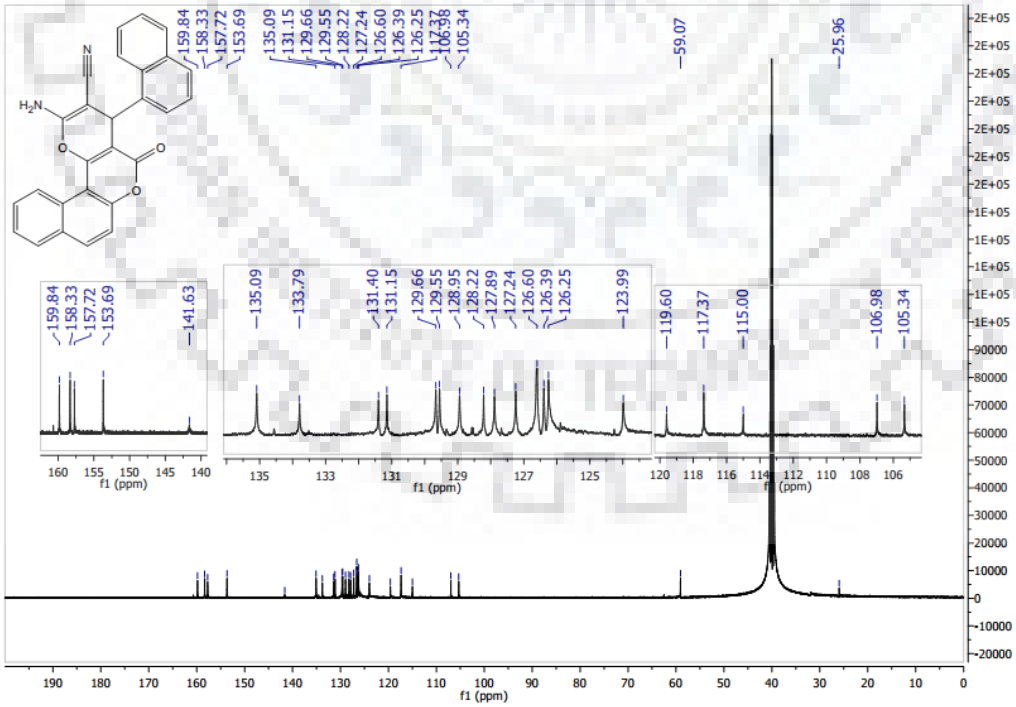
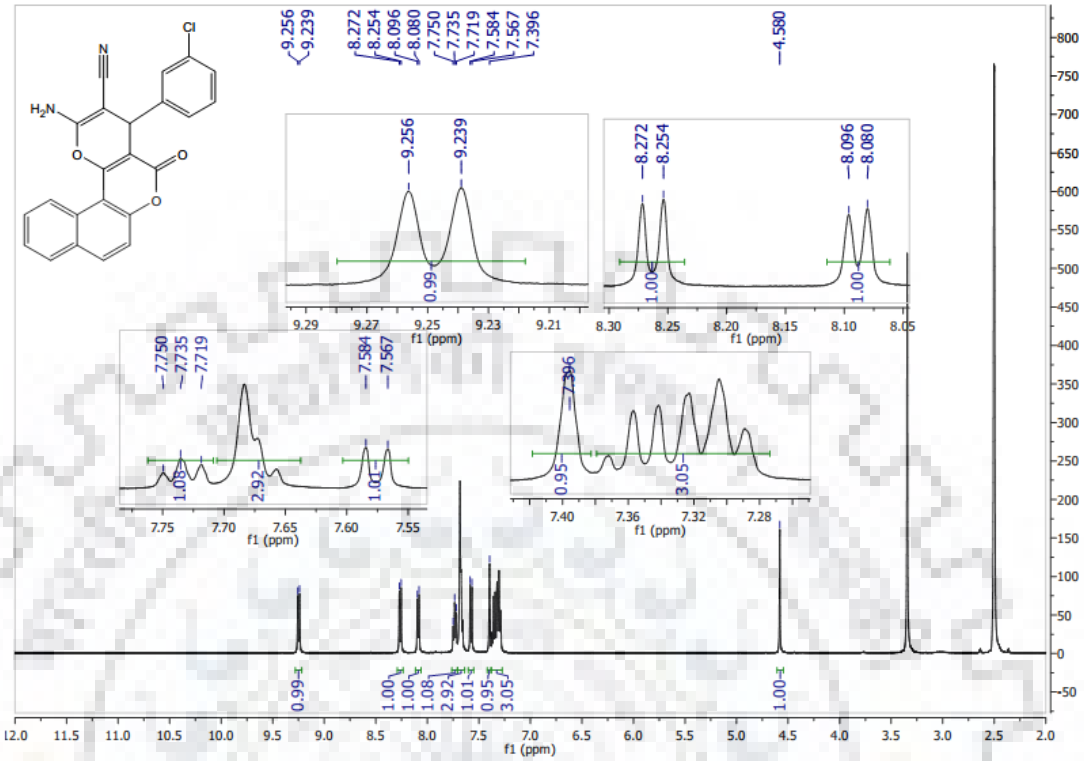


^{13}C NMR of 8n



^{1}H NMR of 8o



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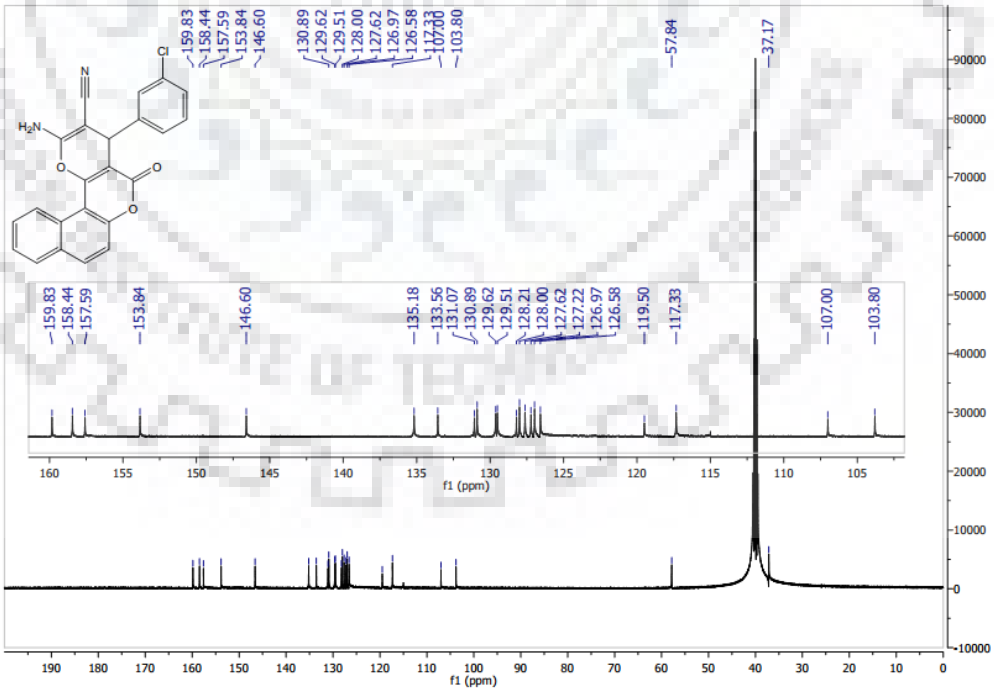

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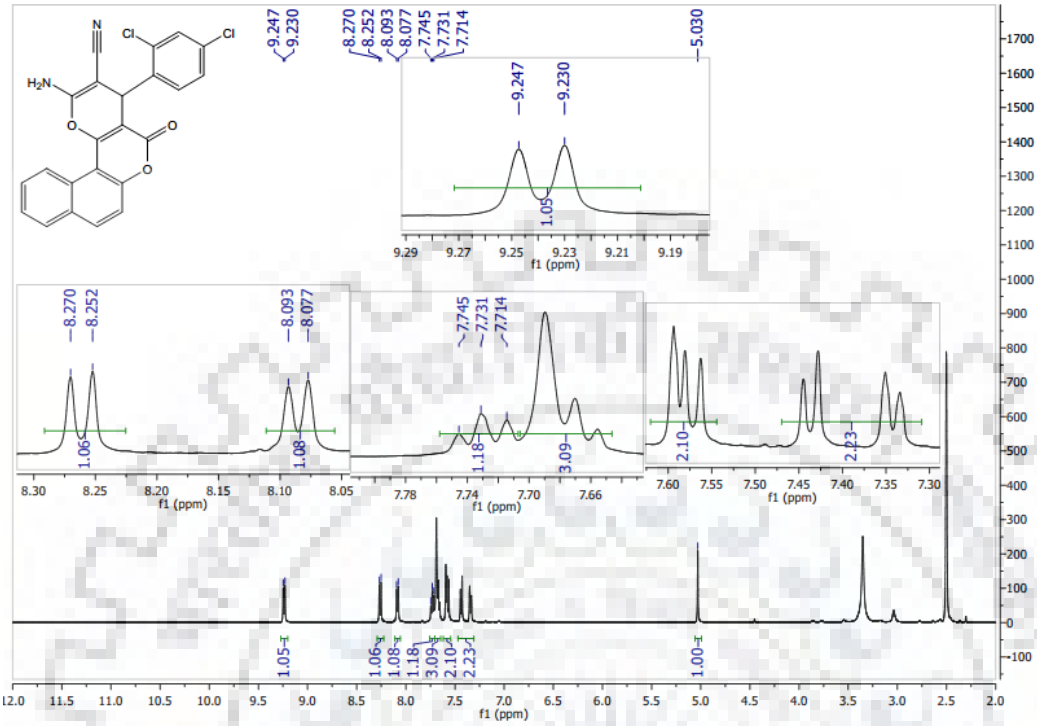
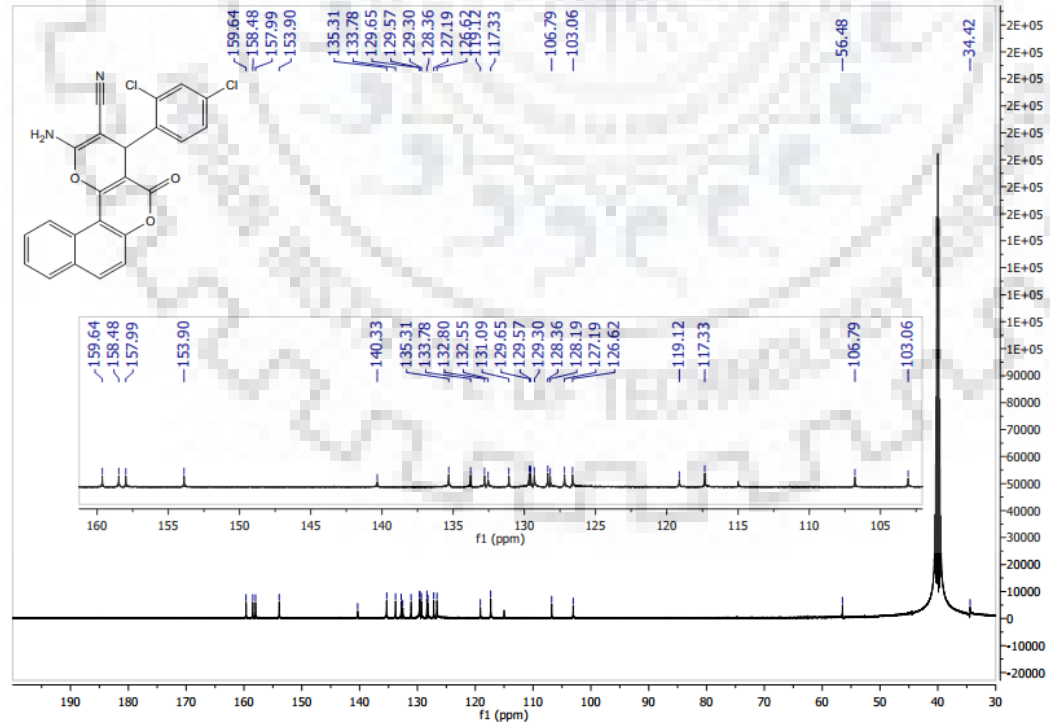
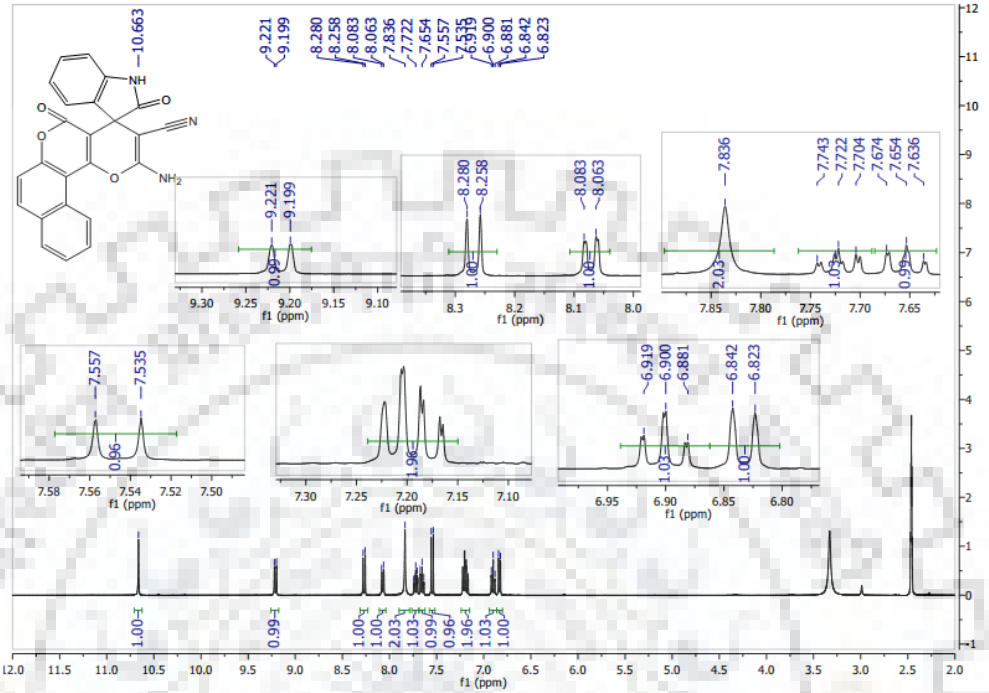


^{13}C NMR of 8p

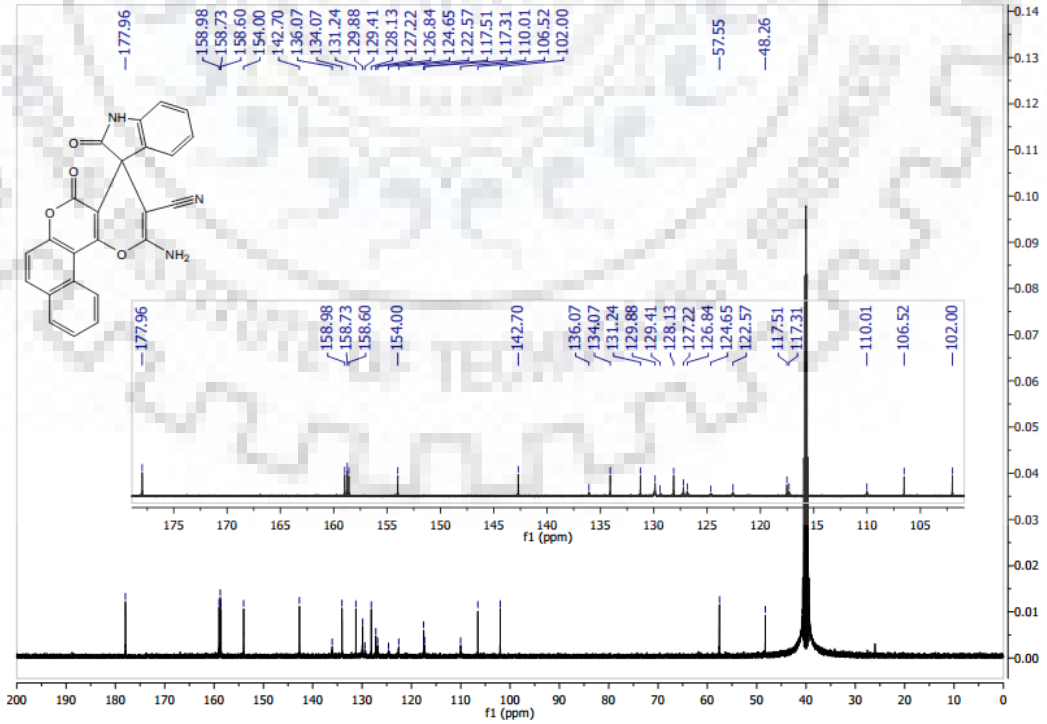


Chapter 3: Spectral information for spriro-fused benzopyrans (6a-6r)

