Regioselective Bromination of Substituted 2'-Hydroxy Chalcones and Synthesis of Fused Nitrogen Heterocycles

A Dissertation Submitted to the
Indian Institute of Technology Guwahati
As Partial Fulfillment for the Degree of

DOCTOR OF PHILOSOPHY

by

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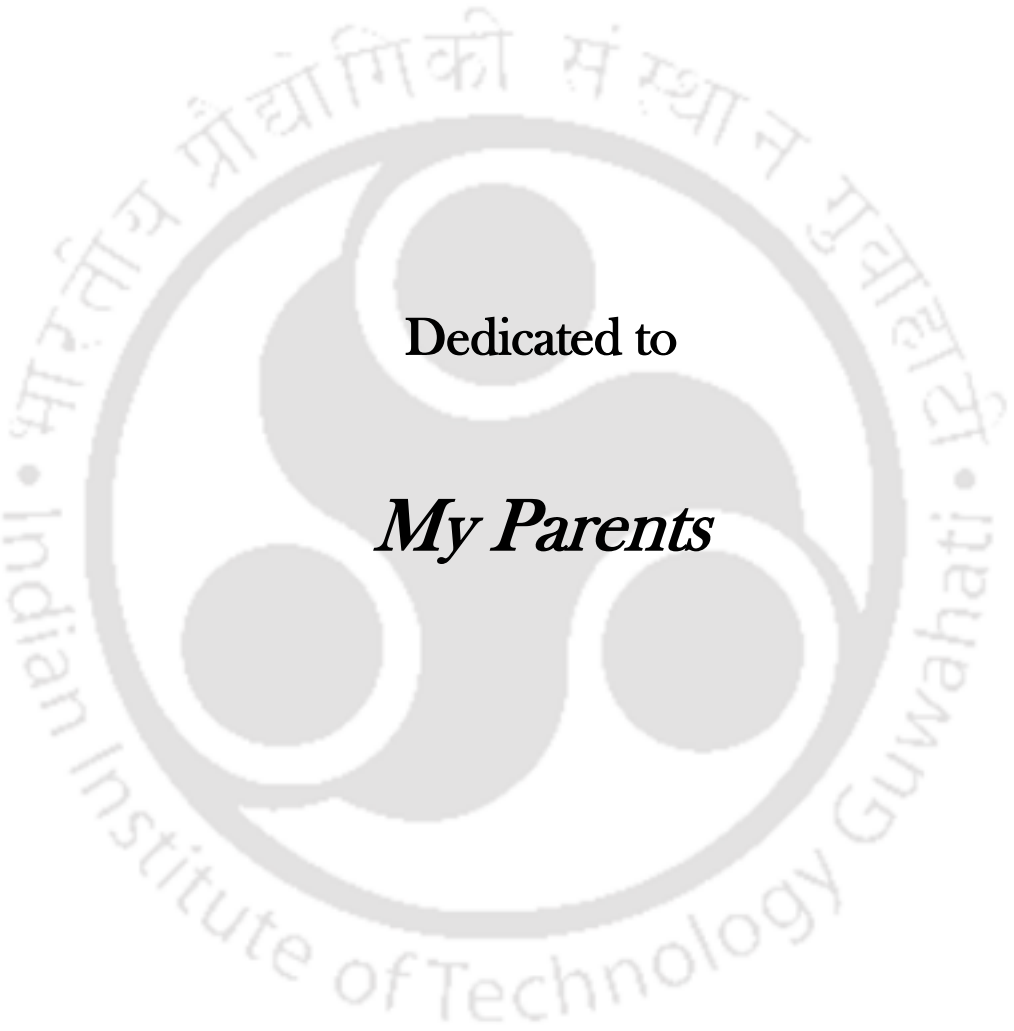

Dedicated to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Department of Chemistry

DECLARATION

I do hereby declare that the matter embodied in this thesis entitled "***Regioselective Bromination of Substituted 2'-Hydroxy Chalcones and Synthesis of Fused Nitrogen Heterocycles***" is the result of investigations carried out by me under the supervision of Prof. Abu T. Khan and co-supervision of Prof. Parameswar K. Iyer in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

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

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CERTIFICATE

This is to certify that Mr. Abhik Choudhury has been working in my research group since August, 2009 (first as a regular registered Ph. D. student and then from Feb, 2011 onwards as a part-tme student). I am forwarding his thesis entitled "***Regioselective Bromination of Substituted 2'-Hydroxy Chalcones and Synthesis of Fused Nitrogen Heterocycles***" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

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This is to certify that Mr. Abhik Choudhury has completed his Ph. D. Thesis work from August, 2009 (first as a regular registered Ph. D. student and then from Feb, 2011 onwards as a part-tme student) under my colleague Prof. Abu T. Khan. I have been appointed as a Co-Supervisor when Prof. Khan joined as Vice-Chancellor of Aliah University in West Bengal on deputation from IIT Guwahati. I am forwarding his thesis as a Co-supervisor entitled "***Regioselective Bromination of Substituted 2'-Hydroxy Chalcones and Synthesis of Fused Nitrogen Heterocycles***" being submitted for the Ph. D. (Science) Degree of this Institute. I also certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

IIT Guwahati
April , 2016

Prof. P. K. Iyer
(Thesis Co-Supervisor)

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At the very outset I take the opportunity to express my deepest sense of gratitude to my Ph.D. supervisor, Prof. Abu T. Khan, Department of Chemistry, IIT Guwahati for his incisive guidance, decisive insights, constant encouragement and moral support at each and every step of my research work, which enabled me to complete my thesis work. I find myself privileged and honored to have worked under his kind guidance. My everlasting gratitude goes towards him.

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I wish to acknowledge my sincere gratitude to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial assistance and IIT Guwahati for all the facilities that were made available to me. I also thank Central Instrument Facility of the institute for providing the Instrument facility and DST for providing the X-ray facility.

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I owe my sincere thanks to our technical staff Abhilasha di, Lipika di, Aniruddha da, Diganta da, Shyamul da and office staffs Nilotpal da, Santanu da as well as Subal da for their help and support.

My Ph. D. endeavour could not have been completed without the unending support of my parents. I am forever grateful to them for their boundless love and encouragement. I also wish to express my sincere gratitude to my wife for her support and encouragement.

At last, I thank Almighty God for always being there for me.

(Abhik Choudhury)

CONTENTS

SUMMARY OF THE THESIS

The content of the thesis entitled "Regioselective Bromination of Substituted 2'-Hydroxy Chalcones and Synthesis of Fused Nitrogen Heterocycles" has been divided into two main parts namely Part A and Part B. Part A of the thesis comprises of two chapters i.e. Chapter 1 and Chapter 2. Similarly, Part B of the dissertation consists of four chapters namely Chapter 1, Chapter 2, Chapter 3 and Chapter 4. Chapter 1 of each part of the dissertation describes a brief review on the work on the relevant topics. The other chapters of the thesis elaborates successful results and discussions along with experimental work.

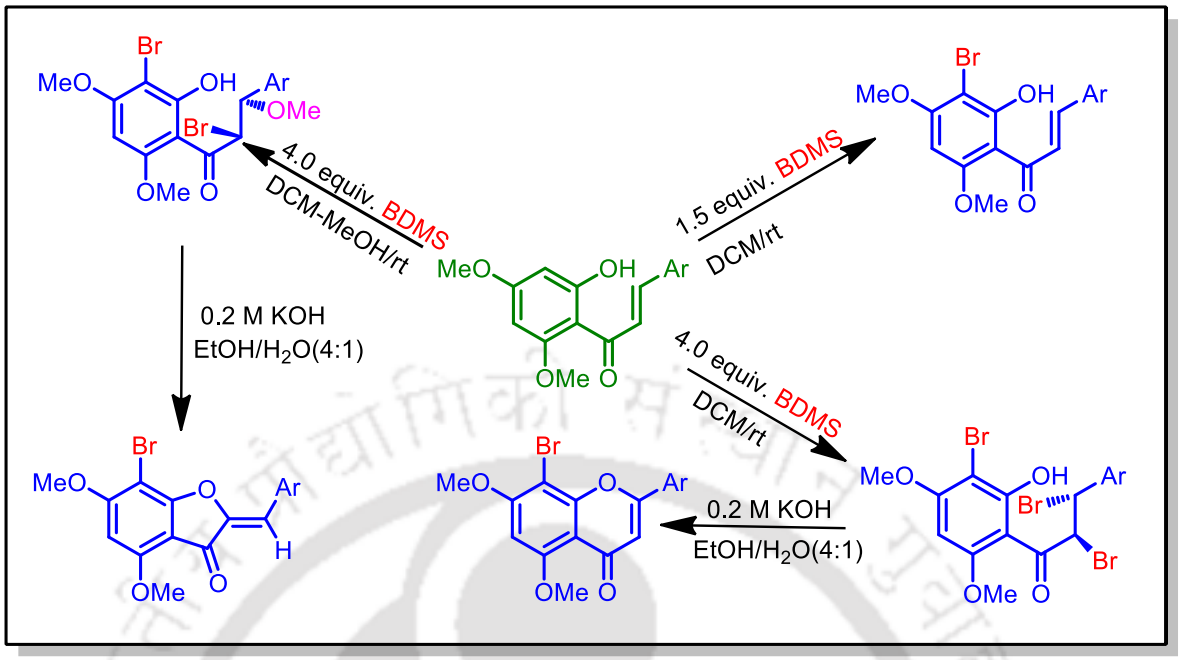
PART A

Chapter 1 highlights the importance of hydroxy and bromochalcones and gives a brief account of their reactivity and biological importance. It consists of a brief discussion on their significance as starting materials in organic synthesis.

Chapter 2 demonstrates synthesis of a wide variety of monobrominated compounds in good yields from (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones through regioselective ring monobromination using 1.5 equiv. of bromodimethylsulfonium bromide (BDMS) at the room temperature. In addition, some of the 2'-hydroxychalcones have been converted directly into tribromides and dibromides by employing 4.0 equiv. of BDMS under different reaction conditions which in turn have been transformed into 8-bromoflavones and 7-bromoaurones on treatment with 0.2 M ethanolic KOH solution. Some of the salient features of this protocol are mild reaction conditions, good yields and avoidance of chromatographic separation (Scheme 1).

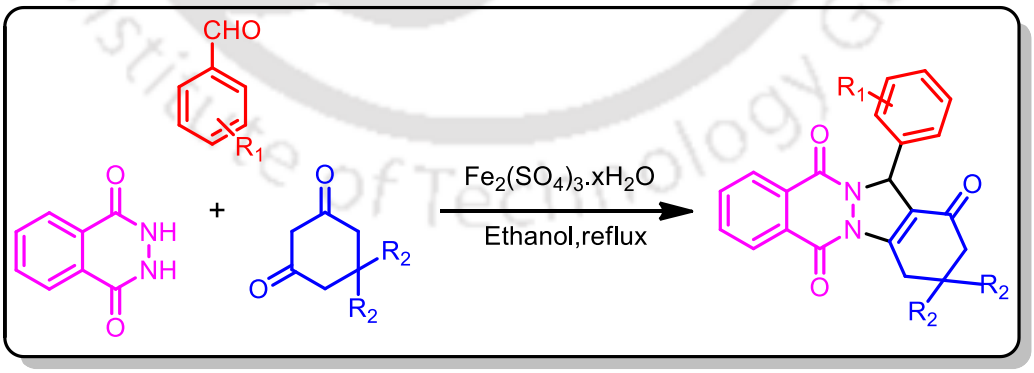
PART B

Chapter 1 gives a brief review on tandem-Knoevenagel-Michael initiated ring closure reaction. The tandem-Knoevenagel-Michael reaction represents an elegant approach, which has been used extensively for the construction of small/medium sized nitrogen or oxygen containing heterocyclic compounds. The importance of these reactions for the construction heterocyclic compounds has also been addressed in this chapter.



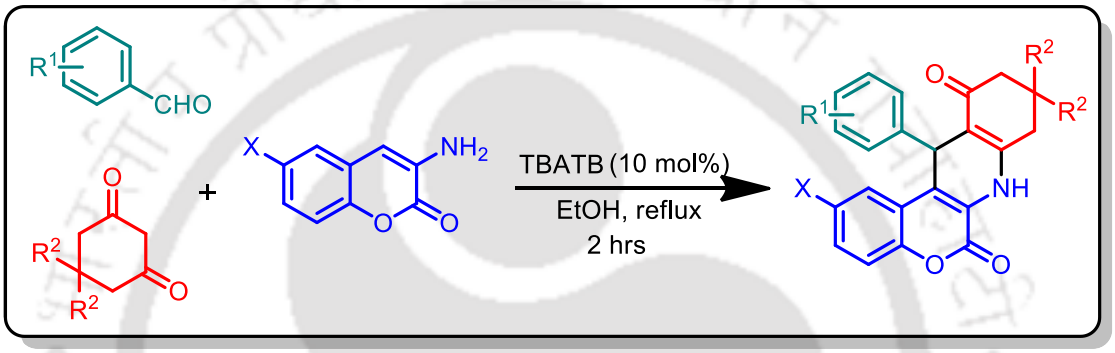
Scheme 1

Chapter 2 focuses on the efficient synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones accomplished through one-pot condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic-1,3-diketones in ethanol under reflux using hydrated ferric sulfate [$Fe_2(SO_4)_3{\cdot}xH_2O$] as a reusable catalyst (Scheme 2). The salient features of this protocol are: good yields, shorter reaction time, ease of recovery of the catalyst, involvement of inexpensive environmentally benign heterogeneous catalyst and avoidance of chromatographic separation.



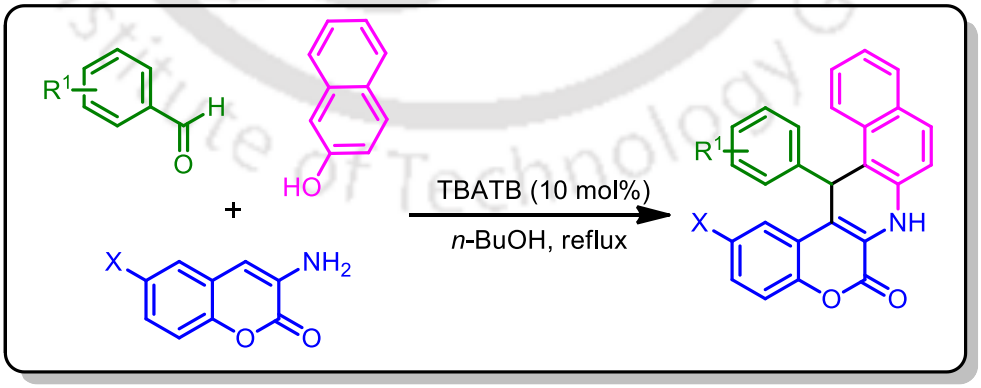
Scheme 2

Chapter 3 illustrates the one-pot synthesis of chromeno[3,4-*b*]quinoline-6,11-dione derivatives through tandem-Knoevenagel-Michael initiated ring closure reactions by employing three-component condensation of aromatic aldehydes, 3-aminocoumarins and cyclic 1,3-diketones in the presence of catalytic amount of TBATB in ethanol under reflux conditions. It is worth mentioning that three new bonds (two *C*-*C* and one *C*-*N*) and one stereocenter are formed in the course of this reactions. The significant features of this protocol are shorter reaction times, environmentally benign, superior atom economy, the easy accessibility of the catalyst, cost effectiveness, simplicity of the procedure and good to excellent yields (Scheme 3).



Scheme 3

Chapter 4 elaborates the synthesis of a wide variety of benzo[*f*]chromeno[3,4-*b*]quinolin-6-ones *via* one-pot three-component reaction of 2-naphthol, aromatic aldehydes and 3-aminocoumarins in the presence of catalytic amount of TBATB in *n*-butanol under reflux condition through tandem-Knoevenagel-Michael initiated ring closure reactions. (Scheme 4).



Scheme 4

In conclusion, the thesis describes a new and effective synthetic methodology for the regioselective ring monobromination of substituted 2'-hydroxychalcones and synthesis of 8-bromoflavones and 7-bromoaurones. Further it also shows the utility of tandem-Knoevenagel-Michael reaction for the synthesis of fused nitrogen heterocycles. It is expected that these methodologies will be applicable in target-oriented synthesis and the synthesised compounds will act as valuable precursors in the arsenal of synthetic organic chemistry.

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781039, Assam during the period from August, 2009 to November, 2015 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

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

ABBREVIATIONS

Ac	acetyl
AS	aureusidin synthase
BDMS	bromodimethylsulfonium bromide
Bu	butyl
CAN	ceric ammonium nitrate
CCDC	cambridge crystallographic data centre
DCE	1,2-Dichloroethene
DCM	dichloromethane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DOS	diversity-oriented synthesis
Et	ethyl
g	gram
HRMS	High-resolution Mass Spectrometry
h	hour
HIV	human immunodeficiency virus
IR	infrared
MCR	Multicomponent reaction
Me	methyl
mg	milligram
m.p	melting point
MS	molecular sieves
MW	microwave
NMR	nuclear magnetic resonance
Ph	phenyl
p-TSA	*p*-toluenesulfonic acid
PHC	pentahydroxychalcone

RNA	ribonucleic acid
rt	room temperature
ROS	reactive oxygen species
SGLTs	sodium/glucose cotransporters
TBATB	n-tetrabutylammonium bromide
THP	tetrahydropyranones
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
w	weight
XRD	x-ray diffraction

PART A

CHAPTER 1

Brief Review on Hydroxy and Bromochalcones

1. Introduction:

Flavonoids belong to a large group of abundant plant secondary metabolites, which can be found in vascular plants such as ferns, conifers and flowering plants.[1-3] These natural compounds are generally divided into various classes on the basis of their molecular structures including chalcones, flavones, flavanones, flavanols, and anthocyanidins (Figure 1). Approximately, 4000 varieties of flavonoids have been identified and many of these are intense pigments, providing a spectrum of yellow, red and blue colors in flowers, fruits and leaves.[3-6] Besides their contribution to plant color, flavonoids have several pharmacological benefits (e.g. anticancer, antiinflammatory, antiallergic, etc.) and are known as effective antioxidants, metal chelators and free radical scavengers.[3, 7, 8] Natural and synthetic flavonoids are therefore of considerable interest in the development of novel therapeutic agents for various diseases and are generally believed to be non-toxic compounds since they are widely distributed in the human diet.[2, 5]

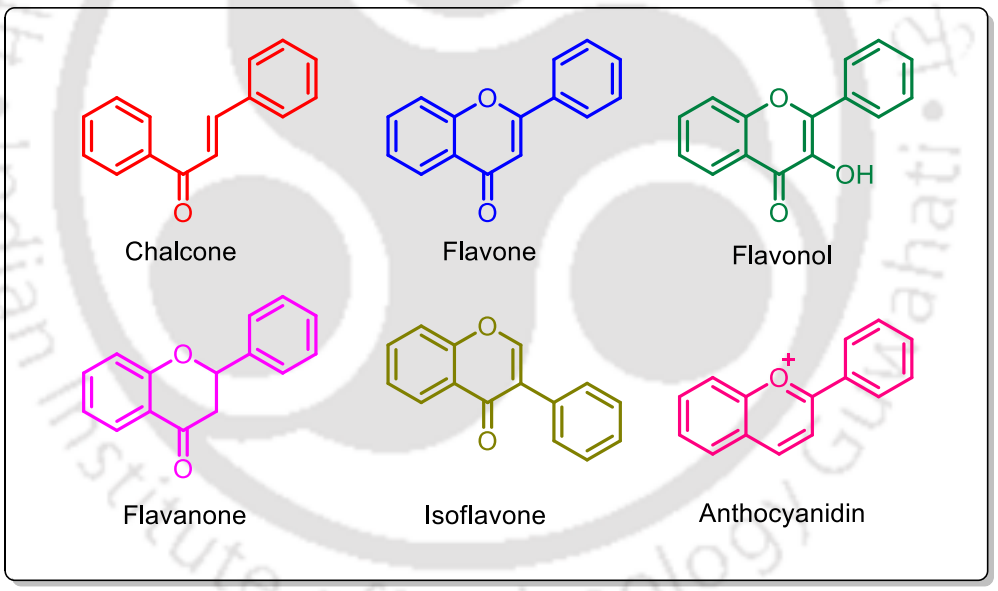


Figure 1

Chalcone

Chemically, chalcone is 1,3-diphenyl-2-propen-1-one (Figure 2). The structure of chalcones differ considerably from the others members of the flavonoid family, since chalcones are open-chain analogs in contrast to the other family members. The name "Chalcones" was given by Kostanecki and Tambor[9]. These compounds are also known as benzalacetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcones are unsaturated ketones containing the reactive ketoethylenic group

(–CO–CH=CH–). These are coloured compounds because of the presence of the chromophore (–CO–CH=CH–). Chalcone is a privileged structure, demonstrating promising anti-inflammatory and anticancer activities.

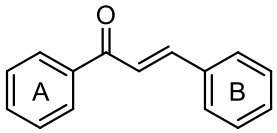


Figure 2. The general structure of chalcones

Carthamin a red pigment was first obtained as red needles with green iridescence using pyridine solvent from the flowers of *cartharmus tinctoria* (safflower) by Kametaka and Perkin[10] and this was the first known example of chalcone in nature (Figure 3).

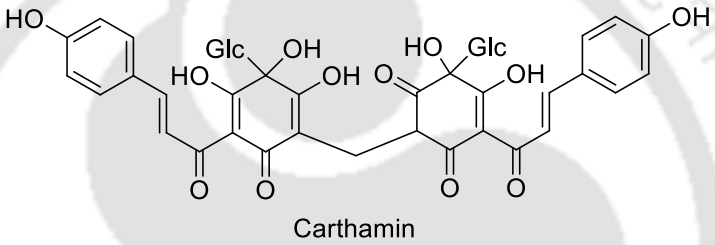


Figure 3

Chalcones are abundantly present in nature starting from ferns to higher plants.[11] It constitutes one of the major classes of flavonoids with widespread distribution in edible plants such as vegetables, fruits, tea and soyabean.[3, 12] The most common chalcones found in foods are phloretin and its glucoside phloridzin (phloretin 2′-*O*-β-glucopyranoside), and chalconaringenin (Figure 4).

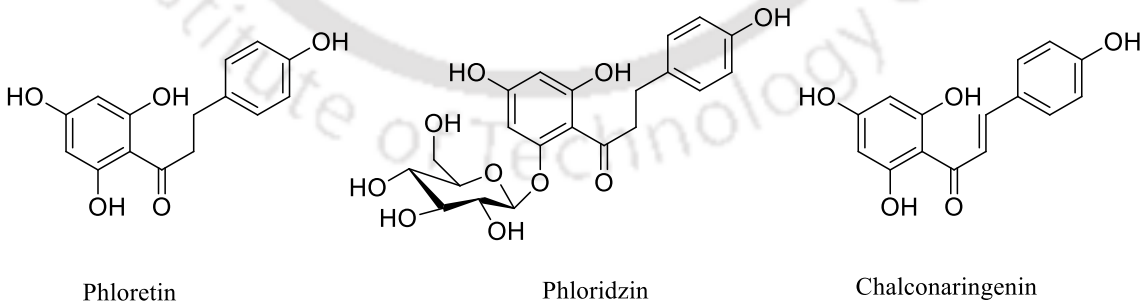


Figure 4

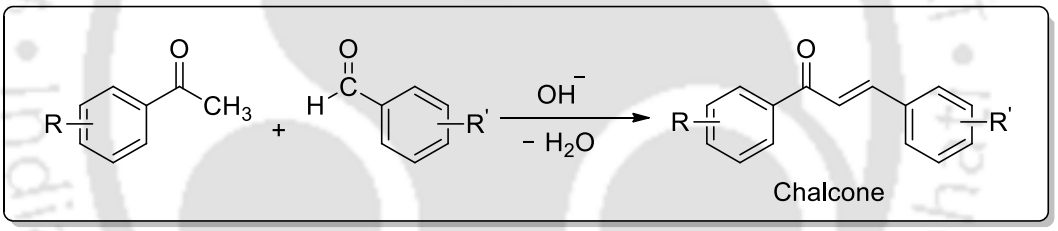
Among flavonoids, Chalcones have been identified as interesting compounds that are associated with several biological activities. Prehistoric therapeutic applications of chalcones can be associated with the thousand-year old use of plants and herbs for the treatment of

different medical disorders.[13] Contemporary studies report a generous variation of significant pharmacological activities of chalcones including antiproliferative, antioxidant, antiinflammatory and anticancer effects.[12, 14]

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency, lesser toxicity and good pharmacological actions. Chalcone has become an object of continued interest in both academia and industry.

Synthetic methods of preparing chalcones

Different methods are available in literature for the synthesis of chalcones and substituted chalcones in the laboratory.[16-24] The most convenient method is the one that involves the Claisen-Schimidt condensation of equimolar quantities of a substituted acetophenone with substituted aldehydes in presence of aqueous alcoholic alkali (Scheme 1).[25]



Scheme 1

The concept of "Microwave induced organic reaction enhancement"[26] chemistry has proved very useful in the efficient synthesis of chalcones. The procedure involves condensation of ketones and aromatic aldehydes with ethanol as energy transfer medium. This process is carried out in the presence of sodium hydroxide in open glass vessel under microwave irradiation. The obtained products have better yield and rate of reaction has also been enhanced. The reaction time is reduced from hours to minutes, thus providing the versatility of the process.

Besides these several other condensing agents such as aluminium chloride,[27,28] anhydrous boron trifluoride,[29] amino acids,[30] hydrochloric acid,[31,32] phosphorous oxychloride,[33] piperidine,[34] perchloric acid,[35,36] aqueous solution of borax,[37] magnesium tert-butoxide,[38] chlorotrimethylsilane (TMSCl)[39] and organocadmium compounds[40] etc have also been used in the synthesis of chalcones.

Chalcones as starting materials in organic synthesis:

An interesting feature of chalcones is that they bear a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed (Figure 5). Hence they serve as starting materials for the synthesis of various heterocyclic compounds such as cyanopyridines,[41] pyrazolines,[42] isoxazoles,[43] pyrimidines,[44] thiazepines[45], quinolines,[46] dihydropyrans[47] and fused coumarin derivatives.[48] Chalcones are also precursor compounds for the biosynthesis of flavonoids in plants. Cyclization of hydroxychalcones leads to the formation of flavanones and subsequently to a large number of flavonoid groups including flavones, flavonols, dihydroflavonols, aurones and isoflavones.[49]

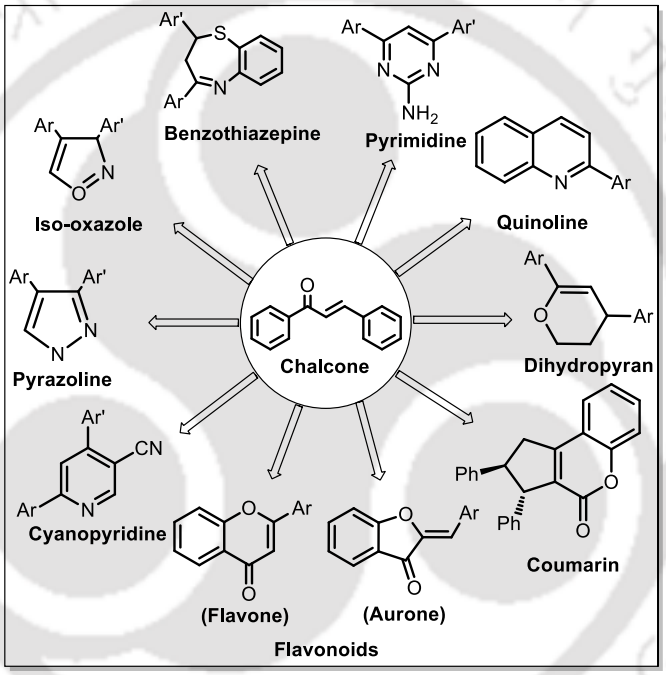


Figure 5

The presence of α,β-unsaturated carbonyl system in chalcones makes it biologically active.[50] They have shown antibacterial activity against *S. aureus*, *E. coli*, *C. albicans*, *T. utilis*, *S. sake*, *W. anomala* and some other organisms.[51] Depending on the substitution pattern on the two aromatic rings, a wide range of pharmacological activities have been identified for various chalcones.

2. Halogenated Chalcones

Naturally occurring organohalogen compounds are widely distributed in nature, which has been compiled recently by Gribble.[52] Some of the naturally occurring organohalogen compounds exhibit interesting biological activity such as cytoxicity towards four different human tumor cell lines,[53] Na,K-ATPase inhibitory activity[53] and antihistamine activity[54].

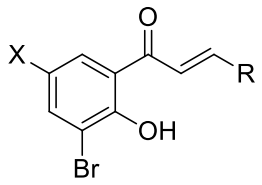
In addition, some of the brominated and iodinated compounds are already known as valuable drug molecules for the treatment of various diseases such as polycythemia vera: a condition in which the bone marrow produces excess red blood cells, tranquilizer and muscle relaxant, causing behavioral disorders in older people.

Since halogens like chlorine, bromine are very useful in the modulation of electronic and steric characteristics of drugs and may also influence the hydrophilic-hydrophobic balance of molecules, hence halogen substitution on the phenyl rings of chalcone can cause structural modification and modulation of basic pharmacophore of the chalcone.

Organohalogen compounds particularly bromo and iodo compounds serve as synthetic precursors for Wurtz,[55] Sonogashira[56] and Suzuki coupling reactions[57] as well as for the preparation of Organolithium, Grignard,[58] and Wittig reagents,[59] which are extensively used in *C-C* bond forming reactions in organic synthesis.

The importance of bromo compounds is well known in organic synthesis from the early days of chemistry. Many of them are naturally occurring having structural diversity ranging from very simple to very complex ones. Interestingly, some of them possess remarkable biological activities. They also serve as industrial intermediates in the manufacture of chemicals, pharmaceuticals and agrochemicals.

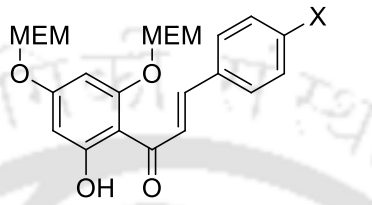
Luthman *et al*. synthesized[60] a series of dihalogenated 2'-hydroxychalcones containing bromine atom at 3' position in ring A (Figure 6) and evaluated their effect on microtubule assembly and antiproliferative activity in different cancer cell lines. They established that all compounds showed cytotoxic activity.



X = Cl, Br

Figure 6

Boumendjel *et al.*[61] prepared a series of chalcones (Figure 7) to explore their role as potential modulators of P-glycoprotein mediated multidrug resistance of cancer cells. They observed that substitution of the chalcone hydrogen at position 4 of B ring by different halogen atoms gradually enhanced the binding affinity, with a strong dependence on the nature of the halogen. They concluded that the iodo and bromo substituted chalcones exhibit high-affinity binding to P-glycoprotein.



X = F, Cl, Br, I

MEM = $-CH_2OCH_2CH_2OCH_3$

Figure 7

Nakamura *et al*. designed and synthesized[62] some fluorinated 3, 4-dihydroxychalcones and showed that all of them exhibit 5-lipoxygenase inhibition on rat basophilic leukemia-1 (RBL-1) cells and inhibitory action on lipid peroxidation in rat liver microsomes. They further found that the compound 6-Fluoro-3,4-dihydroxy-2',4'-dimethoxy chalcone (Figure 8) was the most effective compound in the in vitro assay using a human cancer cell line panel.

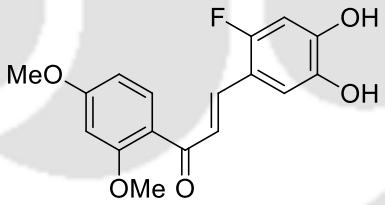
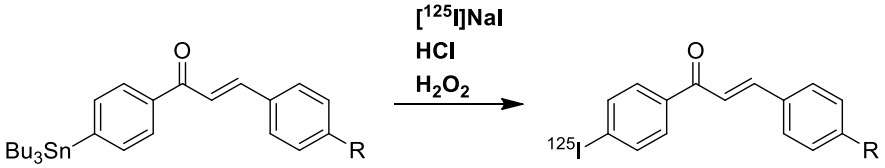


Figure 8

Ono *et al.*[63] successfully prepared a novel series of radioiodinated chalcones through an iododestannylation reaction from the corresponding tributyltin derivatives using hydrogen peroxide as the oxidant in high yields and with high radiochemical purities and showed their efficacy as amyloid imaging agents for detecting β-amyloid plaques in Alzheimer's brains (Scheme 2).



Scheme 2

Dias *et al*.[64] synthesised a series of chalcones (Figure 9) and performed a pharmacological evaluation with human colorectal carcinoma cell line. They found that halogenated chalcones show superior anticancer activity over the natural flavonol quercetin, a major dietary flavonoid which has been widely studied, considering the potent anticancer activity of this compound. They also found that antiproliferative activity of halogenated derivatives increases as the substituent in the 3- or 4-positon of the B-ring goes from F to Cl and to Br.

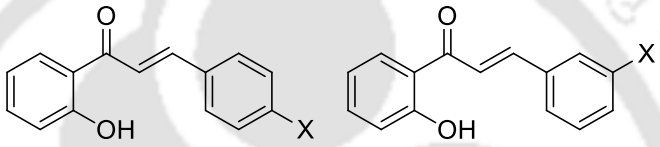


Figure 9

Hasan *et al*. Synthesised[65] some mono and di-halogenated chalcones and flavonols and found most of them to be active against the tested fungi and in some cases even stronger than the standard antifungal drugs. They further noticed that chalcones having a phenolic hydroxyl group at 2' position in ring A (Figure 10) showed more antifungal activity than that of its corresponding flavonol, in which the 2'-hydroxy group is lost on cyclization.

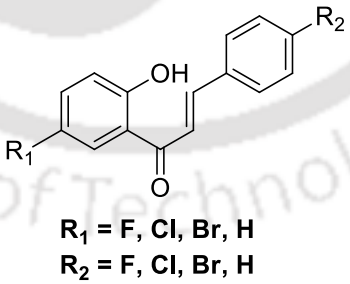


Figure 10

Rossi-Bergmann *et al*.[66] synthesized analogues of an active natural chalcone and tested them for selective activity against both promastigotes and intracellular amastigotes of *Leishmania amazonensis* in vitro. They showed that 2'-hydroxychalcone containing bromine atom at 3' position in ring A (Figure 11) exhibits better antileishmanial activity as compared to 2'-hydroxychalcone itself.

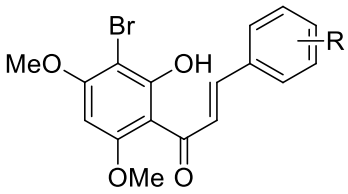


Figure 11

3. Importance of hydroxychalcones

A vast number of naturally occurring chalcones are polyhydroxylated in the aryl rings. 2'-hydroxychalcones in particular are essential intermediates for biosynthesis of flavonoids in plants and many of them are found as such in nature.[67] 2'-hydroxychalcones display a wide range of biological activities such as antitumoral,[68–70] antiinflammatory,[71] antibacterial,[72] antiulcerogenic,[73] antioxidant,[72,74,75] antimalarial[76] and antileishmanial activities.[76,77]

Williams *et.al* in 1989 isolated[78] a new dihydroxychalcone, kukulkanins A (2',4'-dihydroxy-3',4-dimethoxychalcone) and a new trihydroxychalcone, kukulkanins B (2',4',4-trihydroxy-3'-methoxychalcone) (Figure 12) from the powdered bark of the plant *Mimosa tenuefolia* which has been historically used in treatment of burns and prevention of inflammation.

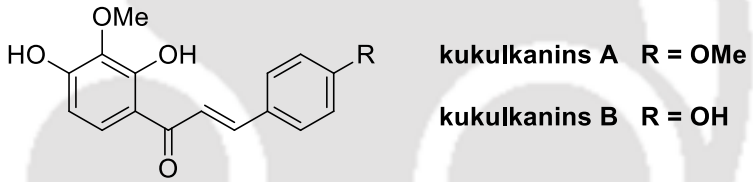


Figure 12

In the year 2004 Yoshimura and group reported that Naringenin chalcone (Figure 13) is the main active component of tomato skin extract,[79] which has anti-allergic activity.

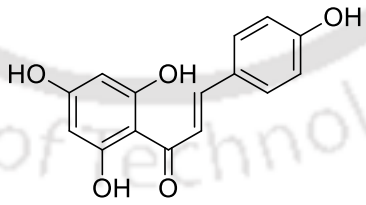
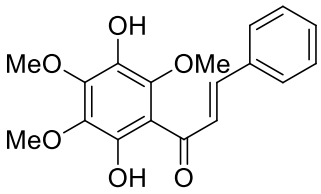


Figure 13

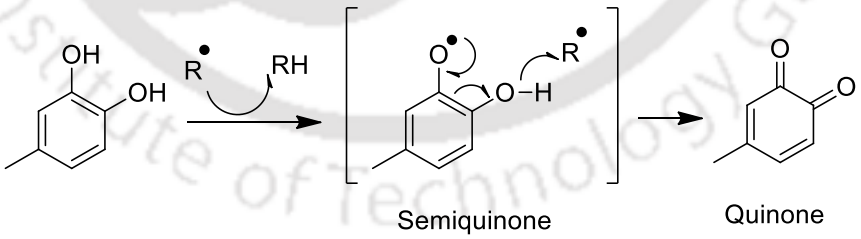
Pais and co-workers in 1995 isolated[80] anti-mitotic chalcone pedicin (2',5' dihydroxy-3',4',6'-trimethoxychalcone) (Figure 14) from an ethylacetate extract of *Fissistigma lanuginosum*.



Pedicin

Figure 14

Chalcones serve in plant defence mechanisms to counteract reactive oxygen species (ROS) in order to survive and prevent molecular damage and damage by microorganisms, insects, and herbivores. They are known to possess antioxidant character at various extents. The antioxidant activity of chalcones is related to a number of different mechanisms such as free radical scavenging, hydrogen donation, singlet oxygen quenching, metal ion chelation and acting as a substrate for free radicals such as superoxide and hydroxide. The antioxidant properties of chalcones are known to be influenced to a great extent by the two aryl structures, *i.e.* the substituents on two aryl rings of chalcone molecule and their substitution patterns. Especially, the hydroxyl substituent which is widespread among chalcones from natural sources[81] is one of the key groups to enhance greatly the antioxidant activity of chalcone mainly due to its easy conversion to phenoxy radicals through the hydrogen atom transfer mechanism. This phenoxy radical formation may be central to the antioxidant properties of hydroxyl substituted chalcones (Scheme 3). The radical quenching properties of the phenolic groups present in many chalcones have raised interest in using the compounds or chalcone rich plant extracts as drugs or food preservatives.[82]



Scheme 3

Several chalcones have been reported to act as cytotoxic agents or as microtubule destabilizing agents, targeting the colchicines binding site.[83] The majority of these are naturally occurring chalcones substituted with electron donating hydroxy and/or methoxy groups at various positions.[84] Particularly interesting are the properties of hydroxychalcones in the induction of apoptosis[85] and their ability to change mitochondrial membrane potential

of cancer cells.[86] It was observed that chalcones with fewer hydroxyl groups on rings A and B were more effective in this regards, as compared to chalcones containing more hydroxyl groups. This difference was attributed to the acidity of the phenolic hydroxyl groups.

Srinivasan and group demonstrated[87] the synthesis of 3-hydroxy-4,3′,4′,5′ tetramethoxy-chalcone (Figure 15) and its analogues and their potent cytotoxicity against lung cancer cells.

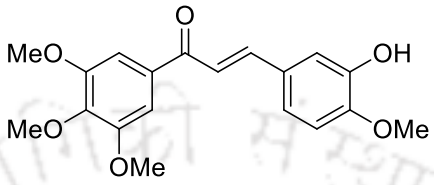


Figure 15

Ramirez-Tagle and group synthesized[88] 2'-hydroxychalcones with different methoxy subtitutions on ring B (Figure 16) and evaluated the relationship between the structural characteristic of the synthetic chalcones and their antitumoral activity. They reported that these chalcones inhibit cellular proliferation and induce apoptosis in hepatocellular carcinoma cells.

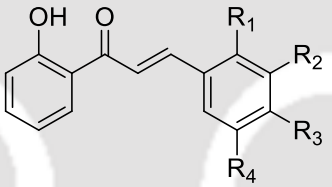
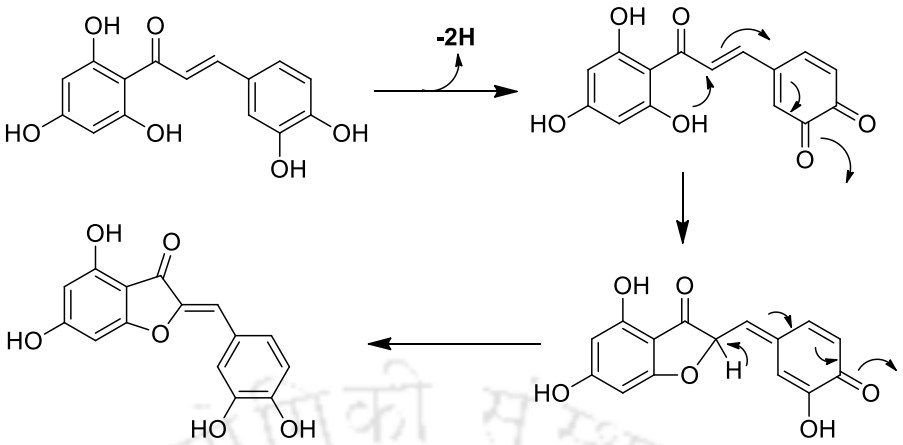


Figure 16

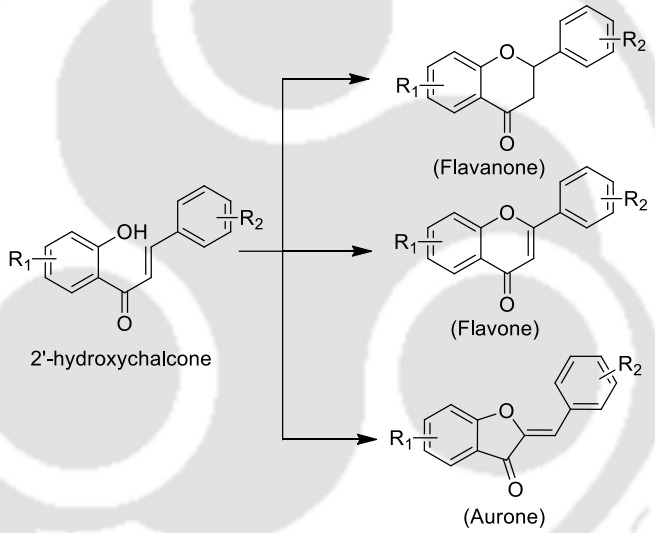
Link and Sorensen reported[89] that 2',4',6',4-tetrahydroxychalcone is a key precursor for phlorizin (Figure 4) which is used for inhibition of the sodium/glucose cotransporters (SGLTs) and thereby lowering the blood glucose levels in diabetic animals.

Apart from their wide range of biological activities, hydroxychalcones also have synthetic utility as ideal precursors for the synthesis of flavonoids. In plant tissues, aurones are biosynthesized from 2'-hydroxychalcones precursors, utilizing the enzyme Aureusidin synthase (AS). The biosynthesis of aureusidin (Scheme 4) from 2',3,4,4',6'-pentahydroxy-chalcone (PHC) catalyzed by AS has been proposed to involve three steps, with only the first being enzyme-dependent.[90] In this step, the enzyme-catalyzed reaction generates a chalcone with an *o*-quinonoid B-ring. Cyclization via formation of a benzofuranone ring followed by rearomatization yields Aureusidin as the thermodynamically more stable Z-geometric isomer.



Scheme 4. Aureusidin biosynthesis

Different methods have been reported in the literature for the laboratory synthesis of flavanones,[91-93] flavones,[92-95] aurones,[93, 95, 96] etc from 2'-hydroxychalcone.

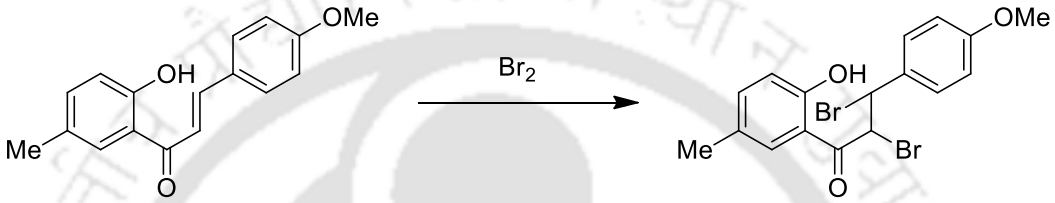


Scheme 5

4. Bromination of chalcones

As the chalcones contain a double bond in the vicinity of a ketonic group, the action of bromine on them affords an interesting study. Under usual conditions, α-β dibromides of the chalcones are formed.

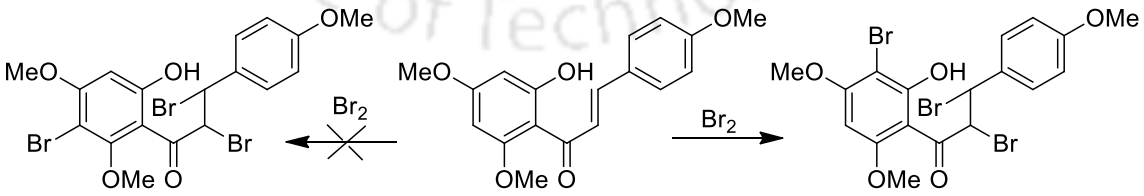
Chalcone (1,3-diaryl prop-2-en-1-one) is usually brominated by molecular bromine in different organic solvents[97] to give chalcone dibromide. For example 2'-hydoxy-5'-methyl-4-methoxyphenyl propan-1-one on bromination by bromine gives (2,3-dibromo-1-(2'-hydroxy-5'-methyl) phenyl-3-(4-methoxy)-phenyl propan-1-one (Scheme 6).



Scheme 6

Dibromochalcones have also been obtained by bromination of chalcones using different other brominating agents such as pyridinium hydrobromide perbromide,[98] bromine vapours,[99] tetrabutylammonium tribromide,[100] phenyl trimethylammonium bromide,[101] bromodimethylsulfonium bromide,[102] boric acid with potassium bromide,[103] 1,2-dipyridiniumditribromide ethane[104] etc.

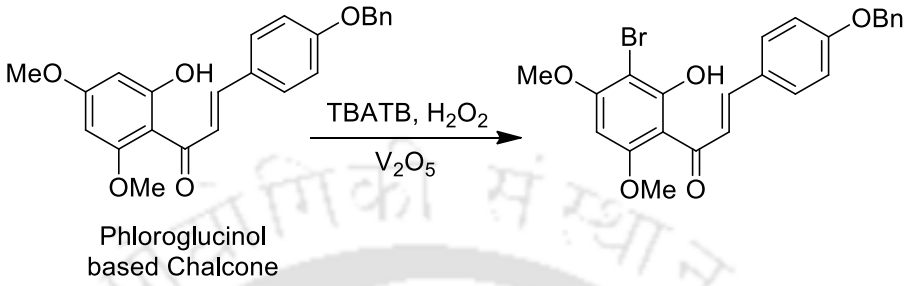
Phloroglucinol based chalcones are an important synthetic precursor for naturally occuring flavonoids like Vitexin,[105] Aciculatin.[106] Since Kostanecki and Tambor[107] reported nuclear substitution in the bromination of chalcones derived from phloroglucinol, other workers[108-110] have assumed that it occurs in the 5'-position to form a tribromide. Donnelly[111] in 1959 proved that the nuclear bromination with molecular bromine actually occurs in the 3'-position and not in the 5'-position as assumed earlier (Scheme 7).



Scheme 7

Chaudhuri *et al.*[112] carried out selective bromination of the activated aromatic ring of phloroglucinol based chalcone in presence of the olefinic double bond using

tetrabutylammonium bromide (TBATB) promoted by hydrogen peroxide and V_2O_5. For example the substrate on selective bromination of the activated aromatic ring gave rise to the 3'-bromo product, 4-benzyloxy-3'-bromo-4',6'-dimethoxy-2'-hydroxychalcone exclusively (Scheme 8).



Phloroglucinol based Chalcone

Scheme 8

PART A

CHAPTER 2

Regioselective Monobromination of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones and Synthesis of 8-bromoflavones and 7-bromoaurones

Results and Discussion

Background of the present work

Naturally occurring C-aryl glycosides are widely distributed in plants and exhibit numerous interesting physiological activities. One of the important classes is C-glycosylflavones (Figure 17) which are found in Rutaceous, Compositous and Fabaceous plants.[113] The naturally occurring C-glycosylflavones are generally linked either at C-6 or C-8 on the A-ring of flavonoid nucleus with various monosaccharides such as D-Glucose, D-Galactose, D-Arabinose, L-Rhamnose etc. These compounds show a wide variety of biological activities such as antiviral,[114] antiinflammatory,[115] cytotoxic and DNA binding activity.[116]

Because of their wide range of biological activity and application as drugs, the synthesis of naturally occurring C-aryl glycosides has gained considerable attention of synthetic organic chemists.[117]

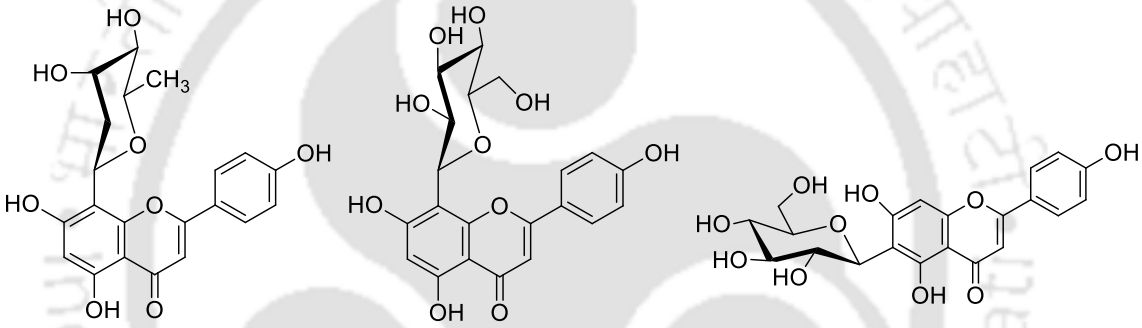


Figure 17

Bisflavones such as amentoflavone[118] and robustaflavone,[119] (Figure 18) which are biologically potent compounds, are well known in literature.

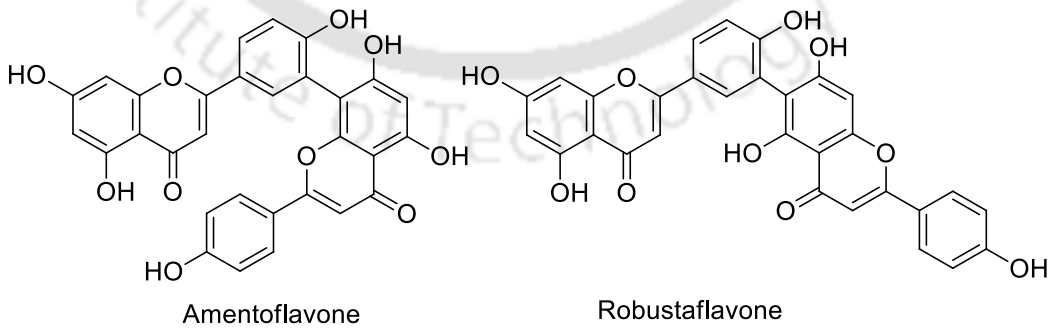
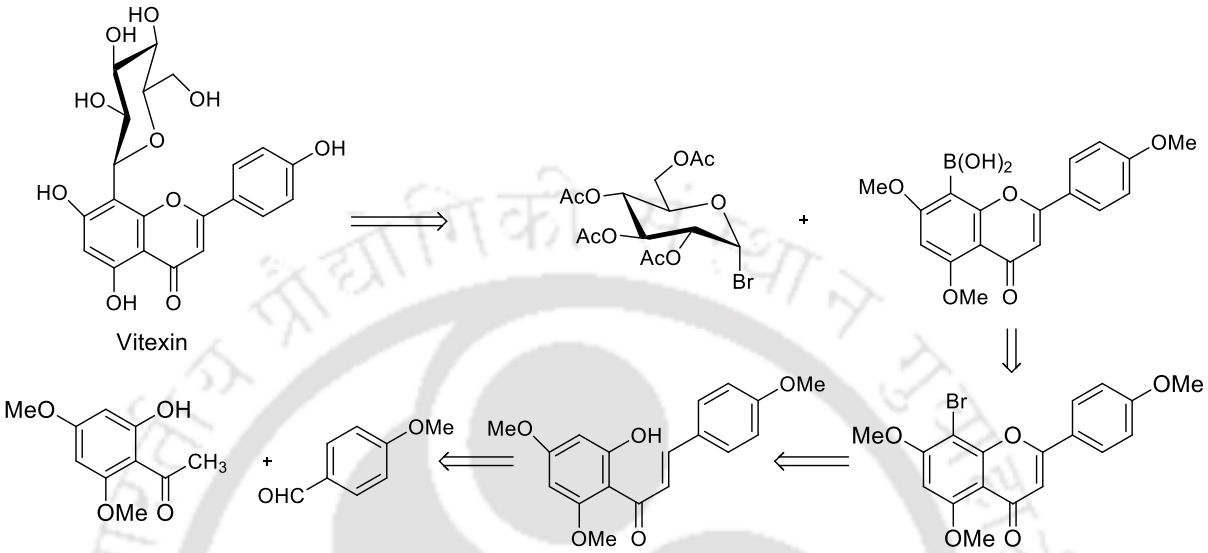


Figure 18

In the year 1991 the synthesis of amentoflavone has been achieved by using 8-bromo flavones.[118] Similarly the synthesis of robustaflavone was reported by using 6-iodoflavone.[120] Thus from the literature review and also from retrosynthetic analysis (Scheme 9) we realized

that bromo derivatives of flavones particularly 8-bromoflavone derivatives, namely 8-bromo-5,7,4'-trimethoxyflavone might be the appropriate synthetic precursors for the synthesis of biologically active naturally occurring C-glycosylflavones such as vitexin[105] and aciculatin.[106]



Scheme 9. Retrosynthetic Analysis of Vitexin

From the literature survey we have also found that much work has not been done in this field. Only few methods are known for the synthesis of 8-bromoflavone. Synthesis of the compound 8-bromo-5,7,4'-trimethoxyflavone was first reported by Wheeler and Hutchins[121] from the corresponding 2'-hydroxy-4,4',6'-trimethoxychalcone by bromination using molecular bromine followed by cyclization under basic conditions. Later, in 1961 Chen and his group reported[122] the synthesis of this compound in a sequence that used selenium dioxide oxidation. Donnelly *et al.*[123] also synthesized this compound along with 7-bromo-aurone derivative in the ratio 8:5 by cyclization of 2'-hydroxy-4,4',6'-trimethoxychalcone dibromide using ethanolic KOH solution. The synthesis of brominated flavones from 2'-hydroxychalcone can be accomplished using molecular bromine followed by cyclization with a base or from 2-hydroxy-4,6-dimethoxyacetophenone in three subsequent steps. Both procedures have drawbacks since both molecular bromine and selenium dioxide are harmful chemicals. At the same time, molecular bromine is difficult to handle and provides relatively low yields of the brominated products. The synthesis of brominated 2'-hydroxychalcones is highly desirable from biological point of view, therefore, a methodology that is environmentally benign, clean, efficient and yet unambiguous is still required.

