Exploration of Multicomponent Reactions for the Construction of Chromenes and Highly Substituted Benzene Derivatives

A Dissertation Submitted to the
Indian Institute of Technology Guwahati
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DOCTOR OF PHILOSOPHY

by

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Dedicated to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "*Exploration of Multicomponent Reactions for the Construction of Chromenes and Highly Substituted Benzene Derivatives"* is the result of investigations carried out by me under the supervision of Prof. Abu 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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17th October, 2016

Dr. M. Qureshi
(Thesis Co-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.

Suchandra Bhattacharjee

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GENERAL REMARKS

The present investigations were carried out at the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam during the period from 21st July, 2011 to 17thOctober 2016 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. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) was 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 Rota vapor using Büchi R-114V instrument. 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 MHz, Bruker 600 MHz and Varian 100 MHz, Bruker 150 MHz 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 recorded using ESI (TOF) mode. 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 296 K.

ABBREVIATIONS

Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
BDMS	bromodimethylsulfonium bromide
BETAC	benzyl triethyl ammonium chloride
Bn	benzyl
Bu	butyl
^{t}Bu	*tert*-Butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CCDC	Cambridge crystallographic data centre
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DCE	1,2-dichloroethene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPT 135	Distortionless Enhancement by Polarization Transfer.
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	*N*,*N*-dimethylaminopyridine
DMSO	dimethylsulfoxide
Et	ethyl
Et_3N	triethylamine
g	gram
h	hour
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High-resolution Mass Spectrometry
IR	infrared
LC-MS	Liquid chromatography–mass spectrometry
MCR	Multicomponent reaction
mp	melting point

MW	microwave
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid program
o-QM	*ortho*-quinone methide
Ph	phenyl
Pr	propyl
i-Pr	isopropyl
ppm	parts per million
Py	pyridine
p-TSA	*p*-toluenesulfonic acid
rt	room temperature
TBAB	tetrabutylammonium bromide
TBATB	tetrabutylammonium tribromide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
TfOH	triflic acid
w	weight
XRD	X-ray diffraction

Part A

Chapter I

Introduction of MCRs, Chromenes, Benzo[f]chromene and Flavones

1.1 Introduction

Heterocyclic compounds are widely distributed in nature. All 'Human beings' are made up of genes and these genes are in turn made up of DNA, which contains heterocycles like purine and pyrimidine as bases.[1] Besides these, some naturally occurringalkaloids[2] such as morphine, vinblastine, papaverine, phenazine; antibiotics[3] such as penicillin, cephalosporin etc possess heterocyclic moiety. Heterocyclic subunits are also found in vitamin B complex,[4] ascorbic acids,[5] chlorophyll,[6] hemoglobin,[7] ATP,[8] soft drinks,[9] dyes,[10] amino acids,[11] flowers, and fruits.[12] Consequently, the design of a structurally diverse heterocyclic compound is one of the driving forces for the development of organic chemistry. The ability to create new heterocyclic entities in an involuntary and efficient manner is fundamental in many fields; for instance, in the industry heterocyclic compounds are used[13] in making cosmetics, textiles, plastics, lubricants and paints. Moreover, they are most extensively used in pharmaceuticals, because 90% of the medicines like analgesic,[14] antitumors,[15] anticancer,[16] antihypertensive[17] drugs are made up of heterocyclic compounds.Therefore, the precise synthesis of heterocyclic compounds is one of the main aims for an organic chemist.

Multicomponent reactions[18] (MCRs) have been used very successfully to construct new heterocyclic molecules with relevant biological activity. These remarkable handy protocols have been known for over 150 years and occupy a central position in synthetic organic methodologies.[19]

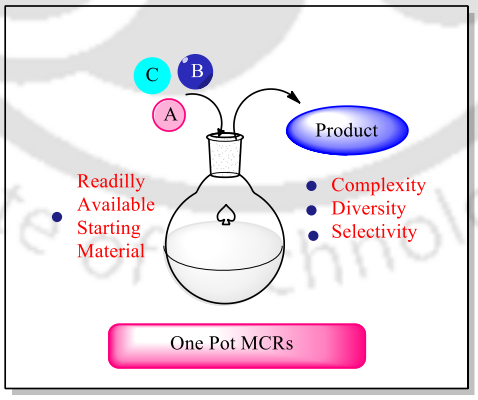


Figure 1. Schematic representation of MCRs

Multicomponent reactions can be defined[20] as "*The reactions where more than two reactants combine in a sequential manner, to give highly selective products that retain majority of the atoms of the starting materials''.* The schematic representation of multicomponent reactions is shown in Figure 1.

MCRs hold an advantageous position in modern organic synthesis because it provides the best way to generate complex molecules with various functional substituents from three or more readily available starting materials in a limited step.[21] These reactions have frequently been used to create ecofriendly, cost effective, and convenient chemical methods for the discovery of new chemical entities necessary for industries.[22] Moreover, multicomponent reactions are usually one pot synthesis, so, it is easy to accomplish the reactions with a good yield as compared to multistep synthesis[23] which is shown in Figure 2.

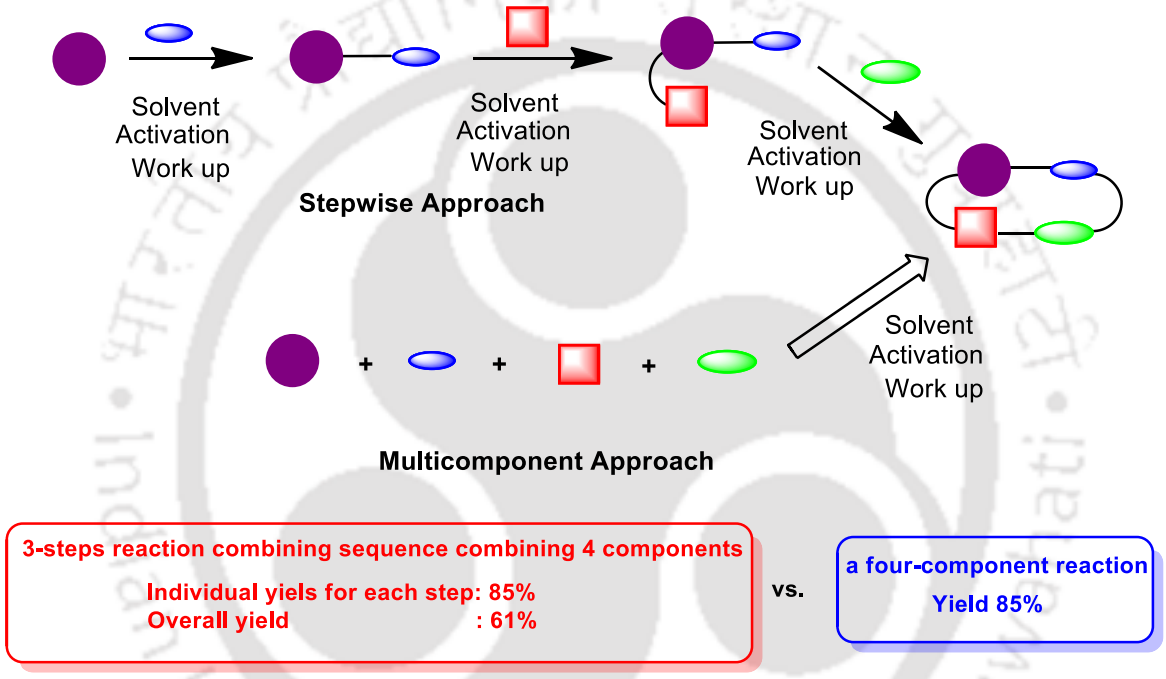
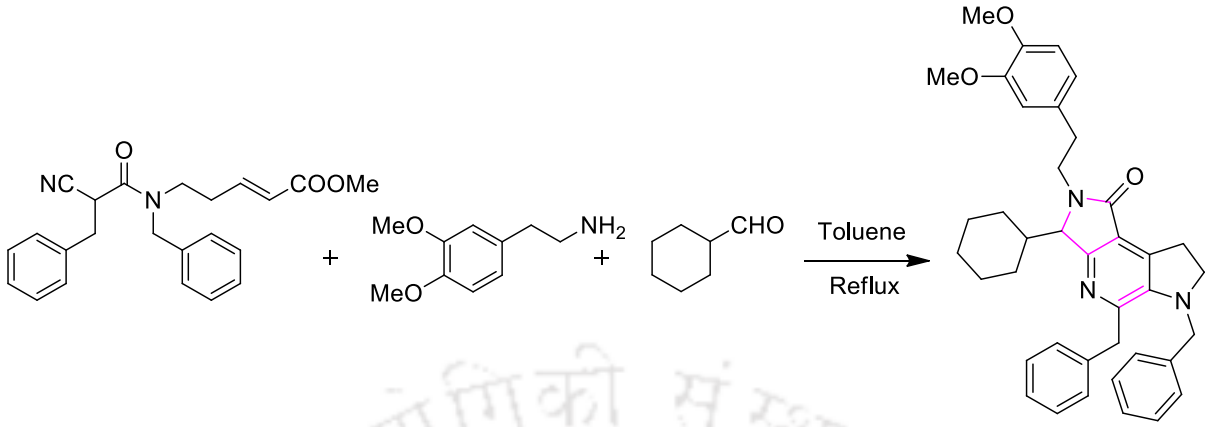


Figure 2.Schematic Representation of Multistep reactions and Multicomponent Reactions

The most important features of MCR's are numerous bond formations in a single step without changing the reaction conditions by adding more reagents. As a result, it minimizes the formation of by-products in the reactions. Scheme 1 shows an example of bond forming efficiency (BFE) of MCR.[24]



Scheme 1. BFE of MCR (BFE =5)

So, from the above discussions we can conclude that MCR has several significant advantages over conventional reactions, such as (i) high substrates variability (ii) readily available starting materials (iii) operationally simple (iv) reduced cost, reaction time and human labour (v) high bond forming efficiency (BFE) (vi) resource effective and (vii) superior atom economy etc.

1.2 History and Synthetic Utility of Multicomponent Reactions

The history of multicomponent reactions began at 1850 by Strecker, a huge footstep for the development of organic chemistry. Some remarkable developments are shown in Figure 3.

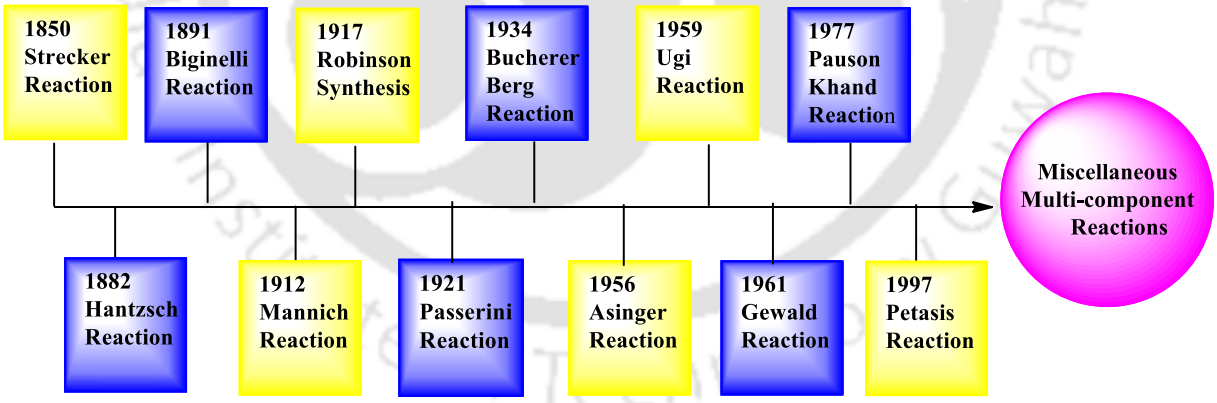
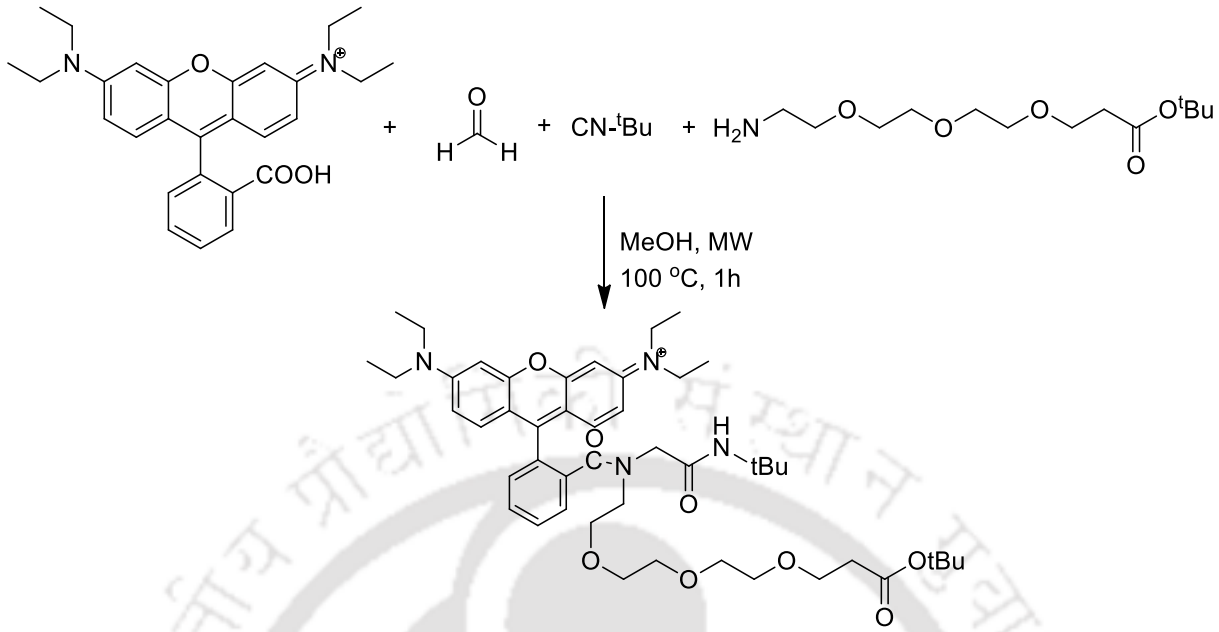


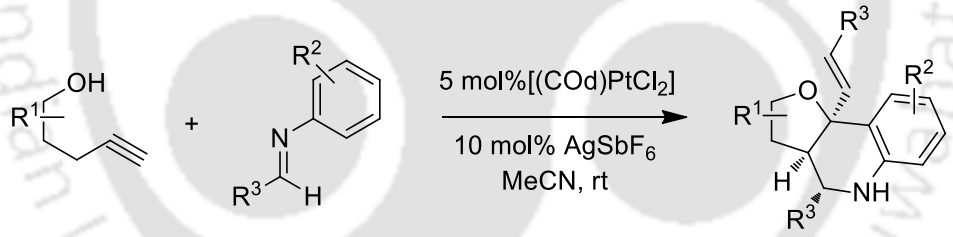
Figure3. Schematic Representation of the Development of MCRs

It was proved that Ugi-4-component Reaction is an excellent method for preparing rhodamine dyes[25] for protein detection by reacting rhodamine B which is a carboxylic acid, an amino ether and formaldehyde with *tert*-butyl isocyanides as shown in Scheme 2.



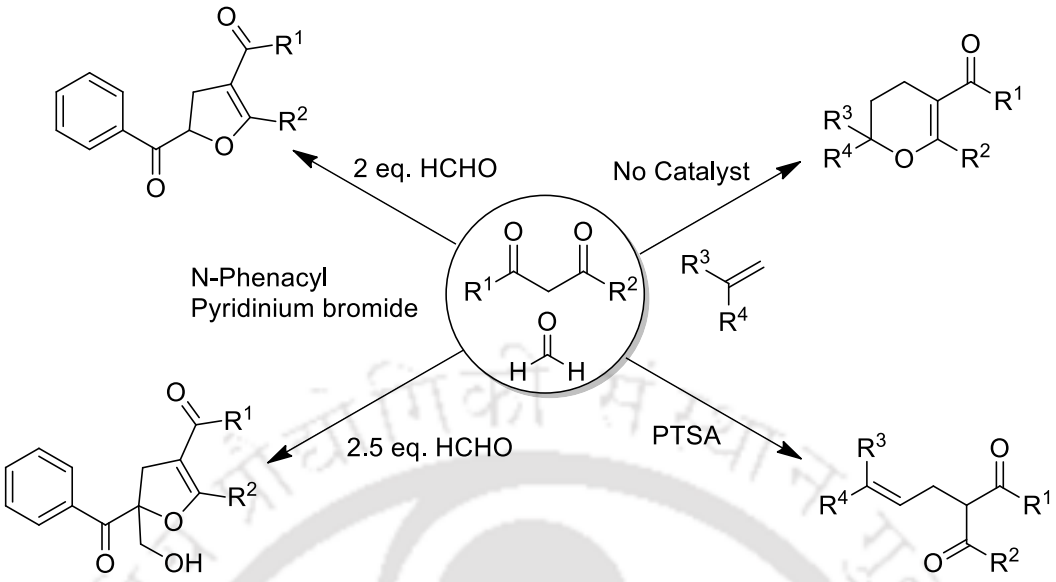
Scheme 2. Preparation of Rhodamine dye using Ugi-4-component reaction

Furoquinoline derivatives are alkaloids, mainly isolated from *Solanaceae* and *Rutaceae* plant species, were synthesised by Barluenga *et al.*[26] from*N*-arylaldimines and alkynol where platinum complex and silver salts are used as catalysts, shown in Scheme 3.



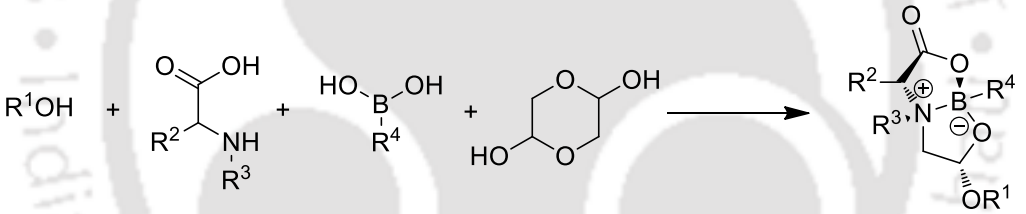
Scheme 3. Synthesis of Furoquinoline

Conditions dependent multicomponent reactions are clearly explained by Gu *et al.*[27] different products could be obtained selectively by changing the reaction parameters, from the same combination of starting materials, involving 1,3-dicarbonyl compounds and formaldehyde as shown in Scheme 4.



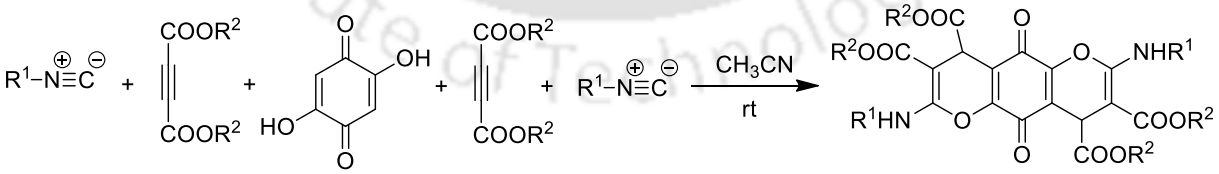
Scheme 4. Conditions dependent MCRs

Gois *et al.*[28] prepared natural product like framework *via* highly efficient one pot four component reactions, as shown in Scheme 5.



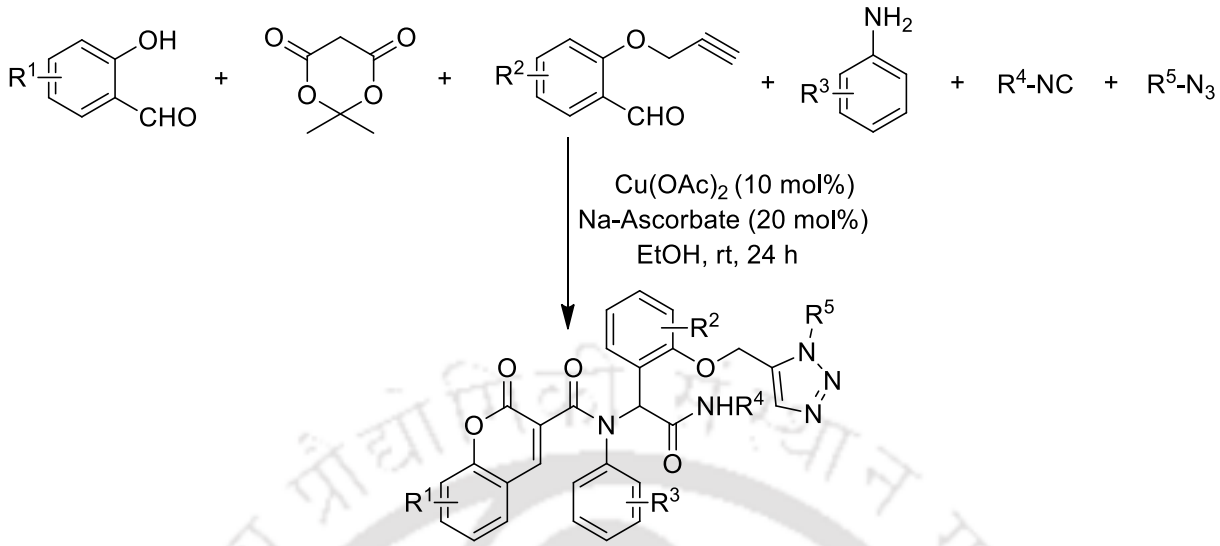
Scheme 5. One–Pot four component Reactions

Shaabani and his associates,[29] described the pseudo five component one-pot reactions for the synthesis of highly functionalised bis(4*H*-chromene) derivatives from readily available substrates as shown in Scheme 6.



Scheme 6. Preparation of bis(4*H*-chromene) derivatives

Recently, the one-pot six component reaction was also studied by the same group, where Shaabani *et al.*[30] efficiently synthesized coumarin-3-carboxamides compounds bearing a triazole ring as shown in Scheme 7.



Scheme 7. One-Pot Six-Component Multicomponent Reaction

The above discussion showed us the significant development of multicomponent reactions towards the synthesis of highly valuable heterocyclic entities. The thesis work is mainly focused on the synthesis of oxygen containing heterocycles using multicomponent reactions.

1.3 Chromene and its importance

Oxygen containing heterocycles are extensively distributed in nature. Especially, chromene moieties are commonly found in plants, edible vegetables and fruits.[31] Chromene is the IUPAC name of fused benzene and pyran ring given by Houben in 1904.[32] Classification of chromenes are based on the position and the type of substituent present on the ring. Out of 9 carbons, 8 carbons are sp^2 and one carbon is sp^3. Depending upon the position of sp^3 carbon of the polycyclic ring, chromenes are named as 2*H* and 4*H*- chromenes. Similarly, when sp^3 carbon is replaced by carbonyl functional group, the moiety named as 2*H*-chromene-2-one and 4*H*-chromene-4-one. The presence of aryl group at 2nd carbon of 4*H*-chromene-4-one gives a new moiety known as Flavone. Similarly, when the aryl group adhered to 3rd carbon it is known as Isoflavone and the aryl group stick on the 4th carbon of 2*H*-chromene-2-one is known as Neoflavone. Moreover, fusion of benzene or naphthalene ring to the chromene moiety generates various molecular structure as shown in Figure 4.

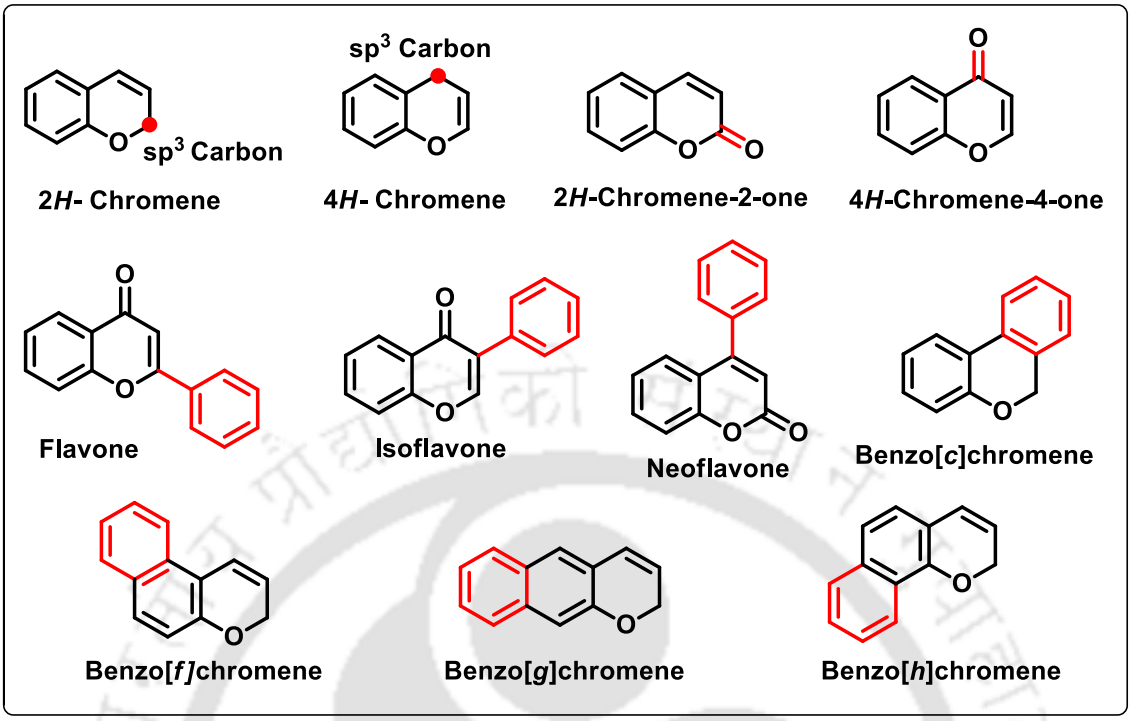


Figure 4. Different types of chromene moiety

Among the vast chromene family members, 4*H*-chromenes are quite unusual. The 4*H*-chromene scaffold and its derivatives exhibit useful biological and pharmacological activities.[33] Rhodomyrtone, rhodomyrtosone B are effective antibiotics,[34] CXLO17,[35] EPC2407[36] and MX58151[37] are used for various cancer treatments, among them, MX58151 is the promising anti-breast cancer agent. HA14-1[38] is an efficient apoptosis inducer for myeloid leukemia cells of the human being whereas acyl phloroglucinol, myrtucommulone E, are useful α-glucosidase inhibitor with antibacterial activity.[39] (+) Miroestrol and (+) Deoxymiroestrol were isolated from a plant '*KwaoKeur*' to prevent cancer growth.[40] Some examples of biologically active natural products containing 4*H*-chromene moiety are shown in Figure 5.

Fused chromenes have a broad therapeutic activities, such as antibacterial,[41] anticoagulant, anti-helminthic,[42] antiviral,[43] antiproliferative,[44] sex pheromone,[45] mutagenicity,[46] antitumor,[47] and central nervous system activity.[48] Benzo[*f*]chromene is a prime class of naphthopyran derivatives, widely implicated in material science and engineering, for its well-known photochemical and photo-physical properties.[49] More than 50 years ago, Becker *et al*.[50] studied the photochromic properties of naphthopyran derivatives. Since then, the scaffolds

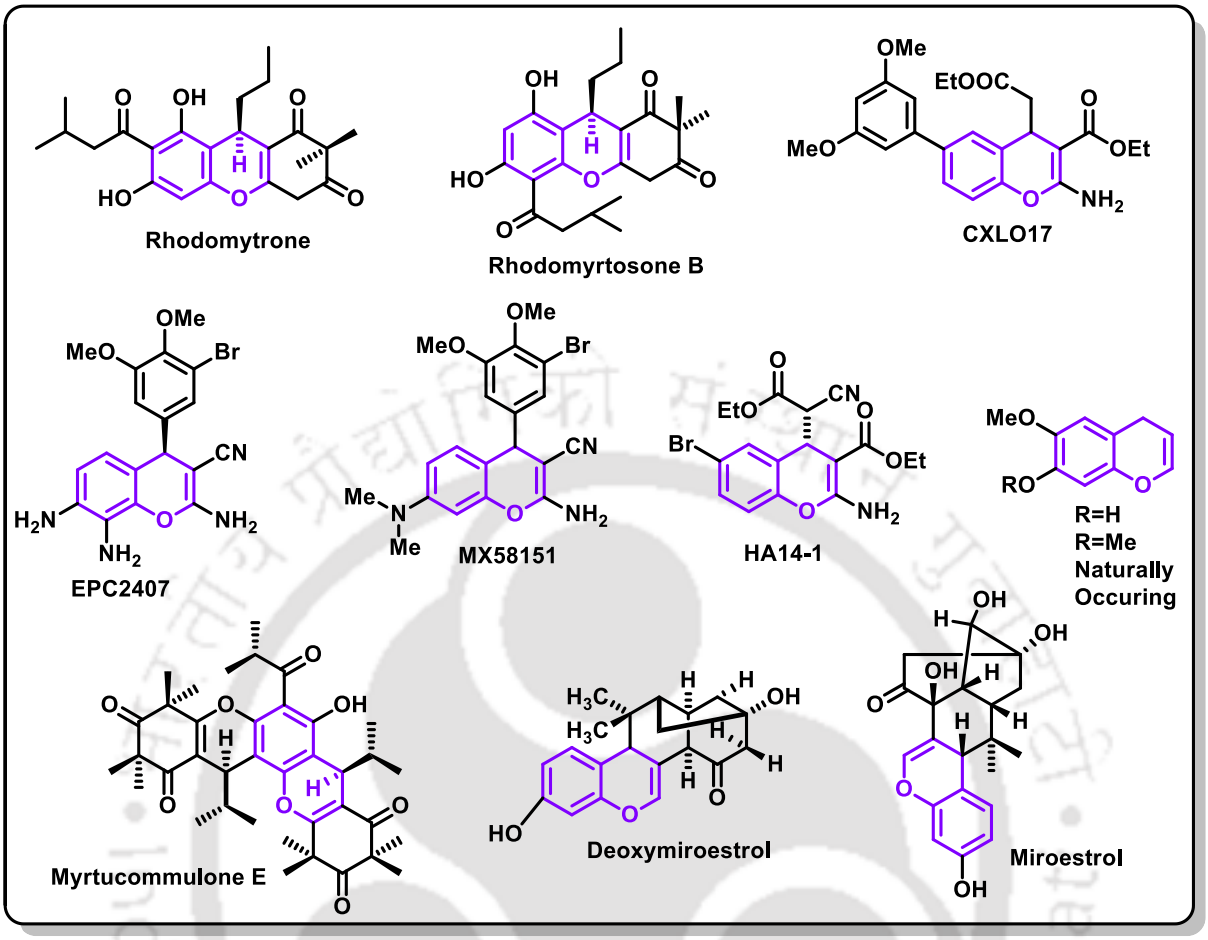


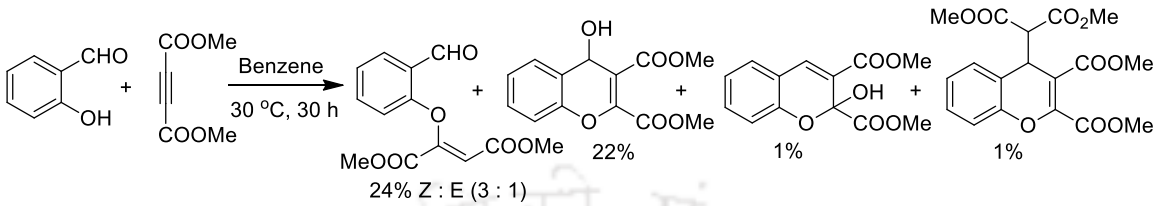
Figure 5.Naturally occurring and biologically active 4*H*-chromene moieties

are used for making ophthalmic lenses with high color ability, and rapid color reversibility; also employed in temporary or permanent memories, electronic display systems,optical switches, etc.[51] Silica-based nanoparticles with silylated benzo[*f*]chromene derivatives were promising photochromic nanomaterials, in respect of fast coloration and higher optical distinction.[52] From the roots of the plant, *Pentasbussei K. Krause*, methyl 5,10-dihydroxy-7-methoxy-3-methyl-3-[4-methyl-3-pentenyl]-3H-benzo[*f*]chromene-9-carboxylateis extracted, and the decoction of it is used as a medicine against syphilis, gonorrhea and dysentery.[53] Some other benzo[*f*]chromene derivatives are also exhibited antibacterial[54] and anticancer activities[55] studied by different research groups.

1.3a Synthetic methodology of 4*H*-chromene and benzo[*f*]chromenes derivatives

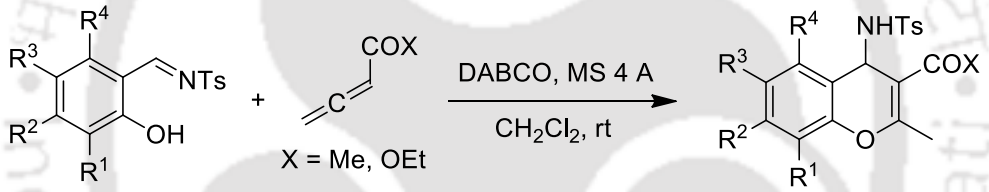
Due to their wide applications in various fields, it catches eye to the researcher for the development of 4*H*-chromene scaffolds. Very recently, number of methods has been reported, which are briefly described below.

In 1975, George *et al.*[56] depicted the reaction between salicylaldehyde and dimethyl acetylenedicarboxylate giving mixtures of chromenes and Michael addition adducts shown in Scheme 8.



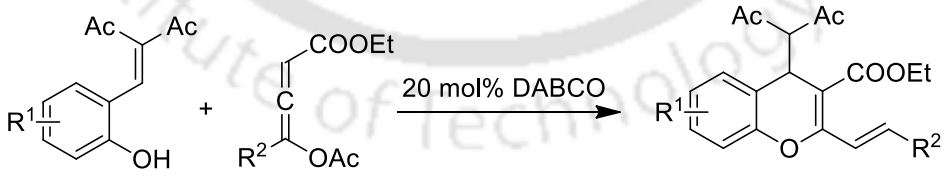
Scheme 8

Shi *et al.*[57a] synthesized the highly functionalized chromene derivatives from allenic esters and ketones with salicyl-*N*-tosylimines which is depicted in Scheme 9. Later on, the same group reported[57b] the reactions with diethyl acetylene carboxylate by modifying the reaction parameters.



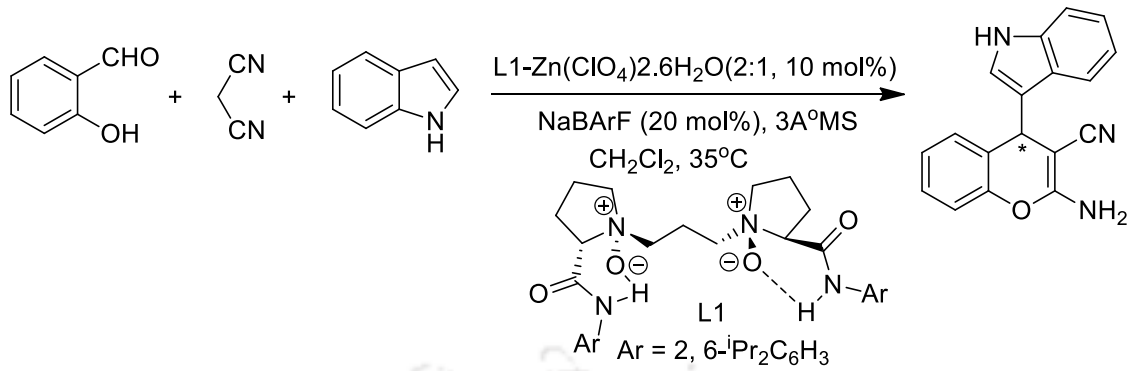
Scheme 9

Recently, Tong *et al.*[58] customized the reaction conditions by using allenoates with an aromatic group at δ carbon reacted preferably with salicylaldehyde derivatives delivering multisubstituted 4*H*-chromene derivatives, is represented in Scheme 10.



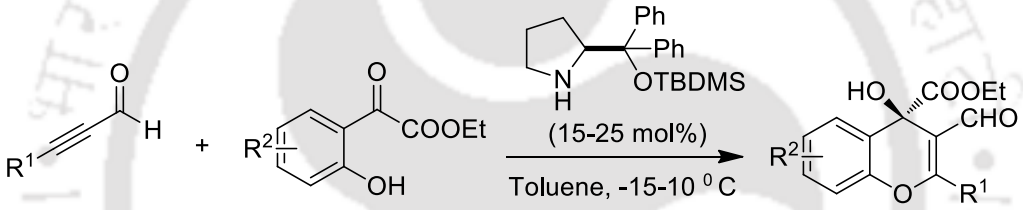
Scheme 10

Feng *et al.*[59] presented an enantioselective one-pot synthesis of 2-amino-4-(indol-3-yl)-4*H*-chromenes *via* a Knoevenagel/Pinner/Friedel-Crafts reaction of salicylaldehyde, malononitrile, and indole as shown in Scheme 11.



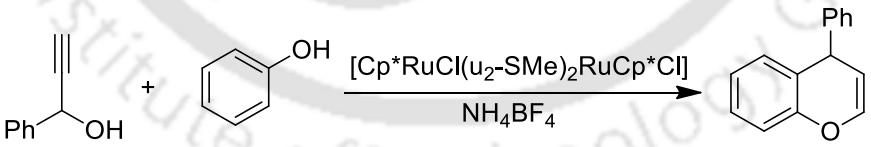
Scheme 11

Wang and his co-workers,[60] developed an enantioselective cascade Michael-aldol reaction by using an organo-catalyst for the synthesis of chiral 4*H*-chromene moiety as shown in Scheme 12.



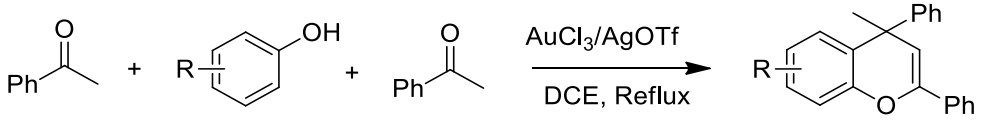
Scheme12

Cycloaddition of propargylic alcohol and phenol derivatives promoted by [Cp*RuCl(μ_2-SMe)$_2$RuCp*Cl] afforded 4*H*-chromene derivatives which was described by Uemura *et al.*[61] as shown in Scheme 13.



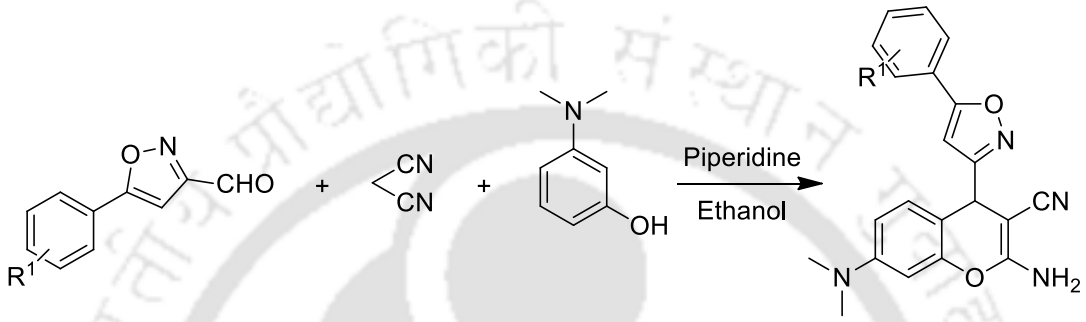
Scheme 13

Xu *et al.*[62a] have successfully synthesized 4*H*-chromene derivatives from ketone and phenol by using Gold (III) catalyst as shown in Scheme 14. Soon after, Wu and his collaborator prepared the moiety by exploiting TsOH.H_2O in a sealed tube at 100ºC.[62b]



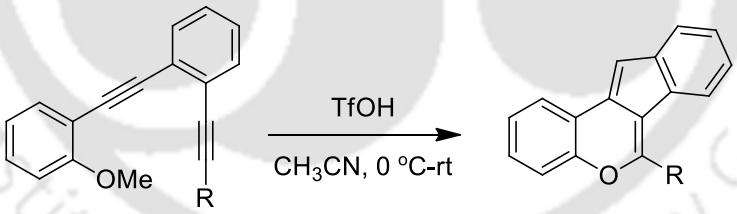
Scheme 14

Akbarzadeh *et al.*[63] explored the reaction of 5-arylisoxazole-3-carboxaldehydes, malononitrile and 3-(dimethylamino)phenol in in the presence of piperidine in EtOH afforded 2-amino-7-dimethylamino-4-(5-arylisoxazol-3-yl)-4*H*-chromene-3-carbonitrile as shown in Scheme 15. The synthesized compound was further studied against a group of five human tumor cell lines including MCF-7 (breast cancer), KB (nasopharyngeal epidermoid carcinoma), Hep-G2 (liver carcinoma), MDA-MB-231 (breast cancer), and SKNMC (human neuroblastoma).



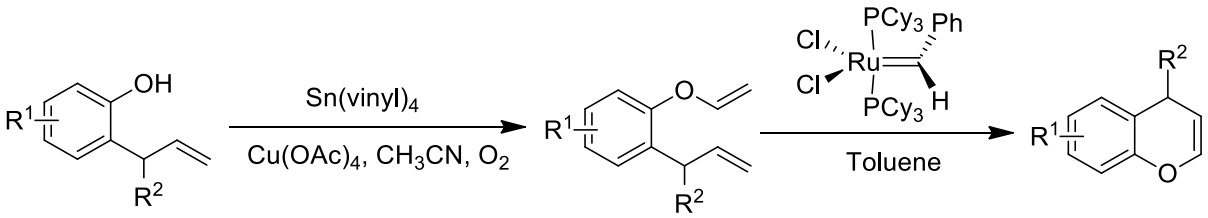
Scheme 15

Zin and his associates,[64] demonstrated a novel synthetic route for the synthesis of 4*H*-chromene derivatives from cyclization of ortho anisole substituted aryldiynes catalyzed by triflic acid (TfOH) at room temperature as shown in Scheme 16. Further, the synthesized compounds showed high photovoltaic performances in dyesensitized solar cells (DSCs).



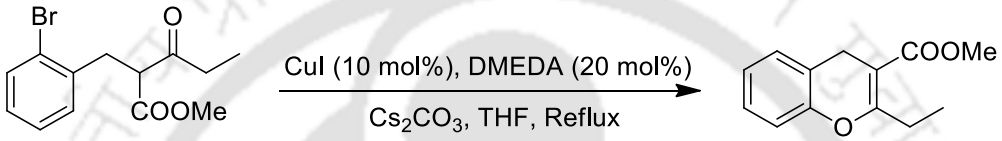
Scheme 16

The synthesis of 4*H*-chromenes by RCM was first reported by Van Otterlo *et al.*[65] from phenolic vinyl ether by using 5 mol% of Ruthenium complexes to deliver the targeted compound in good to excellent yields is depicted in Scheme 17.



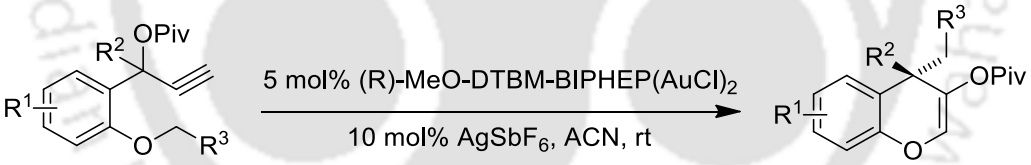
Scheme17

Li *et al.*[66] prepared 4*H*-chromene from, α-(2-bromobenzyl)-β-ketoester *via* O-arylation in the presence of *N, N*-dimethylethylenediamine, Cs_2CO_3 and catalytic amount of CuI (10 mol%) as shown in scheme 18.



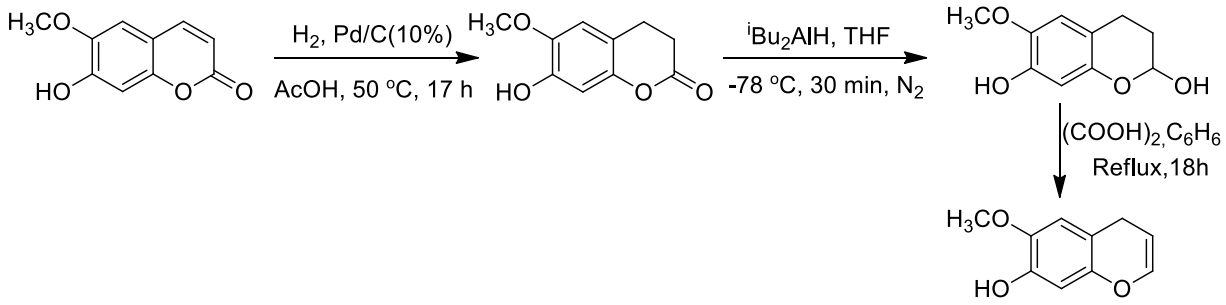
Scheme 18

Toste *et al.*[67] demonstrated a new route for the preparation of chromene moiety via rearrangement of allylicoxonium intermediates with the help of Gold (I) catalystis shown in Scheme 19.



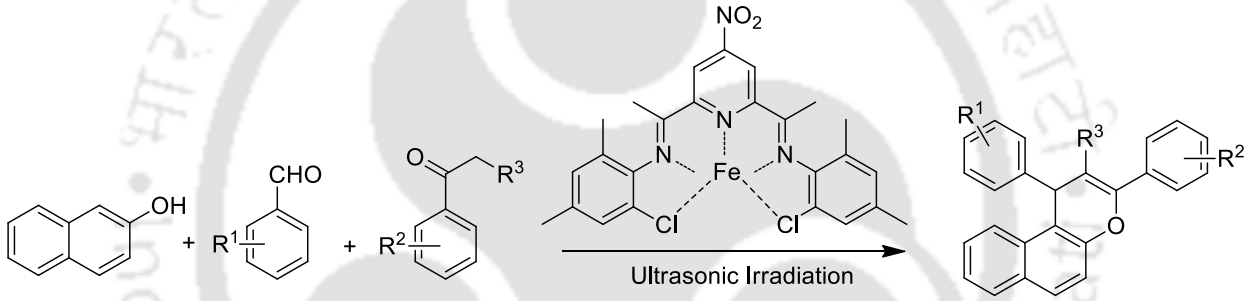
Scheme 19

An example of a naturally occurring 4*H*-chromene is 7-hydroxy-6-methoxy-4*H*-chromene which has interesting organoleptic properties was isolated from the plant *Wisteriasinensis* along with the compound 6,7-dimethoxy-4*H*-chromene (shown in Figure 5).[68] In 2002, De Kimpe and his co-workers[69] was efficiently synthesized the moiety by sequential reduction of double bond and carbonyl group asshown in Scheme 20.



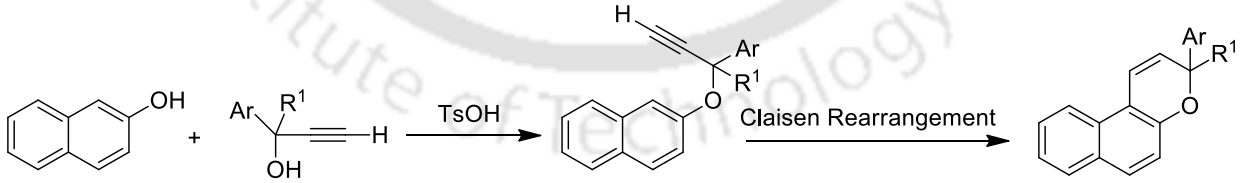
Scheme 20

Sandaroos *et al.*[70] synthesized trisubstituted benzo[*f*]chromene derivatives by pursuing one-pot three-component reaction of 2-naphthols, aromatic aldehydes, and acetophenone with the iron-based catalyst, 4-nitro-2,6-diacetylpyridinebis(2,4,6-trimethylaniline) $FeCl_2$, under ultrasonic conditions as shown in Scheme 21.



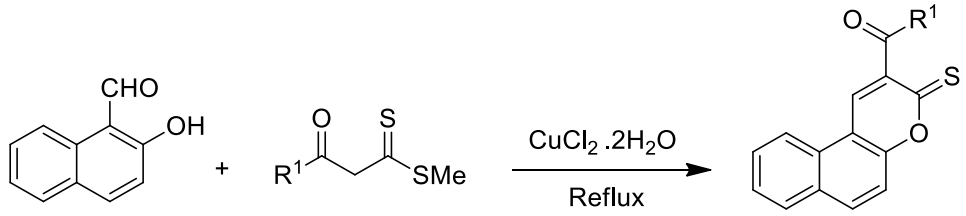
Scheme 21

Simple and efficient methods were described by Tanaka *et al.*[71] for the synthesis of benzo[*f*]chromene derivatives from 1,1-diaryl-2-propyn-1-ol and 2-naphthol in the solid state via Claisen rearrangement as shown in Scheme 22.



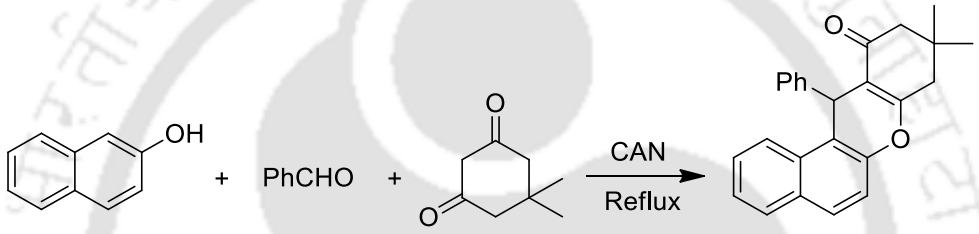
Scheme 22

Singh *et al.*[72] have been developed a facile route for the synthesis of benzo[*f*]chromenes derivatives by the condensation of readily available *β*-oxodithioesters with 2-hydroxy-1-naphthaldehyde in the presence of a catalytic amount of $CuCl_2$ as shown in Scheme 23.



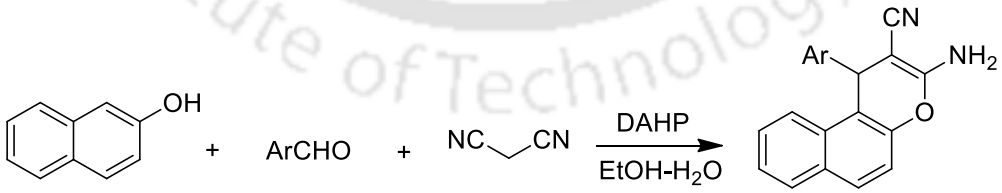
Scheme 23

Kumar *et al*.[54] focused on the synthesis of benzo[*f*]chromenes derivatives *via* one-pot three component reactions of 2-naphthol, benzaldehyde and dimedone using CAN under solvent free conditions as shown in Scheme 24. The derivatives were further studied for anti-proliferative activities and some of the compounds displayed major activity in various cancer cell lines.



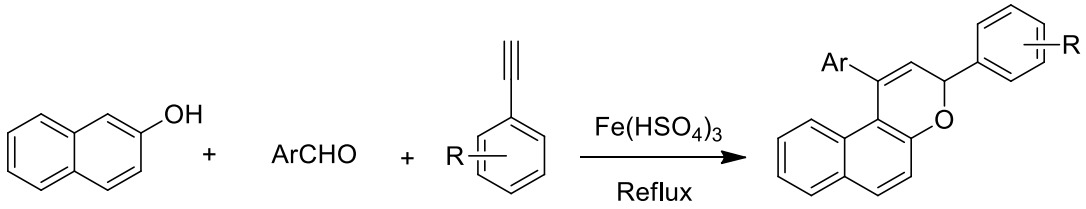
Scheme 24

Rafinejad *et al*.[73] depicted the one-pot three component reaction of *β*-naphthol, malononitrile and aromatic aldehyde in the presence of diammonium hydrogen phosphate for the synthesis of 2-amino-4-aryl-4*H*-benzo[*f*]chromene-3-carbonitrile derivatives as shown in Scheme 25 and all the synthesized compounds were judged for inhibition of Src kinase and cell proliferation in breast carcinoma (BT-20) cell lines. Some of the compounds showed Src kinas inhibitory effect with IC_{50} and most of the compounds are moderately active against BT-20.



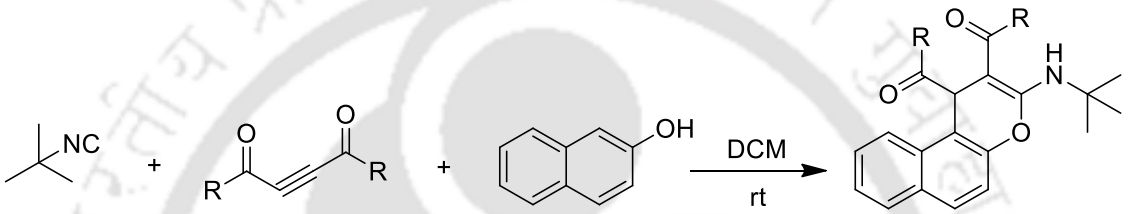
Scheme 25

A facile method for the synthesis of 3*H*-benzo[*f*]chromene derivatives from2-naphthol, aromatic aldehyde and phenyl acetylene in the presence of ferric hydrogen sulfate has been described by Eshghi *et al*.[74] as shown in Scheme 26.



Scheme 26

Yavari *et al*.[75] demonstrated the reaction of DMAD with *tert*-butyl isocyanide in the company of 2-naphthol proceeded spontaneously at room temperature in dichloromethane and successfully afforded benzo[*f*]chromene derivatives as illustrated in Scheme 27.



Scheme 27

1.4 Flavone and its importance

The name Flavone is derived from Latin word '*Flavus'* meaning 'Yellow' is a class of flavonoids. It is also known as 2-aryl-4*H*-chromene-4-one, are widely distributed in nature, chiefly found in cereals and herbs. Natural flavones such as quercetin, apigenin, luteolin, tangeritin, chrysin, baicalein, scutellarein, wogonin and so on are found in many plants, leaves, Citrus peels and flowers etc. Most of the naturally occurring as well as synthetic flavones are pharmacologically active because of their exceptional capability to regulate with various enzyme systems.[76] Apigenin is a strong inhibitor of CYP2C9,[77] an enzyme responsible for the metabolism of many pharmaceutical drugs in human body.Wogonin has been found to possess anticonvulsant effects.[78] Quercetin is renowned for its anti-oxidant activity,[79] whereas Tangeritin induced apoptosis in leukemia cells without effecting normal cells.[80] Some of the naturally occurring, biologically active flavones have been represented in Figure 6.

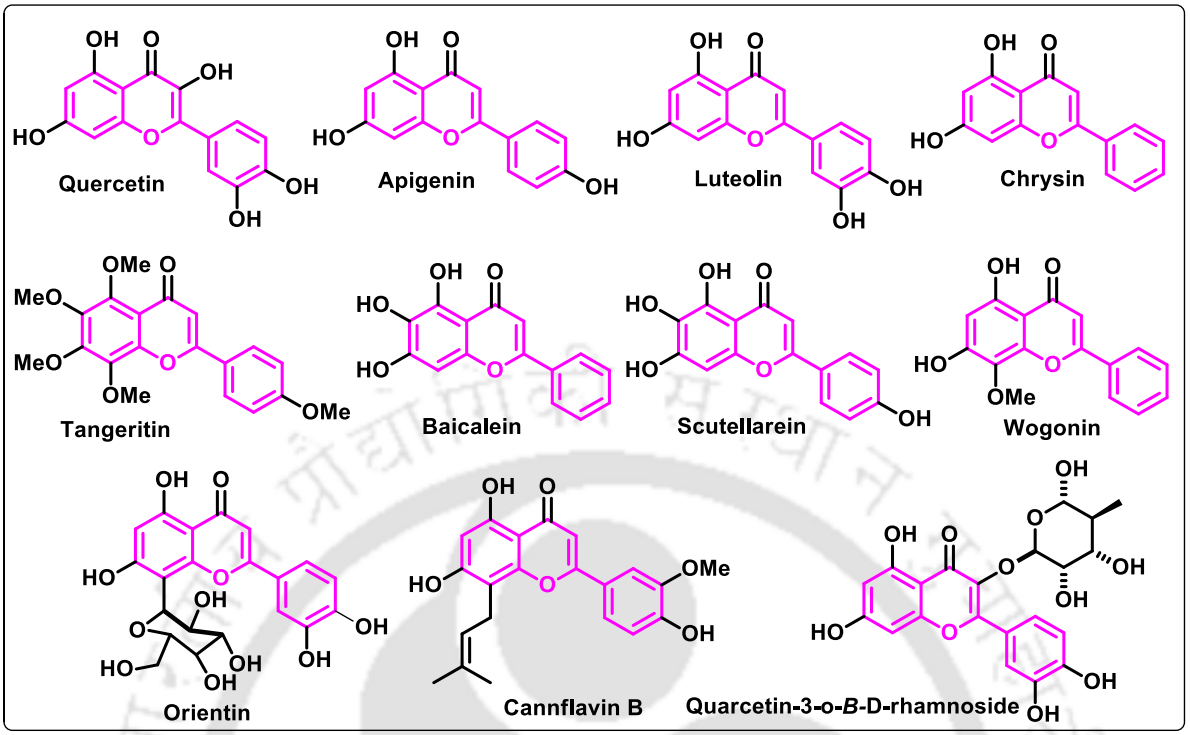


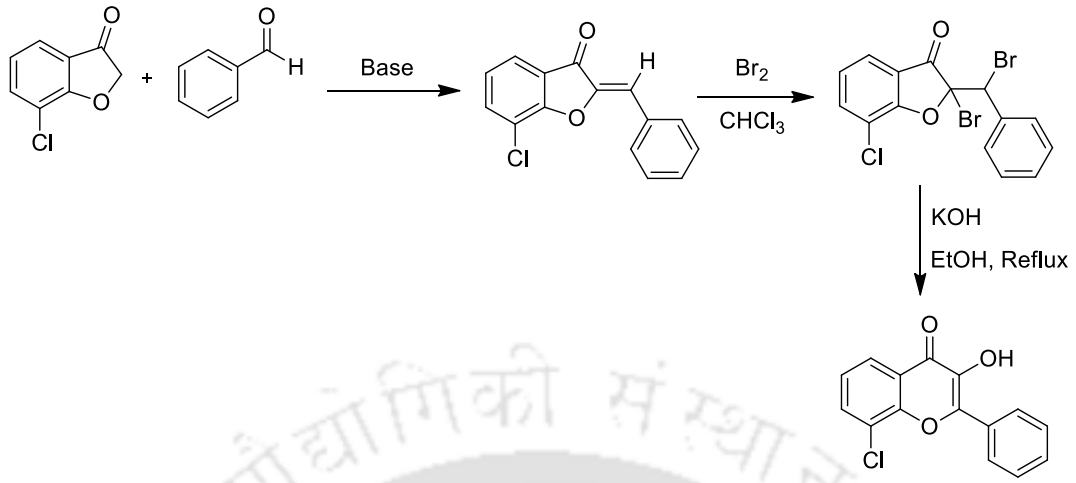
Figure 6. Naturally occuring Flavone moieties

1.4a Synthetic methodology of Flavone derivatives

The synthesis of Flavones and their derivatives has fascinated considerable attention of organic and medicinal chemists for many years, as a large number of biologically active molecule contain this oxygen containing a heterocyclic nucleus.