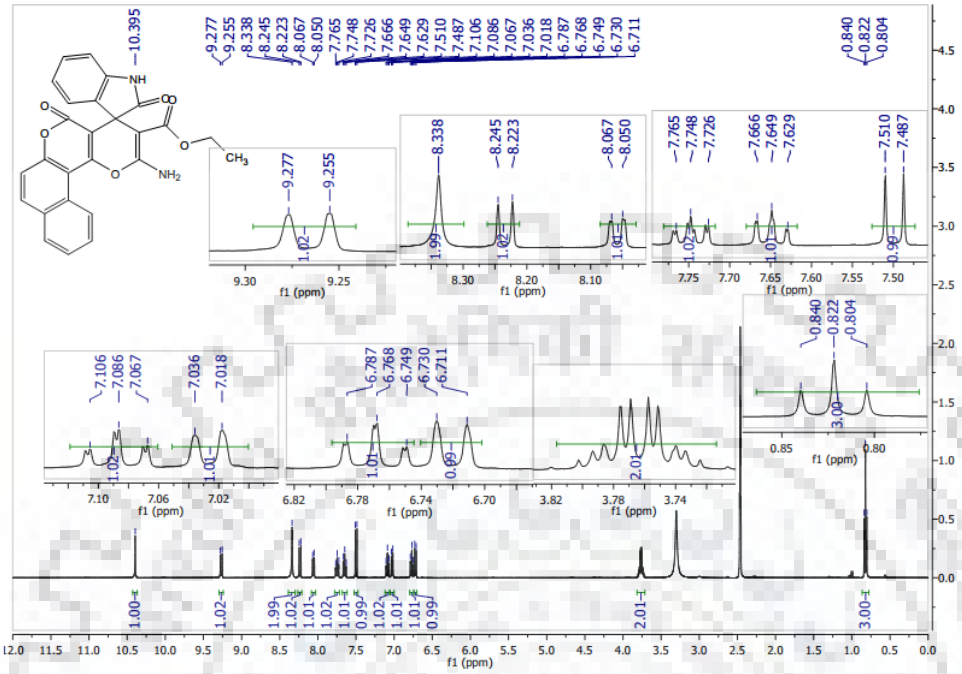
^{1}H NMR of 6a



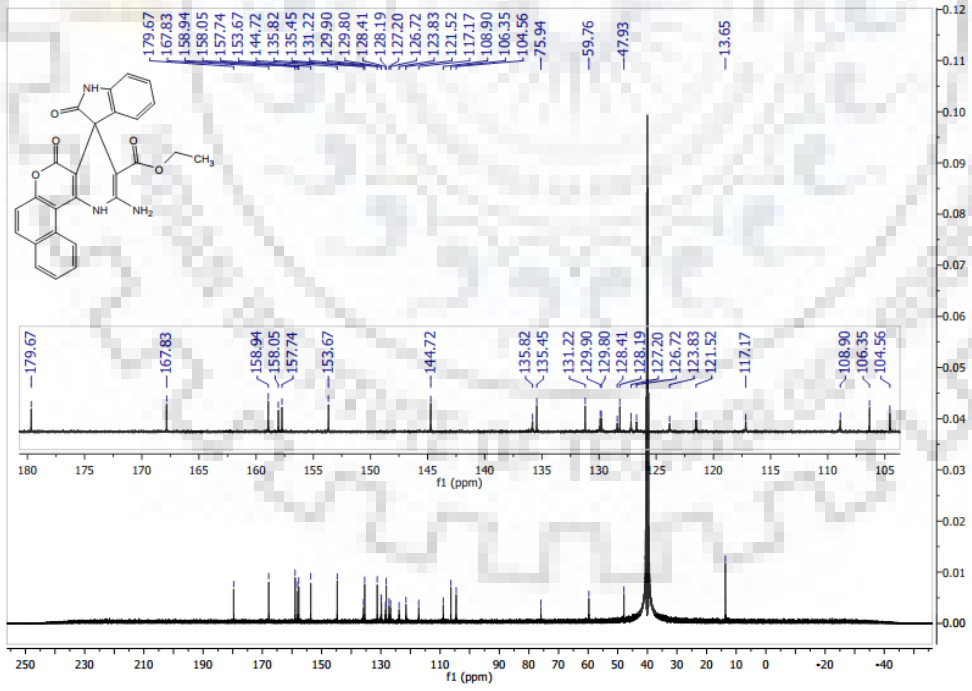
^{13}C NMR of 6a



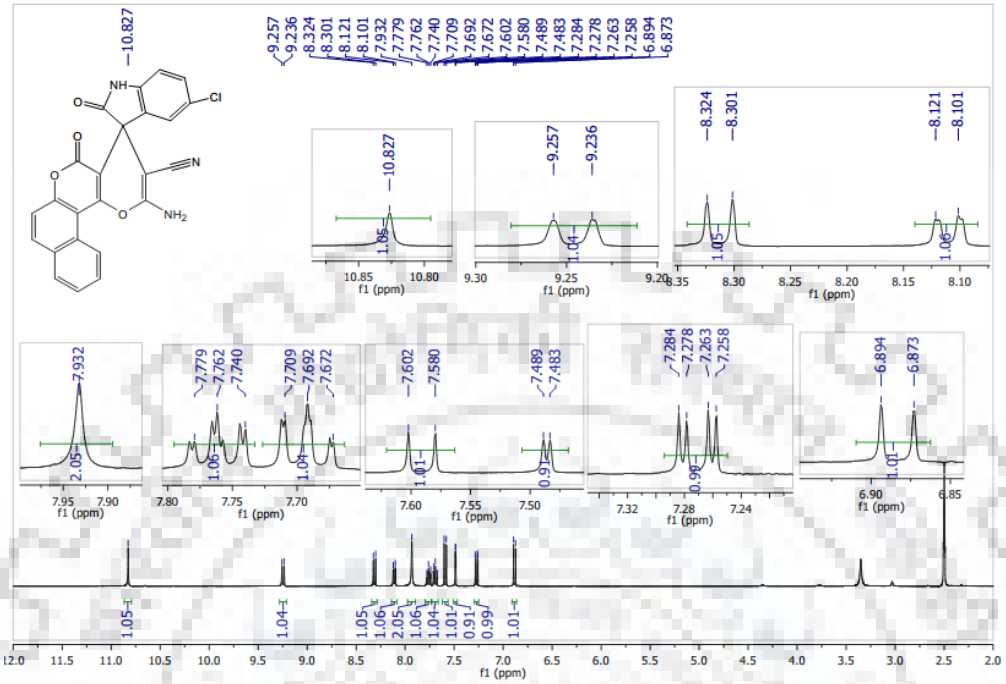
^{1}H NMR of 6b



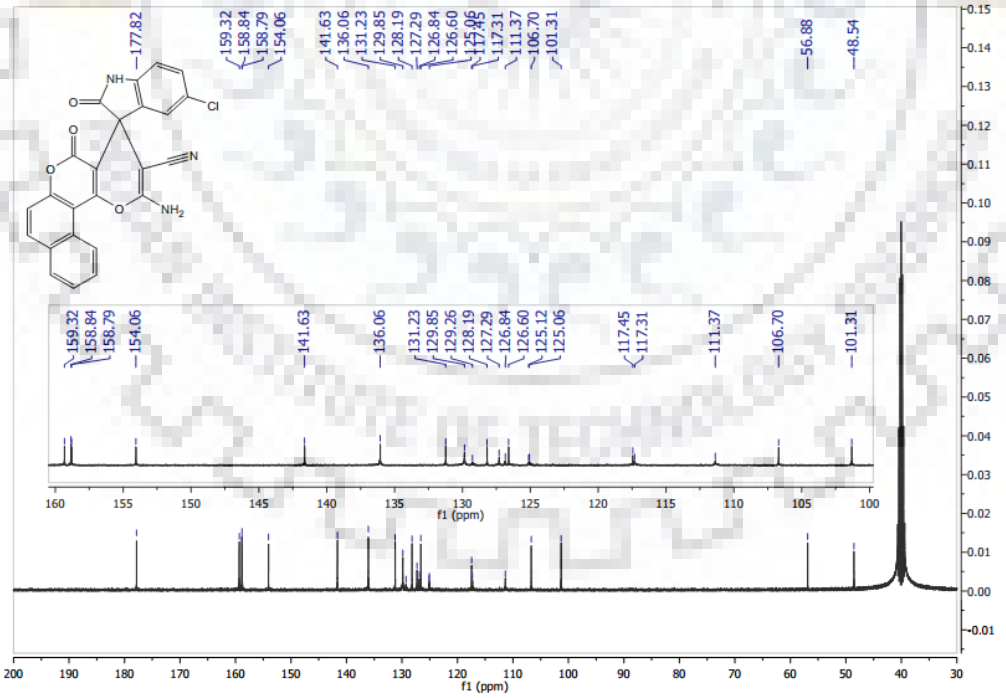
^{13}C NMR of 6b



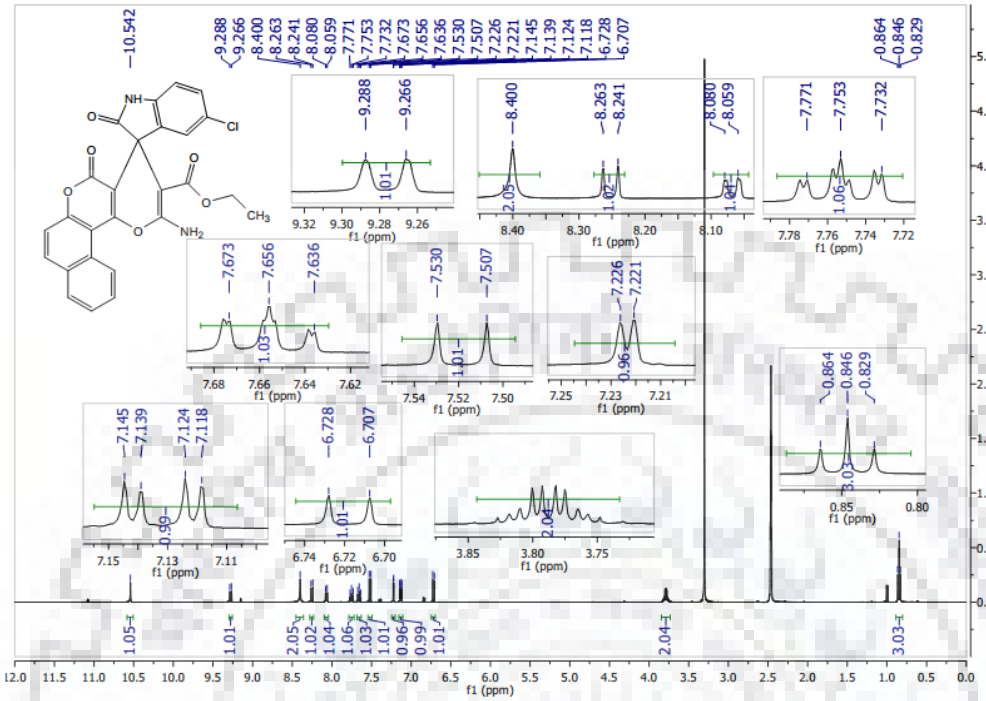
^{1}H NMR of 6c



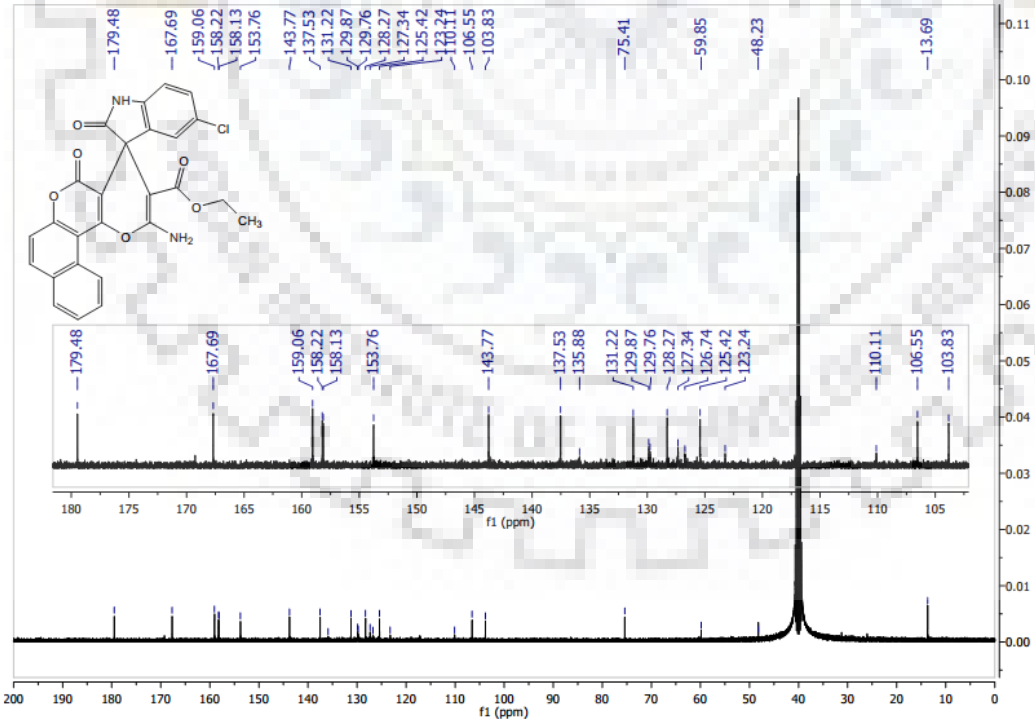
^{13}C NMR of 6c



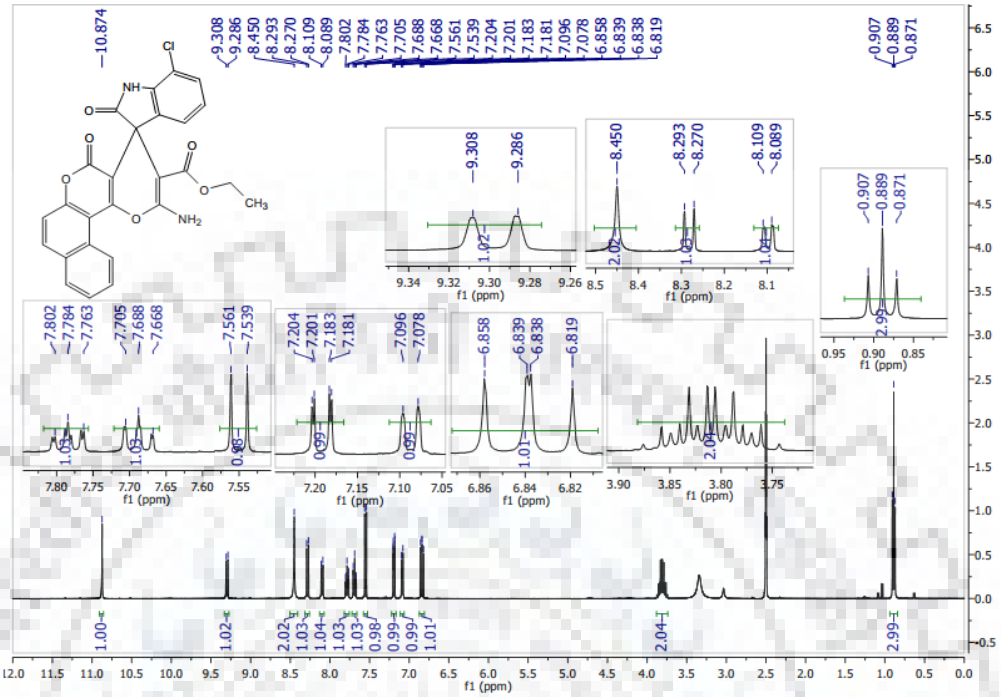
^{1}H NMR of 6d



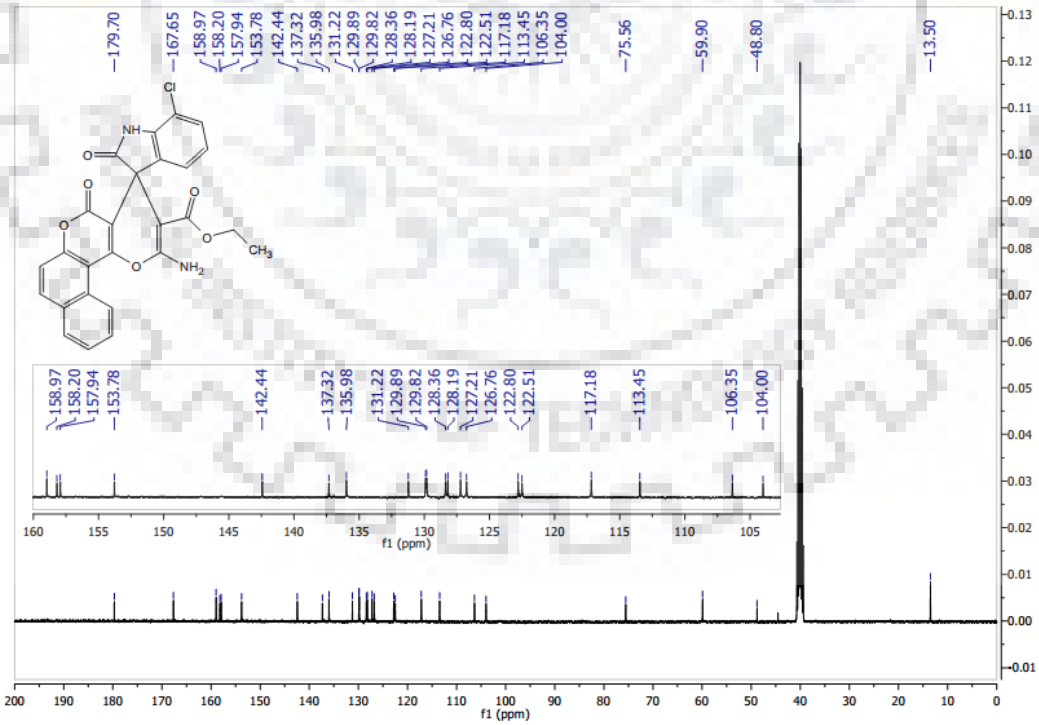
^{13}C NMR of 6d



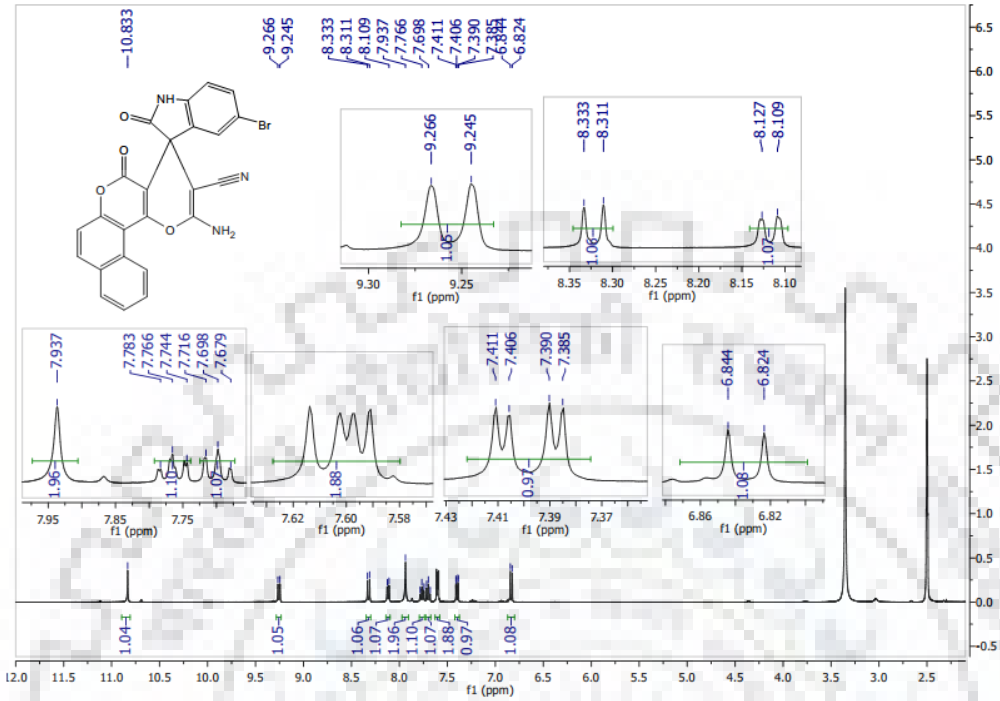
^{1}H NMR of 6e



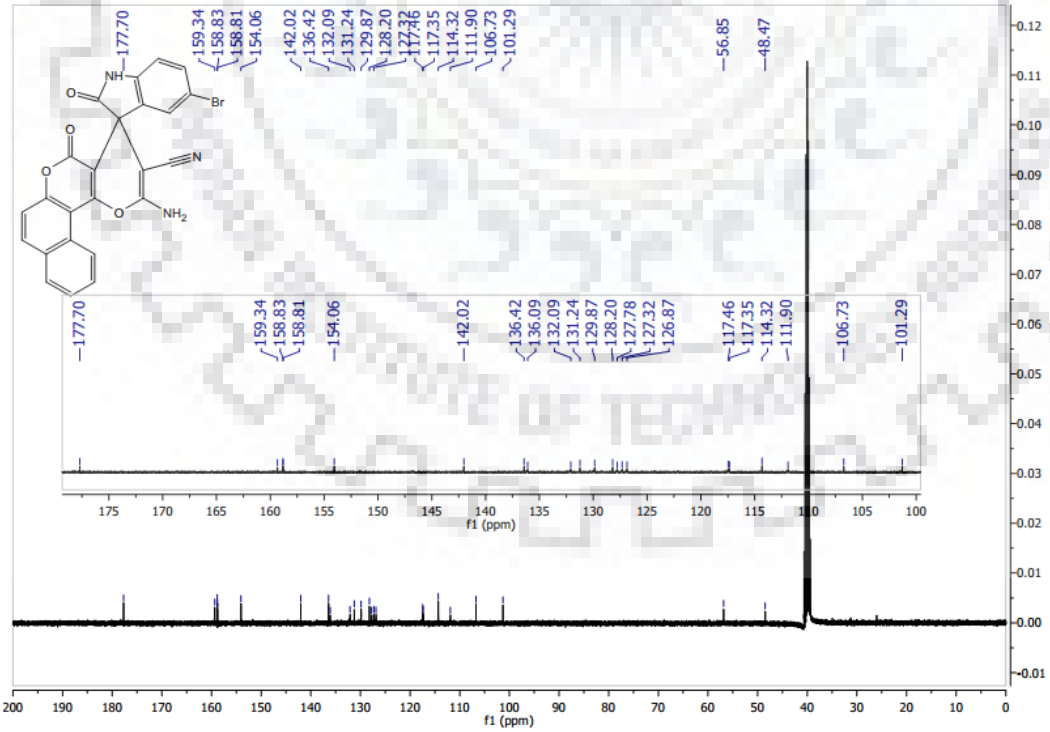
^{13}C NMR of 6e



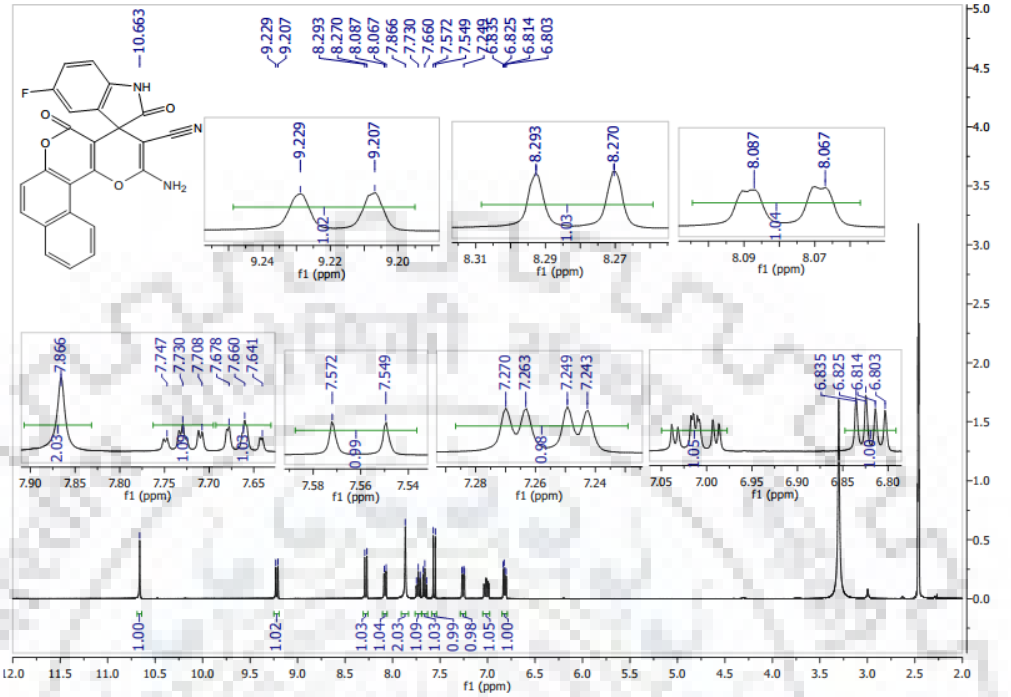
^{1}H NMR of 6f



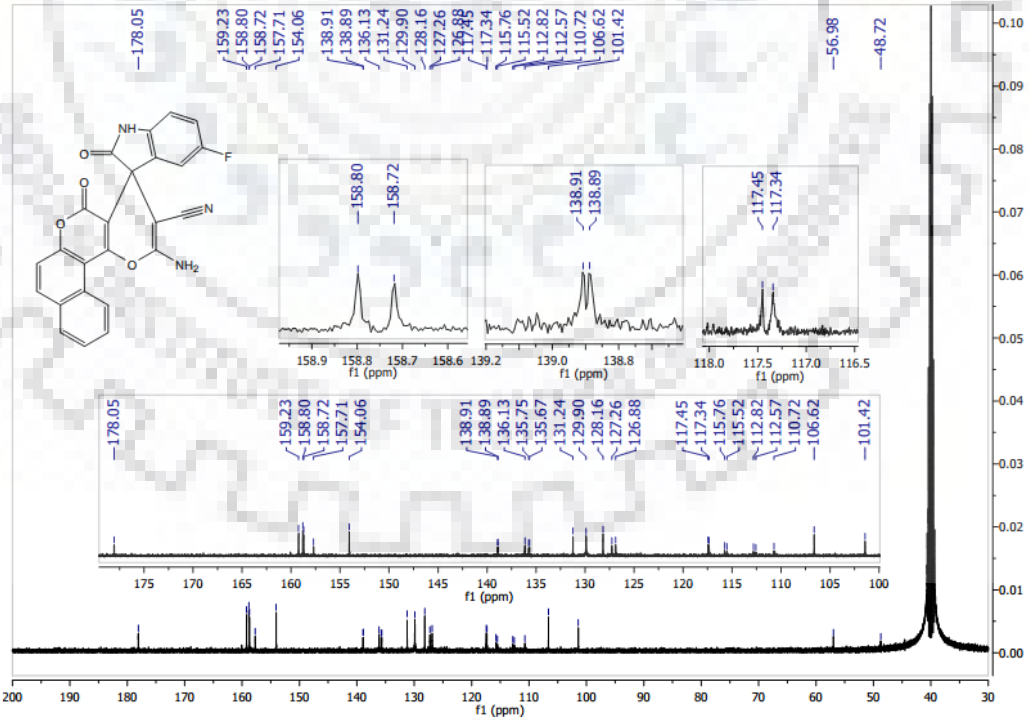