Results and Discussion

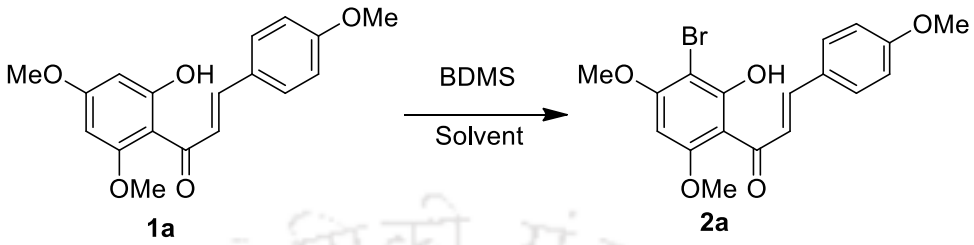
In the past few years, our research group[124] as well as others[125] have demonstrated that bromodimethylsulfonium bromide (BDMS) can serve as a useful brominating reagent and an effective catalyst in various organic transformations. It is easier to handle as compared to hazardous molecular bromine. We have also shown its usefulness in multicomponent reactions for the synthesis of heterocyclic compounds[126] as well as in carbohydrate chemistry.[127] Due to its unique reactivity and properties, we perceived that it can be explored further for bromination of 2'-hydroxychalcones. In this chapter, we report the regioselective mono bromination of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**1**) (Scheme 10).

Scheme 10. Synthesis of (*E*)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones using BDMS

For the present study, the brominating reagent, bromodimethylsulfonium bromide (BDMS)[128] and (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**1**) were prepared by following the literature procedures. Subsequently, the substrate **1a**, (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones (0.5 mmol), in 2 mL of dichloromethane (DCM) was treated with 1.0 equiv amount of BDMS at room temperature. The brominated compound **2a** was isolated in 67% yield within 5 min and it was characterized from ^{1}H and ^{13}C NMR spectra and elemental analysis. After getting the desired product, the reaction condition was optimized by carrying out the experiment with different amounts of BDMS under various solvent systems. The best result obtained in terms of yield, time and selectivity is mentioned in Table 1. We observed that the best yield of the mono brominated product, (*E*)-1-(3'-bromo-2'-hydroxy 4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**2a**) was obtained using 1.5 equiv. of BDMS in dichloromethane. It is noteworthy that in (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**1**), there are three possible sites where bromination might occur which includes the 3'-position and 5'-position of the A ring and also

the alkene double bond. However on using 1.5 equiv. of BDMS bromination occurs exclusively at the 3'-position of the A ring.

Table 1 Optimization of the reaction conditions[a]

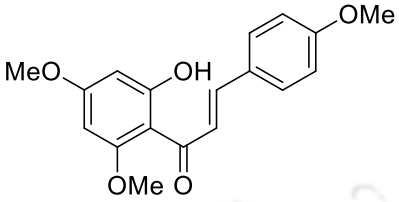
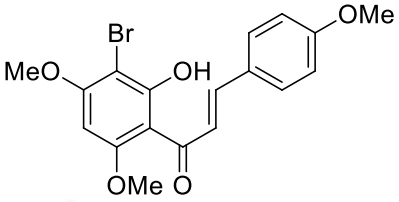
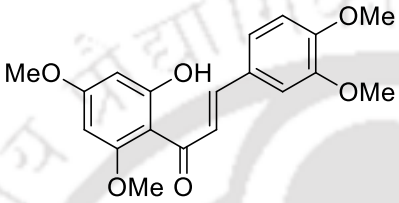
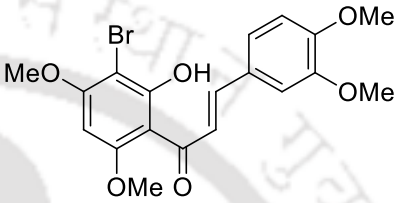
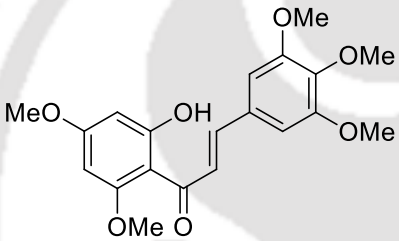
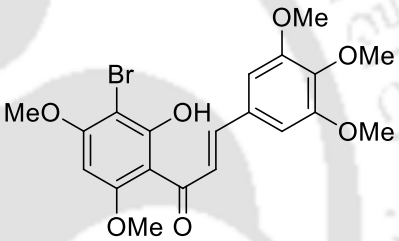
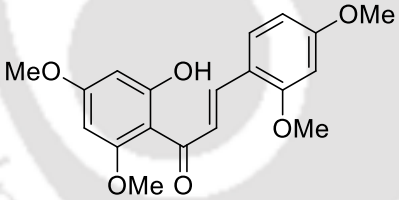
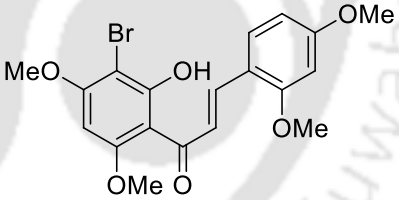
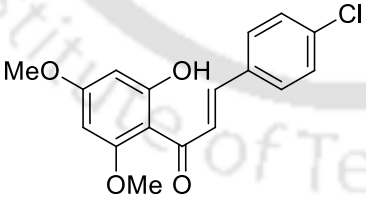
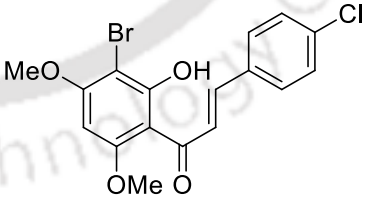
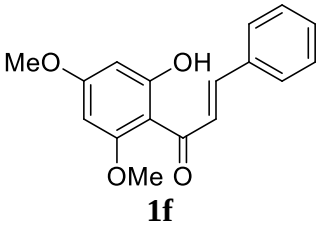
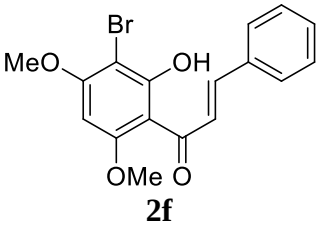


S. No.	BDMS/equiv.	Solvent	Time/min	Yield[b] /%
1	1.0	DCM	45	67
2	1.5	DCM	5	96
3	2.0	DCM	5	95
4	1.5	MeCN	10	81
5	1.5	EtOAc	5	86

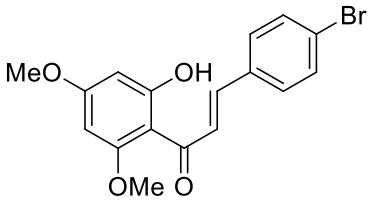
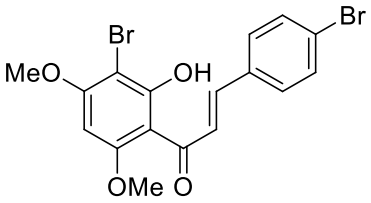
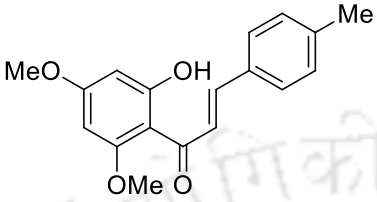
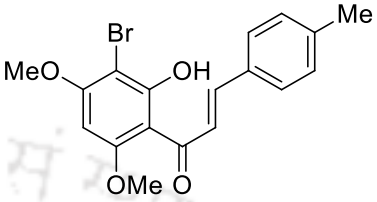
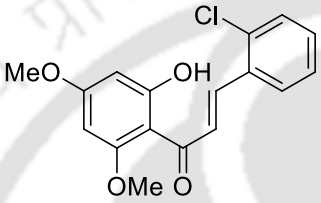
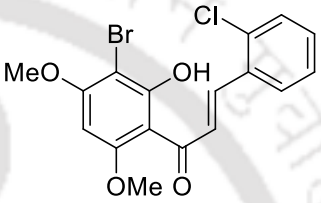
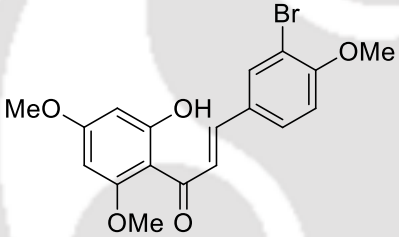
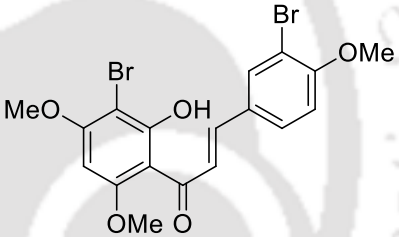
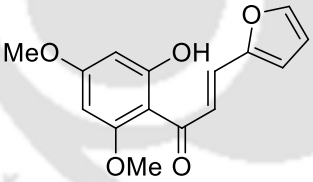
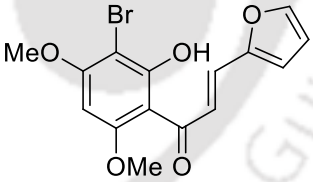
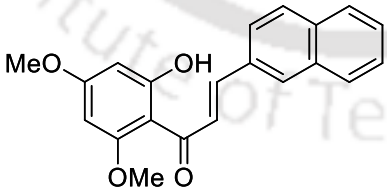
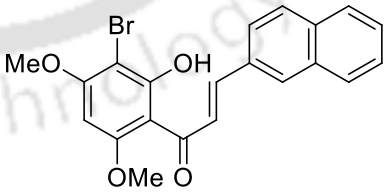
[a]*The reactions were carried out with 0.5 mmol of the substrate.* [b]*Isolated yields.*

After optimization, the reaction of (*E*)-1-(2'-hydroxy-4',6' dimethoxyphenyl)-3-aryl-2-propen-1-one (**1b**) was carried out under identical reaction conditions and the product **2b** was isolated in 93% yield. Encouraged by these successful results, a wide range of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**1c–l**) were also examined with 1.5 equiv. of BDMS under similar reaction conditions and the desired regioselective monobrominated products (**2c–l)** were obtained in excellent yields as shown in Table 2.

Table 2. Regioselective monobromination of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones by employing bromodimethylsulfonium bromide[a]

Entry	Substrate(1)	Product (2)	Yield[b] (%)
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	93
3	 **1c**	 **2c**	98
4	 **1d**	 **2d**	94
5	 **1e**	 **2e**	90
6	 **1f**	 **2f**	87

continued

7	 **1g**	 **2g**	85
8	 **1h**	 **2h**	94
9	 **1i**	 **2i**	97
10	 **1j**	 **2j**	82
11	 **1k**	 **2k**	95
12	 **1l**	 **2l**	85

[a]*The reactions were carried out with 0.5 mmol of the substrate in DCM using 1.5 equiv. amount of BDMS.* [b]*Isolated yields.*

The products were characterized by usual spectroscopic methods and also by single crystal XRD data. The XRD data revealed that regioselective monobromination occurs at the position adjacent to the OH group (Figure 19).

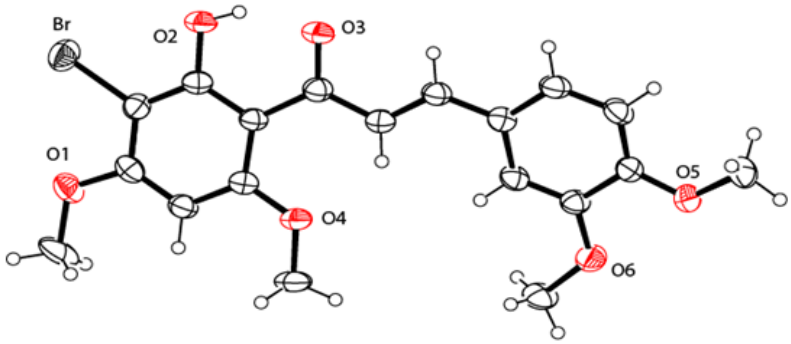
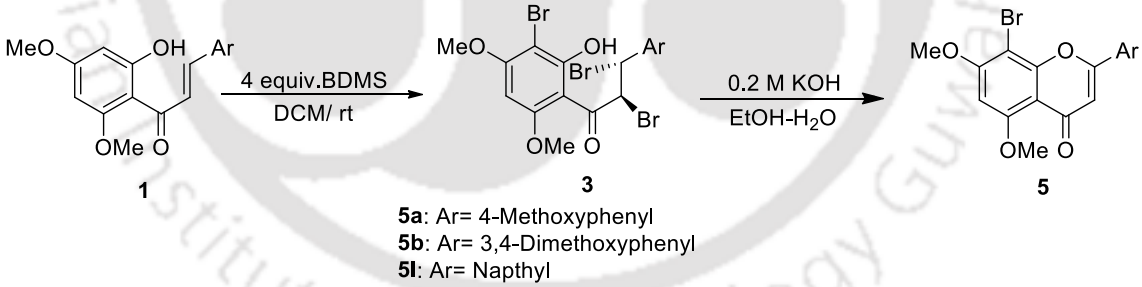


Figure 19. X-ray crystal structure of (*E*)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxy-phenyl)-3-aryl-2-propen-1-one (**2b)**

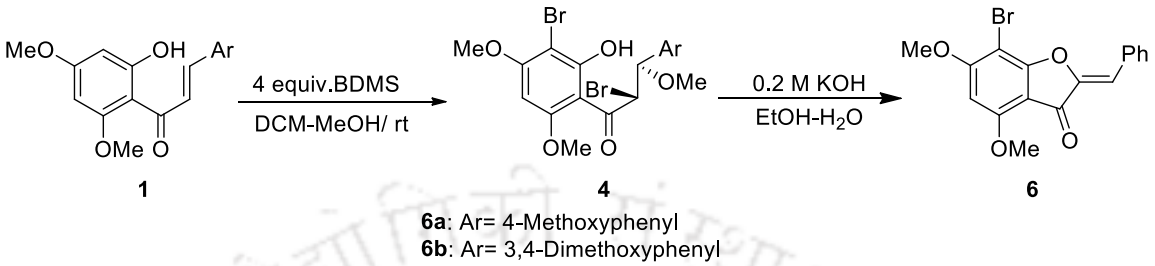
It is a well-known fact that (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones are key starting materials for the synthesis of flavones and aurones. We conceived that 8-bromoflavones and 7-bromoaurones can be synthesized easily from (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones since there still exists a further possibility for bromination. Consequently, the scope and generality of the reaction were also examined with increased amounts of BDMS. It was noted that compound **1a** on treatment with 4.0 equiv. of BDMS in DCM provided the tribrominated product **3a** in 84% yield which was smoothly converted into 8-bromoflavone (**5a**) on treatment with 0.2 M ethanolic KOH solution (Scheme 11).



Scheme 11. Synthesis of 8-bromoflavones

The structure was confirmed by usual spectroscopic techniques and from single crystal XRD data. It is clear that the cyclization took place at the β-position with respect to carbonyl group. Likewise, other substrates **1b** and **1l** were also converted into desired 8-bromoflavone derivatives **5b** and **5l** by following the two-step procedure. It is well-established in the literature that the bromination of alkene can give methoxy brominated compound on treatment with molecular Br_2 in MeOH.[129] We thought that methoxy group can be incorporated at the β-position of the (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones if the reaction is carried out with DCM-MeOH system. Subsequently, the

substrate **1a** was treated with 4.0 equiv. of BDMS in DCM/MeOH (5:2) and the product **4a** was isolated in 80% yield. Then, the compound **4a** was further transformed into 7-bromoaurone (**6a**) on treatment with 0.2 M ethanolic KOH solution (Scheme 12).



Scheme 12. Synthesis of 7-bromoaurones

Likewise, the substrate **1b** was converted into the corresponding 7-bromoaurone derivative **6b** by performing the similar sequence of reactions. All the products were fully characterized by IR, ^{1}H, and ^{13}C NMR spectra as well as elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compounds **2a**, **2b**, **2k**, **5a** and **6a** are given in the experimental section (Figure 21, 22, 23, 24 and 25). The structures of 8-bromoflavone and 7-bromoaurone were further confirmed by X-ray crystallography studies (Fig 20a and 20b).

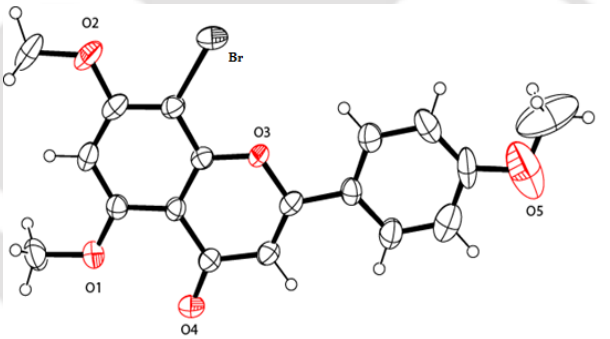


Figure 20a. X-ray crystal structure of 8-bromoflavone **5a**

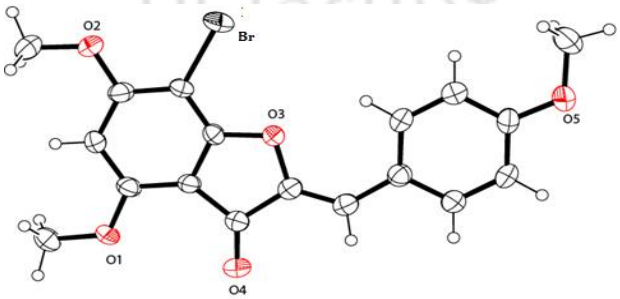


Figure 20b. X-ray crystal structure of 7-bromoaurone **6a**

In conclusion, we have achieved regioselective monobromination of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones using BDMS under mild reaction conditions. In addition, 8-bromoflavones and 7-bromoaurones were also synthesized by bromination with BDMS followed by base catalyzed cyclization using ethanolic KOH solution. The 7-bromoaurone and 8-bromoflavone can be utilized for the synthesis of vitexin, bisflavones, and aureusidin.

PART A

CHAPTER 2

Regioselective Monobromination of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones and Synthesis of 8-bromoflavones and 7-bromoaurones

Experimental Section

Experimental

Preparation of bromodimethylsulfonium bromide (BDMS)

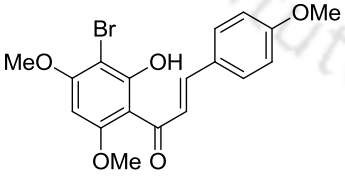
Dimethyl sulfide (1.83 mL, 25 mmol) was dissolved in 5 mL of dry dichloromethane in a 150 mL standard joint conical flask. Bromine (25 mmol, 1.3 mL) dissolved in 5 mL of dry dichloromethane was added slowly to the above solution at ice-bath temperature over a period of 5 min. During the addition, light orange crystals of bromodimethylsulfonium bromide begin to separate out. After the complete addition of bromine, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vacuum. 4.3 g of the yellow crystalline product was obtained in 77% yield, m.p. 80 ^{0}C.

General method for the regioselective synthesis of (*E*)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones (2)

To a well stirred solution of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones (0.5 mmol) in 3 mL of DCM was added BDMS (0.167 g, 0.75 mmol) at room temperature. The reaction was complete instantaneously and the excess bromine was quenched with 10% sodium metabisulphite solution. The reaction mixture was extracted with DCM (2x15 mL), washed with water, and dried over anhydrous sodium sulfate. After removal of solvent in rotary evaporator, the pure product was obtained as yellow solid.

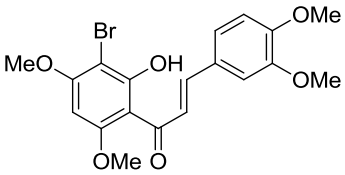
Spectral data of (*E*)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2 propen-1-ones:

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one ***(2a)*****:**



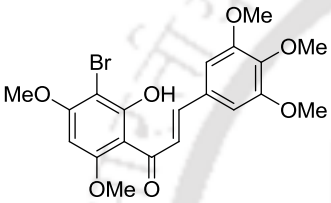
Yellow solid, mp 178-179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.99 (s, 3H) , 4.00 (s, 3H), 6.08 (s, 1H), 6.94 (d, 2H, *J* = 8.8 Hz), 7.57 (d, 2H, *J* = 8.8 Hz), 7.76 (d, 1H, *J* = 15.6 Hz), 7.84 (d, 1H, *J* = 15.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.6, 56.3, 56.5, 87.3, 92.1, 107.1, 114.6 (2C), 124.7, 128.2, 130.5 (2C), 143.7, 161.8, 161.9, 162.4, 163.4, 192.8; **IR** (KBr, cm^{-1}): 1622, 1551, 1219, 1171; **Anal. Calcd** for $C_{18}H_{17}BrO_5$: C, 54.98; H, 4.36; found C, 54.92; H, 4.27%.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one ***(2b)*****:**



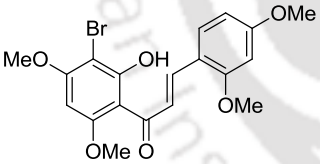
Yellow solid, mp 200-201 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.93 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.05 (s, 1H), 6.90 (d, 1H, *J* = 8.4 Hz), 7.11 (d, 1H, *J* = 2.0 Hz), 7.21 (dd, 1H, *J* = 1.6, 8.0 Hz), 7.73 (d, 1H, *J* = 15.2 Hz), 7.80 (d, 1H, *J* = 15.6 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 55.5, 55.7, 56.6, 56.8, 88.9, 90.6, 106.7, 110.9, 111.8, 123.2, 124.5, 127.5, 143.9, 149.0, 151.4, 161.3, 161.5, 161.9, 192.3; **IR** (KBr, cm^{-1}): 1627, 1557, 1518, 1261, 1218; **Anal. Calcd** for $C_{19}H_{19}BrO_6$: C, 53.92; H, 4.52; found C, 53.85; H, 4.43%.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one ***(2c)*****:**



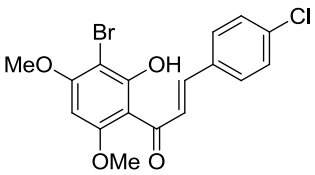
Yellow solid, mp 213°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.92 (s, 6H), 3.99 (s, 6H), 6.07 (s, 1H), 6.84 (s, 2H), 7.75 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d6): δ 56.3, 56.5, 61.2, 87.3, 92.1, 105.9, 107.0, 126.4, 131.0, 140.5, 143.6, 153.6, 162.1, 162.4, 163.4, 192.6; **IR** (KBr, cm^{-1}): 1633, 1580, 1283, 1223, 1127; **Anal. Calcd** for $C_{20}H_{21}BrO_7$: C, 52.99; H, 4.67; found C, 52.91; H, 4.59.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one ***(2d)*****:**



Yellow solid, mp 203-204°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.90 (s, 3H) , 3.98 (s, 6H), 6.06 (s, 1H), 6.47 (d, 1H, *J* = 2.4 Hz), 6.53 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.54 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 15.6 Hz), 8.14 (d, 1H, *J* = 15.6 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 55.2, 55.9, 56.3, 89.7, 92.4, 104.5, 106.5, 107.3, 121.4, 123.3 128.4, 142.5 145.2, 150.7, 160.9, 162.3, 163.9, 189.7; **IR** (KBr, cm^{-1}): 1618, 1550, 1216; **Anal. Calcd** for $C_{19}H_{19}BrO_6$: C, 53.92; H, 4.52; found C, 53.84; H, 4.41%.

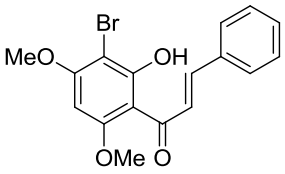
(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(4-chlorophenyl)prop-2-en-1-one ***(2e)*****:**



Yellow solid, mp 229-230 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 3.98 (s, 3H), 6.05 (s, 1H), 7.37 (d, 2H, *J* = 8.0 Hz), 7.51 (d, 2H, *J* = 8.4 Hz), 7.74 (d, 1H, *J* = 15.6 Hz), 7.80 (d, 1H, *J* = 15.2 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 55.7, 56.3, 89.7, 95.4, 104.5, 121.4, 127.8, 128.8, 133.3, 133.5, 145.2, 162.1, 162.9, 166.3, 191.5; **IR** (KBr,

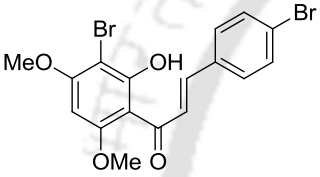
cm^{-1}): 1631, 1553, 1218, 1127; **Anal. Calcd** for $C_{17}H_{14}BrClO_4$: C, 51.35; H, 3.55; found C, 51.23; H, 3.47%.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-phenyl prop-2-en-1-one ***(2f)*****:**



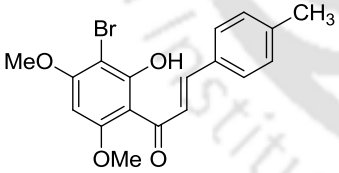
Yellow solid, mp 173-174 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 3.99 (s, 3H), 6.06 (s, 1H), 7.39-7.40 (m, 3H, *J* = 2 Hz, 5.2 Hz), 7.58-7.60 (m, 2H, *J* = 2.0, 5.6 Hz), 7.80 (d, 1H, *J* = 15.6 Hz), 7.85 (d, 1H, *J* = 15.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 57.0, 57.1, 89.3, 91.4, 106.9, 127.2, 128.9, 129.5, 132.1, 133.9, 143.5, 161.5, 162.1, 162.4, 192.8; **IR** (KBr, cm^{-1}): 1628, 1558, 1423, 1330, 1213, 1126; **Anal. Calcd** for $C_{17}H_{15}BrO_4$: C, 56.22; H, 4.16; found C, 56.14; H, 4.08%.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(4-bromophenyl)prop-2-en-1-one ***(2g)*****:**



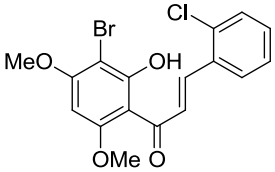
Yellow solid, mp 235-236 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 3.98 (s, 3H), 6.05 (s, 1H), 7.44 (d, 2H, *J* = 6.4 Hz), 7.52 (dd, 2H, *J* = 2.0, 8.4 Hz), 7.72 (d,1H, *J* = 15.6 Hz), 7.81(d,1H, *J* = 15.6 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 55.2, 55.9, 88.7, 94.4, 105.7, 120.1, 122.3, 128.6, 131.6, 134.2, 144.5, 162.6, 163.9, 165.3, 189.7; **IR** (KBr, cm^{-1}): 1630, 1553, 1418, 1218, 1127; **Anal. Calcd** for $C_{17}H_{14}Br_2O_4$: C, 46.18; H, 3.19; found C, 46.11; H, 3.09%.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-p-tolyl prop-2-en-1-one ***(2h)*****:**



Yellow solid, mp 192-193 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 6.07 (s, 1H), 7.22 (d, 2H, *J* = 8.0 Hz), 7.51 (d, 2H, *J* = 8.0 Hz), 7.83 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.7, 56.3, 56.5, 87.3, 92.1, 107.0, 126.0, 127.7, 128.9, 132.7, 141.1, 143.7, 162.0, 162.4, 163.4, 193.0; **IR** (KBr, cm^{-1}): 1629, 1556, 1412, 1216, 1130; **Anal. Calcd** for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54. $C_{18}H_{17}BrO_4$: C, 53.92; H, 4.52; found C, 57.23; H, 4.45%.

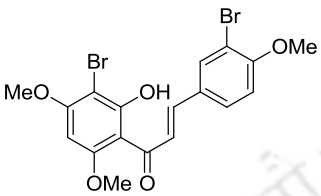
(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(2-chlorophenyl)prop-2-en-1-one ***(2i)*****:**



Yellow solid, mp 211-212 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.99 (s, 6H), 6.06 (s, 1H), 7.30-7.32 (m, 2H), 7.43-7.44 (m, 1H), 7.68-7.70 (m, 1H), 7.83 (d, 1H, *J* = 15.6 Hz), 8.17 (d, 1H, *J* = 15.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$:DMSO-d6): δ 55.2, 55.3, 86.8, 89.9, 97.3, 126.2,

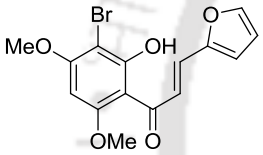
126.7, 128.2, 128.9, 130.1, 131.7, 133.6, 136.8, 147.2, 161.0, 161.3, 191.0; **IR** (KBr, cm^{-1}): 1626, 1587, 1426, 1379, 1279; **Anal. Calcd** for $C_{17}H_{14}BrClO_4$: C, 51.35; H, 3.55; found C, 51.29; H, 3.44%.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(3-bromo-4methoxyphenyl)prop-2-en-1-one ***(2j)*****:**



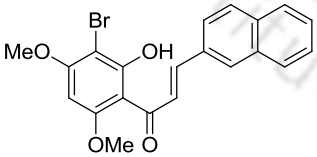
Yellow solid, mp 217-218 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.95 (s, 3H), 3.40 (s, 3H), 4.01 (s, 3H) , 6.07 (s, 1H), 6.92 (d, 1H, *J* = 8.4 Hz), 7.50 (dd, 1H, *J* = 2.0 Hz, 8.8 Hz), 7.73 (s, 2H), 7.83 (d, 1H, *J* = 2.0 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 54.9, 56.6, 56.7, 88.9, 111.3, 113.0, 125.8, 128.9, 129.6, 133.2, 141.7, 157.2, 161.1, 162.0, 192.2; **IR** (KBr, cm^{-1}): 1628, 1552, 1216, 1124; **Anal. Calcd** for $C_{18}H_{16}Br_2O_4$: C, 45.79; H, 3.42; found 45.71; H, 3.33%.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(furan-2-yl)prop-2-en-1-one ***(2k)*****:**



Yellow solid, mp 146-147 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.99 (s, 3H), 4.00 (s, 3H) , 6.07 (s, 1H), 6.52 (dd, 1H, *J* = 2.0 Hz, 3.2 Hz), 6.70 (d, 1H, *J* = 3.2 Hz), 7.53 (d, 1H, *J* = 1.6 Hz), 7.62 (d, 1H, *J* = 15.6 Hz), 7.76 (d, 1H, *J* = 15.2 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 56.9, 57.1, 89.2, 90.6, 106.7, 113.7, 118.1, 123.6, 130.5, 146.9, 151.4, 161.8, 162.1, 162.3, 191.9; **IR** (KBr, cm^{-1}): 1633, 1604, 1424, 1317, 1225, 1136; **Anal. Calcd** for $C_{15}H_{13}BrO_5$: C, 51.01; H, 3.71; found C, 50.95; H, 3.62%.

(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(naphthalen-2-yl)prop-2-en-1-one ***(2l)*****:**



Yellow solid, mp 195-198°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.01 (s, 3H), 4.04 (s, 3H), 6.10 (s, 1H), 7.52-7.54 (m, 2H), 7.74-7.76 (m, 1H), 7.82-7.89 (m, 3H), 7.95-8.03 (m,2H); **^{13}C NMR** (100 MHz, DMSO-d6): δ 55.2, 55.9, 88.6, 91.9, 104.5, 121.4, 123.5, 125.1, 126.4, 127.7, 128.1, 133.2, 133.6, 145.2, 162.6, 163.9, 165.3, 189.7; **IR** (KBr, cm^{-1}): 1630, 1553, 1418, 1218, 1127; **Anal. Calcd** for $C_{21}H_{17}BrO_4$: C, 61.03; H, 4.15; found C, 60.95; H, 4.06%.

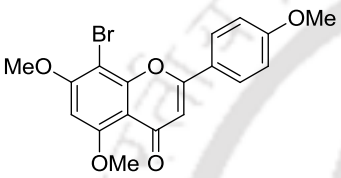
Procedure for the synthesis of 8- bromoflavones (5)

To a well stirred solution of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-one (0.5 mmol) in 5 mL of DCM was added BDMS (0.444 g, 2 mmol) at room temperature. The

reaction was complete within 10 min and it was quenched by adding 10% sodium metabisulphite solution. The reaction mixture was extracted with DCM (2×15 mL), washed with water, and dried over anhydrous sodium sulfate to obtain the tribromo derivatives **3**. The pure tribromide was obtained after recrystallization in DCM-hexane. Then the tribrominated compounds **3** on treatment with 0.2 M KOH (0.5 mL) in EtOH/H_2O (4:1) yielded 8-bromoflavones after usual work-up procedure.

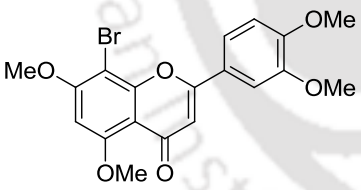
Spectral data of 8-bromoflavones:

8-bromo-5,7-dimethoxy-2-(4-methoxyphenyl)-4H-chromenen-4-one ***(5a)*****:**



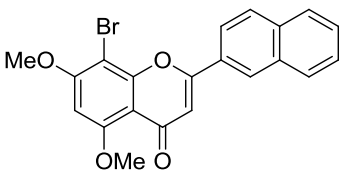
Pale yellow solid, mp 237-239 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.03 (s, 3H) , 4.05 (s, 3H), 6.46 (s, 1H), 6.64 (s, 1H), 7.03 (d, 2H, *J* = 8.8 Hz), 7.96 (d, 2H, *J* = 9.2 Hz); **^{13}C NMR** (100 MHz, DMSO-d6/$CDCl_3$): δ 55.4, 56.4, 56.8, 92.1, 93.0, 106.2, 110.9, 114.5 (2C), 118.1, 122.8, 127.8 (2C), 160.1, 160.3, 162.1, 163.3, 176.4; **IR** (KBr, cm^{-1}): 1639, 1593, 1341; **Anal. Calcd** for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86; found C, 55.18; H, 3.81%.

8-bromo-5,7-dimethoxy-2-(3,4-dimethoxyphenyl)-4H-chromenen-4-one ***(5b)***:



Pale yellow solid, mp 229–230 °C; **^{1}H NMR** (400 MHz, CDCl3): δ 3.94 (s, 3H), 3.94 (s, 3H) , 3.98 (s, 3H), 3.99 (s, 3H), 6.05 (s, 1H), 6.90 (s, 1H), 7.21 (dd, 1H, *J* = 1.6, 8.0 Hz), 7.73 (d, 1H, *J* = 15.2 Hz), 7.80 (d, 1H, *J* = 15.6 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 56.3, 56.9, 57.2, 87.3, 92.7, 103.5, 104.8, 113.6, 117.2, 120.7, 124.7, 149.0, 149.7, 155.0, 160.9, 162.7, 163.6, 185.2; **IR** (KBr, cm^{-1}): 1610, 1516, 1219, 1111; **Anal. Calcd** for $C_{19}H_{17}BrO_6$: C, 54.17; H, 4.07%; found C, 54.11; H, 4.01%.

8-bromo-5,7-dimethoxy-2-(naphthalen-2-yl)-4H-chromenen-4-one ***(5l)*****:**



Pale yellow solid, mp 315-316 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.04 (s, 3H), 4.06 (s, 3H) , 6.48 (s, 1H), 6.86 (s, 1H), 7.57-7.59 (m, 2H), 7.96-8.01 (m, 3H), 8.60 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d6): δ 55.7, 55.9, 97.3, 98.7, 104.5, 105.8, 122.5, 124.1, 125.0, 125.4, 125.7, 127.1, 129.2, 131.2, 131.6, 133.5, 155.8, 161.9, 162.7, 164.8, 181.2; **IR**

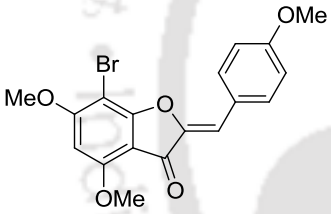
(KBr, cm^{-1}): 1641, 1592, 1324, 1212; **Anal. Calcd** for $C_{21}H_{15}BrO_4$: C, 61.33; H, 3.68; found C, 61.27; H, 3.61%.

Procedure for the synthesis of 7-bromoaurones (6)

To a well stirred solution of (*E*)-1-(2'-hydroxy-4',6'- dimethoxyphenyl)-3-aryl-2-propen-1-one (0.5 mmol) in DCM/MeOH (5:2), BDMS (0.444 g, 2 mmol) was added at room temperature. The reaction was over within 10 min and it was quenched by adding 10% sodium metabisulfite solution. The reaction mixture was extracted with DCM (2×15 mL), washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated in rotary evaporator and the crude product recrystallized in DCM-hexane mixture to get the pure dibrominated product **4**. The dibrominated product on treatment with 0.2 M KOH (0.5 mL) in EtOH/H_2O (4:1) afforded 7-bromoaurones.

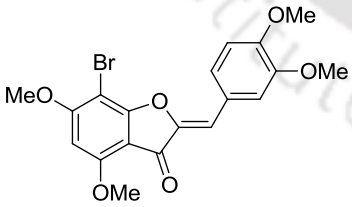
Spectral data of 7-bromoaurones:

(Z)-2-(4-methoxybenzylidene)-7-bromo-4,6-dimethoxybenzofuran-3(2H)-one ***(6a)*****:**



Pale yellow solid, mp 252-254°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.05 (s, 6H) , 6.21 (s, 1H), 6.84 (s, 1H), 7.01 (d, 2H, *J* = 8.4 Hz), 7.92 (d, 2H, *J* = 8.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.6, 56.7, 57.2, 85.4, 90.8, 106.2, 112.5, 114.7 (2C), 125.2, 133.5 (2C), 146.6, 159.0, 161.1, 164.2, 164.8, 180.6; **IR** (KBr, cm^{-1}): 1598, 1513, 1173, 1102; **Anal. Calcd** for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86; found C, 55.19; H, 3.78%.

(Z)-2-(3,4-dimethoxybenzylidene)-7-bromo-4,6-dimethoxybenzofuran-3(2H)-one ***(6b)*****:**



Pale yellow solid, mp 217-218 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 4.01 (s, 9H) , 6.18 (s, 1H), 6.80 (s, 1H), 6.90 (d, 1H, *J* = 8.4 Hz), 7.31 (dd, 1H, *J* = 1.6, 8.4 Hz), 7.81 (d, 1H, *J* = 1.6 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 55.5, 55.7, 56.6, 56.8, 88.9, 90.6, 106.7, 110.9, 111.8, 123.2, 124.5, 127.5, 143.9, 149.0, 151.4, 161.3, 161.5, 161.9, 192.3; **IR** (KBr, cm^{-1}): 1609, 1517, 1247, 1111; **Anal. Calcd** for $C_{19}H_{17}BrO_6$: C, 54.17; H, 4.07; found C, 54.11; H, 4.01%.

Crystallographic Description

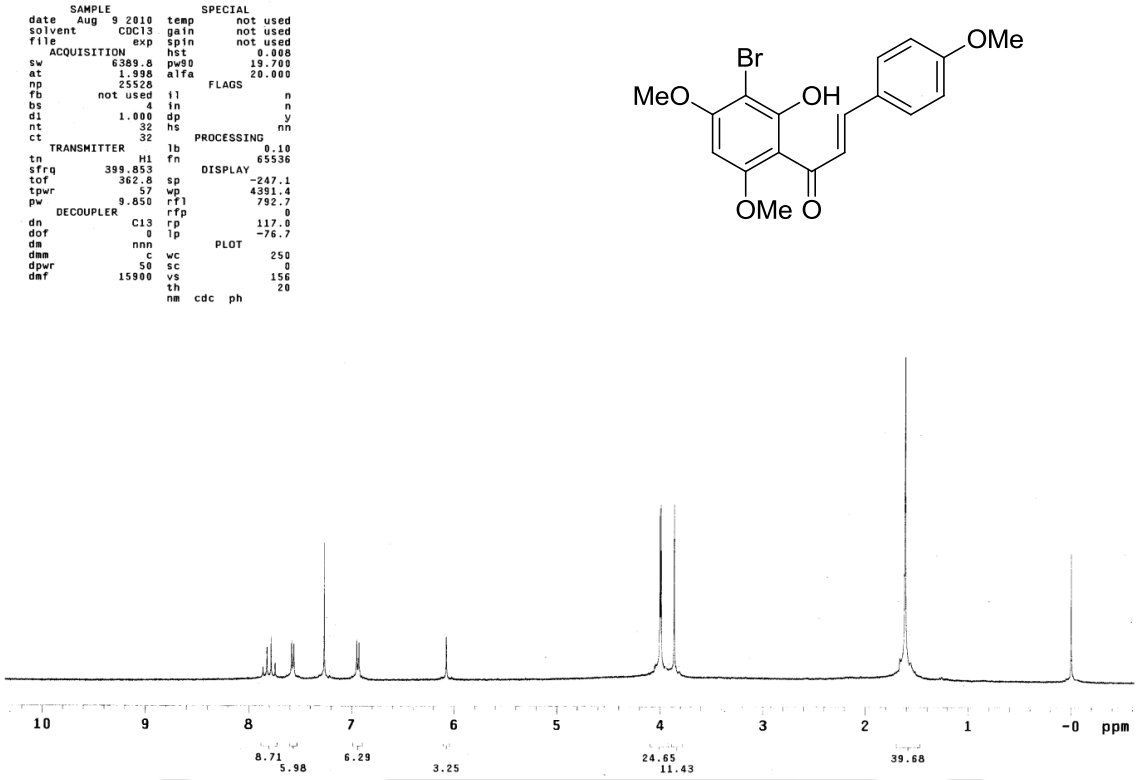
Complete crystallographic data of compounds **2b**, **5a** and **6a** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication, CCDC no. 810812, 810814 and 810813, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 3. Crystal data and structure refinement for compounds **2b**, **5a** and **6a** .

Parameters	**Compound 2b**	**Compound 5a**	**Compound 6a**
Identification code	2b	5a	6a
Empirical formula	C19 H19 Br O6	C18 H15 Br O5	C18 H15 Br O5
Formula weight	423.24	391.21	391.20
Temperature	293(2) K	296(2) K	296(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Triclinic	Triclinic
Space group	P -1	P -1	P -1
Unit cell dimensions			
a	8.5294(6) Å	9.0893(3) Å	9.2495(3) Å
b	10.2914(6) Å	9.3742(3) Å	9.8572(6) Å
c	21.7464(15) Å	10.9307(4) Å	10.3761(3) Å
α	95.692º(4)	78.409º(2)	106.161º(2)
β	94.174º(4)	67.077º(2)	109.684º(2)
γ	105.428º(3)	69.942º(2)	99.749º(2)
Volume	1821.2(2) $Å^3$	803.33(5) $Å^3$	818.55(6) $Å^3$
Z	4	**2**	**2**
Density (calculated)	1.544 g/cm^3	1.617 g/cm^3	1.587 g/cm^3
Absorption coefficient	2.290 mm^{-1}	2.584 mm^{-1}	2.536 mm^{-1}
F(000)	864.0	396.0	396.0
Theta range for data collection	2.03 to 21.45 º	2.03 to 24.99 º	2.24 to 28.31 º
Index ranges	-10<=h<= 11, -11<=k<=13, -29<=l<=28	-10<=h<= 10, -11<=k<=11, -12<=l<=11	-12<=h<=11, -12<=k<=10, -12<=l<=13
Reflections collected	21347	7933	6817
Independent reflections	9125	2642	4087
Completeness to θº	100% (θ = 28.37º)	98% (θ = 24.99º)	100% (θ =28.31º)
Refinement	Full-matrix least-	Full-matrix least-	Full-matrix least-

method	squares on F2	squares on F2	squares on F2
Data / restraints / parameters	9125 / 0 / 479	2642 / 7 / 220	4087 / 0 / 220
Goodness-of-fit on F2	1.026	0.961	1.006
Final R indices [>2sigma(I)]	R_{obs} = 0.0469, wR_{obs} = 0.0991	R_{obs} = 0.0583, wR_{obs} = 0.1756	R_{obs} = 0.0397, wR_{obs} = 0.0911
R indices (all data)	R_{all} = 0.1071, wR_{all} = 0.1230	R_{all} = 0.0686, wR_{all} = 0.1901	R_{all} = 0.0650, wR_{all} = 0.0977
Largest diff. peak and hole	0.794 and -0.578 e.Å^{-3}	1.937 and -1.170 e.Å^{-3}	0.347 and -0.513 e.Å^{-3}

^{1}H NMR (400 MHz, $CDCl_3$): *(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-one* ***(2a)***



^{13}C NMR (100 MHz, $CDCl_3$): *(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-one* ***(2a)***

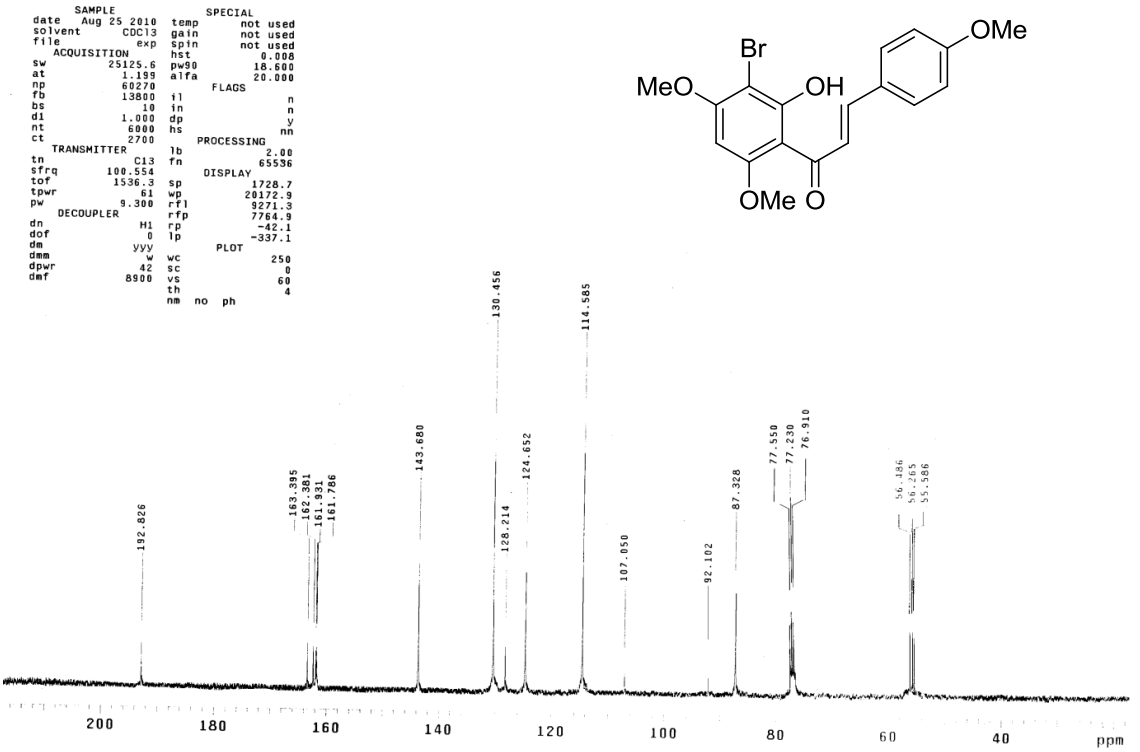
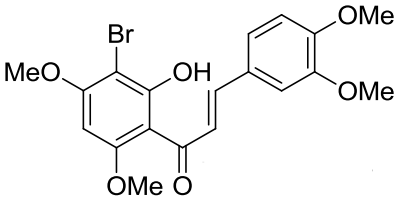
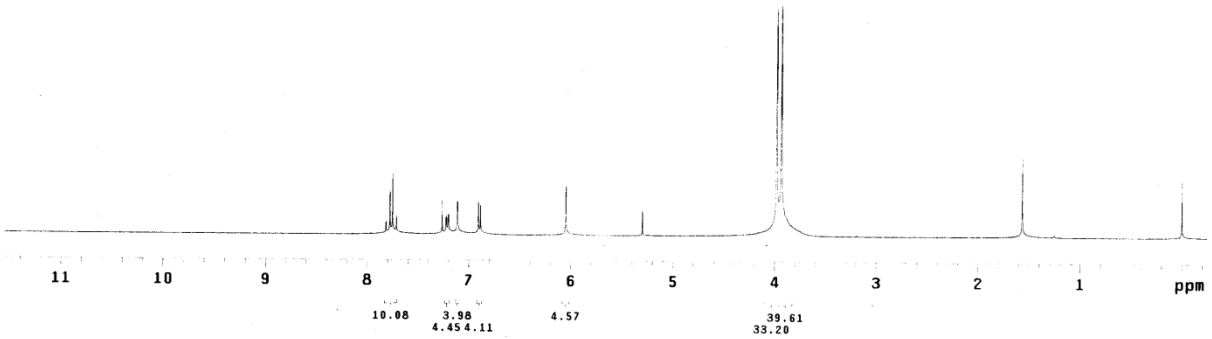


Figure 21

^{1}H NMR (400 MHz, $CDCl_3$): *(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-one* ***(2b)***

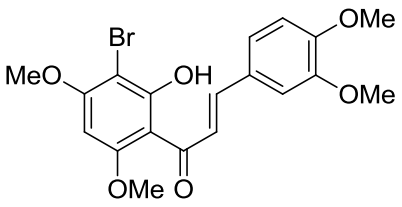
```
      SAMPLE                 SPECIAL
date    Aug 24 2010   temp       not used
solvent       CDCl3   gain       not used
file            exp   spin       not used
   ACQUISITION        hst          0.008
sw          6389.8    pw90        19.700
at            1.998   alfa        20.000
np            25528       FLAGS
fb        not used    il                n
bs               4    in                n
d1           1.000    dp                y
nt              32    hs               nn
ct              32       PROCESSING
    TRANSMITTER       lb             0.10
tn               H1   fn            65536
sfrq        399.853       DISPLAY
tof           362.8   sp            -111.3
tpwr             57   wp            4819.6
pw            9.850   rfl            791.3
    DECOUPLER         rfp               0
dn               C13  rp            127.7
dof                0  lp            -88.7
dm               nnn       PLOT
dmm                c   wc              250
dpwr              50   sc                0
dmf            15900   vs               47
                       th               20
                       nm  cdc   ph
```





^{13}C NMR (100 MHz, DMSO-d6)*: (E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-one* ***(2b)***

```
      SAMPLE                 SPECIAL
date    Sep 30 2010   temp       not used
solvent       DMSO    gain       not used
file            exp   spin       not used
   ACQUISITION        hst          0.008
sw         25125.6    pw90        18.600
at            1.199   alfa        20.000
np            60270       FLAGS
fb            13800   il                n
bs               10   in                n
d1            1.000   dp                y
nt             4000   hs               nn
ct              640      PROCESSING
    TRANSMITTER       lb             2.00
tn               C13  fn            65536
sfrq        100.554       DISPLAY
tof           1536.3  sp            -1567.1
tpwr              61  wp            25125.6
pw            9.300   rfl           5538.6
    DECOUPLER         rfp           3971.5
dn               H1   rp              59.4
dof                0  lp            -344.0
dm               yyy       PLOT
dmm                w   wc              250
dpwr              42   sc                0
dmf             8900   vs               32
                       th                3
                       nm  no  ph
```



