Exploration of 3-Aminocoumarins for Construction of Pyridocoumarins and Pyrrolocoumarins & Synthesis of Fused Oxazoles and Thiazoles via Oxidative C-H Bond Functionalization

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

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled *"Exploration of 3-Aminocoumarins for Construction of Pyridocoumarins and Pyrrolocoumarins & Synthesis of Fused Oxazoles and Thiazoles via Oxidative C-H Bond Functionalization"* is the result of investigations carried out by me under the supervision of Prof. Abu T. Khan in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

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

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CERTIFICATE

This is to certify that Md. Belal has been working under my supervision since July, 2012 as a regular registered Ph. D. student. His thesis entitled *"Exploration of 3-Aminocoumarins for Construction of Pyridocoumarins and Pyrrolocoumarins & Synthesis of Fused Oxazoles and Thiazoles via Oxidative C-H bond Functionalization"* contains the results obtained from the research work carried out by him in the Department of Chemistry, Indian Institute of Technology Guwahati, India. I am forwarding his thesis to submit for the Ph. D. (Science) degree from this institute as he has fulfilled all the requirements according to the rules of this institute and this work has not submitted elsewhere for a degree.

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This is to certify that Md. Belal has completed his Thesis Work from July, 2012 as a regular registered Ph. D. 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 *"Exploration of 3-Aminocoumarins for Construction of Pyridocoumarins and Pyrrolocoumarins & Synthesis of Fused Oxazoles and Thiazoles via Oxidative C-H Bond Functionalization"* being submitted for the Ph. D. (Science) degree from 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.

IIT Guwahati
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Last but not least, I would like to thank my parents and my family members for their immense support. Their encouragement and belief in me to prosper in life always have been the driving force to my success.

Content of the Thesis

Abbreviations

Ac	acetyl
BDMS	bromodimethylsulfonium bromide
Bn	benzyl
Boc	tert-butoxycarbonyl
Bu	butyl
t-Bu	tert-butyl
t-BuOH	tert-butyalcohol
Bz	benzoyl
CCDC	cambridge crystallographic data centre
CDC	cross dehydrogenative coupling
DCE	1,2- dichloroethane
DCM	dichloromethane
DMAP	*N*, *N*-4-dimethylaminopyridine
DMF	*N*, *N*-dimethylformaide
DMSO	dimethylsulfoxide
ESI	electron spray ionization
Et	ethyl
EtOH	ethanol
Et_3N	trithylamine
HRMS	high resolution mass spectrometry
IR	infrared
MCR	multicomponent reaction
Me	methyl
MP	melting point
MS	molecular sieve
MW	microwave
MWI	microwave induced
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid program
PDCA	pyridine dicaboxylic acid
i-pr	isopropyl
Ph	phenyl
PPA	polyphosphoric acid
ppm	parts per million

pr	propyl
TBHP	tert-butyl-hydroproxide
p-TSA	p-toulenulfonic acid
PTSA	p-toulenulfonic acid
Py	pyridine
rt	room temperature
TEMPO	2,2,6,6-tetramethyl pyridine-N-oxide
TFA	trifluorocaetic acid
TfOH	trifluoromethansulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	trifluoromethansulfonic acid
XRD	x-ray diffraction

CHAPTER I

Literature Survey on the Importance of Aminocoumarins and 3-Aminocoumarins for Construction of Pyridocoumarins and Pyrrolocoumarins

• I.1. Introduction

Coumarins are naturally occurring heterocyclic compounds. They are known as benzopyrones having a benzene ring fused with a pyrone ring and is also called as 2-*H*-chromen-2-one. Coumarins constitute the important class of heterocyclic compounds having a broad spectrum of biological activities.[1] Both naturally occurring and synthesized coumarin containing heterocyclic compounds have shown interesting and valuable medicinal and pharmaceutical properties. Therefore, recently the synthetic chemists have given considerable effort to achieve these compounds in an easier and economically fruitful ways.[2] Coumarin based heterocyclic compounds are the good chromophores and they are used as florescence probes and non-linear optical chromophores which give the chemists a further reason to explore the field of coumarin chemistry.[3]

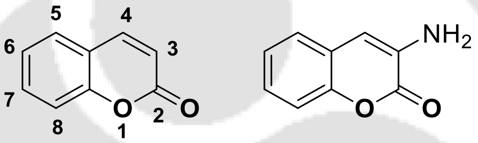


Figure 1. Structure of coumarin and 3-aminocoumarin

3-Aminocoumarin itself does not occur naturally unlike many other coumarin derivatives but it is the core structures of natural antibiotics.[4] Aminocoumarins, mostly 4-aminocoumarins and 6-aminocouamarins have been used widely for the synthesis of heterocyclic compounds whereas 3-aminocoumarin is very much less explored.[5] Therefore the thesis work has been put forward for the synthesis of heterocycles exploring 3-aminocoumarins.

• I.2. Importance of Coumarins

Simple coumarin was first isolated from Tonka bean by Vogel in 1820. Since its isolation, a library of natural products containing coumarin moieties have been discovered and their biological activities are being explored (Fig. 2).[6] Umbelliferone which is actually 7-hydroxycoumarin, found in carrots, coriander and garden angelica are used as sunscreen agent, a fluorescence indicator and as a dye indicator.[7] Warfarin isolated from woodruff and lavender are used as anti-coagulant.[8] Dicoumarol, isolated from mouldy, wet, sweet-clover hay, is also a good anticoagulant.[9] Aesculitin and scopolin isolated from *Santolina oblongifolia* plant and Esculin found in *Aesculus hippocastanum L.* (Horse-chestnut) have been found as potent anti-inflammatory agents.[10a,b] Calophyllum species which are pyranocoumarins, well known for their anti HIV-1 RT activity.

(+)-Calanolide A was first isolated from *Calophyllum lanigerum* in 1987, is a non-nucleoside reverse transcriptase inhibitor with potent activity against HIV-1. (+)-Cordatolide A, isolated from the leaves of C. *Cordatooblangum* in 1985 also shows anti-HIV RT activity. (+)-Inophyllum B isolated from *C. inophyllum* was found to be most active against HIV-reverse transcriptase.[11]

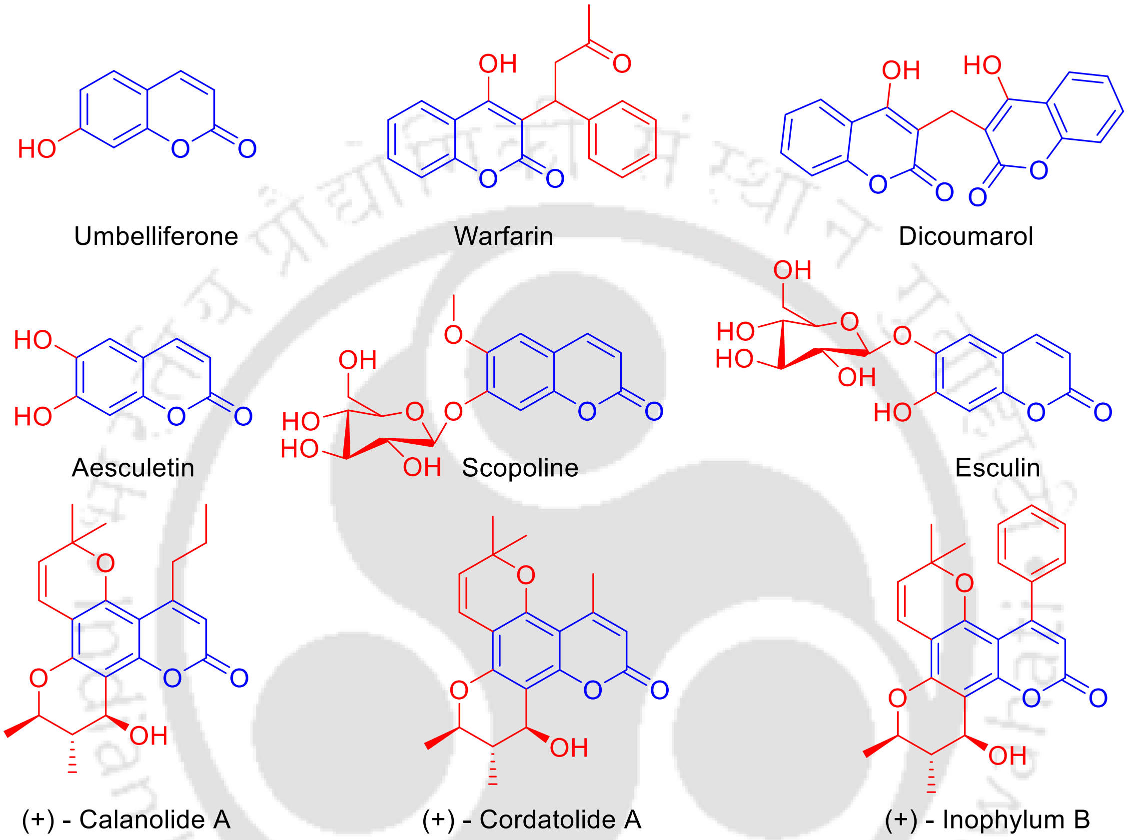


Figure 2. Naturally occurring coumarins

• I.3. Importance of 3-Aminocoumarins

The 3-aminocoumarin moiety is found in marine alkaloid like Lamellarin D and Ningalin B. It is also the part of alkaloid santiagonamine (Fig. 3). Nigalin B is pyrrolocoumarin based drugs which shows multidrug resistance activities.[12] Lamellarin D is also a pyrrolocoumarin and has potent cytotoxic activity. It has also found to be a good inhibitor of topoisomerase I and was first isolated in 1985 by Faulkner and co-workers from the marine prosobranch mollusc *Lamellaria* sp.[13] Santiagonamine is an alkaloid containing pyridocoumarin moiety which shows excellent healing property and was isolated from the stems and branches of the South American shrub *Berberis darwinii* Hook in 1984 by Shamma et al.[14] 3-Aminocoumarin is the core structures of natural antibiotics such as Novobiocin, Chlorobiocin and Coumermycin (Fig.3) and they are the inhibitors of bacterial gyrase.[4]

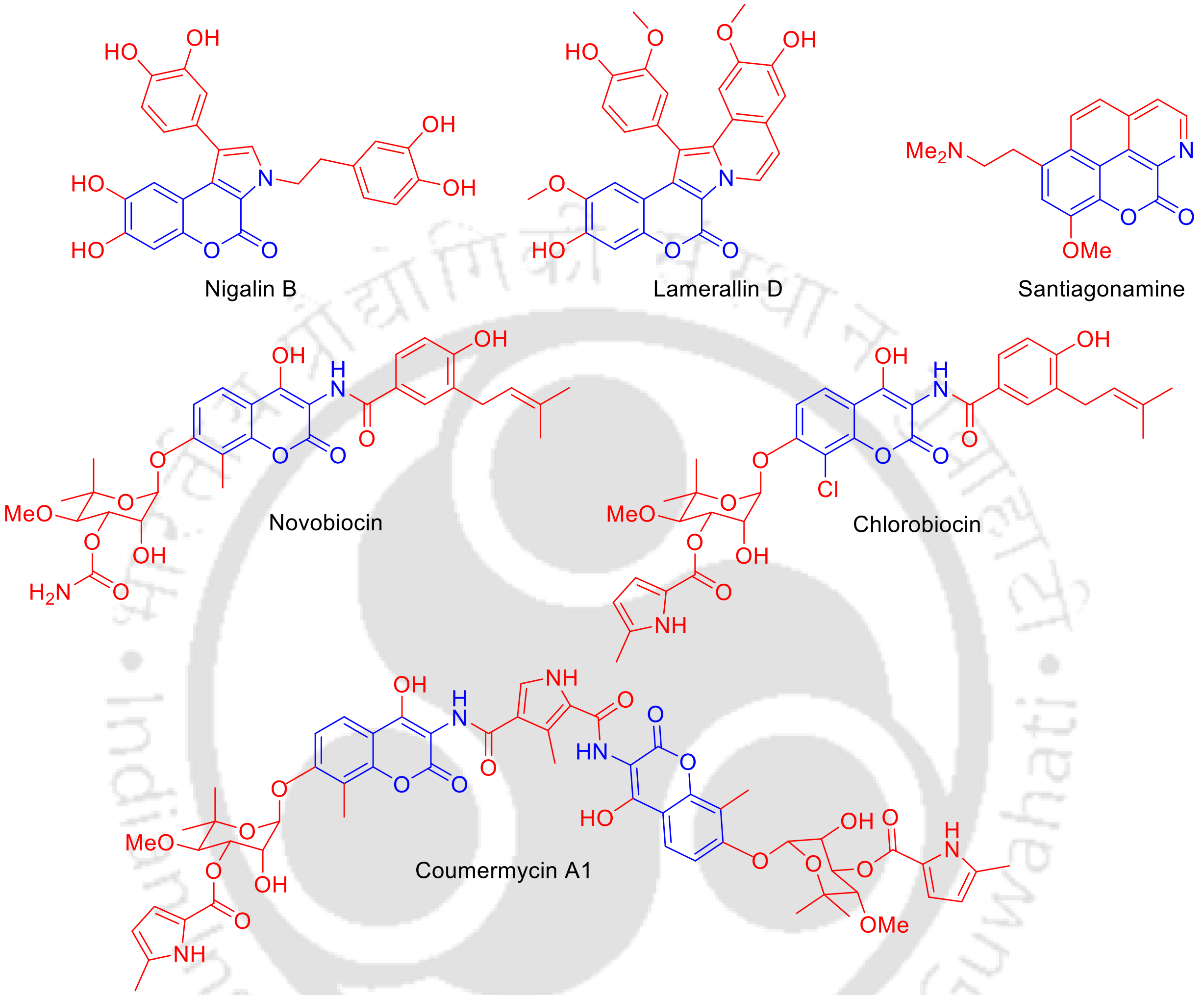


Figure 3. Naturally occurring 3-aminocoumarin derivatives

Occurrence of 3-aminocoumarins derivatives in nature and their biological significance suggest that various new fused 3-aminocoumarin derivatives may show interesting biological activities.

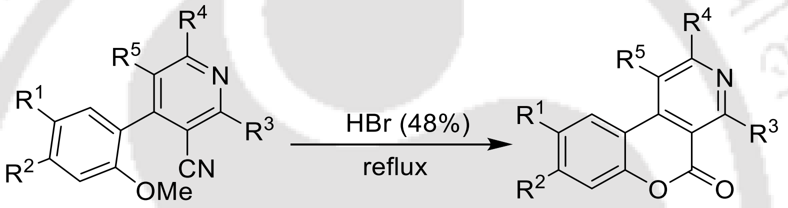
• I.4. Synthesis of Pyridocoumarins and Pyrrolocoumarins

Pyridocoumarins and pyrrolocoumarins are important organic moieties. Pyridocoumarins have been found to possess anti-tumor, anti-bacteria and anti-inflammatory activities.[15] Pyrroles are the part of many naturally occurring marine alkaloids.[16] Moreover, coumarin fused pyrroles are the basic core of the biologically active alkaloids Ningalin B and Lamerallin D. Various groups have synthesized these compounds to study their biological activities.[17] Some of the methods for the synthesis of coumarin fused pyridines and pyrroles, have been discussed in this section.

• I.4.1 Synthesis of Pyridocoumarins

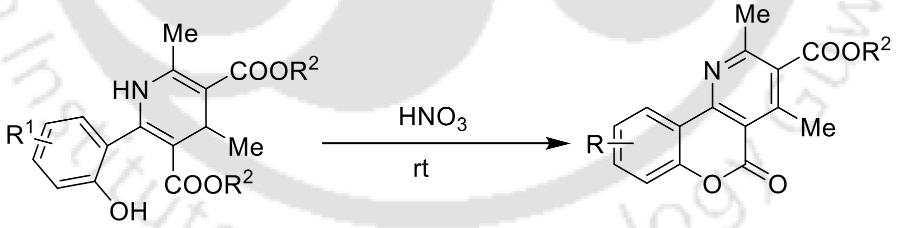
There are several routes for the synthesis of pyridocoumarins starting from substituted pyridine derivatives, substituted coumarins, and the condensation of salicylaldehydes and β-ketoesters. Recently, in some of the reports Aza Diel Alder reactions have been used to synthesize coumarin fused pyridine derivatives. Some of the reported methods for the synthesis of pyridocoumarins are listed below.

Petrov et al. achieved pyridocoumarin derivatives by the cyclization of 4-(2-methoxyphenyl)-pyridine derivatives on heating in presence of 48% HBr as shown in Scheme 1.[18]



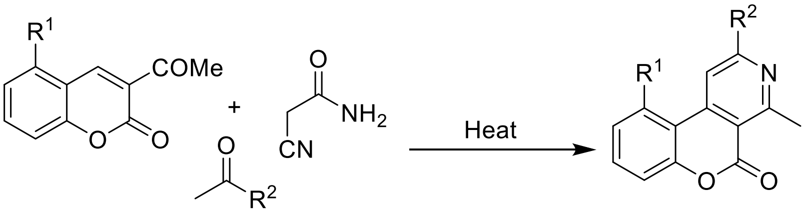
Scheme 1

O'Callaghan, accomplished the synthesis of coumarin fused pyridine derivatives by the oxidation of 2-(2-hydroxyphenyl)-l,2-dihydropyridines with con. HNO_3 as depicted in Scheme 2.[19]



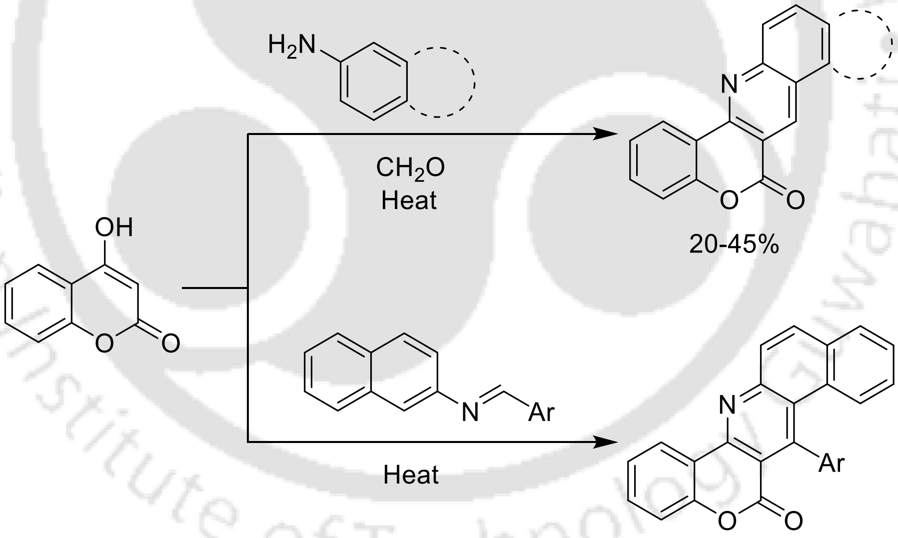
Scheme 2

Koelesch and co-workers demonstrated the condensation of 3-acetylcoumarin, cynoacetamides and ketones leading to the formation of a number of pyrido(3,2-c)derivatives with 21-64% yields where the cynoacetamide was used as source of ammonia for the synthesis of the chromenone derivatives as represented in Scheme 3.[20]



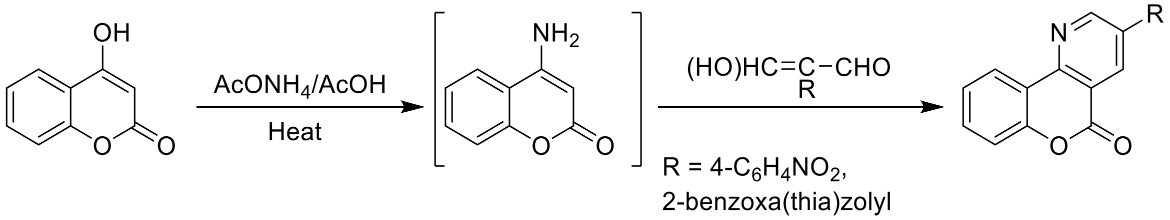
Scheme 3

Buu-Hoi and co-workers reported the synthesis of pyrido(3,2-c)coumarin derivatives by the condensation of 4-hydroxycoumarin, arylamines and paraformaldehydes. 4-Hydroxycoumarin undergoes Ullmann-Fetvadjian-type condensation with the arylamines and para formaldehyde to generate pyrido(3,2-c)coumarin derivatives. Apart from aniline, various other arylmines like α-naphthylamine, β-naphthylamine, 5-amino-3-phenylthianaphthene, 4-aminofluorene and 5-amino-8-methylquinoline were used for the synthesis of structurally complex pyrido(3,2-c)coumarins. The pyridocoumarin was also obtained in good yield using the imine and 4-hydroxycoumarins as described in Scheme 4.[21]



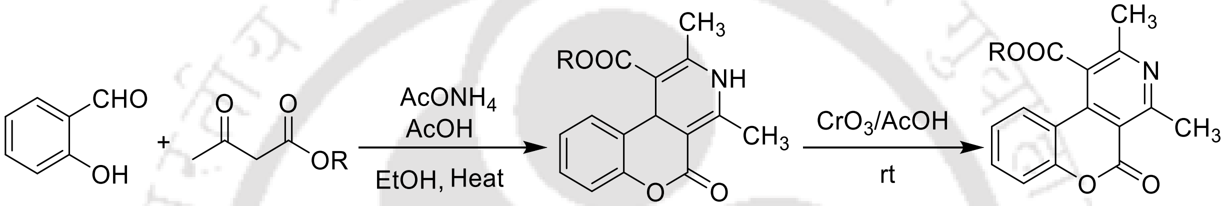
Scheme 4

Joshi et al. reported that 4-hydroxycoumarin, on heating with $AcONH_4$/AcOH gives the corresponding 4- aminocoumarin, without further purification, on addition of malondialdehydes into the same pot, pyrido(3,2)coumarin derivatives were obtained in 59-65% yield, shown in Scheme 5.[22]



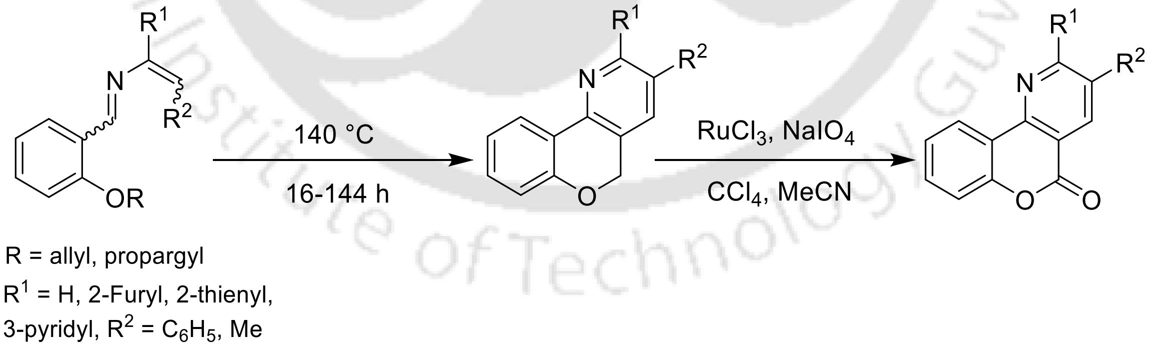
Scheme 5

O'Callaghan described that when salicylaldehyde is condensed with a mixture of β-ketoester, AcOH with 30% aq.NH_3 and EtOH, the dihydropyridine is formed which on oxidation with CrO_3 provides the pyridocoumarin as represented in Scheme 6.[19]



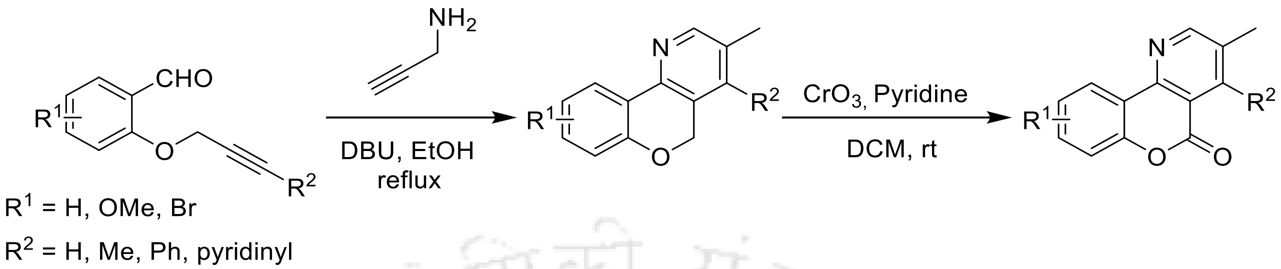
Scheme 6

Palacios et al. synthesized the azadienes from Wittig reaction of *N*-vinylphosphazenes and corresponding allyloxy/propargyloxybenzaldehydes. The azadienes on heating at 140 °C undergo Aza Diels Alder reaction to give pyridine derivatives which on oxidation provide the pyridocoumarins as shown in Scheme 7.[23]



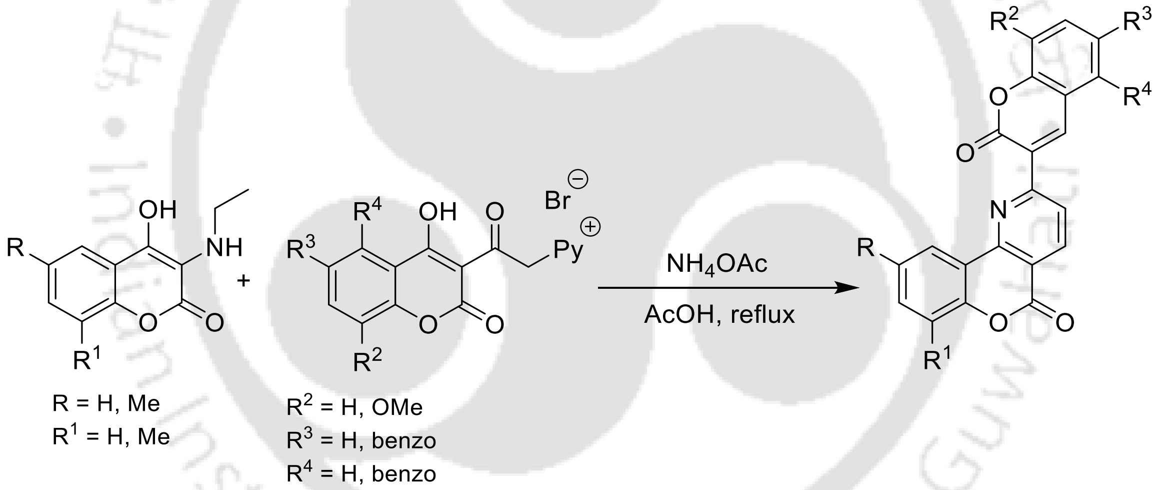
Scheme 7

Recently Balci et al. used propargylated salicylaldehydes and propargylamines in presence of DBU to obtain the chromene derivatives. The reaction takes place through an Aza Diel alder reaction of the imine formed from propargylated salicylaldehyde and the propargylamine forming a chromenopyridine derivative which on further oxidation with CrO_3 gives the corresponding pyridocoumarin derivative (Scheme 8).[24]



Scheme 8

Brahmbhatt et al. synthesized the pyridocoumarin derivatives via one pot three component reaction of the Manich base (3-amino-4-hydroxy coumarin derivatives), pyridinium salts and ammoniumacetate in refluxing glacial acetate as described in Scheme 9.[25]

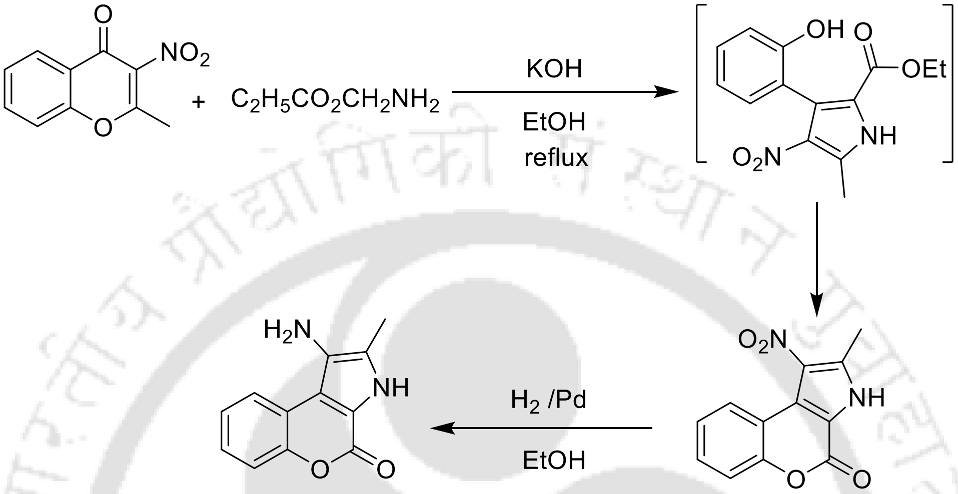


Scheme 9

• I.4.2. Synthesis of Pyrrolocoumarins

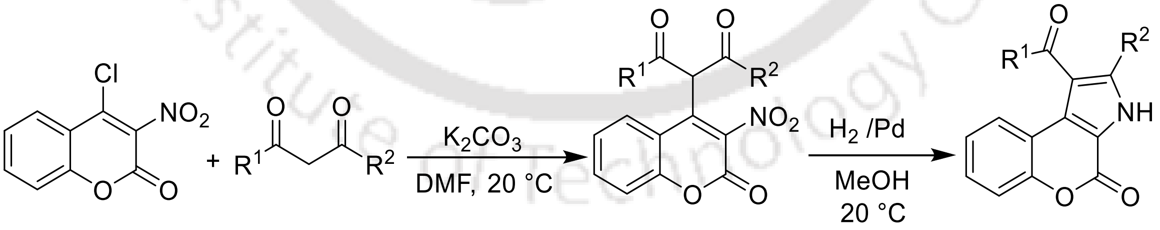
There are numerous methods reported in literature for the synthesis of pyrroles but only very few methods are available for the synthesis of pyrrolocoumarins. Amongst the reported methods traditional as well as some transition metal catalyzed annulation reaction have been found in literature for the synthesis of pyrrolocoumarins. Some of the reported methods are described in the following section.

In 1987, Takagi et al. synthesized the pyrrolocoumarin derivative from 2-methyl-3-nitrochromenone and ethyl aminoethanoate in the presence of EtOH/KOH under reflux conditions. The nitro pyrrolocoumarin thus formed gaves 1-amino-2-methylchromeno[3,4-*b]*pyrrol-4(3*H*)-one in 44% yield on reduction with H_2/Pd in EtOH as shown in Scheme 10.[26]



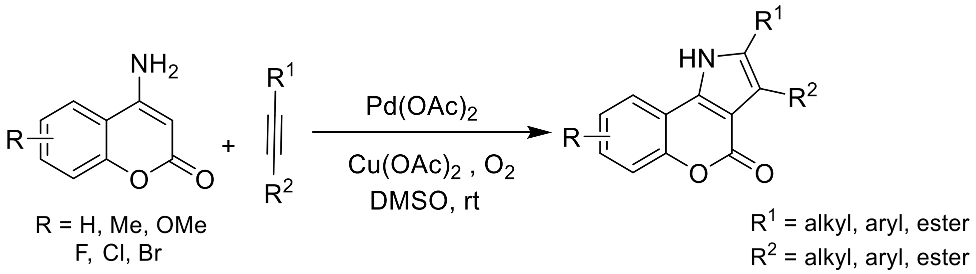
Scheme 10

Langer et al. developed the synthesis of various chromeno[3,4-*b*]pyrrol-4(3*H*)-ones via base mediated cyclocondensation of 4-choloro-3-nitrocoumarin and beta-diketone. The reaction between 4-choloro-3-nitrocoumarin and beta-diketone in the presence of K_2CO_3 as base in DMF at 20 ^{o}C gives a condensed product which on reduction followed by cyclization affords the coumarin fused pyrrole as represented in Scheme 11.[27]



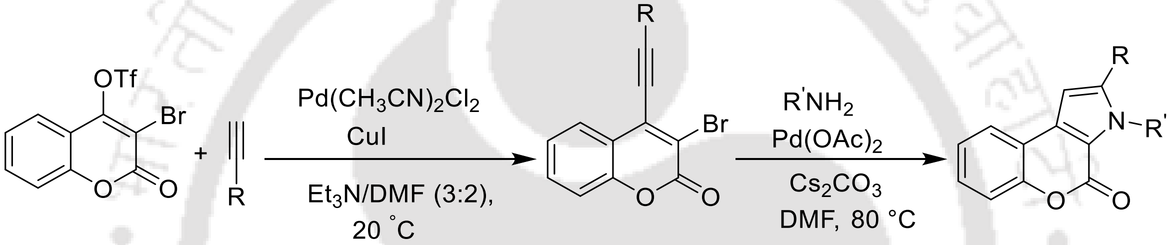
Scheme 11

Wang et al. demonstrated the synthesis of pyrrolocoumarin derivatives from 4-aminocoumarins and substituted acetylene derivatives via C-H activation employing $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ as oxidant at room temperature as shown in Scheme 12.[28]



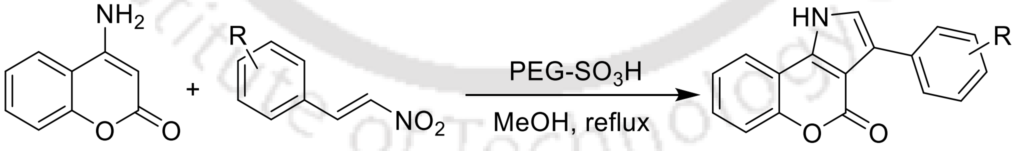
Scheme 12

In another work, Langer and coworkers synthesized various pyrrolocoumarins by Pd catalyzed C-N bond formation. A number of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones were reported from the alkynylated bromocoumarins which were synthesized by the Sonogashira reaction between, the coumarin bearing triflate and bromide group and the terminal alkynes, shown in Scheme 13.[29]



Scheme 13

Das and coworkers developed the synthesis of coumarin fused pyrrole derivatives using 4-aminocoumarin and nitroalkenes employing PEG-SO_3H as a catalyst in refluxing MeOH as depicted in Scheme 14. They also showed that the product can also be achieved using a multicomponent strategy where 4-aminocoumarin, aldehyde and nitromethan were mixed together and $CuFe_2O_4$ was used as a catalyst.[30]



Scheme 14

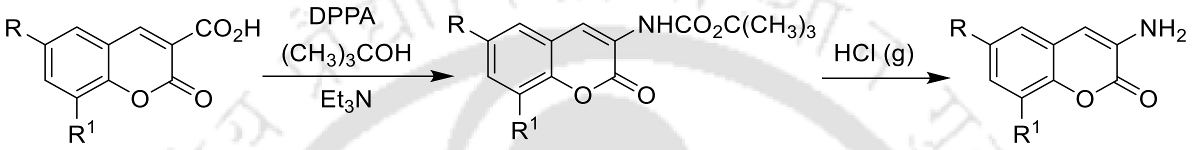
• I.5. 3-Aminocoumarins in Organic Synthesis

This section of the chapter describes various methodologies for the synthesis of 3-aminocoumrains and the use of 3-aminocoumarins for the synthesis of pyridocoumarins and pyrrolocoumarins.

• I.5.1. Synthesis of 3-Aminocoumarins

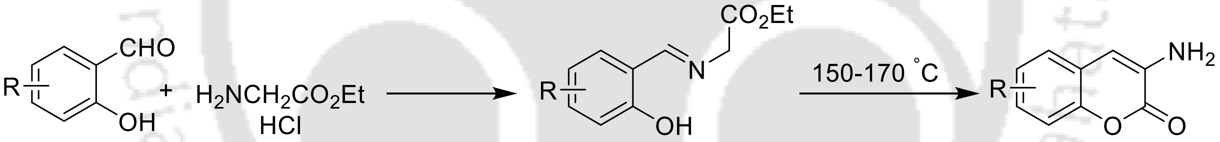
There are several methods reported in the literature for the synthesis of 3-amincoumarins, all having their own merits and demerits. Some of them have been summarized in this section as follow.

Bonsignore et al. synthesized various 3-aminocoumarin derivatives treating coumarin-3-carboxylic acids with triethylamine, diphenylphosphorylazide (DPPA) in t-butylalcohol to obtain tert-butyl (2-oxo-2*H*-chromen-3-yl)carbamates, which were transformed to the corresponding 3-aminocoumarins on treatment with gaseous HCl as described in Scheme 15.[31]



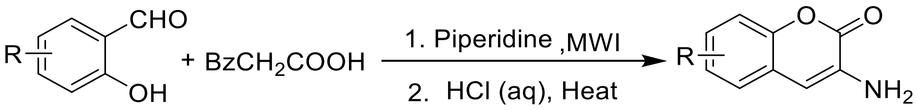
Scheme 15

Khoo and co-workers synthesized various 3-aminocoumarin derivatives by the condensation of salicylaldehydes and ethyl glycinate hydrochloride followed by heating of the ethyl *N*-hydroxyarylideneglycinates formed, at 150-170 ˚C (Scheme 16) [32]



Scheme 16

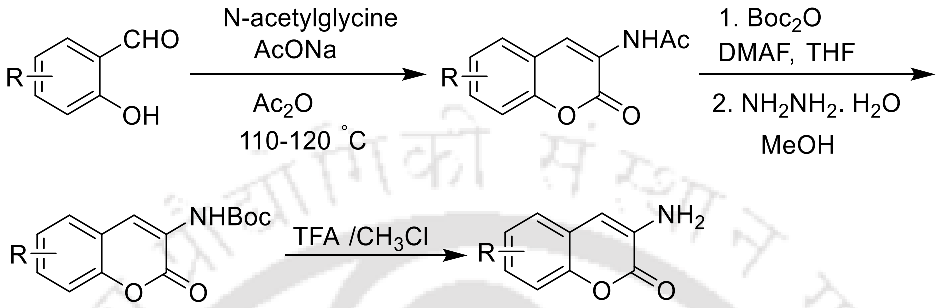
Valizadeh et al. reported the synthesis of various 3-aminocoumarins from salicylaldehydes and benzylglycine, catalyzed by piperidine under microwave and solvent-free condition. Initially, salicylaldehydes react with benzoylglycine under microwave condition in presence of piperidine forming *N*-benzoylaminocoumarins which subsequently on acid hydrolysis in the next step give the 3-aminocoumarins shown in Scheme 17.[33]



Scheme 17

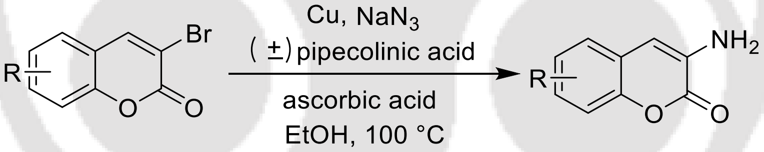
Bodwell et al. reported the synthesis of 3-aminocoumarins starting from 3-acetamidocoumarins which in turn were prepared from salicylaldehydes and *N*-acetylglycine. The

3-acetamidocoumarins were further converted to Boc-protected 3-aminocoumarins in the presence of DMAP and Boc-anhydride followed by reaction with hydrazine hydrate to remove the acetyl group. The Boc-protected 3-aminocoumarins were then deprotected to give 3-aminocoumarins through the action of 15% TFA/$CHCl_3$ as depicted in Scheme 18.[34]



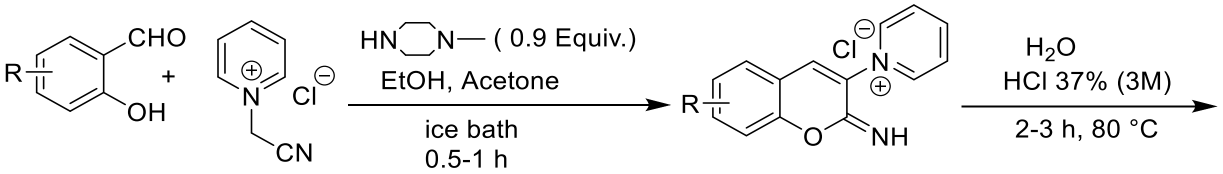
Scheme 18

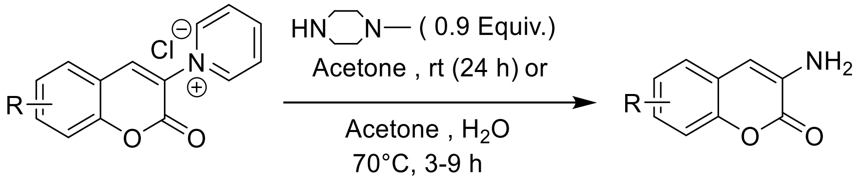
Alami et al. established the synthesis of different 3-aminocoumarins starting from 3-bromocoumarins via copper catalyzed C−N bond formation reactions in EtOH. They used pipecolinic acid as the ligand, ascorbic acid as the additive and NaN_3 the source of nitrogen for the synthesis of various 3-aminocoumarins as shown in Scheme 19.[35]



Scheme 19

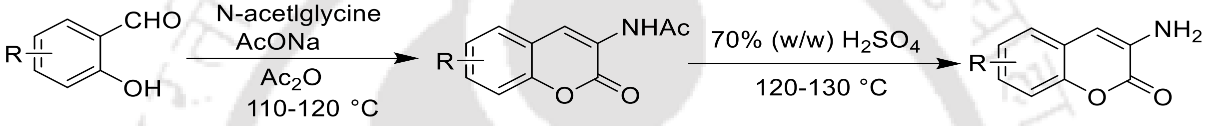
Proenca et al. synthesized 3-Aminocoumarines from the Zincke-ring opening reaction of the corresponding 2*H*-chromen-3-pyridinium chlorides using *N*-methylpiperazine. The 2*H*-chromen-3-pyridinium chlorides were prepared by base-catalyzed Knoevenagel condensation of salicylaldehydes and 1-(cyanomethyl)pyridinium chloride followed by hydrolysis with 37 % HCl at 80 °C as shown in Scheme 20.[36]





Scheme 20

Our group has also developed a mild an efficient approach to access various 3-aminocoumarin derivatives. The 3-acetamidcoumarins synthesized from a Bidwell's reported method, were hydrolyzed with 70% (w/w) H_2SO_4 to afford the corresponding 3-aminocoumarins in good to excellent yields with a large number of substrate scopes. The hydrolysis step was achieved in just 30 minutes when the reaction was carried out in 5 mmol scale (Scheme 21).[37]

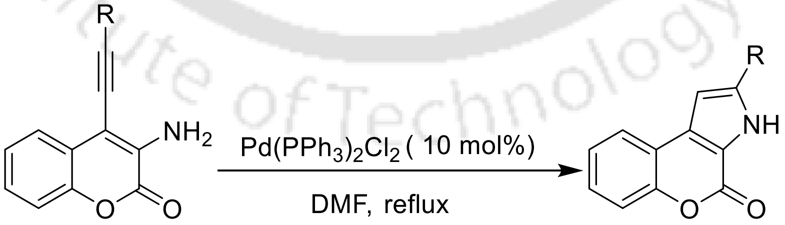


Scheme 21

• I.5.2. Synthesis of Fused Heterocycles Exploring 3-Aminocoumarins

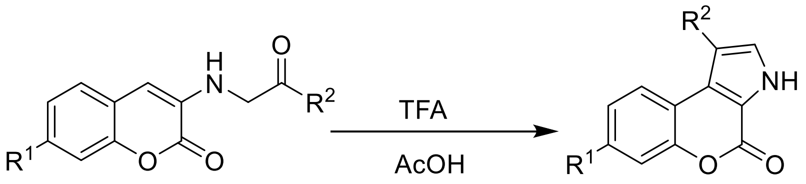
The 3-aminocoumarin moiety is not much explored for construction of heterocycles. However, there are some reports where 3-aminocoumarins and its derivatives have been used for the synthesis of fused heterocycles including the synthesis of coumarin fused pyridines and dihydropyridines from our own group.

Xu et al. reported an straight forward synthesis of various pyrrolocoumarins derivatives by palladium catalyzed cyclization of acetylenyl 3-aminocoumarins (Scheme 22).[38]



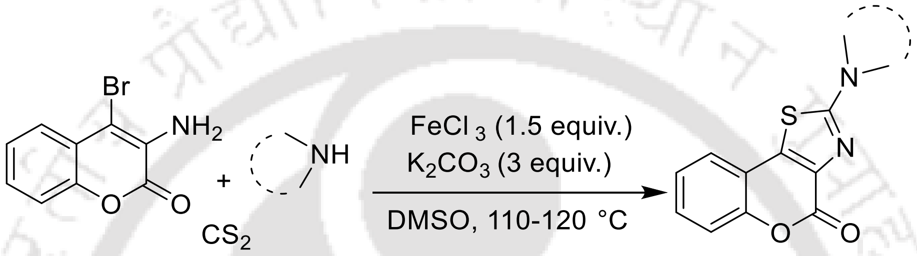
Scheme 22

Soman et al. synthesized the pyrrolocoumarins from 3-acetamidocoumarins obtained from α-haloketones and 3-aminocoumarins using catalytic amount of TFA in AcOH (Scheme 23).[39]



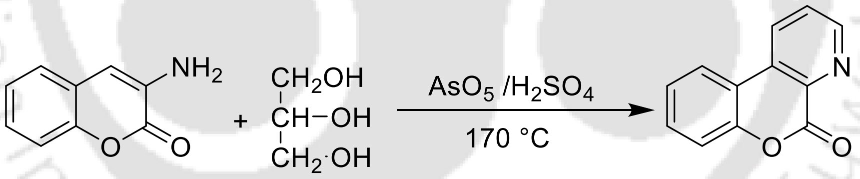
Scheme 23

Majumdar et al. reported a multicomponent approach for the synthesis of coumarin fused 2-aminothiazole derivatives from 3-amino-4-bromocoumarin and secondary amines using CS_2 in the presence of $FeCl_3$ as catalyst in DMSO as shown in Scheme 24.[40]



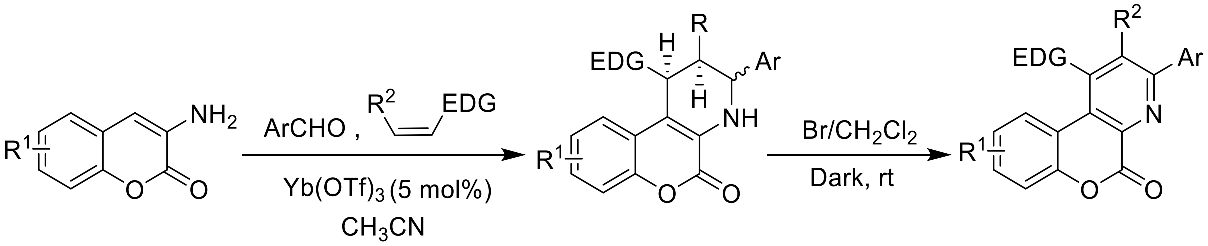
Scheme 24

Skraupe synthesis is a very familiar reaction to access quinolone derivatives. Khan et al. used this method for synthesizing pyrido(2,3-c)coumarin using 3-aminocoumarin as source of amine, glycerol, arsenic pentoxide and H_2SO_4 at 170 °C as shown in Scheme 25.[41]



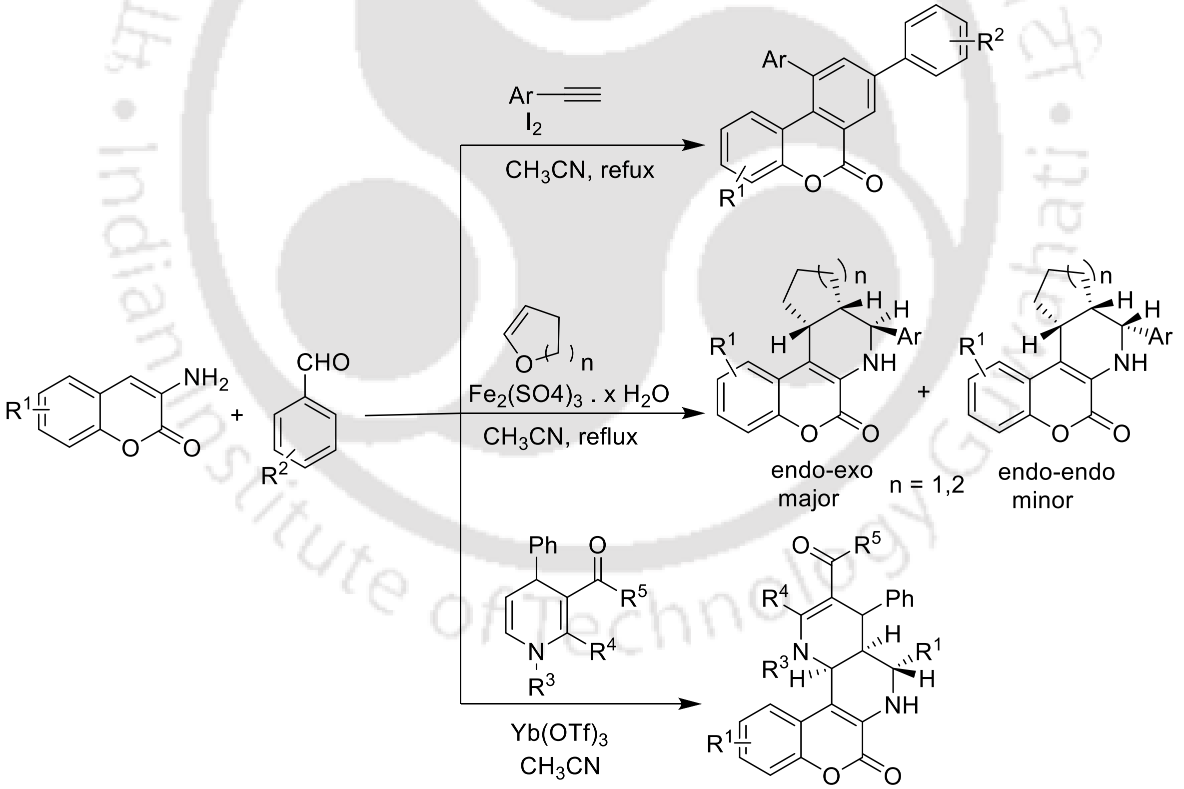
Scheme 25

Povarov reaction has been a very useful tool for the synthesis of dihydrorpyridine and pyridine derivatives. The reaction has also been extended for the synthesis of coumarin fused dihydropyridine and pyridine derivatives. Bodwell et al. reported the synthesis of pyridocoumarins using Povarov reactions from 3-aminocoumarins, aldehydes and electron rich olefins in one pot three component reactions in the presence of $Yb(OTf)_3$ as catalyst. Initially, the 1,2,3,4-tetrahydropyrido(2,3-c)coumarins are formed, which on oxidation with Br_2 give the corresponding pyrido(2,3-c)derivatives shown in Scheme 26.[42]



Scheme 26

Our group has been working on 3-aminocoumarin for long time. Various pyridcoumarins and coumarin fused dihydropyridines were reported using 3-aminocoumarin as one of the starting material. The synthesis of pyrido(2,3-c)coumarin derivatives was reported in 72-94% yield by one pot three components reaction using 3-aminocoumarins, aldehydes and phenylacetylene as electron rich dienophile in the presence of I_2 as catalyst in CH_3CN under reflux conditions as described in Scheme 27.[43]



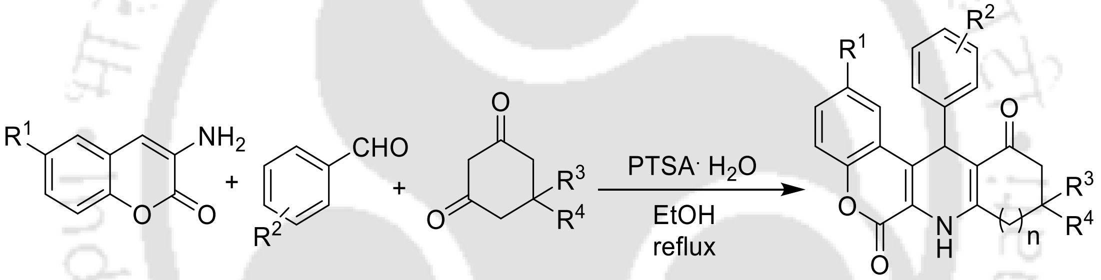
Scheme 27

A number of tetrahydropyrido(2,3-c)coumarin derivatives were synthesized from 3-aminocoumarins and aldehyde employing dihdrofuran as the electron rich dienophile using

$Fe_2(SO4)_3 \cdot x\, H_2O$ as the catalyst. Two diastreomers *endo-ex*o and *endo-endo* were reported where *endo-exo* was the major products (Scheme 27).[44]

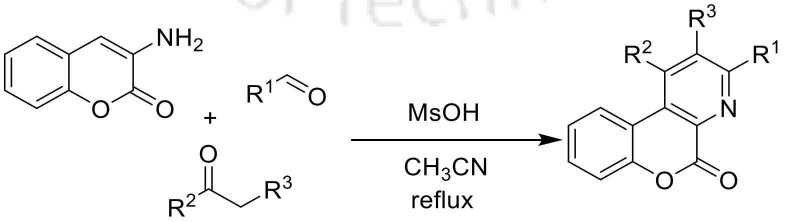
In another Povarov reaction, dihyropyridine derivatives were applied as electron rich dinophile and Yb(OTf) as catalyst. Various tetrahydropyrido(2,3-c)coumarin derivatives were synthesized in good yield. Moreover, in this case only a single diastreomers were obtained (Scheme 27)[45]

Several coumarin fused dihydropyridine derivatives were achieved via Michael Initiated ring closure reaction using $PTSA \cdot H_2O$ as catalyst. The three component reaction of 3-aminocoumarins, aldehyde and 1,3-cyclic diketons in the presence of $PTSA \cdot H_2O$ and EtOH as solvent in reflux conditions gave a number of coumarin fused dihydroquinoline derivatives. The reaction was believed to proceed through Knoevengel condensation of the aldehyde and 1,3-cyclic diketones followed Michel addition of 3-aminocoumarin shown in Scheme 28.[46]



Scheme 28

Chan and co-workers demonstrated the synthesis of pyrido(2,3-c)coumarin derivatives by one pot three component reactions of 3-aminocoumarin, aromatic aldehyde and ketones in the presence of methansulphonic acid as catalyst in acetonitrile solvent in reflux conditions as depicted in Scheme 29.[47] The reaction was a demonstration of inverse Diels Ader reaction to synthesize pyridocoumarins.

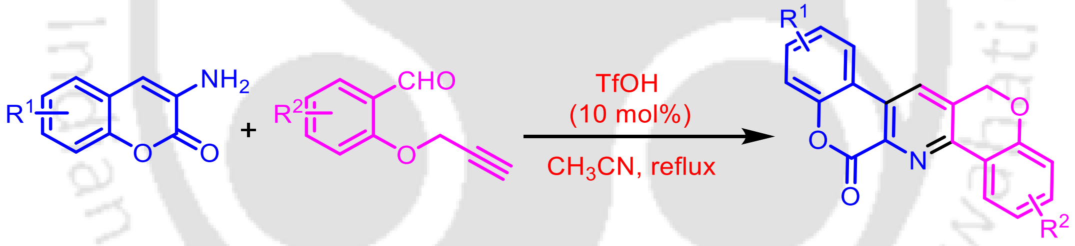


Scheme 29

From the literature survey, it reveals that synthesis of pyridocoumarins and pyrrolocoumarins are not much explored. Some of the existing methods for their synthesis have very limited substrate scopes whereas the reaction conditions are very tedious in other cases. Moreover, there are very few reports where 3-aminocoumarin has been used to achieve pyridocoumarins and pyrrolocoumarins. Therefore, the research topic is chosen to explore 3-aminocoumarins for further construction of pyridocoumarins and pyrrolocoumarins having 3-aminocoumarin as the backbone. The next two chapters of the thesis namely Chapter IIA and IIB gives an account of the synthesis of various pyridocoumarins whereas chapter III describes the synthesis of pyrrolocoumarins, using 3-aminocoumarins as one of the starting material.

