SYNTHESIS OF BIOACTIVE ORGANIC HETEROCYCLIC COMPOUNDS USING NOVEL CATALYSTS

A thesis submitted to the

UNIVERSITY OF NORTH BENGAL

For the award of

DOCTOR OF PHILLOSOPHY IN CHEMISTRY

By

SOURAV DEY

(M.sc in Chemistry)

Supervised by

Prof. PRANAB GHOSH
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NORTH BENGAL
SEPTEMBER 2022

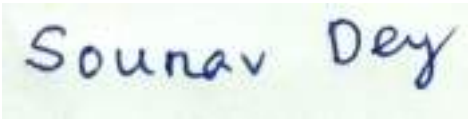
Dedicated

to My

Beloved Parents

DECLARATION

I declare that the thesis entitled "**SYNTHESIS OF BIOACTIVE ORGANIC HETEROCYCLIC COMPOUNDS USING NOVEL CATALYSTS**" has been prepared by me under the guidance of Dr. Pranab Ghosh, Professor of Chemistry, University of North Bengal. No element of this thesis has formed the origin for the award of any degree or fellowship earlier.



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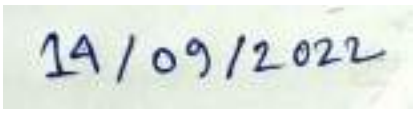

UNIVERSITY OF NORTH BENGAL

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CERTIFICATE

I certify that **Mr. Sourav Dey** has prepared the thesis entitled "**SYNTHESIS OF BIOACTIVE ORGANIC HETEROCYCLIC COMPOUNDS USING NOVEL CATALYSTS**" for the award of Ph.D. degree of the University of North Bengal, under my supervision. He has carried out the research work at the Department of Chemistry, University of North Bengal. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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about bioactive compound. The area of application of bioactive compounds are wide such as: plant science, modern pharmacology, geo-medicine, agrochemicals, cosmetics, food industry, nano-bioscience...etc. Thus it is a very promising area in full development, which has resulted in research works more and more numerous, designed to diversify the resources of bioactive compounds and improve their salvage pathways or synthesis. At first we need to prepare the synthon of such bioactive compound. As their natural availability is not so promising, henceforth we feel to pursue our research interest to synthesize the precursor of bioactive compounds in a novel way. In Chapter II, It deals with green synthetic approach towards one pot multi component synthesis of hexahydroquinoline and 9-arylhexahydroacridine-1,8- dione derivatives catalyzed by sulphonated rice husk. An efficient, straight

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ABSTRACT

The research work incorporated in this thesis entitled **" SYNTHESIS OF BIOACTIVE ORGANIC HETEROCYCLIC COMPOUNDS USING NOVEL CATALYSTS "** is mainly focused on the development of efficient and environment benign methodologies for the new and efficient methodologies to synthesize synthons of bioactive compounds. The entire work depicted in this thesis has been divided into four chapters. In the beginning, **Chapter I** which deals with a brief idea about bioactive compound. The area of application of bioactive compounds are wide such as: plant science, modern pharmacology, geo-medicine, agrochemicals, cosmetics, food industry, nano-bioscience...etc. Thus it is a very promising area in full development, which has resulted in research works more and more numerous, designed to diversify the resources of bioactive compounds and improve their salvage pathways or synthesis. At first we need to prepare the synthon of such bioactive compound. As their natural availability is not so promising, henceforth we feel to pursue our research interest to synthesize the precursor of bioactive compounds in a novel way. In **Chapter II**, It deals with green synthetic approach towards one pot multi component synthesis of hexahydroquinoline and 9-arylhexahydroacridine-1,8-dione derivatives catalyzed by sulphonated rice husk. An efficient, straight

forward, eco-friendly procedure to the synthesis of biologically active hexahydroquinoline derivatives and hexahydroacridine-1,8-diones have been designed using a novel bio-degradable heterogeneous catalyst, sulphonated rice-husk (SRH). SRH provide high density of acid groups making it different from conventional solid acids containing single acid groups. An efficient protocol for the synthesis of hexahydroquinolines and hexahydroacridine-1,8-diones using acid catalyst (SRH) under both solvent free and greener solvent condition respectively. Operational simplicity, greener reaction condition, reusability of the catalyst, excellent product yields (upto 98%) are the fundamental features of this procedure. The metal free catalyst was characterised using different spectroscopic techniques-FTIR, SEM, EDX, Powder XRD, ICP-AES.

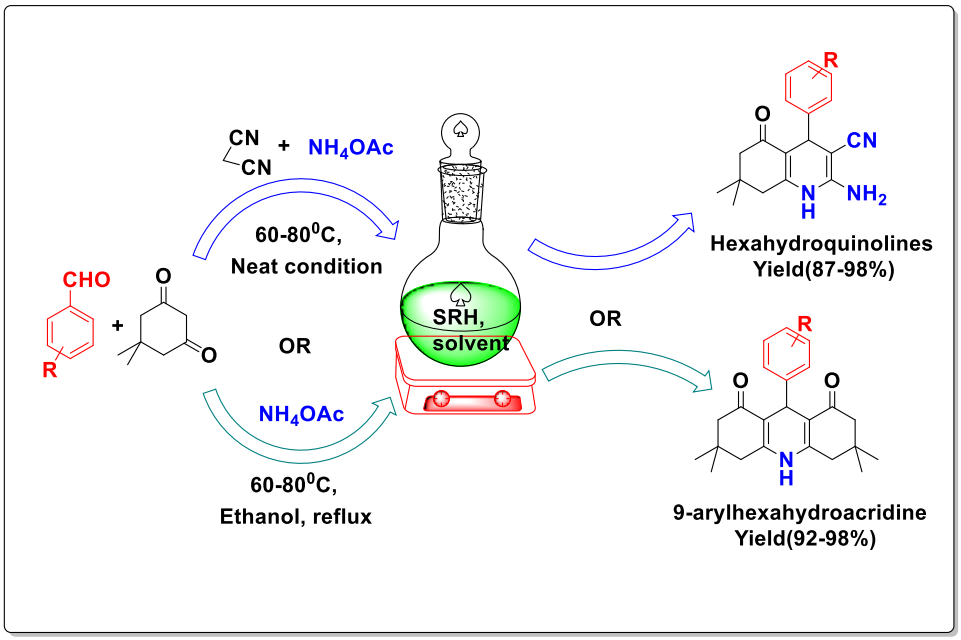

Figure: Graphical abstract of Chapter II

In **Chapter III**, It describes about convenient and greener root towards one pot multi-component synthesis of substituted pyrano-dichromeneo-dione and chromeno-pyrido-pyrimidinone derivatives using rice husk based heterogeneous catalyst. Very good to excellent yields in reasonably short reaction times, high atom economy and usage of readily available starting material, operational simplicity and easy workup are the fundamental features of this protocol. An efficient pseudo three component synthetic method for 7-aryl/heteroaryl substituted pyranodichromene-6,8-dione and 7-aryl/heteroaryl substituted chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidinone derivatives using this greener catalyst (SRH) under reasonable reaction condition. The operational simplicity, hassle free recovery of product and reusability of the catalyst with excellent product yield (up to 98%) are the fundamental features of this procedure. The toxic metal free catalyst was prepared in a convenient manner, characterized by using different spectroscopic techniques-FTIR, Powder XRD, SEM, & EDX an finally used up for the greener synthetic target.

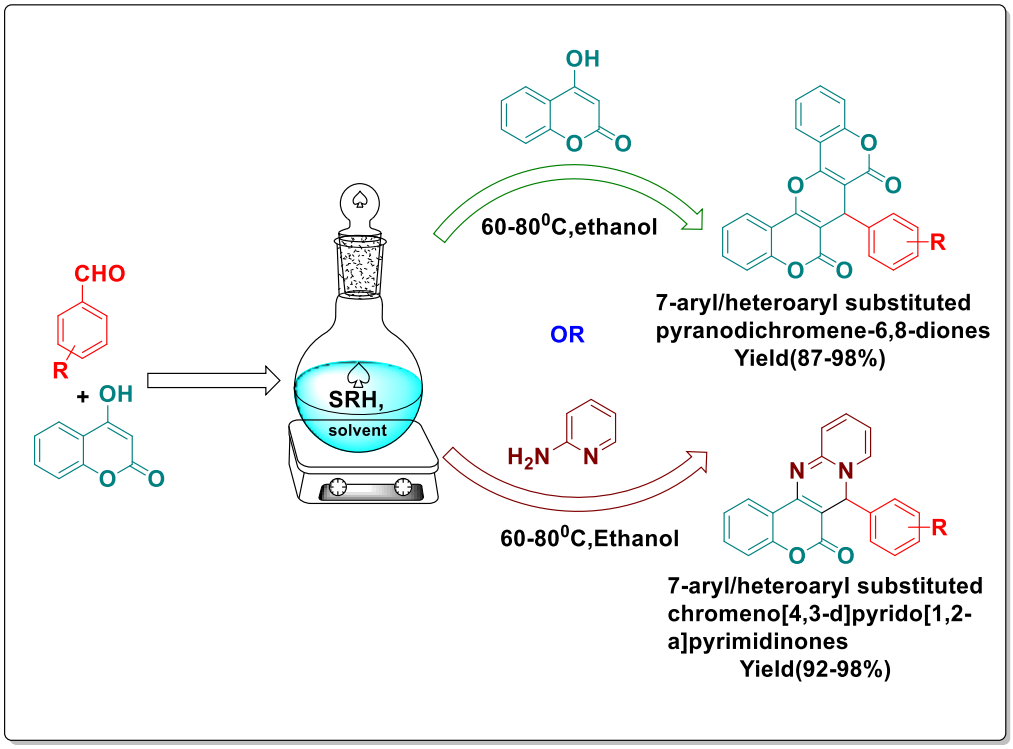

Figure: Graphical abstract of Chapter III

In Chapter IV, it deals with laboratory studies on one pot multi-component synthesis of a few varieties of heterocyclic compounds (dihydro-dichromeno-pyridine-6,8-diones, tetrahydrotetrazolo[5,1-*b*]quinazolinones and 2,4-diaryl hexahydroquinoline-5-ones) following greener approach using rice husk based greener catalyst. A straight forward and sustainable synthetic procedures for these important class of bioactive heterocyclic compounds have been designed using a novel bio-degradable heterogeneous catalyst-sulphonated rice-husk (SRH). The greener catalyst contains high density of acid groups with high porosity which has made it a different and advantageous material for green

catalysis as compared to other conventional homogenous solid acid catalyst. The operational simplicity, easy recovery of the product, avoidance, metal free technique and reusability of the catalyst along with excellent product yield (up to 98%) are the important and promising fundamental features of this procedure. The prepared solid heterogeneous catalyst was subjected for characterization using different spectroscopic techniques like FTIR, SEM, EDX, Powder XRD before its application for the the particular desired reactions for the synthesis of above heterocyclic compounds.

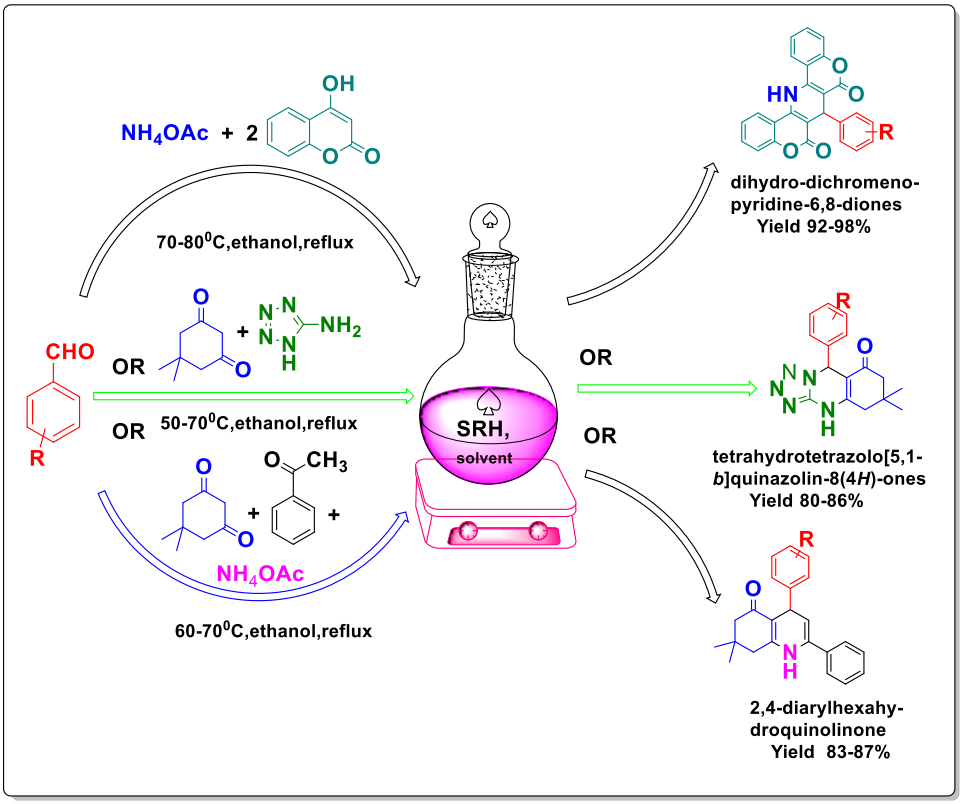

Figure: Graphical abstract of Chapter IV

PREFACE

Bioactive compounds have broad periphery of applications: plant science, modern pharmacology, geo-medicine, agrochemicals, cosmetics, food industry, nanobio-science... etc. Bioactive compounds contain chemicals that are found in small quantities in plants. As their natural availability is not so hopeful, researchers feel to prepare such compounds in a synthetic manner. The thesis starts with Chapter I, discussed about brief idea about the synthetic approaches towards the synthesis of heterocyclic moieties of bioactive heterocyclic compounds and brief idea about the heterogeneous catalyst for catalysis. Chapter II, deals with green synthetic approach towards one pot multi component synthesis of hexahydroquinoline and 9-arylhexahydroacridine-1,8-dione derivatives catalyzed by sulphonated rice husk. Chapter III, describes about convenient and greener root towards one pot multi-component synthesis of substituted pyrano-dichromeneo-dione and chromeno-pyrido-pyrimidinone derivatives using rice husk based heterogeneous catalyst. Lastly, Chapter IV deals with collective laboratory studies on one pot multi-component synthesis of a few varieties of heterocyclic compounds following greener approach using rice husk based greener catalyst.

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First, foremost, I would like to express my heartfelt gratitude to ***Almighty God****, for his showers of blessings by providing me the strength, patience and required courage throughout my research work after all the challenges and difficulties.*

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I would like to express special thanks to my ***Puja di*** *and* ***Niloy*** *for supporting in various technical issues during my research progress.*

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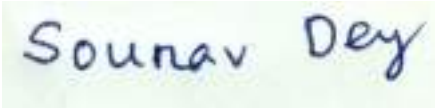

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Abbreviations

Å	Angstrom
Acac/acac	Acetylacetonate
AcOH	Acetic acid
^{0}C	Degree Celsius
Cm	Centimeter
Cy	Cyclohexyl
d	Doublet
DBH	Dibenzoylhydrazine
DCE	1, 2-Dichloroethane
DCH	1,2-diaminocyclohexane
DMAP	4-dimethylaminopyridine
DME	1, 2–Dimethoxyethane
DMF	N, N–Dimethylformamide
DMSO	Dimethyl sulfoxide
Dppe	1, 2-Bis(diphenylphosphino)ethane
Dppf	1, 1-Bis(diphenylphosphino)ferrocene
DS	Dodecyle sulphate
Eqv.	Equivalent
EtOH	Ethanol

EDX	Energy dispersive X-ray
FT-IR	Fouriertransform infraredspectroscopy
g	Gram/grams
h	Hour/hours
HRMS	High-resolution mass spectroscopy
ILS	Ionic liquides
m	Multiplet
m	Meta
MHz	Mega hertz
min.	Minute/Minutes
mL	Milliliter
mmol	Millimole
MNP	Metal nao-particles
Mole%	Mole percent
mp	Melting point
MSAIm	3-methyl-1-sulphonic acid -imidazolium hydrogen sulphate
MW	Microwave
nm	Nanometer
NMR	Nuclear magnetic resonance
o	ortho
p	para
PEG	Polyethylene glycol

Ph	Phenyl
Pr	Propyl
RT/rt	Room temperature
s	Singlet
SEM	Scanning electron microscope
t	Triplet
t-BuOCl	tert-butyl hypochlorite
TEA	Triethylamine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TfOH	Triflic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography

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CHAPTER I

BRIEF IDEA ABOUT THE SYNTHETIC APPROACHES TOWARDS THE SYNTHEIS OF HETEROCYCLIC MOIETIES OF BIOACTIVE HETEROCYCLIC COMPOUNDS AND BRIEF IDEA ABOUT THE HOMOGENEOUS AND HETROGENEOUS CATALYST FOR CATALYSI

I.1. Introduction

Bioactive compounds are active organic molecules having a broad range of application in several fields such as medicinal chemistry, bio organic materials, plant science, modern pharmacology, agrochemicals, cosmetics, food industry, nano-bio-technology etc. Though the range of bioactive compounds is wide, the definition of “bioactive compounds” is quite ambiguous. To answer this, the term "bioactive" should be noticed first. According to etymology: the term ‘bio’ has been derived from the Greek word "bios" which refers life and ‘active’ word has been derived from Latin word "activus" which means full of energy or with energy or involves an activity [1-4]. In broad sense, the activity means a functioning or a process and thus a bioactive compound is a substance that has a biological activity. In medical vocabulary, a bioactive substance is a substance having an impact in living tissues or cells or triggers a response in the living tissue [5-6]. Generally bioactive compounds are non-essential and cannot play two physiological roles simultaneously in the same organism such as nutritional role and bioactivity. Nutritional roles involve the degradation of the compound or molecule to liberate the essential

energy for the functioning of the organism and the bioactivity involves the interaction of the compound or molecule in its integrality with one or more components of the living tissue. Therefore, a bioactive compound is a compound which has the capability to interact with one or more component(s) of the living tissue.

I.2. Sources of bioactive heterocyclic compounds

Sources of bioactive compounds are generally from plants, medicinal plants but there are also synthetic source of bioactive substances. Certain foods such as citrious fruits, nuts, unprocessed vegetables oils have actions in the body that can promote good health which is due to the presence of specific bio-active substances naturally added to it [7-8]. For example, citrious fruits contain vitamin C, some vegetable oils contain high amount of ergosterol which helps to produce vitamin D in body in presence of sunlight.[9-10] Thus essential food along with other natural food materials naturally contain bioactive substances and participates in the biological functions of the body.[11] Typical and certain bioactive compounds are produced by plants as secondary metabolites not used for daily functioning of cells of tissues but play important role in the competition, defense, attraction and signaling [13-14]. Bioactive compounds in the plants have

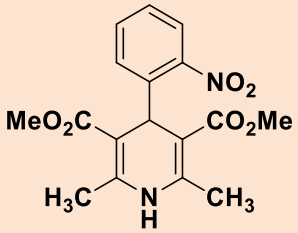
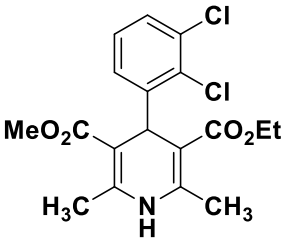
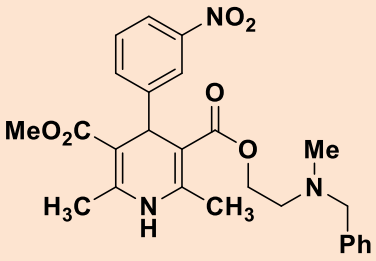
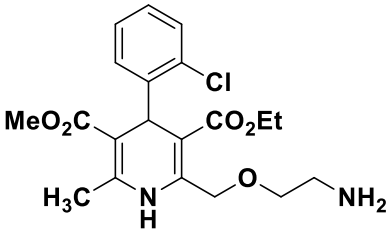
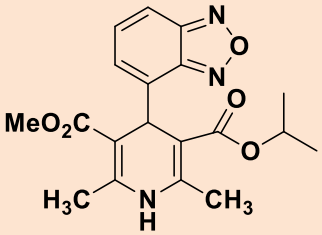
pharmacological or toxicological effects in humans and animals and plants are not the solitary source of bioactive substances there are substances also found in other living organisms and microorganisms, such as bacteria, mushroom and in some groups of animals.[14-19]. It should be noted that natural bioactive substances had the ability to synthesize a wide variety of bioactive molecules in past, but the development of pharmaceutical chemistry and the emergence of new tools for chemical synthesis thereby adding synthetic source of bioactive molecules.[20-21]. Thus a bioactive compound may be of natural or synthetic origin. This is a very encouraging area in full development, which has resulted in research works more and more numerous, designed to diversify the resources of bioactive compounds and improve their salvage pathways or synthesis.[22-23]

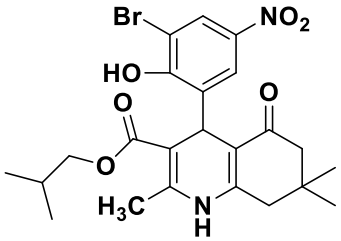
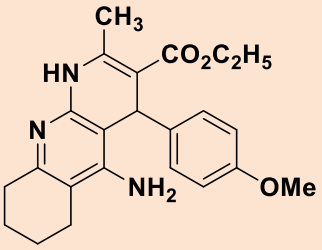
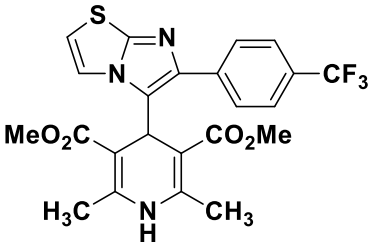
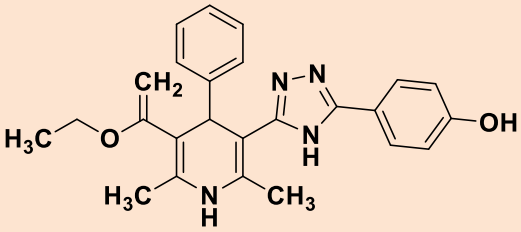
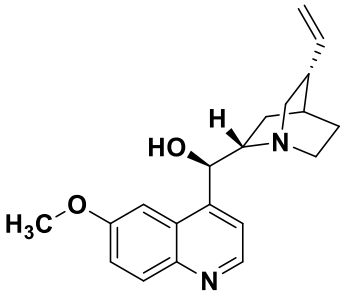
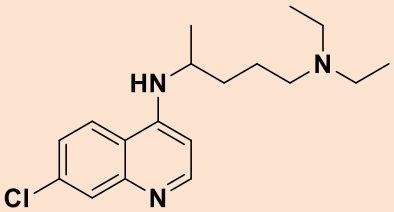
I.3. Bio active compounds and their activities

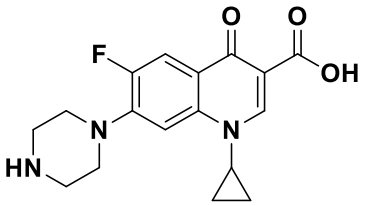
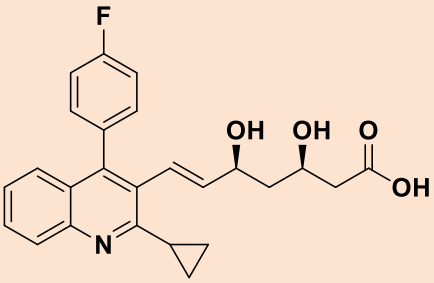
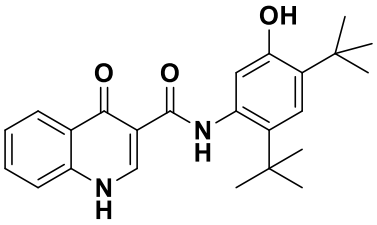
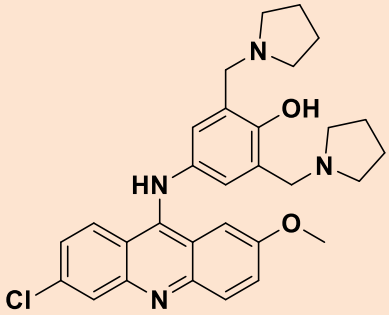
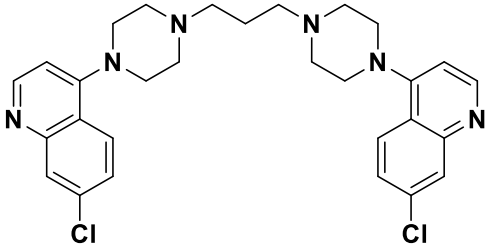
Some examples of bioactive compounds along with their application in living tissue are shown below.

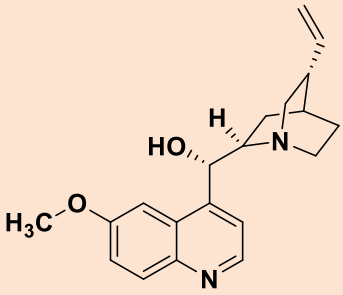
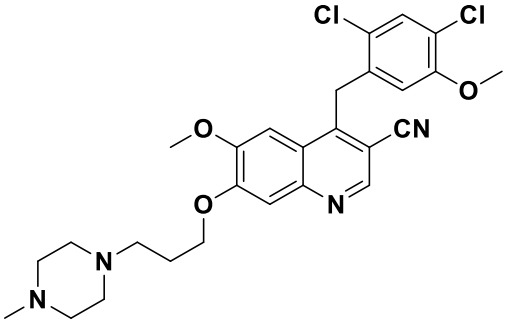
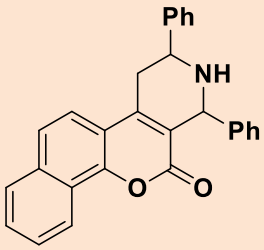
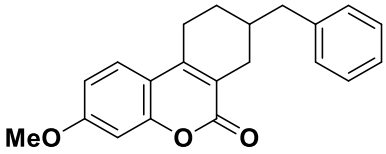
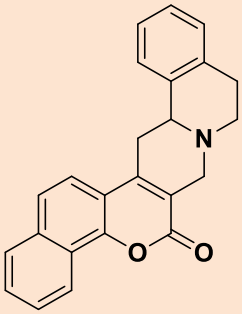
Table I.1. Examples of some bio-active compounds and their bio activity

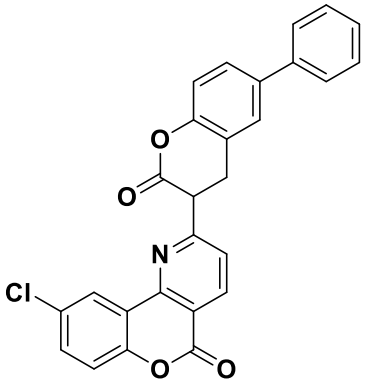
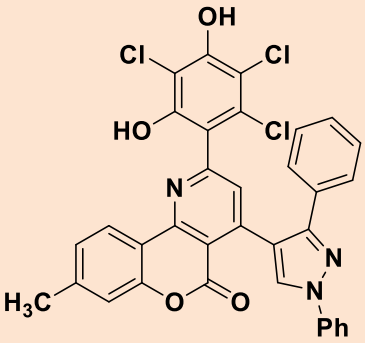
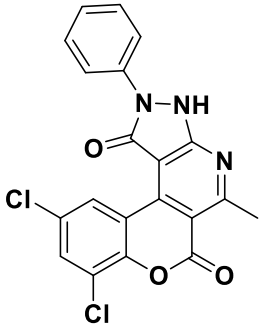
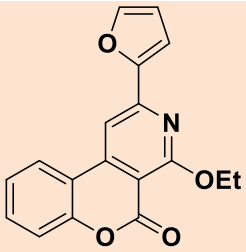
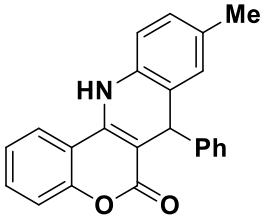
Entry	Examples of bioactive compounds	Bio activity

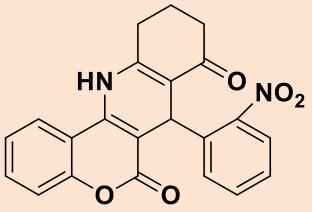
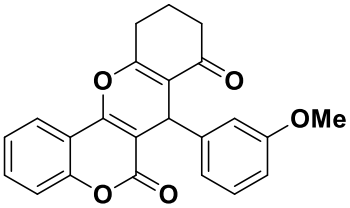
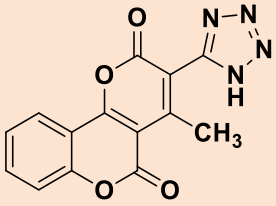
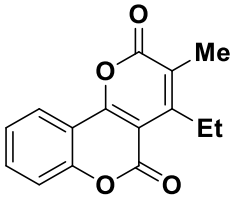
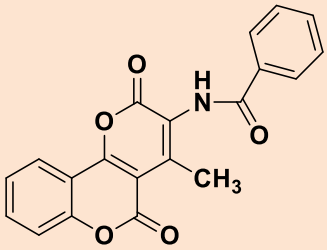
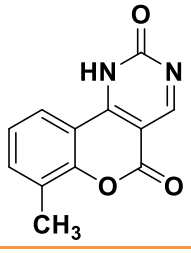
1	 Nifedipine	Calcium channel blocker
2	 Felodipine	Calcium channel blocker
3	 Nicardipine	Calcium channel blocker
4	 Amlodipine	Anti-bacterial
5	 Isradipine	Calcium channel blocker

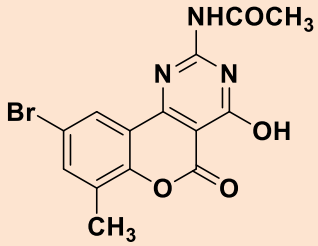
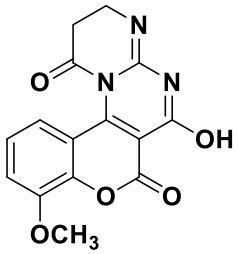
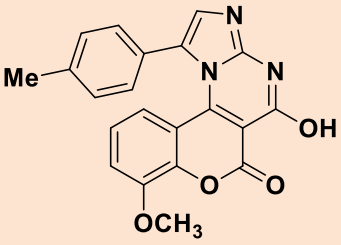
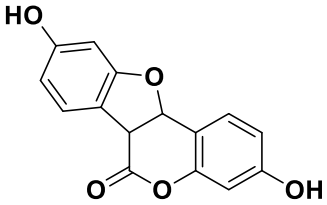
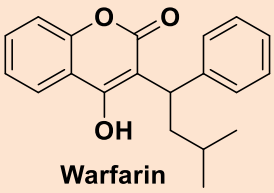
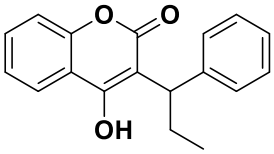
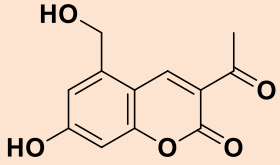
6		Cardiovascular Activity
7		Anti- Alzheimer active
10		CFTR activity
11		Analgesic
12	 Quinine	Antimalarial
13	 Chloroquine	Antimalarial

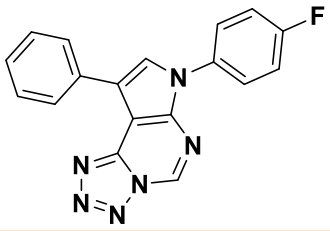
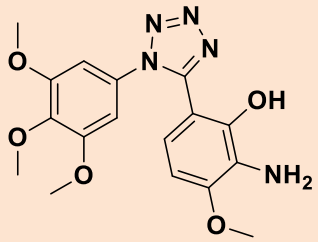
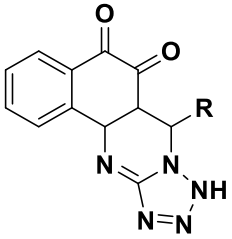
14	 Ciprofloxacin	Antibiotic
15	 Pitavastatin	Hypolipidemic
16	 Ivacaftor	Cystis fibrosis
17	 Pyronaridine	Antimalarial
18	 Piperaquine	Antimalarial

19	 Quinidine	**Antimalarial**
20	 Bosutinib hydrate	**Anti-leuckemic**
21		**Antifungal**
22		**Antipsychotic**
23		**Antimicrobial**

24		**Antimicrobial**
25		**Antibacterial**
26		**Antibacterial**
27		**Anti-inflamatory**
28		**Anticancer**

29		**Anticancer**
30		**Anticancer**
31		**Antibacterial**
32		**Antibacterial**
33		**Antibacterial**
34		**Antibacterial**

35		**Antibacterial**
36		**Anti cancer**
37		**Anti cancer**
38	 Cumestrol	**Estrogenic activity**
39	 Warfarin	**Anticoagulant**
40	 Phenprocoumon	**Anti-thrombotic**
41	 Armillarisin A	**Antibacterial**

42		**Antibacterial**
43		**Anticancer**
44		**Anti-tumour**

I.4. Precursor of bioactive compounds

In chemistry, precursors are smaller chemical compounds that participate in chemical reaction and produces another compound important for various applications. Therefore, precursors of bioactive compounds means that a compound from which desired bioactive compounds can be derived for medicinal and pharmaceutical usage. Some examples of precursors of bio-active compounds are shown below.(**Figure I.1**)

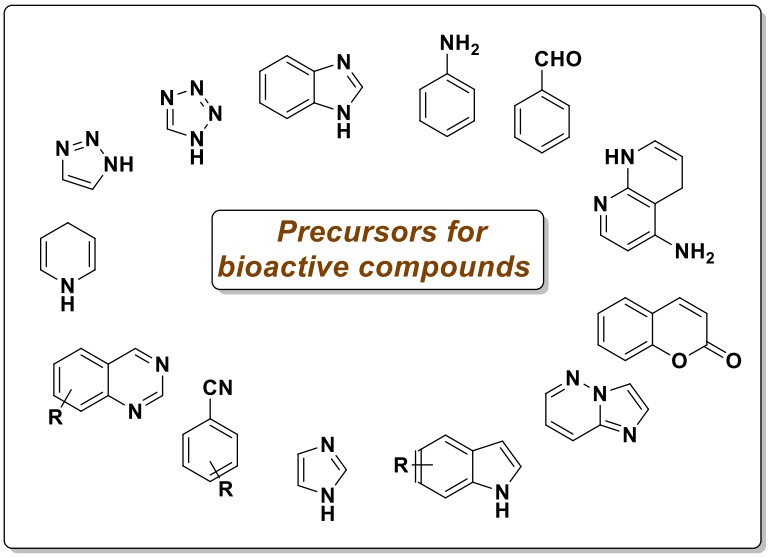
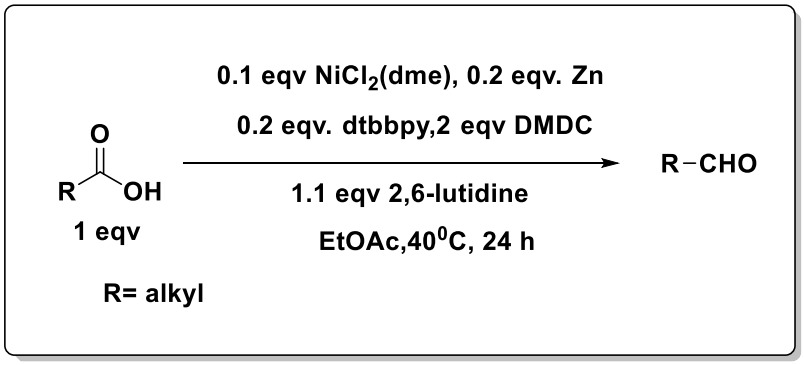


Figure I.1 Some examples of precursors of bioactive compounds

I.5. Some synthetic approaches towards the precursor of bioactive compounds

I.5.A. Synthesis of aldehydes

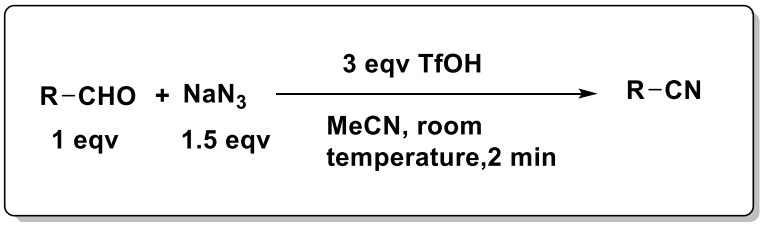
Recently, in 2019, Iosub *et. al* synthesized a wide range of aldehydes from carboxylic acids by direct but controlled reduction using a combination of Ni precatalyst, dimethyl dicarbonate as an activator and diphenylsilane as reductant (**Scheme I.1**). [24]



Scheme I.1 Synthesis of aldehydes from carboxylic acids

I.5.B. Synthesis of nitriles

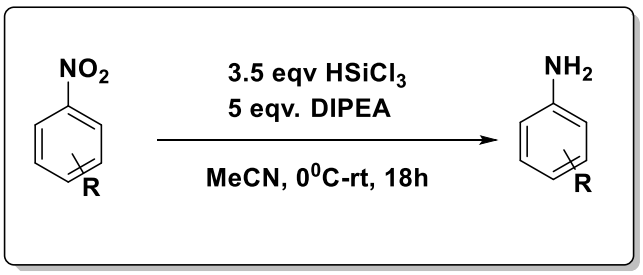
Recently in 2012, Rokade *et. al* reported a varty of nitriles which are synthesised from aldehydes by Schmidt reaction in a quantitative yield in presence of TfOH as catalyst and in acetonitrile solvent under room temperature condition(**Scheme I.2**).[25]



Scheme I.2 Synthesis of nitriles from aldehydes

I.5.C. Synthesis of anilines

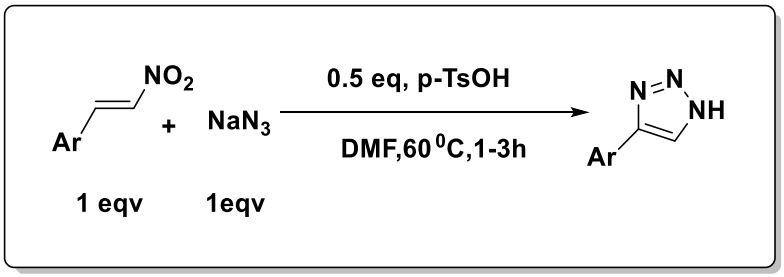
Recently in 2015, Orlandi *et. al* reported a metal free reduction of substituted nitrobenzenes to synthesise a varty of anilines in a quantitative yield with a combination of $HSiCl_3$ and tertiary amine and in acetonitrile solvent under freezing to room temperature condition(**Scheme I.3**).[26]



Scheme I.3 Synthesis of substituted anilines from substituted nitobenzaldehydes

I.5.D. Synthesis of triazoles

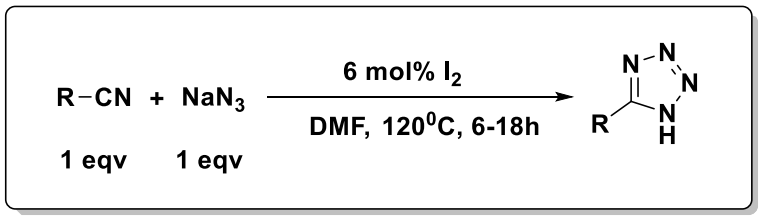
In 2014, Quan *et.al* repoted a synthesis of a variety of substituted triazoles from *β*-nitrostyrenes in presence of catalytic amount of *p*-TsOH in DMF solvent at 60^0C within a short reaction time(**Scheme I.4**).[27]



Scheme I.4 Synthesis of substituted triazoles from *β*-nitrostyrines

I.5.E. Synthesis of tetrazoles

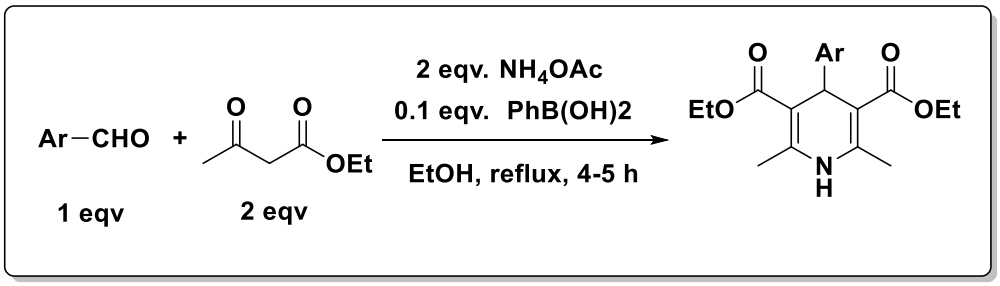
In 2010, Das *et. al* reported a synthesis of a variety of tetrazoles from nitriles in presence of iodine catalyt at 120^0C in DMF solvent (**Scheme I.5**). [28]



Scheme I.5 Synthesis of substituted tetrazoles from nitriles

I.5.F. Synthesis of dihydropyridines

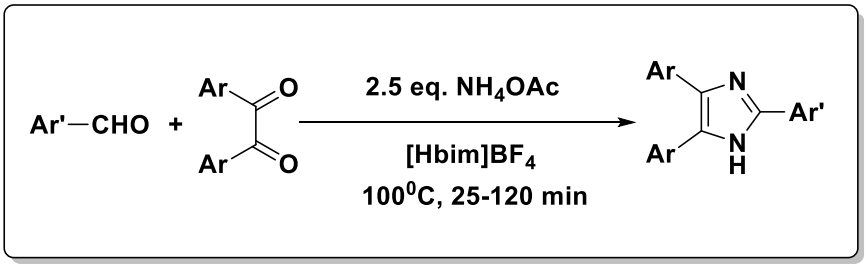
In 2008, Debache *et. al* reported a facile synthesis of a variety of dihydropyridines using aldehyde and 1,3-dicarbonyl compounds and ammonium acetate in presence of phenyl borronic acid as catalyt in ethanol solvent under reflux condition (**Scheme I.6**).[29]



Scheme I.6 Synthesis of substituted dihydropyridines from aromatic aldehydes

I.5.G. Synthesis of imidazoles

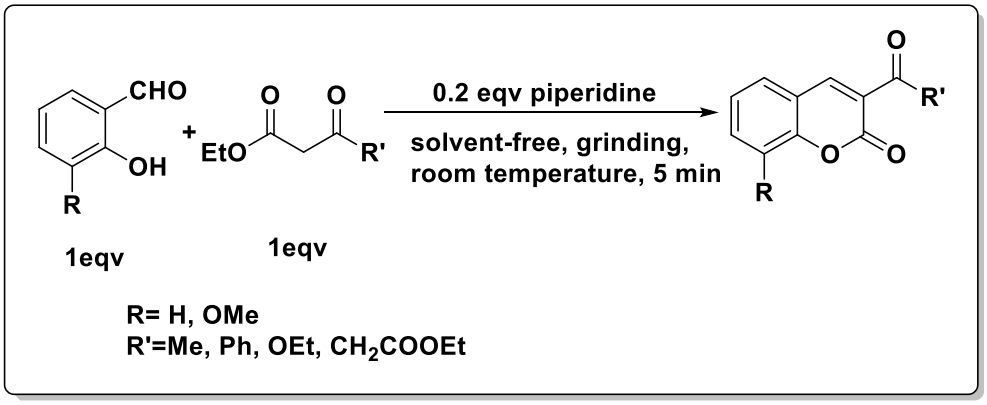
In 2005, Siddiqui *et. al* reported a facile synthesis of a variety of of imidazoles using aldehyde and 1,2-dicarbonyl compounds and ammonium acetate in presence of ionic liquid as catalyt at 100^0C under solvent free condition (**Scheme I.7).[**30]



Scheme I.7 Synthesis of substituted imidazoles from aromatic aldehydes

I.5.H. Synthesis of coumarine derivative

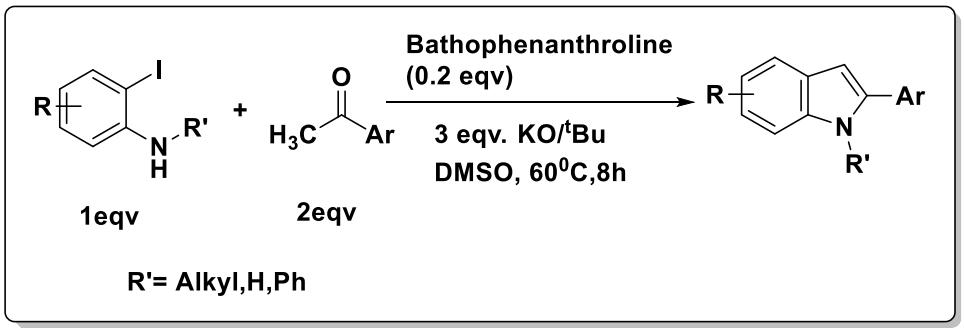
In 2001, Sugino *et. al* reported synthesis of a variety of a variety of coumarin derivatives using substituted *o*-hydroxy benzaldehydes and 1,3-dicarbonyl compounds in presence of base catalyt under solvent free condition (**Scheme I.8**).[31]



Scheme I.8 Synthesis of substituted coumarine derivatives from aromatic aldehydes

I.5.I. Synthesis of indoles

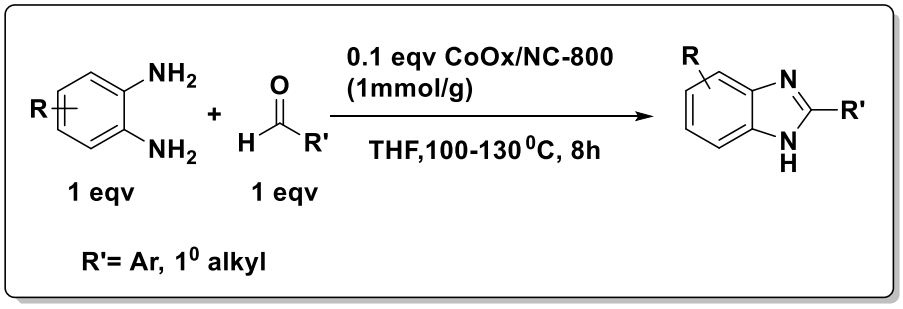
Recently in 2001, Chung *et. al* reported synthesis of a variety of a variety of indole derivatives from *o*-iodoanilines and aryl substituted keto-methyl compounds in presence of base catalyt in DMSO solvent (**Scheme I.9**).[32]



Scheme I.9 Synthesis of substituted indoles from o-iodoanilines and aryl substituted keto-methyl compounds

I.5.I Synthesis of benzimidazoles

Recently in 2019, Wang *et. al* reported synthesis of a variety of a variety of bezimidazole derivatives from *o*-dianilines and aldehydes in presence of Co-oxide catalyt at 100-130^{0}C in THF solvent (**Scheme I.10**). [33]



Scheme I.10 Synthesis of substituted benzimidazoles from o-iodoanilines and aryl substituted keto-methyl com-pounds

The above synthetic procedures draw an interest to synthesise different types precursors useful for the synthesis of a variety bioactive heterocyclic compounds in a more convenient way but some of the

processes have large number of limitations such as (i) Use of non available reagents (ii) High temperature (iii) Use of corrosive chemical (iv) Use of organic hazardous solvents (v) Difficult reaction setup (vi) Time consuming process (vi) costly and hazardous catalyst and some of the processes are not environmentally and economically friendly and also some processes are not viable to do due to absence of sophisticated industry grade laboratory set up and hence minimizing the drawbacks of those processes above, I feel to pursue one my research interest to synthesize some important precursors (which are not easily available in market and are also inconvenient to prepare) by following pevious convenient methods given in literature for my targeted research interest about bioactive heterocyclic compounds in a novel and convenient way.

I.6. Catalyst

In chemistry, catalyst is a substance which when added to any progress of the chemical reaction that increases the rate of the reaction by lowering the activation energy of the reactants without itself being consumed. There are so many examples of organic and inorganic chemical reactions involving chemical reactions. On the basis of physical behavior there are two types of catalyst present in the literature of chemical science - (A) homogeneous catalyst and (B) heterogeneous

catalyst and all the kinds of catalysts involving metallic, non metallic, toxic, non-toxic, enzymatic, bio-derived and biodegradable catalyst involve these two catagories. But sometimes there there occurs chemical reactions without any addition of catalysts and on that case reactants acts as autocatalyst to perform the reaction easily.

I.6.A Homogeneous catalyst

In this type of catalyst, it involves catalysts and reactants remaining in the same physical states of matter and the process is referred to as homogeneous catalysis. For example, the common homogeneous catalyst involves mineral acids and alkalies. Usually homogeneous catalyst and substrates dissolves in solvent and participate in desired reaction. There are so many examples of homogeneous catalysis such as hydrolysis, solvolysis, esterification, hydrogenation, metathesis and coupling reactions.

I.6.B Heterogeneous catalyst

In this type of catalyst, the physical state of the catalyst is different from the physical state of the reaction medium, reacting specieses. For example, preparation of ammonia by Haber's process, manufacturing of sulphuric acid by contact process, hydrogenation in unsaturated hydrocarbons involves the use of heterogeneous catalysts. Organic

chemical reactions involving amorphous silica, mesoporous silica, functionalized resin, graphite powder, grapheme oxide etc. are also examples of heterogeneous catalysts.

I.6.C Difference between homogeneous and heterogeneous catalyst

Based on the literature survey and the experiences shared in reported journals and also with practical experiences, a few distinct points between homogeneous and heterogeneous catalysts has been shown in the table (**Table I.2.**)

Table I.2. Difference between homogeneous and heterogeneous Catalyst

Entry	Homogeneous catalyst	Heterogeneous catalyst
1	Activity of homogeneous catalyst is slightly higher due to its solubility in reaction medium.	Activity of heterogeneous catalyst is slightly lower to that of homogeneous catalyst but depends upon the density of functional groups attached and the porous nature of the catalyst.
2	Catalyst shows reproducible results.	Catalyst shows difficulty in reproducible results.
3	Catalyst shows relatively higher selectivity.	Catalyst shows difficulty to control selectivity.

4	Catalyst has low volume, high cost and have economically disadvantages.	Catalyst has high volume but have lower cost and is effective for large scale industrial production also.
5	Molecular active sites for this Catalyst are well defined here.	Molecular active sites for this Catalyst are not well defined rather it has random active sites.
6	Catalyst life is relatively shorter and it is rarely reusable.	Catalyst life is longer and it is reusable up to several times depend upon the reaction conditions.
7	Catalyst is less susceptible and sensitive to water and oxygen.	Catalyst is highly susceptible.
8	Catalyst shows accessible reaction kinetics, mechanism & catalytic activity.	Reaction kinetics and mechanism for this catalyst is complex and difficult to establish.
9	Used in for specific and fine chemicals manufacturing.	Used in bulk scale for industrial product manufacturing.
10	Catalysts are not diffusion controlled.	Catalysts are diffusion controlled.
11	Catalysts are difficult to	Catalysts are quite easy to

	separate from reaction mixture.	separate from the reaction mixture.

I.6. Conclusion

Finally in conclusion, I feel to pursue my research interest to synthesize bioactive heterocyclic compounds by following pevious convenient methods and by gathering knowledge from literature survey for my targeted research interest about bioactive heterocyclic compounds in a novel and convenient way. And minimizing the drawbacks of the previous processes for the synthesis of bioactive heterocyclic compounds, I also feel to pursue my research interest to synthesise new convenient greener heterogeneous catalyst and use it for the synthesis of bioactive heterocyclic compounds under greener condition.

I.7. References

References are given BIBLIOGRAPHY under Chapter I.

CHAPTER II

A GREEN SYNTHETIC APPROACH TOWARDS ONE POT MULTI COMPONENT SYNTHESIS OF HEXAHYDROQUINOLINE AND 9-ARYLHEXAHYDROACRIDINE-1,8-

DIONE DERIVATIVES CATALYZED BY SULPHONATED RICE HUSK

II.1 Introduction

Over the past decade, green chemistry has been emerged as an important environmental aspect to reduce the use of toxic and hazardous reagents in synthetic and industrial chemistry. In recent years industrial use of agricultural wastage has received much interest due to economical and environmental reasons. RH is a major agricultural by-product in south Asian countries that can be a promising feedstock of industrial use [1-2]. Rice husk (RH) contains cellulose, hemicelluloses, lignin, ash like other lignocellulosic material. The features like high silica content, high porosity, light weight and high external surface area turn it a good catalyst support for many industrial synthesis [3-4]. The use of eco-friendly catalysts and selected green solvents are demanding in recent years for the synthesis of organic compounds [5]. In terms of

green chemistry, the development of efficient multi-component reactions (MCRs) has attracted much consideration regarding the use of heterogeneous catalyst [2-3]. One-pot MCRs are energy saving processes that eliminates the multiple steps and increases the productivity with high level of structural diversity [5-10]. MCRs are convergent in nature and an important toolbox of green chemistry to synthesize different biologically active heterocyclic compounds. A large variety of MCRs are catalyzed by homogeneous and heterogeneous acid catalyst. However, solid acid catalyst have gained attention due to their heterogeneous nature and are favoured over homogeneous one as they can be easily separated from the reaction system. Quinolines are ubiquitous in nature and they represent a wide variety of pharmaceutical (**Figure II. 3**) and agrochemical products [11]. Substituted quinolines exhibit diverse biological activities and they are found as major building blocks in various natural products [12]. Quinolines possess considerable interest due to their biological activity including antibacterial, antifungal, antioxidant, anticancer, anticonvulsant, and antiviral activity [12-16]. Substituted quinolines and tetrahydroquinolines (THQ) are a class of heterocycles that serve as chemotherapeutic agents also [17-19]. Many heterocyclic [25],

compounds containing the quinoline nucleus display anti-inflammatory activity and they serve as antagonist inhibitors [20]. Quinolines with 1,4-Dihydropyridine (DHP) nucleus have been found efficient in cardiovascular diseases as calcium channel blockers [21-22]. Along with these, this heterocyclic moiety have vast application in agricultural field also [23]. Many recent research works are carried on this unique heterocyclic motif due to its diverse biological activity [24-25]. Several homogeneous and heterogeneous catalysts have been employed for the synthesis of substituted hexahydroquinolines derivatives. Among them, the synthesis using nano-ZnO/ultrasound nano-Fe_3O_4 [26], AcOH [27], K_2CO_3 [28], triethylamine [29], Fe_3-x$TixO_4$@SPDETATSA (N-(3-silyl propyl) diethylene triamine N,N',N''-tri-sulfonic acid immobilized on Fe_3-x$TixO_4$ magnetic nanoparticles [30] are noteworthy to mention.

Acridine derivatives are also important class of heteterocyclic compound and those derivatives containing keto functional groups are found to be good anti-malarial agents and substituted hexahydroacridine-1,8-dione being resemble to dihydropyridine molecule can act as a K-channel openers in urinary-bladder smooth muscle [31-32]. These acridinediones were also found to act as laser dyes due to electron delocalization and exhibit fluorescence and laser

activity [33-34]. The effectiveness of lasing is dependent upon the substituents at C-9 and N-10 of the acridine chromophore. Apart from the above applications, acridinediones also possess other important photo-physical and electrochemical properties [35]. Acridine dyes can bind with photo damaged nucleic acids which have increasing interest as mutagens in micro-organisms[36]. The usefulness of acridines have led to the development of numerous methods of their synthesis by the three component Hantzsch condensation of aldehydes with *β*-diketones and ammonium acetate or appropriate primary amines. Many procedures describe the synthesis of acridinedione derivatives by cyclocondensation between dimedone and aldehyde and primary amine in the presence of heat in organic solvents with a varity of catalysts such as Fe_3O_4@B-MCM-41, [37] $(SO_4)_2/TiO_2$NPs, [38] Scolecite, [39] Pd-nanoparticle, [40] MNPsN-propyl-benzoguanamine-SO_3H, [41] silica bonded N-propyl sulfamic acid,[42] CH_3SO_3H, [43] tetrabutylammonium hexatungstate, [44] Nano-TiO_2, [45] $SiO_2/ZnCl_2$, [46] protic pyridinium ionic liquid,[47] $CsCO_3$,[48] ceric ammonium nitrate(CAN), [49] organocatalysts,[50] Ni-nanoparticles,[51] MgO,[52] thiamine hydrochloride,[53] SnO_2,[54] La_2O_3/TFE (2,2,2-trifluoroethanol),[55] $Cd(NO_3)_2$.$4H_2O$ [56]. However, many protocols

suffer from some limitations such as harsh reaction conditions, costly and non recyclable catalyst and tedious purification, use of toxic reagents and generation of hazardous wastes. By eliminating the drawbacks of previous methods, it is important to find out new greener protocols for the synthesis of substituted quinolines and hexahydroacridine-1,8-dione. Eco-friendly heterogeneous solid acid catalysts have gained much attention over homogeneous catalysts owing to its easy separation process. Amongst them carbon-based sulphonated catalysts are most promising because of the presence of different acidic functional groups and large carbon framework. Owing to the low price and simple preparation, biomass waste (RH) is extensively used in several field as mentioned above. With increasing demand in green chemistry, the use of heterogeneous solid acid catalyst has attracted the researchers regarding environmental issues. An ideal solid acid catalyst should be the one which have excellent stability, high porosity, active acidic sites, low cost and hydrophobic surfaces. Among them carbon-based acidic catalysts are most promising as they can be extensively prepared from biomass material (RH). However, RH based alkaline catalyst and solid acid catalyst under MW irradiation has been reported previously [57-58]. Herein, we report a conventional heating

technique for the preparation of sulphonated RH (SRH) and characterisation as well. We report the use of this novel green catalyst SRH for feasible synthesis of hexahydroquinoline and hexahydroacridine-1,8-diones derivatives in one-pot strategy.

II.2 Quinoline

Quinoline is a weak tertiary organic base and was discovered in 1834 as a colourless hygroscopic liquid by distillation of coal tar by Friedlieb Ferdiland Runge and in 1871, Dewar observed the chemical similarity between pyridine and quinoline having rigid heterocyclic core of benzene ortho-fused with a pyridine ring (**Figure II. 1**). [59] Coal tar is a principal commercial source for quinoline synthesis but numerous reactions have been developed for its laboratory synthesis. Quinoline itself has a few applications but many of its derivatives are useful in various chemical reactions for laboratory synthesis.

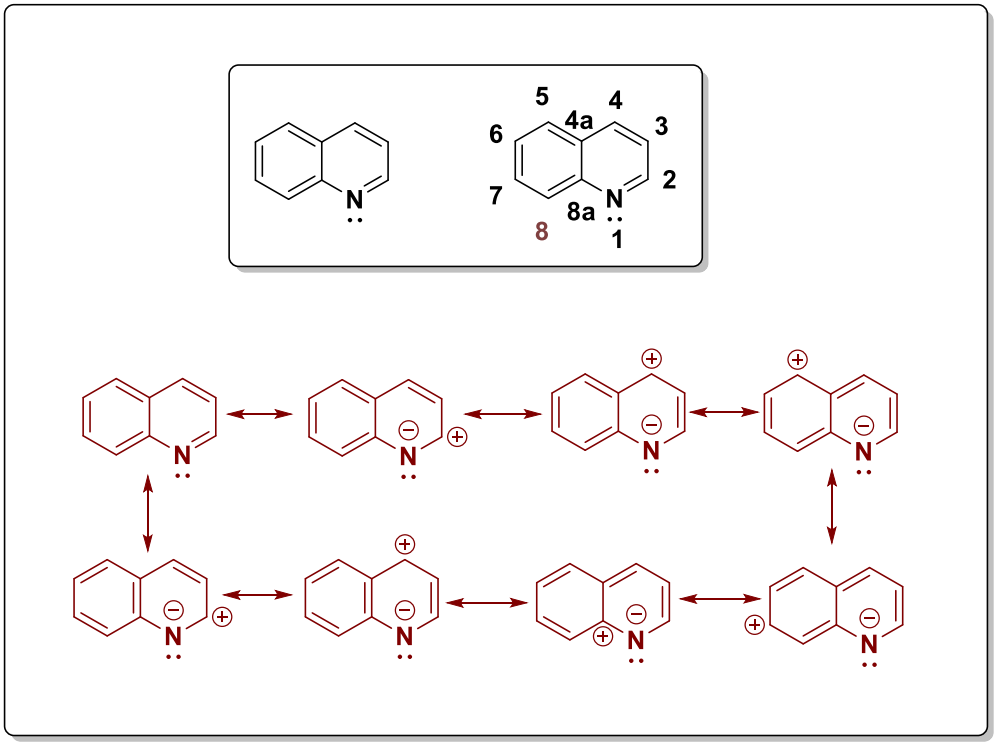


Figure II. 1 Chemical structures and resonating structures of quinoline moiety

There are several reported classical synthetic routes for synthesising the quinoline structural motifs and such classical synthetic routes which are widely used include Skraup reaction, Conrad-Limpach reaction, Doebner reaction, Combes reaction, Povarov reaction, Doebner-Miller reaction, Gould Jacobs reaction and Riehm reaction. Which are majorly utilizes aniline as one of the common reactants (**Figure II. 2**). However, there are several other reactions such as Knorr reaction, Friedländer reaction, Pfitzinger reaction, Niementowski reaction, Meth-Cohn reaction and Camps reaction which requires

special substituted anilines or other substituted reactants to yield quinoline structural motiffs.

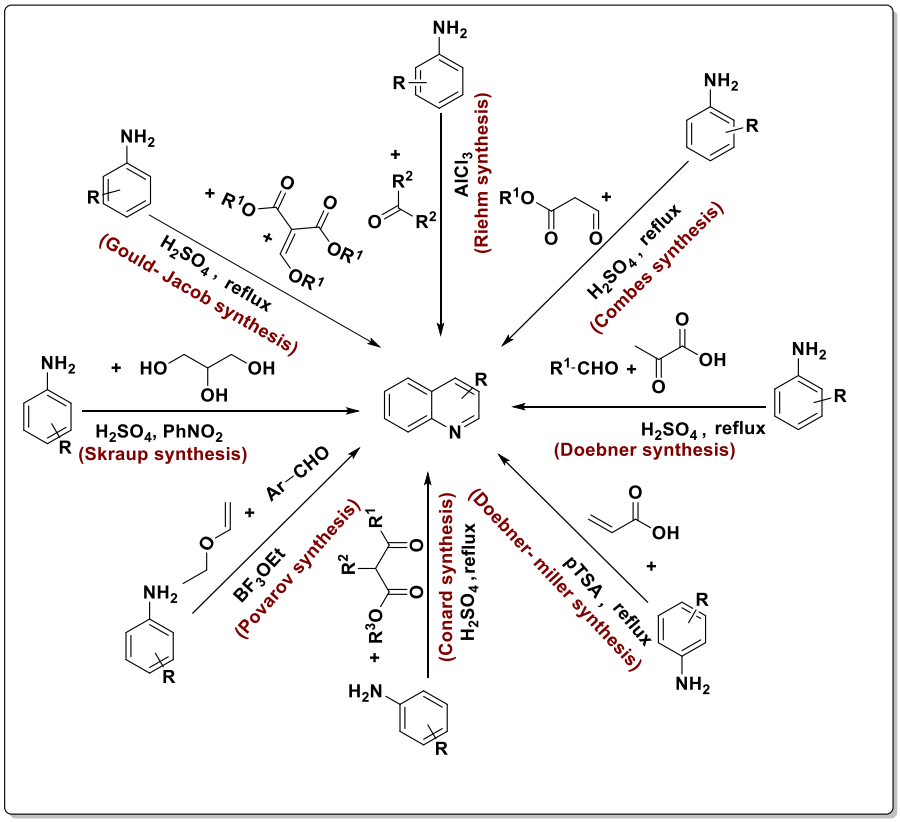


Figure II. 2 Diverse synthetic routes for the synthesis of quinoline structures

II.3 Biological importances of quinolines

Quinoline scaffolds are well-known entity under alkaloid class of natural products and is present in various biologically active plants, pharmaceuticals, agrochemicals, dyes etc.[60-61] They are also used as chelating agent due to multiple N-donor ligands and quinoline pharmacophore is a crucial functionalitydue to variety of pharmacological activities (**Figure II. 3**) such as antimalarial,

antiprotozoal, antitubercular, antibacterial, anticancer, antiproliferative, antitumor, anti-inflammatory, antifungal, antioxidant, DNA binding, antihypertensive, anti-HIV agents. [62-70] High magnitude of pharmacological importance of natural or synthesized quinoline derivatives has urged various chemists world wide to examine the utility and prominence of this scaffold by means of research reviews.

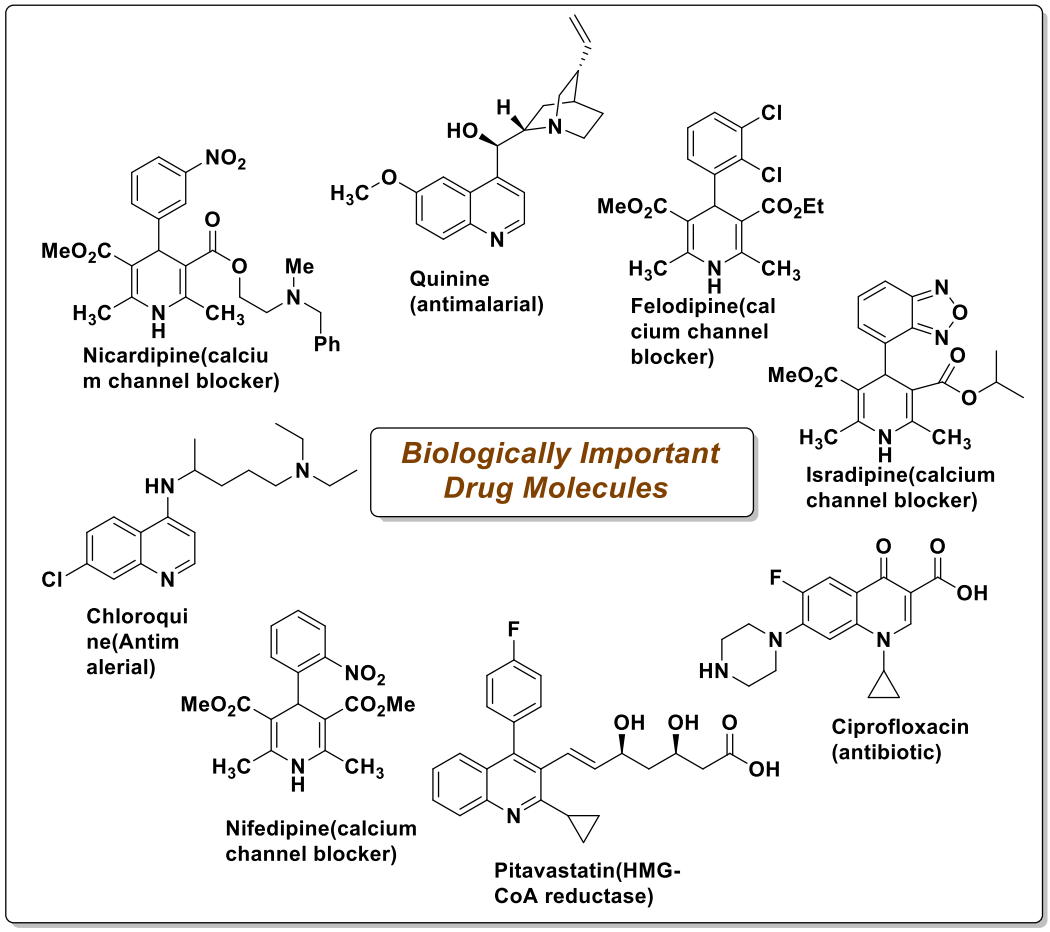
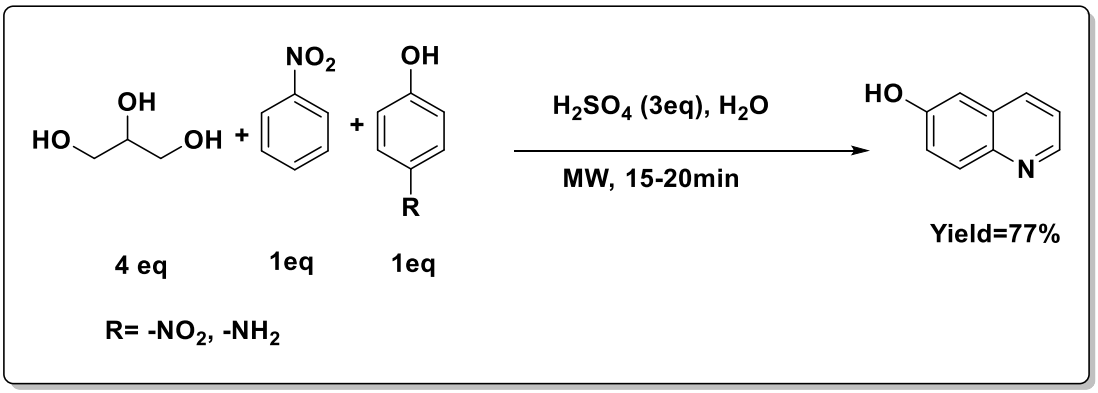


Figure II. 3 Some important pharmaceutically active drug molecule

By doing studies on works in various journals and reviews related to quinolines, substituted quinolines, unsaturated quinolines and their derivatives and taking biological importances of their derivatives in knowledge, in this following part of the chapter II, it has been focused on the synthesis of quinoline derivatives in a new and convenient manner using available laboratory chemicals.

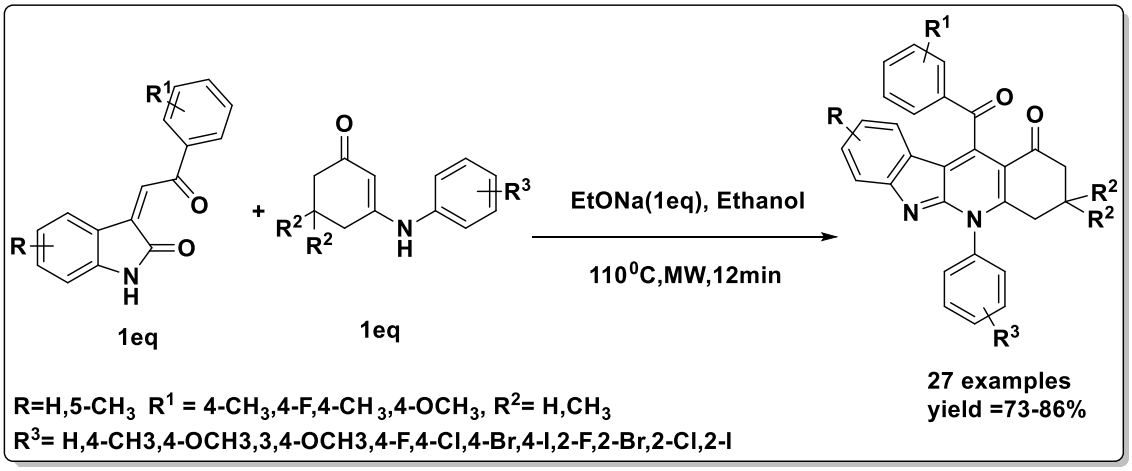
II.4 Previous methods of synthesis of quinoline derivatives

In 2014, Saggadi *et al.* had developed a synthetic method following Skraup reaction and Bamberger rearrangement reaction in water using glycerol, nitrobenzene and *p*-aminophenol or *p*-nitrophenol as reactants under microwave condition (**Scheme II.1).** [71]



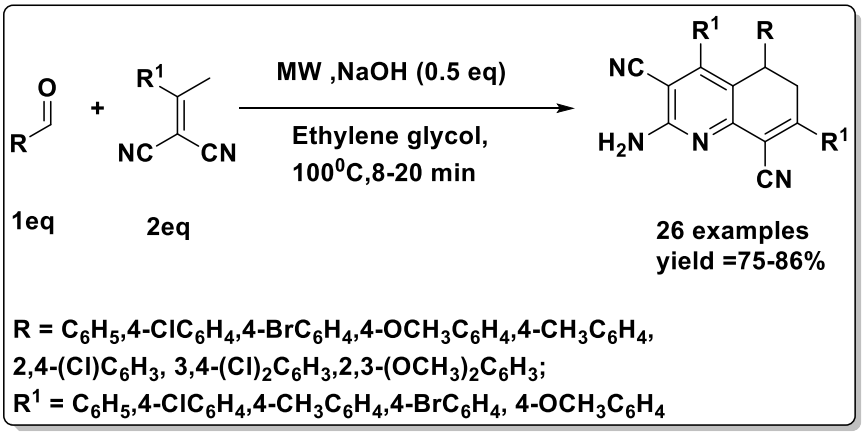
Scheme II.1 Modified Skraup reaction and Bamberger rearrangment reported by Saggadi *et al*.

In 2014, Li *et al*. developed a protocol to synthesize biologically active quinolines using 3-aroylidene-2-oxindoles with enaminones in presence of sodium ethoxide in ethanol at 110°C under microwave condition (**Scheme II.2**). [72]



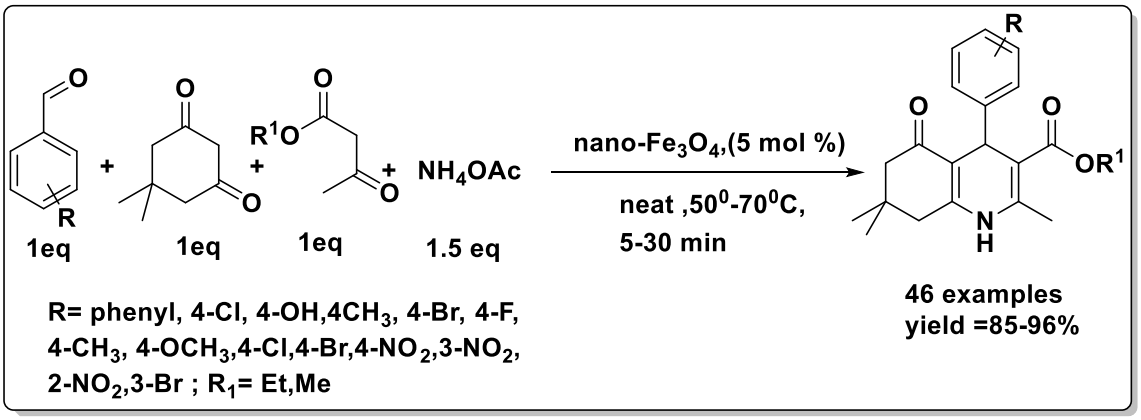
Scheme II.2 Base promoted cycloaddition reaction under microwave condition reported by *Li et al*.

In 2012, *Yu et al*. designed a three component synthesis of polysubstituted dihydroquinoline from aromatic aldehydes and 1-arylethylidenemalononitrile in presence of sodium hydroxide as base in ethylene glycol under microwave irradiation (**Scheme II.3**). [73]



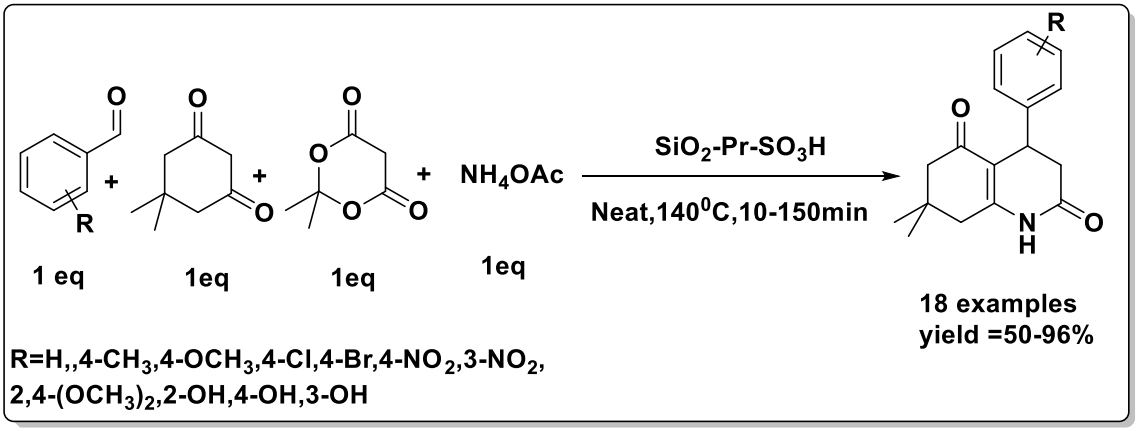
Scheme II.3 Base catalyzed Domino reaction under microwave reported by Yu et al.

In 2014, Esfahani *et al*. and Khazaei *et al*. performed iron (III) oxide nanoparticles catalyzed synthesis of polyhydroquinolines under solvent free conditions using aromatic, cyclic and heterocyclic aldehydes, dimedone, β-ketoesters and ammonium acetate at 50°C under solvent free conditions (**Scheme II.4**). [74-75]



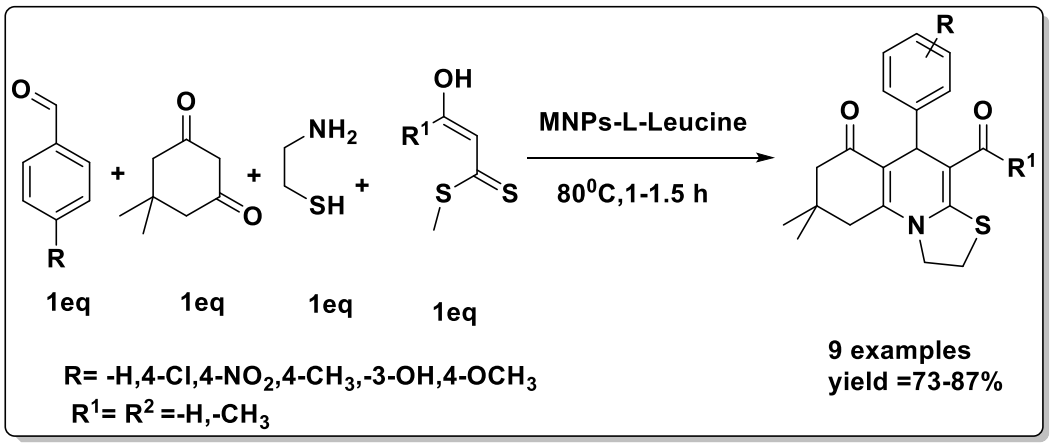
Scheme II.4 Nano-Fe_3O_4 catalysed solvent free reaction reported by Esfahani *et al.*

In 2015, Ziarani *et al.*, synthesized dioxo-octahydroquinolines in one pot method using aromatic aldehydes , dimedone , Meldrum's acid and ammonium acetate and sulfonic acid functionalized SiO_2-Pr-SO_3H as catalyst under solvent-free condition (**Scheme II.5**).[76]



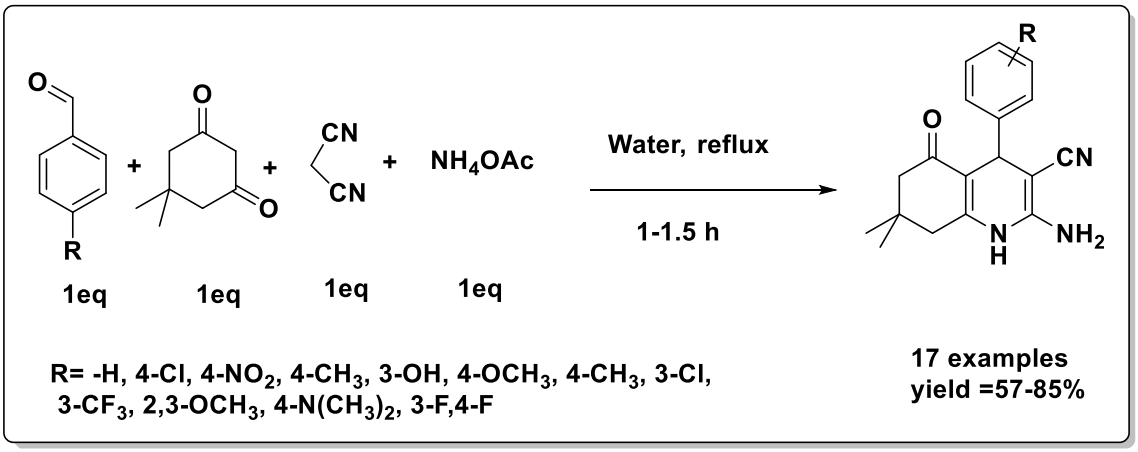
Scheme II.5 Silica based catalyst induced reaction for octahydroquinolines by Ziarani *et al*.

In 2016, Arabpoor *et al*. synthesized synthesis of thiazoloquinolines using superparamagnetic silica-encapsulated ϒ-Fe_2O_3 supported L-Leucine nanoparticles by the four-component reaction of α-enolicdithioesters, cysteamine, aromatic aldehydes and dimedone under thermal solvent-free condition at 80°C in one hour (**Scheme II.6**).[77]



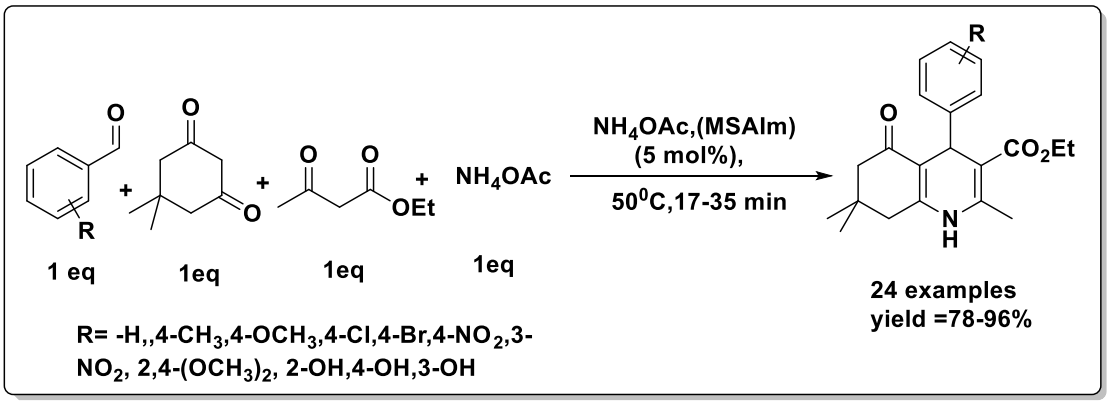
Scheme II.6 MNP-L-Leucine based reaction protocol reported by Arabpoor *et al*.

In 2017, Patil *et al*. had done a catalyst-free method for the synthesis of hexahydroquinolinones in single pot four component method taking dimedone, ammonium acetate, aryl aldehydes and malanonitrile as substrate in water (**Scheme II.7**).[78]



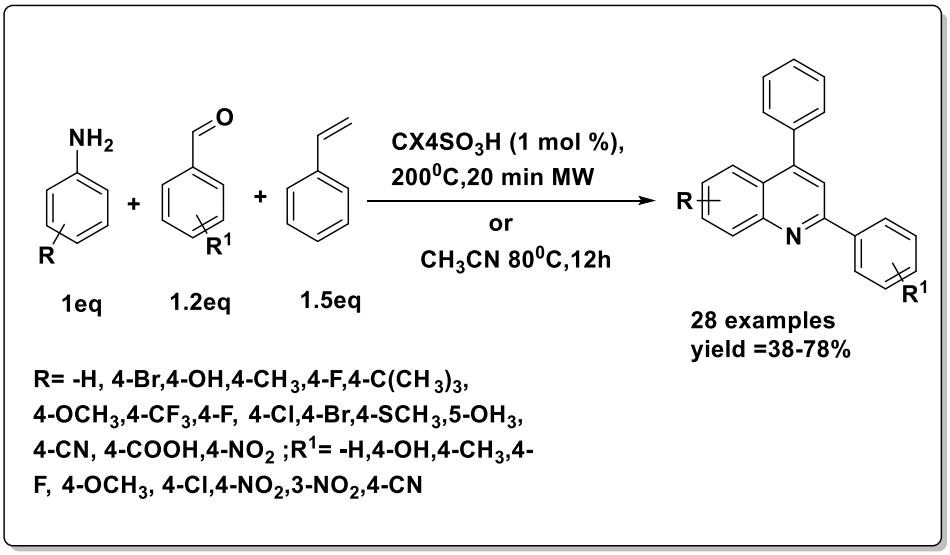
Scheme II.7 Catalyst free synthesis protocol reported by Patil *et al*.

In 2014, Khaligh *et al*. had done a four-component one-pot synthesis of synthesis of unsymmetrical polyhydroquinoline derivatives from aryl/heteroaryl aldehydes, ethylacetoacetate, dimedone and ammonium acetate under solvent-free conditions at 50^0C (**Scheme II.8**). [79]



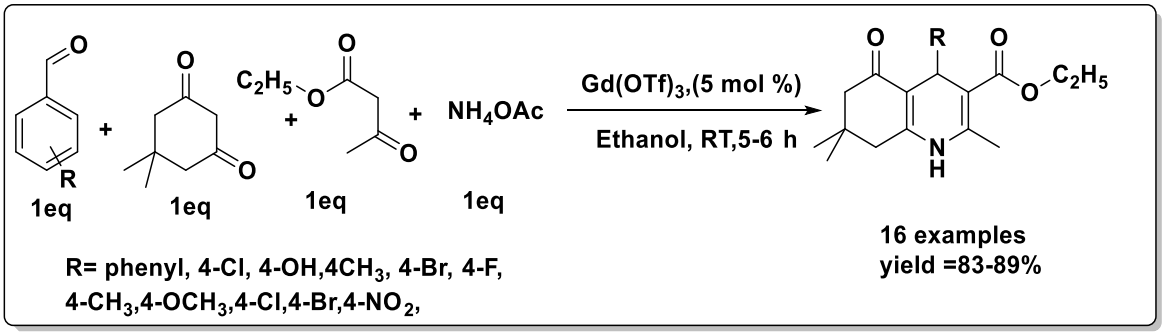
Scheme II.8 MSAIm catalysed Solvent free reaction reported by Khaligh *et al.*

In 2017, Liberto *et al*. has taken a protocol for the synthesis of 2,4-disubstituted quinolines using aromatic aldehydes, aromatic amines, styrene under at 200^0C temperature Microwave condition using CX4SO_3H catalyst or at 80^0C temperature in acetonitrile solvent (**Scheme II.9**). [80]



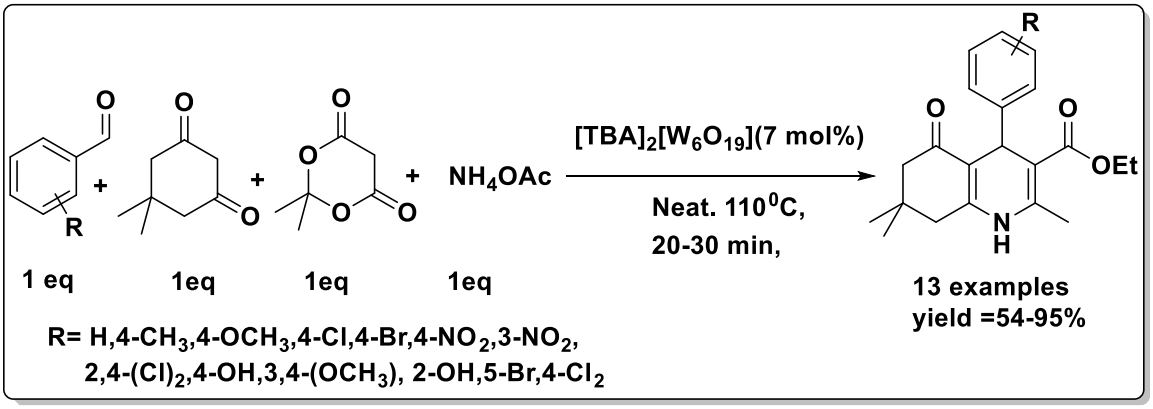
Scheme II.9 Microwave assisted solvent free reaction reported by Liberto *et al*.

In 2017, Mansoor *et al*. reported a muticomponent method by for the synthesis of hexahydeoquinolones by using $Gd(OTf)_3$ as catalyst from aldehydes, 5,5-dimethyl-1,3-cyclohexaedione dimedone, ethyl acetoacetate and ammonium acetate by using $Gd(OTf)_3$ as catalyst at room temperature (**Scheme II.10**). [81]



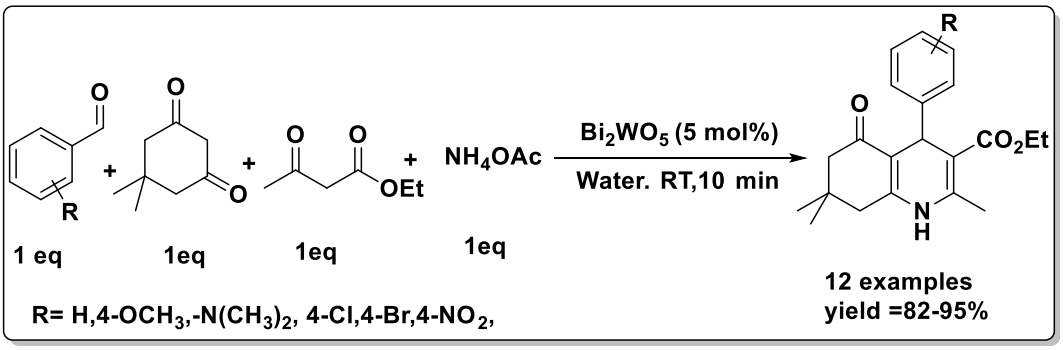
Scheme II.10 $Gd(OTf)_3$ catalysed synthesis of polyhydroquinolines in ethanol reported by Mansoor *et al*.

In 2011, Khojastehnezhad *et al*. reported a synthetic method for the synthesis of hexahydroquinolinones in one-pot, four-component method taking dimedone , aldehydes , ethyl acetoacetate and ammonium acetate under solvent-free conditions using $[TBA]_2[W_6O_{19}]$ catalyst (**Scheme II.11**). [82-83]



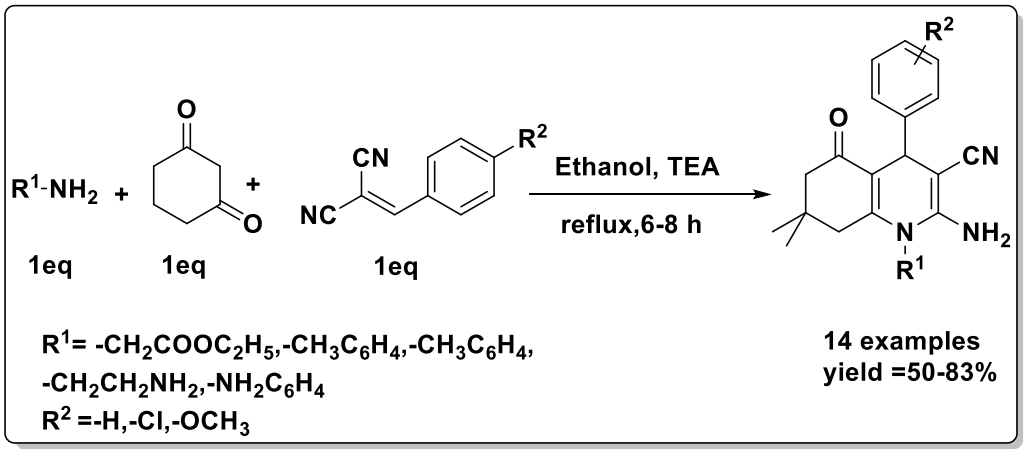
Scheme II.11 Solvent free reaction reported by Davoodnia *et al*. and Khaligh *et al*.

In 2014, Paplal *et al*. synthesized different types of functionalized polyhydroquinolines by reaction of substituted aromatic aldehydes, ethyl acetoacetate, dimedone and ammonium acetate in aqueous medium using Bi_2WO_5 as catalyst (**Scheme II.12**).[84]



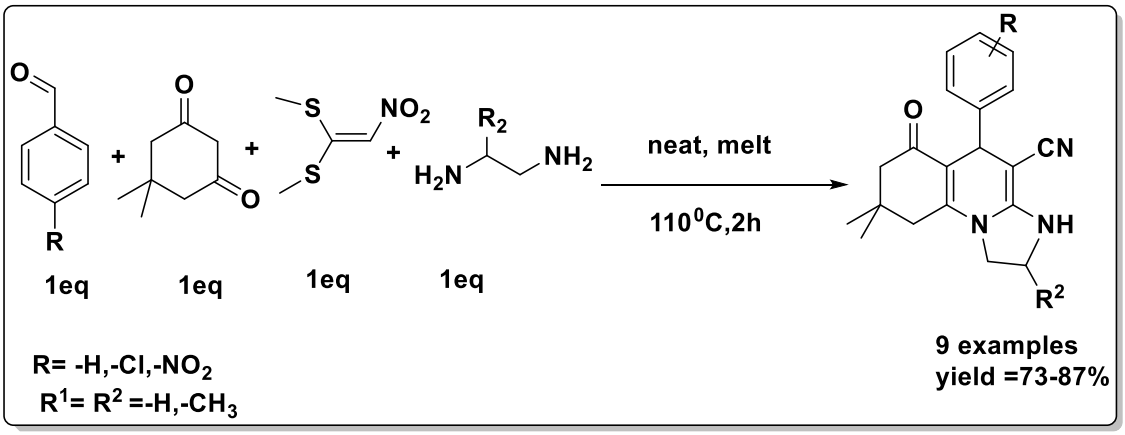
Scheme II.12 Synthesis of functionalized polyhydroquinolines reported by Paplal *et al.*

In 2017, Abdelhamid *et al*. had made a protocol for the three-component cyclocondensation synthetic method of hexahydroquinoline derivatives from 1,3-cyclohexanedione, primary amine in presence of ethanol, TEA under reflux condition (**Scheme II.13**). [85]



Scheme II.13 Three-component cyclocondensation with TEA in ethanol reported by Abdelhamid *et al*.

In 2014, Alizadeh *et al*. sythesised the octahydro-imidazo[1,2-*a*]quinoline derivatives under solvent free conditions from aromatic aldehyde, dimidone as amazor component (**Scheme II.14**). [86].



Scheme II.14 Solvent free reaction reported by Alizadeh *et al*.

II. 5 Acridine

Acridine is a nitrogeneous heterocyclic compound having planner shaped structural motif and it is also structurally closely resembles to anthracene with one of the central C-H group is replaced by 'N' atom. It is a basic organic compound due to the presence of Sp^2-hybridised 'N' atom and the unsubstituted compound is generally colourless crystalline solid.[87] In 1870 Carl Grabe and Heinrich Caro first isolated acidine from coal tar by extracting with dil. H_2SO_4 .[88] Acrinines have broad range of research and industrial applications in various fields such as in medicinal chemistry, fluorescent organic dye, chemosensor, photo catalysis, as hole transport materials in solar cell and photovoltaic applications.[89-97] Acridinium ions are used as efficient organic photo catalyst for many organic transformations due to their long excited state lifetime and tunable redox potential.[98-99] There are various procedures [100-109] for the synthesis of acridine structural motifs but at the very first Bernthsen *et. al* have synthesized it in laboratory by using diphenylamine and carboxylic acid in presence of anhydrous $ZnCl_2$.[110]. There are also other methods (**Figure II. 4**) which have been developed in recent years and which has opened a broad window for the organic synthesis of acridine structural motifs.

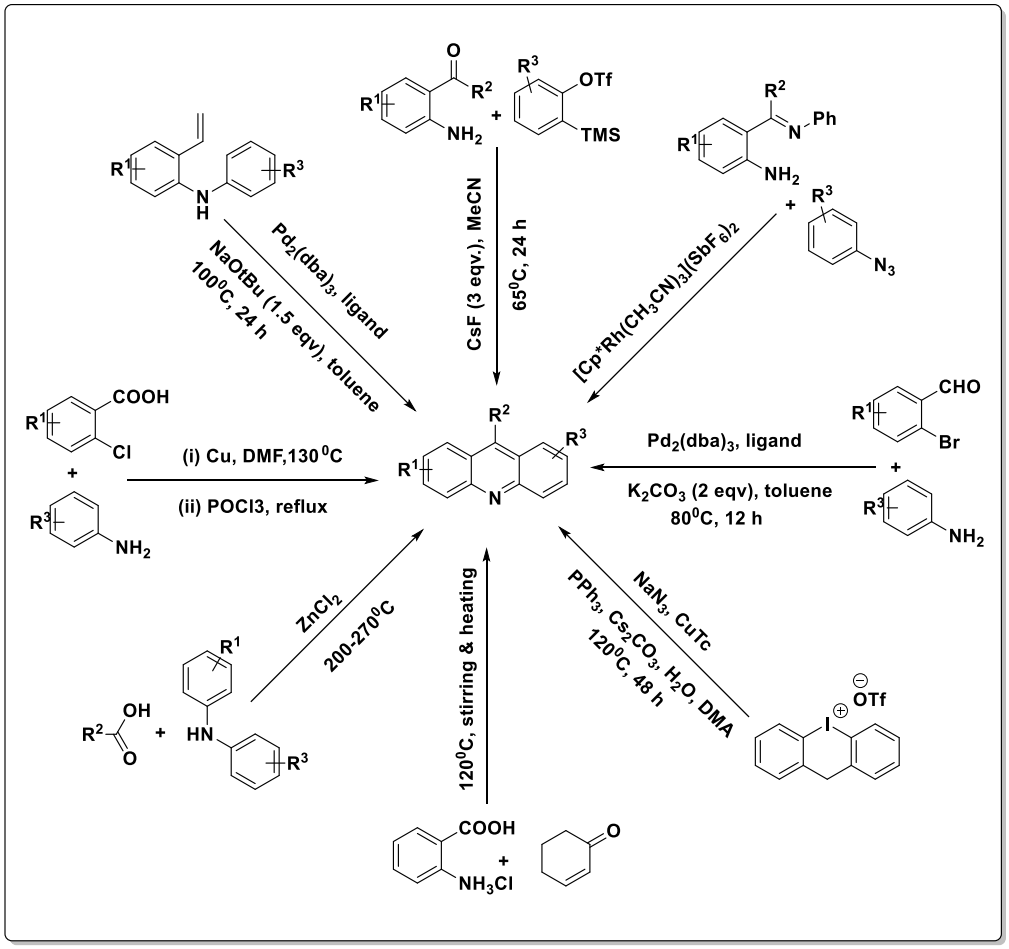


Figure II. 4 Diverse synthetic routes for the synthesis of acridine structures

II. 6 Biological importance of Acridines

Acridine derivatives have been used for the preparation of labeled medicinal conjugates such as nucleic acids, peptides, and proteins that exhibit antitumor and DNA-binding properties [111-113]. Among other acridine derivatives, substituted 1,8-Dioxo-decahydroacridines and their derivatives have been widely used in medicinal chemisty as can behave as alternative of 1,4-dihydropyridines from a variety of viewpoints such

as biological activities and due to close resemblance with 1,4-dihydropyridines in respect of the biological properties 1,8-Dioxo-decahydroacridines have been used as calcium channel blockers for the treatment of defibrillation and hypertension disease [114-116]. They also possesses antimalarial, antiviral, antibacterial, antiallergic and anicancer properties and recently, acridines showed some inhibition properties for multidrug resistance in tumour cell lines and some of the acridine drugs are exhibiting promising anticancer activity both in vitro and in vivo against a range of murine and human cancers cells (**Figure II. 5**).[117-120] And additionally due to having fluorescent properties they are being used as molecular probes for monitoring polymerization processes in biological cells.[121]

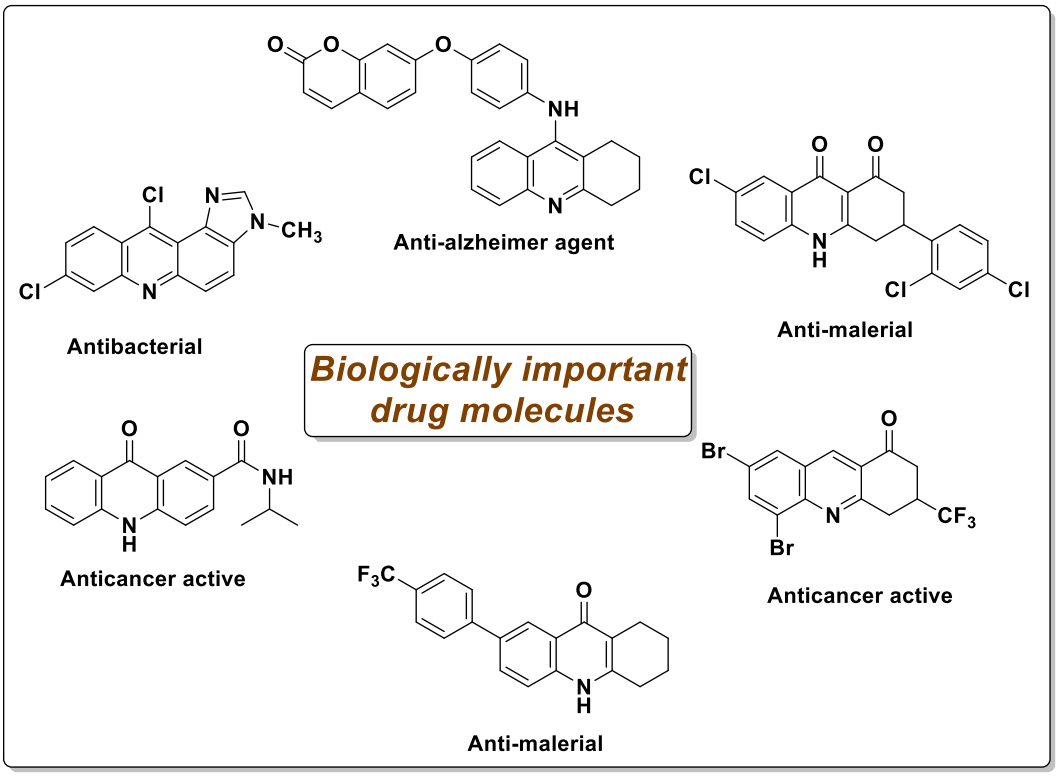


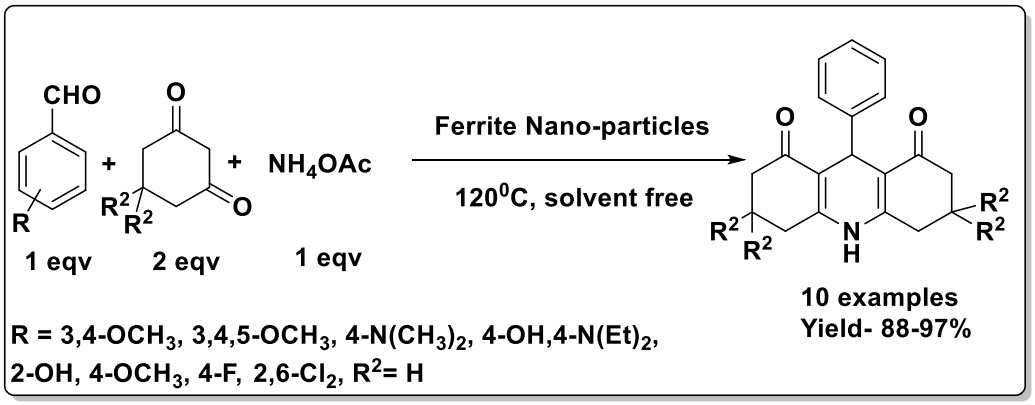
Figure II. 5 Some important pharmaceutically active drug molecule

By doing studies on works in various journals related to acridines, acridinediones and their derivatives and taking biological importances of acridines, acridinediones and their derivatives in knowledge , in this following part of the chapter II, it has been focused on the acridine-dione derivatives in a new and convenient manner using cheap laboratory chemicals.

II. 7 Previous methods synthesis of acridine derivatives

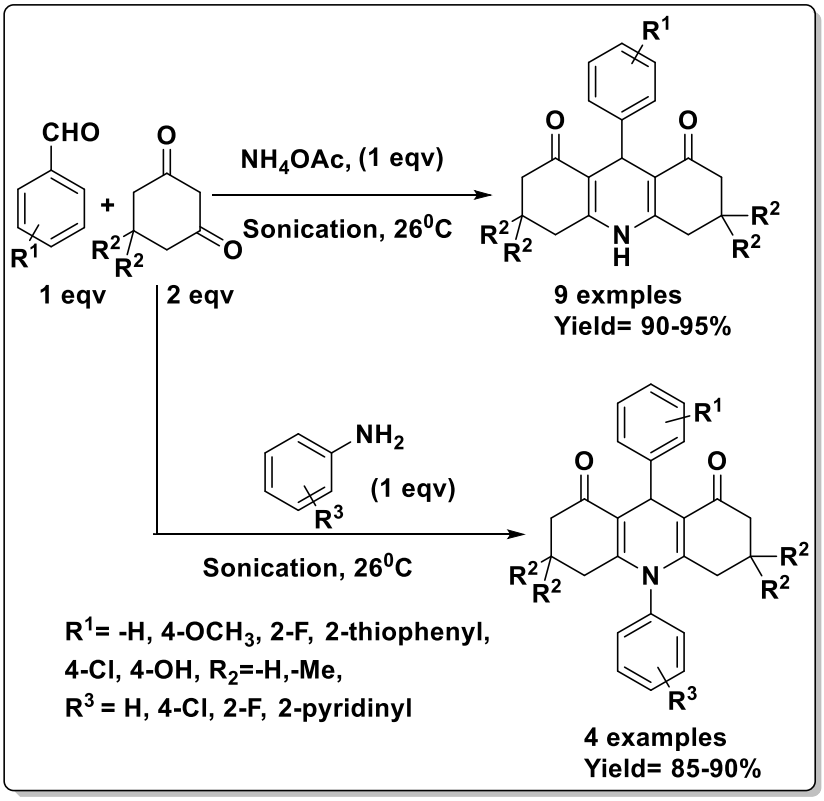
In 2016, Sunkara *et al.* had done the synthesis of 9-aryl substituted acridinedione derivatives under solvent free conditions. A one-pot

reaction methodology was adopted with the use of 1,3-cyclohexanedione, aldehydes and ammonium acetate using nano ferrite at 120^0C for the preparation of acridinediones and their derivatives (**Scheme II.15**).[122]



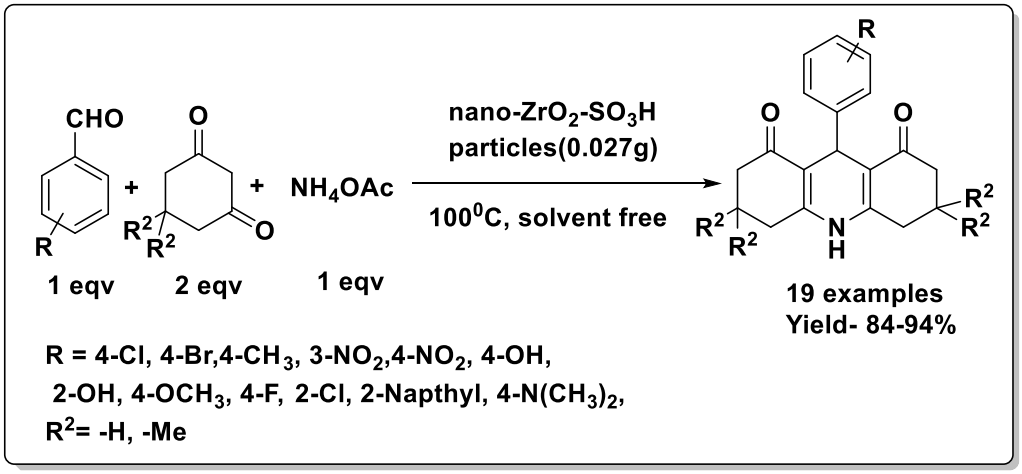
Scheme II.15 Ferrite nano-particles catalysed facile synthesis of acridinediones by Sunkara *et al*.

