Access to Tetrahydro(pyrimidines/quinolines) and Fused Coumarin Containing Nitrogen Heterocycles Using Multicomponent Reactions

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DOCTOR OF PHILOSOPHY

by

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Dedicated to

My Late Father

&

My Family Members

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Department of Chemistry

DECLARATION

I do hereby declare that the matter embodied in this thesis entitled "*Access to Tetrahydro(pyrimidines/quinolines) and Fused Coumarin Containing Nitrogen Heterocycles Using Multicomponent Reactions"* is the result of investigations carried out by me under the supervision of Prof. A. T. Khan in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that Mr. Deb Kumar Das has been working in my research group since 29th July, 2008 as a regular registered Ph. D. student. I am forwarding his thesis entitled "*Access to Tetrahydro(pyrimidines/quinolines) and Fused Coumarin Containing Nitrogen Heterocycles Using Multicomponent Reactions*" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

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Prof. A. T. Khan
(Thesis Supervisor)

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At last but not least, I thank God for being there for me in a way no one else can.

Deb Kumar Das

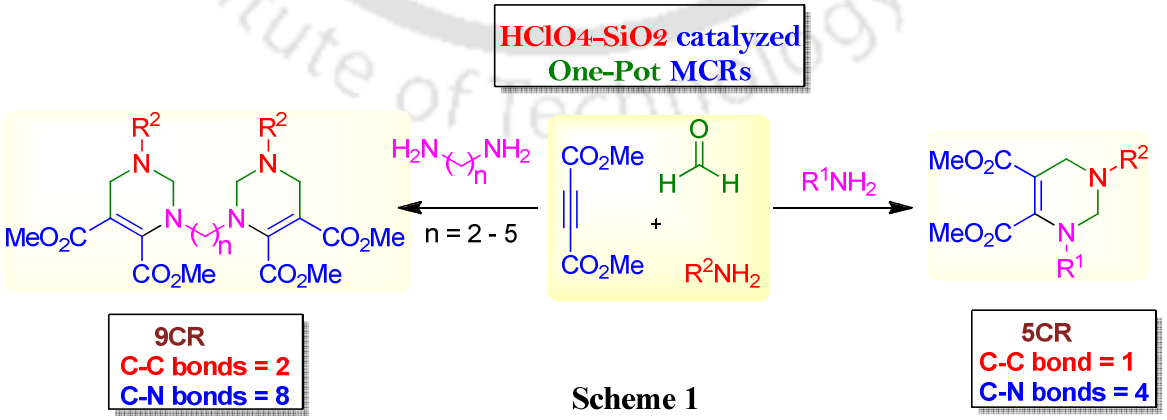
SUMMARY OF THE THESIS

The contents of the thesis entitled "Access to Tetrahydro(pyrimidines/quinolines) and Fused Coumarin Containing Nitrogen Heterocycles Using Multicomponent Reactions" has been divided into three main parts namely **Part A**, **Part B** and **Part C**. **Part A** of the thesis comprises two chapters such as Chapter IA and Chapter IIA. Similarly, **Part B** of the dissertation consists of five chapters namely Chapter IB, Chapter IIB, Chapter IIIB, Chapter IVB and Chapter VB. Likewise, **Part C** of the thesis covers three chapters such as Chapter IC, Chapter IIC and Chapter IIIC. First Chapter of each part of the dissertation describes a brief review on the work on the relevant topics. The other chapters of the thesis elaborate successful results and discussion along with experimental section.

PART A

Chapter IA highlights a brief literature survey on the development of multicomponent reactions and its importance in organic synthesis. In addition, a brief literature survey on the importance, synthetic utility and methods of preparation for tetrahydropyrimidine derivatives is presented.

Chapter IIA demonstrates the synthesis of the substituted tetrahydropyrimidines from dimethyl acetylenedicarboxylate (DMAD), amines and formaldehyde in methanol at room temperature using silica supported perchloric acid ($HClO_4$-SiO_2) through multicomponent reactions in good yields. In addition, the synthesis of *bis*-tetrahydropyrimidine derivatives the same synthetic strategy has also been achieved. We have demonstrated that silica supported perchloric acid ($HClO_4$-SiO_2) is an inexpensive, nontoxic, reusable, environmentally benign as well as highly efficient catalyst for the above transformation (Scheme 1).

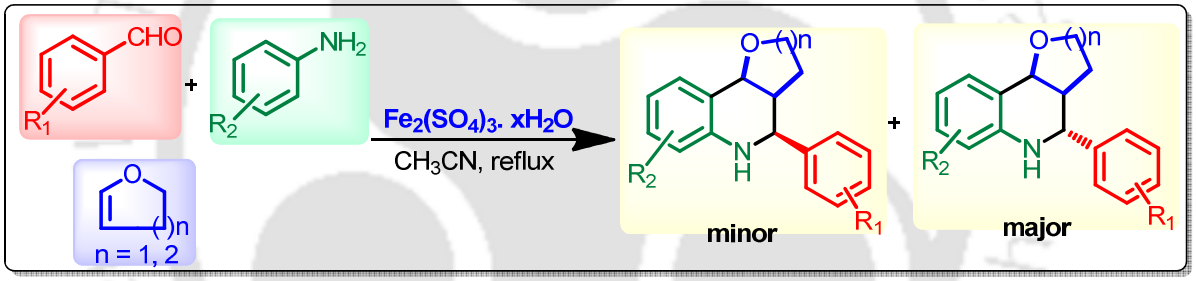


Scheme 1

PART B

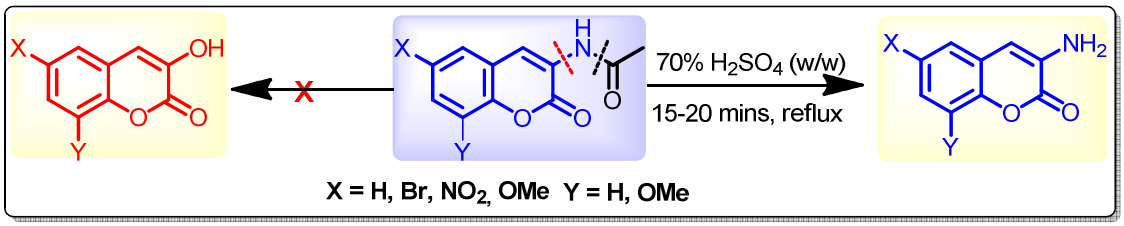
Chapter IB highlights a brief literature review on the recent development of hetero-Diels-Alder reaction with special emphasis on Povarov reaction for the construction of heterocyclic molecules. The Povarov reactions are valuable tools in a contemporary organic synthesis for the construction of *N*-polyheterocycles such as alkaloids and it has also been efficiently explored towards natural product synthesis namely alkaloid synthesis.

Chapter IIB describes the importance of tetrahydroquinoline derivatives and their methods of preparation. In addition, we have discussed our successful results on the synthesis and characterization of tetrahydroquinoline derivatives using Povarov reaction through one-pot multicomponent reaction using hydrated ferric sulfate [$Fe_2(SO_4)_3.xH_2O$] as an efficient heterogeneous catalyst (Scheme 2).



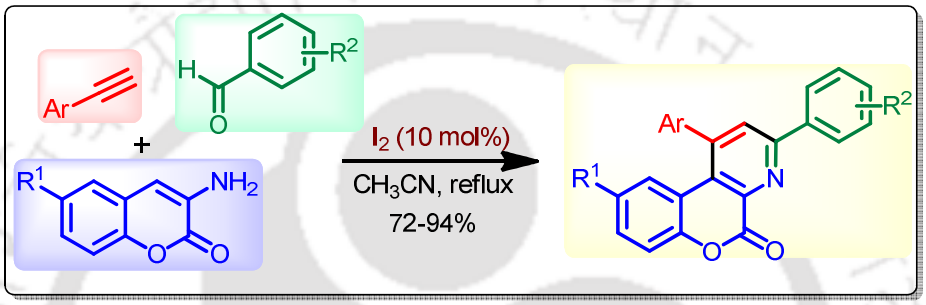
Scheme 2

In **Chapter IIIB**, we have shown an efficient method for the synthesis of various 3-aminocoumarin derivatives in good yields from regioselective hydrolysis of 3-acetamidocoumarins using 70% (w/w) of sulfuric acid. This method is also being a useful alternative for the large scale preparation of 3-aminocoumarin derivatives in a greener manner (Scheme 3).



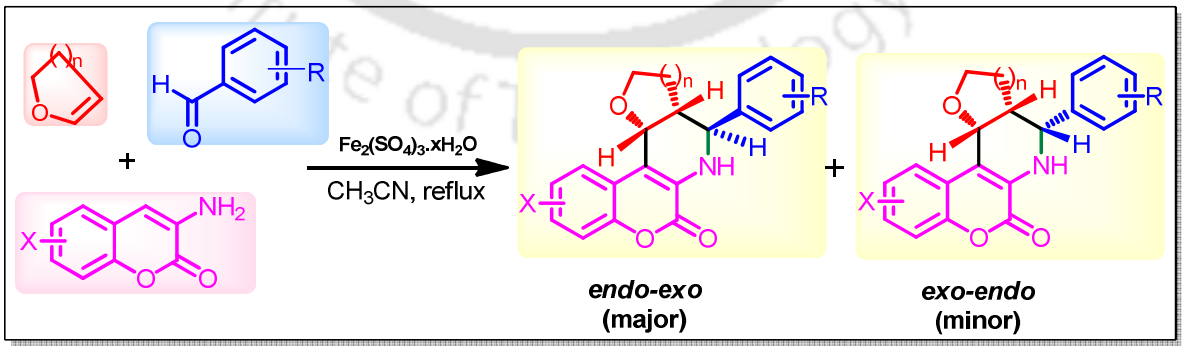
Scheme 3

Chapter IVB elaborates the synthesis and characterization of substituted pyrido[2,3-*c*] coumarin derivatives from 3-aminocoumarins, aromatic aldehydes and alkynes in presence of 10 mol% molecular iodine in acetonitrile under reflux conditions through one-pot Povarov reactions. The reaction conditions are simple and transformation is quite effective for a wide range of aldehydes and phenylacetylenes as well as 3-aminocoumarins. The products are easily isolable in good to excellent yields without aqueous work-up, chromatographic separation and involvement of metal catalyst (Scheme 4).



Scheme 4

Chapter VB demonstrates the synthesis of 3,4-fused tetrahydropyrido[2,3-*c*]coumarin via Povarov reaction from 3-aminocoumarins, aromatic aldehydes and cyclic enol ethers using hydrated ferric sulfate [$Fe_2(SO_4)_3.xH_2O$] as an efficient heterogeneous catalyst as shown in Scheme 5. We have also explained the diastereoselectivity of the adducts in this chapter. The key features of this protocol are good yields, high diastereoselectivities, applications to a wide range of substrates, using an inexpensive, readily available and recyclable catalyst and environmentally benign reaction conditions.

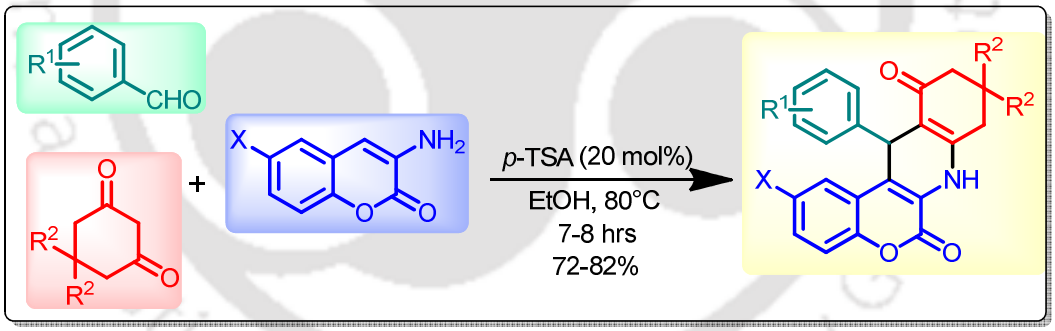


Scheme 5

PART C

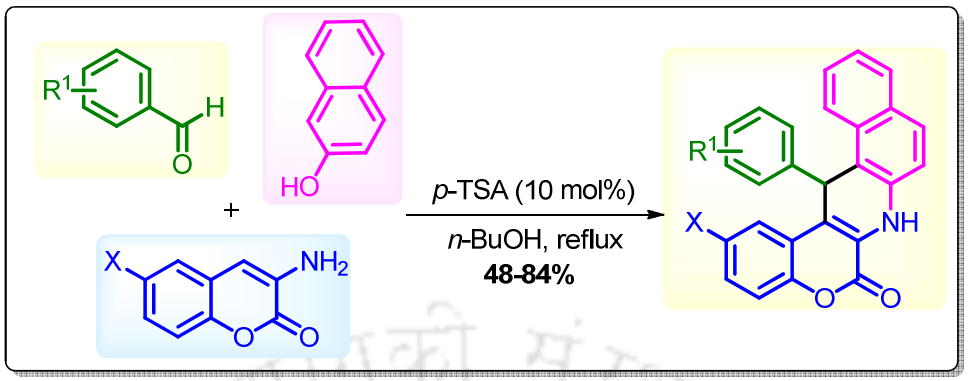
Chapter IC describes a brief review on tandem-Knoevenagel-Michael initiated ring closure reaction. The tandem-Knoevenagel-Michael reaction represents an elegant approach, which has been used extensively for the construction of small/medium sized nitrogen or oxygen containing heterocyclic compounds. The importance of these reactions for the construction heterocyclic compounds has also been addressed in this chapter.

Chapter IIC illustrates the one-pot synthesis of chromeno[3,4-b]quinoline derivatives through tandem-Knoevenagel-Michael reactions followed by ring closure by employing three-component condensation of aromatic aldehydes, 3-aminocoumarins and cyclic 1,3-diketones in the presence of catalytic amount of *p*-toluenesulfonic (*p*-TSA) acid in ethanol under reflux conditions. It is worth mentioning that the three new bonds (two *C*-*C* and one *C*-*N*) and one stereocenter are formed in the course of the reactions. Shorter reaction times, environmentally benign, superior atom economy, the easy accessibility of the catalyst and its cost effectiveness, simplicity of the procedure and good to excellent yields are some of the most significant features of the present protocol (Scheme 6).



Scheme 6

Chapter IIIC elaborates the synthesis of wide variety of benzo[f]chromeno[3,4-b]quinolin-6-one via one-pot three-component reaction of 2-naphthol, aldehydes and 3-aminocoumarins in the presence of catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in *n*-butanol under reflux condition through tandem-Knoevenagel-Michael initiated ring closure reactions. The synthesized benzo[f]chromeno[3,4-b]quinolin-6-one derivatives may be promising candidates for organic fluorophore. We believe some of them be may display important biological activities for biomedical screening (Scheme 7).



Scheme 7

In summary, the dissertation describes some new and effective synthetic methodologies for the synthesis of tetrahydro(pyrimidines/quinolones) as well as for substituted heterocyclic compounds containing 3-aminocoumarin structural backbone. It is expected that all these methodologies might be applicable in a target-oriented synthesis and some of the synthesized molecules may exhibit pharmacological activity, which might be useful in future for mankind.

CONTENTS

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam during the period from 29th July, 2008 to 17th September, 2013 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50 ^{o}C for 8 hours. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent were used. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in a rotavapor using Büchi R-114V instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 281 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 spectrometer TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in the order: multiplicity, no of protons and coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), brs (broad singlet), dq (doublet of quartet), dt (doublet of triplet) and ddt (doublet of doublet of triplet). HRMS spectra were collected on Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS and WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K.

ABBREVIATIONS

Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
abs	absolute
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Boc_2O	Di-tert-butyl dicarbonate
Bu	butyl
CAN	ceric ammonium nitrate
CCDC	cambridge crystallographic data centre
CDA	carbo-Diels-Alder
CDC	cross-dehydrogenative-coupling
CNS	central nervous system
CR	component reaction
CSA	camphorsulfonic acid
DA	Diels-Alder
DCE	1,2-Dichloroethane
DCM	dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl acetylenedicarboxylate
DHF	2,3-dihydrofuran
DHP	3,4-dihydropyran
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DOS	diversity-oriented synthesis
dr	diastereomeric ratio
ee	enatiomeric excess

EDG	electron donating group
EWG	electron withdrawing groups
FMO	frontier molecular orbital
Fg	functional group
g	gram
HDA	Hetero-Diels-Alder
HOMO	highest occupied molecular orbital
HRMS	High-resolution Mass Spectrometry
h	hour
IR	infrared
L	ligand
LA	lewis acid
LUMO	lowest unoccupied molecular orbital
MCR	Multicomponent reaction
MEK	Methyl ethyl ketone
MIRC	Michael initiated ring closure
m.p	melting point
MS	molecular sieves
MW	microwave
NaAsc	Sodium ascorbate
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid program
o-QM	ortho-quinone methide
PDB	protein data bank
PET	photoinduced electron transfer
PG	protecting group
PPA	polyphosphoric acid
Ph	phenyl
ppm	parts per million
Py	pyridine
p-TSA	*p*-toluenesulfonic acid

rt	room temperature
TBAB	n-Tetrabutylammonium bromide
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPT	2,4,6-triphenylpyrylium tetrafluoroborate
TOS	target-oriented synthesis
TfOH	Triflic acid
Tf_2O	Triflic anhydride
t-BHP	tert-Butyl hydroperoxide
S_N	substitution nucleophilic
w	weight
XRD	x-ray diffraction

PART A

CHAPTER IA

Brief review on Multicomponent reactions (MCRs) and Tetrahydropyrimidine Derivatives

Review

1. Importance of Heterocyclic Compounds

Heterocycles are special class of organic compounds as they are biologically and industrially important for a developed nation.[1] They are widely distributed in nature as alkaloids, carbohydrates, flavonoids and macrolides.[2] In addition, they are of great significance to life because of structural subunits of nucleic acids. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles[3] and they also play a major role in a biochemical process. Numerous heterocyclic compounds can be designed with diverse physical, chemical and biological properties[4,5] with the combinations of carbon, hydrogen and various heteroatoms. The most commonly found heteroatoms are nitrogen, oxygen and sulfur; while heterocycles containing other polyvalent elements such as boron, silicon, phosphorus, selenium and arsenic are also known in recent times. The pharmacological importance of synthetic heterocyclic scaffolds has been reviewed recently.[6] It has been found that heterocyclic subunits are present in vitamin B complex,[7] alkaloids,[8] antibiotics,[9] haemoglobin,[10] chlorophylls,[11] other plant pigments,[12] amino acids,[13] ATP,[14] dyes,[15] drugs[16] and the genetic materials.[17]

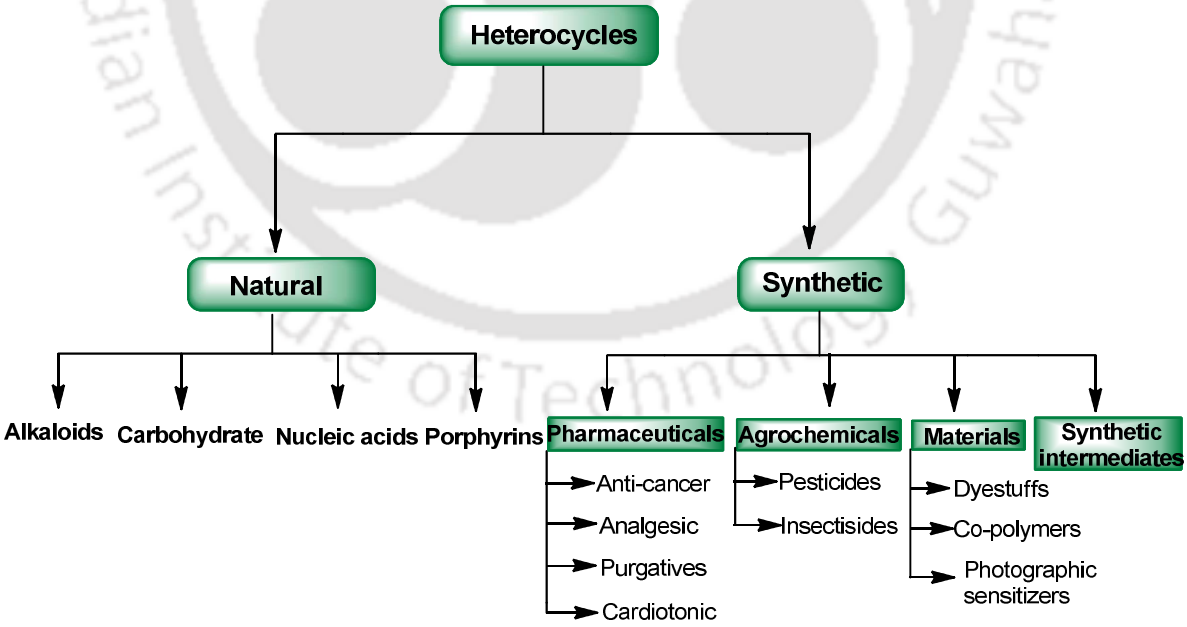


Figure 1. Various applications of heterocycles

With regard to practical applications, these compounds are also known as additives and modifiers in a number of industries like cosmetics, reprography, information storage and plastics industry. They are used as solvent, antioxidants and vulcanization accelerators. Finally, heterocyclic chemistry is an inexhaustible resource of new and useful materials for an applied science. The subdivision of heterocycles and some of their practical utilities is summarized in Figure 1.

Therefore, organic chemists are on a continuous endeavor to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides and weed killers based on transcripting natural models. In particular, techniques that can provide access to heterocyclic cores with a diversity and a manipulated set of substituents are still a challenging task. The most efficient strategies involve multicomponent reactions (MCRs) for the rapid introduction of molecular diversity. This dissertation focuses mainly on construction of heterocyclic entities *via* one-pot multicomponent reactions.

2. One-pot multicomponent reactions (MCRs)

Organic synthesis is one of the main facets in the development of chemistry and a solution addressing several scientific challenges currently encountered by our society. The capability to generate new chemical entities in a programmed and efficient manner plays a pivotal role in medicinal chemistry, chemical biology, materials science and so on. Rapid and efficient syntheses of functional and biologically active molecules have encouraged synthetic chemists to explore and develop intelligent synthetic strategies. Traditional organic synthesis proceeds with individual bonds formation in a sequence and hence involves isolation, purification of intermediates and often alteration of reaction conditions for the next synthetic step. For 'an ideal synthesis', a target molecule is accomplished from readily available starting materials in a simple, safe, environmentally friendly and resource-efficient operation that proceeds quickly yet provide a high quantitative yield (Figure 2).[18] In the past decade, many research groups have aimed for the realization of the concept of ideal synthesis by the development of a multi-step single operation protocol to construct complex molecules in which several bonds are formed in a chain of events without isolating the intermediates. The concept is commonly termed as tandem reactions,[19] that allow economically and

environmentally favorable synthesis of a wide range of organic molecules. A special class of tandem sequential reactions constitutes the multicomponent reactions (MCRs).

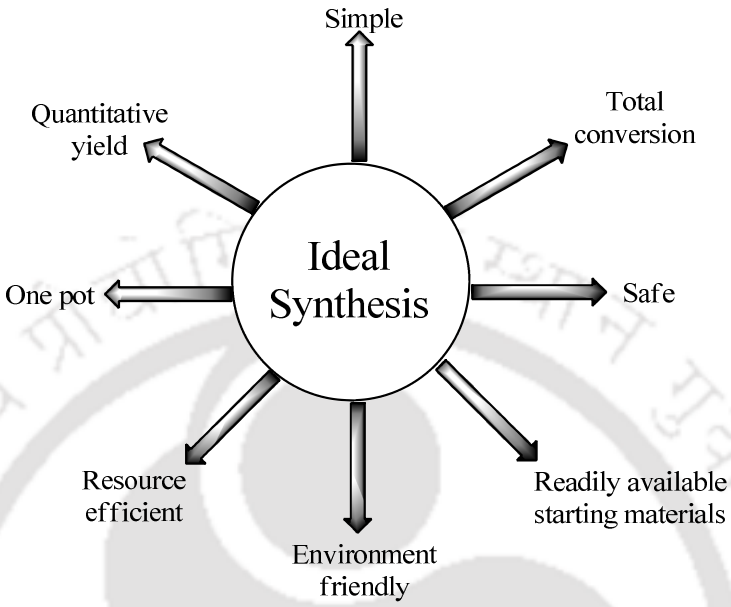


Figure 2. The ideal chemical synthesis

Besides the crucial issues of chemo-, regio- and stereoselectivity in a synthetic method, the importance of economic and ecological aspects of 'Green Chemistry' is also important.[20] In recent years, multicomponent reactions (MCRs) have been proven to be an elegant and scientific approach to access complex structures in a single operation from the simple and readily available starting materials with high atom economy and high selectivity. By definition, multicomponent reactions (MCRs) is a process in which three or more components are combined together in a single reaction vessel to produce a final product displaying features of all inputs and thus offers greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. The definitions[18] of MCRs can also be written as follows:

"Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product."

In addition, MCRs are well amenable for the construction of heterocyclic cores with high degree of complexity as well as diversity for a targeted set of scaffolds with a minimal number of synthetic operations.[21]

A wide variety of products may be possible from the same set of reaction as shown in Figure 3.

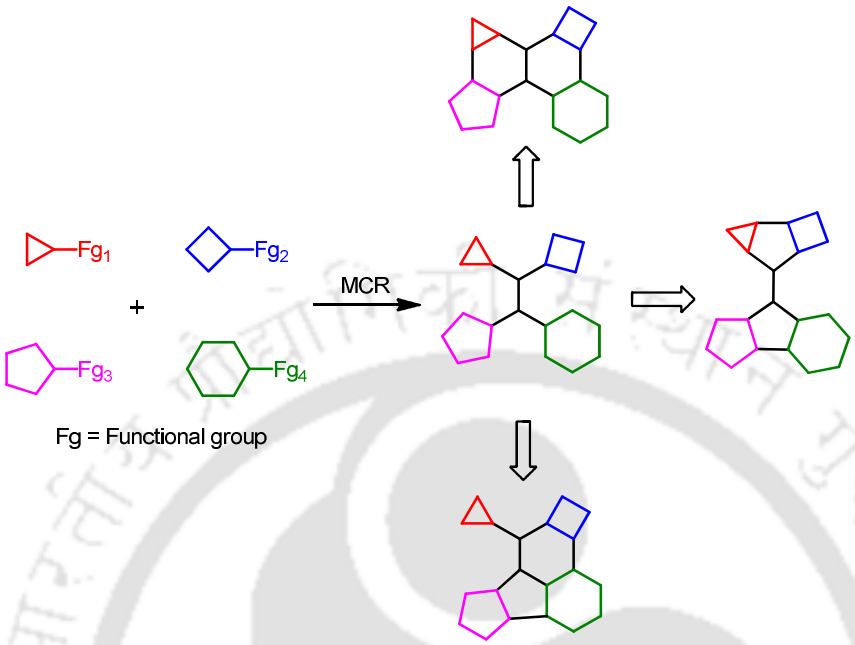


Figure 3

The efficiency of a MCR is determined by bond forming efficiency *(BFE)* that is the number of bonds that are formed during the process. Moreover, they are easier to carry out as compared to multistep synthesis[22] since they are conventionally one-pot reactions, which is shown below in Figure 4.

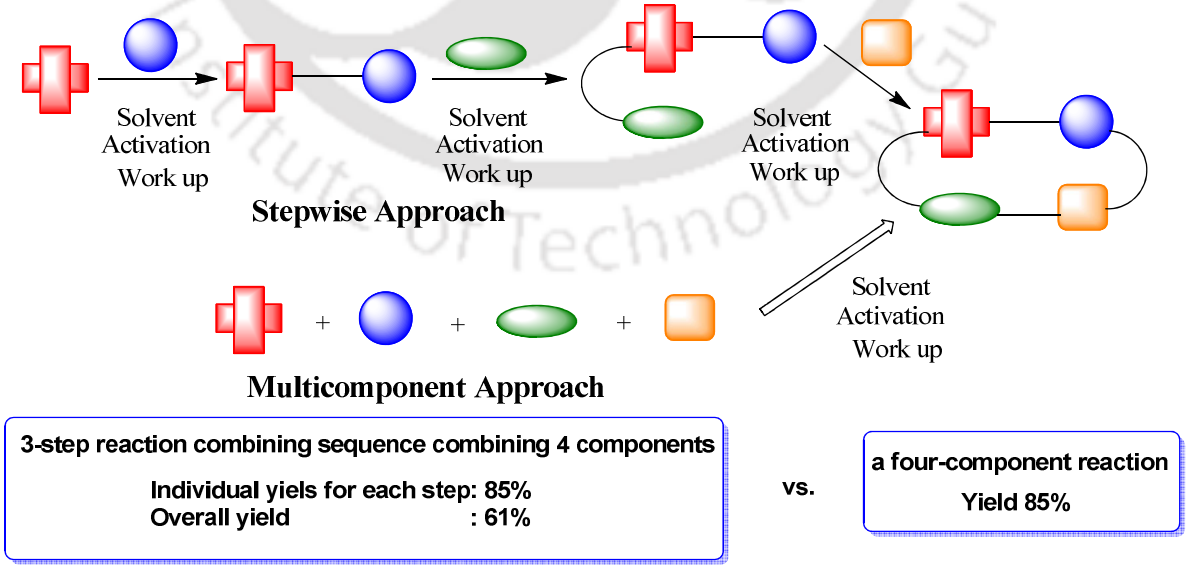
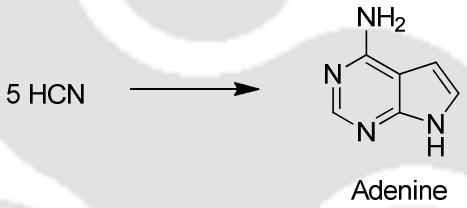


Figure 4. *Stepwise vs. Multicomponent Approach*

MCRs have significant advantages over conventional reactions in several aspects as (a) reduced cost and reaction time; (b) readily available starting materials; (c) operationally simple; (d) variable and high bond forming efficiency; (e) resource effective; (f) atom economy and (g) eco-compatibility.

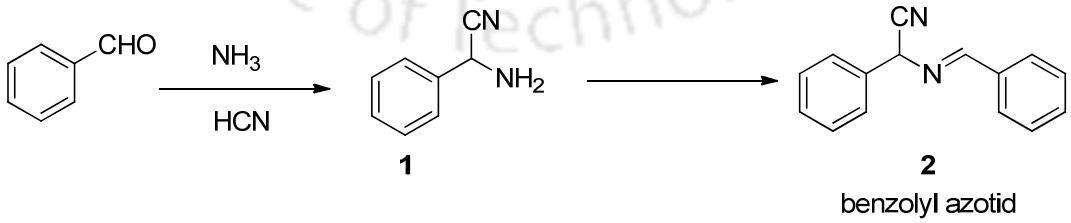
3. History of MCRs

The concept of MCRs is not unknown to nature and is important especially in evolution. It seems that adenine, one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN in a reaction catalyzed by NH_3 (Scheme 1).[23] The other nucleic acid bases have also been generated in a similar manner involving HCN and H_2O.



Scheme 1 Prebiotic synthesis of adenine

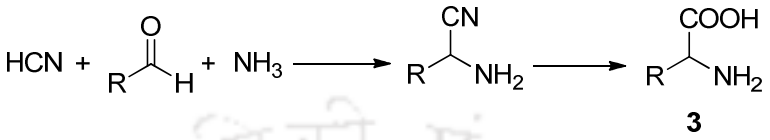
The formation of cyanohydrins imines **2** from bitter almond oil and ammonia, first described by Gerhard and Laurent in 1838, can be considered as the first multicomponent reaction.[24] In this reaction, the cyanohydrin derived from benzaldehyde and hydrocyanic acid reacts with ammonia to give amino benzyl cyanide **1**. Finally, it was converted into a Schiff base on reaction with benzaldehyde known as benzoyl azotid **2**, as shown in Scheme 2.



Scheme 2

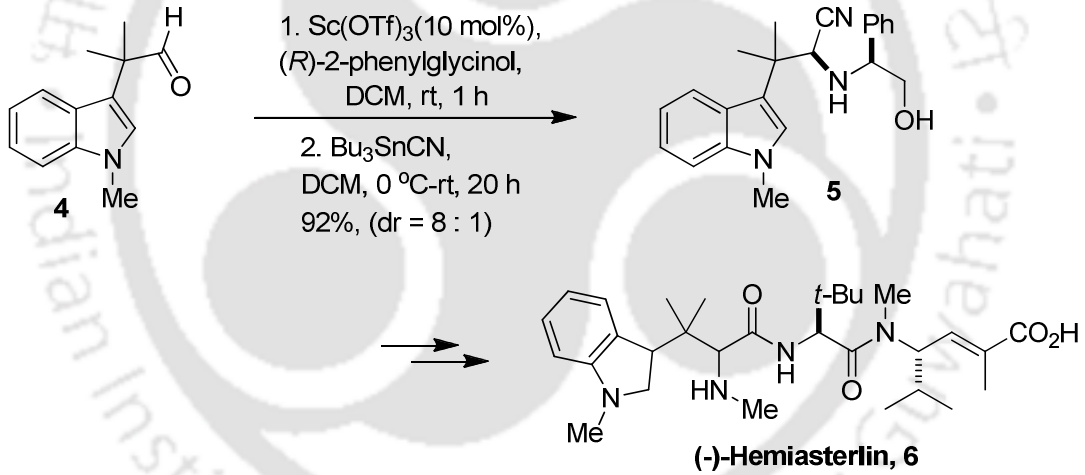
Adolph Strecker[25] made the first and modern contribution to the development of multicomponent reaction. In 1850 he demonstrated the synthesis of α-amino acids from α-

amino nitriles, with the starting materials being aldehydes, HCN and NH_3 in a one-pot manner. Subsequently, it was hydrolyzed to the corresponding α-amino acid **3** as shown in Scheme 3.



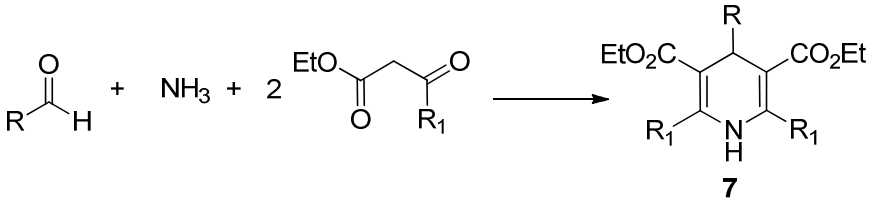
Scheme 3. Strecker's synthesis of α-amino acids

Vedejs and co-workers[26] demonstrated the utility of asymmetric Strecker reaction for the construction of the key intermediate tetramethyl tryptophan **5** for the enantioselective total synthesis of (-)-hemiasterlin **6**, a marine tri-peptide having cytotoxic and antimitotic activity, as illustrated in Scheme 4.



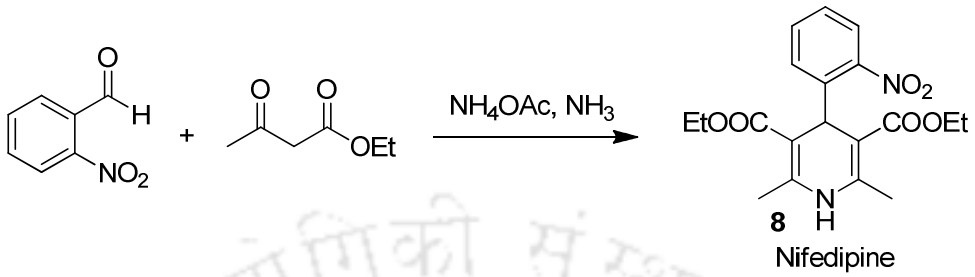
Scheme 4

Arthur Rudolf Hantzsch first reported[27] preparation of 1,4-dihydropyridine derivatives **7** using two equivalent of β-keto esters, aldehyde and ammonia or ammonium salts, which is shown in Scheme 5.



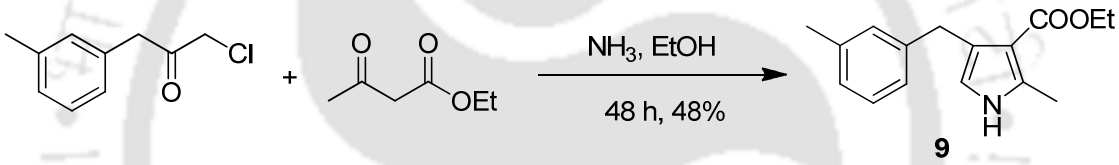
Scheme 5. Hantzsch synthesis of 1,4-dihydropyridine derivatives

His approach was further exploited for the synthesis of nifedipine (**8**) used for cardiovascular disease as depicted in Scheme 6.[28]



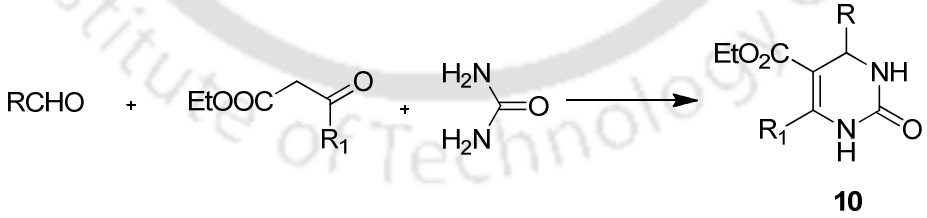
Scheme 6

Moreover, the synthesis of substituted pyrroles derivatives **9** was also demonstrated by Hantzsch involving three-component reaction from α-halogenated β-carbonyl compound, β-ketoesters, and ammonia (or primary amine) as in Scheme 7.[29]



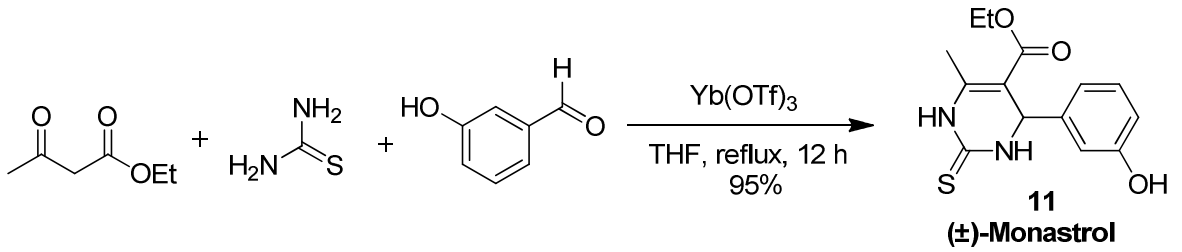
Scheme 7. Hantzsch's synthesis of pyrroles

The Biginelli reaction is also one of the most popular and useful multicomponent reactions, discovered by Pietro Biginelli in 1893, for the synthesis of dihydropyrimidine derivatives **10** from β-keto esters, aldehyde and urea in the presence of acid catalysts[30] as shown in Scheme 8.



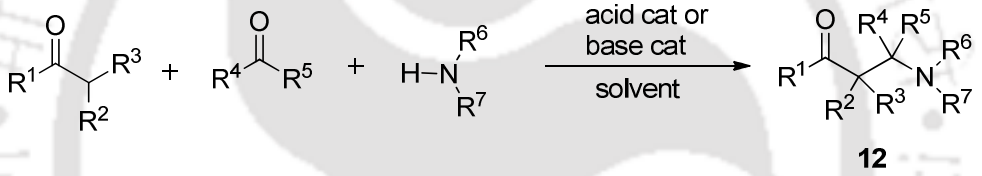
Scheme 8. Biginelli synthesis of dihydropyrimidines

The traditional intermolecular three-component version of the *Biginelli reaction* was utilized for the improved synthesis of racemic monastrol **11** by Dondoni and his co-workers,[31] as shown in Scheme 9.



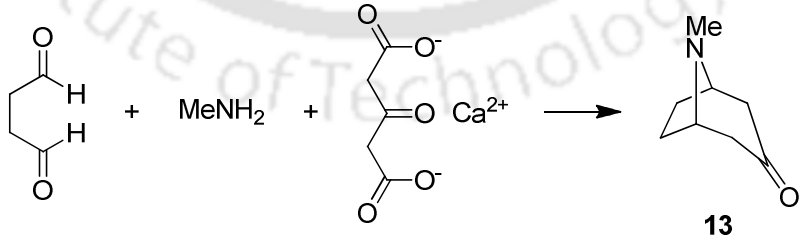
Scheme 9

Mannich reaction was first reported in 1912,[32] and it involves the condensation of an active methylene compound, a non-enolizable aldehyde or ketone and a primary or a secondary amine to afford β-amino carbonyl derivatives **12**, as shown in Scheme 10. Its tremendous synthetic utility has been further explored for the synthesis of numerous pharmaceuticals and natural products.[33]



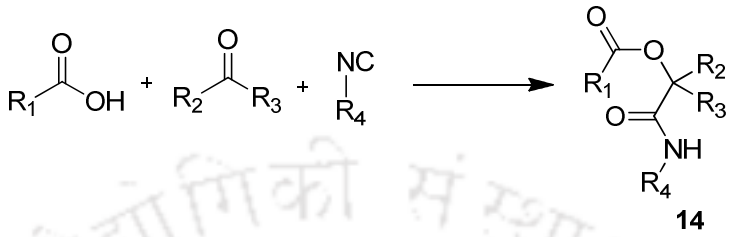
Scheme 10

In 1917, the application of MCR in natural product synthesis was first demonstrated by Robinson through his pioneering work on the synthesis of alkaloid tropinone (**13**) from succinic dialdehyde, methylamine and calcium salt of acetone dicarboxylic acid as illustrated in Scheme 11.[34]



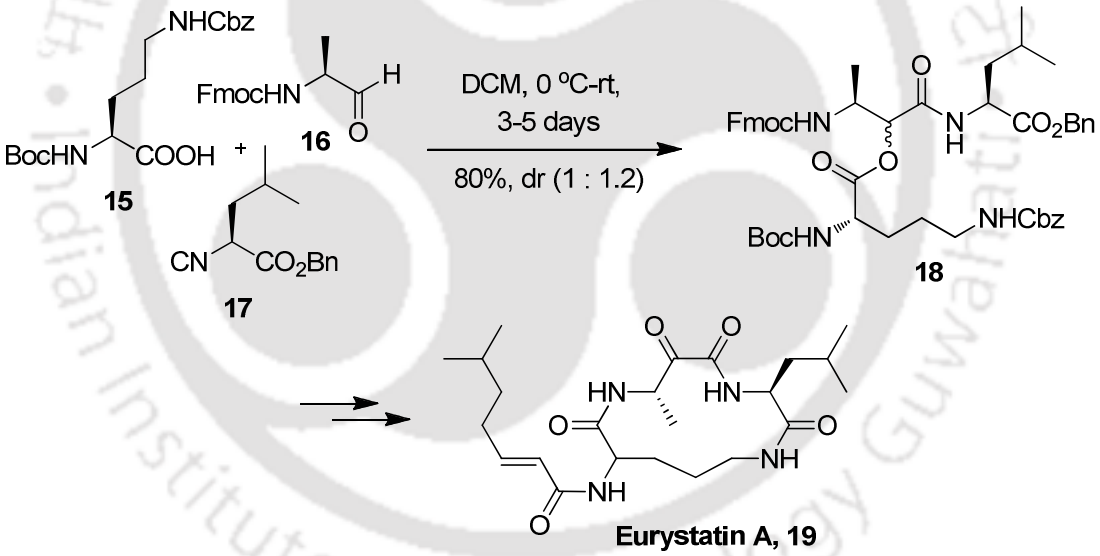
Scheme 11

Mario Passerini in 1921 endorsed isocyanide based MCR for the synthesis of α-acyloxy carboxamide (**14**)[35] involving carboxylic acid, carbonyl compound and isocyanide as shown in Scheme 12.



Scheme 12. Passerini 3-component reaction

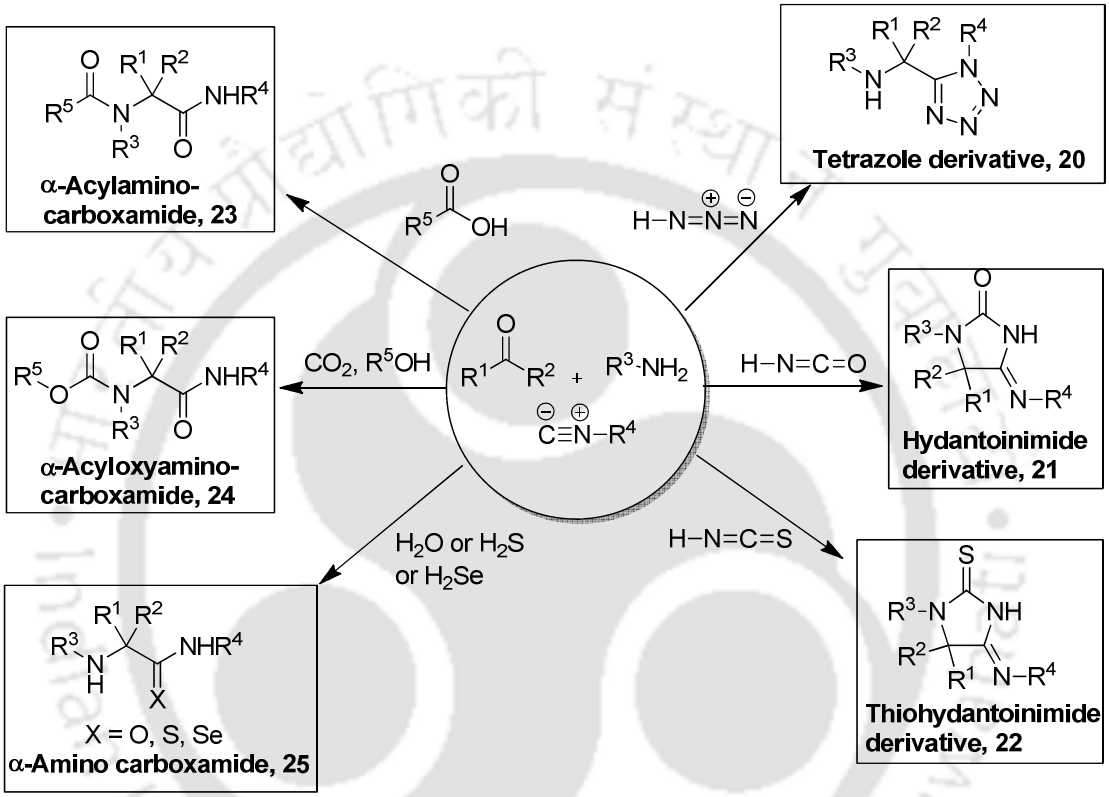
Owens *et al.* reported the synthesis of eurystatin A (**19**), which is a 13-membered macrocyclic natural product, using Passerini reaction by designing the key starting material **18** through MCR as depicted in Scheme 13.[36]



Scheme 13

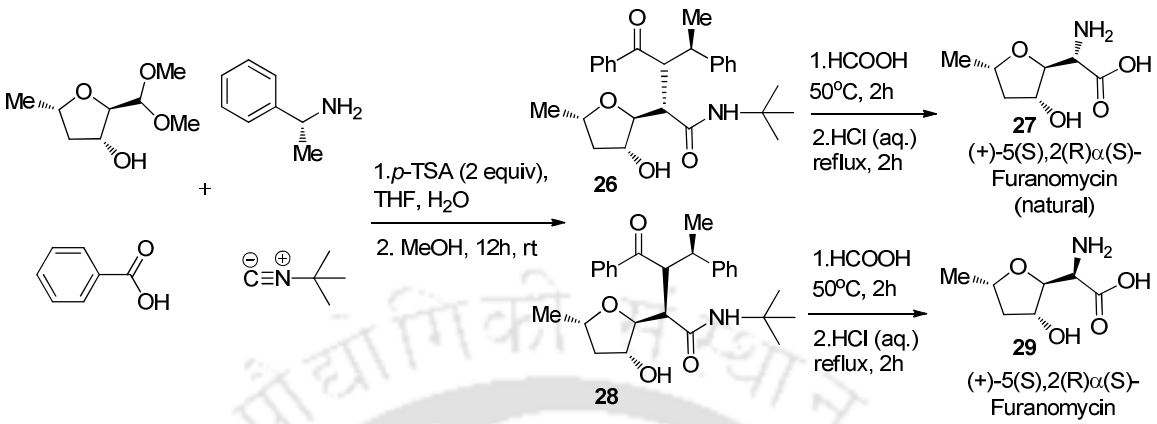
After four decades, Ugi and his co-workers had discovered one of the most utilized multicomponent reactions based on isocyanide as a key building block. The isocyanides undergo a four-component reaction (4-CR) in the presence of an amine, aldehyde or ketone and a nucleophile to afford a single condensation product. The most commonly used nucleophiles are carboxylic acids, hydrazoic acid, cyanates, thiocyanates, carbonic acid monoesters, water, hydrogen sulfide and hydrogen selenide. Today, this transformation is

popularly known as the Ugi's four-component reaction (Ugi-4CR).[37] The Ugi reaction also found a widespread application in combinatorial chemistry, where the synthetic power of the reaction coupled with modern techniques allow the quick assembly of a large number of molecules from simple starting materials as represented in Scheme 14.[38]



Scheme 14

The potential application of the Ugi-4CR reaction for amino acid and polypeptide natural product synthesis was first demonstrated by M. M. Joullié and his co-workers.[39] A representative example is the total synthesis of a naturally occurring antibiotic (+)-furanomycin (**29**) as shown in Scheme 15.



Scheme 15

After Ugi's discovery, a plethora of isocyanide based MCRs have been reported in the literature and it was further extended towards the synthesis of various heterocyclic compounds.[18] At the same time, a wide range of new miscellaneous multicomponent reactions have also been described in the current literature.

4. Classification of MCRs

The classifications of multicomponent reactions have been comprehensively described for a better understanding in a recent review by Orru and his co-workers.[40] MCRs can be further subdivided based on their rational design strategies as: a) Single reactant replacement (SRR), b) Modular reaction sequences (MRS), c) Conditions-based divergence (CBD) and d) Combination of MCRs.

To expand the scope of MCRs (beyond four components) by unifying two or more MCRs, two different approaches[41] have been successfully applied as shown in Figure 5.

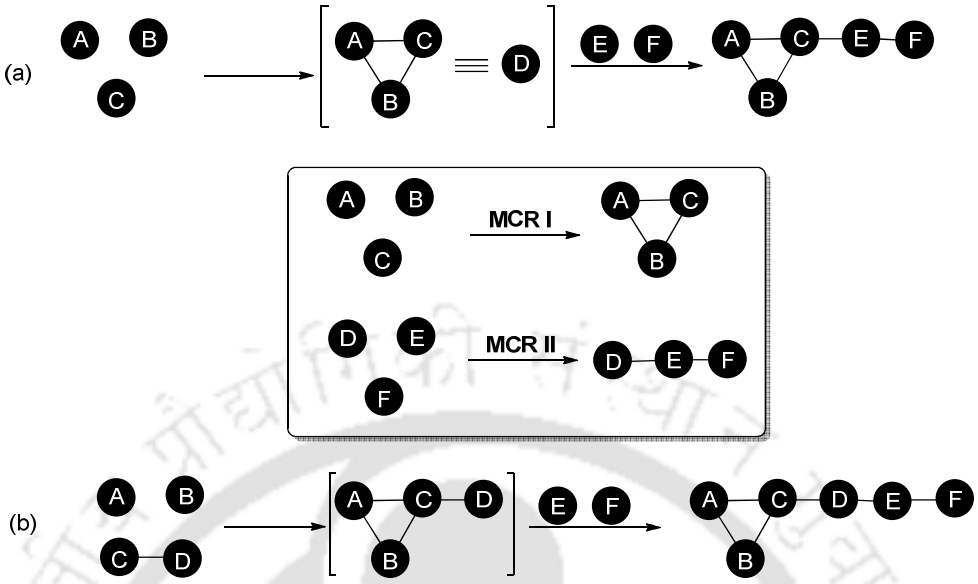


Figure 5. Unification of MCRs. Schematic representation of unifying two MCRs via (a) intermediate generation for a successive MCR, or (b) combination of MCRs with orthogonal functionalities.

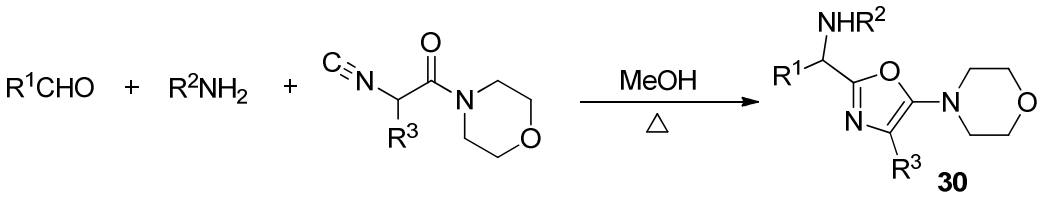
The first MCR (Figure 5a) generates intermediate structure D, which is able to act as starting material in the subsequent MCR, resulting in a product made up of five different starting materials.

The second type of a combined MCR (Figure 5b) utilizes a starting compound equipped with two different reactive groups, allowing two orthogonal MCR reactions to take place simultaneously.

These reactions can be performed either as a one-pot process, keeping the reaction conditions constant during the entire reaction (i.e. ‘‘true’’ MCR), or as a sequential process whereby the reaction conditions of the first MCR are altered according to the demands of the subsequent MCR (i.e. tandem MCR).

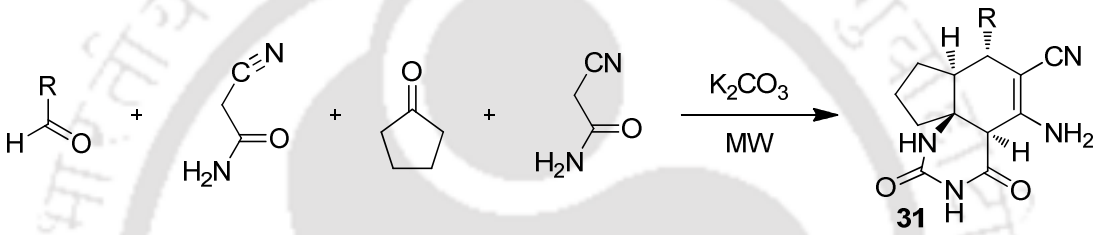
5. Interesting MCRs of the last decade towards construction of heterocyclic compounds:

Zhu and his coworkers have shown a novel multicomponent synthesis of polysubstituted 5-aminooxazole **30**, in good to excellent yield starting from aldehyde, an amine, and a suitably functionalized isocyanoacetamide as shown in Scheme 16.[42]



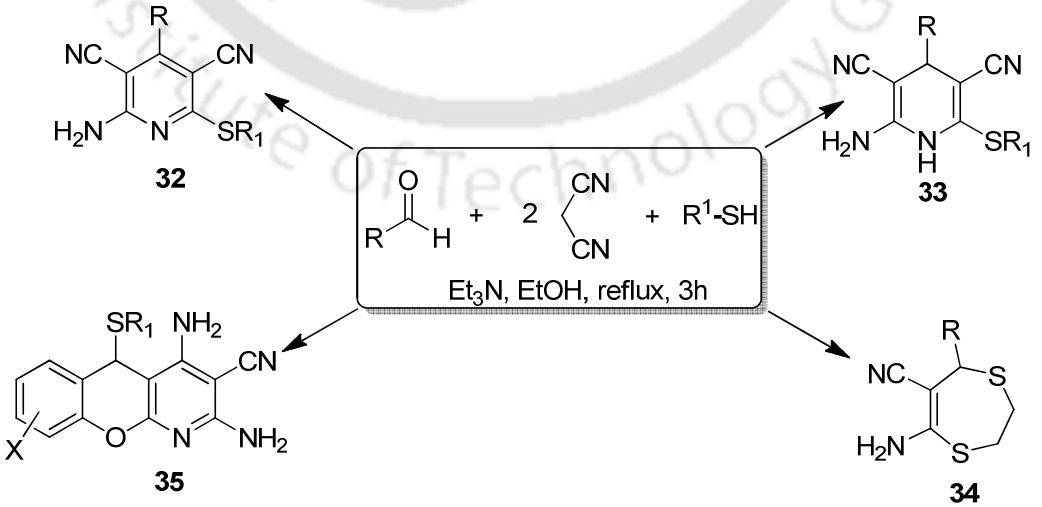
Scheme 16

Jiang *et al.*[43] established a novel multicomponent domino reaction by condensing aldehydes, cycloketones and cyanoamides, which act as both substrates and nucleophiles to give important scaffolds with highly substituted quinazoline derivatives **31**, as illustrated in Scheme 17.



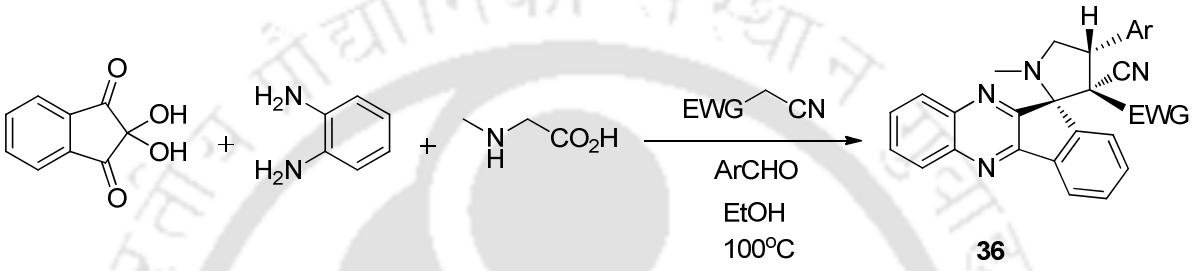
Scheme 17

Magedov *et al*. have demonstrated a new multicomponent reaction for the generation of medicinal scaffolds namely pyridine, 1,4-dihydropyridine, chromeno[2,3-*b*]-pyridine and dihydro-1,4-dithiepine frameworks, respectively through one-pot multicomponent reaction using variation of structurally diverse aldehydes with various thiols and malononitrile as shown in Scheme 18.[44]



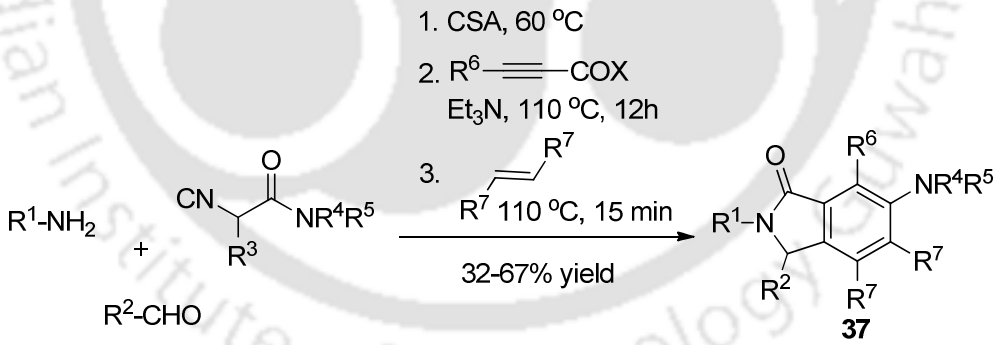
Scheme 18

An interesting and newly developed autocatalytic five-component reaction (5CR) leading to the highly regio- and stereoselective formation of spiropyrrolidines **36**, was recently demonstrated by Ming Li and his co-workers.[45] The five components involved in this reaction include ninhydrin, 1,2-phenylenediamine, sarcosine, an aldehyde and malononitrile (or cyanacetic ester), of which sarcosine plays a crucial role in this autocatalytic MCR as shown in Scheme 19.



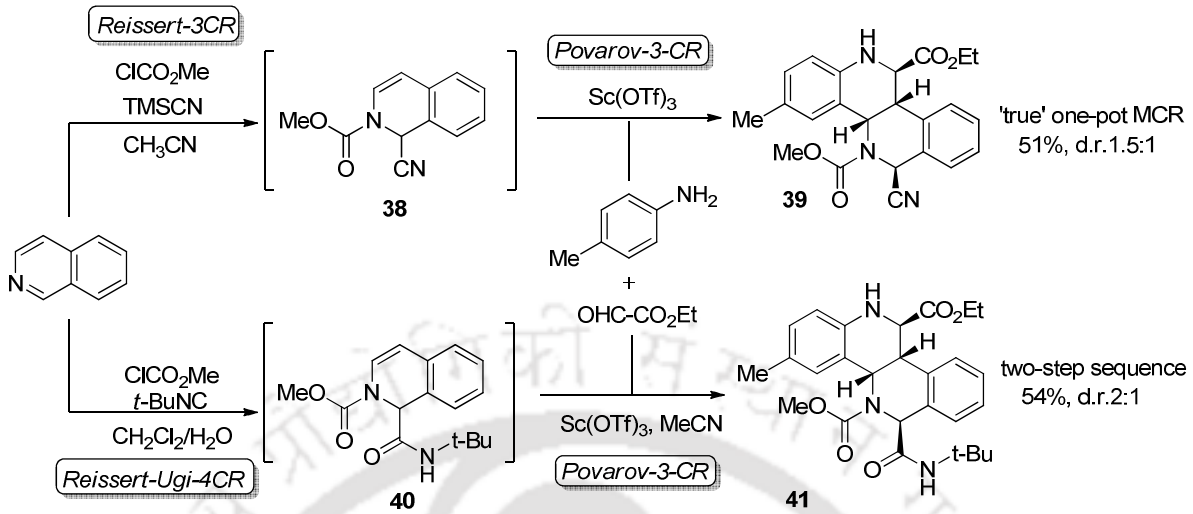
Scheme 19

Zhu and his co-workers reported the development of a novel 5CR by sequentially applying at least one MCR in a single reaction vessel leading to the formation of a highly functionalized heterocycle **37** as shown in Scheme 20.[46]



Scheme 20

Lavilla and his co-workers were able to sequentially combine the Reissert-3CR with the Povarov-3CR in a single reaction vessel. This noble 5CR yielded highly substituted dibenzo[c,h][1,6]-naphthyridines **39** and **41** and as mixtures of diastereoisomers at the ester α-position as shown in Scheme 21.[47]

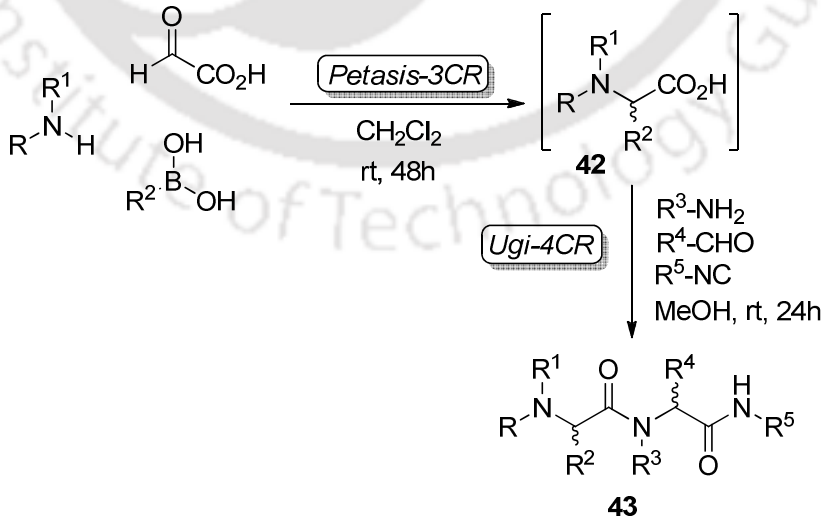


Scheme 21. Two novel MCRs based on the unification of the Reissert-3CR or Reissert–Ugi-4CR and Povarov-3CR (major isomer shown).

Development of MCRs beyond 5-components:

Six component reaction

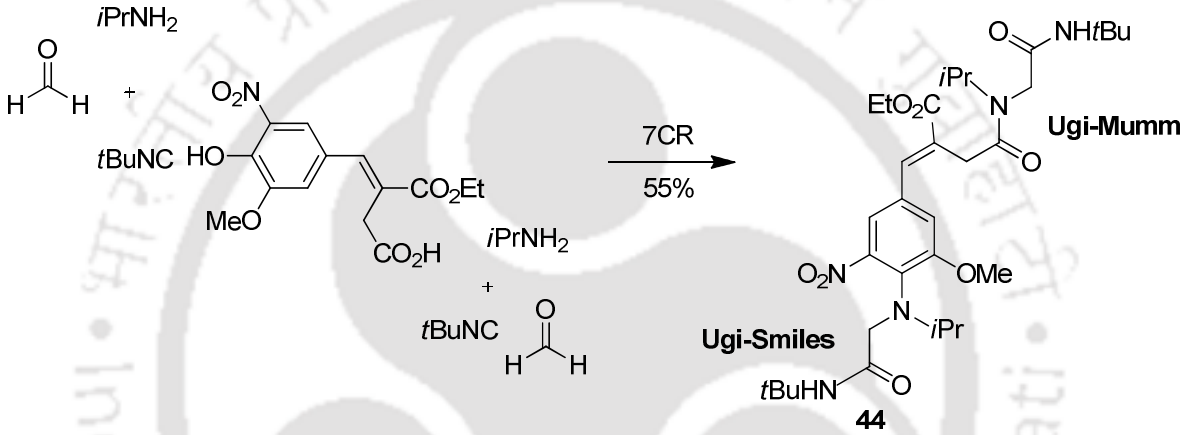
The combination of a Petasis-3CR and an Ugi-4CR (Pt-U-6CR) was recently described by Portlock and his co-workers.[48] The dipeptide amides **43** could be synthesized as 1:1 mixtures of racemic diastereomers with yields ranging from 80-95% with formation of six new bonds and the introduction of six points of diversity as shown in Scheme 22. The amino acid **42**, formed by the Petasis-3CR, serves as the carboxylic acid component in the following Ugi-4CR.



Scheme 22. Novel 6CR by combination of the Petasis-3CR and Ugi-4CR

Seven component reaction

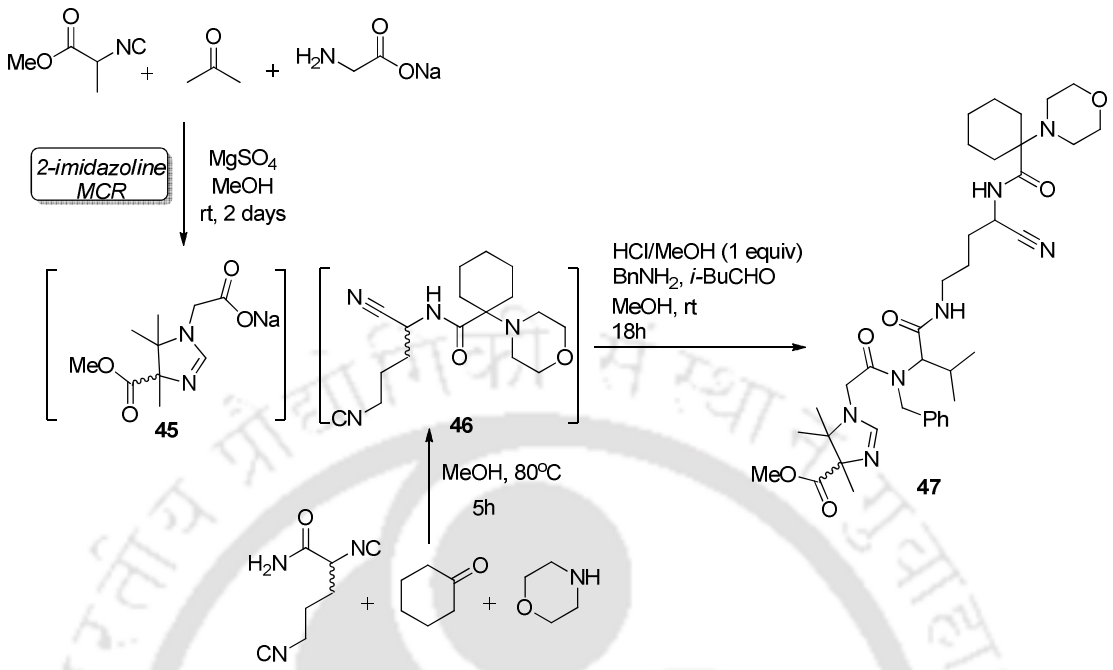
Brauch *et al.*[49] reported a seven-component reaction by utilizing the different chemoselectivities of the Ugi–Mumm and the Ugi–Smiles reaction. The sequential multicomponent reaction has led to highly diverse peptide and glycopeptide like structures **44** from formaldehyde, *iso*-propyl amine and *tert*-butyl isonitrile. The Ugi–Mumm/Ugi–Smiles product was formed in 55% yield and the yield for each bond-forming step exceeds 90% as depicted in Scheme 23.



Scheme 23

Eight component reaction

In 2009, Orru and his coworker have shown[50] the first example of an eight component reaction. This 8CR unifies three different MCRs with nine new bonds formed, creating highly complex and structurally versatile drug-like compounds **47** as shown in Scheme 24.



Scheme 24

It is apparent that development of novel multicomponent reactions is a great challenge in synthetic organic chemistry. The MCRs have been extensively utilized for the construction of new heterocyclic entities in the last one decade and it has been compiled recently.[51] In this part of my thesis, we aimed towards the synthesis of tetrahydropyrimidine derivatives. Therefore, I would like to address their importance as well as recently developed synthetic methods.

6. Importance of Tetrahydropyrimidines

Pyrimidine and its analogues are important class of nitrogenous and heterocyclic pharmacophores, which are present in many pharmaceuticals. Some of them are in clinical and preclinical trial stages as they exhibit interesting biological activities[52] like muscarinic agonist activity,[53] antiviral activity,[54] anti-inflammatory activity[55] and protein-nucleic acid interactions.[56] Pyrimidine skeleton is a key structural motif found in various naturally occurring compounds[57] such as manzacidins, A, B, and C compounds isolated as bioactive constituents of the Okinawan sponge, Hymeniacidon (structure **I** and **II**, Figure 6) and they also serve as building block for various organic synthesis.[58]

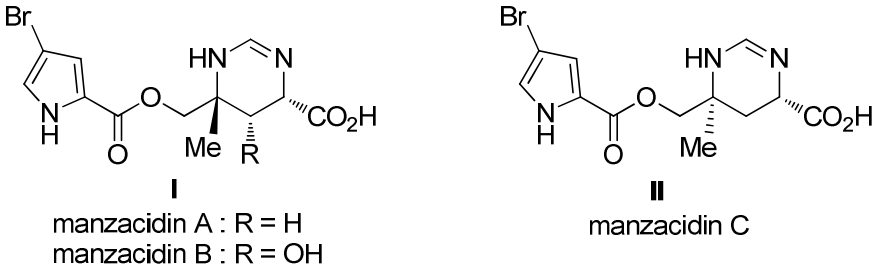


Figure 6

Ectoine (**III**) and hydroxyectoine (**IV**) possess a 3,4,5,6-tetrahydropyrimidine moiety; in nature they are mostly found in betaines. These secondary amino acids act as agonist or antagonists[59] for the receptors of peptidic molecules and are ubiquitous bacterial osmoprotectants [60] as shown in Figure 7.

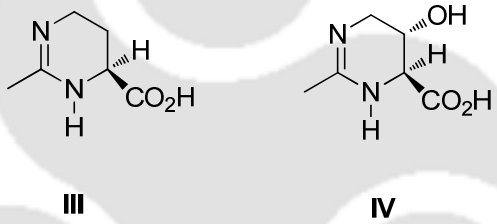


Figure 7

Tetrahydropyrimidine is an important heterocyclic ring and its synthesis was explored in the past decade due to interesting biological activities. It is also responsible for salt and heat sensitivity of protein–DNA interactions.[61] They have been used as preventative and prophylactic drugs in the treatment of male erectile dysfunction.[62] Specifically, tetrahydropyrimidines containing an amino acid unit have attracted much attention due to their potential biological activities such as for treatment of human immunodeficiency virus (HIV) protease inhibitors[63] and others as inhibitors against mycobacterium tuberculosis.[64] N-[2-(5-Hydroxy-4,6-tetrahydropyrimidine)]-3-amino-5-hydroxybenzoic acid (**V**) is an $\alpha_v\beta_3$ integrin antagonist,[65] as shown in Figure 8. Tetrahydropyrimidine derivative (V**I)** was reported as antihistaminic and antibacterial[66] and compound **(VII)** is identified as bioisosteric congeners of arecoline, which is also a muscarinic agonist for treatment of Alzheimer's disease,[67] as shown in Figure 8. The tetrahydropyrimidine compounds (**VIII**)

are found to possess antihypertensive, anti-inflammatory, analgesic and acute ulcerogenesis activites.[68]

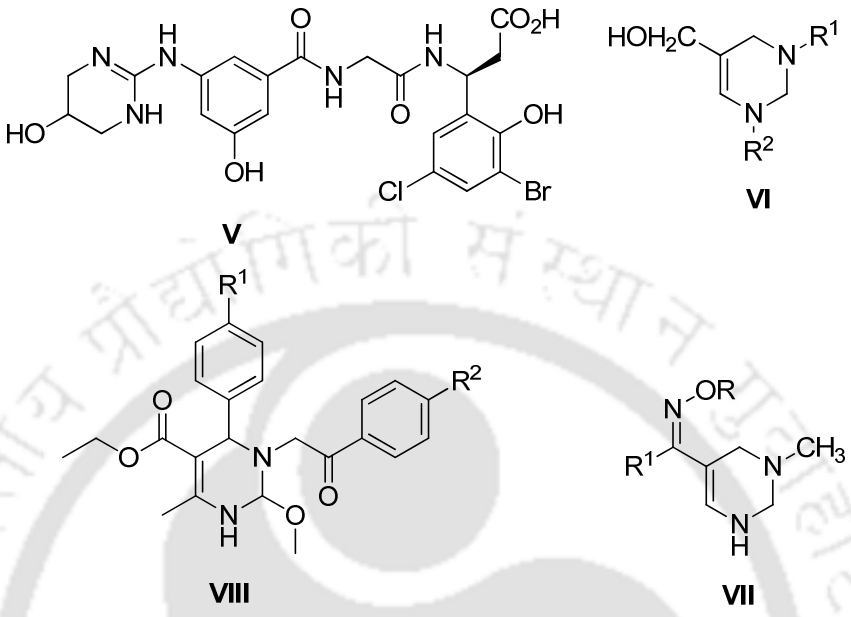
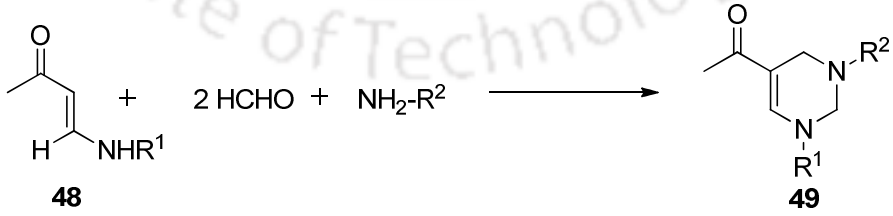


Figure 8

Owing to the importance of tetrahydropyrimidine derivatives, a considerable attention has been paid to the synthesis of these compounds over the years.

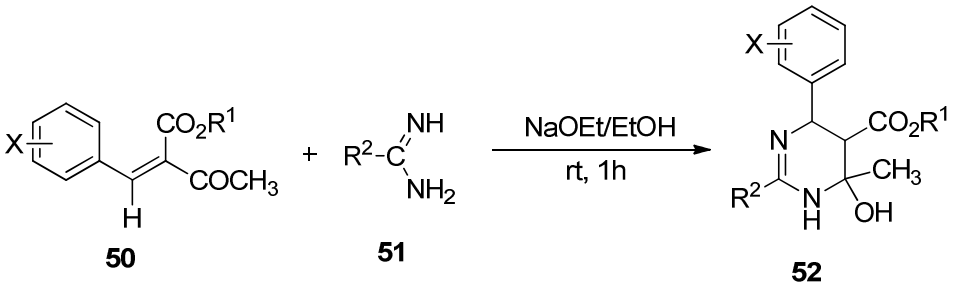
7. Synthesis of Tetrahydropyrimidines

In 1981, Moehrle and Reinhardt reported the synthesis of acetylated 1,2,3,4-tetrahydropyrimidines **49** from the reaction of enaminoketones **48** with primary amines and formalin as shown in Scheme 25.[69]



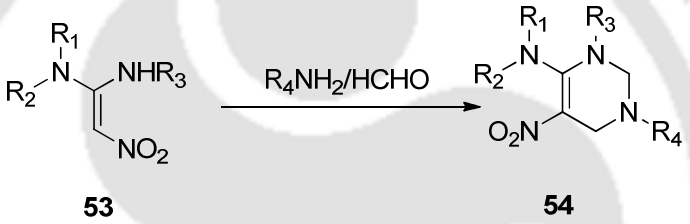
Scheme 25

Subsequently, Cho et al. synthesized highly substituted tetrahydropyrimidines **52**, from the reaction of ethyl 2-acetyl-3-aryl-2-propenoate (**50**) with 1.1 equivalent of acetamidine (**51**) in presence of ethanolic NaOEt at room temperature as shown in Scheme 26.[70]



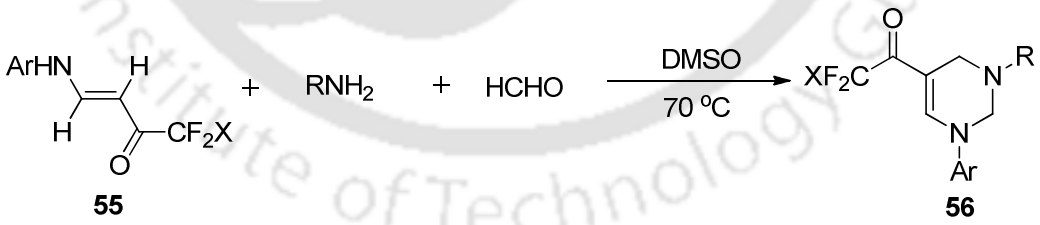
Scheme 26

Later on, Takashi and his co-workers demonstrated the synthesis of tetrahydropyrimidines **54** from (*E*)-N,N,N'-trialkyl-2-nitroethene-1,1-diamine **53**, amines and formaldehyde in alcohol as solvent at room temperature or reflux conditions as shown in Scheme 27.[71]



Scheme 27

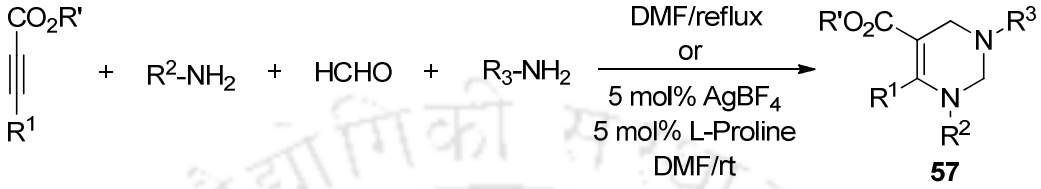
The fluorine-containing polyfunctional 1,2,3,4-tetrahydropyrimidines[72] **56** was reported by Zhao and his co-worker in high yields from fluoro alkylated enaminoketones **55** on reaction with primary amines and formalin under mild reaction conditions Scheme 28.



Scheme 28

In 2007, Jiang et al. reported the synthesis of multisubstituted tetrahydropyrimidines **57** by employing one-pot multicomponent reaction of electron-deficient alkynes such as diethyl acetylenedicarboxylate (DEAD), aliphatic amines and formaldehyde under reflux condition in absence of catalyst.[73] Later on the same group modified the reaction conditions and reported Ag(I) catalyzed synthesis of 1,2,3,4-tetrahydropyrimidines from other electron-

deficient alkynes such as ethyl phenyl propiolate, methyl oct-2-ynoate or ethyl propiolate as shown in Scheme 29.[74] In 2009, Jiang et al. synthesized the same 1,2,3,4-tetrahyropyrimidines from but-2-ynedioates, amines and formaldehyde at room temperature using acetic acid as catalyst.[75]

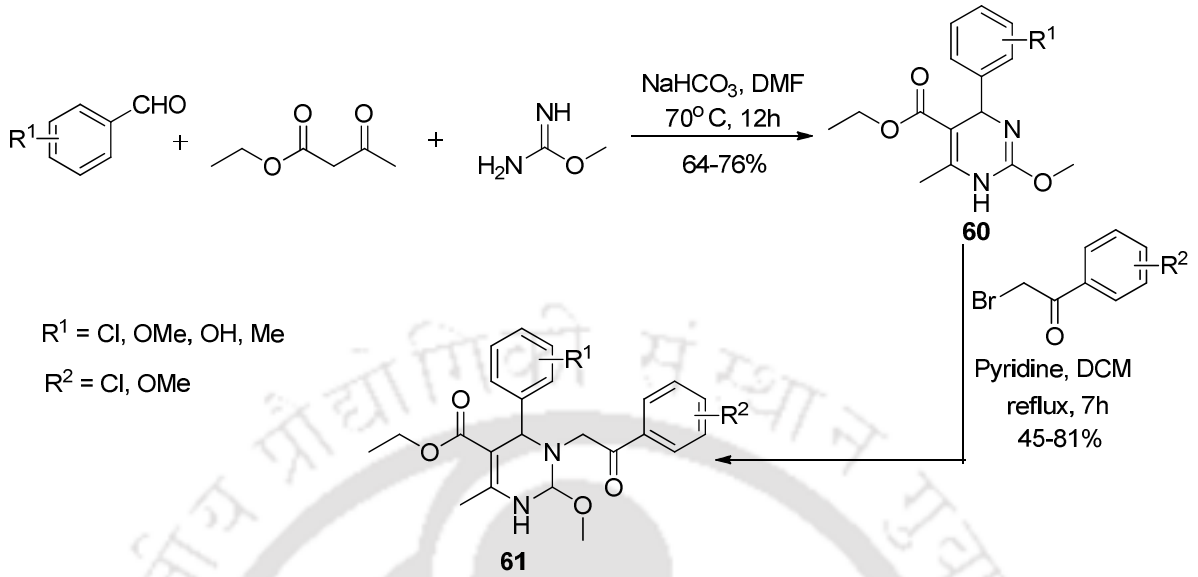


Scheme 29

New reaction of diaziridine ring expansion resulting in diethyl 1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **59**[76] derivatives was discovered by Makhova and his co-workers in 2009, under the action of diethyl acetylenedicarboxylate on 1,2-di- and 1,2,3-trialkyldiaziridines **58**, in ionic liquids as shown in Scheme 30.

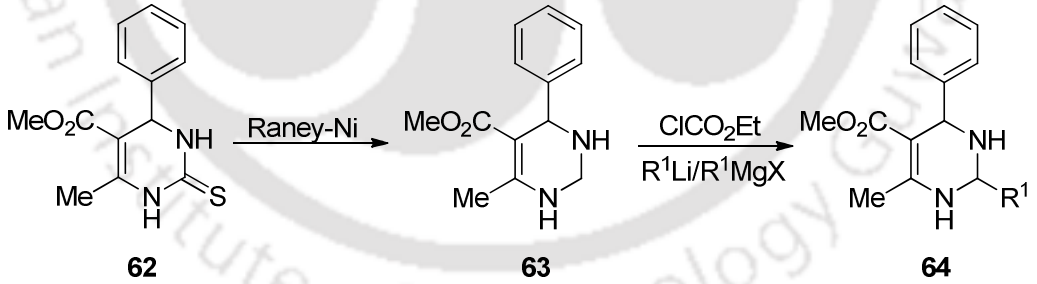
Scheme 30

The reaction of o-methylisourea hydrogen sulfate with ethyl acetoacetate and aldehydes followed by nucleophilic substitution reaction with various phenacyl bromides provided tetrahydropyrimidine derivatives **61** as shown in Scheme 31.[68] These compounds were evaluated for antihypertensive, anti-inflammatory, analgesic and acute ulcerogenesis activities.



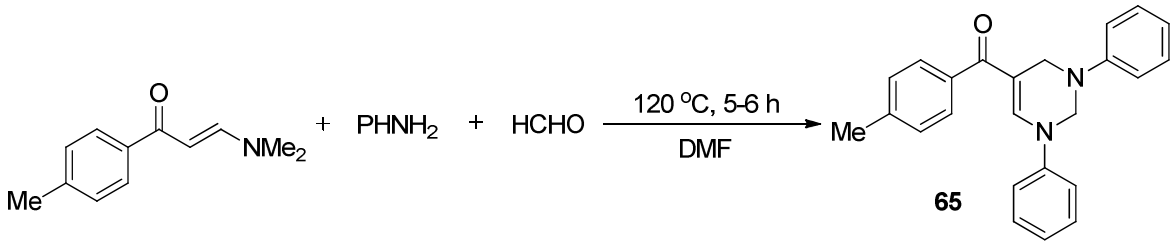
Scheme 31

Multifunctionalized tetrahydropyrimidines derivatives (**64**) have been synthesized efficiently from 3,4-dihydropyrimidin-2-(1H)-thiones (DHPM, **62**). The transformation includes desulfurization of DHPMs with Raney nickel and subsequent regioselective C-2 functionalization using a variety of C-nucleophiles with simultaneous activation with ethyl chloroformate as shown in Scheme 32.[77]



Scheme 32

In 2012, Perumal et al reported the synthesis of tetrahydropyrimidine (**65**) in 21% yield using (*E*)-3-(dimethylamino)-1-(4-methylphenyl)prop-2-en-1-one, aniline and formaldehyde in different molar ratios in DMF at 120 ºC. These reactants were used in 1:2:2 and 1:2:3 molar ratios for the transformation as shown in Scheme 33.[78]



Scheme 33

From the literature, it is evident that the pyrimidine and tetrahydropyrimidine derivatives are present in natural products and exhibit a diverse range of biological activities. Though various methods have been reported for the synthesis of tetrahydropyrimidine over the years but some of these methods are associated with certain limitations. Therefore, the development of new methodology related to the synthesis of tetrahydropyrimidine and *bis*-tetrahydropyrimidine is our current interest, which will be discussed in Chapter IIA.

PART A

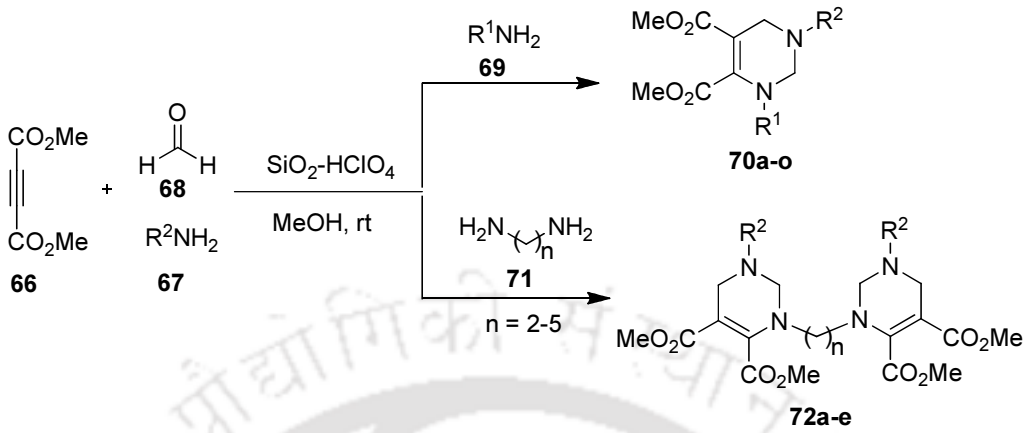
CHAPTER IIA

Silica-Supported Perchloric Acid ($HClO_4$–SiO_2): An Efficient Catalyst for One-Pot Synthesis of Functionalized Tetrahydropyrimidine Derivatives

Result & Discussion
Experimental

Results and Discussion

MCRs have been considered as a powerful synthetic tool in organic synthesis due to their numerous advantages over the conventional multi-step synthesis, which is highlighted in Chapter IA of Part A. In addition, the review of literatures also revealed the gradual advancement of multicomponent reactions (MCRs) in organic synthesis. Moreover, the importance, synthetic utility and some recent strategies for the synthesis of tetrahydropyrimidine have also been discussed in Chapter IA. In continuation of our endeavour to explore the application of new reagents in organic synthesis, we sought to examine the catalytic activity of $HClO_4$-SiO_2 as an acid catalyst for the development of new methodology in multicomponent reactions leading to functionalized tetrahydropyrimidine and *bis*-tetrahydropyrimidine derivatives. Due to their medicinal and synthetic importance, we perceived that a new methodology for the synthesis of tetrahydropyrimidine derivatives using multicomponent reaction would be pertinent. Owing to the importance of tetrahydropyrimidine derivatives, a considerable attention has been paid to the synthesis of these compounds over the years. These methods are associated with certain limitations such as use of expensive and excess amount of catalyst, longer reaction times and drastic reaction conditions. In addition, the synthesis of *bis*-tetrahydropyrimidine derivatives using MCRs has not yet been reported. Therefore, there is a need to develop a synthetic methodology using a catalyst, which might work under milder reaction conditions. It is well known that $HClO_4$-SiO_2 is an inexpensive, nontoxic, reusable, environmentally benign as well as highly efficient catalyst and it has been utilized for various organic transformations.[79] The usefulness of this catalyst has been demonstrated by our research group for geminal diacylation of aldehydes,[80a] tetrahydropyranylation, oxathioacetalization and thioacetylation[80b] and aza-Michael reaction.[80c] The efficiency of $HClO_4$-SiO_2 was shown by others for one-pot multi-component reactions.[81] In this chapter, results for the synthesis of substituted tetrahydropyrimidine and *bis*-tetrahydropyramidine derivatives using $HClO_4$-SiO_2 as a heterogeneous catalyst as shown in Scheme 34 is highlighted.

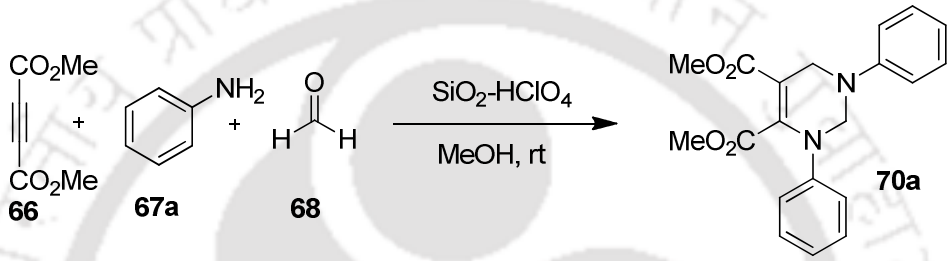


Scheme 34. One-pot domino MCRs catalyzed by $HClO_4$-SiO_2.

For the present study, the catalyst $HClO_4$-SiO_2 was prepared by following the literature procedure.[80a] The reaction of dimethyl acetylenedicarboxylate (DMAD, **66**), aniline (**67a**) and formaldehyde (**68**) using $HClO_4$-SiO_2 as a catalyst at room temperature was examined and it smoothly converted into the functionalized tetrahydropyrimidine derivative **70a** in 95% yield within 1.5 h. The reaction conditions were optimized by varying the amount of catalyst and stoichiometric ratios of the reactants (DMAD, aniline and formaldehyde) to obtain best result in terms of reaction time and yield (Table 1, entries 1-4). The optimized amount of catalyst ($HClO_4$-SiO_2) was found to be 25 mg (0.125 mmol). The optimal amount of the reactants such as DMAD (**66**), aniline (**67a**) and formaldehyde (**68**) was found to be 1.0, 2.0 and 2.5 equiv, respectively. Various solvents namely MeCN, DMF, DCM, MeOH, EtOH and H_2O were also screened and MeOH was found to be the best choice of solvent among them. (Table 1, entries 4-9). The reaction was performed without the catalyst in methanol at room temperature, which gave only 52% yield after 5h (Table 1, entry 10). In the case of neat reaction, the product **70a** was obtained in 55% yield using the same amount of catalyst. These results indicate that the catalyst and solvent have a definite role in the reaction, both in terms of time and yield. This might be due to lack of proper interaction between the reactants (Table 1, entry 11). The product **70a** was characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, and elemental analysis. Appearance of strong absorption peaks in the IR spectrum at 1743 and 1650 cm^{-1} indicates the presence of ester carbonyl group and olefinic double bond. Similarly, it shows characteristic signals in ^{1}H NMR spectrum at δ

3.58 (s, 3 H, -CO_2CH_3), 3.74 (s, 3 H, -CO_2CH_3), 4.27 (s, 2 H, -CH_2), 4.92 (s, 2 H, CH_2), 6.91 (d, J = 8.4 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 2 H), 7.16-7.29 (m, 6 H). Likewise, ^{13}C NMR signals come at δ 47.7, 51.7, 52.6, 69.0, 100.7, 118.0, 121.3, 125.2, 126.6, 129.4, 143.8, 146.7, 148.4, 164.7 (C=O), 166.3 (C=O), which confirmed the formation of tetrahydropyrimidine **70a**.

Table 1. Screening of reaction conditions for the synthesis of tetrahydropyrimidine **70a**



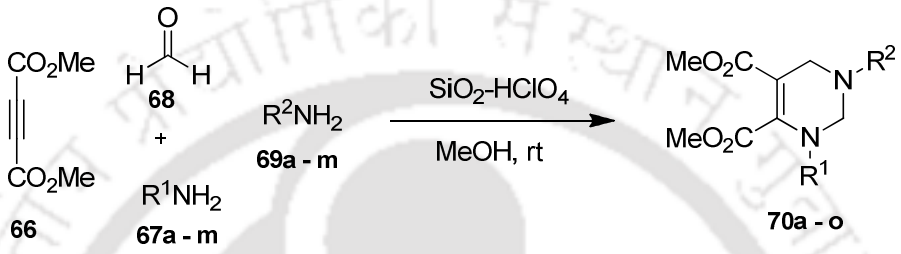
Entry	Solvent	Amount of Catalyst (in mg)	Molar ratio (1:2:3)	Time (h)	Yield[a] (%)
1	CH_3OH	25	1:2:4	1.5	95
2	CH_3OH	50	1:2:4	1.5	94
3	CH_3OH	25	1:2:3	1.5	95
4	**CH_3OH**	**25**	**1:2:2.5**	**1.5**	**95**
5	CH_3CN	25	1:2:3	2	88
6	DMF	25	1:2:3	2.5	88
7	DCM	25	1:2:3	2	76
8	EtOH	25	1:2:3	1.5	89
9	H_2O	25	1:2:3	2	72
10	CH_3OH	No catalyst	--	5	52
11	No solvent	25	1:2:3	5	55

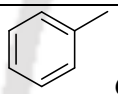
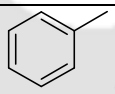
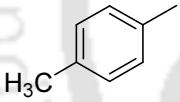
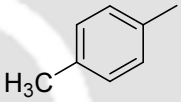
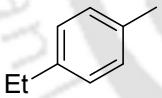
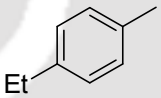
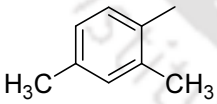
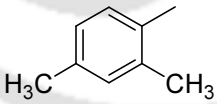
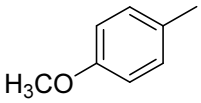
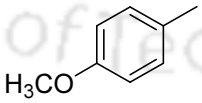
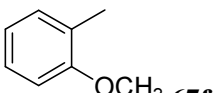
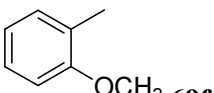
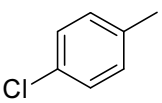
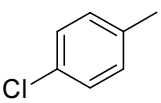
[a]Isolated yield.

After optimization of the reaction conditions, the reaction of 4-methylaniline (2.0 mmol) with DMAD (1.0 mmol), formaldehyde (2.5 mmol) using $HClO_4$-SiO_2 (25 mg, 2.5 mol%) in methanol was performed. The product **70b** was obtained in 96% yield. The scope of this

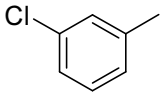
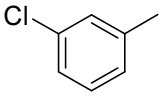
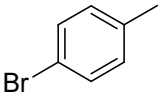
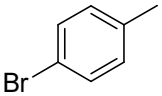
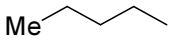
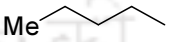
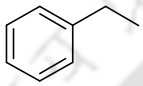
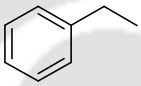
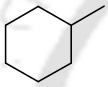
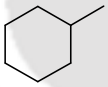
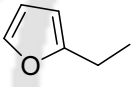
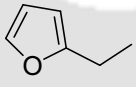
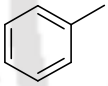
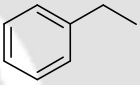
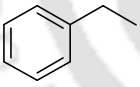
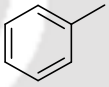
protocol was investigated using the same reaction condition for substituted anilines. Me, Et, OMe, Cl and Br were the substituents that was used in these studies. The desired products **70c-i** were obtained in good to excellent yields.

Table 2. Scope of the one-pot synthesis of tetrahydropyrimidines (**70**) catalyzed by $HClO_4$-SiO_2[a]



Entry	R^1	R^2	Time (h)	Product	Yield[b] (%)
1	 **67a**	 **69a**	1.5	**70a**	95
2	 **67b**	 **69b**	1.5	**70b**	96
3	 **67c**	 **69c**	1.5	**70c**	92
4	 **67d**	 **69d**	2.5	**70d**	91
5	 **67e**	 **69e**	1.5	**70e**	92
6	 **67f**	 **69f**	2.0	**70f**	84
7	 **67g**	 **69g**	2.0	**70g**	94

Continued

8	 **67h**	 **69h**	2.0	**70h**	88
9	 **67i**	 **69i**	2.0	**70i**	93
10	 **67j**	 **69j**	1.0	**70j**	95
11	 **67k**	 **69k**	1.0	**70k**	92
12	 **67l**	 **69l**	1.0	**70l**	96
13	 **67m**	 **69m**	1.5	**70m**	91
14	 **67a**	 **69k**	2	**70n**	86
15	 **67k**	 **69a**	2	**70o**	88

[a] All the reactions were carried out using DMAD (1.0 mmol), amine (2.0 mmol) and formaldehyde (2.5 mmol) at room temperature in 3 mL of methanol. [b]Isolated yield.

The present method was also tested with aliphatic amines namely *n*-butylamine, benzylamine, furfurylamine and cyclohexylamine under identical reaction conditions to furnish tetrahydropyrimidines **70j-m** in good yields (Table 2, entries 10-13). It is observed that the aliphatic amines require shorter reaction time than the aromatic amines due to more basicity of the aliphatic amines.

The synthetic utility of the present protocol was further extended by synthesizing *bis*-pyrimidine derivatives. The reaction of DMAD (**66**, 2 mmol) with ethylenediamine (**71a**, 1 mmol), followed by addition of aniline (**67a**, 2 mmol) and formaldehyde (5 mmol) using

$HClO_4$-SiO_2 (50 mg, 5 mol%) as a catalyst provides a *bis*-tetrahydropyrimidine derivative **72a** (Table 3, entry 1). The product **72a** was fully characterized by ^1H and ^{13}C NMR spectra as well as elemental analysis. The strong absorption peaks appear in the IR spectrum at 1741 and 1684 cm^{-1}, which indicates the presence of ester carbonyl group and olefinic double bond. In ^1H NMR spectrum characteristic signals appear at δ 2.98 (s, 4 H), 3.71 (s, 6 H, -CO_2CH_3), 3.88 (s, 6 H, -CO_2CH_3), 4.01 (s, 4 H, CH_2- CH_2), 4.44 (s, 4 H, CH_2), 6.92-6.96 (m, 6 H), 7.25-7.29 (m, 4 H); the singlet at 4.01 ppm confirms the formation of tetrahydropyrimidine **72a**. Similarly, ^{13}C NMR signals comes at δ = 46.3, 50.5, 51.6, 53.3, 67.9, 96.2, 118.1, 121.7, 129.6, 148.2, 148.5, 165.4 and 166.2 respectively. The ^1H NMR spectra and ^{13}C NMR spectra of products **70a, 70e, 70j, 72b** and **72s** are given in Figures **10-14**, respectively in the experimental section. The structure of compound **72a** was also confirmed by single X-ray crystallographic data. The tetrahydropyrimidine ring adopted envelope conformation and the orientation of two rings are found to be anti to each other as shown in Figure 9.

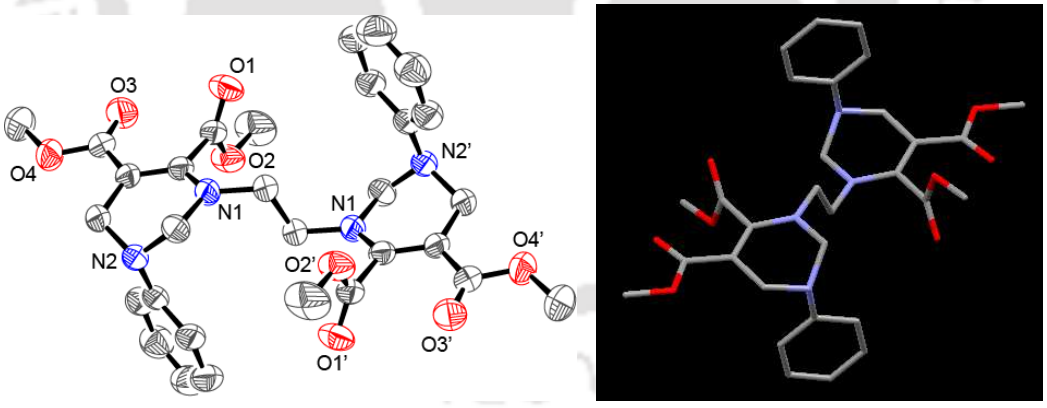
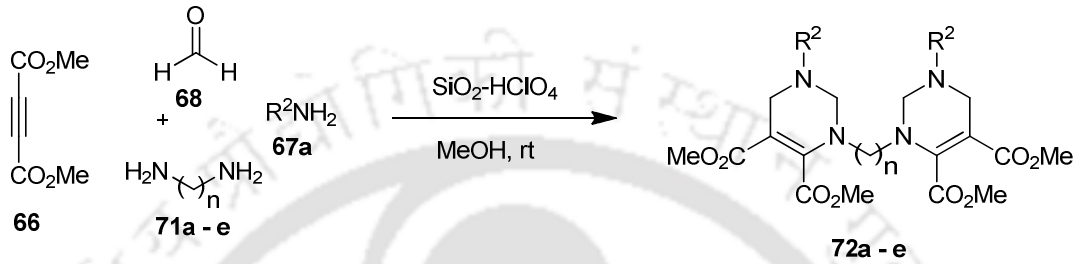


Figure 9. X-ray crystal structure of **72a** (CCDC no. is 756205).

The reaction of other aliphatic diamines viz, 1,3-diamine (**71b**), 1,4-diamine (**71c**), 1,5-diamine (**71d**) and 1,6-diamine (**71e**) were examined individually with DMAD (**66**), aniline

(**67a**) and formaldehyde (**68**) under the same experimental conditions and the results are summarized in Table 3.

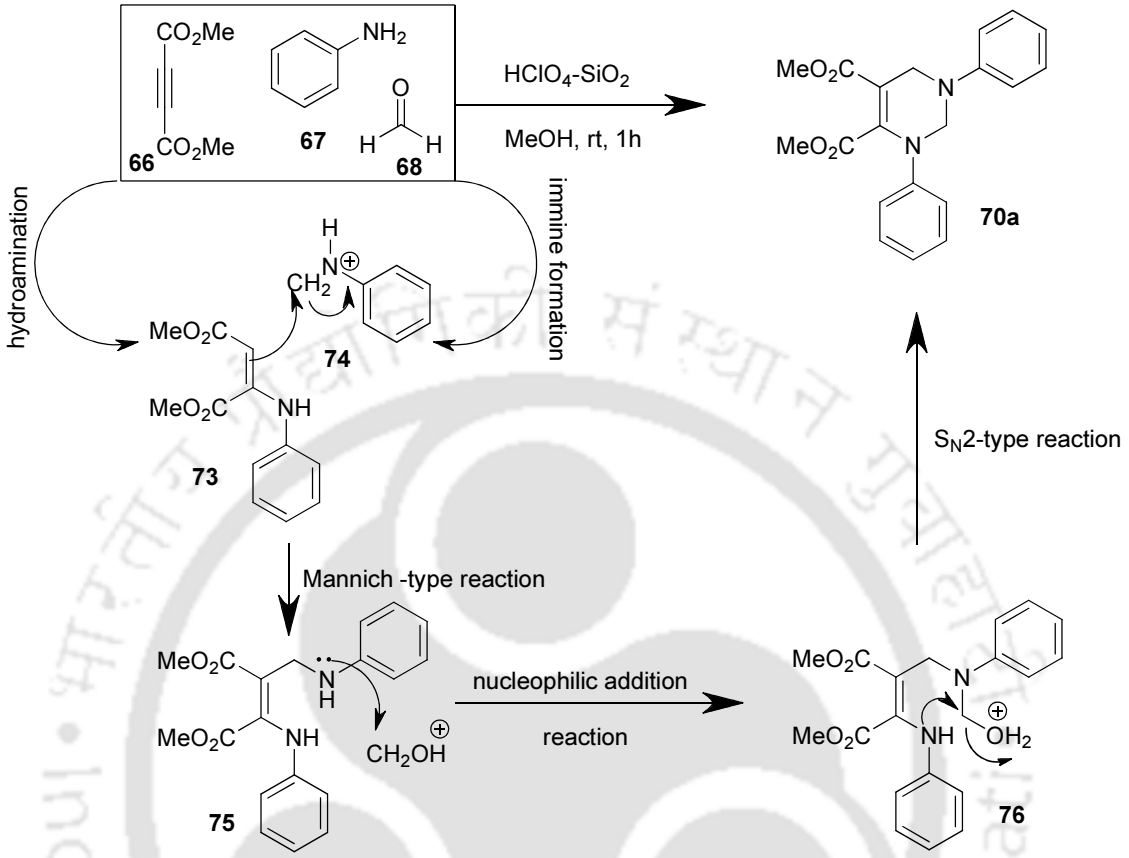
Table 3. Scope of the one-pot domino reaction for the synthesis of *bis*-tetrahydropyrimidines



Entry	n	Time (h)	Product	Yield[a] (%)
1	2, **71a**	2	**72a**	74
2	3, **71b**	2	**72b**	71
3	4, **71c**	2	**72c**	76
4	5, **71d**	2	**72d**	68
5	6, **71e**	2	**72e**	78

[a]Isolated yields.

A plausible mechanism for the formation of tetrahydropyrimidine **70a** involves the initial formation of hydroamination product **73**, which reacts with acid protonated imine **74** to form intermediate **75** *via* Mannich-type reaction. The intermediate **75** reacts with acid protonated formaldehyde to give species **76** by nucleophilic addition reaction. Finally, the intermediate **76** undergoes intramolecular S_N2 type reaction to furnish the desired product **70a** via elimination of a water molecule as shown in Scheme 35.



Scheme 35. Plausible mechanism for the formation of tetrahydropyrimidines.

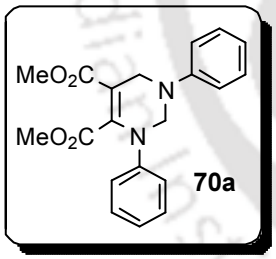
In conclusion, the efficacy and generality of $HClO_4$-SiO_2 as a versatile catalyst for the synthesis of tetrahydropyrimidines using DMAD, amines and formaldehyde has been demonstrated. In addition, the synthesis of novel *bis*-tetrahydropyrimidine derivatives has been achieved using aliphatic diamines under the same experimental conditions. The salient features of this protocol are good yields, mild reaction conditions, superior atom economy, environmentally benign, easy accessibility of the catalyst and its cost effectiveness.

***General procedure for the synthesis of tetrahydropyrimidine derivatives**:*

A mixture of dimethyl acetylenedicarboxylate (DMAD, 1 mmol) and amine (2 mmol) was taken in MeOH (3 mL) in a 25 mL round bottomed flask and it was stirred at room temperature for 10 min. Then 38% formaldehyde solution (200 mg, 2.5 mmol) in methanol (2 mL) and the catalyst $HClO_4$–SiO_2 (25 mg, 1.25 mol%) were added successively into the reaction flask. After completion of reaction as monitored by TLC, methanol was removed and the crude residue was extracted with dichloromethane (2 x 20 mL). The organic layer was washed with $NaHCO_3$ solution, brine followed by water and finally dried over anhydrous Na_2SO_4. The solvent was removed and crude material was purified through a silica gel column chromatography to get the pure product. The similar procedure was followed and all the products **70a-o** were eluted with ethyl acetate/hexane (1:9) mixture.

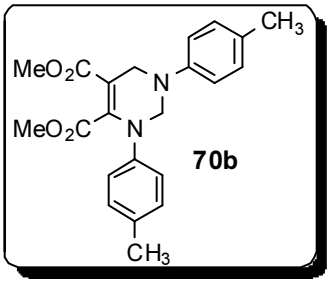
Spectral data of tetrahydropyrimidines:

*Dimethyl 1,3-diphenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70a**):*



Yellow liquid (0.334 g, 95%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.58 (s, 3 H), 3.74 (s, 3 H), 4.27 (s, 2 H), 4.92 (s, 2 H), 6.91 (d, J = 8.4 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 2 H), 7.16-7.29 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 47.7, 51.7, 52.6, 69.0, 100.7, 118.0, 121.3, 125.2, 126.6, 129.4, 143.8, 146.7, 148.4, 164.7, 166.3; **IR** (KBr): 2950, 1743, 1697, 1580, 1495, 1261, 1112 cm^{-1}; **Anal. Calcd** for $C_{20}H_{20}N_2O_4$ (352.39): C, 68.17; H, 5.72; N, 7.95; Found: C, 68.01; H, 5.61; N, 7.73.