^{13}C NMR of 6f



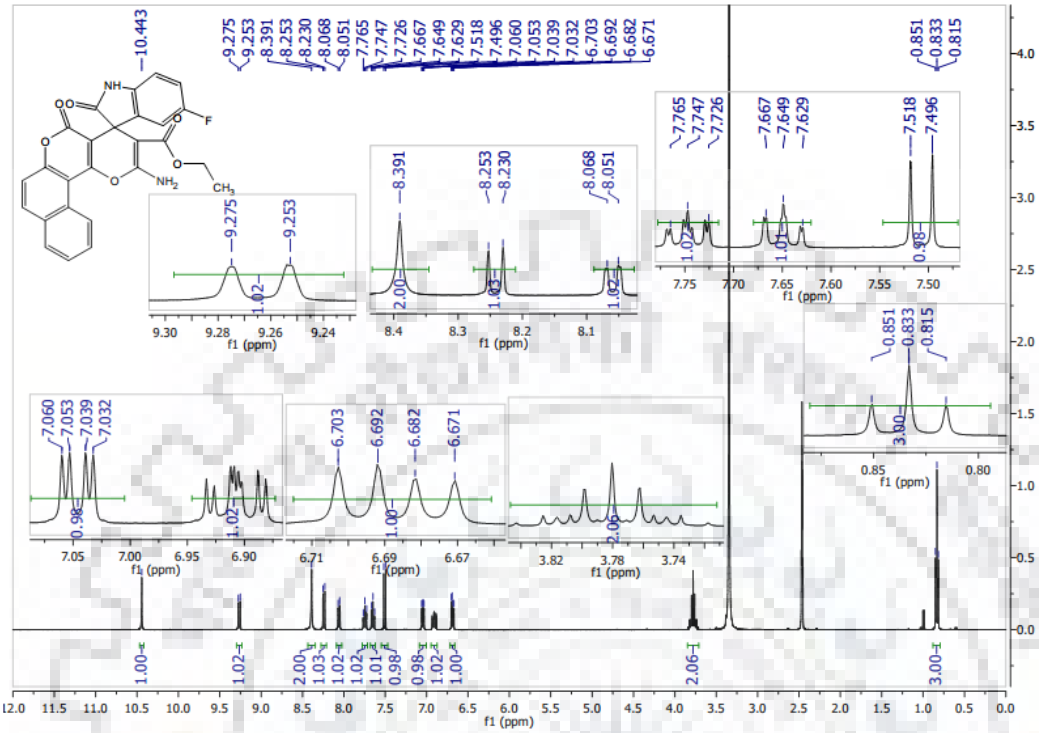
^{1}H NMR of 6g



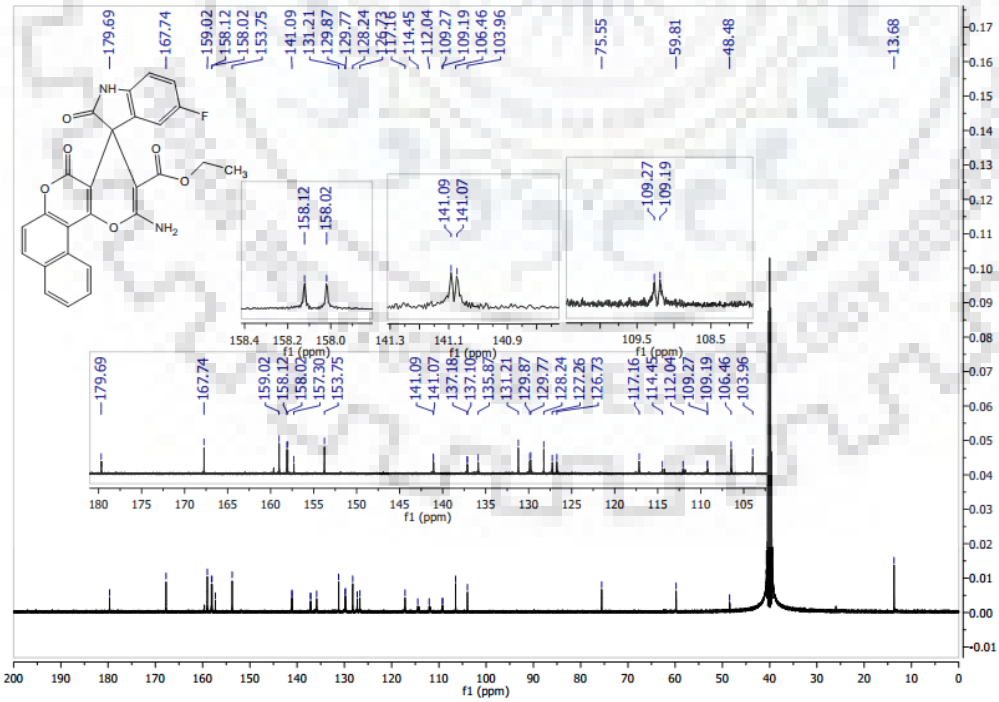
^{13}C NMR of 6g



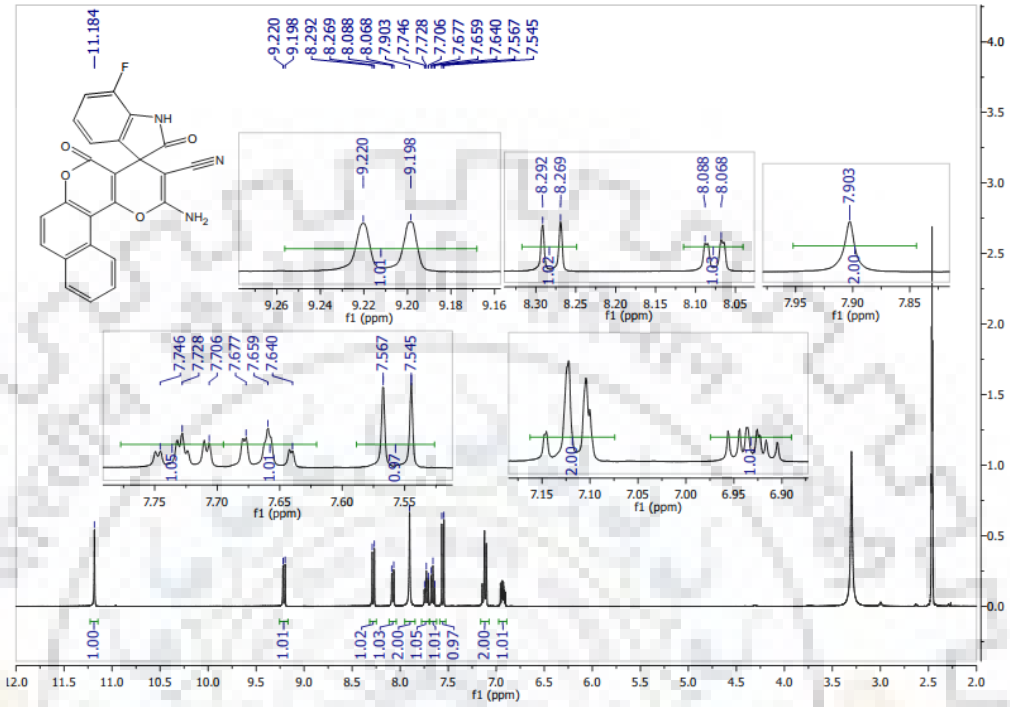
^{1}H NMR of 6h



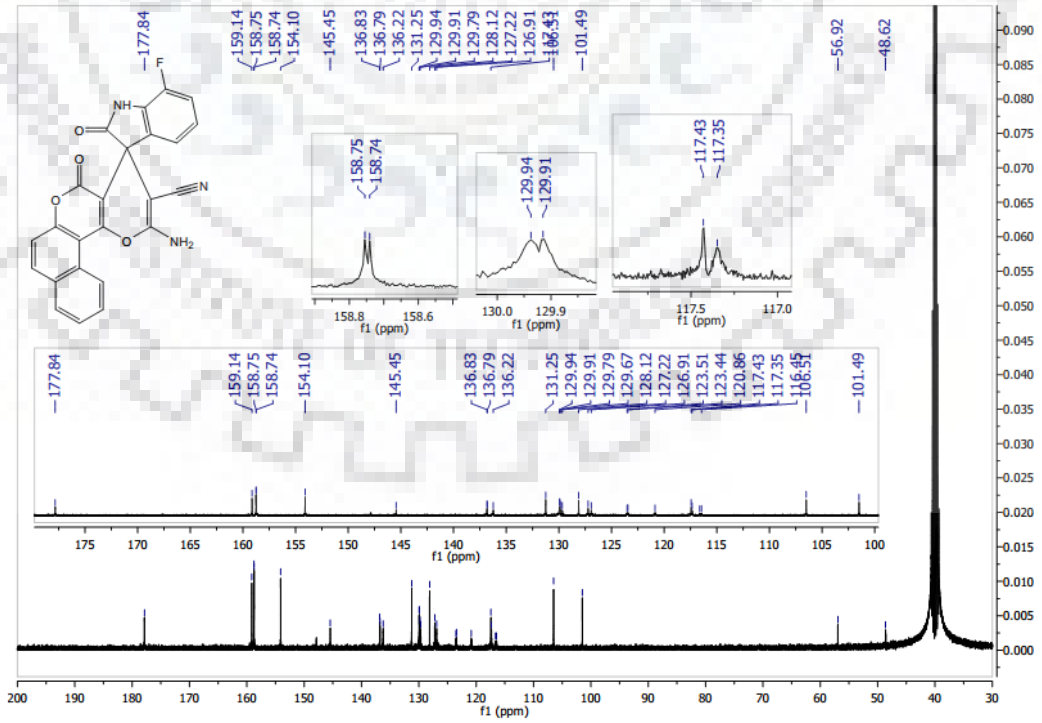
^{13}C NMR of 6h



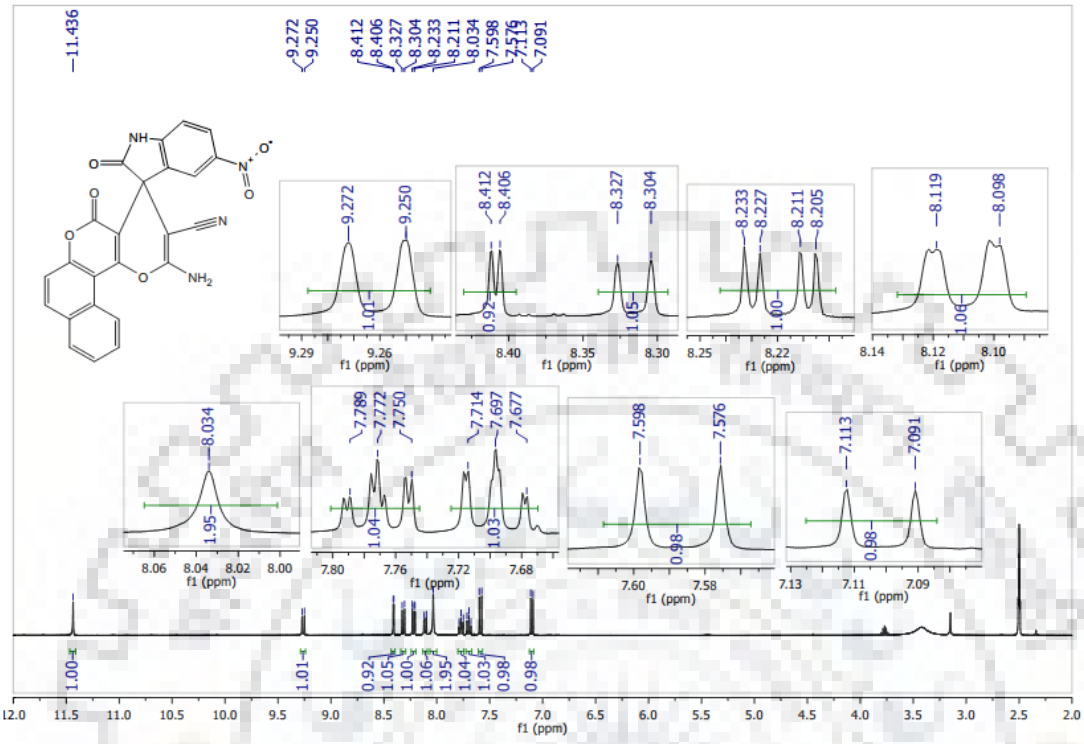
^{1}H NMR of 6i



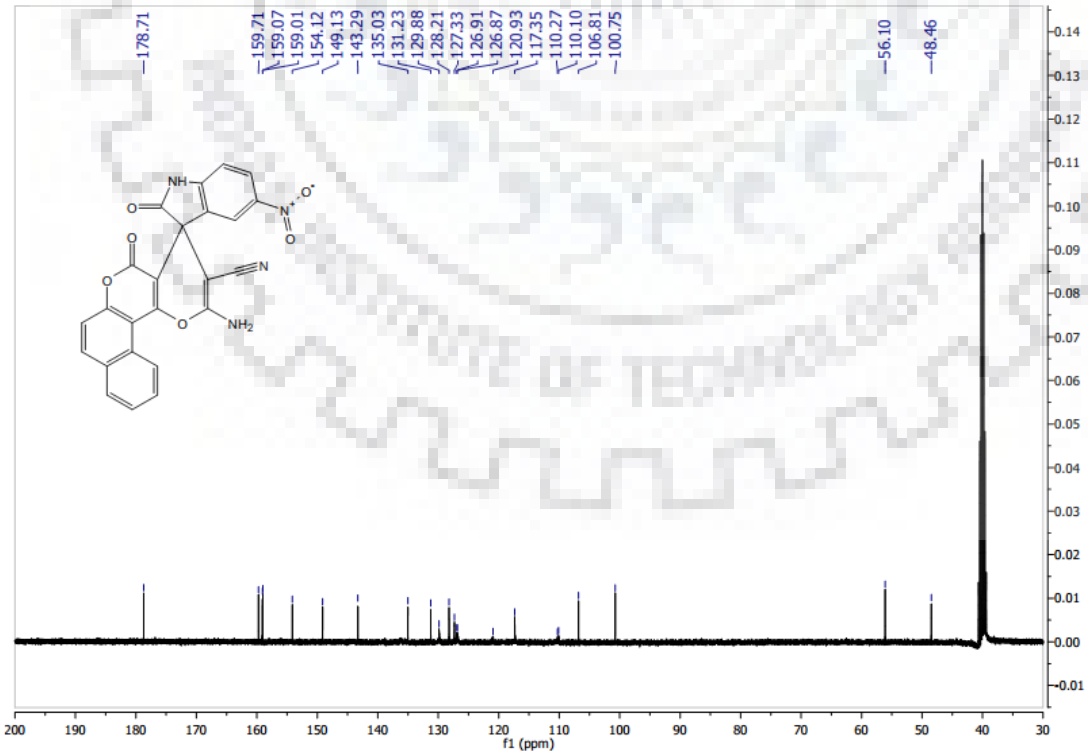
^{13}C NMR of 6i



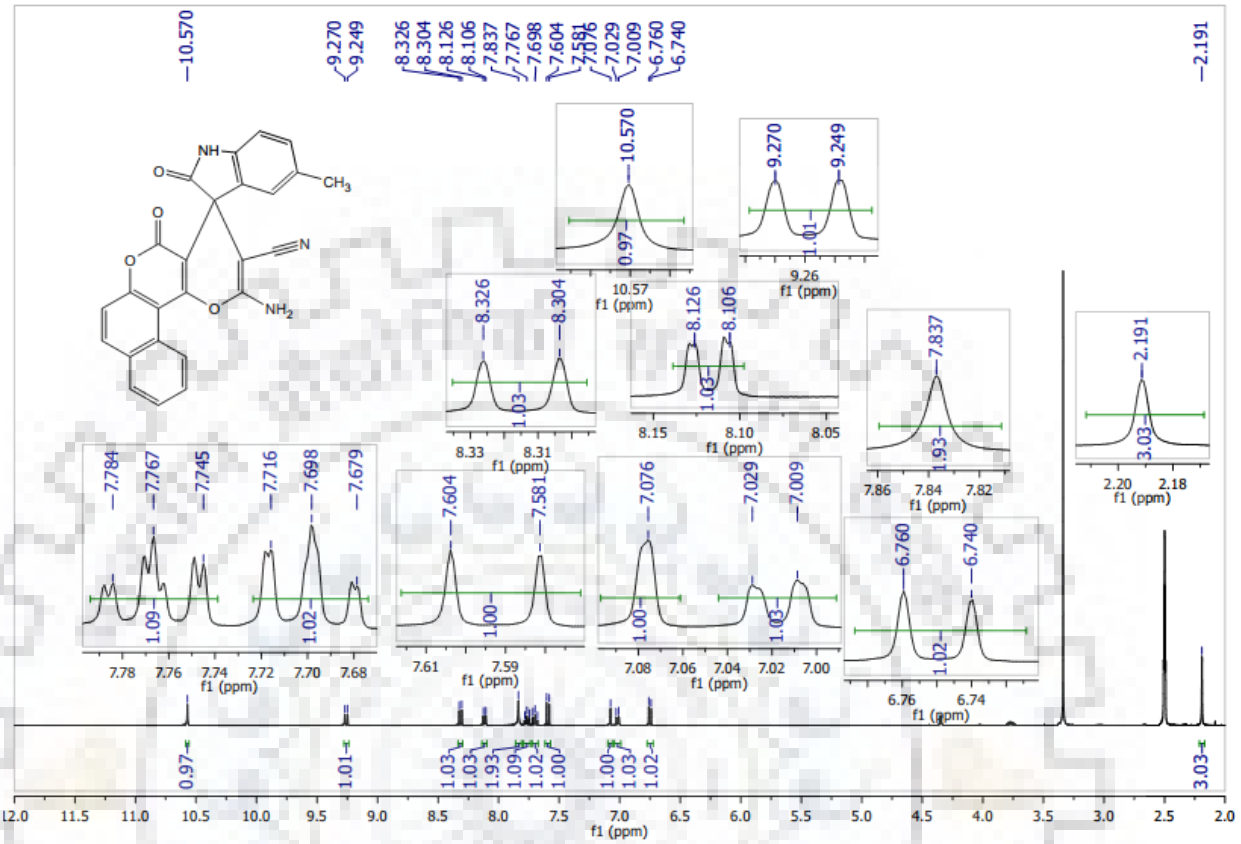
^{1}H NMR of 6j



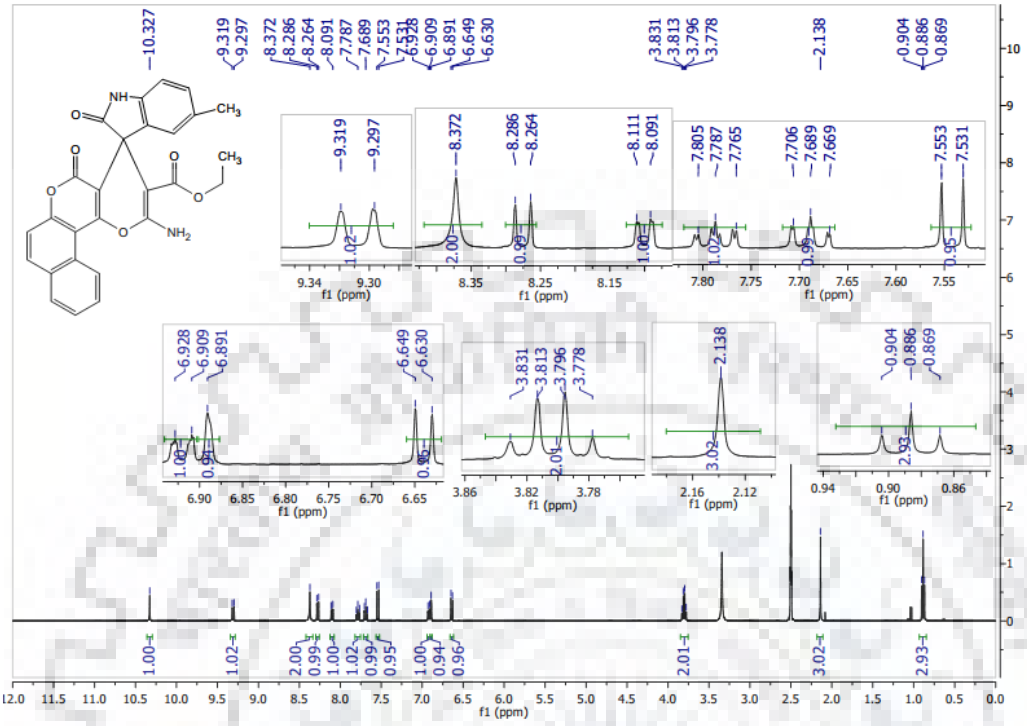
^{13}C NMR of 6j



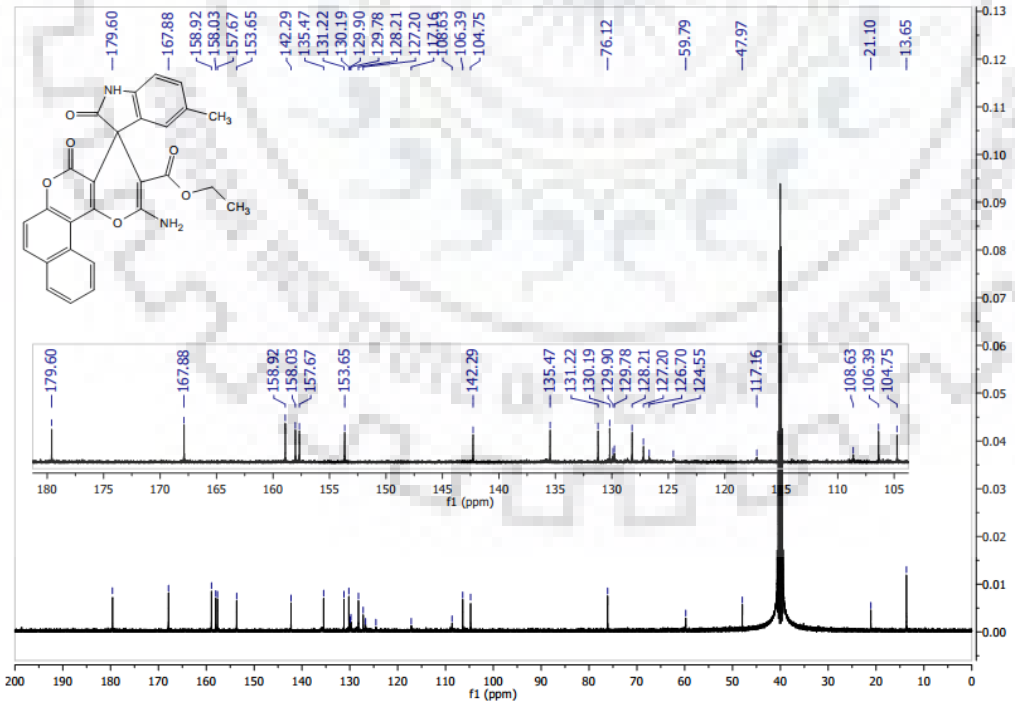
^{1}H NMR of 6k


10.570
9.270
9.249
8.326
8.304
8.126
8.106
7.837
7.767
7.698
7.604
7.581
7.076
7.029
7.009
6.760
6.740
2.191
NH
O
CH3
O
O
N
O
NH2
f1 (ppm)