In 2013, A Facile Synthesis of N-H- and N-Substituted Acridine-1,8-diones under Sonic Condition by Sudha *et. al*. Here ceric ammonium nitrate (CAN) was used along with aromatic aldehydes and aromatic amines or ammonium acetate and dimedone or cyclohexyl-1,3-diones at 26^0C under sonic condition (**Scheme II.16**). [123]



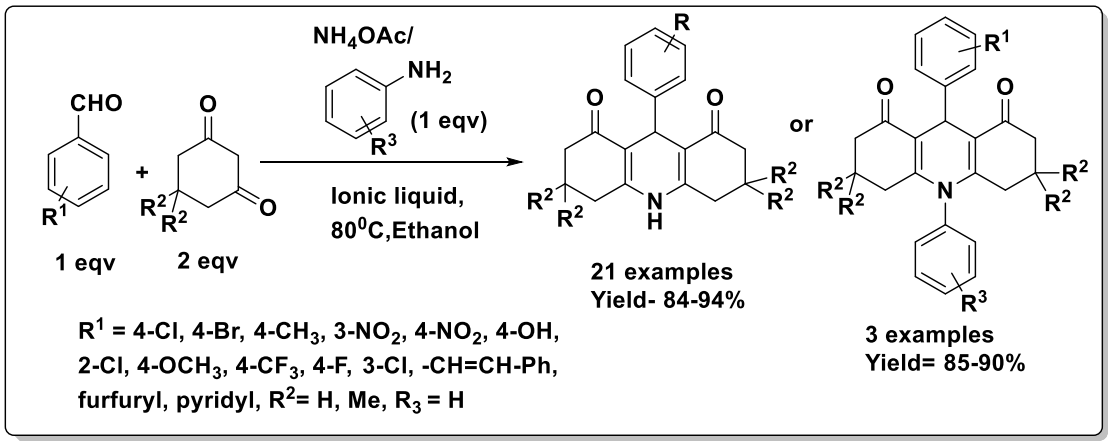
Scheme II.16 Ultasound sonication induced synthesis of acridinedione derivatives by Sudha *et. al*.

In 2016, Amoozadeh *et al*. synthesized 9-arylhexahydroacridines with taking a mixture of various 1,3-cyclic diketone, aromatic aldehydes, and ammonium acetate in presence of n-ZrSA as catalyst at 100 °C (in an oil bath) in solvent free conditions (**Scheme II.17**). [124]



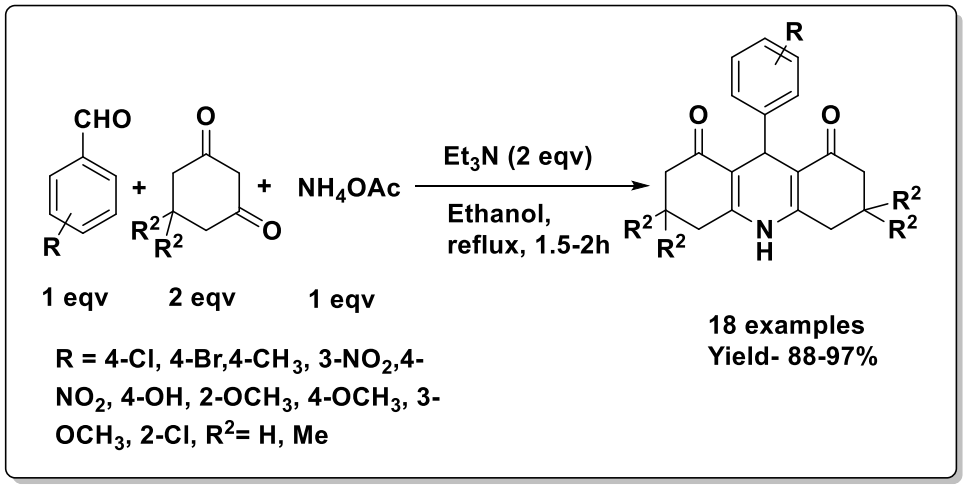
Scheme II.17 Nano-ZrO_2-SO_3H catalysed synthesis of acridinedione derivatives by Amoozadeh *et al*.

In 2017, Zhu *et al*. reported the synthesis of 9-arylhexahydroacridines using aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione, NH_4OAc and corresponding amount of ionic liquid were mixed with 1 ml ethanol, and then heated at 80^0C by using a series of ionic liquids based on betainium cation (Hbet) with different anions (**Scheme II.18**). [125]



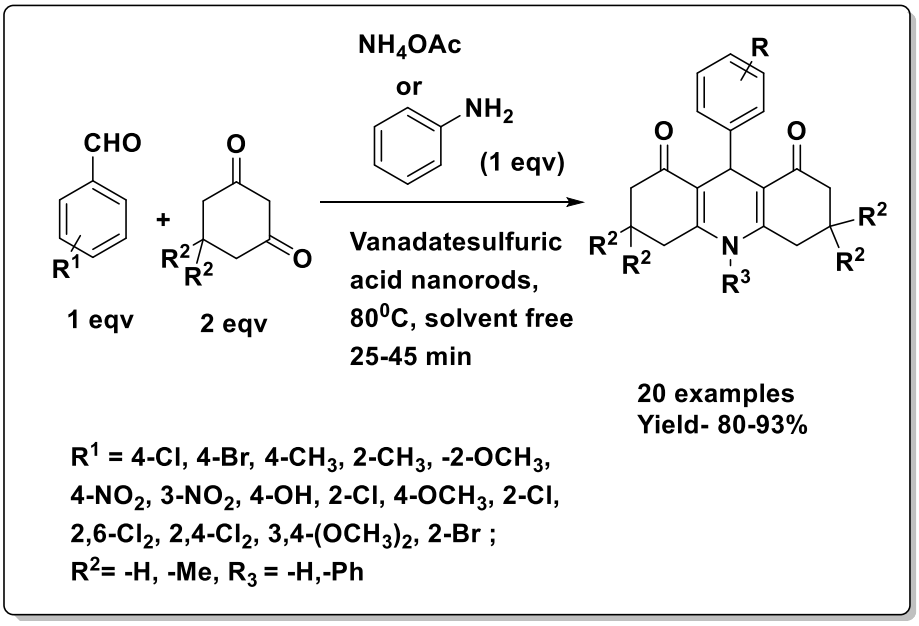
Scheme II.18 Ionic liquids catalysed synthesis of acridinedione derivatives by Zhu *et al*.

In 2018, Djemoui *et al*. reported an efficient approach to the synthesis of 1,8-dioxo-decahydroacridines and hexahydroquinolines via one-pot multi-component condensation of an aromatic aldehyde, cyclic 1,3-diketones and NH_4OAc in ethanol with use of Triethylamine (TEA) at reflux condition (**Scheme II.19**).[126]



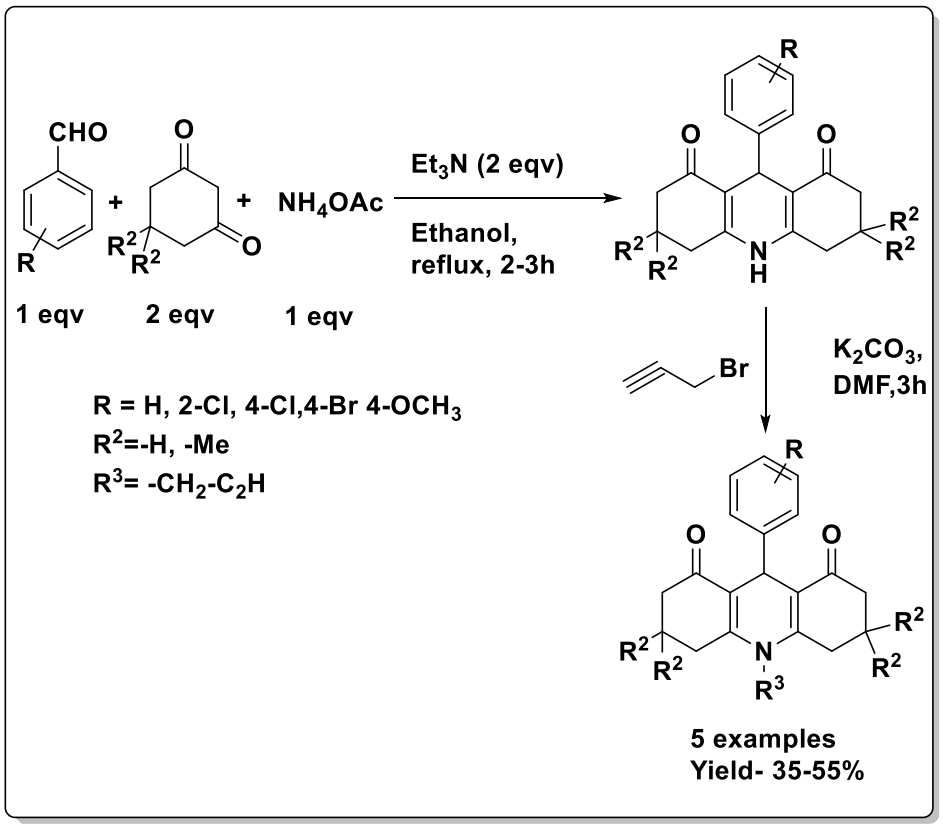
Scheme II.19 Base catalysed synthesis of acridinedione derivatives by Djemoui *et al*.

In 2015, Nasr-Esfahani *et al.* reported a synthesis of hexahydroacridine-1,8-diones using 1,3- cyclohexanedione derivatives, aldehydes and ammonium acetate or aniline under solvent-free conditions. Nanorod vanadatesulfuric acid (VSA-NRs), was used as catalyst as a novel, recyclable and eco-benign catalyst to synthis hexahydroacridine-1,8-diones (**Scheme II.20**). 127]



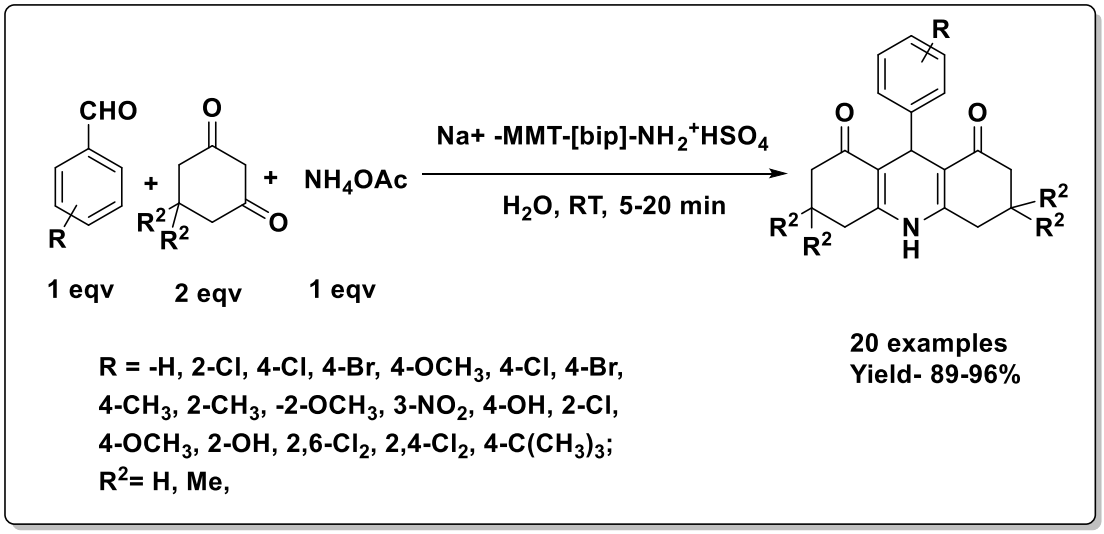
Scheme II.20 Vanadate sulfuric acid catalysed synthesis of acridinedione derivatives by Nasr-Esfahani *et al*.

In 2020, Naouri *et al*. reported a procedure for the preparation of 1,8-dioxodecahydroacridine derivatives via a one-pot three-component condensation of aromatic aldehydes, 1,3-cyclohexanedione and ammonium acetate in ethanolic medium under reflux condition catalyzed by triethylamine (TEA) to give the desired product (**Scheme II.21**).[128]



Scheme II.21 Et_3N catalysed synthesis of acridinedione derivatives by Naouri *et al*.

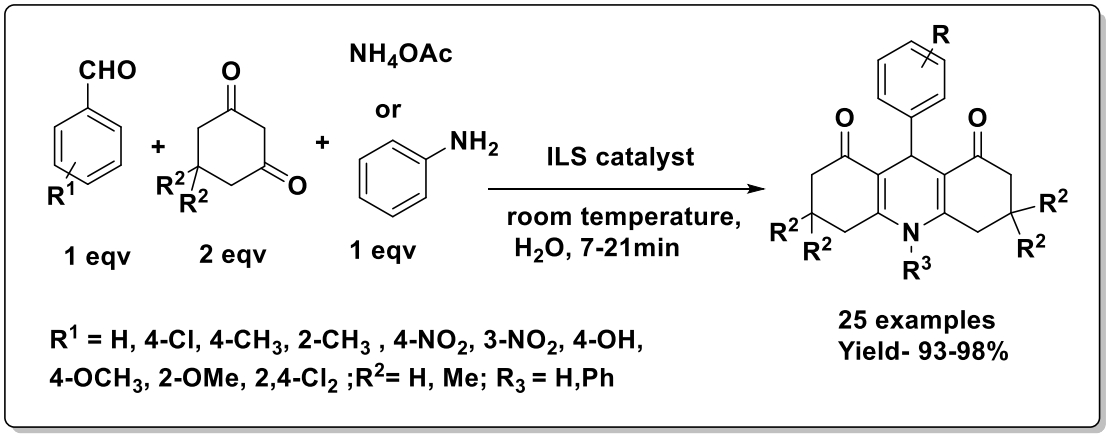
In 2020, Mazloumi *et al*. reported the synthesis of hexahydroquinolines and 1,8-dioxo-decahydroacridines via Hantzsch condensations using a new nanoporous catalyst formulated as Na+ -MMT-[bip]-$NH_2^+HSO_4^-$. All reactions were performed under mild reaction conditions taking mixture of a *β*-ketoester derivative, 1,3-cyclohexanedione derivatives, aldehyde, and ammonium acetate(**Scheme II.22**). [129]



Scheme II.22. Ionic liquid catalysed synthesis of acridinedione derivatives by Mazloumi *et al.*

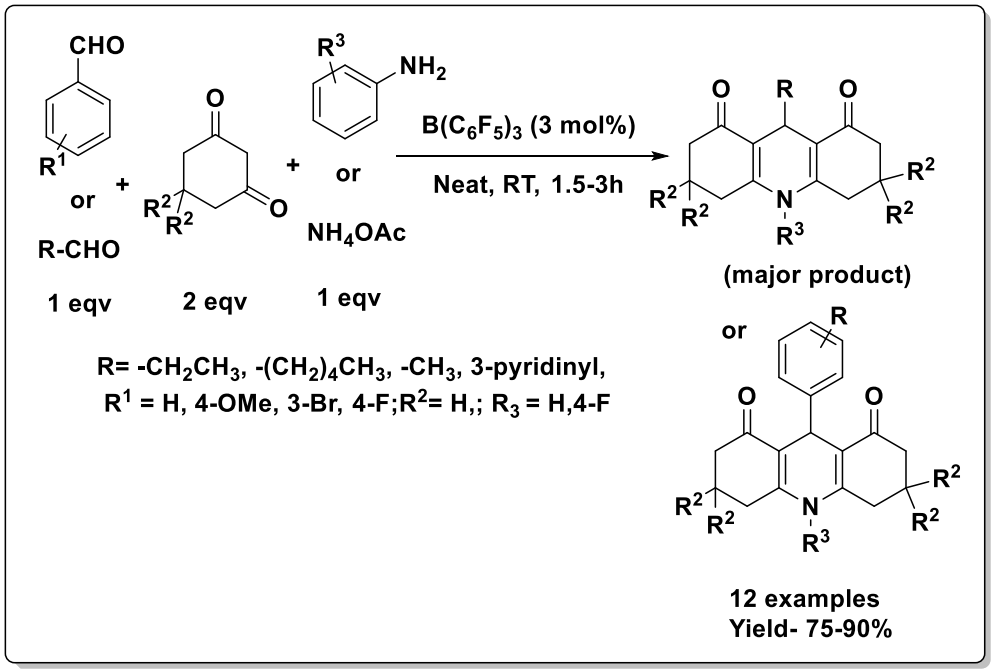
In 2011, Vahdat *et al*. had synthesised 1,8-dioxodecahydroacridines by using ionic liquid with multi-SO_3H groups

attached with it via the one-pot method with excellent yield within at room temperature in water medium (**Scheme II.23**).[130]



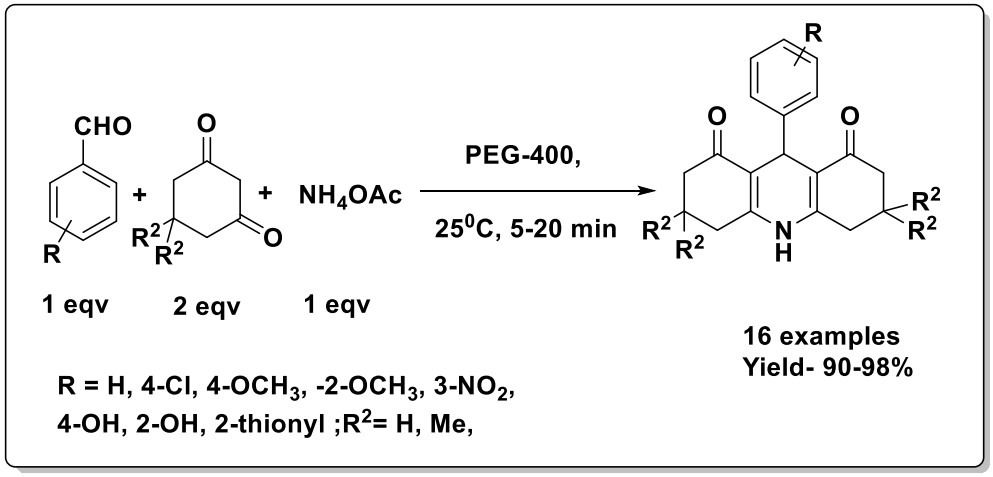
Scheme II.23. Ionic liquid catalysed synthesis of acridinedione derivatives by Vahdat *et al*.

In 2008, A mild and efficient method for the synthesis of 1,8-dioxodecahydroacridines has been developed by Chandrasekhar *et al*. via a three-component reaction of a cyclic 1,3-dione, an aldehyde and an amine, under solvent-free conditions, at room temperature catalyzed by tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] (**Scheme II.24**).[131]



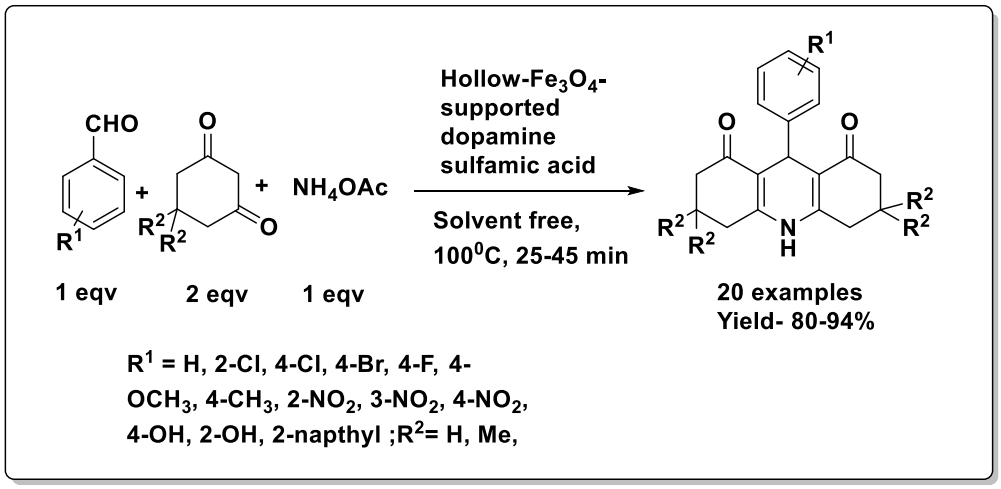
Scheme II.24. $B(C_6F_5)_3$ catalysed synthesis of acridinedione derivatives by Chandrasekhar *et al*.

In 2010, Kidwai *et al*. synthesized decahydroacridine-1,8-diones in the presence of polyethylene glycol (PEG) which was found to be an inexpensive non-toxic and effective medium for one pot synthesis of the product with higher yields (**Scheme II.25**). [132]



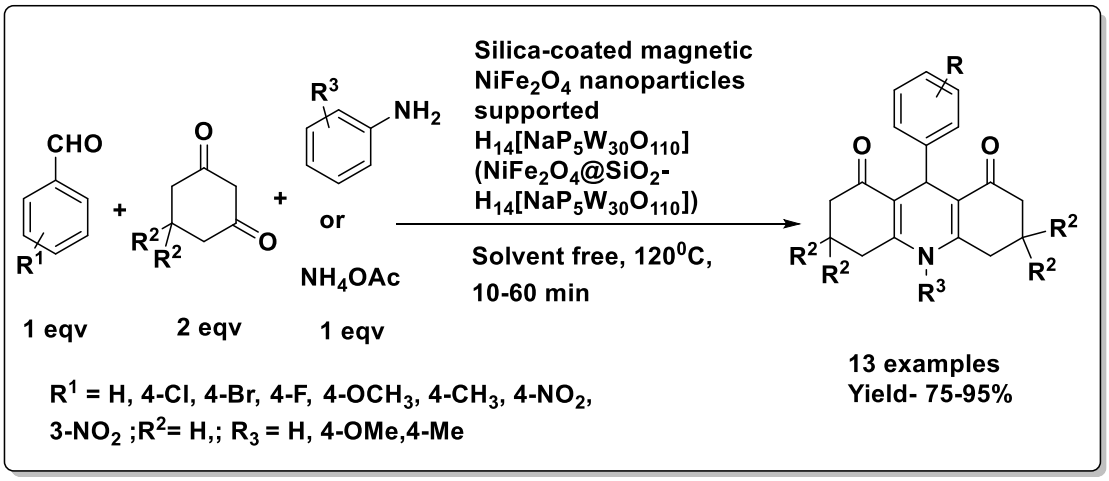
Scheme II.25. PEG-400 catalysed synthesis of acridinedione derivatives by Kidwai *et al*.

In 2017, Mirhosseyni *et al*. reported the synthesis of 1,8-dioxodecahyroacridine derivatives using H-Fe_3O_4@DA-SO_3H as catalyst by using aldehyde , ethyl acetoacetate or 1,3-cyclohexanedione NH_4OAc at 100^0C under solvent-free condition (**Scheme II.26**). [133]



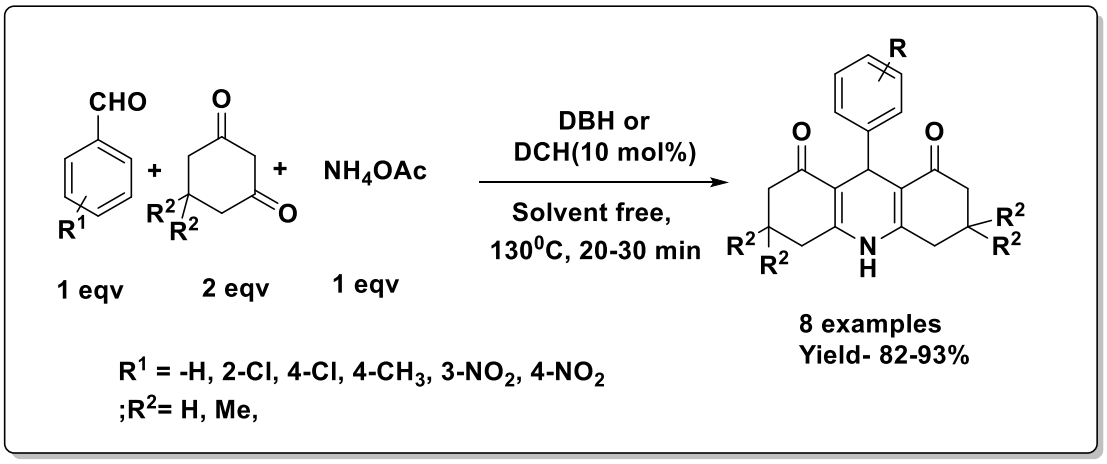
Scheme II.26. Hollow Fe_3O_4 supported dopamine sulfamic acid catalysed solvent free synthesis of acridine dione derivatives by Mirhosseyni *et al*.

In 2017 Malekia *et al*. reported Silica-coated magnetic $NiFe_2O_4$ nanoparticles-supported $NiFe_2O_4@SiO_2$-$H_{14}[NaP_5W_{30}O_{110}]$ was successfully synthesized and shown to be a versatile and highly efficient heterogeneous catalyst for one-pot multicomponent synthesis of 1,4-dihydropyridine derivatives under solvent-free condition. The synthesized catalyst can be magnetically recovered and reused four times without significant loss in catalytic efficiency (**Scheme II.27**).[134]



Scheme II.27. Silica coated magnetic nanoparicles catalysed solvent free synthesis of acridine dione derivatives by Maleki *et al.*

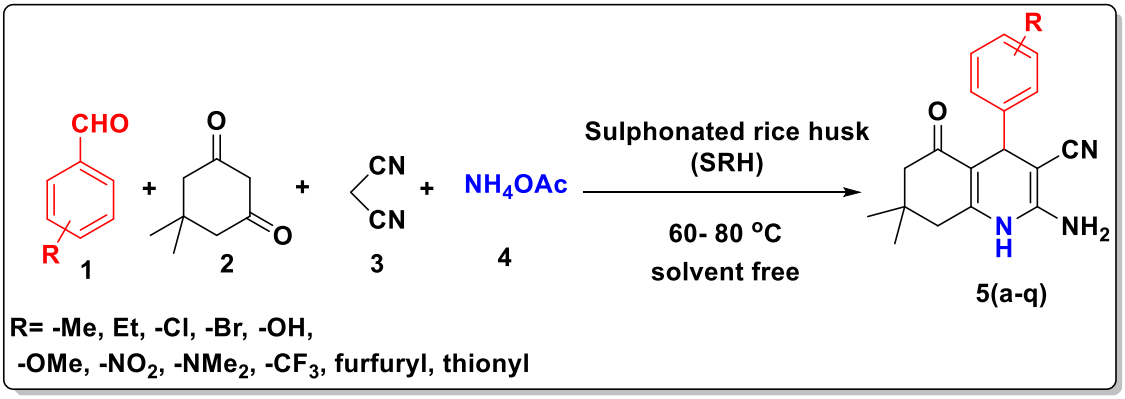
In 2013, Maleki *et al*. reported a solvent free one pot synthesis of 1,8-dioxodecahydro acridine derivatives which have been described via Hantzsch condensation of various aldehydes, ammonium acetate,cyclic 1,3-dicarbonyl compounds in a very simple, efficient and environmentally benign method with excellent yield (**Scheme II.28**). [135]



Scheme II.28. DBH or DCH catalysed solvent free synthrsis of acridine dione derivatives by Maleki *et al*.

II.8 Present work

The present work leads to the synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives (**Scheme II.29)** by using greener heterogeneous catalyst sulphonated rice husk (SRH) .



Scheme II.29 Synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives using sulphonated rice husk

II.8.A Result & discussion

II.8.A.1 Catalyst Characterisation

The prepared catalyst was characterised by FTIR spectroscopy, scanning electron microscopy (SEM), powder X-ray diffraction (XRD) and ICP-AES for quantifying weight percentage of sulphur and other elements.The comparison of FTIR, SEM image and XRD pattern of RH and SRH strongly supports the synthesis of the sulphonated catalyst through a completely new method. The comparison of SEM images of RH and SRH shows that a molecular aggregation occurs in SRH resulted from the incorporation of $–SO_3H$ functional group into the skeleton of rice husk material (**Figure II.6**). EDX analysis of sulphonated rice husk

and rice husk showed a measurable difference in the weight percentage of the elements especially carbon, slicon, sulphur and oxygen (Figure II.6, Experimental section of Chapter II. The newly appearing band with a peak 1098cm^{-1} represents the symmetric and asymmetric streatching of S=O bonds of $–SO_3H$ (sulphonic acid).The the new broad band at 3342 cm^{-1} along with the band at 1098 cm^{-1} both confirmly denoting the incorporation of $–SO_3H$ groups in SRH after sulphonation of rice husk (**Figure II.8**) . The powder XRD analysis shows characteristics peaks at $2\theta = 20.82^o, 22.28^o, 26.67^o$ in which a broad peak at around 20^o is due to the carbon composed aromatic sheets which are oriented in a random manner (**Figure II. 7**).[58] ICP-AES analysis showed that weight percentage sulphur is 1% to that of total weight of all the elements present. To make surety in broad aspect all the results and graphs were thoroughly viewd and compared with other sulphonated materials such as sulphonated rice husk ash [59], CBSC (carbon-based sulphonated catalyst) [57] which confirmly showed that SRH was morphologically and compositionally different from those reported sulphonated catalysts. Detailed characterization informations are given into the experimental section (**II.8.A.12.i** and **II.8.A.12.j**) of the Chapter II.

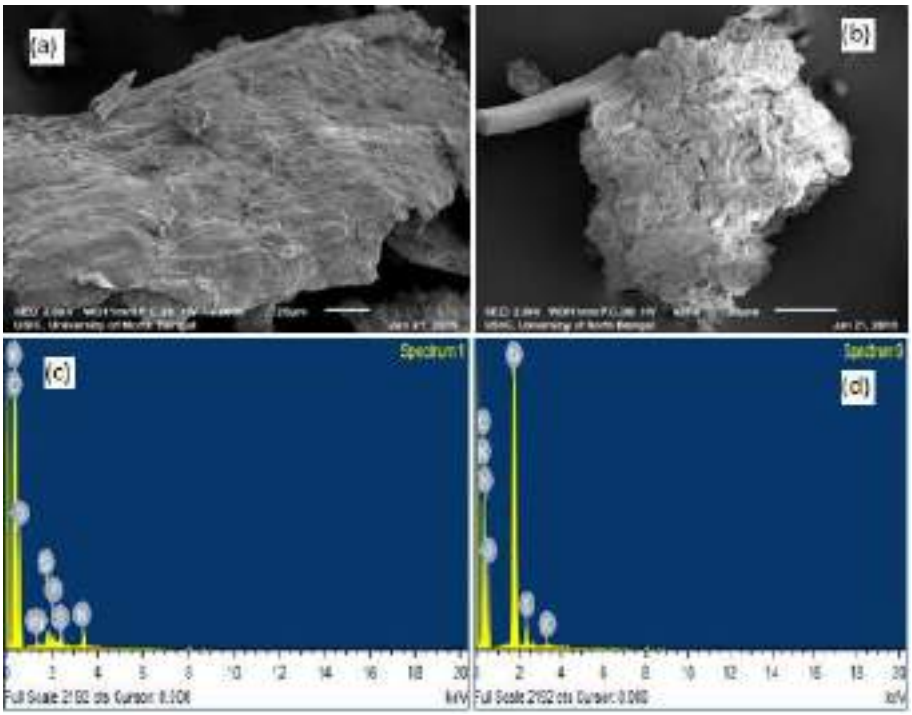


Figure II.6 (a) SEM image of rice husk(RH) (b) SEM image of sulphonatrice husk (SRH) (c)EDX of RH (d) EDX of SRH

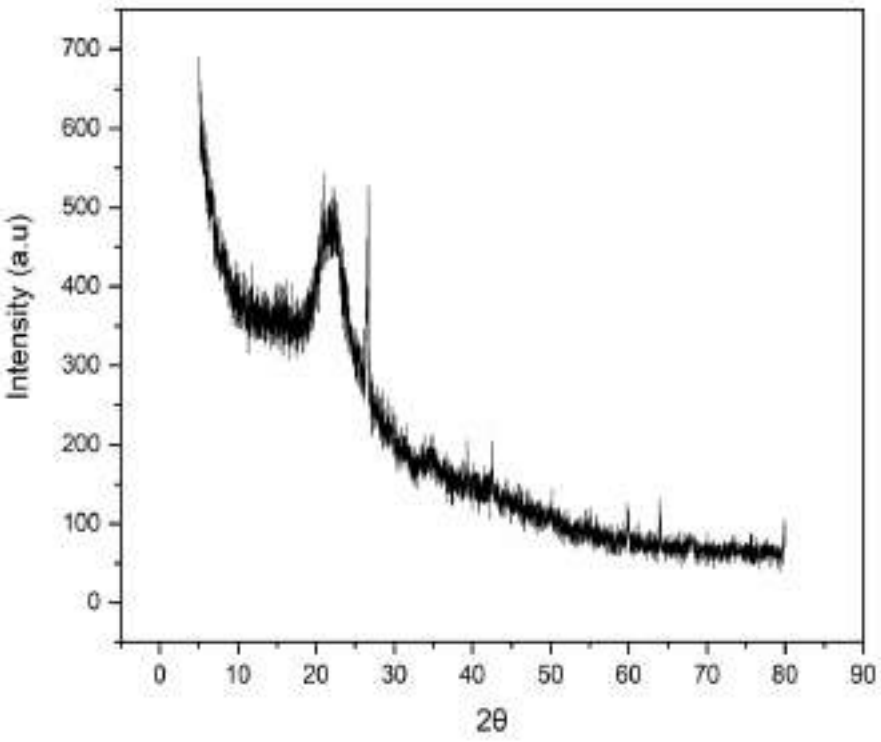


Figure II.7 Powder XRD plot of SRH

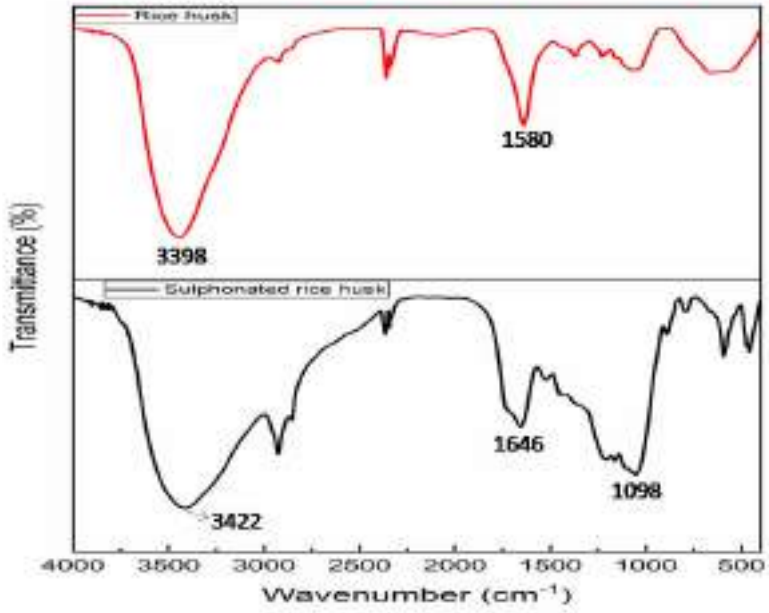


Figure II.8 FTIR of RH and SRH

II.8.A.2 Optimization of the reaction condition for the synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinolines.[a]

Initially, for screening the reaction *p*-tolualdehyde (1 mmol), malononitrile (1 mmol), ammonium acetate (1.2 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) were taken in a 25 mL RB. However, in absence of catalyst the formation of the corresponding product was diminished (**Table II.1**, entry 10). Excellent yield was observed in presence of 100 mg of SRH catalyst in ethanol solvent at 80 ^{o}C temperature (**Table II.1**, entry 1). With decreasing the amount of catalyst, the yield of the product decreases slightly in ethanol. From the optimized condition it is clear that SRH catalyst is proved to be suitable for the conversion of hexahydroquinoline with excellent yield in short reaction time. The amount of the catalyst and time of the reaction was further checked to find out the optimized condition of the reaction. It was observed that the best result was obtained at 70 ^{o}C temperature using 60 mg of catalyst SRH under neat reaction contion (**Table II.1**, entry 13). The progress of the reaction was monitored by thin layer chromatography (TLC) and the pure product was separated by column chromatography with petroleum ether/ethyl acetate (v/v ratio70/30) mixture.

Table II.1 Optimisation of the reaction condition for the synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinolines.[a]

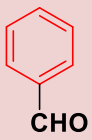
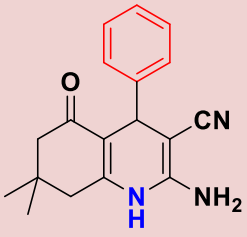
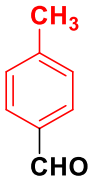
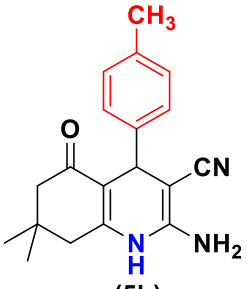
Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	100	Ethanol	80	40	96
2	80	Ethanol	80	30	96
3	70	Ethanol	80	30	94
4	50	Ethanol	80	30	85
5.	40	Ethanol	80	30	78
6.	40	Ethanol	100	30	80
7.	30	Neat	50	120	80
8.	30	Neat	50	90	70
9.	20	Neat	60	60	64
10.	None	Neat	80	120	30
11	80	Neat	70	40	96
12.	80	Neat	70	30	96
13.	**60**	**Neat**	**70**	**20**	**96**
14	60	Neat	60	20	92
15	80	Methanol	80	30	94

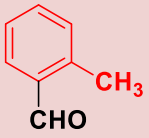
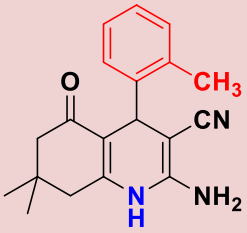
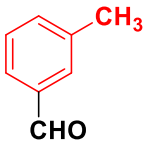
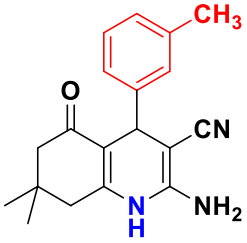
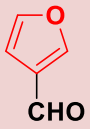
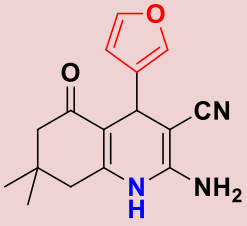
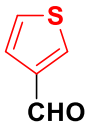
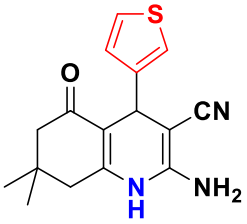
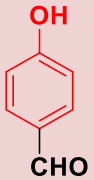
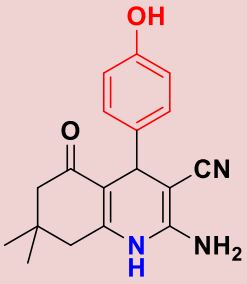
[a] Reaction of p-tolueldehyde (1mmol), malononitrile (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione(1mmol), ammonium acetate (1.2 mmol). [b] Isolated yield after purification through column chromatography.

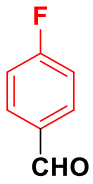
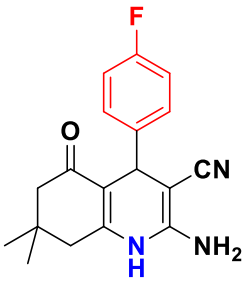
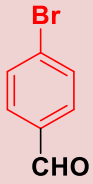
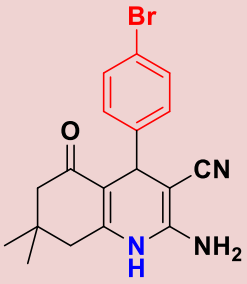
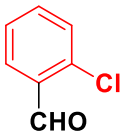
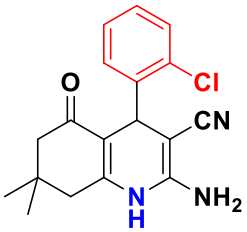
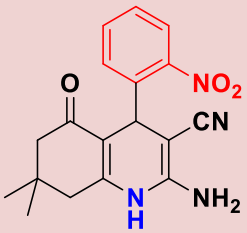
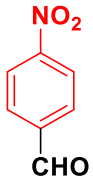
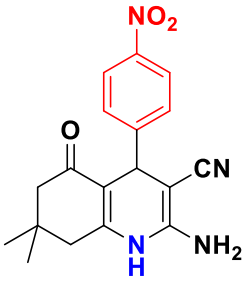
II.8.A.3 Synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives.[a]

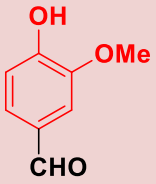
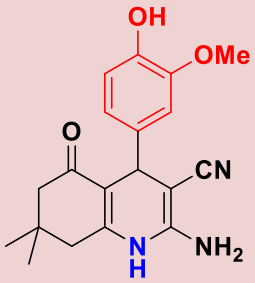
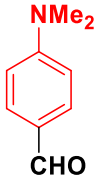
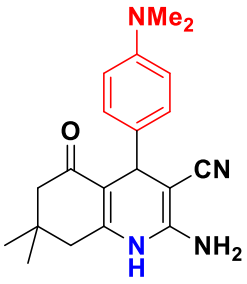
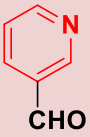
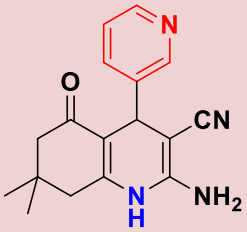
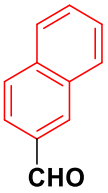
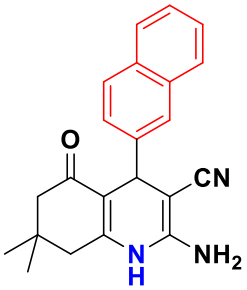
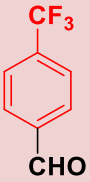
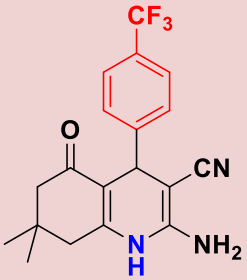
The generality of the reaction was also observed with a variety of aromatic and heterocyclic aldehydes (**Scheme II. 29**). There is no significant difference in the yield of the desired product with electron donating and electron withdrawing substituents at *ortho*, *meta* and *para* position of the aromatic aldehyde. The target compounds (5a-5q) are successively synthesized using SRH as efficient catalyst under neat reaction condition and short reaction time. (**Table II. 2**)

Table II.2 Synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinolines using sulphonated rice husk.[a]

Entry	Reactant	Product	Time	Yield(%)[b]
1		 (5a)	30 min	96
2		 (5b)	30 min	96

3		 (5c)	30 min	93
4		 (5d)	30 min	96
5		 (5e)	30 min	95
6		 (5f)	30 min	994
7		 (5g)	30 min	95

8		 (5h)	30 min	97
9		 (5i)	30 min	98
10		 (5j)	30 min	96
11		 (5k)	30 min	90
12		 (5l)	30 min	92

13		 (5m)	30 min	95
14		 (5n)	30 min	96
15		 (5o)	30 min	94
16		 (5p)	30 min	92
17		 (5q)	30 min	96

[a] Reaction of aromatic aldehyde (1mmol), malononitrile (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1mmol), ammonium acetate (1.2 mmol) and SRH (60 mg). [b]Isolated yield through column chromatography.

II.8.A.4 Comparison of efficiency of the catalyst

Few controlled experiments were carried out to compare our prepared catalyst (SRH) with some conventional solid and liquid acid catalyst (**Table II.3**). It was observed from the results that most of the acid catalyst showed good activity in ethanol solvent. However, some base catalyst was also employed and they exerted the corresponding product with high yield in 30 minutes (**Table II.3**, entry 8-9). The effectiveness of SRH over other acid catalyst was established as it requires very short reaction time under solvent free condition and easily seperable from the reaction mixture (**Table II. 3**, entry 11).

Table II.3 Comparison of efficiency of the catalyst for the synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinolines.[a]

Entry	Catalyst	Solvent	Temperature (^{o}C)	Time(min)	Yield (%)[b]
1	PTSA(60mg)	Ethanol	80	30	93
2	PEG-400(5mL)	-	80	40	80
3	PEG-	-	80	60	70

	200(5mL)				
4	Glycerol(5mL)	-	80	60	72
5.	H_2SO_4 (5mL)	Ethanol	70	30	85
6.	AcOH (5mL)	-	80	30	80
7.	$HClO_4$ (5mL)	-	70	30	90
8.	K_2CO_3 (60mg)	Neat	80	30	94
9.	Et_3N(5mL)	-	80	30	95
10.	Fe_3O_4 (60 mg)	Neat	80	30	91
11.	SRH (60mg)	**Neat**	**70**	**20**	**96**

[a]Reaction of p-toluealdehyde (1mmol), malononitrile (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1mmol), ammonium acetate (1.2 mmol). [b] Isolated yield after purification through column chromatography.

II.8.A.5 Plausible Mechanism

A plausible SRH catalyzed synthesis of hexahydroquinoline is established by considering the acidic behaviour of the catalyst (**Figure II.9**). At very first step of the reaction, protonation occurs at aldehyde oxygen of aromatic aldehyde followed by the Knoevenagel condensation of malononitrile and aromatic aldehyde. After that, Michael addition reaction occurs between 5,5-dimethylecyclohex-1,3-dione and 2-arylidenemalononitrile, resulting a intermediate. However, this

intermediate rapidly undergoes in cyclization and exters the target hexahydroquinoline product.

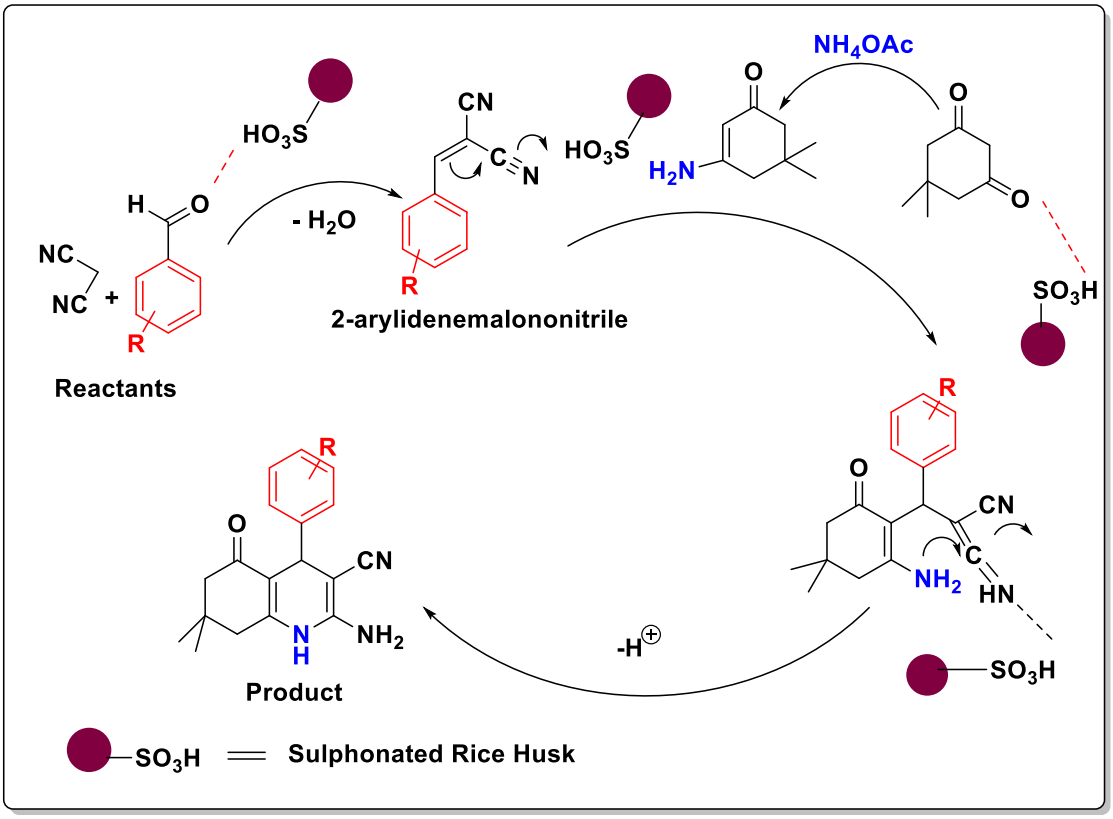
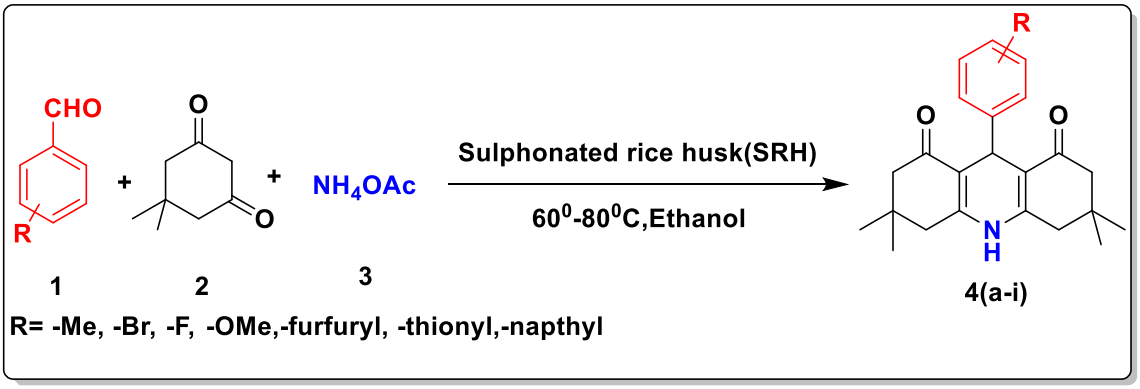


Figure II.9 The plausible mechanism for the synthesis of hexahydroquinoline

The next present work leads to the synthesis of substituted 9-arylhexahydroacridine-1,8-dione derivatives (**Scheme II.30**) by using greener catalyst heterogeneous catalyst sulphonated rice husk (SRH) .



Scheme II.30 Synthesis of substituted 9-arylhexahydroacridine-1,8-dione derivatives using sulphonated rice husk[a]

II.8.A.6 Optimization of the reaction condition for the Synthesis of substituted 9-arylhexahydroacridine-1,8-dione derivatives

Initially, the reaction was started with anisaldehyde (1 mmol), ammonium acetate (1.2 mmol) and 5,5-dimethylecyclohex-1,3-dione (2 mmol) taken in a 25 mL round bottom flask. Excellent yield was observed in presence of 40 mg of SRH catalyst in ethanol solvent at 60 ^{o}C temperature (**Table II.4**, entry 7) with reaction time of 50 minutes. With decreasing the amount of catalyst, the yield of the product decreases slightly in ethanol. However, in absence of catalyst the formation of the product was diminished (**Table II.4**, entry 13). The performance of the reaction is almost similar in methanol solvent but for greener aspect ethanol is considered as more safer solvent than methanol to get the maximum yield. (**Table II.4**, entry 7 & 8). From the optimized

condition it is clear that SRH catalyst is proved to be suitable for the conversion of hexahydroacridine-1,8-dione with excellent yield in short reaction time. The amount of the catalyst and time of the reaction was checked to find out the optimized condition of the reaction. It was observed that the best result was obtained at 60 ^{o}C temperature using minimum amount of catalyst SRH (40 mg) in ethanol (**Table II.4**, entry 7).The progress of the reaction was monitored continuously by thin layer chromatography (TLC) and the pure product was separated only by recrystallisation procedure in ethyl acetate and petroleum ether (1:1)

Table II.4 Optimisation of the reaction condition for the synthesis of hexahydroacridine-1,8-dione. [a]

Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	90	Ethanol	80	120	97
2	80	Ethanol	80	90	97
3	70	Ethanol	80	70	97
4	60	Ethanol	80	60	97
5.	50	Ethanol	70	60	95
6.	40	Ethanol	70	60	95
7.	**40**	**Ethanol**	**60**	**50**	**95**
8	40	Methanol	60	60	94

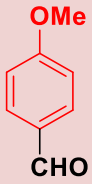
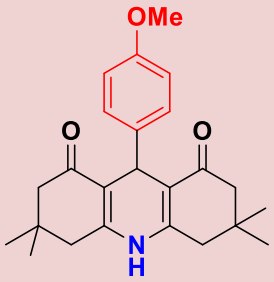
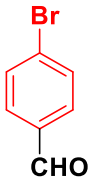
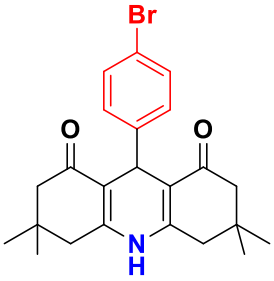
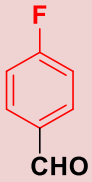
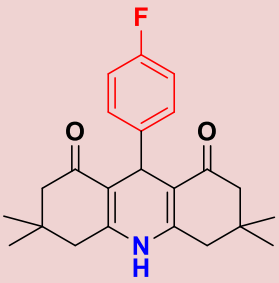
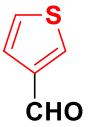
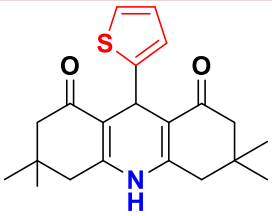
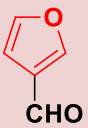
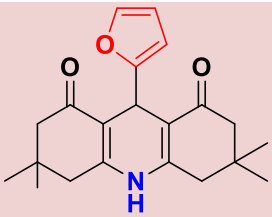
9.	40	Neat	60	50	84
10.	40	Neat	80	90	86
11.	40	Ethanol/H_2O (3:1)	70	60	62
12.	40	Methanol/H_2O(3:1)	70	60	58
13.	None	Ethanol	70	120	20

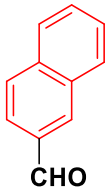
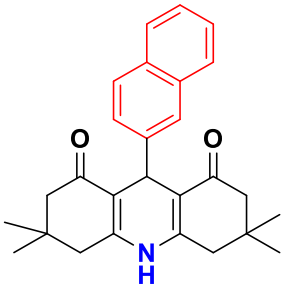
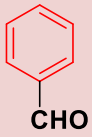
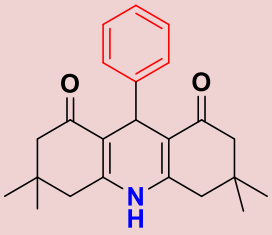
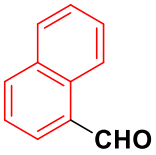
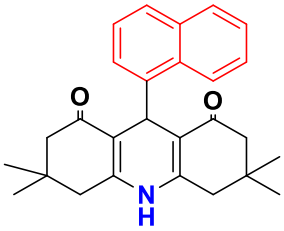
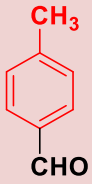
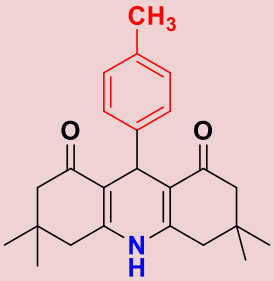
[a] Reaction of anisaldehyde (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione(2mmol), ammonium acetate (1.2 mmol). [b]Isolated yield after purification through recrystalisation procedure.

II.8.A.7 Synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives.[(a)]

The generality of the reaction was also observed with a variety of aromatic and heterocyclic aldehydes (**Scheme II. 30**). There is no significant difference in the yield of the desired product with electron donating and electron withdrawing substituents at *ortho*, *meta* and *para* position of the aromatic aldehyde. The targeted compounds (5a-5q) are successively synthesized using SRH as efficient catalyst under neat reaction condition and short reaction time. (**Table II. 5**)

Table II.5 Synthesis of substituted 9-arylhexahydroacridine-1,8-dione derivatives using sulphonated rice husk. [a]

Entry	Reactant	Product	Time	Yield(%)[b]
1		 (4a)	50 min	97
2		 (4b)	50 min	94
3		 (4c)	50 min	93
4		 (4d)	50 min	94
5		 (4e)	50 min	92

6		 (4f)	50 min	94
7		 (4g)	50 min	91
8		 (4h)	50 min	94
9		 (4i)	50 min	95

[a] Reaction of aromatic aldehyde (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (2mmol), ammonium acetate (1.2 mmol) and SRH. [b] The yields are isolated through recrystalisation.

II.8.A.8 Plausible mechanism

A plausible SRH catalyzed synthesis of hexahydroacridine-1,8-dione are established considering the acidic behaviour of the catalyst

(**Figure II.10**). At very first step of the reaction, protonation occurs at aldehyde oxygen of aromatic aldehyde followed by Hantzsch condensation of aldehydes with β-diketones and ammonium acetate. Intermediates are produced in situ rapidly undergo cyclization and exerts the targeted hexahydroacridine-1,8-dione product.

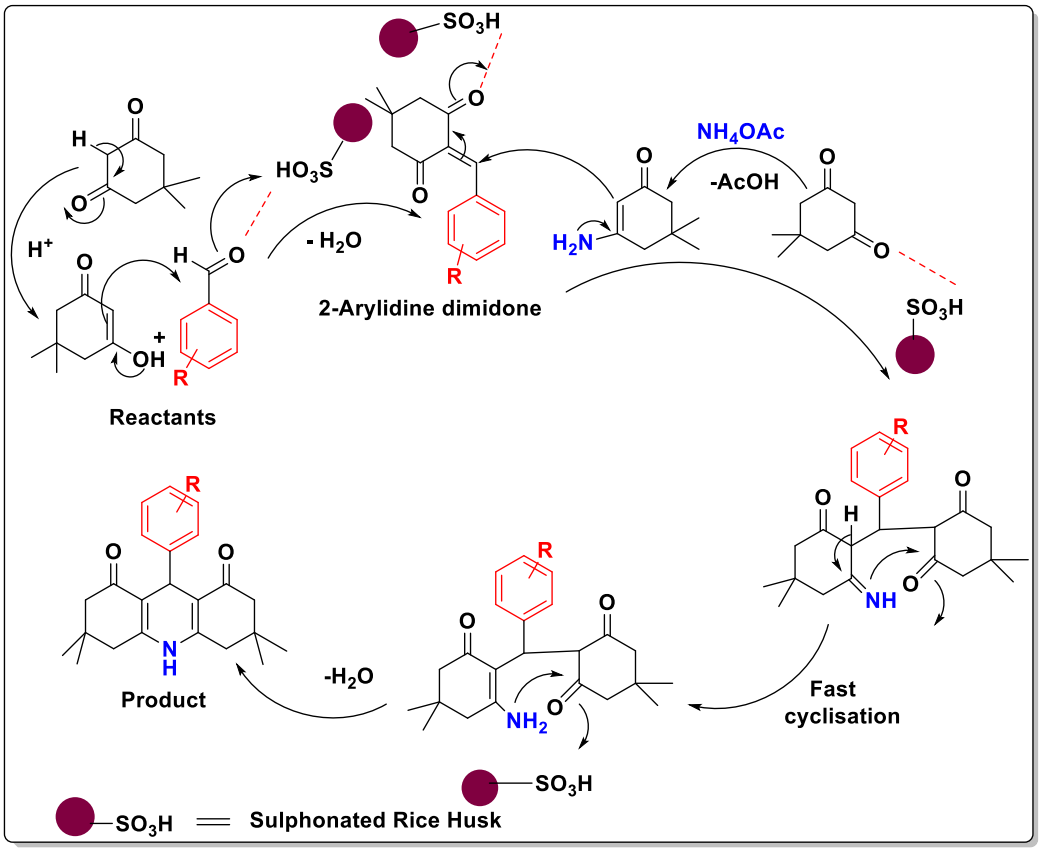


Figure II.10 The plausible mechanism for the synthesis of hexahydroacridine-1,8-dione

II.8.A.9 Catalyst Recyclability Experiment

To check the recyclability of the catalyst, a model reaction between benzaldehyde (1.6mmol), malononitrile(1.6mmol), ammonium acetate(1.92 mmol) and 5,5-dimethylecyclohex-1,3-dione(1 mmol) in presence of 100 mg of sulphonated rice husk was carried out under optimised reaction condition. After successful completion of the each reaction step, ethyl acetate (10 ml) and water was added to the reaction mixture. The supernatant liquid (ethyl acetate extract) was decanted off and this process was repeated thrice. The catalyst was then filtered and washed with water and acetone repeatedly and dried under vaccum. The recovered catalyst weight was measured after every recovery step and the next reaction was repeated in required proportion of the reactants to that of weight of the recovered catalyst. The temperature and time of the reaction were kept constant in this regard. Amount of catalyst, aldehyde, reaction time,temperature and yield percentage of the product have been shown in **Table II.6** (entry 1-7) The catalyst can easily be separated from the reaction mixture by simple filtration and was found to retain its acidic property, even after 7th run (**Figure II.11**). This was further supported by comparing the FTIR spectra of fresh SRH catalyst and recovered catalyst after successive reactions (**Figure II.12**).

Table II.6 Table for the amount of recovred catatyst with isolated product yield in successive runs[a]

Entry	Catalyst (mg)	Aldehyde (x mmol)	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	100	1.6 mmol	70	20	96
2	80	1.3 mmol	70	20	94
3	60	1.0 mmol	70	20	90
4	50	0.8 mmol	70	20	87
5.	40	0.6 mmol	70	20	82
6.	30	0.5 mmol	70	20	76
7.	20	0.3 mmol	70	20	71

[a] Reaction of benzaldehyde (x mmol), malononitrile (x mmol), 5,5-dimethyl-cyclohexane-1,3-dione (2x mmol), ammonium acetate (1.2x mmol). [b] Isolated yield after purification through recrystalisation.

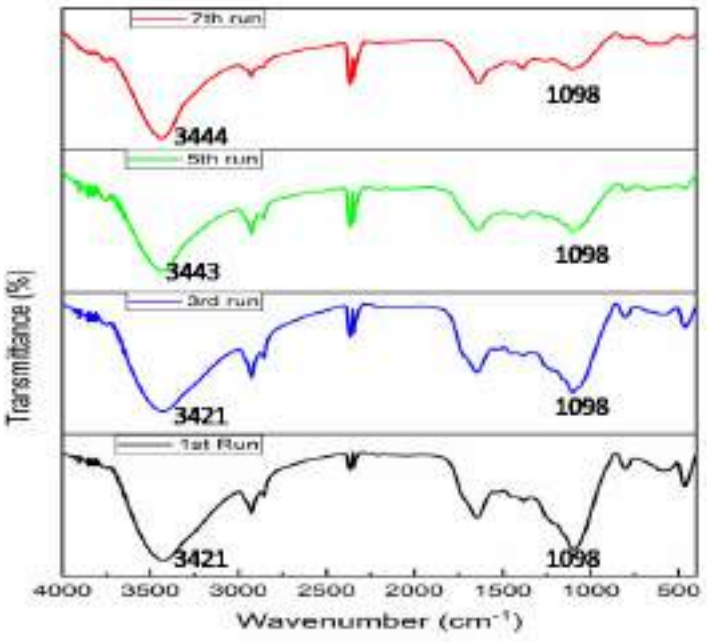


Figure II.11 FTIR spectra of reused catalysts after 1st , 3rd, 5th and 7th run.

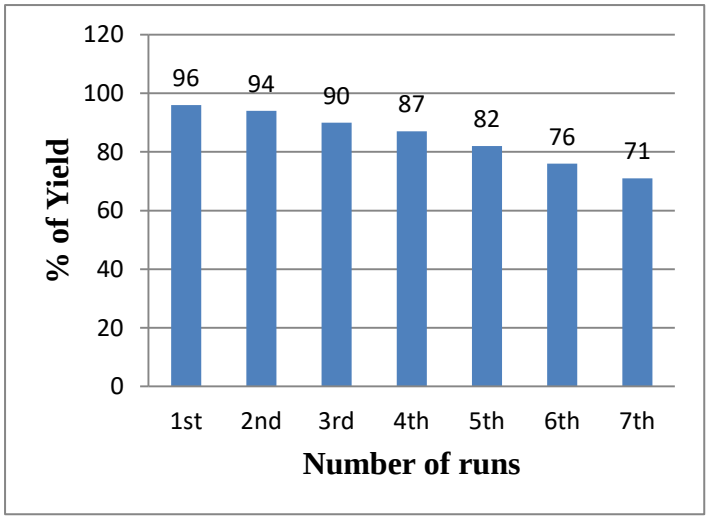


Figure II.12 Recyclability experiment of catalyst

II.8.A.10 Conclusion

In conclusion, a simple and greener methodology for the synthesis of variety of hexahydroquinolines and hexahydroacridine-1,8-dione from commercially available aldehydes has been established. We have introduced a new cheap and green heterogeneous catalyst SRH (Sulphonated rice husk) for the synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline and 9-Arylhexahydroacridine-1,8-dione derivatives with excellent yield. This heterogeneous catalyst is found to be highly efficient for the synthesis of hexahydroquinoline and hexahydroacridine-1,8-dione in short reaction time. The catalyst is highly recyclable upto 7^{th} run and has profound effect to catalyze a wide range of acid-catalysed reactions.

II.8.A.11 Acknowledgement

One of the authors (S.D) is thankful to UGC, New Delhi for financial support, USIC (NBU) for SEM, EDX analysis, IIT Bombay for ICP-AES & IACS (Kolakata) for powder XRD analysis for this above work.

II.8.A.12 Experimental

II.8.A.12.a Catalyst preparation

The heterogeneous catalyst (SRH) was prepared by direct sulphonation of rice husk (RH). The rice husk was collected from a nearby rice mill and was blended finely before use. RH was first washed with dilute H_2SO_4 for five times and next thoroughly washed with water followed by methanol. After washing the solvent was fully evaporated through rotary evaporator. 5g of dry material was taken into 250 mL of a round bottom flask and 150 mL dichloromethane (DCM) was added to it. Then, 5 mL of pure Chlorosulphonic acid (98%) was added dropwise with continuous stiring until the whole suspension turned into brown. The suspension was then stirred for 20 h on a magnetic stirrer at room temperature. After stirring the solid catalyst was filtered off and washed with water and acetone repeatedly until the filtrate became light brown colour. Then the sample was dried in reduced pressure and later characterized by different spectroscopic techniques.

II.8.A.12.b General procedure for synthesis of hexahydroquinoline derivatives

A mixture of 5,5-Dimethylcyclohexane-1,3-dione (1 mmol), aromatic aldehyde (1.0 mmol), malononitrile (1 mmol), ammonium acetate (NH_4OAc) (1.2 mmol), and SRH (60 mg) in a 50-mL round bottom flusk was stirred at 60 ^oC temperature for 20 min (Scheme II. 29). The progress of the reaction was monitored by thin-layer

chromatography (TLC) (**Scheme II.29**). After completion of the reaction, the product was extracted with ethyle acetate and the catalyst was separated by simple filtration. Then ethyl acetate extract was concentrated and further purified by coloumn chromatography using ethyl acetate/petroleum ether (3:7) as eluent to get the pure product. All the synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and the spectral data were compared with the reported spectral data of corresponding compound.

II.8.A.12.c General procedure for synthesis of Acridine-1,8-dione derivatives

A mixture of 5,5-Dimethylcyclohexane-1,3-dione (2 mmol), aromatic aldehyde (1 mmol), ammonium acetate (NH_4OAc) (1.2 mmol), and SRH (50 mg) in a 25-mL round bottom flusk was stirred at 60^0C temperature for 60 minutes. The progress of the reaction was monitored by thin-layer chromatography (TLC) (**Scheme II.30**). After completion of the reaction, the product was extracted with ethyle acetate and the catalyst was separated by simple filtration. Then ethyl acetate extract was concentrated and product was sperated by simple precipitation with petroleum ether and purified by recrystalisation with (1:1) ethylacetate and petroleum ether mixture. After isolation all the synthesized

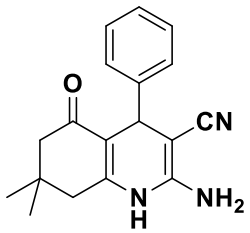
compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and the spectral data were compared with the reported spectral data of corresponding compound.

II.8.A.12.d General Procedure for ^{1}H & ^{13}C NMR

NMR spectra of all the products were taken in DMSO-d_6 (TMS as an internal standard) using a Bruker 400MHz spectrometer operating for ^{1}H at 400 MHz and for ^{13}C at 100 MHz. ^{1}H-NMR spectroscopic data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br = broad), integration, coupling constants in Hertz (Hz). ^{13}C NMR spectroscopic data are reported in ppm.

II.8.A.12.e Spectral data of the compounds mentioned in Scheme II.29

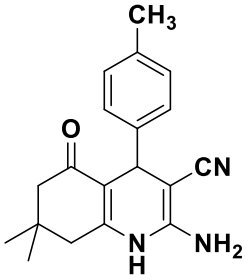
2-Amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitril (5a)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.95(s,3H),1.04(s,3H),2.10(d,1H),2.25(d,1H),2.51(s,2H),4.17(s,1H),7.00 (s,2H),7.13-7.30(m,5H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)27.27,28.86,32.27,36.03,50.44,58.76,113.20,120.18,127.02,127.61,128.79, 145.21,158.95,162.95, 196.10.

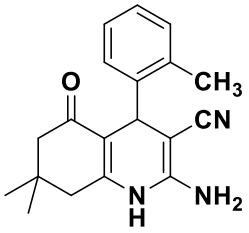
2-Amino-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5b)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.92(s,3H),1.01(s,3H),2.10(m,2H),2.22(s,3H),2.53(s,2H),4.09(s,1H), 6.94(s,2H), 6.98-7.07(m,4H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)21.55,27.22,28.88,32.26,35.63,50.45,58.89,113.33,120.22,127.54,129.34,136 .08, 142.29,158.89,162.75, 196.10.

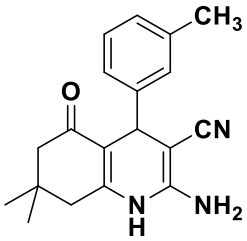
2-Amino-4-(2-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5c)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm) 0.93(s,3H),1.01(s,3H),2.02-2.23(m,2H),2.43-.55(m,6H),4.44(s,1H),6.92(s,2H), 7.01-7.08(m,4H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)19.54,27.26,28.89,31.83,32.34,50.41,58.70,113.92,120.22,126.85,127.74,130 .36, 135.22,144.04,158.74,162.98, 196.25.

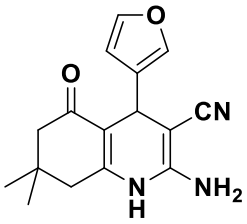
2-Amino-4-(3-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5d)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.93(s,3H),1.01(s,3H),2.05-2.54(m,7H),4.09(s,1H),6.88-7.16(m,6H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)21.55,27.21,28.89,32.29,35.95,50.45,58.86,113.23,120.21,124.76,127.72,128.17, 128.71, 137.76,145.19,158.91,162.90, 196.10.

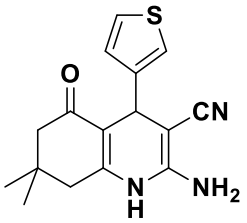
2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5e)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.96(s,3H),1.00(s,3H),2.14(d,1H),2.26(d,1H),2.40-2.53(m,2H),4.30(s,1H),6.03(d,1H)6.30(dd,1H),7.06(s,2H),7.13-7.45(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)27.01,28.89,29.44,32.28,50.35,55.84,105.52,110.82,120.03,142.21,156.18, 159.77,163.74, 195.92.

2-Amino-4-(thiophene-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5f)



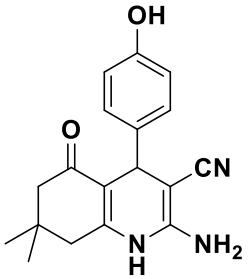
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm) 0.94(s,3H),1.00(s,3H),2.03-
.53(m,4H),4.61(s,1H),6.85(d,2H),7.08(s,2H),7.27(d,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)26.41,28.63,30.43,31.75,49.89,58.10,112.95,119.59,124.00,124.41,126.81,14
9.28, 158.93,162.49,195.51.

2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5g)



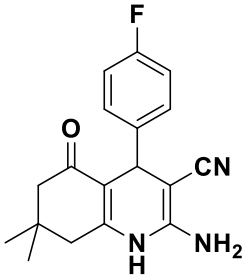
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.91(s,3H),1.00(s,3H),2.10(d,1H),2.25(d,1H),2.51(s,2H),4.17(s,1H),7.00(s,2
H),7.13-7.30(m,5H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)27.22,28.89,32.24,35.17,50.50,59.24,113.65,115.45,120.35,128.61,135.63,15
6.44, 158.85, 162.45, 196.12.

2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5h)



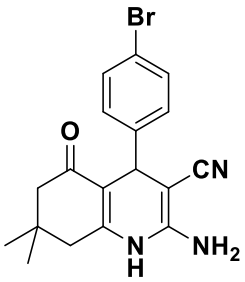
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.94(s,3H),1.02(s,3H),1.98(s,1H),2.10(d,1H),2.24(d,1H),2.50(s,2H),
4.20(s,1H), 7.04(s,2H), 7.08-7.19(m,4H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)27.28,28.78,32.25,35.37,50.41,58.53,113.06,120.10,129.47,129.55,141.39,15
8.94, 162.56, 170.79,196.13.

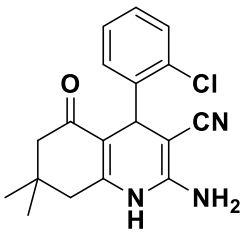
2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**5i)**



^{1}H-NMR(400MHz,DMSO-d$_6$)
δ(ppm)0.92(s,3H),1.00(s,3H),1.96(s,1H),2.06(d,1H),2.21(d,1H),2.47(s,2H),4.15(s,1 H), 7.04(s,2H),7.08(d,3H)7.45(d,2H).

^{13}C-NMR(400MHz,DMSO-d$_6$)
δ(ppm)27.35,28.77,32.26,35.67,50.43,58.21,112.75,120.65,129.98,131.66,131.66,14 4.64,158.96,163.08,170.77,196.10.

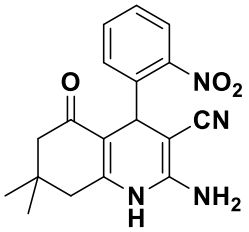
2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5j)



^{1}H-NMR(400MHz,DMSO-d$_6$)
δ(ppm)0.95(s,3H),1.01(s,3H),2.05(d,1H),2.22(d,1H),2.44-2.55(m,3H),4.67(s,1H),7.02(s,2H), 7.14-7.35(m,4H).

^{13}C-NMR(400MHz,DMSO-d$_6$)
δ(ppm)26.88,28.43,31.78,32.86,49.94,56.82,111.79,119.27,127.45,128.21,129.45,129.96,13 2.10, 141.58,158.68,163.16, 195.56.

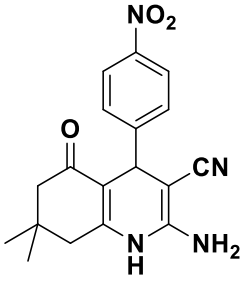
2-Amino-4-(2-nitrophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5k)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.93(s,3H),1.05(s,3H),2.10(d,1H),2.21(d,1H),2.69(s,2H),5.33(s,1H),7.61-7.72(m,6H),9.51(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)27.40,28.67,32.51,32.75,50.09,58.76,111.83,117.03,126.92,127.02,129.72,128.79, 135.40,149.52,158.34,164.84, 196.42.

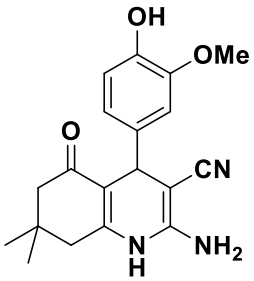
2-Amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5l)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.96(s,3H),1.00(s,3H),1.94(s,1H),2.03(d,1H),2.22(d,1H),2.48(d,2H),4.34(s,1H),7.14 (s,2H),7.41(d,2H),8.13(d,2H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)26.93,28.26,31.81,35.68,49.87,57.01,111.75,119.33,123.66,128.63,146.26,152.30, 158.60,163.10,170.32,195.67.

2-Amino-4-(3-methoxy,4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5m)



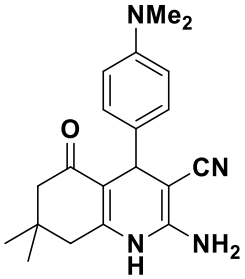
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.94(s,3H),1.01(s,3H),2.07(d,1H),2.23(d,1H),2.47(s,2H),3.68(s,3H),4.05(s,1H),6.48-6.65(m,3H),6.89(s,2H),8.80(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)26.62,28.53,31.77,34.97,50.03,55.57,58.71,111.39,113.02,115.33,119.37,135.82, 145.24, 147.23,158.36,162.17, 195.72.

2-Amino-4-(4-N,N dimethylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5n)



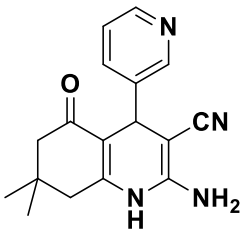
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.92(s,3H),1.00(s,3H),2.06(d,1H),2.22(d,1H),2.47(s,2H),2.81(s,6H),4.01(s,1 H),6.60(d,2H), 6.86-6.92(m,3H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)26.75,28.49,30.70,31.78,34.57,50.06,58.94,112.34,113.28,119.95,127.72,132 .54, 149.23,158.35,161.85, 195.67.

2-Amino-4-(pyridine-3-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5o)



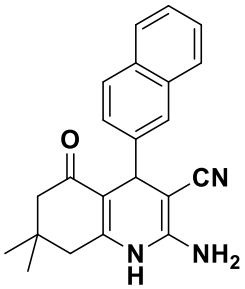
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.92(s,3H),1.01(s,3H),2.06(d,1H),2.23(d,1H),2.50(m,3H),4.23(s,1H),7.10(s,2 H), 7.29(dd, 1H),7.51(d,1H),8.38(s,2H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)26.93,28.24,31.84,33.40,49.91,57.32,111.79,119.51,123.66,134.75,140.05,147.85,14 8.69, 158.59,162.97, 195.74.

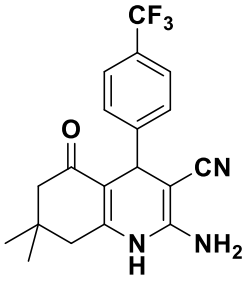
2-Amino-4-(naphthalene-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5p)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.93(s,3H),1.02(s,3H),2.07(m,2H),2.23(d,1H),2.53(s,2H),4.36(s,1H),7.05(s,2H), 7.26(d, 1H),7.45(m,2H),7.65(s,1H),7.81-7.87(m,3H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)26.75,28.43,30.70,31.83,35.90,50.00,58.10,112.54,119.75,125.56,125.66,126.20, 127.45,127.6 6,128.12,132.01,132.85,142.05, 158.50,162.59, 195.76.

2-Amino-4-(4-trifluoromethylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carbonitrile (**5q)**



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.92(s,3H),1.00 (s,3H),1.95(s,1H),2.07(d,1H),2.22(d,1H),2.46-2.54(m,2H),4.26(s,1H), 7.08(s,2H),7.34(d,2H)7.62(d2H).

^{13}C-NMR(100MHz,DMSO-d_6)
δ(ppm)27.27,28.86,32.27,36.03,50.44,58.76,113.20,120.18,127.02,127.61,128.79,145.21, 158.95,162.95, 196.10.

II.8.A.12.f Sanned copies of compounds mentioned in Scheme II.29

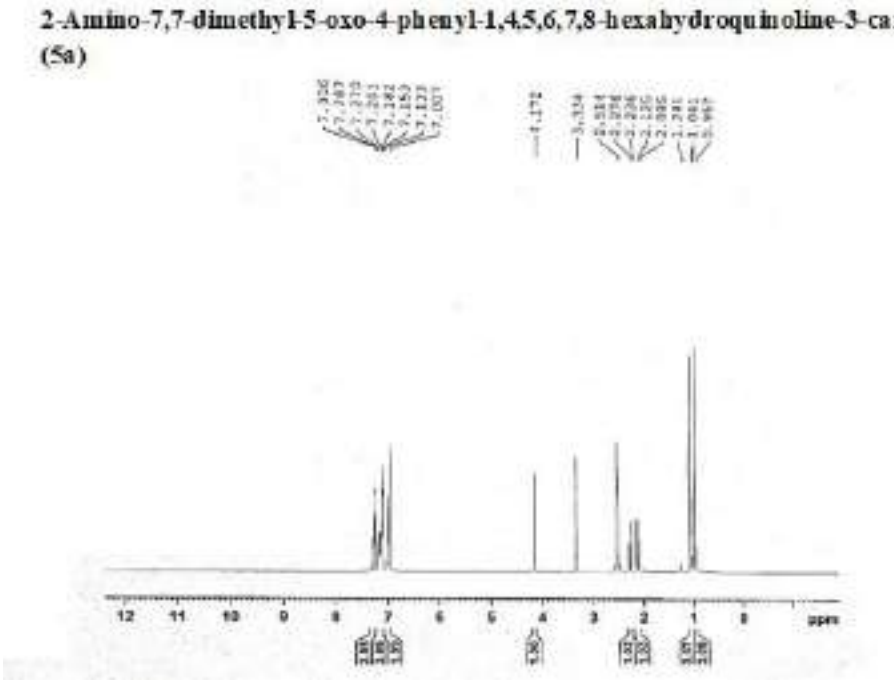


Figure II.13 - ^{1}H-NMR of compound 5a

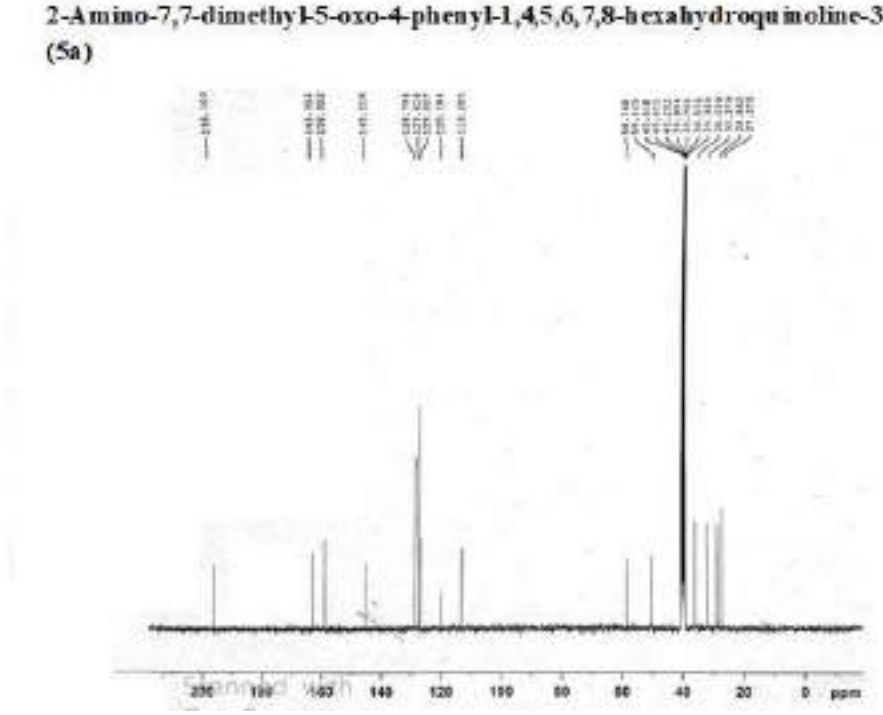


Figure II.14 - ^{13}C-NMR of compound 5a

2-Amino-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5b)

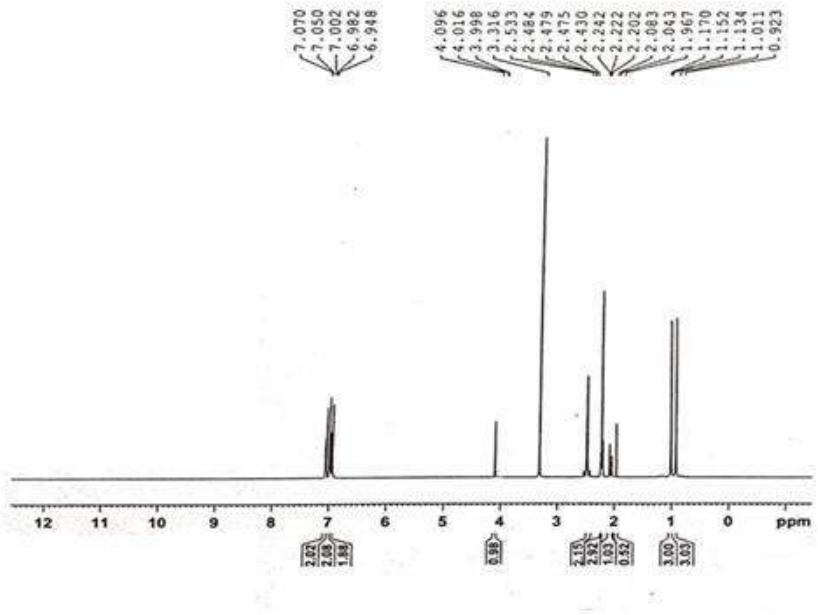


Figure II.15 - ^{1}H-NMR of compound 5b

2-Amino-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5b)

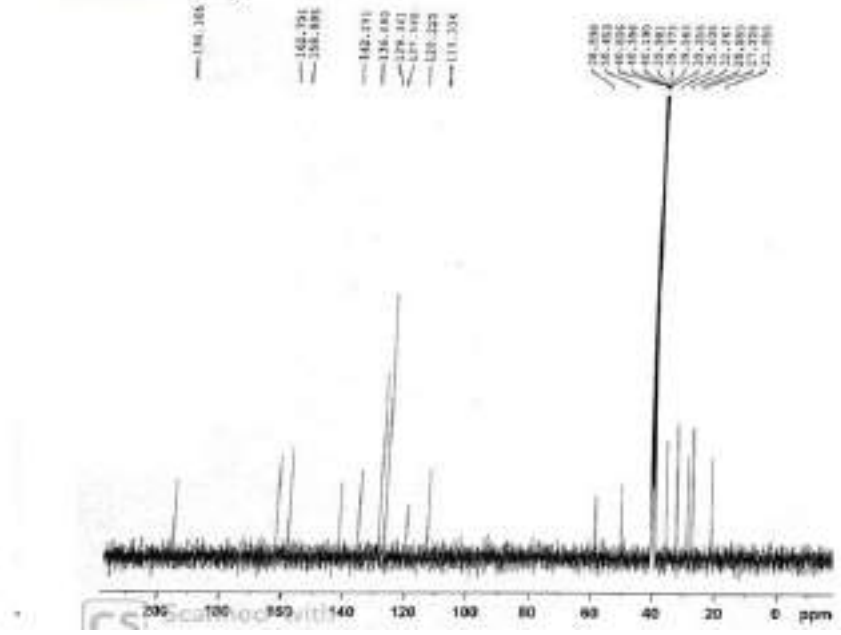


Figure II.16 - ^{13}C-NMR of compound 5b

2-Amino-4-(2-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5c)

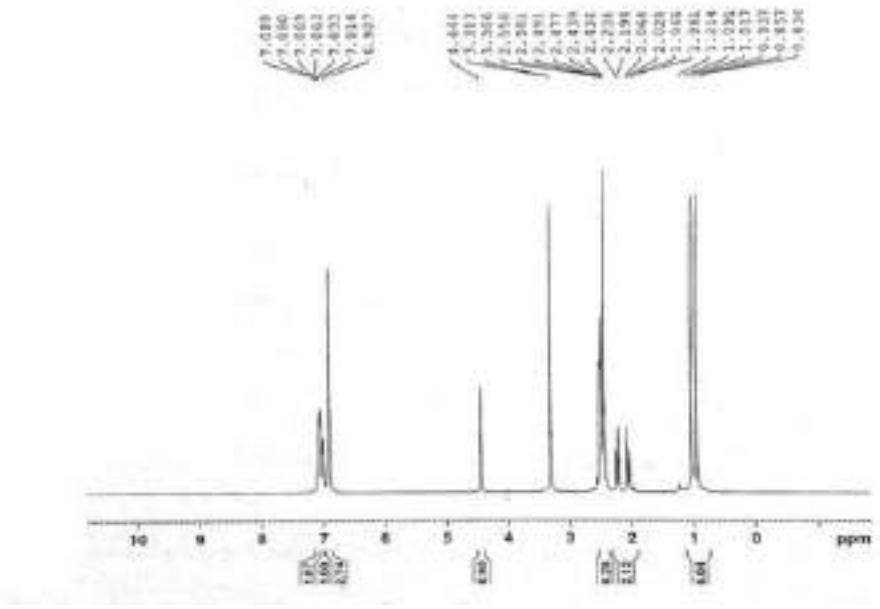


Figure II.17 - ^{1}H-NMR of compound 5c

2-Amino-4-(2-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5c)

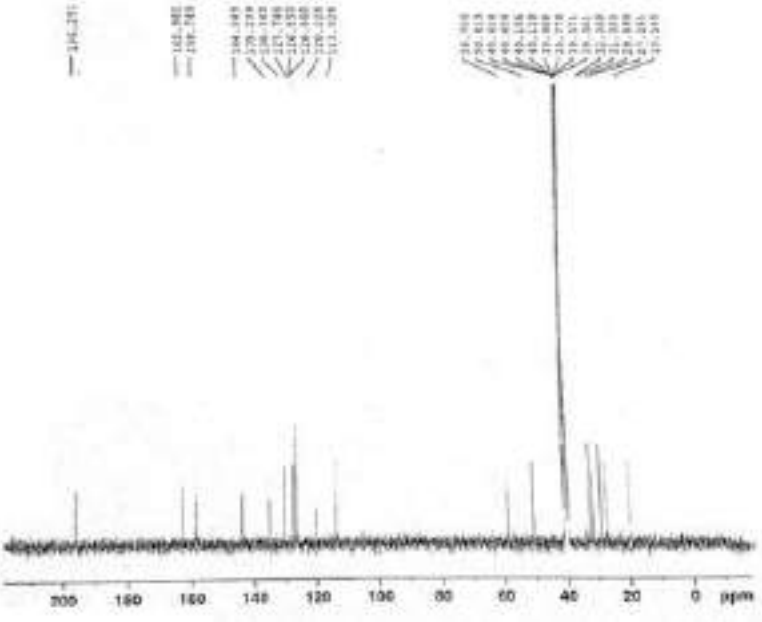


Figure II.18 - ^{13}C-NMR of compound 5c

2-Amino-4-(3-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5d).

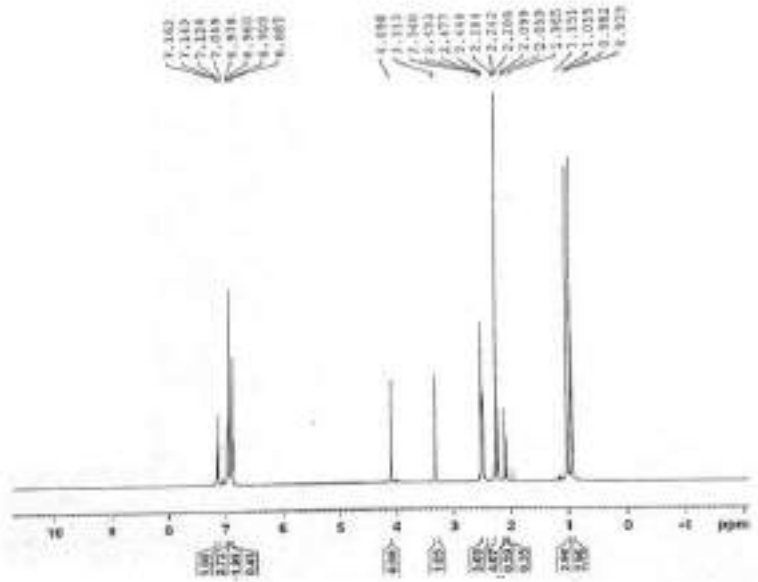


Figure II.19 - ^{1}H-NMR of compound 5d

2-Amino-4-(3-methylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5d)

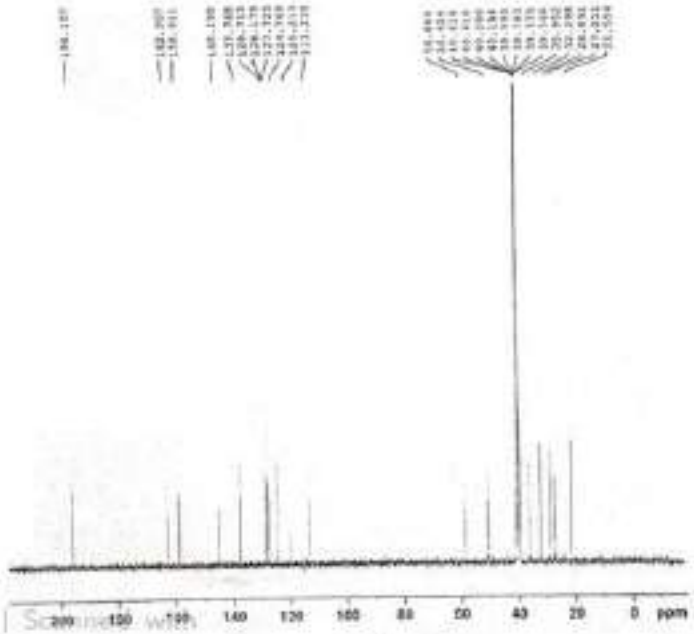


Figure II.20 - ^{13}C-NMR of compound 5d

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5e)

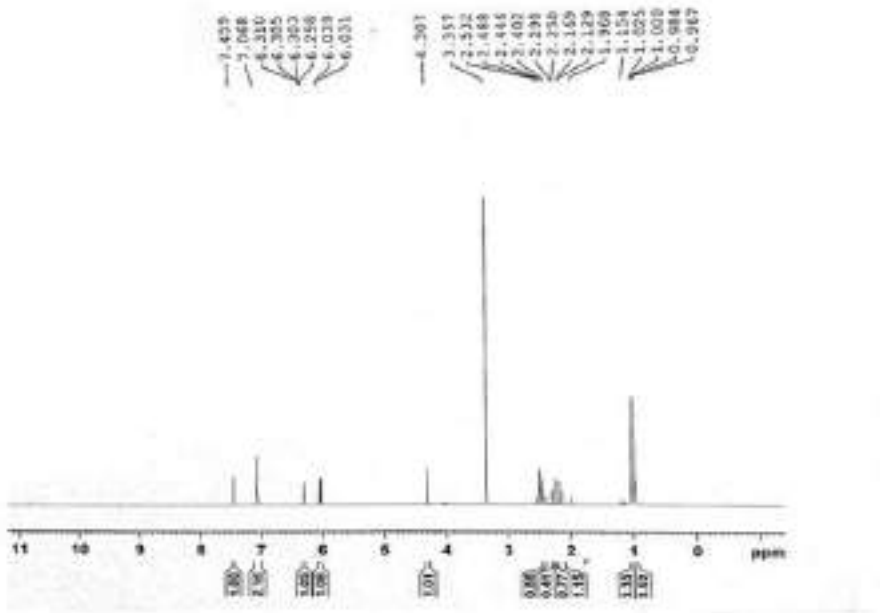


Figure II.21 - ^{13}C-NMR of compound 5e

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5e)

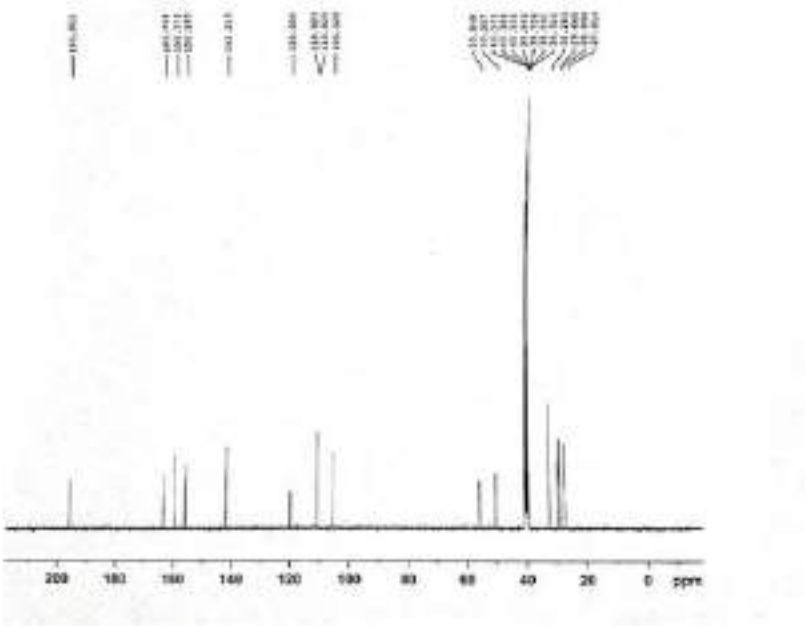


Figure II.22- ^{13}C-NMR of compound 5e

2-Amino-4-(thiophene-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5f)

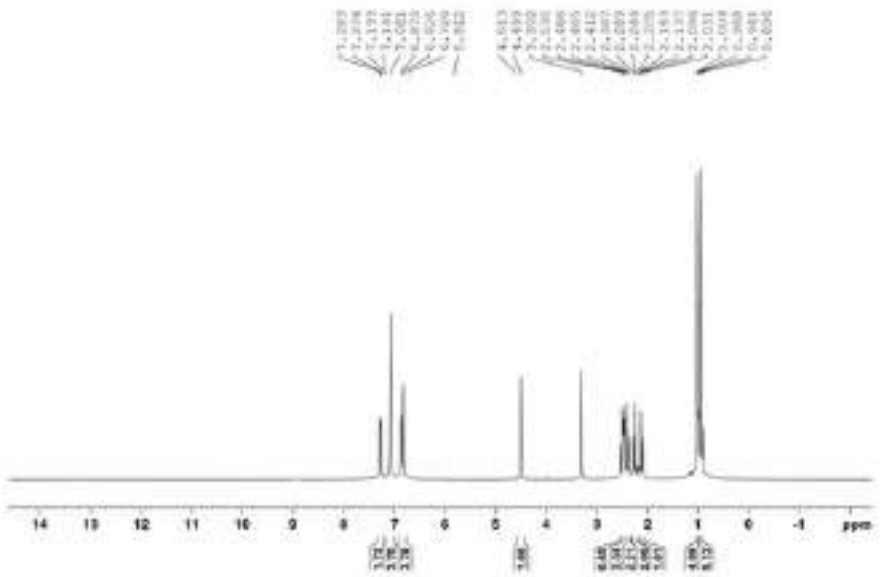


Figure II.23 - ^{1}H-NMR of compound 5f

2-Amino-4-(thiophene-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5f)

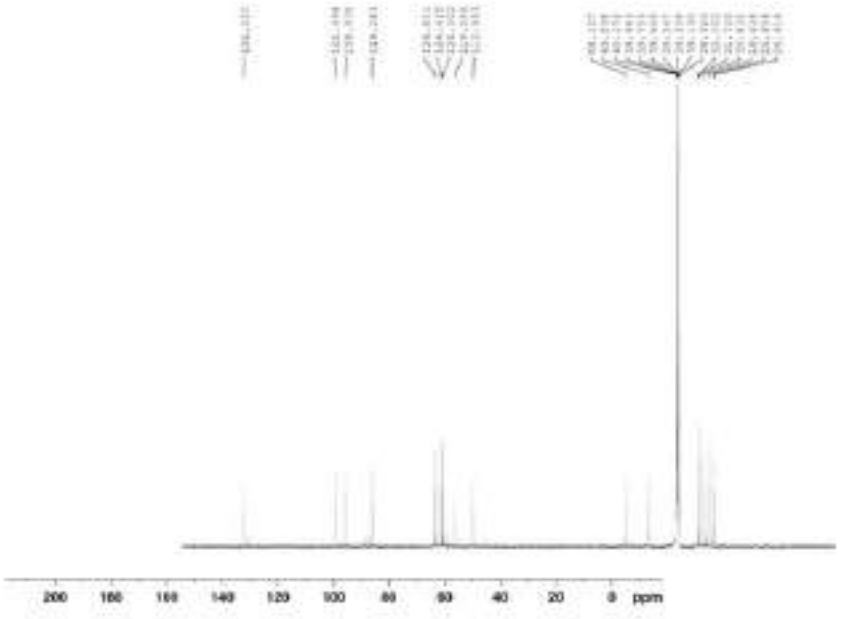


Figure II.24 - ^{13}C-NMR of compound 5f

2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5g)

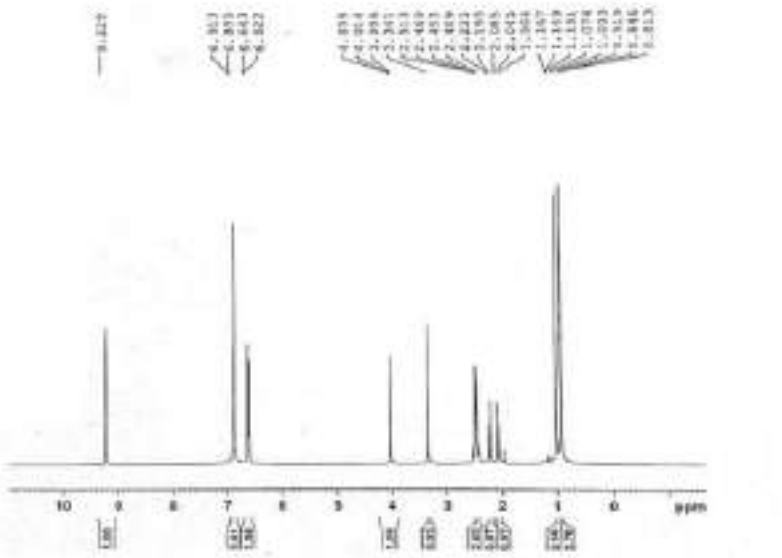


Figure II.25 - ^{1}H-NMR of compound 5g

2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5g)

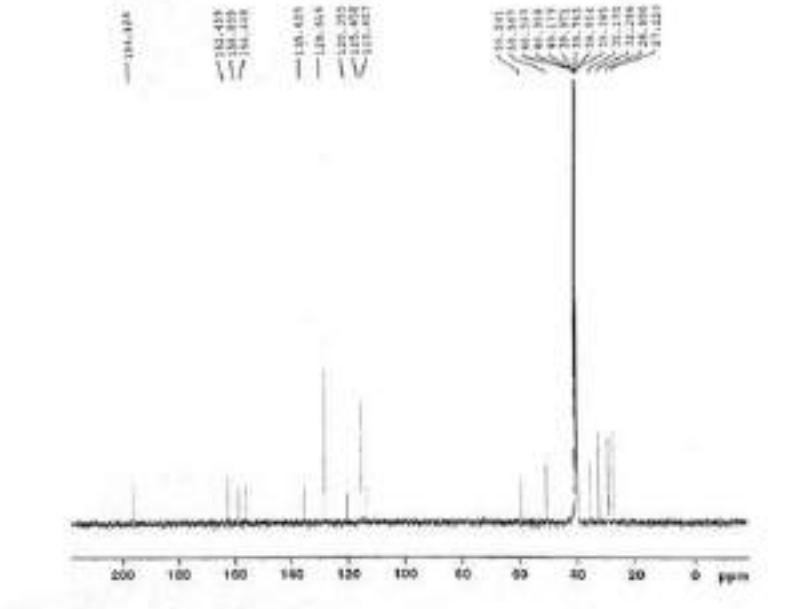


Figure II.26 - ^{13}C-NMR of compound 5g

2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5h)

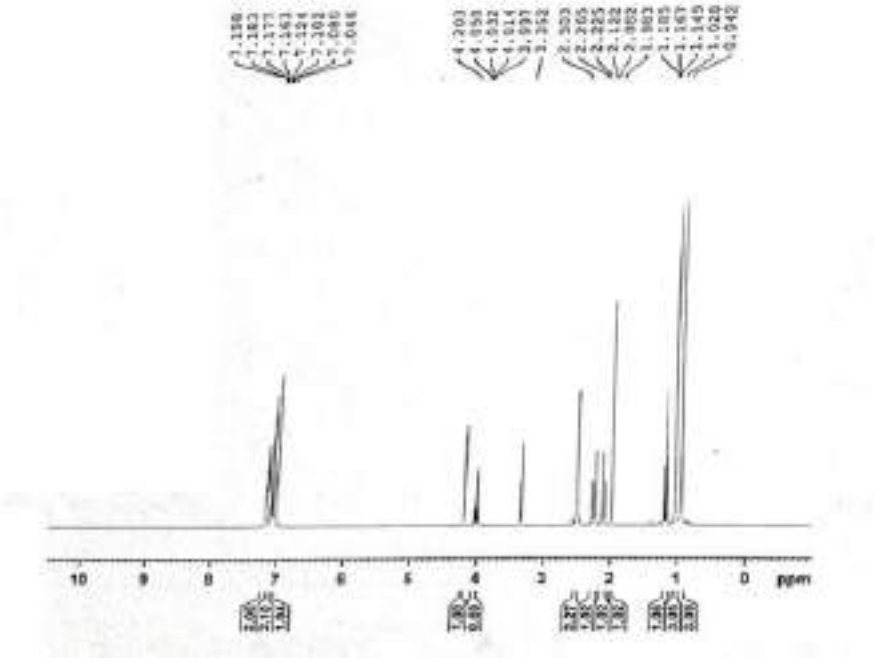


Figure II.27 - ^{1}H-NMR of compound 5h

2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5h)

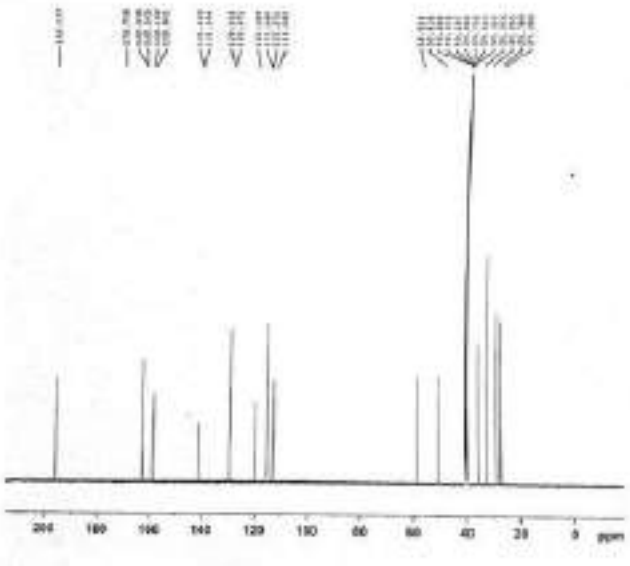


Figure II.28 - ^{13}C-NMR of compound 5h

2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5i)

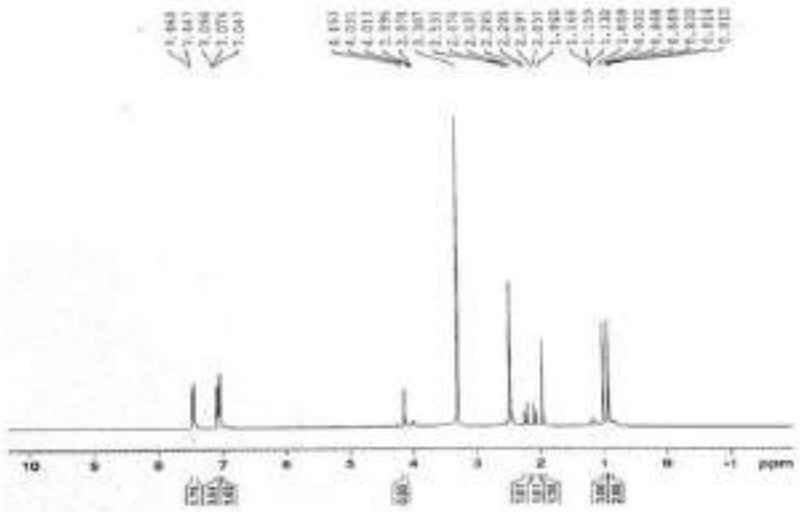


Figure II.29 - ^{1}H-NMR of compound 5i

2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5i)