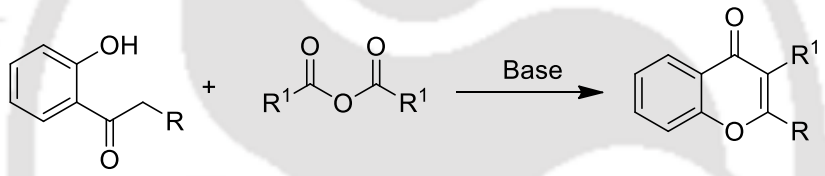
The Auwers synthesis, the Allan–Robinson reaction, the Baker–Venkataraman rearrangement and the Algar–Flynn–Oyamada reaction, are some of the fundamental reactions used for the synthesis of Flavone derivatives, which are briefly described below.

In 1908, Karl Von Auwers[81] first reported the synthesis of flavone derivatives from benzaldehyde and coumarone via series of organic reactions as depicted in Scheme 28.



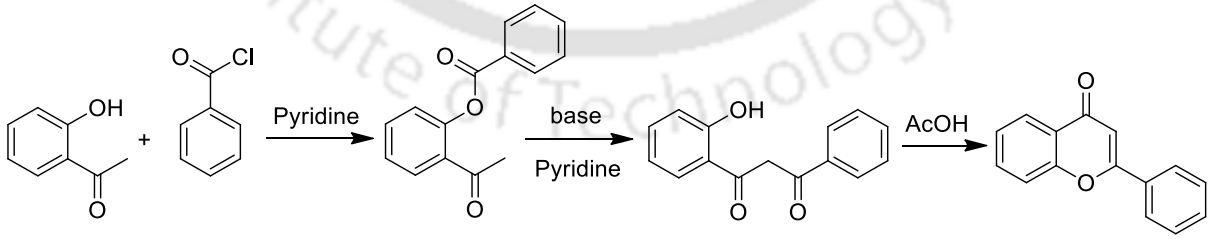
Scheme 28

In 1924 Allan–Robinson[82] synthesised flavone from the reaction of *o*-hydroxyaryl ketones and aromatic anhydride and their sodium salts as shown in Scheme 29.



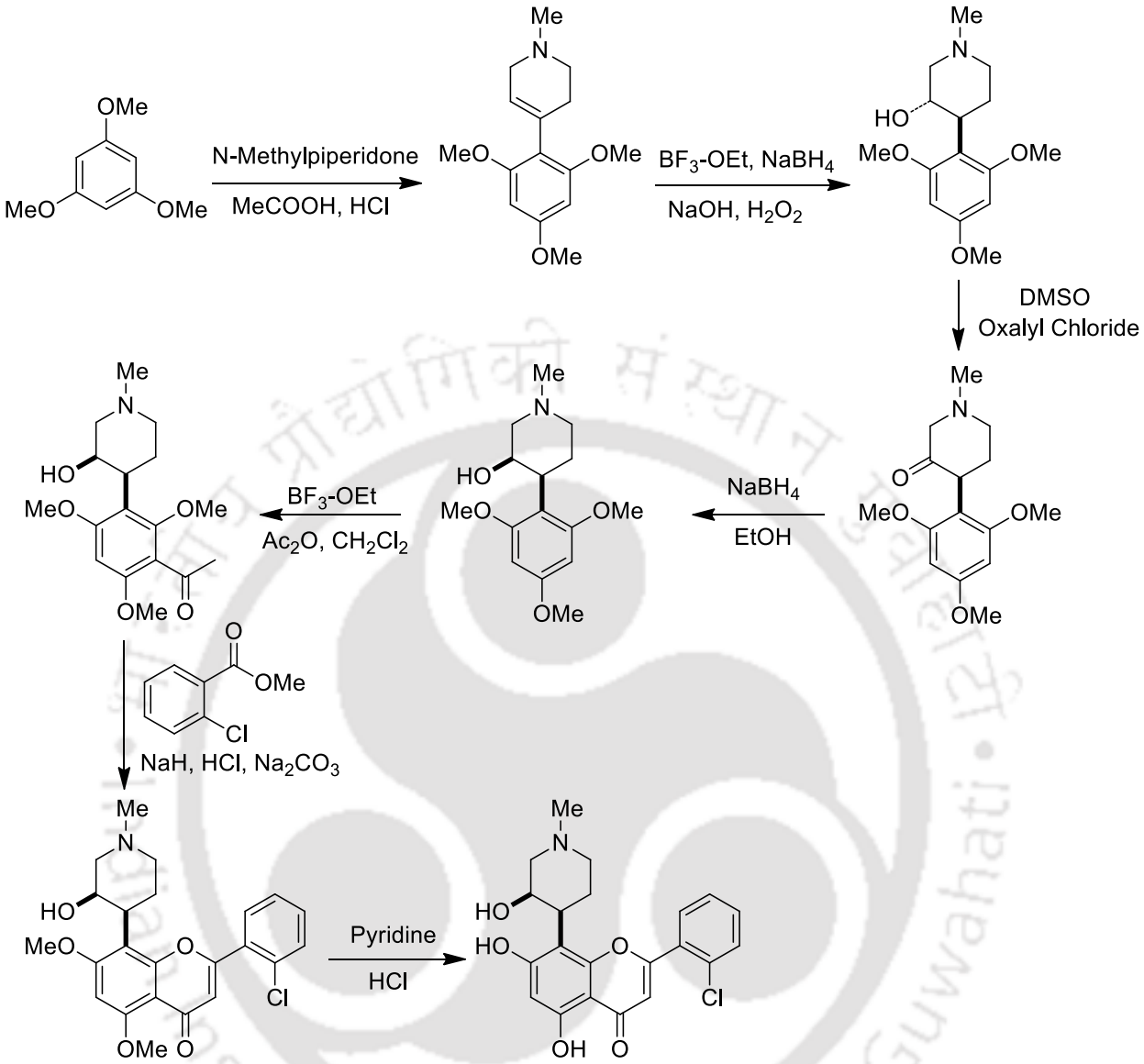
Scheme 29

Natural flavones baicalein and scutellarein were synthesized via a Baker-Venkataraman rearrangement[83] in a basic medium for the construction of *β*-diketones and cyclodehydration in presence of glacial acetic acid. The typical step involved in Baker-Venkataraman rearrangement is portrayed in Scheme 30.



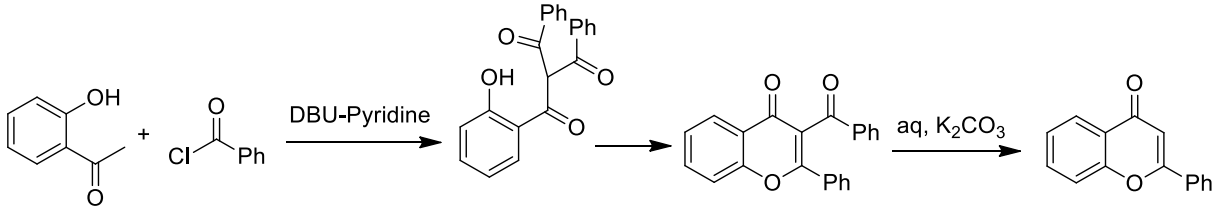
Scheme 30

Kattige and his co-workers[84] prepared an anticancer agents flavopiridol from 1,3,5-trimethoxybenzene through number of steps involving organic reactions as shown in Scheme 31.



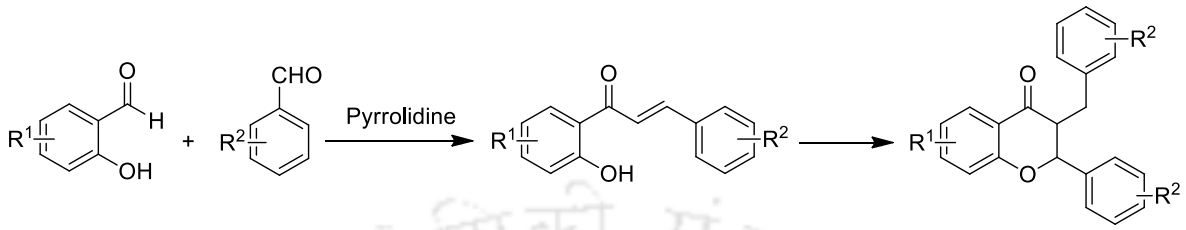
Scheme 31

Ganguly *et al*.[85] prepared 3-acylflavones through a triketo intermediate by using DBU and pyridine which further convertedto flavones by refluxing with aqueous K_2CO_3 as depicted in Scheme 32.



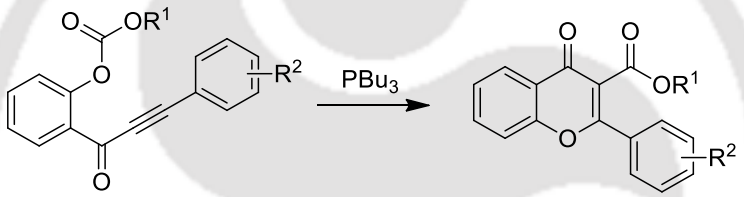
Scheme 32

One-pot synthesis of 3-substituted flavone derivatives was proposed by Dong *et al.*[86] fromo-hydroxyacetophenones and benzaldehydes in presence of sufficient amount of pyrrolidine through the intermediacy of 2-hydroxy chalcone as shown in Scheme 33.



Scheme 33

Yoshida *et al.*[87] proposed the tandem acyl transfer-cyclization of carbonates by tributylphosphine (PBu_3) to afford 3-methoxycarbonyl flavone derivatives in excellent yields as shown in Scheme 34.



Scheme 34

Overall literature survey discloses that the oxygen-containing heterocycles constitutes foremost components in natural products and extensively employed in the various field, especially in medical science and industries. From this point of view, the researchers are constantly trying to build up new synthetic roots for developing such a valuable heterocycles. Although there are numerous methods have been reported, for the synthesis of 4*H*-chromene, benzo[*f*]chromene and flavone derivatives, but some of these methods are associated with certain limitations like harsh reaction conditions, use of excess amount of expensive catalyst, longer reaction times, multi-step reaction conditions and tedious work-up procedure. As a consequence, there is a wide scope to improve a new methodology which can overcome the problems and give better results in terms of substrate compatibility, yield, time and procedure The present thesis work is based on oxygen-containing heterocycles, and successfully prepared 4*H*-chromene, flavone and benzo[*f*]chromene derivatives respectively. 4*H*-Chromene derivatives are described in Chapter 2, and Chapter 3 of Part A. Flavone and benzo[*f*]chromene derivatives will be discussed in Chapter 2 and Chapter 3 of Part B respectively.

Part A

Chapter II

Ammonium chloride catalyzed three-component reaction for the synthesis of fused 4H-chromene derivatives in aqueous medium

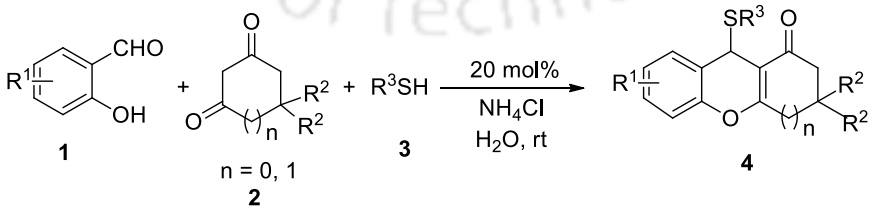
Results & Discussion

Experimental Section

The Multicomponent reaction is a practical protocol for constructing new biological active heterocyclic molecules, which has been already, highlighted in Part A of Chapter I. Bearing Green Chemistry[88] in mind, designing of MCRs in an aqueous medium for synthesizing heterocyclic scaffolds with medicinal activities is one of the trending research issues among modern chemists. Water is playing a vital role in various life-sustaining processes, so, it is a nature's reaction medium. Since water is found in high abundance hence it is cost-effective and a green solvent for organic transformations[89] owing to its non-flammable and non-toxic nature. Moreover, it exhibits unique properties like high dielectric constant, cohesive energy density puts an extraordinary effect on reaction rates with unique selectivity and reactivity.[90] The importance and synthetic utility of 4*H*-chromene derivatives have also been discussed in Part A-Chapter I. In the extension of our investigations into the synthesis of novel heterocyclic compounds under aqueous conditions,[91] we conceived to explore the synthesis of 4*H*-chromene compounds using more environmentally benign reaction conditions.

In continuation, of our effort to investigate the new reagents in organic synthesis, we explored the catalytic activity of ammonium chloride in an aqueous medium. Ammonium chloride is readily available and inexpensive catalyst, which is a good source of the proton, in an aqueous medium. It can activate the carbonyl group through hydrogen bonding,[92] and can easily react with carbonyl groups in the presence of amines to form imines, which can act as dienophiles in Diels-Alder reactions.[93] Thus NH_4Cl was considered to be a potential catalyst for various organic reactions.

In this Chapter, we have demonstrated a new, handy, highly competent greener protocol for the synthesis of 4*H*-chromene via three component condensations of salicylaldehydes, cyclic 1,3-dicarbonyl compounds and aromatic or aliphatic thiols catalyzed by ammonium chloride in water at room temperature as shown in Scheme 35.



R^1 = H (**1a**), 5-Br (**1b**), 5-OMe (**1c**), 3-OMe (**1d**), 3-OEt (**1e**)

R^2 = Me (**2a**), H (**2b**), n = 1
R^2 = H (**2c**), n = 0

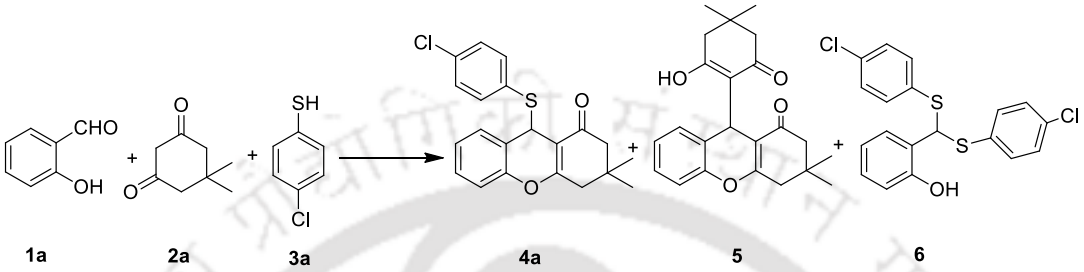
R^3 = Aryl/Alkyl/Benzyl

Scheme 35.One-pot three components synthesis of 4*H*-chromene derivatives

In our initial efforts to synthesize 4*H*-chromene derivative **4a**, a reaction was carried out with a mixture of salicylaldehyde (1 mmol), dimedone (1 mmol) and 4-chlorothiophenol (1 mmol) in water in the absence of acatalyst at room temperature. The reaction did not proceed to completion even after 12h and resulting inthe isolation of product 4*H*-chromene derivative **4a** and 1-oxo-hexahydroxanthene derivative[94] (5) in 22% and 48% yields (Table 1, entry 1), respectively which was confirmed by IR, ^{1}H NMR,^{13}C NMR spectra and elemental analysis. In IR, the compound shows a strong absorptions peak at 1681 cm^{-1}, which indicates the presence of carbonyl group. Similarly, in ^{1}H spectra it shows the characteristic signals at 7.24 (d, *J* = 8.0 Hz, 1H), 7.21-7.16 (m, 1H), 7.13-7.11 (m, 3H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 2H), 6.84 (d, *J*= 8.0 Hz, 1H), 5.29 (s, 1H), 2.42-2.33 (m, 4H), 1.17 (s, 3H), 1.08 (s, 3H) ppm. Also, in ^{13}C NMR signals are present at 195.6,166.2, 150.5, 137.4, 135.0, 130.4, 129.3, 128.3, 128.2, 125.0, 122.2, 116.1, 109.5, 50.7, 41.2, 40.9, 31.9, 28.5, 28.2 ppm which established the formation of 4*H*-chromene **4a** derivatives. The same reactions were also carried out using 10 mol% of NH_4Cl in water which afforded the product **4a** along with the formation of a trace amount of compound (5) in 67% and 7% yields (Table 1, entry 2), respectively. To reduce the formation of the by-product as well to increase the yield of the desired 4*H*-chromene **4a**, the similar reaction was executed using 20 and 30 mol% of NH_4Cl to afford compound **4a** in 78% and 74% yields. It was noted that the yield of the product **4a** has increased from 67 to 78% by increasing the amount of catalyst from 10% to 20% with the trace amount of product **5** and also shortened the reaction time significantly (Table 1, entry 3). However, increasing the amount of catalyst from 20% to 30% did not improve the yield of the product further (Table 1, entry 4). The reactions were very sluggish and incomplete even after 16h, when the same reaction was carried out in presence of 20 mol% of NH_4Cl under solvent free conditions (Table 1, entry 6). These results show catalyst NH_4Cl have a remarkable effect in suppressing the formation of by-product and controlling the reaction selectivity in water. To examine the efficacy of the catalyst, several reactions were also performed in the presence of other mild acid catalyst such as TBAB, TBAI, BETAC and TBATB under identical reaction conditions but all of them delivered poorer results in terms of yield and selectivity toward **4a** (Table 1, entries 8-11) and gave 2-(bis((4-chlorophenyl)thio)methyl)phenol (**6**) as another by-product. It is worthwhile to mention that the same reaction gave comparatively similar yields when 20 mol % of NH_4Br was used in water (Table 1, entry 7). Since the yield has not increased significantly and cost of

the NH_4Br is higher as compared to NH_4Cl, all the reactions were performed using 20 mol% of NH_4Cl in water.

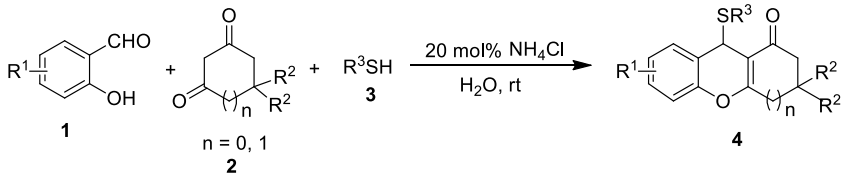
Table 1: Optimization of reaction conditions for the synthesis 3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**4a**)[a]



Entry	Catalyst (mol%)	Solvent	Time/h	Yield[b]/%		
				4a	**5**	**6**
1	None	H_2O	12.0	22	48	--
2	NH_4Cl (10)	H_2O	12.0	67	7	--
3	**NH_4Cl (20)**	**H_2O**	**5**.0	**78**	**trace**	**--**
4	NH_4Cl (30)	H_2O	5.0	74	trace	--
5	NH_4Cl (20)	EtOH	5.0	29	14	17
6	NH_4Cl (20)	Neat	16.0	46	8	--
7	NH_4Br (20)	H_2O	6.0	74	trace	--
8	TBAB (20)	H_2O	12.0	37	36	26
9	TBAI (20)	H_2O	16.0	38	26	20
10	BETAC (20)	H_2O	12.0	42	22	24
11	TBATB (20)	H_2O	12.0	38	18	42

[a]Reaction conditions: 2-hydroxybenzaldehyde, dimedone and 4-chlorothiophenol were taken in 1:1:1 ratio at room temperature. [b]Isolated yields after column chromatography.

Table 2: Substrate scope for the synthesis of 4*H*-chromene derivatives (**4**)



Entry	1	2	R^3	Time/h	Product[a]	Yield[b]/ %
A	**1a**	**2a**	4-Cl-Ph	5.0	**4a**	78
B	**1a**	**2a**	Ph	5.0	**4b**	79
C	**1a**	**2a**	4-Br-Ph	4.5	**4c**	76
D	**1a**	**2a**	4-Me-Ph	4.0	**4d**	71
E	**1a**	**2a**	4-MeO-Ph	4.0	**4e**	74
F	**1a**	**2a**	2-Naphthyl	6.0	**4f**	70
G	**1a**	**2a**	Et	5.0	**4g**	77
H	**1a**	**2a**	Propyl	4.5	**4h**	75
I	**1b**	**2b**	Benzyl	5.0	**4i**	55
J	**1c**	**2b**	4-Me-Ph	4.0	**4j**	62
K	**1c**	**2a**	4-Cl-Ph	4.0	**4k**	75
L	**1d**	**2a**	Propyl	3.0	**4l**	71
M	**1d**	**2a**	Ph	4.0	**4m**	79
N	**1e**	**2a**	Ph	4.0	**4n**	77
O	**1a**	**2c**	Ph	3.0	**4o**	72
P	**1b**	**2c**	Ph	3.0	**4p**	69

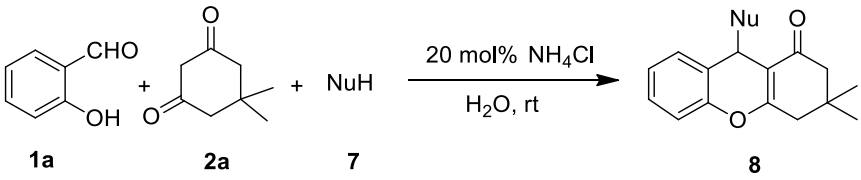
[a]Reaction conditions: Salicylaldehydes (1), 1,3-cyclic ketones (2) and thiols (3) were taken in 1:1:1 ratio in presence of 20 mol% of NH_4Cl in 5 mL of water at room temperature. Entry o and p was at reflux. [b]Isolated yields.

The above observations indicate that the reaction proceeds well in the presence of 20 mol% of NH_4Cl in aqueous media. The mild reaction conditions and clean TLC pattern are the main advantages of the present reaction in water. With the optimized conditions in hand, we next embarked on an investigation of the substrate scope of the present multicomponent reaction for the synthesis of 4*H*-chromene derivatives with different salicylaldehydes, cyclic-1,3-diketones and thiols. Performing the reaction with a mixture of salicylaldehyde, dimedone and thiophenol under identical conditions, the desired product **4b** was obtained in 79% yield (Table 2, entry b). To explore the synthetic scope and the generality of the present protocol, various reactions were performed with a wide variety of aromatic thiols containing different substituents on the aromatic ring such as Br, Me, OMe with salicylaldehyde and dimedone. The reaction time and percentage yield of the products (**4c-f**) are shown in Table 2 (entries c-f). Likewise, aliphatic thiols such as ethane thiol and propane thiol were tested under identical reaction condition to provide the desired 4*H*-chromene products **4g-h** in good yields (Table 2, entries g-h).

For verifying the generality of the present method, other substituted salicylaldehyde derivatives bearing Br, MeO and OEt substituents in the ring were also examined with dimedone and different aliphatic or aromatic thiols under identical reaction conditions to provide the desired 4*H*-chromene products **4i-n** in moderate to good yields (Table 2, entries i-n). Furthermore, the reactions with other cyclic 1,3-diketones such as 1,3-cyclohexadione and 1,3-cyclopentadione with salicylaldehydes and thiophenol were also performed to give the desired products **4i-j** and **4o-p** and (Table 2, entries i-j & o-p). It was observed that the similar transformation is afailure in case of acyclic 1,3-diketone such as acetyl acetone and also for malononitrile.

The present protocol was further examined by carrying out two consecutive reactions with salicylaldehyde, dimedone and with a nucleophile such as indole(**7a**) and *β*-naphthol (**7b**) under the identical condition and the desired product **8a** & **8b** were isolated in 81% and 58% yield, respectively as shown in Table 3.

Table 3: Substrate scope for the synthesis of 4*H*-chromene derivatives (**8**)



Entry	NuH (7)	Time/h	Product[a]	Yield[b]/%
a	Indole	5.0	**8a**	81
b	2-naphthol	6.0	**8b**	58

[a]Salicylaldehyde (1a), dimedone (2a) and nucleophile (7) were taken in 1:1:1 ratio in presence of 20 mol% of NH_4Cl in 5 mL of water. For the entry a, reaction was carried out at room temperature, whereas, in case of entry b, reaction carried out under reflux. [b]Isolated yields.

All the synthesized compounds were characterized by IR, NMR, and elemental analysis. The products **4a**–**p** exhibited a diagnostic signal in the range of δ = 4.96–5.38 assignable to H-9 at the point of attachment of 4*H*-chromene to the thiol moiety depending on the nature of the substituent in salicylaldehydes and thiols. The ^{1}H NMR and ^{13}C NMR spectra of the products **4f, 4h, 4m, 8a** and **8b** are shown in Figure **8-12** respectively in the experimental section. Finally, the structure of one of the representative compounds such as 9-((4-chlorophenyl)thio)-7-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4k**) was confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 7).

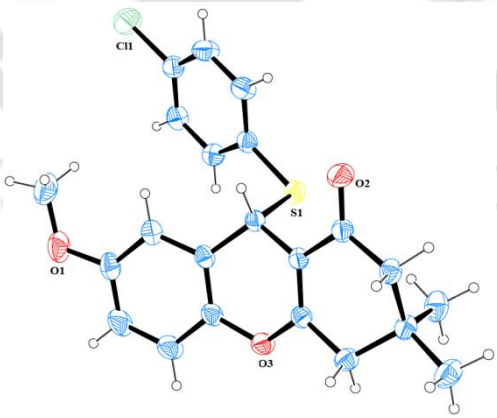
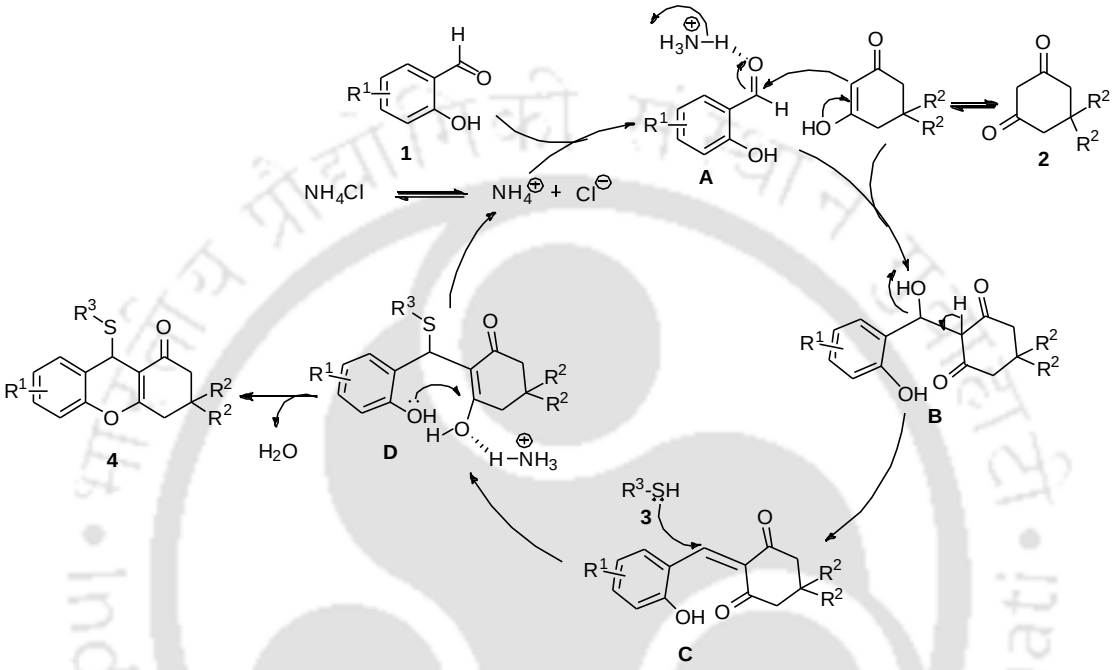


Figure 7. X-Ray Crystal structure of 4*H*-chromene (**4k**) (CCDC No. 926004)

The formation of the product may be explained as follows: The first step is believed to be the condensation reaction between salicylaldehyde (**1**) with cyclic-1,3-diketone (**2**) to give a Knoevenagel product **C**, which can act as a suitable Michael acceptor. The role of ammonium

chloride is a source of proton which activates carbonyl group through hydrogen bonding. Then a nucleophile such as thiol reacts at the exocyclic benzylidene double bond of the Knoevenagel product **C**, to form intermediate **D** which further undergoes intra-molecular ring closure reaction followed by dehydration to give the desired 4*H*-chromene compounds (**4**) as shown in Scheme 36.



Scheme 36. Proposed NH_4Cl catalyzed formation of 4*H*-chromene derivatives (**4**)

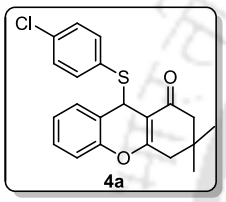
In conclusion, we have demonstrated an efficient and eco-friendly protocol for the synthesis of 4*H*-chromene derivatives by employing environmentally benign catalyst NH_4Cl via one-pot three-component condensation reaction from a wide variety of salicylaldehydes, cyclic 1,3-diketones and aromatic or aliphatic thiols employing water as the reaction medium. This new methodology is endowed with several advantages such as green reaction medium, environmentally benign reaction conditions with good yields, superior atom economy, the easy accessibility of the catalyst and its cost effectiveness.

Experimental

*General procedure for the synthesis of 4H-Chromene derivatives (**4**)*

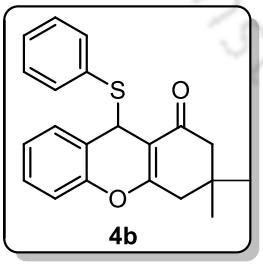
A mixture of salicylaldehyde (1 mmol), cyclic 1, 3-diketone (1mmol), nucleophile (1 mmol), and NH_4Cl (0.2mmol) in H_2O (5 mL) was stirred at rt. for 3–6 h in a 25 mL round bottomed flask. The progress of the reaction was monitored by TLC (eluent: EtOAc–hexane, 1:9). After the completion of the reaction, the crude reaction mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with H_2O (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh, eluent: EtOAc-hexane, 1:9) to afford the final product.

*9-((4-chlorophenyl)thio)-3,3 Dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4a**)* **:**



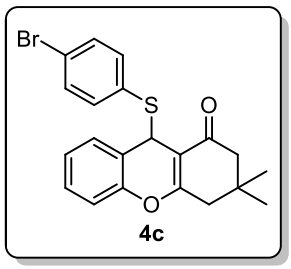
Orange liquid, **IR** (KBr): 3061, 2925, 2854, 1681, 1644, 1602, 1574, 1485, 1471, 1416, 1385, 1239, 1175, 1091, 1042, 1011, 988, 909, 820 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ = 7.24 (d, *J* = 8.0 Hz, 1H), 7.21-7.16 (m, 1H), 7.13-7.11 (m, 3H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.29 (s, 1H), 2.42-2.33 (m, 4H), 1.17 (s, 3H), 1.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.6, 166.2, 150.5, 137.4, 135.0, 130.4, 129.3, 128.3, 128.2, 125.0, 122.2, 116.1, 109.5, 50.7, 41.2, 40.9, 31.9, 28.5, 28.2; **Anal. Calcd** for $C_{21}H_{19}ClO_2S$ (370.89): C, 68.00; H, 5.16. Found C, 68.24; H, 5.24.

*3,3-Dimethyl-9-(Phenylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4b**)* **:**



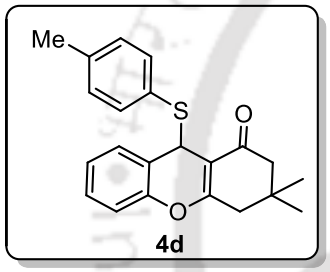
Orange liquid, **IR** (KBr): 3056, 2952, 2952, 2909, 2871, 1668, 1643, 1580, 1480, 1437, 1385, 1238, 1178, 1140, 1066, 1013, 973, 868, 753, 692,662cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.29-7.23 (m, 2H), 7.18-7.11 (m, 4H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.29 (s, 1H), 2.41-2.24 (m, 4H), 1.16 (s, 3H), 1.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.4, 166.0, 150.3, 136.1, 131.6, 129.2, 128.5, 128.0, 127.9, 124.7, 122.4, 115.8, 109.4, 50.61, 41.0, 40.5, 31.7, 28.3, 28.2; **MS (ESI)**: m/z [M + Na^+], Calcd For: $C_{21}H_{20}NaO_2S^+$ (359.1082); Found: 359.1076; **Anal. Calcd** for $C_{21}H_{20}O_2S$ (336.45): C, 74.97; H, 5.99. Found C, 74.83; H, 6.04.

*9-(4-Bromophenylsulfanyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4c**)***:***



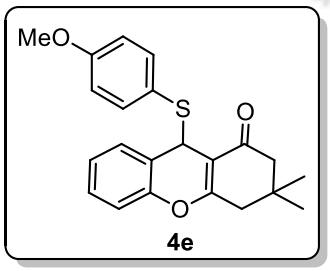
Orange liquid, **IR** (KBr):3061, 2958, 2871, 1668, 1645, 1582, 1485, 1470, 1384, 1235, 1177, 1144, 1090, 1067, 1010, 925, 872, 820 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.19-7.08 (m, 3H), 6.90 (dd, *J* = 8.4, 1.6 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.28 (s, 1H), 2.40-2.27 (m, 4H), 1.15 (s, 3H), 1.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.5, 166.2, 150.5, 137.5, 131.3, 131.2, 129.3, 128.2, 125.0, 123.3, 122.2, 116.1, 109.5,50.7, 41.2, 40.9, 31.9, 28.3, 28.2; **Anal. Calcd** for $C_{21}H_{19}BrO_2S$ (415.34): C, 60.73; H, 4.61. Found: C, 60.83; H, 4.66.

*3,3-Dimethyl-9-(p-tolylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4d**)* **:**



Orange liquid, **IR** (KBr):3020, 2958, 2926, 2875, 1662, 1644, 1582, 1486, 1460, 1383, 1293, 1235, 1177, 1019, 910, 873, 809, 751, 663 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 7.6 Hz, 2H), 7.18-7.09 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.26 (s, 1H), 2.38–2.35 (m, 4H), 2.31 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.9, 166.3, 150.6, 136.4, 128.0, 129.5, 129.1, 128.5, 128.2, 125.0, 122.8, 116.1, 109.8, 50.9, 41.3, 40.7, 32.1, 28.5, 28.4, 21.3; **MS (ESI)**: m/z [M + Na^+],Calcd. For: $C_{22}H_{22}NaO_2S^+$ (373.1233); Found: 373.1358; **Anal. Calcd** for $C_{22}H_{22}O_2S$ (350.47): C, 75.39; H, 6.33. Found: C, 75.46; H, 6.28.

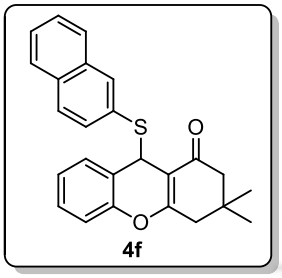
*9-[(4-Methoxyphenyl)thio]-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4e**)* **:**



Orange solid, mp 107-108 °C; **IR** (KBr): 2954, 1659, 1640, 1589, 1462, 1380, 1232, 1172, 1030, 758, 533 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2H), 7.17–7.12 (m, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 2H), 5.22 (s, 1H), 3.78 (s, 3H), 2.39-2.28 (m, 4H), 1.18 (s, 3H), 1.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.4, 165.8, 160.1, 150.4, 137.8, 129.3, 127.7, 124.6, 122.3, 121.9, 115.7, 113.5, 109.3, 54.9, 50.5, 40.9, 40.5, 31.7, 28.2, 28.1; **MS (ESI)**: m/z [M + Na^+], Calcd. For $C_{22}H_{22}NaO_3S^+$: (389.1182);

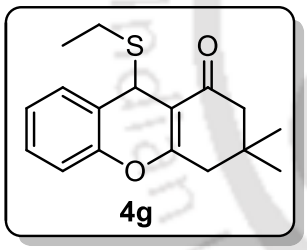
Found: 389.1198; **Anal. Calcd** for $C_{22}H_{22}O_3S$ (366.47): C, 72.10; H, 6.05. Found: C, 72.18; H, 6.10.

3,3-Dimethyl-9-(naphthalen-2-ylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one ***(4f)*** **:**



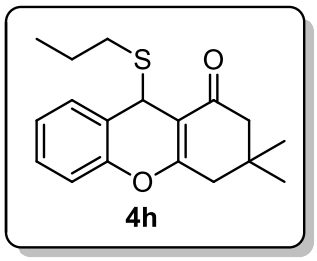
Orange liquid, **IR** (KBr): 2956, 2926, 1665, 1643, 1581, 1498, 1460, 1381, 1266, 1176, 1143, 1129, 1031, 1013, 943 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.2 Hz, 1H), 7.69-7.58 (m, 2H), 7.54 (s, 1H), 7.52-7.41 (m, 2H), 7.28-7.23 (m, 1H),7.21-7.09 (m, 3H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.39 (s, 1H), 2.47-2.31 (m, 4H), 1.15 (s, 3H), 1.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 196.0, 166.4, 150.6, 136.1, 133.2, 133.0, 132.7, 129.5, 129.4, 128.2, 127.7, 127.6, 126.6, 126.5, 126.2, 125.1, 122.8, 116.1, 109.7, 50.8, 41.3, 41.0, 32.0, 28.6, 28.3; **MS (ESI)**: m/z [M + Na^+], Calcd. For $C_{25}H_{22}NaO_2S^+$ (409.0233); Found: 409.0143; **Anal. Calcd** for $C_{25}H_{22}O_2S$ (386.51): C, 77.69; H, 5.74. Found: C, 77.74; H, 5.78.

9-(Ethylthio)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthene-1-one ***(4g)*** **:**



Orange solid, mp 63-64 °C; **IR** (KBr): 2960, 1662, 1645, 1458, 1380, 1235, 1176, 1141, 1017, 754 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.27-7.15 (m, 2H), 7.03 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.04 (s, 1H), 2.59-2.47 (m, 2H), 2.45-2.27 (m, 4H), 1.17 (s, 3H), 1.13 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 196.0, 165.8, 150.5, 129.4, 127.9, 125.1, 122.6, 116.0, 110.7, 50.5, 41.2, 34.8, 31.8, 29.2, 27.1, 23.5, 13.9; **MS (ESI)**: m/z [M + Na^+], Calcd.For $C_{17}H_{20}NaO_2S^+$ (311.1076); Found: 311.1143; **Anal. Calcd** for $C_{17}H_{20}O_2S$ (288.40): C, 70.80; H, 6.99. Found: C, 70.86; H, 6.92.

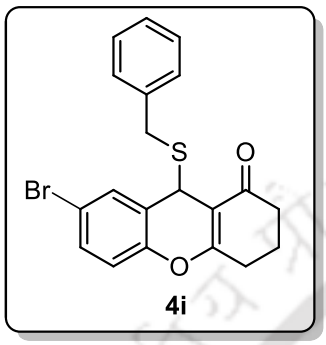
3,3-Dimethyl-9-(propylthio)-2,3,4,9-tetrahydro-1H-xanthene-1-one (***4h***) **:**



Orange liquid, **IR** (KBr): 2959, 1662, 1645, 1582, 1457, 1379, 1291, 1234, 1176, 1144, 1012, 871, 754, 701, 663, 542 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 5.02 (s, 1H), 2.59–2.46 (m, 2H), 2.40-2.19 (m, 4H), 1.48-1.41 (m, 2H), 1.17 (s, 3H), 1.13 (s, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.3, 165.2, 150.2, 129.1, 127.6,124.7, 122.4, 115.7, 110.4, 50.1,

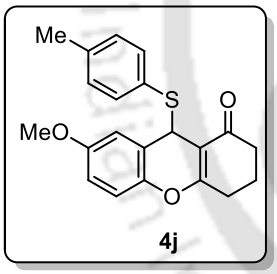
40.8, 34.4, 31.4, 31.2, 28.9, 26.6, 22.0, 13.2; **MS (ESI)**: m/z [M + Na^+], Calcd. For $C_{18}H_{22}NaO_2S^+$ (325.1200); Found: 325.1286; **Anal. Calcd** for $C_{18}H_{22}O_2S$ (302.43): C, 71.48; H, 7.33. Found: C, 71.55; H, 7.38.

*9-(Benzylthio)-7-bromo-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4i**) :*



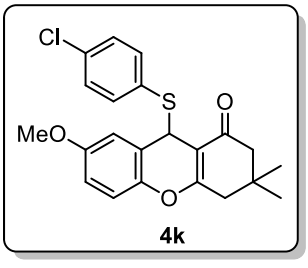
Colorless liquid, **IR** (KBr): 2928, 1659, 1640, 1473, 1410, 1377, 1231, 1166, 1130, 995, 703 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.30-7.18 (m, 7H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.96 (s, 1H), 3.61 (s, 2H), 2.43-2.29 (m, 4H), 1.19-1.18 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 196.4, 167.1, 149.8, 138.5, 132.7, 131.4, 129.0, 128.5, 127.1, 124.7, 118.0, 117.7, 111.8, 36.8, 35.1, 27.7, 20.0; **MS (ESI):** m/z [M + Na^+], Calcd. For $C_{20}H_{17}Na^{79}BrO_2S^+$ (425.0025); Found: 425.0139; **Anal. Calcd** for $C_{20}H_{17}BrO_2S$ (401.32): C, 59.86; H, 4.27. Found: C, 59.92: H, 4.33.

*7-Methoxy-9-(p-tolylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4j**)* **:**



Orange solid, mp 145-146 °C; **IR** (KBr): 2952, 2927, 1654, 1637, 1493, 1459, 1339, 1260, 1225, 1198, 1033, 998, 874, 808, 753 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.75-6.72 (m, 3H), 5.25 (s, 1H), 3.77 (s, 3H), 2.41-2.37 (m, 4H), 2.32 (s, 3H), 2.01-2.04 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 196.2, 168.3, 156.7, 144.9, 139.2, 137.0, 129.1, 128.1, 123.6, 117.0, 115.3, 112.4, 109.9, 55.8, 41.2, 37.0, 27.7, 21.4, 20.4; **MS (ESI)**: m/z [M + Na^+] Calcd. For $C_{21}H_{20}NaO_3S^+$ (375.1025); Found: 375.1018; **Anal. Calcd** for $C_{21}H_{20}O_3S$ (352.45): C, 71.56; H, 5.72. Found: C, 71.60; H, 5.78.

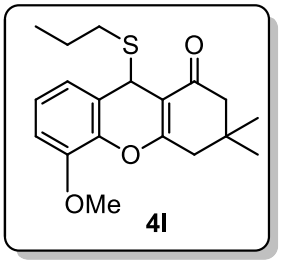
*9-[(4-Chlorophenyl)thio]-7-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one(**4k**)***:**



Orange solid, mp 112-113 °C; **IR** (KBr): 2955, 1659, 1643, 1497, 1380, 1216, 1038, 824 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.80-6.73 (m, 2H), 6.69 (d, *J* = 2.8 Hz, 1H), 5.28 (s, 1H), 3.76 (s, 3H), 2.40-2.31 (m, 4H), 1.15 (s, 3H), 1.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.9, 166.7, 156.6, 144.9, 137.5, 135.2, 130.7, 128.5, 123.0, 117.3, 115.3, 112.3, 108.8, 55.7,

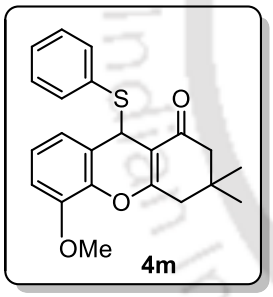
50.9, 41.7, 41.4, 32.1, 28.6, 28.4; **Anal. Calcd** for $C_{22}H_{21}ClO_3S$ (400.92): C, 65.91; H, 5.28. Found: C, 65.89: H, 5.34.

*5-Methoxy-3,3-dimethyl-9-(propylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4l**)* **:**



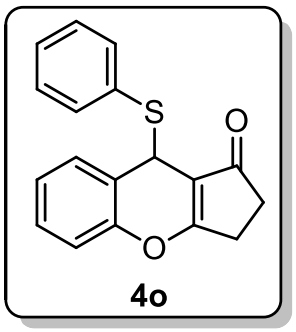
Orange solid, mp 128-129 °C; **IR** (KBr): 3009, 2955, 1655, 1639, 1612, 1582, 1485, 1381, 1271, 1228, 1124, 1094, 764, 734, 544 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.10 (t, *J* = 8.0Hz, 1H), 6.98 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.01 (s, 1H), 3.91 (s, 3H), 2.66 (d, *J* = 17.2 Hz, 1H), 2.56 (d, *J* = 17.6 Hz, 1H), 2.41-2.19 (m, 4H), 1.48-1.39 (m, 2H), 1.17 (s, 3H), 1.13 (s, 3H),0.86 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.8, 165.3, 147.1, 140.2, 124.7, 123.5, 120.7, 110.4, 109.9, 55.8, 50.5, 41.1, 34.7, 31.8, 31.3, 29.1,27.0, 22.2, 13.5; **MS (ESI)**: m/z [M + Na^+], Calcd. For $C_{19}H_{24}NaO_3S^+$ (355.1338); Found: 355.1335; **Anal. Calcd** for $C_{19}H_{24}O_3S$ (332.46): C, 68.64; H, 7.28. Found: C, 68.72; H, 7.36.

*5-Methoxy-3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4m**)* **:**



Orange solid, mp 102-105 °C; **IR** (KBr): 3055, 2958, 1670, 1645, 1583, 1470, 1385, 1274, 1228,1186, 1124, 1093, 954, 841, 789, 737, 665 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.34-7.27 (m, 1H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.11-7.02 (m, 3H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 5.30 (s, 1H), 3.82 (s, 3H), 2.48-2.28 (m, 4H), 1.15 (s, 3H), 1.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 195.8, 166.0, 147.4, 140.5, 136.1, 131.9, 128.8, 128.2, 124.7, 123.5, 120.9, 110.5, 109.6, 56.1, 50.8, 41.3, 40.8, 32.0, 28.4; **MS (ESI):** m/z [M + Na^+], Calcd. For $C_{22}H_{22}NaO_3S^+$ (389.1182); Found: 389.1198; **Anal. Calcd** for $C_{22}H_{22}O_3S$ (366.47): C, 72.10; H, 6.05. Found: C, 72.18; H, 6.10.

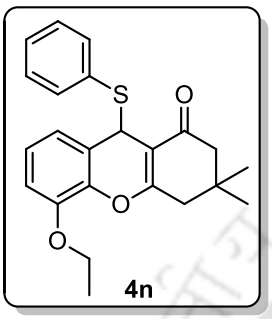
*5-Ethoxy-3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4n**)***:**



Orange liquid, **IR** (KBr): 2957, 1664, 1645, 1582, 1473, 1438, 1383, 1275, 1226,1189, 1083, 750, 692 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 6.6 Hz, 1H), 7.17 (t ,*J* = 7.8 Hz, 2H), 7.13-7.09 (m, 2H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.80(d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 5.29 (s, 1H), 4.14-3.92 (m, 2H), 2.48-2.32 (m, 4H), 1.38 (t, *J* = 6.9 Hz, 3H), 1.16 (s, 3H), 1.07 (s, 3H); **^{13}C NMR**

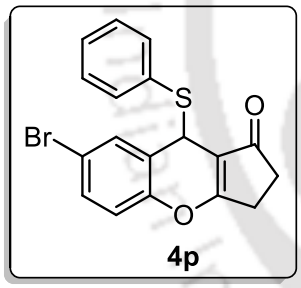
(150 MHz, $CDCl_3$): δ = 195.9, 166.2, 146.6, 140.8, 136.1, 132.1, 128.6, 128.2, 124.6, 123.6, 120.9, 112.3, 109.6,64.8, 50.8, 41.2, 40.9, 32.1, 28.4, 28.3, 14.7; **MS (ESI)**: [M + Na^+],Calcd For $C_{23}H_{24}NaO_3S^+$ (403.1338); Found:403.1375; **Anal. Calcd** for $C_{23}H_{24}O_3S$ (380.49): C, 72.60; H, 6.36. Found: C, 72.68; H, 6.44.

*9-(Phenylthio)-2,3-dihydrocyclopenta[b]chromen-1(9H)-one (**4o**)***:**



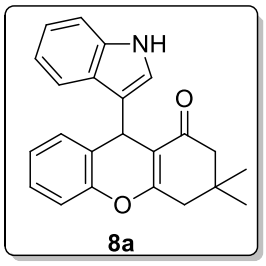
Brown liquid, **IR** (KBr): 2923, 1704, 1651, 1574, 1438, 1393, 1249, 1163, 1119, 744, 695 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51-7.49 (m, 1H), 7.31-7.27 (m, 1H), 7.25-7.20 (m, 2H), 7.14 (t, *J* = 7.2 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.85-6.83 (m, 1H), 5.13 (s, 1H), 2.57-2.36 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 201.5, 179.9, 151.3, 136.8,131.0, 130.9, 129.2, 128.8, 128.4, 125.8, 122.2, 116.6, 114.0,40.5, 33.6, 25.3; **MS (ESI)**: m/z [M + Na^+], Calcd For $C_{18}H_{14}NaO_2S^+$ (317.0607); Found: 317.0610; **Anal. Calcd** for $C_{18}H_{14}O_2S$ (294.37): C, 73.44; H, 4.79. Found: C, 73.53; H, 4.82.

*7-Bromo-9-(phenylthio)-2,3-dihydrocyclopenta[b]chromen-1(9H)-one (**4p**)***:**



Brown solid, mp 182-183 °C; **IR** (KBr): 2920, 1700, 1649, 1470, 1437, 1384, 1245, 1194, 1160,1119, 1014, 823, 740, 697 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 2.4 Hz, 1H), 7.36-7.31 (m, 2H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.00 (dd, *J* = 8.4, 1.2 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 1H), 5.07 (s, 1H), 2.62-2.51 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 201.1, 179.5, 150.3, 136.8,133.5, 131.7, 130.4, 129.5, 128.6, 124.3, 118.3, 118.1, 113.7, 40.1, 33.6, 25.3; **MS (ESI):** m/z [M + Na^+], Calcd. For $C_{18}H_{13}NaBrO_2S^+$ (396.9692); Found: 396.9662; **Anal. Calcd** for $C_{18}H_{13}BrO_2S$ (373.26): C, 57.92; H, 3.51. Found: C, 57.98; H, 3.55.

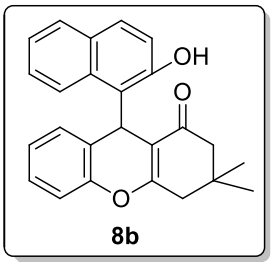
*9-(1H-Indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**8a**)***:**



Orange solid, mp 200-202 °C; **IR** (KBr): 3329, 1643, 1467, 1421, 1375, 1228, 1179 cm^{-1}; **^{1}HNMR** (300 MHz, $CDCl_3$): δ = 8.00 (s, 1H), 7.39 (d, *J* = 7.5 Hz,2H), 7.32-7.22 (m, 2H), 7.20-7.05 (m, 3H), 6.96 (d, *J* = 4.5 Hz, 2H), 5.32 (s, 1H), 2.64-2.15 (m, 4H), 1.11 (s, 3H), 1.04 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 197.4, 164.3, 149.4, 136.5, 130.1,127.3, 125.5, 125.2, 124.8, 122.4, 121.4, 120.1, 119.1, 118.9, 116.1, 112.6, 111.2, 50.8, 41.4, 32.0, 29.4, 29.0, 27.5; **MS (ESI):** m/z [M + Na^+], Calcd. For

$C_{23}H_{21}NaNO_2^+$ (366.1455); Found: 366.1467; **Anal. Calcd** for $C_{23}H_{21}NO_2$ (343.15): C, 80.44; H, 6.16. Found: C, 80.47; H, 6.18.

*9-(2-Hydroxynaphthalen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**8b**)***:***



White solid, mp 229-231 °C; **IR** (KBr): 3204, 2960, 1655, 1634, 1484, 1431, 1382, 1182, 1143cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 9.27 (s, 1H), 7.79 (d, *J* = 9.0 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.37 (q, *J* = 5.7 Hz, 3H), 7.01 (s, 2H), 6.60 (s, 2H), 5.77 (s, 1H), 2.61 (s, 2H), 2.39 (d, *J* = 5.7 Hz, 2H), 1.15 (s, 3H), 0.99 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 200.6, 166.8, 152.7, 147.7, 132.6, 131.4, 131.0, 129.0, 128.7, 128.1, 127.8, 127.4, 125.2, 123.3, 121.4,118.7, 117.3, 116.5, 113.8, 50.1, 41.5, 32.3, 28.9, 27.9, 27.1; **MS (ESI):** m/z [M + H$^+$] Calcd.For: $C_{25}H_{23}O_3$ (371.1642); Found:371.1642; **Anal. Calcd** for $C_{25}H_{22}O_3$ (370.15): C, 81.06; H, 5.99. Found: C, 81.09; H, 5.94.