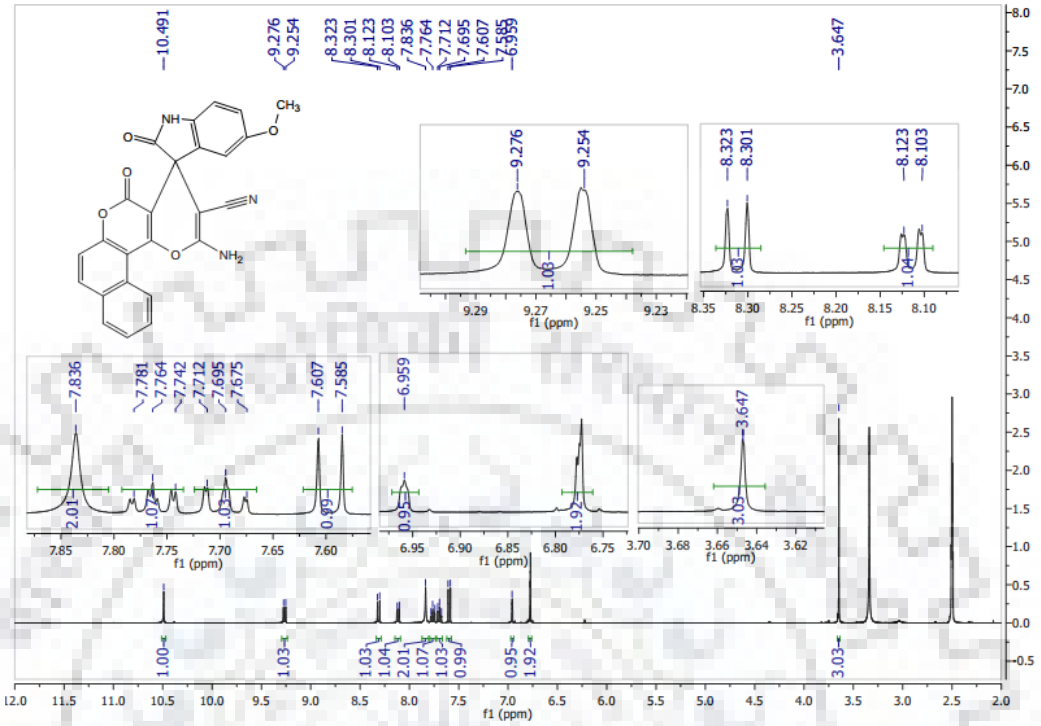
^{1}H NMR of 6l



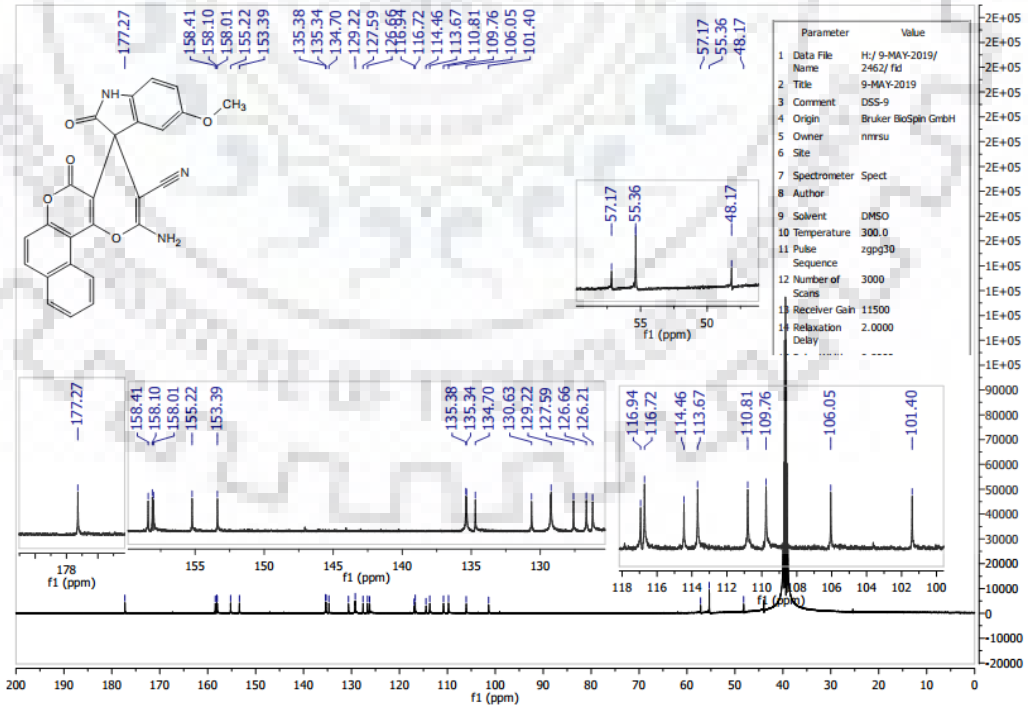
^{13}C NMR of 6l



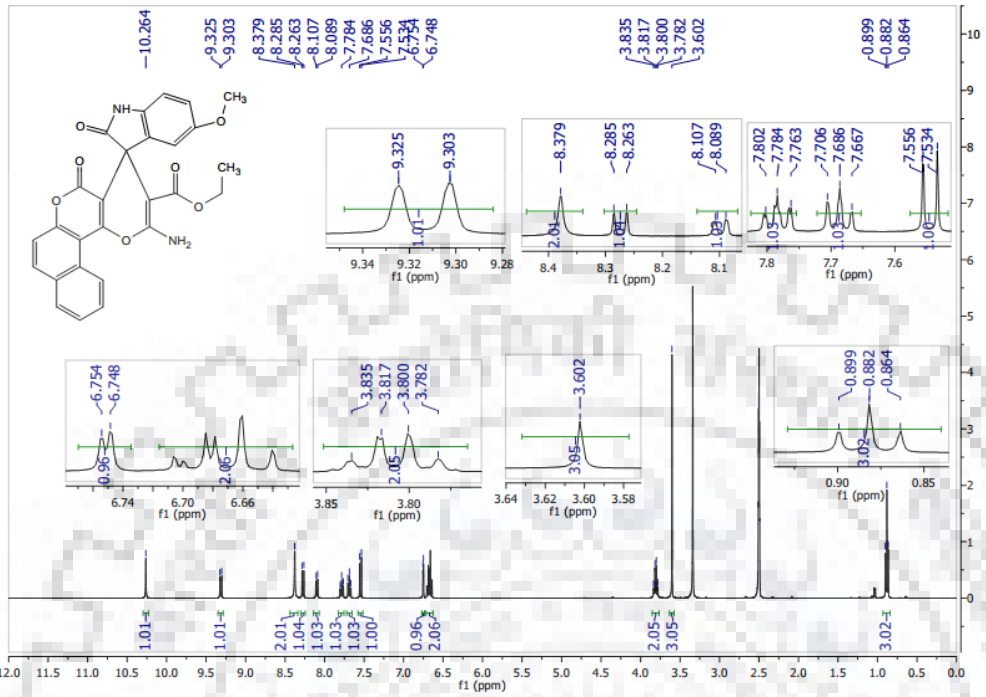
^{1}H NMR of 6m



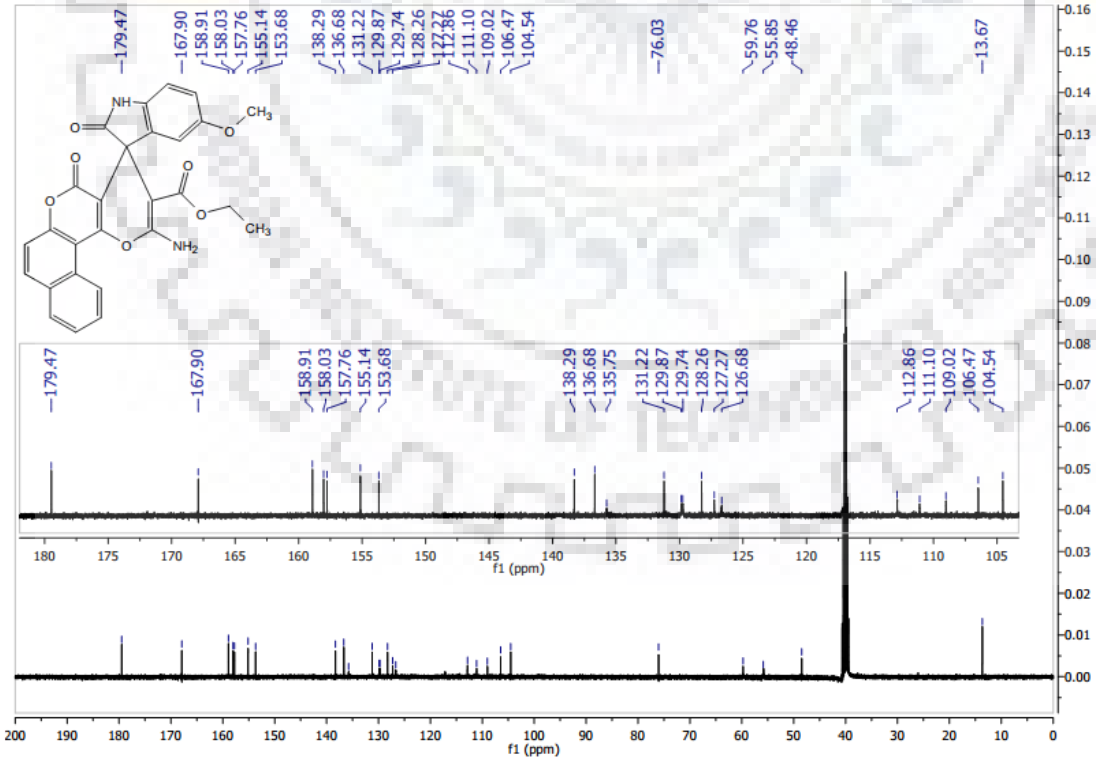
^{13}C NMR of 6m



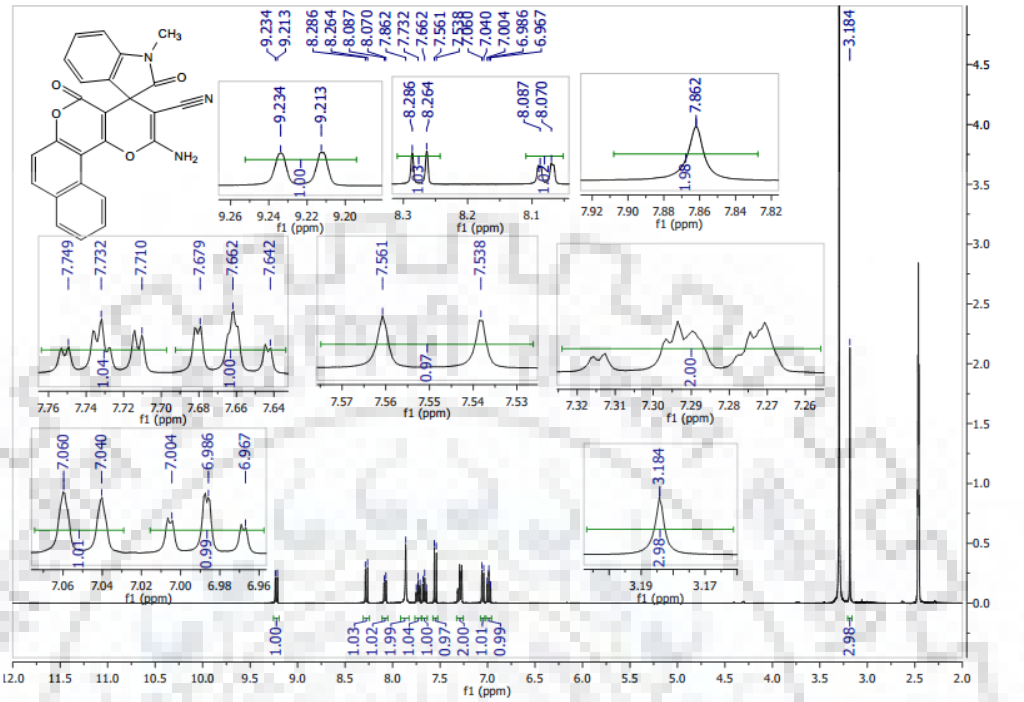
^{1}H NMR of 6n



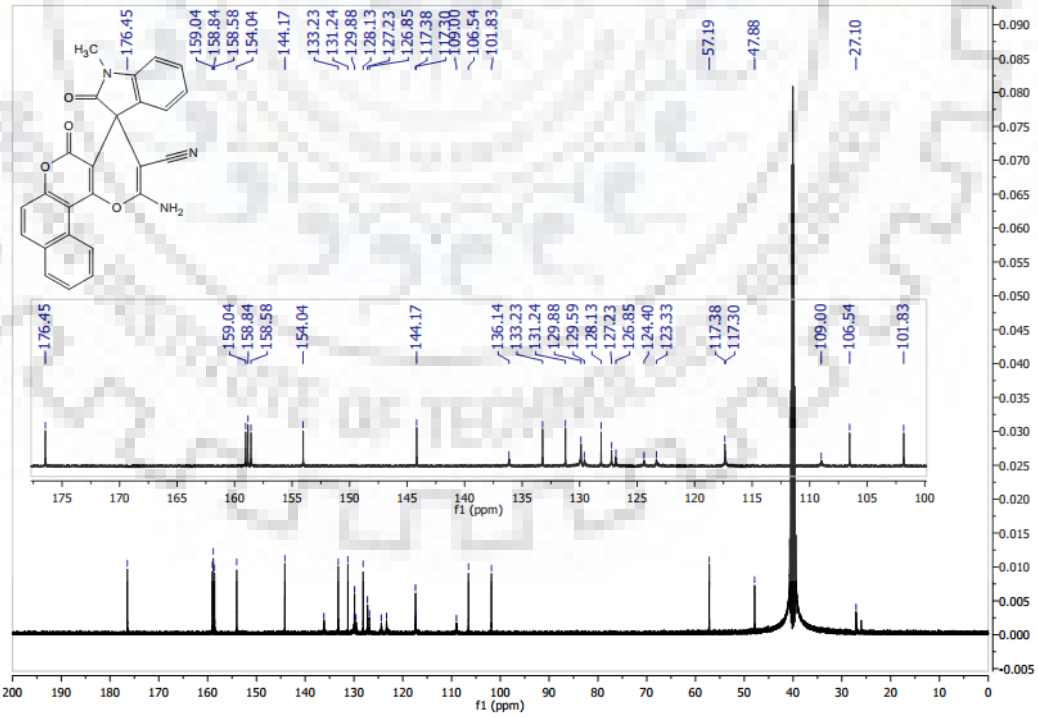
^{13}C NMR of 6n



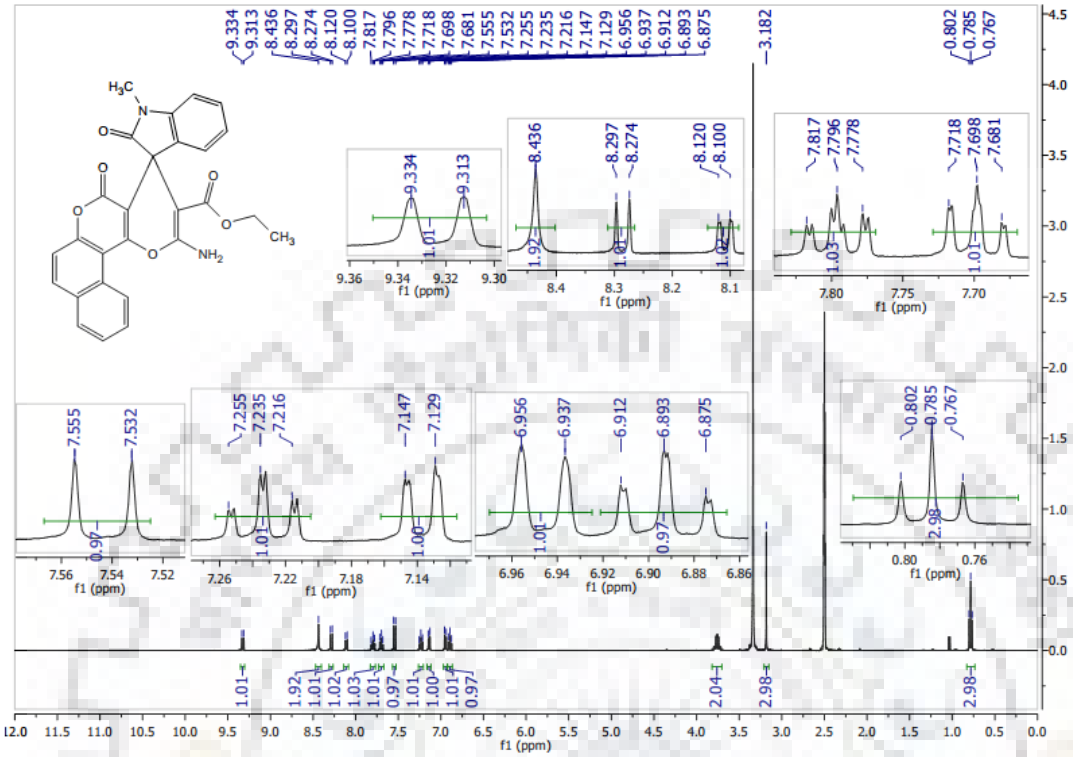
^{1}H NMR of 6o



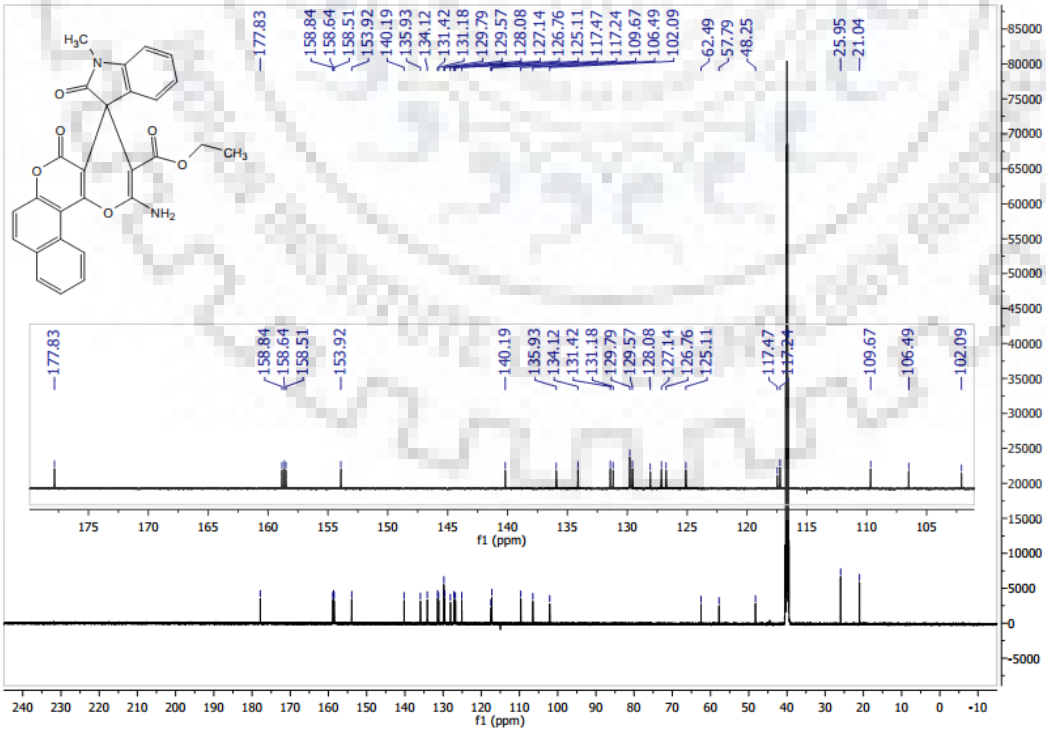
^{13}C NMR of 6o



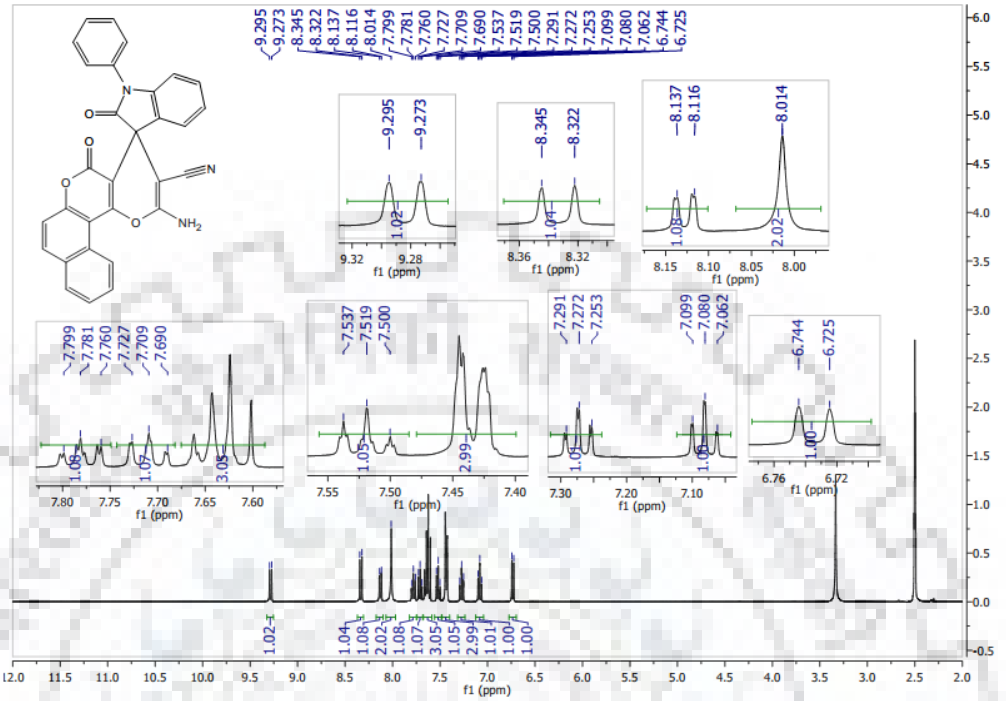
^{1}H NMR of 6p



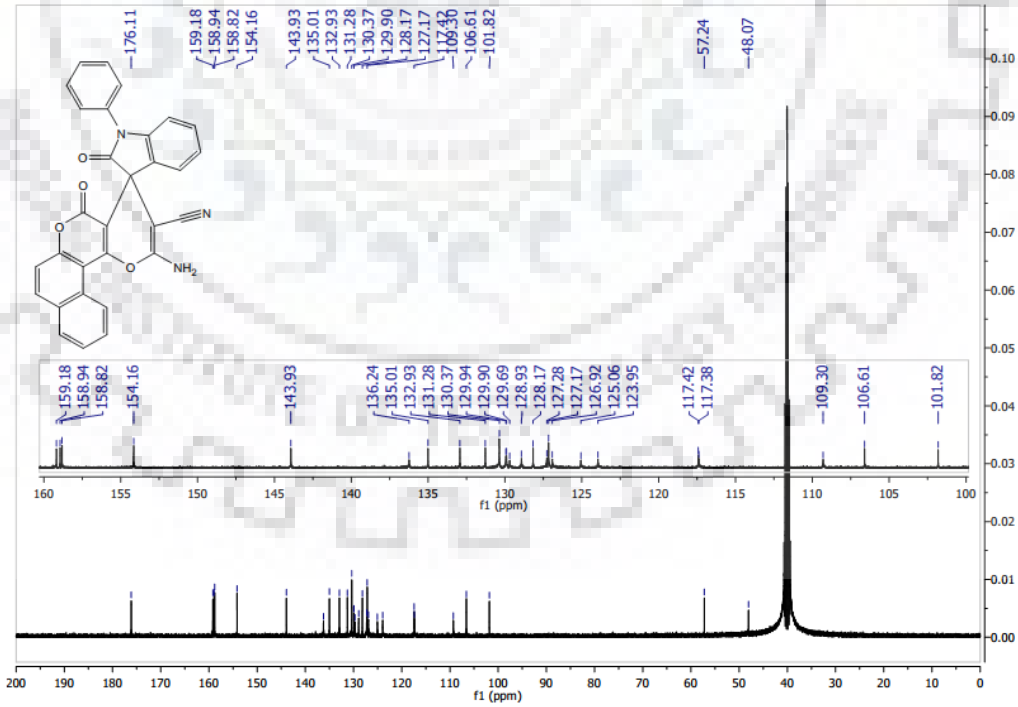
^{13}C NMR of 6p



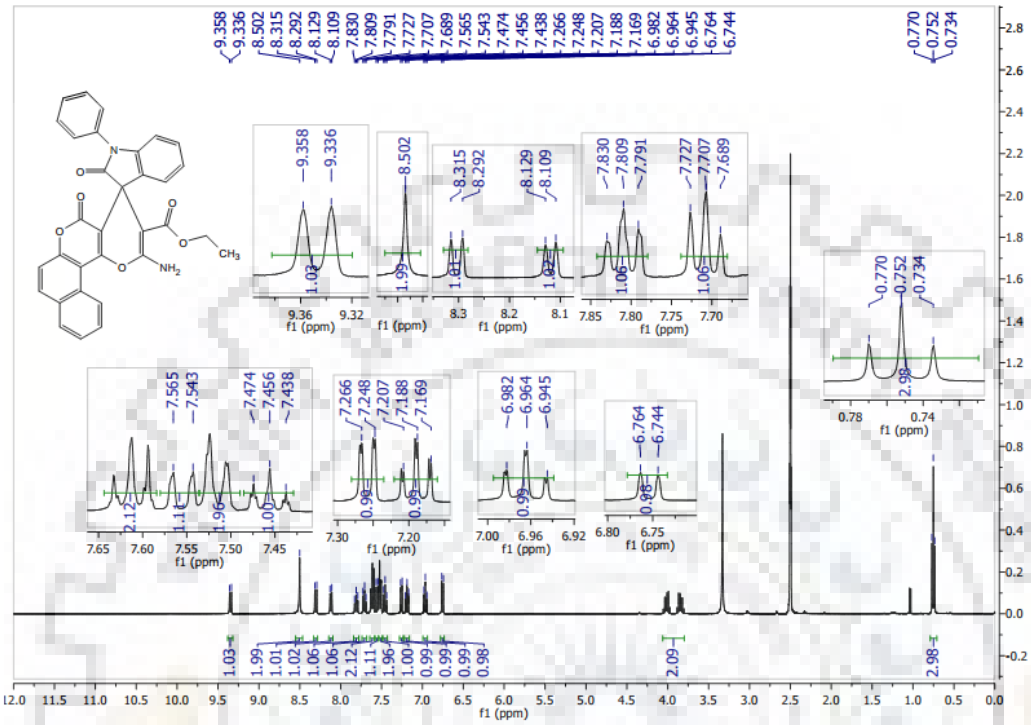
^{1}H NMR of 6q



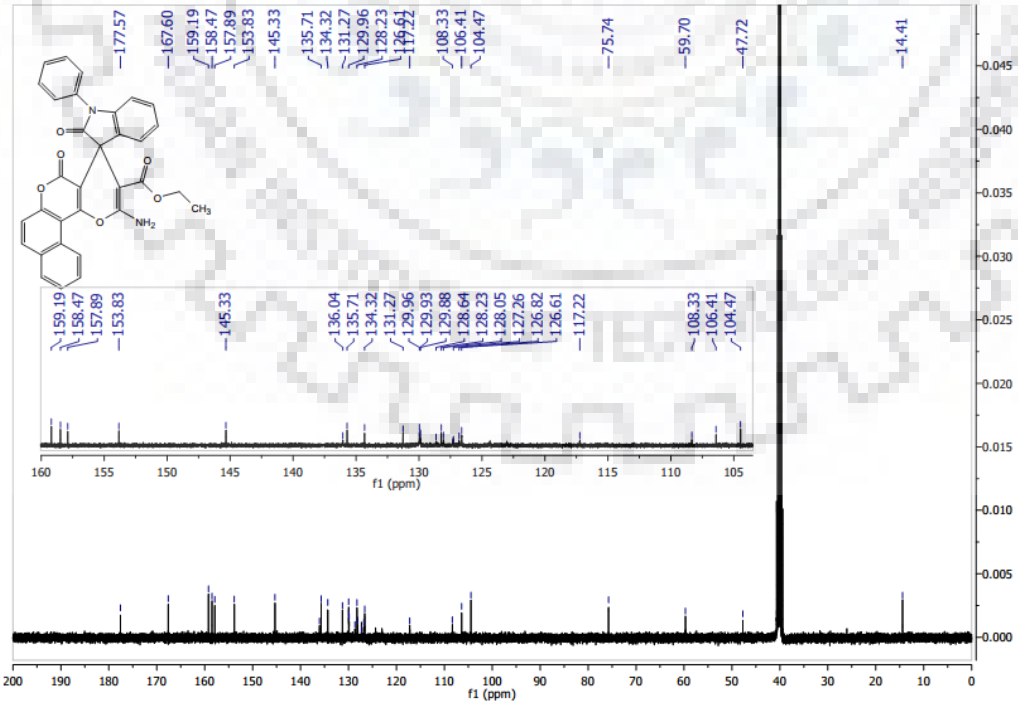
^{13}C NMR of 6q



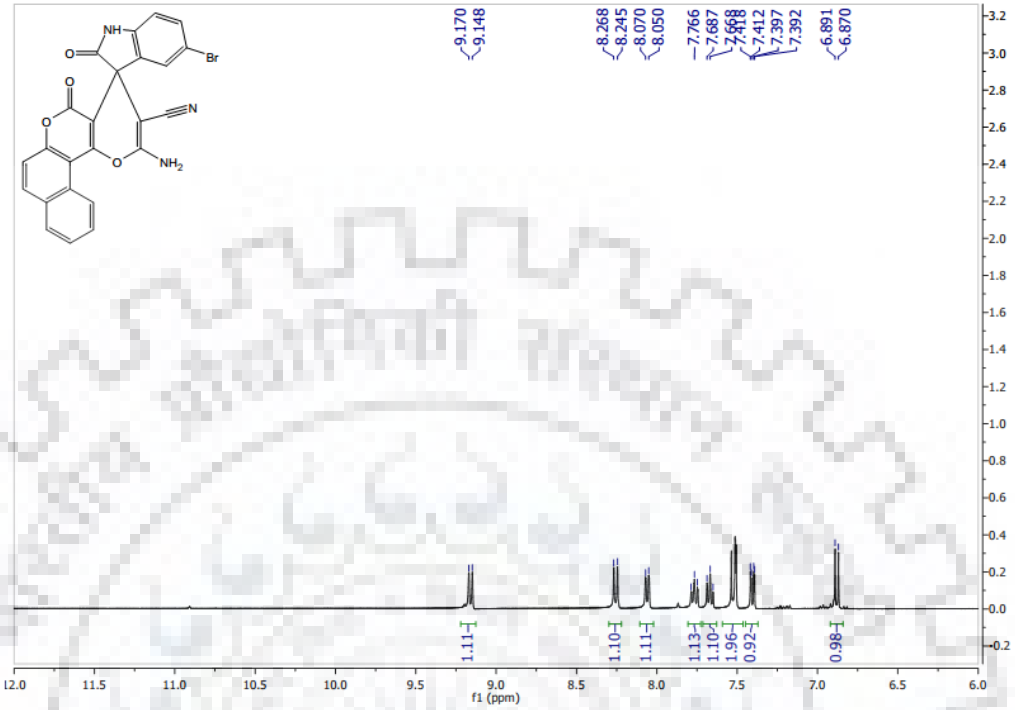
^{1}H NMR of 6r



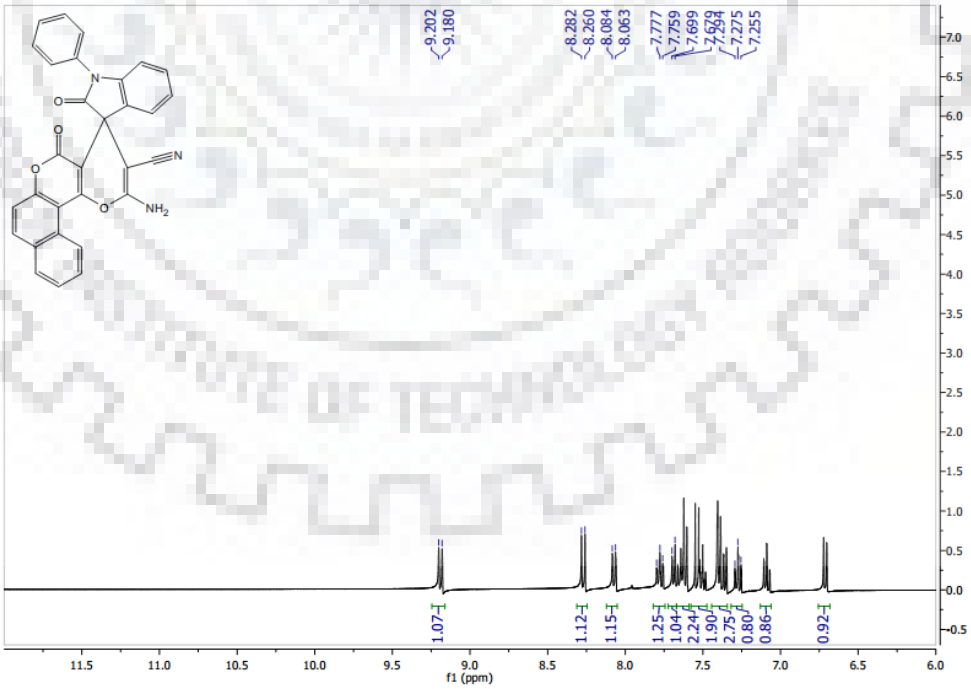
^{13}C NMR of 6r



^{1}H NMR of 6f in D_2O

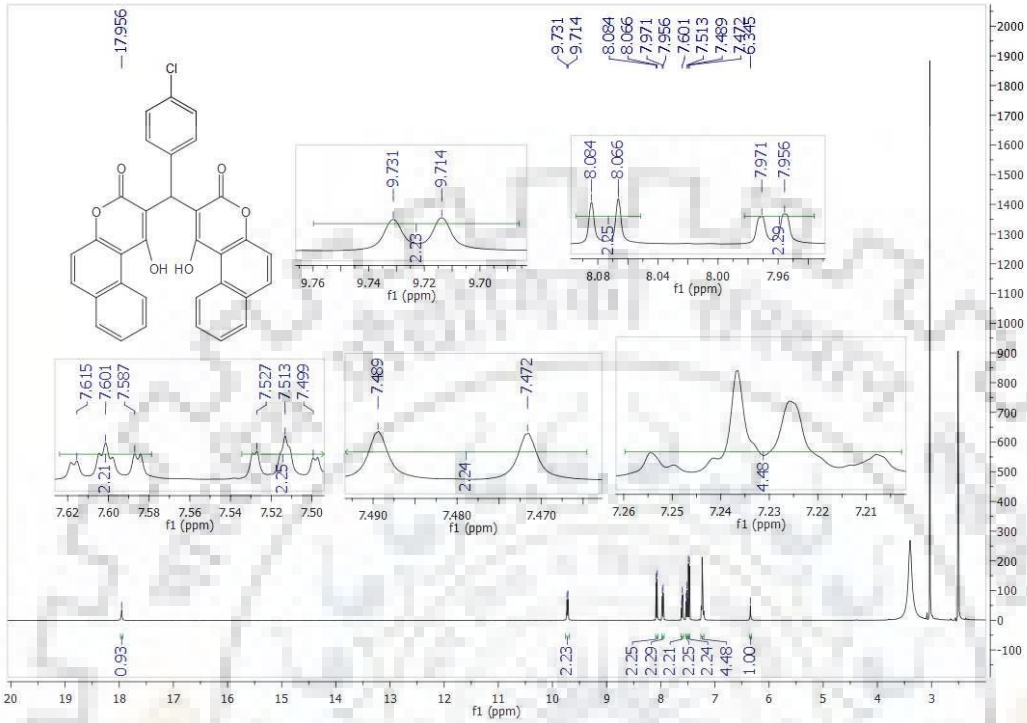


^{1}H NMR of 6q in D_2O:

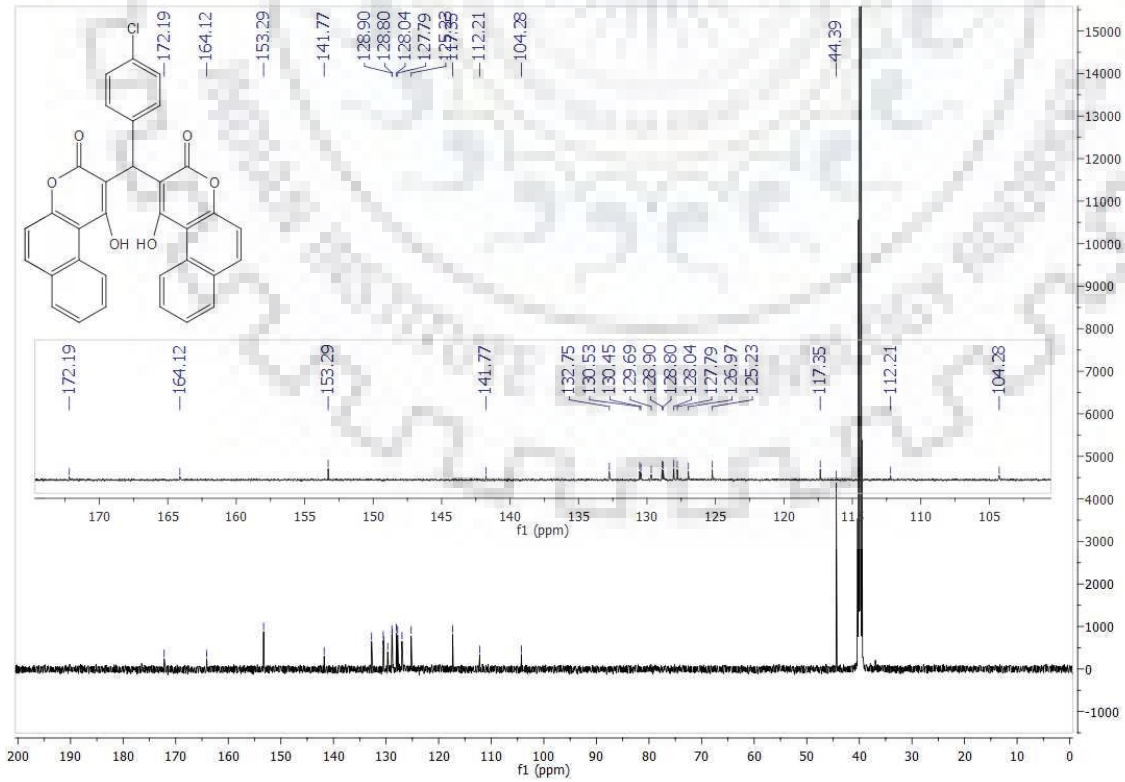


Chapter 4: Spectral information for bis(1-hydroxy-3*H*-benzo[*f*]chromenones (5a-5n)