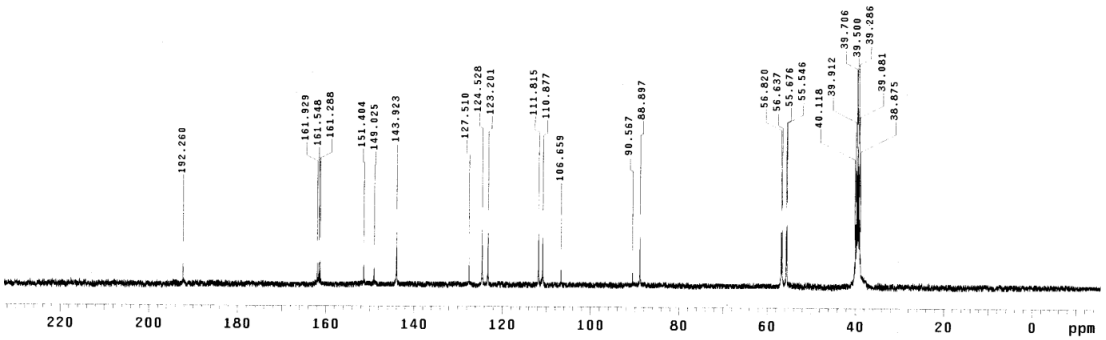
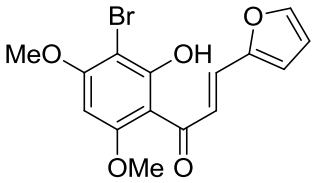
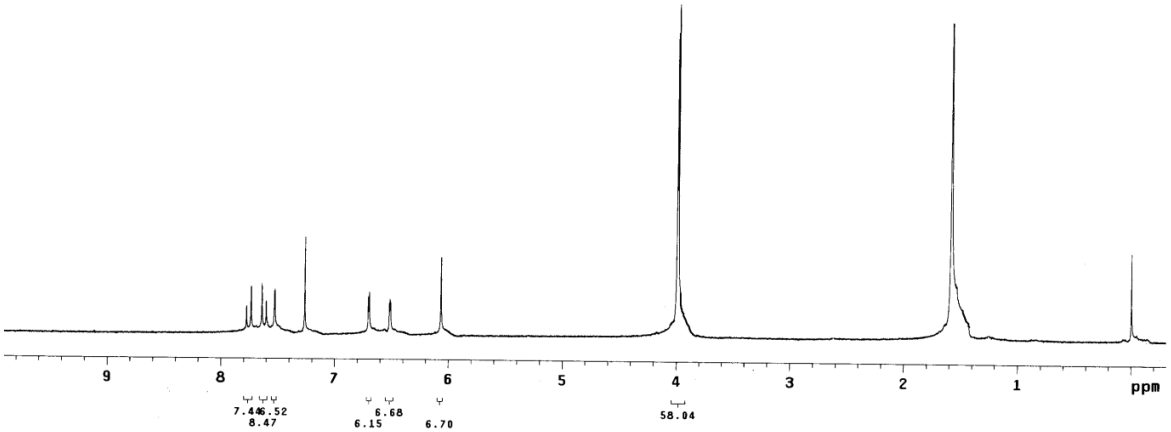


Figure 22

^{1}H NMR (400 MHz, $CDCl_3$): *(E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-one* ***(2k)***

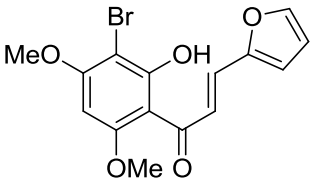
SAMPLE		SPECIAL	
date	May 18 2011	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	6389.8	pw90	18.700
at	1.998	alfa	20.000
np	25528	FLAGS	
fb	not used	il	n
bs	4	in	n
dl	1.000	dp	y
nt	32	hs	nn
ct	32	PROCESSING	
TRANSMITTER		lb	0.10
tn	H1	fn	65536
sfrq	399.853	DISPLAY	
tof	362.8	sp	-122.7
tpwr	57	wp	4156.2
pw	9.850	rfl	794.3
DECOUPLER		rfp	0
dn	C13	rp	120.5
dof	0	lp	-69.0
dm	nnn	PLOT	
dmm	c	wc	250
dpwr	50	sc	0
dmf	15900	vs	102
		th	14
		nm	cdc ph





^{13}C NMR (100 MHz, DMSO-d6)*: (E)-1-(3'-bromo-2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-one* ***(2k)***

SAMPLE		SPECIAL	
date	May 16 2011	temp	not used
solvent	DMSO	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	25125.6	pw90	18.600
at	1.199	alfa	20.000
np	60270	FLAGS	
fb	13800	il	n
bs	10	in	n
dl	1.000	dp	y
nt	5000	hs	nn
ct	1390	PROCESSING	
TRANSMITTER		lb	2.00
tn	C13	fn	65536
sfrq	100.554	DISPLAY	
tof	1536.3	sp	2095.1
tpwr	61	wp	18918.4
pw	9.300	rfl	5507.1
DECOUPLER		rfp	3971.5
dn	H1	rp	58.2
dof	0	lp	-362.5
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	42	sc	0
dmf	8900	vs	57
		th	2
		nm	no ph



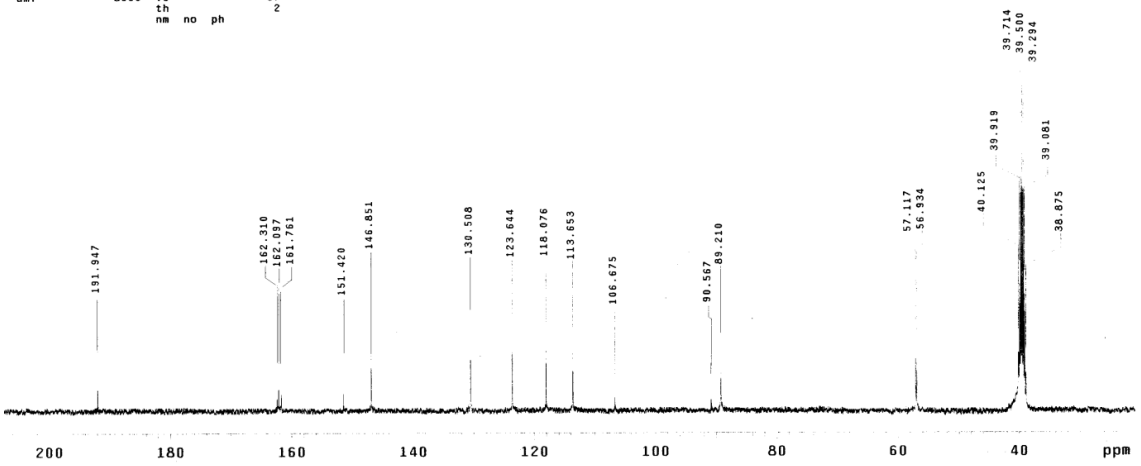
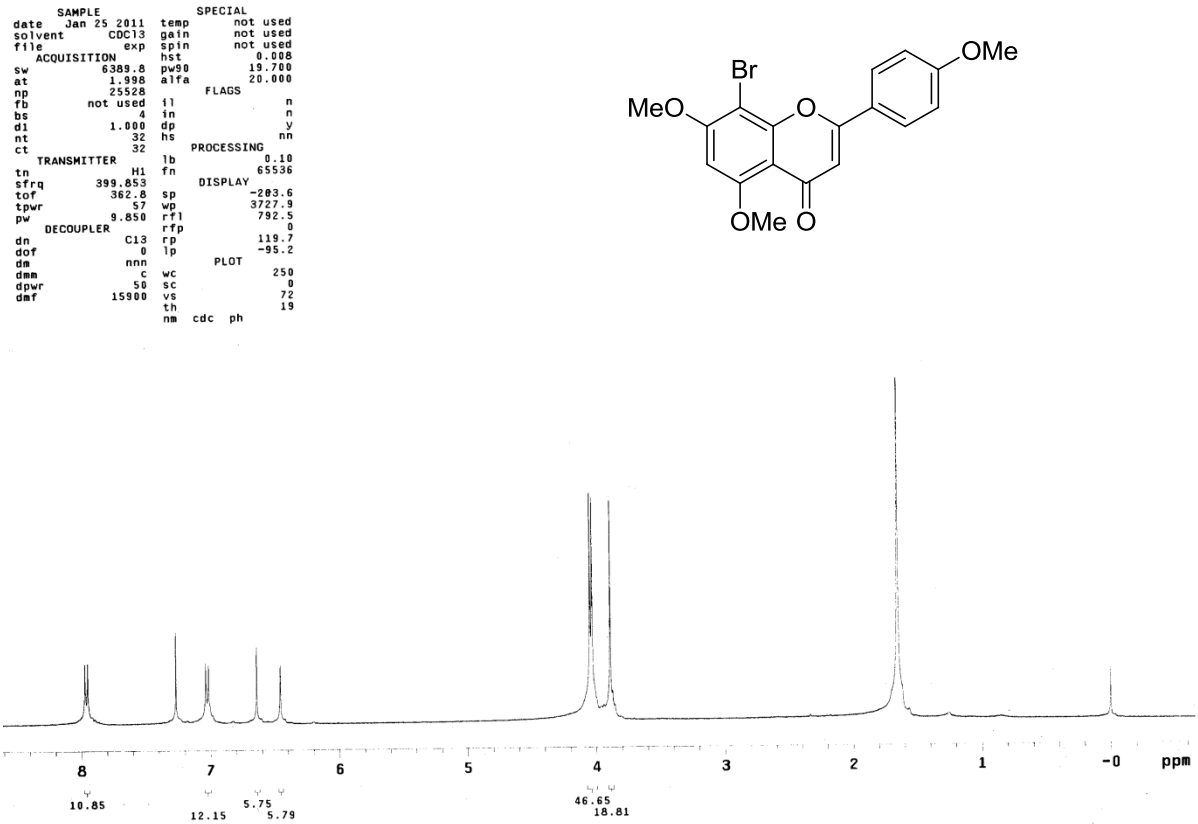


Figure 23

^{1}H NMR (400 MHz, $CDCl_3$): *8-bromoflavones* ***(5a)***



^{13}C NMR (100 MHz, DMSO-d6/$CDCl_3$): *8-bromoflavones* ***(5a)***

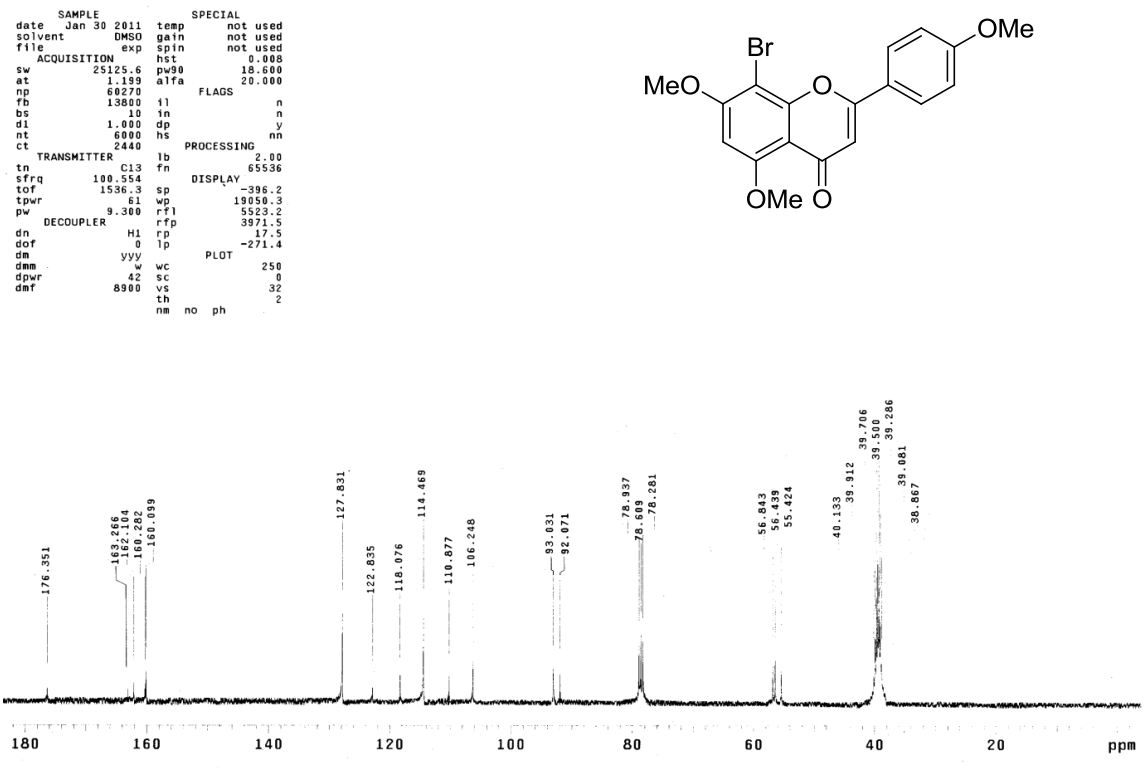
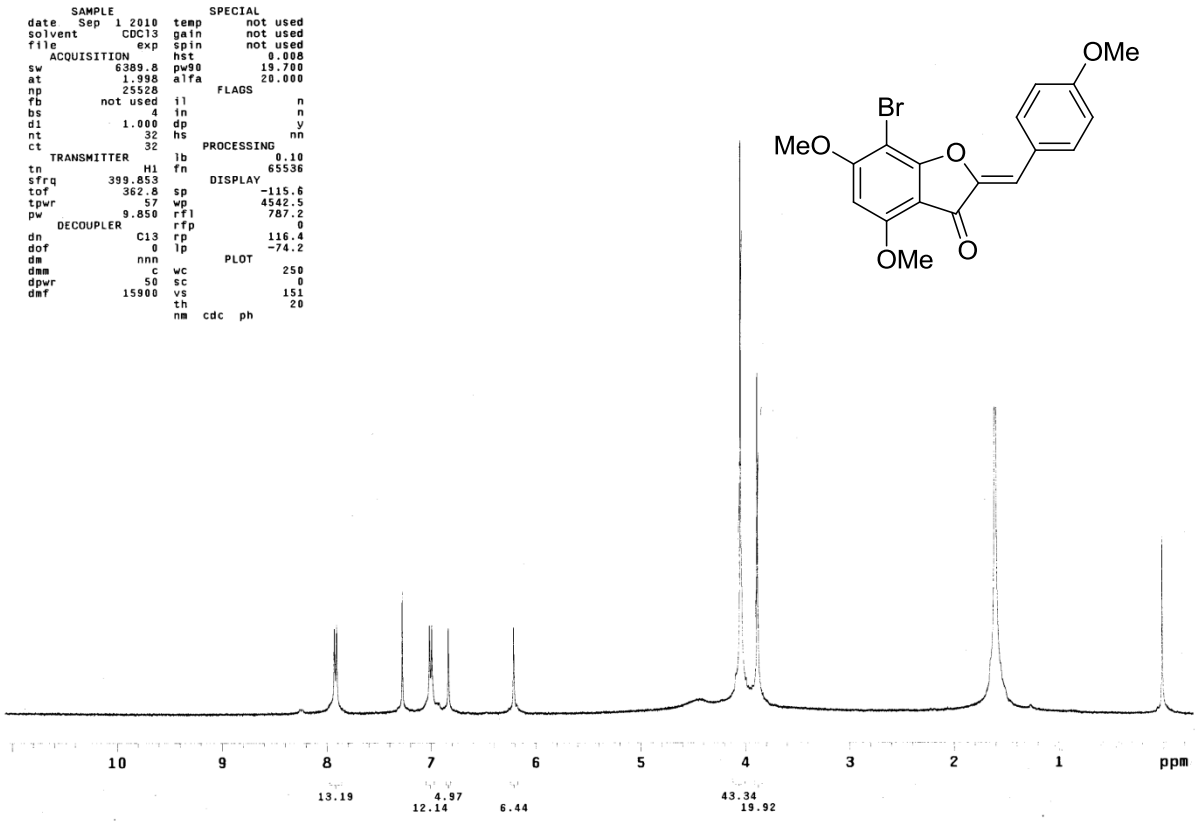


Figure 24

^{1}H NMR (400 MHz, $CDCl_3$): *7-bromoaurones* ***(6a)***



^{13}C NMR (100 MHz, $CDCl_3$): *7-bromoaurones* ***(6a)***

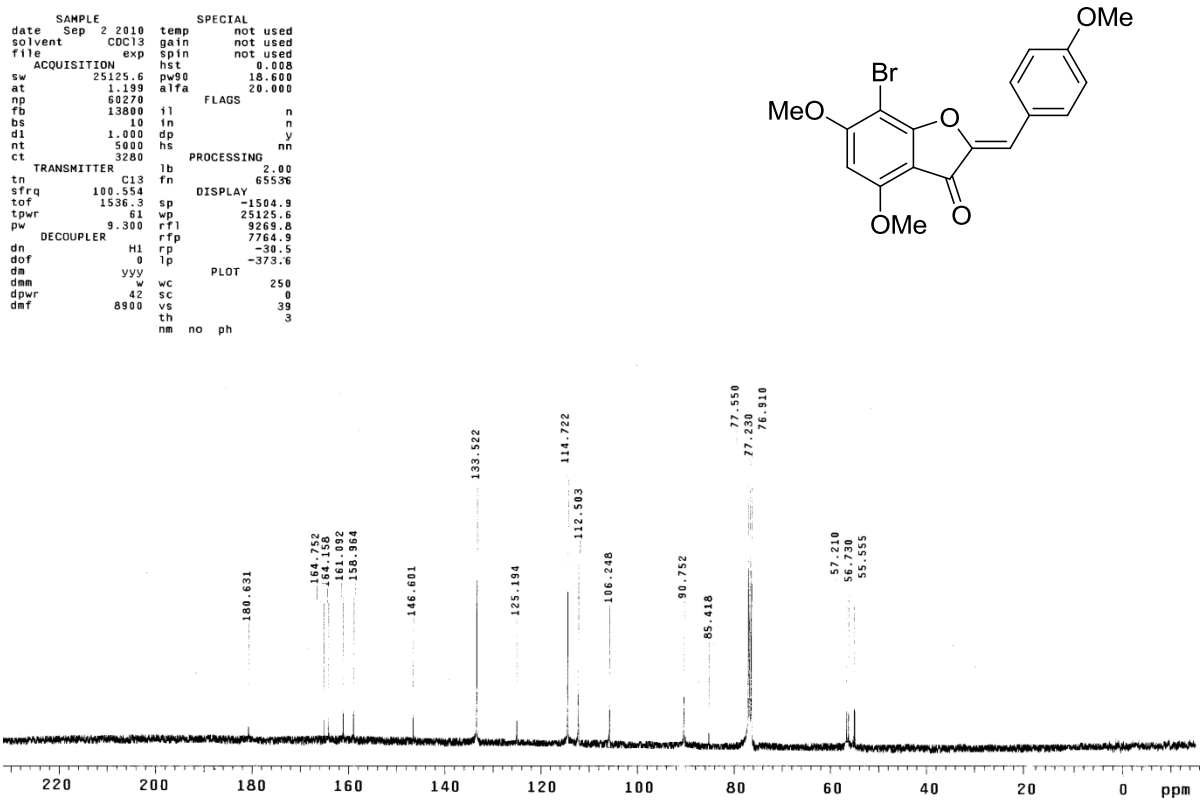


Figure 25

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PART B

CHAPTER 1

Brief Review on Exploration of Tandem Knoevenagel-Michael Reaction through Multi-component Reactions (MCRs) in Organic Synthesis

Introduction

In recent times due to increasing economic and ecological pressure in society, new concepts and methodologies of organic synthesis which are environmentally benign and acceptable are in great demand. Among the various synthetic strategies, multicomponent reaction (MCR)[1] is one of the most well-designed approaches to achieve complex heterocyclic molecules and they have gained considerable attention nowadays among the synthetic organic chemists by taking into account the criterion of Green and Sustainable Chemistry. Multicomponent Reaction (MCR) chemistry applied to the synthesis of heterocycles with all its variations and extensions has undergone a massive and meaningful upturn. Seeds sown in the last century have grown enormously and provided a plurality of novel reactions, new smart strategies as well as forward-looking methods and high product diversity.

Multicomponent Reactions

The conventional procedures in organic synthesis utilize stepwise formation of individual bonds and therefore require many synthetic steps. In contrast to such multistep processes, multicomponent reactions (MCRs) are one pot single step transformations. A multicomponent reaction (or MCR) is defined[2] as "*a reaction in which three or more starting materials react in a single operation to form a single product where basically all or most of the atoms contribute to the newly formed product*". The reactants can be different molecules or different functional groups in a single compound. Linear total syntheses require significant amounts of time and money to advance starting materials to complex targets. MCRs minimize cost in the form of time and material by generating complex targets in a single convergent step (Figure 26).

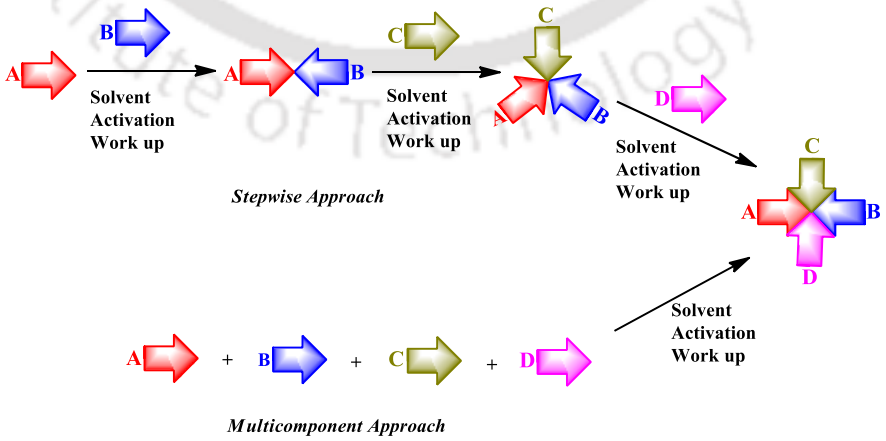
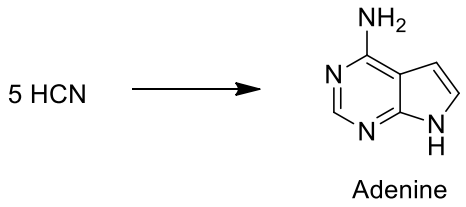


Figure 26. Stepwise vs. Multicomponent Approach

Since the collision of three or more independent molecules is highly unlikely, MCRs typically involve a number of sub reactions. In many cases, most of the intermediate steps are equilibrium reactions and only the final step is an irreversible process, such as a C-C bond formation or a rearrangement. MCRs have attracted the attention of synthetic organic chemists due to their inherent convergence and high productivity in combination with their exploratory and complexity generating power. They have significant advantages over conventional reactions in several aspects, such as (a) reduced cost and reaction time; (b) readily available starting materials; (c) operational simplicitry; (d) variable and high bond forming efficiency; (e) resource effective; (f) atom economy and (g) eco-compatibility compared to the classical approaches that are linear or divergent. The number of possible products from an MCR increases exponentially with the multiplicity of the reaction. Due to all these advantages, MCRs have become very popular in all areas of organic chemistry.

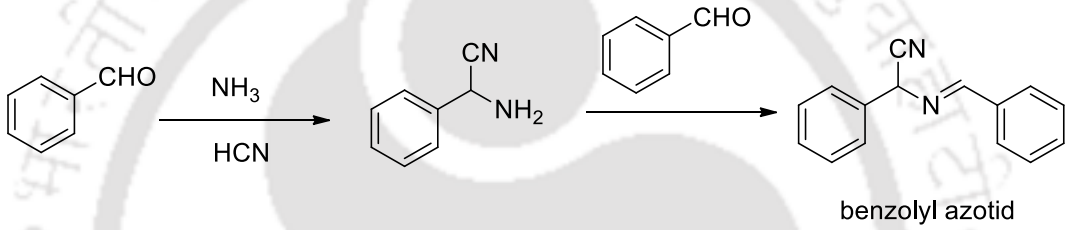
MCRs typically run at mild temperatures and do not require many reagents in excess of the participating substrates. MCRs are an especially attractive synthetic strategy to provide easy and rapid access to large libraries of organic compounds and they serve as starting points for Diversity-Oriented Synthesis (DOS). Coupled with high-throughput library screening, this strategy is an important development in the field of drug discovery in the context of rapid identification and optimization of biologically active compounds. Libraries of small organic molecule are perhaps the most desired class of potential drug candidates. With a small set of starting materials, very large libraries can be built up within a short period of time, which may then be used in pharmaceuticals. Therefore, MCRs have become a rapidly evolving field in the context of drug discovery for the preparation of libraries of molecules in a time- and cost-effective manner, and they are now key tools in industrial and academic research.

Nature played an important role in evolution of MCR and it has made significant contribution to the synthesis of various organic compounds. For example, adenine, one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN in a reaction catalyzed by NH_3 (Scheme 13).[3] Other nucleic acid bases have also been generated in a similar manner involving HCN and H_2O.



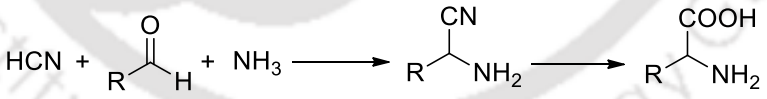
Scheme 13 Prebiotic synthesis of adenine

The history of MCRs can be traced back to the work of Laurent and Gerhardt, who in 1838 from the reaction of bitter almond oil and ammonia isolated a poorly soluble product which they called "benzoyl azotid". In this reaction[4] the cyanohydrin derived from benzaldehyde and hydrocyanic acid reacts with ammonia giving amino benzyl cyanide whose Schiff base with benzaldehyde was called benzoyl azotid (Scheme 14).



Scheme 14

The first modern contribution to the development of multicomponent chemistry by Strecker[5] was the synthesis of α-amino nitrile derivatives which involves condensation of an aldehyde or a ketone with amine and hydrogen cyanide. Subsequently, it was hydrolyzed to the corresponding α-amino acid (Scheme 15).



Scheme 15

The historical overview of MCRs[5-10] is shown in Figure 27

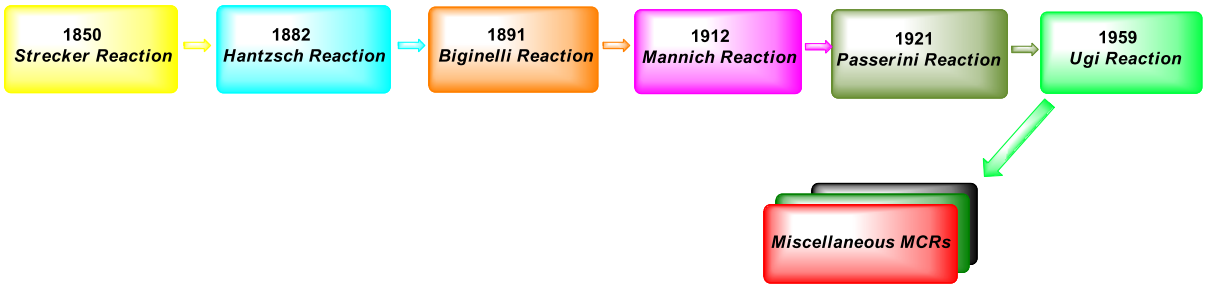


Figure 27

Tandem Reaction

In modern day organic synthesis one of the primary motivating goals is the design of cleaner, more efficient and shortened synthetic routes to carry out complex organic transformations. Developing a protocol using tandem reaction is one way to do this. Tandem reactions are those which occur in succession; they are combinations of two or more reactions whose occurrence is in a specific order, and if they involve sequential addition of reagents the secondary reagents must be integrated into the products.[11] These reactions are one-pot multi-step processes and hence, very powerful tool for the rapid construction of complex organic molecules in a single transformation[12] thereby opening up novel avenues of research and new reaction development. Tandem reactions does not involve the isolation and purification of intermediates, thus it becomes easier to work with sensitive or unstable intermediates. It also reduces the waste generation, hence these reactions can fall under category of Green Chemistry. Tandem reaction also reduces labour and time required to effect a given transformation. Tandem reactions can be classified into three categories[13]

(i). Cascade or domino reactions in which both or all reactions take place without the need for additional reagents or a change in reaction conditions. Everything that is necessary for both reactions is incorporated into the starting materials.

(ii). Consecutive reactions, where the intermediate formed in the first reaction has the necessary functionality, but additional energy must be added in order to overcome the activation barrier.

(iii). Sequential reactions, where the functionality for the second reaction has been created but additional reagents must be added in order to achieve the second reaction.

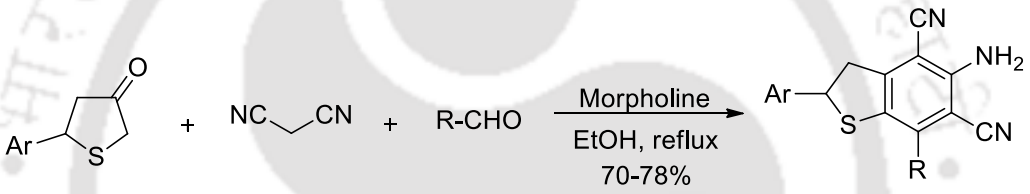
The Tandem reaction has been nicely described for a better understanding in recent books and reviews.[11-13] Among the numerous known organic reactions available to be used in tandem reaction, Knoevenagel and Michael reaction has attracted the attention of synthetic organic chemists in recent years.

Knoevenagel condensation[14] and Michael addition[15] are well known fundamental organic reactions and their combination into a tandem reaction has emerged as a powerful strategy in organic synthesis. Generally, this type of tandem reaction starts from the initial formation of a corresponding carbanion of compound involving an active methylene group (e.g. malononitrile, dimedone, acetylacetone, nitromethane etc.), followed by a nucleophilic addition to a carbonyl compound and the elimination of a water molecule to generate

polarized alkene, which is the Knoevenagel product. The formed Knoevenagel condensation product further serves as a Michael acceptor, which reacts with a nucleophile to complete the cascade reaction. Sometimes the intermediate product can undergo cyclisation to give new heterocyclic compounds.

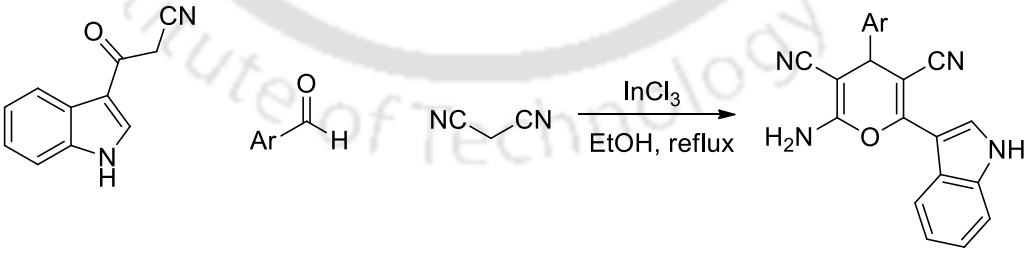
Recent use of tandem Knoevenagel-Michael reaction towards the construction of complex heterocyclic compounds

Kumar *et al*. demonstrated the synthesis of 5-amino-2,7-diaryl-2,3-dihydro-benzo[*b*]thiophene-4,6-dicarbonitriles in good yields through one-pot domino reactions of 5-aryldihydro-3(2*H*)-thiophenones, malononitrile and aromatic aldehydes in the presence of morpholine as catalyst. This transformation presumably involves Knoevenagel-Michael addition–intramolecular cyclization-tautomerization–elimination sequence of reactions (Scheme 16).[16]



Scheme 16

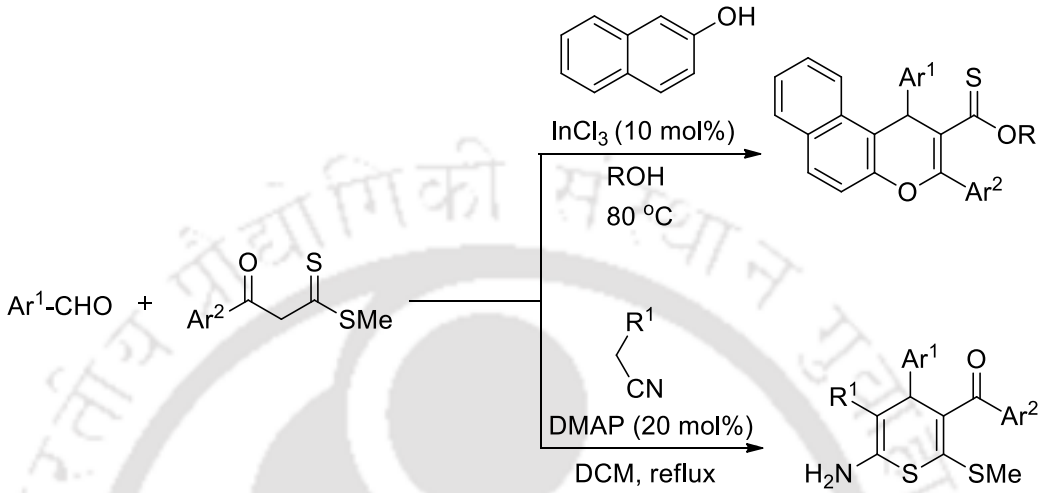
A simple and convenient method for the one-pot three-component synthesis of 3-pyranyl indoles has been accomplished by tandem Knoevenagel-Michael reaction of 3-cyanoacetyl indole, various aromatic aldehydes and malononitrile catalyzed by $InCl_3$ in ethanol in good yields under reflux conditions (Scheme 17).[17]



Scheme 17

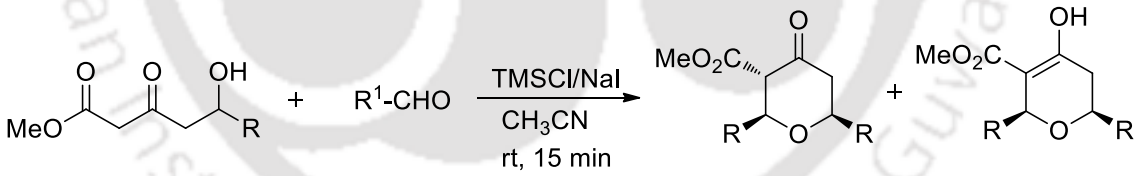
Singh *et al*. described a highly efficient regioselective protocol for the synthesis of 4*H*-benzo[*f*]chromenes by one-pot four-component coupling of aromatic aldehydes, β-naphthol, β-oxodithioesters and primary alcohols in the presence of $InCl_3$. This transformation presumably proceeds via tandem-Knoevenagel-Michael reaction followed by intramolecular

cyclodehydration and transesterification sequence creating four new bonds and one stereocenter in the final product. Later on, the same group used this cascade Knoevenagel condensation/Michael addition/cyclization sequence for the synthesis of highly functionalized 4*H*-thiopyrans (Scheme 18).[18]



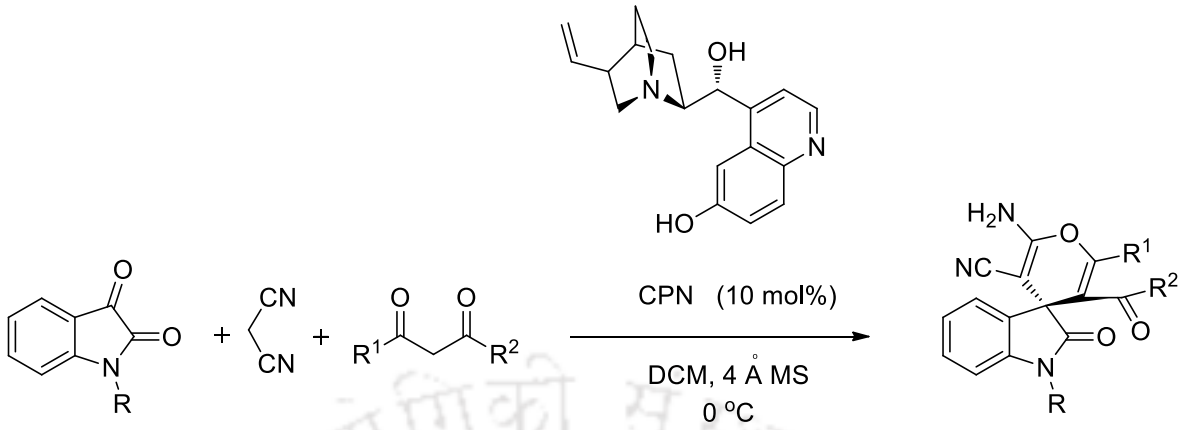
Scheme 18

The synthesis of functionalized tetrahydropyranones has been achieved at room temperature with iodotrimethylsilane by a tandem Knoevenagel condensation of aldehydes with aldol adducts, prepared from β-keto esters and aldehydes, followed by a Michael reaction giving the THP products (Scheme 19).[19]



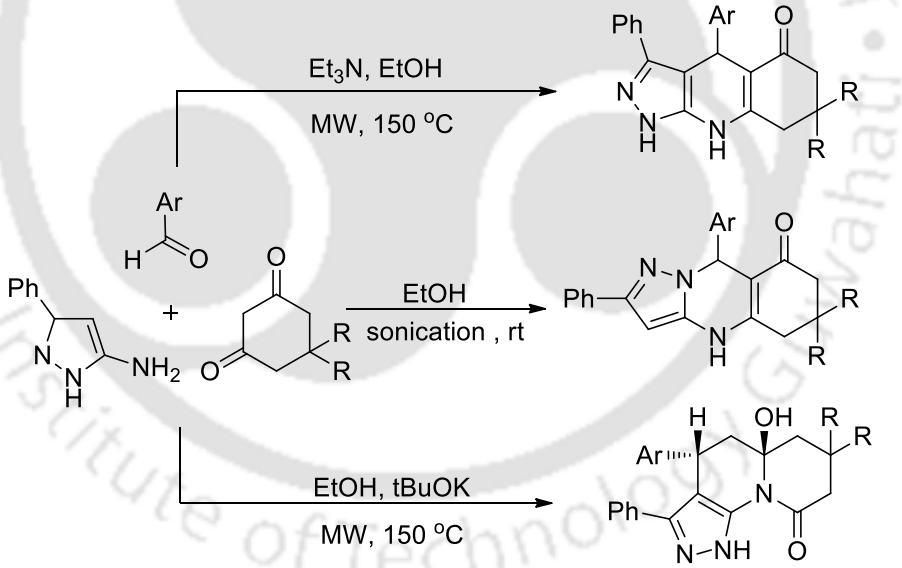
Scheme 19

Yuan *et al.* demonstrated three-component reactions *via* a tandem Knoevenagel/Michael followed by cyclization sequence for the synthesis of wide range of optically active *spiro*-4*H*-pyran-3,3′-oxindoles, with an excellent yield and enantioselectivity from simple and readily available starting materials under mild reaction conditions (Scheme 20).[20]



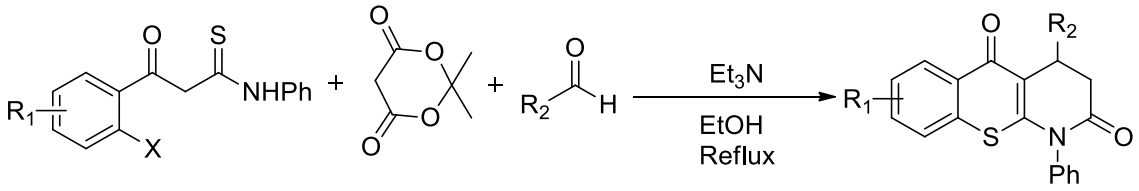
Scheme 20

Chebanov *et al*. described multicomponent protocols using tandem Knoevenagel-michael reaction for the synthesis of 1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-ones, 5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8-ones and 5a-hydroxy-4,5,5a,6,7,8-hexa-hydropyrazolo[4,3-*c*]quinolizin-9-ones starting from 5-amino-3-phenylpyrazole, cyclic 1,3-dicarbonyl compounds and aromatic aldehydes (Scheme 21).[21]



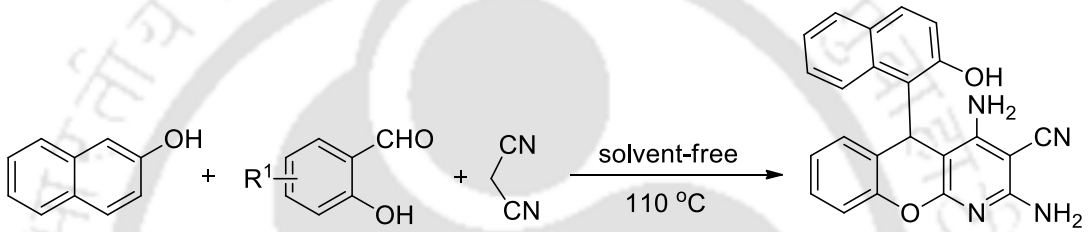
Scheme 21

Tricyclic thiochromeno[2,3-*b*]pyridine derivatives have been successfully synthesized from *ortho*-halo-β-aroylthioamides, Meldrum's acid, and aromatic aldehydes in an unusual one-pot multicomponent tandem reaction (Scheme 22).[22] The reaction presumably proceeds *via* Knoevenagel condensation-Michael addition-cyclocondensation-decarboxylation-rearrangement reaction sequence for the formation of the final product.



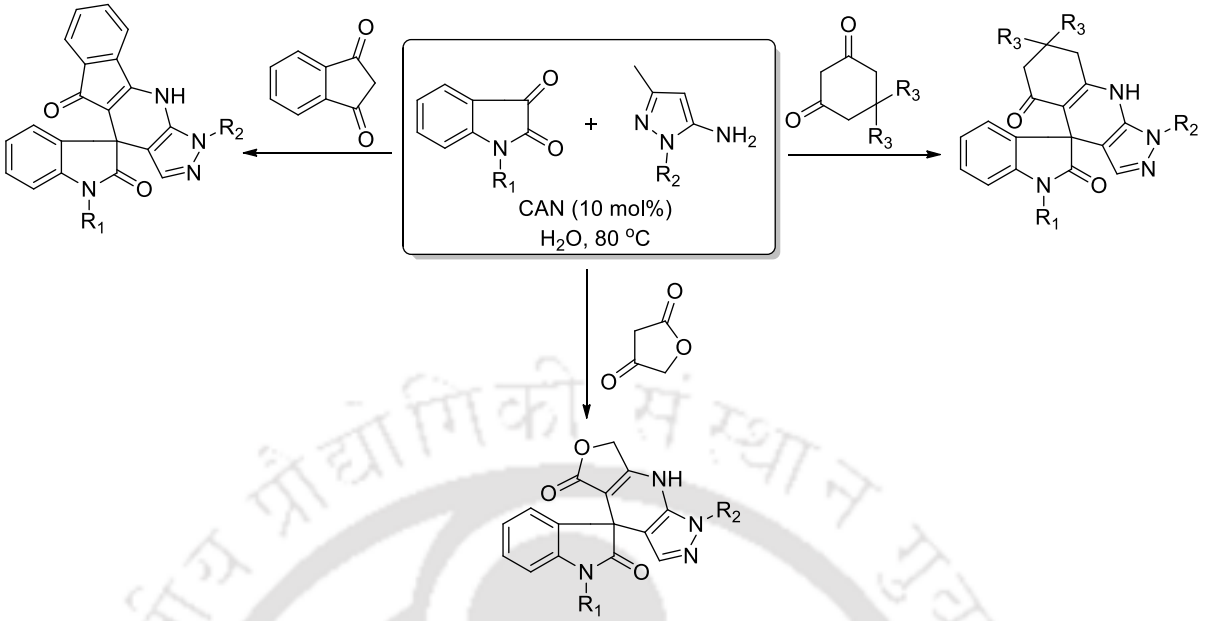
Scheme 22

Olyaei *et al*. described a facile one-pot pseudo four-component synthesis of benzopyrano[2,3-*b*]pyridines (Scheme 23).[23] The reaction is achieved by Michael addition of β-naphthol to iminocoumarin derivatives obtained from Knoevenagel condensation of salicylaldehydes with malononitrile, which is further attacked by another molecule of malononitrile to afford the benzopyrano[2,3-*b*]pyridine products.



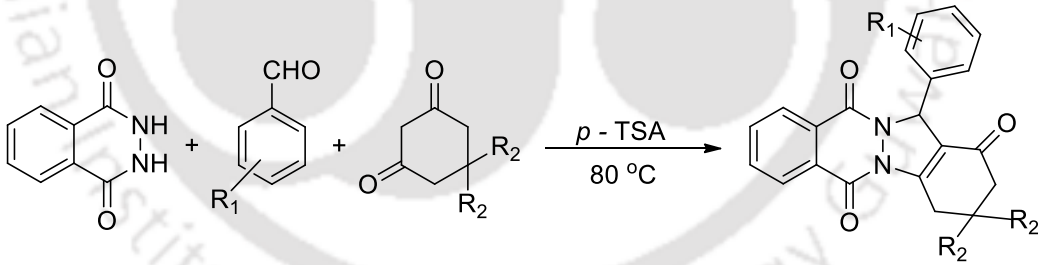
Scheme 23

Shi *et al*. reported CAN-catalyzed synthesis of *spiro*[indoline-3,4′-pyrazolo[3,4 *b*]quinoline]-dione, *spiro*[indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]dione and *spiro*[furo-[3,4-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]dione derivatives *via* three-component reaction of isatin, 5-amino-3-methylpyrazole and 1,3-dicarbonyl compounds in aqueous medium. The protocol involves formation of Knoevenagel adduct from isatin and 5-amino-3-methylpyrazole, which further act as a Michael acceptor and reacts with cyclic 1,3-dicarbonyl compounds to give the *spiro*-products (Scheme 24).[24]



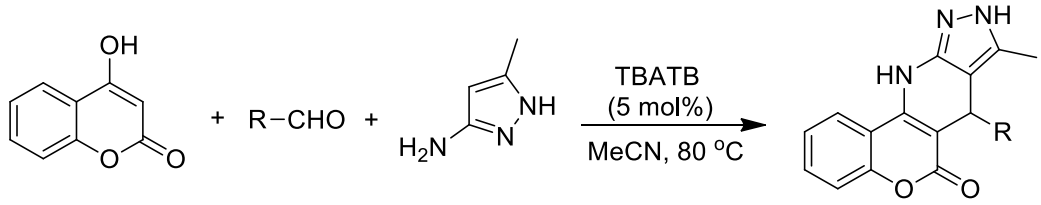
Scheme 24

Bazgir *et al*. demonstrated synthesis of indazolo[2,1-*b*]phthalazine-triones, from three-component condensation reaction of phthalhydrazide, dimedone, and aromatic aldehydes under solvent-free conditions. The procedure involves the initial reaction of dimedone and aldehyde for the formation of Knoevenagel product which reacts with phthalhydrazide *via* Michael reaction to give the final product indazolo[2,1-*b*]phthalazine-trione (Scheme 25).[25]



Scheme 25

Recently Khan *et al*. also reported the synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones through one-pot three-component reaction from 4-hydroxycoumarin, aldehydes, and 3-amino-5-methyl-pyrazole in acetonitrile using 5 mol % TBATB as the catalyst under reflux condition (Scheme 26).[26] The product formation is through tandem Knoevenagel–Michael reaction followed by concomitant cyclization.



Scheme 26

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

PART B

CHAPTER 2

Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones by Using an Efficient and Reusable Catalyst Ferric sulfate

Results and Discussion

Hydrated ferric sulfate [$Fe_2(SO_4)_3 \cdot xH_2O$] has been found to be an effective catalyst for various organic transformations such as tetrahydropyranlations of alcohols,[27] preparation of acylals from aldehydes,[28] 2,3-unsaturated glycosides *via* Ferrier rearrangement,[29] per-*O*-acetylation of sugars,[30] synthesis of tetrahydroquinolines[31] through Povarov reaction and synthesis of 1*H*-pyrazole-4-carbodithioate[32] using MCRs. The unique solubility of the catalyst in ethanol and insolubility in DCM enables its usage as both homogenous and heterogeneous catalyst and is recoverable by DCM after the reaction. As a part of our ongoing research work by employing MCRs to synthesize new molecules,[33] we conceived that $Fe_2(SO_4)_3 \cdot xH_2O$ can be exploited further as a reusable catalyst for the synthesis of heterocycles by employing multicomponent reactions.

The efficient high-throughput synthesis of biologically active organic compounds is one of the most important and challenging endeavors in modern drug discovery. Organic reactions should be fast, neat and clean, and the target products should be easily separable with high purity and good yields. To cover all the above aspects, multicomponent reactions[34] (MCRs) play an important role in combinatorial chemistry because of their ability to synthesize target molecules with greater efficiency, higher atom-economy, structural diversity and complexity in a single step from three or more reactants. These reactions are very effective for synthesizing highly functionalized organic molecules from readily available starting materials.

The synthesis of heterocyclic compounds has gained considerable attention among synthetic organic chemists due to their immense potentiality in pharmaceuticals. Heterocyclic systems are found abundantly in nature as alkaloids, flavonoids and isoflavonoids[35] and they are considered to be essential to life. Among various nitrogen containing heterocycles, phthalazine skeleton is present in many naturally occurring compounds and they exhibit interesting pharmacological properties (Figure 27). The compounds having fused phthalazines possess many biological activities such as anticonvulsant,[36] cardiotonic,[37] vasorelaxant,[38] antimicrobial,[39] antifungal,[40] anticancer,[41] and antiinflammatory[42] activities**.** They are also highly potent inhibitors of vascular endothelial growth factor receptor II (VEGFR-2).[43-45] Moreover, these compounds might be useful materials for luminescence or fluorescence studies.[46] The synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives have been reported involving one-pot condensation of phthalhydrazide, aromatic aldehydes and 1,3-

diketones using numerous catalysts.[47,48] Though all these protocols are quite useful, still there is a need to develop a new methodology using an inexpensive and reusable catalyst.

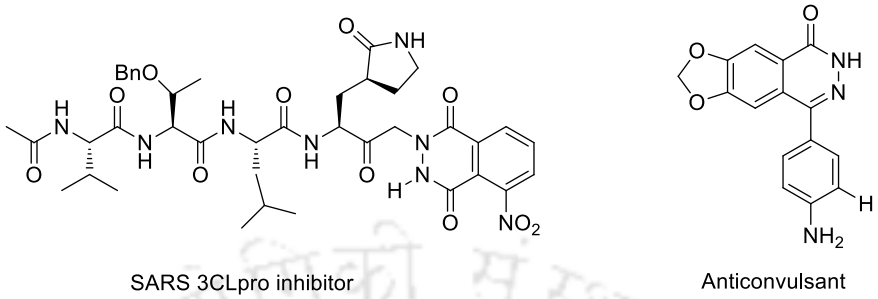
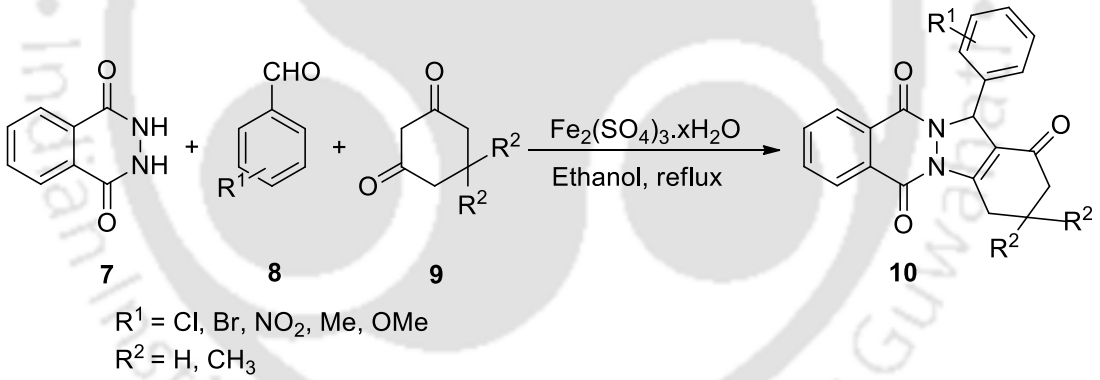


Figure 27

Results and Discussion

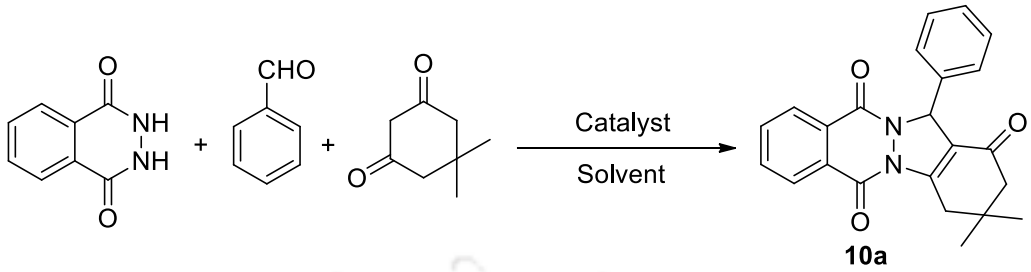
In this chapter, we have discussed the hydrated ferric sulfate catalyzed one pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives (**10**) *via* three-component condensation reaction of phthalhydrazide (**7**), aromatic aldehydes (**8**) and cyclic 1,3-dicarbonyl compounds (**9**) in ethanol under reflux conditions (Scheme 27).