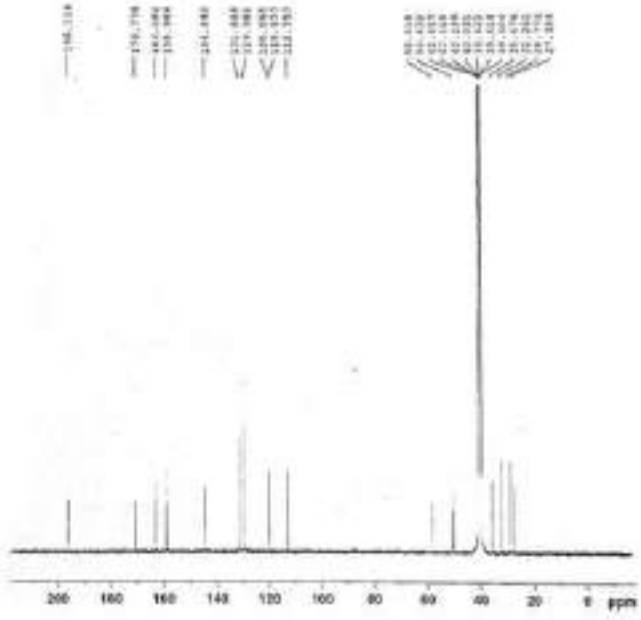


Figure II.30- ^{13}C-NMR of compound 5i

2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5j)

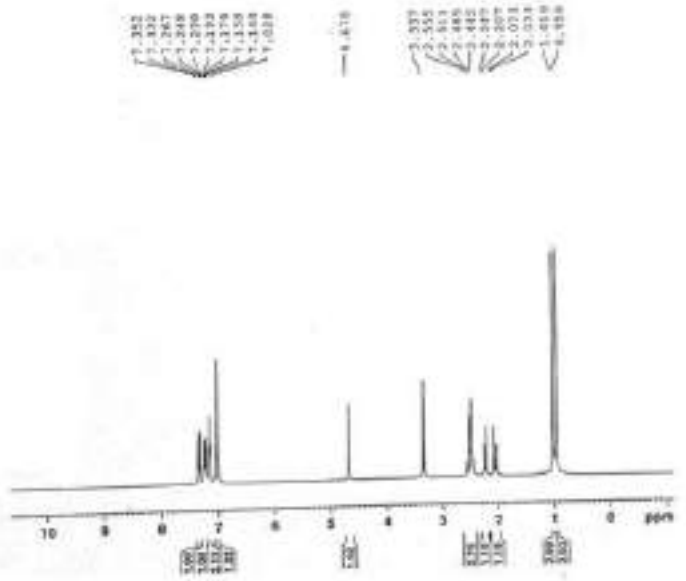


Figure II.31 - ^{1}H-NMR of compound 5j

2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5j)

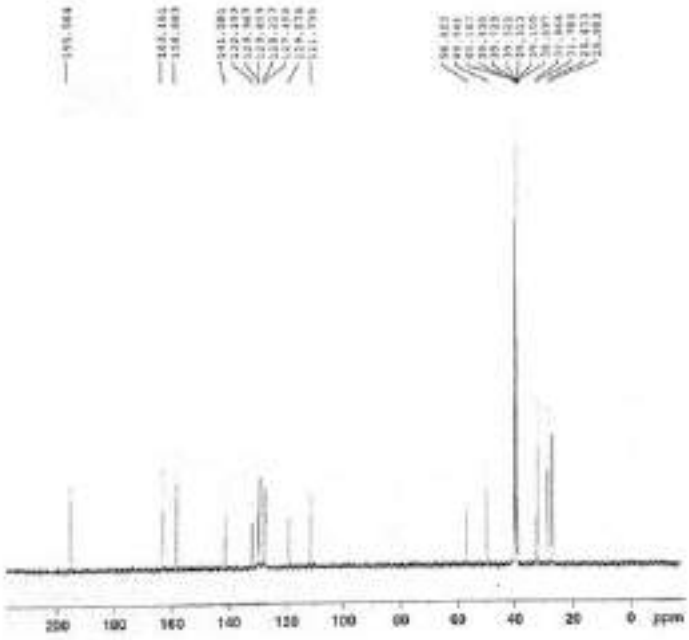


Figure II.32- ^{13}C-NMR of compound 5j

2-Amino-4-(2-nitrophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5k)

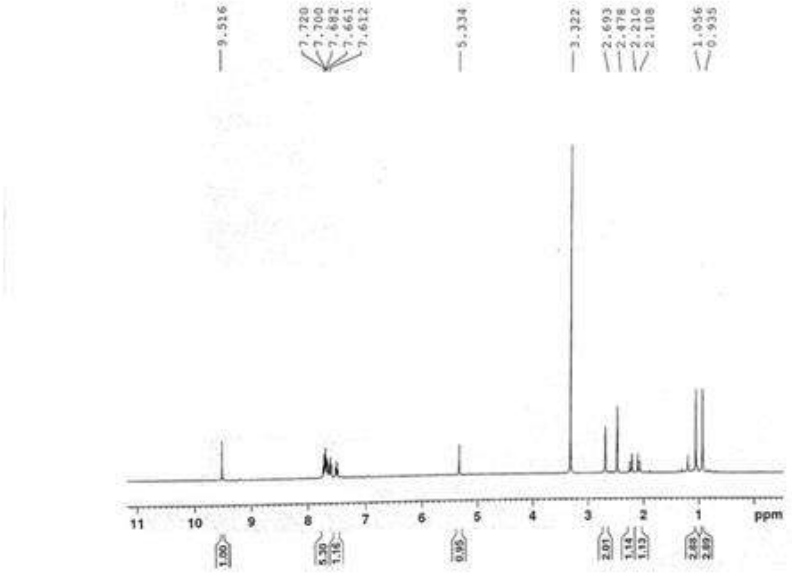


Figure II.33-^{1}H-NMR of compound 5k

2-Amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5l)

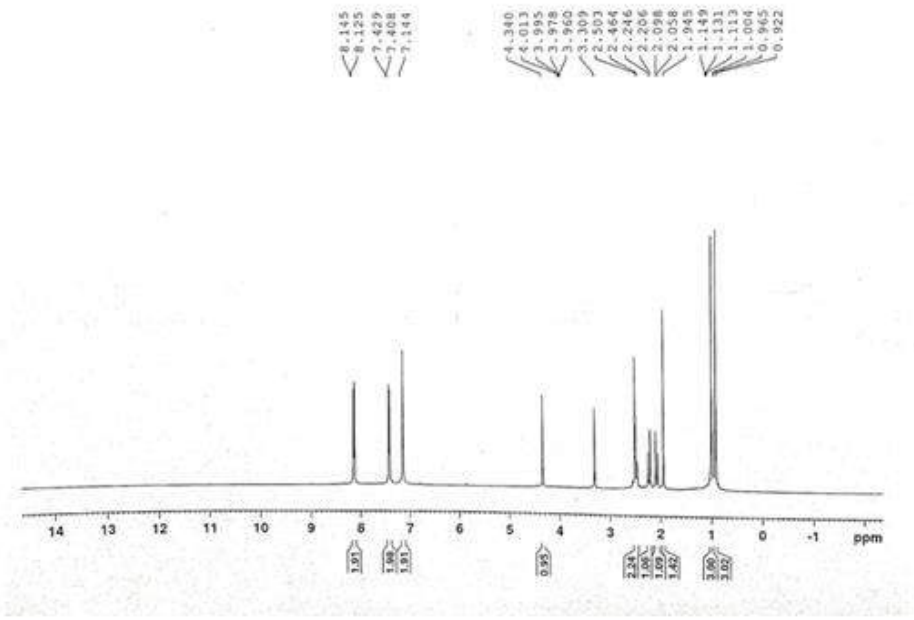


Figure II.34 - ^{1}H-NMR of compound 5l

2-Amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5l)

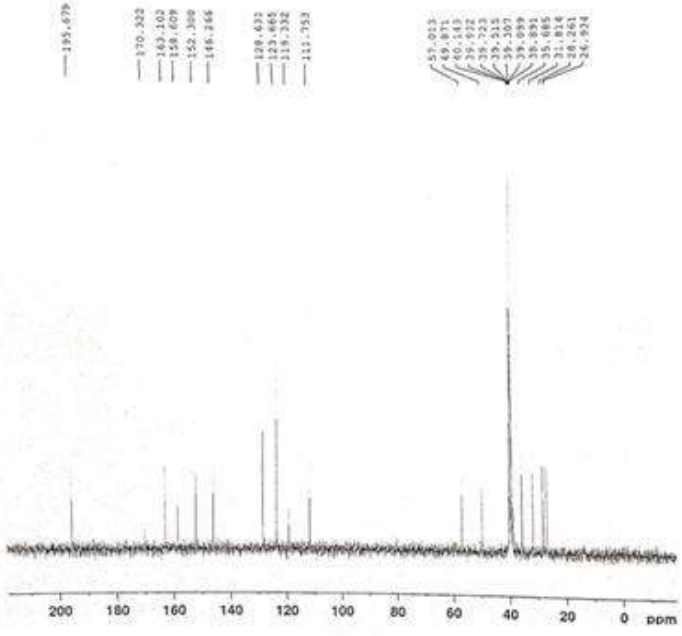


Figure II.35- ^{13}C-NMR of compound 5l

2-Amino-4-(3-methoxy,4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carbonitrile (5m)

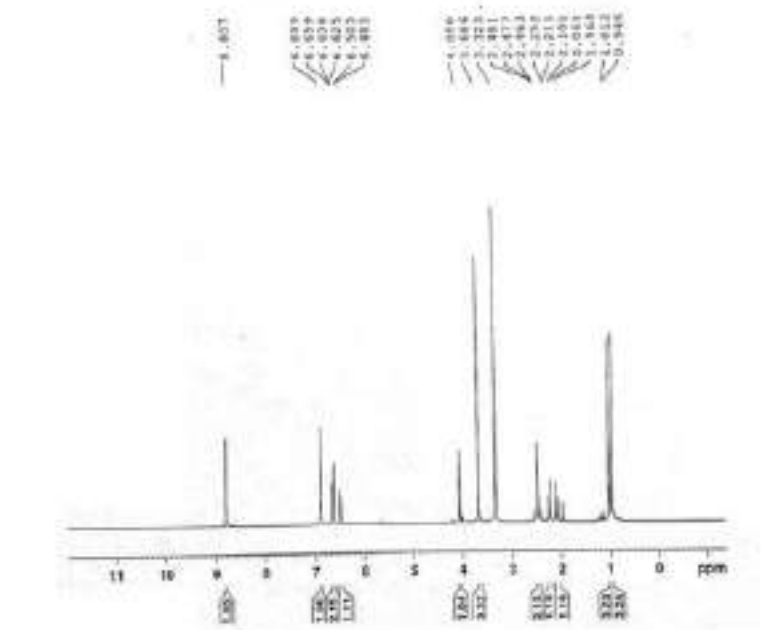


Figure II.36-^{1}H-NMR of compound 5m

2-Amino-4-(3-methoxy,4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carbonitrile (5m)

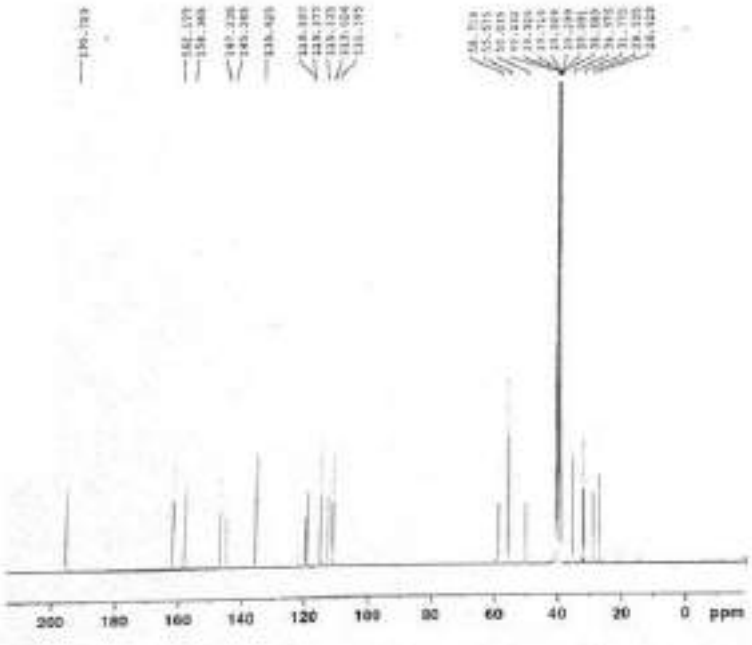


Figure II.37-^{13}C-NMR of compound 5m

2-Amino-4-(4-N,N dimethylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carbonitrile (5n)

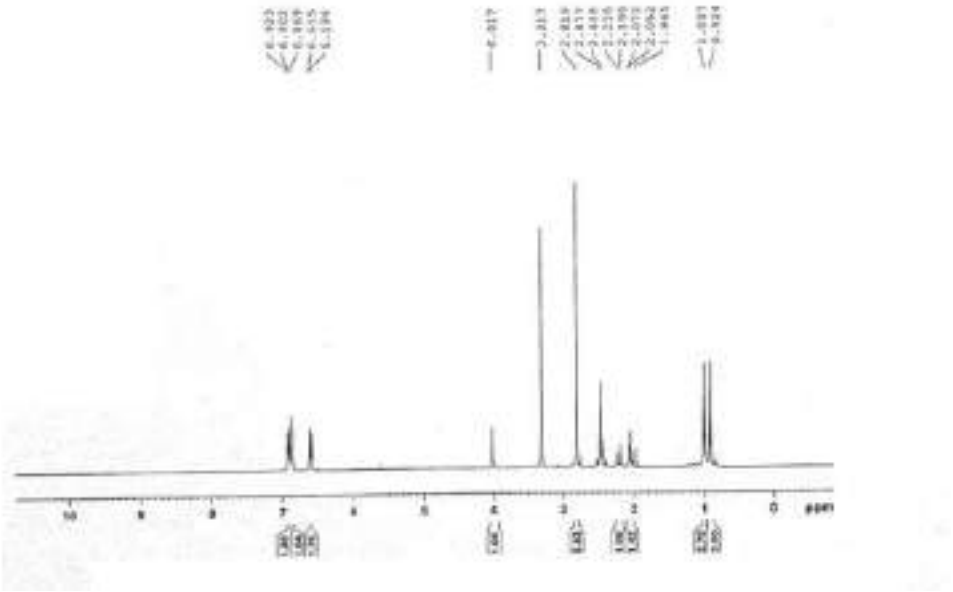


Figure II.38 - ^{1}H-NMR of compound 5n

2-Amino-4-(4-N,N dimethylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carbonitrile (5n)

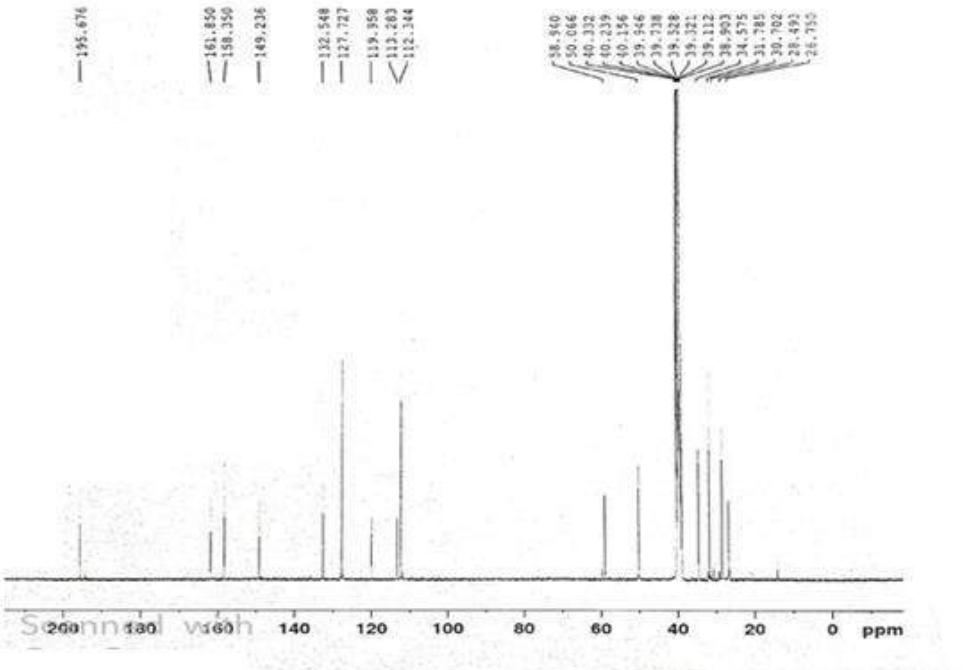


Figure II.39- ^{13}C-NMR of compound 5n

2-Amino-4-(pyridine-3-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5o)

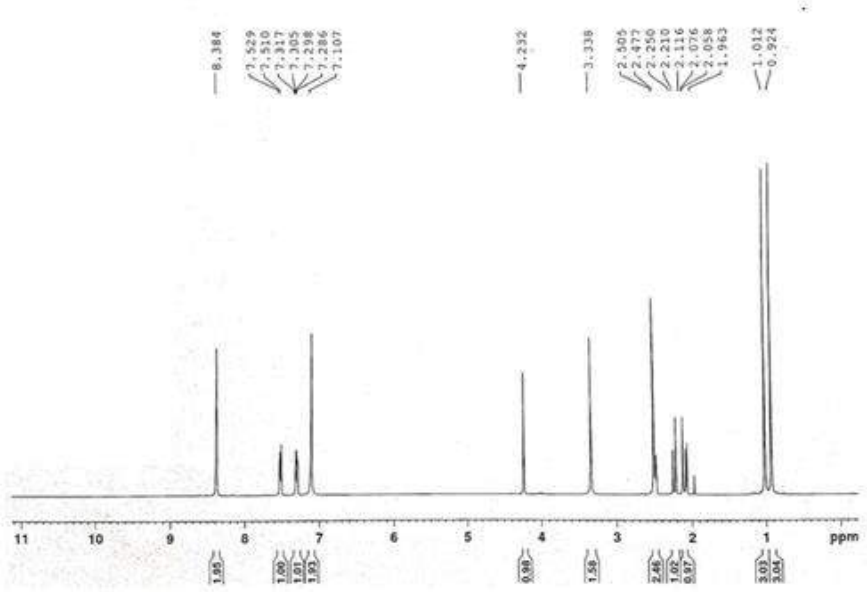


Figure II.40 - ^{1}H-NMR of compound 5o

2-Amino-4-(pyridine-3-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5o)

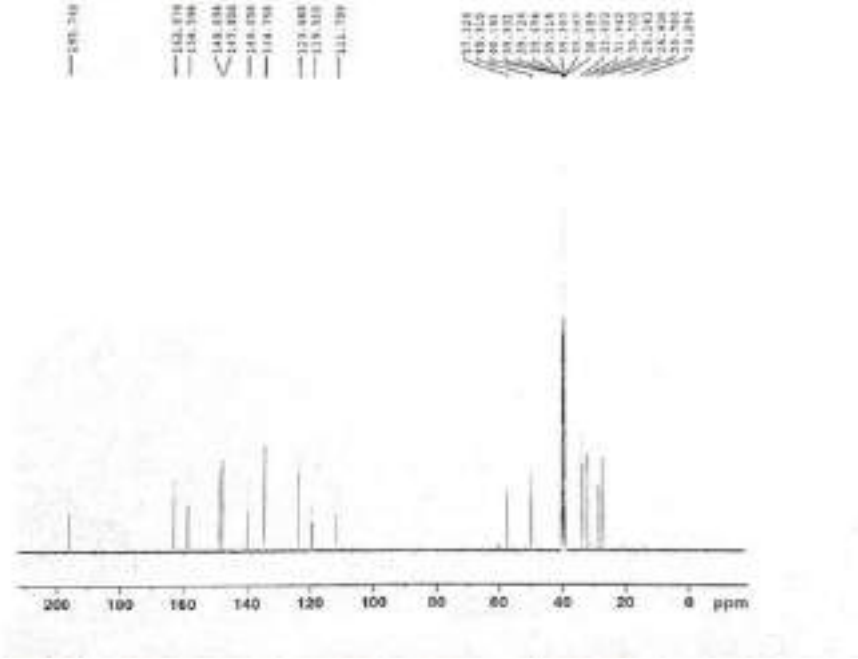


Figure II.41- ^{13}C-NMR of compound 5o

2-Amino-4-(naphthalene-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carbonitrile (5p)

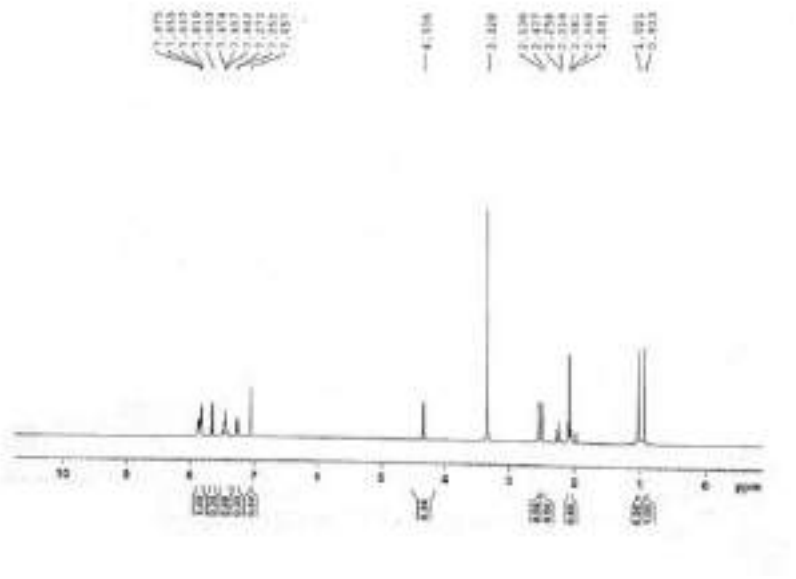


Figure II.42 - ^{1}H-NMR of compound 5p

2-Amino-4-(4-trifluoromethylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carbonitrile (5q)

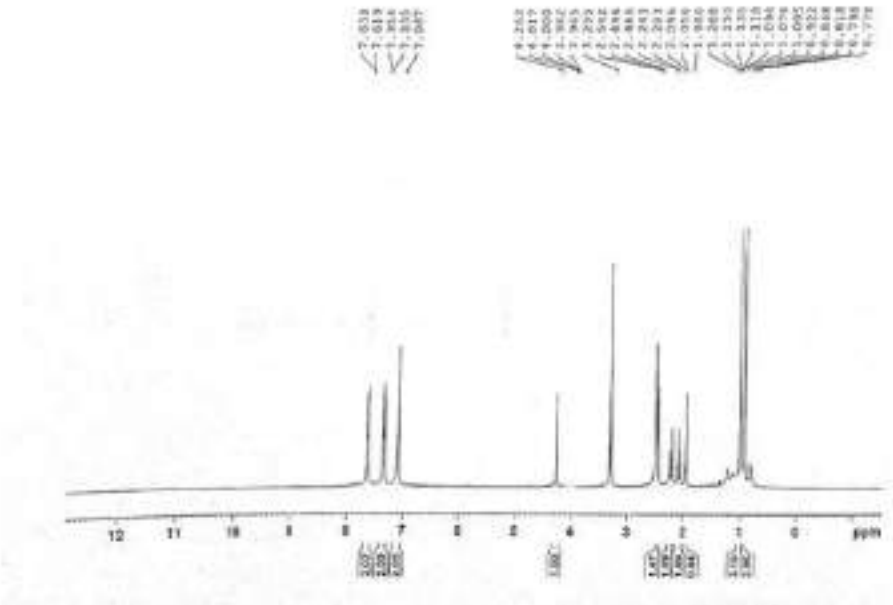


Figure II.43- ^{13}C-NMR of compound 5q

2-Amino-4-(4-trifluoromethylphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carbonitrile (5q)

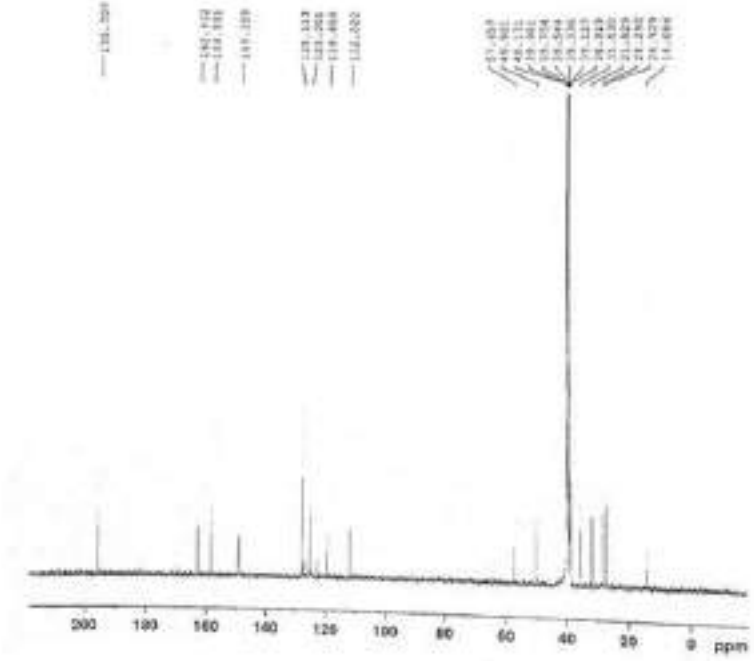
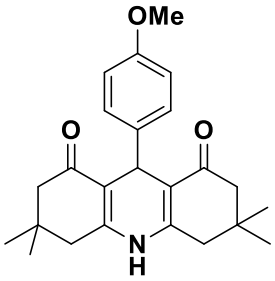


Figure II.44-^{13}C-NMR of compound 5q

II.8.A.12.g. Spectral data of the compounds mentioned in Scheme II.30

9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione(4a)

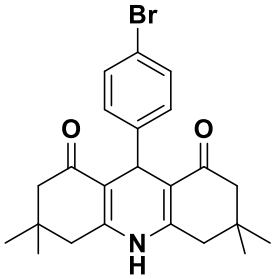


^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.84(s,6H),0.98(s,6H),1.95(d,2H),2.14(d,2H),2.13(d,2H),2.39-2.481(m,2H),3.66(s,3H), 4.72(s,1H),6.68(d,2H),7.02(d,2H),9.21(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)27.05,29.66,32.43,32.67,50.82,55.37,112.25,113.47,129.63,140.69,149.59,157.62, 194.94.

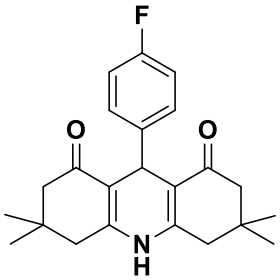
9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione(4b)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.83(s,6H),1.03(s,6H),1.96(d,2H),2.12(d,2H),2.30(d,2H),2.40-2.481(m,2H), 4.77(s,1H), 6.95(m,2H),7.11-7.15(m,2H),9.21(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)27.03,28.48,32.69,32.84,50.74,111.86,114.63,114.84,143.90,149.93, 194.94.

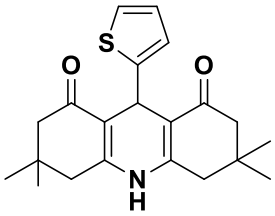
9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4c)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.84(s,6H),0.98(s,6H),1.88-2.32(m,8H) 4.63(s,1H), 6.95(m,2H), 7.03(d,2H), 9.21(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)27.05,29.66,32.43,32.67,50.82,55.37,112.25,113.47,129.063,140.069,149.59, 157.62, 194.94.

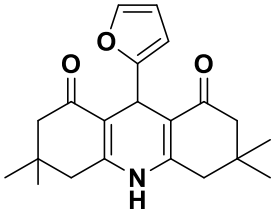
3,3,6,6-tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione(4d)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.91(s,6H),0.96(s,6H),1.96-1.48(m,8H), 5.12(s,1H),6.63(s,1H),6.75-6.77(m,1H), 7.10-7.12(m,1H),9.41(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)27.07,27.84,29.74,32.64,50.75,111.43,123.40,123.62,126.78,149.59,150.21,151.54, 194.91.

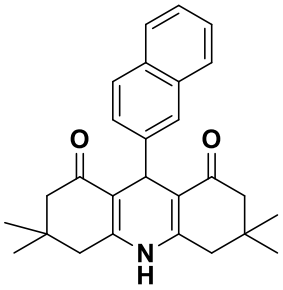
9-(furan-2-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione(4e)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)0.86(s,6H),0.96(s,6H),1.96-2.48(m,8H),5.12(s,1H),6.62(d,1H), 6.77(t,1H), 7.12(t,1H), 9.21(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)27.07,27.84,29.73,32.64,50.74,111.43,123.40,123.64,126.77,150.21,151.53, 194.91.

3,3,6,6-tetramethyl-9-(naphthalen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4f)

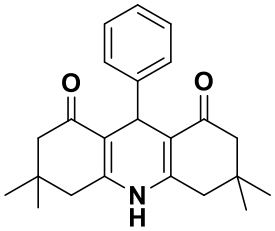


^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.83(s,6H),0.96(s,6H),1.88-1.96(m,2H),2.16(d,2H),2.32-2.48(m,4H),4.96(s,1H),7.34-7.41(m,4H),7.68-7.76(m,3H),9.36(s,1H).

^{13}C-NMR(400MHz,DMSO-d$_6$)
δ(ppm)26.95,29.68,32.70,33.82,50.82,111.83,125.61,126.12,126.26,127.38,127.64, 127.78, 128.09,132.09,133.28,145.13,150.02, 194.98.

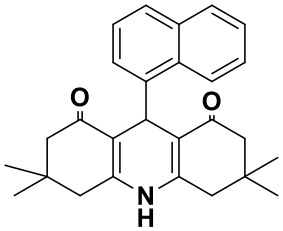
3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione(4g)



^{1}H-NMR(400MHz,DMSO-d$_6$)
δ(ppm)0.84(s,6H),0.98(s,6H),1.95(d,2H),2.14(d,2H),2.30(d,2H),2.32-2.53(m,2H), 4.78(s,1H), 6.68(d,2H),7.12-7.18(m,5H),9.26(s,1H).

^{13}C-NMR(400MHz,DMSO-d$_6$)
δ(ppm)27.01,29.64,32.69,33.37,50.80,112.00,126.00,128.11,128.15,149.87,194.91.

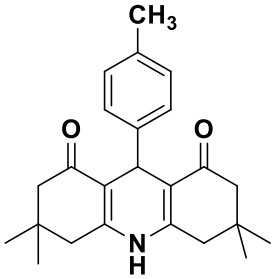
3,3,6,6-tetramethyl-9-(naphthalen-1-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione(4h)



^{1}H-NMR(400MHz,DMSO-d$_6$)
δ(ppm)0.79(s,6H),0.98(s,6H),1.84(d,2H),2.12(d,2H),2.33(d,2H),2.48-2.50 (m,2H,DMSO-6H), 5.56(s,1H),7.27-7.61(m,7H),9.37(s,1H).

^{13}C-NMR(400MHz,DMSO-d$_6$)
δ(ppm)26.83,28.90,29.71,32.67,50.75,113.72,125.38,125.60,125.90,126.52,126.68,126.81, 128.02,131.23,133.32.149.43,195.03.

3,3,6,6-tetramethyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione(4i)



^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.83(s,6H),0.96(s,6H),1.88-1.96(d,2H),2.1-2.15(m,2H),2.(d,2H),2.26-2.39(m,2H,DMSO-6H), 2.48(s,3H),4.73(s,1H),6.92(d,2H),7.00(d,2H),9.23(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)21.11,27.11,29.67,31.24,32.96,50.82,112.16,128.09,128.67,134.80,144.86, 149.68, 194.89.

II.8.A.12.h. Sanned copies of compounds mentioned in Scheme II.30

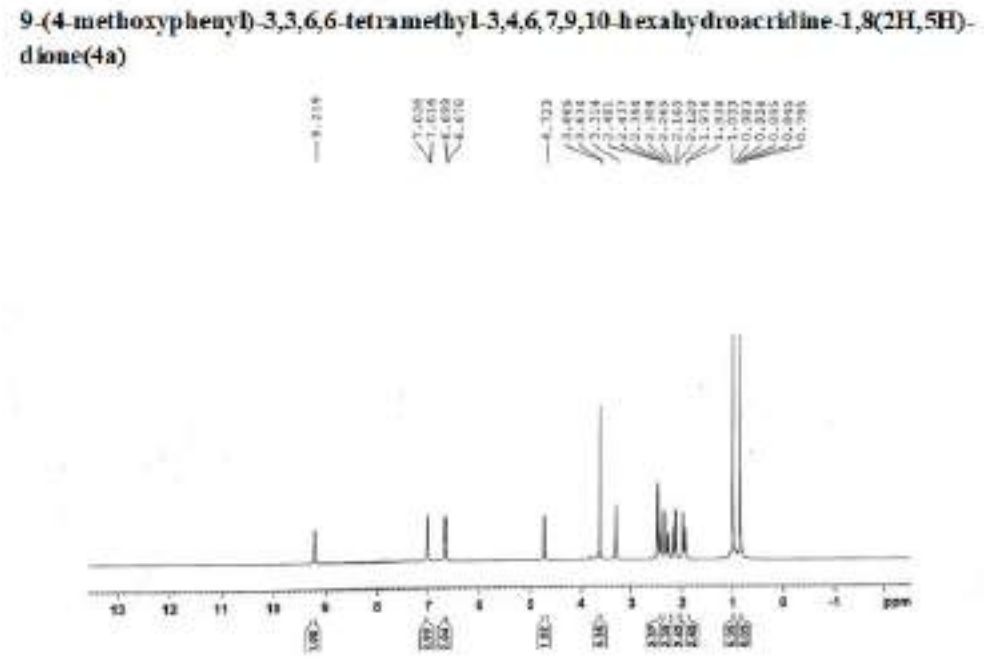


Figure II.45-^{1}H-NMR of compound 4a

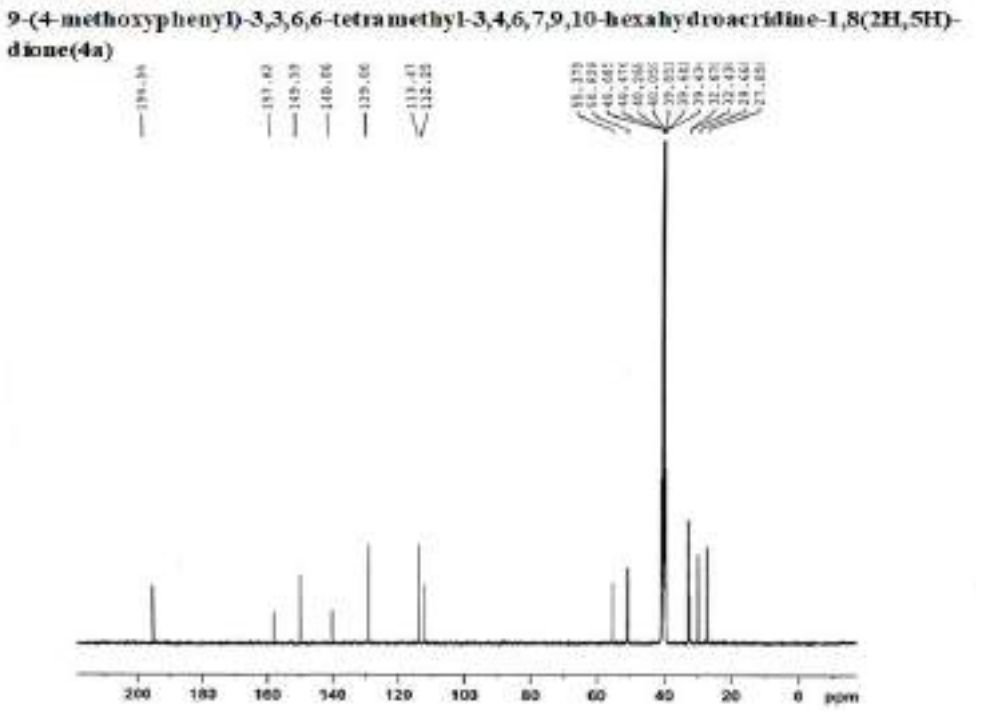


Figure II.46-^{13}C-NMR of compound 4a

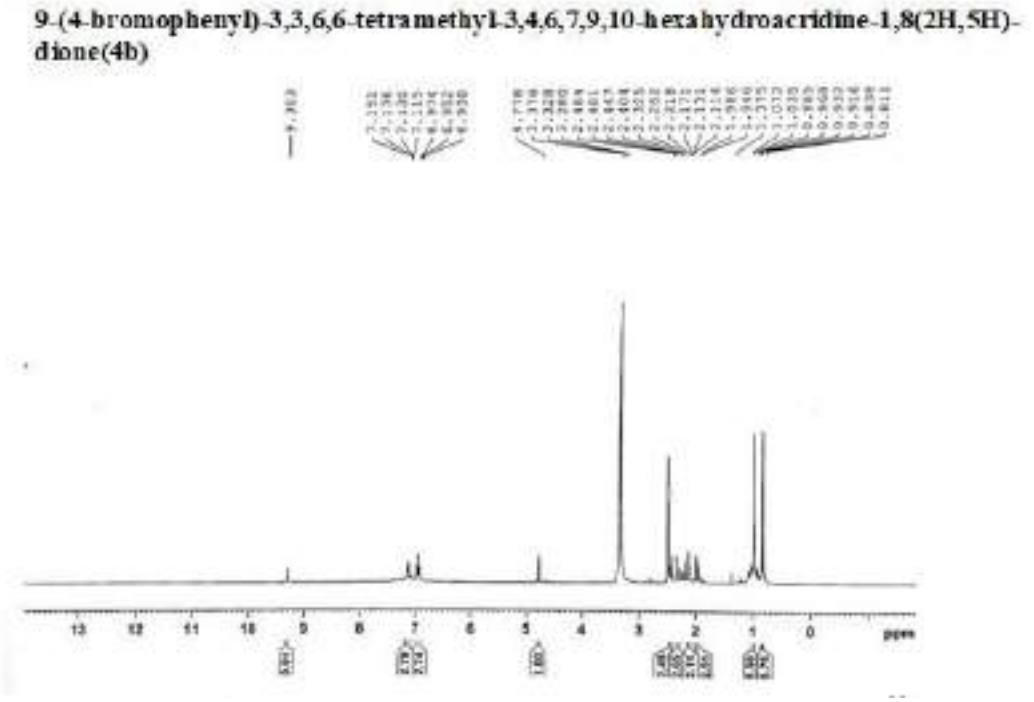


Figure II.47-^{1}H-NMR of compound 4b

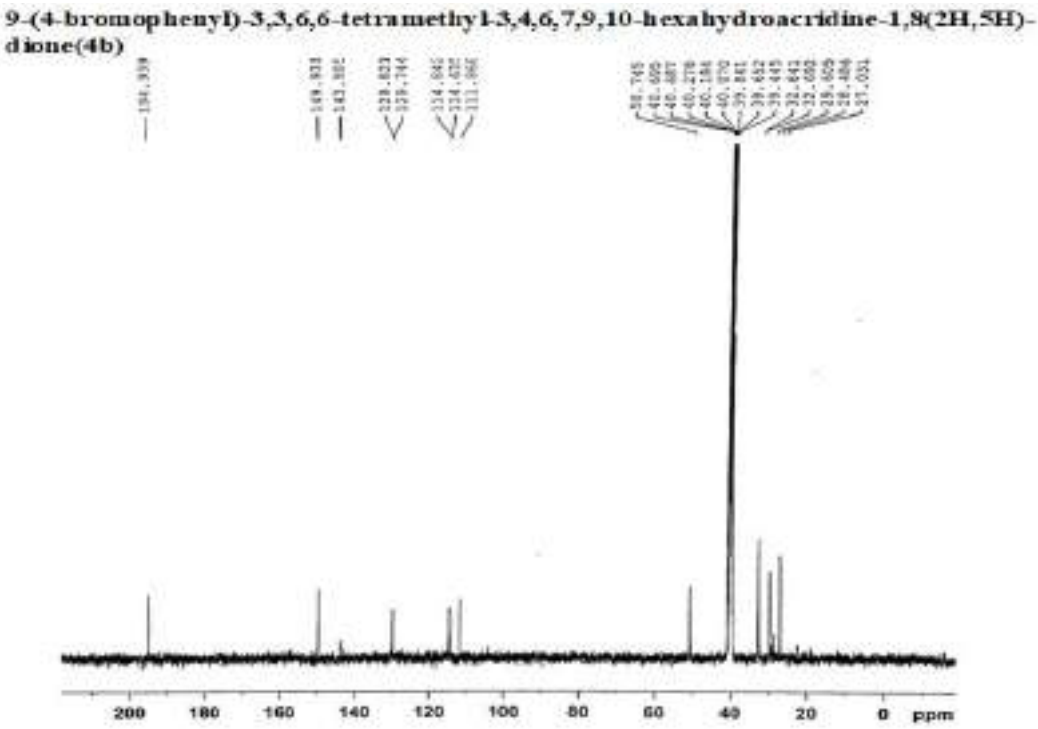


Figure II.48-^{13}C-NMR of compound 4b

9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4c)

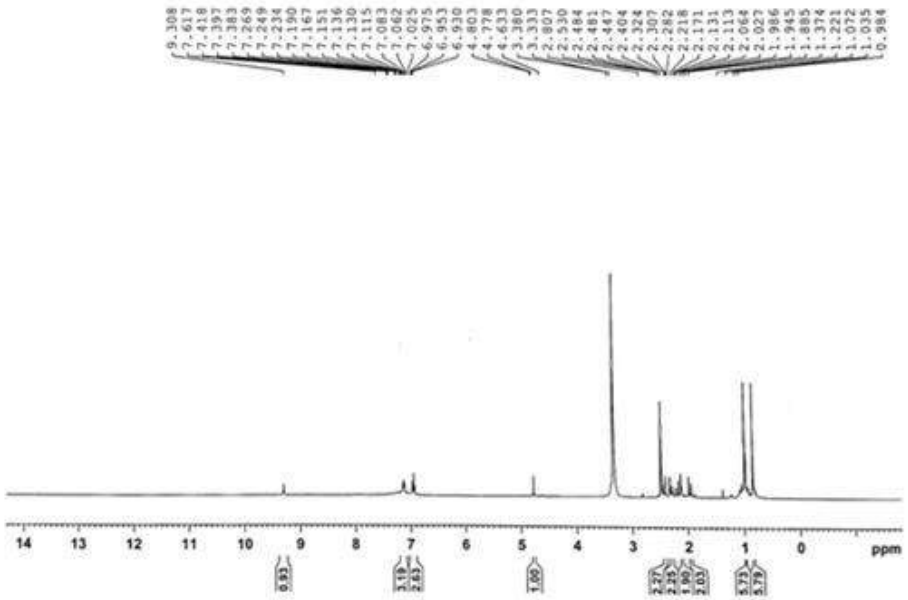


Figure II.49-^{1}H-NMR of compound 4c

9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4c)

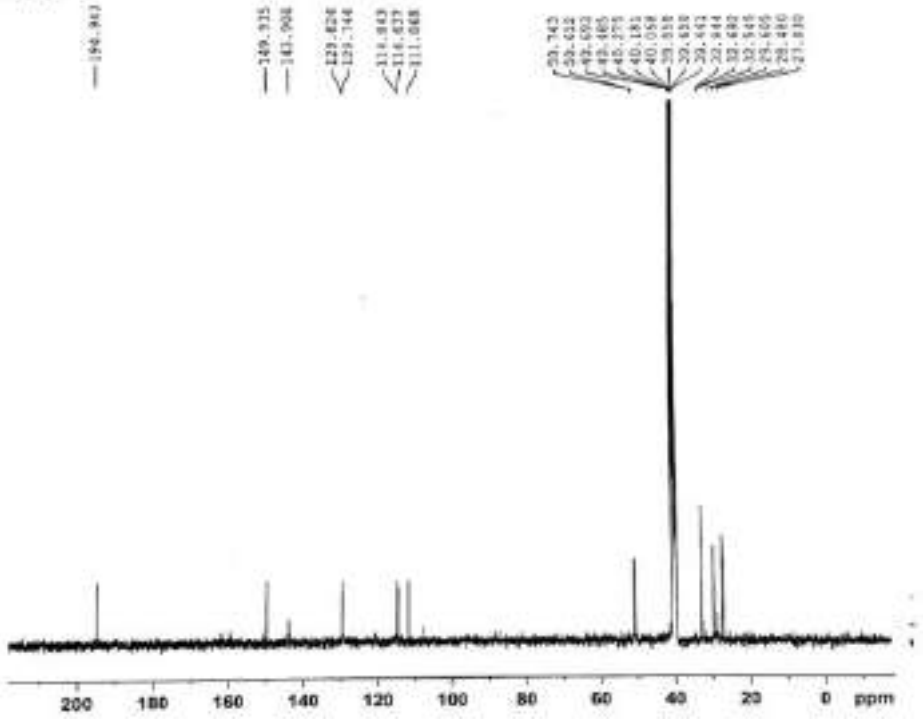


Figure II.50-^{13}C-NMR of compound 4c

3,3,6,6-tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(4d)

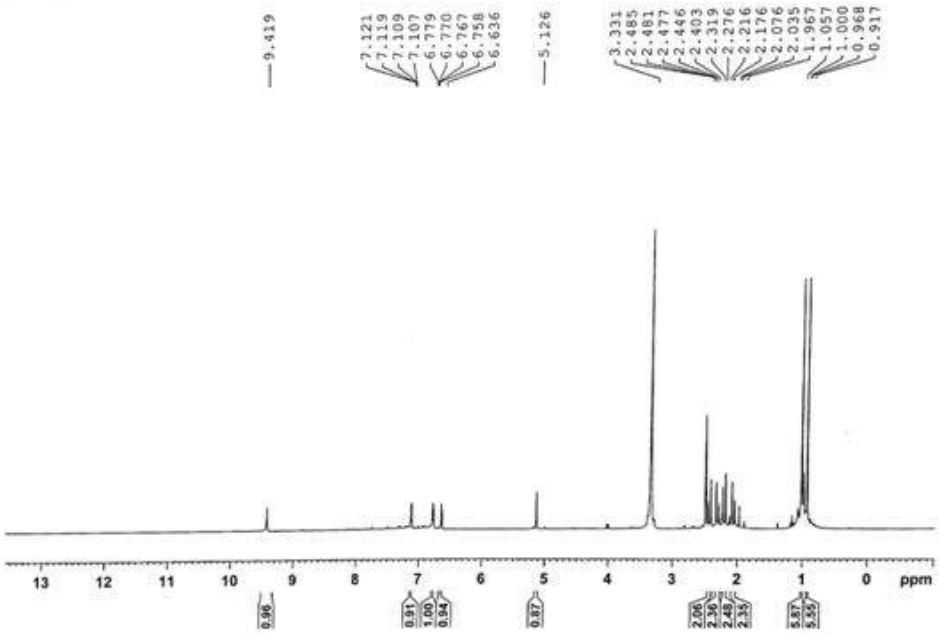


Figure II.51-^{1}H-NMR of compound 4d

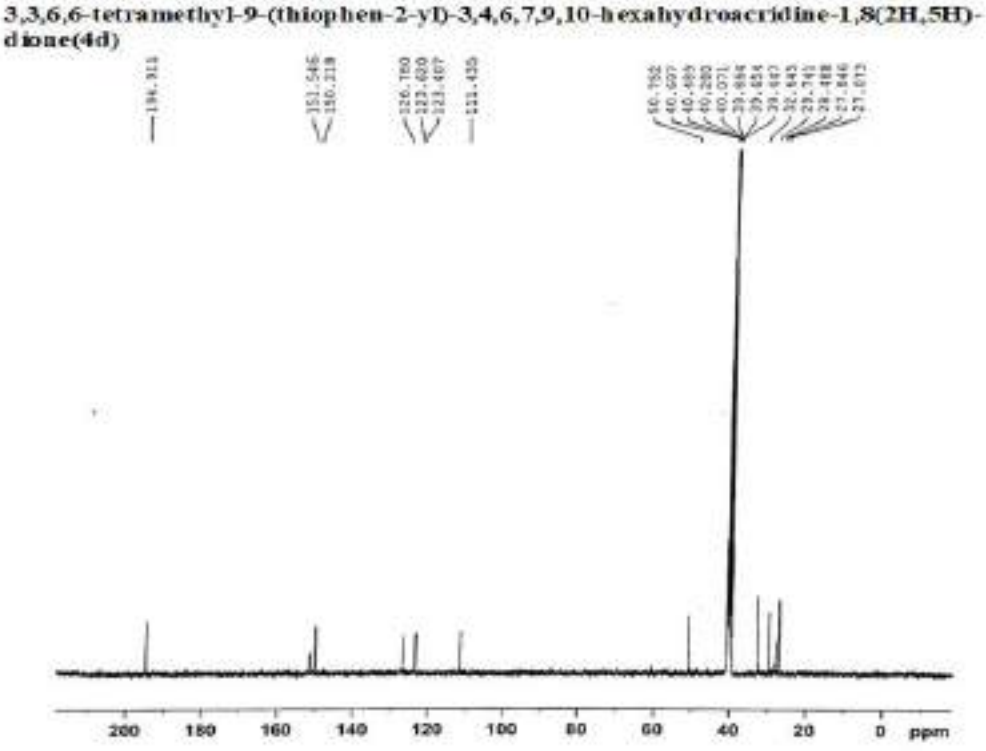


Figure II.52-^{13}C-NMR of compound 4d

9-(furan-2-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(4e)

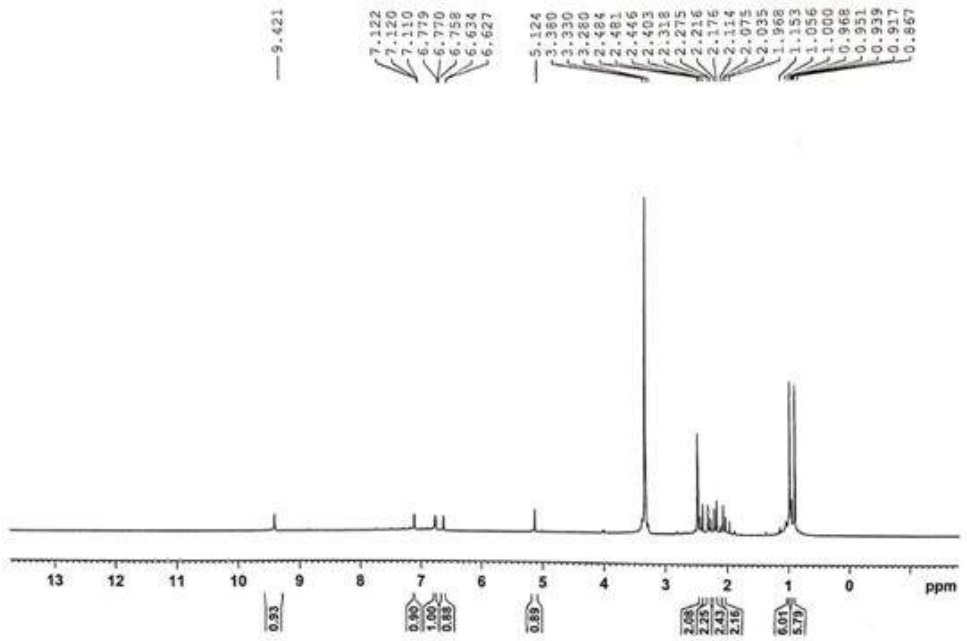


Figure II.53-^{1}H-NMR of compound 4e

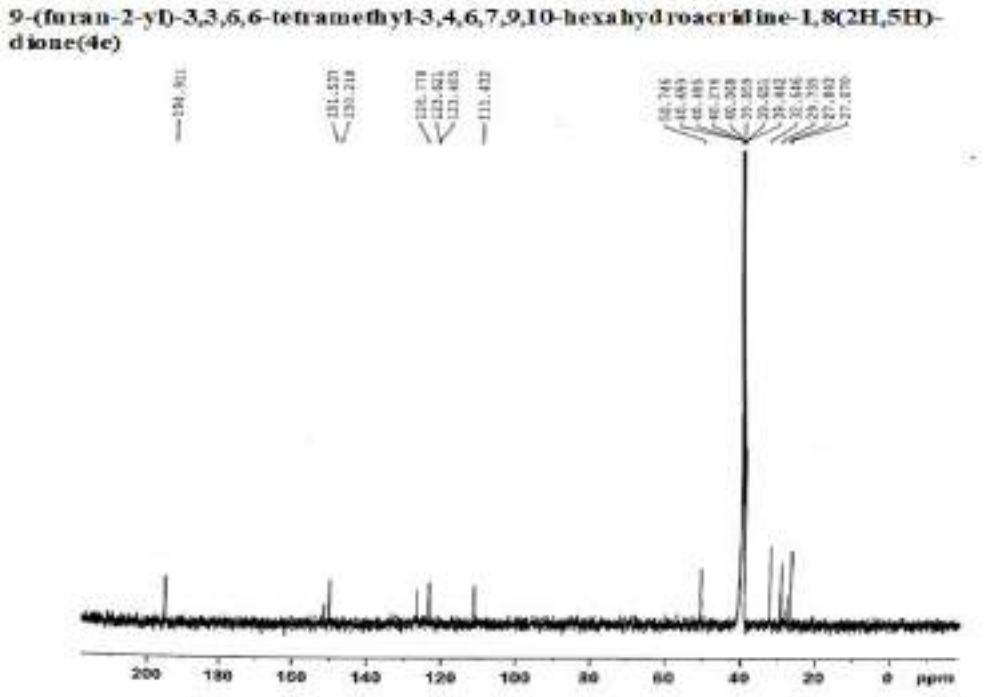


Figure II.54-^{13}C-NMR of compound 4e

3,3,6,6-tetramethyl-9-(naphthalen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4f)

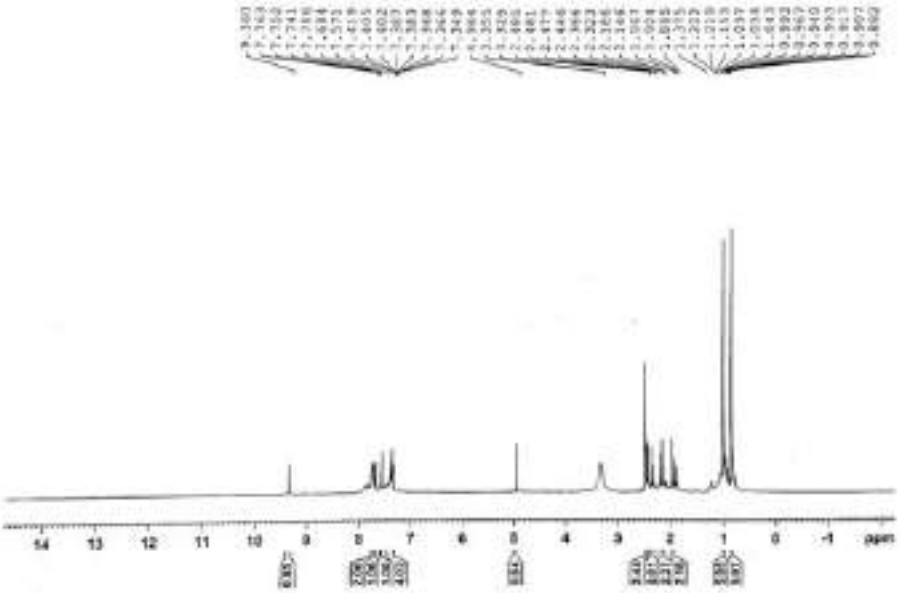


Figure II.55-^{1}H-NMR of compound 4f

3,3,6,6-tetramethyl-9-(naphthalen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4f)

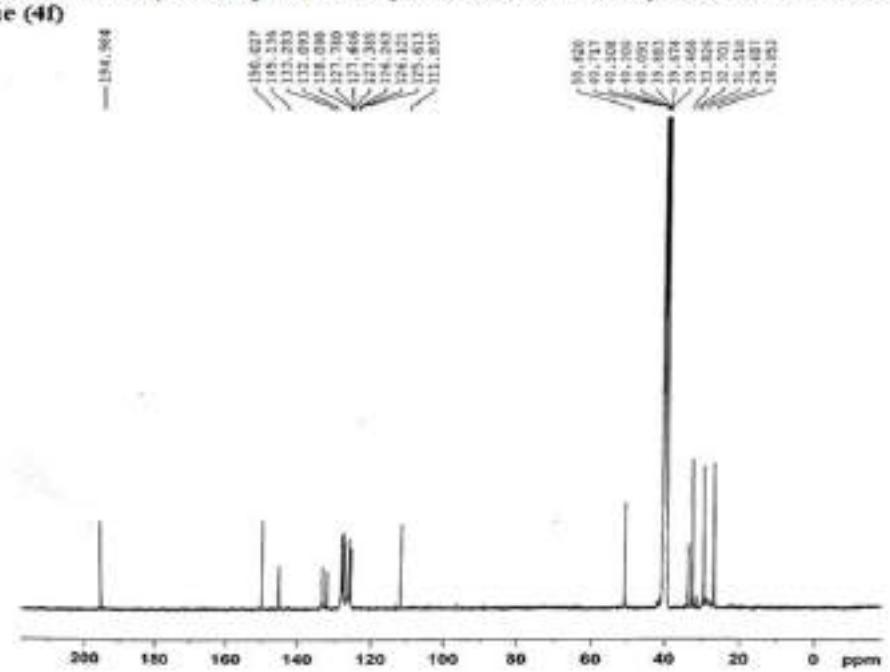


Figure II.56-^{13}C-NMR of compound 4f

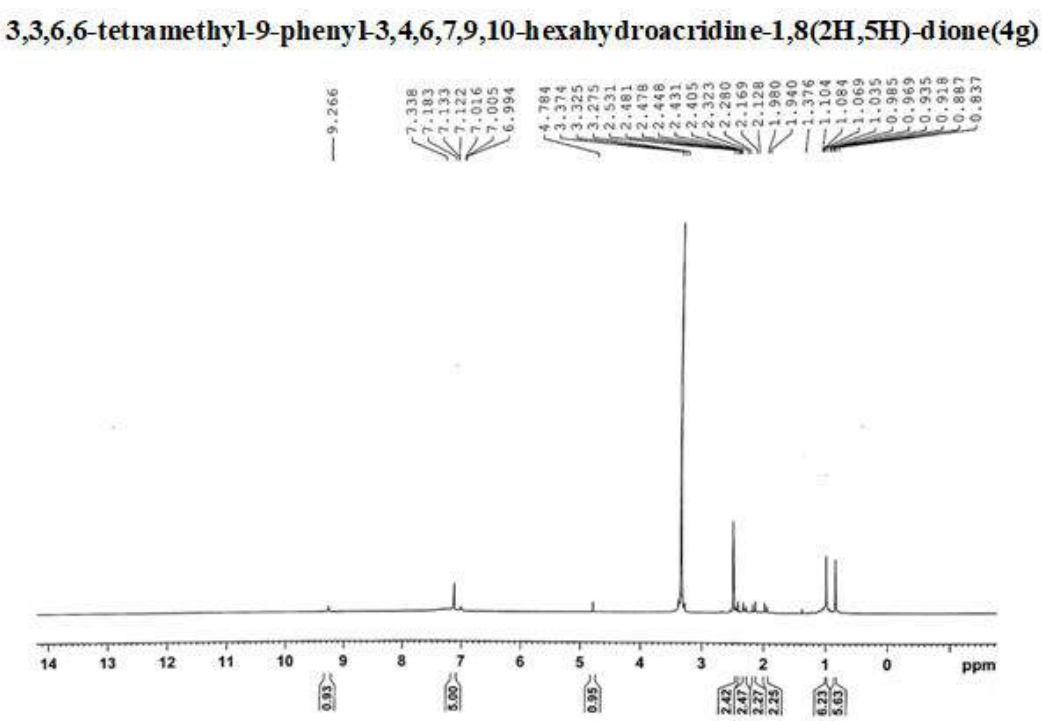


Figure II.57-^{1}H-NMR of compound 4g

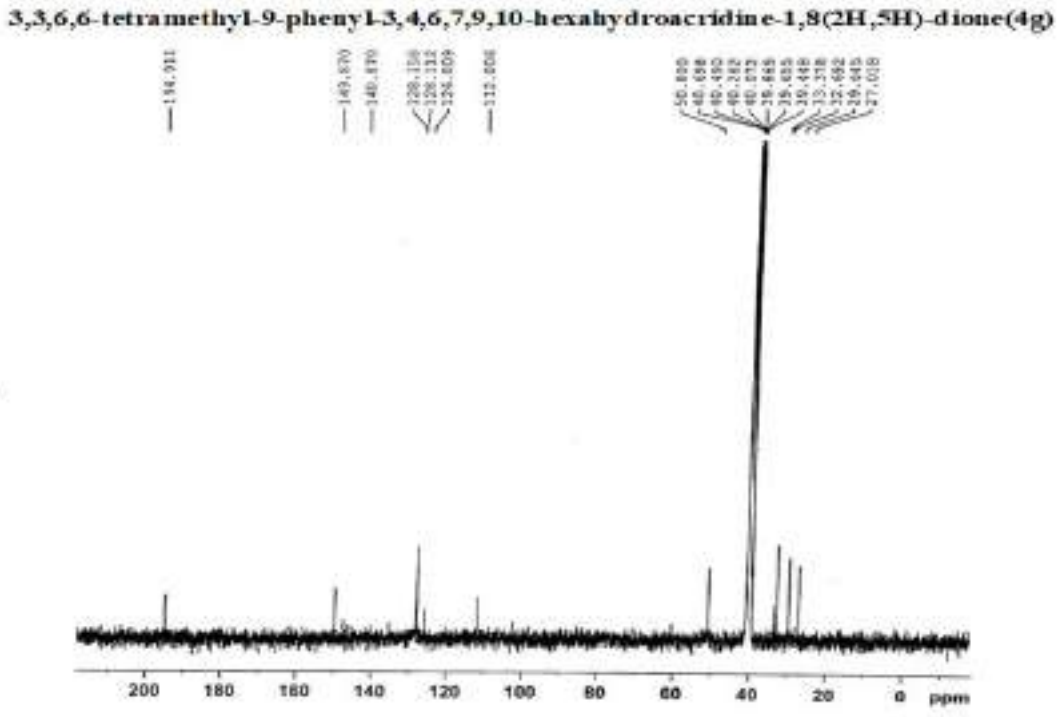


Figure II.58-^{13}C-NMR of compound 4g

3,3,6,6-tetramethyl-9-(naphthalen-1-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(4h)

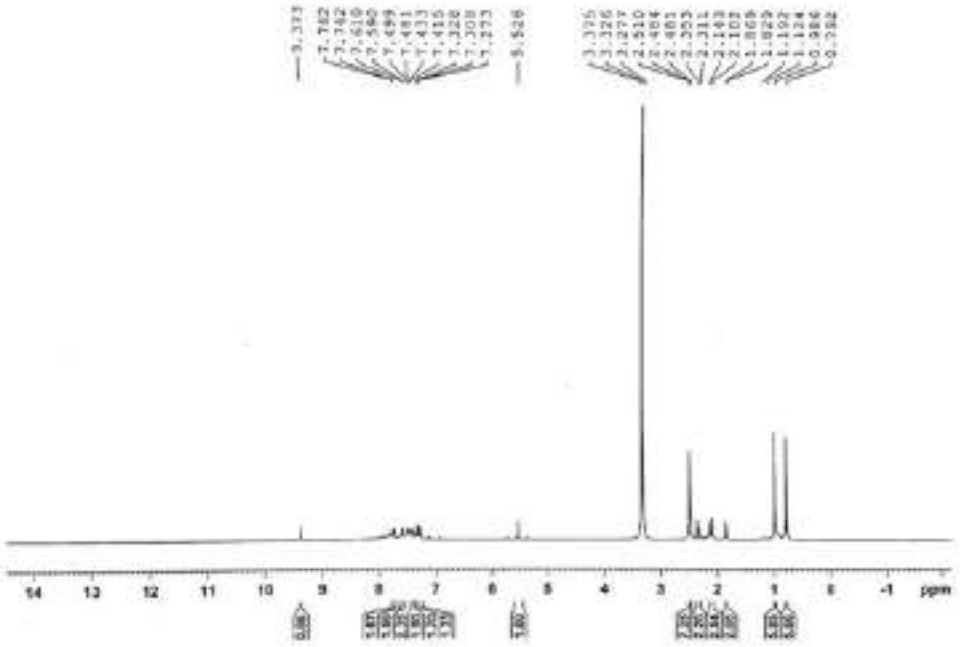


Figure II.59-^{1}H-NMR of compound 4h

3,3,6,6-tetramethyl-9-(naphthalen-1-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(4h)

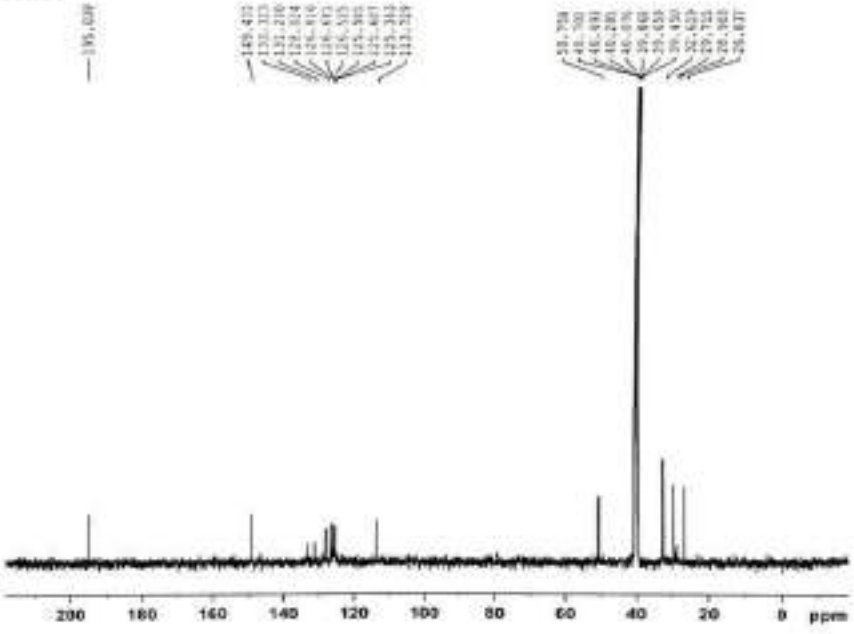


Figure II.60-^{13}C-NMR of compound 4h

3,3,6,6-tetramethyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(4i)

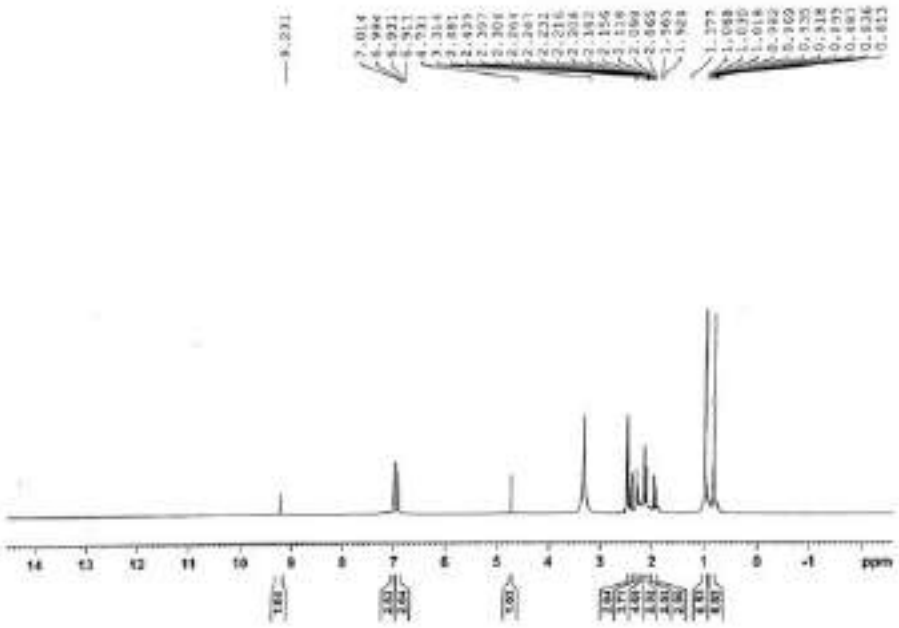


Figure II.61-^{1}H-NMR of compound 4i

3,3,6,6-tetramethyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(4i)

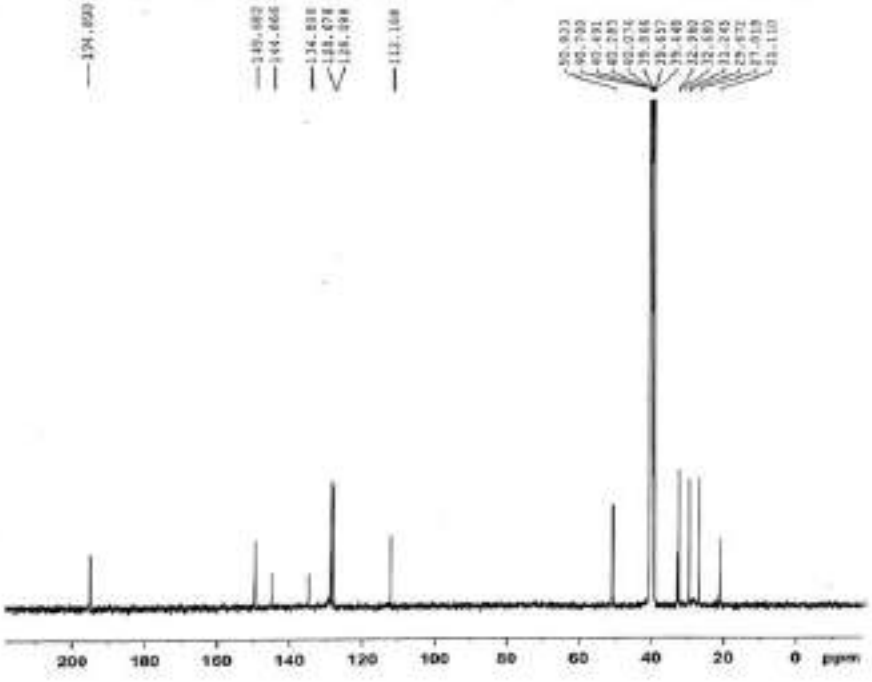


Figure II.62-^{13}C-NMR of compound 4i

II.8.A.12.i EDX data of sulphonated rice husk and rice husk

EDX data of sulphonated rice husk and rice husk are given below respectively

EDX data of sulphonated rice husk

Spectrum processing :

Peaks possibly omitted : 8.022, 8.603 keV

Processing option : All elements analyzed (Normalised)

Number of iterations = 7

Standard :

C CaCO3 1-Jun-1999 12:00 AM

N Not defined 1-Jun-1999 12:00 AM

O SiO2 1-Jun-1999 12:00 AM

Si SiO2 1-Jun-1999 12:00 AM

S FeS2 1-Jun-1999 12:00 AM

K MAD-10 Feldspar 1-Jun-1999 12:00 AM

Element	App Conc.	Intensity Corrn.	Weight%	Weight% Sigma	Atomic%
C K	59.21	0.5571	50.22	1.32	59.25
N K	1.16	0.0766	7.14	1.57	7.22
O K	22.42	0.3340	31.71	1.03	28.09
Si K	18.60	0.8924	9.85	0.29	4.97
S K	1.61	0.8551	0.89	0.06	0.39
K K	0.43	1.0184	0.20	0.03	0.07
Totals			100.00		

EDX data of rice husk

Spectrum processing :

Peaks possibly omitted : 8.039, 8.622 keV

Processing option : All elements analyzed (Normalised)

Number of iterations = 5

Standard :

C CaCO3 1-Jun-1999 12:00 AM

O SiO2 1-Jun-1999 12:00 AM

Mg MgO 1-Jun-1999 12:00 AM

Si SiO2 1-Jun-1999 12:00 AM

P GaP 1-Jun-1999 12:00 AM

S FeS2 1-Jun-1999 12:00 AM

K MAD-10 Feldspar 1-Jun-1999 12:00 AM

Element	App Conc.	Intensity Corrn.	Weight%	Weight% Sigma	Atomic%
C K	141.00	1.0152	51.20	0.71	58.76
O K	55.00	0.4323	46.90	0.71	40.41
Mg K	0.56	0.5959	0.35	0.05	0.20
Si K	0.76	0.8312	0.34	0.04	0.17
P K	1.40	1.2425	0.42	0.04	0.19
S K	0.27	0.9292	0.11	0.03	0.05
K K	1.98	1.0586	0.69	0.04	0.24
Totals			100.00		

II.8.A.12.j ICP-AES data of sulphonated rice husk

ICP-AES data of sulphonated rice husk is given below

ICP-AES (weight percentage of Sulphur) data for sulphonated rice husk

Ref: -ICP-AES-106
Date: 30/09/2019

Analytical report of the samples submitted by **Mr. Sourav Dey, University of North Bengal, Darjeeling-734013,** using Inductively Coupled Plasma Atomic Emission Spectroscopy.

Sample	**S**
	%
SAMPLE	**1.04**

II.9 References

References are given in BIBLIOGRAPHY under Chapter II.

CHAPTER III

A DESIGN FOR CONVENIENT AND GREENER ROOT TOWARDS ONE POT MULTI-COMPONENT SYNTHESIS OF SUBSTITUTED PYRANO-DICHROMENEO-DIONE AND CHROMENO-PYRIDO-PYRIMIDINONE DERIVATIVES USING RICE HUSK BASED HETEROGENEOUS CATALYST

III.1 Introduction

Coumarins are important class of heterocyclic compounds which contain a basic flavinoid like skeleton and have both natural and synthetic origin that show diverse pharmaceutical and biological activities.[1] As coumarin scaffolds are one of the important fused ring heterocyclic bioactive compounds, a considerable effort have been made by researchers towards the fruitful synthesis of these useful bio-active coumarine heterocycles. Coumarins can be derived from natural resources and scaffold can be used extensively in laboratory for generation of newer drug molecules. Their derivatives are no doubt a class of bioactive agents which show a broad range biological activities such as anti-inflamatory [2], anticancer [3], antitubercular [4], anti-viral [5], anti-fungal [6]. A varity of scientific research have been made towards the synthesis coumarin analogues to find their significant applications in the field of medicinal chemistry and a number of coumarin derivatives have been obtained by following famous reactions procedures such as Knoevenagel, Perkin, Reformatsky, Michael etc. [7] Some coumarine derivatives also showed excellent fluorescent properties and thus a series of coumarin based molecular probes are being used to investigate drug action in cellular biological researches.[8]

Among the coumarin-fused heterocycles 7-aryl substituted pyranodichromene-6,8-dione and 7-aryl substituted chromeno[4,3-d]pyrido[1,2-a]pyrimidinone derivatives have attracted our keen attention for organic synthesis under green condition. Because of having several biological and pharmaceutical activities the chromene moiety has been generally employed in the expansion of compounds and one-pot multi-component reactions (MCRs) in this regard has helped us a lot as because it provides convenient, energy and time saving root over multi-step process for the synthesis of annelated coumarine derivatives. In our described project, one pot three component and pseudo three component reactions have shown potential effectiveness in generating good product yield in a hassle-free manner. It is observed that both homogeneous and heterogeneous catalysts are capable enough to increase the productivity in MCRs but however, heterogeneous catalysts have more importance over homogeneous one because of their easy separation and recovery from the reaction mixture. In this context, rice husk (RH) based heterogeneous support has been chosen for the synthesis of our targeted substituted pyranodichromene-6,8-dione and chromeno[4,3-d]pyrido[1,2-a]pyrimidinone derivatives considering a sustainable way. Rice husk is an agricultural by-product having high

silica content and the characteristics like high porosity, light weight and high external surface area attracted us to use it as a good heterogeneous catalyst.[9-10] There are also more reasons to select rice husk based greener catalyst for chemical reactions due to its economic advantage, non-toxicity, high abundance, and bio-degradability and furthermore it is more economically cheaper than other heterogeneous materials.[11] The use of rice husk based eco-friendly catalysts and the use of safer and greener solvents are on demand in recent years for the greener synthesis of organic compounds to achieve a sustainable goal and so derived and modified natural substances from agricultural waste can make a major contribution as a bio-derived catalyst in future research for the synthesis of various important heterocyclic compounds. And following the principles of "Green Chemisty", applying the one-pot multi-component reaction technique (MCRs) along with greener catalyst (SRH), greener solvent, a versatile and powerful way has been presented in the whole work for the targeted synthesis of fused-ring coumarine derivatives. As a part of our research interest on the synthesis of substituted pyrano-dichromeneo-dione and chromeno-pyrido-pyrimidinone derivatives of biological significance, we report here the preparation of catalyst and the

whole synthetic process those above mentioned coumarin derivatives via a simplest hassle free route under sustainable and greener technique.

III.2 Chromene

According to IUPAC systems of nomanclatures, benzopyran systems are generally known as chromenes.[12] There are two isomers of benzopyran such as chromene and isochromene and additionally there are several types of chromenes reported in literature depending upon its structural variation and presence of ring substitution. Out of nine carbons in the ring system, eight carbons are sp^2 and one carbon is sp^3 hybridized and depending upon the position of sp^3 carbon with respect to ring oxygen naming of chromenes are done as 2*H*-, 3*H*- and 4*H*-chromenes and the replacement of sp^3 hybridized carbon by carbonyl group leads to make 2*H*-, 3*H*- and 4*H*- chromenone or chromone rings.[13-14] A list of various types of chromenes have been shown in **Figure III.1** containing triclic and tetracyclic rings also.

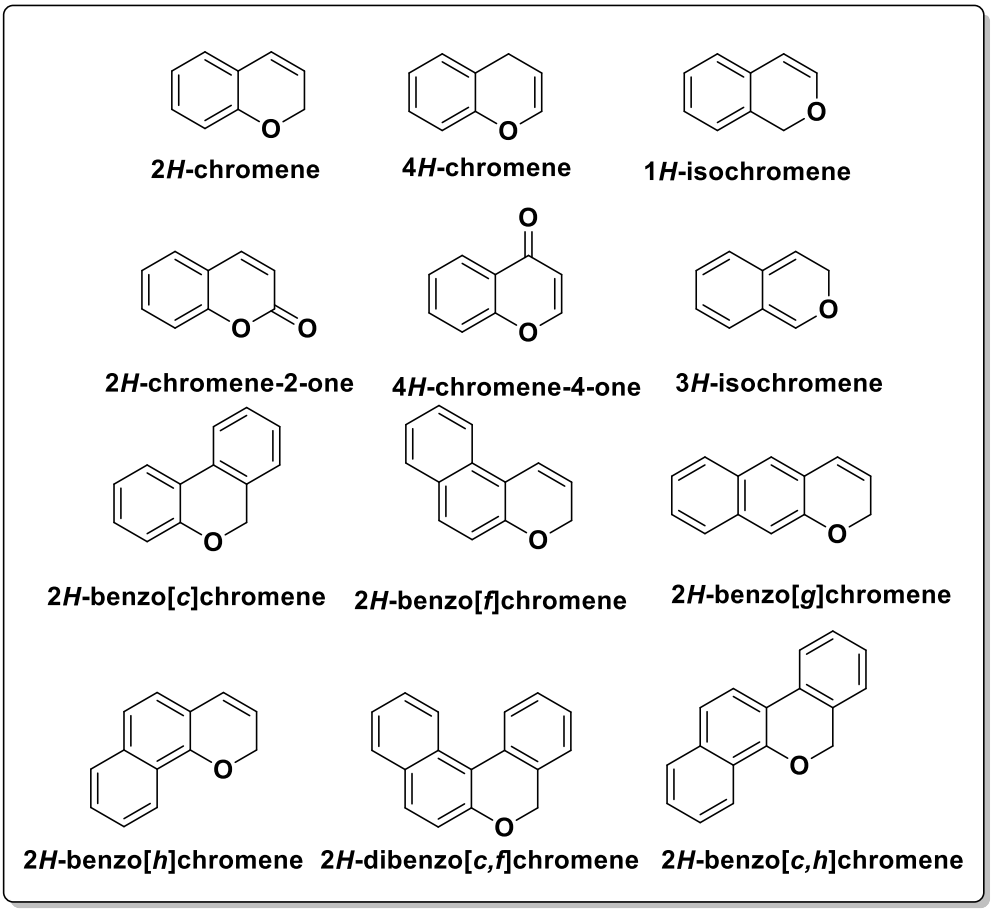


Figure III.1 Different types of chromene scaffolds

III.2.A Coumarine

Coumarine or 2*H*-chromene-2-one is an organic colourless solid compound with sweet odour having a lactone like ring fused with a benzene ring. Coumarines are also a class of chromene molecues where sp^3 hybridized carbon atom of 2*H*-chromene moelecule is replaced by carbonyl (C=O) group having both chemical and pharmaceutical importance. Coumarins are widely spread in the nature and can be found

in many plants as secondary metabolites.[15] There are several reported isolation process of coumarines from natural resources [16-30] and also there have methods of laboratory synthsis of both coumarine, substituted coumarines (**Figure III.2**) and other coumarine derivatives.

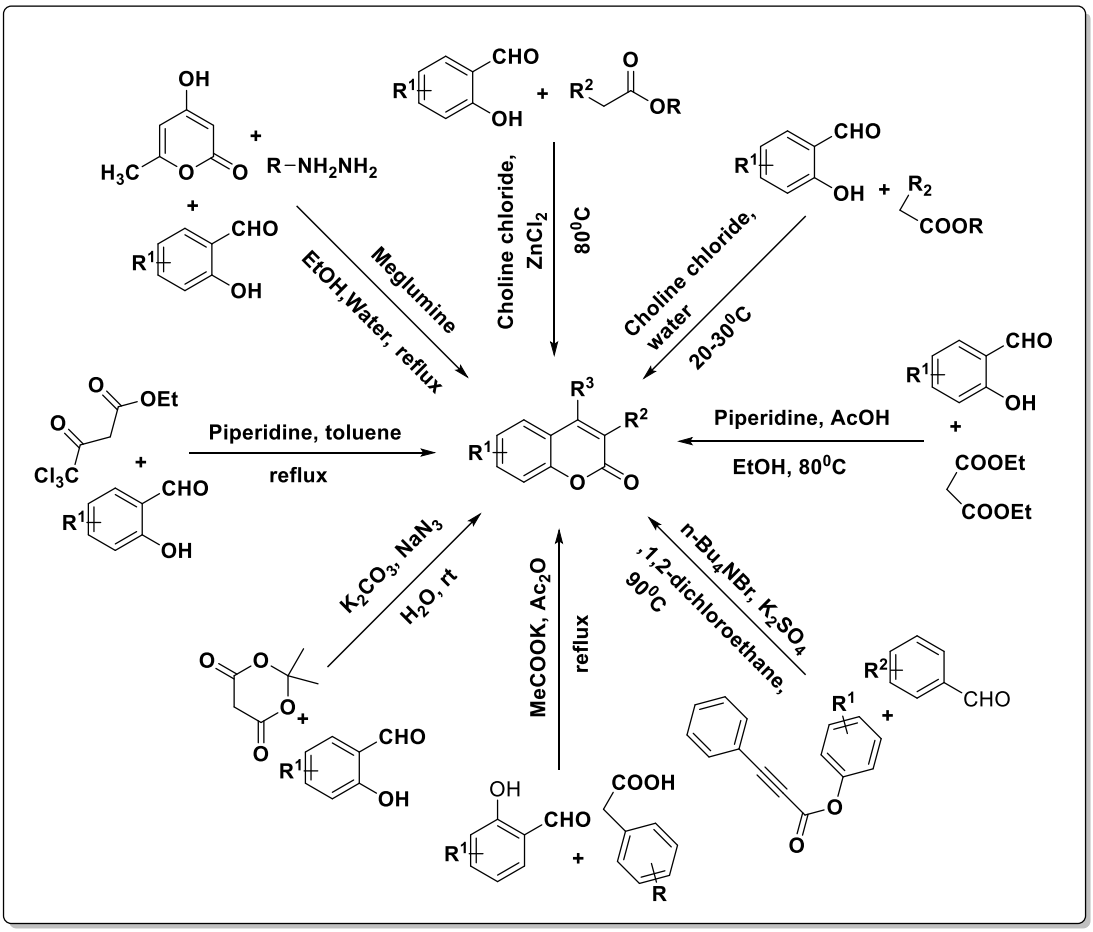


Figure III.2 Diverse synthetic routes for the synthesis of coumarine structures

III.3 Biological importance of chromenes and coumarines

Synthetic chromene derivatives possesses potent anticancer, antibacterial and antifungal, antirheumatic, anti-inflamatory properties and a vast number of chromene heterocycles are found to have

significant biological activity and some of them are used as potent drugs.[31] A large number of potent bioactive chromene heterocycles are reported in literature having anti-HIV, anti-inflamatory, anti-toumour, antihepatitic, anticancer, anticoagulant and antagonist activities(**Figure III.3**).[32-46] Therefore, synthetic chemists are always motivated to synthesize such potent analogous for pharmaceutical activities [47-50].

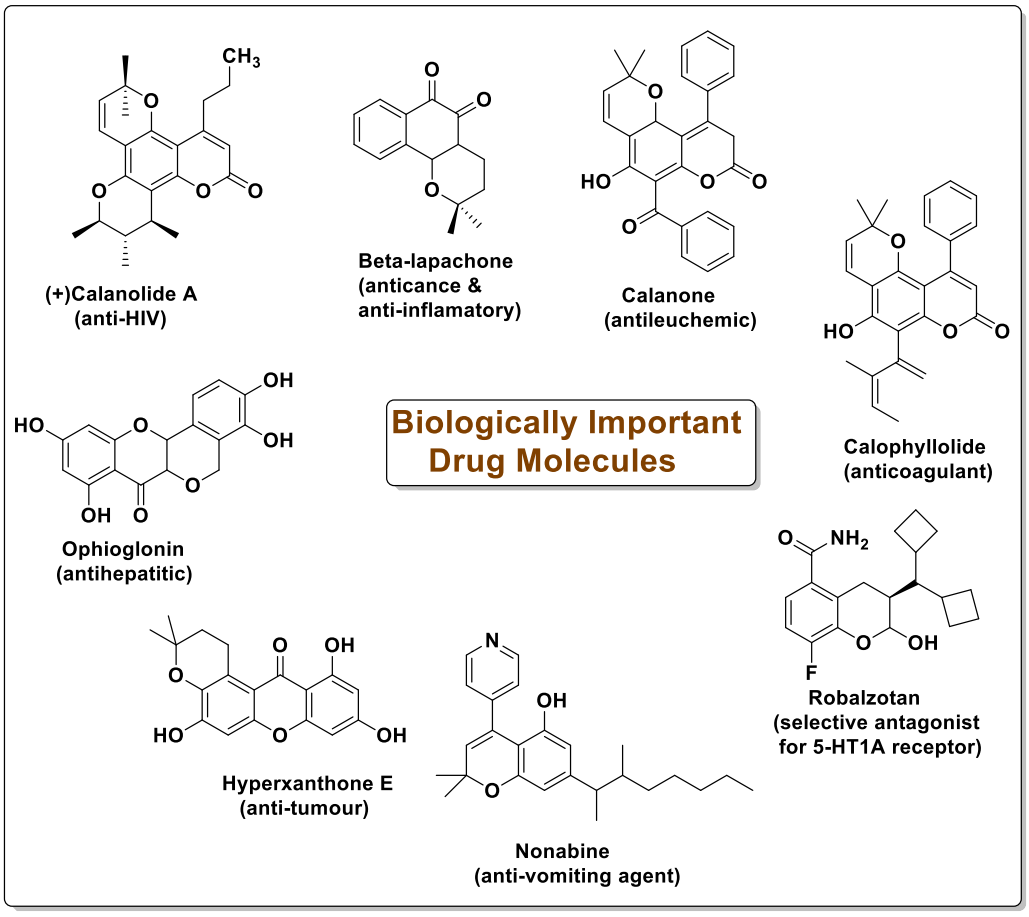


Figure III.3 Some important pharmaceutically active drug molecule containing chromene structural skeletons

Coumarins possess broad range of biological activities such as-antifungal, anti-bacterial, anti-inflammatory, anti-HIV, anticancer, antituberculosis, anticoagulant, antiviral and significant antioxidant activities (**Figure III.4)** [51-62]. Some coumarins are derived as acetylcholinesterase inhibitors and so are useful drug in Alzheimer disease treatment [63].

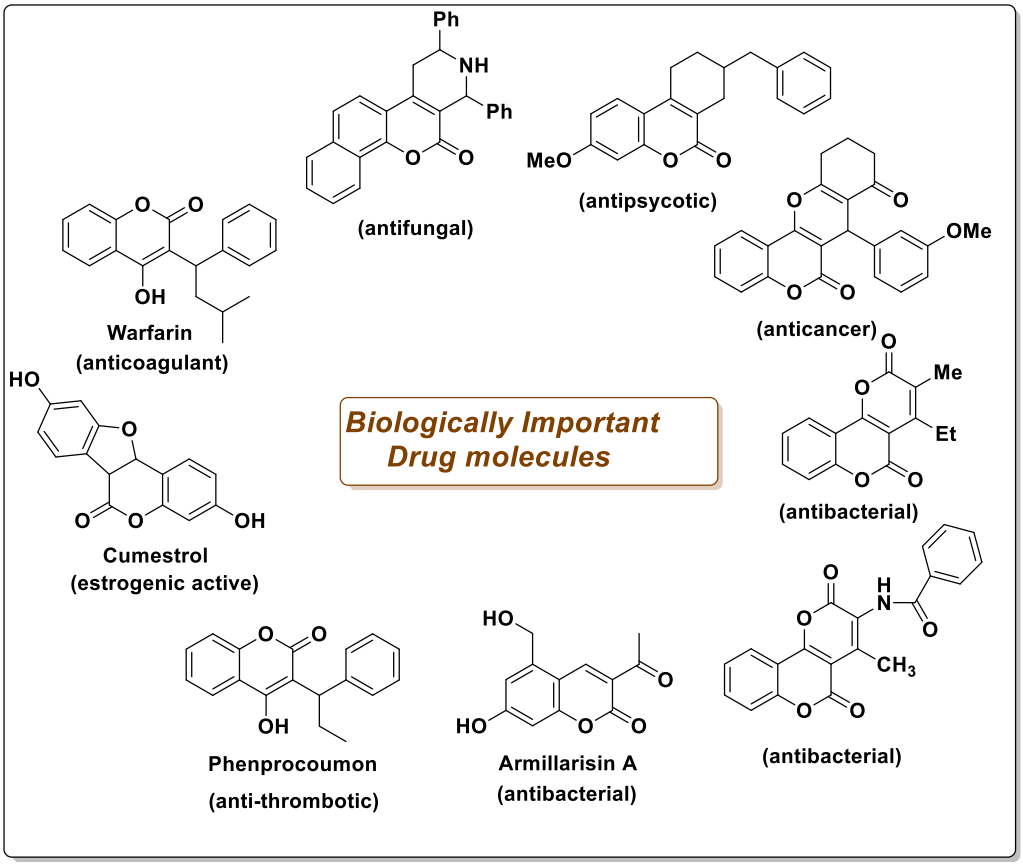


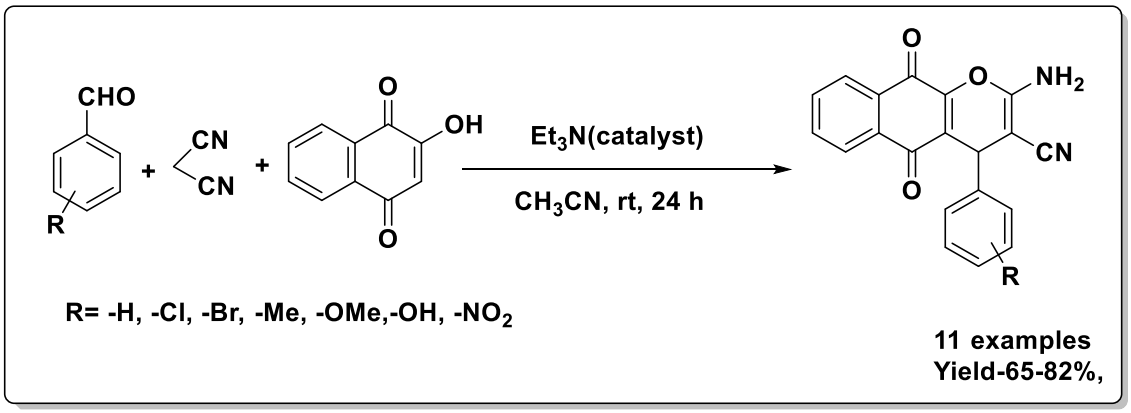
Figure III.4 Some important pharmaceutically active drug molecule containing coumarine structural skeletons

By doing studies on works in various journals related to chromenes, coumarines, and their derivatives and taking biological importances of

chromenes, coumarines, and their derivatives in knowledge in this following part of the chapter III, it has been focused on the chromene derivatives in a new and convenient manner using cheap laboratory chemicals.

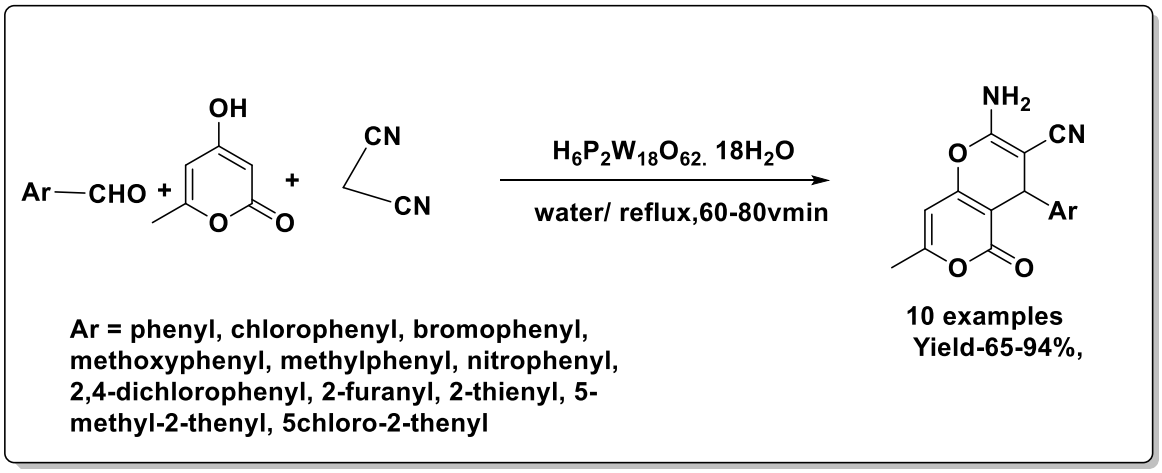
III.4 Previous methods for synthesis of chromene and coumarine derivatives

In 2009, Shaabani *et al*. reported a room-temperature based synthesis of benzo[g]chromene derivatives via one-pot multicomponent reaction of aldehyde, malononitrile with 2-hydroxynaphthalene-1,4-dione or 2,5- dihydroxycyclohexa-2,5-diene-1,4-dione in presence of base catalyst Et_3N in CH_3CN solvent (**Scheme III.1**). [64].



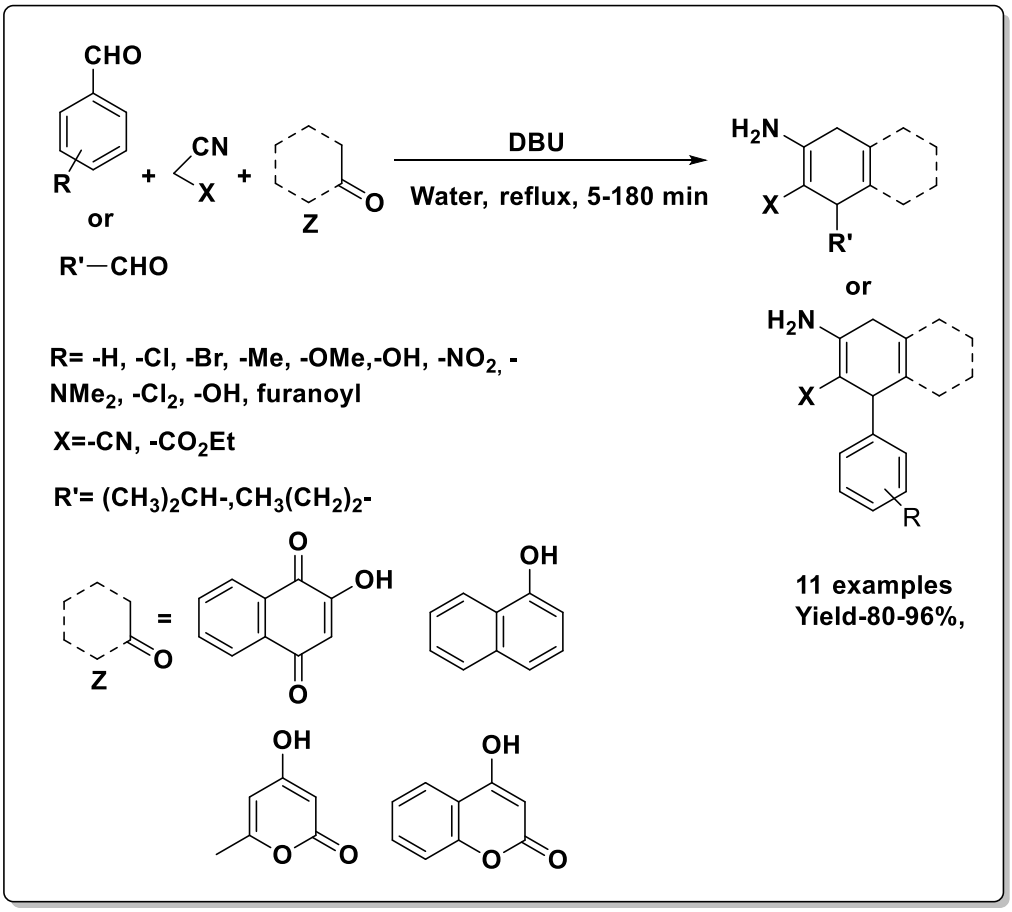
Scheme III.1 One pot synthesis of benzo[g]chromene derivatives by Shaabani *et al.*

In 2013, Rajguru *et al*. had reported a synthetic procedure for the synthesis of 4*H*-chromenes using aromatic aldehyde, malononitrile and C-H activated pyran-2-one to synthesise 2-amino-4*H*-chromene derivatives (**Scheme III. 2**). [65].



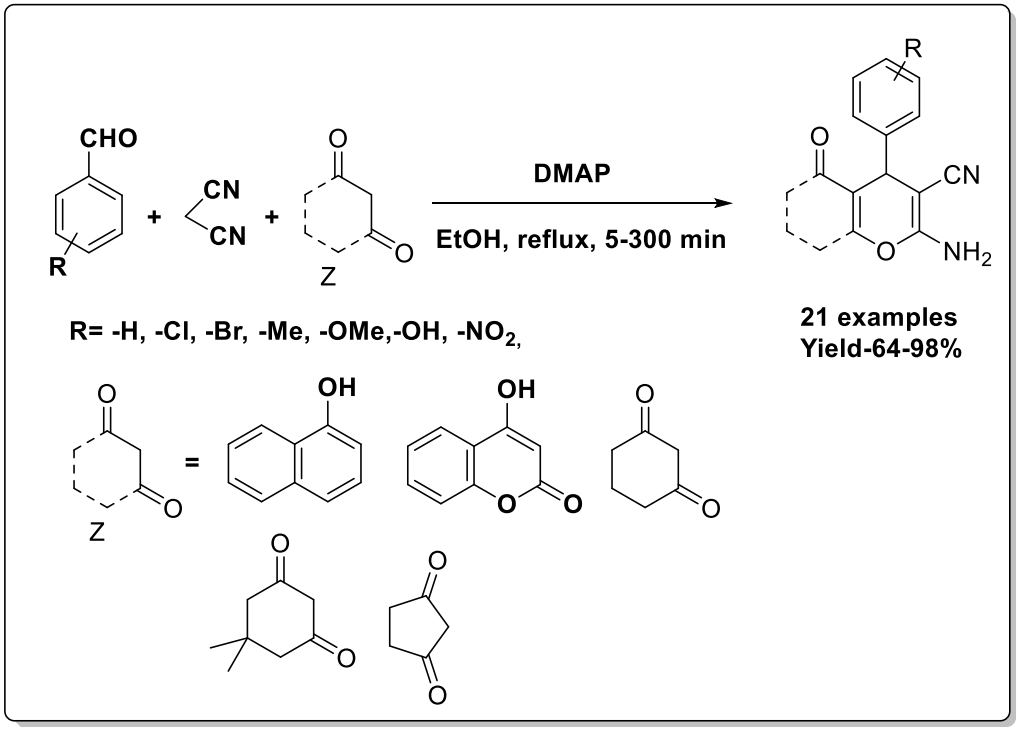
Scheme III.2 One pot synthesis of chromene heterocycles derivatives by Rajguru *et al*.

In 2010, Khurana *et al*. reported a synthetic procedure for pyran annulated heterocycles in one pot using DBU catalyst at reflux condition using 4-hydroxycoumarin, 4-hydroxy-6-methylpyrone, 1-naphthol and 2-hydroxynaphthalene-1,4-dione, with good yields (**Scheme III.3**).[66]



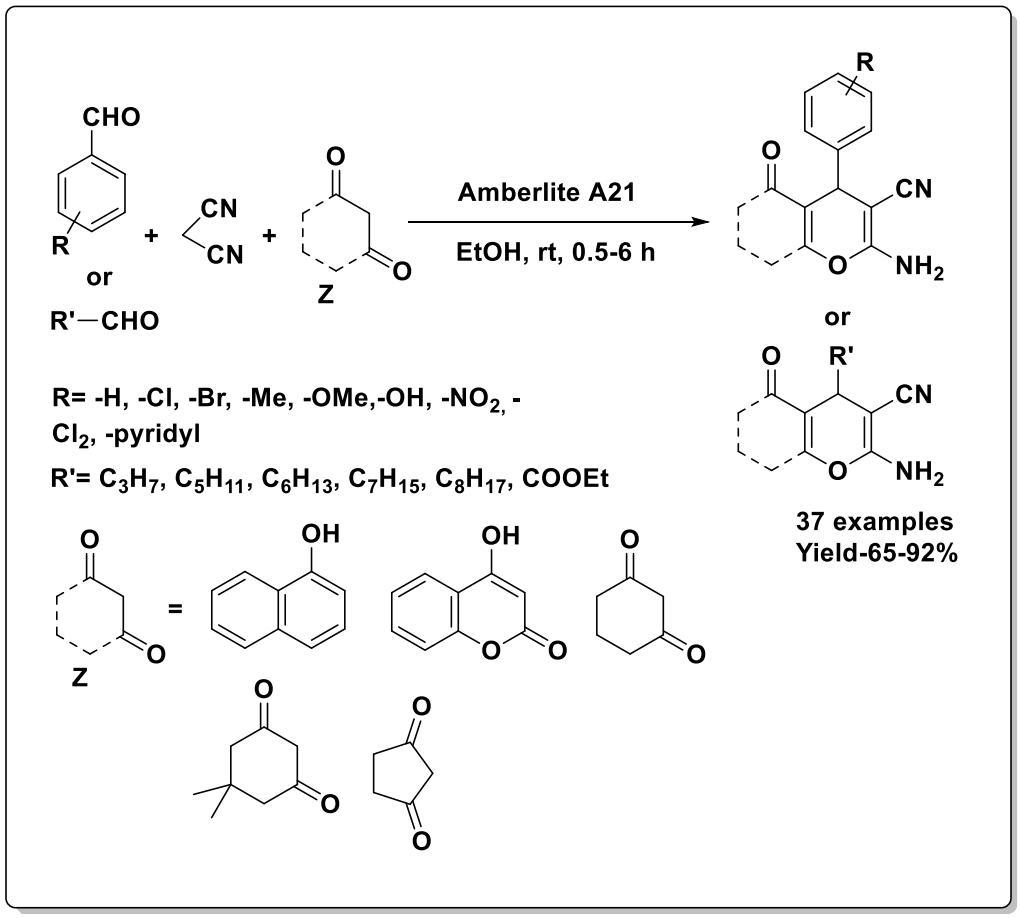
Scheme III.3 One pot synthesis of chromene heterocycles derivatives by Khurana *et al.*

In 2011, Khan *et al*. repoted a three-component condensation reactions between aromatic aldehydes, ethyl cyanoacetate or malononitrile and diverse C–H activated acidic compounds (Z) in the presence of catalytic amount of DMAP in ethanol under reflux conditions for the synthesis of chromenes (**Scheme III.4**). [67].



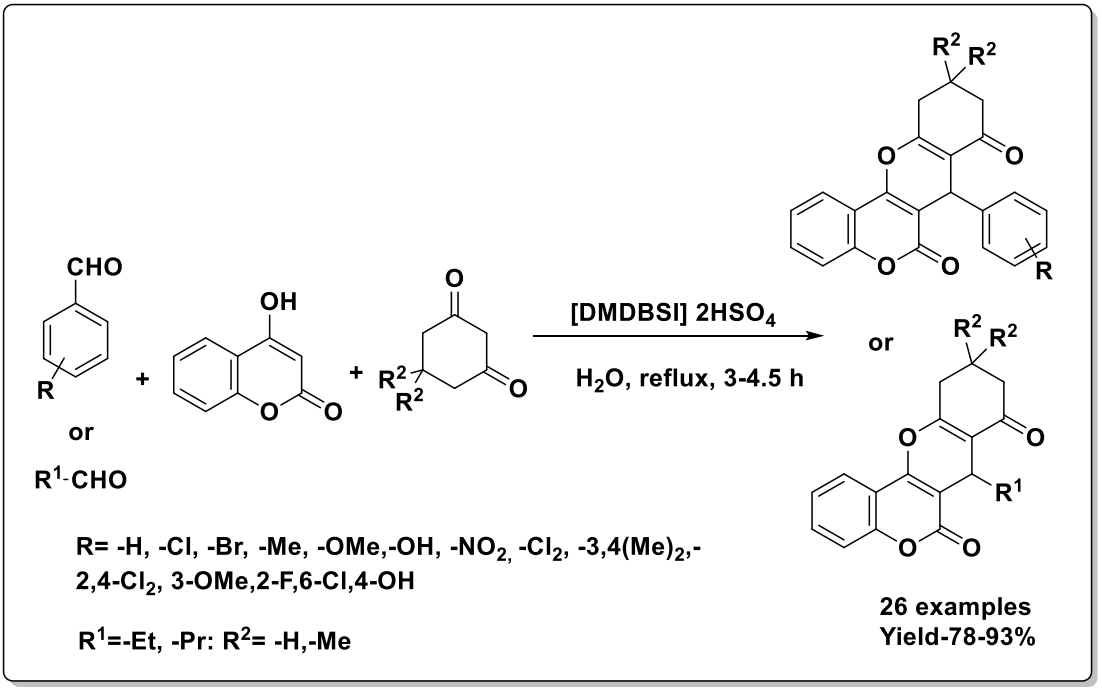
Scheme III.4 One pot synthesis of chromene heterocycles derivatives by Khan et al.