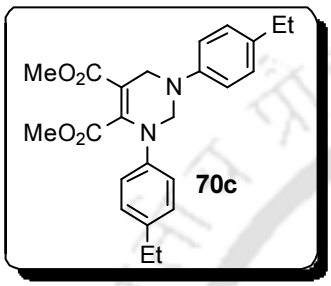
*Dimethyl 1,3-di-p-tolyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70b**):*



Yellow liquid (0.365 g, 96%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 2.30 (s, 3 H), 3.58 (s, 3 H), 3.72 (s, 3 H), 4.22 (s, 2 H), 4.85 (s, 2 H), 6.83 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 7.02 (d, J = 8.4 Hz, 2 H), 7.06 (d, J = 8.4 Hz, 2 H); **^{13}C NMR**

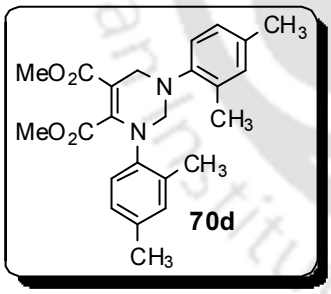
(100 MHz, $CDCl_3$): δ = 20.5, 21.0, 47.6, 51.4, 52.4, 69.2, 98.9, 118.1, 125.1, 129.8, 129.9, 130.6, 136.4, 140.9, 146.0, 147.0, 164.6, 166.2; **IR** (KBr): 2949, 2863, 1742, 1698, 1588, 1514, 1434, 1259, 1112 cm^{-1}; **Anal. Calcd** for $C_{22}H_{24}N_2O_4$ (380.45): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.54; H, 6.23; N, 7.12.

*Dimethyl 1,3-bis(4-ethylphenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70c**):*



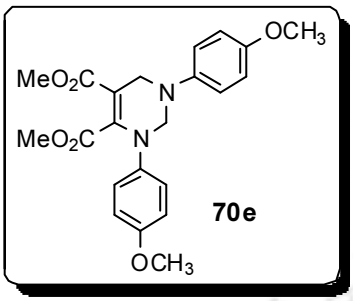
Semi solid (0.376 g, 92%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.19 0 (t, J = 7.6 Hz, 3 H), 1.21 (t, J = 7.2 Hz, 3 H), 2.53-2.63 (m, 4 H), 3.58 (s, 3 H), 3.73 (s, 3 H), 4.23 (s, 2 H), 4.86 (s, 2 H), 6.86 (d, J = 8.4 Hz, 2 H), 6.91 (d, J = 8.4 Hz, 2 H), 7.06 (d, J = 8.4 Hz, 2 H), 7.09 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 15.5, 15.9, 28.1, 28.5, 47.8, 51.6, 52.6, 69.3, 99.2, 118.3, 125.3, 128.7, 128.8, 137.3, 141.1, 142.8, 146.3, 147.1, 164.8, 166.4; **IR** (KBr): 2963, 2872, 1744, 1697, 1588, 1514, 1434, 1260, 1110 cm^{-1}; **Anal. Calcd** for $C_{24}H_{28}N_2O_4$ (408.50): C, 70.57; H, 6.91; N, 6.86. Found: C, 70.51; H, 6.80; N, 6.66.

*Dimethyl 1,3-bis(2,4-dimethylphenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70d**):*



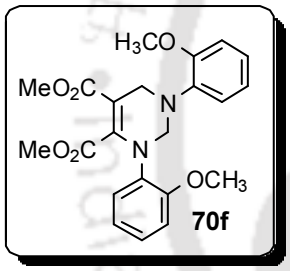
Yellow liquid (0.378 g, 91%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 2.20 (s, 3 H), 2.24 (s, 3 H), 2.27 (s, 3 H), 3.52 (s, 3 H), 3.71 (s, 3 H), 4.04 (s, 2 H), 4.32 (d, J = 11.6 Hz, 1 H), 4.49 (d, J = 11.6 Hz, 1 H), 6.78 (d, J = 8.0 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 6.95 (d, J = 8.0 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 1 H), 7.14 (d, J = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.0, 18.1, 20.9, 21.1, 48.8, 51.4, 52.4, 69.8, 96.9, 121.4, 127.1, 127.3, 128.8, 131.7, 132.0, 137.7, 133.9, 136.4, 138.0, 138.8, 146.0, 148.4, 164.9, 166.5; **IR** (KBr): 2950, 2859, 1744, 1697, 1592, 1502, 1435, 1263, 1111 cm^{-1}; **Anal. Calcd** for $C_{24}H_{28}N_2O_4$ (408.50): C, 70.57; H, 6.91; N, 6.86. Found: C, 70.43; H, 6.79; N, 6.71.

*Dimethyl 1,3-bis(4-methoxyphenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70e**):*



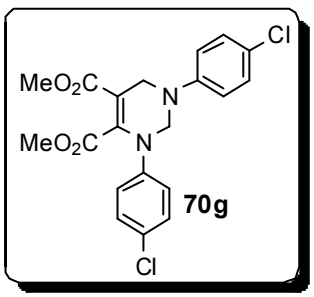
Yellow liquid (0.379 g, 92%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.56 (s, 3 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.18 (s, 2 H), 4.77 (s, 2 H), 6.76 (d, J = 8.8 Hz, 2 H), 6.81 (d, J = 9.2 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.95 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 47.9, 51.5, 52.6, 55.5, 55.7, 70.8, 97.5, 114.4, 114.6, 120.5, 127.5, 136.2, 142.4, 147.7, 154.9, 158.4, 164.7, 166.4; **IR** (KBr): 2950, 2837, 1742, 1694, 1579, 1511, 1435, 1247, 1110 cm^{-1}; **Anal. Calcd** for $C_{22}H_{24}N_2O_6$ (412.45): C, 64.07; H, 5.87; N, 6.79. Found: C, 63.96; H, 5.72; N, 6.48.

*Dimethyl 1,3-bis(2-methoxyphenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70f**):*



Yellow liquid (0.346 g, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50 (s, 3 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 4.21 (s, 2 H), 4.80 (br s, 2 H), 6.67-6.71 (m, 2 H), 6.77 (d, J = 8.0 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 7.6 Hz, 1 H), 6.99 (t, J = 7.6 Hz, 1 H), 7.12 (td, J = 7.2 Hz, J = 2.4 Hz, 1 H), 7.19 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.0, 51.4, 52.4, 55.5, 55.9, 68.4, 97.4, 111.3, 111.9, 120.4, 120.8, 121.0, 124.0, 128.5, 128.52, 131.7, 137.9, 147.8, 152.2, 155.4, 164.6, 166.4; IR (KBr): 2949, 2838, 1743, 1693, 1581, 1501, 1436, 1264, 1108 cm^{-1}; **Anal. Calcd** for $C_{22}H_{24}N_2O_6$ (412.45): C, 64.07; H, 5.87; N, 6.79. Found: C, 64.01; H, 5.71; N, 6.63.

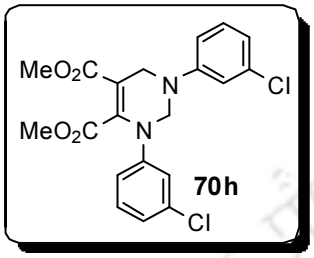
*Dimethyl 1,3-bis(4-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70g**):*



Light **y**ellow solid (0.396 g, 94%); mp 128–130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.61 (s, 3 H), 3.75 (s, 3 H), 4.23 (s, 2 H), 4.85 (s, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 6.90 (d, J = 8.8 Hz, 2 H), 7.18 (d, J = 8.8 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 47.6, 51.9, 52.9, 69.1, 101.6, 119.3, 126.2, 126.5, 129.4, 129.7, 132.3, 142.2, 146.1, 146.7, 164.4, 165.9; **IR**

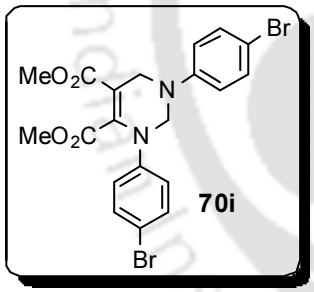
(KBr): 2953, 1744, 1688, 1571, 1491, 1266, 1228, 1117 cm^{-1}; **Anal. Calcd** for $C_{20}H_{18}N_2O_4Cl_2$ (421.28): C, 57.02; H, 4.30; N, 6.65. Found: C, 56.91; H, 4.19; N, 6.42.

*Dimethyl 1,3-bis(3-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70h**):*



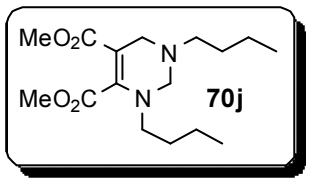
Yellow liquid (0.371 g, 88%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.65 (s, 3 H), 3.76 (s, 3 H), 4.23 (s, 2 H), 4.87 (s, 2 H), 6.72 (dd, J = 8.4 Hz, J = 2.4 Hz, 1 H), 6.83 (t, J = 2.0 Hz, 1 H), 6.86 (dq, J = 8.0 Hz, J = 0.8 Hz, 1 H), 6.90 (dq, J = 8.0 Hz, J = 1.2 Hz, 1 H), 7.04 (t, J = 2.4 Hz, 1 H), 7.12 (t, J = 8.0 Hz, 1 H), 7.17 (m, 1 H), 7.22 (t, J = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 47.7, 52.0, 52.9, 68.2, 103.4, 115.5, 117.7, 121.3, 122.6, 124.7, 126.7, 130.5, 130.6, 135.2, 135.3, 144.9, 145.6, 149.2, 164.5, 165.9; **IR** (KBr): 2950, 2843, 1742, 1703, 1591, 1482, 1262, 1114 cm^{-1}; **Anal. Calcd** for $C_{20}H_{18}N_2O_4Cl_2$ (421.28): C, 57.02; H, 4.30; N, 6.65. Found: C, 56.98; H, 4.17; N, 6.50.

*Dimethyl 1,3-bis(4-bromophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70i**):*



Light yellow solid (0.474 g, 93%); mp 150–152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.62 (s, 3 H), 3.75 (s, 3 H), 4.22 (s, 2 H), 4.85 (s, 2 H), 6.75 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.40 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 47.6, 51.8, 52.9, 68.8, 101.8, 113.7, 119.5, 120.1, 126.3, 132.3, 132.6, 142.7, 145.9, 147.2, 164.4, 165.9; **IR** (KBr): 2951, 1744, 1689, 1591, 1568, 1487, 1265, 1227, 1116 cm^{-1}; **Anal. Calcd** for $C_{20}H_{18}N_2O_4Br_2$ (510.20): C, 47.08; H, 3.56; N, 5.49. Found: C, 47.01; H, 3.42; N, 5.29.

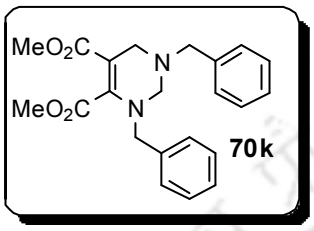
*Dimethyl 1,3-dibutyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70j**):*



Yellow liquid (0.297 g, 95%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.2 Hz, 3 H), 0.93 (t, J = 7.2 Hz, 3 H), 1.24-1.32 (m, 2 H), 1.34-1.41 (m, 2 H), 1.47-1.56 (m, 4 H), 2.53 (t, J = 7.6 Hz, 2 H), 3.01 (t, J = 7.6 Hz, 2 H), 3.50 (s, 2 H), 3.64 (s, 3 H), 3.90 (s, 3 H), 3.98 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.9, 14.2, 20.0, 20.6, 30.3, 31.4, 48.2,

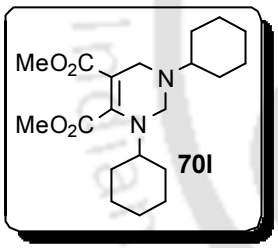
51.0, 52.6, 52.8, 67.7, 91.1, 148.4, 165.6, 167.1; **IR** (KBr): 2956, 2870, 1743, 1689, 1582, 1434, 1285, 1249, 1145 cm^{-1}; **Anal. Calcd** for $C_{16}H_{28}N_2O_4$ (312.41): C, 61.51; H, 9.03; N, 8.97. Found: C, 61.51; H, 8.92; N, 8.81.

*Dimethyl 1,3-dibenzyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70k**):*



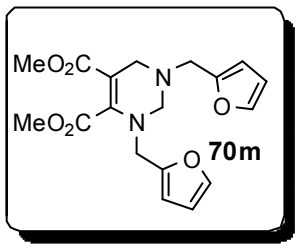
Yellow liquid (0.350 g, 92%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.55 (s, 2 H), 3.60 (s, 2 H), 3.65 (s, 3 H), 3.84 (s, 2 H), 3.91 (s, 3 H), 4.16 (s, 2 H), 7.15-7.18 (m, 2 H), 7.22-7.32 (m, 8 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 48.4, 51.3, 53.1, 54.4, 57.1, 66.1, 92.2, 127.4, 128.2, 128.24, 128.5, 128.9, 136.3, 138.1, 148.4, 165.8, 167.1; **IR** (KBr): 2949, 2855, 1740, 1689, 1582, 1434, 1286, 1110 cm^{-1}; **Anal. Calcd** for $C_{22}H_{24}N_2O_4$ (380.45): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.39; H, 6.25; N, 7.18.

*Dimethyl 1,3-dicyclohexyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70l**):*



Yellow liquid (0.350 g, 96%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.03-1.3 (m, 8 H), 1.35-1.45 (m, 2 H), 1.62-1.92 (m, 10 H), 2.43-2.52 (m, 1 H), 2.97 (tt, J = 11.6 Hz, J = 4.8 Hz, 1H), 3.54 (s, 2 H), 3.64 (s, 3 H), 3.90 (s, 3 H), 4.01 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 25.3, 25.6, 25.9, 26.1, 30.5, 31.4, 45.5, 51.0, 52.8, 59.0, 60.0, 60.2, 92.7, 149.0, 166.0, 166.8; **IR** (KBr): 2932, 1742, 1688, 1582, 1435, 1287, 1239, 1117 cm^{-1}; **Anal. Calcd** for $C_{20}H_{32}N_2O_4$ (364.49): C, 65.91; H, 8.85; N, 7.69. Found: C, 65.79; H, 8.75; N, 7.53.

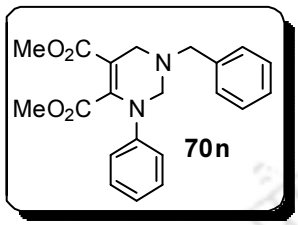
*Dimethyl 1,3-bis(furan-2-ylmethyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70m**):*



Yellow liquid (0.328 g, 91%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.59 (s, 2 H), 3.63 (s, 2 H), 3.65 (s, 3 H), 3.92 (s, 3 H), 4.05 (s, 2 H), 4.19 (s, 2 H), 6.13 (d, J = 3.2 Hz, 1 H), 6.26 (d, J = 3.2 Hz, 1 H), 6.30 (d, J = 3.0 Hz, 1 H), 6.33 (d, J = 3.0 Hz, 1 H), 7.37-7.38 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 46.9, 47.8, 49.2, 51.3, 66.3, 92.5, 109.2, 110.3, 110.8, 142.7, 143.0, 149.9, 151.5, 165.3, 166.9; **IR** (KBr): 2951,

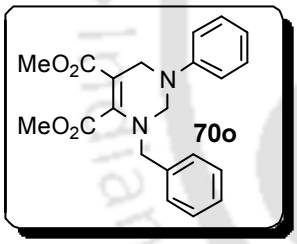
1739, 1688, 1582, 1435, 1284, 1247, 1188, 1109 cm^{-1}; **Anal. Calcd** for $C_{18}H_{20}N_2O_6$ (360.37): C, 59.99; H, 5.59; N, 7.77. Found: C, 59.91; H, 5.48; N, 7.61.

*Dimethyl 1-benzyl-3-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70n**):*



Yellow liquid (0.315 g, 86%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.63 (s, 3 H), 3.67 (s, 3 H), 3.71 (s, 2 H), 3.81 (s, 2 H), 4.36 (s, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.24 (br s, 5 H), 7.30 (t, J = 7.2 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 48.8, 51.4, 52.6, 56.7, 69.8, 97.3, 124.8, 126.3, 127.5, 128.4, 129.0, 129.3, 137.8 143.7, 145.9, 164.8, 166.8; **IR** (KBr): 2951, 2860, 1739, 1688, 1582, 1284, 1247, 1109 cm^{-1}; Anal. Calcd for $C_{21}H_{22}N_2O_4$ (366.42): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.72; H, 5.91; N, 7.49.

*Dimethyl 3-benzyl-1-phenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**70o**):*



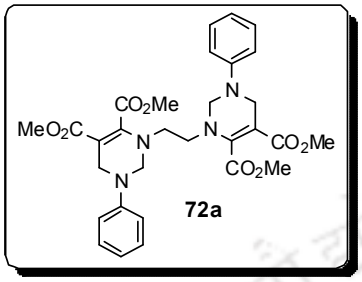
Yellow liquid (0.322 g, 88%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H), 3.85 (s, 3 H), 4.12 (s, 2 H), 4.21 (s, 2 H), 4.42 (s, 2 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.90 (t, J = 7.6 Hz, 1 H), 7.17-7.24 (m, 4 H), 7.26-7.31 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 46.4, 51.4, 53.0, 54.5, 65.4, 94.8, 117.8, 121.2, 128.0, 128.1, 128.8, 129.3, 135.8, 148.4, 149.0, 165.5, 166.4; **IR** (KBr): 2963, 2872, 1744, 1697, 1588, 1514, 1260, 1110 cm^{-1}; **Anal. Calcd** for $C_{21}H_{22}N_2O_4$ (366.42): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.72; H, 5.88; N, 7.48.

General reaction procedure for functionalized bis-tetrahyropyrimidines (72)

A mixture of dimethyl acetylenedicarboxylate (DMAD, 1 mmol) and diamines (1 mmol) in MeOH (2 mL) was stirred at room temperatutre for 20 min. Aniline (2 mmol) in MeOH (1 mL) and formaldehyde (38%, 400 mg, 5 mmol) in methanol (2 mL) were added into it. Finally, the catalyst silica supported perchloric acid (50 mg, 2.5 mol%) was added into the reaction vessel. After completion of reaction as monitored by TLC, the same work up procedure was followed as above. The products **72a-e** were obtained by purification through column chromatography using ethyl acetate/hexane (1:9) as eluent.

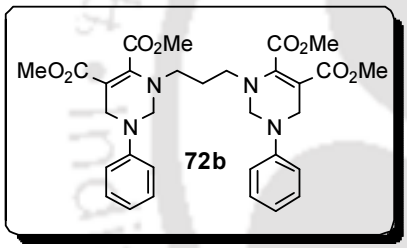
Spectral data of *bis*-tetrahydropyrimidines:

*Functionalized bis-tetrahyropyrimidine (**72a**):*



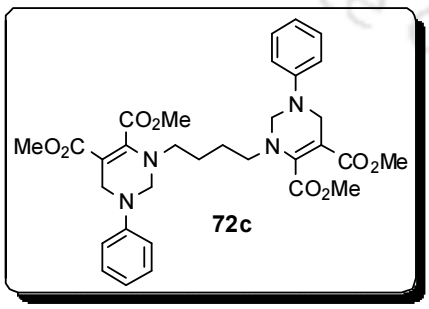
Light yellow solid (0.428 g, 74%); mp 104–106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.98 (s, 4 H), 3.71 (s, 6 H), 3.88 (s, 6 H), 4.01 (s, 4 H), 4.44 (s, 4 H), 6.92-6.96 (m, 6 H), 7.25-7.29 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 46.3, 50.5, 51.6, 53.3, 67.9, 96.2, 118.1, 121.7, 129.6, 148.2, 148.5, 165.4, 166.2; **IR** (KBr): 2949, 1741, 1684, 1575, 1497, 1427, 1270, 1219, 1151, 1097 cm^{-1}; Anal. Calcd for $C_{30}H_{34}N_4O_8$ (578.63): C, 62.27; H, 5.92; N, 9.68. Found: C, 62.11; H, 5.83; N, 9.82.

*Functionalized bis-tetrahyropyrimidine (**72b**):*



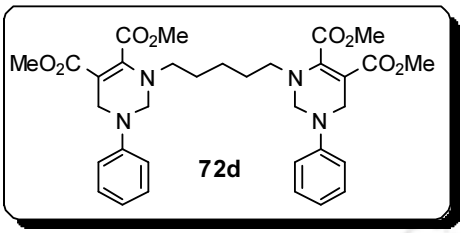
Yellow liquid (0.421 g, 71%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.48 (t, J = 7.2 Hz, 2 H), 2.90 (t, J = 7.2 Hz, 4 H), 3.69 (s, 6 H), 3.84 (s, 6 H), 4.04 (s, 4 H), 4.36 (s, 4 H), 6.93-6.96 (m, 6 H), 7.28 (t, J = 7.6 Hz, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 28.4, 46.6, 48.6, 51.5, 53.1, 66.5, 95.3, 118.5, 121.8, 129.6, 148.7, 165.5, 166.3; **IR** (KBr): 2950, 1739, 1689, 1596, 1583, 1435, 1257, 1149 cm^{-1}; **Anal. Calcd** for $C_{31}H_{36}N_4O_8$ (592.65): C, 62.83; H, 6.13; N, 9.45. Found: C, 62.70; H, 6.02; N, 9.22.

*Functionalized bis-tetrahyropyrimidine (**72c**):*



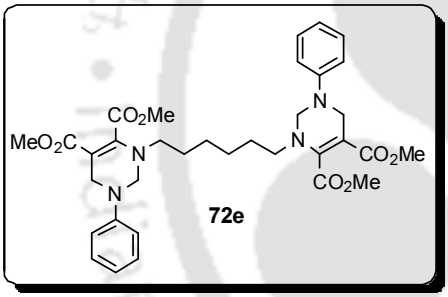
Yellow liquid (0.461 g, 76%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.24 (br s, 4 H), 2.88 (br s, 4 H), 3.70 (s, 6 H), 3.85 (s, 6 H), 4.05 (s, 4 H), 4.43 (s, 4 H), 6.93 (t, J = 7.6 Hz, 2 H), 6.96 (d, J = 8.8 Hz, 4 H), 7.62 (t, J = 7.6 Hz, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 25.9, 46.3, 50.5, 51.3, 52.9, 66.1, 94.0, 118.2, 121.4, 129.4, 148.6, 148.9, 165.3, 166.3; **IR** (KBr): 2949, 1739, 1688, 1580, 1434, 1258, 1145 cm^{-1}; **Anal. Calcd** for $C_{32}H_{38}N_4O_8$ (606.68): C, 63.35; H, 6.31; N, 9.24. Found: C, 63.21; H, 6.11; N, 9.00.

*Functionalized bis-tetrahyropyrimidine (**72d):***



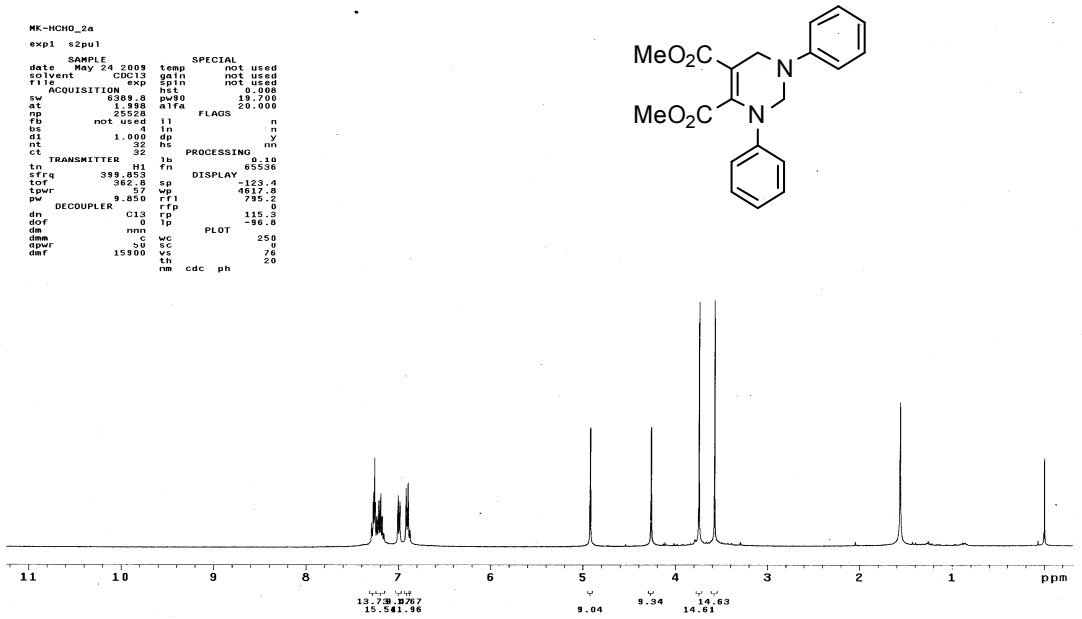
Yellow liquid (0.422 g, 68%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.94-0.99 (m, 2 H), 1.25-1.32 (m, 4 H), 2.92 (t, J = 7.6 Hz, 4 H), 3.70 (s, 6 H), 3.85 (s, 6 H), 4.08 (s, 4 H), 4.09 (s, 4 H), 6.94 (t, J = 7.2 Hz, 2 H), 6.98 (d, J = 7.6 Hz, 4 H), 7.28 (t, J = 7.6 Hz, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.5, 28.8, 46.5, 51.0, 51.4, 53.0, 66.4, 93.9, 118.4, 121.6, 129.5, 148.8, 149.0, 165.4, 166.4; **IR** (KBr): 2950, 1739, 1687, 1579, 1434, 1257, 1146, 1090 cm^{-1}; **Anal. Calcd** for $C_{33}H_{40}N_4O_8$ (620.70): C, 63.86; H, 6.49; N, 9.03. Found: C, 63.73; H, 6.43; N, 9.21.

*Functionalized bis-tetrahyropyrimidine (**72e):***



White solid (0.495 g, 78%); mp 150–152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.01 (br s, 4 H), 1.33 (br s, 4 H), 2.96 (t, J = 7.2 Hz, 4 H), 3.70 (s, 6 H), 3.86 (s, 6 H), 4.09 (s, 4 H), 4.50 (s, 4 H), 6.93 (t, J = 7.2 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 4 H), 7.28 (t, J = 7.6 Hz, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 26.3, 29.0, 46.5, 51.2, 51.4, 53.0, 66.4, 93.8, 118.4, 121.5, 129.5, 148.8, 149.1, 165.4, 166.4; **IR** (KBr): 2945, 1736, 1686, 1579, 1432, 1257, 1146, 1092 cm^{-1}; **Anal. Calcd** for $C_{34}H_{42}N_4O_8$ (634.73): C, 64.34; H, 6.67; N, 8.83. Found: C, 64.30; H, 6.52; N, 8.69.

^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahyropyrimidine (**70a**)*



(***^{13}C NMR (100 MHz, $CDCl_3$)***: *Tetrahyropyrimidine* ***(70a)***

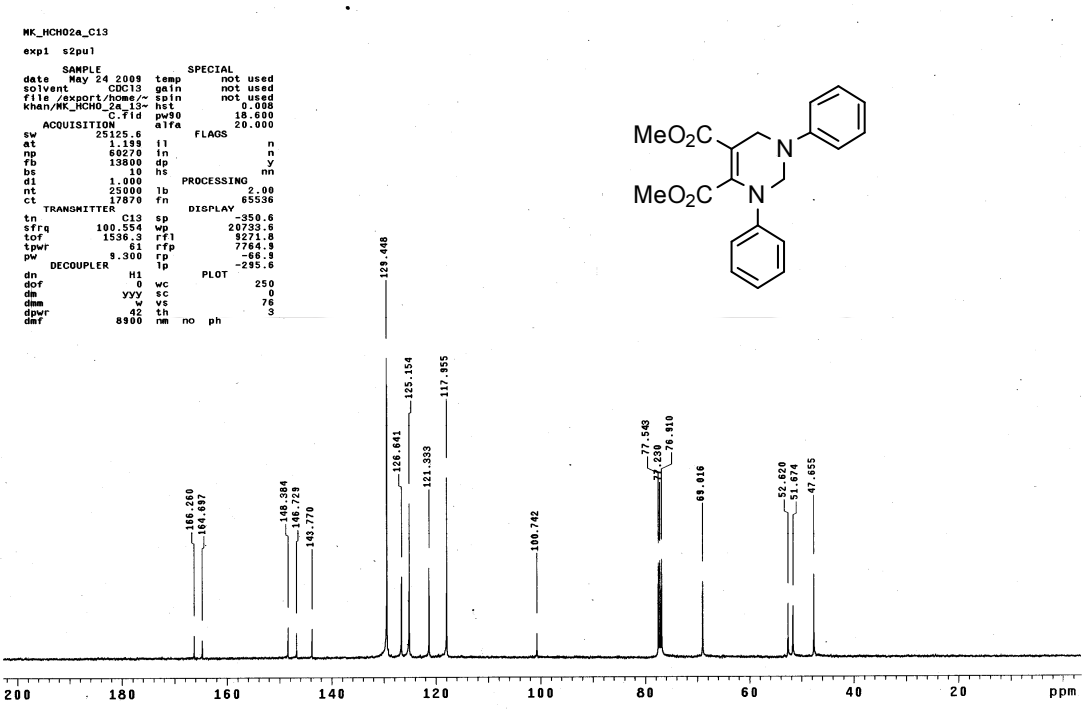
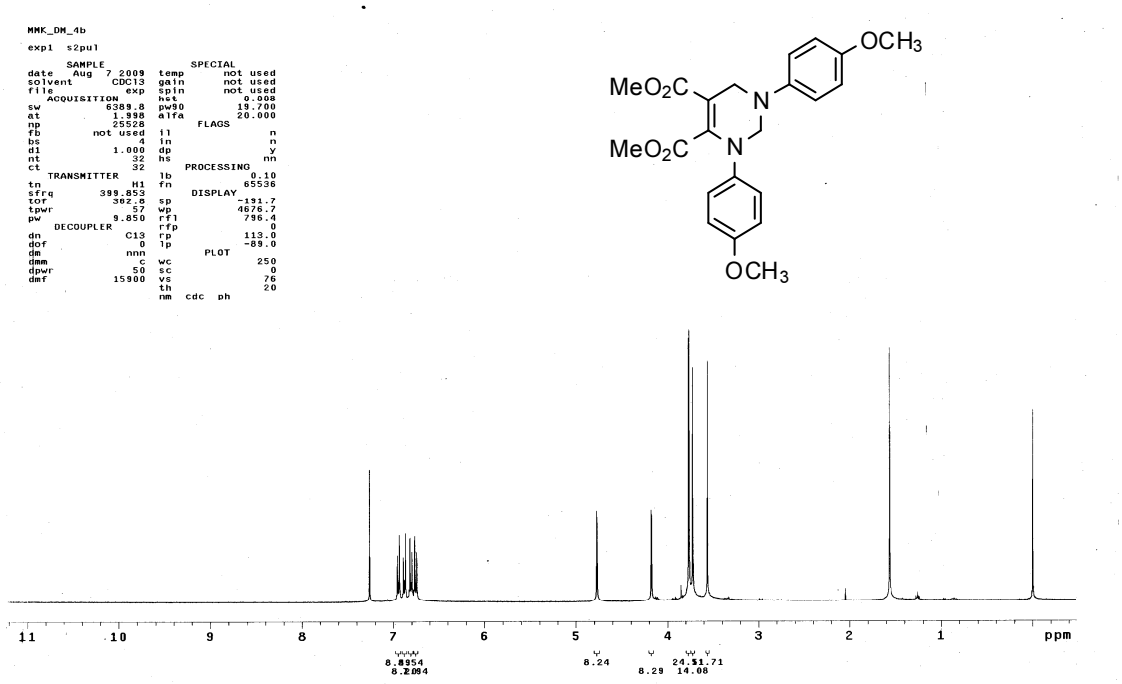


Figure 10

^{1}H NMR (400 MHz, $CDCl_3$): Tetrahyropyrimidine (70e)



^{13}C NMR (100 MHz, $CDCl_3$): Tetrahyropyrimidine (70e)

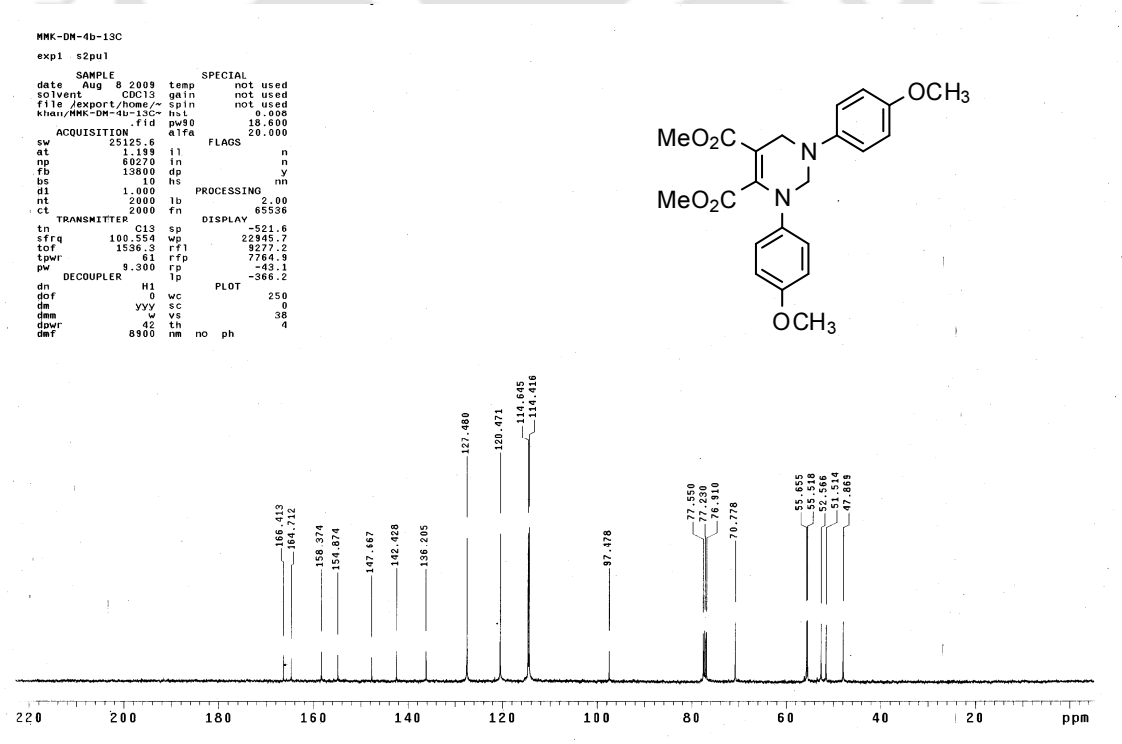
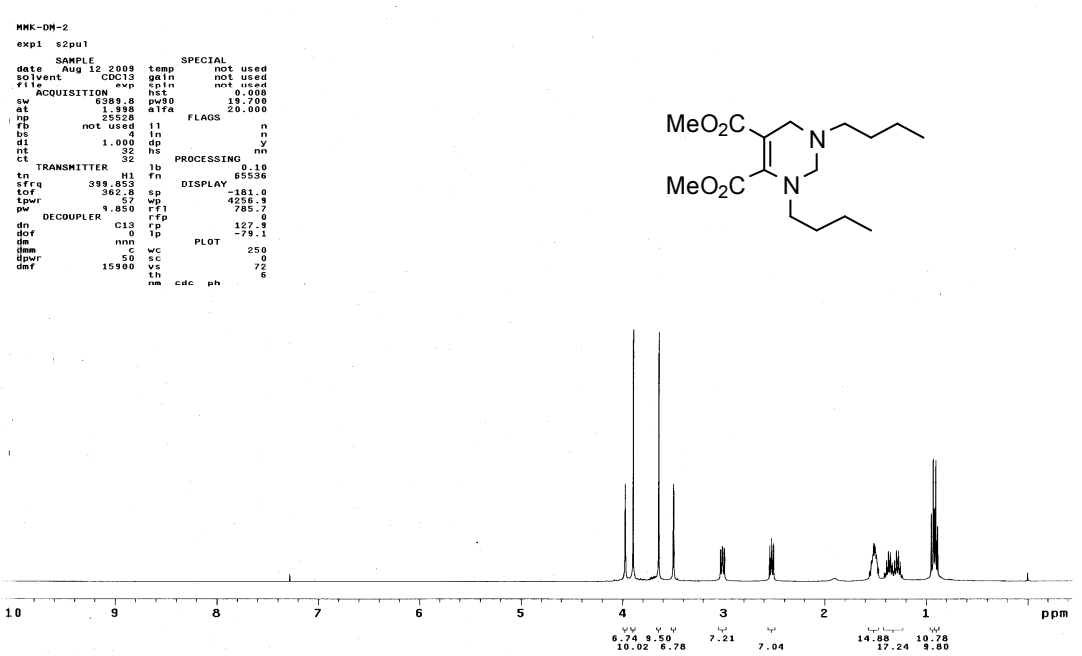


Figure 11

^{1}H NMR (400 MHz, $CDCl_3$): Tetrahyropyrimidine (70j)



^{13}C NMR (100 MHz, $CDCl_3$): Tetrahyropyrimidine (70j)

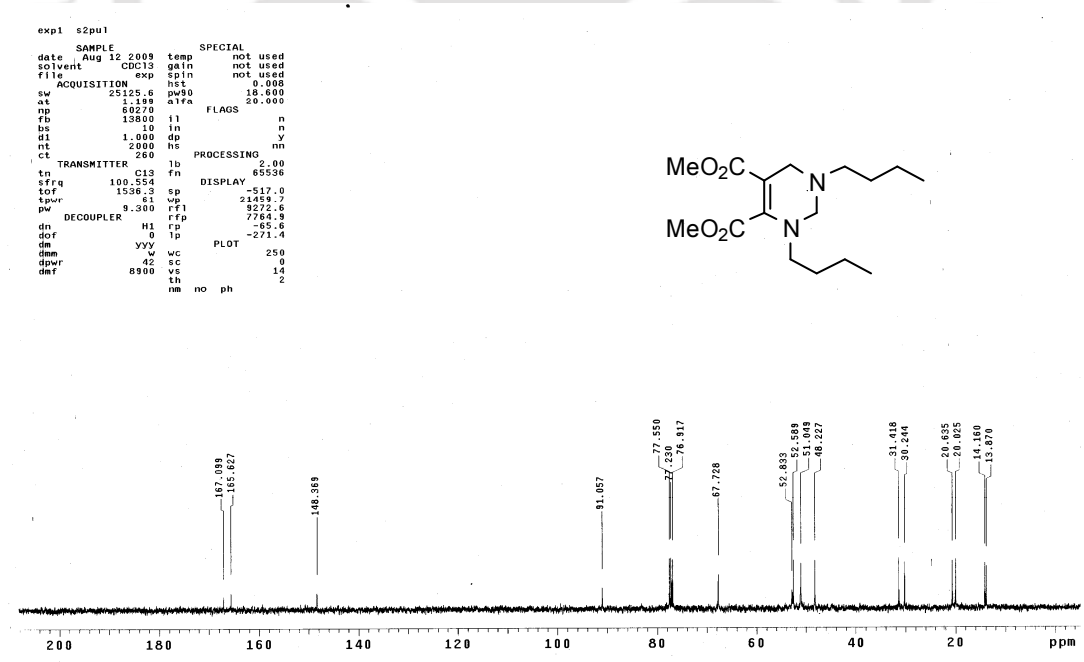
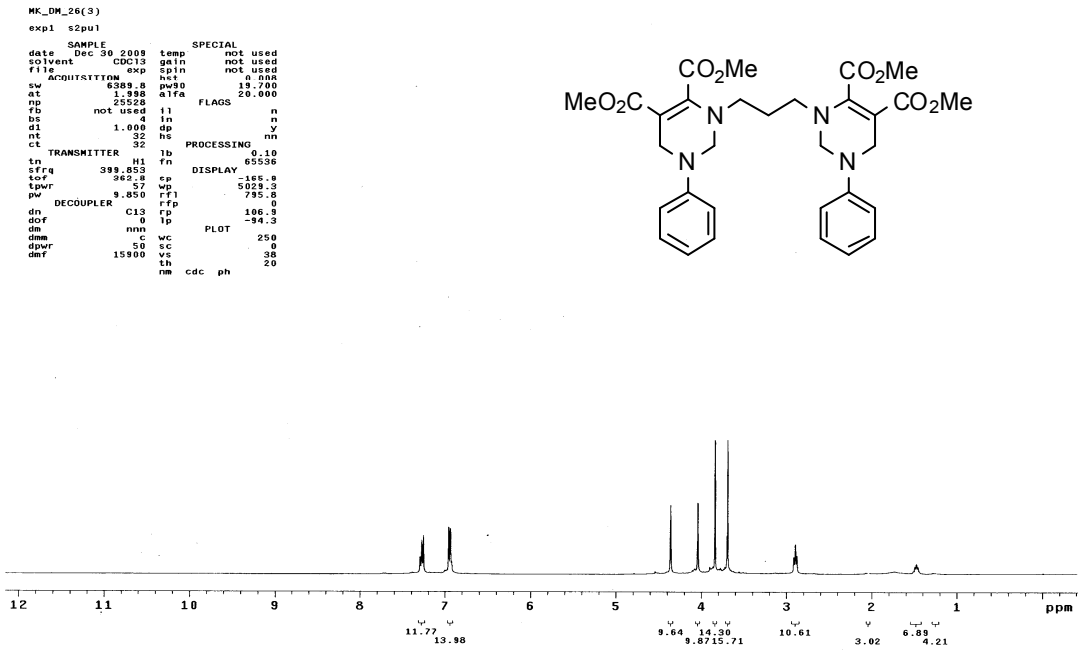


Figure 12

^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahyropyrimidine* ***(72b)***



^{13}C NMR (100 MHz, $CDCl_3$): *Tetrahyropyrimidine* ***(72b)***

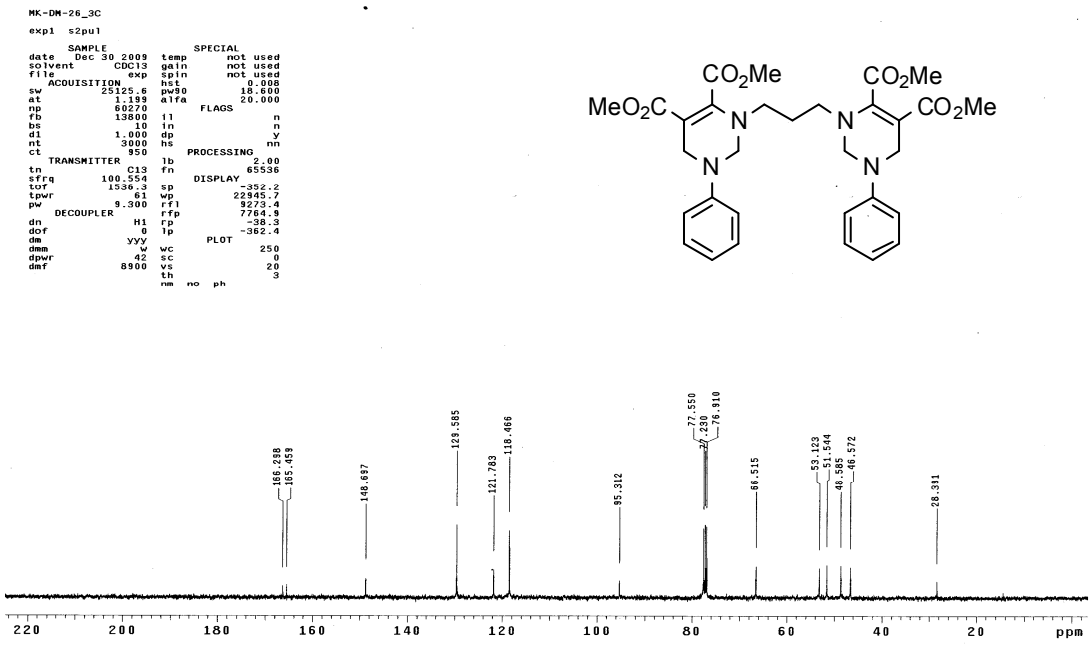
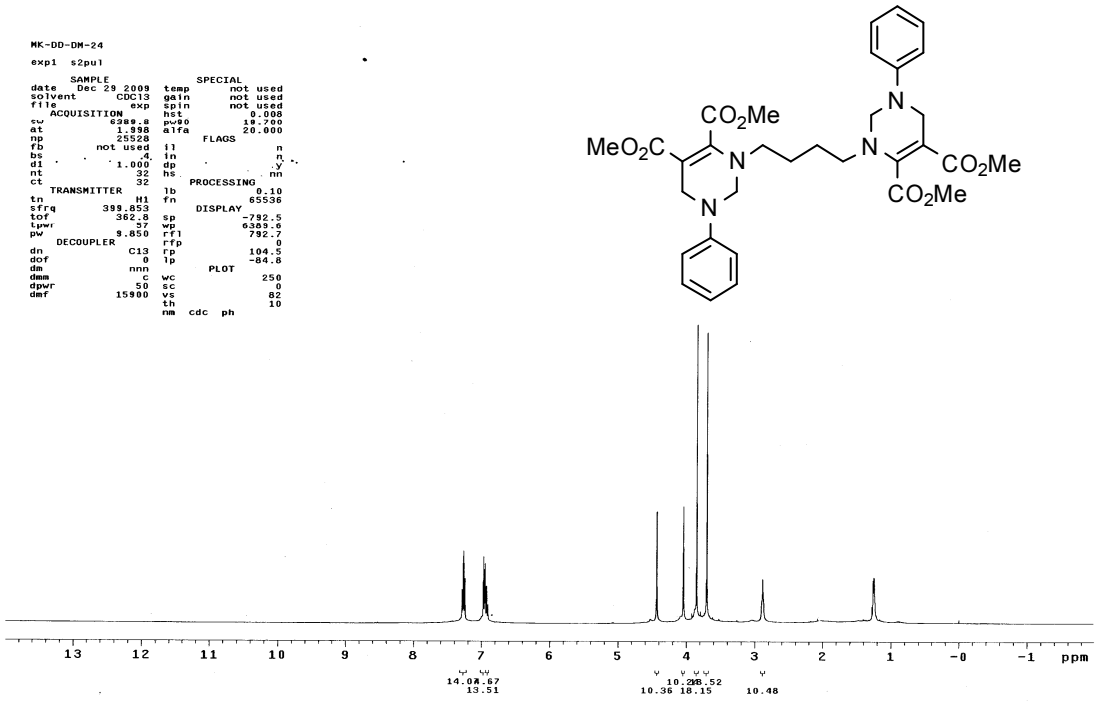


Figure 13

^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahyropyrimidine* **(72c)**



^{13}C NMR (100 MHz, $CDCl_3$): *Tetrahyropyrimidine* **(72c)**

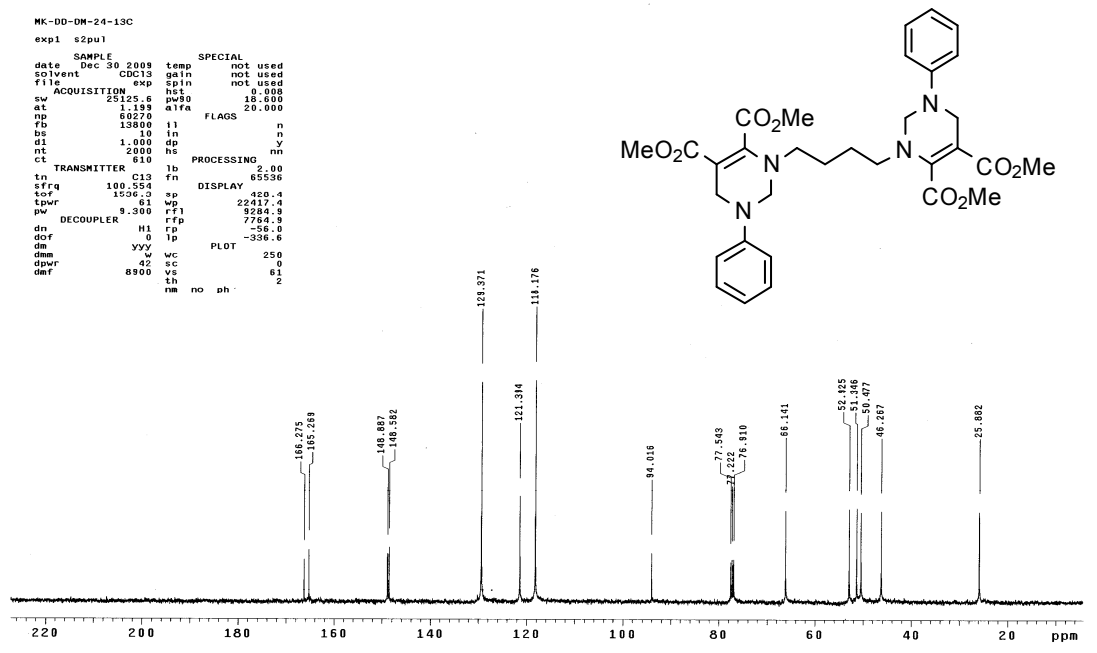


Figure 14

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PART B

CHAPTER IB

Brief review on Povarov Reaction

1. Introduction

The Diels–Alder (DA) reaction is recognized as a powerful reaction in the synthetic strategies for the synthesis of natural and non-natural carbocycles and heterocycles.[1] It has been used extensively for the construction of six-membered ring systems with excellent regio-, diastereo-, and enantioselective manner using a suitable diene and dienophile partner. The DA reaction contains mainly two basic variants, which can be classified as carbo-DA reaction (CDA) and hetero-DA reaction (HDA), which can be subdivided as like oxa-DA reaction (HDA of carbonyl compounds) and imino/aza-DA reaction (HDA of imines). One of the special type imino/aza-DA reaction is known as Povarov reaction. These are summarized in Figure 1.[2]

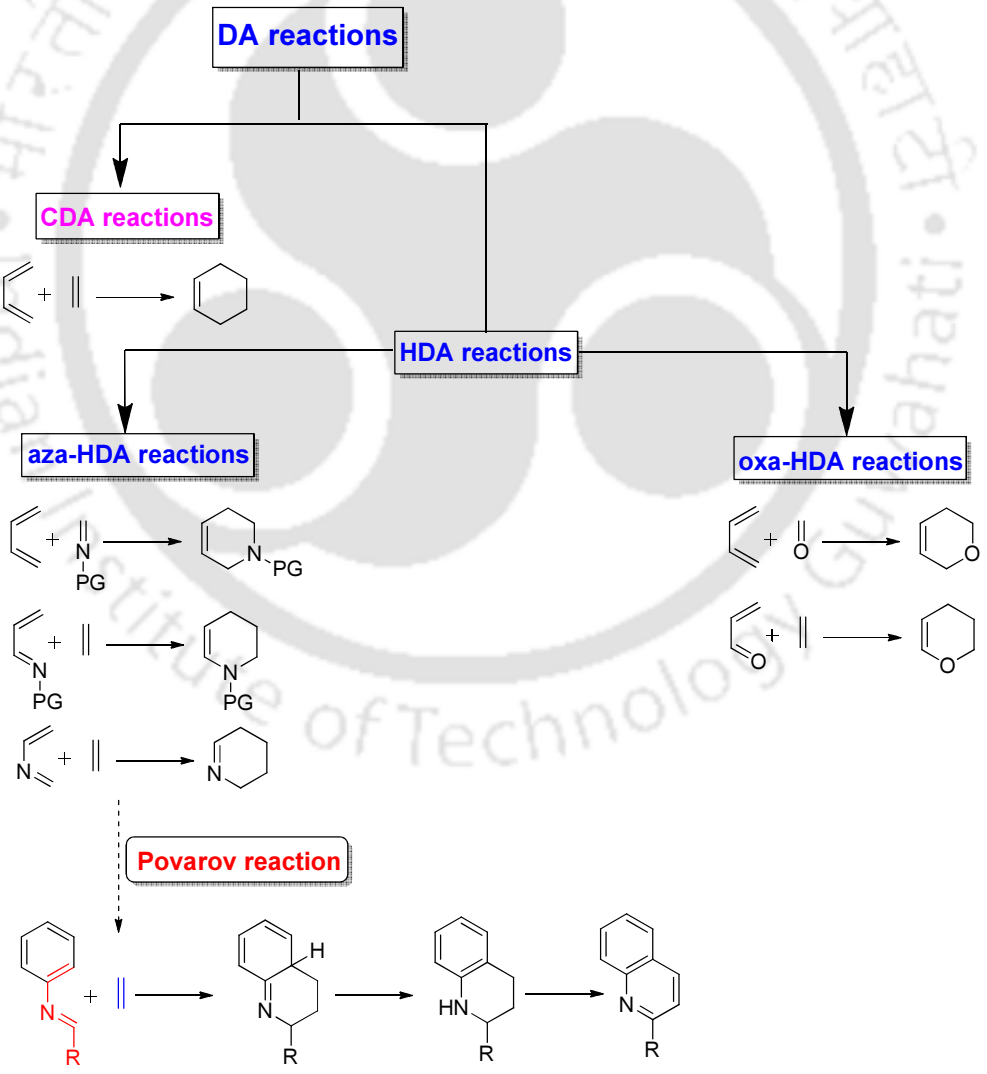


Figure 1

The DA reaction can also take place intra-molecularly when a molecule contains both the diene and dienophile, which are connected by a chain at position C-1 of the diene (Type I intramolecular DA reaction) or at position C-2 of the diene (Type II intramolecular DA reaction).[3] As a matter of fact, a bicyclic adduct from Type I or a bridged bicyclic compound from type II can be accessed as shown in Figure 2.

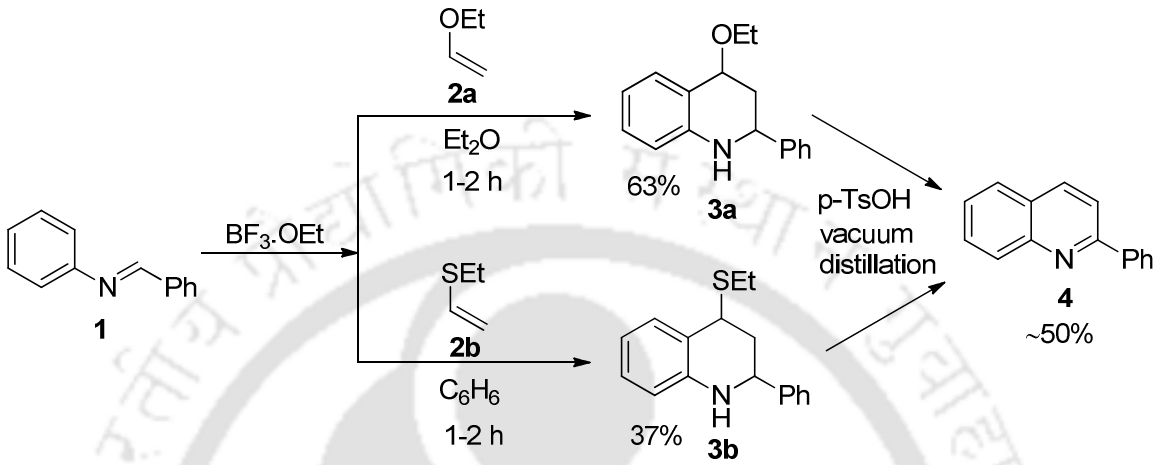
Figure 2

In the middle of the 20th century, Povarov, Mikhailov and Grigos[4] described an elegant approach for the synthesis of tetrahydroquinolines and quinolines from *N*-aryl imines with activated electron-enriched alkenes such as vinyl ethers, alkyl vinyl sulfides through [4+2] cycloaddition reaction in presence of BF_3.OEt. Today, this reaction is popularly known as the Povarov reaction or aza-Diels-Alder reaction. In the last decade, numerous catalysts based on rare-earth metal triflates have been explored for Povarov reaction, which has been reviewed[5] in 2008. Nowadays, Povarov reactions are valuable tools in a contemporary organic synthesis for the construction of *N*-polyheterocycles such as alkaloids and it has been efficiently explored in natural product synthesis.[6] Indeed, Povarov reactions have also gained popularity in both diversity-oriented synthesis (DOS) and target-oriented synthesis (TOS).

2. Development of Povarov reaction

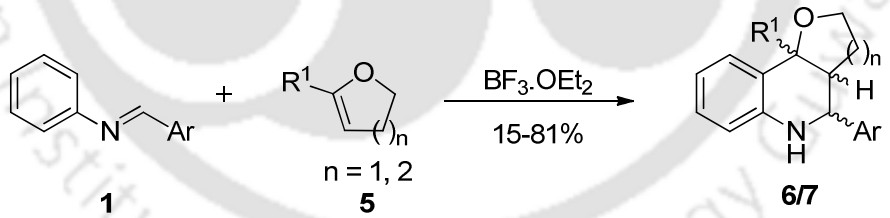
In the year 1960, Povarov and Grigos showed that the condensation of ethyl vinyl ether (**2a**) with Schiff's base (PhN=CHPh) or anils (**1**) in the presence of catalytic amounts (5 mol% - 10 mol %) of BF_3-OEt in benzene provided a substituted 4-ethoxy-1,2,3,4-tetrahydroquinolines (**3a**) in moderate yields. Then it was converted into 2-phenylquinoline (**4**) on treatment with *p*-toluenesulfonic acid followed by oxidation with atmospheric oxygen or $KMnO_4$ as shown in Scheme 1.[4] Likewise, vinyl sulfide (**1b**) can be used for similar transformation for the synthesis of 2-phenylquinoline (**4**). Different Schiff's bases can be prepared from a wide variety of aromatic aldehydes and aromatic amines that contain

substituents both in the aniline residue and the benzene ring of the aromatic aldehyde. It has been also found that a Schiff base of non-aromatic unsaturated aldehydes can also undergo the Povarov reaction.



Scheme 1

Cyclic vinyl ethers such as 2-methyl-2,3-dihydrofuran (**5a,** R^1 = Me, n = 1) and 2,3-dihydropyran can be used as electron-rich dienophiles in a Povarov reaction for the synthesis of furo[3,2-c]quinolines (n = 1, **6)** and pyrano[3,2-c]quinolines (n = 2, **7**), respectively as shown in Scheme 2.[4]

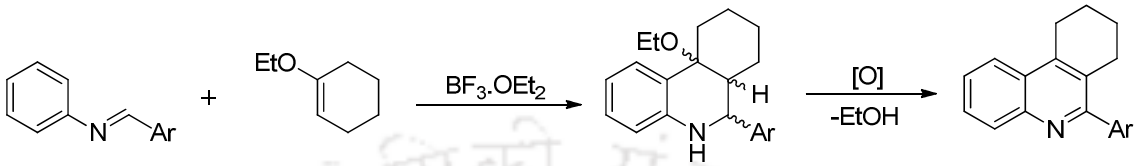


Scheme 2

The reactions from scheme 1 can create two new asymmetric centers in the product **3a** or **3b** whereas the reactions from scheme 2 can generate three new asymmetric centers in the adduct **6** or **7**. Though the stereochemistry of the products was not ascertained by Povarov and his co-workers, but two diastereomeric isomer of compound **3** were isolated in the ratio 1:1.

The usefulness of Povarov reaction was extended for the synthesis of ethoxyoctahydrophenanthridines (**9**) using *N*-aryl imine (**2**) and cyclic enol ether (**8**).

Interestingly, the product (**9**) was converted into 6-phenyltetrahydrophenanthridines (**10**) by spontaneous elimination of ethanol followed by aromatization of the quinoline ring[4] as depicted in Scheme 3.

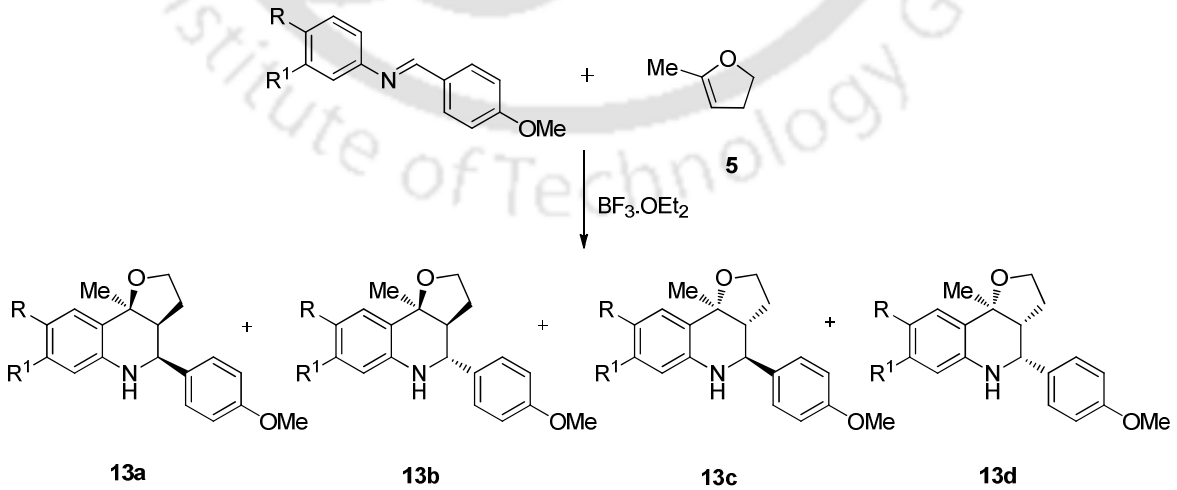


Scheme 3

In addition to vinyl ethers, the reaction with benzylideneaniline (**2**) can also proceed with alkoxyacetylenes such as ethoxy acetylene (**11**) to give 2-phenyl-4-ethoxy-quinoline **12** in 51% yield as shown in Scheme 4.[4]

Scheme 4

Further, studies of stereoselectivity of the Povarov reaction was determined by Perricone et al. by carrying out BF_3-catalysed reaction of 5-methyl-2,3-dihydro-furan (**5**) with imines for the synthesis of tetrahydroquinolines and they isolated four diastereomers **13a**, **13b**, **13c** and **13d** as shown in Scheme 5.[7]



Scheme 5

Subsequently research efforts were focused towards the search for new effective catalysts of this reaction. Besides $BF_3.OEt_2$, numerous other Lewis acids were used for similar reaction such as $ZnCl_2$,[8] $AlCl_3$,[8] $EtAlCl_2$,[8] $SnCl_4$,[8] $TiCl_4$ both in the free state and as complexes with chiral alcohols,[9] SmI_2,[10] $FeCl_3$[11a-c] supported on K-10 montmorillonite clay, $FeCl_3$-NaI,[11d] metal chlorides MCl_3[12] [M=In, Bi, V, Gd, Sb], salts such as $LiBF_4$,[13] lithium perchlorate.[14] Similarly, various Brónsted acids were developed such as triphenylphosphonium perchlorate,[15] CF_3CO_2H,[16] $KHSO_4$,[17] sulfamic acid,[18] phosphoric acid derivative of a chiral binaphthol (BINOL),[19] , acidic clay K-10,[20] cation exchange resins,[21] trimethyl chlorosilane,[22] molecular iodine,[23] dicobalt hexacarbonyl,[24] and lanthanide triflates.[25] Different solvents were used in the Povarov reaction such as acetonitrile, benzene, nitromethane, tetrahydrofuran, toluene, dichloromethane and dichloromethane-toluene mixture. However, acetonitrile proved to be the solvent of choice. Moreover, trifluoroethanol and hexafluoro-isopropyl alcohol can also be used as alternative solvents.[26] A reaction in which liquid SO_2 simultaneously served as the solvent and the catalyst was described.[27] Povarov reaction can also be conducted in water in presence of ion-exchange resins.[21] Later, it was shown that the Povarov reaction easily proceeds in ionic liquids,[28] using microwave radiation[16a] and under solvent-free reaction condition.[29] The catalysts explored for Povarov reaction is summarized in Table 1.

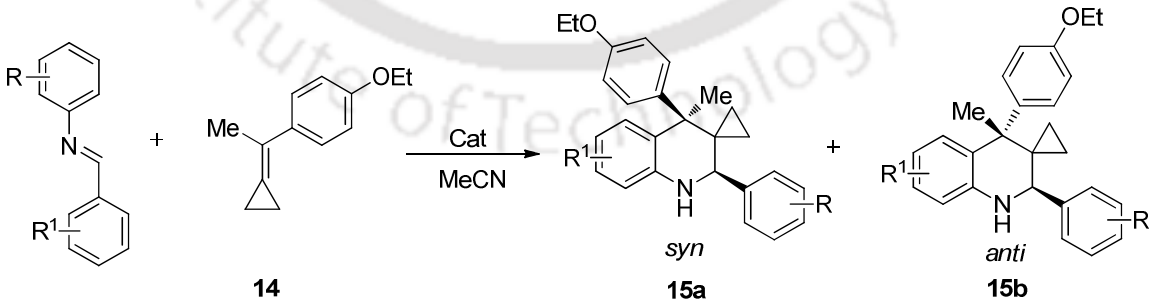
Table 1. Catalysts Used for the Povarov reaction

Lewis acids and metal salt-related catalysts	**Brønsted acids and others**
$BF_3.OEt$	CF_3CO_2H
$Ln(OTf)_3$; Ln = La, Pr, Nd, Sm, Eu, Gd, Dy, Ho, Er, Tm, Yb and Lu	$(CF_3)_2CHOH$, CF_3CH_2OH, CF_3SO_3H
$Sc(OTf)_3$, $Y(OTf)_3$	HCl
Yb(OTf)3/(R)-(+)-BINOL	*p*-TSA
CAN	PPA
I_2, SmI_2	NH_2SO_3H
$CuBr_2$	Phosphomolybdic acid
$ZnCl_2$, $ZnCl_2/SiO_2$	Polymer-supported π-acid

Continued

$TiO_2/h\gamma$	Camphorsulfonic acid (CSA)
$BiCl_3$, $InCl_3$	Photoinduced electron transfer (PET)
$TiCl_3$, $TiCl_4$-PPh_3, ABDDP-$TiCl_2$	Molecular sieves
$GdCl_3$, $SbCl_3$	Ionic liquids
$FeCl_3$, $ZrCl_4$	Selenium ionic liquid salts
$SnCl_4$, $TiCl_4$-PPh_3	Montmorillonite KSF
Et_2AlCl, $EtAlCl_2$, $MeAlCl_2$	2,4,6-triphenylpyrylium tetrafluoroborate (TPT)
$LiClO_4$, $KHSO_4$	Resin AG50W-X2
Et_3N-$AlCl_3$	Fe^{3+}-K-10 clay
$Ar_3N^+.SbCl_6^-$	$Co_2(CO)_8$
$PPh_3.HClO_4$	TMSCl
$PPh_3.Tf_2O$	

In addition to the quest for new catalysts for the Povarov reaction, attempts were undertaken to involve new substrates aimed at the synthesis of new biologically active tetrahydroquinoline derivatives which is described in brief in reviews on Povarov reaction.[2,5] Treatment of a wide variety of imines derived from arylamines and ethylglyoxalate, and methylenecyclopropanes with a catalytic amount of triflic acid (TfOH) or the acidic clay montmorillonite K-10 afforded good to excellent yields of tetrahydroquinolines (**15a,b**) bearing a cyclopropane ring at the 3-position as shown in Scheme 6.[30]



14 **15a** **15b**

Scheme 6

3. Role of Catalyst in Povarov reaction

Hetero-Diels-Alder (HDA) can be classified into two types, the normal HDA and inverse electron demand HDA based on the relative energies of the frontier molecular orbitals (FMOs) of the diene and the dienophile as shown in Figure 3.[31,32] The normal electron demand reaction is a $HOMO_{diene}$–$LUMO_{dienophile}$-controlled HDA reaction which predominantly occurs between electron-rich dienes and electron-deficient dienophiles (Figure 3, left, dashed line). The inverse electron demand HDA reaction is primarily controlled by a $LUMO_{diene}$–$HOMO_{dienophile}$ interaction. The basic concept of activation in HDA reaction is to utilize the lone pair of electrons of the carbonyl and imine functionality for coordination to the Lewis acid. The coordination of the dienophile to the Lewis acid changes the FMOs of the dienophile and for the normal electron demand reactions a decrease of the LUMO and HOMO energies is observed leading to a better interaction with the dienophile (Figure 3, left, solid line). The energy difference between the $HOMO_{diene}$ and the $LUMO_{dienophile}$ is thus reduced compared with that for the absence of a Lewis acid, and can therefore account for the activating effect of the Lewis acid. The catalytic properties of the Lewis acid for the inverse electron demand HDA is due to the coordination of the Lewis

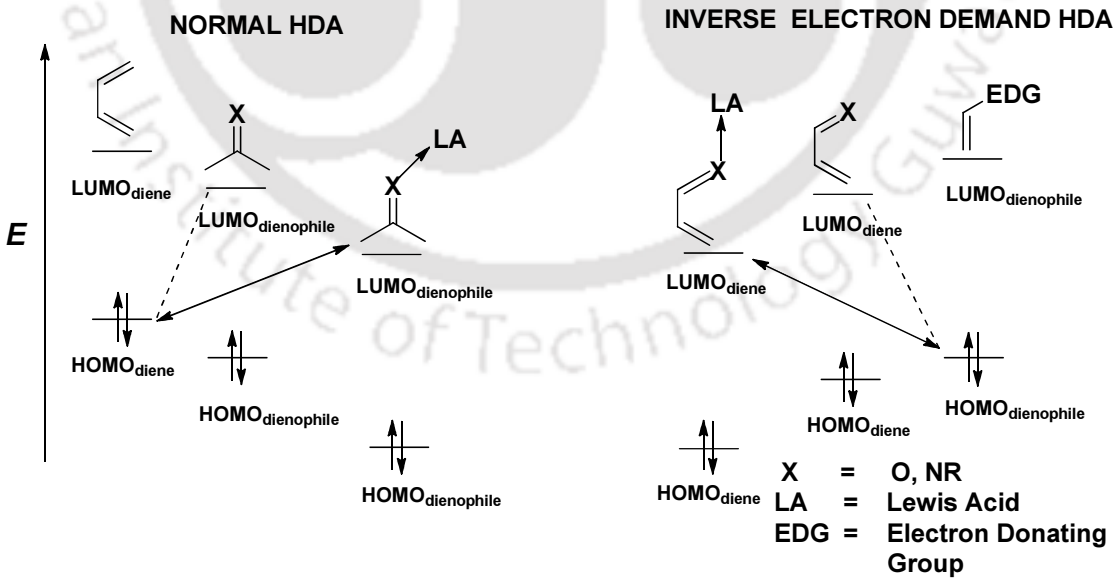


Figure 3. A FMO diagram of the normal (left; $HOMO_{diene}$-$LUMO_{dienophile}$-controlled) and inverse electron demand HDA reaction (right; $LUMO_{diene}$-$HOMO_{dienophile}$-controlled) in the absence and presence of lewis acid.

acid to a heteroatom of the 1,3-diene, leading to a decrease of the $LUMO_{diene}$ and $HOMO_{dienophile}$ energies, and thus based on a FMO way of reasoning, a more favorable interaction with the electron-rich alkene takes place (Figure 3, right, solid line).

4. Stereochemical features of the reaction

The stereochemistry of a product formed in aza-HDA or Povarov reaction depends on the face-selective approach of the electron rich alkene i.e., the dienophile toward the aza-diene: the aza-diels-alder reaction can proceed endo or exo as shown in Figure 4.

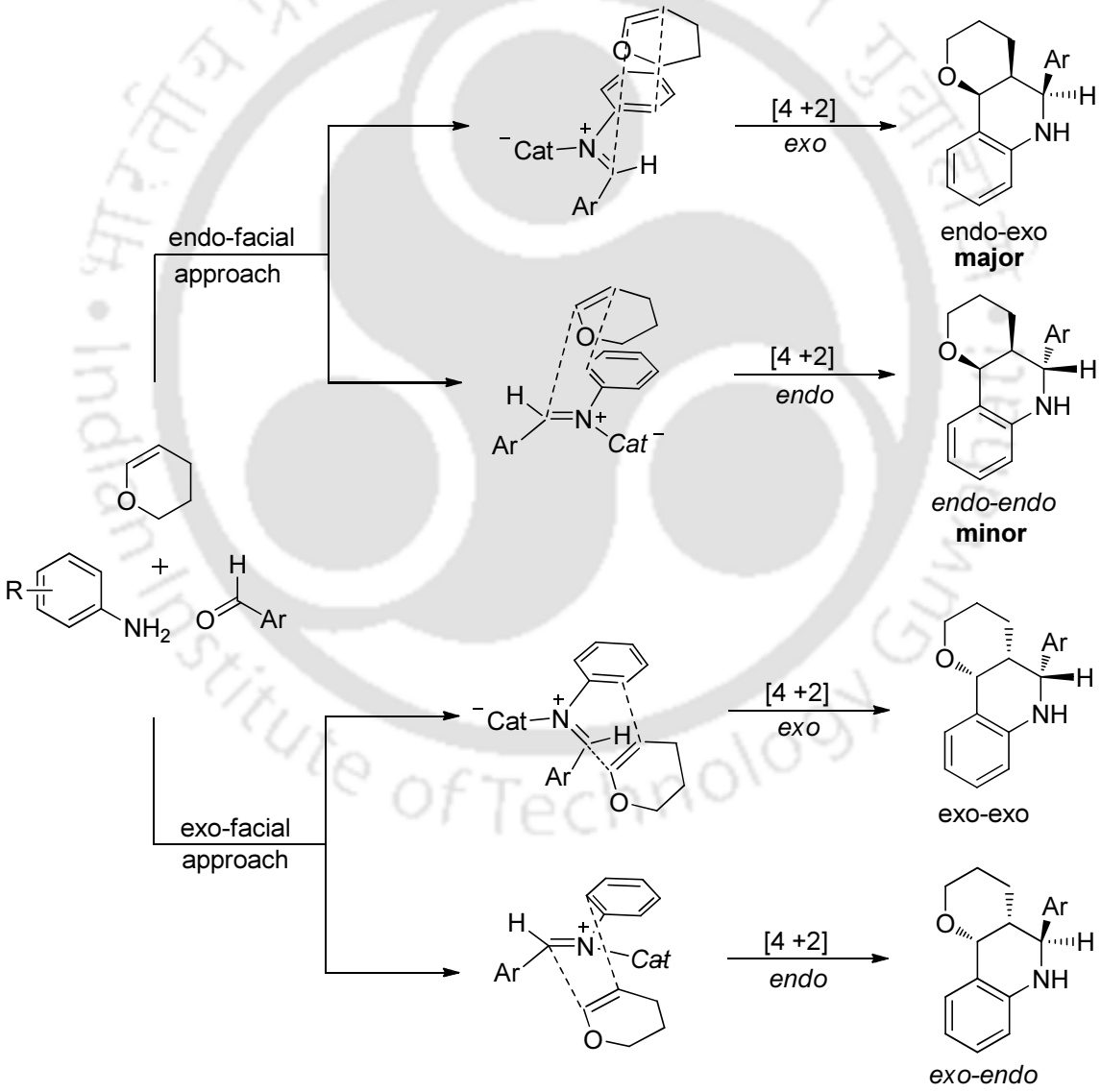


Figure 4

In each case, the ratio of diastereomers formed (*endo-endo or endo-cis* and *endo-exo* or *endo-trans*) is determined by the types of the catalyst and solvent; most often, trans-isomers slightly predominate[11c, 12d-e, 21a, 23a,33] which was caused by steric effects of substituents in the transition state, although the opposite case is also observed.[11d, 25a,34,35]

5. Reaction Mechanism

Two mechanistic pathways[36] have generally been taken into account for the aza-DA reaction. (i) a concerted [4 + 2]-like mechanism or (ii) a stepwise Mannich-like process as shown in Figure 5. Povarov et al.[4] assumed that the reactions of aromatic Schiff bases with activated alkenes proceed as conjugated [4+2] cycloaddition. However, more recent numerous experimental studies,[25a, 26c,37,38] provided evidence in favour of the stepwise mechanism of the coupling of aromatic Schiff bases with activated alkenes catalysed by the Lewis or Brønsted acids.

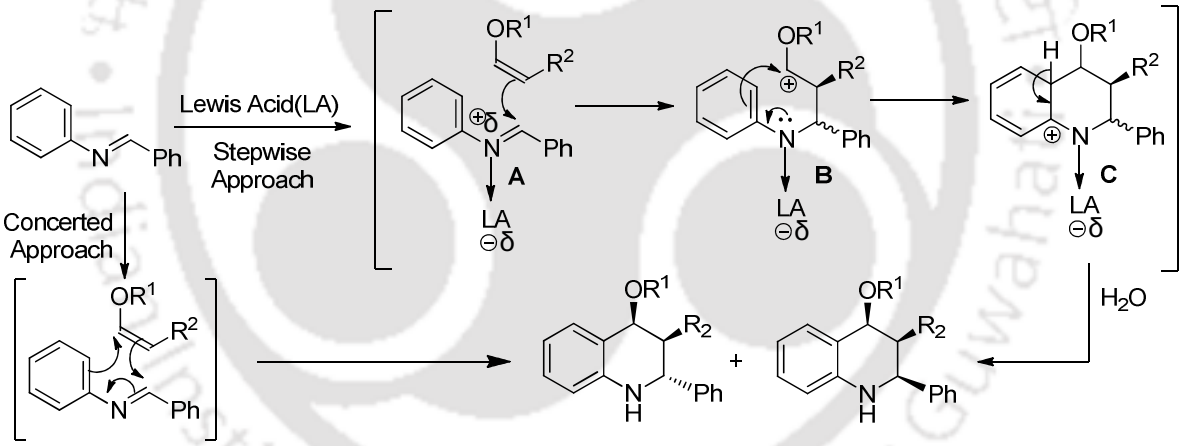
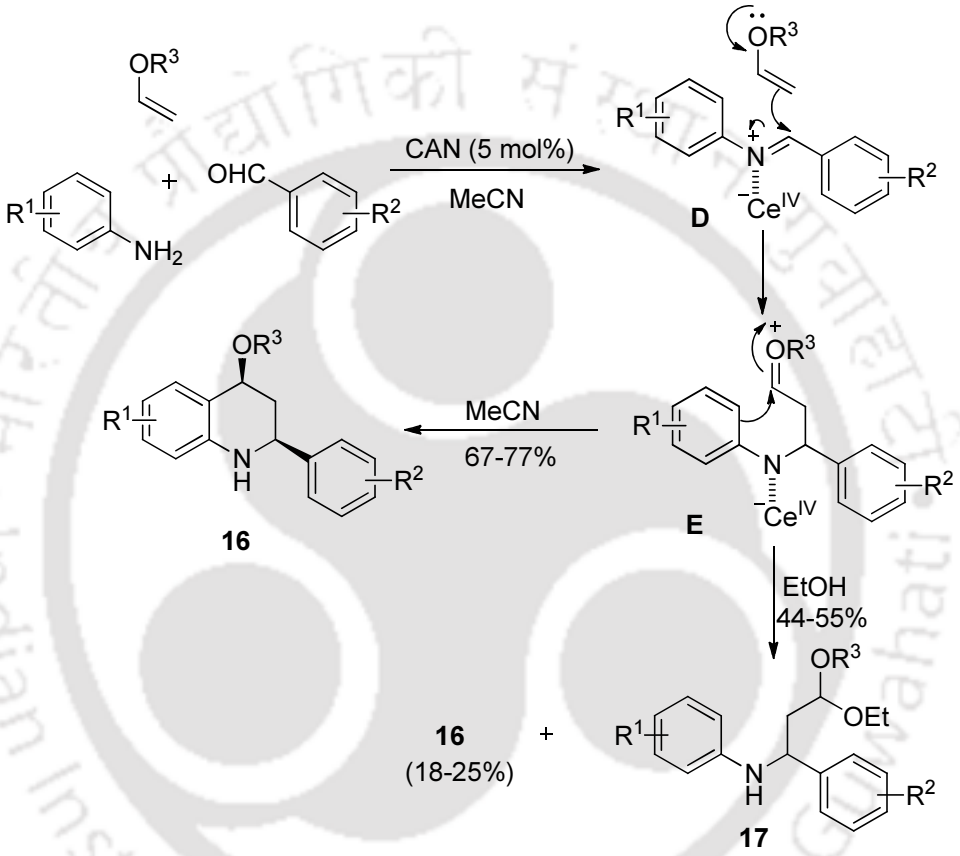


Figure 5

To study the mechanism of Povarov reaction, Menédez and co-workers performed the CAN catalyzed three-component reaction between arylamines, aromatic aldehydes and vinyl ethers for the diastereoselective synthesis of 4-alkoxy-2-ary-1,2,3,4-tetrahydroquinolines (**16**)[39] in good yields and diastereoselectivity (dr = 92:8 to 97:3), regardless of the nature of the substituents on the *N*-aryl ring (Scheme 7). Interestingly, when the reaction was carried out in ethanol, acetals **17** were isolated as the major products together with small amounts of tetrahydroquinolines **16**. It was clear from this observation that the vinyl ethers added to the Lewis acid (CAN)-activated *N*-aryl imine **D** generate the oxonium species **E**, which

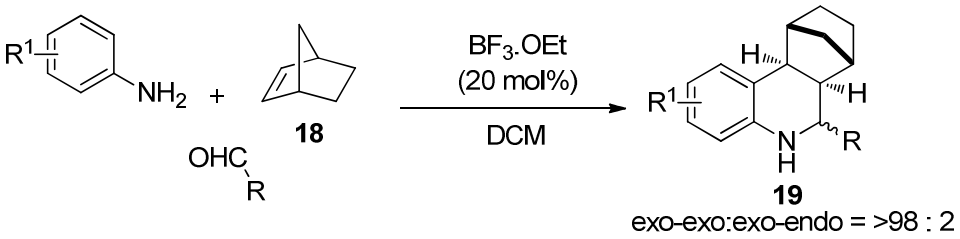
subsequently underwent an intramolecular electrophilic substitution reaction to afford tetrahydroquinolines **16**. On the other hand, when the reaction was performed in ethanol, the oxonium species **E** was trapped by the nucleophilic solvent to furnish acetals **17**, for confirming the generation of the carbocation intermediate. The stepwise mechanism is shown in Scheme 7.



Scheme 7

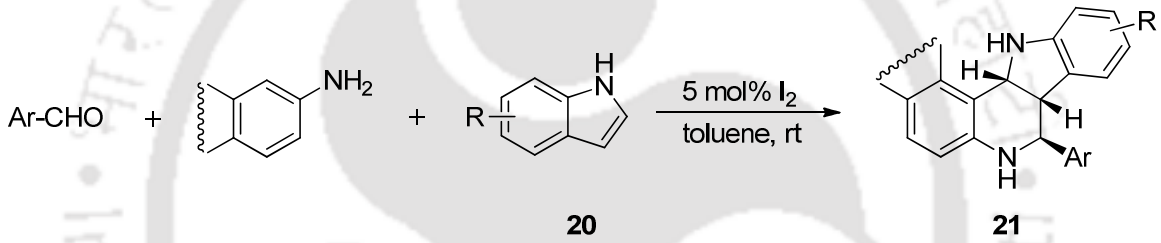
6. Povarov reaction through MCR approach:

Recently, Batey and his co-workers demonstrated the $BF_3{\cdot}OEt_2$-catalyzed three-component reaction of aromatic aldehydes, aromatic amines and strained norbornene-derived dienophiles (**18**) for the diastereoselective synthesis of bridged tetrahydroquinolines (**19**) in good to excellent yields.[40] with *exo*-facial selectivity as shown in Scheme 8.



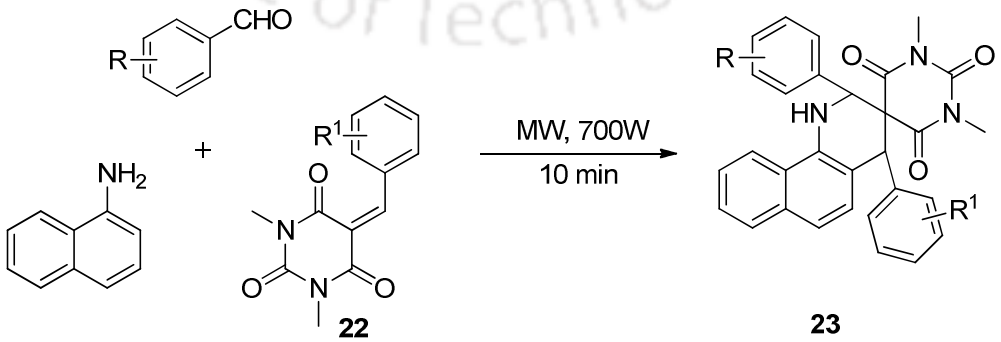
Scheme 8

Wang et al. reported an iodine-catalyzed Povarov reaction using MCR by employing indole **20**, as a dienophile as shown in Scheme 9. The three-component reaction of aromatic aldehydes, different amines and an indole has been proved to be an efficient method for the synthesis of *exo*-indolo[3,2-c]quinoline derivatives **21**, in good yield with high stereoselectivity.[34]



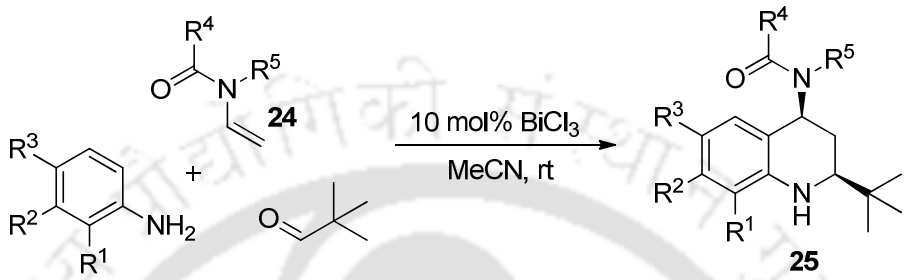
Scheme 9

Prajapati and co-workers developed a microwave-assisted, one-pot three-component aza-Diels–Alder reaction strategy where 5-benzylidene-1,3-dimethyl pyrimidine-2,4,6-trione (**22)** has been used as dienophile component. The protocol describes the synthesis of spiroquinoline derivatives **23**, from 1-aminonaphthalene, aromatic aldehyde, and 5-benzylidene-1,3-dimethyl pyrimidine-2,4,6-trione without catalyst- in solvent-free conditions as shown in Scheme 10.[41]



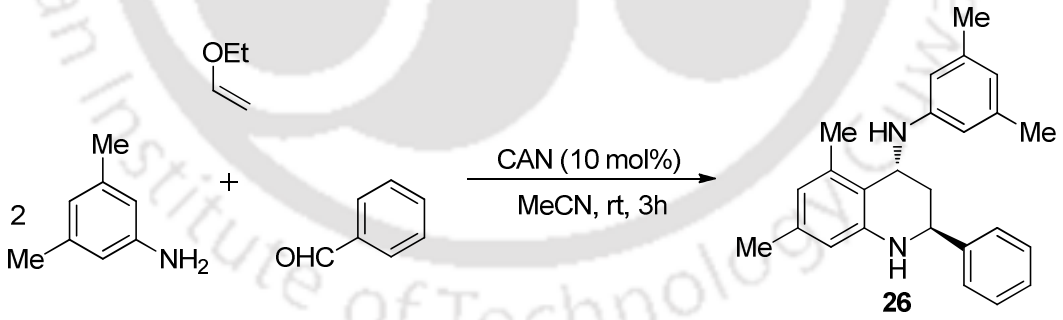
Scheme 10

Recently, Kouznetsov et al. reported the use of *N*-vinyl amide **24**, as dienophile in Povarov reaction. The protocol describes the $BiCl_3$-catalyzed one-pot preparation of these *cis*-4-amido-*N*-yl-2-*tert*-butyl-1,2,3,4-tetrahydroquinolines **25**, using the aliphatic aldehydes and anilines, and *N*-vinyl amide as shown in Scheme 11.[42]



Scheme 11

However, Menéndez et al. developed an efficient method for the synthesis of *trans*-2-aryl-4-arylamino-tetrahydroquinolines (**26**) from 3,5-disubstituted anilines (2 eqiv.), vinyl ethers (1 eqiv.) and aromatic aldehydes (1 eqiv.) in presence of 10 mol% CAN in MeCN at room temperatures as shown in Scheme 12.[43] From the above observations of Kouznetsov and Menéndez, it is well established that the diastereoselectivity of the Povarov reaction can be controlled by tuning the reaction condition.



Scheme 12

Thus, it can be concluded that the Povarov reaction or multicomponent *aza*-DA reaction is a well-established synthetic strategy for the generation of moderate to large libraries of related *N*-heterocyclic compounds such as highly functionalized tetrahydroquinolines with well-defined stereochemistry. Many natural products or intermediates have been synthesized

involving this reaction as a key step. Thus we were motivated to work on this promising field of chemistry to synthesize new heterocyclic compounds.

In Part B of my dissertation, we have aimed for the synthesis of *N*-heterocycles such as tetrahydroquinoline, pyridocoumarin and tetrahydropyridocoumarin derivatives through MCRs. The successful results will be discussed in Chapters IIB, IIIB, IVB and VB respectively along with a brief review on the importance of the synthesized products as well as their methods of preparation.

PART B

CHAPTER IIB

Ferric sulfate [$Fe_2(SO_4)_3.xH_2O$]: an efficient heterogeneous catalyst for the synthesis of tetrahydroquinoline derivatives

Review
Result & Discussion
Experimental

Tetrahydroquinoline and its importance

The tetrahydroquinoline ring system is a very common structural motif found in numerous biologically active natural products and pharmacologically relevant therapeutic agents. Because of their importance in drug discovery and medicinal chemistry, the development of new methodologies for the synthesis of tetrahydroquinoline derivatives has been found to be a very active field of research, as evidenced from the appearance of large number of articles in this area during the past decade. Tetrahydroquinoline derivatives exhibit interesting biological activities. For example, 2-aryl-2,3-dihydro-4-quinolone (**27**) showed antitumor activity[44] and 2-aryl-1,2,3,4-tetrahydroquinoline (**28**) is a core structure of the compounds possessing lipoxygenase inhibitor properties as well as potential therapeutic application in asthma[45] as shown in Figure 6.

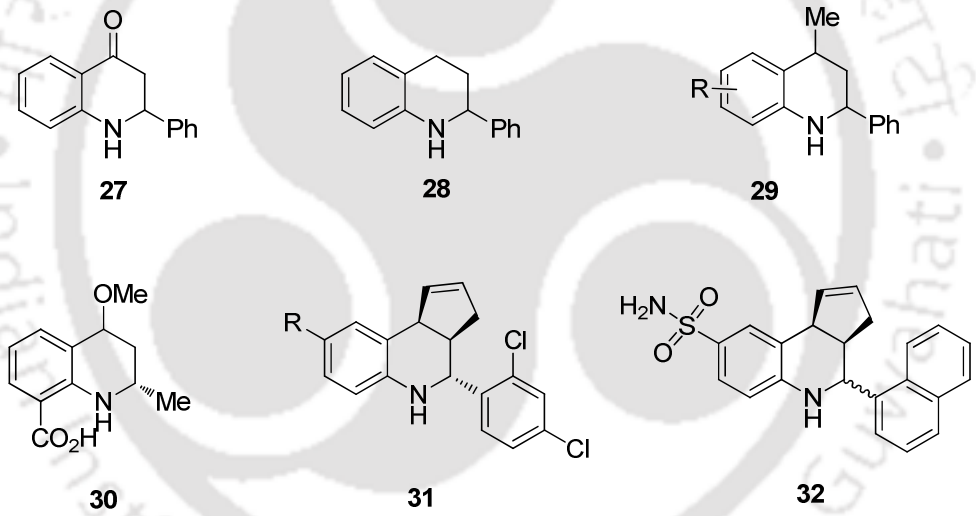


Figure 6. Some biologically active tetrahydroquinoline derivatives

Among various tetrahydroquinolines and their analogues, the compounds (**29**) was shown to have antifungal activity,[46] which was attributed mainly to chitin synthase inhibition property of this compounds. Helquinoline (**30**), a tetrahydroquinoline antibiotic isolated from *Janibacter limosus* species, also showed antibacterial activity.[47] Tetrahydroquinolines (**31**),[48] were identified as agonists of the calcium-activated potassium channel (BKCa), one of which was shown to reduce neuronal excitability by inducing membrane hyperpolarization following a large potassium ion efflux. Tetrahydroquinolines (**32**) is a positive allosteric modulator of the R7 nicotinic

acetylcholine receptor[49] as shown in Figure 7. The naturally occurring 1,2,3,4-tetrahydroquinoline alkaloids **33**[50] were isolated from Streptomyces sp., which show inhibitory activity against glutamate toxicity and lipid peroxidation. A couple of novel pyrroloquinoline alkaloids (**34**), martinellic acid and martinelline[51] were isolated from the roots of the tropical plant *Martinella iquitosensis* and many attempts have been made for their synthesis by various research groups.[52]

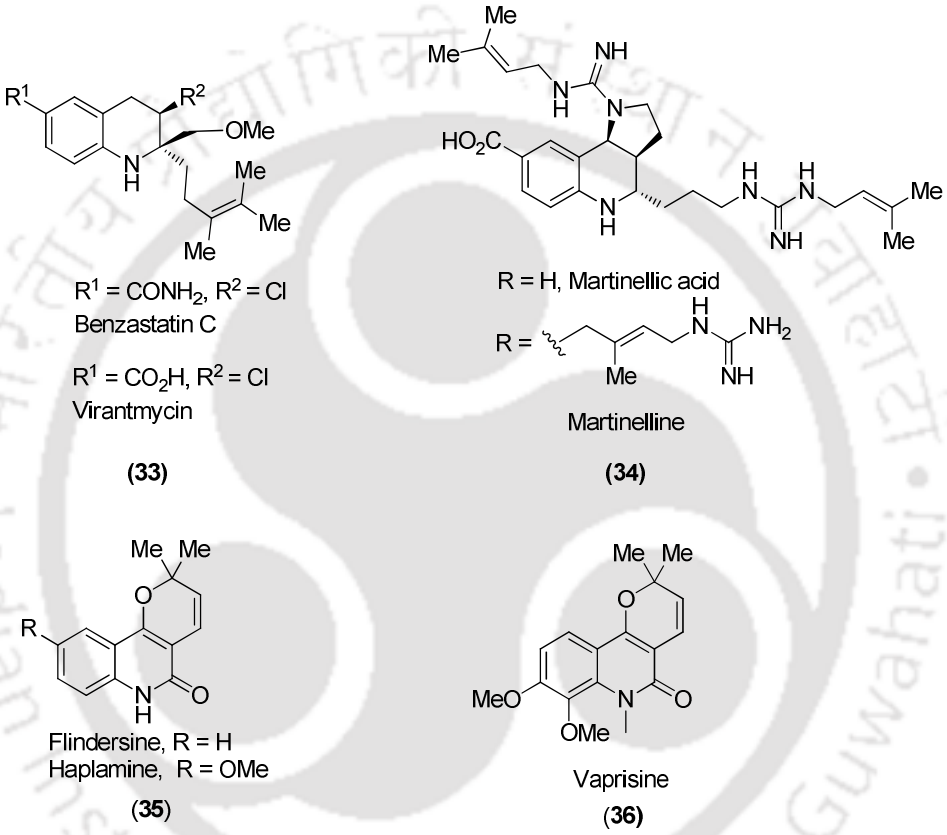


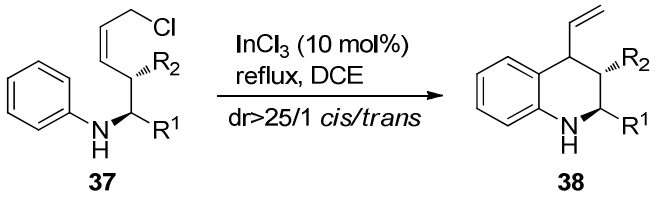
Figure 7. Alkaloids containing tetrahydroquinoline structural motif

Pyranoquinoline moiety is present in many alkaloids[53] such as flindersine and its derivative (**35**), and vaprisine (**36**). They also possess a wide range of biological activities such as psychotropic activity,[54] anti-allergic activity,[55] anti-inflammatory activity,[56] estrogenic activity[57] and used as potential pharmaceuticals.[58]

Some of the recent methods for tetrahydroquinoline derivatives

Schneider et al. reported the synthesis of highly enantiomerically enriched 1,2,3,4-tetrahydroquinolines **38**, in good yields with excellent diastereoselectivity from allyl

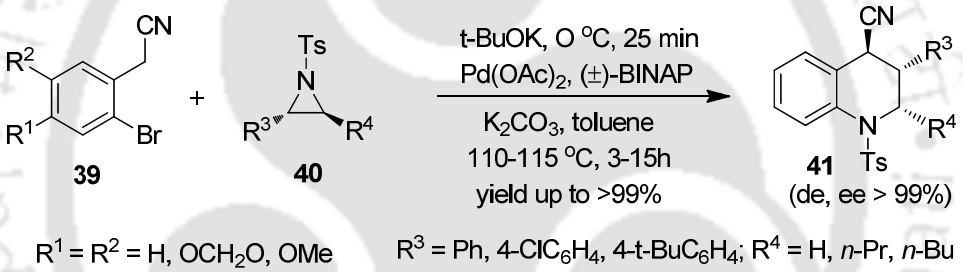
chlorides tethered to an *N*-aryl moiety via $InCl_3$ catalyzed Friedel-Crafts reactions as shown in Scheme 13.[59]



37 **38**

Scheme 13

Later on, Ghorai and his co-workers demonstrated a useful strategy for the synthesis of optically active substituted tetrahydroquinolines **41**, through regio- and stereoselective manner via ring opening of *N*-tosylaziridines with carbon nucleophiles generated from 2-(bromoaryl)acetonitriles followed by palladium-catalyzed intramolecular C-N cyclization in excellent yields and stereoselectivity as shown in Scheme 14.[60]

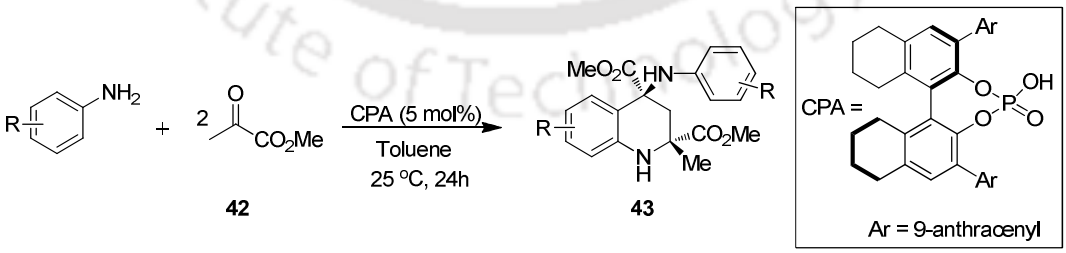


39 **40** **41**

$R^1 = R^2 = H, OCH_2O, OMe$ $R^3 = Ph, 4\text{-}ClC_6H_4, 4\text{-}t\text{-}BuC_6H_4; R^4 = H, n\text{-}Pr, n\text{-}Bu$

Scheme 14

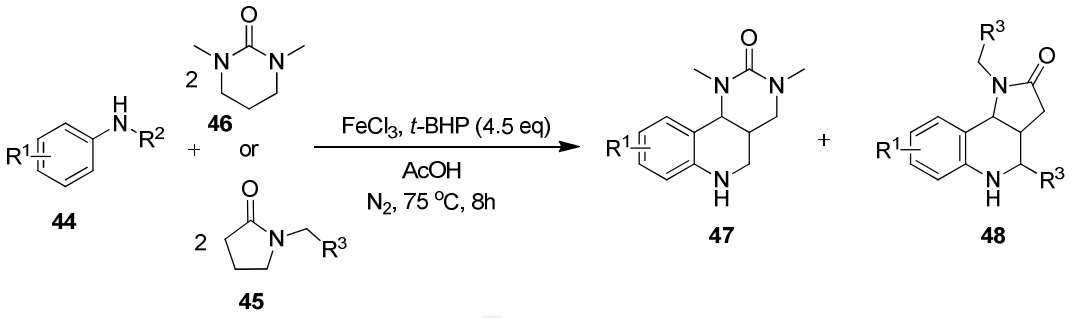
Huang and co-workers described asymmetric synthesis of tetrahydroquinoline derivatives **43** containing two quaternary stereogenic centers with excellent *ee* and *dr* via a four-component cyclization reaction of anilines with activated ketones such as pyruvates catalyzed by a chiral phosphoric acid as shown in Scheme 15.[61]



42 **43**

Scheme 15

Bao et al. reported a new one-pot synthesis of tricyclic tetrahydroquinolines **47** and **48** *via* multiple cross-dehydrogenative-coupling (CDC reactions) from arylamines and lactams catalyzed by $FeCl_3$ as shown in Scheme 16.[62]



Scheme 16

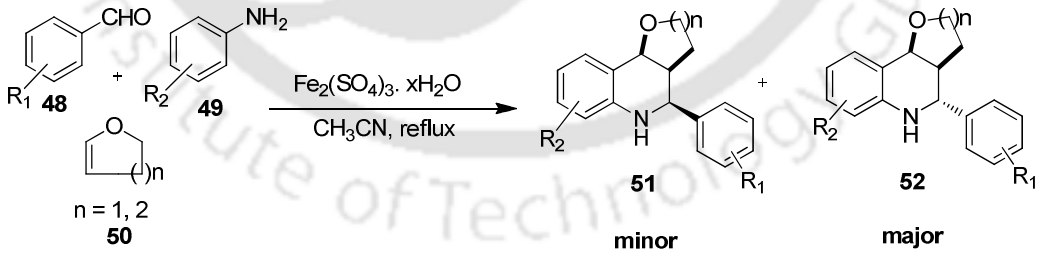
Among several synthetic strategies, the *aza*-Diels-Alder reaction between *N*-arylimine with electron rich dienophile can be considered as powerful method for the construction of tricyclic tetrahydroquinoline ring systems. From this literature review, we have found that tetrahydroquinoline skeleton exists in many natural products and many non-natural derivatives are also widely used in the pharmaceutical and biochemical fields. Some of them such as pyrano- and furanoquinolines, have attracted special attention as a result of high degrees of structural diversity with wide range of biological activities. Due to its pharmaceutical importance, the development of new methods for the construction of a tetrahydroquinoline framework is in continuous interest to the synthetic organic chemists.

Recently, multicomponent reactions (MCRs) have received considerable attention among synthetic chemists for construction of complex molecules, which has been elaborated in Chapter IA. The [4+2] aza-Diels-alder reaction between *N*-arylimines (heterodiene) and dihydropyran or dihydrofuran (dienophiles) under Lewis acid catalysis conditions have long been well recognized as one of the most convenient methods for the synthesis of tetrahydroquinolines. For the aza-DA reaction, it has been found that in situ generated diene is preferred over a preformed heterodiene, leading to a one-pot procedure, which is especially useful when the diene is unstable, sensitive to moisture and difficult to purify by column chromatography. From the pioneering work of Povarov, which was discussed in details in Chapter IB, this approach has been used for the synthesis of fused tetrahydroquinoline derivatives by employing aromatic aldehydes, aromatic amines and 3,4-dihydropyran (DHP) or 2,3-dihydrofuran in the presence of suitable catalysts via multicomponent reaction. These reactions have been extensively studied with numerous catalysts such as proline triflate,[63a] 4-nitrophthalic acid,[63b] SmI_2,[63c] $NbCl_5$,[63d] TMSCl,[63e] lanthanide triflates,[63f] silica chloride or amberlyst-15,[63g] $GdCl_3$,[63h] I_2[23,63i] and $SbCl_3$.[63j] Very recently, $Mg(ClO_4)_2$,[64a] $SnCl_2$,[64b] and polyaniline-*p*-toluene sulfonate[64d] have been

found to be effective catalysts for the synthesis of the pyranoquinoline derivatives. Some of these methods are associated with certain limitations such as use of excess catalyst.[63h,i] In addition, some of them are expensive[63f] and non-reusable catalyst. Consequently, there is a further scope to find out a greener catalyst, which may provide a better yield, good selectivity and improved methodology for the synthesis of tetrahydroquinoline derivatives.

In recent years, ferric sulfate [$Fe_2(SO_4)_3 \cdot xH_2O$] has received considerable attention as a mild, inexpensive and reusable catalyst for various organic transformations such as tetrahydropyranylation of alcohols,[65a] preparation of acylals from aldehydes,[65b] 2,3-unsaturated glycosides via Ferrier rearrangement[65c] and per-*O*-acetylation of sugars,[65d] and synthesis of pyrazole.[65e] The unique solubility of the catalyst in acetonitrile/ethanol and insolubility in DCM enables its uses as both homogenous and heterogenous catalyst; and it is easily recovarable at the end of reactions by adding DCM. Due its wide applicability as an effective catalyst, we presume that it would be an efficient catalyst for the one-pot three-component synthesis of the fused tetrahydroquinoline derivatives by employing Povarov reaction.

In this chapter we would like to discuss that ferric sulfate catalyzed the imino-DA of 3,4-dihydro-2H-pyran or 2,3-dihydrofuran with *N*-arylimines generated in situ from aromatic aldehydes and aromatic amines in acetonitrile under reflux condition as shown in Scheme 17.



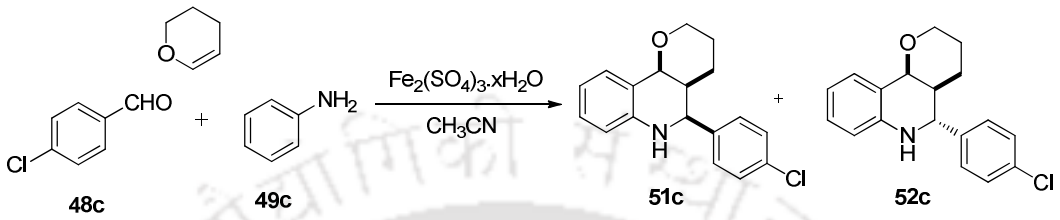
Scheme 17

Result and Discussion

For the present study, the mixture of benzaldehyde (1 mmol), aniline (1 mmol) and 3,4-dihydropyran (DHP) (1 mmol) was treated with 10 mol% of $Fe_2(SO_4)_3.xH_2O$ in acetonitrile (2 mL) at room temperature. Pyranoquinolines **51c** and **52c** were obtained in 54% combined yield with good diastereoselectivity (30:70). For optimizing the amount

catalyst and choosing the suitable solvent, various trial reactions were carried out with a combination of 4-chlorobenzaldehyde, aniline and 3,4-dihydropyran. The results and observations are summarized in Table 2.

Table 2. Optimisation of reaction conditions



48c 49c 51c 52c

Entry	Solvent	Catalyst (mol%)	Temperature	Time (h)	Ratio[a] (**51c** : **52c**)	Yield[b] (%)
1	CH_3CN	10	rt	12	30 : 70	54
2	CH_3CN	05	reflux	03	20 : 80	66
3	**CH_3CN**	**10**	**reflux**	**1.5**	**19 : 81**	**87**
4	CH_3CN	15	reflux	1.5	24 : 76	85
5	EtOH	10	reflux	03	19 : 81	62
6	CH_2Cl_2	10	reflux	12	20:80	20
7	DMF	10	reflux	04	17 : 83	56
8	$PhCH_3$	10	reflux	08	--	trace
9	H_2O	10	reflux	10	29 : 71	68

[a]The product ratio was determined from ^1H NMR spectra. [b]Isolated yields.

It was noted that 10 mol% of the catalyst provides the best result for the formation of product under reflux conditions. It has also been observed that acetonitrile is conducive for the present reaction as compared to other solvents such as ethanol, dichloromethane, dimethylformamide, toluene and water. After optimizing the reaction conditions, the mixture of benzaldehyde (1 mmol), aniline (1 mmol) and 3,4-dihydropyran (1 mmol) in acetonitrile was treated with 10 mol% $Fe_2(SO_4)_3.xH_2O$ under identical reaction conditions and the desired tetrahydroquinoline derivatives **51a** and **52a** were obtained in

87% combined yield. The products were characterized by ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. The ^{1}H NMR spectra and ^{13}C NMR spectra of the products **51a, 52a, 51d, 52d, 52q, 51s** and **52s** are given in Figures **10-16**, respectively in the experimental section. The absorption peaks for compound **51a** appeared at 3380 cm^{-1} in the IR spectrum, which indicates the presence of NH group. Similarly, it shows signals at δ = 1.26-1.60 (m, 4 H), 2.15 (m, 1 H), 3.43 (td, J = 2.4 Hz, 11.2 Hz, 1 H, OCH_2), 3.58 (dd, J = 4.0 Hz, 11.2 Hz, 1 H, OCH_2), 3.87 (br s, 1 H, NH), 4.68 (d, J = 2.0 Hz, 1 H, OCH_2), 5.33 (d, J = 5.6 Hz, 1 H, *CHPh*), 6.06 (d, J = 8.0 Hz, 1 H), 6.79 (t, J = 7.2 Hz, 1 H), 7.09 (t, J = 8.0 Hz, 1 H), 7.28-7.43 (m, 6 H) ppm in ^{1}H NMR spectrum. Likewise, in ^{13}C NMR signals appeared at δ = 18.2, 25.6, 39.2, 59.5, 60.8, 73.0, 114.6, 118.5, 121.1, 127.0, 127.7, 127.8, 128.3, 128.6, 141.3, 145.4 ppm. Similarly, the absorption peaks for compound **52b** appeared at 3357 in the IR spectrum for NH group. The compound **52b** shows signals at δ = 1.26-1.34 (m, 1 H), 1.42-1.48 (m, 1 H), 1.59-1.68 (m, 1 H), 1.78-1.89 (m, 1 H), 2.05-2.12 (m, 1 H), 3.71 (td, J = 2.0 Hz, 11.2 Hz, 1 H, OCH_2), 4.02-4.12 (m, 2 H, OCH_2, *NH*), 4.38 (d, J = 2.8 Hz, 1 H, OCH_2), 4.70 (d, J = 10.8 Hz, 1 H, *CHPh*), 6.50 (d, J = 8.0 Hz, 1 H), 6.69 (t, J = 7.6 Hz, 1 H), 7.07 (t, J = 7.6 Hz, 1 H), 7.21 (d, J = 7.2 Hz, 1 H), 7.29-7.42 (m, 5 H) ppm in ^{1}H NMR spectrum. ^{13}C NMR signals for compound **52b** appeared at δ = 22.2, 24.3, 39.1, 55.0, 68.8, 74.8, 114.3, 117.6, 120.8, 128.0, 128.1, 128.8, 129.5, 131.1, 142.5, 144.9 ppm. The stereochemistry of the fused ring junctures and other positions were established from their coupling constant values. The coupling constant between H_{4a} and H_{10b} ($J_{4a,10b}$) was found to be 2.0-2.9 Hz for all the products indicating a *cis* ring junction between the quinoline and pyran rings.