CHAPTER IIA

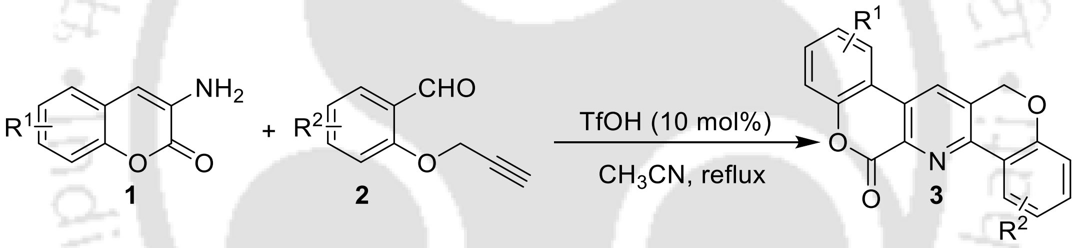
Synthesis of Pyrido(2,3-c)coumarin Derivatives by an Intramolecular Povarov Reaction



RESULTS AND DISCUSSION

• Results and Discussion

The importance of 3-aminocoumarins as well as the synthesis of pyridocoumarins from aminocoumarins has been discussed in the previous chapter. The synthesis of pyridocoumarin from 3-aminocoumarin through inter molecular povarov reaction was reported from our group earlier.[43] In this chapter, the synthesis of pyridocoumarins via intra molecular Povarov reaction from 3-aminocoumarins and propargylated salicylaldehydes is discussed. Previously, Bodwell and co-workers reported the synthesis of pyridocoumarin using 3-aminocoumarin and propargylated salicylaldehyde using $Yb(OTf)_3$ and obtained 47 % yield in 9 days of heating.[48] Therefore, there was further scope for the synthesis of pyridocoumarin using 3-aminocoumarin in lesser time via intramolecular the Povarov reaction. TfOH as a catalyst has been reported by various group to achieve Povarov reaction.[49] In this chapter of the thesis, the synthesis of pyridocoumarins by an intramolecular Povarov reaction using 3-aminocoumarins and propargylated salicylaldehydes employing TfOH as a catalyst is discussed (Scheme 30).

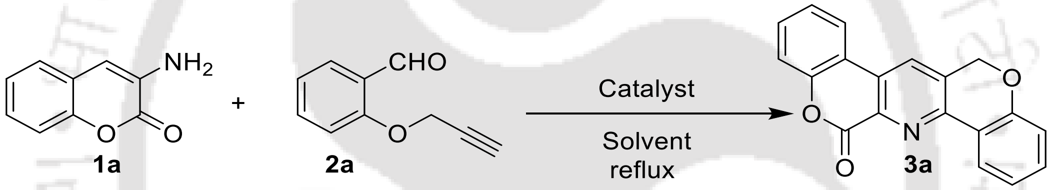


Scheme 30. Synthesis of pyrido(2,3-c)coumarin derivatives

The reaction was started with a mixture of 3-aminocoumarin (**1a**, 0.5 mmol) and 2-(propargyloxy)benzaldehyde (**2a**, 0.5 mmol) in presence of 5 mol% of TfOH in acetonitrile (3 mL) under reflux condition. A solid product precipitated out during the progress of the reaction and it was filtered and washed with a mixture of solvent such as ethyl acetate and hexane mixture (1:10). The light greenish solid compound was obtained in 56% yield and characterized by NMR, IR spectra and HRMS. The compound was found to be **3a** (Table 1), characterized by the IR absorption peak of the lactone ring at 1738.84 cm^{-1}, two singlet in the H^1 NMR spectrum at δ 8.14 and 5.39 ppm characteristic of the C-CH= proton of the pyridine ring and OCH_2- protons respectively (see page no. 33 for NMR spectra of compound **3a**) and the HRMS peak at 302.0812.

Later on, several reactions were performed to obtain the optimized reaction conditions. It was noted that the yield of the product was increased significantly to 77% by increasing the amount of catalyst from 5 mol% to 10 mol% whereas excess loading of the catalyst (15 mol %) decreased the yield to 72% (Table 1, entry 2-3). The same reaction was unsuccessful when it was carried out at room temperature (Table 1, entry 4). To find out a suitable solvent system, the similar reactions were examined in various solvent systems such as ethanol, dichloroethane (DCE), toluene, DMF and DMSO under reflux conditions, respectively (Table 1, entries 5-9). It was noted that the shortest reaction time and best yield are obtained in acetonitrile (Table 1, entry 2) under reflux conditions. To examine the efficacy of TfOH as compared to other catalysts, several reactions were also performed in the presence of catalysts such as PTSA, I_2, $InCl_3$ and CuI, respectively (Table 1, entries 10-13). These catalysts provided lower yields and required longer reaction times. After optimization of the reaction conditions, it was found that the best yield is obtained in triflic acid as a catalyst in acetonitrile solvent. Notably, yield was very low when the reaction was carried out without any catalyst under reflux condition (Table 1, entry 14).

Table 1. Optimization of reaction condition[a]

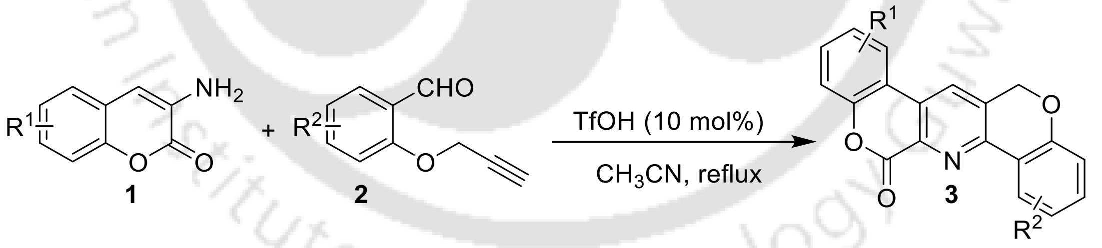


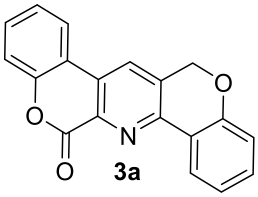
Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	TfOH (5)	CH_3CN	3	56
2	**TfOH (10)**	**CH_3CN**	**3**	**77**
3	TfOH (15)	CH_3CN	3	72
4[c]	TfOH (10)	CH_3CN	24	NR
5	TfOH (10)	EtOH	24	NR
6	TfOH (10)	DCE	24	12
7	TfOH (10)	Toluene	24	17
8	TfOH (10)	DMF	24	NR
9	TfOH (10)	DMSO	24	NR
10	*p*-TSA (10)	CH_3CN	24	60
11	I_2 (10)	CH_3CN	24	25
12	$InCl_3$ (10)	CH_3CN	24	54
13	CuI (10)	CH_3CN	24	32
14	No catalyst	CH_3CN	24	20

[a]All the reactions were performed with 3-aminocoumarin **1a** (0.5 mmol) and 2-(propargyloxy)benzaldehyde **2a** (0.5 mmol) in 3 mL of solvent under reflux condition. [b]Isolated yield. [c]room temperature, NR = no reaction

Next, a mixture of 5-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde and 3-aminocoumarin under identical reaction conditions gave the desired product **3b** in 71% yield (Table 2). To explore the synthetic scope further and the generality of the present protocol, various reactions were examined with other *O*-propargylated salicylaldehydes containing substituents in the aromatic ring such as Br, NO_2 and Cl respectively with 3-aminocoumarin (**1a**). The reaction time and percentage yield of the products (**3c-e**) are shown in Table 2. For verifying the generality of the present method, other substituted 3-aminocoumarins such as 6-methoxy-3-aminocoumarin, 8-methoxy-3-aminocoumarin and 8-ethoxy-3-aminocoumarin were also scrutinized with *O*-propargylated salicylaldehydes under identical reaction conditions and the desired pyrido(2,3-*c*)coumarin derivatives **3f-n** were obtained in good yields (Table 2). It was noted that *O*-propargylated salicylaldehydes containing electron withdrawing group provided better yield (Table 2, entries **3c-e**, **3h**, **3k**, **3m** and **3n**) as compared to *O*-propargylated salicylaldehydes having electron donating group in the present reaction. Interestingly, the substituents of R^1 in 3-aminocoumarin did not significantly affect the reaction and the yields of the products were remarkably similar (Table 2, entries **3a**, **3f**, **3i**, **3o**, **3p** and **3q**). The reactions occurred smoothly with 3-aminocumarin derivatives having Br, NO_2, and Cl electron- withdrawing groups on it. In case with the NO_2 substituent, the yield is comparatively low (62%, **3o**, Table 2)

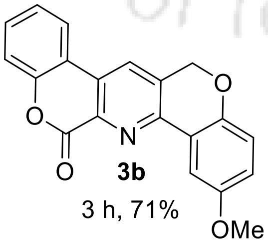
Table 2. Scope of various propargylated aldehydes and 3-aminocoumarins [a,b]





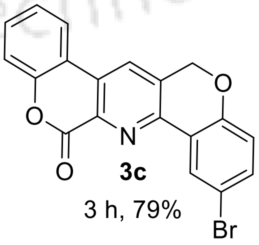
3a

3 h, 77 %



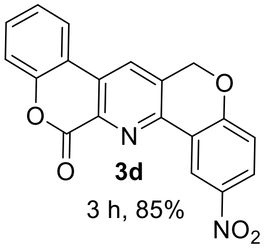
3b

3 h, 71%



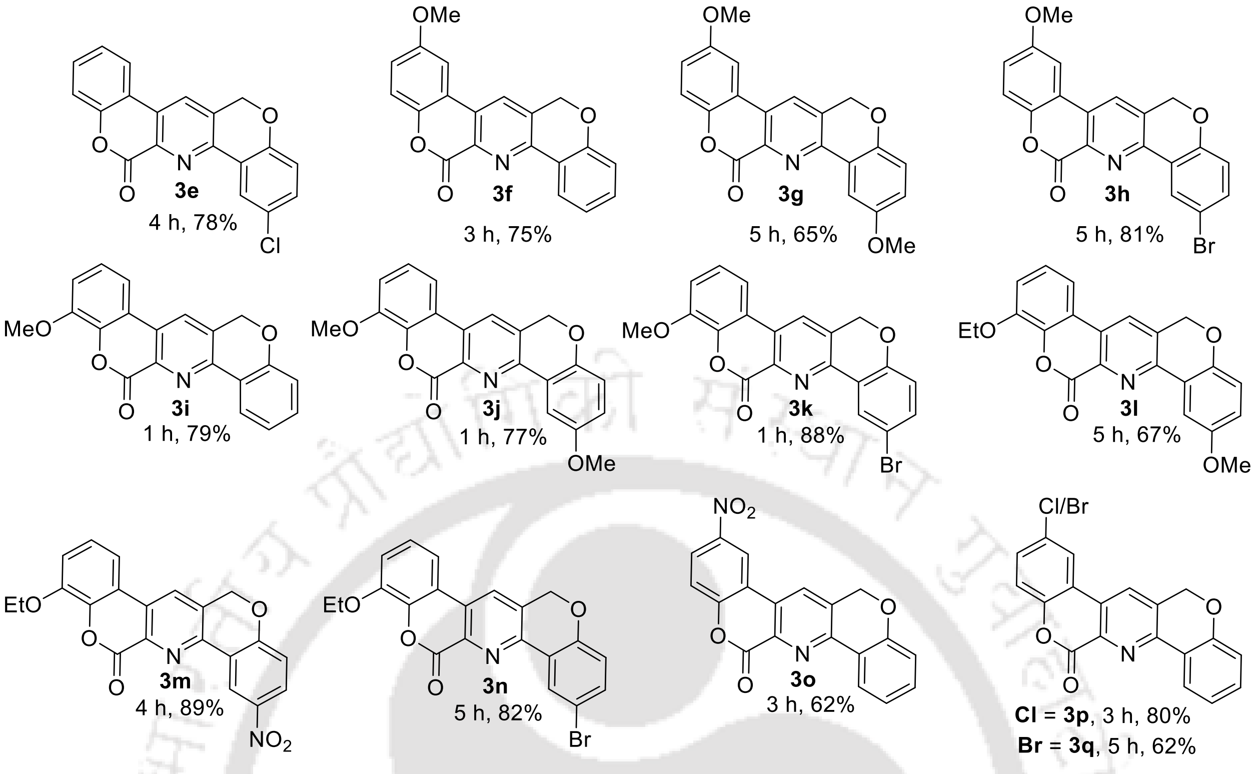
3c

3 h, 79%



3d

3 h, 85%



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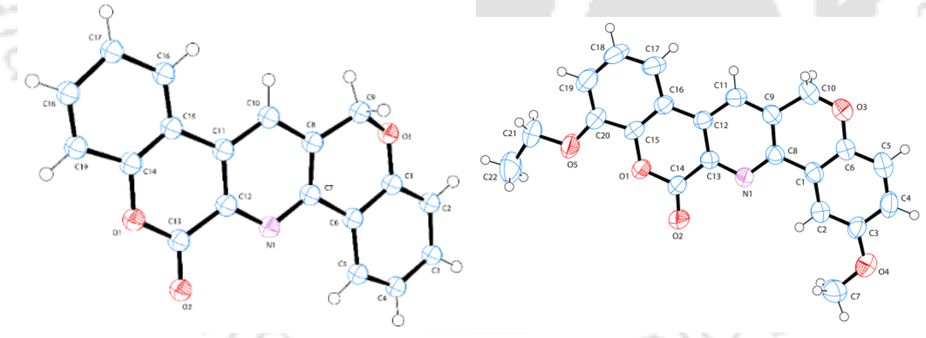
[a]All the reactions were performed with 3-aminocoumarins **1** (0.5 mmol) and 2-(propargyloxy)benzaldehydes **2** (0.5 mmol) in 3 mL of CH_3CN in the presence of 10 mol% TfOH under reflux condition. [b]Isolated yield

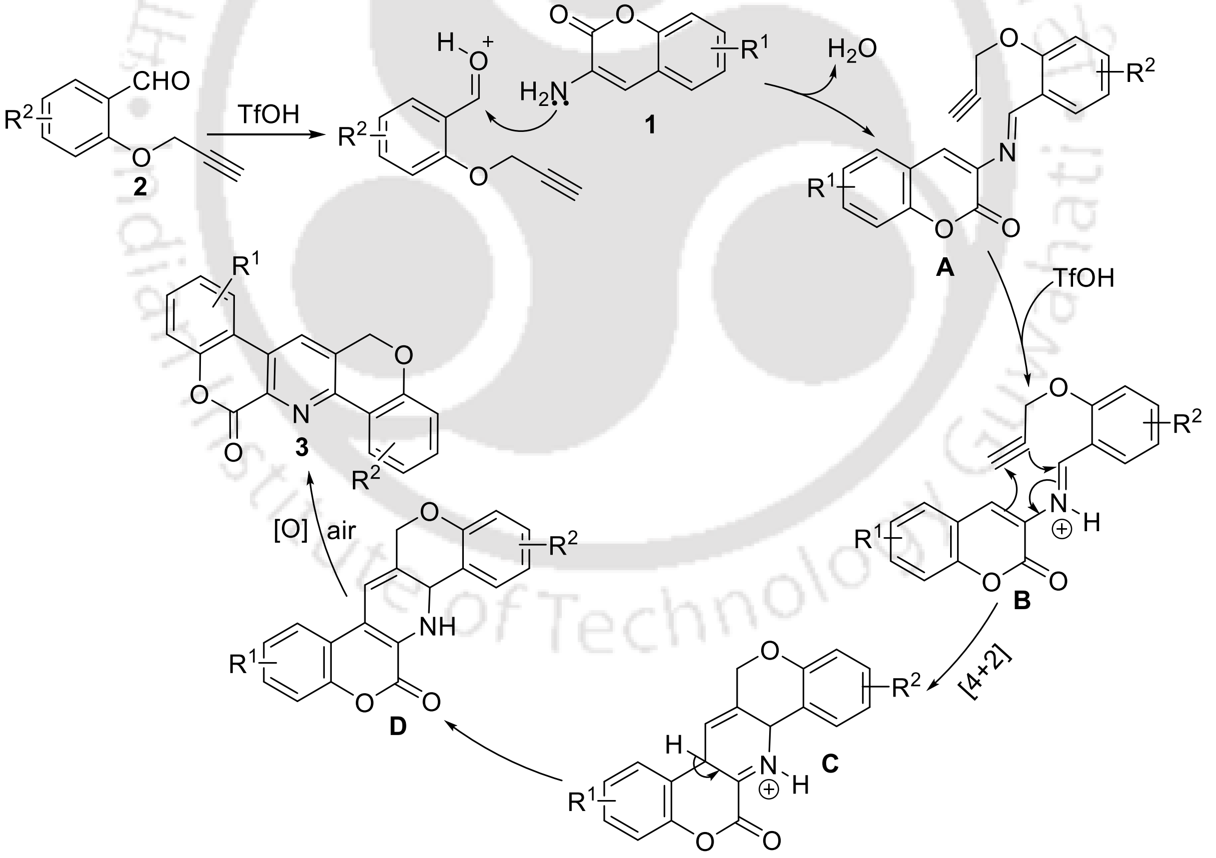


Compound **3a** (CCDC number 981642) Compound **3l** (CCDC 1003777)

Figure 4.Crystallographic structure of **3a** and **3l**

It is worthwhile to mention that the pure product was separated by filtration and washing with ethyl acetate and hexane mixture (1:10). After washing, the catalyst triflic acid goes into the filtrate and the pure unprotonated pyrido(2,3-*c*)coumarin derivatives were easily accomplished. The structures of products **3a-q** were determined from their usual spectroscopic data. In its IR spectra, it showed characteristic absorption peaks between 1729-1753 cm^{-1} due to lactone carbonyl group. The characteristic peaks for **3a-q** in the ^1H NMR spectra are two singlets for the $–OCH_2$ protons between $\delta = 4.60$-5.74 ppm and for C-CH= proton of pyridine ring at 14 position of the product at $\delta = 8.02$–9.07 ppm (see pages 23-32 for NMR, IR and HRMS data). The structure of the representative compounds such **3a** and **3l** were also confirmed unambiguously by single crystal X-ray analysis (Figure 4).

A probable mechanism for the intramolecular Povarov reaction for the synthesis of pyrido(2,3-*c*)coumarin derivatives is depicted in Scheme 31. The first step is the condensation reaction between 3-aminocoumarin (**1**) and *O*-propargylated salicylaldehyde (**2**) leading to the formation of intermediate imines **A**, which on protonation undergoes cyclization *via* intramolecular Povarov reaction to afford pyrido(2,3-*c*)coumarin derivatives **3** through the intermediate dihydropyridine **D**, followed by aerial oxidation as shown in Scheme 31.



Scheme 31. Plausible reaction mechanism for the formation of **3**

In summary, an efficient and expedient protocol for the synthesis of pyrido(2,3-*c*)coumarin derivatives has been illustrated involving 2-(propargyloxy) benzaldehyde derivatives and 3-aminocoumarins using triflouromethanesulfonic acid (TfOH) as catalyst in acetonitrile. No co-oxidant was required for aromatization of the desired products. The reaction methodology is simpler, requires lesser time and the products are easily isolable without column chromatography and aqueous work up.

CHAPTER IIA

Synthesis of Pyrido(2,3-c)coumarin Derivatives by an Intramolecular Povarov Reaction

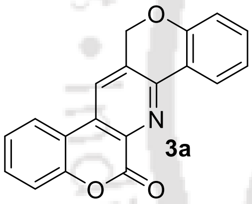
EXPERIMENTAL SECTION

• Experimental Section

General procedure for the synthesis of pyrido(2,3-*c*)coumarin derivatives:

Into a 25mL round bottomed flask was taken a mixture of 3-aminocoumarin (0.5 mmol) and propargylated salicylaldehyde (0.5 mmol) in 3 mL of CH_3CN. Then 10 mol% triflic acid was added into it and the reaction mixture was refluxed in a preheated oil bath. The progress of the reaction was monitored by checking TLC time to time. Towards the end of the reaction, a solid precipitate starts appearing slowly after specified time as mentioned in the Table 2. The reaction flask was then removed from the oil-bath and it was brought to room temperature for complete precipitation. The solid precipitate was just filtered off through a Büchner funnel and it was washed with cold 10 mL of hexane-ethyl acetate mixture (10:1) to remove unreacted starting materials. Finally, it was dried through a vacuum pump and the pure product pyrido(2,3-*c*)coumarin derivatives **3a-q** was obtained in 65-89% yield.

***Dichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (3a):**



3a

Reaction Time: 3.0 h **Colour & State:** pale green solid

Yield: 77% (166 mg) **Melting Point:** 230 °C

IR (KBr): 3078.49, 2959.14, 2848.11, 1738.84, 1606.39, 1235.89, 1090.80, 1052.83, 1037.76, 1013.21 cm^{-1}.

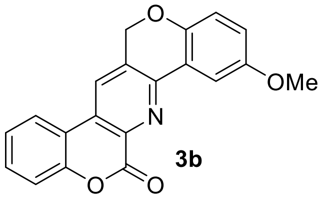
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.47 (dd, *J* = 9.0, 1.2 Hz, 1 H), 8.14 (s, 1 H), 7.98 (t, *J* = 1.2 Hz, 1 H), 7.52 (m, 1 H), 7.38 (m, 3 H), 7.13 (t, *J* = 7.2 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 5.39 (s, 2 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 158.6, 150.7, 149.4, 136.7, 136.0, 133.6, 132.6, 131.7, 131.3, 126.7, 126.1, 124.1, 123.7, 118.7, 118.4, 117.0, 115.0, 67.6 ppm.

HRMS (ESI) calcd for $C_{19}H_{11}NO_3$ (M + H$^+$) = 302.0812, found 302.0812.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{11}NO_3$	C 75.74	75.92
(301.30)	H 3.68	3.60
	N 4.65	4.54

9-Methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3b):**



3b

Reaction Time: 3.0 h **Colour & State:** pale green solid

Yield: 71% (118 mg) **Melting Point:** 300 °C

IR (KBr): 2995.32, 2844.80, 1734.06, 1609.45, 1237.79, 1092.55, 1040.81, 1018.93 cm^{-1}.

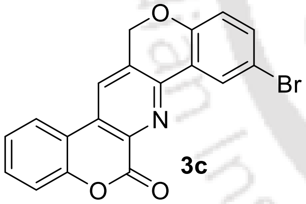
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.79 (s, 1 H), 8.31 (t, *J* = 7.8 Hz, 1 H), 7.41 (d, *J* = 3 Hz, 1 H), 7.63 (m, 1 H), 7.47 (dd, *J* = 14.4, 7.8 Hz, 2 H), 7.04 (m, 2 H), 5.43 (s, 2 H), 3.84 (s, 3 H).ppm.

^{13}C NMR (100 MHz, CDCl$_3$: TFA = 4:1): δ 156.4, 156.1, 154.8, 151.0, 148.1, 137.9, 135.0, 134.6, 133.6, 128.3, 127.7, 127.4, 124.0, 120.9, 116.2, 113.9, 113.7, 107.4, 67.4, 56.4 ppm.

HRMS (ESI) calcd for $C_{20}H_{13}NO_4$ (M + H$^+$) = 332.0917, found 332.0918.

Elemental Analysis	Calculated	Found
MF $C_{20}H_{13}NO_4$	C 72.50	72.32
(331.33)	H 3.95	3.90
	N 4.23	4.13

9-Bromodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3c):**



3c

Reaction Time: 3.0 h **Colour & State:** white solid

Yield: 79% (150 mg**)** **Melting Point:** 230 °C

IR (KBr): 3092.37, 2909.18, 2853.66, 1748.32, 1606.15, 1235.66, 1091.97, 1051.54, 1009.40 cm^{-1}.

^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.82 (s, 1 H), 8.30 (dd, *J* = 8.4, 7.8 Hz, 2 H), 7.62 (m, 2 H), 7.47 (t, *J* = 6.6 Hz, 2 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 5.54 (s, 2 H) ppm.

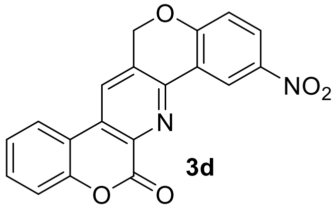
^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 159.0, 156.5, 151.3, 147.1, 142.3, 137.9, 135.8, 135.6, 134.5, 128.5, 127.8, 124.3, 121.4, 119.0, 115.1, 67.4 ppm.

HRMS (ESI) calcd for $C_{19}H_{10}BrNO_3$ (M + H$^+$) = 379.9917, found 379.9917.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{10}BrNO_3$	C 60.02	59.81

(380.20)	H 2.65	2.61
	N 3.68	3.54

***9-Nitrodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (3d):**



3d

Reaction Time: 3.0 h **Colour & State:** white solid

Yield: 85% (147 mg) **Melting Point:** > 300 °C

IR (KBr): 3077.41, 2917.50, 1744.31, 1621.26, 1245.60, 1092.38, 1046.70, 1015.68 cm^{-1}.

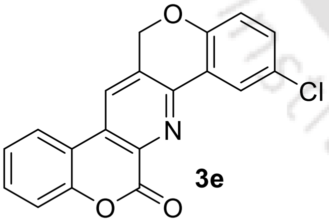
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 9.00 (d, *J* = 2.4 Hz, 1 H), 8.87 (s, 1 H), 8.31 (m, 2 H), 7.66 (m, 1 H), 7.49 (t, *J* = 7.8 Hz, 2 H), 7.30 (d, *J* = 9 Hz, 1 H), 5.74 (s, 2 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 163.4, 151.0, 147.6, 143.4, 135.7, 134.7, 134.5, 132.7, 132.2, 131.1, 127.5, 124.1, 122.7, 120.4, 118.8, 114.8, 68.2 ppm.

HRMS (ESI) calcd for $C_{19}H_{10}N_2O_5$ (M + H$^+$) = 347.0662, found 347.0662.

Elemental Analysis	**Calculated**	**Found**
MF $C_{19}H_{10}N_2O_5$	C 65.90	65.80
(346.30)	H 2.91	2.87
	N 8.09	7.99

***9-Chlorodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (3e):**



3e

Reaction Time: 4.0 h **Colour & State:** pale green solid

Yield: 78% (131 mg) **Melting Point:** > 300 °C

IR (KBr): 3085.37, 3060.74, 2918.40, 2847.23, 1749.88, 1602.43, 1234.48, 1088.33, 1051.54, 1008.03 cm^{-1}.

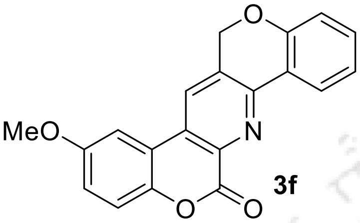
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.82 (s, 1 H), 8.31 (t, *J* = 7.8 Hz, 1 H), 8.15 (d, *J* = 2.4 Hz, 1 H), 7.64 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.49 (m, 3 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 5.54 (s, 2 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 158.3, 151.2, 147.4, 139.1, 138.9, 135.4, 135.3, 134.4, 130.7, 127.6, 125.5, 124.2, 121.1, 121.1, 118.9, 111.8, 67.7 ppm.

HRMS (ESI) calcd for $C_{19}H_{10}ClNO_3$ (M + H$^+$) = 336.0422, found: 336.0425.

Elemental Analysis	**Calculated**	**Found**
MF $C_{19}H_{10}ClNO_3$	C 67.97	68.13
(335.74)	H 3.00	3.07
	N 4.17	4.08

2-Methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3f):**



3f

Reaction Time: 3.0 h **Colour & State:** yellowish solid

Yield: 75% (125 mg) **Melting Point:** 280 °C

IR (KBr): 2992.58, 1741.46, 1604.16, 1242.57, 1084.55, 1043.89, 1007.40 cm^{-1}.

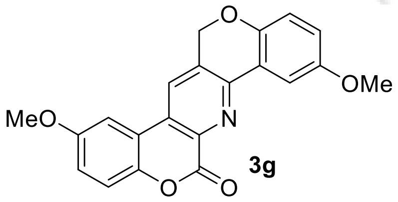
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.85 (s, 1 H), 8.23 (dd, *J* = 7.8, 1.2, Hz, 1 H), 7.79 (d, *J* = 3.0 Hz, 1 H), δ 7.43 (m, 1 H), 7.40 (d, *J* = 9.6 Hz, 1 H), 7.20 (m, 2 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 5.49 (s, 2 H), 3.89 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$: TFA = 4:1): δ 160.0, 158.2, 156.0, 148.0, 145.4, 139.70, 137.8, 135.8, 133.5, 127.5, 126.1, 124.8, 122.1, 119.9, 119.6, 114.3, 107.3, 67.5, 56.5 ppm.

HRMS (ESI) calcd for $C_{20}H_{13}NO_4$ (M + H$^+$) = 332.0917, found 332.0918.

Elemental Analysis	**Calculated**	**Found**
MF $C_{20}H_{13}NO_4$	C 72.50	72.41
(331.33)	H 3.95	3.88
	N 4.2	3.90

2,9-Dimethoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3g):**



3g

Reaction Time: 5.0 h **Colour & State:**yellowish solid

Yield: 65% (118 mg) **Melting Point:** 265 °C

IR (KBr): 3069.20, 2448.79, 1736.21, 1227.22, 1083.88, 1040.66, 1020.15 cm^{-1}.

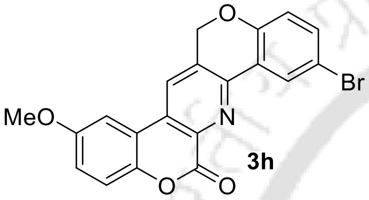
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.02 (s, 1 H), 6.96 (d, *J* = 3.0 Hz, 1 H), δ 6.87 (d, *J* = 3.0 Hz, 1 H), 6.58 (d, *J* = 9.0 Hz, 1 H), 6.37 (dd, *J* = 9.0, 2.4, Hz, 1 H), 6.22 (m, 2 H), 4.60 (s, 2 H), 3.07 (s, 3 H), 3.00 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 158.7, 156.7, 156.8, 155.7, 148.2, 145.7, 138.6, 136.1, 129.6, 126.9, 122.5, 121.5, 120.3, 114.5, 113.3, 107.9, 107.6, 67.9, 56.8, 56.7 ppm ppm.

HRMS (ESI) calcd for $C_{21}H_{15}NO_5$ (M + H$^+$) = 362.1023, found: 362.1024.

Elemental Analysis	Calculated	Found
MF $C_{21}H_{15}NO_5$	C 69.80	69.71
(361.35)	H 4.18	4.15
	N 3.88	3.70

***9-Bromo-2-methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (3h):**



3h

Reaction Time: 5.0 h **Colour & State:** pale green solid

Yield: 81% (166) mg **Melting Point:** MP > 300 °C

IR (KBr): 2929.64, 2853.01, 1729.44, 1222.74, 1084.50, 1048.64, 1032.07 cm^{-1}.

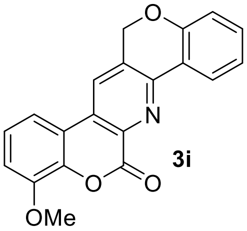
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.88 (s, 1 H), 8.29 (d, *J* = 2.4 Hz, 1 H), 7.80 (d, *J* =3 Hz, 1 H), 7.62 (dd, *J* = 7.8, 2.4 Hz, 1 H), 7.43 (d, *J* = 9.0 Hz, 1 H), 7.21 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 5.54 (s, 2 H), 3.9 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$: TFA = 4:1**):** δ 158.0, 157.8, 148.0, 145.2, 139.8, 136.1, 133.2, 132.5, 128.4, 121.2, 120.7, 119.8, 118.8, 116.0, 107.0, 67.6, 56.4 ppm.

HRMS (ESI) calcd for $C_{20}H_{12}BrNO_4$ (M + H$^+$) =; 410.0022, found 410.0022.

Elemental Analysis	Calculated	Found
MF $C_{20}H_{12}BrNO_4$	C 58.56	58.51
(410.22)	H 2.95	2.90
	N 3.41	3.32

***4-Methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (3i):**



3i

Reaction Time: 1.0 h **Colour & State:** brown solid

Yield: 79% (131 mg) **Melting Point:** > 300 °C

IR (KBr): 3011.74, 2836.59, 1741.48, 1615.06, 1246.52, 1070.59, 1030.81 cm^{-1}.

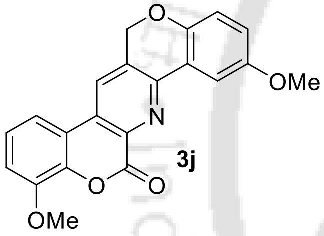
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.76 (s, 1 H), 8.24 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 1 H), 7.46 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.40 (t, *J* = 8.4 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.20 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 5.50 (s, 2 H), 3.94 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 160.0, 155.7, 148.4, 148.2, 140.7, 139.7, 137.7, 135.5, 133.8, 127.6, 125.9, 124.9, 119.6, 117.6, 116.6, 114.9, 114.6, 67.2, 56.8 ppm.

HRMS (ESI) calcd for $C_{20}H_{13}NO_4$ (M + H$^+$) = 332.0917; found 332.0917.

Elemental Analysis	Calculated	Found
MF $C_{20}H_{13}NO_4$	C 72.50	72.32
(331.33)	H 3.95	3.90
	N 4.23	4.13

***4, 9-Dimethoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (3j):**



3j

Reaction Time: 1.0 h **Colour & State:** yellowish brown solid

Yield: 77% (140 mg) **Melting Point:** > 300 °C

IR (KBr): 2992.58, 2926.90, 1739.13, 1613.76, 1245.06, 1085.53, 1073.13, 1036.77 cm^{-1}.

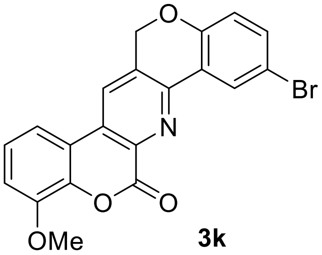
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.76 (s, 1 H), 7.83 (t, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 3.0 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.31 (d, *J* = 7.8 Hz, 1 H), 7.03 (m, 2 H), 5.43(s, 2 H), 3.95 (s, 3 H), 3.83 (s, 3 H).ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 156.6, 155.8, 155.6, 148.5, 148.2, 140.8, 138.5, 135.9, 134.3, 129.4, 128.0, 126.8, 121.4, 117.1, 115.2, 114.5, 107.3, 67.4, 56.9, 56.6 ppm.

HRMS (ESI) calcd for $C_{21}H_{15}NO_5$ (M + H$^+$) = 362.1023; found 362.1030.

Elemental Analysis	Calculated	Found
MF $C_{21}H_{15}NO_5$	C 69.80	69.72
(361.35)	H 4.18	4.09
	N 3.88	3.73

9-Bromo-4-methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3k):**



3k

Reaction Time: 1.0 h **Colour & State:** silvery white solid

Yield: 88% (181 mg) **Melting Point:** > 300 °C

IR (KBr): 3069.20, 2844.80, 1733.96 1617.09, 1241.82, 1080.99, 1071.88, 1047.79 cm^{-1}.

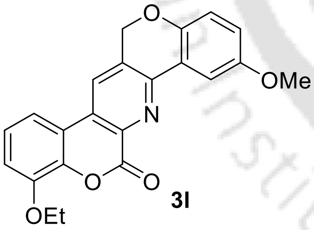
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.79 (s, 1 H), 8.29 (d, *J* = 2.4 Hz, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 7.62 (dd, *J* = 9.0, 3.0, Hz, 1 H), 7.41 (t, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 1 H), δ 7.07(d, *J* = 8.4 Hz, 1 H), 5.40 (s, 2 H), 3.95 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 158.2, 157.4, 148.3, 147.9, 140.5, 136.7, 134.1, 134.0, 130.1, 128.6, 127.4, 120.9, 117.0, 116.2, 115.3, 115.1, 67.8, 56.8 ppm.

HRMS (ESI) calcd for $C_{20}H_{12}BrNO_4$ (M + H$^+$) = 410.0022, found: 410.0024.

Elemental Analysis	**Calculated**	**Found**
MF $C_{20}H_{12}BrNO_{44}$	C 58.56	58.49
(410.22)	H 2.95	2.89
	N 3.41	3.38

4-Ethoxy-9-methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3l):**



3l

Reaction Time: 5.0 h **Colour & State:** pale green solid

Yield: 67% (126 mg) **Melting Point:** 279 °C

IR (KBr): 2981.60, 2841.33, 1737.72, 1618.16, 1065.17, 1036.38, 1022.78 cm^{-1}.

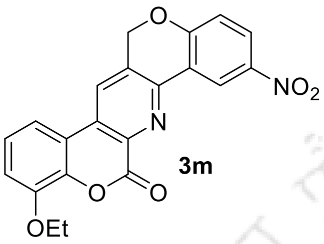
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.74 (s, 1 H), 7.81 (d, *J* = 7.8 Hz, 1 H), 7.70 (d, *J* = 2.4 Hz, 1 H), 7.37 (t, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H) 7.04 (m, 2 H), 5.42 (s, 2 H), 4.2 (q, *J* = 6.6 Hz, 2 H), 3.84 (s, 3H), 1.44 (t *J* = 6.6, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 156.5, 156.2, 154.4, 148.6, 147.8, 140.8, 137.2, 134.0, 133.5, 128.8, 127.7, 127.2, 120.6, 117.1, 115.1, 114.9, 114.7, 107.3, 67.6, 65.9, 56.4, 14.6 ppm.

HRMS (ESI) calcd for $C_{22}H_{17}NO_5$ (M + H$^+$) = 376.1179, found 376.1187.

Elemental Analysis	**Calculated**	**Found**
MF $C_{22}H_{17}NO_{56}$	C 70.39	70.32
(375.38)	H 4.56	4.52
	N 3.73	3.60

4-Ethoxy-9-nitrodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3m):**


3m

Reaction Time: 4.0 hrs. **Colour & State:** white solid

Yield: 89% (174 mg) **Melting Point:** > 300 °C

IR (KBr): 3093.83, 2987.11, 1739.92, 1618.85, 1246.42, 1065.43, 1049.12, 1000.97 cm^{-1}.

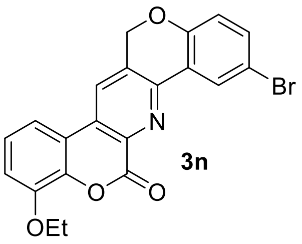
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.98 (d, *J* = 2.4 Hz, 1 H), 8.82 (s, 1 H), 8.30 (dd, *J* = 8.4, 2.4, Hz, 1 H), 7.82 (d, *J* = 7.8 Hz, 1 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 7.29 (d, *J* = 9.0 Hz, 1 H), 5.72 (s, 2 H), 4.21 (q, *J* = 6.6 Hz, 2 H), 1.45 (t, *J* = 6.8, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 162.7, 148.4, 147.5, 143.2, 140.5, 134.5, 134.3, 133.8, 130.6, 130.4, 129.7, 127.0, 122.4, 119.7, 116.5, 114.9, 68.4, 66.1, 14.3 ppm.

HRMS (ESI) calcd for $C_{21}H_{14}N_2O_6$ ($M + H^+$) = 391.0925, found 391.0930.

Elemental Analysis	**Calculated**	**Found**
MF $C_{21}H_{14}N_2O_6$	C 64.62	64.56
(390.35)	H 3.62	3.58
	N 7.18	7.01

9-Bromo-4-ethoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3n):**


3n

Reaction Time: 5.0 h **Colour & State:** white solid

Yield: 82% (175 mg) **Melting Point:** > 300 °C

IR (KBr): 3080.15, 2981.63, 1744.57, 1244.35, 1098.22, 1065.12, 1048.66 cm^{-1}.

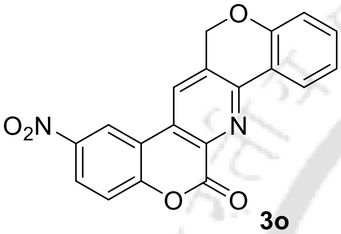
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.77 (s, 1 H), 8.28 (d, *J* = 2.4 Hz, 1 H), 7.81 (d, *J* = 7 8 Hz, 1 H), 7.61 (dd, *J* = 9.0, 2.4, Hz, 1 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 1 H), 7.06 (d, *J* = 9.0 Hz, 1 H), 5.53 (s, 2 H), 4.20 (q, *J* = 6.6 Hz, 2 H), 1.44 (t, *J* = 6.6 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 157.8, 147.6, 140.6, 140.2, 139.8, 133.7, 128.6, 128.5, 127.3, 127.2, 120.8, 120.7, 117.2, 117.0, 116.9, 114.9, 111.8, 67.9, 66.1, 14.5 ppm.

HRMS (ESI) calcd for $C_{21}H_{14}BrNO_4$ (M + H$^+$) = 426.0159; found 426.0162.

Elemental Analysis	**Calculated**	**Found**
MF $C_{21}H_{14}BrNO_4$	C 59.45	59.40
(424.25)	H 3.33	3.25
	N 3.30	3.15

***2-Nitrodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (3o):**



3o

Reaction Time: 3.0 hrs. **Colour & State:** pale green solid

Yield: 62 % (108 mg) **Melting Point:** > 300 °C

IR (KBr): 2923.78, 2853.38, 1753.43, 1600.79, 1249.46, 1044.75, 1016.08 cm^{-1}.

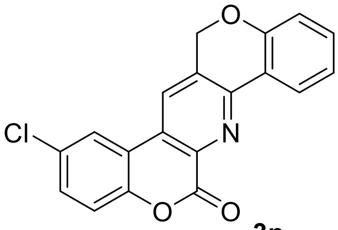
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 9.17 (d, J = 3.0 Hz, 1 H), 9.07 (s, 1 H), 8.43 (dd, J = 9.0, 3.0 Hz, 1 H), 8.27 (dd, J = 7.8, 1.2 Hz, 1 H), 7.71 (d, J = 9.0 Hz, 1 H), 7.48 (dd, J = 8.4, 1.8 Hz, 1 H), 7.22 (t, J = 7.8 Hz, 1 H), 7.09 (d, J = 8.4 Hz, 1 H), 5.53 (s, 2 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 160.8, 155.0, 154.8, 149.9, 146.1, 140.9, 139.0, 135.9, 132.4, 129.4, 128.5, 126.5, 125.4, 121.1, 120.7, 120.1, 115.2, 67.7 ppm.

HRMS (ESI) calcd for $C_{19}H_{10}N_2O_5$ (M + H$^+$) = 347.0668, found 347.0660.

Elemental Analysis	**Calculated**	**Found**
MF $C_{19}H_{10}N_2O_5$	C 65.90	65.69
(346.30)	H 2.91	2.85
	N 8.09	8.13

***2-Chlorodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (2p):**



3p

Reaction Time: 3.0 h **Colour & State:** pale green solid

Yield: 80 % (146 mg) **Melting Point:** > 300 °C

IR (KBr): 2923.87, 2841.75, 1749.49, 1600.47, 1239.49, 1075.42, 1050.28, 1036.43, 1015.91 cm^{-1}.

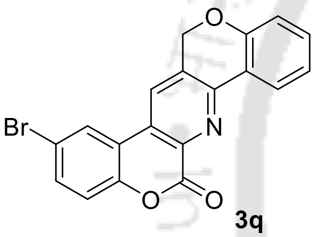
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.87 (s, 1 H), 8.42 (d, *J* = 2.4 Hz, 1 H), 8.24 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.65 (d, *J* = 9.0, 2.4 Hz, 1 H), 7.51 (d, *J* = 9.0 Hz, 1 H), 7.47 (dd, *J* = 9.0, 1.2 Hz, 1 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 5.48 (s, 2 H)·ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 159.9, 149.4, 139.8, 139.6, 134.7, 134.6, 133.4, 126.4, 126.3, 124.9, 123.8, 120.2, 119.6, 119.6, 115.2, 67.6 ppm.

HRMS (ESI) calcd for $C_{19}H_{10}ClNO_3$ (M + H$^+$) =366.0422, found 336.0428.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{10}ClNO_3$	C 67.97	68.15
(335.74)	H 3.00	3.08
	N 4.17	4.10

2-Bromodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one **(3q):**



3q

Reaction Time: 5.0 hr **Colour & State:** pale green solid

Yield: 76 % (144 mg) **Melting Point:** 279 °C

IR (KBr): 2925.83, 2849.96, 1749.98, 1600.29, 1239.57, 1071.30, 1050.53, 1015.07 cm^{-1}.

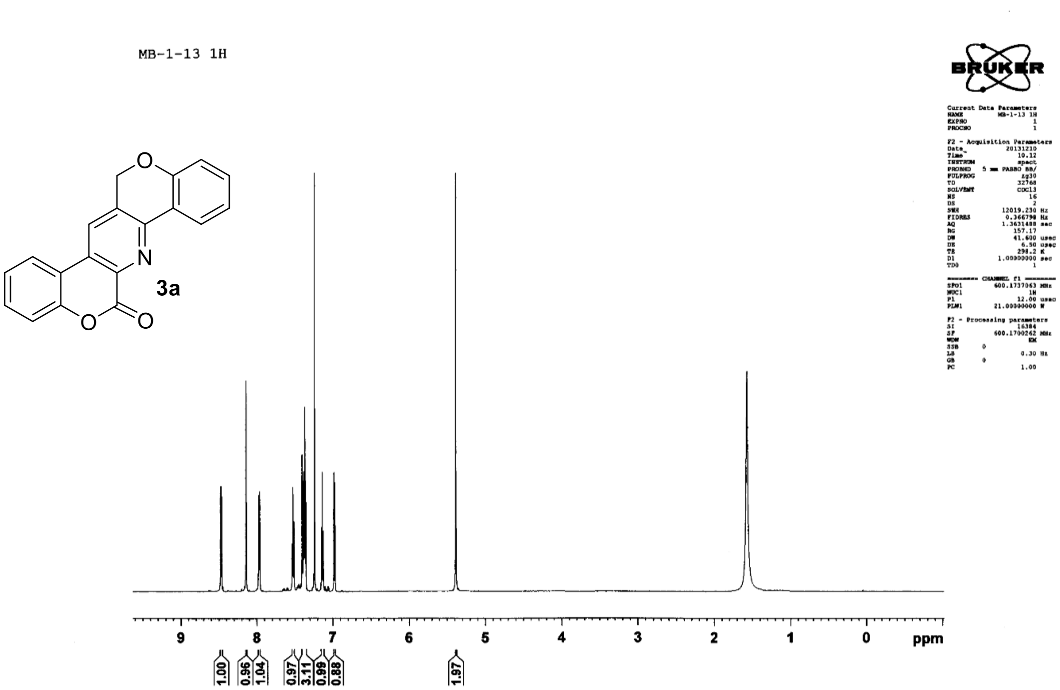
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 8.85 (s, 1 H), 8.55 (d, *J* = 2.4 Hz, 1 H), 8.24 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.76 (d, *J* = 9.0, 2.4, 1 H), 7.47 (dd, *J* = 8.4, 1.8, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 7.07 (d, *J* = 7.8, 1H), 5.48 (s, 2 H)·ppm.

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): δ 159.0, 157.5, 149.8, 149.7, 137.8, 136.7, 132.1, 131.5, 126.5, 126.3, 124.4, 120.2, 120.0, 118.9, 116.5, 67.6 ppm.

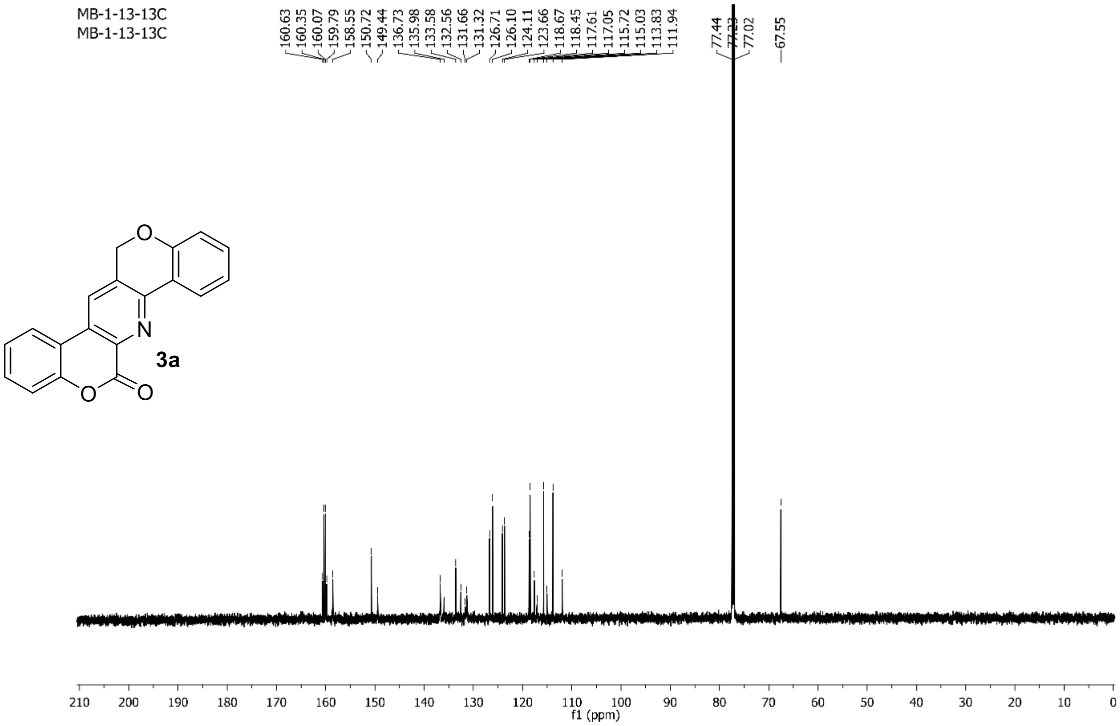
HRMS (ESI) calcd for $C_{19}H_{10}BrNO_3$ (M + H$^+$) = 379.9922, found 379.9909.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{10}BrNO_3$	C 60.02	60.23
(380.20)	H 2.65	2.63
	N 3.68	4.62

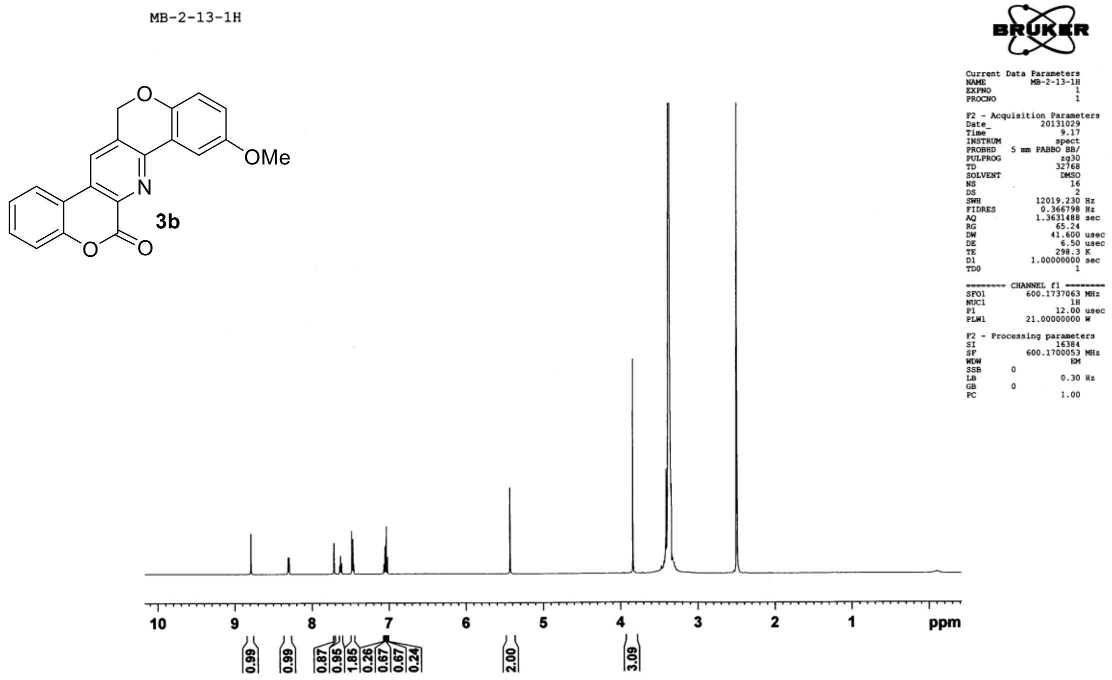
^{1}H NMR (600 MHz, DMSO-d_6): *Dichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (**3a**)



^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): *Dichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (**3a**)



***^{1}H NMR* (*600 MHz, DMSO-d_6*)**: *9-Methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (**3b**)



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PROCNO                 1

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PULPROG             zg30
TD                 32768
SOLVENT             DMSO
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                 65.24
DW                41.600 usec
DE                  6.50 usec
TE                 298.3 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
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NUC1                  1H
P1                 12.00 usec
PLW1         21.00000000 W

F2 - Processing parameters
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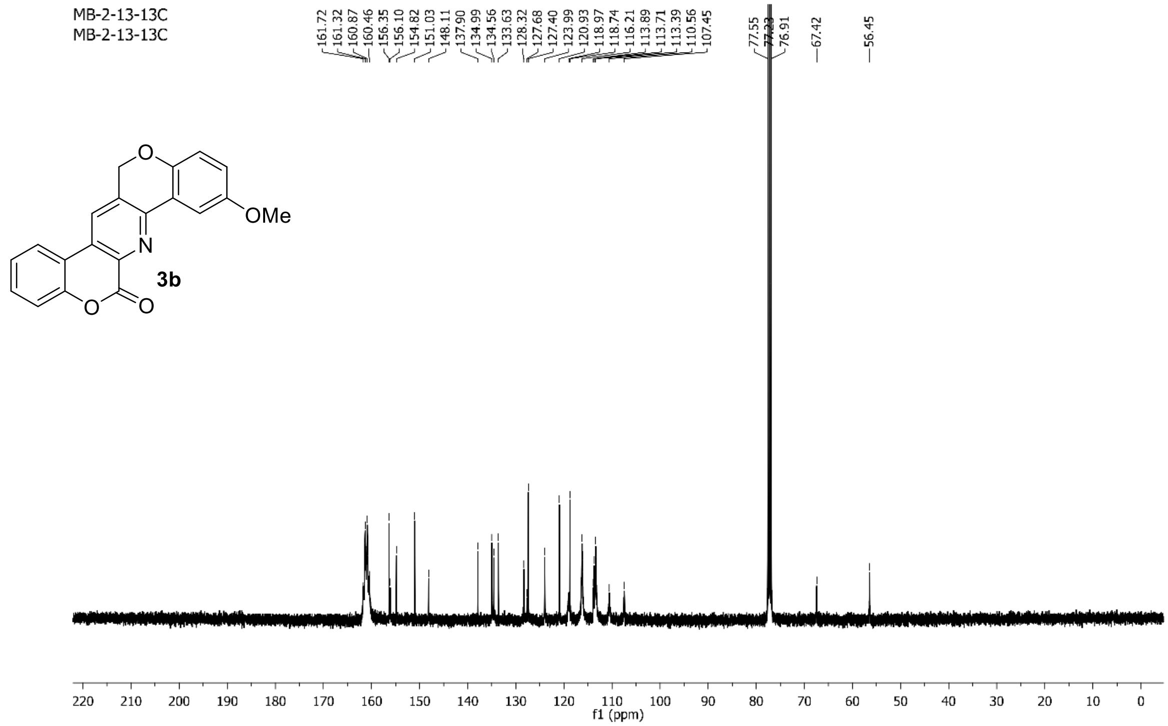
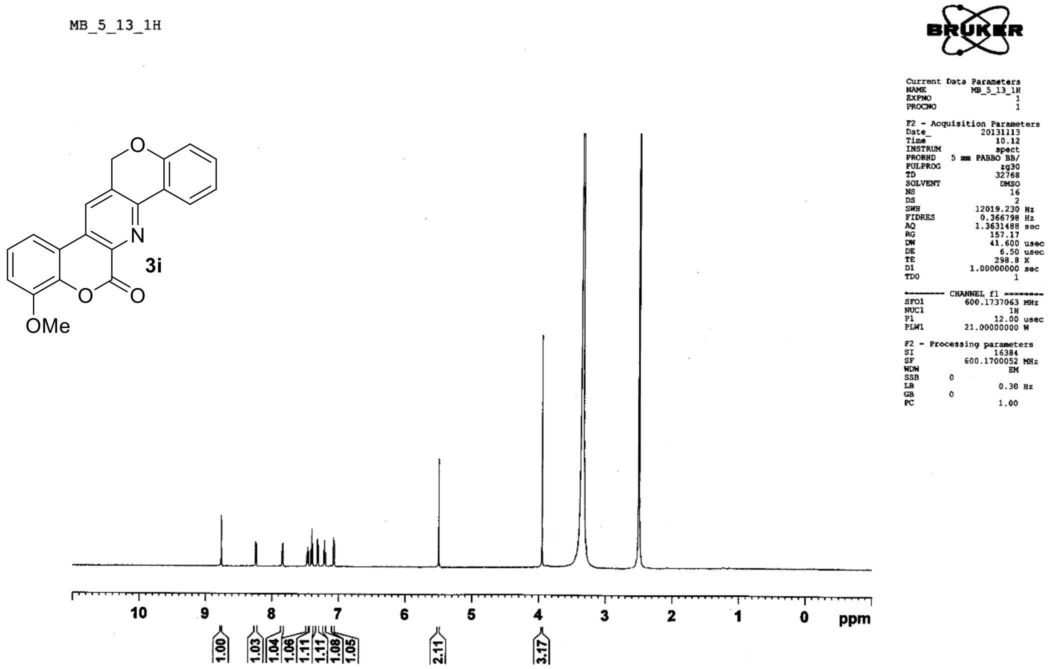
SF           600.1700053 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