In 2013, Bihani *et al.* synthesized chromenes and annulated heterocycles using aldehyde, malononitrile and diverse C–H activated acidic compounds (Z) in presence of amberlyst-A21 in ethanolic medium at room temperature (**Scheme III.5**). [68]



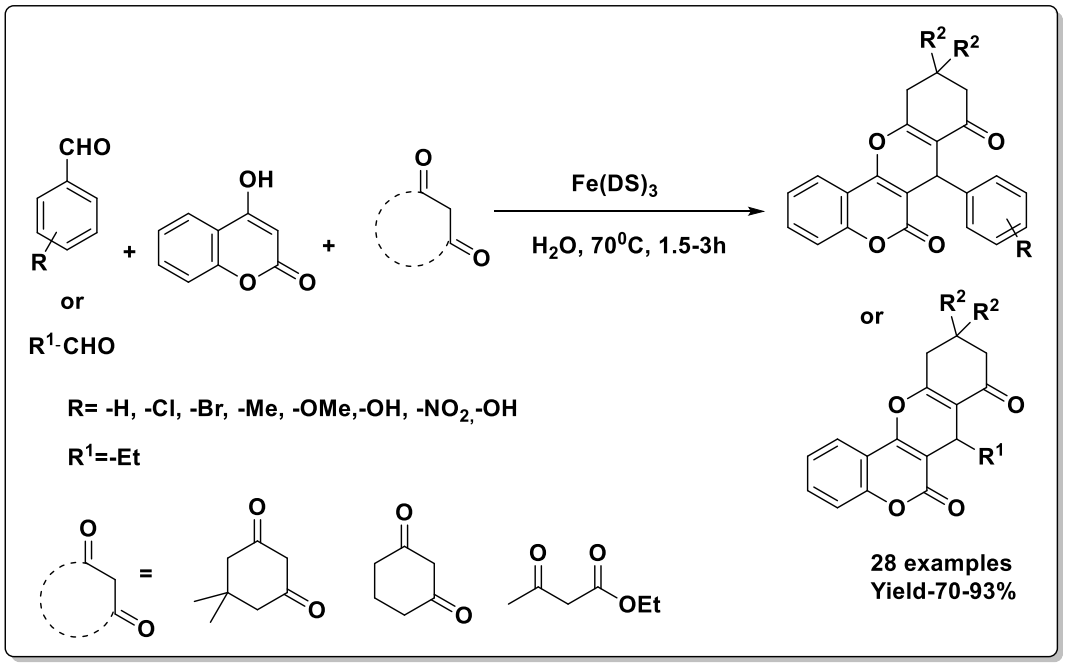
Scheme III.5 One pot synthesis of chromene heterocycles derivatives by Bihani *et al*.

In 2011, Chen *et al*. reported a three-component reaction between 4-hydroxycoumarin, aldehydes, and cyclic 1,3-dicarbonyl compounds in water at reflux condition to produce a series of 10,11-dihydrochromeno[4,3-*b*]chromene-6,8-(7*H*,9*H*)-dione derivatives in good yields task specific ionic liquid, short reaction time, easy product separation and purification (**Scheme III.6**). [69].



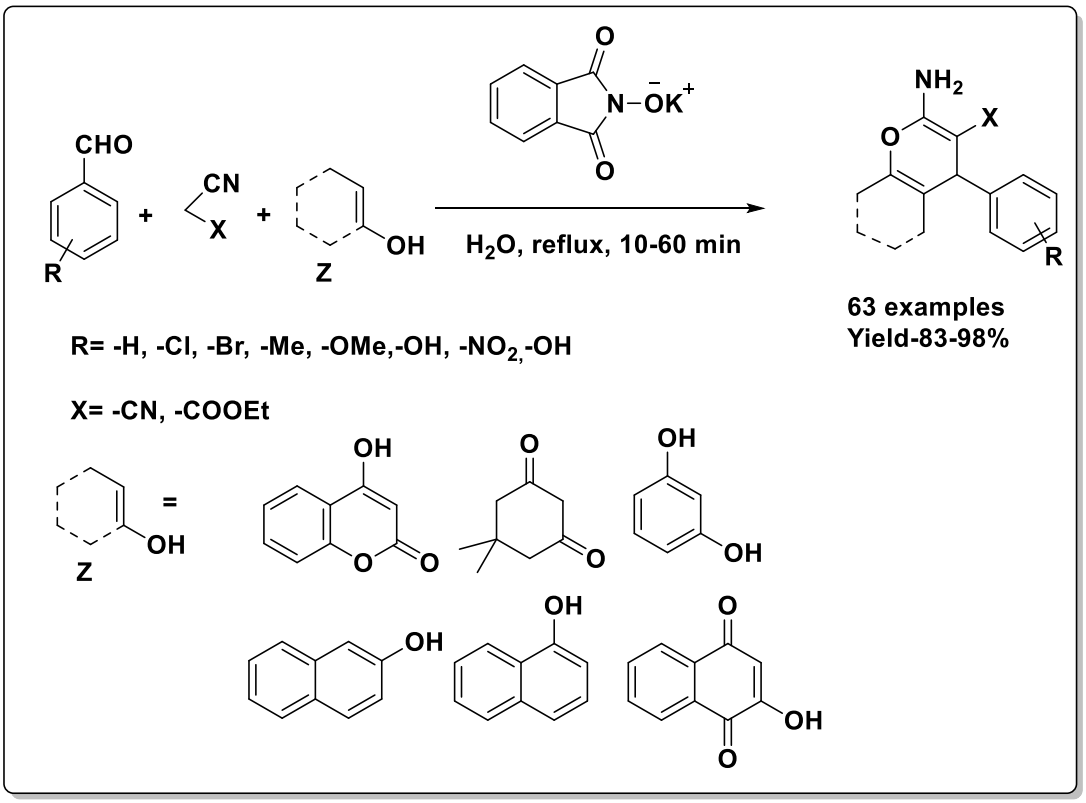
Scheme III. 6 One pot synthesis of chromene heterocycles derivatives by Chen *et al.*

In 2013, Pradhan *et al*. described the synthesis of a series of chromeno[4,3-*b*]chromene derivatives via three-component reaction of aldehydes, 1,3-diketones, and 4-hydroxycoumarin in aqueous medium under reflux condition by using a Lewis acid-surfactant-combined catalyst $[Fe(DS)_3]$ (**Scheme III.7**) [70].



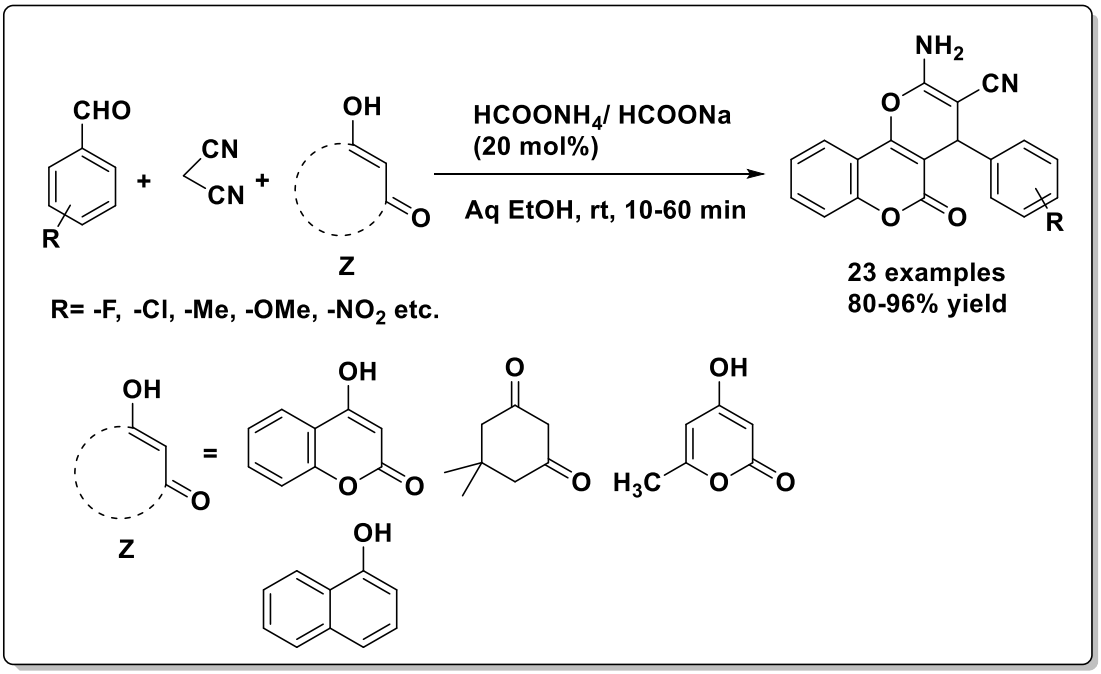
Scheme III.7 One pot synthesis of chromene heterocycles derivatives by Pradhan *et al*.

In 2013, Deacamin *et al*. synthesized chromene derivatives via three component coupling of aldehydes, active methylene compounds, and C-H activated compounds (Z) like dimedone, 4-hydroxycoumarin, 2-hydroxynaphthalene-1,4-dione, activated phenols in the presence of potassium phthalimide-N-oxyl as organocatalyst in aqueous medium under reflux condition (**Scheme III.8**). [71].



Scheme III.8 One pot synthesis of chromene heterocycles derivatives by Deacamin *et al*.

In 2014, Bramhachari *et al*. reported MCR synthesis of substituted chromene heterocycles via three-component condensation reaction of aldehydes, malononitrile, and C-H activated acidic compounds (Z) in aqueous ethanol using 20 mol% ammonium or sodium formate and 20 mol% urea as organo catalyst (**Scheme III.9**). [72]



Scheme III.9 One pot synthesis of chromene heterocycles derivatives by Bramhachari *et al*.

III.5. Pyrido-pyrimidine

The pyridopyrimidines are a of class of heterocyclic organic compounds having 6–6 bicyclic systems containing two or three nitrogen atoms in both six-membered rings. The compounds are also named as diaza- or triaza-naphthalenes which shows the structure of all possible types of pyridopyrimidines such as 4*H*-Pyrido[1,2-*a*]pyrimidin, 1*H*-Pyrido[1,2c]pyrimidin, Pyrido[2,3-*d]*pyrimidin, Pyrido[3,2-*d*]pyrimidin, Pyrido[3,4-*d*]pyrimidin, Pyrido[4,3-*d*]pyrimidin. (**Figure. III. 5**). Inspite of being natual abundance of pyridopyriminines and their

derivatives there are several reported methods of the synthesis of such kind of bicyclic-aza compounds.[73] Among these pyridopyrimidines, 4*H*-Pyrido[1,2-*a*]pyrimidin, 1*H*-Pyrido[1,2-*c*]pyrimidin show tatumeric effect in solid state and solution phase depend upon the pH condition of the supporting medium and in acidic medium their structure acquires cationic characteristics and in basic medium the shows anionic character.[74]

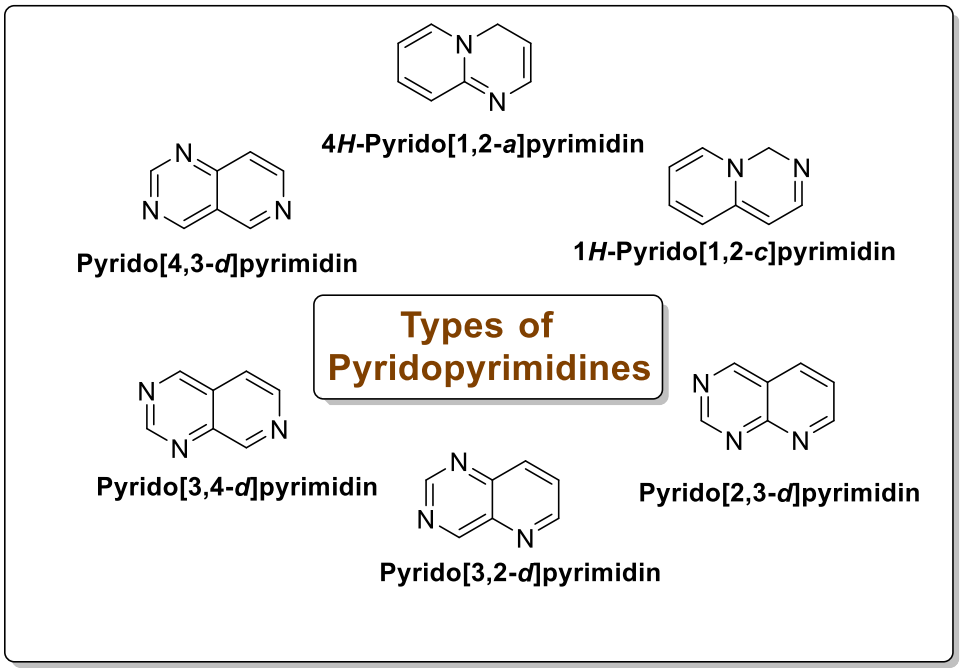


Figure. III. 5 Various types of pyrido-pyrimidine skeleton

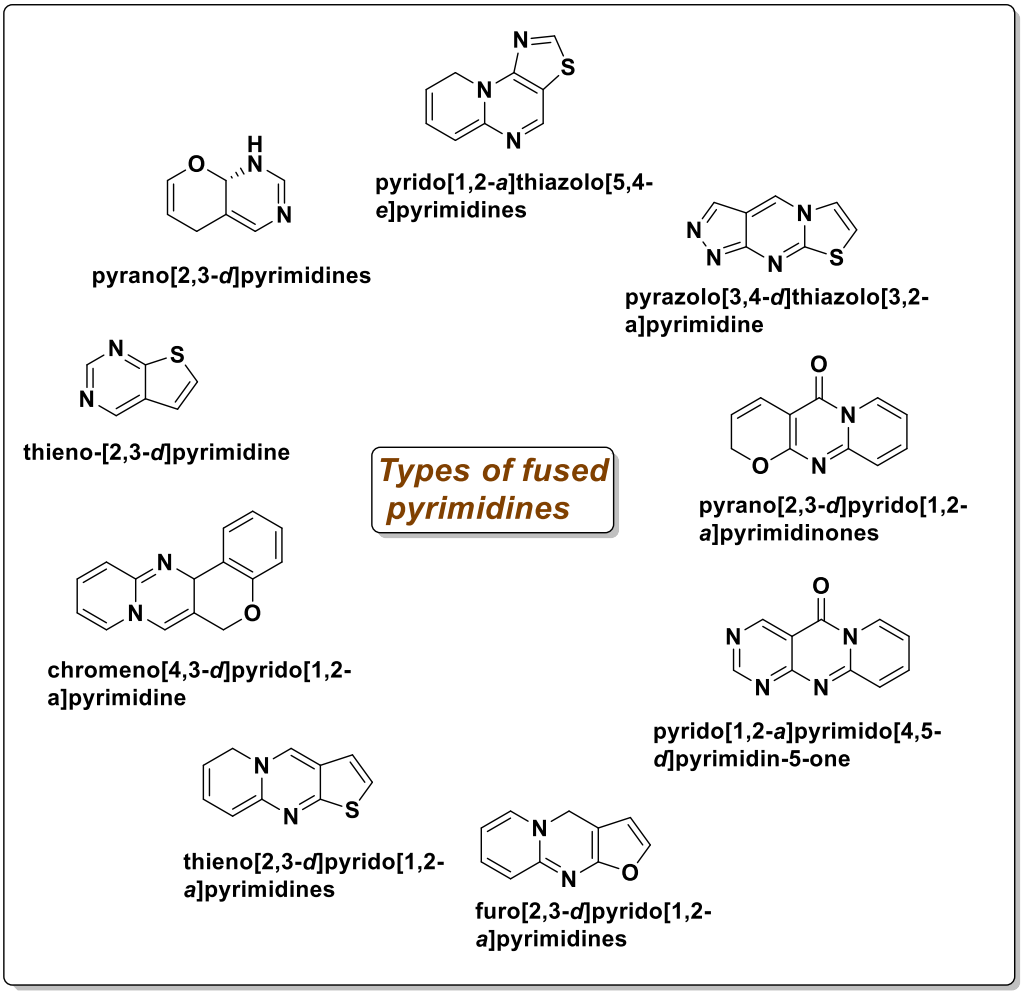


Figure. III. 6 Various types of fused pyrimidine skeleton

The compounds are generally basic in nature due to the presence of available donatable electron pairs over 'N'-atoms to protons and have broad range of biological importance in medicinal and biochemistry fields. There are also examples of other fused ring pyrimidines such as chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidine, thieno-[2,3-*d*]pyrimidine, pyrano[2,3-*d*]pyrimidines, pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidine,

furo[2,3-*d*]pyrido[1,2-*a*]pyrimidines, pyrido[1,2-*a*]thiazolo[5,4-*e*]pyrimi-dines, pyrido[1,2-*a*]pyrimido[4,5-*d*]pyrimidin-5-one, pyrano[2,3-*d*]pyrido[1,2-*a*]pyrimidinones, pyrimido-thienopyrido[1,2-*a*]pyrimidinone, thieno[2,3-*d*]pyrido[1,2-*a*]pyrimidines, pyrazolo-pyrido[1,2-*a*]pyrimidines and isoxazolo-pyrido[1,2-*a*]pyrimidines (**Figure III.6**) have already been reported. Fused pyrimidines can act as interesting scaffolds and key structures in chemistry and medicine as they show diverse biological and medical properties.

III.6. Biological importance of pyrido-pyrimidines

Among several types pyridopyrimidines, pyrido[2,3-*d*]pyrimidines are the most abundance isomer in the literature and have wide range of biological activities. Pyrido[2,3-*d*]pyrimidines have anti-inflammatory, antihypertensive, anticancer, antimicrobial, analgesic, antiviral activity and with addition they also act as tyrosine kinase inhibitor , CDK4-inhibitor, and anti-diuretic drugs.[75-79] However, the pyrido[3,2-*d*]pyrimidine, pyrido[3,4-*d*]pyrimidines, pyrido[4,3-*d*]pyrimidines, Pyrido[1,2-*a*]pyrimidines, and pyrido[1,2-*c*]pyrimidines have also biological activities like pyrido[2,3-*d*]pyrimidines such as anti-inflammatory, antimicrobial activities anticancer, antimalarial, anti-psychotropic, antibacterial, antituberculars tyrosinekinases inhibitor,

antiallergic, anti-ulcer, CNS stimulant, urease inhibitor activities activities (**Figure III. 7**).[80-88]

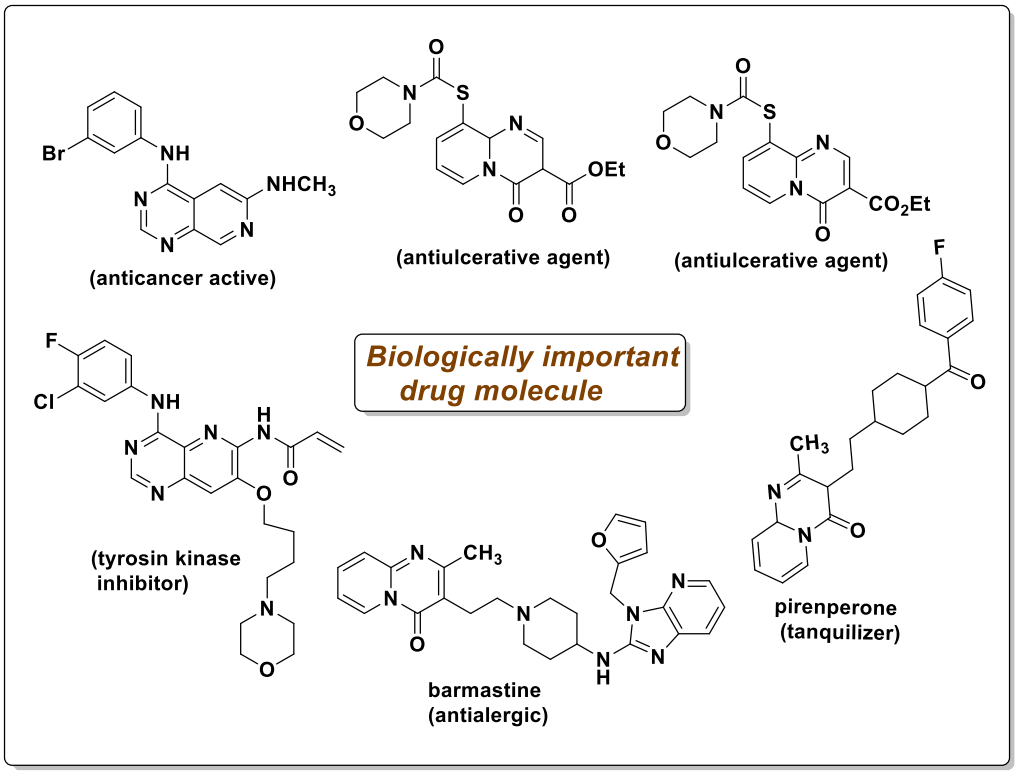
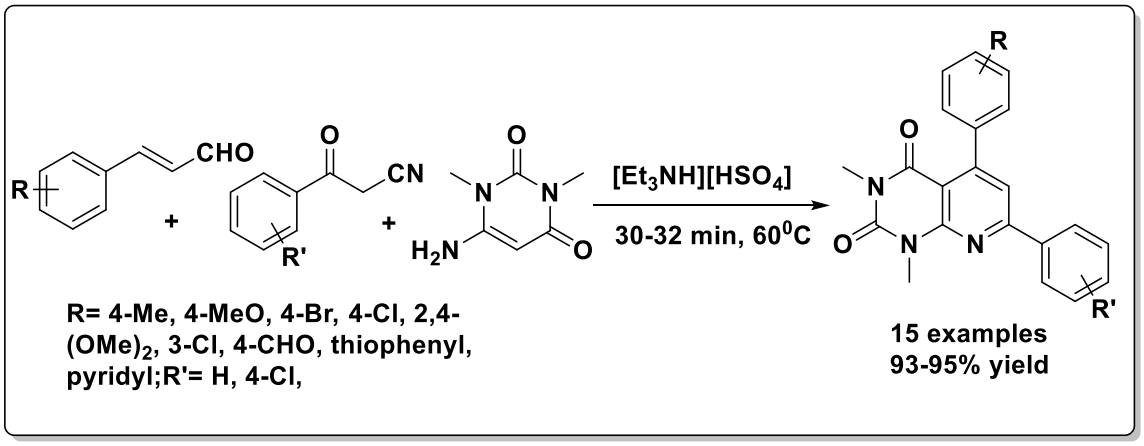


Figure III. 7 Some important pharmaceutically active drug molecule

By doing studies on works in various journals and literature reviews related to pyrido-pyrimidines and their various derivatives derivatives and following their biological importances and keeping innovative ideas in knowledge in this following part of the chapter III, it has been focused on the synthesis of pyrido-pyrimidine derivatives in a new and convenient manner using cheap laboratory chemicals.

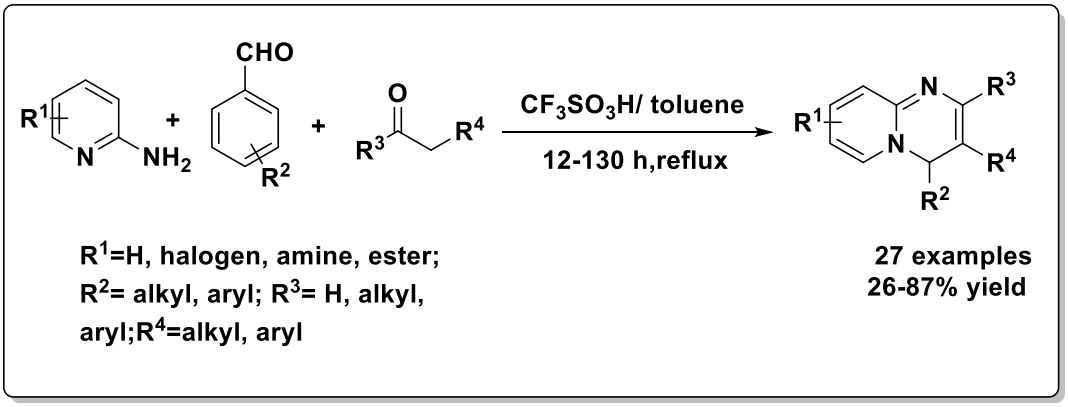
III.7 Previous works on synthesis of pyrido-pyrimidine derivatives

In 2021, Jadhav *et al*. synthesised pyrazolo[3,4-*b*]pyridine derivatives in excellent yields (92−94%) via one-pot multicomponent reaction method using aminouracils and aminopyrazoles, aldehyde, and acyl acetonitrile in presence of $[Et_3NH][HSO_4]$ under solvent-free conditions (**Scheme III.10**). [89]



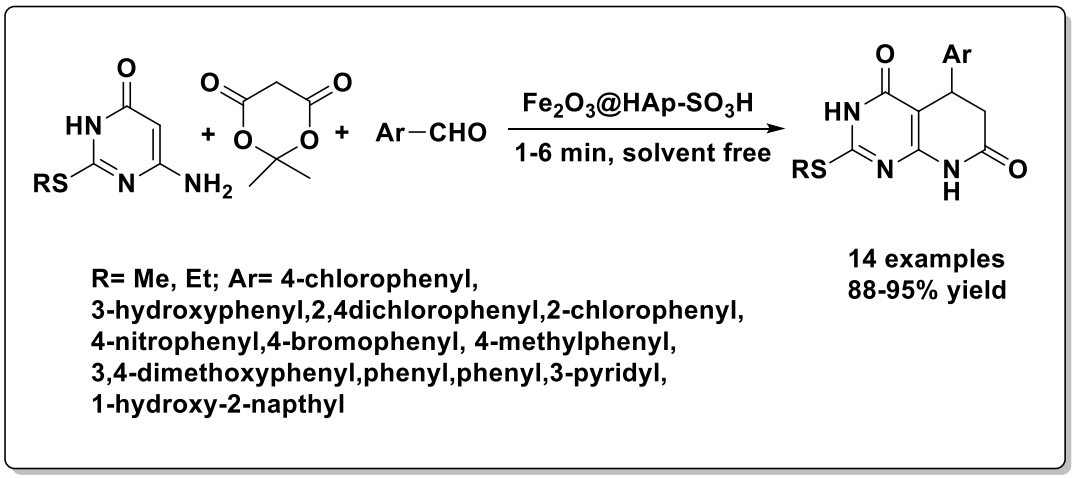
Scheme III.10 One pot synthesis of pyrido-pyrimidine derivatives by Jadav *et al.*

In 2013, Yang *et al*. reported a one-pot three-component reaction method for the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidines by condensation of 2-aminopyridines, aldehydes, and ketones/ aldehydes in presence of CF_3COOH acid catalyst in toluene solvent (**Scheme III.11**). [90]



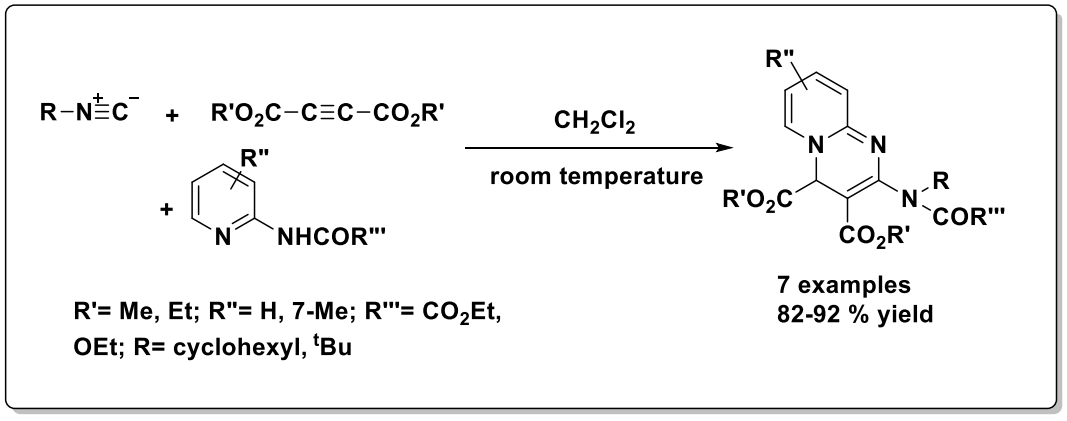
Scheme III.11 One pot synthesis of pyrido-pyrimidine derivatives by Yang *et al*.

In 2014, Mohssenimehra *et al.* designed a synthesis for Novel pyrido[2,3-*d*]pyrimidine derivatives were synthesized via one-pot threevcomponent methodology taking 6-amino-2-(methylthio or ethylthio)pyrimidin-4(3*H*)-one, 2,2-dimethyl-1,3-dioxane-4,6-dione and aryl aldehydes using HAp-encapsulated-γ-Fe_2O_3 catalyst at 60^0C and under solvent-free conditions (**Scheme III.12**). [91]



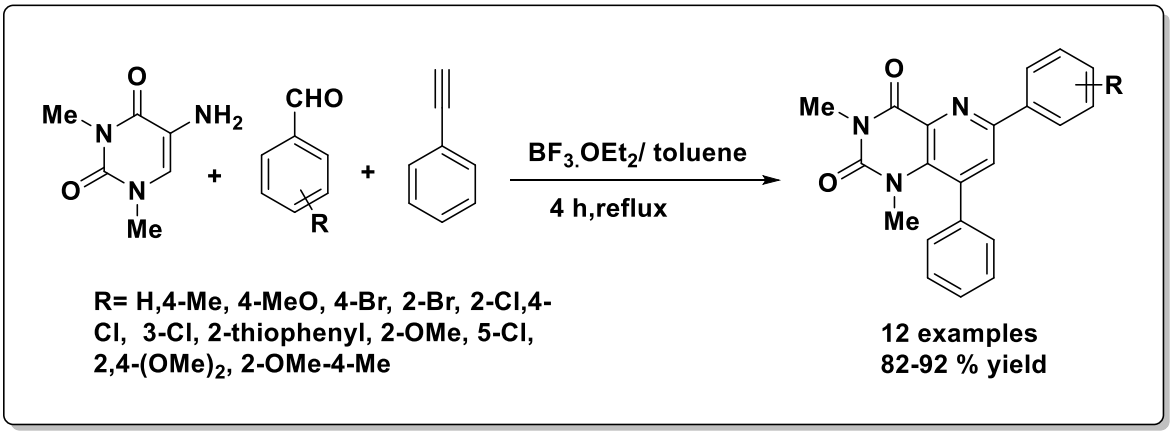
Scheme III.12 One pot synthesis of pyrido-pyrimidine derivatives by Mohssenimehra *et al.*

In 2007, Adib *et al*. had reported a new, one-pot and three-component synthesis of 4*H*-pyrido[1,2-*a]*pyrimidines by using isocyanides, alkynes and N-substituted-2-aminopyridines at room temperature condition (**Scheme III.13**). [92]



Scheme III.13 One pot synthesis of pyrido-pyrimidine derivatives by Adib *et al.*

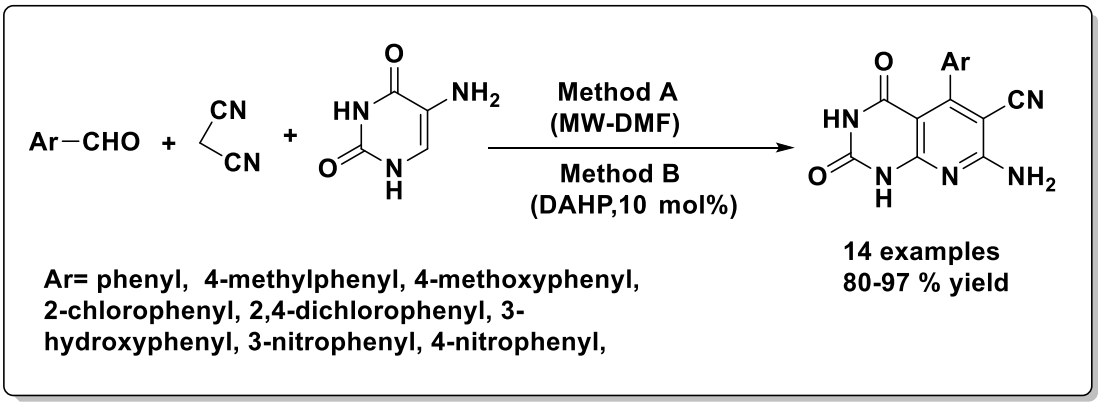
In 2011, Majumdar *et al*. had reported a mild and efficient synthetic method for the synthesis of pyrido[3,2-*d*]pyrimidine derivatives via three-component reaction between amines, aldehydes, and terminal unactivated alkynes in presence of using $BF_3.OEt_2$ as Lewis acid catalyst in one pot. The features of this procedure are mild reaction conditions, good to high yields, and shorter reaction time with operational simplicity (**Scheme III.14**). [93]



Scheme III.14 One pot synthesis of pyrido-pyrimidine derivatives by Majumdar *et al.*

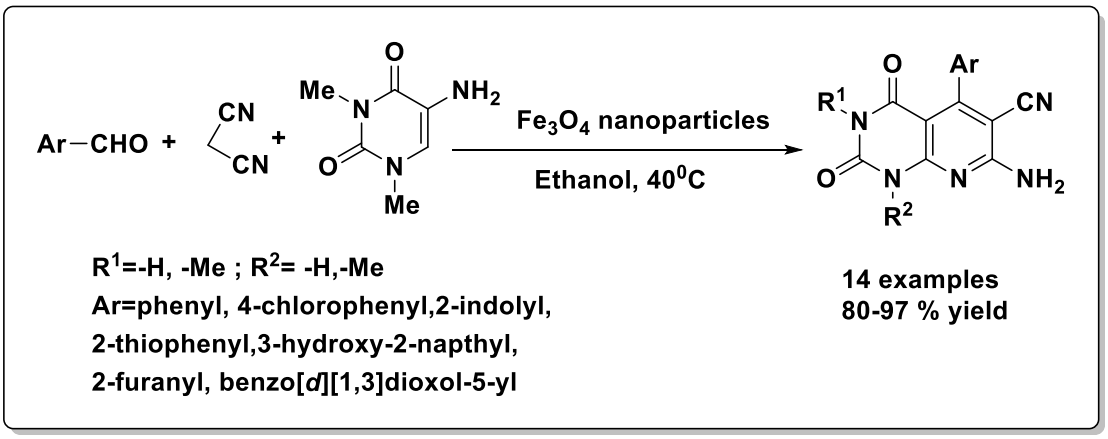
In 2012, Abdolmohammadi *et al*. sythesised a series of pyrido[2,3-*d*]pyrimidines via one-pot three-component reaction between aminouracil, malononitrile and aromatic aldehydes. using catalytic

amount of diammonium hydrogen phosphate (DAHP) in aqueous medium. The reaction proceeds via domino Knoevenagel-Michael-cyclization reactions to give the Pyrido[2,3-*d*]pyrimidine derivatives. (**Scheme III.15**). [94]



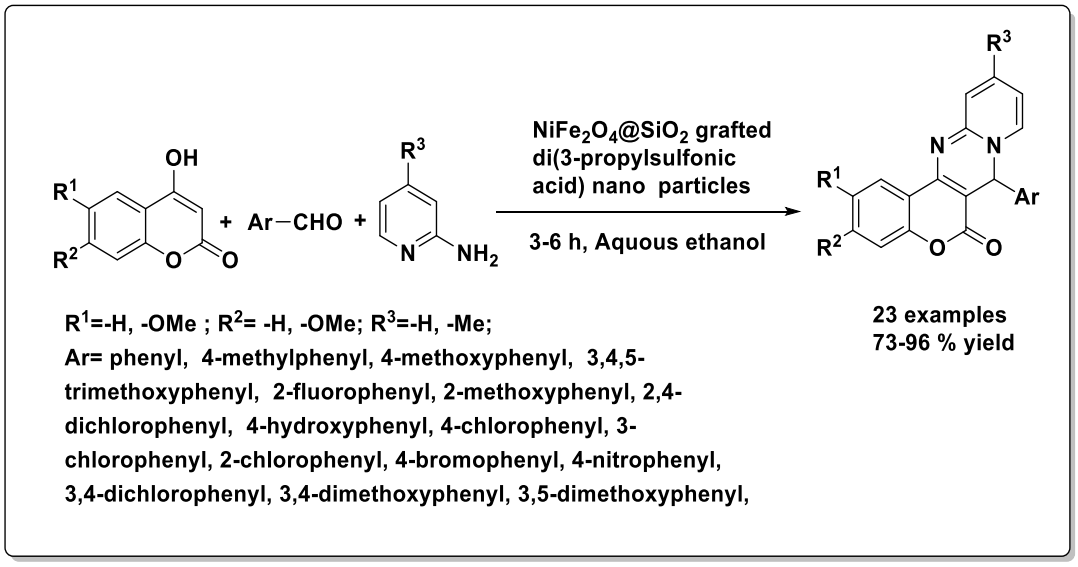
Scheme III.15 One pot synthesis of pyrido-pyrimidine derivatives by Abdolmohammadi *et al*.

In 2012, Kidwai *et al*. reported a synthetic procedure for the synthesis of pyrido[2,3-*d*]pyrimidines through environmentally benign process by the reaction of aldehyde, malononitrile, 5-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione and utilizing Fe_3O_4 magnetic nanoparticles at 40^0C (**Scheme III.16**). [95]



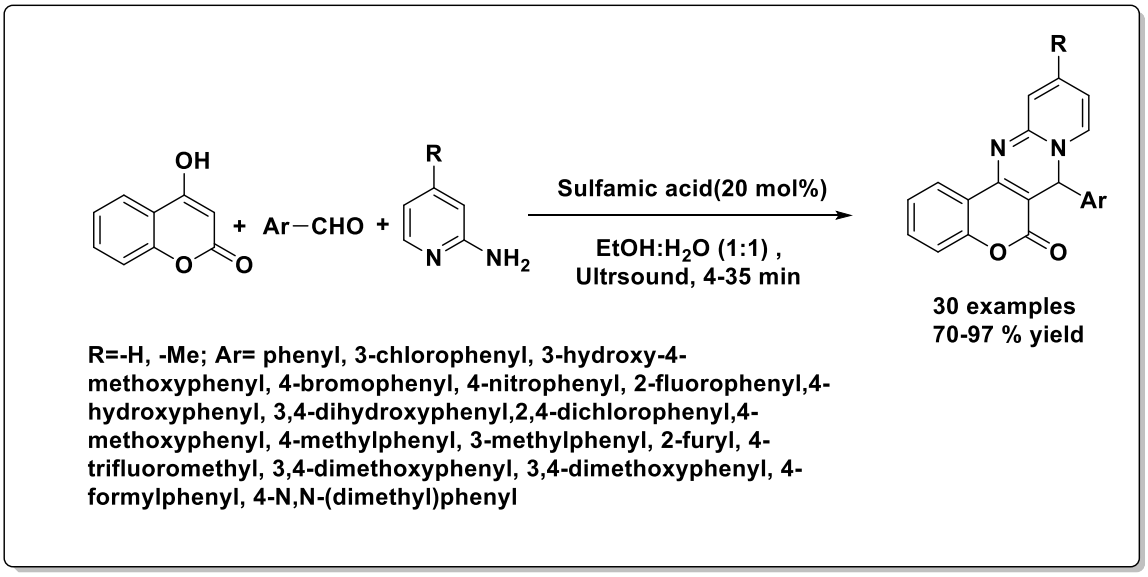
Scheme III.16 One pot synthesis of pyrido-pyrimidine derivatives by Kidwai *et al*.

Recently in 2021 Khalaj *et al*. synthesized a variety of chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidine derivatives via the three-component condensation reaction between 4-hydroxycoumarin, aldehydes, and 2-aminopyridines in presence of $NiFe_2O_4@SiO_2$ grafted di(3-propylsulfonic acid) nanoparticles (**Scheme III.17**).[96]



Scheme III.17 One pot synthesis of pyrido-pyrimidine derivatives by Khalaj *et al*.

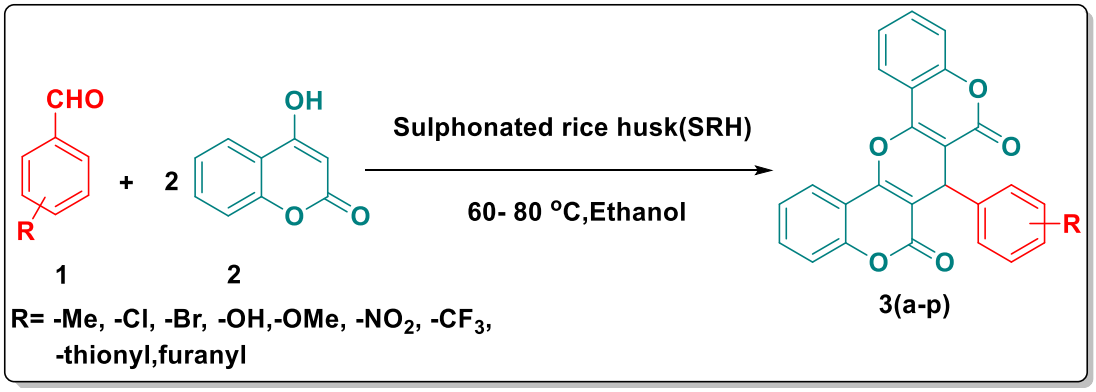
In 2018, Brahmachari *et al*. applied an ultrasound-assisted methods for one-pot synthesis of a new series of pharmaceutically relevant and diversely functionalized 7-aryl/heteroarylchromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6(7*H*)-ones. A one pot three-component tandem reaction between 4-hydroxycoumarin, substituted aromatic aldehydes, and 2-aminopyridines were subjected for doing reaction in the presence of sulfamic acid as a catalyst (**Scheme III.18**). [97]



Scheme III.18 One pot synthesis of pyrido-pyrimidine derivatives by Bramhachari et al.

III.8 Present work

The present work leads to the synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-c:5,6-c']dichromene-6,8-dione derivatives (**Scheme III.19)** by using greener heterogeneous catalyst sulphonated rice husk (SRH) .



Scheme III.19 Synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-c:5,6-c']dichromene-6,8-dione derivatives [a]

III.8.A Results and discussion

III.8.A.1 Catalyst Characterization

The prepared catalyst was characterized by FTIR spectroscopy first and the comparison with FTIR spectrum of rice husk clearly indicated the transformation of rice husk into sulphonated rice husk (SRH) (Figure III. 8b). The new broad band at 3420 cm^{-1} along with the band at 1100

cm^{-1} both denoting the incorporation of $–SO_3H$ groups into rice husk after sulphonation. The band with a peak $1100cm^{-1}$ represents the symmetric and asymmetric streatching of S=O bonds of $–SO_3H$ groups and the broadened band at $3420cm^{-1}$ represent the -OH groups vibration after the incorporation of $–SO_3H$ groups [98]. Scanning electron microscopy (SEM) analysis (**Figure III.9**) and powder X-ray diffraction (p-XRD) (**Figure III.8a**) have also made a clear path for confirmation of the prepared catalyst from the rice husk. The powder XRD analysis shows characteristics peaks at $2\theta = 20.83^{o}$ which is a broad peak indicating some carbon composed aromatic sheets oriented in a random manner.[99] The rough surfaces in SEM images of SRH has been considered to be resulted from sulphonation of rice husk material and which is a indication of a promising change in surface morphology after sulphonation. The Comparison of EDX images of SRH & RH also reflecting a visible changes in the elemental composition and a considerable changes in atomic weight percentage of certain elements such as C, Si, O, & S was noticed from the EDX data analysis of RH & SRH. Detailed information of EDX data are included in experimental section (**III.7.A.12.i**) of the Chapter III.

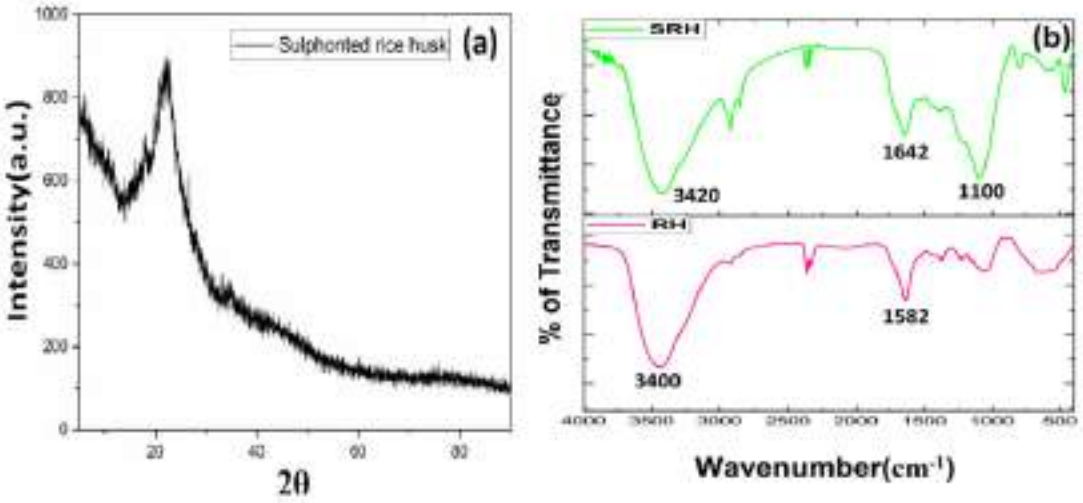


Figure III. 8 (a) Powder XRD image of SRH. (b) FTIR images of RH & SRH

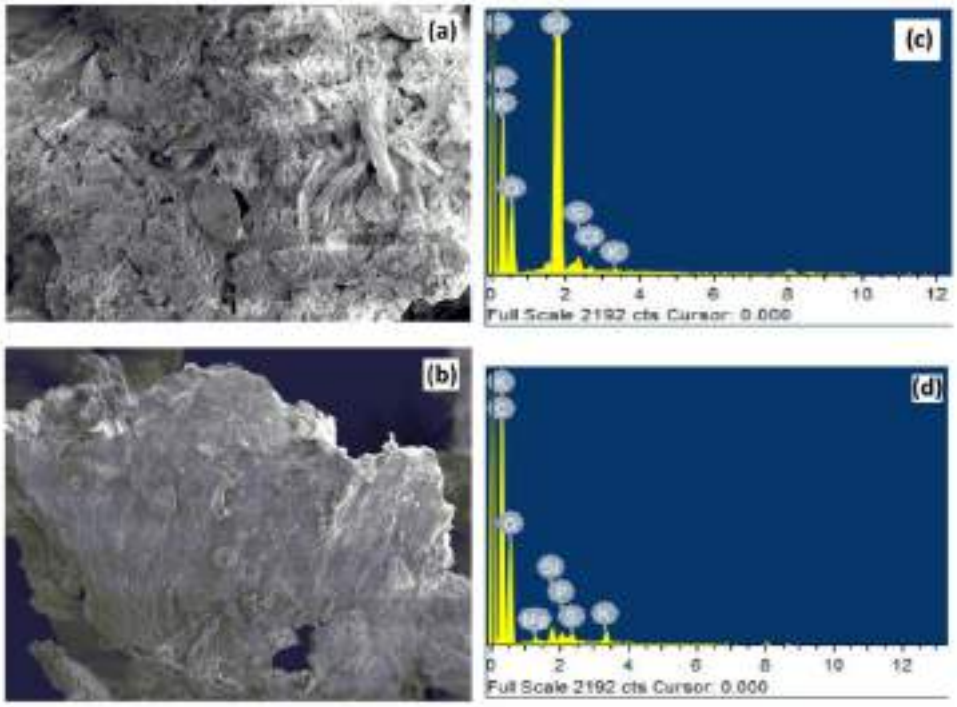


Figure III. 9 (a) SEM image of SRH. (b) SEM image of RH. (c) EDX image of SRH (d) EDX image of RH.

The above promising data analysis and literature survey has given us a sound confirmation that the heterogeneous catalyst (SRH) has been formed without any doubt and not demanding any further quantitative analytical support and is now finally ready for suitable organic reactions to be used up as heterogeneous catalyst under greener reaction condition.

III.8.A.2 Optimisation of reaction condition 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-c:5,6-c']dichromene-6,8-dione derivatives

Initially, the reaction was carried out by taking anisaldehyde (1 mmol), 4-hydroxycumarine (2 mmol) at a time in a 25 mL round bottom flusk and in presence of catalyst the expected product was obtained with an excellent yield. Satisfactory yield was obtained in presence of 90 mg of SRH catalyst in ethanol solvent at 80^0C temperature (**Table III.1**, entry 2). However, in absence of catalyst the formation of the desired product was not obtained (**Table III.1**, entry 11,12). With decreasing the amount of catalyst, the yield of the product decreased slightly along with reaction temperature and time of the reaction. Optimized condition was determined by taking anisaldehyde (1mmol) and 4-hydroxycoumarine(2 mmol) in a 25 mL round bottom

flask fitted with condenser and it was observed that at 70^0C temperature with minimum 70 mg of catalyst SRH in ethanol giving best result with yield up to 96% (**Table III.1**, entry 6). From this optimization table (**Table III.1**), it is clear that SRH catalyst is suitable for one pot synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-c:5,6-c']dichromene-6,8-dione with excellent yield in short reaction time. The amount of the catalyst and time of the reaction was further checked again to report the accurate optimized condition of the reaction. Role of methanol (**Table III.1**,entry 7,12) and water (**Table III. 1**,entry 13,14,15,16) have also been observed and it was observed that the product yield in methanol is quite unaltered to that of ethanol and in distilled water the reaction did not happened due to damage of the catalyst in water medium. Observation with addition of water into ethanol solvent revealed that the role of water is unfriendly until the ratio of ethanol/water exceeds 3:1(v/v) (**Table III.1**, entry 15) with decreased amount of yield. The catalyst can sustain its activity in alcohol/water mixed solvent with minimum quantity of water with a satisfactory product yield and for greener aspect of reaction, methanol is advised to be avoided for its toxicity and adversity in reaction medium. From the optimized reaction condition, it is clear that SRH

catalyst is undoubtedly a suitable one for the synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-c:5,6-c']dichromene-6,8-dione with excellent yield in short reaction time.

Table III.1. Optimisation of the reaction condition for the synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c*']dichromene-6,8-dione derivatives [a]

Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	90	Ethanol	90	310	98
2	90	Ethanol	80	280	98
3	85	Ethanol	80	260	98
4	85	Ethanol	80	240	96
5.	80	Ethanol	70	220	96
6.	**70**	**Ethanol**	**70**	**190**	**96**
7.	70	Methanol	70	190	96
8.	65	Ethanol	60	190	94
9.	60	Ethanol	60	180	94
10.	60	Ethanol	60	160	92
11.	None	Ethanol	70	190	-
12.	None	Methanol	70	190	-
13.	70	H_2O	70	190	-
14.	70	Ethanol/H_2O(6:1)	70	190	84

15.	70	Ethanol/H_2O(3:1)	70	190	78
16.	70	Ethanol/H_2O(1:1)	70	190	54

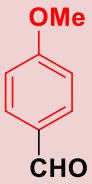
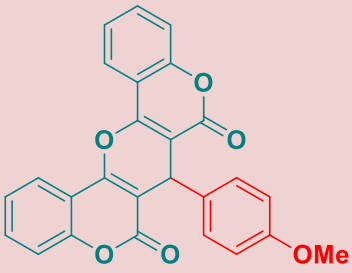
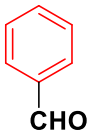
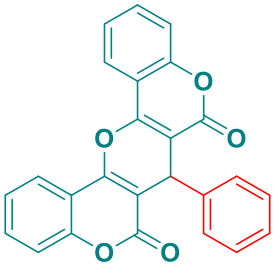
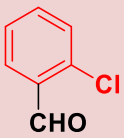
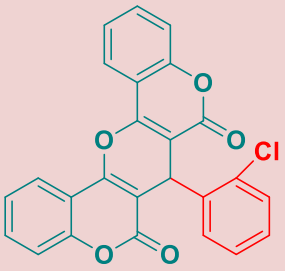
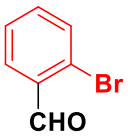
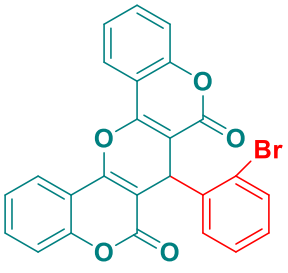
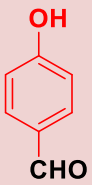
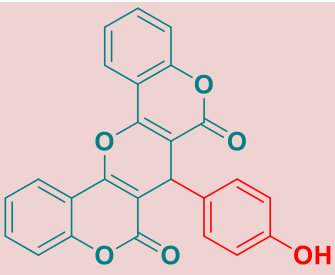
[a]Reaction of anisaldehyde (1mmol), 4-hydroxycumarine (2mmol) and SRH .

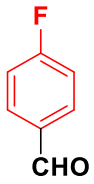
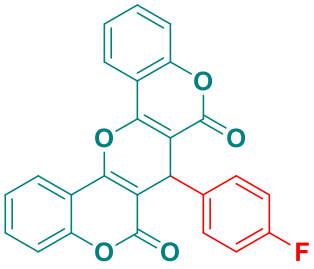
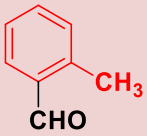
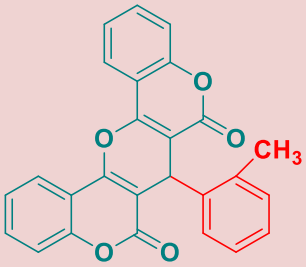
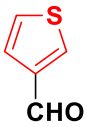
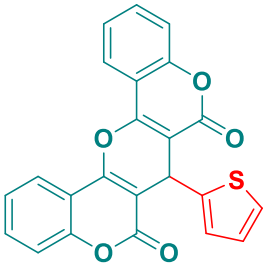
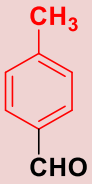
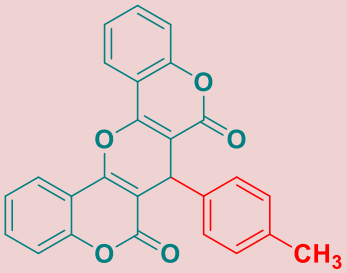
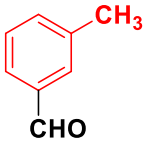
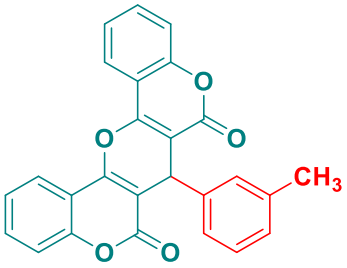
[b]Isolated yield through recrystalysation.

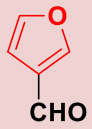
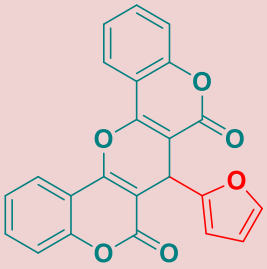
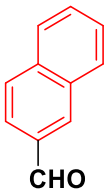
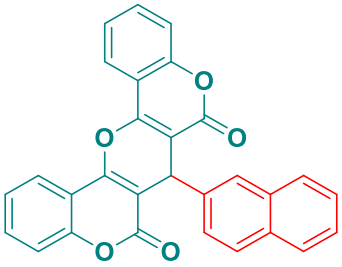
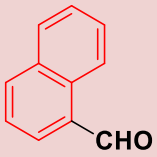
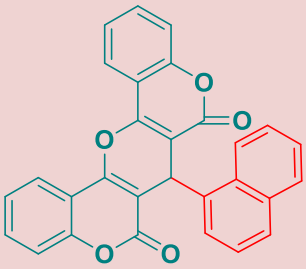
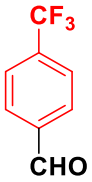
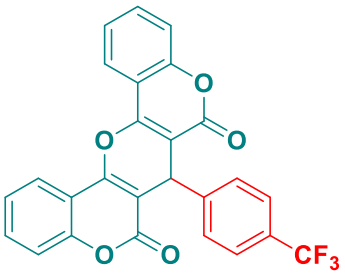
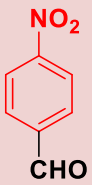
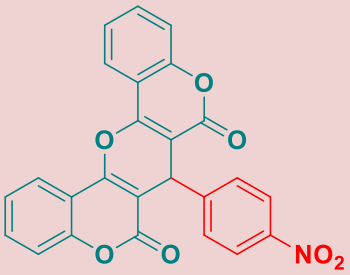
III.8.A.3 Synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-c:5,6-c']dichromene-6,8-dione derivatives

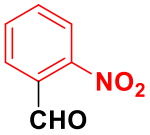
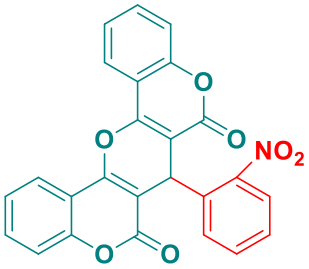
The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (**Scheme III.19**) with electron donating and electron withdrawing substituent at *ortho*, *meta* and *para* position. The targeted compounds (3a-3o) are successively synthesized using sulphonated rice husk (SRH) as efficient catalyst under greener reaction condition and within short reaction time. The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (**Scheme III.19**) with electron donating and electron withdrawing substituent at *ortho*, *meta* and *para* position. The targeted compounds (3a-3o) are successively synthesized using sulphonated rice husk (SRH) as efficient catalyst under greener reaction condition and within short reaction time.

Table III.2. Synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-c:5,6-c']dichromene-6,8-dione derivatives [a]

Entry	Reactant	Product	Time	Yield(%)[b]
1		 (3a)	200 min	98
2		 (3b)	200 min	94
3		 (3c)	200 min	97
4		 (3d)	200 min	96
5		 (3e)	200 min	98

6		 (3f)	200 min	96
7		 (3g)	200 min	90
8		 (3h)	200 min	87
9		 (3i)	200 min	98
10		 (3j)	200 min	97

11		 (3k)	200 min	87
12		 (3l)	200 min	98
13		 (3m)	200 min	91
14		 (3n)	200 min	96
15		 (3o)	200 min	95

16		 (3p)	200 min	92

[a]Reaction of aromatic aldehyde (1mmol), 4-hydroxycumarine (2mmol) and SRH .

[b] Isolated yield through recrystalysation.

III.8.A.4 Comparison of catalyst efficiency

Table III.3. Comparison of catalyt efficiency for the reaction under scheme III.19[a]

Entry	Catalyst	Solvent	Temperature (^{o} C)	Time(min)	Yield (%)[b]
1	PTSA(60mg)	Ethanol	70	190	83
2	PEG-200(3mL)	-	70	240	70
3	H_2SO_4(3mL)	-	70	220	80
4	Glycerol(5mL)	-	70	220	72
5	AcOH(0.1mL)	Ethanol	70	190	74
6	Fe_3O_4 (60 mg)	Ethanol	70	190	81
7	K_2CO_3 (60mg)	Ethanol	70	190	70
8	Et_3N(2mL)	-	70	190	95
9	$FeCl_3$(60 mg)	Ethanol	70	180	78
10	SRH (70mg)	**Ethanol**	**70**	**190**	**96**

[a]Reaction of anisaldehyde (1mmol), 4-hydroxycumarine (2mmol) and catalyst (x mg). [b] Isolated yield through recrystalysation.

Taking this as a model reaction (**Scheme III.19**), a few experiments were carried out to compare catalyst efficiency of (SRH) with other conventional homogeneous acid and base catalysts as well as metal catalysts also (**Table III.3** entry 1-10). It was observed that the results of most of the acid catalysts as well as base catalysts in ethanol showed good activity at 70 ^{o}C temperature (**Table III.3** entry 1,3,5,7,8) and the comparison of results to that of the performance of SRH revealed a satisfactory result over other homogeneous catalysts with respect to reaction time and yield of the product (**Table III.3**, entry 10). The progress of the reaction was monitored by thin layer chromatography (TLC) and the pure product was obtained by recrystallization in petroleum ether/ethyl acetate (v/v ratio80/20) mixture. The effectiveness of SRH over other acid catalyst was established as it requires short reaction time and is easily separable from the reaction mixture (**Table III.3**, entry 10)

III.8.A.5 Plausible mechanism

A plausible mechanism (**Figure III.10**) for the synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione derivatives is established by considering the porosity, active rough surface (**Figure III.10**) and the acidic behaviour of the surface of the catalyst. At the very first step of the reaction as usual protonation occurs at aldehyde oxygen of aromatic aldehyde and then a condensation reaction starts with 1 mol 4-hydroxycoumarine giving a aryledine-chromanedione intermediate and after that fast Michael addition reaction occurs between another remaining 1 mol of 4-hydroxycoumarine and aryledine-chromanedione intermediate to give bis-coumarol as another intermediate.[97] Finally, a intramolecular cyclization followed with expulsion of 1 mol of water results in the formation of the desired product 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c*']dichromene-6,8-dione.

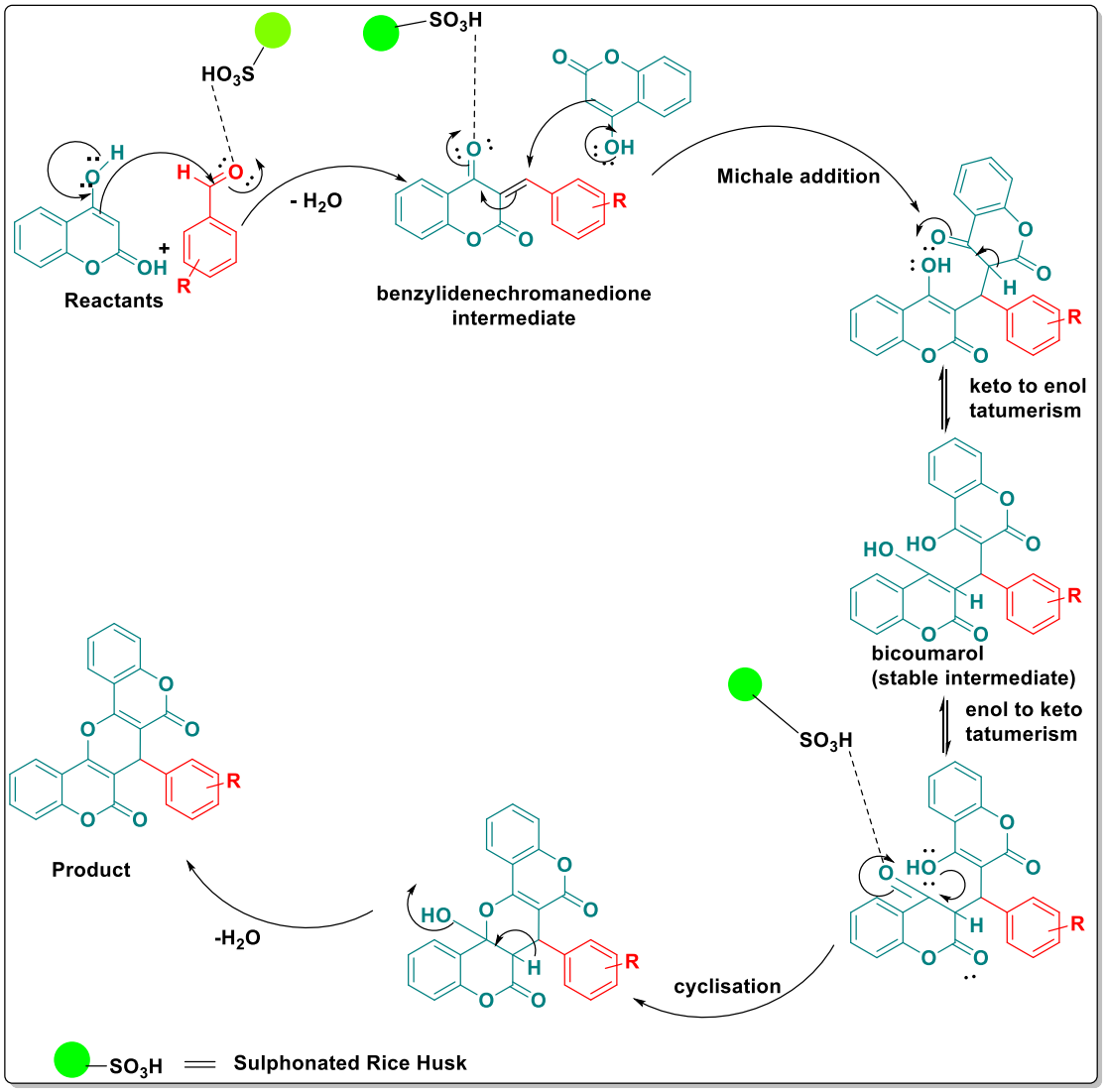
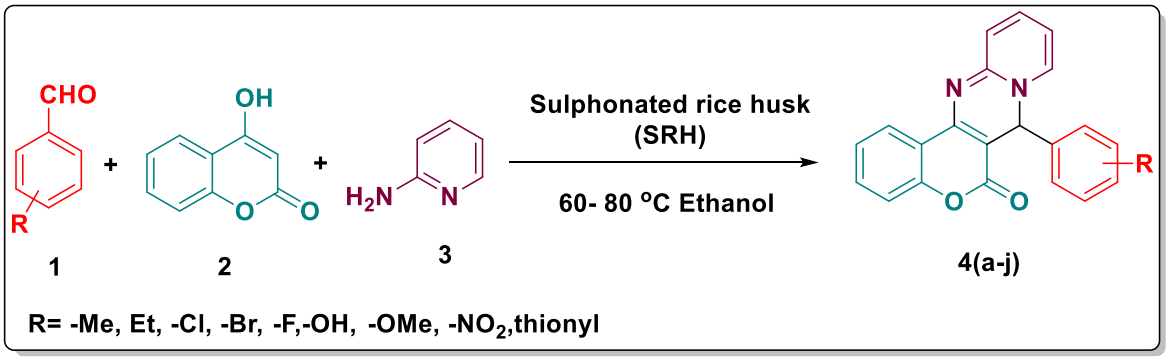


Figure III.10 The plausible mechanism for the synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-c:5,6-c']dichromene-6,8-dione

The next present work leads to the synthesis of 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives (**Scheme III.20**)) by using greener catalyst heterogeneous catalyst sulphonated rice husk (SRH) .



Scheme III.20 Synthesis of 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno [4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives using sulphonated rice husk[a]

III.8.A.6 Optimisation of reaction condition Synthesis of 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives

Initially, the reaction was carried out with Anisaldehyde (1 mmol), 4-hydroxycumarine (1mmol), 2-aminopyridine (1 mmol) in a 25 mL round bottom flask. Excellent yield was observed for a varity of aldehydes in presence of 80 mg of SRH catalyst in ethanol solvent at 70^{o}C temperature with reaction time of 190 minutes. From the optimization table (**Table III.4**) it is clear that with decrease in the amount of catalyst, the yield of the product decreases slightly and in absence of catalyst yield of the product was diminished (**Table III.4**, entry 10,11). The performance of the reaction is almost similar in methanol (**Table III.4**, entry 5 & 12) but for greener aspect ethanol is more safer solvent than methanol whether to achieve the maximum yield. The role of water in

ethanol and methanol was also observed in this case and the results reflecting the some short of lower yield than that of pure ethanol and methanol. It may be due to the reduced efficacy of the catalyst in presence of water. From the optimized condition it is clear that SRH catalyst is a suitable one for the conversion of 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives with excellent yield in short reaction time. It was observed that at 60^{o}C temperature using minimum amount of catalyst SRH (60 mg) in ethanol giving the best result (**Table III. 4**, entry 7).The progress of the reaction was monitored by thin layer chromatography (TLC) and finally the off white solid crude product was isolated from concentrated ethylacetate extract of reaction mixture by adding mixed solvent containing ethyl acetate and petroleum ether (1:10v/v) slowly dropwise. Finally the obtained solid was purified by slowly washing the crude with solvent containing ethyl acetate and petroleum ether (1:4v/v).

Table III.4. Optimisation of the reaction condition for the synthesis of Synthesis of 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one derivatives[a]

Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	100	Ethanol	90	320	98

2	90	Ethanol	90	280	98
3	80	Ethanol	80	260	98
4	80	Ethanol	70	230	96
5.	70	Ethanol	70	210	96
6.	60	Ethanol	70	180	96
7.	**60**	**Ethanol**	**60**	**180**	**94**
8.	60	Ethanol	60	160	92
9.	50	Ethanol	50	160	80
10.	None	Ethanol	70	215	53
11	None	Methanol	70	220	53
12.	70	Methanol	70	190	96
13	80	H_2O	70	190	-
14	80	Ethanol/H_2O (6:1)	70	220	92
15	80	Ethanol/H_2O (3:1)	70	250	82
16	80	Ethanol/H_2O (1:1)	70	300	72

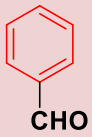
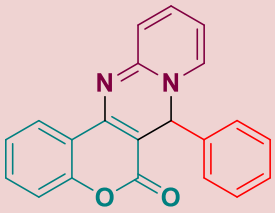
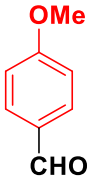
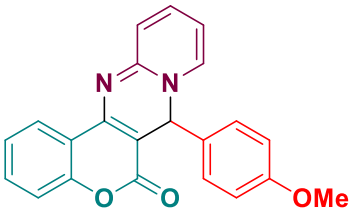
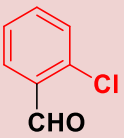
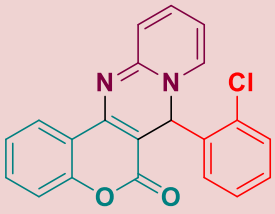
[a]Reaction of anisaldehyde (1mmol), 4-hydroxycumarine (1mmol), 2-aminopyridine (1 mmol) and SRH. [b]The yields are isolated through recrystalisation.

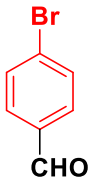
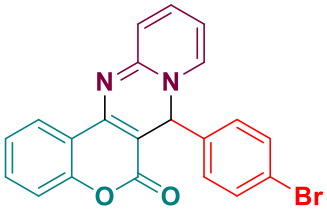
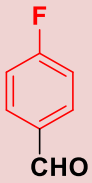
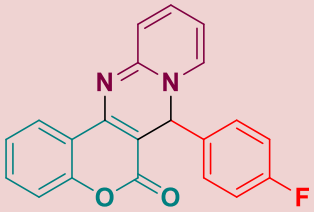
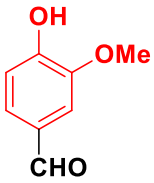
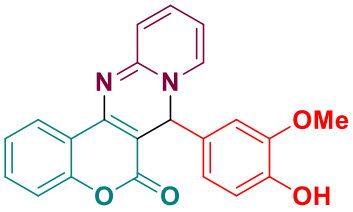
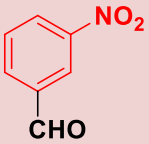
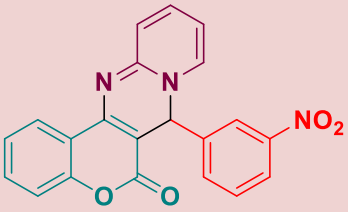
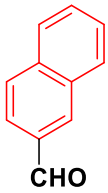
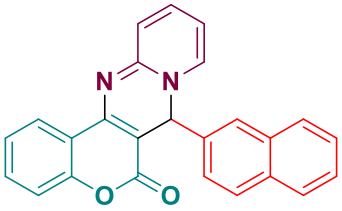
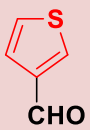
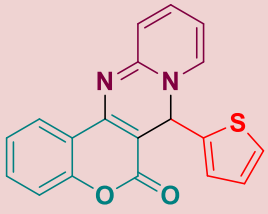
III.8.A.7 Synthesis of 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives

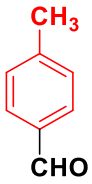
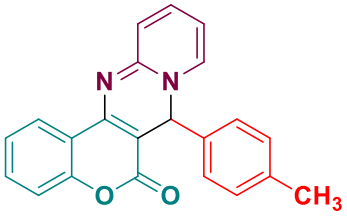
The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (**Scheme III. 20**) with electron donating and

electron withdrawing substituents at *ortho*, *meta* and *para* position also under optimized reaction condition and the targeted compounds (4a-4j) are successively synthesized using SRH as efficient catalyst under green reaction condition.(**Table III. 5**)

Table III.5. Table for synthesis of 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives using sulphonated rice husk[a]

Entry	Reactant	Product	Time	Yield(%)[b]
1		 (4a)	200 min	95
2		 (4b)	200 min	98
3		 (4c)	200 min	96

4		 (4d)	200 min	98
5		 (4e)	200 min	97
6		 (4f)	200 min	96
7		 (4g)	200 min	95
8		 (4h)	200 min	98
9		 (4i)	200 min	92

10		 (4j)	200 min	97

[a]Reaction of aromatic aldehydes (1mmol), 4-hydroxycumarine (1mmol), 2-aminopyridine (1 mmol) and SRH. [b] The yields are isolated through recrystalisation.

III.8.A.8 Plausible Mechanism

A plausible mechanism of synthesis (**Figure III.11**) of 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives are established by considering the acidic behaviour of the catalyst. Initially a fast protonation at aldehyde oxygen followed by condensation reaction with 1 mol of 4-hydroxycoumarine to give a aryledine-chromanedione intermediate and then Michael addition reaction occurs between 2-aminopyridine and aryledine-chromanedione followed by intramolecular cyclisation along with fast condensation results in the formation of desired 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives.[97]

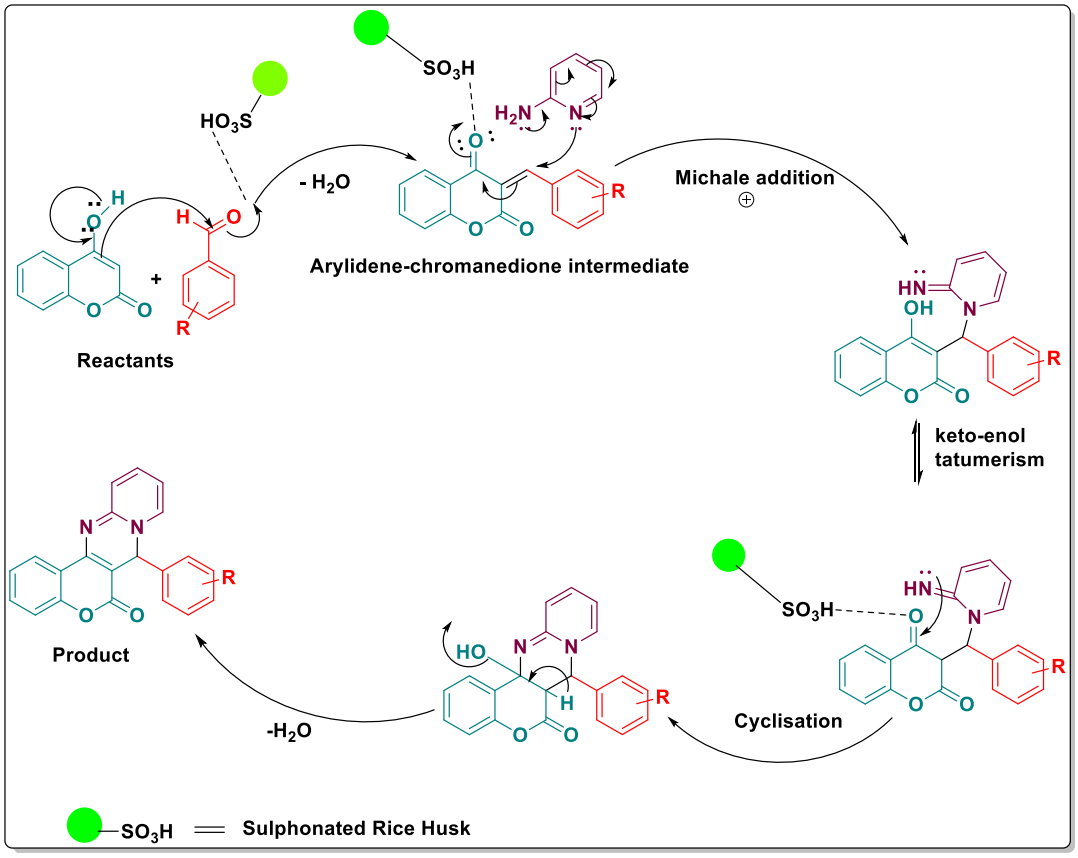


Figure III.11 The plausible mechanism for the synthesis 7-aryl/heteroaryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-d]pyrido[1,2-a]pyrimidin-6-one derivatives

III.8.A.9 Catalyst Recyclability Experiment

To check the recyclability of the catalyst, a model reaction was performed between anisaldehyde(1.8mmol), 4-hydroxycoumarine (1.8mmol), 2-aminopyridine(1.8 mmol) in presence of 110 mg of sulphonated rice husk following the optimized reaction condition (**Scheme III.20, Table III.4**, entry 7). After the successful completion of the each reaction step the reaction mixture was extracted with ethyl acetate until the catalyst was completely washed off. The catalyst was further

washed with ethanol at the end finally then it was dried under vaccum and the recovered catalyst weight was measured. After every recovery step of the catalyst the next reaction was repeated following optimized reaction condition (mentioned in **Table III.4** above) with required proportion of the reactants to that of weight of the recovered catalyst (**Table III.6**). Amount of catalyst, aldehyde, reaction time, temperature and yield percentage of the product have been shown in the table (**Table III.6**, entry 1-5). The catalyst was easily recovered from the reaction mixture with minimum loss by centrifugation and it was found to retain its acidic property, even after 5th run for this particular model reaction (**Figure III.13**). This was further supported by FTIR spectra of the recovered SRH catalysts after successive reactions (**Figure III.12**).

Table III.6. Table for the amount of recovered catatyst with isolated product yield [a]

Entry	Catalyst (mg)	Aldehyde (x mmol)	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	110	1.80	70	180	96
2	80	1.30	70	180	94
3	60	0.90	70	180	87
4	50	0.75	70	180	83

5.	40	0.60	70	180	72

[a] Reaction of anisaldehyde(x mmol), 4-hydroxycoumarine (x mmol), 2-aminopyridine (x mmol).[b] Isolated yield.

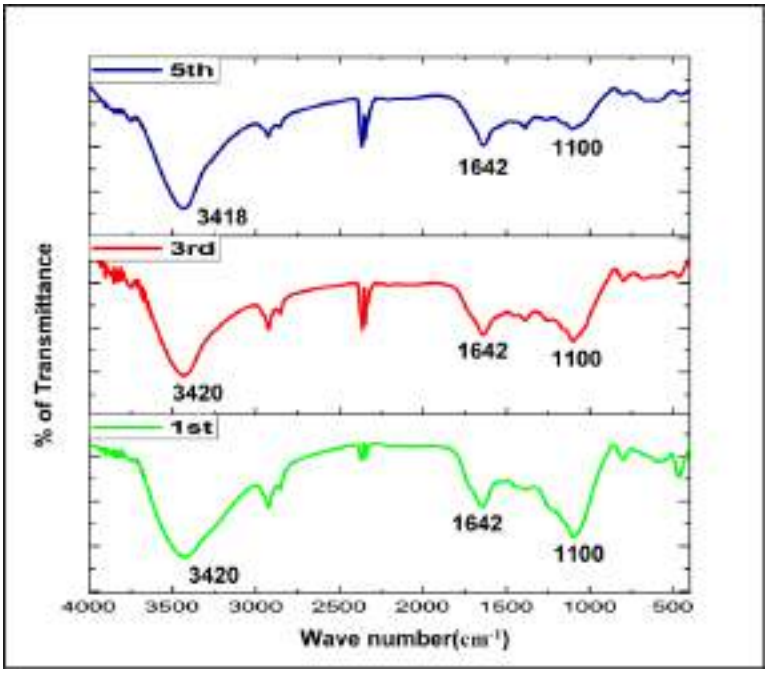


Figure III.12. FTIR spectra of reused catalysts after 1st , 3rd and 5th and run

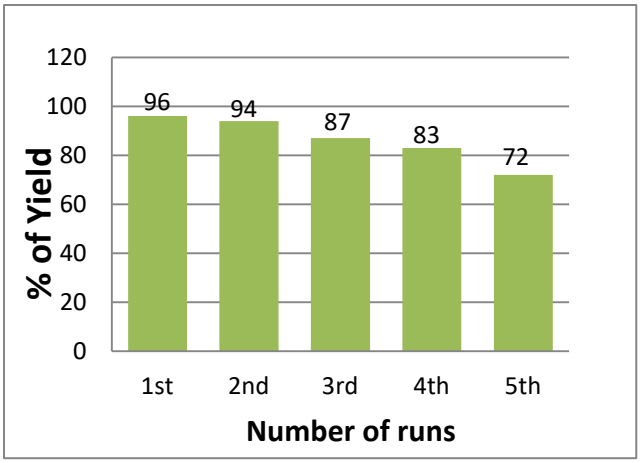


Figure III.13. Recyclability experiment

III.8.A.10 Conclusion

In conclusion, a simple and greener methodology for the synthesis of variety of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione and 7-aryl/heteroaryl-6*a*,13*a*-dihydro-6*H*,7*H*-chromeno [4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one derivatives from commercially available aldehydes has been established. We have introduced a new greener method using newly developed cheaper heterogeneous catalyst Sulphonated rice husk (SRH) for the synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c*']dichromene-6,8-dione and 7-aryl/ heteroaryl-6*a*,13*a*-dihydro-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimi din-6-one derivatives with excellent yield. This heterogeneous catalyst is found to be highly efficient for the synthesis 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c*']dichromene-6,8-dione and 7-aryl/hetero-aryl-6a,13a-dihydro-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one derivatives in short reaction time. The catalyst is recyclable up to 5^{th} run for above mentioned model reaction and has broad aspect to catalyze a wide range of multi-component reactions bearing condensation and cyclization steps.

III.8.A.11 Acknowledgement

One of the authors (S.D) is thankful to UGC, New Delhi for financial support, USIC (NBU) for SEM, EDX analysis, & Panjab University SAIF for powder XRD analysis for this work.

III.8.A.12 Experimental

III.8.A.12.a Materials and methods

Crude rice-husk was collected from nearby rice mill and the chemicals including aldehydes, 4-hydroxycumarine, 2-aminopyride were supplied from Sigma Aldrich chemical Co. (USA) which have been used directly without further purification. The chemical purity of the compounds was confirmed by Thin layer Chromatography(TLC) on commercial alluminium baked plates of silica gel, 60 F254. NMR spectra of all the products were taken in DMSO-d_6 (TMS as an internal standard) using a Bruker 400MHz spectrometer(operating for ^{1}H at 400 MHz and for ^{13}C at 100 MHz) and Bruker Advance NEO 500MHz spectrometer(operating for ^{1}H at 500 MHz and for ^{13}C at 125 MHz). IR spectra of the prepared catalyst were recorded on Perkin Elmer-Spectrum RX-IFTIR spectrophotometer, Powder XRD and SEM-EDX analysis of the prepared catalyst was carried out by Panalytical's X'pert

Pro X-Ray diffractometer and JSM-IT700HR Advanced SEM Spectrometer.

III.8.A.12.b General procedure for catalyst preparation

The heterogeneous catalyst (SRH) was prepared by direct sulphonation of rice husk (RH) following our previous synthetic method. [100] The rice husk (RH) was collected from a nearby rice mill and was blended finely before use. The fibrous part of the blended rice husk was first washed with dilute H_2SO_4 continuously for several times and next the whole aggregate was thoroughly washed with water and finally by ethanol. After washing the solvent was fully evaporated through rotary evaporator and then fully dried 5g of chemically treated rice husk material was taken into 250 mL of a round bottom flask followed by addition of 150 mL dichloromethane (DCM). Then, 5 mL of pure Chlorosulphonic acid (98%) was added dropwise with continuous stirring until the whole suspension turned into brownish and finally set to stir for 20 hours on a magnetic stirrer at room temperature. After the completion of reaction the solid material was filtered off and washed with water to remove excess chlorosulphonic acid and finally acetone repeatedly to remove other organic substances till the filtrate shows very light brownish appearance. After leaching, the final material was

dried in reduced pressure and later characterised by different spectroscopic techniques.[100]

III.8.A.12.c General procedure for synthesis of 7-aryl/heteroaryl-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione derivatives

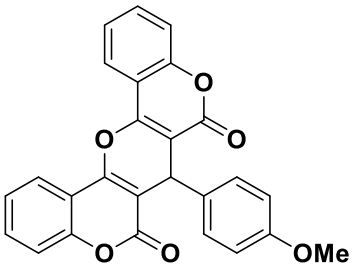
A mixture of 4-hydroxycumarine (2 mmol), aromatic aldehyde (1.0 mmol), and SRH (80 mg) in a 25-mL round bottom flusk was stirred at 60-80 ^{o}C temperature for 240 minutes and the progress of the reaction was monitored by thin-layer chromatography (TLC) (**Scheme III.19**). After completion of the reaction, the product was extracted with ethyl acetate and the catalyst was removed by filtration. Then ethyl acetate extract was concentrated and white crude product was isolated by the addition of petroleum ether slowly dropwise until white precipitation appears. Then white crude product was further purified by recrystallisation in petroleum ether/ethyl acetate (v/v ratio 80/20) mixture to get the pure product. All the synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and the spectral data were compared with the reported spectral data of corresponding compound.

III.8.A.12.d General procedure for synthesis of 7-aryl/heteroaryl-6*a*,13*a*-dihydro-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one derivatives

A mixture of 2-aminopyridine (1 mmol), 4-hydroxycumarine (1 mmol), aromatic aldehyde (1 mmol), and SRH (60 mg) in a 25-mL round bottom flusk was stirred at 60-80 ^{o}C temperature for 210 minutes. The progress of the reaction was monitored by thin-layer chromatography (TLC) (**Scheme III.20**). After completion of the reaction, the product was extracted with ethyl acetate and the catalyst was separated by simple filtration and the ethyl acetate extract was concentrated and crude product was separated by simple precipitation with addition of mixed solvent containing ethyl acetate and petroleum ether (1:10v/v) slowly dropwise. Finally the obtained solid was purified by slowly washing the crude with solvent containing ethyl acetate and petroleum ether (1:4v/v). After isolation, all the synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and the spectral data were compared with the reported spectral data of corresponding compound.

III.8.A.12.e Spectral data of the compounds mentioned in scheme III.19

7-(4-methoxyphenyl)-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3a)



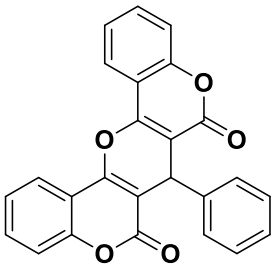
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)3.65(s,3H),6.17(s,1H),6.70(d,3H),6.96(d,2H),7.18-7.24(m,4H),7.45-7.49(m,2H),7.78(dd,2H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)35.90,55.43,104.26,113.68,116.00,120.40,123.42,124.62,128.16,131.43,134.50,153.02,157.36,165.08,167.96.

7-phenyl-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3b)



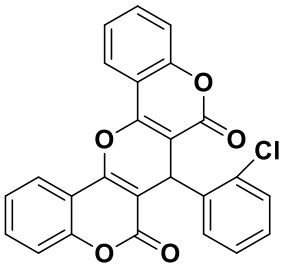
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)6.24(s,1H),7.02-7.08(m,3H),7.11-7.15(m,2H),7.22-7.29(m,4H),7.45-7.50(m,2H),7.77(q,2H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)36.68,103.95,116.00,120.50,123.41,124.67,125.34,127.20,128.23,131.44,142.93,153.06, 165.12,168.25.

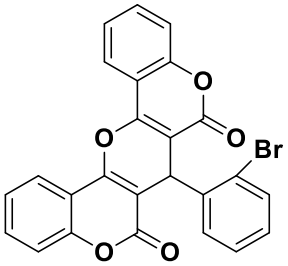
7-(2-chlorophenyl)-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3c)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)6.12(s,1H),7.08-7.18(m,3H),7.21(d,4H),7.37(d,1H),7.44-7.77(m,2H),7.78(d,2H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)36.66,103.32,115.99,120.46,123.44,124.59,126.52,127.57,129.88,130.91,131.37,133.24,140.95,152.96,164.41,168.24.

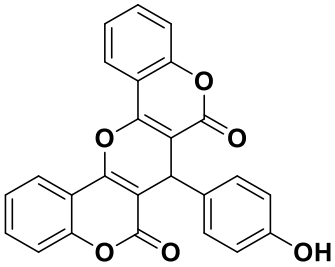
7-(2-bromophenyl)-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3d)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)5.99(s,1H),7.02(t,1H),7.17-7.22(m,5H),7.38(dd,2H),7.46(t,2H),7.77(d,2H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)38.89,103.46,116.00,120.47,123.43,124.57,127.06,127.88,131.11,131.34,133.32,152.97,164.35,168.17.

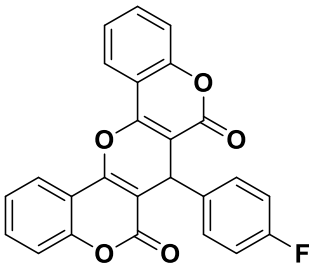
7-(4-hydroxyphenyl)-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3e)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)6.12(s,1H),6.52(d,2H),6.84(d,2H),7.17-7.22(m,4H),7.44-7.48(m,2H),7.77(dd,2H),8.90(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)35.86,104.36,115.04,115.95,120.58,123.34,124.64,128.08,131.31,132.83,153.03,155.17.165.12, 168.11.

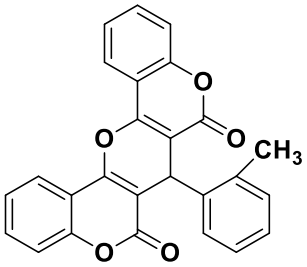
7-(4-fluorophenyl)-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3f)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)6.21(s,1H),7.02-7.08(m,3H),7.11-7.15(m,2H),7.22-7.29(m,4H),7.45-7.50(m,2H),7.77(q,2H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)36.68,103.95,116.00,120.50,123.41,124.67,125.34,127.20,128.23,131.44,142.93,153.06,165.12,168.25.

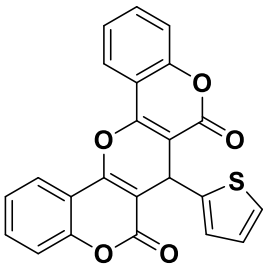
7-(2-methylphenyl)- 6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c*']dichromene-6,8-dione(3g)



^{1}H-NMR(400MHz,DMSO-d_6)
δ(ppm)1.96(s,3H),6.09(s,1H),6.97(s,3H),7.22-7.27(m,5H),7.47(d,2H),7.80(d,2H).

^{13}C-NMR(400MHz,DMSO-d_6)
δ(ppm)21.63,36.55,105.20,116.14,120.03,123.66,124.64,126.31,127.78,128.31,131.68,137.06,142.16, 152.96,165.26,168.96.

7-(thiophen-2-yl)- 6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c*']dichromene-6,8-dione(3h)



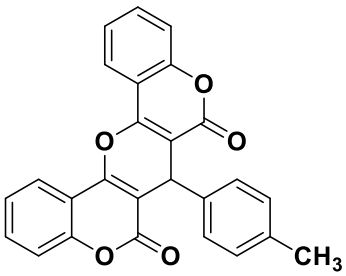
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)6.38(s,1H),6.57(t,1H),6.78(t,1H),7.12(d,1H),7.19-7.30(m,3H),7.40-7.52(m,2H),7.82(t,2H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)33.47,104.27,116.06,120.42,123.21,123.52,123.56,124.77,126.66,131.66,148.61,153.03,164.67,168.48.

7-(4-methylphenyl)- 6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3i)



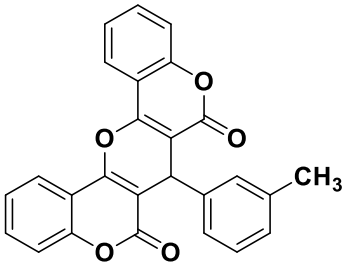
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)2.19(s,3H),6.19(s,1H),6.94(s,4H),7.20(q,4H),7.46-7.50(m,2H),7.78(d,2H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)21.06,36.30,104.09,115.99,120.50,123.42,124.64,127.11,128.84,131.42,134.04,139.73,153.03,165.16,168.21.

7-(3-methylphenyl)- 6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3j)



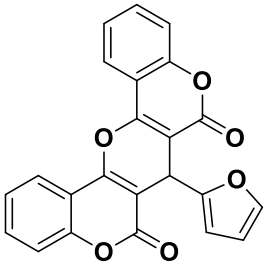
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)2.16(s,3H),6.24(s,1H),6.89(d,3H),7.04(t,1H),7.21-7.28(m,4H),7.48-7.53(m,2H),7.82(dd,2H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)21.83,104.20,116.14,120.03,123.66,124.44,124.64,126.31,127.78,128.21,131.69,137.06, 142.36,152.96,165.25,167.74

7-(furan-2-yl)- 6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3k)



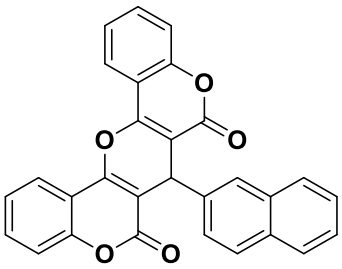
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)6.36(s,1H),6.56(t,1H),6.77(t,1H),7.12(d,1H),7.18-7.31(m,3H),7.42-7.52(m,2H),7.80-7.85(m,2H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)32.47,105.26,116.06,120.42,123.21,123.52,123.56,124.77,126.66,131.66,148.61,153.03,164.67,168.48.

7-(naphthalen-2-yl)- 6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3l)



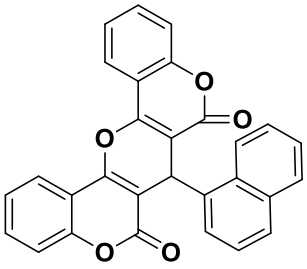
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.42(s,1H),7.22-7.30(m,5H),7.37-7.39(m,2H),7.51-7.54(m,3H),7.57-7.72(m,2H),
7.78-7.83(m,3H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.42,103.28,114.39,115.30,115.42,119.87,122.71,122.82,124.04,124.06,124.66,125.43,126.20,127.01,127.03,127.35,127.42,130.86,131.28,132.92,140.03,152.37,152.46,164.53,167.83.

7-(naphthalen-1-yl)- 6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3m)



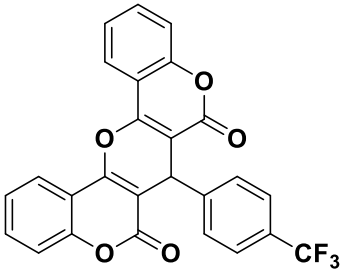
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)6.73(s,1H),7.18-7.26(m,3H),7.33-7.37(m,3H),7.45-7.50(m,3H),7.68(d,1H), 7.76-7.83(m,3H),7.99(dd,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)35.46,104.80,116.07,120.27,123.59,124.60,124.73,125.42,125.54,125.94,126 .27,126.69,129.05,131.53,132.19,134.22,138.67,152.84,164.78,168.64.

7-(4-(trifluoromethyl)phenyl)-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3n)



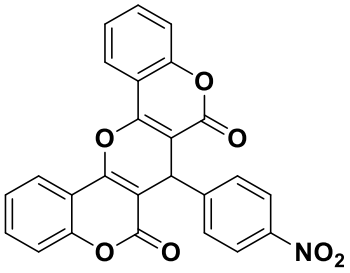
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.34(s,1H),7.23-7.34(m,6H),7.51-7.56(m,4H),7.83(q,2H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.30,102.85,115.47,119.69,122.93,123.48,124.10,124.61,124.64,125.56,125 .64,125.81,127.30,131.06,147.49,152.47,164.47,167.86.

7-(4-nitrophenyl)- 6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3o)



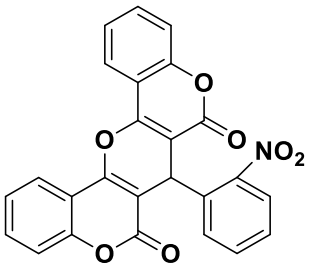
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.37(s,1H),7.23-7.30(m,4H),7.38(d,2H),7.51-7.55(m,2H),7.83(dd,2H),8.08(d,2H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.67,102.68,115.50,119.61,122.98,123.03,124.11,127.79,131.15,145.22,151 .37,152.48,164.34,167.93

7-(2-nitrophenyl)-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione(3p)



^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.50(s,1H),7.21-7.26(m,4H),7.34-7.38(m,2H),7.49-7.55(m,4H),7.78(d,2H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)33.83,102.14,115.43,119.46,122.86,123.76,124.02,126.53,129.52,130.94,131.81,135.23,149.52,152.44,163.54,167.88.