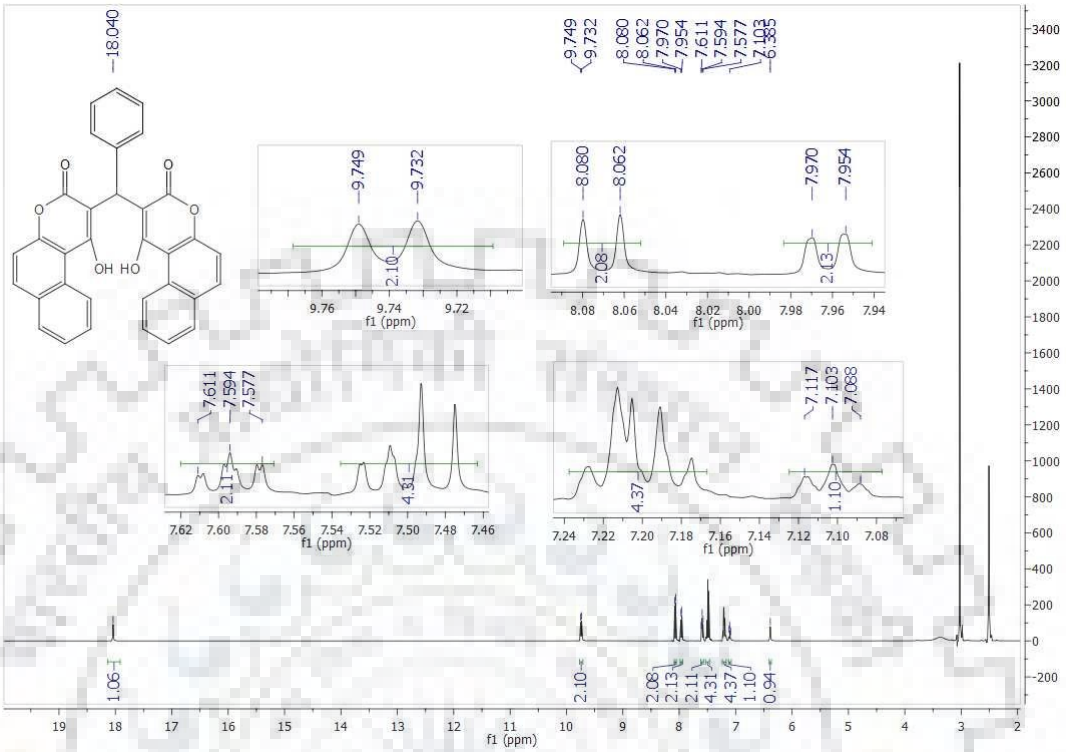
^{1}H NMR of 5a



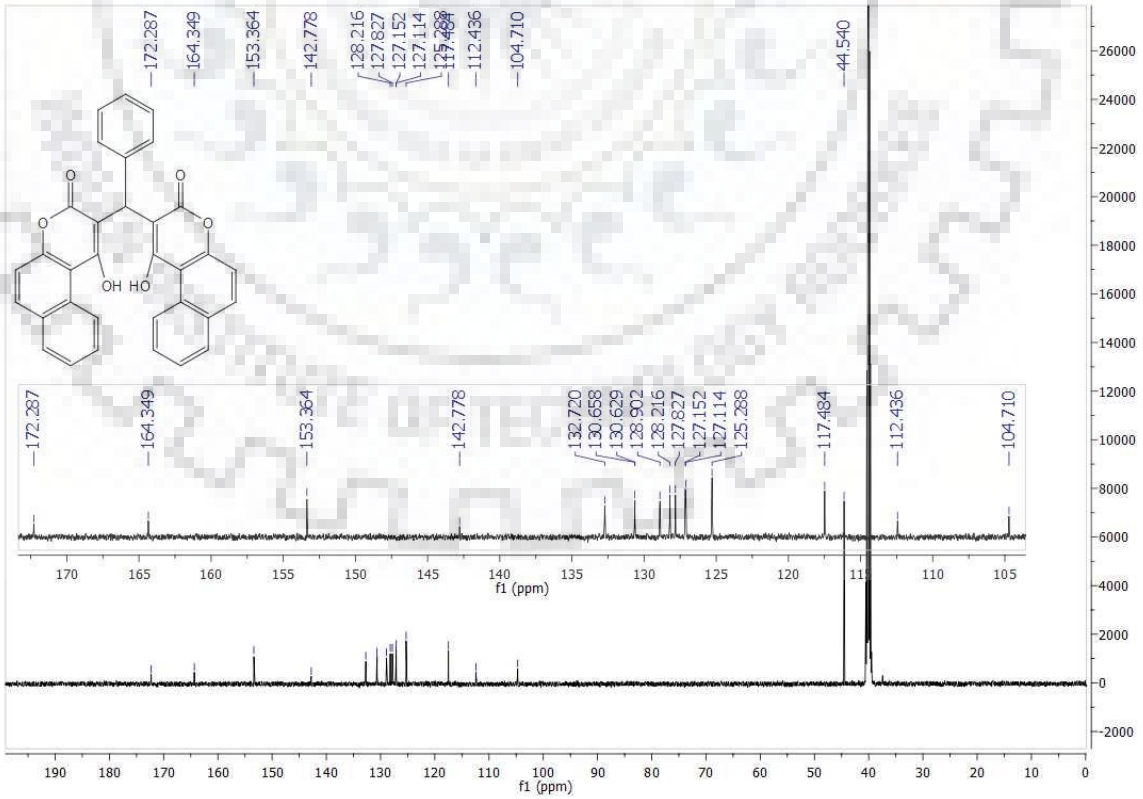
^{13}C NMR of 5a



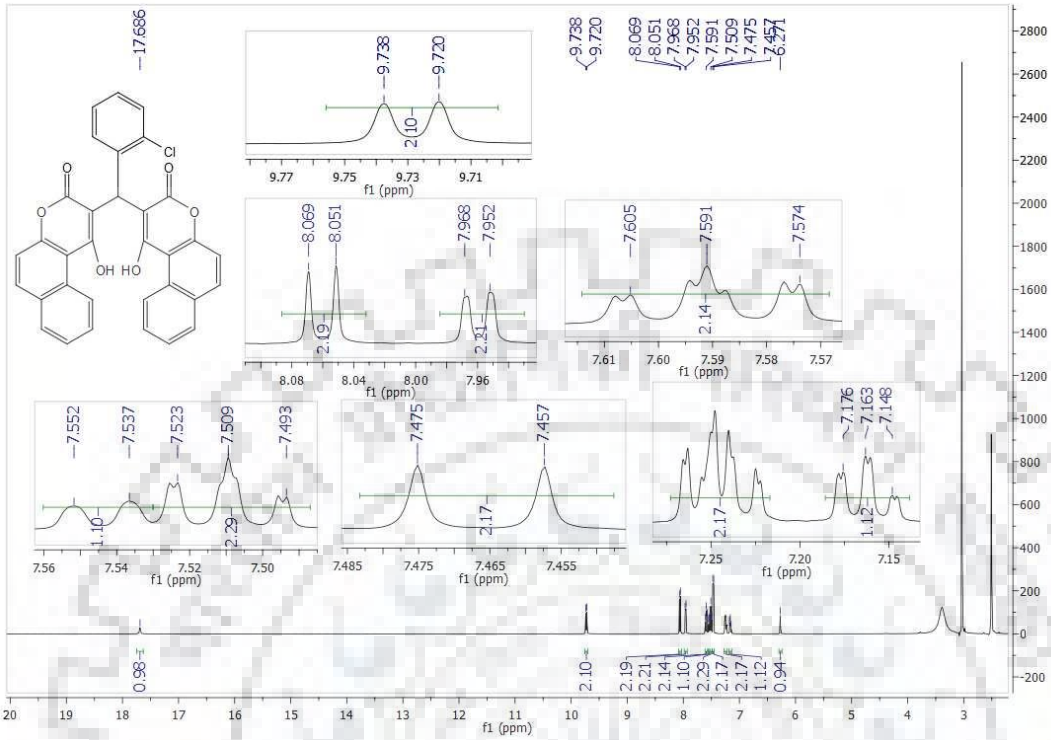
^{1}H NMR of 5b



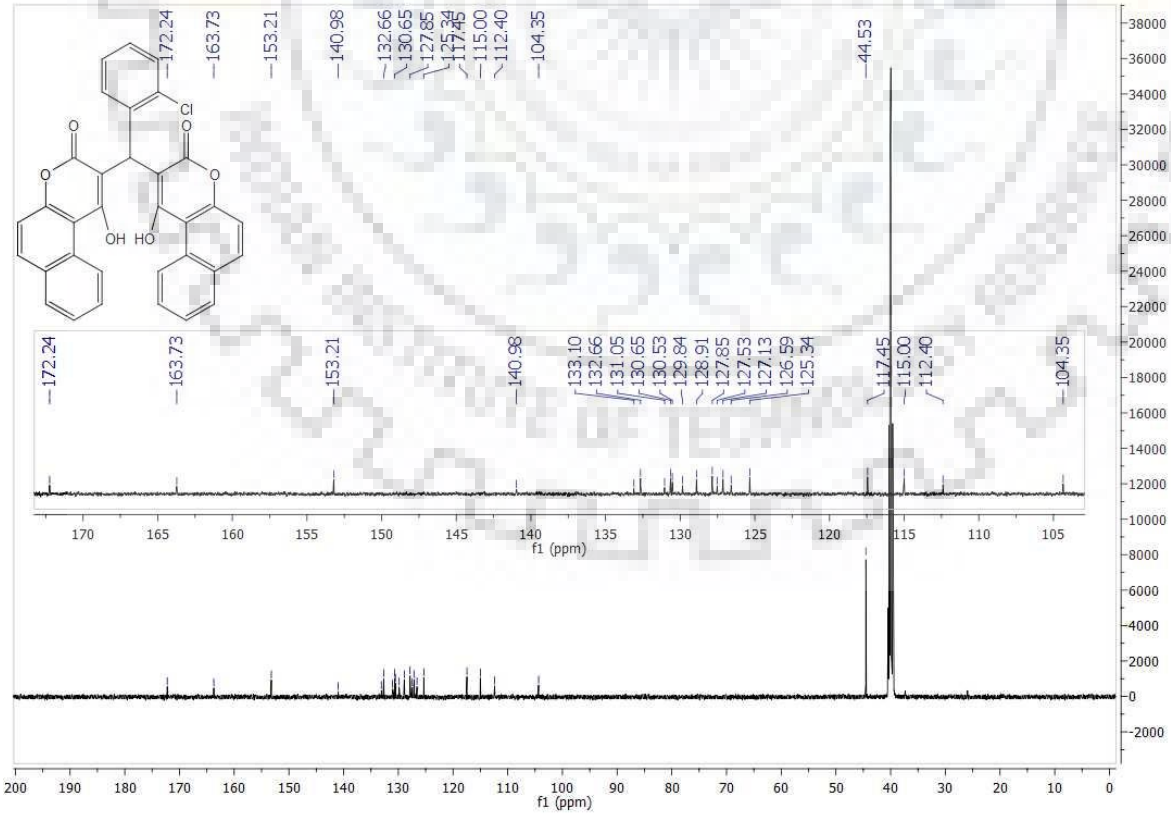
^{13}C NMR of 5b



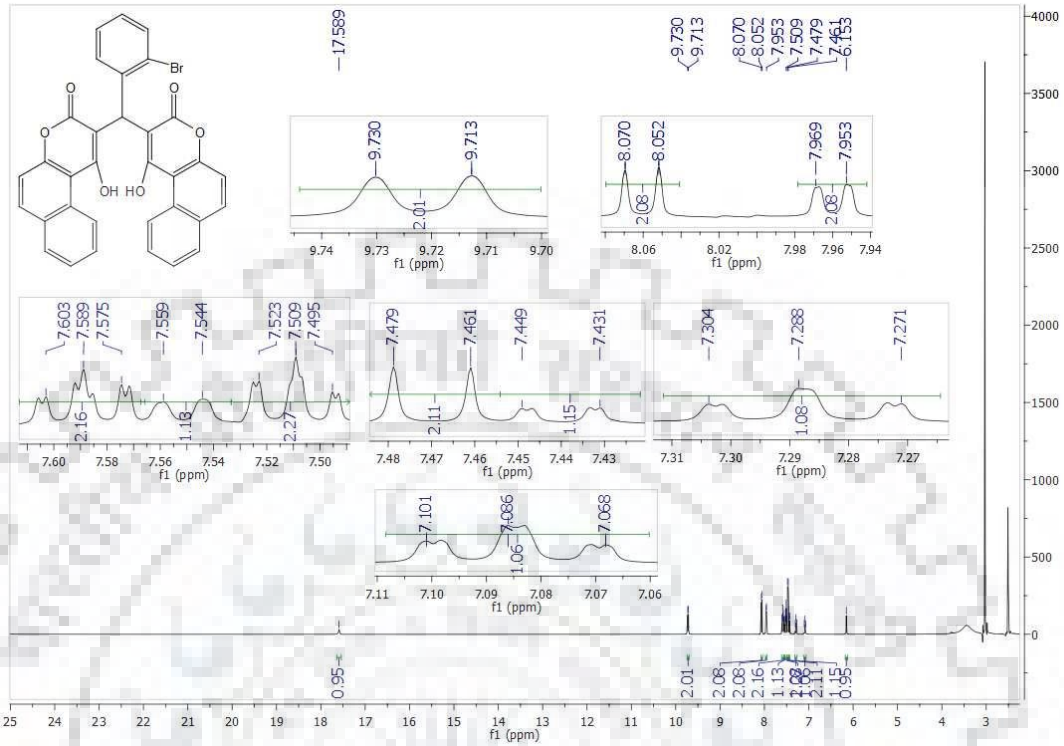
^{1}H NMR of 5c



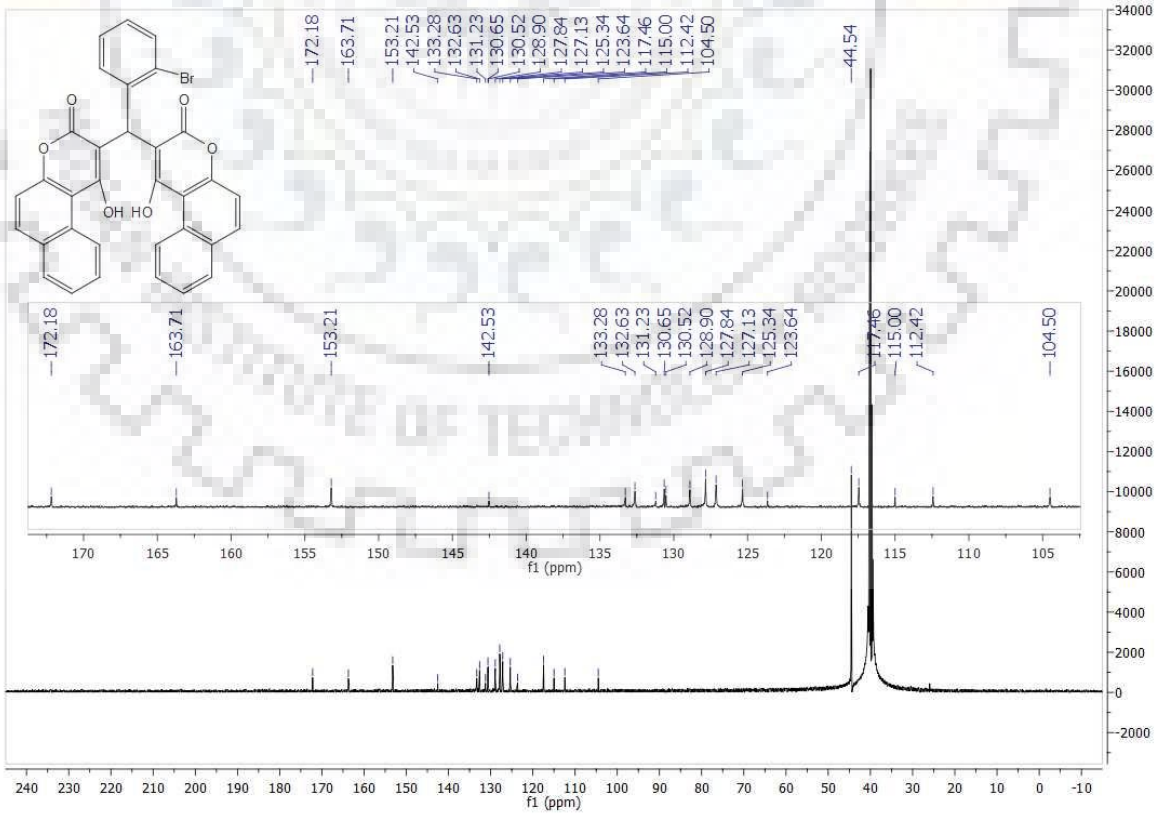
^{13}C NMR of 5c



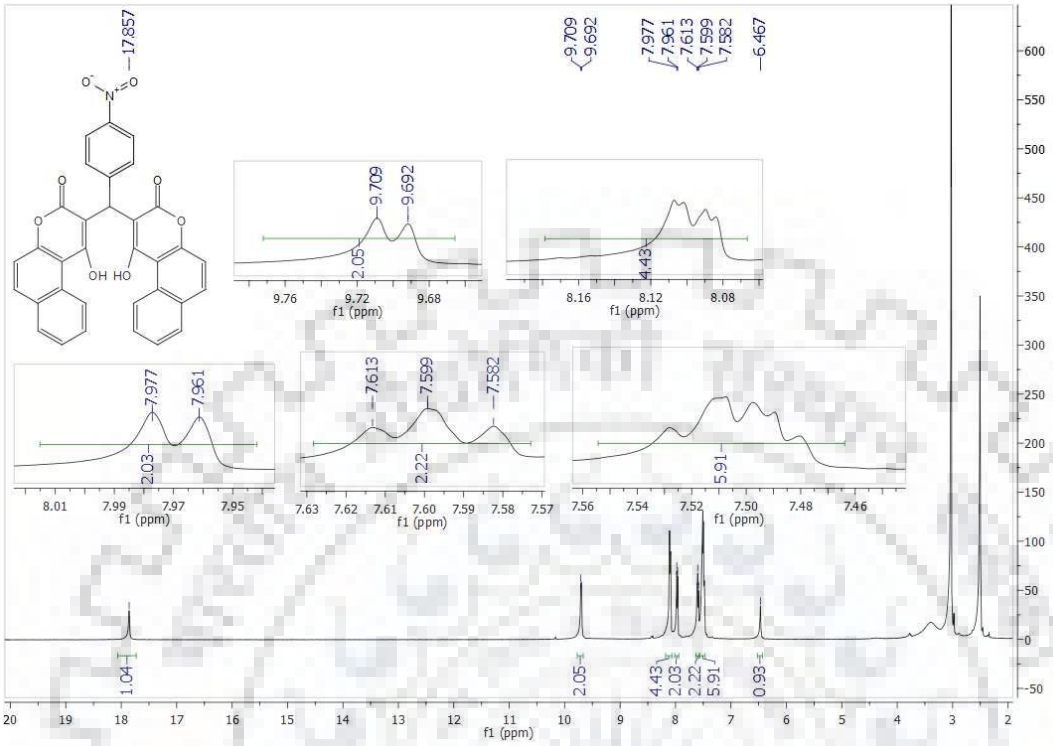
^{1}H NMR of 5d



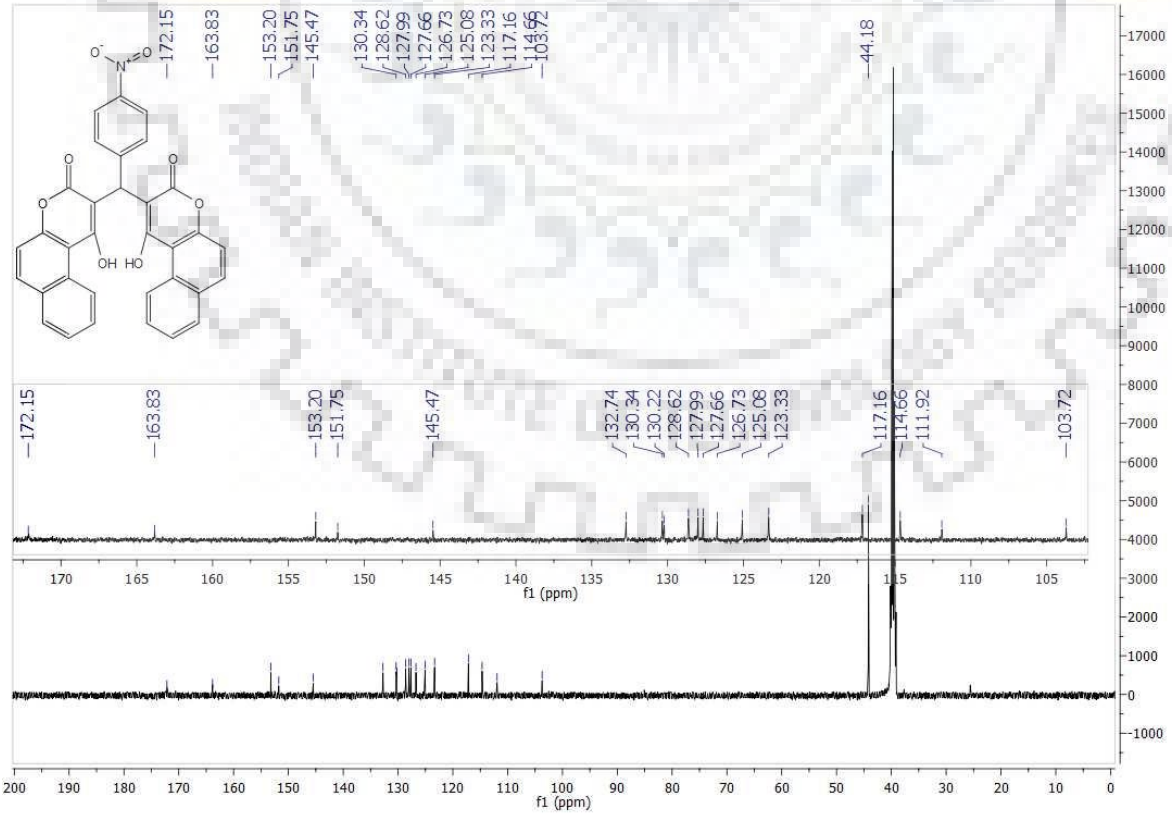
^{13}C NMR of 5d



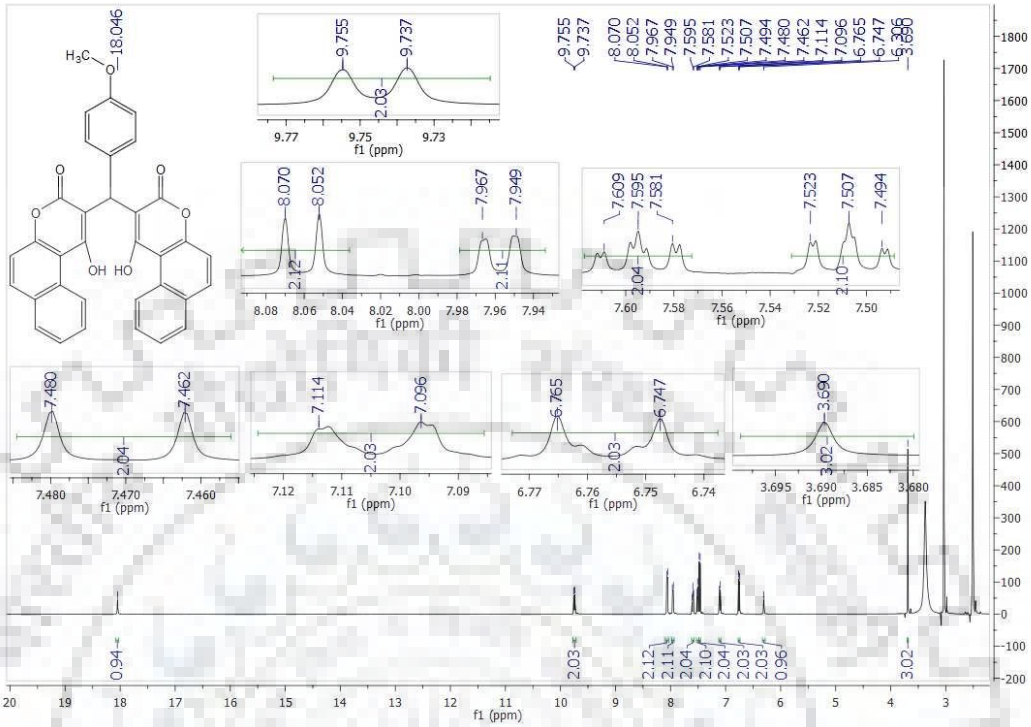
^{1}H NMR of 5e



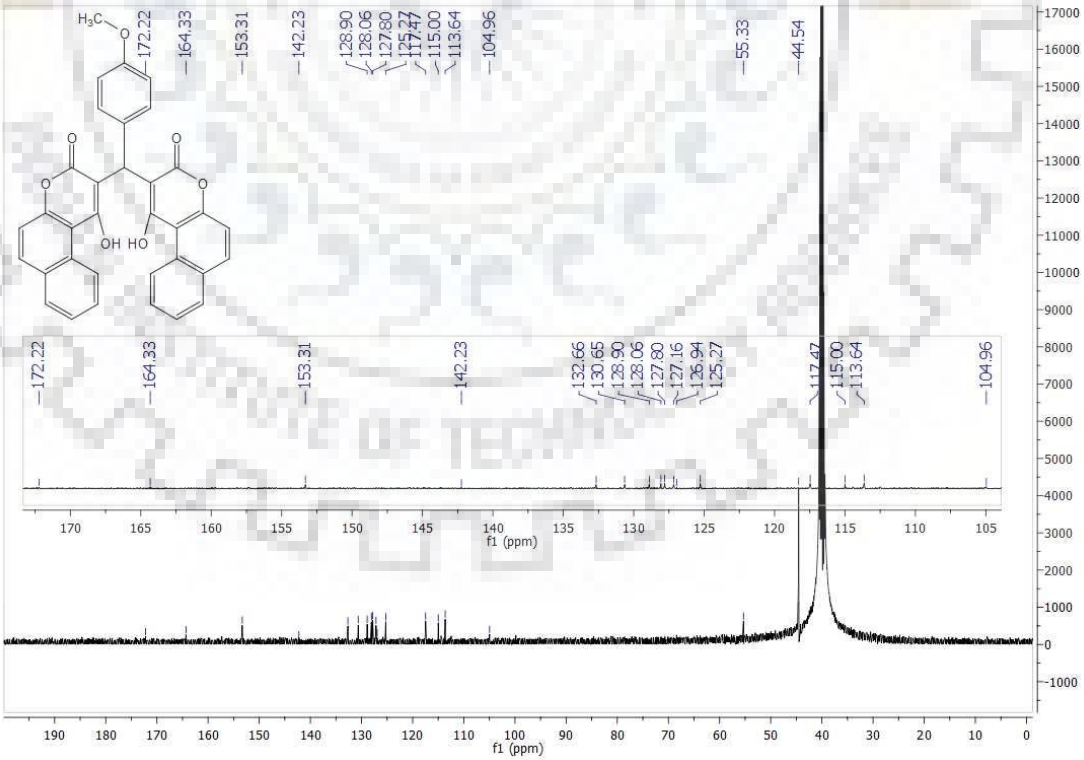
^{13}C NMR of 5e



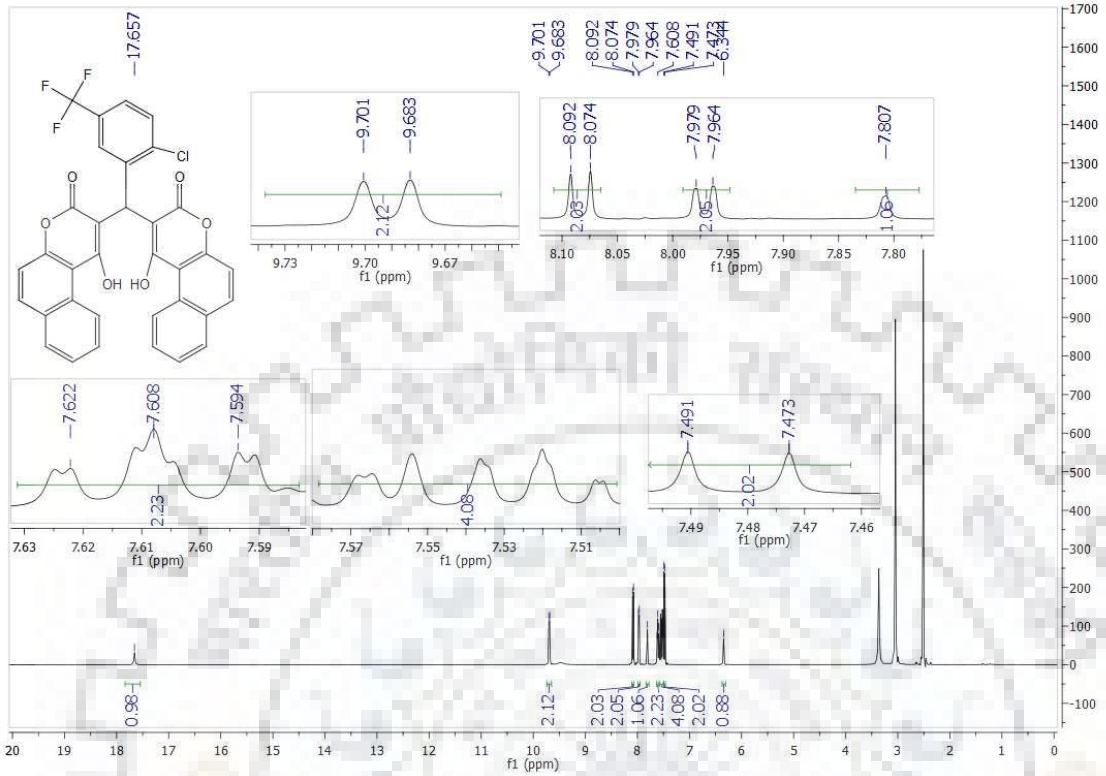
^{1}H NMR of 5f



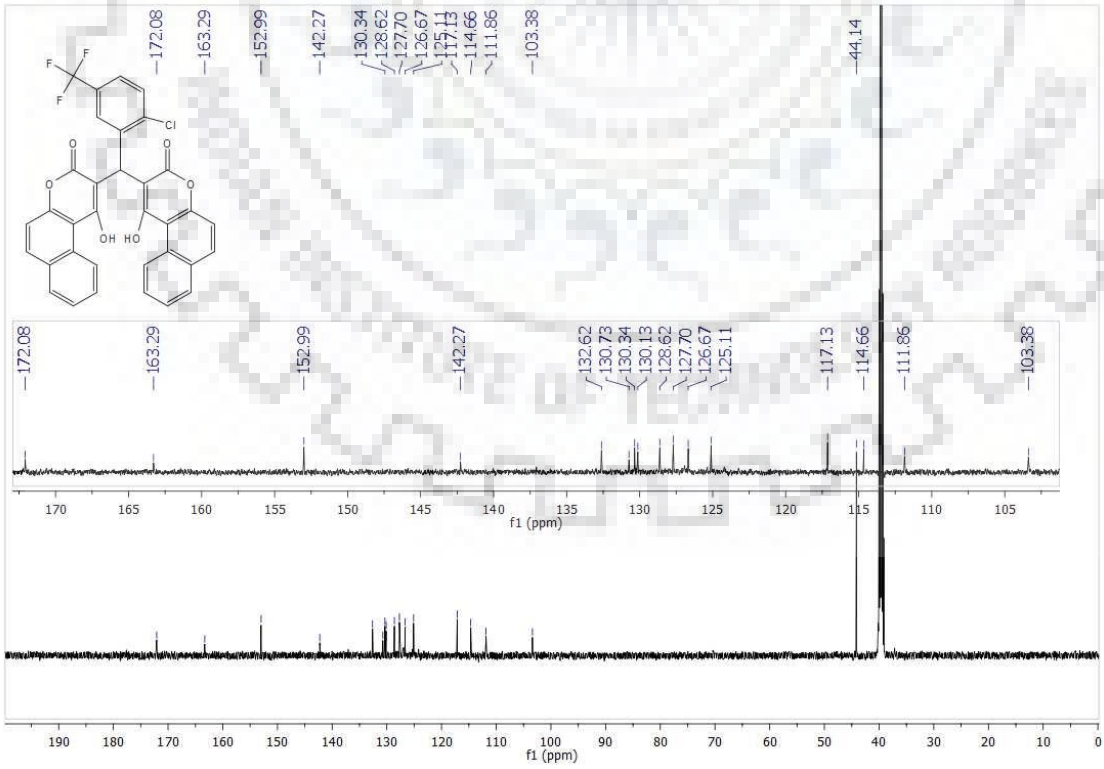
^{13}C NMR of 5f



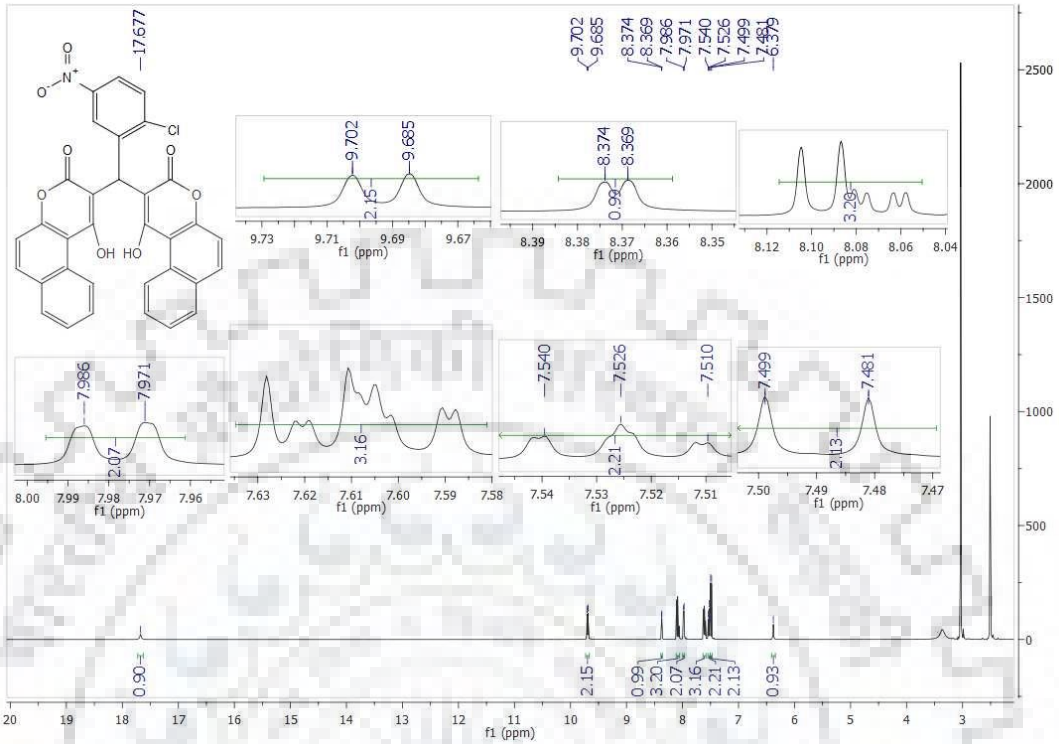
^{1}H NMR of 5g



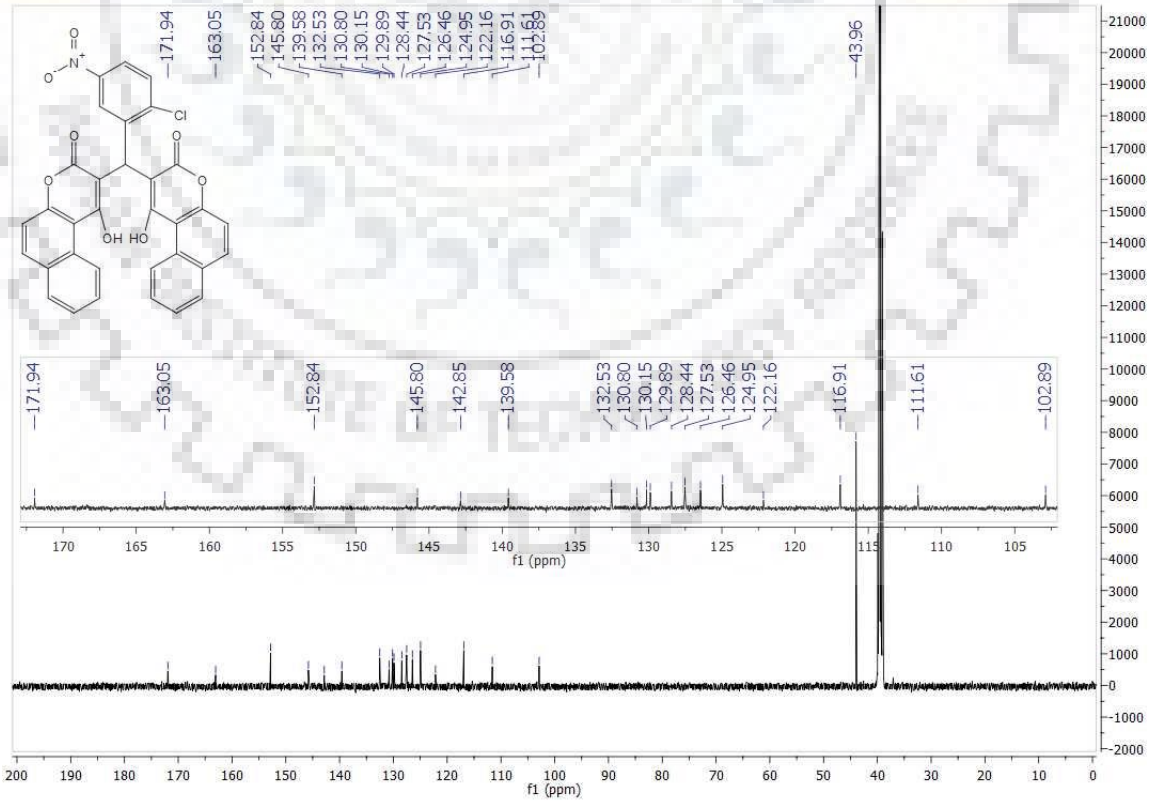
^{13}C NMR of 5g



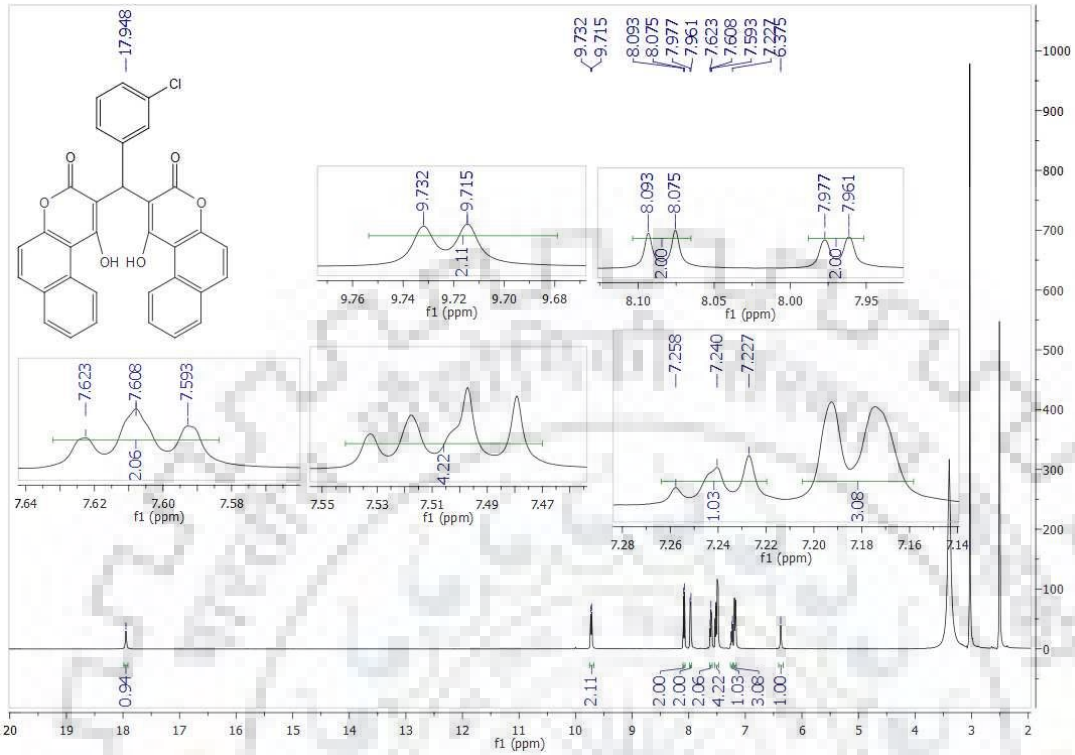
^{1}H NMR of 5h



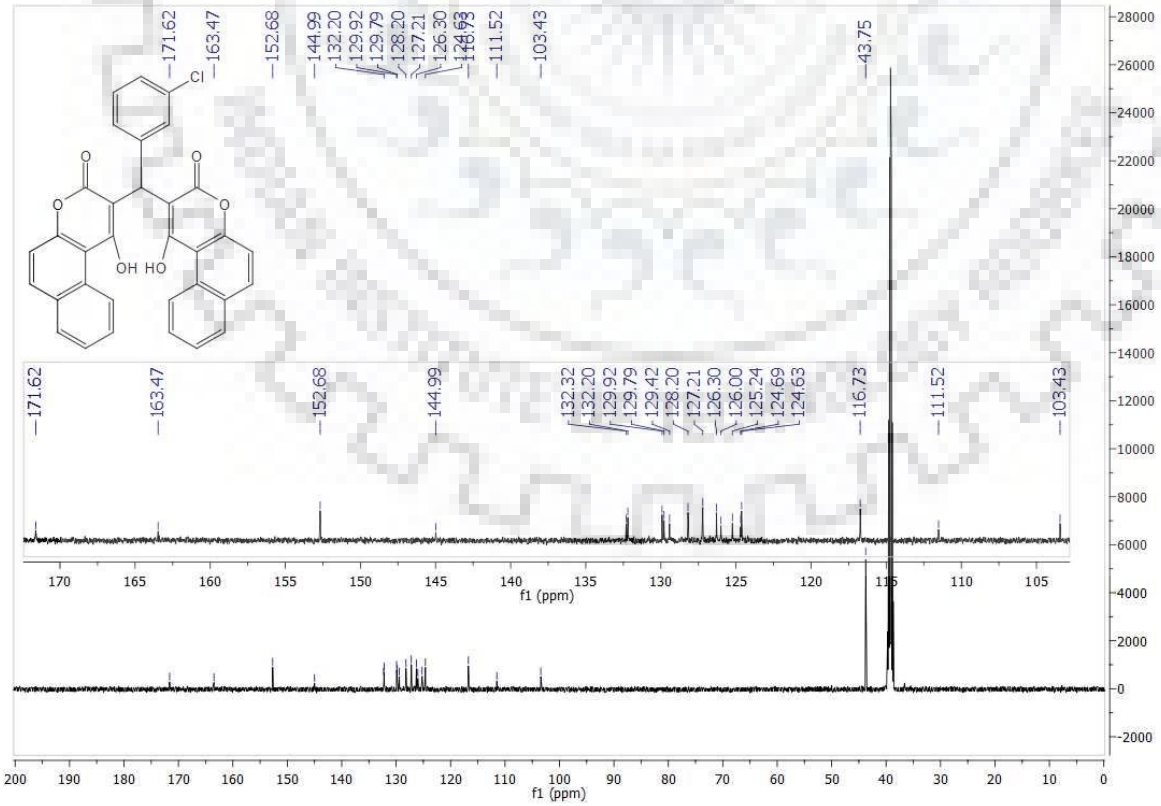