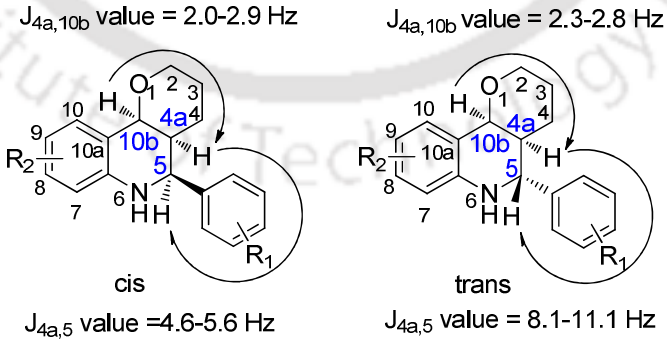


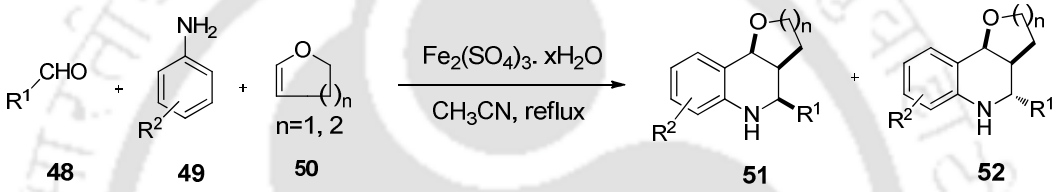
Figure 8. Coupling constant values used for determining stereochemistry

Similarly, the coupling constant value between H_{4a} and H_5 ($J_{4a,5}$) was found to be 5.6 Hz in **51a** indicates the *cis* relationship, whereas the coupling constant value is 10.8 Hz in

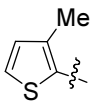
case of *trans* isomer **52a** as shown in Figure 8, which is in agreement with the reported literature value.

The reaction with various substituted aromatic aldehydes such as Me, OMe, Cl, Br, and NO_2 with aniline and 3,4-dihydropyran were carried out under the same reaction conditions. The reaction time, % yield and *cis:trans* ratio of the products **51** and **52** are shown in Table 3 (entries **b-g**). Likewise, various other aldehydes such as 2-furaldehyde, 2-naphthaldehyde and 3-methyl-2-thiophenecarboxaldehyde were reacted with aniline and dihydropyran under identical reaction conditions to provide the desired imino-Diels-Alder products (Table 3, entries **h-j**).

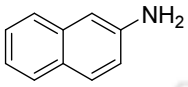
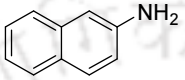
Table 3. Scope of various substituted pyrano/furanotetrahydroquinoline derivatives



48 **49** **50** **51** **52**

Entry	R^1	2	n	Time (h)	Yield[a] (%)	Ratio[b] (51 : 52)
a	Ph	$PhNH_2$	2	1.5	87	22 : 78
b	4-Me-Ph	$PhNH_2$	2	1.0	91	20 : 80
c	4-Cl-Ph	$PhNH_2$	2	1.5	87	19 : 81
d	4-Br-Ph	$PhNH_2$	2	1.5	89	22 : 78
e	4-MeO-Ph	$PhNH_2$	2	1.0	88	19 : 81
f	3-NO_2-Ph	$PhNH_2$	2	1.5	84	23 : 77
g	4-NO_2-Ph	$PhNH_2$	2	1.5	86	18 : 82
h	2-furyl	$PhNH_2$	2	1.5	82	21 : 79
i	2-naphthyl	$PhNH_2$	2	1.5	86	21 : 79
j		$PhNH_2$	2	1.5	78	0 : 100
k	Ph	4-Me-$PhNH_2$	2	1.0	92	20 : 80
l	Ph	4-Cl-$PhNH_2$	2	1.5	89	14 : 86

Continued

m	Ph	4-MeO-PhNH$_2$	2	1.0	91	21 : 79
n	Ph	4-Br-PhNH$_2$	2	1.5	87	17 : 83
o	4-Cl-Ph	4-Cl-PhNH$_2$	2	1.0	91	20 : 80
p	Ph		2	2.5	82	0 : 100
q	2-naphthyl		2	1.5	85	0 : 100
r	4-Me-Ph	PhNH$_2$	1	1.5	87	23:77
s	2-furyl	PhNH$_2$	1	1.5	82	22:78
t	Ph	4-Cl-PhNH$_2$	1	1.5	85	21:79

[a]Isolated yields. [b]The product ratio was determined from crude ^{1}H NMR spectra.

Furthermore, reactions with several substituted anilines were also studied with aromatic aldehydes and dihydropyran with the same amount of catalyst under similar reaction conditions (Table 3, entries **k-o**). The desired products **51k-o** and **52k-o** were obtained in good yields with similar diastereoselectivity. In case of 2-naphythylamine we have also isolated the *trans* products **52p** and **52q** exclusively.

The structure of compound **52q** was determined through single crystal XRD data as shown in Figure 9. However, 4-hydroxybenzaldehyde did not provide the desired tetrahydroquinoline on reaction with amine and DHP under identical conditions even after prolonging the reaction for 12 h. Similarly, 4-nitroaniline also did not undergo Povarov reaction with other aromatic aldehydes. The scope of presented protocol was verified with other enol ether e.g. 2,3-dihydrofuran (Table 3, entries **r-t**).

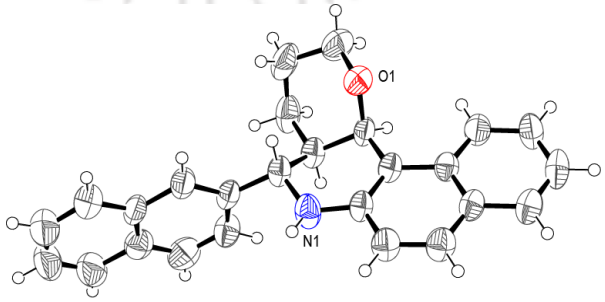
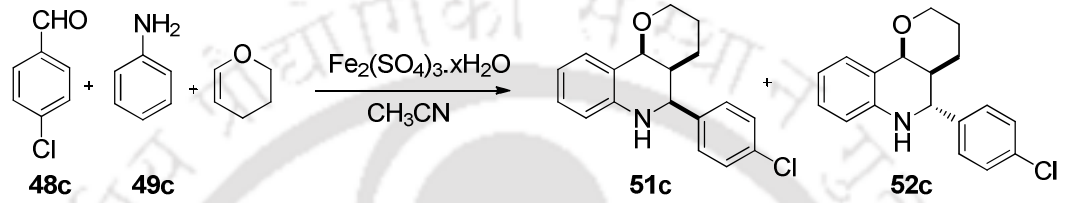


Figure 9. Single crystal X-ray structure of **52q** (CCDC no. 793766)

In view of a greener chemistry, the efficient recovery of the catalyst is highly desirable. In the present protocol, the catalyst $Fe_2(SO_4)_3 \cdot xH_2O$ can be recovered conveniently from the reaction mixture at the end of the reaction. The reusability of the recovered catalyst was examined and the results are summarized in Table 4. It clearly indicates that the catalyst can be reused for three successive times without losing activity.

Table 4. Results of the study on the recovery and reusability of $Fe_2(SO_4)_3 \cdot xH_2O$[a]



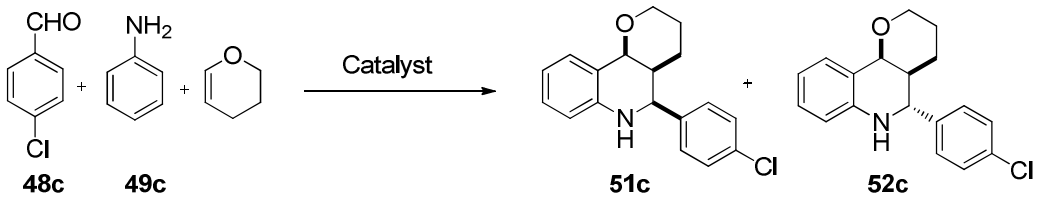
48c **49c** **51c** **52c**

Round	Catalyst recovered/mg	Reaction time (h)	Ratio[b] **51c** : **52c**	Yield[c](%)
1	415	1.5	19 : 81	87
2	410	1.5	21 : 79	86
3	405	1.6	20 : 80	84

[a]Reaction was carried out with 10 mmol scale. [b]The product ratio was determined from ^{1}H NMR spectra. [c]Isolated yields.

The efficiency and generality of the present protocol can be realized at a glance by comparing our results with those of some reported procedures as shown in Table 5. The results have been compared with respect to the mole percent of the catalyst used, yields and diastereoselectivity. The similar Povarov Reaction was reported by Laszlo and co-workers using $FeCl_3$ in combination of other co-catalyst.[11b] It is worthy to mention that the present protocol provides better diastereoselectivity and avoidance of co-catalyst as compare to $FeCl_3$ method. Considering all these parameters, we believe that $Fe_2(SO_4)_3 \cdot xH_2O$ is a better catalyst for Povarov Reaction.

Table 5. Comparison of our result with other results using different catalysts



48c **49c** **51c** **52c**

Entry	Catalyst	Amount	Condition	Time (h)	Ratio[a] **51a** : **52a**	Yield[b,c]
1	$FeCl_3$	10 mol %	rt	6	50 : 50	82[11b]
2	Proline triflate	5 mol %	rt	5	25 : 75	85[63a]
3	4-Nitrophthalic acid	25 mol %	50 °C	3.5	39 : 61	90[63b]
4	I_2	30 mol %	rt	3	23 : 77	84[63i]
5	**$Fe_2(SO_4)_3 \cdot xH_2O$**	**10 mol %**	**reflux**	**1.5**	**19 : 81**	**87**

[a]The product ratio was determined from ^{1}H NMR spectra. [b]Isolated yields. [c]Reported method with other catalysts.

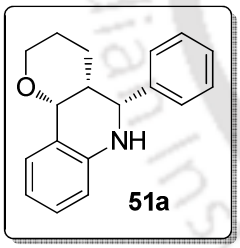
In conclusion, we have demonstrated that $Fe_2(SO_4)_3 \cdot xH_2O$ is a useful catalyst for one-pot povarov reaction for the synthesis of pyrano- and furano[3,2-c]quinoline derivatives. In comparison to other Lewis acids catalyst, it has found to be effective, mild and less expensive. In addition, it requires shorter reaction times, provides better yields and diastereoselectivity. Moreover due to its recyclability, the present method may open up an environmentally benign pathway for the synthesis of fused pyrano- and furano-tetrahydroquinolines.

General procedure for the synthesis of tetrahydroquinoline derivatives:

Into a 25 mL round bottom flask, a mixture of aniline (1 mmol) and benzaldehyde (1 mmol) in acetonitrile (2 mL) was taken and left for stirring for 10 min at room temperature. Then, enol ether (1 mmol) and the catalyst ferric sulfate (0.042 g, 10 mol%) were added successively into the above reaction mixture. Finally, the reaction flask is fitted with a reflux condenser and kept for refluxing in a pre-heated oil-bath. The progress of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was removed in a rotatory evaporator and it was extracted with dichloromethane (2 x 15 mL). The organic layer was washed with water and dried over anhydrous sodium sulfate. Dichloromethane was removed and the crude residue was passed through a silica gel (60-120 mesh) column. The products **51a** was eluted first followed by **52a** in ethyl acetate/hexane (05:95) in 87 % overall yield after column chromatographic separation. Similar procedure was followed for synthesizing other tetrahydroquinoline derivatives.

Spectral data of Compounds

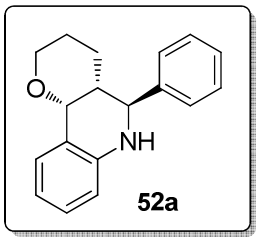
pyrano[3,2-c]quinoline ***(51a):***



51a

White solid (0.051 g, 19%): m.p. 130°C; R_f (5% ethyl acetate/hexane) 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.26-1.60 (m, 4 H), 2.15 (m, 1 H), 3.43 (td, J = 2.4 Hz, 11.2 Hz, 1 H), 3.58 (dd, J = 4.0 Hz, 11.2 Hz, 1 H), 3.87 (br s, 1 H), 4.68 (d, J = 2.0 Hz, 1 H), 5.33 (d, J = 5.6 Hz, 1 H), 6.06 (d, J = 8.0 Hz, 1 H), 6.79 (t, J = 7.2 Hz, 1 H), 7.09 (t, J = 8.0 Hz, 1 H), 7.28-7.43 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.2, 25.6, 39.2, 59.5, 60.8, 73.0, 114.6, 118.5, 121.1, 127.0, 127.7, 127.8, 128.3, 128.6, 141.3, 145.4; **IR** (KBr): 3380, 3309, 3023, 2940, 2869, 1607 cm^{-1}. **Anal. Calcd** for $C_{18}H_{19}NO$ (265.35): C, 81.47; H, 7.22; N, 5.28; found C, 81.20; H, 7.10; N, 5.40.

pyrano[3,2-c]quinolone ***(52a):***

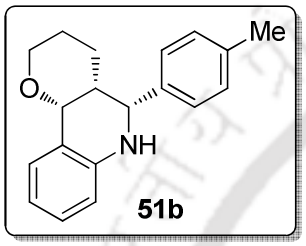


52a

Viscous liquid (0.180 g, 68%); R_f (5% ethyl acetate/hexane) 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.26-1.34 (m, 1 H), 1.42-1.48 (m, 1 H), 1.59-1.68 (m, 1 H), 1.78-1.89 (m, 1 H), 2.05-2.12 (m, 1 H), 3.71 (td, J = 2.0 Hz, 11.2 Hz, 1 H), 4.02-4.12 (m, 2 H), 4.38 (d, J = 2.8

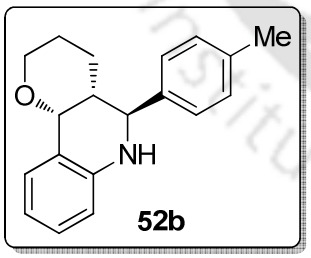
Hz, 1 H), 4.70 (d, J = 10.8 Hz, 1 H), 6.50 (d, J = 8.0 Hz, 1 H), 6.69 (t, J = 7.6 Hz, 1 H), 7.07 (t, J = 7.6 Hz, 1 H), 7.21 (d, J = 7.2 Hz, 1 H), 7.29-7.42 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.2, 24.3, 39.1, 55.0, 68.8, 74.8, 114.3, 117.6, 120.8, 128.0, 128.1, 128.8, 129.5, 131.1, 142.5, 144.9; **IR** (KBr): 3357, 3020, 2938, 2860, 1598 cm^{-1}. **Anal. Calcd** for $C_{18}H_{19}NO$ (265.35): C, 81.47; H, 7.22; N, 5.28; found C, 81.68; H, 7.13; N, 5.15.

*pyrano[3,2-c]quinoline (**51b**):*



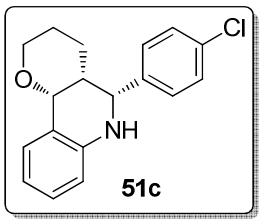
White solid (0.051 g, 18%): m.p. 126°C; R_f (5% ethyl acetate/hexane) 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.30-1.36 (m, 1 H), 1.42-1.57 (m, 3 H), 2.11-2.17 (m, 1 H), 2.36 (s, 3 H), 3.43 (td, J = 2.8 Hz, 8.0 Hz, 1 H), 3.56-3.60 (m, 1 H), 3.87 (br s, 1 H), 4.66 (d, J = 2.0 Hz, 1 H), 5.32 (d, J = 5.2 Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.79 (t, J = 7.6 Hz, 1 H), 7.09 (t, J = 8.0 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.42 (d, J = 6.8, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.3, 21.3, 25.7, 39.2, 59.3, 60.9, 73.0, 114.6, 118.4, 120.1, 126.9, 127.9, 128.3, 129.3, 137.4, 138.3, 143.5; **IR** (KBr): 3363, 3318, 2931, 2863, 1605, 1518 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO$ (279.38): C, 81.68; H, 7.58; N, 5.01; found C, 81.85; H, 7.48; N, 5.15.

*pyrano[3,2-c]quinolone (**52b**):*



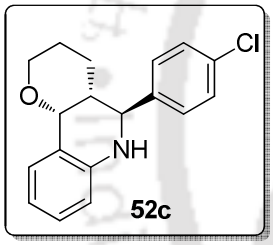
White solid (0.203 g, 73%): m.p. 123°C; R_f (5% ethyl acetate/hexane) 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.28-1.35 (m, 1 H), 1.44-1.52 (m, 1 H), 1.64 (tt, J = 4.4 Hz, 13.6 Hz, 1 H), 1.84 (qt, J = 4.4 Hz, 12.4 Hz, 1 H), 2.02-2.10 (m, 1 H), 2.36 (s, 3 H), 3.72 (td, J = 2.4 Hz, 11.6 Hz, 1 H), 4.08-4.12 (m, 2 H), 4.38 (d, J = 2.8 Hz, 1 H), 4.68 (d, J = 10.8 Hz, 1 H), 6.50 (d, J = 8.0 Hz, 1 H), 6.69 (t, J = 7.6 Hz, 1 H), 7.08 (td, J = 2.0 Hz, 8.4 Hz, 1 H), 7.16-7.22 (m, 3 H), 7.31 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.3, 22.2, 24.3, 39.0, 54.6, 68.8, 74.8, 114.3, 117.5, 120.8, 126.4, 127.9, 128.5, 129.5, 131.1, 137.8, 139.5, 145.0; **IR** (KBr): 3370, 3019, 2937, 2855, 1609 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO$ (279.38): C, 81.68; H, 7.58; N, 5.01; found C, 81.39; H, 7.71; N, 5.13.

pyrano[3,2-c]quinoline ***(51c):***



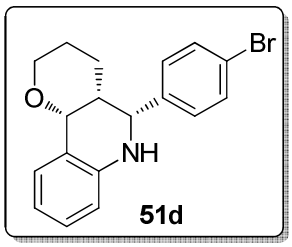
White solid (0.050 g, 17%): m.p. 170°C; R_f (5% ethyl acetate/hexane) 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.22-1.30 (m, 1 H), 1.43-1.55 (m, 3 H), 2.12 (m, 1 H), 3.42 (t, J = 11.2 Hz, 1 H), 3.59 (d, J = 11.2 Hz, 1 H), 3.82 (s, 1 H), 4.66 (s, 1 H), 5.31 (d, J = 5.2 Hz, 1 H), 6.61 (d, J = 8.0 Hz, 1 H), 6.81 (t, J = 7.6 Hz, 1 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.25-7.43 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.2, 25.6, 39.2, 59.0, 60.8, 72.8, 114.8, 118.8, 120.2, 127.8, 128.4, 128.7, 133.4, 139.9, 145.1; **IR** (KBr): 3388, 2940, 2894, 1604, 1485 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}ClNO$ (299.79): C, 72.11; H, 6.05; N, 4.67; found C, 72.00; H, 6.15; N, 4.76.

pyrano[3,2-c]quinoline ***(52c):***



White solid (0.211 g, 70%): m.p. 123°C; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.15-1.75 (m, 4 H), 1.91-1.94 (m, 1 H), 3.61 (t, J = 11.6 Hz, 1 H), 3.93 (s, 1 H), 3.98 (d, J = 11.6 Hz, 1 H), 4.27 (s, 1 H), 4.58 (d, J = 10.8 Hz, 1 H), 6.42 (d, J = 8.0 Hz, 1 H), 6.61 (t, J = 7.6 Hz, 1 H), 6.99 (t, J = 7.6 Hz, 1 H), 7.11 (d, J = 7.6 Hz, 1 H), 7.24 (s, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.2, 24.2, 39.1, 54.5, 68.8, 74.6, 114.4, 117.9, 120.9, 129.0, 129.3, 129.6, 131.1, 133.7, 141.0, 144.7; **IR** (KBr): 3368, 3018, 2936, 2852, 1609. 1588 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}ClNO$ (299.79): C, 72.11; H, 6.05; N, 4.67; found C, 71.95; H, 6.12; N, 4.74.

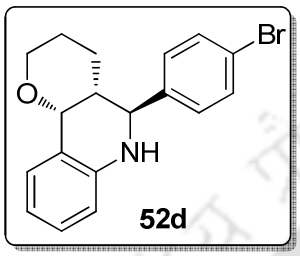
pyrano[3,2-c]quinoline ***(51d)****:*



White solid (0.067 g, 20%): m.p. 124°C; R_f (5% ethyl acetate/hexane) 0.34; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25-1.30 (m, 1 H), 1.42-1.57 (m, 3 H), 2.11-2.12 (m, 1 H), 3.42 (td, J = 2.0 Hz, 11.6 Hz, 1 H), 3.57- 3.61 (m, 1 H), 3.82 (br s, 1 H), 4.65 (d, J = 2.0 Hz, 1 H), 5.31 (d, J = 5.6 Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.81 (t, J = 7.6 Hz, 1 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.30 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 7.6 Hz, 1 H), 7.50 (dd, J = 2.4, 6.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.2, 25.6, 39.1,

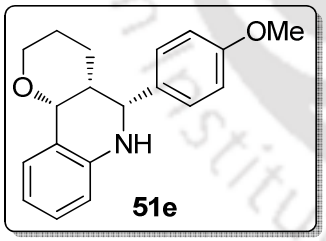
59.1, 60.8, 72.8, 114.8, 118.8, 120.2, 121.4, 127.8, 128.4, 128.7, 131.7, 140.4, 145.1; **IR** (KBr): 3445, 3379, 2932, 2851, 1605, 1482 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}BrNO$ (344.25) : calcd. C, 62.80; H, 5.27; N, 4.07; found C, 62.98; H, 5.19; N, 4.01

*pyrano[3,2-c]quinoline (**52d**):*



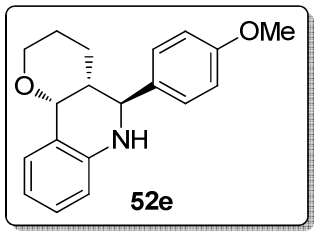
White solid (0.239 g, 69%): m.p. 133°C; R_f (5% ethyl acetate/hexane) 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.33-1.37 (m, 1 H), 1.42-1.47 (m, 1 H), 1.61-1.71 (m, 1 H), 1.75-1.83 (m, 1 H), 2.02-2.05 (m, 1 H), 3.72 (td, J = 2.0 Hz, 11.2 Hz, 1 H), 4.03 (br s, 1 H), 4.08-4.11 (m, 1 H), 4.38 (d, J = 2.4 Hz, 1 H), 4.69 (d, J = 10.8 Hz, 1 H), 6.53 (d, J = 8.4 Hz, 1 H), 6.72 (t, J = 7.6 Hz, 1 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.22 (d, J = 7.6 Hz, 1 H), 7.30 (d, J = 7.6 Hz, 2 H), 7.50 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.1, 24.2, 39.0, 54.4, 68.7, 74.5, 114.4, 117.8, 120.8, 121.7, 129.5, 129.6, 131.0, 131.9, 141.5, 144.6; **IR** (KBr): 3312, 2937, 2838, 1613. 1487 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}BrNO$ (344.25): calcd. C, 62.80; H, 5.27; N, 4.07; found C, 62.61; H, 5.19; N, 4.22.

*pyrano[3,2-c]quinoline **(51e):***



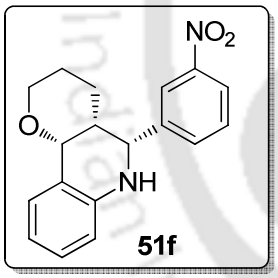
White solid (0.049 g, 17%): m.p. 159°C; R_f (5% ethyl acetate/hexane) 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.28-1.50 (m, 4 H), 2.11 (m, 1 H), 3.43 (t, J = 12.0 Hz, 1 H), 3.58 (d, J = 11.2 Hz, 1 H), 3.82 (bs, 4 H, OCH_3, NH), 4.64 (s, 1 H), 5.31 (d, J = 5.2 Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.79 (t, J = 7.6 Hz, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.11 (t, J = 7.6 Hz, 1 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.2, 25.7, 39.3, 55.5, 59.0, 60.9, 73.0, 113.9, 114.5, 118.4, 120.1, 127.8, 128.1, 128.3, 130.3, 133.3, 145.5; **IR** (KBr): 3397, 2995, 2930, 2855, 1595 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_2$ (295.38): C, 77.26; H, 7.17; N, 4.74; found C, 77.01; H, 7.06; N, 4.59

pyrano[3,2-c]quinoline ***(52e):***



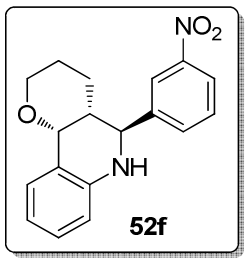
White solid (0.211 g, 71%): m.p. 132°C; R_f (5% ethyl acetate/hexane) 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.30-1.34 (m, 1 H), 1.46-1.50 (m, 1 H), 1.57-1.68 (m, 1 H), 1.81-1.85 (m, 1 H), 2.16-2.19 (m, 1 H), 3.72 (td, J = 2.4 Hz, 11.6 Hz, 1 H), 3.82 (s, 3 H), 4.02 (br s, 1 H), 4.10 (dd, J = 2.1 Hz, 3.9 Hz, 1 H), 4.40 (d, J = 2.4 Hz, 1 H), 4.68 (d, J = 10.8 Hz, 1 H), 6.52 (d, J = 8.4 Hz, 1 H), 6.70 (t, J = 7.2 Hz, 1 H), 6.91 (d, J = 8.8 Hz, 2 H), 7.09 (td, J = 1.2 Hz, 8.0 Hz, 1 H), 7.22 (d, J = 7.6 Hz, 1 H), 7.33 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.1, 24.2, 39.0, 54.2, 55.4, 68.8, 74.8, 114.1, 114.2, 117.4, 120.8, 129.0, 129.4, 131.0, 134.4, 145.0, 159.4; **IR** (KBr): 3365, 2997, 2930, 2830, 1597 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_2$ (295.38): calcd. C, 77.26; H, 7.17; N, 4.74; found C, 77.10; H, 7.28; N, 4.58.

pyrano[3,2-c]quinoline ***(51f)****:*



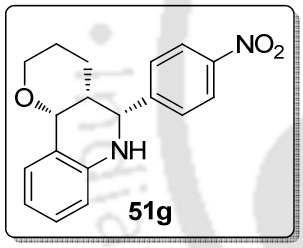
Yellow solid (0.060 g, 19%): m.p. 182°C; R_f (5% ethyl acetate/hexane) 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.19-1.25 (m, 1 H), 1.47-1.63 (m, 3 H), 2.18-2.25 (m, 1 H), 3.44 (td, J = 2.8 Hz, 11.6 Hz, 1 H), 3.59-3.60 (m, 1 H), 3.90 (br s, 1 H), 4.81 (d, J = 2.0 Hz, 1 H), 5.36 (d, J = 5.6 Hz, 1 H), 6.67 (d, J = 8.0 Hz, 1 H), 6.85 (t, J = 7.6 Hz, 1 H), 7.14 (t, J = 8.0 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.57 (t, J = 8.0 Hz, 1 H), 7.77 (d, J = 7.6 Hz, 1 H), 8.17-8.19 (m, 1 H), 8.33 (s, 1 H)); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.1, 25.4, 39.1, 59.1, 60.8, 72.7, 115.1, 119.3, 120.2, 121.9, 122.9, 127.9, 128.5, 129.6, 133.2, 143.7, 144.6, 148.6; **IR** (KBr): 3407, 3370, 2944, 2858, 1606, 1529 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}N_2O_3$ (310.35): C, 69.66; H, 5.85; N, 9.03; found: C, 69.50; H, 5.74; N, 9.18

pyrano[3,2-c]quinoline ***(52f):***



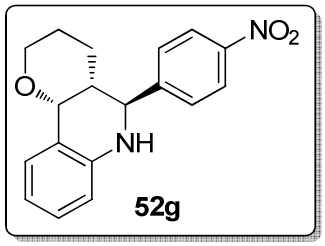
Yellow solid (0.201 g, 65%): m.p. 161°C; R_f (5% ethyl acetate/hexane) 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.38-1.42 (m, 2 H), 1.64-1.75 (m, 1 H), 1.79-1.90 (m, 1 H), 2.10-2.13 (m, 1 H), 3.45 (td, J = 2.0 Hz, 11.2 Hz, 1 H), 4.10-4.13 (m, 2 H), 4.41 (d, J = 2.8 Hz, 1 H), 4.85 (d, J = 10.8 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.76 (t, J = 7.6 Hz, 1 H), 7.12 (t, J = 7.6 Hz, 1 H), 7.24 (d, J = 7.6 Hz, 1 H), 7.56 (t, J = 8.0 Hz, 1 H), 7.77 (d, J = 7.6 Hz, 1 H), 8.17-8.20 (m, 1 H), 8.32 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.3, 24.3, 39.2, 54.7, 68.7, 74.3, 114.6, 118.4, 120.9, 122.9, 123.2, 129.7, 129.7, 131.0, 134.2, 144.3, 145.0, 148.8; **IR** (KBr): 3390, 2946, 2843, 1612, 1531, 1491 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}N_2O_3$ (310.35): C, 69.66; H, 5.85; N, 9.03; found: C, 69.48; H, 5.78; N, 9.16.

pyrano[3,2-c]quinoline ***(51g)****:*



Yellow solid (0.048 g, 15%): m.p. 151°C; R_f (5% ethyl acetate/hexane) 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.18-1.22 (m, 1 H), 1.45-1.60 (m, 3 H), 2.16-2.21 (m, 1 H), 3.44 (td, J = 2.8 Hz, 11.6 Hz, 1 H), 3.59-3.63 (m, 1 H), 3.90 (br s, 1 H), 4.81 (d, J = 2.8 Hz, 1 H), 5.35 (d, J = 5.6 Hz, 1 H), 6.58 (d, J = 7.6 Hz, 1 H), 7.17 (t, J = 7.6 Hz, 1 H), 7.54 (d, J = 8.8 Hz, 1 H), 7.62 (d, J = 8.8 Hz, 1 H), 8.08 (d, J = 8.8 Hz, 1 H), 8.19 (d, J = 8.8 Hz, 1 H), 8.26 (d, J = 9.2 Hz, 1 H), 8.40 (d, J = 8.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.2, 25.4, 39.1, 47.8, 60.8, 72.7, 113.1, 118.4, 120.2, 123.9, 127.8, 129.5, 130.7, 144.6, 147.5, 149.0; **IR** (KBr): 3407, 3076, 2987, 2856, 1601, 1530 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}N_2O_3$ (310.35): C, 69.66; H, 5.85; N, 9.03; found: C, 69.49; H, 5.76; N, 9.17.

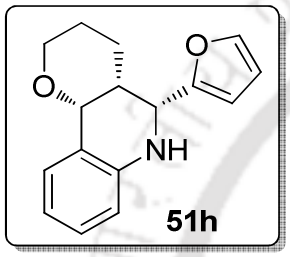
pyrano[3,2-c]quinoline ***(52g):***



Yellow solid (0.219 g, 71%): m.p. 181°C; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.36-1.44 (m, 2 H), 1.71 (tt, J = 4.8 Hz ,14.8 Hz, 1 H), 1.83 (qt, J = 4.0 Hz, 12.8 Hz, 1 H), 2.07-2.14 (m, 1 H), 3.74 (td, J = 2.4 Hz,

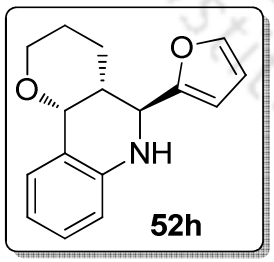
11.2 Hz, 1 H), 4.05-4.14 (m, 2 H), 4.40 (d, *J* = 2.8 Hz, 1 H), 4.84 (d, *J* = 10.4 Hz, 1 H), 6.58 (d, *J* = 8.0 Hz, 1 H), 6.76 (t, *J* = 7.2 Hz, 1 H), 7.13 (t, *J* = 7.2 Hz, 1 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.61 (d, *J* = 8.8 Hz, 2 H), 8.24 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.3, 24.3, 39.3, 54.8, 68.6, 74.2, 114.6, 118.4, 120.8, 124.1, 128.9, 129.7, 131.0, 144.3, 148.0, 150.3; **IR** (KBr): 3407, 3076, 2987, 2856, 1601, 1530 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}N_2O_3$ (310.35): calcd. C, 69.66; H, 5.85; N, 9.03; found: C, 69.81; H, 5.80; N, 8.90

pyrano[3,2-c]quinoline ***(51h):***



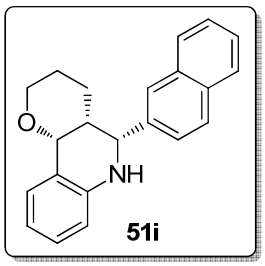
White solid (0.044 g, 17%): m.p. 121°C; R_f (5% ethyl acetate/hexane) 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.45-1.70 (m, 4 H), 2.34-2.42 (m, 1 H), 3.41 (t, *J* = 11.6 Hz, 1 H), 3.60 (dd, *J* = 4.4 Hz, 11.6 Hz, 1 H), 3.95 (br s , 1 H), 4.71 (d, *J* = 2.0 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 6.29 (d, *J* = 3.2 Hz, 1 H), 6.38 (dd, *J* = 2.0 Hz, 3.2 Hz, 1 H), 6.60 (d, *J* = 8.0 Hz, 1 H), 6.80 (t, *J* = 7.6 Hz, 1 H), 7.09 (t, *J* = 7.2 Hz, 1 H), 7.40 (d, *J* = 1.2 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.0, 25.5, 36.5, 54.0, 60.9, 72.1, 106.2, 110.4, 114.7, 118.8, 120.3, 127.9, 128.3, 141.8, 144.6, 154.3; **IR** (KBr): 3360, 3020, 2975, 2880, 1594 cm^{-1}. **Anal. Calcd** for $C_{16}H_{17}NO_2$ (255.31): calcd. C, 75.27; H, 6.71; N, 5.49; found: C, 75.39; H, 6.78; N, 5.37.

pyrano[3,2-c]quinoline ***(52h):***



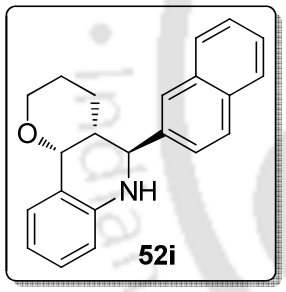
White solid (0.165 g, 65%): m.p. 131° C; R_f (5% ethyl acetate/hexane) 0.18; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.37-1.41 (m, 1 H), 1.53-1.57 (m, 1 H), 1.70-1.86 (m, 2 H), 2.24-2.29 (m, 1 H), 3.69 (td, *J* = 2.8, 11.2 Hz, 1 H), 4.04 (d, *J* = 11.2 Hz, 1 H), 4.07 (br s, 1 H), 4.41 (d, *J* = 2.8 Hz, 1 H), 4.82 (d, *J* = 10.8 Hz, 1 H), 6.34 (d, *J* = 3.2 Hz, 1 H), 6.35-6.37 (m, 1 H), 6.54 (d, *J* = 8.0 Hz, 1 H), 6.71 (t, *J* = 7.6 Hz, 1 H), 7.08 (t, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.40 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.3, 24.5, 37.3, 49.2, 68.3, 74.3, 107.7, 110.4, 114.7, 118.0, 120.8, 129.5, 130.8, 142.4, 144.3, 155.3; **IR** (KBr): 3360, 3020, 2975, 2880, 1594 cm^{-1}. **Anal. Calcd** for $C_{16}H_{17}NO_2$ (255.31): C, 75.27; H, 6.71; N, 5.49; found: C, 75.02; H, 6.78; N, 5.40

*pyrano[3,2-c]quinoline (**51i**):*



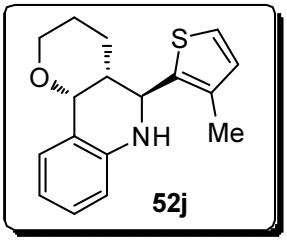
Colourless solid (0.057 g, 18%): m.p. 243°C; R_f (5% ethyl acetate/hexane) 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25-1.34 (m, 1 H), 1.40-1.65 (m, 3 H), 2.24-2.32 (m, 1 H), 3.45 (td, J = 2.0 Hz, 11.2 Hz, 1 H), 3.58-3.62 (m, 1 H), 4.0 (br s, 1 H), 4.58 (d, J = 2.4 Hz, 1 H), 5.38 (d, J = 5.6 Hz, 1 H), 6.67 (d , J = 8 Hz, 1 H), 6.82 (t, J = 7.2 Hz, 1 H), 7.13 (t, J = 8.0 Hz, 1 H), 7.45-7.53 (m, 4 H), 7.85-7.87 (m, 3 H), 7.90 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.4, 25.6, 39.1, 59.6, 60.9, 73.0, 114.7, 118.6, 120.2, 121.5, 125.3, 125.4, 126.1, 126.5, 127.9, 128.1, 128.3, 128.4, 133.2, 133.4, 138.8, 145.4; **IR** (KBr): 3370, 3019, 2937, 2855, 1609 cm^{-1}. **Anal. Calcd** for $C_{22}H_{21}NO$ (315.41): C, 83.78; H, 6.71; N, 4.44; found: C, 83.59; H, 6.59; N, 4.57.

*pyrano[3,2-c]quinoline (**52i**):*



Viscous liquid (0.214 g, 68%); R_f (5% ethyl acetate/hexane) 0.18; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25-1.34 (m, 1 H), 1.42-1.48 (m, 1 H), 1.65 (tt, J = 4.4 Hz, 14.0 Hz, 1 H), 1.91 (qt, J = 4.4 Hz, 12.4 Hz, 1 H), 2.18-2.22 (m, 1 H), 3,74 (td, J = 2.4 Hz, 11.6 Hz, 1 H), 4.10-4.17 (m, 2 H), 4.42 (d, J = 2.4 Hz, 1 H), 4.88 (d, J = 10.8 Hz, 1 H), 6.55 (d, J = 8 Hz, 1 H), 6.72 (t, J = 7.2 Hz, 1 H), 7.10 (t, J = 7.2 Hz, 1 H), 7.23-7.26 (m, 1 H), 7.46-7.53 (m, 2 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.80-7.88 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.2, 24.4, 38.9, 55.1, 68.9, 74.8, 114.4, 117.8, 121.0, 125.5, 126.2, 126.4, 127.3, 127.9, 128.0, 128.8, 129.6, 131.2, 133.4, 133.5, 139.8, 144.9; **IR** (KBr): 3370, 3019, 2937, 2855, 1609 cm^{-1}. **Anal. Calcd** for $C_{22}H_{21}NO$ (315.41): calcd. C, 83.78; H, 6.71; N, 4.44; found: C, 81.45; H, 7.45; N, 5.08

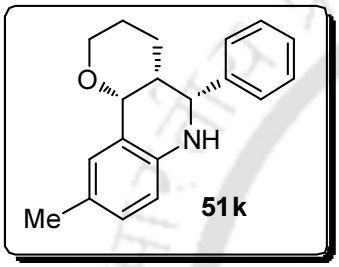
*pyrano[3,2-c]quinoline (**52j**):*



White solid (0.222 g, 78%): m.p. 120.7°C; R_f (5% ethyl acetate/hexane) 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.31-1.40 (m, 1 H), 1.54-1.62 (m, 1 H), 1.64-1.81 (m, 2 H), 2.02-2.11 (m, 1 H), 2.28 (s, 3 H), 3.69 (td, J = 2.4 Hz, 12.0 Hz, 1 H), 4.06-4.09 (m,

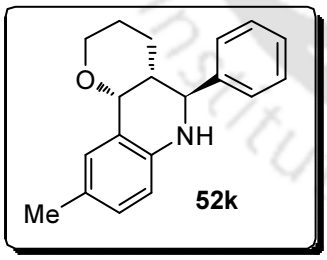
1 H), 4.12 (br s, 1 H), 4.37 (d, *J* = 2.8 Hz, 1 H), 5.06 (d, J = 10.8 Hz, 1 H), 6.48 (d, *J* = 8.0 Hz, 1 H), 6.69 (t, *J* = 7.6 Hz, 1 H), 6.78 (d, *J* = 4.8 Hz, 1 H), 7.06 (td, *J* = 1.6 Hz, 8.0 Hz, 1 H), 7.17-7.20 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.4, 22.5, 24.1, 40.6, 48.1, 68.9, 74.8, 114.3, 117.9, 120.7, 124.0, 129.5, 129.7, 131.1, 135.0, 139.7, 144.3; **IR** (KBr): 3375, 3087, 2935, 2857 1611 cm^{-1}. **Anal. Calcd** for $C_{17}H_{19}NOS$ (285.12): calcd. C, 71.54; H, 6.71; N, 4.91; S, 11.23; found: C, 71.35; H, 6.78; N, 4.81; S, 11.01.

pyrano[3,2-c]quinoline ***(51k):***



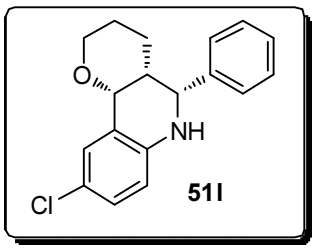
White solid (0.051 g, 18%): m.p. 130°C; R_f (5% ethyl acetate/hexane) 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.26-1.38 (m, 1 H), 1.41-1.44 (m, 1 H), 1.53-1.55 (m, 2 H), 2.12-2.19 (m, 1 H), 2.28 (s, 3 H), 3.44 (td, *J* = 2.8 Hz, 11.6 Hz, 1 H), 3.60-3.61 (m, 1 H), 3.76 (br s, 1 H), 4.65 (d, *J* = 2.4 Hz, 1 H), 5.31 (d, *J* = 5.2 Hz, 1 H), 6.54 (d, *J* = 8.0 Hz, 1 H), 6.92 (dd, *J* = 1.6 Hz, 8.0 Hz, 1 H), 7.25-7.28 (m, 1 H), 7.28-7.32 (m, 2 H), 7.35-7.43 (m, 3 H); **IR** (KBr): 3397, 2995, 2930, 1600 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO$ (279.38): C, 81.68; H, 7.58; N, 5.01; found: 81.44; H, 7.67; N, 5.16.

pyrano[3,2-c]quinoline ***(52k):***



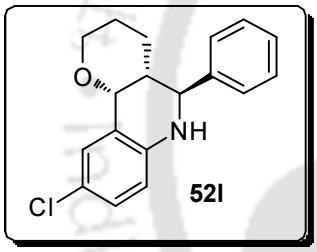
Viscous liquid (0.206 g, 74%); R_f (5% ethyl acetate/hexane) 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.29-1.32 (m, 1 H), 1.40-1.46 (m, 1 H), 1.51-1.65 (m, 1 H), 1.80-1.85 (m, 1 H), 2.05-2.09 (m, 1 H), 2.22 (s, 3 H), 3.70 (td, *J* = 2.4 Hz, 11.6 Hz, 1 H), 3.95 (br s, 1 H), 4.07-4.11 (m, 1 H), 4.35 (d, *J* = 2.4 Hz, 1 H), 4.67 (d, *J* = 10.8 Hz, 1 H), 6.45 (d, *J* = 8.0 Hz, 1 H), 6.90 (dd, *J* = 1.6 Hz, 8.0 Hz, 1 H), 7.03 (s, 1 H), 7.29-7.41 (m, 5 H); **IR** (KBr): 3390, 2995, 2925, 1595 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO$ (279.38): C, 81.68; H, 7.58; N, 5.01; found: C, 81.51; H, 7.50; N, 4.85.

pyrano[3,2-c]quinoline ***(51l):***



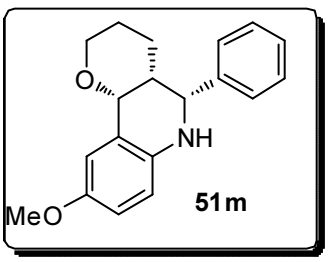
White solid (0.037 g, 12%): m.p. 170 °C; R_f (5% ethyl acetate/hexane) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.33-1.56 (m, 4 H), 2.15 (m, 1 H), 3.41 (t, J = 7.2 Hz, 1 H), 3.60-3.62 (m, 1 H), 3.89 (br s, 1 H), 4.66 (s, 1 H), 5.27 (d, J = 5.2 Hz, 1 H), 6.53 (d, J = 8.4 Hz, 1 H), 7.02-7.05 (m, 1 H), 7.26-7.39 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.0, 25.3, 38.6, 59.3, 60.8, 72.4, 115.6, 121.6, 123.1, 126.8, 127.3, 127.7, 128.0, 128.4, 140.7, 143.7; **IR** (KBr): 3398, 3000, 2940, 2865, 1600 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}ClNO$ (299.11): calcd. C, 72.11; H, 6.05; N, 4.67; found: C, 72.26; H, 6.19; N, 4.51.

pyrano[3,2-c]quinoline ***(52l)*:**



White solid (0.229 g, 77%): m.p. 124°C; R_f (5% ethyl acetate/hexane) 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.33-1.37 (m, 1 H), 1.45-1.48 (m, 1 H), 1.61-1.70 (m, 1 H), 1.78-1.85 (m, 1 H), 2.04-2.07 (m, 1 H), 3.07 (td, J = 2.4 Hz, 10.8 Hz, 1 H), 4.07 (dd, J = 2.1 Hz, 10.8 Hz, 1 H), 4.34 (d, J = 2.8 Hz, 1 H), 4.67 (d, J = 10.4 Hz, 1 H), 6.45 (d, J = 8.8 Hz, 1 H), 7.03 (dd, J = 2.4 Hz, 8.4 Hz, 1 H), 7.21 (d, J = 2.4 Hz, 1 H), 7.25-7.40 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.0, 24.0, 38.6, 54.9, 68.5, 73.9, 115.3, 121.8, 121.9, 127.7, 128.0, 128.7, 129.2, 130.4, 142.0, 143.3; **IR** (KBr): 3370, 3020, 2940, 2855, 1598 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}ClNO$ (299.11): C, 72.11; H, 6.05; N, 4.67; found: C, 72.16; H, 6.18; N, 4.53.

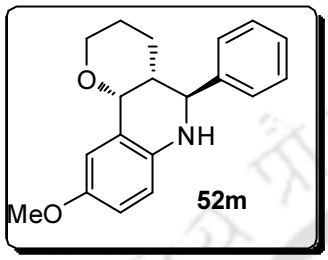
*pyrano[3,2-c]quinoline (****51m****)*:



White solid (0.056 g, 19%): m.p. 144°C; R_f (5% ethyl acetate/hexane) 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.25-1.33 (m, 1 H), 1.42-1.58 (m, 3 H), 2.14-2.17 (m, 1 H), 3.40-3.46 (m, 1 H), 3.58-3.66 (m, 2 H) 3.78 (s, 3 H), 4.62 (d, J = 2.0 Hz, 1 H), 5.31 (d, J = 5.6 Hz, 1 H), 6.57 (d, J = 8.8 Hz, 1 H), 6.72 (dd, J = 3.2 Hz, 8.8 Hz, 1 H), 7.03-7.04 (m, 2 H), 7.35-7.42 (m, 4 H); **^{13}C NMR** (100 MHz,

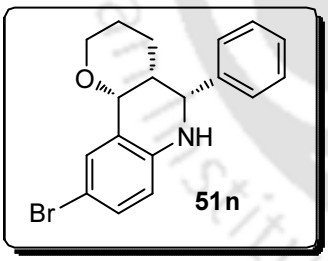
$CDCl_3$): δ = 17.9, 25.3, 39.1, 55.8, 59.6, 60.8, 72.9, 111.9, 115.0, 115.7, 121.1, 126.8, 127.4, 128.3, 139.1, 144.3, 152.9; **IR** (KBr): 3343, 3010, 2970, 2865, 1620 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_2$ (295.38): C, 77.26; H, 7.17; N, 4.74; found C, 77.18; H, 7.09; N, 4.69.

pyrano[3,2-c]quinoline ***(52m):***



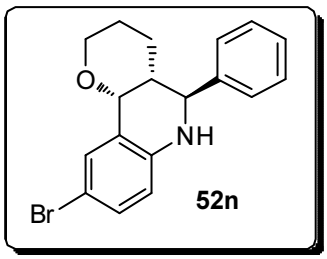
White solid (0.216 g, 72%): m.p. 100 °C; R_f (5% ethyl acetate/hexane) 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.32-1.35 (m, 1 H), 1.46-1.49 (m, 1 H), 1.60-1.68 (m, 1 H), 1.81-1.84 (m, 1 H), 2.09-2.11 (m, 1 H), 3.69-3.76 (m, 4 H), 4.10 (d, J = 11.2 Hz, 1 H), 4.38 (d, J = 2.8 Hz, 1 H), 4.67 (d, J = 10.4 Hz, 1 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.75 (dd, J = 2.8 Hz, 7.2 Hz, 1 H), 6.82 (d, J = 2.8 Hz, 2 H), 7.30-7.43 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.0, 24.1, 38.9, 55.9, 55.4, 68.5, 74.5, 114.8, 115.5, 116.8, 121.3, 126.2, 127.8, 128.5, 138.9, 142.3, 152.0; **IR** (KBr): 3345, 3015, 2985, 2860, 1615 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_2$ (295.38): C, 77.26; H, 7.17; N, 4.74; found C, 77.12; H, 7.25; N, 4.62.

pyrano[3,2-c]quinoline ***(51n):***



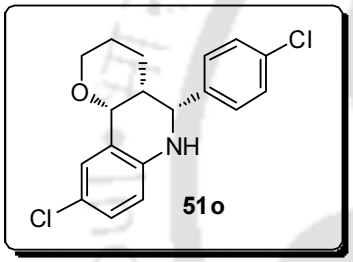
White solid (0.051 g, 15%): m.p. 137°C; R_f (5% ethyl acetate/hexane) 0.28; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.27-1.34 (m, 1 H), 1.39-1.62 (m, 3 H), 2.15-2.16 (m, 1 H), 3.38-3.45 (m, 1 H), 3.60-3.64 (m, 2 H), 4.66 (d, J = 2.0 Hz, 1 H), 5.27 (d, J = 5.4 Hz, 1 H), 6.50 (d, J = 8.4 Hz, 1 H), 7.17 (dd, J = 2.1 Hz, 8.7 Hz, 1 H), 7.31-7.42 (m, 5 H), 7.54 (s, 1 H); **IR** (KBr): 3400, 3000, 2935, 2845, 1600 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}BrNO$ (344.25): C, 62.80; H, 5.27; N, 4.07; found C, 62.52; H, 5.19; N, 4.15.

pyrano[3,2-c]quinoline ***(52n):***



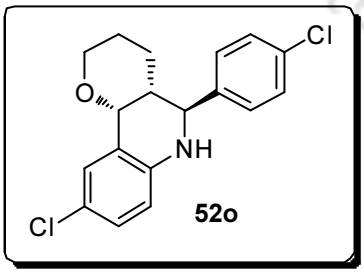
White solid (0.248 g, 72%): m.p. 130°C; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.34-1.38 (m, 1 H), 1.43-1.50 (m, 1 H), 1.60-1.72 (m ,1 H), 1.75-1.90 (m, 1 H), 2.08-2.10 (m, 1 H), 3.71 (td, J = 2.2 Hz, 11.4 Hz, 1 H), 4.07-4.11 (m, 1 H), 4.36 (d, J = 2.5 Hz, 1 H), 4.68 (d, J = 10.7 Hz, 1 H), 6.43 (d, J = 8.5 Hz, 1 H), 7.17 (dd, J = 2.3 Hz, 8.4 Hz, 1 H), 7.29-7.41 (m, 6 H), 7.54 (s, 1H); **IR** (KBr): 3396, 2997, 2932, 2855, 1595 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}BrNO$ (344.25): C, 62.80; H, 5.27; N, 4.07; found C, 62.62; H, 5.21; N, 4.18.

pyrano[3,2-c]quinoline ***51o:***



White solid (0.061 g, 18%): m.p. 188 °C; R_f (5% ethyl acetate/hexane) 0.38; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.23-1.30 (m, 1 H), 1.40-1.55 (m, 3 H), 2.08-2.22 (m, 1 H), 3.41 (td, J = 2.8 Hz, 11.6 Hz, 1 H), 3.59-3.62 (m, 1 H), 3.83 (br s, 1 H), 4.63 (d, J = 2.4 Hz, 1 H), 5.25 (d, J = 5.6 Hz, 1 H), 6.51 (d, J = 8.4 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 1 H), 7.26-7.39 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.9, 25.4, 38.8, 59.0, 61.0, 72.5, 116.1, 122.6, 127.5, 128.3, 126.8, 129.0, 129.3, 133.2, 137.7, 146.5; **IR** (KBr): 3389, 3068, 2926, 2868, 1598, 1497 cm^{-1}. **Anal. Calcd** for $C_{18}H_{17}Cl_2NO$ (334.24): calcd. C, 64.68; H, 5.13; N, 4.19; found: C, 64.52; H, 5.18; N, 4.07.

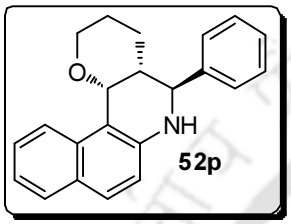
pyrano[3,2-c]quinoline ***(52o)****:*



White solid (0.243 g, 73%): m.p. 152 °C; R_f (5% ethyl acetate/hexane) 0.28; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.34-1.39 (m, 1 H), 1.41-1.48 (m, 1 H), 1.66 (tt, J = 4.4 Hz, 13.6 Hz, 1 H), 1.73-1.84 (m, 1 H), 1.98-2.04 (m, 1 H), 3.71 (td, J = 2.8 Hz, 11.2 Hz, 1 H), 4.06-4.10 (m, 2 H), 4.34 (d, J = 2.0 Hz, 1 H), 4.65 (d, J = 10.8 Hz, 1 H), 6.47 (d, J = 8.8 Hz, 1 H), 7.04 (dd, J = 2.4 Hz, 8.8 Hz, 1 H), 7.20 (d, J = 2.4 Hz, 1 H), 7.31-7.64 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.2, 24.1, 38.9, 54.6, 68.7, 74.0, 115.6, 122.1, 122.3, 129.1, 129.2,

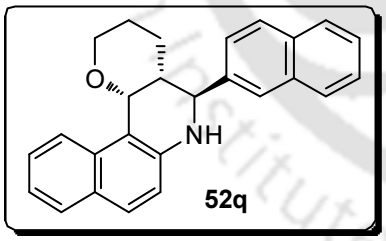
129.5, 130.6, 133.9, 140.7, 143.3; **IR** (KBr): 3344, 2932, 2845, 1612, 1491 cm^{-1}. **Anal. Calcd** for $C_{18}H_{17}Cl_2NO$ (334.24): C, 64.68; H, 5.13; N, 4.19; found: C, 64.81; H, 5.08; N, 4.11.

*pyrano[3,2-c]quinoline (**52p**):*



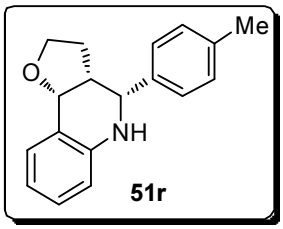
White solid (0.265 g, 82%): m.p. 204 °C; R_f (5% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.35-1.41 (m, 1 H), 1.52-1.56 (m, 1 H), 1.76 (tt, J = 5.2 Hz, 13.6 Hz, 1 H), 1.91 (qt, J = 4.0 Hz, 8.8 Hz, 1 H), 2.14-2.17 (m, 1 H), 3.86 (td, J = 2.0 Hz, 12.4 Hz, 1 H), 4.15-4.19 (m, 1 H), 4.24 (br s, 1 H), 4.86 (d, J = 11.6 Hz, 1 H), 4.98 (d, J = 2.4 Hz, 1 H), 6.73 (d, J = 8.8 Hz, 1 H), 7.20 (t, J = 7.6 Hz, 1 H), 7.33-7.49 (m, 6 H), 7.59 (d, J = 8.8 Hz, 1 H), 7.64 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.2, 24.4, 39.0, 54.9, 69.1, 71.5, 111.1, 117.8, 121.8, 122.0, 127.2, 128.3, 128.6, 129.0, 130.2, 133.9, 142.2, 142.7; **IR** (KBr): 3382, 3058, 2945, 2903, 2857, 2839, 1625, 1602 cm^{-1}. $C_{22}H_{21}NO$ (315.16): calcd. C, 83.78; H, 6.71; N, 4.44; found: C, 83.57; H, 6.79; N, 4.31.

*pyrano[3,2-c]quinoline (**52q**):*



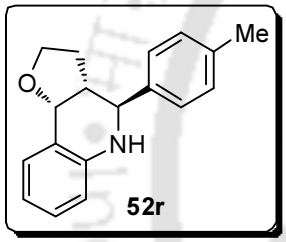
White solid (0.310 g, 85%): m.p. 214 °C; R_f (5% ethyl acetate/hexane) 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.30-1.34 (m, 1 H), 1.45-1.51 (m, 1 H), 1.70 (tt, J = 4.4 Hz, 9.2 Hz, 1 H), 1.87-1.97 (qt, J = 4.0 Hz, 8.8 Hz, 1 H), 2.20-2.30 (m, 1 H), 3.83 (t, J = 11.2 Hz, 1 H), 4.17 (dd, J = 3.6 Hz, 10.8 Hz, 1 H), 4.26 (br s, 1 H), 4.96 (s, 1 H), 4.99 (d, J = 7.6 Hz, 1 H), 6.69 (d, J = 8.8 Hz, 1 H), 7.20 (t, J = 7.6 Hz, 1 H), 7.42-7.50 (m, 3 H), 7.56 (t, J = 8.4 Hz, 2 H), 7.64 (d, J = 8.0 Hz, 1 H), 7.82-7.90 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.1, 24.3, 38.7, 54.9, 69.0, 71.4, 111.2, 117.9, 121.7, 122.0, 125.6, 126.2, 126.4, 127.2, 127.5, 127.9, 128.0, 128.1, 128.5, 128.7, 130.2, 133.4, 133.5, 133.9, 139.5, 142.7; **IR** (KBr): 3391, 3055, 2931, 2900, 2839, 1620, 1518 cm^{-1}. **Anal. Calcd** for $C_{26}H_{23}NO$ (365.18): C, 85.45; H, 6.34; N, 3.83; found: C, 85.14; H, 6.39; N, 3.71.

furo[3,2-c]quinoline ***(51r):***



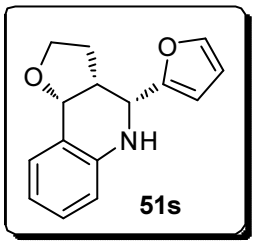
White solid, m.p. 114 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.49-1.56 (m, 1 H), 2.15-2.25 (m, 1 H), 2.36 (s, 3 H), 2.72-2.79 (m,1 H), 3.67-3.80 (m, 2 H), 4.65 (s, 1 H), 5.26 (d, J = 7.6 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.80 (t, J = 7.2 Hz, 1 H), 7.07 (t, J = 7.6 Hz, 1 H), 7.19 (d, J = 7.6 Hz, 2 H),7.34 (d, J = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.3, 24.9, 46.0, 57.5, 67.0, 76.2, 115.1, 119.3, 122.9, 126.6, 128.5, 129.5, 130.3, 137.5, 139.4, 145.3; **IR** (KBr): 3360, 3020, 2975, 2880, 1594 cm^{-1}. **Anal. Calcd** for $C_{18}H_{19}NO$ (265.35): C, 81.47; H, 7.22; N, 5.28. found: C, 81.23; H, 7.27; N, 5.18

furo[3,2-c]quinoline ***(52r):***



White solid, m.p. 121 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.65-1.74 (m, 1 H), 1.94-2.03(m, 1 H), 2.36 (s, 3 H), 2.37-2.45 (m, 1 H), 3.74 (d, J = 10.8 Hz, 1 H), 3.78-3.84 (m, 1H), 3.97-4.03 (m, 1 H), 4.10 (brs, 1 H), 4.57 (d, J = 5.2 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.77 (t, J = 7.2 Hz, 1 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.18 (d, J = 7.6 Hz, 2 H),7.31 (d, J = 8.0 Hz, 2 H) 7.37 (d, J = 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.3, 29.0, 43.5, 57.6, 65.3, 76.4, 114.8, 118.4, 120.2, 128.3, 129.1, 129.5, 131.4, 138.0, 138.9, 145.6; **IR** (KBr): 3331, 3020, 2978, 2879, 1610 cm^{-1}. **Anal. Calcd** for $C_{18}H_{19}NO$ (265.35): C, 81.47; H, 7.22; N, 5.28. found: C, 81.27; H, 7.09; N, 5.39.

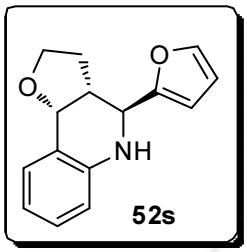
furo[3,2-c]quinoline ***(51s):***



White solid, m.p. 121 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.77-1.87 (m, 1 H), 2.15-2.25 (m, 1 H), 2.95 (qd, J = 2.2, 8.8 Hz, 1 H), 3.71-3.81 (m, 2 H), 3.95(brs,1H), 4.69 (d, J = 2.8 Hz, 1 H), 5.22 (d, J = 8.0 Hz, 1 H), 6.27-6.28 (m, 1 H), 6.36-6.37 (m, 1H), 6.58 (d, J = 8.0 Hz, 1 H), 6.81 (t, J = 7.6, Hz, 1 Hz), 7.08 (t, J = 8.0 Hz, 1 H), 7.33 (d, J = 7.2 Hz, 1 H), 7.38 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 25.5, 42.5, 51.7, 66.7, 75.6, 106.0, 110.5, 115.1, 119.6, 122.1, 128.6, 130.3, 141.9, 144.6, 155.1; **IR** (KBr):

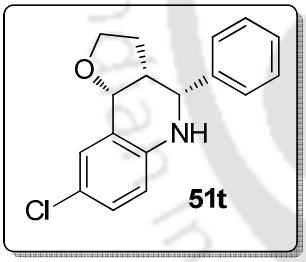
3366, 2972, 2877, 1609, 1481 cm^{-1}. **Anal. Calcd** for $C_{15}H_{15}NO_2$ (241.29): C, 74.67; H, 6.27; N, 5.81. found: C, 74.52; H, 6.24; N, 5.89

*furo[3,2-c]quinoline (**52s**)*:



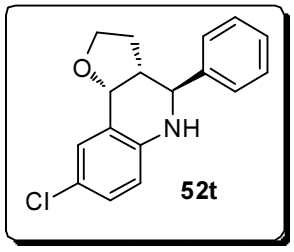
White solid, m.p. 151 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.76-1.84 (m, 1 H), 2.10-2.19 (m, 1 H), 2.58-2.64 (m , 1 H), 3.77-3.84 (m, 1 H), 3.93-4.00 (m, 2 H), 4.22 (brs, 1 H), 4.59 (d, J = 5.2 Hz, 1 H), 6.30 (d J = 2.8 Hz, 1 H), 6.36 (d, J = 2.8 Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.77 (t, J = 7.6 Hz, 1 H), 7.09 (t, J = 8.0 Hz, 1 H), 7.35 (d, J = 7.6, 1 H), 7.40 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 29.3, 40.9, 51.3, 65.4, 75.9, 107.6, 110.4, 115.1, 118.8, 120.2, 129.0, 131.2, 142.5, 144.7, 154.8; **IR** (KBr): 3368, 3114, 2936, 2861, 1612, 1589 cm^{-1}. **Anal. Calcd** for $C_{15}H_{15}NO_2$ (241.29): C, 74.67; H, 6.27; N, 5.81. found: C, 74.55; H, 6.20; N, 5.98.

*furo[3,2-c]quinoline (**51t**)*:



White solid, m.p. 155°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.50-1.59 (m, 1 H), 2.11-2.21 (m, 1 H), 2.71-2.81 (m,1 H), 3.73 (q, J = 8.8 Hz, 1 H), 3.83 (td, J = 3.2, 8.8 Hz, 1 H), 3.86 (brs, 1 H), 4.68 (d, J = 2.4 Hz , 1 H), 5.21 (d, J = 8.0 Hz, 1 H), 6.53 (d, J = 8.4 Hz, 1 H), 7.03 (dd, J = 2.0, 8.4 Hz, 1 H), 7.30-7.34 (m, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.42-7.48 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 24.7, 45.6, 57.5, 67.1, 75.8, 116.3, 123.9, 124.3, 126.7, 128.0, 128.5, 128.9, 129.9, 142.0, 143.6; **IR** (KBr): 3371, 2923, 2940, 1601, 1475 cm^{-1}. **Anal. Calcd** for $C_{17}H_{16}ClNO$ (285.77): C, 71.45; H, 5.64; N, 4.90. found: C, 71.19; H, 5.57; N, 4.78.

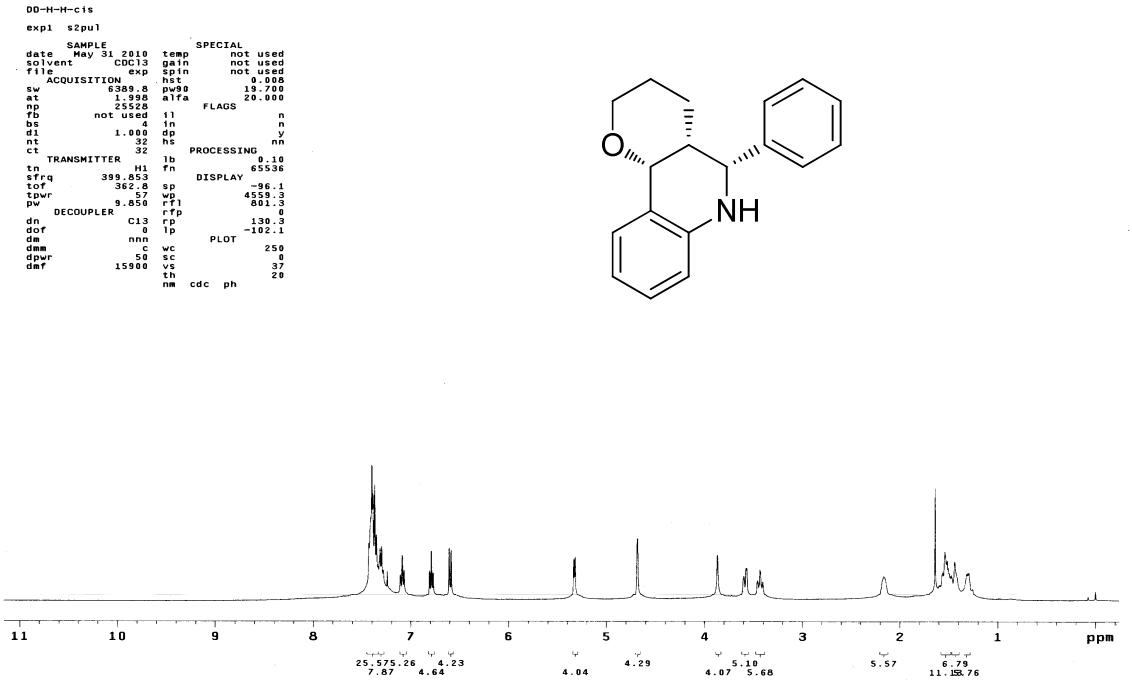
*furo[3,2-c]quinoline **52t**:*



White solid, m.p. 103°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.67-1.74 (m, 1 H), 1.97-2.06 (m, 1 H), 2.41-2.47 (m, 1 H), 3.75 (d, J = 10.8 Hz, 1 H), 3.80-3.86 (m, 1 H), 3.99-4.04 (m, 1 H), 4.15 (brs, 1 H), 4.54 (d, J = 4.8 Hz , 1 H), 6.55 (d, J = 8.4 Hz, 1 H), 7.07 (dd, J

= 2.0, 8.4 Hz, 1 H), 7.32-7.44 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 29.0, 43.5, 58.0, 65.5, 75.9, 116.1, 123.1, 126.7, 128.4, 128.5, 129.0, 129.1, 131.0, 141.5, 144.2; **IR** (KBr): 3386, 2928, 2872, 1607, 1490 cm^{-1}. **Anal. Calcd** for $C_{17}H_{16}ClNO$ (285.77): C, 71.45; H, 5.64; N, 4.90. found: C, 71.21; H, 5.72; N, 4.99.

^{1}H NMR (400 MHz, $CDCl_3$): *pyrano[3,2-c]quinolone* ***(51a)***



^{13}C NMR (100 MHz, $CDCl_3$)*: pyrano[3,2-c]quinolone* ***(51a)***

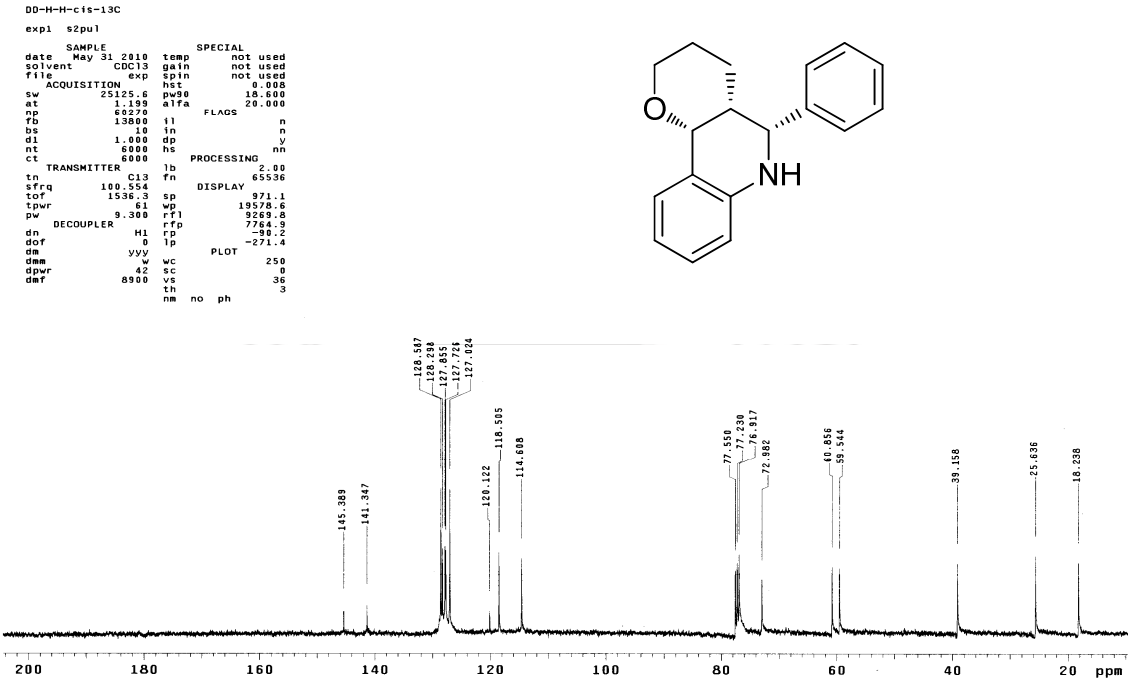
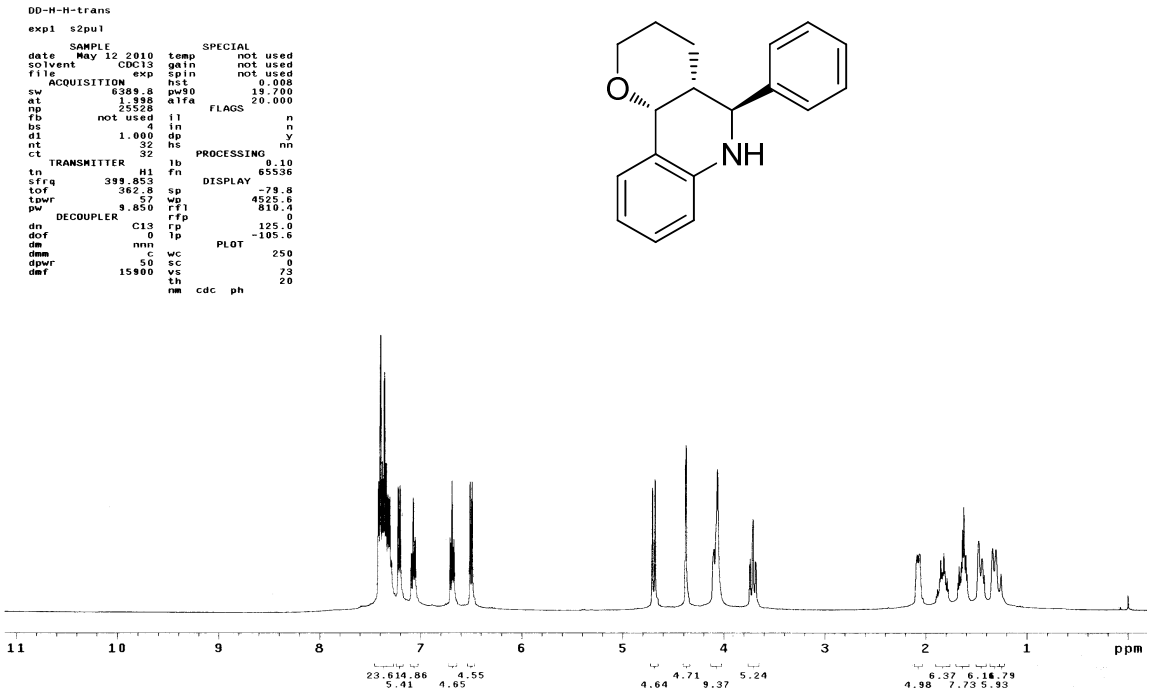


Figure 10

^{1}H NMR (400 MHz, $CDCl_3$): *pyrano[3,2-c]quinolone* ***(52a)***



^{13}C NMR (100 MHz, $CDCl_3$)*: pyrano[3,2-c]quinolone* ***(52a)***

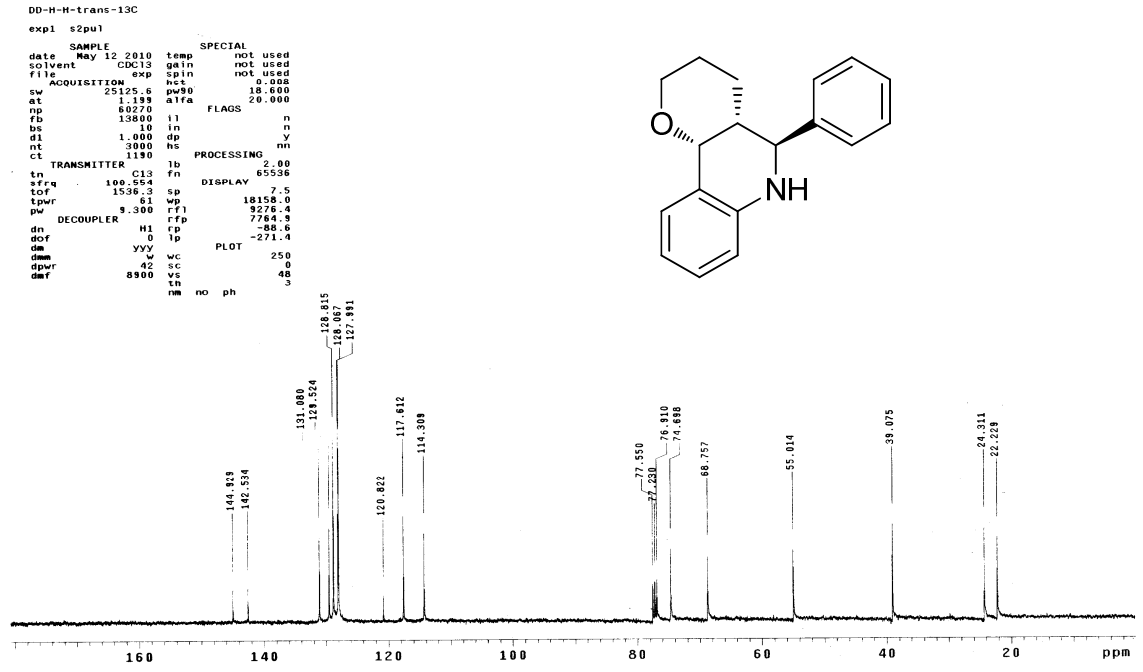
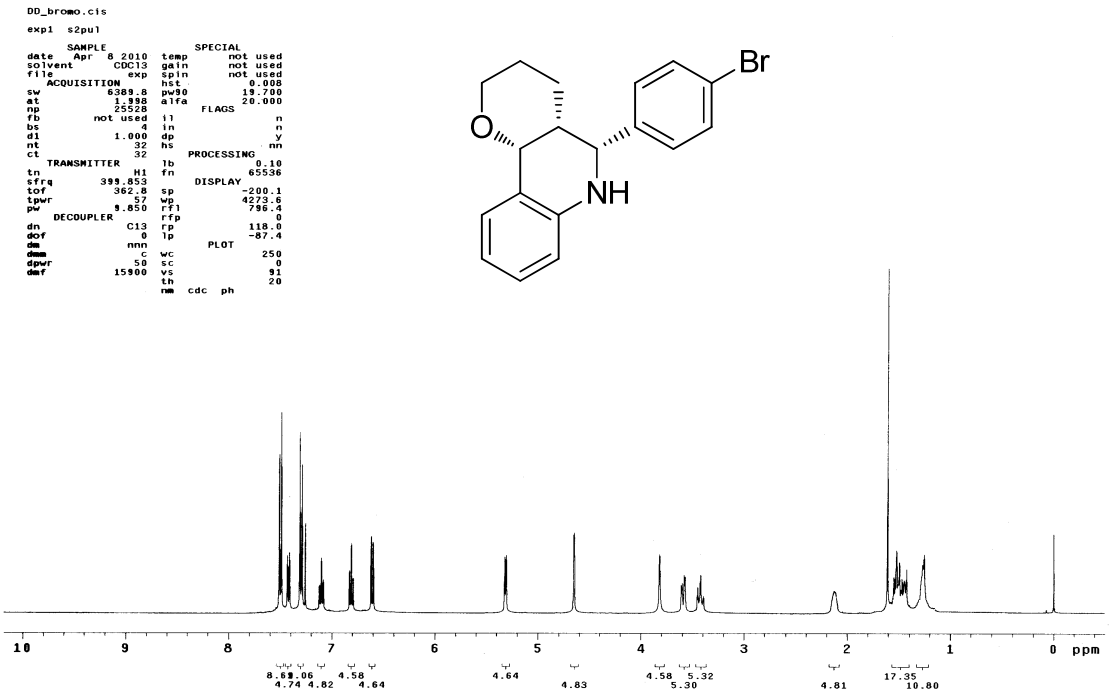


Figure 11

^{1}H NMR (400 MHz, $CDCl_3$): *pyrano[3,2-c]quinolone* ***(51d)***



^{13}C NMR (100 MHz, $CDCl_3$): *pyrano[3,2-c]quinolone* ***(51d)***

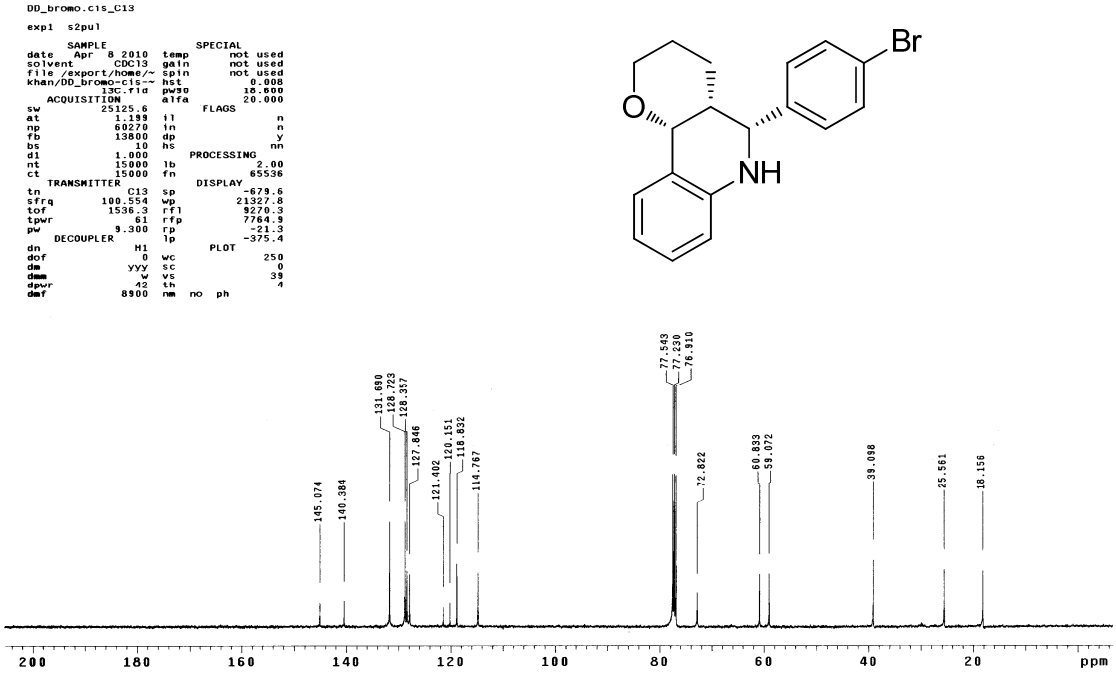
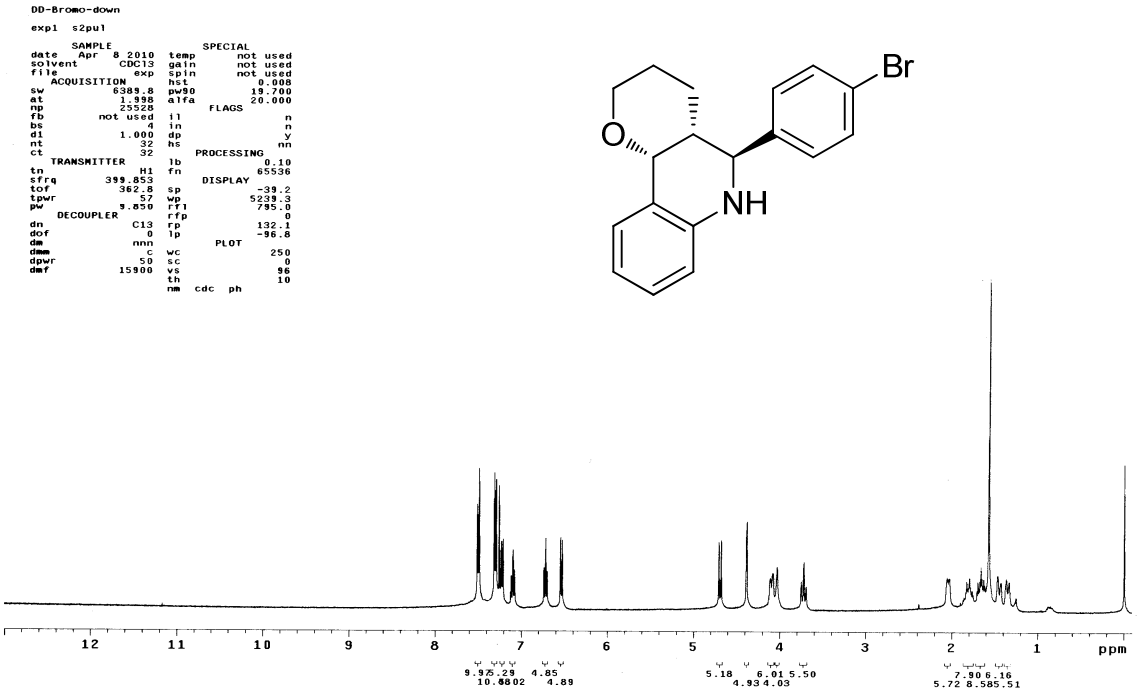


Figure 12

^{1}H NMR (400 MHz, $CDCl_3$): *pyrano[3,2-c]quinolone* ***(52d)***



^{13}C NMR (100 MHz, $CDCl_3$): *pyrano[3,2-c]quinolone* ***(52d)***

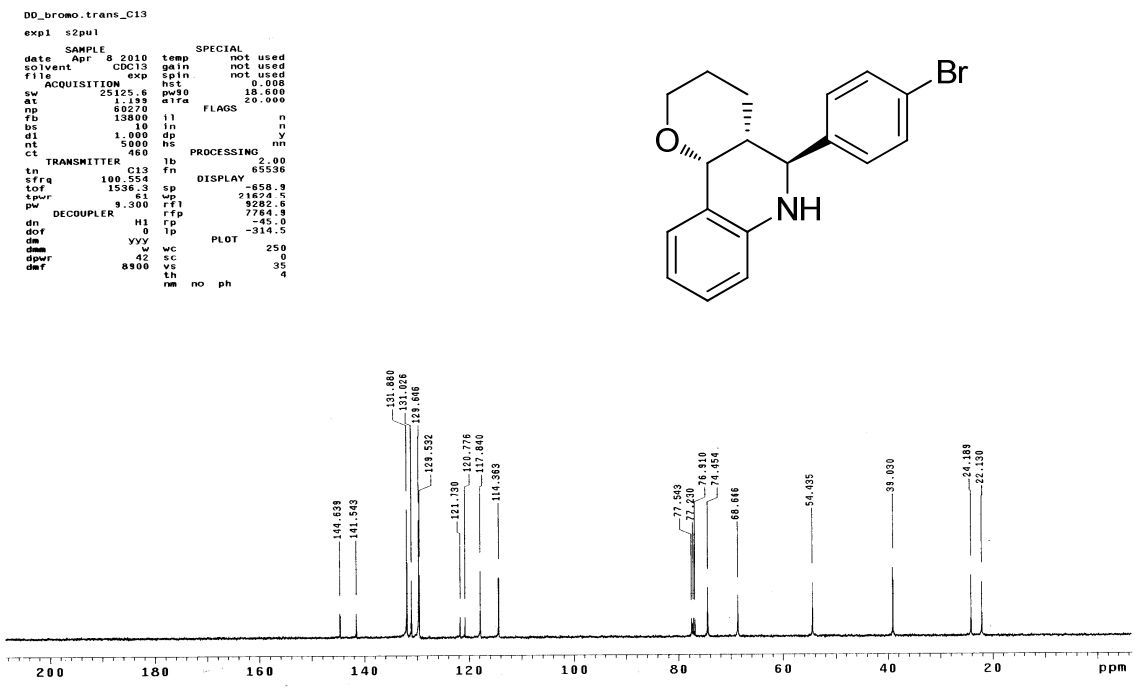
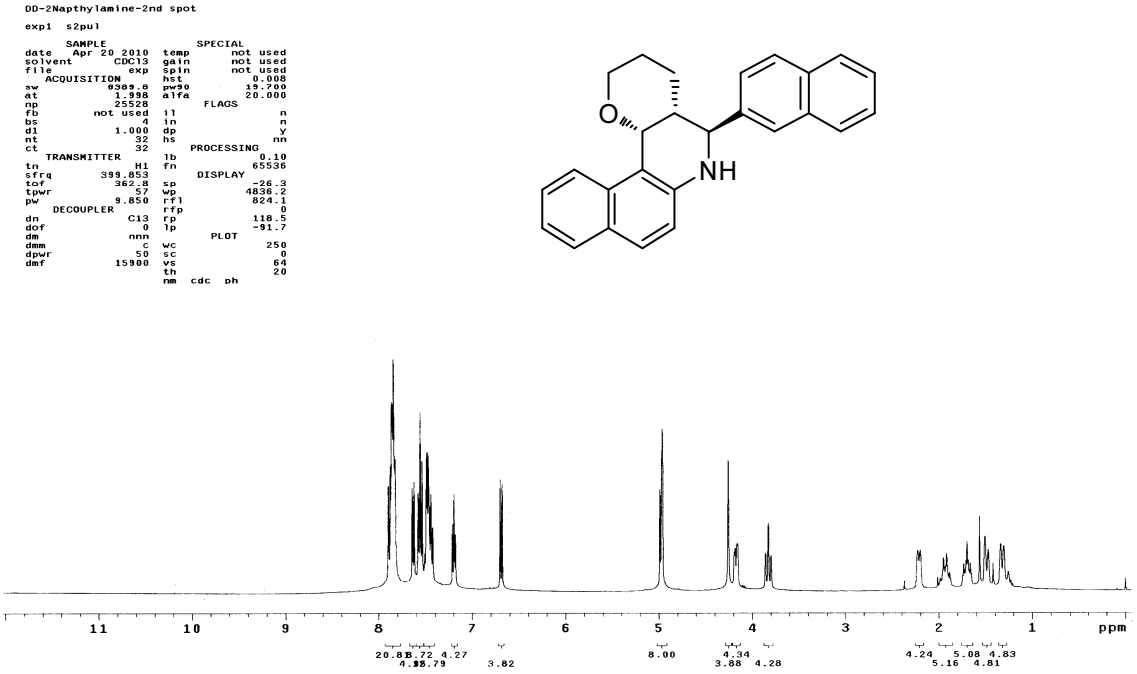


Figure 13

^{1}H NMR (400 MHz, $CDCl_3$): *pyrano[3,2-c]quinolone* **(52*q*)**



^{13}C NMR (100 MHz, $CDCl_3$): *pyrano[3,2-c]quinolone* **(52*q*)**

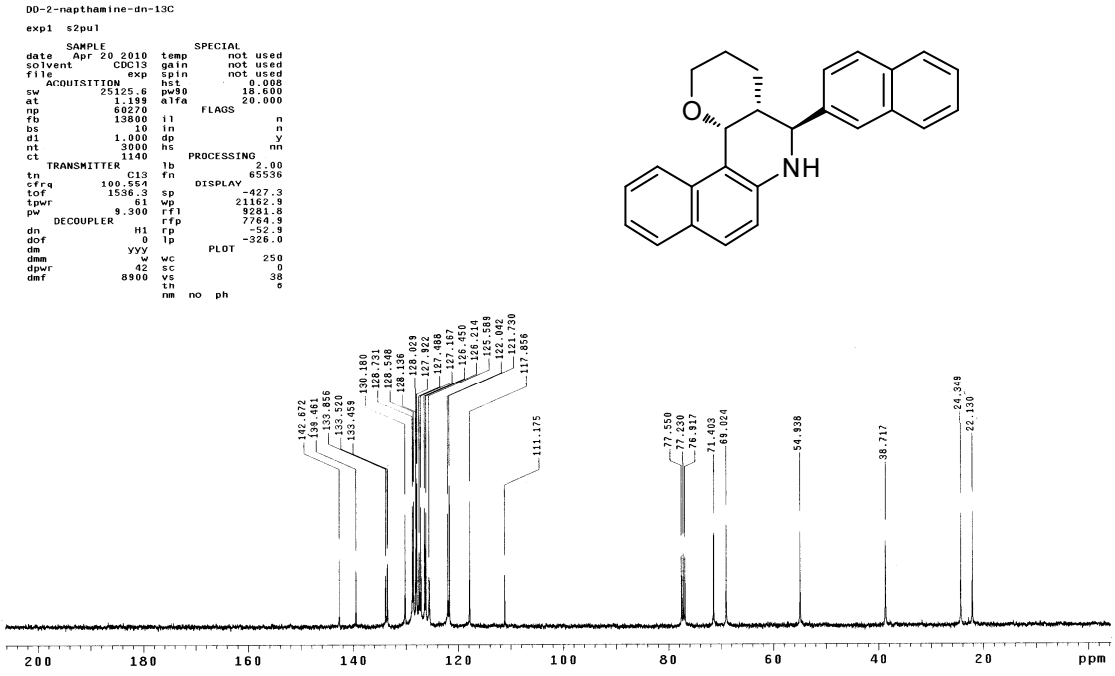
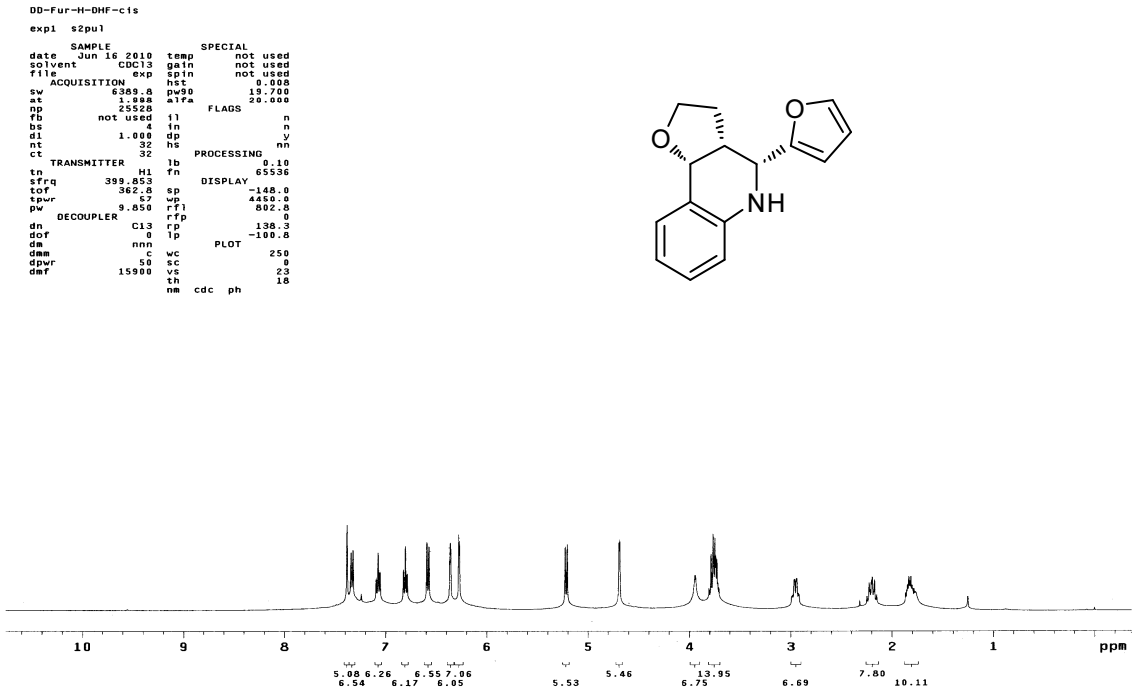


Figure 14

^{1}H NMR (400 MHz, $CDCl_3$): *furo[3,2-c]quinolone* ***(51s)***



^{13}C NMR (100 MHz, $CDCl_3$): *furo[3,2-c]quinoline* ***(51s)***

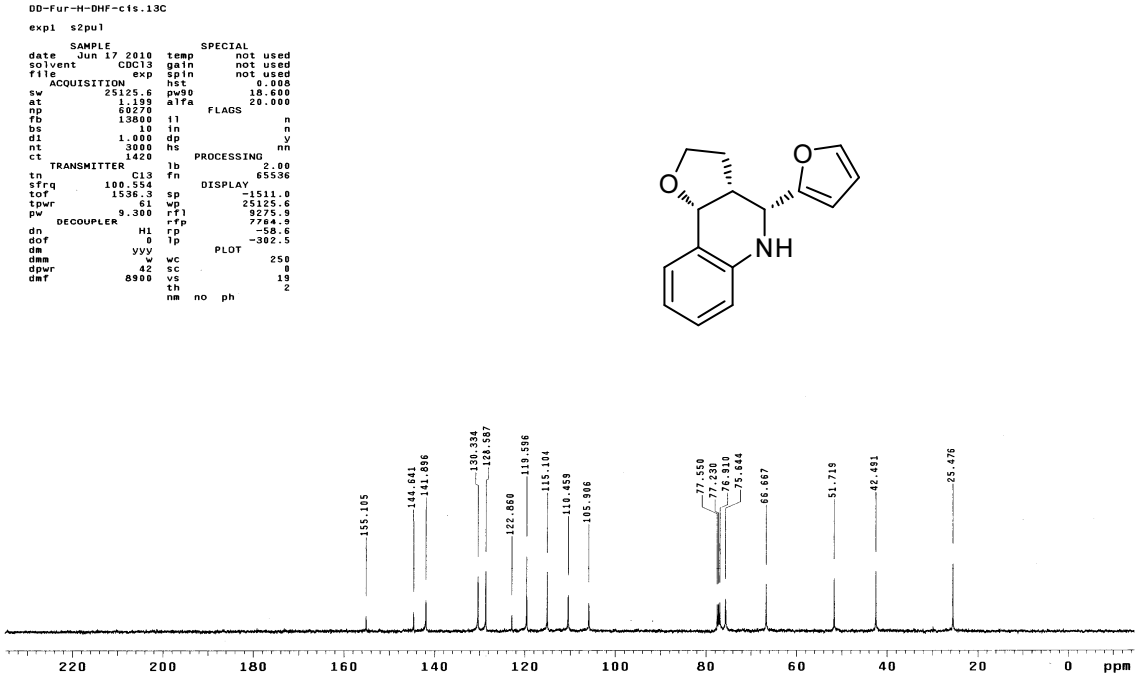
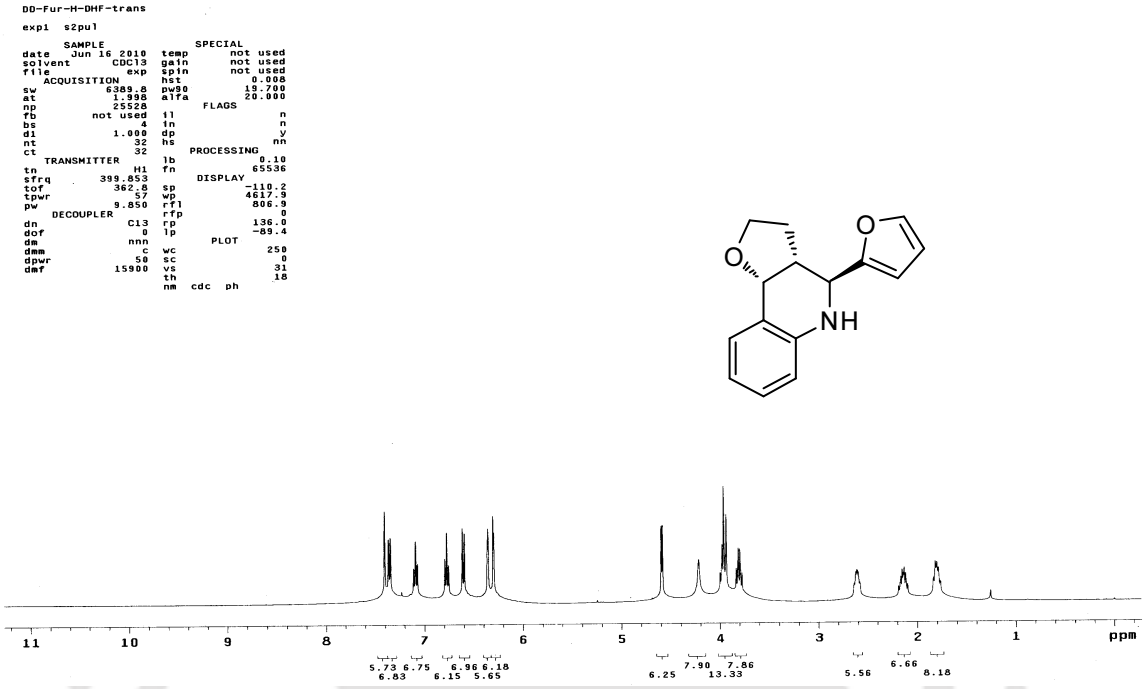


Figure 15

^{1}H NMR (400 MHz, $CDCl_3$): *furo[3,2-c]quinolone* **(52s)**



^{13}C NMR (100 MHz, $CDCl_3$): *furo[3,2-c]quinolone* **(52s)**

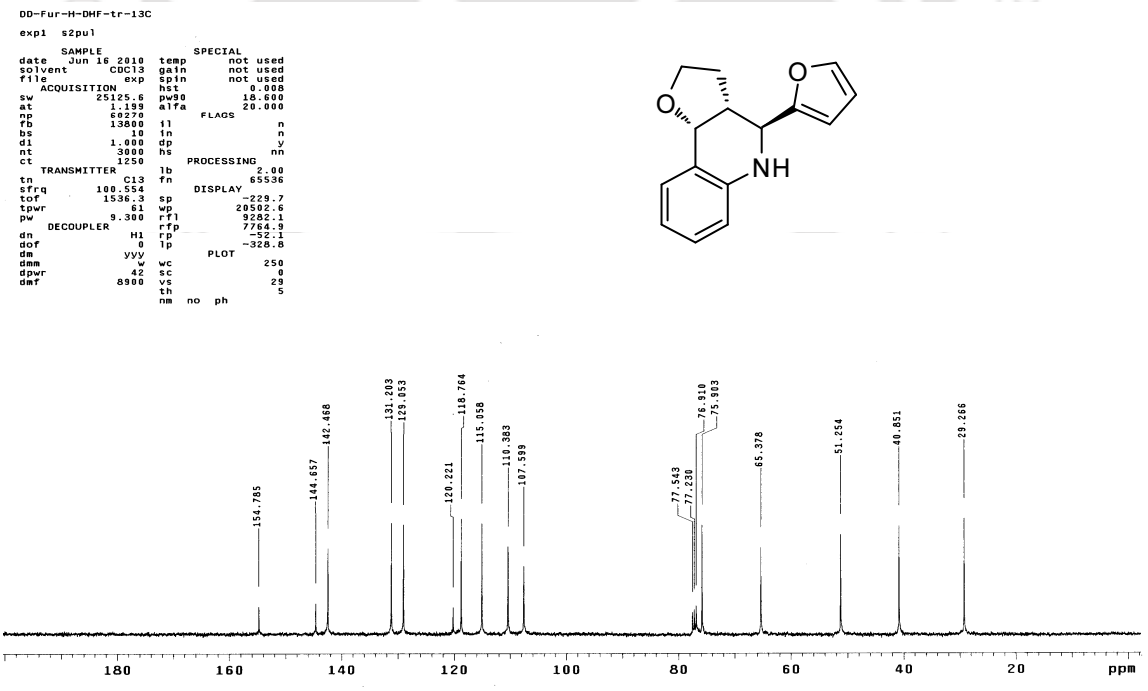


Figure 16

PART B

CHAPTER IIIB

Large Scale Synthesis of 3-aminocoumarins

Review
Result & Discussion
Experimental

Importance of 3-aminocoumarins

Coumarins are oxygen heterocycles widely distributed in nature[66] and their derivatives are considered as "privileged structures" in pharmaceutical and agrochemical industries.[67] Coumarins fused with heterocyclic compounds have gained great attention due to their potential biological activities.[68] 3-Aminocoumarin structural moiety is present in a number of natural products[69] as shown in Figure 17. Novobiocine is a 3-aminocoumarin derived antibiotic, an ATP competitive inhibitor of gyrase subunit blocking the negative supercoiling of relaxed DNA.[70] A number of analogues of novobiocin such 3-acylamino-4-hydroxycoumarin[71] and 7,8-dihydroxy-3-aminocoumarin have been found to exhibit antibacterial[72] and antifungal[73] activity. Some of the derivatives of 3-aminocoumarins are found to possess a wide range of relevant activities as CNS depressant,[74a] anti-tumor,[74b] anti-inflammatory,[74] anti-microbial[74d] and anti-coagulant.[74e] Coumarins fused to pyridines have been reported to have antialergic,[75a] antidiabetic,[75b] and analgesic[75c] properties.

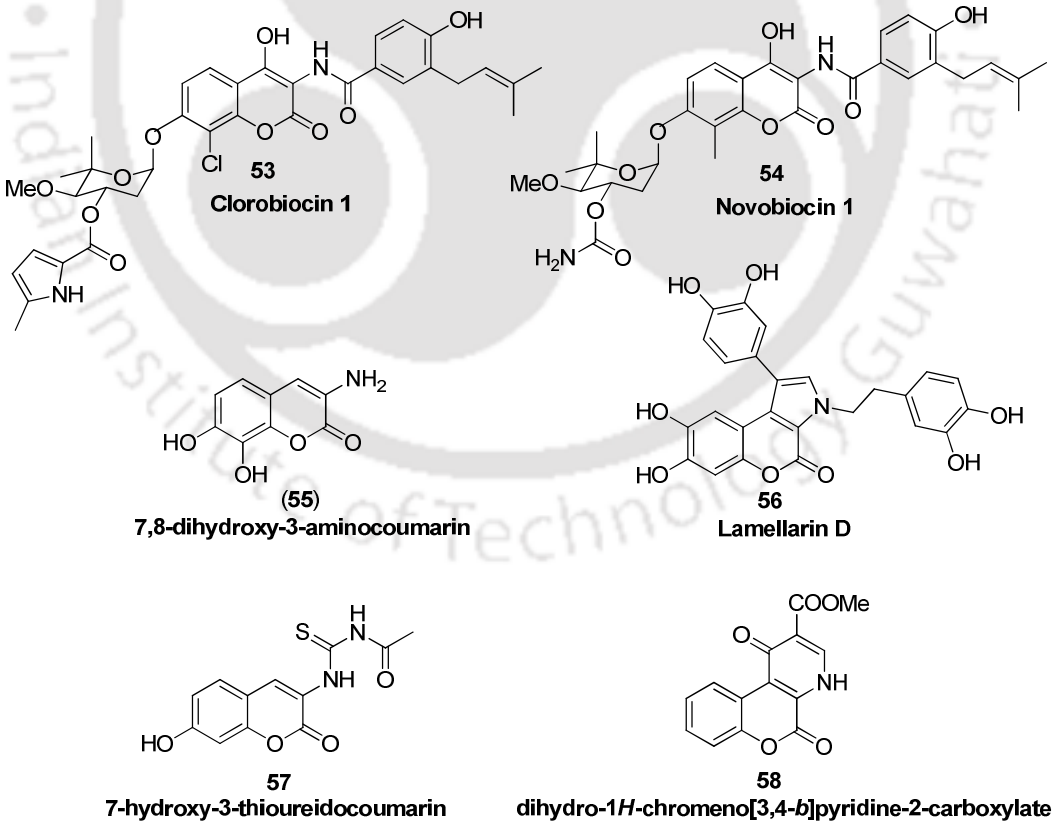
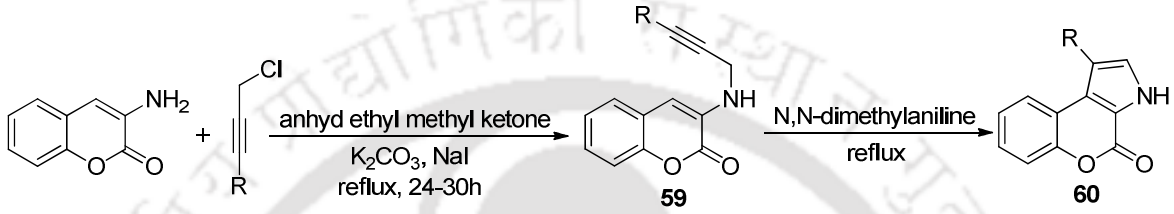


Figure 17. Important heterocyclic compounds containing 3-aminocoumarin skeleton.

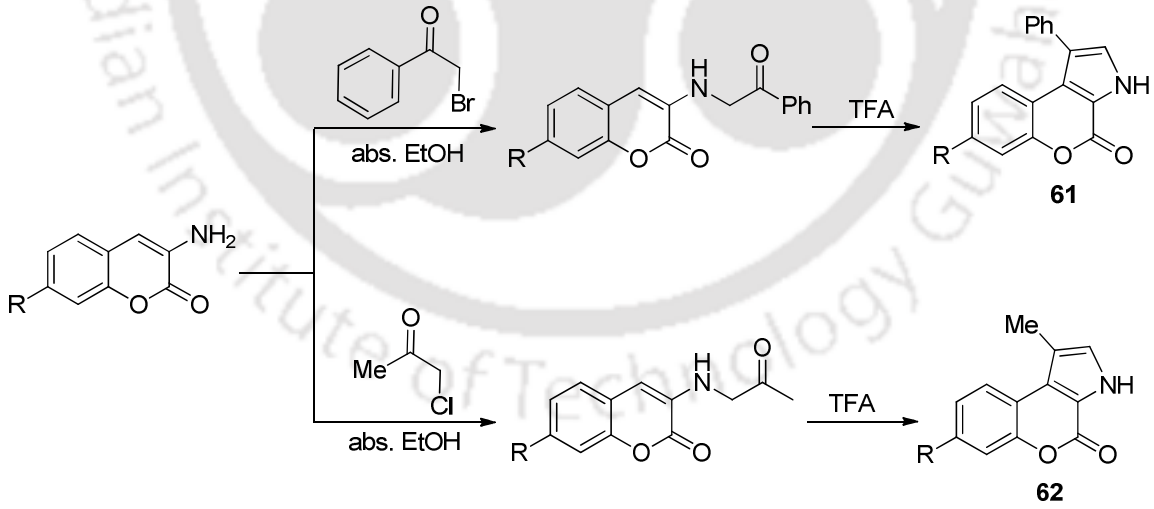
Moreover, Coumarin derivatives are excellent chromogenic and fluorogenic dyes that are extensively used in chemosensors.[76]

Majumdar and co-workers synthesized pyrrolocoumarins[77] **60** and its derivatives in excellent yields through amino-Claisen rearrangement of 3-N-propargylaminocoumarin and 3-N-(aryloxybut-2-ynyl)aminocoumarins, Scheme 18.