^{13}C NMR (100 MHz, $CDCl_3$: TFA = 4:1): *9-Methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (**3b**)



^{1}H NMR (600 MHz, DMSO-d_6): *4-Methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (**3i**)



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FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                157.17
DW                41.600 usec
DE                  6.50 usec
TE                 298.8 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
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NUC1                  1H
P1                 12.00 usec
PLW1         21.00000000 W

F2 - Processing parameters
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SF           600.1700052 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```
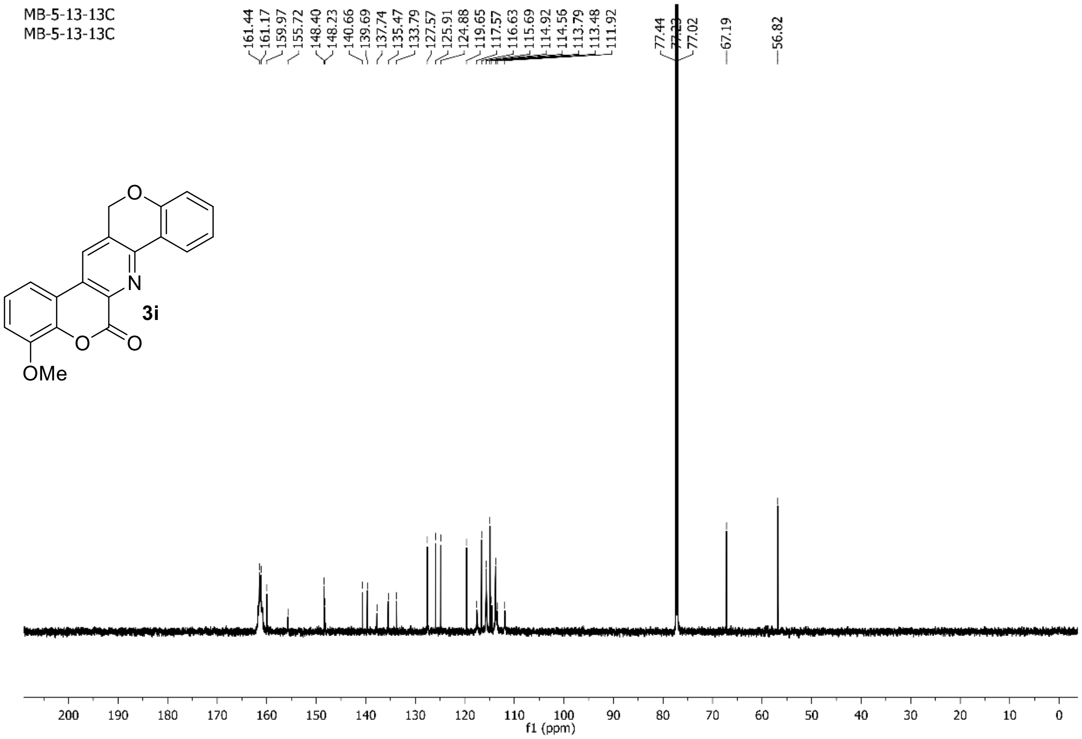
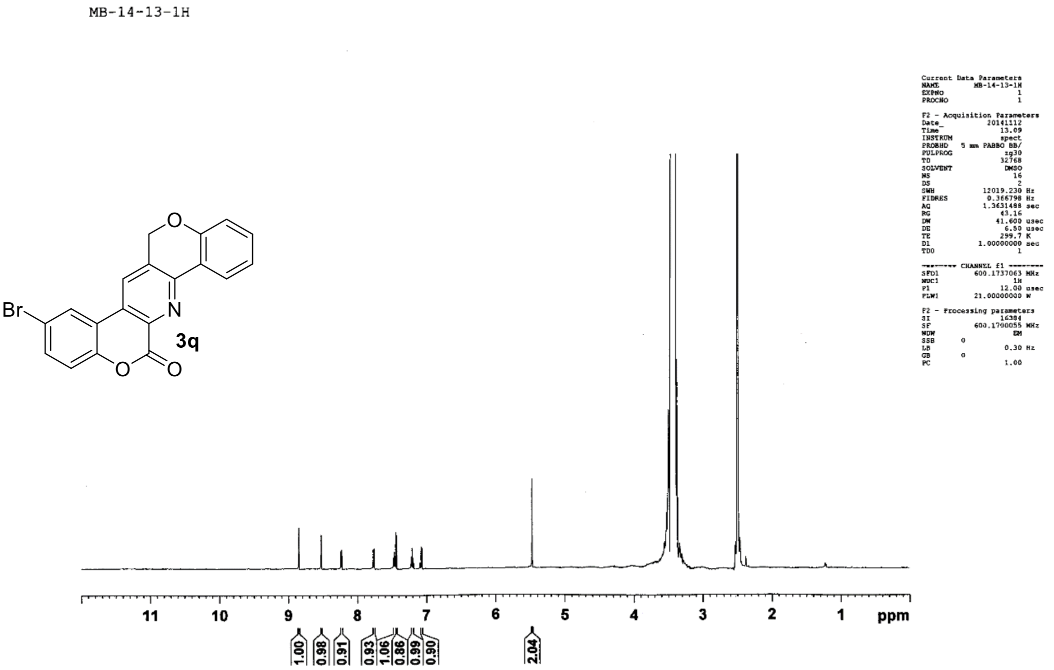
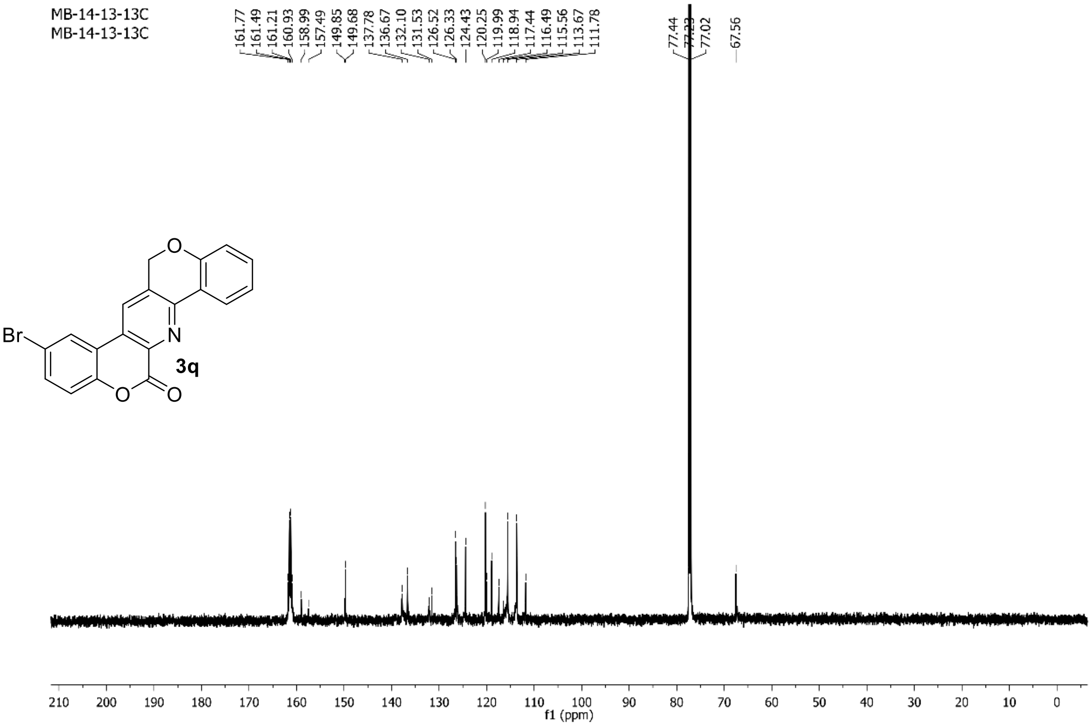

^{13}C NMR (150 MHz, CDCl$_3$: TFA = 4:1): *4-Methoxydichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (**3i**)



^{1}***H NMR (600 MHz, DMSO-d$_6$)***: *2-Bromodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (**3q**)



^{13}***C NMR (150 MHz, CDCl$_3$: TFA = 4:1)***: *2-Bromodichromeno[3,4-b:3',4'-e]pyridin-6(13H)-one* (**3q**)



Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 296 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

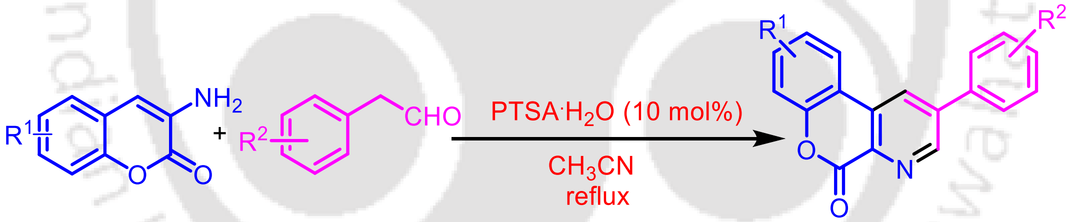
Table 3. Crystal data and structure refinements of compounds **3a** and **3l**. For atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check CIF.

Parameters	**Compound 3a**	**Compound 3l**
Empirical Formula	$C_{19}H_{11}NO_3$	$C_{22}H_{17}NO_5$
Formula Weight	301.29	375.37
Temperature	293 K	296 K
CCDC No.	981642	1003777
Wavelength (A^o)	0.71073	0.71073
Crystal System	Monoclinic	Monoclinic
Space group	P c	P 21/c
Radiation type	MoK\a	MoK\a
Radiation source	'fine-focus sealed tube'	fine-focus sealed tube
a (A^o)	7.4838(5)	15.1343(12)
b (A^o)	8.9794(6)	7.9297(7)
c (A^o)	21.4898(14)	15.8206(13)
α(^{o})	90.00	90.00
β (^{o})	106.872(5)	111.832(6)
γ (^{o})	90.00	90.00
Cell Voloume	1381.95(16)	1762.5(3) $Å^3$
z	4	4
Density	1.448	1.415

F (0 0 0)	624.0	784.0
Theta ranges	2.84 to 21.64	1.45 to 25.00
Index ranges	$-9 \leq h \geq 9$, $-11 \leq k \geq 0$, $-27 \leq l \geq 8$	$-17 \leq h \leq 17$, $-8 \leq k \leq 9$, $-18 \leq l \leq 18$
Reflection collected	3164	13054
Independent reflections	3164	3018
Completeness to theta	1.000	0.974
Number of parameters	415	255
Number of restraints	2	0
Godness of fit (GOF)on F^2	1.042	1.032
Refinement method	Full- matrix least square on F2	Full- matrix least square on F2

CHAPTER IIB

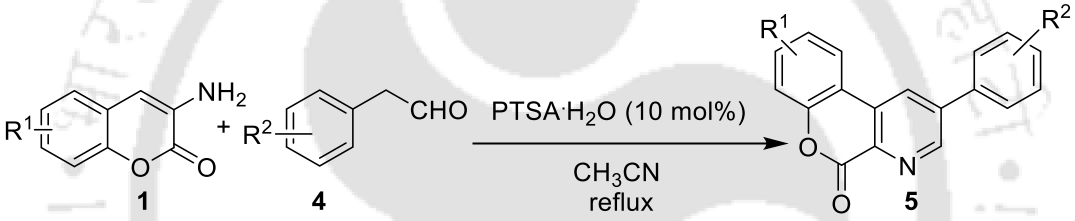
PTSA·H_2O Catalyzed Reaction of 3-Aminocoumarins and Phenylacetaldehyde Derivatives; A Route to Access Various Pyrido(2, 3-c)coumarin Derivatives



RESULTS AND DISCUSSION

• Results and Discussion

Haung et al. recently reported one pot C-C/C-N bond formation and C-C bond cleavage for the construction of substituted quinolone derivatives from anilines and phenylacetaldehydes using catalytic amount of Cu(II)/air and CF_3SO_3H as an additive.[50] Similar strategy was further expanded by Bharate et al using ionic liquid for the synthesis of quinolone derivatives.[51] Taking cue from these two observations, 3-aminocoumarin was extended for the construction of fused pyridine derivatives. Previously in Chapter IIA, TfOH as a catalyst has been used for the synthesis of pyridocoumarins by an intramolecular Povarov reaction from 3-aminocoumarins and propargylated salicylaldehydes. The present chapter describes the synthesis of pyridocoumarins using 3-aminocoumarin and phenylacetaldehyde derivatives in presence of $PTSA{\cdot}H_2O$ (Scheme 32).

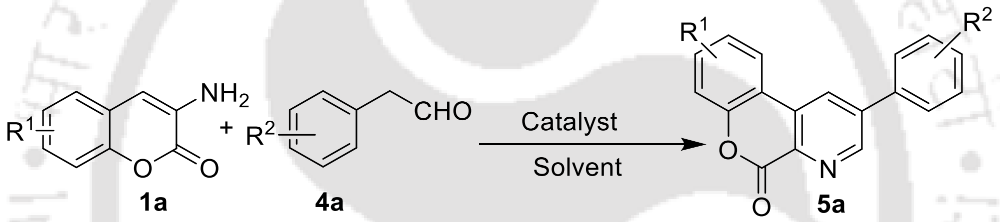


Scheme 32. Synthesis of various pyrido(2,3-*c*)coumarin derivatives

For the initial study, a reaction of 3-aminocoumarin (**1a**) was carried out with phenylacetaldehyde (**4a**) using CF_3COOH in acetonitrile in reflux condition. The product obtained was separated by column chromatography and characterized by IR, NMR spectra and HRMS. The isolated compound was found to be **5a** (Table 4), characterized by IR peak at 1735.13 cm^{-1}, the two meta coupled doublets at δ 9.15 and 8.57 ppm due to the two protons of the pyridine ring and the HRMS peak at 274.0861(see page no. 45 for NMR data and 56 for spectra of compound **5a**).

To reach the optimized conditions, several reactions were carried out using 3-aminocoumarin (**1a**) and phenyacetaldehyde (**4a**). The desired product **5a** was obtained in 60% yield when the reaction was carried out in acetonitrile using 5 mol% CF_3COOH as a catalyst (Table 4, entry 1). The yield was slightly improved to 66% when 10 mol% CF_3COOH was used (Table 4, entry 2). Other protic acid like TfOH, PDCA and $PTSA{\cdot}H_2O$ were also found effective as catalyst affording the desired product in good yield (Table 4, entry, 3-5). However, no product was achieved by using AcOH as catalyst (Table 3, entry 8). The best yield was obtained when $PTSA{\cdot}H_2O$ was used as the catalyst in acetonitrile under reflux condition (Table 4, entry 5-7). Employing 5% and 10 mol% of $PTSA\cdot H_2O$, 78% and 84% yields of the desired product were accomplished respectively whereas only a slight increase in yield was obtained loading the catalyst amount to 15 mol% (Table 4, entry 7). Moreover, with Lewis acid like I_2, $Yb(OTf)_3$ and $FeCl_3$ as catalysts, the reaction was promoted with 70-74 % yield (Table 4, entry 9-11) but no desired product was obtained with CuI as a catalyst (Table 4, entry 12). Apart from acetonitrile, several other solvents such as EtOH, MeOH, DMSO, DMF and Toulene were also sreened to reach the optimized condition and a moderate to good yield was obtained in these solvents (Table 4, entry, 13-17) but the efficacy of $CHCl_3$ as solvent was found to be very poor (Table 4, entry 18). Moreover the reaction was not feasible without any catalyst and the desired was obtained in low yield at ambient temperature (Table 4, entry 19-20).

Table 4. Optimization of reaction condition[a]



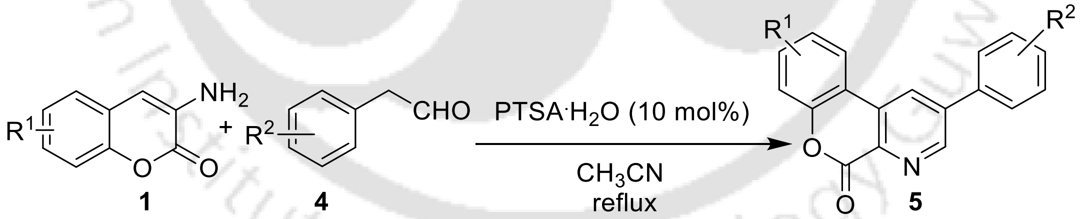
Entry	Catalyst (mol%)	Solvent	Time/h	Yield(%) [b]
1	CF_3COOH (5)	CH_3CN	14	60
2	CF_3COOH (10)	CH_3CN	14	66
3	TfOH (10)	CH_3CN	14	78
4	PDCA (10)	CH_3CN	14	70
5	$PTSA\cdot H_2O$ (10)	CH_3CN	14	84
6	$PTSA\cdot H_2O$ (5)	CH_3CN	14	78
7	$PTSA\cdot H_2O$ (15)	CH_3CN	14	86
8	AcOH (10)	CH_3CN	24	NR
9	I_2 (10)	CH_3CN	14	70
10	$Yb(OTf)_3$ (10)	CH_3CN	14	72
11	$FeCl_3$ (10)	CH_3CN	14	74
12	CuI (10)	CH_3CN	24	NR
13	$PTSA\cdot H_2O$ (10)	EtOH	14	40
14	$PTSA\cdot H_2O$ (10)	MeOH	14	45

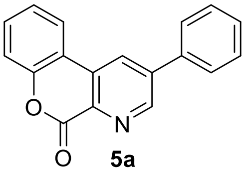
15[c]	PTSA·H_2O (10)	DMSO	14	60
16[c]	PTSA·H_2O (10)	DMF	24	52
17[c]	PTSA·H_2O (10)	Toulene	24	56
18	PTSA·H_2O (10)	$CHCl_3$	24	10
19	…..	CH_3CN	24	NR
20*	PTSA·H_2O (10)	CH_3CN	24	20

[a] Unless otherwise mentioned, all the reaction were carried out using 0 .5 mmol of **1a** and 1.0 mmol of **4a** under reflux condition. [b] Isolated yields. [c] In case of DMF and DMSO and Toulene the temperature was maintained at 80 °C. *Room temperature.

After achieving the optimized reaction condition, various derivatives of 3-aminocoumarin and phenylacetaldehye derivatives were scrutinized under the standard reaction conditions to explore the substrate scope of the reaction protocol. Initially, a number of phenylacetaldehyde derivatives were reacted with 3-aminocoumarins to transform them to the desired pyrido(2, 3-*c*)coumarins. Interestingly, the respective products were achieved in significant yields with both electron donating (**5b** and **5c**) and withdrawing substituents (**5d-g)** on phenylacetaldehyde moiety (Table 5). Notably, the desired products were not obtained with aliphatic aldehydes. Furthermore a wide range of 3-aminocoumarins containing 7-MeO-, 8-MeO-, 8-EtO-, 6-Cl-, 6-Br, 6,8-dichloro, substituents were investigated and a good to excellent yield ware obtained with these substrates (Table 5, **5h-q**).

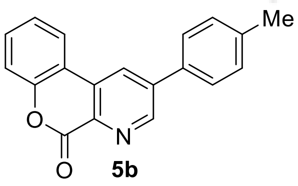
Table 5. Synthesis of various pyrido(2,3-*c*)coumarin derivatives [a,b]





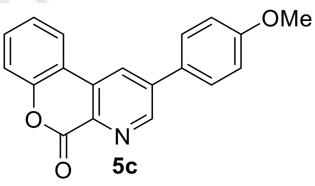
5a

12 h, 80%



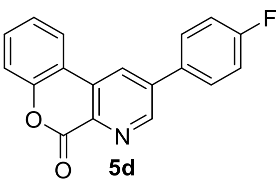
5b

13 h, 82%



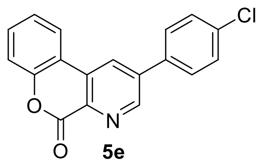
5c

13 h, 83%



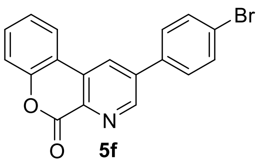
5d

14 h, 77%



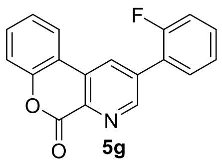
5e

14 h, 77%



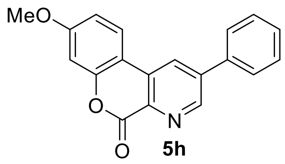
5f

12 h, 80%



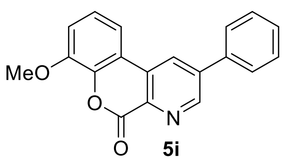
5g

12 h, 78%



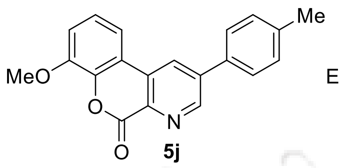
5h

12 h, 82%



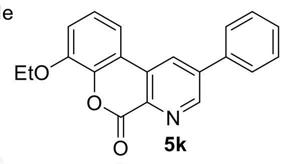
5i

12 h, 83%



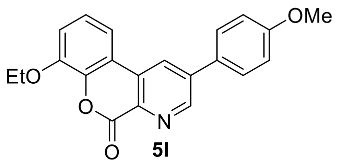
5j

12 h, 81%



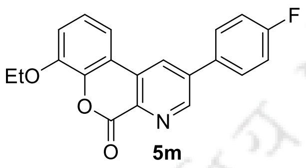
5k

14 h, 80%



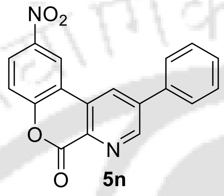
5l

14 h, 84%



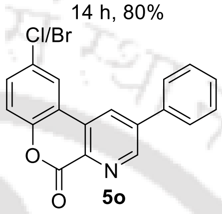
5m

14 h, 81%



5n

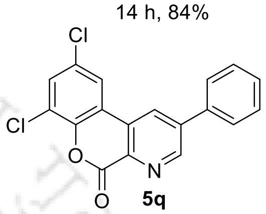
15 h, 78%



5o

Cl = **5o**, 14 h, 80%

Br = **5p**, 12 h, 81%



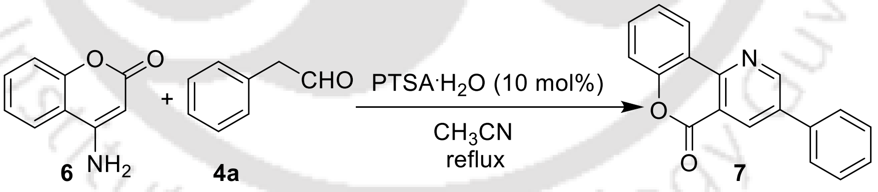
5q

14 h, 80%

[a]All the reaction were carried out using 0 .5 mmol of **1** and 1.0 mmol of **4** with 10 mol% of PTSA in acetonitrile under reflux condition.[b] Isolated yields

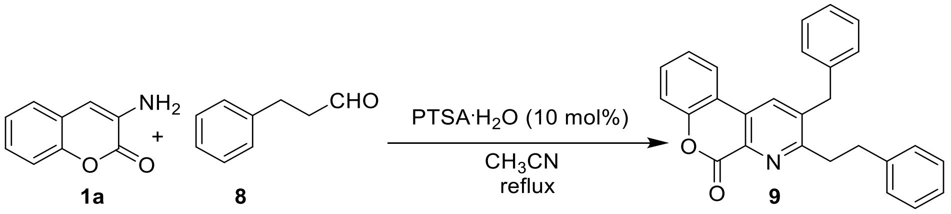
Moreover, when 4-aminocoumarin was evaluated for further scope of aminocoumarin moiety under the standard reaction conditions with phenylacetaldehyde, the product (**7**) was obtained in 80% yield (Scheme 33). Further, a different product **(9)** was obtained on replacing phenylacetaldehyde with 3-phenylpropionaldehyde (Scheme 34).

Scheme 33. Synthesis of 3-phenyl-5*H*-chromeno[4,3-*b*]pyridin-5-one



16 h, 80%

Scheme 34. Synthesis of 2-benzyl-3-phenethyl-5*H*-chromeno[3,4-*b*]pyridin-5-one



16 h, 82%

All the products (**5a-q**, **7** and **9**) were characterized by their I.R, ^{1}H NMR, ^{13}C NMR, and HRMS spectra analysis (see pages 45-55 for IR, NMR and HRMS data.). Futher, compound **5i** was characterized by crystallographic structure (Figure 5).

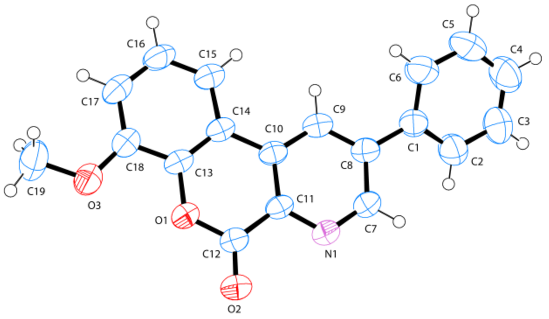
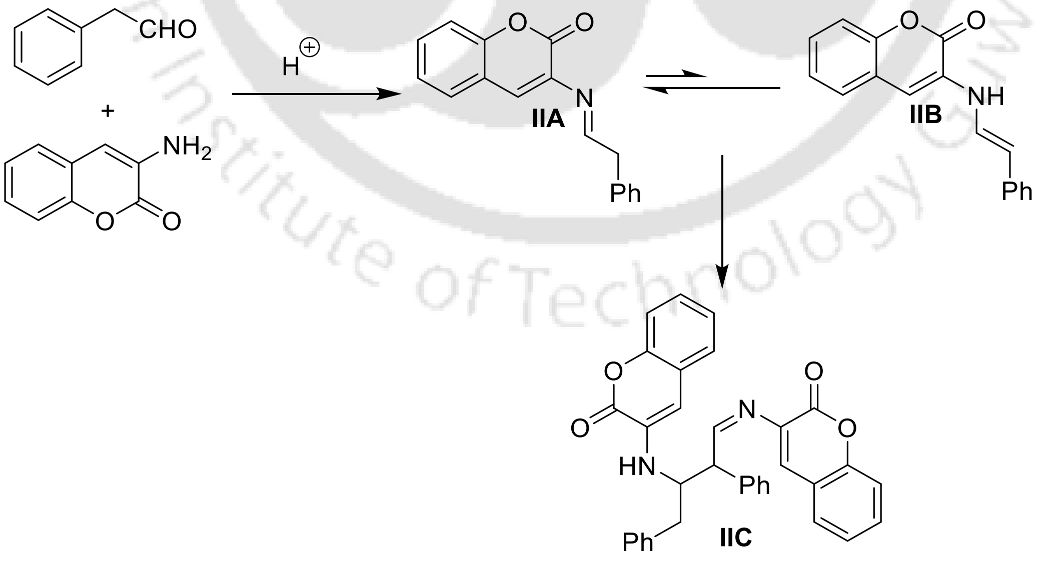
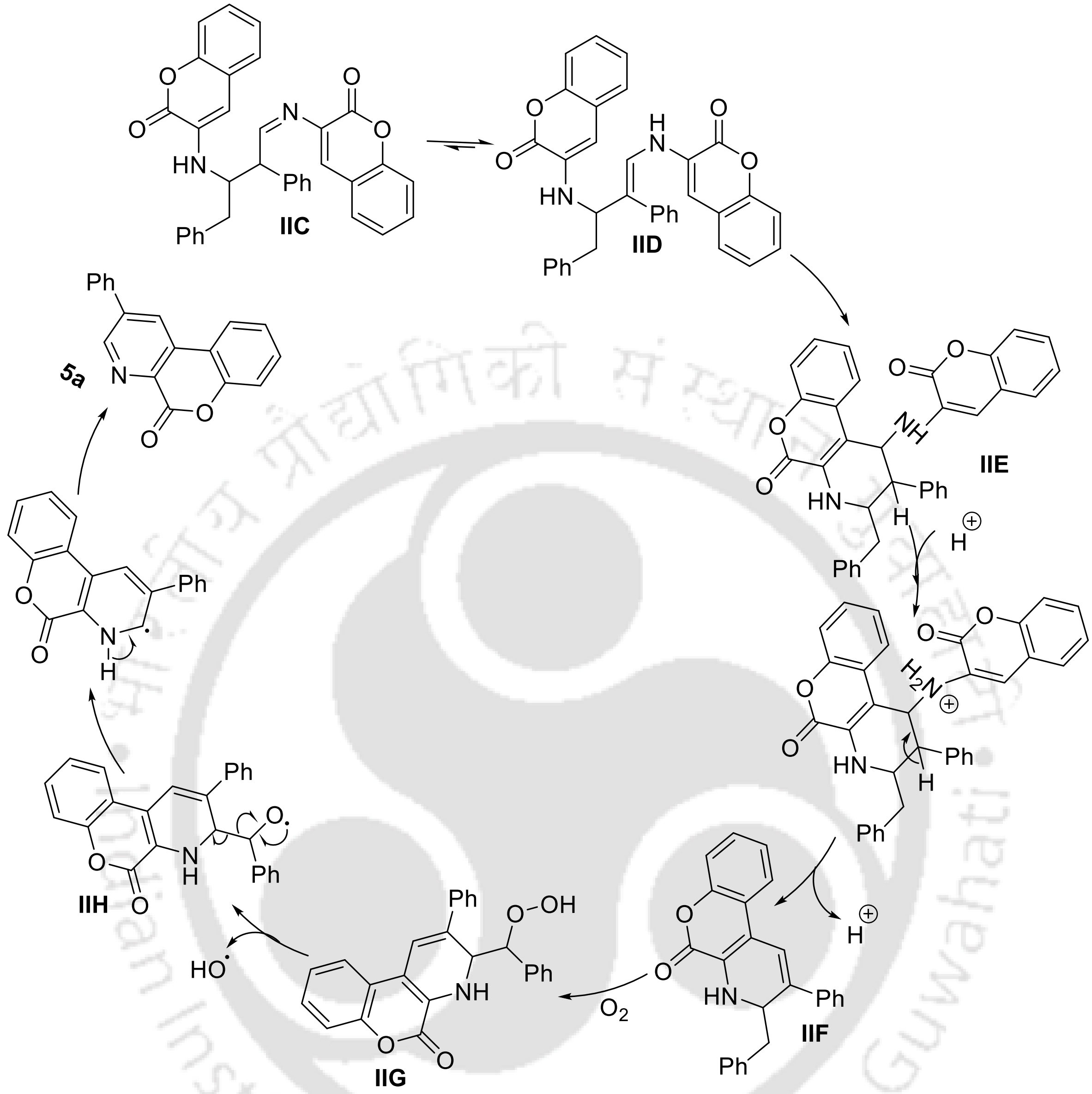


Figure 5. Crystal structure of **5i** (CCDC number1477324)

From our experimental results and literature survey[50, 51] a plausible mechanism has been drawn as shown in Scheme 35. Initially phenylacetaldehyde reacts with 3-aminocoumarin to form an imine (**IIA)** in the presence of PTSA·H_2O. The imine **(IIA)** tautomerizes to an enamine (**IIB)**. The reaction of imine (**IIA**) and enamine (**IIB**) gives **IIC** which tautomerizes to **IID**. The intermediate **IID** cyclizes to **IIE**. The intermediate **IIE** on protonation and loss of 3-aminocoumarin followed by aerial oxidation provides **IIF** and **IIF** on oxidation gives **IIG** which produces **IIH**. Finally, **IIH** on C-C bond cleavage followed by aromatization gives the final product **5a**.





Scheme 35. Plausible mechanism of formation of **5a**

In conclusion, synthesis of various pyrido(2, 3-*c*)coumarin derivtives from phenylacetaldehyde derivatives and 3-aminoucoumarins has been demonstrated. The protocols gives an easy access to a number of substituted pyrido(2, 3-*c*)coumarins derivatives with large number of substrate scope.

CHAPTER IIB

$\mathrm{PTSA\cdot H_2O}$ Catalyzed Reaction of 3-Aminocoumarins and Phenylacetaldehyde Derivatives; A Route to Access Various Pyrido(2, 3-c)coumarin Derivatives

EXPERIMENTAL SECTION

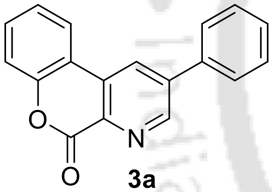
• Experimental Section

Synthesis of various derivatives of pyrido(2, 3-c)coumarin (5a-q, 7 and 9):

Into a 25 mL round bottomed flask was taken 0.5 mmol of 3-aminocoumarin and 1.0 mmol of phenyacetaldehyde in 3 mL of acetonitrile. Then, 10 mol% of PTSA·H_2O was added into it. The reaction mixture was refluxed for 12-16 h in a preheated oil bath. After completion of the reaction checked by TLC, acetonitrile was removed in a rotary evaporator and the reaction mixture was extracted with DCM. After removing DCM in a rotary evaporator, the crude residue was purified through column chromatography using hexane: ethylacetate = 3:1 mixture to obtain the pure products.

In case of **5e, 5f, 5n-q and 9**, after completion of the reaction checked by TLC, the solid precipitate was filtered off and it was washed with acetonitrile to remove the impurities. All the products after purification was characterized with IR. ^{1}H NMR, ^{13}C NMR and HRMS spectra.

***2-Phenyl-5H-chromeno[3,4-b]pyridin-5-one* (5a):**



3a

Reaction Time: 12 h **Colour & State:** pale yellow solid

Yield: 80% (110 mg) **Melting Point:** 192-194 °C

IR (KBr): 3052.31, 2924.10, 2853.28, 1753.31, 1611.63, 1178.06, 1095.47 cm^{-1}.

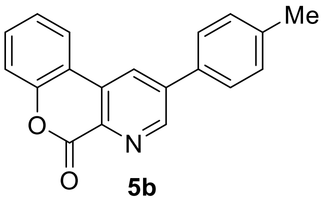
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.15 (d, *J* = 2.1 Hz, 1 H), 8.57 (d, *J* = 1.9 Hz, 1 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 7.73 (d, *J* = 8 Hz, 2 H), 7.56 (m, 4 H), 7.41 (t, *J* = 8.1 Hz, 2 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 159.1, 151.4, 150.4, 141.6, 136.7, 136.2, 131.8, 131.7, 129.8, 129.7, 127.9, 127.8, 125.1, 123.2, 118.2, 116.8 ppm.

HRMS (ESI) calcd for $C_{18}H_{11}NO_2$ (M + H$^+$) = 274.0863, found 274.0861.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{11}NO_2$	C 79.11	79.23
(273.29)	H 4.06	3.99
	N 5.13	5.05

***2-(p-Tolyl)-5H-chromeno[3,4-b]pyridin-5-one* (5b):**



5b

Reaction Time: 13 h **Colour & State:** pale yellow solid

Yield: 82% (118 mg) **Melting Point:** 242-245 °C

IR (KBr): 3055.35, 2921.34, 1738.31, 1607.41, 1243.87, 1177.55, 1099.50 cm^{-1}.

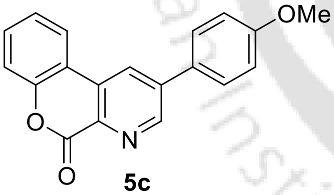
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.11 (d, *J* = 2.0 Hz, 1 H), 8.53 (d, *J* = 2.0 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 7.61 (dd, *J* = 8.1, 1.7 Hz, 2 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.38 (m, 4 H), 2.45 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 159.2, 151.4, 150.3, 141.6, 140.1, 136.4, 133.3, 131.8, 131.6, 130.4, 127.6, 127.4, 125.0, 123.2, 118.2, 117.0, 21.5 ppm.

HRMS (ESI) calcd for $C_{19}H_{13}NO_2$ (M + H$^+$) = 288.1019, found 288.1018.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{13}NO_2$	C 79.43	79.30
(287.32)	H 4.56	4.51
	N 4.88	4.80

2-(4-Methoxyphenyl)-5H-chromeno[3,4-b]pyridin-5-one **(5c):**



5c

Reaction Time: 13 h **Colour & State:** pale yellow solid

Yield: 83% (126 mg) **Melting Point:** 190-193 °C

IR (KBr): 3050.73, 2925.83, 2834.23, 1752.89, 1605.66, 1250.25, 1179.11, 1087.48 cm^{-1}.

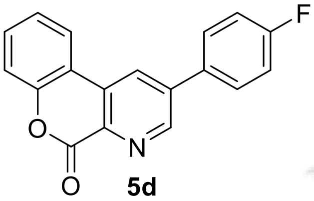
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.08 (s, 1 H), 8.47 (s, 1 H), 8.08 (d, *J* = 7.9 Hz, 1 H), 7.65 (d, *J* = 7.9 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 7.37 (t, *J* = 8.4 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 3.88 (s, 3 H).

^{13}C NMR (150 MHz, CDCl$_3$): δ 161.2, 159.2, 151.4, 150.0, 141.2, 136.1, 131.8, 131.6, 129.0, 128.4, 126.8, 125.0, 123.2, 118.2, 117.0, 115.2, 55.7

HRMS (ESI) calcd for $C_{19}H_{13}NO_3$ (M + H$^+$) = 304.0968, found 304.0968.

Elemental Analysis	**Calculated**	**Found**
MF $C_{19}H_{13}NO_3$	C 75.24	75.35
(303.32)	H 4.32	4.36
	N 4.62	4.55

***2-(4-Fluorophenyl)-5H-chromeno[3,4-b]pyridin-5-one* (5d):**



5d

Reaction Time: 14 h **Colour & State:** pale yellow solid

Yield: 77% (112 mg) **Melting Point:** 218-221 °C

IR (KBr): 2917.50, 2845.34, 1750.69, 1613.08, 1255.75, 1162.05, 1006.88 cm^{-1}.

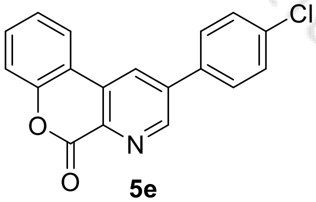
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.09 (d, *J* = 2.0 Hz, 1 H), 8.53 (d, *J* = 2.1 Hz, 1 H), 8.06 (d, *J* = 7.6 Hz, 1 H), 7.67 (m, 2 H), 7.56 (td, *J* = 8.0, 1.4 Hz, 1 H), 7.35 (m, 2 H), 7.22 (m, 2 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 165.2, 162.7, 158.9, 151.4, 150.0, 140.8, 136.5, 132.4, 131.9, 129.7, 129.6, 127.9, 125.2, 123.2, 118.2, 117.0, 116.8, 116.7 ppm.

HRMS (ESI) calcd for $C_{18}H_{10}FNO_2$ (M + H$^+$) = 292.0768, found 292.0762.

Elemental Analysis	**Calculated**	**Found**
MF $C_{18}H_{10}FNO_2$	C 74.22	74.11
(291.28)	H 3.46	3.38
	N 4.81	4.75

***2-(4-Chlorophenyl)-5H-chromeno[3,4-b]pyridin-5-one* (5e):**



5e

Reaction Time: 14 h **Colour & State:** pale yellow solid

Yield: 77% (118 mg) **Melting Point:** 188-190 °C

IR (KBr): 1756.59, 1615.10, 1286.20, 1179.42, 1104.93, 1004.58 cm^{-1}.

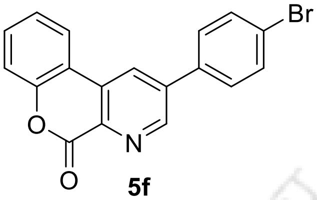
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.13 (s, 1 H), 8.56 (s, 1 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 7.59 (m, 3 H), 7.44 (m, 2 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$: TFA = 10:1): δ 155.5, 151.6, 145.0, 144.1, 139.5, 135.8, 135.4, 135.3, 131.0, 129.2, 127.2, 124.0, 119.1, 113.7 ppm.

HRMS (ESI) calcd for $C_{18}H_{10}ClNO_2$ (M + H^+) = 308.0473, found 308.0471.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{10}ClNO_2$	C 70.26	70.40
(307.73)	H 3.28	3.24
	N 4.55	4.50

***2-(4-Bromophenyl)-5H-chromeno[3,4-b]pyridin-5-one* (5f):**



5f

Reaction Time: 12 h **Colour & State:** pale yellow solid

Yield: 80% (140 mg) **Melting Point:** 334-336 °C

IR (KBr): 1752.19, 1684.27, 1285.53, 1179.41, 1102.59, 1070.98 cm^{-1}.

^{1}HNMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1 H), 8.56 (s, 1 H), 8.12 (d, *J* = 7.9 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 7.60 (m, 3 H), 7.46 (d, *J* = 9.1 Hz, 1 H), 7.42 (d, *J*= 8.8 Hz, 1 H) ppm.

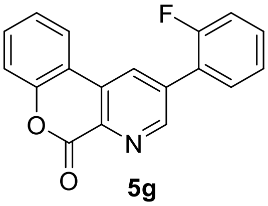
^{13}C NMR (150 MHz, $CDCl_3$: TFA = 10:1): δ 155.8, 151.6, 144.6, 135.0, 133.8, 131.6, 129.8, 129.3, 128.6, 127.5, 127.0, 125.9, 123.9, 119.1, 114.0 ppm.

HRMS (ESI) calcd for $C_{18}H_{10}BrNO_2$ (M + H^+) = 351.9968, found 351.9965 & 353.9947.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{10}BrNO_2$	C 61.39	61.25
(352.19)	H 2.86	2.90
	N 3.98	3.92

***2-(2-Fluorophenyl)-5H-chromeno[3,4-b]pyridin-5-one* (5g):**

Reaction Time: 12 h **Colour & State:** pale yellow solid



5g

Yield: 78% (114 mg) **Melting Point:** 184-188 °C

IR (KBr): 3066.17, 2923.97, 2853.23, 1761.15, 1615.12, 1592.01, 1227.96, 1087.95 cm^{-1}.

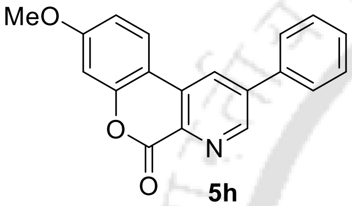
^{1}HNMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1 H), 8.64 (s, 1 H), 8.09 (d, *J* = 7.9 Hz, 1 H), 7.58 (m, 2 H), 7.51 (m, 1 H), 7.41 (m, 2 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.28 (m. 1 H) ppm.

^{13}C NMR (100 MHz,CDCl$_3$): δ 161.4, 159.1, 158.9, 151.5, 151.4, 151.4, 136.9, 136.8, 131.8, 131.8, 131.7, 131.6, 130.74, 130.7, 130.3, 130.2, 125.38, 125.4, 125.2, 124.3, 124.1, 123.3, 118.2, 117.0, 116.8 ppm.

HRMS (ESI) calcd for $C_{18}H_{10}FNO_2$ (M + H$^+$) = 292.0768, found 292.0771.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{10}FNO_2$	C 74.22	74.38
(291.28)	H 3.46	3.39
	N 4.81	4.76

***8-Methoxy-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (5h):**



5h

Reaction Time: 12 h **Colour & State:** pale yellow solid

Yield: 82% (124 mg) **Melting Point:** 196-199 °C

IR (KBr): 2923.05, 2839.78, 1744.01, 1617.70, 1259.32, 1118.38, 1037.88 cm^{-1}.

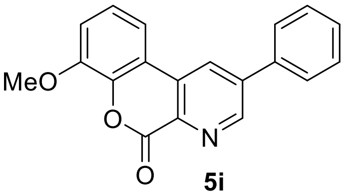
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.04 (d, J = 1.4 Hz, 1 H), 8.42 (d, J = 1.5 Hz, 1 H), 7.96 (d, J = 8.9 Hz, 1 H), 7.71 (d, J = 7.7 Hz, 2 H), 7.54 (m, Hz, 3 H), 6.95 (dd, J = 8.8, 2.4 Hz, 1 H), 6.87 (d, J = 2.3 Hz, 1 H), 3.89 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 162.5, 159.4, 152.8, 149.4, 141.6, 136.4, 135.5, 132.2, 129.7, 129.6, 127.8, 127.2, 124.2, 113.1, 109.8, 101.9, 56.0 ppm.

HRMS (ESI) calcd for $C_{19}H_{13}NO_3$ (M + H$^+$) = 304.0968, found 304.0975.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{13}NO_3$	C 75.24	75.33
(303.32)	H 4.32	4.47
	N 4.62	4.54

***7-Methoxy-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (5i):**



5i

Reaction Time: 12h **Colour & State:** pale yellow solid

Yield: 83% (126 mg) **Melting Point:** 204-206 °C

IR (KBr): 3078.79, 2835.54, 1744.06, 1273.35, 1101.30 cm^{-1}.

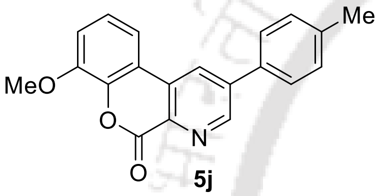
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.14 (s, 1 H), 8.54 (s, 1 H), 7.72 (d, *J* = 7.4 Hz, 2 H), 7.66 (d, *J* = 8.1 Hz, 1 H), 7.55 (m, 3 H), 7.32 (t, *J* = 8.1 Hz, 1 H), 7.10 (d, *J* = 8.1 Hz, 1 H), 3.98 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 158.6, 150.5, 148.4, 141.6, 141.3, 136.8, 136.4, 132.0, 129.8, 129.7, 128.4, 127.8, 125.0, 117.7, 114.3, 113.5, 56.5 ppm.

HRMS (ESI) calcd for $C_{19}H_{13}NO_3$ (M + H$^+$) = 304.0968, found 304.0974.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{13}NO_3$	C 75.24	75.12
(303.32)	H 4.32	4.26
	N 4.62	4.70

7-Methoxy-2-(p-tolyl)-5H-chromeno[3,4-b]pyridin-5-one **(5j):**



5j

Reaction Time: 12 h **Colour & State:** pale yellow solid

Yield: 81% (128 mg) **Melting Point:** 260-263 °C

IR (KBr): 3067.39, 3017.42, 2831.46, 1736.79, 1615.82, 1274.92, 1203.67, 1176.08, 1094.24 cm^{-1}.

^{1}HNMR (400 MHz, CDCl$_3$): δ 9.13 (s, 1 H), 8.51 (s, 1 H), 7.65 (d, *J* = 8.3 Hz, 1 H), 7.62 (d, *J* = 7.8 Hz, 2 H), 7.36 (d, *J* = 7.8 Hz, 2 H), 7.31 (t, *J* = 8.1 Hz, 1 H), 7.09 (d, *J* = 8.1 Hz, 1 H), 3.96 (s, 3 H), 2.44 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 158.6, 150.4, 148.4, 141.5, 140.1, 136.5, 133.4, 132.0, 130.4, 127.9, 127.6, 124.9, 117.8, 114.3, 113.4, 56.5, 21.5 ppm.

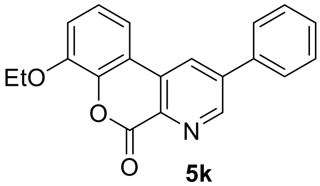
HRMS (ESI) calcd for $C_{20}H_{15}NO_3$ (M + H$^+$) = 318.1125, found 318.1132.

Elemental Analysis	Calculated	Found
MF $C_{20}H_{15}NO_3$	C 75.70	75.83
(317.34)	H 4.76	4.70
	N 4.41	4.35

7-Ethoxy-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one **(5k):**

Reaction Time: 14h **Colour & State:** pale yellow solid

Yield: 80% (126 mg) **Melting Point:** 218-219 °C



5k

IR (KBr): 2923.05, 2845.34, 1751.17, 1596.54, 1275.63, 1094.35, 1082.17, 1042.26 cm^{-1}.

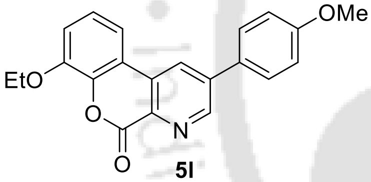
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.14 (d, *J* = 1.9 Hz, 1 H), 8.53 (d, *J* = 1.9 Hz, 1 H), 7.72 (d, *J* = 7.1 Hz, 2 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.54 (m, 3 H), 7.29 (t, *J* = 8.1 Hz, 1 H), 7.08 (d, *J* = 8.1 Hz, 1 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 1.52 (t, *J* = 7.0 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 158.8, 150.4, 147.8, 141.6, 141.5, 136.8, 136.4, 132.0, 129.8, 129.7, 128.4, 127.8, 124.9, 117.8, 114.7, 114.2, 65.2, 15.0 ppm.

HRMS (ESI) calcd for $C_{20}H_{15}NO_3$ (M + H$^+$) = 318.1125, found 318.1130.

Elemental Analysis	Calculated	Found
MF $C_{20}H_{15}NO_3$	C 75.70	75.55
(317.34)	H 4.76	4.80
	N 4.41	4.35

***7-Ethoxy-2-(4-methoxyphenyl)-5H-chromeno[3,4-b]pyridin-5*-one (5l):**



5l

Reaction Time: 14 h **Colour & State:** pale yellow solid

Yield: 84% (146 mg) **Melting Point:** 246-249 °C

IR (KBr): 2978.57, 2928.60, 1743.52, 1733.63, 1605.29, 1247.08, 1198.11, 1178.81, 1112.35, 1096.97 cm^{-1}.

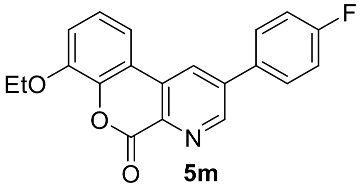
^{1}HNMR (600 MHz, CDCl$_3$): δ 9.10 (s, 1 H), 8.47 (s, 1 H), 7.67 (d, *J* = 7.7 Hz, 2 H), 7.63 (d, *J* = 7.9 Hz, 1 H), 7.28 (t, *J* = 8.1, Hz, 1 H), 7.07 (d, *J* = 7.8 Hz, 3 H), 4.18 (q, *J* = 6.5 Hz, 2 H), 3.89 (s, 3 H), 1.51 (t, *J* = 6.5 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 161.1, 158.9, 150.1, 147.8, 141.5, 141.1, 136.1, 132.0, 129.0, 128.6, 127.4, 124.9, 117.9, 115.2, 114.6, 114.2, 65.2, 55.7, 15.0 ppm.

HRMS (ESI) calcd for $C_{21}H_{17}NO_4$ (M + H$^+$) = 348.1230, found 348.1234.

Elemental Analysis	Calculated	Found
MF $C_{21}H_{17}NO_4$	C 72.61	72.76
(347.37)	H 4.93	4.87
	N 4.03	4.29

7-Ethoxy-2-(4-fluorophenyl)-5H-chromeno[3,4-b]pyridin-5-one **(5m):**



Reaction Time: 14 h **Colour & State:**pale yellow solid

Yield: 81% (132 mg) **Melting Point:** 259-261 °C

IR (KBr): 2981.34, 2920.28, 2853.66, 1751.53, 1601.12, 1273.71, 1239.06, 1165.37, 1075.35 cm^{-1}.

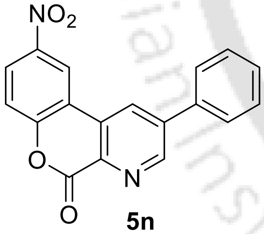
^{1}HNMR (400 MHz, CDCl$_3$): δ 9.10 (s, 1 H), 8.51 (s, 1 H), 7.71 (dd, *J* = 8.6, 5.3 Hz, 2 H), 7.65 (d, *J* = 8.1 Hz, 1 H), 7.29 (m, 3 H), 7.10 (d, *J* = 8.1 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 1.53 (t, *J* = 7.0 Hz, 3 H) pm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 164.8, 163.1, 158.7, 150.2, 147.8, 141.6, 140.7, 136.8, 132.6, 132.2, 129.8, 129.7, 128.3, 125.0, 117.7, 117.0, 116.8, 114.8, 114.2, 65.3, 15.0 ppm.

HRMS (ESI) calcd for $C_{20}H_{14}FNO_3$ (M + H$^+$) = 336.1030, found 336.1037.

Elemental Analysis	Calculated	Found
MF $C_{20}H_{14}FNO_3$	C 71.64	71.75
(335.33)	H 4.21	4.16
	N 4.18	4.24

9-Nitro-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one **(5n):**



Reaction Time: 15 h **Colour & State:** pale yellow solid

Yield: 78% (124 mg) **Melting Point:** 330-333 °C

IR (KBr): 3064.61, 2917.50, 1757.02, 1619.10, 1269.30, 1101.64, 1079.82, 1037.77 cm^{-1}.

^{1}HNMR (600 MHz, DMSO-d$_6$): δ 9.56 (s, 1 H), 9.38 (s, 1 H), 9.34 (s, 1 H), 8.44 (d, *J* = 8.8 Hz, 1 H), 8.11 (d, *J* = 7.1 Hz, 2 H), 7.70 (d, *J* = 9.0 Hz, 1 H), 7.62 (d, *J* = 7.1 Hz, 2 H), 7.58 (d, *J* = 6.6 Hz, 1 H) ppm.

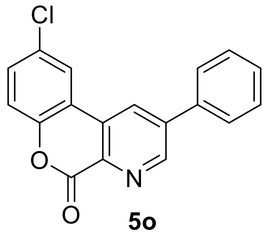
^{13}C NMR (100 MHz, CDCl$_3$: TFA= 10:1): δ 154.9, 154.4, 147.0, 145.6, 136.4, 133.9, 132.8, 131.9, 130.7, 129.2, 128.1, 120.7, 120.5, 115.1 ppm.

HRMS (ESI) calcd for $C_{18}H_{10}N_2O_4$ (M + H$^+$) = 319.0713, found 319.0714.

Elemental Analysis	Calculated	Found

MF $C_{18}H_{10}N_2O_4$	C 67.93	68.04
(318.29)	H 3.17	3.13
	N 8.80	8.88

***9-Chloro-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (5o):**


5o

Reaction Time: 14 h **Colour & State:** white yellow solid

Yield: 80% (122 mg) **Melting Point:** 267-270 °C

IR (KBr): 1752.19, 1632.71, 1269.43, 1172.73, 1109.41, 1078.38 cm^{-1}.

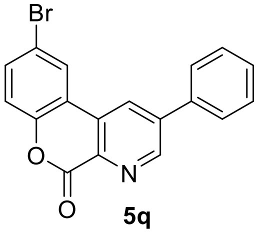
^{1}HNMR (400 MHz, $CDCl_3$): δ 9.19 (d, *J* = 2.0 Hz, 1 H), 8.51 (d, *J* = 2.0 Hz, 1 H), 8.08 (d, *J* = 2.3 Hz, 1 H), 7.75 (d, *J* = 7.6, Hz, 2 H), 7.58 (m, 3 H), 7.52 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 151.1, 150.0, 142.0, 136.8, 136.0, 131.7, 130.8, 130.7, 130.0, 129.8, 128.0, 127.9, 123.0, 119.7, 118.4 ppm.

HRMS (ESI) calcd for $C_{18}H_{10}ClNO_2$ (M + H$^+$) = 308.0473, found 308.0474.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{10}ClNO_2$	C 70.26	70.14
(307.73)	H 3.28	3.24
	N 4.55	4.49

***9-Bromo-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (5p):**


5q

Reaction Time: 12 h **Colour & State:** white solid

Yield: 81% (142 mg) **Melting Point:** 280-282 °C

IR (KBr): 3061.77, 1756.74, 1601.32, 1274.79, 1100.79, 1073.71 cm^{-1}.

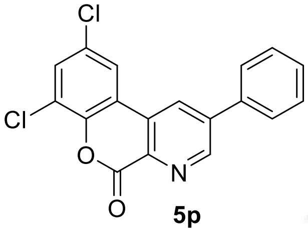
^{1}HNMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1 H), 8.50 (s, 1 H), 8.22 (d, *J* = 1.6 Hz, 1 H), 7.74 (d, *J* = 7.5 Hz, 2 H), 7.65 (dd, *J* = 8.7, 1.6 Hz, 1 H), 7.56 (m, 3 H), 7.32 (d, *J* = 8.8 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 151.1, 150.4, 142.0, 136.7, 136.0, 134.5, 130.7, 130.0, 129.8, 127.9, 127.8, 126.0, 120.0, 118.8, 118.0 ppm.