^{13}C NMR of 5h



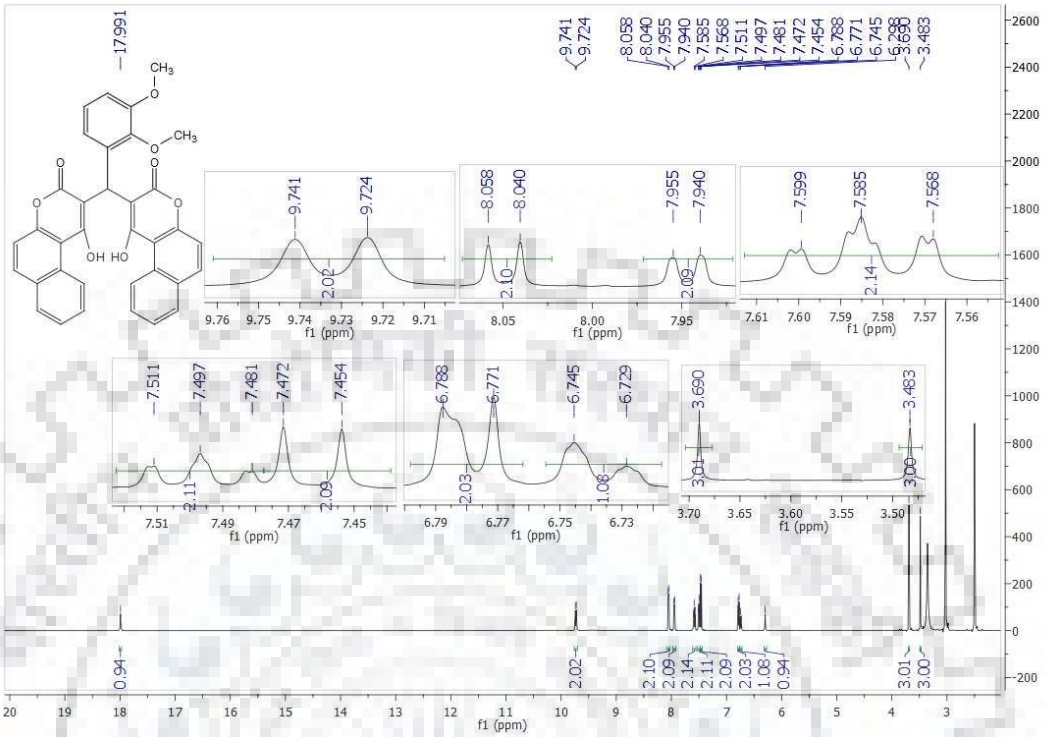
^{1}H NMR of 5i



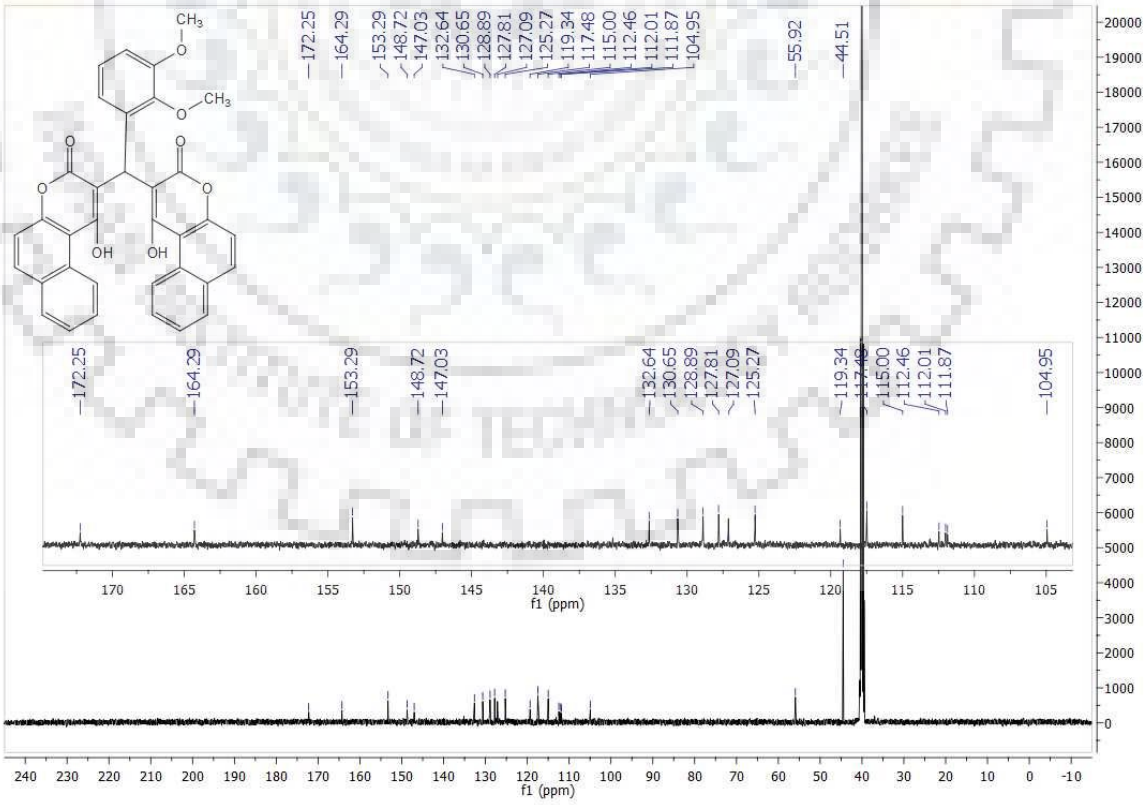
^{13}C NMR of 5i



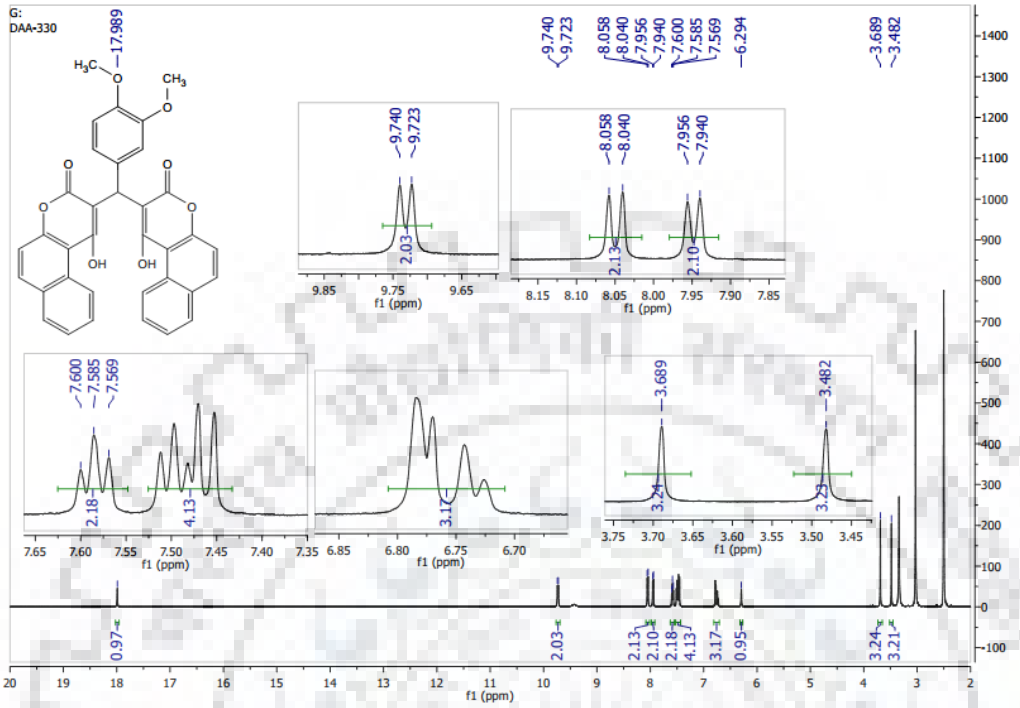
^{1}H NMR of 5j



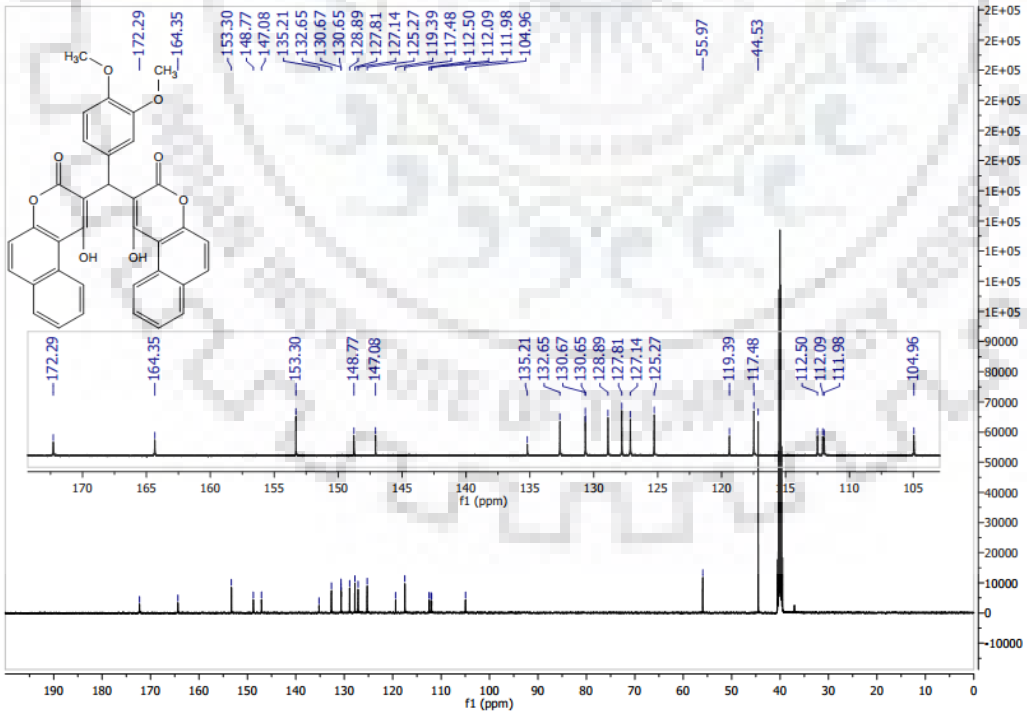
^{13}C NMR of 5j



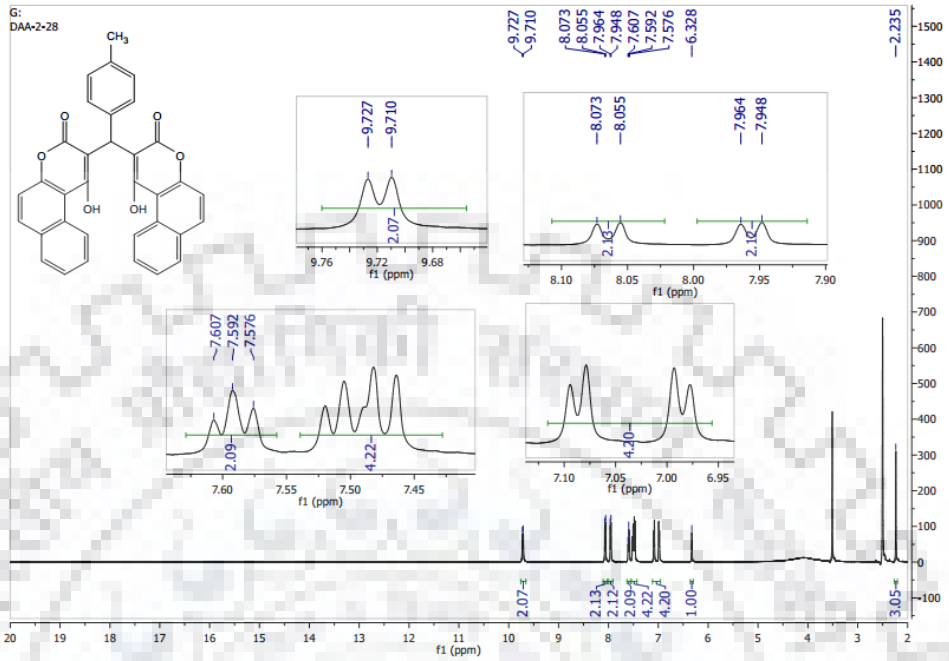
^{1}H NMR of 5k



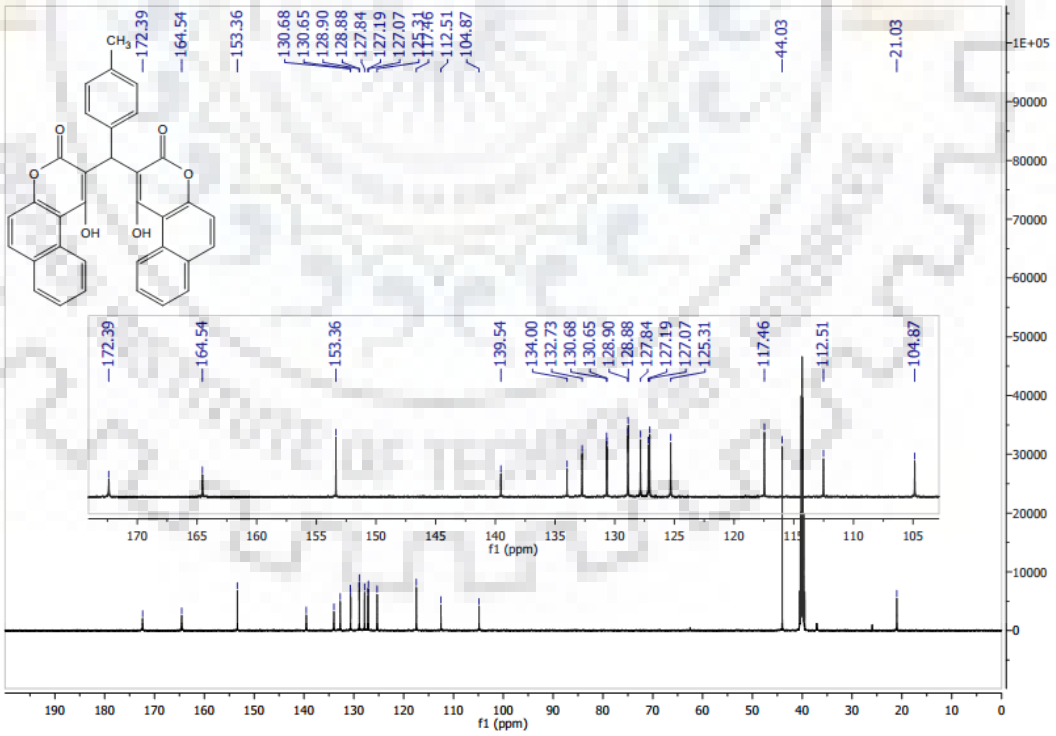
^{13}C NMR of 5k



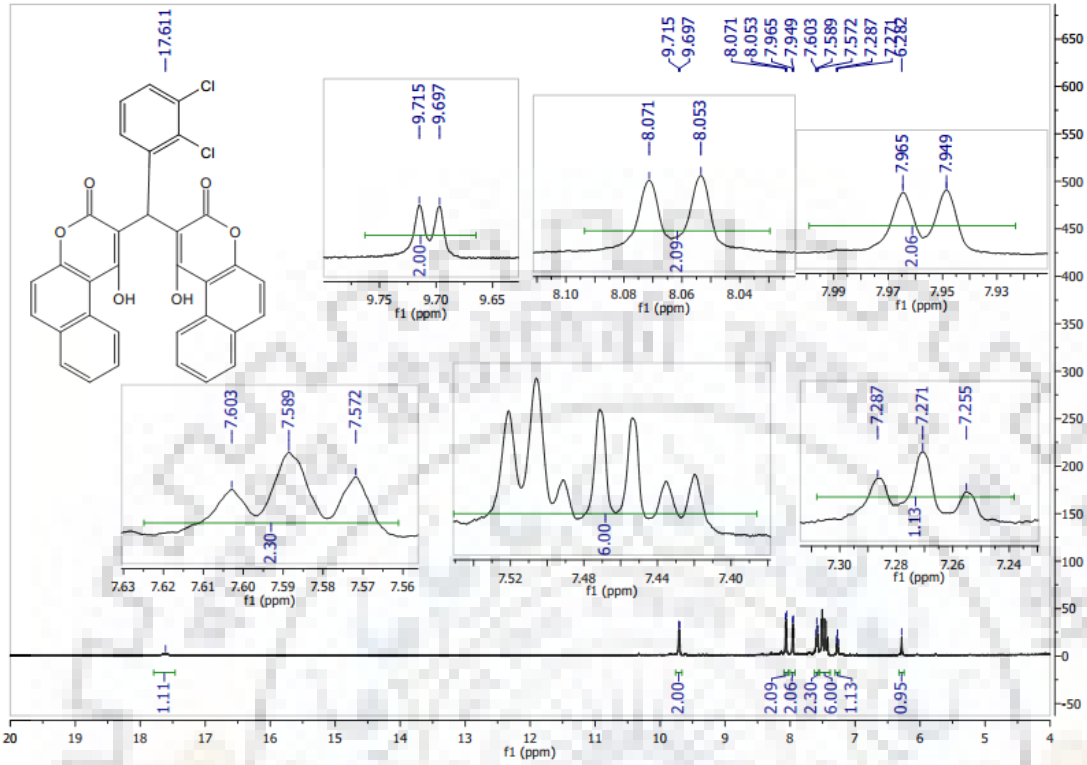
^{1}H NMR of 5l



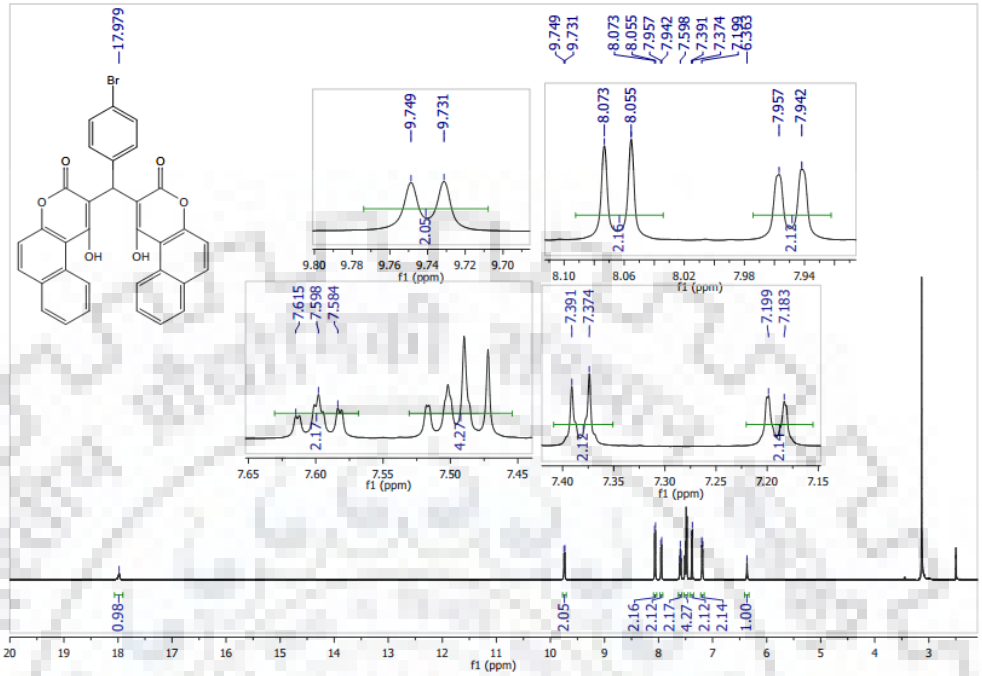
^{13}C NMR of 5l



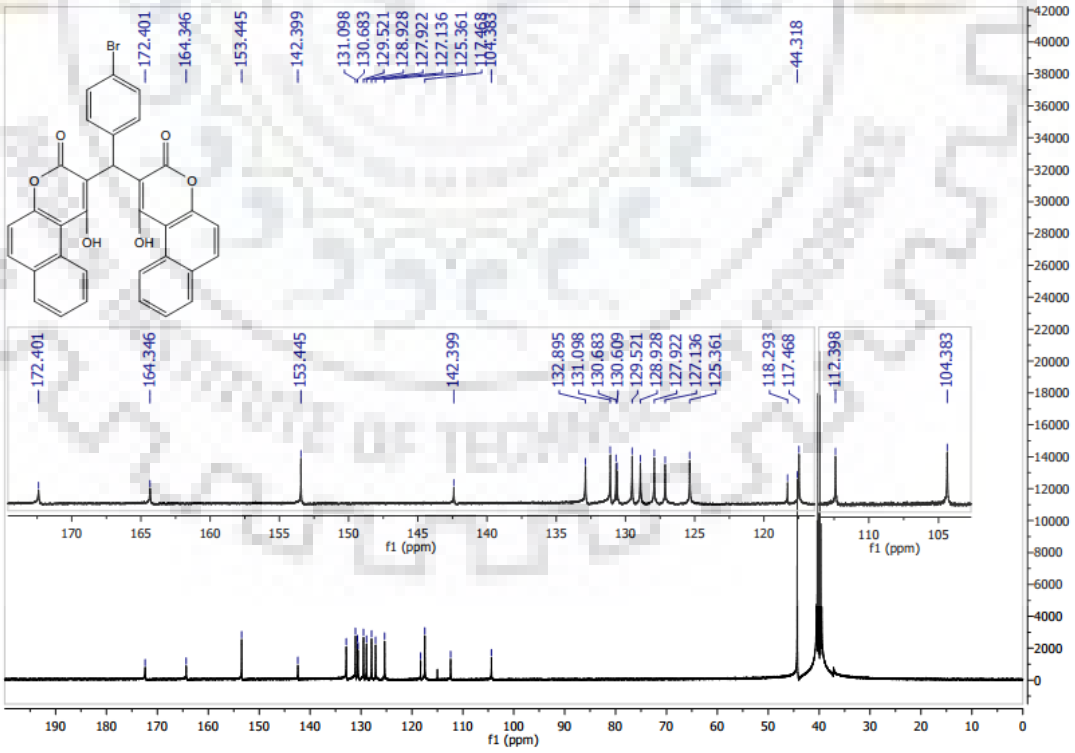
^{1}H NMR of 5m


17.611
Cl
Cl
O
O
O
O
OH
OH
9.715
9.697
8.071
8.053
7.965
7.949
7.603
7.589
7.572
7.287
7.271
6.282
2.00
2.09
2.06
2.30
6.00
1.13
0.95
1.11
f1 (ppm)

^{1}H NMR of 5n

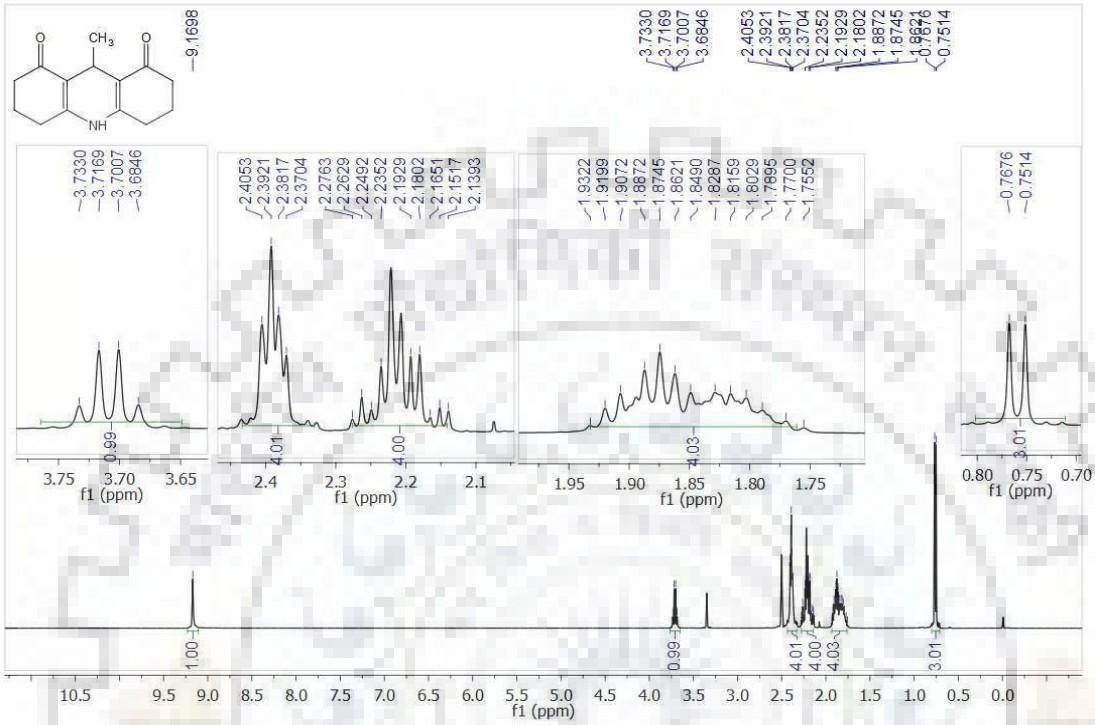


^{13}C NMR of 5n

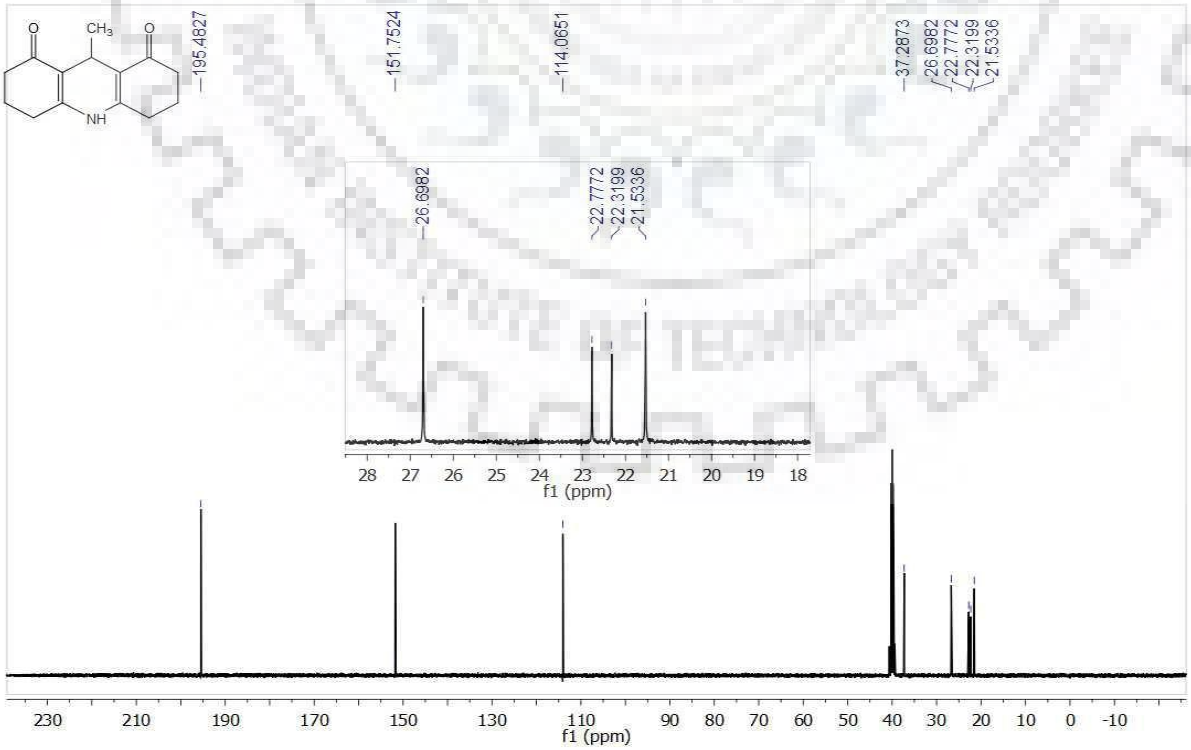


Chapter 5: Spectral information for methyl substituted hexahydroacridine-1,8(2*H*,5*H*)-dione (19a-19d)