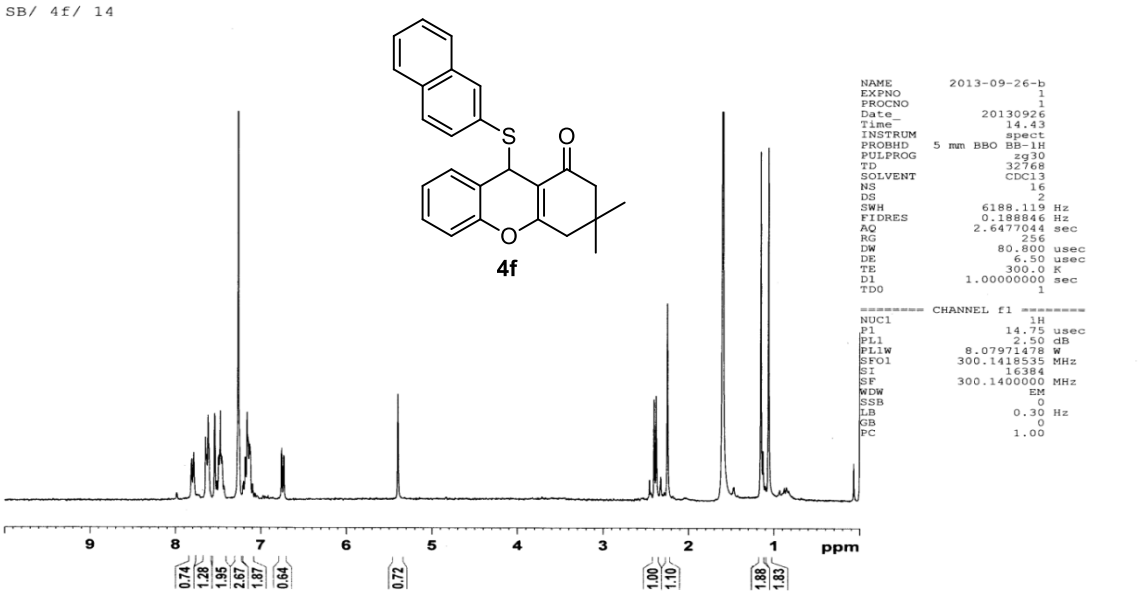
Compound **4k** was recrystallized from chloroform. Complete crystallographic data of **4k** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication with CCDC no. 926004. Copies of this information may be obtained free of charge from 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 4. Crystal data and structure refinement for **4k**. For atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**Compound 4k**	**Parameters**	**Compound 4k**
Identification code	SB-SH-9	Z	8
Empirical formula	$C_{22}H_{21}ClO_3S$	Density (calculated)	1.320 g/cm^3
Formula weight	400.90	Absorption coefficient	0.312 mm^{-1}
Temperature	296 (2) K	F(000)	1680
Wavelength	0.71073Å	Theta range for data collection	2.81 to 25.23 °
Crystal system	Orthorhombic	Index ranges	-14<=h<= 14,

			-10<=k<=11, -44<=l<=44
Space group	C2/c	Reflections collected	23708
Unit cell dimensions		Independent reflections	3629 R_{int} = 0.0638
a	11.6732(9) Å	Completeness to θº	99% (θ = 25.23 º)
b	9.2582(7) Å	Refinement method	Full-matrix least-squares on F2
c	37.329(3) Å	Data / restraints / parameters	3629 / 0 / 247
α	90.00º	Goodness-of-fit on F2	1.007
β	90.00º	Final R indices [>2sigma(I)]	R_{obs} = 0.0476, wR_{obs} = 0.0889
γ	90.00º	R indices (all data)	R_{all} = 0.0616, wR_{all} = 0.0938
Volume	4034.3(5) $Å^3$	Largest diff. peak and hole	0.157 and -0.190e.$Å^{-3}$

***^{1}H NMR (300 MHz, $CDCl_3$)**: 3,3-Dimethyl-9-(naphthalen-2-ylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one(**4f**)*



***^{13}C NMR (100 MHz, $CDCl_3$)**: 3,3-Dimethyl-9-(naphthalen-2-ylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one(**4f**)*

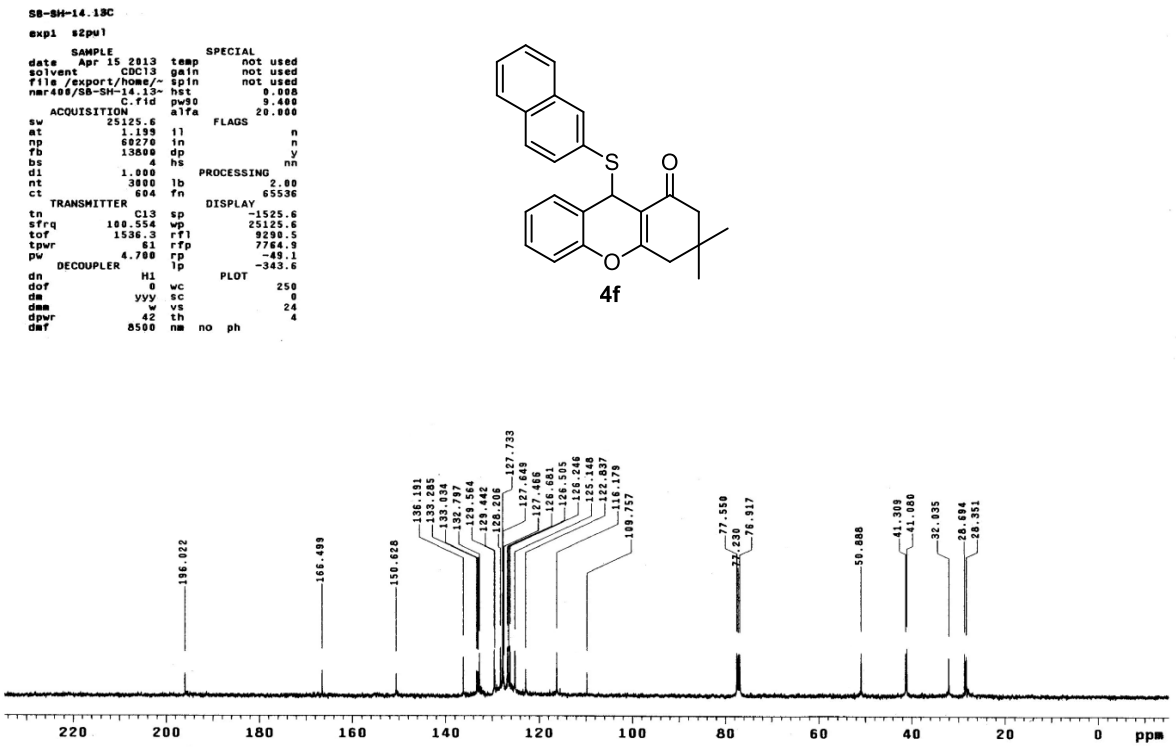
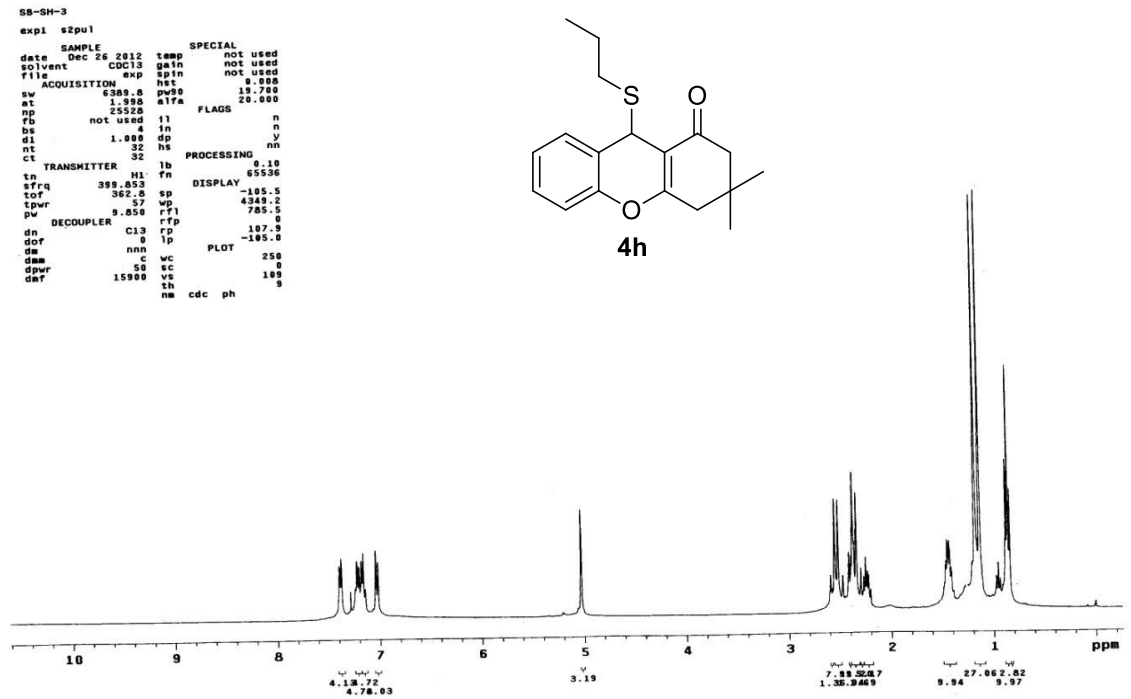


Figure 8

^{1}H NMR (400 MHz, $CDCl_3$)**: 3,3-Dimethyl-9-(propylthio)-2,3,4,9-tetrahydro-1H-xanthene-1-one* (4h***)



^{13}C NMR (100 MHz, $CDCl_3$)**: 3,3-Dimethyl-9-(propylthio)-2,3,4,9-tetrahydro-1H-xanthene-1-one* (4h***)

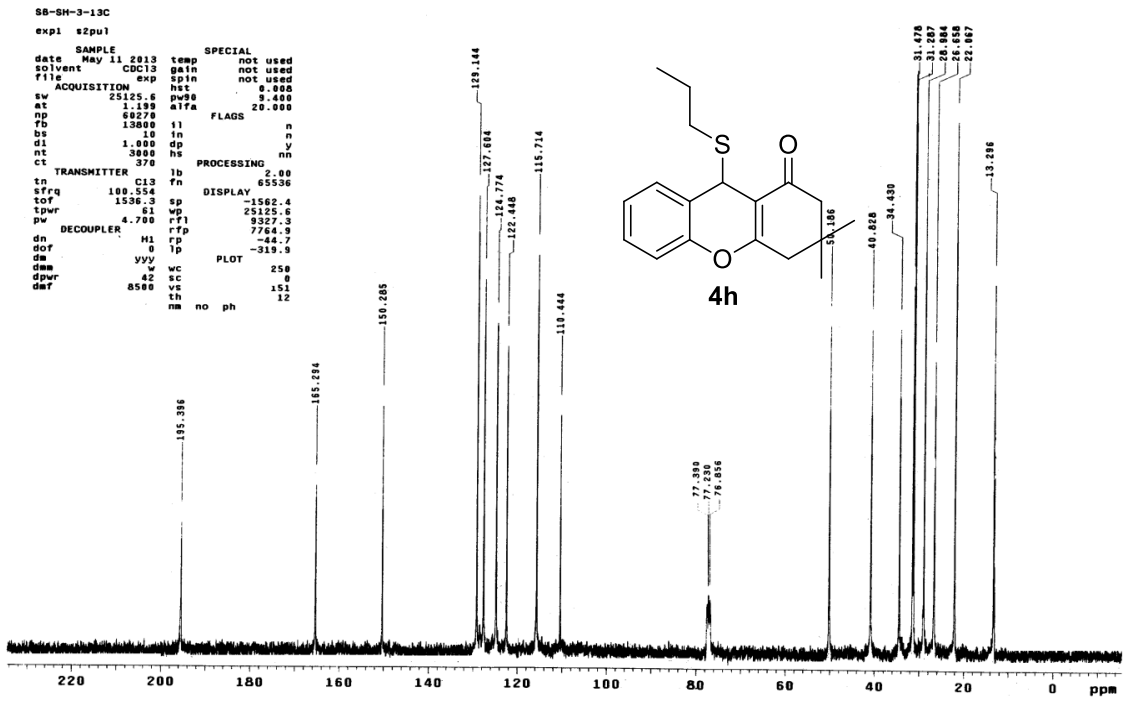
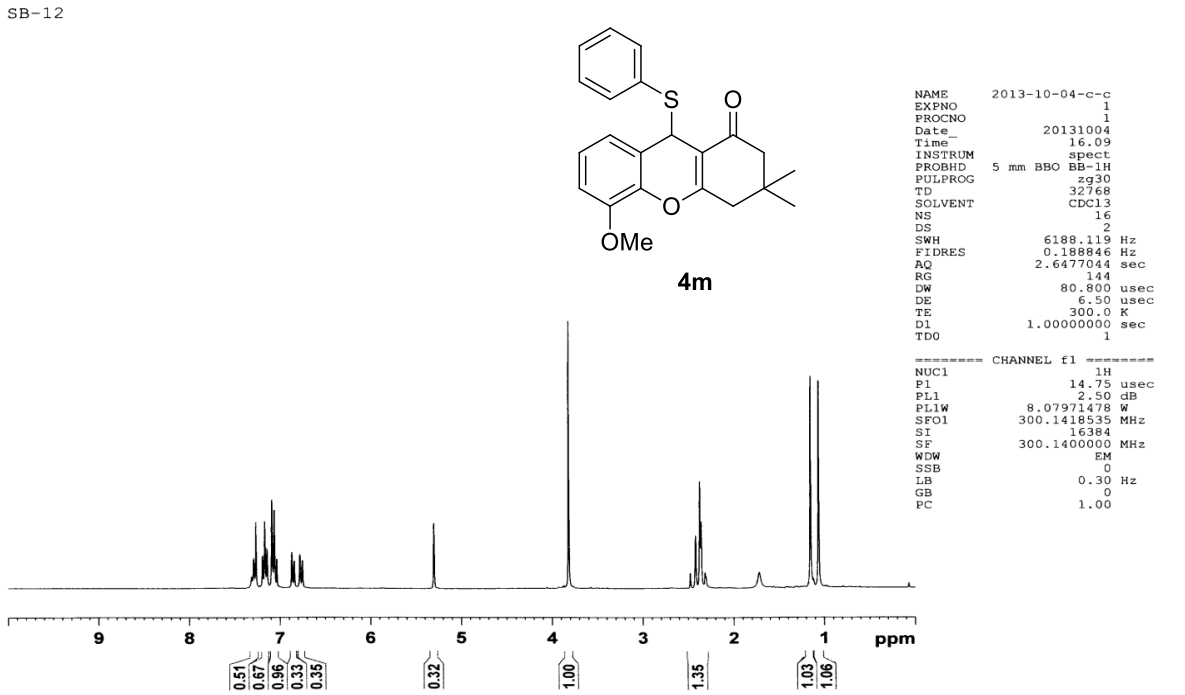


Figure 9

***^{1}H NMR (300 MHz, $CDCl_3$)**:5-Methoxy-3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4m**)*



***^{13}C NMR (100 MHz, $CDCl_3$)**:5-Methoxy-3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4m**)*

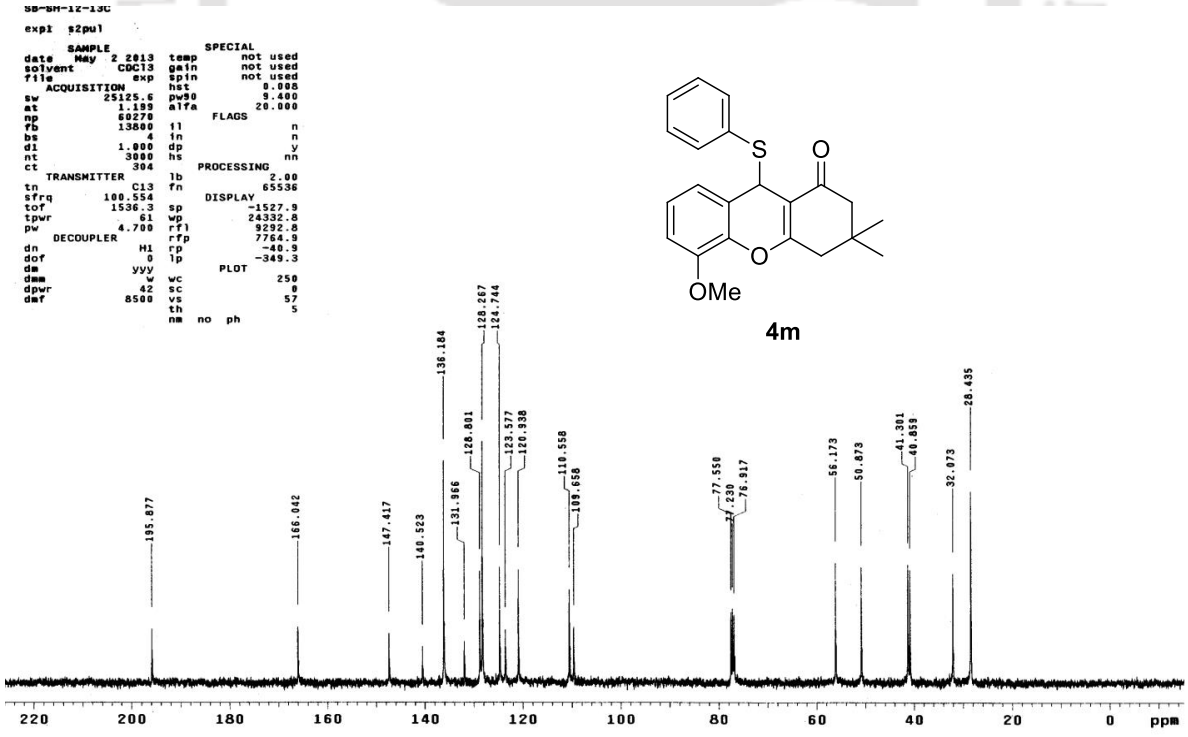
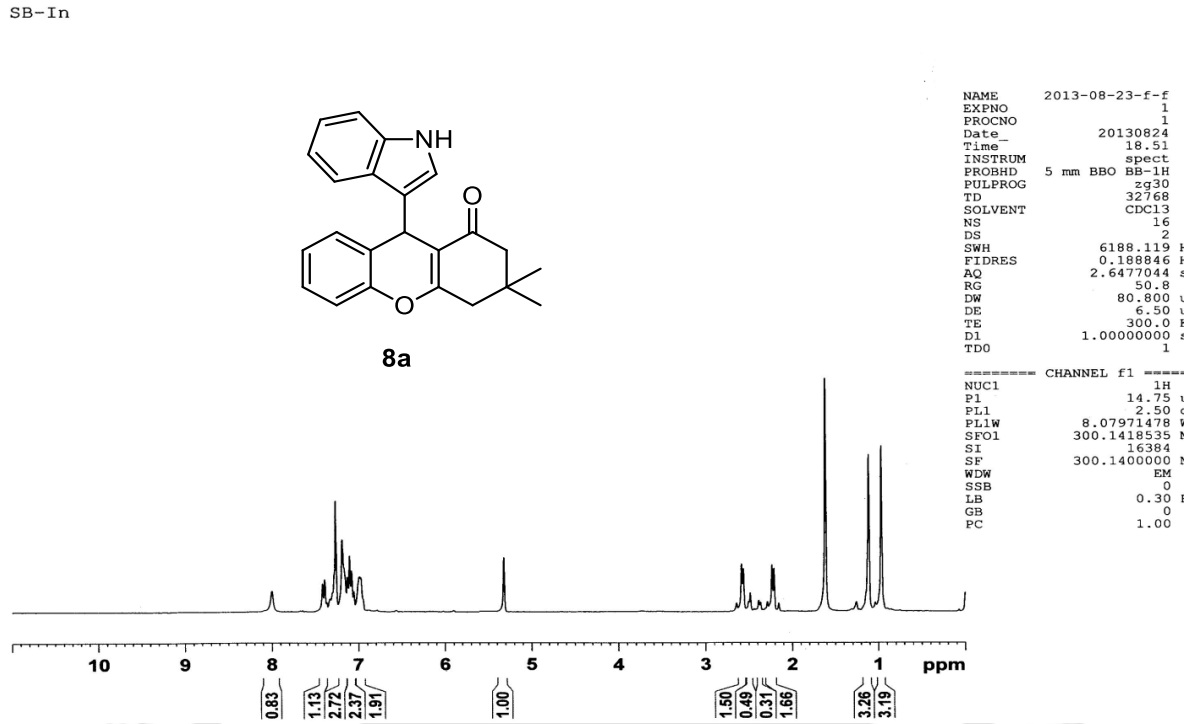


Figure 10

***^{1}H NMR (300 MHz, $CDCl_3$)**: 9-(1H-Indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**8a**)*



***^{13}C NMR (75 MHz, $CDCl_3$)**: 9-(1H-Indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**8a**)*

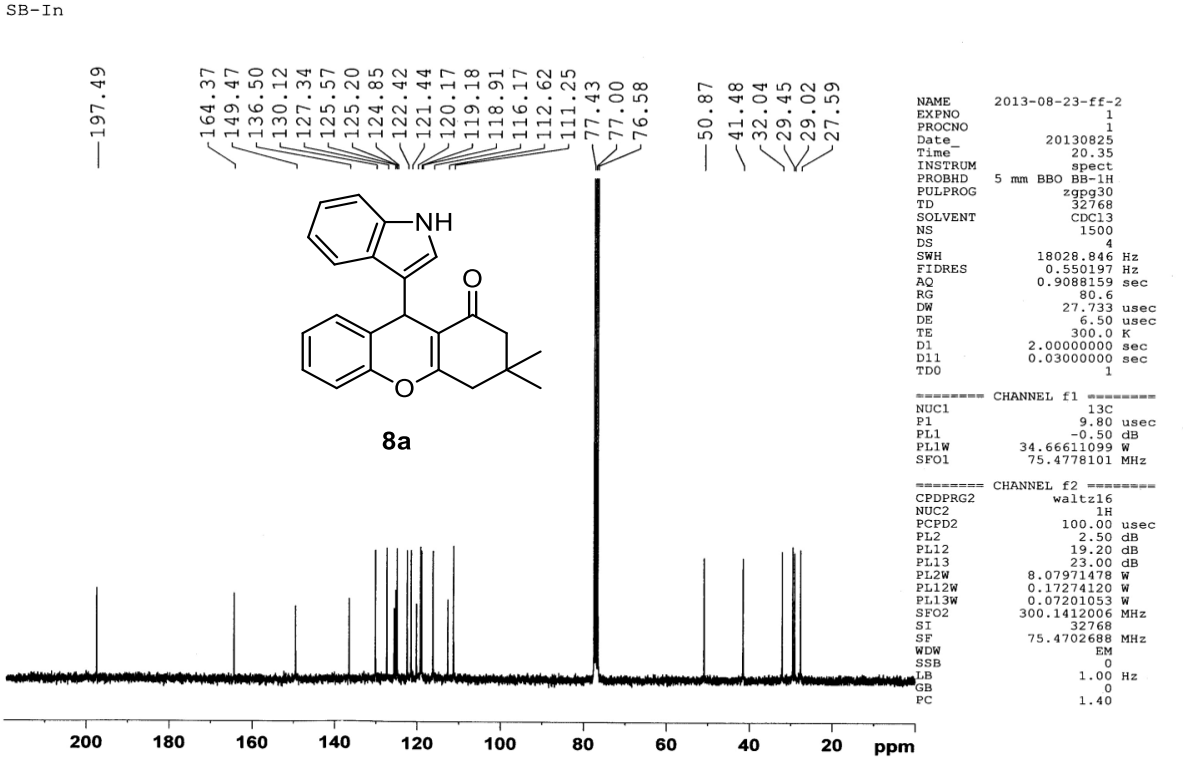
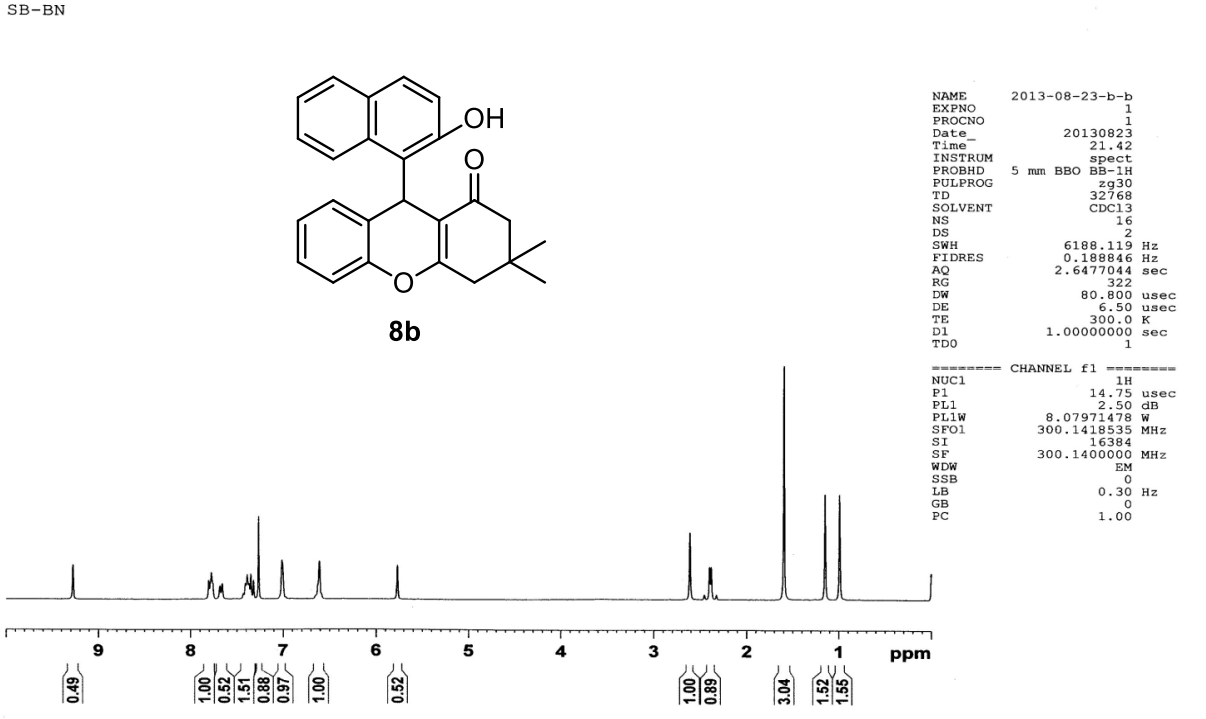


Figure 11

^{1}H NMR (300 MHz, $CDCl_3$)**: 9-(2-Hydroxynaphthalen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one **(8b)



^{13}C NMR (75 MHz, $CDCl_3$)**: 9-(2-Hydroxynaphthalen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one **(8b)

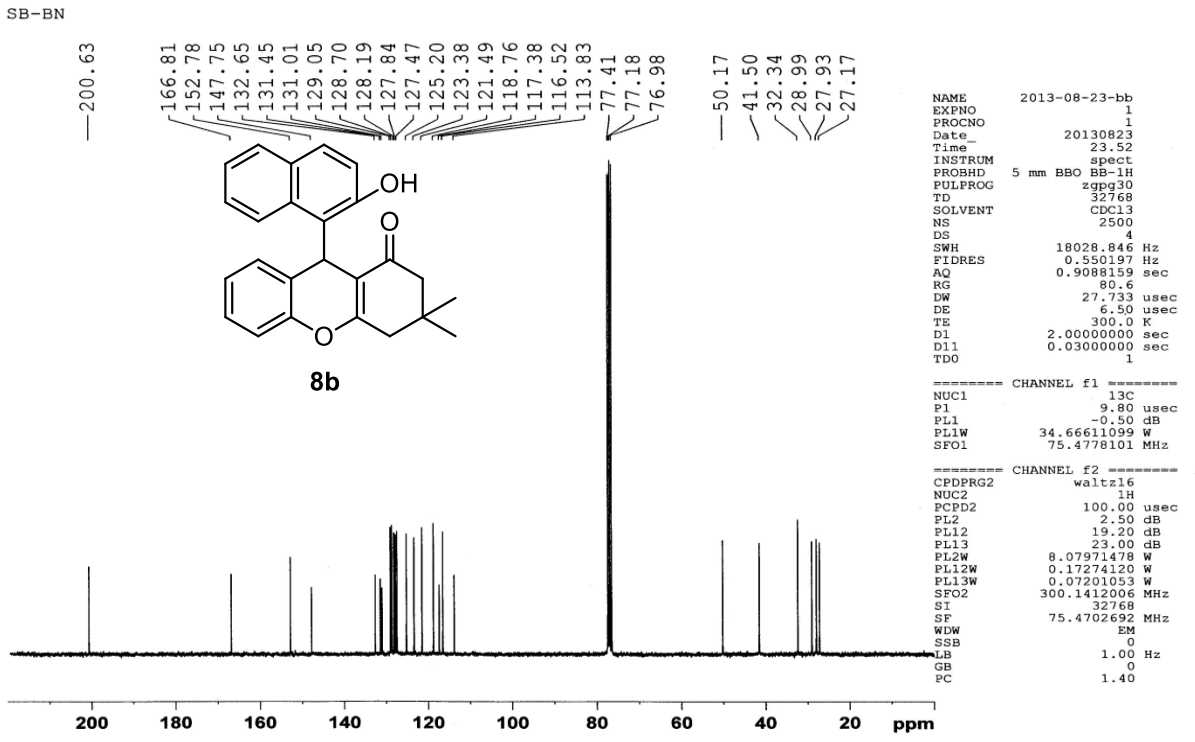


Figure 12

Part A

Chapter III

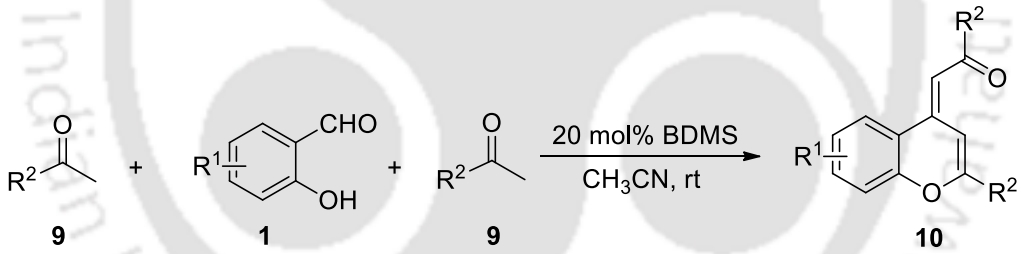
Bromodimethylsulfonium bromide: an efficient catalyst for one-pot synthesis of 4-phenacylidene flavene derivatives

Results & Discussion

Experimental Section

In the previous chapter, we have demonstrated the synthesis of 4*H*-chromene derivatives. On the basis of our familiarity and extension of the research work, we next tried to synthesize the substituted 4*H*-chromene moiety, like 4-phenacylidene flavene moiety, which has a 4*H*-chromene scaffold.

Recently, our research group[95] as well as others,[96] have demonstrated that bromodimethylsulfonium bromide (BDMS), is a constructive catalystfor various organic transformations and multicomponent reactions. The importance and usefulness of BDMS have been recently reviewed by our group.[97] BDMS is less expensive, non-toxic, easy to handle and environmentally acceptable pre-catalyst thus we have perceived that it can be explored further for the synthesis of 4-phenacylidene flavene derivatives. In continuation of our study of the catalytic activity of BDMS for the synthesis of various heterocycles through MCR, we report herein a straight forward, simple protocol for the synthesis of 4-phenacylidene flavene derivatives using pseudo three component condensations of one molecule of salicylaldehyde, and two molecules of acetophenone in acetonitrile at room temperature, shown in scheme 37.



R^1= H/ Br/ OMe/ OEt

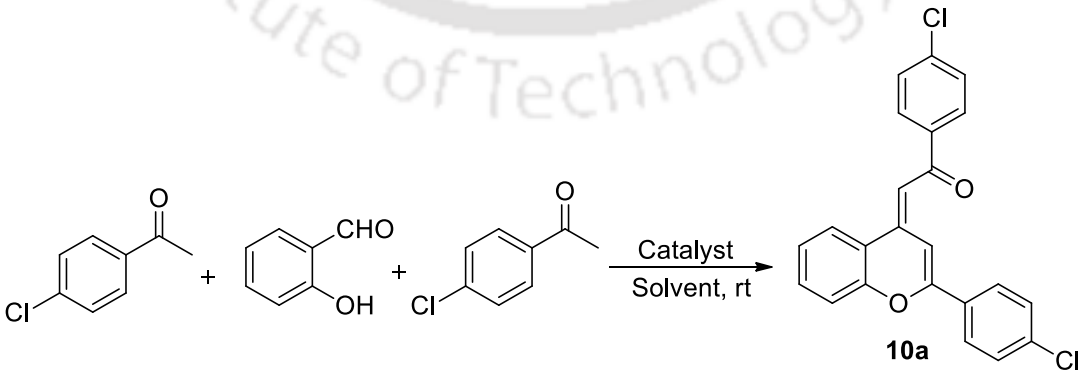
R^2= Thiophene/ C_6H_5/ *p*-$OMeC_6H_4$/ *p*-MeC_6H_4/ *p*-FC_6H_4/ *p*-ClC_6H_4/ *p*-BrC_6H_4/ *p*-$NO_2C_6H_4$/ *m*-$NO_2C_6H_4$

Scheme 37. One-pot pseudo three-component synthesis of4-phenacylidene flavene derivatives

For the present study, the mixture of salicylaldehyde (1 mmol) and 4′-chloro acetophenone (2 mmol) was stirred in presence of 10 mol % of BDMS in acetonitrile (3 mL) for 6h at room temperature. The product 4-phenacylidene flavene**10a** was isolated in 56% yield after chromatographic purification (Table 5, entry 1).The same set of reactions were also carried out using 15 mol% and 20 mol% of BDMS in acetonitrile under identical reaction condition and it provided the desired product **10a** (Table 5, entry 2 and 3) in 69%, and 78% yields, respectively.From these observations, it is clear that the yield of the product **10a** increases

slowly with increasing the amount of catalyst from 10% to 20%.It was noted that the yield of the product **10a** did not increase significantly by increasing the amount of catalyst from 20% to 30% (Table 5, entry 4). For scrutinizing the suitable solvent system, the similar reactions (Table 5, entries 5-8) were conducted in ethanol, DCM, THF and toluene under identical reaction conditions and the highest yields and the shortest reaction times were obtained in acetonitrile. To examine the efficacy of the catalyst, several reactions were carried out in the presence of other acidic catalysts (Table 5, entries 9-12) under identical reaction conditions. From these observations, it seems to us that BDMS is an optimal catalyst for the present reaction. The reactions were very sluggish and incomplete even after 24 h of stirring at room temperatures when the same reaction was carried out in presence of protic acids such as acetic acid and hydrobromic acid (Table 5, entries 13 and 14). It was also observed that no desired product was obtained in absence of catalyst even after 24 h of stirring at room temperature and only the starting substrates were recovered (Table 5, entry 15). The product **10a** was exemplified by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. In IR, the compound shows strong absorptions peak at 1743 and 1640 indicates the presence of carbonyl group and olefinic double bond. Similarly, in ^{1}H spectra it shows the characteristic signals at 8.90 (s, 1H), 8.01-7.88 (m, 5H), 7.55 (d, *J*= 7.2 Hz, 1H), 7.50-7.30 (m, 6H), 7.08 (s, 1H) ppm. Equally, in ^{13}C NMR, signals are present at 189.1, 155.3, 153.1, 142.8, 139.8, 138.1, 136.9, 132.2, 131.2, 129.3, 129.2, 128.9, 127.5, 125.4, 123.4, 120.5, 118.8, 103.3, 103.1 ppm. The molecular ion peak exhibited at 394.0429 which confirmed the formation of product **10a**.

Table 5: Optimization table for the synthesis of 4-phenacylidene flavene **10a**[a]

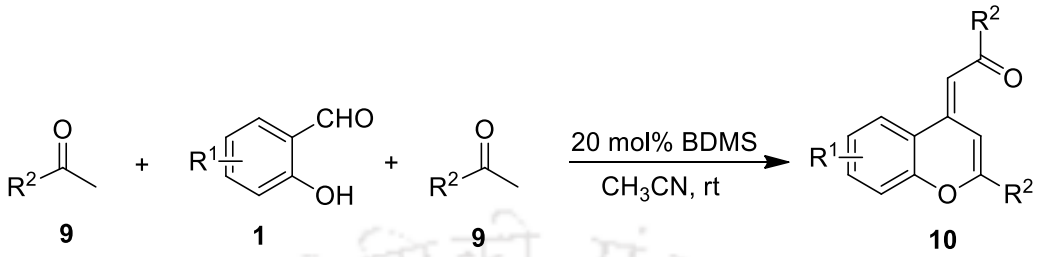


Entry	Catalyst	Solvent	Mol% of catalyst	Time (h)	Yield[b] %
1	BDMS	MeCN	10	6.0	56
2	BDMS	MeCN	15	3.5	69
3	**BDMS**	**MeCN**	**20**	**2.5**	**78**
4	BDMS	MeCN	30	3.0	79
5	BDMS	EtOH	20	5.0	62
6	BDMS	DCM	20	5.0	41
7	BDMS	THF	20	5.0	52
8	BDMS	Toluene	20	4.5	64
9	*p*-TSA	MeCN	20	4.0	72
10	TBATB	MeCN	20	4.0	65
11	$ZnCl_2$	MeCN	20	4.0	28
12	NH_4Cl	MeCN	20	4.0	48
13	CH_3COOH	MeCN	20	24.0	15
14	HBr	MeCN	20	24.0	22
15	None	MeCN	00	24.0	00

[a]All the reactions were performed with salicylaldehyde (1 mmol) and 4′-chloro acetophenone (2 mmol) in the presence of indicated catalyst in 3 mL of indicated solvent at room temperature. [b]Isolated yields.

After optimizing the reaction condition, we performed a reaction with a mixture of salicylaldehyde (1 mmol) and acetophenone (2 mmol) under identical conditions and the desired product **10b** was isolated in 76% yield (Table 6, entry 2). Next, we turned our attention to investigating the scope and applicability of this reaction by carrying out the synthesis of substituted 4-phenacylidene flavenes using different acetophenone derivatives with electron-withdrawing or electron-donating groups on the ring (Table 6). Acetophenone derivatives with electron-donating or electron-withdrawing groups produced 4-phenacylidene flavene derivatives **10c–f** in moderate to good yields (Table 6, entries 3–6). It is worthwhile to mention that acetophenone with electron-donating groups on the ring (Table 6, entry 5 and 6) react faster as compared to acetophenone with electron-withdrawing groups (Table 6, entry 3 and 4) for the present protocol.

Table 6: Substrate scope and yields of 4-phenacylidene flavene derivatives (**10**)[a,]

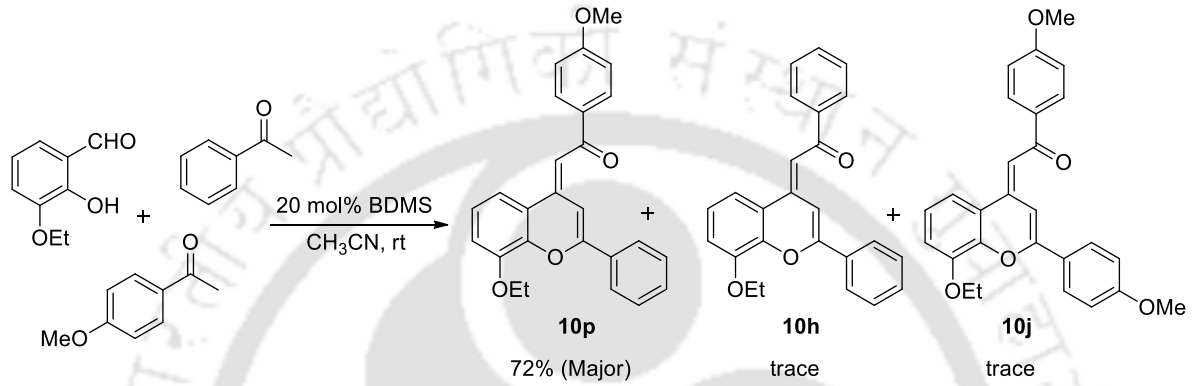


Entry	R^1	R^2	Time (h)	Yield[b]/(%)	Product
1	H	4-ClC_6H_4	2.5	78	**10a**
2	H	C_6H_5	2.0	76	**10b**
3	H	4-$NO_2C_6H_4$	6.0	66	**10c**
4	H	3-$NO_2C_6H_4$	5.0	64	**10d**
5	H	4-MeC_6H_4	4.0	82	**10e**
6	H	4-$OMeC_6H_4$	3.0	86	**10f**
7	H	Thiophene	3.0	91	**10g**
8	3-OEt	C_6H_5	3.0	75	**10h**
9	3-OEt	4-FC_6H_4	2.0	74	**10i**
10	3-OEt	4-$OMeC_6H_4$	4.0	80	**10j**
11	3-OMe	4-ClC_6H_4	5.0	76	**10k**
12	3-OMe	4-MeC_6H_4	2.0	82	**10l**
13	5-OMe	C_6H_5	5.0	74	**10m**
14	5-OMe	4-BrC_6H_4	7.0	76	**10n**
15	5-Br	4-ClC_6H_4	5.0	73	**10o**

[a]The reactions were carried out with salicylaldehydes (1 mmol) and acetophenones (2 mmol) in the presence of 20 mol % of BDMS in 3 mL of CH_3CN at room temperature. [b]Isolated yields.

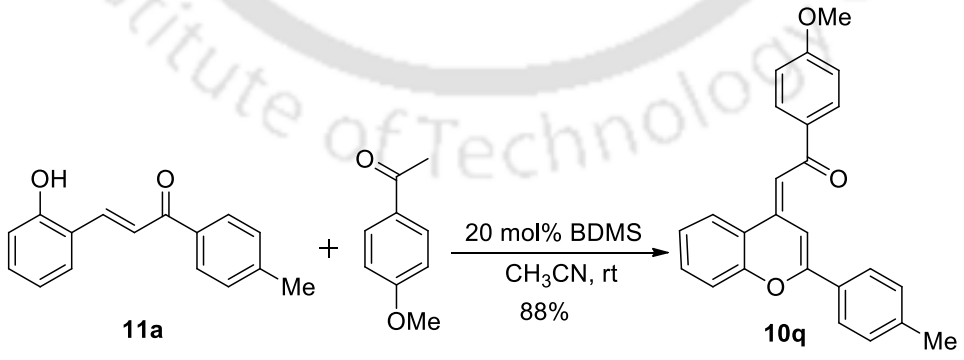
Likewise, heteroaryl methyl ketone, 2-acetylthiophene, also providedthe desired product **10g** (Table 6, entry 7) in excellent yield. To verify the generality of the present protocol, the reaction was explored with other substituted salicylaldehydes bearing OEt, OMe and Br substituent in the ring with different acetophenone derivatives and the desired products**10h–o** were obtained in good yield (Table 6, entries 8-15).

For an attempt to synthesize the unsymmetrical flavene moiety, we have performed the reaction with 3-OEt salicylaldehyde (1 mmol), acetophenone (1 mmol) and 4′-OMe acetophenone (1 mmol) under the identical reaction condition, which afforded the unsymmetrical product **10p** after 4h with 72% yield, along with the formation of trace amount of symmetrical products **10h** and **10j** as shown inScheme 38.



Scheme 38. One-pot synthesis of unsymmetrical 4-phenacylidene flavene **10p**

To minimize the formation of side product in unsymmetrical reaction, we next explored the reaction with chalcone (*E*)-3-(2-hydroxyphenyl)-1-(*p*-tolyl)prop-2-en-1-one **11a** which was synthesized from salicylaldehyde and 4′-Me acetophenone according to the reported method[98] and consecutively treated with 4′-OMe acetophenone using 20 mol% of BDMS in acetonitrile at room temperature, the reaction results in the formation of desired product **10q** exclusively with 88% yield after 1.5h as shown in Scheme 39.



Scheme 39. One-pot synthesis of unsymmetrical 4-phenacylidene flavene**10q**

Similarly, reaction of chalcone derived from 3-OEt salicylaldehyde and acetophenone which is (*E*)-3-(3-ethoxy-2-hydroxyphenyl)-1-phenylprop-2-en-1-one **11b** with 4′-OMe

acetophenone gave the desired unsymmetrical product **10p** exclusively in 81% yield under identical reaction conditions.

All the products from **10a-10q** were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectrometry. In FTIR spectrum, it showed characteristic absorptions peaks in between 1690-1743 due to one carbonyl group in product **10**. Similarly, the compound **10** showed a diagnostic signal at the range of δ = 8.74-9.08 in the ^{1}H NMR spectrum assignable to the olefinic hydrogen trans to the carbonyl group. The ^{1}H NMR and ^{13}C NMR spectra of the products **10g, 10h, 10n, 10p** and **10q** are shown in Figure**14-18** respectively in the experimental section. Finally, the structure of one of the representative compound **10f** was confirmed unambiguously by single crystal X-ray diffraction analysis (Fig. 13).

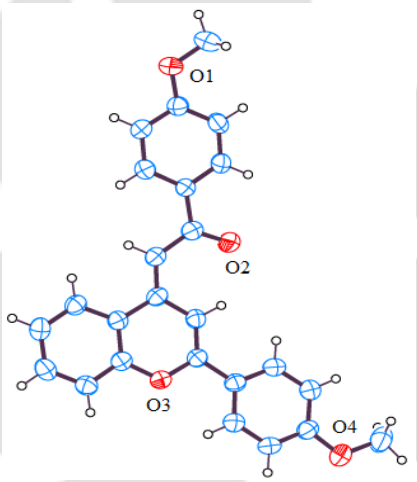
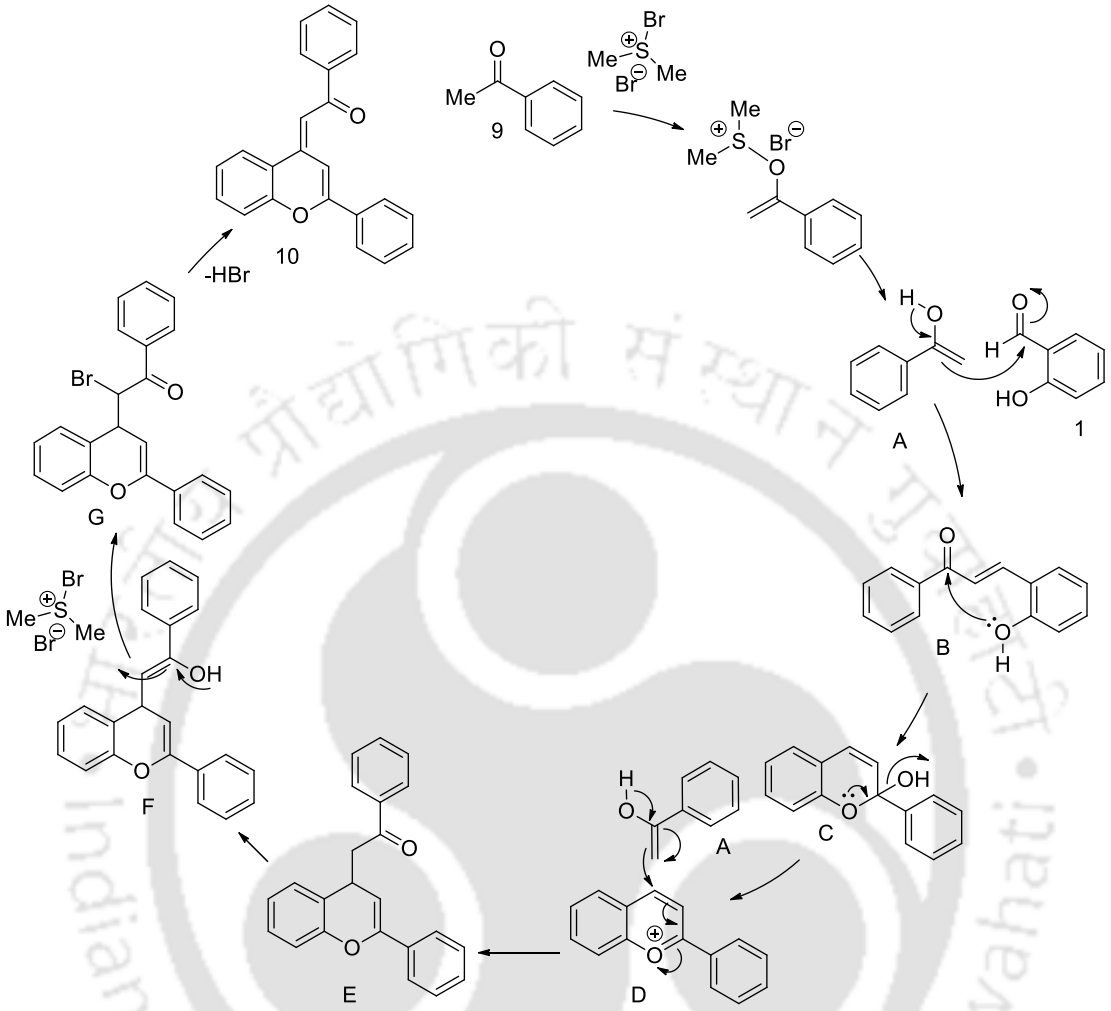


Figure 13.X-Ray Crystal structure of 4-phenacylidene flavene (**10f**) (CCDC No. 1008522)

On the basis of the reported literature,[96, 97] we have proposed a mechanism for the formation of product **10** as shown in Scheme 40. The first step is believed to be the formation of enolic acetophenone **A** in presence of catalyst BDMS and it reacts with salicylaldehyde to give 2-hydroxy chalcone **B**, which undergoes intramolecular cyclization, to hemiacetal species **C**, which then gets converted to the more reactive flavylium ion **D**.[99] Enolic form of acetophenone **A** reacts as C-nucleophiles and attacks flavylium ion **D** to form intermediate **E**. Subsequently, intermediate **E** undergoes enol tautomerism and forms **F**. Next, in presence of BDMS, intermediate **F** forms α-bromo ketone **G,** which finally releases HBr to form the desired final product **10** as shown in Scheme 40.



Scheme 40. Proposed BDMS catalyzed formation of 4-phenacylidene flavenederivatives (**10**)

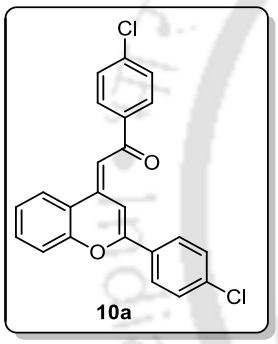
In conclusion, we have developed a simple one pot pseudo three components reaction for the synthesis of 4-phenacylidene flavene derivatives from readily available salicylaldehydes and acetophenones, using a mild catalyst at room temperature. The reaction conditionis simple and transformation is quite effective for a widerange of salicylaldehyde and acetophenone derivatives. The protocol is blessed with several advantages like one-pot, good yield, use of environment friendly catalyst, mild reaction condition and atom economy.

Experimental

*General procedure for the synthesis of 4-phenacylidene flavene derivatives (**10**)*:

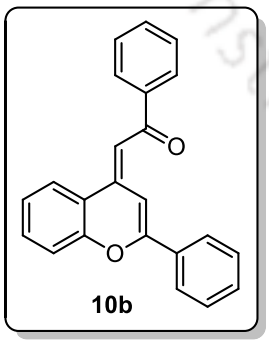
A mixture of salicylaldehyde (1 mmol), acetophenone (2 mmol), and BDMS (0.2 mmol) in CH_3CN (3 mL) was stirred at room temperature for 2-7 h in 25 mL round bottomed flask. The progress of the reaction was monitored by TLC (eluent: EtOAc-hexane, 1:9). After the completion of the reaction, the crude reaction mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with H_2O (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh, eluent: EtOAc-hexane, 1:9) to afford the pure products in 64-91%yields.

*(E)-1-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-4H-chromen-4-ylidene)ethanone (**10a**):*



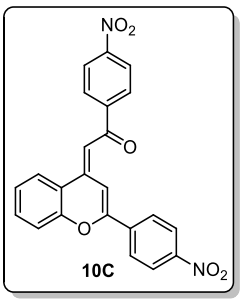
Yellow solid, mp 170-172 °C; **IR**(KBr): 2923, 2853, 1743, 1640, 1092, 754 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 8.01-7.88 (m, 5H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.50-7.30 (m, 6H), 7.08 (s, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 189.1, 155.3, 153.1, 142.8, 139.8, 138.1, 136.9, 132.2, 131.2, 129.3, 129.2, 128.9, 127.5, 125.4, 123.4, 120.5, 118.8, 103.3, 103.1; **MS (ESI)**: [M + H^+], Calcd. For: $C_{23}H_{15}{}^{35.5}Cl_2O_2$ (394.0341); Found: 394.0429.

*(E)-1-phenyl-2-(2-phenyl-4H-chromen-4-ylidene)ethanone (**10b**):*



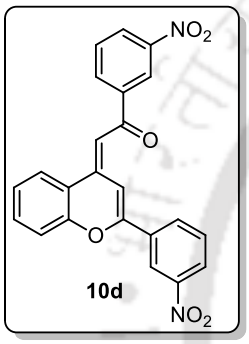
Yellow solid, mp 129-130 °C; **IR** (KBr): 1700, 1635, 1533, 1263, 752 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.96 (s, 1H), 8.03 (t, *J* = 8.0 Hz, 4H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 5.2 Hz, 6H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.15 (s, 1H);**^{13}C NMR** (150 MHz, $CDCl_3$): δ = 190.5, 156.2, 153.2, 142.6, 141.5, 132.7, 131.9, 131.8, 130.7, 128.9, 128.6, 127.9, 126.2, 125.2, 123.3, 120.6, 118.7, 103.3, 103.1; **MS (ESI)**: [M+ H^+], Calcd. For: $C_{23}H_{17}O_2$ (325.1184); Found: 325.1163.

*(E)-1-(4-nitrophenyl)-2-(2-(4-nitrophenyl)-4H-chromen-4-ylidene)ethanone (**10c**):*



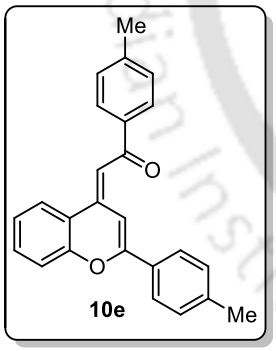
Red solid, mp 202-204 °C; **IR** (KBr): 2997, 2914, 1690, 1601, 1518, 1341, 1203, 1003, 854, 748 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.08 (s, 1H), 8.36 (t, *J* = 7.2 Hz, 4H), 8.17 (t, *J* = 8.8 Hz, 4H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.17 (s, 1H); **MS (ESI)**: [M + H^+], Calcd. For: $C_{23}H_{15}N_2O_6$ (415.0885); Found: 415.0871.

*(E)-1-(3-nitrophenyl)-2-(2-(3-nitrophenyl)-4H-chromen-4-ylidene)ethanone (**10d**):*



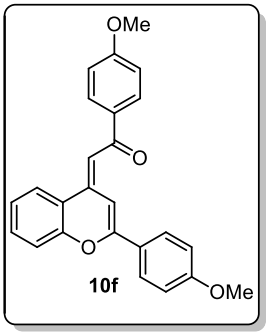
Yellow solid, mp 248-249 °C; **IR** (KBr): 2923, 2852, 1734, 1638, 1546, 1527, 1347, 1021, 728 cm^{-1}; **^{1}H NMR**(400 MHz, $CDCl_3$): δ =9.05 (s, 1H), 8.85 (s, 2H), 8.40 (d, *J* = 7.6 Hz, 1H), 8.35 (t, *J* = 8.0 Hz, 3H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.74-7.67 (m, 2H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.18 (s, 1H); **MS (ESI)**: [M+ H^+], Calcd. For: $C_{23}H_{15}N_2O_6$ (415.0885); Found: 415.0756.

*(E)-1-(p-tolyl)-2-(2-(p-tolyl)-4H-chromen-4-ylidene)ethanone (**10e**):*



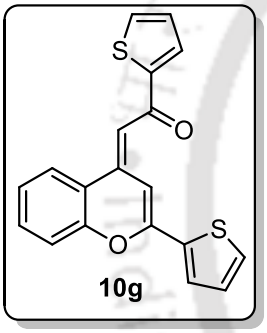
Yellow solid, mp 147-149 °C;**IR** (KBr): 2920, 1730, 1633, 1536, 1265, 1004, 756 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.94 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.97-7.90 (m, 4H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 5H), 2.43 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 190.0, 156.2, 153.0, 142.7, 142.2, 141.0, 138.8, 131.7, 130.7, 129.6, 129.2, 127.9, 126.0, 125.0, 123.2, 120.5, 118.6, 102.7, 102.4, 21.8, 21.7; **MS (ESI):** [M+ H^+], Calcd. For: $C_{25}H_{21}O_2$ (353.1536); Found: 353.1536.

*(E)-1-(4-methoxyphenyl)-2-(2-(4-methoxyphenyl)-4H-chromen-4-ylidene)ethanone (**10f**):*



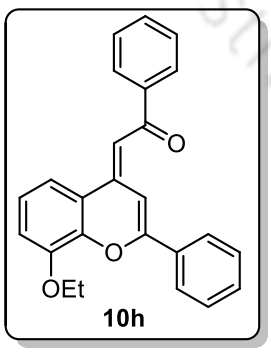
Yellow solid, mp 168-170 °C; **IR** (KBr): 2925, 2837, 1685, 1640, 1603, 1532, 1251, 1170, 1004, 758 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.87 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 3H), 7.95(d, *J* = 8.0 Hz, 2H), 7.58-7.49 (m, 1H), 7.39 (d, *J* = 9.2 Hz, 1H), 7.36-7.29 (m, 1H), 7.10 (s, 1H), 6.98 (d, *J* = 7.6 Hz, 4H), 3.89 (s, 6H);**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 188.8, 162.3, 161.4, 155.6, 152.8, 142.1, 134.1, 131.3, 129.7, 127.5, 124.9, 124.7, 122.9, 120.4, 118.3, 113.9, 113.6, 102.0, 101.4, 55.3;**MS (ESI)**: [M + H^+], Calcd. For: $C_{25}H_{21}O_4$ (385.1395); Found: 385.1397.

*(E)-1-(thiophen-2-yl)-2-(2-(thiophen-2-yl)-4H-chromen-4-ylidene)ethanone (**10g**):*



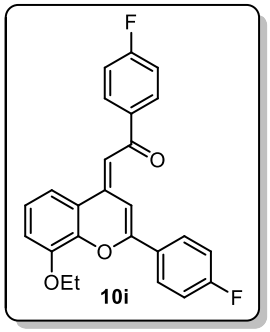
Yellow solid, mp 138-139 °C; **IR** (KBr): 2924, 1630, 1537, 1263, 977, 758 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.74 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 3.6 Hz, 1H), 7.68 (d, *J* = 3.6 Hz, 1H), 7.53 (d, *J* = 4.8 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.35-7.26 (m, 2H), 7.13-7.09 (m, 2H), 6.94 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 181.8, 152.2, 151.5, 148.5, 141.5, 136.0, 131.8, 131.6, 129.1, 128.6, 127.9, 127.8, 126.9, 124.9, 122.9, 119.6, 118.1, 101.9, 101.7; **MS (ESI):** [M + H^+], Calcd. For: $C_{19}H_{13}O_2S_2$ (337.0312); Found: 337.0348.