III.8.A.12.f Sanned copies of compounds mentioned in Scheme III. 19

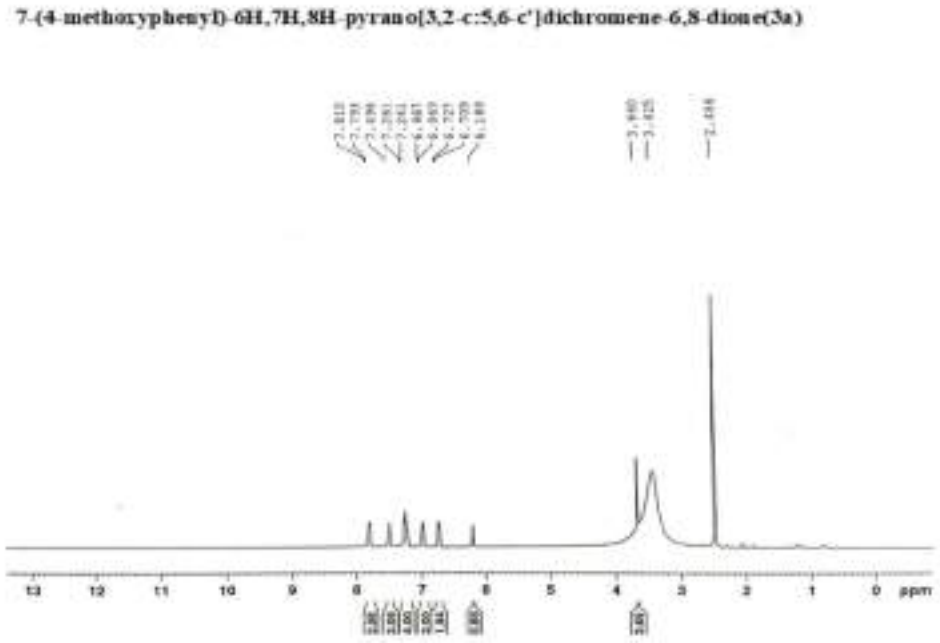


Figure III.14-^{1}H-NMR of compound 3a

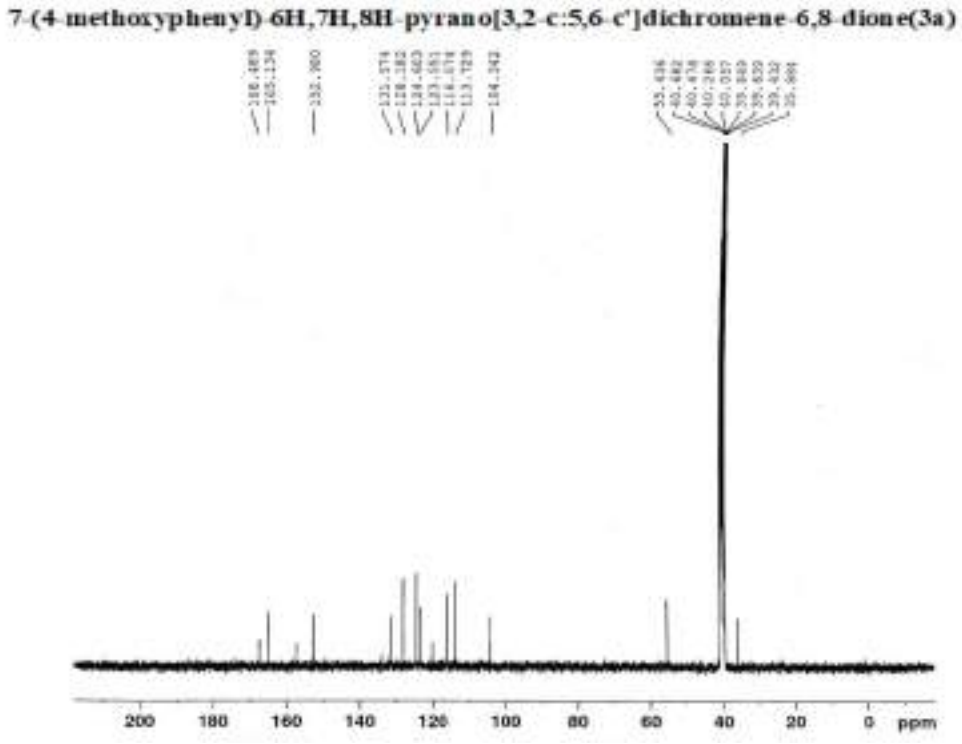


Figure III.15-^{13}C-NMR of compound 3a

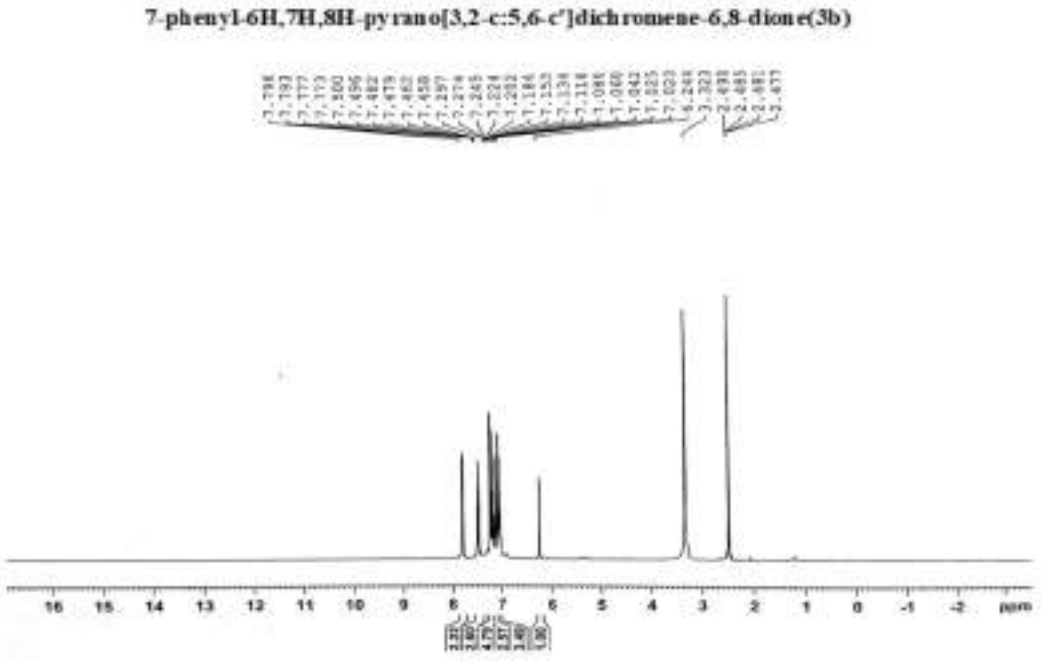


Figure III.16-^{1}H-NMR of compound 3b

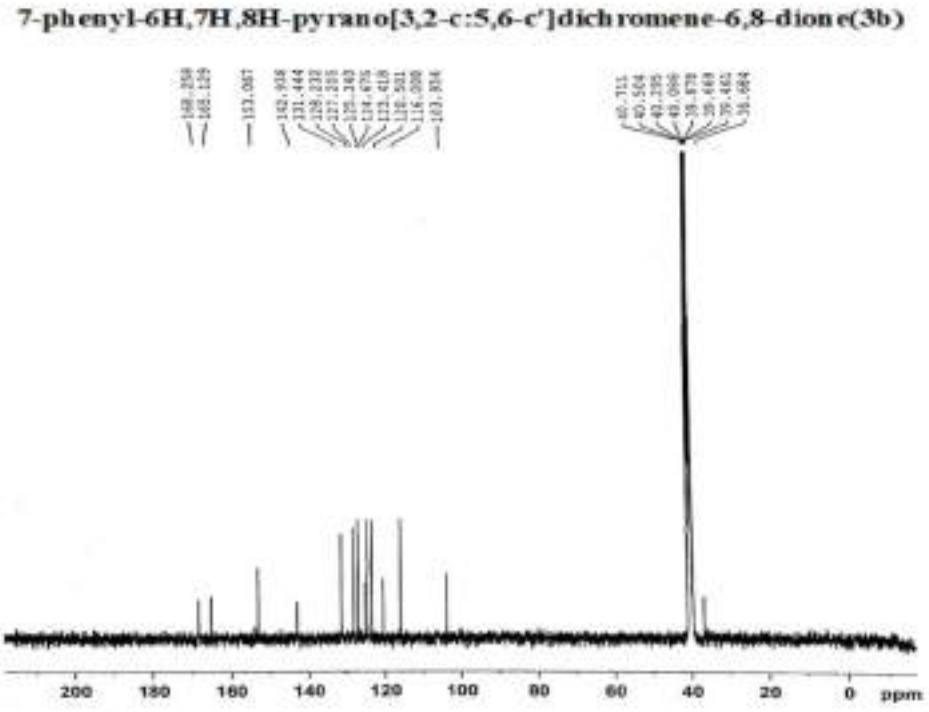


Figure III.17-^{13}C-NMR of compound 3b

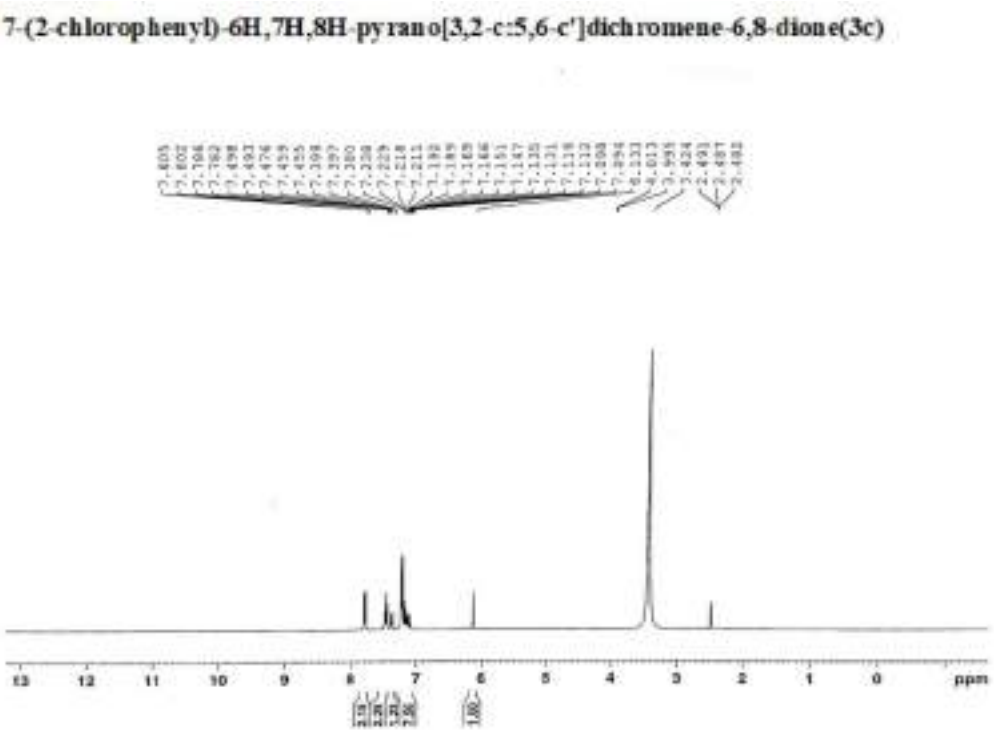


Figure III.18-^{1}H-NMR of compound 3c

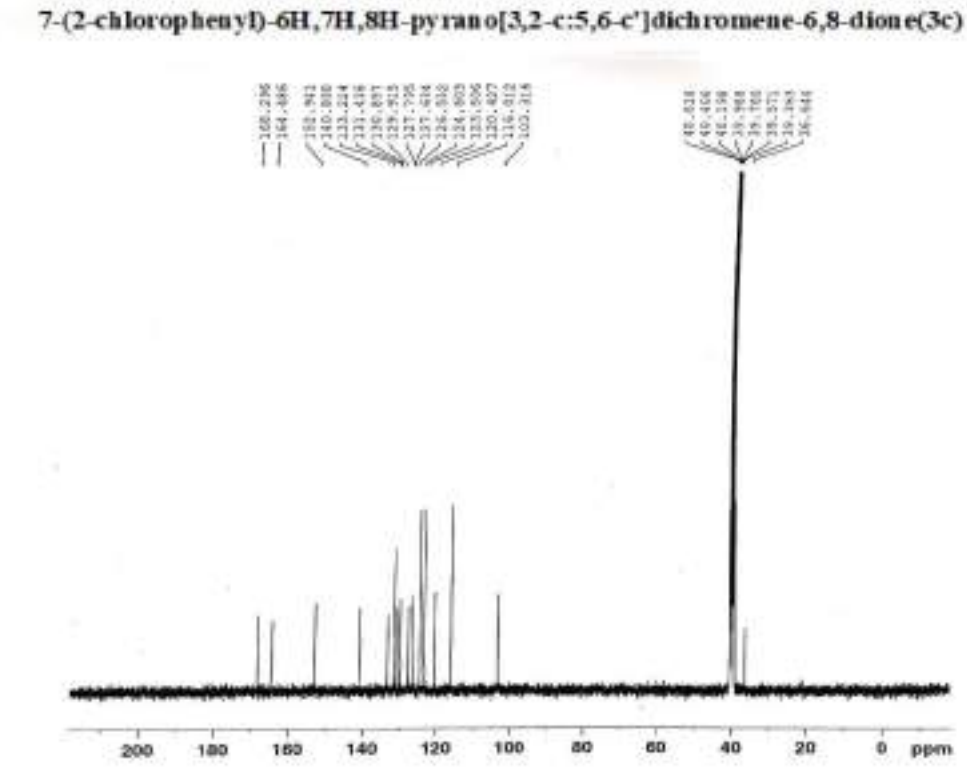


Figure III.19-^{13}C-NMR of compound 3c

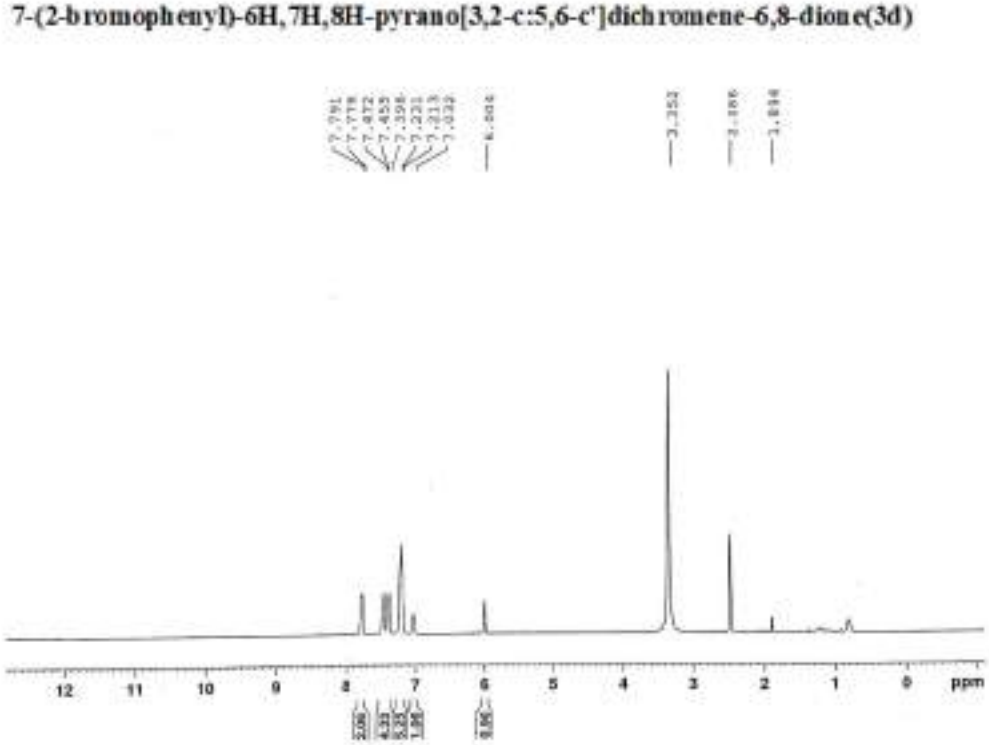


Figure III.20-^{1}H-NMR of compound 3d

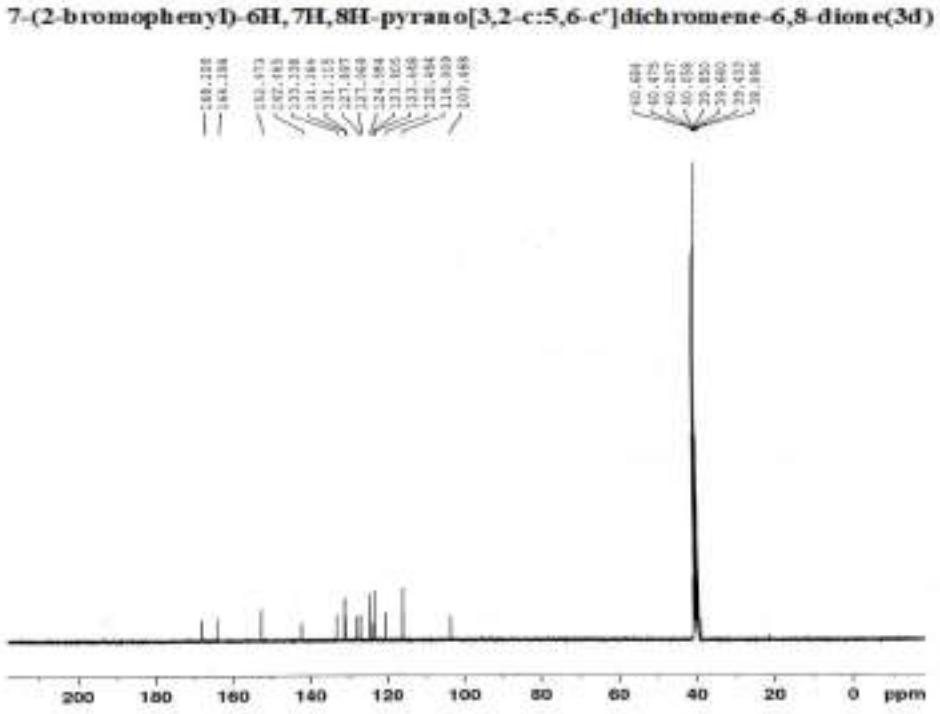


Figure III.21-^{13}C-NMR of compound 3d

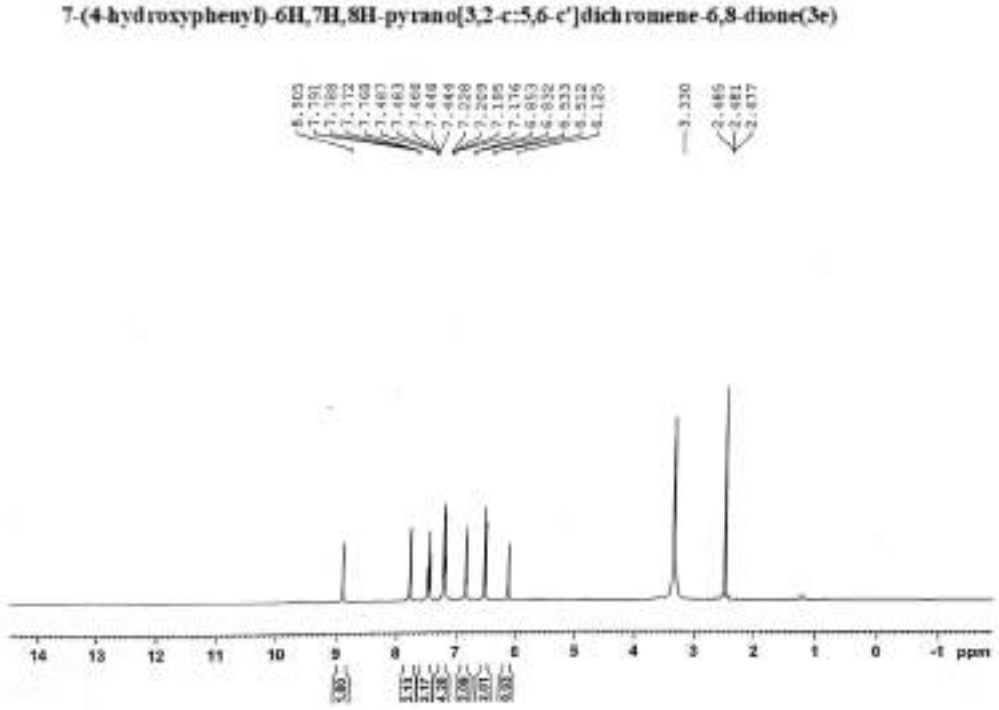


Figure III.22-^{1}H-NMR of compound 3e

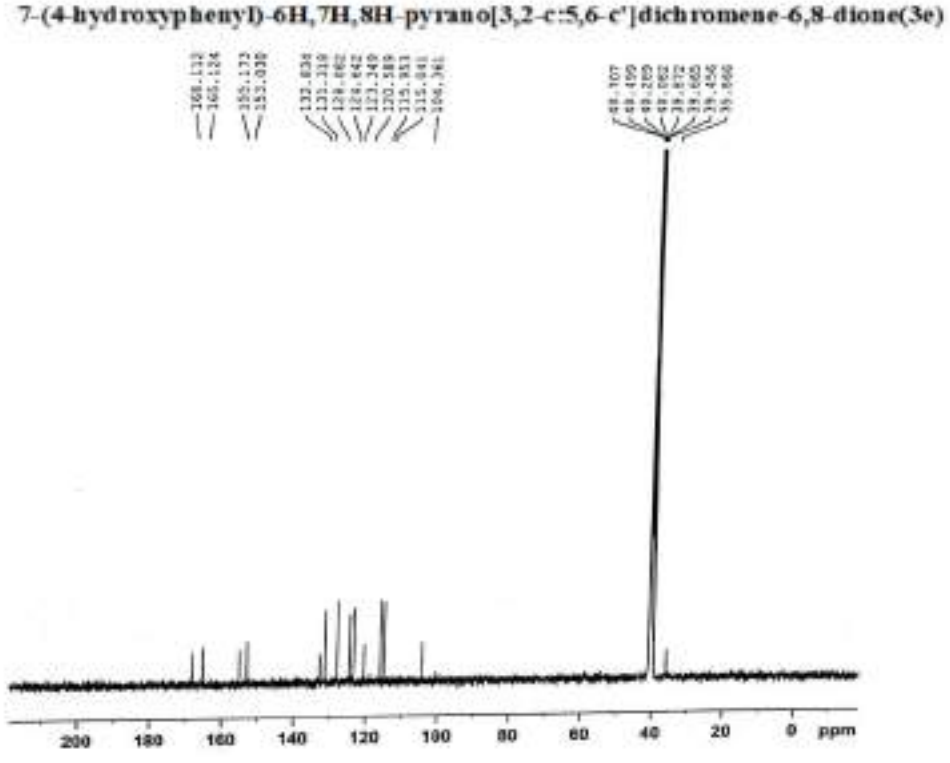


Figure III.23-^{13}C-NMR of compound 3e

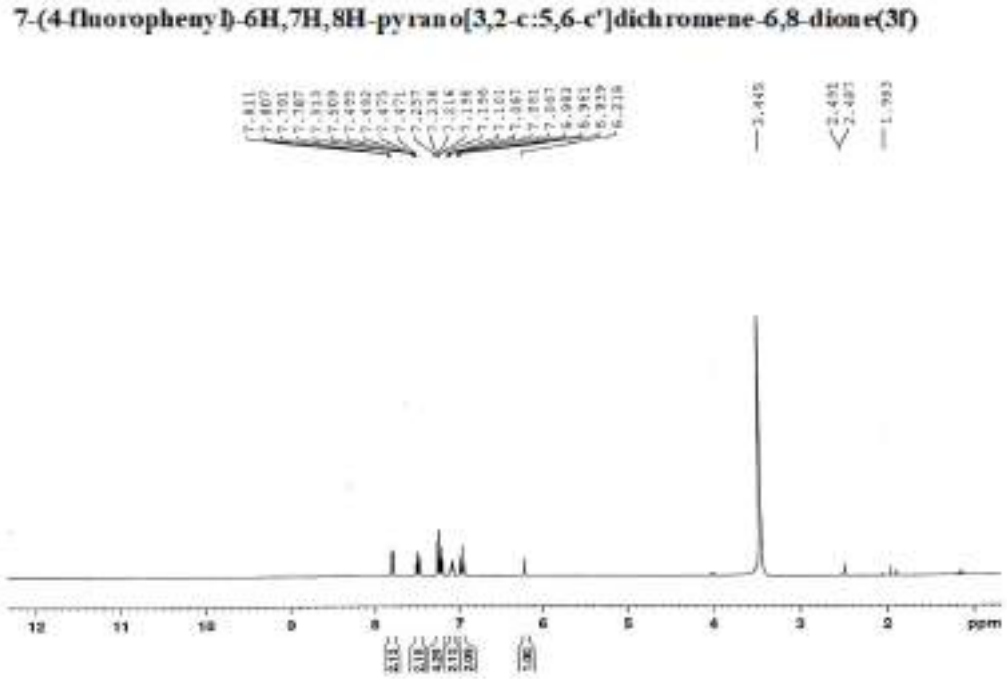


Figure III.24-^{1}H-NMR of compound 3f

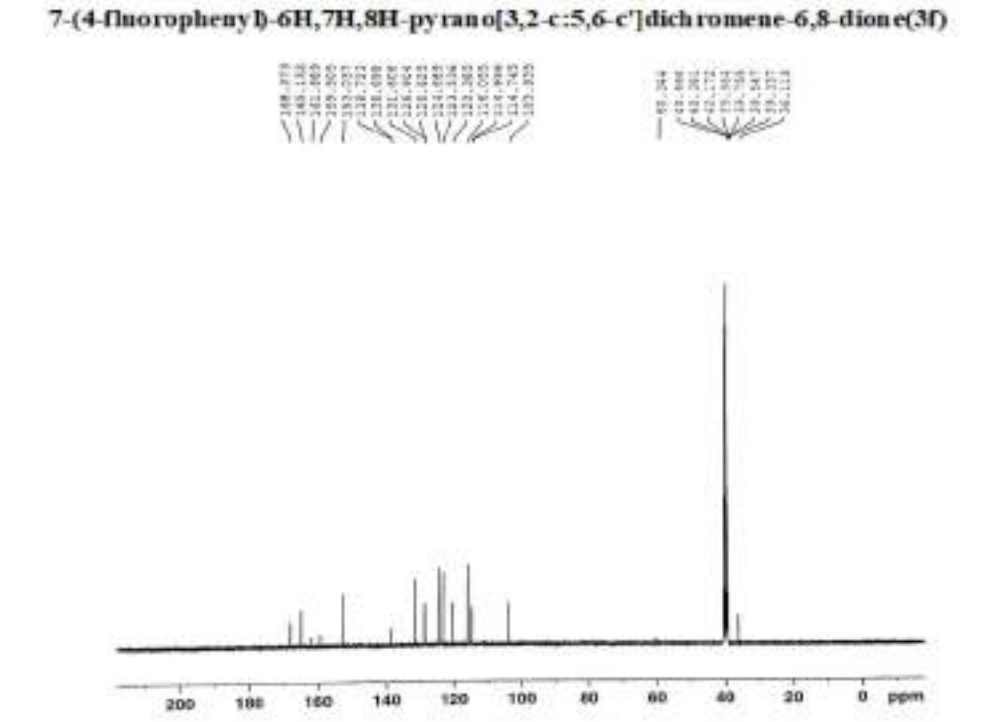


Figure III.25-^{13}C-NMR of compound 3f

7-(2-methylphenyl)-6H,7H,8H-pyrano[3,2-c:5,6-c']dichromene-6,8-dione(3g)

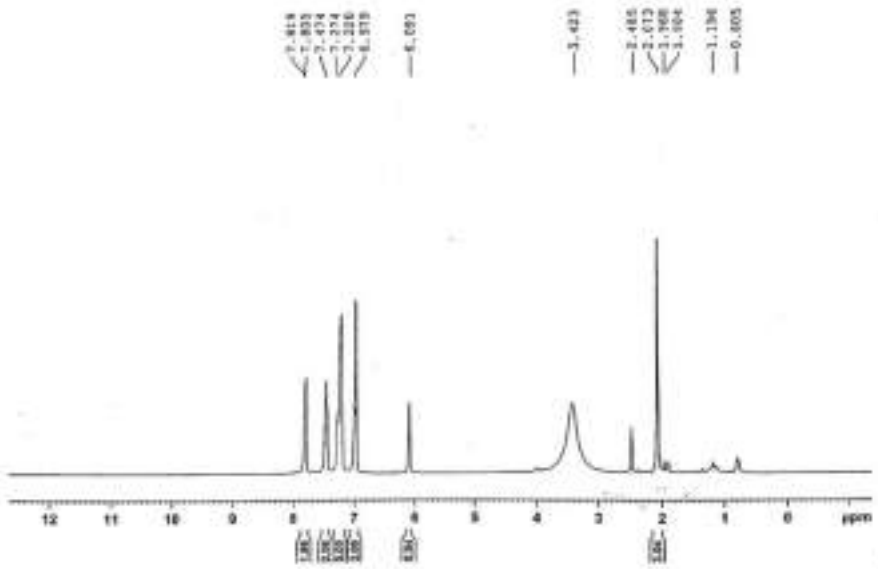


Figure III.26-^{1}H-NMR of compound 3g

7-(2-methylphenyl)-6H,7H,8H-pyrano[3,2-c:5,6-c']dichromene-6,8-dione(3g)

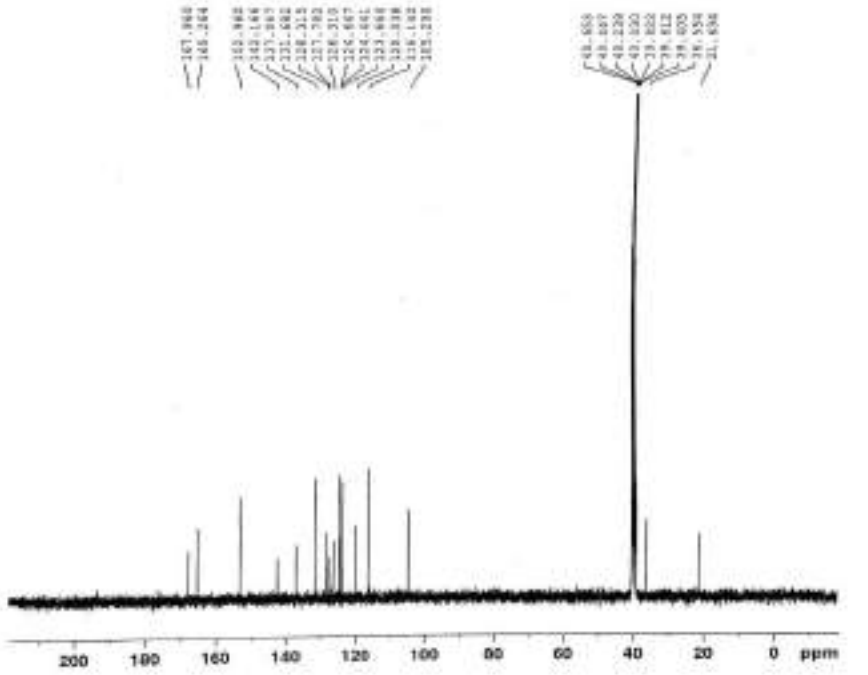


Figure III.27-^{13}C-NMR of compound 3g

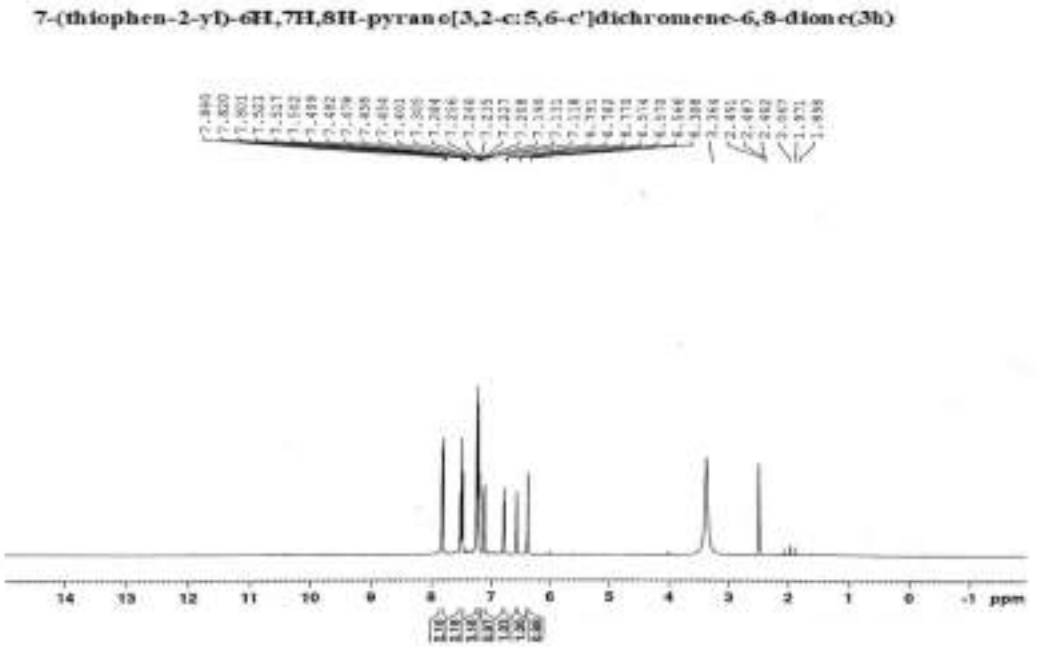


Figure III.28-^{1}H-NMR of compound 3h

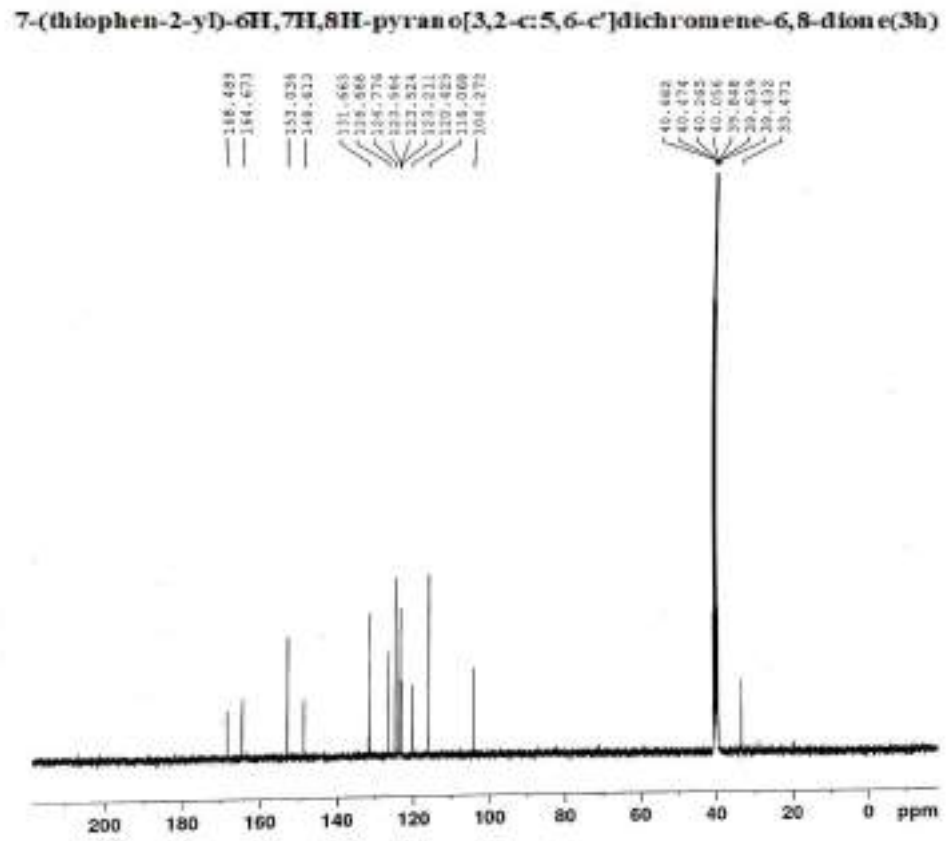


Figure III.29-^{13}C-NMR of compound 3h

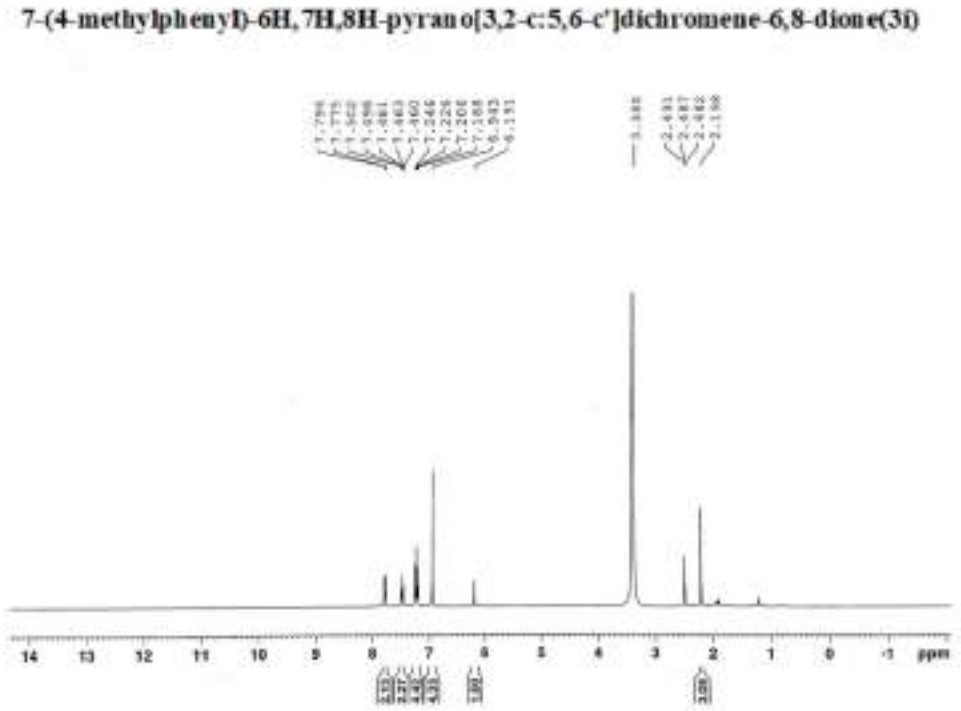


Figure III.30-^{1}H-NMR of compound 3i

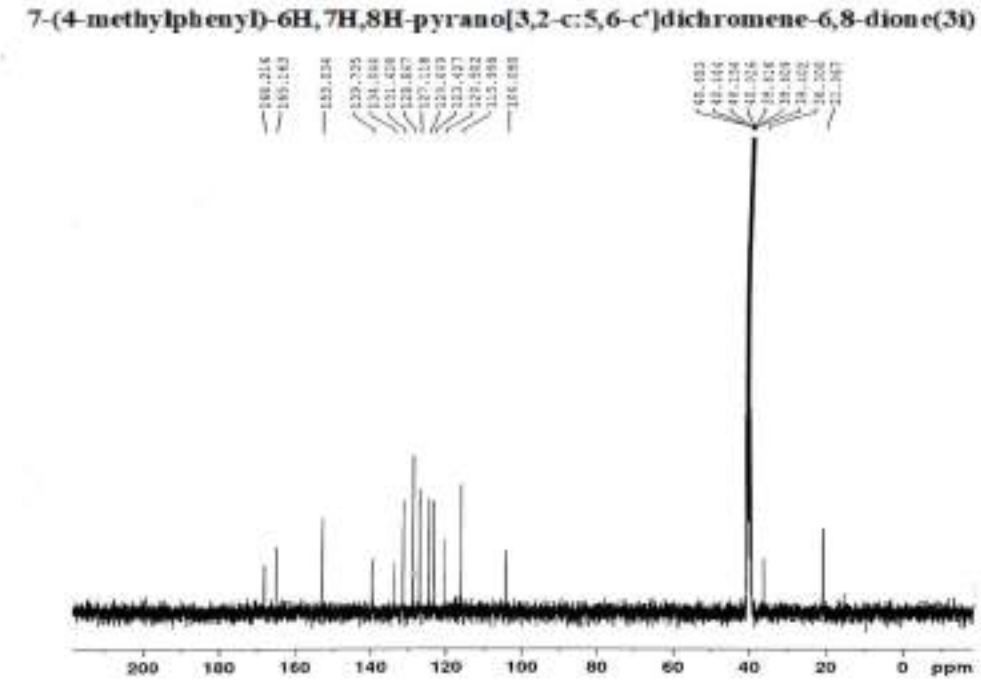


Figure III.31-^{13}C-NMR of compound 3i

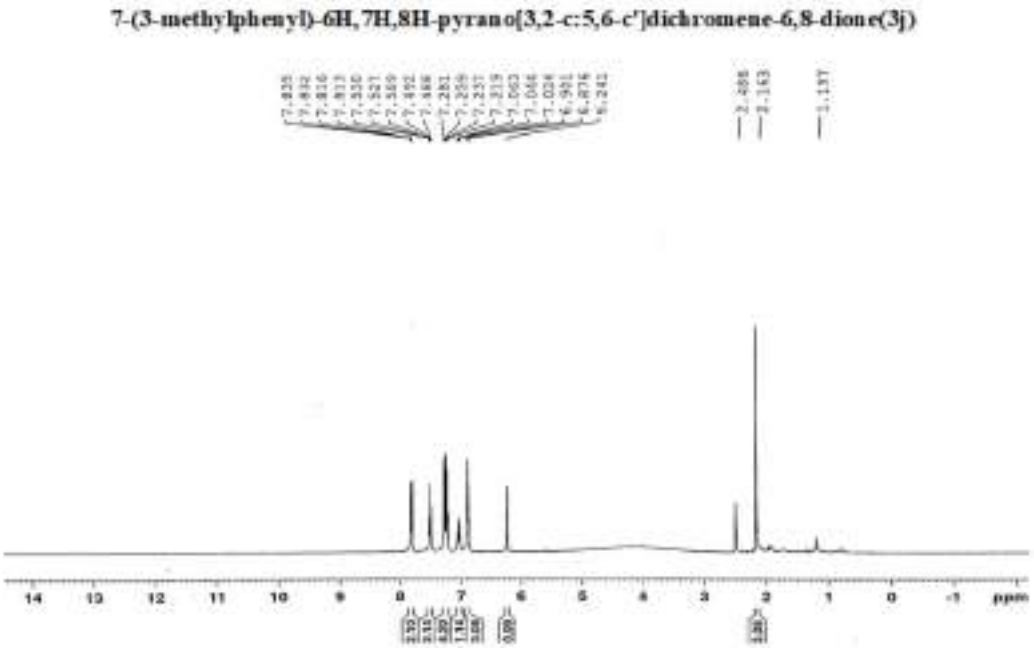


Figure III.32-^{1}H-NMR of compound 3j

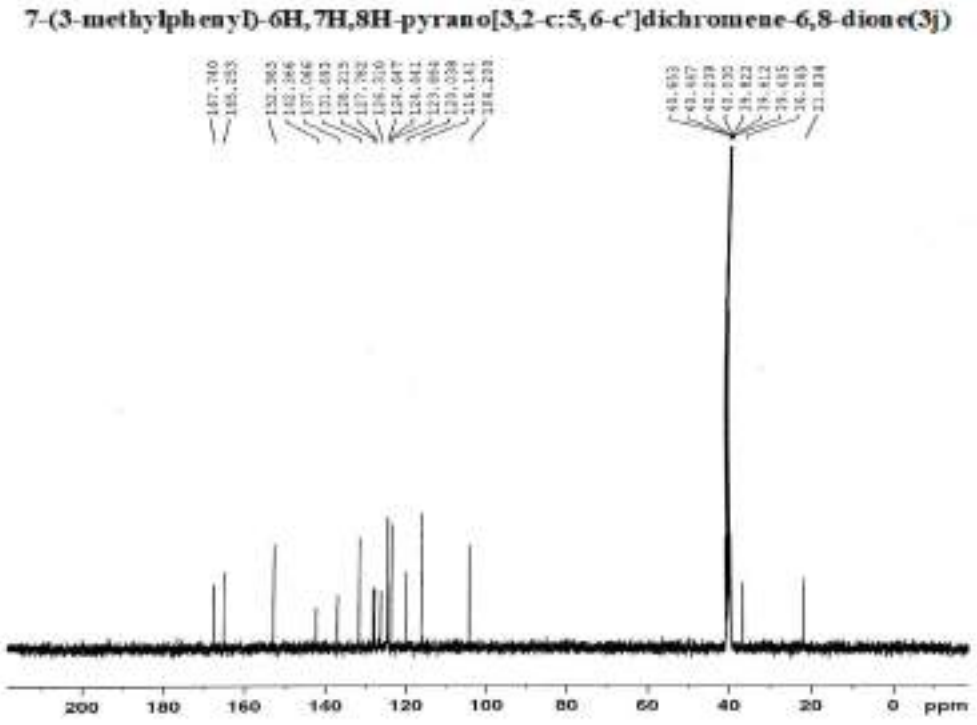


Figure III.33-^{13}C-NMR of compound 3j

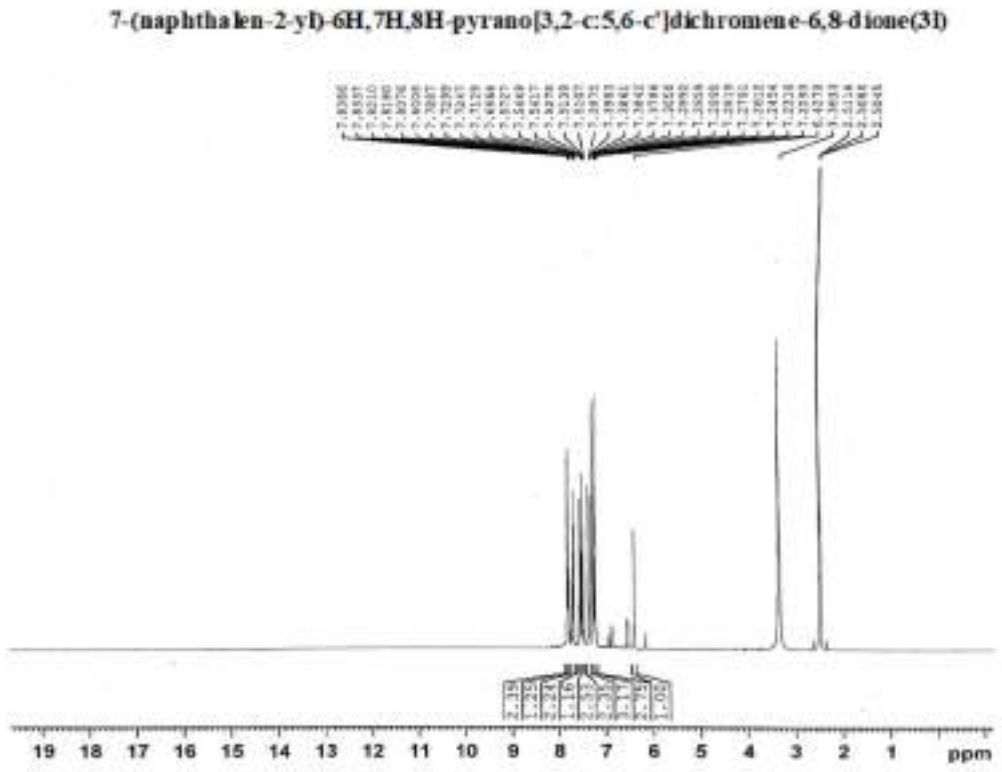


Figure III.34-^{1}H-NMR of compound 3l

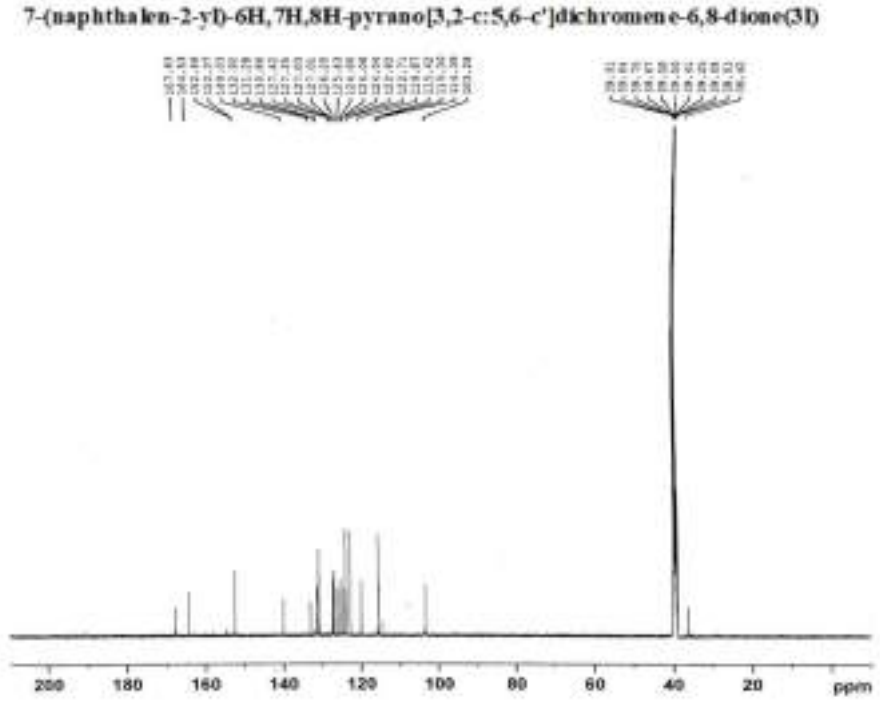


Figure III.35-^{13}C-NMR of compound 3l

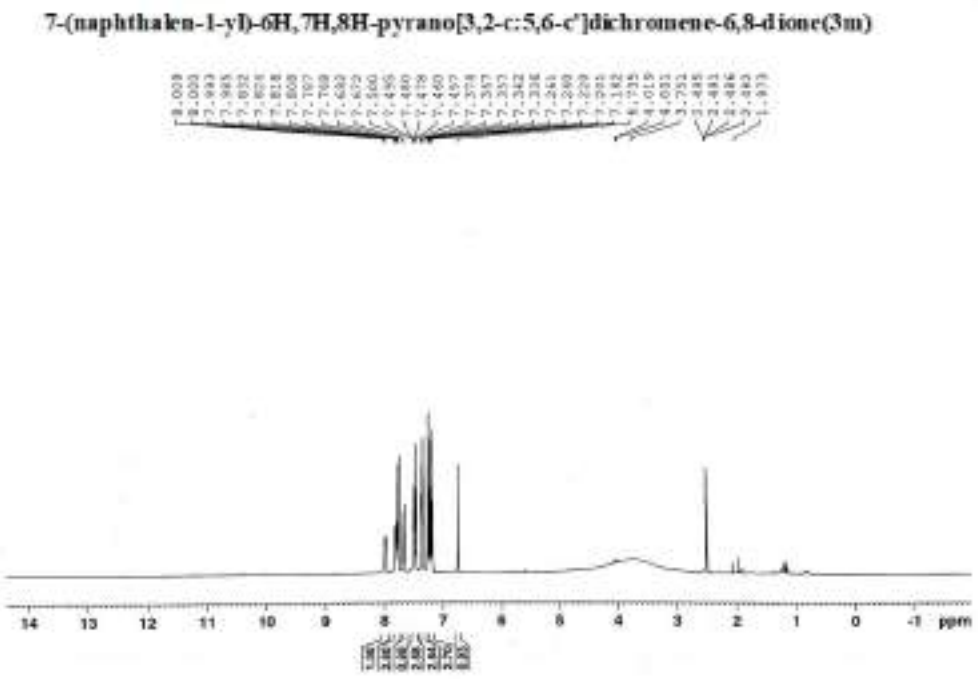


Figure III.36-^{1}H-NMR of compound 3m

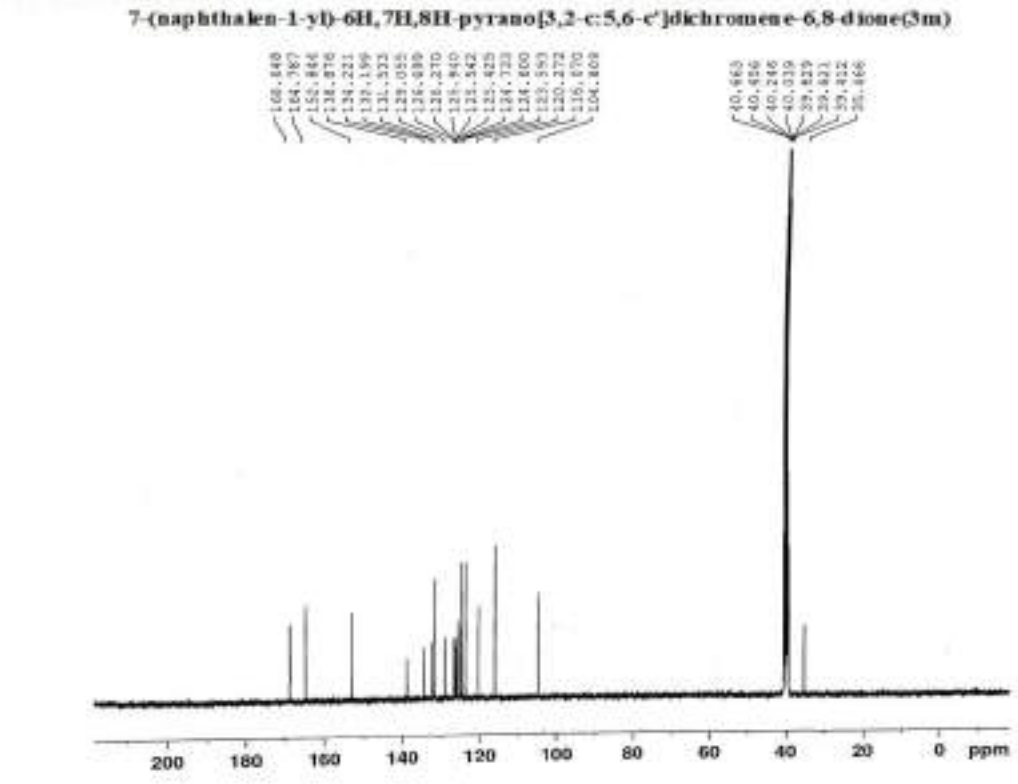


Figure III.37-^{13}C-NMR of compound 3m

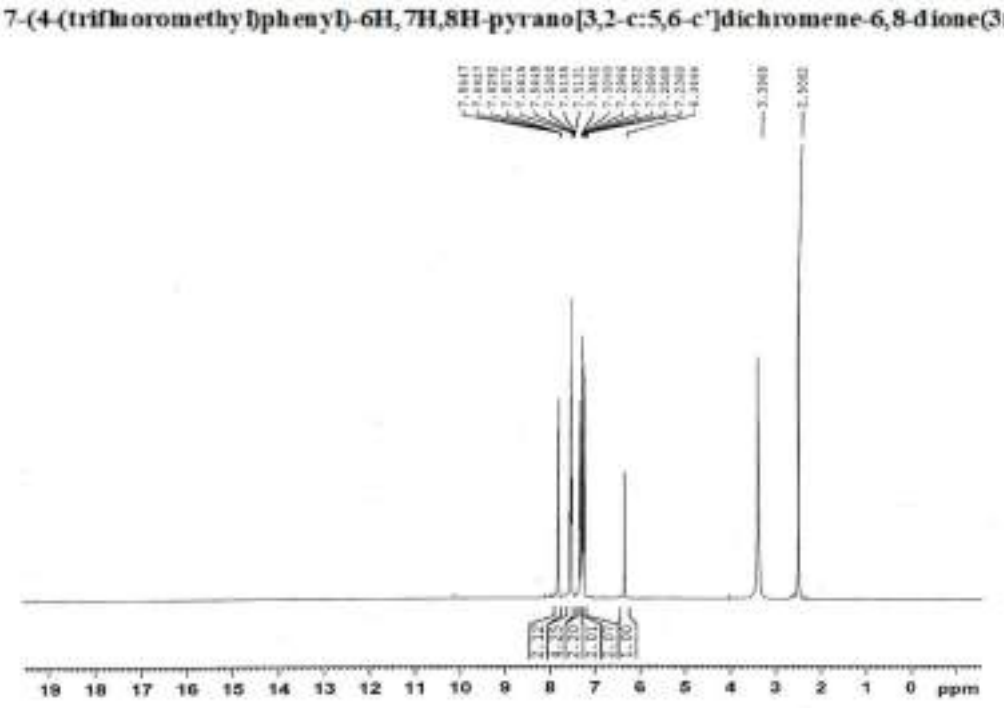


Figure III.38-^{1}H-NMR of compound 3n

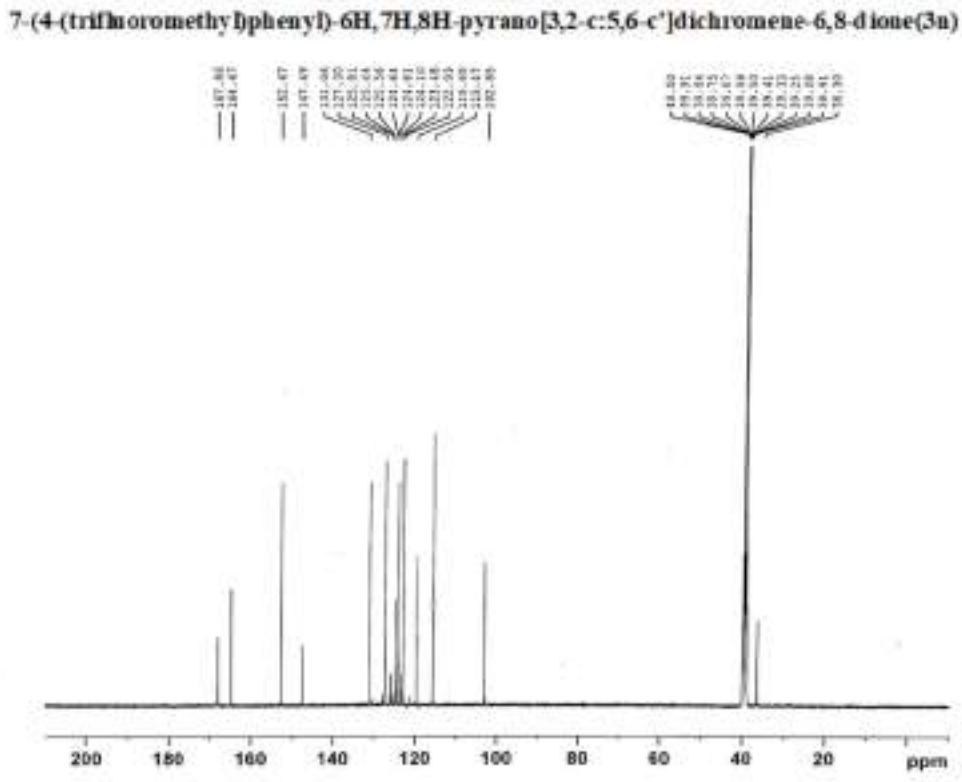


Figure III.39-^{13}C-NMR of compound 3n

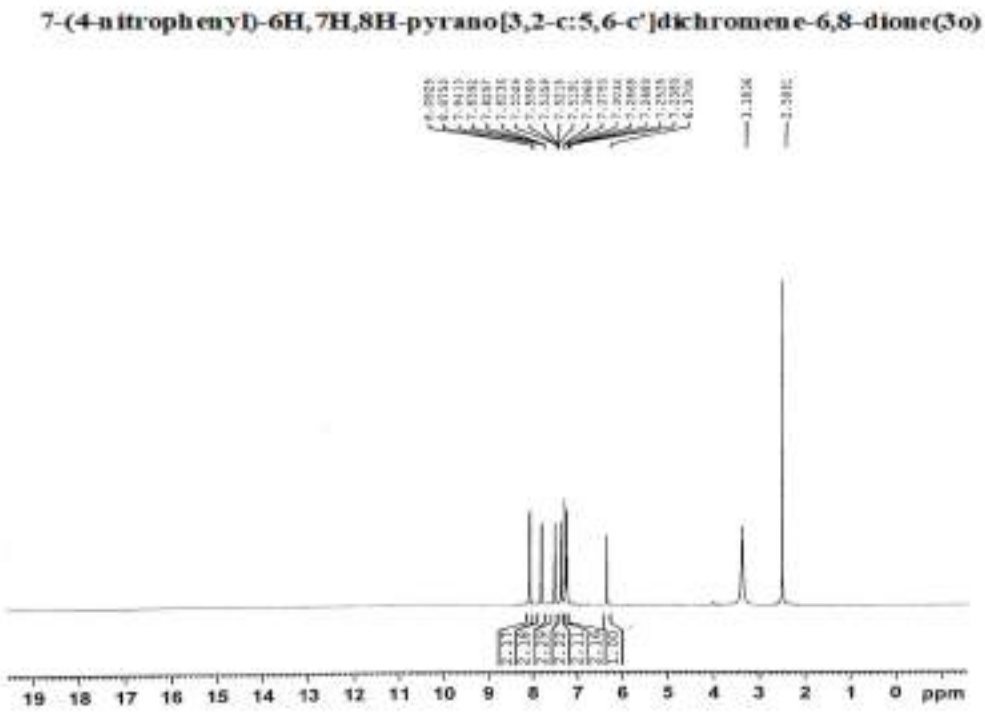


Figure III.40-^{1}H-NMR of compound 3o

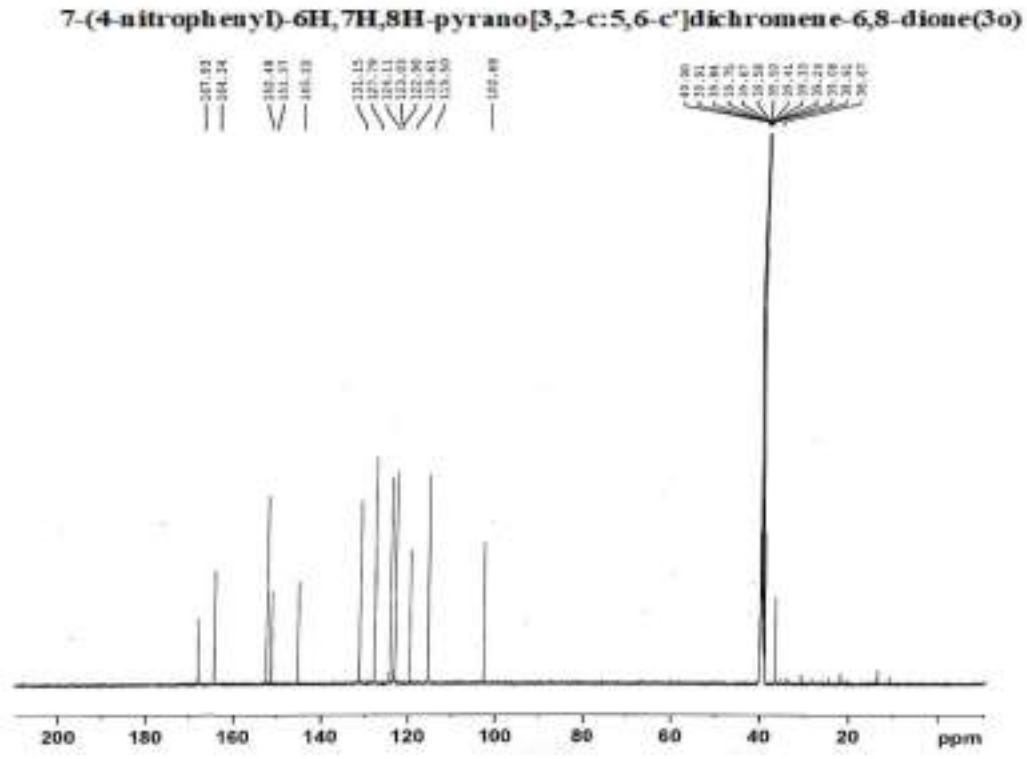


Figure III.41-^{13}C-NMR of compound 3o

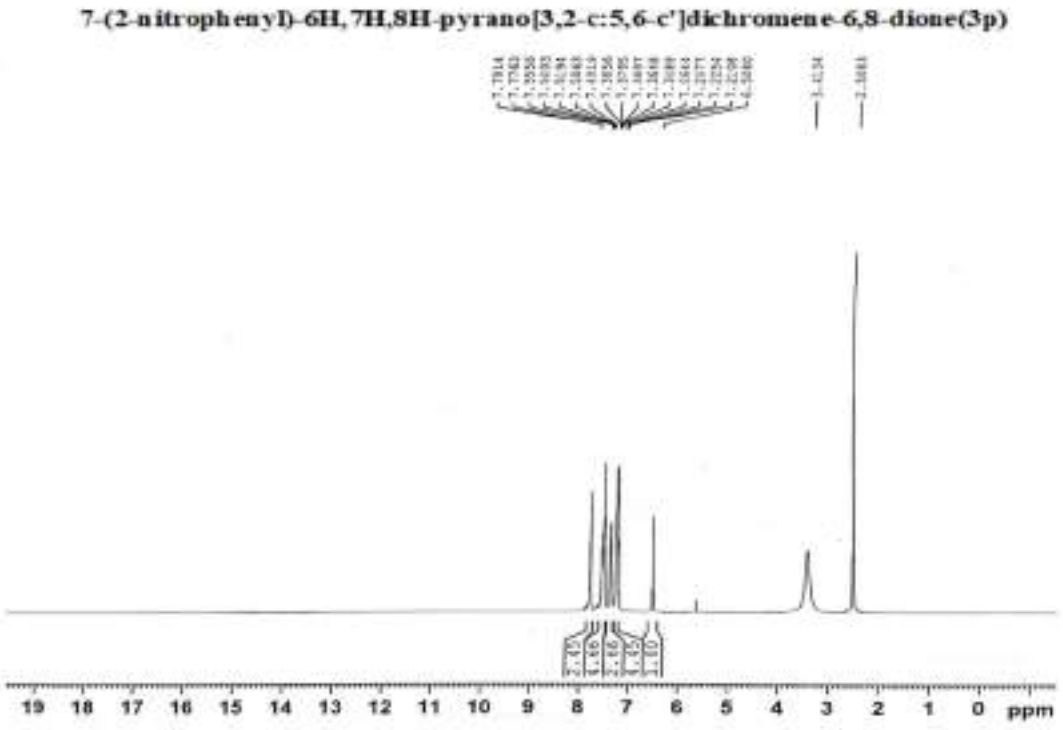


Figure III.42-^{1}H-NMR of compound 3p

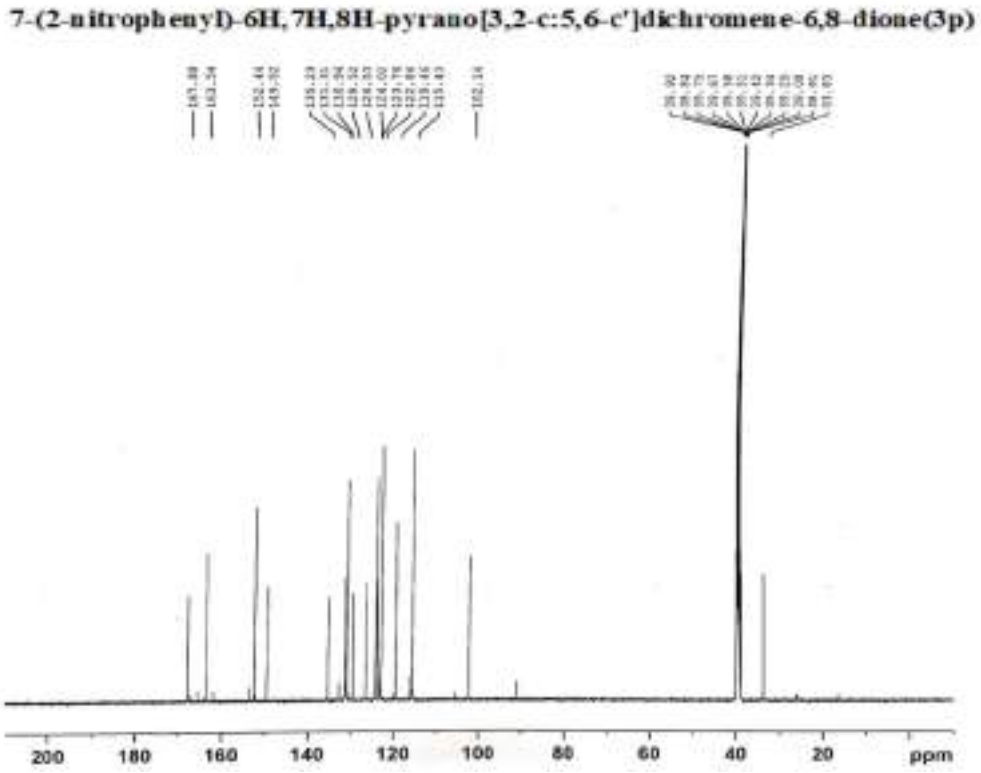
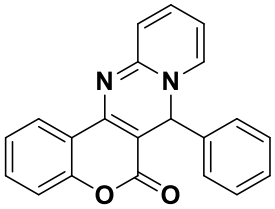


Figure III.43-^{13}C-NMR of compound 3p

III.8.A.12.g Spectral data of the compounds mentioned in scheme III.20

7-phenyl-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4a)



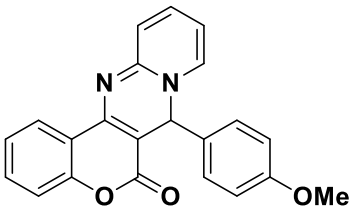
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.31(s,1H),6.81-6.83(m,1H),6.94-7.08(m,1H),7.12-7.15(m,1H),7.17-7.27(m,4H),
7.48-7.52(m,2H),7.83-7.92(m,4H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.06,103.34,112.01,113.01,115.36,119.86,122.79,124.04,124.71,126.57,127.60,130.81,136.58,142.24,143.57,152.42,154.13,164.61,167.71.

7-(4-methoxyphenyl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4b)



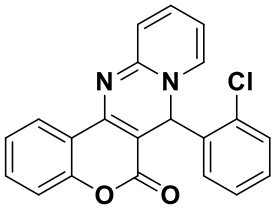
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)3.68(s,3H),6.21(s,1H),6.74(d,2H),6.99(d,2H),7.20-7.26(m,3H),7.48-7.51(m,2H),7.80(d, 1H),7.82(d,2H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)35.25,54.76,103.56,111.71,113.00,114.40,115.31,119.88,122.71,123.98,127.49,130.70,131.69,134.00,139.40,141.85,152.38,155.53,156.67,164.45,167.51.

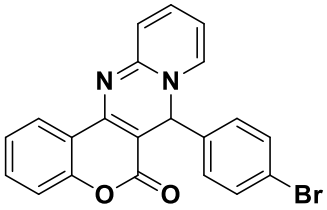
7-(2-chlorophenyl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4c)



^{1}H-NMR(500MHz,DMSO-d_6)
δ(ppm)6.10(s,1H),6.82(m.1H),6.96(d,1H)7.11-7.25(m,5H),7.42(dd,1H),7.47-7.50(m,2H),7.81-7.92(m,3H).

^{13}C-NMR(500MHz,DMSO-d_6)
δ(ppm)36.02,102.68,112.02,113.14,115.34,119.81,122.80,123.95,125.87,126.93,129.23,130.27,130.72,132.60,136.26,140.29,143.78,152.31,153.96,163.82,167.63.

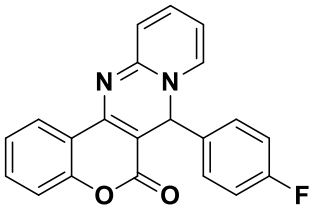
7-(4-bromophenyl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4d)



^{1}H-NMR(500MHz,DMSO-d_6)
δ(ppm)6.24(s,1H),6.80-6.83(m,1H),6.94(d,1H),7.05-7.07(dd,1H),7.21-7.27(m,3H),7.33-7.36(m,1H),7.49-7.52(m,1H),7.81-7.92(m,4H).

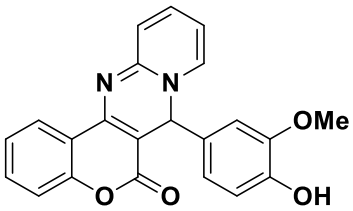
^{13}C-NMR(500MHz,DMSO-d_6)
δ(ppm)35.76,102.98,111.99,112.94,115.39,117.70,119.73,122.83,124.03,128.92,130.43,130.92,136.70,141.85,143.50,152.42,154.18,164.39,167.69.

7-(4-fluorophenyl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4e)



^{1}H-NMR(500MHz,DMSO-d_6)
δ(ppm)6.27(s,1H),6.79-82(m,1H),6.92(d,1H),6.93-7.00(m,2H),7.11-7.14(m,1H),7.21-7.27(m,3H),7.49-7.52(m,1H),7.82-7.92(m,3H).
^{13}C-NMR(500MHz,DMSO-d_6)
δ(ppm)35.51,103.31,111.99,112.78,114.08,114.25,115.38,119.80,122.82,124.04,128.21,128.27,130.88,137.06,138.13,138.15,143.28,152.42,154.37,159.10,161.00,164.47,167.70.

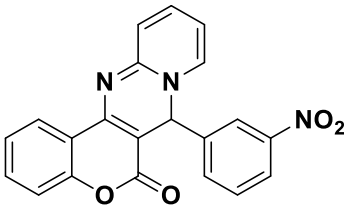
7-(4-hydroxy-3-methoxyphenyl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4f)



^{1}H-NMR(500MHz,DMSO-d_6)
δ(ppm)3.54(s,3H),6.19(s,1H),6.52-6.54(m,1H),6.58(d,1H),6.82(s,1H),6.94(d,1H),
7.21-7.25(m,3H),7.47-7.51(m,1H),7.82-7.87(m,3H),8.53(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)
δ(ppm)35.56,55.59,103.72,111.68,112.04,112.98,114.81,115.33,119.20,119.93,122.
76,124.00,130.70,133.09,136.68,143.56,144.00,146.89,152.37,154.18,164.55,167.61
.

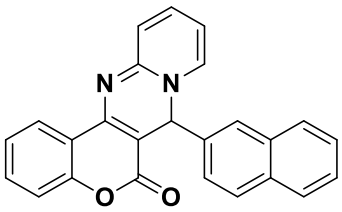
7-(3-nitrophenyl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4g)



^{1}H-NMR(500MHz,DMSO-d_6)
δ(ppm)6.40(s,1H),6.81-6.83(m,1H),6.94(d,1H),7.23-7.30(m,2H),7.49-7.61(m,3H),
7.59-7.61(m,1H),7.83-7.94(m,4H),7.99-8.01(m,1H).

^{13}C-NMR(500MHz,DMSO-d_6)
δ(ppm)36.19,102.57,111.99,113.02,115.52,119.59,120.25,121.00,123.00,124.11,129
.28,131.17,133.74,136.55,143.58,145.05,147.68,152.48,154.12,164.37,167.94.

7-(naphthalen-2-yl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4h)



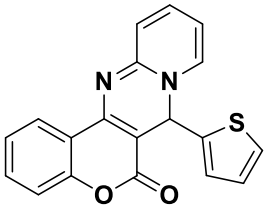
^{1}H-NMR(500MHz,DMSO-d_6)
δ(ppm)6.46(s,1H),6.76-6.79(m,1H),6.90(d,1H),7.23-7.32(m,1H),7.29-7.32(m,2H),

7.36-7.40(m,1H),7.51-7.54(m,2H),7.59(s,1H),7.70-7.72(dd,2H),7.78-7.85(m,3H),7.90(d,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.46,103.31,111.97,112.54,115.44,119.89,122.85,124.09,124.67,125.45,126.22,127.03,127.06,127.35,130.88,131.30,132.94,137.55,140.05,142.96,152.48,154.61,164.60,167.89.

7-(thiophen-2-yl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4i)



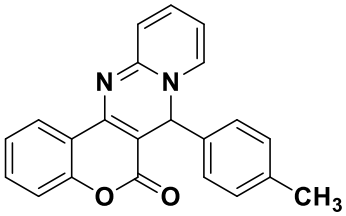
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.44(s,1H),6.60-6.61(m,1H),6.79-6.84(m,1H),6.95(d,1H),7.13-7.14(m,1H),7.22-7.26(m,3H),7.49-7.52(m,1H),7.85-7.91(m,3H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)32.84,103.64,112.01,113.08,115.40,119.79,122.54,122.86,122.93,124.13,126.02,130.99,136.41,143.69,147.99,152.39,154.04,164.05,167.86.

7-(p-tolyl)-6*H*,7*H*-chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidin-6-one(4j)



^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)2.21(s,3H),6.21(s,1H),6.78-6.80(m,1H),6.88(d,1H),6.94-6.98(m,3H),7.20-7.25(m,3H),7.47-7.51(m,1H),7.79-7.84(m,2H),7.91-7.92(m,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)20.39,35.65,103.42,111.96,112.34,115.30,119.87,122.70,123.98,126.46,128.15,130.70,133.32,137.97,139.14,142.76,152.38,154.80,164.42,167.50.

III.8.A.12.h Sanned copies of compounds mentioned in scheme III.20

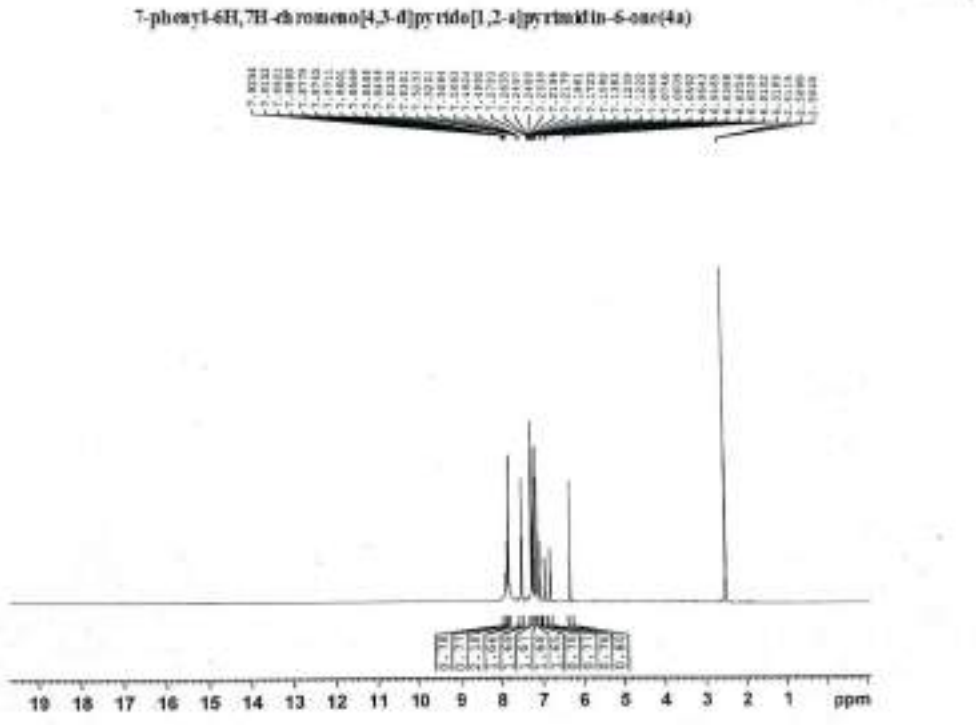


Figure III.44-^{1}H-NMR of compound 4a

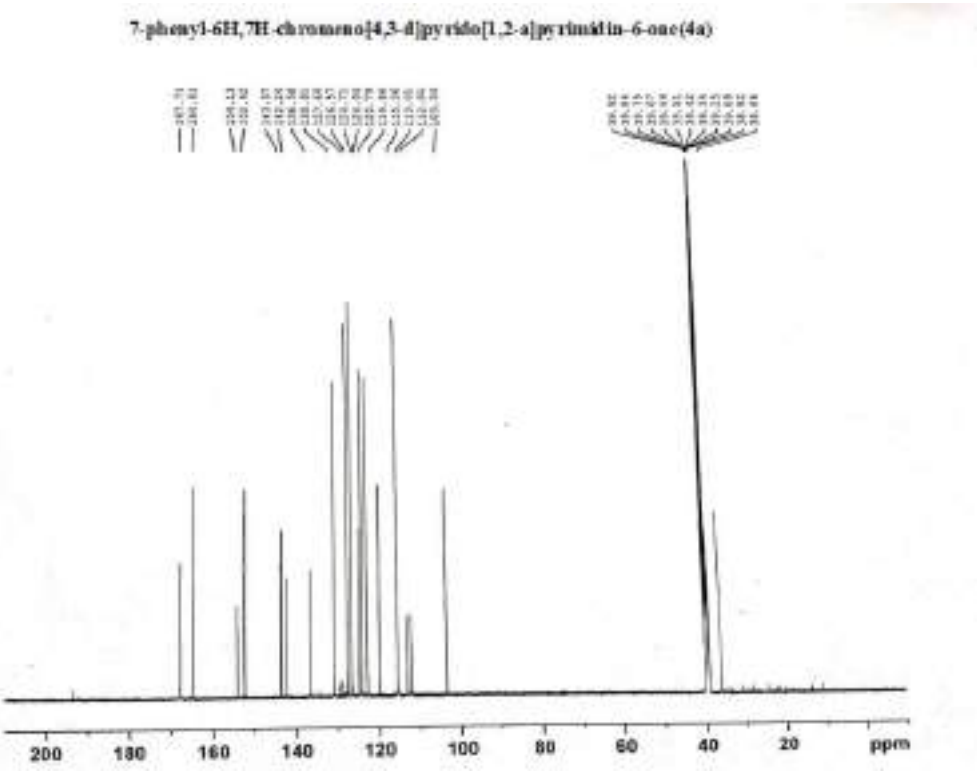


Figure III.45-^{13}C-NMR of compound 4a

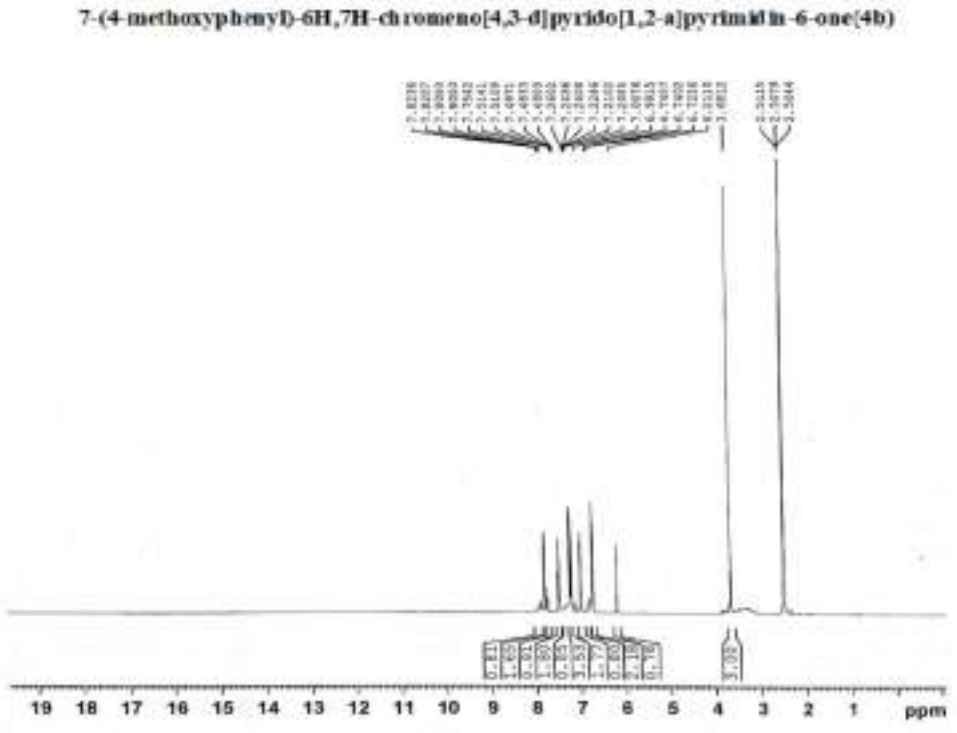


Figure III.46-^{1}H-NMR of compound 4b

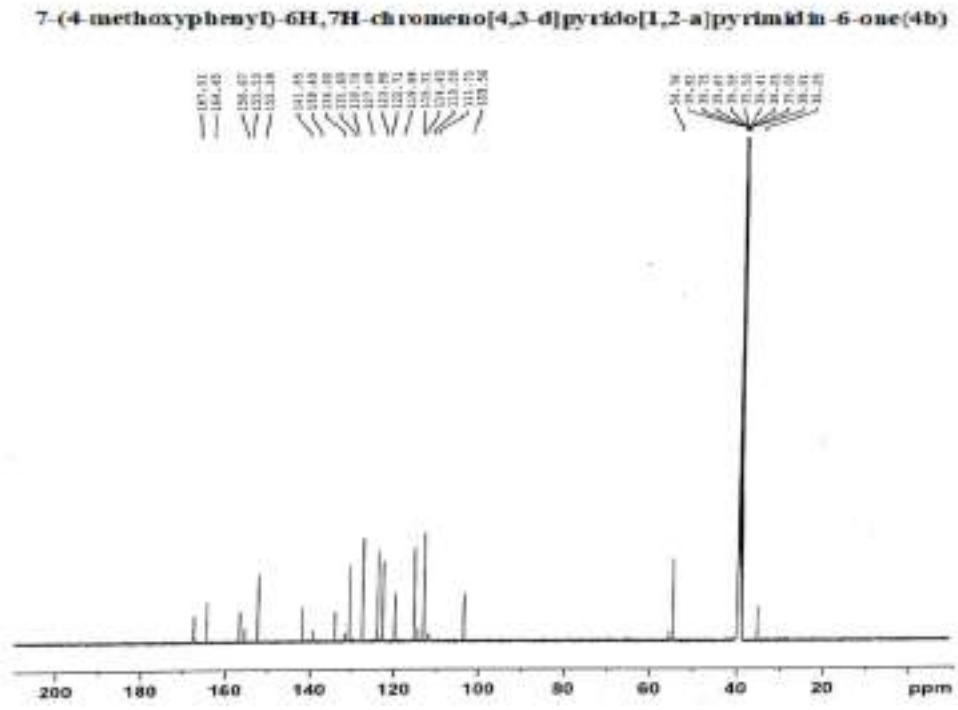


Figure III.47-^{13}C-NMR of compound 4b

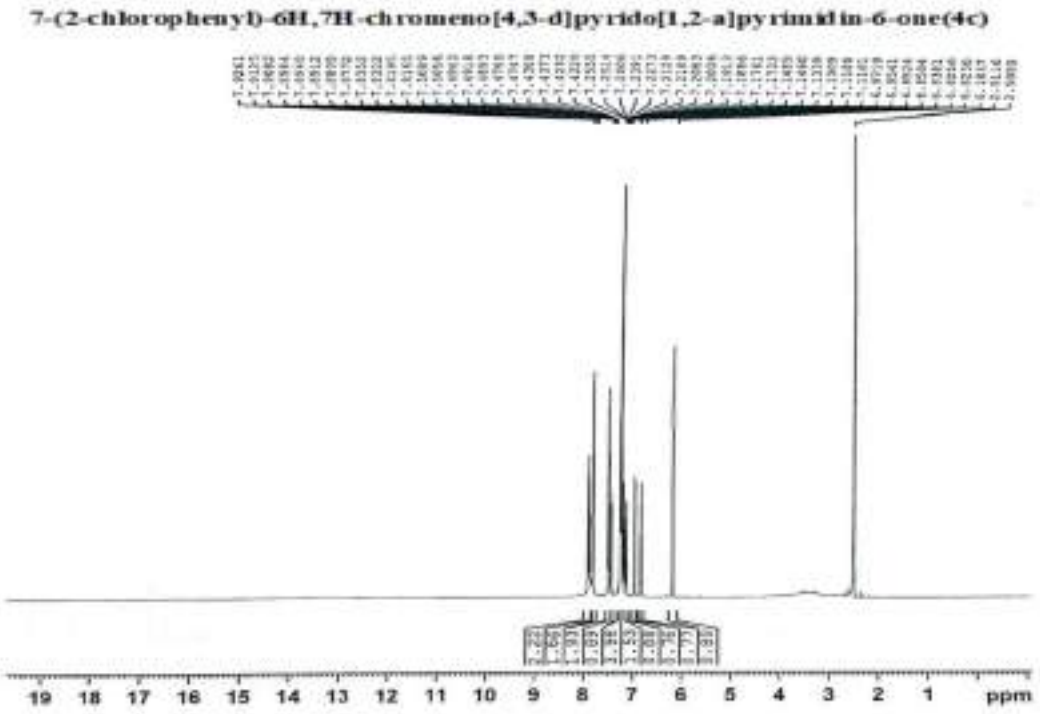


Figure III.48-^{1}H-NMR of compound 4c

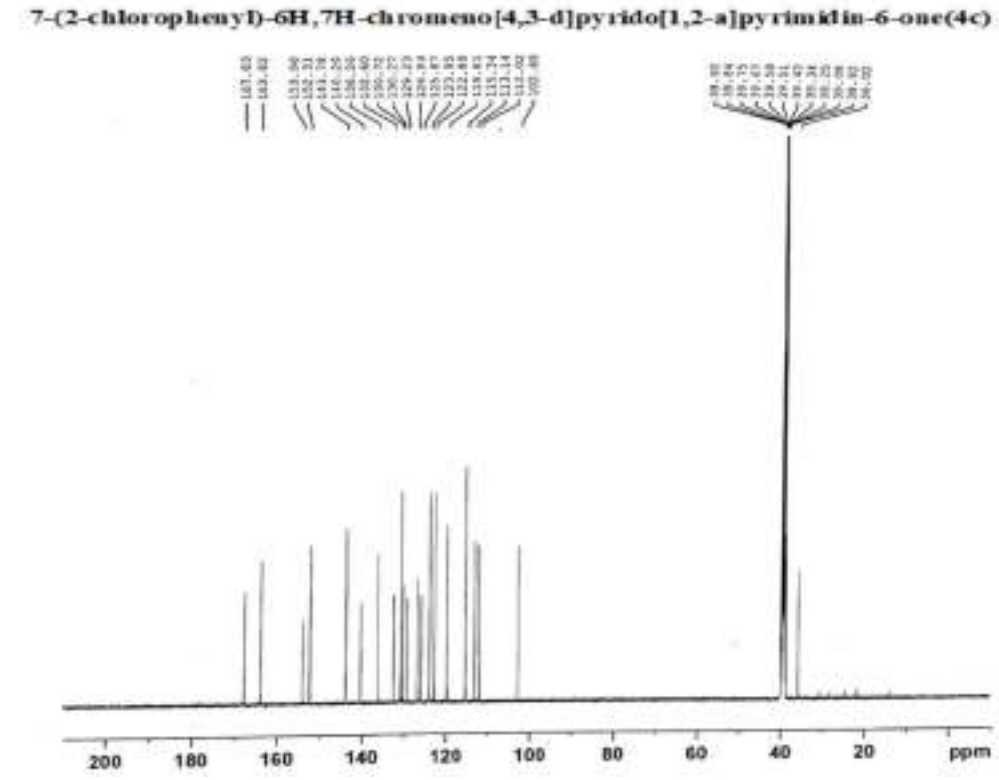


Figure III.49-^{13}C-NMR of compound 4c

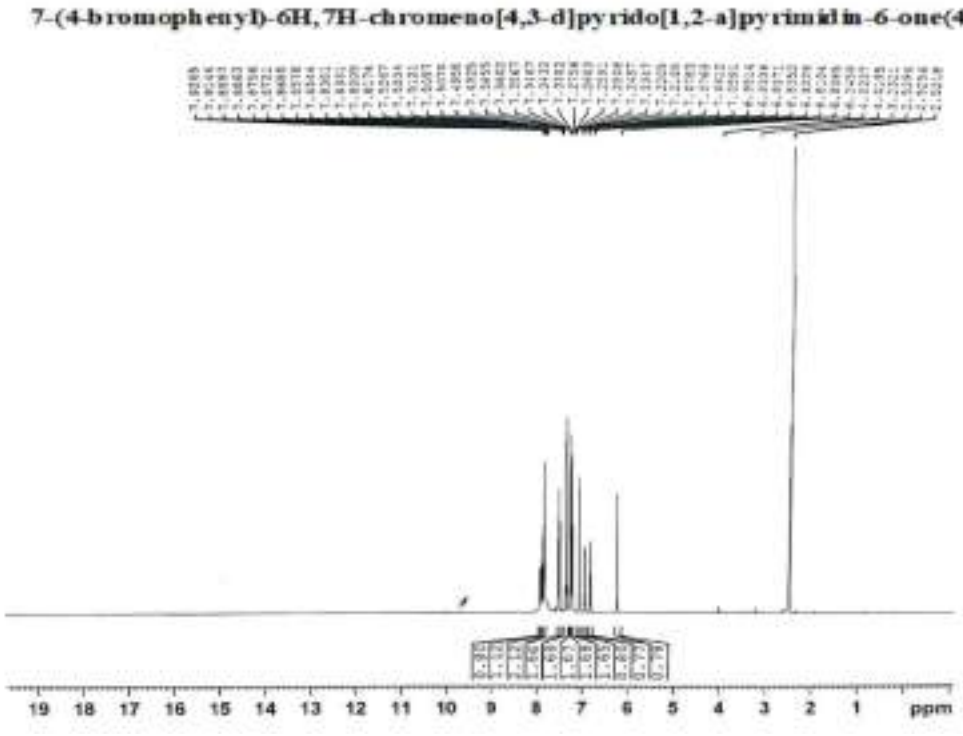


Figure III.50-^{1}H-NMR of compound 4d

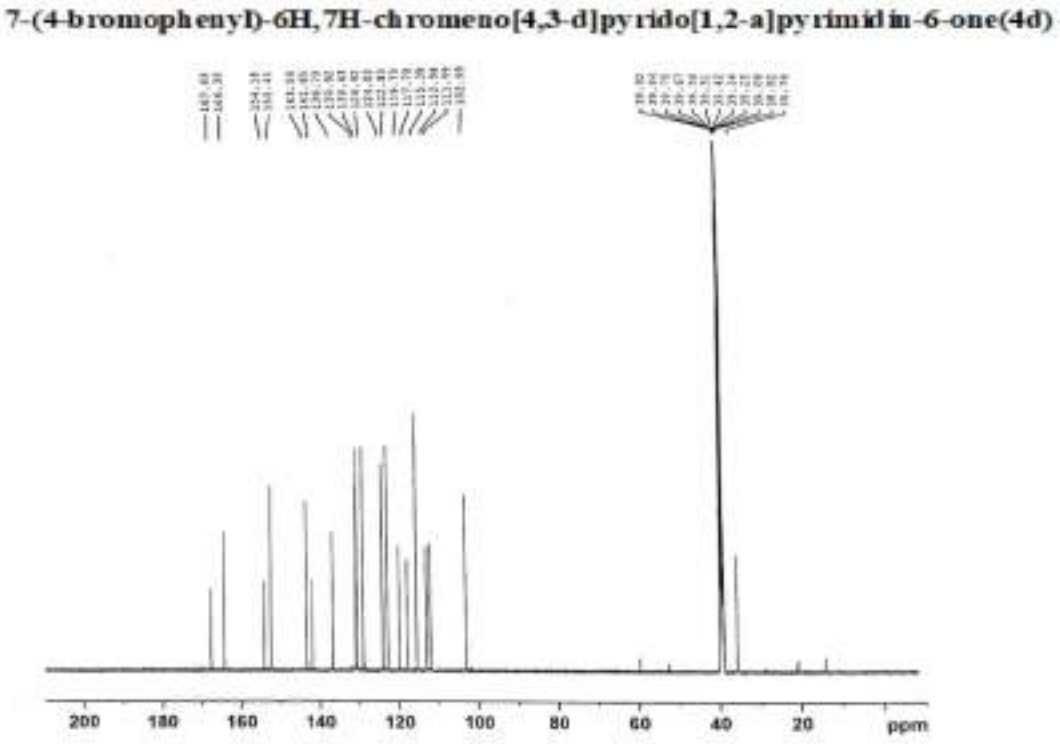


Figure III.51-^{13}C-NMR of compound 4d

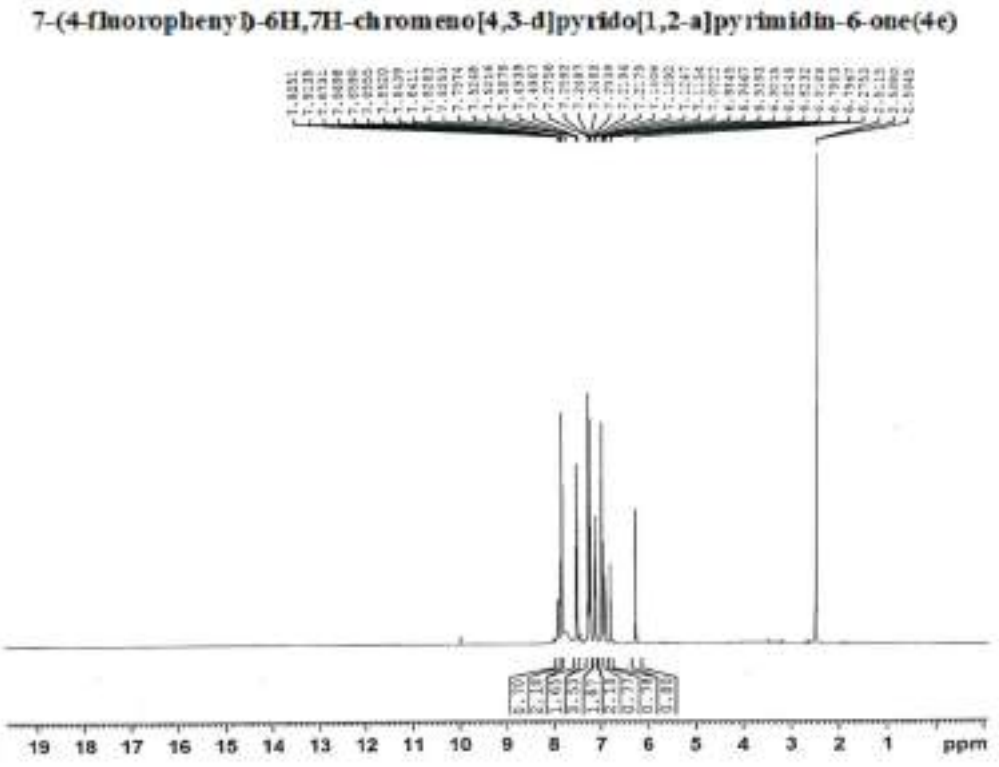


Figure III.52-^{1}H-NMR of compound 4e

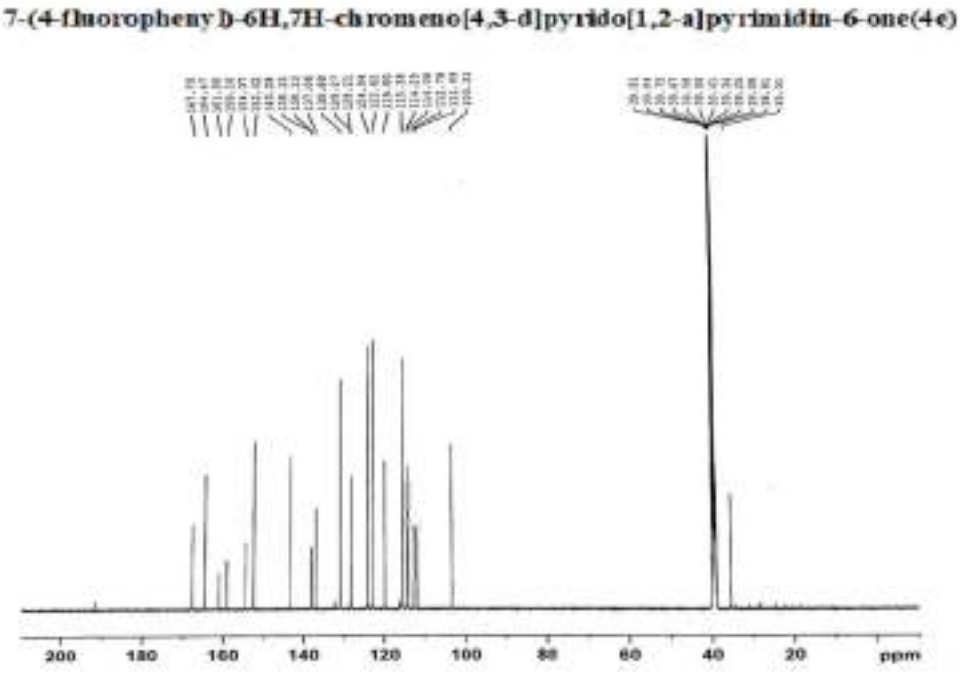


Figure III.53-^{13}C-NMR of compound 4e

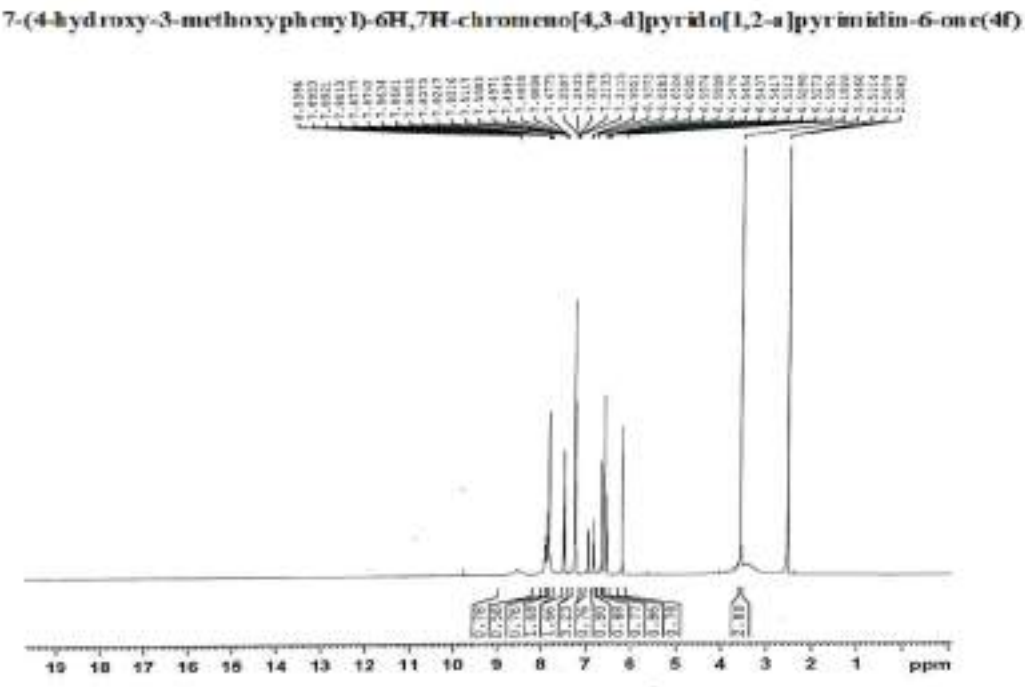


Figure III.54-^{1}H-NMR of compound 4f

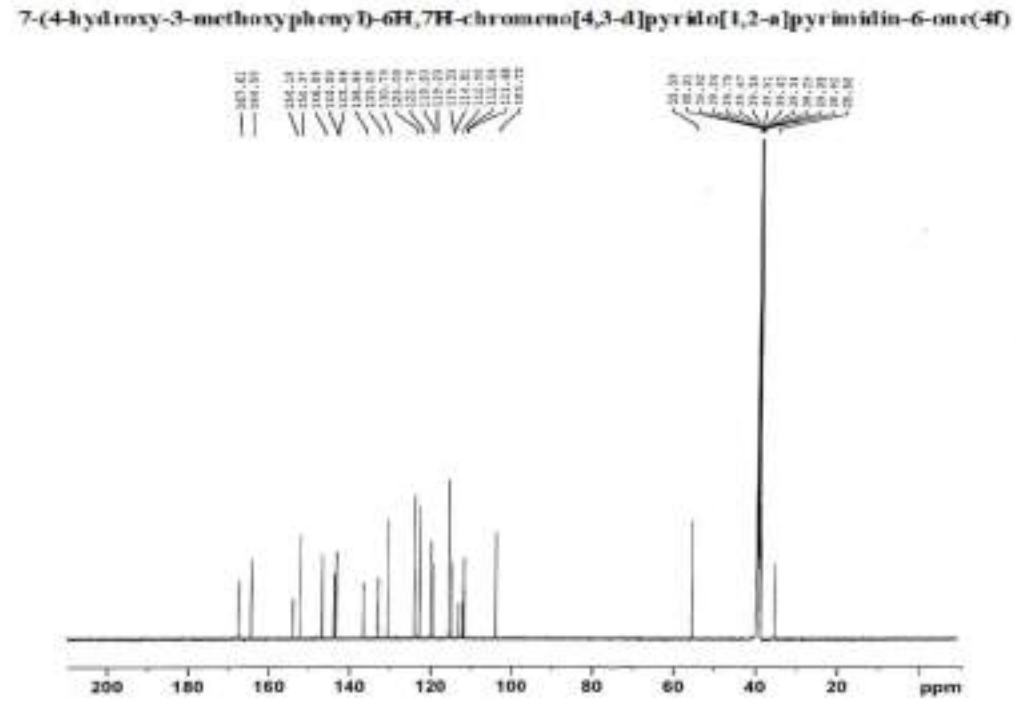


Figure III.55-^{13}C-NMR of compound 4f

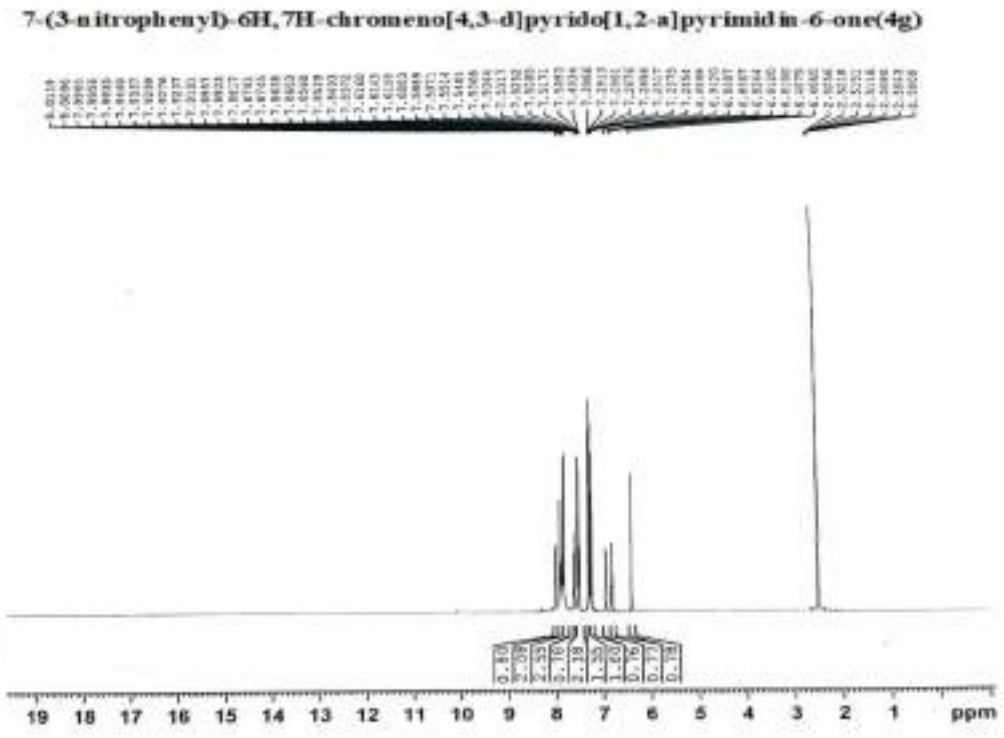


Figure III.56-^{1}H-NMR of compound 4g

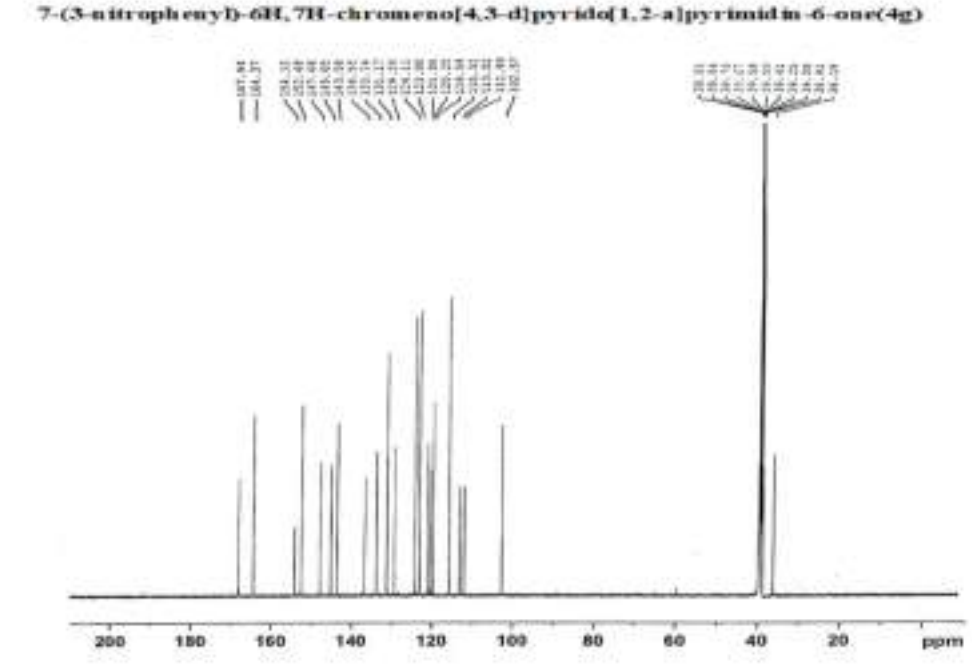


Figure III.57-^{13}C-NMR of compound 4g

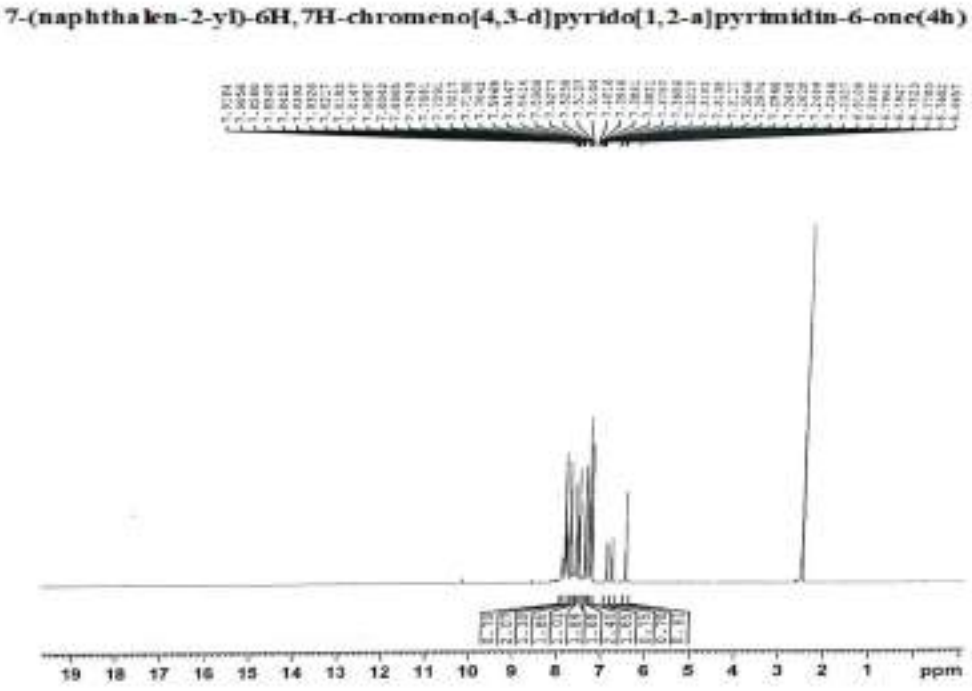


Figure III.58-^{1}H-NMR of compound 4h

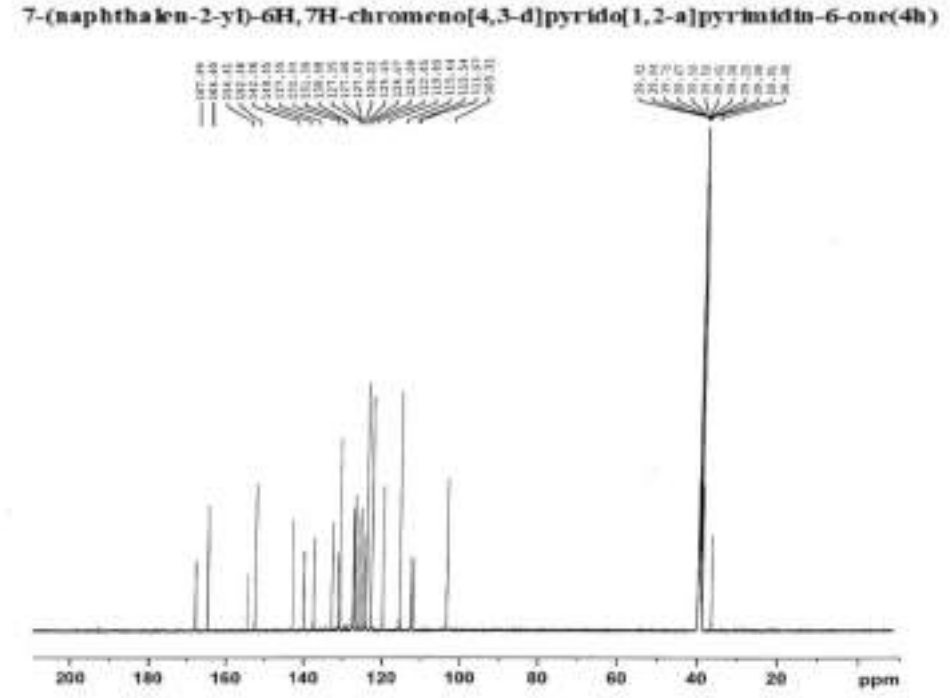


Figure III.59-^{13}C-NMR of compound 4h

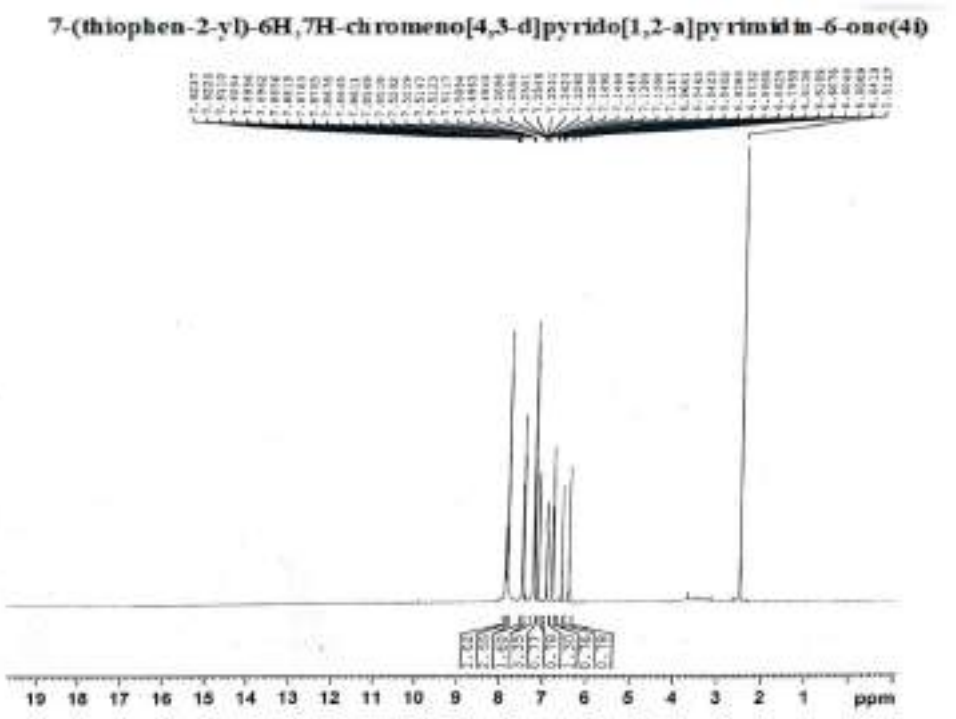


Figure III.60-^{1}H-NMR of compound 4i

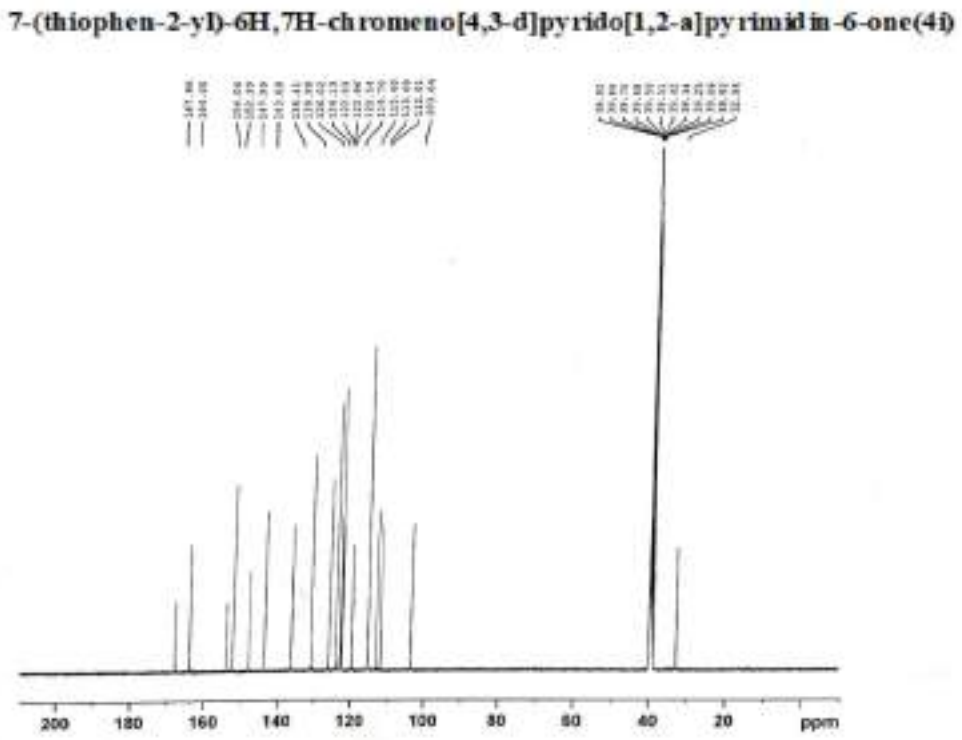


Figure III.61-^{13}C-NMR of compound 4i

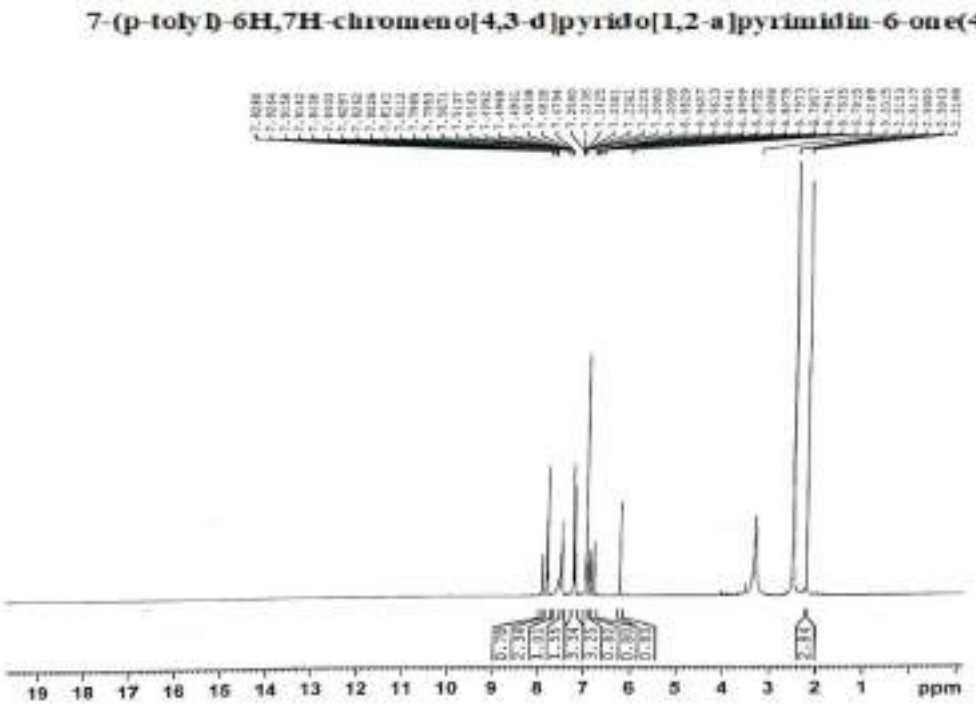


Figure III.62-^{1}H-NMR of compound 4j

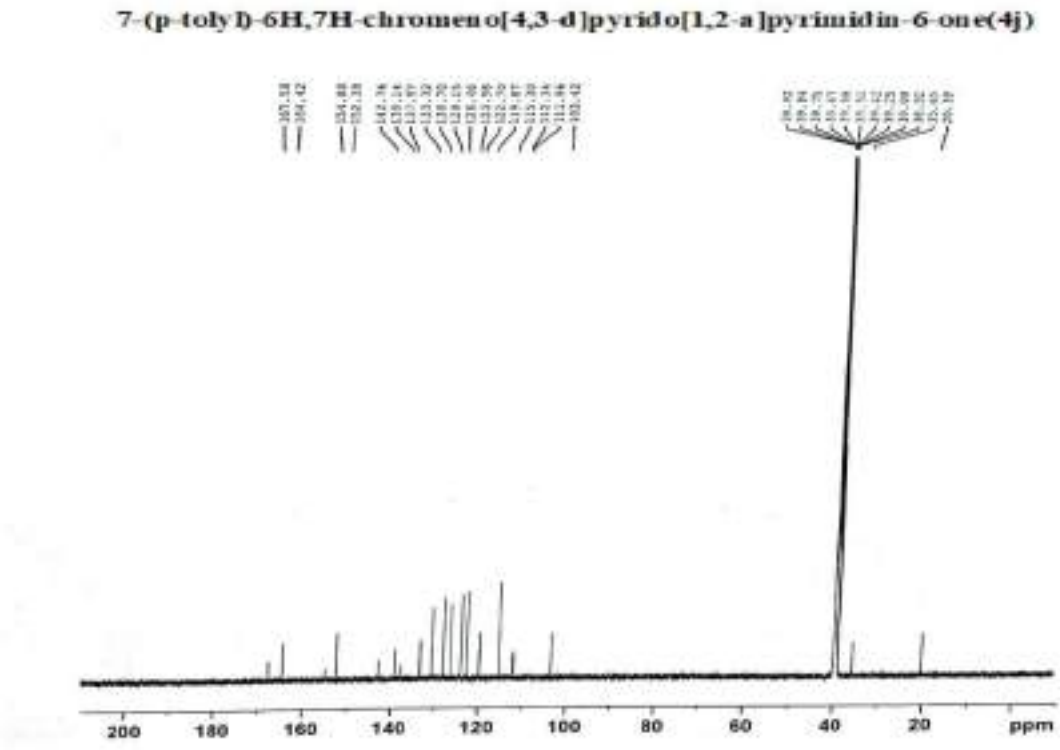


Figure III.63-^{13}C-NMR of compound 4j

III.7.A.12.i EDX data of sulphonated rice husk (SRH) and rice husk(RH)

EDX data of SRH and RH respectively are given below-

Project 1

1/21/2019 2:26:03 PM

Spectrum processing :

Peaks possibly omitted : 8.043, 8.626 keV

Processing option : All elements analyzed (Normalised)

Number of iterations = 6

Standard :

C CaCO3 1-Jun-1999 12:00 AM

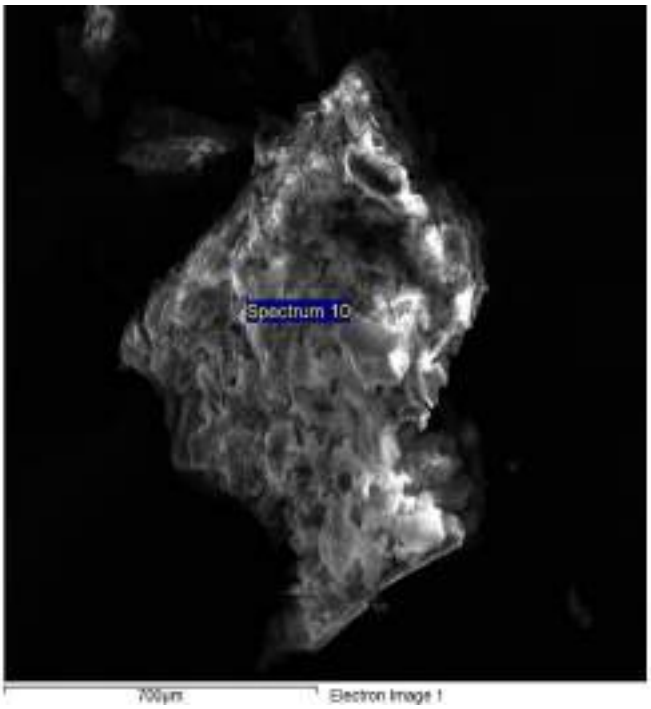
O SiO2 1-Jun-1999 12:00 AM

Si SiO2 1-Jun-1999 12:00 AM

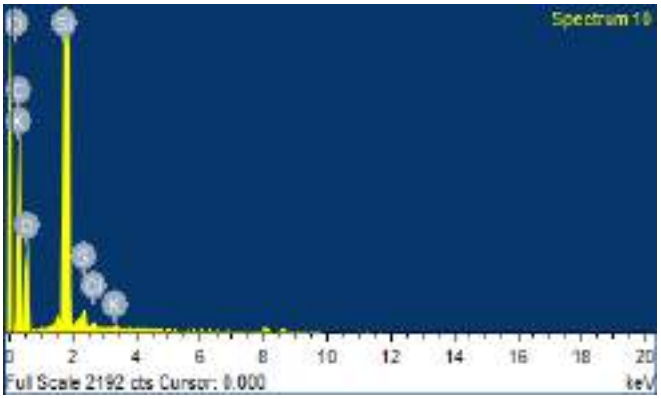
S FeS2 1-Jun-1999 12:00 AM

Cl KCl 1-Jun-1999 12:00 AM

K MAD-10 Feldspar 1-Jun-1999 12:00 AM



Element	App Conc.	Intensity Corrn.	Weight%	Weight% Sigma	Atomic%
C K	71.39	0.4111	57.29	0.88	68.73
O K	24.20	0.3287	24.30	0.70	21.88
Si K	50.69	0.9435	17.73	0.37	9.09



Comment:sourav

S K	0.96	0.7957	0.40	0.04	0.18
Cl K	0.40	0.7250	0.18	0.03	0.07
K K	0.30	0.9905	0.10	0.03	0.04

Totals	100.00

Project 1

1/21/2019 2:13:48 PM

Spectrum processing :

Peaks possibly omitted : 8.036, 8.640, 8.905 keV

Processing option : All elements analyzed (Normalised)

Number of iterations = 5

Standard :

C CaCO3 1-Jun-1999 12:00 AM

O SiO2 1-Jun-1999 12:00 AM

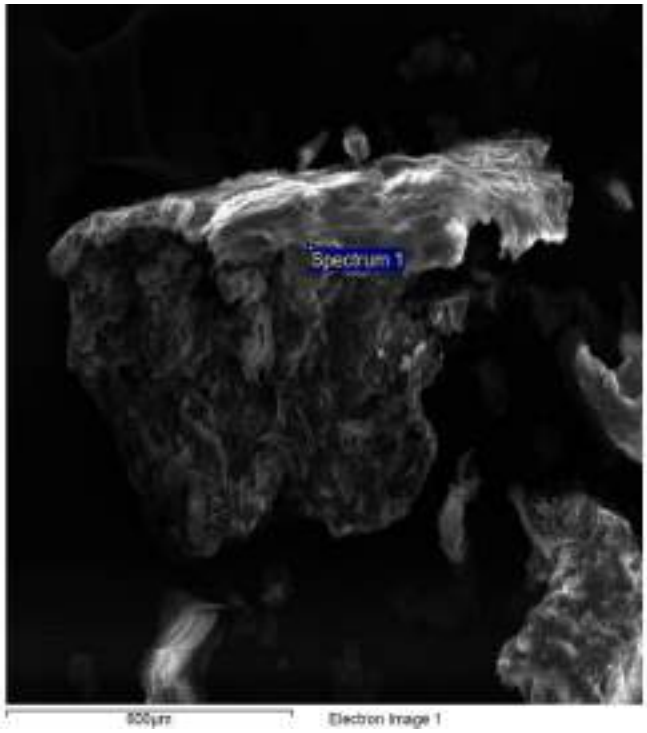
Mg MgO 1-Jun-1999 12:00 AM

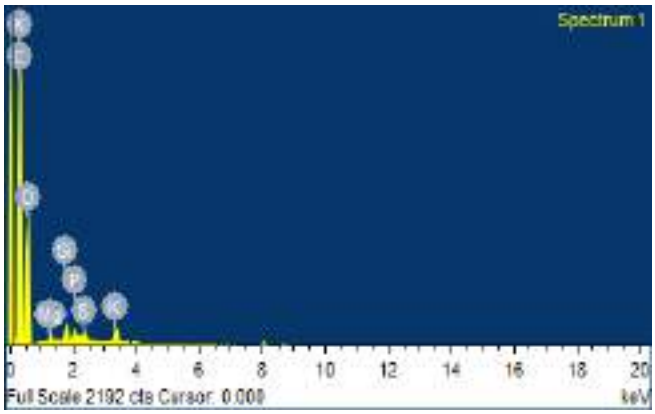
Si SiO2 1-Jun-1999 12:00 AM

P GaP 1-Jun-1999 12:00 AM

S FeS2 1-Jun-1999 12:00 AM

K MAD-10 Feldspar 1-Jun-1999 12:00 AM





Element	App Conc.	Intensity Corrn.	Weight%	Weight% Sigma	Atomic%
C K	122.06	1.0292	55.96	0.82	63.40
O K	34.95	0.3931	41.95	0.81	35.68

Comment:sourav

Mg K	0.42	0.6145	0.32	0.05	0.18
Si K	0.87	0.8459	0.48	0.04	0.23

P K	0.92	1.2546	0.35	0.05	0.15
S K	0.69	0.9358	0.35	0.04	0.15
K K	1.32	1.0579	0.59	0.04	0.20
Totals			100.00		

III.9 References

References are given in BIBLIOGRAPHY under Chapter III.