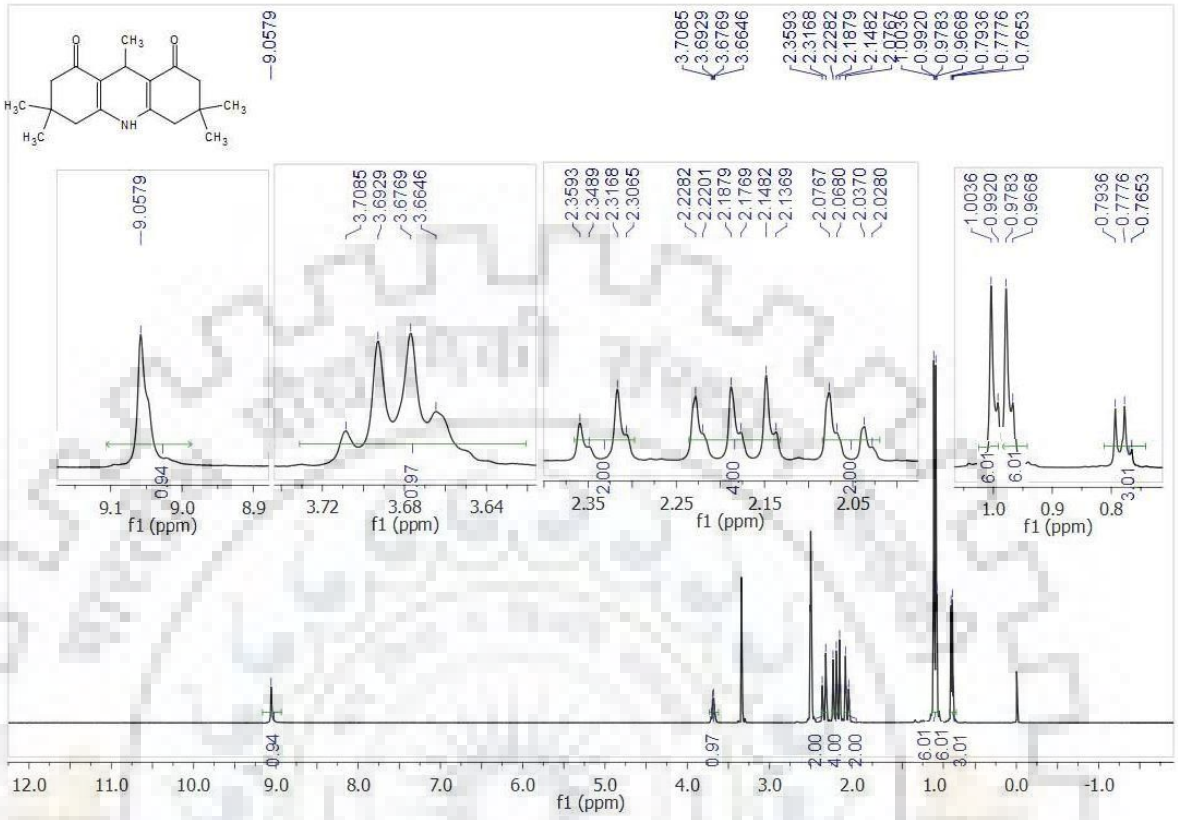
^{1}H NMR of 19a



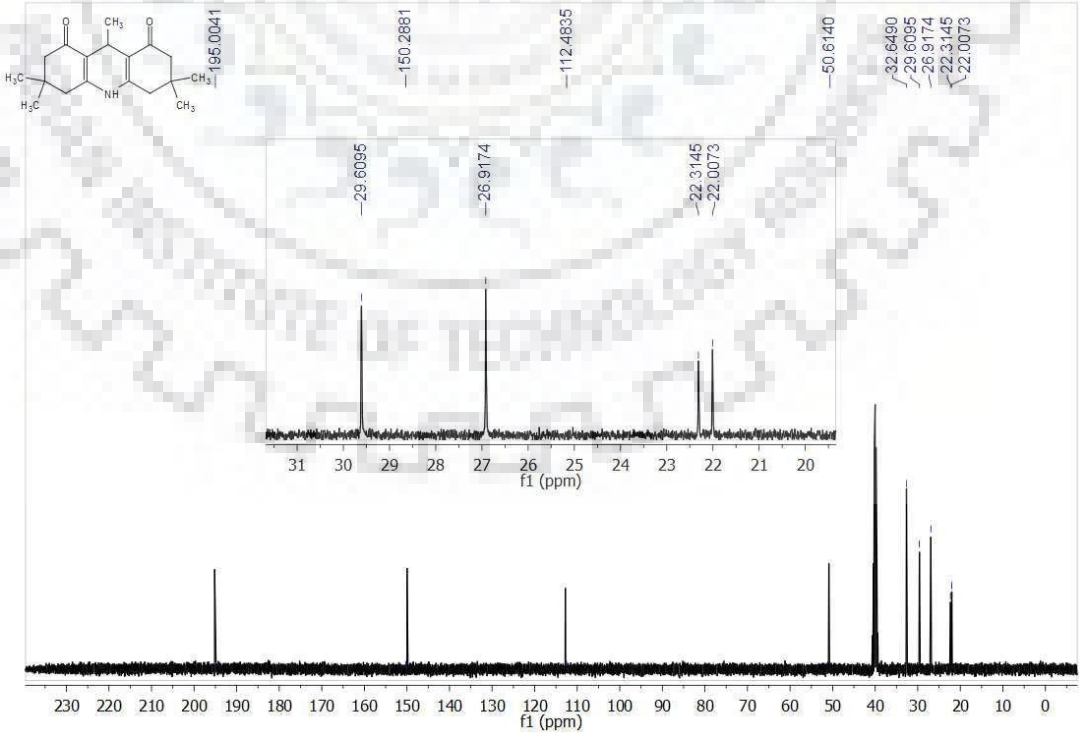
^{13}C NMR of 19a



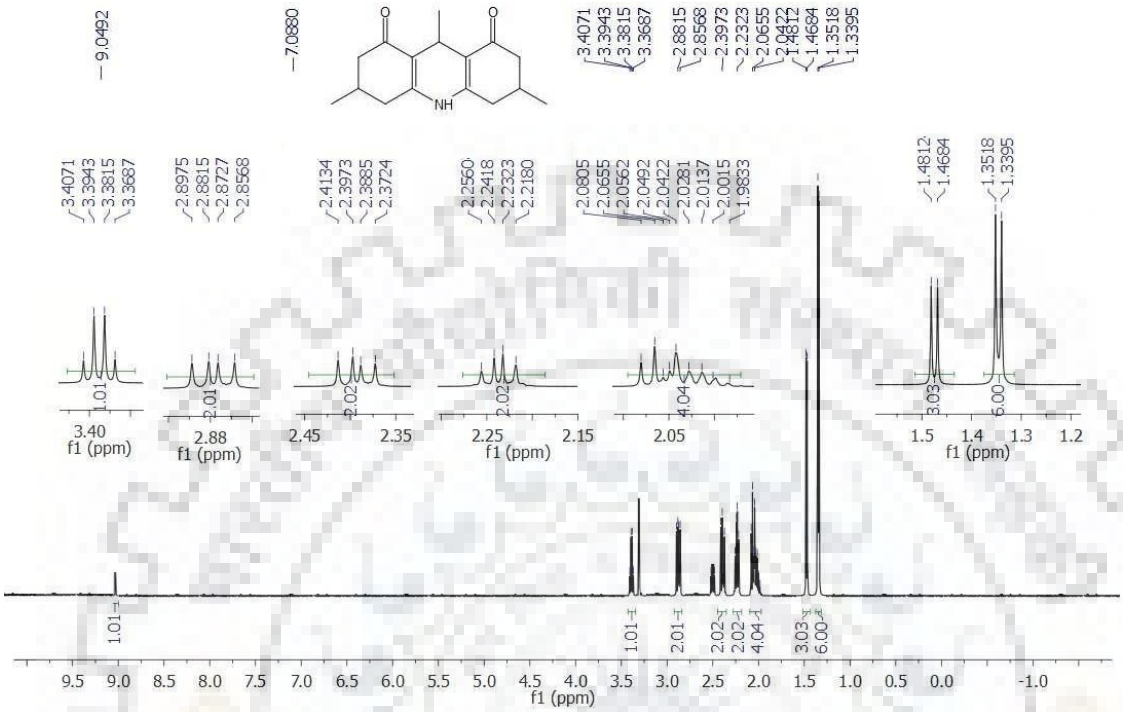
^{1}H NMR of 19b



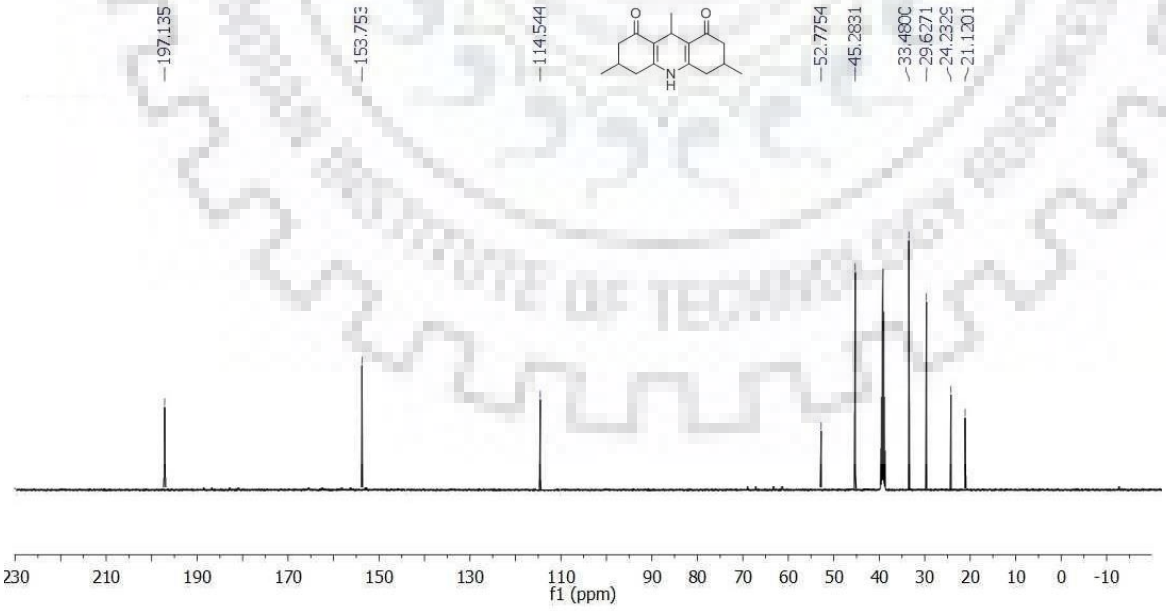
^{13}C NMR of 19b



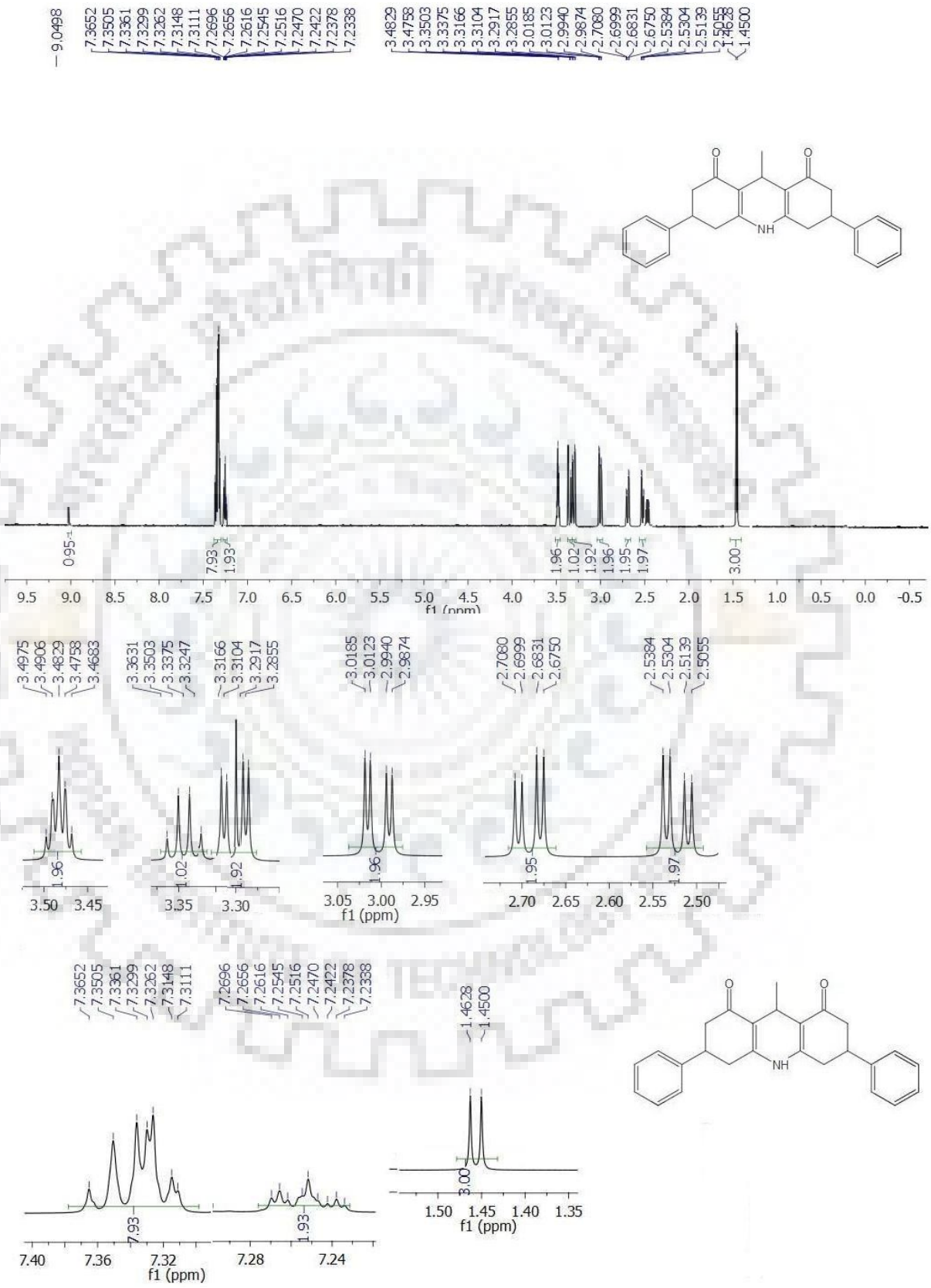
^{1}H NMR of 19c



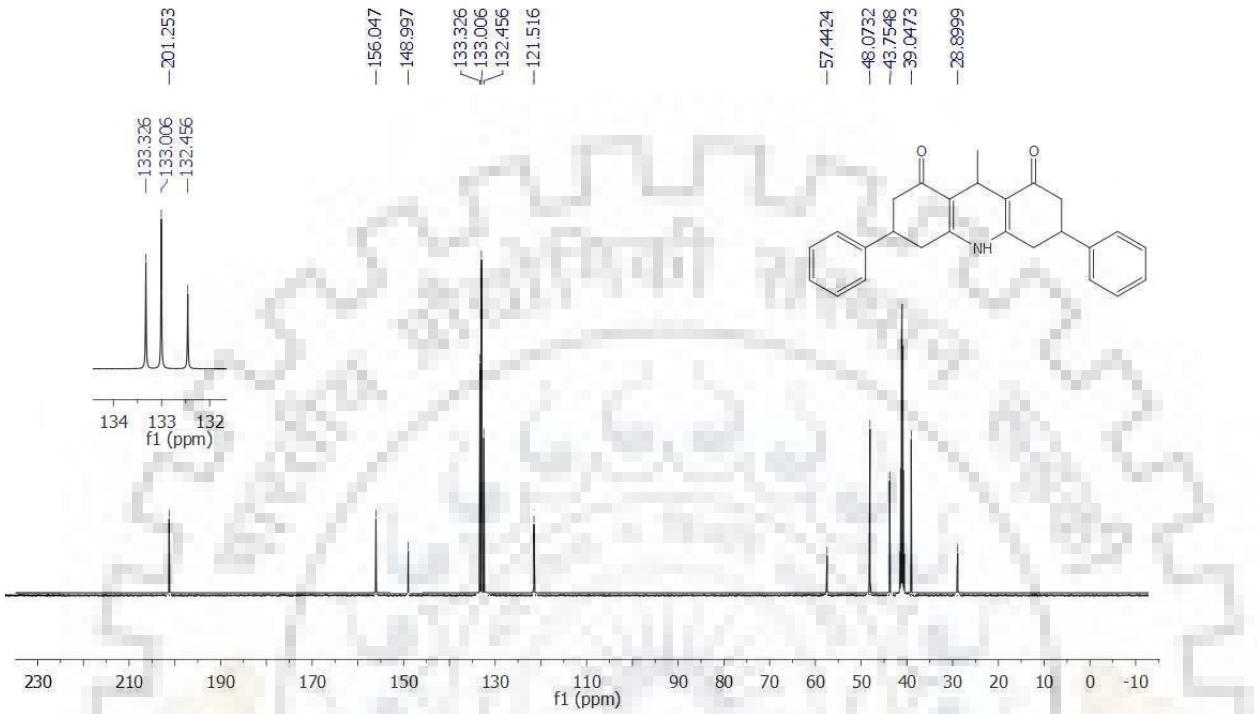
^{13}C NMR of 19c



^{1}H NMR of 19d

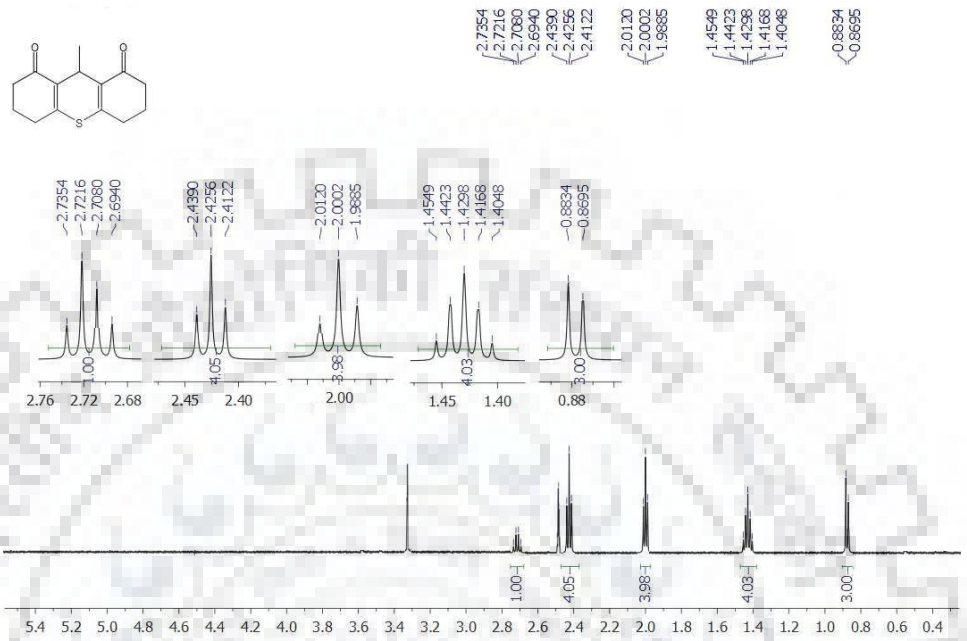

9.0498
7.3652
7.3505
7.3361
7.3299
7.3262
7.3148
7.3111
7.2696
7.2656
7.2616
7.2545
7.2516
7.2470
7.2422
7.2378
7.2338
3.4829
3.4758
3.3503
3.3375
3.3166
3.3104
3.2917
3.2855
3.0185
3.0123
2.9940
2.9874
2.7080
2.6999
2.6831
2.6750
2.5384
2.5304
2.5139
2.5055
1.4628
1.4500
NH
0.95
7.93
1.93
1.96
1.02
1.92
1.96
1.95
1.97
3.00
f1 (ppm)
1.96
1.02
1.92
1.96
1.95
1.97
f1 (ppm)
7.93
1.93
3.00
f1 (ppm)

^{13}C NMR of 19d

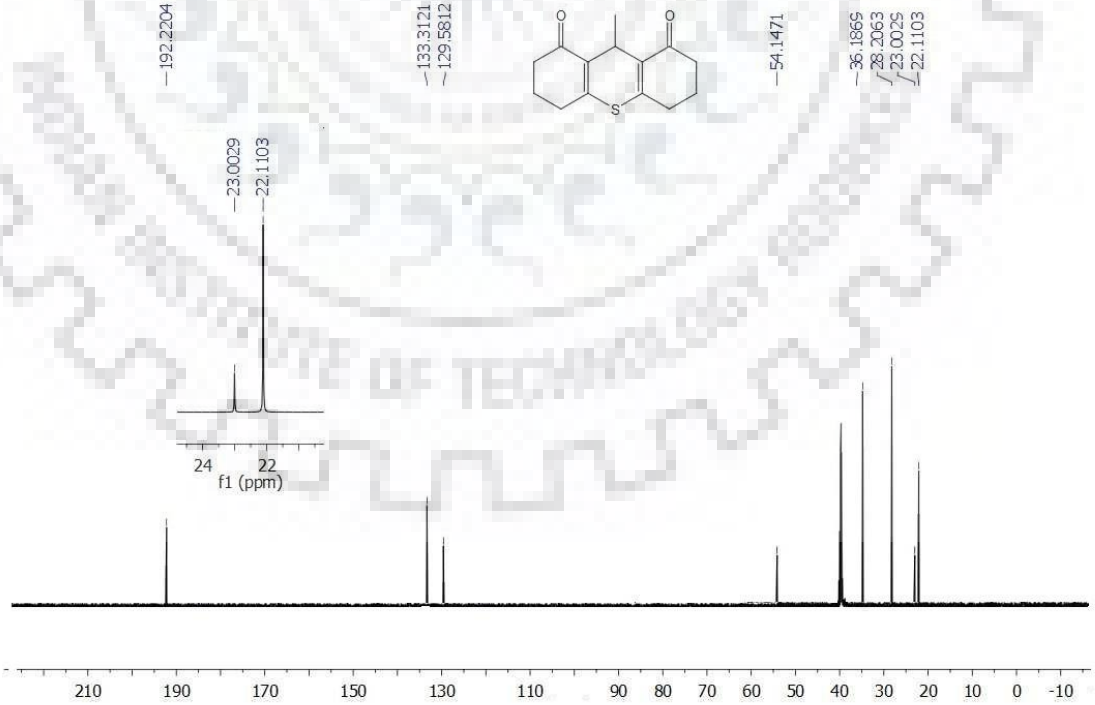


Spectral information for methyl substituted thioxanthene-1,8(2*H*)-dione (21a-21c)

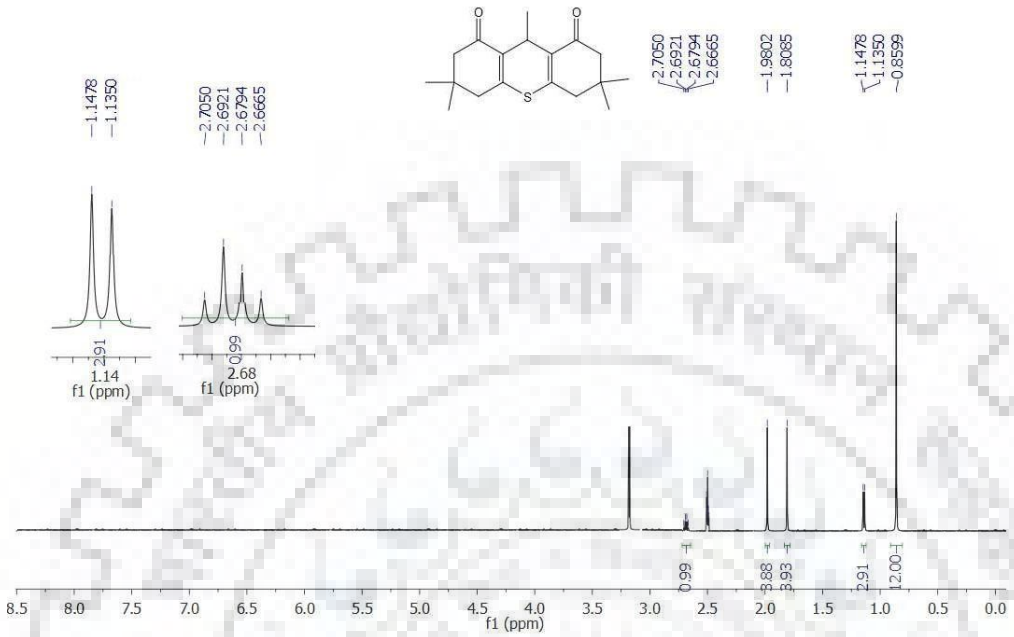
^{1}H NMR of 21a



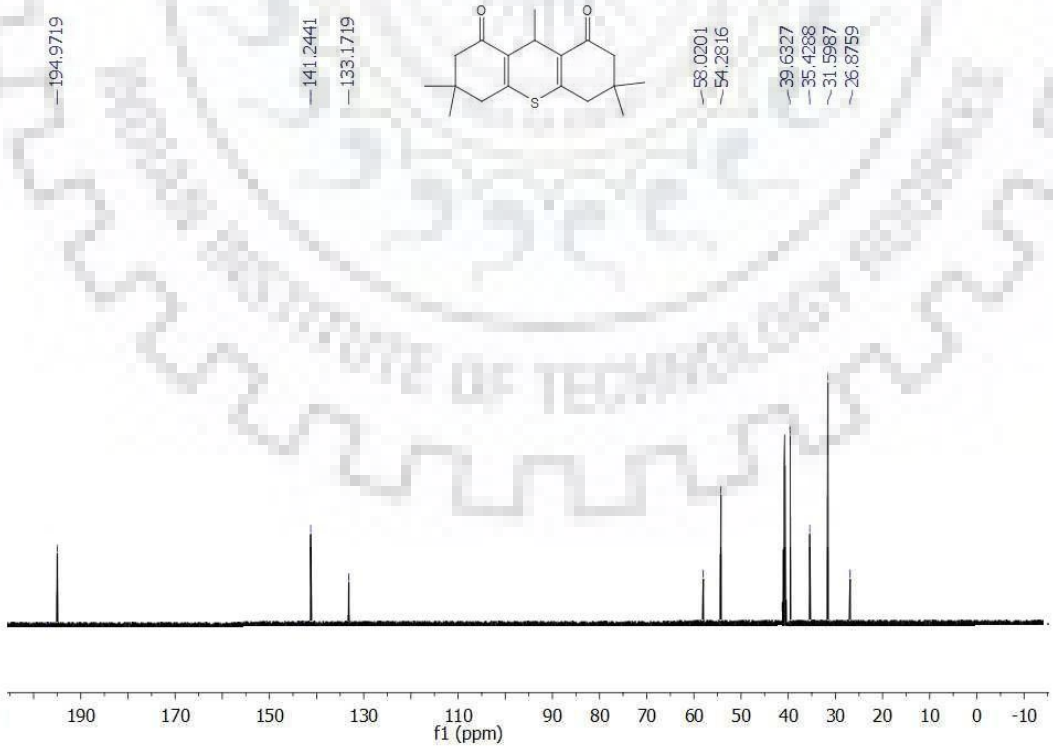
^{13}C NMR of 21a



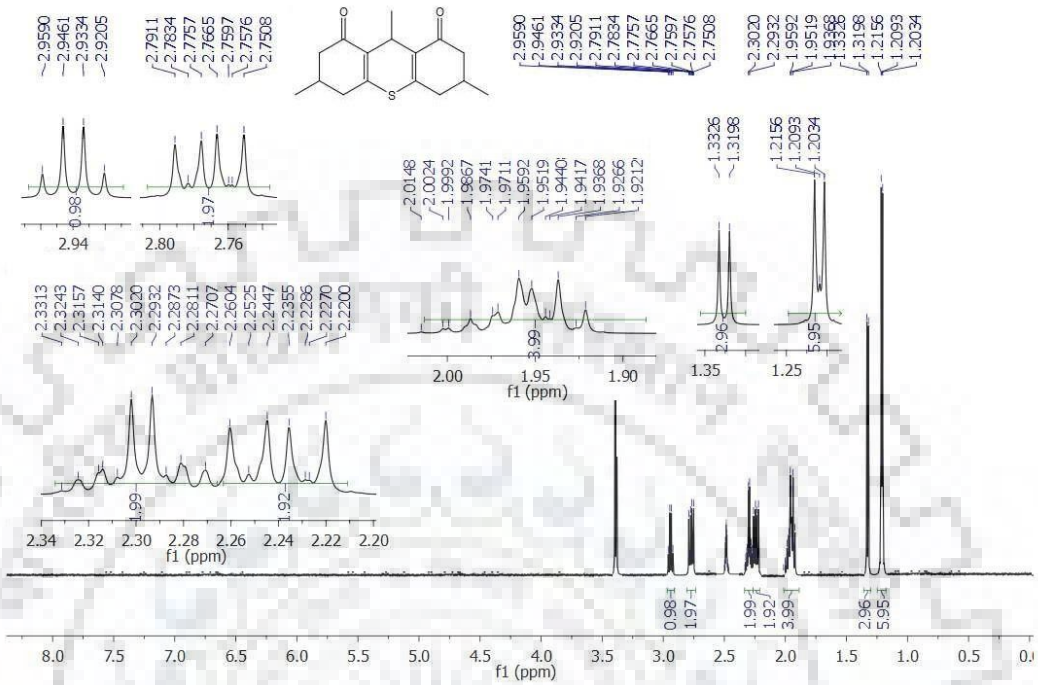
^{1}H NMR of 21b



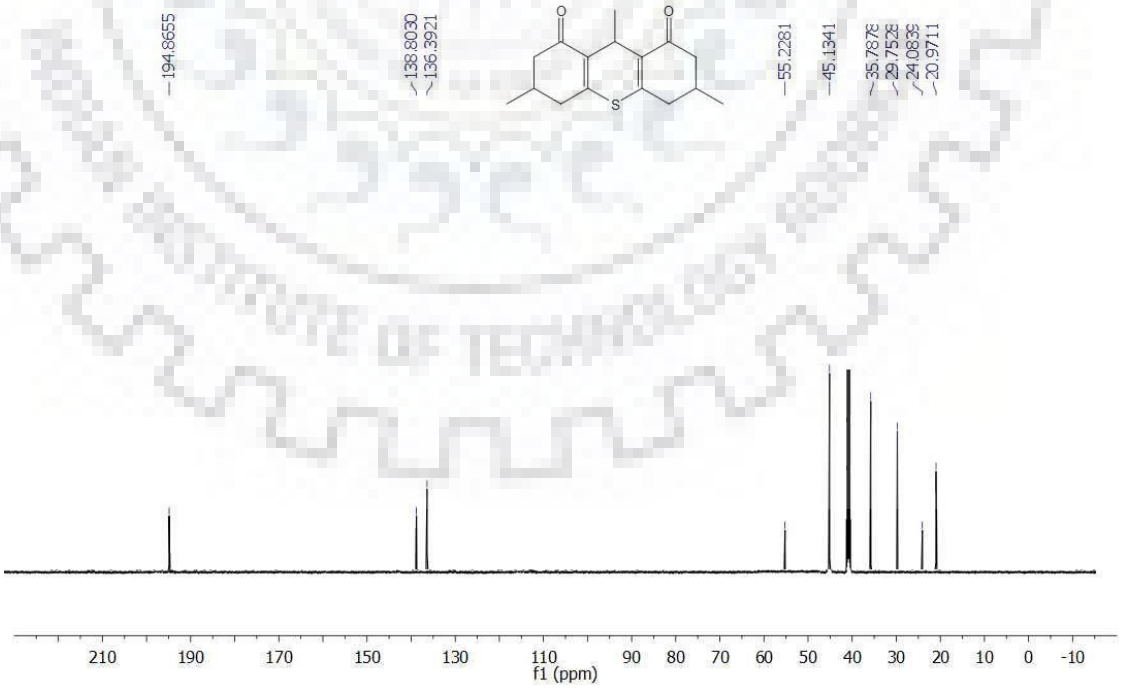
^{13}C NMR of 21b



^{1}H NMR of 21c

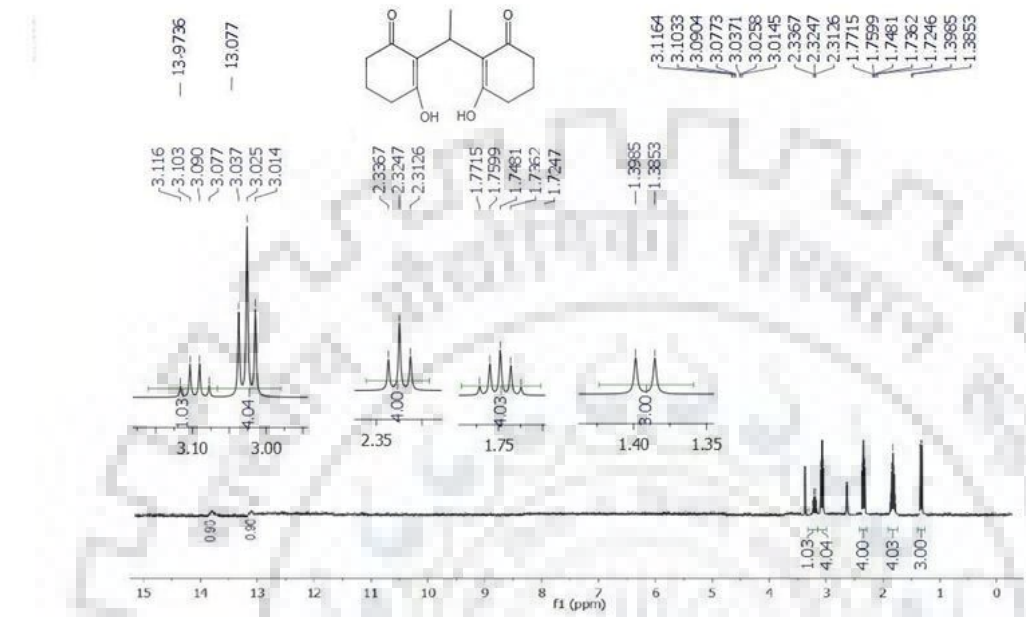


^{13}C NMR of 21c

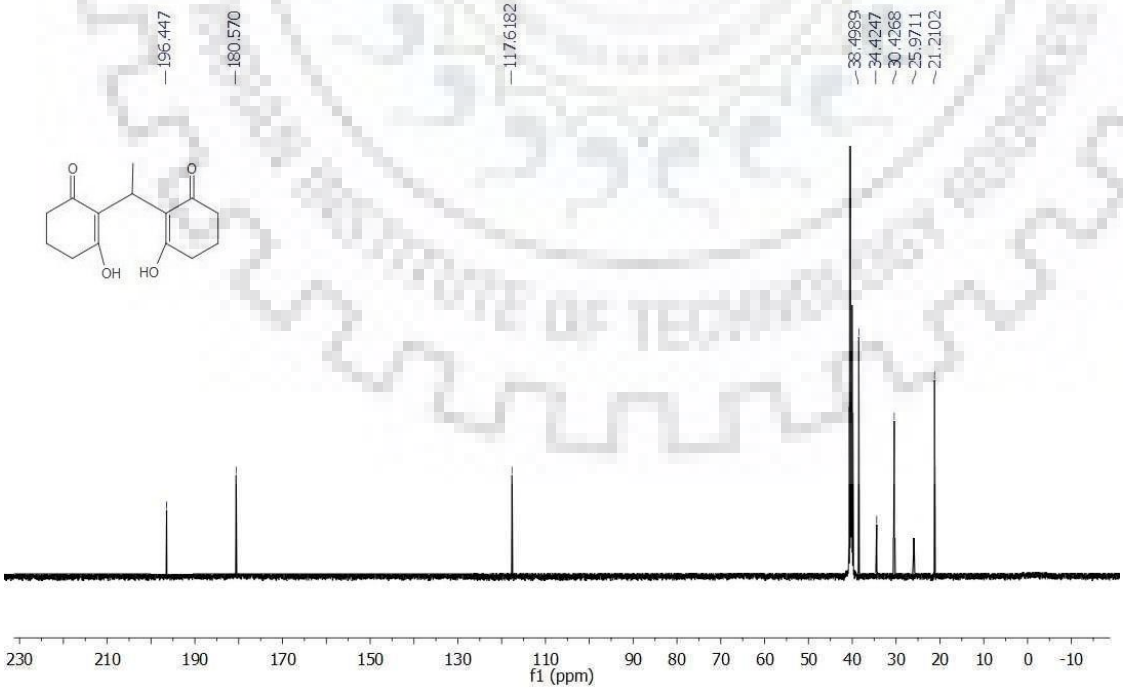


Spectral information for methyl substituted bis(3-hydroxycyclohex-2-enone) (22a-22d)