Scheme 18

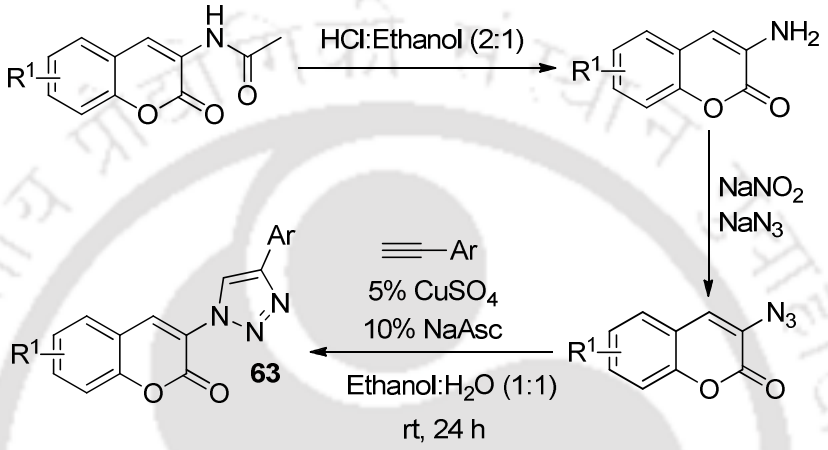
Soman and co-workers showed condensing α-halo ketones with 3-aminocoumarins followed by cyclization using triflic acid furnished chromeno[3,4-*b*]pyrrol-4(3H)-ones **61** & **62**, in good yields as shown in Scheme 19.[78] The synthesized chromeno[3,4-*b*]pyrrol-4(3H)-one derivatives showed cytotoxic activity against lung, colon, and breast cancer cell lines.



Scheme 19

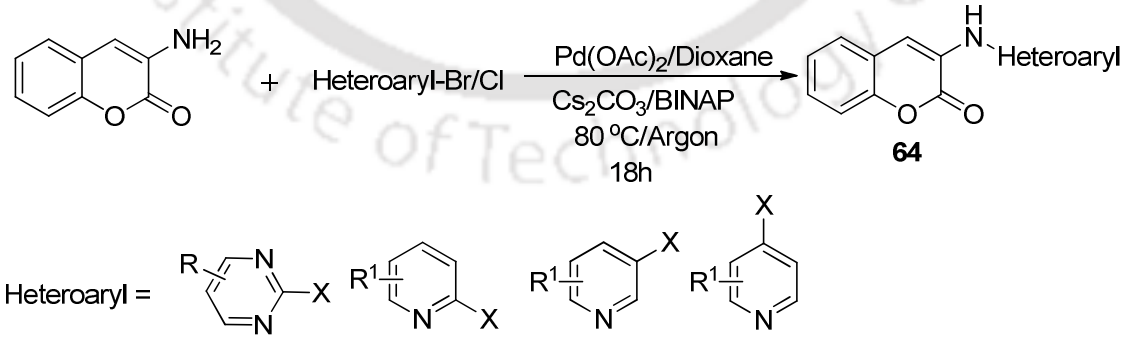
Wang et al. demonstrated the synthesis of 1,2,3-triazole products **63**, via copper(I)-catalyzed 1,3-dipolar cycloaddition reaction of 3-azidocoumarins with terminal alkynes as shown in

Scheme 20. The 3-azidocoumarins were derived from 3-aminocoumarin which was synthesized from hydrolysis of 3-acetamidocoumarin using HCl/EtOH mixture in 2:1 ratio. The obtained triazole products showed intense fluorescence compared to the non-fluorescent starting materials and have immense potential in bio-conjugation and bio-imaging applications.[79]



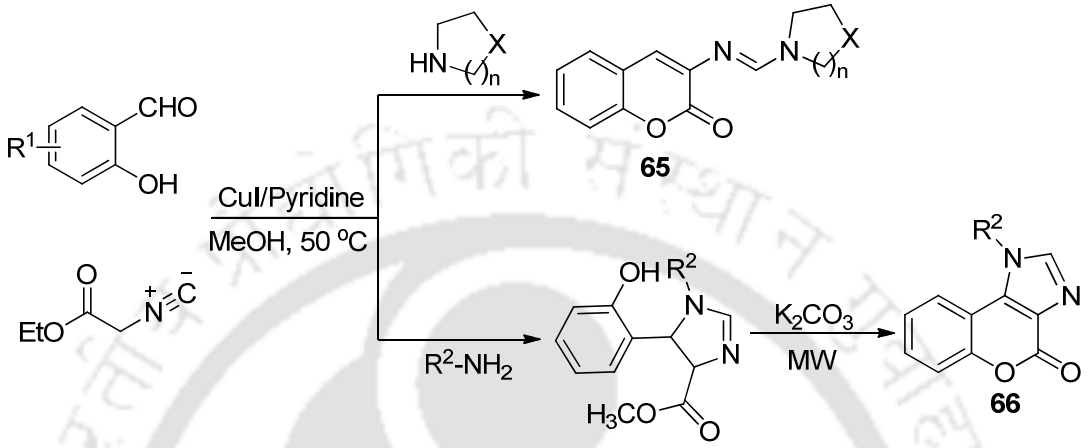
Scheme 20

Das and co-workers synthesized 3-(heteroaryl)aminocoumarin derivatives **64** in moderate to good yields from 3-aminocoumarin applying optimized Buchwald–Hartwig amination conditions using palladium acetate, cesium carbonate, and BINAP in 1,4-dioxane as shown in Scheme 21.[80]



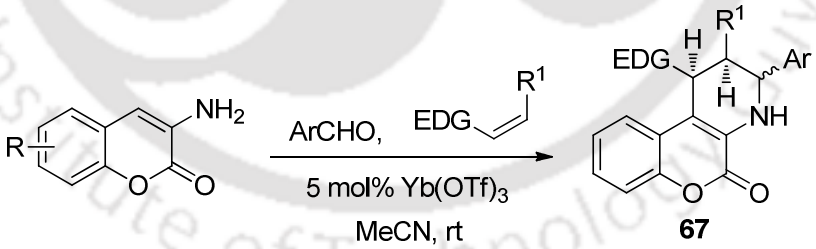
Scheme 21

Shen et al. developed an efficient method for the one-pot copper (I)-catalyzed synthesis of 3-aminocoumarin and its derivatives, such as 3-substituted methylideneaminocoumarins **65** and chromeno-[3,4-d]imidazol-4(1H)-ones **66**, Scheme 22.[81]



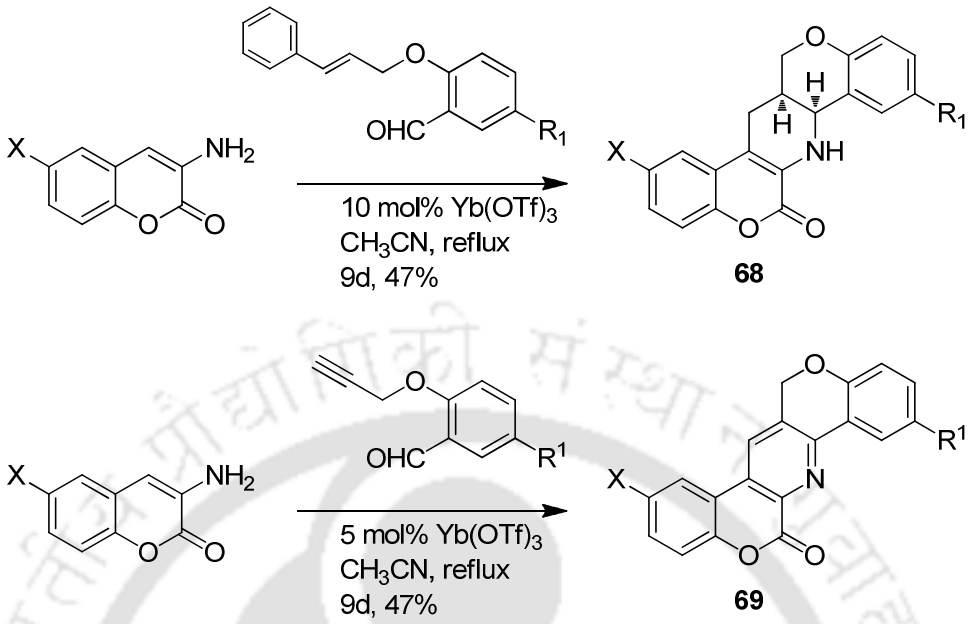
Scheme 22

Bodwell et al. reported the synthesis of 1,2,3,4-tetrahydropyrido[2,3-c]coumarins **67** from aromatic aldehyde and 3-aminocoumarin and different electron withdrawing dienophiles via Povarov reaction as shown in Scheme 23. It was shown that 3-aminocoumarin could function as the aromatic amine component as required in aza-diels-alder reaction.[82]



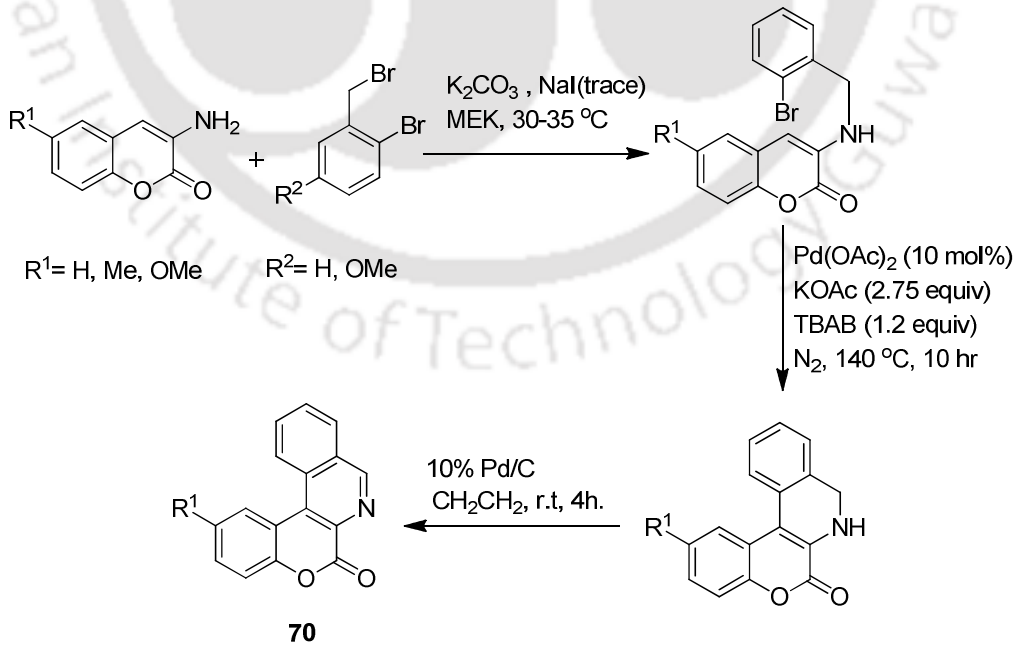
Scheme 23

Later on the same group reported the synthesis of pentacyclic tetrahydropyrido[2,3-c]coumarins **68** and pyrido[2,3-c]coumarins **69**, involving intramolecular Povarov reaction from 3-aminocoumarin and O-cinnamylsalicylaldehydes or 2-(propargyloxy)benzaldehyde as shown in Scheme 24.[83]



Scheme 24

Majumdar et al. further devised a new synthetic protocol for the synthesis of pyrido[2,3-c]coumarins **70** through palladium catalyzed intramolecular Heck reaction followed by dehydrogenation with 10% palladium charcoal as shown in Scheme 25.[84]

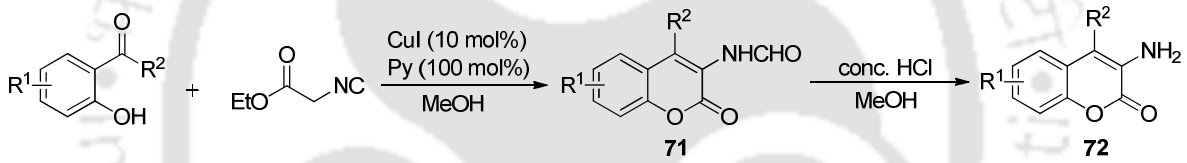


Scheme 25

We found from the above literature survey that 3-aminocoumarins are valuable starting materials. Therefore, the synthesis of 3-aminocoumarins in large scale in a more efficient way is essential.

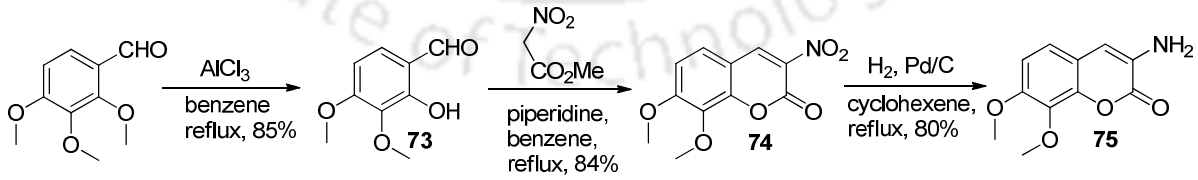
Synthesis of 3-aminocoumarins

Due to their wide range of biological activities, various research groups have put considerable efforts to synthesize 3-aminocoumarin derivatives.[85] Shen and his co-workers synthesized various 3-formamidocoumarin intermediates **71** from one-pot copper (I)-catalyzed reaction of salicylaldehydes or 2'-hydroxyacetophenones with ethyl isocyanoacetate. The formyl group of the 3-formamidocoumarin derivatives was removed using 5 equivalents of concentrated HCl in methanol that afforded the pure 3-aminocoumarins **72** as depicted in Scheme 26.[81]



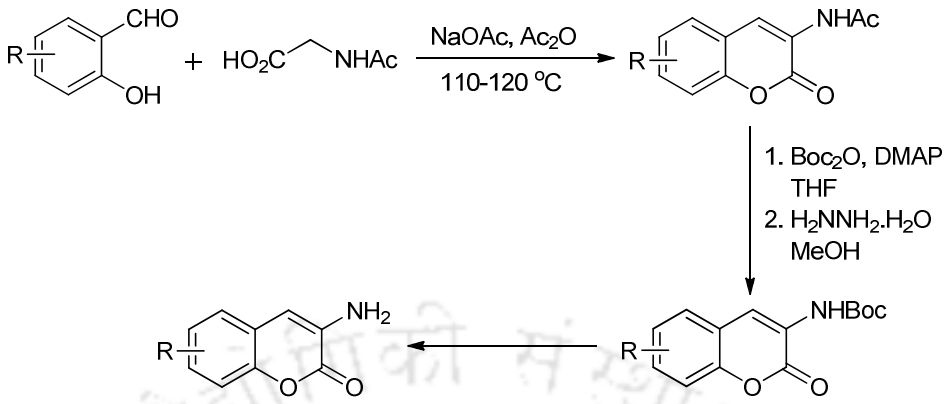
Scheme 26

Selective demethylation of trimethoxybenzaldehyde gave compound **73**, which was condensed with nitroacetate to give nitrocoumarin **74** in 84% yield. Hydrogenation of **74** with H_2, Pd/C gave 3-aminocoumarin as the final product **75** in 80% yield as shown in Scheme 27.[86]



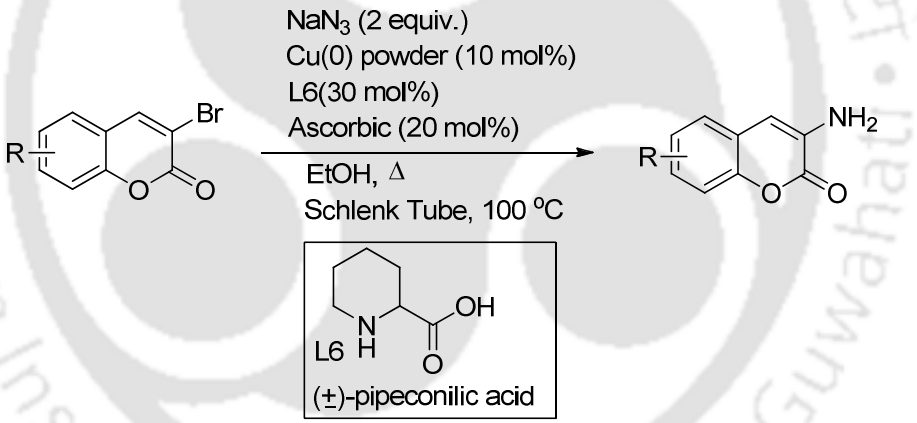
Scheme 27

Bodwell and co-workers reported a hydrolysis-free synthesis of 3-aminocoumarins from 3-acetamidocoumarins by acylation-deacylation sequences as shown in Scheme 28.[87]



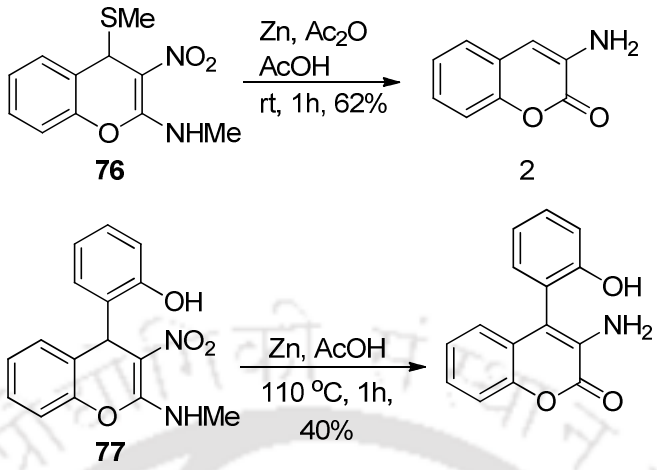
Scheme 28

Messaoudi et al. developed an efficient method for the synthesis of various 3-aminocoumarins from 3-bromocoumarins using copper powder as the catalyst in the presence of pipecolinic acid and ascorbic acid in ethanol as shown in Scheme 29.[88]



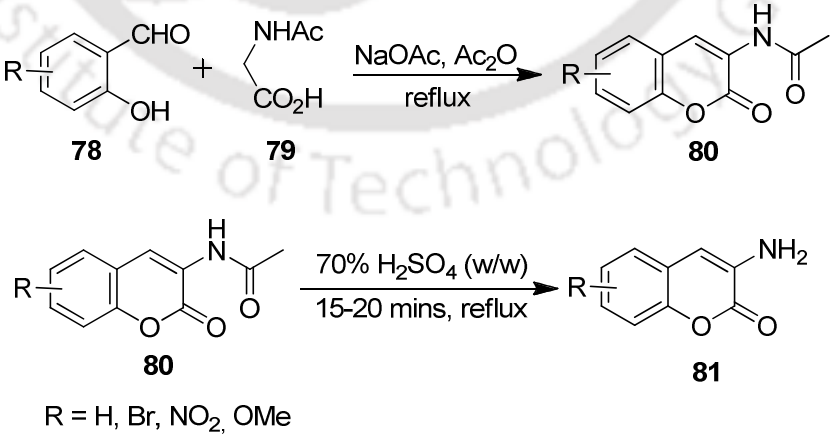
Scheme 29

Rao and co-workers synthesized 3-aminocoumarin in 62% yield during reduction of 2-methylamino-3-nitro-4-methylsulfanyl-4*H*-chromene **76** using Zn/Ac_2O-AcOH mixture as shown in Scheme 30.[89] The same group synthesized 4-substituted 3-aminocoumarin from reduction of 2-(2-(methylamino)-3-nitro-4H-chromen-4-yl)phenol **77** using Zn/AcOH under reflux.



Scheme 30

Some of the procedures described above have limitations such as requirement of multistep transformations,[85f,h,86,87] use of expensive catalysts,[86-89] harsh conditions and low yield for large preparations. So there is a need of a suitable protocol for the synthesis of 3-aminocoumarin derivatives. This chapter will provide an insight into the improved synthesis procedure of 3-aminocoumarin in term of simplicity and mildness over the known procedures. A convenient large-scale synthesis of 3-aminocoumarin derivatives **81** using different salicylaldehyde **78** and *N*-acetylglycine **79** followed by regioselective hydrolysis is shown in Scheme 31.



Scheme 31. Preparation of 3-aminocoumarins by regioselective hydrolysis

Results and Discussion

3-acetamidocoumarins **80** were prepared from N-acetylglycine and different salicylaldehyde derivatives as mentioned in the reported literature.[87,90] Aqueous hydrolysis provides both 3-hydroxycoumarins and 3-aminocoumarins.[91] As a matter of fact, the acid hydrolysis of 3-acetamidocoumarins sometimes lack reproducibility and give poor yield of 3-aminocoumarins due to the formation of undesired product 3-hydroxycoumarins. To overcome this difficulty, Bodwell and co-workers reported hydrolysis-free synthesis of 3-aminocoumarins from 3-acetamidocoumarins by acylation-deacylation sequences.[87] The main demerit of Bodwell's protocol is requirement of expensive reagents such as Boc-anhydride and triflic acid. We conceived the idea that 3-acetamidocoumarins could be protonated under highly acidic conditions. In such cases we may get major amount 3-aminocoumarin instead of 3-hydroxycoumarin. With this goal in mind, we tried to hydrolyze 3-acetamidocoumarins using different amount of H_2SO_4 in water, Figure 18. It was found that 70% H_2SO_4 gave 3-aminocoumarin exclusively as the hydrolyzed product.

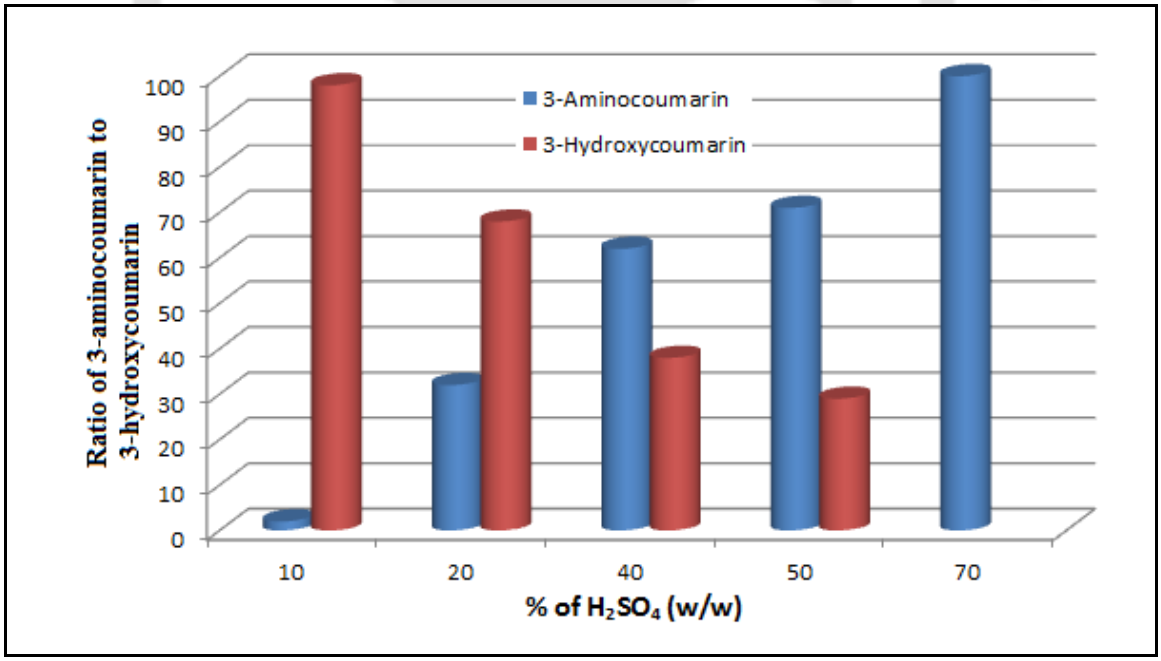
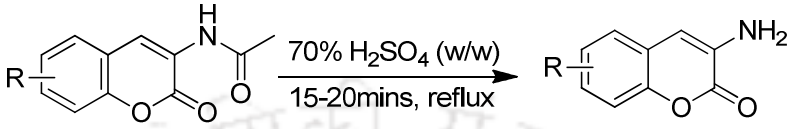


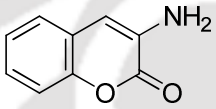
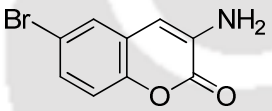
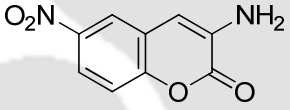
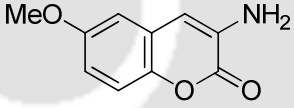
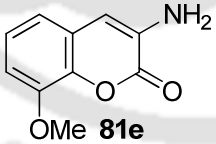
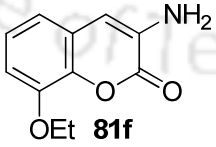
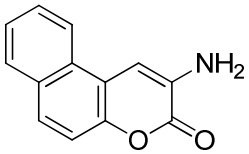
Figure 18 : Formation of 3-aminocoumarins versus 3-hydroxycoumarins from 3-acetamidocoumarin under various acid concentration.

To generalize our protocol, we have hydrolyzed other substituted 3-acetamidocoumarins under identical reaction conditions to give the products (**81b-g**) and the successful results are shown in Table 6.

Table 6. Conversion of 3-acetamidocoumarins (**80**) into 3-aminocoumarins[a] (**81**)



80 **81**

Entry	R	Product	Yield[b]%	m.p °C (obs)	m.p °C (lit)
1	H	 **81a**	81	138-140 °C	135-136 °C
2	5-Br	 **81b**	75	208-209 °C	205-206 °C
3	5-NO_2	 **81c**	78	201-202 °C	201-202 °C
4	5-OMe	 **81d**	74	119-120 °C	120-123 °C
5	8-OMe	 **81e**	61	124-125 °C	124-126 °C
6	8-OEt	 **81f**	66	125-126 °C	--
7	5,6-Benzo	 **81g**	72	152-153 °C	156-158 °C

[a]All the reactions were conducted in 5 mmol scale. [b]Isolated yield.

Further to synthesize 3-aminocoumarin (**81a**) in a large scale, we tried to hydrolyze 8.12 g of 3-acetamidocoumarin **80a** (40 mmol) using 60 mL of 70% (w/w) H_2SO_4 solution. However, after carrying out the reaction for 20 minutes, it was observed from TLC analysis that the reaction was incomplete and thus the reaction mixture was left for stirring under reflux condition for 3 hours until all the 3-acetamidocoumarin was found to be fully consumed. 5.23 gram of 3-aminocoumarin was isolated after neutralization and work up of the reaction mixture.

The structure of one of the representative compounds such **81e** was confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 19). All the structures were confirmed from ^{1}H NMR, ^{13}C NMR spectra and from their elemental analysis. The ^{1}H NMR spectra and ^{13}C NMR spectra of the products **81a-f** are given in Figures **20-26**, respectively in the experimental section.

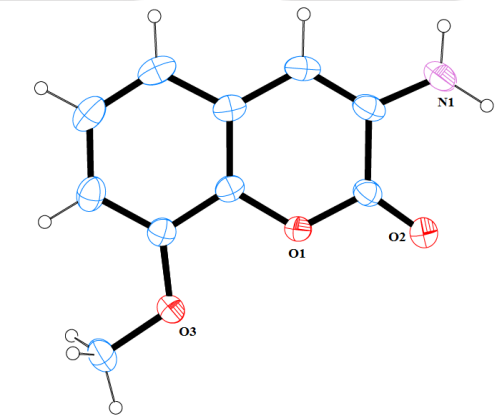
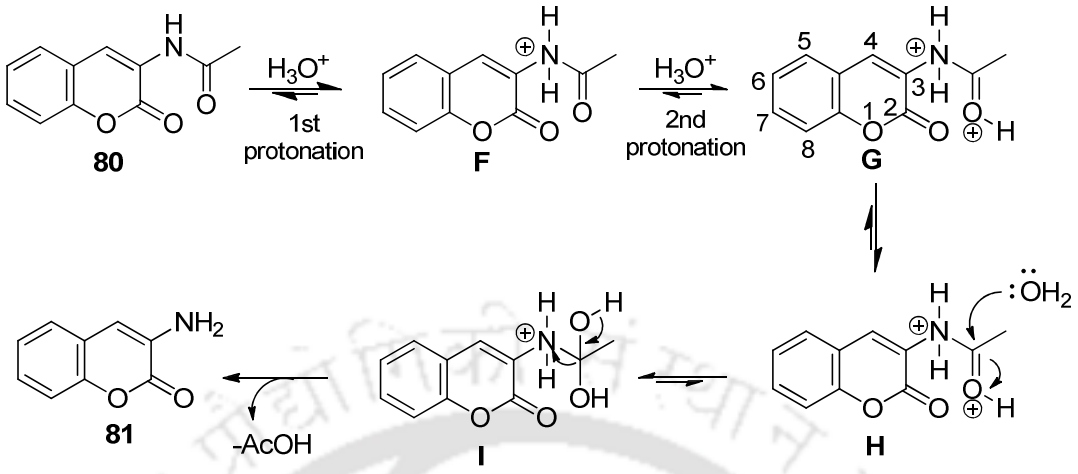


Figure 19. X-Ray Crystal structure of 3-aminocoumarin **81e** (CCDC 935727)

The mechanism for the formation of 3-aminocoumarins can be depicted as in Scheme 32. We believe that nitrogen atom of 3-acetamidocoumarin **80**, undergoes protonation to give intermediate **F** in higher concentration of sulfuric acid. As a result, the electrophilicity of the carbonyl group is increased and second protonation is favoured to give intermediate **G**. The water molecule may attack at the 3- position of coumarin ring (sp2 hybridized carbon) or the carbonyl group of intermediate **G**. The water molecule reacts preferably at the carbonyl center to give intermediate **H**, which is converted into 3-aminocoumarin **81**, by eliminating one molecule of acetic acid.



Scheme 32. Proposed mechanism for the formation of 3-aminocoumarins.

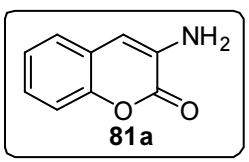
In conclusion, we have developed a convenient protocol for the synthesis of 3-aminocoumarins in multigram scale and without the formation of 3-hydroxycoumarins.

General procedure for the synthesis of 3-Aminocoumarins (81a-g):

An oven-dried 250-mL round-bottomed flask equipped with a 3.0 cm teflon-coated cylindrical magnetic stir bar was charged with a mixture of 3-acetamidocoumarin **80a**, (40.0 mmol) and 60 mL of 70% (w/w) H_2SO_4 solution. 70% (w/w) H_2SO_4 solution was prepared by adding slowly 58 mL of Conc. H_2SO_4 in 42 mL of distilled water at ice-bath temperature. The reaction flask was heated with constant stirring in a pre-heated oil-bath at 120 ^oC. During heating the solid mass dissolved slowly and it produced red colour solution. The progress of the reaction was monitored by TLC analysis from time to time by taking out some aliquot from the reaction vessel, which was neutralized with 2 N NaOH followed by extraction with DCM. After 3 hrs when the reaction was complete, the red colored solution was poured into a 2 litre beaker containing 250 mL of ice-cold water. Then, the beaker was cooled in an ice-bath at 0-5 ^oC and it was neutralized by adding 763 mL of 2 N NaOH dropwise with stirring by a glass rod till the pH of the solution in between 6-7. The solid product of 3-aminocoumarins precipitated out slowly, which was filtered off through a Büchner funnel. The red coloured final product was washed with 5 x 20 mL of distilled water and it was dried in air using blotting paper. The dried crude product of 3-aminocoumarin was dissolved in 400 mL of dichloromethane, which was poured in a separatory funnel and it was washed with water (4 x 75 mL). The organic layer was dried over anhydrous sodium sulfate and it was concentrated in a rotary evaporator to obtain pure 3-aminocoumarin **81a** in 81 % yield. Similar procedure was followed for the preparation of other 3-aminocoumarin derivatives (**81b-g**).

Spectral data of 3-aminocoumarins

*3-Aminocoumarin (**81a**):*

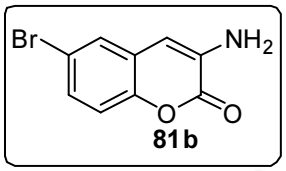


81a

White solid; m.p. 138-140°C; R_f (10% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.30-7.21 (m, 3H), 7.19-7.7.18 (m, 1H), 6.71 (s, 1H), 4.34 (bs, 2H, NH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.62, 149.07, 132.16, 126.67, 125.20, 124.73, 121.33, 116.18, 111.03; **IR** (KBr) 3429, 3331, 1707, 1647, 741 cm^{-1}; **Anal. Calcd** for $C_9H_7NO_2$ (161.05): C,

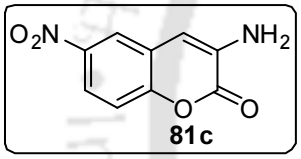
67.09; H, 4.42; N, 8.70; found C, 67.16; H, 4.34; N, 8.72; **MS** (ESI) *m/z*: 162.055 (M^++1).

*6-Bromo-3-aminocoumarin (**81b**):*



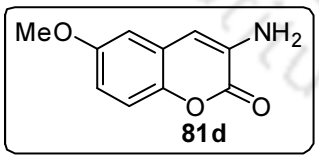
White solid; m.p. 208-209°C; R_f (10% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.42 (d, *J* = 2.4 Hz, 1 H), 7.34 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.15 (d, *J* = 8.8 Hz, 1 H), 6.59 (s, 1 H), 4.37 (bs, 2 H, NH_2); **^{13}C NMR** (100 MHz, DMSO-d_6) 158.15, 146.74, 134.12, 127.34, 126.60, 124.10, 117.47, 116.38, 105.81; **IR** (KBr) 3407, 3347, 1717, 1644, 808 cm^{-1}; **Anal. Calcd** for $C_9H_6BrNO_2$ (238.96): C, 45.09; H, 2.58; N, 5.89; found C, 45.03; H, 2.52; N, 5.83. **MS** (ESI) *m/z*: 239.965 (M^++1).

*6-Nitro-3-aminocoumarin (**81c**):*



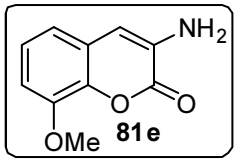
Yellow solid; m.p. 202-203°C; R_f (10% ethyl acetate/hexane) 0.10; **IR** (KBr) 3437, 3347, 1704, 1543, 1344, 836 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.42 (d, *J* = 2.4 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.4 Hz, 1H),7.15(d, *J* = 8.8 Hz, 1H), 6.59 (s, 1H), 4.37 (bs, 2H, NH_2); **^{13}C NMR** (100 MHz, DMSO-d_6) 157.70, 151.14, 143.89, 134.60, 122.74, 120.01, 119.61, 116.59, 105.60; **Anal. Calcd** for $C_9H_6N_2O_4$ (206.03): C, 52.49; H, 2.98; N, 13.62; found C, 52.43; H, 2.93; N, 13.59.

*6-Methoxy-3-aminocoumarin (**81d**):*



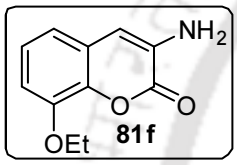
White solid; m.p. 202-203°C; R_f (10% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.16 (d, *J* = 9.2 Hz, 1H), 6.82 (dd, *J* = 9.2, 2.8 Hz, 1H),6.71 (d, *J* = 2.8 Hz, 1H), 6.64 (s, 1H), 4.37 (bs, 2H, NH_2), 3.80 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) 159.65, 156.47, 143.56, 132.52, 121.94, 117.08, 113.90, 110.78, 107.94, 55.81 ppm. **IR** (KBr) 3451, 3352, 1698, 1633, 879 cm^{-1}; **Anal. Calcd** for $C_{10}H_9NO_3$ (191.06): C, 62.87; H, 4.82; N, 7.36; found C, 62.82; H, 4.74; N, 7.33. **MS** (ESI) *m/z*: 192.065 (M^++1).

*8-Methoxy-3-aminocoumarin (**81e**):*



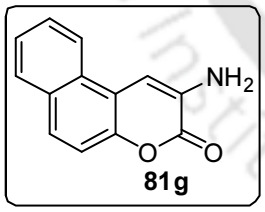
White solid; m.p. 124-125°C; R_f (10% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.13 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.68 (s, 1H), 4.30 (bs, 2H, NH_2), 3.94 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.14, 147.04, 138.52, 132.46, 124.60, 122.14, 117.18, 111.03, 109.09, 56.23; **IR** (KBr) 3452, 3354, 1696, 1634, 874 cm^{-1}; **Anal. Calcd** for $C_{10}H_9NO_3$ (191.06) requires C, 62.86; H, 4.78; N, 7.37; found C, 62.82; H 4.74; N, 7.33. **MS** (ESI) *m/z*: 192.063 (M^++1).

*8-Ethoxy-3-aminocoumarin (**81f**):*



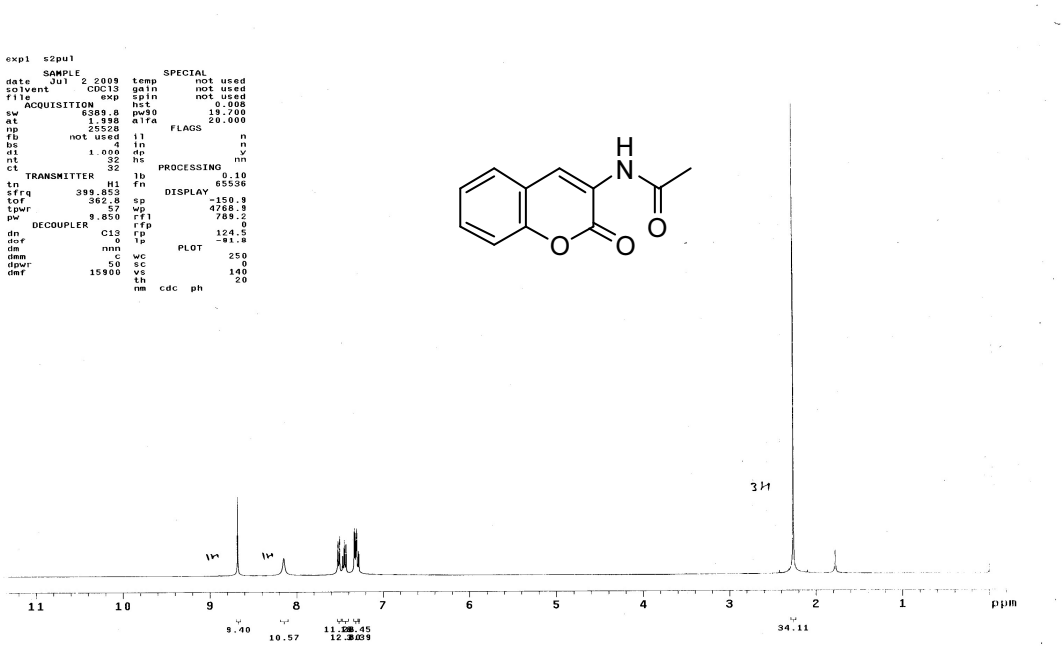
White solid; m.p. 125-126°C; R_f (10% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.09 (td, *J* = 8.0, 0.8 Hz, 1 H), 6.87-6.81 (m, 2 H), 6.68 (s, 1H), 4.33 (bs, 2H, NH_2), 4.17 (q, *J* = 6.8 Hz, 2 H), 1.48 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.28, 147.00, 138.72, 132.38, 124.51, 122.21, 117.03, 111.11, 110.34, 64.84, 14.87; **IR** (KBr) 3466, 3368, 1695, 1630, 872 cm^{-1}; **Anal. Calcd** for $C_{11}H_{11}NO_3$ (205.21) requires C, 64.38; H, 5.40; N, 6.83; found C, 64.50; H, 5.46; N, 6.96.

*2-amino-3H-benzo[f]chromen-3-one (**81g**)*



White solid; m.p. 152-153°C; R_f (10% ethyl acetate/hexane) 0.25; **^{1}H NMR** (300 MHz, $CDCl_3$): 8.15 (d, *J* = 11.2 Hz, 1 H), 7.88 (d, *J* = 10.4 Hz, 1 H), 7.74 (d, *J* = 12.0 Hz, 1 H), 7.64-7.42 (m, 3 H), 7.26 (s, 1H), 4.29 (bs, 2 H, NH_2), 4.17 (q, *J* = 6.8 Hz, 2 H), 1.48 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) 159.50, 147.10, 132.22, 130.82, 128.91, 128.20, 127.49, 127.05, 125.77, 121. 98, 116.61, 115.52, 107.57; **IR** (KBr) 3456, 3362, 1696, 1632 cm^{-1}; **Anal. Calcd** for $C_{13}H_9NO_2$ (211.22): C, C, 73.92; H, 4.29; N, 6.63; found C, 74.08; H, 4.36; N, 6.72.

^{1}H NMR (400 MHz, $CDCl_3$):*3-acetamidocoumarin (80a)*



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

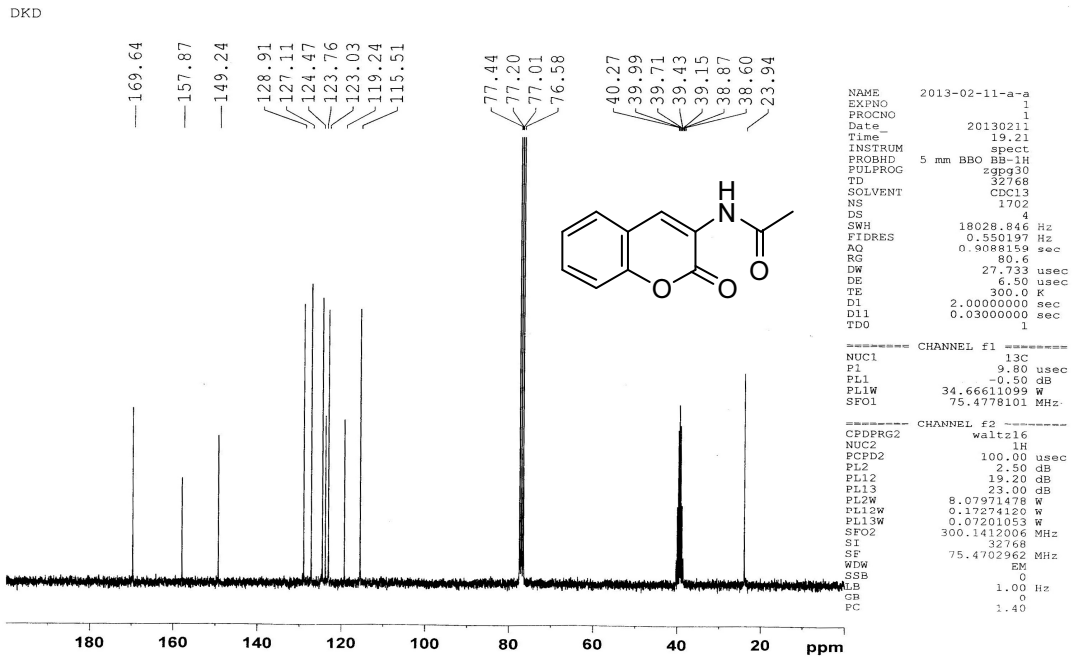
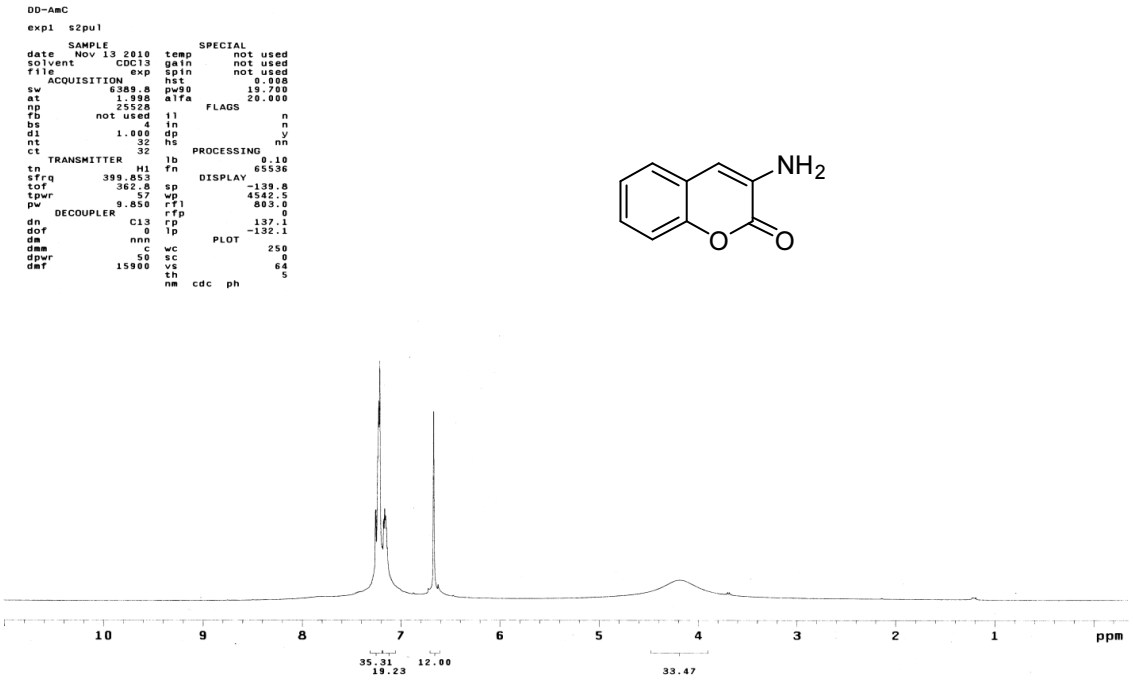


Figure 20

^{1}H NMR (400 MHz, $CDCl_3$): *3-Aminocoumarin (**81a**)*



^{13}C NMR (100 MHz, $CDCl_3$): *3-Aminocoumarin (**81a**)*

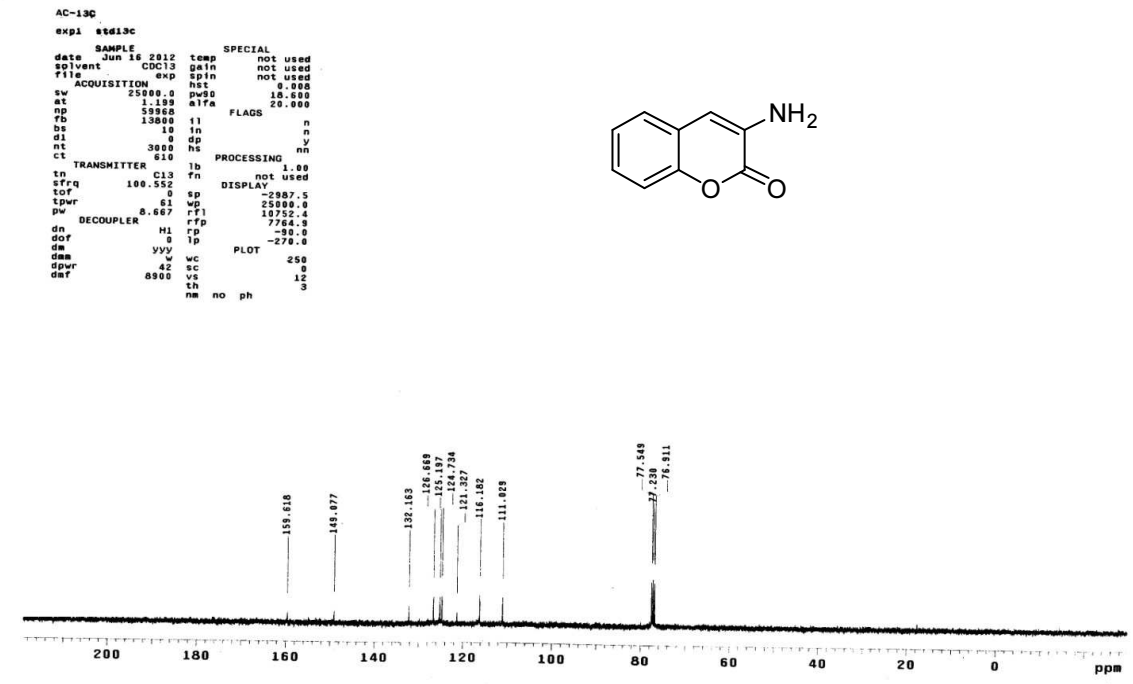
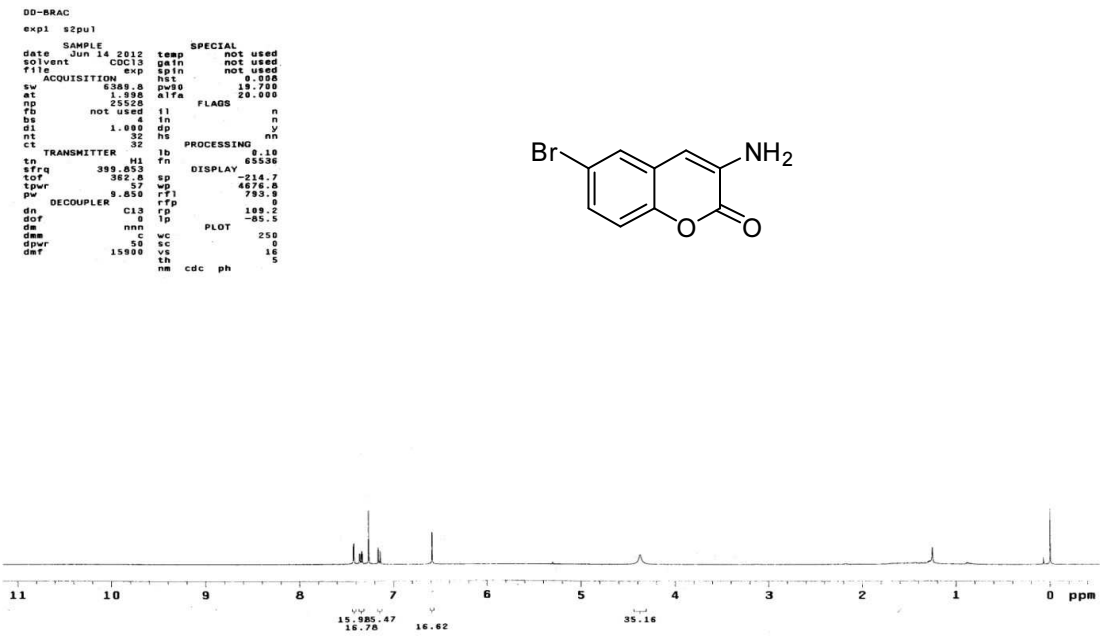


Figure 21

^{1}H NMR (400 MHz, $CDCl_3$): *6-Bromo-3-aminocoumarin (**81b**)*



^{13}C NMR (100 MHz, $CDCl_3$): *6-Bromo-3-aminocoumarin (**81b**)*

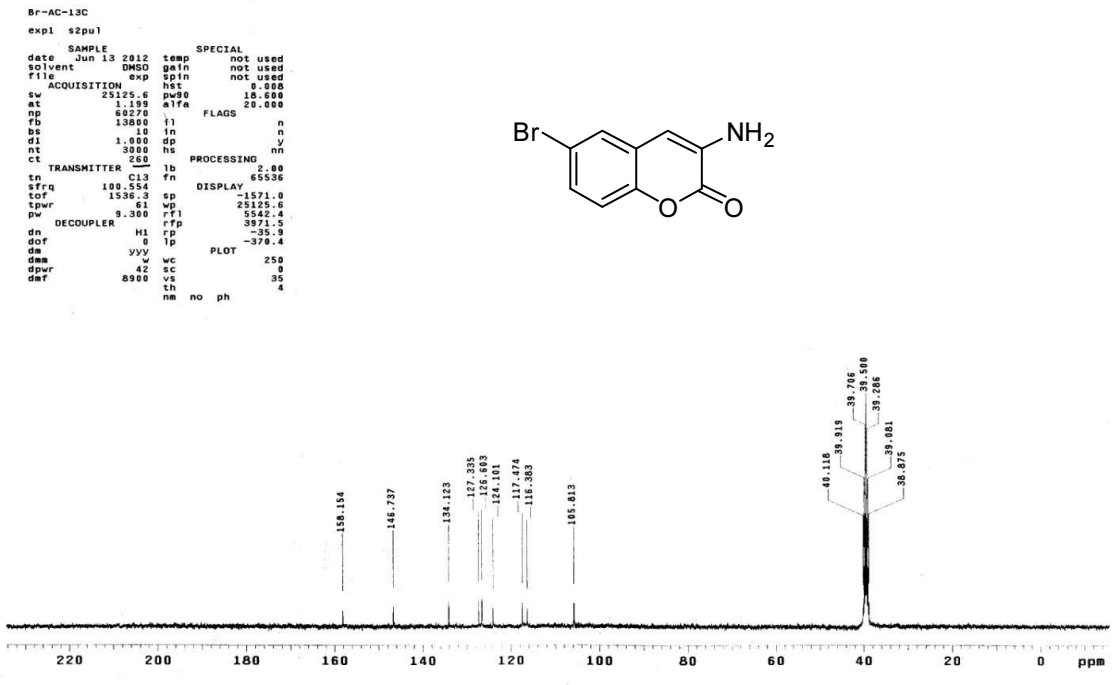
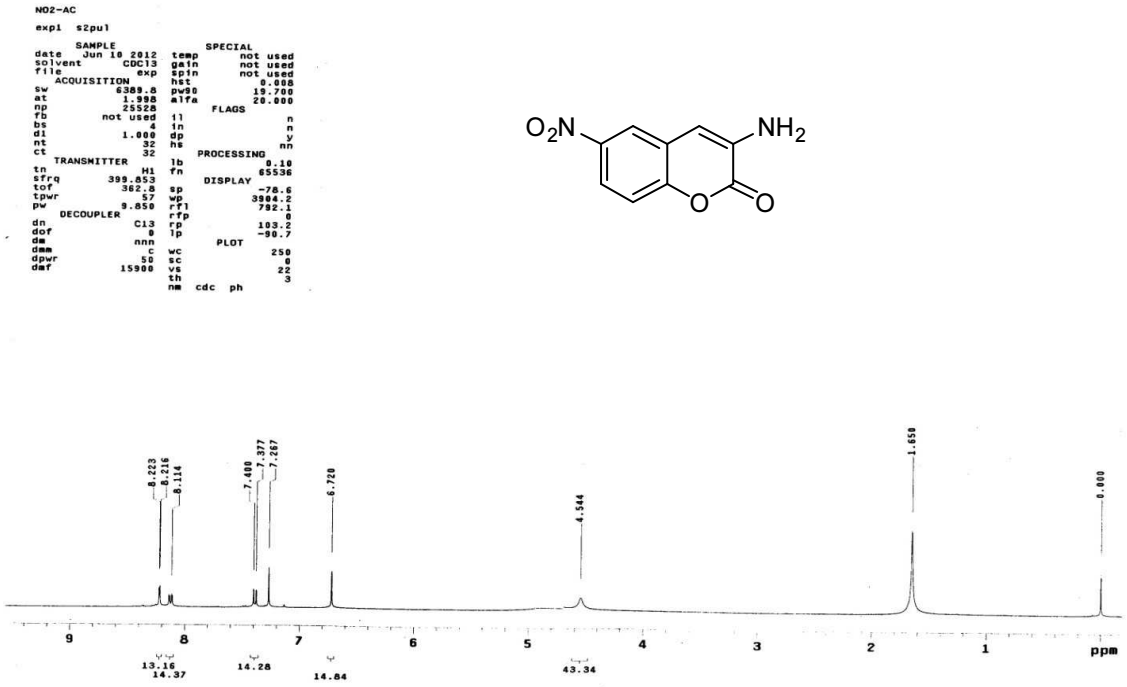


Figure 22

^{1}H NMR (400 MHz, $CDCl_3$): *6-Nitro-3-aminocoumarin (**81c**)*



^{13}C NMR (100 MHz, $CDCl_3$): *6-Nitro-3-aminocoumarin (**81c**)*

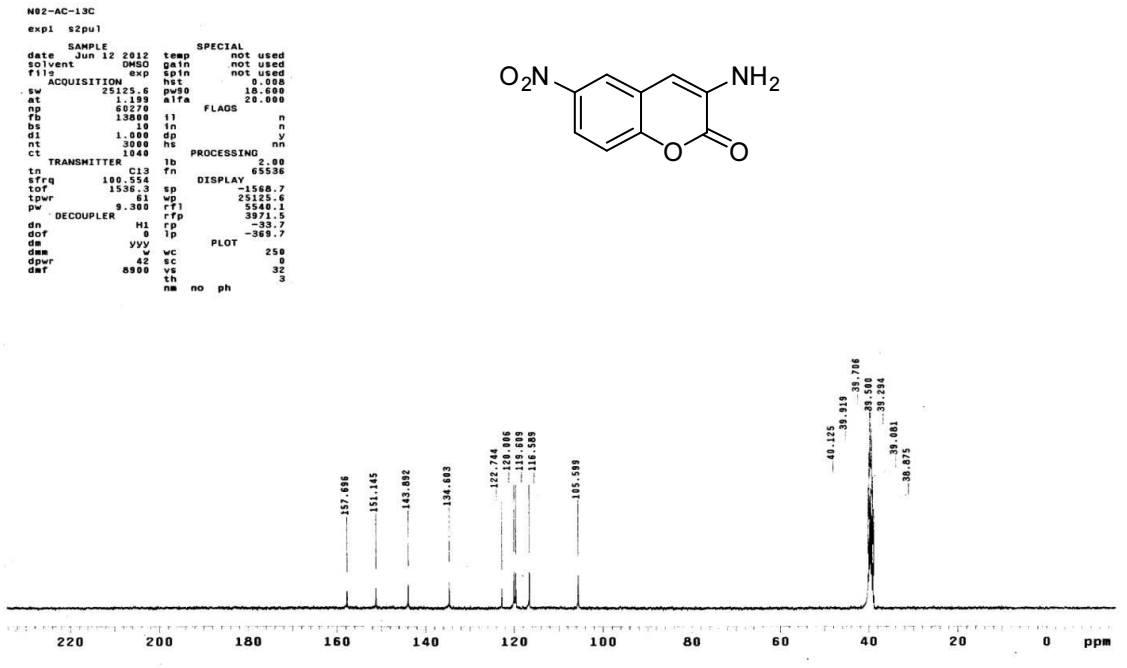
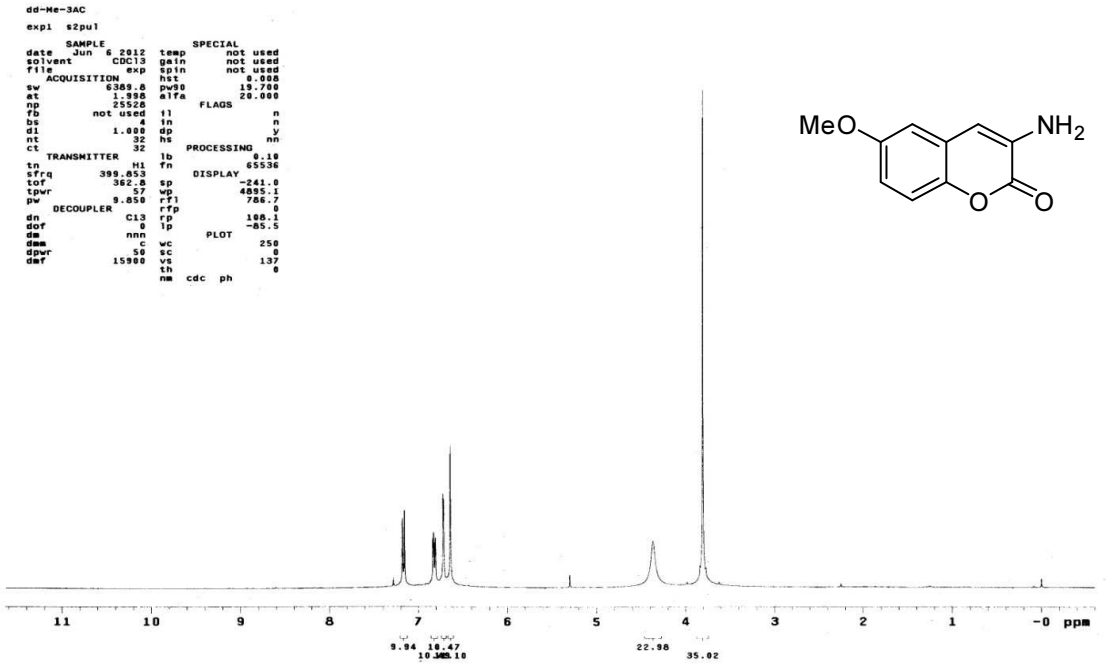


Figure 23

^{1}H NMR (400 MHz, $CDCl_3$): *6-Methoxy-3-aminocoumarin* ***(81d)***



^{13}C NMR (100 MHz, $CDCl_3$): *6-Methoxy-3-aminocoumarin* ***(81d)***

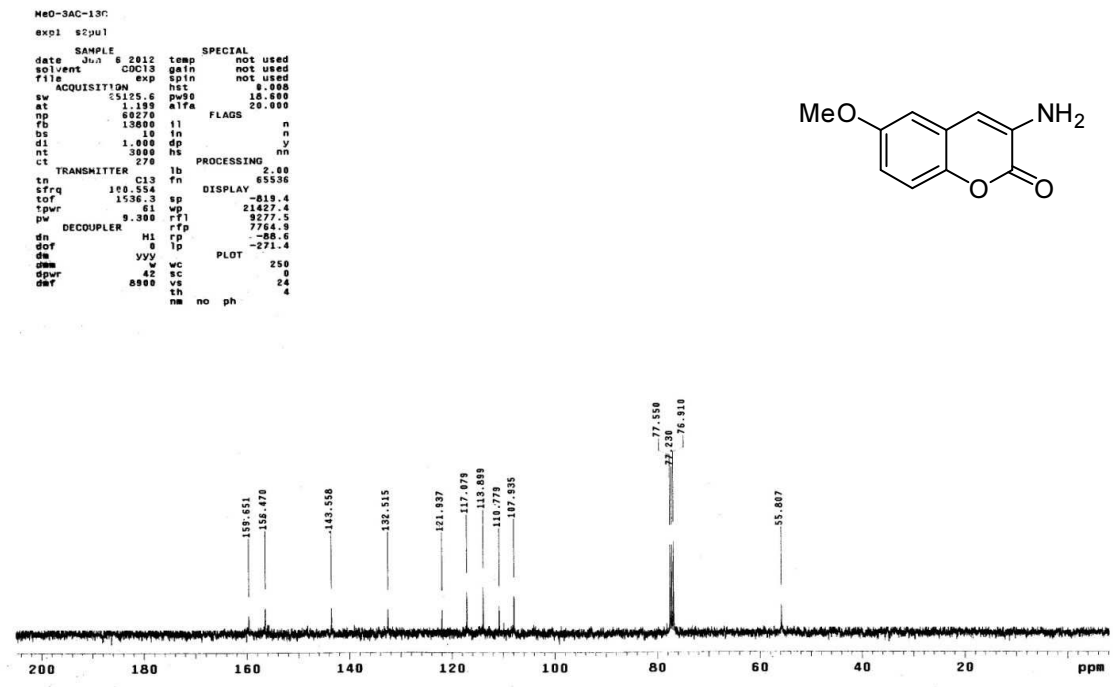
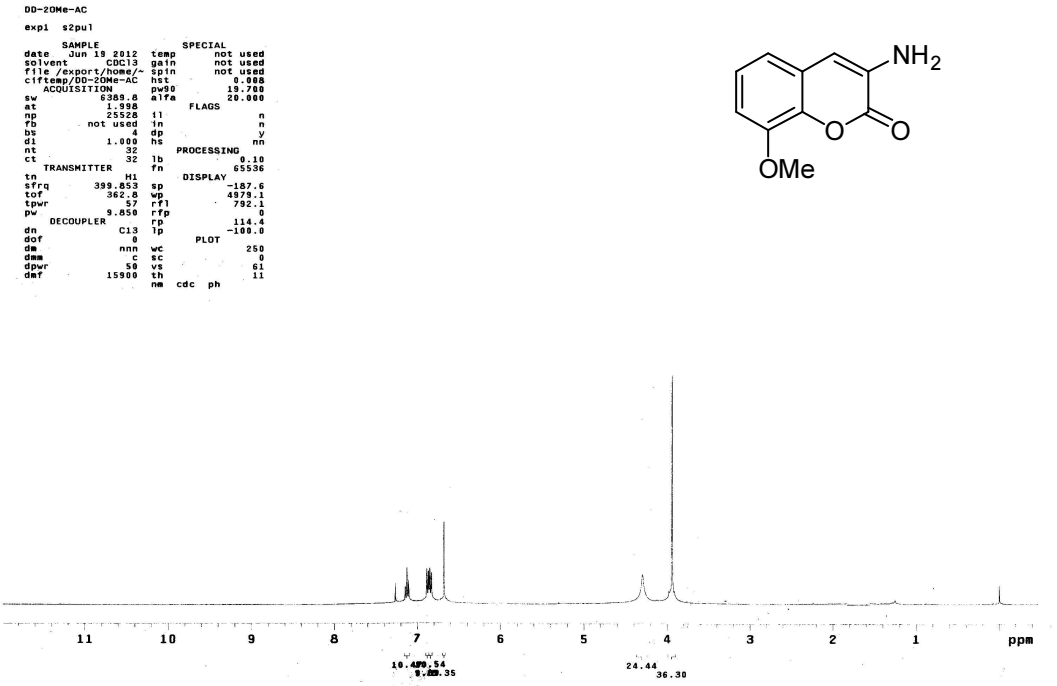


Figure 24

^{1}H NMR (400 MHz, $CDCl_3$): *8-Methoxy-3-aminocoumarin (**81e**)*



^{13}C NMR (100 MHz, $CDCl_3$): *8-Methoxy-3-aminocoumarin (**81e**)*

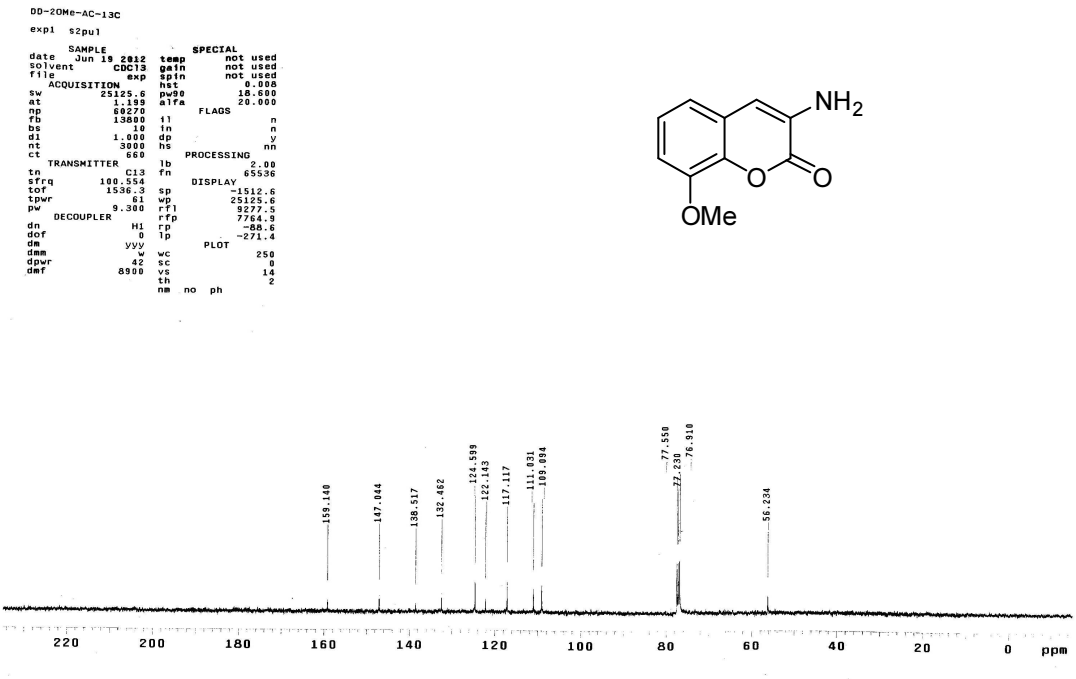
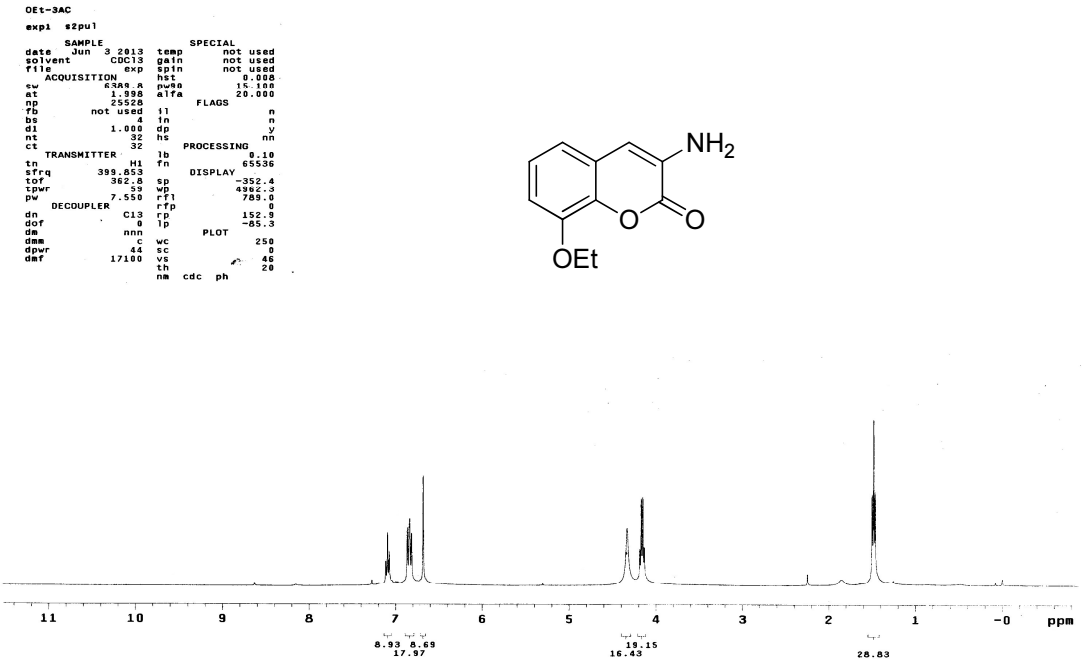


Figure 25

^{1}H NMR (400 MHz, $CDCl_3$): *8-Ethoxy-3-aminocoumarin (**81f**)*



^{13}C NMR (100 MHz, $CDCl_3$): *8-Ethoxy-3-aminocoumarin (**81f**)*

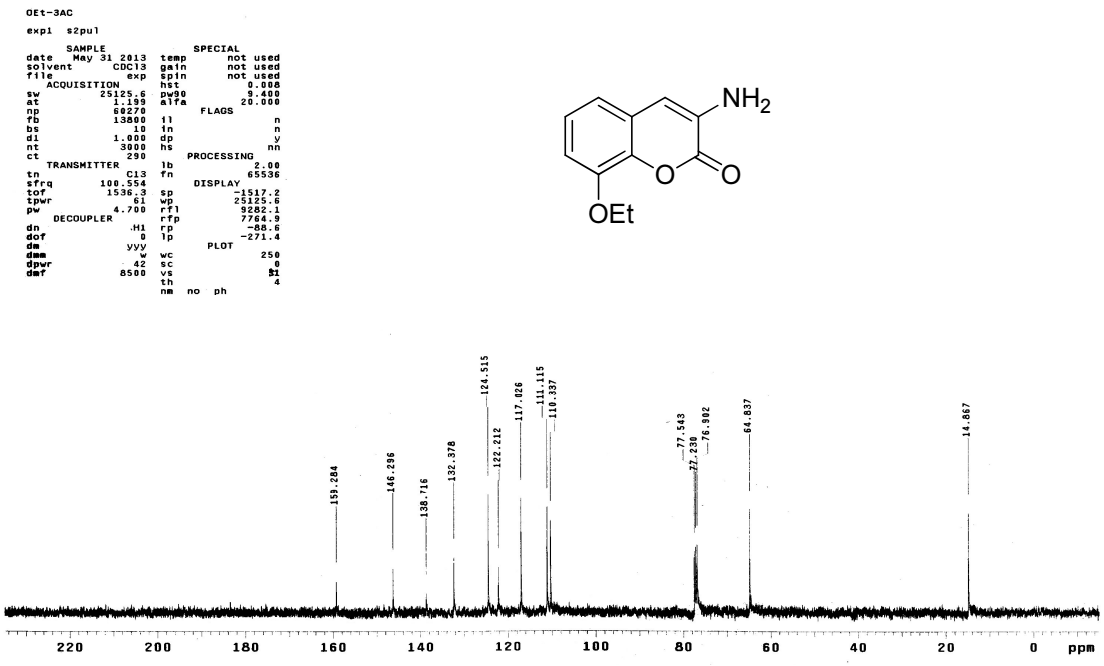


Figure 26

PART B

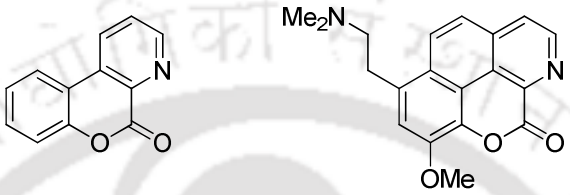
CHAPTER IVB

Iodine catalyzed three-component reaction: a straightforward expedient synthesis of functionalized pyrido[2,3-*c*] coumarin derivatives under metal-free condition

Review
Result & Discussion
Experimental

Pyridocoumarins and its importance

Pyridocoumarin derivatives are considered one of the 'privileged structures' in the medicinal chemistry due to their immense potentiality.[92] The pyrido[2,3-c]coumarin skeleton **82** constitutes the backbone of Santiagonamine **83** (Figure 27).[93] This alkaloid has been isolated from Berberis Darwinii (Berberidacea) and has shown interesting wound healing properties.[94]



82 **83**

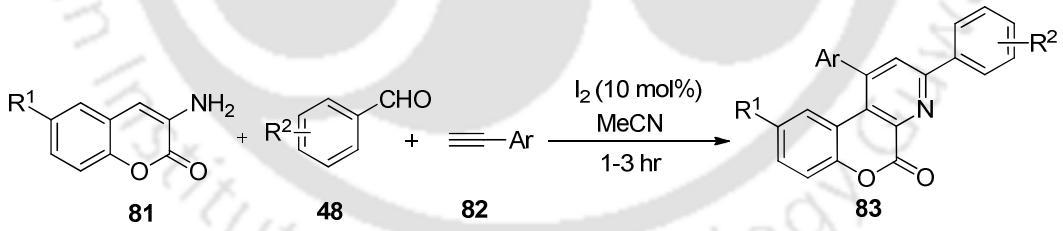
Figure 27

Pyridocoumarin derivatives are well known for their CNS depressant,[74a] anti-tumor,[74c] anti-inflammatory[74c] and anti-microbial activities.[71] Furthermore, they also exhibit interesting photochemical properties and have been used as laser dyestuffs,[95a-c] luminescence intensifiers,[96] and spasmolytics.[97] The wide range of biological activities exhibited by these compound motivated various research groups to put considerable efforts to synthesize these compounds in recent times.

Methods of synthesizing functionalized pyrido[2,3-c]coumarin

From the literature it is found that only few methods are known so far for the synthesis pyrido[2,3-*c*]coumarin. The first synthesis of pyrido[2,3-*c*]coumarin was reported by Gremal and his co-worker[98a] from 3-aminocoumarin in a moderate yield through Skraup reaction. A few years ago, Guillaumet *et al.* demonstrated the synthesis of these derivatives from 3-hydroxycoumarin in three steps sequence followed by dehydrogenation with DDQ.[98b] A few more methods for the synthesis of pyrido[2,3-*c*]coumarin derivatives from 3-aminocoumarin have already been discussed in previous chapter IIIB.[82-84] The demerits of all these protocols are low yield,[98a] requirement of expensive metal catalysts[82-84] and prolong reaction time.[84] Consequently, there is a further scope to develop a synthetic methodology using less expensive and environmentally benign catalyst.

Recently, we have also reported the synthesis of tetrahydroquinoline derivatives through one-pot multicomponent reaction involving Povarov reaction which is discussed in Chapter IIB of Part B. Therefore, we intended to explore Povarov reaction for the synthesis of pyrido[2,3-c]coumarin derivatives from 3-aminocoumarins, aromatic aldehydes and phenylacetylenes. It is well established in the literature that the combination of aryl amines, aromatic aldehydes and alkynes has been exploited for the synthesis of various quinoline derivatives through MCRs using molecular iodine in nitromethane[99a] or using expensive metal catalysts.[99b-e] Likewise, the synthesis of imidazo[1,2-a]pyridines were accomplished from 2-aminopyridine, aromatic aldehydes and acetylenes.[100] Majumdar et al. demonstrated synthesis of pyrano[3,2-g] quinoline derivatives using either 6-aminocoumarin or 6-amino quinolone through Povarov reaction using $BF_3.OEt_2$.[101] Recently it has found that molecular iodine is a suitable catalyst for MCRs as it is a less expensive, non-toxic, easily available and environmentally acceptable. Hence, it has been used for MCRs by us[103] as well as by others.[102] The importance and usefulness of molecular iodine in various organic transformations has been reviewed recently.[104] In this chapter, a one-pot synthesis of pyrido[2,3-c]coumarin derivatives involving molecular iodine via imino-Diels-Alder reaction using 3-aminocoumarins, aromatic aldehydes, and phenylacetylenes is presented as shown in Scheme 33.



Scheme 33

Results and Discussion

For the present study, the mixture of 4-chlorobenzaldehyde (1 mmol), 3-aminocoumarin (1 mmol) and phenylacetylene (1.5 mmol) in 4 mL of acetonitrile was refluxed in presence of 5 mol% of molecular iodine and the product pyrido[2,3-c]coumarin derivative **83b** was obtained in 68% yield (Table 7, entry 1). The product **83b** was characterized by ^1H NMR, ^{13}C NMR spectra and elemental analysis. The same set of reactions was carried out using 10 mol% and 20 mol% I_2 (entries 2-3, Table 7)

successively and the desired product **83b** was obtained in 82 % and 78% yield, respectively. It was observed that the yield of the product was increased significantly by increasing the amount of catalyst from 5% to 10%.

Table 7. Optimization of reaction conditions for the synthesis of pyrido[2,3-c]coumarin derivative (**83b**)

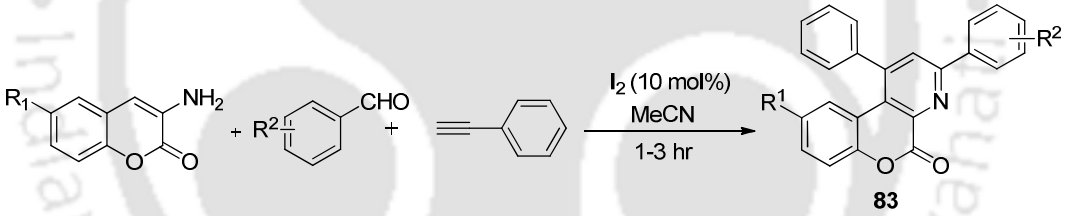
Entry	Catalyst	mol% of catalyst	Solvent	Reaction Condition	Time/h	Yield[b]
1	Iodine	5	CH_3CN	reflux	3.5	68
2	Iodine	10	CH_3CN	reflux	2.5	82
3	Iodine	20	CH_3CN	reflux	2.5	78
4	Iodine	10	CH_3NO_2	reflux	2.5	78
5	Iodine	10	Toluene	reflux	3.5	70
6	Iodine	10	DCE	reflux	3.5	56
7	Iodine	10	EtOH	reflux	6.0	42
8	Iodine	10	CH_3CN	rt	12.0	22
9	CAN	10	CH_3CN	reflux	12.0	26
10	TfOH	10	CH_3CN	reflux	12.0	48
11	$InCl_3$	10	CH_3CN	reflux	12.0	36
12	AgOTf	10	CH_3CN	reflux	12.0	00
13	--		CH_3CN	reflux	12.0	00

[a]All the reactions were performed with 3-aminocoumarin (1.0 mmol), 4-chlorobenzaldehyde (1.0 mmol) and phenylacetylene (1.5 mmol). [b] Isolated yields.

For scrutinizing a suitable solvent system, similar reactions (entries 4-7) were conducted in various solvent systems such as nitromethane, toluene, dichloroethane (DCE) and ethanol under reflux conditions. It was noted that the shortest reaction time and best yield are obtained in acetonitrile (entry 2) under reflux conditions. It was also noted that similar reaction can be performed with nitromethane in the same yield. However, all the reactions were carried out in acetonitrile due to its low cost and reduced toxicity as compared to nitromethane. Interestingly, the same reaction provided low yield when it was carried out in room temperature (Table 7, entry 8). Now to examine the efficacy of molecular iodine as compared to other catalysts, several reactions were also scrutinized in the presence of catalysts like CAN, AgOTf and $InCl_3$ (Table 7, entries 9-12).

We performed a reaction with a mixture of 3-aminocoumarin, benzaldehyde and phenylacetylene under the optimized conditions and the desired product **83a** was obtained in 78% yield. To explore the synthetic scope and the generality of the present protocol,[20] various reactions were examined with a wide variety of aromatic aldehydes containing different substituents in the aromatic ring such as Br, F, Me, OMe, and NO_2 with 3-aminocoumarin and phenylacetylene. The reaction time and percentage yield of the products (**83c-i**) are shown in Table 8 (entries 3-9). It is worthwhile to mention that the pure products were isolated simply by filtration, which was purified by recrystallization using dichloromethane-hexane solvent system. Other substituted 3-aminocoumarins such as 6-bromo-3-aminocoumarin and 6-methoxy-3-aminocoumarin were also tested with aromatic aldehyde and phenyl acetylene under the optimized reaction conditions and the desired pyrido[2,3-c]coumarin derivatives **83j-o** were obtained in good yields (Table 8, entries 10-15).

Table 8. Synthesis of various substituted pyrido[2,3-c]coumarin derivatives using Povarov reaction[a]



83

Entry	R_1	R_2	Product	Time/h	Yield[b] %
1	H	H	**83a**	3	78
2	H	4-Cl	**83b**	2.5	82
3	H	4-Br	**83c**	1	88
4	H	4-F	**83d**	3	82
5	H	2-Cl	**83e**	3	72
6	H	4-Me	**83f**	1	88
7	H	4-OMe	**83g**	1	89
8	H	4-NO_2	**83h**	0.25	94
9	H	4-CN	**83i**	0.5	91
10	Br	4-Cl	**83j**	3	81
11	Br	4-Br	**83k**	3	78
12	Br	4-Me	**83l**	2	77

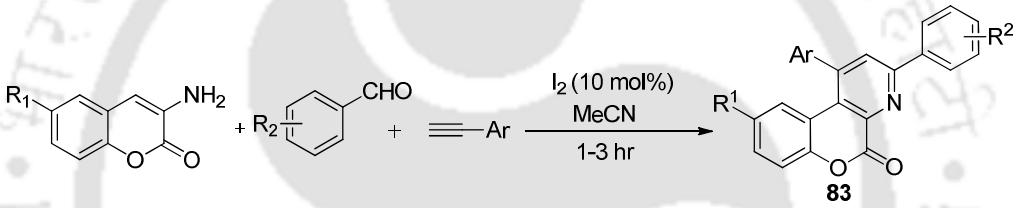
Continued

13	Br	4-MeO	**83m**	2	76
14	OMe	4-Cl	**83n**	2	78
15	OMe	4-Me	**83o**	2	76

[a]The reactions were carried out with 3-aminocoumarins (1.0 mmol), aromatic aldehydes (1.0 mmol) and phenylacetylene (1.5 mmol) in presence of 10 mol % of iodine in 4 mL of CH_3CN under reflux conditions. [b]Isolated yields.

Furthermore, the same reactions were also executed with different substituted phenylacetylenes with 3-aminocoumarin and aromatic aldehyde to give the products (**83p-v**) (Table 9, entries 1-7). However, we did not get the desired product when aliphatic aldehyde such as cyclohexaldehyde was treated with 3-aminocoumarin and phenylacetylene in presence of I_2 under identical reaction conditions.

Table 9. Synthesis of various substituted pyrido[2,3-c]coumarin derivatives using Povarov reaction[a]



83

Entry	R_1	R_2	Ar	Product	Time	Yield
1	H	4-Cl	4-$CH_3C_6H_4$-	**83p**	2	75
2	OMe	H	4-$CH_3C_6H_4$-	**83q**	2	72
3	OMe	4-F	4-$CH_3C_6H_4$-	**83r**	2	78
4	H	4-Cl	3,4-$(CH_3)_2C_6H_3$-	**83s**	2	76
5	H	4-Cl	3,5-$(CH_3)_2C_6H_3$-	**83t**	2	81
6	H	4-Cl	4-*tert*-Bu-C_6H_4-	**83u**	2	82
7	H	4-Cl	1-$C_{10}H_7$-	**83v**	2.5	78

[a]The reactions were carried out with 3-aminocoumarins (1.0 mmol), aromatic aldehydes (1.0 mmol) and substituted phenylacetylenes (1.5 mmol) in presence of 10 mol % of iodine in 4 mL of CH_3CN under reflux conditions. [b]Isolated yields.

The structure of one of the representative compounds such **83o** was confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 28). All the structures were confirmed from ^1H NMR, ^{13}C NMR spectra and from their elemental analysis. The ^1H NMR spectra and ^{13}C NMR spectra of the products **83a, 83g, 83o** and **83s** are given in Figures **29-34**, respectively in the experimental section.

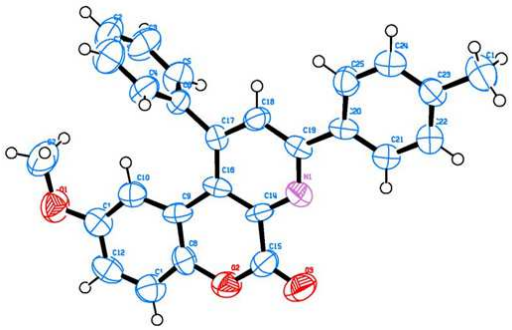
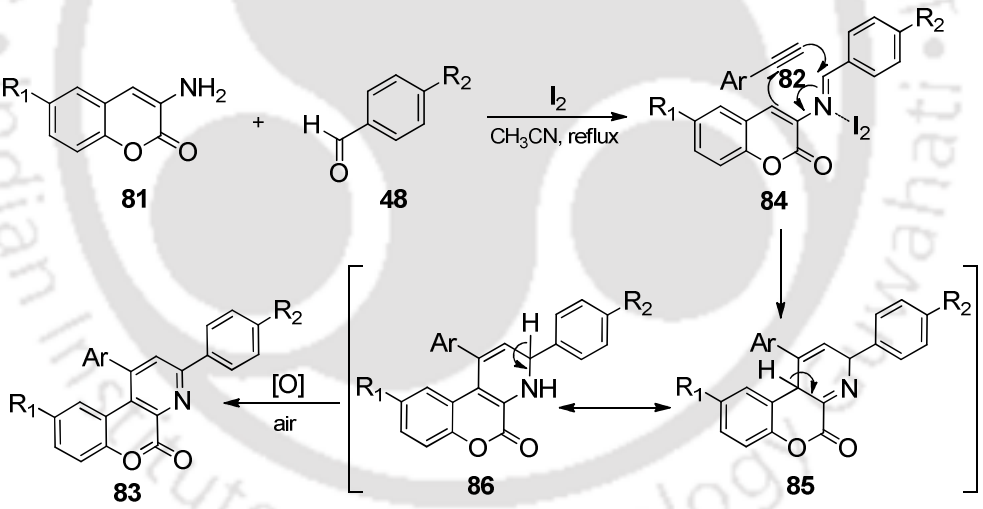


Figure 28. Single crystal X-ray structure **83o** (CCDC 876435)

The formation of the product may be explained as follows: We believe that the condensation reaction between 3-aminocoumarin **81** and aromatic aldehyde **48** leads to the formation of intermediate imines **84**, which undergoes Povarov reaction with dienophile such as alkyne **82** to afford pyrido[2,3-c]coumarin derivatives **83** through the intermediate dihydropyridine **85** followed by aerial oxidation as shown in Scheme 34.



Scheme 34: Mechanism for the formation for the synthesis of pyrido[2,3-c]coumarin derivatives

In conclusion, we have demonstrated a more efficient and expedient synthetic protocol for the synthesis of pyrido[2,3-*c*] coumarin derivatives by employing environmentally benign catalyst molecular I_2 *via* one-pot three-component condensation reaction from a wide variety of 3-aminocoumarins, aromatic aldehydes and phenylacetylenes without

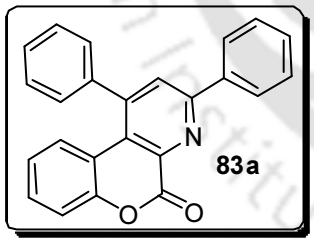
involving any co-oxidant in good yields. In addition, co-oxidant such as nitromethane can be avoided which is harmful and expensive. The reaction conditions are simple and transformation is quite effective for a wide range of aldehydes and phenylacetylenes. The products can be easily isolated in good to excellent yields without aqueous work-up or chromatographic separation or involvement of metal catalyst.

Genaral procedure for the synthesis of pyrido[2,3-c]coumarin derivative

A mixture of 3-aminocoumarin (1.0 mmol) and aromatic aldehyde (1.0 mmol) in 4 mL of CH_3CN was taken in a 25 mL round bottomed flask. Then, phenyl acetylene (1.5 mmol) and 10 mol% of molecular iodine (0.025 g) were added successively into the above reaction mixture. Then, the reaction flask was transferred into a heated oil-bath for refluxing. The progress of the reaction was monitored by checking TLC from time to time. As soon as the reaction approaches towards its end, a solid precipitate starts appearing slowly after stipulated time as mentioned in the Tables 8 and 9. The reaction flask was then removed from the oil-bath and it was brought to room temperature for complete precipitation. The solid precipitate was filtered off through a Büchner funnel and was washed with cold 10 mL of hexane-ethyl acetate mixture (1:1) to remove any unreacted starting materials. Finally it was dried through a vacuum pump and the pure product pyrido[2,3-c]coumarin derivative was obtained after recrystallization from dichloromethane and hexane.

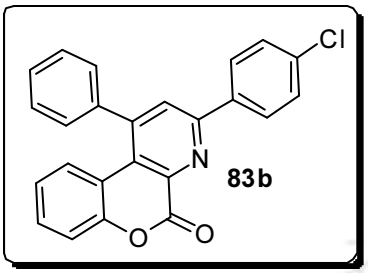
Spectral data of pyrido[2,3-c]coumarins

*1,3-diphenyl-5H-chromeno[3,4-b]pyridin-5-one (**83a**).*



White powder (0. 272 g, 78%); mp 224-225 °C; R_f (30% ethyl acetate/hexane) 0.37; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.86-6.90 (m, 1 H), 7.05 (d, J = 8 Hz, 1 H), 7.34-7.38 (m, 2 H), 7.42-7.51 (m, 5 H), 7.52-7.60 (m, 3 H), 7.96 (s, 1 H), 8.11 (d, J = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) 117.20, 117.82, 123.83, 127.45, 127.60, 127.78, 128.34, 129.02, 129.25, 129.66, 130.30, 130.49, 137.18, 139.32, 139.84, 149.03, 150.98, 157.51, 159.12; **IR** (KBr) = 3084, 1757, 1606 cm^{-1}; **Anal. Calcd** for $C_{24}H_{15}NO_2$ (349.38) requires C, 82.50; H, 4.33; N, 4.01%; found: C, 82,56; H, 4.41; N, 4.09. **HRMS** (ESI): $[M+H]^+$, Found: *m/z* 350.1317. $C_{24}H_{15}NO_2$ requires 350.1103.

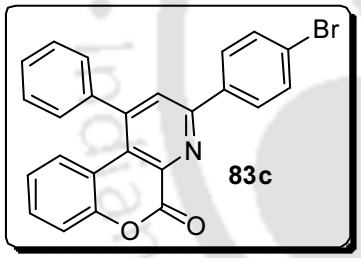
*3-(4-chlorophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83b**).*



83b

White powder. (0.314 g, 82%); mp 249-250 °C; R_f (10% ethyl acetate/hexane) 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.16 (d, J = 8.4 Hz, 2H), 7.92 (s, 1H) 7.59-7.55 (m, 3H), 7.49-7.42 (m, 4H), 7.39-7.36 (m, 2H), 7.05 (d, J = 8 Hz, 1H), 6.90-6.86 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.09, 156.26, 151.08, 149.32, 139.77, 139.41, 136.65, 135.66, 130.72, 129.76, 129.41, 129.30, 128.76, 128.61, 128.37, 127.86, 127.38, 123.96, 117.95, 117.13; **IR** (KBr) =3086, 1758, 1590 cm^{-1}; **HRMS** (ESI): $[M+H]^+$, Found: *m/z* 384.1109. $C_{24}H_{14}ClNO_2$: $[M+H]^+$, 384.0713. **Anal. Calcd** for $C_{24}H_{14}ClNO_2$ (383.82) requires C, 75.19; H, 3.74; N, 3.73; found: C, 75.10; H, 3.68; N, 3.65.

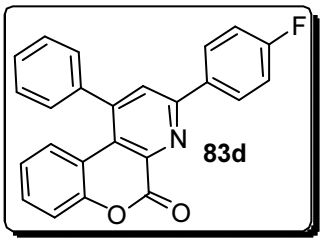
*3-(4-bromophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one(**83c**):*



83c

White powder. (0.376 g, 88%); R_f (10% ethyl acetate/hexane) 0.40; mp 279-280 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.09 (d, J = 8.4 Hz, 2H), 7.92 (s, 1H) 7.62 (d, J = 8.4 Hz, 1H), 7.59-7.56 (m, 3H), 7.46-7.43 (m, 2H), 7.38-7.34 (m,2H), 7.05 (d, J = 8 Hz, 1H), 6.90-6.86 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.07, 156.36, 151.10, 149.37, 139.77, 139.49, 136.14, 132.28, 130.74, 129.78, 129.42, 129.01, 128.68, 128.37, 127.87, 127.34, 125.12, 123.97, 117.98, 117.15. **IR** (KBr) = 3082, 1756, 1585 cm^{-1}. **Anal. Calcd** for $C_{24}H_{14}BrNO_2$(427.27) requires C, 67.31; H, 3.29; N, 3.27; found: C, 67.41; H, 3.36; N, 3.22.

*3-(4-fluorophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83d**):*

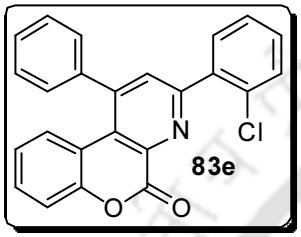


83d

White powder (0.301 g, 82%);. mp 224-225 °C; R_f (10% ethyl acetate/hexane) 0.41; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.23-8.19 (m, 2H), 7.91 (s, 1H) 7.58-7.56 (m, 3H), 7.46-7.43 (m, 2H), 7.37 (d, J = 4 Hz, 2H), 7.18(t, J = 8.4 Hz, 2H), 7.05 (d, J =7.6 Hz, 1H), 6.91-6.86 (m, 1H); **^{13}C NMR** (100 MHz,

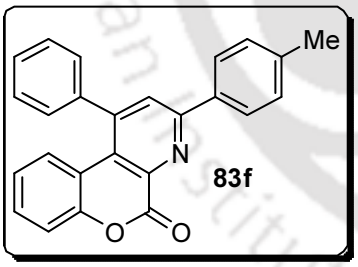
$CDCl_3$) 159.16, 156.50, 151.04, 149.28, 139.81, 139.36, 133.48, 130.62, 129.74, 129.56, 129.47, 129.37, 128.36, 127.81, 127.34, 123.93, 117.93, 117.17, 116.21, 116.0; **IR** (KBr) 3082, 1751, 1602 cm^{-1}; **Anal. Calcd** for $C_{24}H_{14}FNO_2$ (367.37) requires C, 78.46; H, 3.84; N, 3.81; found: C, 78.51; H, 3.92; N, 3.93.

*3-(2-chlorophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one: (**83e**):*



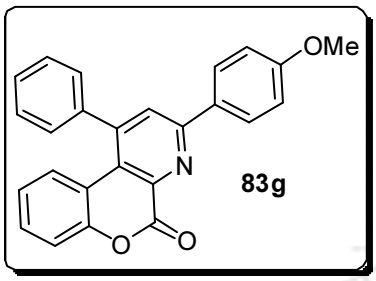
White powder. (0.275 g, 72%); mp 297-298 °C; R_f (10% ethyl acetate/hexane) 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.95 (s, 1H), 7.86 (dd, J =7.6, 1.6 Hz, 1H), 7.55-7.52 (m, 3H), 7.50-7.42 (m, 3H), 7.41-7.35 (m, 4H), 7.10 (d, J =8.0 Hz, 1H), 6.91-6.86 (m,1H); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.12, 157.45, 151.26, 147.98, 139.57, 138.82, 138.92, 137.50, 132.43, 130.89, 130.74, 130.27, 129.72, 129.37, 128.79, 128.44, 128.05, 127.59, 123.93, 118.02, 117.13. **IR** (KBr)3057, 1746, 1604 cm^{-1} **Anal. Calcd** for $C_{24}H_{14}ClNO_2$ (383.82) requires C, 75.10; H, 3.68; N, 3.65; found: C, 75.16; H, 3.74; N, 3.78.

*1-phenyl-3-p-tolyl-5H-chromeno[3,4-b]pyridin-5-one (**83f**):*



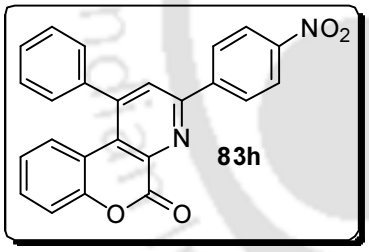
White powder. (0.319 g, 88%); mp 236-237 °C; R_f (10% ethyl acetate/hexane) 0.47; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.11 (d, J = 8.0 Hz, 2H), 7.92 (s, 1H) 7.61-7.52 (m, 3H), 7.47-7.42 (m, 2H), 7.34-7.32 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 1H) 6.85-6.89 (m, 1H), 2.41 (s, 3H, -Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.28, 157.56, 150.97, 148.94, 140.65, 139.98, 139.30, 134.41, 130.36, 129.79, 129.65, 129.22, 128.40, 128.06, 127.75, 127.36, 123.81, 117.84,117.33, 21.53; **IR** (KBr) 2919, 1754, 1607 cm^{-1}. **Anal. Calcd** for $C_{25}H_{17}NO_2$(363.40) requires C, 82.63; H, 4.72; N, 3.85; found: C, 82.69; H, 4.76; N, 3.91.

*3-(4-methoxyphenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83g**):*



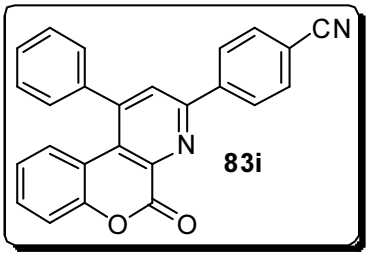
White powder. (0.337 g, 89%); mp 207-208 °C; R_f (10% ethyl acetate/hexane) 0.42; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.19 (d, *J* = 9.2 Hz, 2H), 7.89 (s, 1H), 7.57-7.55 (m, 3H), 7.47-7.42 (m, 2H), 7.37-7.32 (m, 2H), 7.04-6.90 (m, 3H), 6.89-6.85 (m, 1H), 3.88 (s, 3H, -OMe); **^{13}C NMR** (100 MHz, $CDCl_3$) 161.41, 159.08, 156.86, 150.69, 148.70, 139.84, 138.98, 130.06, 129.51, 129.06, 128.75, 128.30, 127.56, 127.46, 126.65, 123.64, 117.57,117.19, 114.20, 55.36; **IR** (KBr) 2939, 1757, 1605 cm^{-1}. **HRMS** Calcd. for $C_{25}H_{17}NO_3$: $[M+H]^+$, 380.1063. Found: *m/z* 380.1063. **Anal. Calcd** for $C_{25}H_{17}NO_3$(379.40) requires C, 79.14; H, 4.52; N, 3.69; found: C, 79.21; H, 4.58; N, 3.74.

*3-(4-nitrophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83h**):*



White powder. (0.370 g, 94%); mp 304-305 °C; R_f (10% ethyl acetate/hexane) 0.28; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.41 (d, *J* = 8.8 Hz, 2H), 8.36 (d, *J* =8.8 Hz, 2H), 8.03 (s, 1H), 7.61-7.58 (m, 3H), 7.47-7.44 (m, 2H), 7.42-7.39 (m, 2H), 7.09 (d, *J* =7.6 Hz, 1H), 6.93-6.89 (m, 1H); **IR** (KBr) 3072, 1753, 1603 cm^{-1}; **HRMS** Calcd. for $C_{24}H_{14}N_2O_4$: $[M+H]^+$, 395.0954. Found: *m/z* 395.1018. **Anal. Calcd** for $C_{24}H_{14}N_2O_4$ (394.38) requires C, 73.09; H, 3.58; N, 7.10; found: C, 73.11; H, 3.66; N, 7.09.

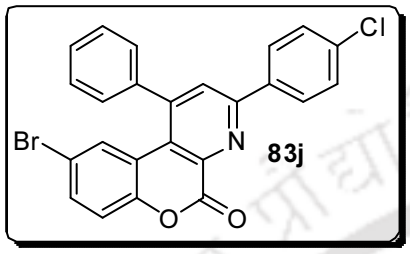
*4-(5-oxo-1-phenyl-5H-chromeno[3,4-b]pyridin-3-yl)benzonitrile (**83i**)*:



White powder. (0.340 g, 91%); Mp 302-303 °C; R_f (10% ethyl acetate/hexane) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.33 (d, *J* = 8.0 Hz, 2H), 7.98 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.60-7.58 (m, 3H), 7.47-7.44 (m, 2H), 7.42-7.35 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.90 (t, *J* = 8.4 Hz, 1H). **IR**

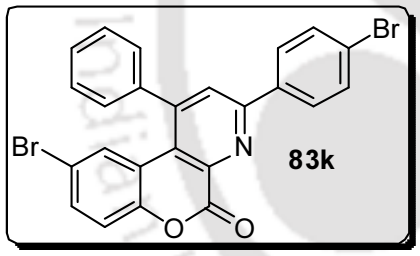
(KBr) 3056, 2223, 1754, 1605 cm^{-1}. **Anal. Calcd** for $C_{25}H_{14}N_2O_2$ (374.39) requires C, 80.20; H, 3.77; N, 7.48; found: C, 80.26; H, 3.78; N, 7.51.

*9-bromo-3-(4-chlorophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one(**83j**)*:



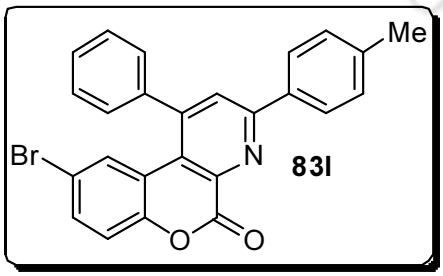
White powder. (0.372 g, 81%); R_f (10% ethyl acetate/hexane) 0.37; mp 291-292 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.16 (d, *J* = 8.4 Hz, 2H), 7.96 (s, 1H), 7.63-7.61 (m, 3H), 7.48-7.41 (m, 5H), 7.22 (d, *J* =8.8 Hz, 1H), 7.05 (d, *J* =2.0 Hz, 1H); **IR** (KBr) 2953, 1752, 1588 cm^{-1}; **HRMS** Calcd. for $C_{24}H_{13}BrClNO_2$: $[M+H]^+$, 461.9818. Found: *m/z* 461.9850. **Anal. Calcd** for $C_{24}H_{13}BrClNO_2$(460.72) requires C, 62.30; H, 2.83; N, 3.03; found: C, 62.46; H, 2.93; N, 3.01.

*9-bromo-3-(4-bromophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83k**)*:



White powder. (0.393 g, 78%); Mp 292-293 °C; R_f (10% ethyl acetate/hexane) 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.10 (d, *J* = 8.8 Hz, 2H), 7.97 (s, 1H), 7.65-7.60 (m, 5H), 7.48-7.41 (m, 3H), 7.25 (d, *J* =8.8 Hz, 1H), 7.06 (d, *J* =2.4 Hz, 1H). **IR** (KBr) 3139, 1753, 1602 cm^{-1}; **Anal. Calcd** for $C_{24}H_{13}Br_2NO_2$(504.17) requires C, 56.84; H, 2.58; N, 2.76; found: C, 56.91; H, 2.64; N, 2.82

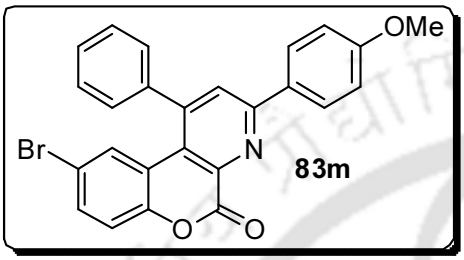
*9-bromo-1-phenyl-3-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one(**83l**)*:



White powder. (0.339 g, 77%); mp 306-307 °C; R_f (10% ethyl acetate/hexane) 0.37 **^{1}H NMR** (400 MHz, $CDCl_3$) 8.11 (d, *J* = 8.0 Hz, 2H), 7.96 (s, 1 H), 7.61-7.59 (m, 3H), 7.43-7.41 (m, 3H), 7.29 (d, *J* = 8.0Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 2.41 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 158.67, 158.23, 149.94, 149.19, 141.0, 139.21, 134.28, 133.08, 130.59, 129.88, 129.59,

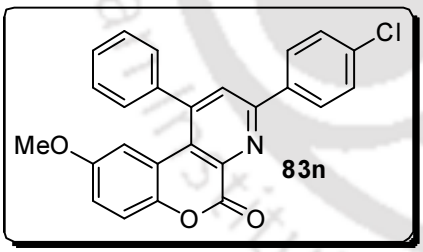
128.27, 127.49, 127.18, 126.98, 119.47, 119.08, 116.64, 21.61; **IR** (KBr) 3121, 1750, 1588 cm^{-1}; **Anal. Calcd** for $C_{25}H_{16}BrNO_2$ (441.30) requires C, 67.89; H, 3.65; N, 3.17; found: C, 67.91, H, 3.73; N, 3.22.

*9-bromo-3-(4-methoxyphenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83m**):*



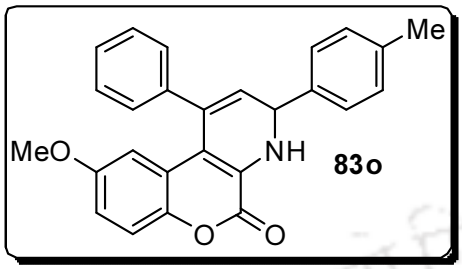
White powder. (0.347 g, 76%); mp 266-267 °C; R_f (10% ethyl acetate/hexane) 0.37; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.18 (d, *J* = 8.8 Hz, 2H), 7.93 (s, 1H), 7.62-7.59 (m, 3H), 7.44-7.41 (m, 3H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.03-6.99 (m, 3H), 3.88 (s, 3H, OMe); **^{13}C NMR** (100 MHz, $CDCl_3$) 161.80, 158.63, 157.71, 149.79, 149.06, 139.21, 132.86, 130.45,129.81, 129.51, 129.02, 128.24, 126.63, 126.49, 119.36, 119.07, 116.54, 114.45, 55.55; **IR** (KBr) 3056, 2933, 1750, 1606 cm^{-1}; **HRMS** Calcd. for $C_{25}H_{16}BrNO_3$: $[M+H]^+$, 458.0314. Found: *m/z* 458.1036. **Anal. Calcd** for $C_{25}H_{16}BrNO_3$ (458.30) requires C, 65.52; H, 3.52; N, 3.06; found: C, 65.56; H, 3.46; N, 3.12.