CHAPTER IV

A COLLECTIVE LABORATORY STUDIES ON ONE POT MULTI-COMPONENT SYNTHESIS OF A FEW VARIETIES OF HETEROCYCLIC COMPOUNDS FOLLOWING GREENER APPROACH USING RICE HUSK BASED GREENER CATALYST

IV. 1 Introduction

Aromatic heterocyclic compounds always have a special importance over other class of organic compounds from the very fast age of its discovery. They got the importance when scientists observed their biological activity in various cell related problems and its ability to eradicate viral, fungal and microbial activities. They especially act as drugs for their efficiency in curing various diseases and health problems. They act as inhibitor in various disordered enzyme activities which are generally responsible for the particular diseases in animals and as well as human beings. There are various kinds of aromatic compounds reported previously in literature and among them few types of bicyclic and tricyclic aromatic compounds have got the keen interest from the rearchers due to its significant role in medicinal chemistry. Due to the low natural abundance of some kinds of heterocyclic compounds and for the future interest of new drug discovery, scientists are always in work to invent new types of heterocyclic molecules. Coumarin derivatives, hexahydroqunolines derivatives, and tetrahydroterazoloqunazolines, in this context are observed as an important class of heterocyclic compounds which contain active molecular parts to show biological activities. Coumarins have a basic flavinoid like skeleton which

constitutes a natural privileged scaffold and their analogues have significant application in functional material chemistry for their excellent fluorescent properties and thus used up as molecular probes in cell biology research.[1-2] Dihydro-dichromeno-pyridine-6,8-dione derivatives also contain coumarin scaffolds which are considered as one of the important fused ring heterocyclic bioactive compounds and thus a varity of scientific research have been made towards the targeted synthesis coumarin analogues to find their significant applications in the field of medicinal chemistry. Coumarins can be derived also from natural resources and scaffold can be used extensively for the preparation of derivatives and their derivatives have no doubt a broad range of biological activities such as anti-fungal,[3] anti-inflammatory,[4] anti-tubercular activities,[5] antiviral,[6] anticancer,[7] etc. A number of fused ring coumarin derivatives have been obtained by following conventional techniques using hazardous chemicals [8] and thus a new sustainable development in synthetic procedure is needed for the synthesis of dihydro-dichromeno-pyridine-6,8-dione derivatives as our targeted product.

Another important class of heterocyclic compound is fused ring tetrazole derivatives and tetrazole fused bicyclo aromatic compounds

have prominent biological activity in various biological aspect. Tetrahydrotetrazolo[1,5-*a*] quinazolinones falls in the category of fused ring tetrazole derivatives and they are structurally analogous with tetrazolopyrimidines. Tetrazole fused pyrimidines have broad range of biological properties, including antimicrobial,[9] antituberculosis[10] and antidepressant,[11] activities. There are a few examples of methods reported for the synthesis of tetrazolopyrimidines which involve initial synthesis of base catalysed chalcones followed by cyclocondensation reaction with 5-aminotetrazole. Wang and co-workers had reported also the synthesis of dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-a] quinazolinones catalysed via heavy metal ion Hg^{2+} [12] moreover a variety of catalysts like Iodine,[13] TBBDA,[14] [bmim+][BF_4^-],[15] acetic acid,[16] di-isopropylammonium trifluoroacetate [17] had been used to mediate the reaction. It remains a challenging task to develop a greener route for the synthesis of a varity of tetrahydrotetrazolo[1,5-a]quinazolinones and isolation and purification of final products and therefore, we intended to develop an sustainable and convenient synthetic route for the synthesis of tetrahydrotetrazolo[1,5-*a*]quinazolinones.

Quinolines and substituted quinolines and quinolinones are also important class of heterocycles which have a wide variety of pharmaceutical and agrochemical activities and they are found as prominent building blocks in various natural products and possess considerable interest due to their broad range of bio-activities such as antibacterial, antifungal, antioxidant, anticancer, anticonvulsant, and antiviral activity [18-22]. Substituted quinolines, quinolinones, tetrahydroquinolines, hexahydroquinolines serve as chemotherapeutic agents also [23-25] and many heterocyclic [26] compounds containing the quinoline nucleus display anti-inflammatory activity and they serve as antagonist inhibitors [27]. Quinolines with 1,4-Dihydropyridine (DHP) nucleus have been found to be efficient in cardiovascular diseases as calcium channel blockers also [28-29]. Due to these collective importances many recent research works are still on progress considering this heterocyclic motif [30-31]. 2,4-diarylhexahydro-quinoline-5-ones in this regard got our interest and it was observed that several homogeneous and heterogeneous catalysts have been employed for their synthesis. A number of methods have been reported such as $HClO_4$-SiO_2, [32] ionic liquid [33], DMF [34], microwave irradiation,[35] but, however, for the synthesis of 2,4-diaryl

hexahydroquinoline-5-ones sustainable and greener procedures have not applied before for the future environmental aspect of large scale industrial synthesis.

One pot multi-component reactions (MCRs) can also give strong support by following the basic principles of “Green Chemistry” for the synthesis of those three types of heterocycles mentioned above. And one-pot MCRs are considered as sustainable technique for making the whole synthetic process smart, energy saving and time consuming. A large number of complex molecules have been synthesized by one-pot MCRs and there exist a considerable importance when heterogeneous catalyst additionally selected excluding the concept of multistep method. Keeping the catalytic activity in one side, heterogeneous catalysts have more importance over homogeneous one in this regard because of easy separation and recovery from the reaction mixture and also for their active surface area where the reaction is conceived to be happened. [36] There are so many reported heterogeneous catalysts developed for the successful synthesis of various multi-component reactions but the use of natural resources as heterogeneous catalyst have attracted us very much and we considered rice husk as prominent greener solid support for catalysis. Rice husk is very common agricultural by-product highly

abundant in south asian countries. It contains cellulose, hemicellulose, lignocellulosic material along with high silica content. [37-38] It is an agricultural waste material and has utility in commercial purpose such as production of cattle food, rice-bran oil etc. A few characteristics like light weight, high external surface area and porosity, economic advantage, non-toxicity, high abundance, and bio-degradability have attracted us to use it as a good bio-derived heterogeneous catalyst for the synthesis of heterocyclic compounds in a suitable convenient manner.[39] Here in this work, we used up the rice husk based heterogeneous catalyst and report the synthesis of dihydro-dichromeno-pyridine-6,8-dione, tetrahydrotetrazolo[5,1-b]quinazolinone and 2,4-diaryl hexahydroquinoline-5-one derivatives using aromatic aldehydes as primary reactant using rice husk based greener catalyst.

IV.2 1,4-dihydropyridine

1,4-dihydropyridines are a class of heterocyclic compound having low molecular weight having both commercial and biolological importance. In 1882, the synthesis of a 1,4-dihydropyridines are three component cyclocondensation reaction of acetoacetic ester, aldehyde and ammonia and after that there several methods of synthesis of 1,4-dihydropyridine

skeleton are innovated by researchers using various novel catalysts (**Figure IV.1**).[40]

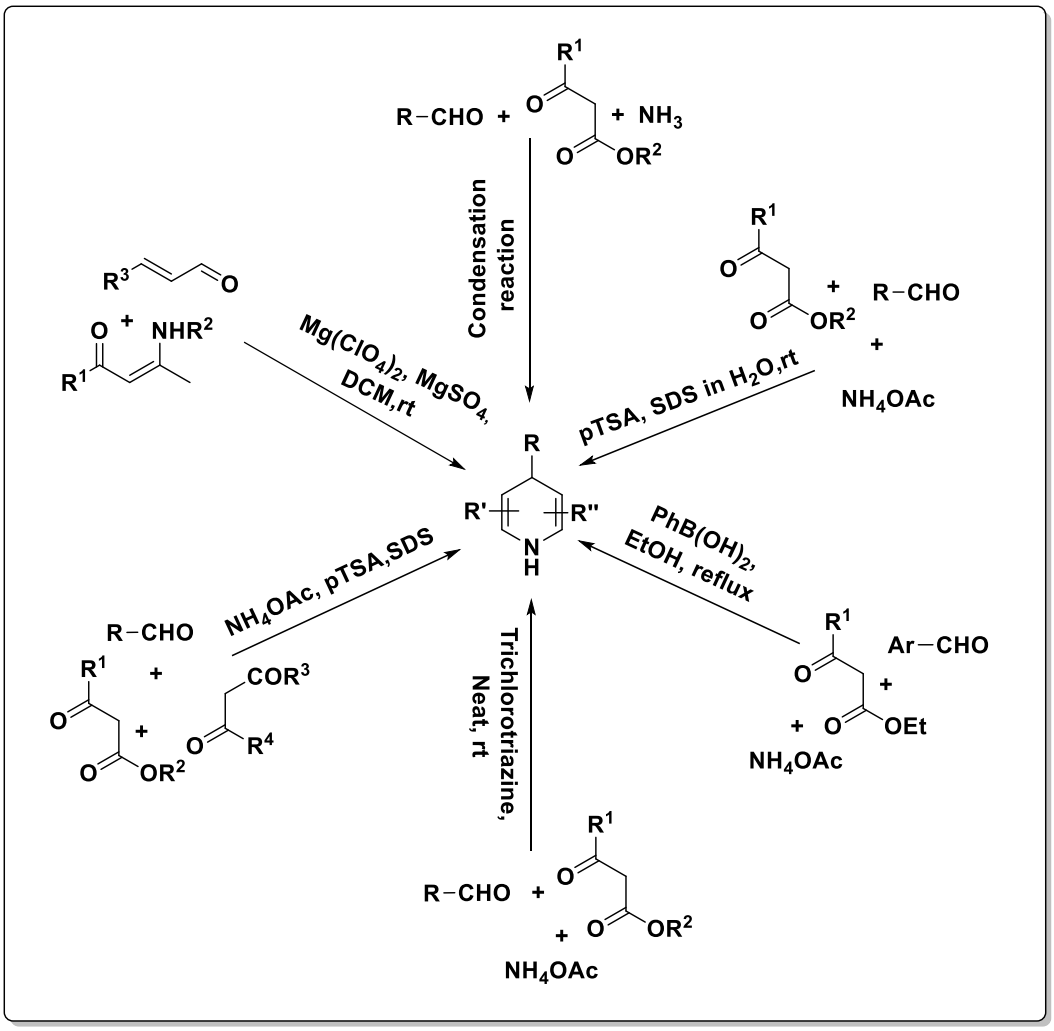


Figure IV. 1 Diverse synthetic routes for the synthesis of 1,4-dihydropyridine structures

Dihydro-chromeno-pyridines are important class of heterocyclic compounds containing a 1,4-dihydropyridine ring fused with chromene moiety. They are treated as polycyclic 1,4-dihydropyridines and as they also belongs to the class of 1,4-dihydropyridine family they have a broad

range of biological importance due to the presence of both dihydropyridine ring and fused chromene ring in it.[41-42] Dihydro-chromeno-pyridines may contain two chromene rings fused with 1,4-dihydropyridine ring or it may contain one chromene ring fused with 1,4-dihydropyridine ring. Inspite of having several synthetic procedures of skeletons of 1,4-dihydropyridines there are few reported synthetic procedure for the synthesis of dihydro-chromeno-pyridines skeleton using various catalysts.

IV.3 Biological importance of 1,4-dihydropyridines and dihyro-chromeno-pyridines

Due to the presence of both chromene moiety and dihydropyridine rings these dihydro-chromeno-pyridine molecules have both biological and pharmaceutical importance.(Figure IV.2) Due to the presence of two bioactive chromene and dihydropyridine moieties these types of bioactive compounds largely exhibit diverse activities such as antimicrobial, anticancer, antitumor, antimalarial, and antidiarrheal effects.[43-54]

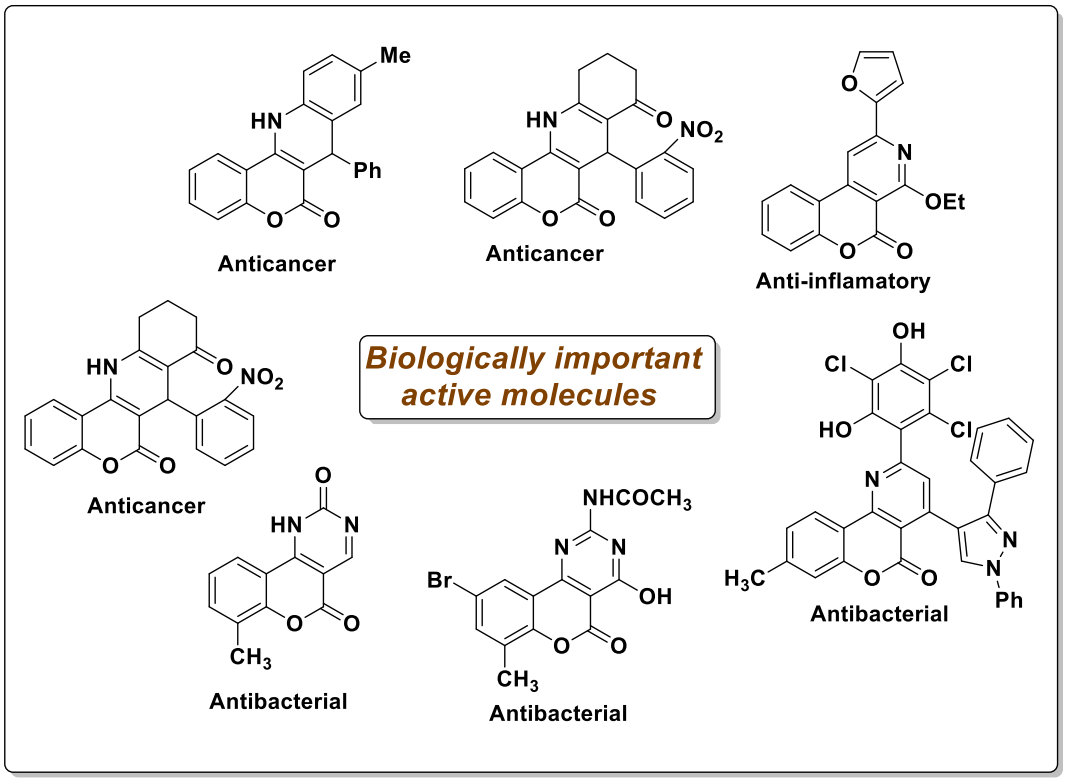
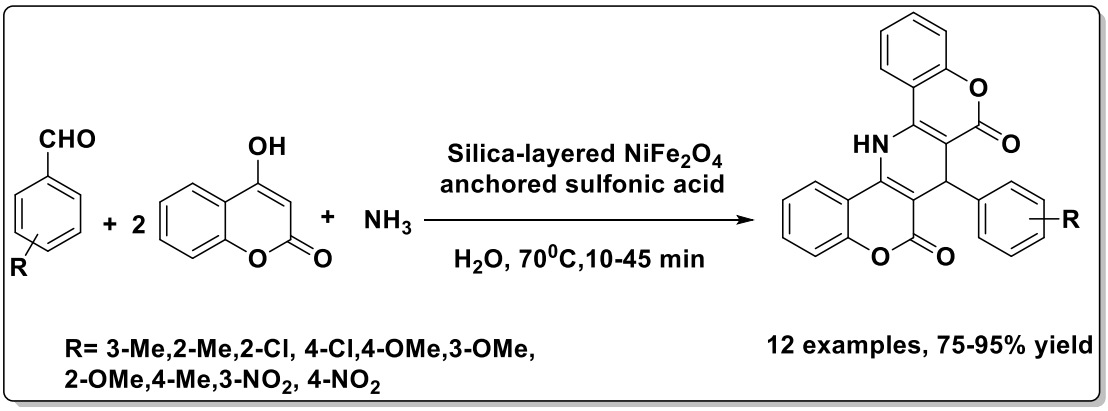


Figure IV.2 Some important pharmaceutically active drug molecule

By doing studies on works in various journals related to dihydropyridines, chromes and chromenopyridines and their derivatives and taking biological importances of dihydropyridines, chromes and chromenopyridines and their derivatives in mind, in this following part of the Chapter IV, it has been focused on the dihydro-dichromeno-pyridine-6,8-diones derivatives in a new and convenient manner using cheap laboratory chemicals.

IV.4 Previous works on Synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives

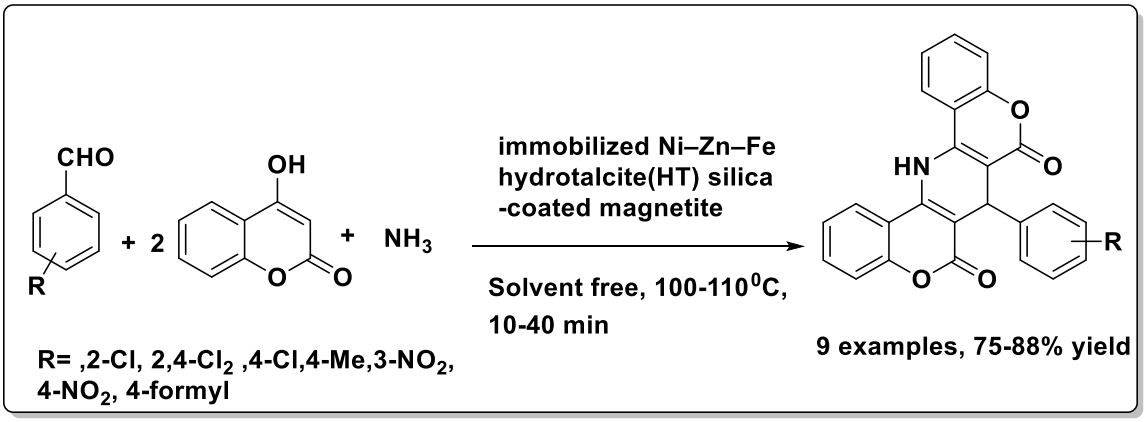
In 2017, Zeynizadeh *et al.* reported the synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives via one-pot condensation reaction of 1,3-diketones (ethyl acetoacetate or 4-hydroxycoumarin), aromatic aldehydes and aqueous ammonia in H_2O (70^0C) as a green solvent by using silica-layered nickel ferrite, ($NiFe_2O_4@SiO_2@SO_3H$) with excellent yield. (**Scheme IV.1**). [55]



Scheme IV.1 One pot synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives Zeynizadeh *et al.*

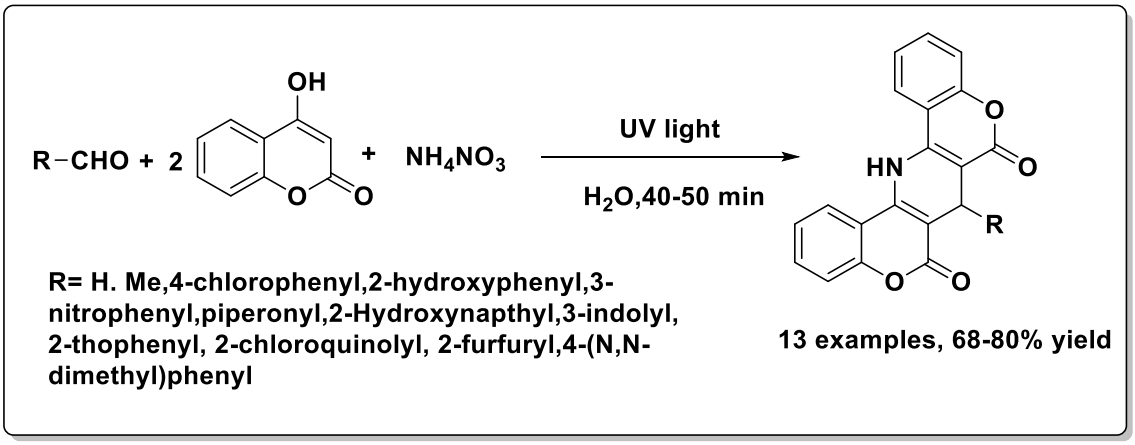
In 2019, Gilanizadeh *et al*. had reported an efcient ecofriendly approach has been developed for one-pot multicomponent synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives by Tandem condensation of aromatic aldehydes, 4-hydroxycoumarin, and

ammonium acetate by using heterogeneous Fe_3O_4@SiO_2@Ni–Zn–Fe hydrotalcite catalyst under solvent-free conditions (**Scheme IV.2**). [56]



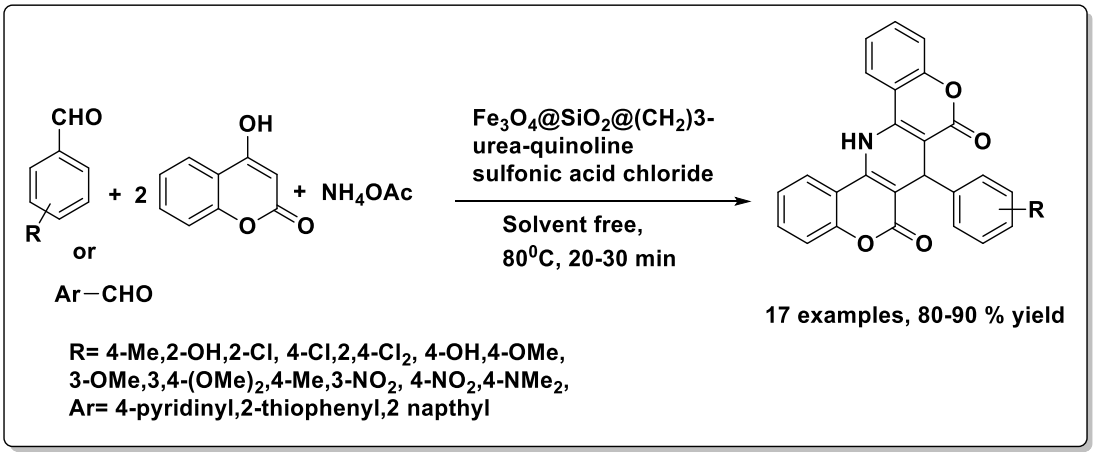
Scheme IV.2 One pot synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives Gilanizadeh *et al*.

In 2004, Kidwai *et al*. reported an ecofriendly approach for one-pot multicomponent synthesis of fused dihydro-dichromeno-pyridine-6,8-dione derivatives by condensation of aromatic aldehydes, 4-hydroxycoumarin, and ammonium acetate using UV light in presence of water solvent with considerable good product yield (**Scheme IV.3**). [57]



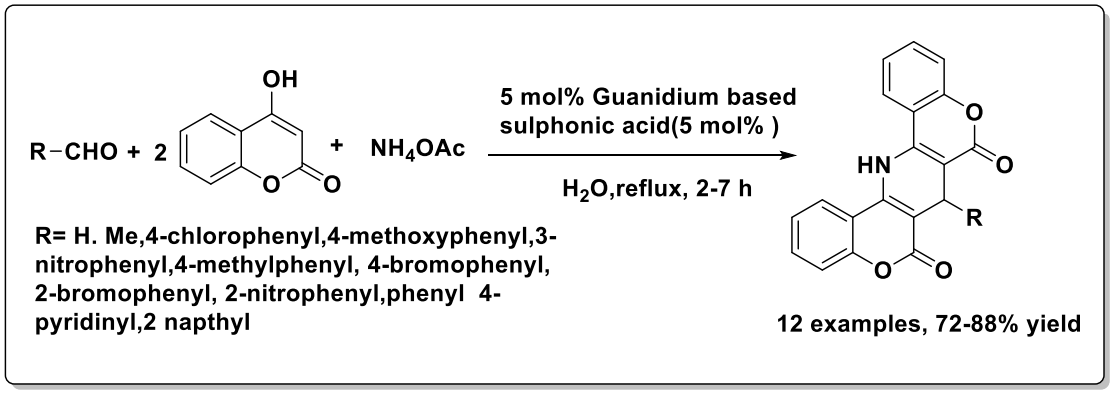
Scheme IV.3 One pot synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives Kidwai *et al.*

In 2020, Saffarian *et al*. has reported a synthetic method of dihydro-dichromeno-pyridine-6,8-dione derivatives by using Fe_3O_4@SiO_2@$(CH_2)_3$-urea-quinoline sulfonic acid chloride, as nanomagnetic catalyst bearing under solvent free condition at 80^0C temperature with reasonable yield (**Scheme IV.4**). [58]



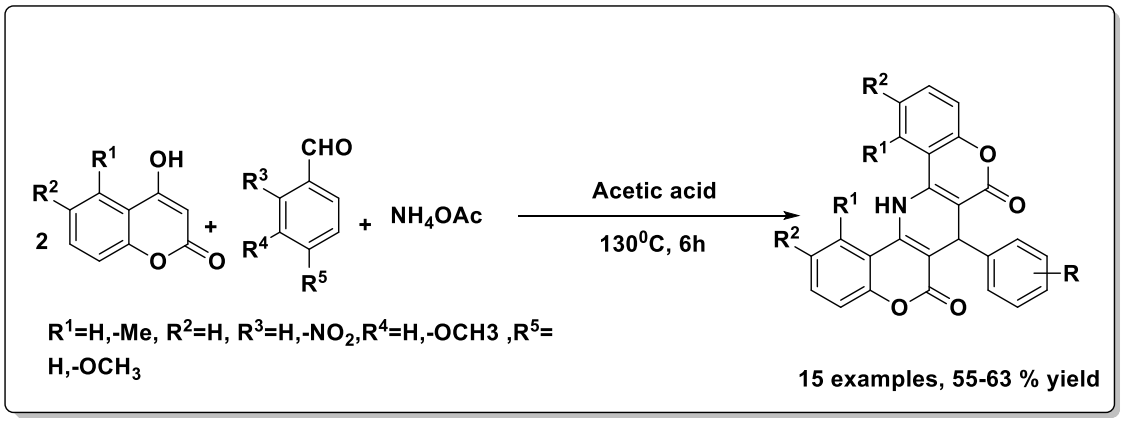
Scheme IV.4 One pot synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives Saffarian *et al.*

In 2016, Shaabani *et al*. reported a synthetic protocol for the synthesis of dihydro-dichromeno-pyridine-6,8-dione scaffolds with reasonable yield by using guanidinium-based sulfonic acid as a Brønsted acid as well as organocatalyst in water medium under reflux condition (**Scheme IV.5**). [59]



Scheme IV.5 One pot synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives Shaabani *et al*.

In 2004, Brahmbhatt *et al*. reported a synthetic protocol for the synthesis of dihydro-dichromeno-pyridine-6,8-diones with reasonable yield by using acetic acid as a Brønsted acid as well as organocatalyst as well as solvent at 130^0C temperature (**Scheme IV.6**). [60]



Scheme IV.6 One pot synthesis of dihydro-dichromeno-pyridine-6,8-diones derivatives Brahmbhatt *et al.*

IV.5 Tetrazole

Tetrazoles are a class of synthetic organic heterocyclic compound consisting five membered ring containing four nitrogen atoms and one carbon atoms. The first preparation of tetrazole was carried out from HCN and HN_3. There have different types of tetrazole depending upon

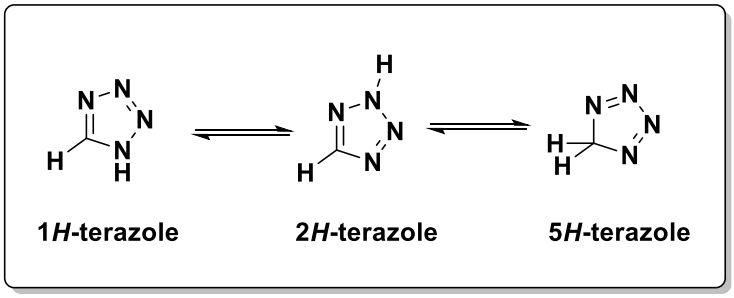


Figure IV. 3 Structures of 3 types of tatumeric tetrazoles

the position of the double bond and the presence of substitution on Carban atom such as 1*H*,2*H*,3*H*-tetrazole, aminotertazoles, thiotetrazole

and several synthetic methods of tetrazole skeletons are reported (**Figure IV. 3, Figure IV. 4**)

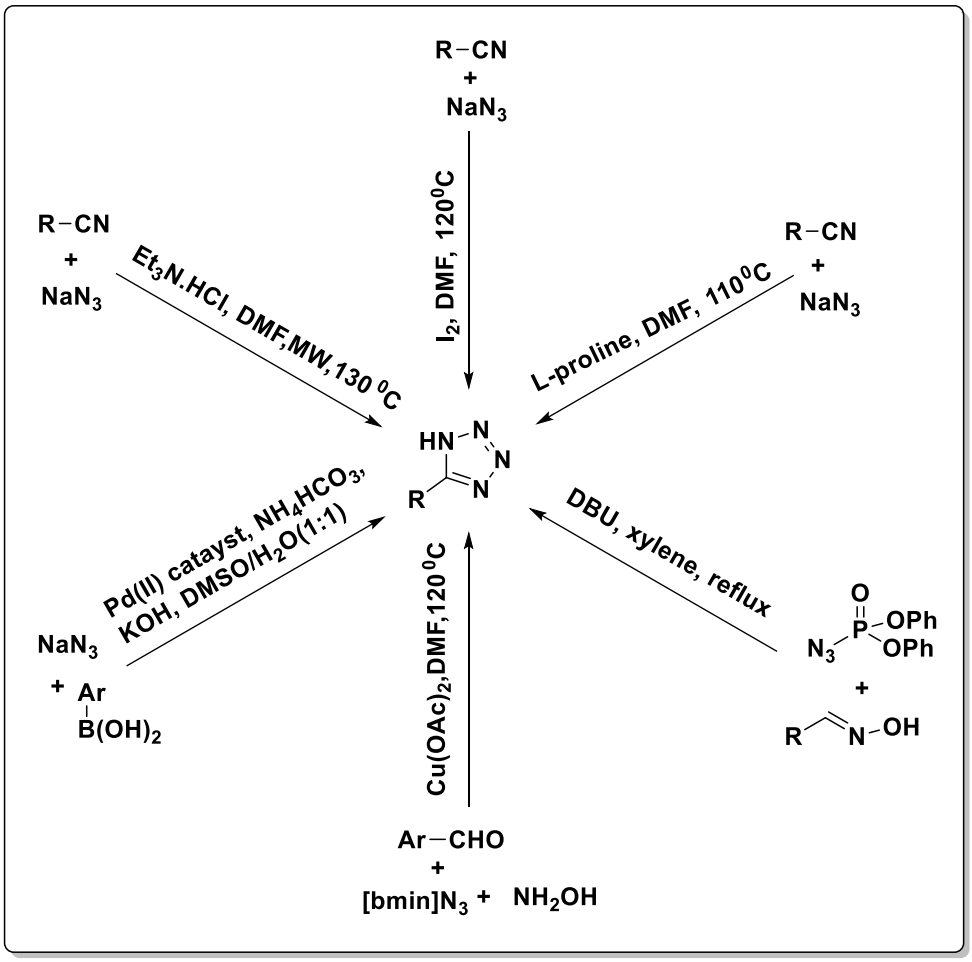


Figure IV. 4 Diverse synthetic routes for the synthesis of 1,4-dihydropyridine structures

IV.6 Quinazolinone

Quinazolinones are generally oxidized derivatives of quinazolines and they are classified into five categories based on the substitution

patterns of the ring system (**Figure IV.5**). According to literature 4(3*H*)-quinazolinones are most abundant as natural products and 2(1*H*)-quinazolinones are predominantly a product of benzamides with nitriles.[62] In the most common approach for the synthesis of quinazolinone compounds 2-aminobenzoic acid is used as a precursor. There are other methods reported for the synthesis of various types of quinazolinones below. (**Figure IV.6**)

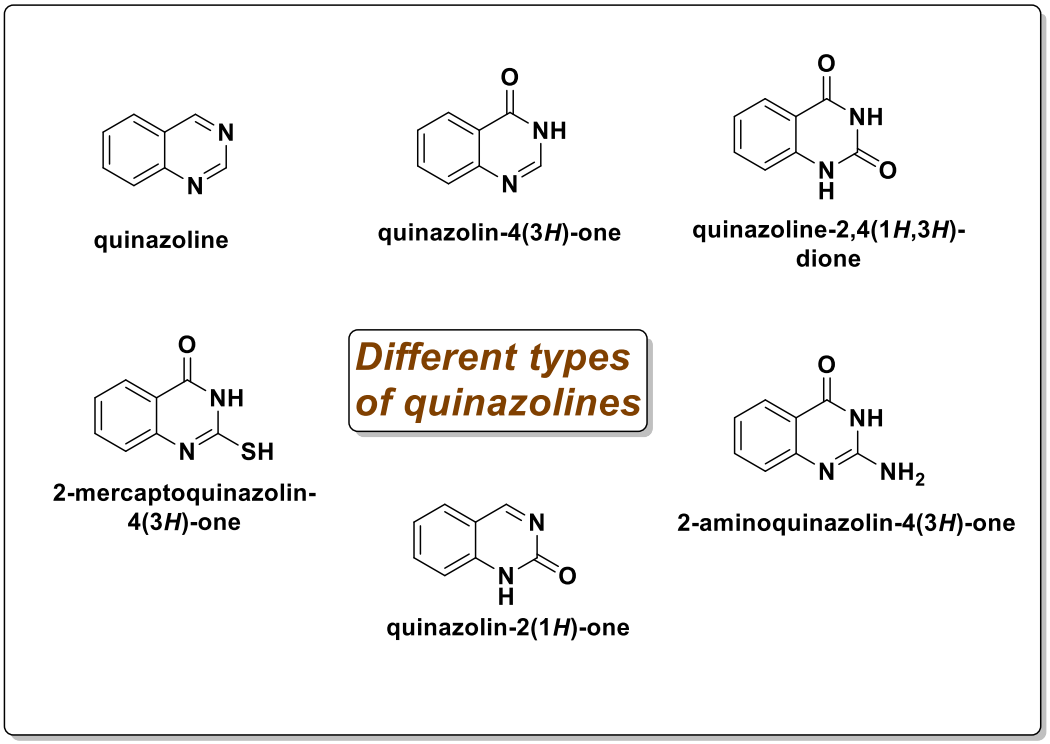


Figure IV.5 Different types of quinazoline scaffolds

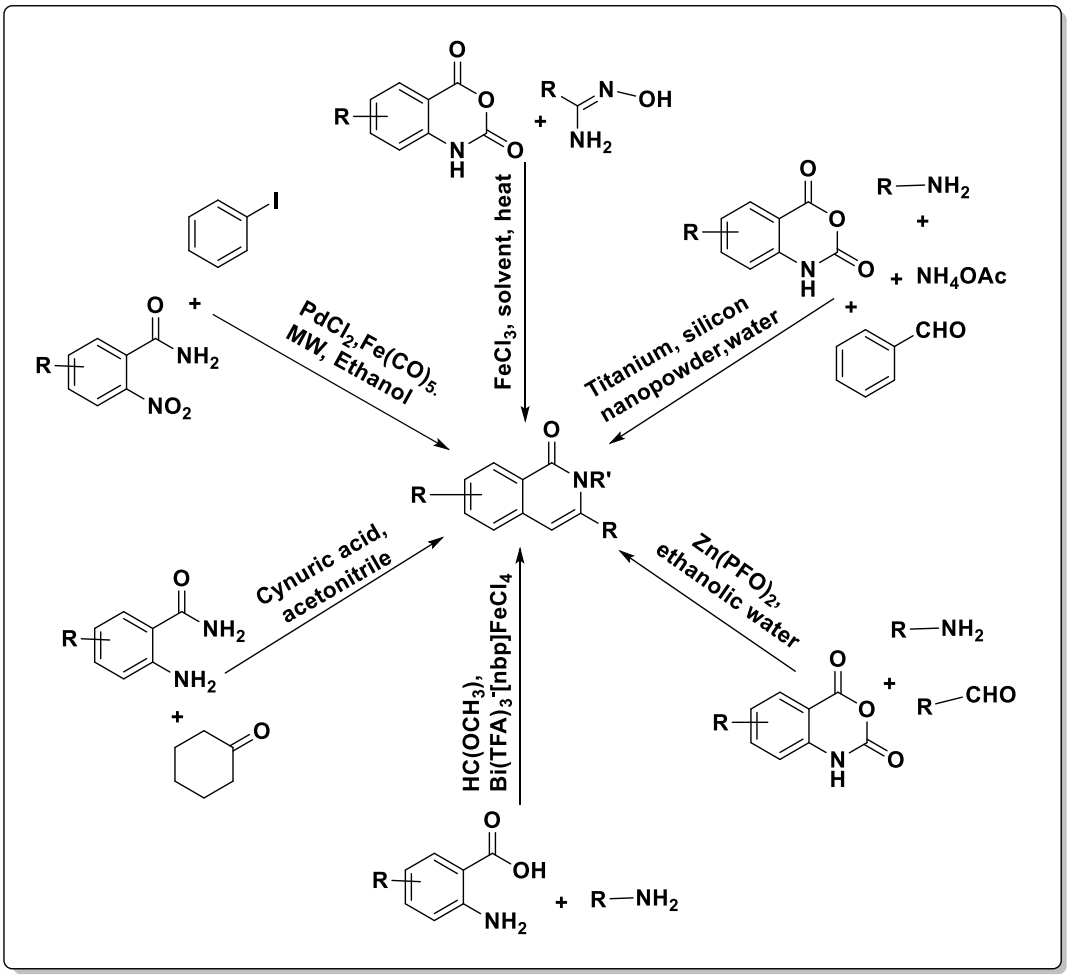


Figure IV.6 Different synthetic routes of quinazolinone skeleton

IV.7 Biological importance of tetrazole and quinazolinone derivatives

Tetrazoles have a broad rang of biological activities such as antibacterial, antifungal, anticancer, analgesic, anti-inflamatory, anti-diabetic, antitubercular activities.[63-69] Quinazolinone moiety is a building block for approximately naturally occurring alkaloids and quinazolinone derivatives have attracted significant attention due to their diverse pharmacological activities such as antimalarial, antimicrobial,

anti-inflammatory, anticonvulsant, antihypertensive, anti-diabetic, cholinesterase inhibition and anticancer activities and kinase inhibitor properties (**Figure IV.7**).[70-79]

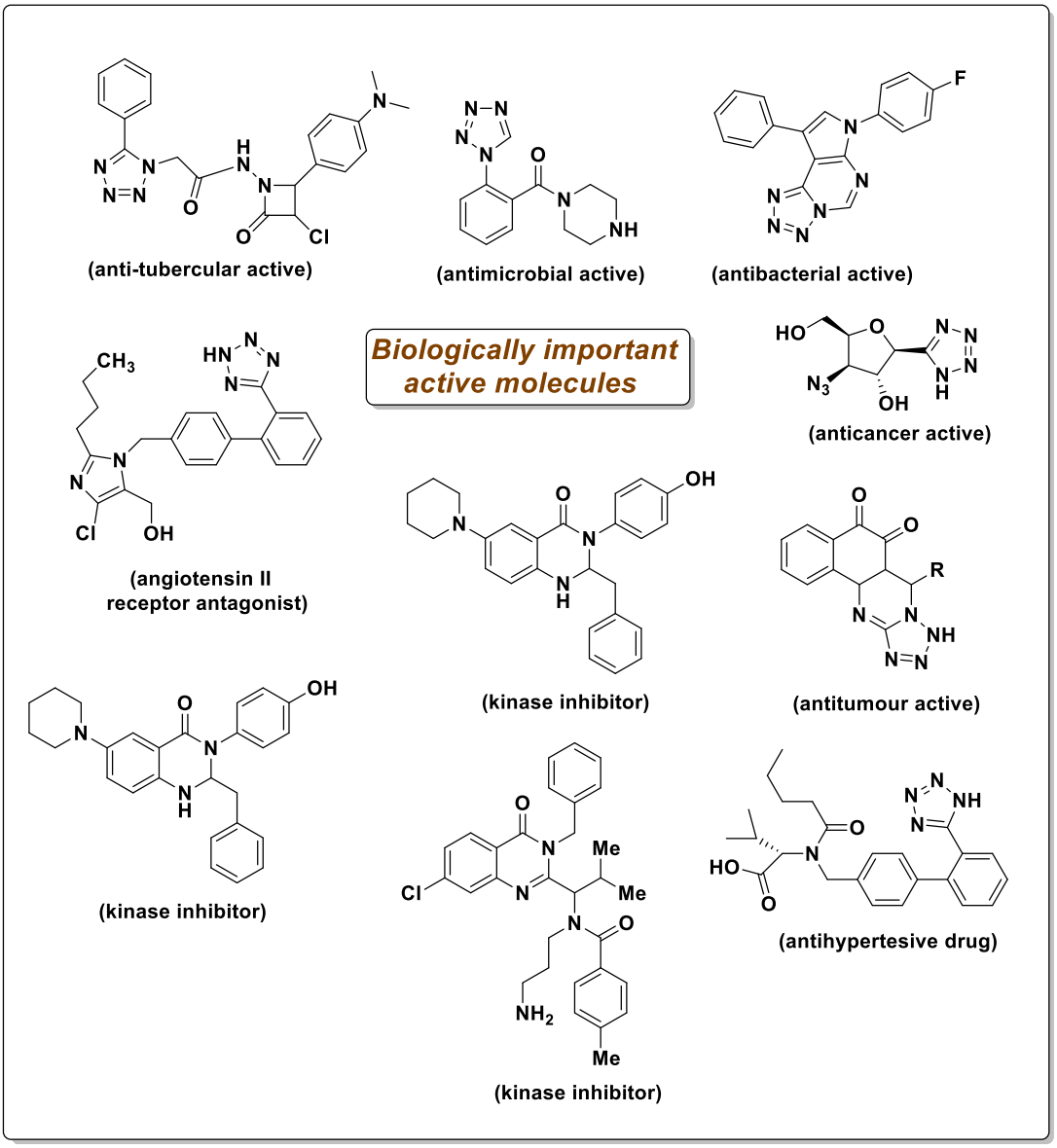


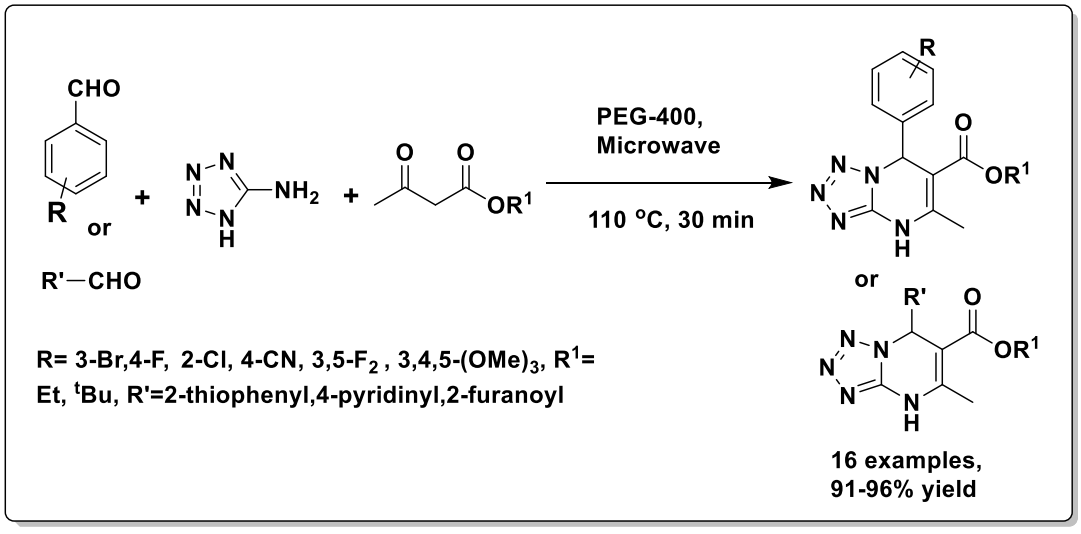
Figure IV.7 Some important pharmaceutically active drug molecule

By doing studies on works in various journals related to tetrazoles, quinazoline, quinazolinones and their derivatives and taking biological

importances of tetrazoles, quinazoline, quinazolinones and their derivatives in mind, in this following part of the Chapter IV, it has been focused on the synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives in a new and convenient manner using cheap laboratory chemicals.

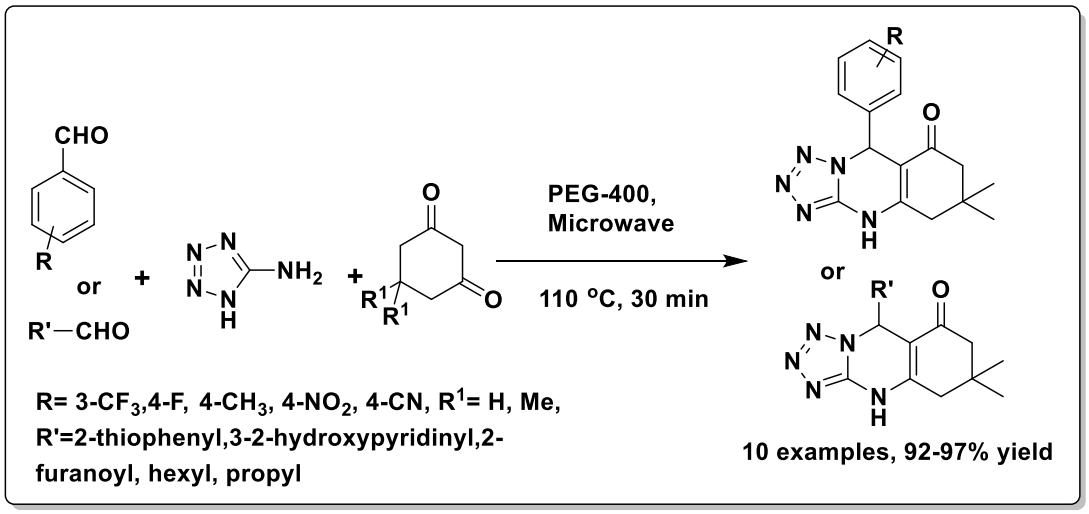
IV.8 Previous works on synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives

In 2019, Basha *et al.* reported a facile one-pot synthesis of tetrazolo[1,5-*a*]pyrimidine derivatives via a one pot three-component reaction between aldehydes, 5-aminotetrazole and 1,3-diketones in PEG-400 under microwave irradiation at 110^0C. (**Scheme IV.7**). [80]



Scheme IV.7 One-pot synthesis of tetrazolo[1,5-*a*]pyrimidine derivatives by Basha *et al.*

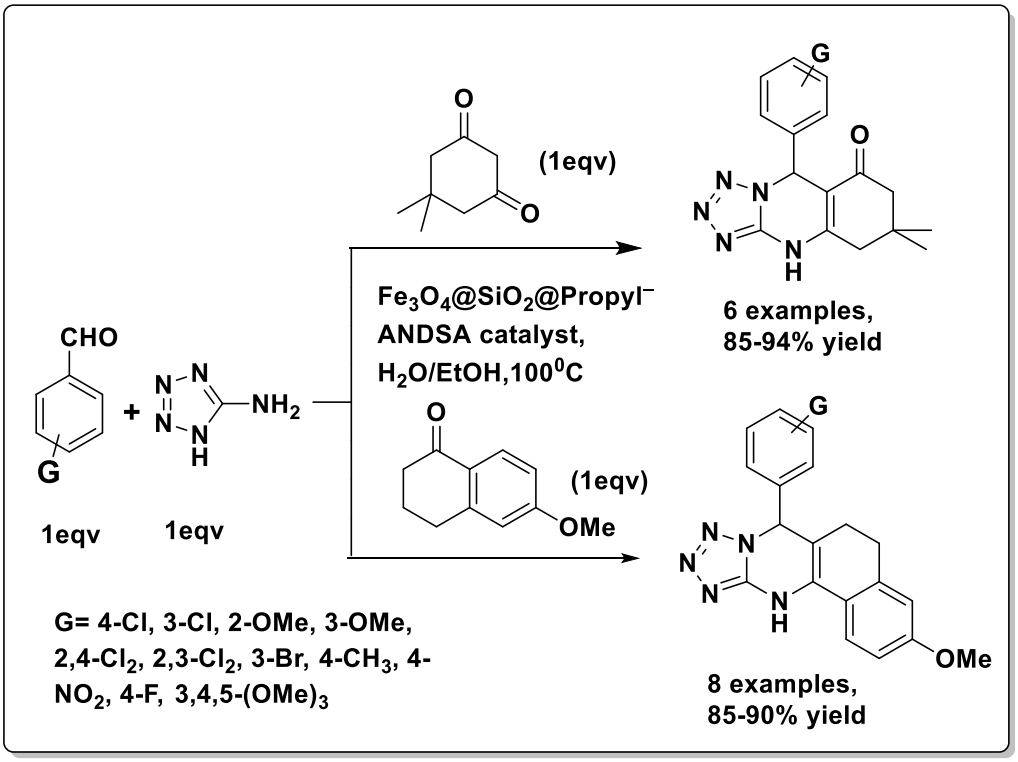
In 2019, Basha *et al.* also reported a facile synthesis of tetrahydrotetrazolo [5,1-*b*]quinazolinones via one one pot method by the reactions of aldehydes , 5-aminotetrazole and dimidone in presence of PEG-400 solvent under microwave irradiation at 110^0C temperature. (**Scheme IV.8**). [81]



Scheme IV.8 One-pot synthesis of tetrahydrotetrazolo [5,1-*b*]quinazolinones derivatives by Basha *et al*.

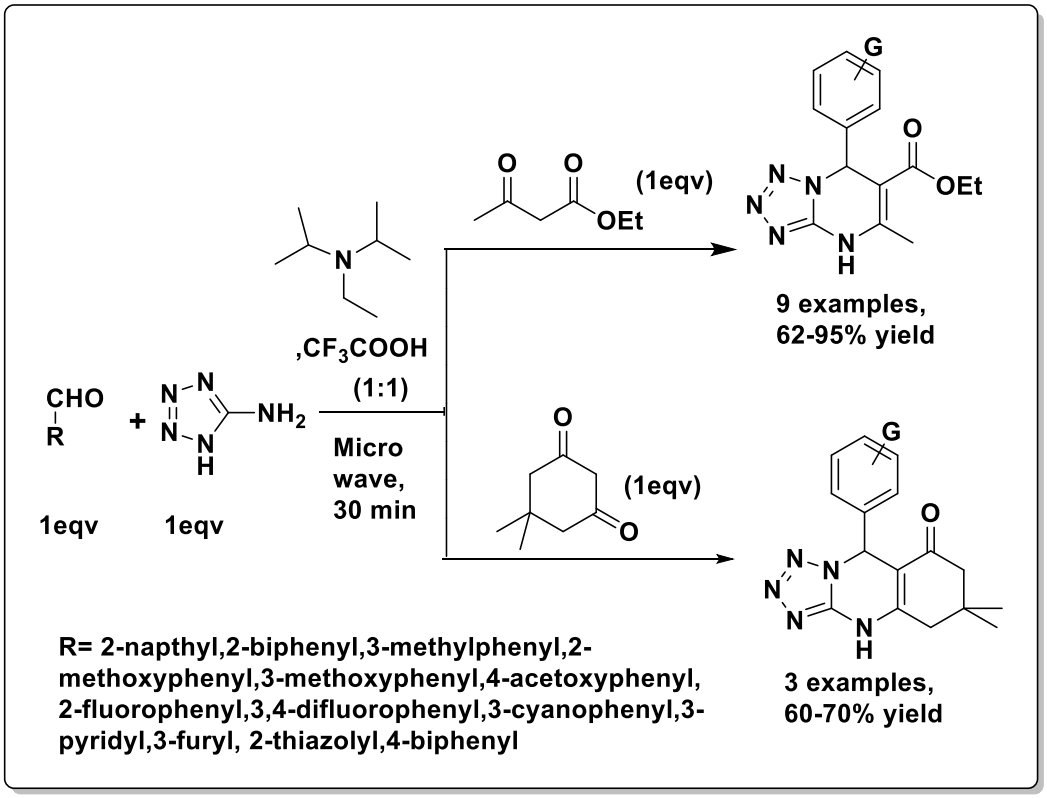
In 2019, Ghorbani-Vaghei *et al*. has reported a facile synthesis of tetrahydrotetrazolo[1,5-*b*]quinazolines and tetrahydrobenzo[h] tetrazolo[5,1-b]quinazolines from the reaction of aldehydes, 5-aminotetrazole, and dimedone as cyclic 1,3 diketone in presence of

Fe_3O_4@SiO_2@Propyl–ANDSA catalyst at 100^0C in H_2O/EtOH as the solvent. (**Scheme IV.9**). [82]



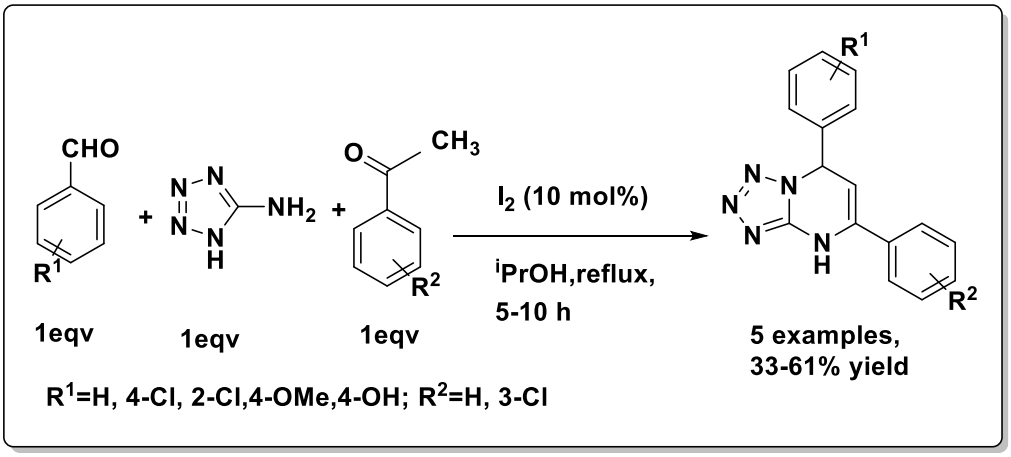
Scheme IV.9 A facile synthesis of tetrahydrotetrazolo[1,5-*b*]quinazolines and tetrahydrobenzo[*h*]tetrazolo[5,1-*b*] quinazolines by Ghorbani-Vaghei *et al*.

In 2012, Raju *et al*. has reported a facile synthesis of tetrazolo[1,5-a]pyrimidine derivatives from the reaction of aldehydes, 5-aminotetrazole, and ethylacetoacetate as acyclic 1,3 diketone in presence of a 1:1 mixture of N,N,N-triisopropylamine and CF_3COOH under microwave condition having reasonable yield (**Scheme IV.10**). [83]



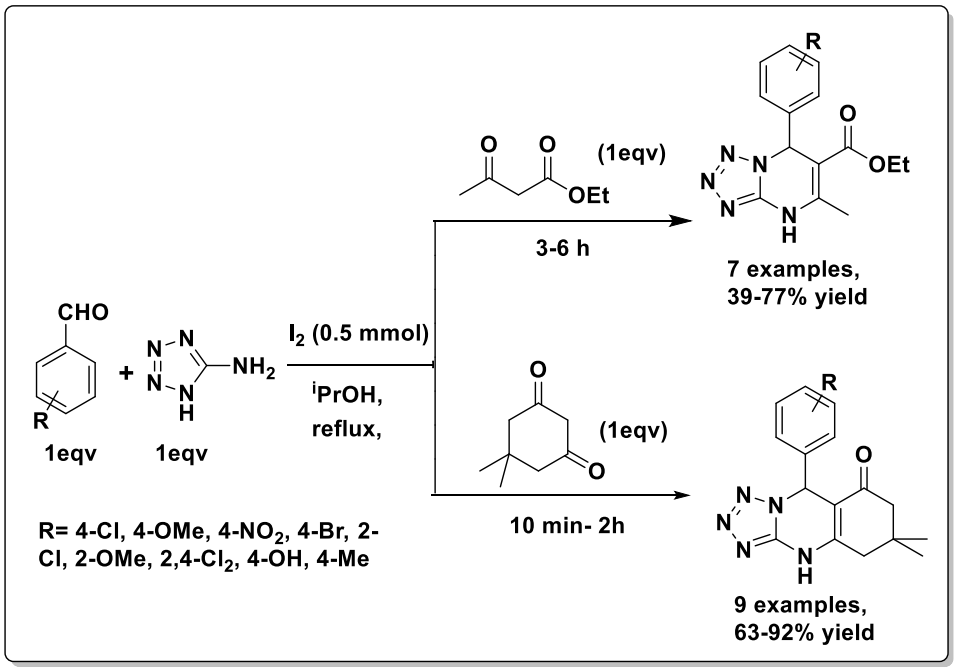
Scheme IV.10 A facile synthesis of tetrazolo[1,5-*a*]pyrimidine derivatives by Raju *et al*.

In 2010, Zeng *et al*. reported a novel reaction for the synthesis of dihydrotetrazolo[1,5-*a*]pyrimidines by the reaction of 5-aminotetrazole with aryl aldehydes and acetophenone catalyzed by iodine in presence of isopropyl alcohol under refluxing condition in one pot method (**Scheme IV.11**). [84]



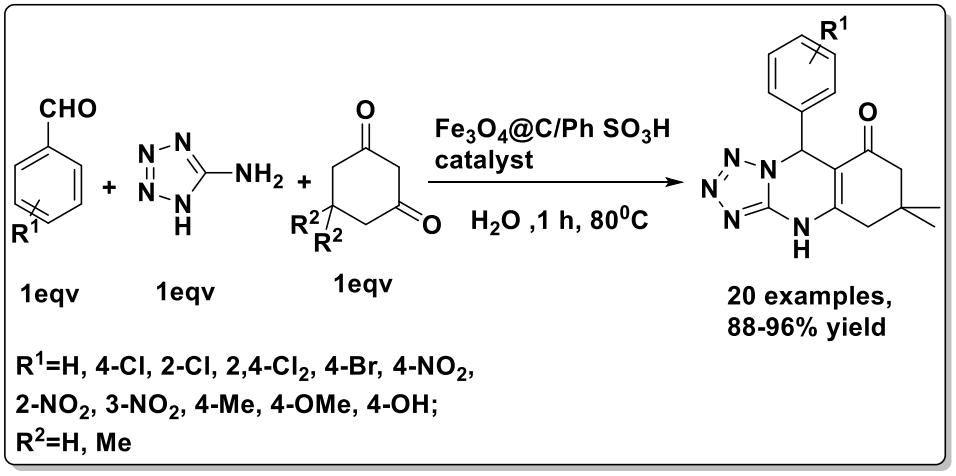
Scheme IV.11 A facile synthesis of dihydrotetrazolo[1,5-*a*]pyrimidines by Zeng *et al*.

In 2010, Zeng *et al*. also reported methods for the synthesis of dihydrotetrazolo[1,5-*a*]pyrimidine and tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives in one pot method in presence of iodine in isopropyl alcohol under reflux condition (**Scheme IV.12**). [85]



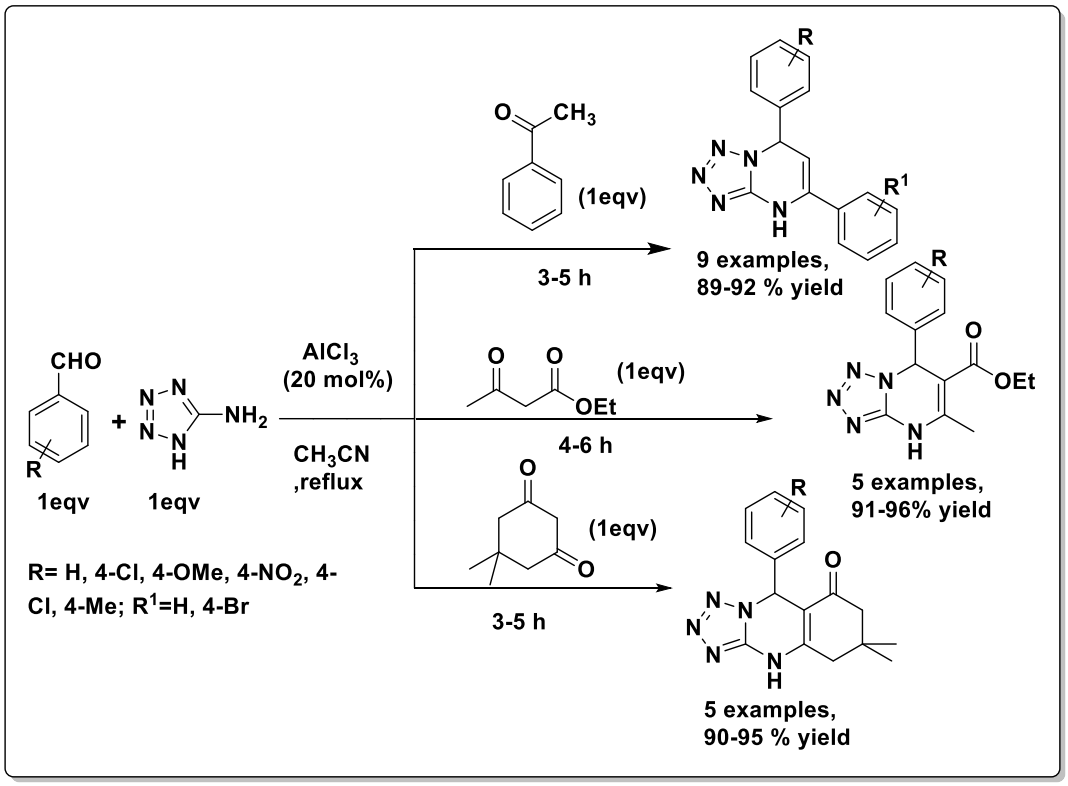
Scheme IV.12 Synthesis of dihydrotetrazolo[1,5-*a*]pyrimidine and tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives by Zeng *et al*.

In 2021, Hassankhani *et al*. reported a synthetic method for the synthesis of tetrahydrotetrazolo[5,1-b]quinazolinone derivatives by using synthesized Fe_3O_4@meso-C immobilized with activated 4-aminobenzenesulfonic acid as catalyst in presence of water at 80^0C with good yields (**Scheme IV.13**). [86]



Scheme IV.13 Synthetis of tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives by Hassankhani *et al.*

In 2017, Kour *et al*. reported facile synthetic methods for the synthesis of dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones via one pot multi-component method by the reaction of 5-aminotetrazole, aldehyde and active methylene compounds (e.g. acetophenone, alkylacetoacetates, dimedone) in presence of $AlCl_3$ catalyst under reflux condition in acetonitrile solvent with reasonable yields (**Scheme IV.14**). [87]



Scheme IV.14 One pot synthesis of dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones by Kour *et al*.

IV.9 2,4-diaryl hexahydroquinoline-5-one

2,4-diarylhexahydroquinolines are a class of quinoline family having 2 double bonds at 3 and 5 position of the biclyclic system having aryl groups attached with 2 and 4 position. This 2,4-diarylhexahydroquinlones are generally synyhesised from Chalcones followed by addition of basic ammonium salt and cyclic-1,3-diketo compounds. Sometimes aldehydes with acetophenones are used in absence of chalcone. There are several synthetic methods for the

synthesis of the synthesis of hexahydroquinoline (**Figure IV.8**) skeleton but there is still a shortage of reported methods related to green synthesis of hexahydroquinolines.

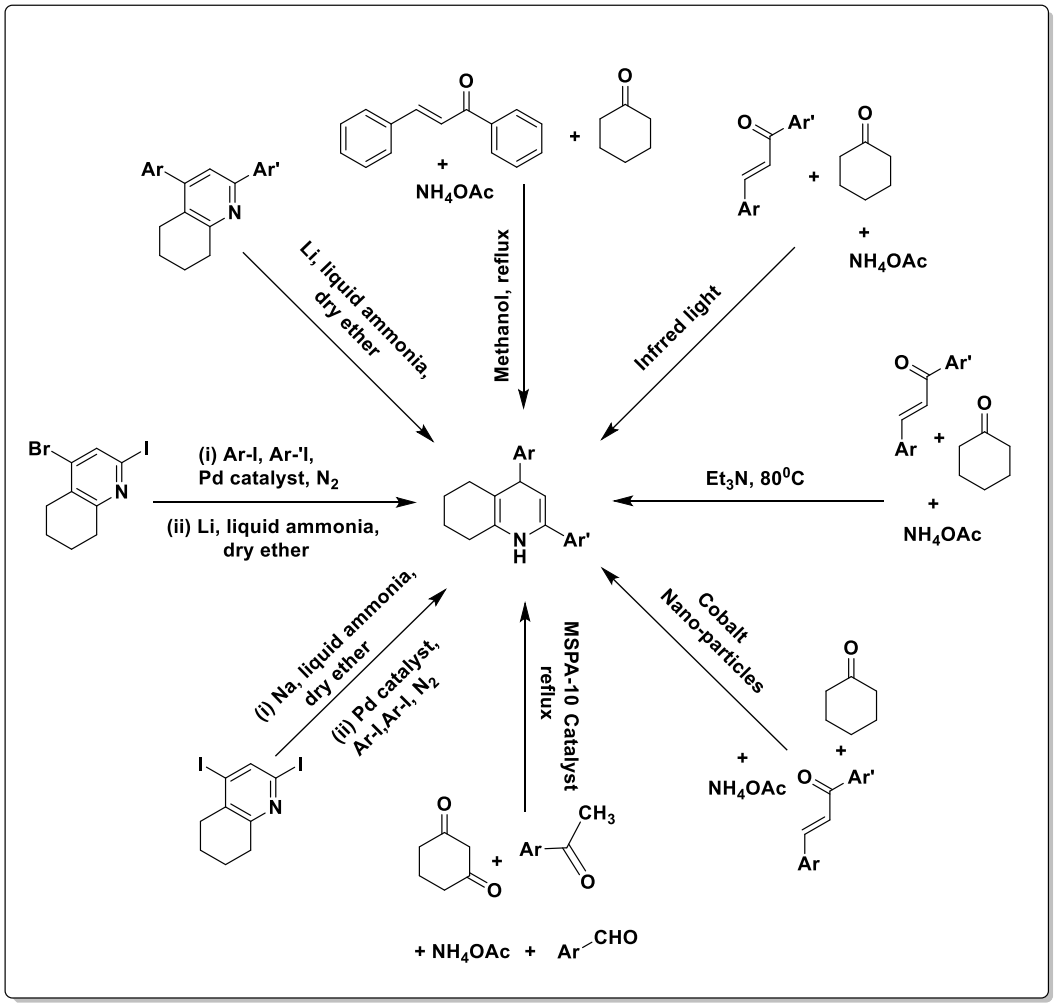


Figure IV.8 Diverse synthetic route for the synthesis of 2,4-diarylhexahydroquinoline ring synthesis

IV.10 Biological importance of 2,4-diaryl hexahydroquinoline-5-one derivatives

2,4-diarylhexahydroquinoline derivatives have structural resemlence with 1,4-dihydropyridines have thus they can behave as alternatives of 1,4-dihydropyridines from a variety of viewpoints such as biological activities and due to close resemblance with 1,4-dihydropyridines in respect of the biological properties (**Figure IV.9**) their derivatives can be used as calcium channel blockers for the treatment of defibrillation and hypertension disease [88]. They also possesses antimalarial, antiviral, antibacterial, antiallergic and anicancer properties and recently, acridines showed some inhibition properties [89-93]

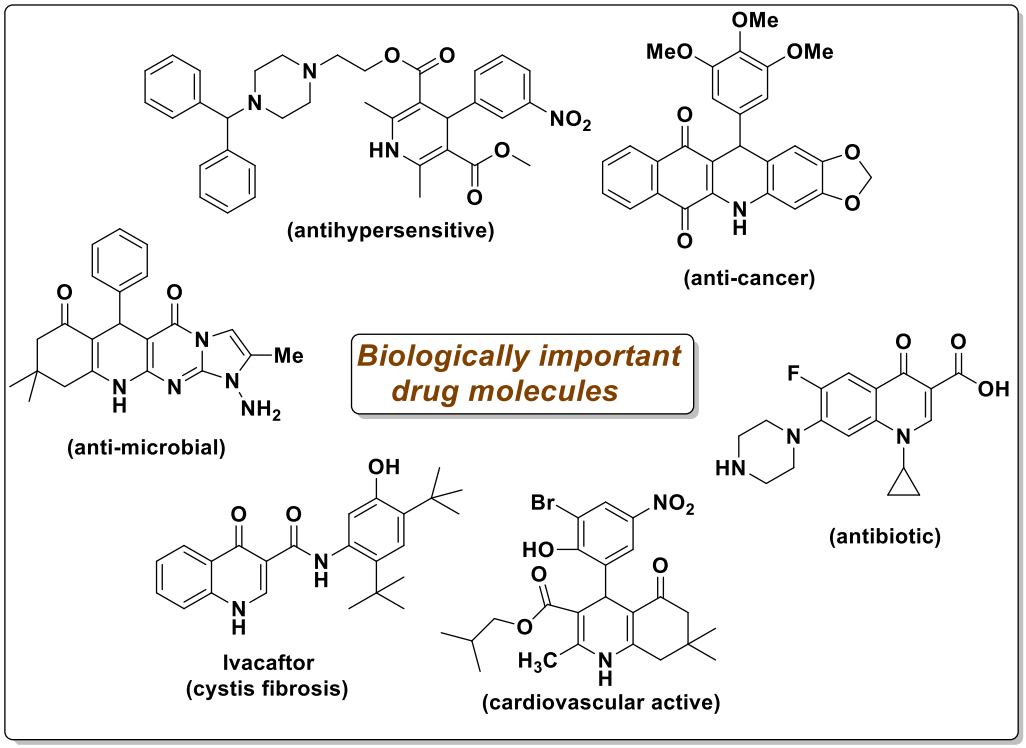
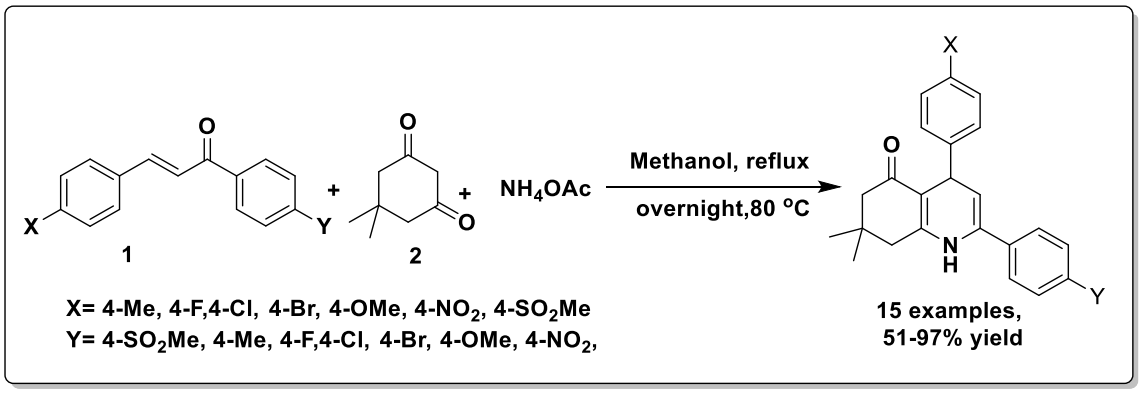


Figure IV.9 Some important pharmaceutically active drug molecule

By observing various journals among quinolines, quionolones and their derivatives and taking biological importances of quinolines and quinolones and their derivatives in mind, in this following part of the chapter IV, it has been focused on the synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives in a new and convenient manner using cheap laboratory chemicals.

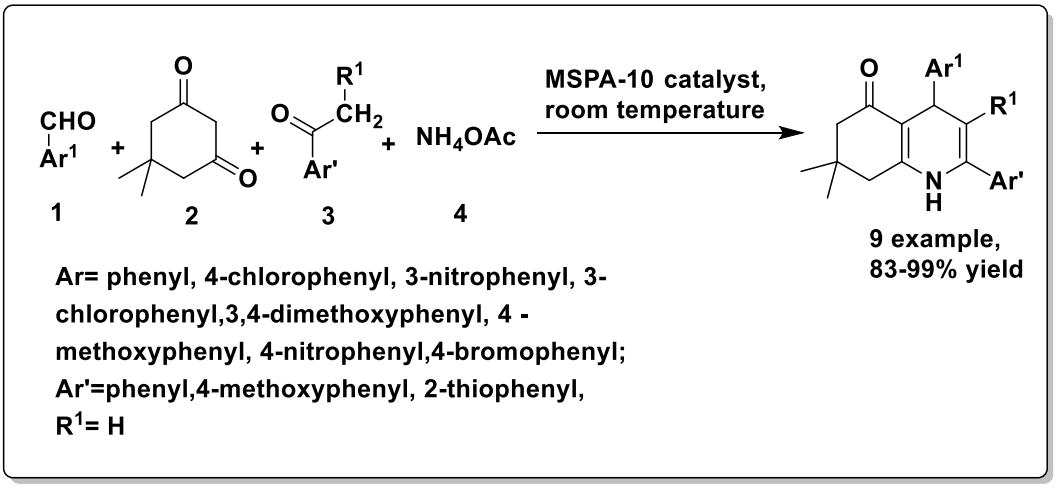
IV.11 Previous works on synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives

In 2014, Zarghia *et al*. has reported a synthesis of 2,4-diarylhexahydroquinolines by the one pot reaction between mixture of 5, 5-dimethyl-1,3-cyclohexandion, 1,3-diaryl-2-propen1-one, ammonium acetate in methanol under refluxed condition at 80^0C for overnight (**Scheme IV.15**). [94]



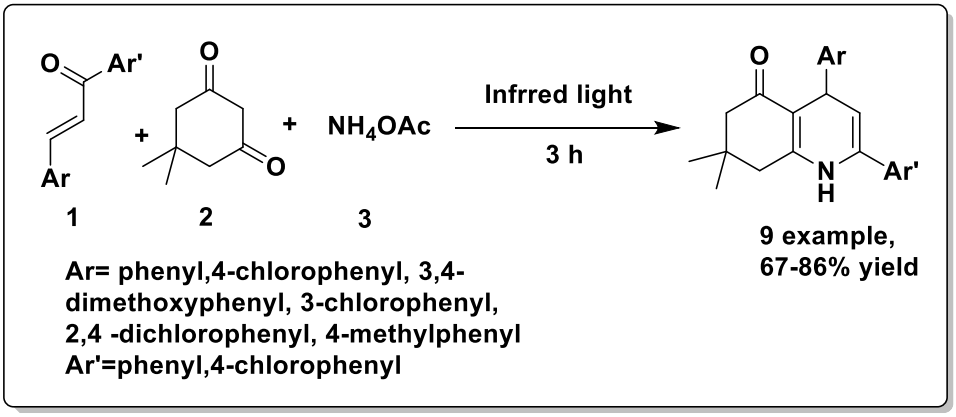
Scheme IV.15 One pot synthesis of 2,4-diarylhexahydroquinolines by Zarghia *et al.*

In 2013, Ray *et al*. has reported a synthesis of 2,4-diarylhexahydroquinolines by carring out a one pot 4-component reactions between aromatic aldehydes, dimedone and acetophenone and ammonium acetate by using a new heterogeneous MCM-41 silica supported HPF_6 catalyst (**Scheme IV.16**). [95]



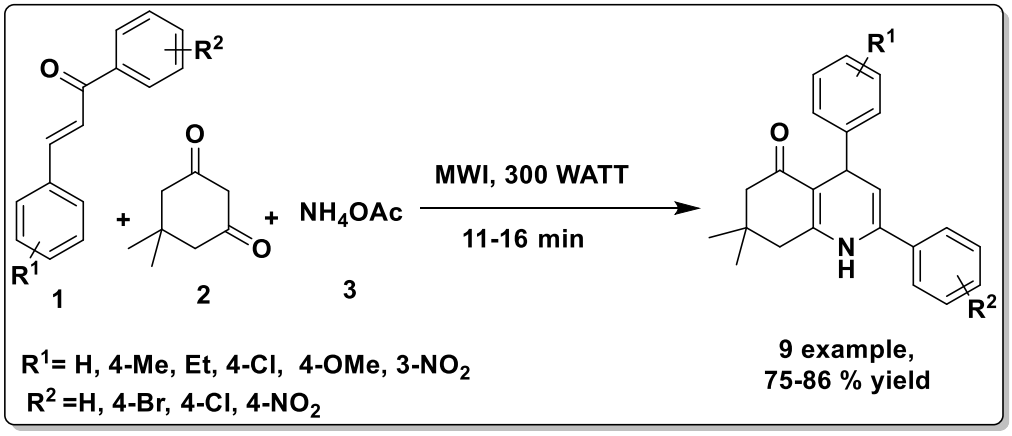
Scheme IV.16 One pot synthesis of 2,4-diarylhexahydroquinolines by Ray *et al.*

In 2006, Wang *et al*. reported a synthetic procedure for the synthesis of 2,4-diarylhexahydroquinolines by doing a one pot 3-component reactions between Chalcones, dimedone and ammonium acetate by infrared irradiation (IR) irradiation promoted the synthesis with 67-86% yield (**Scheme IV.17**). [96]



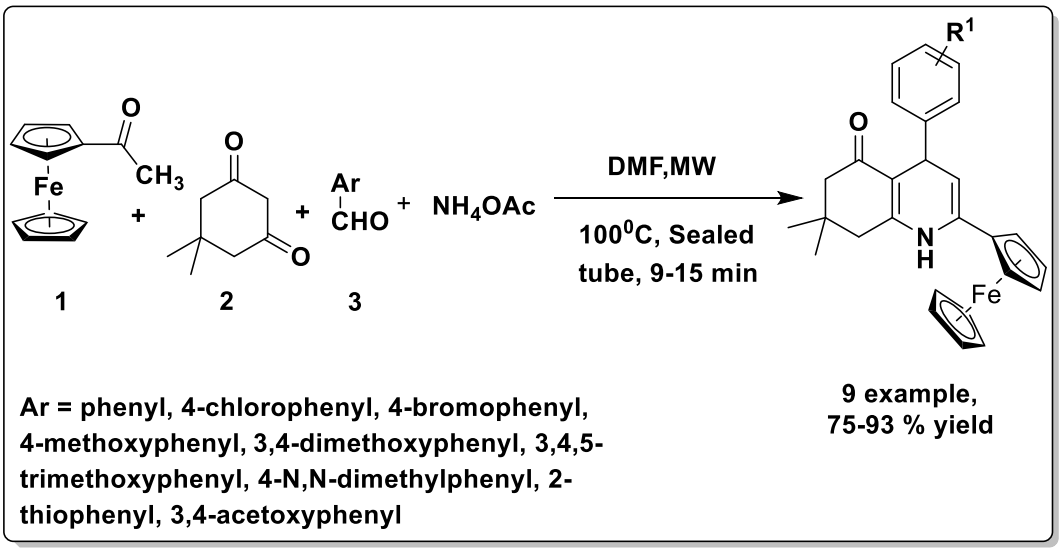
Scheme IV.17 One pot synthesis of 2,4-diarylhexahydroquinolines by Wang *et al.*

In 2005, Hua *et al*. reported a synthetic procedure for the synthesis of 2,4-diarylhexahydroquinolines by doing a one pot 3-component reactions between Chalcones, dimedone and ammonium acetate by microwave irradiation (mwi 300 watt) the synthesis with 75-86% yield (**Scheme IV.18**). [97]



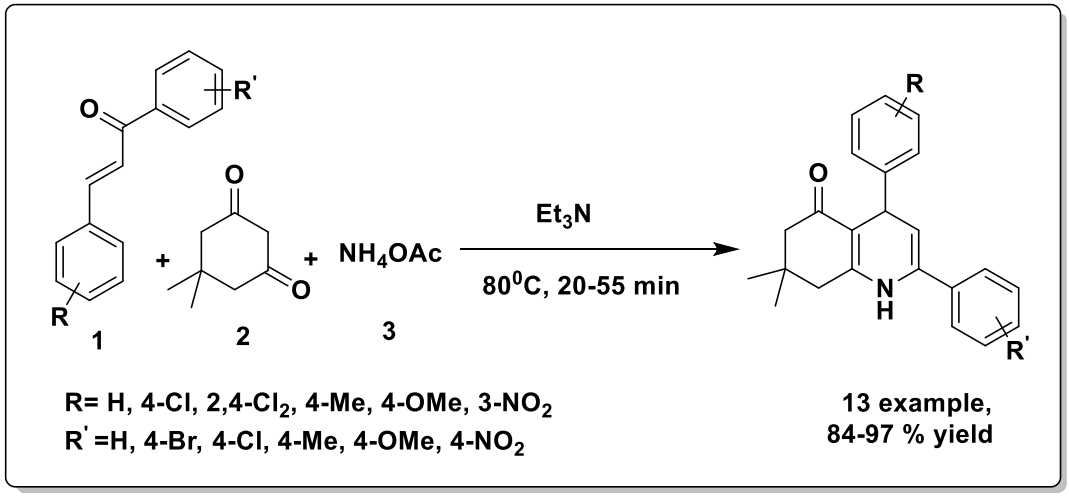
Scheme IV.18 One pot synthesis of 2,4-diarylhexahydroquinolines by Hua *et al*.

In 2009, Tu *et al*. reported a synthetic procedure for the synthesis of 2,4-diarylhexahydroquinolines by doing a one pot 4-component reactions between aromatic aldehydes, dimedone, ammonium acetate and ferrocenyl active metheline compound by microwave irradiation (MW) in presence of DMF solvent with 75-93% yield (**Scheme IV.19**). [98]



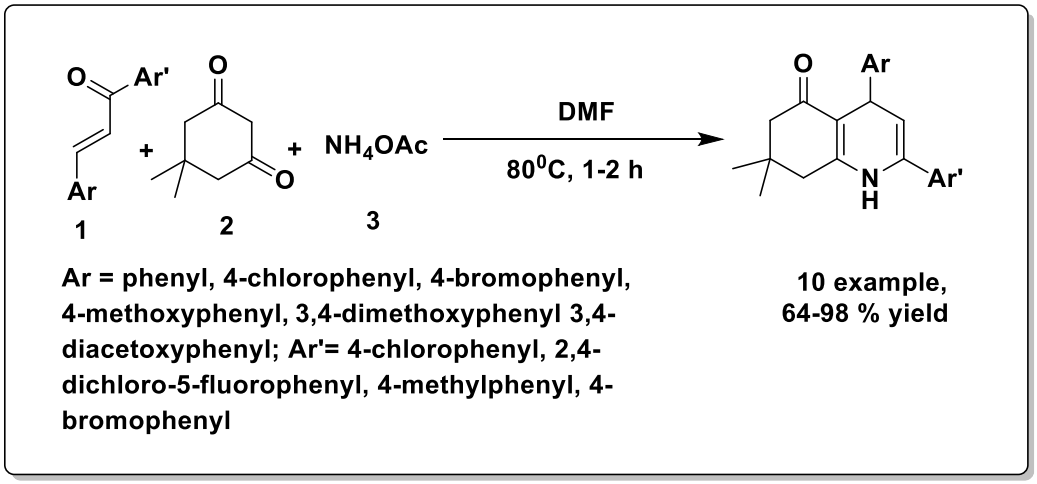
Scheme IV.19 One pot synthesis of 2,4-diarylhexahydroquinolines by Tu *et al*.

In 2015, Karimi-Jaberi *et al.* reported a convenient and efficient protocol for the synthesis of 2,4-diaryl hexahydroquinoline derivatives by a three-component reaction between Chalcones, dimedone and ammonium acetate catalyzed by triethylamine under solvent-free conditions with yield 84-97% (**Scheme IV.20**). [99]



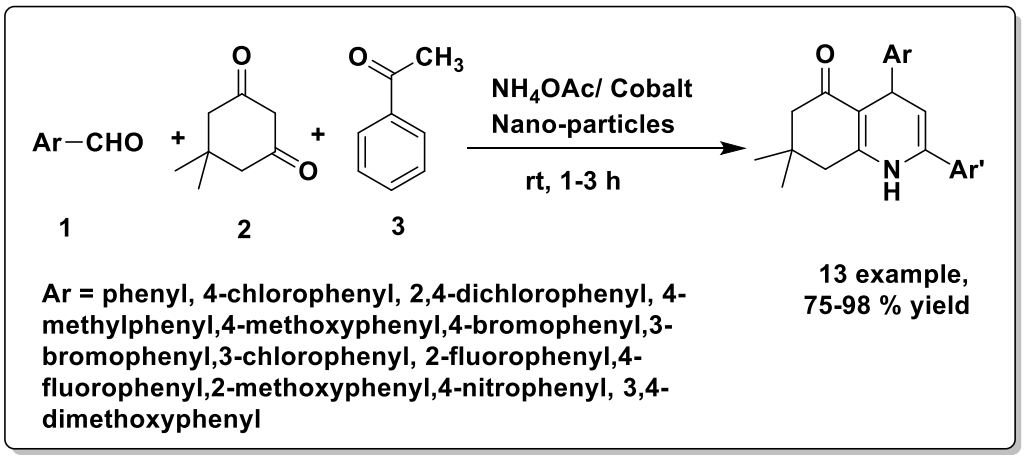
Scheme IV.20 One pot synthesis of 2,4-diarylhexahydroquinolines by Karimi-Zaberi *et al.*

In 2002, Wang *et al*. reported a series of substituted 2,4-diarylhexahydroquinoline derivatives by a 3-component reaction of dimedone ammonium acetate and 1,3-diaryl-2-propen-1-one (Chalcones) in DMF at 80^0C temperature with yields 64–98% (**Scheme IV.21**). [100]



Scheme IV.21 One pot synthesis of 2,4-diarylhexahydroquinolines by Wang *et al*.

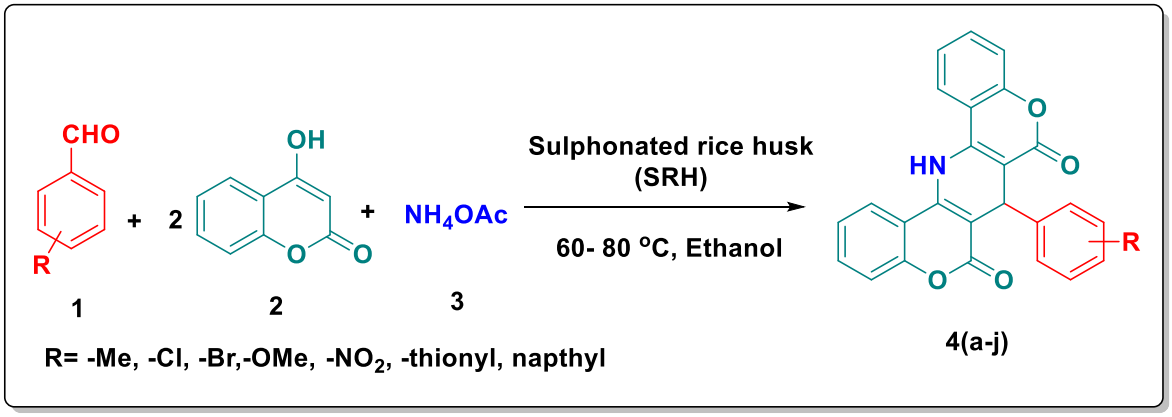
In 2011, Safari *et al*. reported a straightforward method for the synthesis of 2,4-diarylhexahydroquinoline derivatives by the reaction between dimedone, acetophenone, aromatic aldehydes, and ammonium acetate in the presence of a catalytic amount of Cobalt nanoparticles at room temperature with 75-98% yield (**Scheme IV.22**). [101]



Scheme IV.22 One pot synthesis of 2,4-diarylhexahydroquinolines by Safari *et al.*

IV. 12 Present Work

The present work leads to the synthesis of dihydro-dichromeno-pyridine-6,8-dione derivatives (**Scheme IV.23)** by using greener catalyst heterogeneous catalyst sulphonated rice husk (SRH) .



Scheme IV.23 Synthesis of substituted dihydro-dichromeno-pyridine-6,8-dione derivatives using sulphonated rice husk[a]

IV.12.A Results and discussion

IV.12.A.1 Catalyst characterization

The prepared catalyst was characterized by powder XRD, FTIR spectroscopy and SEM-EDX analysis. Detailed literature studies along with comparison of the physical characterization data of the material including of FTIR spectra (**Figure IV.10a**) and SEM-EDX analysis (**Figure IV.11**) and power XRD data (Figure IV.10) curves of both the catalyst (SRH) to that of rice husk (RH) clearly indicated the formation of the rice husk based heterogeneous catalyst. The the new broad band arround 3400 cm^{-1} along with the band arround 1100cm^{-1} indicating the incorporation of $–SO_3H$ groups into RH surface after sulphonation and the band arround 1100cm^{-1} represents the symmetric and asymmetric

streatching of S=O bonds of $–SO_3H$ groups groups.[61] SEM-DEX (**Figure IV. 11**)analysis and powder XRD have made a clear pathway for comparison of RH and SRH and confirmation of the prepared catalyst from the rice husk. The powder XRD analysis of both RH and SRH shows characteristic changes in 2θ values and different nature of both RH and SRH clearly indicates the SRH has been formed from RH due to sulphonation. (**Figure IV. 10b**). Detailed characterization informations EDX analysisof SRH and RH are given into the experimental section (**IV.12.A.14.l.**) of the Chapter IV.

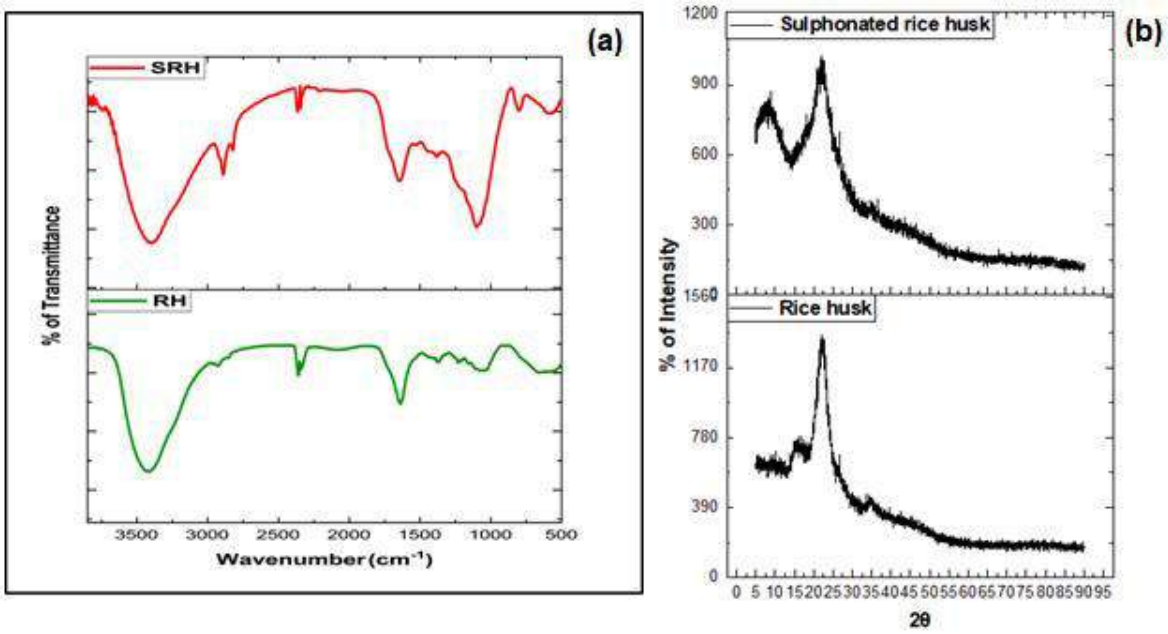


Figure IV.10 (a) FTIR spectra of RH and SRH. (b) Powder XRD spectra of RH and SRH

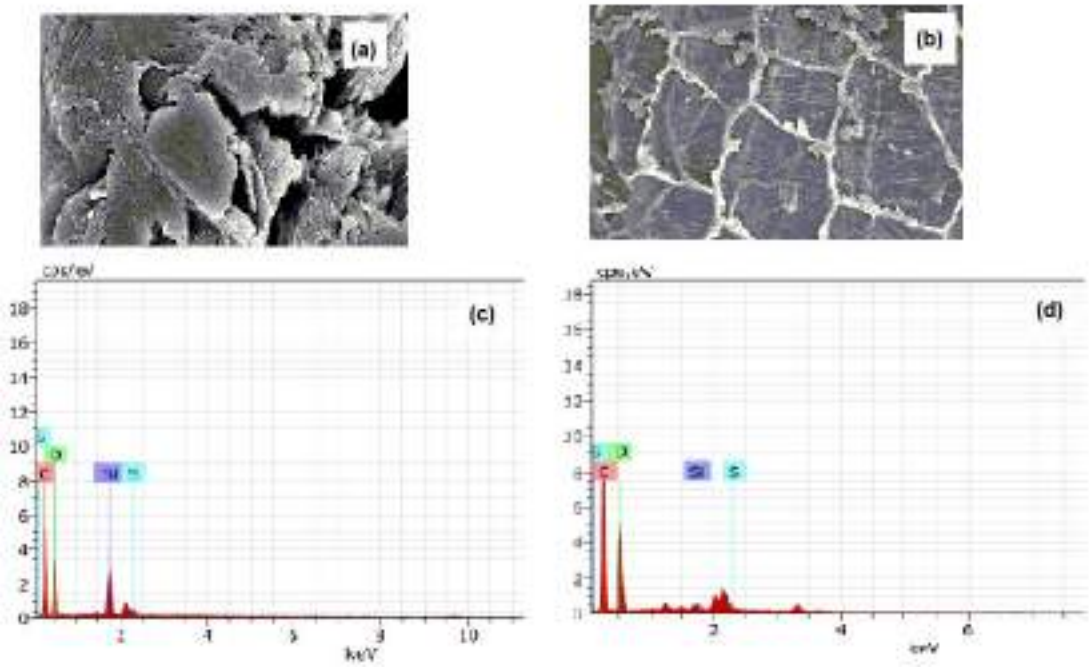


Figure IV.11 (a) SEM image of SRH. (b) SEM image of RH. (c) EDX-image of SRH. (d) EDX-image of RH

IV.12.A.2 Optimisation of the reaction condition for the synthesis of dihydro-dichromeno-pyridine-6,8-dione

Initially the reaction was started with taking anisaldehyde (1 mmol), 4-hydroxycoumarine (2 mmol), ammonium acetate (1.2 mmol) at a time in a 25 mL glass made sealed reaction tube vessel. In absence of catalyst, it was observed that the formation of the corresponding product had a poor yield produced may be due to by solvent induced catalysis (**Table IV.1,** entry 11) but excellent yield was observed in presence of arbitrary amount of 100 mg of SRH catalyst in ethanol solvent at 80^0 C temperature (**Table IV.1,** entry 2). The role of catalytic efficiency was

observed by decreasing the amount of catalyst through sequence wise experiment and the yield of the product was observed with amount of catalyst. From the optimized condition, it is clear that SRH catalyst is suitable as a greener catalyst for the conversion of dihydro-dichromeno-pyridine-6,8-dione with excellent yield in short reaction time. The amount of the catalyst and the time of the reaction was further checked to find out the optimized condition of the reaction. It was observed that the best result was obtained at 70^0 C temperature using 60 mg of catalyst SRH in ethanol (**Table IV.1, entry 7**). A comparison experiment was done with our prepared catalyst (SRH) with other conventional acid catalysts (**Table IV.7**) following the above reaction scheme (**Scheme IV.23**) and it was observed that the yield of product for few acid catalyst is almost similar which had suggested a comparison of effectiveness of SRH with other acid catalyst taking a short reaction time. The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (**Scheme IV.23**) having electron donating and electron withdrawing substituents of the aromatic aldehydes. The targeted compounds (4a-4j) are successively synthesized using SRH as an efficient catalyst under greener reaction condition and the progress of the reaction was monitored by thin layer chromatography (TLC) and the

pure product was separated by recrystallisation of the crude product in petroleum ether/ethyl acetate (v/v ratio70/30) mixture.