*(E)-2-(8-ethoxy-2-phenyl-4H-chromen-4-ylidene)-1-phenylethanone (**10h**):*



Yellow solid, mp 155-156 °C;**IR** (KBr): 2924, 1690, 1632, 1571, 1532, 1283, 1222, 1150, 1065, 765 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.99 (s, 1H), 8.05-8.00 (m, 4H), 7.54-7.45 (m, 7H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.09 (s, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 4.19 (q, *J* = 4.4 Hz, 2H), 1.54 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 190.5, 148.9, 143.0, 141.7, 132.9, 131.7, 130.7, 128.9, 128.7, 128.6, 128.4, 127.9, 126.3, 124.7, 121.6, 114.6, 114.2, 103.4, 102.9, 65.2, 15.1; **MS (ESI)**: [M + H^+], Calcd. For: $C_{25}H_{21}O_3$ (369.1446); Found: 369.1432.

(E)-2-(8-ethoxy-2-(4-fluorophenyl)-4H-chromen-4-ylidene)-1-(4-fluorophenyl)ethanone

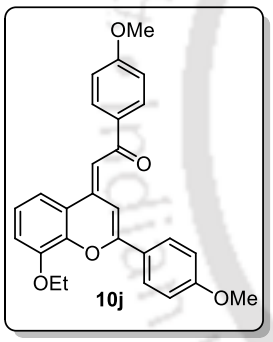


10i

(10i):

Yellow solid, mp 159-160 °C; **IR** (KBr): 2977, 1637, 1602, 1527, 1506, 1333, 1273, 1219, 1156, 1067, 783 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 8.05-8.01 (m, 4H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 4.4 Hz, 1H), 7.14 (t, *J* = 8.8 Hz, 3H), 7.06 (s, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 4.19 (q, *J* = 6.8 Hz, 2H), 1.55 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 188.8, 166.3, 165.6, 163.8, 163.1, 155.0, 148.9, 143.6, 143.2, 130.3, 130.2, 128.3, 128.2, 124.8, 121.3, 116.2, 115.9, 115.6, 115.5, 114.4, 114.0, 102.8, 102.5, 65.0, 15.0; **MS (ESI)**: [M + H^+], Calcd. For: $C_{25}H_{19}F_2O_3$ (405.1258); Found: 405.1251.

(E)-2-(8-ethoxy-2-(4-methoxyphenyl)-4H-chromen-4-ylidene)-1-(4-methoxyphenyl)ethanone

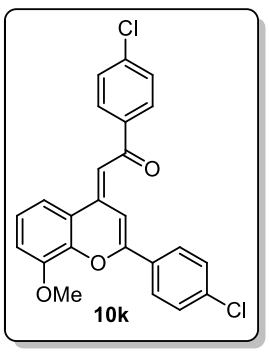


10j

(10j):

Yellow solid, mp 184-187 °C; **IR** (KBr): 2924, 1690, 1636, 1601, 1541, 1511, 1259, 1167, 1072, 1024, 829 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.89 (s, 1H), 8.03-7.95 (m, 4H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.03-7.00 (m, 2H),6.96 (t, *J* = 8.0 Hz, 4H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 6H), 1.54 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 189.0, 162.5, 161.6, 155.5, 148.8, 143.6, 142.6, 134.5, 129.9, 127.8, 125.4, 124.4, 121.6, 114.4, 114.3, 113.8, 113.7, 102.3, 101.4, 64.9, 55.6, 15.0; **MS (ESI):** [M + H^+] Calcd. For: $C_{27}H_{25}O_5$ (429.1657); Found: 429.1645.

(E)-1-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-8-methoxy-4H-chromen-4-ylidene)ethanone



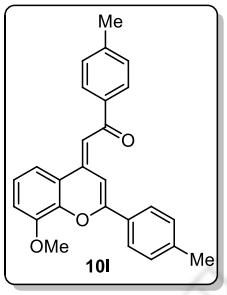
10k

(10k):

Yellow solid, mp 262-264 °C; **IR** (KBr): 2923, 1690, 1639, 1571, 1538, 1245, 1221, 1072, 1012, 777 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.92 (s, 1H), 7.98-7.92 (m, 4H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 4H), 7.26-7.23(m, 1H),7.06 (d, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 3.99 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 189.0, 155.0, 149.6, 143.4, 143.1, 139.8, 138.1, 136.9, 131.2, 129.3, 129.2,

128.9, 127.5, 124.9, 121.3, 114.5, 112.9, 103.2, 103.1, 56.5; **MS (ESI):** [M + H^+] Calcd. For: $C_{24}H_{17}{}^{35.5}Cl_2O_3$ (424.0447); Found: 424.0449.

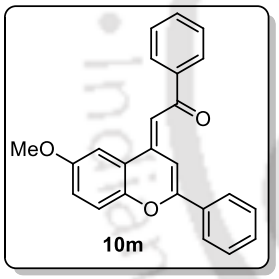
(E)-2-(8-methoxy-2-(p-tolyl)-4H-chromen-4-ylidene)-1-(p-tolyl)ethanone ***(10l):***



10l

Yellow solid, mp 180-183 °C; **IR** (KBr): 2922, 1734, 1636, 1607, 1569, 1521, 1230, 1154, 1075, 1014, 784 cm^{-1}; **^{1}H NMR**(400 MHz, $CDCl_3$): δ = 8.95 (s, 1H), 7.94 (d, *J* = 7.2 Hz, 4H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 5H), 7.08 (s, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.00 (s, 3H), 2.42 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 190.2, 155.9, 149.6, 143.6, 142.7, 142.2, 141.0, 139.0, 130.1, 129.7, 129.3, 127.9, 126.2, 124.5, 121.6, 114.6, 112.7, 103.1, 102.3, 56.5, 21.8, 21.7; **MS (ESI):** [M + H^+] Calcd. For: $C_{26}H_{23}O_3$ (383.1602); Found: 383.1601.

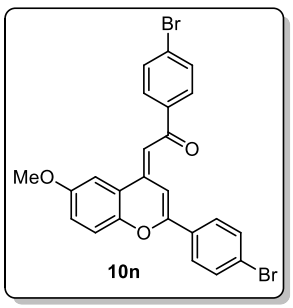
(E)-2-(6-methoxy-2-phenyl-4H-chromen-4-ylidene)-1-phenylethanone ***(10m):***



10m

Yellow solid, mp 114-115 °C;**IR** (KBr): 2928, 1700, 1660, 1626, 1486, 1271, 1152, 1036, 794 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.96 (s, 1H), 8.02 (brs, 2H), 7.48 (brs, 4H), 7.39 (brs, 3H), 7.33 (brs, 2H), 6.93 (t, *J* = 9.6 Hz, 1H), 6.74 (d, *J* = 7.2 Hz, 1H), 6.56 (s, 1H), 3.74 (s, 3H);**^{13}C NMR** (150 MHz, $CDCl_3$): δ = 196.3, 156.3, 152.9, 130.7, 128.9, 128.6, 127.8, 126.2, 125.5, 120.3, 119.9, 118.9, 117.6, 115.4, 114.1, 113.9, 105.6, 102.9, 102.5, 56.1; **MS (ESI):** [M + H^+] Calcd. For: $C_{24}H_{19}O_3$ (355.1289); Found: 355.1289.

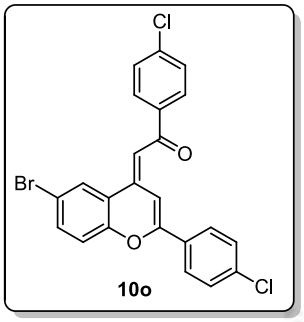
(E)-1-(4-bromophenyl)-2-(2-(4-bromophenyl)-6-methoxy-4H-chromen-4ylidene)ethanone ***(10n):***



10n

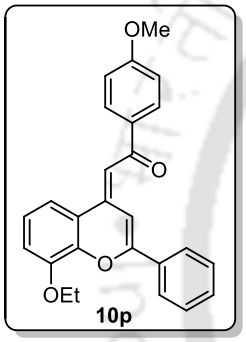
Yellow solid, mp 163-164 °C; **IR** (KBr): 2924, 1734, 1639, 1611, 1528, 1211, 1024, 1006, 794, cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.93 (s, 1H), 7.88 (t, *J* = 7.2 Hz, 4H), 7.62 (brs, 3H), 7.39 (d, *J* = 9.6 Hz, 1H), 7.35 (s, 1H), 7.26 (brs, 1H), 7.18 (d, *J* = 9.2 Hz, 1H), 6.96 (s, 1H), 3.94 (s, 3H);**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 189.2, 157.0, 155.3, 147.7, 143.1, 140.3, 132.2, 131.9, 131.6, 129.5, 127.6, 126.6, 125.3, 120.9, 120.0, 119.9, 105.6, 102.6, 102.5, 56.1;. **MS (ESI)**: $[M]^+$, Calcd. For: $C_{24}H_{16}{}^{79}Br_2O_3$ (512.9520); Found: 512.9501.

(E)-2-(6-bromo-2-(4-chlorophenyl)-4H-chromen-4-ylidene)-1-(4-chlorophenyl)ethanone ***(10o):***



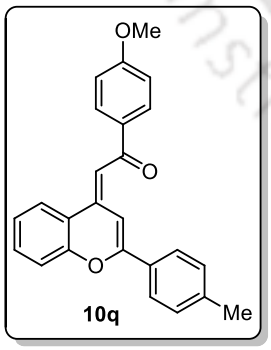
Yellow solid, mp 248-250 °C; **IR**(KBr): 2922, 1734, 1644, 1545, 1007, 826 cm^{-1}; **^{1}H NMR**(400 MHz, $CDCl_3$): δ = 8.86 (s, 1H), 8.08 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 4H), 7.30 (d, *J*= 9.2 Hz, 1H), 6.99 (s, 1H); **MS (ESI)**: $[M]^+$, Calcd. For: $C_{23}H_{13}{}^{79}Br\ {}^{35.5}Cl_2O_2$ (472.9527); Found: 472.9523.

(E)-2-(8-ethoxy-2-(4-methoxyphenyl)-4H-chromen-4-ylidene)-1-phenylethanone (***10p):***



Yellow solid, mp 131-133 °C; **IR** (KBr): 2925, 1729, 1635, 1533, 1227, 1067, 728 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.95 (s, 1H), 8.10-8.02 (m, 4H), 7.49-7.43 (m, 4H), 7.22 (t, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 3.6 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 4.20 (q, *J* =7.2 Hz, 2H), 3.89 (s, 3H), 0.88 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 189.3, 162.7, 155.5, 148.9, 143.8, 142.4, 134.4, 132.9, 130.6, 130.1, 128.9, 126.2, 124.6, 121.7, 114.6, 114.2, 113.8, 103.4, 102.9, 65.2, 55.7, 15.1; **MS (ESI):** $[M + H^+]$ Calcd. For: $C_{26}H_{23}O_4$ (399.1552); Found: 399.1542.

(E)-1-(4-methoxyphenyl)-2-(2-(p-tolyl)-4H-chromen-4-ylidene)ethanone ***(10q):***



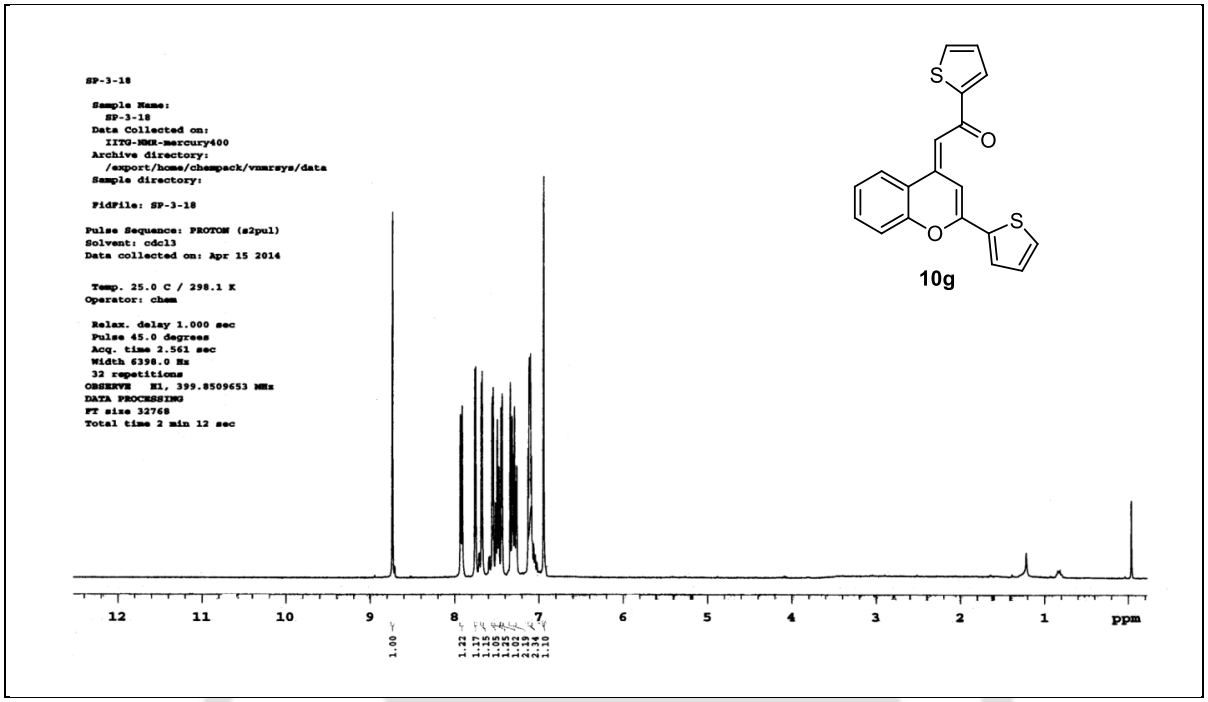
Yellow solid, mp 153-155 °C; **IR**(KBr): 2920, 1729, 1634, 1607, 1546, 1323, 1262, 1002, 752, cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.88 (s, 1H), 8.02-7.95 (m, 3H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.31-7.25 (m, 3H), 7.09 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 3.86 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 189.0, 162.5, 155.9, 153.0, 142.1, 140.9, 134.3, 131.6, 129.9, 129.6, 127.9, 125.9, 124.9, 123.2, 120.7, 118.6, 113.7, 102.7, 102.4, 55.5, 21.6; **MS (ESI):** $[M + H^+]$ Calcd. For: $C_{25}H_{21}O_3$ (369.1446); Found: 369.1431.

Complete crystallographic data of **10f** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication with CCDC no. 1008522.

Table 7: Crystal data and structure refinement for **10f**. For atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**Compound 10f**	**Parameters**	**Compound 10f**
Identification code	**sb-320**	Z	4
Empirical formula	$C_{25}H_{20}O_4$	Density (calculated)	1.321g/cm^3
Formula weight	384.41	Absorption coefficient	0.089mm^{-1}
Temperature	296 K	F(000)	808.0
Wavelength	0.71073Å	Theta range for data collection	1.45 to 25.24 º
Crystal system	Orthorhombic	Index ranges	-6<=h<= 6, -15<=k<=14, -31<=l<=33
Space group	$P2_{(1)}2_{(1)}2_{(1)}$	Reflections collected	23107
Unit cell dimensions		Independent reflections	3496 R_{int} = 0.0743
a	5.2558(8) Å	Completeness to θº	99%(θ = 25.24 º)
b	13.1158(16)Å	Refinement method	Full-matrix least-squares on F2
c	28.043(4)Å	Data / restraints / parameters	3496 / 0 / 264
α	90.00º	Goodness-of-fit on F2	0.952
β	90.00º	Final R indices [>2sigma(I)]	R_{obs} = 0.0498, wR_{obs} = 0.1339
γ	90.00º	R indices (all data)	R_{all} = 0.0839, wR_{all} = 0.1568
Volume	1933.1(5)Å^3	Largest diff. peak and hole	0.145 and -0.181e.Å^{-3}

***^{1}H NMR (400 MHz, $CDCl_3$)**: (E)-1-(thiophen-2-yl)-2-(2-(thiophen-2-yl)-4H-chromen-4-ylidene)ethanone(**10g**):*



***^{13}C NMR (100MHz, $CDCl_3$)**:(E)-1-(thiophen-2-yl)-2-(2-(thiophen-2-yl)-4H-chromen-4-ylidene)ethanone(**10g**):*

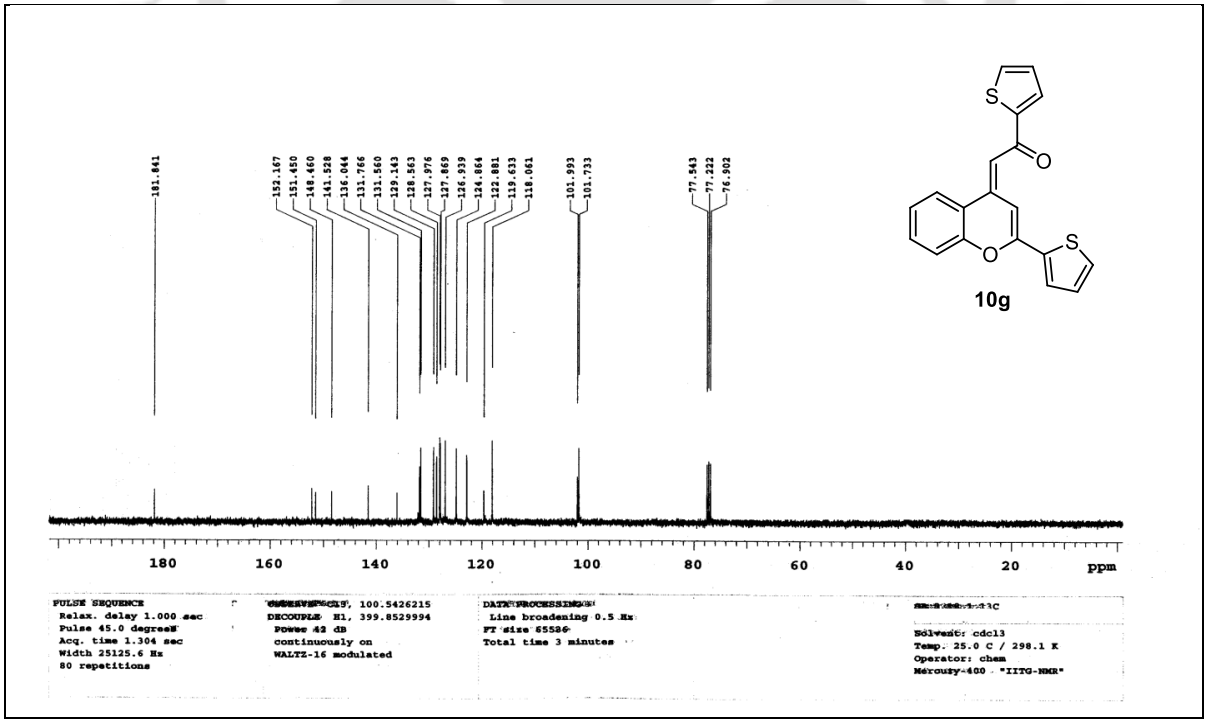
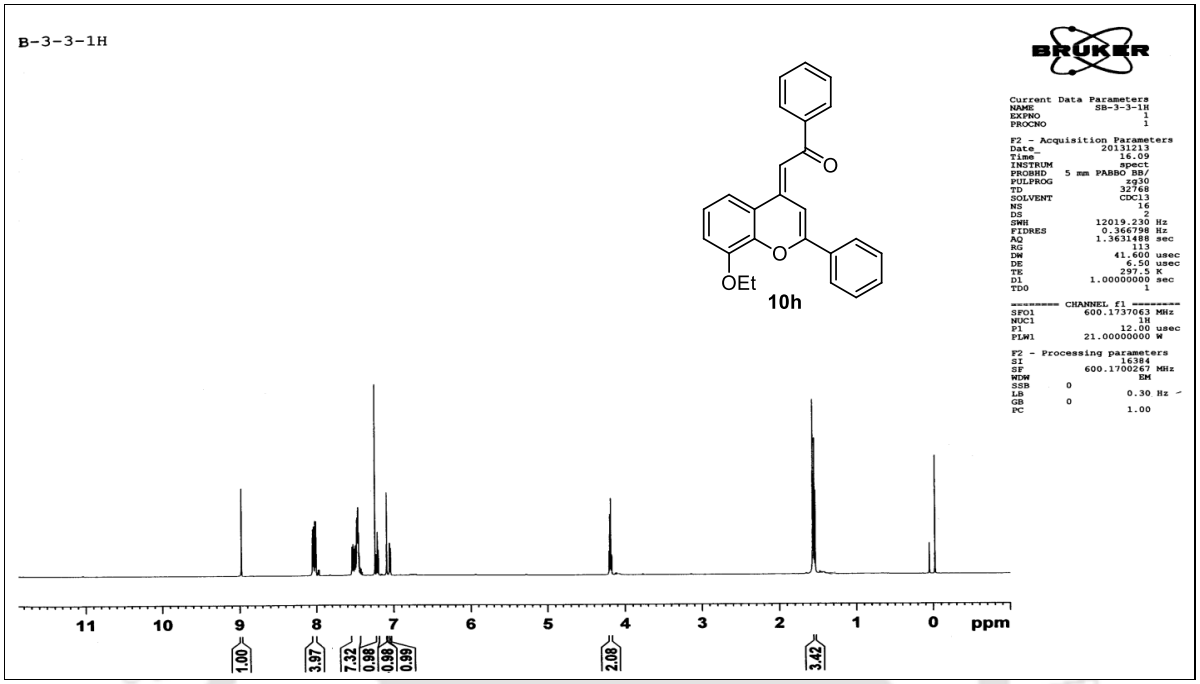


Figure 14

***^{1}H NMR (600MHz, $CDCl_3$)**:(E)-2-(8-ethoxy-2-phenyl-4H-chromen-4-ylidene)-1-phenylethanone(**10h**):*



***^{13}C NMR (150MHz, $CDCl_3$)**:(E)-2-(8-ethoxy-2-phenyl-4H-chromen-4-ylidene)-1-phenylethanone(**10h**):*

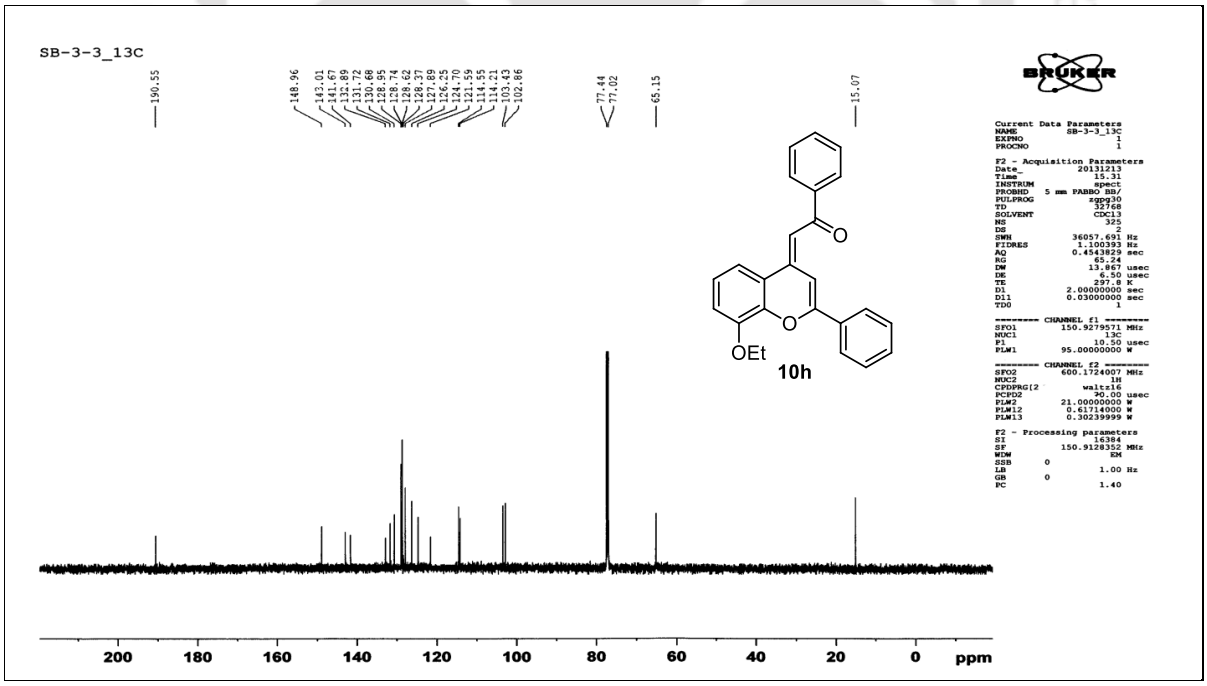
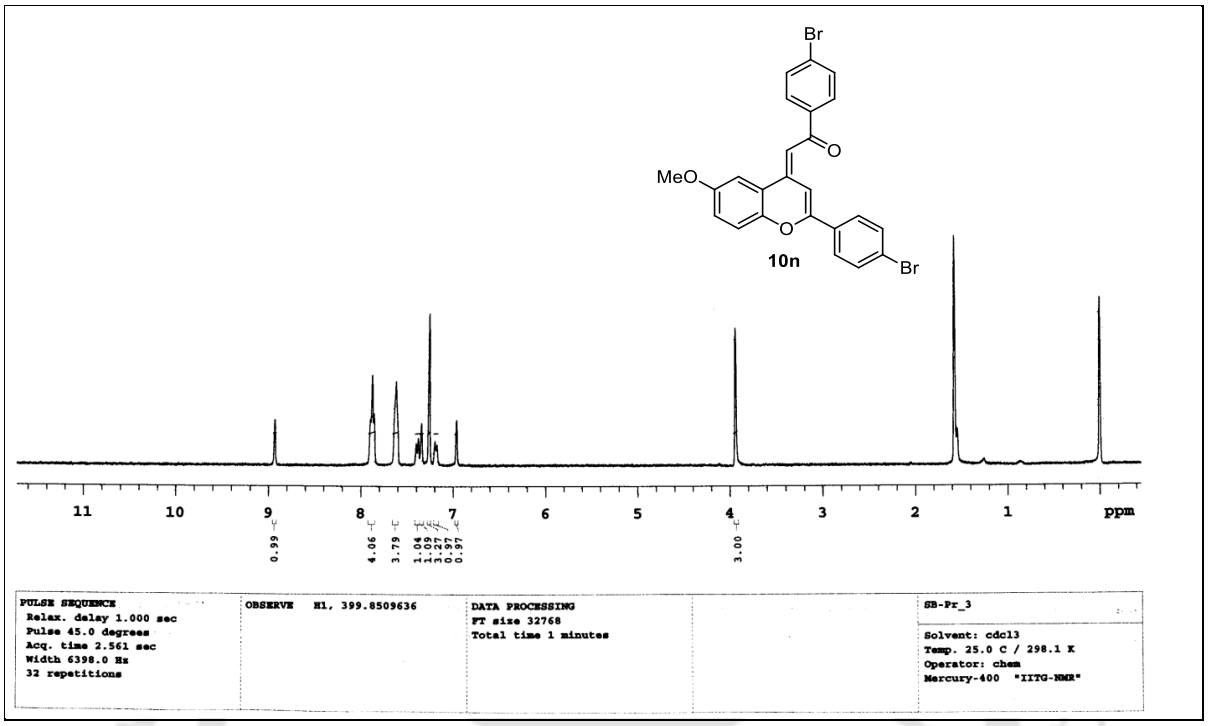


Figure 15

***^{1}H NMR (400 MHz, $CDCl_3$)**: (E)-1-(4-bromophenyl)-2-(2-(4-bromophenyl)-6-methoxy-4H-chromen-4 ylidene)ethanone (**10n**):*



***^{13}C NMR (150MHz, $CDCl_3$)**: (E)-1-(4-bromophenyl)-2-(2-(4-bromophenyl)-6-methoxy-4H-chromen-4 ylidene)ethanone (**10n**):*

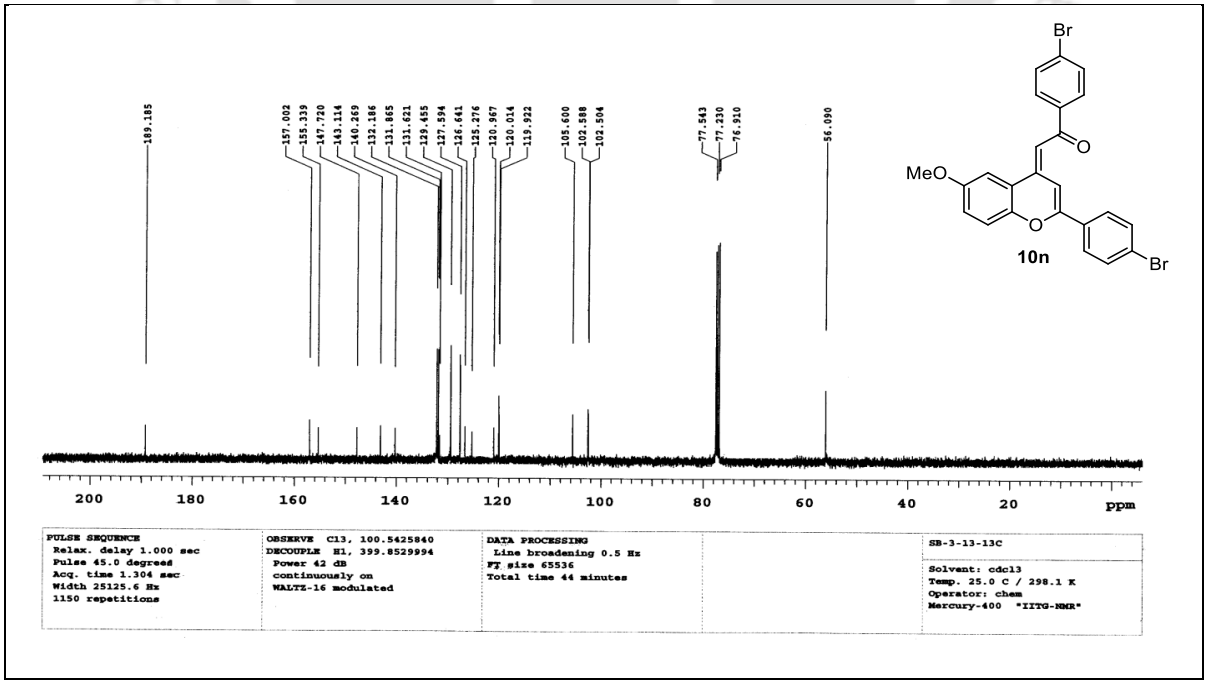
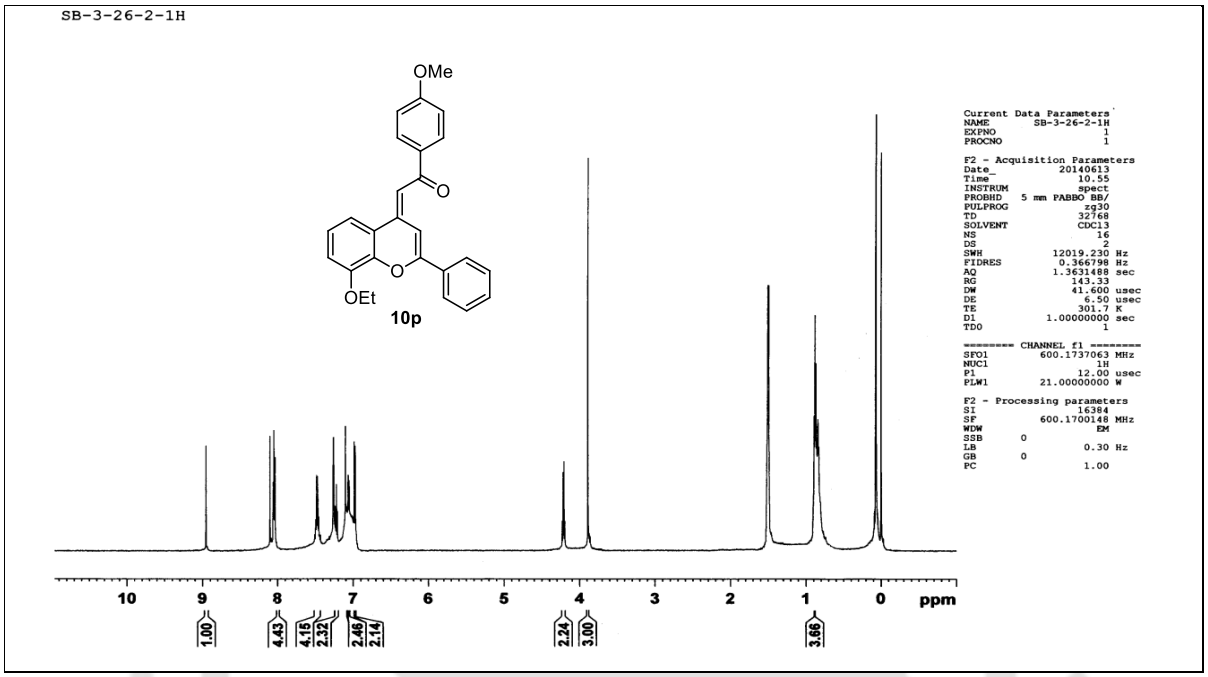


Figure 16

^{1}H NMR (600 MHz, CDCl$_3$)*:(E)-2-(8-ethoxy-2-(4-methoxyphenyl)-4H-chromen-4-ylidene)-1-phenylethanone(**10p**):*



^{13}C NMR (100MHz, CDCl$_3$)*:(E)-2-(8-ethoxy-2-(4-methoxyphenyl)-4H-chromen-4-ylidene)-1-phenylethanone(**10p**):*

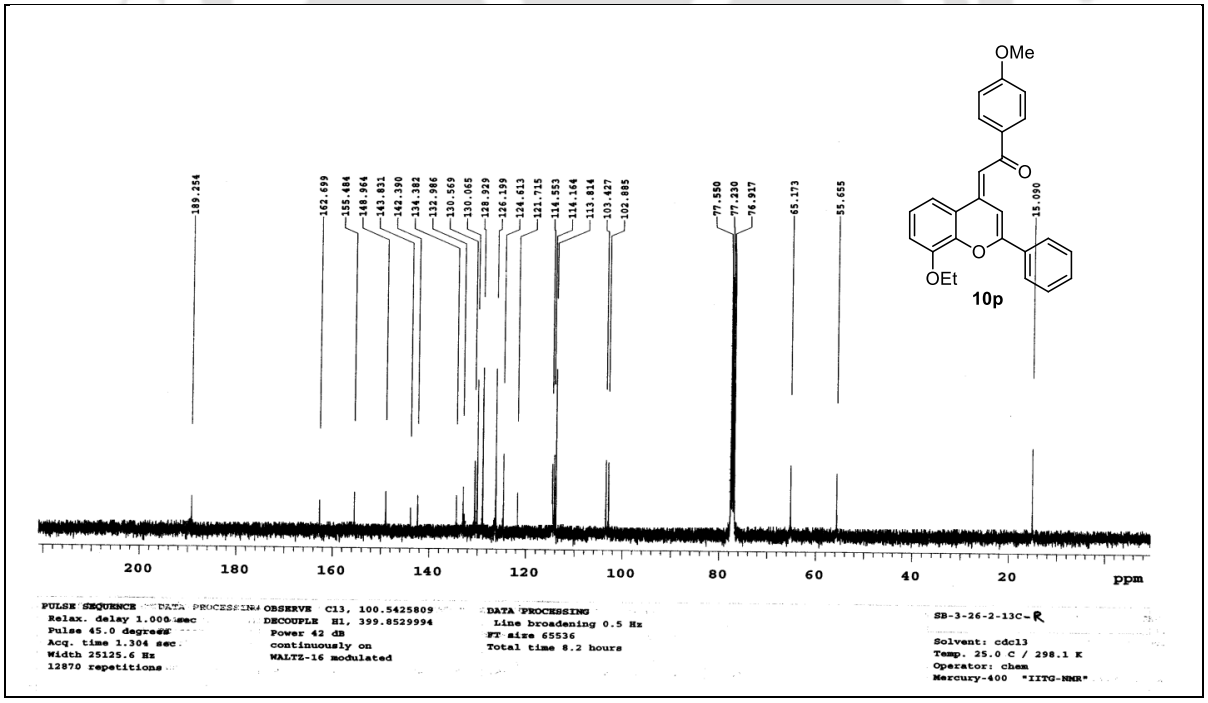
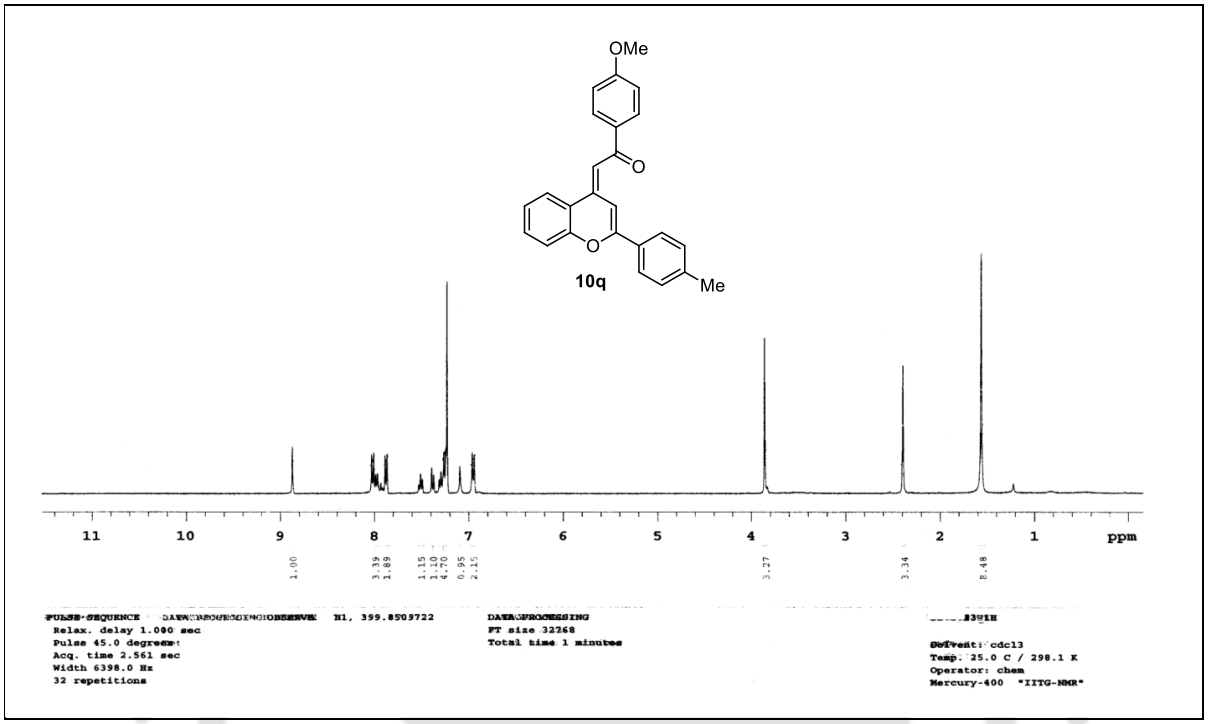


Figure 17

^{1}H NMR (400 MHz, $CDCl_3$): *(E)-1-(4-methoxyphenyl)-2-(2-(p-tolyl)-4H-chromen-4-ylidene)ethanone* ***(10q):***



^{13}C NMR (100MHz, $CDCl_3$): *(E)-1-(4-methoxyphenyl)-2-(2-(p-tolyl)-4H-chromen-4-ylidene)ethanone* ***(10q):***

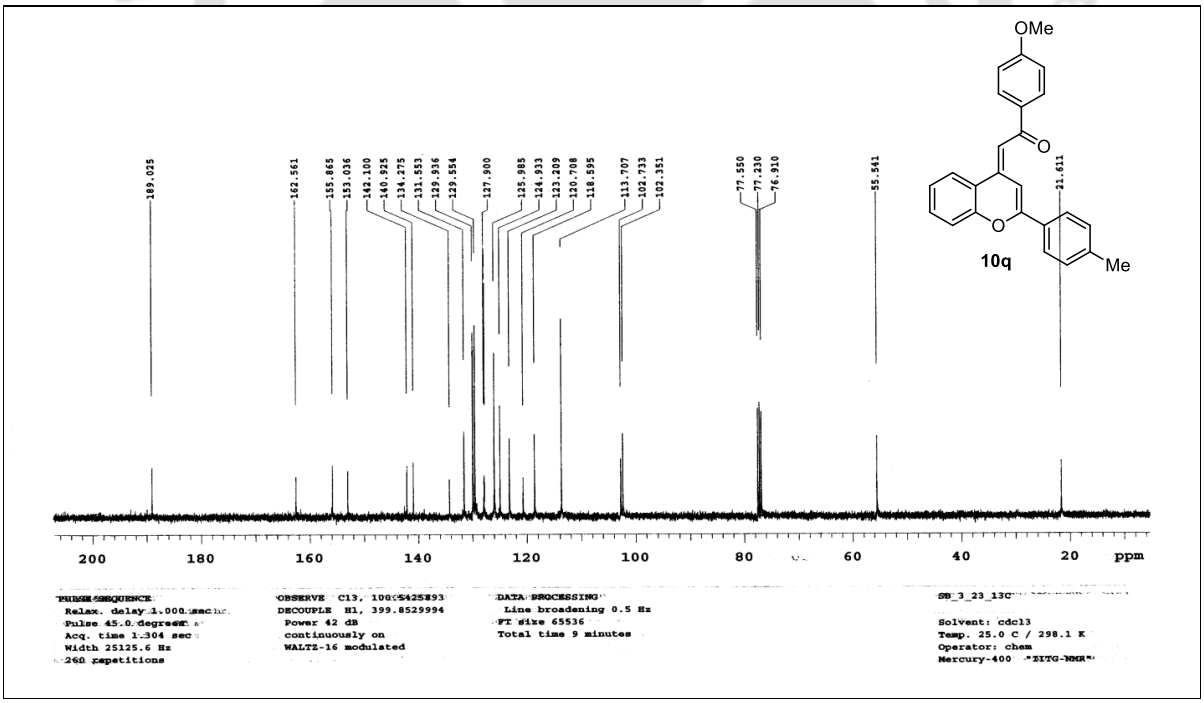


Figure 18

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Chapter I – Chapter III

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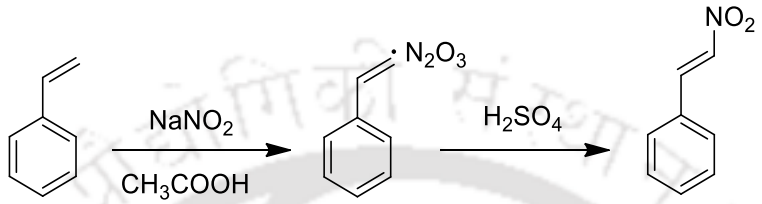
Part B

Chapter I

Introduction of Nitro-alkene and 2,6-Dicyanoaniline Derivatives

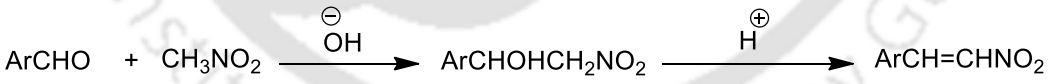
1.1.Introduction

β-Nitrostyrene is an aromatic compound, which is also known as 1-nitro-2-phenylethylene. In 1839, Simon[1] first reported the preparation of *β*-nitrostyrene in small yield by distilling styrene with nitric acid followed by treating the nitrogen trioxide adduct with sulfuric acid as shown in Scheme 41.



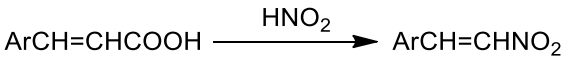
Scheme 41

In 1883, Priebs[2] acceptably confirmed the synthesis of *β*-nitrostyrene by heating benzaldehyde and nitromethane at 160°C in presence of $ZnCl_2$ catalyst, obtained 30-40% yield. Thiele,[3] in 1899, used the catalytic amount of alcoholic KOH in the reaction mixture of benzaldehyde and nitromethane, the intermediate nitrophenethyl alcohol was isolated and further treated with acid, successfully gave *β*-nitrostyrene, as shown in Scheme 42. The method was tremendously utilized for the preparation of various *β*-nitrostyrene moiety, but gives poorer result for substituted benzaldehyde, and entirely ineffective for nitroethane and 1-nitropropane. Later on, various other catalyst[4] was developed for attaining better result such as alcoholic methylamine, ammonium acetate in acetic acid etc.



Scheme 42

β-Nitrostyrene was also prepared from cinnamic acid by nitration,[5] as shown in Scheme 43.



Scheme 43

The demand of *β*-nitrostyrene moiety and its derivatives has further increased due to the discovery of its biological activity.

1.2.Application of Nitro-alkene

Over the last few decades, scientists has identified that a lot of *β*-nitrostyrene derivatives are biologically active. They are an effective inhibitor of human Telomerase. Among the other nitrostyrene, 3-(3,5-dichlorophenoxy)-nitrostyrene showed the most potent inhibitory effect. It can efficiently hold the growth of cancer cell, and subsequently, lead to the demises of the cell.[6] Further studies have proposed that nitrostyrene can function as phospholipase (A2) inhibitors [7] tyrosine phosphatase inhibitors (PTP1B, SHP1, Yop)[8] or tyrosine kinase inhibitors (Src, Syk, FAK).[9] *β*-Nitrostyrene moiety is also found as an essential pharmacophore for apoptosis induction,[10] and prospective antibacterial agents.[11]

Moreover, nitro-alkene is a precious organic compound for the modern chemist. Owing to the remarkable reactivity of nitro-alkene, it is generally known as 'Synthetic Chameleon.'

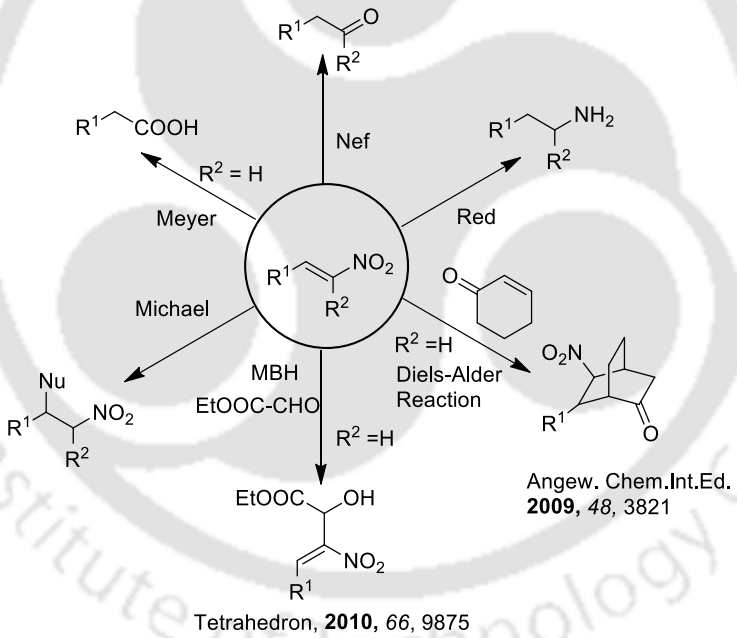


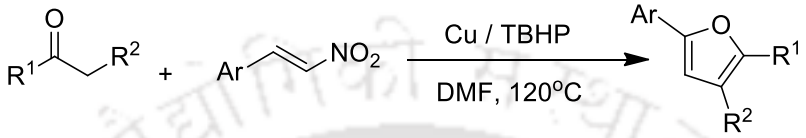
Figure 19. Organic molecules derived from nitro-alkene

Extremely widespread reactions experienced by nitro-alkenes are Michael addition reactions with different nucleophiles,[12] Morita-Baylis–Hillman reactions,[13] and Friedel-Craft alkylations.[14] Because of the electron–withdrawing nature of nitro group, nitro-alkene behaves as a dienophile in cycloaddition reactions[15] and dienes in hetero-Diels-Alder reactions.[16] It also takes part in cross coupling reactions.[17] Moreover, nitro group of nitro-alkene can be

transformed into nitrile-oxide, reduced to amino-group, altered to carbonyl group by application of Nef reaction, as shown in Figure 19.

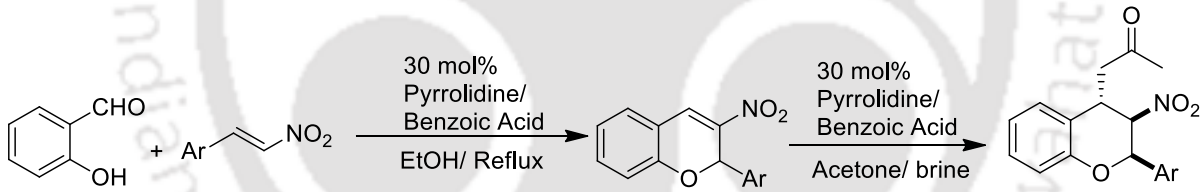
1.3.Literature Review on synthetic application of Nitro-alkene

Hajra *et al*. [18] synthesized a substituted furan ring by means of coupling reaction between *β*-nitrostyrene and ketone, as shown in Scheme 44.



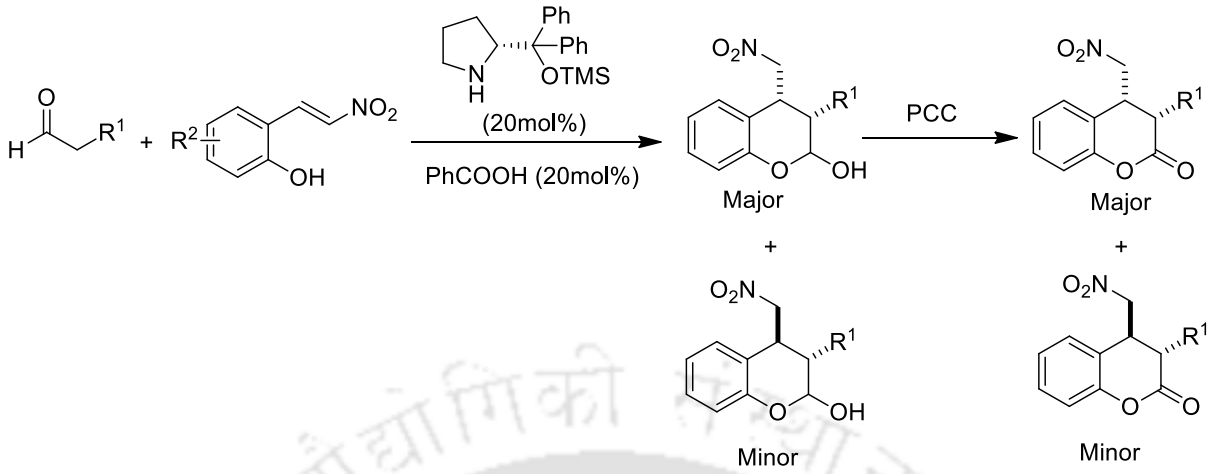
Scheme 44

Wang *et al*.[19a] demonstrated the synthesis of 2-aryl-3-nitro-2*H*-chromenes, by oxa-Michael-Henry reaction of salicylaldehyde with *β*-nitrostyrenes. Moreover, the Michael reactions of 2-aryl-3-nitro-2*H*-chromenes with acetone were also carried out under the same catalytic system, as shown in Scheme 45. Later on, Korotaev *et al*.[19b] used the 2-aryl-3-nitro-2*H*-chromenes for synthesizing more complex and valuable molecules.



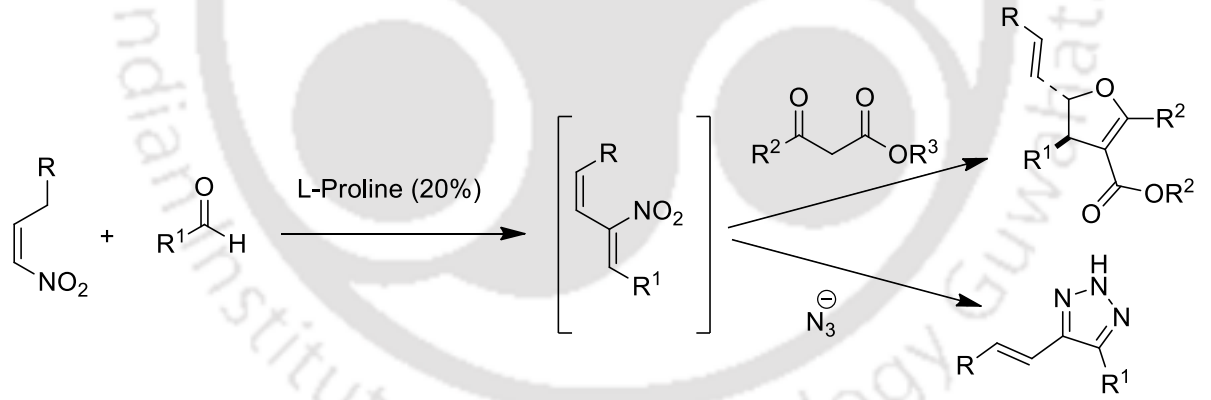
Scheme 45

Ramachary *et al*.[20] described the asymmetric synthesis of pharmaceutically active chiral 3-alkyl-4-nitromethylchromans compound, from the reaction of 2-(2-nitrovinyl) phenols and aldehydes in the presence of a catalytic amount of (R)-DPPOTMS and $PhCO_2H$, as shown in Scheme 46.



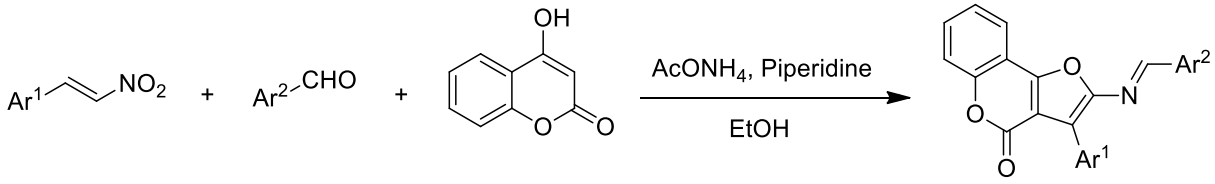
Scheme 46

Shi *et al.*[21] demonstrated that multicomponent condensation reactions are very beneficial for synthesizing of complex molecules which can be achieved by treating the nitro-alkene with aldehyde to form extremely reactive intermediate. Subsequently, reaction with the third component gave substituted heterocyclic compounds, such as 1,2,3-triazoles and dihydrofuran, in one-pot, as shown in Scheme 47.



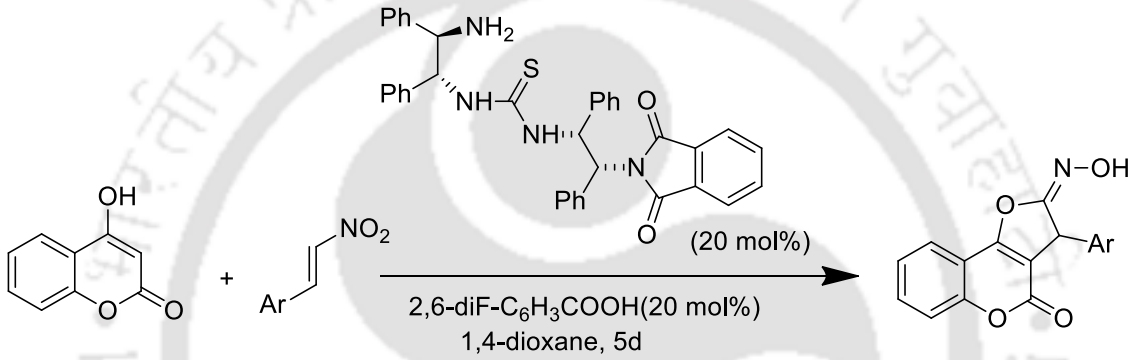
Scheme 47

Zhou *et al.*[22] synthesized 2-alkylamino-3-aryl-4*H*-furo[3,2-c]chromen-4-ones using one-pot, multicomponent reaction of substituted nitrostyrenes with aromatic aldehydes, 4-hydroxycoumarin, and ammonium acetate, as shown in Scheme 48. The reaction involves sequential Michael addition, aza-nucleophilic addition of imine to the double bond followed by intermolecular nucleophilic addition, and dehydration reactions.



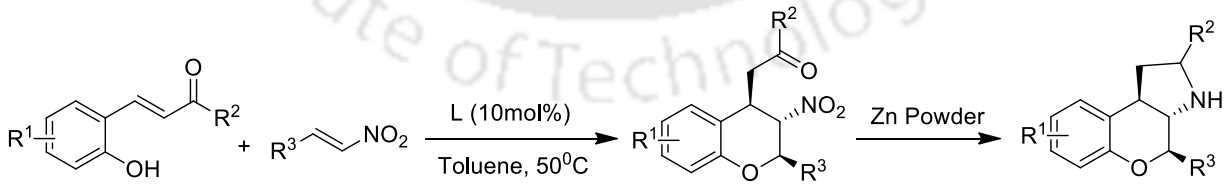
Scheme 48

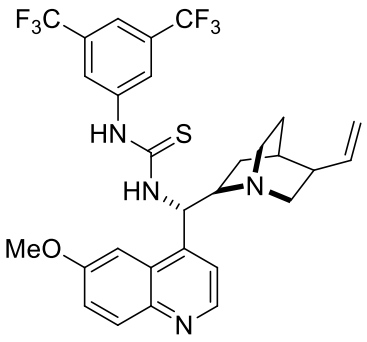
Mei and associates;[23] developed an organocatalytic asymmetric Michael/cyclization tandem reaction of 4-hydroxycoumarin to nitro-alkenes which afforded 2,3-dihydrofuro[3,2-c]-coumarin type adducts in moderate yields with good enantioselectivities, as illustrated in Scheme 49.