Scheme 27. Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives.

To find out suitable reaction conditions, benzaldehyde (1.2 mmol), dimedone (1 mmol), and phthalhydrazide (1 mmol) were chosen as the model substrates. The reactions were examined in presence of various catalysts in different solvent systems and the results are summarized in Table 4. It was noted that the reaction did not provide any desired product in absence of catalyst after heating to 80 ^{o}C for 10 h either in neat or in ethanol (Table 4, entries 1 and 2). Interestingly, the desired product **10a** was isolated in 40% yield (Table 4, entry 4) when the same reaction mixture was heated in presence of 5 mol% hydrated ferric sulfate.

Table 4. Optimization for one-pot condensation of phthalhydrazide, benzaldehyde and dimedone[a].



10a

Entry	Catalysts (mol%)	Solvent	Time/h	Yield/%[b]
1	None	Neat	10	0
2	None	EtOH	10	0
3	$Fe_2(SO_4)_3{\cdot}xH_2O$ (5)	Neat	10	Trace
4	$Fe_2(SO_4)_3{\cdot}xH_2O$ (5)	EtOH	10	40
5	$Fe_2(SO_4)_3{\cdot}xH_2O$ (10)	EtOH	7	56
6	$Fe_2(SO_4)_3{\cdot}xH_2O$ (15)	EtOH	4	70
7	$Fe_2(SO_4)_3{\cdot}xH_2O$ (20)	EtOH	3	87
8	$Fe_2(SO_4)_3{\cdot}xH_2O$ (25)	EtOH	3	88
9	$Fe_2(SO_4)_3{\cdot}xH_2O$ (20)	DCE	3	71
10	$Fe_2(SO_4)_3{\cdot}xH_2O$ (20)	MeCN	3	72
11	$Fe_2(SO_4)_3{\cdot}xH_2O$ (20)	H_2O	3	Trace
12	$FeCl_3{\cdot}6H_2O$(20)	EtOH	3	75
13	$NiCl_2$ (20)	EtOH	3	60
14	$SnCl_2$ (20)	EtOH	3	74
15	AcOH (20)	EtOH	3	40

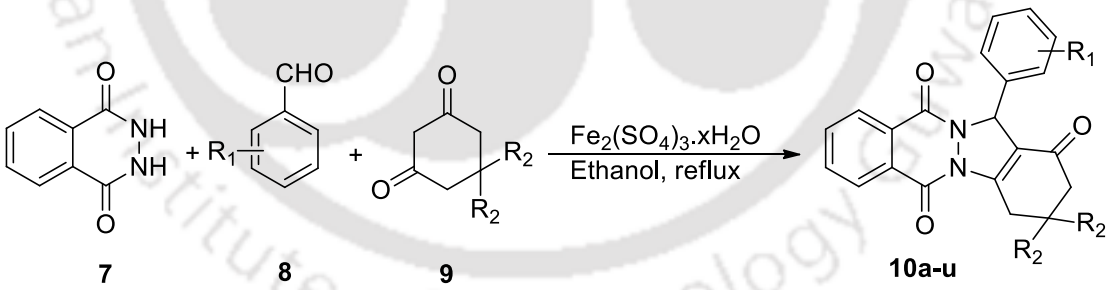
[a]*The reactions were carried out using phthalhydrazide (1.0 mmol), benzaldehyde (1.2 mmol) and dimedone (1.0 mmol).* [b]*Isolated Yield.*

So, we further carried out similar set of reactions in the presence of 10 mol%, 15 mol%, 20 mol% and 25 mol% (Table 4, entries 5-8), respectively. From these observations, we have found out that 20 mol % of the catalyst is the suitable choice to obtain best yield. For scrutinizing a suitable solvent system, the similar reaction was executed in a range of solvents such as dichloroethane, acetonitrile and water under identical reaction conditions. We found that the maximum yield of product **10a** was obtained in ethanol under reflux conditions (Table 4, entry 7). To examine the efficacy of the other catalysts, the similar reactions were

performed in presence of $FeCl_3.6H_2O$, $NiCl_2$, $SnCl_2$ and CH_3COOH (Table 4, entries 12-15), respectively and we have obtained moderate to good yields. However, we have used hydrated ferric sulfate because it gives high yields and is reusable.

To generalize our protocol, a wide variety of aromatic aldehydes having electron-donating and electron-withdrawing substituents in the aromatic ring were reacted with phthalhydrazide, and dimedone under similar reaction condition and the desired 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives (**10b-o**) were obtained in very good yields. Likewise, cyclohexane-1,3-dione also provided the desired 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives (**10p-u**) in high yields under identical reaction conditions. All the products were fully characterized by IR, ^1H, and ^{13}C NMR spectra as well as elemental analysis. The ^1H NMR and ^{13}C NMR spectra of compounds **10a**, **10f**, **10j**, **10n 10p, 10q,** and **10r** are given in the experimental section (Figure 28, 29, 30, 31, 32, 33 and 34). It is worthwhile to mention that aromatic aldehydes having electron-withdrawing group required relatively shorter reaction time as well as also provided better yields. Unfortunately, the similar kind of cyclized product was not obtained when the reaction was carried out with acyclic 1,3 diketones. All the successful results (Table 5) clearly demonstrate that hydrated ferric sulfate is an efficient catalyst for this three-component reaction.

Table 5. Synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones



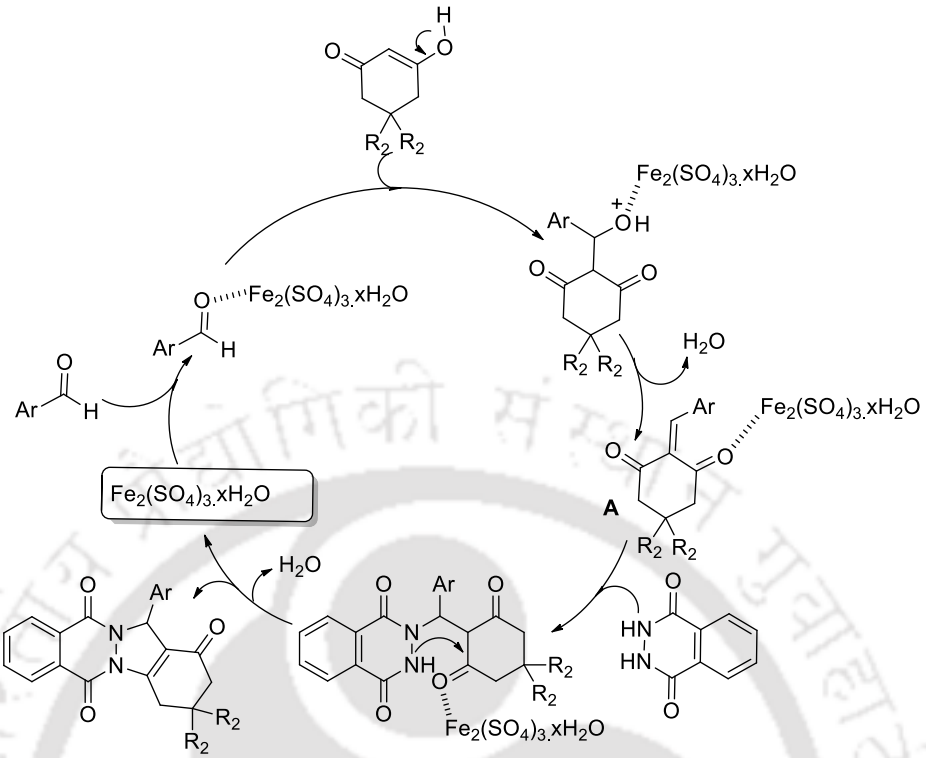
Entry	R^1	R^2	Time/ h	Product[a]	Yield(%)[b]
1	H	CH_3	3	**10a**	87
2	4-OCH_3	CH_3	4	**10b**	83
3	2-OCH_3	CH_3	4	**10c**	81
4	3,4-$(OCH_3)_2$	CH_3	4	**10d**	86
5	3,4,5-$(OCH_3)_3$	CH_3	4	**10e**	84
6	4-OH-3-OCH_3	CH_3	4	**10f**	85

7	4-CH_3	CH_3	4	**10g**	84
8	4-NO_2	CH_3	2	**10h**	93
9	3- NO_2	CH_3	2	**10i**	92
10	2- NO_2	CH_3	2	**10j**	87
11	4-Cl	CH_3	2	**10k**	89
12	2- Cl	CH_3	2	**10l**	84
13	4-Br	CH_3	2	**10m**	90
14	3-Br	CH_3	2	**10n**	91
15	3-OH	CH_3	4	**10o**	80
16	H	H	3	**10p**	86
17	4-Cl	H	2	**10q**	89
18	4-NO_2	H	2	**10r**	90
19	4-OCH_3	H	4	**10s**	83
20	4-OH-3-OCH_3	H	4	**10t**	79
21	2-OCH_3	H	4	**10u**	80

[a]*All the reactions were carried out using phthalhydrazide (1.0 mmol), aromatic aldehydes (1.2 mmol)and dimedone (1.0 mmol)/cyclohexane-1,3-dione (1.0 mmol) using 0.2 mmol of catalyst.*
[b]*Isolated Yield.*

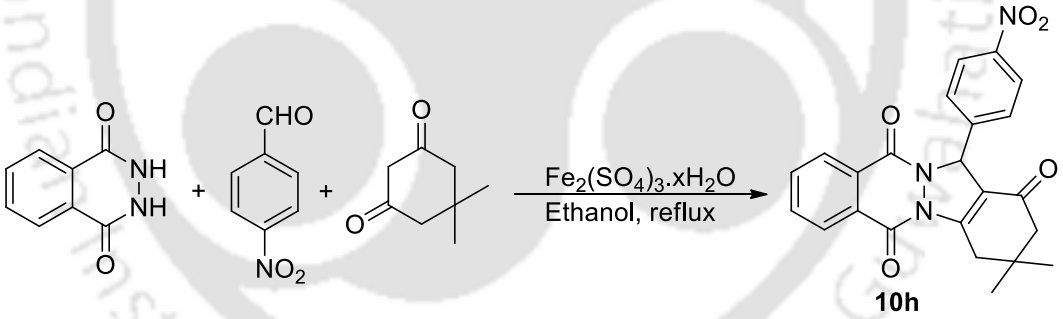
The probable mechanism for the formation of product may be rationalized as follows: Aromatic aldehyde reacts with dimedone in the presence of hydrated ferric sulfate to provide Knoevenagel product **A** which is 2-benzylidene-5,5-dimethylcyclohexane-1,3-dione. Then the intermediate undergoes 1,4-Michael addition with phthalhydrazide followed by concomitant cyclization to give the desired product (Scheme 28).

In view of greener chemistry, efficient recovery and reuse of the catalyst are highly desirable. As a matter of fact, the catalyst $Fe_2(SO_4)_3{\cdot}xH_2O$ was recovered conveniently from the reaction mixture at the end of the reactions and it was reused another four times for the same set of reaction. The results are shown in Table 6.



Scheme 28. Probable mechanism for the formation of product

Table 6. Reusability of the catalyst [$Fe_2(SO_4)_3{\cdot}xH_2O$]



Round	Catalyst recovered/mg	Reaction time/h	Yield[b]/%
1	418	3	94
2	413	3	92
3	403	3	91
4	395	3	90
5	388	3	89

[a]The same set of reaction was performed with phthalhydrazide (5.0 mmol), 4-nirobenzaldehyde (5.5 mmol) and dimedone (5.0 mmol) in each time. [b]Isolated yield.

In summary, we have shown that hydrated ferric sulfate is an efficient and reusable catalyst for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives via one-pot three-component condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic-1,3-diketones in ethanol under reflux conditions.

PART B

CHAPTER 2

Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones by Using an Efficient and Reusable Catalyst Ferric sulfate

Experimental Section

Experimental

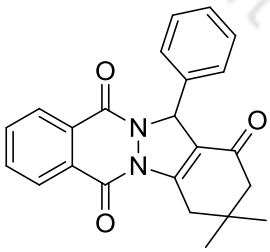
General experimental procedure for the Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives:

Hydrated ferric sulfate (0.20 mol, 0.084 g) was added to a mixture of an aromatic aldehyde (1.2 mmol), a cyclic 1,3-dicarbonyl compound (1.0 mmol) and phthalhydrazide (1.0 mmol) in 3 mL of ethanol. The reaction mixture was kept for refluxing in a preheated oil-bath. After completion of the reaction (as monitored by TLC), it was brought to room temperature. The solid product **10** precipitated out after adding 6 mL of water into it and it was filtered off through a Büchner funnel. The precipitate was washed with ethanol (2 mL) and dried in a vacuum pump.

For checking reusability of the catalyst, a reaction mixture of phthalhydrazide (0.810 g, 5.0 mmol), 4-nirobenzaldehyde (0.831 g, 5.5 mmol) and dimedone (0.700 g, 5.0 mmol) in presence of hydrated ferric sulfate (0.418 g, 1 mmol) was refluxed in 10 mL of ethanol. After completion of the reaction, the catalyst was recovered by removing ethanol in a rotary evaporator followed by addition of 15 mL of CH_2Cl_2. The catalyst was precipitated out due to its poor solubility in CH_2Cl_2 and it was filtered off through a Büchner funnel. The desired product **10h** was obtained after concentrating the organic solvent in a rotary evaporator. The reusability of the recovered catalyst was examined for five consecutive times using the same substrates.

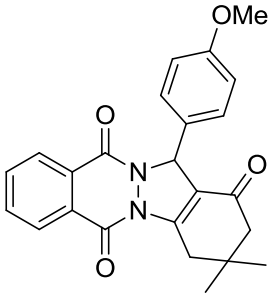
Spectral data of 2*H*-indazolo[2,1-*b*]phthalazine-triones (10):

3,3-dimethyl-13-phenyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione ***(10a)***:



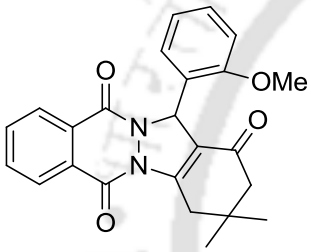
Pale yellow solid, mp 210-212°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (s, 6H), 2.34 (s, 2H), 3.24 (d, *J* = 18.8, 1H), 3. 41 (d, *J* = 19.2, 1H), 6.45 (s, 1H), 7.26-7.35 (m, 3H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.84-7.86 (m, 2H), 8.26-8.28 (m, 1H), 8.34-8.37 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.6, 28.8, 34.8, 38.2, 51.1, 65.1, 118.7, 127.3 (2C), 127.8, 128.1, 128.8 (3C), 129.1, 129.2, 133.7, 134.6, 136.5, 151.0, 154.4, 156.1, 192.3; **IR** (KBr, cm^{-1}): 1660 (-CO); **Anal. Calcd** for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52; found: C, 74.01; H, 5.32; N, 7.32%.

13-(4-methoxyphenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione ***(10b)***:



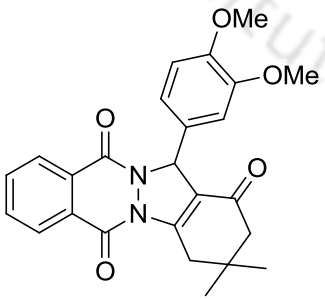
Yellow solid, mp 218-220 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.22 (s, 3H), 2.34 (s, 2H), 3.24 (dd, J_1 = 2.4 Hz, J_2 = 19.2 Hz, 1H), 3.42 (dd, J_1 = 1.2 Hz, J_2 = 19.2 Hz, 1H), 3.76 (s, 3H), 6.42 (s, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.83-7.85 (m, 2H), 8.26-8.28 (m, 1H), 8.33-8.36 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.6, 28.8, 34.8, 38.2, 51.1, 55.3, 64.7, 114.2 (2C), 118.7, 127.8, 128.0, 128.5, 128.6 (2C), 129.1, 129.3, 133.6, 134.6, 150.9, 154.4, 156.2, 159.8, 192.4; **IR** (KBr, cm^{-1}): 1651 (-CO); **Anal. Calcd** for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96; found: C, 71.49; H, 5.43; N, 6.85%.

*3,4-dihydro-13-(2-methoxyphenyl)-3,3-dimethyl-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10c**)***:**



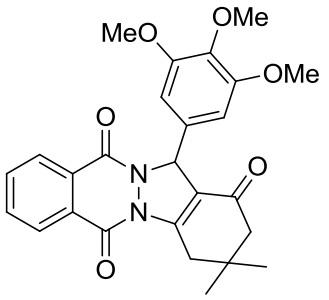
Pale yellow solid, mp 226-229 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.21 (s, 3H), 2.26 (d, *J* = 16.0 Hz, 1H), 2.34 (d, *J* = 16.0 Hz, 1H), 3.18 (d, *J* = 18.8 Hz, 1H), 3.44 (d, *J* = 19.2 Hz, 1H), 3.71 (s, 3H), 6.58 (s, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 7.20 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.83-7.85 (m, 2H), 8.24-8.26 (m, 1H), 8.35-8.37 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.9, 29.0, 34.6, 38.1, 51.0, 55.8, 62.8, 111.4, 117.5, 121.0 (2C), 123.7, 127.6, 127.8, 129.1, 130.0, 130.3, 133.3, 134.3, 151.4, 154.0, 156.2, 157.3, 192.2; **IR** (KBr, cm^{-1}): 1651 (-CO); **Anal. Calcd** for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96; found: C, 71.69; H, 5.57; N, 6.94%.

*13-(3,4-dimethoxyphenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10d**)***:**



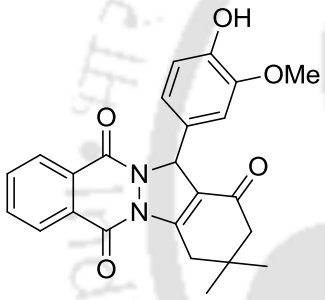
Yellow solid, mp 197-200 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.21 (s, 3H), 2.33 (s, 2H) , 3.21 (d, *J* = 19.2 Hz, 1H), 3.42 (d, *J* = 19.2 Hz, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 6.40 (s, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 7.81-7.86 (m, 2H), 8.25-8.27 (m, 1H), 8.32-8.34 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.4, 28.9, 34.7, 38.2, 51.1, 55.9, 56.1, 64.9, 111.2, 111.3, 118.6, 119.5, 127.8, 128.1, 128.9, 129.1, 129.3, 133.6, 134.6, 149.1, 149.4, 150.9, 154.5, 156.2, 192.4; **IR** (KBr, cm^{-1}): 1657 (-CO); **Anal. Calcd** for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48; found: C, 69.25; H, 5.54; N, 6.37%.

*3,3-dimethyl-13-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10e**)***:**



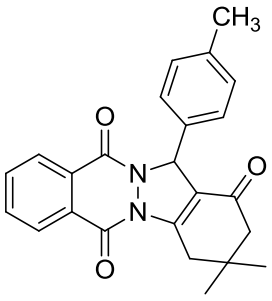
Yellow solid, mp 235-237 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.24 (s, 3H), 2.36 (s, 2H), 3.21 (d, *J* = 18.8 Hz, 1H), 3.46 (d, *J* = 19.2 Hz, 1H), 3.80 (s, 3H), 3.83 (s, 6H), 6.39 (s, 1H), 6.63 (s, 2H), 7.86-7.88 (m, 2H), 8.29-8.31 (m, 1H), 8.35-8.37 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.5, 29.1, 34.7, 38.2, 51.1, 56.3, 60.8, 65.1, 104.8, 118.4, 127.8, 128.1, 129.1, 129.2, 131.9, 133.7, 134.7, 138.4, 151.0, 153.5, 154.7, 156.2, 192.3; **IR** (KBr, cm^{-1}): 1655 (-CO); **Anal. Calcd** for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06; found: C, 67.51; H, 5.59; N, 5.94%.

*13-(4-hydroxy-3-methoxyphenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10f**)*:



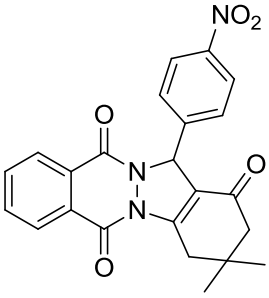
Yellow solid, mp 260-262 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.23 (s, 3H), 2.35 (s, 2H), 3.22 (d, *J* = 19.2 Hz, 1H), 3.43 (d, *J* = 19.2 Hz, 1H), 3.91 (s, 3H), 5.68 (bs, 1H), 6.39 (s, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 7.84-7.86 (m, 2H), 8.27-8.29 (m, 1H), 8.34-8.36 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.6, 28.3, 34.2, 37.3, 50.3, 55.7, 64.2, 112.0, 115.0, 117.4, 120.3, 126.7, 127.4, 128.1, 128.8, 129.0, 133.6, 134.4, 146.5, 147.2, 151.0, 153.6, 155.3, 191.9; **IR** (KBr, cm^{-1}): 3362 (-OH), 1659 (-CO); **Anal. Calcd** for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69; found: C, 68.72; H, 5.24; N, 6.58%.

*13-(4-methylphenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10g**)*:



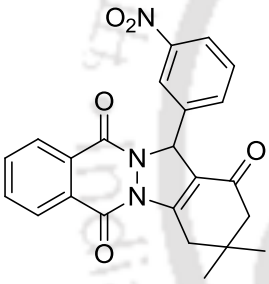
Pale yellow solid, mp 230-232 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (s, 6H), 2.29 (s, 3H), 2.33 (s, 2H), 3.23 (d, *J* = 19.6 Hz, 1H), 3.41 (d, *J* = 19.2 Hz, 1H), 6.42 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.84 (dd, *J* = 3.6 Hz, *J* = 6.0 Hz , 2H), 8.26-8.28 (m, 1H), 8.34-8.36 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4, 28.6, 28.8, 34.8, 38.2, 51.1, 65.0, 118.8, 127.2, 127.8 (2C), 128.0, 129.1, 129.3, 129.6 (2C), 133.6 (2C), 134.6, 138.6, 150.9, 154.4, 156.2, 192.3; **IR** (KBr, cm^{-1}): 1657 (-CO); **Anal. Calcd** for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25; found: C, 74.38; H, 5.71; N, 7.17%.

*3,3-dimethyl-13-(4-nitrophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10h**)*:



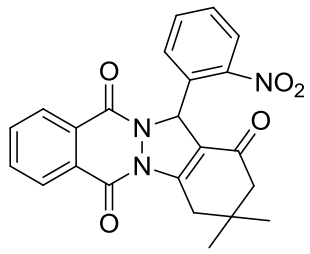
Pale yellow solid, mp 226-228 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.22 (s, 3H), 2.33 (d, *J* = 16.4 Hz, 1H), 2.34 (d, *J* = 16.4 Hz, 1H), 3.26 (d, *J* = 19.2 Hz, 1H), 3.40 (d, *J* = 19.2 Hz, 1H), 6.51 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.88-7.91 (m, 2H), 8.21 (d, *J* = 8.0 Hz, 2H), 8.25-8.27 (m, 1H), 8.37-8.39 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.5, 28.8, 34.8, 38.1, 50.9, 64.3, 117.4, 124.1 (2C), 127.8, 128.2 (2C), 128.3, 128.7, 129.1, 134.1, 134.9, 143.6, 148.0, 151.8, 154.7, 156.1, 192.2; **IR** (KBr, cm^{-1}): 1660 (-CO); 1523 (NO_2), 1365 (NO_2); **Anal. Calcd** for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07; found: C, 66.01; H, 4.52; N, 9.98%.

*3,3-dimethyl-13-(3-nitrophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10i**)*:



Pale yellow solid, mp 266-269 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (s, 6H), 2.35 (s, 2H), 3.26 (d, *J* = 19.6 Hz, 1H), 3.43 (d, *J* = 19.6 Hz, 1H), 6.52 (s, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.86-7.91 (m, 3H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.24-8.26 (m, 1H), 8.37-8.40 (m, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 27.8, 28.0, 34.3, 37.2, 50.1, 63.7, 116.2, 122.4, 123.0, 126.8, 127.5, 128.4, 129.2, 129.8, 133.8, 134.2, 134.5, 139.7, 147.7, 152.0, 154.0, 155.5, 191.9; **IR** (KBr, cm^{-1}): 1658 (-CO), 1528 (NO_2), 1346 (NO_2); **Anal. Calcd** for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07; found: C, 65.99; H, 4.53; N, 10.13%.

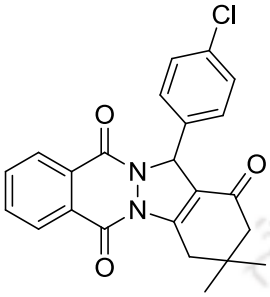
*3,4-dihydro-3,3-dimethyl-13-(2-nitrophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10j**)*:



Pale yellow solid, mp 245-248 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.21 (s, 3H), 2.30 (d, *J* = 16.40 Hz, 1H), 2.36 (d, *J* = 16.4 Hz, 1H), 3.26 (d, *J* = 19.2 Hz, 1H), 3.39 (d, *J* = 19.2 Hz, 1H), 7.33 (bs, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.84-7.89 (m, 2H), 7.93 (d, *J* = 7.6 Hz, 1H), 8.24-8.26 (m, 1H), 8.35-8.38 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.6, 28.8, 34.8, 38.2, 50.9, 60.7, 117.0, 125.3, 127.9, 128.3, 128.8, 129.1, 129.6, 130.9, 133.3, 133.9, 134.8, 149.4, 152.2, 154.5, 156.1, 192.0; **IR** (KBr, cm^{-1}): 1664 (-CO), 1528 (-NO_2), 1360 (-NO_2);

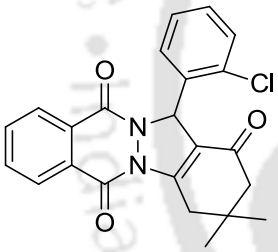
Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07; found: C, 66.01; H, 4.51; N, 9.94%.

*13-(4-chlorophenyl)-3,4-dihydro-3,3-dimethyl-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10k**)*:



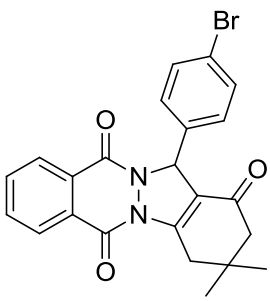
Pale yellow solid, mp 260-263 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (s, 6H), 2.34 (s, 2H), 3.24 (d, *J* = 19.2 Hz, 1H), 3.40 (d, *J* = 18.8 Hz, 1H), 6.41 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.85-7.87 (m, 2H), 8.26-8.28 (m, 1H), 8.35-8.37 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.5, 28.8, 34.7, 38.1, 51.0, 64.4, 118.1, 127.8, 128.1, 128.7 (2C), 129.0 (2C), 133.8, 134.6, 134.7, 135.1, 151.2, 154.5, 156.1, 192.2; **IR** (KBr, cm^{-1}): 1665 (-CO); **Anal. Calcd** for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89; found: C, 67.72; H, 4.68; N, 6.79%.

*13-(2-chlorophenyl)-3,4-dihydro-3,3-dimethyl-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10l**)*:



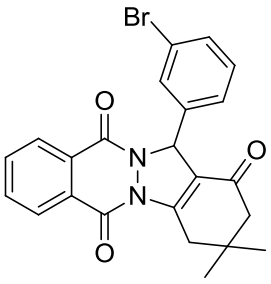
White solid, mp 265-268 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (s, 6H), 2.32 (s, 2H), 3.23 (d, *J* = 18.8 Hz, 1H), 3.40 (d, *J* = 18.8 Hz, 1H), 6.68 (s, 1H), 7.20-7.33 (m, 3H), 7.48 (bs, 1H), 7.85 (bs, 2H), 8.25 (bs, 1H), 8.37 (bs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.5, 28.9, 34.7, 38.1, 50.9, 64.1, 109.9, 116.8, 127.3, 127.7, 128.1, 128.8, 129.1, 130.0, 130.6, 132.7, 133.2, 133.7, 134.6, 151.9, 154.3, 156.2, 192.2; **IR** (KBr, cm^{-1}): 1659 (-CO); **Anal. Calcd** for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89; found: C, 67.71; H, 4.63; N, 6.78%.

*13-(4-bromophenyl)-3,4-dihydro-3,3-dimethyl-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10m**)*:



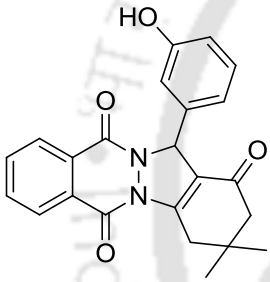
Yellow solid, mp 262-265 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (s, 6H), 2.33 (s, 2H), 3.24 (d, *J* = 19.2 Hz, 1H), 3.40 (d, *J* = 19.2 Hz, 1H), 6.40 (s, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.85-7.87 (m, 2H), 8.26-8.28 (m, 1H), 8.35-8.37 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.6, 28.8, 34.8, 38.2, 51.0, 64.5, 118.1, 122.9, 127.9, 128.2, 128.9, 129.0 (2C), 129.1, 132.1 (2C), 133.8, 134.8, 135.7, 151.3, 154.5, 156.1, 192.2; **IR** (KBr, cm^{-1}): 1654 (-CO); **Anal. Calcd** for $C_{23}H_{19}BrN_2O_3$: C, 61.21; H, 4.24; N, 6.21; found: C, 61.01; H, 4.18; N, 6.07%.

*13-(3-bromophenyl)-3,4-dihydro-3,3-dimethyl-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10n**)*:



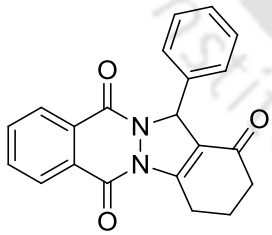
Yellow solid, mp 216-219 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.21 (s, 3H), 2.34 (s, 2H), 3.22-3.27 (d, *J* = 19.6 Hz, 1H), 3.40 (d, *J* = 19.2 Hz, 1H), 6.39 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.48 (s, 1H), 7.86-7.88 (m, 2H), 8.26-8.28 (m, 1H), 8.35-8.38 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.6, 28.8, 34.8, 38.1, 51.0, 64.4, 118.0, 122.9, 126.5, 127.9, 128.2, 129.0, 129.1, 130.0, 130.4, 132.0, 133.8, 134.8, 138.8, 151.4, 154.5, 156.1, 192.2; **IR** (KBr, cm^{-1}): 1658 (-CO); **Anal. Calcd** for $C_{23}H_{19}BrN_2O_3$: C, 61.21; H, 4.24; N, 6.21; found: C, 61.02; H, 4.18; N, 6.09%.

*3,4-dihydro-13-(3-hydroxyphenyl)-3,3-dimethyl-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10o**)*:



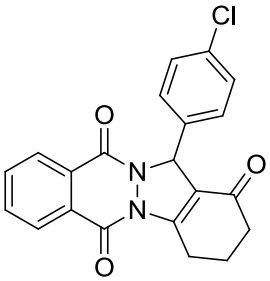
Pale yellow solid, mp 261-264 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.12 (s, 6H), 2.26 (s, 2H), 3.16 (s, 2H), 6.17 (s, 1H), 6.67-7.09 (m, 4H), 7.93-8.22 (m, 4H), 9.44 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 27.8, 28.1, 34.3, 37.3, 50.3, 64.2, 114.5, 115.0, 117.6, 117.8, 126.8, 127.5, 128.6, 128.9, 129.3, 133.7, 134.6, 138.8, 151.1, 153.7, 155.3, 157.2, 191.9; **IR** (KBr, cm^{-1}): 3288 (-OH), 1646 (-CO); **Anal. Calcd** for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21; found: C, 71.00; H, 5.13; N, 7.06%.

*13-phenyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10p**)*:



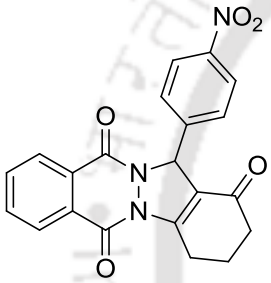
Pale yellow solid, mp 228-231 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.25 (quin, *J* = 6.4 Hz, 2H), 2.47 (dt, J_1 = 2.4 Hz, J_2 = 12.8 Hz, 2H), 3.32 (dt, J_1 = 6.4 Hz, J_2 = 19.2 Hz, 1H), 3.57 (dt, J_1 = 5.6 Hz, J_2 = 19.2 Hz, 1H), 6.45 (s, 1H), 7.28 (t, *J* = 8.8 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.42 (d, J = 7.2 Hz, 2H), 7.83-7.85 (m, 2H), 8.25-8.28 (m, 1H), 8.34-8.37 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.4, 24.6, 37.0, 65.1, 119.8, 127.3 (2C), 127.8, 128.1, 128.8 (3C), 129.1, 129.2, 133.6, 134.6, 136.5, 152.4, 154.3, 156.1, 192.6; **IR** (KBr, cm^{-1}): 1659 (-CO); **Anal. Calcd** for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13; found: C, 73.01; H, 4.61; N, 8.02%.

*13-(4-chlorophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10q**)*:



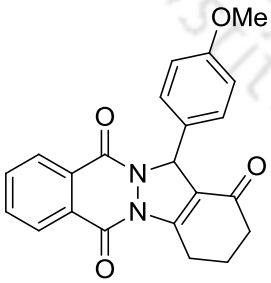
Pale yellow solid, mp 286-289 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.26 (quin, J = 6.4 Hz, 2H), 2.47 (t, J_1 = 5.6 Hz, 2H), 3.35 (dt, J_1 = 5.6 Hz, J_2 = 19.2 Hz, 1H), 3.57 (dt, J_1 = 5.6 Hz, J_2 = 19.2 Hz, 1H), 6.42 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.85-7.87 (m, 2H), 8.25-8.28 (m, 1H), 8.35-8.37 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.4, 24.7, 37.0, 64.5, 119.3, 127.9, 128.2, 128.8 (2C), 129.1 (2C), 133.8, 134.7, 134.8, 135.1, 152.7, 154.5, 156.2, 192.6; **IR** (KBr, cm^{-1}): 1661 (-CO); **Anal. Calcd** for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40; found: C, 66.41; H, 3.89; N, 7.29%.

*13-(4-nitrophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10r**)*:



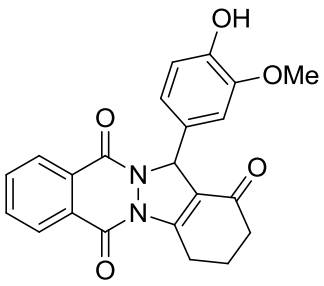
Pale yellow solid, mp 266-268 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.26 (quin, J = 6.4 Hz, 2H), 2.48 (t, J_1 = 6.4 Hz, 2H), 3.35 (dt, J_1 = 6.0 Hz, J_2 = 19.2 Hz, 1H), 3.57 (dt, J_1 = 5.2 Hz, J_2 = 19.2 Hz, 1H), 6.51 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.88-7.90 (m, 2H), 8.21 (d, J = 8.0 Hz, 2H), 8.25-8.27 (m, 1H), 8.38-8.40 (m, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 21.8, 24.1, 36.3, 63.8, 117.4, 123.3 (2C), 126.8, 127.6, 128.4, 128.9 (2C), 129.1, 133.9, 134.6, 144.7, 147.2, 153.6, 153.8, 155.4, 192.3; **IR** (KBr, cm^{-1}): 1656 (-CO), 1534 (-NO_2), 1370 (-NO_2); **Anal. Calcd** for $C_{21}H_{15}N_3O_5$: C, 64.78; H, 3.88; N, 10.79; found: C, 64.51; H, 3.79; N, 10.62%.

*13-(4-methoxyphenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10s**)*:



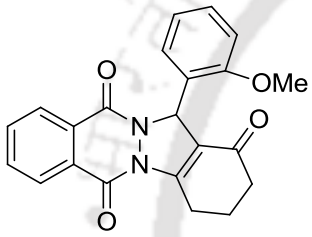
Yellow solid, mp 264-266 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2. 26 (quin, J = 6.4 Hz, 2H), 2.47 (dt, J_1 = 4.0 Hz, J_2 = 16.4 Hz, 2H), 3.33 (dt, J_1 = 6.4 Hz, J_2 = 19.6 Hz, 1H), 3.57 (dt, J_1 = 5.6 Hz, J_2 = 19.2 Hz, 1H), 3.76 (s, 3H), 6.42 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.83-7.85 (m, 2H), 8.26-8.28 (m, 1H), 8.33-8.36 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.4, 24.6, 37.1, 55.3, 64.7, 114.2 (2C), 119.8, 127.8, 128.0, 128.4, 128.7 (2C), 129.1, 129.3, 133.6, 134.6, 152.3, 154.3, 156.2, 159.9, 192.7; **IR** (KBr, cm^{-1}): 1658 (-CO); **Anal. Calcd** for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48; found: C, 70.41; H, 4.79; N, 7.41%.

*13-(4-hydroxy-3-methoxyphenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10t**)*:



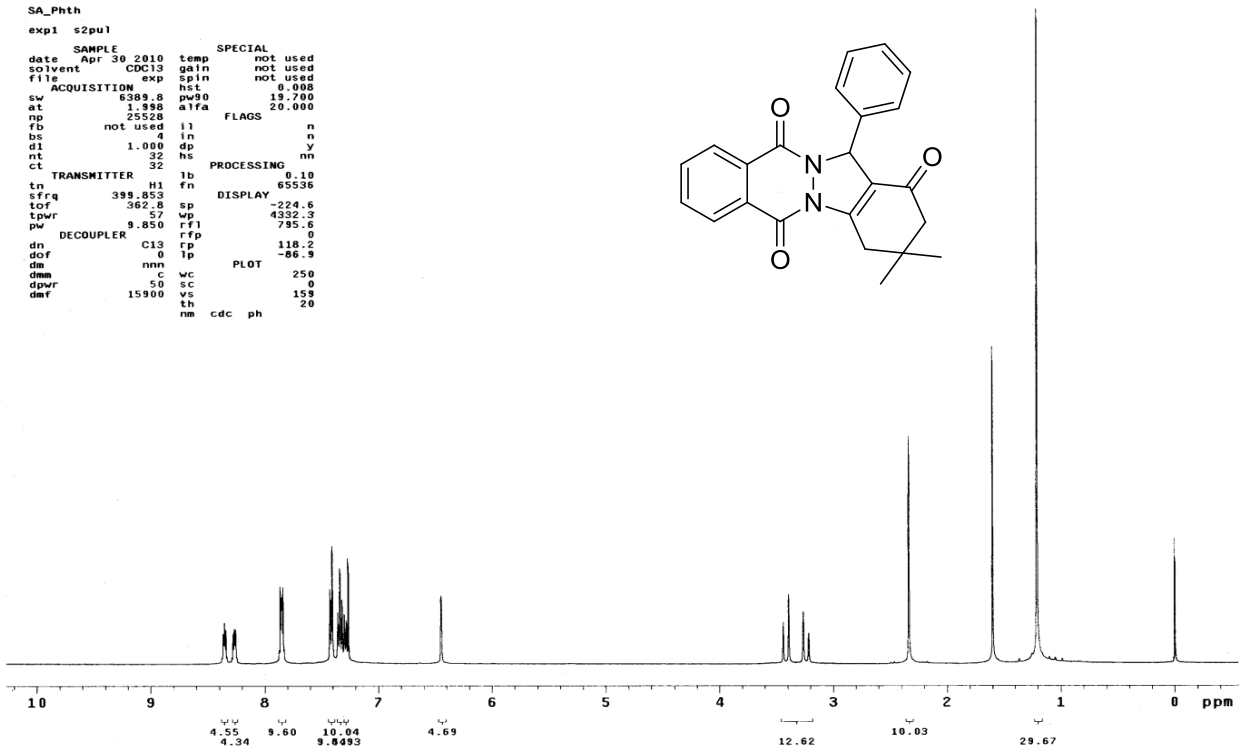
Yellow solid, mp 267-270 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.26 (quin, *J* = 6.0 Hz, 2H), 2.47 (q, *J* = 6.4 Hz, 2H), 3.32 (dt, J_1 = 6.0 Hz, J_2 = 17.6 Hz, 1H), 3.57 (dt, J_1 = 6.0 Hz, J_2 = 19.2 Hz, 1H), 3.93 (s, 3H), 5.64 (s, 1H), 6.40 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 7.10 (s, 1H), 7.83-7.87 (m, 2H), 8.23-8.27 (m, 1H), 8.34-8.36 (m, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 22.0, 24.1, 36.6, 55.8, 64.3, 112.3, 115.1, 118.5, 120.2, 126.8, 127.5, 128.1, 128.8, 129.0, 133.7, 134.5, 146.6, 147.2, 152.8, 153.6, 155.4, 192.5; **IR** (KBr, cm^{-1}): 3237 (-OH), 1665 (-CO); **Anal. Calcd** for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18; found: C, 67.49; H, 4.61; N, 7.05%.

*13-(2-methoxyphenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**10u**)*:



Yellow solid, mp 277-280 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.23 (quin, *J* = 5.6 Hz, 2H), 2.43 (t, J_1 = 6.4 Hz, 2H), 3.35 (dt, J_1 = 6.4 Hz, J_2 = 19.2 Hz, 1H), 3.52 (dt, J_1 = 6.0 Hz, J_2 = 19.2 Hz, 1H), 3.73 (s, 3H), 6.59 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.82-7.84 (m, 2H), 8.23-8.26 (m, 1H), 8.35-8.37 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.5, 24.7, 37.1, 56.0, 62.8, 111.7, 118.9, 121.1, 124.0, 127.8, 128.0, 129.2, 129.3, 130.1, 130.2, 133.4, 134.4, 152.8, 154.1, 156.3, 157.5, 192.7; **IR** (KBr, cm^{-1}): 1665 (-CO); **Anal. Calcd** for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48; found: C, 70.39; H, 4.73; N, 7.29%.

^{1}H NMR (400 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10a)***



^{13}C NMR (100 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10a)***

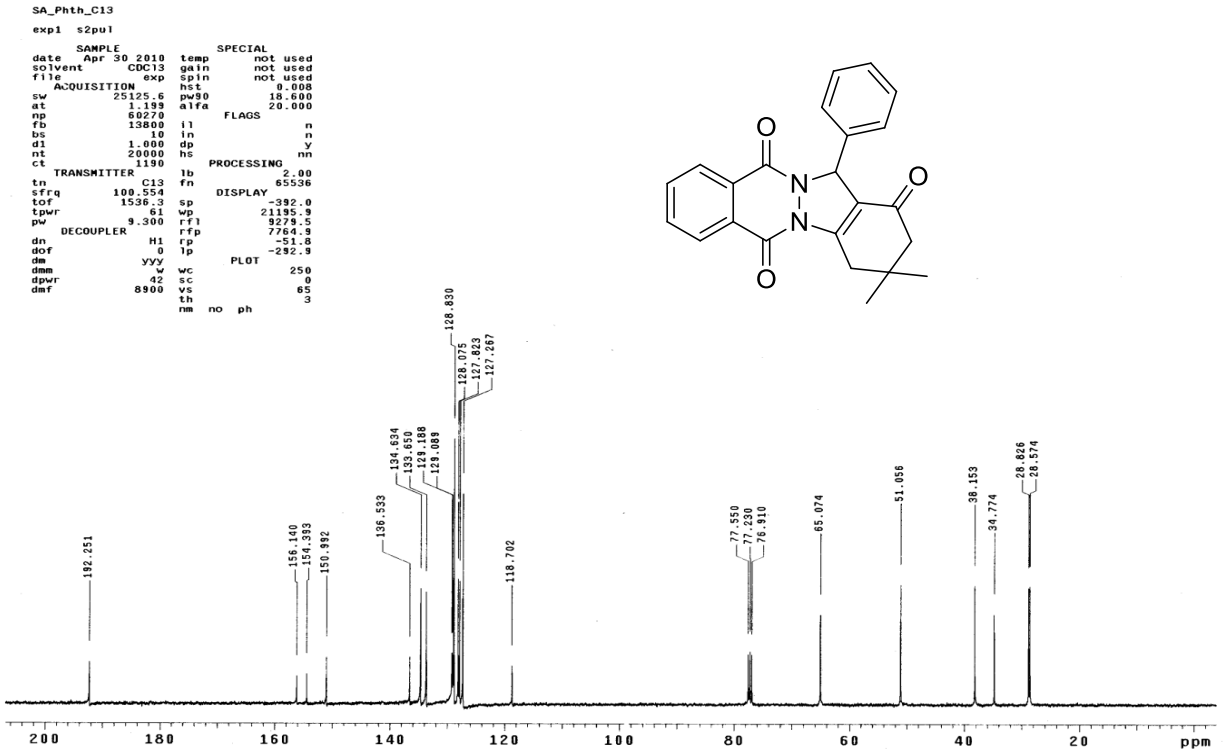
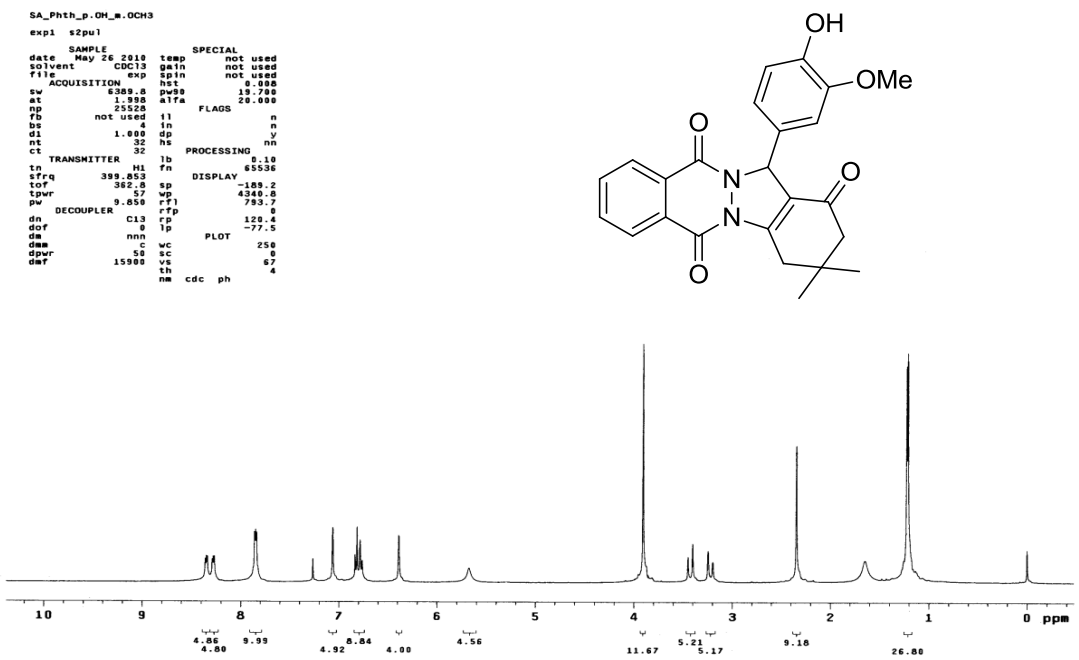


Figure 28

^{1}H NMR (400 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10f)***



^{13}C NMR (100 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10f)***

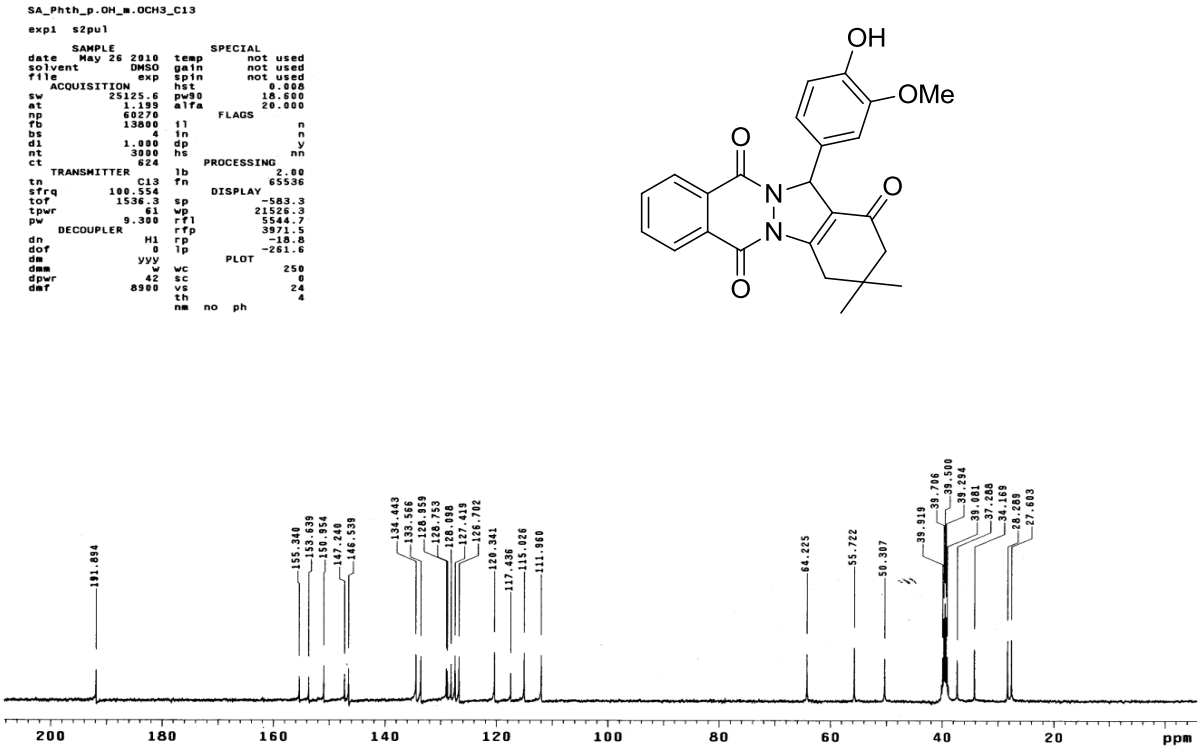
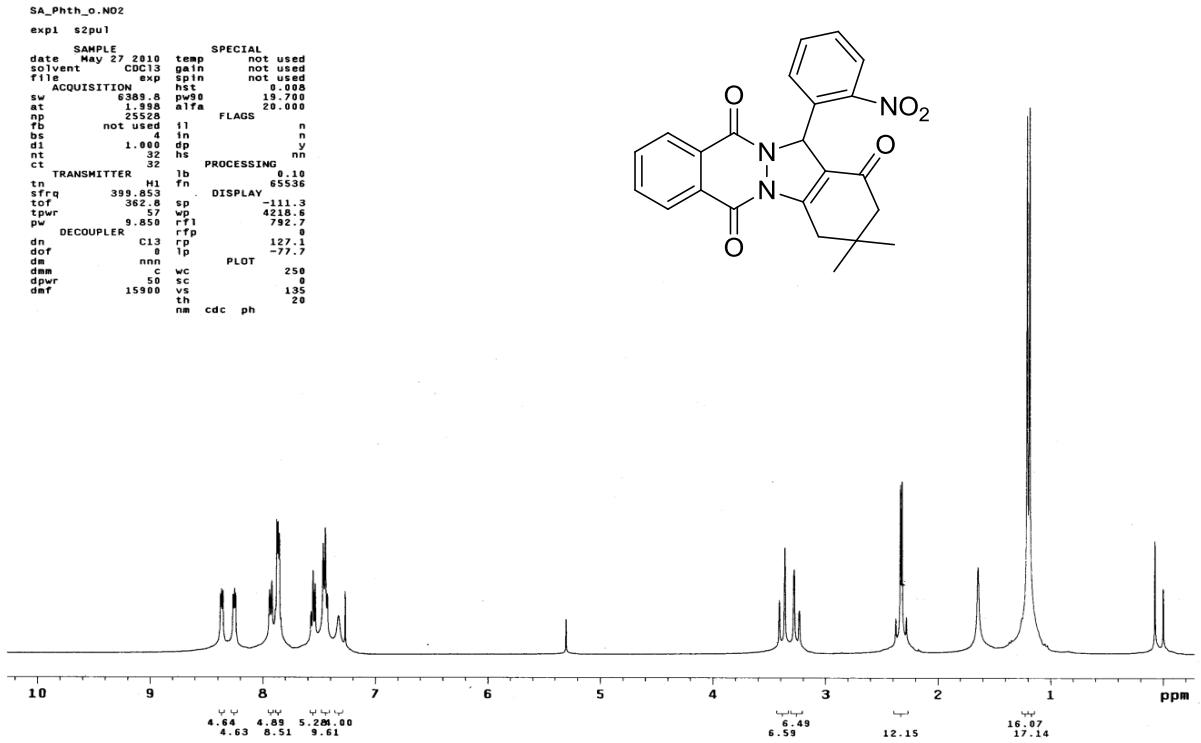