*3-(4-chlorophenyl)-9-methoxy-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83n**):*



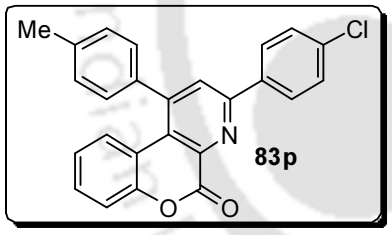
White powder. (0.322 g, 78%); mp 266-267 °C; R_f (10% ethyl acetate/hexane) 0.42; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.13 (d, *J* = 8.4 Hz, 2H), 7.89 (s, 1H) 7.62-7.53 (m, 3H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 9.2 Hz, 1H), 6.89 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 3.24 (s, 3H,-OMe); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.12, 156.06, 155.37, 149.19, 145.28, 139.89, 139.37, 136.67, 135.57, 129.79, 129.26, 128.71, 128.59, 128.42, 127.10, 119.19, 118.76, 117.24, 109.89, 54.97. **IR** (KBr) 3050, 1752, 1600 cm^{-1}. **Anal. Calcd** for $C_{25}H_{16}ClNO_3$(413.85) requires C, 72.55; H, 3.90; N, 3.38; found: C, 72.59; H, 3.96; N, 3.32

*9-methoxy-1-phenyl-3-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one (**83o**):*



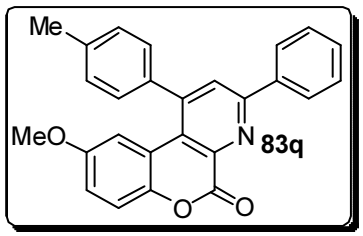
White powder. (0.298 g, 76%); Mp 219-220 °C; R_f (10% ethyl acetate/hexane) 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.13 (d, *J* = 8.0 Hz, 2 H), 7.94 (s, 1H), 7.62-7.52 (m, 3H), 7.47 (d, *J* = 8.0 2H), 7.32-7.28 (m, 3H), 6.93 (dd, *J* = 8.8, 2.8 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 3.25 (s, 3H, OMe), 2.43 (s, 3H, -Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.28, 157.27, 155.23, 148.75, 145.14, 140. 58, 140.07, 139.20, 134.28, 129.72, 129.66, 129.08, 128.60, 127.83, 127.28, 126.97, 118.8, 118.59, 117.40, 109.76, 54.89, 21.49. **IR** (KBr) 2986, 1745, 1598 cm^{-1}. **Anal. Calcd** for $C_{26}H_{19}NO_3$ (393.43) requires C, 79.37; H, 4.87; N, 3.56; found: C, 79.42; H, 4.92; N, 3.52.

*3-(4-chlorophenyl)-1-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one (**83p**):*



White powder. (0.298 g, 75%); Mp 221-222°C; R_f (10% ethyl acetate/hexane) 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.16 (d, *J* = 7.6 Hz, 2H), 7.90 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.39-7.35 (m, 5H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.93-6.89 (m, 1H), 2.51 (s, 3H, -Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 158.94, 155.94, 150.89, 149.36, 139.35, 139.19, 136.69, 136.43, 135.56, 130.49, 130.32, 129.12, 128.59, 128.18, 127.79, 127.32, 123.81, 117.70, 117.12, 21.53. **IR** (KBr) 3068, 1756, 1604 cm^{-1}. **Anal. Calcd** for $C_{25}H_{16}ClNO_2$ (397.85) requires C, 75.47; H, 4.05; N, 3.52; found: C, 75.42; H, 4.09; N, 3.58.

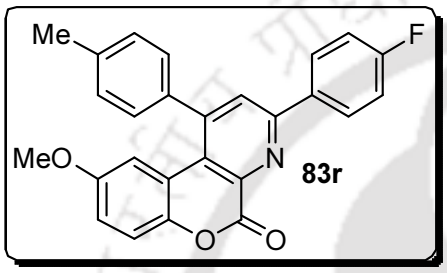
*9-methoxy-3-phenyl-1-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one (**83q**):*



White powder. (0.283 g, 72%); Mp 223-224 °C; R_f (10% ethyl acetate/hexane) 0.47; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.22 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.91 (s, 1H), 7.53-7.46 (m, 4H), 7.40 (d, *J* = 8.0, 2H), 7.36 (d, *J* = 8.0, 2H), 6.93 (dd, *J* = 8.8, 3.2 Hz, 1H), 6.64 (d, *J* = 2.8 Hz, 1H), 3.28 (s, 3H, -

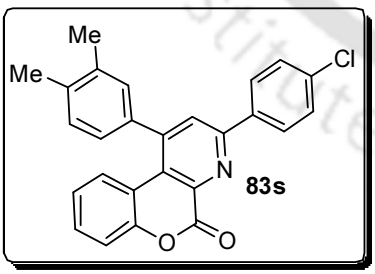
OMe), 2.48 (s, 3H, -Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.39, 157.47, 155.33, 149.12, 145.28, 139.39, 139.20, 137.31, 137.05, 130.31, 129.05, 128.52, 128.37, 127.50 ,118.70, 117.51, 109.96, 54.83, 21.44. **IR** (KBr) 2995, 1747, 1601 cm^{-1}; **Anal. Calcd** for $C_{26}H_{19}NO_3$ (393.43) requires C, 79.37; H, 4.87; N, 3.56; found: C, 79.42; H, 4.91; N, 3.62

*3-(4-fluorophenyl)-9-methoxy-1-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one (**83r**):*



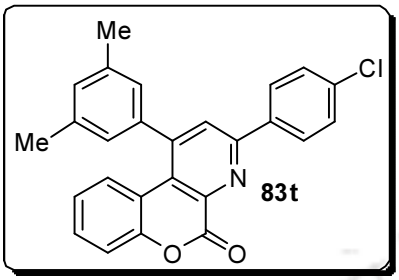
White powder (0.320 g, 78%); mp 246-247 °C; R_f (10% ethyl acetate/hexane) 0.37; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.21 (dd, *J* = 9.2,5.6 Hz, 2H), 7.90 (s, 1H) 7.40 (d, *J* = 8.8 Hz, 2H), 7.36-7.34 (m, 2H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.18 (t, *J* = 8.8 Hz, 2H), 6.92 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 3.28 (s, 3H, -OMe), 2.48 (s, 3H, -Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.21, 156.20, 155.20, 149.25, 145.18, 139.23, 136.88, 133.38, 130.29, 129.45, 129.36, 128.46, 128.23, 127.06, 118.93, 118.60, 117.35, 116.09, 115.87, 109.90, 54.80, 21.40. **IR** (KBr) 3000, 1746, 1599 cm^{-1}. **Anal. Calcd** for $C_{26}H_{18}FNO_3$(411.42) requires C, 75.90; H, 4.41; N, 3.40; found: C, 75.96; H, 4.48; N, 3.42

*3-(4-chlorophenyl)-1-(3,4-dimethylphenyl)-5H-chromeno[3,4-b]pyridin-5-one (**83s**):*



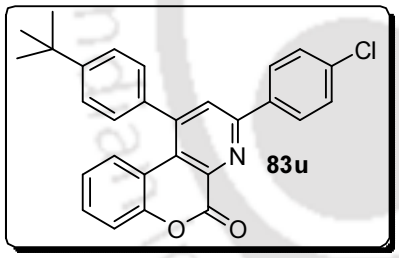
White powder. (0.312 g, 76%); mp 231-232 °C; R_f (10% ethyl acetate/hexane) 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.16 (d, *J* = 8.8 Hz, 2H), 7.91 (s, 1H) 7.46 (d, *J* = 8.8 Hz, 2H), 7.42-7.37 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.21 (s, 1H), 7.18-7.14 (m, 2H) 6.94-6.90 (m, 1H), 2.40 (s, 3 H, Me), 2.36 (s, 3 H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.03, 155.91, 150.87, 149.52, 139.15, 137.94, 137.11, 136.38, 135.62, 130.77, 130.47, 129.20, 129.12, 128.60, 127.89, 127.38, 125.67, 123.81, 117.68,117.19, 19.96, 19.85. **IR** (KBr) 2919, 1755, 1606 cm^{-1}; **Anal. Calcd** for $C_{26}H_{18}ClNO_2$(411.87) requires C, 75.82; H, 4.40; N, 3.40; Found: C, 75.96; H, 4.42; N, 3.46

*3-(4-chlorophenyl)-1-(3,5-dimethylphenyl)-5H-chromeno[3,4-b]pyridin-5-one (**83t**):*



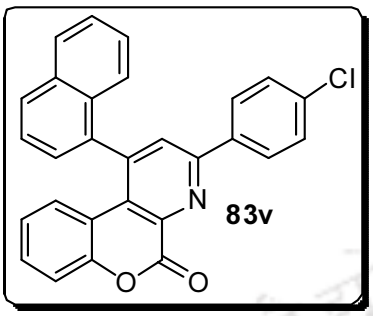
White powder. (0.333 g, 81%); mp 233-234 °C; R_f (10% ethyl acetate/hexane) 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.17 (d, *J* = 8.4 Hz, 2H), 7.91 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.39-7.37 (m, 3H), 7.19-7.13 (m, 2H), 7.03 (s, 1H) 6.94-6.89 (m, 1H), 2.40 (s, 6H, 2 x -Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.22, 156.18, 151.05, 149.77, 139.68, 139.50, 139.37, 136.57, 135.79, 130.90, 130.64, 129.28, 128.77, 128.63, 128.01, 127.37, 125.91, 123.94, 117.88,117.27, 21.54; **IR** (KBr) 2909, 1757, 1605 cm^{-1}; **HRMS** Calcd. for $C_{26}H_{18}ClNO_2$: $[M+H]^+$, 412.1026. Found: *m/z* 412.0956. **Anal. Calcd** for $C_{26}H_{18}ClNO_2$(411.87) requires C, 75.82; H, 4.40; N, 3.40; found: C, 75.91; H, 4.46; N, 3.51.

*1-(4-tert-butylphenyl)-3-(4-chlorophenyl)-5H-chromeno[3,4-b]pyridin-5-one (**83u**):*



White powder (0. 360 g, 82%); mp 289-290°C; R_f (10% ethyl acetate/hexane) 0.47; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.09 (d, *J* = 8.4 Hz, 2H), 7.86 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.40-7.36 (m, 4H), 7.34-7.24 (m, 2H), 7.08 (dd, *J = 8.4* Hz, 1H), 6.89-6.84 (m, 1H), 1.43 (s, 9H, 3x-Me); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.03, 155.97, 152.69, 150.91, 149.39, 139.22, 136.66, 136.45, 135.59, 130.52, 129.16, 128.63, 128.02, 127.83, 127.36, 126.56, 123.85, 117.75, 117.20, 35.0, 31.49; **IR** (KBr) 2963, 1751, 1605 cm^{-1}; **HRMS** Calcd. for $C_{25}H_{22}NO_2$: $[M+H]^+$, 440.1339. Found: *m/z* 440.2073. **Anal. Calcd** for $C_{28}H_{22}ClNO_2$ (439.93) requires C, 76.44; H, 5.04; N, 3.18; found: C, 76.49; H, 5.11; N, 3.22.

*3-(4-chlorophenyl)-1-(naphthalen-1-yl)-5H-chromeno[3,4-b]pyridin-5-one (**83v**).*



83v

White powder. (0.338 g, 78%); mp 279-280 °C; R_f (10% ethyl acetate/hexane) 0.37; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.14 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 8.4, 1H), 8.01-7.98 (m, 2H), 7.67(t, *J* = 7.6 Hz, 1H) 7.55-7.52 (m, 2H), 7.42-7.34 (m, 4H), 7.31-7.23 (m, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.64-6.60 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) 159.15, 156.35, 150.96, 147.76, 139.39, 137.16, 136.68, 135.57, 133.91, 130.68, 129.79, 129.64, 129.30, 128.87, 128.78, 128.35, 127.57, 127.22, 127.04, 126.39, 126.13, 125.10, 124.25, 117.85, 116.97. **IR** (KBr) 3058, 1752, 1608 cm^{-1}; **Anal. Calcd** for $C_{28}H_{16}ClNO_2$ (433.88) requires C, 77.51; H, 3.72; N, 3.23; found: C, 77.54; H, 3.79; N, 3.27.

*XRD for Compound **83o***

Complete crystallographic data of **83o** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication with CCDC no. 876435. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 10. Crystal data and structure parameters for **83o**.[a]

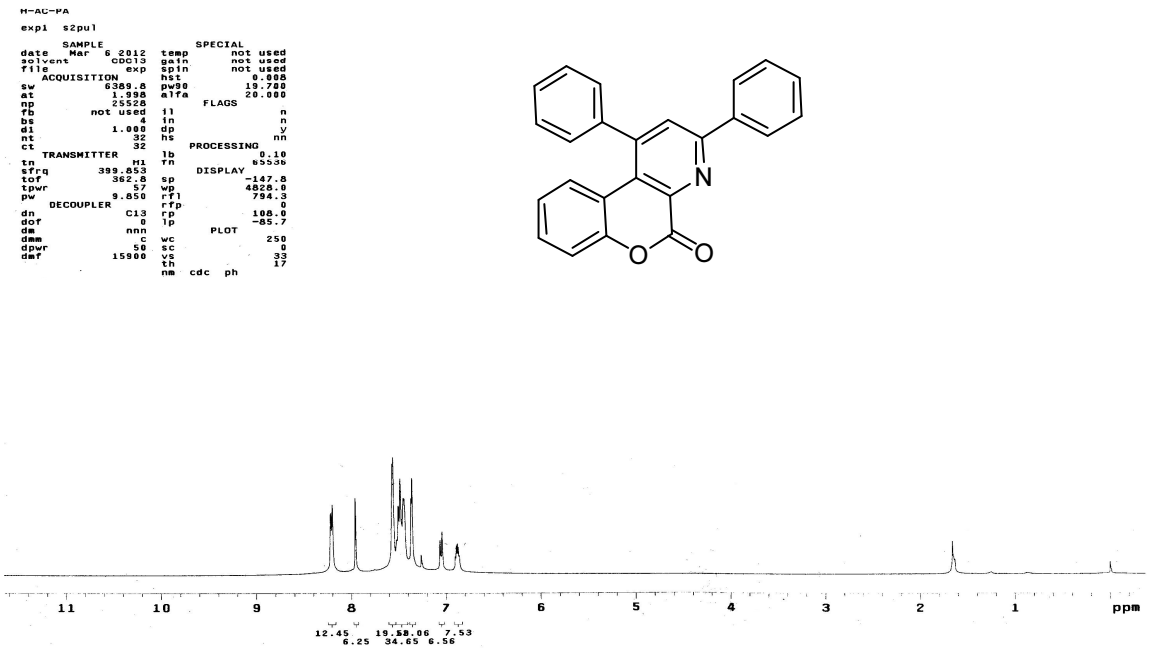
Parameters	**Compound 83o**	**Parameters**	**Compound 83o**
Empirical formula	C26 H19 N O3	Volume	2004.2(3)Å^3
Formula weight	393.42	Z	4
Temperature	298(2) K	Density (calculated)	1.304 g/cm^3
Wavelength	0.71073 Å	F(000)	824.0
Crystal system	Monoclinic	Theta range for data collection	2.21 to 16.72º
Space group	P 21/n	Index ranges	-9<=h<= 9, -12<=k<=12, -

Continued

			9<=l<= 9
Unit cell dimensions	a = 11.2920(9) Å , b = 15.4641(12)Å, c = 12.1879(10)Å	Independent reflections	1120 R_{int} = 0.0863
	α = 90.00º, β =109.659(5) º, γ =90.00	Completeness to θº	100% (θ = 16.83º)
Absorption coefficient	0.085 mm^{-1}	Reflections collected	11256
Data / restraints / parameters	7315 / 0 / 273	Final R indices [>2sigma(I)]	R_{obs} = 0.0394, wR_{obs} = 0.1047
Goodness-of-fit on F2	0.947	R indices (all data)	R_{all} = 0.0489, wR_{all} = 0.1163

[a]Refinement methods: full-matrix least-square on F^2.

^{1}H NMR (400 MHz, $CDCl_3$): *1,3-diphenyl-5H-chromeno[3,4-b]pyridin-5-one* ***(83a)***



^{13}C NMR (100 MHz, $CDCl_3$): *1,3-diphenyl-5H-chromeno[3,4-b]pyridin-5-one* ***(83a)***

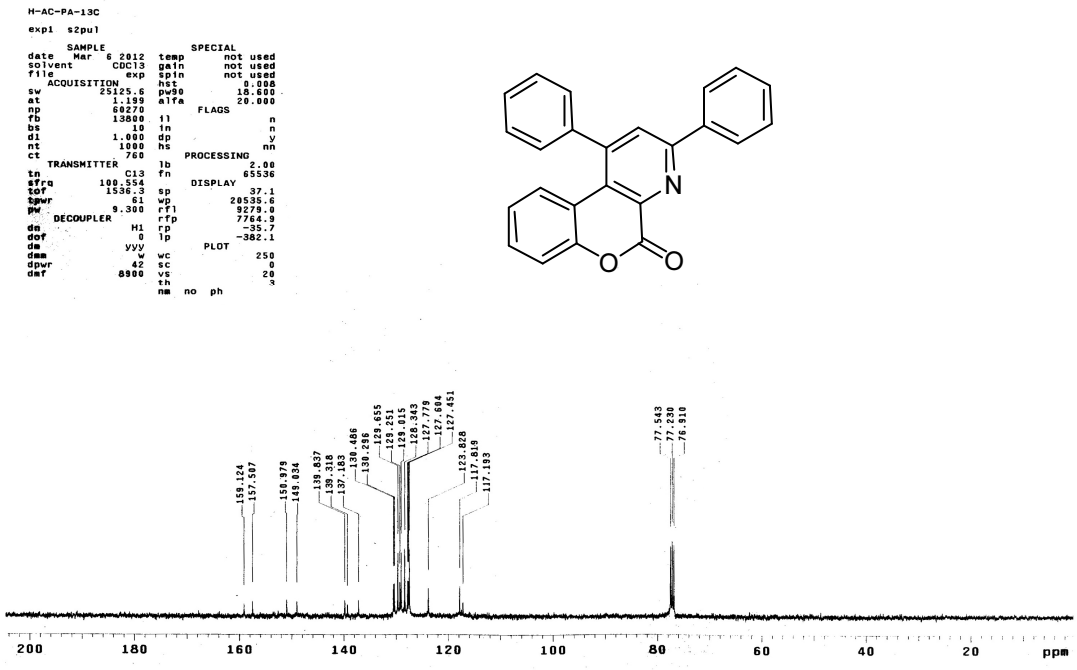
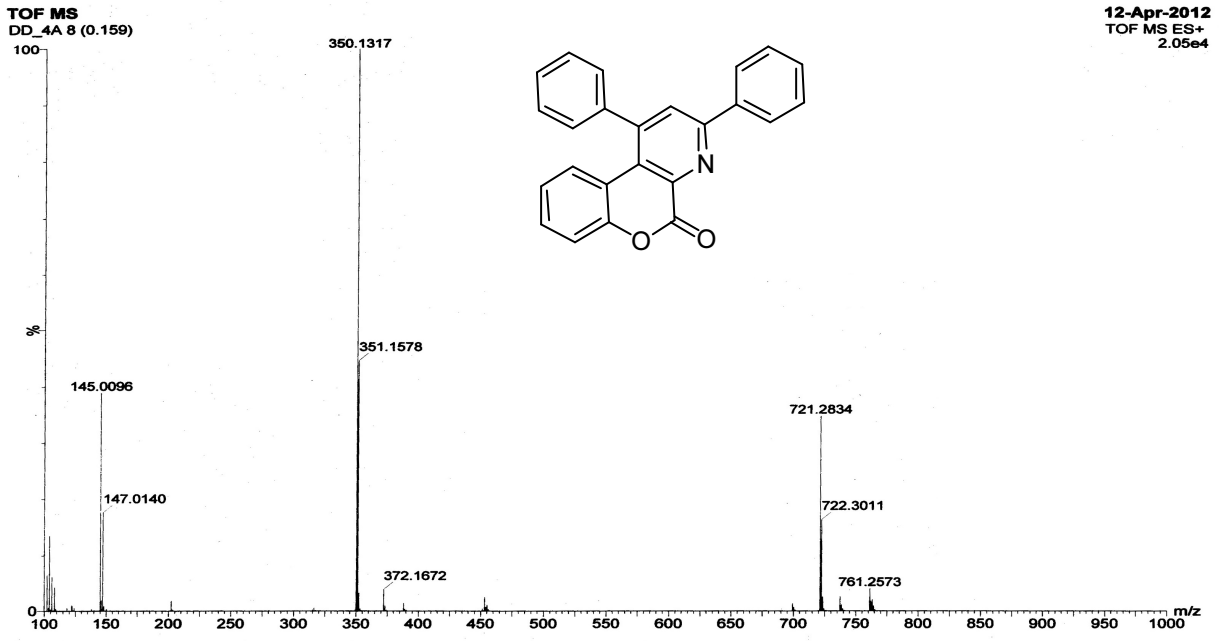


Figure 29

HRMS: *1,3-diphenyl-5H-chromeno[3,4-b]pyridin-5-one (**83a**)*



^{1}H NMR (400 MHz, $CDCl_3$): *3-(4-methoxyphenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83g**)*

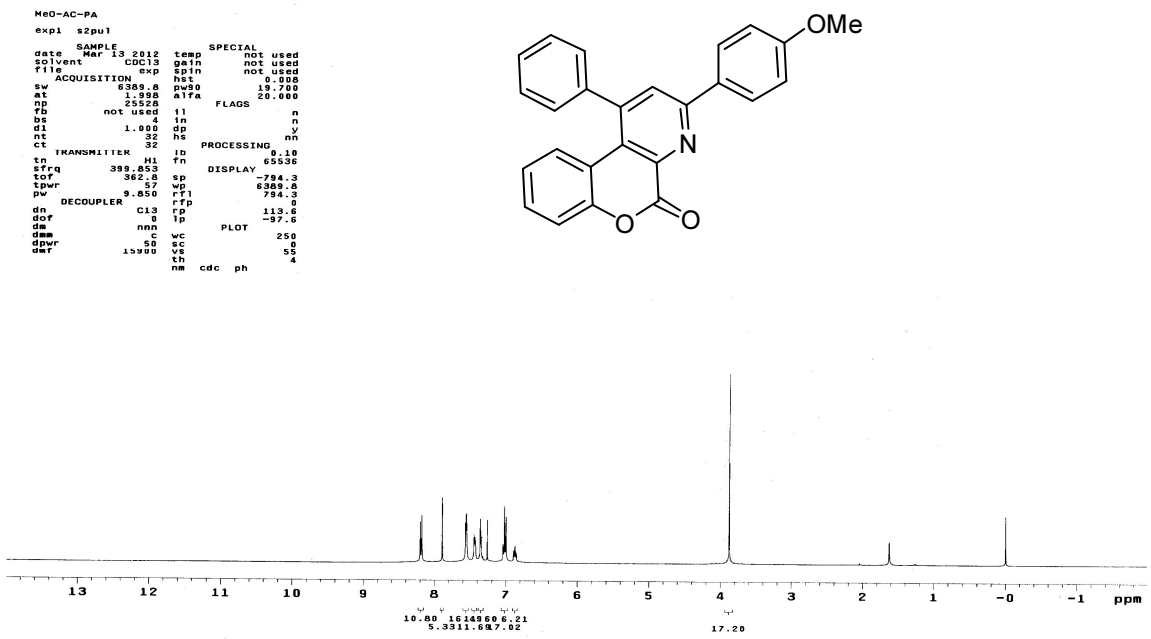
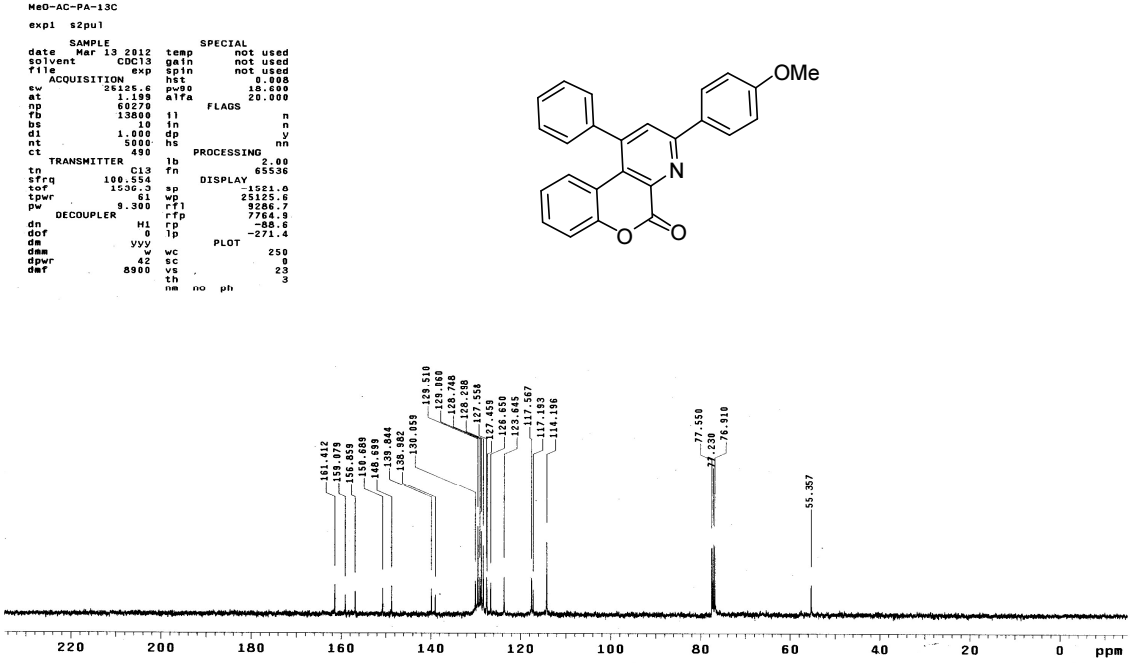


Figure 30

^{13}C NMR (100 MHz, $CDCl_3$): *3-(4-methoxyphenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one* ***(83g)***



HRMS: *3-(4-methoxyphenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one* ***(83g)***

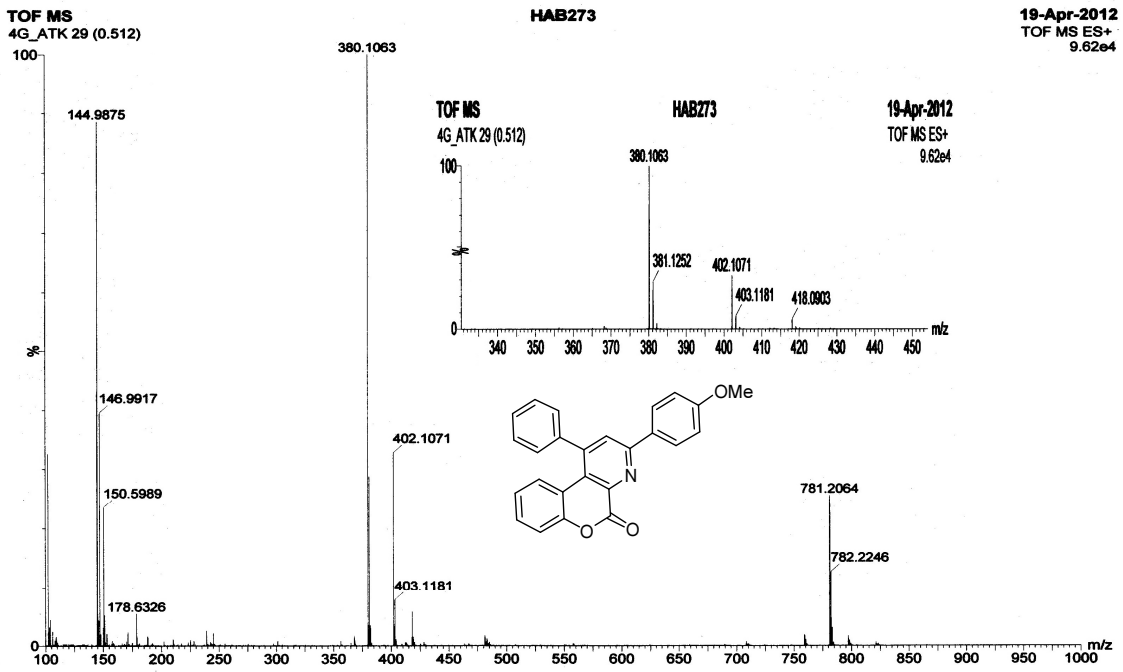
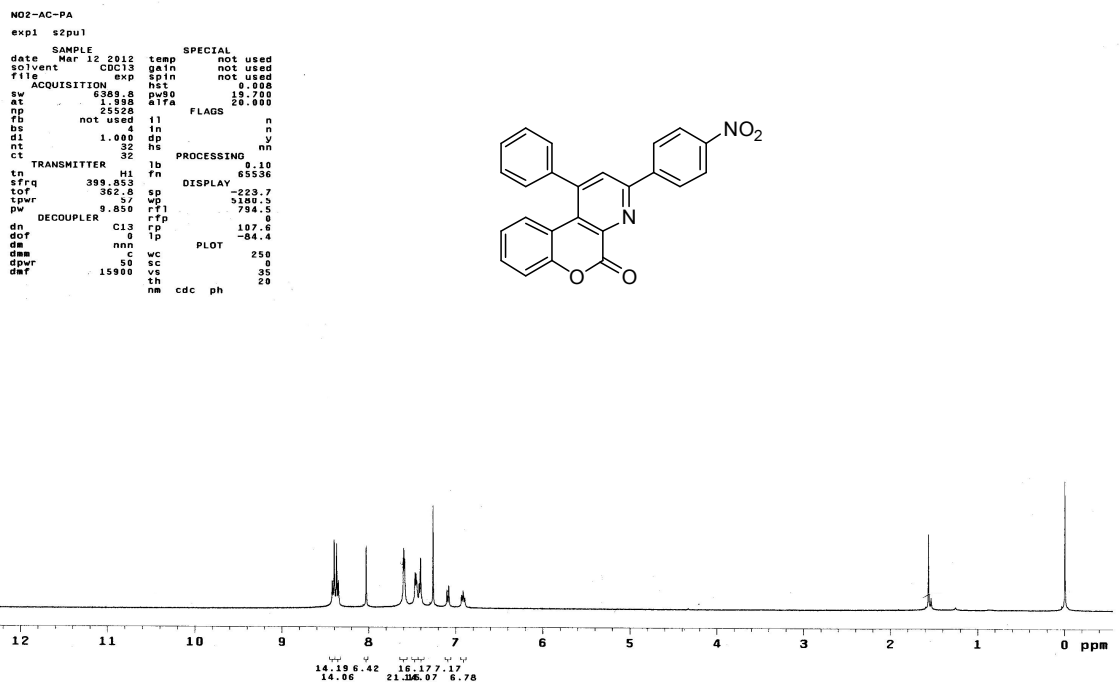


Figure 31

^{1}H NMR (400 MHz, $CDCl_3$): *3-(4-nitrophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83h**)*



HRMS: *3-(4-nitrophenyl)-1-phenyl-5H-chromeno[3,4-b]pyridin-5-one (**83h**)*

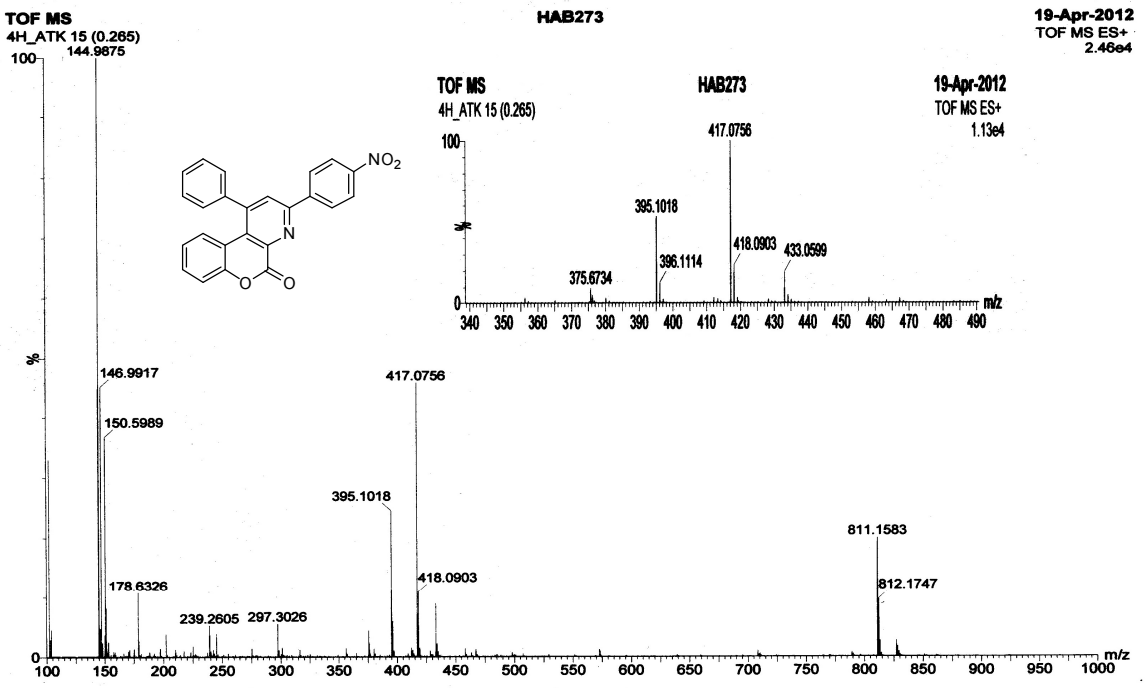
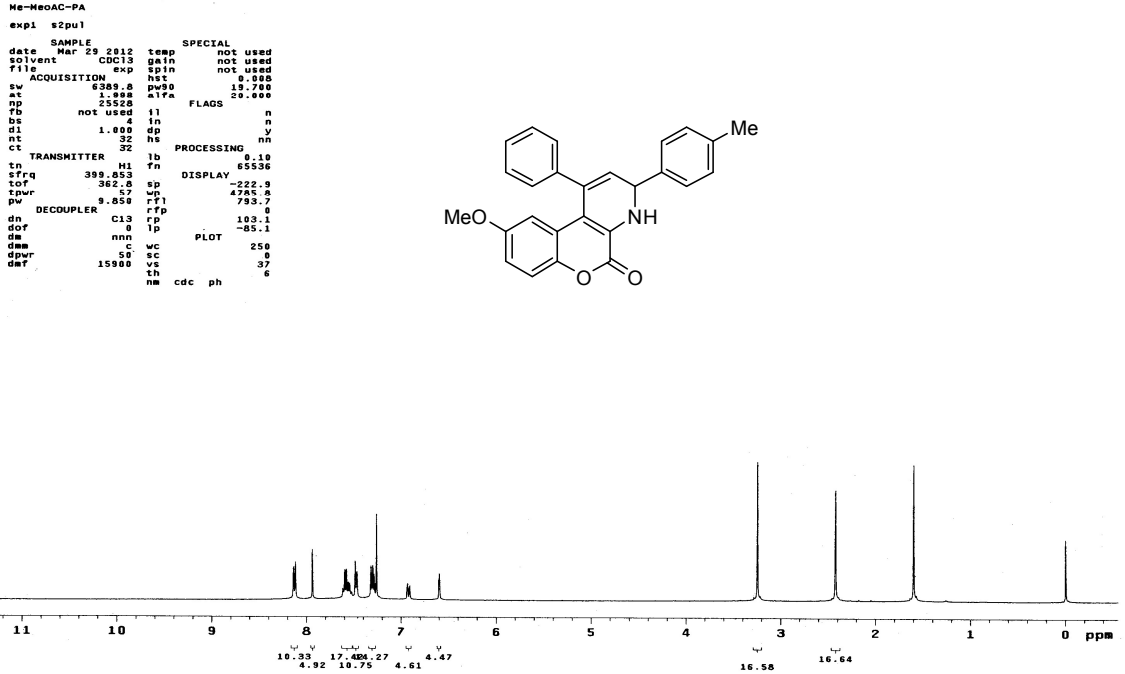


Figure 32

^{1}H NMR (400 MHz, $CDCl_3$): *9-methoxy-1-phenyl-3-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one (**83o**)*



^{13}C NMR (100 MHz, $CDCl_3$): *9-methoxy-1-phenyl-3-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one (**83o**)*

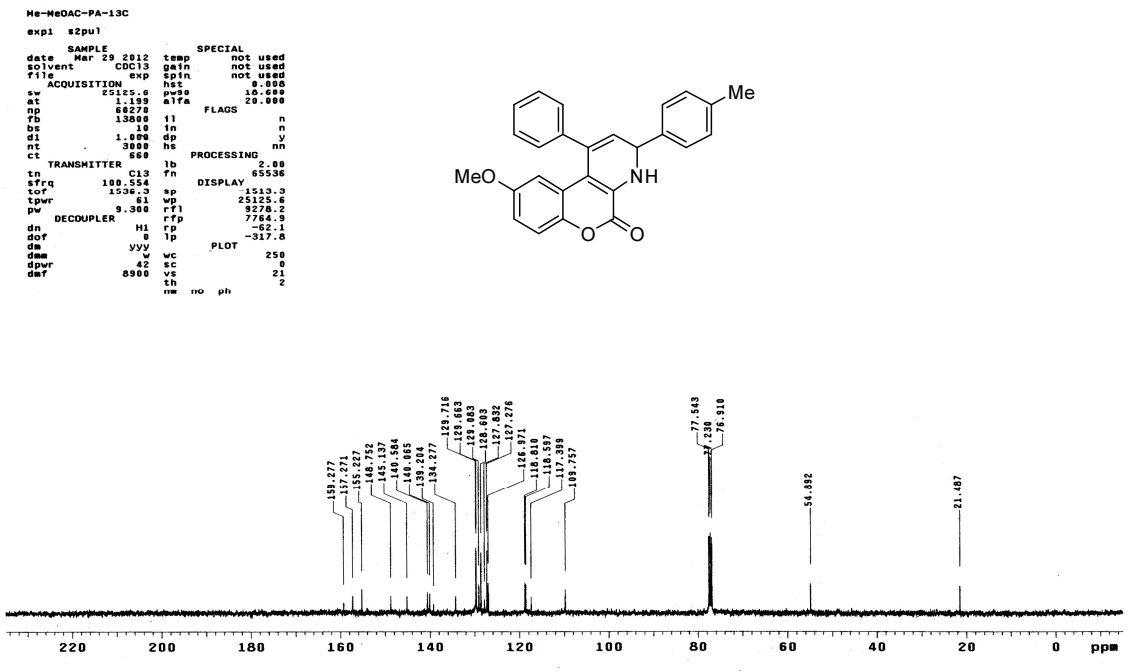
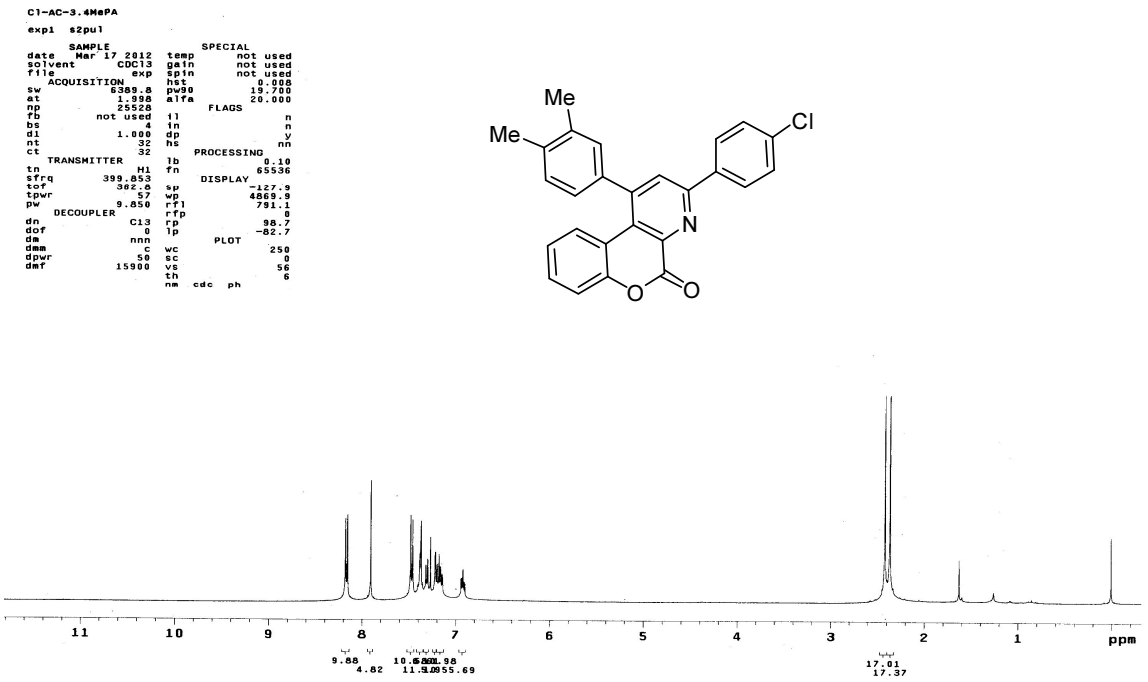


Figure 33

^{1}H NMR (400 MHz, $CDCl_3$): *3-(4-chlorophenyl)-1-(3,4-dimethylphenyl)-5H-chromeno[3,4-b]pyridin-5-one (**83s**)*



^{13}C NMR (100 MHz, $CDCl_3$): *3-(4-chlorophenyl)-1-(3,4-dimethylphenyl)-5H-chromeno[3,4-b]pyridin-5-one (**83s**)*

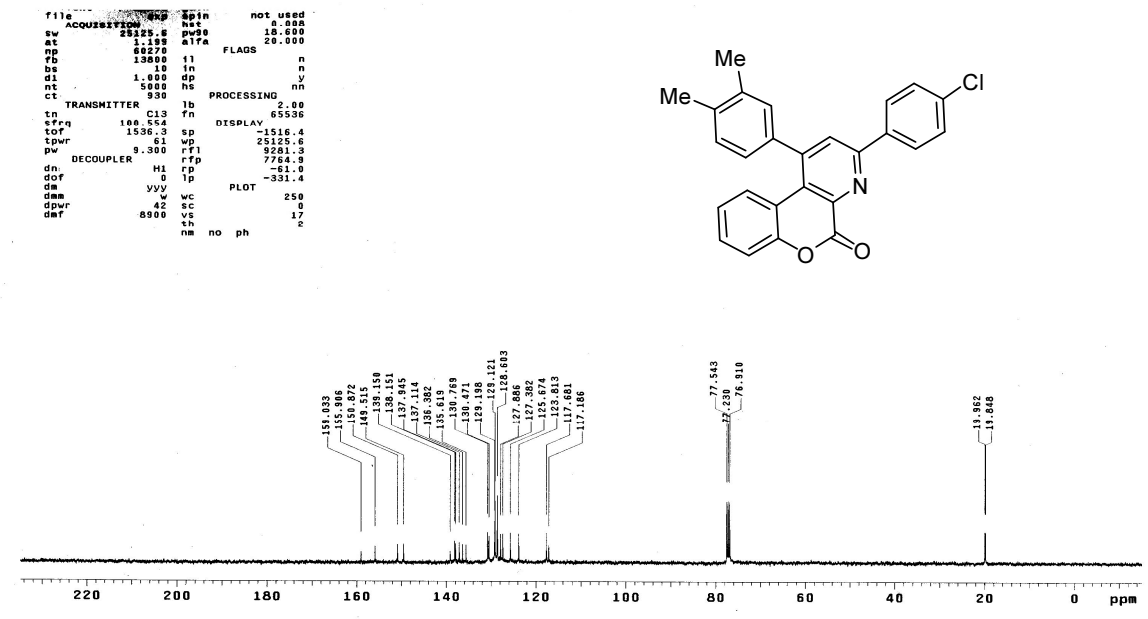


Figure 34

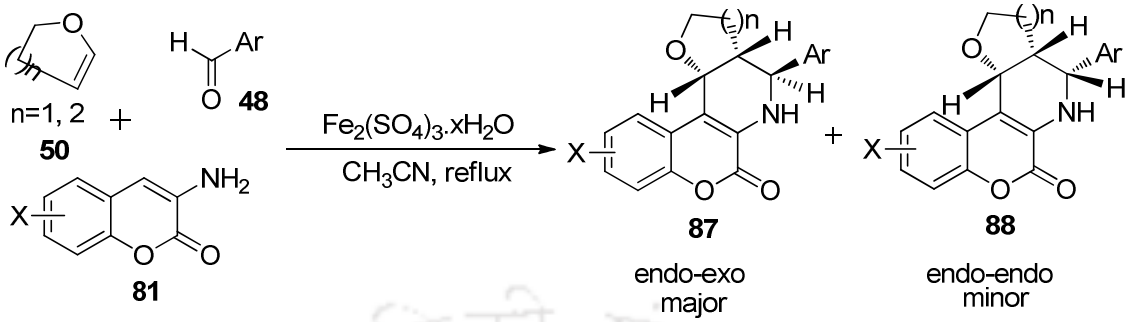
PART B

CHAPTER VB

Synthesis of fused tetrahydropyrido[2,3-*c*]coumarin derivatives, a potential inhibitor for dopamine d3 receptors, catalyzed by hydrated ferric sulfate

Review
Result & Discussion
Experimental

Naturally occurring heterocycles are widely distributed in nature and many of them also exhibit interesting pharmacological activities. In the previous chapters IIB and IVB we have demonstrated the synthesis tetrahydroquinoline and pyrido[2,3-c]coumarin through multicomponent reaction (MCR). We thought that tetrahydropyrido[2,3-*c*]coumarin can be synthesized involving 3-aminocoumarin if we use cyclic enol ether like 3,4-dihydropyran or 2,3-dihydrofuran instead of phenylacetylenes as a dienophile. Povarov reaction is one of the most important approaches for the construction of tetrahydroquinolines from *N*-arylimine and cyclic enol ethers with high stereo-, chemo- and regioselectivity, which has been reviewed in details in Chapter IB of Part B. A few years ago, Bodwell et al. demonstrated the synthesis of tetrahydropyrido[2,3-c]coumarin derivatives from 3-aminocoumarins, aromatic aldehydes having solely electron-withdrawing substitutents in the aromatic ring and cyclic or acyclic enol ethers using $Yb(OTf)_3$ as catalyst.[82] Though the above method is quite useful, but it has some limitations such as low yields when it was carried out in a one-pot manner, requirement of expensive and non-reusable catalyst and lack of substrates variability. We have reported the usefulness of hydrated ferric sulfate $[Fe_2(SO_4)_3 \cdot xH_2O]$ as an efficient heterogenous catalyst for Povarov reaction for the synthesis of tetrahydroquinoline derivatives using three-component reactions from aromatic amines, aromatic aldehydes and cylic enol ethers in Chapter IIB of Part B. Ferric sulfate $[Fe_2(SO_4)_3 \cdot xH_2O]$ is a mild, inexpensive and readily available catalyst for various organic transformations. The unique solubility of the catalyst in acetonitrile/ethanol and insolubility in DCM enables its uses as both homogenous and heterogenous catalyst; and it is easily recovarable at the end of reactions by adding DCM. In this chapter, we present our successful results for one-pot synthesis of tetrahydropyrido[2,3-c]coumarin derivatives from 3-aminocoumarins, aromatic aldehydes and cyclic enol ethers as shown in Scheme 35 as well as diastereoselectivity of the adducts.



Scheme 35. One-pot synthesis of tetrahydropyrido[2,3-c]coumarins derivatives

Results and Discussion

Various 3-aminocoumarins were synthesized from 3-acetamidocoumarins, which were prepared by controlled regioselective acid hydrolysis as discussed in Chapter IIIB of Part B. For the present study, a mixture of 4-chlorobenzaldehyde (1 mmol), 3-aminocoumarin (1 mmol) and 3,4-dihydropyran (DHP) (1.1 mmol) in acetonitrile (4 mL) was refluxed in a pre-heated oil-bath in presence of 5 mol% of hydrated $Fe_2(SO_4)_3 \cdot xH_2O$ and the diastereomeric products, tetrahydropyrido[2,3-c]coumarins **87c** and **88c**, were isolated in 66% overall yield with an *endo-exo* and *endo-endo* diastereoselectivity 80:20. The diastereomeric ratio was determined from ^{1}H NMR spectra of the crude reaction mixture and they were also characterized after purification by ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.

For optimizing reaction conditions, various reactions were examined using a combination of 3-aminocoumarin, 4-chlorobenzaldehyde and 3,4-dihydropyran with different amount of catalyst and different solvents (entries 1-6, Table 11). It was noted that 10 mol% of the hydrated ferric sulfate provided the best result for the formation of products in terms of yield and reaction time (entry 2, Table 11). It has also been observed that acetonitrile is the best choice of solvent for the present reaction as compared to other solvents such as ethanol, DMF and water. Other catalysts such as *p*-TSA, $In(OTf)_3$, CAN and SiO_2 were also scrutinized in acetonitrile under reflux conditions (entries 7-10, Table 11). These catalysts provided either lower yields and required longer reaction times or the reactions were unsuccessful (entries 7-10, Table 11). It is worth-while to mention that reaction did not take place in the absence of catalyst (entry 11, Table 11).

Table 11. Optimization of reaction conditions for the synthesis of tetrahydropyrido[2,3-c]coumarins **87c** and **88c**.

Entry	Catalyst (mol%)	Solvent	Time/h	Ratio[a] 4c : 5c	Yield[b](%)
1	A (05)	MeCN	3.0	80 : 20	66
2	**A (10)**	**MeCN**	**2.5**	**84 : 16**	**87**
3	A (15)	MeCN	2.5	76 : 24	82
4	A (10)	EtOH	3.0	81 : 19	61
5	A (10)	DMF	12.0	83 : 17	56
6	A (10)	H_2O	12.0	71 : 29	48
7	*p*-TSA (10)	MeCN	12.0	81 : 19	59
8	$In(OTf)_3$ (10)	MeCN	12.0	79 : 21	66
9	CAN (10)	MeCN	12.0	--	NR
10	SiO_2 (10)	MeCN	12.0	--	NR
11	None	MeCN	12.0	--	NR

[a]The product ratio was determined from ^{1}H NMR spectra. [b]Isolated yields. NR = no reaction. A = hydrated ferric sulfate [$Fe_2(SO_4)_3 \cdot xH_2O$].

After optimizing the reaction conditions, the mixture of 3-aminocoumarin, benzaldehyde and 3,4-dihydropyran in acetonitrile was refluxed using 10 mol% $Fe_2(SO_4)_3 \cdot xH_2O$ under identical reaction conditions and the desired tetrahydropyrido[2,3-c]coumarin derivatives **87a** and **88a** were isolated in 81% combined yield with (81:19) *endo-exo*:*endo-endo* selectivity (entry a, Table 12).

Table 12. Scope of various substituted tetrahydropyrido[2,3-c]coumarin derivatives[a]

Entry	Ar	X	n	Time/h	Yield[b] %	Ratio[c] (87:88)
a	Ph	H	2	2.0	81	81 : 19
b	4-Me-Ph	H	2	2.0	84	77 : 23
c	4-Cl-Ph	H	2	2.5	87	84 : 16
d	4-Br-Ph	H	2	2.5	86	80 : 20

Continued

e	4-F-Ph	H	2	2.5	87	84 : 16
f	4-OMe-Ph	H	2	2.0	87	100 : 00
g	3,4(OMe)$_2$Ph	H	2	2.0	89	100 : 00
h	Furfural	H	2	2.0	86	100 : 00
i	2-Naphthyl	H	2	2.5	74	84 : 16
j	4-NO$_2$-Ph	H	2	2.0	68	76 : 24
k	Ph	H	1	2.0	85	70 : 30
l	4-Cl-Ph	H	1	2.5	79	71 : 29
m	4-Br-Ph	H	1	2.5	81	68 : 32
n	4-MeO-Ph	H	1	2.5	88	70 : 30
o	Furfural	H	1	2.0	78	60 : 40
p	4-Cl-Ph	Br	2	2.5	81	75 : 25
q	Furfural	Br	2	2.5	77	78 : 22
r	4-Me-Ph	NO$_2$	2	2.5	78	78 : 22
s	4-Cl-Ph	OMe	2	2.0	82	79 : 21

[a]The reactions were performed in 1 mmol scale. [b]Isolated yields. [c]The product ratio was determined from ^{1}H NMR spectra of the crude reaction mixture.

Encouraged by these successful results, we have carried out similar reaction with 3-aminocoumarin, 4-methylbenzaldehyde and 3,4-dihydropyran under identical conditions (entry b, Table 12) and the desired products **87b** and **88b** were obtained in 84% overall yield with diastereoselectivity 77:23. Likewise, a mixture of 3-aminocoumarin, various aromatic aldehydes having substituents such as Br, F, OMe groups in the aromatic ring as well as 2-furaldehyde and 3,4-dihydropyran were examined in the presence of 10 mol% hydrated ferric sulfate under identical reaction conditions. The reaction time, %yield and diastereomeric products ratio i.e. *endo-exo*:*endo-endo* ratio are shown in Table 12 (entries a-h). It is note-worthy to mention that we have obtained 100% *endo-exo* selectivity for the aldehydes 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde and furfurylaldehyde respectively. Furthermore, the reaction was carried out with 3-aminocoumarin (1 mmol), 2-naphthaldehyde (1 mmol) and 3,4-dihydropyran (1.1 mmol) under identical reaction conditions and the desired products were obtained 74% overall yield with

diastereoselectivity 84:16. Moreover, we have also performed a reaction of 3-aminocoumarin (1 mmol), 4-nitrobenzaldehyde (1 mmol) and 3,4-dihydropyran (1.1 mmol) in presence of 10 mol% hydrated ferric sulfate and isolated the products in 68 % overall yield, a distinct improvement on that reported previously (40%).[82] Inspired by all these successful results, we also examined the reactions with other enol ether like 2,3-dihydrofuran with 3-aminocoumarin and a wide variety of aromatic aldehydes using same amount of catalyst under similar reaction conditions (Table 12, entries k-o). The isolated yield of the desired products, reaction times and diastereoselectivities are shown in Table 12. For generalizing the present protocol, we have further verified the reaction with other substituted 3-aminocoumarins and their successful results are mentioned in Table 12 (entries p-s). The reaction was unsuccessful with aliphatic aldehydes under similar reaction condition, which is the only limitation of the present protocol. The ^{1}H NMR spectra and ^{13}C NMR spectra of the products **87a, 88a, 87d, 88d, 87m** and **88m** are given in Figures **39-44**, respectively in the experimental section.

Determination of stereochemistry of the reaction products:

The stereochemistry of the fused ring junctures and other positions of compounds **87c** and **88c** were established from their coupling constant values from ^{1}H-NMR spectra.

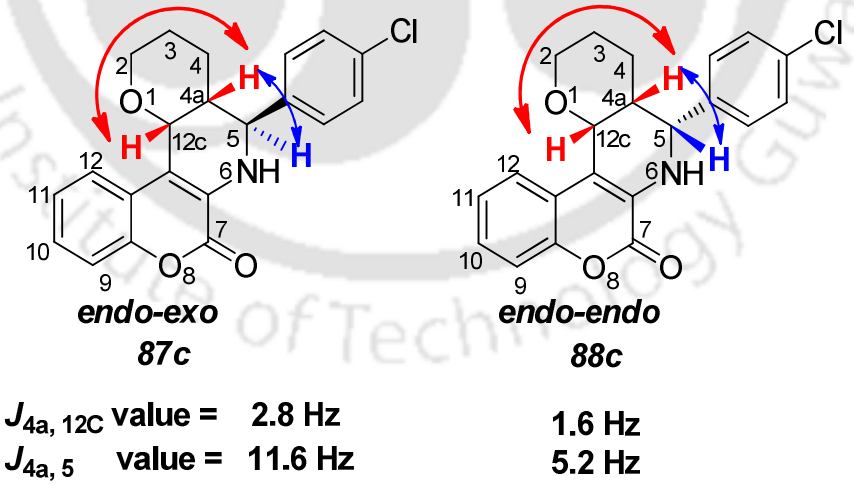


Figure 35. Coupling constant values used for determining stereochemistry

In compound **87c** (*endo-exo* isomer), exhibits coupling constant values for $J_{4a,12c}$ and $J_{4a,5}$ are 2.8 Hz and 11.6 Hz, respectively whereas in case of the *endo-endo* isomer (**88c**) coupling constant values for $J_{4a,12c}$ and $J_{4a,5}$ are 1.6 Hz and 5.2 Hz, respectively, which is

shown Figure 35. The coupling constant values are in full agreement with the earlier reported tetrahydroquinoline products discussed in Chapter IIB of Part B.

Moreover, the structure of compounds **87c** and **88o** were further ascertained through single XRD crystallographic data and their ORTEP diagram is shown in Figure 36 (see Table 13 in experimental section of Chapter VB). The torsional angle (H-5-C-5-C-4a-H-4a) for the X-ray crystal structure of trans isomer **87c** was determined to be 171.47° which is consistent with the observed $^{3}J_{4a,5}$ coupling constants of 11.6 Hz with H-5 and H-4a adopting pseudo-axial positions with an anti relationship. In contrast, the measured torsional angle (H-5-C-5-C-4a-H-4a) for *endo-endo* isomer **88o** was determined to be 56.41° which is consistent with the observed $^{3}J_{3a,4}$ coupling constants of 7.6 Hz for the compound **88o**, characteristic of the syn relationship of these protons in a pseudo-axial-equatorial relationship.

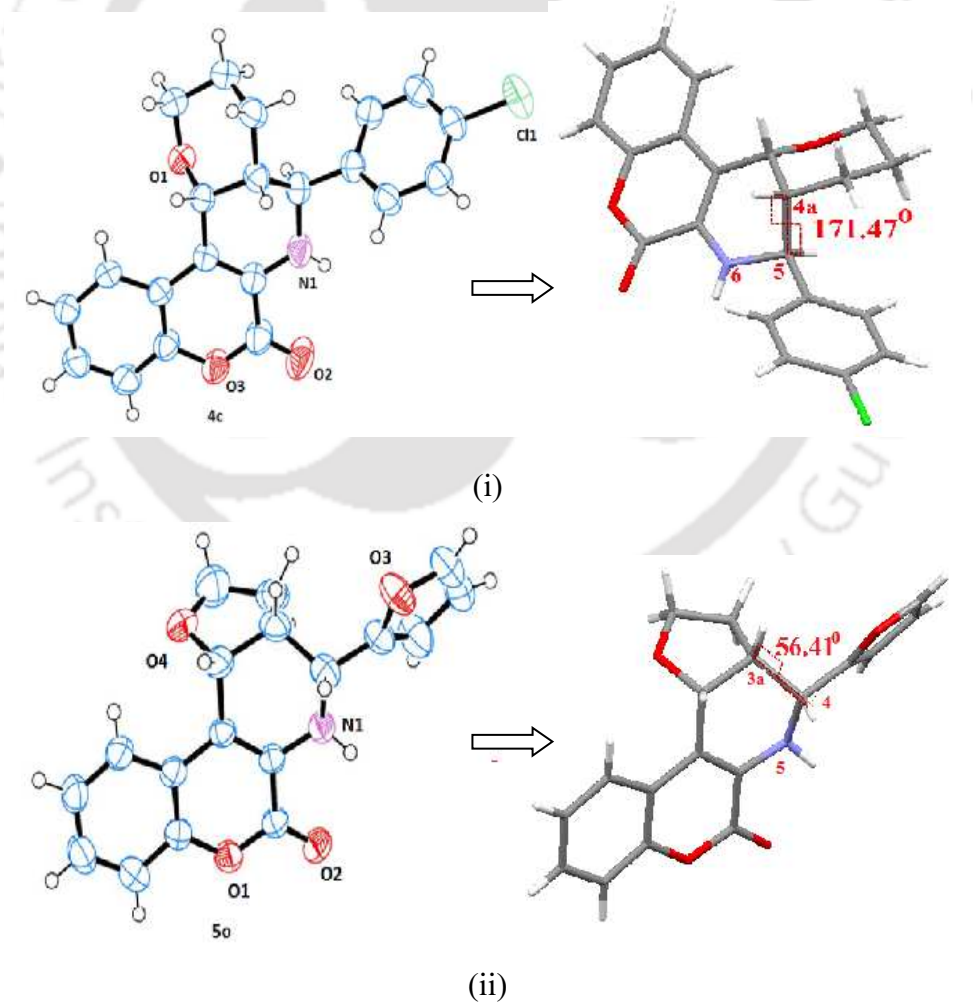
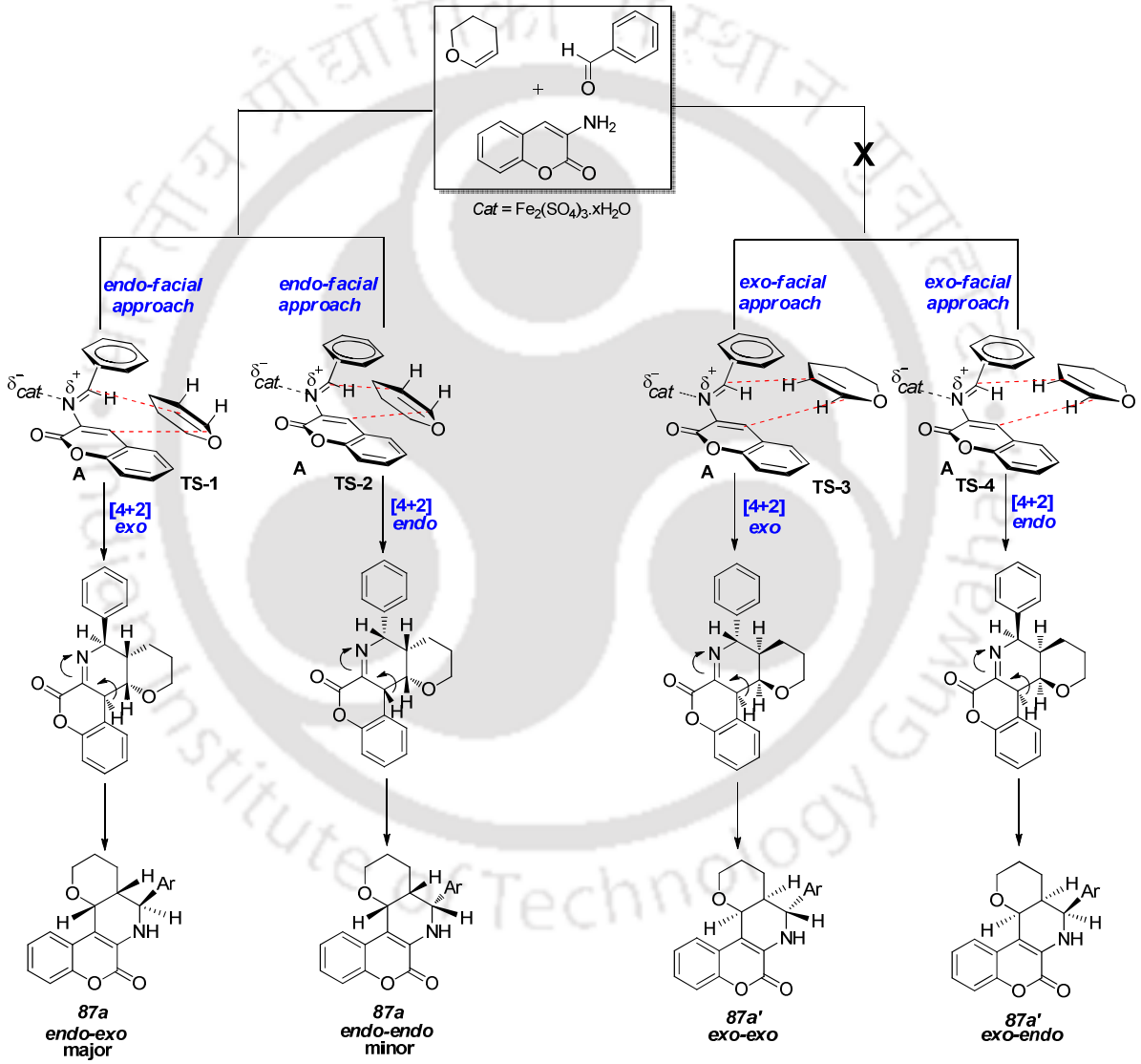


Figure 36. X-ray crystal structures of (i) **87c** (CCDC 811857) and (ii) **88o** (CCDC 838311)

The formation of tetrahydropyrido[2,3-c]coumarins may be explained as follows: We believe that the condensation reaction between aromatic aldehyde (**1**) and 3-aminocoumarin (**2**) leads to the formation of intermediate N-arylimine **A** (2-azadienes), which undergoes cycloaddition reaction with electron-rich dienophile namely 3,4-dihydropyran or 2,3-dihydrofuran in presence of hydrated ferric sulfate. The dienophile may approach either *endo* face or *exo*-face, which is shown in Scheme 36.



Scheme 36. Endo selectivity for the formation of tetrahydropyrido[2,3-c]coumarins from the Povarov reaction

In the present study, we have found only *endo*-face selectivity over *exo*-face selectivity. However, Batey et al.[40] have reported recently exo- face selectivity with *N*-arylimines, derived from aromatic amines and aromatic aldehydes, and strained norbornene-derived dienophiles. The expected major product would be *endo-endo* **88a,** but we have obtained major product *endo-exo* **87a** due to steric repulsion between aryl ring and tetrahydropyran ring as shown in Scheme 36. Another possibility is a stepwise mechanism as proposed by Lavilla and his co-workers.[25c]

The reusability test of the catalyst was performed as follows: A mixture of benzaldehyde (10 mmol), 3-aminocoumarin (10 mmol), 3,4-DHP (11 mmol, 1 mL) and $Fe_2(SO_4)_3 \cdot H_2O$ (1 mmol, 0.410 g) was taken in 30 mL of acetonitrile and it was refluxed for 2 h in a pre-heated oil-bath. After completion of reaction, acetonitrile was recovered in a rotatory evaporator and the crude residue was dissolved in DCM (25 mL). The catalyst separated out as soon as DCM was added into it. Then, it was filtered off through a Büchner funnel, washed with another 5 mL of DCM and dried.

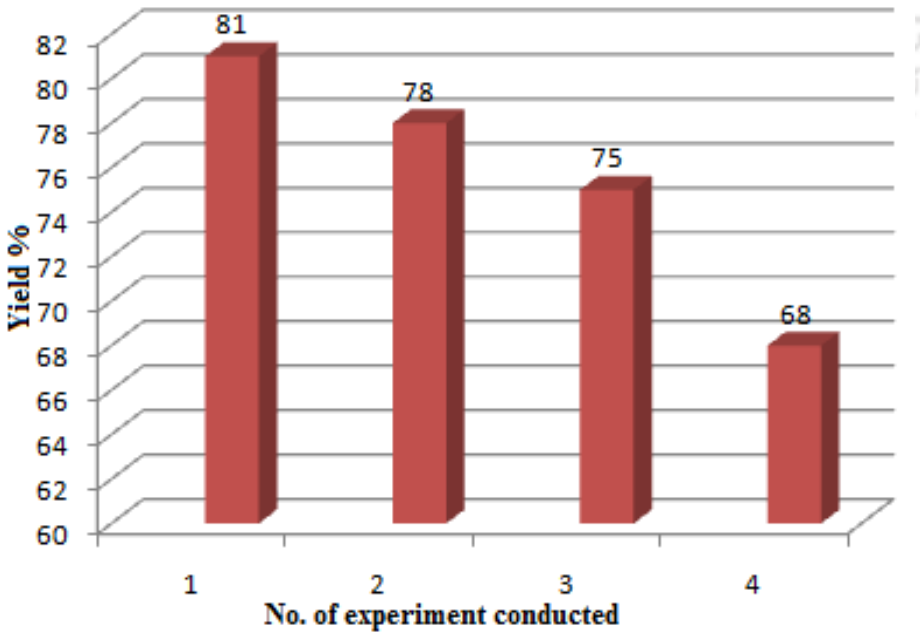


Figure 37. Reusability of the catalyst

The recovered catalyst was used for similar set of reactions for three more consecutive cycles. The yields and the number of experiments conducted is shown in the bar diagram in Figure 37. The products tetrahydropyrido[2,3-c]coumarins contain in the filtrate, which was

concentrated and purified to obtain the pure products. It was observed that the yield decreases in fourth cycle which may be due to weight loss of the catalyst during handling.

Next, docking studies of the synthesized 3-aminocoumarins derivatives against D3R have been carried out to find out its therapeutic prospects for neuropsychiatric pharmacotherapy. Dopamine is a vital neurotransmitter in the central nervous system of human that modulates cognitive and emotional functions through the activation of dopamine receptors, a class of the G protein-coupled receptor (GPCR) superfamily.[105] Blockade of dopamine D3 receptors (D3R) has been proved to be effective for potential pharmacotherapy for Schizophrenia, Parkinson's disease, enhancement of cognition and also in several neuropsychiatric disorders especially in drug addiction.[106] Taking advantage of the experimentally determined structure of human D3R (PDB Id: 3PBL),[107] the potentiality of our synthesized compounds as D3R inhibitors were studied through docking studies. Docking serves as a computational tool to understand the interactions between the protein and ligand.[108] Investigation on the structural details of the interactions between D3R and synthesized compounds corroborate with the importance of the inhibitors binding at the extracellular binding pocket of D3R. Our synthesized compounds had better binding affinity than the co-crystallized known inhibitor, eticlopride (PDB Ligand ID: ETQ) (see Table 14). The compounds of series **88** showed better predicted inhibition efficacy as compared to series of compounds **87**. Surprisingly, compound **87f** also showed comparable efficacy. This phenomenon may rise to the orientation of the tetrahydropyrido[2,3-c]coumarin ring in the vicinity of the extracellular binding pocket of D3R. Most of the **88** series compounds bound with the specific orientation at the proximity of highly conserved residues Asp110, Val111, Ser192, Phe345 and Tyr373 that bound tightly in the hydrophobic cavity, [107] which reflects that these compounds may exhibit better inhibition. Pi interaction was observed with the conserved Phe345 with the individual aromatic ring of the synthesized compounds. The poor binding affinity of the compounds **88h**, **88o** and **88q** which have a furfuryl ring instead of benzene ring reflects the requirement of the orientation for the better binding. The best hit was found to be the compound **88r** which has the necessary above mentioned interactions as shown in Figure 38 and also has a hydrogen bond between the nitro group of the individual aromatic ring and the conserved Ser192 of D3R. To summarize our docking analysis, the results were

comparable with the theoretical studies reported in literature[106c] and also demonstrate the necessity of orientation and aromaticity of the potential inhibitors at the extracellular binding pocket of D3R (See Table 14 in experimental section of this chapter).

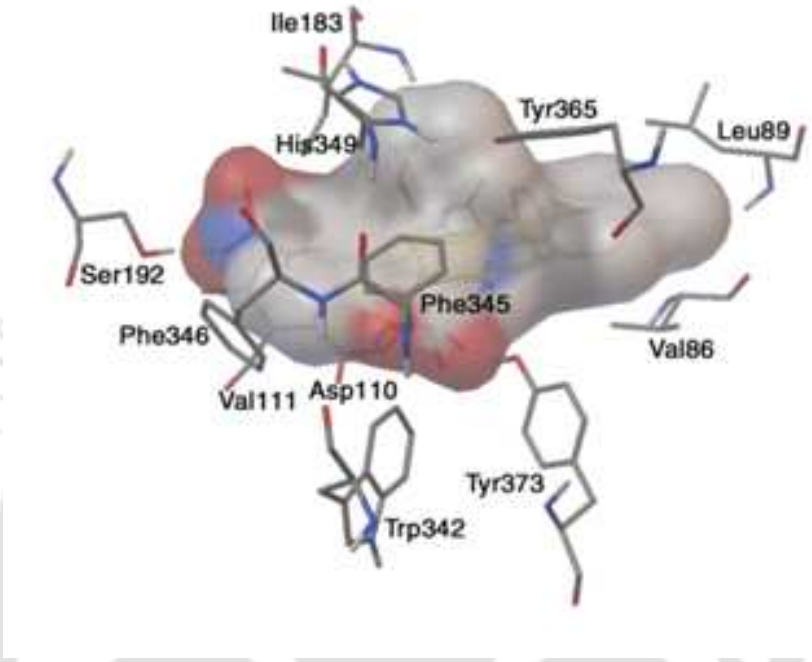


Figure 38. Interaction mode of the best hit **88r** with dopamine D3 receptor. H-bond is depicted as green dots while pi interactions are depicted as ray lines.

In conclusion, we have demonstrated that hydrated ferric sulfate is an efficient catalyst for Povarov reaction for the one-pot synthesis of furo- and tetrahydropyrido[2,3-c]coumarins derivatives from 3-aminocoumarins, aromatic aldehydes and cyclic ethers. In comparison to $Yb(OTf)_3$, hydrated ferric sulfate is cheaper and it provides good yields. The present protocol is more generalized one as it works with a wide variety of aromatic aldehydes and it also gives good diastereoselectivity like other Lewis acid catalyzed Povarov reactions. Moreover, it was observed that the attack of the *N*-arylimine took place exclusively from the *endo*-face of the dienophiles and the predominant formation of *endo-exo* adducts over *endo-endo* adducts, which was further confirmed through single XRD data and ^{1}H-NMR spectra. From the docking studies, it was found that some of the synthesized tetrahydropyrido[2,3-*c*] coumarin derivatives display inhibition activity against human dopamine D3 receptor, which might be the potential lead molecules for antipsychotic drugs.

General procedure for the synthesis of tetrahydropyrido[2,3-c]coumarin derivatives:

Into a 25 mL round bottom flask, a mixture of 3-aminocoumarin (0.161 g, 1 mmol) and benzaldehyde (0.106 g, 1 mmol) was taken in 3 mL of acetonitrile and kept for stirring at room temperature for 10 min. Then, dihydropyran (100 µL,1.1 mmol) and hydrated ferric sulfate (42 mg, 10 mol%) were added successively to the reaction mixture. Finally, the reaction mixture was refluxed on a pre-heated oil-bath and the progress of the reaction was monitored by TLC from time to time. After completion of the reaction, the solvent was removed and dichloromethane (5 mL) was added to separate out the catalyst. Then, the filtrate was extracted with dichloromethane (2 x 10 mL), washed with water and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was concentrated *in vacuo* and the crude product was purified by column chromatography using hexane and ethyl acetate (98:02) as eluent to give tetrahydropyrido[2,3-c]coumarin **87a** and **88a** in 81 % yield. The similar procedure was followed for the other substrates.

Crystallographic Description

Compound **87c** empirical formula $C_{21}H_{18}ClNO_3$, colorless crystal, formula wt 367.81, Triclinic, P-1, a = 9.4104(10) Å, b = 9.6627(9) Å, c = 10.6311(10) Å, V = 866.08(15) $Å^3$, Z = 2, F (0 0 0) = 384, GOF(S) = 1.004. Final indices R_{obs} = 0.0384, wR_{obs} = 0.0815 with I > 2r(I); R_{all} = 0.0504, wR_{all} = 0.0865 for all data. Compound **88o** empirical formula $C_{18}H_{15}NO_4$, colorless crystal, formula wt 309.31, Monoclinic, P 21/c, a = 11.8099(5) Å, b = 9.7399(5) Å, c = 12.7370(6) Å, V = 1461.83(12) $Å^3$, Z = 4, F (0 0 0) = 648, GOF(S) = 1.031. Final indices R_{obs} = 0.0503, wR_{obs} = 0.1131 with I > 2r(I); R_{all} = 0.0920, wR_{all} = 0.1292 for all data.

Table 13. Crystal data and structure refinement for **87c** and **88o**.

Parameters	Compound **87c** (trans CCDC811857)	Compound **88o** (cis CCDC 838311)
Identification code	Cl-AC-DHP	Fur-AC-DHP
Empirical formula	$C_{21}H_{18}ClNO_3$	$C_{18}H_{15}NO_4$
Formula weight	367.81	309.31
Temperature	296(2) K	296(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Monoclinic
Space group	P-1	'P 21/c'

Unit cell dimensions		
a	9.4104(10) Å	11.8099(5) Å
b	9.6627(9) Å	9.7399(5) Å
c	10.6311(10) Å	12.7370(6) Å
α	78.191(5)	90.00°
β	66.629(6)°	93.828°(2)
γ	89.263(5)°	90.00°
Volume	866.08(15) $Å^3$	1461.83(12) $Å^3$
Z	2	4
Density (calculated)	1.410 g/cm^3	1.405 g/cm^3
Absorption coefficient	0.242 mm^{-1}	0.100 mm^{-1}
F(000)	384	648
Theta range for data collection	2.14 to 28.34°	1.73 to 34.04°
Index ranges	-11 <=h<=11, -11<=k<=12, -12<=l<=14	-18<=h<=18, -13<=k<=13, -18<=l<=19
Reflections collected	6806	22111
Independent reflections	4322 R_{int} = 0.0415	5974 R_{int} = 0.0273
Completeness to θ°	98.4% (θ = 28.34°)	97.8% (θ = 34.04°)
Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2
Data / restraints / parameters	4322 / 0 / 240	5448 / 0 / 212
Goodness-of-fit on F2	1.004	1.031
Final R indices [>2sigma(I)]	R_{obs} = 0.0384, wR_{obs} = 0.0815	R_{obs} = 0.0503, wR_{obs} = 0.1131
R indices (all data)	R_{all} = 0.0504, wR_{all} = 0.0865	R_{all} = 0.0920, wR_{all} = 0.1292

Table 14. Docking analysis of the synthesized compounds on chain A of human dopamine D3 receptor (PDB Id: 3PBL)

Product	Score	Substituents, n	Conformations in the largest cluster [out of 100]	H-bond interactions	Pi interactions	Hydrop-hobic contact residues
88r	-10.56	Me($C_{4'}$), NO_2(C_{10}), n=2	100	S192	F345	V86
88g	-10.46	OMe($C_{4'}$), OMe($C_{3'}$), H(C_{10}), n=2	100	-	F345	V86, L89, V111, I183
88d	-9.94	Br($C_{4'}$), H(C_{10}), n=2	100	-	F345	V86, V111, I183
88c	-9.73	Cl($C_{4'}$), H(C_{10}), n=2	100	-	F345	V86, V111, I183
88b	-9.6	Me($C_{1'}$), H(C_{10}), n=2	100	-	F345	V86, V111, I183
88f	-9.54	OMe($C_{4'}$), H(C_{10}), n=2	100	-	F345	V86, L89, V111, I183
88m	-9.51	Br ($C_{4'}$), H(C_{10}), n=1	100	-	F345	V86, V111
88l	-9.28	Cl ($C_{4'}$), H(C_{10}), n=1	100	-	F345	V86, V111, F345
87f	-9.26	OMe($C_{4'}$), H(C_{10}), n=2	100	Y365	-	V86, L89, F106, V107, T369
88p	-9.24	Cl($C_{4'}$), Br(C_{10}), n=2	100	-	F345	V107, I183, F345
88a	-9.11	H($C_{4'}$), H(C_{10}), n=2	100	-	F345	V86, L89, V111,

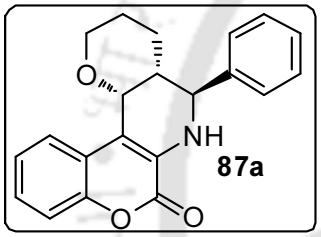
						I183
88e	-9.10	F($C_{4'}$), H(C_{10}), n=2	100	-	F345	V86, V111, I183
88n	-9.09	MeO($C_{4'}$), H(C_{10}), n=1	100	-	F345	V86, V111, I183
88k	-8.92	H($C_{4'}$), H(C_{10}), n=1	100	-	F345	V111, C114, F346
88s	-8.80	Cl, ($C_{4'}$), MeO (C_{10}), n=2	100	-	F345	V86, V107, I183, F345
88o	-8.39	Furfuryl (C_4), H(C_{10}), n=1	100	I183	-	V111, C114, S196
88h	-8.36	Furfuryl(C_4), H(C_{10}), n=2	100	-	F345	I183
88q	-8.11	Furfuryl(C_4), Br (C_{10}), n=2	100	-	F345	V107, I183
87g	-8.10	OMe($C_{4'}$), OMe($C_{3'}$), H(C_{10}), n=2	100	D110	F345	I183, F345, H349, T369
87s	-8.01	Cl, ($C_{4'}$), MeO (C_{10}), n=2	100	Y365	-	V86, L89, F106, V107, T369
87d	-7.99	Br($C_{4'}$), H(C_{10}), n=2	100	Y365	-	V86, L89, F106, V107, T369
87o	-7.98	Furfuryl (C_4), H(C_{10}), n=1	100	Y365	-	V86, L89, F106, V107, T369

87k	-7.94	H($C_{4'}$), H(C_{10}), n=1	100	D110	F345	I183, F345, H349
87h	-7.91	Furfuryl(C_4), H(C_{10}), n=2	100	Y365	F345	S182, F345, T369, F345
87b	-7.89	Me($C_{4'}$), H(C_{10}), n=2	100	Y365	-	V86, L89, F106, V107, T369
87c	-7.86	Cl($C_{4'}$), H(C_{10}), n=2	100	Y365	-	V86, L89, F106, V107, T369
87l	-7.64	Cl ($C_{4'}$), H(C_{10}), n=1	100	D110	F345	S182, W342, F345, T369, F345
87p	-7.32	Cl($C_{4'}$), Br(C_{10}), n=2	100	Y365	-	V86, T369
87q	-7.30	Furfuryl(C_4), Br (C_{10}), n=2	100	D110	F345	I183, F345
87m	-7.28	Br ($C_{4'}$), H(C_{10}), n=1	100	D110	F345	L89, F345
87c	-7.27	Cl($C_{4'}$), H(C_{10}), n=2	100	Y365	-	V86, L89, F106, V107, T369
87e	-7.12	F($C_{4'}$), H(C_{10}), n=2	100	Y365	-	V86, L89, F106, V107, T369
87a	-7.04	H($C_{4'}$), H(C_{10}), n=2	72	D110	F345	S182, F345,

						H349, T369
87r	-6.95	Me($C_{4'}$), NO_2(C_{10}), n=2	100	D110	F345	L89, S182, W342, F345, T369
87n	-6.40	MeO($C_{4'}$), H(C_{10}), n=1	85	D110	F345	L89, F345
ETQ*	-8.207	compute_AutoDock41_score.py				

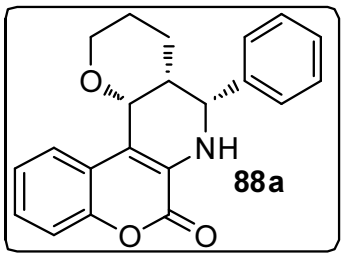
Spectral data of *Tetrahydropyrido[2,3-c]coumarin*s

*Tetrahydropyrido[2,3-c]coumarin (**87a**):*



White Solid (0.218 g, 65.7%). Mp. 243.6°C; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.38-1.42 (m, 1 H), 1.52-1.58 (m, 1 H), 1.74 (tt, J = 4.4, 14.0 Hz, 1 H), 1.90 (qt, J = 4.0, 12.8 Hz, 1 H), 2.09-2.04 (m, 1 H), 3.79 (td, J = 2.4, 11.2, Hz, 1 H), 4.16 (dd, J = 4.0, 10.8 Hz, 1 H), 4.67 (d, J = 2.8 Hz, 1 H), 4.73 (d, J = 11.6 Hz, 1 H), 5.10 (s, 1 H), 7.20-7.28 (m, 3 H), 7.33-7.42 (m, 5 H), 7.53-7.56 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.96, 23.48, 38.49, 54.44, 69.26, 69.98, 114.24, 116.54, 120.73, 121.80, 124.91, 126.06, 128.0 (2 C), 128.57, 129.01(2 C), 130.26, 140.33, 148.26, 158.98; **IR** (KBr): 1629, 1707, 2841, 2924, 3407 cm^{-1}. **MS** calcd. for $C_{21}H_{19}NO_3$ [MH]+ 334.1365; found 334.1438. **Anal. Calcd** for $C_{21}H_{19}NO_3$ (333.38): C, 75.66; H, 5.74; N, 4.20. Found C, 75.78; H, 5.83; N, 4.11.

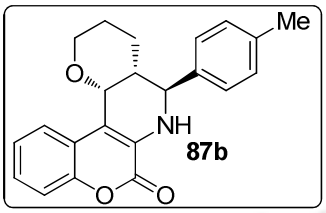
*Tetrahydropyrido[2,3-c]coumarin (**88a**):*



White solid (0.051 g, 15.3%). mp 188-189°C; R_f (5% ethyl acetate/hexane) 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.39-1.73 (m, 4 H), 2.24-2.34 (m, 1 H), 3.17 (t, J = 11.2 Hz, 1 H), 3.61 (d, J = 11.2 Hz, 1 H), 4.69 (s, 1 H), 5.05 (s, 1 H), 5.50 (d, J = 5.6 Hz, 1 H), 7.22-7.42 (m, 8 H), 8.22 (d, J = 7.6 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 19.42, 24.57, 38.47, 59.18, 62.49, 72.12, 115.49, 116.47, 120.65, 124.71, 124.89, 126.49, 126.94 (2 C), 128.04, 128.73 (2 C), 131.26, 139.42, 148.23,

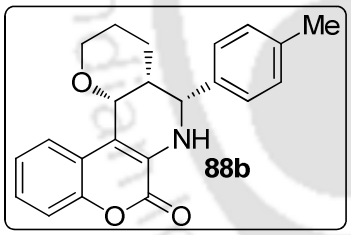
158.53; **IR** (KBr): 1613, 1718, 2841, 2949, 3422 cm^{-1}; **Anal. Calcd** for $C_{21}H_{19}NO_3$ (333.38): C, 75.66; H, 5.74; N, 4.20. Found C, 75.80; H, 5.84; N, 4.09.

*Tetrahydropyrido[2,3-c]coumarin (**87b**)*:



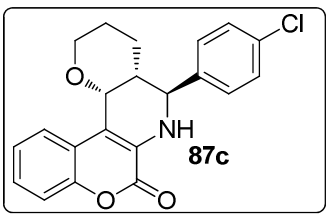
White solid (0.224 g, 64.7%). mp 204.4°C; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.39 (d, J = 13.2 Hz, 1 H), 1.56 (d, J = 14.0 Hz, 1 H), 1.68-1.78 (m, 1 H) 1.82-1.94 (m, 1 H), 2.00-2.06 (m, 1 H), 2.37 (s, 3 H), 3.78 (t, J = 11.2 Hz, 1 H), 4.11-4.18 (m, 1 H), 4.67 (s, 1 H), 4.70 (d, J = 11.6 Hz, 1 H), 5.07 (s, 1 H), 7.17-7.31 (m, 7 H), 7.54 (d, J = 7.2 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.34, 21.99, 23.55, 38.49, 54.17,69.29, 70.08, 114.13, 116.57, 120.82, 121.80, 124.93, 126.02, 127.92 (2 C), 129.70(2 C), 130.34, 137.30, 138.33, 148.29, 159.04; **IR** (KBr):1626, 1712, 2851, 2934, 3402 cm^{-1}; **MS** calcd. for $C_{22}H_{21}NO_3$ [MH]+ 348.1521; found 348.1612. **Anal. Calcd** for $C_{22}H_{21}NO_3$ (347.41): C, 76.06; H, 6.09; N, 4.03. Found C, 76.20; H, 6.14; N, 4.14.

*Tetrahydropyrido[2,3-c]coumarin (**88b**):*



White solid (0.067 g, 19.3%). mp 173.6°C; R_f (5% ethyl acetate/hexane) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.42-1.68 (m, 4 H), 2.22-2.30 (m, 1 H), 2.37 (s, 3 H), 3.17 (t, J = 11.2 Hz, 1 H), 3.62 (dd, J = 3.6, 12.8 Hz, 1 H), 4.66 (d, J = 1.6 Hz, 1 H), 5.02 (s, 1 H), 5.50 (d, J = 5.6 Hz, 1 H), 7.18-7.34 (m, 7 H), 8.22 (d, J = 7.6 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 19.46, 21.34, 24.68, 38.61, 59.03, 62.50, 72.21, 115.45, 116.52, 120.76, 124.77, 124.92, 126.48, 126.88 (2 C), 129.43 (2 C), 131.40, 136.39, 137.82, 148.27, 158.61; **IR** (KBr): 1613, 1717, 2851, 2923, 3427 cm^{-1}; **Anal. Calcd** for $C_{22}H_{21}NO_3$ (347.41): C, 76.06; H, 6.09; N, 4.03. Found C, 76.16; H, 6.16; N, 4.07.

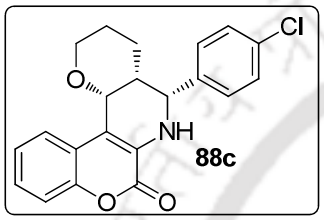
*Tetrahydropyrido[2,3-c]coumarin (**87c**):*



White solid (0.282g, 73.1%). mp 226.4°C; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.40-1.46 (m, 1 H), 1.50-1.55 (m, 1 H), 1.71-1.93 (m, 2 H), 2.00-2.08 (m, 1 H), 3.80 (td, J = 11.6, 2.4 Hz, 1 H), 4.12-4.18 (m, 1 H),

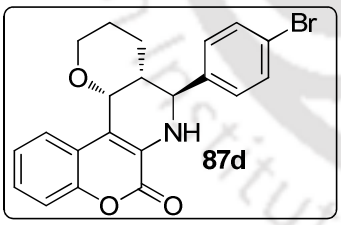
4.68 (d, *J* = 2.8 Hz, 1 H), 4.73 (d, *J* = 11.6 Hz, 1 H), 5.06 (s, 1 H), 7.24-7.29 (m, 3 H), 7.32-7.40 (m, 4 H), 7.52-7.57 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.97, 23.50, 38.65, 53.95, 69.31, 69.92, 114.70, 116.65, 120.59, 121.88, 125.0, 126.35, 129.28 (2 C), 129.38 (2 C), 130.19, 134.37, 138.92, 148.39, 158.97; **IR** (KBr): 1628, 1716, 2851, 2934, 3399 cm^{-1}; **Anal. Calcd** for $C_{21}H_{18}ClNO_3$ (367.83): C, 68.57; H, 4.93; N, 3.81. Found C,68.68; H, 4.86; N, 3.92.

*Tetrahydropyrido[2,3-c]coumarin (**88c**):*



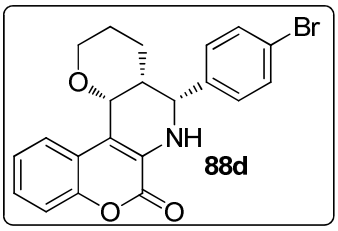
White solid (0.051 g, 13.9%). mp 163.2°C ; R_f (5% ethyl acetate/hexane) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.28-1.61 (m, 3 H); 2.16-2.22 (m, 1 H), 3.11 (t, *J* = 10.8 Hz, 1 H), 3.54 (d, *J* = 11.2 Hz, 1 H), 4.28 (d, *J* = 5.6 Hz, 1 H), 4.58 (d, *J* = 1.6 Hz, 1 H), 4.91 (s, 1 H), 5.39 (d, *J* = 5.2 Hz, 1 H), 7.07-7.28 (m, 7 H), 8.12 (d, *J* = 7.6 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 19.46, 24.43, 38.30, 58.64, 62.63, 71.96, 115.84, 116.52, 120.50, 124.96, 125.37, 126.24, 126.70, 128.35 (2 C), 128.9 (2 C), 129.2, 131.0, 138.1, 148.3, 158.5; **IR** (KBr): 1615, 1713, 2852, 2925, 3387 cm^{-1}; **Anal. Calcd** for $C_{21}H_{18}ClNO_3$ (367.83): C, 68.57; H, 4.93; N, 3.81. Found C, 68.74; H, 4.86; N, 3.98.

*Tetrahydropyrido[2,3-c]coumarin (**87d**):*



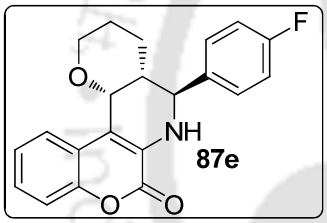
White solid (0.284 g, 68.8%). mp 245.2°C; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.43-1.47 (m, 1 H), 1.68-1.85 (m, 2 H), 1.92-1.98 (m, 1 H), 3.22 (q, *J* = 14.8, 7.6 Hz, 1 H), 3.72 (td, *J* = 2.4, 11.2 Hz, 1 H), 4.06-4.12 (m, 1 H), 4.60 (d, *J* = 3.2 Hz, 1 H), 4.63 (d, *J* = 11.6 Hz, 1 H), 4.98 (s, 1 H), 7.16-7.24 (m, 7 H), 7.45 (d, *J* = 8.4 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.95, 23.48, 38.59, 53.99, 69.31, 69.88, 114.72, 116.64, 120.56, 121.87, 122.46, 125.01, 126.36, 129.72 (2 C), 130.15, 132.22 (2 C), 139.42, 148.36, 158.96; **IR** (KBr): 1626, 1715, 2849, 2937, 3396 cm^{-1}; **Anal. Calcd** for $C_{21}H_{18}BrNO_3$ (412.28): C, 61.18; H, 4.40; N, 3.40. Found C, 61.34; H, 4.48; N, 3.52. **MS** calcd. for $C_{21}H_{18}BrNO_3$ [MH]+ 412.0470; found 412.0494.

*Tetrahydropyrido[2,3-c]coumarin (**88d**):*



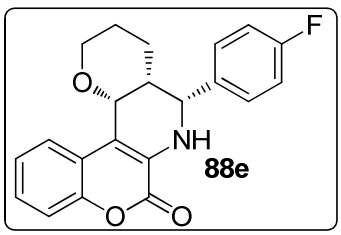
White solid (0.071 g, 17.2%). mp 184.4°C; R_f (5% ethyl acetate/hexane) 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.32-1.39 (m, 2 H); 1.42-1.58 (m, 2 H), 2.13-2.22 (m, 1 H), 3.12 (t, *J* = 11.2 Hz, 1 H), 3.54-3.57 (m, 1 H), 4.58 (s, 1 H), 4.92 (s, 1 H), 5.41 (d, *J* = 5.6 Hz, 1 H), 7.16-7.26 (m, 5 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 8.14 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 19.50, 24.48, 38.36, 58.77, 62.67, 72.01, 116.58, 120.53, 121.91, 124.75, 125.0, 126.76, 128.72 (2 C), 131.07, 131.90 (2 C), 138.60, 148.39, 158.54; **IR** (KBr): 1614, 1707, 2853, 2923, 3383 cm^{-1}; **Anal. Calcd** for $C_{21}H_{18}BrNO_3$ (412.28): C, 61.18; H, 4.40; N, 3.40. Found C, 61.28; H, 4.46; N, 3.54.

*Tetrahydropyrido[2,3-c]coumarin (**87e**):*



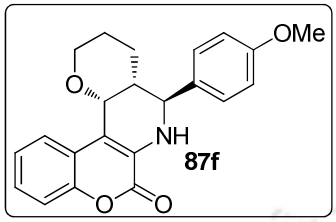
White solid (0.256 g, 73.1%). mp 204°C ; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.39-1.42 (m, 1 H); 1.50-1.54 (m, 1 H), 1.71-1.93 (m, 2 H), 2.00-2.04 (m, 1 H), 3.79 (td, *J* = 2.0, 11.6 Hz, 1 H), 4.13-4.17 (m, 1 H), 4.67 (d, *J* = 3.2 Hz, 1 H), 4.72 (d, *J* = 11.6 Hz, 1 H), 5.05 (s, 1 H), 7.08 (t, *J* = 8.8 Hz, 2 H), 7.21-7.28 (m, 3 H), 7.35-7.39 (m, 2 H), 7.52-7.55 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.97, 23.44, 38.63, 53.78, 69.27, 69.92, 114.58, 115.84, 116.05, 116.58, 120.61, 121.85, 124.96 (2 C), 126.24 (2 C), 129.85, 130.17, 136.12, 148.32, 158.96; **IR** (KBr): 1634, 1714, 2830, 2935, 3421 cm^{-1}; **Anal. Calcd** for $C_{21}H_{18}FNO_3$ (351.37): requires C, 71.78; H, 5.16; N, 3.99. Found C, 71.90, H, 5.22; N, 3.84. **MS** calcd. for $C_{21}H_{18}FNO_3$ [MH]+ 352.1271; found 352.1352.

*Tetrahydropyrido[2,3-c]coumarin (**88e**):* semi solid (0.048 g, 13.9%). R_f (5% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.71-1.42 (m, 4 H), 2.31-2.22 (m, 1 H), 3.19 (t, *J* = 11.6 Hz, 1 H), 3.64-3.61 (m, 1 H), 4.68 (d, *J* = 2.0 Hz, 1 H), 4.99 (s, N H, 1 H), 5.48 (d, *J* = 5.2 Hz, 1 H), 7.40-7.16 (m, 7 H), 8.21 (d, *J* = 8.0 Hz, 1 H); **IR** (KBr): 1509, 1626, 1699, 2925, 3408 cm^{-1};



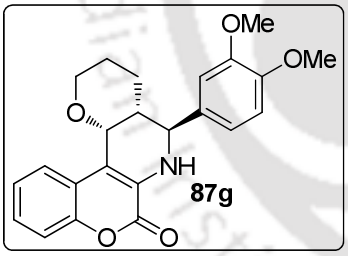
Anal. Calcd for $C_{21}H_{18}FNO_3$ (351.37): requires C, 71.78; H, 5.16; N, 3.99. Found C, 71.94, H, 5.24; N, 3.82.

*Tetrahydropyrido[2,3-c]coumarin (**87f**):*



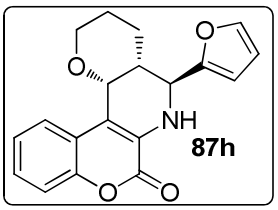
White solid (0.316 g, 87%). mp 221.2°C; R_f (5% ethyl acetate/hexane) 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.32 (d, J = 13.2 Hz, 1 H); 1.49 (d, J = 13.6 Hz, 1 H), 1.64-1.71 (m, 1 H), 1.75-1.85 (m, 1 H), 1.94-1.97 (m, 1 H), 3.71 (t, J = 11.6 Hz, 1 H), 3.75 (s, 3 H), 4.08 (d, J = 11.2 Hz, 1 H), 4.62-4.64 (m, 2 H), 4.98 (s, 1 H), 6.84 (d, J = 7.6 Hz, 2 H), 7.16-7.19 (m, 3 H), 7.24 (d, J = 7.6 Hz, 2 H), 7.47 (d, J = 7.2 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.98, 23.54, 38.57, 53.83, 55.53, 69.34, 70.12, 114.19, 114.40 (2 C), 116.59, 120.81, 121.79, 124.95, 126.06, 129.12 (2 C), 130.36, 132.28, 148.28, 159.36, 159.81; **IR** (KBr): 1628, 1716, 2849, 2928, 3402 cm^{-1}; **Anal. Calcd** for $C_{22}H_{21}NO_4$ (363.41): C, 72.71; H, 5.82; N, 3.85. Found C,72.82; H, 5.94; N, 3.94.

*Tetrahydropyrido[2,3-c]coumarin (**87g**):*



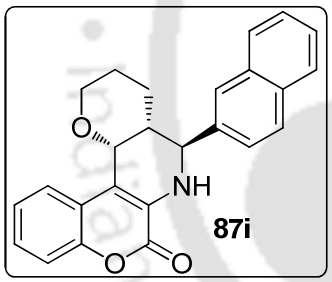
White solid (0.350 g, 89%). mp 194.7°C; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.38 (d, J = 12.4 Hz, 1 H), 1.52 -1.58 (m, 1 H), 1.74 (tt, J = 4.8, 13.2 Hz, 1 H), 1.92-2.10 (m, 2 H), 3.76 (td, J = 2.4, 11.6 Hz, 1 H), 3.82 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 4.12 (d, J = 7.6 Hz, 1 H), 4.68 (d, J = 2.8 Hz, 1 H), 4.95 (s, 1 H), 5.21 (bs, 1 H), 6.49 (d, J = 2.4 Hz, 1 H), 6.53 (dd, J = 2.0, 8.4 Hz, 1 H), 7.20-7.28 (m, 3 H), 7.32 (d, J = 8.4 Hz, 1 H), 7.57 (d, J = 8 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 22.23, 23.87, 38.23, 55.54, 55.57, 69.08, 70.27, 98.52, 105.22, 113.65, 116.45, 121.08, 121.20, 121.80, 124.83, 125.71(2 C), 129.08, 130.68, 148.16, 158.98, 159.11, 160.68; **IR** (KBr): 1627, 1717, 2841, 2951, 3401 cm^{-1}; **Anal. Calcd** for $C_{23}H_{23}NO_5$ (393.43): C, 70.21; H, 5.89; N, 3.56. Found C,70.38; H, 5.96; N, 3.67.

*Tetrahydropyrido[2,3-c]coumarin (**87h**):*



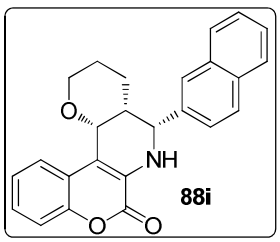
White solid (0.278 g, 86%). mp 245.2°C; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.45 (d, J = 6.8 Hz, 1 H), 1.62-1.68 (m, 1 H), 1.80 -1.96 (m, 2 H), 2.27 (d, J = 11.6 Hz, 1 H), 3.79 (t, J = 11.2 Hz, 1 H), 4.14 (d, J = 11.2 Hz, 1 H), 4.71 (d, J = 3.2 Hz, 1 H), 4.90 (d, J = 11.6 Hz, 1 H), 5.09 (s, 1 H, N H), 6.41 (s, 2 H), 7.18-7.29 (m, 3 H), 7.44 (s, 1 H), 7.46-7.60 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.97, 23.84, 36.74, 48.26, 69.22, 69.84, 108.80, 110.57, 114.53, 116.65, 120.59, 121.85, 124.98, 126.32, 129.83, 142.88, 148.37, 153.07, 158.91; **IR** (KBr): 1631, 1714, 2940, 3392 cm^{-1}; **Anal. Calcd** for $C_{19}H_{17}NO_4$ (323.34): C, 70.58; H, 5.30; N, 4.33. Found C, 70.73; H, 5.38; N, 4.22. **MS** calcd. for $C_{19}H_{17}NO_4$ [MH]+ 324.1158; found 324.1185.

*Tetrahydropyrido[2,3-c]coumarin (**87i**):*



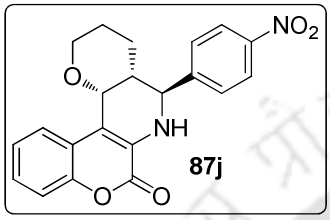
White solid (0.238 g, 62.2%). mp 198°C (Reported mp. 240-241°C); R_f (5% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.42-1.38 (m, 1 H); 1.53-1.56 (m, 1 H), 1.71-1.78 (m, 1 H), 1.94-1.99 (m, 1 H), 2.17-2.20 (m, 1 H), 3.81 (t, J = 11.2 Hz, 1 H), 4.18-4.20 (m, 1 H), 4.72 (s, 1 H), 4.91 (d, J = 11.2 Hz, 1 H), 5.19 (s, 1 H), 7.26-7.28 (m, 3 H), 7.56-7.58 (m, 4 H), 7.85-7.90 (m, 4 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.95, 23.47, 38.33, 54.54, 69.24, 69.91, 114.39, 116.51, 120.68, 121.82, 124.89, 125.12, 126.08, 126.37, 126.54, 127.43, 127.88, 127.98, 128.89, 130.23, 133.38, 133.47, 137.62, 148.25, 158.96; **IR** (KBr): 1506, 1628, 1704, 2840, 2938, 3362 cm^{-1}; **Anal. Calcd** for $C_{25}H_{21}NO_3$ (383.45): requires C, 78.30; H, 5.52; N, 3.65. Found C, 78.44; H, 5.60; N, 3.76. **MS** calcd. for $C_{25}H_{21}NO_3$ [MH]+ 384.1521; found 384.1604.

*Tetrahydropyrido[2,3-c]coumarin (**88i**):* Semi solid (Reported solid, mp. 201-202°C); (0.045 g, 11.8%). R_f (5% ethyl acetate/hexane) 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.71-1.41 (m, 4 H); 2.42-2.39 (m, 1 H), 3.20 (t, J = 11.2 Hz, 1 H), 3.65-3.61 (m, 1 H), 4.86 (s, 1 H), 5.18 (s, N H, 1H), 5.57 (d, J = 5.6 Hz, 1 H), 7.55-7.46 (m, 4 H), 7.92-7.81 (m, 5



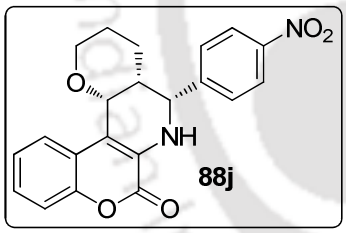
H), 8.08 (s, 1 H), 8.25 (d, *J* = 7.6 Hz, 1 H); **IR** (KBr):1088, 1261, 1613, 1710, 2923, 3413 cm^{-1}; **Anal. Calcd** for $C_{25}H_{21}NO_3$ (383.45): requires C, 78.30; H, 5.52; N, 3.65. Found C, 78.46; H, 5.58; N, 3.80.

*Tetrahydropyrido[2,3-c]coumarin (**87j**):*

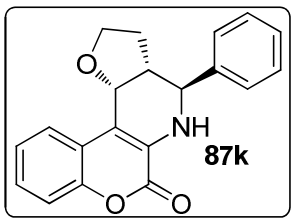


Yellow solid (0.195 g, 51.6%). mp 267 °C; R_f (5% ethyl acetate/hexane) 0.14; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.46-1.49 (m, 2 H), 1.78-1.93 (m, 2 H), 2.07-2.12 (m, 1 H), 3.82 (t, *J* = 11.2 Hz, 1 H), 4.17-4.21 (m, 1 H), 4.72 (d, *J* = 2.8 Hz, 1 H), 4.85 (d, *J* = 11.2 Hz, 1 H), 5.10 (s, 1 H, N H), 7.26-7.30 (m, 3 H), 7.56-7.57 (m, 1 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 8.28 (d, *J* = 8.8 Hz, 2 H); **IR** (KBr): 1343, 1513, 1634, 1713, 2845, 2945, 3393 cm^{-1}; **Anal. Calcd** for $C_{21}H_{18}N_2O_5$ (378.38): C, 66.66; H, 4.79; N, 7.40. Found. C, 66.81; H, 4.86; N, 7.54. **HRMS** calcd. for $C_{21}H_{18}N_2O_5$ [MH]+ 379.1216; found 379.1279.

*Tetrahydropyrido[2,3-c]coumarin (**88j**):* Semi solid (0.061 g, 16.4%). R_f (5% ethyl acetate/hexane) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.72-1.42 (m, 4 H), 2.41-2.31 (m, 1 H), 3.23 (t, *J* = 10.8 Hz, 1 H), 3.65-3.63 (m, 1 H), 4.80 (d, *J* = 2.4 Hz, 1 H), 5.07 (s, NH, 1H), 5.48 (d, *J* = 5.2 Hz, 1 H), 7.33-7.17 (m, 5 H), 7.54 (d, *J* = 8.8 Hz, 1 H), 7.62 (d, *J* = 8.4 Hz, 1 H) ppm. **IR** (KBr): 1345, 1513, 1626, 1715, 2926, 3396 cm^{-1}; **Anal. Calcd** for $C_{21}H_{18}N_2O_5$ (378.38): C, 66.66; H, 4.79; N, 7.40. Found. C, 66.84; H, 4.88; N, 7.52.



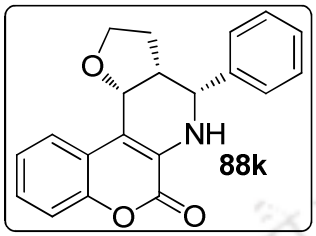
*Tetrahydropyrido[2,3-c]coumarin (**87k**):*



White solid(0.190 g, 59.5%). mp 168.9°C; R_f (5% ethyl acetate/hexane) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.76-1.83 (m, 1 H); 2.06-2.16 (m, 1 H), 2.46-2.53 (m, 1 H), 3.79 (d, *J* = 11.2 Hz, 1 H), 3.94 (q, *J* = 6.0 Hz, 1 H), 4.08 (q, *J* = 8.0 Hz, 1 H), 4.73 (d, *J* = 5.2 Hz, 1 H), 5.26 (s, 1 H), 7.25-7.29 (m, 3 H), 7.36-7.46 (m, 5 H), 7.72-7.78 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 28.49, 42.88, 57.58, 65.68, 72.88, 115.82, 116.52, 121.28, 123.13, 125.08, 126.69, 128.43(2 C), 128.81, 129.08 (2 C),

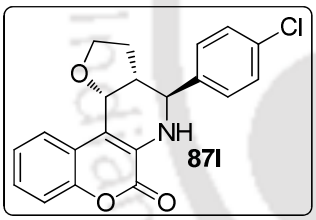
130.85, 140.0, 148.35, 158.89; **IR** (KBr): 1708, 2873, 2923, 3405 cm^{-1}; **Anal. Calcd** for $C_{20}H_{17}NO_3$ (319.3539): C, 75.22; H, 5.37; N, 4.39. Found C, 75.36; H, 5.44; N, 4.52.

*Tetrahydropyrido[2,3-c]coumarin (**88k**):*



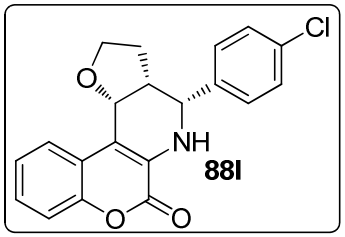
White solid (0.081 g, 25.5%. mp 163.7°C; R_f (5% ethyl acetate/hexane) 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.57-1.64 (m, 1 H); 2.15-2.25 (m, 1 H), 2.91-2.98 (m, 1 H), 3.77 (q, J = 6.4, 14.8 Hz, 1 H), 3.89 (td, J = 8.4, 2.8 Hz, 1 H), 4.70 (d, J = 2.8 Hz, 1 H), 4.97 (s, 1 H), 5.48 (d, J = 8 Hz, 1 H), 7.2-7.305 (m, 3 H), 7.35 (d, J = 7.2 Hz, 1 H), 7.40 (t, J = 7.2 Hz, 2 H), 7.48 (d, J = 7.2 Hz, 2 H), 7.79-7.82 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 25.28, 46.32, 57.19, 67.69, 73.04, 116.54, 118.62, 120.40, 124.41, 124.82, 126.67, 126.94, 128.26, 128.44, 129.02 (2 C), 129.92, 140.54, 148.79, 158.98; **IR** (KBr): 1632, 1700, 2895, 2929, 3362 cm^{-1}; **Anal. Calcd** for $C_{20}H_{17}NO_3$ (319.35): C, 75.22; H, 5.37; N, 4.39. Found C, 75.39; H, 5.46; N, 4.48.