Table IV.1 Optimisation of the reaction condition for the synthesis of dihydro-dichromeno-pyridine-6,8-dione.[a]

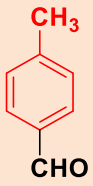
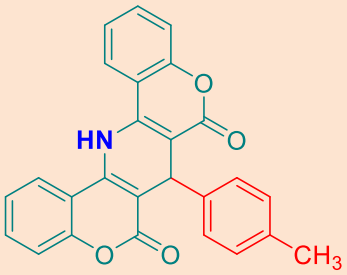
Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	110	Ethanol	90	360	98
2	100	Ethanol	80	318	98
3	90	Ethanol	80	300	98
4	80	Ethanol	80	258	98
5.	70	Ethanol	70	240	98
6.	70	Ethanol	70	198	98
7.	**60**	**Ethanol**	**70**	**180**	**96**
8.	50	Ethanol	70	180	94
9.	50	Ethanol	60	180	90
10.	50	Ethanol	60	150	90
11.	None	Ethanol	70	190	60
12.	None	Methanol	70	190	50
13.	60	Methanol	70	200	95
14.	80	Ethanol/H_2O (4:1)	70	200	90
15.	80	Ethanol/H_2O (1:1)	70	200	84

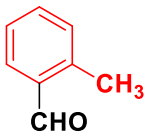
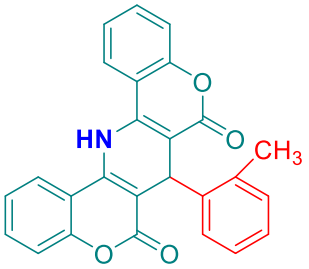
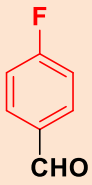
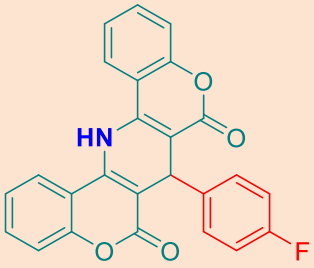
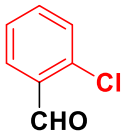
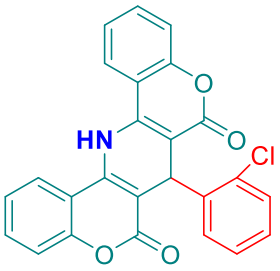
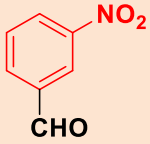
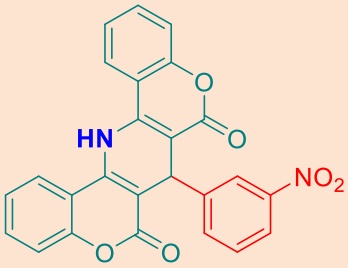
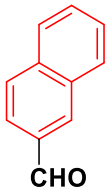
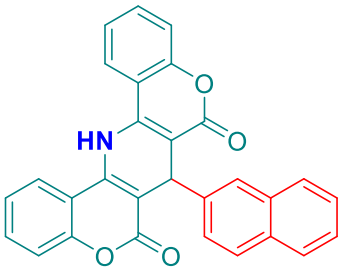
[a] Reaction of anisaldehyde (1 mmol), 4-hydroxycoumarine (2 mmol), and ammonium acetate(1.2 mmol) [b] Isolated yield after purification through recrystalisation.

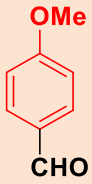
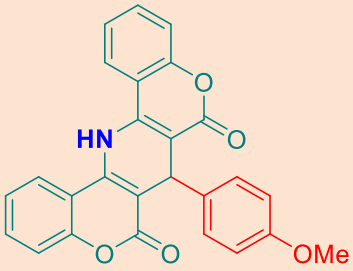
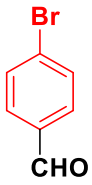
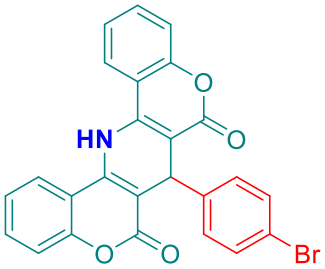
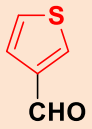
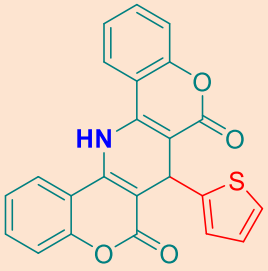
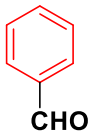
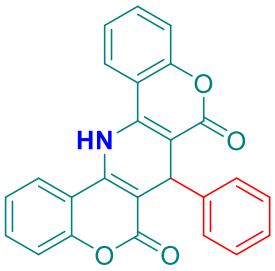
IV. 12.A.3 Synthesis of dihydro-dichromeno-pyridine derivatives

The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (**Scheme IV.23**) having electron donating and electron withdrawing substituents at *ortho*, *meta* and *para* position of the aromatic aldehyde. The targeted compounds (4a-4j) are successively synthesized using SRH as an efficient catalyst under greener reaction condition. (**Table IV.2**) The progress of the reaction was monitored by thin layer chromatography (TLC) and the pure product was separated by recrystallisation of the crude product in petroleum ether/ethyl acetate mixture given in experimental section.

Table IV.2 Synthesis of dihydro-dichromeno-pyridine-6,8-dione derivatives using sulphonated rice husk[a]

Entry	Reactant	Product	Time	Yield(%)[b]
1		 (4a)	240 min	96

2		 (4b)	240 min	93
3		 (4c)	240 min	95
4		 (4d)	240 min	94
5		 (4e)	240 min	97
6		 (4f)	240 min	92

7		 (4g)	240 min	98
8		 (4h)	240 min	97
9		 (4i)	240 min	92
10		 (4j)	240 min	96

[a] Reaction of p-toluealdehyde (1 mmol), 4-hydroxycoumarine (2 mmol), and ammonium acetate(1.2 mmol) [b] Isolated yield after purification through recrystalisation.

IV.12.A.4 Plausible Mechanism

A plausible mechanism for the synthesis of dihydro-dichromeno-pyridine-6,8-dione is established by considering the acidic behaviour of the catalyst (**Figure IV.12**). At the very first step of the reaction, protonation occurs at aldehyde oxygen of aromatic aldehyde and then a successive condensation reaction occurs between 2 molecules of 4-hydroxy coumarine with 1 molecule of aldehyde to give a bis-coumarol intermediate.[62] Now, the bis-coumarol intermediate undergo totomerisation followed by a cyclocondensation reaction with NH_4OAc to give the final product dihydro-dichromeno-pyridine-6,8-dione

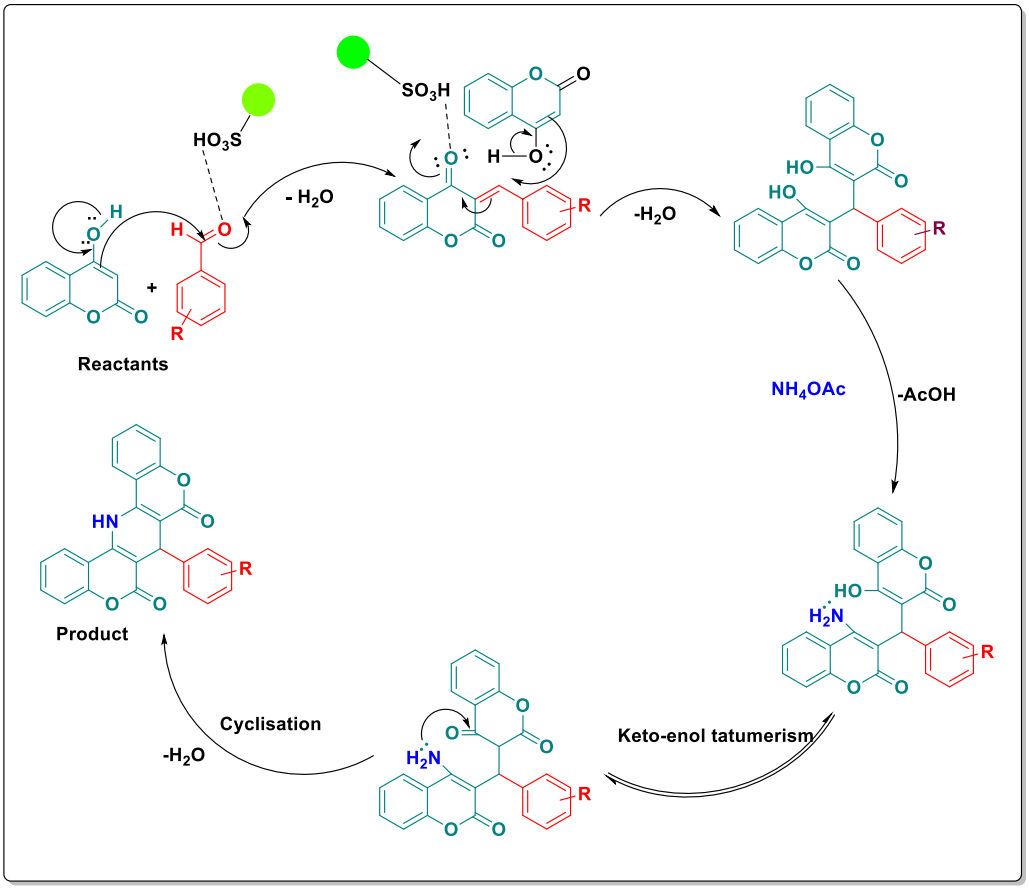
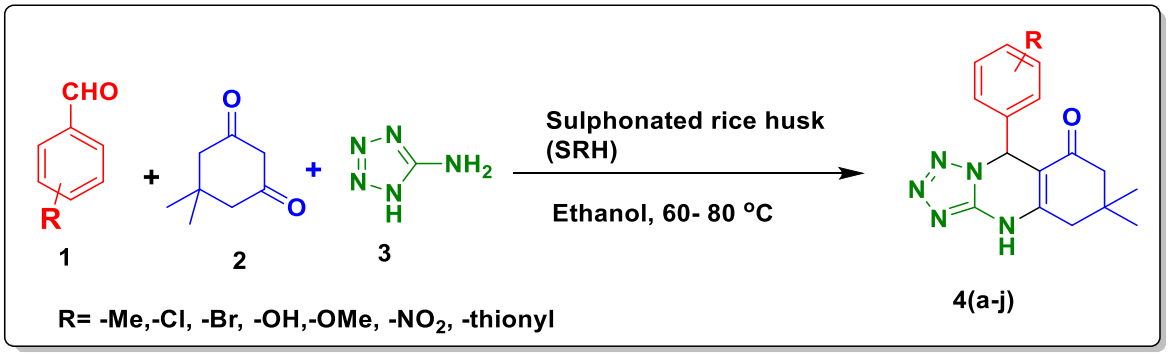


Figure IV.12The plausible mechanism for the synthesis of dihydro-dichromeno pyridine-6,8-dione

The next present work leads to the synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives (**Scheme IV.24)** by using greener catalyst heterogeneous catalyst sulphonated rice husk (SRH) .



Scheme IV.24 Synthesis of substituted tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives using sulphonated rice husk[a]

IV.12.A.5 Optimization of synthesis of substituted tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives

One pot synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolinones, initially carried out with taking anisaldehyde (1 mmol), 5-amino-1*H*-tetrazole (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) taken in a 25 mL RB. It was observed that in presence of 100 mg of the catalyst in ethanol solvent at 70^0 C temperature (**Table IV.3,** entry 7) with reaction

time of 13 hours maximum yield was observed. The optimized reaction condition was observed with the amount of catalyst and for screening the optimized reaction condition, anisaldehyde (1 mmol) along with 5-amino-1*H*-tetrazole (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) were taken in ethanol. In absence of catalyst the formation of the expected product was not formed (**Table IV.3,** entry 13) and with addition of 100 mg of catalyst, the performance of the reaction was observed with satisfactory yield (84%) in ethanol solvent. (**Table IV.3,** entry 7). The amount of the catalyst and time of the reaction was checked thoroughly to find out the optimized reaction condition and it was observed that the best result was obtained at 70^0C temperature using minimum amount of catalyst SRH (90 mg) in presence of ethanol solvent (**Table IV.3**, entry 9). The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (**Scheme IV.24**) containing electron donating and electron withdrawing substituents and the targeted compounds (4a-4i) are successively synthesized using SRH as an efficient greener catalyst under greener reaction condition. The progress of the reaction was monitored continuously by thin layer chromatography (TLC) and the crude product was separated from ethylacetate extract by addition of petroleum ether

followed by purification through washing with ethylacetate and petroleum ether mixture {petroleum ether/ethyl acetate (v/v ratio70/20) mixture}.

Table IV.3 Optimisation of the reaction condition for the synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives [a]

Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time	Yield (%)[b]
1	100	Ethanol	90	15 h	84
2	120	Ethanol	100	16 h	70
3	120	Ethanol	80	16 h	84
4	110	Ethanol	80	16 h	84
5.	110	Ethanol	70	15 h	84
6.	100	Ethanol	70	14 h	84
7.	100	Ethanol	70	13 h	84
8.	90	Ethanol	70	12 h	84
9.	90	Ethanol	70	11 h	84
10.	90	Ethanol	70	10 h	83
11.	90	Ethanol	60	11 h	72
12.	90	Ethanol	60	15 h	73
13.	None	Ethanol	70	15 h	Trace
14.	90	H_2O	70	15 h	-
15.	80	Ethanol/H_2O(4:1)	70	10 h	Trace
16.	80	Ethanol/H_2O(1:1)	70	10 h	Trace

17.	90	Methanol	70	10 h	83

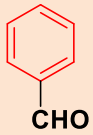
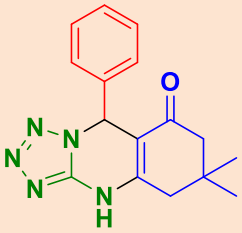
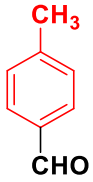
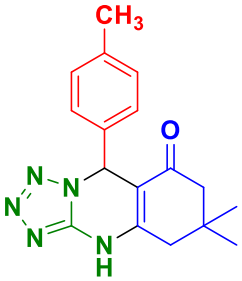
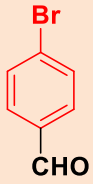
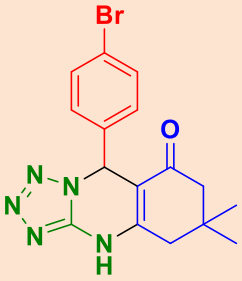
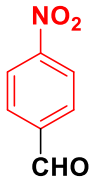
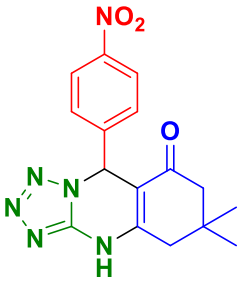
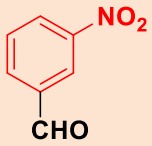
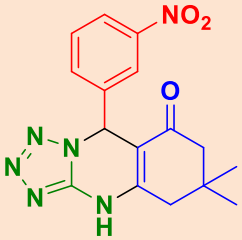
[a]Reaction of anisaldehyde (1 mmol), 5-amino-1*H*-tetrazole (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) . [b]The yields are isolated through recrystalisation.

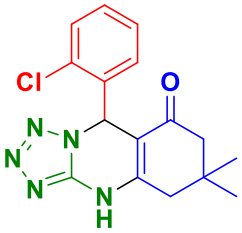
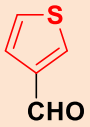
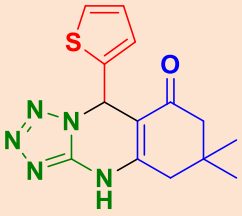
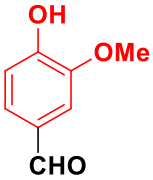
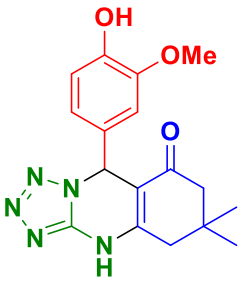
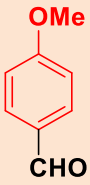
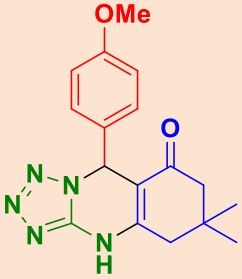
IV.12.A.6 Synthesis of substituted tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives

The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (**Scheme IV. 24**) having electron donating and electron withdrawing substituents at *ortho*, *meta* and *para* position of the aromatic aldehyde. (**Table IV.4**) The targeted compounds (4a-4j) are successively synthesized using SRH as an efficient catalyst under greener reaction condition. The progress of the reaction was monitored continuously by thin layer chromatography (TLC) and the crude product was separated from ethylacetate extract by addition of petroleum ether followed by purification through washing with ethylacetate and petroleum ether mixture given in experimental section.

Table IV. 4 Synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives[a]

Entry	Reactant	Product	Time	Yield(%)[b]

1		 (4a)	14 h	80
2		 (4b)	12 h	84
3		 (4c)	11 h	83
4		 (4d)	10 h	82
5		 (4e)	10 h	80

6		 **(4f)**	14 h	82
7		 **(4g)**	15 h	83
8		 **(4h)**	15 h	84
9		 **(4i)**	13 h	86

[a]Reaction of aromatic aldehydes (1 mmol), 5-amino-1*H*-tetrazole (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) . [b]The yields are isolated through recrystalisation.

IV.12.A.7 Plausible Mechanism

A plausible SRH catalyzed synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives are established considering the acidic

behaviour of the catalyst (**Figure III.13**). At very first step of the reaction, protonation occurs at aldehyde oxygen of aromatic aldehyde followed by Hantzsch condensation of aldehydes with β-diketones and ammonium acetate. Intermediates are produced in situ rapidly undergo cyclization and exters the targeted tetrahydrotetrazolo[5,1-*b*]quinazolinone derivatives product.

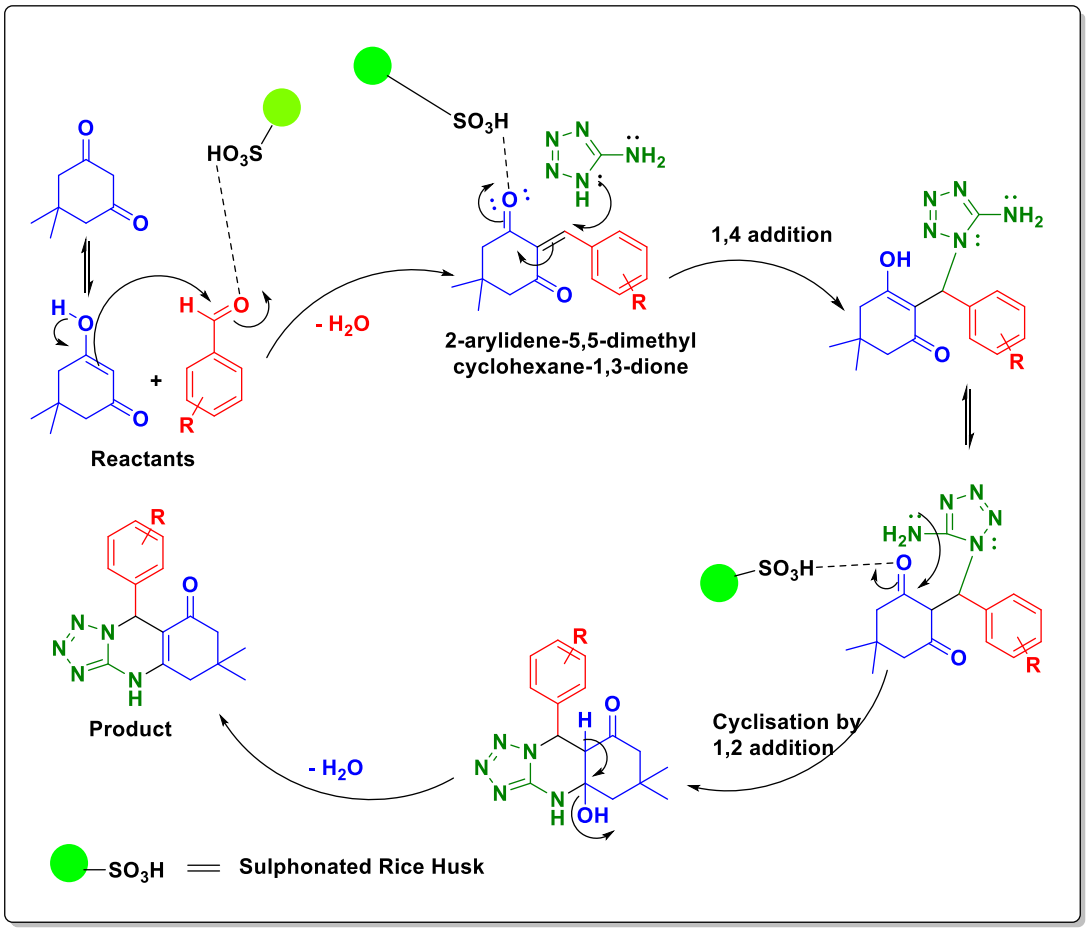
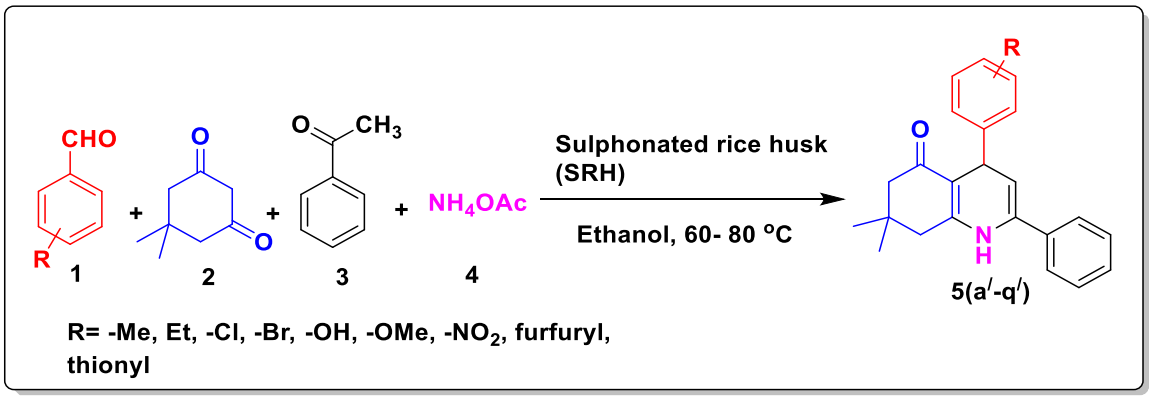


Figure IV.13 The plausible mechanism for the synthesis of tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one

The next present work leads to the synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives (**Scheme IV.25)** by using greener catalyst heterogeneous catalyst sulphonated rice husk (SRH) .



Scheme IV.25 Synthesis of substituted 2,4-diaryl hexahydroquinoline-5-one derivatives using sulphonated rice husk[a]

IV.12.A.8 Optimization of synthesis of substituted 2,4-diarylhexahydroquinoline-5-one derivatives

One pot synthesis of 2,4-diarylhexahydroquinoline-5-one derivatives was initially carried out with taking aromatic aldehyde (1 mmol) along with acetophenone (1 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) and ammonium acetate (1 mmol) taken in a 15 mL glassed sealed reaction tube. It was observed that when the reactants are taken at a time in a vessel to react randomly in presence of 120 mg arbitrary amount of catalyst, it produced 9-arylhexahydroacridine as a

major product. Literature studies along with a few controlled experiment suggested that formation of in situ chalcone derivative is important for the synthesis of 2,4-diaryl hexahydroquinoline-5-one as major product. After observing the science behind it, the reaction was started first with condensation reaction between the participated aromatic aldehyde (1 mmol) and acetophenone (1 mmol) in presence of SRH catalyst only for 1 hour followed by addition of 5,5-dimethylecyclohex-1,3-dione (1 mmol) and ammonium acetate (1 mmol) at a time into the reaction mixture. After addition of 5,5-dimethylecyclohex-1,3-dione (1 mmol) and ammonium acetate (1 mmol) the progress of the reaction was monitored continuously by thin layer chromatography (TLC) until the reaction was adequately completed. For determining the optimized reaction condition, vaniline (1 mmol) was taken as the participating aromatic aldehyde along with other substituents. The variation of the amount of catalyst along with temperature were made to determine the precise optimized condition for the reaction (**Table IV.5**). The optimized reaction condition was followed for the synthesis of other compounds under **Scheme IV.25** (5a-5k). The generality of the reaction was observed for the aromatic aldehydes having electron withdrawing, electron donating substituents along with fluorinated, heterocyclic and

polyaromatic aromatic aldehydes. All the products were isolated from ethyl acetate extract of the reaction mixture by column chromatograpy using petroleum ether/ethyl acetate (v/v 70:30).

Table IV.5 Optimization of the reaction condition for the synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives[a]

Entry	Catalyst (mg)	Solvent	Temperature (^{o} C)	Time	Yield (%)[b]
1	100	Ethanol	100	15 h	85
2	120	Ethanol	100	15 h	85
3	120	Ethanol	120	15 h	85
4	110	Ethanol	90	15 h	85
5.	100	Ethanol	90	14 h	85
6.	90	Ethanol	80	13 h	85
7.	90	Ethanol	70	12 h	85
8.	80	Ethanol	70	12 h	85
9.	70	Ethanol	70	12 h	84
10.	**70**	**Ethanol**	**70**	**11 h**	**82**
11	60	Ethanol	70	11 h	74
12.	70	Neat	70	12 h	30
13.	70	H_2O	70	12 h	-
14	70	Ethanol/H_2O	70	12 h	-
15	70	Methanol	80	12 h	70

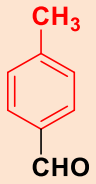
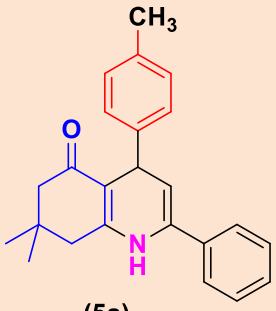
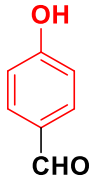
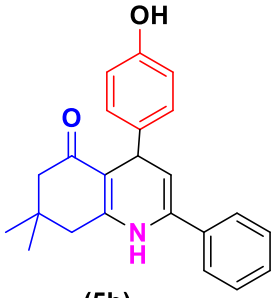
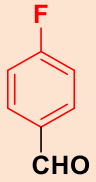
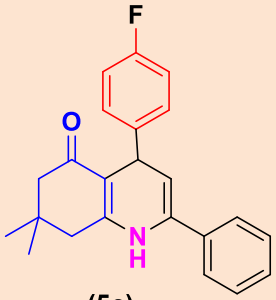
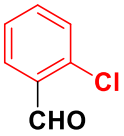
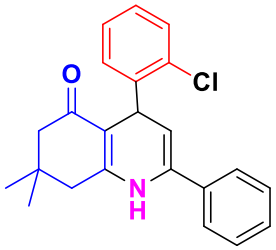
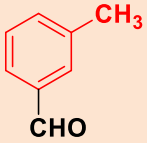
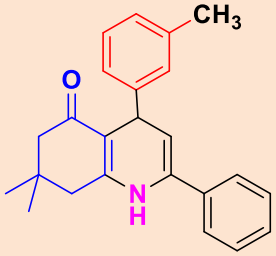
[a] Reaction of Vaniline (1mmol), acetophenone (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1mmol), ammonium acetate (1.2 mmol) and SRH (60 mg). [b] The yields are isolated through column chromatography.

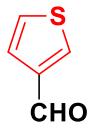
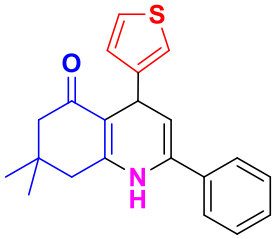
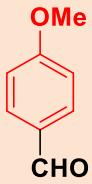
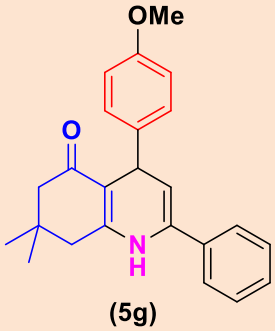
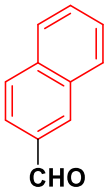
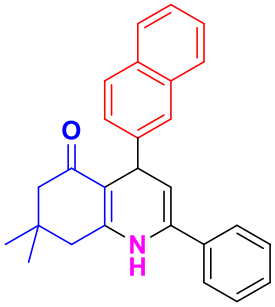
IV.12.A.9 Synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives

The generality of the reaction was observed with a variety of aromatic and heterocyclic aldehydes (**Scheme IV.25**) having electron donating and electron withdrawing substituents at *ortho*, *meta* and *para* position of the aromatic aldehyde. The targeted compounds (4a-4j) are successively synthesized using SRH as an efficient catalyst under greener reaction condition.(**Table IV.6**) The progress of the reaction was monitored continuously by thin layer chromatography (TLC) and the crude product was separated from ethylacetate extract by addition of petroleum ether followed by purification through washing with petroleum ether/ethyl acetate mixture given in experimental section.

Table IV.6 Synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives[a]

Entry	Reactant	Product	Time	Yield(%)[b]

1		 **(5a)**	12 h	86
2		 **(5b)**	12 h	86
3		 **(5c)**	12 h	83
4		 **(5d)**	12 h	86
5		 **(5e)**	12 h	85

6		 **(5f)**	12 h	84
7		 **(5g)**	12 h	85
8		 **(5h)**	12 h	87

[a] Reaction of aromatic aldehyde (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1 mmol), acetophenone (1 mmol) cyclohexylamine (1 mmol) and SRH (50 mg). The yields are isolated through column chromatography.

IV.12.A.10 Plausible Mechanism

The mechanism of the reaction starts with the protonation of the aldehyde and the condensation of aldehyde and acetophenone to give chalcone derivative. (**Figure IV.14**) And then successive cyclocondensation of chalcone, present dimedone and ammonium

acetate (NH_4OAc) catalysed by SRH catalyst gives rise to the formation of 2,4-diarylhexahydroquinoline.

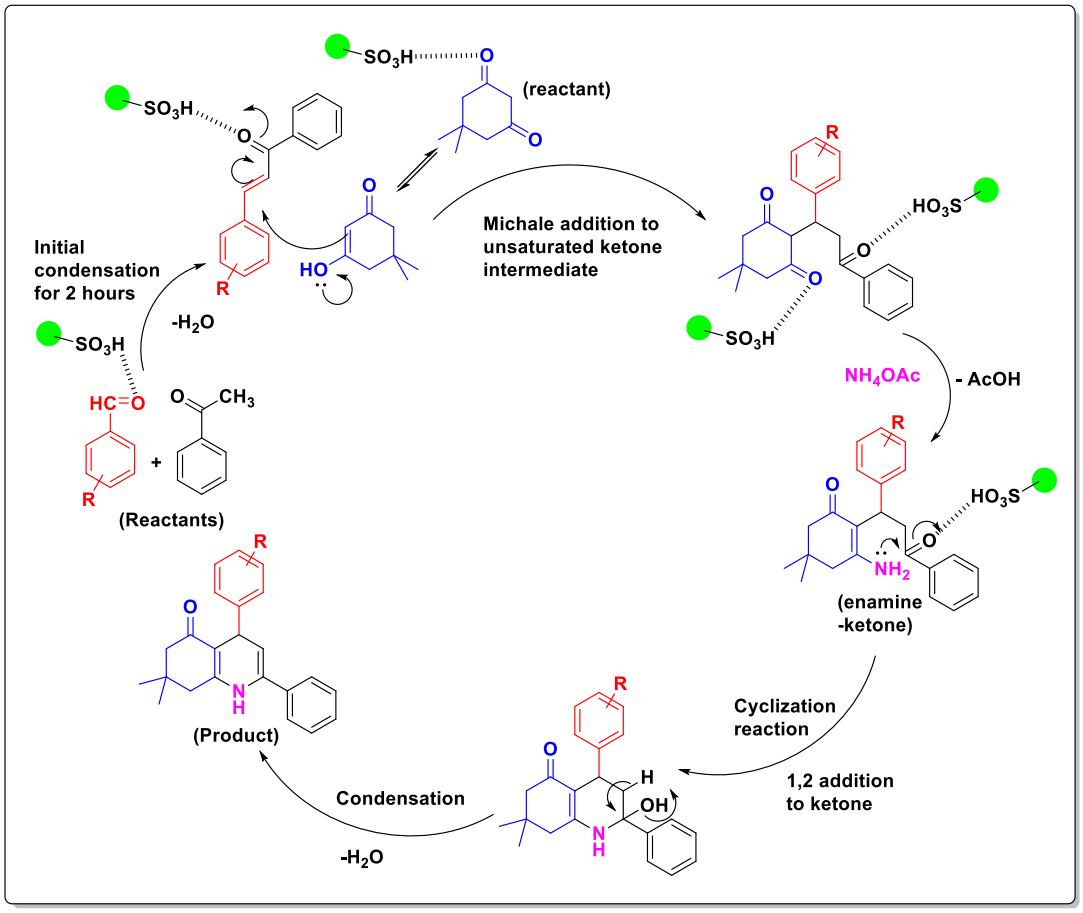


Figure IV.14 The plausible mechanism for the synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives

IV.12.A.11 Catalyst Recyclability Experiment

To check the recyclability of the catalyst, a model reaction between benzaldehyde (2 mmol), 4-hydroxycoumarine (4 mmol), ammonium acetate (2 mmol) in presence of 120 mg of sulphonated rice husk was

carried out under optimised reaction condition. (**Scheme IV.25, Table IV.7**) After successful completion of the each reaction step, ethyl acetate (10 ml) was added to the reaction mixture. The supernatant liquid (ethyl acetate extract) was decanted off and this process was repeated until the catalyst was free from reaction mixture. Then the recovered catalyst was washed with acetone repeatedly and dried under vaccum. The recovered catalyst weight was measured after every recovery step and the next reaction was repeated with that amount of recovered catalyst by following proportionality with the aldehyde amount (mmol). The temperature and time of the reaction were kept constant following optimized reaction condition. Amount of catalyst, reactant (aldehyde), reaction time, temperature and yield percentage of the product have been shown in **Table IV.7** (**entry 1-6**). The FTIR spectra of recovered SRH catalyst after successive reactions was added here for further support of the catalyst efficiency. (**Figure IV. 15 and Figure IV. 16**).

Table IV.7 Table for the amount of recovered catatyst with isolated [a]

Entry	Catalyst (mg)	Aldehyde (x mmol)	Temperature (^{o} C)	Time (min)	Yield (%)[b]
1	120	2.00 mmol	70	180	98
2	110	1.83 mmol	70	180	94

3	100	1.66 mmol	70	180	87
4	90	1.50 mmol	70	180	80
5.	80	1.33 mmol	70	180	75
6.	70	1.16 mmol	70	180	70

[a] Reaction of anisaldehyde (x mmol), 4-hydroxycoumarine (2x mmol), ammonium acetate (x mmol), [b] Isolated yield

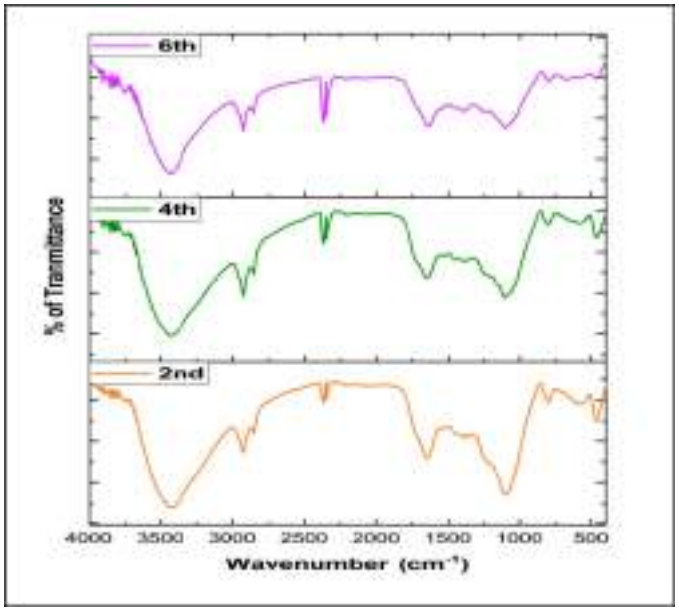


Figure IV.15 FTIR spectra of reused catalysts after 2nd, 4th and 6th run.

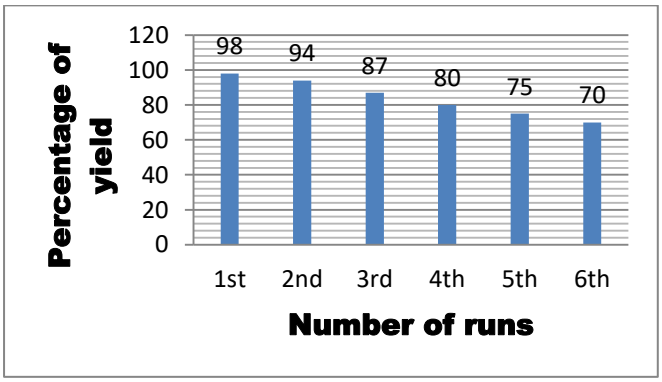


Figure IV.16 Recyclability experiment of catalyst

IV.12.A.12 Conclusion

In conclusion, a simple and greener methodology for the synthesis of a variety of substituted dihydro-dichromeno-pyridine-6,8-diones, tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones and 2,4-diarylhexahydroquinolinone derivatives with a good yield. This heterogeneous catalyst is found to be sufficiently efficient for the synthesis of dihydro-dichromeno-pyridine-6,8-diones, tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones and 2,4-diarylhexahydroquinolinone derivatives in a greener way. The greener catalyst is highly recyclable upto 6^{th} run and has the ability to catalyse wide range of acid-catalysed reactions or cyclocondensation reactions.

IV.12.A.13 Acknowledgement

. One of the authors (S.D) is thankful to UGC, New Delhi for financial support, PU Saif for SEM, EDX, powder XRD and NMR analysis for this above work.

IV.12.A.14 Experimental

IV.12.A.14.a Catalyst preparation

The heterogeneous catalyst (SRH) was prepared by direct sulphonation of rice husk (RH) already described in Chapter II .[102]

IV.12.A.14.b General procedure for synthesis of dihydro-dichromeno-pyridine-6,8-dione derivatives

A mixture of 4-hydroxycoumarine (2 mmol), aromatic aldehyde (1 mmol), ammonium acetate (NH_4OAc) (1.2 mmol), and SRH (60 mg) in a 20-mL glass sealed tube was stirred at 60^0C temperature for 240 min. The progress of the reaction was monitored by thin-layer chromatography (TLC) (**Scheme IV.23**). After completion of the reaction, the product was first extracted with ethyle acetate solvent and the catalyst was separated by simple filtration with filter paper. Then ethyl acetate extract was concentrated and the product was isolated in petroleum ether and the crude product was purified by washing the crude with petroleum ether, ethylacetate-petroleum ether mixed solvent (1:6 and 1:4).

IV.12.A.14.c General procedure for synthesis of tetrahydrotetrazolo[5,1-b]quinazolin-8(4H)-one derivatives

A mixture of 5,5-Dimethylcyclohexane-1,3-dione (1 mmol), aromatic aldehyde (1 mmol), 5-aminoterazole (1.2 mmol), and SRH (100 mg) in a 25-mL round bottom flusk was stirred at 70 ^{o}C temperature for 15h in

ethanol. The progress of the reaction was monitored by thin-layer chromatography (TLC) (**Scheme IV.24**). After completion of the reaction, the product was extracted with ethyle acetate and the catalyst was separated by simple filtration. Then ethyl acetate extract was concentrated and crude product was sperated by simple preceipitation in petroleum ether then was purified by washing the crude with ethyacetate/petroleum ether mixture (1:4)

IV.12.A.14.d General procedure for synthesis of 2,4-diarylhexahyroquinolines

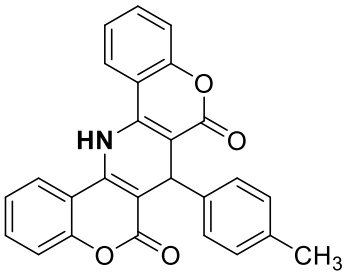
A mixture aromatic aldehyde (1 mmol) and acetophenone (1 mmol) was strirred at 70^0C temperature for 1 hour in a sealed tube in ethanol in presence of SRH catalyst then of 5,5-Dimethylcyclohexane-1,3-dione (2 mmol) and ammonium acetate (NH_4OAc) (1.2 mmol) was added to it and stirred at 70 ^{o}C temperature for 60 minutes. The progress of the reaction was monitored by thin-layer chromatography (TLC) (Scheme IV.25). After completion of the reaction, the product was extracted with ethyle acetate and the pure product was separated by column chromatography.

IV.12.A.14.e General Procedure for ^{1}H & ^{13}C NMR

NMR spectra of all the products were taken in DMSO-d_6 (TMS as an internal standard) using a Bruker 400MHz spectrometer(operating for ^{1}H at 400 MHz and for ^{13}C at 100 MHz) and Bruker Advance NEO 500MHz spectrometer(operating for ^{1}H at 500 MHz and for ^{13}C at 125 MHz). ^{1}H-NMR spectroscopic data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br = broad), integration, coupling constants in Hertz (Hz). ^{13}C NMR spectroscopic data are reported in ppm.

IV.12.A.14.f Spectral data of the compounds mentioned in Scheme IV.23

7-(p-tolyl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4a)



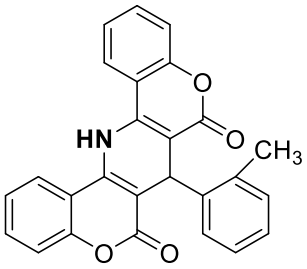
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)2.23(s,3H),6.25(s,1H),6.97-7.01(m,5H),7.23-7.26(q,2H),7.27-7.28(d,2H),7.49-7.53(m,2H),7.83-7.85(m,2H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)20.42,35.67,103.57,115.43,119.59,122.91,123.99,126.51,128.26,130.92,133.54,138.71,152.36,164.64,167.29.

7-(o-tolyl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4b)



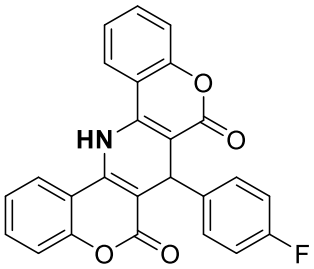
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)2.08(s,3H),6.09(s,1H),6.69-7.02(m,3H),7.20-7.29(m,6H),7.47-7.50(m,2H),7.80-7.82(m,2H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)19.47,35.44,103.05,115.80,119.82,122.77,123.94,124.62,124.98,128.16,129.92,130.64,135.47,152.24,163.98,167.81.

7-(4-fluorophenyl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4c)



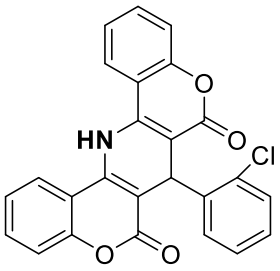
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.26(s,1H),6.97-7.14(m,2H),7.22(m,2H),7.24-7.28(m,2H),7.33-7.37(m,2H),7.49-7.53(m,2H),7.82-7.84(m,2H),17.59(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.52,103.33,114.12,114.28,115.42,119.89,122.89,124.07,128.23,128.29,130.95138.07,138.09,152.14,159.23,161.04,164.58,167.79.

7-(2-chlorophenyl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4d)



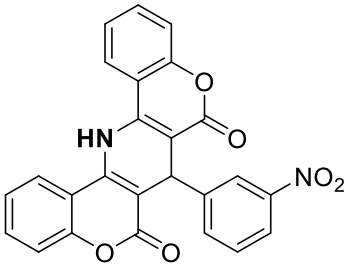
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.18(s,1H),7.20-7.26(m,9H),7.42-7.51(m,3H),7.82-7.84(m,2H),17.15(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.02,90.71,103.29,115.33,116.24,119.84,122.73,123.74,124.66,126.54,126.56,127.56,130.76,132.51,142.29,152.40,153.45,161.85,164.44,165.84,167.57.

7-(3-nitrophenyl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4e)



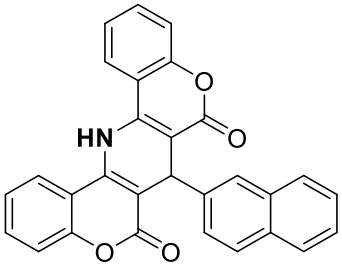
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.39(s,1H),7.24-7.31(m,4H),7.49-7.55(m,3H),7.59-7.61(m,1H),7.83-7.85(m,2H),7.92(d,1H), 8.00-8.02(m,2H),17.48(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.19,102.59,115.55,119.59,120.28,121.01,123.06,124.13,129.31,131.76,145.00,147.70,152.49,164.44,167.99.

7-(naphthalen-2-yl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4f)



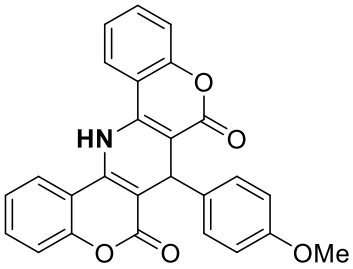
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)6.44(s,1H),7.23-7.31(m,5H),7.36-7.40(m,3H),7.51-7.59(m,3H),7.70-7.72(m,2H),7.78-7.80(m,2H),7.82-7.84(m,2H),17.55(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.43,103.30,114.32,115.43,115.72,116.26,116.70,119.88,122.85,123.11,123.15,123.82,124.06,124.08,124.67,125.45,126.21,127.03,127.05,127.36,130.88,131.30,132.04,132.60,132.94,140.02,152.47,153.43,153.59,155.50,161.54,161.82,164.59,165.58,167.88.

7-(4-methoxyphenyl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4g)



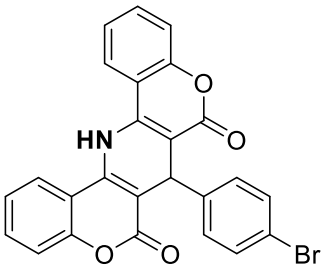
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)3.68(s,3H),6.20(s,1H),6.72-6.74(dd,2H),7.00(d,2H),7.21-7.26(m,4H),7.48-7.51(m,2H),7.80-7.82(dd,2H),17.59(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)35.25,54.77,103.56,113.01,115.32,119.86,122.74,123.98,127.50,130.73,133.94,152.37,156.69,164.50,167.54.

7-(4-bromophenyl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4h)



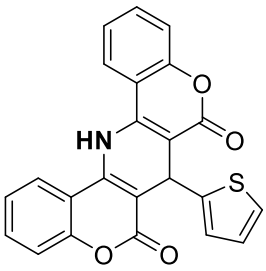
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.23(s,1H),7.06-7.08(m,2H),7.22-7.28(m,4H),7.34-7.37(m,2H),7.49-7.53(m,2H),7.82-7.84(m,2H),17.53(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)35.77,103.00,115.43,117.74,119.73,122.89,124.06,128.94,130.46,130.98,141.79,152.43,164.50,167.78.

7-(thiophen-2-yl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4i)



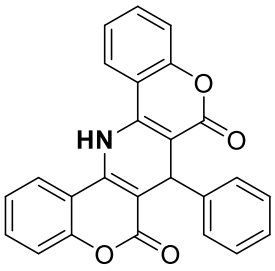
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.42(s,1H),6.60-6.61(m,1H),6.80-6.81(dd,1H),7.14-7.15(dd,1H),7.23-7.27(m,5H),7.50-7.53(m,2H),7.85-7.87(dd,3H),17.91(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)32.85,103.64,115.42,119.79,122.55,122.89,122.94,124.14,126.02,131.02,147.96,152.39,164.08,167.88.

7-phenyl-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3',4'-*e*]pyridine-6,8-dione(4j)



^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)6.27(s,1H),7.05-7.10(m,3H),7.14-7.17(m,2H),7.21-7.26(m,4H),7.33-7.37(m,1H),7.485-7.519(m,2H),7.62-7.66(m,1H),7.80-7.84(m,3H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)36.02,103.29,116.24,119.84,122.73,123.74,124.66,126.54,127.56,130.76,132.51,142.29, 153.45,164.44,167.57.

IV.12.A.14.g Sanned copies of compounds mentioned in Scheme IV.23

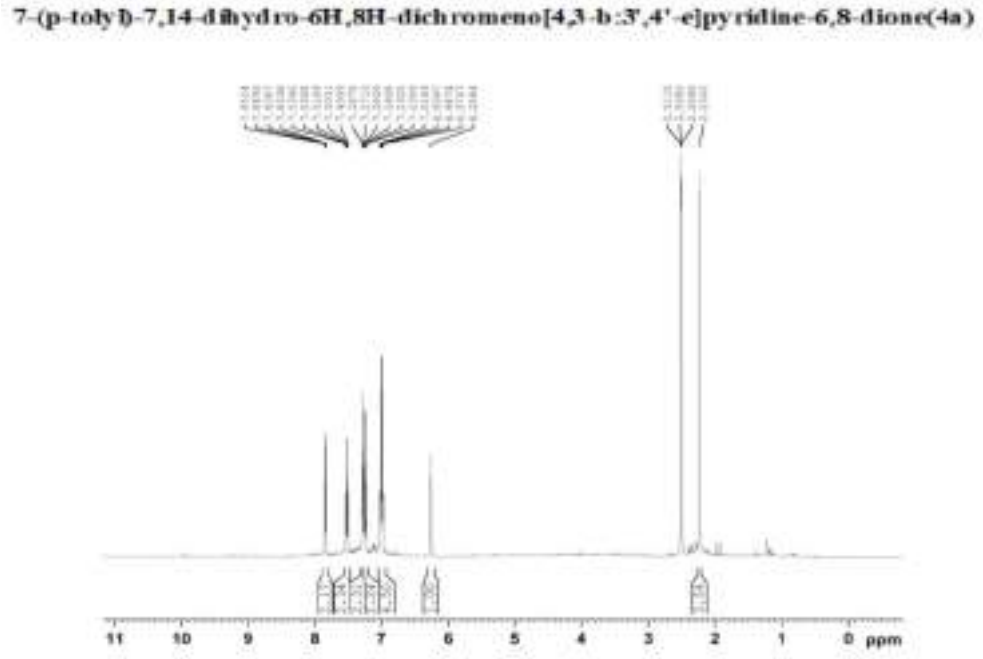


Figure IV.17-^{1}H-NMR of compound 4a

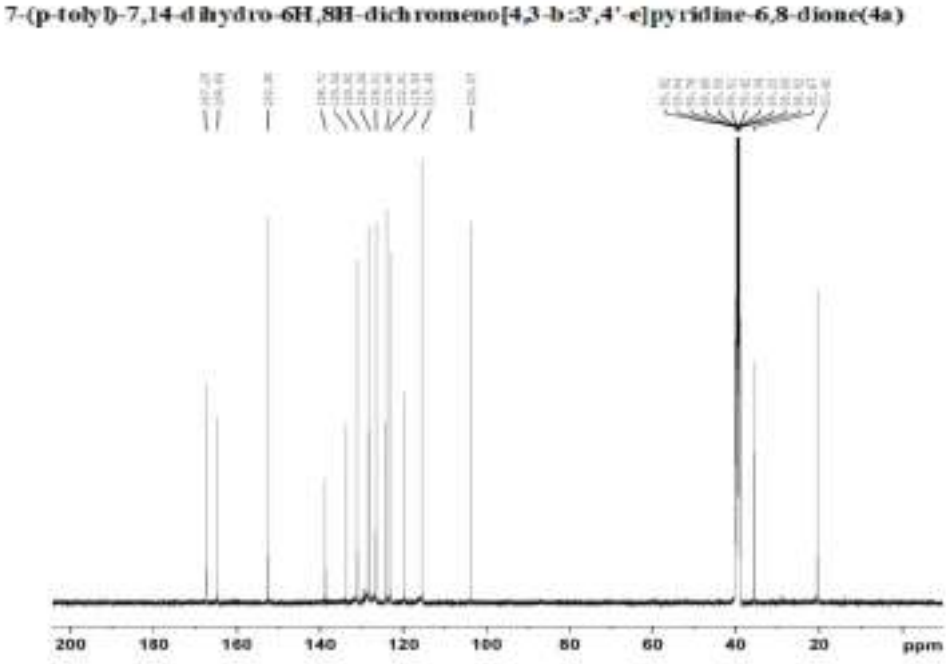


Figure IV.18-^{13}C-NMR of compound 4a

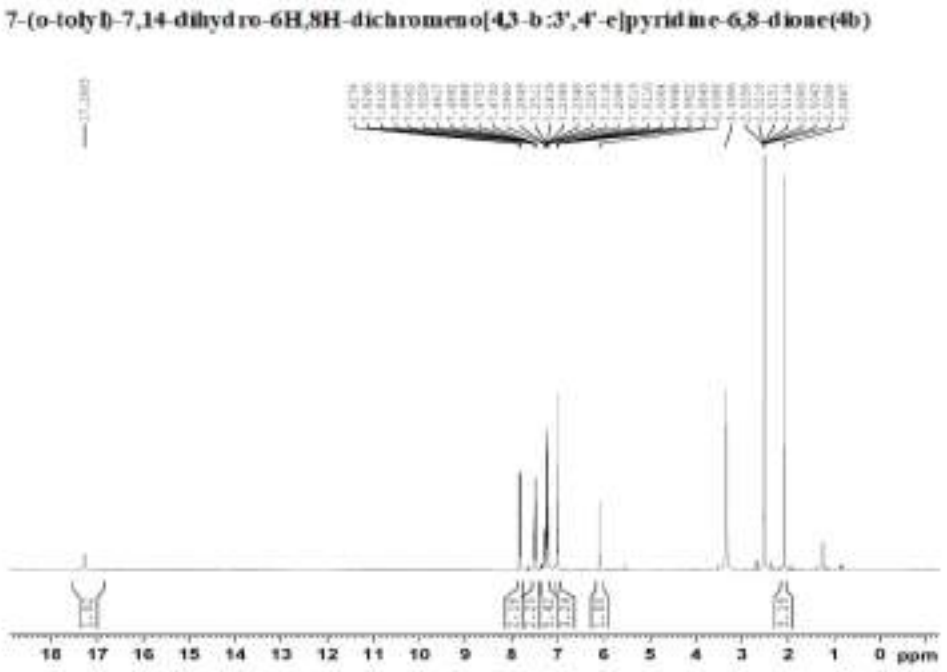


Figure IV.19-^{1}H-NMR of compound 4b

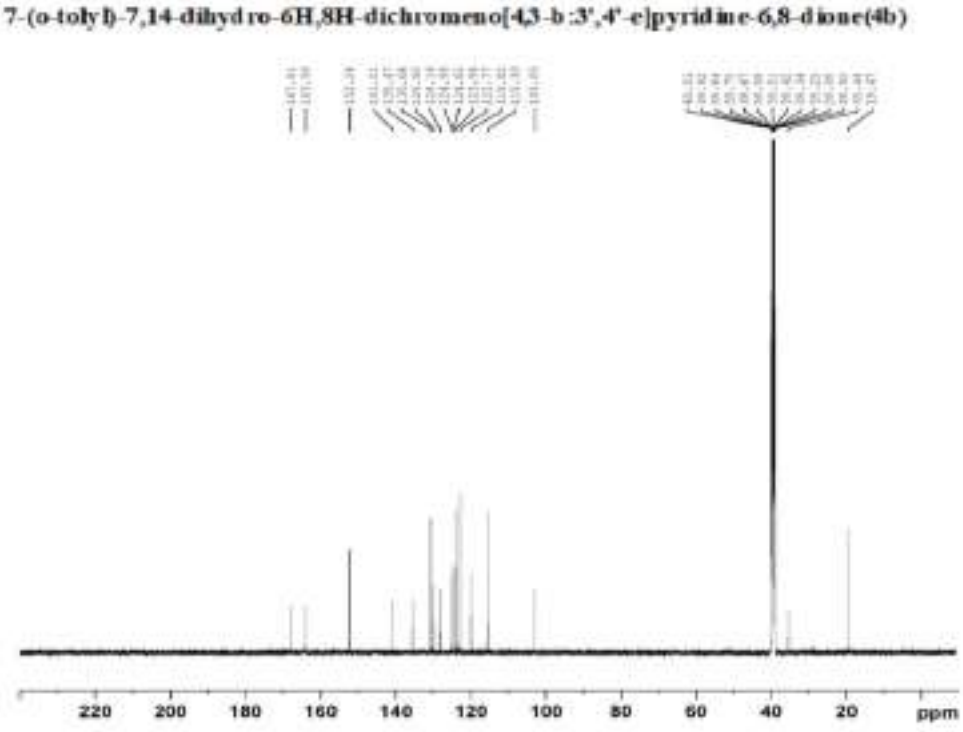


Figure IV.20-^{13}C-NMR of compound 4b

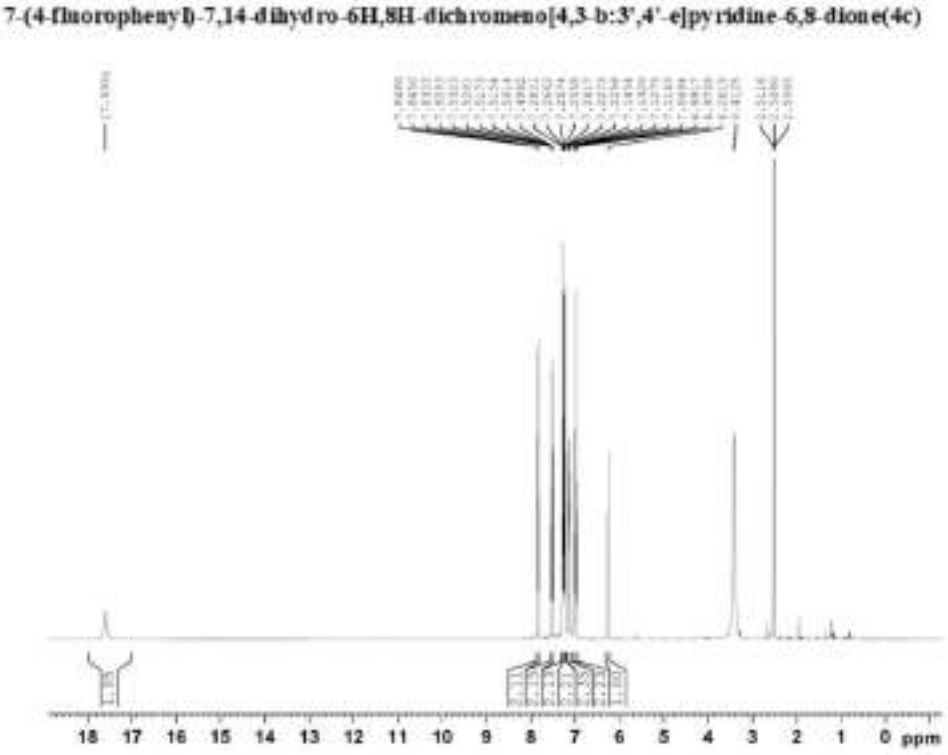


Figure IV.21-^{1}H-NMR of compound 4c

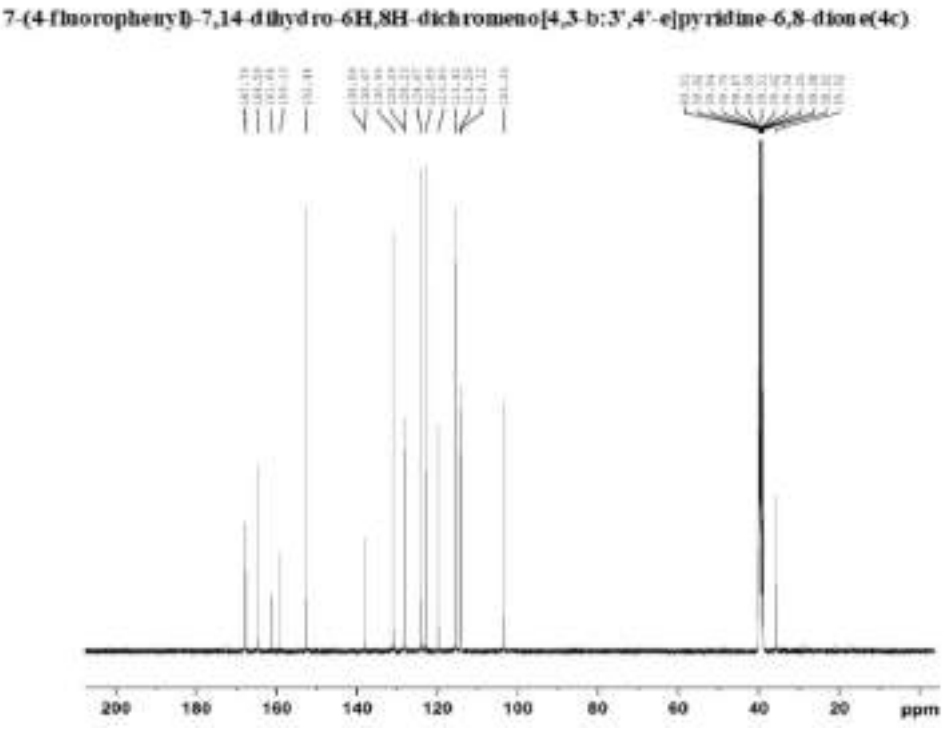


Figure IV.22-^{13}C-NMR of compound 4c

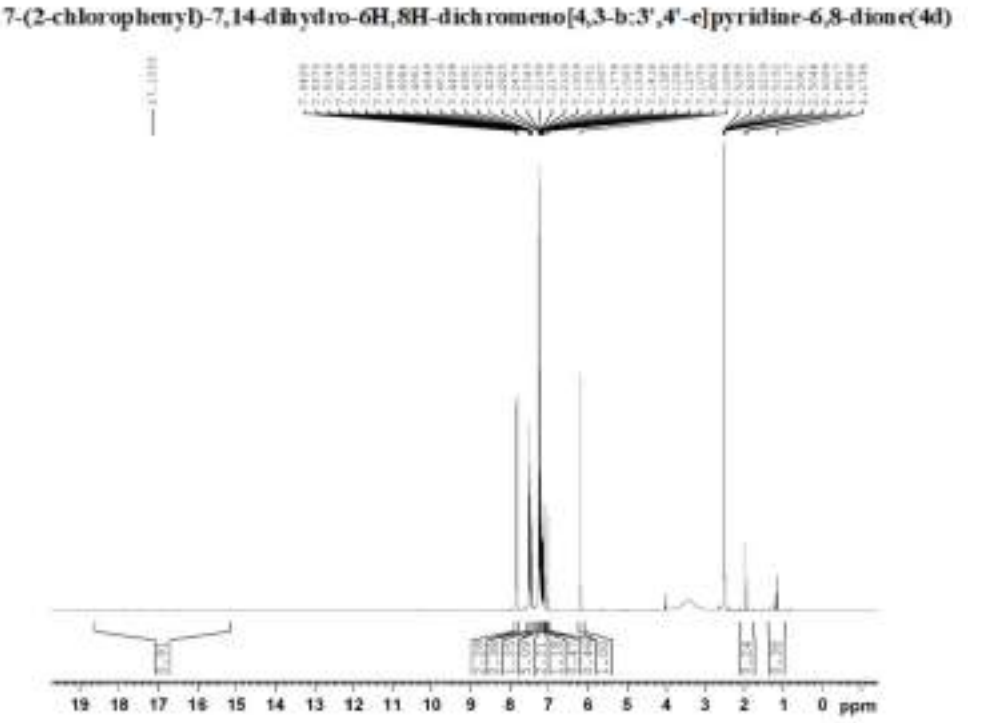


Figure IV.23-^{1}H-NMR of compound 4d

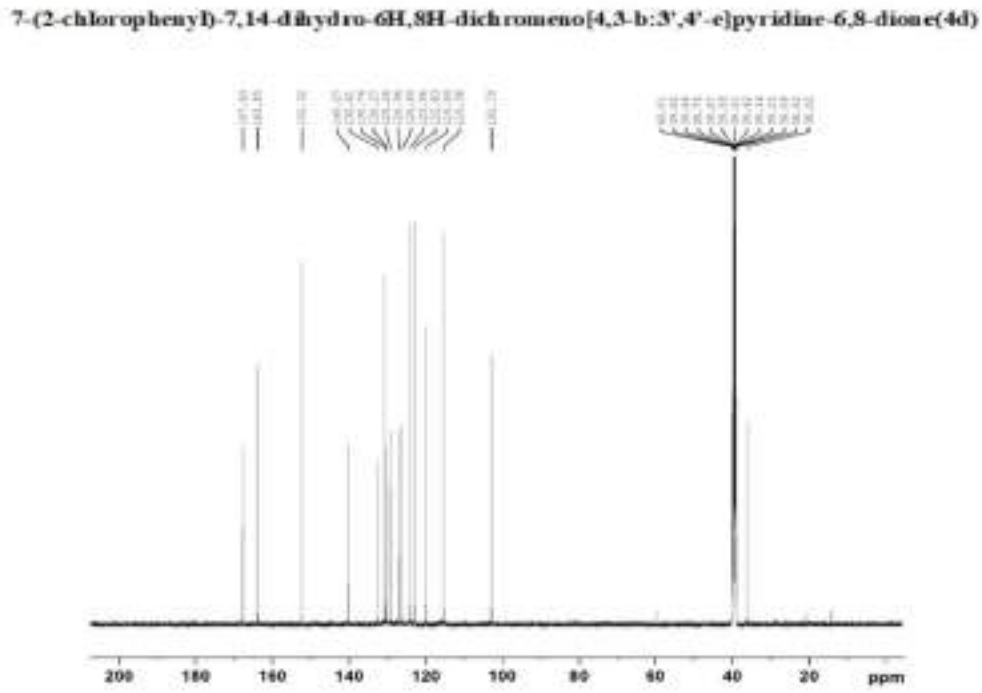


Figure IV.24-^{13}C-NMR of compound 4d

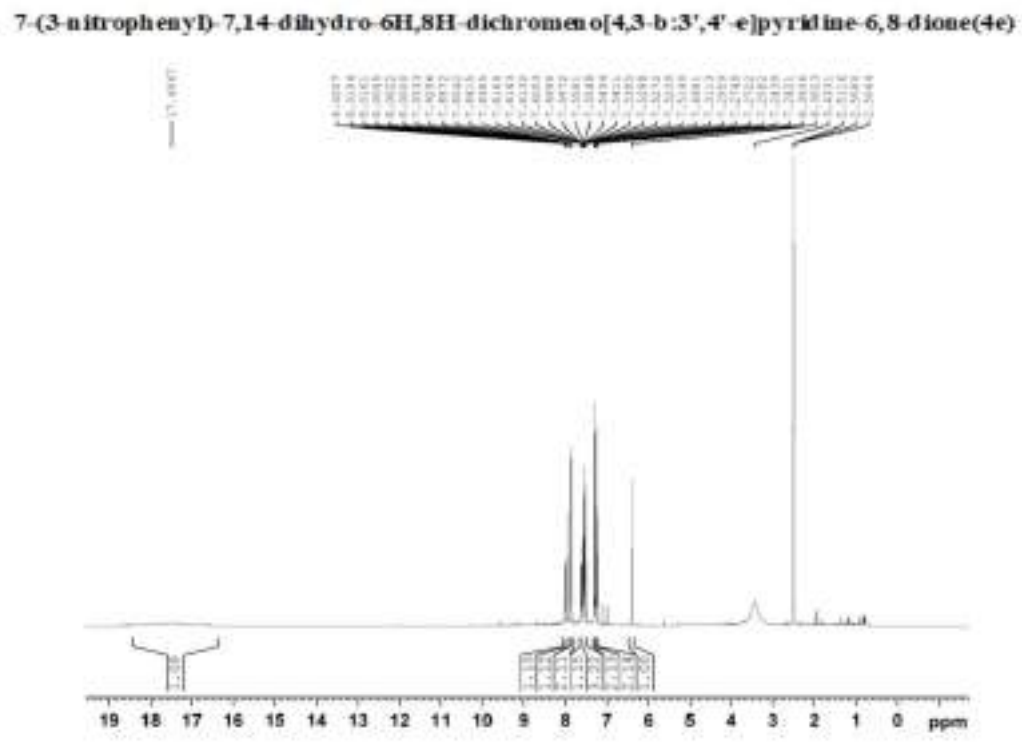


Figure IV.25-^{1}H-NMR of compound 4e

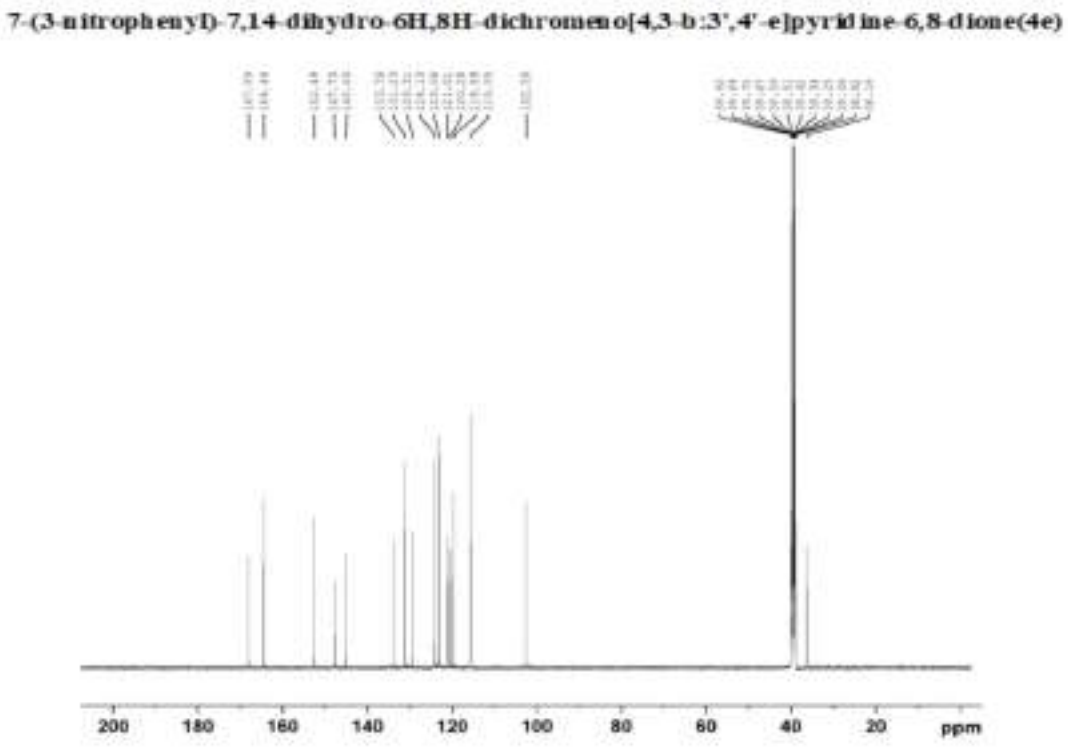


Figure IV.26-^{13}C-NMR of compound 4e

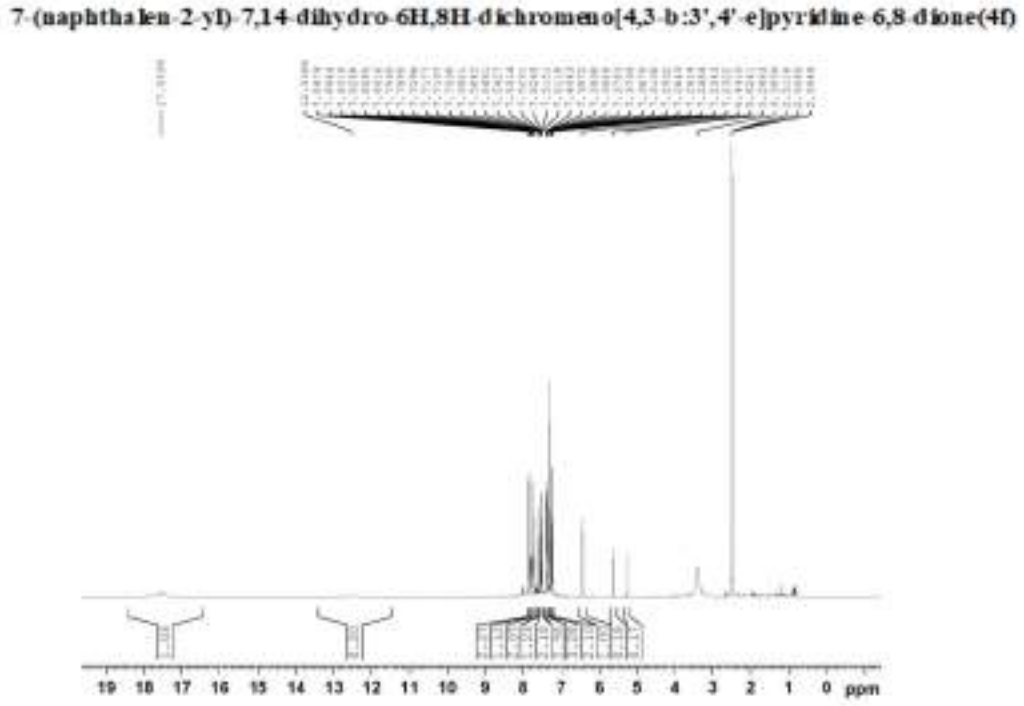


Figure IV.27-^{1}H-NMR of compound 4f

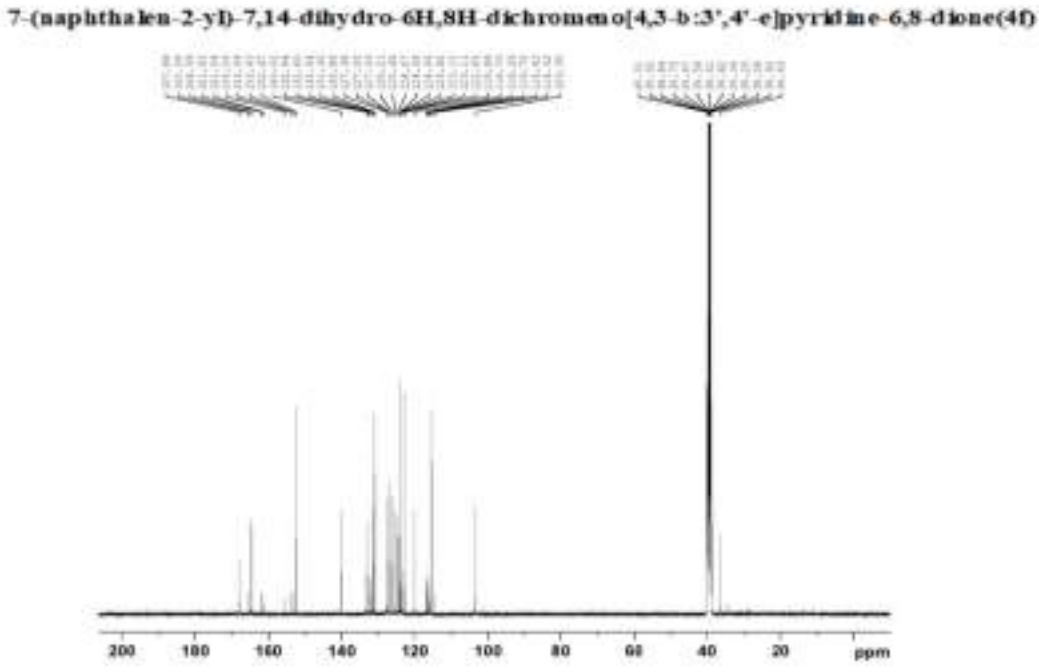


Figure IV.28-^{13}C-NMR of compound 4f

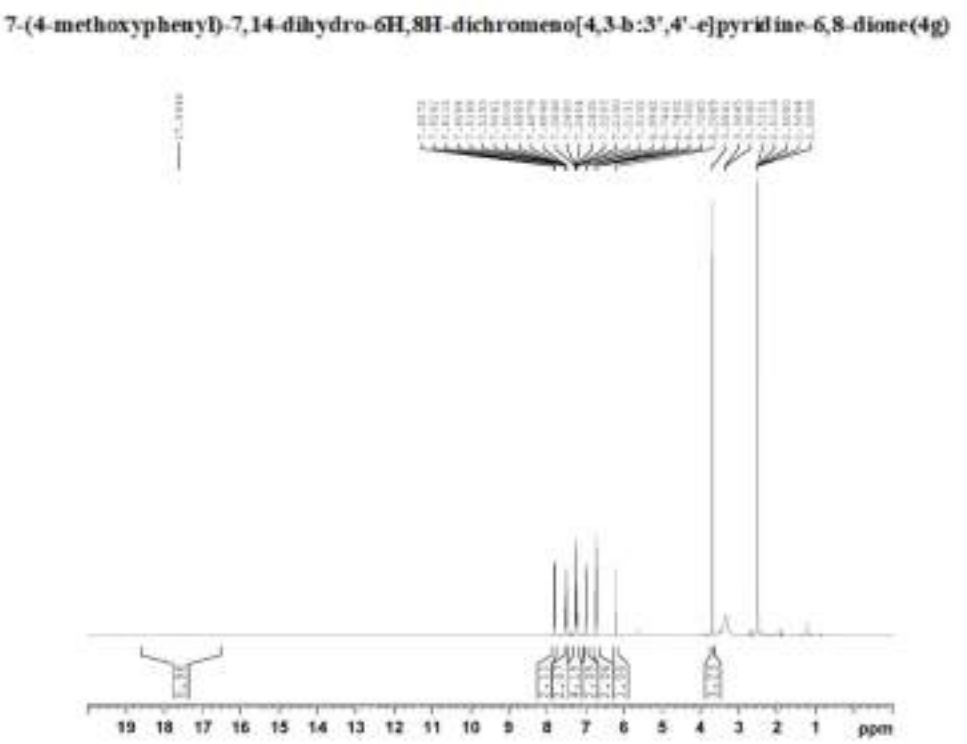


Figure IV.29-^{1}H-NMR of compound 4g

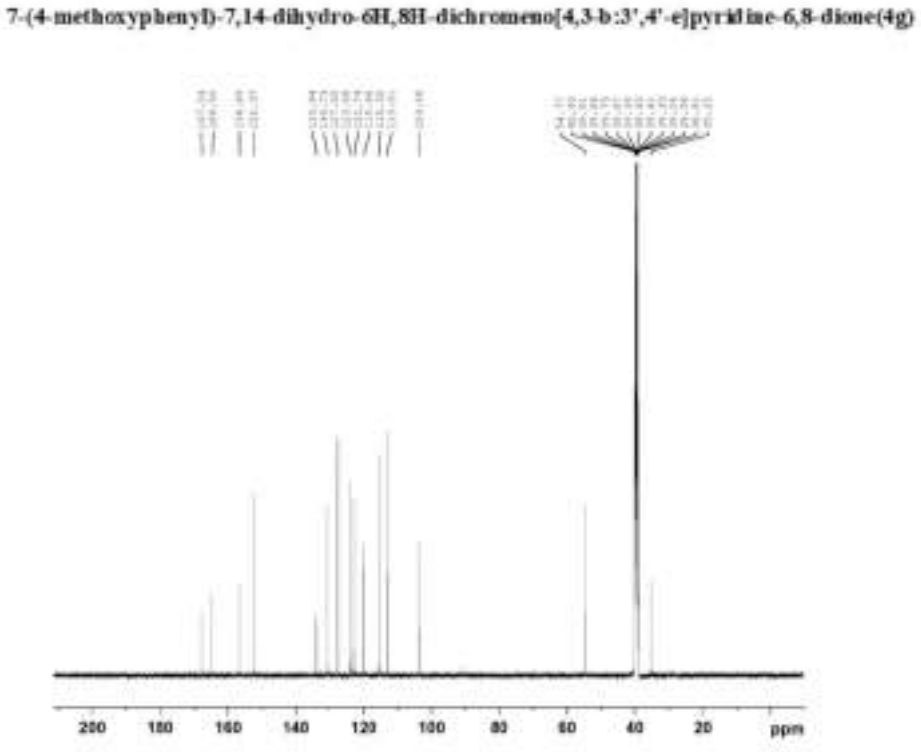


Figure IV.30-^{13}C-NMR of compound 4g

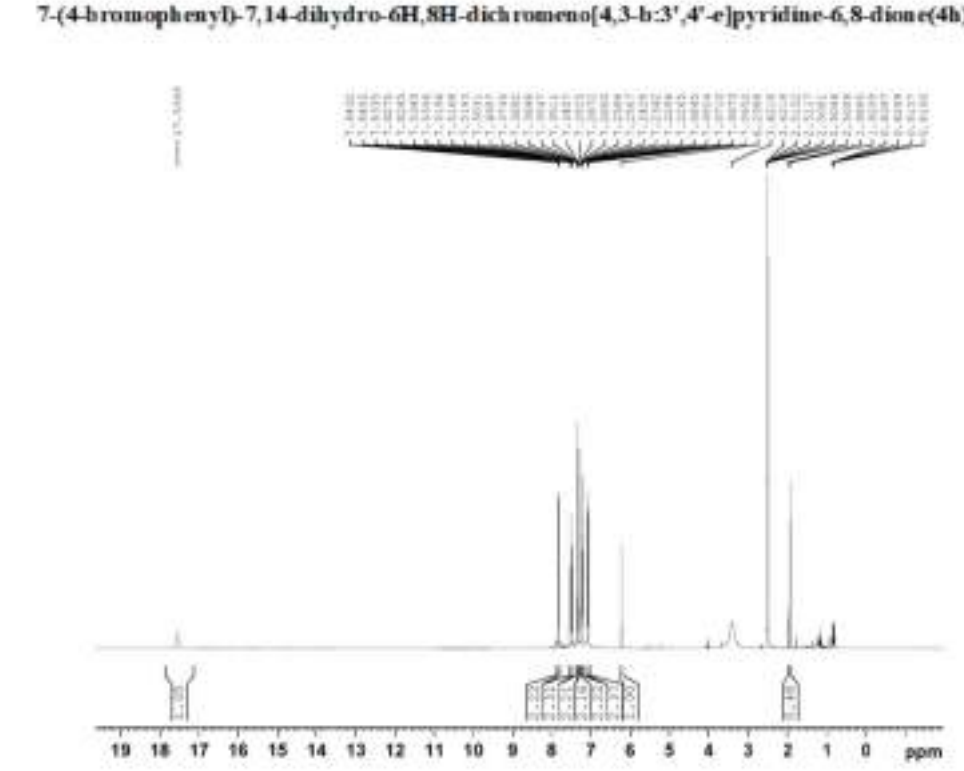


Figure IV.31-^{1}H-NMR of compound 4h

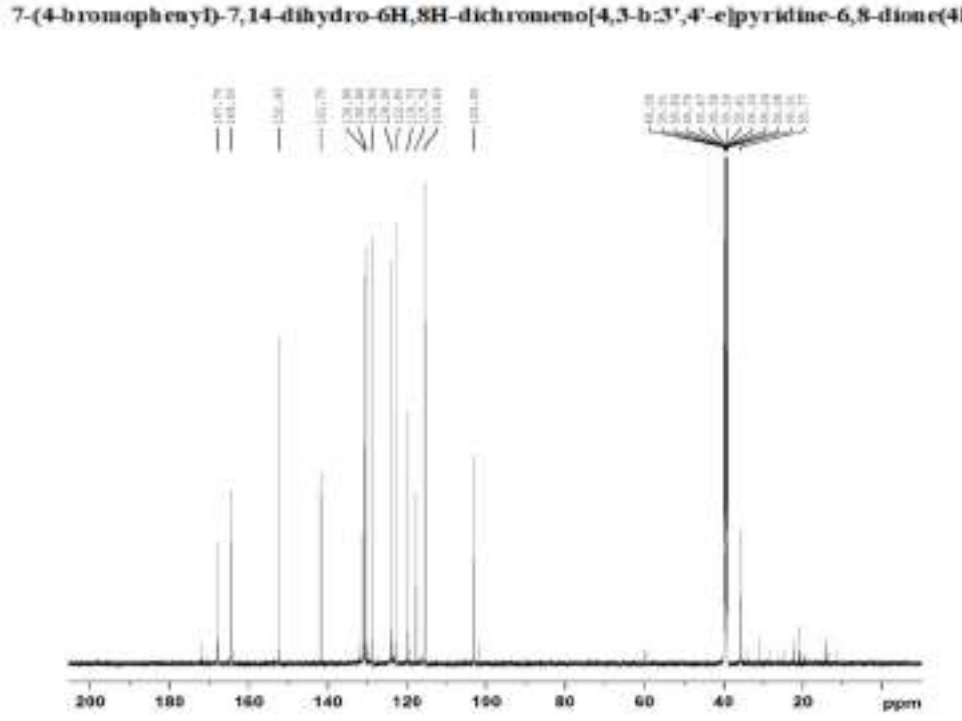


Figure IV.32-^{13}C-NMR of compound 4h

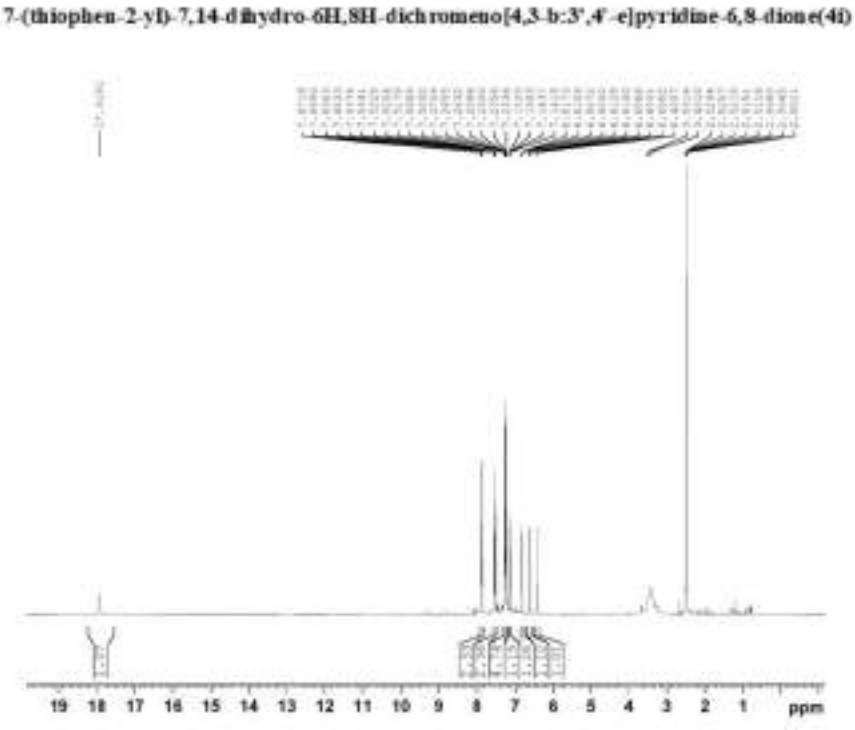


Figure IV.33-^{1}H-NMR of compound 4i

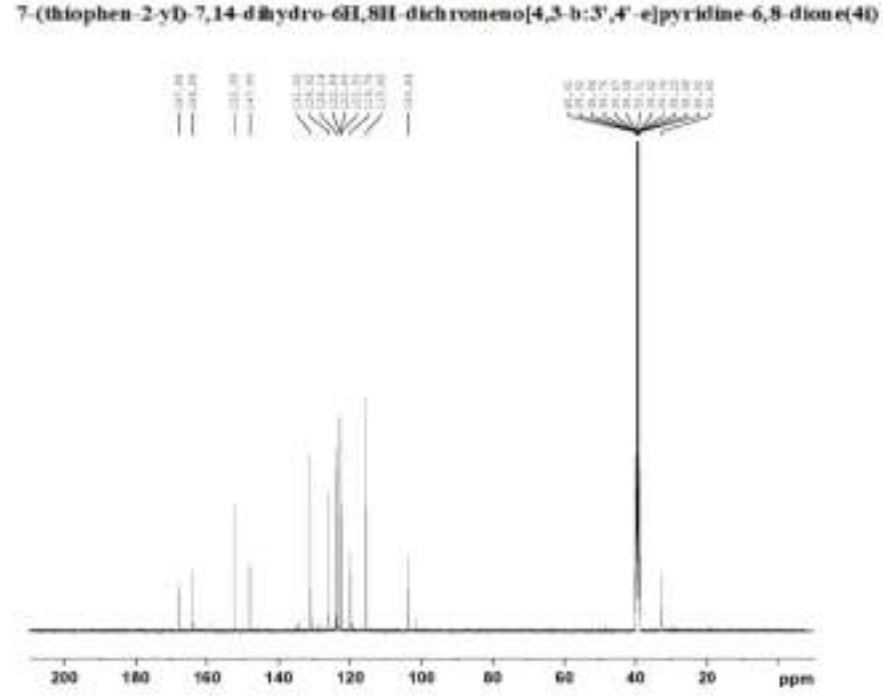


Figure IV.34-^{13}C-NMR of compound 4i

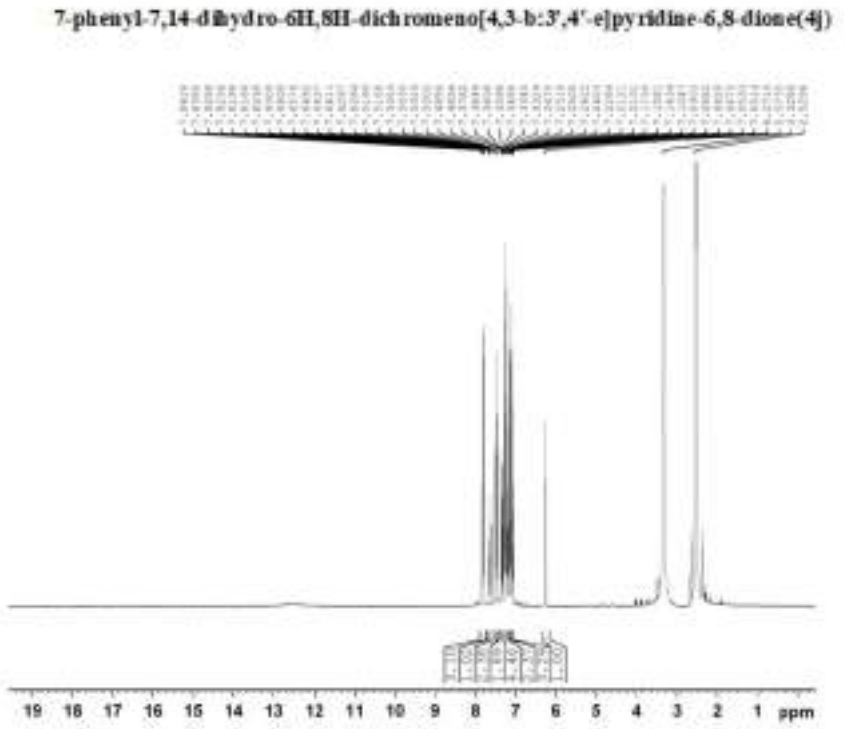


Figure IV.35-^{1}H-NMR of compound 4j

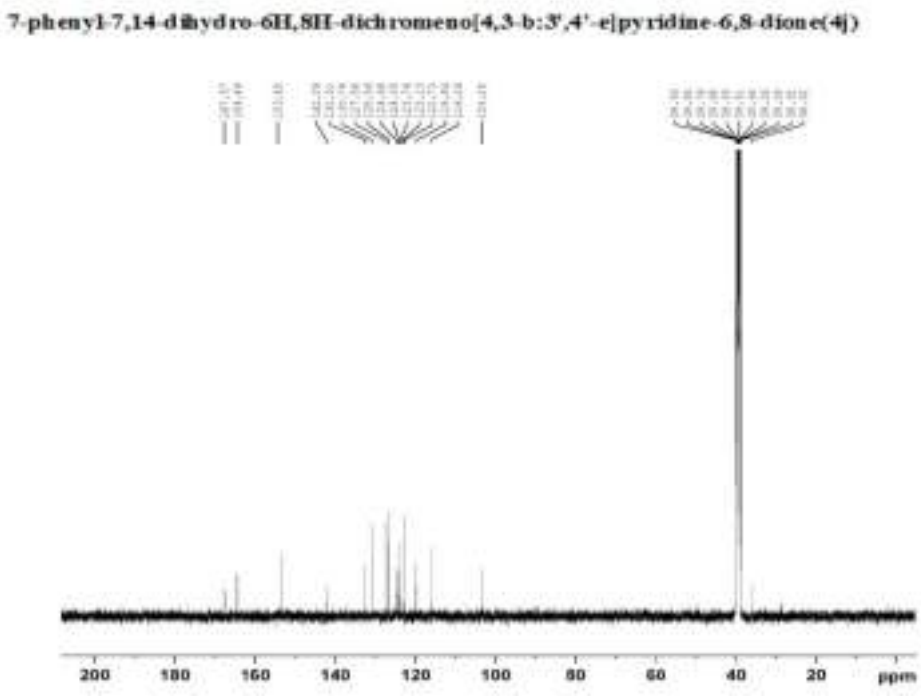
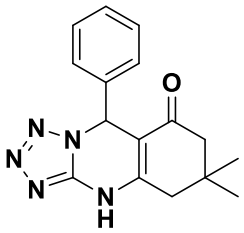


Figure IV.36-^{13}C-NMR of compound 4j

IV.12.A.14.h Spectral data of the compounds mentioned in Scheme IV. 24

6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4a)



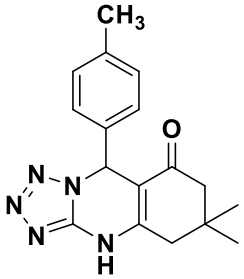
^{1}H-NMR(500MHz,DMSO-d$_6$)

δ(ppm)1.00(s,3H),1.06(s,3H),2.13(d,1H),2.23(d,1H),2.60-2.64(dd,2H),6.63(s,1H),7.13-7,17(m,3H),7.34-7.36(m,2H),11.62(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d$_6$)

δ(ppm)26.97,28.06,32.18,38.91,49.69,56.66,105.36,115.19,115.37129.21,129.28136.64,136.66,148.27,150.45,160.71,162.66,192.91.

6,6-dimethyl-9-(p-tolyl)-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4b)



^{1}H-NMR(500MHz,DMSO-d$_6$)

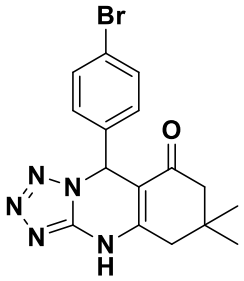
δ(ppm)1.00(s,3H),1.05(s,3H),2.12(d1H),2.22(d,1H),2.24(s,3H),2.59(s,2H),6.55

(s,1H),7.11-7.17(dd,4H),11.56(broad s,1H).

^{13}C-NMR(500MHz,DMSO-d$_6$)

δ(ppm)20.51,26.83,28.19,23.16,49.71,57.07,105.67,126.91,128.99,137.55,137.59,148.32,150.19,192.85.

9-(4-bromophenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4c)



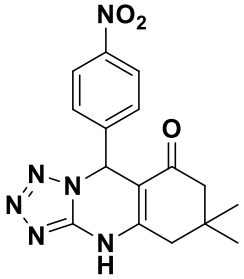
^{1}H-NMR(500MHz,DMSO-d$_6$)

δ(ppm)0.99(s,3H),1.05(s,3H),2.12-2.24(dd,2H),2.56-2.63(m,2H),6.61(s,1H),7.25-7.28(m,2H),7.51-7.54(m,2H),11.65(s,1H).

^{13}C-NMR(500MHz,DMSO-d$_6$)

δ(ppm)20.51,26.83,28.19,23.16,49.71,57.07,105.67,126.91,128.99,137.55,137.59,148.32,150.19,192.85.

6,6-dimethyl-9-(4-nitrophenyl)-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4d)



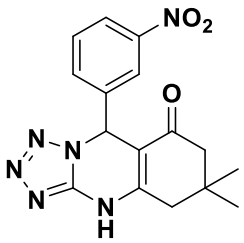
^{1}H-NMR(500MHz,DMSO-d$_6$)

δ(ppm)0.99(s,3H),1.01(s,3H),2.14(dd,1H),2.23(dd,1H),2.51-2.62(m,2H),6.78(s,1H),7.60-7.63(m,2H),8.17-8.20(m,2H),11.76(s,1H).

^{13}C-NMR(500MHz,DMSO-d$_6$)

δ(ppm)27.04,27.97,32.25,49.62,56.83,104.83,123.69,128.73,146.94,147.22,148.33,151.00,192.99.

6,6-dimethyl-9-(3-nitrophenyl)-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4e)



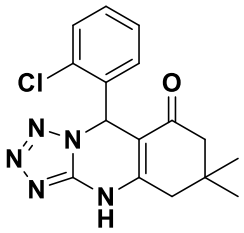
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)1.02(s,3H),1.04(s,3H),1.99-2.26(m,2H),2.63(d,2H),6.84(s,1H),7.66(t,1H),7.77(m,1H),8.15-8.21(m,2H), 11.65(s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)26.94,28.05,32.26,49.62,56.74,104.66,122.04,123.27,130.26,133.84,142.14,147.66,148.28,151.18,193.05.

9-(2-chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4f)



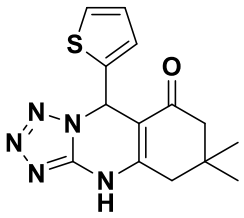
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)1.03(s,3H),1.06(s,3H),2.10(d,1H),2.22(d,1H),2.52-2.59(m,2H),6.44(s,1H),6.9.(s,1H),7.30-7.33(m,2H),7.42-7.44(m,2H),11.68(s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)26.89,27.74,28.13,32.11,49.69,104.50,127.34,129.76,130.00,132.06,148.45,151.04,156.36,192.84.

6,6-dimethyl-9-(thiophen-2-yl)-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4g)



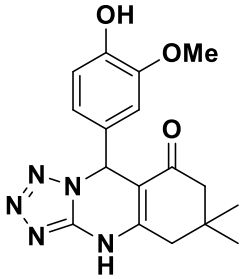
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)1.04(s,3H),1.08(s,3H),2.19(d,1H),2.29(d,1H),2.54-2.65(m,2H),6.96-6.97(m,2H),7.12-7.13(m,1H),7.44-7.45(m,1H),11.69(s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)26.64,28.49,32.10,49.65,52.01,105.41,126.52,126.98,143.39,148.08,150.65,192.86.

9-(4-hydroxy-3-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4h)



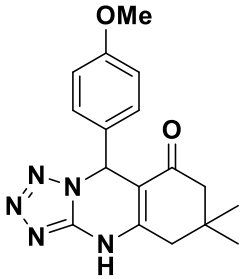
^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)1.03-1.17(m,6H),2.10-2.16(m,1H),2.23-2.27(m,1H),2.60(d,2H),3.73(s,3H),6.50(s,1H),6.60-6.71(m,2H),6.87(d,1H),9.09(s,1H),11.51(s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)26.71,28.39,32.12,40.00,49.77,55.55,57.08,105.71,111.42,112.42,114.63,114.89,115.32,119.53,120.20,131.42,135.34,144.83,146.63,146.80,147.31,148.22,150.19,162.51,192.95,196.03.

9-(4-methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4i)



^{1}H-NMR(500MHz,DMSO-d_6)

δ(ppm)1.00(s,3H),1.02(s,3H),2.13(d,1H),2.23(d,1H),2.60(s,2H),3.71(s,1H),6.56(s,1H),6.87(dd,2H),7.21(dd,2H),11.57(s,1H).

^{13}C-NMR(500MHz,DMSO-d_6)

δ(ppm)26.09,28.03,31.96,38.73,49.56,54.79,56.62,105.53,113.60,128.09,132.42,148.11,149.95,158.83,192.69.