Figure 29

^{1}H NMR (400 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10j)***



^{13}C NMR (100 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10j)***

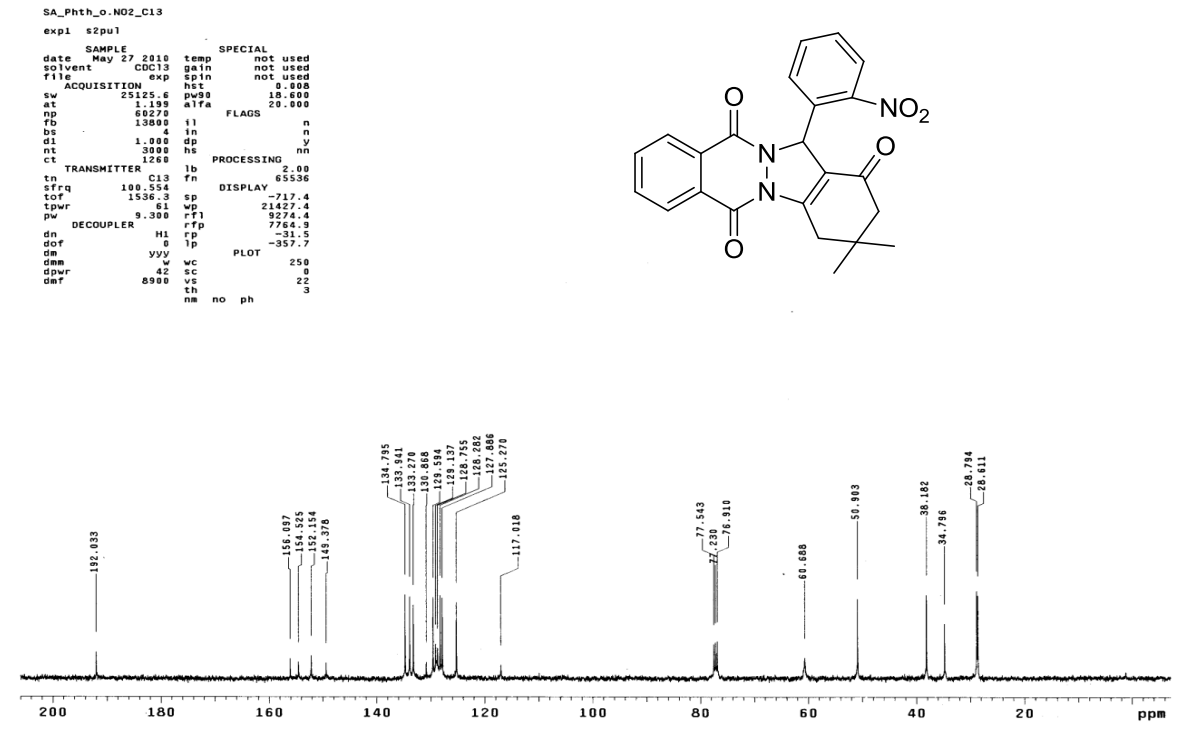
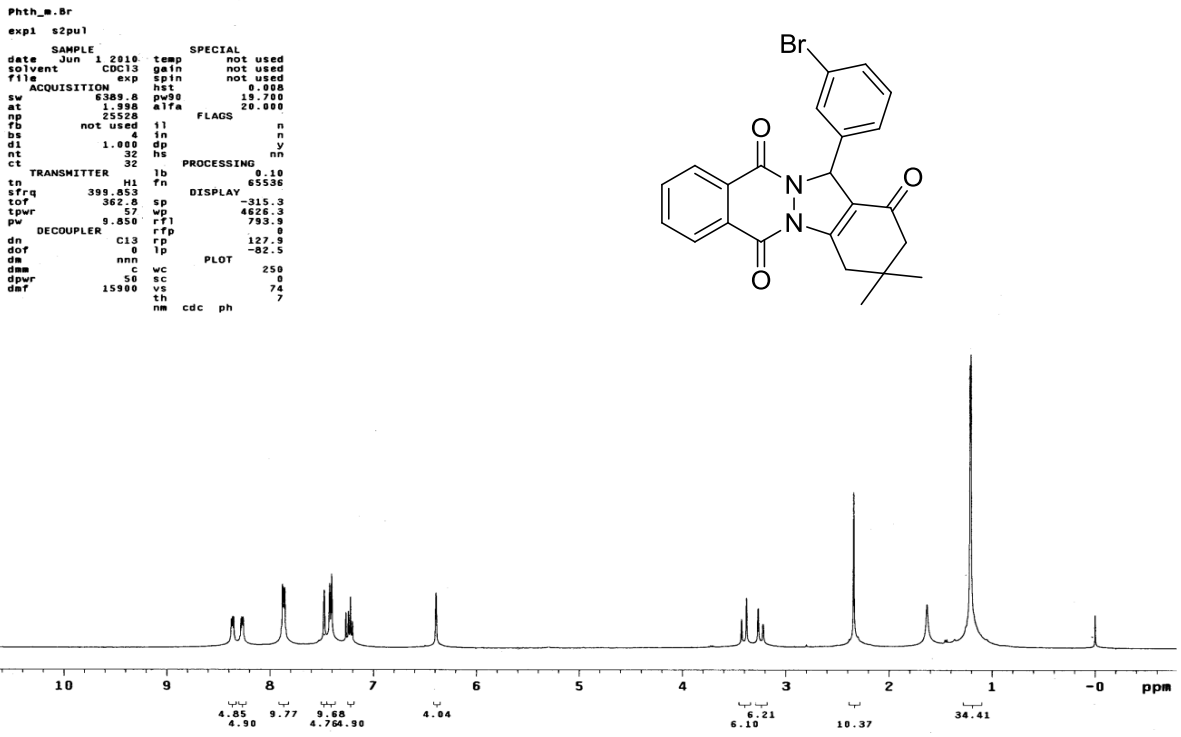


Figure 30

^{1}H NMR (400 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10n)***



^{13}C NMR (100 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10n)***

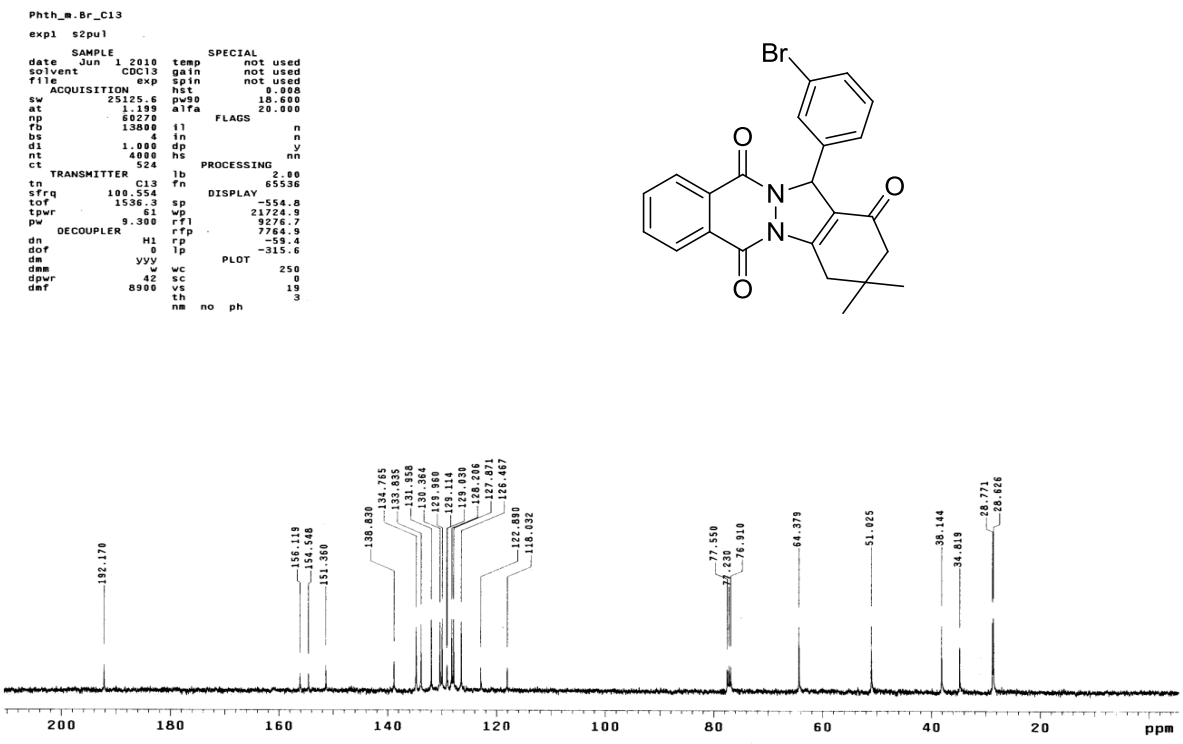
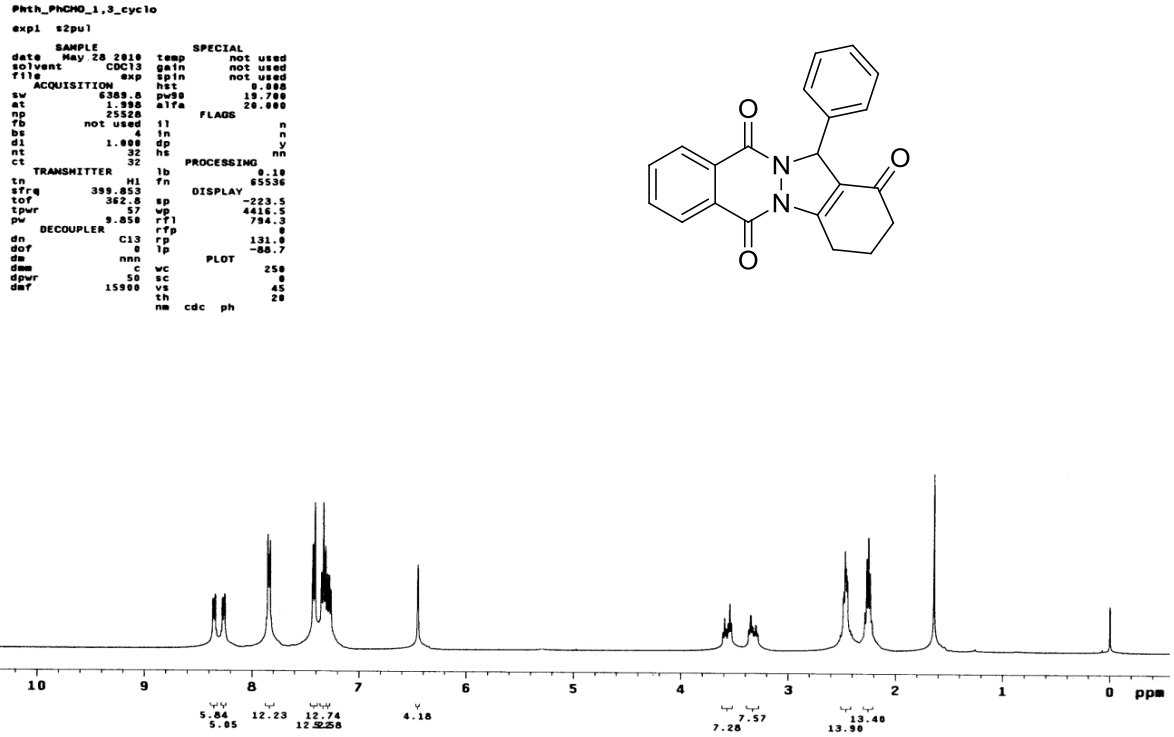


Figure 31

^{1}H NMR (400 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10p)***



^{13}C NMR (100 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10p)***

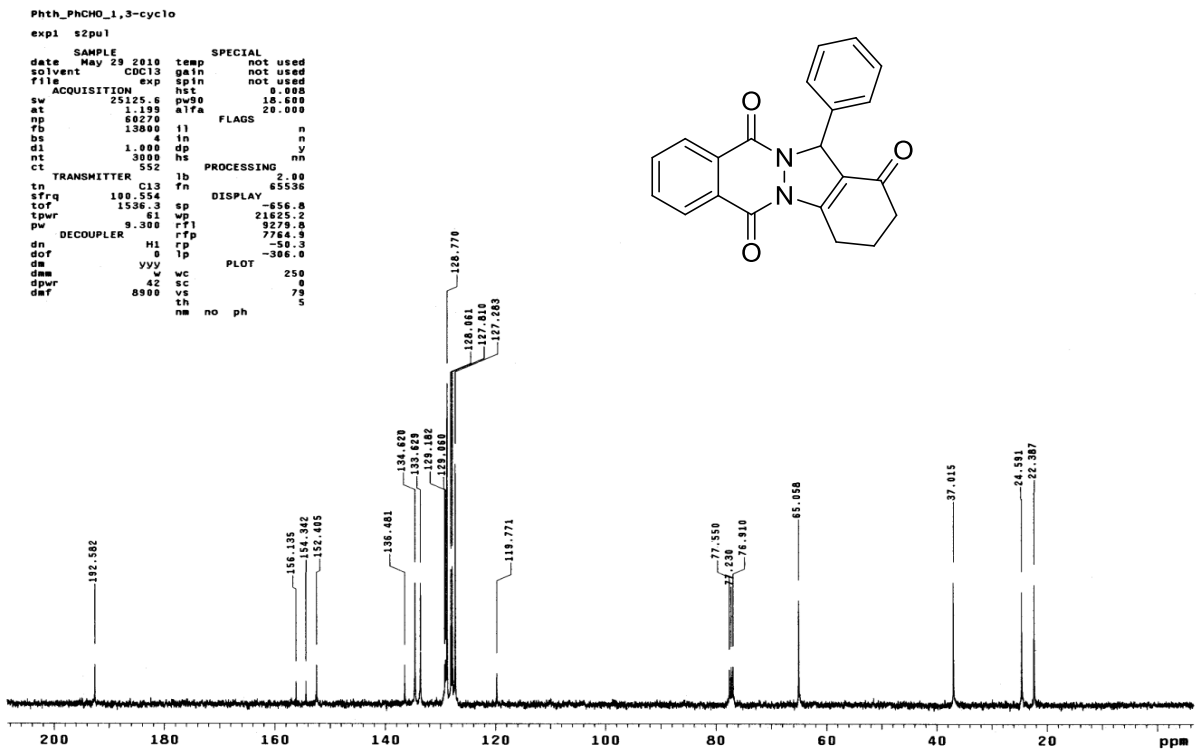
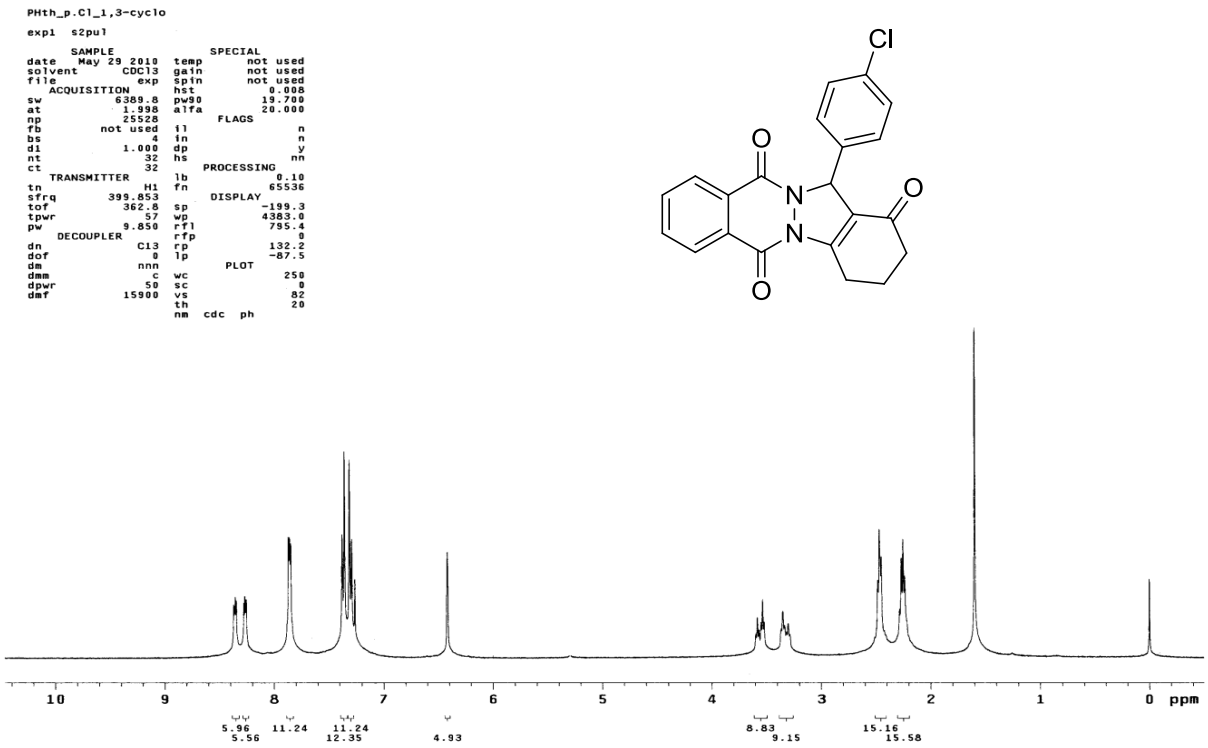


Figure 32

^{1}H NMR (400 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10q)***



^{13}C NMR (100 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10q)***

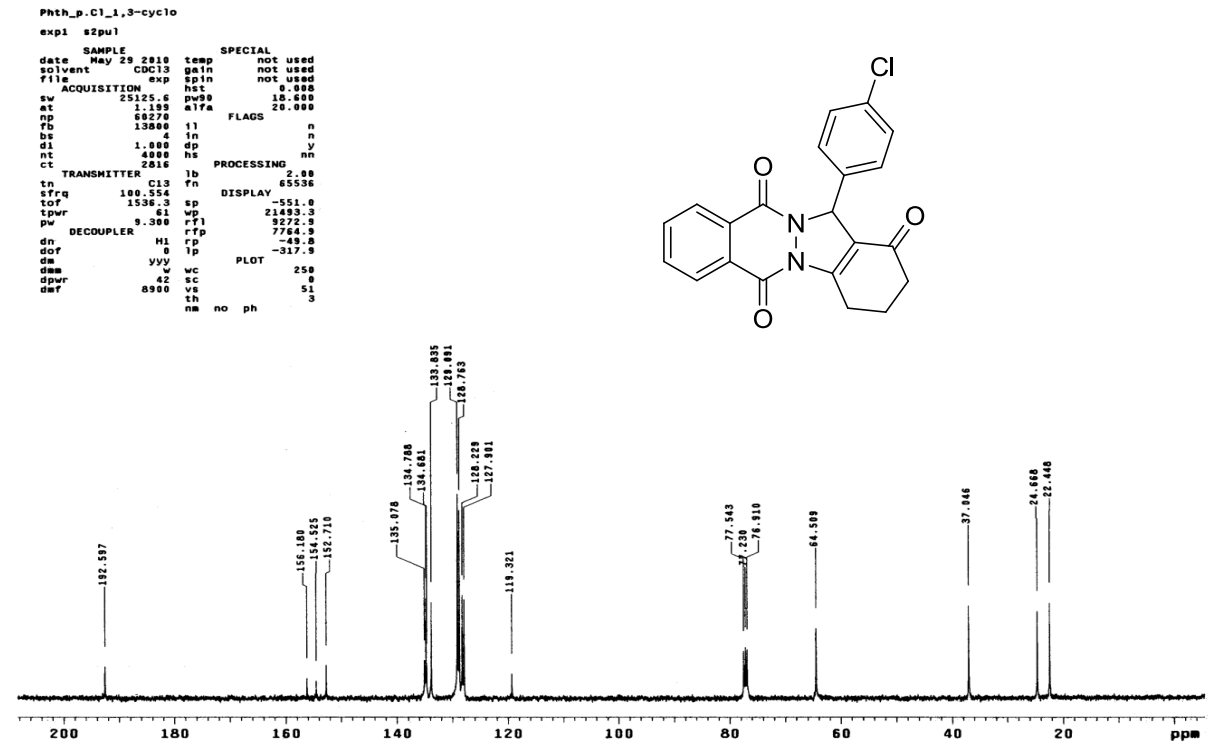
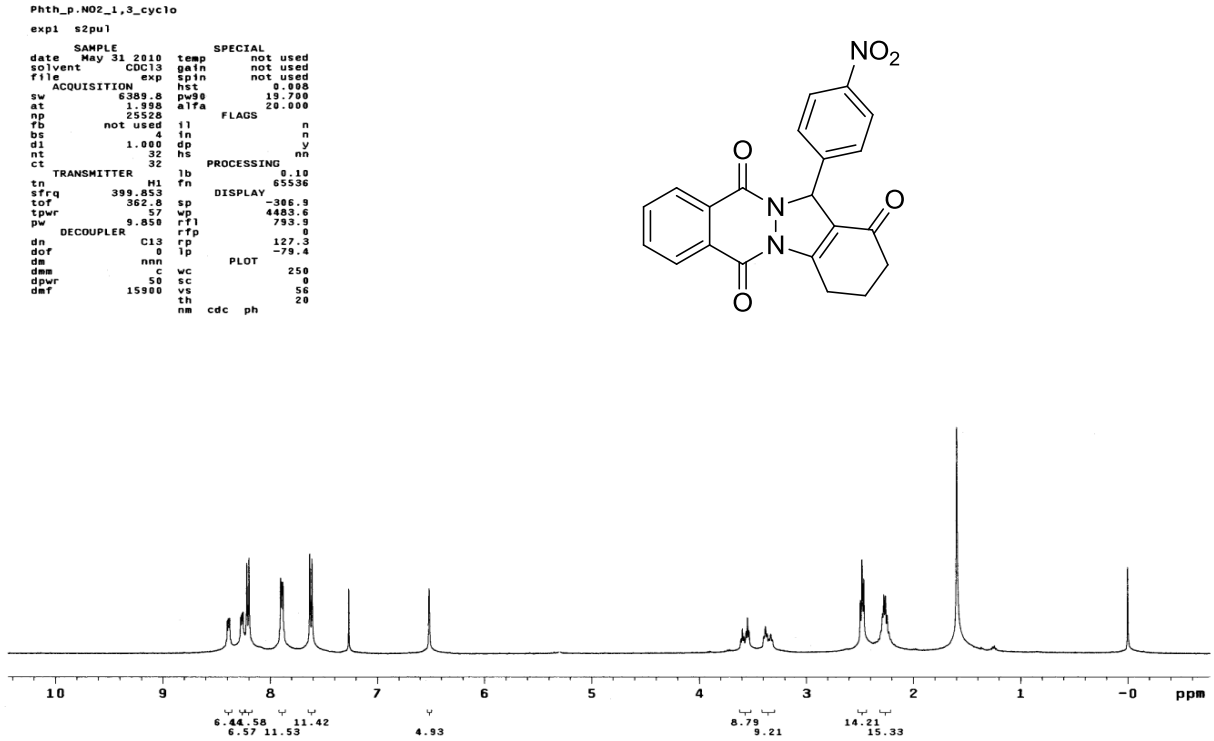


Figure 33

^{1}H NMR (400 MHz, $CDCl_3$): *2H-indazolo[2,1-b]phthalazine-trione* ***(10r)***



^{13}C NMR (100 MHz, DMSO): *2H-indazolo[2,1-b]phthalazine-trione* ***(10r)***

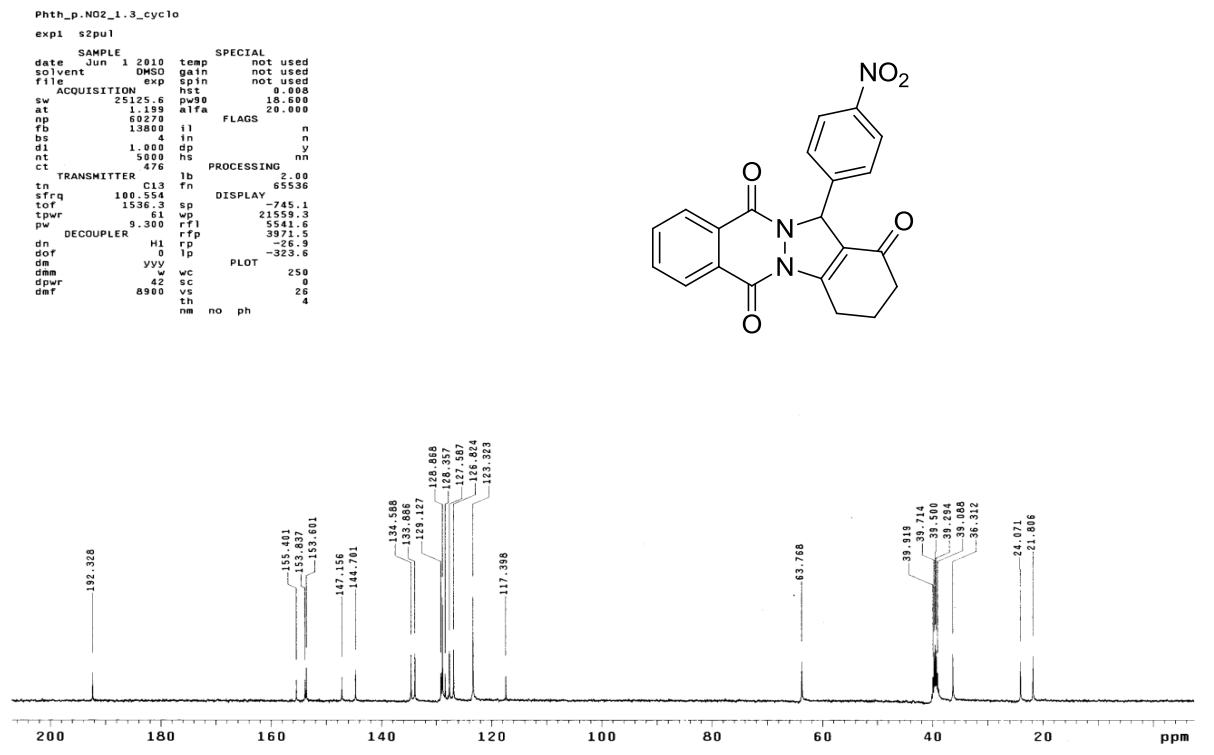


Figure 34

PART B

CHAPTER 3

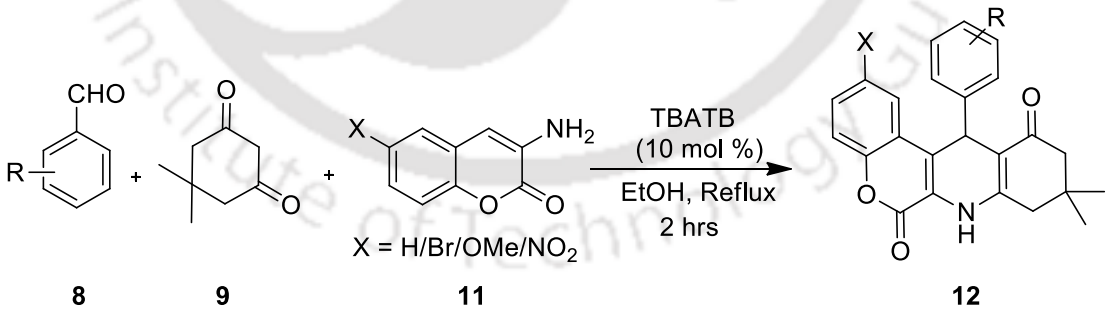
Synthesis of Chromeno[3,4-*b*]quinolin-6,11-dione Derivatives via One-pot Three Component Reactions Using TBATB

Results and Discussion

Results and discussion

Quinoline and its annulated derivatives are an important class of heterocycles because of their diverse applications.[49] Compounds containing quinoline moiety have wide application in medicinal chemistry[50] with a broad spectrum of biological activities like antimalarial, antiinflammatory, antiasthmatic, antihypertensive, antibacterial, anticancer and tyrosine kinase inhibitor.[51] On the other hand, chromene nucleus is also found in many naturally occurring biologically active compounds displaying antihypertensive, antiischemic and anti-HIV activities.[52] Chromenoquinoline derivatives have been therapeutically[53] used as drugs that modulate the transcriptional activity of human progesterone receptor. Some of them can be used as antagonists[54] and anti-inflammatory agents such as cortisone and cortisol.[55]

A few years ago, Chaudhuri and his collaborators first reported the environmentally benign synthesis of TBATB and its application in bromination reactions.[56] Later on, our group also demonstrated its usefulness for the deprotection of dithioacetals,[57a] inter-conversion of carbonyl compounds into 1,3-oxathiolanes and vice-versa,[57b] synthesis of α-bromo enones,[57c] piperidines[57d] and naturally occurring flavone derivatives[57e] as well as in carbohydrate chemistry.[57f] A wide variety of organic transformations have also been developed by other groups utilizing TBATB.[58] Knowing the unique behaviour, properties and stability of organic ammonium tribromides, we conceived that TBATB might act as a useful catalyst for the one-pot synthesis of Chromeno[3,4-*b*]quinoline-6,11-dione derivatives (**12**) from aromatic aldehydes (**8**), cyclic 1,3-diketones (**9**) and 3-aminocoumarins (**11**) (Scheme 29).



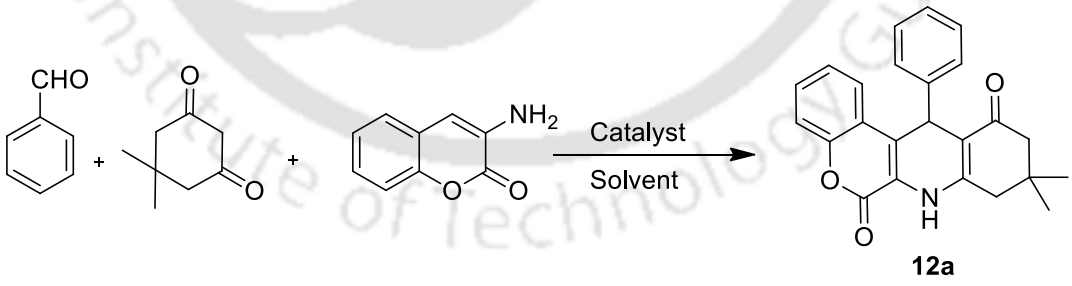
Scheme 29. One-pot three-component condensation reaction for the synthesis of Chromeno[3,4-*b*]quinoline-6,11-dione derivatives.

To find out the optimized reaction condition for the synthesis of Chromeno[3,4-*b*]quinoline-6,11-diones, one-pot three-component reaction was carried out using dimedone (1.0 mmol), benzaldehyde (1.0 mmol) and 3-aminocoumarin (1.0 mmol) in ethanol under reflux condition in presence of 5 mol% of TBATB and the desired product **12a** was isolated in 54% yield. The

product was characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and by elemental analysis. In IR spectrum, it showed characteristic absorptions peaks at 3290 (NH), 1713 (C=O) and 1623 cm^{-1} (conjugated C=O). Similarly, the compound **12a** showed a diagnostic signal at δ 5.59 in the ^{1}H NMR spectrum assignable to H-12 at the point of attachment of dihydropyridine ring to the aryl moiety.

The same reaction was then executed successively using 10 mol% and 20 mol% of TBATB (entries 2 and 3, Table 7), which gave rise to the desired product **12a** in 85% and 86% yield, respectively. It was noted that the yield of the product did not increase significantly by increasing the amount of catalyst from 10% to 20%. From these observations, it appeared that 10 mol% of the catalyst is sufficient to obtain best result. For scrutinizing the suitable solvent system, similar reactions were also performed in methanol and acetonitrile (Table 7, entry 4 & 5) and it was found that the maximum yield was obtained in ethanol. As a result, ethanol was chosen as the reaction solvent. To examine the efficacy of the catalyst, similar reactions were carried out in presence of other catalysts such as $FeCl_3.6H_2O$, HCl, aq 48% HBr and $HClO_4$-SiO_2 (Table 7, entries 7-10). It was observed that the reaction does not proceed on using HCl as catalyst while, on using 20 mol% of aq 48% HBr, only a trace amount of product was obtained. From these observations, we concluded that the highest yields and shortest reaction times were obtained on using 10 mol% of TBATB as catalyst. The successful results are summarized in Table 7.

Table 7. Optimization of reaction conditions for the synthesis of Chromeno[3,4-*b*]quinoline-6,11-dione derivative **12a**[a]



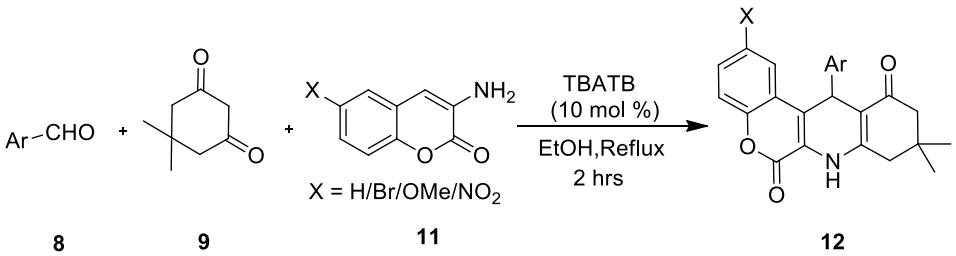
12a

Entry	Catalyst	Solvent	Catalyst (mol%)	Time (h)	Yield[b] (%)
1	TBATB	EtOH	5	4	54
2	TBATB	EtOH	10	2	85
3	TBATB	EtOH	20	2	86
4	TBATB	MeOH	10	4	66
5	TBATB	MeCN	10	4	62
6	*p*-TSA	EtOH	20	7	77
7	$FeCl_3$	EtOH	10	4	38
8	HCl	EtOH	20	4	00
9	aq.48% HBr	EtOH	20	4	33
10	$HClO_4$-SiO_2	EtOH	10	4	44

[a]*All the reactions were carried out with benzaldehyde, dimedone and 3-aminocoumarin in 1:1:1 ratio in presence of catalyst in 3 mL of indicated solvent.*
[b]*Isolated yields.*

To explore the synthetic scope and the generality of the present protocol, reactions under prior optimized conditions were performed using dimedone, a wide variety of substituted aromatic aldehydes and 3-aminocoumarins. The reaction time and percentage yield of the products (**12b-p**) are shown in Table 8 (entries 2-16). It is worthwhile to mention that the pure products can be obtained from all these reactions just by filtration of the solid products followed by recrystallization of the crude products from dichloromethane and ethanol mixture thereby avoiding aqueous work-up and tedious column-chromatographic separation.

Table 8. Substrate scope of chromeno[3,4-*b*]quinoline-6,11-dione derivatives



8 9 11 12

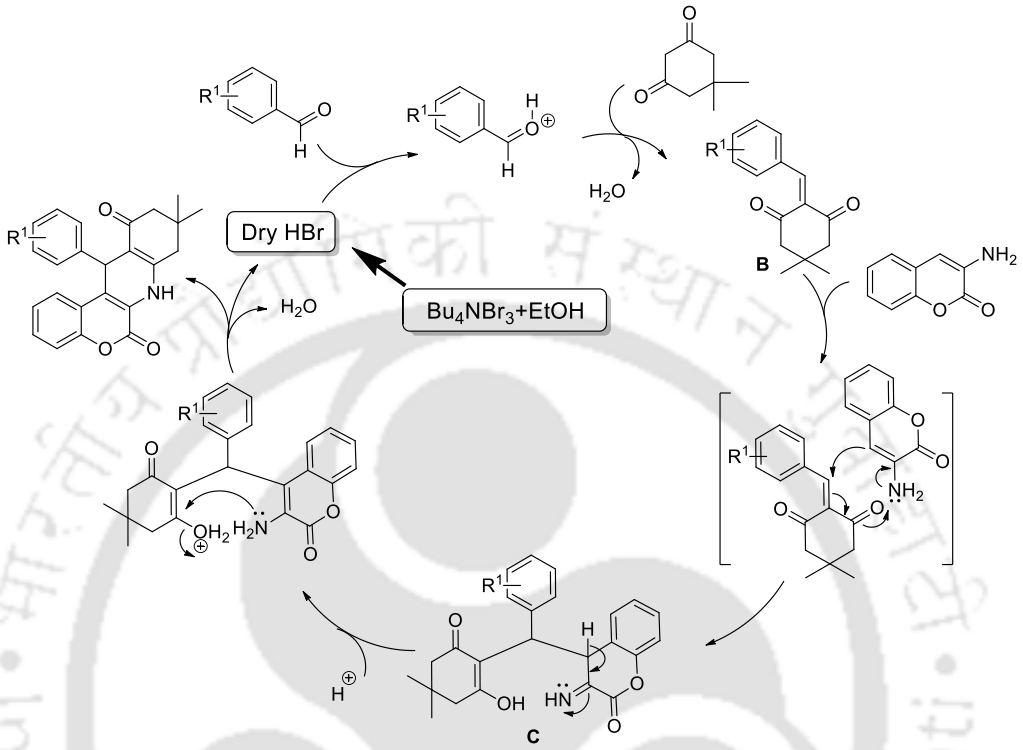
Entry	Ar	X	Product	Yield[b] (%)
1	C_6H_5	H	**12a**	85
2	4-Me-C_6H_4	H	**12b**	91
3	4-F-C_6H_4	H	**12c**	87
4	4-Cl-C_6H_4	H	**12d**	88
5	4-Br-C_6H_4	H	**12e**	90
6	3-F-C_6H_4	H	**12f**	85
7	4-CN-C_6H_4	H	**12g**	87
8	2-Thiophene	H	**12h**	85
9	C_6H_5	OMe	**12i**	84
10	4-Cl-C_6H_4	OMe	**12j**	89
11	2-Thiophene	OMe	**12k**	87
12	2-Napthyl	OMe	**12l**	88
13	4-Cl-C_6H_4	NO_2	**12m**	89
14	4-F-C_6H_4	NO_2	**12n**	86
15	4-Br-C_6H_4	Br	**12o**	85
16	4-Me-C_6H_4	Br	**12p**	91

[a]*Reaction conditions: aromatic aldehydes, dimedone and 3-aminocoumarin were taken in 1:1:1 ratio in presence of TBATB (0.048 g, 0.1 mmol) in 3 ml ethanol.*
[b]*Combined yield after recrystallization.*

All the products were fully characterized by IR, ^{1}H, and ^{13}C NMR spectra as well as elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compounds **12f**, **12g**, **12h**, **12i 12k, 12l, 12o** and **12p** are given in the experimental section (Figure 36, 37, 38, 39, 40, 41, 42 and 43).

The formation of the products may be explained as follows: It was earlier reported that benzyltrimethyl ammonium bromide on reaction with ethanol can produce dry HBr in the reaction medium.[59] We believe that TBATB reacts with ethanol to generate dry HBr in the reaction medium which actually catalyzes the product formation. First the aromatic aldehyde reacts with dimedone in presence of TBATB as catalyst to provide Knoevenagel product **B**, which is benzylidenecyclohexane-1,3-dione intermediate. The intermediate **B** act a suitable Michael acceptor and reacts with 3-aminocoumarin to give intermediate **C** by Michael

reaction, which undergoes intra-molecular ring closure reaction followed by elimination of H_2O molecule to give product **12** (Scheme 30).



Scheme 30

The structure of the representative compound **12o** was confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 35).

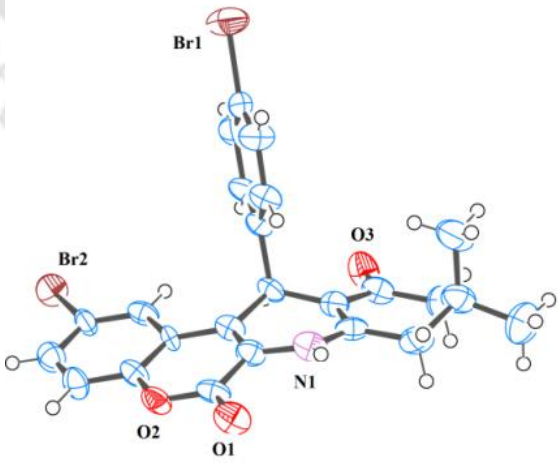


Figure 35. X-ray crystal structures of **12o** (CCDC 910378)

In summary, we have provided an effective route for the synthesis of a series of Chromeno[3,4-*b*]quinoline-6,11-dione derivatives *via* one-pot three component reaction. The significant features of the present protocol are short reaction times, superior atom economy, simplicity of the procedure and good to excellent yields.

PART B

CHAPTER 3

Synthesis of Chromeno[3,4-*b*]quinolin-6,11-dione Derivatives via One-pot Three Component Reactions Using TBATB

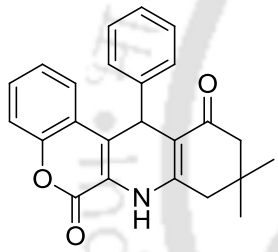
Experimental Section

General procedure for synthesis of Chromeno[3,4-*b*]quinoline-6,11-diones (12)

To a solution of a mixture of cyclic 1,3-diketone (1.0 mmol), aromatic aldehyde (1.0 mmol) and 3 aminocoumarins (1.0 mmol) in ethanol (3 mL) was added *n*-tetrabutylammonium tribromide (TBATB) (0.048 g, 0.1 mmol) and the resulting reaction mixture was refluxed for 2 hours in a pre-heated oil bath. After completion of reaction, the reaction mixture was brought to room temperature and the solid product was precipitated out. The precipitate was filtered off through a Büchner funnel and it was washed with 1 mL of ethanol and finally it was dried in a vacuum pump to get the pure product. The filtrate was concentrated further and it was kept for recrystallization in DCM-EtOH (1:1) mixture.

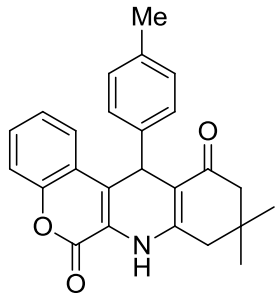
Spectral data of Chromeno[3,4-*b*]quinoline-6,11-diones (12)

9,10-Dihydro-9,9-dimethyl-12-phenyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione ***(12a)*****:**



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

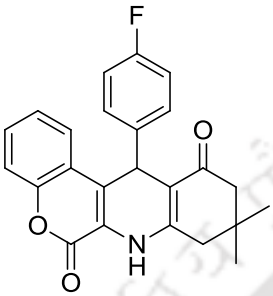
9,10-Dihydro-9,9-dimethyl-12-p-tolyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione ***(12b)*****:**



Yellow solid, m.p. 252-254°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (3 H, s), 1.08 (3 H, s), 2.20 (3 H, s), 2.21 (1 H, d, *J* = 16.4 Hz), 2.27 (1 H, d, *J* = 16.4 Hz), 2.39 (1 H, d, *J* = 16.4 Hz), 2.45 (1 H, d, *J* = 16.4 Hz), 5.52 (1 H, s), 7.00 (2 H, d, *J* = 8 Hz), 7.15 (1 H, s, NH), 7.19 (1 H, td, *J* = 7.6 Hz), 7.27 (3 H, m), 7.35-7.28 (1 H, m), 7.65 (1 H, dd, *J* = 8, 1.2 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.17, 27.30, 29.40, 32.85, 36.26, 41.37, 50.83, 108.93, 116.79, 119.18, 121.80, 124.13, 125.20, 126.92, 128.13, 129.20,

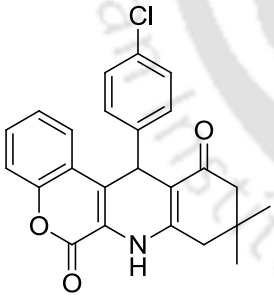
129.40, 136.66, 141.35, 149.09, 150.62, 157.61, 195.32; **IR** (KBr, cm^{-1}): 3338 (NH), 1699 (C=O), 1630 (C=O), 1598 (C=C), 1567, 1509 ; **Anal. Calcd** for $C_{25}H_{23}NO_3$ (385.46): C, 77.90; H, 6.01; N, 3.63; Found: C, 77.98; H, 6.06; N, 3.67%.

*12-(4-Fluorophenyl)-9,10-dihydro-9,9-dimethyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12c**)*:



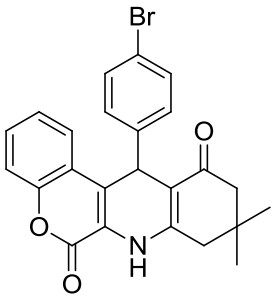
Yellow solid, m.p. 241-243 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (3H, s), 1.10 (3 H, s), 2.22 (1 H, d, *J* = 16.8 Hz), 2.29 (1 H, d, *J* = 16.4 Hz), 2.40 (1 H, d, *J* = 16.8 Hz), 2.48 (1 H, d, *J* = 16.8 Hz), 5.58 (1 H, s), 6.94-6.89 (2H, m), 7.08 (1 H, s, NH), 7.23 (1 H, td, *J* = 7.6, 1.2 Hz),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

*12-(4-Chlorophenyl)-9,10-dihydro-9,9-dimethyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12d**)*:



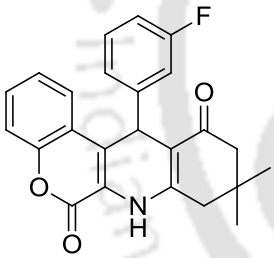
Yellow solid, m.p. 251-253 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (3 H, s), 1.10 (3 H, s), 2.21 (1 H, d, *J* = 16.4 Hz), 2.30 (1 H, d, *J* = 16.4 Hz), 2.43 (1 H, d, *J* = 16.8 Hz), 2.50 (1 H, d, *J* = 16.8 Hz), 5.55 (1 H, s), 7.16 (1 H, s, NH), 7.22-7.19 (2 H, m), 7.28 (1 H, d, *J* = 8 Hz), 7.38-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

*12-(4-Bromophenyl)-9,10-dihydro-9,9-dimethyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione(**12e**)*:



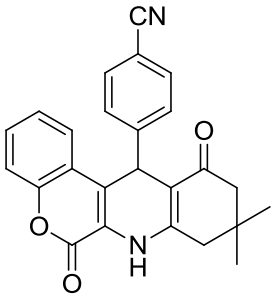
Yellow solid; m.p. 280-282 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (3H, s), 1.03 (3 H, s), 2.14 (1 H, d, *J* = 16.4 Hz), 2.27 (1 H, d, *J* = 16.8 Hz), 2.35 (1 H, d, *J* = 17.2 Hz), 2.43 (1 H, d, *J* = 16.8 Hz), 5.48 (1 H, s), 7.14 (1 H, td, *J* = 7.6, 1.2 Hz), 7.20 (1 H, s, NH), 7.32-7.21 (6 H,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

*12-(3-fluorophenyl)-9,10-dihydro-9,9-dimethyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12f**)*:



Yellow solid, m.p. 243-245 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (3 H, s), 1.11 (3 H, s), 2.23 (1 H, d, *J* = 16.8 Hz), 2.30 (1 H, d, *J* = 16.4 Hz), 2.42 (1 H, d, *J* = 16.8 Hz), 2.50 (1 H, d, *J* = 16.8 Hz), 5.60 (1 H, s), 6.80-6.85 (1H, m), 7.07-7.09 (2H, m), 7.16-7.26 (3 H, m), 7.33 (1 H, d, *J* = 7.2 Hz), 7.39 (1 H, t, *J* = 8.4 Hz), 7.60 (1 H, d, *J* = 7.6 Hz; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.18, 29.38, 32.81, 36.43, 41.30, 50.81, 108.40, 114.20, 115.30, 116.90, 119.00, 122.12, 124.00, 125.30, 126.00, 129.40, 130.11, 146.47, 149.42, 150.60, 157.43, 162.00, 164.40, 195.26; **IR** (KBr, cm^{-1}): 3414 (NH), 1712 (C=O), 1618 (C=O), 1596 (C=C); **Anal. Calcd** for $C_{24}H_{20}FNO_3$(389.42): C, 74.02; H, 5.18; N, 3.60; Found: C, 74.09; H, 5.12; N, 3.56%.

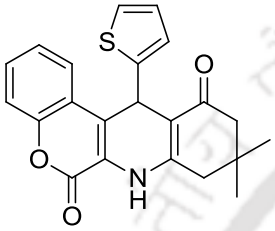
*12-(4-Cyanophenyl)-9,10-dihydro-9,9-dimethyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12g**)*:



Yellow solid, m.p. 261-263 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (3 H, s), 1.12 (3 H, s), 2.22 (1 H, d, *J* = 16.0 Hz), 2.30 (1 H, d, *J* = 16.4 Hz), 2.43 (1 H, d, *J* = 16.8 Hz), 2.50 (1 H, d, *J* = 16.8 Hz), 5.66 (1 H, s), 7.15 (1H, s), 7.23 (1H, t, *J* = 8 Hz), 7.34 (1 H, d, *J* = 8.4 Hz),

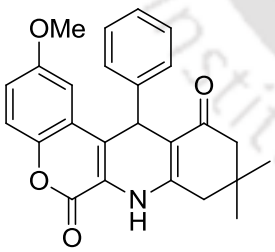
7.41 (1 H, t, *J* = 8.4 Hz), 7.50-7.57 (5 H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.15, 29.34, 32.83, 36.96, 41.30, 50.72, 107.84, 110.92, 117.03, 118.66, 118.82, 122.34, 123.70, 125.13, 125.42, 129.05, 129.70, 132.63, 148.93, 149.71, 150.60, 157.25, 195.18; **IR** (KBr, cm^{-1}): 3414 (NH), 1729 (C=O), 1638 (C=O), 1617 (C=C); **Anal. Calcd** for $C_{25}H_{20}N_2O_3$ (396.44): C, 75.74; H, 5.08; N, 7.07; Found: C, 75.69; H, 5.13; N, 7.01%.

12-(thiophen-2-yl)-9,10-dihydro-9,9-dimethyl-6H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione ***(12h)***:



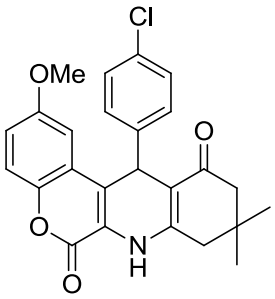
Yellow solid, m.p. 290-295 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (3 H, s), 1.09 (3 H, s), 2.29 (1 H, s), 2.42-2.44 (3 H, m), 5.90 (1 H, s), 6.78 (1H, t, *J* = 3.6 Hz Hz), 6.86 (1H, d, *J* = 3.2 Hz), 7.05 (1 H, d, *J* = 5.2 Hz), 7.13 (1 H, s), 7.25 (1H, t, *J* = 7.6 Hz), 7.31 (1 H, d, *J* = 8.0 Hz), 7.38 (1 H, t, *J* = 7.2 Hz), 7.71 (1 H, d, *J* = 8.8 Hz) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.30, 29.52, 31.10, 32.80, 41.13, 50.80, 108.05, 116.83, 119.00, 121.70, 124.00, 124.60, 125.03, 125.24, 125.50, 126.70, 129.34, 147.00, 149.76, 150.60, 157.41, 195.24; **IR** (KBr, cm^{-1}): 3264 (NH), 1719 (C=O), 1629 (C=O), 1597 (C=C); **Anal. Calcd** for $C_{22}H_{19}NO_3S$ (377.46): C, 70.00; H, 5.07; N, 3.71; Found: C, 70.09; H, 5.12; N, 3.74%.

2-Methoxy-12-phenyl-9,10-dihydro-9,9-dimethyl-6H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione ***(12i)***:



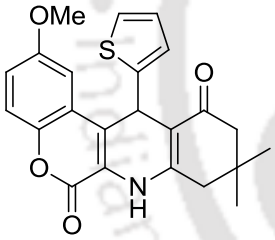
Yellow solid, m.p. 247-249 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (3 H, s), 1.11 (3 H, s), 2.22 (1 H, d, *J* = 16.4 Hz), 2.29 (1 H, d, *J* = 16.4 Hz), 2.41 (1 H, d, *J* = 16.4 Hz), 2.48 (1 H, d, *J* = 16.8 Hz), 3.76 (3 H, s), 5.53 (1 H, s), 6.92 (1H, dd, *J* = 2.8 Hz, 8.8 Hz), 7.06-7.13 (2H, m), 7.15 (1 H, s, NH), 7.22-7.27 (3 H, m), 7.40-7.42 (2 H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.24, 29.41, 32.86, 37.04, 41.41, 50.85, 55.84, 106.60, 108.90, 117.01, 117,77, 119.72, 122.12, 126.59, 127.16, 128.32, 128.75, 144.28, 144.99, 149.03, 156.66, 157.65, 195.34; **IR** (KBr, cm^{-1}): 3414 (NH), 1698 (C=O), 1632 (C=O), 1599 (C=C); **Anal. Calcd** for $C_{25}H_{23}NO_4$ (401.45): C, 74.79; H, 5.77; N, 3.49; Found: C, 74.73; H, 5.83; N, 3.42%.