*Tetrahydropyrido[2,3-c]coumarin (**87l**):*



White solid(0.199 g, 56.1%). mp 226-227 °C; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.70-1.76 (m, 1 H); 2.05-2.15 (m, 1 H), 2.40-2.46 (m, 1 H), 3.76 (d, J = 7.2 Hz, 1 H), 3.90-3.96 (m, 1 H), 4.0-4.10 (m, 1 H), 4.70 (d, J = 4.8 Hz, 1 H), 5.22 (s, 1 H), 7.26-7.28 (m, 3 H), 7.32-7.42 (m, 4 H), 7.72-7.75 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 28.37, 42.93, 56.97, 65.63, 72.74, 116.14, 116.49, 121.06, 123.14, 125.08, 126.85, 129.23 (2 C), 129.71 (2 C), 130.65, 134.55, 138.52, 148.33, 158.76; **IR** (KBr): 1627, 1716, 2921, 3383 cm^{-1}; **Anal. Calcd** for $C_{20}H_{16}ClNO_3$ (353.80): C, 67.90; H, 4.56; N, 3.96. Found C, 67.99; H, 4.64; N, 4.08. **HRMS** calcd. for $C_{20}H_{16}ClNO_3$ [MH]+ 354.0819; found 354.0808.

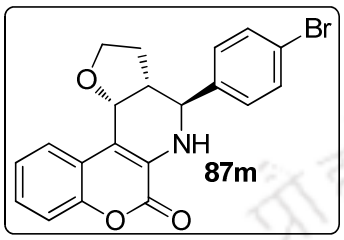
*Tetrahydropyrido[2,3-c]coumarin (**88l**):*



White solid (0.081g, 22.9%). mp 176-177°C; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.55-1.66 (m, 1 H), 2.11-2.21 (m, 1 H), 2.87-2.93 (m, 1 H), 3.77 (q, J = 8.4 Hz, 1 H), 3.89 (t, J = 8.4 Hz, 1 H), 4.68 (s, 1 H), 4.91 (s, 1 H), 5.47 (d, J = 8.0 Hz, 1 H), 7.25-7.32 (m, 3 H), 7.38 (d,

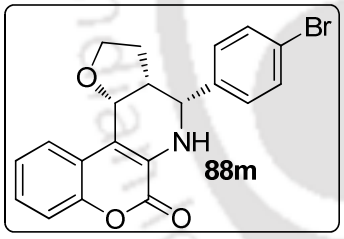
J = 8.4 Hz, 2 H), 7.42 (d, *J* = 7.6 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 1 H) ppm. **IR** (KBr): 1626, 1710, 2868, 2928, 3368 cm^{-1}; **Anal. Calcd** for $C_{20}H_{16}ClNO_3$ (353.80): C, 67.90; H, 4.56; N, 3.96. Found C, 68.08; H, 4.64; N, 4.09.

*Tetrahydropyrido[2,3-c]coumarin (**87m**):*



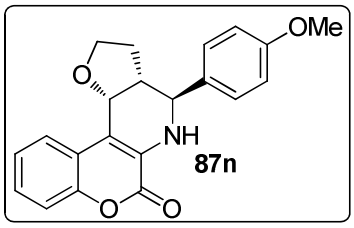
White solid (0.219 g, 55.1%). mp 237-238 °C; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.71-1.78 (m, 1 H), 2.07-2.16 (m, 1 H), 2.41-2.47 (m, 1 H), 3.76 (d, *J* = 11.2 Hz, 1 H), 3.94 (q, *J* = 9.2 Hz, 1 H), 4.08 (q, *J* = 8.4 Hz, 1 H), 4.71 (d, *J* = 5.2 Hz, 1 H), 5.22 (s, 1 H), 7.27-7.32 (m, 5 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.73-7.75 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 28.41, 42.96, 57.09, 65.68, 72.77, 116.20, 116.56, 121.07, 122.74, 123.17, 125.14, 126.92, 130.07, 130.68, 132.25 (2 C), 139.07 (2 C), 148.39, 158.81; **IR** (KBr): 1627, 1712, 2917, 3380 cm^{-1}; **Anal. Calcd** for $C_{20}H_{16}BrNO_3$ (398.25): C, 60.32; H, 4.05; N, 3.52. Found.C, 60.48; H, 4.15; N, 3.68.

*Tetrahydropyrido[2,3-c]coumarin (**88m**):*



White solid (0.103 g, 25.9%). mp 168-169 °C; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.45-1.53 (m, 1 H), 2.06 (q, *J* = 9.6 Hz, 1 H), 2.77 -2.84 (m, 1 H), 3.68 (q, *J* = 8.8, 1 Hz, 1 H), 3.79 (td, *J* = 2.4, 11.6 Hz, 1 H), 4.57 (d, *J* = 2.4 Hz, 1 H), 4.83 (s, 1 H), 5.37 (d, *J* = 8 Hz, 1 H), 7.17-7.23 (m, 3 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 9.2 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 25.13, 46.01, 56.60, 67.54, 72.84, 116.49, 118.86, 120.16, 121.97, 124.41, 124.81, 127.08, 128.31 (2 C), 129.58, 132.09(2 C), 139.58, 148.74, 158.82; **IR** (KBr): 1710, 2871, 2917, 3368 cm^{-1}; **Anal. Calcd** for $C_{20}H_{16}BrNO_3$ (398.25): C, 60.32; H, 4.05; N, 3.52. Found C, 60.42; H, 4.11; N, 3.67.

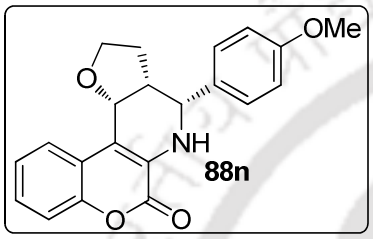
*Tetrahydropyrido[2,3-c]coumarin (**87n**):*



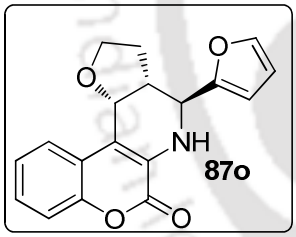
White solid (0.214 g, 61.6%). mp 186-187°C ; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.73-1.80 (m, 1 H), 2.04-2.15 (m, 1 H), 2.42-2.49 (m, 1 H), 3.74 (d, *J* = 11.2 Hz, 1 H), 3.83 (s, 3 H), 3.88-3.95 (m, 1 H), 4.06 (q, *J*

= 8.0 Hz, 1 H), 4.72 (d, *J* = 5.2 Hz, 1 H), 5.22 (bs, 1 H, N H), 6.93 (d, *J* = 8.4 Hz, 2 H), 7.25-7.29 (m, 3 H), 7.34 (d, *J* = 8.4, 2 H), 7.72 -7.75 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 28.41, 42.73, 55.39, 56.81, 65.49, 72.81, 114.27 (2 C), 115.61, 116.30, 121.22, 123.01, 124.90, 126.45, 129.37 (2 C), 130.73, 131.85, 148.15, 158.70, 159.81; **IR** (KBr): 1627, 1712, 2917, 3380 cm^{-1}; **Anal. Calcd** for $C_{21}H_{19}NO_4$ (349.38): C, 72.19; H, 5.48; N, 4.01. Found C, 72.32; H, 5.55; N, 3.90.

*Tetrahydropyrido[2,3-c]coumarin (**88n**):* Semi solid (0.092 g, 26.4%). R_f (5% ethyl acetate/hexane) 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.68-1.60 (m, 1 H), 2.22-2.10 (m, 1 H), 2.94-2.88 (m, 1 H), 3.74 (s, OMe, 3 H), 3.77-3.70 (m, 1 H), 4.21-4.15 (m, 1 H), 4.47 (d, *J* = 4.8 Hz, 1 H), 5.30 (d, *J* = 8.0 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 7.17-7.08 (m, 4 H), 7.25-7.18 (m, 2 H), 7.65-7.62 (m, 1 H); **IR** (KBr):1626, 1715, 2932, 3394 cm^{-1}; **Anal. Calcd** for $C_{21}H_{19}NO_4$ (349.38): C, 72.19; H, 5.48; N, 4.01. Found C, 72.36; H, 5.54; N, 3.92.

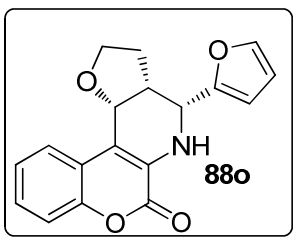


*Tetrahydropyrido[2,3-c]coumarin (**87o**):*



White solid (0.145 g, 46.8%). mp 153-154 °C ; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.85-1.93 (m, 1 H), 2.21-2.30 (m, 1 H), 2.65-2.72 (m, 1 H), 3.90-4.07 (m, 3 H), 4.75 (d, *J* = 5.6 Hz, 1 H), 5.28 (s, 1 H), 6.37-6.40 (m, 2 H), 7.27-7.29 (m, 3 H), 7.43 (d, *J* = 2.0 Hz, 1 H), 7.71-7.74 (m, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 28.84, 40.15, 50.78, 65.77, 72.42, 108.45, 110.57, 116.0, 116.48, 121.01, 123.15, 125.03, 126.79, 129.96, 142.97, 148.34, 152.85, 158.68; **IR** (KBr): 1634, 1711, 2864, 2966, 3400 cm^{-1}; **Anal. Calcd** for $C_{18}H_{15}NO_4$ (309.32): C, 69.89, H, 4.89, N, 4.53. Found C, 69.99, H, 4.98, N,4.68.

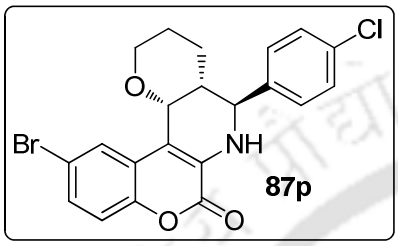
*Tetrahydropyrido[2,3-c]coumarin (**88o**)*:



White solid (0.96 g, 31.2%). mp 162-163 °C; R_f (5% ethyl acetate/hexane) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.88-1.96 (m, 1 H), 2.21 (q, *J* = 8.8 Hz, 1 H), 3.08-3.15 (m, 1 H), 3.82-3.87 (m, 2 H), 4.74 (d, *J* = 2 Hz, 1 H), 5.02 (s, 1 H, N H), 5.42 (d, *J* = 7.6 Hz, 1 H), 6.38 (d, *J* = 7.6 Hz, 2 H), 7.26-7.31 (m, 3 H), 7.41 (s,

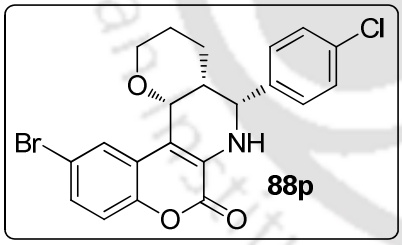
1 H), 7.80 (dd, *J* = 7.2, 1.6 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 25.74, 42.81, 51.17, 67.38, 72.52, 110.61, 106.68, 116.53, 118.63, 120.24, 124.35, 124.83, 127.04, 129.46, 142.34, 148.78, 153.23, 158.71; **IR** (KBr): 1634, 1715, 2929, 3375 cm^{-1}; **Anal. Calcd** for $C_{18}H_{15}NO_4$ (309.32): C, 69.89, H, 4.89, N, 4.53. Found C, 69.98, H, 4.92, N, 4.65.

*Tetrahydropyrido[2,3-c]coumarin (**87p**):*

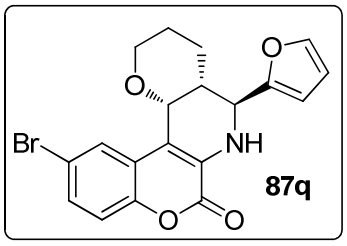


White solid (0.270 g, 60.7%). mp 219-220 °C; R_f (5% ethyl acetate/hexane) 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.42-1.47 (m, 1 H), 1.52-1.56 (m, 1 H), 1.74-1.90 (m, 2 H), 2.01-2.05 (m, 1 H), 3.82 (td, *J*.= 2.4, 11.6 Hz, 1 H), 4.18 (d, *J* = 9.2 Hz, 1 H), 4.63 (d, *J* = 2.8 Hz, 1 H), 4.75 (d, *J* = 11.2 Hz, 1 H), 5.16 (s, 1 H, N H), 7.15 (d, *J* = 8.8 Hz, 1 H), 7.32-7.36 (m, 3 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 2.4 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.82, 23.35, 38.40, 53.79, 69.29, 69.60, 113.12, 118.01, 118.17, 122.47, 124.31, 128.83, 129.28 (2 C), 130.65, 134.41, 138.55, 147.0, 158.25; **IR** (KBr): 1627, 1731, 2854, 2953, 3382 cm^{-1}; **Anal. Calcd** for $C_{21}H_{17}BrClNO_3$ (446.72): C, 56.46, H, 3.84, N, 3.14. Found C, 56.59, H, 3.92, N, 3.28. **MS** calcd. for $C_{21}H_{17}BrClNO_3$ [MH]+ 446.0080; found 446.0204.

*Tetrahydropyrido[2,3-c]coumarin (**88p**):* Semi solid (0.090 g, 20.3%); R_f (5% ethyl acetate/hexane) 0.36; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.68-1.41 (m, 4 H), 2.38-2.19 (m, 1 H), 3.17 (t, *J* = 11.6 Hz, 1 H), 3.68-3.65 (m, 1 H), 4.68 (d, *J* = 2.4 Hz, 1 H), 5.08 (s, NH, 1 H), 5.42 (d, *J* = 5.6 Hz, 1 H), 7.58-7.22 (m, 6 H), 8.21 (s, 1 H); **IR** (KBr): 1085, 1498, 1623, 1714, 2856, 3379 cm^{-1}; **Anal. Calcd** for $C_{21}H_{17}BrClNO_3$ (446.72): C, 56.46, H, 3.84, N, 3.14. Found C, 56.62, H, 3.94, N, 3.26.

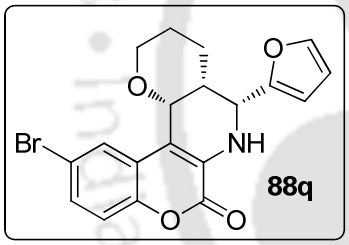


*Tetrahydropyrido[2,3-c]coumarin (**87q**):*



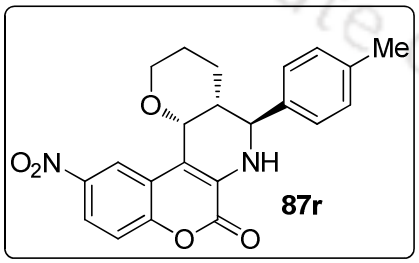
White solid (0.241 g, 60.1%). mp 176°C; R_f (5% ethyl acetate/hexane) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.43-1.50 (m, 1 H), 1.61-1.67 (m, 1 H), 1.84-1.90 (m, 2 H), 2.23 (d, J = 11.2 Hz, 1 H), 3.78 (td, J = 2.0, 11.6 Hz, 1 H), 4.11 (dd, J = 2.0, 11.2 Hz, 1 H), 4.61 (d, J = 2.4 Hz, 1 H), 4.87 (d, J = 11.6 Hz, 1 H), 5.17 (s, 1 H, N H), 6.39-6.42 (m, 2 H), 7.11 (d, J = 8.4 Hz, 1 H), 7.30 (dd, J = 2.0, 8.8 Hz, 1 H), 7.43 (s, 1 H), 7.60 (d, J = 2.0 Hz, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.83, 23.69, 36.44, 48.12, 69.20, 69.56, 108.94, 110.56, 112.92, 118.0, 118.18, 122.49, 124.29, 128.80, 130.31, 142.95, 146.99, 152.63, 158.21; **IR** (KBr): 1628, 1721, 2944, 3405 cm^{-1}; **Anal. Calcd** for $C_{19}H_{16}BrNO_4$ (402.24): C, 56.73, H, 4.01, N, 3.48. Found C, 56.88; H, 4.08; N, 3.38.

*Tetrahydropyrido[2,3-c]coumarin (**88q**):*



White solid (0.68 g, 16.94%). mp 176-177°C; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.57-1.75 (m, 3 H) 2.42-2.47 (m, 1 H), 3.24 (t, J = 10.4 Hz, 1 H), 3.67 (d, J = 12.0 Hz, 1 H), 4.37 (d, J = 5.6 Hz, 1 H), 4.72 (s, 1 H), 5.18 (s, 1 H), 5.29 (d, J = 5.2 Hz, 1 H), 6.33-6.34 (m, 1 H), 6.38 (d, J = 2 Hz, 1 H), 7.17 (d, J = 8.8 Hz, 1 H), 7.37 (dd, J = 2.4, 8.6, Hz, 1 H), 7.38-7.41 (m, 1 H), 8.26 (s, 1 H); **IR** (KBr): 1628, 1721, 2862, 2925, 2944, 3405 cm^{-1}; **Anal. Calcd** for $C_{19}H_{16}BrNO_4$ (402.24): C, 56.73, H, 4.01, N, 3.48. Found C, 56.89, H, 4.08, N 3.60.

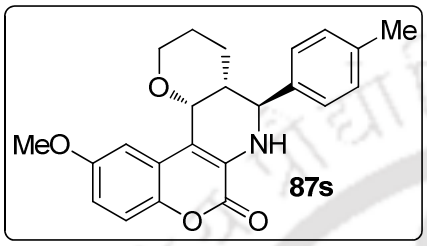
*Tetrahydropyrido[2,3-c]coumarin (**87r**):*



White solid (0.238, 60.8%). mp 246-247 °C ;R_f (5% ethyl acetate/hexane) 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.42-1.48 (m, 1 H) , 1.56-1.64 (m, 1 H), 1.75-1.94 (m, 2 H), 2.05-2.11 (m, 1 H), 2.39 (s, 3 H), 3.88 (t, J = 3.2 Hz, 1 H), 4.18 (d, J = 9.2 Hz, 1 H), 4.72 (d, J = 2.0 Hz, 1 H), 4.75 (d, J = 12.4 Hz, 1 H), 5.28 (s, 1 H, N H), 7.23 (d, J = 7.2 Hz, 2 H), 7.28 (d, J = 8 Hz, 2 H), 7.36 (d, J = 8.8 Hz, 1 H), 8.08 (d, J = 8.8 Hz, 1 H), 8.39 (s, 1 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.36, 21.84, 23.36, 38.23, 54.19, 69.44, 69.71, 112.43, 117.44, 117.73, 120.71,

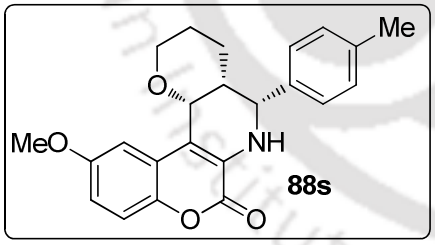
121.75, 127.87, 129.89, 131.39, 136.60, 138.73, 145.04, 151.39, 157.76; **IR** (KBr): 1341, 1525, 1635, 1733, 2943, 3369 cm^{-1}; **Anal. Calcd** for $C_{22}H_{20}N_2O_5$ (392.41): C, 67.34, H, 5.14, N, 7.14. Found.C, 67.48, H, 5.22, N, 7.10. **MS** calcd. for $C_{22}H_{20}N_2O_5$ [MH]+ 393.1372; found 393.1477.

*Tetrahydropyrido[2,3-c]coumarin (**87s**):*

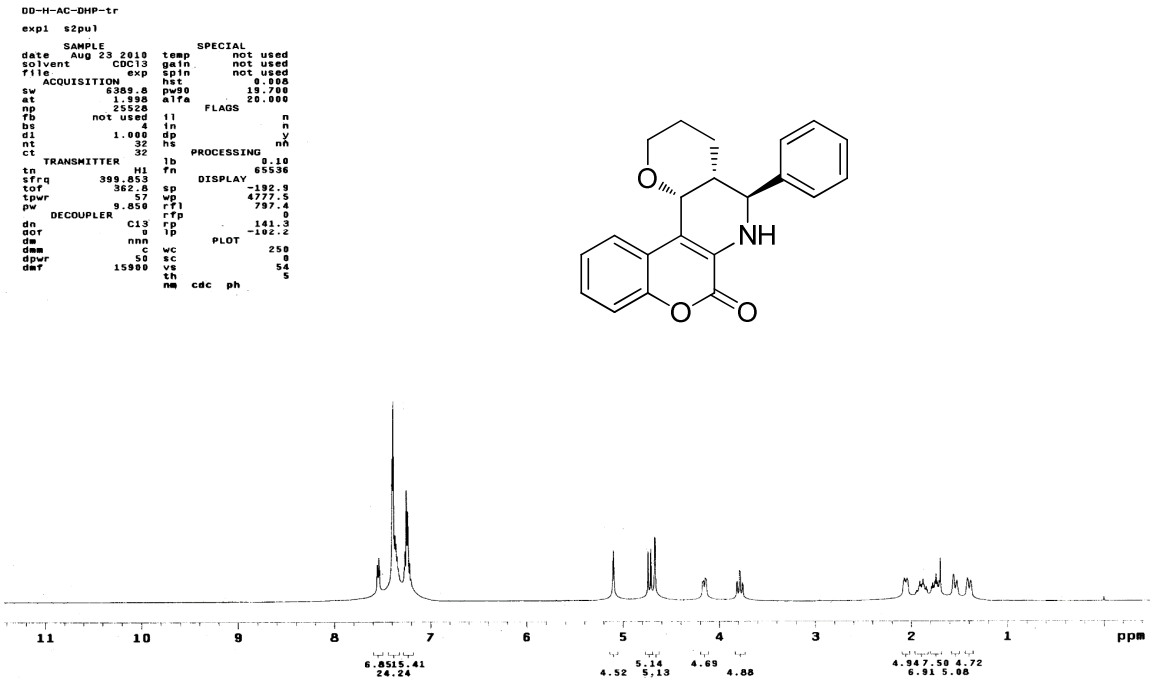


White solid (0.257g, 64.8%). mp 190°C; R_f (5% ethyl acetate/hexane) 0.21; **^{1}H NMR** (400 MHz, CDCl3): δ = 1.40 (d, J = 12.4 Hz, 1 H); 1.50 (d, J = 13.2 Hz, 1 H), 1.74-1.85 (m, 2 H), 1.97-2.0 (m, 1 H), 3.74-3.79 (m, 1 H), 3.83 (s, 3 H), 4.12-4.15 (m, 1 H), 4.59 (s, 1 H), 4.66 (d, J = 11.2 Hz, 1 H), 5.00 (s, 1 H), 6.74-6.81 (m, 1 H), 6.95-6.98 (m, 1 H), 7.17 (dd, J = 1.6, 8.8 Hz, 1 H), 7.32-7.37 (m, 4 H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 21.87, 23.37, 38.52, 53.80, 55.78, 69.17, 69.87, 105.87, 112.32, 114.24, 117.26, 121.28, 129.16, 129.30, 130.36,134.22, 138.84, 142.77, 156.66, 158.87; **IR** (KBr): 1510, 1634, 1716, 3405 cm^{-1}; **Anal. Calcd** for $C_{22}H_{20}ClNO_4$ (397.85) C 66.42, H, 5.07, N, 3.52. Found C, 66.60, H, 5.12; N, 3.39. **MS** calcd. for $C_{22}H_{20}ClNO_4$ [MH]+ 398.1081; found 398.1156.

*Tetrahydropyrido[2,3-c]coumarin (**88s**):* Semi solid (0.068g, 17.2%); R_f (5% ethyl acetate/hexane) 0.26; **^{1}H NMR** (400 MHz, CDCl3): δ = 1.63-1.41 (m, 4 H), 2.24-2.21 (m, 1 H), 3.21 (t, J = 10.8 Hz, 1 H), 3.64 (dd, J = 2.0, 9.6 Hz, 1 H), 3.83 (s, OMe, 3 H), 4.67 (d, J = 2.4 Hz, 1 H), 5.02 (s, N H, 1 H), 5.46 (d, J = 5.6 Hz, 1 H), 6.88 (dd, J = 2.8, 8.8 Hz, 1 H), 7.22 (d, J = 9.2 Hz, 1 H), 7.39-7.32 (m, 4 H), 7.75 (d, J = 2.8 Hz, 1 H); **IR** (KBr): 1085, 1505, 1617, 1709, 2936, 3390 cm^{-1}; **Anal. Calcd** for $C_{22}H_{20}ClNO_4$ (397.85) C 66.42, H, 5.07, N, 3.52. Found C, 66.62, H, 5.16; N, 3.34.



^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahydropyrido[2,3-c]coumarin (**87a**)*



^{13}C NMR (100 MHz, $CDCl_3$): *Tetrahydropyrido[2,3-c]coumarin (**87a**)*

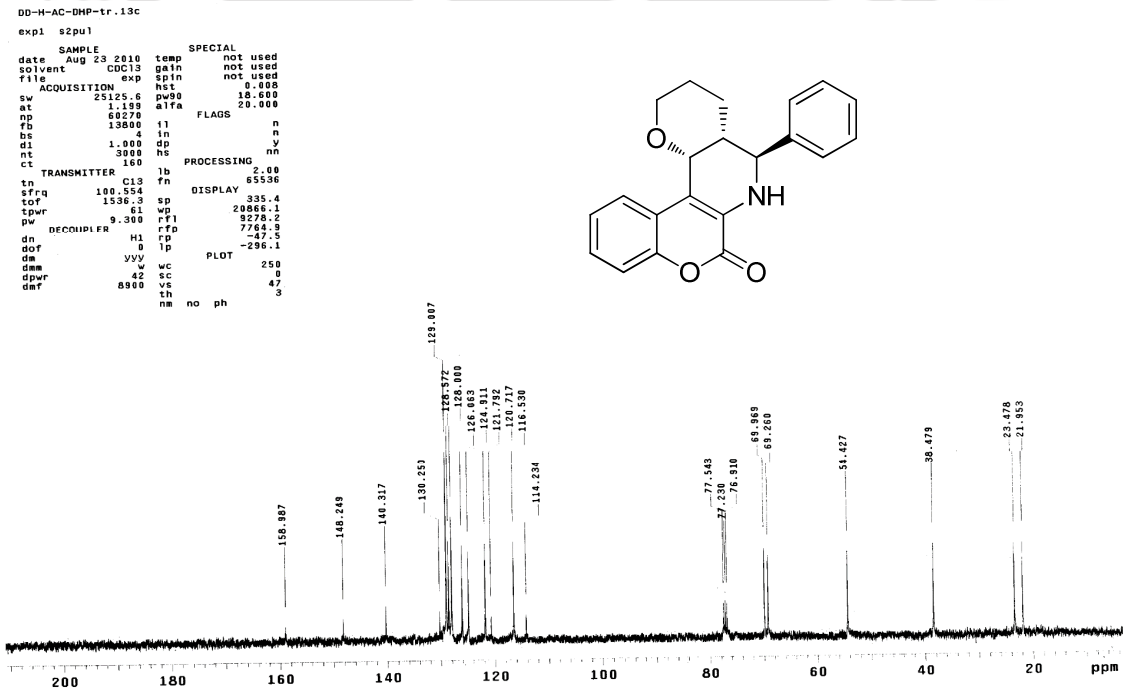
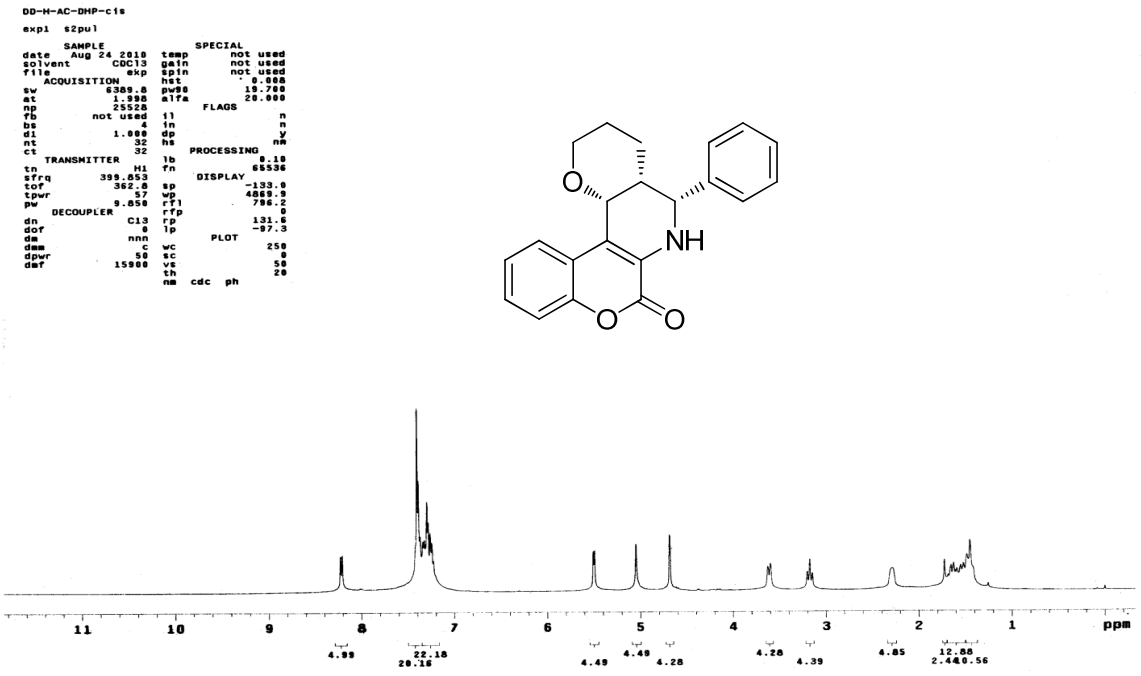


Figure 39

^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahydropyrido[2,3-c]coumarin (**88a**)*



^{13}C NMR (100 MHz, $CDCl_3$)*: Tetrahydropyrido[2,3-c]coumarin (**88a**)*

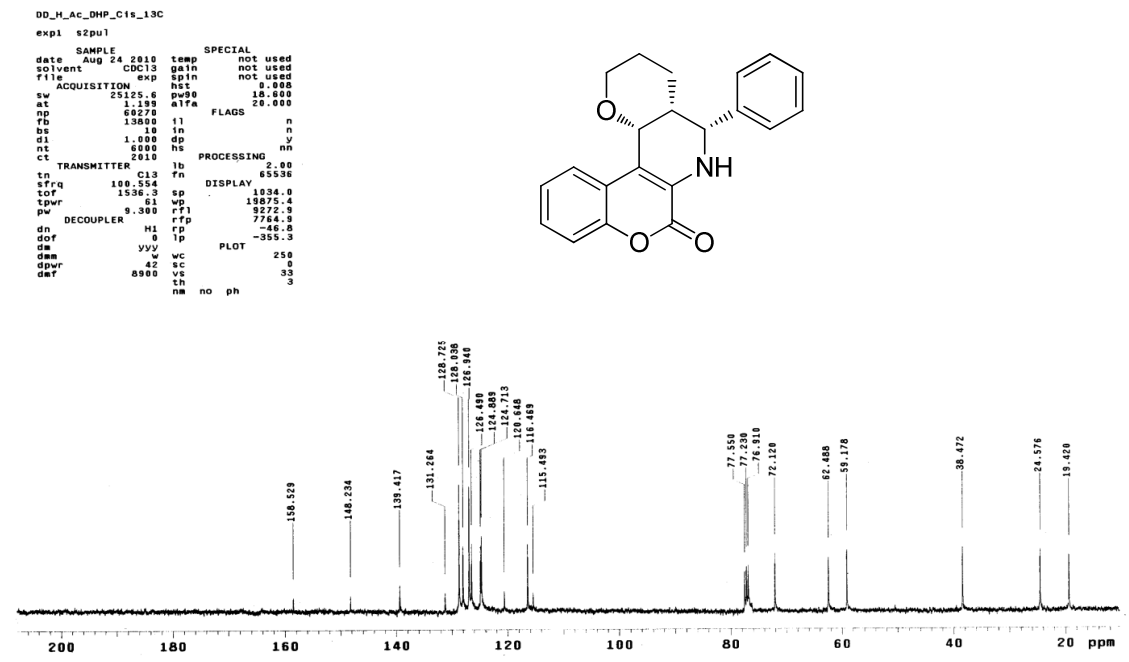
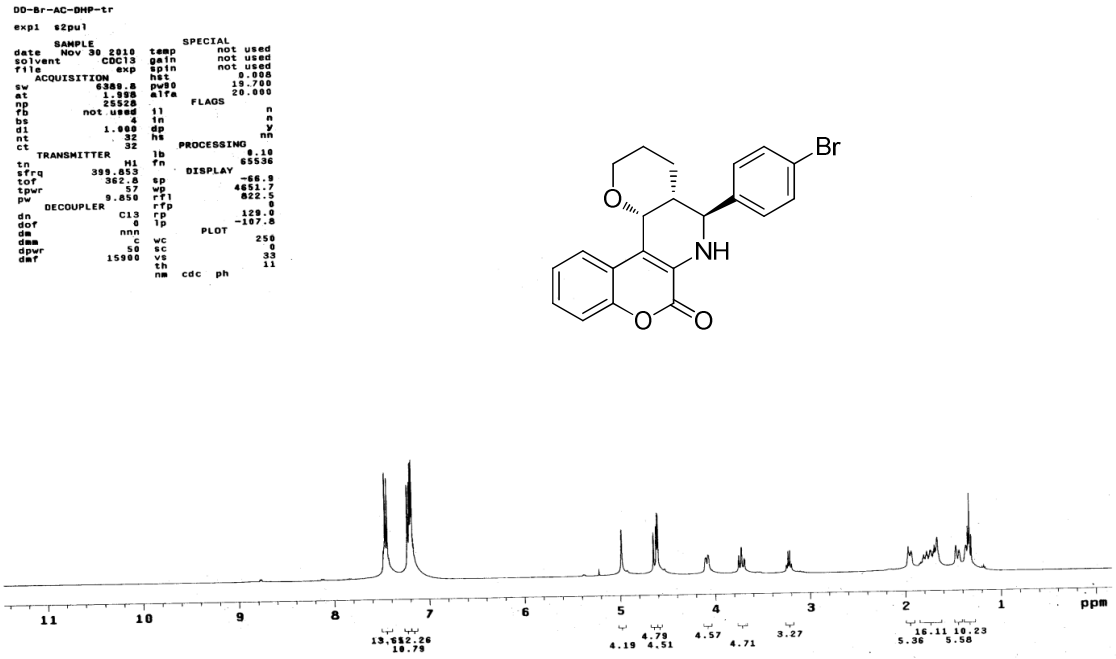


Figure 40

^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahydropyrido[2,3-c]coumarin (**87d**)*



^{13}C NMR (100 MHz, $CDCl_3$)*: Tetrahydropyrido[2,3-c]coumarin (**87d**)*

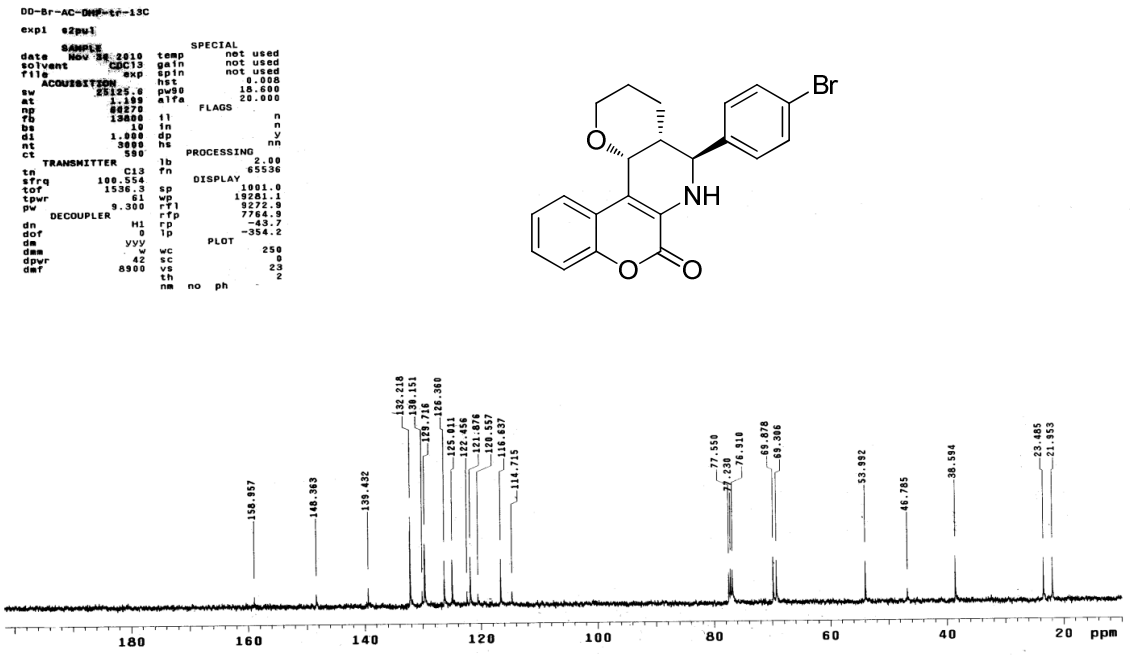
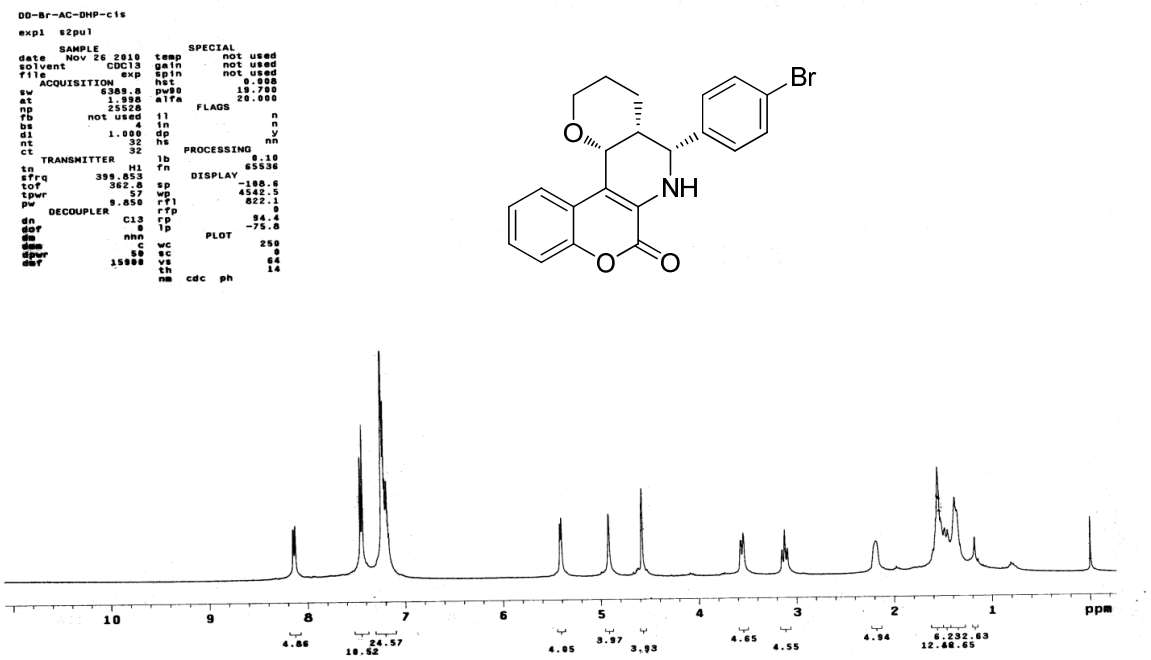


Figure 41

^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahydropyrido[2,3-c]coumarin (**88d**)*



^{13}C NMR (100 MHz, $CDCl_3$)*: Tetrahydropyrido[2,3-c]coumarin (**88d**)*

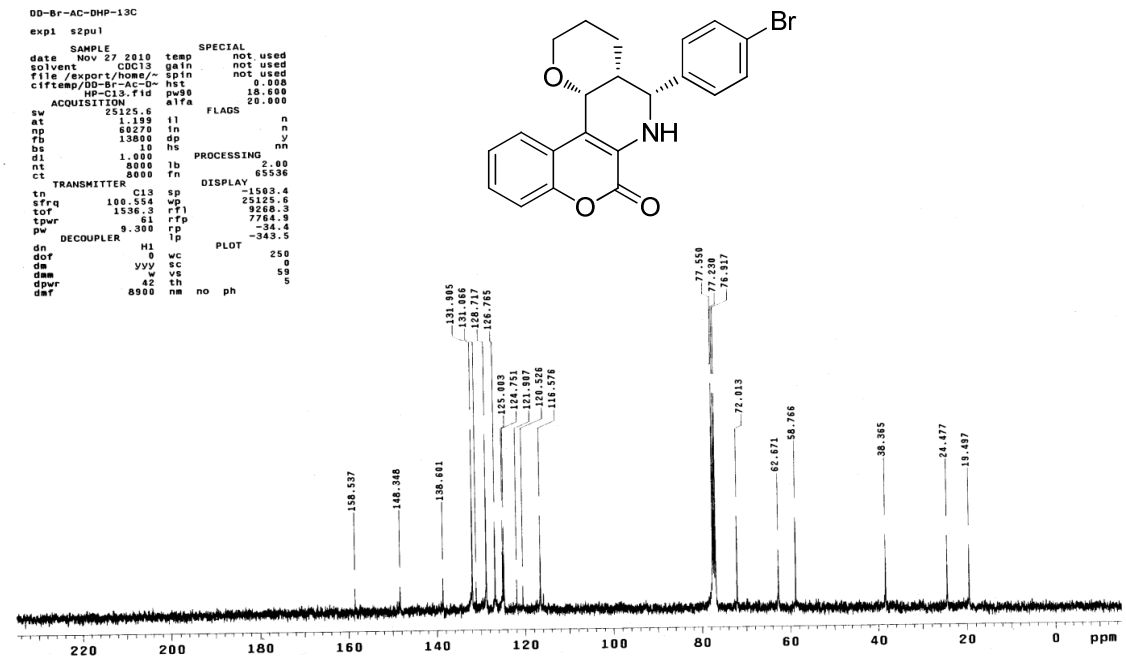
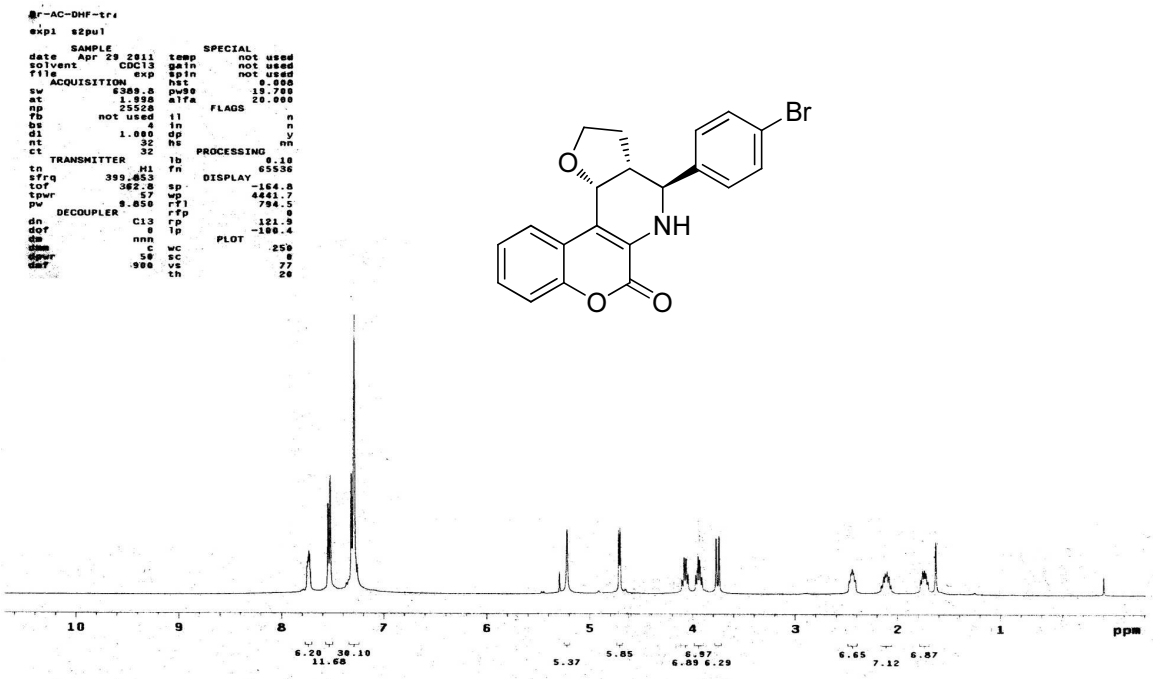


Figure 42

^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahydropyrido[2,3-c]coumarin (**87m**)*



^{13}C NMR (100 MHz, $CDCl_3$): *Tetrahydropyrido[2,3-c]coumarin (**87m**)*

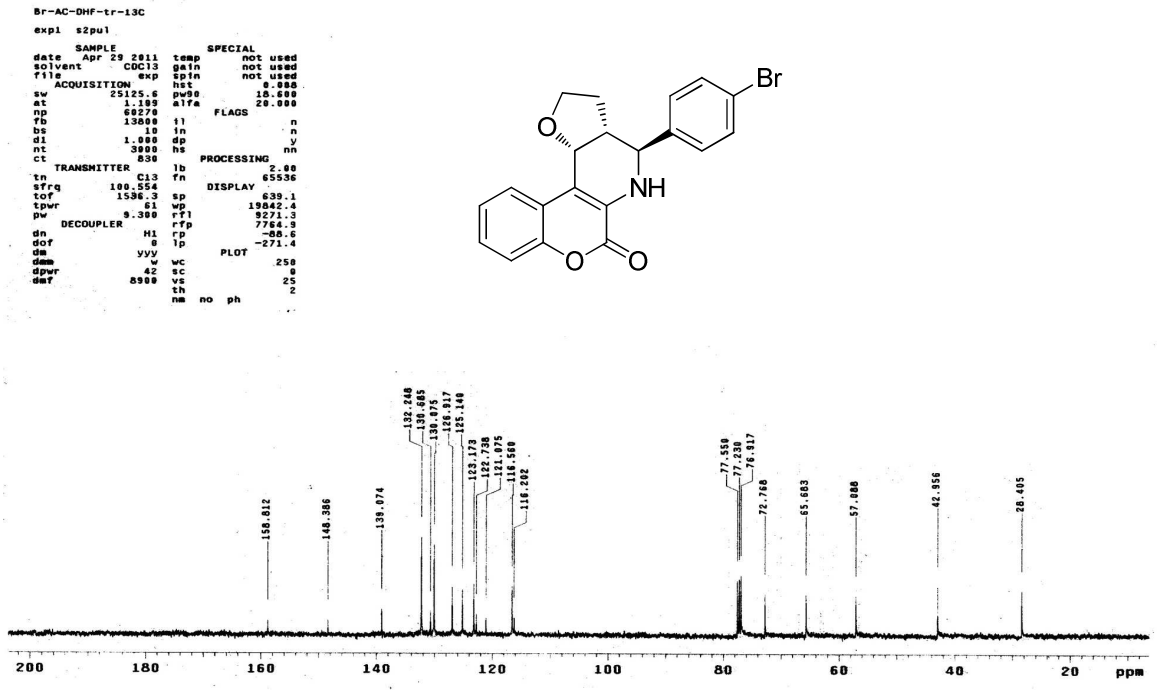
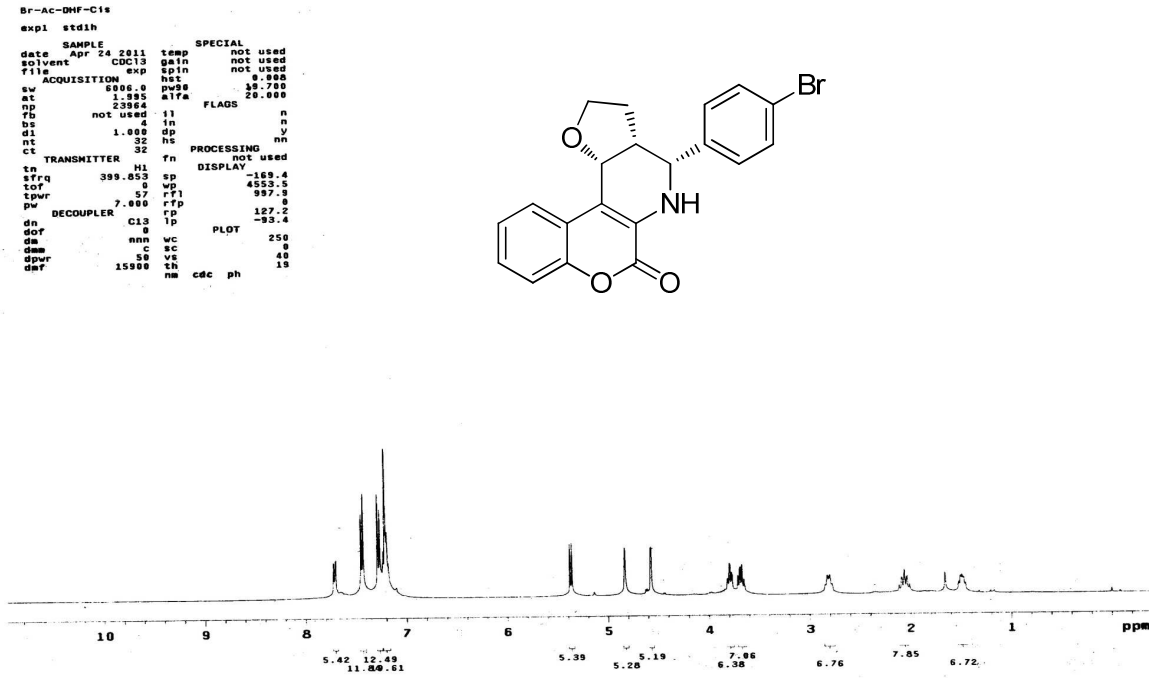


Figure 43

^{1}H NMR (400 MHz, $CDCl_3$): *Tetrahydropyrido[2,3-c]coumarin (**88m**)*



^{13}C NMR (100 MHz, $CDCl_3$)*: Tetrahydropyrido[2,3-c]coumarin (**88m**)*

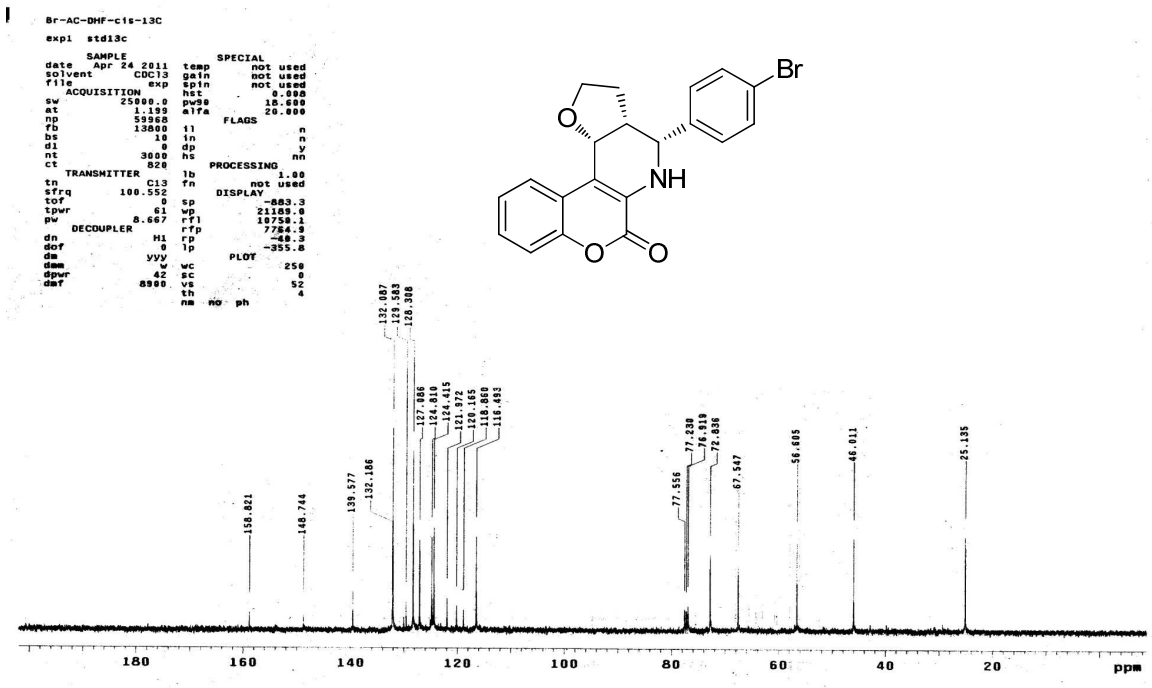


Figure 44

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PART C

CHAPTER IC

Short review on Tandem-Knoevenagel-Michael initiated ring closure reactions

Review

1. Introduction

Designing a "one-pot" sequence for the construction of highly complex molecules is a major driving force in organic synthesis nowadays. Chemists are constantly working to find out a new and improved reaction. One of the primary motivating goals is the development of cleaner, more efficient transformations to shorten syntheses. One of way to shorten syntheses is to develop a protocol using tandem reaction. Tandem reaction is the combination of two or more reactions whose occurrence is in a specific order. These reactions are also one-pot multi-step processes and hence, very powerful tool for the rapid construction of complex organic molecules in a facile and efficient manner.[1] These reactions can fall under category of Green Chemistry as they obviate the isolation and purification of intermediates, which reduces the waste generation. A tandem sequence can also lead to an increase in molecular complexity by combining a series of reactions in one synthetic operation.[2]

The definitions of Tandem reaction can be written as follows:

Tandem reactions are those which occur in succession; they are combinations of two or more reactions whose occurrence is in a specific order, and if they involve sequential addition of reagents the secondary reagents must be integrated into the products.[3]

Tandem reactions have several advantages over a series of individual reactions such as it becomes easier to work with sensitive or unstable intermediates since the intermediates are not isolated. In fact, tandem reactions have been considered as very effective and attractive for the development of new reactions in organic chemistry because of saving cost and amounts of reagents, solvents and reduce the amount of waste that is generated.

Tandem reactions can be classified into three categories.[4] First one is "cascade or domino" reactions in which both or all reactions take place without the need for additional reagents or a change in reaction conditions. Everything that is necessary for both reactions is incorporated into the starting materials. The second one is "consecutive" reactions, where the intermediate formed in the first reaction has the necessary functionality, but additional energy must be added in order to overcome an activation barrier. The third one is "sequential," where the functionality for the second reaction has been created but additional

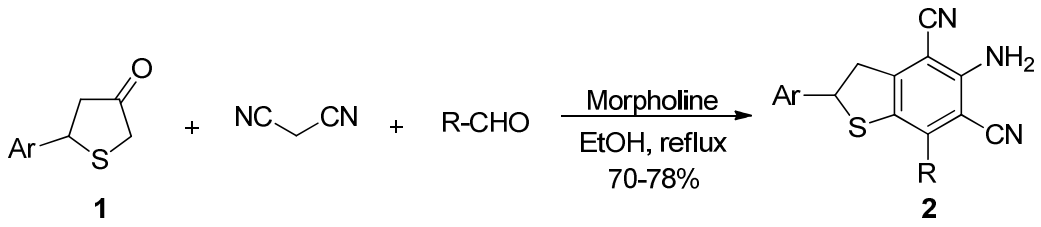
reagents must be added in order to achieve the second reaction. The Tandem reaction has been nicely described for a better understanding in recent books and reviews.[1-4]

Among numerous known organic reactions available to use in tandem reaction, Knoevenagel and Michael reaction are particularly attractive in organic synthesis. They have been used for the synthesis of various heterocyclic compounds in recent times. The chapter I of Part C will be addressed on tandem Knoevenagel-Michael reactions and the synthetic strategy will be used for the construction of heterocyclic compounds, which will be discussed in Chapter IIC and IIIC.

Knoevenagel condensation[5] and Michael addition[6] are well known fundamental organic reactions. Their combination into a tandem reaction has emerged as a powerful strategy in organic synthesis due to the fact that this approach allows molecular complexity and diversity to be created by assembling two or more reactions into a simple one-pot transformation. Generally, this type of tandem reactions start from the initial formation of a corresponding carbanion of compound involving an active methylene group (e.g. malononitrile, dimedone, acetylacetone, nitromethane, etc.), followed by a nucleophilic addition to a carbonyl compound and an elimination of a water molecule to generate polarized alkene, which is the Knoevenagel product. The formed Knoevenagel condensation product further serve as a Michael acceptor, which reacts with a nucleophile to complete the cascade reaction. Sometimes the intermediate product can undergo cyclisation to synthesize new heterocyclic compounds. Thus, these reactions might be referred as either Michael reaction or Michael Initiated Ring Closure (MIRC) reaction.

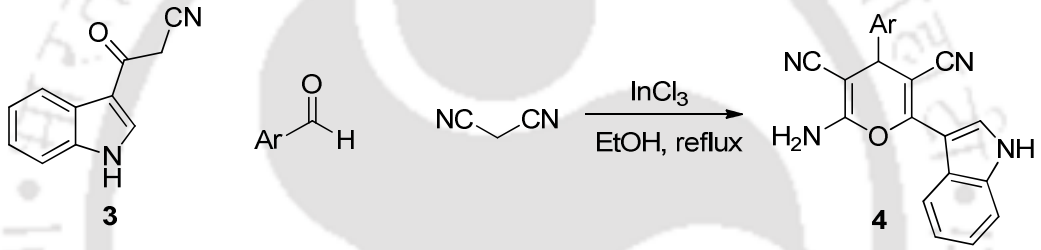
2. Recent use of tandem Knoevenagel-Michael reaction toward the construction of heterocyclic compounds

Kumar et al. demonstrated the synthesis of 5-amino-2,7-diaryl-2,3-dihydro benzo[b]thiophene-4,6-dicarbonitriles (**2**) in good yields through one-pot domino reactions of 5-aryldihydro-3(2H)-thiophenones, malononitrile and aromatic aldehydes in the presence of morpholine as catalyst. This transformation presumably involves Knoevenagel condensation-Michael-addition-intramolecular-cyclization-tautomerization–elimination sequence of reactions as shown in Scheme 1.[7]



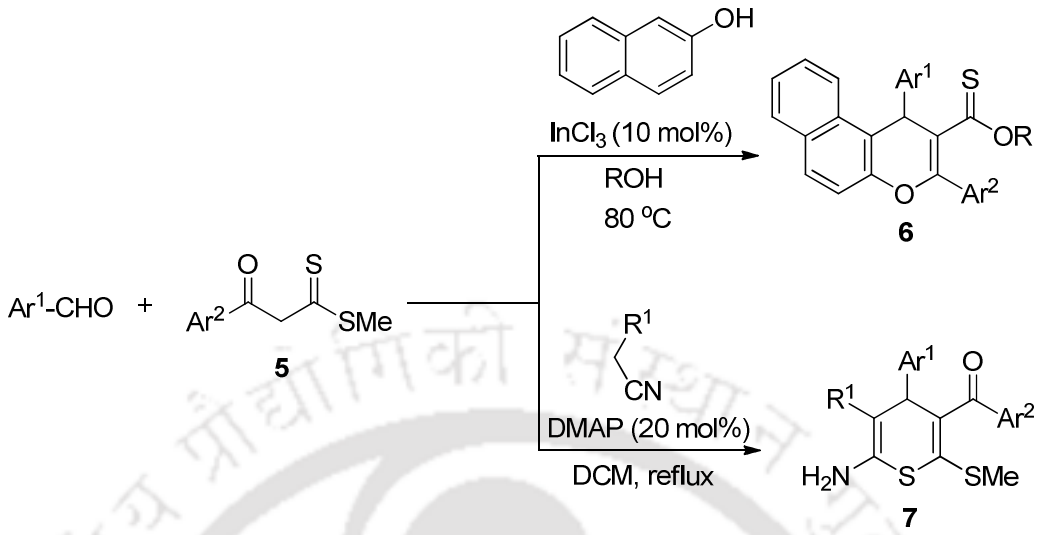
Scheme 1

A simple and convenient method for the one-pot three-component synthesis of 3-pyranyl indoles (**3**) has been accomplished by tandem Knoevenagel-Michael reaction of 3-cyanoacetyl indole **4**, various aromatic aldehydes and malononitrile catalyzed by $InCl_3$ in ethanol in good yields under reflux conditions as shown in Scheme 2.[8]



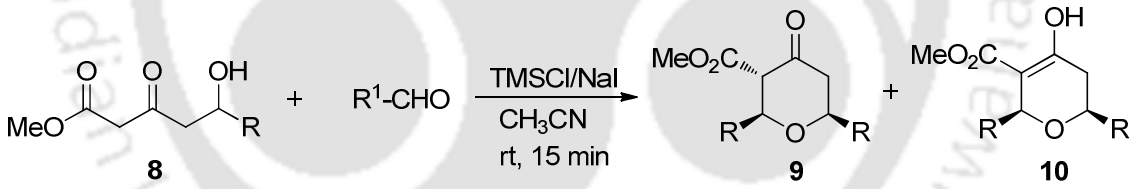
Scheme 2

Singh et al. described a highly efficient regioselective protocol for the synthesis of 4*H*-benzo[*f*]chromenes (**6**) by one-pot four-component coupling of aromatic aldehydes, β-naphthol, β-oxodithioesters (**5**) and primary alcohols in the presence of $InCl_3$. This transformation presumably proceeds via tandem-Knoevenagel-Michael reaction followed by intramolecular cyclodehydration and transesterification sequence creating four new bonds and one stereocenter in the final product as shown in Scheme 3. Later on, the same group used this cascade Knoevenagel condensation/Michael addition/cyclization sequence for the synthesis of highly functionalized 4*H*-thiopyrans **7**, as shown in Scheme 3.[9]



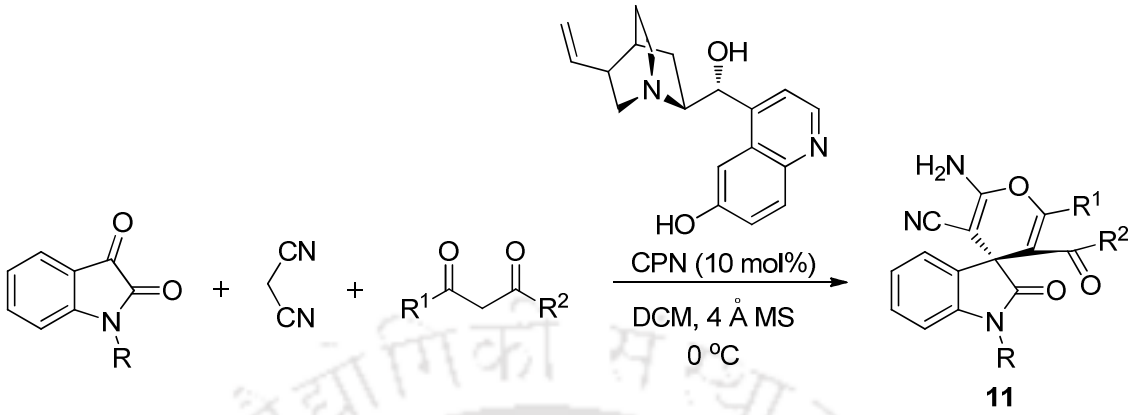
Scheme 3

The synthesis of functionalized tetrahydropyranones **9** and **10** has been achieved at room temperature with iodotrimethylsilane by a tandem Knoevenagel condensation of aldehydes with aldol adducts **8**, prepared from β-keto esters and aldehydes, followed by a Michael reaction giving the THP products as shown in Scheme 4.[10]



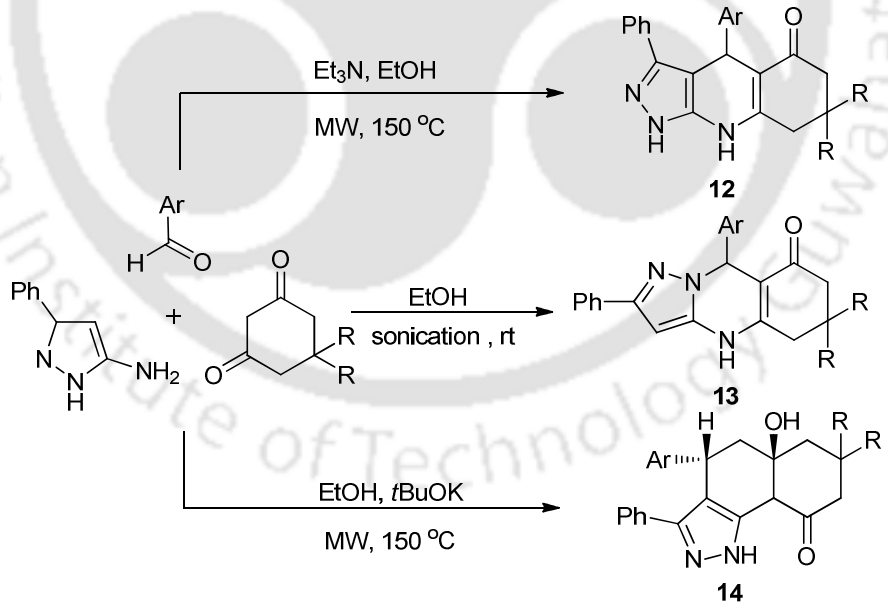
Scheme 4

Yuan et al demonstrated three-component reactions via a tandem Knoevenagel/Michael followed by cyclization sequence for the synthesis of wide range of optically active spiro-*4H*-pyran-3,3′-oxindoles **11**, with an excellent yield and enantio-selectivity from simple and readily available starting materials under mild reaction conditions as shown in Scheme 5.[11]



Scheme 5

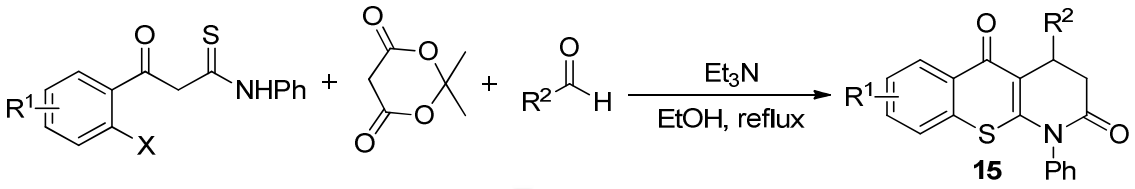
Chebanov et al. described multicomponent protocols using tandem Knoevenagel-Michael reaction for the synthesis of 1,4,6,7,8,9-hexahydro-1*H*pyrazolo[3,4-*b*]quinolin-5-ones **12**, 5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8-ones **13**, and 5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones **14** starting from 5-amino-3-phenylpyrazole, cyclic 1,3-dicarbonyl compounds and aromatic aldehydes as shown in Scheme 6.[12]



Scheme 6

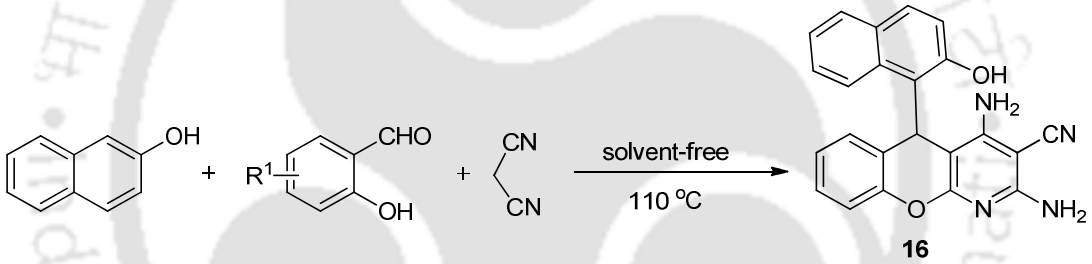
Tricyclic thiochromeno[2,3-b]pyridine derivatives (**15**) have been successfully synthesized from *ortho*-halo-β-aroylthioamides, Meldrum's acid, and aromatic aldehydes in an unusual one-pot multicomponent tandem reaction as shown in Scheme 7.[13] The reaction presumably

proceeds via Knoevenagel condensation-Michael addition-cyclocondensation-decarboxylation-rearrangement reaction sequence for the formation of the final product.



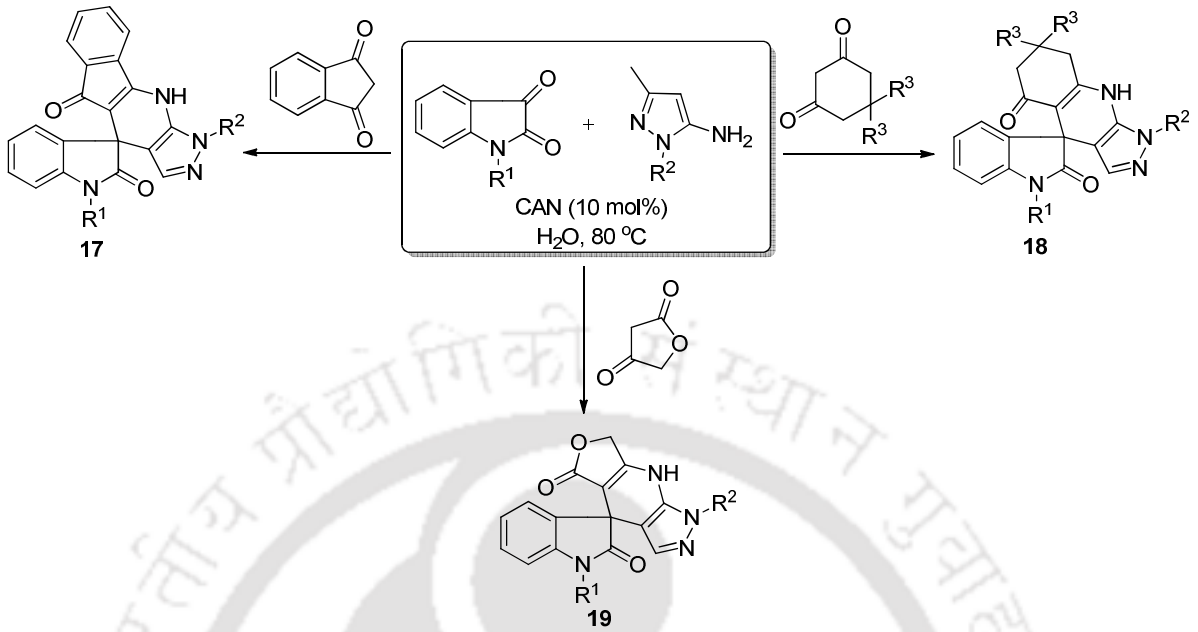
Scheme 7

Olyaei et al. described a facile one-pot pseudo four-component synthesis of benzopyrano[2,3-b] pyridines **16**, as shown in Scheme 8.[14] The reaction is achieved by Michael addition of β-naphthol to iminocoumarin derivatives obtained from Knoevenagel condensation of salicylaldehydes with malononitrile, which is further attacked by another molecule of malononitrile to afford the benzopyrano[2,3-b] pyridine products.



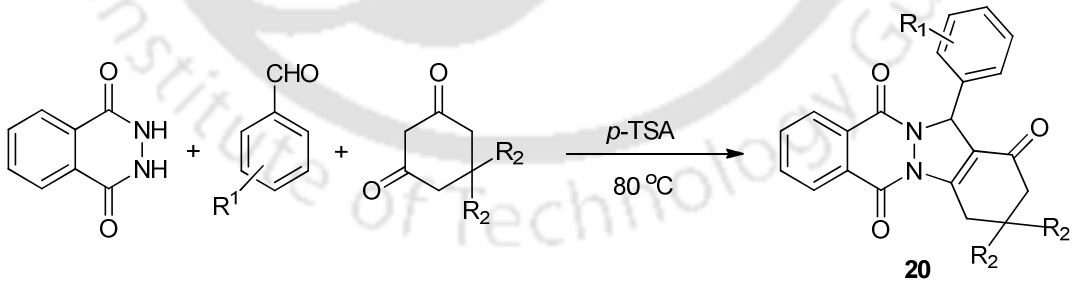
Scheme 8

Shi et al. reported CAN-catalyzed synthesis of spiro[indoline-3,4′-pyrazolo[3,4 *b*]quinoline]dione **17**, spiro[indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]dione **18** and spiro[furo-[3,4-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]dione **19** derivatives via three-component reaction of isatin, 5-amino-3-methylpyrazole and 1,3-dicarbonylcompounds in aqueous medium. The protocol involves formation of Knoevenagel adduct from isatin and 5-amino-3-methylpyrazole, which further act as a Michael acceptor and reacts with cyclic 1,3-dicarbonylcompounds to give the spiro-products as shown in Scheme 9.[15]



Scheme 9

Bazgir et al. demonstrated synthesis of indazolo[2,1-b]phthalazine-triones **20**, from three-component condensation reaction of phthalhydrazide, dimedone, and aromatic aldehydes under solvent-free conditions. The procedure involves the initial reaction of dimedone and aldehyde for the formation of Knoevenagel product which reacts with phthalhydrazide via Michael reaction to give the final indazolo[2,1-b]phthalazine products as shown in Scheme 10.[16]



Scheme 10

In conclusion the above discussion clearly demonstrates the diversity and power of tandem Knoevenagel-Michael reaction in the field of synthetic organic chemistry.

PART C

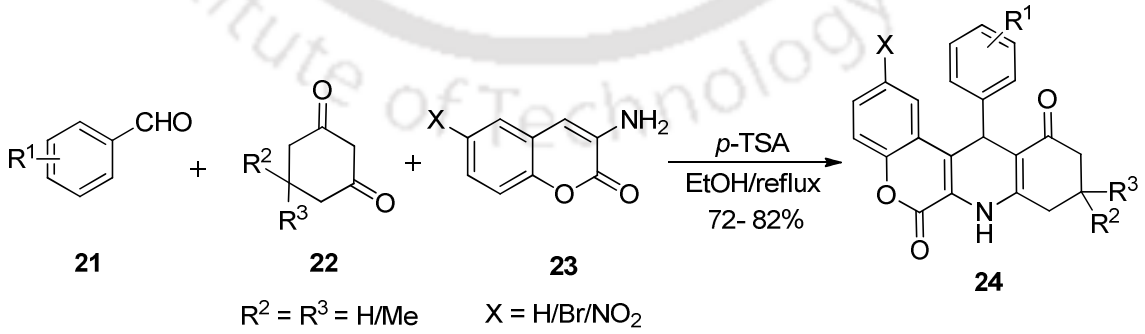
CHAPTER IIC

Michael initiated ring closure (MIRC) reaction on *in situ* generated benzylidenecyclohexane-1,3-diones for the construction of chromeno[3,4-b] quinoline derivatives

Result & Discussion
Experimental

MIRC (Michael Initiated Ring Closure) reaction represents an elegant approach, which has been used extensively for the construction of cyclopropane rings,[17] carbocyclic compounds[18] and small/medium sized nitrogen[19] or oxygen[20] containing heterocyclic compounds. The MIRC reaction strategy can also be cleverly achieved through one-pot multicomponent reaction, which is gaining interest to the synthetic organic chemists in recent times.[21] We perceived that cyclic 1,3-diketones may react with various aromatic aldehydes in the presence of a suitable acid catalyst to generate benzylidenecyclohexane-1,3-dione derivatives, which might be reacted instantly with carbon nucleophile such as 3-aminocoumarin through Michael type reaction followed by ring closure reaction leading to chromeno[3,4-b] quinoline derivatives. A similar synthetic strategy has also been demonstrated by others for the construction of 4-aza-2,3-didehydropodophyllotoxin[22a] and tricyclic dihydropyridine analogues,[22b] and pharmacological properties of these compounds have also been studied.

p-Toluenesulfonic acid (*p*-TSA) is a readily available catalyst which has been used extensively in place of mineral acids. In recent times, it was used as an efficient acid catalyst for the synthesis of 4(3*H*)-quinazolinones,[23] the regio- specific nitration of phenols[24] and the carbonylation of formaldehyde.[25] In this chapter, we discuss our successful results for the synthesis of chromeno[3,4-b]quinoline derivatives through MIRC reaction using one-pot condensation of aromatic aldehydes, cyclic 1,3-dicarbonyl compounds and 3-aminocoumarins under reflux condition in ethanol using *p*-TSA catalyst as shown in Scheme 11.



Scheme 11. One-pot three-component condensation reaction for the synthesis of chromeno[3,4-b] quinoline derivatives.

To find the optimal conditions, a mixture of benzaldehyde (1.0 mmol), dimedone (1 mmol) and 3-aminocoumarin (1.0 mmol) in ethanol was refluxed in presence of 5 mol % *p*-toluenesulfonic acid for 12 h in a pre-heated oil-bath and it provided the desired chromeno[3,4-b] quinoline derivative **24a** in 54% yield (Table 1, entry 1). The same reactions were also examined successively using 10 mol%, 20 mol% and 30 mol% *p*-TSA (entries 2-4, Table 1) and the desired product **24a** were isolated in 68%, 77 % and 78% yield, respectively. It was noted that the yield of the product **24a** did not increase significantly by increasing the amount of catalyst from 20% to 30%. For scrutinizing the suitable solvent system, similar reactions (entries 5-7) were conducted in methanol, acetonitrile and water under identical reaction conditions, respectively and the highest yields and shortest reaction times were obtained in ethanol To examine the efficacy of the catalyst, several reactions were carried out in the presence of other acidic and basic catalysts (entries 8-11), respectively. From these observations, it is clear that *p*-toluenesulfonic acid (*p*-TSA) is an effective catalyst. We have also examined the reactions with protic acids such as acetic acid and conc. hydrochloric acid (entries 12 and 13). The reactions were very sluggish and incomplete even after 24 h of refluxing when the same reaction was carried out in presence of protic acid (Table 1, entries 12 and 13).

Table 1. Optimization of reaction conditions for the synthesis of chromeno[3,4-b]quinoline derivative **24a**[a]

Entry	Catalyst	Solvent	Catalyst (mol%)	Reaction condition	Time (h)	Yield[b] (%)
1	*p*-TSA	EtOH	5	reflux	12	54
2	*p*-TSA	EtOH	10	reflux	12	68
3	*p*-TSA	EtOH	20	reflux	7	77
4	*p*-TSA	EtOH	30	reflux	7	78
5	*p*-TSA	MeOH	20	reflux	12	62
6	*p*-TSA	MeCN	20	reflux	12	66
7	*p*-TSA	H_2O	20	reflux	10	42
8	$ZnCl_2$	EtOH	20	reflux	12	38

Continued

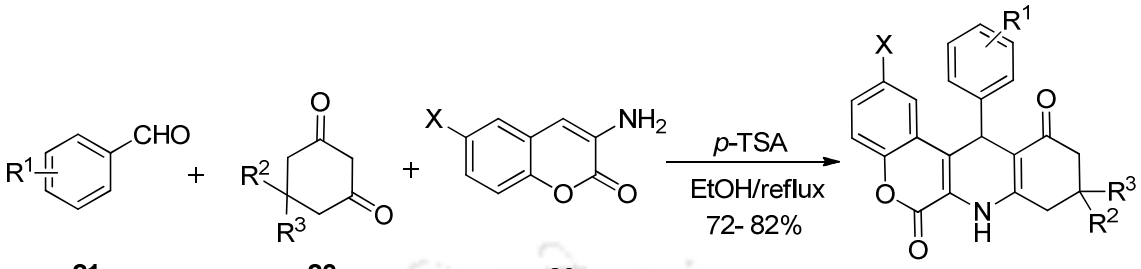
9	SiO_2	EtOH	20	reflux	12	28
10	Et_3N	EtOH	20	reflux	12	24
11	Piperidine	EtOH	20	reflux	12	26
12	Acetic acid	EtOH	20	reflux	24	22
13	HCl	EtOH	20	reflux	24	00
14	No catalyst	*n*-BuOH	0	reflux	24	00
15	*p*-TSA	*n*-BuOH	20	reflux	4.5	75

[a] Reaction conditions: Benzaldehyde, dimedone and 3-aminocoumarin were taken in 1:1:1 ratio.
[b] Isolated yields.

We presume that *p*-toluenesulfonic acid provides a more optimal balance between unprotonated fraction of the amine group and a protonated fraction of the 1,3-diketone. The results are summarized in Table 1. To verify the role of temperature, we have carried out two reactions in the solvent *n*-butanol (b.p. 116-119 ^oC) with and without catalyst (entries 14 and 15). It is worthwhile to mention that the same reaction was complete relatively faster in *n*-butanol. Since the yield was not increased significantly and cost of the *n*-butanol is higher as compared to ethanol, all the reactions were performed in ethanol.

The product **24a** was characterized by recording IR, ^1H NMR, ^{13}C NMR spectra and by elemental analysis. In IR spectrum, it showed characteristic absorptions peaks at 3290, 1713 and 1623 cm^{-1} due to one NH and two carbonyl group in product **24a**. Similarly, the compound **24** showed a diagnostic signal at ***δ* 5.59** in the ^1H NMR spectrum assignable to H-12 at the point of attachment of dihydropyridine ring to the aryl moiety. To explore the synthetic scope and the generality of the present protocol, various reactions were performed with a wide variety of aromatic aldehydes containing different substituents in the aromatic ring such as Me, OMe, Cl, Br, F, and NO_2 with dimedone and 3-aminocoumarin. The reaction time and percentage yield of the products (**24b-k**) are shown in Table 2 (entries 2-11**).** It is interesting to note that the pure products of all these reactions can be obtained just by recrystallization of the crude materials from ethanol by avoiding aqueous work-up and tedious column-chromatographic separation.

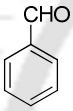
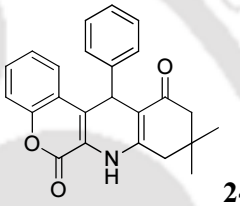
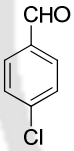
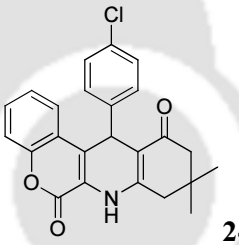
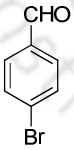
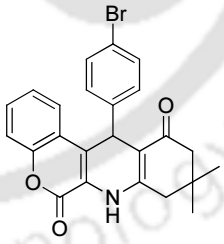
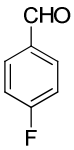
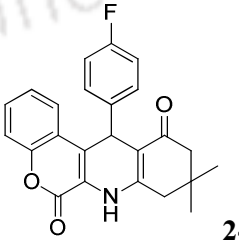
Table 2. Scope of various substituted chromeno[3,4-b]quinoline derivatives[a]



21 **22** **23** **24**

$R^2 = R^3 = H/Me$: **22a**
$R^2 = R^3 = H/Me$: **22b**

X = H : **23a**
X = Br : **23b**
X = NO_2 : **23c**

Entry	Aldehyde	22	23	Product	Time (h)	Yield[b]
1		**22a**	**23a**	 **24a**	7	77
2		**22a**	**23a**	 **24b**	8	78
3		**22a**	**23a**	 **24c**	8	82
4		**22a**	**23a**	 **24d**	7	73

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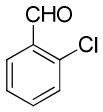
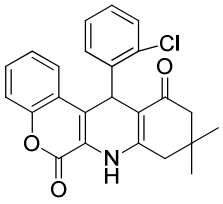
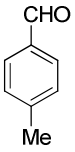
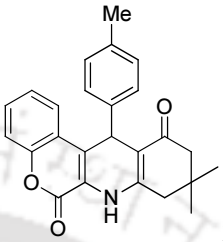
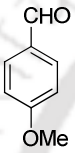
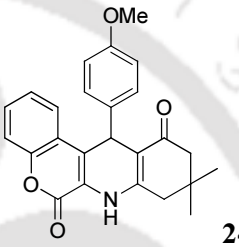
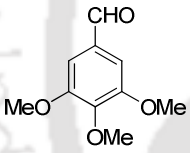
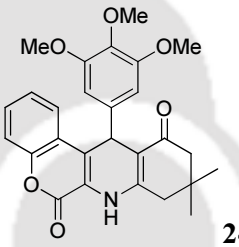
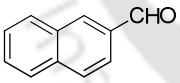
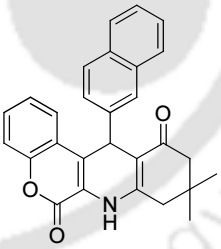
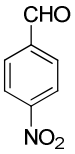
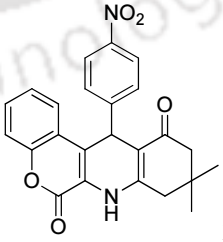
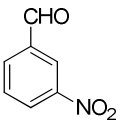
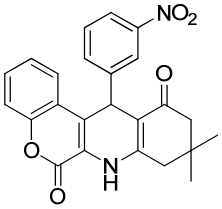
5		**22a**	**23a**	 **24e**	8	78
6		**22a**	**23a**	 **24f**	7	82
7		**22a**	**23a**	 **24g**	8	72
8		**22a**	**23a**	 **24h**	8	74
9		**22a**	**23a**	 **24i**	7	79
10		**22a**	**23a**	 **24j**	7	77
11		**22a**	**23a**	 **24k**	7	76

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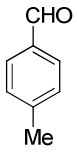
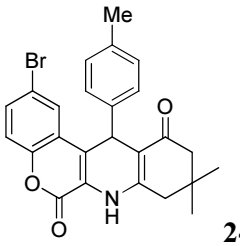
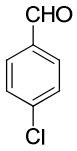
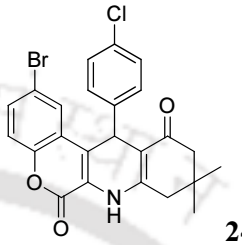
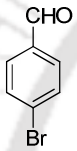
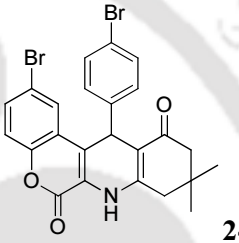
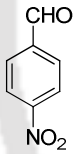
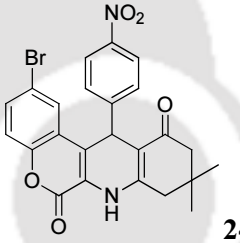
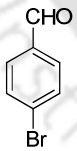
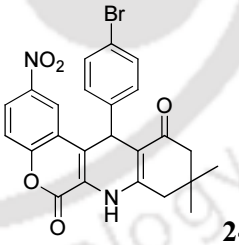
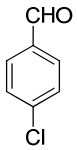
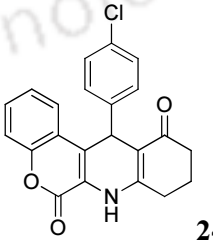
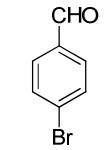
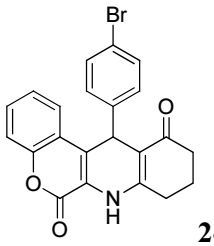
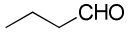
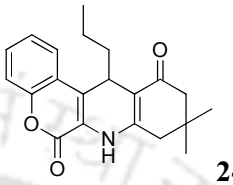
12		**22a**	**23b**	 **24l**	7	81
13		**22a**	**23b**	 **24m**	7	74
14		**22a**	**23b**	 **24n**	8	76
15		**22a**	**23b**	 **24o**	7	79
16		**22a**	**23c**	 **24p**	7	72
17		**22b**	**23a**	 **24q**	7	77

Continued

18		**22b**	**23a**	 **24r**	7	76
19		**22a**	**23a**	 **24s**	12	00

[a] Reaction conditions: Aromatic aldehyde, 1,3-cyclic ketone and 3-aminocoumarin were taken in 1:1:1 ratio in presence of 20 mol% of *p*-TSA in ethanol under reflux conditions. [b]Isolated yields.

For verifying the generality of the present approach, other substituted 3-aminocoumarins such as 6-bromo-3-aminocoumarin and 6-nitro-3-aminocoumarin were also examined with aromatic aldehyde and dimedone under identical reaction conditions to provide the desired chromeno[3,4-b]quinoline products (Table 2, entries 12-16, **24l-p**). Furthermore, the reactions with 1,3-cyclohexadione with 3-aminocoumarin and aromatic aldehyde were also performed (Table 2, entries 17-18, **24q-r**). When aliphatic aldehydes such as acetaldehyde, or butyraldehyde was treated with cyclic 1,3-diketones and 3-aminocoumarin in presence *p*-TSA under identical reaction conditions, the desired product was not obtained. (Table 2, entry 19, **24s**). It was also noted that similar transformation failed while the reaction was carried out with acyclic 1,3-diketone such as benzoylacetone. The ^{1}H NMR spectra and ^{13}C NMR spectra of the products **24c, 24g, 24q** and **24n** are given in Figures **2-6**, respectively in the experimental section.

Finally, the structure of one of the representative compounds such as 12-(4-chlorophenyl)-9,10-dihydro-9,9-dimethyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**24c)** was confirmed unambiguously by single crystal X-ray diffraction analysis as shown in Figure 1.(see Table 3 in experimental section)

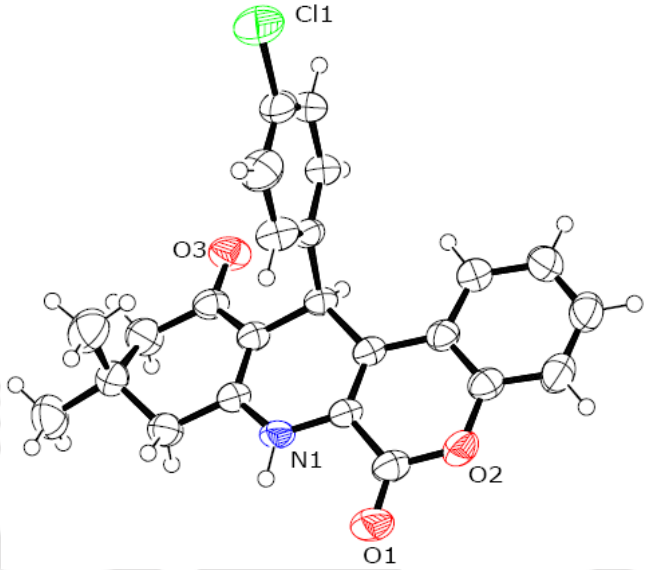
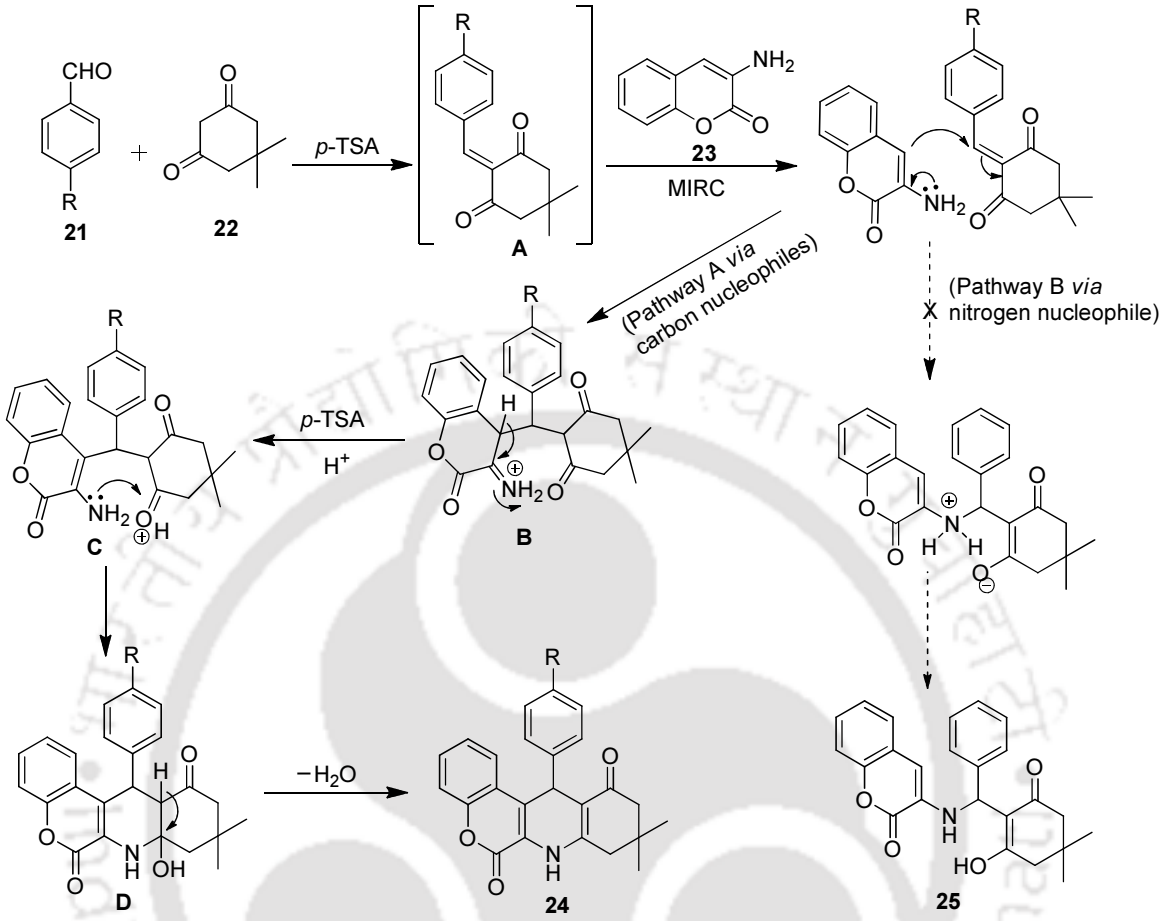


Figure 1. Single crystal X-ray structure **24c** (CCDC 827568)

The formation of the product may be explained as follows: The first step is believed to be the condensation reaction between aromatic aldehyde (**21**) with dimedone (**22**) to give Knoevenagel product **A**, benzylidenecyclohexane-1,3-dione,[26] which can act as a suitable Michael acceptor as shown in Scheme 12. We have also tried to isolate the intermediate **A** by performing the reaction of dimedone and *p*-chlorobenzaldehyde in presence of 10% *p*-TSA. But we did not get the intermediate **A**. Still we may believe that the intermediate **A** reacts with 3-aminocoumarin (**23**) at the position 4 of the coumarin ring to provide reactive intermediate **C** *via* **B**, which undergoes intra-molecular ring closure reaction followed by dehydration to give the desired chromeno[3,4-b]quinoline **24** as shown in ***Pathway A*** in Scheme 12. However, we did not obtain the product **25**, which may be possible by the nucleophilic attack of the NH_2 group of 3-aminocoumarin to Knoevenagel adduct (**A**) as shown in ***Pathway B***. Thus in this reaction we observed selective behavior of 3-aminocoumarin as C-nucleophile rather than acting as N-nucleophile. It is reported by Kadutskii and his co-worker that reaction of aromatic amines, formaldehyde and dimedone provides spirosubstituted piperidines,[27] which we did not observe in our present study.



Scheme 12. Proposed mechanism for the formation of products catalyzed by *p*-TSA

In conclusion, we have achieved the synthesis of novel heterocyclic compounds chromeno[3,4-b]quinoline derivatives (**24a-r**) using a high-yielding one-step multicomponent Michael Initiated Ring Closure (MIRC) reaction. It is worth mentioning that the three new bonds (two *C*-*C* and one *C*-*N*) and one stereocenter are formed in the course of the reactions. This method is quite general as it works for a wide variety of aromatic aldehydes, cyclic 1-3-diketones and different substituted 3-aminocoumarins. Shorter reaction times, environmentally benign, superior atom economy, easy accessibility of the catalyst and its cost effectiveness, simplicity of the procedure and good to excellent yields are some of the most significant features of the present protocol.

Genaral procedure for the synthesis of chromeno[3,4-b]quinoline compounds(24a-r)

A mixture of aromatic aldehyde (1.0 mmol), cyclic 1,3-dicarbonyl compound (1.0 mmol) and 3-aminocoumarin (1.0 mmol) in 2 mL of ethanol was refluxed in presence of *p*-TSA (0.2 mmol) in a pre-heated oil-bath. The progress of the reaction was monitored by TLC using ethyl acetate–petroleum ether (30:70, v/v). After the completion of the reaction, the solid product came out under hot condition at the stipulated time mentioned in the Table 2. The reaction mixture was brought to room temperature and the solid product was filtered off through a Büchner funnel. The precipitate was washed with ethanol and dried. The pure product chromeno[3,4-b]quinoline was obtained in good yield.

Crystallographic Description

Complete crystallographic data of **24c** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication CCDC no. is 827568. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

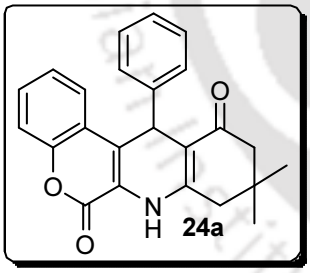
Table 3. Crystal data and structure refinement for **24c**.

Parameters	**Compound 24c**	**Parameters**	**Compound 24c**
Identification code	**24c**	Z	4
Empirical formula	C24 H20 Cl N O3	Density (calculated)	1.324 g/cm^3
Formula weight	405.86	Absorption coefficient	0.213 mm^{-1}
Temperature	296(2) K	F(000)	848.0
Wavelength	0.71073 Å	Theta range for data collection	2.01 to 21.03°
Crystal system	Triclinic	Index ranges	-11<=h<= 11, -13<=k<=15, -18<=l<=19
Space group	P-1	Reflections collected	17226
Unit cell dimensions		Independent reflections	7704 R_{int} = 0.0878

a	9.8026(3) Å	Completeness to θº	100% (θ = 25.65º)
b	13.5317(5) Å	Refinement method	Full-matrix least-squares on F2
c	16.4910(6) Å	Data / restraints / parameters	7315 / 0 / 535
α	73.396º(2)	Goodness-of-fit on F2	0.958
β	76.635º(2)	Final R indices [>2sigma(I)]	R_{obs} = 0.0532, wR_{obs} = 0.1411
γ	89.208º(2)	R indices (all data)	R_{all} = 0.0786, wR_{all} = 0.1577
Volume	2036.28(12) $Å^3$	Largest diff. peak and hole	0.477 and -0.563 $e.Å^{-3}$

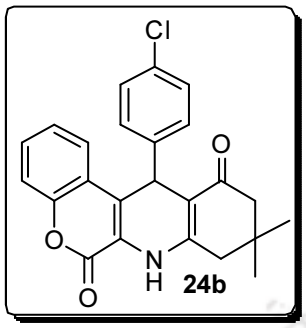
Spectral data of Chromeno[3,4-b] quinolines

*Chromeno[3,4-b] quinoline (**24a**)*



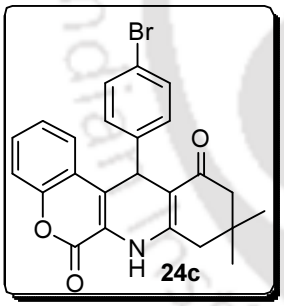
Yellow solid (285 mg, 77 %); m.p. 237-239 °C; R_f (30% ethyl acetate/hexane) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.66 (1 H, d, J = 8.0 Hz), 7.41 (2 H, d, J = 7.6 Hz), 7.35 (1 H, d, J = 7.2 Hz), 7.30 (1 H, d, J = 8.4 Hz), 7.26-7.19 (3 H, m), 7.14-7.10 (2 H, m), 5.59 (1 H, s), 2.49 (1 H, d, J = 16.4 Hz), 2.42 (1 H, d, J = 16.4 Hz), 2.30 (1 H, d, J = 16.4 Hz), 2.22 (1 H, d, J = 16.4 Hz), 1.11 (3 H, s), 0.95 (3 H, s) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.28, 157.66, 150.70, 148.93, 144.16, 129.34, 128.79, 128.30, 127.16, 126.77, 125.29, 124.22, 121.94, 119.20, 116.91, 108.99, 50.89, 41.54, 36.74, 32.94, 29.42, 27.31 ppm. **IR** (KBr): 3290(NH), 1713 (C=O), 1623 (C=O), 1595 (C=C), 1567, 1504 cm^{-1}; **HRMS** (ESI): MH^+, found 372.1596. $C_{24}H_{21}NO_3$ requires 372.1594. **Anal. Calcd** for $C_{24}H_{21}NO_3$ (371.15) requires C, 77.61; H, 5.70; N, 3.77; found: C, 77.68; H, 5.76; N, 3.83.

*Chromeno[3,4-b] quinoline (**24b**)*



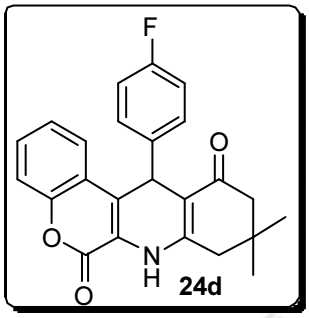
Yellow solid (316 mg, 78%); m.p. 251-253 °C; R_f (30% ethyl acetate/hexane) 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.55 (1 H, d, J = 8 Hz), 7.38- 7.33 (4 H, m), 7.28 (1 H, d, J = 8 Hz), 7.22-7.19 (2 H, m), 7.16 (1 H, s, NH), 5.55 (1 H, s), 2.50 (1 H, d, J = 16.8 Hz), 2.43 (1 H, d, J = 16.8 Hz), 2.30 (1 H, d, J = 16.4 Hz), 2.21 (1 H, d, J = 16.4 Hz), 1.10 (3 H, s), 0.93 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.27, 157.42, 150.57, 149.30, 142.61, 132.79, 129.62, 129.42, 128.86, 126.08, 125.28, 123.92, 122.04, 118.89, 116.90, 108.45, 50.78, 41.30, 36.17, 32.81, 29.40, 27.18; **IR** (KBr): 3147(NH), 1730(C=O), 1625(C=O), 1589(C=C), 1567, 1501 cm^{-1}; **HRMS** (ESI): MH^+, found 406.1206. $C_{24}H_{20}ClNO_3$ requires 406.1204. **Anal. Calcd** for $C_{24}H_{20}ClNO_3$ (405.87) requires C, 71.02; H, 4.97; N, 3.45; found: C, 71.08; H, 5.02; N, 3.52.

*Chromeno[3,4-b] quinoline (**24c**)*



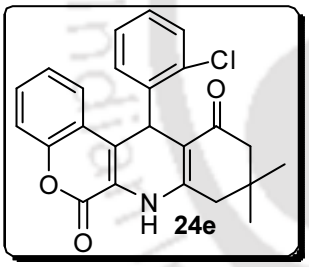
Yellow solid (368 mg, 82 %); m.p. 280-282 °C; R_f (30% ethyl acetate/hexane) 0.47; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.48 (1 H, dd, J = 8.0, 2.9 Hz), 7.32-7.21 (6 H, m), 7.20 (1 H, s, NH), 7.14 (1 H, td, J = 7.6, 1.2 Hz), 5.48 (1 H, s), 2.43 (1 H, d, J = 16.8 Hz), 2.35 (1 H, d, J = 17.2 Hz), 2.27 (1 H, d, J = 16.8 Hz), 2.14 (1 H, d, J = 16.4 Hz), 1.03 (3 H, s), 0.87 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.27, 157.45, 150.60, 149.21, 143.11, 131.84, 130.01, 129.46, 126.02, 125.32, 123.95, 122.07, 121.03, 118.91, 116.95, 108.45, 50.82, 41.38, 36.29, 32.87, 29.41, 27.25; **IR** (KBr): 3151, 1730 (C=O), 1626 (C=O), 1590 (C=C), 1567, 1503 cm^{-1}; **HRMS** (ESI): MH^+, found 450.0691. $C_{24}H_{20}BrNO_3$ requires 450.0698. **Anal. Calcd** for $C_{24}H_{20}BrNO_3$ (450.32) requires C, 64.01; H, 4.48; N, 3.11; found: C, 64.08; H, 4.52; N, 3.18.

*Chromeno[3,4-b] quinoline (**24d**)*



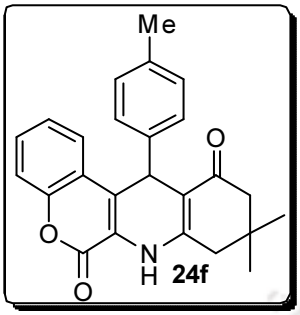
Yellow solid (368 mg, 82 %); m.p. 241-243 °C; R_f (30% ethyl acetate/hexane) 0.37; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.60 (1 H, d, J =8.0, 1,2 Hz), 7.41-7.30 (4 H, m), 7.23 (1 H, td, J = 7.6, 1.2 Hz), 7.08 (1 H, s, NH), 6.94-6.89 (2H, m), 5.58 (1 H, s), 2.48 (1 H, d, J = 16.8 Hz), 2.40 (1 H, d, J = 16.8 Hz), 2.29 (1 H, d, J = 16.4 Hz), 2.22 (1 H, d, J = 16.8 Hz), 1.10 (3 H, s), 0.95 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.30, 157.39, 150.54, 149.29, 140.02, 129.80, 129.28, 126.28, 125.18, 123.91, 121.98, 118.93, 116.79, 115.56, 115.36, 108.61, 50.78, 41.19, 35.92, 32.75, 29.40, 27.07. **IR** (KBr): 3290(NH), 1714 (C=O), 1627 (C=O), 1599 (C=C), 1505 cm^{-1}; **Anal. Calcd** for $C_{24}H_{20}FNO_3$ (389.42) requires C, 74.02; H, 5.18; N, 3.60; found: C, 74.07; H, 5.28; N, 3.68.

*Chromeno[3,4-b] quinoline (**24e**)*



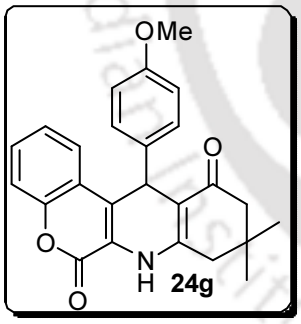
Yellow solid (315 mg, 78 %); m.p. 278-280 °C; R_f (30% ethyl acetate/hexane) 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.92 (1 H, d, J = 8 Hz), 7.41 (1 H, d, J = 7.6 Hz), 7.36 (1 H, d, J = 7.2 Hz), 7.30-7.24 (3 H, m), 7.18-7.06 (2 H, m), 7.05 (1 H, s, NH), 5.89 (1 H, s), 2.52 (1 H, d, J = 16.8 Hz), 2.42 (1 H, d, J = 16.8 Hz), 2.29 (1 H, d, J = 16.8 Hz), 2.18 (1 H, d, J = *16.4* Hz), 1.12 (3 H, s), 0.97 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.13, 157.54, 150.22, 149.40, 142.31, 132.47, 131.40, 130.15, 129.30, 128.50, 127.49, 126.65, 125.38, 124.32, 122.18, 119.28, 116.78, 108.70, 50.80, 41.44, 35.01, 32.72, 29.53, 27.13; **IR** (KBr): 3144 (NH), 1730 (C=O), 1588 (C=C),1566, 1501 cm^{-1}; **HRMS** (ESI): MH$^+$, found 406.1204. $C_{24}H_{20}ClNO_3$ requires 406.1204. **Anal. Calcd** for $C_{24}H_{20}ClNO_3$ (405.87) requires C, 71.02; H, 4.97; N, 3.45; found: C, 71.12; H, 5.06; N, 3.50.

*Chromeno[3,4-b] quinoline (**24f**)*



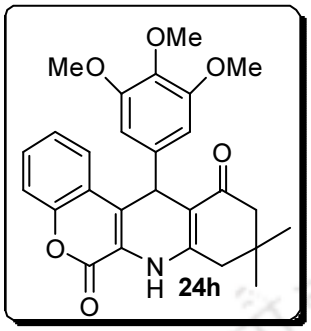
Yellow solid (316 mg, 82%); m.p. 252-254°C; R_f (30% ethyl acetate/hexane) 0.39; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.65 (1 H, dd, J = 8, 1.2 Hz), 7.35-7.28 (1 H, m), 7.27 (3 H, m), 7.19 (1 H, td, J = 7.6 Hz), 7.15 (1 H, s, NH), 7.00 (2 H, d, J = 8 Hz), 5.52 (1 H, s), 2.45 (1 H, d, J = 16.4 Hz), 2.39 (1 H, d, J = 16.4 Hz), 2.27 (1 H, d, J = 16.4 Hz), 2.21 (1 H, d, J = 16.4 Hz), 2.20 (3 H, s), 1.08 (3 H, s), 0.94 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.32, 157.61,150.62, 149.09, 141.35, 136.66, 129.40, 129.20, 128.13, 126.92, 125.20, 124.13, 121.80, 119.18, 116.79, 108.93, 50.83, 41.37, 36.26, 32.85, 29.40, 27.30, 21.17; **IR** (KBr): 3338 (NH), 1699 (C=O), 1630 (C=O), 1598 (C=C), 1567, 1509 cm^{-1}; **HRMS** (ESI): MH$^+$, found 386.1753. $C_{25}H_{23}NO_3$ requires 386.1751. **Anal. Calcd** for $C_{25}H_{23}NO_3$ (385.46) requires C, 77.90; H, 6.01; N, 3.63; found: C, 77.98; H, 6.06; N, 3.67.