Scheme 49

Sing *et al*.[24] developed a well-organized approach for the construction of polysubstituted chiral chroman derivatives from *β*-nitrostyrene, by the use of an oxa-Michael−Michael cascade reaction, catalyst by a bifunctional thiourea. Products containing three adjacent chiral centers were acquired in the reaction, as depicted in Scheme 50. In addition; the products were transformed into tricyclicchromans, which has a broad spectrum of biological activity.

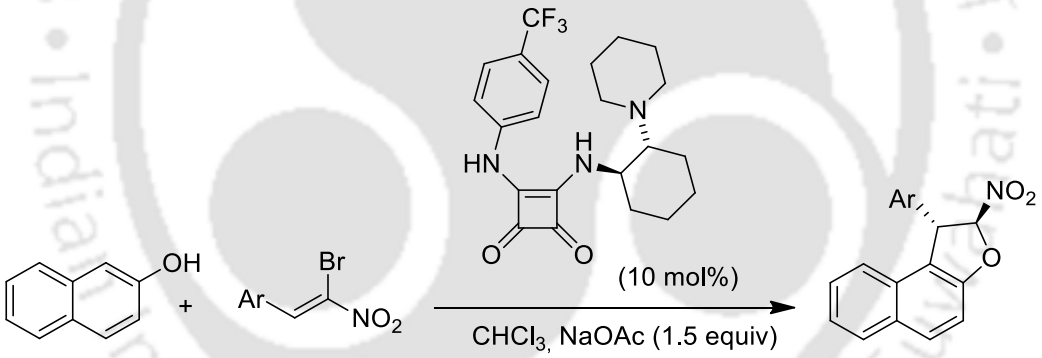




L(catalyst)

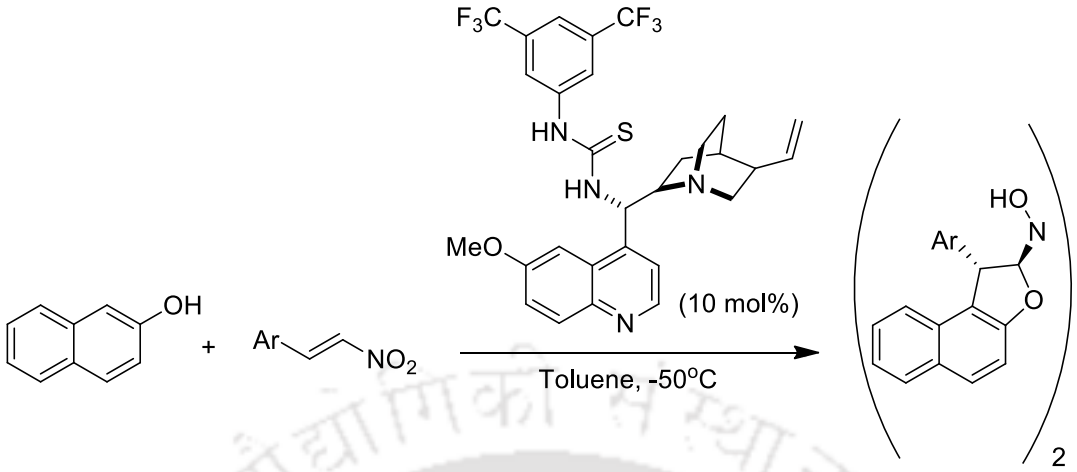
Scheme 50

Aleman *et al*.[25] depicted a protocol for the synthesis of trans-dihydroarylfuran derivatives from (*Z*)-bromonitroalkenes and 2-naphthol derivatives by using squaramide catalysis, as shown in Scheme 51. The reaction involves Michael–Friedel–Crafts reaction followed by a nucleophilic substitution on the bromide carbon.



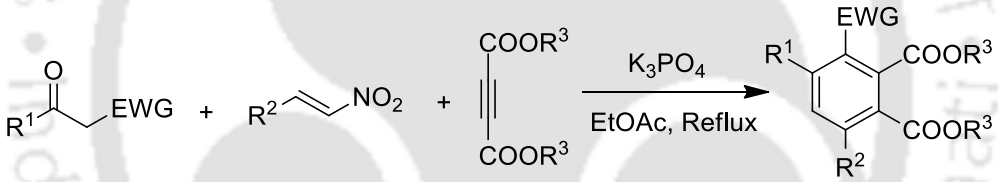
Scheme 51

The same reaction when carried out in presence of thiourea–tertiary amine organocatalysts, the dimeric 1,2-dihydronaphtho[2,1-*b*]-furanyl-2-hydroxylamine was obtained by Chen and co-workers,[26] as depicted in Scheme 52.



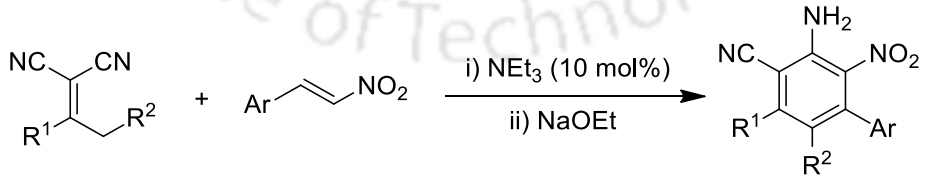
Scheme 52

Wu *et al.*[27] illustrated the use of *β*-nitrostyrene in multicomponent reactions for construction of polysubstituted benzene, by reacting *β*-nitrostyrene, diacetylenedicarboxylate and ketone under metal free conditions, as shown in Scheme 53.



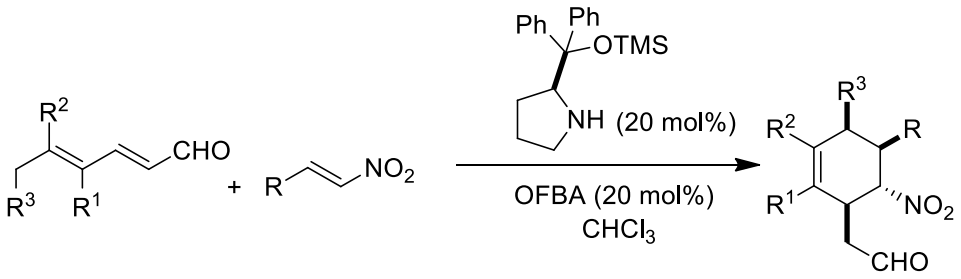
Scheme 53

Polysubstituted benzene derivatives were synthesized from nitro-alkenes and vinyl malononitriles *via*, one-pot two-step procedure, demonstrated by Xue *et al.*[28a] as shown in Scheme 54. Later on, Su *et al.* used $Cu(OTf)_2$/ NEt_3 to synthesize benzene derivatives from *β*-nitrostyrene.[28b]



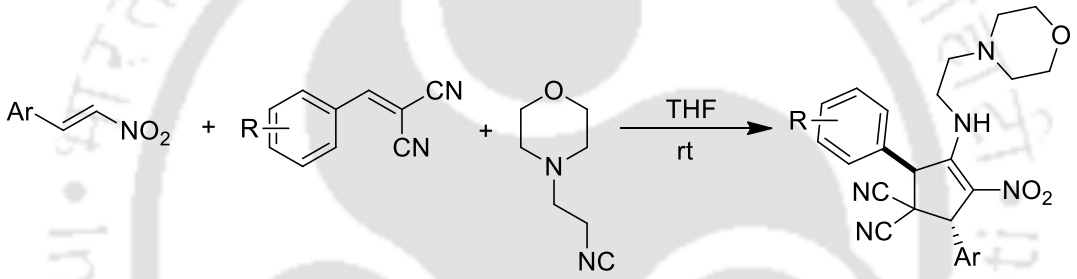
Scheme 54

Diversely substituted 2,4-dienals undergoes Diels-Alder reactions with *β*-nitrostyrene catalyzed in presence of 20 mol% of chiral secondary amine and *o*-fluorobenzoic acid as catalyst in $CHCl_3$ at ambient temperature, for the synthesize of cyclohexene derivatives, which was described by Jia *et al.* [29] as shown in Scheme 55.



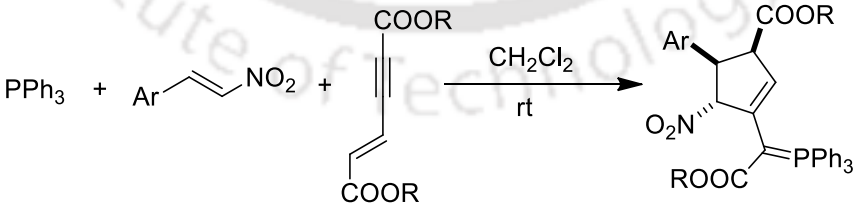
Scheme 55

Sagırli *et al.*[30] illustrated the utilization of *β*-nitrostyrene for constructing polysubstituted cyclopentene ring. Addition of isocyanide and benzylidenemalononitrile generate 1,3-dipolar structure, which further undergoes a dipolar cycloaddition reaction with *β*-nitrostyrene, afforded the cyclopentene ring, as shown in Scheme 56.



Scheme 56

Yan *et al.*[31] also reported the method for cyclopentene ring from *β*-nitrostyrene. The one -pot three component reactions of triphenylphosphine, dimethyl hex-2-en-4-ynedioate, and *β*-nitrostyrene was carried out in DCM at room temperature effectively afforded the polysubstituted cyclopentene ring as shown in Scheme 57.



Scheme 57

Review of literature discloses that, nitro alkenes are broadly recognized as versatile building blocks in a synthetic organic chemistry. The thesis has been enriched by employing such an attractive organic compound for synthesizing the valuable compounds like flavone derivatives, benzo[*f*]chromene and 2,6-dicyano-3,5-disubstituted aniline derivatives. Importance of 2,6-

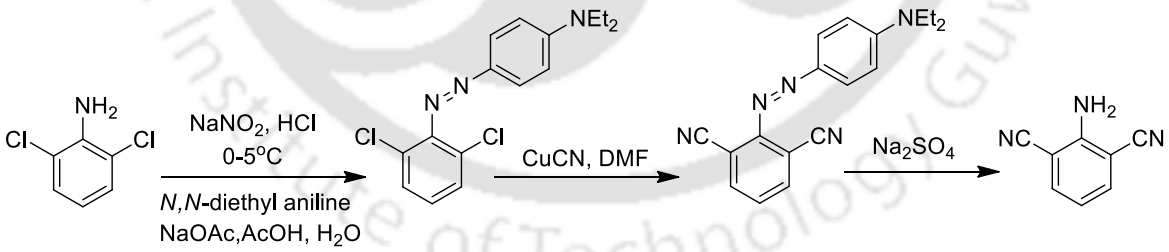
dicyano-3,5-disubstituted aniline moieties is briefly described in this chapter. Significance and synthetic utility of flavone and benzo[*f*]chromene moieties were already described in Part A-Chapter I.

1.4. 2,6-Dicyanoaniline and its importance

2,6-Dicyanoanilines constitutes three contiguous functional group having an acceptor-donor-acceptor (A-D-A) systems, exhibit varied applications. In industries, the 2,6-dicyanoanilines and its derivatives are widely utilized for making fluorescent materials,[32] diodes,[33] dyes,[34] heat resistant polymers,[35] light absorbing polymers[36] etc. Chemist has explored these moieties as building blocks for large number of valuable organic compounds,[37] for instance, imines, indoles, indazoles, fluorenones, quinazolines, benzoxazines, benzotriazinones etc. It is a precursor for asymmetric and regioselective synthesis,[38] and intermediates for chiral phases in chromatography.[39] The scaffold possesses wide spectrum of biological activities such as antileishmanial,[40] antihyperglycemic,[41] antimicrobial,[42] anticancer,[43] anti-amyotrophic lateral sclerosis,[44] growth promoting agents,[45] anti-inflammatory[46] and antifungal[47] activities etc.

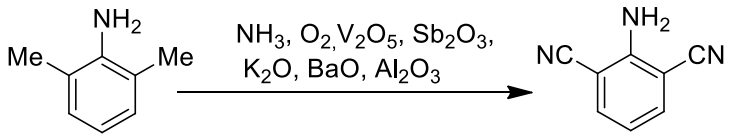
1.4a. Synthetic methodology of 2,6-Dicyanoaniline derivatives

In 1977, Griffiths *et al.*[48] have reported the synthesis of 2,6-dicyanoaniline from 2,6-dichloroaniline by employing various chemical reactions, which afforded the desired product in 23% yield as shown in Scheme 58.



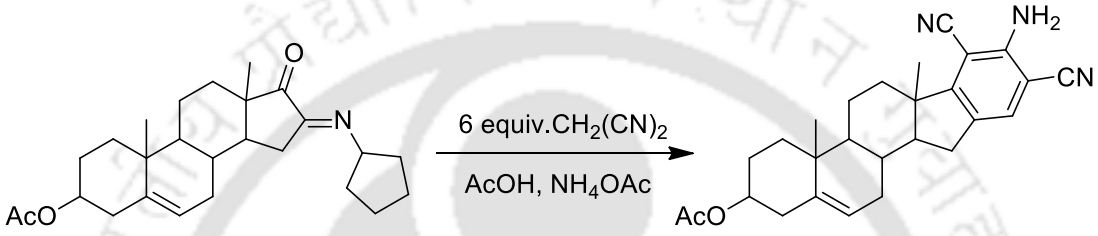
Scheme 58

Grund *et al.*[49] have depicted the preparation of 2,6-dicyanoaniline in 21% yield from 2,6-dimethylaniline by using mixture of catalyst like vanadium pentoxide, antimony trioxide, potassium oxide, barium oxide and alumina as shown in Scheme 59.



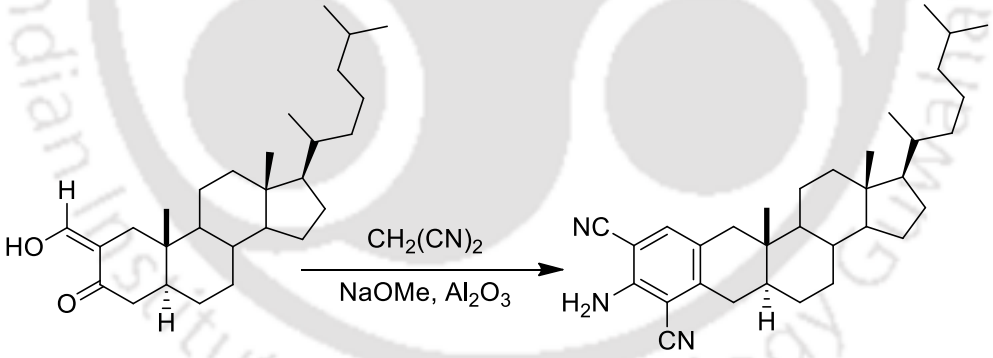
Scheme 59

Green *et al.*[50] successfully prepared 2,6-dicyanoaniline derivatives by using a steroidal ketone with 6 equiv. of malononitrile, in presence of ammonium acetate and acetic acid, however, the yield was only modest (42%), as shown in Scheme 60.



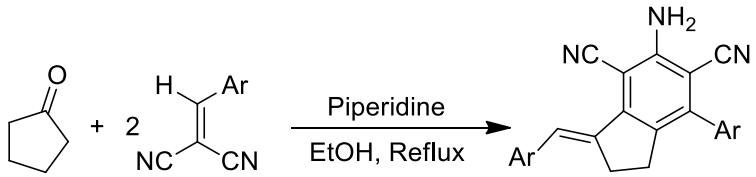
Scheme 60

Barthakur *et al.*[51] obtained the moiety with a good yield from steroidal 3-keto-2-hydroxymethylene with malononitrile in presence of base, as shown in Scheme 61.



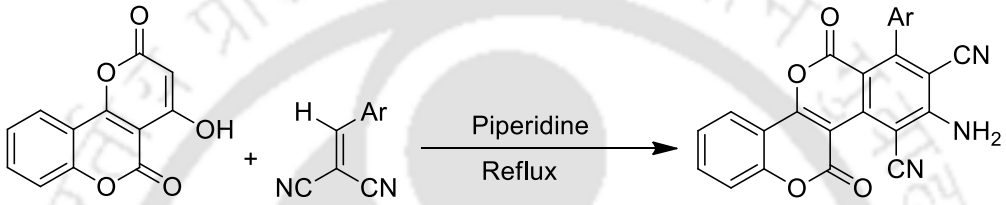
Scheme 61

Sofan *et al.*[52] demonstrated the synthesis of 5-amino-7-aryl-3-arylidene-2,3-dihydro-4,6-indenedicarbonitriles from the reactions of 2 equivalent of arylidenemalononitriles and cyclopentanone in presence of base, as shown in Scheme 62.



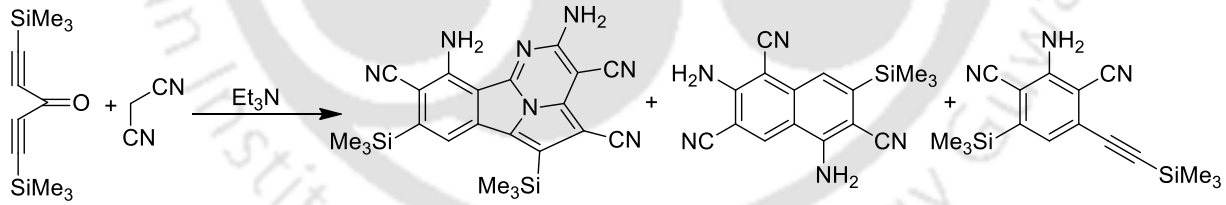
Scheme 62

Reaction of pyrano[3,2-c]coumarin with benzylidenemalononitrile in presence of piperidine was studied by El-Taweel *et al.*[53] to afford 6*H*,11*H*-[2]benzopyrano[4,3-c]-[1]benzopyran-6,11-dione, as depicted in Scheme 63.



Scheme 63

Yi *et al.*[54] investigated the 2,6-dicyanoanilines as a product from the reaction of 1,5-bis (trimethylsilyl) penta-1,4-diyn-3-one with malononitrile, as shown in Scheme 64. The products showed strong fluorescence emission, either in the blue, red, or green part of the spectrum emission in fluorescence study.



Scheme 64

From the comprehensive study of the literature, it is worthwhile to mention that 2,6-dicyanoanilines based organic molecules possess enormous potential for the synthesis of numerous industrial as well as pharmaceutical products. Moreover, various methods are reported for the synthesis of the moiety using a variety of catalyst, but most of the strategies are associated with some limitations, like harsh reaction conditions,[53] expensive starting materials,[50,51] low yield [48,54] etc. These facts always keep the gate open for the development of new and efficient strategy for the synthesis of 2,6-dicyanoanilines derivatives in economic and eco-friendly manners with good yield. Thus, the thesis work is intended to synthesize the 2,6-dicyanoanilines derivatives, which will be discussed in Chapter III of Part B.

Part B

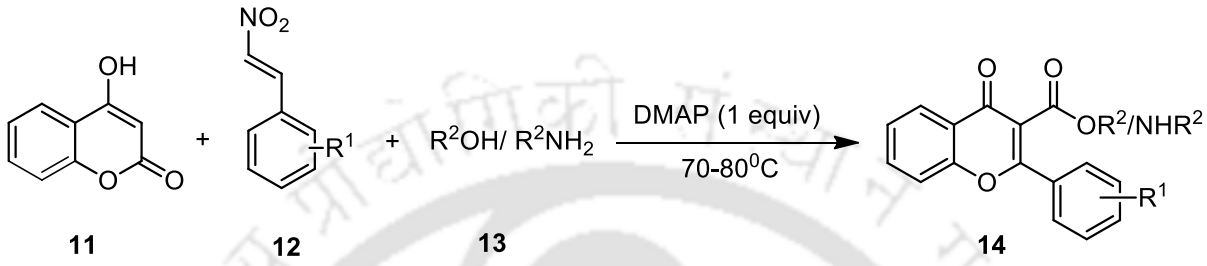
Chapter II

Synthesis of 3-substituted carboxylate/carboxamide flavone derivatives from 4-hydroxycoumarin, β-nitrostyrene and alcohol/amine using multicomponent reaction

Results & Discussion

Experimental Section

The importance and synthetic approaches of flavone derivatives have already been described in Part A Chapter I and the utility of *β*-nitrostyrene moiety is described in Part B Chapter I. In this chapter a favorable method was worked out for the synthesis of 3-substituted flavone derivatives by utilizing 4-hydroxycoumarin, *β*-nitrostyrene and alcohol/amine in presence of DMAP, as shown in Scheme 65.



R^1 = H, 4-Cl, 4-Br, 4-Me, 4-OMe, 3,4,5(-OMe)$_3$, 2-NO_2
R^2OH; R^2 = Me, Et, Allyl, Furfuryl, Crotyl, Propargyl, 4-Pentene
R^2NH_2 ; R^2 = Butyl, (s)-Phenyl ethyl, Cyclohexyl, Benzyl

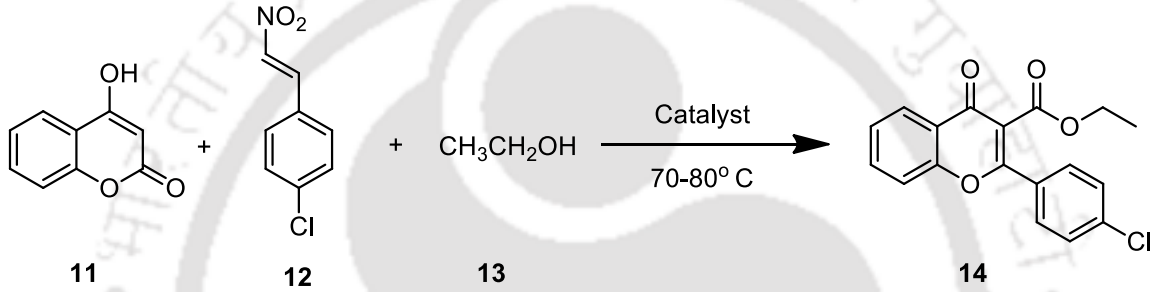
Scheme 65. One-pot three-component synthesis of3-substituted flavone derivatives (**14**)

N,*N*-dimethyl-4-aminopyridine (DMAP) is a Lewis base, extensively employed as a nucleophilic-catalyst for various organic reactions such as trans esterification,[55] acylation,[56] Michael addition,[57] and Baylis–Hillman reactions.[58] The catalyst has also been used for different multicomponent reactions for the synthesis of heterocycles by us[59] as well as by other research groups.[60] In continuation of our constant efforts in a survey of DMAP for the construction of biologically active heterocycles, we resolve to explore DMAP for the synthesis of 3-substituted-flavone derivatives.

To find the optimal conditions for the synthesis of 3-substituted flavone derivatives, various reactions were tried out with 4-hydroxycoumarin (1 mmol), 4-chloro phenyl nitrostyrene (1mmol) and ethanol (4 mmol). Initially, the reaction has been carried out with 0.2 mmol of DMAP (Table 8; entry 1) furnished only 17% of the required product after 24 h of refluxing. The product was purified by chromatographic separation and found to be 3-substituted flavone **14aa**, as confirmed by IR, ^{1}H NMR and mass spectra. In IR strong absorption peak at 1731 and 1645 cm^{-1} indicates the presence of carbonyl groups, Similarly, in ^{1}H NMR spectra of product **14aa**, the quartet at δ 4.25 for 2H and triplet at δ 1.19 for 3H clearly indicate the presence of an ethoxy group into the molecule. Repeating the above experiment with 0.4 mmol, 0.6 mmol and 1 mmol of DMAP, the yield of the product was substantially increased from 30% to 80% accompanied by the decrease of duration of the reaction from 24 h to5 h. (Table 8, entries 2-

4). Performing similar experiment with 1.5 mmol of DMAP resulted in an insignificant change in yield and time (Table 8, entry 5). The identical reaction was found unproductive at room temperature with no product formation (Table 8, entry 6). The same set of reactions was carried out withother basic catalysts like piperidine, DBU, DABCO and NaOH and was proved ineffective (Table 8, entries 7-10). No product was formed in the absence of a catalyst (Table 8; entry 11). From these experimental outcomes, it was clear that catalyst played an important role in formation of the product **14aa**, and 1 mmol of DMAP was adequate enough to carry out the reaction in terms ofefficacy of time and yield.

Table 8: Optimized condition for the synthesis of3-substituted flavone derivatives



11 **12** **13** **14**

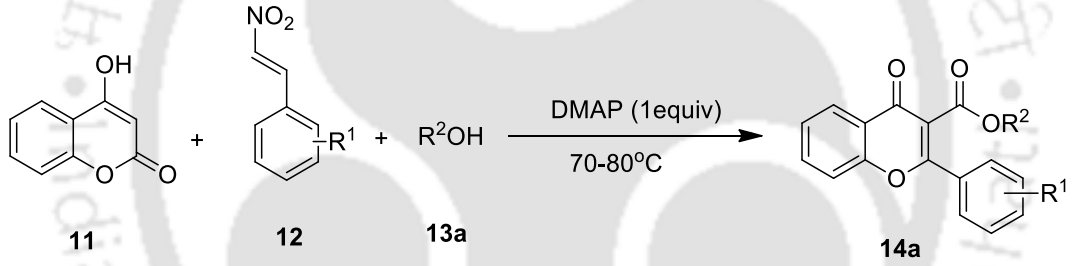
Entry	Catalyst	Tem	Mol%	Time	Yield%
1	DMAP	70°C	0.2	24 h	17
2	DMAP	70°C	0.4	24 h	30
3	DMAP	70°C	0.6	18 h	50
4	**DMAP**	**70°C**	**1.0**	**5 h**	**80**
5	DMAP	70°C	1.5	4.5 h	81
6	DMAP	RT	1.0	24 h	00
7	piperidine	70°C	1.0	24 h	00
8	DBU	70°C	1.0	24 h	00
9	DABCO	70°C	1.0	24 h	00
10	NaOH	70°C	1.0	24 h	00
11	None	70°C	00	24 h	00

[a]The reactions were carried out with 4-hydroxycoumarin (1 mmol), 4-chloro phenyl nitrostyrene (1 mmol), and ethanol (4 mmol) in the presence of different catalyst at reflux. [b]Isolated yields.

To establish the optimal reaction conditions, we initially investigated a reaction with a mixture of 4-hydroxycoumarin, (*E*)-(2-nitrovinyl)benzene in ethanol under similar conditions, the desired product **14ab** was obtained in 85% yield (Table 9, entry 2). The scope and efficacy of

the synthetic routes were explored by reacting 4-hydroxycoumarin with *β*-nitrostyrene having key functional groups such as halides, nitro, methyl, methoxy, etc. under optimized reaction conditions and the desired products were obtained in good yields. It was noted that, *β*-nitrostyrene having electron-donating group reacted faster and gave the better yield than *β*-nitrostyrene with electron-withdrawing groups (Table 9, entries 1, 3-7). Next, the protocol was examined by treating 4- hydroxycoumarin, 4- methyl nitrostyrene with various alcohols. Using alcohol with bigger aliphatic groups, the yields of the desired compounds were found to decrease. Reaction in methanol proceeds smoother and faster, and was able to produce the best yield (Table 9, entry 13) than any other alcohols in the series (Table 9, entries 8-13). The reaction with 4-penten-1-ol was slowest and produces the least yield (Table 9, entry 12). The protocol was found ineffective in cases of sterically hindered alcohols like *t*-butanol, 3-phenyl-1-propanol (Table 9, entries 14-15) as well as aromatic alcohol like phenol (Table 9, entry 16).

Table 9: Substrate scope and yields of 3-carboxylate flavone derivatives (**14a**)[a]



11 12 13a 14a

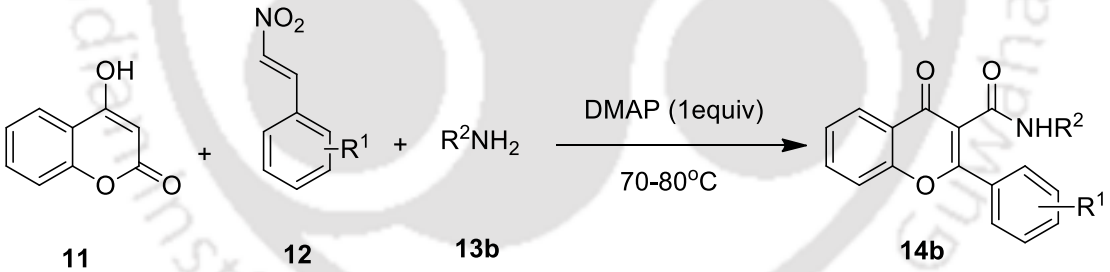
Entry	R^1	R^2OH	Time (h)	Yield (%)[b]	product
1.	4-Cl	Et-OH	5.0	80	**14aa**
2.	H	Et-OH	4.5	85	**14ab**
3.	4-Br	Et-OH	5.0	79	**14ac**
4.	4-Me	Et-OH	2.0.	86	**14ad**
5.	4-OMe	Et-OH	2.5	88	**14ae**
6.	3,4,5- tri OMe	Et-OH	3.0	87	**14af**
7.	2- NO_2	Et-OH	5.5	79	**14ag**
8.	4-Me	allyl-OH	6.0	77	**14ah**
9.	4-Me	furfuryl-OH	8.0	72	**14ai**
10	4-Me	crotyl-OH	7.0	76	**14aj**

11	4-Me	Propargyl-OH	4.0	78	**14ak**
12	4-Me	4-pentene-OH	9.0	70	**14al**
13	4-Me	Me-OH	2.0	90	**14am**
14	4-Me	t-butanol	12.0	N.R	-
15	4-Me	3-phenyl-1-propanol	12.0	N.R	-
16	4-Me	Phenol	24.0	N.R	-

[a]The reactions were carried out with 4-hydroxycoumarin (1 mmol), *β*-nitrostyrene (1 mmol), and alcohol (4 mmol) in the presence of 1 mmol of DMAP at reflux. [b]Isolated yields.

On the lookout for the further scope of the reaction, we investigated the nucleophilicity of the reaction by amine as shown in Table 10. Various amine moieties like aliphatic, benzylic, cyclic amines were considered by conducting the reaction with 4-hydroxycoumarin and 4-methyl nitrostyrene, the desired products **14ba-14bd** were obtained in moderate yield. Unfortunately, reactions failed to give the desired product in case of aromatic amine like aniline and secondary amine, for example, diisopropylamine (Table 10, entry 5 and 6) respectively.

Table 10: Substrate scope and yields of 3-carboxamide flavone derivatives **(14)**[a]



Entry	R^1	R^2NH_2	Time (h)	Yield (%)[b]	Product
1.	4-Me	Butyl amine	12	65	**14ba**
2.	4-Me	(s)-Phenyl ethyl amine	8	69	**14bb**
3.	4-Me	Cyclohexyl amine	15	68	**14bc**
4.	4-Me	Benzyl amine	6	66	**14bd**
5.	4-Me	Aniline	24	N.R	-
6.	4-Me	Diisopropyl amine	24	N.R	-

[a]The reactions were carried out with 4-hydroxycoumarin (1 mmol), *β*-nitrostyrene (1 mmol), and amine (4 mmol) in the presence of 1 mmol of DMAP at reflux. [b]Isolated yields.

All the synthesized compounds were fully characterized by IR, NMR and Mass Spectra. In IR spectrum, compound **14aa-14am** and **14ba-14bd** showed two characteristic strong absorptions at the range of 1718-1732 cm^{-1} and 1638-1645 cm^{-1} due to the carbonyl group present in the molecule. The mass spectra of all the compounds exhibited molecular ion peaks at the appropriate m/z values. For further confirmation, the structure of the compound **14ad** was determined by single-crystal X-ray crystallography (Figure 20). The ^{1}H NMR and ^{13}C NMR spectra of the products **14ac, 14ah, 14al, 14ba** and **14bd** are shown in Figure 21-25 respectively in the experimental section.

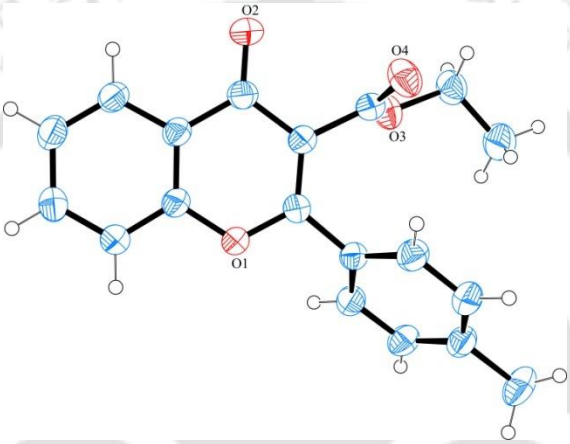
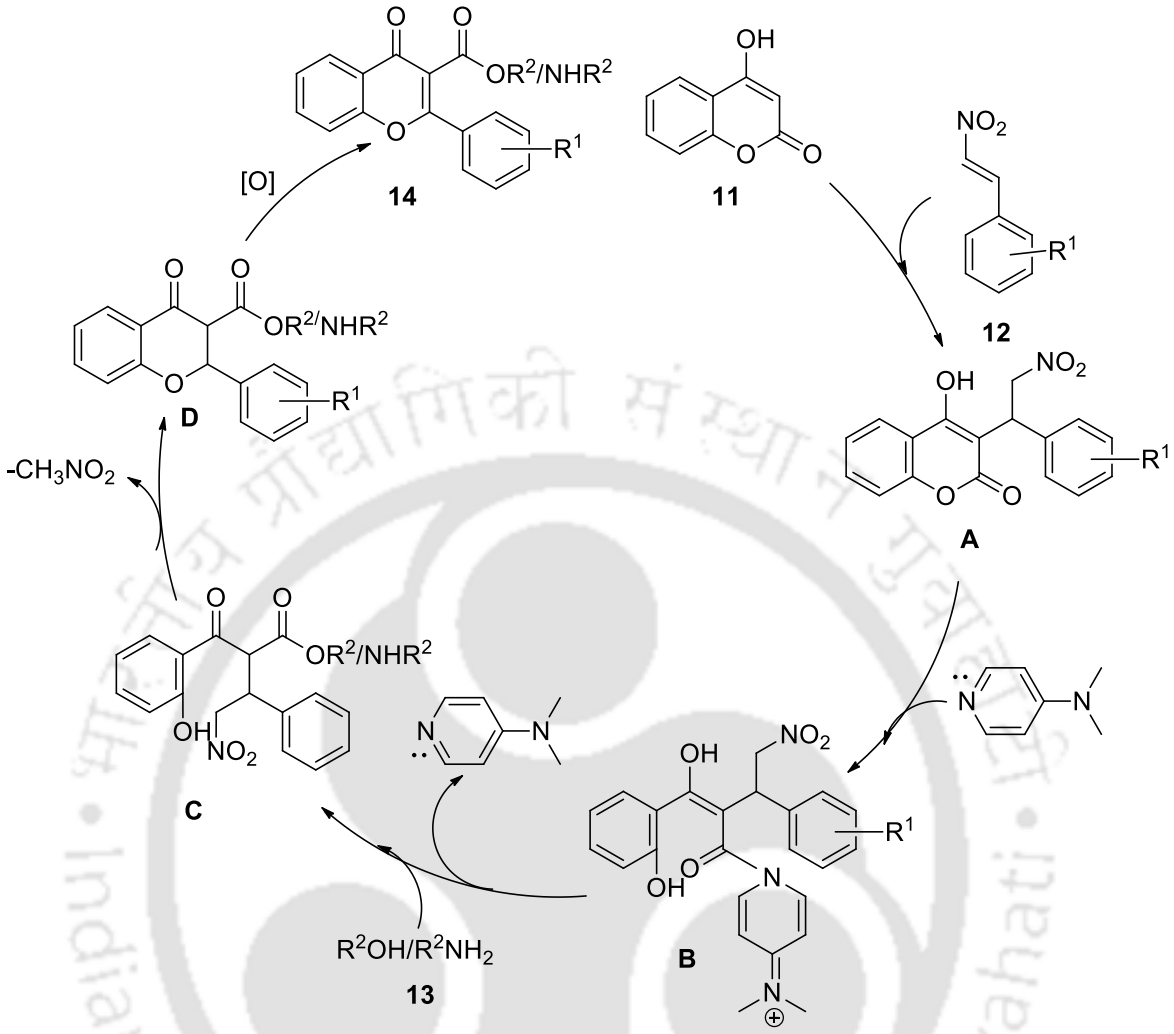


Figure 20.X-ray crystal structure of 3-carboxylate flavone derivative **14ad**

Although the mechanism of the reaction was not established experimentally, the product **14** can be believed formed by using the following mechanistic pathway: First 4-hydroxycoumarin undergoes Michael-addition reaction with nitro-olefin in presence of DMAP, resulting in an adduct **A**. DMAP being a strong nucleophile, attacks at the carbonyl center of **A** leading to the formation of the reactive amide center in **B**. The intermediate **B** cannot form any side products but immediately reacts with an alcohol or amine forming an intermediate **C**. Eventually intermediate **C**, undergoes an intramolecular cyclization by releasing nitro methane to form **D**, which undergoes an oxidation resulting in the final product **14** (Scheme 66).



Scheme 66. Plausible mechanism for the formation of 3-substituted flavone derivatives (**14**)

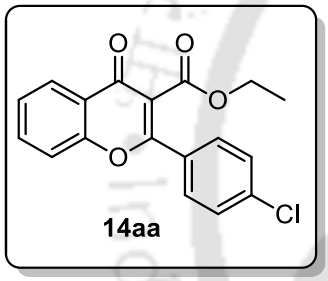
In summary, we have demonstrated a new synthetic protocol for the synthesis of 3-substituted flavone derivatives using one pot three component reactions of 4-hydroxycoumarin, *β*-nitro styrene and alcohol/amine by utilizing an organo-catalyst DMAP. The present protocol is enhanced in terms of yield, reaction time and conditions as compared to the previous methods. Moreover, the protocol was successful for the synthesis of 3-carboxamide-flavone derivatives, which was not reported earlier.

Experimental

*General procedure for the synthesis of 3-substituted flavone derivatives (**14**)*:

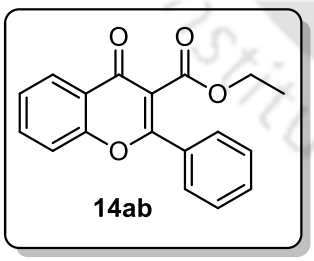
4-hydroxycoumarin (1 mmol), different derivatives of *β*-nitrostyrene(1 mmol), various alcohols or amines (4 mmol) and DMAP(1 mmol) were taken in a round bottom flask. The reaction mixtures werere fluxed at 70-80 °C. The completion of the reaction (directed by thedisappearing of starting material and formation of new spot) was observedby TLC in Ethyl acetate and hexane (15: 85). After the formation of theproduct, the crude reaction mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with H_2O (10 mL), and dried (Na_2SO_4).The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh) to afford the pure products in 65–90% yields.

*Ethyl 2-(4-chlorophenyl)-4-oxo-4H-chromene-3-carboxylate (**14aa**).***:***



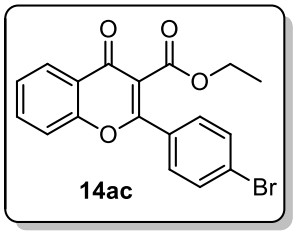
Orange semi solid, **IR** (KBr): 1731, 1645, 1575, 1466, 1381, 1090, 1015, 761 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 6.8 Hz, 3H), 7.50-7.43 (m, 4H), 4.25 (q, *J* = 6.0 Hz, 2H), 1.19 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =174.7, 164.8, 161.4, 155.5, 137.8, 134.4, 130.2, 129.3, 129.0, 125.8, 125.7, 122.8, 118.3, 118.0, 61.9, 13.8; **MS (ESI)**: [M + H^+], Calcd. For: $C_{18}H_{14}{}^{35.5}ClO_4$ (329.0575); Found: 329.0579.

*Ethyl 4-oxo-2-phenyl-4H-chromene-3-carboxylate (**14ab**)***:***



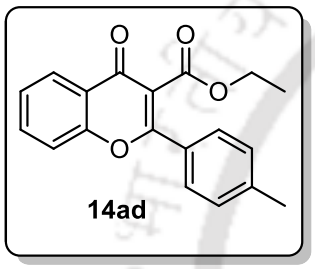
Yellow solid, mp 80-82^{0}C; **IR** (KBr): 1729, 1638, 1567, 1436, 1396, 1089, 760 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.56-7.45 (m, 4H), 7.42 (t, *J* = 6.8 Hz, 1H), 4.25 (q, *J* = 6.8 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =175.1, 165.1, 163.1, 155.8, 134.4, 131.9, 131.7, 128.8, 128.1, 126.1, 125.7, 123.2, 118.1, 61.9, 13.9; **MS (ESI)**: [M + H^+], Calcd. For:$C_{18}H_{15}O_4$ (295.0965); Found: 295.0970.

*Ethyl 2-(4-bromophenyl)-4-oxo-4H-chromene-3-carboxylate (**14ac**)***:***



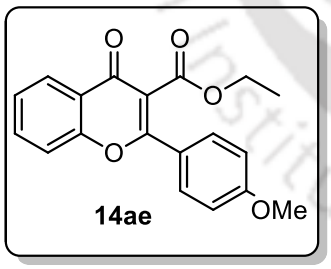
Orange semi solid, **IR** (KBr): 1730, 1645, 1384, 1012, 905 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.65-7.62 (m, 4H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 175.0, 165.0, 161.9, 155.9, 134.6, 132.9, 130.9, 126.5, 126.3, 125.9, 124.2, 123.1, 118.6, 118.2, 62.2, 14.0; **MS (ESI):** [M + H^+], Calcd. For: $C_{18}H_{14}{}^{79}BrO_4$ (375.0052); Found: 375.0067.

*Ethyl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14ad**)* **:**



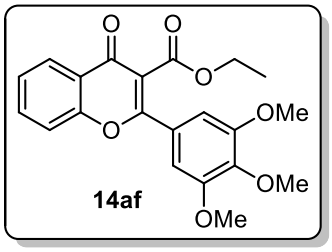
Orange solid, mp 99-101°C; **IR** (KBr): 1731, 1640, 1618, 1566, 1466, 1398, 1089, 1025, 769 cm^{-1};**^{1}H NMR** (400 MHz, $CDCl_3$): δ = .8.23 (d, *J* = 8.0 Hz, 1H), 7.71-7.62 (m, 3H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 6.8 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 4.30 (q, *J* = 6.8 Hz, 2H), 2.42 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$):δ = 174.9, 165.2, 162.8, 155.7, 142.2, 134.2, 129.5, 129.4, 128.9, 127.9, 125.8, 125.5, 122.9, 117.9, 61.7, 21.4, 13.8; **MS (ESI)**: [M + H^+], Calcd. For: $C_{19}H_{17}O_4$ (309.1127); Found: 309.1135.

*Ethyl 2-(4-methoxyphenyl)-4-oxo-4H-chromene-3-carboxylate(**14ae**)* **:**



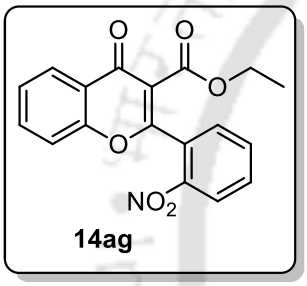
Orange solid, mp 98-100°C; **IR** (KBr): 1730, 1642, 1607, 1512, 1466, 1382, 1090, 1028, 738 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ = 8.23 (d, *J* = 8.0 Hz, 1H), 7.73-7.68 (m, 3H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 4.31 (q, *J* = 6.8 Hz, 2H), 3.87 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$):δ = 174.9, 165.4, 162.4, 162.2, 155.5, 134.1, 129.7, 125.7, 125.4, 123.8, 122.9, 117.9, 117.1, 114.1, 61.7, 55.4, 13.8; **MS (ESI)**:[M + H^+], Calcd. For: $C_{19}H_{17}O_5$ (325.1071); Found: 325.1087.

*Ethyl 4-oxo-2-(2,4,6-trimethoxyphenyl)-4H-chromene-3-carboxylate (**14af**)* **:**



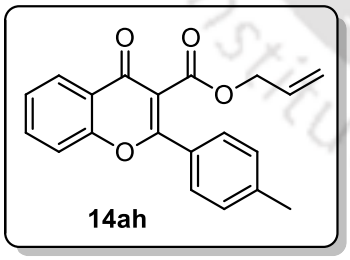
Orange solid, mp 94-96°C; **IR** (KBr): 1726, 1641, 1504, 1462, 1380, 1094, 1018, 763 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 6.8 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.00 (s, 2H), 4.30 (q, *J* = 6.8 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 6H), 1.22 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$):δ = 174.7, 165.2, 162.1, 155.5, 153.2, 140.9, 134.3, 126.7, 125.6, 125.5, 122.8, 118.0, 105.5, 61.8, 60.8, 56.3, 13.8; **MS (ESI)**: [M + H^+], Calcd. For: $C_{21}H_{21}O_7$ (385.1282);Found: 385.1291.

Ethyl 2-(2-nitrophenyl)-4-oxo-4H-chromene-3-carboxylate (***14ag)*** **:**



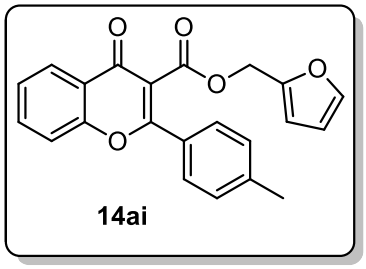
Brown semi solid, **IR** (KBr): 1731, 1638, 1531, 1462, 1398, 1384, 1098, 764 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.24-8.22 (m, 2H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 6.8 Hz, 1H), 7.55 (d, *J* = 5.6 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (**100 MHz, $CDCl_3$):δ =174.3, 163.4, 163.3, 155.8, 147.2, 134.7, 133.9, 132.0, 130.9, 127.6, 126.3, 126.2, 125.0, 123.6, 118.1, 118.0, 61.6, 13.7; **MS (ESI**): [M + H^+], Calcd. For: $C_{18}H_{14}NO_6$ (340.0776);Found: 340.0701.

*Allyl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14ah**)* **:**



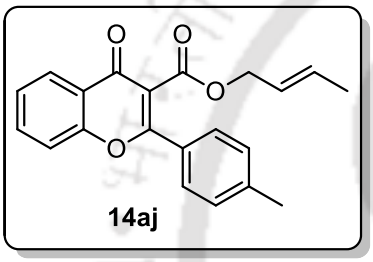
Orange solid, mp 94-96°C; **IR** (KBr): 1728, 1617, 1565, 1465, 1386, 1089, 762 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 7.6 Hz, 1H), 7.71 (brs, 1H), 7.64 (d, *J* = 6.0 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 6.4 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 2H), 5.28-5.25 (m, 2H), 5.19 (d, *J* = 9.2Hz, 1H), 4.73 (brs, 2H), 2.43 (s 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 174.9, 164.9, 163.2, 155.7, 142.3, 134.3, 131.3, 129.5, 128.9, 127.9, 125.9, 125.6, 123.0, 119.0, 118.0, 117.6, 66.7, 21.5; **MS (ESI**): [M + H^+], Calcd. For: $C_{20}H_{17}O_4$ (321.1121); Found: 321.1119.

*Furan-2-ylmethyl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14ai**)* **:**



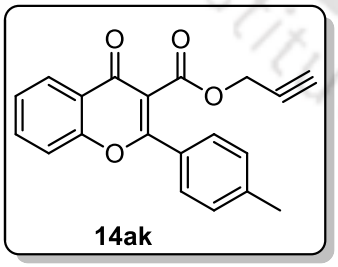
White solid, mp 147-149°C; **IR** (KBr): 1729, 1636, 1613, 1562, 1463, 1385, 1091, 756 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 6.8 Hz, 1H), 7.62-7.59 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 3H), 7.35-7.32 (m, 1H), 7.29 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.33-6.28 (m, 2H), 5.24 (s, 2H), 2.41(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.1, 164.9, 163.6, 155.8, 148.8, 143.3, 142.3, 134.4, 129.5, 128.7, 127.9, 126.3, 126.1, 125.7, 123.1, 118.1, 111.5, 110.6, 59.1, 21.6;. **MS (ESI)**: [M + H^+], Calcd. For: $C_{22}H_{17}O_5$ (361.1071); Found: 361.1087.

*(E)-but-2-en-1-yl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate(**14aj**)* **:**



Orange solid, mp 88-90 °C; **IR** (KBr): 1726, 1635, 1565, 1466, 1384, 1366, 1088, 762 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 5.77-5.69 (m, 1H), 5.53-5.48 (m, 1H), 4.66 (d, *J* = 6.4 Hz, 2H), 2.44(s, 3H), 1.68 (d, *J* = 6.4 Hz, 3H);**^{13}C NMR** (100 MHz, $CDCl_3$): δ =174.9, 165.0, 163.0, 155.7, 142.2, 134.2, 132.1, 129.4, 128.9, 127.9, 125.9, 125.5, 124.2, 122.9, 118.0, 117.7, 66.4, 21.5, 17.8; **MS (ESI):** [M + H^+], Calcd. For: $C_{21}H_{19}O_4$ (335.1278); Found: 335.1275.

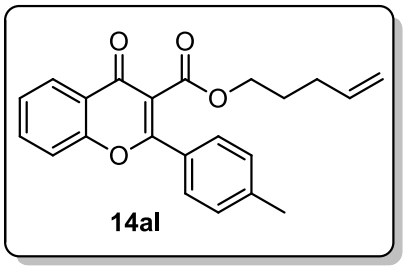
*prop-2-yn-1-yl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14ak**)* **:**



Yellow solid, mp 100-102 °C; **IR** (KBr): 2132, 1732, 1632, 1558, 1466, 1386, 1226, 1094, 762 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.0 Hz, 1H), 7.76-7.65 (m, 3H), 7.53 (brs, 1H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.31-7.27 (m, 2H), 4.85 (s, 2H), 2.48 (s, 1H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 174.8, 164.5, 163.4, 155.6, 142.5, 134.4, 129.5, 128.4, 127.9, 125.7, 125.6, 122.7, 118.0, 116.6, 76.9, 75.6, 53.0, 21.5; **MS (ESI):** [M + H^+], Calcd. For: $C_{20}H_{15}O_4$ (319.0965); Found: 319.0960.

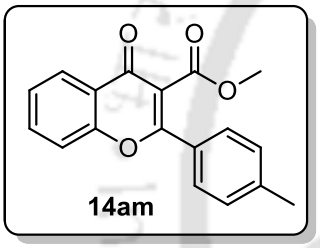
*Pent-4-en-1-yl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14al**)* **:**

Yellow solid, mp 63-65 °C; **IR** (KBr): 1732, 1644, 1619, 1466, 1392, 1091, 761 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.64-5.59 (m, 1H), 4.88 (s, 1H), 4.85 (d, *J* = 3.2 Hz, 1H), 4.16 (t, *J* = 6.4 Hz, 2H), 2.36 (s, 3H), 1.83(q, *J*= 7.2 Hz, 2H), 1.58 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =175.2, 165.5, 163.4, 156.0, 142.5, 137.5, 134.4, 129.7, 129.4, 128.2, 126.3, 125.8, 123.3, 118.2, 118.1, 115.3, 65.4, 29.9, 27.6, 21.7; **MS (ESI):** [M + H^+], Calcd. For: $C_{22}H_{21}O_4$ (349.1434); Found: 349.1435.



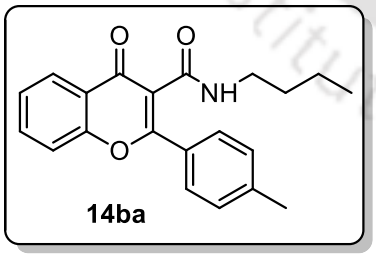
*Methyl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14am**)* **:**

Orange solid, mp 127-129 °C; **IR** (KBr): 1737, 1643, 1618, 1465, 1383, 1091, 760 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.0 Hz, 1H), 7.71-7.68 (m, 1H), 7.63 (d, *J* = 6.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.45-7.40 (m, 1H), 7.31 (d, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.2, 165.9, 163.3, 155.8, 142.5, 134.4, 129.7, 129.1, 128.0, 126.1, 125.7, 123.1, 118.1, 52.9, 21.6; **MS (ESI)**: [M + H^+], Calcd. For: $C_{18}H_{15}O_4$ (295.0956); Found: 295.0865.

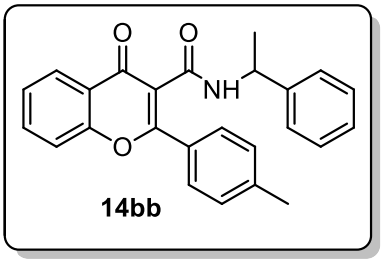


*N-butyl-4-oxo-2-(p-tolyl)-4H-chromene-3-carboxamide (**14ba**)* **:**

Brown solid, mp 101-103°C; **IR** (KBr): 3425, 1721, 1590, 1464, 1341, 941, 757 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 3.24-3.17 (m, 2H), 2.43 (s, 3H), 1.64-1.54 (m, 2H), 1.41-1.32 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 181.7, 175.5, 167.3, 159.8, 154.1, 139.3, 133.7, 130.7, 129.4, 125.9, 125.7, 123.3, 116.5, 96.7, 45.1, 31.6, 21.4, 19.7, 13.4; **MS (ESI)**: [M + H^+], Calcd. For: $C_{21}H_{22}NO_3$ (336.1594); Found: 336.1607.

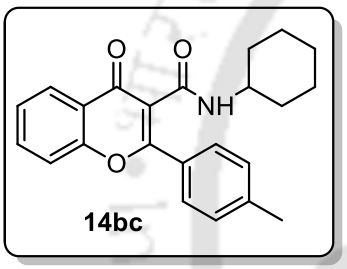


*4-oxo-N-(1-phenylethyl)-2-(p-tolyl)-4H-chromene-3-carboxamide (**14bb**)* **:**



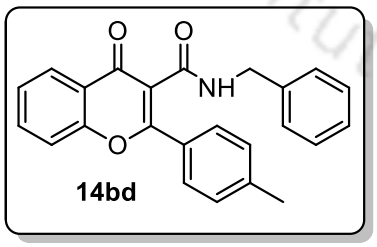
Orange liquid, **IR** (KBr): 3423, 1718, 1609, 1556, 1464, 1344, 761 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 6.8 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 6.0 Hz, 3H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 3H), 6.86 (d, *J* = 7.6 Hz, 1H), 4.63-4.59 (m, 1H), 2.45 (s, 3H), 1.60 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 181.9, 174.4, 161.2, 154.1, 141.5, 139.3, 133.8, 130.5, 129.4, 129.2, 128.9, 127.8, 125.8, 125.7, 125.5, 123.4, 116.5, 96.8, 54.9, 23.6, 21.4; **MS (ESI)**: [M + H^+], Calcd. For: $C_{25}H_{22}NO_3$ (384.1555); Found: 384.1456.

*N-cyclohexyl-4-oxo-2-(p-tolyl)-4H-chromene-3-carboxamide (**14bc**)* **:**



Orange semi solid, **IR** (KBr): 3425, 1718, 1608, 1563, 1465, 1344, 760 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 6.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 3.32 (brs, 1H), 2.44 (s, 3H), 1.87-1.73 (m, 5H), 1.51-1.43 (m, 3H), 1.26-1.18 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 181.9, 174.3, 161.6, 154.4, 139.5, 133.9, 131.0, 129.7, 126.0, 125.8, 123.6, 120.8, 116.8, 96.8, 54.0, 33.5, 25.1, 24.1, 21.7; **MS (ESI)**: [M + H^+], Calcd. For: $C_{23}H_{24}NO_3$ (362.1751); Found: 362.1751.