HRMS (ESI) calcd for $C_{18}H_{10}B_rNO_2$ (M + H$^+$) = 351.9968, found 351.9974.

Elemental Analysis	**Calculated**	**Found**
MF $C_{18}H_{10}BrNO_2$	C 61.39	61.56
(352.19)	H 2.86	2.90
	N 3.98	3.90

***7,9-Dichloro-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (5q):**


5p

Reaction Time: 14 h **Colour & State:** white solid

Yield: 80% (136 mg) **Melting Point:** 339-341 °C

IR (KBr): 3078.49, 2925.83, 2850.89, 1740.47, 1586.59, 1253.86, 1174.05, 1116.86, 1091.19, 1055.84 cm^{-1}

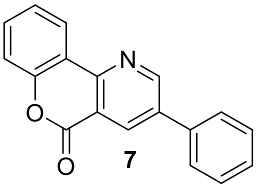
^{1}HNMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1 H), 8.52 (s, 1 H), 8.00 (d, *J* = 2.0 Hz, 1 H), 7.75 (d, *J* = 7.0 Hz, 2 H), 7.65 (d, *J* = 2.1 Hz, 1 H), 7.59 (m, 3 H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$: TFA = 10: 1): δ, 154.4, 147.0, 146.1, 145.4, 136.4, 135.1, 134.0, 133.0, 132.9, 132.0, 130.8, 128.0, 127.6, 125.6, 122.3, 116.3 ppm.

HRMS (ESI) calcd for $C_{18}H_9Cl_2NO_2$ (M + H^+) = 342.0083, found 342.0083.

Elemental Analysis	**Calculated**	**Found**
MF $C_{18}H_9Cl_2NO_2$	C 63.18	63.30
(342.18)	H 2.65	2.61
	N 4.09	4.08

***3-Phenyl-5H-chromeno[4,3-b]pyridin-5-one* (7):**


7

Reaction Time: 16 h **Colour & State:** pale yellow solid

Yield: 80% (110 mg) **Melting Point:** 188-189 °C

IR (KBr): 3442.09, 1736.82, 1653.62, 1609.79, 1600.54, 1170.42, 1085.04 cm^{-1}.

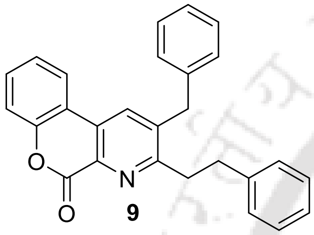
^{1}HNMR (400 MHz, $CDCl_3$): δ 9.26 (s, 1 H), 8.79 (s, 1 H), 8.60 (d, *J* = 7.8 Hz, 1 H), 7.70 (d, *J* = 7.6 Hz, 2 H), 7.56 (m, 3 H), 7.48 (d, *J* = 7.2 Hz, 1 H), 7.42 (m, 2 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 161.6, 154.5, 152.7, 150.6, 137.1, 136.3, 135.8, 132.3, 129.6, 129.2, 127.3, 125.2, 124.9, 119.4, 117.5, 117.4 ppm.

HRMS (ESI) calcd for $C_{18}H_{11}NO_2$ (M + H$^+$) = 274.0863, found 274.0868.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{11}NO_2$	C 79.11	79.22
(273.29)	H 4.06	4.01
	N 5.13	5.20

***2-Benzyl-3-phenethyl-5H-chromeno[3,4-b]pyridin-5-one* (9):**



9

Reaction Time: 16 h **Colour & State:**white solid

Yield: 82% (160 mg) **Melting Point:** 224-226 °C

IR (KBr): 3022.98, 2961.91, 2884.19, 1749.67, 1601.81, 1590.30, 1286.56, 1176.01, 1159.97, 1130.44 cm^{-1}.

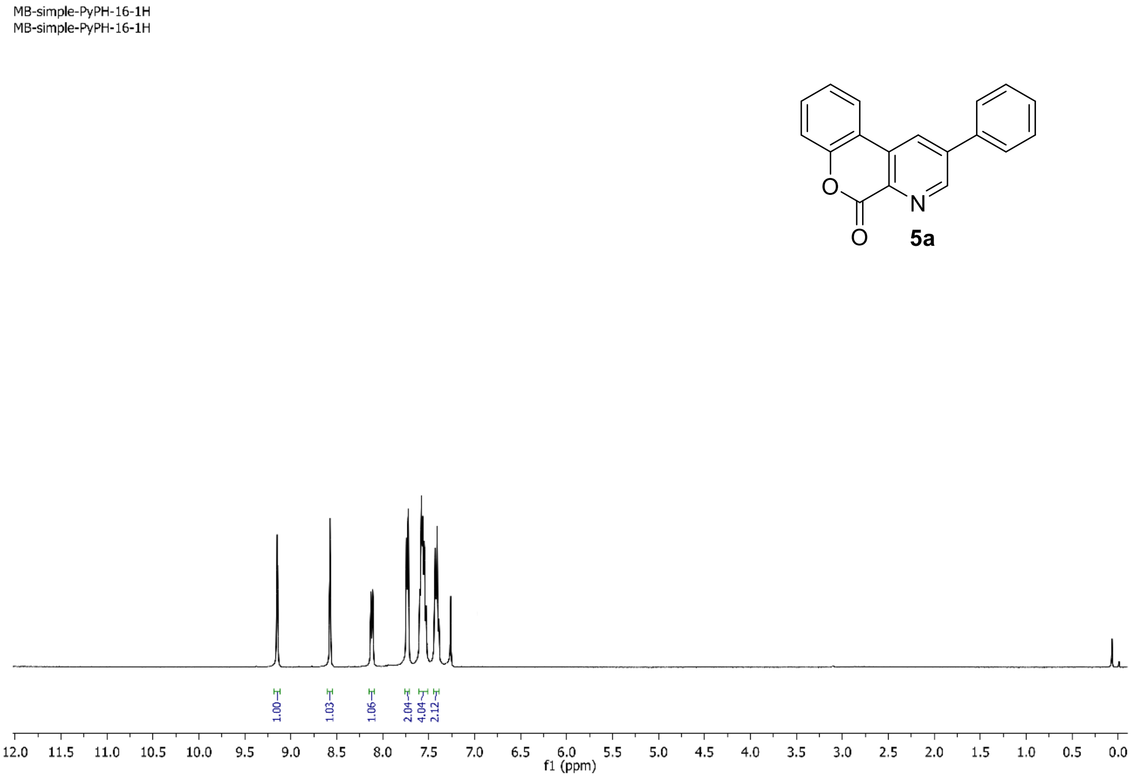
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.99 (s, 1 H), 7.82 (d, *J* = 7.9 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.38 (t, *J* = 8.4 Hz, 1 H), 7.31 (m, 4 H), 7.22 (m, 3 H), 7.14 (d, *J* = 7.2 Hz, 2 H), 7.07 (d, *J* = 7.3 Hz, 2 H), 4.03 (s, 2 H), 3.28 (t, *J* = 8 Hz, 2 H), 3.09 (t, , *J* = 8 Hz, 2 H) ppm.

^{13}C NMR (100 MHz,CDCl$_3$): δ 163.1, 159.4, 151.2, 141.5, 141.1, 137.9, 136.0, 131.1, 131.0, 129.9, 129.2, 129.1, 128.8, 128.6, 127.2, 126.3, 124.8, 123.0, 118.0, 117.1, 38.8, 37.3, 35.4 ppm.

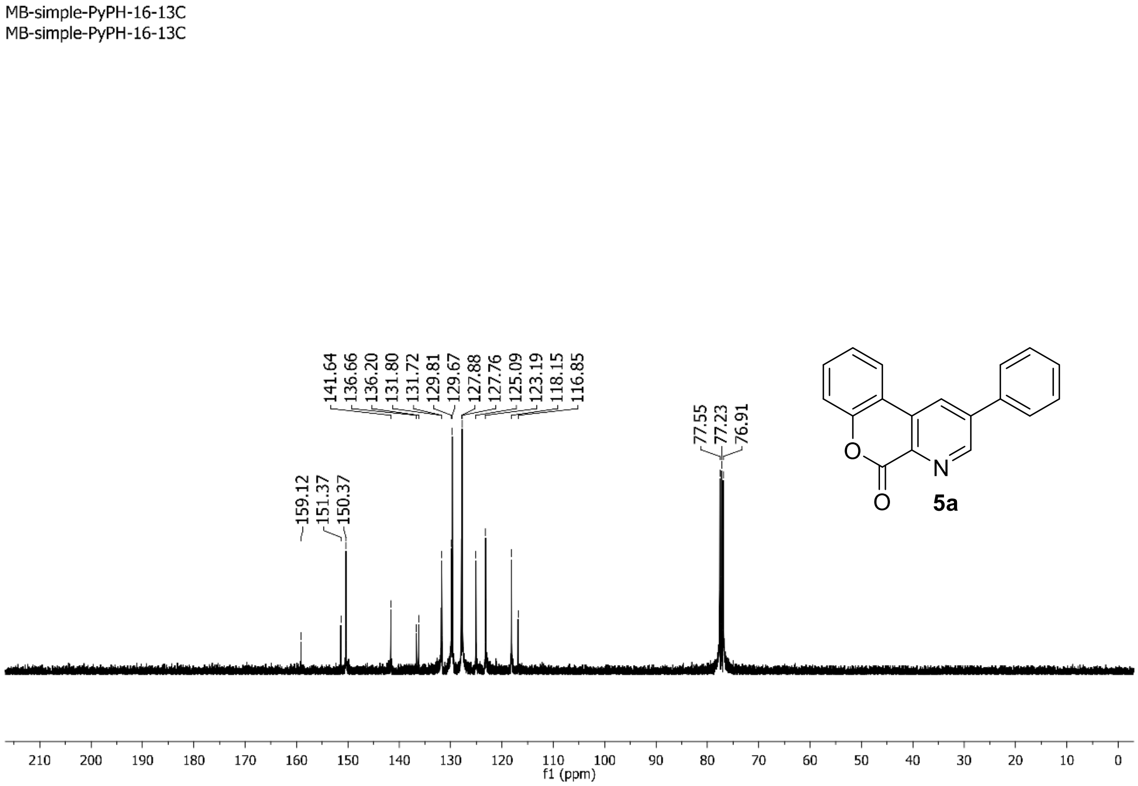
HRMS (ESI) calcd for $C_{27}H_{21}NO_2$ (M + H$^+$) = 392.1645, found 392.1651.

Elemental Analysis	Calculated	Found
MF $C_{27}H_{21}NO_2$	C 82.84	82.98
(391.47)	H 5.41	5.38
	N 3.58	3.50

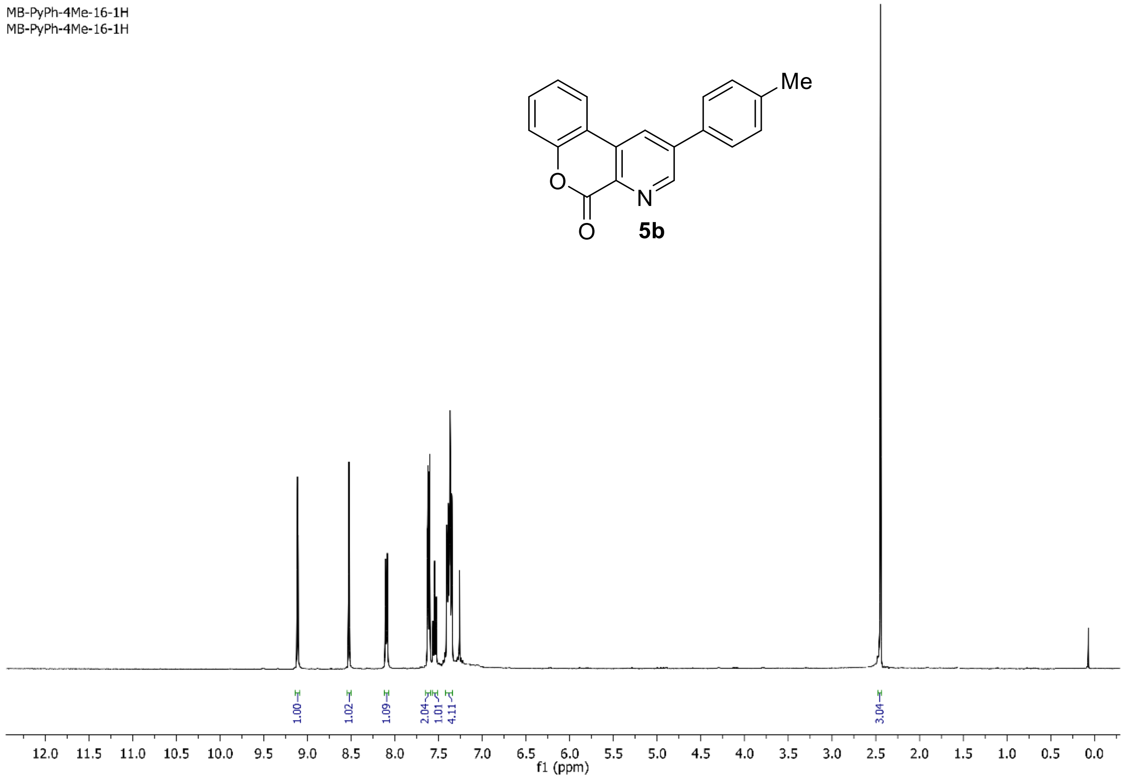
^{1}HNMR (400 MHz, CDCl$_3$): *2-Phenyl-5H-chromeno[3,4-b]pyridin-5-one* (**5a**)



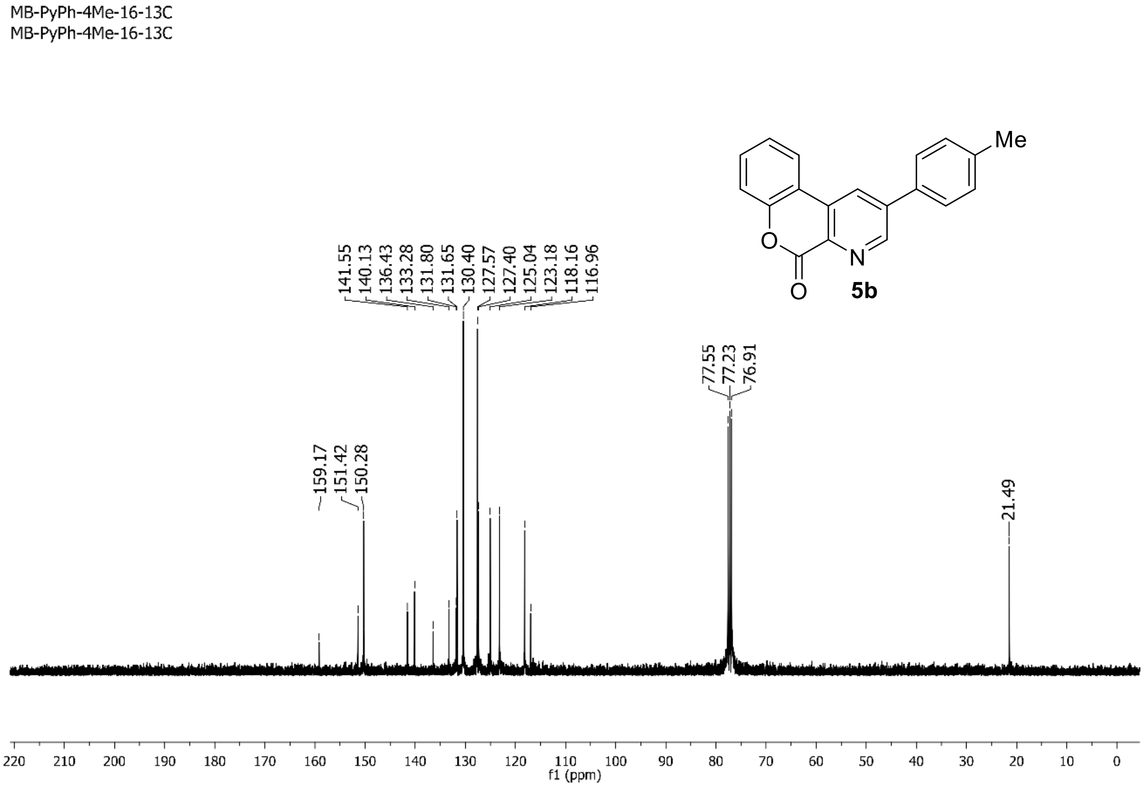
^{13}C NMR (100 MHz, CDCl$_3$): *2-Phenyl-5H-chromeno[3,4-b]pyridin-5-one* (**5a**)



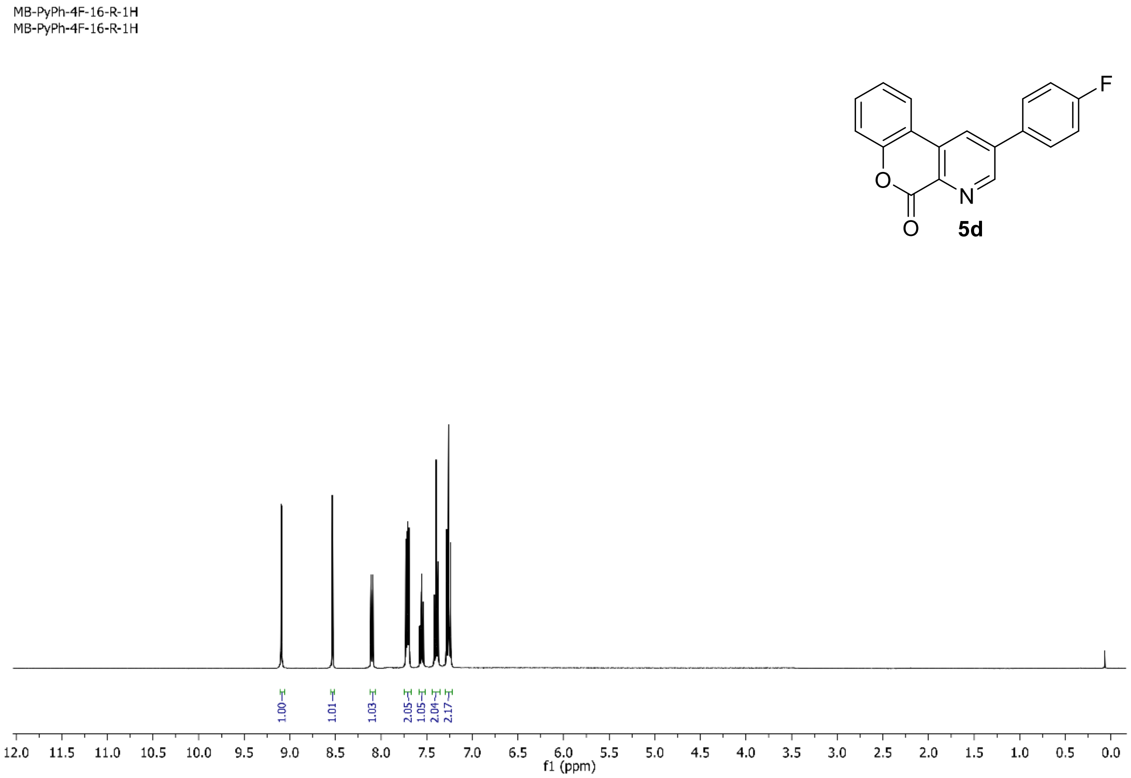
^{1}HNMR (400 MHz, CDCl$_3$): *2-(p-Tolyl)-5H-chromeno[3,4-b]pyridin-5-one* (**5b**)



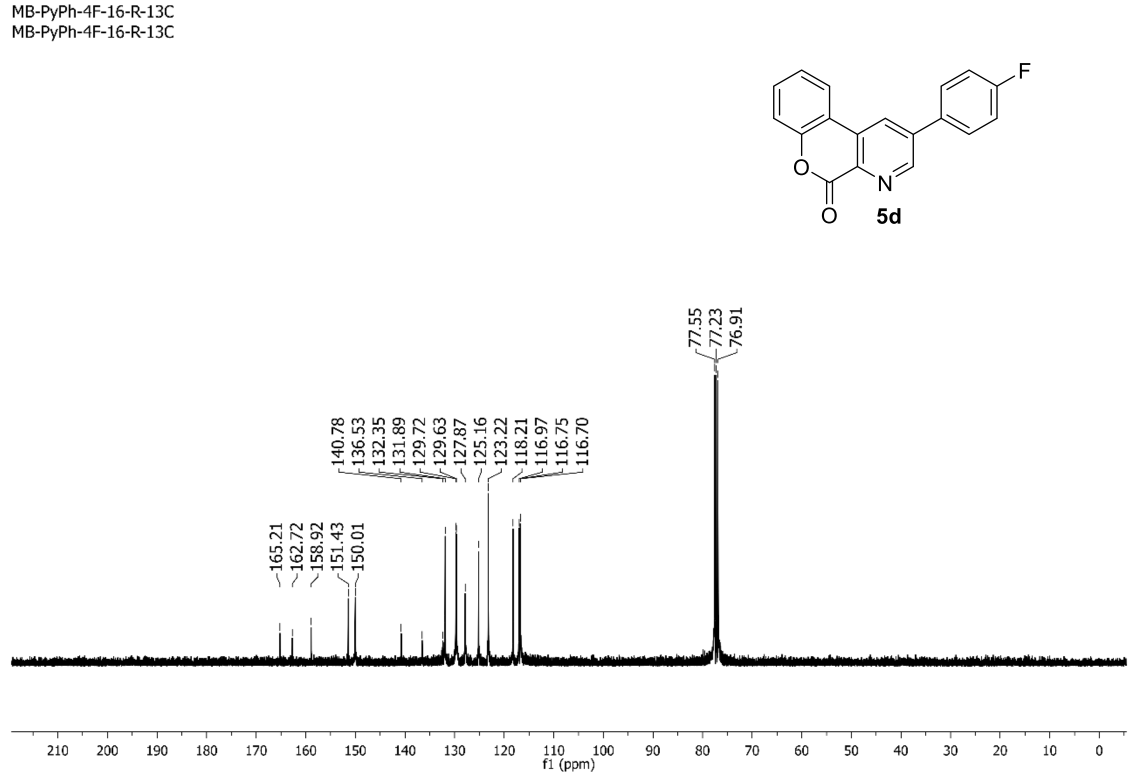
^{13}C NMR (101 MHz ,CDCl$_3$): *2-(p-Tolyl)-5H-chromeno[3,4-b]pyridin-5-one* (**5b**)



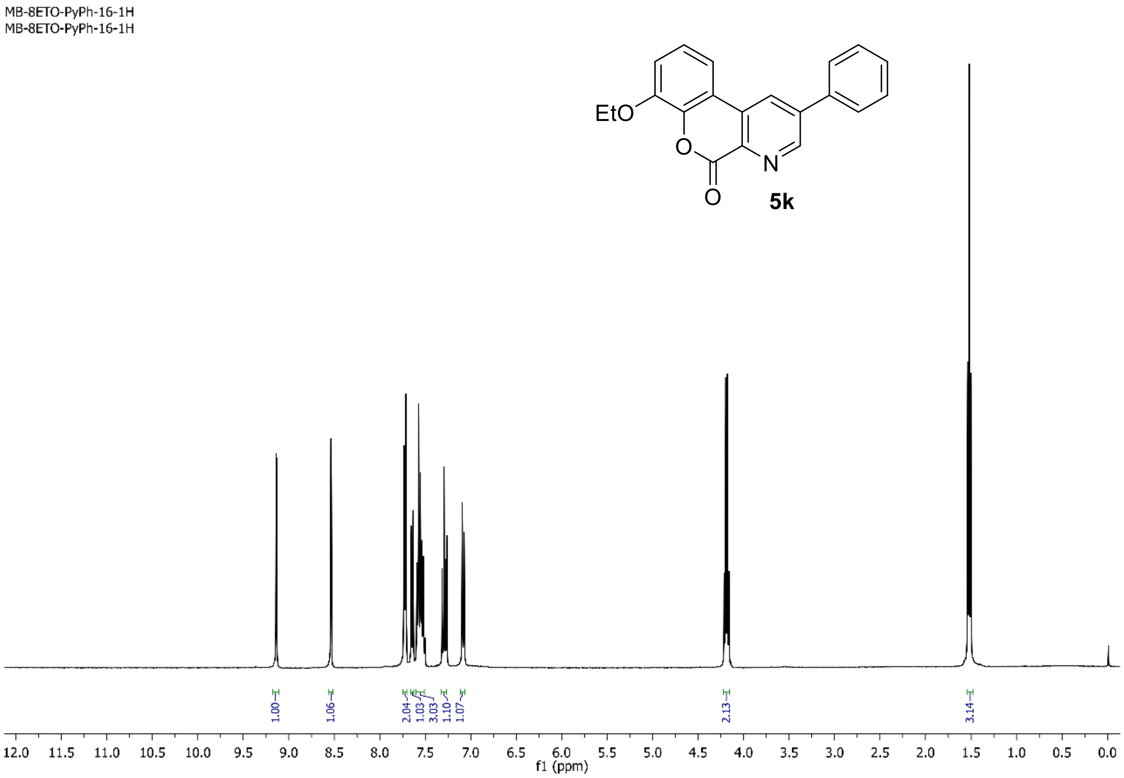
^{1}HNMR (400 MHz, $CDCl_3$): *2-(4-Fluorophenyl)-5H-chromeno[3,4-b]pyridin-5-one* (**5d**):



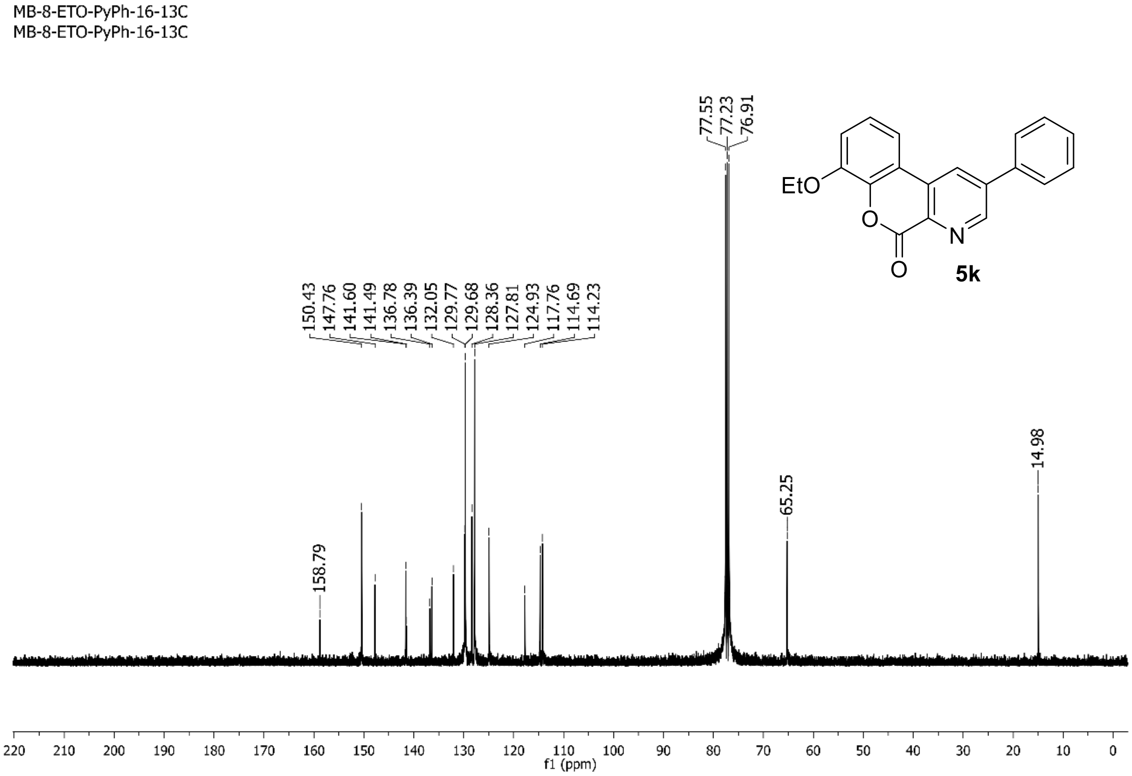
^{13}C NMR (101 MHz,$CDCl_3$): *2-(4-Fluorophenyl)-5H-chromeno[3,4-b]pyridin-5-one* (**5d**):



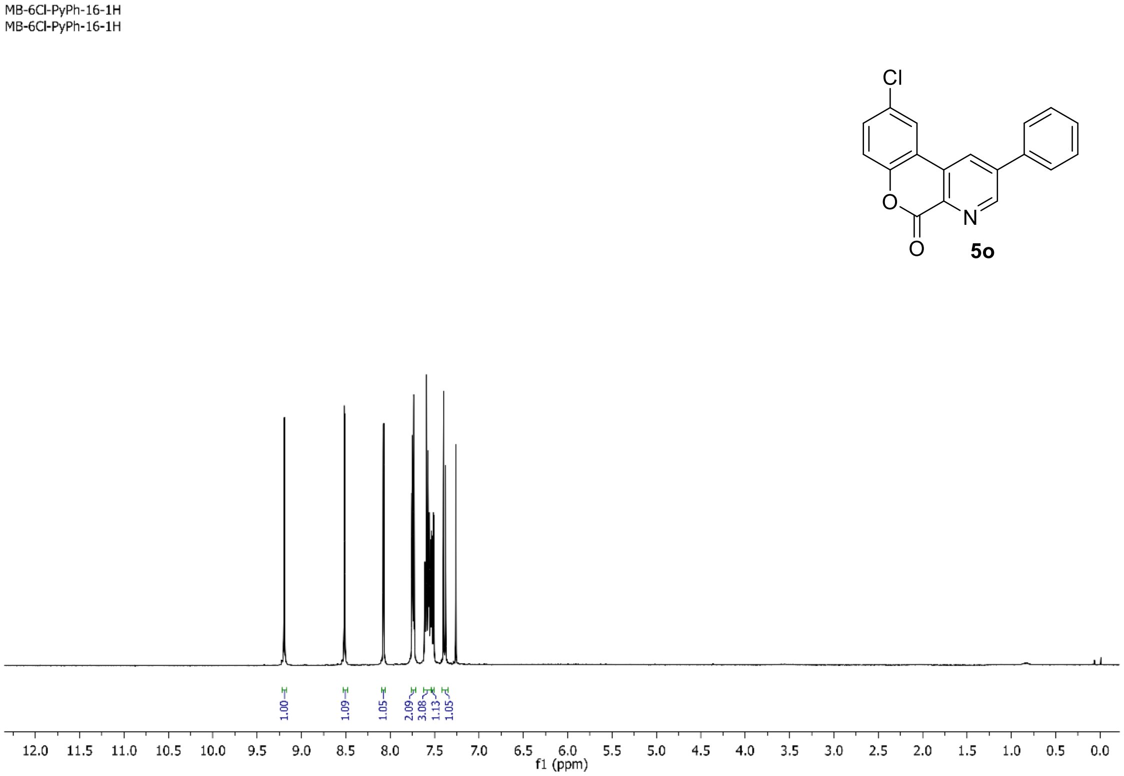
^{1}HNMR (400 MHz, CDCl$_3$): *7-Ethoxy-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (**5k**)



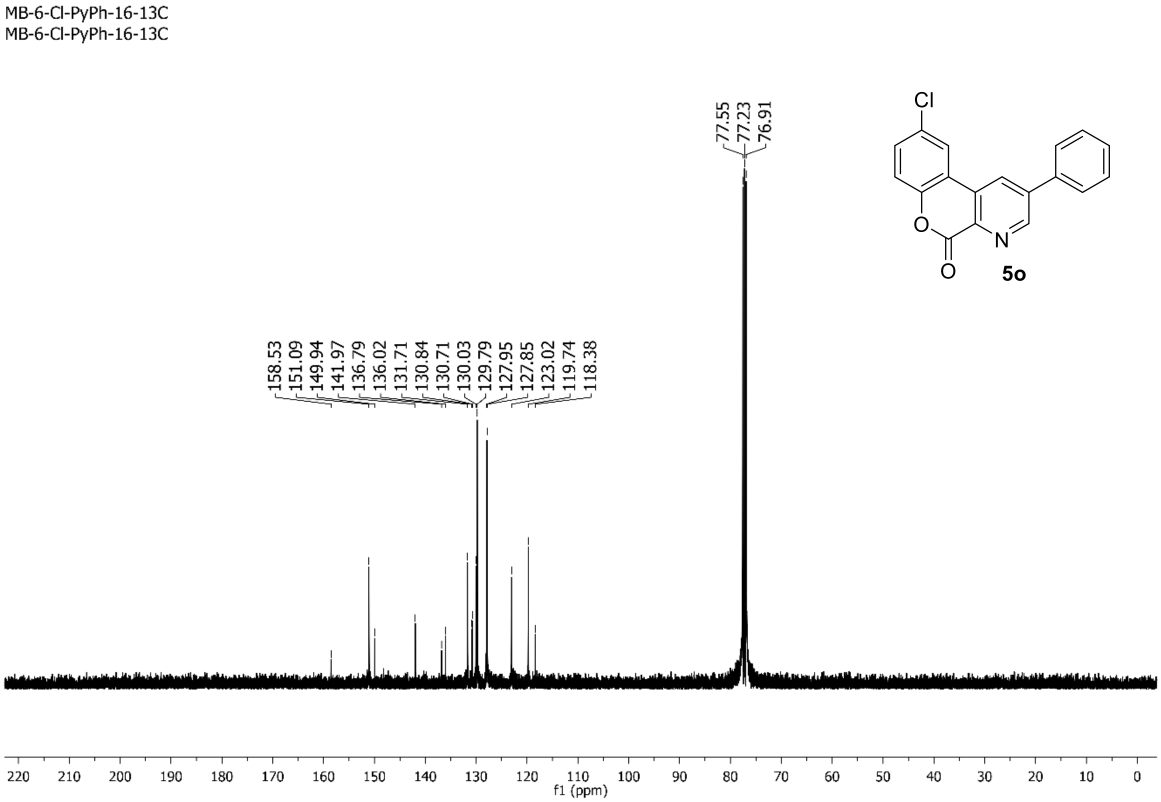
^{13}C NMR (101 MHz,CDCl$_3$): *7-Ethoxy-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (**5k**):



***^{1}HNMR (400 MHz, CDCl$_3$)**: 9-Chloro-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (**5o**)



***^{13}C NMR (101 MHz, CDCl$_3$)**: 9-Chloro-2-phenyl-5H-chromeno[3,4-b]pyridin-5-one* (**5o**)



Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

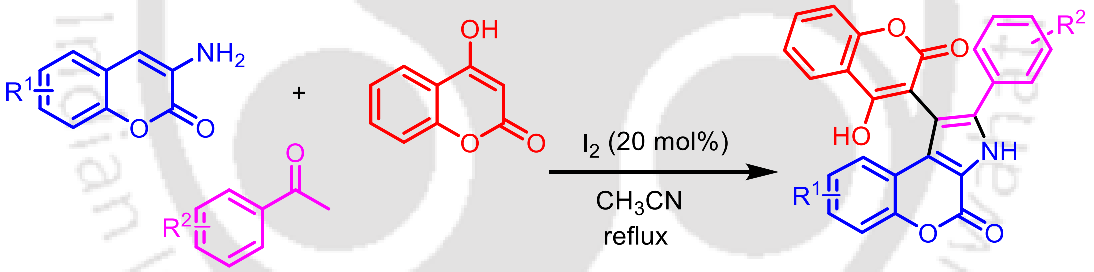
Table 6. Crystal data and structure refinements of compounds **5j**. For atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check CIF.

Parameters	**Compound 5j**
Empirical Formula	$C_{19}H_{13}NO_3$
Formula Weight	303.30
Temperature	298 K
CCDC No.	CCDC 1477324
Wavelength (A^o)	0.71073
Crystal System	triclinic
Space group	P -1
Radiation type	MoK\a
Radiation source	fine-focus sealed tube
a (A^o)	7.7181(10)
b (A^o)	8.7813(9)
c (A^o)	11.4970(10)
α(^{o})	96.875(8)
β (^{o})	105.660(10)
γ (^{o})	97.672(10)
Cell Voloume	733.60(14)
z	2
Density	1.373

F (0 0 0)	316
Theta ranges	3.25 to 24.99
Index ranges	$-9 \leq h \leq 8$, $-10 \leq k \leq 10$, $13 \leq l \leq 13$
Reflection collected	5135
Independent reflections	2584
Completeness to theta	0.998
Number of parameters	209
Number of restraints	0
Godness of fit (GOF)on F^2	0.986
Refinement method	Full-matrix least square on F2

CHAPTER III

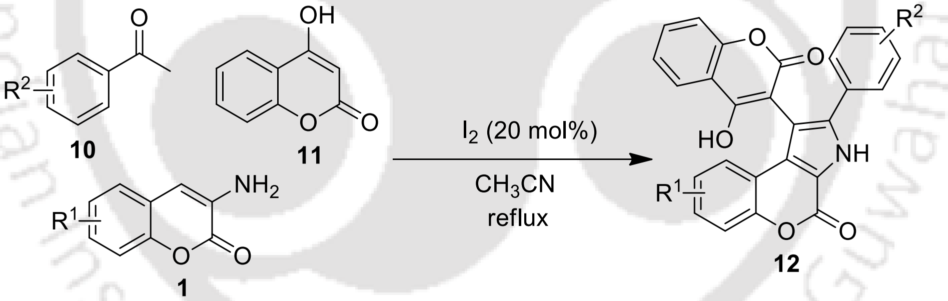
Iodine Catalyzed Multicomponent Approach to Access Various Pyrrolo(2,3-c)coumarin Derivatives using 3-Aminocoumarins, Acetophenones and 4-Hydroxycoumarin



RESULTS AND DISCUSSION

• Results and Discussion

Multicomponent reactions (MCRs) have proven to be a useful tool for the synthesis of heterocyclic compounds because of its high atom economy and bond forming efficiency. MCRs is an easy approach to accomplishe very complex and diversified molecular frameworks starting from simple and readily available starting materials.[52] Synthesis of phenylglyoxaldehyde (2-oxo-2-phenylacetaldehyde) from acetophenone using iodine and DMSO via Kornblum oxidation is a very familiar reaction.[53] Recently, phenylglyoxaldehyde derivatives have been widely used in the synthesis of heterocyclic compounds.[54] Bhuyan et al reported the synthesis of indole derivatives in presence of PTSA$\cdot$$H_2O$/$FeCl_3$ as catalyst through reductive alkylation of the ketoimine, synthesized from aniline and phenylglyoxaldehyde monohydrate, by cyclic diketones/indoles.[55] Moreover, Shi et al. demonstrated the synthesis of indole derivatives via three component reaction of phenylglyoxal monohydrate ,1,3-dicarbonyl compounds and enaminones.[56] The present chapter of the thesis describes the iodine catalyzed multicomponent access to various coumarin fused pyrrole derivatives from 3-aminocoumarins and phenylglyoxaldehydes, generated, *in situ*, from acetophenones and 4-hydroxycoumarin in presence of iodine as a catalyst (Scheme 36).

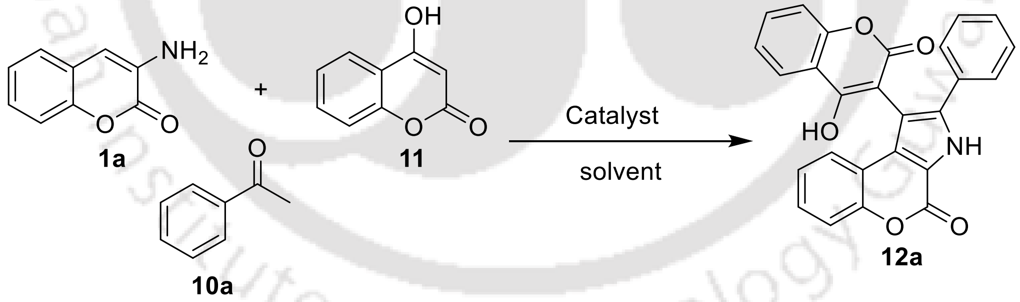


Scheme 36. Synthesis of pyrrolocoumarins

Initially, 2-oxo-2-phenylacetaldehyde was synthesized from acetophenone in DMSO using 50 mol% of iodine at 110 °C. Then a reaction was carried out using 3-aminocoumarin, 4-hydroxycoumarin and the *in situ* generated phenyglyoxaldehyde employing $FeCl_3\cdot 6H_2O$ as a catalyst in CH_3CN under reflux condition. A solid product was formed which was filtered off after completion of the reaction and the precipitate was washed with acetonitrile. The product was characterized by IR, NMR and HRMS spectra analysis. The compound was obtained in 66% yield and found to be **12a** (Table 7) showing characteristic IR absorption peaks at 1701 cm^{-1} and 1684 cm^{-1} for carbonyl groups of the two lactone rings and an ^{1}H NMR peak corresponding to proton of the pyrrole ring at δ 13.17 (see page 81 for NMR spectra of compound **12**a).

To proceed further to obtain the optimized reaction conditions various other Lewis acid catalysts were tested. The desired product (**11a**) was obtained in 64% yield using CuI as a catalyst (Table 7, entry 2). The yield increased to 76% when 10 mol% of iodine was used as catalyst (Table 7, entry 3). Loading the amount of I_2 to 5 mol%, the yield decreased to 70% (Table 7, entry 4) whereas compound **12a** was obtained in 65% yield when $Yb(OTf)_3$ was employed as a catalyst (Table 7, entry, 6). The reaction was also performed in presence of protic acid like PTSA, TfOH and AcOH in acetonitrile under reflux conditions. The expected product **12a** was obtained in 77% and 79% yield using PTSA and TfOH as catalyst respectively whereas only 40% of the product was obtained having AcOH as catalyst (Table 7, entries, 7-9). A number of solvents like EtOH, MeOH, DMSO and DMF were also screened to get the optimized conditions. A moderate to good yield was obtained in these solvents (Table 7, entries 10-13). The desired product **12a** was obtained in very poor yield at room temperature and also the yield was very low when the reaction was conducted without any catalyst (Table 7, entries 14-15). The best outcome was obtained in CH_3CN using 20 mol% I_2 as catalyst under reflux conditions (Table 7, entry 5).

Table 7. Optimization of reaction conditions[a]



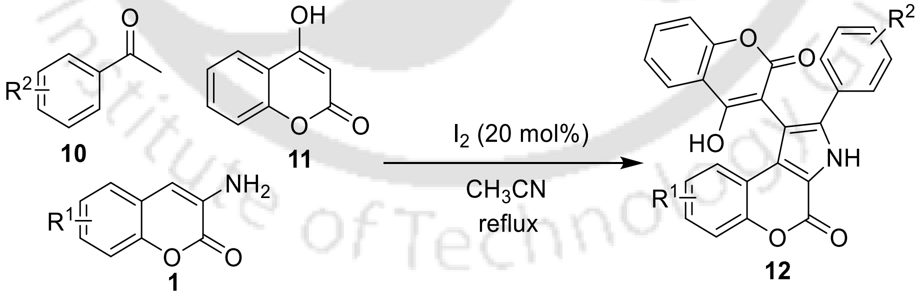
Entry	Catalyst	Solvent	Time/h	Yield (%) [b]
1	$FeCl_3.6H_2O$	CH_3CN	20	66
2	CuI	CH_3CN	20	64
3	I_2	CH_3CN	20	76
4	I_2	CH_3CN	20	70
5	**I_2**	**CH_3CN**	**20**	**83**
6	$Yb(OTf)_3$	CH_3CN	20	65
7	PTSA	CH_3CN	20	77
8	TfOH	CH_3CN	20	79

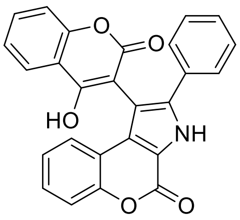
9	AcOH	CH_3CN	20	40
10	I_2	EtOH	20	70
11	I_2	MeOH	20	72
12	I_2	DMSO	20	25
13	I_2	DMF	20	20
[c]14	I_2	CH_3CN	20	10
15	….	CH_3CN	24	15

[a]All the reaction has been carried out using 0.5 mmol each 3-aminocoumrin (**1a**), acetophenone (**10a**) and 4-hydroxycoumarin (**11**) in presence of 3 mL of solvent at 80 °C. [b] Isolated yield, [c]room temp.

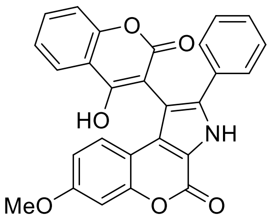
After the optimizing reaction conditions, various derivatives of pyrrolo(2,3-*c*)coumarin were synthesized in acetonitrile under reflux conditions using 20 mol% of I_2. Initially, the substituents on the 3-aminocoumarin moiety were varied. A wide range of 3-aminocoumarin moieties containing both electron donating as well as electron withdrawing substituents afforded the respective desired product in appreciable yield (Table 8, entries **12b-j**). Several derivatives of acetophenone (**10**) were also evaluated for their scope in the reaction protocols. Notably, acetophenones (**10)**, with both electron donating and electron withdrawing groups on them at different position were tolerable and desired coumarin fused pyrrole derivatives were obtained in good to excellent yields (Table 8, entries **12k-o**). For further substrate scope, 2-acetylthiophene and 2-acetonaphthone were also scrutinized and the respective desired products were obtained in 78% and 82% yields (Table 8, entries **12p** and **12q**).

Table 8. Synthesis of various pyrrolo(2,3-*c*)coumarin derivatives

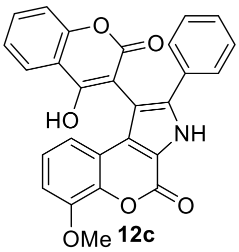




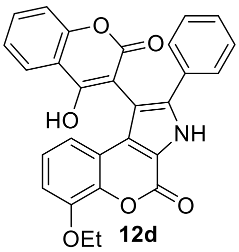
12a
18 h, 83%



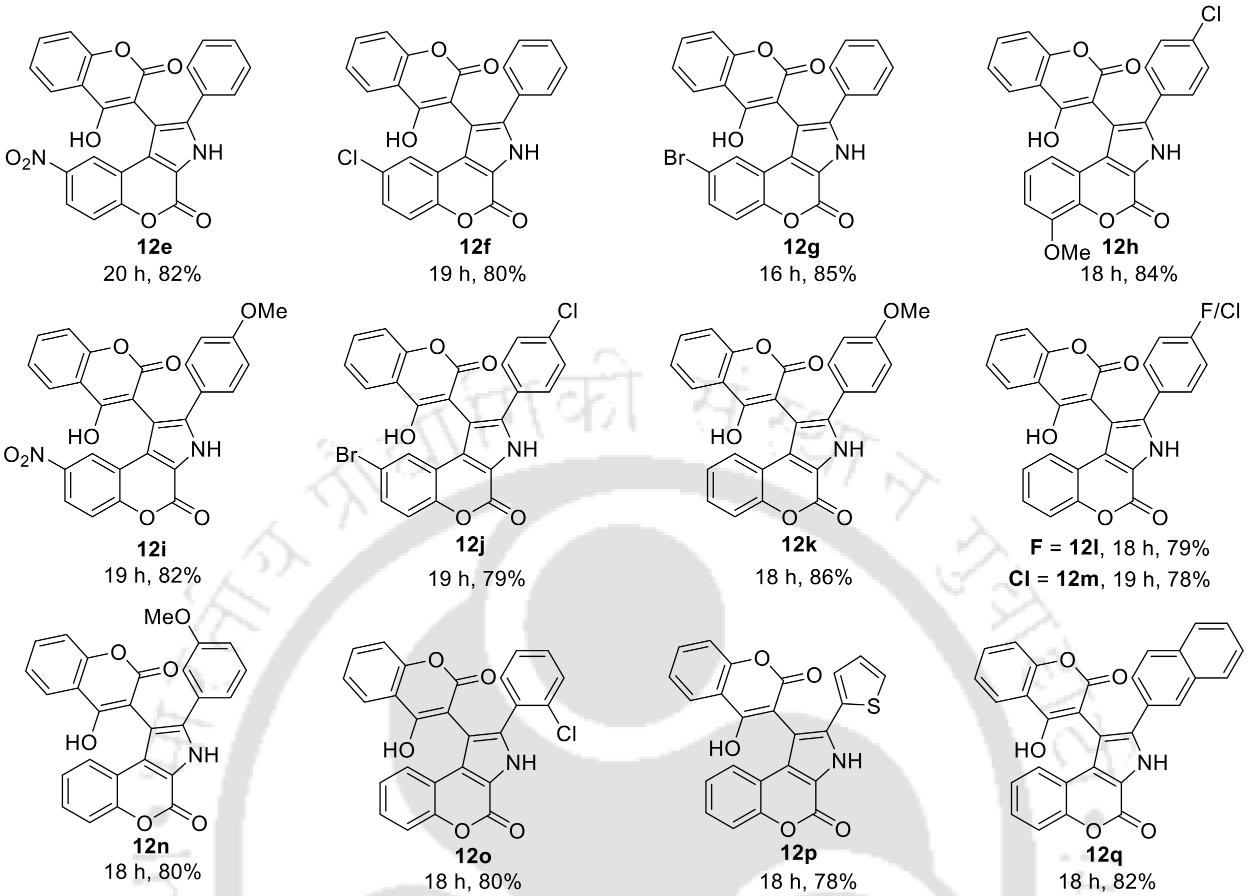
12b
19 h, 83%



12c
19 h, 80%



12d
18 h, 81%



12e
20 h, 82%

12f
19 h, 80%

12g
16 h, 85%

12h
18 h, 84%

12i
19 h, 82%

12j
19 h, 79%

12k
18 h, 86%

F = **12l**, 18 h, 79%
Cl = **12m**, 19 h, 78%

12n
18 h, 80%

12o
18 h, 80%

12p
18 h, 78%

12q
18 h, 82%

[a]All the reaction has been carried out using 0.5 mmol of each 3-aminocoumrain (**1**), acetophenone (**9**) and 4-hydroxycoumarin (**10**) in presence of 3 mL of CH_3CN and 20 mol% of Iodine at reflux condition °C. [b]Isolated yield

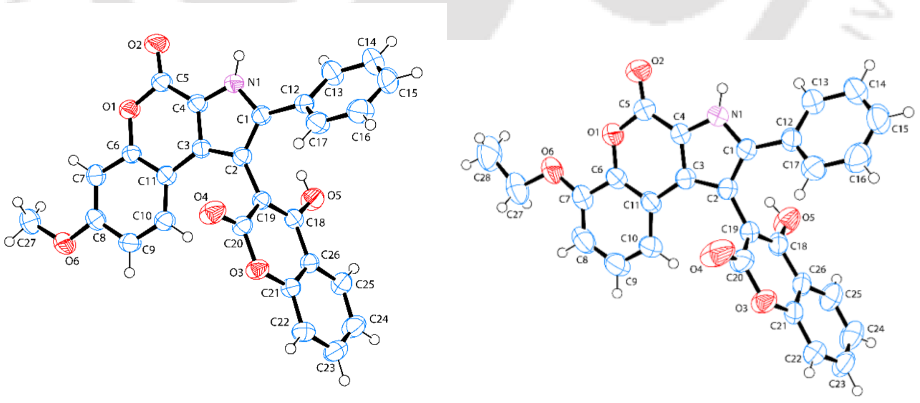
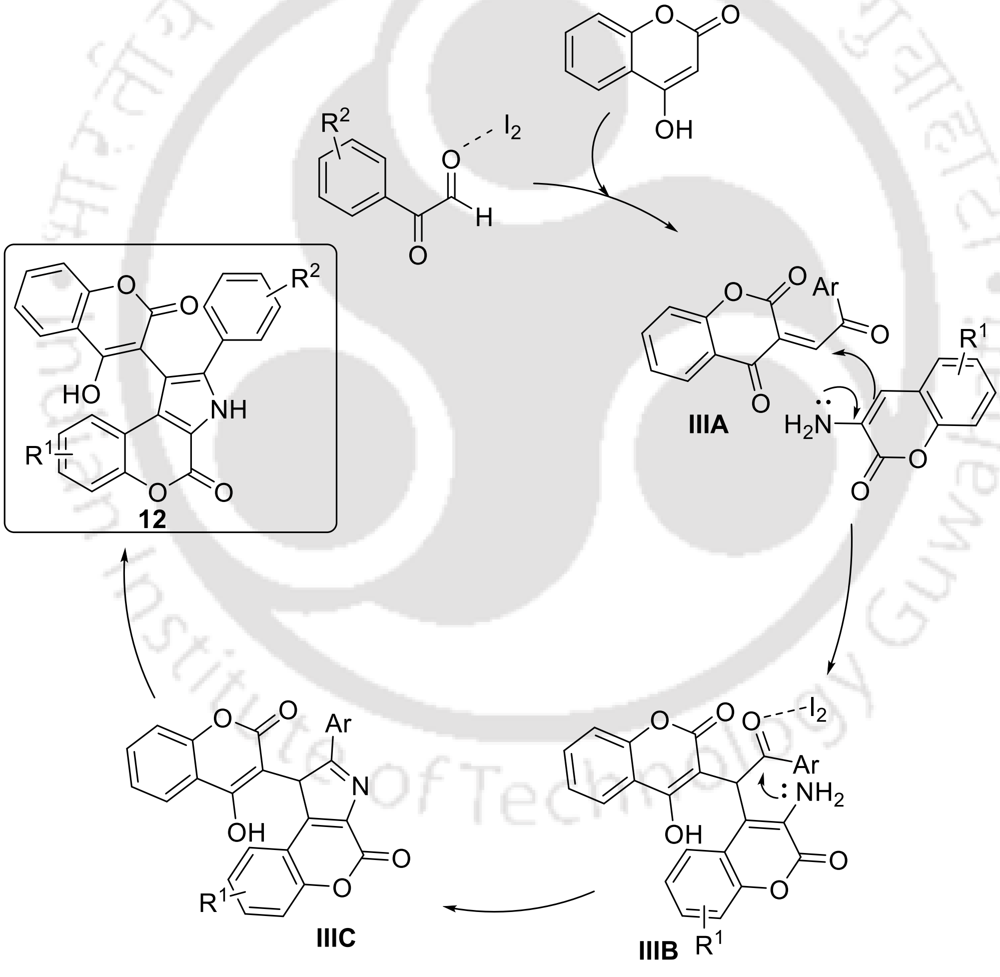


Figure 6. Crystal structure of **12b** (CCDC 1498213) Crystal structure of **12d** (CCDC 1498412)

All the compounds (**12a-q**) were characterized by IR, ^{1}H NMR, ^{13}C NMR, HRMS (see pages 69-80 for IR, NMR and HRMS data of compounds **12a-q**). Further, compounds **12b** and **12d** were unambiguously confirmed by their crystallographic structures (Figure **6**).

From the experimental results, a plausible reaction mechanism has been drawn (Scheme 37). Initially, in situ generated glyoxalaldehyde from acetophenone reacts with 4-hydroxycoumarin in presence of iodine to form a Knoevenagel product (**IIIA**), which acts as a Michael acceptor and reacts subsequently with 3-aminocoumarin to provide the intermediate **IIIB**. Then, the intermediate **IIIB** undergoes condensation reaction to give intermediate **IIIC**, which finally rearranges to the desired product **12**.



Scheme 37. Plausible reaction mechanism for the formation of **12**

In conclusion, the synthesis of various coumarin fused pyrrole derivatives using I_2 as a catalyst through multicomponent reaction has been demonstrated. The various acetophenones and 3-aminocoumarin derivatives were evaluated for the synthesis of substituted pyyrole derivatives. No need of column chromatography and aqueous work up are the salient features of the reaction protocol as the pure products were achieved simply by filtration and washing of the precipitate obtained after the stipulated time with acetonitrile.

CHAPTER III

Iodine Catalyzed Multicomponent Approach to Access Various Pyrrolo(2,3-c)coumarin Derivatives using 3-Aminocoumarins, Acetophenones and 4-Hydroxycoumarin

EXPERIMENTAL SECTION

• Experimental Section

General procedure for the synthesis of various 1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one (12a-q):

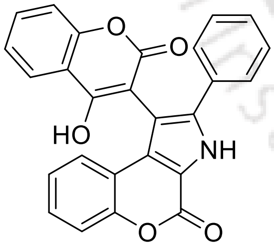
Step I

In a 25 mL round bottomed flask was taken 0.50 mmol of acetophenone, 3 mL of DSMO, and 0.50 equivalent of iodine. The reaction mixture was heated at 110 °C till the acetophenone disappears to give 2-oxo-2-phenylacetaldehyde as a single product. The reaction mixture was extracted with ethyl acetate (15 x 2 mL) and the organic layer was washed with $Na_2S_2O_3$ and brine solution. The organic layer dried over anhydrous Na_2SO_4. After removing the solvent, the aldehyde was used in next step without further purification.