*2-Methoxy-12-(4-chlorophenyl)-9,10-dihydro-9,9-dimethyl-6H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12j**)*:



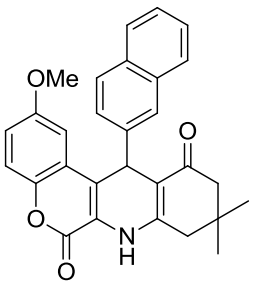
Yellow solid, m.p. 225-230 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (3 H, s), 1.11 (3 H, s), 2.22 (1 H, d, *J* = 17.2 Hz), 2.29 (1 H, d, *J* = 16.4 Hz), 2.40 (1 H, d, *J* = 16.4 Hz), 2.48 (1 H, d, *J* = 16.8 Hz), 3.76 (3 H, s), 5.51 (1 H, s), 6.94 (1H, dd, *J* = 2.8 Hz, 8.8 Hz), 6.98 (1H, d, *J* = 2.4 Hz), 7.11 (1 H, s, NH), 7.20-7.23 (2 H, m), 7.26 (1 H, d, *J* = 6.4 Hz,), 7.36 (2 H, d, *J* = 1.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.31, 29.42, 32.90, 35.86, 41.45, 50.89, 55.29, 109.11, 114.07, 116.87, 119.19, 121.75, 124.18, 125.23, 126.92, 129.25, 129.31, 136.65, 148.73, 150.67, 157.66, 158.53, 195.37; **IR** (KBr, cm^{-1}): 3336 (NH), 1698 (C=O), 1636 (C=O), 1573 (C=C); **Anal. Calcd** for $C_{25}H_{22}ClNO_4$ (435.90): C, 68.88; H, 5.09; N, 3.21; Found: C, 68.96; H, 5.14; N, 3.17%.

*2-Methoxy-12-(thiophen-2-yl)-9,10-dihydro-9,9-dimethyl-6H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12k**)***:***



Yellow solid, m.p. 232-235 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.04 (3 H, s), 1.13 (3 H, s), 2.31-2.32 (2 H, m), 2.47 (1 H, d, *J* = 16.8 Hz), 2.49 (1 H, d, *J* = 16.4 Hz), 3.81 (3 H, s), 5.90 (1 H, s), 6.82 (1H, dd, *J* = 3.2 Hz, 4.8 Hz), 6.89-6.90 (1H, m), 6.96 (1 H, dd, *J* = 2.4 Hz, 8.8 Hz), 7.08 (1 H, dd, *J* = 1.2 Hz, 5.2 Hz), 7.14 (1H, d, *J* = 2.8 Hz), 7.25 (2 H, m), ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.25, 29.52, 31.25, 32.76, 41.13, 50.74, 55.91, 106.24, 108.10, 117.13, 117.80, 119.50, 121.82, 124.60, 125.14, 125.43, 126.73, 144.95, 147.04, 149.72, 156.72, 157.50, 195.27; **IR** (KBr, cm^{-1}): 3413 (NH), 1698 (C=O), 1637 (C=O), 1573 (C=C); **Anal. Calcd** for $C_{23}H_{21}NO_4S$ (407.48): C, 67.79; H, 5.19; N, 3.44; Found: C, 67.75; H, 5.25; N, 3.39%.

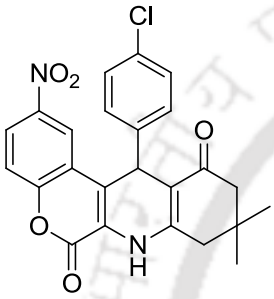
*2-Methoxy-12-(naphthalene-2-yl)-9,10-dihydro-9,9-dimethyl-6H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12l**)***:***



Yellow solid, m.p. 253-255 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.92 (3 H, s), 1.10 (3 H, s), 2.19 (1 H, d, *J* = 16.4 Hz), 2.30 (1 H, d, *J* = 16.4 Hz), 2.42 (1 H, d, *J* = 16.8 Hz), 2.49 (1 H, d, *J* = 16.4 Hz), 3.73 (3 H, s), 5.70 (1 H, s), 6.88 (1H, dd, *J* = 2.8 Hz, 8.8 Hz), 7.11-7.12 (2H, m),

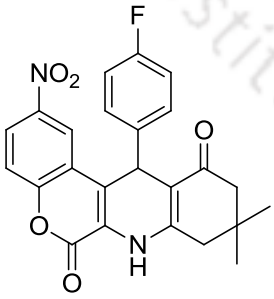
7.21 (1 H, d, *J* = 9.2 Hz), 7.37-7.43 (2 H, m), 7.59 (1 H, dd, *J* = 1.6 Hz, 8.4 Hz), 7.74 (3 H, m), 7.81 (1H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.14, 29.35, 32.68, 37.18, 41.16, 50.77, 55.69, 106.59, 108.57, 116.84, 117.67, 119.66, 122.18, 125.86, 126.16, 126.31, 126.66, 126.96, 127.60, 128.01, 128.49, 132.53, 133.46, 141.77, 144.90, 149.30, 156.53, 157.58, 195.36; **IR** (KBr, cm^{-1}): 3413 (NH), 1699 (C=O), 1636 (C=O), 1600 (C=C); **Anal. Calcd** for $C_{29}H_{25}NO_4$ (451.51): C, 77.14; H, 5.58; N, 3.10; Found: C, 77.08; H, 5.62; N, 3.14%.

*12-(4-chlorophenyl)-9,10-dihydro-9,9-dimethyl-2-nitro-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12m**)*:



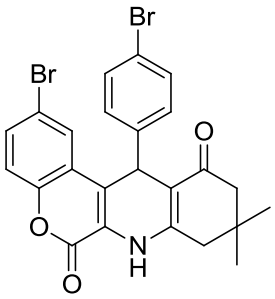
Yellow solid, m.p. 258-262 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.98 (3 H, s), 1.13 (3 H, s), 2.25 (1 H, d, *J* = 16.4 Hz), 2.32 (1 H, d, *J* = 16.8 Hz), 2.46 (1 H, d, *J* = 16.4 Hz), 2.53 (1 H, d, *J* = 16.8 Hz), 5.58 (1 H, s), 7.22-7.27 (3 H, m), 7.39 (2H, dd, *J* = 2.0 Hz, 8.4 Hz), 7.44 (1 H, dd, *J* = 2.4 Hz, 8.8 Hz), 8.22 (1 H, d, *J* = 9.2 Hz), 8.51 (1 H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.34, 29.36, 32.99, 36.48, 41.40, 50.73, 109.05, 118.07, 119.74, 119.88, 121.66, 123.36, 124.07, 124.32, 129.97, 132.26, 142.43, 144.88, 148.51, 153.74, 156.32, 195.23; **IR** (KBr, cm^{-1}): 3358 (NH), 1727 (C=O), 1632 (C=O), 1529 (C=C); **Anal. Calcd** for $C_{24}H_{19}ClN_2O_5$(450.87): C, 63.93; H, 4.25; N, 6.21; Found: C, 63.88; H, 4.30; N, 6.18%.

*12-(4-Fluorophenyl)-9,10-dihydro-9,9-dimethyl-2-nitro-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12n**)*:



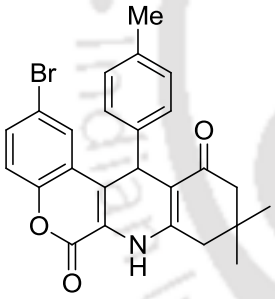
Yellow solid, m.p. 250-255 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (3 H, s), 1.13 (3 H, s), 2.24 (1 H, d, *J* = 16.8 Hz), 2.31 (1 H, d, *J* = 16.4 Hz), 2.44 (1 H, d, *J* = 16.8 Hz), 2.51 (1 H, d, *J* = 16.0 Hz), 5.58 (1 H, s), 6.96 (2H, t, *J* = 8.4 Hz), 7.06 (1H, s), 7.39-7.45 (3 H, m), 8.23 (1 H, dd, *J* = 2.4 Hz, 8.8 Hz), 8.52 (1 H, d, *J* = 2.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.24, 31.36, 34.48, 43.48, 51.37, 115.07, 115.14 119.64, 119.84, 120.71, 121.36, 122.04, 122.32, 125.97, 130.72, 137.72, 145.26, 149.43, 156.88, 158.51, 156.32, 196.23; **IR** (KBr, cm^{-1}): 3358 (NH), 1727 (C=O), 1601 (C=O), 1529 (C=C); **Anal. Calcd** for $C_{24}H_{19}FN_2O_5$(434.42): C, 66.35; H, 4.41; N, 6.45; Found: C, 66.42; H, 4.37; N, 6.50%.

*2-Bromo-12-(4-bromophenyl)-9,10-dihydro-9,9-dimethyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12o**)*:



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

*2-Bromo-9,10-dihydro-9,9-dimethyl-12-p-tolyl-7H-chromeno[3,4-b]quinoline-6,11(8H,12H)-dione (**12p**)*:



Yellow solid, m.p. 324-326 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (3 H, s), 1.10 (3 H, s), 2.22 (1 H, d, *J* = 16.4), 2.24 (3 H, s), 2.30 (1 H, d, *J* = 16.4 Hz), 2.41 (1 H, d, *J* = 16.4 Hz), 2.48 (1H, d, *J* = 16.4 Hz), 5.45 (1H, s), 7.04 (1 H, s, NH), 7.07 (2 H, d, *J* = 8.0 Hz), 7.17 (1 H, d, *J* = 8.4 Hz), 7.27 (2 H, d, *J* = 8.0 Hz), 7.43 (1H, dd, *J* = 8.8, 2.0 Hz),7.78 (1 H, d, *J* = 2.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.24, 27.37, 29.40, 33.00, 36.17, 41.43, 50.84, 109.28, 118.26, 118.47, 121.03, 122.49, 125.41, 126.70, 128.06, 129.64, 131.97, 137.04, 140.88, 148.62, 149.45, 157.15, 195.29; **IR** (KBr, cm^{-1}): 3177 (NH), 1724 (C=O), 1626 (C=O), 1591 (C=C), 1558, 1494 cm^{-1}; **Anal. Calcd** for $C_{25}H_{22}BrNO_3$ (464.35): C, 64.66; H, 4.78; N, 3.02; found: C, 64.73; H, 4.82; N, 3.09%.

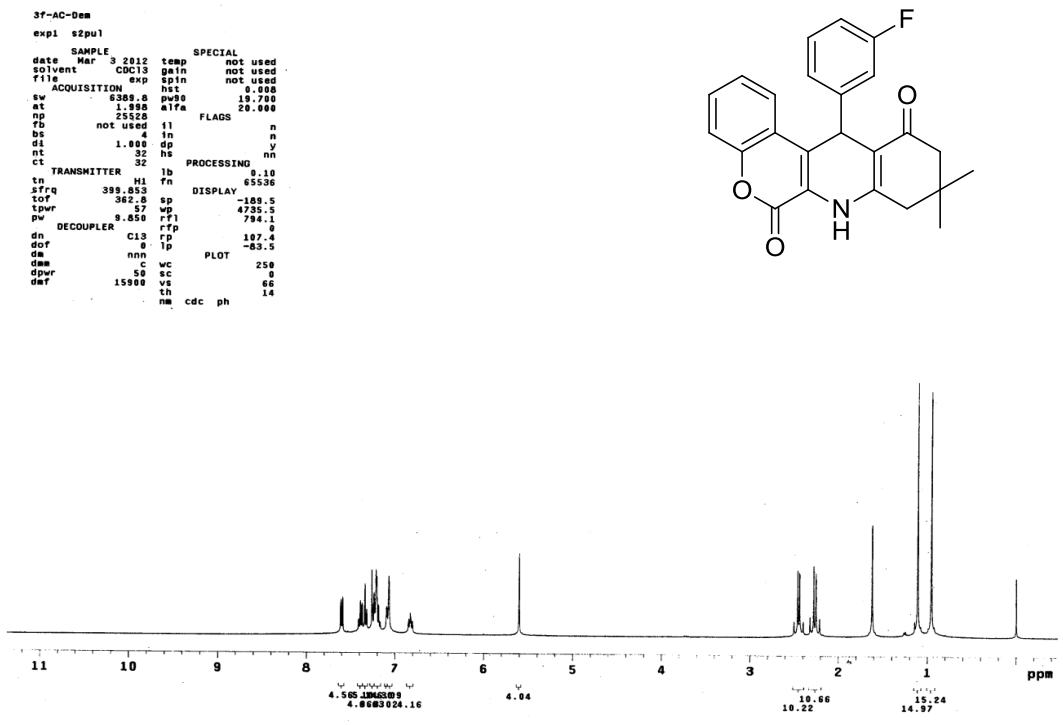
Crystallographic Description

Complete crystallographic data of compound **12o** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication, CCDC no. 910378. 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 9. Crystal data and structure refinement for compound **12o**

Parameters	**Compound 12o**	**Parameters**	**Compund 12o**
Identification code	12o	Z	2
Empirical formula	C24 H19 Br2 N O3	Density (calculated)	1.512 g/cm^3
Formula weight	529.22	Absorption coefficient	3.512 mm^{-1}
Temperature	296(2) K	F(000)	528
Wavelength	0.71073 Å	Theta range for data collection	1.42 to 30.05 º
Crystal system	Triclinic	Index ranges	-7<=h<= 10, -15<=k<=15, -21<=l<=20
Space group	P -1	Reflections collected	6328
Unit cell dimensions		Independent reflections	2315
a	7.3260(17) Å	Completeness to θº	93% (θ = 30.05 º)
b	11.186(3) Å	Refinement method	Full-matrix least-squares on F2
c	15.199(4) Å	Data / restraints / parameters	6328 / 0 / 292
α	102.961º(13)	Goodness-of-fit on F2	1.263
β	102.739º(13)	Final R indices [>2sigma(I)]	R_{obs} = 0.0762, wR_{obs} = 0.1884
γ	97.616º(13)	R indices (all data)	R_{all} = 0.2344, wR_{all} = 0.2678
Volume	1162.1(5) Å^3	Largest diff. peak and hole	1.593 and -2.008 e.Å^{-3}

^{1}H NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12f)***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12f)***

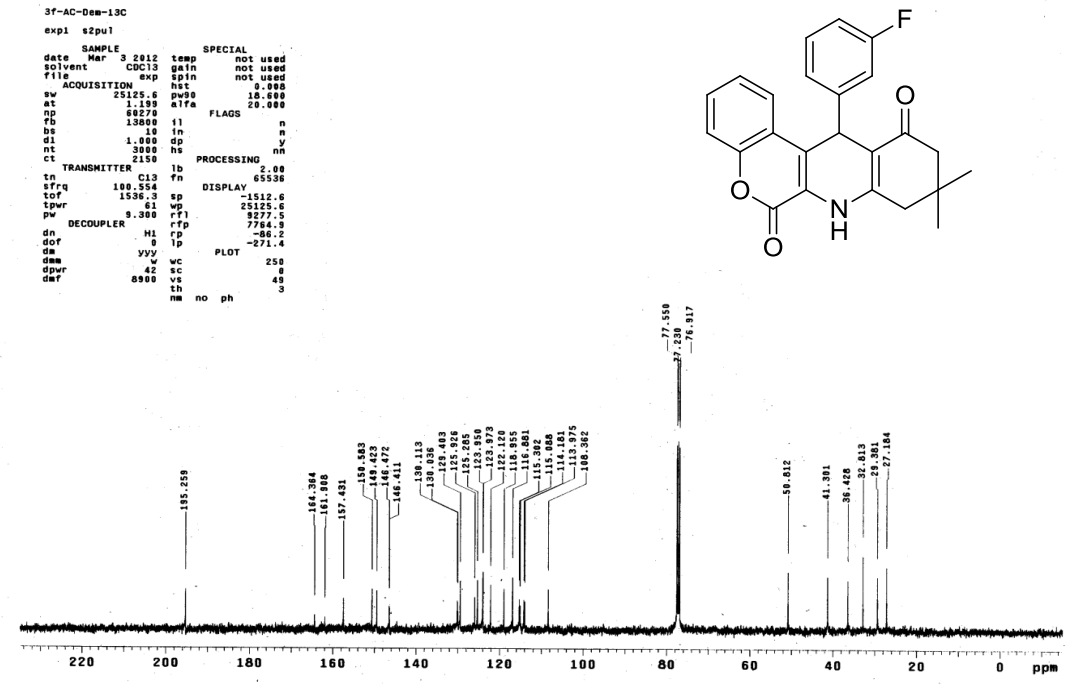
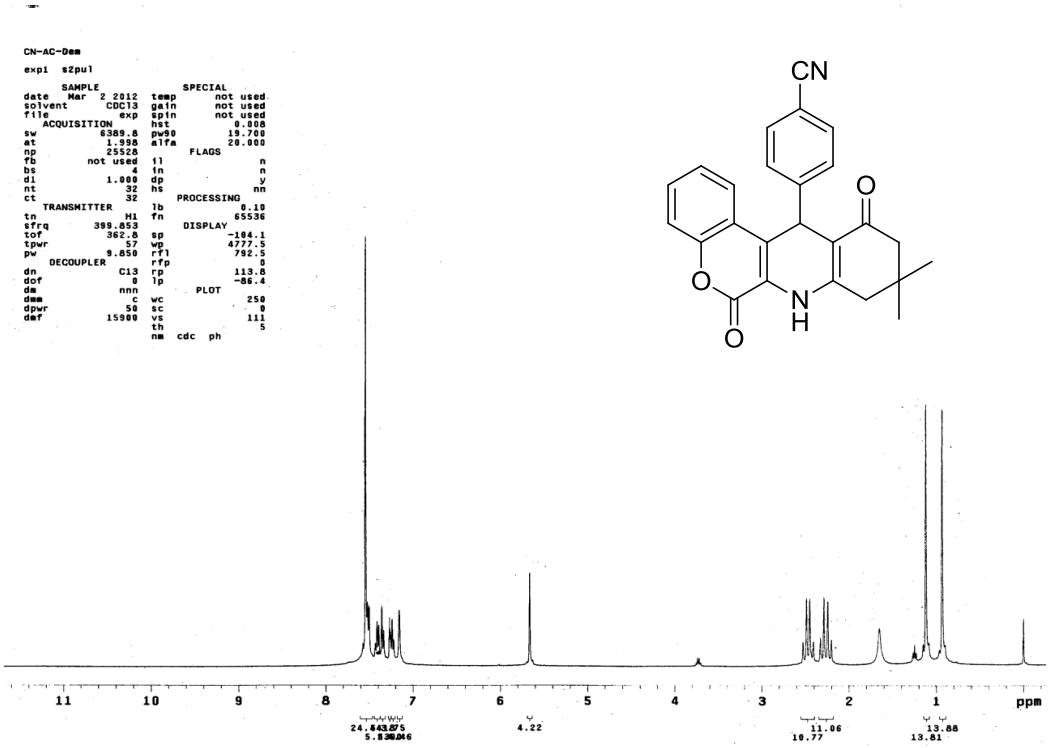


Figure 36

^{1}H NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12g)***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12g)***

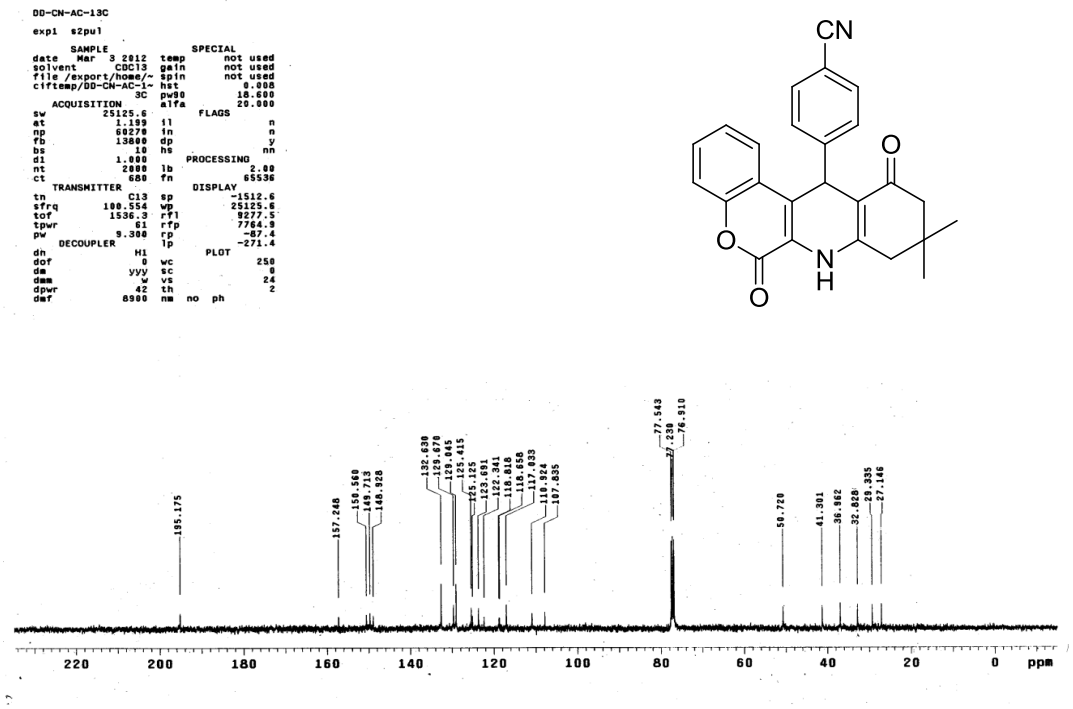
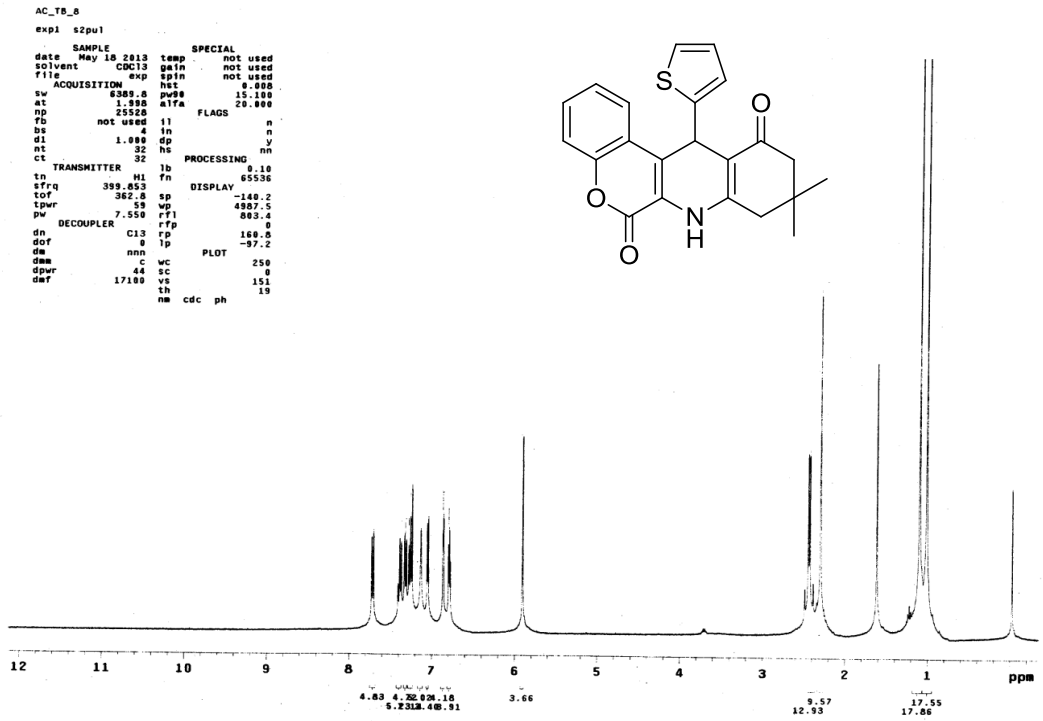


Figure 37

^{1}H NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12h)***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12h)***

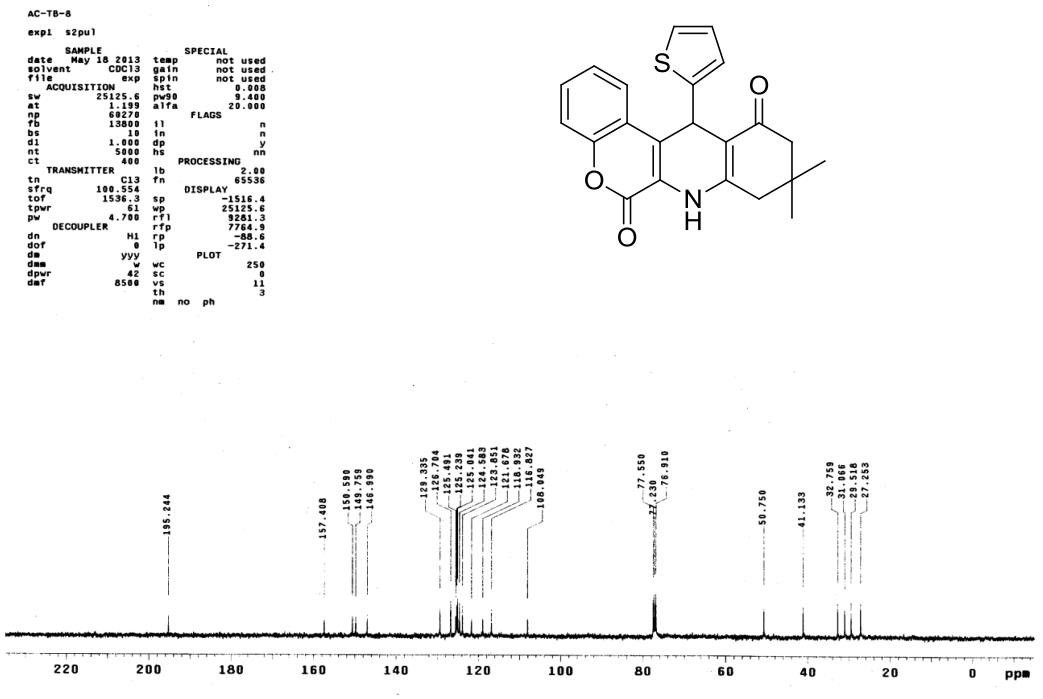
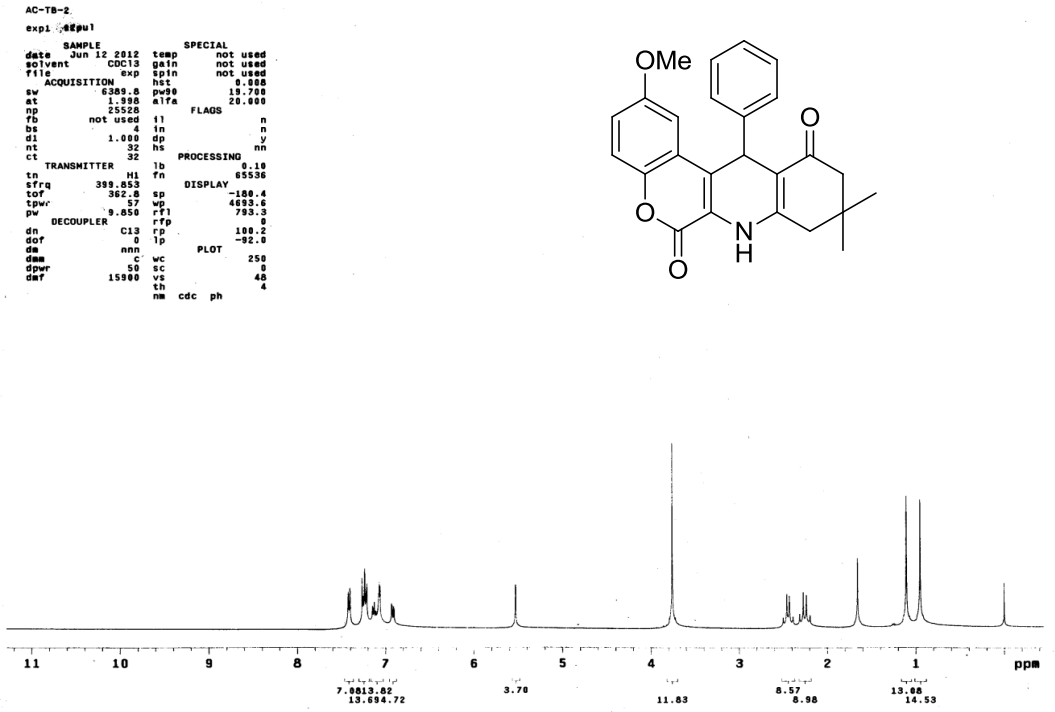


Figure 38

^{1}H NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12i)***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione (* ***12i)***

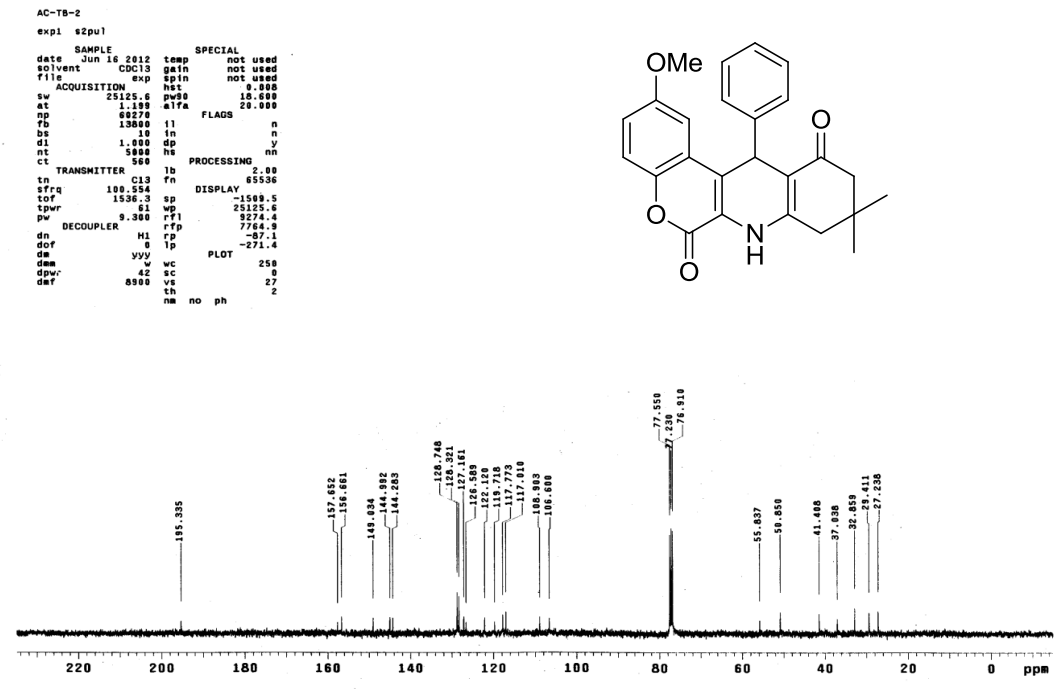
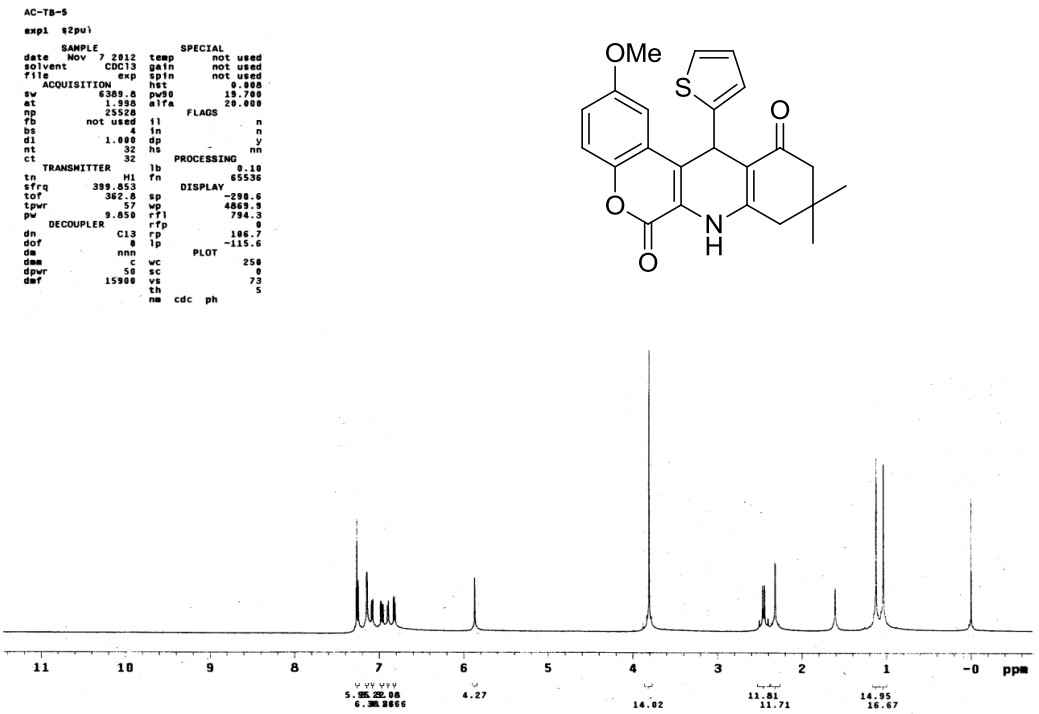


Figure 39

^{1}H NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12k)***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione (* ***12k)***

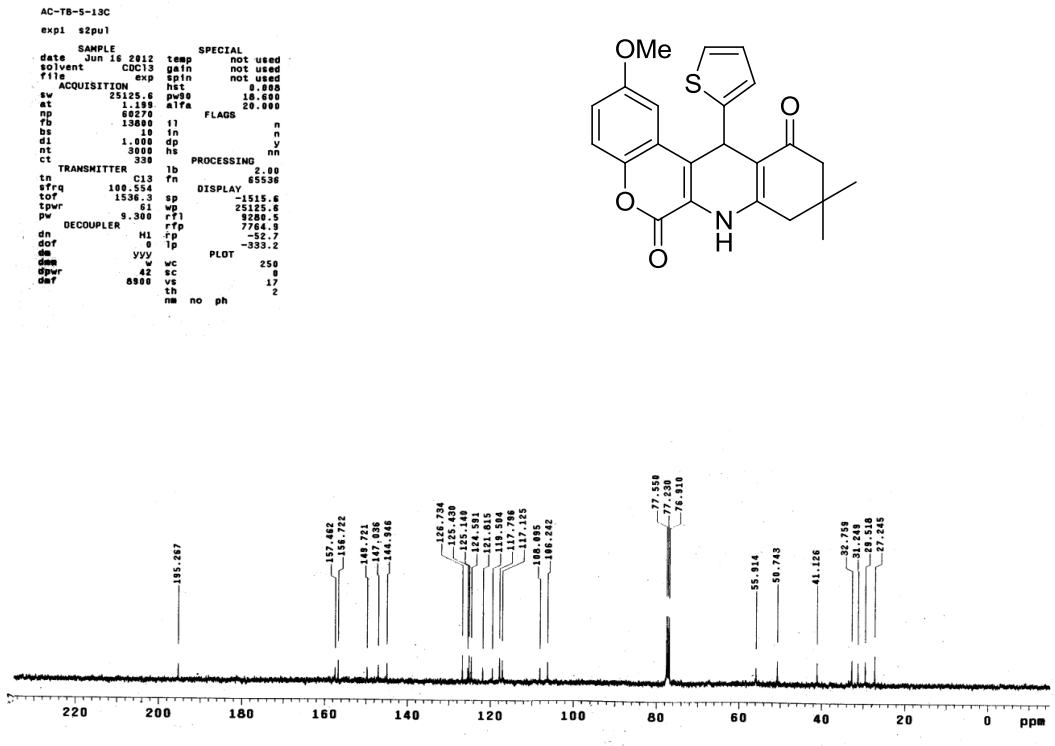
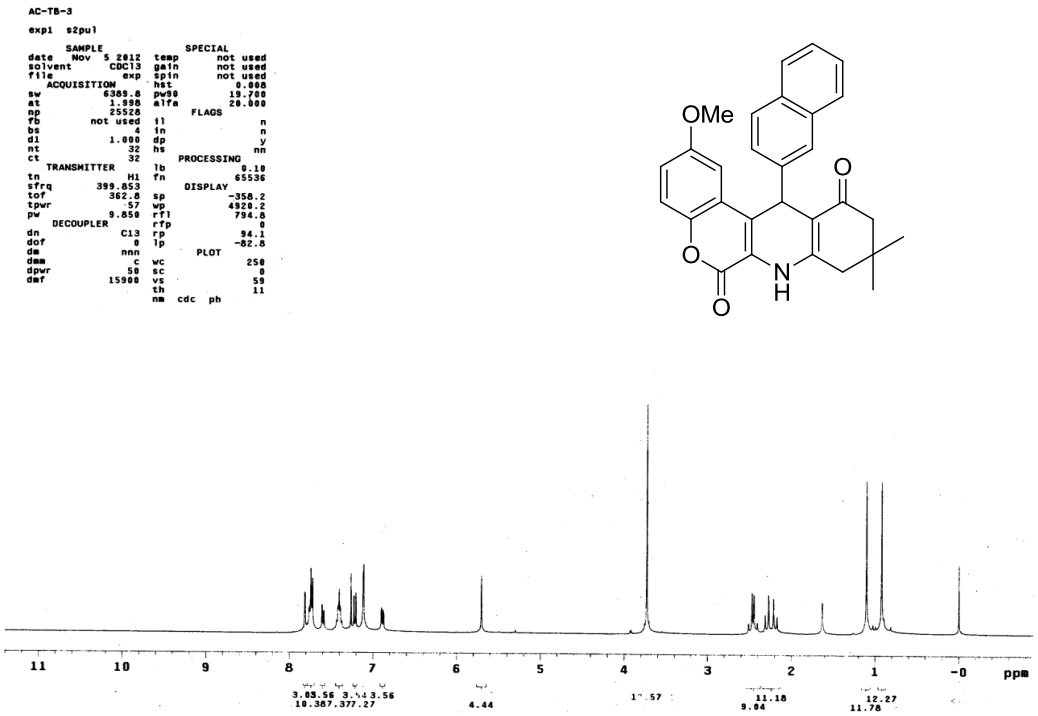


Figure 40

^{1}H NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12l)***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12l)***

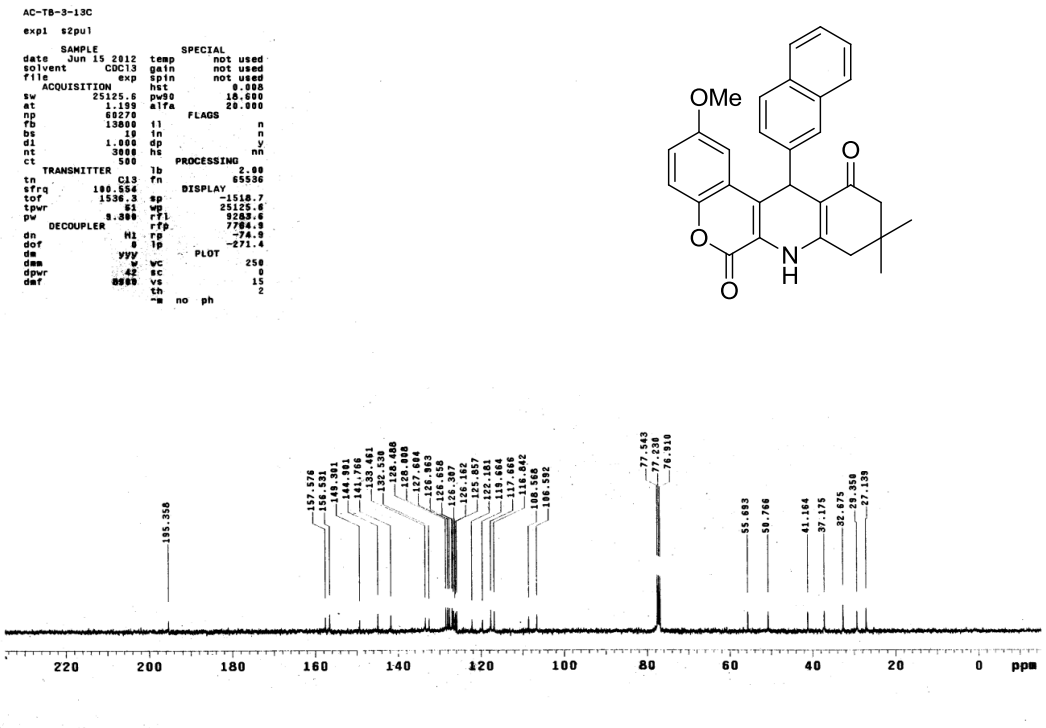
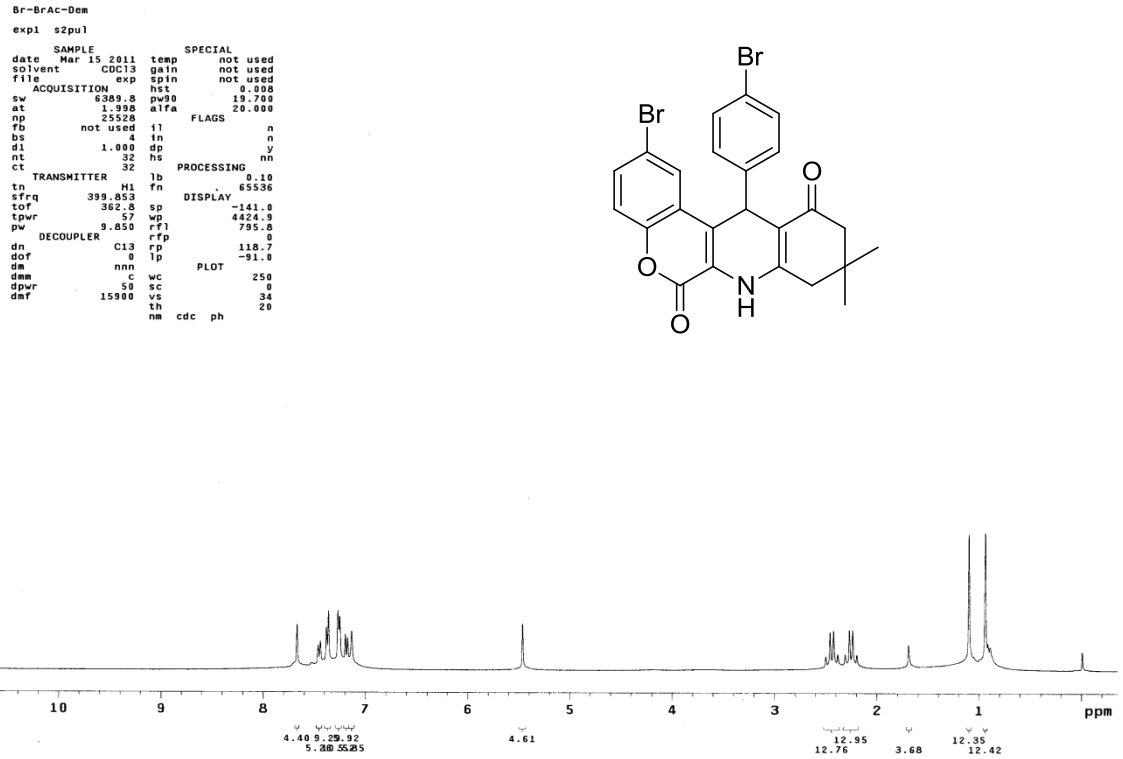


Figure 41

^{1}H NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12o)***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12o)***

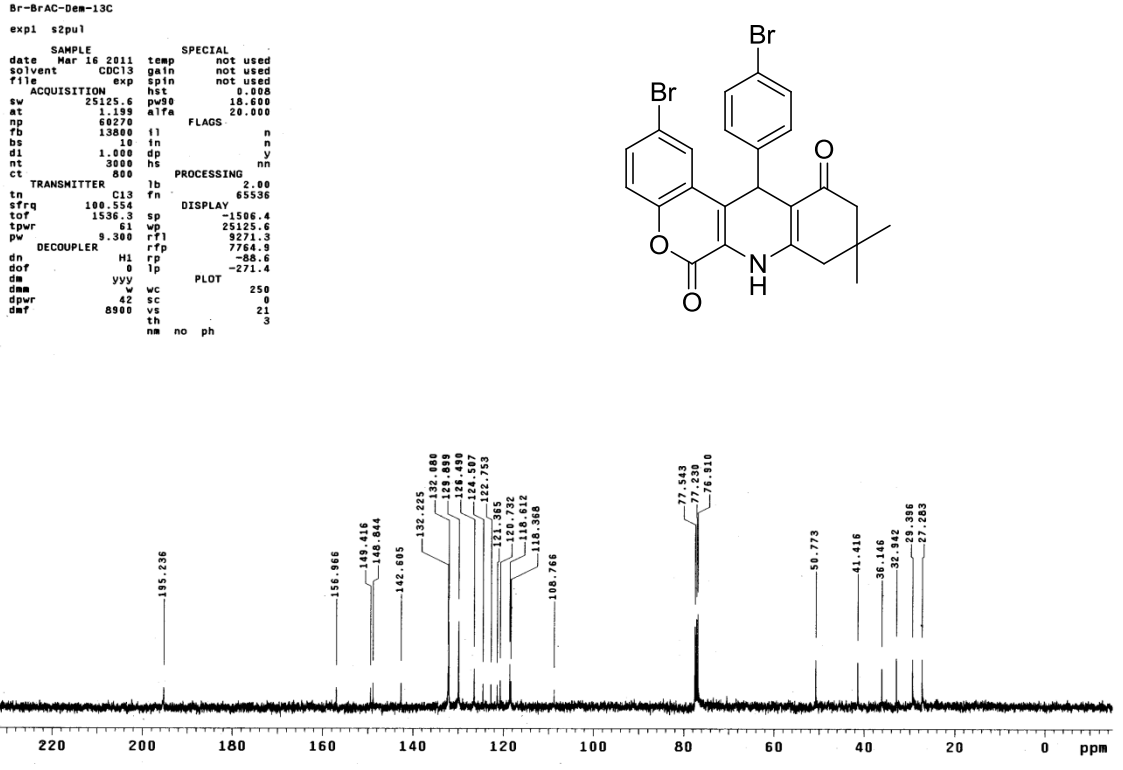
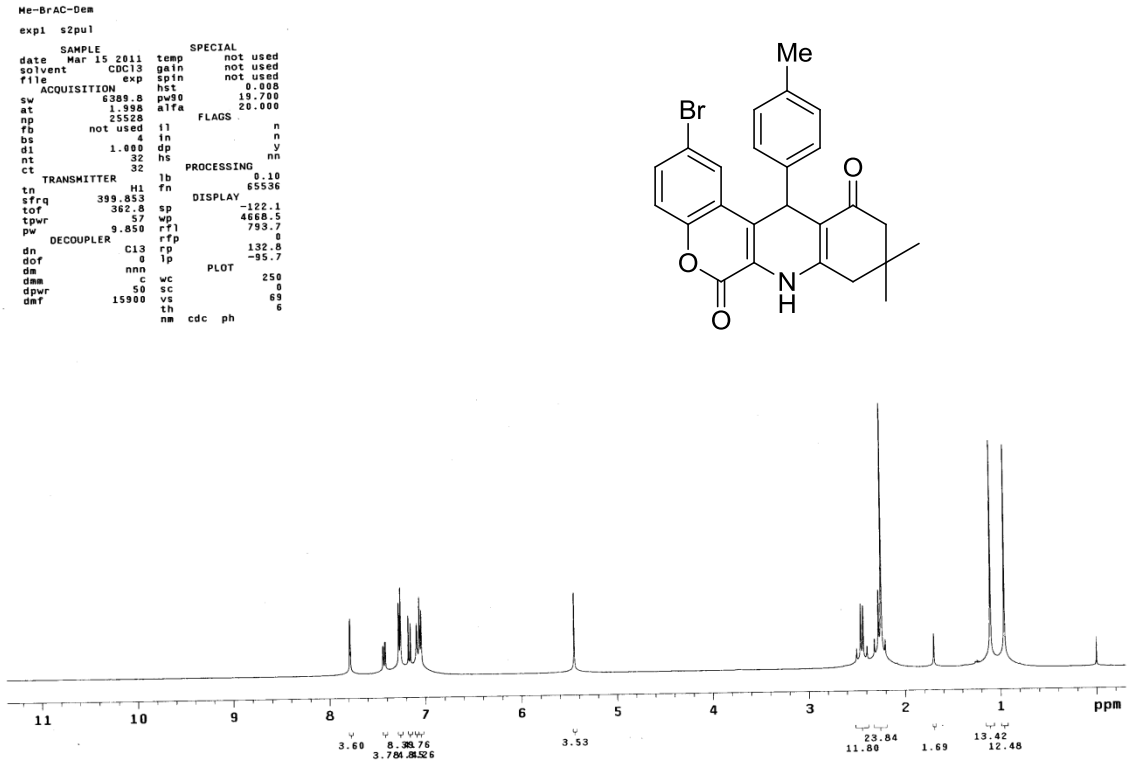


Figure 42

^{1}H NMR (400 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12p)***



^{13}C NMR (100 MHz, $CDCl_3$): *Chromeno[3,4-b]quinoline-6,11-dione* ***(12p)***

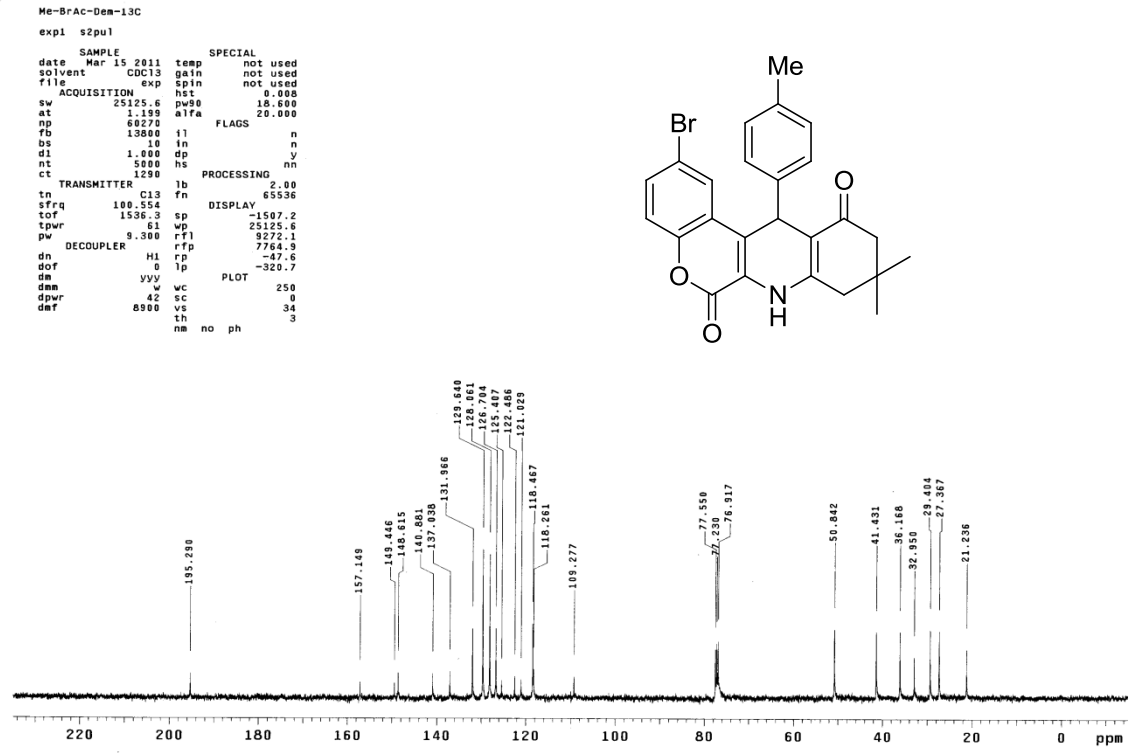


Figure 43

PART B

CHAPTER 4

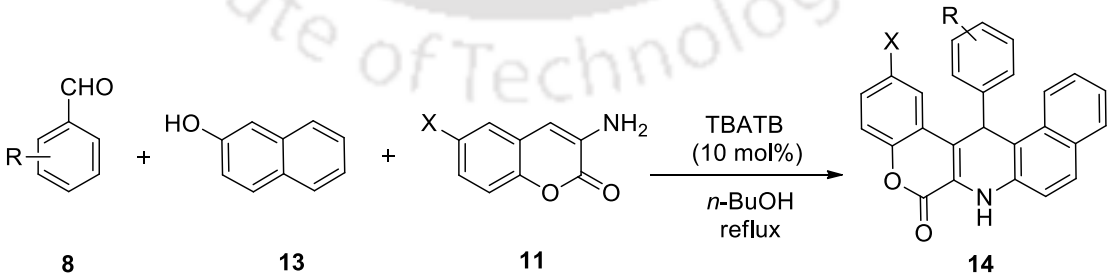
Synthesis of Benzo[*f*]chromeno[3,4-*b*]quinolin-6-one Derivatives Using TBATB Catalyst via One-pot Three Component Reaction

Results and Discussion

Quinone methides are short-lived and highly reactive intermediates,[60] which have been exploited for the synthesis of complex natural products[61] and pharmaceuticals,[62] These intermediates undergo either 1,4 Michael type additions namely aza-[63] and thia-Michael[64] reactions with various nucleophiles or hetero-Diels–Alder reaction.[65] A few years ago, Katritzky and his co-worker reported the generation of 2-naphthoquinone-1-methide intermediate from α-(α-benzotriazolylalkyl)phenols, which was trapped with electron-rich olefin for the construction of chroman ring system.[66] Very recently, Popik and his co-worker demonstrated[67a] that *in situ* generated 2-naphthoquinone-3-methide intermediate is useful precursor for light induced hetero-Diels-Alder reaction.[67b]

We conceived that 2-naphthol and aromatic aldehyde might react in presence of a suitable catalyst to generate 2-naphthoquinone-1-methide intermediate, which can be trapped with 3-aminocoumarin to furnish new heterocyclic entities through Tandem-Knoevenagel-Michael reactions.