*N-benzyl-4-oxo-2-(p-tolyl)-4H-chromene-3-carboxamide (**14bd**)* **:**



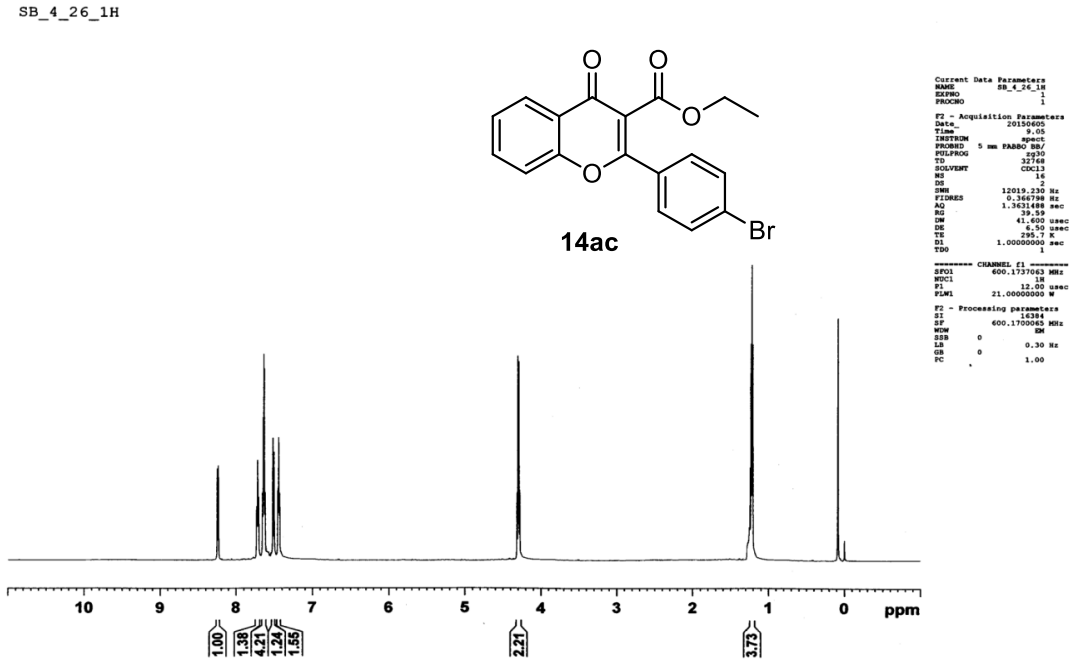
Brown semi solid, **IR** (KBr): 3421, 1709, 1604, 1563, 1452, 1384, 759 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 6.6 Hz, 1.2 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 5.4 Hz, 2H), 7.33-7.29 (m, 3H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 3H), 7.14 (d, *J* = 7.8 Hz, 2H), 4.41 (d, *J* = 6.0 Hz, 2H), 2.44 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 182.0, 175.9, 161.3, 154.2, 139.6, 135.7, 133.9, 129.6, 129.0, 128.2, 127.3, 125.9, 123.5, 116.7, 97.1, 49.1, 21.5; **MS (ESI)**: [M + H^+], Calcd. For: $C_{24}H_{20}NO_3$ (370.1398); Found: 370.1308.

Complete crystallographic data of **14ad** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication with CCDC no. 1430662. 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 11. Crystal data and structure refinement for **14ad**. For atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Identification code	Sb-1	Z	4
Empirical formula	$C_{19}H_{16}O_4$	Density (calculated)	1.313 g/cm^3
Formula weight	308.32	Absorption coefficient	0.092 mm^{-1}
Temperature	0 K	F(000)	648.0
Wavelength	0.71073Å	Theta range for data collection	1.65 to 28.39 º
Crystal system	monoclinic	Index ranges	-17<=h<= 17, -11<=k<=11, -20<=l<=20
Space group	P 21/c	Reflections collected	16096
Unit cell dimensions		Independent reflections	3872 R_{int}= 0.1132
a	13.0619 (7)Å	Completeness to θº	99% (θ = 28.39 º)
b	8.3099 (4) Å	Refinement method	Full-matrix least-squares on F2
c	15.2142(8) Å	Data / restraints / parameters	3872/0 / 210
α	90.00º	Goodness-of-fit on F2	0.865
β	109.198 (2)	Final R indices [>2sigma(I)]	R_{obs} = 0.0591, wR_{obs} = 0.1455
γ	90.00º	R indices (all data)	R_{all} = 0.60561, wR_{all} = 0.1592
Volume	1559.56 (14) Å^3	Largest diff. peak and hole	0.251and -0.367e.Å^{-3}

^{1}H NMR (600 MHz, $CDCl_3$):*Ethyl 2-(4-bromophenyl)-4-oxo-4H-chromene-3-carboxylate (**14ac**)*



^{13}C NMR (150MHz, $CDCl_3$): *Ethyl 2-(4-bromophenyl)-4-oxo-4H-chromene-3-carboxylate (**14ac**)*

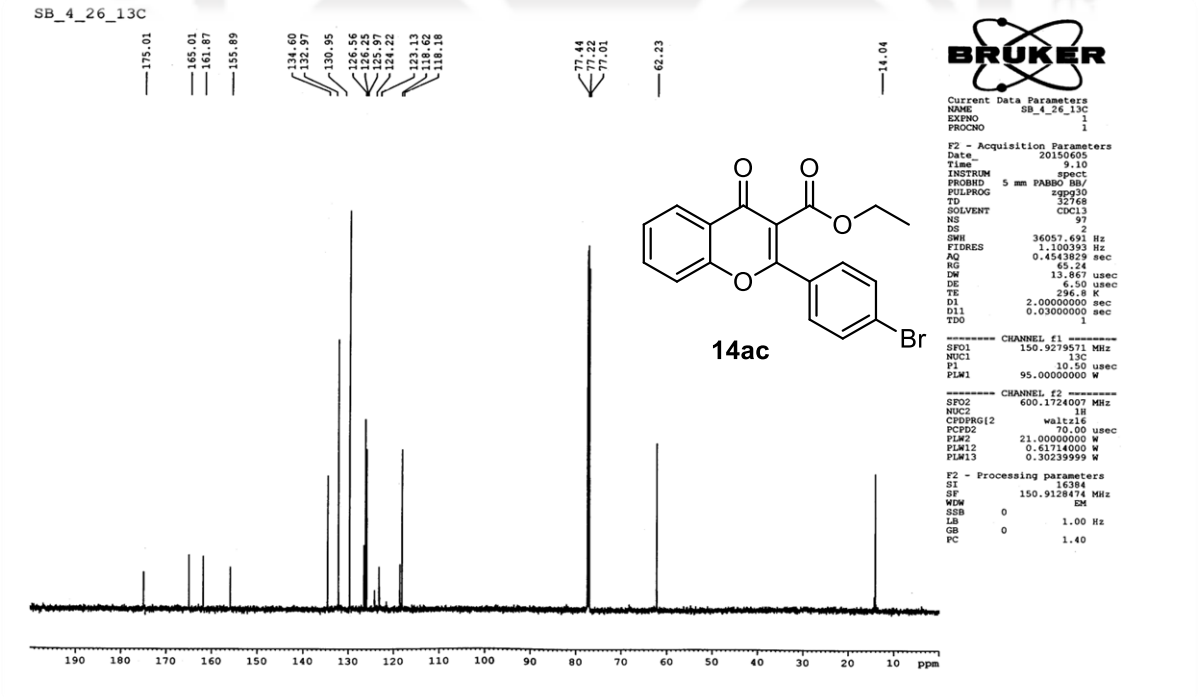
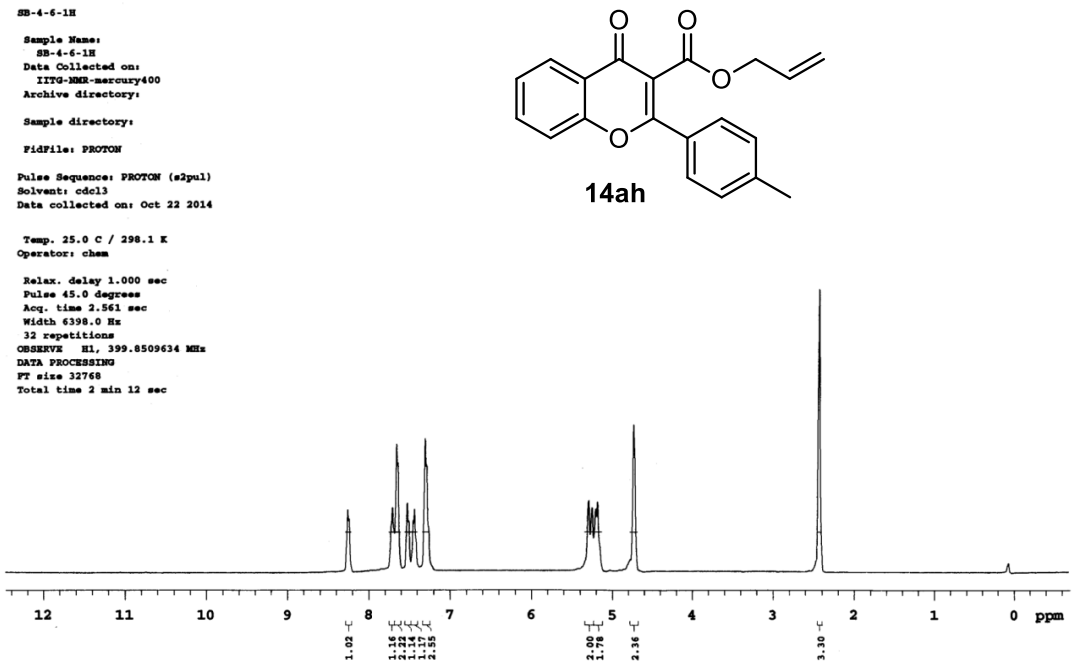


Figure 21

^{1}H NMR (400 MHz, $CDCl_3$)**:Allyl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14ah)



^{13}C NMR (100MHz, $CDCl_3$)**:Allyl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14ah)

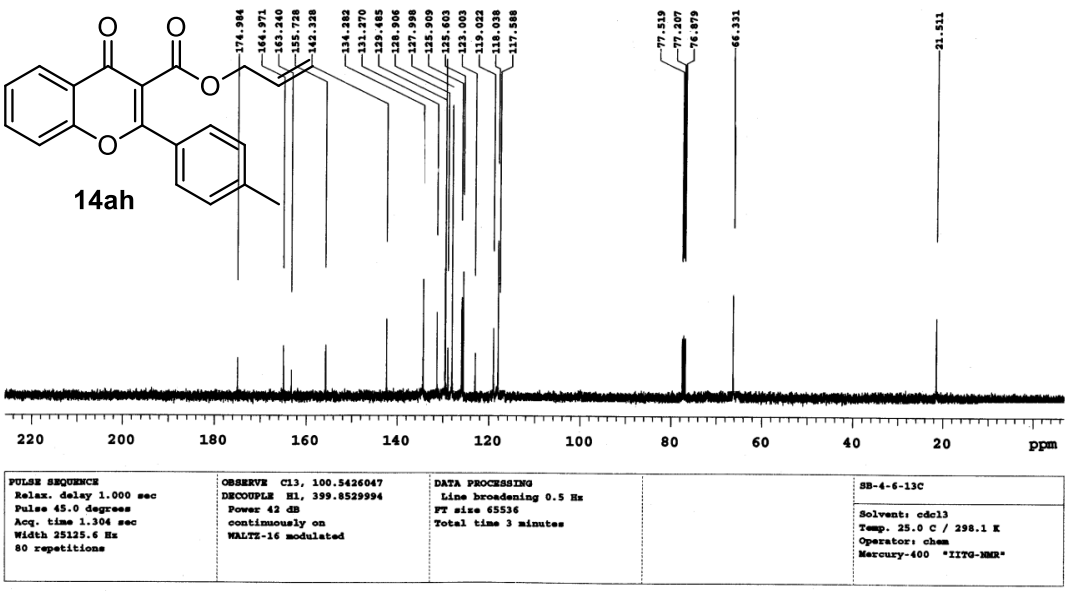
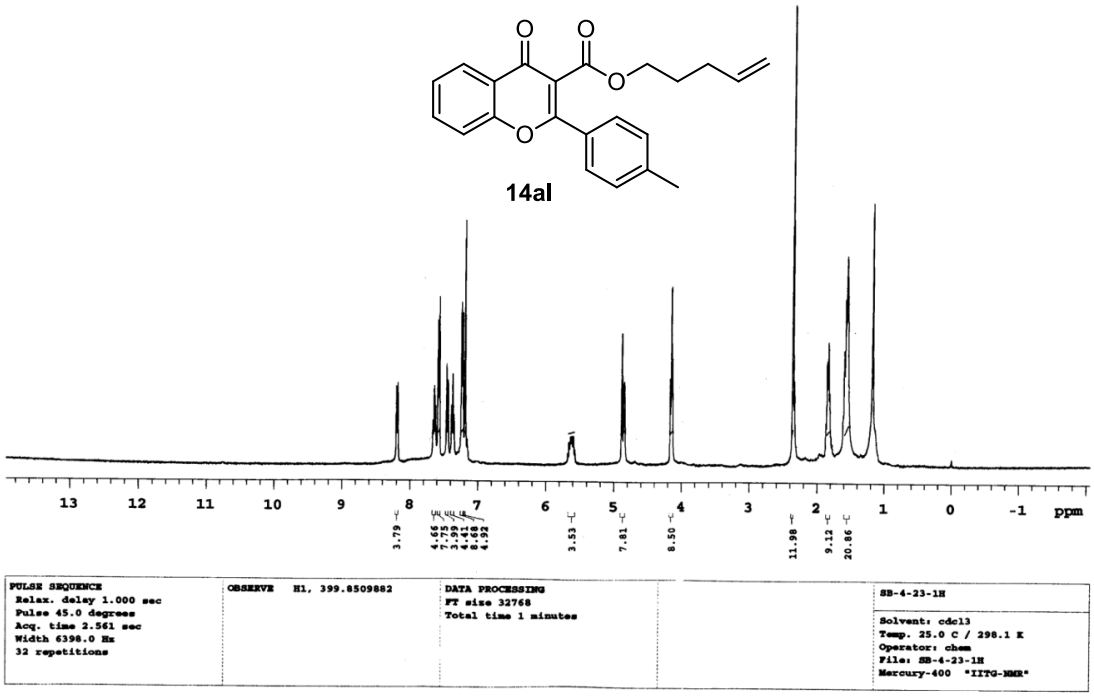


Figure 22

***^{1}H NMR (400 MHz, $CDCl_3$)**:Pent-4-en-1-yl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14al**):*



***^{13}C NMR (100MHz, $CDCl_3$)**:Pent-4-en-1-yl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**14al**):*

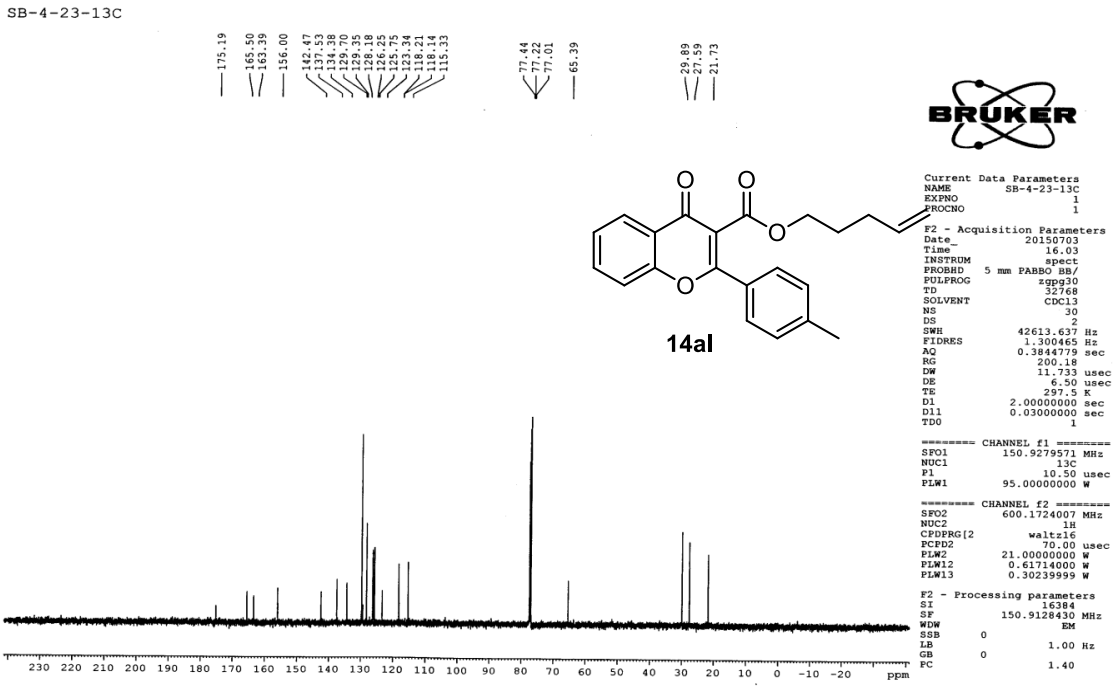
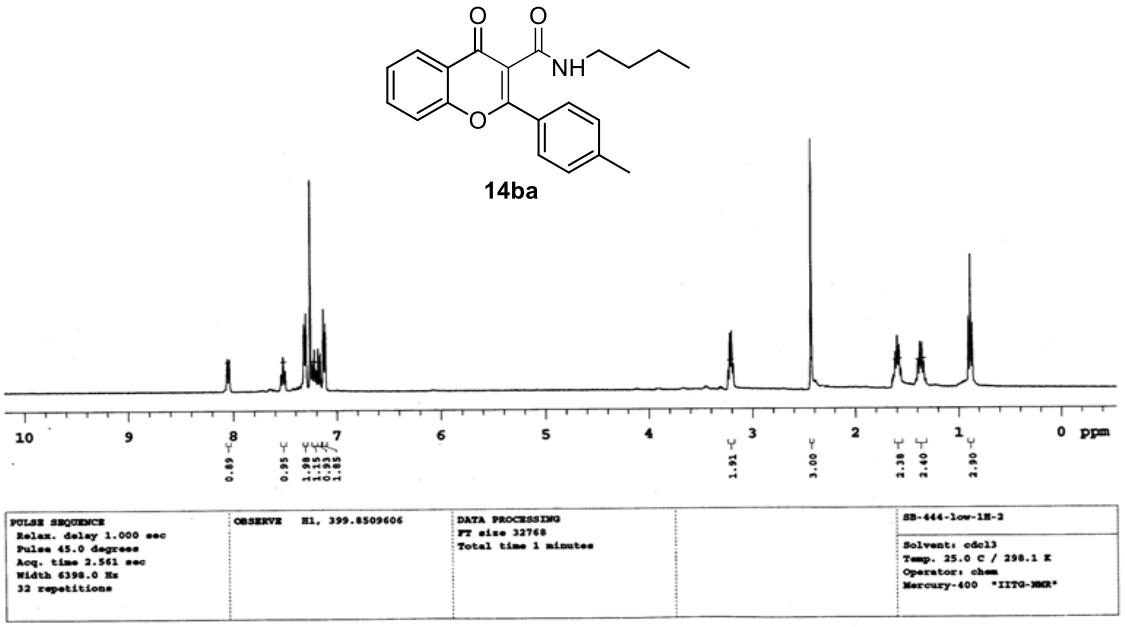


Figure 23

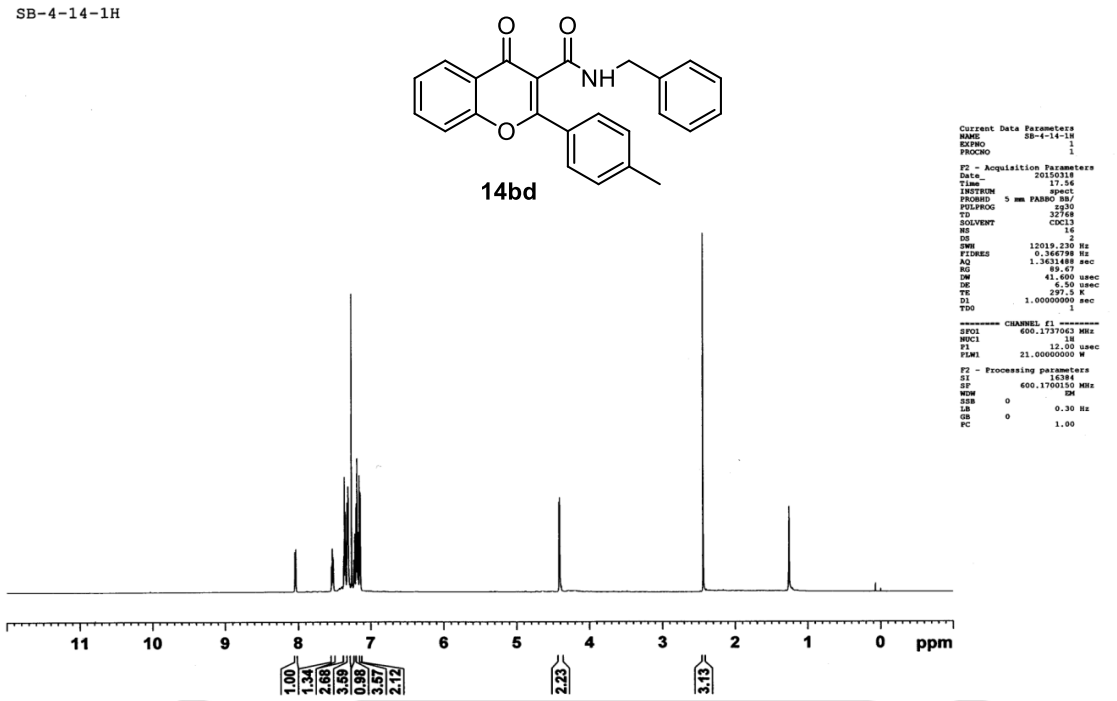
***^{1}H NMR (400 MHz, $CDCl_3$)**: N-butyl-4-oxo-2-(p-tolyl)-4H-chromene-3-carboxamide(**14ba**):*



***^{13}C NMR (100MHz, $CDCl_3$)**:N-butyl-4-oxo-2-(p-tolyl)-4H-chromene-3-carboxamide(**14ba**)*

Figure 24

*^{1}H NMR (400 MHz, $CDCl_3$): N-benzyl-4-oxo-2-(p-tolyl)-4H-chromene-3-carboxamide (**14bd**)*



*^{13}C NMR (100MHz, $CDCl_3$):N-benzyl-4-oxo-2-(p-tolyl)-4H-chromene-3-carboxamide (**14bd**)*

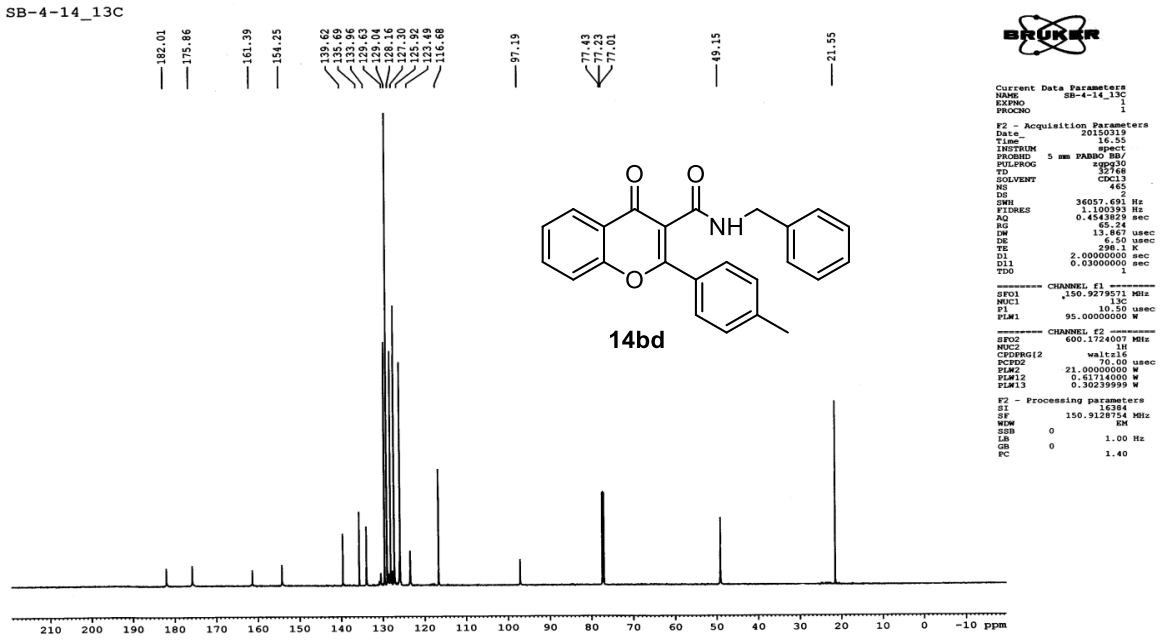


Figure 25

Part B

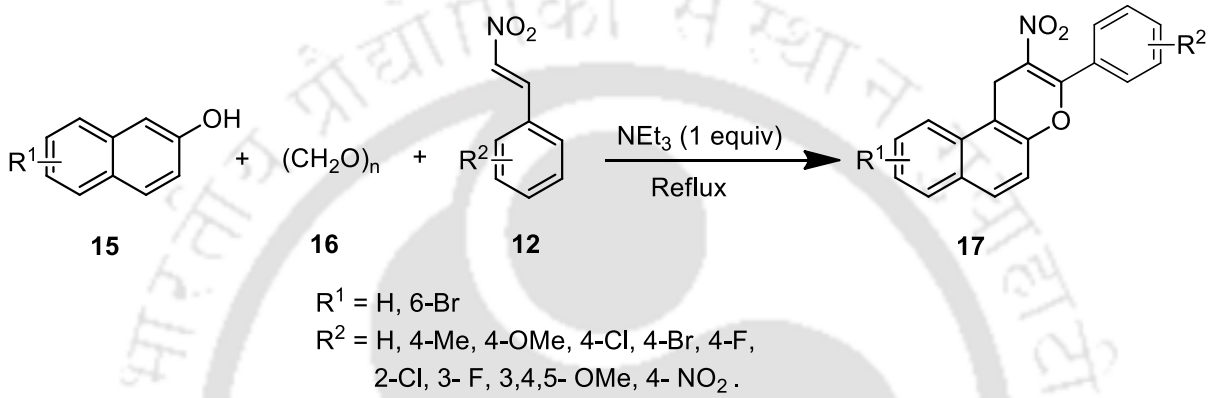
Chapter III

Triethylamine catalyzed one-pot synthesis of Benzo[f]chromene derivatives via Diels-Alder Reaction

Results & Discussion

Experimental Section

Fused chromene derivatives are widely distributed in nature and most of them are biologically active compounds. Chapter I of Part A illustrated the importance and synthetic approaches of benzo[*f*]chromene derivatives and in Chapter I of Part B the utility of *β*-nitrostyrene moiety is briefly described. In this chapter, a suitable method for the synthesis of benzo[*f*]chromene derivatives was explored by exploiting *β*-naphthol, *β*-nitrostyrene and formaldehyde in presence of triethylamine, as shown in Scheme 67.

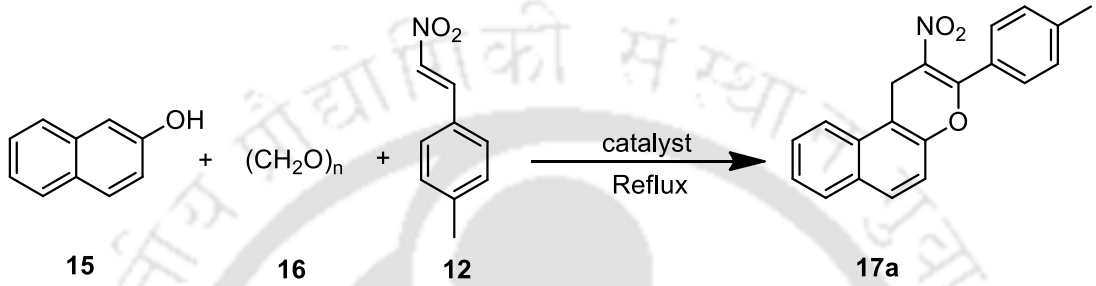


Scheme 67. One-pot three-component synthesis of benzo[*f*]chromene derivatives (**17**)

To find the optimum reaction conditions for the synthesis of benzo[*f*]chromene derivatives, the mixture of *β*-naphthol (1 mmol), *4*-methyl-phenylnitrostyrene (1 mmol) and formaldehyde (1.3 mmol) was taken in a round bottom flask and treated by using a choice of catalysts, under different reaction conditions (Table 12, entries 1-15). The reaction was initially heated under reflux with 20 mol% of triethylamine as a catalyst, for 16 h and the product was obtained only 30% (Table 12, entry 1). Later, the reaction was examined by varying the amount of catalyst (Table 12, entries 2-5), and it was found that 1 mmol of triethylamine successfully afforded the desired product with 79% of yield (Table 12, entry 4). Further, the reaction was carried out with 1.5 mmol of the respective catalyst, and it was identified that the increase in the amount of catalyst does not effectively increase the yield of the product (Table 12, entry 5). It was surprisingly noted that the reaction was entirely unsuccessful when any solvent was used as a medium for the reaction (Table 12, entries 6–9). Moreover, the reaction was also carried out with other basic catalysts like DMAP, Piperidine, DBU, K_2CO_3, Pyridine etc. (Table 12, entries 10-14), and it was observed that the product was obtained only in case of DBU and K_2CO_3 with yield of 68% and 64% respectively (Table 12, entries 12-13). The starting material remained unreacted, when the reaction was monitored in absence of any catalyst. Thus, from

Table 12, it was established that 1 mmol of triethylamine in reflux was the best condition for obtaining the targeted benzo[*f*]chromene derivatives, from the mixture of *β*-naphthol, *4*-methyl-phenylnitrostyrene and formaldehyde. The structure of the product **17a** was deduced by NMR, IR and mass spectrometry.

Table 12: Optimization table for the synthesis of benzo[*f*]chromene **17a**[a]



Entry	Catalyst	Solvent	Mol%	Time (h)	Yield[b] %
1	NEt_3	-	0.2	16	30
2	NEt_3	-	0.4	13	50
3	NEt_3	-	0.6	6	65
4	**NEt_3**	**-**	**1.0**	**2**	**79**
5	NEt_3	-	1.5	2	81
6	NEt_3	EtOH	1.0	24	-
7	NEt_3	DCE	1.0	24	-
8	NEt_3	MeCN	1.0	24	-
9	NEt_3	H_2O	1.0	24	-
10	DMAP	-	1.0	24	-
11	Piperidine	-	1.0	24	-
12	DBU	-	1.0	5	68
13	K_2CO_3	-	1.0	12	64
14	Pyridine	-	1.0	24	-
15	None	-	0.0	24	-

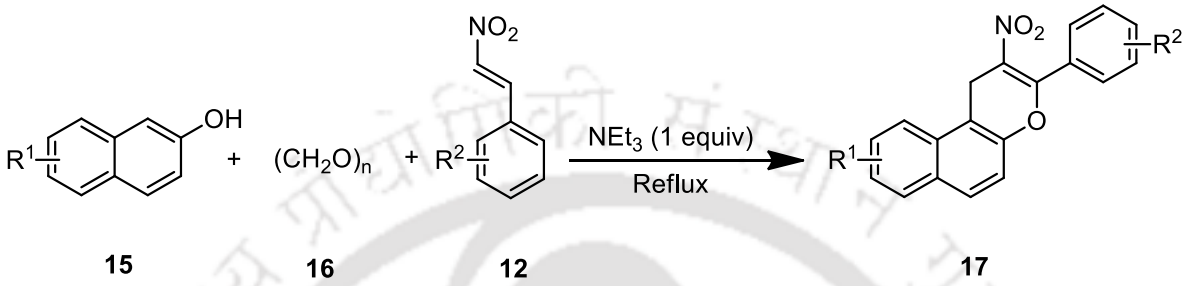
[a]All the reactions were performed with *β*-naphthol (1 mmol), 4-Methyl phenyl nitrostyrene (1 mmol), and formaldehyde (1.3 mmol, 37% solution) in the presence of indicated catalyst at reflux conditions. [b]Isolated yields.

From the study of ^{1}HNMR and HSQC of the compound **17a**, it was found that the aromatic proton on C10, C7, C6 and C5 appeared as doublets at 7.93, 7.84, 7.75 and 7.68 ppm respectively having *J* values of 8.4 Hz. The aromatic proton on C9 and C8 arrived as a broad singlet at 7.41 and 7.32 ppm. The protons on C2`, C3`, C5`, C6` emerge as doublets having *J* values of 7.8 Hz, at 7.42 and 7.33 ppm respectively. The benzylic proton on C1 approached at 4.72 ppm as singlet. The methyl group attached with C4` appeared at 2.54 as a singlet for 3H. In ^{13}C NMR peak found at 152.1, 152.0, 138.0, 131.0, 130.4, 129.9, 129.6, 129.1, 128.6, 126.4, 126.2, 124.5, 123.4, 121.9, 121.8, 112.6, 56.2, 21.6 ppm. From DEPT 135, it was clear that the peaks at 130.2, 129.5, 128.9, 126.2, 126.0, 124.3, 123.2, 112.4 ppm were designated for aromatic –CH group respectively, the peak at 55.1 represents –CH_2 peak and the methyl group appears at 21.6 ppm. The peak at 152.1 (C3), 152.0 (C4), 138.0 (C12), 131.0 (C4`), 129.9 (C13), 128.6 (C1`), 121.9 (C11) and 121.8 (C2) represents the tertiary carbon or the carbon having no proton. Furthermore, from HMBC, it was confirmed that singlet at 4.72 ppm i.e benzylic hydrogen attached to C1 has an interaction with the peak at 152.1 ppm (C3) and the peak at 152.0 ppm (C4) respectively. Similarly, the spectra have showed the interaction of C1 with 121.8 ppm (C2) and 121.9 ppm (C11) respectively, from which the structure of **4a** can be easily portrayed. Moreover, in IR, the absorption peak for the compound appeared at 1507 and 1384 cm^{-1} which indicated the presence of the NO_2 group. C=C stretching frequency is observed at 1632 cm^{-1} for the compound **17a.**

The protocol was first scrutinized with *β*-naphthol (1 mmol), (*E*)-(2-nitrovinyl) benzene (1 mmol) and formaldehyde (1.3 mmol) under the identical reaction conditions, the desired product **17b** was obtained with 75% yield (Table 13, entry 2). In consideration of the success of the above reactions, the procedure was examined for the wide variety of the reactions to perceive the scope and limitations of the reaction conditions. Accordingly, under the standard reaction conditions, various *β*-nitrostyrene moieties in reaction with *β*-naphthol or its analogs and formaldehyde effectively generates the corresponding benzo[*f*]chromene derivatives in moderate to good yield (Table 13, entries 1-15). It is noteworthy that, the *β*- nitrostyrene having electron donating group reacts faster and gave better result compared to the *β*- nitrostyrene having electron withdrawing group (Table 13, entries 1-8). The desired product with a good yield was also obtained in the case of ortho and meta substituted *β*- nitrostyrene moieties, under the indistinguishable reaction conditions (Table 13, entries 9-10). Reactions with the heteronuclear substituent, like (*E*)-2-(2-nitrovinyl)thiophene furnished 78% yield of the desired

product (Table 13, entry 11). Similarly, when a range of reactions was carried out with 6-bromo-2-naphthol with different substituted *β*- nitrostyrene moieties, the preferred product **17l-17o** were isolated in 68–74% respectively (Table 13 entries 12-15).

Table 13: Substrate scope and yields of benzo[*f*]chromene derivatives (**17**)[a]



15 **16** **12** **17**

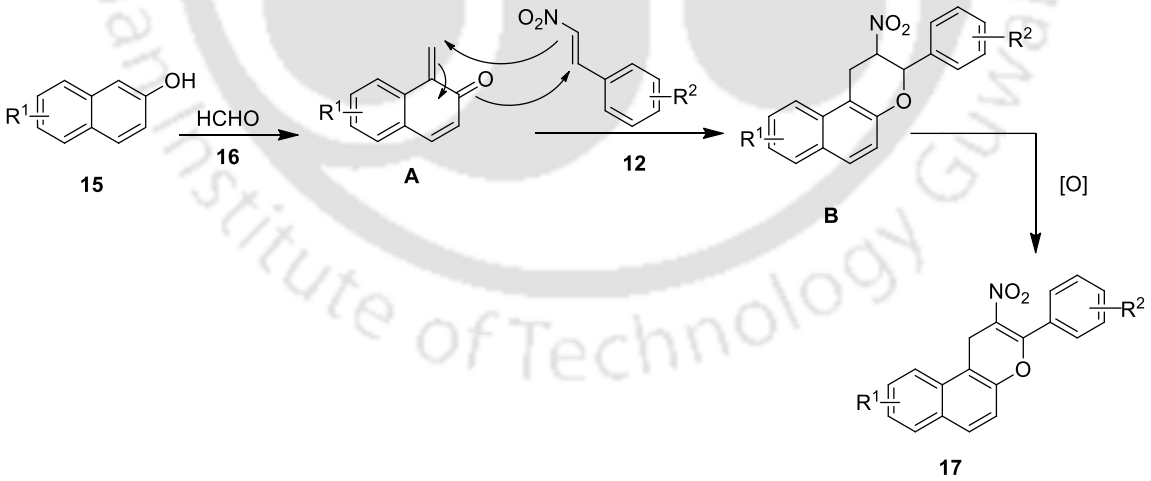
Entry	R^1	R^2	Time (h)	Yield[b]/(%)	Product
1	H	4-Me	2.0	79	**17a**
2	H	H	5.0	75	**17b**
3	H	4-OMe	2.5	76	**17c**
4	H	3-OMe-4-OMe-5-OMe	4.0	77	**17d**
5	H	4-Cl_4	8.0	72	**17e**
6	H	4-Br	8.5	73	**17f**
7	H	4-F	9.0	73	**17g**
8	H	4-NO_2	7.0	70	**17h**
9	H	2-Cl	12.0	71	**17i**
10	H	3-F	10.0	72	**17j**
11	H	Thiophene	6.0	78	**17k**
12	6-Br	H	6.0	70	**17l**
13	6-Br	4-Me	3.0	74	**17m**
14	6-Br	3-OMe-4-OMe-5-OMe	6.0	73	**17n**
15	6-Br	4-Cl	12.0	68	**17o**

[a]All the reactions were performed with *β*-naphthol (1 mmol), 4-Methyl phenyl nitrostyrene (1 mmol), and formaldehyde (1.3 mmol, 37% solution) in the presence of triethyl amine (1mmol) as catalyst at reflux conditions. [b]Isolated yields.

To explore the diversity of the protocol, we have used *β*-naphthyl amine in place of *β*-naphthol, but in that case, the desired product was not obtained. Similarly, when formaldehyde was replaced by other aromatic aldehydes, under the same reaction conditions, the path of the reactions found ineffective.

All the synthesized compounds were fully characterized by IR, NMR and elemental analysis. In IR spectrum, compound **17a-17o** showed two characteristic strong absorptions at the range of 1515-1507cm^{-1} and 1384-1339 cm^{-1} due to the nitro group present in the molecule. The products **17a–o** exhibited a diagnostic signal in the range of δ = 4.63–4.80 assignable to the benzylic hydrogen attached to the C1, depending on the nature of the substituent present in the moiety. The ^{1}H NMR and ^{13}C NMR spectra of the products**17a, 17j, 17k** and **17n,** are given in Figure 26-31 respectively in the experimental section.HSQC, HMBC, DEPT 135 and MS spectra of **17a** are also represented in the experimental section in figure 27-28.

A mechanistic pathway has been suggested for the formation of the compound **17** as; initially, *o*-quinine methides **A** formed from *β*-naphthol**15** and formaldehyde **16.** *O-Quinine* methides represent an important class of intermediates for organic synthesis, which is a good electrophilic Michael acceptors, so easily undergoes Diels-Alder reactions with *β*-nitrostyrene, followed by oxidation, and furnished the desired product **17** as shown in Scheme 68.



Scheme 68. Proposed mechanism for the formation of benzo[*f*]chromenederivatives (**17**)

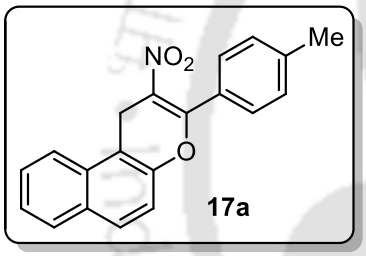
In conclusion, we have developed a new efficient protocol for the synthesis of benzo[*f*] chromene derivatives, which is gifted with various advantages such as solvent-free, environmentally benign reaction conditions with good yields, superior atom economy, the easy accessibility of the catalyst and its cost effectiveness.

Experimental

*General procedure for the synthesis of Benzo[f] Chromene derivatives (**17**)*:

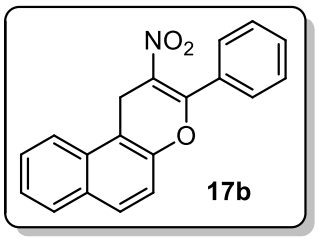
β-Naphthol (1 mmol), different derivatives of *β*-nitrostyrene (1 mmol), formaldehyde (1.3 mmol, 37% solution) and NEt_3 (1 mmol) were taken in a round bottom flask. The reaction mixtures were refluxed at 70-80°C. The completion of the reaction (directed by thedisappearing of starting material and formation of new spot) was observedby TLC of Ethyl acetate and hexane (15: 85). After the formation of the product, the crude reaction mixture was extracted with EtOAc (3× 10 mL), the combined organic layers were washed with H_2O (20 mL), and dried (Na_2SO_4).The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh) to afford the pure products in 68–79% yields.

*2-nitro-3-(p-tolyl)-1H-benzo[f]chromene **(17a)***:



Orange semi solid, **IR** (KBr): 2923, 1632, 1507, 1384, 1014, 928, 744 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.8 Hz, 1H, C_{10}-H), 7.84 (d, *J* = 8.4 Hz, 1H, C_7-H), 7.75 (d, *J* = 8.4 Hz, 1H, C_6-H), 7.68 (d, *J* = 8.4 Hz, 1H, C_5-H), 7.42 (d, *J* = 7.8 Hz, 2H, C'_2-H, C'_3-H), 7.41 (brs, 1H, C_9-H), 7.33 (d, *J* = 7.8 Hz, 2H, C'_5-H, C'_6-H), 7.32 (brs, 1H, C_8-H), 4.72 (s, 2H, C_1-H), 2.53 (s, 3H, C'_4-H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 152.1 (C_3), 152.0 (C_4), 138.0 (C_{12}), 131.0 (C'_4), 130.4, 129.9 (C_{13}), 129.6, 129.1, 128.6 (C'_1), 126.4, 126.2, 124.5, 123.4, 121.9 (C_{11}), 121.8 (C_2), 112.6 (C_5), 56.2 (C_1), 21.6 (C'_4); **MS (EI, M/Z)**: [M^+], Calcd. For: $C_{20}H_{15}NO_3$ (317.1052); Found: 317.2419; **Anal. Calcd** for $C_{20}H_{15}NO_3$ (317.10): C, 75.70; H, 4.76; N, 4.41 Found: C, 75.82; H, 4.81; N, 4.49.

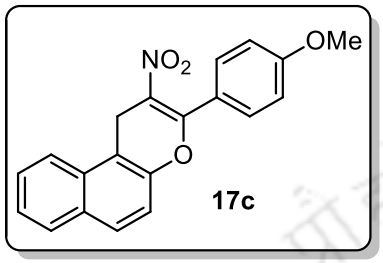
*2-nitro-3-phenyl-1H-benzo[f]chromene **(17b)***:



Light reddish semi solid, **IR** (KBr): 2924, 1628, 1515, 1384, 1015, 761 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.52 (brs, 2H), 7.43-7.38 (m, 2H), 7.31 (t, *J* = 9.6 Hz, 2H), 7.05 (d, *J* = 1.2 Hz, 1H), 4.79 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.1, 151.9, 133.1, 131.0, 130.6, 129.1, 128.9, 128.5, 128.3, 126.5, 126.2, 124.5, 123.3, 121.8, 112.6, 110.2, 56.2; **MS (EI, M/Z)**: [M + H^+], Calcd. For: $C_{19}H_{14}NO_3$ (304.0929); Found: 304.2451;

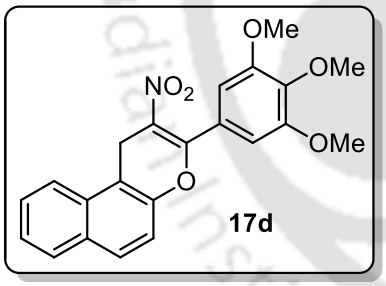
Anal. Calcd for $C_{19}H_{13}NO_3$ (303.31): C, 75.24; H, 4.32; N, 4.62Found: C, 75.38; H, 4.35; N, 4.70.

*3-(4-methoxyphenyl)-2-nitro-1H-benzo[f]chromene **(17c)*:**



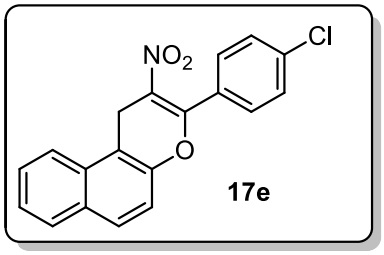
Redgummy liquid, **IR** (KBr): 2925, 1622, 1599, 1510, 1463 1385,1246, 1174, 1032, 808 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.67 (s, 1H), 7.63 (t, *J* = 8.8 Hz, 1H), 7.45 (brs, 1H), 7.43-7.40 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.33-7.28 (m, 2H), 4.70 (s, 2H), 3.91 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.7, 152.1, 151.7, 131.7, 129.1, 129.0, 128.9, 126.9, 126.4, 126.2, 124.5, 123.4, 123.3, 118.3, 114.4, 112.6, 56.3, 55.6; **MS (EI, M/Z)**: [M + H^+], Calcd. For: $C_{20}H_{16}NO_4$ (334.1035); Found: 334.1208; **Anal. Calcd** for $C_{20}H_{15}NO_4$ (333.33): C, 72.06; H, 4.32; N, 4.20Found: C, 72.20; H, 4.36; N, 4.28.

*2-nitro-3-(3,4,5-trimethoxyphenyl)-1H-benzo4[f]chromene**(17d)*:**



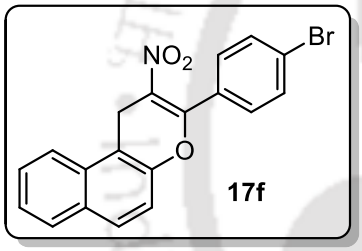
Red semi solid, **IR** (KBr): 2940, 1583, 1509, 1460, 1415, 1349, 1239, 1124, 1006, 805 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 9.6 Hz, 1H), 6.75 (brs, 2H), 4.76 (s, 2H), 3.98 (s, 3H), 3.96 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 153.5, 152.0, 137.8, 130.9, 129.1, 128.5, 128.3, 126.5, 126.3, 124.6, 123.4, 121.8, 121.7, 112.6, 107.5, 61.2, 56.4, 56.2; **MS (EI, M/Z)**: [M^+], Calcd. For: $C_{22}H_{19}NO_6$ (393.1212); Found: 393.2739; **Anal. Calcd** for $C_{22}H_{19}NO_6$ (393.12): C, 67.17; H, 4.87; N, 3.56 Found: C, 67.30; H, 4.92; N, 3.65.

3-(4-chlorophenyl)-2-nitro-1H-benzo[f]chromene ***(17e)*****:**



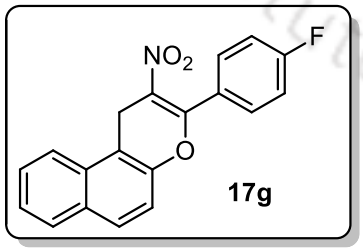
Reddish-orange semi solid, **IR** (KBr): 2924, 1603, 1384, 1010, 807, 760 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H),7.68 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 4.8 Hz, 3H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 6.8 Hz, 2H), 4.70 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.2, 151.5, 134.2, 131.9, 131.5, 130.9, 129.2, 128.3, 126.6, 126.4, 124.6, 122.9, 121.6, 120.6, 112.6, 55.9; **MS (EI, M/Z)**: [M + H^+], Calcd. For: $C_{19}H_{13}{}^{35.5}ClNO_3$ (338.0506); Found: 338.3383; **Anal. Calcd** for $C_{19}H_{12}ClNO_3$ (337.75): C, 67.56; H, 3.58; N, 4.15 Found: C, 67.45; H, 3.52; N, 4.07.

3-(4-bromophenyl)-2-nitro-1H-benzo[f]chromene ***(17f)*****:**



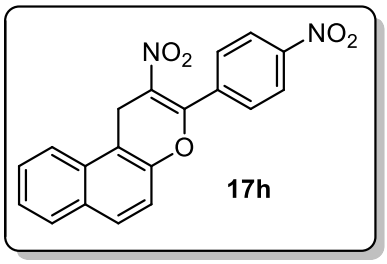
Orange semi solid, **IR** (KBr): 2924, 1603, 1384, 1010, 805, 744 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.0 Hz, 1H), 7.78-7.75 (m, 2H), 7.66 (d, *J* = 8.8 Hz, 3H), 7.46-7.40 (m, 3H), 7.36 (t, *J* = 8.4 Hz, 1H), 4.68 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.2, 152.0, 132.2, 132.1, 132.0, 131.0, 129.3, 128.3, 126.7, 126.4, 124.7, 123.1, 122.6, 121.5, 120.7, 112.6, 56.1; **Anal. Calcd** for $C_{19}H_{12}BrNO_3$ (382.21): C, 59.71; H, 3.16; N, 3.66 Found: C, 59.82; H, 3.22; N, 3.73.

3-(4-fluorophenyl)-2-nitro-1H-benzo[f]chromene ***(17g)*****:**



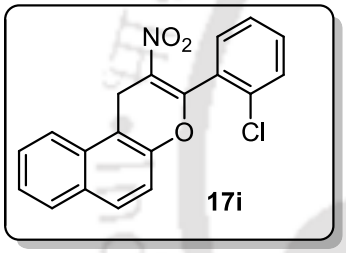
Orange semi solid, **IR** (KBr): 2923, 1627, 1507, 1384, 1223, 1093, 765 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 1H), 7.81-7.75 (m, 2H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.54 (t, *J* = 6.8 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.69 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 164.2, 152.1, 132.3, 132.2, 130.9, 129.3, 128.4, 126.6, 126.3, 124.6, 123.1, 121.8, 116.1, 115.9, 112.6, 56.1; **MS (EI, M/Z)**: [M + H^+], Calcd. For: $C_{19}H_{13}FNO_4$ (322.0835); Found: 322.2922; **Anal.Calcd** for $C_{19}H_{12}FNO_3$ (321.30): C, 71.02; H, 3.76; N, 4.36 Found: C, 71.15; H, 3.80; N, 4.45.

2-nitro-3-(4-nitrophenyl)-1H-benzo[f]chromene ***(17h)*****:**



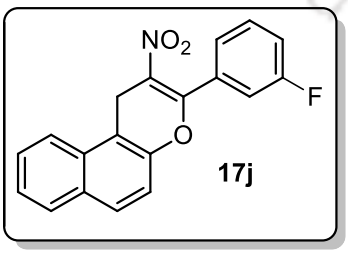
Yellow semi liquid, **IR** (KBr): 2924, 1621, 1597, 1515, 1462, 1396, 1347, 1263, 1216, 1044, 995, 803 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 9.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 9.6 Hz, 1H), 7.24 (brs, 4H), 7.06 (d, *J* = 8.8 Hz, 1H), 4.80 (s, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 151.8, 151.3, 140.4, 133.7, 131.5, 129.8, 129.1, 128.9, 128.7, 126.8, 124.3, 123.9, 123.7, 123.4, 118.1, 117.6, 51.1; **Anal. Calcd** for $C_{19}H_{12}N_2O_5$ (348.07): C, 65.52; H, 3.47; N, 8.04 Found: C, 65.65; H, 3.52; N, 8.10.

3-(2-chlorophenyl)-2-nitro-1H-benzo[f]chromene ***(17i)*****:**



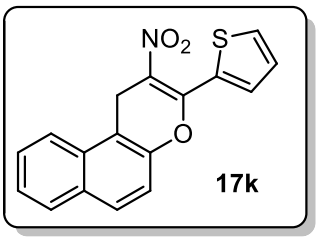
Red liquid, **IR** (KBr): 2924, 1607, 1384, 1010, 807, 760 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 5.2 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 6.8 Hz, 2H), 7.44-7.31 (m, 4H), 7.25 (d, *J* = 6.8 Hz, 1H) 4.73 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.3, 152.1, 135.2, 132.7, 132.1, 130.9, 130.2, 130.1, 129.0, 128.8, 128.4, 127.3, 126.5, 124.6, 123.3, 122.8, 118.7, 112.6, 56.4; **MS (EI, M/Z)**: [M + H^+], Calcd. For: $C_{19}H_{13}{}^{35.5}ClNO_3$ (338.0506); Found: 338.0353; **Anal.Calcd** for $C_{19}H_{12}ClNO_3$ (337.75): C, 67.56; H, 3.58; N, 4.15 Found: C, 67.47; H, 3.55; N, 4.10.

3-(3-fluorophenyl)-2-nitro-1H-benzo[f]chromene ***(17j)*****:**



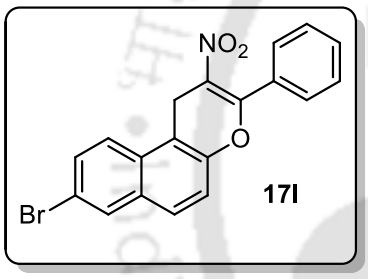
Yellow semi solid, **IR** (KBr): 2924, 1627, 1507, 1384, 1092, 764 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.45–7.40 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 9.6 Hz, 1H), 7.14 (t, *J* = 8.8 Hz, 1H), 4.63 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 162.8 ($^1J_{C-F}$ = 250 Hz), 152.1, 152.0, 130.9, 130.5, 130.4, 129.2, 128.2, 126.6, 126.4, 124.6, 123.1, 121.4, 117.6, 117.4, 115.4, 115.3, 112.5, 55.9; **MS (EI, M/Z)**: [M + H^+], Calcd. For: $C_{19}H_{13}FNO_4$ (322.0835); Found: 322.2724; **Anal. Calcd** for $C_{19}H_{12}FNO_3$ (321.30): C, 71.02; H, 3.76; N, 4.36 Found: C, 71.14; H, 3.80; N, 4.44.

2-nitro-3-(thiophen-2-yl)-1H-benzo[f]chromene ***(17k)*****:**



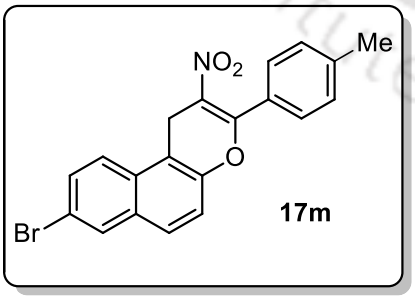
Orange semi solid, **IR** (KBr): 2924, 1627, 1599, 1382, 1014, 801 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.60-7.51 (m, 1H), 7.47-7.42 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 6.8 Hz, 1H), 7.16 (brs, 1H), 4.73 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 153.7, 152.0, 130.9, 129.3, 129.1, 128.9, 127.8, 127.3, 126.8, 126.6, 126.4, 124.7, 123.3, 123.1, 117.5, 112.5, 56.1; **MS (EI, M/Z)**: [M^+], Calcd. For: $C_{17}H_{11}NO_3S$ (309.0460); Found: 309.1371; **Anal.Calcd** for $C_{17}H_{11}NO_3S$ (309.04): C, 66.01; H, 3.58; N, 4.53 Found: C, 66.13; H, 3.62; N, 4.62.

8-bromo-2-nitro-3-phenyl-1H-benzo[f]chromene ***(17l)*****:**



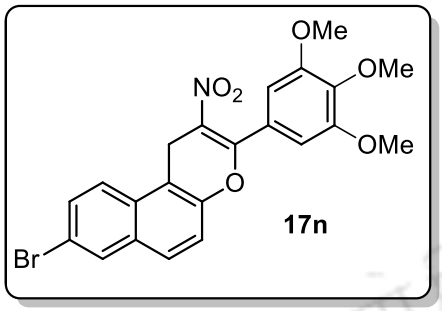
Brown gummy liquid, solid, **IR** (KBr): 2922, 1628, 1512, 1384, 1015, 761cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.88 (brs, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.35 (td, *J* = 8.8 Hz, 1.6 Hz,3H), 4.68 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.5, 152.1, 132.6, 132.3, 131.1, 130.5, 129.4, 129.0, 128.5, 126.9, 125.4, 124.9, 122.0, 121.6, 118.3, 113.7, 56.1; **Anal. Calcd** for $C_{19}H_{12}BrNO_3$ (382.20): C, 59.71; H, 3.16; N, 3.66 Found: C, 59.80; H, 3.20; N, 3.71.

8-bromo-2-nitro-3-(p-tolyl)-1H-benzo[f]chromene ***(17m)*****:**



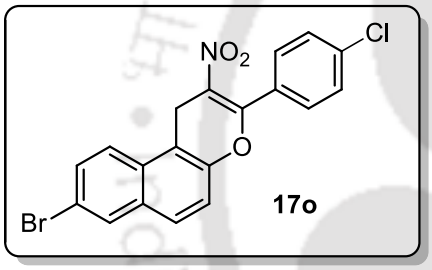
Orange gummy liquid, **IR** (KBr): 2924, 1627, 1507, 1384, 1014, 926, 742 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.00 (s, 1H),7.92 (d, *J* = 9.2 Hz, 1H), 7.80 (brs, 1H), 7.63-7.56 (m, 2H), 7.32 (d, *J* = 6.4 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 4.63 (s, 2H), 2.41 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.4, 151.9, 138.3, 132.2, 131.0, 130.3, 129.7, 129.5, 129.3, 126.9, 125.3, 125.0, 122.1, 121.6, 118.2, 113.6, 56.1, 21.9; **MS (EI, M/Z)**: [M + H^+], Calcd. For: $C_{20}H_{15}{}^{81}BrNO_3$ (396.0157); Found: 396.0902; **Anal. Calcd** for $C_{20}H_{14}BrNO_3$ (396.23): C, 60.62; H, 3.56; N, 3.53 Found: C, 60.73; H, 3.60; N, 3.60.