Step II

Then, 0.50 mmol of each 4-hydroxycoumarin (**11**) and 3-aminocoumarin (**1**) were taken into a 25 mL round bottomed flask containing the 2-oxo-2-phenylacetaldehyde, synthesized in step I. Subsequently 4 mL of acetonitrile and 20 mol% of iodine were added into it. The content was refluxed on a preheated oil bath kept on a magnetic stirrer for 18-20 h. The solid precipitate obtained at the end which was filtered off and washed with CH_3CN to get the pure products **12a-q**.

1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one **(12a):**



12a

Reaction Time: 18 h **Colour & State:** pale yellow solid

Yield: 83% (175 mg) **Melting Point:** > 300 °C

IR (KBr): 3481.46, 3206.17, 1701.24, 1684.42, 1186.38, 1128.59, 1042.13 cm^{-1}.

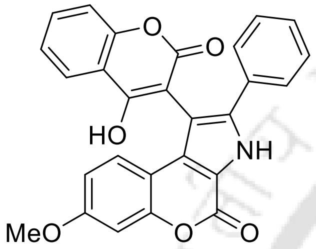
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 13.17 (s, 1 H), 7.91 (d, *J* = 7.7 Hz, 1 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.56 (t, *J* = 6.5 Hz, 3 H), 7.47 (t, *J* = 9 Hz, 2 H), 7.38 (t, *J* = 7.5 Hz, 4 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.19 (t, *J* = 7.5 Hz, 1 H) ppm.

^{13}C NMR (150 MHz, DMSO-d$_6$): δ 163.4, 162.1, 154.3, 153.0, 150.9, 142.3, 133.0, 130.9, 128.8, 128.7, 128.6, 127.9, 127.8, 124.6, 124.4, 124.1, 122.5, 118.3, 118.2, 117.1, 116.6, 116.0, 106.8, 98.4 ppm.

HRMS (ESI) calcd for $C_{27}H_{15}NO_5$ (M + H^+) = 422.1023, found 422.1028.

Elemental Analysis	Calculated	Found
MF $C_{26}H_{15}NO_5$	C 74.11	74.26
(421.41)	H 3.59	3.66
	N 3.32	3.41

***1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-7-methoxy-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (12b):**



12b

Reaction Time: 19 h **Colour & State:** brown solid

Yield: 83% (187 mg) **Melting Point:** > 300 °C

IR (KBr): 3480.96, 3311.64, 1717.06, 1617.46, 1242.79, 1125.00, 1111.20, 1026.12 cm^{-1}.

^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.02 (s, 1 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 7.69 (t, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 7.3 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.38 (m, 5 H), 7.05 (s, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 3.78 (s, 3 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.5, 162.0, 159.1, 154.4, 153.0, 152.2, 142.2, 132.9, 131.0, 129.1, 128.6, 127.6, 124.3, 124.0, 123.2, 116.6, 116.0, 115.7, 112.0, 111.3, 106.1, 101.7, 98.2, 55.6 ppm.

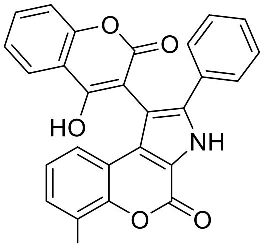
HRMS (ESI) calcd for $C_{27}H_{17}NO_6$ (M + H^+) = 452.1129, found 452.1134.

Elemental Analysis	Calculated	Found
MF $C_{27}H_{17}NO_6$	C 71.84	71.96
(451.43)	H 3.80	3.85
	N 3.10	3.17

***1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-6-methoxy-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (12c)**:

Reaction Time: 19 h **Colour & State:** white solid

Yield: 80% (180 mg) **Melting Point:** > 300 °C



12c

IR (KBr): 3381.03, 3236.70, 1741.87, 1686.99, 1269.39, 1207.34, 1091.59 cm^{-1}.

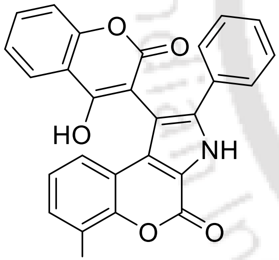
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.19 (s, 1 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 7.70 (t, *J* = 7.8 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 2 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 3 H), 7.33 (m, 1 H), 7.11 (m, 3 H), 3.91 (s, 3 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.2, 161.9, 153.8, 152.9, 147.3, 142.2, 140.1, 132.9, 130.8, 128.6, 127.7, 124.5, 124.3, 124.0, 118.8, 117.0, 116.5, 115.8, 113.8, 110.4, 106.8, 98.3, 55.9 ppm.

HRMS (ESI) calcd for $C_{27}H_{17}NO_6$ (M + H$^+$) = 452.1129, found 452.1135.

Elemental Analysis	Calculated	Found
MF $C_{27}H_{17}NO_6$	C 71.84	71.97
(451.43)	H 3.80	3.77
	N 3.10	3.18

6-Ethoxy-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one (12d):



12d

Reaction Time: 18 h **Colour & State:** white solid

Yield: 81% (195 mg) **Melting Point:** > 300 °C

IR (KBr): 3410.53, 3211.72, 1738.08, 1695.86, 1271.88, 1193.31, 1085.82 cm^{-1}.

^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.20 (s, 1 H), 11.67 (s, 1 H), 7.90 (d, *J* = 7.7 Hz, 1 H), 7.70 (t, *J* = 7.6 Hz, 1 H), 7.54 (d, *J* = 7.1 Hz, 2 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.39 (t, *J* = 7.0 Hz, 3 H), 7.34 (d, *J* = 6.6 Hz, 1 H), 7.08 (d, *J* = 11.2 Hz, 3 H), 4.15 (q, *J* = 6.3 Hz, 2 H), 1.42 (t, *J* = 5.9 Hz, 3 H) ppm.

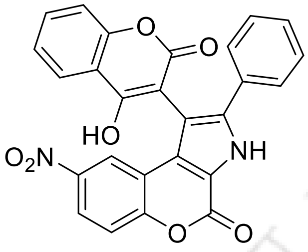
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.2, 162.0, 154.0, 152.9, 146.6, 142.2, 140.2, 133.0, 130.8, 128.7, 127.7, 124.5, 124.4, 124.0, 118.9, 117.1, 116.6, 115.8, 113.7, 111.3, 106.7, 98.4, 64.2,14.8 ppm.

HRMS (ESI) calcd for $C_{28}H_{19}NO_6$ (M+H$^+$) = 466.1285, found 466.1293.

Elemental Analysis	Calculated	Found

MF $C_{28}H_{19}NO_6$	C 72.25	72.38
(465.46)	H 4.11	4.06
	N 3.01	2.92

1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-8-nitro-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one (12e):



12e

Reaction Time: 20 h **Colour & State:** pale yellow

Yield: 82% (191 mg) **Melting Point:** > 300 °C

IR (KBr): 3461.53, 3200.16, 1717.78, 1684.03, 1172.41, 1114.47, 1001.09 cm^{-1}.

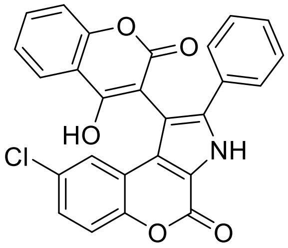
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.46 (s, 1 H), 8.33 (s, 1 H), 8.22 (d, *J* = 9.1 Hz, 1 H), 7.93 (d, *J* = 7.4 Hz, 1 H), 7.71 (m, 2 H), 7.59 (d, *J* = 6.8 Hz, 2 H), 7.52 (d, *J* = 8.1 Hz, 1 H), 7.39 (m, 4 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 164.2, 161.9, 154.6, 153.03, 152.99, 143.5, 142.9, 133.1, 130.6, 128.9, 128.7, 127.7, 126.9, 124.4, 124.1, 122.8, 118.6, 118.4, 118.0, 116.8, 116.5, 116.0, 107.6, 97.2 ppm.

HRMS (ESI) calcd for $C_{26}H_{14}N_2O_7$ (M+H$^+$) = 467.0874, found 467.0876.

Elemental Analysis	Calculated	Found
MF $C_{26}H_{14}N_2O_7$	C 66.96	66.83
(466.40)	H 3.03	2.98
	N 6.01	6.10

8-Chloro-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one (12f):



12f

Reaction Time: 19 h **Colour& State:** pale yellow solid

Yield: 80% (182 mg) **Melting Point:**> 300 °C

IR (KBr): 3442.42, 3185.74, 1700.43, 1653.91, 1210.41, 1002.06 cm^{-1}.

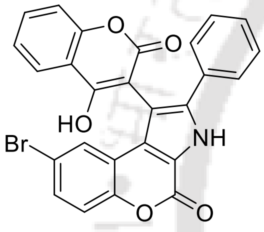
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.33 (s, 1 H), 7.92 (d, *J* = 7.8 Hz, 1 H), 7.71 (t, *J* = 7.8 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 2 H), 7.51 (t, *J* = 7.8 Hz, 2 H), 7.38 (m, 6 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.8, 161.9, 153.7, 152.9, 149.5, 142.5, 133.1, 130.7, 128.8, 128.7, 128.2, 127.7, 127.5, 127.1, 124.4, 124.1, 121.5, 119.7, 119.0, 117.1, 116.6, 115.9, 107.1, 97.6 ppm.

HRMS (ESI): calcd for $C_{26}H_{14}ClNO_5$ (M+H$^+$) = 456.0633, found 456.0636.

Elemental Analysis	Calculated	Found
MF $C_{26}H_{14}ClNO_5$	C 68.51	68.62
(455.85)	H 3.10	3.14
	N 3.07	3.02

***8-Bromo-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (12g):**



12g

Reaction Time: 16 h **Colour & State:** pale yellow solid

Yield: 85% (212 mg) **Melting Point:** > 300 °C

IR (KBr): 3394.82, 1723.95, 1270.45, 1158.59, 1111.09, 993.35 cm^{-1}.

^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.33 (s, 1 H), 7.92 (d, *J* = 7.9 Hz, 1 H), 7.71 (t, J = 7.8 Hz, 1 H), 7.54 (m, 4 H), 7.45 (m, 2 H), 7.35 (m, 4 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.9, 161.9, 153.7, 152.9, 149.9, 142.5, 133.1, 130.7, 130.3, 128.8, 128.7, 127.7, 127.0, 124.6, 124.5, 124.1, 120.2, 119.4, 117.1, 116.6, 116.2, 115.9, 107.1, 97.5 ppm.

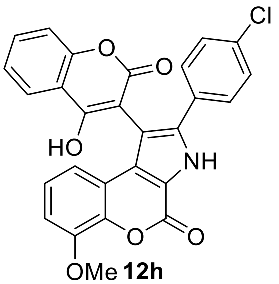
HRMS (ESI): calcd for $C_{26}H_{14}BrNO_5$ (M+H$^+$) = 500.0128, found 500.0128.

Elemental Analysis	Calculated	Found
MF $C_{26}H_{14}BrNO_5$	C 62.42	62.56
(500.30)	H 2.82	2.78
	N 2.82	2.72

***2-(4-Chlorophenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-6-methoxychromeno[3,4-b]pyrrol-4(3H)-one* (12h)**:

Reaction Time: 18 h **Colour & State:** white solid

Yield: 84% (196 mg) **Melting Point:** > 300 °C



12h

IR (KBr): 3517.04, 3203.39, 1713.08, 1678.80, 1275.14, 1106.66, 1041.03 cm^{-1}.

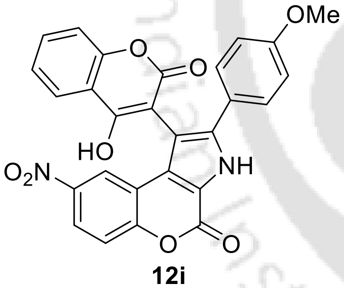
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.28 (s, 1 H), 7.90 (d, *J* = 7.9 Hz, 1 H), 7.70 (t, *J* = 7.8 Hz, 1 H), 7.56 (m, 2 H), 7.48 (m, 3 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.11 (m, 3 H), 3.91 (s, 3 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.5, 161.9, 153.8, 153.0, 147.4, 140.9, 140.1, 133.5, 132.9, 129.7, 129.4, 128.8, 128.6, 124.5, 124.3, 124.0, 118.8, 117.2, 116.6, 115.9, 113.8, 110.4, 107.3, 97.9, 55.9 ppm.

HRMS (ESI): calcd for $C_{27}H_{16}ClNO_6$ (M+H$^+$) = 486.0739, found 486.0735.

Elemental Analysis	Calculated	Found
MF $C_{27}H_{16}ClNO_6$	C 66.74	66.60
(485.88)	H 3.32	3.36
	N 2.88	2.96

***1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-(4-methoxyphenyl)-8-nitrochromeno[3,4-b]pyrrol-4(3H)-one* (12i):**



12i

Reaction Time: 19 h **Colour & State:** pale yellow solid

Yield: 82% (203 mg) **Melting Point:** > 300 °C

IR (KBr): 3508.71, 3325.52, 1738.09, 1675.74, 1262.45, 1127.55, 1042.58, 995.32 cm^{-1}.

^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.34 (s, 1 H), 8.32 (s, 1 H), 8.21 (d, *J* = 9.1 Hz, 1 H), 7.94 (d, *J* = 7.8 Hz, 1 H), 7.73 (t, *J* = 7.8 Hz, 1 H), 7.68 (d, *J* = 9.1 Hz, 1 H), 7.53 (t, *J* = 6.3 Hz, 3 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 3.74 (s, 3 H) ppm.

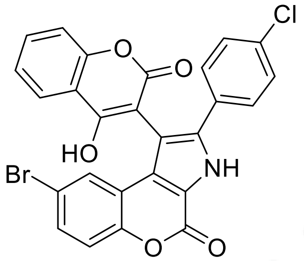
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 164.5, 162.2, 160.1, 155.0, 153.4, 153.3, 143.8, 143.4, 133.4, 129.4, 127.4, 124.7, 124.5, 123.3, 123.1, 119.0, 118.7, 118.3, 116.9, 116.7, 116.4, 114.6, 107.2, 97.8, 55.6 ppm.

HRMS (ESI): calcd for $C_{27}H_{16}N_2O_8$ (M+H$^+$) = 497.0979, found 497.0985.

Elemental Analysis	Calculated	Found
MF $C_{27}H_{16}N_2O_8$	C 65.33	65.19

(496.43)	H 3.25	3.20
	N 5.64	5.55

***8-Bromo-2-(4-chlorophenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)chromeno[3,4-b]pyrrol-4(3H)-one* (12j):**



12j

Reaction Time: 19 h **Colour & State:** white solid

Yield: 79% (210 mg) **Melting Point:** > 300 °C

IR (KBr): 3550.35, 3114.57, 1733.26, 1674.18, 1270.11, 1156.91, 998.05 cm^{-1}.

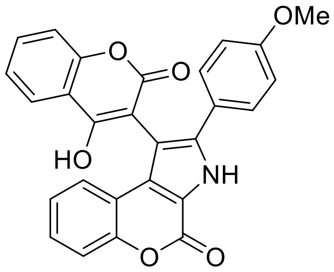
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.41 (s, 1 H), 7.93 (d, *J* = 7.9 Hz, 1 H), 7.71 (t, *J* = 7.8 Hz, 1 H), 7.57 (s, 1 H), 7.54 (m, 3 H), 7.54 (d, *J* = 8.3Hz, 1 H), 7.45 (m, 3 H), 7.40 (t, *J* = 7.7 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.9, 161.8, 153.6, 152.9, 149.8, 141.2, 133.6, 133.1, 130.3, 129.5, 129.4, 128.8, 126.9, 124.6, 124.4, 124.1, 120.1, 119.3, 117.3, 116.6, 116.2, 115.9, 107.4, 97.3 ppm.

HRMS (ESI): calcd for $C_{26}H_{13}BrClNO_5$ (M+H$^+$) = 533.9738, found 533.9732.

Elemental Analysis	**Calculated**	**Found**
MF $C_{26}H_{13}BrClNO_5$	C 58.40	58.56
(534.75)	H 2.45	2.41
	N 2.62	2.53

***1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-(4-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3H)-one* (12k):**



12k

Reaction Time: 18 h **Colour & State:** white solid

Yield: 86% (194 mg) **Melting Point:** > 300 °C

IR (KBr): 3442.30, 3181.51, 1699.71, 1671.24, 1253.67, 1184.09, 1111.45 cm^{-1}.

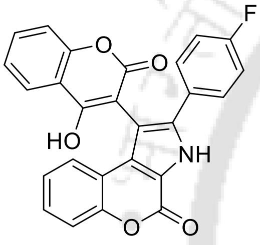
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.04 (s, 1 H), 7.90 (d, *J* = 7.9 Hz, 1 H), 7.70 (t, *J* = 7.7 Hz, 1 H), 7.49 (m, 5 H), 7.38 (m, 2 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 6.95 (d, *J* = 8.5 Hz, 2 H), 3.73 (s, 3 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.5, 162.0, 159.5, 154.1, 153.0, 150.8, 142.2, 132.8, 129.0, 128.5, 127, 124.5, 124.2, 124.0, 123.2, 122.4, 118.3, 117.0, 116.6, 116.5, 114.1, 106.1, 98.1, 55.2 ppm.

HRMS (ESI): calcd for $C_{27}H_{17}NO_6$ (M+H$^+$) = 452.1129, found 452.1129.

Elemental Analysis	Calculated	Found
MF $C_{27}H_{17}NO_6$	C 71.84	71.96
(451.43)	H 3.80	3.85
	N 3.10	3.01

2-(4-Fluorophenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)chromeno[3,4-b]pyrrol-4(3H)-one (12l):



12l

Reaction Time: 18 h **Colour & State:** white solid

Yield: 79% (173 mg) **Melting Point:** > 300 °C

IR (KBr): 3480.96, 3211.72, 1699.00, 1684.42, 1269.77, 1110.34, 1040.04 cm^{-1}.

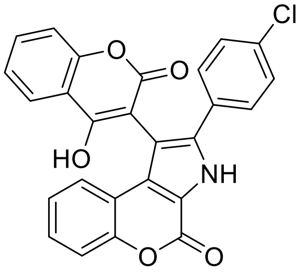
^{1}HNMR (600 MHz, DMSO-d$_6$): δ 13.18 (s, 1 H), 7.90 (d, *J* = 7.7 Hz, 1 H), 7.70 (t, *J* = 7.7 Hz, 1 H), 7.58 (dd, *J* = 8.3, 5.6 Hz, 2 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.47 (t, J = 9.0 Hz, 2 H), 7.39 (t, *J* = 7.6 Hz, 2 H), 7.25 (t, *J* = 8.8 Hz, 2 H), 7.20 (t, *J* = 7.5 Hz, 1 H).ppm.

^{13}C NMR (150 MHz, DMSO-d$_6$): δ 163.6, 163.0, 162.0, 161.4, 154.2, 153.0, 150.8, 141.2, 132.9, 130.0, 129.9, 128.4, 127.9, 127.3, 124.6, 124.3, 124.0, 122.4, 118.2, 117.0, 116.9, 116.6, 116.0, 115.8, 115.6, 106.8, 98.0 ppm.

HRMS (ESI): calcd for $C_{26}H_{14}FNO_5$ (M+H$^+$) = 440.0929, found 440.0923.

Elemental Analysis	Calculated	Found
MF $C_{26}H_{14}FNO_5$	C 71.07	71.22
(439.40)	H 3.21	3.15
	N 3.19	3.11

***2-(4-Chlorophenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)chromeno[3,4-b]pyrrol-4(3H)-one* (12m):**



12m

Reaction Time: 19 h **Colour & State:** pale yellow solid

Yield: 78% (177 mg) **Melting Point:** > 300 °C

IR (KBr): 3481.51, 3160.55, 1699.74, 1623.45, 1282.53, 1186.65, 1040.38, 1013.75 cm^{-1}.

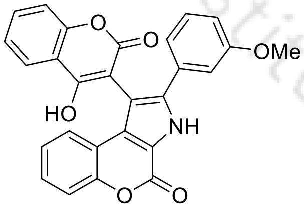
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.27 (s, 1 H), 7.91 (d, *J* = 7.2 Hz, 1 H), 7.69 (d, *J* = 6.7 Hz, 1 H), 7.55 (s, 3 H), 7.47 (d, *J* = 7.6 Hz, 4 H), 7.39 (s, 2 H), 7.20 (s, 1 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.5, 161.9, 154.1, 153.0, 150.8, 140.8, 133.4, 132.9, 129.7, 129.4, 128.7, 128.4, 127.8, 124.6, 124.2, 124.0, 122.5, 118.1, 117.2, 117.0, 116.6, 116.0, 107.1, 97.8 ppm.

HRMS (ESI): calcd for $C_{26}H_{14}ClNO_5$ (M+H$^+$) = 456.0633, found 456.0633.

Elemental Analysis	Calculated	Found
MF $C_{26}H_{14}ClNO_5$	C 68.51	68.69
(455.85)	H 3.10	3.00
	N 3.07	3.14

***1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-(3-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3H)-one* (12n):**



12n

Reaction Time: 18 h **Colour & State:** pale yellow solid

Yield: 80% (180 mg) **Melting Point:** > 300 °C

IR (KBr): 3448.09, 3258.17, 1706.03, 1683.46, 1231.28, 1130.73 cm^{-1}.

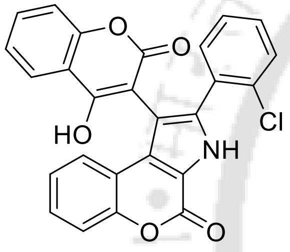
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.16 (s, 1 H), 7.91 (d, *J* = 7.1 Hz, 1 H), 7.70 (d, *J* = 7.2 Hz, 1 H), 7.54 (d, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 8.8 Hz, 2 H), 7.39 (s, 2 H), 7.26 (d, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 7.7 Hz, 2 H), 7.11 (d, *J* = 7.3 Hz, 1 H), 6.89 (d, *J* = 7.8 Hz, 1 H), 3.68 (s, 3 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.5, 162.0, 159.2, 154.2, 153.0, 150.8, 141.8, 132.9, 132.0, 129.8, 128.5, 127.9, 124.6, 124.3, 124.0, 122.5, 119.8, 118.2, 117.02, 116.95, 116.6, 116.0, 114.6, 112.9, 106.9, 98.3, 55.0 ppm

HRMS (ESI): calcd for $C_{27}H_{17}NO_6$ (M+H$^+$) = 452.1129 (found 452.1124).

Elemental Analysis	Calculated	Found
MF $C_{27}H_{17}NO_6$	C 71.84	71.95
(451.43)	H 3.80	3.75
	N 3.10	3.16

***2-(2-Chlorophenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)chromeno[3,4-b]pyrrol-4(3H)-one* (12o):**



12o

Reaction Time: 18 h **Colour & State:** pale yellow solid

Yield: 80% (182 mg) **Melting Point:** > 300 °C

IR (KBr): 3504.06, 3185.45, 1700.96, 1619.85, 1280.85, 1110.98 cm^{-1}.

^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.18 (s, 1 H), 7.85 (d, *J* = 7.8 Hz, 1 H), 7.64 (t, *J* = 7.7 Hz, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.45 (m, 3 H), 7.36 (m, 5 H), 7.21 (t, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.4, 161.8, 154.6, 153.2, 151.2, 140.1, 133.3, 133.1, 132.5, 131.1, 130.6, 130.0, 128.23, 128.18, 127.3, 124.9, 124.5, 124.3, 123.3, 118.7, 117.3, 117.2, 116.8, 116.4, 109.3, 98.1 ppm.

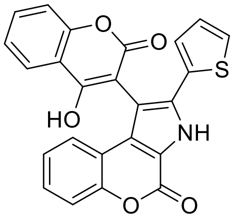
HRMS (ESI): calcd for $C_{26}H_{14}ClNO_5$ (M+H$^+$) = 456.0633, found 456.0639.

Elemental Analysis	Calculated	Found
MF $C_{26}H_{14}ClNO_5$	C 68.51	68.40
(455.85)	H 3.10	3.02
	N 3.07	3.03

Elemental Analysis	Calculated	Found
MF $C_{30}H_{17}NO_5$	C 76.43	76.56
(471.46)	H 3.63	3.68

	N 2.97	3.04

1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-(thiophen-2-yl)chromeno[3,4-b]pyrrol-4(3H)-one (12p):



12p

Reaction Time: 18 h **Colour & State:** white solid

Yield: 78% (167 mg) **Melting Point:** > 300 °C

IR (KBr): 3445.90, 3168.01, 1706.35, 1680.36, 1191.68, 1128.92, 1007.86 cm^{-1}.

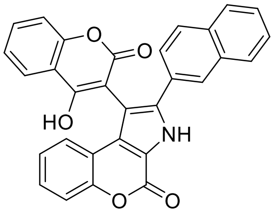
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.24 (s, 1 H), 7.96 (d, *J* = 7.8 Hz, 1 H), 7.88 (d, *J* = 2.5 Hz, 1 H), 7.74 (t, *J* = 7.8 Hz, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 8.3 Hz, 1 H), 7.48 (d, *J* = 5.0 Hz, 1 H), 7.41 (m, 3 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 7.12 (t, *J* = 3.8 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 165.2, 162.2, 154.5, 153.6, 151.2, 136.6, 133.6, 132.3, 129.1, 128.4, 128.2, 127.9, 127.0, 125.0, 124.7, 124.6, 122.7, 118.4, 117.4, 117.2, 117.0, 116.6, 106.8, 97.7 ppm.

HRMS (ESI): calcd for $C_{24}H_{13}NO_5S$ (M+H$^+$) = 428.0587, found 428.0593.

Elemental Analysis	Calculated	Found
MF $C_{24}H_{13}NO_5S$	C 67.44	67.56
(427.43)	H 3.07	3.01
	N 3.28	3.35

1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-(naphthalen-2-yl)chromeno[3,4-b]pyrrol-4(3H)-one (12q):



12q

Reaction Time: 18 h **Colour & State:** white solid

Yield: 82% (193 mg) **Melting Point:** > 300 °C

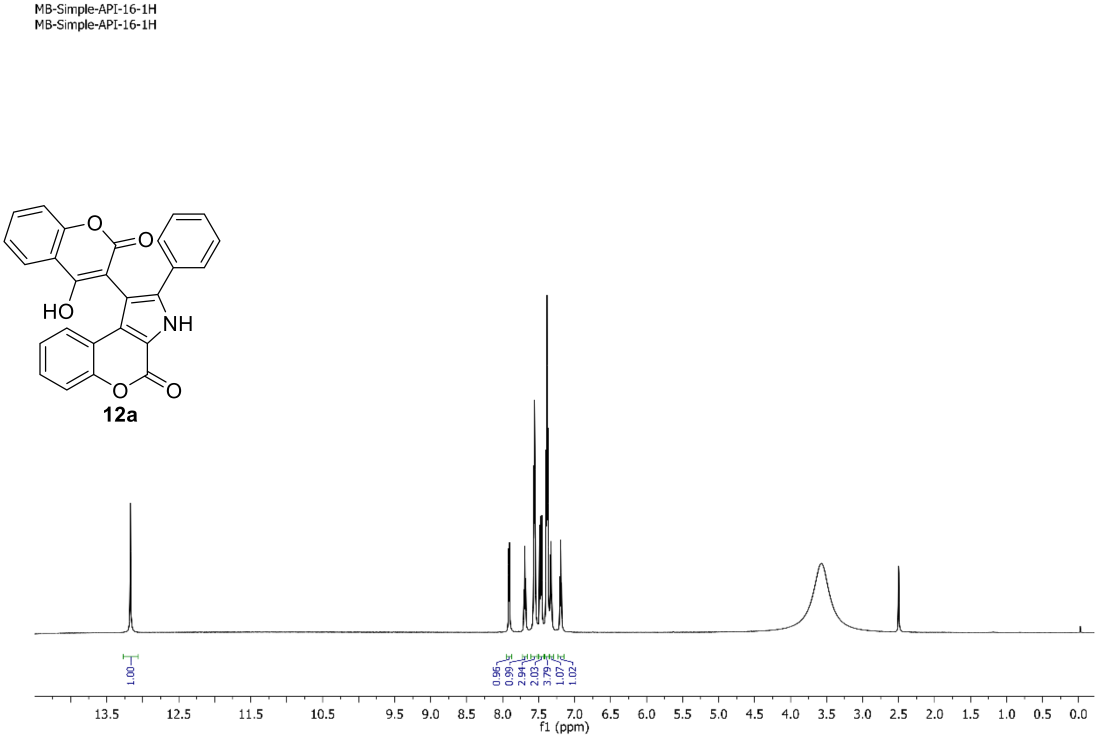
IR (KBr): 3446.32, 3112.98, 1700.01, 1653.77, 1252.57, 1123.87, 1046.08 cm^{-1}.

^{1}HNMR (400 MHz, DMSO-d$_6$): δ 13.34 (s, 1 H), 8.17 (s, 1 H), 7.91 (t, *J* = 6.4 Hz, 2 H), 7.86 (t, *J* = 9.4 Hz, 2 H), 7.69 (t, *J* = 7.8 Hz, 1 H),7.63 (m, 2 H), 7.51 (m, 4 H), 7.39 (m, 2 H), 7.23 (t, *J* = 7.6 Hz, 1 H) ppm.

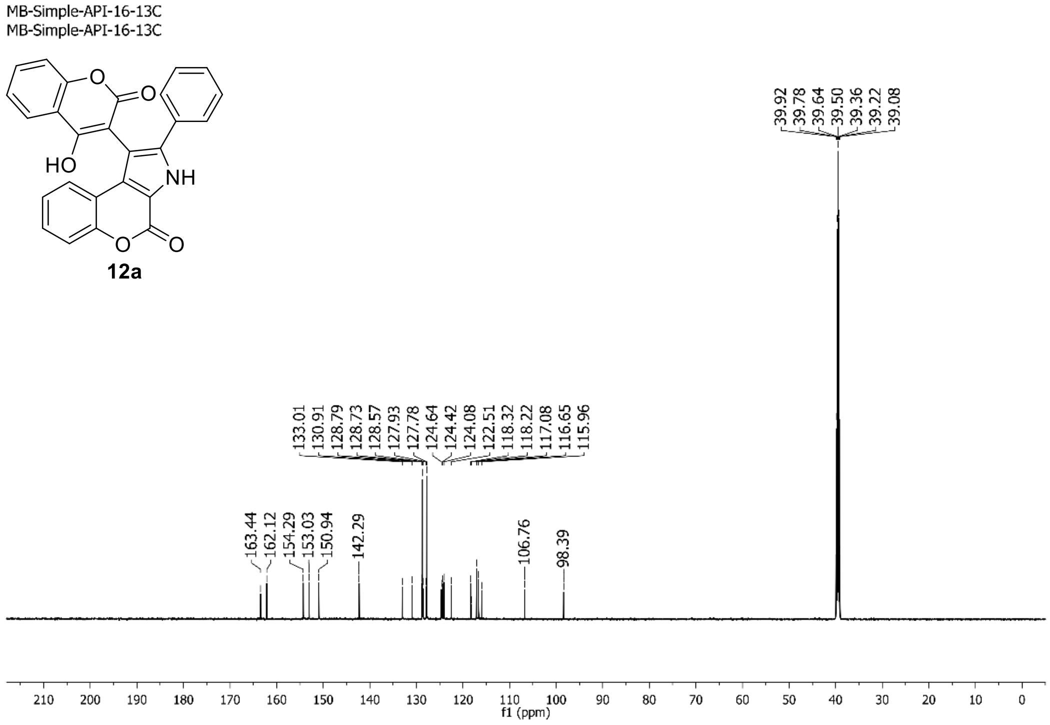
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 163.5, 162.0, 154.2, 153.0, 151.8, 142.0, 132.8, 132.62, 132.56, 128.5, 128.4, 128.1, 128.0, 127.8, 127.6, 127.2, 126.82, 126.75, 125.1, 124.6, 124.2, 124.0, 122.6, 118.3, 117.2, 117.0, 116.5, 116.0, 107.2, 98.3 ppm.

HRMS (ESI): calcd for $C_{30}H_{17}NO_5$ (M+H$^+$) = 472.1179, found 472.1186.

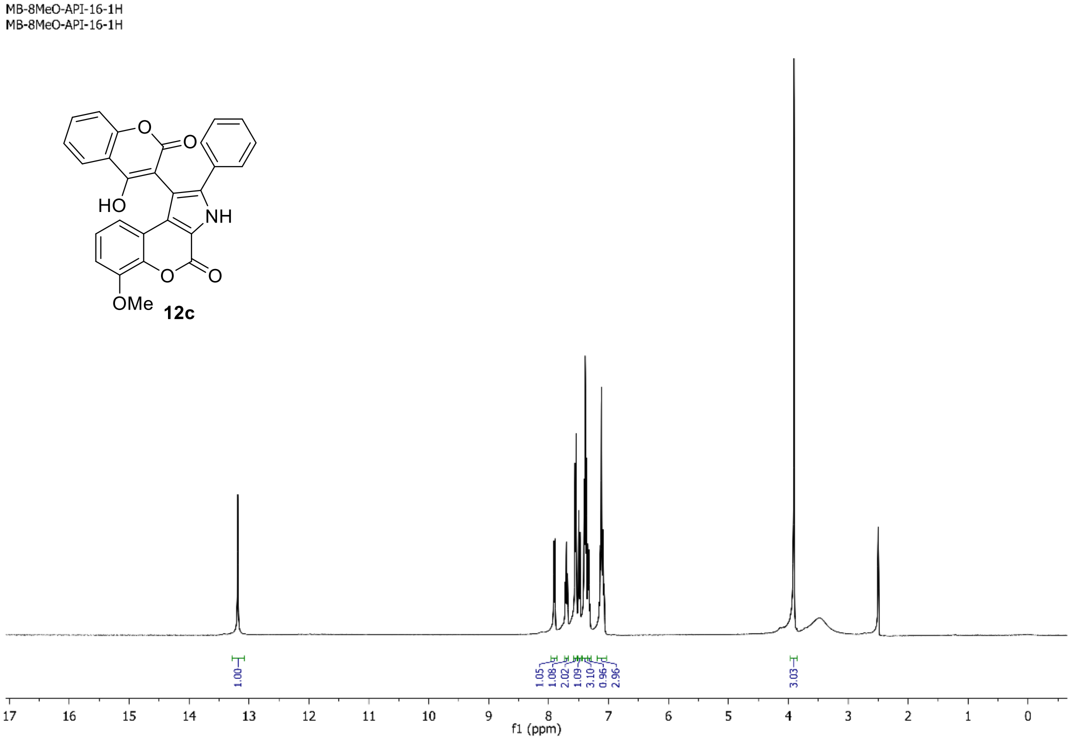
^{1}HNMR (600 MHz, DMSO-d$_6$): *1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (**12a**)



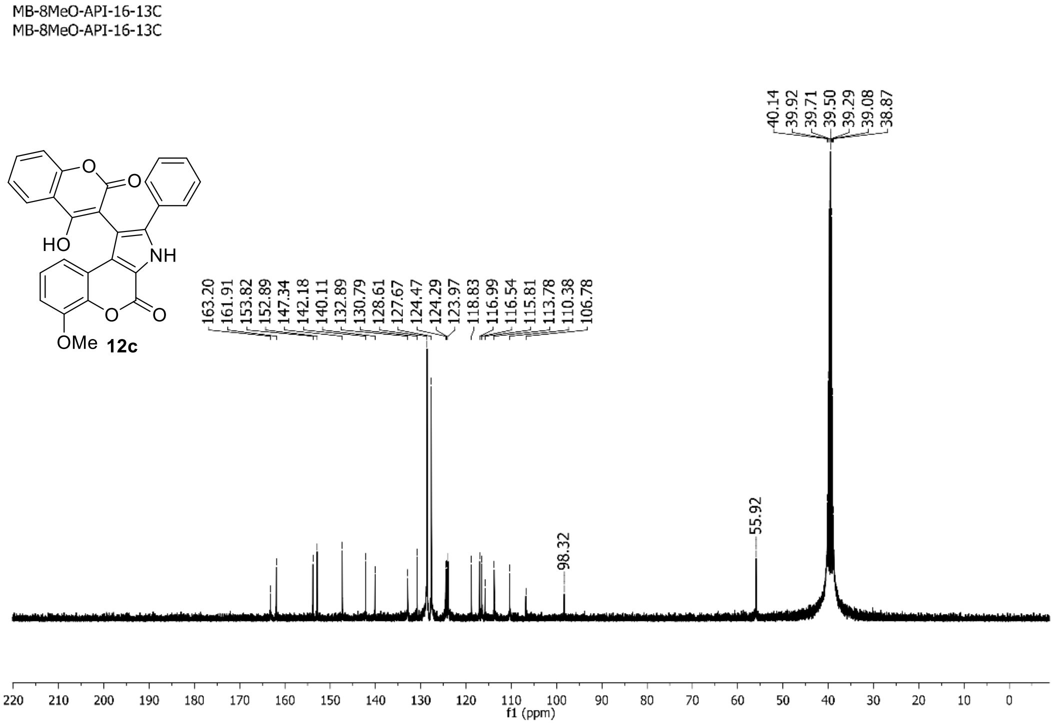
^{13}C NMR (150 MHz, DMSO-d$_6$): *1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (**12a**)



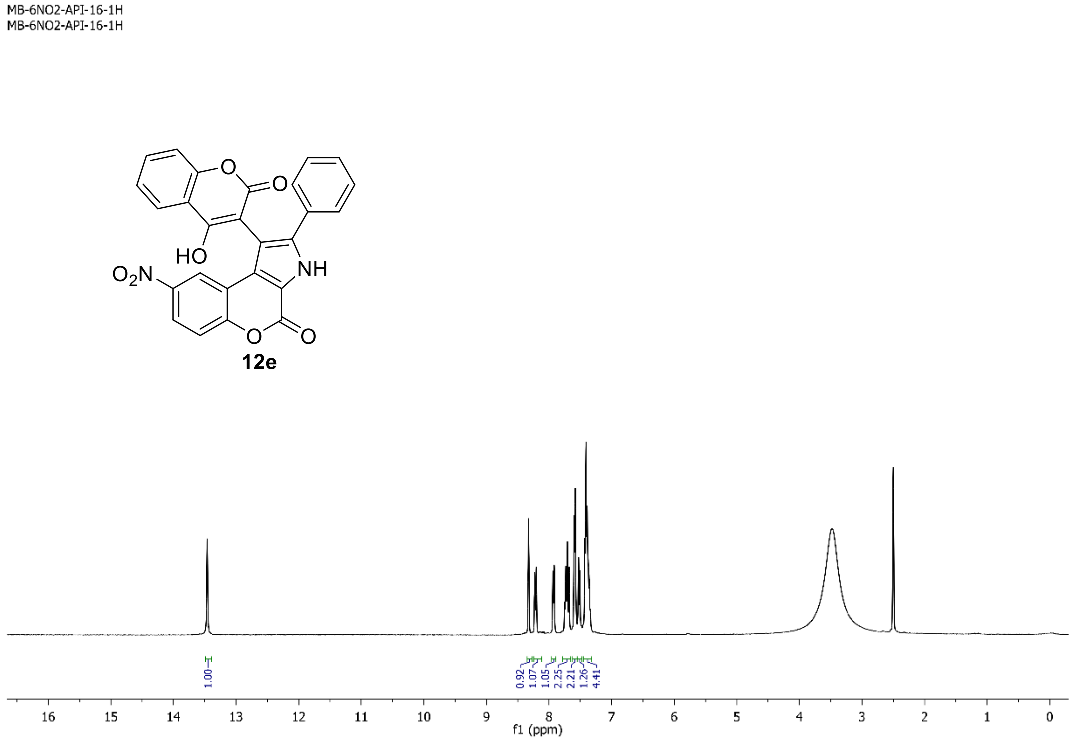
^{1}HNMR (400 MHz, DMSO-d_6): *1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-6-methoxy-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (**12c**)



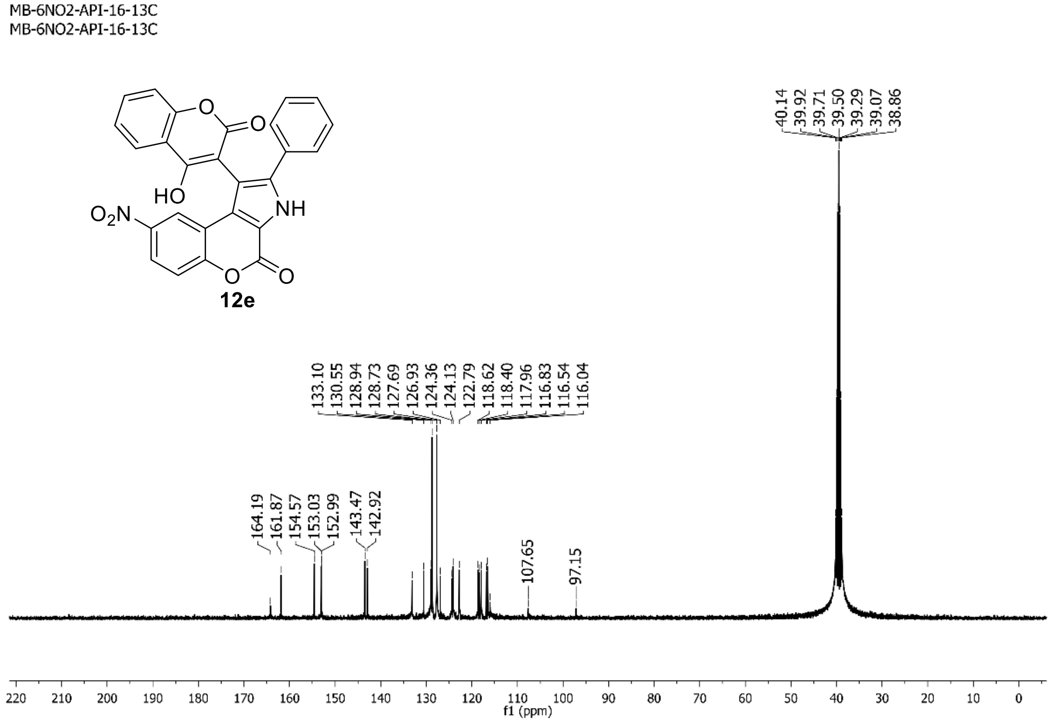
^{13}C NMR (100 MHz, DMSO-d_6): *1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-6-methoxy-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (**12c**)



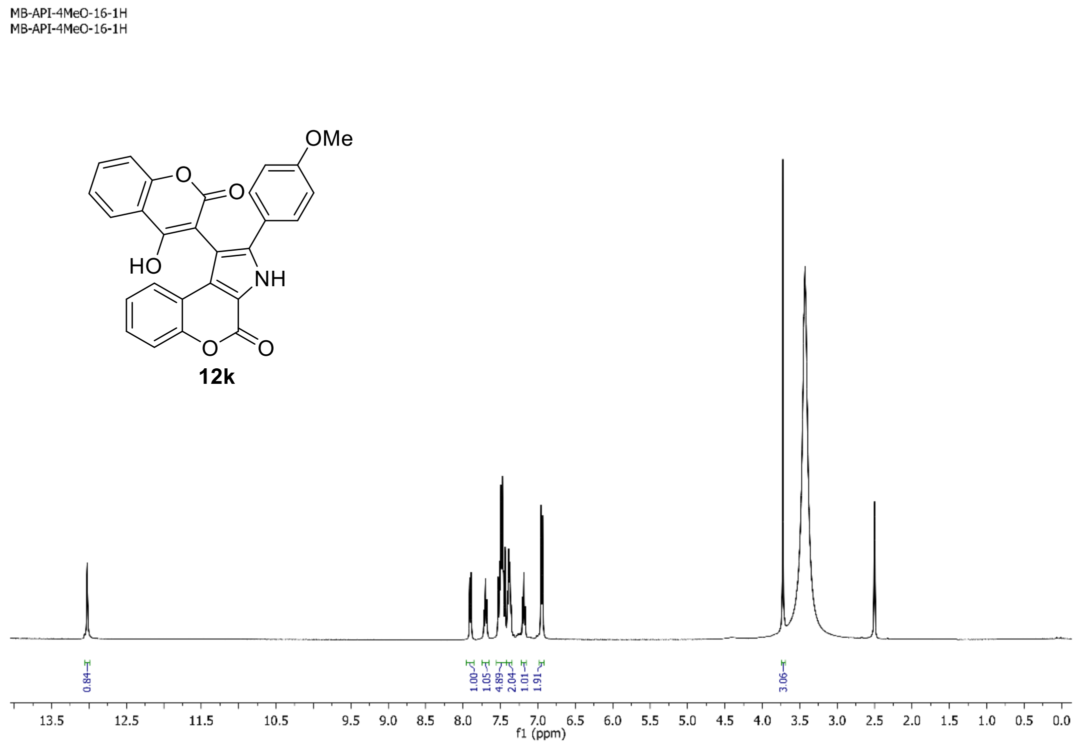
^{1}HNMR (400 MHz, DMSO-d$_6$): *1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-8-nitro-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (**12e**)



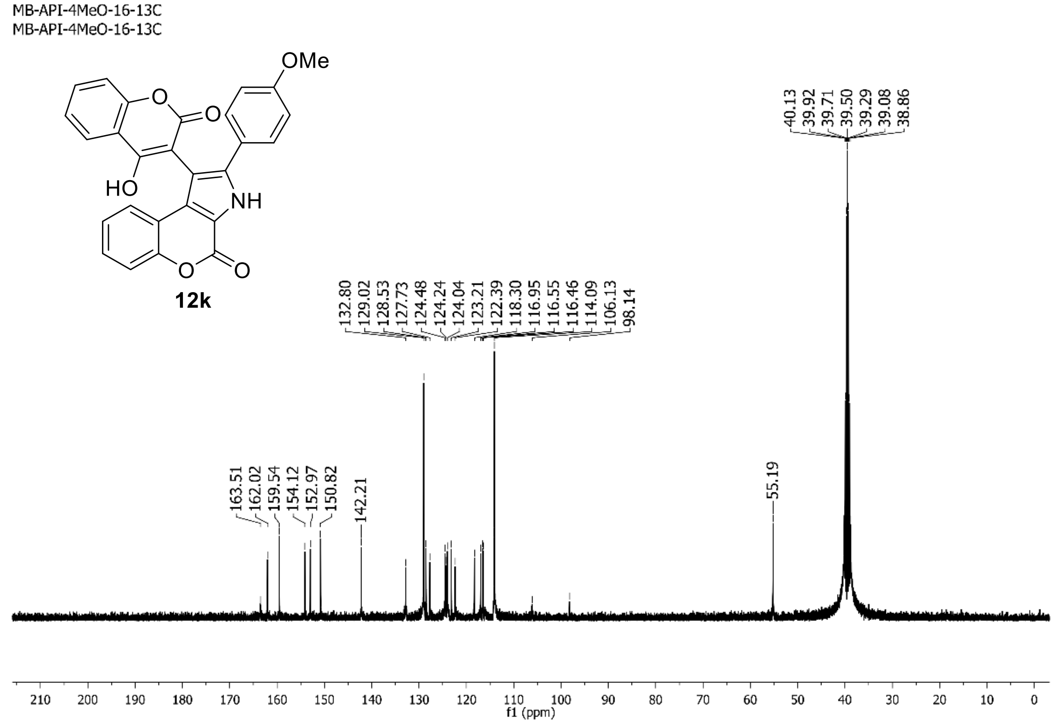
^{13}C NMR (100 MHz, DMSO-d$_6$): *1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-8-nitro-2-phenylchromeno[3,4-b]pyrrol-4(3H)-one* (**12e**)



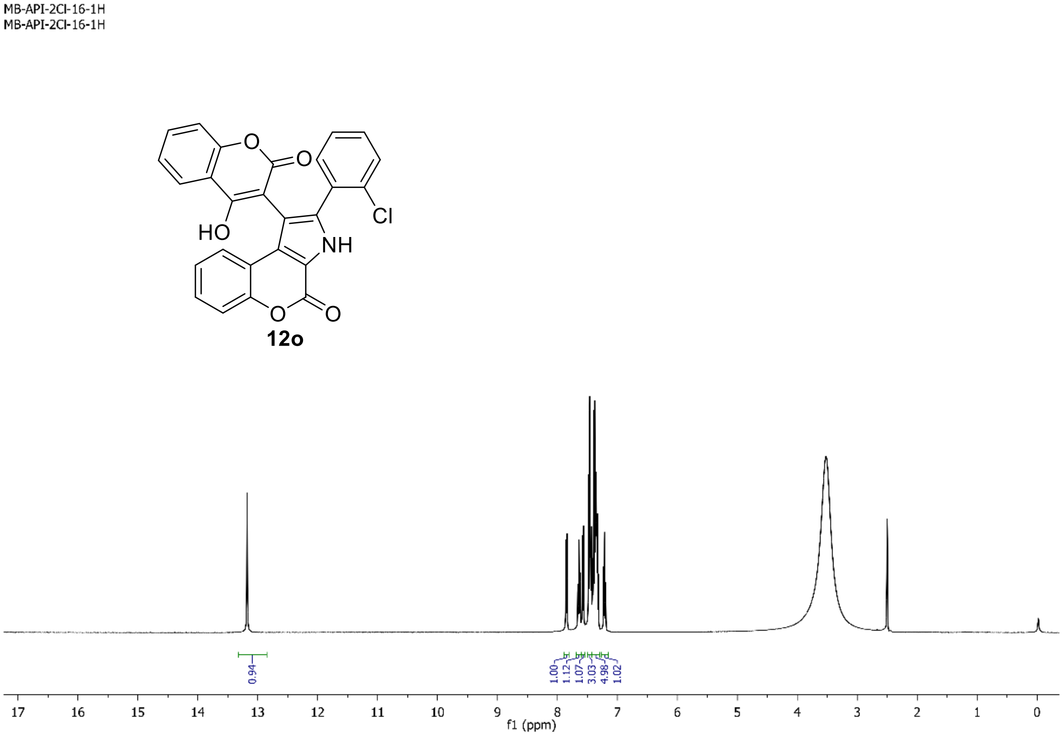
^{1}HNMR (400 MHz, DMSO-d_6): *1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-(4-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3H)-one* (**12k**)



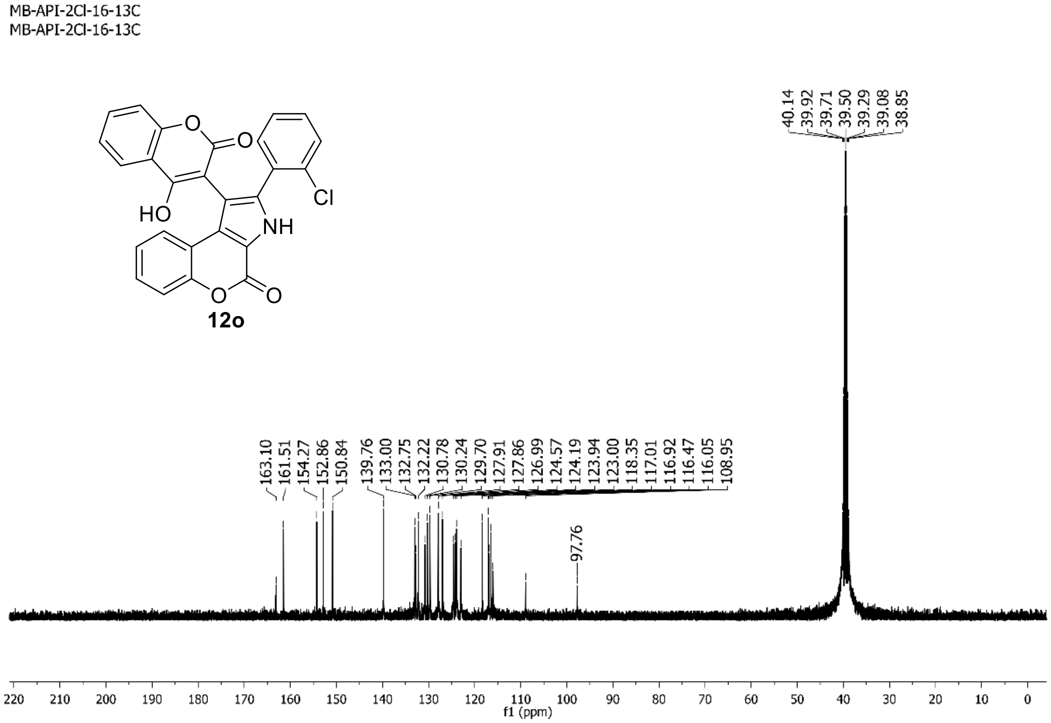
^{13}C NMR (100 MHz, DMSO-d_6): *1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-(4-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3H)-one* (**12k**)



^{1}HNMR (400 MHz, DMSO-d_6): *2-(2-Chlorophenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)chromeno[3,4-b]pyrrol-4(3H)-one* (**12o**)



^{13}C NMR (100 MHz, DMSO-d_6): *2-(2-Chlorophenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-yl)chromeno[3,4-b]pyrrol-4(3H)-one* (**12o**)



Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

Table 9. Crystal data and structure refinements of compounds **4b** and **4d**. For atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check CIF.

Parameters	**Compound 12b**	**Compound 12d**
Empirical Formula	$C_{31}H_{27}NO_8S_2$	$C_{32}H_{31}NO_8S_2$
Formula Weight	605.66	621.70
Temperature	298 (2) K	296 (2) K
CCDC No.	1498213	1498412
Wavelength (A^{o})	0.71073	0.71073
Crystal System	triclinic	Monoclinic
Space group	P -1	P 21/n
Radiation type	MoK\a	MoK\a
Radiation source		fine-focus sealed tube
a (A^{o})	11.1717(4)	9.2820(2)
b (A^{o})	11.6891(6)	18.5563(4)
c (A^{o})	12.2032(9)	18.4475(5)
α (^{o})	70.452(6)	90.00
β (^{o})	80.727(5)	101.5990(10)
γ (^{o})	82.641(4)	90.00
Cell Voloume	1477.38(15)	3112.50(13)
z	2	4

Density	1.362	1.327
F (0 0 0)	632	1304.0
Theta ranges	3.5510 to 27.7570	2.47 to 24.45
Index ranges	$-13 \leq h \leq 14$ $-10 \leq k \leq 14$ $-15 \leq l \leq 16$	$-11 \leq h \leq 11$ $-21 \leq k \leq 22$ $-22 \leq l \leq 22$
Reflection collected	11823	39886
Independent reflections	6667	5611
Completeness to theta	0.957	0.996
Number of parameters	392	394
Number of restraints	0	0
Godness of fit (GOF)on F^2	1.055	1.051
Refinement method	Full-matrix least square on F2	Full-matrix least square on F2

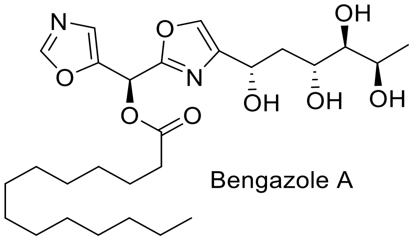
CHAPTER IV

An Introduction to Oxidative C-H Bond Functionalization and Coumarin Fused Oxazoles and Thiazoles

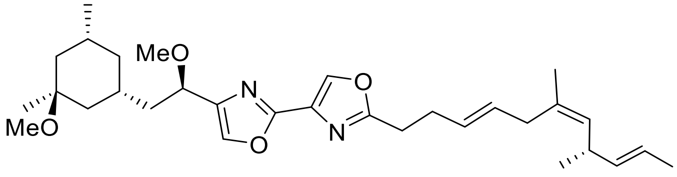
• IV.1. Introduction

C-H bond functionalization has emerged as an ideal and versatile synthetic tool for the chemists to construct C-C and C-heteroatom bonds. The above strategy has advantage over the classical synthesis where the reaction is failed using the classical methods. Synthetic route following C-H bond functionalization provides an alternative to the chemists avoiding prefuntionalization and defunctionalization involving in the tradition synthesis and thus make synthetic schemes shorter, more efficient and highly desirable for C-C and C-X (X = N, O, S) bond formation.[57] There is a rapid competition amongst the researchers to develop different reaction conditions like new catalysts and oxidants to achieve C-H bond functionalization in a simplified manner. A number of transition metal catalyzed and also metal free reaction protocols have been developed in recent decades which give an access to varieties of heterocyclic compounds of biological significance.[58] The fast growing field of C-H functionalization has made its route in the arena of total synthesis and the synthetic chemists are exploring these new methodologies presently to architect complex molecular structures of biological and pharmaceutical importance.[59] C-H bond functionalization to construct C-C and C-X bonds can be achieved in various ways. In the following chapter, oxidative functionalization of an sp^3 C-H bond adjacent to alpha to a nitrogen atom will be discussed.