Chromeno-quinolines are fused poly-heterocyclic systems comprising both coumarin and quinoline motifs which are known to possess interesting biological properties like bacteriostatic activity,[68] glucocorticoid modulators,[69] antiinflammatory effects[70] and selective progesterone receptor modulators.[71] We have discussed the synthesis of chromeno[3,4-*b*]quinoline-6,11-diones *via* Tandem-Knoevenagel-Michael reaction on *in situ* generated benzylidenecyclohexane-1,3-diones using 3-aminocoumarin as a key building block in the previous chapter. In this chapter, we report the one-pot synthesis of benzo[*f*]chromeno[3,4-*b*]quinolin-6-one derivatives (**14**) involving aromatic aldehydes (**8**), 2-naphthol (**13**) and 3-aminocoumarins (**11**) in *n*-butanol using 10 mol% of TBATB catalyst under reflux condition by trapping of 2-naphthoquinone-1-methide intermediate (Scheme 31).

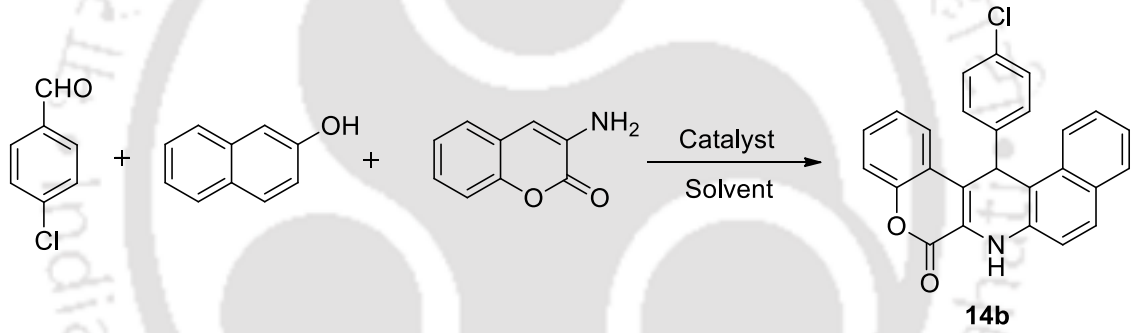


Scheme 31. One-pot synthesis of benzo[*f*]chromeno[3,4-*b*]quinolin-6-one derivatives

For the synthesis of benzo[*f*]chromeno[3,4-*b*]quinolin-6-one **14**, a mixture of 4-chlorobenzaldehyde (1.0 mmol), 2-naphthol (1.0 mmol), and 3-aminocoumarin (1.0 mmol)

was stirred under reflux in 3 mL of ethanol in presence of 10 mol% TBATB. The reaction was very sluggish and even incomplete after 24 hours. Increasing the amount of TBATB from 10 to 20 mol% did not improve the yield of the product **14b**. Then we tried the same set of reaction in different solvent mediums like *n*-butanol, dichloroethane, methanol and acetonitrile (Table 10, entry 4-9). It was observed that when the reaction was performed in *n*-butanol in presence of 10 mol% TBATB, the yield of the product **14b** increased significantly (Table 10, entry 5). 10 mol% of other catalysts such as anhydrous $Fe_2(SO_4)_3{\cdot}xH_2O$, Iodine, and $InCl_3$ could not accelerate the reaction in terms of time or yield (Table 10, entry 10-12). Also, in absence of catalyst no product formation was observed (Table 10, entry 13). So we came to the conclusion that 10 mol% of TBATB catalyst in *n*-butanol as solvent is the best reaction condition in terms of both yield and reaction time.

Table 10. Optimization of reaction conditions for synthesis of benzo[*f*]chromeno[3,4-*b*]quinolin-6-one (**14b**)[a]



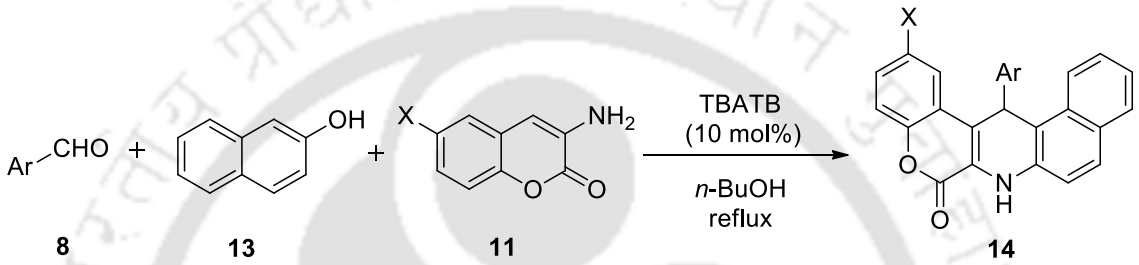
14b

Entry	Catalyst	Solvent	Mol% of Catalyst	Time (h)	Yield[b]%
1	TBATB	EtOH	5	24	15
2	TBATB	EtOH	10	24	19
3	TBATB	EtOH	15	24	26
4	TBATB	*n*-BuOH	5	12	58
5	TBATB	*n*-BuOH	10	8	78
6	TBATB	*n*-BuOH	20	8	70
7	TBATB	DCE	20	8	36
8	TBATB	MeOH	10	8	29
9	TBATB	MeCN	10	8	21
10	$Fe_2(SO_4)_3.xH_2O$	*n*-BuOH	10	8	37
11	Iodine	*n*-BuOH	10	8	33
12	$InCl_3$	*n*-BuOH	10	8	00
13	No Catalyst	*n*-BuOH	10	12.0	00

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

The reaction of some other aromatic aldehydes was examined with 2-naphthol and 3-aminocoumarin under identical reaction conditions which resulted in products **14c-g** (Table 11, entries 3-7) in good yields. Substituted 3-aminocoumarins such as 6-bromo-3-aminocoumarin and 6-methoxy-3-aminocoumarin were also examined with aromatic aldehyde and 2-naphthol under identical reaction conditions and we found that they provide the desired benzo[*f*]chromeno[3,4-*b*]quinolin-6-ones **14h-l** (Table 11, entries 8-12) in good yields.

Table 11. Scope of various benzo[*f*]chromeno[3,4-*b*]quinolin-6-one derivatives[a]



8 13 11 14

Entry	Ar	X	Product	Time	Yield[b]
1	C_6H_5	H	**14a**	8	72
2	4-Cl-C_6H_5	H	**14b**	8	78
3	4-Br-C_6H_5	H	**14c**	8	73
4	4-F-C_6H_5	H	**14d**	6	78
5	4-Me-C_6H_5	H	**14e**	6	86
6	4-MeO-C_6H_5	H	**14f**	6	71
7	2-$C_{10}H_7$-	H	**14g**	8	82
8	4-Cl-C_6H_5	MeO	**14h**	8	79
9	4-F-C_6H_5	MeO	**14i**	8	76
10	4-Me-C_6H_5	MeO	**14j**	8	82
11	4-Me-C_6H_5	Br	**14k**	6	82
12	4-F-C_6H_5	Br	**14l**	6	81

[a]*Reaction Condition: aromatic aldehyde, 2-naphthol and 3-aminocoumarin were taken in 1:1:1ratio in presence of 10 mol% of TBATB in n-butanol under reflux conditions.*
[b] *Isolated Yields*

All the products were fully characterized by IR, ^{1}H, and ^{13}C NMR spectra as well as elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compounds **14b**, **14c**, **14d**, **14e 14j,** and **14k** are given in the experimental section (Figure 45, 46, 47, 48, 49 and 50).

Finally the structures of one of the representative compounds **14d** were confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 44).

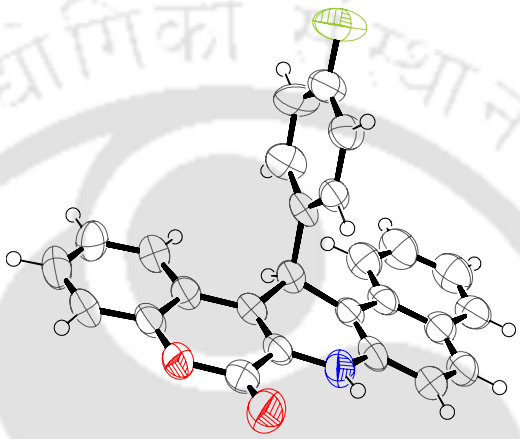
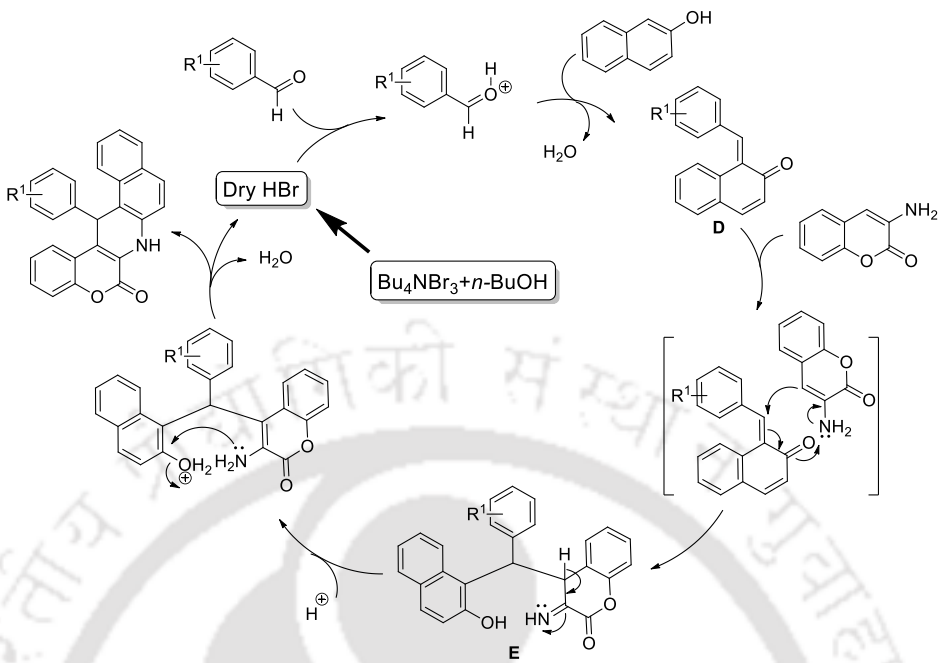


Figure 44. X-ray crystal structures of **14d** (CCDC 897315)

The formation of **14** could be explained by a proposed mechanism (Scheme 32). We believe that TBATB reacts with *n*-butanol to generate dry HBr in the reaction medium which actually catalyzes the product formation. It was supposed that the reaction occurred *via* the *o*-quinone methide intermediate **D**, which was formed by the nucleophilic addition of β-naphthol to aldehyde catalyzed with HBr. *o*-quinone methide intermediate **D** can act a suitable Michael acceptor and reacts with 3-aminocoumarin at the position 4 of the coumarin ring to provide reactive intermediate **E**, which undergoes intra-molecular ring closure reaction followed by elimination of one molecule of H_2O to give the desired product **14** (Scheme 32).



Scheme 32

In summary, we have provided an effective route for the synthesis of a series of benzo[*f*]chromeno[3,4-*b*]quinolin-6-one derivatives *via* one-pot three component reaction. The most significant features of the present protocol are short reaction times, superior atom economy, simplicity of the procedure and good to excellent yields.

PART B

CHAPTER 4

Synthesis of Benzo[*f*]chromeno[3,4-*b*]quinolin-6-one Derivatives Using TBATB Catalyst via One-pot Three Component Reaction

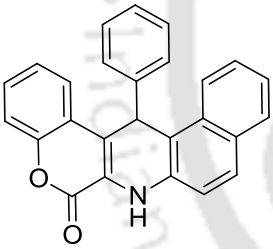
Experimental Section

General procedure for the synthesis of benzo[*f*]chromeno[3,4-*b*]quinolin-6-one (14)

In a 25 mL round bottomed flask was taken aromatic aldehyde (1.0 mmol), 2-naphthol (1.0 mmol) and 3-aminocoumarin (1.0 mmol) in 3 mL of *n*-butanol. Then, the catalyst *n*-tetrabutylammonium tribromide (TBATB) (0.048 g, 0.1 mmol) was added into it and the reaction mixture was kept for refluxing in a heated oil bath. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was brought to room temperature and *n*-butanol was removed in a rotary evaporator. The crude residue was extracted with dichloromethane (2 x 10 mL) and it was washed with water and dried over anhydrous sodium sulfate. The organic layer was concentrated in a rotary evaporator and the crude residue purified through column chromatography by eluting in ethyl acetate/hexane (05:95).

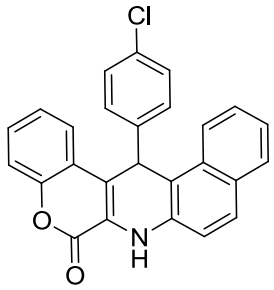
Spectral data of benzo[f]chromeno[3,4-b]quinolin-6-ones (14):

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



Yellow solid, mp: 244-245°C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.24 (s, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 3H), 7.29-7.35 (m, 4H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.73-7.78 (m, 3H), 7.96-8.10 (m, 1H), 8.18 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 37.18, 110.90, 114.83, 116.66, 118.28, 120.87, 121.36, 121.85, 122.19, 123.27, 125.33 (2C), 125.86, 126.57 (2C), 126.91, 127.07 (3C), 127.74, 128.94, 129.86, 133.93, 143.87, 148.06, 155.86; **IR** (KBr, cm^{-1}): 3348, 1683, 1527, 745. **Anal. Calcd** for $C_{26}H_{17}NO_2$ (375.42): C, 83.18; H, 4.56; N, 3.73; Found: C, 83.34; H, 4.62; N, 3.88%.

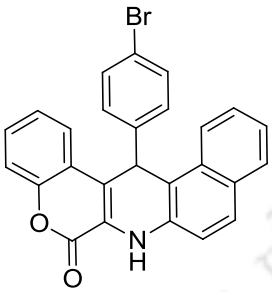
14-(4-chlorophenyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one ***(14b)***



Yellow solid, mp: 254-255°C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.22 (s, 1 H), 7.14 (d, *J* = 7.2 Hz, 1 H), 7.19 (d, *J* = 8.8 Hz, 4 H), 7.33-7.38 (m, 4 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.52 (t, *J* = 8 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 38.96, 112.49, 117.19, 117.26, 119.73, 120.11, 121.98, 122.36, 123.56, 124.09, 125.07,

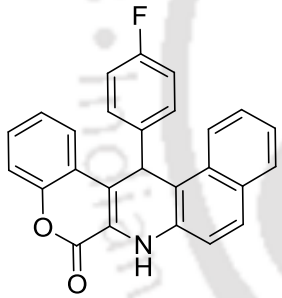
127.50, 128.09, 129.12 (3C), 129.22, 129.49 (2C), 131.07, 131.57, 133.09, 134.59, 142.81, 150.09, 158.27; **IR** (KBr, cm^{-1}): 3362, 2924, 1702, 1524, 741. **Anal. Calcd** for $C_{26}H_{16}ClNO_2$ (409.86): C, 76.19; H, 3.93; N, 3.42; Found: C, 76.32; H, 3.99; N, 3.53%.

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



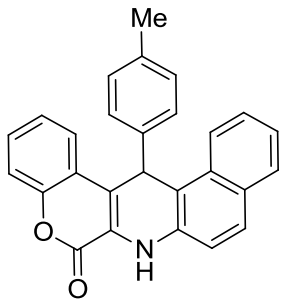
Yellow solid; mp: 272-274°C **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.19 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.37-7.28 (m, 9 H), 7.52 (t, *J* = 8 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.77(d, *J* = 8.4 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 39.03, 112.38, 117.18, 117.25, 119.70, 119.99, 121.21, 121.96, 122.33, 123.54, 124.07, 125.06, 127.48, 128.08, 129.55, 129.83 (3C), 131.09, 131.54, 132.05 (2C), 134.56, 143.32, 150.06, 158.25; **IR** (KBr, cm^{-1}): 3341, 2922, 1702, 1525, 741. **Anal. Calcd** for $C_{26}H_{16}BrNO_2$ (454.31): C, 68.74; H, 3.55; N, 3.08; Found: C, 68.92; H, 3.64; N, 3.22%.

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



Yellow solid, mp: 256-257°C **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.09 (s, 1 H) , 6.76 (t, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.18-7.29 (m, 5H), 7.33-7.36 (m, 2H), 7.42 (t, *J* = 8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.82-7.83 (m, 1H), 8.01 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 38.73, 112.74, 115.69, 115.90, 117.20 (2C), 119.78, 119.99, 120.35, 122.03, 122.39, 124.0, 125.01, 127.41, 127.99, 129.18, 129.64, 129.72 (2C), 129.83, 131.04, 131.56, 134.59, 140.24, 150.09, 158.30; **IR** (KBr, cm^{-1}): 3362, 2924, 1702, 1524, 742. **Anal. Calcd** for $C_{26}H_{16}FNO_2$ (393.41): C, 79.38; H, 4.10; N, 3.56; Found: C, 79.56; H, 4.18; N, 3.70%.

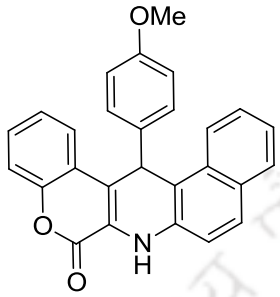
*14-(p-tolyl)-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**14e**)*



Yellow solid, mp: 276-277°C **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.15 (s, 3 H), 6.18 (s, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 7.29-7.35 (m, 5 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.50 (td, *J* = 1.6, 8.4 Hz, 1 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.97-8.01 (m, 1 H), 8.16 (d, *J* = 8.4 Hz, 1 H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 21.12, 39.16, 113.09, 117.08, 117.16, 119.95, 120.81, 122.25, 122.62,

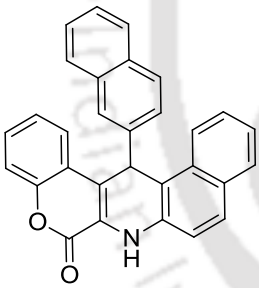
123.36, 123.86, 124.94, 127.29, 127.83, 128.10, 129.06, 129.19, 129.60, 131.03, 131.71, 134.54, 136.94, 141.55, 150.12, 158.43; **IR** (KBr, cm^{-1}): 3337, 1701, 1527, 736. **Anal. Calcd** for $C_{27}H_{19}NO_2$ (389.44): C, 83.27; H, 4.92; N, 3.60; Found: C, 83.44; H, 4.99; N, 3.72%.

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



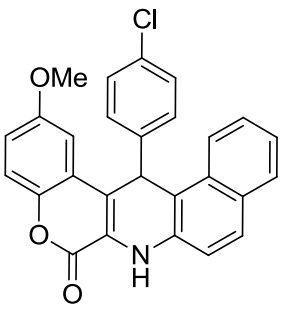
Yellow solid, mp: 282-284°C **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.65 (s, 3H, -OMe), 6.20 (s, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.30-7.38 (m, 5H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 8.0Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.98-8.10 (m, 1H),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

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



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

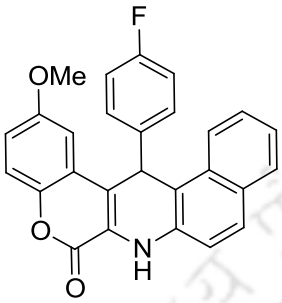
*14-(4-chlorophenyl)-2-methoxy-7,14-dihydro-6H-benzo[f]chromeno[3,4-b]quinolin-6-one (**14h**)*



Yellow solid, mp: 291-292 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.90 (s, 3H, -OMe), 6.11(s, 1H), 6.91-6.88 (m 1H), 7.18-7.13 (m, 3H), 7.27-7.24 (m, 1H), 7.34-7.32 (m, 3H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.53-7.49 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.75(d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 38.20, 55.43, 105.84, 108.68, 111.58, 113.54, 116.87, 117.53, 118.34, 119.90,

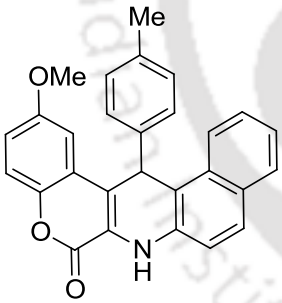
121.67, 123.06, 123.55, 126.45, 128.17 (2C), 128.30, 128.37, 128.82, 129.08 (2C), 130.17, 134.69, 143.21, 143.54, 155.93, 157.21. **IR** (KBr, cm^{-1}): 3326, 1702, 1529, 806. **Anal. Calcd** for $C_{27}H_{18}ClNO_3$ (439.89): C, 73.72; H, 4.12; N, 3.18; Found: C, 73.94; H, 4.20; N, 3.30%.

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



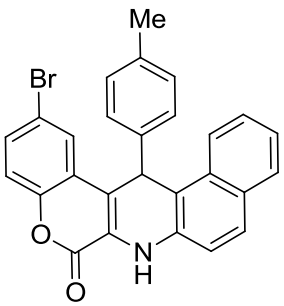
Yellow solid, mp: 258-260 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.91 (s, 3H, -OMe), 6.17 (s, 1H), 6.87 (t, *J* = 8.4 Hz, 2H), 6.92 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 9.2 Hz, 1H), 7.33-7.38 (m, 3H), 7.45 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.52 (t, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 37.68, 55.58, 106.13, 112.11, 113.81, 114.80 (2C), 115.0, 116.82, 117.81, 118.77, 120.01, 122.26, 123.06, 125.59, 126.41, 128.17, 128.25(2C), 129.47 (2C), 130.13, 130.99, 134.93, 143.53, 155.99, 157.03; **IR** (KBr, cm^{-1}): 3343, 1697, 1527, 741. **Anal. Calcd** for $C_{27}H_{18}FNO_3$ (423.43): C, 76.59; H, 4.28; N, 3.31; Found: C, 76.74; H, 4.36; N, 3.34%.

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



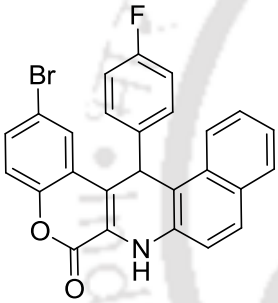
Yellow solid, mp: 281-283 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 3.91 (s, 3H, -OMe), 6.11 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.40-7.34 (m, 5H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 19.98, 38.02, 54.93, 105.24, 111.66, 113.13, 116.32, 117.10, 118.54, 119.60, 121.38, 122.45, 122.91, 125.05, 127.12 (2C), 127.62 (2C), 128.33(2C), 129.67, 130.50, 134.21, 135.50, 141.34, 143.10, 155.41, 156.86; **IR** (KBr, cm^{-1}): 3335, 2923 1702, 1529, 736. **Anal. Calcd** for $C_{28}H_{21}NO_3$ (419.47): C, 80.17; H, 5.05; N, 3.34; Found: C, 80.32; H, 5.12; N, 3.42%.

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



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

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



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

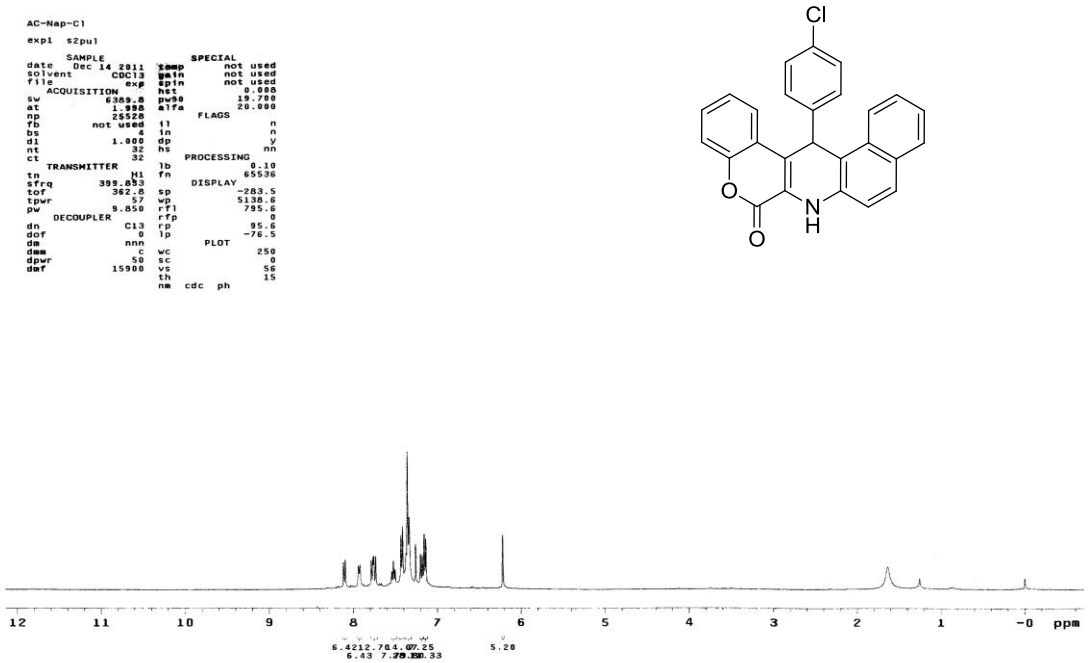
Crystallographic Description

Complete crystallographic data of compound **14d** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication, CCDC no. 897315. 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 12. Crystal data and structure refinement for compound **14d**

Parameters	**Compound 14d**	**Parameters**	**Compund 14d**
Identification code	14d	Z	6
Empirical formula	C26 H12 F N O2	Density (calculated)	1.352 g/cm^3
Formula weight	389.37	Absorption coefficient	0.093 mm^{-1}
Temperature	296(2) K	F(000)	1200
Wavelength	0.71073 Å	Theta range for data collection	1.27 to 27.54 º
Crystal system	Triclinic	Index ranges	-16<=h<= 11, -17<=k<=17, -18<=l<=22
Space group	P -1	Reflections collected	11742
Unit cell dimensions		Independent reflections	3145
a	12.9401(9) Å	Completeness to θº	89% (θ = 27.54º)
b	13.9507(13) Å	Refinement method	Full-matrix least-squares on F2
c	17.1595(15) Å	Data / restraints / parameters	11742 / 0 / 811
α	101.029º(5)	Goodness-of-fit on F2	1.009
β	106.389º(5)	Final R indices [>2sigma(I)]	R_{obs} = 0.0592, wR_{obs} = 0.1072
γ	96.666º(5)	R indices (all data)	R_{all} = 0.2138, wR_{all} = 0.1589
Volume	2869.0(4)Å^3	Largest diff. peak and hole	0.269 and -0.415 e.Å^{-3}

^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(14b)***



^{13}C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(14b)***

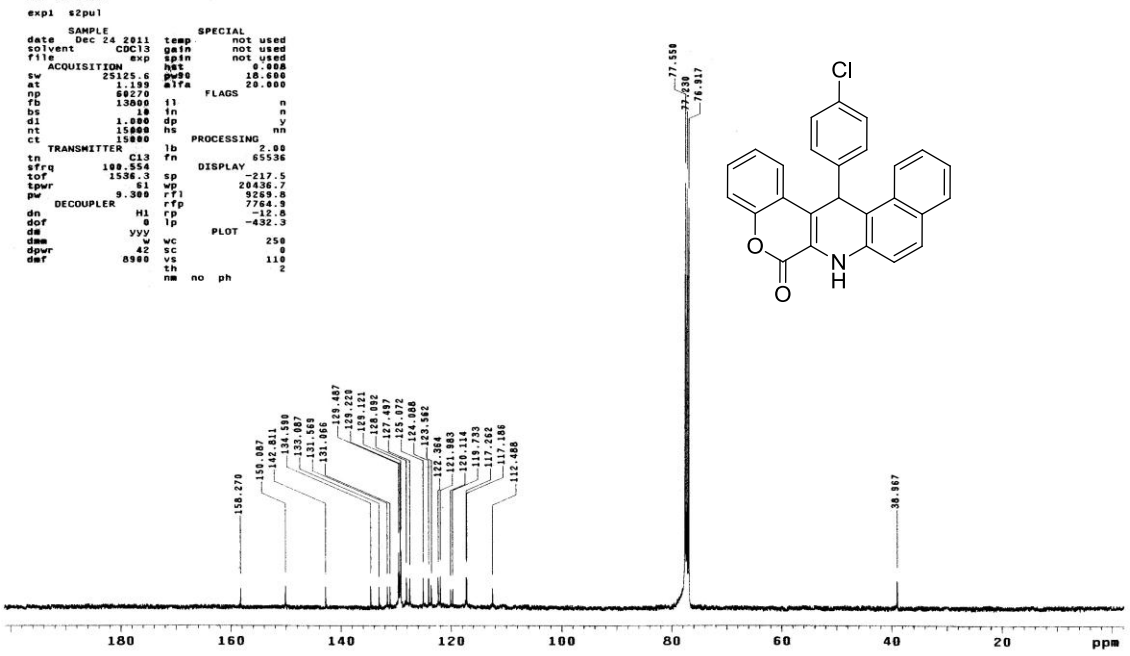
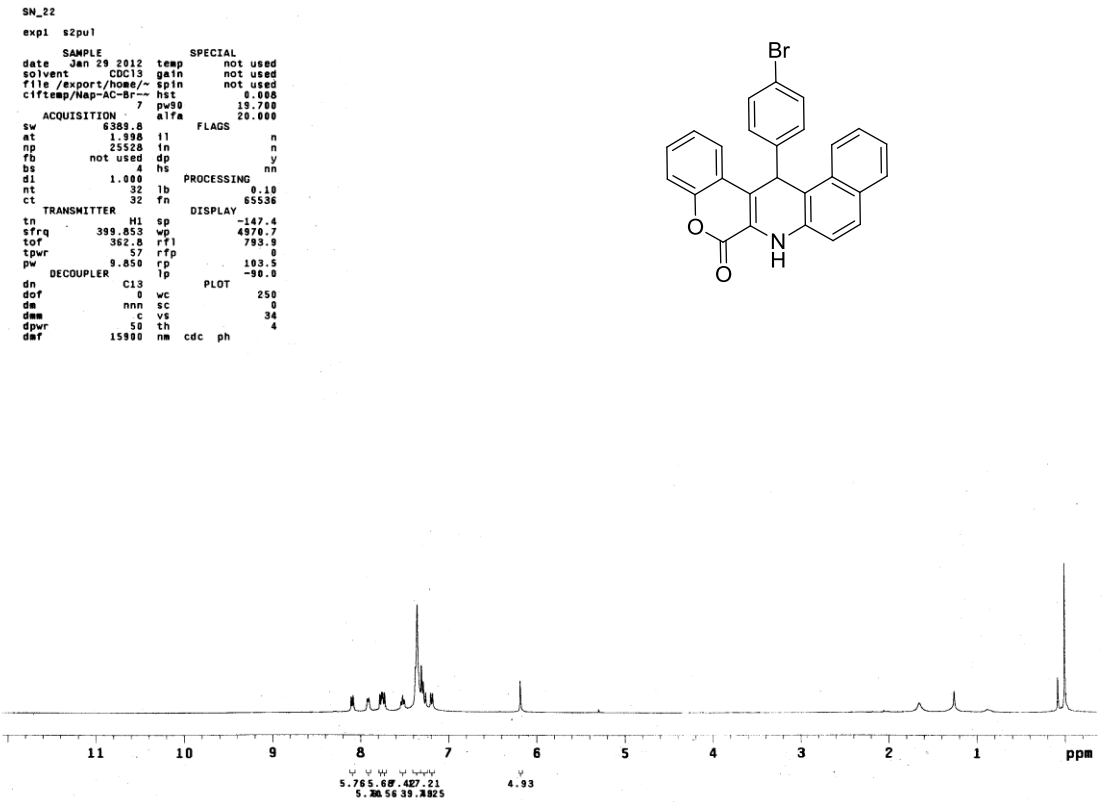


Figure 45

^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(14c)***



^{13}C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one* ***(14c)***

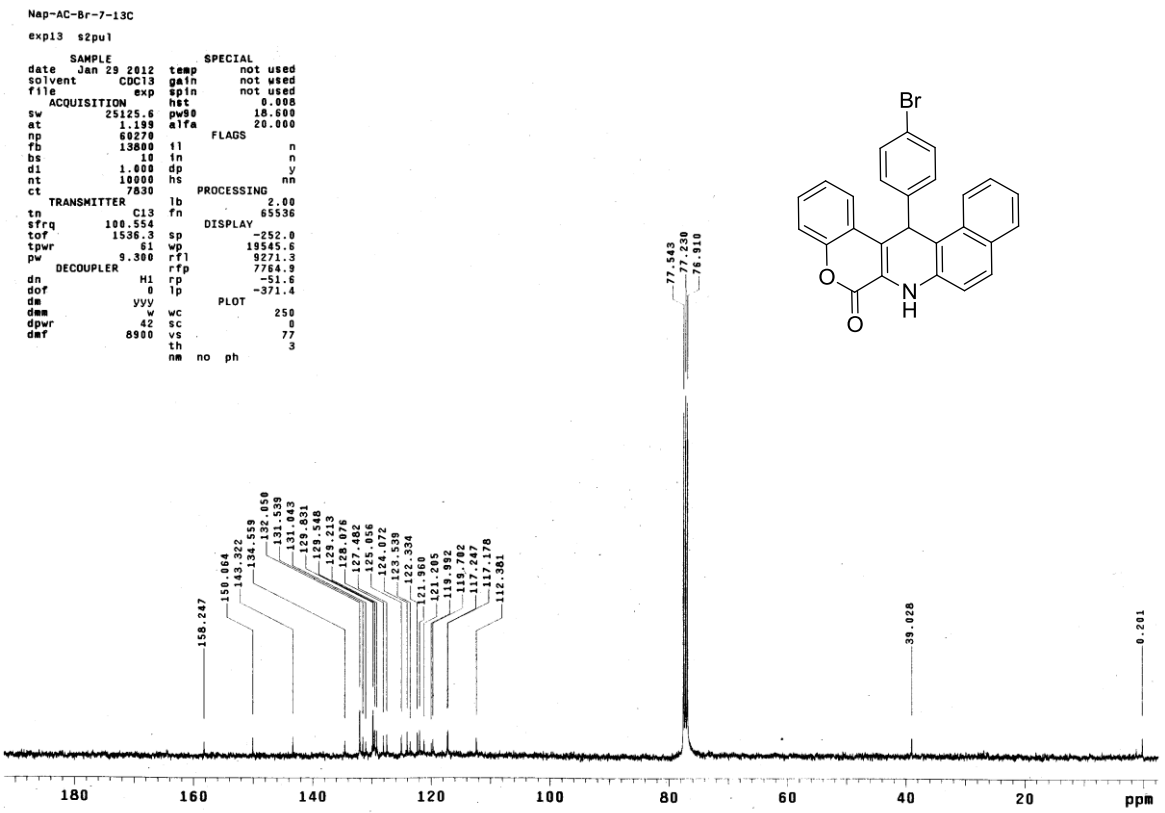
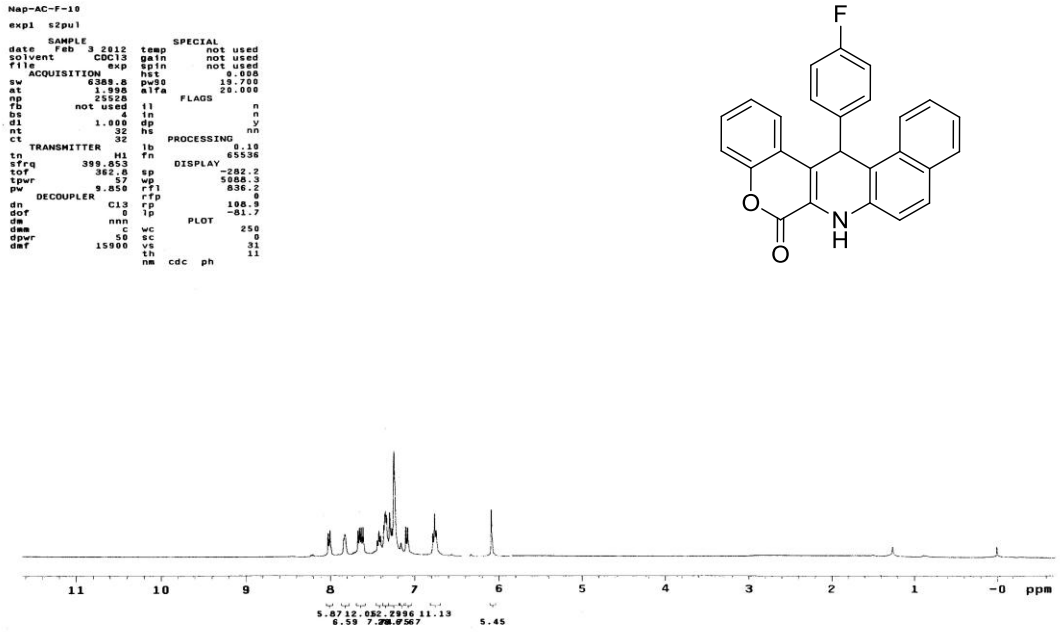


Figure 46

^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**14d**)*



^{13}C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**14d**)*

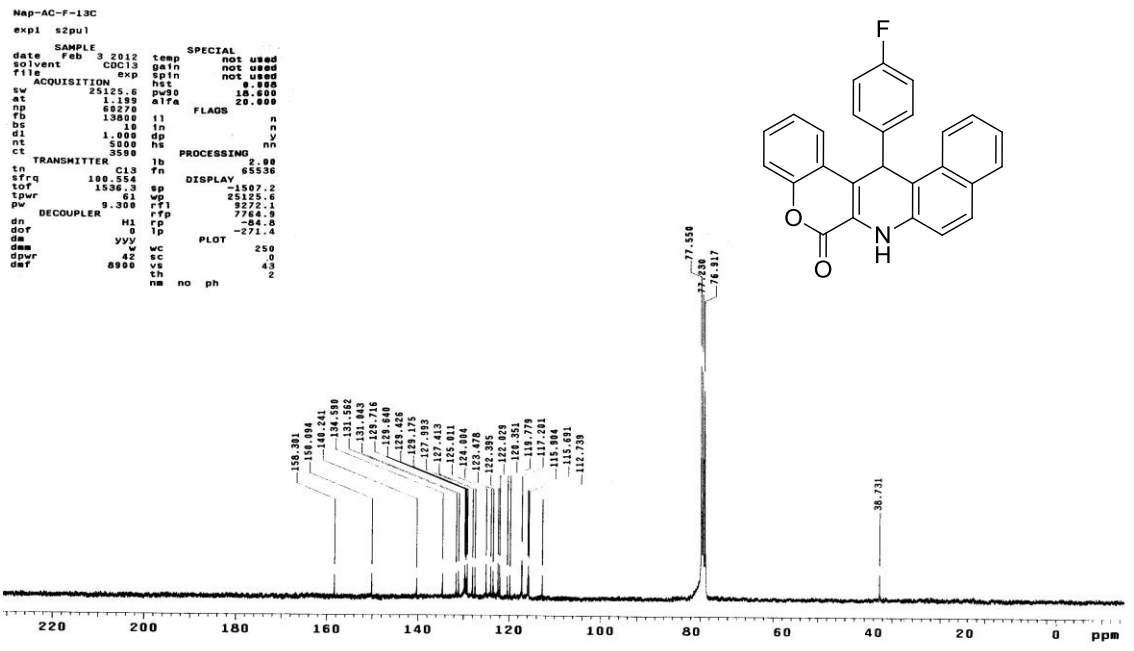
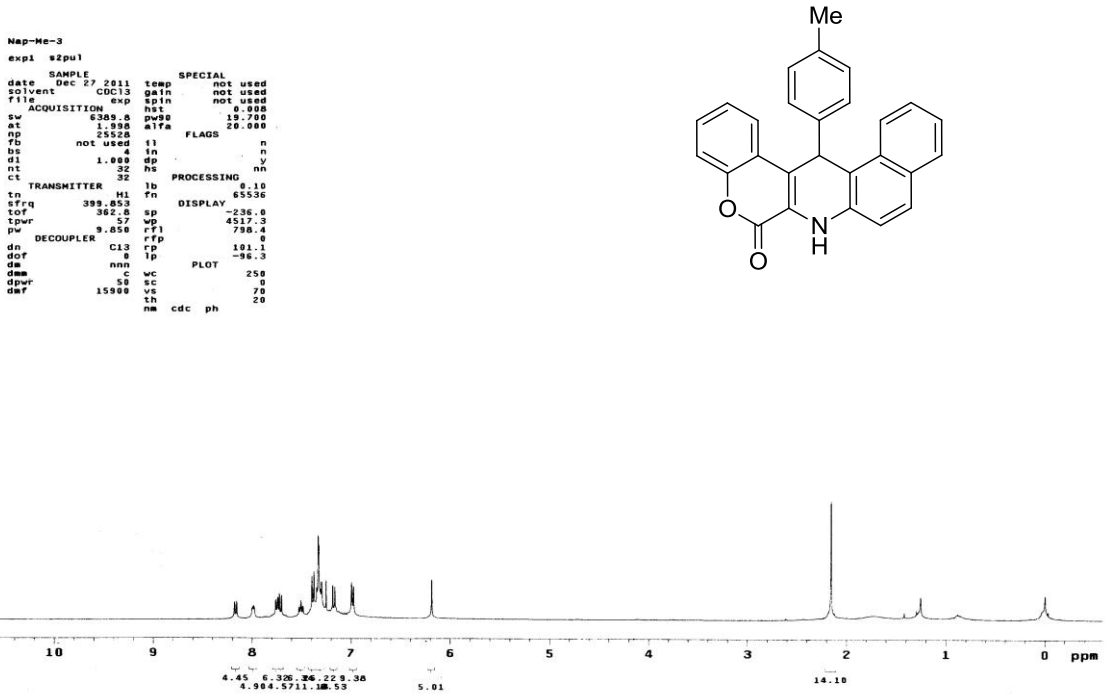


Figure 47

[1]NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**14e**)*



[13]C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**14e**)*

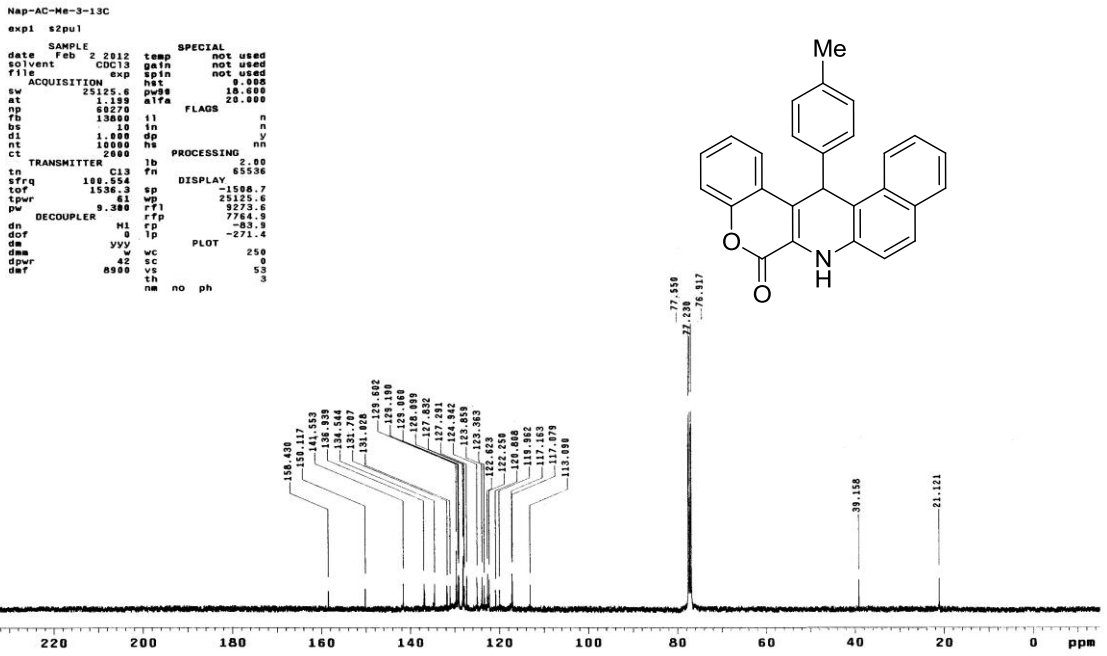
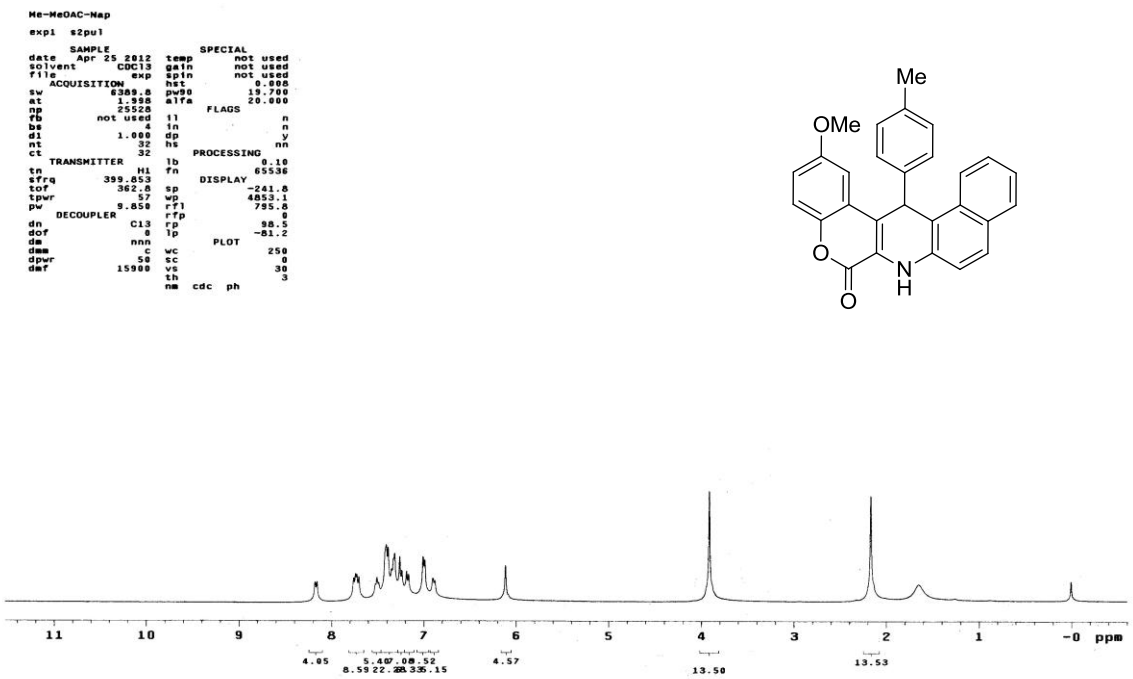


Figure 48

^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**14j**)*



^{13}C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**14j**)*

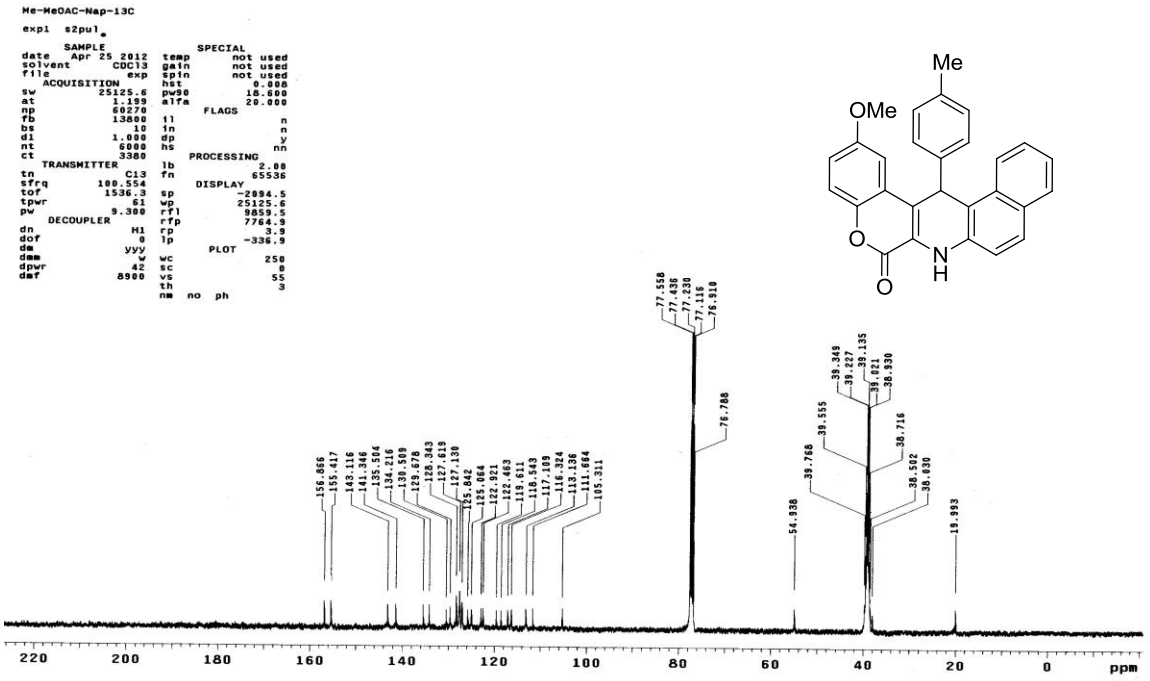
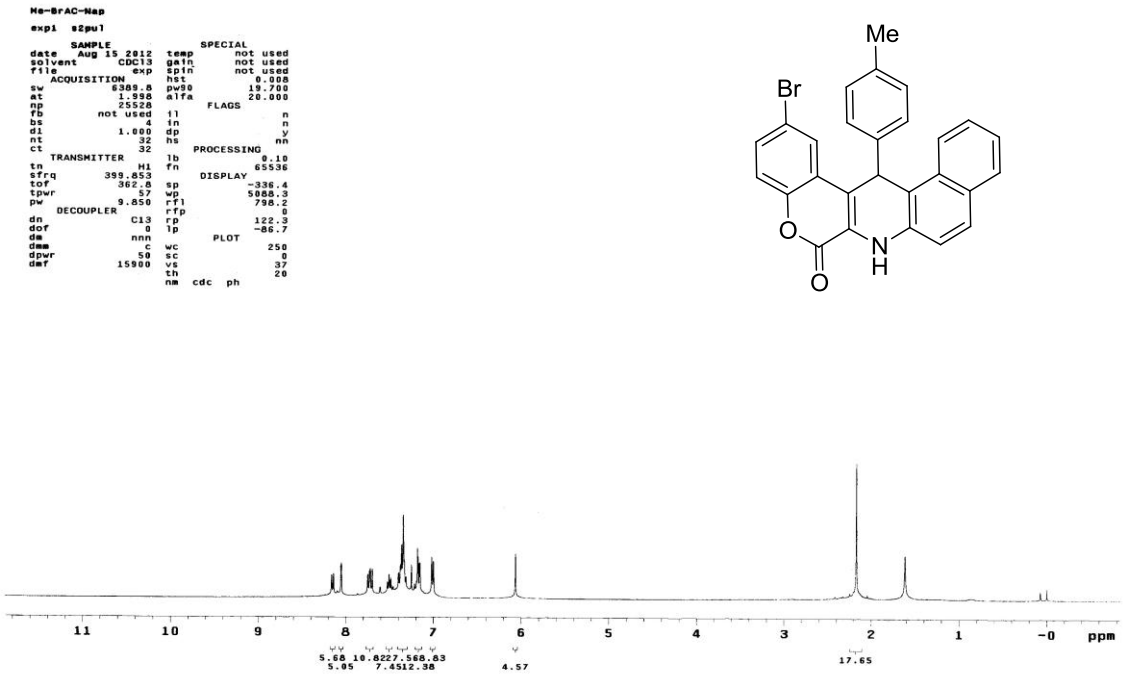


Figure 49

^{1}H NMR (400 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**14k**)*



^{13}C NMR (100 MHz, $CDCl_3$): *benzo[f]chromeno[3,4-b]quinolin-6-one (**14k**)*

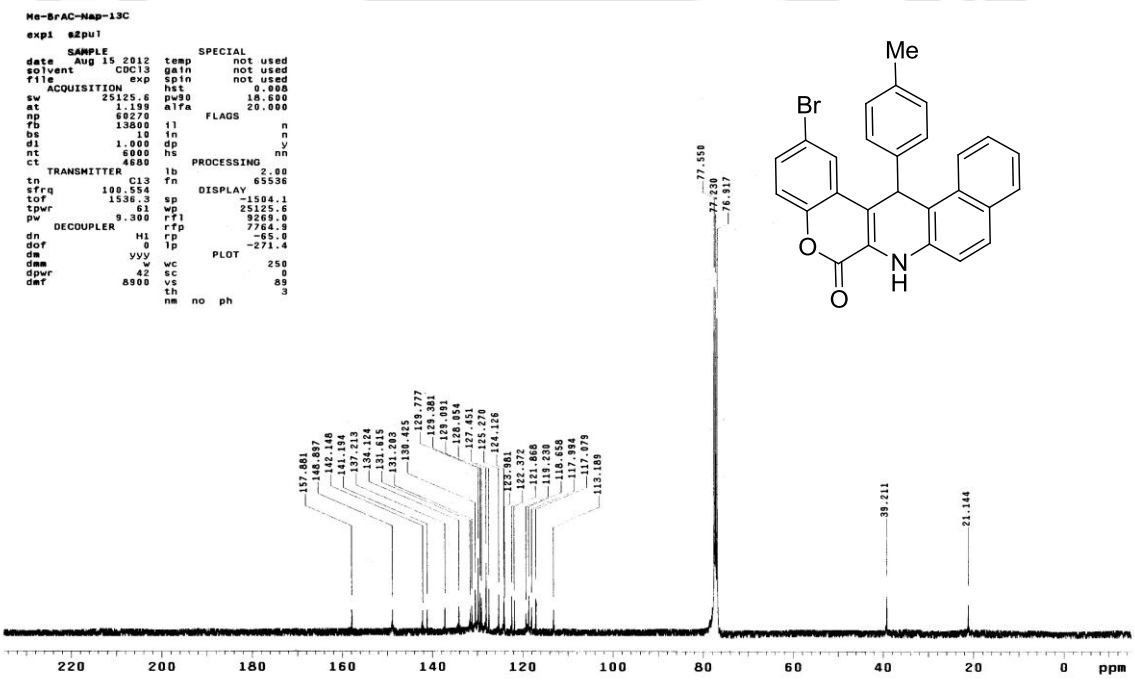


Figure 50

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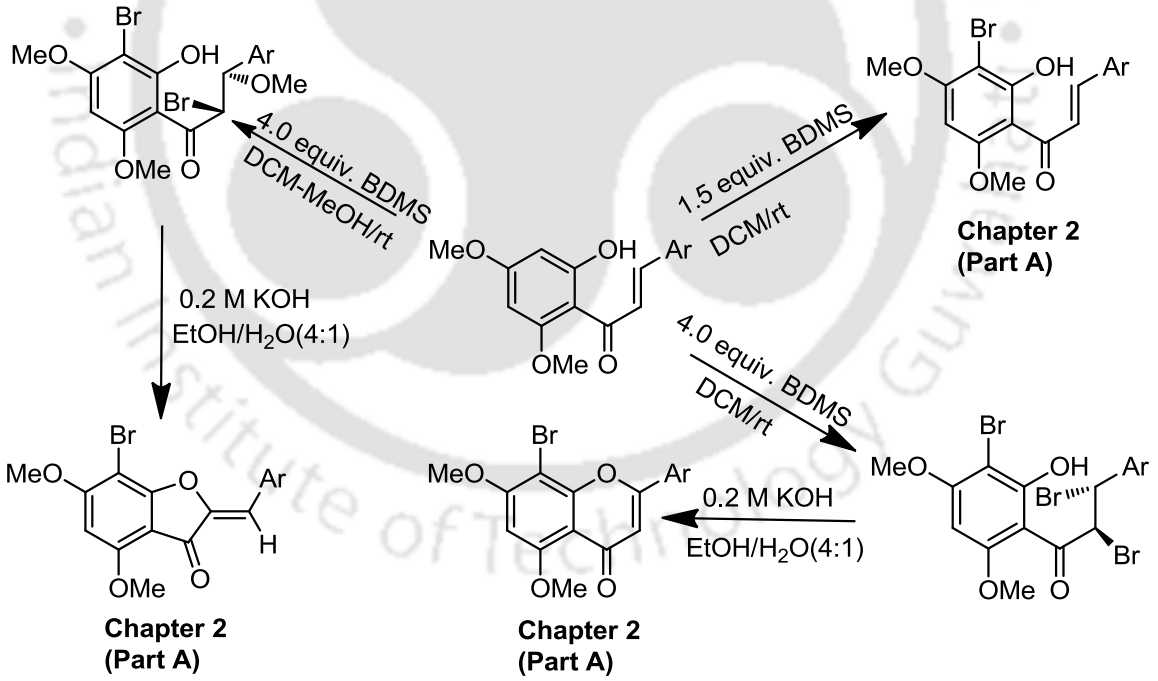
APPENDIX

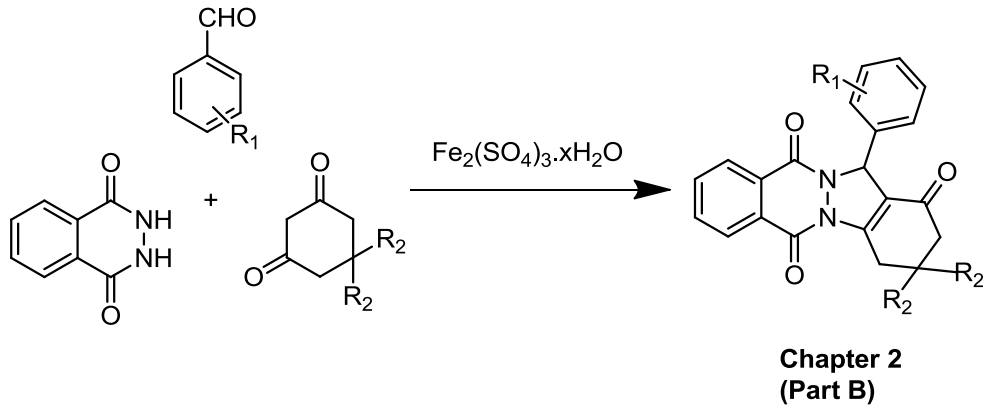
Conclusion and Future Perspectives

We have developed a new synthetic protocol for the regioselective monobromination of (*E*)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-aryl-2-propen-1-ones using BDMS. Further we have also successfully accomplished the synthesis of 7-bromoaurone and 8-bromoflavone derivatives from the brominated products by cyclization on treatment with 0.2 M ethanolic KOH solution.The protocol has several advantages such as non-hazardous, high efficiency, and selectivity.