8-bromo-2-nitro-3-(3,4,5-trimethoxyphenyl)-1H-benzo[f]chromene ***(17n)*****:**



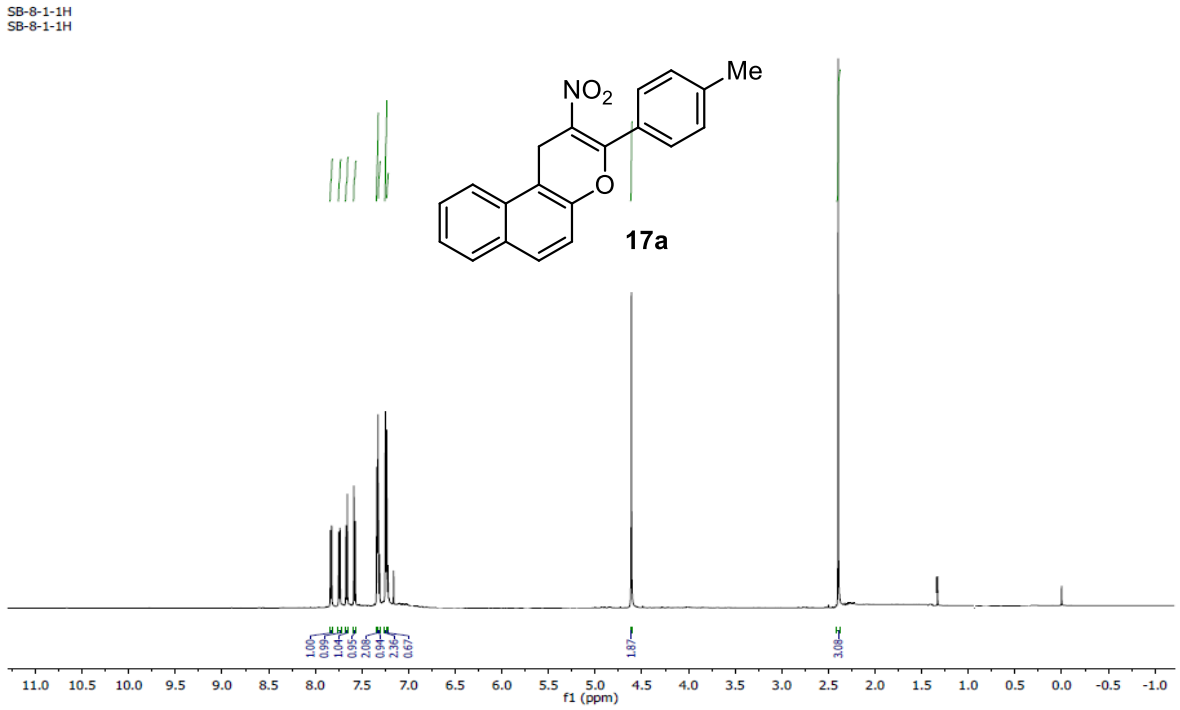
Orange semi solid, **IR** (KBr): 2930, 1585, 1509, 1460, 1415, 1384, 1239, 1007, 805cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (s, 1H),7.75 (d, *J* = 9.2 Hz, 1H), 7.72–7.65 (m, 2H), 7.44 (dd, *J* = 5.2 Hz, 1.6 Hz,1H), 6.73 (s, 2H), 4.76 (s, 2H), 4.00 (s, 3H), 3.86 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 153.6, 152.5, 151.9, 137.9, 132.2, 131.1, 129.4, 128.0, 126.7, 125.4, 125.1, 121.8, 121.6, 118.3, 113.9, 107.4, 61.2, 56.3, 56.1; **Anal. Calcd** for $C_{22}H_{18}BrNO_6$ (472.28): C, 55.95; H, 3.84; N, 2.97 Found: C, 55.87; H, 3.80; N, 2.94.

8-bromo-3-(4-chlorophenyl)-2-nitro-1H-benzo[f]chromene ***(17o):***



Brown semi solid, **IR** (KBr): 2921, 1633, 1603, 1384, 1091, 761 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.01 (brs, 1H),7.92 (d, *J* = 8.4 Hz, 1H), 7.81 (brs, 1H), 7.62-7.59 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.45 (dd, *J* = 6.4 Hz, 2.0 Hz,2H), 7.39-7.37 (m, 1H), 4.64 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.6, 152.0, 134.5, 132.4, 131.8, 131.2, 129.6, 129.3, 127.9, 126.7, 125.6, 124.7, 123.9, 123.6, 118.3, 113.7, 56.1; **MS (EI, M/Z)**: [M+ H^+], Calcd. For: $C_{19}H_{12}{}^{81}Br^{35.5}ClNO_3$ (415.0611); Found: 415.1492; **Anal.Calcd** for $C_{19}H_{11}BrClNO_3$ (415.06): C, 54.77; H, 2.66; N, 3.36 Found: C, 54.86; H, 2.70; N, 3.43.

***^{1}H NMR (600 MHz, $CDCl_3$)**:2-nitro-3-(p-tolyl)-1H-benzo[f]chromene (**17a**)*



***^{13}C NMR (150MHz, $CDCl_3$)**:2-nitro-3-(p-tolyl)-1H-benzo[f]chromene (**17a**)*

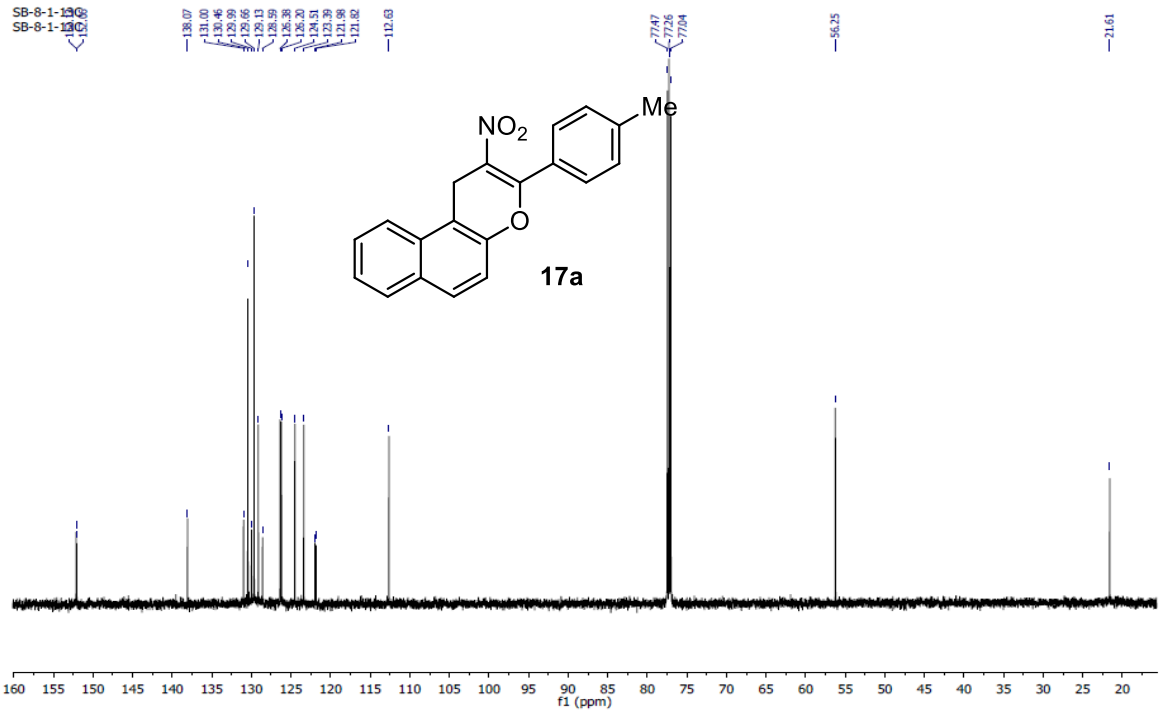
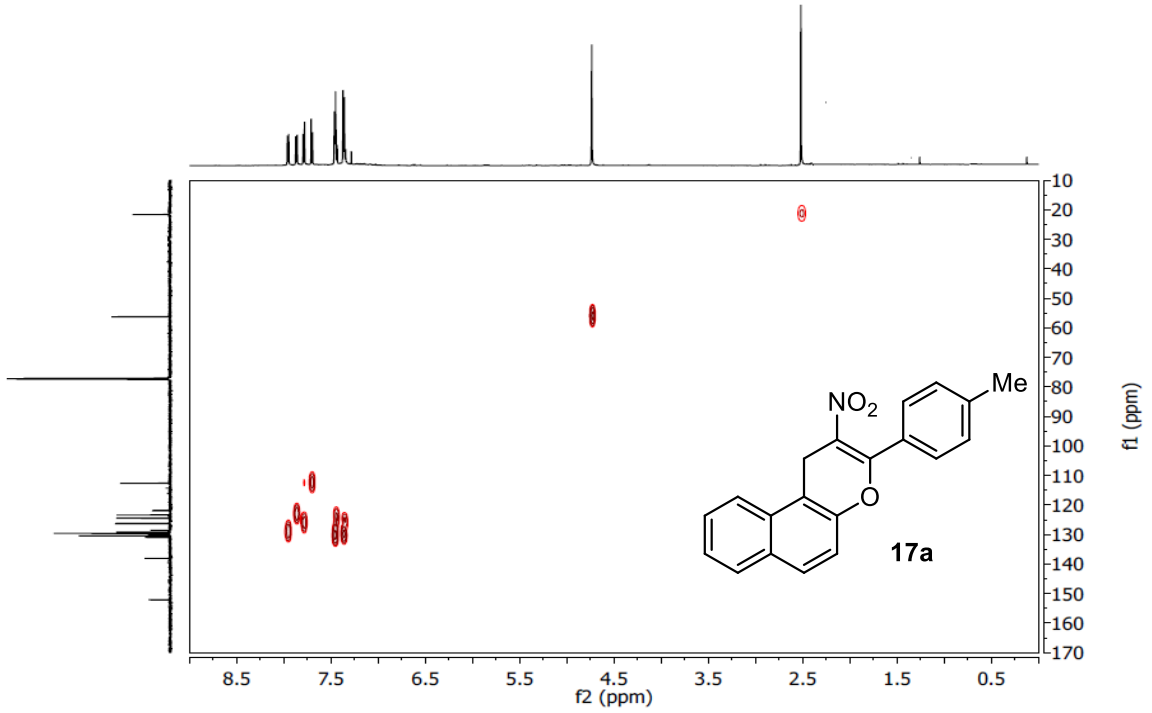


Figure 26

***HSQC (600 MHz, $CDCl_3$)**:2-nitro-3-(p-tolyl)-1H-benzo[f]chromene (**17a**)*



***HMBC (600 MHz, $CDCl_3$)**:2-nitro-3-(p-tolyl)-1H-benzo[f]chromene (**17a**)*

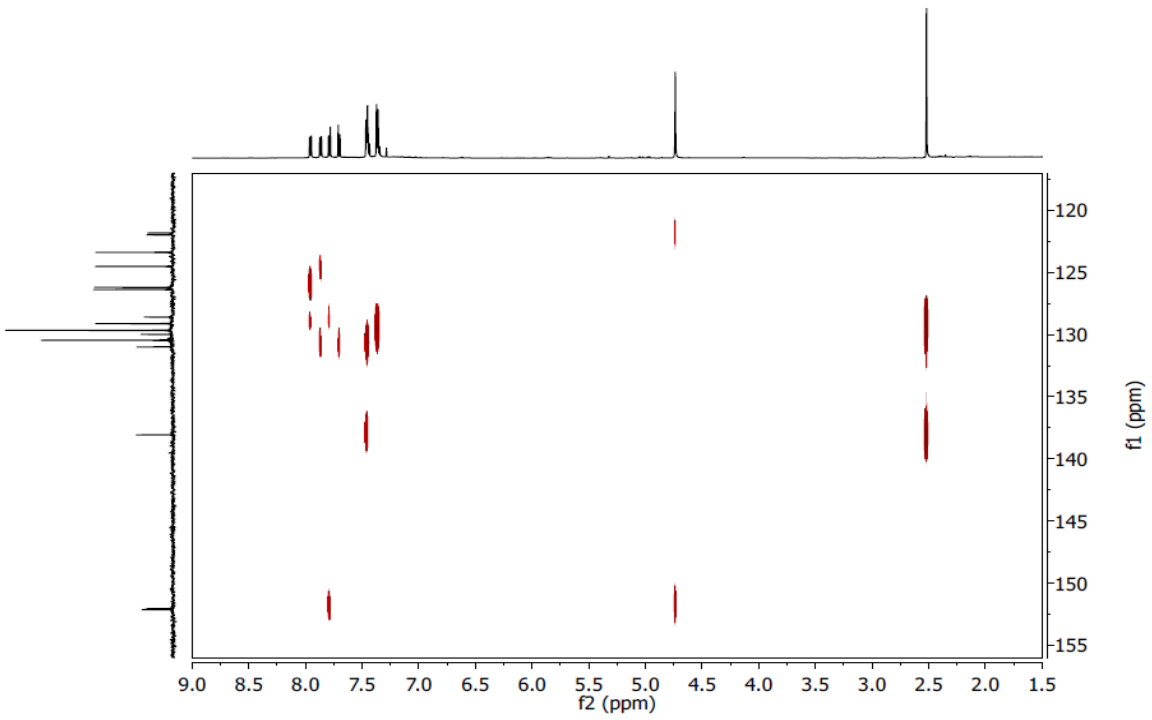
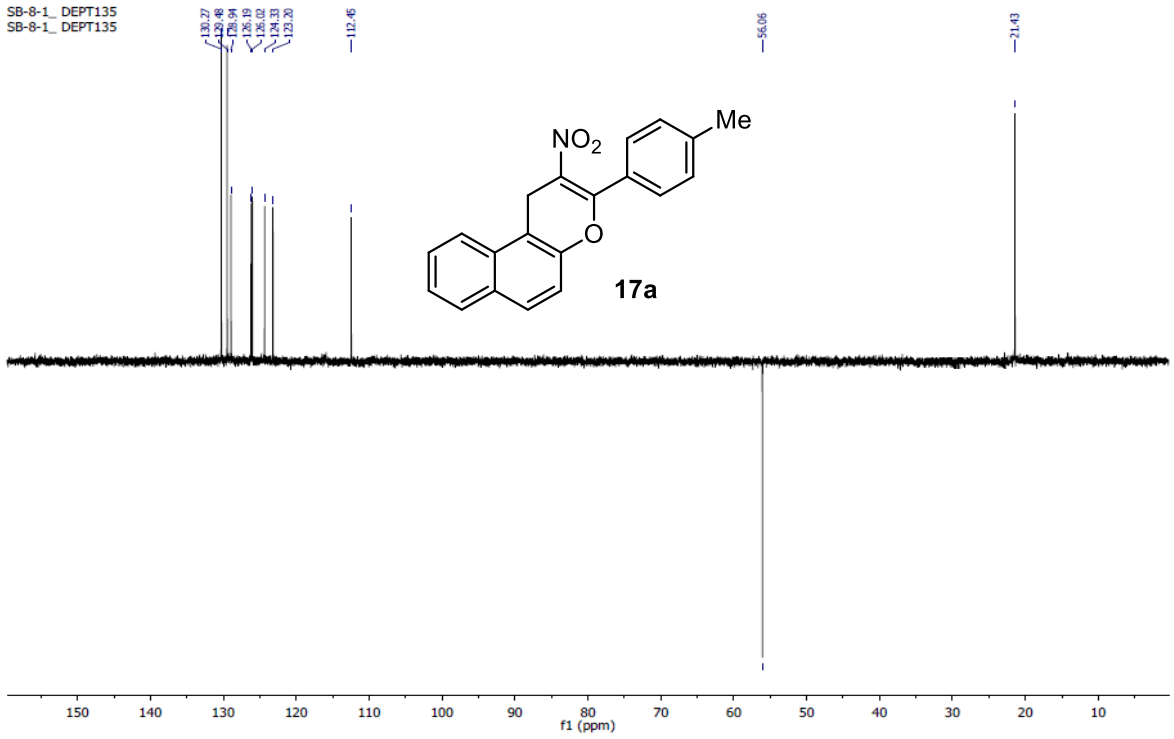


Figure 27

***DEPT 135 (600 MHz, $CDCl_3$)**:2-nitro-3-(p-tolyl)-1H-benzo[f]chromene (**17a**)*



***MS (ESI):** 2-nitro-3-(p-tolyl)-1H-benzo[f]chromene (**17a**)*

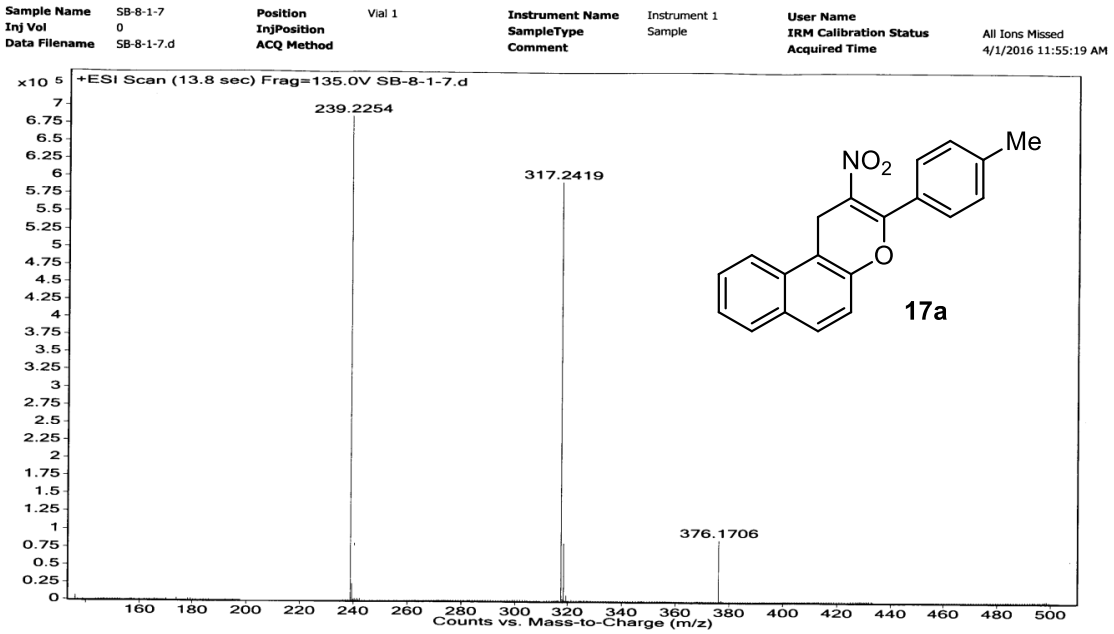
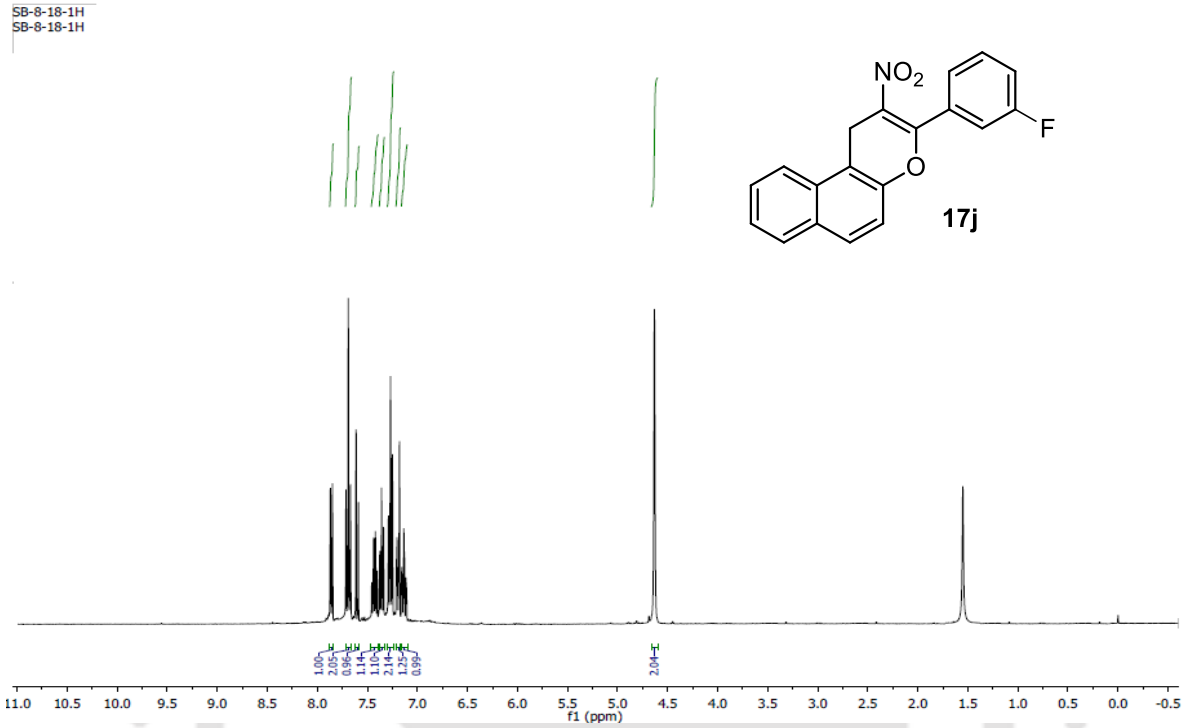


Figure 28

***[1]H NMR (400 MHz, CDCl3)**:3-(3-fluorophenyl)-2-nitro-1H-benzo[f]chromene (**17j**)*



***[13]C NMR (100MHz, CDCl3)**:3-(3-fluorophenyl)-2-nitro-1H-benzo[f]chromene (**17j**)*

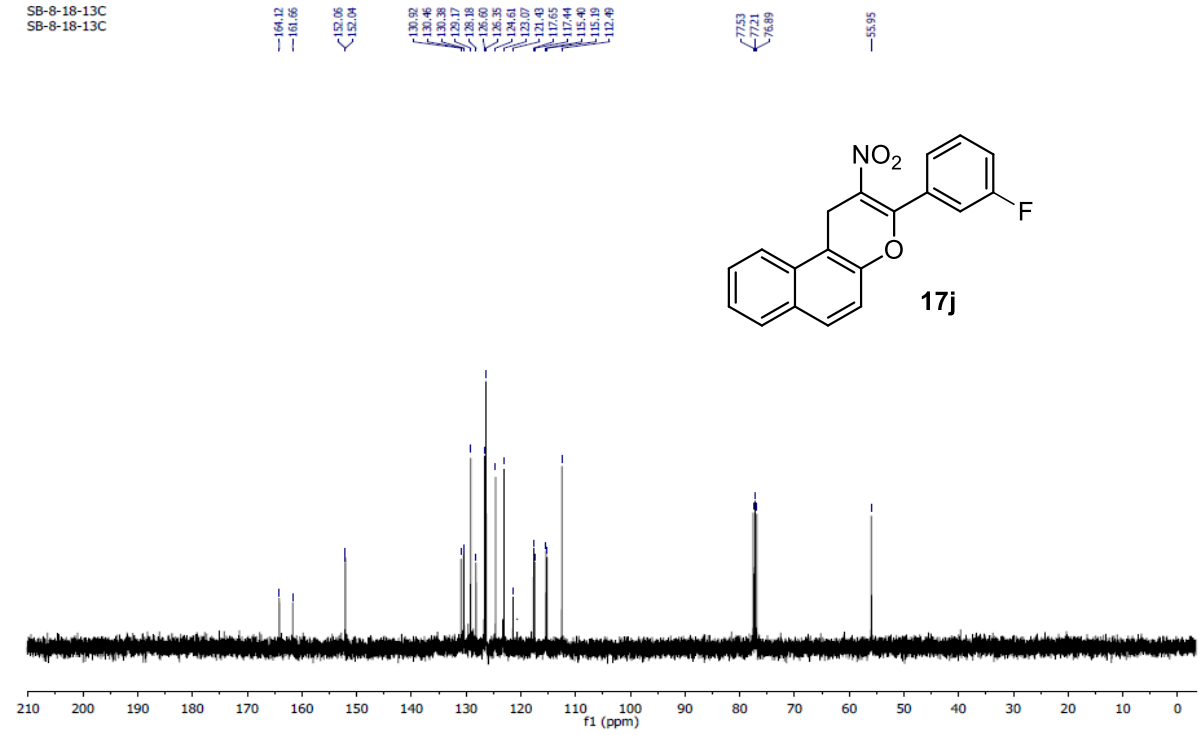
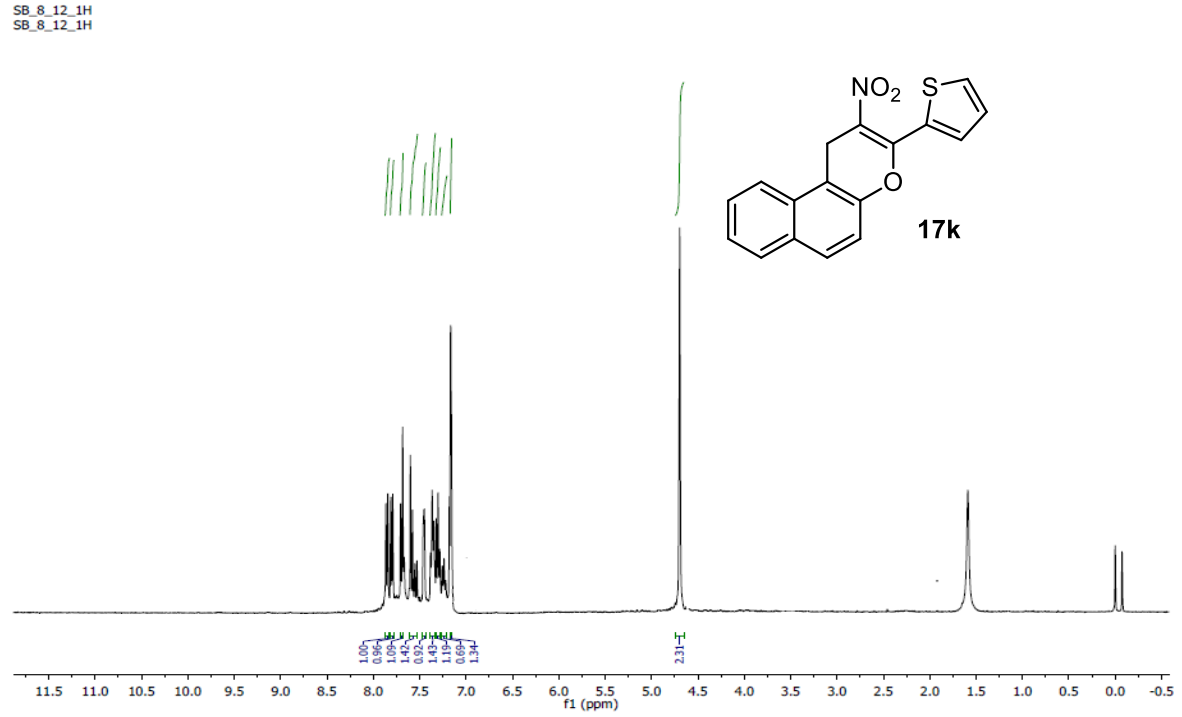


Figure 29

^{1}H NMR (400 MHz, $CDCl_3$): *2-nitro-3-(thiophen-2-yl)-1H-benzo[f]chromene(**17k**)*



^{13}C NMR (100MHz, $CDCl_3$): *2-nitro-3-(thiophen-2-yl)-1H-benzo[f]chromene(**17k**)*

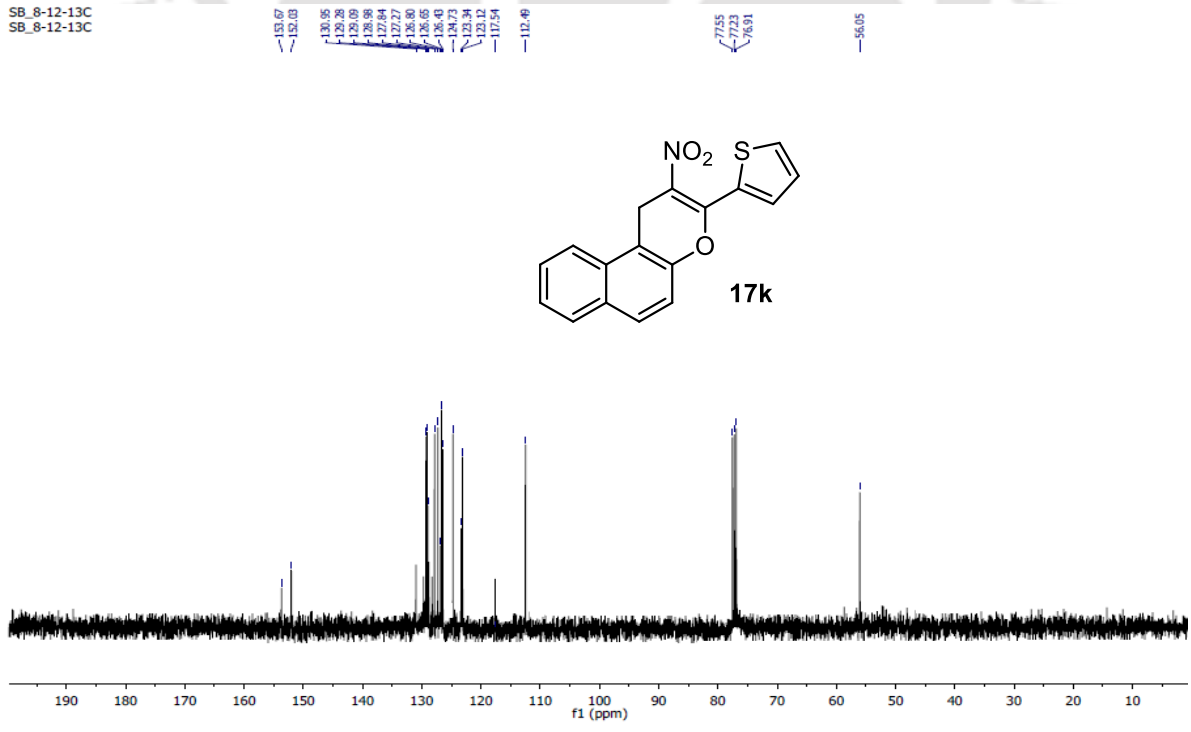
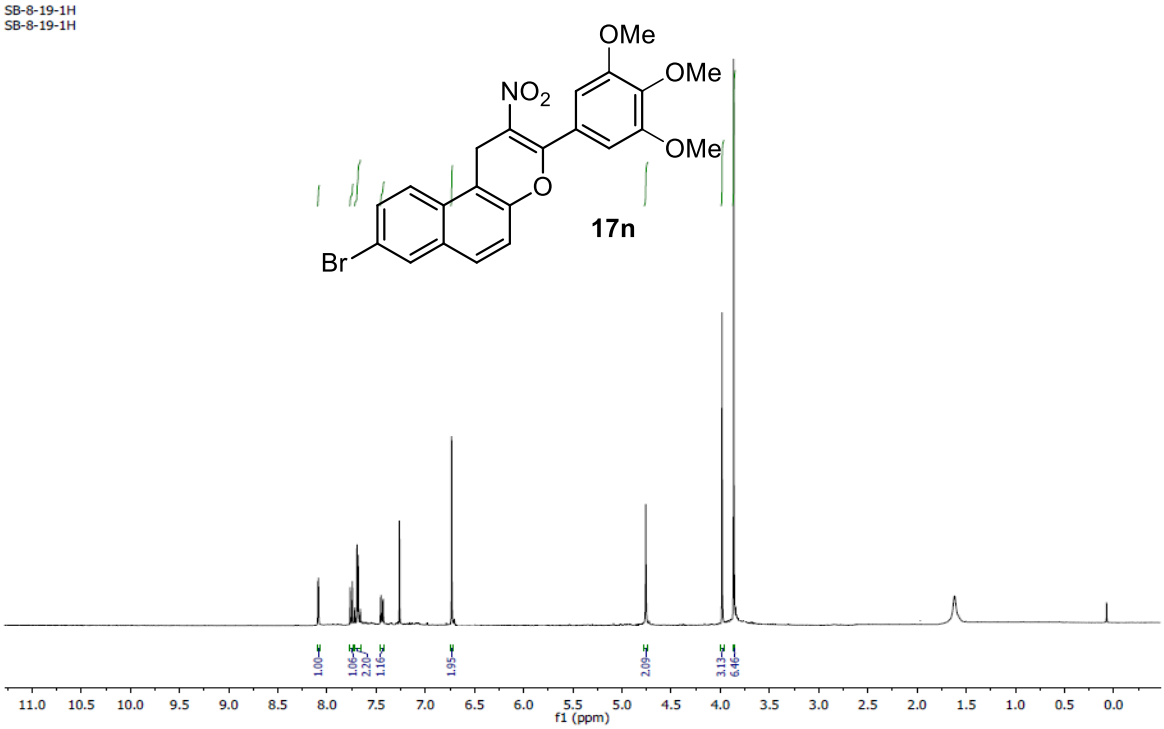


Figure 30

***[1]H NMR (400 MHz, CDCl3)**:8-bromo-2-nitro-3-(3,4,5-trimethoxyphenyl)-1H-benzo[f]chromene (**17n**)*



***[13]C NMR (100MHz, CDCl3)**:8-bromo-2-nitro-3-(3,4,5-trimethoxyphenyl)-1H-benzo[f]chromene (**17n**)*

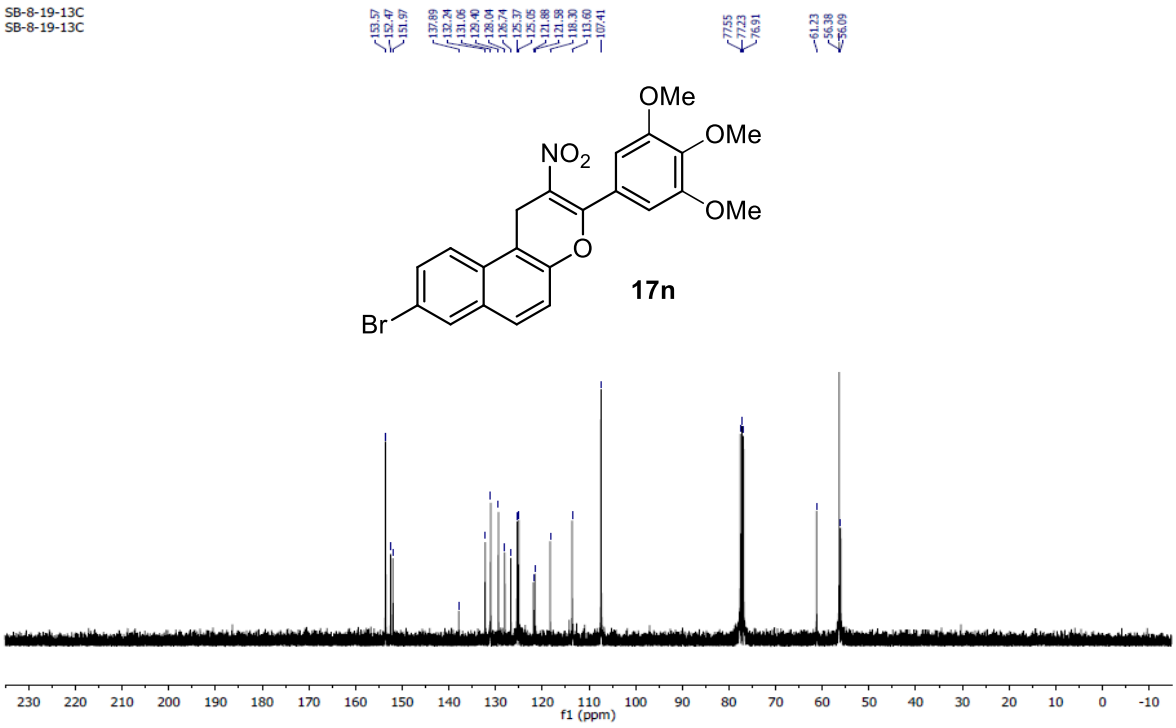


Figure 31

Part B

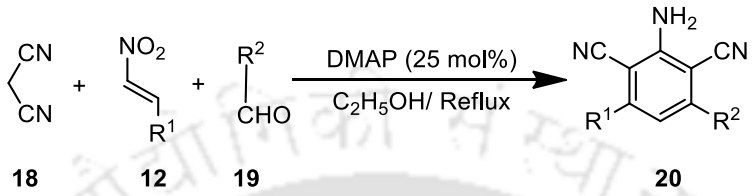
Chapter IV

One-pot three component synthesis of 3,5-disubstituted-2,6-dicyanoaniline derivatives using 4-dimethylaminopyridine (DMAP)as a catalyst

Results & Discussion

Experimental Section

The enormous potentiality and synthetic approaches of the 2,6-dicyanoaniline derivatives are briefly depicted in theChapter I of Part B. In this chapter, a suitable method was explored for the synthesis of 3,5-disubstituted-2,6-dicyanoaniline derivatives by utilizing aldehydes, *β*-nitrostyrene and malononitrile in presence of DMAP, as shown in Scheme 69.



Scheme 69. One-pot synthesis of 3,5-disubstituted-2,6-dicyanoaniline derivatives (**20**)

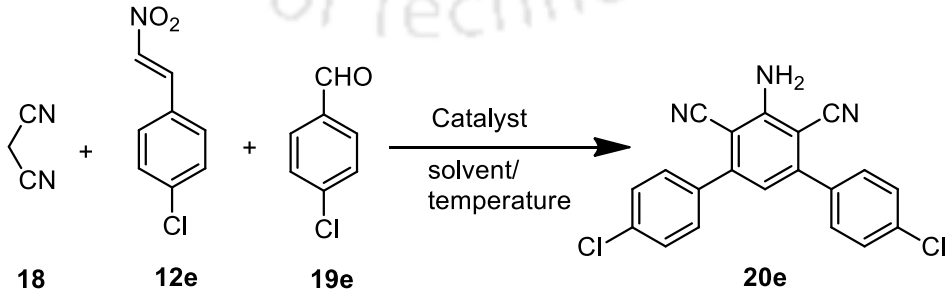
The main considered class of 2,6-dicyanoaniline is 3,5-disubstituted-2,6-dicyanoaniline. Various methods have been reported in the literature for the synthesis of this class of aniline derivatives. The conventional method involves the reaction of either chalcone with malononitrile under different catalytic conditions[61] or one pot, three-component reaction of a variety of aldehydes, ketones with malononitrile.[62] Adib *et al.*[63] synthesized a series of 3-aryl-2,6-dicyano-5-methylanilines at the expense of nitrostyrene and malononitrile. Although a variety of methods were reported for the synthesisof 3,5-disubstituted-2,6-dicyanoaniline derivatives, but these methods suffer from several drawbacks such as using of excess starting material,[61] lower product yields,[61,62] and intolerance of functional group.[61,63] To develop a simple and efficient method for synthesizing 2,6-dicyanoaniline can be considered as convincing research work.

N,*N*-Dimethyl-4-aminopyridine (DMAP) is an inexpensive, nontoxic organo-catalyst employed in various organic transformations. Many have reported it as an effective catalyst for acylation, silylation, and sulfonylation reaction of amino and hydroxyl groups as already described in Chapter II of Part B.[59, 60] Our goal was to develop a newer methodology for the synthesis of 3,5-disubstituted-2,6-dicyanoaniline derivatives via one-pot cascade annulation of nitro-olefin, malononitrile and aldehydes using DMAP as a catalyst under reflux condition (Scheme 69).

To find the optimum reaction condition for the synthesis of 3,5-disubstituted-2,6-dicyanoaniline derivatives, various trial reactions were executed with 4-cholorophenyl nitrostyrene (1 mmol), malononitrile (2 mmol) and 4-chlorobenzaldehyde (1 mmol) (Table 14). Initially, the above reaction was performed with 10 mol % of DMAP in 3 mL of EtOH at reflux

(Table 14, entry 1) and the desired product was obtained in 46% yield and it was characterized by IR and ^{1}H NMR spectra. Similar reactions were carried out using 20 mol %, and 25 mol %, of DMAP (Table 14, entries 2 and 3); the desired product was obtained in 68%, and 72%, yields respectively. By increasing the amount of catalysts further, to 30% the yield of the desired product was not improved significantly (Table 14, entry 4). The reaction conditions were additionally optimized by carrying out the reaction at room temperature, where the rate of the reaction was found effectively poorer, which increases the reaction time to 10 h. (Table 14, entry 5). To observe the efficacy of the catalyst an identical set of a reaction was performed in the presence of other basic catalysts (Table 14, entries 6-7), under the reflux conditions; the desired product was obtained in 12% and 60% yield, respectively. In the absence of a catalyst the reaction proved futile and did not result in any product formation even after 24 h of refluxing (Table 14, entry 8). Carrying out the reactions with various other basic catalysts such as NEt_3, CH_3COONa and $NaHCO_3$ proved fruitless even after a prolonged reaction time (Table 14, entries 9–11). In order to find the efficient solvent system, CH_3CN, DMF and THF were examined (Table 14, entries 12–14). In summary, we can conclude that 25 mol % DMAP in EtOH at reflux was the most appropriate condition for this particular transformation. The product **20e** was exemplified by IR, ^{1}H NMR and ^{13}C NMR spectra. In IR, the compound shows a strong absorptions peak at 3464, 3361 and 2219 cm^{-1} indicates the presence of amine and cyano group respectively. Similarly, in ^{1}H spectra it shows the characteristic signals at 7.49 (brs, 8H), 6.82 (s, 1H), 5.42 (s, 2H) ppm. Equally, in ^{13}C NMR, signals are present at 153.4, 148.3, 135.4, 135.0, 129.3, 128.4, 118.2, 115.3, 94.2ppm which confirmed the formation of product **20e**.

Table 14: Optimization of reaction conditions[a]

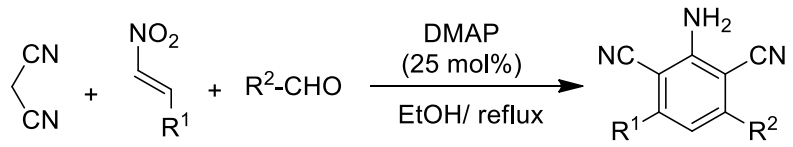


Entry	Catalyst (mol %)	Solvent	Temp	Time (h)	Yield[b]
1	DMAP (10)	EtOH	reflux	3	46
2	DMAP (20)	EtOH	reflux	1.5	68
3	**DMAP (25)**	**EtOH**	**reflux**	**1**	**72**
4	DMAP (30)	EtOH	reflux	1	73
5	DMAP (25)	EtOH	rt	10	65
6	K_2CO_3(25)	EtOH	reflux	8	12
7	Piperidine (25)	EtOH	reflux	8	60
8	None	EtOH	reflux	24	00
9	NEt_3(25)	EtOH	reflux	24	00
10	CH_3COONa (25)	EtOH	reflux	24	00
11	$NaHCO_3$(25)	EtOH	reflux	24	00
12	DMAP (25)	CH_3CN	reflux	1.5	64
13	DMAP (25)	DMF	reflux	1	68
14	DMAP (25)	THF	reflux	5	60

[a]All the reactions were performed with p-chloro benzaldehyde (1mmol), p-chloro phenyl nitrostyrene (1mmol) and malononitrile (2mmol) in the presence of indicated catalyst in 3 mL of indicated solvent at various temperature.[b]Isolated yields.

With the optimal conditions in hand, the versatility of the protocol was investigated for the construction of 3,5-disubstituted-2,6-dicyanoaniline derivatives through all permutations and combinations of the substrates (Table 15, entries 1–16). Initially, from the combination of benzaldehyde (1 mmol), malononitrile (2 mmol) and (E)-(2-nitrovinyl) benzene (1 mmol) under identical reaction condition (Table 15, entry 1), the desired product **20a** was obtained in 71% yield. A wide variety of reactions were examined with aromatic aldehydes (19) and a range of nitrostyrene (12) having both electron-withdrawing as well as electron-donating substituents at different positions on the aromatic rings of **12** and **19**; the required products **20b–20m** were obtained in 62–75% yields (Table 15, entries 2–13). Under the optimized reaction condition, the protocol was studied for aliphatic sets, and the expected products were isolated in 66–62% yield (Table 15, entries 14–16). However, the reaction with hetero aromatic aldehydes like 2-furfural and 2-thiophenecarboxaldehyde were found to be ineffective under the optimized reaction condition (Table 15, entries 17 and 18).

Table 15: Substrate scope and yields of 3,5-disubstituted-2,6-dicyanoaniline derivatives (**20**)[a]



18 **12** **19** **20**

Entry	R^1	R^2	Product (**20**)	Time (h)	% Yield[b]
1	C_6H_5	C_6H_5	**20a**	2.0	71
2	4-Me-C_6H_4	4-Me-C_6H_4	**20b**	2.5	70
3	4-OMe-C_6H_4	4-OMe-C_6H_4	**20c**	3.0	70
4	3-OMe-4-OMe-5-OMe-C_6H_2	3-OMe-4-OMe-5-OMe-C_6H_2	**20d**	4.0	68
5	4-Cl-C_6H_4	4-Cl-C_6H_4	**20e**	1.0	72
6	4-Br-C_6H_4	4-Br-C_6H_4	**20f**	1.5	72
7	4-F-C_6H_4	4-F-C_6H_4	**20g**	1.5	70
8	2- Cl-C_6H_4	2- Cl-C_6H_4	**20h**	3.0	68
9	4-Me-C_6H_4	4-OMe-C_6H_4	**20i**	5.0	67
10	4-Cl-C_6H_4	4-OMe-C_6H_4	**20j**	4.0	75
11	4-OMe-C_6H_4	*n*-Propyl	**20k**	7.0	68
12	4-Br-C_6H_4	3-F-C_6H_4	**20l**	1.5	74
13	4-OMe-C_6H_4	4-NO_2-C_6H_4	**20m**	6.0	62
14	*n*-Butyl	*n*-Butyl	**20n**	4.0	65
15	*n*-Propyl	*n*-Propyl	**20o**	4.0	66
16	Isobutyl	Isobutyl	**20p**	7.0	62
17	2-Thiophenyl	2-Thiophenyl	-	24.0	N.R
18	2-Furfural	2-Furfural	-	24.0	N.R

All the reactions were performed with aldehyde (1 mmol),nitro-olefins (1 mmol) and malononitrile (2 mmol) in the presence of 25 mol % of catalyst in 3 mL of EtOH at 80°C.[b]Isolated yields.

All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra as well as elemental analysis. The product **20a–20p** exhibits an indicative signal in the range of δ = 5.42-4.94 due to the proton of the amino group, depending upon the nature of the substituent present in 3,5-position of 2,6-dicyanoaniline. In FTIR spectrum, owing to the presence of two cyano groups

in product **20**, it showed characteristic absorption over the range of 2254-2211 cm^{-1}. The structure of one of the representative compoundssuch as **20b** was unequivocally confirmed by X-ray diffraction analysis (Fig. 32).The ^{1}H NMR and ^{13}C NMR spectra of the products **20d, 20k, 20l, 20m** and **20o** are shown in Figure 34-38 respectively in the experimental section.

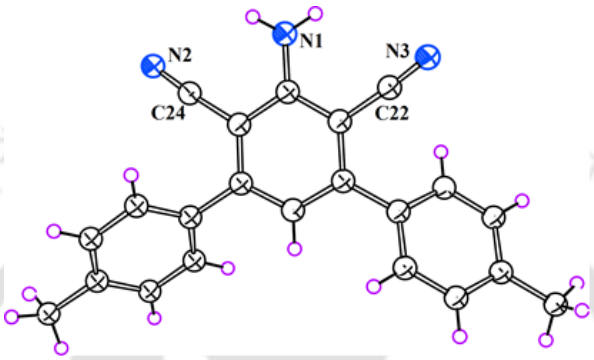
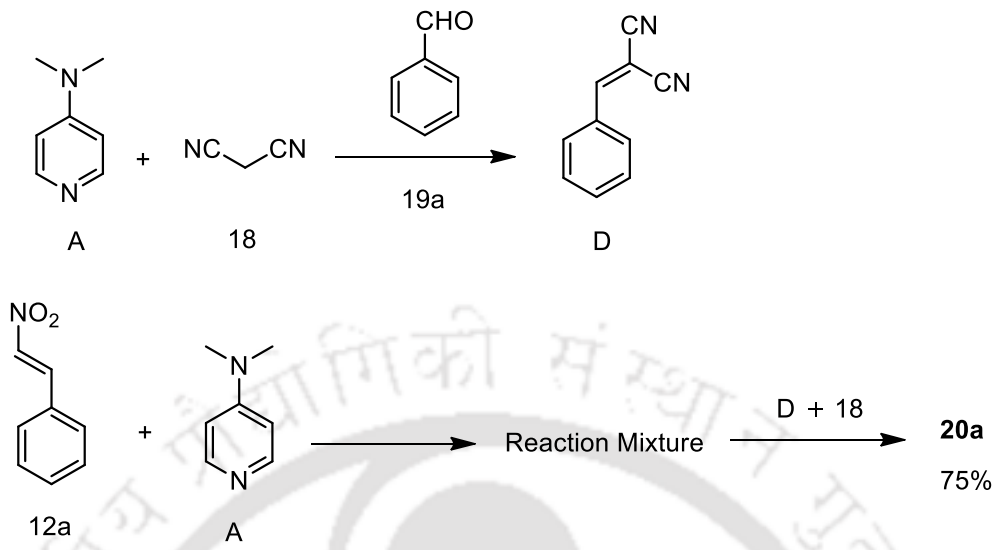


Fig 32. Ortep diagram of compound **20b** (with 50% thermal ellipsoids) (CCDC no.1007419).

Keeping in mind, that the world's greatest problem is environment pollution, analysis of E-factor is required for the synthesis of organic molecules. Perfect E factor value is zero.[64] E-factor of all the products was calculated and found in the range of 0.77–1.38.

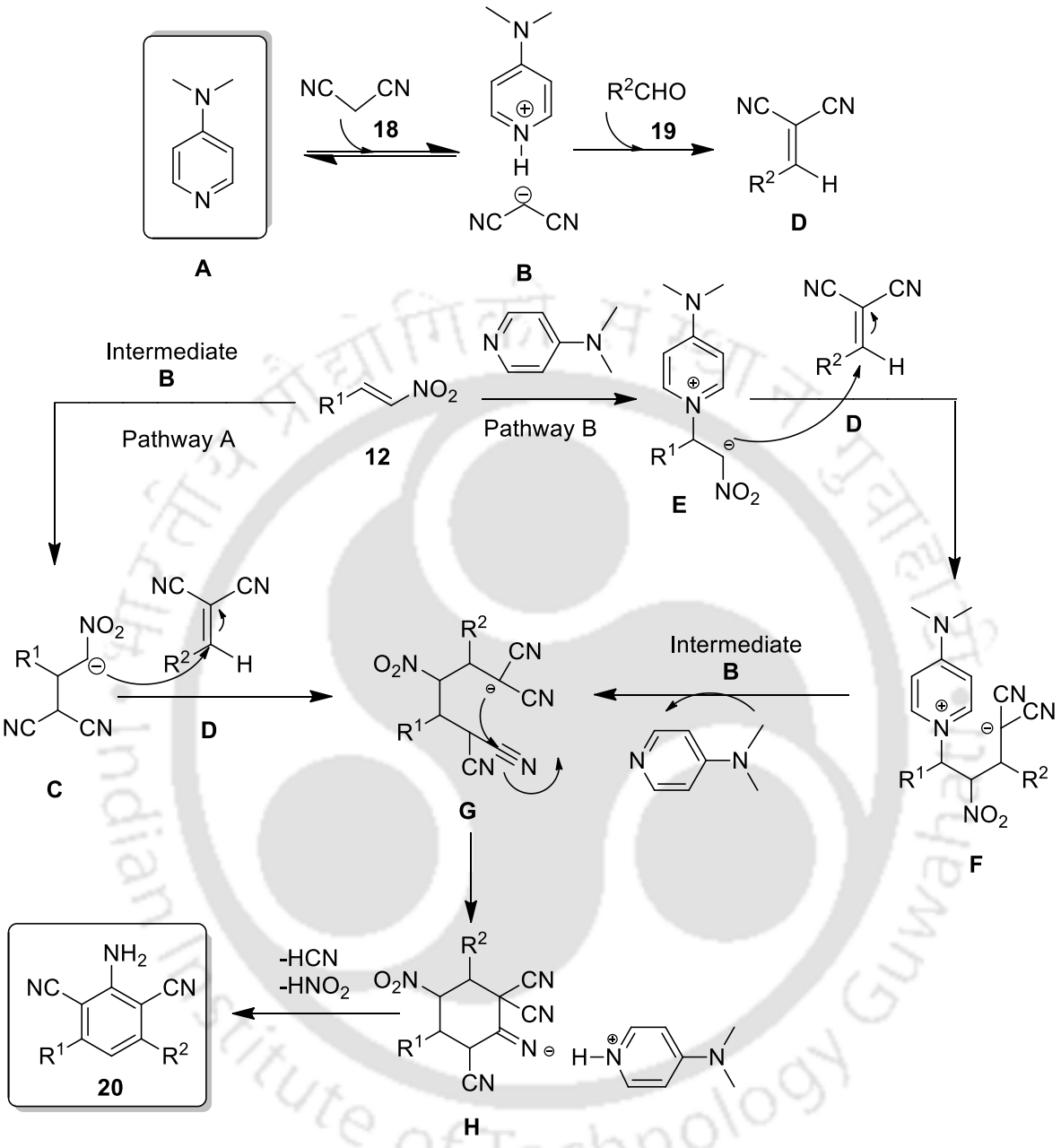
To study the mechanism of the reactions keenly, the reactions were performed in a step-wise manner. At first, 1 mmol of malononitrile was taken in 3 ml of ethanol and DMAP (15 mg, 12.5 mol%) was added to it. After 25 min of reflux, the color changed into reddish brown, and then 1 mmol of benzaldehyde was added and the intermediate product **D** was isolated in 81% yield. Next, the nitro-olefin (1 mmol) was treated with DMAP (15 mg, 12.5 mol %), and after 20 min of reflux, intermediate product **D** and 1 mmol of malononitrile were added, and the product (**20a**) was obtained after 30 min with 75% yield, as shown in Scheme 70.



Scheme 70. Step-wise reaction for mechanistic study

In spite of the pKa values of DMAP and malononitrile, the first step is believed to be the abstraction of acidic proton from the methylene group of malononitrile by the catalyst DMAP (**A**) to form **B**. The formation of **B** is a reversible step. As a result, the initial step is likely to be the rate determining step. Subsequently, **B** undergoes a nucleophilic addition reaction with aldehydes and furnishes ethyledienemalononitrile (intermediate product **D**). Next, there are two possible mechanistic pathways to generate an intermediate **G**. In pathway A, **B** undergoes a nucleophilic addition reaction with nitro-olefin to produce an intermediate **C**, which further undergoes an addition reaction with ethyledienemalononitrile (intermediate **D**) to generate carbanion **G**. In pathway B, the nucleophilic catalyst DMAP undergoes Michael addition reactions with nitro-olefin to produce a zwitterion, nitronate (intermediate **E**). Thereafter, nitronate goes through an addition reaction with ethyledienemalononitrile (intermediate product **D**) to generate carbanion **F**. Carbanion **F** further protonates from the system. Elimination of DMAP from **F** can be done by reacting with another molecule of **B**, and form **G**.

Finally, carbanion **G** undergoes an intramolecular cyclization by attacking one of the nitrile groups of the molecule and constructs **H**, from which the desired product **20** is produced by eliminating HCN and HNO_2 as illustrated in Scheme 71.



Scheme 71. Plausible mechanism for the formation of 3,5-disubstituted-2,6-dicyanoaniline (**20**)

Both pathway A and pathway B can generate intermediate **G**, but, we believe that pathway B is more effective than pathway A. From optimization table, it is noted that, the reaction was found ineffective when explored by the more basic catalyst. So, it is assumed that DMAP is acting as a nucleophile rather than a base in the present reaction condition.

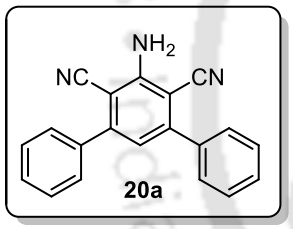
In conclusion, we have successfully designed a new methodology for the construction of densely substituted benzene, from a wide variety of aldehydes, malononitrile and β-nitro-olefins by using a nucleophilic catalyst DMAP. Moderate to good yield, atom economic, cost-effectiveness and short reaction times are the most attractive features of the present protocol.

Experimental

*General procedure for the synthesis of 3,5-disubstituted 2,6-dicyano aniline derivatives (**20**)*:

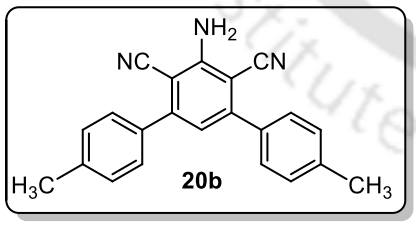
Malononitrile (2 mmol), nitro-olefin (1 mmol), aliphatic or aromatic aldehyde (1 mmol), and DMAP (0.25 mmol, 30 mg) in EtOH (3 mL) was taken in a 25 mL round bottom flask and the reaction mixture was refluxed for 1-7 h depending upon the completion of the reaction. The progress of the reaction was monitored by examining TLC time to time. After the completion of the reaction, EtOH was removed in a rotatory evaporator and the crude reaction mixture was extracted with ethyl acetate (2 ×10 mL).The organic layer was washed with water and finally it was dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo and crude residue was purified through a column chromatography using ethyl acetate/hexane in (1:9) ratio as eluent to obtain the pure product**20**.