*Chromeno[3,4-b] quinoline (**24g**)*



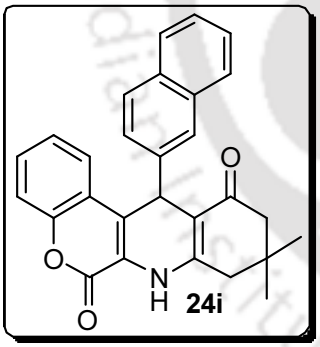
Yellow solid (288 mg, 72%); m.p. 232-234 °C; R_f (30% ethyl acetate/hexane) 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.65 (1H, d, J = 8.0 Hz), 7.37-7.25 (4H, m), 7.21 (1H, t, J = 7.2 Hz), 7.15 (1H, NH), 6.75 (2H, d, J = 8.8 Hz), 5.53 (1H, s), 3.71 (3H, s, OMe), 2.48(1H, d, J = 16.8 Hz), 2.41(1H, d, J = 16.4 Hz), 2.30 (1H, d, J = 16.4 Hz), 2.22 (1H, d, J = 16.4 Hz), 1.10 (3H, s), 0.96 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.37, 158.53, 157.66, 150.67, 148.73, 136.65, 129.31, 129.25, 126.92, 125.23, 124.18, 121.75, 119.19, 116.87, 114.07, 109.11, 55.29, 50.89, 41.45, 35.86, 32.90, 29.42, 27.31; **IR** (KBr): 3351(NH), 1704(C=O), 1632(C=O), 1599(C=C), 1504 cm^{-1}; **HRMS** (ESI): MH$^+$, found 402.1710. $C_{25}H_{23}NO_4$ requires 402.1700. **Anal. Calcd** for $C_{25}H_{23}NO_4$ (401.45) requires C, 74.79; H, 5.77; N, 3.49; found: C, 74.88; H, 5.73; N, 3.57.

*Chromeno[3,4-b] quinoline (**24h**)*



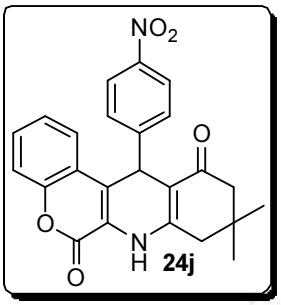
Yellow solid (341 mg, 74%); m.p. 253-255 °C; R_f (30% ethyl acetate/hexane) 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.61 (1 H, dd, *J*= 8.0, 0.8 Hz), 7.32-7.21 (2 H, m), 7.18-7.16 (1 H, m), 7.14 (1 H, s, NH), 6.55 (2H, s), 5.44 (1H, s), 3.70 (6 H, s), 3.67 (3 H, s), 2.44 (1 H, d, *J* = 16.8 Hz), 2.36 (1 H, d, *J* = 16.8 Hz), 2.22 (1 H, d, *J* = 16.8 Hz), 2.17(1 H, d, *J* = 16.4 Hz), 1.02 (3 H, s), 0.90 (3 H, s) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.31, 157.49, 153.28, 150.52, 149.09, 139.78, 137.10, 129.30, 126.44, 125.14, 124.09, 121.74, 119.12, 116.80, 108.66, 105.63, 60.80, 56.27, 50.78, 41.29, 36.69, 32.77, 29.39, 27.07. **IR** (KBr): 3405 (NH), 1719 (C=O), 1636 (C=O), 1602 (C=C), 1499, 1474 cm^{-1}; **Anal. Calcd** for $C_{27}H_{27}NO_6$ (461.51) requires C, 70.27; H, 5.90; N, 3.03; found: C, 70.35; H, 5.93; N, 3.07.

*Chromeno[3,4-b] quinoline (**24i**)*



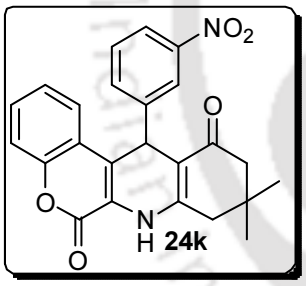
Yellow solid (332 mg, 79%); m.p. 265-267 °C; R_f (30% ethyl acetate/hexane) 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 (1 H, s), 7.76 (1 H, d, *J* = 8.4 Hz), 7.73-7.68 (3 H, m), 7.58 (1 H, d, *J* = 8.4 Hz), 7.42-7.35 (2 H, m), 7.33-7.30 (2 H, m), 7.31-7.30 (1 H, m), 7.21-7.17 (1 H, m), 7.16 (1 H, s, NH), 5.76 (1 H, s), 2.48 (1 H, d, *J* = 16.8 Hz), 2.42 (1 H, d, *J* = 16.8 Hz), 2.29 (1 H, d, *J* = 16.4 Hz), 2.19 (1 H, d, *J* = 16.4 Hz), 1.09 (3 H, s), 0.91 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.35, 157.71, 150.68, 149.00, 141.59, 133.53, 132.61, 129.35, 128.63, 128.21, 127.69, 126.99, 126.64, 126.20, 125.93, 125.31, 124.25, 122.02, 119.17, 116.90, 108.79, 50.87, 41.51, 36.92, 32.90, 29.38, 27.34; **IR** (KBr): 3328 (NH), 1699 (C=O), 1633 (C=O), 1599 (C=C), 1567, 1509 cm^{-1}; **HRMS** (ESI): MH^+, found 422.1759. $C_{28}H_{23}NO_3$ requires 422.1759. **Anal. Calcd** for $C_{28}H_{23}NO_3$ (421.49) requires C, 79.79; H, 5.50; N, 3.32; found: C, 79.86; H, 5.54; N, 3.38.

*Chromeno[3,4-b] quinoline (**24j**)*



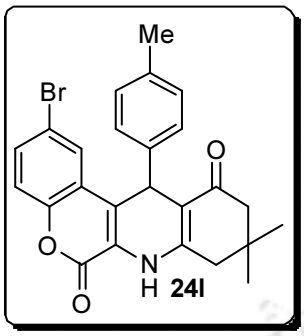
Yellow solid (0.317 g, 76%); m.p. 242-244 °C; R_f (30% ethyl acetate/hexane) 0.48; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.13 (1 H, d, J= 8.8 Hz), 7.59 (2 H, d, J = 8.8 Hz), 7.41-7.32 (2H, m), 7.25-7.22 (1H, m), 7.21 (1H, s, NH), 5.71 (1 H, s), 2.51 (1H, d, J = 16.4 Hz), 2.43 (1 H, d, J = 16.8 Hz), 2.30 (1 H, d, J = 16.4 Hz), 2.20 (1 H, d, J = 16.4 Hz), 1.11 (3H, s), 0.92 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.15, 157.28, 150.87, 150.67, 149.65, 147.00, 129.80, 129.24, 125.51, 125.08, 124.13, 123.73, 122.38, 118.68, 117.17, 107.88, 50.78, 41.49, 36.90, 32.92, 29.37, 27.24; **IR** (KBr): 3343 (NH), 1726 (C=O), 1632 (C=O), 1598 (C=C), 1518, 1482, 1343 cm^{-1}; **HRMS** (ESI): MH^+, found 417.1448. $C_{24}H_{20}N_2O_5$ requires 417.1445. **Anal. Calcd** for $C_{24}H_{20}N_2O_5$ (416.43) requires C, 69.22; H, 4.84; N, 6.73; found: C, 69.36; H, 4.91; N, 6.89.

*Chromeno[3,4-b] quinoline (**24k**)*



Yellow solid (0.317 g, 76%); m.p. 242-244 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.20 (1H, s), 8.01 (1H, d, J = 8.4 Hz), 7.84 (1H, d, J = 7.8 Hz), 7.54 (1H, d, J = 8.0 Hz), 7.46-7.33 (3H, m), 7.24 (1H, t, J = 7.8 Hz), 7.19 (1H, s, NH), 5.72 (1H, s), 2.52 (1H, d, J = 16.8 Hz), 2.46 (1H, d, J = 17.2 Hz), 2.32 (1H, d, J = 16.8 Hz), 2.22 (1H, d, J = 16.8 Hz), 1.12 (3H, s), 0.94 (3H, s) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 193.11, 155.10, 150.05, 148.94, 146.77, 145.23, 133.13, 128.25, 127.71, 123.70, 122.60, 122.10, 121.72, 121.32, 120.39, 117.32, 115.13, 105.39, 49.23, 39.01, 34.90, 31.01, 27.95, 25.41. **IR** (KBr): 3337 (NH), 1720 (C=O), 1632(C=O), 1605 (C=C), 1519, 1503, 1349 cm^{-1}. **Anal. Calcd** for $C_{24}H_{20}N_2O_5$ (416.43) requires C, 69.22; H, 4.84; N, 6.73; found: C, 69.31; H, 4.92; N, 6.79.

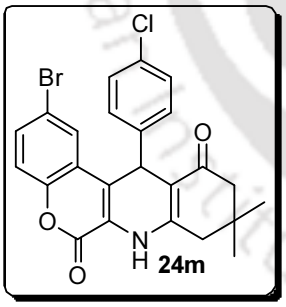
*Chromeno[3,4-b] quinoline (**24l**)*



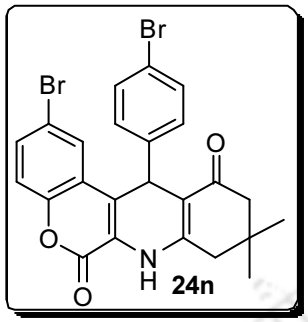
Yellow solid (0.375 g, 81%); m.p. 324-326 °C; R_f (30% ethyl acetate/hexane) 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (1 H, d, J = 2.4 Hz), 7.43 (1H, dd, J = 8.8, 2.0 Hz), 7.27 (2 H, d, J = 8.0 Hz), 7.17 (1 H, d, J = 8.4 Hz), 7.07 (2 H, d, J = 8.0 Hz), 7.04 (1 H, s, NH), 5.45 (1H, s), 2.48 (1H, d, J = 16.4 Hz), 2.41 (1 H, d, J = 16.4 Hz), 2.30 (1 H, d, J = 16.4 Hz), 2.24 (3 H, s), 2.22 (1 H, d, J = 16.4), 1.10 (3 H, s), 0.96 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.29, 157.15, 149.45, 148.62, 140.88, 137.04, 131.97, 129.64, 128.06, 126.70, 125.41, 122.49, 121.03, 118.47, 118.26, 109.28, 50.84, 41.43, 36.17, 32.95, 29.40, 27.37, 21.24; **IR** (KBr): 3177 (NH), 1724 (C=O), 1626 (C=O), 1591 (C=C), 1558, 1494 cm^{-1}; **HRMS** (ESI): MH^+, found 464.0851 $C_{25}H_{22}BrNO_3$ requires 464.0817. **Anal. Calcd** for $C_{25}H_{22}BrNO_3$ (464.35) requires C, 64.66; H, 4.78; N, 3.02; found: C, 64.73; H, 4.82; N, 3.09.

*Chromeno[3,4-b] quinoline (**24m**)*

Yellow solid (0.357 g,%); m.p. 250-252 °C; R_f (30% ethyl acetate/hexane) 0.43; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.68 (1 H, d, J = 2.4 Hz), 7.46 (1 H, dd, J = 8.8, 2.4 Hz), 7.33 (2 H, d, J = 8.8 Hz), 7.24-7.20 (3 H, m), 7.18 (1 H, s, NH), 5.49 (1 H, s), 2.50 (1 H, d, J = 16.4 Hz), 2.42 (1 H, d, J = 17.2 Hz), 2.30 (1 H, d, J = 16.4 Hz), 2.23 (1 H, d, J = 16.8 Hz), 1.11 (3 H, s), 0.95 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.30, 156.93, 149.36, 149.01, 142.12, 133.11, 132.14, 129.51, 129.08, 126.44, 124.58, 122.75, 120.72, 118.54, 118.31, 108.73, 50.74, 41.30, 36.02, 32.88, 29.40, 27.21. **IR** (KBr): 3276 (NH), 1717 (C=O), 1624 (C=O), 1593 (C=C), 1498, 1473 cm^{-1}; **Anal. Calcd** for $C_{24}H_{19}BrClNO_3$ (484.77) requires C, 59.46; H, 3.95; N, 2.89; found: C, 59.51; H, 3.99; N, 2.96

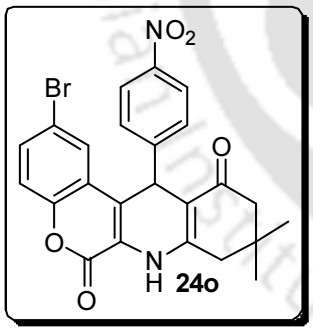


*Chromeno[3,4-b] quinoline (**24n**)*



Yellow solid (0.399 g, 76%); m.p. 305-307 °C; R_f (30% ethyl acetate/hexane) 0.54; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67 (1 H, s), 7.45 (1 H, d, J = 8.8 Hz), 7.37 (2 H, d, J = 7.2 Hz), 7.26 (2 H, d, J = 7.2 Hz), 7.19 (1 H, d, J = 8.8 Hz), 7.14 (1 H, s, NH), 5.47 (1 H, s), 2.48 (1 H, d, J = 16.4 Hz), 2.40 (1 H, d, J = 16.4 Hz), 2.29 (1 H, d, J = 16.8 Hz), 2.22 (1 H, d, J = 16.4 Hz), 1.10 (3 H, s), 0.94 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.27, 156.97, 149.42, 148.84, 142.60, 132.22, 132.08, 129.90, 126.49, 124.51, 122.75, 121.37, 120.73, 118,61, 118.37, 108.77, 50.77, 41.42, 36.15, 32.94, 29.40, 27.28; **IR** (KBr): 3298 (NH), 1716 (C=O), 1625 (C=O), 1593 (C=C), 1560, 1498 cm^{-1}; **HRMS** (ESI): MH^+, found 527.9811. $C_{24}H_{19}Br_2NO_3$ requires 527.9804. **Anal. Calcd** for $C_{24}H_{19}Br_2NO_3$ (526.97) requires C, 54.47; H, 3.62; N, 2.65; found: C, 54.56; H, 3.72; N, 2.76

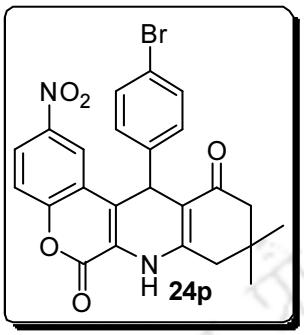
*Chromeno[3,4-b] quinoline (**24o**)*



Yellow solid (0.390g, 79%); m.p. 294-296 °C; R_f (30% ethyl acetate/hexane) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.14 (2 H, d, J = 8.8 Hz), 7.62-7.59 (3 H, m), 7.58 (1 H, d, J = 8.8 Hz), 7.49 (1 H, dd, J = 8.8 Hz), 7.22 (1 H, d, J = 8.8 Hz) 7.17 (1 H, s, NH), 5.64 (1 H, s), 2.52 (1 H, d, J = 16.8 Hz), 2.43 (1 H, d, J = 16.8 Hz), 2.31 (1 H, d, J = 16.8 Hz), 2.22 (1 H, d, J = 16.8 Hz), 1.121 (3 H, s), 0.93 (3 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 194.95, 156.17, 150.75, 150.56, 149.02, 146.56, 131.68, 128.80, 125.68, 123.76, 123.45, 122.67, 120.38, 118.22, 117.77, 107.00, 50.46, 40.36, 36.28, 32.35,29.14, 26.70. **IR** (KBr): 3343 (NH), 1720 (C=O), 1634 (C=O), 1603 (C=C), 1592, 1521 cm^{-1}; **Anal. Calcd** for $C_{24}H_{19}BrN_2O_5$ (494.05) requires C, 58.20; H, 3.87; N, 5.66; found: C, 58.26; H, 3.92; N, 5.72

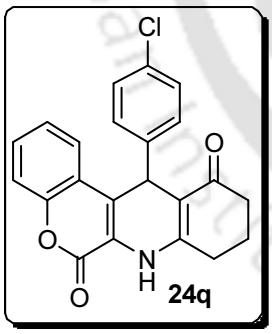
*Chromeno[3,4-b] quinoline (**24p**)*

Yellow solid (0.356 g, 72%); m.p. 295-297 °C; R_f (30% ethyl acetate/hexane) 0.36; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.50 (1 H, d, J = 2.4 Hz), 8.23 (1 H, dd, J = 8.8 Hz), 7.45 (1 H, d, J = 9.2 Hz), 7.40 (2 H, d, J = 8.0 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.06 (1H, bs, NH), 5.56 (1H, s), 2.51 (1H, d, J = 16.8 Hz), 2.43 (1H, d, J = 17.2 Hz), 2.31 (1H, d, J = 16.4 Hz), 2.24 (1H, d, J = 16.8 Hz), 1.12 (3H, s), 0.97 (3H, s)); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.23, 156.32,153.74, 148.51, 144.88, 142.43, 132.26,129.97, 124.32, 124.07, 123.36, 121.66, 119.88, 119.74, 118.07, 109.05, 50.73, 41.40, 36.48, 32.99 ,29.36, 27.34; **IR** (KBr): 3292 (NH), 1728 (C=O), 1628 (C=O), 1598 (C=C), 1527, 1499, 1347 cm^{-1}; **HRMS** (ESI): MH$^+$, found 495.0555. $C_{24}H_{19}BrN_2O_5$ requires 495.0550. **Anal. Calcd** for $C_{24}H_{19}BrN_2O_5$ (494.05) requires C, 58.20; H, 3.87; N, 5.66; found: C, 58.29; H, 3.92; N, 5.69.

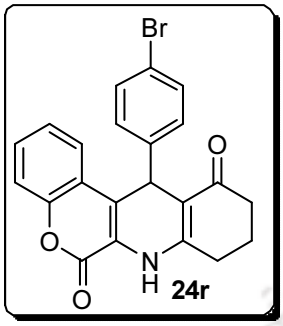


*Chromeno[3,4-b] quinoline (**24q**)*

Yellow solid (0.290g, 77%); m.p. 264-266 °C; R_f (30% ethyl acetate/hexane) 0.32 **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.55 (1 H, d, J = 8 Hz), 7.40-7.31 (4 H, m), 7.24-7.18 (3 H, m), 7.09 (1H, bs, NH), 5.60 (1 H, s), 2.60-2.58 (2 H, m), 2.46-2.32 (2 H, m), 2.09-1.92 (2 H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.58, 157.42, 151.08, 150.54, 142.86, 132.77, 129.69, 129.39, 128.86, 126.09, 125.28, 123.93, 122.04, 118.89, 116.86, 109.66, 37.11, 36.07, 27.69, 21.02; **IR** (KBr): 3143 (NH), 1730 (C=O), 1625 (C=O), 1589 (C=C), 1568, 1501 cm^{-1}; **HRMS** (ESI): MH$^+$, found 378.0898. $C_{22}H_{16}ClNO_3$ requires 378.0891. **Anal. Calcd** for $C_{22}H_{16}ClNO_3$ (377.08) requires C, 69.94; H, 4.27; N, 3.71 %; found: C, 70.03; H, 4.34; N, 3.78

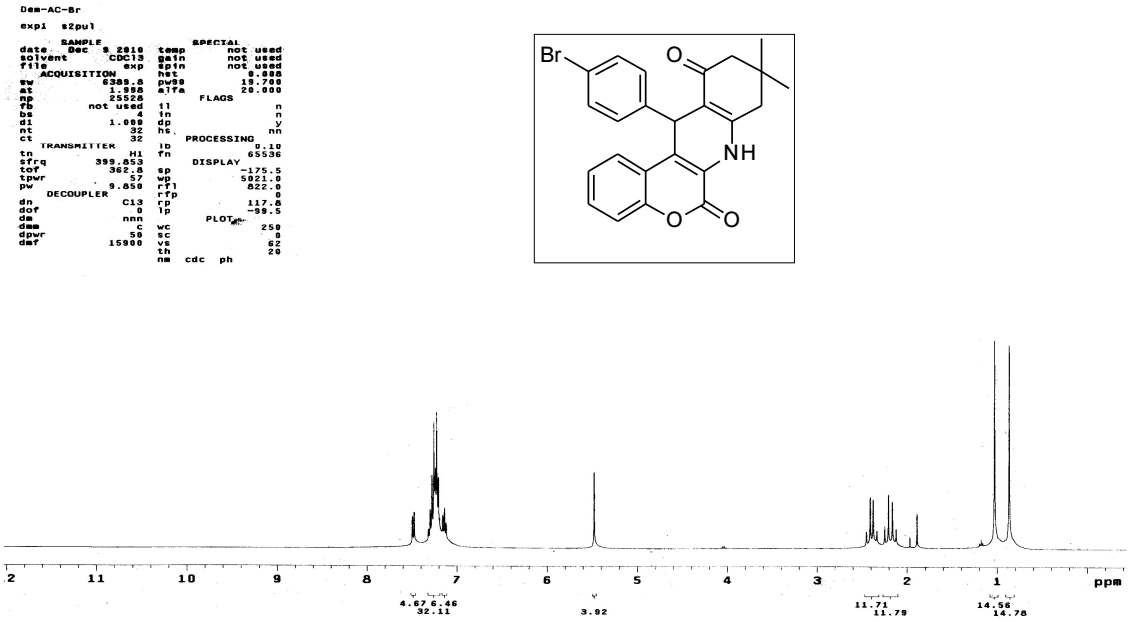


*Chromeno[3,4-b] quinoline (**24r**)*



Yellow solid (0.320 g, 76%); m.p. 286-288°C; R_f (30% ethyl acetate/hexane) 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.55 (1 H, d, J = 8 Hz), 7.40-7.31 (4 H, m), 7.29-7.20 (3 H, m), 7.09 (1H, bs, NH), 5.59 (1 H, s), 2.59-2.57 (2 H, m), 2.45-2.32 (2 H, m), 2.06-1.93 (2 H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.56, 157.48, 150.85, 150.63, 143.32, 131.89, 130.10, 129.50, 126.07, 125.36, 124.00, 122.03, 121.04, 118.92, 116.97, 109.73, 37.13, 36.21, 27.84, 21.05; **IR** (KBr): 3141(NH), 1731(C=O), 1625(C=O), 1587(C=C), 1568, 1504 cm^{-1}; **HRMS** (ESI): MH^+, found 422.0397. $C_{22}H_{16}BrNO_3$ requires 422.0386. **Anal. Calcd** for $C_{22}H_{16}BrNO_3$ (421.03) requires C, 62.57; H, 3.82; N, 3.32; found: C, 70.03; H, 4.34; N, 3.78

^{1}NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b] quinoline* ***24c***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b] quinoline* ***24c***

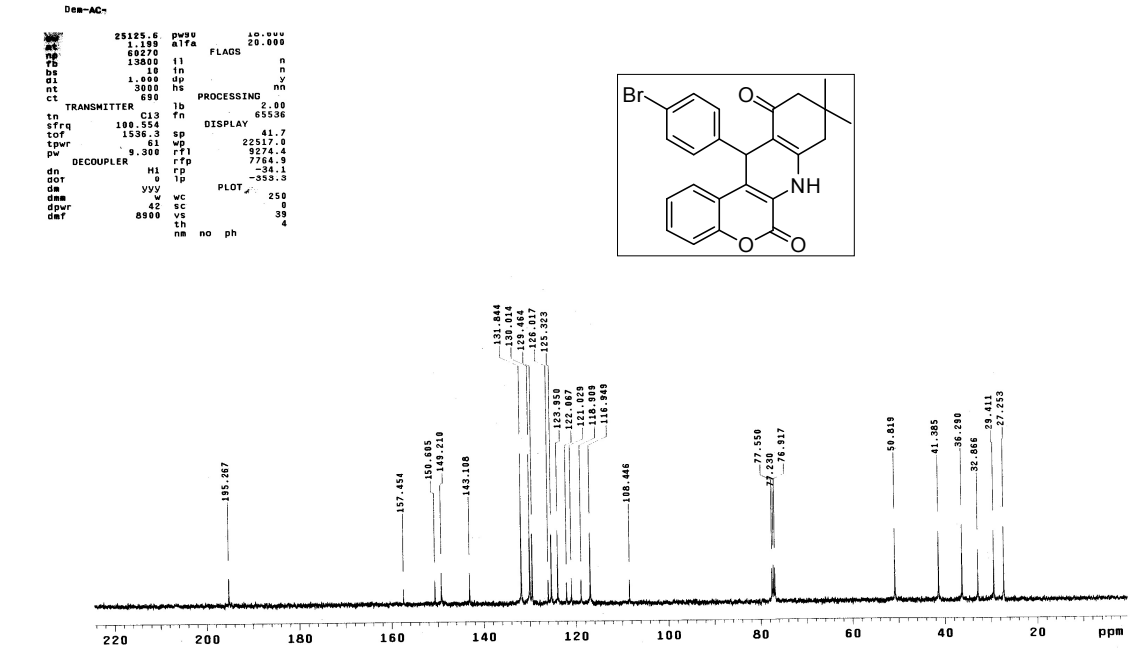
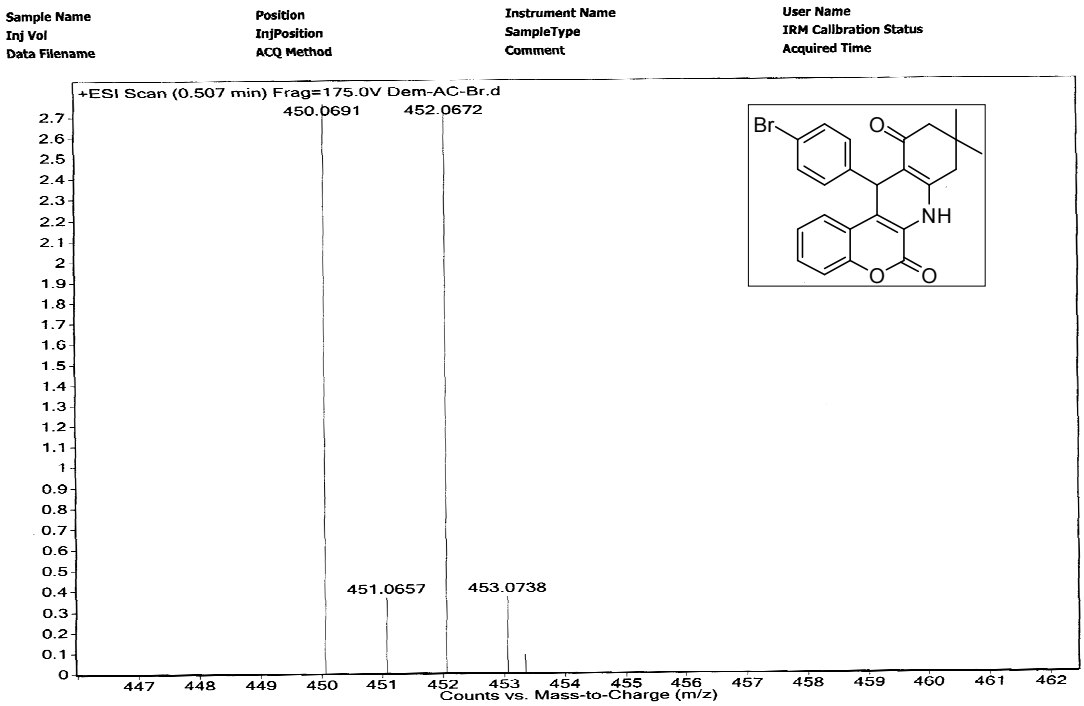


Figure 2

HRMS: *Chromeno[3,4-b] quinoline* ***24c***



^{1}NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b] quinoline* ***24g***

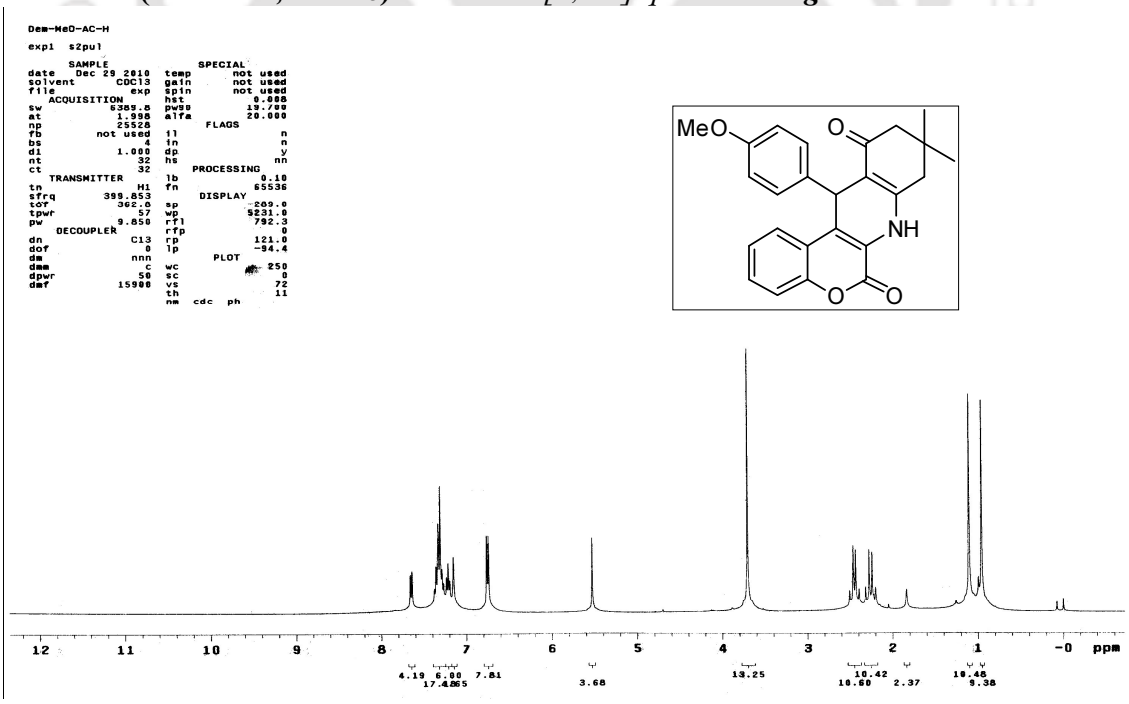
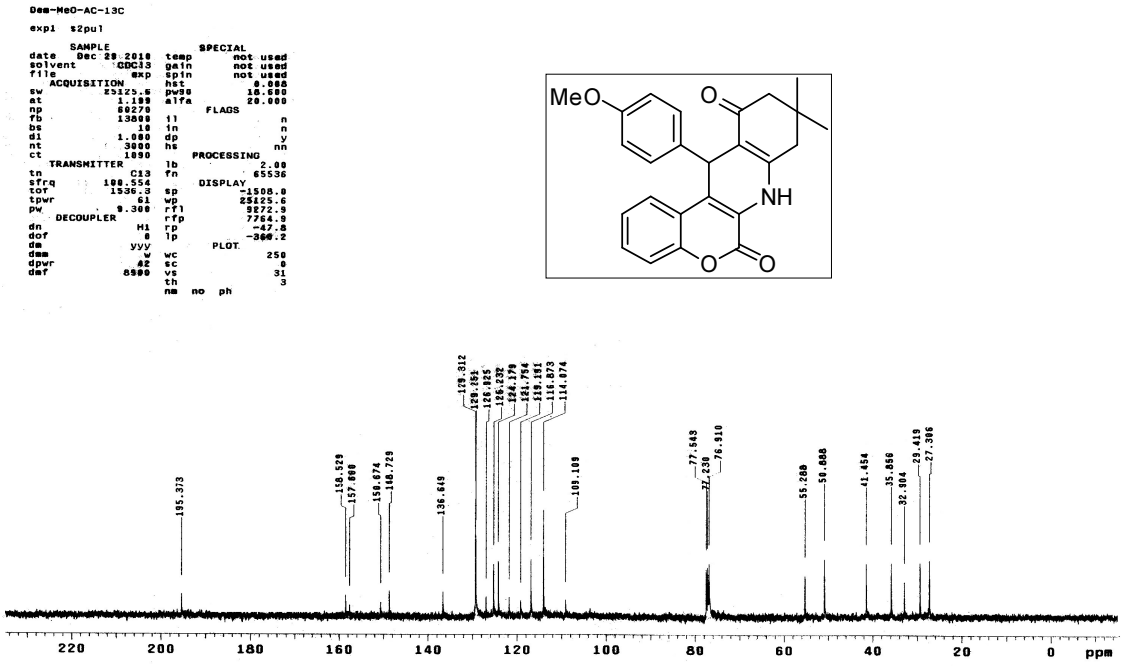


Figure 3

^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b] quinoline* ***24g***



HRMS: *Chromeno[3,4-b] quinoline* ***24g***

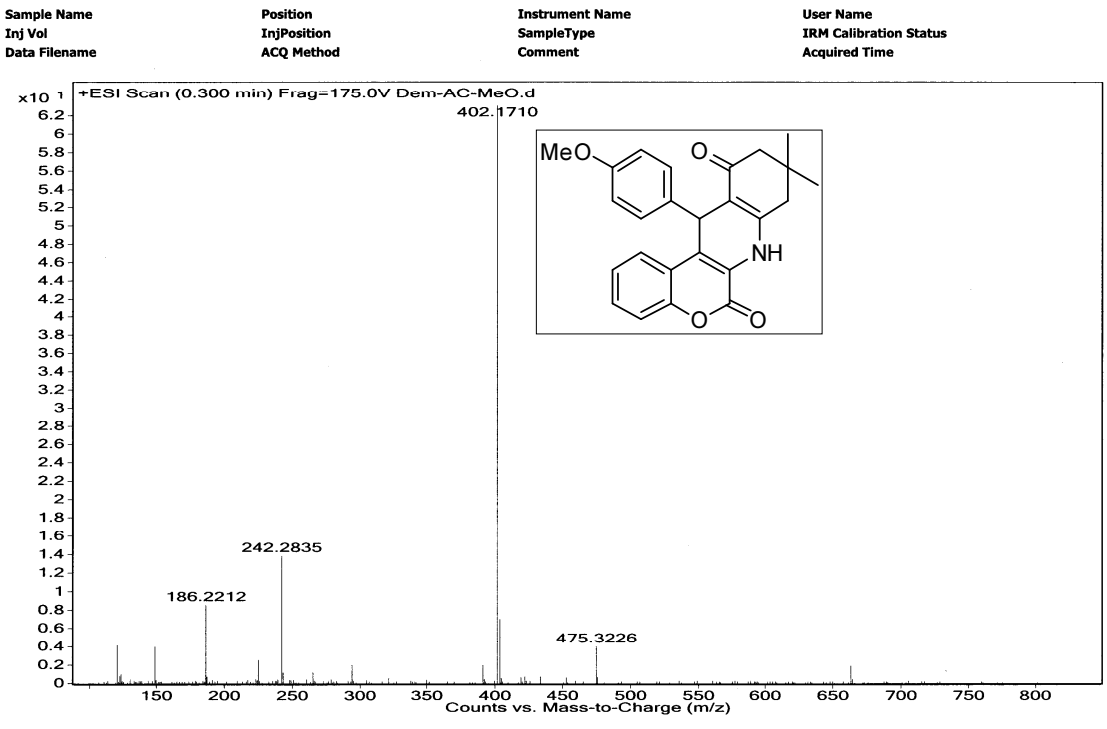
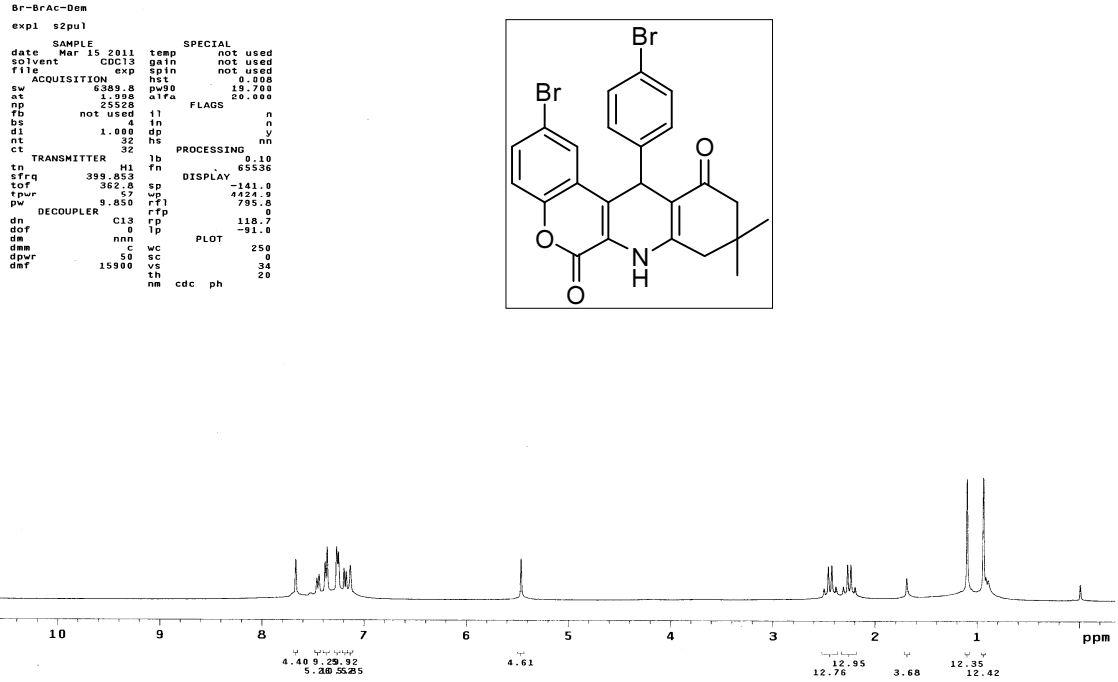


Figure 4

^{1}NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b] quinoline* ***24n***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b] quinoline* ***24n***

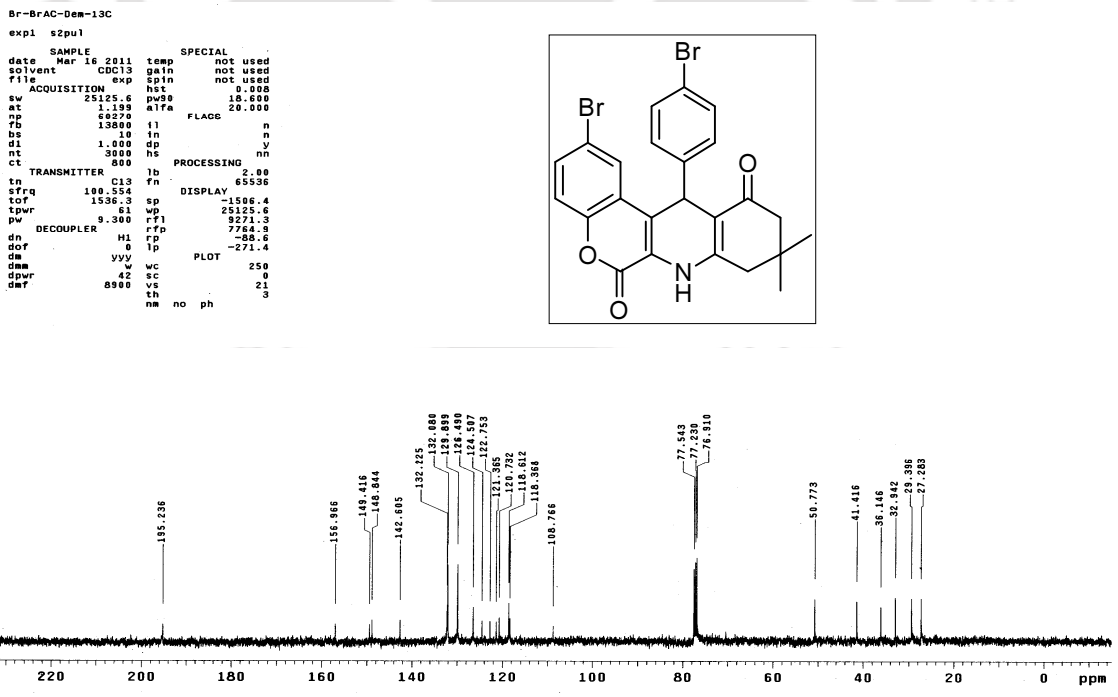
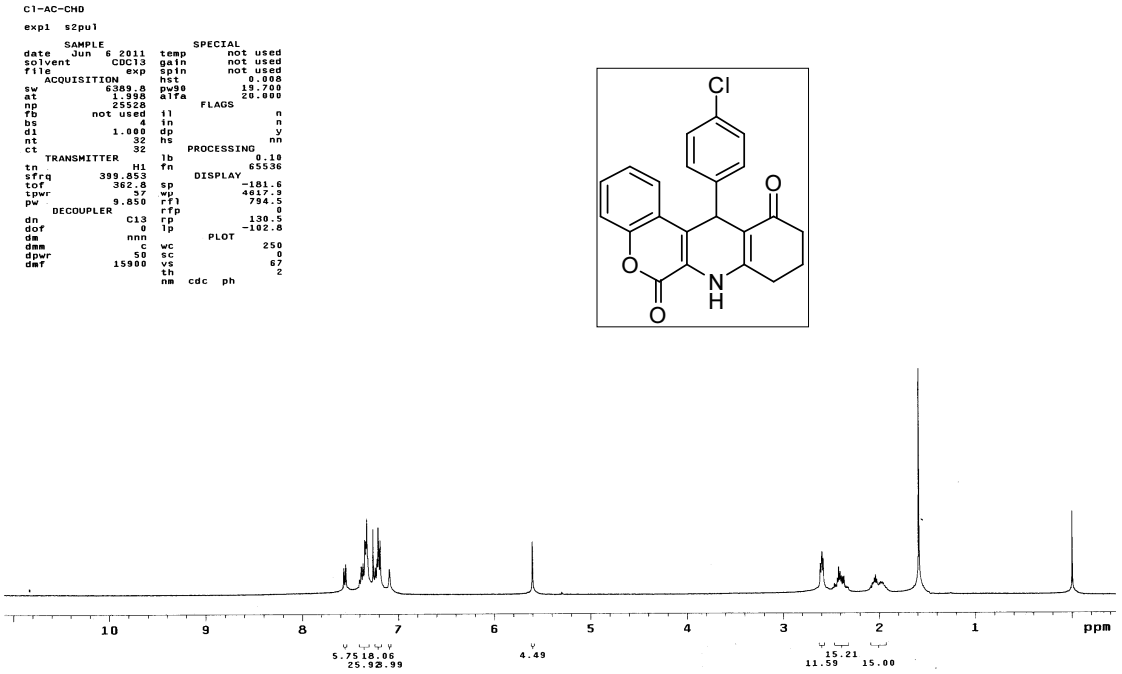


Figure 5

^{1}NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b] quinoline* ***24q***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b] quinoline* ***24q***

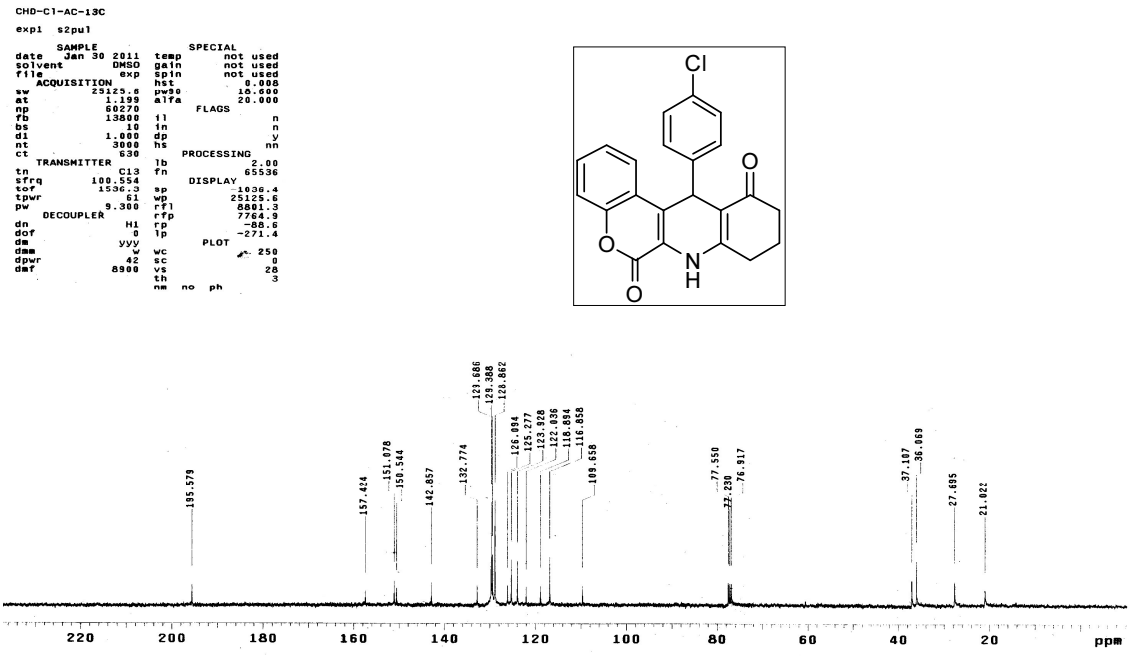


Figure 6

PART C

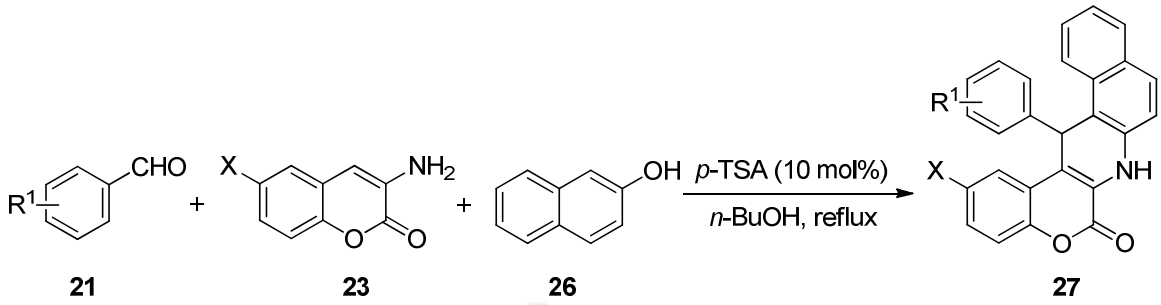
CHAPTER IIIC

Synthesis of benzo[f]chromeno[3,4-b]quinolin-6-one derivatives

Result & Discussion
Experimental

Quinone methides are ephemeral and highly reactive intermediates,[28] which are exploited for the synthesis of complex natural products[29] and pharmaceuticals,[30] These intermediates undergo either 1,4 Michael type additions namely aza-[31] and thia-Michael[32] reactions with various nucleophiles or hetero-Diels–Alder reaction.[33] A few years ago, Katritzky and his co-worker reported the generation of 2-naphthoquinone-1-methide intermediate from α-(α-benzotriazolylalkyl)phenols, which was trapped with electron-rich olefin for the construction of chroman ring system.[34] Very recently, Popik and his co-worker demonstrated[35a] that in situ generated 2-naphthoquinone-3-methide intermediate is useful precursor for light induced hetero-Diels-Alder reaction and for patterned surface derivatization.[35b] It was conceived that 2-naphthol and aromatic aldehyde might react in presence of a suitable catalyst to generate 2-naphthoquinone-1-methide intermediate, which can be trapped with 3-aminocoumarin to furnish new heterocyclic entities through Tandem-Knoevenagel-Michael reactions and has been used extensively in organic synthesis particularly for the construction of nitrogen and oxygen containing heterocycles and has been discussed in Chapter IC of Part C. Tandem-Knoevenagel-Michael reactions are gaining interest among synthetic chemists and can be achieved via Multicomponent reactions (MCRs).

Chromeno-quinolines are fused poly-heterocyclic systems comprising both coumarin and quinoline motifs which are known to possess interesting biological properties like bacteriostatic activity,[36] glucocorticoid modulators,[37] anti-inflammatory effects[38] and selective progesterone receptor modulators.[39] We have reported the synthesis of chromenoquinoline via Michael Initiated Ring Closure (MIRC) reaction on *in situ* generated benzylidenecyclohexane-1,3-diones using 3-aminocoumarin as a key building block in Chapter IIC. In this chapter, we report one-pot synthesis of benzo[f]chromeno[3,4-b]quinolin-6-one derivatives involving aromatic aldehydes (**21**), 3-aminocoumarins (**23**) and β-naphthol (**26**) in *n*-butanol using *p*-TSA catalyst under reflux condition by trapping of 2-naphthoquinone-1-methide intermediate, as shown in Scheme 13.



21 **23** **26** **27**

Scheme 13. One-pot synthesis of benzo[f]chromeno[3,4-b]quinolin-6-one derivatives derivatives

For the present study, a mixture of 4-chlorobenzaldehyde (1mmol), β-napthol (1mmol), and 3-aminocoumarin (1mmol) was stirred in 3 mL of ethanol in presence of 10 mol % *p*-TSA (0.017g). The reaction was very sluggish and incomplete even after 1 day. However, we have observed on TLC a yellow fluorescent spot along with un-reacted starting materials. The new spot were characterized by ^{1}H NMR, ^{13}C NMR spectra and elemental analysis and was found to be benzo[f]chromeno[3,4-b]quinolin-6-one derivative (**27a**). Increasing the mol percentage of *p*-TSA from 10 to 30 % did not improve the yield of the product (Table 4, entry 1). When the same set of reaction was performed in *n*-butanol in presence of 10 mol% *p*-TSA the yield of the product was increased. It was noted that 10 mol% of *p*-TSA in 3 ml of *n*-butanol provided the best yield in minimum reaction time (Table 4, entry 3). 10 mol% of other catalysts such as anhydrous $Fe_2(SO_4)_3{\cdot}xH_2O$, $ZnCl_2$, Iodine, Triflic acid and $InCl_3$ was found not to accelerate the reaction in terms of time or yield (Table 4, entry 6-10). Remarkably, no product formation was observed in absence of catalyst (Table 4, entry 11).

Table 4. Optimization of reaction conditions for the synthesis of benzo[f]chromeno[3,4-b]quinolin-6-one (**27a**)[a]

Entry	Catalyst	Solvent	Mol% of Catalyst	Reaction Condition	Time (h)	Yield[b]%
1	*p*-TSA	EtOH	5, 10, 15	reflux	24	15-26
2	*p*-TSA	*n*-BuOH	5	reflux	12	58
3	*p*-TSA	*n*-BuOH	10	reflux	8	78
4	*p*-TSA	*n*-BuOH	20	reflux	8	70
5	*p*-TSA	DCE	20	reflux	8	36

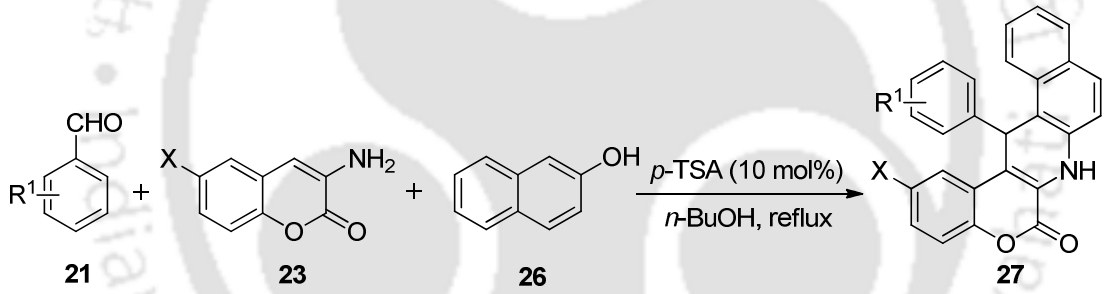
Continued

6	$Fe_2(SO_4)_3.xH_2O$	*n*-BuOH	10	reflux	8	22
7	$ZnCl_2$	*n*-BuOH	10	reflux	8	26
8	Iodine	*n*-BuOH	10	reflux	8	22
9	Triflic acid	*n*-BuOH	10	reflux	8	37
10	$InCl_3$	*n*-BuOH	10	reflux	8	00
11	No Catalyst	*n*-BuOH	10	reflux	12	00

[a]All the reactions were performed with 4-chlorobenzaldehyde (1.0 mmol), 2-napthol (1.0 mmol) and 3-aminocoumarin (1.0 mmol). [b] Isolated yields.

After optimization of the reaction conditions, a mixture of benzaldehyde, 2-napthol, and 3-aminocoumarin in *n*-butanol was treated with 10 mol% *p*-TSA under identical reaction conditions and the desired benzo[f]chromeno[3,4-b]quinolin-6-one derivative **27b** was obtained in 72% yield (Table 5, entry 2).

Table 5. Scope of various benzo[f]chromeno[3,4-b]quinolin-6-one derivatives[a]



Entry	R^1-CHO	X	Product	Time	Yield[b]
1	4-Cl-C_6H_5	H	**27a**	8	78
2	C_6H_5	H	**27b**	8	72
3	4-Br-C_6H_5	H	**27c**	8	73
4	4-F-C_6H_5	H	**27d**	6	78
5	4-Me-C_6H_5	H	**27e**	6	86
6	4-MeO-C_6H_5	H	**27f**	6	71
7	2-$C_{10}H_7$-	H	**27g**	8	82
8	4-Cl-C_6H_5	MeO	**27h**	8	79
9	4-F-C_6H_5	MeO	**27i**	8	76
10	4-Me-C_6H_5	MeO	**27j**	8	82

Continued

11	4-F-C_6H_5	Br	**27k**	6	81
12	4-Me-C_6H_5	Br	**27l**	6	82

[a]Reaction Condition: aromatic aldehyde, β-napthol and 3-aminocoumarin were taken in 1:1:1 ratio in presence of 10 mol % of *p*-TSA in *n*-BuOH under reflux conditions. [b] Isolated Yields

The reaction of various other aromatic aldehydes were examined with 2-napthol and 3-aminocoumarin under identical reaction conditions and resulted products **27c-g** (Table 5, entries 3-7) in good yields. However, 4-nitrobenzaldehyde did not provide the desired benzo[f]chromeno[3,4-b]quinolin-6-one derivative on reaction with 2-napthol and 3-aminocoumarin under identical conditions even after prolonging the reaction for 1day. Likewise, other 3-aminocoumarins such as 6-bromo-3-aminocoumarin and 6-methoxy-3-aminocoumarin were tested with aromatic aldehyde and 2-napthol under identical reaction conditions to provide the desired benzo[f]chromeno[3,4-b]quinolin-6-one **27h-l** (Table 5, entries 8-12). The ^{1}H NMR spectra and ^{13}C NMR spectra of the products **27a, 27d, 27e, 27j,** and **27l** are given in Figures **8-13** respectively in the experimental section.

Finally, the structure of one of the representative compounds such as (**27d)** was confirmed unambiguously by single crystal X-ray diffraction analysis as shown in Figure 7.

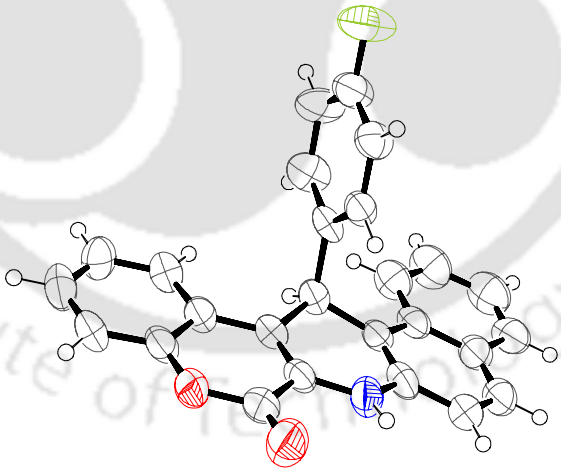
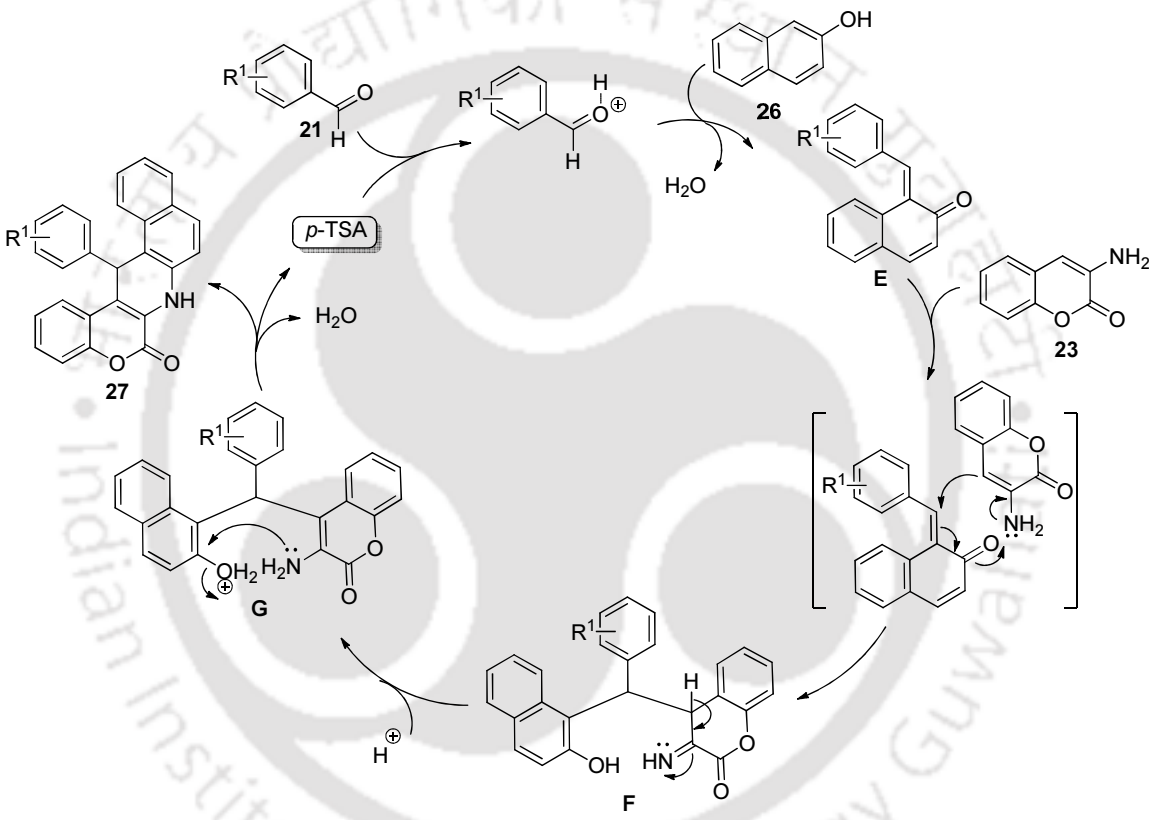


Figure 7. Single crystal X-ray structure **27d** (CCDC 897315)

The formation of **27** could be explained by a proposed mechanism shown in Scheme 14. It was supposed that the reaction occurred via the ortho-quinone methide intermediate **E**, which was formed by the nucleophilic addition of β-naphthol (**26**) to aldehyde (**21**) catalyzed with *p*-TSA. o-Quinone methide intermediate **E** can act a suitable Michael

acceptor and reacts with 3-aminocoumarin at the position 4 of the coumarin ring to provide reactive intermediate **F**, which undergoes intra-molecular ring closure reaction followed by elimination of one molecule of H_2O give the desired **27** as shown in Scheme 14. In the absence of 3-aminocoumarin the second molecules of *β*-naphthol attacks to intermediate **E** leading to benzoxanthenes.[40] The formation of benzoxanthene provides evidence that the reaction goes via *o*-quinone methide intermediate **E.**



Scheme 14. Mechanism for the formation for the synthesis of benzo[f]chromeno[3,4-b]quinolin-6-one derivatives

In summary, we have provided an effective route for the synthesis of a series of benzo[f]chromeno[3,4-b]quinolin-6-one derivatives which may be promising candidates for organic fluorophore and may also display important biological activities for biomedical screening.

General procedure for the synthesis of benzo[f]chromeno[3,4-b]quinolin-6-one

Into a 25 mL round bottomed flask was taken a mixture of aromatic aldehyde (1.0 mmol), 2-naphthol (1.0 mmol) and 3-aminocoumarin (1.0 mmol) in 3 mL of *n*-butanol. Then, the catalyst anhydrous *p*-toluene sulfonic acid (17 mg, 0.1 mmol) was added into it and the reaction mixture was kept for refluxing with stirring in a pre-heated oil bath. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction flask was brought to room temperature and *n*-butanol was removed in a rotary evaporator. The crude residue was extracted with DCM (2 x 10 mL), washed with water and dried over anhydrous sodium sulfate. The products **27a-l** were obtained after removal of DCM followed by chromatographic separation using silica gel (60-120 mesh). The products were eluted with ethyl acetate/hexane mixture (05:95).

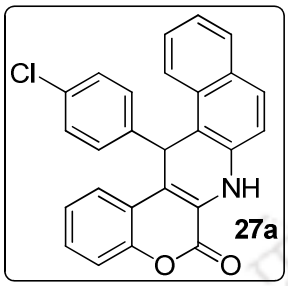
Table 6. Crystallographic data and refinement parameters[a]

Parameters	**Compound 27d**	**Parameters**	**Compund 27d**
Empirical formula	$C_{26}H_{16}FNO_2$	γ	96.666(5)°
M	393.40	V/ Å^3	2869.0(4)
Wavelength Å	0.71073	Z	6
Crystal system	Triclinic	ρ/g cm^{-3}	1.366
Space group	*P*-1	μ/mm^{-1}	0.093
a, Å	12.9401(9)	Reflns collected	31727
b, Å	13.9507(13)	Indep. reflns	12942
c, Å	17.1595(15)	GOF	0.994
α	101.029(5)°	Final R indices [$I>2\sigma(I)$]	$R1$=0.0573 $wR2$ = 0.1042
β	106.389(5)°	R indices (all data)	$R1$ = 0.2104 $wR2$ = 0.1565

[a]Refinement methods: full-matrix least-square on F^2.

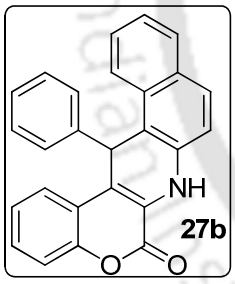
Spectral data of benzo[f]chromeno[3,4-b]quinolin-6-ones:

*14-(4-chlorophenyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27a**)*



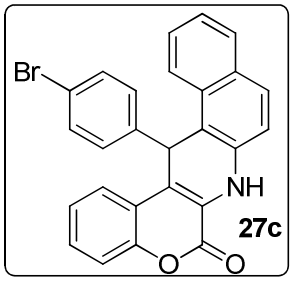
Yellow solid (0.319 g, 78%), mp: 254-255°C; **IR** (KBr): 3362, 2924, 1702, 1524, 741 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.10 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.77(d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.52 (t, *J* = 8 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.38-7.33 (m, 4 H), 7.19 (d, *J* = 8.8 Hz, 4 H), 7.14 (d, *J* = 7.2 Hz, 1 H), 6.22 (s, 1 H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 158.27, 150.09, 142.81, 134.59, 133.09, 131.57, 131.07, 129.49 (2C), 129.22, 129.12 (3C), 128.09, 127.50, 125.07, 124.09, 123.56, 122.36, 121.98, 120.11, 119.73, 117.26, 117.19, 112.49, 38.96; **Anal. Calcd** for $C_{26}H_{16}ClNO_2$ (409.86): C, 76.19; H, 3.93; N, 3.42; Found: C, 76.32; H, 3.99; N, 3.53; HRMS (ESI): m/z cacld for $C_{26}H_{16}ClNO_2$ $[M+H]^+$ 410.0942. Found: 410.0892.

*14-phenyl-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27b**)*



Yellow solid (0.270 g, 72%), mp: 244-245°C; **IR** (KBr): 3348, 1683, 1527, 745 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.18 (d, *J* = 8.0 Hz, 1 H), 8.10-7.96 (m, 1H), 7.77-7.28(m, 3H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.35-7.29 (m, 4H), 7.18 (t, *J* = 7.6 Hz, 3H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.24 (s, 1H).**^{13}C NMR** ($CDCl_3$, 100 MHz) δ =155.46, 148.06, 143.87, 133.93, 129.86, 128.94, 127.74, 127.07 (3C), 126.91, 126.57 (2C), 125.86, 125.33 (2C), 123.27, 122.19, 121.85, 121.36, 120.87, 118.28, 116.66, 114.83, 110.90, 37.18; **Anal. Calcd** for $C_{26}H_{17}NO_2$ (375.42): C, 83.18; H, 4.56; N, 3.73; Found: C, 83.34; H, 4.62; N, 3.88.

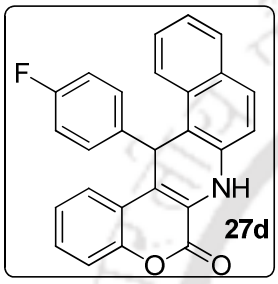
*14-(4-bromophenyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27c**)*



Yellow solid (0.331 g, 73%); mp: 272-274°C **IR** (KBr): 3341, 2922, 1702, 1525, 741 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.10 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.77(d, *J* = 8.4 Hz, 1 H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.52 (t, *J* = 8 Hz, 1H), 7.37-7.28 (m, 9 H), 7.19 (d, *J* = 8.8 Hz, 1H), 6.19 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100

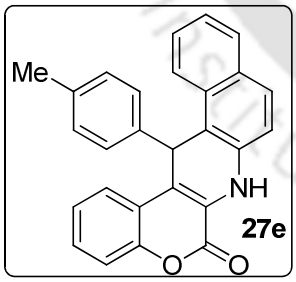
MHz) δ =158.25, 150.06, 143.32, 134.56, 132.05 (2C), 131.54, 131.09, 129.83 (3C), 129.55, 128.08, 127.48, 125.06, 124.07, 123.54, 122.33, 121.96, 121.21, 119.99, 119.70, 117.25, 117.18, 112.38, 39.03. **Anal. Calcd** for $C_{26}H_{16}BrNO_2$ (454.31): C, 68.74; H, 3.55; N, 3.08; Found: C, 68.92; H, 3.64; N, 3.22. HRMS (ESI): m/z cacld for $C_{26}H_{16}BrNO_2$ $[M+H]^+$ 454.0437. Found: *m/z* 454.0437.

*14-(4-fluorophenyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27d**)*



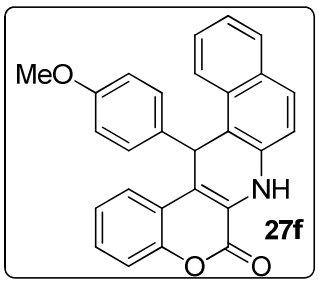
Yellow solid(0.306 g, 78%), mp: 256-257°C **IR** (KBr): 3364, 2926, 1702, 1526, 742 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.01 (d, *J* = 8.4 Hz, 1H), 7.83-7.82 (m, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.36-7.33 (m, 2H), 7.29-7.18 (m, 5H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.76 (t, *J* = 8.4 Hz, 2H), 6.09 (s, 1 H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ =158.30, 150.09, 140.24, 134.59, 131.56, 131.04, 129.83, 129.72 (2C), 129.64, 129.18, 127.99, 127.41, 125.01, 124.0, 122.39, 122.03, 120.35, 119.99, 119.78, 117.20 (2C), 115.90, 115.69, 112.74, 38.73; **Anal. Calcd** for $C_{26}H_{16}FNO_2$ (393.41): C, 79.38; H, 4.10; N, 3.56; Found: C, 79.56; H, 4.18; N, 3.70.

*14-(p-tolyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27e**)*



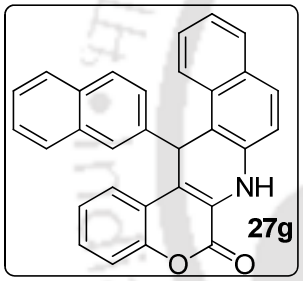
Yellow solid (0.334 g, 86%), mp: 276-277°C **IR** (KBr): 3337, 1701, 1527, 736 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.16 (d, *J* = 8.4 Hz, 1 H), 8.01-7.97 (m, 1 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.50 (td, *J* = 1.6, 8.4 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.35-7.29 (m, 5 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.18 (s, 1 H), 2.15 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 158.43, 150.12, 141.55, 136.94, 134.54, 131.71, 131.03, 129.60, 129.19, 129.06, 128.10, 127.83, 127.29, 124.94, 123.86, 123.36, 122.62, 122.25, 120.81, 119.95, 117.16, 117.08, 113.09, 39.16, 21.12. **Anal. Calcd** for $C_{27}H_{19}NO_2$ (389.44): C, 83.27; H, 4.92; N, 3.60; Found: C, 83.44; H, 4.99; N, 3.72. **HRMS** (ESI): m/z cacld for $C_{26}H_{17}NO_2$ $[M+H]^+$ 390.1489. Found: *m/z* 390.1483.

*14-(4-methoxyphenyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27f**)*



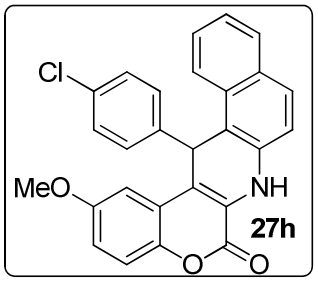
Yellow solid (0.287 g, 71%), mp: 282-284°C **IR** (KBr): 3369, 2923, 1705, 1525, 747 cm^{-1}.**^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.17 (d, *J* = 8.4 Hz, 1H), 8.10-7.98 (m, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 8.0Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.38-7.30 (m, 5H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.20 (s, 1H), 3.65 (s, 3H, -OMe). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 156.62, 155.04, 148.14, 136.21, 133.87, 129.89, 128.98, 127.59 (2C), 127.11, 126.77, 125.80, 125.19, 123.18, 122.02, 121.80, 121.42, 120.95, 118.36, 118.17, 116.69, 114.81, 112.99, 112.39 (2C), 53.48, 36.29. **Anal. Calcd** for $C_{27}H_{19}NO_3$ (405.44): C, 79.98; H, 4.72; N, 3.45; Found: C, 80.12; H, 4.80; N, 3.58.

*14-(naphthalen-2-yl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27g**)*



Yellow solid (0.348 g, 82%), mp: 310-312°C **IR** (KBr): 3341, 1685, 1527, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (d, *J* = 8.4 Hz, 1H), 8.08-8.06 (m, 1H), 8.13 (s, 1H), 7.76-7.72 (m, 3 H), 7.66-7.63 (m, 3H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.41-7.29 (m, 6 H), 7.21 (m, 2H), 6.39 (s 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 158.46, 150.14, 141.78, 134.65, 133.36, 132.59, 131.82, 131.11, 129.47, 129.15, 129.03, 128.14, 127.94, 127.70, 127.41, 126.72 (2C), 126.48, 126.11, 125.03, 123.97, 123.58, 122.68, 122.30, 120.46, 119.97, 117.24, 117.16, 112.84, 39.90. **Anal. Calcd** for $C_{30}H_{19}NO_2$(425.48): C, 84.69; H, 4.50; N, 3.29; Found: C, 84.85; H, 4.58; N, 3.40.

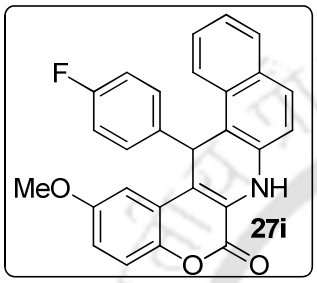
*14-(4-chlorophenyl)-2-methoxy-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27h**)*



Yellow solid (0.346 g, 79%), mp: 291-292 °C **IR** (KBr): 3326, 1702, 1529, 806 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.08 (d, *J* = 8.8 Hz, 1H), 7.75(d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.34-7.32 (m, 3H), 7.27-7.24 (m, 1H), 7.18-7.13 (m, 3H), 6.91-6.88 (m 1H), 6.11(s, 1H), 3.90 (s, 3H, -OMe). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ =

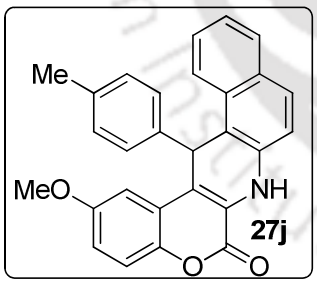
157.21, 155.93, 143.54, 143.21, 134.69, 130.17, 129.08 (2C), 128.82, 128.37, 128.30, 128.17 (2C), 126.45, 123.55, 123.06, 121.67, 119.90, 118.34, 117.53, 116.87, 113.54, 111. 58, 108.68, 105.84, 55.43, 38.20. **Anal. Calcd** for $C_{27}H_{18}ClNO_3$ (439.89): C, 73.72; H, 4.12; N, 3.18; Found: C, 73.94; H, 4.20; N, 3.30.

*14-(4-fluorophenyl)-2-methoxy-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27i**)*



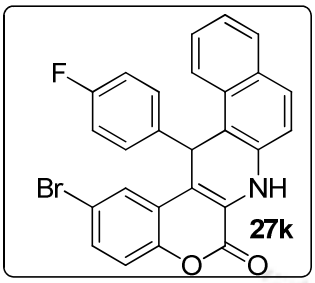
Yellow solid (0.321 g, 76%), mp: 258-260 °C. **IR** (KBr): 3343, 1697, 1527, 741cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.12 (d, *J* = 8.8 Hz, 1H), 7.77(d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.38-7.33 (m, 3H), 7.27 (d, *J* = 9.2 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.87 (t, J = 8.4 Hz, 2H), 6.17 (s, 1H), 3.91 (s, 3H, -OMe). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 157.02, 155.98, 143.57, 134.93, 130.98, 130.13, 129.47 (2C), 128.25(2C), 128.17, 126.41, 125.59, 123.06, 122.26, 120.01, 118.77, 117.81, 116.82, 115.0, 114.80 (2C), 113.81, 112.11, 106.13, 55.58, 37.68; **Anal. Calcd** for $C_{27}H_{18}FNO_3$ (423.43): C, 76.59; H, 4.28; N, 3.31; Found: C, 76.74; H, 4.36; N, 3.342.

*2-methoxy-14-(p-tolyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27j**)*



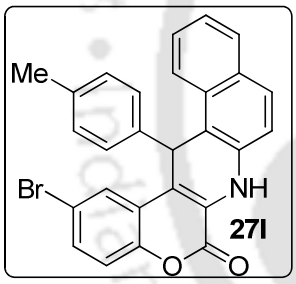
Yellow solid (0.343 g, 82%), mp: 281-283 °C. **IR** (KBr): 3346, 1700, 1526, 746 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.16 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.40-7.34 (m, 5H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.11 (s, 1H), 3.91 (s, 3H, -OMe), 2.16 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 156.86, 155.41, 143.10, 141.34, 135.50, 134.21, 130.50, 129.67, 128.33(2C), 127.62 (2C), 127.12 (2C), 125.05, 122.91, 122.45, 121.38, 119.60, 118.54, 117.10, 116.32, 113.13, 111.66, 105.24, 54.93, 38.02, 19.98. **Anal. Calcd** for $C_{28}H_{21}NO_3$ (419.47): C, 80.17; H, 5.05; N, 3.34; Found: C, 80.32; H, 5.12; N, 3.42.

*2-bromo-14-(4-fluorophenyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27k**)*



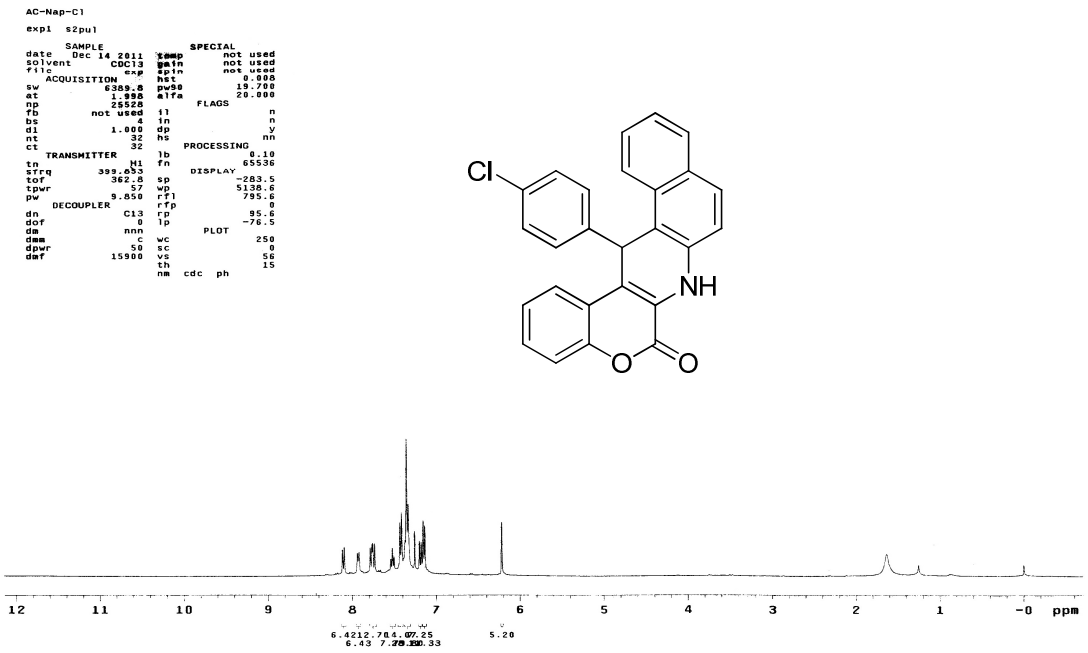
Yellow solid (0.381 g, 81%), mp: 276-278°C **IR** (KBr): 3341, 1703, 1646 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.12 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 2.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.45-7.35 (m, 5H), 7.23-7.17 (m, 3H) 6.89 (t, *J* = 8.4 Hz, 2H), 6.13 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 156.44, 148.14, 141.08, 134.78, 130.96, 130.25, 129.53, 129.35 (2C), 128.96, 128.23 (2C), 126.45, 124.93, 124.16, 123.27, 122.58, 122.38, 121.52, 117.95, 117.78, 117.62, 117.07, 115.12, 114.90, 112.46; Found: C, 66.12; H, 3.20; N, 2.97. **Anal. Calcd** for $C_{26}H_{15}BrFNO_2$ (471.30) requires C, 66.32; H, 3.34; N, 2.98%

*2-bromo-14-(p-tolyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**27l**)*



Yellow solid (0.383 g, 82%), mp: 268-269 °C. **IR** (KBr): 3331, 1701, 1618, 1529 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.15 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.40-7.31 (m, 5 H), 7.18 (d, *J* = 3.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.06 (s, 1H), 2.17 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 157.88, 148.90, 142.15, 141.19, 137.21, 134.12, 131.61, 131.20, 130.42, 129.78(2C), 129.38, 129.09, 128.05(2C), 127.45, 125.27, 124.13, 123.98, 122.37, 121.87, 118.66, 117.99, 117.08, 113.19, 39.21, 21.14. Found: C, 69.24; H, 3.87; N, 2.99. $C_{27}H_{18}BrNO_2$ (468.34) requires C, 69.40; H, 3.94; N, 2.91% **HRMS** (ESI): m/z cacld for $C_{27}H_{18}BrNO_2$ $[M+H]^+$ 468.0594. Found: *m/z* 468.0586.

^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(27a)***



^{13}C NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(27a)***

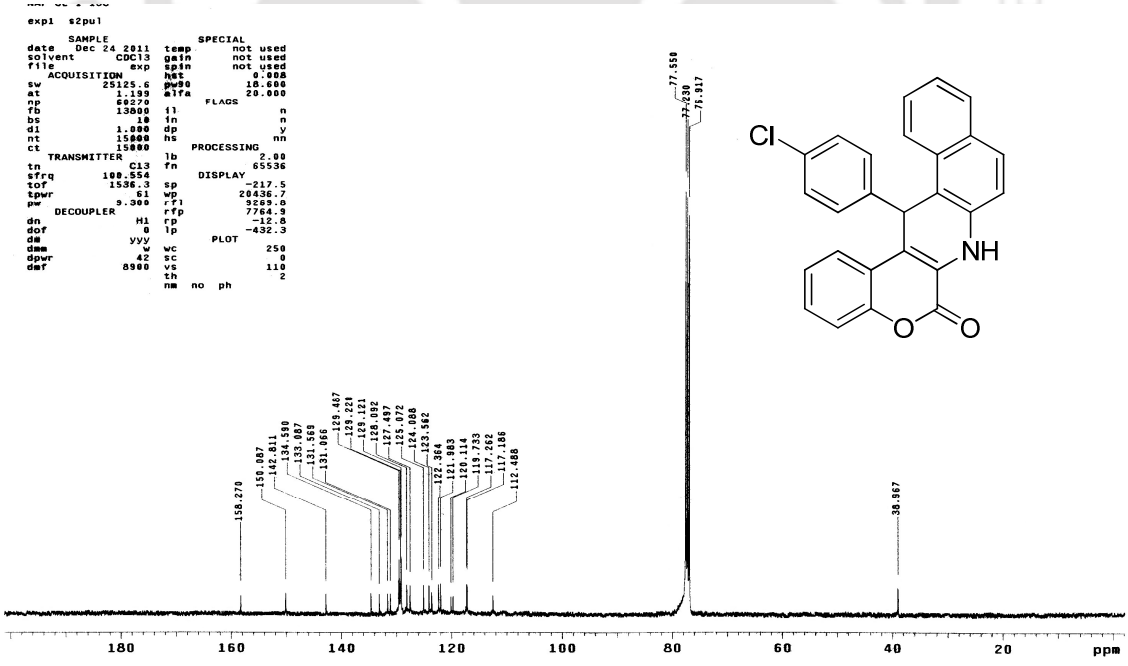
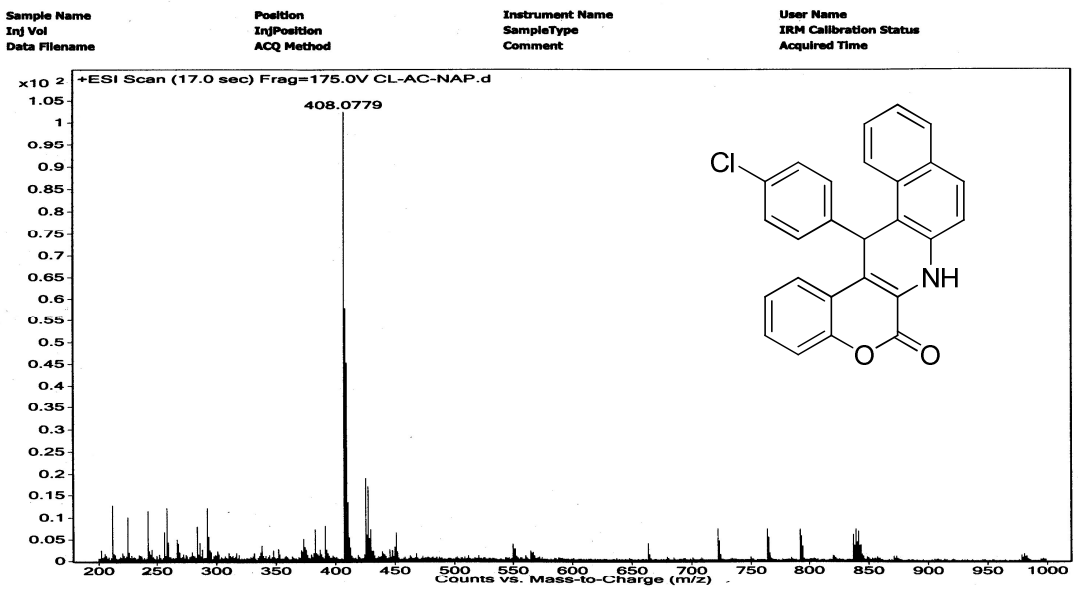


Figure 8

HRMS spectra: *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(27a)***



^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (27d)*

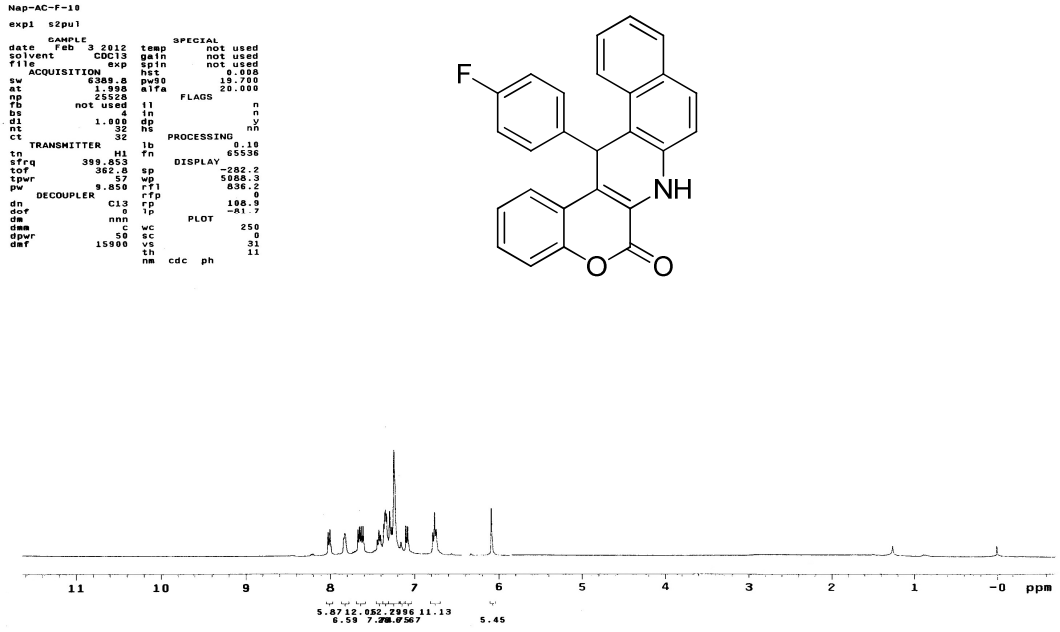
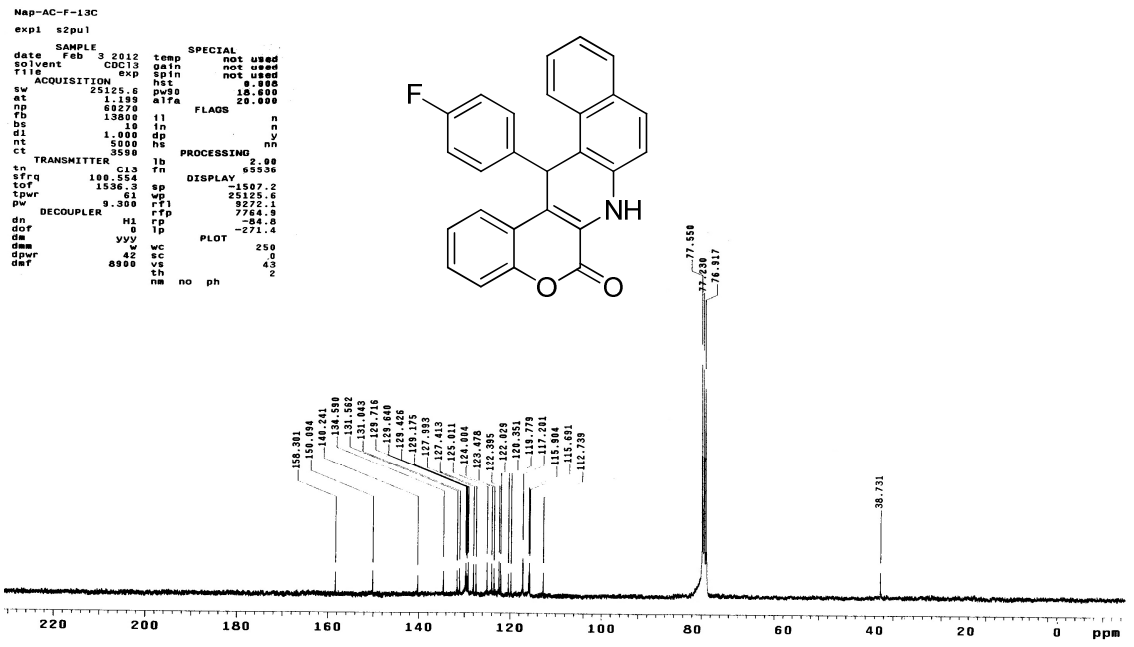


Figure 9

^{13}C NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**27d**)*



^{1}NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**27e**)*

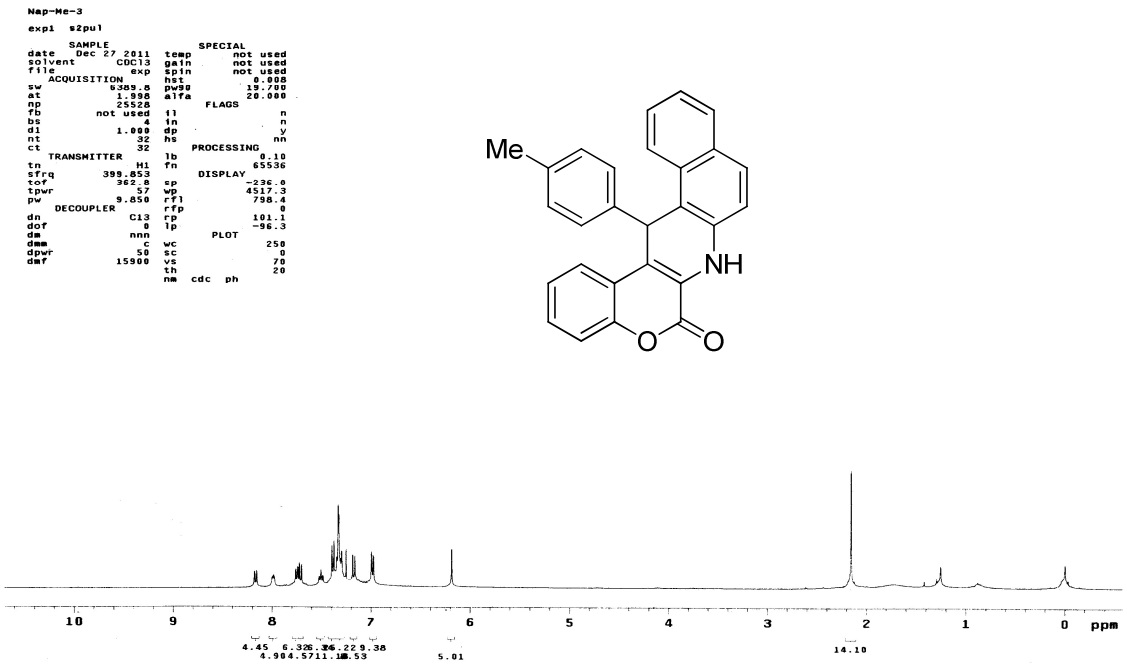
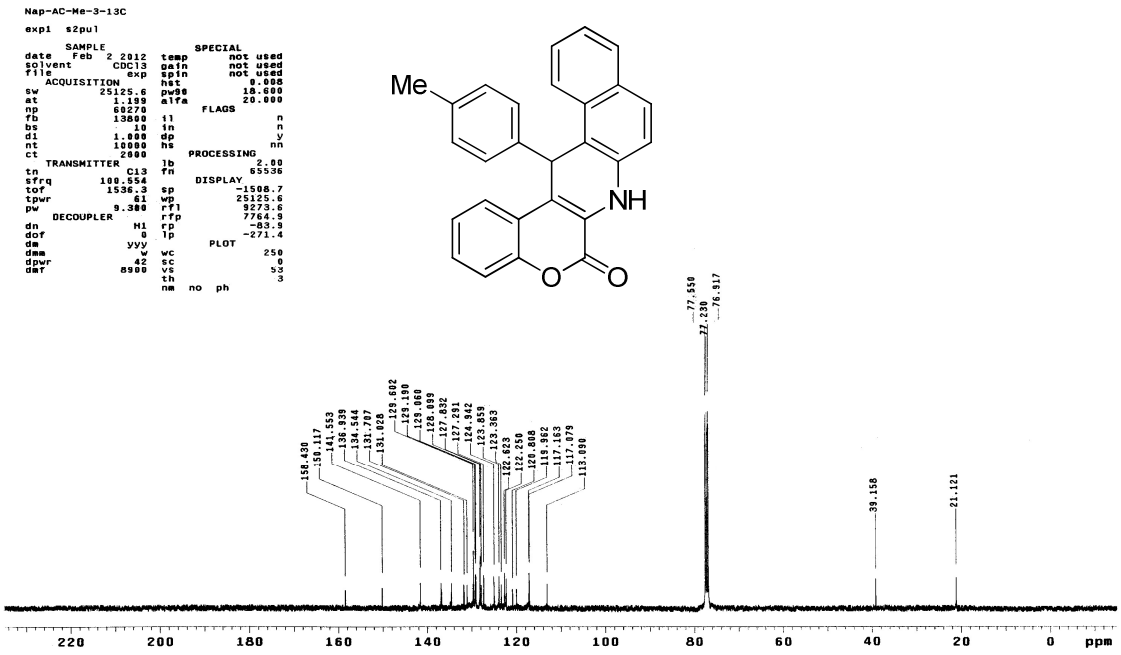


Figure 10

^{13}C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(27e)***



HRMS spectra: *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(27e)***

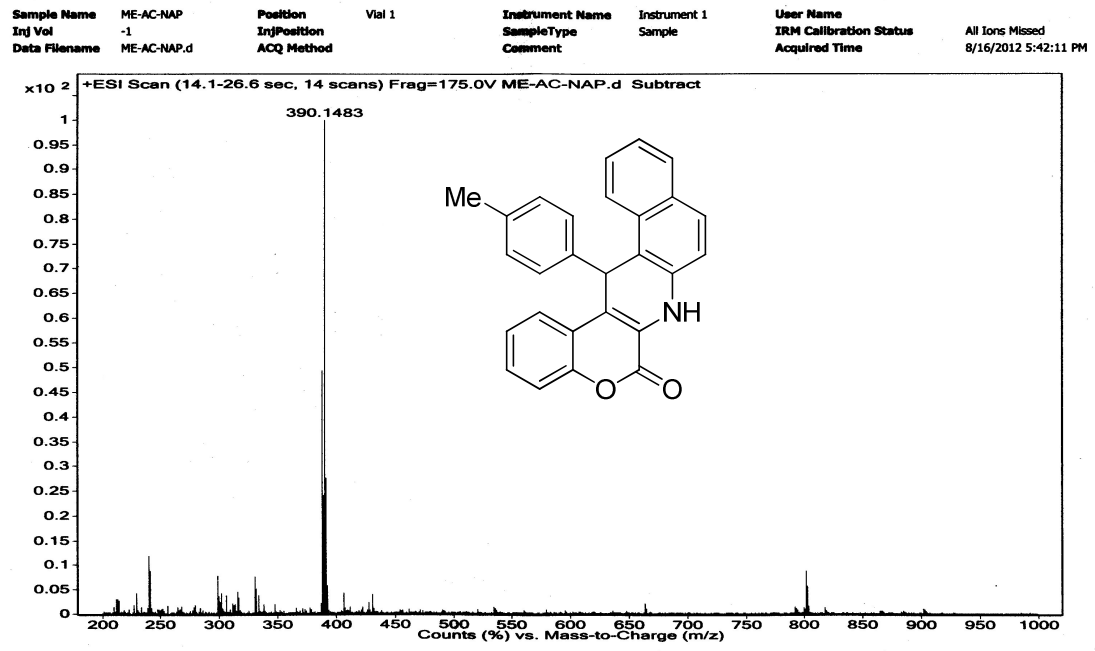
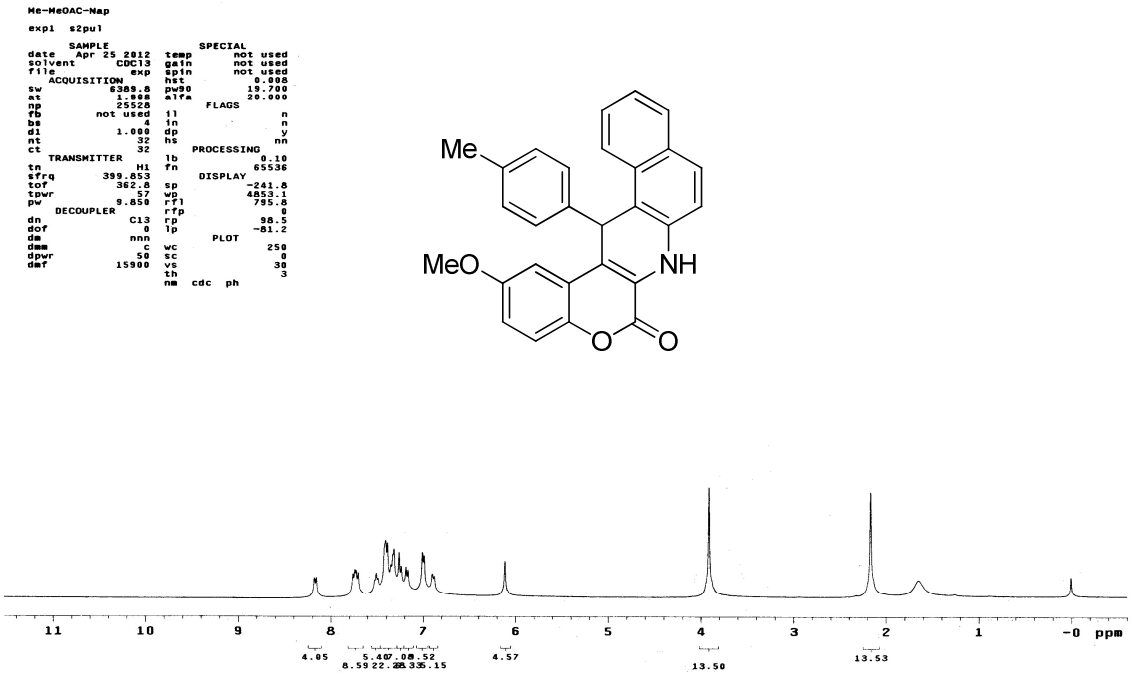


Figure 11

^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**27j**)*



^{13}C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**27j**)*

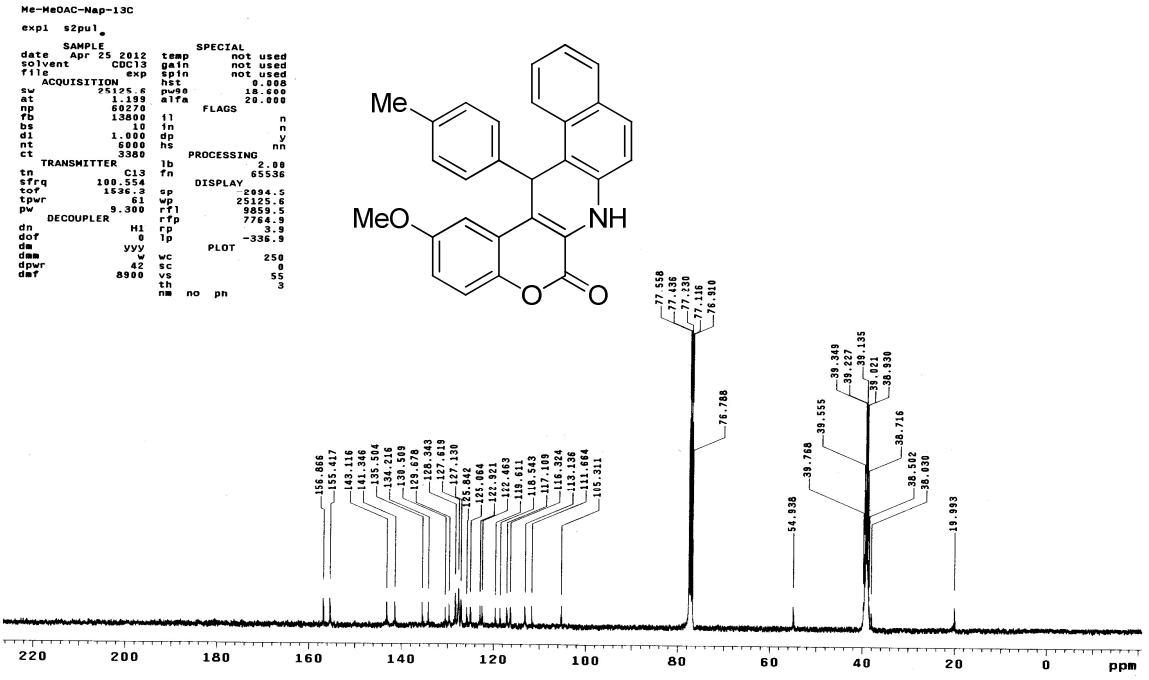
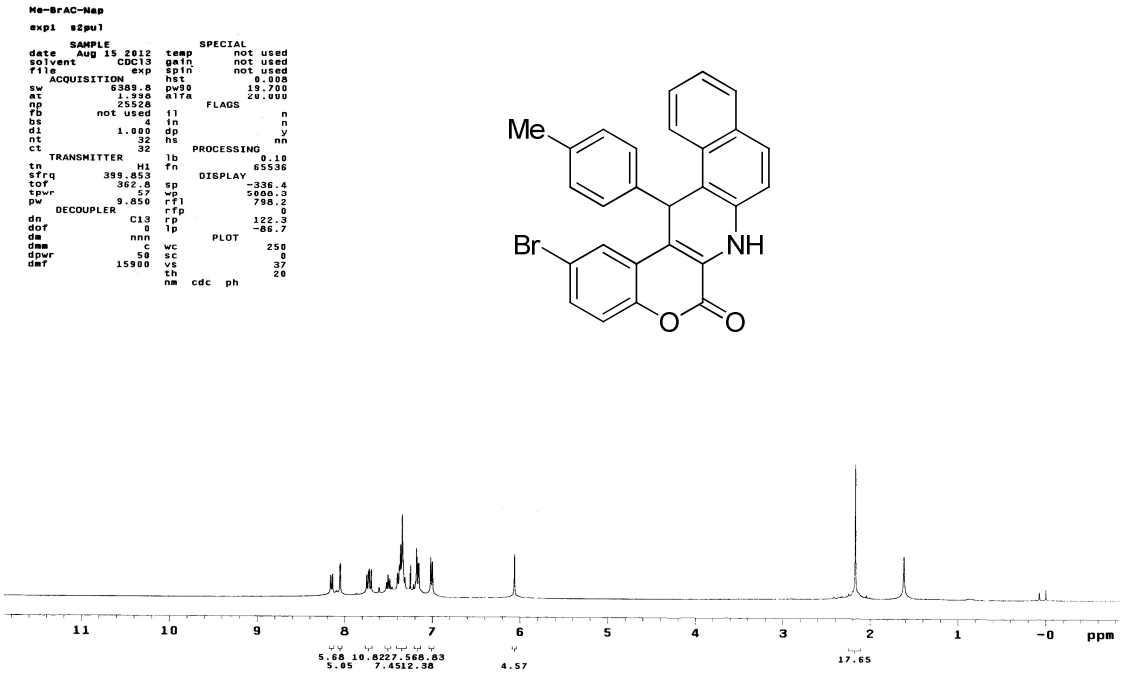


Figure 12

^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**27l**)*



^{13}C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**27l**)*

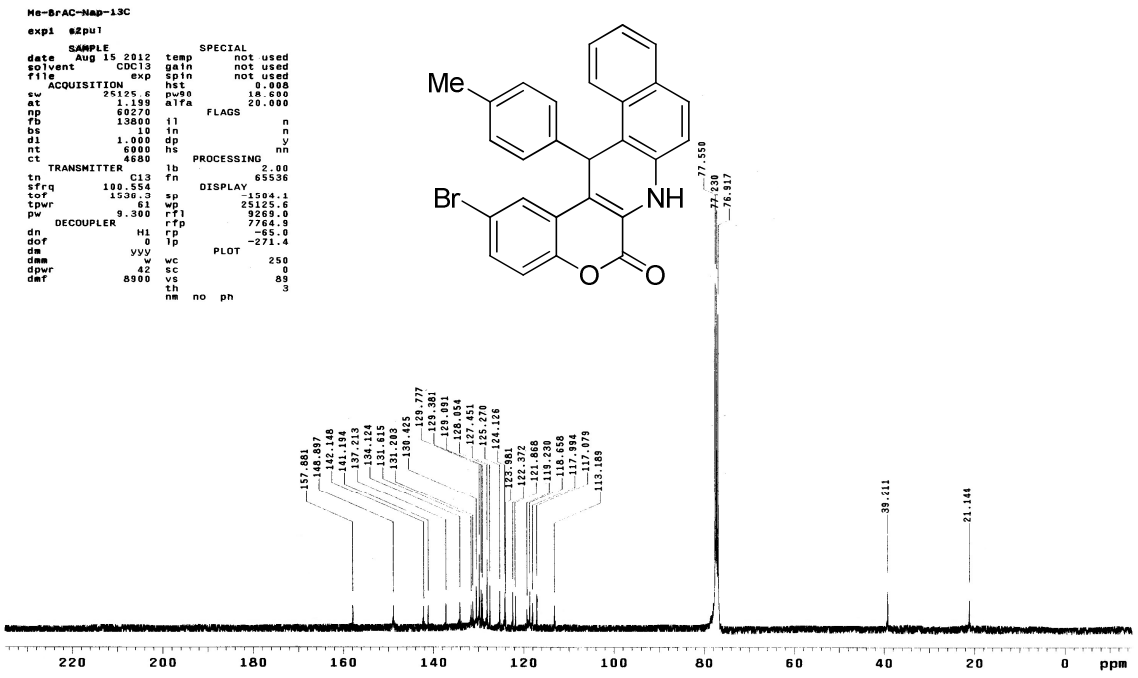


Figure 13

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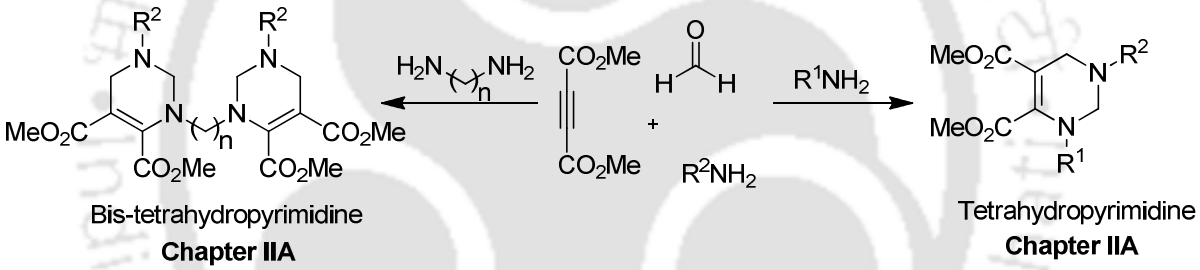
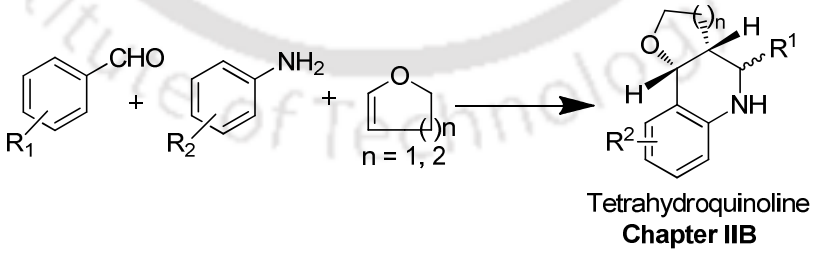
Conclusion and Future Perspective

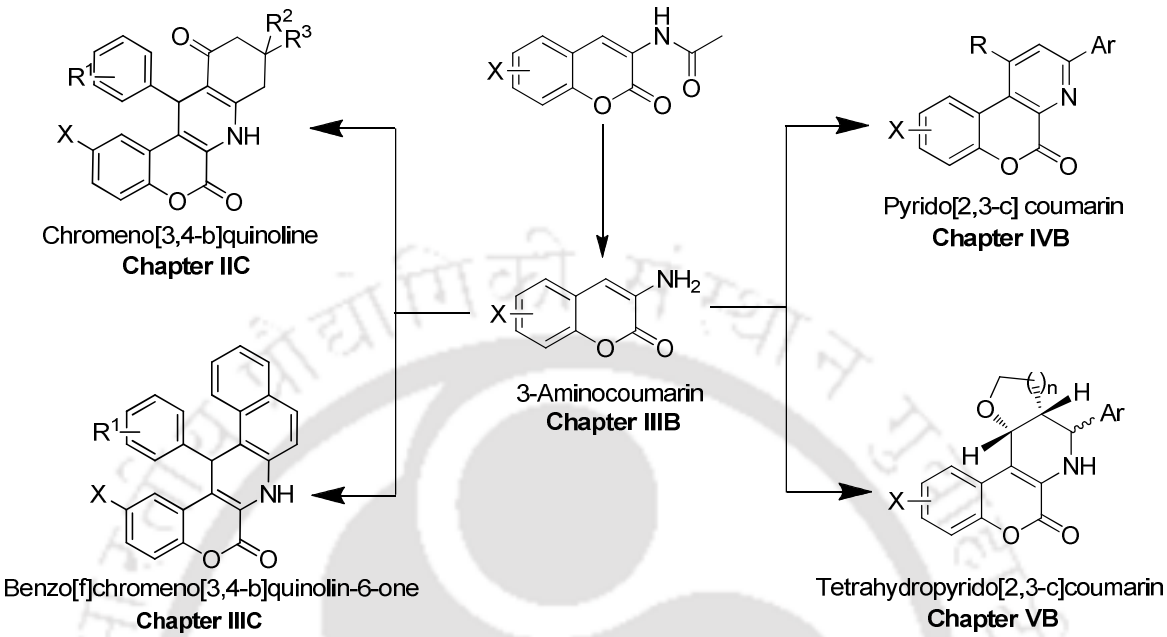
We have successfully accomplished the synthesis of various tetrahydropyrimidine and tetrahydroquinoline derivatives using MCRs. In addition, we have developed an improved synthetic protocol for a large scale preparation of various 3-aminocoumrins, which have been utilized further for the synthesis of pyrido[2,3-c]coumarin and 3,4-fused tetrahydropyrido[2,3-*c*]coumarin derivatives via Povarov reaction by employing molecular iodine and hydrated ferric sulfate as catalysts, respectively. From docking study, it revealed that *cis*-isomer of 3,4-fused tetrahydropyrido[2,3-*c*]coumarin derivatives exhibit biological activity. In addition, we have achieved the synthesis of chromeno[3,4-b]quinoline derivatives and benzo[f]chromeno[3,4-b]quinolin-6-one derivatives using 3-aminocoumarins as the key starting materials. The summarized results is shown below schematically.