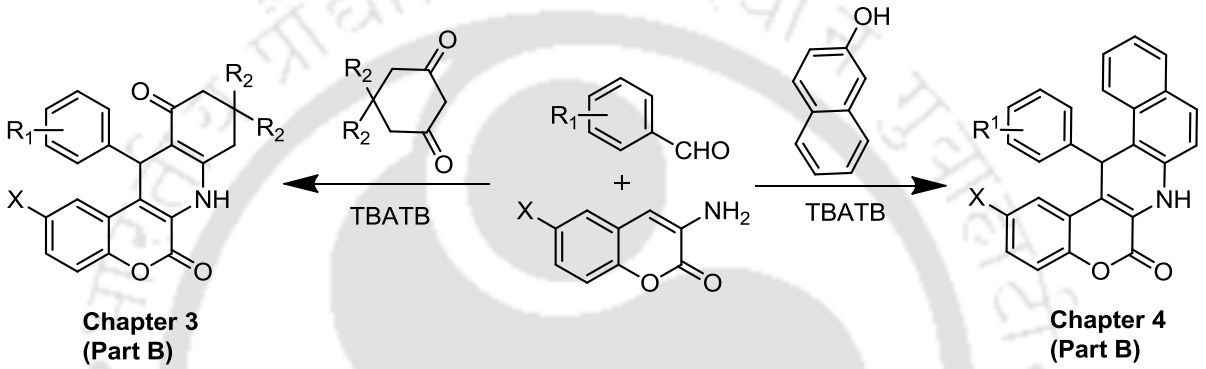
In addition,we have also demonstrated one pot synthesis of some fused nitrogen heterocycles via tandem Knoevanegal-Michael reaction which includes the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones using hydrated ferric sulfate as an efficient, inexpensive and reusable catalyst as well as for the synthesis of chromeno[3,4-*b*]quinolin-6,11-dione and benzo[*f*]chromeno[3,4-*b*]quinolin-6-one derivatives using 3-aminocoumarins as the key starting materials by employing TBATB as catalyst.The summarized results are shown below schematically.



Scheme I



Scheme II



Scheme III

The future scope of our ongoing research includes utilizing the synthesized 8-bromoflavones for the synthesis of biologically active naturally occurring compounds such as Amentoflavone, Vitexin and Aciculatin (Figure I), which can be achieved via Suzuki Coupling reaction.

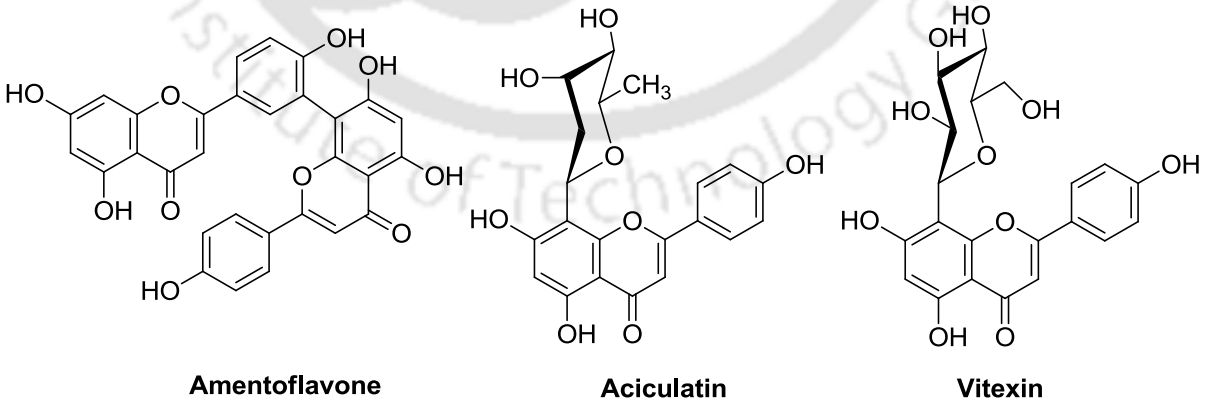


Figure I

Moreover, the synthesis of optically active chromeno[3,4-*b*]quinolin-6,11-dione derivatives and benzo[*f*]chromeno[3,4-*b*]quinolin-6-one derivatives can be explored further using asymmetric organocatalysts.

Further, we would also like to carry out the biological study of the synthesized compounds in collaboration with other research groups in future, which is not possible now due to time constraints.

LIST OF PUBLICATION AND COMMUNICATIONS

1. *Regioselective monobromination of (E)-1-(2'-hydroxy-4',6'-dimethoxyphenyl)-aryl-propen-1-ones using bromodimethylsulfonium bromide and synthesis of 8-bromoflavones and 7-bromoaurones* Abu T. Khan, **Abhik Choudhury**, Shahzad Ali, Md. Musawwer Khan, *Tetrahedron Lett*. **2012**, *53*, 4852.

2. *Hydrated Ferric Sulfate [$Fe_2(SO_4)_3 \cdot xH_2O$]: An efficient and reusable catalyst for one-pot synthesis of 2H-Indazolo[2,1-b]phthalazine-triones* **Abhik Choudhury**, Shahzad Ali, Abu T. Khan, *J. Korean Chem. Soc*. **2015,** *59*, 280.

3. *n-Tetrabutylammoniumtribromide catalyzed synthesis of chromeno[3,4-b]quinoline-6,11-diones and benzo[f]chromeno[3,4-b]quinolin-6-ones using one-pot three component reaction* **Abhik Choudhury**, Deb K. Das, Abu T. Khan. (*Communicated).*

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Regioselective monobromination of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones using bromodimethylsulfonium bromide and synthesis of 8-bromoflavones and 7-bromoaurones

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7-Bromoaurones

ABSTRACT

A wide variety of monobrominated compounds **2a–l** have been prepared in good yields from (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**1a–l**) through regioselective ring bromination using 1.5 equiv of bromodimethylsulfonium bromide (BDMS) at room temperature. Similarly, some of the 2′-hydroxychalcones can be converted directly into tribromides **3** or dibromides **4** by employing 4.0 equiv of BDMS under different reaction conditions which in turn can be transformed into 8-bromoflavones and 7-bromoaurones on treatment with 0.2 M ethanolic KOH solution. Mild reaction conditions, good yields and no chromatographic separation are some of the salient features of the present protocol.

2′-Hydroxychalcones are essential intermediates for biosynthesis of flavonoids in plants and many of them are found as such in nature.[1] In addition, they display a wide range of biological activities such as antitumoral,[2–4] anti-inflammatory,[5] antibacterial,[6] antiulcerogenic,[7] antioxidant,[6,8,9] antimalarial[10] and antileishmaniosis activities.[10,11] Link and Sorensen reported[12] that 2′,4′,6′,4-tetrahydroxychalcone is a key precursor for phlorizin (Fig 1) which is used for inhibition of the sodium/glucose cotransporters (SGLTs) and thereby lowering the blood glucose levels in diabetic animals. A few years ago, Rossi-Bergmann and co-workers have shown[11] that 2′-hydroxychalcone containing bromine atom in ring A of flavones moiety exhibits better antileishmanial activity as compared to 2′-hydroxychalcone itself. Moreover, these brominated compounds might be converted easily into 8-bromoflavones and 7-bromoaurones which are key building blocks for the synthesis of naturally occurring flavonoids such as vitexin, phlorizin, orientin, and cupressuflavone as shown in Figure 1. Therefore, the synthesis of brominated 2′-hydroxychalcones is highly desirable from biological point of view.

In the past few years, our research group[13] as well as others[14] have demonstrated that bromodimethylsulfonium bromide (BDMS) can serve as a useful brominating reagent and an effective catalyst in various organic transformations, which has been reviewed[15] in 2009. It is easier to handle as compared to hazardous molecular bromine. Recently we have further shown its usefulness in multicomponent reactions for the synthesis of heterocyclic compounds[16] as well as in carbohydrate chemistry.[17] Due to its unique reactivity and properties, we have perceived that it can be explored further for regioselective ring bromination over enone double bond of 2′-hydroxychalcones. Though numerous methods for bromination are known in the literature, the regioselective bromination in the aromatic ring remains a challenging task particularly for phenols and amines.[18] In this Letter, we wish to report regioselective mono bromination of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones as depicted in Scheme 1.

For the present study, the brominating reagent, bromodimethylsulfonium bromide (BDMS)[19] and (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones[11](**1**) were prepared by following the literature procedures. Subsequently, the substrate **1a**, (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (0.5 mmol), in 2 mL of dichloromethane (DCM) was treated with 1.0 equiv amount of BDMS at room temperature. The brominated compound **2a** was isolated in 67% yield within 5 min and it was characterized from ^{1}H and ^{13}C NMR spectra and elemental analysis. After getting the desired product, the reaction condition was optimized by carrying out the experiment with different amounts of BDMS under various solvent systems. The best result obtained in terms of yield, time and selectivity is mentioned in Table 1. It was noted that the best yield of the mono brominated

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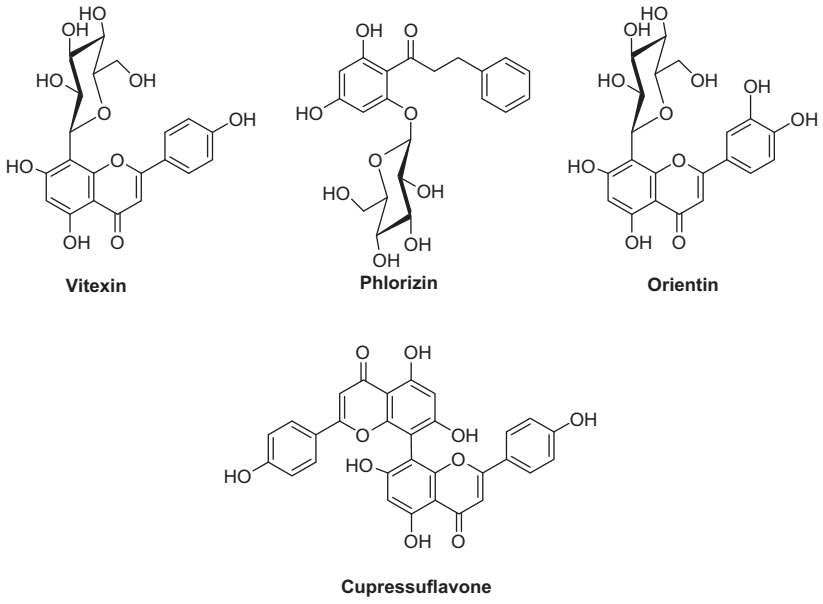
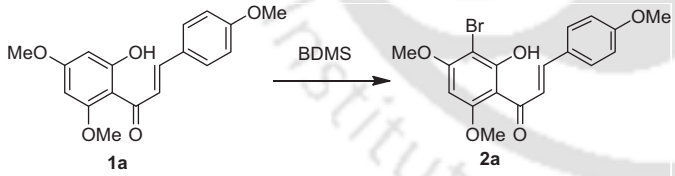


Figure 1. Some naturally occurring flavonoids.

Scheme 1. Synthesis of (*E*)-1-(3′-bromo-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones using BDMS.

Table 1
Optimization of the reaction conditions[a]



S. No.	BDMS/equiv	Solvent	Time/min	Yield[b] (/%)
1	1.0	DCM	45	67
2	1.5	DCM	5	96
3	2.0	DCM	5	95
4	1.5	MeCN	10	81
5	1.5	EtOAc	5	86

[a] The reactions were carried out with 0.5 mmol of the substrate.
[b] Isolated yields.

product, (*E*)-1-(3′-bromo-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**2a**) was obtained using 1.5 equiv of BDMS in dichloromethane.

After optimization, the reaction of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-one (**1b)** was carried out under identical reaction conditions and the product **2b** was isolated in 93% yield.

Encouraged by these successful results, a wide range of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**1c–l**) were also examined with 1.5 equiv amount of BDMS under similar reaction conditions[20] and the desired regioselective monobrominated products **2c–l** were obtained in excellent yields as shown in Table 2.

The products were characterized by usual spectroscopic methods and also by single crystal XRD data. The XRD data reveal that regioselective monobromination occurs at the position adjacent to the OH group as shown in Figure 2.[21]

It is a well-known fact that (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones are key starting materials for the synthesis of flavones and aurones. We conceived that 8-bromoflavones and 7-bromoaurones can be synthesized easily from (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones since there still exists a further possibility for bromination. Consequently, the scope and generality of the reaction were also examined with excess amount of BDMS. It was noted that compound **1a** on treatment with 4.0 equiv of BDMS in DCM provided the tribrominated product **3a** in 84% yield which was smoothly converted into 8-bromoflavone (**5a**) on treatment with 0.2 M ethanolic KOH solution as shown in Scheme 2. The structure was also confirmed by usual spectroscopic techniques and from single crystal XRD data. It is clear that the cyclization took place at the β-position with respect to carbonyl group. Likewise, other substrates **1b** and **1l** were also converted into desired 8-bromoflavone derivatives **5b** and **5l** by following the two-step procedure.[22]

It is well-established in the literature that the bromination of alkene can give methoxy brominated compound on treatment with molecular Br_2 in MeOH.[23] We thought that methoxy group can be incorporated at the β-position of the (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones if the reaction is carried out with DCM-MeOH system. Subsequently, the substrate **1a** was treated with 4 equiv of BDMS in DCM/MeOH (5:2) and the product **4a** was isolated in 80% yield. Then, the compound **4a** was further transformed into 7-bromoaurone (**6a)** on treatment with 0.2 M ethanolic KOH solution as depicted in Scheme 3. Likewise, the substrate **1b** was converted into the corresponding 7-bromoaurone derivative **6b** by performing the similar sequence of reactions.[24]

All the products were fully characterized from IR, ^{1}H, and ^{13}C NMR spectra as well as by their elemental analysis. The structures of 8-bromoflavone and 7-bromoaurone were further confirmed by X-ray crystallography studies as shown in Fig 3a and 3b.[21]

Table 2
Regioselective bromination of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones by employing bromodimethylsulfonium bromide[a]

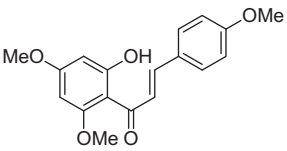
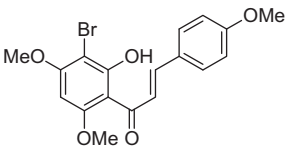
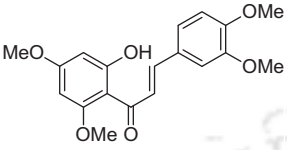
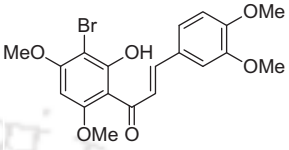
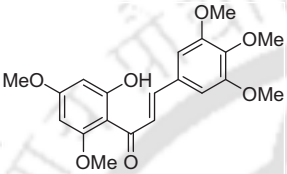
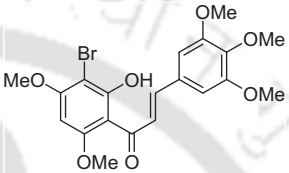
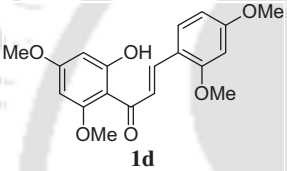
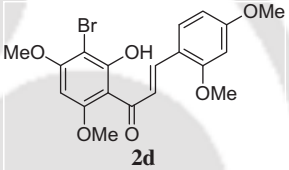
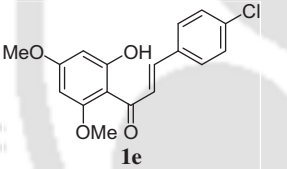
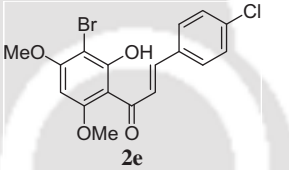
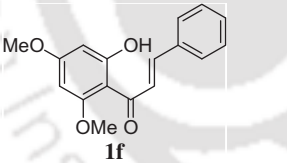
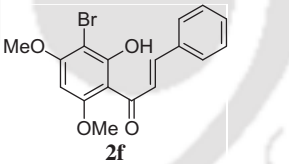
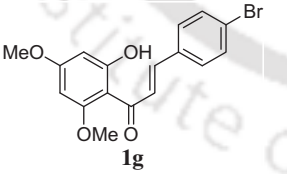
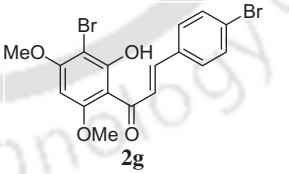
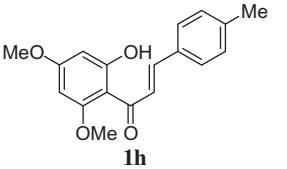
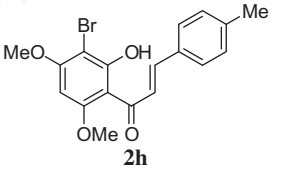
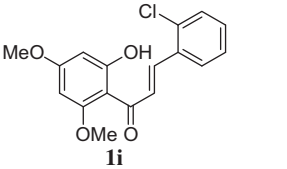
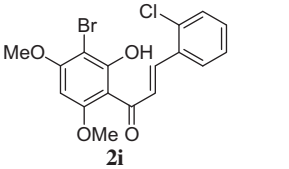
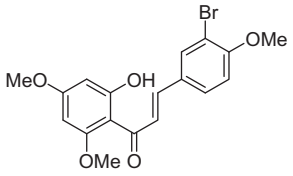
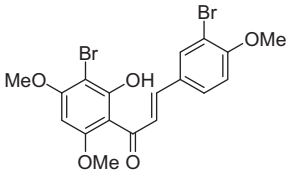
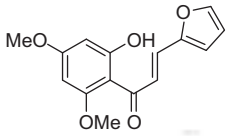
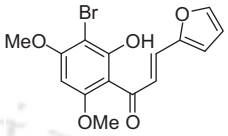
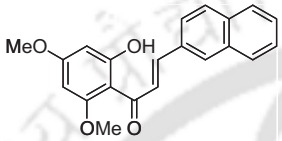
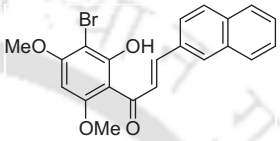
Entry	Substrate (1)	Product (2)	Yield[b] (%)
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	93
3	 **1c**	 **2c**	98
4	 **1d**	 **2d**	94
5	 **1e**	 **2e**	90
6	 **1f**	 **2f**	87
7	 **1g**	 **2g**	85
8	 **1h**	 **2h**	94
9	 **1i**	 **2i**	97

Table 2 (*continued*)

Entry	Substrate (1)	Product (2)	Yield[b] (%)
10	 **1j**	 **2j**	82
11	 **1k**	 **2k**	95
12	 **1l**	 **2l**	85

[a] The reaction was carried out with 0.5 mmol of the substrate in each case using 1.5 equiv amount of BDMS in DCM.
[b] Isolated yields.

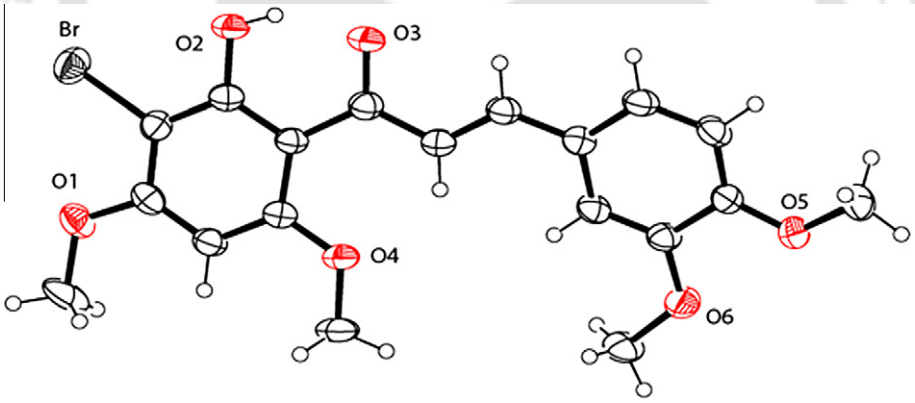
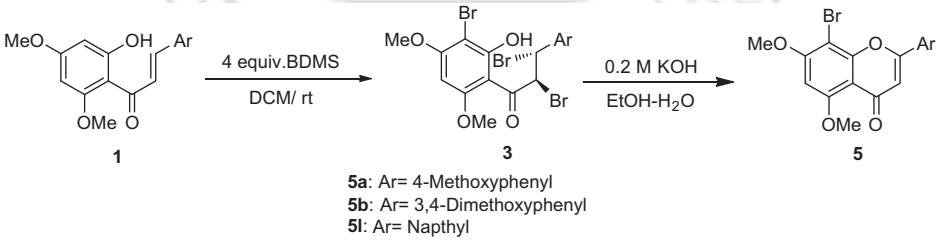


Figure 2. X-ray crystal structure of (*E*)-1-(3′-bromo-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-one (**2b**).



Scheme 2. Synthesis of 8-bromoflavones.

In conclusion, we have achieved regioselective monobromination of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones using BDMS under mild reaction conditions. In addition, 8-bromoflavones and 7-bromoaurones were also synthesized by employing excess amount of BDMS followed by base catalyzed cyclization using ethanolic KOH solution. The 7-bromoaurone and 8-bromoflavone can be utilized for the synthesis of vitexin, bisflavones, and aureusidin which is under progress and will be reported in due course of time.

Acknowledgments

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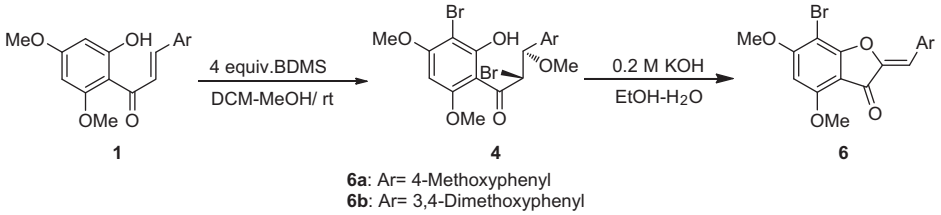

Scheme 3. Synthesis of 7-bromoaurones.

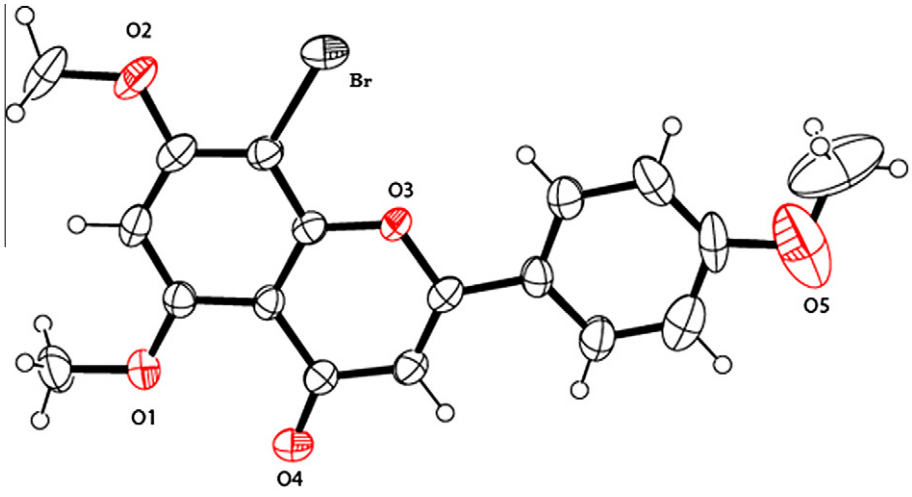

Figure 3a. X-ray crystal structure of 8-bromoflavone **5a**.

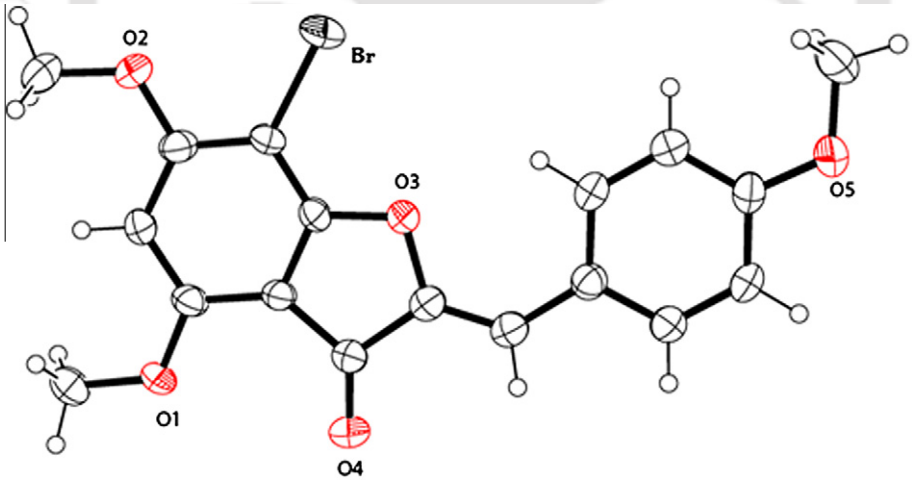

Figure 3b. X-ray crystal structure of 7-bromoaurone **6a**.

ing laboratory facilities and DST-FIST for financial support for creating single crystal XRD facility in the Department of Chemistry. We are thankful to the referees for their valuable comments and suggestions.

Supplementary data

Supplementary data (compounds **2b**, **5a** and **6a**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.122.

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20. *General method for the regioselective synthesis of (E)-1-(3′-bromo-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**2**)*: To a well stirred solution of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (0.5 mmol) in 3 mL of DCM was added BDMS (0.167 g, 0.75 mmol) at room temperature. The reaction was complete instantaneously and the excess bromine was destroyed with 10% sodium metabisulphite solution. The reaction mixture was extracted with DCM (2 × 15 mL), washed with water, and dried over anhydrous sodium sulfate. After removal of solvent in rotary evaporator, the pure product was obtained as yellow solid. *Compound **2a***: Yellow solid, mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.99 (s, 3H) , 4.00 (s, 3H), 6.08 (s, 1H), 6.94 (d, 2H, J = 8.8 Hz), 7.57 (d, 2H, J = 8.8 Hz), 7.76 (d, 1H, J = 15.6 Hz), 7.84 (d, 1H, J = 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 56.3, 56.5, 87.3, 92.1, 107.1, 114.6 (2C), 124.7, 128.2, 130.5 (2C), 143.7, 161.8, 161.9, 162.4, 163.4, 192.8; IR ν_{max}(KBr): cm^{-1} 1622, 1551, 1219, 1171; Anal. Calcd for $C_{18}H_{17}BrO_5$: C, 54.98; H, 4.36%; found C, 54.72; H, 4.27%. Compound **2b:** Yellow solid, mp 200–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.05 (s, 1H), 6.90 (d, 1H, J = 8.4 Hz), 7.11 (d, 1H, J = 2.0 Hz), 7.21 (dd, 1H, J = 1.6, 8.0 Hz), 7.73 (d, 1H, J = 15.2 Hz), 7.80 (d, 1H, J = 15.6 Hz); ^{13}C NMR (100 MHz, DMSO): δ 55.5, 55.7, 56.6, 56.8, 88.9, 90.6, 106.7, 110.9, 111.8, 123.2, 124.5, 127.5, 143.9, 149.0, 151.4, 161.3, 161.5, 161.9, 192.3; IR ν_{max} (KBr): cm^{-1} 1627, 1557, 1518, 1261, 1218; Anal. Calcd for $C_{19}H_{19}BrO_6$: C, 53.92; H, 4.52; found C, 53.75; H, 4.48%. *Compound **2k***: Yellow solid, mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 3H), 4.00 (s, 3H) , 6.07 (s, 1H), 6.52 (dd, 1H, J = 2.0 Hz, 3.2 Hz), 6.70 (d, 1H, J = 3.2 Hz), 7.53 (d, 1H, J = 1.6 Hz), 7.62 (d, 1H, J = 15.6 Hz), 7.76 (d, 1H, J = 15.2 Hz); ^{13}C NMR (100 MHz, DMSO): δ 56.9, 57.1, 89.2, 90.6, 106.7, 113.7, 118.1, 123.6, 130.5, 146.9, 151.4, 161.8, 162.1, 162.3, 191.9; IR ν_{max} (KBr): cm^{-1} 1633, 1604, 1424, 1317, 1225, 1136; Anal. Calcd for $C_{15}H_{13}BrO_5$: C, 51.01; H, 3.71%; found C, 50.95; H, 3.62%.
21. Complete crystallographic data of **2b**, **5a,** and **6a** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 810812, 810814 and 810813, respectively. 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).
22. *Typical procedure for the preparation of tribromides (**3**) and synthesis of 8-bromoflavones (**5**)*: To a well stirred solution of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-one (0.5 mmol) in 5 mL of DCM was added BDMS (0.444 g, 2 mmol) at room temperature. The reaction was complete within 10 min. Then, it was quenched by adding 10% sodium metabisulphite solution and the reaction mixture was extracted with DCM (2 × 15 mL), washed with water, and dried over anhydrous sodium sulfate to obtain the tribromo derivatives **3**. The pure tribromide was obtained after recrystallization in DCM-hexane. Then the tribrominated compounds **3** on treatment with 0.2 M KOH (0.5 mL) in EtOH/H_2O (4:1) yielded 8-bromoflavones after usual work-up procedure. *Compound **5a***: Pale yellow solid, mp 239–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.03 (s, 3H) , 4.05 (s, 3H), 6.46 (s, 1H), 6.64 (s, 1H), 7.03 (d, 2H, J = 8.8 Hz), 7.96 (d, 2H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 56.7 (2C), 91.2, 92.2, 106.9, 109.9, 114.6 (2C), 117.8, 123.5, 128.1 (2C), 160.3, 160.5, 161.0, 162.4, 177.5; IR ν_{max} (KBr): cm^{-1} 1639, 1593, 1341; Anal. Calcd for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86%; found C, 55.18; H, 3.81%. *Compound **5b***: Pale yellow solid, mp 229–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 3H), 3.94 (s, 3H) , 3.98 (s, 3H), 3.99 (s, 3H), 6.05 (s, 1H), 6.90 (s, 1H), 7.21 (dd, 1H, J = 1.6, 8.0 Hz), 7.73 (d, 1H, J = 15.2 Hz), 7.80 (d, 1H, J = 15.6 Hz); IR ν_{max} (KBr): cm^{-1} 1610, 1516, 1219, 1111; Anal. Calcd for $C_{19}H_{17}BrO_6$: C, 54.17; H, 4.07%; found C, 54.11; H, 4.01%. *Compound **5l***: Pale yellow solid, mp 315–316 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (s, 3H), 4.06 (s, 3H) , 6.48 (s, 1H), 6.86 (s, 1H), 7.57–7.59 (m, 2H), 7.96–8.01 (m, 4H), 8.60 (s, 1H); IR ν_{max} (KBr): cm^{-1} 1641, 1592, 1324, 1212; Anal. Calcd for $C_{21}H_{15}BrO_4$: C, 61.33; H, 3.68%; found C, 61.27; H, 3.61%.
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24. *Typical procedure for the preparation of dibromides (**4**) and synthesis of 7-bromoaurones (**6**)*: To a well stirred solution of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-one (0.5 mmol) in DCM/MeOH (5:2), BDMS (0.444 g, 2 mmol) was added at room temperature. The reaction was over within 10 min and it was quenched by adding 10% sodium metabisulfite solution. The reaction mixture was extracted with DCM (2 × 15 mL), washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated in rotary evaporator and the crude product recrystallized in DCM-hexane mixture to get the pure brominated product **4**. The dibrominated product **4** on treatment with 0.2 M KOH (0.5 mL) in EtOH/H_2O (4:1) afforded 7-bromoaurones. *Compound **6a***: Pale yellow solid, mp 250–251 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.05 (s, 6H) , 6.21 (s, 1H), 6.84 (s, 1H), 7.01 (d, 2H, J = 8.4 Hz), 7.92 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 56.7, 57.2, 85.4, 90.8, 106.6, 112.5, 114.7 (2C), 125.2, 133.5 (2C), 146.6, 159.0, 161.1, 163.9, 164.2, 180.6; IR ν_{max} (KBr): cm^{-1} 1598, 1513, 1173, 1102; Anal. Calcd for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86%; found C, 55.19; H, 3.78%. *Compound **6b***: Pale yellow solid, mp 207–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 4.01 (s, 9H) , 6.18 (s, 1H), 6.80 (s, 1H), 6.90 (d, 1H, J = 8.4 Hz), 7.31 (dd, 1H, J = 1.6, 8.4 Hz), 7.81 (d, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, DMSO): δ 55.5, 55.7, 56.6, 56.8, 88.9, 90.6, 106.7, 110.9, 111.8, 123.2, 124.5, 127.5, 143.9, 149.0, 151.4, 161.3, 161.5, 161.9, 192.3; IR ν_{max} (KBr): cm^{-1} 1609, 1517, 1247, 1111; Anal. Calcd for $C_{19}H_{17}BrO_6$: C, 54.17; H, 4.07%; found C, 54.11; H, 4.01%.

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Hydrated Ferric Sulfate [$Fe_2(SO_4)_3 \cdot xH_2O$]: An Efficient and Reusable Catalyst for One-Pot Synthesis of 2*H*-Indazolo[2,1-*b*]phthalazine-triones

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ABSTRACT. Hydrated ferric sulfate can be used as an efficient and reusable catalyst for the synthesis of 2*H*-indazolo[2,1-b]phthalazine-trione derivatives *via* one-pot three-component condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic-1,3-diketones in ethanol under reflux conditions.

Key words: Ferric sulfate hydrate [$Fe_2(SO_4)_3 \cdot xH_2O$], Three component reactions, Phthalhydrazide, Cyclic-1,3-diketones, 2*H*-Indazolo[2,1-*b*] phthalazine-trione derivatives

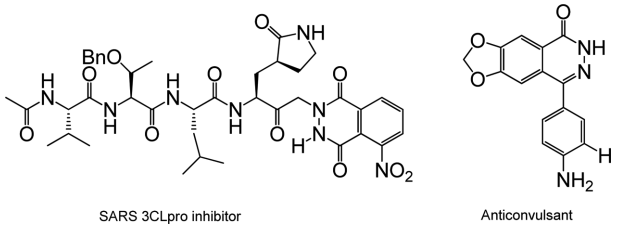
INTRODUCTION

Hydrated ferric sulfate [$Fe_2(SO_4)_3 \cdot xH_2O$] has been found as a catalyst for various organic transformations such as tetrahydropyranlations of alcohols,[1] preparation of acylals from aldehydes,[2] 2,3-unsaturated glycosides *via* Ferrier rearrangement,[3] per-O-acetylation of sugars,[4] synthesis of tetrahydroquinolines[5] through Povarov reaction and synthesis of 1*H*-pyrazole-4-carbodithioate[6] using MCRs. The unique solubility of the catalyst in ethanol and insolubility in DCM enables its usage as both homogenous and heterogeneous catalyst; and is recoverable by DCM after the reaction. As a part of our ongoing research work by employing MCRs to synthesize new molecules,[7] we conceived that $Fe_2(SO_4)_3 \cdot xH_2O$ can be exploited further as a reusable catalyst for the synthesis of heterocycles by employing multicomponent reactions.

The efficient high-throughput synthesis of biologically active organic compounds is one of the most important and challenging endeavors in modern drug discovery. Organic reactions should be fast, neat and clean, and the target products should be easily separable with high purity and good yields. To cover all the above aspects, multicomponent reactions[8] (MCRs) play an important role in combinatorial chemistry because of their ability to synthesize target molecules with greater efficiency, higher atom-economy, structural diversity and complexity in a single step from three or more reactants. These reactions are very effective for synthesizing highly functionalized organic molecules from readily available starting materials.

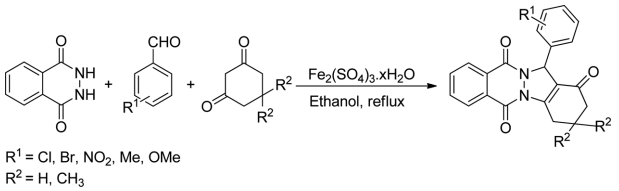
The synthesis of heterocyclic compounds has gained considerable attention among synthetic organic chemists due to their immense potentiality in pharmaceuticals. Heterocyclic systems are found abundantly in nature as alkaloids, flavonoids and isoflavonoids[9] and they are considered to be essential to life. Among various nitrogen containing heterocycles, phthalazine skeleton is present in many naturally occurring compounds and they exhibit interesting pharmacological properties (*Fig.* 1). The compounds having fused phthalazines possess many biological activities such as anticonvulsant,[10]cardiotonic,[11] vasorelaxant,[12] antimicrobial,[13] antifungal,[14] anticancer,[15] and anti-inflammatory[16] activities. They are also highly potent inhibitors of vascular endothelial growth factor receptor II (VEGFR-2).[17–19] Furthermore, these compounds might be useful materials for luminescence or fluorescence studies.[20]

The synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives have been reported involving one-pot condensation of phthalhydrazide, aldehydes and 1,3-diketones using numerous catalysts.[21,22] Though all these protocols are quite useful, still there is a need to develop a new methodology using a reusable catalyst.



SARS 3CLpro inhibitor　　Anticonvulsant

***Figure* 1.** Some biologically active compounds having phthalazine skeleton.



***Scheme* 1.** Synthesis of 2*H*-indazolo[2,1-b]phthalazine-trione derivatives.

In this paper, we have reported hydrated ferric sulfate catalyzed one pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives *via* three-component condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic 1,3-dicarbonyl compounds in ethanol under reflux conditions as shown in *Scheme* 1.

EXPERIMENTAL

General experimental procedure for the Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives

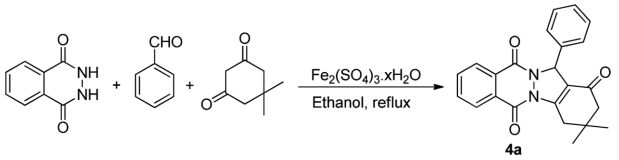
Hydrated ferric sulfate (0.20 mol, 0.084 g) was added to a mixture of an aromatic aldehyde (1.2 mmol), a cyclic 1,3-dicarbonyl compound (1.0 mmol) and phthalhydrazide (1.0 mmol) in 3 mL of ethanol. The reaction mixture was kept for refluxing in a preheated oil-bath. After completion of the reaction (as monitored by TLC), it was brought to room temperature. The solid product precipitated out after adding 6 mL of water into it and it was filtered off through a Büchner funnel. The precipitate was washed with ethanol (2 mL) and dried in a vacuum pump.

For checking reusability, a reaction mixture of phthalhydrazide (0.810 g, 5.0 mmol), 4-nirobenzaldehyde (0.831 g, 5.5 mmol) and dimedone (0.700 g, 5.0 mmol) in presence of hydrated ferric sulfate (0.418 g, 1 mmol) was refluxed in 10 mL of ethanol. After completion of the reaction, the catalyst was recovered by removing ethanol in a rotatory evaporator followed by addition of 15 mL of CH_2Cl_2. The catalyst was precipitated out due to its poor solubility in CH_2Cl_2 and it was filtered off through a Büchner funnel. The desired product **4h** was obtained after concentrating the organic solvent in a rotatory evaporator. The reusability of the recovered catalyst was examined for five consecutive times using the same substrates and the results are summarized in *Table* 3. We have noted that the catalyst can be reused without losing much catalytic activity.

RESULTS AND DISCUSSION

To find out suitable reaction conditions, benzaldehyde (1.2 mmol), dimedone (1 mmol), and phthalhydrazide (1 mmol) were chosen as the model substrates. The reactions were examined in presence of various catalysts in different solvent systems and the results are summarized in *Table* 1.

***Table* 1.** Optimization for one-pot condensation of phthalhydrazide, benzaldehyde and dimedone[a]



Entry	Catalysts (mol%)	Solvent	Time (h)	Yield (%[b])
1	None	Neat	10	0
2	None	EtOH	10	0
3	X (5)	Neat	10	Trace
4	X (5)	EtOH	10	40
5	X (10)	EtOH	7	56
6	X (15)	EtOH	4	70
7	X (20)	EtOH	3	87
8	X (25)	EtOH	3	88
9	X (20)	DCE	3	71
10	X (20)	MeCN	3	72
11	X (20)	H_2O	3	Trace
12	$FeCl_3 \cdot 6H_2O$(20)	EtOH	3	75
13	$NiCl_2$ (20)	EtOH	3	60
14	$SnCl_2$ (20)	EtOH	3	74
15	AcOH (20)	EtOH	3	40

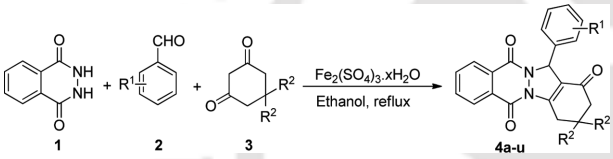
[a]The reactions were carried out using phthalhydrazide (1.0 mmol), benzaldehyde (1.2 mmol) and dimedone (1.0 mmol). [b]Isolated Yield. X = $Fe_2(SO_4)_3 \cdot xH_2O$.

It was noted that the reaction did not provide any desired product in absence of catalyst after heating at 80 °C for 10 h either in neat or in ethanol (*Table* 1, entries 1 and 2). Interestingly, the desired product **4a** was isolated in 40% yield (*Table* 1, entry 4) when the same reaction mixture was heated in presence of 5 mol% hydrated ferric sulfate. Furthermore, we have carried out similar set of reactions in the presence of 10 mol%, 15 mol%, 20 mol% and 25 mol% (*Table* 1, entries 5-8), respectively. From these observations, we have noted that 20 mol% of the catalyst is the suitable choice to obtain best yield. For scrutinizing a suitable solvent system, the similar reaction was executed with similar boiling range of solvent such as dichloroethane, acetonitrile and water under identical reaction conditions. We found that the maximum yield of product **4a** was obtained in ethanol under reflux conditions (*Table* 1, entry 7). To examine the efficacy of the other catalysts, the similar reactions were performed in presence of $FeCl_3 \cdot 6H_2O$, $NiCl_2$, $SnCl_2$ and CH_3COOH (*Table* 1, entries 12-15), respec-

tively and we have obtained moderate to good yield. However, we have used hydrated ferric sulfate because of its reusability.

To generalize our protocol, a wide variety of aromatic aldehydes having electron-donating and electron- withdrawing substituents in the aromatic ring were reacted with phthalhydrazide, and dimedone under similar reaction condition and the desired 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives (**4b-o)** were obtained in good yields. Likewise, cyclohexane-1,3-dione also provided the desired 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives **4p-u** in good yields under identical reaction conditions. It is worthwhile to mention that aromatic aldehydes having electron-withdrawing group require relatively shorter reaction time as well as also provide good yields. Unfortunately, the similar kind of cyclized product was not obtained when the reaction carried out with acyclic 1,3-diketones. All the successful results (*Table* 2) clearly demonstrate that hydrated ferric sulfate is an efficient catalyst for this three-component reaction.

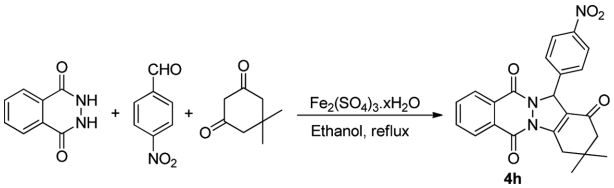
***Table* 2.** Synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones



Entry	R^1	R^2	Time (h)	Product[a]	Yield (%)[b]
1	H	CH_3	3	**4a**	87
2	4-OCH_3	CH_3	4	**4b**	83
3	2-OCH_3	CH_3	4	**4c**	81
4	3,4-$(OCH_3)_2$	CH_3	4	**4d**	86
5	3,4,5-$(OCH_3)_3$	CH_3	4	**4e**	84
6	4-OH-3-OCH_3	CH_3	4	**4f**	85
7	4-CH_3	CH_3	4	**4g**	84
8	4-NO_2	CH_3	2	**4h**	93
9	3- NO_2	CH_3	2	**4i**	92
10	2- NO_2	CH_3	2	**4j**	87
11	4-Cl	CH_3	2	**4k**	89
12	2- Cl	CH_3	2	**4l**	84
13	4-Br	CH_3	2	**4m**	90
14	3-Br	CH_3	2	**4n**	91
15	3-OH	CH_3	4	**4o**	80
16	H	H	3	**4p**	86
17	4-Cl	H	2	**4q**	89
18	4-NO_2	H	2	**4r**	90
19	4-OCH_3	H	4	**4s**	83
20	4-OH-3-OCH_3	H	4	**4t**	79
21	2-OCH_3	H	4	**4u**	80

[a]All the reactions were carried out using phthalhydrazide (1.0 mmol), aromatic aldehydes (1.2 mmol) and dimedone (1.0 mmol)/cyclohexane-1,3-dione (1.0 mmol) using 0.2 mmol of catalyst. [b]Isolated yield.

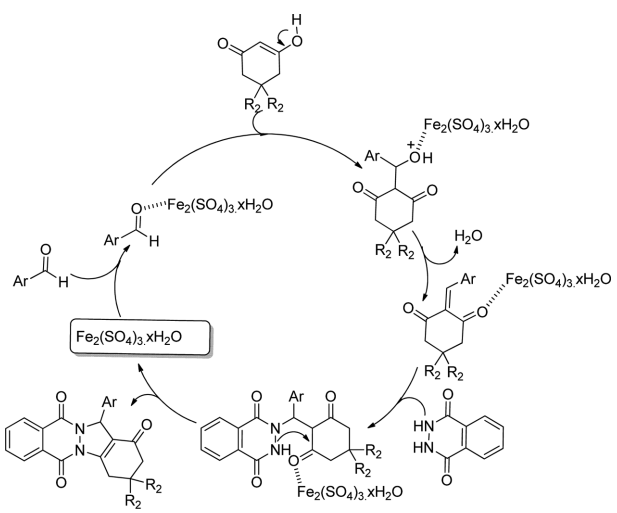
***Table* 3.** Reusability of the catalyst $[Fe_2(SO_4)_3{\cdot}xH_2O]$



Round	Catalyst recovered (mg)	Reaction time (h)	Yield[b] (%)
1	418	3	94
2	413	3	92
3	403	3	91
4	395	3	90
5	388	3	89

[a]The same set of reaction was performed with phthalhydrazide (5.0 mmol), 4-nirobenzaldehyde (5.5 mmol) and dimedone (5.0 mmol) in each time. [b]Isolated yield.

The probable mechanism for the formation of product may be rationalized as follows: Aromatic aldehyde reacts with dimedone to provide Knoevenagel product 2-benzyli-dene-5,5-dimethylcyclohexane-1,3-dione in the presence of hydrated ferric sulfate. Then the intermediate undergoes 1,4-Michael addition with phthalhydrazide followed by concomitant cyclization to give the desired product (*Scheme* 2).



***Scheme* 2.** Probable mechanism for the formation of product.

RECYCLING OF THE CATALYST

In view of greener chemistry, efficient recovery and reuse of the catalyst are highly desirable. As a matter of fact, the catalyst $Fe_2(SO_4)_3{\cdot}xH_2O$ was recovered conveniently

from the reaction mixture at the end of the reactions and it was reused another four times for the same set of reaction.

CONCLUSION

In summary, we have shown that hydrated ferric sulfate is an efficient and reusable catalyst for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives *via* one-pot three-component condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic-1,3-diketones in ethanol under reflux conditions.

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