Oxazole and thiazole derivatives are biologically very important scaffolds (Fig. 7). Many naturally occurring marine drugs and synthetic compounds containing these moieties have valuable medicinal properties.[60] Moreover, coumarin containing thiazoles shows anti-convulsant and anti-inflammatory properties.[61] There are various methodologies reported in literature for the synthesis of oxazoles and thiazoles including numerous methods based on C-H bond functionalization.[62] On the other hand, very few methods are reported for the synthesis of coumarin fused oxazoles and thiazoles as described in section IV.4 and IV.5 of this chapter, respectively. Therefore, synthesis of these compounds has been carried out using mild reaction conditions exploring 3-aminocoumarin derivatives.



Bengazole A



Hennoxazole A

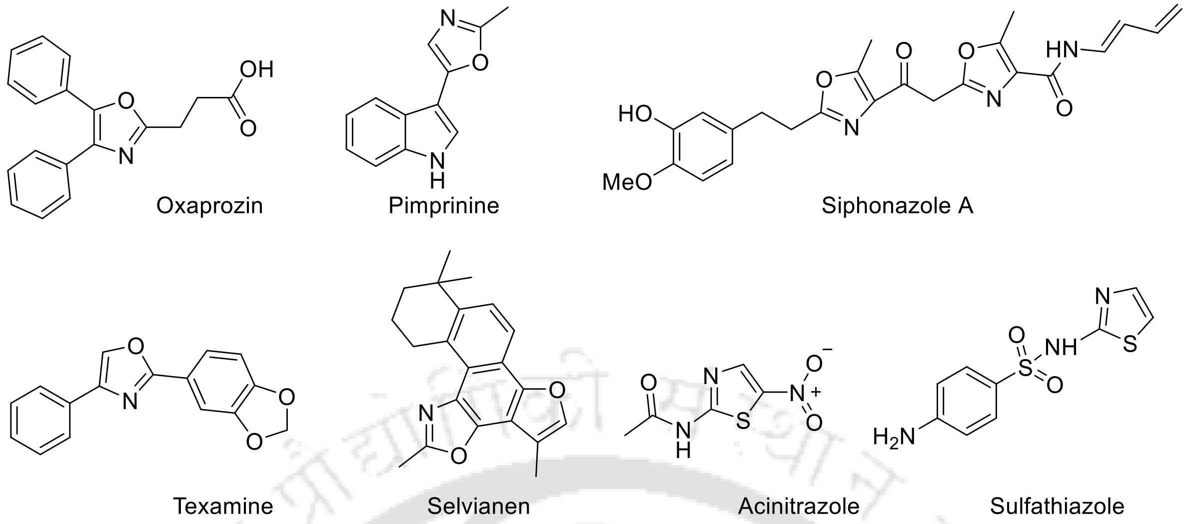
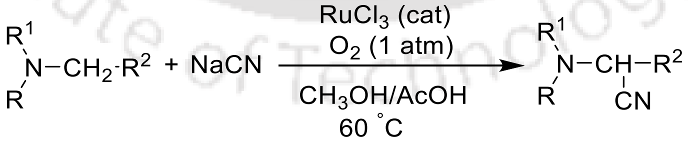


Figure 7. Biologically active oxazoles and thiazoles

• IV.2. C-H bond Functionalization Adjacent to Nitrogen Atom

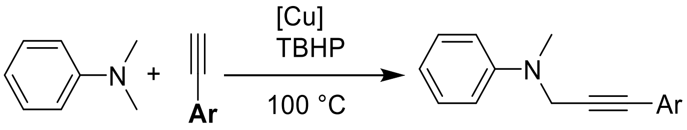
Oxidative C-H bond functionalization alpha to a nitrogen atom to build various C-C and C-heteroatom bonds has been a fascinating strategy to access various molecular transformations. Electron rich amines having C-H bond alpha to nitrogen, easily undergo oxidation to generate iminium ions which are trapped by various nucleophiles to accomplish C-C, C-O, C-N, and C-S bonds.

Murahashi et al. demonstrated a straight forward synthesis of α- aminonitriles via ruthenium catalyzed oxidative cynation of tertiary amines with sodium cynides in presence of AcOH. The mechanism was believed to proceed through an [iminium ion]-Ru^{n}OOH complex which is attacked by HCN generated from AcOH and NaCN to give various α-aminonitriles as shown in Scheme 38.[63]



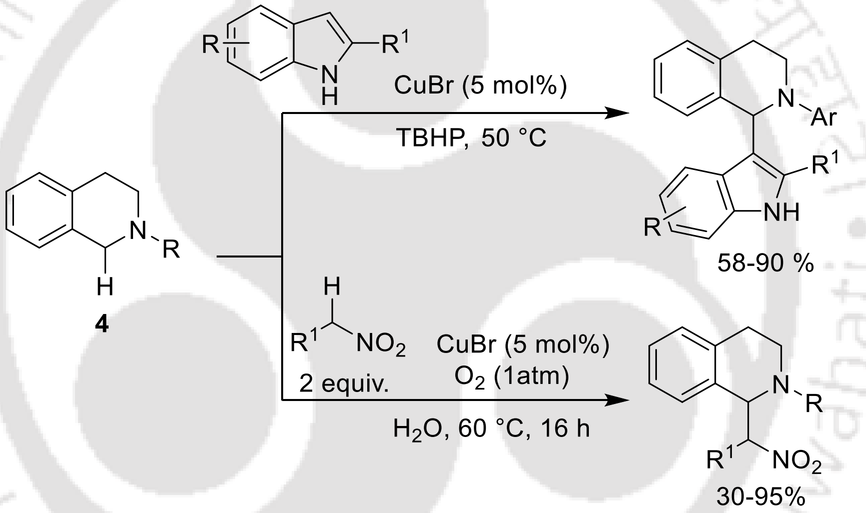
Scheme 38

Li and co-workers were inspired from Murahashi work and reported first catalytic alkynylation reaction of Csp^3-H bond adjacent to a nitrogen atom via oxidative coupling as represented in Scheme 39.[64] Later on the concept was expanded in the form of Cross Dehydrogaenative Coupling reaction (CDC) achieving various C-C bond formation.



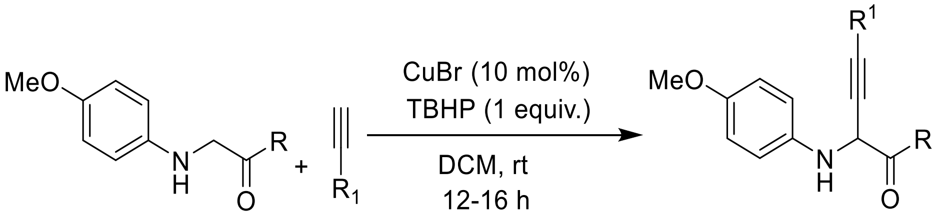
Scheme 39

Li's group first reported various indoles derivatives as Csp^2 nucleophile in the cross dehydrogenative alkenylation of tetrahydroisoquinoline derivatives using Cu salt and TBHP. (Scheme 40).[65] In 2005, the first broadly applicable procedure for the cross-dehydrogenative aza-Henry reaction was introduced by the group of Li. Various *N*-arylated tetrahydroisoquinolines were successfully coupled with an excess of the nitroalkanes as Csp^3-C-H nucleophiles in the presence of catalytic quantities of CuBr and 1.2 equivalents of TBHP at room temperature (Scheme 40).[66]



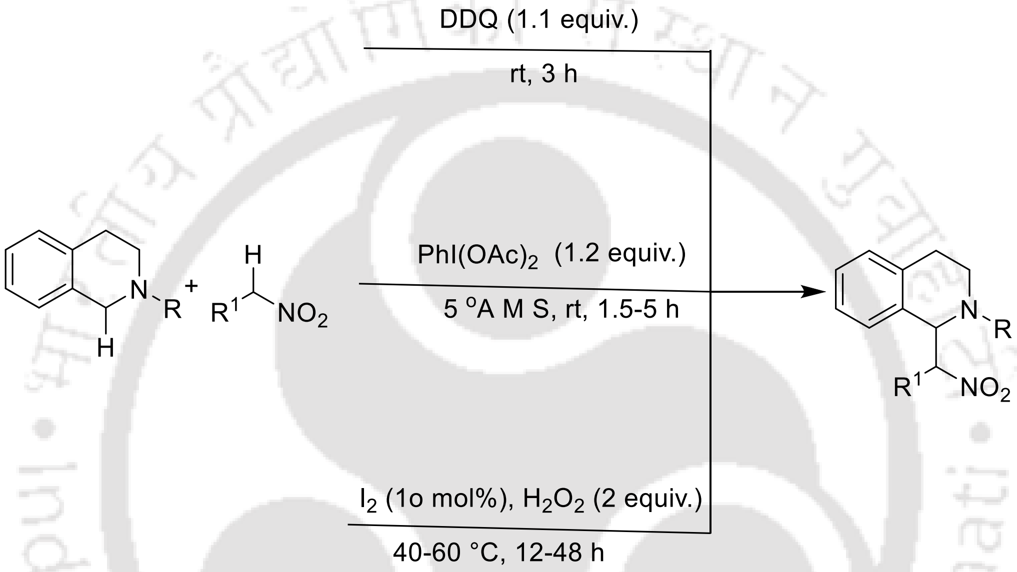
Scheme 40

Secondary amines as substrates for cross dehydrogenative alkynylation was introduced by Li et al. in 2008. Various glycine derivatives were functionalized by alkynylation using CuBr as a catalyst and TBHP as an oxidant in DCM at room temperature as described in Scheme 41.[67]



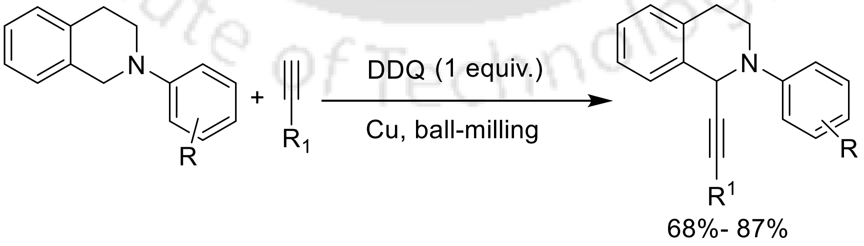
Scheme 41

Several other oxidants were also used in CDC reactions which led to the introduction of various metal free reaction protocols. In 2009, DDQ was introduced as an efficient oxidant to mediate the aza-Henry reaction at room temperature under neat conditions by Todd et al.[68] The organic oxidant (diacetoxy)iodobenzene (DIB) was introduced for this reaction type by Liang and co-workers.[69] Itoh and co-workers demonstrated that catalytic amounts of iodine in combination with hydrogen peroxide effectively catalyze the nitroalkylation of various tetrahydroisoquinoline derivatives by generating, the catalytic active hypoiodous acid (HIO) *in situ* (Scheme 42).[70]



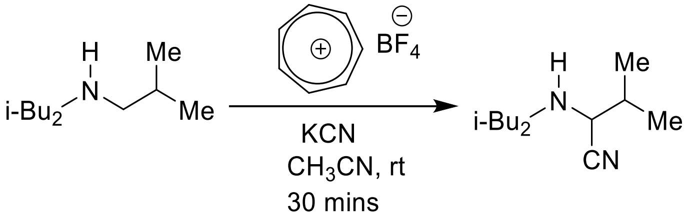
Scheme 42

Su et al. demonstrated the alkynylation of tetrahydroisoquinolines in the presence of 1 equivalent of the oxidant DDQ under solvent-free, high-speed, ball-milling conditions (Scheme 43).[71] The reaction proceeded smoothly with both aliphatic and aromatic alkynes. However, slightly better yields were obtained with aromatic substrates.



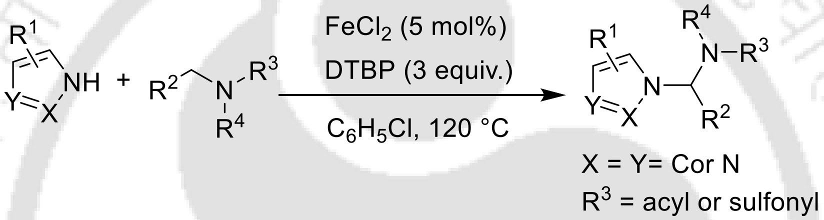
Scheme 43

Lambert et al. described the tropilium ion mediated alpha cynation of amines. The oxidation of amine by tropilium ion gave the iminium ion which was trapped by KCN to give the α-aminonitriles as shown in Scheme 44.[72]



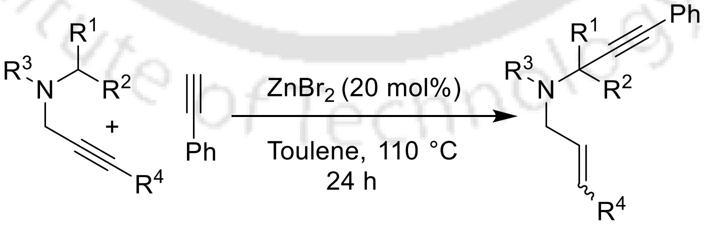
Scheme 44

Iron-catalyzed direct C−N bond formation between azoles and amides was reported by Chen et al. The oxidative coupling reactions of sp^3 C−H bonds adjacent to a nitrogen atom in amides and sulfonamides with the N−H bond in azoles were carried out in the presence of $FeCl_2$ and di-tert-butyl peroxide (DTBP) as described in Scheme 45.[73] They used various amides and sulfonamides as substrates for the oxidative C-H bond functionalization to construct C-N bonds.



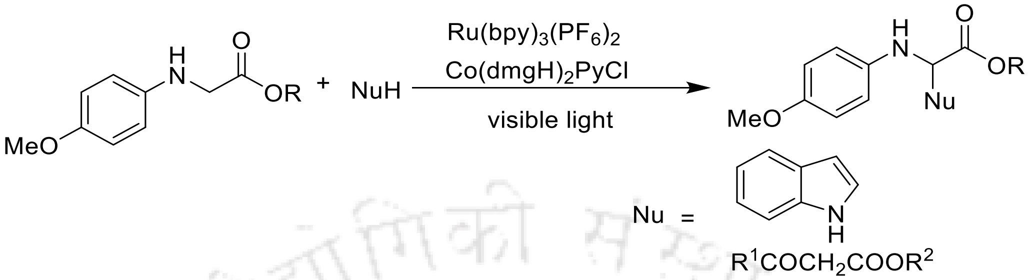
Scheme 45

Nakamura et al. used $ZnBr_2$ as a catalyst to construct C-C bond between propargylic amines and terminal alkyne via redox cross dehydrogenative coupling reaction. They designed the substrate structures with an internal oxidant where reduction of the internal oxidant and catalytic oxidation of the C1(sp^3)−H bond adjacent to the nitrogen atom of tertiary amine provided a reactive iminium intermediate which was attacked by the terminal alkyne to give the final product as shown in Scheme 46.[74]



Scheme 46

Wu et al. demonstrated the C−H bond functionalization without any oxidant using $Ru(bpy)_3(PF_6)_2$ and $Co(dmgH)_2pyCl$ as a catalyst and photosensitizer respectively, as represented in Scheme 47. The C-C bond formation between glycine esters with β-keto esters or indoles derivatives was achieved under visible light irradiation. They proposed a mechanism where electron transfer from glycine to photo excited Ru(bpy)$_3$(PF$_6$)$_2$ takes place which in turn transfer electron to the photosensitizer. The photosensitizer, Co(dmgH)$_2$PyCl oxidizes glycine radical to an iminium ions which by the attack of nucleophile produces final products.[75]

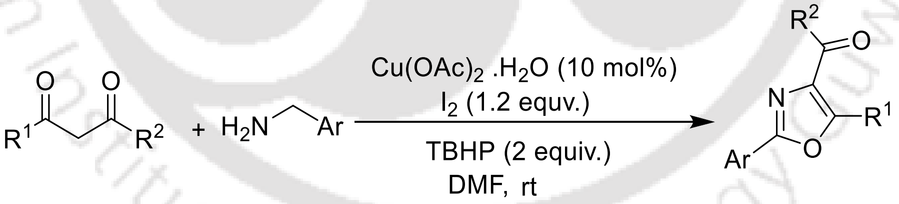


Scheme 47

• IV.3. Oxidative C-H Bond Functionalization for the Synthesis of Heterocycles

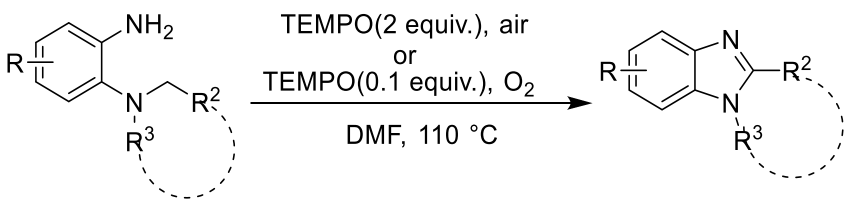
Cross dehydrogenative coupling reaction through functionalization of Csp^3-H bond adjacent to nitrogen atom has led to the synthesis of various heterocyclic compounds. Some of the methods for the synthesis of heterocycles are being discussed in the following section.

Wang and co-workers illustrated a Cu-catalyzed synthesis of polysubstituted oxazoles from benzylamines and β-diketones as represented in Scheme 48.[76] The intermediates, formed by the reaction of benzylamines and β-diketones derivative in the presence of iodine undergo oxidative C-H bond functionalization which is followed by intramolecular cyclization and further oxidation to give oxazole derivatives.



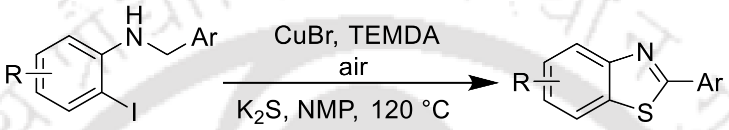
Scheme 48

Long and co-workers developed an efficient metal free approach to access various polysubstituted benzimidazoles using TEMPO–air/cat.TEMPO–O$_2$ combination via oxidative C-H bond functionalization employing *N*^{1}-benzyl/alkyl-1,2-phenylenediamines as substrates (Scheme 49).[77] They also extended the protocol to synthesize oxazole derivatives using 2-benzylaminophenol as the starting material.



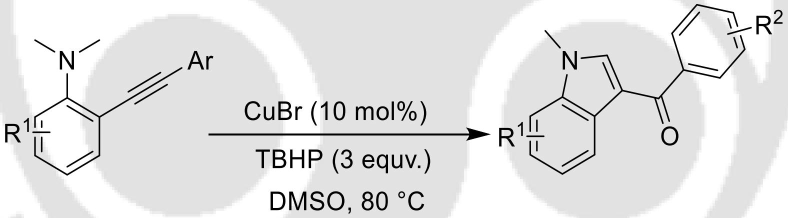
Scheme 49

Liang et al. synthesiszed various thiazole derivatives from *N*-benzyl-2-iodoanilines using K_2S and CuBr in NMO via oxidative C-H bond functionalization of C-H bond alpha to nitrogen atom as shown in Scheme 50.[78]



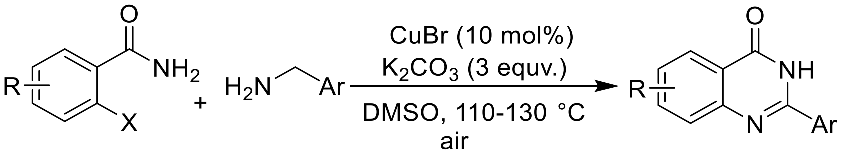
Scheme 50

Patel and co-workers described the synthesis of 3-aroylindoles using CuBr as the catalyst and TBHP as the oxidant via intramolecular oxidative functionalization of *o*-alkynylated *N*, *N*-dimethylamines (Scheme 51).[79] The reaction process involves Cu-catalyzed oxidative dehydrogenation followed by C−C and C−O bonds formation to give the indole derivatives.



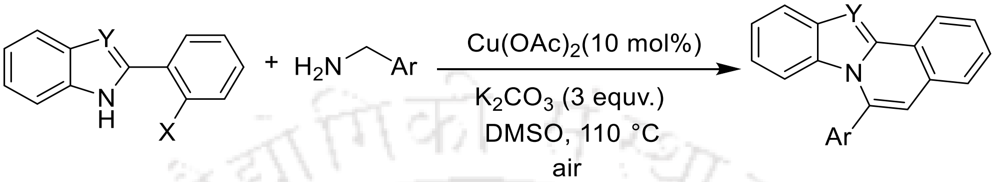
Scheme 51

Fu et al. developed a new method for the synthesis of quinazolinones via Cu-catalyzed oxidative dehydrogenation (Scheme 52). The reaction of substituted 2-halobenzamides and benzylamines using CuBr as the catalyst and air as an oxidant provides the quinazolinone derivatives. The domino reaction undergoes sequential Cu-catalyzed Ullmann-type coupling, aerobic oxidation, an intramolecular nucleophilic addition, and then a further oxidation process to afford the final quinazolinone derivatives.[80]



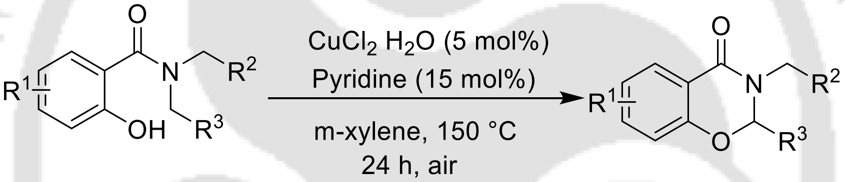
Scheme 52

Zhang and co-workers depicted the construction of six-membered *N*-heterocycles via Cu-catalyzed oxidative dehydrogenation as shown in Scheme 53. The reaction of 2-(2-halophenyl)-*1H*-indoles and benzylamines using air as an oxidant provided indolo(1,2-*c*)quinazolines. The reaction involves Cu catalyzed intermolecular *N*-arylation followed by an intramolecular aerobic oxidative C−H amination.[81]



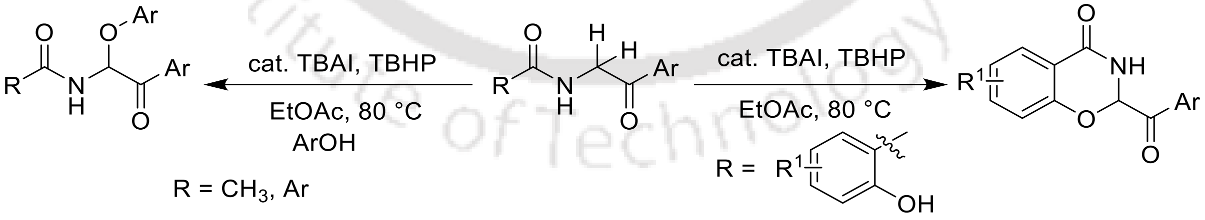
Scheme 53

Maiti and co-workers recently synthesized various dihydrooxazinones via cross dehydrogenative coupling reaction of salicylamides employing $CuCl_2$ as a catalyst as shown in Scheme 54.[82] The reaction is a good example of CDC reaction to construct C-O bond.



Scheme 54

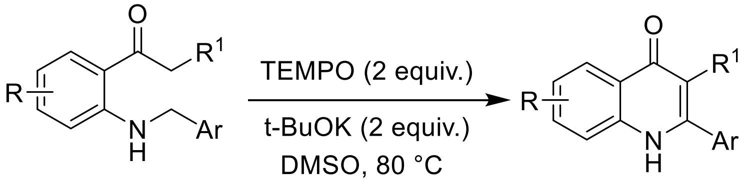
Nachtsheim et al. demonstrated direct oxidative sp^{3}C-H bond functionalization forming C-O bond between phenols and α-aminoacetophenones (Scheme 55) using TBAI as catalyst. The above methodology was further extended toward an intramolecular variant which gave direct access to a range of dihydro-4*H*-benzo[e][1,3]oxazin-4-ones as depicted in (Scheme 55).[83]



Scheme 55

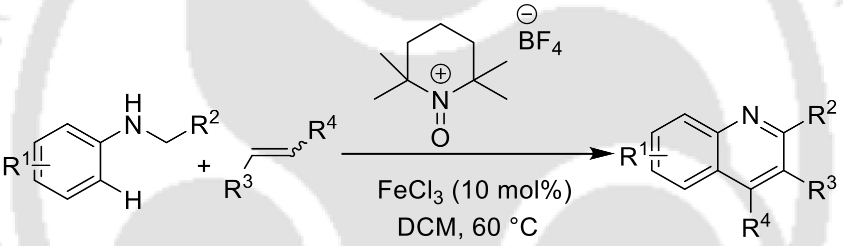
Long and co-workers reported the synthesis of quinolinone derivatives via direct oxidative C-H functionalization adjacent to the nitrogen atom of *N*-arylmethyl-2-aminophenylketones. The reaction is like an intramolecular manich type reaction where oxidation of *N*-arylmethyl-2-

aminophenylketones by TEMPO gives an imine which by intramolecular nucleophilic attack followed by oxidation gives the quinolinone derivatives as shown in Scheme 56.[84]



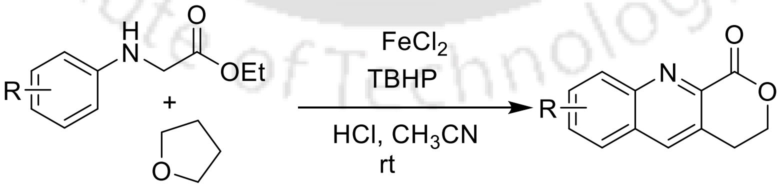
Scheme 56

Various groups have reported oxidative Povarov reaction trapping the iminium ion formed in the oxidative C-H bond functionalization reaction adjacent to a nitrogen atom. Mancheno et al. reported the TEMPO oxoammonium salt-mediated oxidative Povarov reaction where several derivatives of substituted quinolones were synthesized using iron chloride as the catalyst. The iminium ion formed from the oxidation of *N*-alkyl anilines underwent Povarov reaction with olefins to provide the quinolone derivatives (Scheme 57).[85]



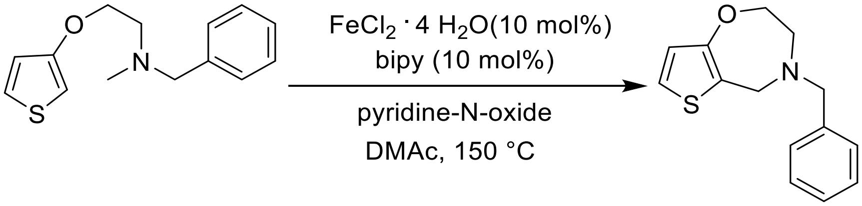
Scheme 57

Huo et al. synthesized various quinolone derivatives fused with lactone rings via oxidative dehyrogenation of glycine derivatives and THF followed by Povarov reaction of the intermediates using iron chloride as catalyst. The final product was obtained by the opening of THF ring in the dihydroquinoline adduct by HCl followed by ester exchange and aerial oxidation (Scheme 58).[86]



Scheme 58

Itami and co-workers synthesized the thiophene fused oxazepine derivative which has good binding affinity towards alpha receptor protein, via the iron catalyzed oxidative coupling of the thiophene moeity with methylamines. The reaction involves a metal-bound iminium species, which then undergoes electrophilic substitution of the thiophene moiety giving the coupling product (Scheme 59).[87]

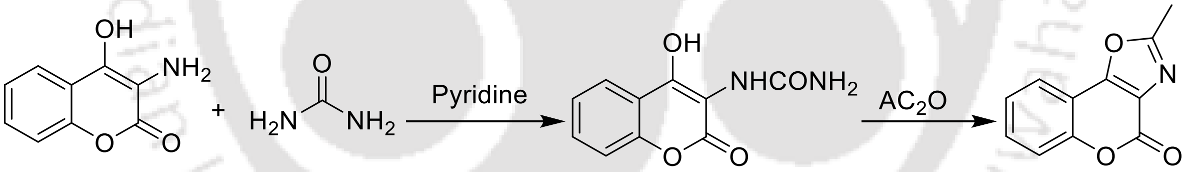


Scheme 59

• IV.4. Synthesis of Coumarin Fused Oxazoles

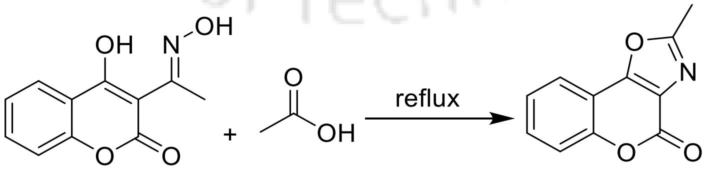
Literature survey reveals that oxazoles containing fused coumarins are very much less explored. There are only few methodologies available in literature to achieve the synthesis of coumarin fused oxazoles, mostly from 3-amino-4-hydroxy coumarins and its derivatives which are described below.

Merchant and coworkers synthesized the oxazole derivatives using 3-amino-4-hydroxycoumarin and urea. The reaction proceeds through the formation of a urea derivative from 3-amino-4-hydroxycoumarin and urea, which undergo cyclization in the presence of Ac_2O to give the coumarin fused oxazole (Scheme 60).[88]



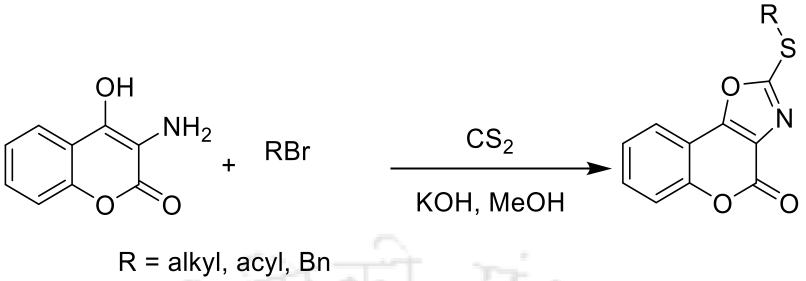
Scheme 60

Gelin and co-workers demonstrated the synthesis of the coumarin fused oxazoles from oxime of 3-acetyl-4-hydroxycoumarin. The Oxime on refluxing in AcOH provides the oxazole derivative in 50% yield along with minor product isoxazole derivatives in 12% yield (Scheme 61).[89]



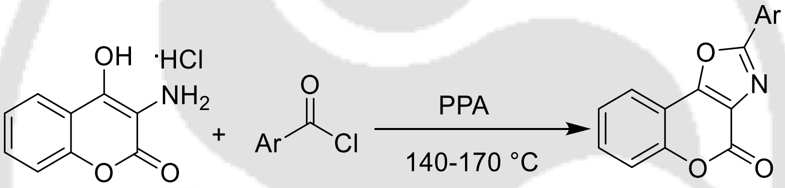
Scheme 61

Reddy et al. established the synthesis of various coumarin fused oxazoles from 3-amino-4-hydroxycoumarin on treatment with CS_2 in the presence of alcoholic KOH producing mercaptobenzopyranoxazolone which is followed by the alkylation/acylation to give the respective thio ether/ thio ester (scheme 62).[90]



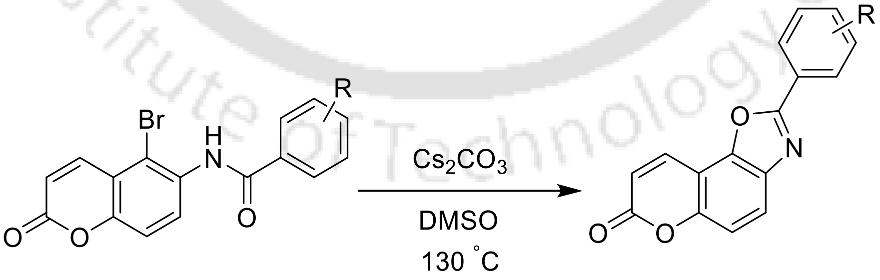
Scheme 62

Ponomarev et al. developed the synthesis of coumarin fused oxazoles starting from 3-nitro-4-hydroxycoumarin. Initially, 3-nitro-4-hydroxycoumarin was reduced with alk. aq. $Na_2S_2O_4$ to corresponding amine salt which was condensed with benzoylchloride to yield the respective oxazoles deivatives of coumarins (Scheme 63).[91]



Scheme 63

Majumdar et al. reported the synthesis of various 2-phenyl-7*H*-chromeno[6,5-*d*]oxazol-7-one derivatives by the intramolecular cyclization of coumarin containing amides in DMSO in the presence of Cs_2CO_3 at 130 ˚C . The oxazoles derivatives were obtained through a nucleophilic addition of amide to form the C–O bond (Scheme 64).[92]

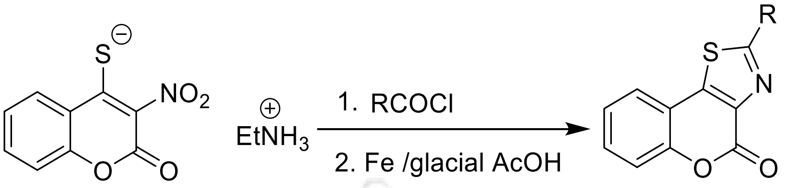


Scheme 64

• IV.5. Synthesis of Coumarin Fused Thiazoles

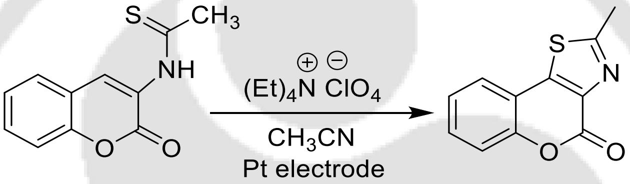
Methods available for the synthesis of coumarin fused thiazoles are very limited. Some traditional methods to access various coumarin fused thiazoles are discussed in this section.

Cecchi and co-workers synthesized coumarin fused thiazole derivatives by the reductive cyclization of 4-aroyl-3-nitrocoumarin which were synthesized by the reaction of triethylammonium salt of 4-mercapto-3-nitrocoumarin with aroyl chlorides (Scheme 65).[93]



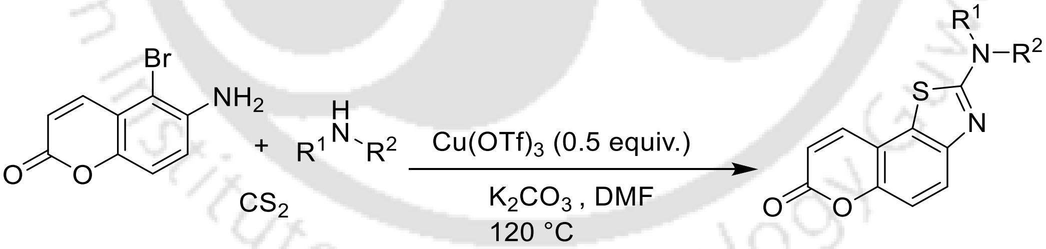
Scheme 65

Tevakovic et al. developed the synthesis of 2-methyl-chromeno[3,4-*d*)]hiazole-4-one from 3-thioacetamidochromeno-2-one using tetraethylammoniumperchlorate in CH_3CN through electrochemical oxidation as shown in Scheme 66.[94]



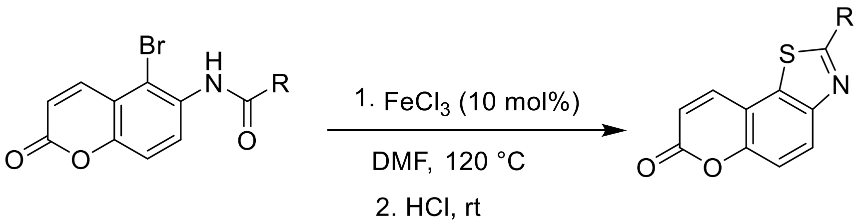
Scheme 66

Majumdar et al. synthesized various coumarin annulated 2-aminothiazole derivatives using 6-bromo-7-aminocoumarin, carbondisulphide and a secondary amine in the presence of $Cu(OTf)_3$ in DMF at 120 °C (Scheme 67).[95]



Scheme 67

They also developed the synthesis of 7*H*-chromeno[6,5-*d*]thiazol-7-one derivatives using $FeCl_3$ as a catalyst in DMF at 120 °C from the acetyl derivatives of 6-amino-4-bromocoumarin derivatives (Scheme 68).[96]

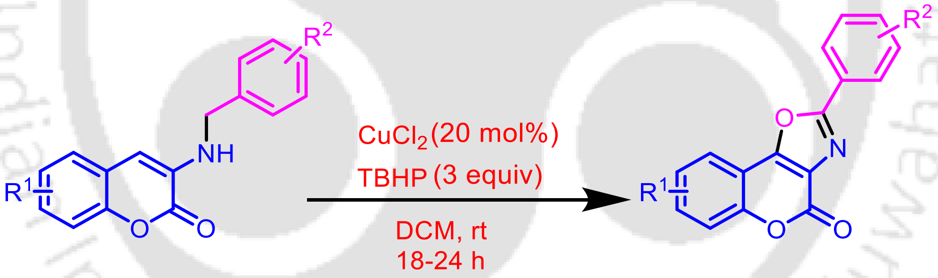


Scheme 68

Thus the literature survey reveals that only traditional methods have been employed so far to achieve coumarin fused oxazoles and thiazoles. The main lacuna in the existing methods is very limited substrate scopes, poor yield and use of harsh reaction condition in some cases. Synthesis of these compounds via oxidative C-H bond functionalization provides an alternative, shorter and atom economic route. The next two chapters of the thesis deals with the synthesis of coumarin fused oxazoles and thiazole using oxidative C-H bond functionalization.

CHAPTER V

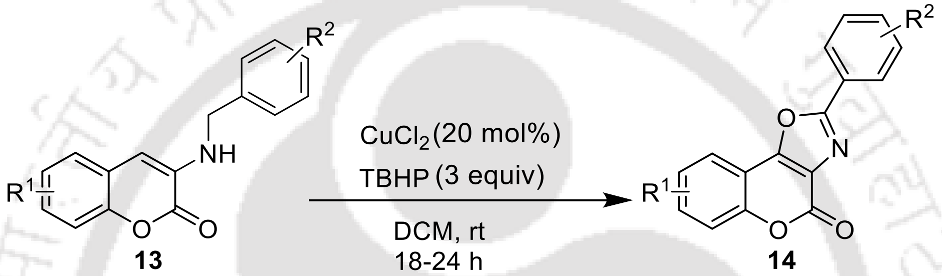
Synthesis of Fused Oxazole Containing Coumarin Derivatives via Oxidative Cross Coupling Reaction using a Combination of $CuCl_2$ and TBHP



RESULTS AND DISCUSSION

• Results and Discussion

In chapter IV, literature on oxidative C-H bond functionalization has been discussed in detail. Li and co-workers explored the tetrahydroisoquinoline moiety to achieve various C-C bonds using TBHP and Cu-salts.[57] The concept is based on the oxidative functionalization of the C-H bond adjacent to nitrogen of tetrahydroisoquinoline to an iminium salt followed by trapping of the imine with various nucleophiles. In this chapter V, similar strategy is used for synthesizing fused oxazoles containing coumarin derivatives by employing $CuCl_2$ as a catalyst and TBHP as an oxidant from various 3-(benzylamino)-2*H*- chromen-2-one (Scheme 69).



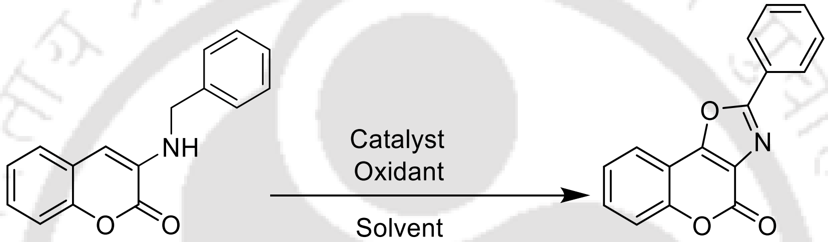
Scheme 69. Synthesis of various coumarin fused oxazoles

Initially, 3-(benzylamino)-2*H*-chromen-2-one (**13a**) was synthesized using 3-aminocoumarin and benzyl bromide in the presence of K_2CO_3 in DMF at 100 °C and characterized by NMR. The starting material (**13a**) was then treated with 10 mol% CuI and TBHP in DCM at room temperature and the reaction was monitored by checking TLC. The major product obtained after completion of the reaction, was separated by column chromatography and characterized by IR, NMR and HRMS. The compound was obtained in 50% yield and found to be **14a** (Table 10**)**, an oxazole derivative of coumarin after analyzing the IR, NMR and HRMS data (see page 120 for NMR spectra of compound **14a**).

To find out the optimal reaction condition, a number of reactions were executed using different copper salts like CuBr, $CuBr_2$, $Cu(OAc)_2 \cdot H_2O$, $CuCl_2$, CuCl, $Cu(NO_2)_2$, $CuSO_4$ as the catalyst and TBHP as the oxidant in DCM at room temperature. The desired product **14a** was obtained from moderate to good yields (Table 10, entries 2-5 and 9-11). Among various copper salts, $CuCl_2$ was found to be the optimized catalyst for the reaction. The desired product **14a** was obtained in 64%, 66% and 72% yield with 10 mol%, 15 mol% and 20 mol% of $CuCl_2$ respectively employing 3 equivalent of TBHP as oxidant in DCM at room temperature (Table 10, entry 5-7).

Lowering the amount of catalyst from 10 mol% to 5 mol%, yield of desired product was decreased to 61% (Table 10, entry 8). Apart from DCM, the desired oxazole product was also obtained in 1,2-dichloroethane (DCE), acetonitrile and chloroform (Table 10, entries 12-15) whereas no product was formed in DMF or DMSO (Table 10, entry 16 and 17). Furthermore, iron salts like $FeCl_2$ and $FeCl_3$ were found ineffective to produce the desired product (Table 10, 18 and 19). Also, the reaction was unsuccessful without any catalyst or oxidant (Table 10, entry 20 and 21) indicating that both are crucial for the formation of product. The reaction was not feasible with other oxidants like H_2O_2 and benzoyl peroxide (Table 10, entry 22 and 23).

Table 10. Optimization of reaction condition[a]



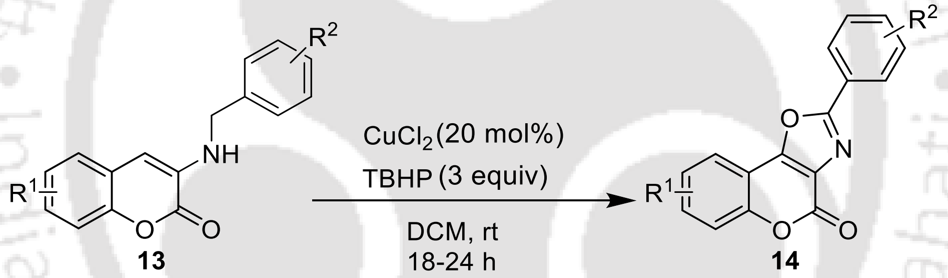
13a **14a**

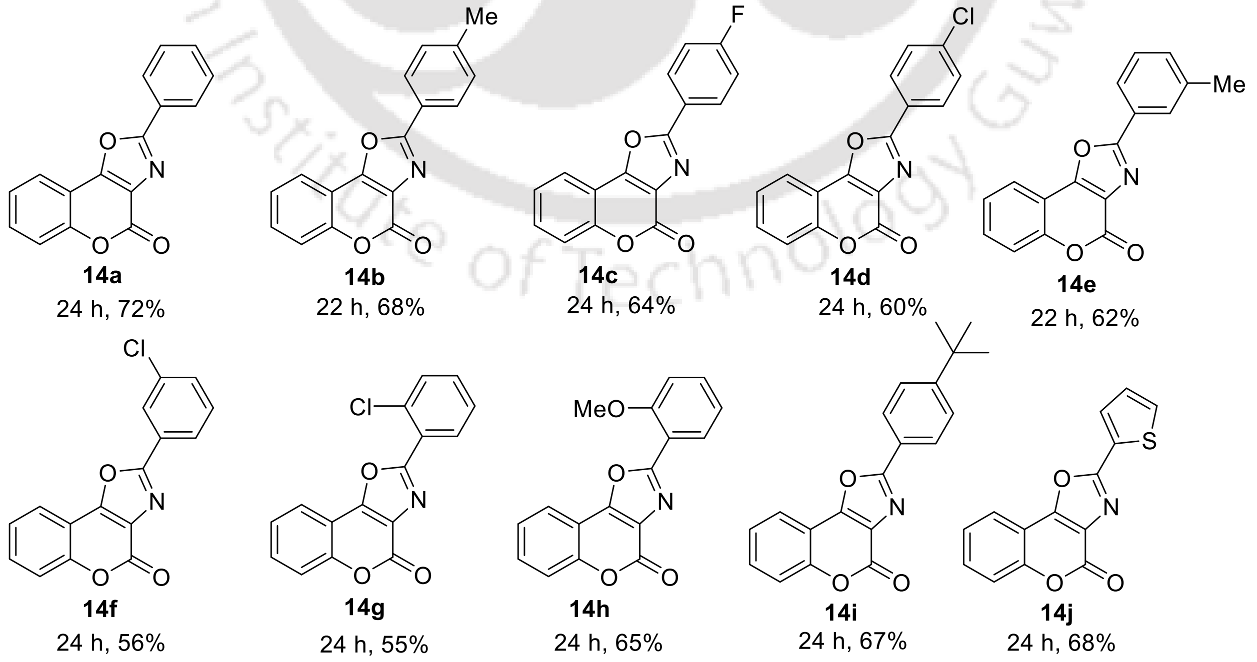
Entry	Catalyst (mol%)	Solvent	Oxidant	Time/h	Yield (%)[b]
1	CuI (10)	DCM	TBHP	18	50
2	CuBr (10)	DCM	TBHP	18	50
3	$CuBr_2$ (10)	DCM	TBHP	20	52
4	$Cu(AcO)_2.H_2O$ (10)	DCM	TBHP	24	10
5	$CuCl_2$ (10)	DCM	TBHP	18	64
6	$CuCl_2$ (15)	DCM	TBHP	18	66
7	**$CuCl_2$ (20)**	**DCM**	**TBHP**	**20**	**72**
8	$CuCl_2$ (5)	DCM	TBHP	18	61
9	CuCl (10)	DCM	TBHP	12	58
10	$Cu(NO_2)_2$ (10)	DCM	TBHP	20	60
11	$CuSO_4$ (10)	DCM	TBHP	20	57
12	$CuCl_2$(10)	DCE	TBHP	14	62
13	$CuCl_2$(20)	DCE	TBHP	14	69
14	$CuCl_2$ (10)	CH_3CN	TBHP	24	45
15	$CuCl_2$ (10)	$CHCl_3$	TBHP	32	45
16	$CuCl_2$ (10)	DMF	TBHP	32	NR
17	$CuCl_2$ (10)	DMSO	TBHP	32	NR
18	$FeCl_2$ (10)	DCM	TBHP	24	NR
19	$FeCl_3$ (10)	DCM	TBHP	24	NR
20	$CuCl_2$ (10)	DCM	-------	24	NR
21	-------	DCM	TBHP	24	NR
22	$CuCl_2$ (10)	DCM	H_2O_2	24	NR
23	$CuCl_2$ (10)	DCM	$Ph_2(CO)_2O_2$	24	NR

[a]Unless otherwise stated all the reactions were carried out with 0.3 mmol of **13a** , 3 equiv. of oxidant, in 3 mL of solvent at rt. [b]Isolated yield

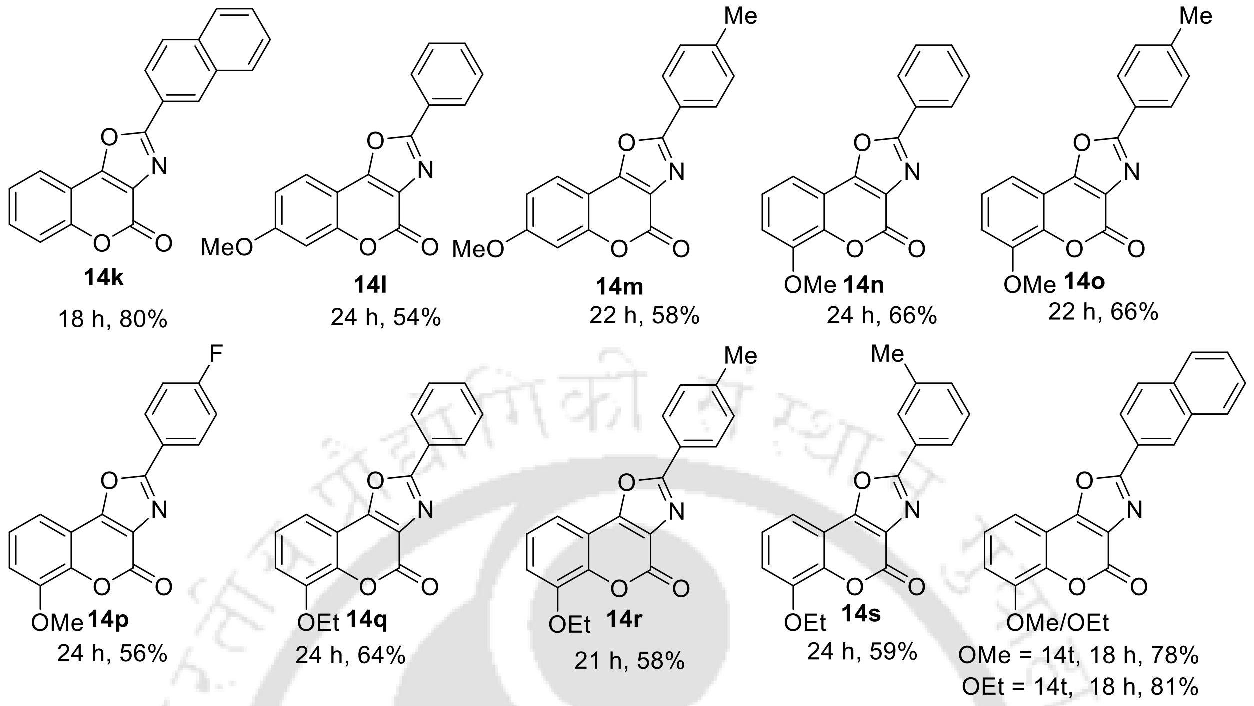
A number of 3-(benzylamino)-2*H*-chromen-2-one derivatives were synthesized using various 3-aminocoumarin and benzyl bromide derivatives and was examined to evaluate the substrates scope of the present protocol. At first, the group tolerance on the benzyl moiety was studied. Interestingly, the desired oxazole derivatives of coumarin were afforded in good yield with both electron donating- (Table 11, **14b**, **14e**, **14h** and **14i**,) and withdrawing substituents (Table 11, **14c**, **14d**, **14f** and **14g**,). Product **14j** was obtained in 68 % yield containing a heteroatom in the benzyl ring. Whereas replacing benzyl moiety with naphthyl moiety, the desired product **14k** were obtained in significant yield, but in lesser time compared to the benzyl derivatives under the optimized conditions (Table 11). The yields were comparable with substituent at the *meta*- and *para* position of the benzyl group indicating no significant role of steric hindrance for the formation of products (Table 11, **14e-h**). Notably, no product was obtained on replacing benzyl moiety with alkyl moiety.

Table 11. Synthesis of coumarin fused oxazole derivatives





14a 24 h, 72%
14b 22 h, 68%
14c 24 h, 64%
14d 24 h, 60%
14e 22 h, 62%
14f 24 h, 56%
14g 24 h, 55%
14h 24 h, 65%
14i 24 h, 67%
14j 24 h, 68%



All the reaction were carried out with 0.3 mmol of **13**, 3 equiv. of TBHP, 20 mol % of the $CuCl_2$ in 3 mL of DCM at rt. ^{b} Isolated yield.

Similarly, 3-(benzylamino)-2*H*-chromen-2-one with substituents on the coumarin moiety such as 7-MeO, 8-MeO and 8-EtO were also examined and the desired products **14l-u** were isolated in satisfactory yield (Table 11). Unfortunately, the present protocol is not feasible with electron withdrawing substituents like 6-NO_2, 6-Cl and 6-Br on the coumarin moiety.

All the products were characterized by H^1 NMR, ^{13}C NMR and HRMS spectra (see pages 107-119 for NMR, IR and HRMS data of compounds **14a-u**). Further, the structure of **14a** was also established from single XRD data (Figure 8).

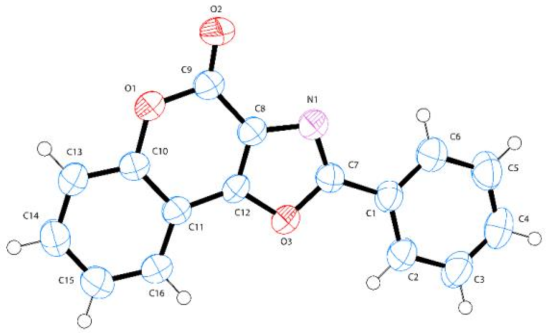
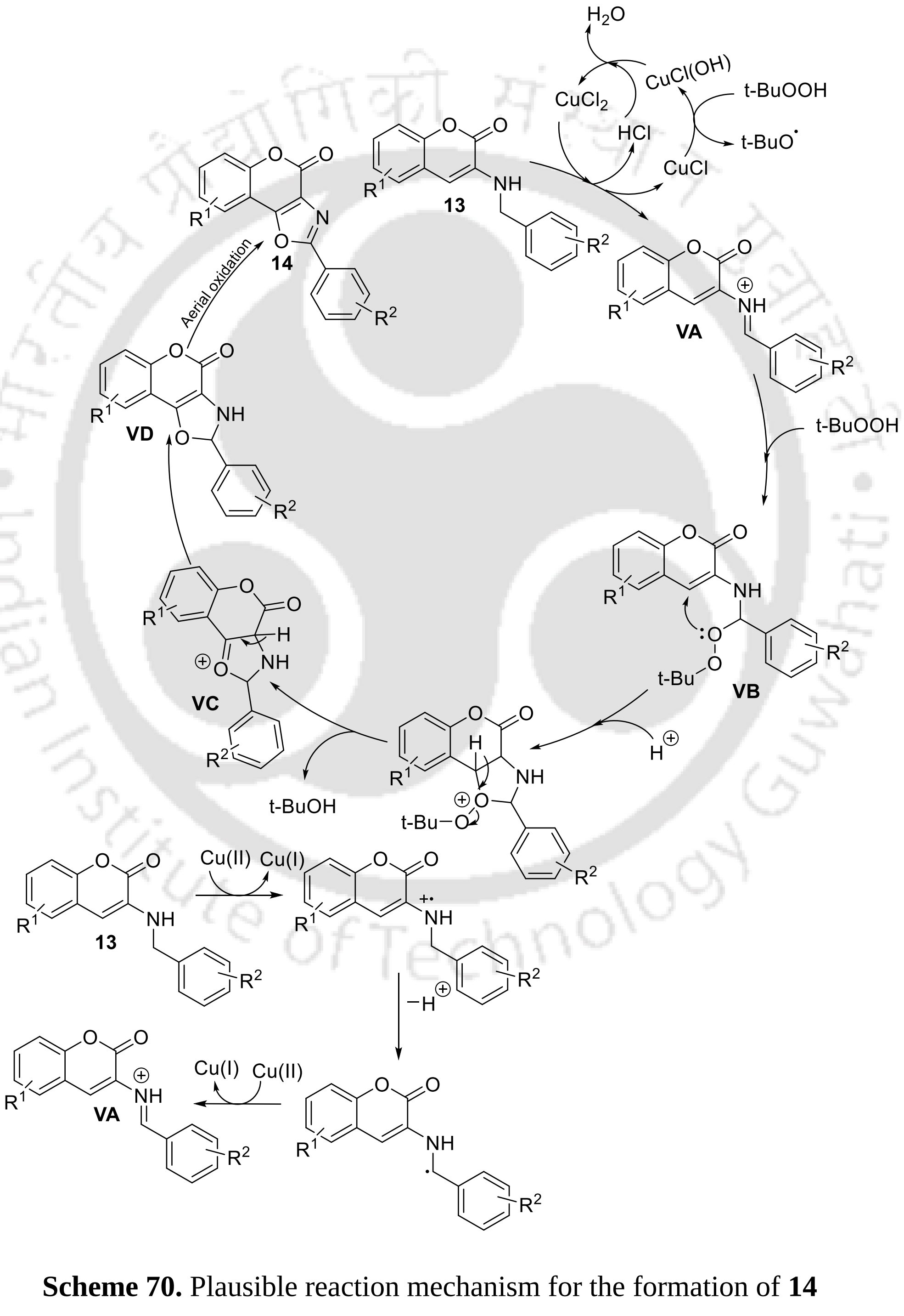


Figure 8.ORTEP diagram of **14a (**CCDC number 1405370)

From literature survey[97] and our experimental results, a plausible mechanism is presented for the formation of **14** from **13**. Initially an iminium ion **VA** (Scheme 70) might be formed from **13** with the help of TBHP/$CuCl_2$ and then another molecule of TBHP attacks the electrophilic centre of **VA** to form intermediate **VB**. Then the intermediate **VB** cyclizes to intermediate **VD** through **VC** and finally **VD** on aerial oxidation provides the desired product **14**.