Scheme 1



Scheme 2



Scheme 3

There is a future scope to develop a new methodology for the synthesis of *cis*-isomer of tetrahydroquinoline derivatives and 3,4-fused tetrahydropyrido[2,3-*c*]coumarin derivatives in major amount. Though we have achieved the synthesis of tetrahydroquinoline and 3,4-fused tetrahydropyrido[2,3-*c*]coumarin by employing Povarov reaction using electron-rich dienophile such as cyclic enol ethers, but there is a further scope to examine the similar reaction with other dienophiles to obtain new products. Moreover, the synthesis of optically active 3,4-fused tetrahydropyrido[2,3-*c*]coumarin derivatives, chromeno[3,4-b]quinoline derivatives and benzo[f]chromeno[3,4-b]quinolin-6-one derivatives can be explored further using asymmetric organocatalyst. Finally, the biological study of the synthesized compounds have to be investigated in collaboration with other laboratory in future. We are not able to complete all the above studies due to time constraints.

LIST OF AUTHOR'S PUBLICATION AND COMMUNICATIONS

1. *'Silica Supported Perchloric Acid ($HClO_4$-SiO_2): an Efficient Catalyst for One-pot Synthesis of Functionalized Tetrahydropyrimidine Derivatives'* Abu T. Khan, Md. Musawwer Khan, **Deb Kumar Das** and Mohan Lal *J. Heterocyclic. Chem.* **2012**, *49*, 1362-1369.
2. '*Ferric Sulfate [$Fe_2(SO_4)_3.xH_2O$] Catalyzed Povarov reaction: An Efficient and Useful Synthetic Protocol for the Synthesis of Tetrahydroquinoline Derivatives'* Abu T. Khan, **Deb K. Das** and Md. Musawwer Khan *Tetrahedron Lett*. **2011**, *52*, 4539-4542.
3. '*Michael Initiated Ring Closure (MIRC) reaction on in situ generated benzylidenecyclohexane-1,3-diones for the construction of chromeno[3,4-b]quinoline derivatives*' Abu T. Khan, **Deb Kumar Das** *Tetrahedron Lett*. **2012**, *53*, 2345-2351.
4. '*A simple and expedient synthesis of functionalized pyrido[2,3-c] coumarin derivatives using molecular iodine catalyzed three-component reaction'* Abu T. Khan, **Deb K. Das**, Kobirul Islam, Pradipta Das *Tetrahedron Lett*. **2012**, *53*, 6418-6422.
5. '*A large scale synthesis of 3-aminocoumarins*' **Deb K. Das**, Satavisha Sarkar and Abu T. Khan (*will be communicated soon*).
6. '*Synthesis of fused tetrahydropyrido[2,3-c]coumarin derivatives as potential inhibitors for dopamine d3 receptors, catalyzed by hydrated ferric sulfate*' **Deb K. Das**, Satavisha Sarkar, Abu T. Khan, Parameswaran Saravanan, Sanjukta Patra (*Submitted to RSC Advances*)
7. 'Synthesis of benzo[f]chromeno[3,4-b]quinolin-6-one derivatives and their solvatochromic studies' **Deb K. Das**, Ashim Malakar and Abu. T. Khan (*Manuscript under preparation*).
8. '*Sodium-Hydroxide-Mediated Synthesis of Highly Functionalized [1,6]-Naphthyridines in a One-Pot Pseudo Five-Component Reaction'* Satavisha Sarkar, **Deb K. Das**, Abu T. Khan *E. J. Org. Chem. 0000-0000,* **2013**.

9. '*Ammonium chloride catalyzed three-component reaction for the synthesis of fused 4H-chromene derivatives in aqueous medium*' Suchandra Bhattacharjee, **Deb K. Das** and Abu T. Khan *Synthesis* (under revision)

10. '*Synthesis of Unsymmetrical Ethers by Capturing of 2-Naphthoquinone-1-methide intermediate with Thiols Followed by Its Cleavage with Bromo-dimethylsulfonium bromide (BDMS)*' Kobirul Islam, **Deb K. Das** and Abu T. Khan (will be *communicated soon*).

LIST OF CONFERENCES AND SYMPOSIUMS

1. Participated and presented a poster in Catalyst 2013, Dr. Reddy's Laboratories Ltd, Hyderabad, India on 9th January, 2013.
2. Participated and presented a poster in *8th Junior National Organic Symposium Trust (JNOST)* Conference, Indian Institute of Technology Guwahati, India, 15-17 December, 2012.
3. Participated and presented a poster in National Seminar on *Emerging Trends in Chemical Science*, Department of Chemistry, Gauhati University, India during 30-31st March, 2012.
4. Participated and presented a poster in National Symposium on *Recent Trends in Chemical Science and Technology, RTCST 2012*. Indian Institute of Technology Patna, India, during March 3-4, 2012.
5. Participated and presented a poster in RSC International Symposium on Advance Chemical Sciences (AICS 2012), Indian Institute of Technology Guwahati, India, on 30th January, 2012.
6. Participated and presented a poster in *12th CRSI National Symposium in Chemistry, IICT Hyderabad,* India 4–7 February, 2010.

Silica-Supported Perchloric Acid ($HClO_4$–SiO_2): An Efficient Catalyst for One-Pot Synthesis of Functionalized Tetrahydropyrimidine Derivatives

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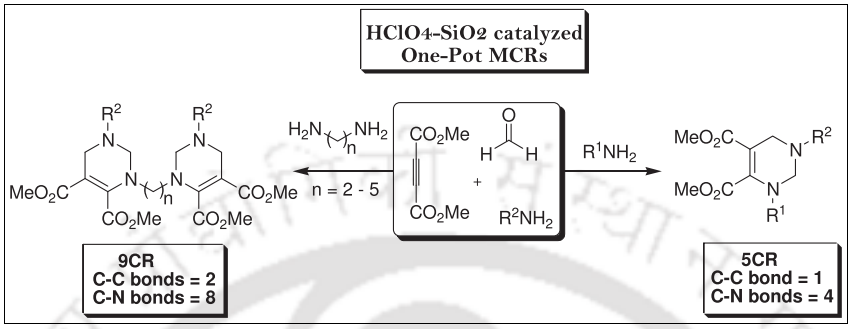


$HClO_4$–SiO_2 has been found to be a highly efficient catalyst for the synthesis of substituted tetrahydropyrimidine and bis-tertahydropyrimidine derivatives in good to excellent yields involving the reaction of dimethyl acetylenedicarboxylate, amines/diamines, and formaldehyde. One-pot, atom economy, high-bond forming efficiency, environmentally benign, good yields, and mild reaction conditions are some of the salient features of this multicomponent reaction.

J. Heterocyclic Chem., **49**, 1362 (2012).

INTRODUCTION

In recent times, multicomponent reactions (MCRs) have emerged as an important and promising tool in organic chemistry for construction of architecturally complex molecules [1,2]. These reactions have been explored in the total syntheses of natural products and synthetic building blocks [2,3]. They avoid time-consuming, expensive processes for purification of various precursors as well as cumbersome steps of protection and deprotection of functional groups. In addition, these reactions are environmentally benign and often proceed with excellent chemoselectivities [4]. Hence, MCRs are considered as a new type of "Green Chemistry." To devise a new selective cascade, reaction is a challenging task at the forefront of organic chemistry so the interest in MCRs is increasing gradually. Of late, the authors have developed various synthetic methodologies using MCR approach to synthesize new entities leading to chemical and pharmaceutical interest [5].

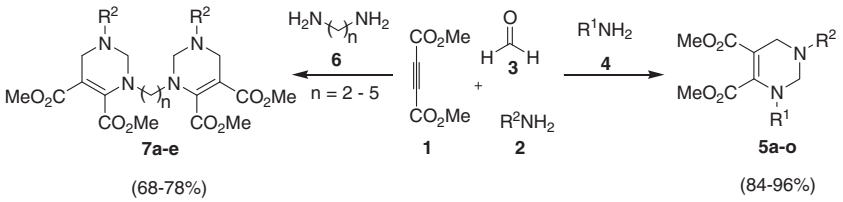
Pyrimidine and its analogs are important class of nitrogen heterocyclic pharmacophores, which are present in many pharmaceuticals. Some of them are in clinical and preclinical trial stage and also exhibits interesting biological activities [6] such as muscarinic agonist activity [7], antiviral activity [8], anti-inflammatory activity [9], and protein–nucleic acid interactions [10]. Pyrimidine skeleton is a key structural motif found in various naturally occurring compounds [11] and they also serve as building block for various organic synthesis [12]. Owing to the importance of tetrahydropyrimidine derivatives, a considerable attention has been paid to the synthesis of these compounds over the years [13,14]. These methods are associated with certain limitations such as use of expensive and excess amount of catalyst, long reaction times and drastic reaction conditions. In addition, the synthesis of bis-tetrahydropyrimidine derivatives using MCRs has not yet been reported. Therefore, there is a need to develop a synthetic methodology using a catalyst, which might work under milder reaction conditions.

$HClO_4$–SiO_2 is an inexpensive, nontoxic, reusable, environmentally benign as well as highly efficient catalyst and it has been utilized for various organic transformations [15]. The usefulness of this catalyst has been demonstrated by the authors for geminal diacylation of aldehydes [16a], tetrahydropyranylation, oxathioacetalization and thioacetylation [16b], and aza-Michael reaction [16c]. The efficiency of $HClO_4$–SiO_2 was shown in other one-pot MCRs [17] and its advantage is going to be explored further. In this article, the authors have reported the synthesis of substituted tetrahydropyrimidine and bis-tetrahydropyramidine derivatives using $HClO_4$–SiO_2 as a heterogeneous catalyst (Scheme 1).

RESULTS AND DISCUSSION

For the present study, the catalyst $HClO_4$–SiO_2 was prepared by following the published reports procedure [17].

Scheme 1. Synthesis of tetrahydropyrimidine derivatives.



The reaction of dimethyl acetylenedicarboxylate (DMAD, **1**), aniline (**2a**), and formaldehyde (**3**) using $HClO_4$–SiO_2 as a catalyst at room temperature was examined and it smoothly converted into the functionalized tetrahydropyrimidine derivative **5a** within 1.5 h giving 95% yield.

The reaction conditions were optimized by varying the amount of catalyst and stoichiometric ratios of the reactants (DMAD, aniline, and formaldehyde) to obtain best result in terms of reaction time and yield (Table 1, entries 1–4). The optimized amount of catalyst ($HClO_4$–SiO_2) was determined to be 25 mg (0.125 mmol). The optimal amount of the reactants such as DMAD (**1**), aniline (**2a**), and formaldehyde (**3**) was found to be 1.0, 2.0, and 2.5 equiv, respectively. Various solvents namely MeCN, DMF, DCM, MeOH, EtOH, and H_2O were also screened and MeOH was found to be the best solvent among them (Table 1, entries 4–9).

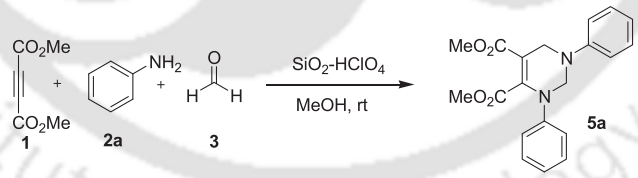
The reaction was performed without the catalyst in methanol at room temperature, which gave only 52% yield after 5 h (Table 1, entry 10). In the case of neat reaction, the product **5a** was obtained in 55% yield using the same amount of catalyst. These results indicate that the catalyst and solvent have definite role in the reaction both in terms of time and yield. This might be due to lack of proper interaction between the reactants (Table 1, entry 11).

After optimization of the reaction conditions, the reaction of 4-methylaniline (2 mmol) with DMAD (1 mmol), formaldehyde (2.5 mmol) using $HClO_4$–SiO_2 (25 mg, 2.5 mol %) in methanol was performed. The product **5b** was obtained in 96% yield. The scope of this protocol was investigated using the same reaction condition for substituted anilines. Me, Et, MeO, Cl, and Br were the substituents that was used in these studies. The desired products **5c–i** were obtained in good to excellent yields.

The present method was also tested with aliphatic amines namely *n*-butylamine, benzylamine, furfurylamine, and cyclohexylamine under identical reaction conditions to furnish tetrahydropyrimidines **5j–m** in good yields (Table 2, entries 10–13). It is observed that the aliphatic amines require shorter reaction time than the aromatic amines.

Table 1

Screening of reaction conditions for the synthesis of tetrahydropyrimidine **5a**.

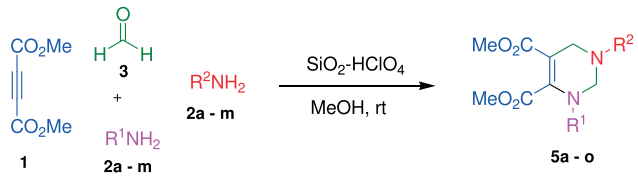


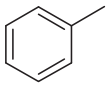
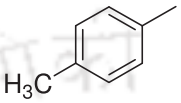
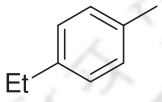
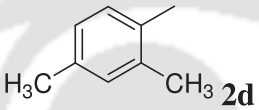
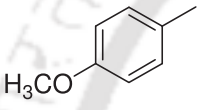
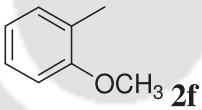
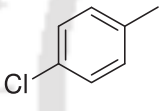
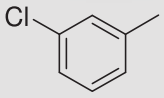
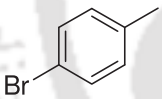
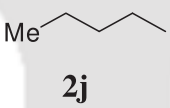
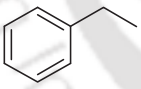
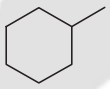
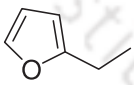
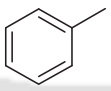
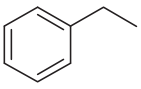
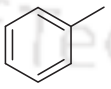
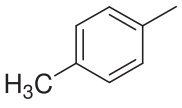
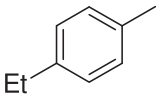
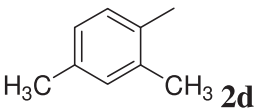
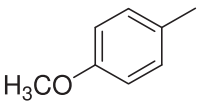
Entry	Solvent	Amount of Catalyst (in mg)	Molar ratio (1:2:3)	Time (h)	Yield[a] (%)
1	CH_3OH	25	1:2:4	1.5	95
2	CH_3OH	50	1:2:4	1.5	94
3	CH_3OH	25	1:2:3	1.5	95
4[b]	**CH_3OH**[b]	**25**[b]	**1:2:2.5**[b]	**1.5**[b]	**95**[b]
5	CH_3CN	25	1:2:3	2	88
6	DMF	25	1:2:3	2.5	88
7	DCM	25	1:2:3	2	76
8	EtOH	25	1:2:3	1.5	89
9	H_2O	25	1:2:3	2	72
10	CH_3OH	No catalyst	1:2:4	5	52
11	No solvent	25	1:2:3	5	55

[a]Isolated yield.
[b]The experimental condition is the best optimized condition for obtaining the product.

Table 2

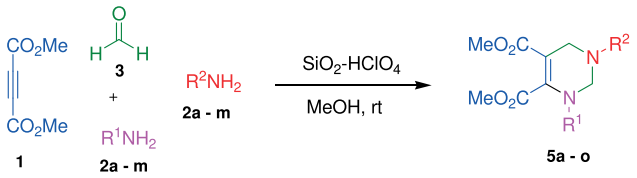
Scope of the one-pot synthesis of tetrahydropyrimidines **5** catalyzed by $HClO_4$–SiO_2.

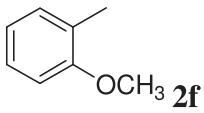
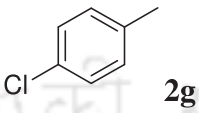
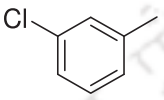
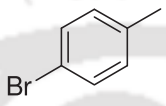
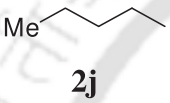
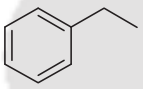
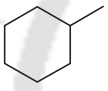
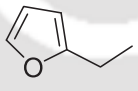
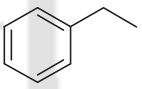
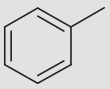


Entry	R^1	R^2	Time (h)	Product	Yield[a] (%)
1	 **2a**	 **2b**	1.5	**5a**	95
2	 **2c**	 **2d**	1.5	**5b**	96
3	 **2e**	 **2f**	1.5	**5c**	92
4	 **2g**	 **2h**	2.5	**5d**	91
5	 **2i**	 **2j**	1.5	**5e**	92
6	 **2k**	 **2l**	2.0	**5f**	84
7	 **2m**	 **2a**	2.0	**5g**	94
8	 **2k**	 **2a**	2.0	**5h**	88
9	 **2b**	 **2c**	2.0	**5i**	93
10	 **2d**	 **2e**	1.0	**5j**	95

(*Continues*)

Table 2. *(Continued)*



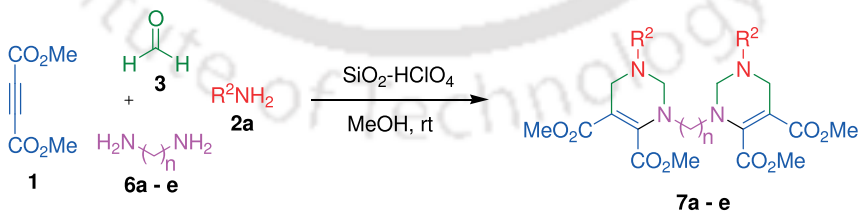
Entry	R^1	R^2	Time (h)	Product	Yield[a] (%)
11	 **2f**	 **2g**	1.0	**5k**	92
12	 **2h**	 **2i**	1.0	**5l**	96
13	 **2j**	 **2k**	1.5	**5m**	91
14	 **2l**	 **2m**	2	**5n**	86
15	 **2k**	 **2a**	2	**5o**	88

[a]Isolated yield.

The substituent pattern of the pyrimidine ring at positions 1 and 3 can be altered by changing the sequence of addition of the amines. The product **5n** was obtained when aniline (**2a**) was added with DMAD followed by the addition of benzylamine (**2k**) and formaldehyde (**3**), while the product **5o** was isolated by changing the order of the

Table 3

Scope of the one-pot domino reaction for the synthesis of bis-tetrahydropyrimidines.



Entry	n	Time (h)	Product	Yield[a] (%)
1	2, **6a**	2	**7a**	74
2	3, **6b**	2	**7b**	71
3	4, **6c**	2	**7c**	76
4	5, **6d**	2	**7d**	68
5	6, **6e**	2	**7e**	78

[a]Isolated yields.

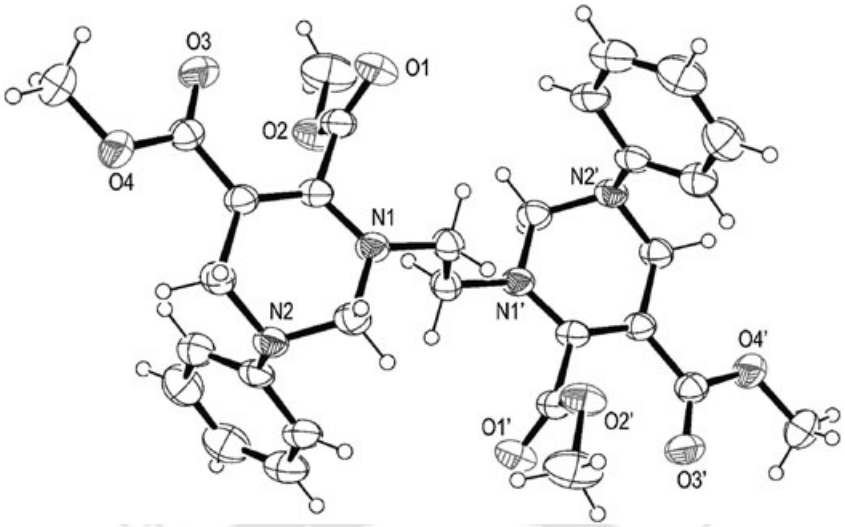


Figure 1. X-ray crystal structure of **7a** (CCDC no. 756205).

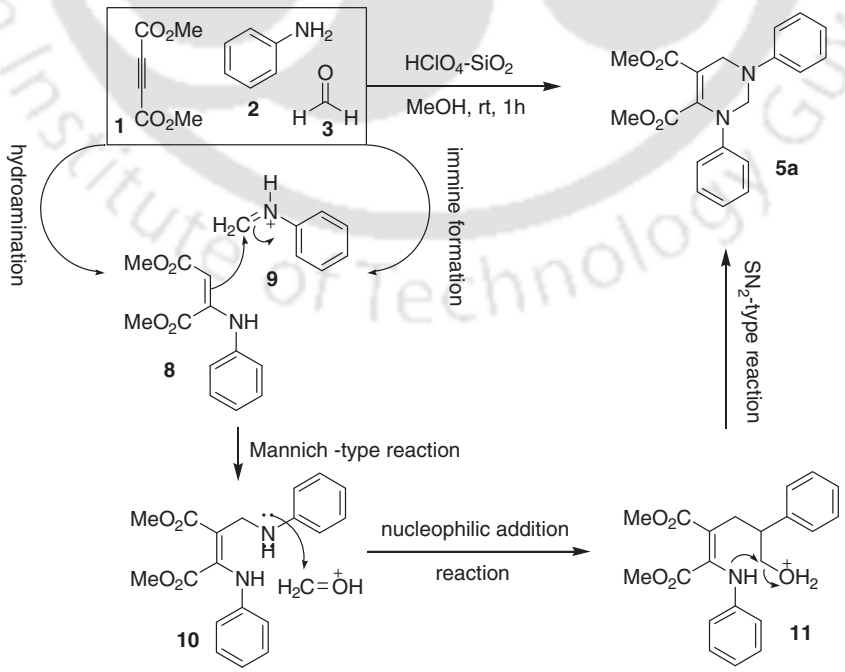
amines that is benzylamine was added first followed by aniline.

The synthetic utility of the present protocol was further extended by synthesizing bis-pyrimidine derivatives. The reaction of DMAD (**1**, 2 mmol) with ethylenediamine (**6a**, 1 mmol), followed by addition of aniline (**2a**, 2 mmol) and formaldehyde (5 mmol) using $HClO_4$–SiO_2 (50 mg, 5 mol %) as a catalyst provides a bis-tetrahydropyrimidine derivative **7a** (Table 3, entry 1). The product **7a** was fully characterized by ^1H and ^{13}C NMR spectra as well as elemental analysis. The structure of compound **7a** was confirmed by single X-ray crystallographic data. The tetrahydropyrimidine ring adopted envelope conformation and the orientation of two rings are found to be anti to each other as shown in Figure 1.

The reaction of other aliphatic diamines such as 1,3-diamine (**6b**), 1,4-diamine (**6c**), 1,5-diamine (**6d**), and 1,6-diamine (**6e**) were examined individually with DMAD (**1**), aniline (**2a**), and formaldehyde (**3**) under the same experimental conditions and the results are summarized in Table 3.

A plausible mechanism for the formation of tetrahydropyrimidine **5a** involves the initial formation of hydroamination

Scheme 2. Plausible mechanism for the formation of tetrahydropyrimidine.



product **8**, which reacts with acid protonated imine **9** to form intermediate **10** via Mannich-type reaction. The intermediate **10** reacts with acid protonated formaldehyde to give species **11** by nucleophilic addition reaction. Finally, the intermediate **11** undergoes intramolecular SN_2 type reaction to furnish the desired product **5a** via elimination of a water molecule as shown in Scheme 2. All the products **5a–o** and **7a–e** were characterized by IR, ^{1}H NMR, ^{13}C NMR spectra, and by elemental analysis.

CONCLUSION

In conclusion, the efficacy and generality of $HClO_4$–SiO_2 as a versatile catalyst for the synthesis of tetrahydropyrimidines using DMAD, amines, and formaldehyde have been demonstrated. In addition, the synthesis of novel bis-tetrahydropyrimidine derivatives has been achieved using aliphatic diamines under the same experimental conditions. The salient features of this protocol are good yields, mild reaction conditions, superior atom economy, environmentally benign, easy accessibility of the catalyst, and its cost effectiveness. These pyrimidine derivatives can be used for other organic transformation and these reactions are under progress.

EXPERIMENTAL

Melting points were determined on a Büchi-melting point apparatus. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 spectrometer using TMS internal standard; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR spectra are reported in the order: multiplicity, coupling constant (J value) in hertz (Hz), and no of protons. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K.

General procedure for the synthesis of tetrahydropyrimidine derivatives 5. A mixture of DMAD (1 mmol) and amines (2 mmol) in MeOH (3 mL) was stirred at room teperatutre for 10 min. Then 38% formaldehyde solution (200 mg, 2.5 mmol) in methanol (2 mL) and the catalyst $HClO_4$–SiO_2 (25 mg, 1.25 mol%) were added successively into the reaction vessel. After completion of reaction as monitored by TLC, methanol was removed and the crude residue was extracted with dichloromethane (2 × 20 mL). The organic layer was washed with $NaHCO_3$ solution, brine, and finally with water. The solvent was removed and crude material was purified by column chromatography using ethyl acetate/hexane (1:9) as eluent to give the pure products **5a–o**.

Compound 5a. Yellow liquid (334 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 (s, 3 H), 3.74 (s, 3 H), 4.27 (s, 2 H), 4.92 (s, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 7.16–7.29 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.7, 51.7, 52.6, 69.0, 100.7, 118.0, 121.3, 125.2, 126.6, 129.4, 143.8, 146.7, 148.4, 164.7, 166.3; IR (KBr): 2950, 1743, 1697, 1580, 1495, 1261, 1112 cm^{-1}; Anal. Calcd for $C_{20}H_{20}N_2O_4$ (352.39): C, 68.17; H, 5.72; N, 7.95; Found: C, 68.01; H, 5.61; N, 7.73.

Compound 5b. Yellow liquid (365 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 2.30 (s, 3 H), 3.58 (s, 3 H), 3.72 (s, 3 H), 4.22 (s, 2 H), 4.85 (s, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 21.0, 47.6, 51.4, 52.4, 69.2, 98.9, 118.1, 125.1, 129.8, 129.9, 130.6, 136.4, 140.9, 146.0, 147.0, 164.6, 166.2; IR (KBr): 2949, 2863, 1742, 1698, 1588, 1514, 1434, 1259, 1112 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.45): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.54; H, 6.23; N, 7.12.

Compound 5c. Semi solid (376 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 0 (t, *J* = 7.6 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 2.53–2.63 (m, 4 H), 3.58 (s, 3 H), 3.73 (s, 3 H), 4.23 (s, 2 H), 4.86 (s, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 15.9, 28.1, 28.5, 47.8, 51.6, 52.6, 69.3, 99.2, 118.3, 125.3, 128.7, 128.8, 137.3, 141.1, 142.8, 146.3, 147.1, 164.8, 166.4; IR (KBr): 2963, 2872, 1744, 1697, 1588, 1514, 1434, 1260, 1110 cm^{-1}; Anal. Calcd for $C_{24}H_{28}N_2O_4$ (408.50): C, 70.57; H, 6.91; N, 6.86. Found: C, 70.51; H, 6.80; N, 6.66.

Compound 5d. Yellow liquid (378 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 2.20 (s, 3 H), 2.24 (s, 3 H), 2.27 (s, 3 H), 3.52 (s, 3 H), 3.71 (s, 3 H), 4.04 (s, 2 H), 4.32 (d, *J* = 11.6 Hz, 1 H), 4.49 (d, *J* = 11.6 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 18.1, 20.9, 21.1, 48.8, 51.4, 52.4, 69.8, 96.9, 121.4, 127.1, 127.3, 128.8, 131.7, 132.0, 137.7, 133.9, 136.4, 138.0, 138.8, 146.0, 148.4, 164.9, 166.5; IR (KBr): 2950, 2859, 1744, 1697, 1592, 1502, 1435, 1263, 1111 cm^{-1}; Anal. Calcd for $C_{24}H_{28}N_2O_4$ (408.50): C, 70.57; H, 6.91; N, 6.86. Found: C, 70.43; H, 6.79; N, 6.71.

Compound 5e. Yellow liquid (379 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 3 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.18 (s, 2 H), 4.77 (s, 2 H), 6.76 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 9.2 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.9, 51.5, 52.6, 55.5, 55.7, 70.8, 97.5, 114.4, 114.6, 120.5, 127.5, 136.2, 142.4, 147.7, 154.9, 158.4, 164.7, 166.4; IR (KBr): 2950, 2837, 1742, 1694, 1579, 1511, 1435, 1247, 1110 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_6$ (412.45): C, 64.07; H, 5.87; N, 6.79. Found: C, 63.96; H, 5.72; N, 6.48.

Compound 5f. Yellow liquid (346 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50 (s, 3 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 4.21 (s, 2 H), 4.80 (br s, 2 H), 6.67–6.71 (m, 2 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 7.12 (td, *J* = 7.2 Hz, *J* = 2.4 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.0, 51.4, 52.4, 55.5, 55.9, 68.4, 97.4, 111.3, 111.9, 120.4, 120.8, 121.0, 124.0, 128.5, 128.52, 131.7, 137.9, 147.8, 152.2, 155.4, 164.6, 166.4; IR (KBr): 2949, 2838, 1743, 1693, 1581, 1501, 1436, 1264, 1108 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_6$ (412.45): C, 64.07; H, 5.87; N, 6.79. Found: C, 64.01; H, 5.71; N, 6.63.

Compound 5g. Light yellow solid (396 mg, 94%); mp 128–130° C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (s, 3 H), 3.75 (s, 3 H), 4.23 (s, 2 H), 4.85 (s, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.6, 51.9, 52.9, 69.1, 101.6, 119.3, 126.2, 126.5, 129.4, 129.7, 132.3, 142.2, 146.1, 146.7, 164.4, 165.9; IR (KBr): 2953, 1744, 1688, 1571, 1491,

1266, 1228, 1117 cm^{-1}; Anal. Calcd for $C_{20}H_{18}N_2O_4Cl_2$ (421.28): C, 57.02; H, 4.30; N, 6.65. Found: C, 56.91; H, 4.19; N, 6.42.

Compound 5h. Yellow liquid (371 mg, 88%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 3 H), 3.76 (s, 3 H), 4.23 (s, 2 H), 4.87 (s, 2 H), 6.72 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H), 6.83 (t, *J* = 2.0 Hz, 1 H), 6.86 (dq, *J* = 8.0 Hz, *J* = 0.8 Hz, 1 H), 6.90 (dq, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 7.04 (t, *J* = 2.4 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.17 (m, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.7, 52.0, 52.9, 68.2, 103.4, 115.5, 117.7, 121.3, 122.6, 124.7, 126.7, 130.5, 130.6, 135.2, 135.3, 144.9, 145.6, 149.2, 164.5, 165.9; IR (KBr): 2950, 2843, 1742, 1703, 1591, 1482, 1262, 1114 cm^{-1}; Anal. Calcd for $C_{20}H_{18}N_2O_4Cl_2$ (421.28): C, 57.02; H, 4.30; N, 6.65. Found: C, 56.98; H, 4.17; N, 6.50.

Compound 5i. Light yellow solid (474 mg, 93%); mp 150–152°C; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.62 (s, 3 H), 3.75 (s, 3 H), 4.22 (s, 2 H), 4.85 (s, 2 H), 6.75 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.6, 51.8, 52.9, 68.8, 101.8, 113.7, 119.5, 120.1, 126.3, 132.3, 132.6, 142.7, 145.9, 147.2, 164.4, 165.9; IR (KBr): 2951, 1744, 1689, 1591, 1568, 1487, 1265, 1227, 1116 cm^{-1}; Anal. Calcd for $C_{20}H_{18}N_2O_4Br_2$ (510.20): C, 47.08; H, 3.56; N, 5.49. Found: C, 47.01; H, 3.42; N, 5.29.

Compound 5j. Yellow liquid (297 mg, 95%); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H), 0.93 (t, *J* = 7.2 Hz, 3 H), 1.24–1.32 (m, 2 H), 1.34–1.41 (m, 2 H), 1.47–1.56 (m, 4 H), 2.53 (t, *J* = 7.6 Hz, 2 H), 3.01 (t, *J* = 7.6 Hz, 2 H), 3.50 (s, 2 H), 3.64 (s, 3 H), 3.90 (s, 3 H), 3.98 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.2, 20.0, 20.6, 30.3, 31.4, 48.2, 51.0, 52.6, 52.8, 67.7, 91.1, 148.4, 165.6, 167.1; IR (KBr): 2956, 2870, 1743, 1689, 1582, 1434, 1285, 1249, 1145 cm^{-1}; Anal. Calcd for $C_{16}H_{28}N_2O_4$ (312.41): C, 61.51; H, 9.03; N, 8.97. Found: C, 61.51; H, 8.92; N, 8.81.

Compound 5k. Yellow liquid (350 mg, 92%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.55 (s, 2 H), 3.60 (s, 2 H), 3.65 (s, 3 H), 3.84 (s, 2 H), 3.91 (s, 3 H), 4.16 (s, 2 H), 7.15–7.18 (m, 2 H), 7.22–7.32 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.4, 51.3, 53.1, 54.4, 57.1, 66.1, 92.2, 127.4, 128.2, 128.24, 128.5, 128.9, 136.3, 138.1, 148.4, 165.8, 167.1; IR (KBr): 2949, 2855, 1740, 1689, 1582, 1434, 1286, 1110 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.45): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.39; H, 6.25; N, 7.18.

Compound 5l. Yellow liquid (350 mg, 96%); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.3 (m, 8 H), 1.35–1.45 (m, 2 H), 1.62–1.92 (m, 10 H), 2.43–2.52 (m, 1 H), 2.97 (tt, *J* = 11.6 Hz, *J* = 4.8 Hz, 1H), 3.54 (s, 2 H), 3.64 (s, 3 H), 3.90 (s, 3 H), 4.01 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 25.6, 25.9, 26.1, 30.5, 31.4, 45.5, 51.0, 52.8, 59.0, 60.0, 60.2, 92.7, 149.0, 166.0, 166.8; IR (KBr): 2932, 1742, 1688, 1582, 1435, 1287, 1239, 1117 cm^{-1}; Anal. Calcd for $C_{20}H_{32}N_2O_4$ (364.49): C, 65.91; H, 8.85; N, 7.69. Found: C, 65.79; H, 8.75; N, 7.53.

Compound 5m. Yellow liquid (328 mg, 91%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.59 (s, 2 H), 3.63 (s, 2 H), 3.65 (s, 3 H), 3.92 (s, 3 H), 4.05 (s, 2 H), 4.19 (s, 2 H), 6.13 (d, *J* = 3.2 Hz, 1 H), 6.26 (d, *J* = 3.2 Hz, 1 H), 6.30 (d, *J* = 3.0 Hz, 1 H), 6.33 (d, *J* = 3.0 Hz, 1 H), 7.37–7.38 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.9, 47.8, 49.2, 51.3, 66.3, 92.5, 109.2, 110.3, 110.8, 142.7, 143.0, 149.9, 151.5, 165.3, 166.9; IR (KBr): 2951, 1739, 1688, 1582, 1435, 1284, 1247, 1188, 1109 cm^{-1}; Anal. Calcd for $C_{18}H_{20}N_2O_6$ (360.37): C, 59.99; H, 5.59; N, 7.77. Found: C, 59.91; H, 5.48; N, 7.61.

Compound 5n. Yellow liquid (315 mg, 86%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.63 (s, 3 H), 3.67 (s, 3 H), 3.71 (s, 2 H), 3.81 (s, 2 H), 4.36 (s, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.24 (br s, 5 H), 7.30 (t, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.8, 51.4, 52.6, 56.7, 69.8, 97.3, 124.8, 126.3, 127.5, 128.4, 129.0, 129.3, 137.8 143.7, 145.9, 164.8, 166.8; IR (KBr): 2951, 2860, 1739, 1688, 1582, 1284, 1247, 1109 cm^{-1}; Anal. Calcd for $C_{21}H_{22}N_2O_4$ (366.42): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.72; H, 5.91; N, 7.49.

Compound 5o. Yellow liquid (322 mg, 88%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H), 3.85 (s, 3 H), 4.12 (s, 2 H), 4.21 (s, 2 H), 4.42 (s, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 6.90 (t, *J* = 7.6 Hz, 1 H), 7.17–7.24 (m, 4 H), 7.26–7.31 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.4, 51.4, 53.0, 54.5, 65.4, 94.8, 117.8, 121.2, 128.0, 128.1, 128.8, 129.3, 135.8, 148.4, 149.0, 165.5, 166.4; IR (KBr): 2963, 2872, 1744, 1697, 1588, 1514, 1260, 1110 cm^{-1}; Anal. Calcd for $C_{21}H_{22}N_2O_4$ (366.42): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.72; H, 5.88; N, 7.48.

General reaction procedure for functionalized bis-tetrahyropyrimidines 7. A mixture of DMAD (1 mmol) and diamines (1 mmol) in MeOH (2 mL) was stirred at room teperatutre for 20 min. Aniline (2 mmol) in MeOH (1 mL) and formaldehyde (38%, 400 mg, 5 mmol) in methanol (2 mL) were added into it. Finally, the catalyst silica supported perchloric acid (50 mg, 2.5 mol %) was added into the reaction vessel. After completion of reaction as monitored by TLC, the same work up procedure was followed as above. The products **7a–e** were obtained by purification through column chromatography using ethyl acetate/hexane (1:9) as eluent.

Compound 7a. Light yellow solid (428 mg, 74%); mp 104–106°C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.98 (s, 4 H), 3.71 (s, 6 H), 3.88 (s, 6 H), 4.01 (s, 4 H), 4.44 (s, 4 H), 6.92–6.96 (m, 6 H), 7.25–7.29 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.3, 50.5, 51.6, 53.3, 67.9, 96.2, 118.1, 121.7, 129.6, 148.2, 148.5, 165.4, 166.2; IR (KBr): 2949, 1741, 1684, 1575, 1497, 1427, 1270, 1219, 1151, 1097 cm^{-1}; Anal. Calcd for $C_{30}H_{34}N_4O_8$ (578.63): C, 62.27; H, 5.92; N, 9.68. Found: C, 62.11; H, 5.83; N, 9.82.

Compound 7b. Yellow liquid (421 mg, 71%); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 7.2 Hz, 2 H), 2.90 (t, *J* = 7.2 Hz, 4 H), 3.69 (s, 6 H), 3.84 (s, 6 H), 4.04 (s, 4 H), 4.36 (s, 4 H), 6.93–6.96 (m, 6 H), 7.28 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 46.6, 48.6, 51.5, 53.1, 66.5, 95.3, 118.5, 121.8, 129.6, 148.7, 165.5, 166.3; IR (KBr): 2950, 1739, 1689, 1596, 1583, 1435, 1257, 1149 cm^{-1}; Anal. Calcd for $C_{31}H_{36}N_4O_8$ (592.65): C, 62.83; H, 6.13; N, 9.45. Found: C, 62.70; H, 6.02; N, 9.22.

Compound 7c. Yellow liquid (461 mg, 76%); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (br s, 4 H), 2.88 (br s, 4 H), 3.70 (s, 6 H), 3.85 (s, 6 H), 4.05 (s, 4 H), 4.43 (s, 4 H), 6.93 (t, *J* = 7.6 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 4 H), 7.62 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 46.3, 50.5, 51.3, 52.9, 66.1, 94.0, 118.2, 121.4, 129.4, 148.6, 148.9, 165.3, 166.3; IR (KBr): 2949, 1739, 1688, 1580, 1434, 1258, 1145 cm^{-1}; Anal. Calcd for $C_{32}H_{38}N_4O_8$ (606.68): C, 63.35; H, 6.31; N, 9.24. Found: C, 63.21; H, 6.11; N, 9.00.

Compound 7d. Yellow liquid (422 mg, 68%); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94–0.99 (m, 2 H), 1.25–1.32 (m, 4 H), 2.92 (t, *J* = 7.6 Hz, 4 H), 3.70 (s, 6 H), 3.85 (s, 6 H), 4.08 (s, 4 H), 4.09 (s, 4 H), 6.94 (t, *J* = 7.2 Hz, 2 H), 6.98 (d, *J* = 7.6 Hz, 4 H), 7.28 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 28.8, 46.5, 51.0, 51.4, 53.0, 66.4, 93.9, 118.4, 121.6, 129.5, 148.8, 149.0, 165.4, 166.4; IR (KBr): 2950, 1739, 1687, 1579, 1434, 1257, 1146, 1090 cm^{-1}; Anal. Calcd for $C_{33}H_{40}N_4O_8$ (620.70): C, 63.86; H, 6.49; N, 9.03. Found: C, 63.73; H, 6.43; N, 9.21.

Compound 7e. White solid (495 mg, 78%); mp 150–152°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (br s, 4 H), 1.33 (br s, 4 H), 2.96 (t, *J* = 7.2 Hz, 4 H), 3.70 (s, 6 H), 3.86 (s, 6 H), 4.09 (s, 4 H), 4.50 (s, 4 H), 6.93 (t, *J* = 7.2 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 4 H), 7.28 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 29.0, 46.5, 51.2, 51.4, 53.0, 66.4, 93.8, 118.4, 121.5, 129.5, 148.8, 149.1, 165.4, 166.4; Anal. Calcd for $C_{34}H_{42}N_4O_8$ (634.73): C, 64.34; H, 6.67; N, 8.83. Found: C, 64.30; H, 6.52; N, 8.69.

Crystallographic description of 7a. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Complete crystallographic data of **7a** has been deposited with the Cambridge Crystallographic Data Centre, CCDC no. is 756205. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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Ferric sulfate [$Fe_2(SO_4)_3{\cdot}xH_2O$]: an efficient heterogeneous catalyst for the synthesis of tetrahydroquinoline derivatives using Povarov reaction

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ABSTRACT

$Fe_2(SO_4)_3{\cdot}xH_2O$ can be used as an efficient and reusable catalyst for the synthesis of pyrano- and furano-tetrahydroquinolines via one-pot three-component Povarov reaction involving aromatic aldehydes, aromatic amines, and cyclic enol ethers. The catalyst is recyclable, economically viable, and environmentally benign. This protocol provides good yields and diastereoselectivity as well as applicability on a wide range of substrates.

In recent years, ferric sulfate [$Fe_2(SO_4)_3{\cdot}xH_2O$] has received considerable attention as a mild, inexpensive, and reusable catalyst for various organic transformations, such as tetrahydropyranylation of alcohols,[1] preparation of acylals from aldehydes,[2] 2,3-unsaturated glycosides via Ferrier rearrangement,[3] and per-*O*-acetylation of sugars.[4] Due its wide applicability as a catalyst, we presume that it would be an efficient catalyst for the one-pot three-component synthesis of the fused tetrahydroquinoline derivatives by employing Povarov reaction.

Tetrahydroquinoline derivatives exhibit interesting biological activities. For example, 2-aryl-2,3-dihydro-4-quinolone (**1**) showed antitumor activity[5] and 2-aryl-1,2,3,4-tetrahydro-quinoline (**2**) is a core structure of the compounds possessing 5-lipoxygenase inhibitor properties as well as potential therapeutic application in asthma[6] as shown in Figure 1. Due to its pharmaceutical importance the development of new methods for the construction of a tetrahydroquinoline framework is in continuous interest to the synthetic organic chemists.[7]

Recently, multicomponent reactions (MCRs) have received considerable interest among synthetic chemists for construction of complex molecules.[8] Using this approach, fused tetrahydroquinoline derivatives can be easily accessible by employing aromatic aldehydes, aromatic amines, and 3,4-dihydropyran (DHP) or 2,3-dihydrofuran in the presence of suitable catalysts.[9] Over the years, a number of reagents have been explored as catalysts to access these compounds, such as proline triflate,[10a] 4-nitrophthalic acid,[10b] SmI_2,[10c] $NbCl_5$,[10d] TMSCl,[10e] lanthanide triflates,[10f] silica chloride or amberlyst-15,[10g] $GdCl_3$,[10h] I_2,[10i] $SbCl_3$,[10j] and Cu $(OTf)_2$.[10k] Some of these methods are associated with certain limitations such as use of excess catalyst,[10h,10i] and some of them are very expensive[10f] and non-reusable catalysts. Consequently, there is further scope to find out a greener catalyst, which provides better yields and selectivity. In this paper, we would like to report $Fe_2(SO_4)_3{\cdot}xH_2O$ as a useful catalyst for synthesis of fused tetrahydroquinoline derivatives.

For the present study, the mixture of benzaldehyde (1 mmol), aniline (1 mmol), and 3,4-dihydropyran (DHP) (1 mmol) was treated with 10 mol % of $Fe_2(SO_4)_3{\cdot}xH_2O$ in acetonitrile (4 mL) at room temperature. Pyranoquinolines **3c** and **4c** were obtained in 54% combined yield with good diastereoselectivity (30:70). The products were characterized from ^1H NMR, ^{13}C NMR spectra, and by their elemental analysis.

For optimizing the amount of catalyst and choosing the suitable solvent, various trial reactions were carried out with a combination of 4-chlorobenzaldehyde, aniline, and 3,4-dihydropyran. The results and observations are summarized in Table S1 (Supplementary data). It was noted that 10 mol % of the catalyst provides the best result for the formation of product under reflux conditions. It has also been observed that acetonitrile is conducive for the present reaction as compared to other solvents, such as ethanol, dichloromethane, dimethylformamide, toluene,
and water.

After optimizing the reaction conditions, the mixture of benzaldehyde (1 mmol), aniline (1 mmol), and 3,4-dihydropyran (1 mmol) in acetonitrile was treated with 10 mol % $Fe_2(SO_4)_3{\cdot}xH_2O$

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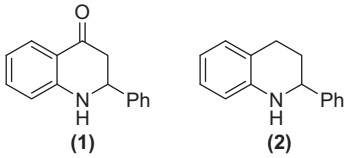


Figure 1. Biologically active tetrahydroquinoline derivatives.

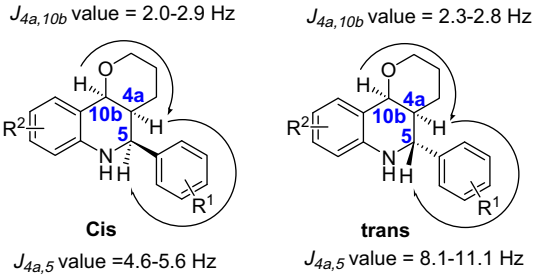


Figure 2. Coupling constant values used for determining stereochemistry.

under identical reaction conditions and the desired tetrahydroquinoline derivatives **3a** and **4a** were obtained in 87% combined yield. The stereochemistry of the fused ring junctures and other positions was established from their coupling constant values. The coupling constant between H_{4a} and H_{10b} ($J_{4a,10b}$) was found to be 2.0–2.9 Hz for all the products indicating a *cis* ring junction between the quinoline and pyran rings. Similarly, the coupling constant value between H_{4a} and H_5 ($J_{4a,5}$) was found to be 5.6 Hz in **3a** indicating the *cis* relationship, whereas the coupling constant value is 10.8 Hz in case of *trans* isomer **4a** as shown in Figure 2, which is in agreement with the reported literature value.[10d]

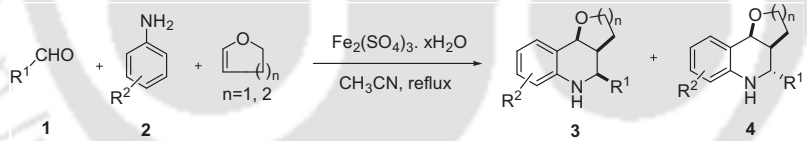
The reaction with various substituted aromatic aldehydes, such as Me, OMe, Cl, Br, and NO_2 with aniline and 3,4-dihydropyran were carried out under the same reaction conditions. The reaction time, percentage yield, and *cis:trans* ratio of the products **3** and **4** are shown in Table 1 (entries b–g). Likewise, various other aldehydes, such as 2-furaldehyde, 2-naphthaldehyde, and 3-methyl-2-thiophenecarboxaldehyde were reacted with aniline and dihydropyran under identical reaction conditions to provide the desired imino-Diels–Alder products (Table 1, entries h–j).

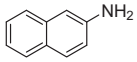
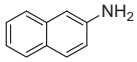
Furthermore, reactions with several substituted anilines were also studied with aromatic aldehydes and dihydropyran with the same amount of catalyst under similar reaction conditions (Table 1, entries k–o). The desired products **3k–o** and **4k–o** were obtained in good yields with similar diastereoselectivity. In the case of 2-naphthylamine, we have isolated the *trans* products **4p** and **4q** exclusively.

The structure of compound **4q** was determined through single crystal XRD data as shown in Figure 3.[12] Unfortunately, 4-hydroxybenzaldehyde did not provide the desired tetrahydroquinoline on reaction with amine and DHP under identical conditions even after prolonging the reaction for 12 h. Similarly, 4-nitroaniline also did not undergo Povarov reaction with other aromatic aldehydes. The scope of the presented protocol was verified with other enol ether, for example, 2,3-dihydrofuran (Table 1, entries r–t).

In view of a greener chemistry, the efficient recovery of the catalyst is highly desirable. In the present protocol, the catalyst $Fe_2(SO_4)_3{\cdot}xH_2O$ can be recovered conveniently from the reaction mixture at the end of the reaction. The reusability of the recovered

Table 1
Scope of various substituted pyrano/furanotetrahydroquinoline derivatives[11]



Entry	R^1	2	*n*	Time (h)	Yield[a] (%)	Ratio[b] (**3**:**4**)
a	Ph	$PhNH_2$	2	1.5	87	22:78
b	4-MeC_6H_4	$PhNH_2$	2	1.0	91	20:80
c	4-ClC_6H_4	$PhNH_2$	2	1.5	87	19:81
d	4-BrC_6H_4	$PhNH_2$	2	1.5	89	22:78
e	4-$MeOC_6H_4$	$PhNH_2$	2	1.0	88	19:81
f	3-$NO_2C_6H_4$	$PhNH_2$	2	1.5	84	23:77
g	4-$NO_2C_6H_4$	$PhNH_2$	2	1.5	86	18:82
h	2-furyl	$PhNH_2$	2	1.5	82	21:79
i	2-naphthyl	$PhNH_2$	2	1.5	86	21:79
j		$PhNH_2$	2	1.5	78	0:100
k	Ph	4-$MeC_6H_4NH_2$	2	1.0	92	20:80
l	Ph	4-$ClC_6H_4NH_2$	2	1.5	89	14:86
m	Ph	4-$MeOC_6H_4NH_2$	2	1.0	91	21:79
n	Ph	4-$BrC_6H_4NH_2$	2	1.5	87	17:83
o	4-ClC_6H_4	4-$ClC_6H_4NH_2$	2	1.0	91	20:80
p	Ph		2	2.5	82	0:100
q	2-naphthyl		2	1.5	85	0:100
r	4-MeC_6H_4	$PhNH_2$	1	1.5	87	23:77
s	2-furyl	$PhNH_2$	1	1.5	82	22:78
t	Ph	4-$ClC_6H_4NH_2$	1	1.5	85	21:79

[a] Isolated yields.
[b] The product ratio was determined from crude ^1H NMR spectra.

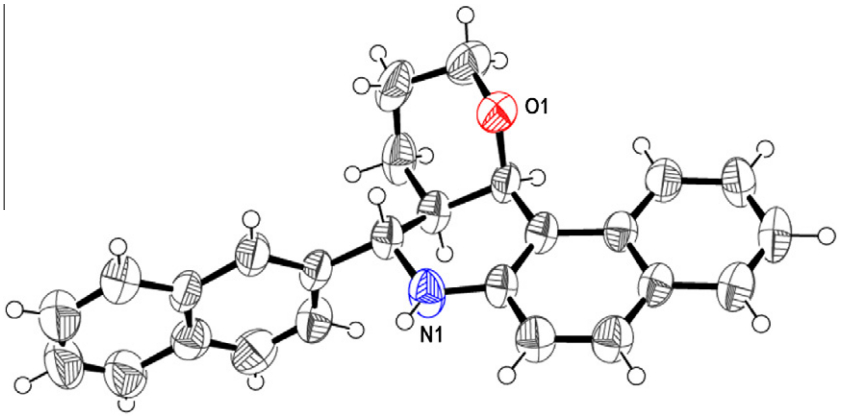
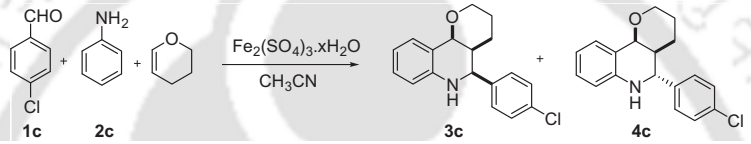


Figure 3. Single crystal X-ray structure of **4q** (CCDC No. 793766).

Table 2
Results of the study on the recovery and reusability of $Fe_2(SO_4)_3{\cdot}xH_2O$[a]



Round	Catalyst recovered/mg	Reaction time (h)	Ratio[b] **3c**:**4c**	Yield[c] (%)
1	415	1.5	19:81	87
2	410	1.5	21:79	86
3	405	1.6	20:80	84

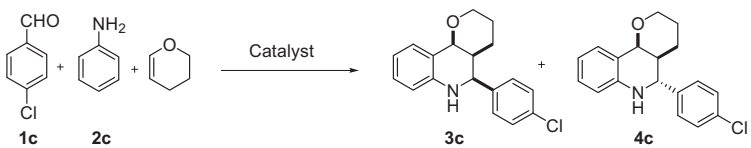
[a] Reaction was carried out with 10 mmol scale.
[b] The product ratio was determined from ^{1}H NMR spectra.
[c] Isolated yields.

catalyst was examined and the results are summarized in Table 2. It clearly indicates that the catalyst can be reused for three successive times without losing activity.

The efficiency and generality of the present protocol can be realized at a glance by comparing our results with those of some reported procedures as shown in Table 3. The results have been compared with respect to the mole percent of the catalyst used, yields, and diastereoselectivity. The similar Povarov reaction was reported by Laszlo and co-workers using $FeCl_3$ in combination of other co-catalyst.[13] It is worthy to mention that the present protocol provides better diastereoselectivity and avoidance of co-catalyst as compared to $FeCl_3$ method. Considering all these parameters, we believe that $Fe_2(SO_4)_3{\cdot}xH_2O$ is a better catalyst for Povarov reaction.

In conclusion, we have demonstrated $Fe_2(SO_4)_3{\cdot}xH_2O$ can be used for one-pot Povarov reaction for the synthesis of pyrano- and furano[3,2-c]quinoline derivatives. In comparison to other Lewis acids catalyst, it has been found to be effective, mild, and less expensive. In addition, it requires shorter reaction times, providing good yields and diastereoselectivity. Moreover, due to its recyclability, the present method may open up an environmentally benign pathway for the synthesis of fused pyrano- and furanotetrahydroquinolines.

Table 3
Comparison of our result with other results using different catalysts



Entry	Catalyst	Amount	Condition	Time (h)	Ratio[a] (3a:4a)	Yield[b,c]
1	$FeCl_3$	10 mol %	rt	6	50:50	82[13]
2	Proline triflate	5 mol %	rt	5	25:75	85[10a]
3	4-Nitrophthalic acid	25 mol %	50 °C	3.5	39:61	90[10b]
4	I_2	30 mol %	rt	3	23:77	84[10i]
5	$Fe_2(SO_4)_3{\cdot}xH_2O$	10 mol %	reflux	1.5	19:81	87[d]

[a] The product ratio was determined from ^{1}H NMR spectra.
[b] Isolated yields.
[c] Reported method with other catalysts.
[d] This present method.

Acknowledgments

D.K.D. is thankful to IIT Guwahati for his research fellowship. M.M.K. acknowledges UGC for his research fellowship. We are thankful to D.S.T. for providing XRD facility under the FIST programme.

Supplementary data

Supplementary data (optimization table, X-ray crystallographic data (CIF file) of **4q**, spectral data of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.080.

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11. *General procedure for the synthesis of tetrahydroquinoline derivatives:* Into a 25 mL round bottomed flask, a mixture of anilines (1 mmol) and aromatic aldehydes (1 mmol) in acetonitrile (2 mL) was taken and left for stirring for 10 min at room temperature. Then, both enol ether (1 mmol) and the catalyst ferric sulfate (0.042 g, 10 mol %) were added successively into the above reaction mixture. Finally, the reaction flask is fitted with a reflux condenser and kept for refluxing in an oil-bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was separated by filtration and usual work-up procedure was followed to obtain the crude products. The products **3** and **4** were eluted in ethyl acetate/hexane (05:95) in 78–92 yield after column chromatographic separation. Spectral data of some selected compounds: Compound **3d**: White solid (0.067 g, 20%); mp 124 °C; R_f (5% ethyl acetate/hexane) 0.34; IR (KBr): 3445, 3379, 2932, 2851, 1605, 1482 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (2H, dd, J = 6.4, 2.4 Hz), 7.42 (1H, d, J = 7.6 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.10 (1H t, J = 7.6 Hz), 6.81 (1H, t, J = 7.6 Hz), 6.60 (1H, d, J = 8.0 Hz), 5.31 (1H, d, J = 5.6 Hz), 4.65 (1H, d, J = 2.0 Hz), 3.82 (1H, br s), 3.61–3.57 (1H, m), 3.42 (1H, td, J = 11.6, 2.0 Hz), 2.12–2.11 (1H, m), 1.57–1.42 (3H, m), 1.30–1.25 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 140.4, 131.7, 128.7, 128.4, 127.8, 121.4, 120.2, 118.8, 114.8, 72.8, 60.8, 59.1, 39.1, 25.6, 18.2. Anal. Calcd for $C_{18}H_{18}BrNO$ (344.25): C, 62.80; H, 5.27; N, 4.07. Found: C, 62.98; H, 5.19; N, 4.01. Compound **4d**: White solid (0.239 g, 69%); mp 133 °C; R_f (5% ethyl acetate/hexane) 0.23; IR (KBr): 3312, 2937, 2838, 1613, 1487 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (2H, d, J = 8.4 Hz), 7.30 (2H, d, J = 7.6 Hz), 7.22 (1H, d, J = 7.6 Hz), 7.10 (1H, t, J = 7.6 Hz), 6.72 (1H, t, J = 7.6 Hz), 6.53 (1H, d, J = 8.4 Hz), 4.69 (1H, d, J = 10.8 Hz), 4.38 (1H, d, J = 2.4 Hz), 4.11–4.08 (1H, m), 4.03 (1H, br s), 3.72 (1H, td, J = 11.2, 2.0 Hz), 2.05–2.02 (1H, m), 1.83–1.75 (1H, m), 1.71–1.61 (1H, m), 1.47–1.42 (1H, m), 1.37–1.33 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 141.5, 131.9, 131.0, 129.6, 129.5, 121.7, 120.8, 117.8, 114.4, 74.5, 68.7, 54.4, 39.0, 24.2, 22.1. Anal. Calcd for $C_{18}H_{18}BrNO$ (344.25): C, 62.80; H, 5.27; N, 4.07. Found: C, 62.61; H, 5.19; N, 4.22. Compound **4q**: White solid (0.310 g, 85%); mp 214 °C; R_f (5% ethyl acetate/hexane) 0.19; IR (KBr): 3391, 3055, 2931, 2900, 2839, 1620, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.82 (5H, m), 7.64 (1H, d, J = 8.0 Hz), 7.56 (2H, t, J = 8.4 Hz), 7.50–7.42 (3H, m), 7.20 (1H, t, J = 7.6 Hz), 6.69 (1H, d, J = 8.8 Hz), 4.96 (1H, s), 4.26 (1H, br s), 4.17 (1H, dd, J = 10.8, 3.6 Hz), 3.83 (t, J = 11.2 Hz, 1H), 2.30–2.20 (m, 1H), 1.97–1.87 (qt, J = 4.0 Hz, 8.8 Hz, 1H), 1.70 (1H, tt, J = 9.2, 4.4 Hz), 1.51–1.45 (1H, m), 1.34–1.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 139.5, 133.9, 133.5, 133.4, 130.2, 128.7, 128.5, 128.1, 128.0, 127.9, 127.5, 127.2, 126.4, 126.2, 125.6, 122.0, 121.7, 117.9, 111.2, 71.4, 69.0, 54.9, 38.7, 24.3, 22.1. Anal. Calcd for $C_{26}H_{23}NO$ (365.18): C, 85.45; H, 6.34; N, 3.83. Found: C, 85.14; H, 6.39; N, 3.71.
12. *Crystallographic data.* The X-ray crystal structures were determined with a Siemens P-4 diffractometer. Complete crystallographic data of **4q** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 793766. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).
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A simple and expedient synthesis of functionalized pyrido[2,3-*c*] coumarin derivatives using molecular iodine catalyzed three-component reaction

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ABSTRACT

A wide variety of substituted pyrido[2,3-*c*] coumarin derivatives have been accomplished from 3-aminocoumarins, aromatic aldehydes, and alkynes in the presence of 10 mol % molecular iodine in acetonitrile under reflux conditions through one-pot Povarov reactions. Good yields, no need of aqueous work-up procedure and chromatographic separation, environmentally benign are some of the salient features of the present protocol.

Coumarins are a well-known important class of naturally occurring compounds[1] and they exhibit a wide range of pharmacological activities such as antifungal, antibacterial, antitumor, anti-HIV, antioxidant, and anti-inflammatory activities.[2] Among the various coumarin derivatives, 3-aminocoumarin structural moiety is present in many naturally occurring alkaloids such as ningalin B,[3a] lamellarin D,[3b] and santigonamin,[3c] which display many biological activities (Fig. 1). Interestingly, the same skeleton is also present in an antibiotic novobiocin,[4] which is produced by the actinomycete *Streptomyces niveus*.[4] It acts as a potent competitive inhibitor of the ATPase reaction catalyzed by GyrB. Moreover, pyridocoumarin derivatives are well known as CNS depressant,[5a] with antitumor,[5b] anti-inflammatory,[5c] and antimicrobial activities.[5d] Furthermore, they also exhibit interesting photochemical properties and have been used as laser dyestuffs,[6a–c] luminescence intensifiers,[7] and spasmolytics.[8]

These compounds are also considered as 'privileged structures' in the medicinal chemistry due to their immense potentiality.[9] Due to their wide range of biological activities, various research groups have put forward considerable efforts to synthesize these compounds in recent times.

From the literature it is found that only a few methods are known so far for the synthesis of pyrido[2,3-*c*] coumarin derivatives. The first synthesis of pyrido[2,3-*c*] coumarin was reported by Gremal and his co-worker[10a] from 3-aminocoumarin in moderate yield through Skraup reaction. A few years ago, Guillaumet et al. demonstrated the synthesis of these derivatives from 3-hydroxycoumarin in a three step sequence followed by dehydrogenation with DDQ.[10b] Later on, Majumdar et al. devised a new synthetic protocol for the synthesis of pyrido[2,3-*c*] coumarins[10c] through the palladium catalyzed intramolecular Heck reaction followed by dehydrogenation with 10% palladium charcoal. Later on, Bodwell and his co-workers reported the synthesis of pyrido[2,3-*c*] coumarin derivatives using $Yb(OTf)_3$ catalyst through the intermolecular Povarov reaction followed by oxidation with molecular bromine or nitrous gases.[10d] Very recently, the same group also reported the synthesis of pyrido[2,3-*c*] coumarins[10c] involving the intramolecular Povarov reaction from 3-aminocoumarin and 2-(propargyloxy)benzaldehyde in 45% yield after 9 days.[10e] The main demerits of the above protocols are low yield,[10a] requirement of expensive metal catalysts,[10c–e] and prolonged reaction time.[10e] Consequently, there is further scope to develop a synthetic methodology using a less expensive and environmentally benign catalyst. Very recently, we have reported the synthesis of fused heterocycles containing 3-aminocoumarin skeleton through multicomponent reactions (MCRs).[11] Therefore, we perceived 3-aminocoumarin could be exploited for the synthesis of pyrido[2,3-*c*] coumarin derivatives through multicomponent reactions.[12] Recently, we have also reported the synthesis of tetrahydroquinoline derivatives through the one-pot multicomponent reaction involving the Povarov reaction.[13] Therefore, we intended to explore the Povarov reaction for the synthesis of pyrido[2,3-*c*] coumarin derivatives from 3-aminocoumarins, aromatic aldehydes, and

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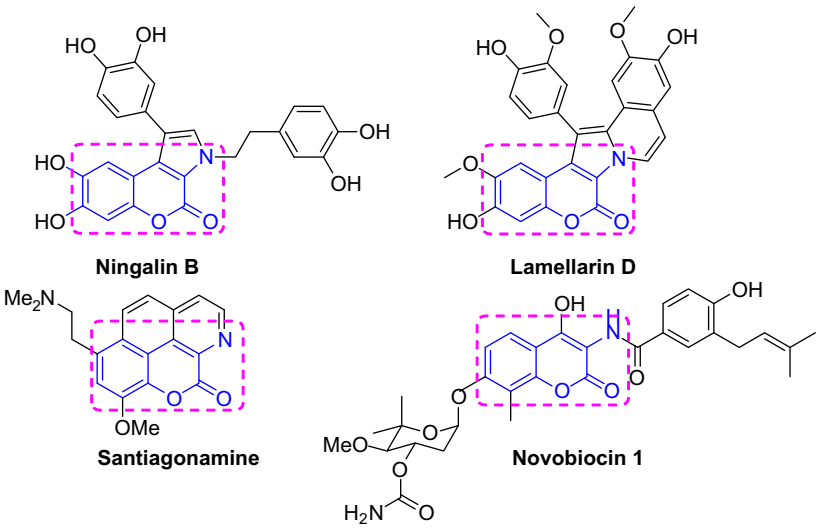
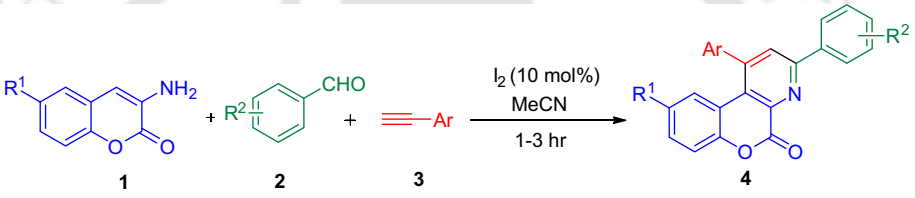


Figure 1. Some of naturally occurring potent alkaloids and antibiotic containing 3-aminocoumarin structural unit.



R^1 = H/ Br/ OMe
R^2 = H/Cl/Br/F/Me/MeO/CN/NO_2
Ar = C_6H_5-/4-$CH_3C_6H_4$-/4-*tert*-Bu-C_6H_4-/3,4-$(CH_3)_2C_6H_3$-/3,5-$(CH_3)_2C_6H_3$-/1-$C_{10}H_7$-

Scheme 1. One-pot synthesis of pyrido[2,3-*c*] coumarin derivatives.

phenylacetylenes. It is well established in the literature that the combination of aryl amines, aromatic aldehydes, and alkynes has been exploited for the synthesis of various quinoline derivatives through MCRs using molecular iodine in nitromethane[14a] or using expensive metal catalysts.[14b–f] Likewise, the synthesis of imidazo[1,2-*a*]pyridines was accomplished from 2-aminopyridine, aromatic aldehydes, and acetylenes.[15] Likewise, Majumdar et al. demonstrated of the synthesis of pyrano[3,2-*g*] quinoline derivatives using either 6-aminocoumarin or 6-amino quinolone through the Povarov reaction using $BF_3.OEt_2$.[16] In recent times, it is found that molecular iodine is a useful catalyst for MCRs since it is less expensive, non-toxic, easily available, and environmentally acceptable, which has been used for MCRs by us[17] as well as by others.[18] The importance and usefulness of molecular iodine in various organic transformations have been reviewed recently.[19] In this Letter, we wish to report the simplest, rapid, and one-pot synthesis of pyrido[2,3-*c*] coumarin derivatives involving molecular iodine via the imino-Diels–Alder reaction using 3-aminocoumarins, aromatic aldehydes, and phenylacetylenes as shown in Scheme 1.

For the present study, the mixture of 4-chlorobenzaldehyde (1 mmol), 3-aminocoumarin (1 mmol), and phenylacetylene (1.5 mmol) in 4 mL of acetonitrile was refluxed in the presence of 5 mol % of molecular iodine and the product pyrido[2,3-*c*] coumarin derivative **4b** was obtained in 68% yield (Table 1, entry 1). Product **4b** was characterized from ^{1}H NMR, ^{13}C NMR spectra, and elemental analysis. The same set of reactions were carried out using 10 mol % and 20 mol % I_2 (Table 1, entries 2 and 3) successively and the desired product **4b** was obtained in 82% and 78% yield, respectively. It was observed that the yield of the product was increased significantly by increasing the amount of catalyst from 5 to 10%.

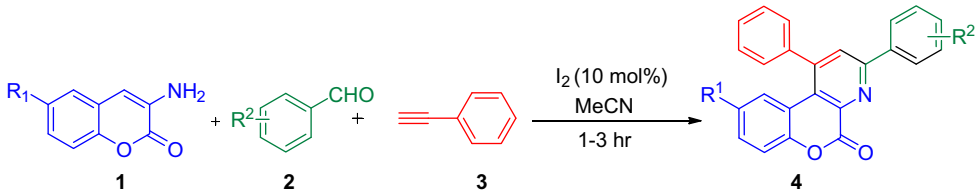
Table 1
Optimization of reaction conditions for the synthesis of pyrido[2,3-*c*] coumarin derivative (**4b**)[a]

Entry	Catalyst	Mol % of catalyst	Solvent	Reaction condition	Time (h)	Yield[b] (%)
1	Iodine	5	CH_3CN	Reflux	3.5	68
2	Iodine	10	CH_3CN	Reflux	2.5	82
3	Iodine	20	CH_3CN	Reflux	2.5	78
4	Iodine	10	CH_3NO_2	Reflux	2.5	78
5	Iodine	10	Toluene	Reflux	3.5	70
6	Iodine	10	DCE	Reflux	3.5	56
7	Iodine	10	EtOH	Reflux	6.0	42
8	Iodine	10	CH_3CN	rt	12.0	22
9	CAN	10	CH_3CN	Reflux	12.0	26
10	TfOH	10	CH_3CN	Reflux	12.0	48
11	$InCl_3$	10	CH_3CN	Reflux	12.0	36
12	AgOTf	10	CH_3CN	Reflux	12.0	00
13	No catalyst		CH_3CN	Reflux	12.0	00

[a] All the reactions were performed with 3-aminocoumarin (1.0 mmol), 4-chlorobenzaldehyde (1.0 mmol), and phenylacetylene (1.5 mmol).
[b] Isolated yields.

For scrutinizing the suitable solvent system, similar reactions (entries 4–7) were conducted in various solvent systems such as nitromethane, toluene, dichloroethane (DCE), and ethanol under reflux conditions, respectively. It was noted that the shortest reaction time and the best yield are obtained in acetonitrile (entry 2) under reflux conditions. It was also noted that a similar reaction can be performed with nitromethane in the same yield. However, all the reactions were carried out in acetonitrile because of its lower cost as well as toxicity than those of nitromethane. Interestingly, the same reaction provided low yield when it was carried out at

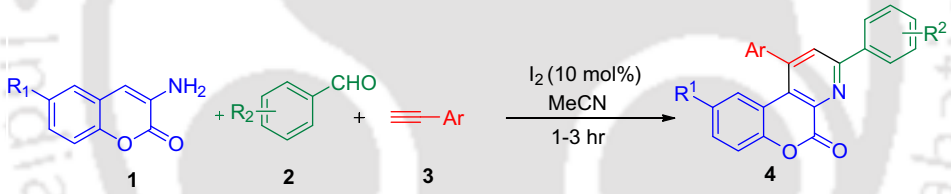
Table 2
Synthesis of various substituted pyrido[2,3-*c*] coumarin derivatives using Povarov reaction[a]



Entry	R_1	R_2	Product	Time (h)	Yield[b] (%)
1	H	H	**4a**	3	78
2	H	4-Cl	**4b**	2.5	82
3	H	4-Br	**4c**	1	88
4	H	4-F	**4d**	3	82
5	H	2-Cl	**4e**	3	72
6	H	4-Me	**4f**	1	88
7	H	4-OMe	**4g**	1	89
8	H	4-NO_2	**4h**	0.25	94
9	H	4-CN	**4i**	0.5	91
10	Br	4-Cl	**4j**	3	81
11	Br	4-Br	**4k**	3	78
12	Br	4-Me	**4l**	2	77
13	Br	4-MeO	**4m**	2	76
14	OMe	4-Cl	**4n**	2	78
15	OMe	4-Me	**4o**	2	76

[a] The reactions were carried out with 3-aminocoumarins (1.0 mmol), aromatic aldehydes (1.0 mmol), and phenylacetylene (1.5 mmol) in the presence of 10 mol % of iodine in 4 mL of CH_3CN under reflux conditions.
[b] Isolated yields.

Table 3
Synthesis of various substituted pyrido[2,3-*c*] coumarin derivatives using Povarov reaction[a]



Entry	R_1	R_2	Ar	Product	Time	Yield[b] (%)
1	H	4-Cl	4-$CH_3C_6H_4$–	**4p**	2	75
2	OMe	H	4-$CH_3C_6H_4$–	**4q**	2	72
3	OMe	4-F	4-$CH_3C_6H_4$–	**4r**	2	78
4	H	4-Cl	3,4-$(CH_3)_2C_6H_3$–	**4s**	2	76
5	H	4-Cl	3,5-$(CH_3)_2C_6H_3$–	**4t**	2	81
6	H	4-Cl	4-*tert*-Bu-C_6H_4-	**4u**	2	82
7	H	4-Cl	1-$C_{10}H_7$–	**4v**	2.5	78

[a] The reactions were carried out with 3-aminocoumarins (1.0 mmol), aromatic aldehydes (1.0 mmol), and substituted phenylacetylenes (1.5 mmol) in the presence of 10 mol % of iodine in 4 mL of CH_3CN under reflux conditions.
[b] Isolated yields.

room temperature (Table 1, entry 8). To examine the efficacy of molecular iodine as compared to other catalysts, several reactions were also scrutinized in the presence of catalysts like CAN, AgOTf, and $InCl_3$, respectively, (Table 1 entries 9–12).

After optimization of the reaction conditions, we performed a reaction with a mixture of 3-aminocoumarin, benzaldehyde, and phenylacetylene under identical conditions and the desired product **4a** was obtained in 78% yield. To explore the synthetic scope further and the generality of the present protocol,[20] various reactions were examined with a wide variety of aromatic aldehydes containing different substituents in the aromatic ring such as Cl, Br, F, Me, OMe, and NO_2 with 3-aminocoumarin and phenylacetylene, respectively. The reaction time and percentage yield of the products (**4b–i**) are shown in Table 2 (entries 2–9). It is worthwhile to mention that the pure products were isolated simply by filtration, which is purified by recrystallization from dichloromethane–hexane solvent system. For verifying the generality of the

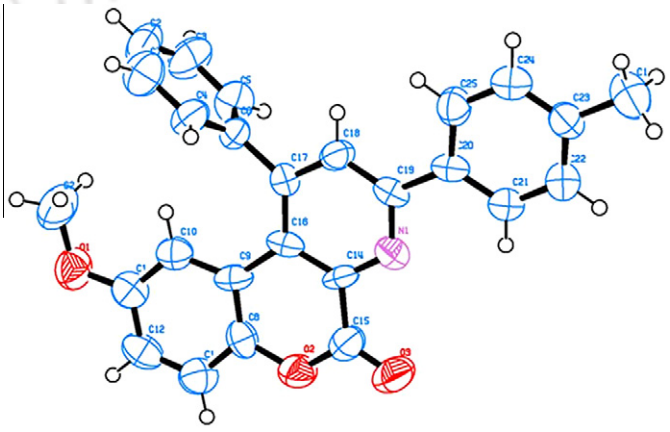
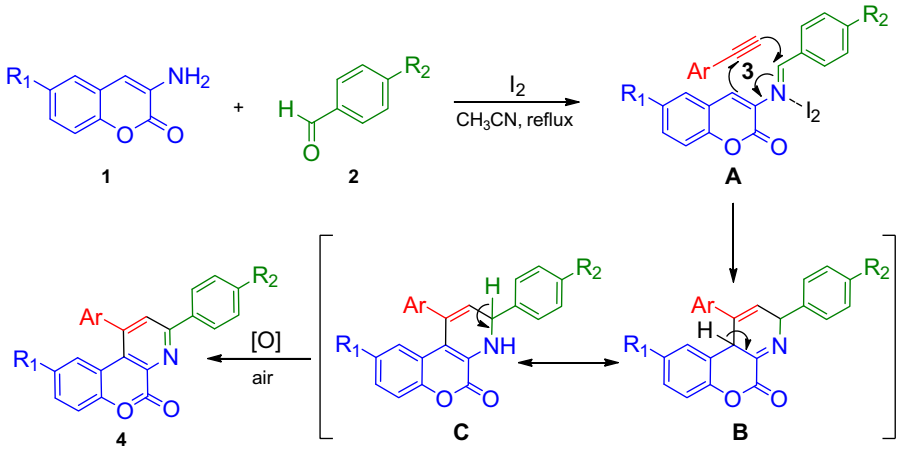


Figure 2. Single crystal X-ray structure **4o** (CCDC 876435).



Scheme 2. Mechanism for the synthesis of pyrido[2,3-*c*] coumarin derivatives.

present method, other substituted 3-aminocoumarins such as 6-bromo-3-aminocoumarin and 6-methoxy-3-aminocoumarin were also tested with aromatic aldehyde and phenyl acetylene under identical reaction conditions and the desired pyrido[2,3-*c*] coumarin derivatives **4j**–**o** were obtained in good yields (Table 2, entries 10–15).

Furthermore, the same reactions were also executed with different substituted phenylacetylenes with 3-aminocoumarin and aromatic aldehyde to give products **4p**–**v** (Table 3, entries 1–7). Unfortunately, we did not get the desired product when aliphatic aldehyde such as cyclohexaldehyde was treated with 3-aminocoumarin and phenylacetylene in the presence of I_2 under identical reaction conditions.

The structure of one of the representative compounds such as **4o** was confirmed unambiguously by single crystal X-ray diffraction analysis (see Supplementary data) (Fig. 2). All the structures were confirmed from ^{1}H NMR, ^{13}C NMR spectra, and from their elemental analysis.

The formation of the product may be explained as follows: We believe that the condensation reaction between 3-aminocoumarin (**1**) and aromatic aldehyde (**2**) leads to the formation of intermediate imines **A**, which undergoes the Povarov reaction with dienophile such as alkyne (**3**) to afford pyrido[2,3-*c*] coumarin derivatives **4** through the intermediate dihydropyridine **B** followed by aerial oxidation as shown in Scheme 2.

In conclusion, we have demonstrated a more efficient and expedient synthetic protocol for the synthesis of pyrido[2,3-*c*] coumarin derivatives by employing environmentally benign catalyst molecular I_2 via one-pot three-component condensation reaction from a wide variety of 3-aminocoumarins, aromatic aldehydes, and phenylacetylenes without involving any co-oxidant in good yields. In addition, co-oxidant such as nitromethane can be avoided which is harmful and expensive in the present protocol. The reaction condition is simple and transformation is quite effective for a wide range of aldehydes and phenylacetylenes. The products are easily isolable in good to excellent yields without aqueous work-up and chromatographic separation, and involvement of metal catalyst. The biological study of these compounds is still underway and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.051.

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20. *General procedure for the synthesis of pyrido[2,3-c] coumarin derivatives*: In a 25 mL round bottomed flask was taken a mixture of 3-aminocoumarin (1.0 mmol) and aromatic aldehyde (1.0 mmol) in 4 mL of acetonitrile. Then, phenyl acetylene (1.5 mmol) and 10 mol % of molecular iodine (0.025 g) were added successively into the above reaction mixture and the reaction flask was transferred for refluxing into a heated oil-bath. The progress of the reaction was monitored by checking TLC from time to time. Towards the end of the reaction a solid precipitate starts appearing slowly, after the stipulated time as mentioned in Tables 2 and 3. The reaction flask was then removed from the oil-bath and it was brought to room temperature for complete precipitation. The solid precipitate was just filtered through a Büchner funnel and it was washed with 10 mL of cold hexane–ethyl acetate mixture (1:1) to remove un-reacted starting materials. Finally it was dried through a vacuum pump and the pure product pyrido[2,3-*c*] coumarin derivative was obtained after recrystallization from dichloromethane and hexane.

*Spectrocopic data of the pyrido[2,3-c] coumarin derivatives: 1,3-diphenyl-5H-chromeno[3,4-b]pyridin-5-one (**4a**).* White powder (272 mg, 78%); [Found: C, 82.56; H, 4.41; N, 4.09. $C_{24}H_{15}NO_2$ (349.1103) requires C, 82.50; H, 4.33; N, 4.01]; mp 224–225 °C; R_f (30% ethyl acetate/hexane) 0.37; ν_{max}(KBr) = 3084, 1757, 1606 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.86–6.90 (m, 1H), 7.05 (d, *J* = 8 Hz, 1H), 7.34–7.38 (m, 2H), 7.42–7.51 (m, 5H), 7.52–7.60 (m, 3H), 7.96 (s, 1H), 8.11 (d, *J* = 7.6 Hz, 2 H); δ_c (100 MHz, $CDCl_3$) 117.20, 117.82, 123.83, 127.45, 127.60, 127.78, 128.34, 129.02, 129.25, 129.66, 130.30, 130.49, 137.18, 139.32, 139.84, 149.03, 150.98, 157.51, 159.12. HRMS (ESI): $[M+H]^+$, Found: *m*/*z* 350.1317. $C_{24}H_{15}NO_2$ requires 350.1103. *15.9-methoxy-1-phenyl-3-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one (**4o**):* White powder. (298 mg, 76%); [Found: C, 79.42; H, 4.92; N, 3.52. $C_{26}H_{19}NO_3$ (393.1365) requires C, 79.37; H, 4.87; N, 3.56]; mp 219–220 °C; R_f (10% ethyl acetate/hexane) 0.45; ν_{max}(KBr) 2986, 1745, 1598 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 8.13 (d, *J* = 8.0 Hz, 2H), 7.94 (s, 1H), 7.62–7.52 (m, 3H), 7.47 (d, *J* = 8.0, 2H), 7.32–7.28 (m, 3H), 6.93 (dd, *J* = 8.8, 2.8, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 3.25 (s, 3H, OMe), 2.43 (s, 3H, -Me); δ_c (100 MHz, $CDCl_3$) 159.28, 157.27, 155.23, 148.75, 145.14, 140. 58, 140.07, 139.20, 134.28, 129.72, 129.66, 129.08, 128.60, 127.83, 127.28, 126.97, 118.8, 118.59, 117.40, 109.76, 54.89, 21.49.

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Michael Initiated Ring Closure (MIRC) reaction on in situ generated benzylidenecyclohexane-1,3-diones for the construction of chromeno[3,4-*b*]quinoline derivatives

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ABSTRACT

One-pot synthesis of chromeno[3,4-*b*]quinoline derivatives have been achieved in good yields through Michael Initiated Ring Closure (MIRC) by employing three-component condensation of aromatic aldehydes, 3-aminocoumarins, and cyclic 1,3-diketones in the presence of catalytic amount of *p*-toluenesulfonic (*p*-TSA) acid in ethanol under reflux condition. The salient features of this protocol are: simple reaction procedure, shorter reaction time, good yields, avoidance of aqueous work-up, and column-chromatographic separation. The merit of this process is highlighted by its high bond efficiency of producing three new bonds and one stereocenter in a single operation.

The Michael Initiated Ring Closure (MIRC) reaction represents an elegant approach, which has been used extensively for the construction of cyclopropane rings,[1] carbocyclic compounds,[2] and small/medium sized nitrogen[3] or oxygen[4] containing heterocyclic compounds. The MIRC reaction strategy can also be cleverly achieved through one-pot multicomponent reaction, which is gaining interest to the synthetic organic chemists in recent times.[5] Multi-component reactions (MCRs) play an important role in the modern synthetic organic chemistry as they generally occur in a single pot and exhibit high atom-economy and selectivity.[6] They also provide a powerful synthetic tool for the synthesis of diverse and complex molecules as well as small and drug-like heterocycles.[7] We have perceived that cyclic 1,3-diketones may react with various aromatic aldehydes in the presence of a suitable acid catalyst to generate benzylidenecyclohexane-1,3-dione derivatives, which might be reacted instantly with carbon nucleophile such as 3-aminocoumarin through Michael type reaction followed by ring closure reaction leading to chromeno[3,4-*b*]quinoline derivatives. The similar synthetic strategy has also been demonstrated by others for the construction of 4-aza-2,3-didehydropodophyllotoxin[8a] and tricyclic dihydropyridine analogues,[8b] and pharmacological properties of these compounds have also been studied. Compounds containing 3-aminocoumarin framework are found in many natural products and some of them are used as antibiotic and antiviral agent.[9,10] For example, novobiocine is a 3-aminocoumarin derived antibiotic which acts as an ATP-competitive inhibitor of the gyrase B subunit, blocking the negative super-coiling of relaxed DNA.[9d,10] On the other hand, the pyrido[2,3-*c*]coumarin skeleton constitutes the backbone of santiagonamine (**B**), an alkaloid (Fig. 1).[11] As a result, there is a continuing effort to prepare this class of compounds for biological studies.*p*-Toluenesulfonic acid (*p*-TSA) is a readily available chemical which has been used extensively in place of mineral acids. In recent times, it was also used as an efficient acid catalyst for the synthesis of 4(3*H*)-quinazolinones,[12] the regiospecific nitration of phenols[13] and the carbonylation of formaldehyde.[14] As a part of our ongoing efforts to develop multi-component reactions to access potentially bioactive scaffolds,[15] we would like to report one-pot three-component reaction for the synthesis of chromeno[3,4-*b*]quinoline derivatives through MIRC reaction using condensation of aromatic aldehydes, cyclic 1,3-dicarbonyl compounds and 3-aminocoumarins under reflux condition in ethanol using *p*-TSA catalyst as shown in Scheme 1.

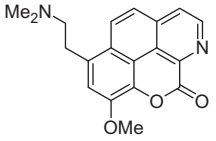

Figure 1. The naturally occurring biologically active alkaloid santiagonamine (**B**).

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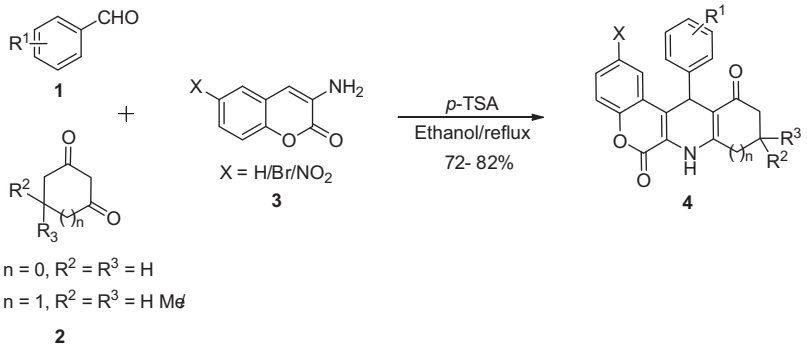


Scheme 1. One-pot three-component condensation reaction for the synthesis of chromeno[3,4-*b*]quinoline derivatives.

Table 1
Optimization of reaction conditions for the synthesis of chromeno[3,4-*b*]quinoline derivative **4a**[a]

Entry	Catalyst	Solvent	Catalyst (mol %)	Reaction condition	Time (h)	Yield[b] (%)
1	*p*-TSA	EtOH	5	Reflux	12	54
2	*p*-TSA	EtOH	10	Reflux	12	68
3	*p*-TSA	EtOH	20	Reflux	7	77
4	*p*-TSA	EtOH	30	Reflux	7	78
5	*p*-TSA	MeOH	20	Reflux	12	62
6	*p*-TSA	CH_3CN	20	Reflux	12	66
7	*p*-TSA	H_2O	20	Reflux	10	42
8	$ZnCl_2$	EtOH	20	Reflux	12	38
9	SiO_2	EtOH	20	Reflux	12	28
10	Et_3N	EtOH	20	Reflux	12	24
11	Piperidine	EtOH	20	Reflux	12	26
12	Acetic acid	EtOH	20	Reflux	24	22
13	HCl	EtOH	20	Reflux	24	00
14	No catalyst	*n*-BuOH	0	Reflux	24	00
15	*p*-TSA	*n*-BuOH	20	Reflux	4.5	75

[a] Reaction conditions: benzaldehyde, dimedone and 3-aminocoumarin were taken in 1:1:1 ratio.
[b] Isolated yields.

Table 2
Scope of various substituted chromeno[3,4-*b*]quinoline derivatives[a]

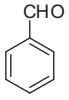
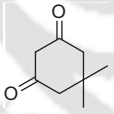
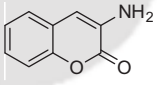
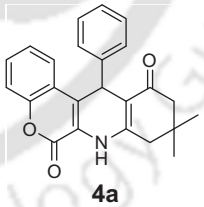
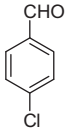
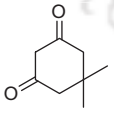
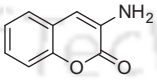
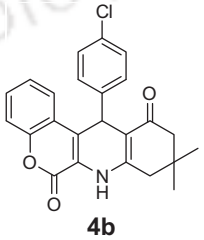
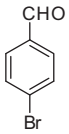
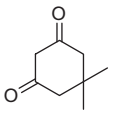
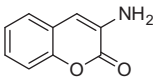
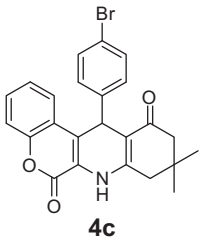
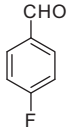
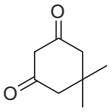
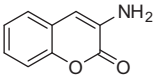
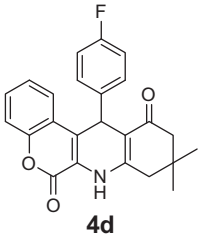
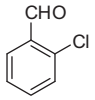
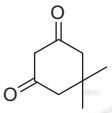
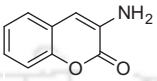
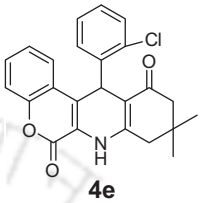
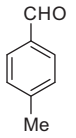
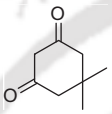
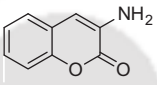
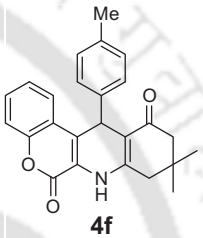
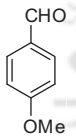
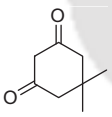
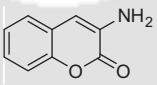
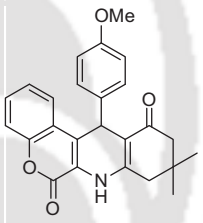
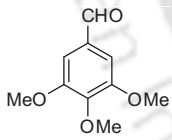
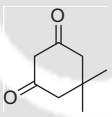
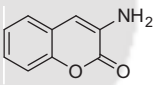
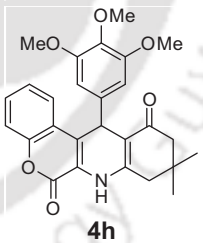
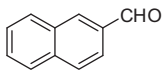
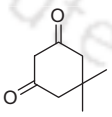
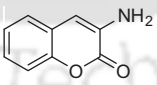
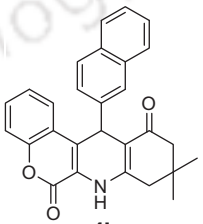
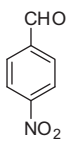
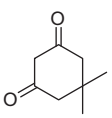
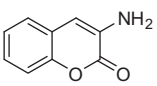
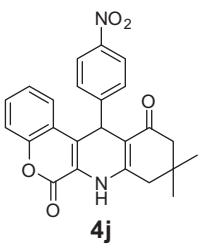
Entry	Aldehyde	1,3-Cyclic diketones	3-Aminocoumarin	Product	Time (h)	Yield[b]
1				 **4a**	7	77
2				 **4b**	8	78
3				 **4c**	8	82

Table 2 (*continued*)

Entry	Aldehyde	1,3-Cyclic diketones	3-Aminocoumarin	Product	Time (h)	Yield[b]
4				 **4d**	7	73
5				 **4e**	8	78
6				 **4f**	7	82
7				 **4g**	8	72
8				 **4h**	8	74
9				 **4i**	7	79
10				 **4j**	7	77

(*continued on next page*)

Table 2 (*continued*)

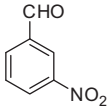
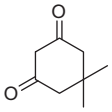
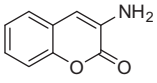
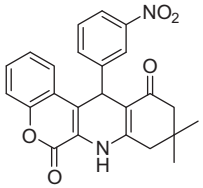
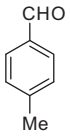
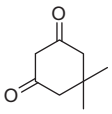
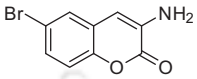
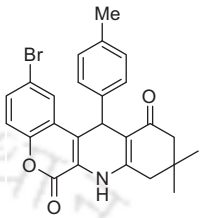
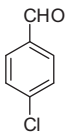
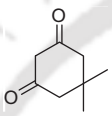
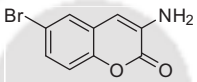
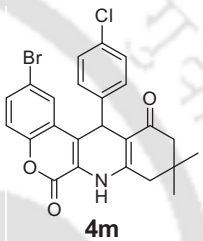
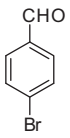
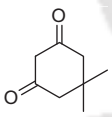
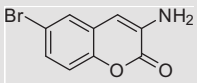
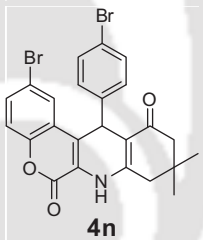
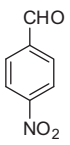
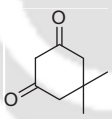
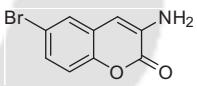
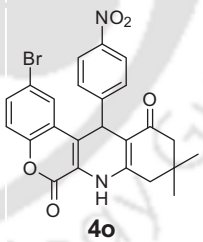
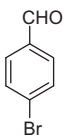
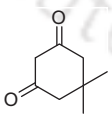
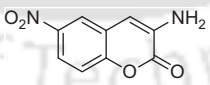
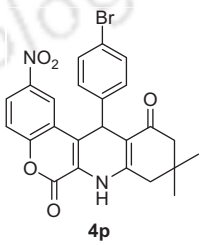
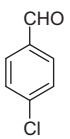
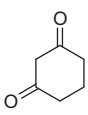
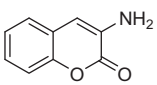
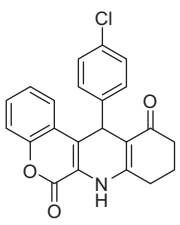
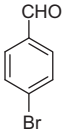
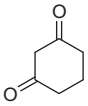
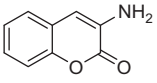
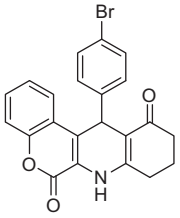
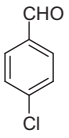
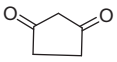
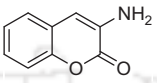
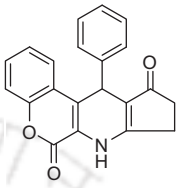
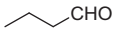
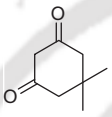
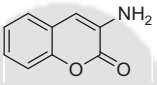
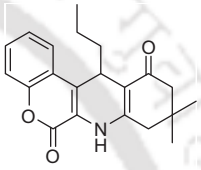
Entry	Aldehyde	1,3-Cyclic diketones	3-Aminocoumarin	Product	Time (h)	Yield[b]
11				 **4k**	7	76
12				 **4l**	7	81
13				 **4m**	7	74
14				 **4n**	8	76
15				 **4o**	7	79
16				 **4p**	7	72
17				 **4q**	7	77

Table 2 (*continued*)

Entry	Aldehyde	1,3-Cyclic diketones	3-Aminocoumarin	Product	Time (h)	Yield[b]
18				 **4r**	7	76
19				 **4s**	7	70
20				 **4t**	12	00

[a] Reaction conditions: aromatic aldehyde, 1,3-cyclic ketone and 3-aminocoumarin were taken in 1:1:1 ratio in presence of 20 mol % of *p*-TSA in ethanol under reflux conditions.
[b] Isolated yields.

To find the optimal conditions, a mixture of benzaldehyde (1.0 mmol), dimedone (1 mmol) and 3-aminocoumarin (1.0 mmol) was refluxed for 12 h in ethanol in the presence of 5 mol % *p*-toluenesulfonic acid and it provided the desired chromeno[3,4-*b*]quinoline derivative **4a** in 54% yield (Table 1, entry 1). The same reactions were also carried out successively using 10, 20, and 30 mol % *p*-TSA (Table 1, entries 2–4) to afford the desired product **4a** in 68%, 77%, and 78% yields, respectively. It was noted that the yield of the product **4a** did not increase significantly by increasing the amount of catalyst from 20% to 30%. For scrutinizing the suitable solvent system, the similar reactions (entries 5–7) were conducted in methanol, acetonitrile and water under otherwise identical reaction conditions, respectively and the highest yields and the shortest reaction times were obtained in ethanol. To examine the efficacy of the catalyst, several reactions were carried out in the presence of other acidic and basic catalysts (entries 8–11), respectively. From these observations, it seems to us that *p*-toluenesulfonic acid (*p*-TSA) is an optimal catalyst. We have also examined the reactions with protic acids such as acetic acid and conc. hydrochloric acid (entries 12 and 13). The reactions were very sluggish and incomplete even after 24 h of refluxing when the same reaction was carried out in presence of protic acid (Table 1, entries 12 and 13). We presume that *p*-toluenesulfonic acid provides a more optimal balance between the unprotonated fraction of amine and a protonated fraction of 1,3-diketone. The results are summarized in Table 1. To verify the role of temperature, we have carried out two reactions in the solvent *n*-butanol (bp 116–119 °C) with and without catalyst (entries 14 and 15). It is worthwhile to mention that the same reaction was complete relatively faster in *n*-butanol. Since the yield has not increased significantly and cost of the *n*-butanol is higher as compared to ethanol, all the reactions were performed in ethanol.

To explore the synthetic scope and the generality of the present protocol,[16] various reactions were performed with a wide variety of aromatic aldehydes containing different substituents in the aromatic ring such as Me, OMe, Cl, Br, F, and NO_2 with dimedone and 3-aminocoumarin. The reaction time and percentage yield of the products (**4b–k**) are shown in Table 2 (entries 2–11). It is interesting to note that the pure products of all these reactions can be obtained just by recrystallization of the crude materials from ethanol by avoiding aqueous work-up and tedious column-chromatographic separation.

For verifying the generality of the present approach, other substituted 3-aminocoumarins such as 6-bromo-3-aminocoumarin and 6-nitro-3-aminocoumarin[17] were also examined with aromatic aldehyde and dimedone under identical reaction conditions to provide the desired chromeno[3,4-*b*]quinoline products (Table 2, entries 12–16). Furthermore, the reactions with 1,3-cyclohexadione and 1,3-cyclopentadione with 3-aminocoumarin and aromatic aldehyde were also performed (Table 2, entries 17–19). When

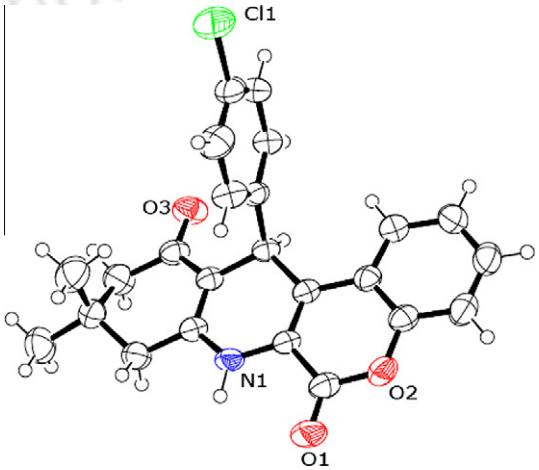
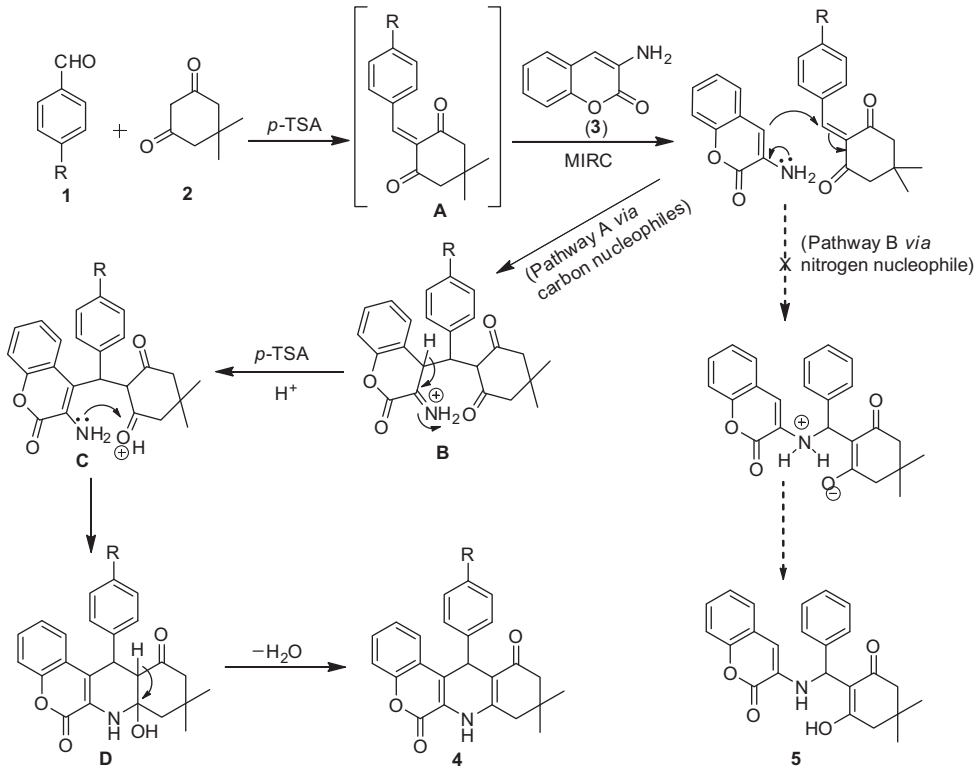


Figure 2. Single crystal X-ray structure **4b** (CCDC 827568).



Scheme 2. Proposed mechanism for the formation of products catalyzed by *p*-TSA.

aliphatic aldehydes such as acetaldehyde, or butyraldehyde was treated with cyclic 1,3-diketones and 3-aminocoumarin in the presence of *p*-TSA under identical reaction conditions, the desired product was not obtained (Table 2, entry 20). It was also noted that the similar transformation fails while the reaction was carried out with acyclic 1,3-diketone such as benzoylacetone.

Finally, the structure of one of the representative compounds such as 12-(4-chlorophenyl)-9,10-dihydro-9,9-dimethyl-7*H*-chromeno[3,4-*b*]quinoline-6,11(8*H*,12*H*)-dione (**4c**) was confirmed unambiguously by single crystal X-ray diffraction analysis (see the Supplementary data) (Fig. 2).

The formation of the product may be explained as follows: The first step is believed to be the condensation reaction between aromatic aldehyde (**1**) with dimedone (**2**) to give Knoevenagel product **A**, benzylidenecyclohexane-1,3-dione,[18] which can act as a suitable Michael acceptor as shown in Scheme 2. We have also tried to isolate the intermediate **A** by performing the reaction of dimedone and *p*-chlorobenzaldehyde in the presence of 10% *p*-TSA. But we did not get the intermediate **A**. Still we may believe that the intermediate **A** reacts with 3-aminocoumarin (**3**) at the position 4 of the coumarin ring to provide reactive intermediate **C**, which undergoes intra-molecular ring closure reaction followed by dehydration to give the desired chromeno[3,4-*b*]quinoline **4** as shown in ***Pathway A*** in Scheme 2. However, we did not obtain the product **5**, which may be possible by the nucleophilic attack of NH_2 group of 3-aminocoumarin to Knoevenagel adduct (A) as shown in ***Pathway B***. Thus in this reaction we observed selective behavior of 3-aminocoumarin as C-nucleophile rather than acting as N-nucleophile. It is reported by Kadutskii and Kozlov that reaction of aromatic amines, formaldehyde, and dimedone provides spirosubstituted piperidines,[19] which we did not observe in our present study.

In conclusion, we have disclosed the synthesis of novel heterocyclic compounds chromeno[3,4-*b*]quinoline derivatives (**4a–r**) using a high-yielding one-step multicomponent Michael Initiated Ring Closure (MIRC) reaction. It is worth mentioning that the three new bonds (two *C*–*C* and one *C*–*N*) and one stereocenter are formed in the course of reactions. This method is quite general which works for a wide variety of aromatic aldehydes, cyclic 1,3-diketones and different substituted 3-aminocoumarins. Shorter reaction times, environmentally benign, superior atom economy, the easy accessibility of the catalyst and its cost effectiveness, simplicity of the procedure and good to excellent yields are some of the most significant features of the present protocol. The biological study of these compounds is under investigation and their asymmetric synthesis will be reported in due course of time.

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Supplementary data

Supplementary data (X-ray crystallographic data (CIF files) of **4c** spectral data of all compounds and copies of ^{1}H and ^{13}C NMR spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.114.

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16. **General procedure for the synthesis of chromeno[3,4-*b*]quinoline:** A mixture of aromatic aldehyde (1.0 mmol), cyclic 1,3-diketone (1.0 mmol), and 3-aminocoumarin (1.0 mmol)[17] was taken in 3 mL of ethanol into a 25 mL round bottomed flask. Then, the catalyst anhydrous *p*-toluenesulfonic acid (0.034 g, 0.2 mmol) was added into it and the reaction mixture was refluxed in an oil bath. The progress of the reaction was monitored by checking TLC time to time. After the completion of the reaction, the solid precipitate appeared slowly under hot conditions at the stipulated time mentioned in the Table 2. Then the reaction mixture was brought to room temperature and the solid precipitate was filtered off on a Büchner funnel. The precipitate was washed with cold EtOH (1 mL) and it was dried finally on vacuum pump. The yields of the pure products, chromeno[3,4-*b*]quinoline derivatives, are shown in the Table 2.
Spectrocopic data of the chromeno[3,4-*b*]quinoline derivatives: *9,10-Dihydro-9,9-dimethyl-12-phenyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione* (**4a**). Yellow solid (285 mg, 77%); [Found: C, 77.68; H, 5.76; N, 3.83. $C_{24}H_{21}NO_3$ (371.15) requires C, 77.61; H, 5.70; N, 3.77%]; mp 237–239 °C; R_f (30% ethyl acetate/hexane) 0.33; ν_{max} (KBr) 3290 (NH), 1713 (C=O), 1623 (C=O), 1595 (C=C), 1567, 1504 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* = 8.0 Hz), 7.41 (2 H, d, *J* = 7.6 Hz), 7.35 (1H, d, *J* = 7.2 Hz), 7.30 (1H, d, *J* = 8.4 Hz), 7.26–7.19 (3 H, m), 7.14–7.10 (2H, m), 5.59 (1 H, s), 2.49 (1H, d, *J* = 16.4 Hz), 2.42 (1H, d, *J* = 16.4 Hz), 2.30 (1H, d, *J* = 16.4 Hz), 2.22 (1H, d, *J* = 16.4 Hz), 1.11 (3 H, s), 0.95 (3H, s); δ_c (100 MHz, $CDCl_3$) 195.28, 157.66, 150.70, 148.93, 144.16, 129.34, 128.79, 128.30, 127.16, 126.77, 125.29, 124.22, 121.94, 119.20, 116.91, 108.99, 50.89, 41.54, 36.74, 32.94, 29.42, 27.31; HRMS (ESI): MH^+, found 372.1596. $C_{24}H_{21}NO_3$ requires 372.1594.
17. 3-Aminocoumarin and substituted 3-aminocoumarins were prepared by following to the reported literature: (a) Kudale, A. A.; Kendall, J.; Warford, C. C.; Wilkins, N. D.; Bodwell, G. J. *Tetrahedron Lett.* **2007**, *48*, 5077–5080; (b) Valizadeh, H.; Shockravi, A. *Heterocycl. Commun.* **2004**, *10*, 475–478; (c) Beccalli, E. M.; Contini, A.; Trimarco, P. *Eur. J. Org. Chem.* **2003**, 3976–3984.
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