*5'-amino-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile (**20a**)***:***



Light yellow solid, E-factor: 0.99; mp 220-222°C; **IR** (KBr): 3450, 3372, 2923, 2214, 1559, 1382, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ =7.54-7.49 (m, 4H), 7.45-7.41 (m, 6H), 6.83 (s, 1H), 5.33 (s, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$):δ = 153.4, 150.3, 137.6, 129.9, 129.8, 129.1, 120.3, 116.2, 95.1; **Anal.Calcd** for $C_{20}H_{13}N_3$ (295.34): C, 81.34; H, 4.44; N, 14.23 Found: C, 81.21; H, 4.35; N, 14.10.

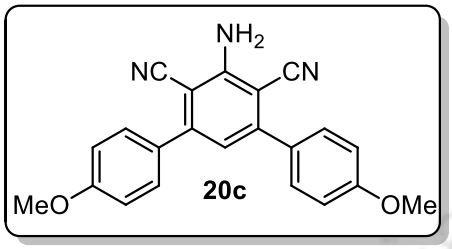
*5'-amino-4,4''-dimethyl-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile **(20b)** :*



Light yellow solid, E-factor: 0.96; mp 224-225°C; **IR** (KBr): 3478, 3364, 2953, 2922, 2215, 1637, 1579, 1547, 1285, 808 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$ and d_6 DMSO): δ =7.48 (d, *J* = 6.0 Hz, 4H), 7.31 (d, *J* = 6.0 Hz, 4H), 6.87 (s, 1H), 5.36 (s, 2H), 2.43 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$):δ = 152.5, 148.0, 137.5, 133.0, 127.6, 126.7, 116.7, 114.5, 92.1, 19.3; **Anal. Calcd** for $C_{22}H_{17}N_3$ (323.39): C, 81.71; H, 5.30; N, 12.99 Found: C, 81.58; H, 5.22; N, 12.87.

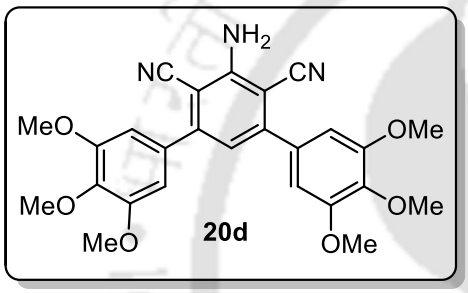
5'-amino-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile ***(20c)*** **:**

Light yellow solid, E-factor: 0.92; mp 142-144°C;**IR** (KBr):3431, 3361, 2924, 2853, 2254, 1642, 1554, 1049, 1025, 1002, 825 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.8 Hz, 4H), 6.99 (d, *J* = 8.8 Hz, 4H), 6.68 (s, 1H), 5.22 (s, 2H), 3.86 (s, 6H); **^{13}C NMR** (100 MHz, DMSO):δ =160.3, 154.3, 149.4, 130.0, 129.1, 118.3, 116.4, 114.2, 93.2, 55.3; **Anal. Calcd** for $C_{22}H_{17}N_3O_2$ (355.39): C, 74.35; H, 4.82; N, 11.82 Found: C, 74.22; H, 4.76; N, 11.71.



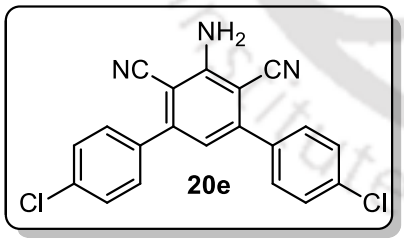
*5'-amino-3,3'',4,4'',5,5''-hexamethoxy-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile****(20d)*** **:**

Light yellow solid, E-factor: 0.84; mp 178-180°C; **IR** (KBr): 3389, 2995, 2934, 2211, 1619, 1509, 1470, 1382, 1186, 1128, 989 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.89 (s, 1H), 6.78 (s, 4H), 5.42 (s, 2H), 3.91 (s, 18H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 153.6, 153.5, 150.1, 139.6, 132.8, 119.6, 116.2, 106.1, 94.8, 61.2, 56.5; **Anal. Calcd** for $C_{26}H_{25}N_3O_6$ (475.49): C, 65.67; H, 5.30; N, 8.84 Found C, 65.52; H, 5.22; N, 8.73.

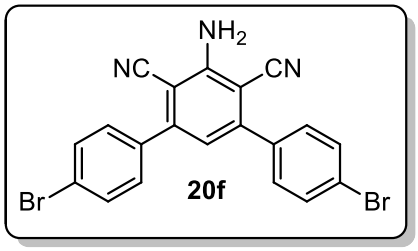


*5'-amino-4,4''-dichloro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile****(20e)*** **:**

Light green solid, E-factor: 0.85; mp 268-270°C; **IR** (KBr): 3464, 3361, 2962, 2922, 2219, 1645, 1496, 1261, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ =7.49 (brs, 8H), 6.82 (s, 1H), 5.42 (s, 2H);**^{13}C NMR** (100 MHz, $CDCl_3$ and d_6 DMSO): δ =153.4, 148.3, 135.4, 135.0, 129.3, 128.4, 118.2, 115.3, 94.2; **Anal. Calcd** for $C_{20}H_{11}Cl_2N_3$ (364.23): C, 65.95, H, 3.04; N, 11.54 Found: C, 65.83; H, 3.00; N, 11.45.

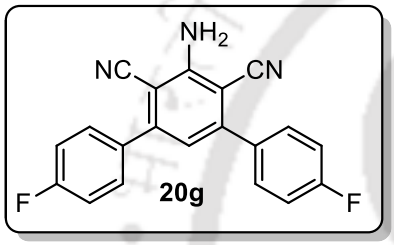


5'-amino-4,4''-dibromo-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile ***(20f)*** **:**



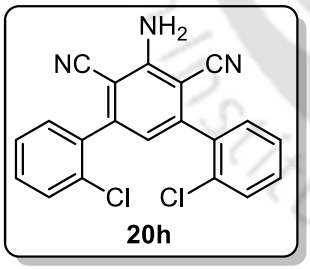
Light green solid, E-factor: 0.75; mp 169-171°C; **IR** (KBr): 3433, 3361, 2922, 2853, 2217, 1643, 1561, 1491, 1286, 1073 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ =7.58 (d, *J* = 8.4 Hz, 4H), 7.38 (d, *J* = 8.4 Hz, 4H), 6.75 (s, 1H), 5.36 (s, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$ and d_6 DMSO): δ = 153.3, 147.9, 135.5, 130.9, 129.2, 122.8, 117.6, 114.8, 93.7; **Anal. Calcd** for $C_{20}H_{11}Br_2N_3$ (453.13): C, 53.01; H, 2.45; N, 9.27 Found: C, 52.89; H, 2.40; N, 9.17.

5'-amino-4,4''-difluoro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile ***(20g)*** **:**



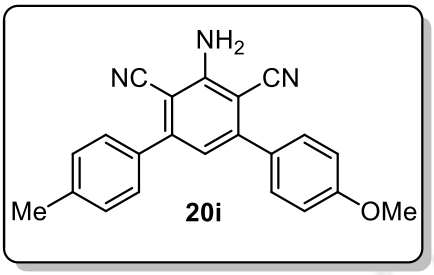
Light yellow solid, E-factor: 0.96; mp 146-147°C; **IR** (KBr): 3477, 3360, 2924, 2853, 2216, 1649, 1557, 1511, 1231, 1158, 893 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ =7.59-7.53 (m, 4H), 7.19 (t, *J* = 8.4 Hz, 4H), 6.82 (s, 1H), 5.41 (s, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 163.8 ($^{1}J_{C\text{-}F}$ =255 Hz), 153.4, 149.3, 133.5, 130.6, 130.5, 120.0, 116.4, 116.3, 115.9, 95.2; **Anal. Calcd** for $C_{20}H_{11}F_2N_3$ (331.32): C, 72.50; H, 3.35; N, 12.68 Found: C, 72.35; H, 3.30; N, 12.57.

5'-amino-2,2''-dichloro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile ***(20h)*** **:**



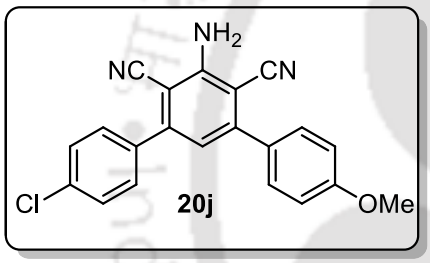
Yellow liquid, E-factor: 0.96; **IR** (KBr):3462, 3371, 2924, 2853, 2221, 1633, 1555, 1383, 1282, 1058, 743 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 7.2 Hz, 2H), 7.39 (brs, 6H), 6.80 (s, 1H), 5.38 (s, 2H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ = 152.2, 147.6, 136.3, 130.9, 130.7, 130.5, 130.4, 127.3, 121.9, 115.1, 97.6; **Anal. Calcd** for $C_{20}H_{11}Cl_2N_3$ (364.23): C, 65.95; H, 3.04; N, 11.54 Found: C, 65.82; H, 3.00; N, 11.46.

*5'-amino-4-methoxy-4''-methyl-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile**(20i)*** **:**



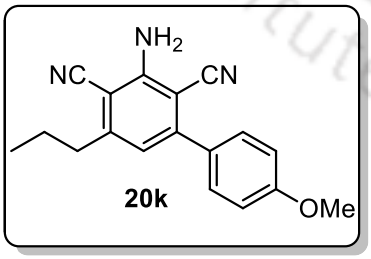
Orange solid, E-factor: 1.03; mp 195-196°C; **IR** (KBr): 3478, 3364, 2922, 2215, 1637,1579, 1434, 1177, 808 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.31-7.27 (m, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.83 (s, 1H), 5.33 (s, 2H), 3.85 (s, 3H), 2.40 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =161.0, 153.5, 150.2, 149.9, 134.8, 131.2, 130.0, 129.9, 129.7, 128.5, 119.9, 116.6, 116.5, 114.5, 94.4, 94.3, 55.6, 21.5; **Anal. Calcd** for $C_{22}H_{17}N_3O$ (339.39): C, 77.86; H, 5.05; N, 12.38 Found: C, 77.71; H, 5.00; N, 12.26.

*5'-amino-4-chloro-4''-methoxy-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile**(20j)***:



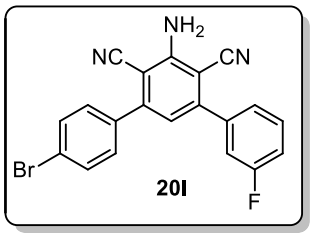
Orange solid, E-factor: 0.78; mp 185-186°C; **IR** (KBr): 3464, 3366, 2925, 2216, 1642, 1609, 1515, 1259, 1179, 1093, 1030, 820, 739 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ = 7.55-7.46 (m, 6H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.82 (s, 1H), 5.37 (s, 2H), 3.86 (s, 3H); **^{13}C NMR (**100 MHz, $CDCl_3$):δ = 161.2, 153.5, 150.2, 148.8, 136.2, 136.1, 130.1, 129.9, 129.7, 129.4, 119.9, 116.3, 116.1, 114.6, 95.1, 94.3, 55.7; **Anal. Calcd** for $C_{21}H_{14}ClN_3O$ (359.81): C, 70.10; H, 3.92; N, 11.68 Found: C, 69.92; H, 3.85; N, 11.55.

*3-amino-4'-methoxy-5-propyl-[1,1'-biphenyl]-2,4-dicarbonitrile **(20k)***:



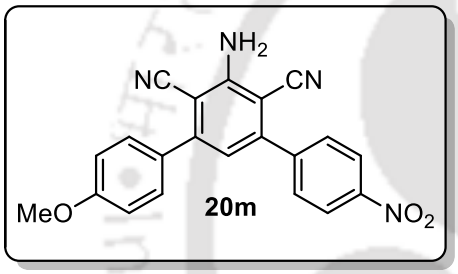
Light green solid, E-factor: 1.09; mp 128-130°C; **IR** (KBr): 3357, 3243, 2957, 2928, 2225, 1636, 1607, 1513, 1251, 1174, 1034, 830 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ = 7.47 (s, 1H), 7.16 (d, *J* = 9.2 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 5.05 (s, 2H), 3.07 (s, 3H), 2.32 (t, *J* = 8.0 Hz, 2H), 1.41-1.32 (m, 2H), 0.76 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.9, 150.4, 137.0, 129.8, 128.9, 116.2, 115.6, 114.6, 114.1, 99.3, 96.0, 55.3, 33.9, 23.9, 13.6; **Anal. Calcd** for $C_{18}H_{17}N_3O$ (291.14): C, 74.20; H, 5.88; N, 14.42 Found: C, 74.11; H, 5.82; N, 14.36.

5'-amino-4''-bromo-3-fluoro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile ***(20l)*****:**



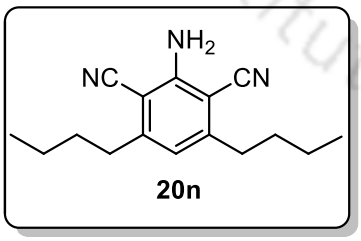
Light yellow semi solid, E-factor: 0.77; **IR** (KBr):3435, 3363, 2256, 2129, 1639, 1605, 1026, 827 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.8 Hz, 2H), 7.75 (s, 1H), 7.65-7.59 (m, 3H), 7.45 (d, *J* = 7.8Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 6.83 (s, 1H), 5.42 (s, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$):δ = 162.9 ($^1J_{C-F}$ = 240 Hz), 153.4, 149.2, 149.0, 139.3, 136.2, 132.4, 130.9, 130.8, 130.1, 124.4, 119.7, 117.1, 116.9, 115.8, 115.7, 115.6, 95.5; **Anal. Calcd** for $C_{20}H_{11}BrFN_3$ (391.01): C, 61.24; H, 2.83; N, 10.71 Found: C, 61.15; H, 2.75; N, 10.62.

5'-amino-4-methoxy-4''-nitro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile ***(20m)*****:**



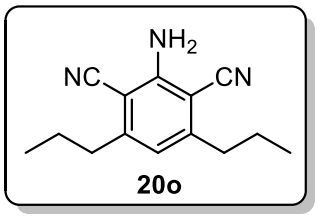
Light orange solid, E-factor: 1.15; mp 105-107°C; **IR** (KBr): 3408, 3352, 2343, 2212, 1603, 1384, 788 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.88 (s, 1H), 5.46 (s, 2H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$ and d_6 DMSO): δ = 160.7, 153.7, 150.1, 147.9, 147.0, 143.7, 131.2, 129.6, 129.4, 123.8, 123.7, 118.7, 114.1, 95.4, 93.5, 55.2; **Anal. Calcd** for $C_{21}H_{14}N_4O_3$ (370.10): C, 68.10; H, 3.81; N, 15.13 Found: C, 68.01; H, 3.76, N, 15.05.

*2-amino-4,6-dibutylisophthalonitrile****(20n)*****:**



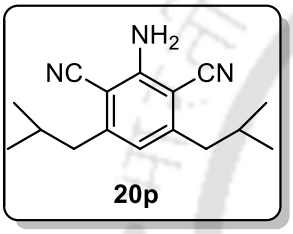
Light green solid, E-factor: 1.28; mp 121-123°C; **IR** (KBr): 3413, 3353, 2957, 2927, 2873, 2222, 1658, 1480, 1301, 1274, 735 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ = 7.35 (s, 1H), 4.95 (s, 2H), 2.77 (t, *J* = 7.2 Hz, 3H), 2.47 (t, *J* = 8.4 Hz, 3H), 1.47 (t, *J* = 7.2 Hz, 4H), 0.97 (d, *J* = 6.8 Hz, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 151.4, 137.2, 130.9, 116.5, 115.9, 95.1, 33.6, 32.9, 32.4, 24.3, 23.1, 14.1, 13.9; **Anal. Calcd** for $C_{16}H_{21}N_3$ (255.17): C, 75.26; H, 8.29; N, 16.43 Found: C, 75.15: H, 8.21; N, 16.35.

*2-amino-4,6-dipropylisophthalonitrile**(20o)*:



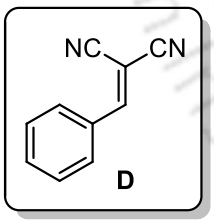
Light green liquid, E-factor: 0.91; **IR** (KBr): 3466, 3367, 2961, 2926, 2220, 1635, 1475, 1378, 1290, 1261, 799 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.35 (s, 1H), 4.94 (s, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.55-2.50 (m, 2H), 1.15 (t, *J* = 7.6 Hz, 5H), 1.02 (t, *J* = 7.6 Hz, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 150.8, 136.2, 132.1, 116.2, 115.6, 94.9, 31.9, 31.4, 24.3, 23.8, 15.0, 14.2; **Anal. Calcd** for $C_{14}H_{17}N_3$ (277.14): C, 73.98; H, 7.54; N, 18.49 Found: C, 73.91; H, 7.49; N, 18.41.

*2-amino-4,6-diisobutylisophthalonitrile**(20p)*:



Light green semi solid, E-factor: 1.38; **IR** (KBr): 3462, 3364, 2962, 2871, 2220, 1635, 1476, 1295,1227, 910 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.39 (s, 1H), 4.95 (brs, 2H), 3.01-2.96 (m, 1H), 2.66 (d, *J* = 7.6 Hz, 2H), 1.88-1.79 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 6H). 0.90 (d, *J* = 6.4 Hz, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =149.9, 148.8, 137.5, 116.5, 116.3, 98.9, 95.4, 40.6, 30.5, 28.2, 23.9, 22.4; **Anal. Calcd** for $C_{16}H_{21}N_3$ (255.36): C, 75.26; H, 8.29; N, 16.46 Found, C, 75.18; H, 8.25; N, 16.40.

*2-benzylidenemalononitrile **(Intermediate D)***:

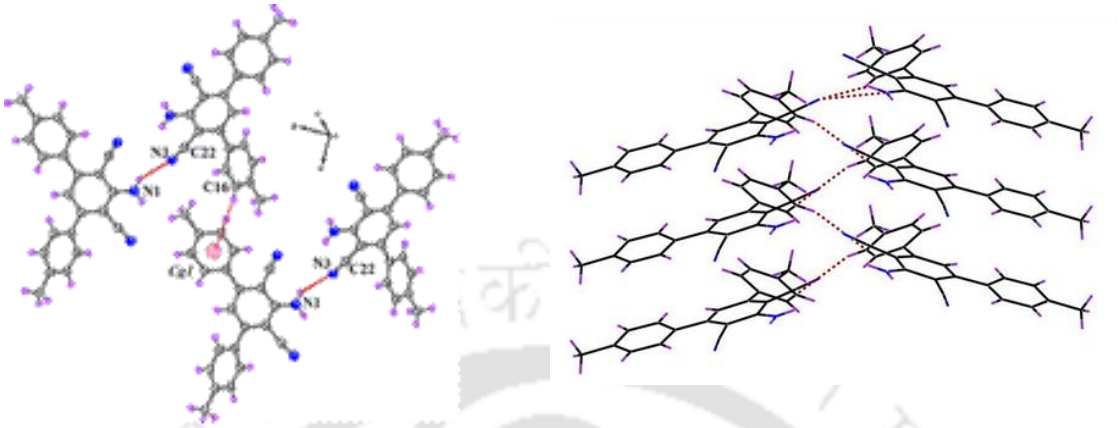


Light yellow solid, mp 84-86°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.22 (s, 1H), 7.10 (d, *J* = 5.6 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.86(d, *J* = 8.0 Hz, 2H), 6.57(d, *J* = 8.0 Hz, 1H); **Anal. Calcd** for $C_{10}H_6N_2$ (154.16): C, 77.91; H, 3.92; N, 18.17 Found: C, 77.85; H, 3.89; N, 18.12.

Complete crystallographic data of **20b** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication with CCDC no. 1007419. 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 16. Crystal data and structure refinement for **20b**. For atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Identification code	Sb-2-2	Z	2
Empirical formula	$C_{22}H_{17}N_3$	Density (calculated)	1.278 g/cm^3
Formula weight	323.39	Absorption coefficient	0.077 mm^{-1}
Temperature	0 K	F(000)	340
Wavelength	0.71073Å	Theta range for data collection	3.16 to 25.25 º
Crystal system	monoclinic	Index ranges	-14<=h<= 14, -4<=k<=4, -12<=l<=21
Space group	P 21	Reflections collected	3128
Unit cell dimensions		Independent reflections	2534 R_{int} = 0.0179
a	11.7462(8) Å	Completeness to θº	99% (θ = 25.25 º)
b	3.9913(3) Å	Refinement method	Full-matrix least-squares on F2
c	18.3202(8) Å	Data / restraints / parameters	2534/ 1 / 228
α	90.00º	Goodness-of-fit on F2	1.068
β	101.982(5)	Final R indices [>2sigma(I)]	R_{obs} = 0.0479, wR_{obs} = 0. 1187
γ	90.00º	R indices (all data)	R_{all} = 0.0661, wR_{all} = 0.1282
Volume	840.18(9) Å^3	Largest diff. peak and hole	0.157 and -0.176e.Å^{-3}

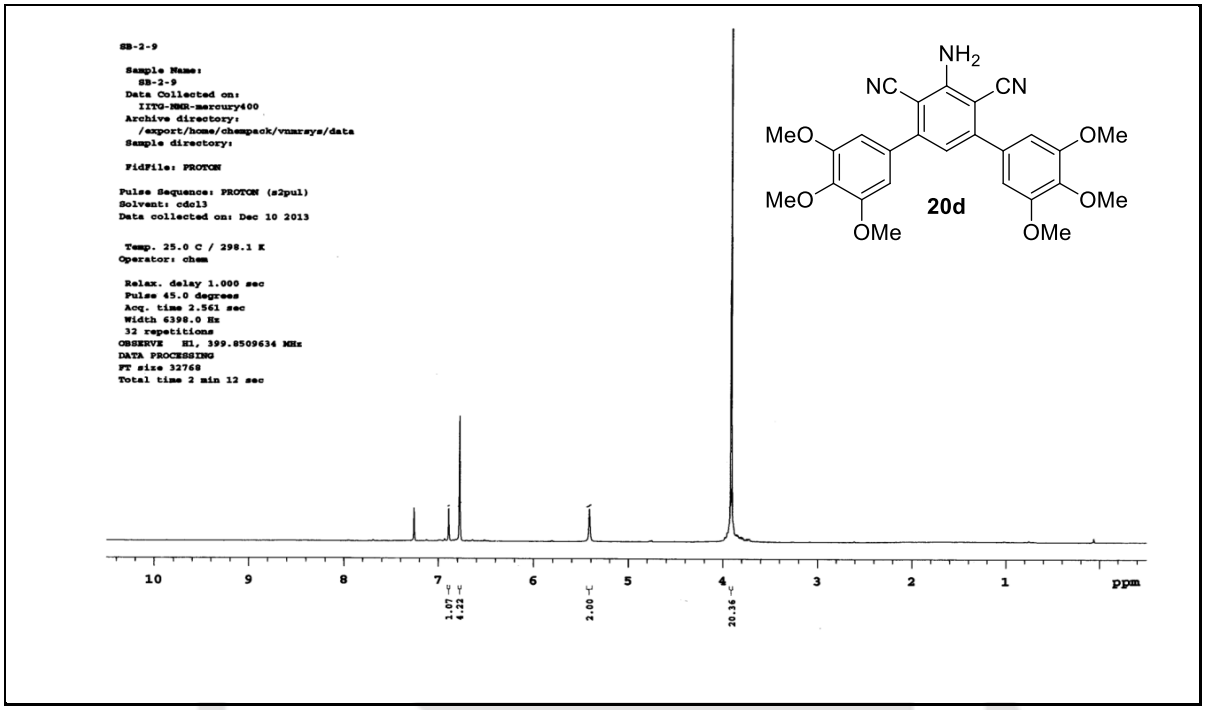


(a) **(b)**

Figure 33: (a) Different non-bonding interactions present in compound **20b** such as N-H…N and C-H…π interactions. (b) Packing diagram of **20b** along z-crystallographic axis which shows zig-zag arrangements of molecules.

Compound **20b** crystallizes in monoclinic P 21 space group. It's asymmetric unit contains one molecule of **20b (**Z'=1). It contains an intermolecular N-H…N interaction with a bond distance of 3.082 Å. Moreover, it shows a weak C-H…π interaction (dC16−H•••π = 4.589 Å, π = centroid of the phenyl ring).

*^{1}H NMR (400 MHz, $CDCl_3$):5'-amino-3,3'',4,4'',5,5''-hexamethoxy-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile**(20d)**:*



*^{13}C NMR (150 MHz, $CDCl_3$):5'-amino-3,3'',4,4'',5,5''-hexamethoxy-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile**(20d)**:*

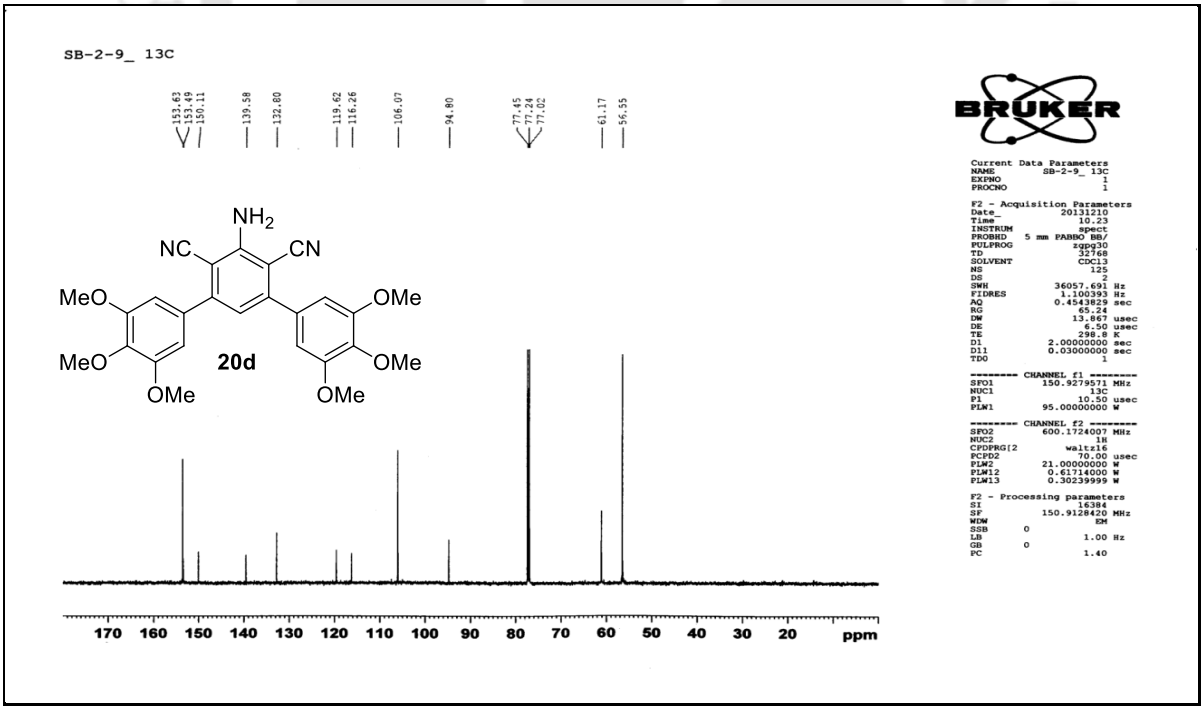
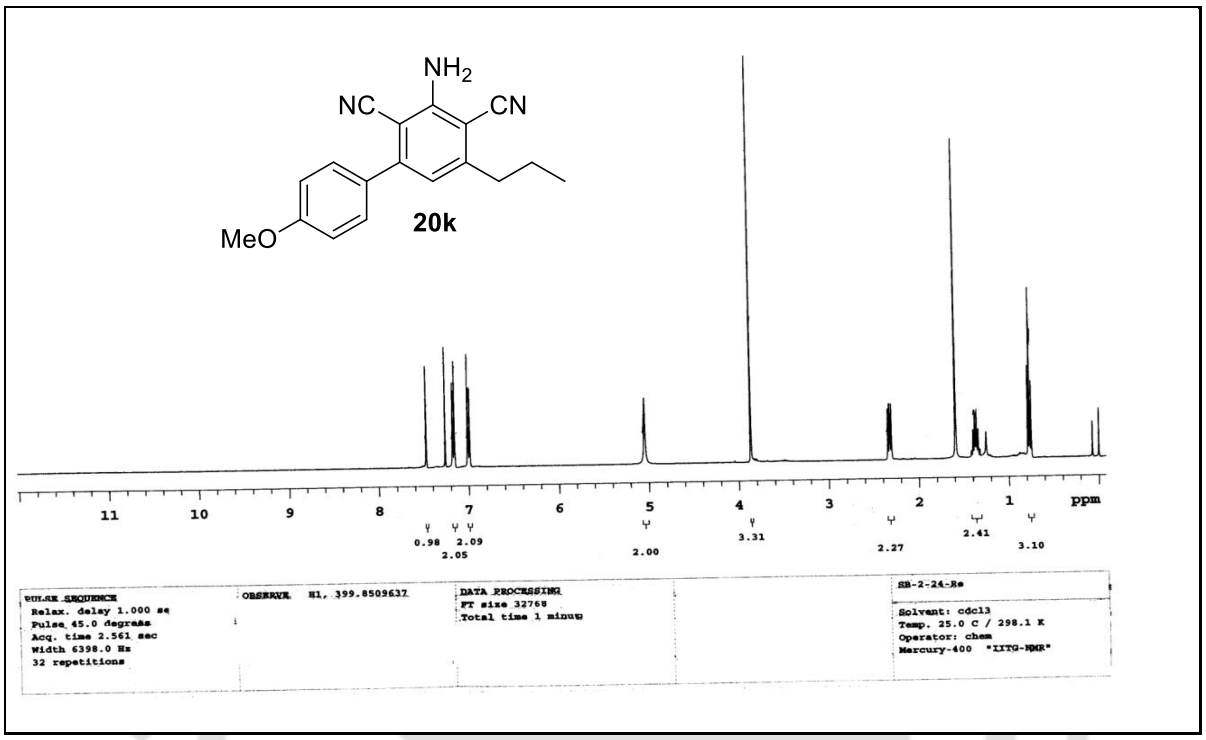


Figure 34

***^{1}H NMR (400 MHz, $CDCl_3$)**:3-amino-4'-methoxy-5-propyl-[1,1'-biphenyl]-2,4-dicarbonitrile **(20k)**:*



***^{13}C NMR (100 MHz, $CDCl_3$)**:3-amino-4'-methoxy-5-propyl-[1,1'-biphenyl]-2,4-dicarbonitrile **(20k)**:*

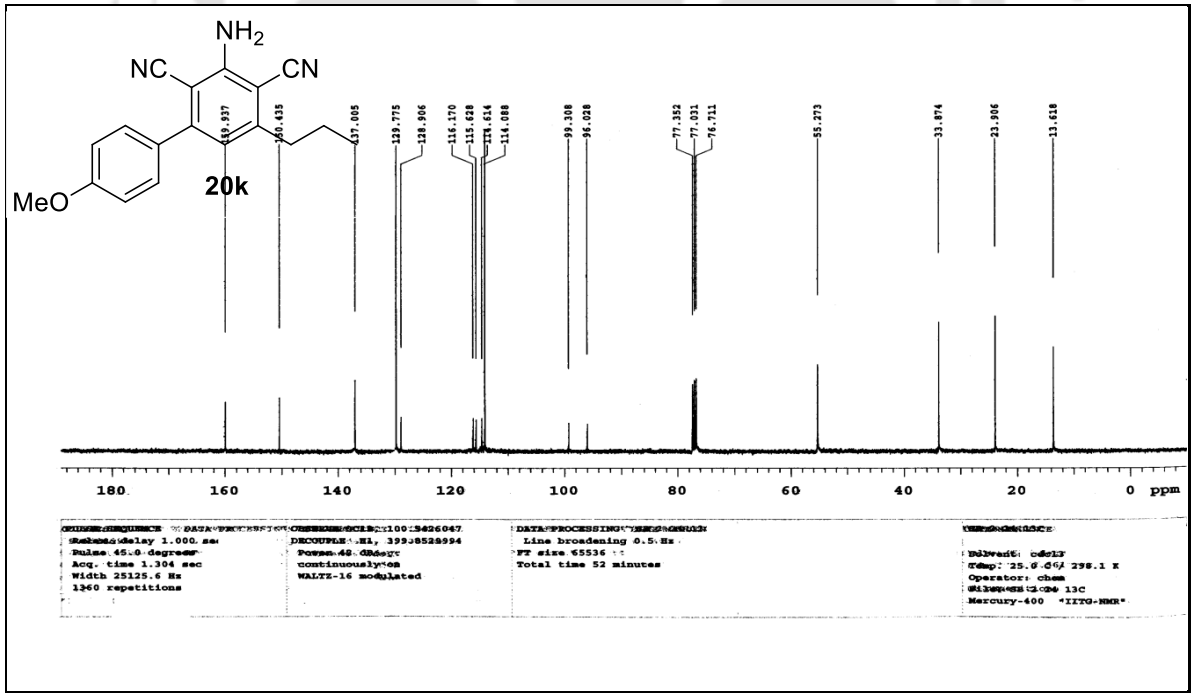
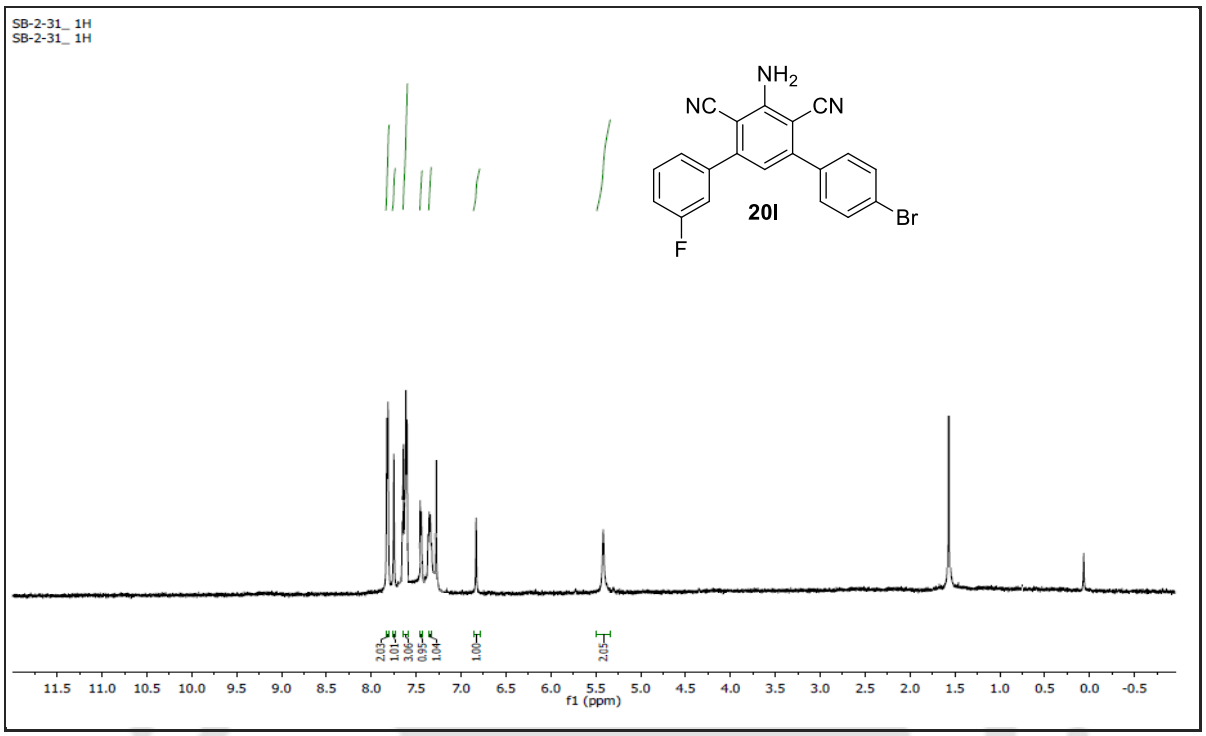


Figure 35

***^{1}H NMR (400 MHz, $CDCl_3$)**:5'-amino-4''-bromo-3-fluoro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile **(20l)**:*



***^{13}C NMR (150 MHz, $CDCl_3$)**:5'-amino-4''-bromo-3-fluoro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile **(20l)**:*

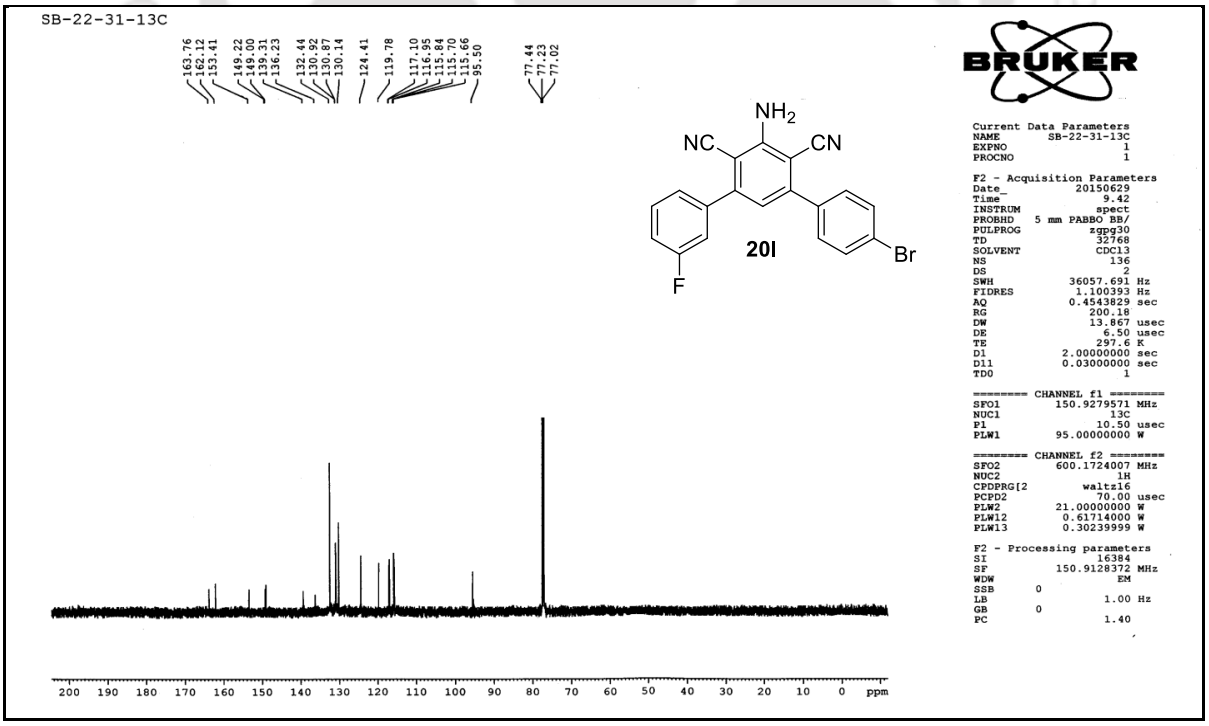
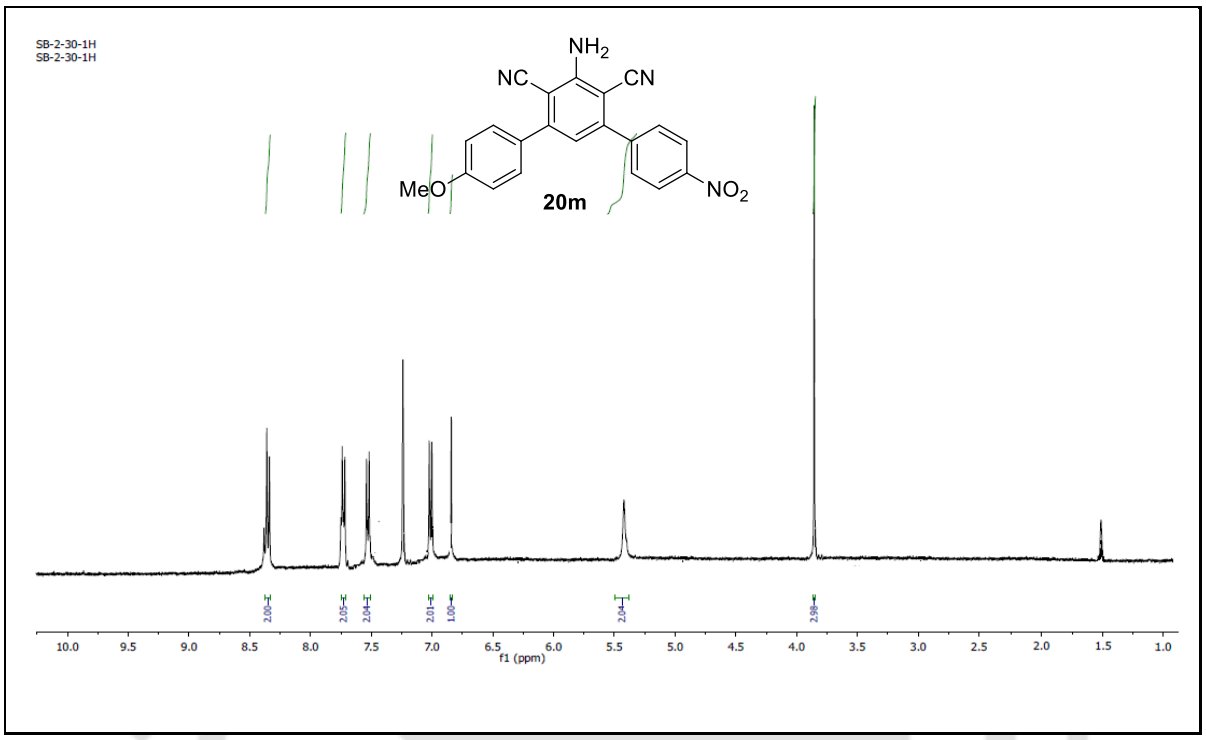


Figure 36

***^{1}H NMR (400 MHz, $CDCl_3$)**:5'-amino-4-methoxy-4''-nitro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile **(20m)**:*



***^{13}C NMR (100 MHz, $CDCl_3$)**: 5'-amino-4-methoxy-4''-nitro-[1,1':3',1''-terphenyl]-4',6'-dicarbonitrile **(20m)**:*

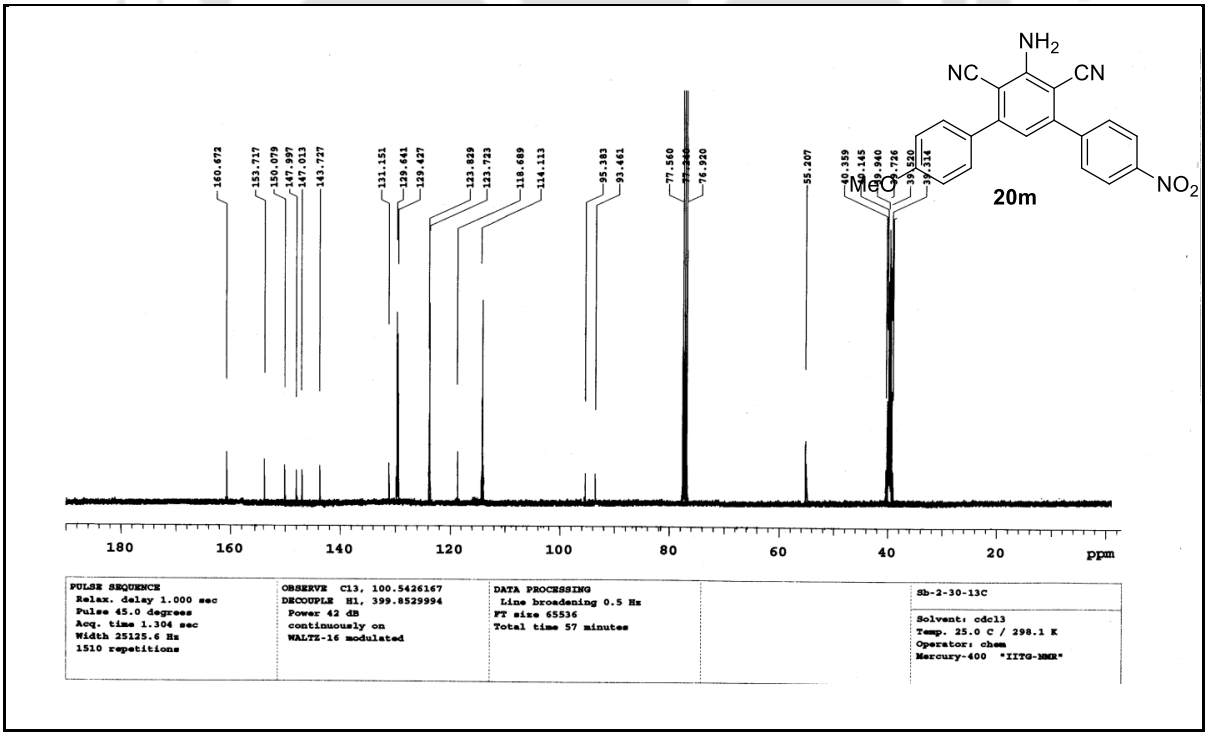
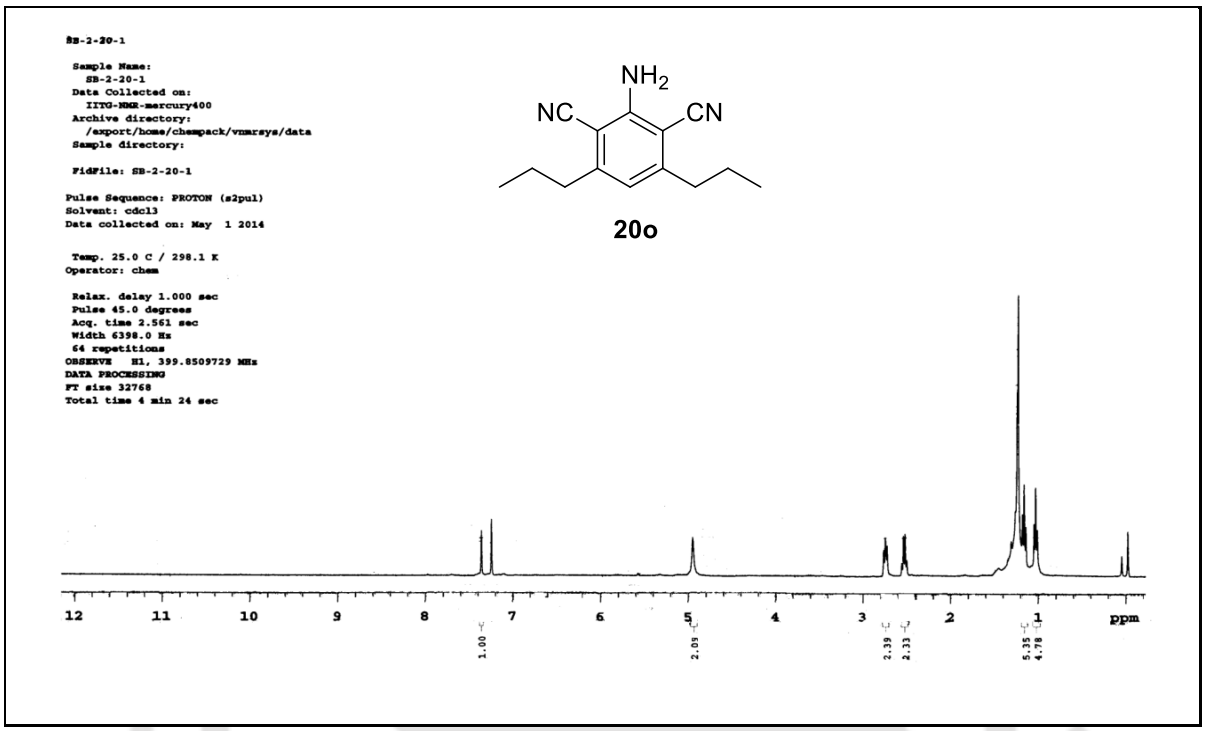


Figure 37

^{1}H NMR (400 MHz, $CDCl_3$)**:2-amino-4,6-dipropylisophthalonitrile**(20o):



^{13}C NMR (100 MHz, $CDCl_3$)**:2-amino-4,6-dipropylisophthalonitrile**(20o):

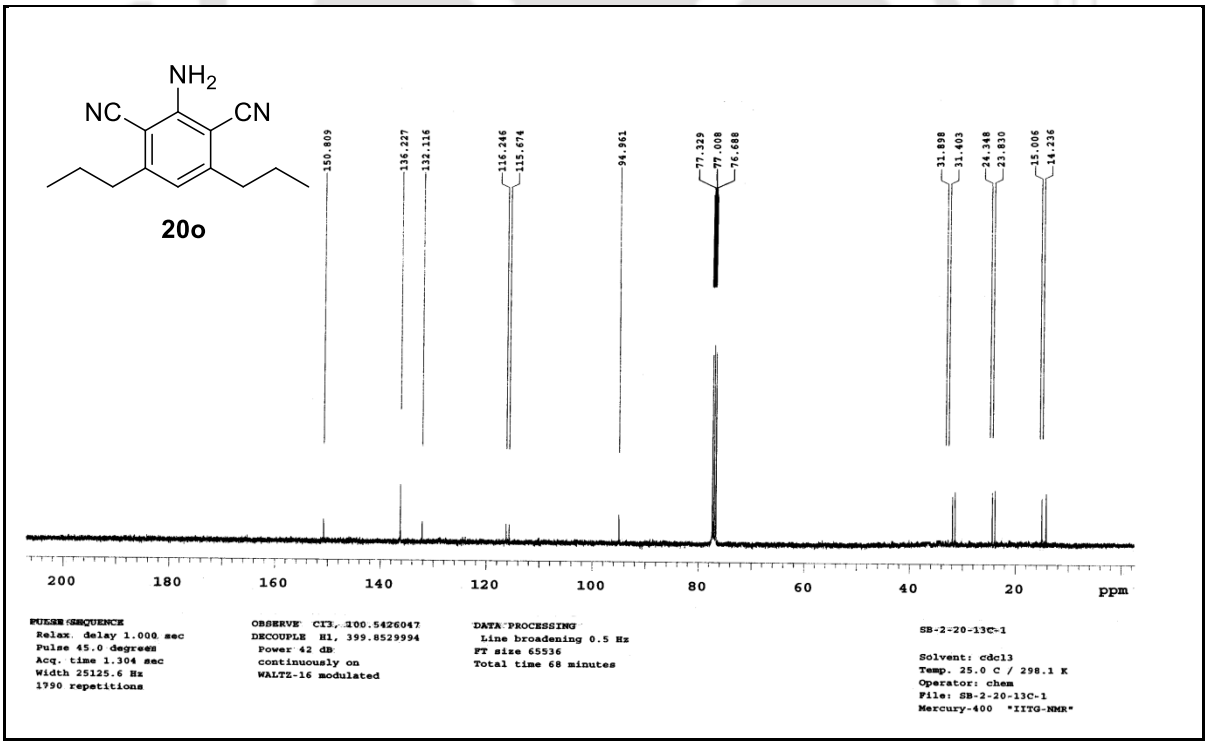
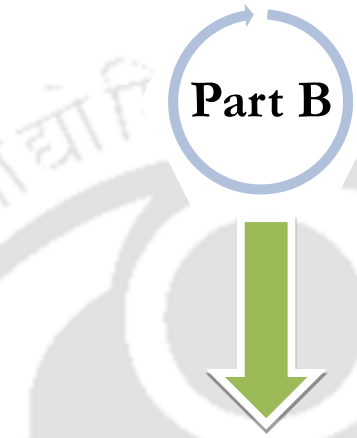


Figure 38



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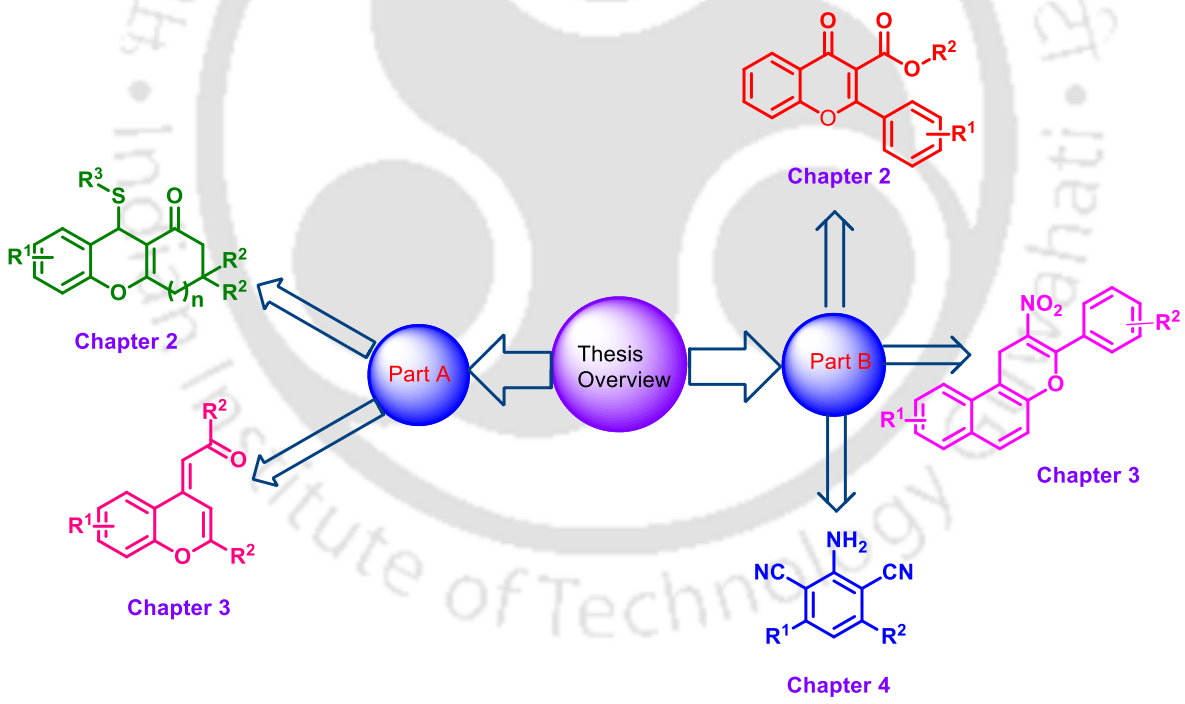
Conclusion

We have accomplished the synthesis of oxygen containing heterocycles, mainly chromene and flavone derivatives, which were fruitfully synthesized by using Multicomponent Reactions. It is evident from the literature that chromene and flavone derivatives are highly biologically active, and used in medicinal chemistry. So, we believe that, our efficient synthetic methodologies will be extremely useful in future for the entrée of some new compounds and can be further studied for biological activities. In addition, we have developed an upgraded synthetic protocol for the synthesis of 3,5-disubstituted-2,6-dicyanoaniline, which is enormously used in industries for numerous purpose. As, the product comprises different functional group that is acceptor-donor-acceptor group, it can be further transformed to a scaffold with different functional group and the moiety can be used for multipurpose. The summarized result of the thesis is schematically shown below.



In future, we suppose that these oxygen based organic molecules could be exploited for synthesis of precious natural products in modern organic synthesis. Besides, we believe that, all the synthesized organic molecules prepared by these methods are useful classes of compounds which could be further studied for their potent biological activities in collaboration with other research groupsin future. We are not able to complete all the above studies due to time constraints.

LIST OF PUBLICATIONS AND COMMUNICATIONS

1. ***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*. **2014**, 73.

2. ***Bromodimethylsulfonium bromide: An Efficient Catalyst for One-pot Synthesis of 4-Phenacylidene Flavene derivatives***
   Suchandra Bhattacharjee, Deb K. Das and Abu T. Khan; *Tetrahedron Letters*. **2015**, *56*, 2412.

3. ***Synthesis of 3-substituted carboxylate/carboxamide flavone derivatives from 4-hydroxycoumarin, β-nitrostyrene and alcohol/ amine using multicomponent reaction***
   Suchandra Bhattacharjee and Abu T. Khan; *Tetrahedron Letters*. **2016**, *57*, 1831.

4. ***One-pot three component synthesis of 3,5-disubstituted-2,6-dicyanoaniline derivatives using 4-Dimethylaminopyridine as a catalyst.***
   Suchandra Bhattacharjee and Abu.T. Khan; *Tetrahedron Letters*. **2016**, *57*, 2994.

5. **Triethylamine catalyzed one-pot synthesis of Benzo[*f*]chromene derivatives via Diels-Alder Reaction**
   Suchandra Bhattacharjee and Abu.T. Khan (communicated)