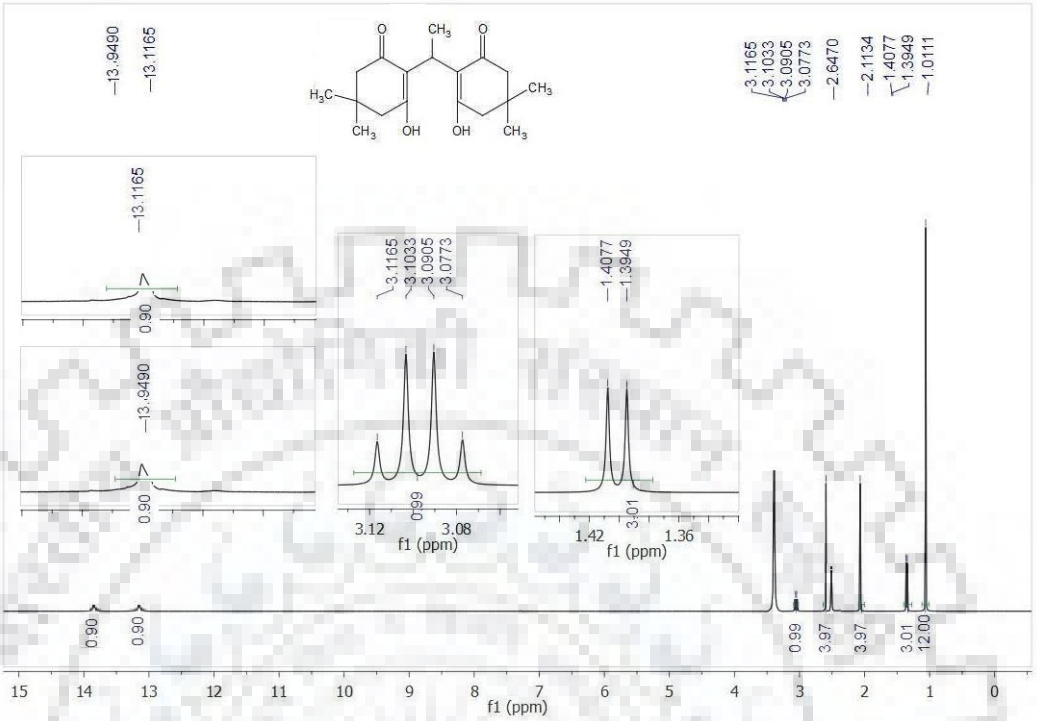
^{1}H NMR of 22a



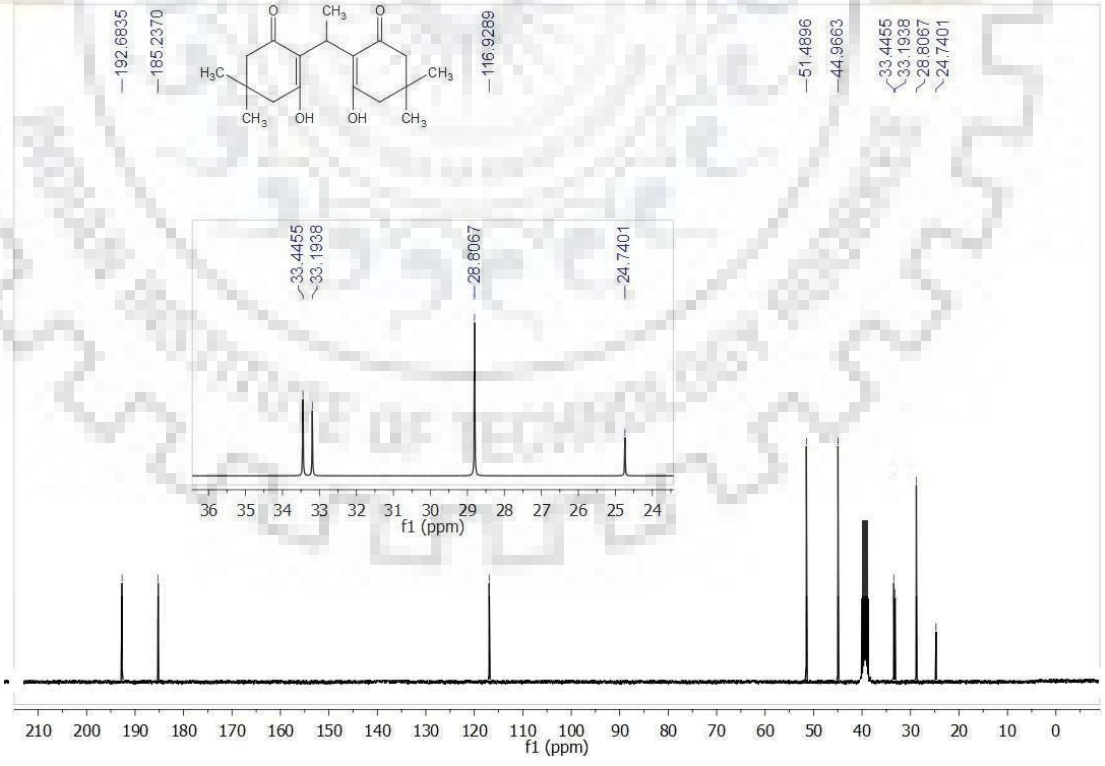
^{13}C NMR of 22a



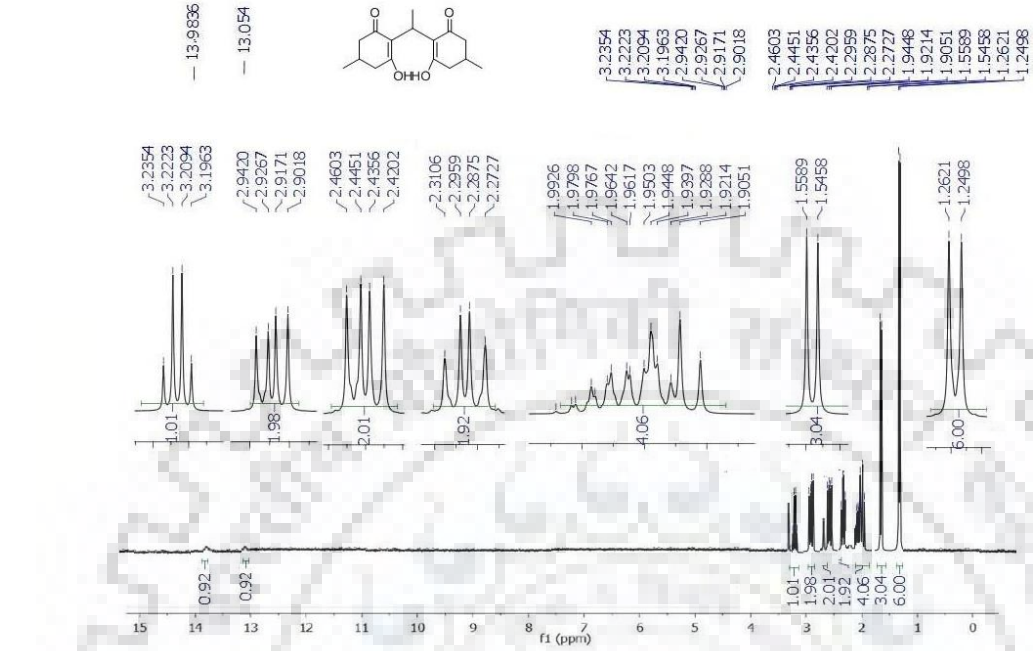
^{1}H NMR of 22b



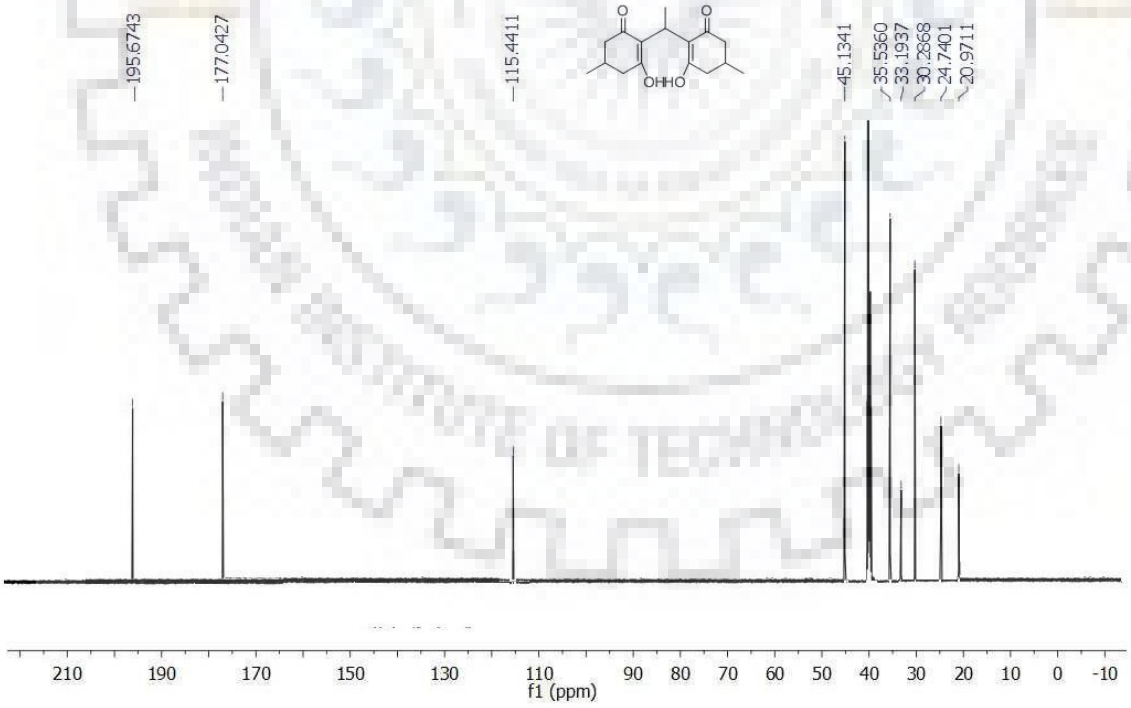
^{13}C NMR of 22b



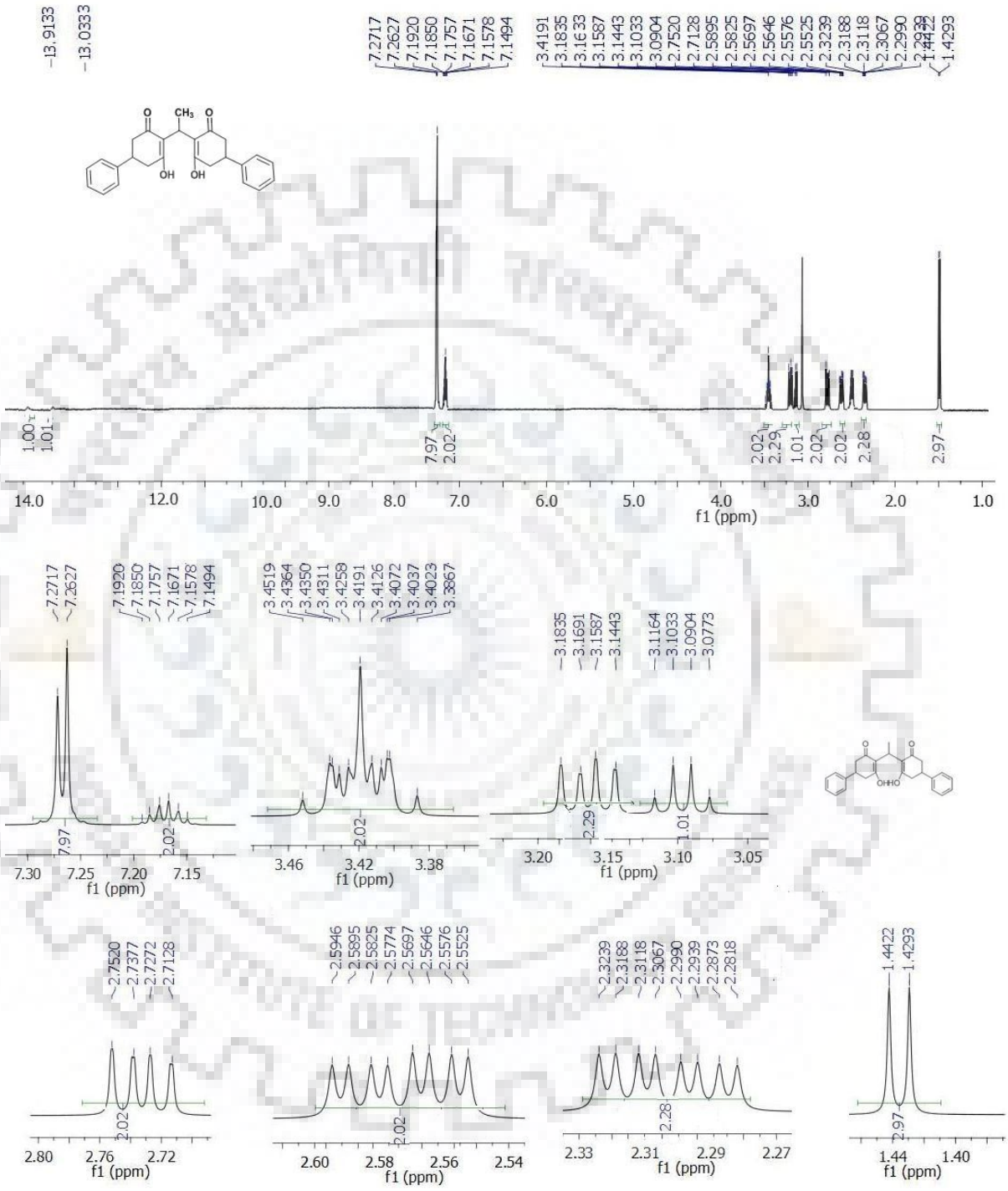
^{1}H NMR of 22c



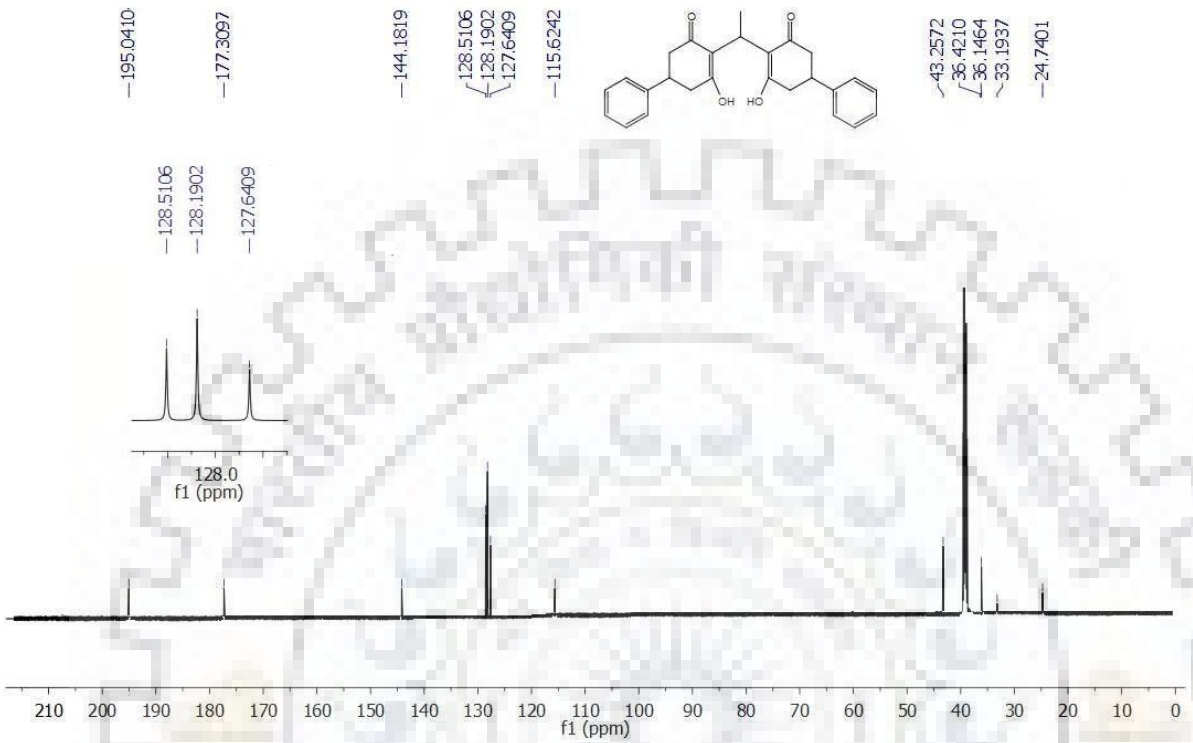
^{13}C NMR of 22c



^{1}H NMR of 22d

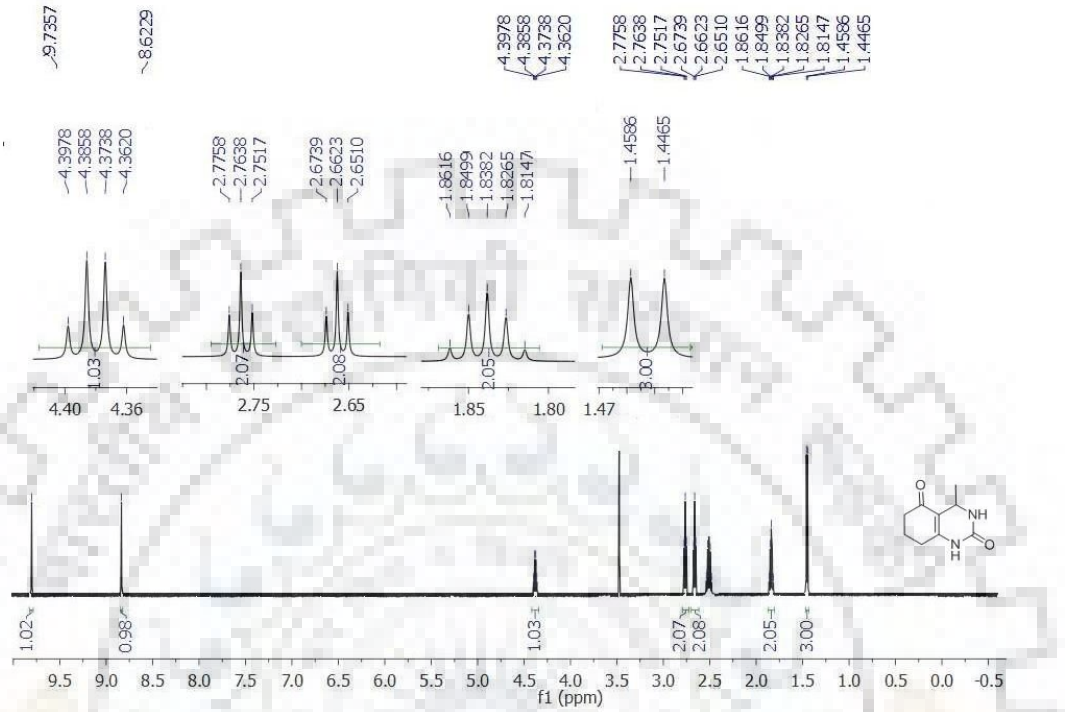


^{13}C NMR of 22d

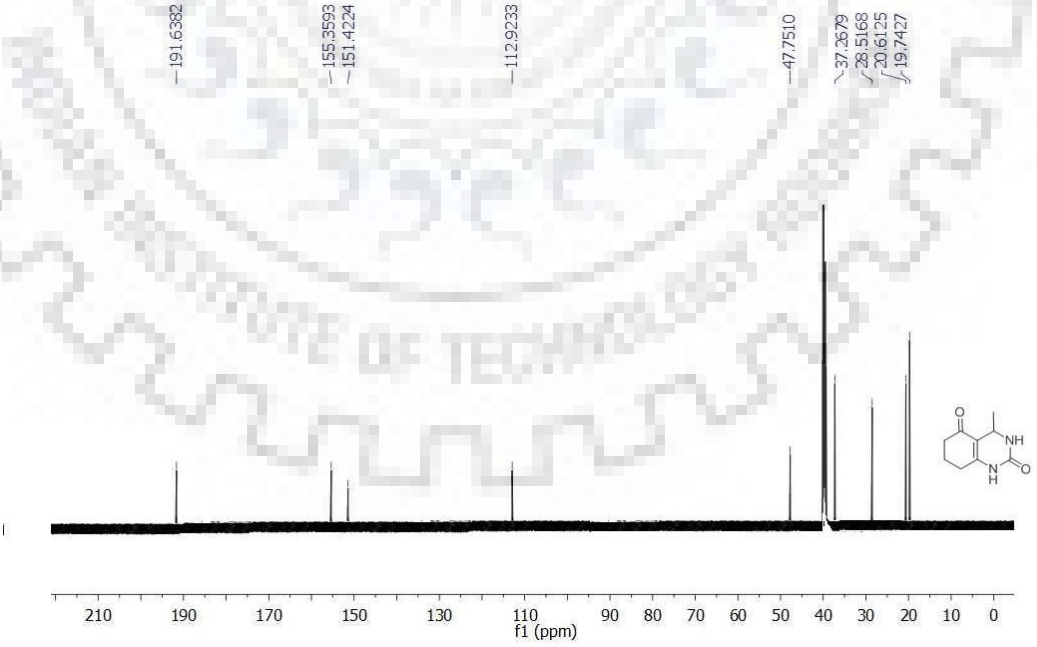


Spectral information for methyl substituted tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (25a-25c)

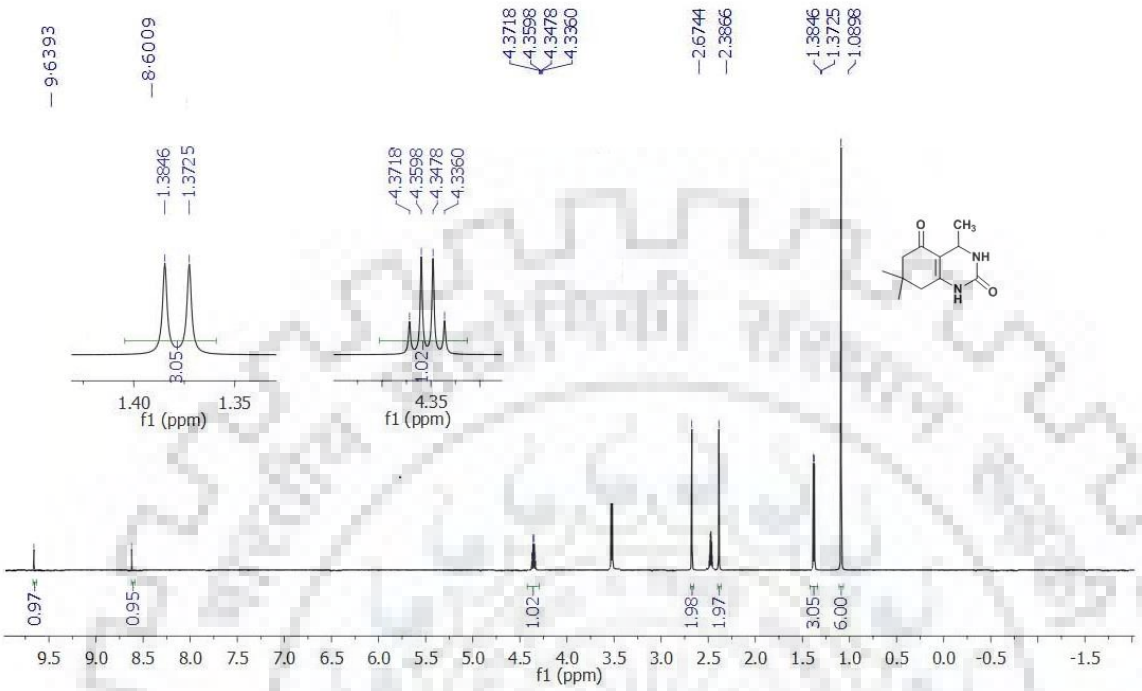
^{1}H NMR of 25a



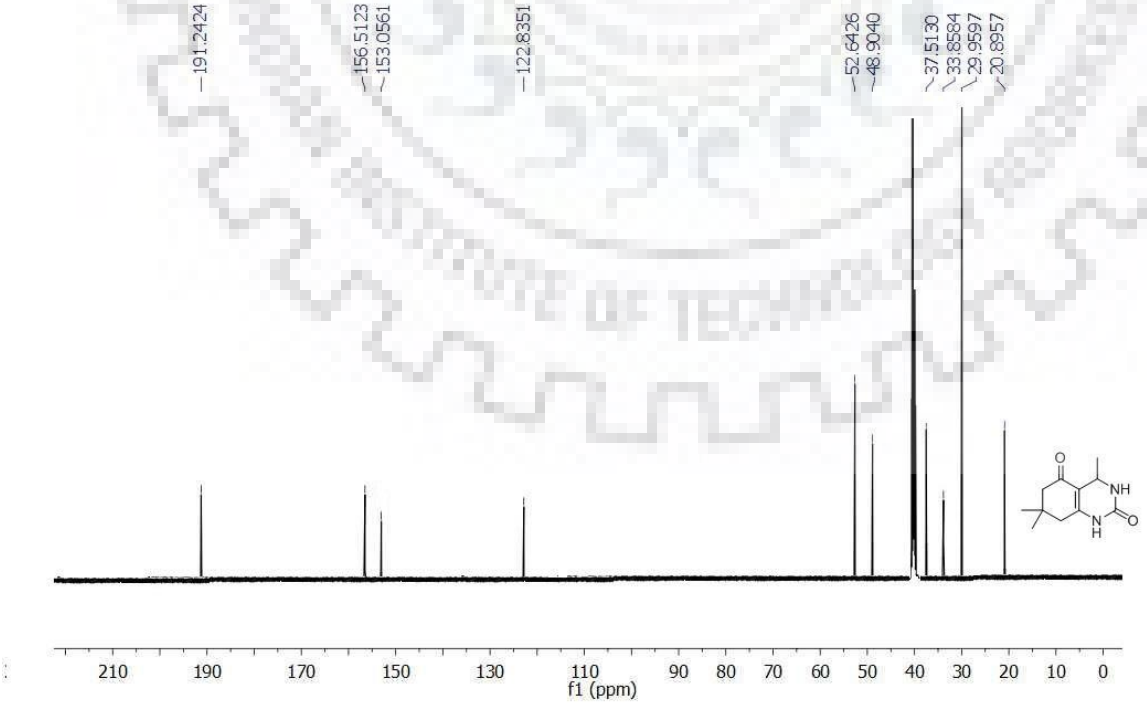
^{13}C NMR of 25a



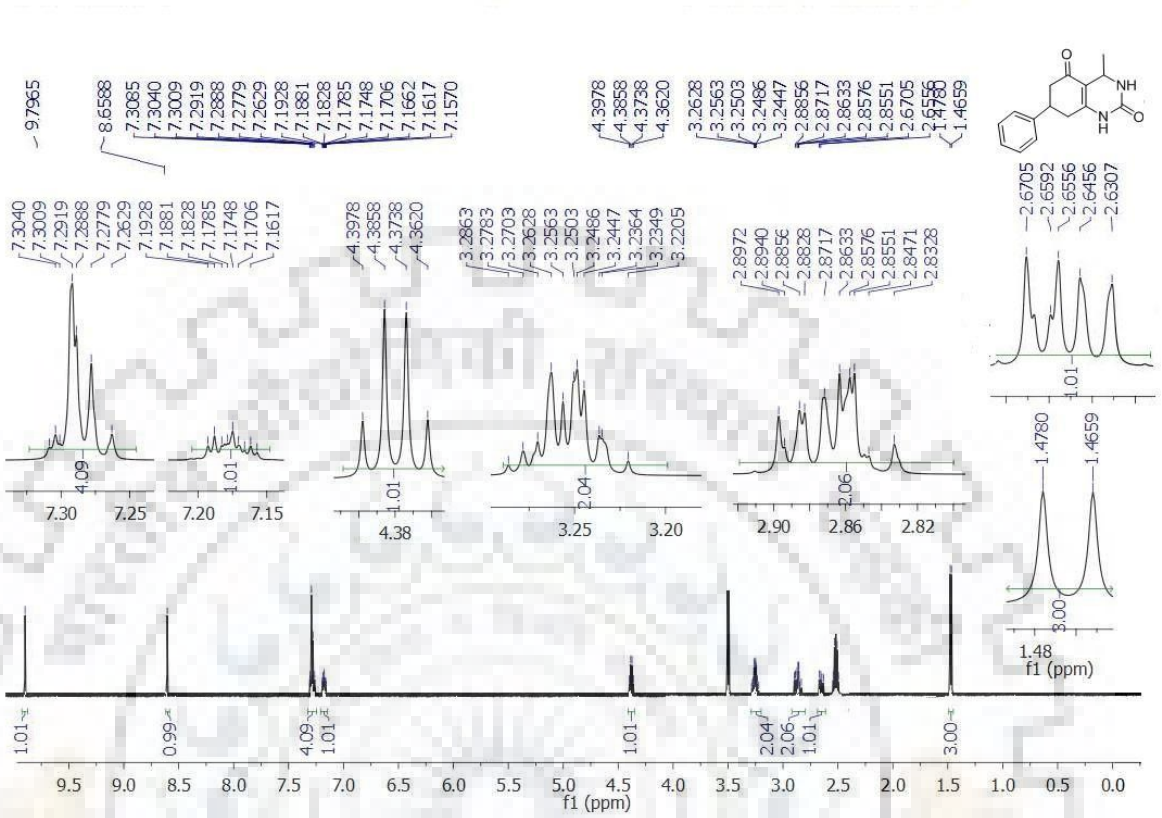
^{1}H NMR of 25b



^{13}C NMR of 25b



^{1}H NMR of 25c



^{13}C NMR of 25c