Scheme 70. Plausible reaction mechanism for the formation of **14**

In summary, a novel approach have been demonstrated for the construction of various fused oxazole containing coumarin derivatives under mild reaction conditions. C-H bond functionalization followed by cyclization to various oxazoles under mild reaction condition are the salient features of the protocol. The synthesized compounds may exhibit interesting biological activity as from literature survey it reveals that coumarin and oxazole both moieties have interesting biological activates.

CHAPTER V

Synthesis of Fused Oxazole Containing Coumarin Derivatives via Oxidative Cross Coupling Reaction using a Combination of $CuCl_2$ and TBHP

EXPERIMENTAL SECTION

• Experimental Section

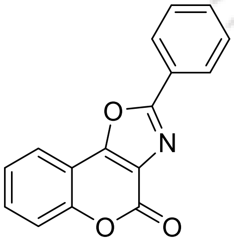
General procedure for the synthesis of various derivatives of 3-(benzylamino)-2H-chromen-2-one (13a-u):

Into a 25 mL round bottom flask was taken a mixture of 3-aminocomarin (1 mmol), benzyl bromide (1 mmol) and K_2CO_3 (1.2 mmol) in 3 mL of DMF. The reaction mixture was heated at 100 °C for 2-8 h and after completion of the reaction, the reaction mixture was worked-up with ethyl acetate. The crude product obtained after evaporation of the solvent in rotary evaporator was treated with ethanol to remove impurities. Finally a solid pure product (**1a-u**) was obtained in 75-85 %.

General procedure for the synthesis of various derivatives of 2-phenyl-4H-chromeno[3,4-d]oxazol-4-one (14a-u):

Into a 10 mL round bottom flask 0.3 mmol of **1** was taken and then 3 mL of DCM was added into it. Then after adding 20 mol % of $CuCl_2$ and 3 equivalent of TBHP, the reaction mixture was stirred at room temperature 18-24 h. The progress of the reaction was checked by TLC. After completion of the reaction, the reaction mixture was worked up with DCM and the crude product obtained after rotary evaporator was purified with column chromatography eluting with hexane and ethylacetate mixture (9:1). The pure product obtained after column chromatography was characterized by ^{1}H NMR, ^{13}C NMR and HRMS.

2-Phenyl-4H-chromeno[3,4-d]oxazol-4-one (**14a**):



14a

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 72% (57 mg) **Melting Point:** 188-190 °C

IR (KBr): 2958.00, 2923.26, 1756.03, 1606.03, 1261.51, 1156.54, 1103.31, 1064.16cm^{-1}.

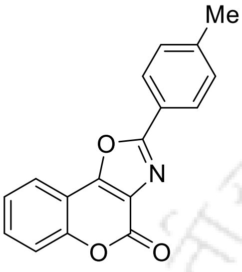
^{1}HNMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.2 Hz, 2 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.52 (m, 5 H), 7.44 (t, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 156.4, 155.5, 153.2, 132.3, 131.9, 129.3, 127.7, 126.1, 126.0, 125.2, 121.6, 118.0, 111.8 ppm.

HRMS (ESI) calcd for $C_{16}H_9NO_3$ ($M+H^+$) = 264.0655, found 264.0655.

Elemental Analysis	**Calculated**	**Found**
MF $C_{16}H_9NO_3$	C 73.00	72.85
(263.25)	H 3.45	3.50
	N 5.32	5.24

***2-(p-Tolyl)-4H-chromeno[3,4-d]oxazol-4-one* (14b):**



14b

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 68% (56 mg) **Melting Point:** 246 °C

IR (KBr): 3062.59, 2920.20, 1756.65, 1639.88, 1261.33, 1155.35, 1101.03, 1065.66 cm^{1}.

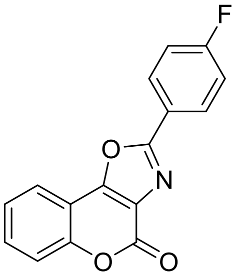
^{1}HNMR (400 MHz, CDCl$_3$) δ 8.13 (d, *J* = 8 Hz, 2 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.42 (t, *J* = 4.8 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 2.44 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 163.8, 156.4, 155.2, 153.1, 143.0, 131.7, 130.0, 127.6, 126.1, 125.1, 123.2, 121.6, 117.9, 111.8, 21.9 ppm.

HRMS (ESI) $C_{17}H_{11}NO_3$ ($M+H^+$) = 278.0812, found 278.0813.

Elemental Analysis	**Calculated**	**Found**
MF $C_{17}H_{11}NO_3$	C 73.64	73.77
(277.28)	H 4.00	3.96
	N 5.05	4.98

***2-(4-Fluorophenyl)-4H-chromeno[3,4-d]oxazol-4-one* (14c):**



14c

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 64% (54 mg) **Melting Point:** 233 °C

IR (KBr): 2924.10, 2853.13, 1737.29, 1634.64, 1229.50, 1097.64, 1068.25, 1027.01 cm^{1}.

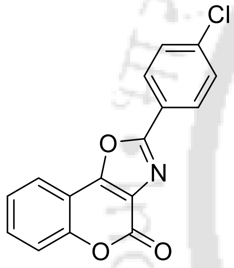
^{1}HNMR (600 MHz, CDCl$_3$): δ 8.27 (t, *J* = 7.8 Hz, 2 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.25 (t, *J* = 8.4 Hz, 2 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.6, 164.0, 162.7, 156.3, 155.5, 153.2, 132.0, 130.0, 129.95, 125.2, 122.3, 121.6, 118.0, 116.8, 116.6, 111.7 ppm.

HRMS (ESI) $C_{16}H_8FNO_3$ (M+H$^+$) = 282.0561, found 282.0567.

Elemental Analysis	Calculated	Found
MF $C_{16}H_8FNO_3$	C 68.33	68.46
(281.24)	H 2.87	2.91
	N 4.98	4.90

2-(4-Chlorophenyl)-4H-chromeno[3,4-d]oxazol-4-one **(14d):**



14d

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 60% (54 mg) **Melting Point:** 226-229 °C

IR (KBr): 2963.49, 2925.09, 2845.34, 1760.06, 1604.80, 1261.57, 1093.47, 1020.06 cm^{1}.

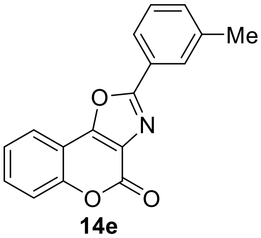
^{1}HNMR (400 MHz, CDCl$_3$) δ 8.18 (d, *J* = 8.4 Hz, 2 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 3 H), 7.43 (t, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$: CD$_2$Cl$_2$ = 5:1): δ 162.5, 156.1, 155.6, 153.2, 138.5, 132.0, 129.7, 128.8, 125.5, 125.2, 124.4, 121.6, 117.8, 111.5 ppm.

HRMS (ESI) calcd for $C_{16}H_8ClNO_3$ (M+H$^+$) = 298.0265 (found 298.0278).

Elemental Analysis	Calculated	Found
MF $C_{16}H_8ClNO_3$	C 64.55	64.69
(297.69)	H 2.71	2.75
	N 4.71	4.78

***2-(m-Tolyl)-4H-chromeno[3,4-d]oxazol-4-one* (14e):**



14e

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 62% (52 mg) **Melting Point:** 188 °C

IR (KBr): 2956.72, 2918.40, 1753.81, 1639.30, 1102.98, 1060.65, 1031.94 cm^{-1}.

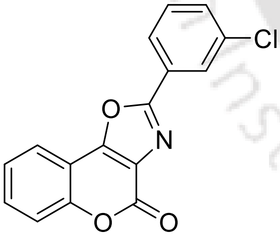
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.08 (s, 1 H), 8.04 (d, *J* = 6.8 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.37 (d, *J* = 7.2 Hz, 1 H), 2.45 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 163.7, 155.4, 153.2, 139.2, 133.1, 131.8, 129.2, 128.2, 125.8, 125.1, 124.8, 121.6, 117.9, 111.8, 21.5 ppm.

HRMS (ESI) calcd for $C_{17}H_{11}NO_3$ (M+H$^+$) = 278.0812, found 278.0817.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{11}NO_3$	C 73.64	73.79
(277.28)	H 4.00	3.95
	N 5.05	4.97

***2-(3-Chlorophenyl)-4H-chromeno[3,4-d]oxazol-4-one* (14f):**



14f

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 56% (50 mg) **Melting Point:** 232-234 °C

IR (KBr): 2923.34, 2852.57, 1755.61, 1638.29, 1286.06, 1096.19, 1052.92, 1029.17 cm^{-1}.

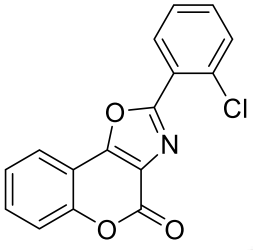
^{1}HNMR (600 MHz, CDCl$_3$): δ 8.26 (t, *J* = 1.8 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H),7.95 (dd, *J* = 7.8, 1.8 Hz, 1 H) 7.64 (m, 1 H), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.50 (t, *J* = 8.4 Hz, 1 H), 7.45 (t, *J* = 7.2 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 162.1, 156.2, 155.7, 153.3, 135.5, 132.3, 132.2, 130.7, 127.6, 127.5, 126.1, 125.7, 125.3, 121.7, 118.0, 111.6 ppm.

HRMS (ESI) calcd for $C_{16}H_8ClNO_3$ (M+H$^+$) = 298.0265, found 298.0271.

Elemental Analysis	**Calculated**	**Found**
MF $C_{16}H_8ClNO_3$	C 64.55	64.33
(297.69)	H 2.71	2.77
	N 4.71	4.62

2-(2-Chlorophenyl)-4H-chromeno[3,4-d]oxazol-4-one (**14g**)**:**



14g

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 55% (49 mg) **Melting Point:** 171-173 °C

IR (KBr): 2924.13, 2852.45, 1757.06, 1641.27, 1167.90, 1068.50, 1034.42cm^{-1}.

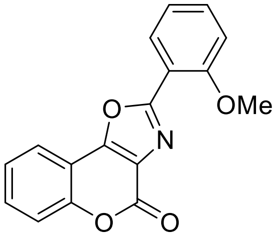
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.23 (d, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 7.6 Hz, 1 H), 7.63 (t, *J* = 8.8 Hz, 1 H), 7.59 (d, *J* = 8.4 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.49 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.46 (d, *J* = 3.6 Hz, 1 H), 7.45 (d, *J* = 3.2 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 161.6, 156.2, 155.8, 153.3, 133.6, 132.8, 132.2, 131.7, 127.4, 125.8, 125.2, 125.0, 121.9, 118.0, 111.7 ppm.

HRMS (APCI) calcd for $C_{16}H_8ClNO_3$ (M+H$^+$) = 298.0265, found 298.0268.

Elemental Analysis	**Calculated**	**Found**
MF $C_{16}H_8ClNO_3$	C 64.55	64.68
(297.69)	H 2.71	2.66
	N 4.71	4.65

2-(2-Methoxyphenyl)-4H-chromeno[3,4-d]oxazol-4-one **(14h):**



14h

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 65 % (57 mg) **Melting Point:** 168-170 °C

IR (KBr): 2956.26, 2924.46, 2853.39, 1751.49, 1652.71, 1265.42, 1161.69, 1069.43, 1021.09 cm^{-1}.

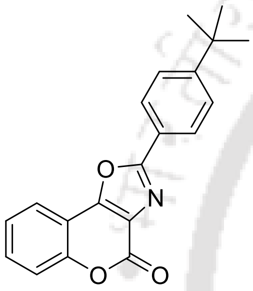
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.16 (d, *J* = 7.2 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.59 (m, 1 H), 7.52 (t, *J* = 8.4 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.11 (m, 2 H), 4.02 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 162.4, 158.6, 156.4, 155.2, 153.2, 138.5, 133.6, 131.7, 131.4, 125.0, 121.7, 121.0, 117.8, 115.0, 112.3, 111.9, 56.2 ppm.

HRMS (ESI) calcd for $C_{17}H_{11}NO_4$ (M+H$^+$) = 294.0761, found 294.0778.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{11}NO_4$	C 69.62	69.80
(293.28)	H 3.78	3.70
	N 4.78	4.87

***2-(4-(tert-butyl)phenyl)-4H-chromeno[3,4-d]oxazol-4-on*e (14i):**



14i

Reaction Time: 24 h

Colour & State: pale yellow solid

Yield: 67% (64 mg)

Melting Point: 207-209 °C

IR (KBr): 3066.92, 2949.93, 1753.50, 1684.67, 1285.19, 1167.19, 1063.56, 1041.90 cm^{-1}

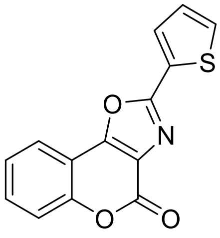
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.19 (d, J = 8.4 Hz, 2 H), 7.94 (d, J = 7.6 Hz, 1 H), 7.61 (t, J = 7.4 Hz, 1 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 1 H), 7.43 (t, J = 7.2 Hz, 1 H), 1.38 (s, 9 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 163.8, 156.6, 156.1, 155.3, 153.1, 131.8, 127.5, 126.3, 126.1, 125.1, 123.1, 121.6, 117.9, 111.8, 35.4, 31.3 ppm.

HRMS (APCI+) calcd for $C_{19}H_{17}NO_3$ (M+H$^+$) = 320.1281, found 320.1280.

Elemental Analysis	Calculated	Found
MF $C_{20}H_{17}NO_3$	C 75.22	75.38
(319.36)	H 5.37	5.41
	N 4.39	4.29

***2-(Thiophen-2-yl)-4H-chromeno[3,4-d]oxazol-4-one* (14j):**



14j

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 68% (55 mg) **Melting Point:** 170-172 °C

IR (KBr): 3095.65, 2924.28, 2853.43, 1752.86, 1634.11, 1210.78, 1101.71, 1068.24, 1032.66 cm^{-1}.

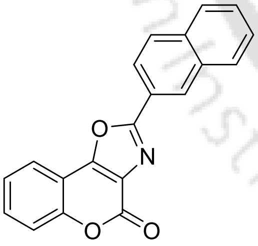
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.95 (d, *J* = 3.2 Hz, 1 H), 7.90 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.60 (m, 2 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.21 (t, *J* = 4.8 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 159.5, 156.2, 155.0, 153.1, 131.9, 131.3, 130.8, 128.6, 128.0, 126.0, 125.2, 121.6, 117.9, 111.5 ppm.

HRMS (ESI) calcd for $C_{14}H_7NO_3S$ (M+H$^+$) = 270.0219, found 270.0240.

Elemental Analysis	Calculated	Found
MF $C_{14}H_7NO_3S$	C 62.45	62.33
(269.27)	H 2.62	2.57
	N 5.20	5.12

***2-(Naphthalen-2-yl)-4H-chromeno[3,4-d]oxazol-4-one* (14k):**



14k

Reaction Time: 18 h **Colour & State:** pale yellow solid

Yield: 80% (75 mg) **Melting Point:** 245 °C

IR (KBr): 2925.03, 2852.61, 1755.81, 1605.26, 1101.74, 1067.46, 1029.24 cm^{-1}.

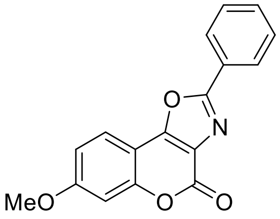
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.77 (s, 1 H), 8.30 (d, *J* = 8.8 Hz, 1 H), 7.99 (d, *J* = 8 Hz, 3 H), 7.90 (d, *J* = 8.8 Hz, 1 H), 7.61 (m, 3 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 163.8, 156.4, 155.5, 153.2, 135.1, 133.0, 131.9, 129.3, 129.2, 128.4, 128.36, 128.2, 127.4, 126.6, 125.2, 123.7, 123.2, 121.7, 118.0, 111.8 ppm.

HRMS (ESI) calcd for $C_{20}H_{11}NO_3$ (M+H$^+$) = 314.0812, found 314.0816.

Elemental Analysis	**Calculated**	**Found**
MF $C_{20}H_{11}NO_3$	C 76.67	76.81
(313.31)	H 3.54	3.47
	N 4.47	4.37

***7-Methoxy-2-phenyl-4H-chromeno[3,4-d]oxazol-4-one* (14l):**



14l

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 54% (47 mg) **Melting Point:** 209 °C

IR (KBr): 2924.88, 2852.86, 1748.58, 1638.71, 1151.36, 1117.36, 1061.23, 1029.99 cm^{-1}.

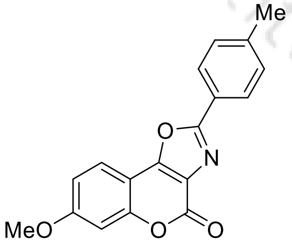
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.22 (d, *J* = 6.4 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.54 (m, 3 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 3.91(s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 162.7, 162.3, 156.3, 155.7, 154.8, 131.7, 129.0, 127.2, 125.8, 123.4, 122.3, 113.3, 104.6, 101.6, 55.8 ppm.

HRMS (ESI) calcd for $C_{17}H_{11}NO_4$ (M+H$^+$) = 294.0761, found 294.0774.

Elemental Analysis	**Calculated**	**Found**
MF $C_{17}H_{11}NO_4$	C 69.62	69.82
(293.28)	H 3.78	3.83
	N 4.78	4.86

***7-Methoxy-2-(p-tolyl)-4H-chromeno[3,4-d]oxazol-4-one* (14m):**



14m

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 58% (53 mg) **Melting Point:** 220 °C

IR (KBr): 2923.23, 2854.65, 1767.39, 1638.09, 1270.71, 1103.27, 1059.04, 1023.23 cm^{-1}.

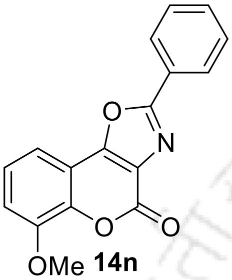
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.10 (d, *J* = 6.4 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 6.4 Hz, 2 H), 6.98 (s, 2 H) 3.83 (s, 3 H), 2.36 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 162.9, 156.7, 155.9, 155.0, 142.7, 130.0, 127.5, 123.7, 123.4, 122.5, 113.6, 105.0, 101.9, 56.1, 21.9 ppm.

HRMS (ESI) calcd for $C_{18}H_{13}NO_4$ ($M+H^+$) = 308.0917, found 308.0931.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{13}NO_4$	C 70.35	70.49
(307.30)	H 4.26	4.20
	N 4.56	4.49

***6-Methoxy-2-phenyl-4H-chromeno[3,4-d]oxazol-4-one* (14n):**



14n

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 66% (58 mg) **Melting Point:** 220 °C

IR (KBr): 3063.33, 2997.68, 2928.07, 2844.55, 1759.97, 1640.76, 1277.78, 1075.41, 1043.28, 1002.19 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 6.0 Hz, 2 H), 7.56 (m, 3 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 4.00(s, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 155.8, 155.6, 148.2, 132.3, 129.3, 129.0, 127.7, 126.2, 126.0, 125.4, 113.9, 112.9, 112.5, 56.6 ppm.

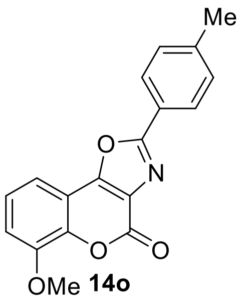
HRMS (ESI) calcd for $C_{17}H_{11}NO_4$ ($M+H^+$) = 294.0761, found 294.0766.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{11}NO_4$	C 69.62	69.45
(293.28)	H 3.78	3.74
	N 4.78	4.70

***6-Methoxy-2-(p-tolyl)-4H-chromeno[3,4-d]oxazol-4-one* (14o):**

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 66% (61 mg) **Melting Point:** 238 °C



14o

IR (KBr): 2923.41, 2850.78, 1753.51, 1610.64, 1275.99, 1081.42, 1048.66, 996.21 cm^{-1}.

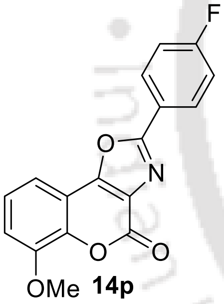
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.11 (d, *J* = 7.2 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.33 (t, *J*= 8.0 Hz, 3 H), 7.11 (d, *J* = 7.6 Hz, 1 H), 3.99 (s, 3 H), 2.43 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 163.8, 155.9, 155.3, 148.1, 143.0, 142.9, 130.0, 127.6, 126.2, 125.3, 123.2, 113.7, 112.9, 112.5, 56.6, 21.9 ppm.

HRMS (ESI) calcd for $C_{18}H_{13}NO_4$ (M+H$^+$) = 308.0917, found 308.0923.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{13}NO_4$	C 70.35	70.50
(307.30)	H 4.26	4.31
	N 4.56	4.48

***2-(4-Fluorophenyl)-6-methoxy-4H-chromeno[3,4-d]oxazol-4-one* (14p):**



14p

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 56% (52 mg) **Melting Point:** 248 °C

IR (KBr): 2923.84, 2852.00, 1751.45, 1637.57, 1277.09, 1100.90, 1081.26, 1046.33 cm^{-1}.

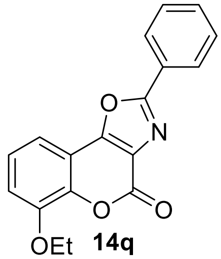
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.26 (dd *J* = 7.6, 5.2 Hz, 2 H), 7.49 (d, *J* = 8 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 4.01 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.6, 164.0, 162.7, 155.8, 155.7, 148.2, 143.0, 130.0, 129.95, 126.2, 125.4, 122.3, 116.8, 116.6, 113.9, 112.9, 112.4, 56.6 ppm.

HRMS (ESI) calcd for $C_{17}H_{10}NO_4$ (M+H$^+$) = 312.0667, found 312.0682.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{10}FNO_4$	C 65.60	65.78
(311.27)	H 3.24	3.20
	N 4.50	4.42

***6-Ethoxy-2-phenyl-4H-chromeno[3,4-d]oxazol-4-one* (14q):**


14q

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 64% (59 mg) **Melting Point:** 218 °C

IR (KBr): 2967.46, 2920.28, 2845.34, 1752.51, 1603.25, 1276.85, 1081.11, 1045.09, 1017.41 cm^{-1}.

^{1}HNMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 6.4 Hz, 2 H), 7.55 (m, 3 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.34 (t, *J* = 8.4 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 4.22 (q, *J* = 6.4 Hz, 2 H), 1.54 (t, *J* = 6.8 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 156.1, 155.7, 147.6, 143.2, 132.3, 129.3, 127.7, 126.0, 125.4, 115.1, 112.9, 112.6, 65.4, 15.0 ppm.

HRMS (ESI) calcd for $C_{18}H_{13}NO_4$ (M+H$^+$) = 308.0917, found 308.0917.

Elemental Analysis	**Calculated**	**Found**
MF $C_{18}H_{13}NO_4$	C 70.35	70.51
(307.30)	H 4.26	4.21
	N 4.56	4.64

***6-Ethoxy-2-(p-tolyl)-4H-chromeno[3,4-d]oxazol-4-one* (14r):**


14r

Reaction Time: 21 h **Colour & State:** pale yellow solid

Yield: 58% (56 mg) **Melting Point:** 195-197 °C

IR (KBr): 2959.14, 2923.05, 2844.49, 1752.97, 1637.36, 1276.51, 1262.41, 1081.73, 1102.88, 1017.50 cm^{-1}.

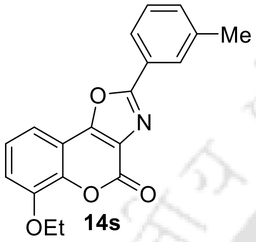
^{1}HNMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.23 (m, 3 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 4.14 (q, *J* = 6.4, 2 H), 2.37 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 156.1, 155.4, 147.5, 143.1, 142.9, 130.0, 127.6, 126.1, 125.3, 123.2, 115.0, 112.8, 112.6, 65.4, 21.9, 15.0 ppm.

HRMS (ESI) calcd for $C_{19}H_{15}NO_4$ (M+H$^+$) = 322.1074, found 322.1077.

Elemental Analysis	**Calculated**	**Found**
MF $C_{19}H_{15}NO_4$	C 71.02	71.21
(321.33)	H 4.71	4.75
	N 4.36	4.26

***6-Ethoxy-2-(m-tolyl)-4H-chromeno[3,4-d]oxazol-4-one* (14s):**



14s

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 59% (57 mg) **Melting Point:** 189 °C

IR (KBr): 2924.09, 2852.21, 1747.07, 1640.50, 1278.12, 1104.94, 1047.03, 1019.35 cm^{-1}.

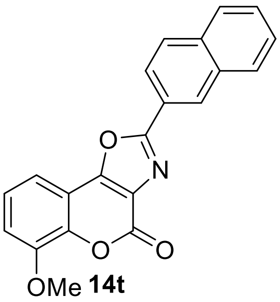
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.08 (s, 1 H), 8.03 (d, J = 7.2 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.40 (t, J = 8.0 Hz, 1 H), 7.36 (t, J = 5.6 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.12 (d, J = 7.6 Hz, 1 H), 4.21 (q, J = 6.8 Hz, 2 H), 2.45 (s, 3 H), 1.52 (t, J = 7.2 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 163.7, 156.0, 155.6, 147.5, 143.1, 139.2, 133.1, 129.2, 128.2, 126.1, 125.8, 125.3, 124.8, 115.0, 112.8, 112.5, 65.4, 21.5, 15.0 ppm.

HRMS (ESI) calcd for $C_{19}H_{15}NO_4$ (M+H$^+$) = 322.1074, found 322.1079.

Elemental Analysis	**Calculated**	**Found**
MF $C_{19}H_{15}NO_4$	C 71.02	71.20
(321.33)	H 4.71	4.66
	N 4.36	4.28

***6-Methoxy-2-(naphthalen-2-yl)-4H-chromeno[3,4-d]oxazol-4-one* (14t):**



14t

Reaction Time: 18 h **Colour & State:** pale yellow solid

Yield: 78% (80 mg) **Melting Point:** 270 °C

IR (KBr): 2924.69, 2852.94, 1759.34, 1603.15, 1603.15, 1273.60, 1111.62, 1048.71 cm^{-1}.

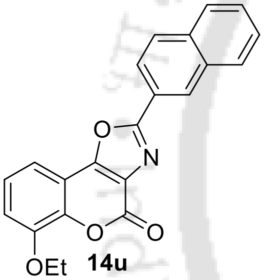
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.76 (s, 1 H), 8.29 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 8 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.59 (t, *J* = 3.6 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 4.01 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 163.8, 155.8, 155.7, 148.2, 135.1, 133.1, 129.3, 129.2, 128.4, 128.36, 128.2, 127.4, 126.4, 125.4, 123.8, 123.2, 113.9, 113.0, 112.5, 56.6 ppm.

HRMS (ESI) calcd for $C_{21}H_{13}NO_4$ (M+H^{+}) = 344.0917, found 344.0923.

Elemental Analysis	**Calculated**	**Found**
MF $C_{21}H_{13}NO_4$	C 73.46	73.31
(343.34)	H 3.82	3.77
	N 4.08	3.99

***6-Ethoxy-2-(naphthalen-2-yl)-4H-chromeno[3,4-d]oxazol-4-one* (14u):**



14u

Reaction Time: 18 h **Colour & State:** pale yellow solid

Yield: 81% (87 mg) **Melting Point:** 221 °C

IR (KBr): 2924.43, 2852.64, 1760.02, 1605.56, 1272.39, 2080.36, 1051.17, 1013.12 cm^{1}.

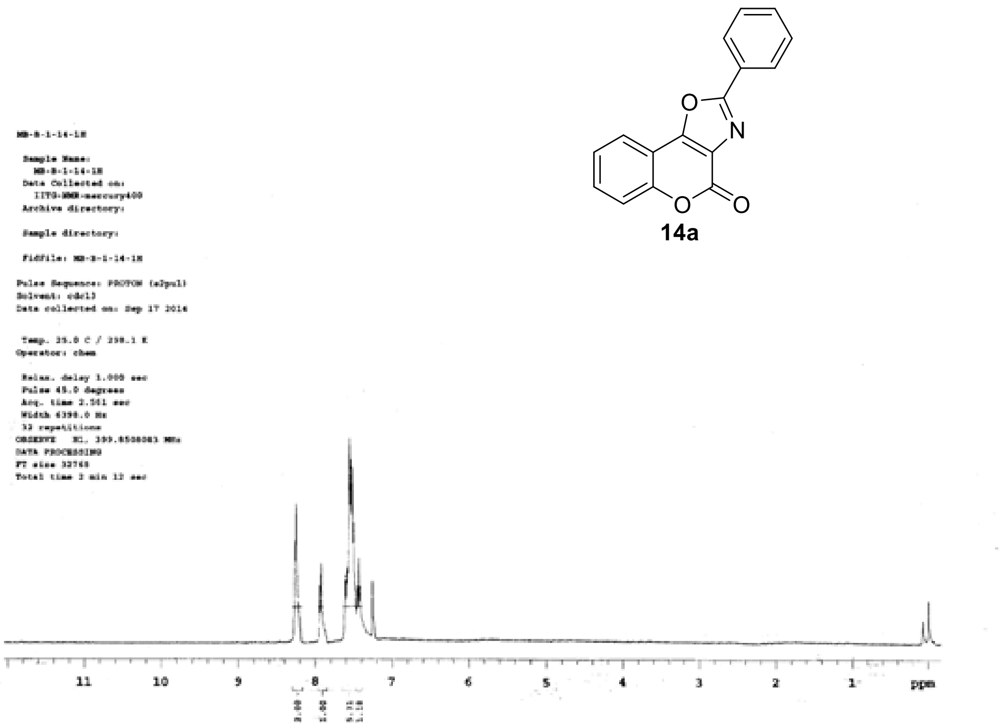
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.76 (s, 1 H), 8.29 (d, *J* = 8.4 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 2 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 7.59 (t, *J* = 4 Hz, 2 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 1.54 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 163.7, 156.1, 155.8, 147.6, 135.1, 133.1, 129.3, 129.2, 128.4, 128.3, 128.2, 127.4, 126.3, 125.4, 123.7, 123.2, 115.2, 112.9, 112.6, 65.4, 15.0ppm.

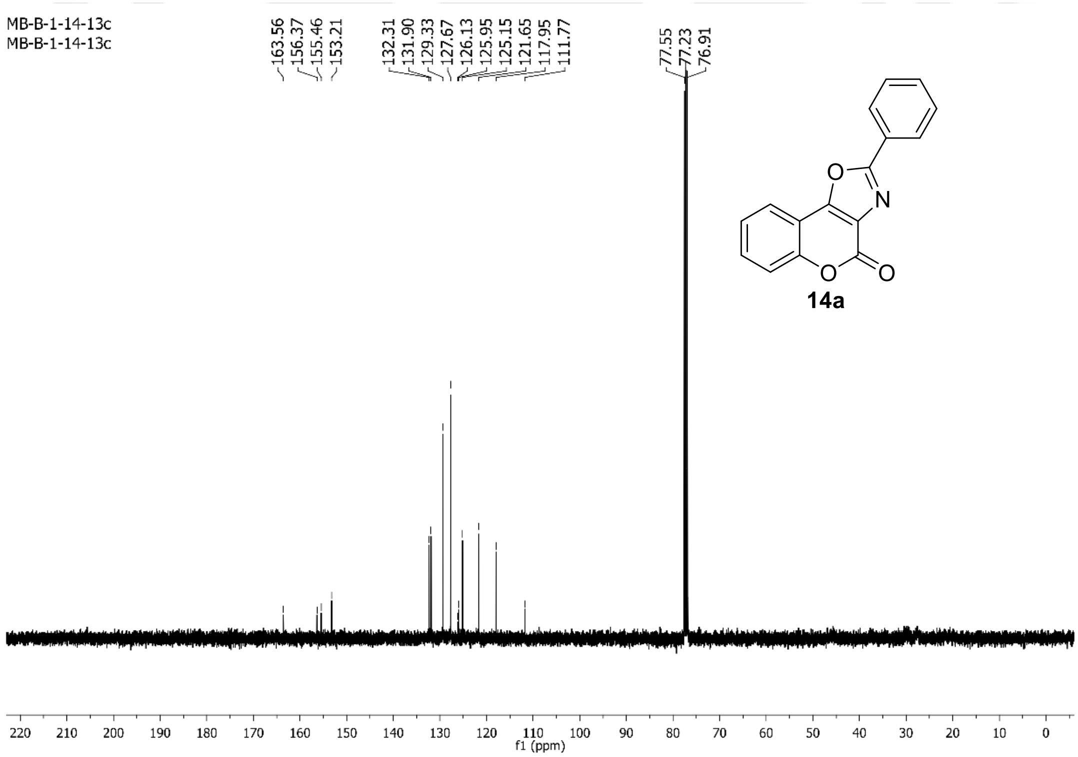
HRMS (ESI) calcd for $C_{22}H_{15}NO_4$ (M+H^{+}) = 358.1074, found 358.1096.

Elemental Analysis	**Calculated**	**Found**
MF $C_{22}H_{15}NO_4$	C 73.94	74.11
(357.36)	H 4.23	4.18
	N 3.92	3.86

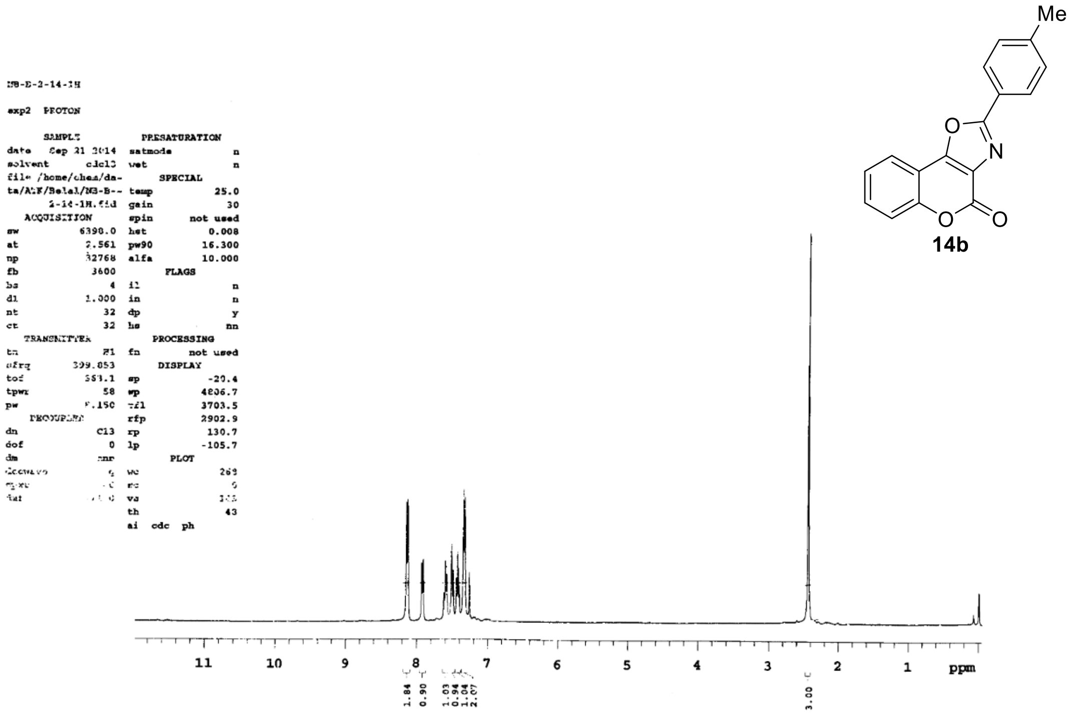
^{1}HNMR (400 MHz, CDCl$_3$): *2-phenyl-4H-chromeno[3,4-d]oxazol-4-one* (**14a**)



^{13}C NMR (100 MHz, CDCl$_3$): *2-phenyl-4H-chromeno[3,4-d]oxazol-4-one* (**14a**)



^{1}***HNMR (400 MHz, CDCl$_3$)***: *2-(p-Tolyl)-4H-chromeno[3,4-d]oxazol-4-one* (**14b**)



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MB-B-2-14-1H

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solvent      cdcl3  wet                n
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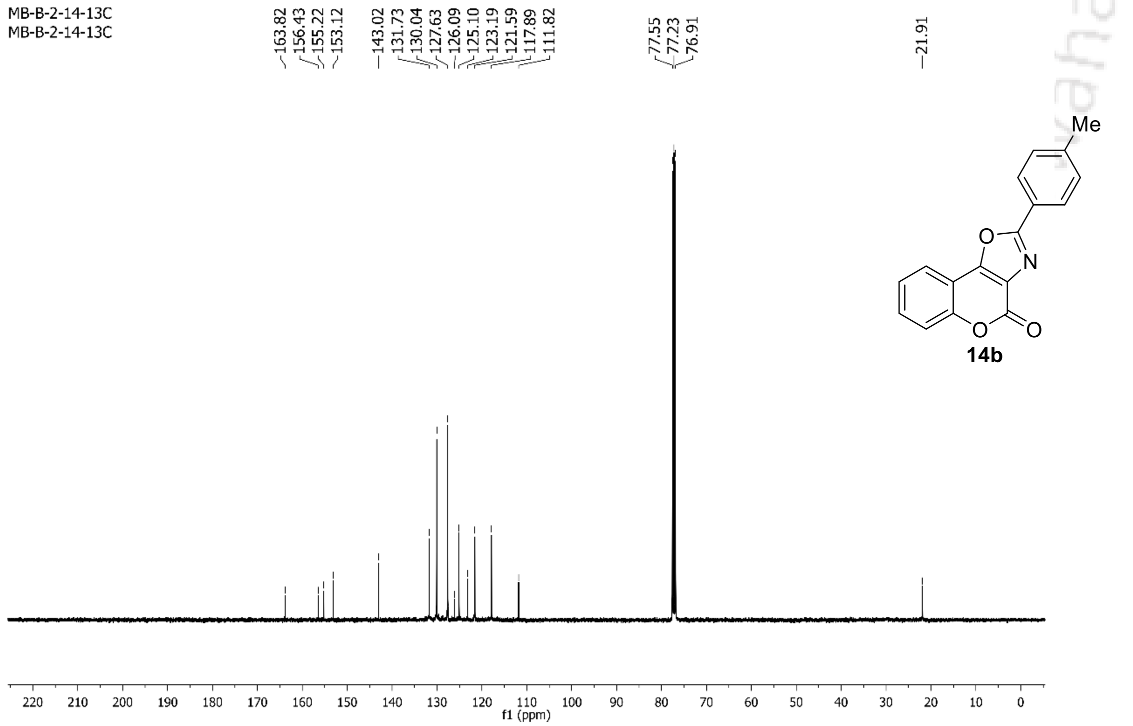
ta/AKF/Belal/MB-B--  temp            25.0
      2-14-1H.fid   gain              30
   ACQUISITION      spin        not used
sw          6398.0  hst            0.008
at           2.561  pw90          16.300
np           32768  alfa          10.000
fb            3600         FLAGS
bs               4  il                 n
dl           1.000  in                 n
nt              32  dp                 y
ct              32  hs                nn
   TRANSMITTER          PROCESSING
tn              H1  fn          not used
sfrq       399.053         DISPLAY
tof          551.1  sp             -20.4
tpwr            58  wp            4806.7
pw           8.150  rfl           3703.5
    DECOUPLER       rfp           2902.9
dn             C13  rp             130.7
dof              0  lp            -105.7
dm             nnn          PLOT
[illegible]         wc               269
[illegible]         sc                 0
[illegible]         vs               [illegible]
                    th                43
                    ai   cdc   ph
```

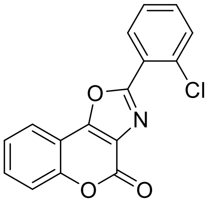
14b

^{13}***C NMR (100 MHz, CDCl$_3$)****: 2-(p-Tolyl)-4H-chromeno[3,4-d]oxazol-4-one* (**14b**)

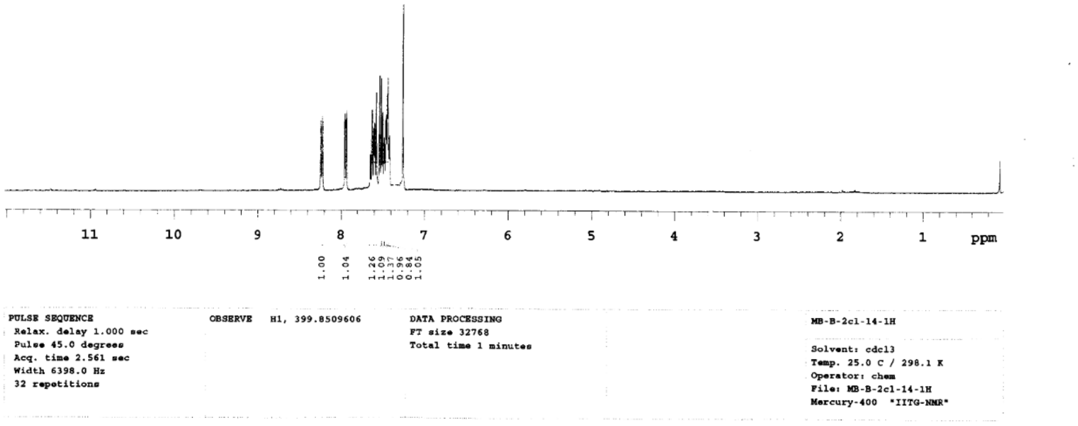


14b

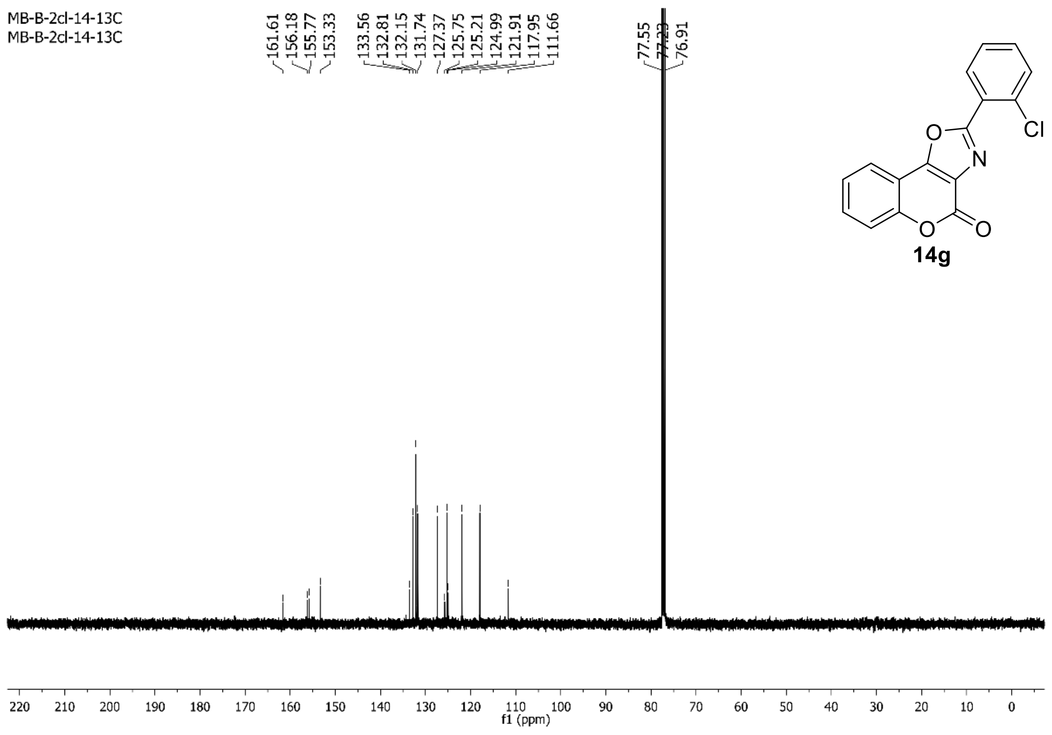
^{1}HNMR (400 MHz, CDCl$_3$): *2-(2-Chlorophenyl)-4H-chromeno[3,4-d]oxazol-4-one* (**14g**)



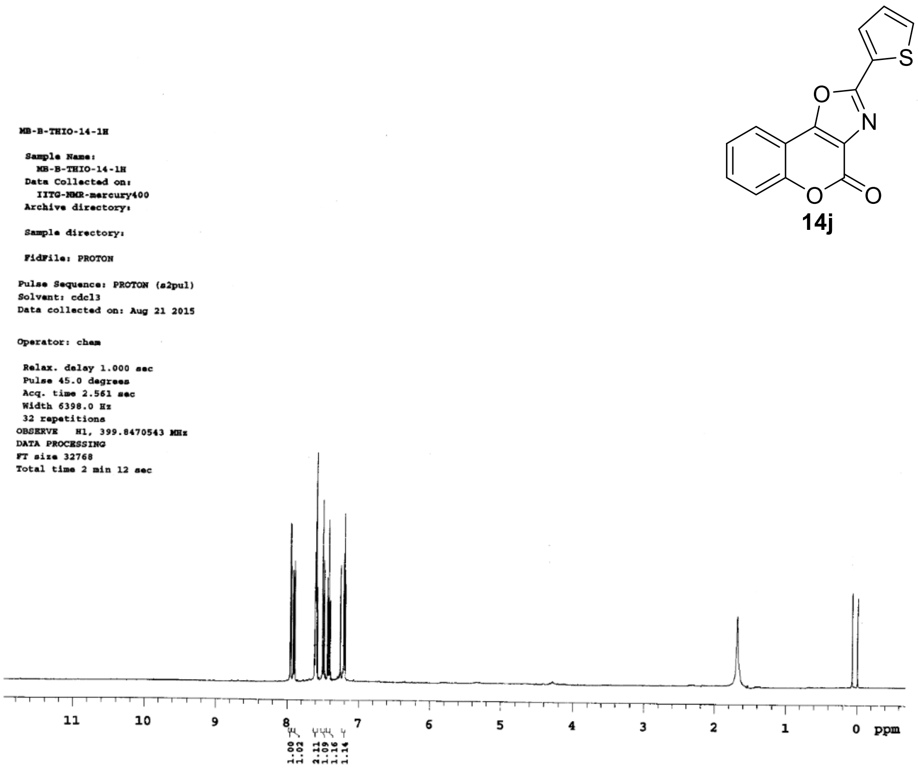
14g



^{13}C NMR (100 MHz, CDCl$_3$): *2-(2-Chlorophenyl)-4H-chromeno[3,4-d]oxazol-4-one* (**14g**)



^{1}HNMR (400 MHz, CDCl$_3$): *2-(Thiophen-2-yl)-4H-chromeno[3,4-d]oxazol-4-one* (**14j**)


MB-B-THIO-14-1H

Sample Name:
MB-B-THIO-14-1H
Data Collected on:
IITG-NMR-mercury400
Archive directory:

Sample directory:

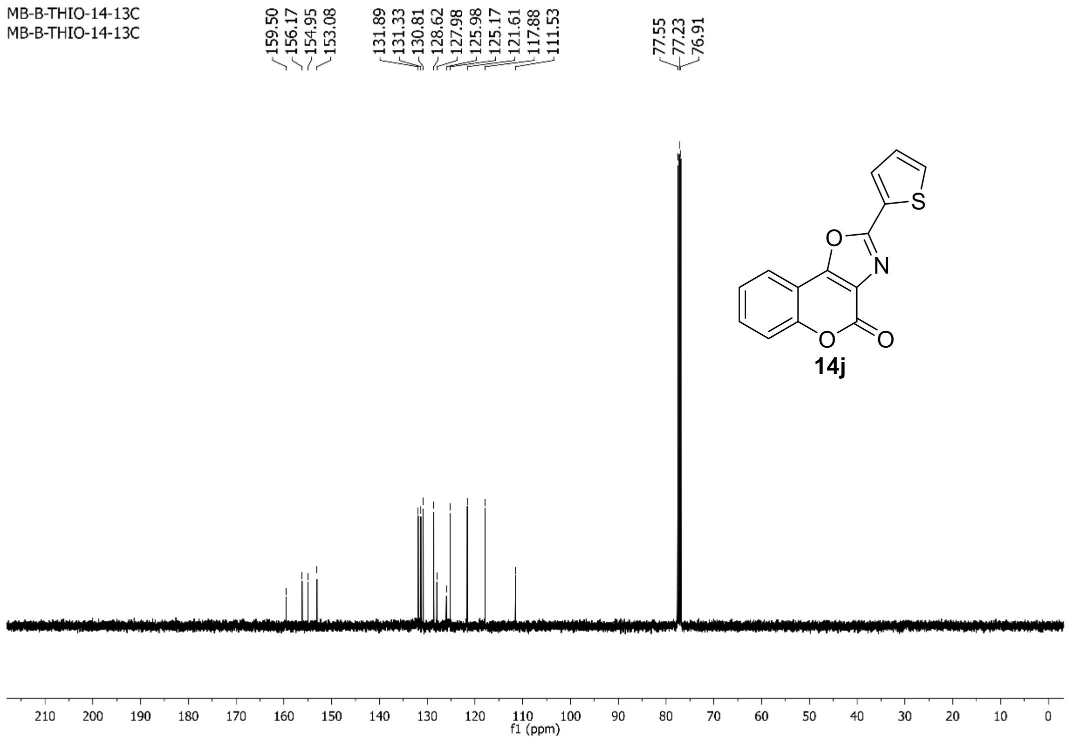
FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 21 2015

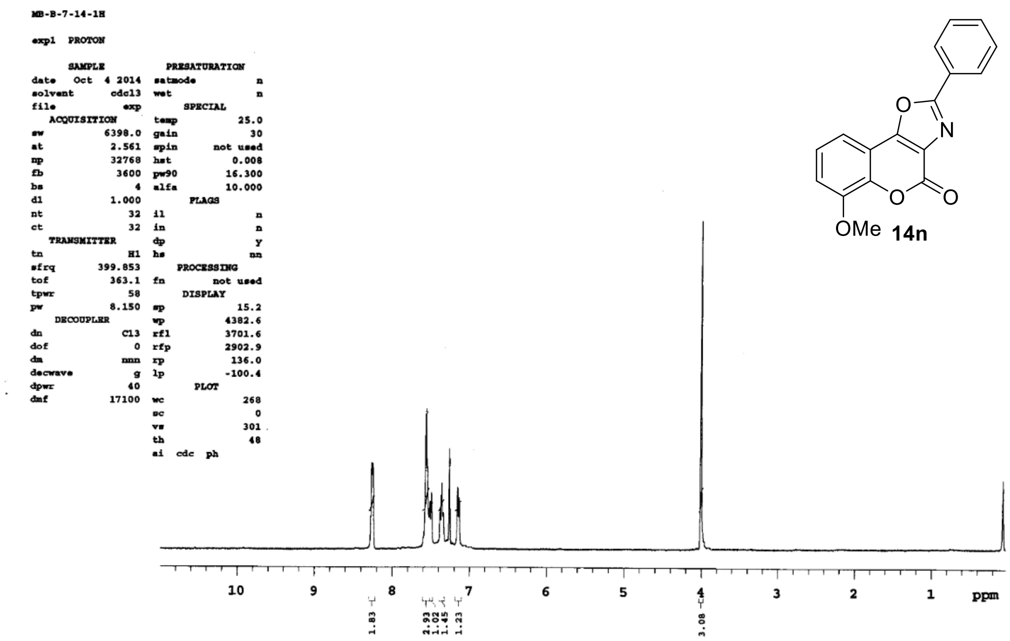
Operator: chem

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions
OBSERVE H1, 399.8470543 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 12 sec

^{13}C NMR (100 MHz, CDCl$_3$): *2-(Thiophen-2-yl)-4H-chromeno[3,4-d]oxazol-4-one* (**14j**)



^{1}HNMR (400 MHz, CDCl$_3$): *6-Methoxy-2-phenyl-4H-chromeno[3,4-d]oxazol-4-one* (**14n**)

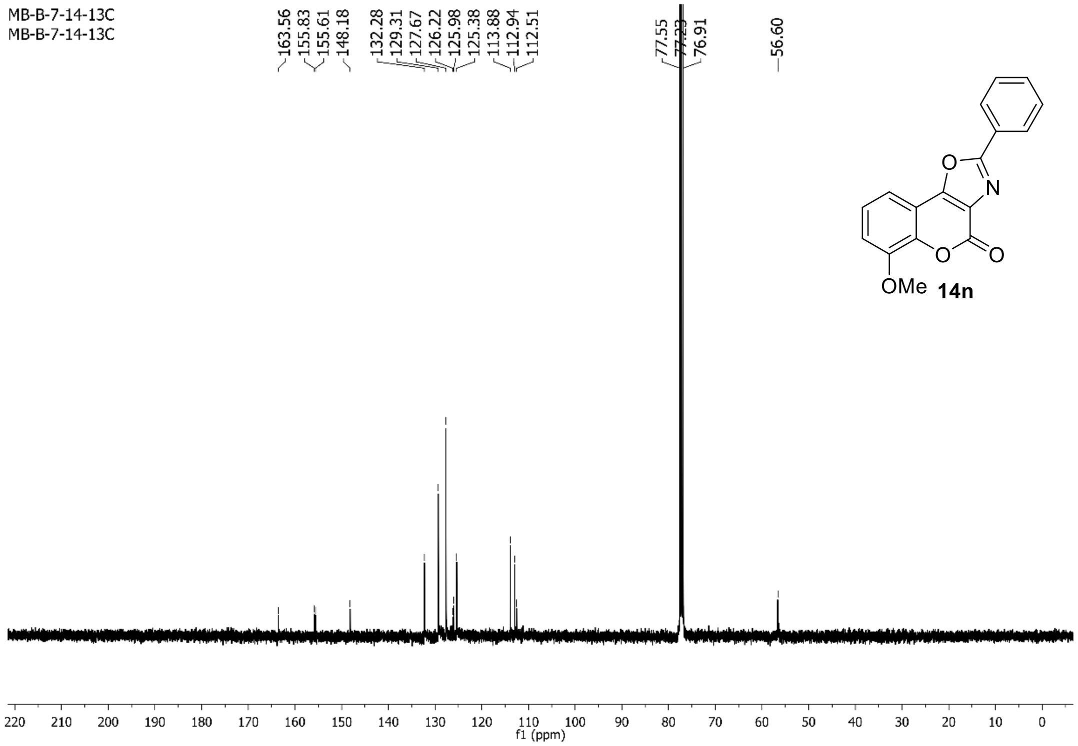