IV.12.A.14.i Scanned copies of compounds mentioned in Scheme IV.24

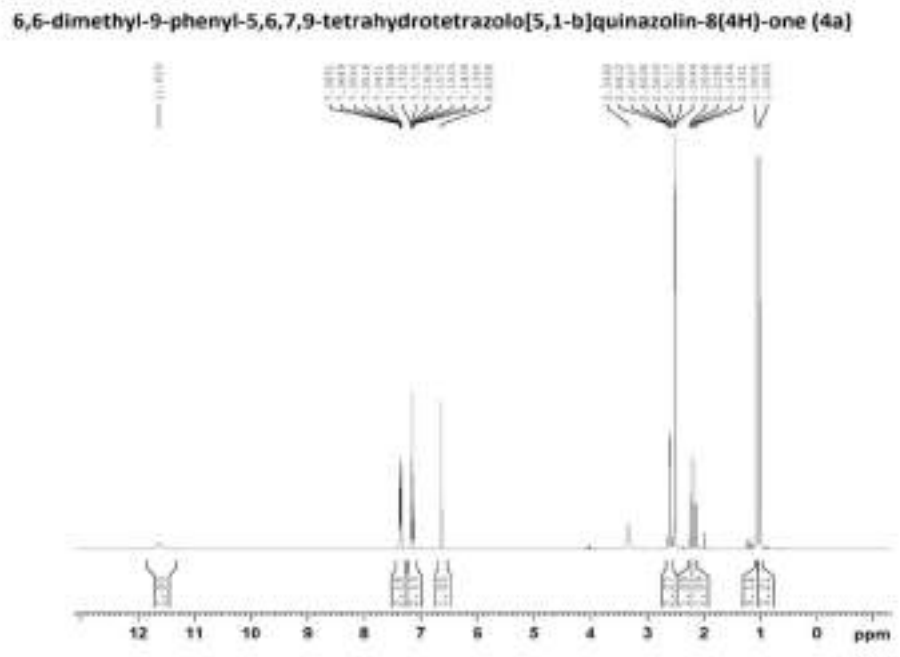


Figure IV.37-^{1}H-NMR of compound 4a

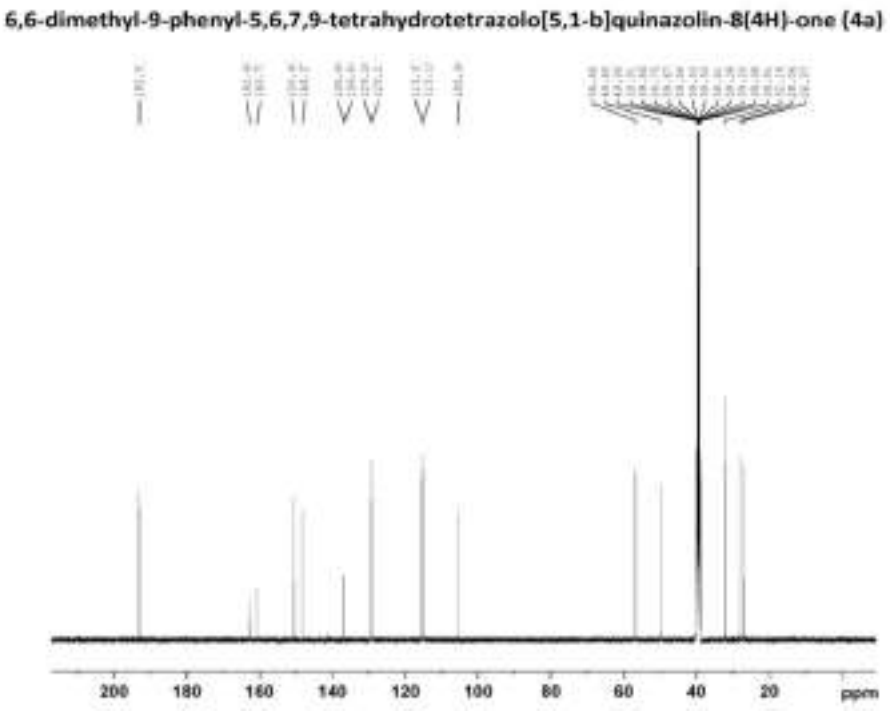


Figure IV.38-^{13}C-NMR of compound 4a

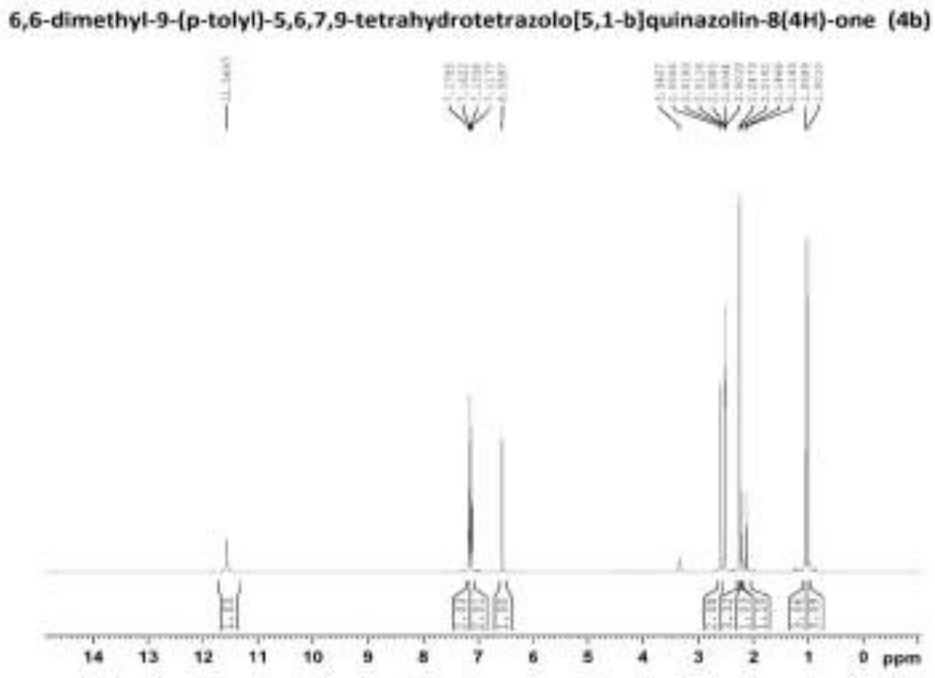


Figure IV.39-^{1}H-NMR of compound 4b

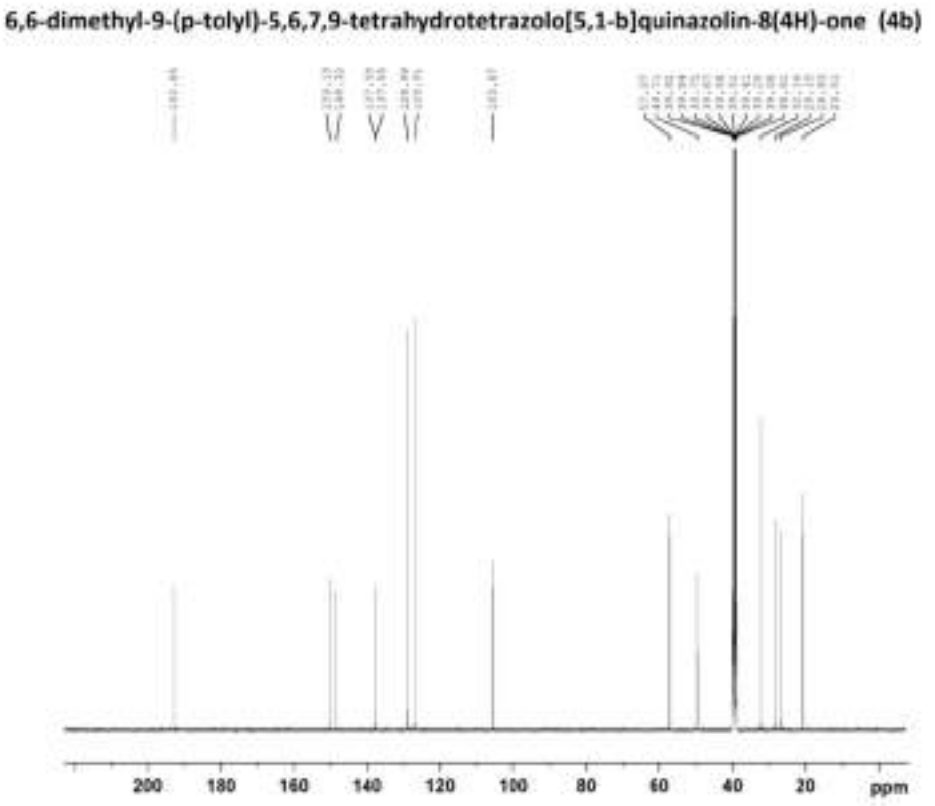


Figure IV.40-^{13}C-NMR of compound 4b

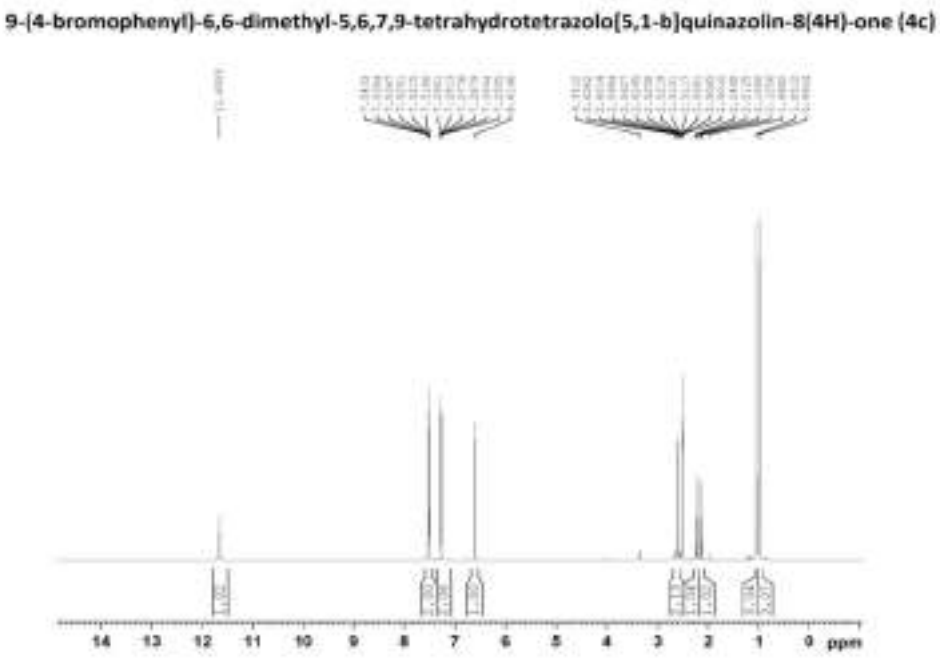


Figure IV.41-^{1}H-NMR of compound 4c

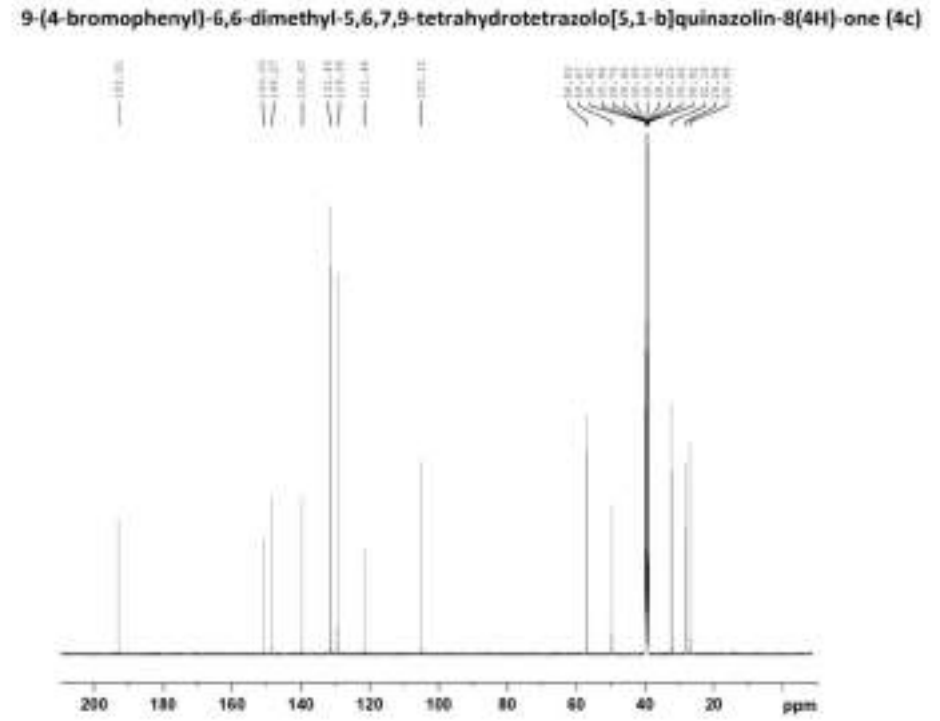


Figure IV.42-^{13}C-NMR of compound 4c

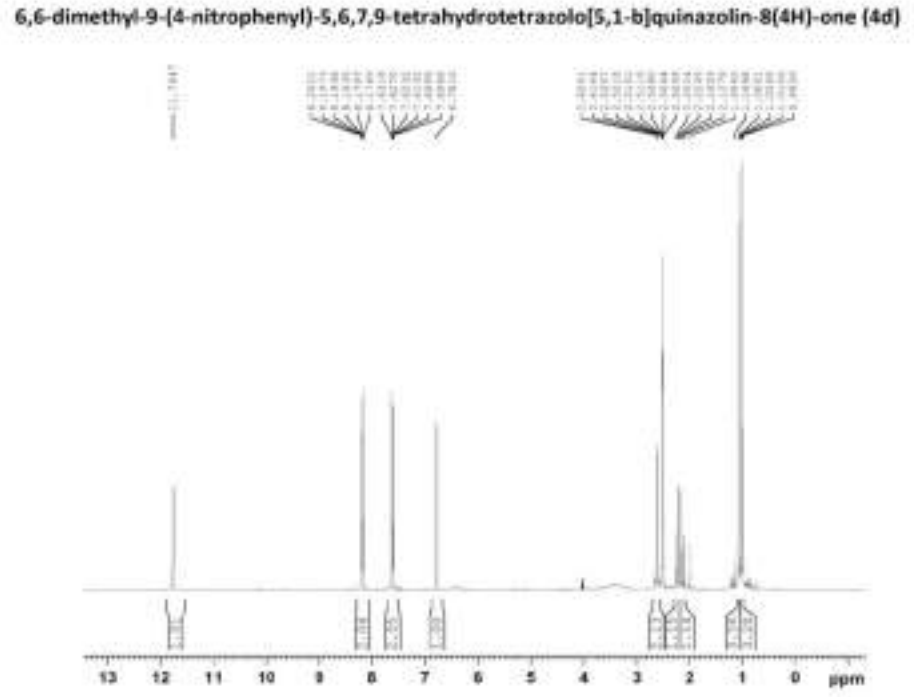


Figure IV.43-^{1}H-NMR of compound 4d

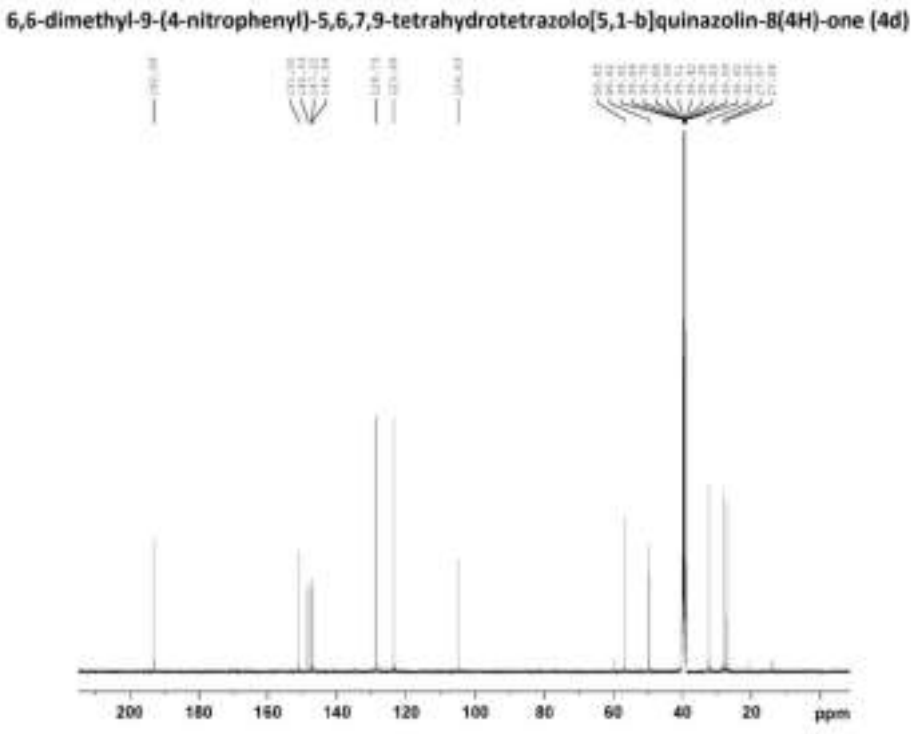


Figure IV.44-^{13}C-NMR of compound 4d

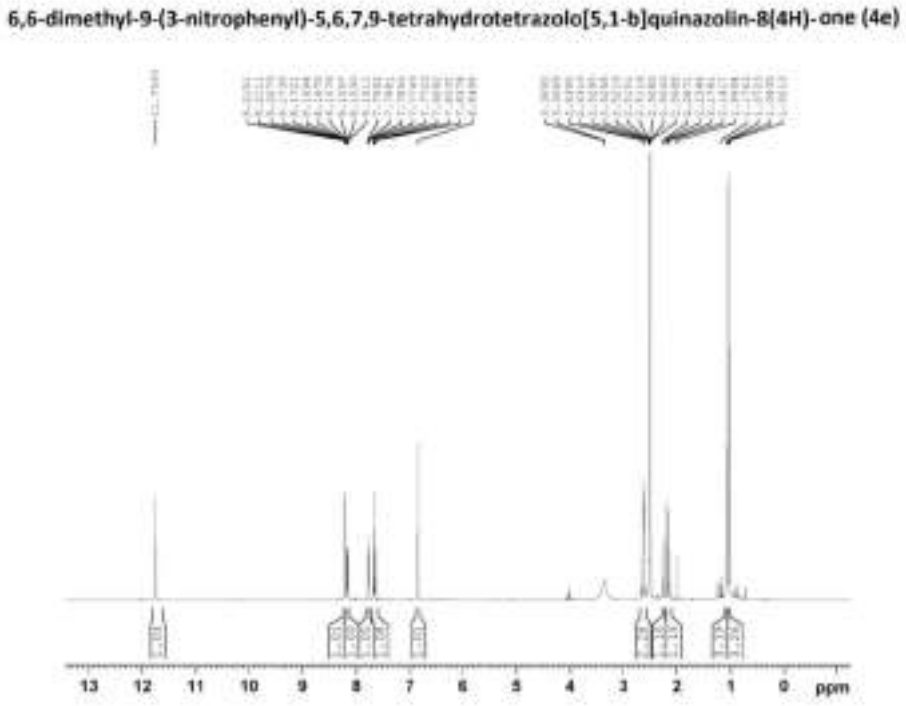


Figure IV.45-^{1}H-NMR of compound 4e

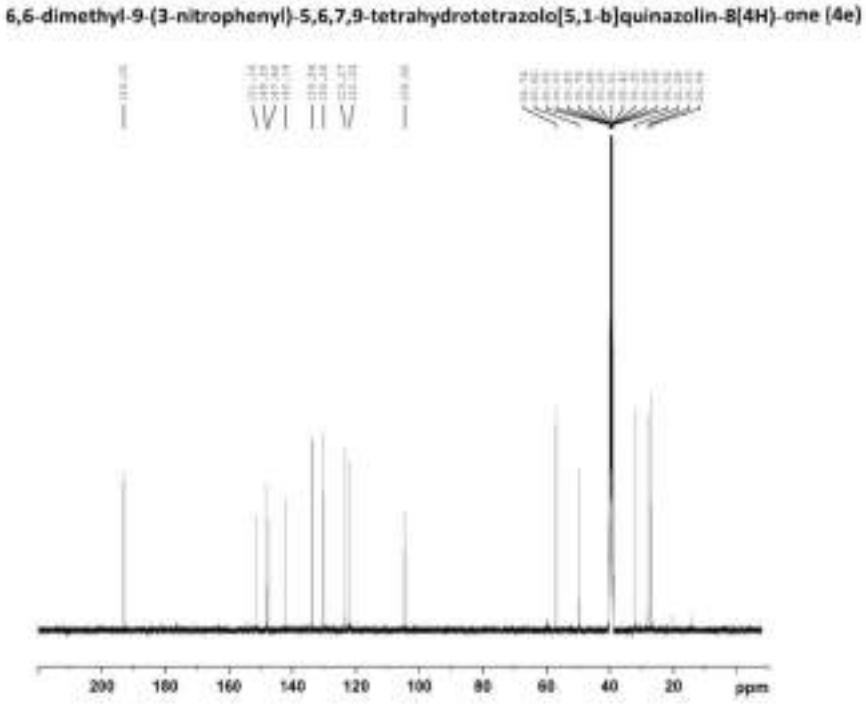


Figure IV.46-^{13}C-NMR of compound 4e

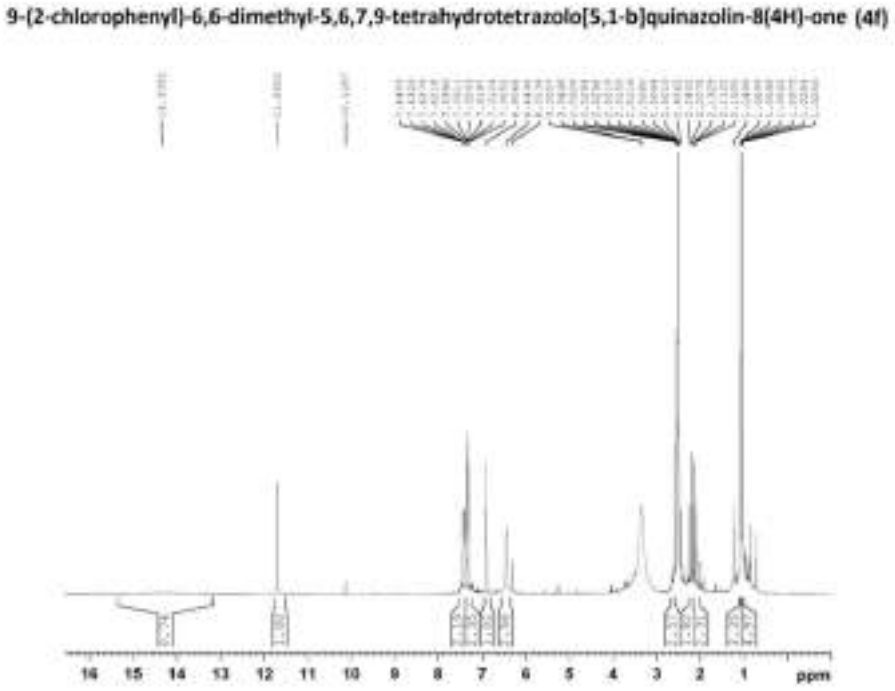


Figure IV.47-^{1}H-NMR of compound 4f

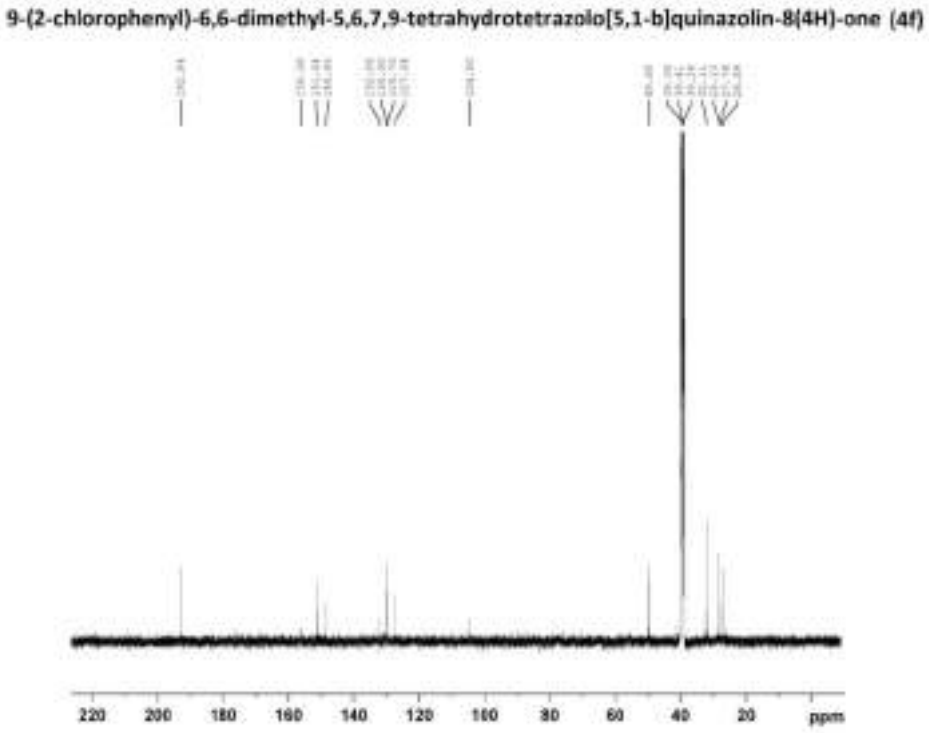


Figure IV.48-^{13}C-NMR of compound 4f

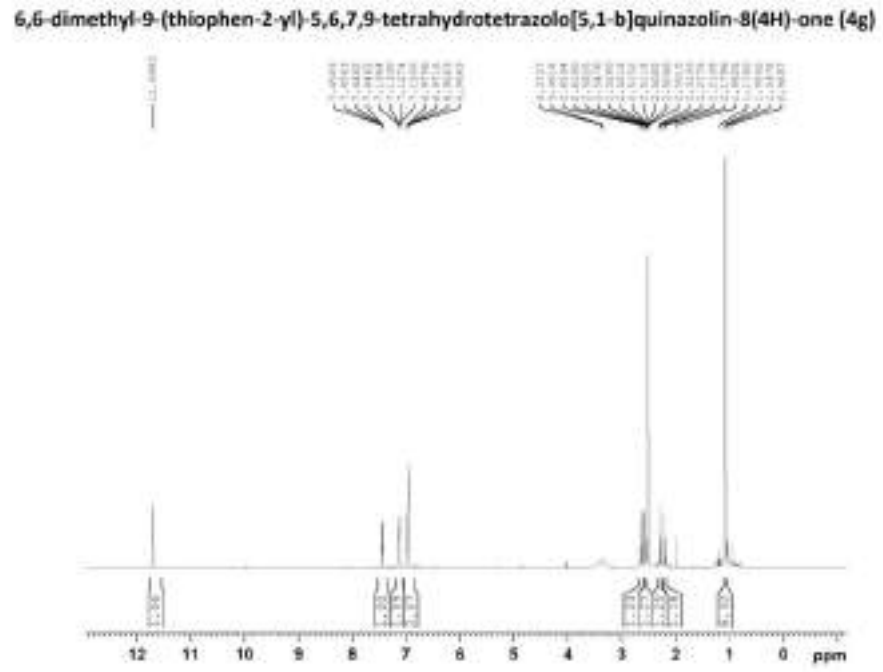


Figure IV.49-^{1}H-NMR of compound 4g

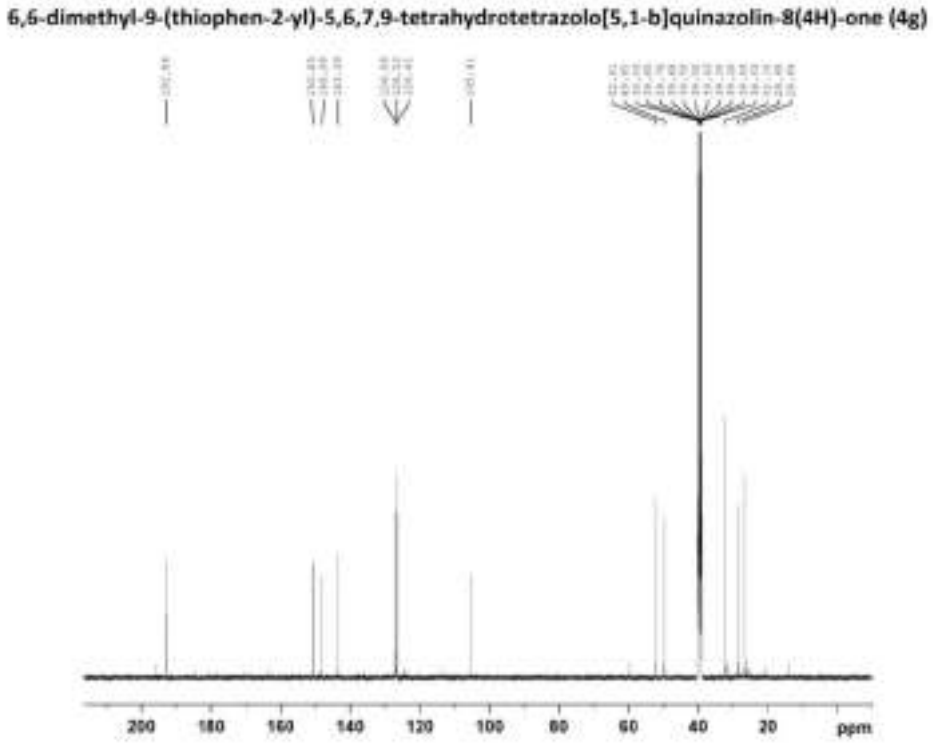


Figure IV.50-^{13}C-NMR of compound 4g

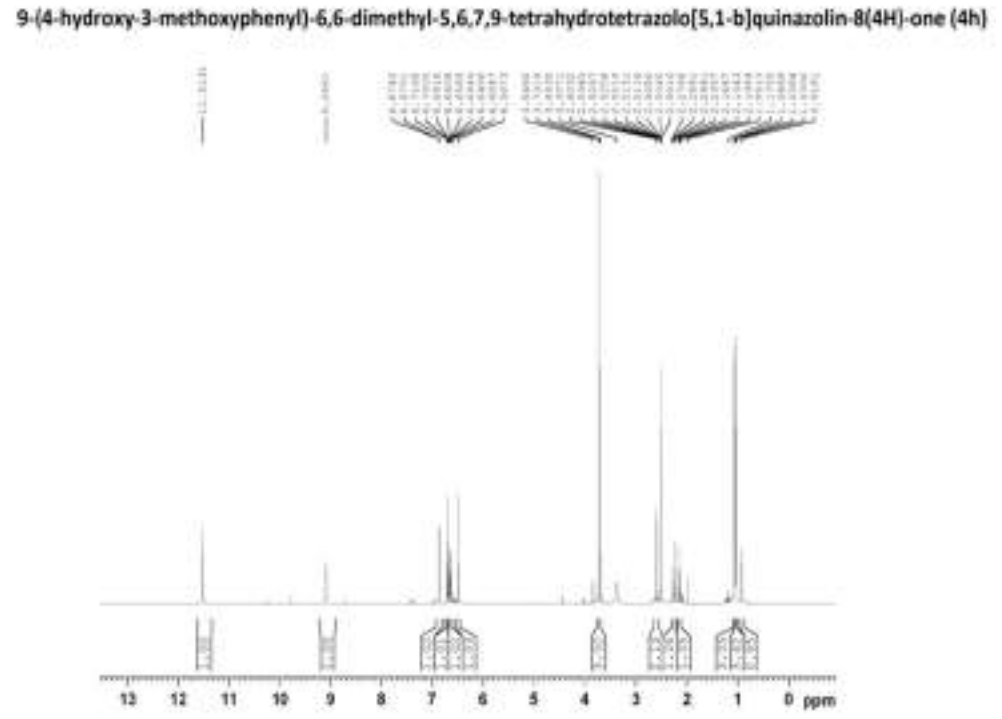


Figure IV.51-^{1}H-NMR of compound 4h

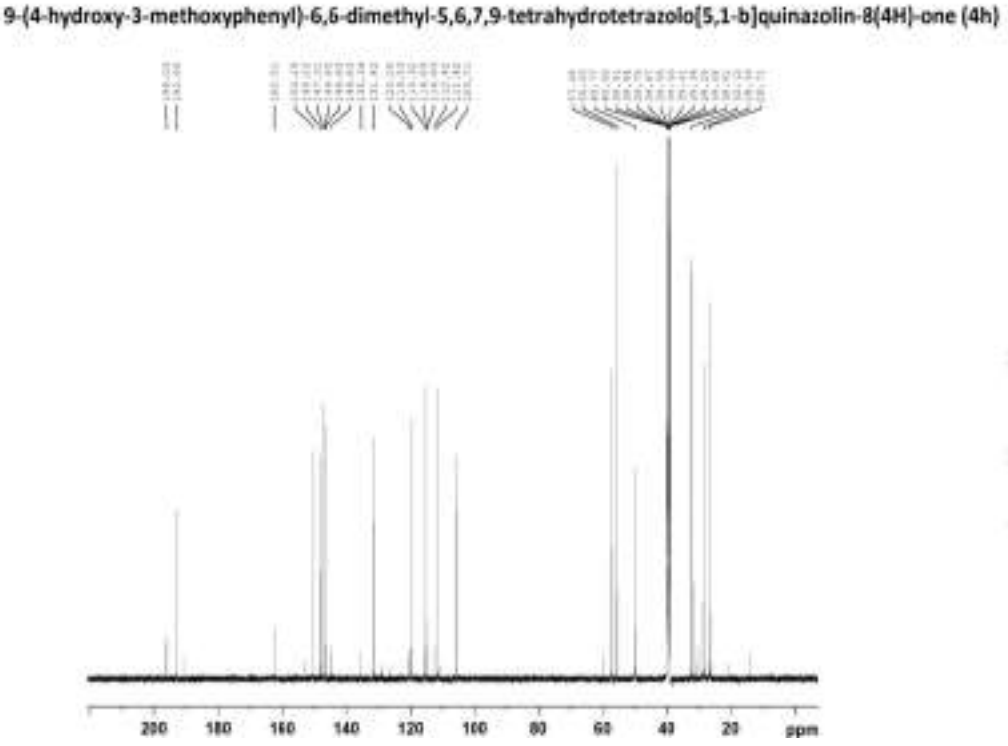


Figure IV.52-^{13}C-NMR of compound 4h

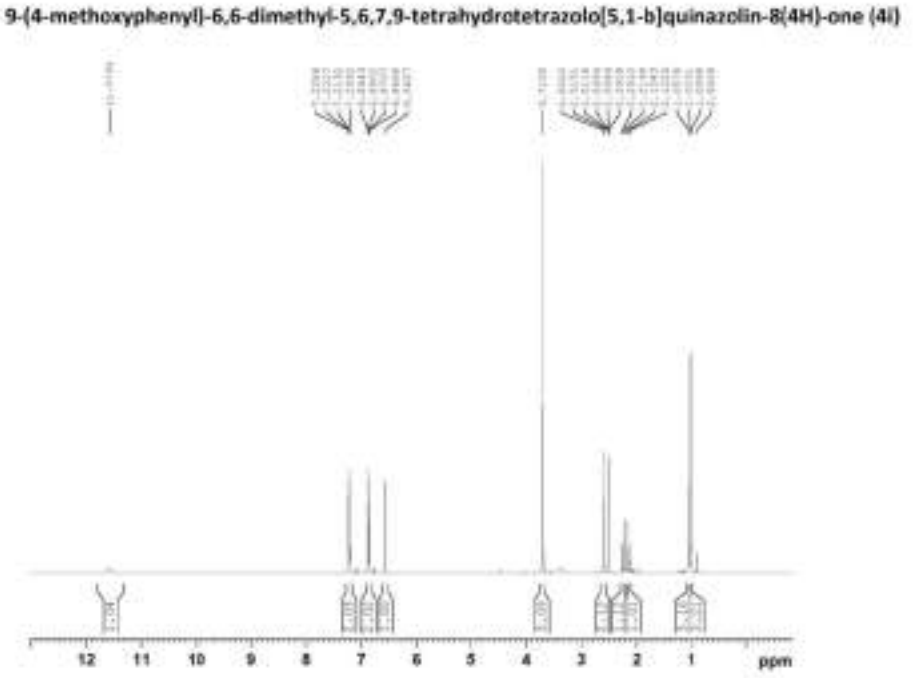


Figure IV.53-^{1}H-NMR of compound 4i

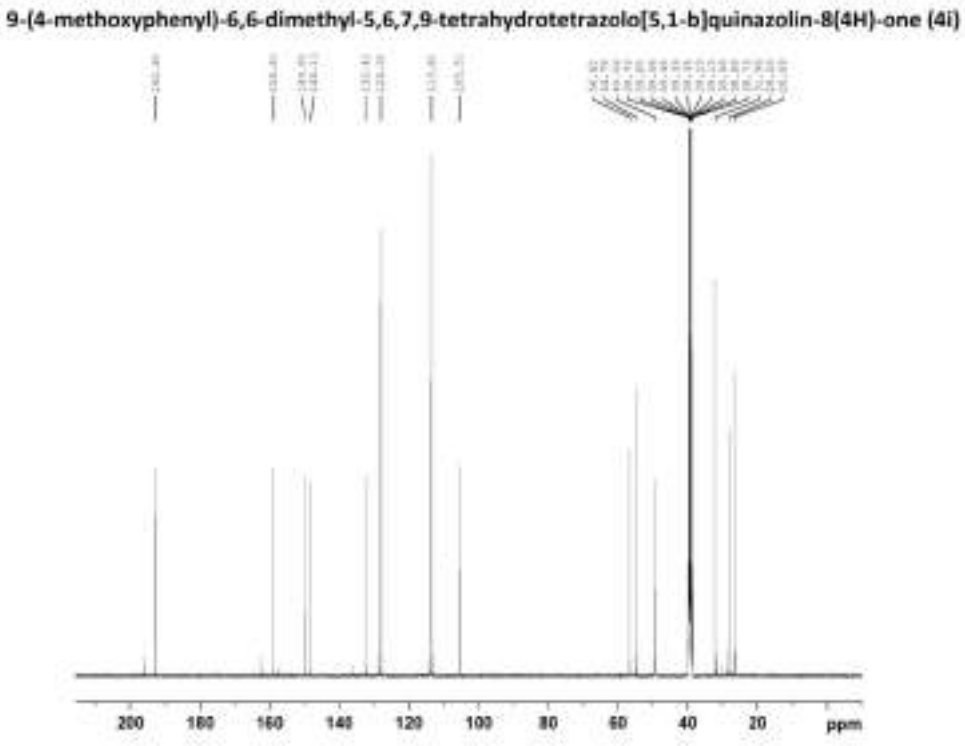
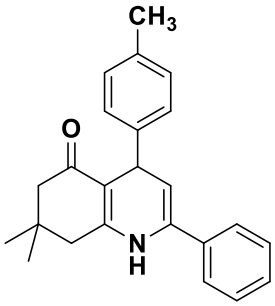


Figure IV.54-^{13}C-NMR of compound 4i

IV.12.A.14.j Spectral data of the compounds mentioned in Scheme IV. 25

7,7-dimethyl-2-phenyl-4-(p-tolyl)-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5a)



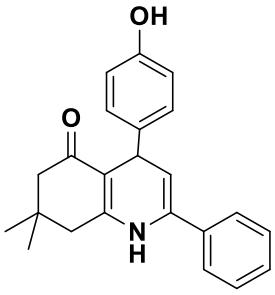
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.92(s,3H),1.05(s,3H),1.94-1.98(m,1H),2.12-2.18(m,1H),2.34(s,3H),2.39-2.47(m,2H),3.65(s,3H),4.49(d,1H),5.16(dd,1H),7.01(d,2H),7.09(d,2H),7.29-7.38(m,3H), 7.43-7.46(m,2H),8.57(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)21.15,27.40,29.80,29.80,32.44,37.35,50.97,106.68,106.72,126.09,127.83,128.81,128.99,129.16,134.88,135.01,135.79,146.15,152.84,194.43.

4-(4-hydroxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5b)



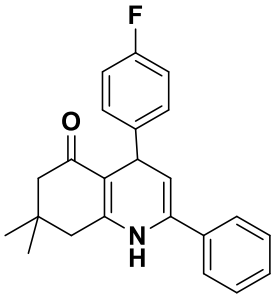
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)1.07(s,6H),2.49-2.57(m,2H),3.12(s,2H),6.78(d,2H),7.19(d,2H),7.50(m,4H), 7.65(d,2H),9.61(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)28.43,32.95,47.65,53.84,115.27,121.54,124.51,127.79,129.36,130.45,130.57, 130.79,138.06,151.99,158.01,158.20,163.63,198.16

4-(4-fluorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5c)



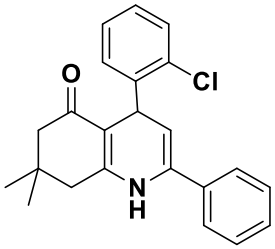
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.94(s,3H),1.32(s,3H),2.00(d,1H),2.17(d,1H),2.46-2.51(m,2H),4.58(d,1H),5.21(t,1H),7.03-7.08(m,2H),7.23-7.26(m,2H),7.33-7.41(m,3H), 7.48-7.50(m,2H),8.66(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)27.42,29.71,32.46,37.03,50.91,106.18,106.56,115.09,115.30,126.18,128.92,129.01,129.54,129.62,135.30,135.68,145.15,152.93,159.80,162.20,194.44

4-(2-chlorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5d)



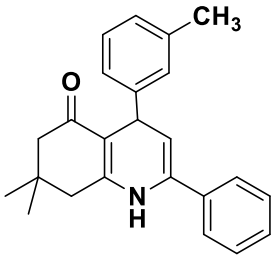
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)1.06(s,3H),1.08(s,3H),2.06(d,1H),2.19(d,1H),2.54(d,2H),4.97(d,1H),5.16(dd,1H),7.12-7.21(m,3H),7.33-7.39(m,4H),7.42-7.44(m,2H),8.69(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)28.12,29.53,32.48,35.37,50.85,104.28,104.96,126.12,127.80,128.01,129.02,129.63,129.97,131.36,135.56,145.48,154.39,194.20

7,7-dimethyl-2-phenyl-4-(m-tolyl)-4,6,7,8-tetrahydroquinolin-5(1*H*)-onev (5e)



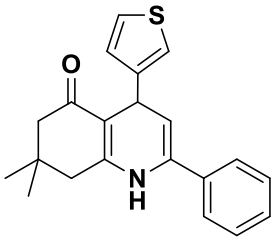
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.98(s,3H),1.04(s,3H),1.99(d,1H),2.17(d,1H),2.24(s,3H),2.47-2.50(m,2H+2H,H_2O),4.51(d,1H),5.19(dd,1H),6.91(d,1H),7.01(d,2H),7.13(d,1H),7.34-7.40(m,3H),7.46-7.49(m,2H),8.59(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)21.73,27.43,29.80,32.47,37.76,50.97,106.49,106.69,125.07,126.08,126.79,128.50,128.57,128.83129.00,134.83,135.74,137.37,149.01,153.00,194.39

7,7-dimethyl-2-phenyl-4-(thiophen-3-yl)-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5f)



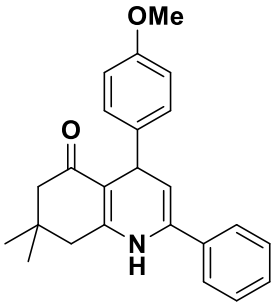
^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.91(s,3H),1.01(s,3H),2.04(d,1H),2.21(d,1H),2.37-2.46(m,2H),4.88(d,1H),5.30(dd,1H),6.80(d,1H),6.87(q,1H)7.22(dd,1H),7.35-7.44(m,3H), 7.50-7.52(m,2H),8.79(s,1H).

^{13}C-NMR(400MHz,DMSO-d_6)

δ(ppm)27.15,29.95,32.12,32.41,50.88,105.13,106.66,122.92,124.14,126.37,127.05,129.06,135.62,135.85,152.61,153.82,194.40.

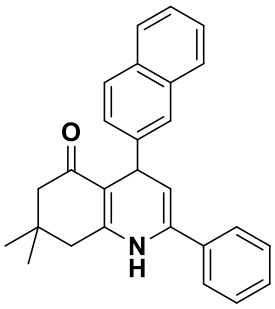
4-(4-methoxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5g)



^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.92(s,3H),0.94(s,3H),1.94(d,1H),2.14(d,1H),2.43(m,2H),3.65(s,3H),4.47(d,1H),5.16(dd,1H),6.77(d,2H),7.11(d,2H),7.32(m,3H), 7.45-7.47(m,2H),8.55(s,1H).

7,7-dimethyl-4-(naphthalen-2-yl)-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5h)



^{1}H-NMR(400MHz,DMSO-d_6)

δ(ppm)0.95(s,3H),1.02(s,3H),1.97(d,1H),2.17(d,1H),2.48(s,2H+3H,H_2O),4.73(s,1H),5.25(s,1H),7.34-7.47(m,9H),7.63(s,1H),7.78-7.80(d,3H),8.66(s,1H).

IV.12.A.14.k Sanned copies of compounds mentioned in Scheme IV.25

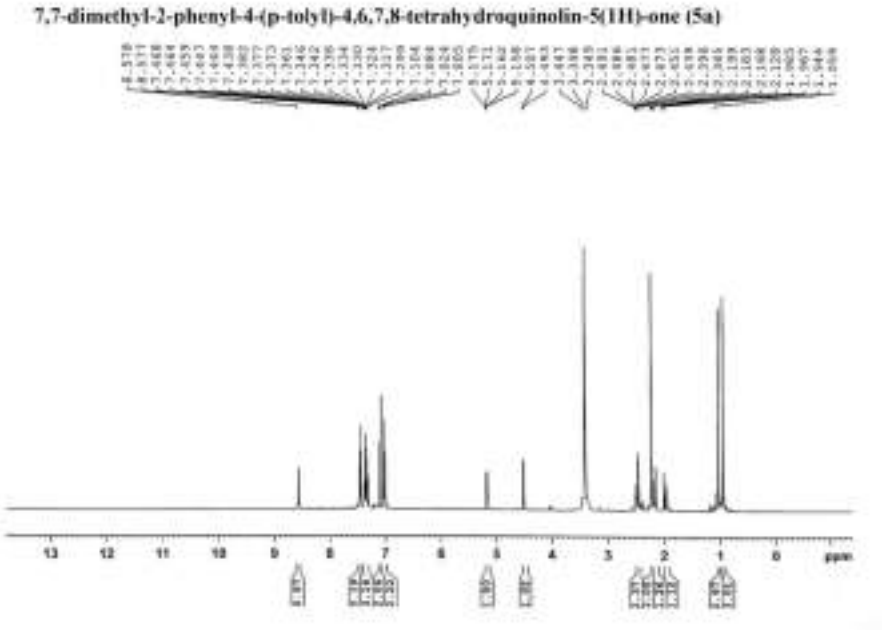


Figure IV.55-^{1}H-NMR of compound 5a

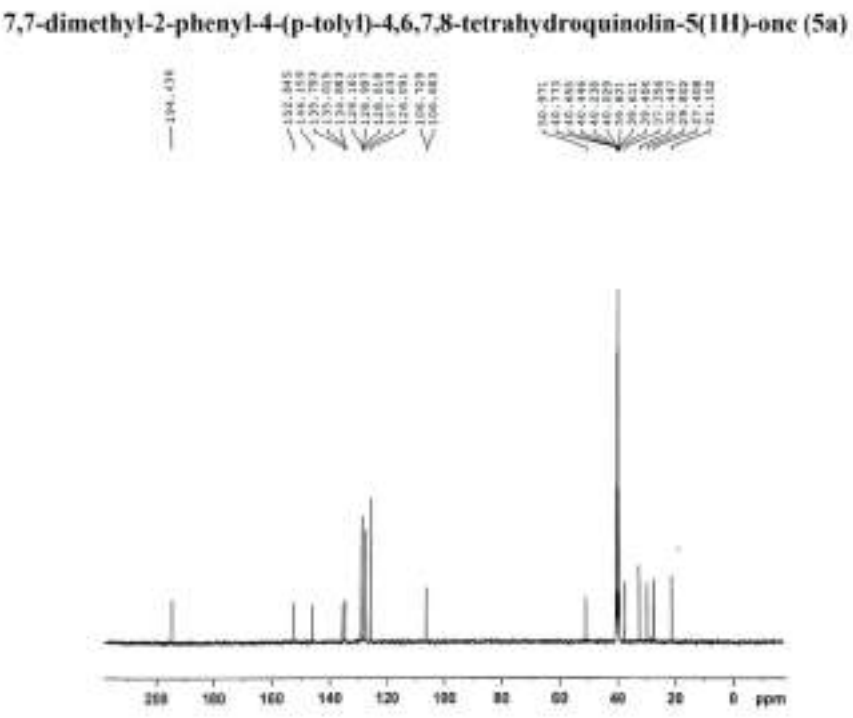


Figure IV.56-^{13}C-NMR of compound 5a

4-(4-hydroxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5b)

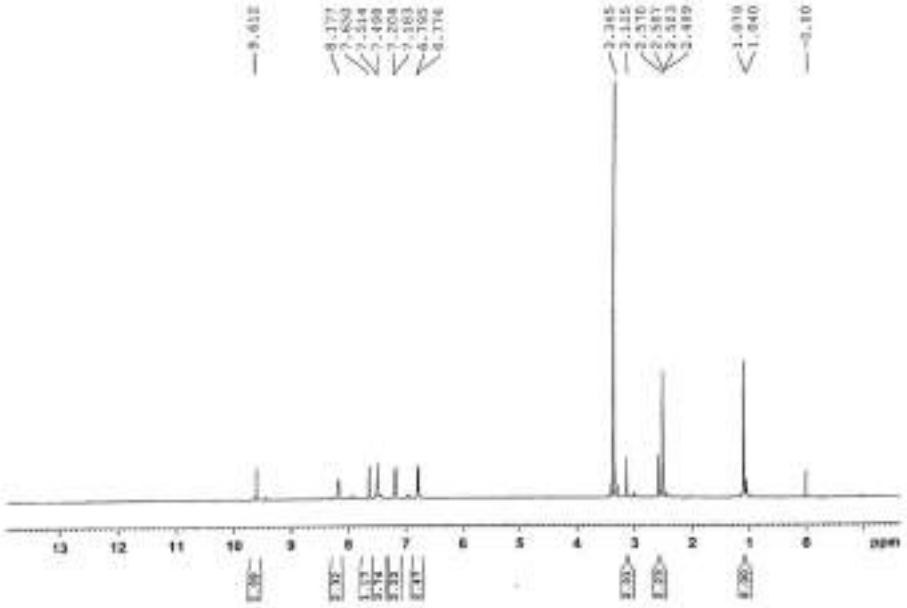


Figure IV.57-^{1}H-NMR of compound 5b

4-(4-hydroxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5b)

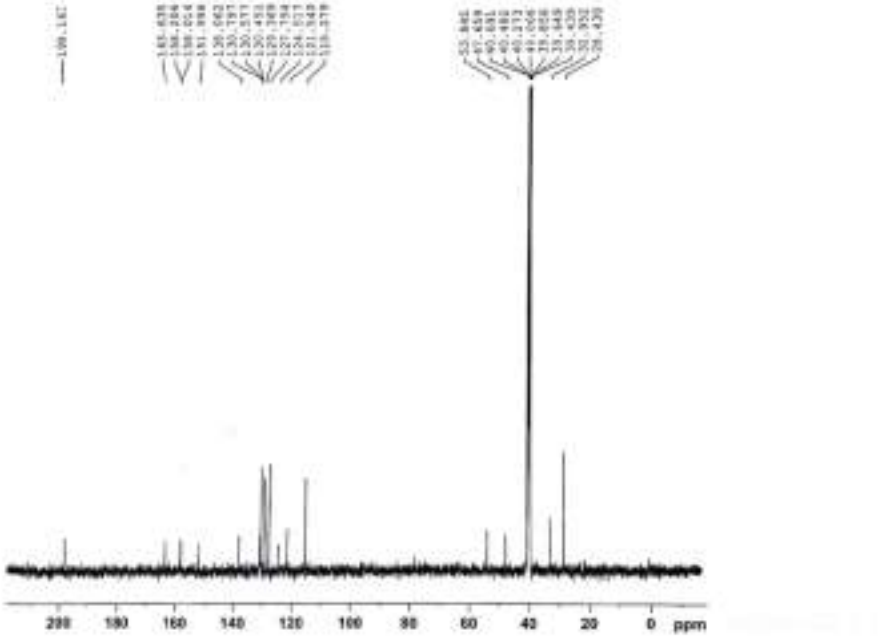


Figure IV.58-^{13}C-NMR of compound 5b

4-(4-fluorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5c)

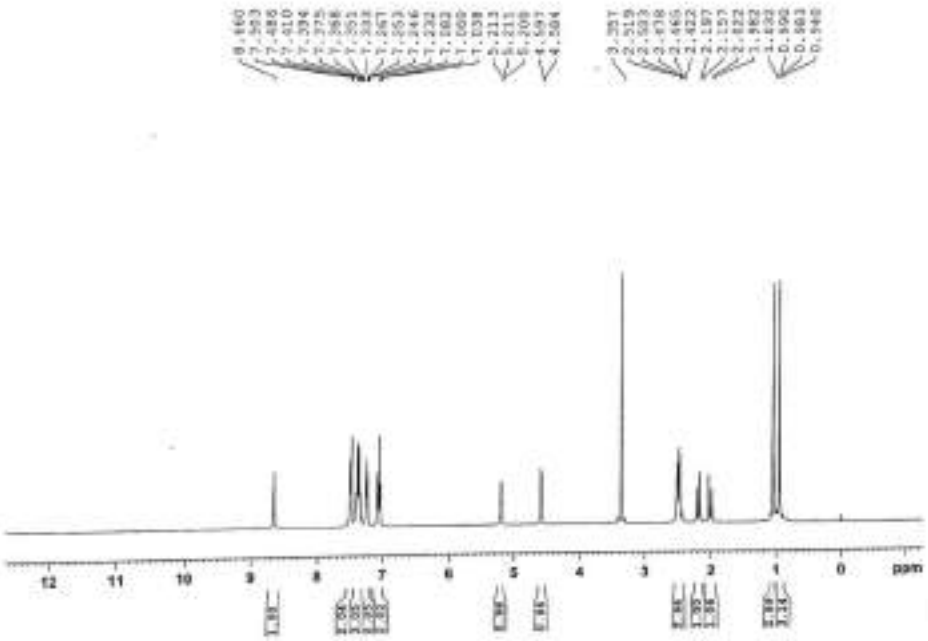


Figure IV.59-^{1}H-NMR of compound 5c

4-(4-fluorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5c)

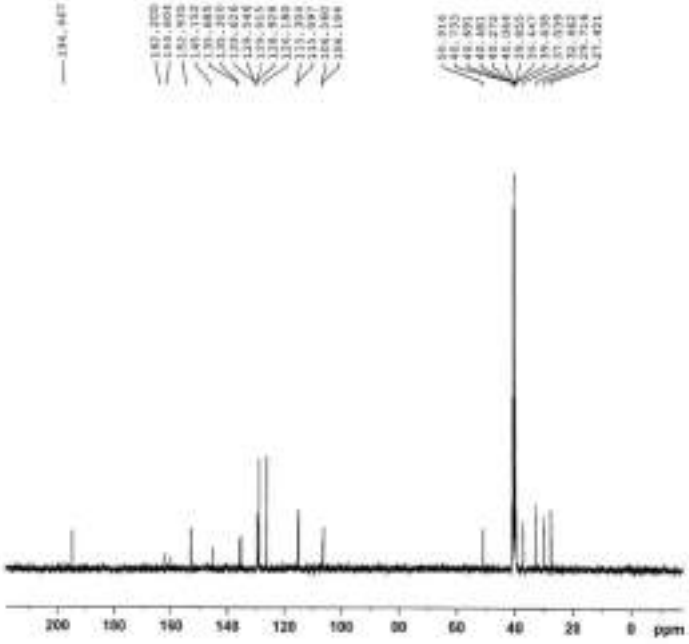


Figure IV.60-^{13}C-NMR of compound 5c

4-(2-chlorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5d)

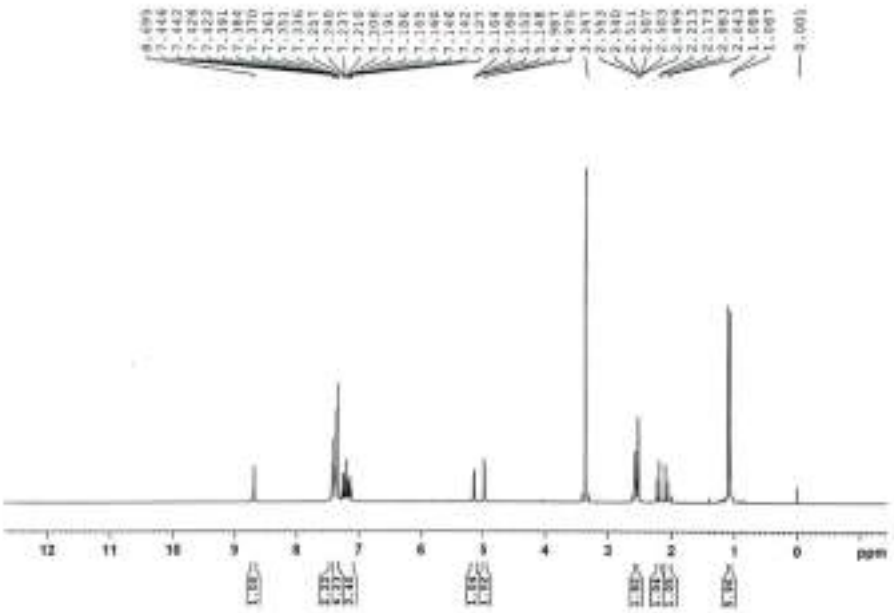


Figure IV.61-^{1}H-NMR of compound 5d

4-(2-chlorophenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5d)

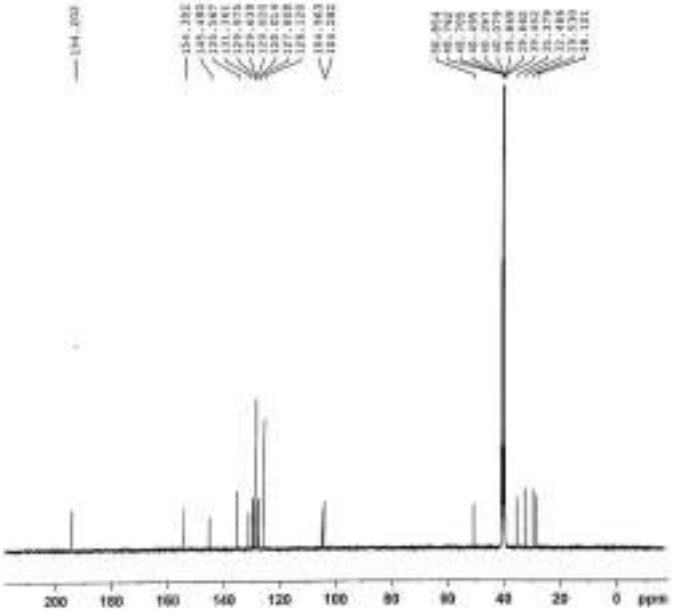


Figure IV.62-^{13}C-NMR of compound 5d

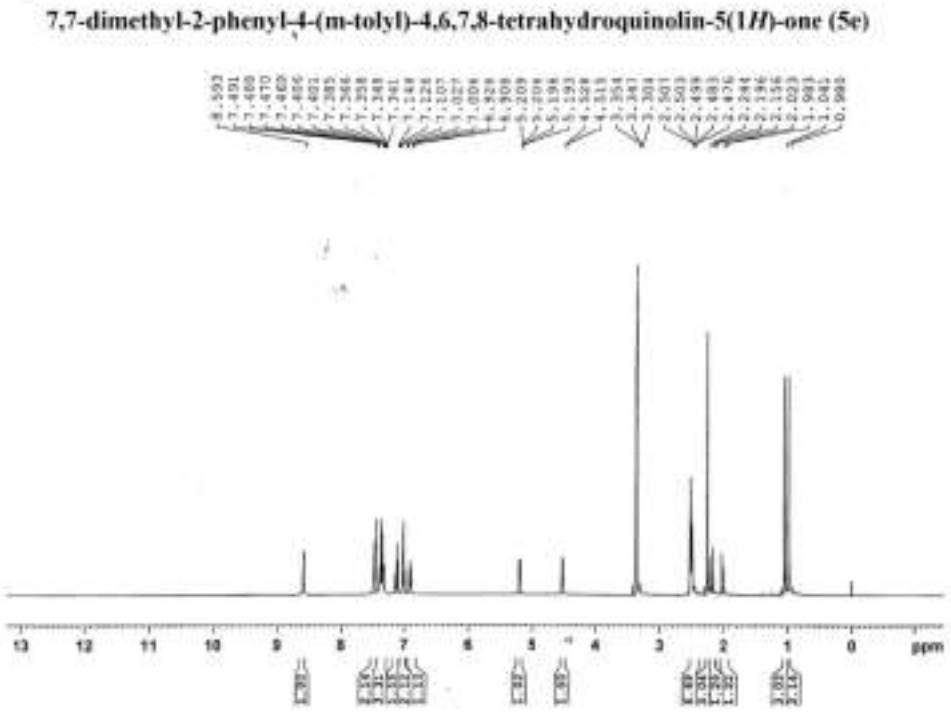


Figure IV.63-^{1}H-NMR of compound 5e

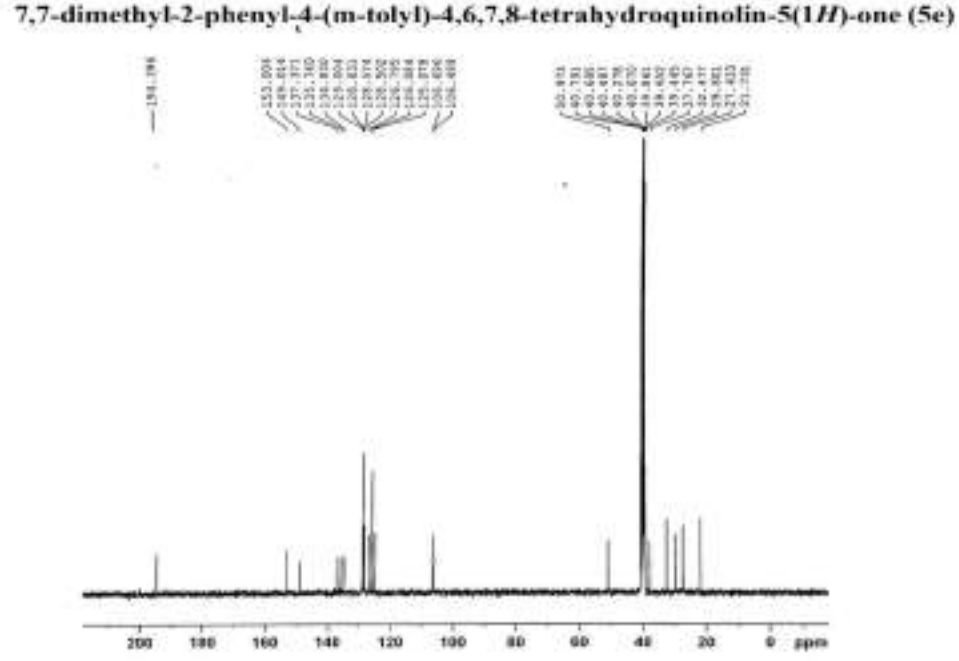


Figure IV.64-^{13}C-NMR of compound 5e

7,7-dimethyl-2-phenyl-4-(thiophen-3-yl)-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5f)

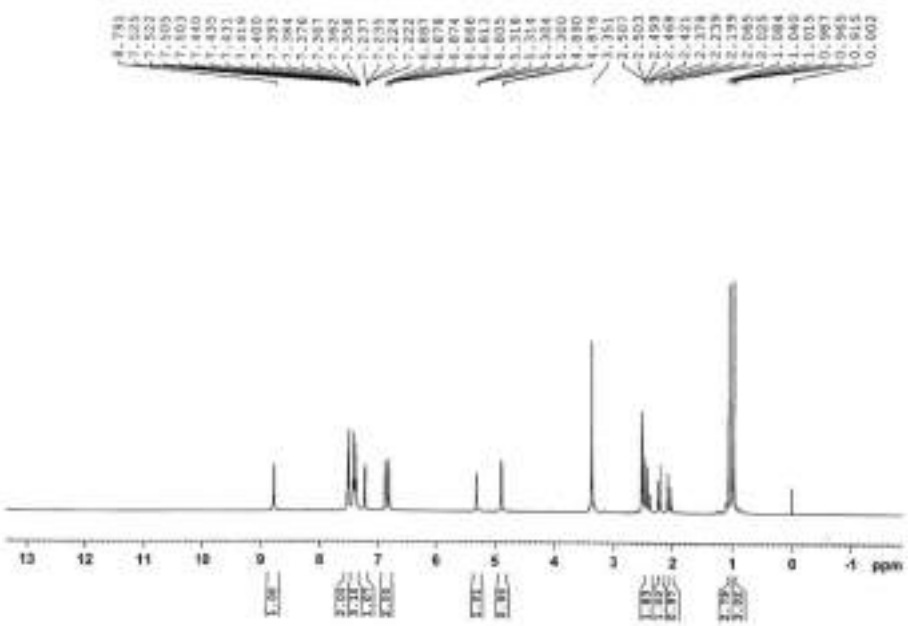


Figure IV.65-^{1}H-NMR of compound 5f

7,7-dimethyl-2-phenyl-4-(thiophen-3-yl)-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5f)

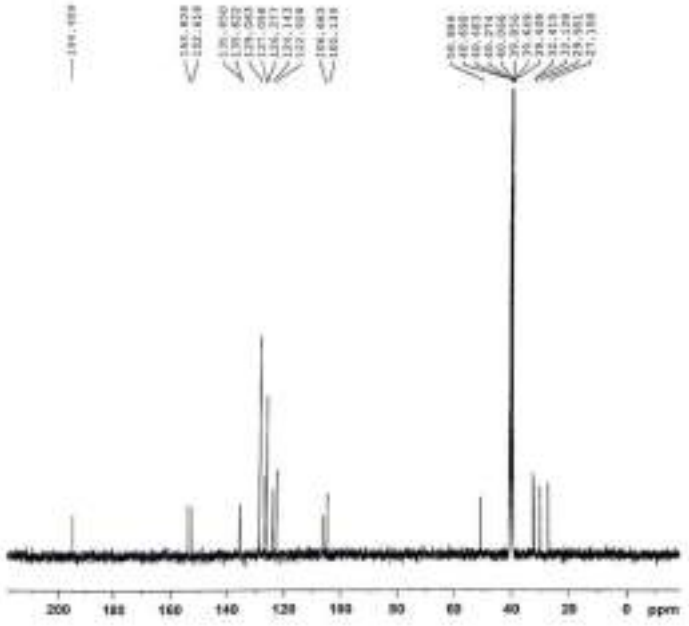


Figure IV.66-^{13}C-NMR of compound 5f

4-(4-methoxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5g)

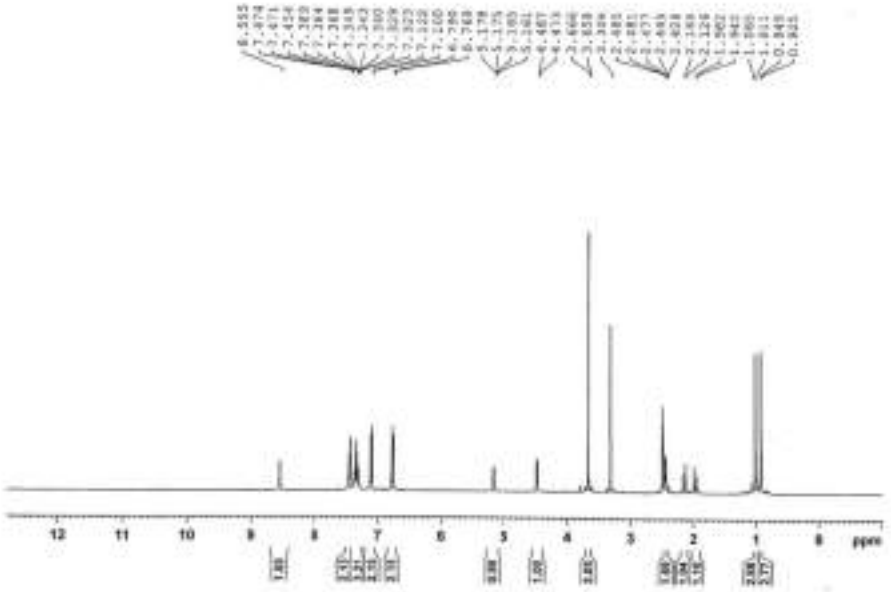


Figure IV.67-^{1}H-NMR of compound 5g

7,7-dimethyl-4-(naphthalen-2-yl)-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5h)

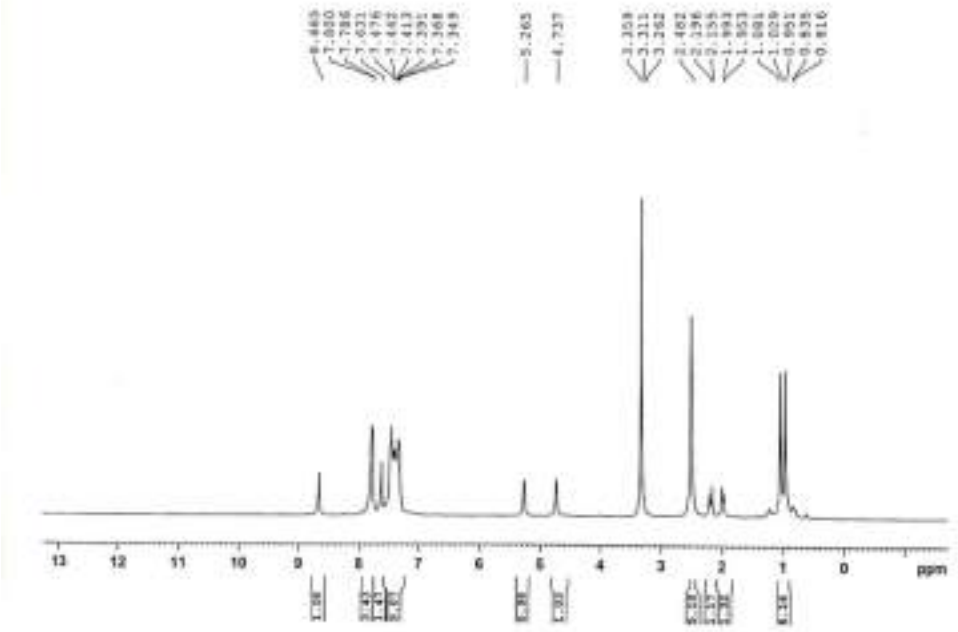


Figure IV.68-^{1}H-NMR of compound 5h

IV.12.A.14.l EDX data of SRH and RH

Spectrum: test 12841

Element	Series	unn. C [wt.%]	norm. C [wt.%]	Atom. C [at.%]	Error (3 Sigma) [wt.%]
Carbon	K-series	52.78	52.78	62.02	24.63
Oxygen	K-series	37.84	37.84	33.38	19.07
Silicon	K-series	7.70	7.70	3.87	1.16
Sulfur	K-series	1.68	1.68	0.74	0.36
Total:		100.00	100.00	100.00	

EDX data of SRH

Spectrum: test 12840

Element	Series	unn. C [wt.%]	norm. C [wt.%]	Atom. C [at.%]	Error (3 Sigma) [wt.%]
Carbon	K-series	53.61	53.61	60.95	21.11
Oxygen	K-series	45.02	45.02	38.42	19.14
Silicon	K-series	0.83	0.83	0.40	0.22
Sulfur	K-series	0.54	0.54	0.23	0.18
Total:		100.00	100.00	100.00	

EDX data of RH

IV.13 References

References are given in BIBLIOGRAPHY under Chapter IV.

Concluding Remarks

So, in this research work focused on **" SYNTHESIS OF BIOACTIVE ORGANIC HETEROCYCLIC COMPOUNDS USING NOVEL CATALYSTS "** is mainly on the development of efficient and environment benign methodologies for the new and efficient methodologies to synthesize synthons of bioactive compounds. **Chapter I** deals with a brief idea about bioactive compounds, precursors of bioactive compounds, idea of catalyst such as homogeneous and heterogeneous catalysts and from **Chapter II** to **Chapter IV** it describes about novel and greener synthetic roots towards one pot synthesis of various precursors of bio-active compounds. **Chapter II**, It deals with green synthetic approach towards one pot multi component synthesis of hexahydroquinoline and 9-arylhexahydroacridine-1,8-dione derivatives catalyzed by sulphonated rice husk. An efficient, straight forward, eco-friendly procedure to the synthesis of biologically active hexahydroquinoline derivatives and hexahydroacridine-1,8-diones have been designed using a novel bio-degradable heterogeneous catalyst, sulphonated rice-husk (SRH). Operational simplicity, greener reaction condition, reusability of the catalyst, excellent product yields (upto 98%) are the fundamental features of this procedure. **Chapter III**, describes about convenient and greener root towards one pot multi-component synthesis of substituted pyrano-dichromeneo-dione and chromeno-pyrido-pyrimidinone derivatives using rice husk based heterogeneous catalyst. An efficient pseudo three component synthetic method for 7-aryl/heteroaryl substituted pyranodichromene-6,8-dione and 7-aryl/heteroaryl substituted chromeno[4,3-*d*]pyrido[1,2-*a*]pyrimidinone derivatives using this greener catalyst

(SRH) under reasonable reaction condition. The operational simplicity, hassle free recovery of product and reusability of the catalyst with excellent product yield (up to 98%) are the fundamental features of this procedure. **In Chapter IV**, it deals with laboratory studies on one pot multi-component synthesis of a few varieties of heterocyclic compounds such as dihydro-dichromeno-pyridine-6,8-diones, tetrahydrotetrazolo[5,1-*b*]quinazolinones and 2,4-diaryl hexahydroquinoline-5-ones following the greener approach using rice husk based greener catalyst. A straight forward and sustainable synthetic procedures for these important class of bioactive heterocyclic compounds have been designed using a novel bio-degradable heterogeneous catalyst-sulphonated rice-husk (SRH). The process has advantageous in the sence of green catalysis as compared to other conventional homogenous solid acid catalyst and the operational simplicity, easy recovery of the product, avoidance, metal free technique and reusability of the catalyst along with excellent product yield (up to 98%) are the important and promising fundamental features of this procedure.

Henceforth, we were succeeded to synthesise different precursors of bioactive compounds in a novel and greener way. But major concernes regarding the synthesis are that some of the processes had complicated purification and lack of gram scale synthesis experiment. So, some works regarding this issues are underway in our laboratory and hope to minimize our limitations to make it best.

Appendix I

List of publications

1) Sulfonated Graphene-Oxide as Metal-Free Efficient Carbocatalyst for the Synthesis of 3-Methyl-4-(hetero)arylmethyleneisoxazole-5(4H)-ones and Substituted pyrazole

Puja Basak, **Sourav Dey** and Pranab Ghosh.

ChemistrySelect, 2020, 5, 626.

2) A Green Synthetic Approach Towards One Pot Multicomponent Synthesis of Hexahydroquinoline and 9-Arylhexahydroacridine-1, 8-dione Derivatives Catalyzed by Sulphonated Rice Husk

Sourav Dey, Puja Basak and Pranab Ghosh.

ChemistrySelect, 2020, 5, 15209.

3) Convenient one-pot synthesis of 1,2,4-oxadiazoles and 2,4,6-triarylpyridines using graphene oxide (GO) as a metal-free catalyst: Importance of dual catalytic activity

Puja Basak, **Sourav Dey** and Pranab Ghosh.

RSC Advances, 2021, 11, 32106.

4) A design for convenient and greener root towards one pot multi-component synthesis of substituted pyrano-dichromeno-dione and chromeno-pyrido-pyrimidinone derivatives using rice husk based heterogeneous catalyst

Sourav Dey, Puja Basak, Subhajit Sarkar and Pranab Ghosh.

Asian Journal of Green Chemistry, 2020, 6, 24-39.

5) A a collective laboratory studies on one pot multi-component synthesis of a few varieties of heterocyclic compounds following greener approach using rice husk based greener catalyst

Sourav Dey, Puja Basak and Pranab Ghosh.

Chemistry Select (communicated, Manuscript No.-slct 202203405).

Appendix II

Seminar and Symposium Attended

- Science Academic Lecture Workshop On " Frontiers in Chemical and Material Sciences: Theory and Practice (February 8-10, 2018)
- International Seminar on "Frontiers in Chemistry 2018"(August 27, 2018)
- National Seminar on "Frontiers in Chemistry-2019"(May 22,2019)
- International Seminar on International Year of the Periodic Table of Chemical Elements-2019 (November 22-23,2019**;Poster presented**)
- National Seminar on Frontiers in Chemistry-2020 (5^{th} March, **Poster presented)**

- International Webinar about "Drug discovery Development and Vaccinatiom"(September 13,2020)

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Catalysis

A Green Synthetic Approach Towards One Pot Multi Component Synthesis of Hexahydroquinoline and 9-Arylhexahydroacridine-1,8-dione Derivatives Catalyzed by Sulphonated Rice Husk

Sourav Dey, Puja Basak, and Pranab Ghosh*[a]

An efficient, straight forward, eco-friendly procedure for the synthesis of biologically active hexahydroquinoline derivatives and hexahydroacridine-1,8-diones has been designed using a novel bio-degradable heterogeneous catalyst, sulphonated rice-husk (SRH). SRH provides high density of acid groups making it different from conventional solid acids containing single acid groups. We report an efficient protocol for the synthesis of hexahydroquinolines and hexahydroacridine-1,8-diones using this carbon based acid catalyst (SRH) in solvent free and greener solvent respectively. Moreover, operational simplicity, greener reaction condition, reusability of the catalyst, excellent yield (upto 98%) are the fundamental features of this protocol. The metal free catalyst was characterised using different spectroscopic techniques FTIR, SEM, EDX, Powder XRD, ICP-AES.

1. Introduction

Over the past decade, green chemistry has emerged as an important environmental aspect to reduce the use of toxic and hazardous reagents in synthetic and industrial chemistry. In recent years industrial usage of agricultural wastage has received much interest due to economical and environmental reasons. Rice husk is a major agricultural by-product in south Asian countries that can be a promising feedstock of industrial use.[1,2] Rice husk (RH) contains cellulose, hemicelluloses, lignin, ash like other lignocellulosic material and the features like high silica content, high porosity, light weight and high external surface area turn it a good catalyst support for many industrial synthesis [3,4]. The use of eco-friendly catalysts and selected green solvents are of being promising demand in recent years for the synthesis of organic compounds.[5] In terms of green chemistry, the development of efficient multi-component reactions (MCRs) has attracted much consideration regarding the use of heterogeneous catalyst.[2–3] One-pot MCRs are energy saving processes that eliminates the multiple steps and increases the productivity with high level of structural diversity.[5–10] MCRs are convergent in nature and an important toolbox of green chemistry to synthesize different biologically active heterocyclic compounds. A large variety of MCRs are catalyzed by homogeneous and heterogeneous acid catalyst. However, solid acid catalyst have gained attention due to their heterogeneous nature and are favoured over homogeneous one as they can be easily separated from the reaction system.

Quinolines are ubiquitous in nature and they represent a wide variety of pharmaceutical (Figure 1and agrochemical products.[11] Substituted quinolines exhibit diverse biological activities and they are found to be major building blocks in various natural products.[12] Quinoline posseses considerable interest due to their biological activity including antibacterial, antifungal, antioxidant, anticancer, anticonvulsant, and antiviral activity.[12–16] Substituted quinolines and tetrahydroquinolines (THQ) are a class of heterocycles that serve as chemotherapeutic agents also.[17–19] Many heterocyclic,[25] compounds containing the quinoline nucleus display anti-inflammatory activity and they serve as antagonist inhibitors.[20]

Many heterocyclic,[25] compounds containing the quinoline nucleus display anti-inflammatory activity and they serve as antagonist inhibitors.[20] Quinolines with 1,4-Dihydropyridine (DHP) nucleus have been found efficient in cardiovascular diseases as calcium channel blockers.[21,22] Along with these, this heterocyclic moiety have vast application in agricultural field also.[23] Many recent research works are carried on this unique heterocyclic motif due to its diverse biological activity.[24–25]

Several homogeneous and heterogeneous catalysts have been employed for the synthesis of substituted hexahydroquinolines derivatives. Among them, the synthesis using nano-ZnO/ultrasound nano-Fe_3O_4,[26] AcOH,[27] K_2CO_3,[28] triethylamine,[29] $Fe_{3-x}Ti_xO_4$@SPDETATSA (N-(3-silyl propyl) diethylene triamine N,N′,N″-tri-sulfonic acid immobilized on $Fe_{3-x}Ti_xO_4$magnetic nanoparticles[30] are noteworthy to mention. Acridine derivatives containing keto functional groups are found to be good anti-malarial agents and substituted hexahydroacridine-1,8-dione being resemble to dihydropyridine molecule can act as a K-channel openers in urinary-bladder smooth muscle.[31,32] These acridinediones were also

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found to act as laser dyes due to electron delocalization and exhibit fluorescence and laser activity.[33,34] The effectiveness of lasing is dependent upon the substituents at C-9 and N-10 of the acridine chromophore. Apart from the above applications, acridinediones also possess other important photo-physical and electrochemical properties.[35] Acridine dyes can bind with photo damaged nucleic acids which have increasing interest as mutagens in micro-organisms.[36] The usefulness of acridines have led to the development of numerous methods of their synthesis by the three component Hantzsch condensation of aldehydes with β-diketones and ammonium acetate or appropriate primary amines. Many procedures describe the synthesis of acridinedione derivatives by cyclocondensation between dimedone and aldehyde and primary amine in the presence of heat in organic solvents with a varity of catalysts such as Fe_3O_4@B-MCM-41,[37] SO_4 2/TiO_2NPs,[38] Scolecite,[39] Pd nanoparticle,[40] MNPsN-propyl-benzoguanamine-SO_3H,[41] silica bonded N-propyl sulfamic acid[42], CH_3SO_3H,[43] tetrabutylammonium hexatungstate,[44] nano TiO_2,[45] $SiO_2/ZnCl_2$,[46] protic pyridinium ionic liquid,[47] $CsCO_3$,[48] ceric ammonium nitrate,[49] organocatalysts,[50] Ni nanoparticles,[51] MgO,[52] thiamine hydrochloride,[53] SnO_2,[54] La_2O_3/TFE (2,2,2-trifluoroethanol),[55] $Cd(NO_3)_2$.$4H_2O$.[56] However, many protocols suffer from some limitations such as harsh reaction conditions, costly and non recyclable catalyst, and tedious purification, use of toxic reagents and generation of hazardous wastes. By eliminating the drawbacks of previous methods, it is important to find out new greener protocols for the synthesis of substituted quinolines and hexahydroacridine-1,8-dione. Eco-friendly heterogeneous solid acid catalysts have gained much attention over homogeneous catalysts owing to its easy separation process. Amongst them carbon-based sulphonated catalysts are most promising because of the presence of different acidic functional groups and large carbon framework. Owing to the low price and simple preparation, biomass waste (RH) is extensively used in several field as mentioned above. With increasing demand in green chemistry, the use of heterogeneous solid acid catalyst has attracted the researchers regarding environmental issues. An ideal solid acid catalyst should be the one which have excellent stability, high porosity, active acidic sites, low cost and hydrophobic surfaces. Among them carbon-based acidic catalysts are most promising as they can be extensively prepared from biomass material (RH). However, RH based alkaline catalyst and solid acid catalyst under MW irradiation has been reported previously.[57,58] Herein, we report a conventional heating technique for the preparation of sulphonated RH (SRH) and characterisation as well. We report the use of this novel green catalyst SRH for feasible synthesis of hexahydroquinoline and hexahydroacridine-1,8-diones derivatives in one-pot strategy.)

2. Results and discussion

The prepared catalyst was characterised by FTIR spectroscopy, scanning electron microscopy (SEM), powder X-ray diffraction (XRD) and ICP-AES for quantifying weight percentage of sulphur and other elements. The comparison of FTIR, SEM image and XRD pattern of RH and SRH strongly supports the synthesis of the sulphonated catalyst through a completely new method. The comparison of SEM images of RH and SRH shows that a molecular aggregation occurs in SRH resulted from the incorporation of $-SO_3H$ functional group into the skeleton of rice husk material (Figure 2). EDX analysis of sulphonated rice husk and rice husk showed a measurable difference in the weight percentage of the elements especially carbon, slicon, sulphur and oxygen (Figure 2).

The newly appearing band with a peak 1098 cm^{-1} represents the symmetric and asymmetric streatching of S=O bonds of $-SO_3H$ (sulphonic acid).The the new broad band at 3342 cm^{-1} along with the band at 1098 cm^{-1} both confirmly denoting the incorporation of $-SO_3H$ groups in SRH after sulphonation of rice husk (Figure 3). The powder XRD analysis shows characteristics peaks at $2\theta = 20.82°$, 22.28°, 26.67° in which a broad peak at around 20° is due to the carbon composed aromatic sheets which are oriented in a random manner (Figure 4).[58]

ICP-AES analysis showed that weight percentage sulphur is 1% to that of total weight of all the elements present. To make surety in broad aspect all the results and graphs were thoroughly viewd and compared with other sulphonated materials such as sulphonated rice husk ash,[59] CBSC (carbon-based sulphonated catalyst)[57] which confirmly showed that SRH was morphologically and compositionally different from those reported sulphonated catalysts. Detailed informations are attached into the supporting information for further support.

Initially, the reaction was first started with benzaldehyde (1 mmol), malononitrile (1 mmol), ammonium acetate (1.2 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) were

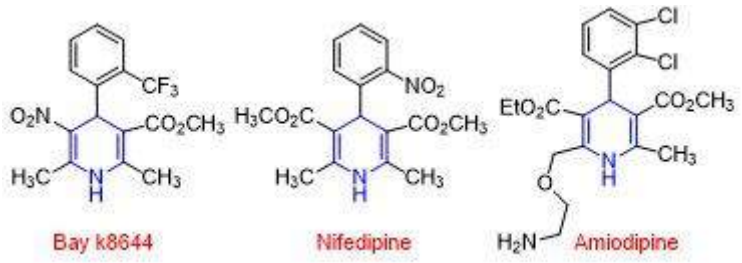


Figure 1. Some examples of biologically active drugs.

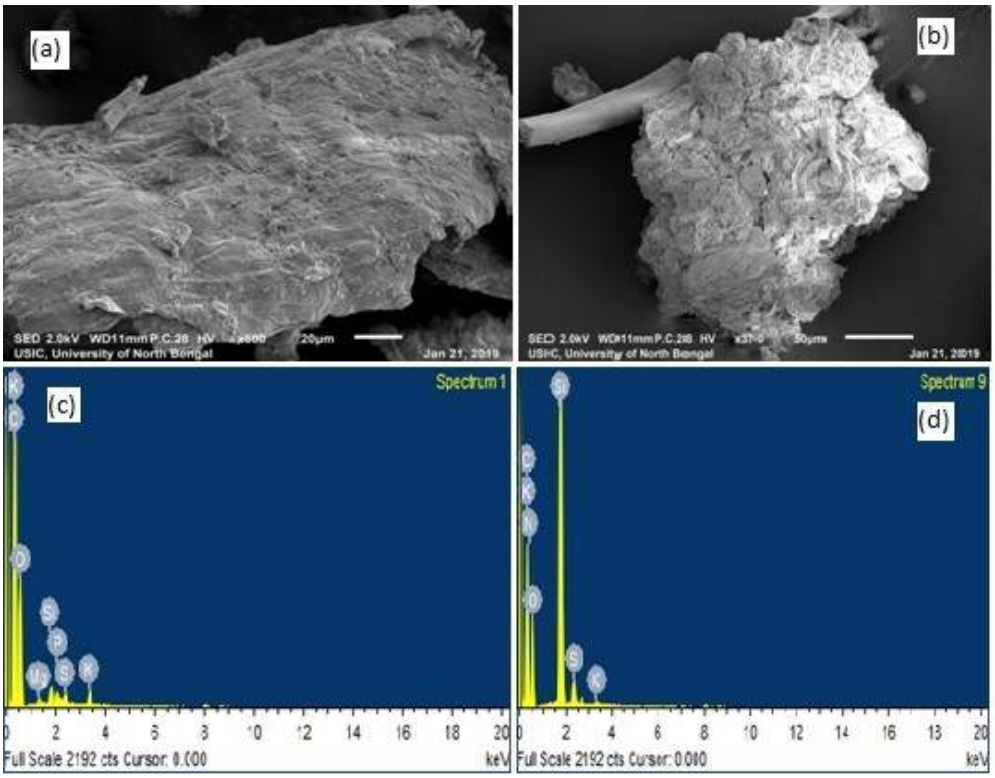


Figure 2. (a) SEM image of rice husk(RH) (b) SEM image of sulphonatrice husk (SRH) (c)EDX of RH (d) EDX of SRH.

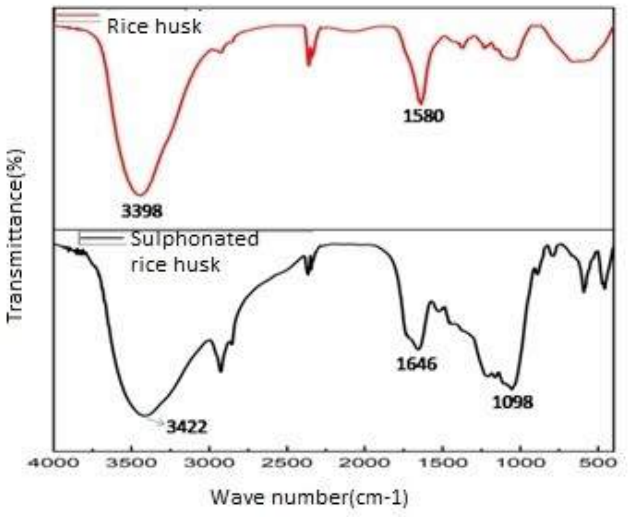


Figure 3. FTIR of RH and SRH.

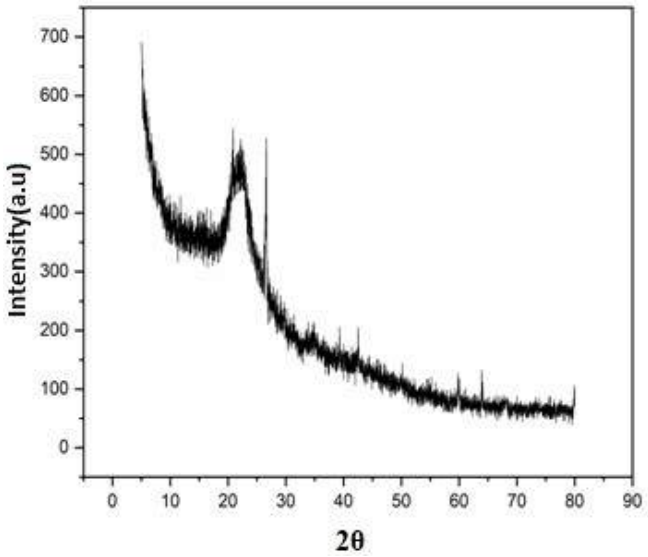


Figure 4. Powder XRD plot of SRH.

taken in a 25 mL RB with 100 mg of catalyst. For screening the reaction p-tolualdehyde (0.5 mmol), ammonium acetate (0.8 mmol) and 5,5-dimethylecyclohex-1,3-dione (1 mmol) were taken in a 25 mL RB.. However, in absence of catalyst the formation of the corresponding product was diminished (Table 1,entry 10). Excellent yield was observed in presence of 100 mg of SRH catalyst in ethanol solvent at 80 °C temperature (Table 1, entry 1).With decreasing the amount of catalyst, the yield of the product decreases slightly in ethanol. From the optimized condition it is clear that SRH catalyst is proved to be suitable for the conversion of hexahydroquinoline with excellent yield in short reaction time. The amount of the catalyst and time of the reaction was further checked to find out the optimized condition of the reaction. It was observed that the best result was obtained at 70 °C temperature using 60 mg of

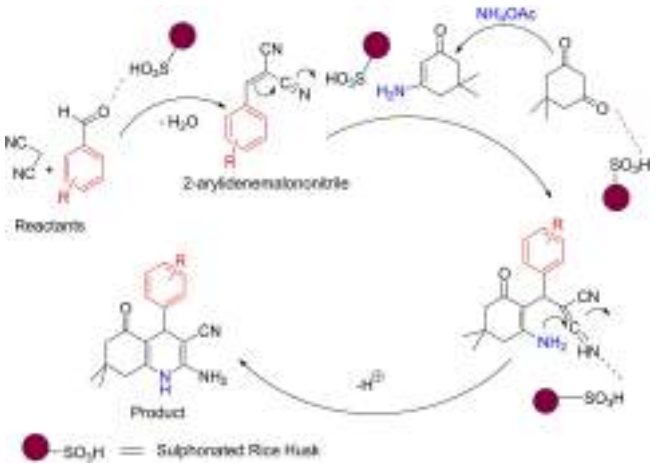


Figure 5. The plausible mechanism for the synthesis of hexahydroquinoline.

Table 1. Optimisation of the reaction condition for the synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinolines.[a]

Entry	Catalyst (mg)	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	100	Ethanol	80	40	96
2	80	Ethanol	80	30	96
3	70	Ethanol	80	30	94
4	50	Ethanol	80	30	85
5	40	Ethanol	80	30	78
6	40	Ethanol	100	30	80
7	30	Neat	50	120	80
8	30	Neat	50	90	70
9	20	Neat	60	60	64
10	None	Neat	80	120	30
11	80	Neat	70	40	96
12	80	Neat	70	30	96
13	60	Neat	70	20	96
14	60	Neat	60	20	92
15	80	Methanol	80	30	94

[a] Reaction of p-toluealdehyde (1mmol), malononitrile (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1mmol), ammonium acetate (1.2 mmol), [b] tableIsolated yield after purification through column chromatography.

catalyst SRH under neat reaction contion (Table 1, entry 13). The effectiveness of SRH over other acid catalyst was established as it requires very short reaction time under solvent free condition and easily seperable from the reaction mixture (Table 2, entry 11). The progress of the reaction was monitored by thin layer chromatography (TLC) and the pure product was separated by column chromatography with petroleum ether/ethyl acetate (v/v ratio70/30) mixture. Role of methanol has also been observed(table 1,entry 15) showing that product yield is quite closer to that of ethanol but methanol is considered as toxic alcohol so it should be avoided in greener aspect of reaction. From the optimized condition it is clear that SRH catalyst is proved to be suitable for the conversion of hexahydroquinoline with excellent yield in short reaction time. The amount of the catalyst and time of the reaction was further checked to find out the optimized condition of the reaction. It was observed that the best result was obtained at 70 °C

Table 2. Comparison of efficiency of the catalyst for the synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinolines.[a]

Entry	Catalyst	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	PTSA(60mg)	Ethanol	80	30	93
2	PEG-400(5mL)	–	80	40	80
3	PEG-200(5mL)	–	80	60	70
4	Glycerol (5mL)	–	80	60	72
5	H_2SO_4 (5mL)	Ethanol	70	30	85
6	AcOH (5mL)	–	80	30	80
7	$HClO_4$ (5mL)	–	70	30	90
8	K_2CO_3 (60mg)	Neat	80	30	94
9	Et_3N(5mL)	–	80	30	95
10	Fe_3O_4 (60 mg)	Neat	80	30	91
11	SRH (60mg)	Neat	70	20	96

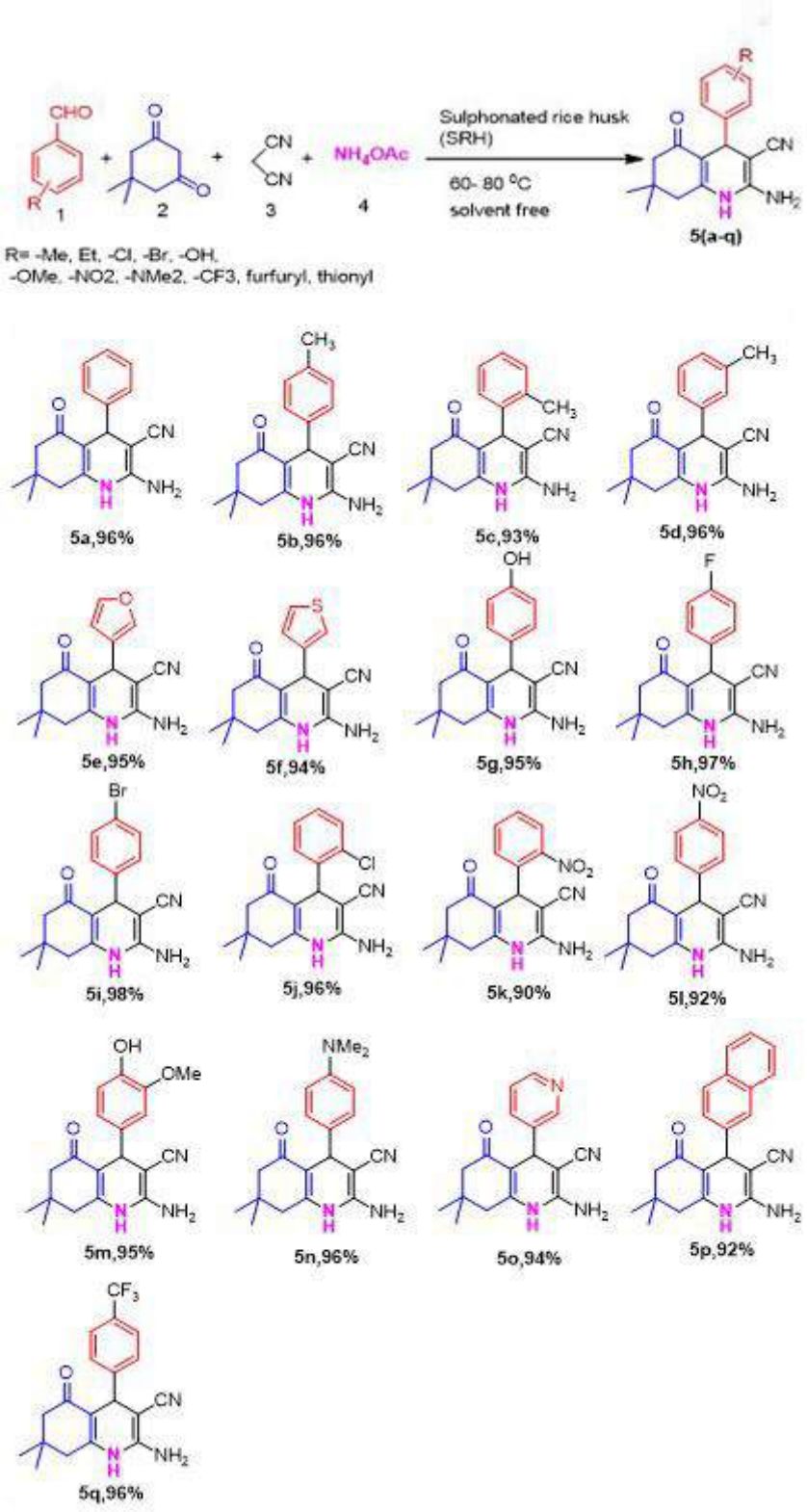
[a] Reaction of p-toluealdehyde (1mmol), malononitrile (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1mmol), ammonium acetate (1.2 mmol), [b] Isolated yield after purification through column chromatography.

temperature using 60 mg of catalyst SRH under neat reaction contion (Table 1, entry 13). Few controlled experiments were carried out to compare our prepared catalyst (SRH) with some conventional solid and liquid acid catalyst (Table 2). It was observed from the results that most of the acid catalyst showed good activity in ethanol solvent. However, some base catalyst was also employed and they exerted the corresponding product with high yield in 30 minutes (Table 2, entry 8–9). The effectiveness of SRH over other acid catalyst was established as it requires very short reaction time under solvent free condition and easily seperable from the reaction mixture (Table 2, entry 11). The progress of the reaction was monitored by thin layer chromatography (TLC) and the pure product was separated by column chromatography with petroleum ether/ethyl acetate (v/v ratio70/30) mixture.

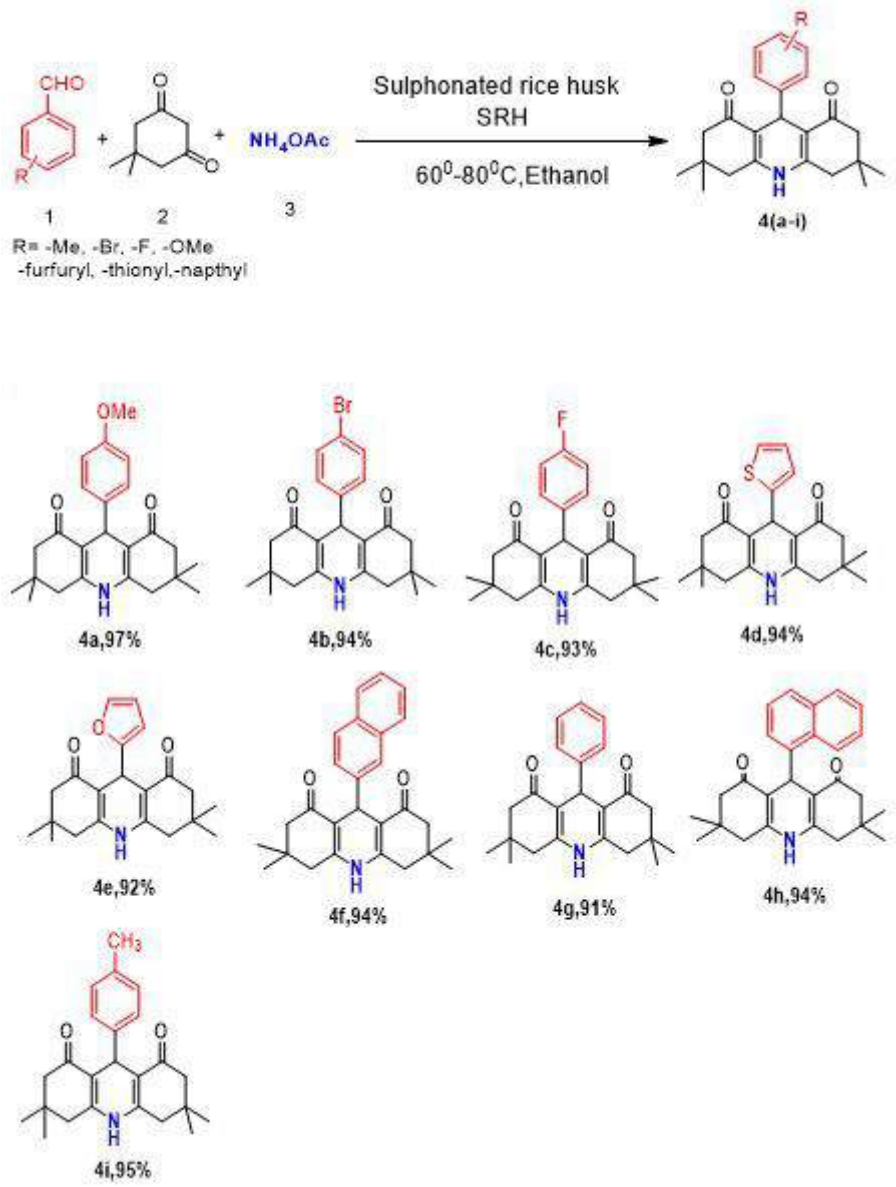
The generality of the reaction was also observed with a variety of aromatic and heterocyclic aldehydes (Scheme 1). There is no significant difference in the yield of the desired product with electron donating and electron withdrawing substituents at *ortho*, *meta* and *para* position of the aromatic aldehyde. The target compounds (5a–5q) are successively synthesized using SRH as efficient catalyst under neat reaction condition and short reaction time.

2.1. Mechanism

A plausible SRH catalyzed synthesis of hexahydroquinoline is established by considering the acidic behaviour of the catalyst (Figure5). At very first step of the reaction, protonation occurs at aldehyde oxygen of aromatic aldehyde followed by the Knoevenagel condensation of malononitrile and aromatic aldehyde. After that, Michael addition reaction occurs between 5,5-dimethylecyclohex-1,3-dione and 2-arylidenemalononitrile, resulting a intermediate. However, this intermediate rapidly



Scheme 1. Synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives using sulphonated rice husk[a] [a] Reaction of aromatic aldehyde (1mmol), malononitrile (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1mmol), ammonium acetate (1.2 mmol) and SRH (60 mg). The yields are isolated through column chromatography.



Scheme 2. Synthesis of substituted 9-arylhexahydroacridine-1,8-dione derivatives using sulphonated rice husk[a] [a] Reaction of aromatic aldehyde (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (2mmol), ammonium acetate (1.2 mmol) and SRH (50 mg). The yields are isolated through recrystalisation.

undergoes in cyclization and exters the target hexahydroquinoline product.

First, the reaction was started with Anisaldehyde (1 mmol), ammonium acetate (1.2 mmol) and 5,5-dimethylecyclohex-1,3-dione (2 mmol) and the catalyst (SRH) in a 25 mL RB. Optimisation reaction was carried out with taking anisaldehyde and excellent yield was observed in presence of 40 mg of SRH catalyst in ethanol solvent at 60 °C temperature (Table 3, entry 7) with reaction time of 50 minutes. With decreasing the amount of catalyst, the yield of the product decreases slightly in ethanol. However, in absence of catalyst the formation of the product was diminished (Table 3, entry 13). The performance of the reaction is almost similar in methanol solvent but for greener aspect ethanol is is considered as more safer solvent than methanol to get the maximum yield. (Table3, entry 7 & 8). From the optimized condition it is clear that SRH catalyst is proved to be suitable for the conversion of hexahydroacridine-1,8-dione with excellent yield in short reaction time. The amount of the catalyst and time of the reaction was checked to find out the optimized condition of the reaction. It was observed that the best result was obtained at 60 °C temperature using minimum amount of catalyst SRH (40 mg) in ethanol (Table 3, entry 7).The progress of the reaction was monitored continuously by thin layer chromatography (TLC) and the pure product was separated only by recrystalisation procedure in ethyl acetate and petroleum ether (1 : 1)

Table 3. Optimisation of the reaction condition for the synthesis of hexahydroacridine-1,8-dione [a]

Entry	Catalyst (mg)	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	90	Ethanol	80	120	97
2	80	Ethanol	80	90	97
3	70	Ethanol	80	70	97
4	60	Ethanol	80	60	97
5	50	Ethanol	70	60	95
6	40	Ethanol	70	60	95
7	40	Ethanol	60	50	95
8	40	methanol	60	60	94
9	40	Neat	60	50	84
10	40	Neat	80	90	86
11	40	Ethanol/H_2O (3:1)	70	60	62
12	40	Methanol/H_2O (3:1)	70	60	58
13	None	Ethanol	70	120	20

[a] Reaction of anisaldehyde (1mmol), 5,5-dimethyl-cyclohexane-1,3-dione (2mmol), ammonium acetate (1.2 mmol). [b] Isolated yield after purification through recrystalisation procedure.

2.2. Mechanism

A plausible SRH catalyzed synthesis of hexahydroacridine-1,8-dione are established considering the acidic behaviour of the catalyst (Figure 6). At very first step of the reaction, protonation occurs at aldehyde oxygen of aromatic aldehyde followed by Hantzsch condensation of aldehydes with β-diketones and ammonium acetate. Intermediates are produced in situ rapidly undergo cyclization and exters the targeted hexahydroacridine-1,8-dione product.

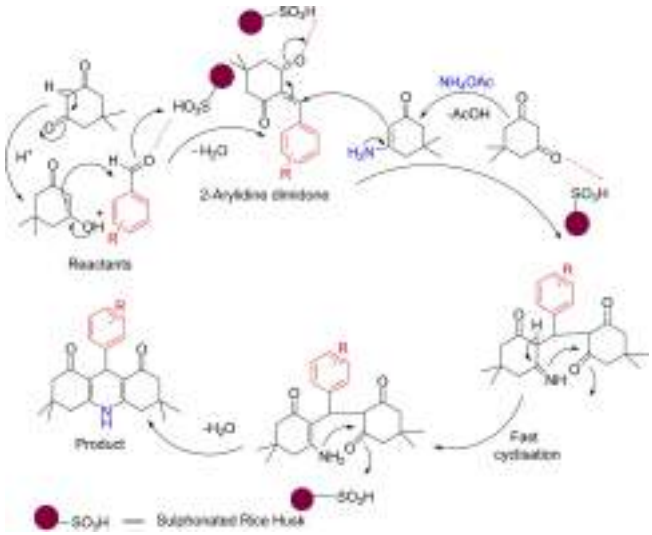


Figure 6. The plausible mechanism for the synthesis of hexahydroacridine-1,8-dione.

2.3. Catalyst Recyclability Experiment

To check the recyclability of the catalyst, a model reaction between benzaldehyde(1.6 mmol), malononitrile(1.6 mmol), ammonium acetate(1.92 mmol) and 5,5-dimethylecyclohex-1,3-dione(1 mmol) in presence of 100 mg of sulphonated rice husk was carried out under optimised reaction condition. After successful completion of the each reaction step, ethyl acetate (10 ml) and water was added to the reaction mixture. The supernatant liquid (ethyl acetate extract) was decanted off and this process was repeated thrice. The catalyst was then filtered and washed with water and acetone repeatedly and dried under vaccum. The recovered catalyst weight was measured after every recovery step and the next reaction was repeated in required proportion of the reactants to that of weight of the recovered catalyst. The temperature and time of the reaction were kept constant in this regard. Amount of catalyst, aldehyde, reaction time,temperature and yield percentage of the product have been shown in table 4 (entry 1–7) The catalyst can easily be separated from the reaction mixture by simple filtration and was found to retain its acidic property, even after 7th run (Figure 8). This was further supported by comparing the FTIR spectra of fresh SRH catalyst and recovered catalyst after successive reactions (Figure 7).

3. Conclusion

In conclusion, a simple and greener methodology for the synthesis of variety of hexahydroquinolines and hexahydroacridine-1,8-dione from commercially available aldehydes has been established. We have introduced a new cheap and green heterogeneous catalyst SRH (Sulphonated rice husk) for the synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline and 9-Arylhexahydroacridine-1,8-dione derivatives with excellent yield. This heterogeneous catalyst is found to be highly efficient for the synthesis of hexahydroquinoline and hexahydroacridine-1,8-dione in short reaction time. The catalyst is highly recyclable upto 7th run and has profound effect to catalyze a wide range of acid-catalysed reactions.

Table 4. Table for the amount of recovered catatyst with isolated product yield[a]

Entry	Catalyst (mg)	Aldehyde (x mmol)	Temperature (°C)	Time (min)	Yield (%)[b]
1	100	1.6 mmol	70	20	96
2	80	1.3 mmol	70	20	94
3	60	1.0 mmol	70	20	90
4	50	0.8 mmol	70	20	87
5	40	0.6 mmol	70	20	82
6	30	0.5 mmol	70	20	76
7	20	0.3 mmol	70	20	71

[a] Reaction of benzaldehyde (x mmol), malononitrile (x mmol), 5,5-dimethyl-cyclohexane-1,3-dione (2x mmol), ammonium acetate (1.2x mmol), [b] Isolated yield after purification through recrystalisation.

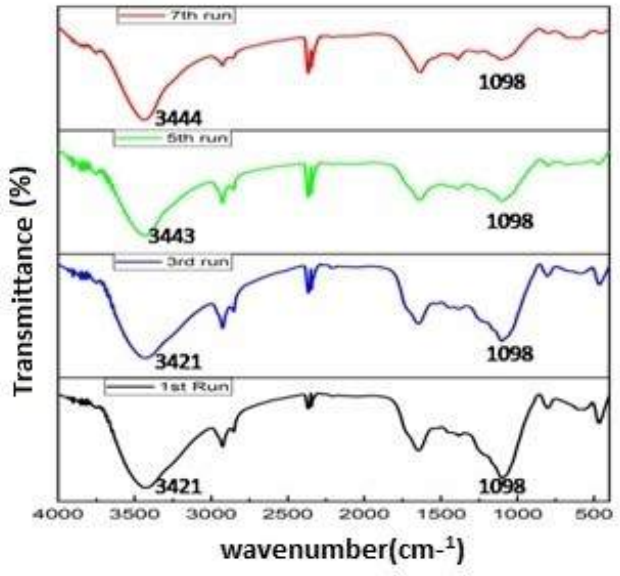


Figure 7. FTIR spectra of reused catalysts after 1st, 3rd, 5th and 7th run.

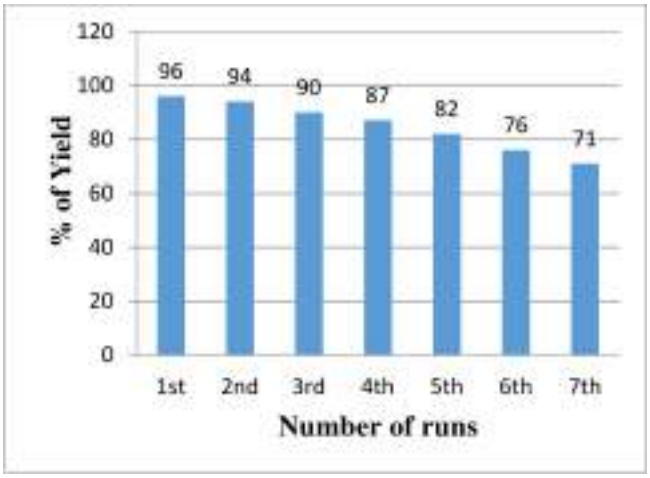


Figure 8. Recyclability experiment.

Supporting Inforamation Summary

Supporting information data are provided in electronic supporting information include experimental details, ^{1}H NMR, ^{13}C NMR spectra of all the synthesized compounds (5a-5p), (4a-4h) and EDX & ICP-AES data of the prepared catalyst.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Sulphonated rice husk · Greener catalyst · Hexahydroquinoline · hexahydroacridine-1,8-diones · Multicomponent reaction

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