```
MB-B-7-14-1H

exp1  PROTON

     SAMPLE             PRESATURATION
date    Oct  4 2014  satmode          n
solvent       cdcl3  wet              n
file            exp       SPECIAL
  ACQUISITION        temp          25.0
sw           6398.0  gain            30
at            2.561  spin      not used
np            32768  hst          0.008
fb             3600  pw90        16.300
bs                4  alfa        10.000
d1            1.000        FLAGS
nt               32  il               n
ct               32  in               n
  TRANSMITTER        dp               y
tn               H1  hs              nn
sfrq        399.853     PROCESSING
tof           363.1  fn        not used
tpwr             58       DISPLAY
pw            8.150  sp            15.2
   DECOUPLER         wp          4382.6
dn              C13  rfl         3701.6
dof               0  rfp         2902.9
dm              nnn  rp           136.0
decwave           g  lp          -100.4
dpwr             40         PLOT
dmf           17100  wc             268
                     sc               0
                     vs             301
                     th              48
                     ai   cdc   ph
```

^{13}C NMR (100 MHz, CDCl$_3$): *6-Methoxy-2-phenyl-4H-chromeno[3,4-d]oxazol-4-one* (**14n**)



Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

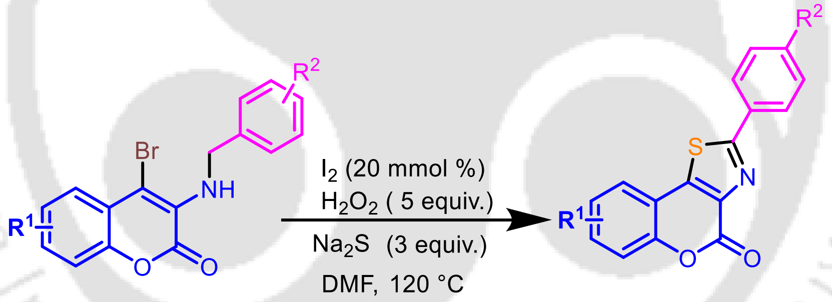
Table 12. Crystal data and structure refinements of compounds **14a**. For atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check CIF.

Parameters	**Compound 14a**
Empirical Formula	$C_{16}H_9NO_3$
Formula Weight	263.24
Temperature	296(2) K
CCDC No.	1405370
Wavelength (A^o)	0.71073
Crystal System	monoclinic
Space group	P2(1)/n
Radiation type	MoK\a
Radiation source	fine-focus sealed tube
a (A^o)	7.1596(4)
b (A^o)	13.3572(7)
c (A^o)	13.0999(6)
α (^{o})	90.00
β (^{o})	98.358(4)
γ (^{o})	90.00
Cell Voloume	1239.47(11)
z	4
Density	1.411
F (0 0 0)	544
Theta ranges	2.19 to 27.50
Index ranges	$-9 \le h \le 9$, $-17 \le k \le 13$, $-16 \le l \le 16$
Reflection collected	14724
Independent reflections	2784
Completeness to theta	0.977
Number of parameters	181

Number of restraints	0
Godness of fit (GOF)on F^2	0.976
Refinement method	Full-matrix least square on F2

CHAPTER VI

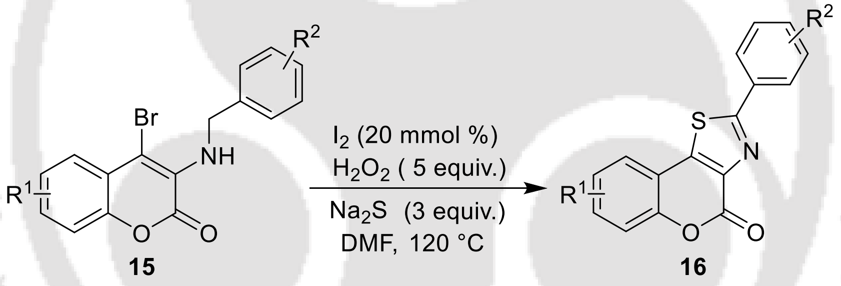
Oxidative Cross Coupling Reaction Mediated by I_2/H_2O_2: A Novel Approach for Construction of Fused Thiazole Containing Coumarin Derivatives



RESULTS AND DISCUSSION

• Results and Discussions

Previously in chapter V, the synthesis of fused oxazole containing coumarin derivatives has been described where 3-(benzylamino)-2*H*-chromen-2-one was used for synthesizing oxazole derivative of coumarin via oxidative C-H bond functionalization employing TBHP and $CuCl_2$. The bromination of 3-(benzylamino)-2*H*-chromen-2-one using stoichiometric amount of bromodimethylsulphonium bromide (BDMS) provides 3-(benzylamino)-4-bromo-2*H*-chromen-2-one (Table 14, **15a**). Liang and co-workers synthesized benzothiazole derivatives from *N*-benzyl-2-iodoanilines using K_2S and CuBr in NMO via oxidative C-H bond functionalization.[78] Further, Itoh et al. reported the nitroalkylation of tetrahydroisoquinoline derivatives using I_2 as a catalyst and H_2O_2 as a terminal oxidant.[70] The present chapter of the thesis describes the construction of fused thiazole derivatives of coumarin via oxidative C-H bond functionalization using I_2/H_2O_2 combination. Various 3-(benzylamino)-4-bromo-2*H*-chromen-2-one derivatives have been explored where Na_2S is used as the source of sulphur atom, shown in Scheme 71.

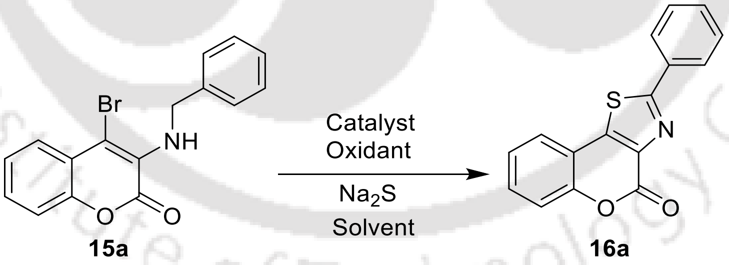


Scheme 71. Synthesis of coumarin fused thiazole derivatives

Initially, bromination of 3-(benzylamino)-2*H*-chromen-2-one (**13a**) was carried out using bromodimethylsulphonium bromide to achieve its bromo derivatives, 3-(benzylamino)-4-bromo-2*H*-chromen-2-one (**15a**, Table 14) which was characterized by IR, NMR, and HRMS spectroscopic techniques. Then a reaction of **15a** was carried out with Na_2S (3 equiv.) using H_2O_2 (5 equiv.) in the presence of 20 mol% of I_2 in acetonitrile under reflux condition. The reaction was monitored by checking TLC and the major product obtained was isolated by column chromatography. The pure product obtained was found to be **16a** (Table 13), a coumarin fused thiazole derivative as characterized by IR, NMR and HRMS (see page 163 for NMR spectra of **16a**).

To improve the yield of the product (**16a**), reactions in various solvents were carried out with different catalysts. A comparable yield was obtained by replacing acetonitrile with DMSO (Table 13, entry 2). No desired product was obtained with H_2O, MeOH, EtOH, $CHCl_3$ or DCM as a solvent (Table 13, entries 3-7). DMF was found to be the best solvent producing the desired product in reasonable yield (Table 13, entry 8). To understand the role of the catalyst and the oxidant, a reaction was executed in the presence of H_2O_2 without molecular iodine but the required product was obtained in poor yield (Table 13, entry 9). Interestingly, only 15 % yield was obtained when the same reaction was performed with 20 mol% of molecular iodine without using H_2O_2 (Table 13, entry 10). A significant reduction in yield was observed on decreasing the amount of the catalyst to 10 mol% (Table 13, entry 11). Further attempts were made to improve the yield of the reaction product by using different catalysts and oxidizing agents. However, on replacing H_2O_2 with TBHP, the yield of the desired product was further decreased to 20 % (Table 13, entry 12). With the same oxidizing agent, the yield was increased to some extent when DMSO was used as solvent in place of DMF (Table 13, entry 13). Apart from molecular iodine, the efficacy of other iodine sources like NIS, TBAI and KI as catalysts were also examined, but the expected thiazole derivative was obtained in poor yields (Table 13, entries 14-16). Notably, the reaction was unproductive at ambient temperature (entry 17).

Table 13.Optimization of the reaction condition[a]



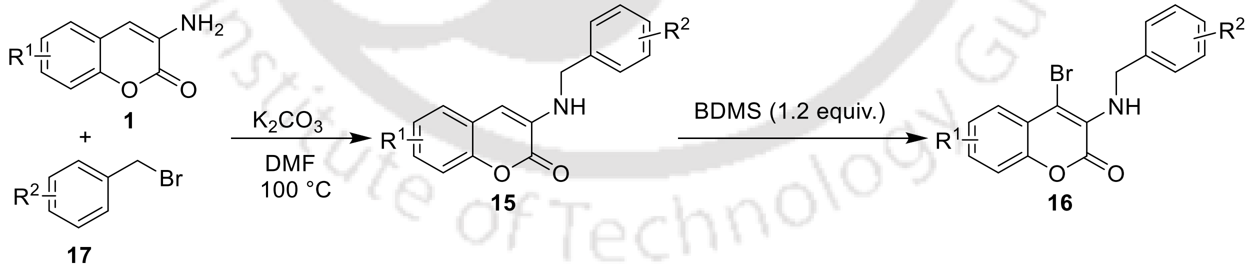
Entry	Solvent	Catalyst (mol %)	Co-oxidant	Yield (%)[b]
1	CH_3CN	I_2 (20)	H_2O_2	60
2	DMSO	I_2 (20)	H_2O_2	50
3[c]	H_2O	I_2 (20)	H_2O_2	NR
4[c]	MeOH	I_2 (20)	H_2O_2	NR
5[c]	EtOH	I_2 (20)	H_2O_2	NR
6[c]	$CHCl_3$	I_2 (20)	H_2O_2	NR
7[c]	CH_2Cl_2	I_2 (20)	H_2O_2	NR

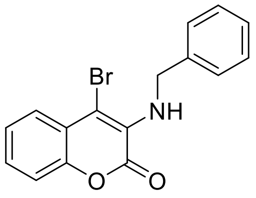
8	**DMF**	**I_2 (20)**	**H_2O_2**	**86**
9	DMF	---	H_2O_2	10
10	DMF	I_2 (20)	---	15
11	DMF	I_2 (10)	H_2O_2	60
12	DMF	I_2 (20)	TBHP	20
13	DMSO	I_2 (20)	TBHP	70
14	DMF	NIS (20)	H_2O_2	10
15	DMF	TBAI (20)	H_2O_2	15
16	DMF	KI (20)	H_2O_2	40
17*	DMF	I_2 (20)	H_2O_2	NR

[a] Unless otherwise stated all the reaction have been carried out with 0.3 mmol of **15a** and 0.9 mmol of Na_2S in the presence of 20 mol % of the catalyst and 5 equivalent of the oxidants in 2 ml of the solvent at 120 °C for 24 h. [b] Isolated yield. [c] at reflux condition. * at room temperature

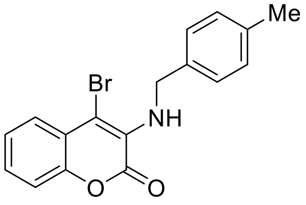
After achieving the optimized conditions several derivatives of 3-(benzylamino)-4-bromo-2*H*-chromen-2-one (Table 14, **15a-v**) were synthesized and used for the synthesis of various thiazole derivatives of coumarin. The effect of different groups attached with the coumarin and benzyl moieties were thoroughly examined. Initially, the benzyl moiety with electron donating (Table15, **16b** and **16f**,) as well as electron withdrawing substituents (Table15, **16c-e** and **16g**) on it were evaluated. Interestingly, in both the cases, the reaction underwent smoothly to produce the desired products in good yields. Even a similar outcome was observed in the presence of methoxy-, ethoxy-, chloro- and bromo- group on the coumarin moiety (Table15, **16j-t**).

Table 14. Synthesis of various 3-(benzylamino)-4-bromo substituted chromenone derivatives

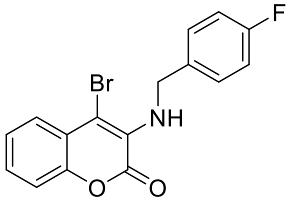




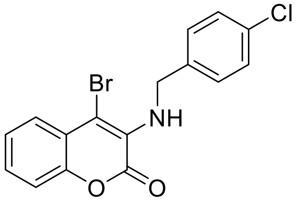
15a
1 h, 82%



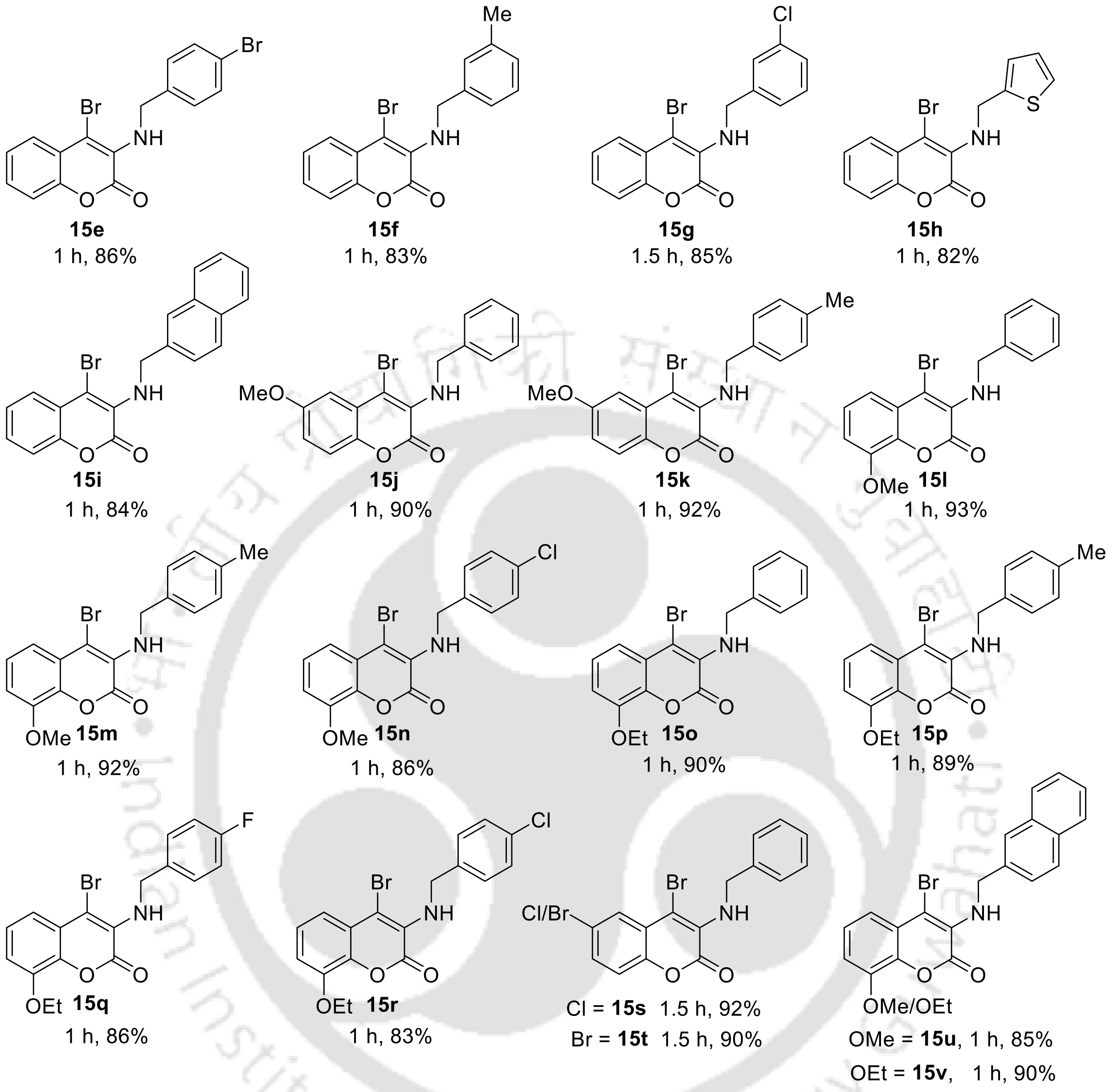
15b
1 h, 90%



15c
1 h, 82%



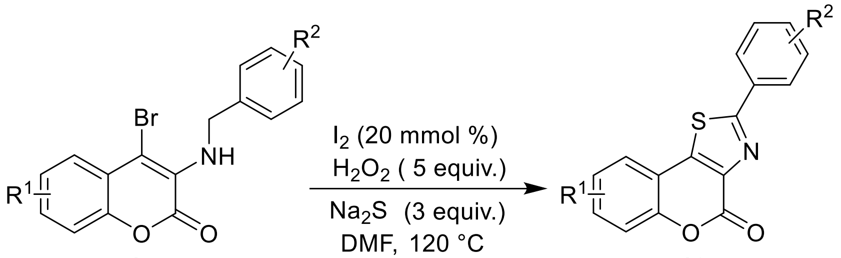
15d
1 h, 92%



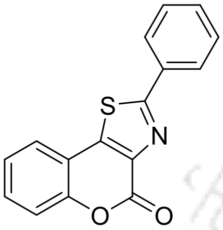
i) All the reactions have been carried out with 1 mmol of each **1** and **17** and 1.2 equiv. of K_2CO_3 in DMFat 100 °C. ii) Bromination is carried out using 0.5 mmol of **C** in DCM at rt. iii) Isolated yield

To explore the diversity of our protocol, the benzyl moiety was replaced with 2-methylnapthalene functionality (Table14, **15i**, **15u** and **15v**). The reactions of **15i**, **15u** and **15v** and Na_2S were carried out under the optimized reaction conditions. The corresponding products 1**6i**, **16u** and **16v** (Table 15) were obtained in 85-89 % yields. Notably, the substituents (R^1) on aryl rings of various coumarin derivatives were found to have no significant effect on the yield of the reaction. In the present case, the yields were comparable to the benzyl derivatives however the reactions were much faster (Table 15, **16i**, **16u** and **16v**).

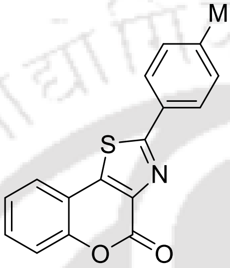
Table 15. Preparation of 2-phenyl-4*H*-chromeno(3,4-*d*)thiazol-4-one derivatives[a,b]



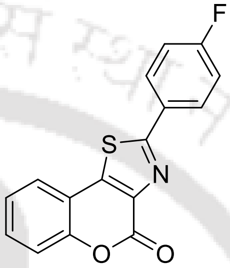
15 **16**



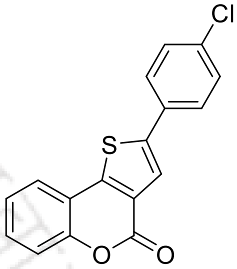
16a
22 h, 86%



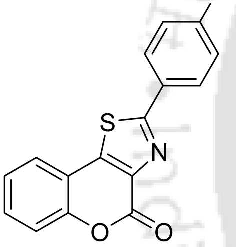
16b
21 h, 79%



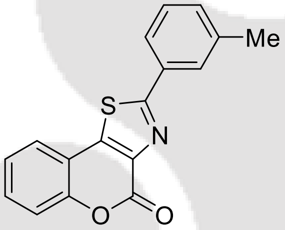
16c
22 h, 83%



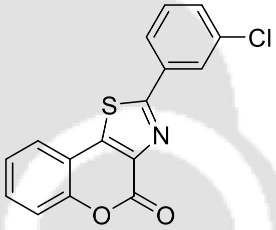
16d
22 h, 80%



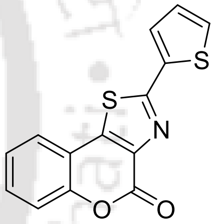
16e
24 h, 78%



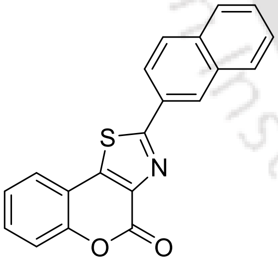
16f
24 h, 78%



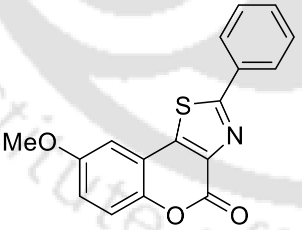
16g
23 h, 65%



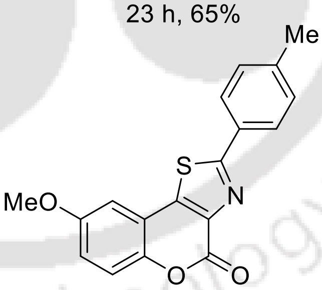
16h
24 h, 66%



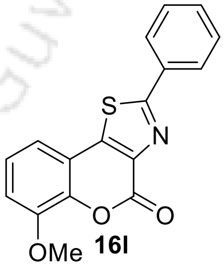
16i
16 h, 89%



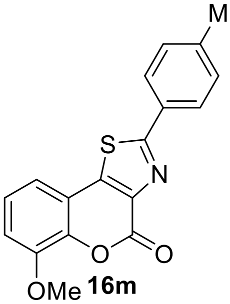
16j
24 h, 80%



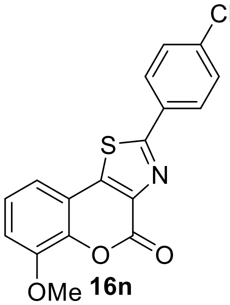
16k
20 h, 82%



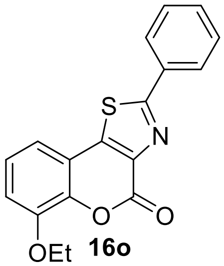
16l
24 h, 85%



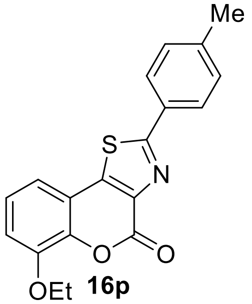
16m
22 h, 86%



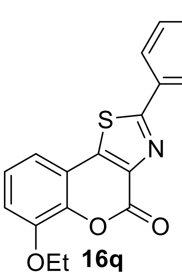
16n
24 h, 84%



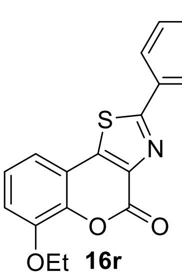
16o
23 h, 82%



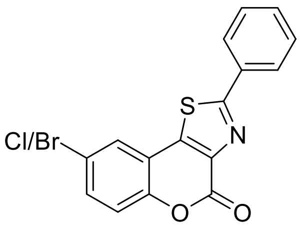
16p
24 h, 80%



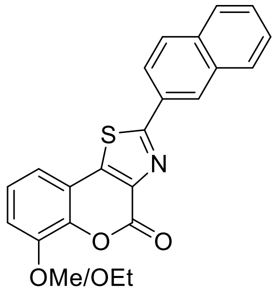
16q
20 h, 85%



16r
22 h, 78%



Cl = **16s**, 24 h, 70%
Br = **16t**, 24 h, 72%



OMe = **16u**, 16 h, 87%
OEt = **16v**, 18 h, 85%

---

[a]All the reaction have been carried out with 0.3 mmol of **15** and 0.9 mmol of Na_2S in the presence of 20 mol % of Iodine and 5 equivalent of H_2O_2 in 2 ml of DMF at 120 °C. [b] Isolated yield

Unfortunately, no product was obtained with *ortho* substituted benzyl moiety in the chromenone ring. The failure of the reaction with *ortho* substitution on the benzyl moiety may be attributed to steric hindrance. Using benzyl moiety containing heteroatom in the ring such as 4-bromo-3-((thiophen-2-ylmethyl)amino)-2*H*-chromen-2-one (**15h**), the desired thiazole derivative (**16h**) was isolated in 66 % yield (Table 15).

All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra analysis (see pages 145-157 for NMR, IR and HRMS data for all the compounds **16a-v**). The structure of the thiazole derivative (**16a**) was also confirmed by single crystal X-ray diffraction analysis (Figure 9).

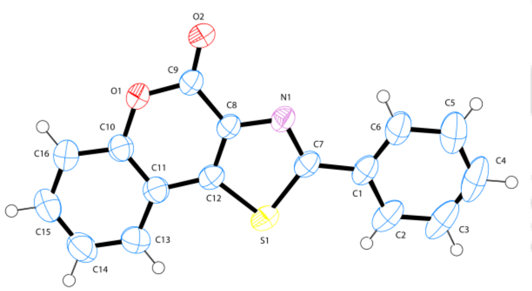
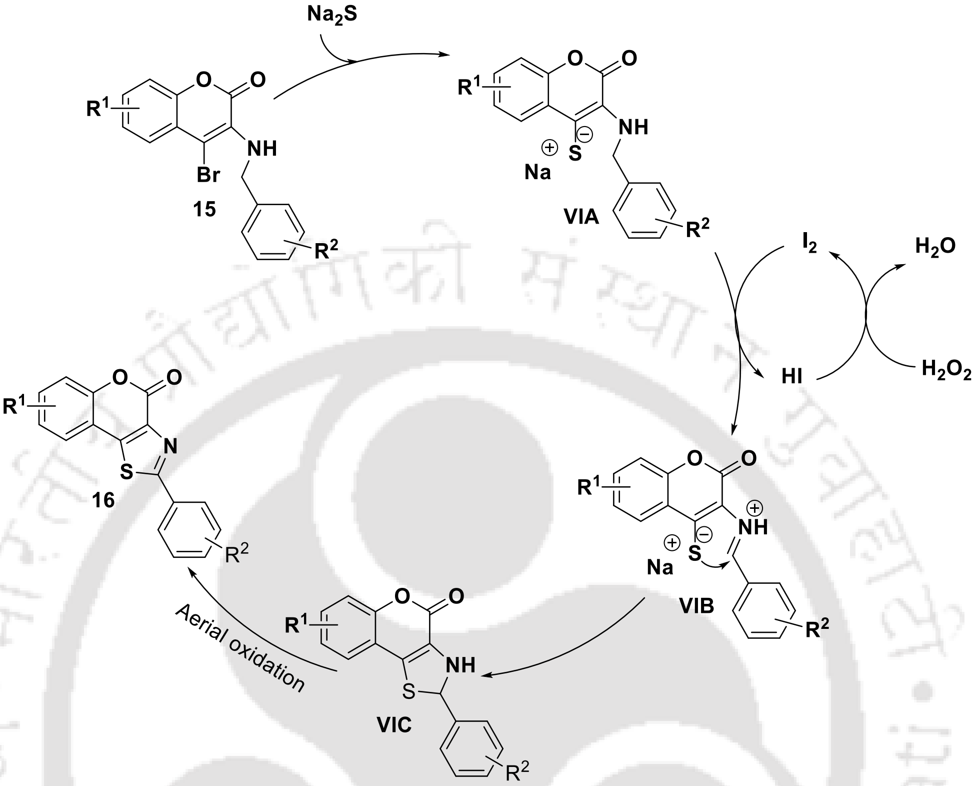


Figure 9.Single crystal structure of **16a** (CCDC: 1013314)

Based on literature survey[70] and our experimental results, a plausible mechanism can be drawn. Initially, Na_2S reacts with **15** to generate the intermediate **VIA** (see Scheme. 15) and then **VIA** is oxidised by iodine to generate an iminium ion intermediate **VIB**. HI generated in the above step is oxidized by H_2O_2 to recycle I_2. The cyclized compound **VIC** is produced via intramolecular nucleophilic attack by the sulfur atom at the electrophilic carbon of the iminium ion (**VIB**). Finally, **VIC** on aerial oxidation provides the desired product **16.**



Scheme 72. Plausible reaction mechanism for the formation of **16**

An efficient protocol for the synthesis of various fused thiazole containing coumarin derivatives has been demonstrated. The metal free C-H activation for C-S bond formation by I_2/H_2O_2 is less expensive and more environmentally benign compared to the metal catalyzed C-H activation. The protocol is diverse and the thiazoles derivatives are obtained in good to excellent yields. Finally, the protocol represents a useful alternative tool to achieve multifarious medicinally active coumarin fused thiazoles.

CHAPTER VI

Oxidative Cross Coupling Reaction Mediated by I_2/H_2O_2: A Novel Approach for Construction of Fused Thiazole Containing Coumarin Derivatives

EXPERIMENTAL SECTION

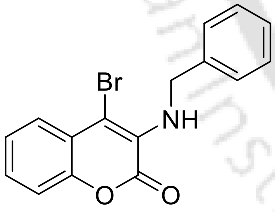
• Experimental Section

General procedure for the synthesis of various 3-(benzylamino)-4-bromo-2H-chromen-2-one derivatives (15a-v):

Step I: Into a 25 mL round bottom flask was taken a mixture of 3-aminocomarin (1 mmol), benzyl bromide (1 mmol) and K_2CO_3 (1.2 mmol) in 3 mL of DMF. The reaction mixture was heated at 100 °C for 2-8 h and after completion of the reaction, the reaction mixture was worked-up with ethyl acetate. The crude product obtained after evaporation of the solvent in rotary evaporator was treated with ethanol to remove impurities. Finally the solid pure product obtained in 75-85% yield, which was used in the next step.

Step II: The solid product (0.5 mmol) obtained in step **I** was taken in a 25 ml round bottom flask and it was dissolved in 4 mL of dry DCM. Then 1.2 equivalent of bromodimethylsulphonium bromide (BDMS) was added into it and the reaction mixture was stirred for 1-1.5 h. After completion of the reaction, the reaction mixture was worked-up with DCM. After evaporating the solvent, the solid residue was purified by column chromatography. The product was eluted in ethyl acetate and hexane mixture (1:24). The pure products **(15a-v)** are obtained in 82-93 % yield, which are characterized by ^{1}H NMR, ^{13}C NMR and HRMS.

***3-(Benzylamino)-4-bromo-2H-chromen-2-one* (15a):**



15a

Reaction Time: 1 h

Colour & State: white solid

Yield: 82% (135 mg)

Melting Point: 89-92 °C

^{1}HNMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.6 Hz, 1 H), 7.34 (m, 4 H), 7.30 (d, *J* = 8 Hz, 1 H), 7.26 (m, 3 H)), 4.83 (s, 2 H) ppm.

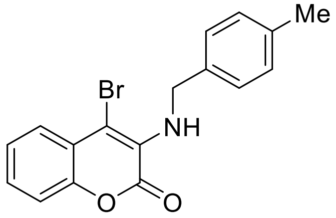
^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 147.7, 139.5, 132.8, 128.9, 128.1, 127.8, 127.7, 125.8, 125.2, 120.9, 116.1, 112.6, 50.0 ppm.

HRMS (APCI) calcd for calcd for $C_{16}H_{12}BrNO_2$ (M+H$^+$) = 330.0124, found 330.0101.

Elemental Analysis	Calculated	Found
MF $C_{16}H_{12}BrNO_2$	C 58.20	58.06
(330.18)	H 3.66	3.71

	N 4.24	4.16

***4-Bromo-3-((4-methylbenzyl)amino)-2H-chromen-2-one* (15b):**



15b

Reaction Time: 1 h **Colour & State:** white solid

Yield: 90% (155 mg) **Melting Point:** 90-92 °C

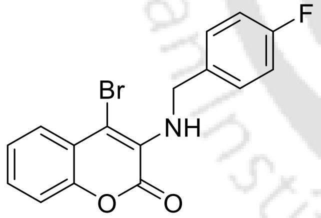
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.69 (d, *J* = 7.8 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.28 (t, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 3 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 4.99 (s, 1 H), 4.79 (s, 2 H), 2.33 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 157.4, 147.7, 137.4, 136.5, 132.9, 129.6, 128.0, 127.8, 125.8, 125.1, 121.0, 116.1, 112.4, 49.8, 21.3 ppm.

HRMS (APCI) calcd for $C_{17}H_{14}BrNO_2$ (M+H$^+$) = 344.0281, found 344.0291.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{14}BrNO_2$	C 59.32	59.50
(344.21)	H 4.10	4.14
	N 4.07	4.00

***4-Bromo-3-((4-fluorobenzyl)amino)-2H-chromen-2-one* (15c):**



15c

Reaction Time: 1 h **Colour & State:** white solid

Yield: 82% (135 mg) **Melting Point:** 78-80 °C

^{1}HNMR (400 MHz, CDCl$_3$): δ 7.71 (d, *J* = 8 Hz, 1 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.33 (m, 2 H), 7.28 (t, *J* = 4.8 Hz, 2 H), 7.02 (t, *J* = 8.4 Hz, 2 H), 4.96 (s, 1 H), 4.78 (d, *J* = 6.8 Hz, 2 H) ppm.

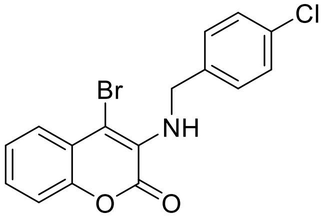
^{13}C NMR (100 MHz, CDCl$_3$): δ 163.6, 161.2, 157.4, 147.8, 135.3, 132.7, 129.6, 129.5, 128.3, 125.9, 125.2, 120.9, 116.1, 115.9, 115.7, 113.1, 49.3 ppm.

HRMS (ESI) calcd for $C_{16}H_{11}BrFNO_2$ (M+H$^+$) = 348.0030, found 348.0035.

Elemental Analysis	Calculated	Found
MF $C_{16}H_{11}BrFNO_2$	C 55.20	55.35
(348.17)	H 3.18	3.14

	N 4.02	4.10

***4-Bromo-3-((4-chlorobenzyl)amino)-2H-chromen-2-one* (15d):**



15d

Reaction Time: 1 h **Colour & State:** white solid

Yield: 92% (159 mg) **Melting Point:** 85-87 °C

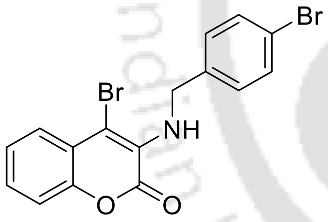
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.68 (d, *J* = 8 Hz, 1 H), 7.32 (m, 5 H), 7.25 (t, *J* = 8 Hz, 2 H), 4.78 (s, 2 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 157.3, 147.9, 138.0, 133.6, 132.5, 129.3, 129.1, 128.5, 126.0, 125.3, 120.8, 116.2, 113.8, 49.3 ppm.

HRMS (APCI) calcd for $C_{16}H_{11}BrClNO_2$ (M+H$^+$) = 363.9734, found 363.9736.

Elemental Analysis	**Calculated**	**Found**
MF $C_{16}H_{11}BrClNO_2$	C 52.71	52.85
(364.62)	H 3.04	3.09
	N 3.84	3.76

***4-Bromo-3-((4-bromobenzyl)amino)-2H-chromen-2-one* (15e):**



15e

Reaction Time: 1 h **Colour & State:** white solid

Yield: 86% (176 mg) **Melting Point:** 115-117 °C

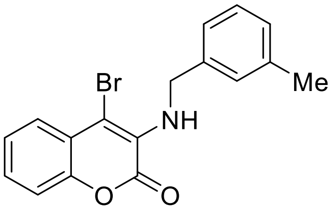
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.70 (d, *J* = 8.4, Hz, 1 H), 7.45 (d, *J* = 8 Hz, 2 H), 7.35 (t, *J* = 8.4 Hz, 1 H), 7.30 (t, *J* = 7.8 Hz, 1 H), 7.27 (d, *J* = 7.8, 1 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 4.77 (s, 2 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 157.4, 147.9, 138.6, 132.6, 132.1, 129.6, 128.4, 126.0, 125.3, 121.6, 120.8, 116.2, 113.4, 49.3 ppm.

HRMS (APCI) calcd for $C_{16}H_{11}Br_2NO_2$ (M+H$^+$) = 407.929, found 407.9230.

Elemental Analysis	**Calculated**	**Found**
MF $C_{16}H_{11}Br_2NO_2$	C 46.98	47.15
(409.08)	H 2.71	2.67
	N 3.42	3.33

4-Bromo-3-((3-methylbenzyl)amino)-2H-chromen-2-one **(15f):**



15f

Reaction Time: 1 h **Colour & State:** white solid

Yield: 83% (143 mg) **Melting Point:** 65-68 °C

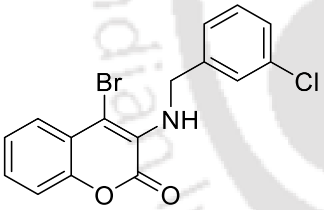
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.62 (d, *J* = 7.2 Hz, 1 H), 7.24 (t, *J* = 7.2 Hz, 1 H), 7.21 (d, *J* = 6.6 Hz, 1 H), 7.18 (dd, *J* = 7.2 Hz, 1 H), 7.14 (d, *J* = 7.8 Hz, 1 H), 7.09 (s, 1 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 4.70 (s, 2 H), 2.26 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 157.5, 147.7, 139.4, 138.6, 132.9, 128.8, 128.7, 128.5, 128.1, 125.8, 125.2, 124.9, 121.0, 116.1, 112.4, 50.1, 21.6 ppm.

HRMS (ESI) calcd for $C_{17}H_{14}BrNO_2$ (M+H$^+$) = 344.0281, found 344.0288.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{14}BrNO_2$	C 59.32	59.21
(344.21)	H 4.10	4.14
	N 4.07	3.99

4-Bromo-3-((3-chlorobenzyl)amino)-2H-chromen-2-one **(15g):**



15g

Reaction Time: 1.5 h **Colour & State:** white solid

Yield: 85% (155 mg) **Melting Point:** 86-88 °C

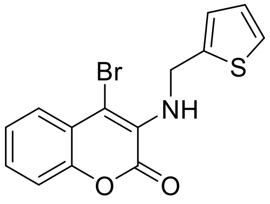
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.69 (t, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 11.4 Hz, 2 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.25 (m, 4 H), 5.00 (s, 1 H), 4.80 (s, 2 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 157.3, 147.8, 141.7, 134.7, 132.4, 130.2, 128.4, 127.92, 127.87, 125.9, 125.8, 125.2, 120.8, 116.2, 113.2, 49.3 ppm.

HRMS (APCI) calcd for $C_{16}H_{11}BrClNO_2$ (M+H$^+$) = 363.9734, found 363.9774.

Elemental Analysis	Calculated	Found
MF $C_{16}H_{11}BrClNO_2$	C 52.71	52.87
(364.62)	H 3.04	2.98
	N 3.84	3.76

***4-Bromo-3-((thiophen-2-ylmethyl)amino)-2H-chromen-2-one* (15h):**



15h

Reaction Time: 1 h **Colour & State:** Gummy black solid

Yield: 82% (138 mg)

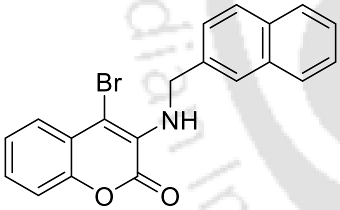
^{1}HNMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.8 Hz, 1 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 4.8 Hz, 1 H), 7.21 (d, *J* = 4.8 Hz, 1 H), 6.99 (s, 1 H), 6.94 (d, *J* = 4.2 Hz, 1 H), 5.00 (s, 2 H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.2, 148.0, 142.4, 129.8, 128.4, 126.3, 126.0, 125.4, 125.3, 125.2, 120.8, 116.2, 114.4, 44.6 ppm.

HRMS (ESI) calcd for $C_{14}H_{10}BrNO_2S$ ($M+H^+$) = 335.9688, found 335.9708.

Elemental Analysis	**Calculated**	**Found**
MF $C_{14}H_{10}BrNO_2S$	C 50.02	50.20
(336.20)	H 3.00	3.04
	N 4.17	4.25

***4-Bromo-3-((naphthalen-2-ylmethyl)amino)-2H-chromen-2-one* (15i):**



15i

Reaction Time: 1 h **Colour & State:** white solid

Yield: 84% (160 mg) **Melting Point:** 100-103 °C

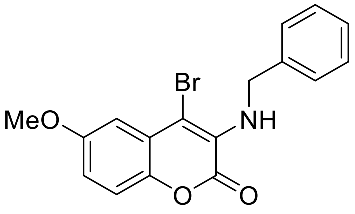
^{1}HNMR (400 MHz, $CDCl_3$): δ 7.82 (m, 4 H), 7.70 (d, *J* = 7.2 Hz, 1 H), 7.47 (dd, *J* = 10.4, 7.2 Hz, 3 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.27 (m, 2 H), 5.12 (s, 1 H, broad.), 4.99 (d, *J* = 5.2 Hz, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 147.7, 136.9, 133.5, 132.9, 132.7, 128.7, 128.1, 128.0, 127.8, 126.6, 126.4, 126.1, 125.9, 125.8, 125.1, 120.9, 116.0, 112.8, 50.1 ppm.

HRMS (ESI) calcd for $C_{20}H_{14}BrNO_2$ ($M+H^+$) = 380.0281, found 380.0286.

Elemental Analysis	**Calculated**	**Found**
MF $C_{20}H_{14}BrNO_2$	C 63.18	63.32
(380.24)	H 3.71	3.76
	N 3.68	3.59

***3-(Benzylamino)-4-bromo-6-methoxy-2H-chromen-2-one* (15j):**



15j

Reaction Time: 1.5 h. **Colour & State:** white solid

Yield: 90% (162 mg) **Melting Point:** 106-109 °C

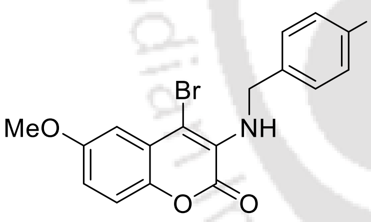
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.34 (s, 4 H), 7.30 (s, 1 H), 7.18 (d, *J* = 9.0 Hz, 1 H), 7.10 (s, 1 H), 6.88 (d, *J* = 6.9 Hz, 1 H), 5.04 (s, 1 H, broad), 4.83 (s, 2 H), 3.85 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 157.5, 156.9, 142.1, 139.5, 133.1, 128.9, 127.9, 127.7, 121.7, 117.2, 115.3, 112.0, 108.9, 56.0, 50.0 ppm.

HRMS (ESI) calcd for $C_{17}H_{14}BrNO_3$ (M+H$^+$) = 360.0230, found 360.0239.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{14}BrNO_3$	C 57.77	57.88
(360.21)	H 3.92	3.87
	N 3.89	3.80

***4-Bromo-6-methoxy-3-((4-methylbenzyl)amino)-2H-chromen-2-one* (15k):**



15k

Reaction Time: 1 h **Colour & State:** white solid

Yield: 92% (172 mg)

^{1}HNMR (600 MHz, CDCl$_3$): δ 7.23 (m, 2 H), 7.17 (d, *J* = 9.0 Hz, 1 H), 7.13 (m, 3 H), 6.88 (dd, *J* = 9.0, 2.4, Hz, 1 H), 5.01 (s, 1 H, broad), 4.78 (s, 2 H), 3.85 (s, 3 H), 2.32 (s, 3 H) ppm.

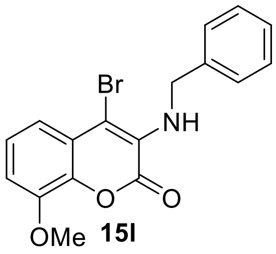
^{13}C NMR (150 MHz, CDCl$_3$): δ 157.6, 156.9, 142.1, 137.4, 136.5, 133.2, 129.6, 127.9, 121.8, 120.9, 117.2, 115.2, 108.9, 56.0, 49.9, 21.3 ppm; HRMS [ESI+] m/z: calcd for $C_{18}H_{16}BrNO_3$ [M+H] = 374.0392 (found 374.0395).

HRMS (ESI) calcd for $C_{18}H_{16}BrNO_3$ (M+H$^+$) = 374.0386, found 374.0395.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{16}BrNO_3$	C 56.69	56.56
(374.23)	H 4.31	4.27

	N 3.74	3.81

***3-(Benzylamino)-4-bromo-8-methoxy-2H-chromen-2-one* (15l):**



15l

Reaction Time: 1 h **Colour & State:** white solid

Yield: 93% (167 mg) **Melting Point:** 102-106 °C

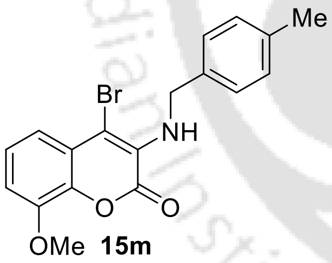
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.34 (s, 4 H), 7.29 (d, *J* = 9.2 Hz, 2 H), 7.21 (t, *J* = 8.4 Hz, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 4.83 (s, 2 H), 3.95 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 156.9, 147.0, 139.5, 137.6, 133.1, 128.9, 127.9, 127.7, 124.8, 121.8, 117.6, 110.5, 110.2, 56.6, 50.1 ppm.

HRMS (APCI) calcd for $C_{17}H_{14}BrNO_3$ (M+H$^+$) = 360.0230, found 360.0240.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{14}BrNO_3$	C 57.77	57.89
(360.21)	H 3.92	3.87
	N 3.89	3.81

***4-Bromo-8-methoxy-3-((4-methylbenzyl)amino)-2H-chromen-2-one* (15m):**



15m

Reaction Time: 1 h. **Colour & State:** white solid

Yield: 92% (172 mg) **Melting Point:** 123-126 °C

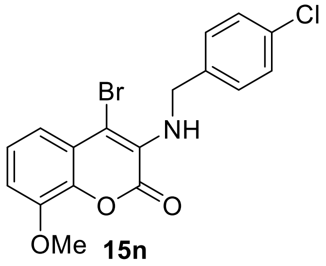
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.27 (t, *J* = 8 Hz, 2 H), 7.21 (t, *J* = 8 Hz, 2 H), 7.12 (d, *J* = 8 Hz, 2 H), 6.90 d, *J* = 8 Hz, 1 H), 4.77 (s, 2 H), 3.94 (s, 3 H), 2.31(s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 156.8, 146.7, 137.2, 136.4, 133.0, 129.5, 129.2, 129.1, 127.8, 124.6, 121.6, 117.3, 110.2, 56.4, 49.7, 21.2 ppm.

HRMS (APCI) calcd for $C_{18}H_{16}BrNO_3$ (M+H$^+$) = 374.0386, found 374.0394.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{16}BrNO_3$	C 56.69	56.54
(374.23)	H 4.31	4.26
	N 3.74	3.66

***Bromo-3-((4-chlorobenzyl)amino)-8-methoxy-2H-chromen-2-one* (15n):**


15n

Reaction Time: 1 h. **Colour & State:** white solid

Yield: 86% (169 mg) **Melting Point:** 124-126 °C

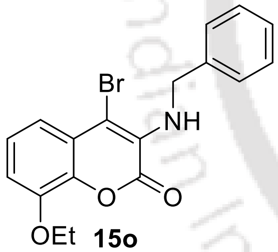
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.28 (s, 5 H), 7.20 (t, *J* = 8.4 Hz, 1 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 5.00 (s, 1 H), 4.78, (d, *J* = 6 Hz, 2 H), 3.94 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 156.7, 146.9, 138.1, 137.5, 133.4, 132.7, 129.2, 129.0, 124.8, 121.5, 117.5, 113.2, 110.5, 56.5, 49.1 ppm.

HRMS (ESI) calcd for $C_{17}H_{13}BrClNO_3$ (M+H$^+$) = 393.9840, found 393.9846.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{13}BrClNO_3$	C 51.74	56.91
(394.65)	H 3.32	3.26
	N 3.55	3.62

***3-(Benzylamino)-4-bromo-8-ethoxy-2H-chromen-2-one* (15o):**


15o

Reaction Time: 1 h **Colour & State:** white solid

Yield: 90% (168 mg) **Melting Point:** 116-122 °C

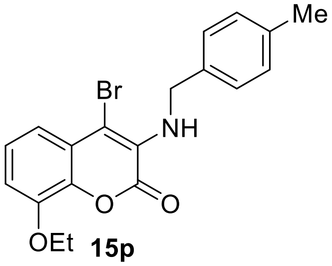
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.32 (m, 4 H), 7.25 (t, *J* = 1.2 Hz, 2 H), 7.18 (dd, *J* = 14.8, 6.4 Hz, 1 H), 6.89 (d, *J* =7.6 Hz, 1 H), 4.81 (s, 2 H), 4.15 (q, *J* = 6.8 Hz, 2 H), 1.48 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 157.0, 146.2, 139.6, 133.0, 128.9, 127.9, 127.7, 124.7, 121.8, 117.4, 112.7, 111.7, 106.0, 65.2, 50.0, 15.0 ppm.

HRMS (APCI) calcd for $C_{18}H_{16}BrNO_3$ (M+H$^+$) = 374.0386, found 374.0350.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{16}BrNO_3$	C 56.69	56.86
(374.23)	H 4.31	4.36
	N 3.74	3.64

***4-Bromo-8-ethoxy-3-((4-methylbenzyl)amino)-2H-chromen-2-one* (15p):**



15p

Reaction Time: 1 h **Colour & State:** white solid

Yield: 89% (173 mg) **Melting Point:** 107-110 °C

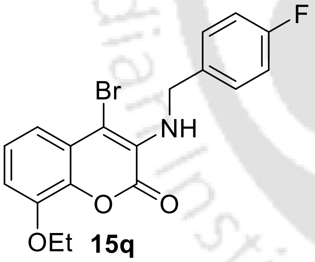
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.26 (d, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 7.2 Hz, 2 H), 7.16 (t, *J* = 8.4, Hz, 1 H), 7.11 (d, J = 7.8 Hz, 2 H), 6.88 (d, *J* =7.8 Hz, 1 H), 4.99 (s, 1 H, broad), 4.76 (s, 2 H), 4.15 (q, *J* = 6.6 Hz, 2 H), 2.31 (s, 3 H), 1.48 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 157.0, 146.2, 137.7, 137.3, 136.5, 133.1, 129.6, 127.9, 124.7, 121.8, 117.4, 112.6, 111.6, 65.2, 49.8, 21.3, 15.0 ppm.

HRMS (APCI) calcd for $C_{19}H_{18}BrNO_3$ ($M+H^+$) = 388.0543, found 388.0506.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{18}BrNO_3$	C 58.78	58.65
(388.26)	H 4.67	3.71
	N 3.61	3.56

***4-Bromo-8-ethoxy-3-((4-fluorobenzyl)amino)-2H-chromen-2-one* (15q):**



15q

Reaction Time: 1 h **Colour & State:** white solid

Yield: 86% (69 mg) **Melting Point:** 111-113 °C

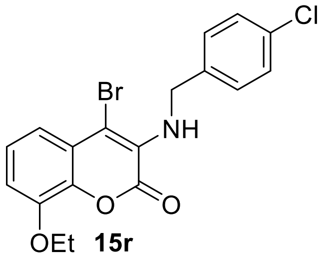
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.29 (m, 3 H), 7.19 (t, *J* =7.8 Hz, 1 H), 7.00 (t, *J* = 8.4 Hz, 2 H), 6.91 (d, *J* = 7.2 Hz, 1 H), 4.78 (s, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 1.49 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 163.2, 161.6, 160.6, 157.0, 146.3, 137.8, 135.4, 132.9, 129.62, 129.56, 124.8, 121.7, 117.5, 115.8, 115.7, 113.4, 111.8, 65.2, 49.2, 15.0 ppm.

HRMS (ESI) calcd for $C_{18}H_{15}BrFNO_3$ ($M+H^+$) = 392.0292, found 392.0292.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{15}BrFNO_3$	C 55.12	55.32
(392.22)	H 3.85	3.80
	N 3.57	3.47

***4-Bromo-3-((4-chlorobenzyl)amino)-8-ethoxy-2H-chromen-2-one* (15r):**



15r

Reaction Time: 1 h **Colour & State:** white solid

Yield: 83% (169 mg) **Melting Point:** 103-106 °C

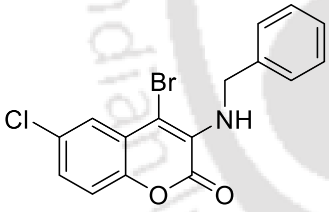
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.34 (d, *J* = 4.4 Hz, 1 H), 7.28 (m, 4 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 6.91 (d, *J* = 8 Hz, 1 H), 4.78 (s, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 1.49 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 156.9, 146.3, 138.1, 133.4, 132.7, 129.2, 129.0, 128.1, 124.8, 121.6, 117.5, 113.5, 111.9, 65.2, 49.2, 15.0 ppm.

HRMS (APCI) calcd for $C_{18}H_{15}BrClNO_3$ (M+H$^+$) = 407.9997, found 407.9958.

Elemental Analysis	**Calculated**	**Found**
MF $C_{18}H_{15}BrClNO_3$	C 52.90	53.06
(408.68)	H 3.70	3.67
	N 3.43	3.70

***3-(Benzylamino)-4-bromo-6-chloro-2H-chromen-2-one* (15s):**



15s

Reaction Time: 1.5 h **Colour & State:** white solid

Yield: 92% (167 mg) **Melting Point:** 103-106 °C

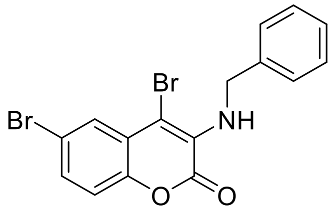
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.67 (d, *J* = 2 Hz, 1 H), 7.34 (m, 5 H), 7.25 (d, *J* = 2.4 Hz, 1 H), 7.19 (d, *J* = 8.8 Hz, 1 H), 4.86 (s, 2 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 156.9, 145.9, 139.2, 133.3, 130.8, 129.0, 127.9, 127.86, 127.81, 125.2, 122.5, 117.5, 109.6, 50.0 ppm.

HRMS (ESI) calcd for $C_{16}H_{11}BrClNO_2$ (M+H$^+$) = 363.9734, found 363.9740.

Elemental Analysis	**Calculated**	**Found**
MF $C_{16}H_{11}BrClNO_2$	C 52.71	52.86
(364.62)	H 3.04	2.99
	N 3.84	3.75

***3-(Benzylamino)-4,6-dibromo-2H-chromen-2-one* (15t):**



15t

Reaction Time: 1.5 h **Colour & State:** white solid

Yield: 90% (184 mg) **Melting Point:** 99-101 °C

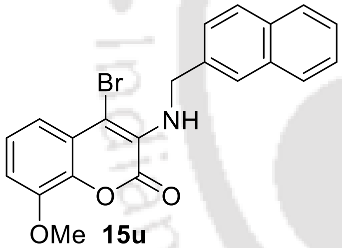
^{1}HNMR (600 MHz, CDCl$_3$): δ 7.82 (d, *J* = 2.4 Hz, 1 H), 7.40 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.34 (m, 4 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 4.86 (s, 2 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 156.8, 146.3, 139.2, 133.3, 130.6, 129.0, 128.8, 128.1, 127.85, 127.81, 122.8, 117.7, 109.2, 49.9 ppm.

HRMS (ESI) calcd for $C_{16}H_{11}Br_2NO_2$ (M+H$^+$) = 407.9229, found 407.9260.

Elemental Analysis	Calculated	Found
MF $C_{16}H_{11}Br_2NO_2$	C 46.98	46.86
(409.08)	H 2.71	2.76
	N 3.42	3.32

***4-Bromo-8-methoxy-3-((naphthalen-2-ylmethyl)amino)-2H-chromen-2-one* (15u):**



15u

Reaction Time: 1 h **Colour & State:** white solid

Yield: 85% (174 mg) **Melting Point:** 116-118 °C

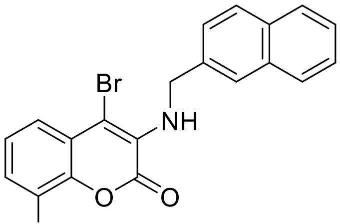
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.80 (t, *J* = 7.6 Hz, 4 H), 7.46 (t, *J* = 4.4 Hz, 3 H), 7.27 (t, *J* = 11.6 Hz, 1 H), 7.19 (t, *J* = 16.4 Hz, 1 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 4.99 (s, 2 H), 3.94 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 156.9, 147.0, 137.6, 137.0, 133.6, 133.1, 133.0, 128.8, 128.1, 127.9, 126.7, 126.4, 126.1, 126.0, 124.8, 121.8, 117.6, 112.8, 110.5, 56.7, 50.1 ppm.

HRMS (APCI) calcd for $C_{21}H_{16}BrNO_3$ (M+H$^+$) = 410.0386, found 410.0391.

Elemental Analysis	Calculated	Found
MF $C_{21}H_{16}BrNO_3$	C 61.48	61.33
(410.27)	H 3.93	3.87
	N 3.41	3.31

***4-bromo-8-ethoxy-3-((naphthalen-2-ylmethyl)amino)-2H-chromen-2-one* (15v):**



15v

Reaction Time: 1 h **Colour & State:** white solid

Yield: 90% (191 mg) **Melting Point:** 113-116 °C

^{1}HNMR (400 MHz, CDCl$_3$): δ 7.69 (t, *J* = 8 Hz, 4 H), 7.35 (t, *J* = 8.8 Hz, 3 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 7.04 (t, *J* = 8 Hz, 1 H), 6.75 (d, *J* = 6.8 Hz, 1 H), 4.87 (s, 2 H), 4.02 (q, *J* =7.2 Hz, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 156.9, 146.1, 137.0, 133.5, 132.9, 128.6, 127.9, 127.8, 127.75, 126.5, 126.3, 126.0, 125.8, 124.8, 124.6, 121.6, 117.3, 112.9, 111.5, 65.1, 50.0, 15.0 ppm.

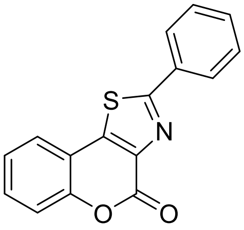
HRMS (ESI) calcd for $C_{22}H_{18}BrNO_3$ (M+H$^+$) = 424.0543, found 424.0548.

Elemental Analysis	Calculated	Found
MF $C_{22}H_{18}BrNO_3$	C 62.28	62.48
(424.29)	H 4.28	4.24
	N 3.30	3.23

General procedure for the synthesis of various 2-phenyl-4H-chromeno(3,4-*d*)thiazol-4-one derivatives (16a-v):

Into a 10 mL round bottomed flask was taken 0.3 mmol of **15** and 0.9 mmol of Na_2S. After adding 2 mL of DMF, 20 mol% of iodine and 5 mmol of H_2O_2 were added into it and the reaction mixture were heated at 120 °C in a preheated oil bath for 16-24 h. The progress of the reaction was checked by TLC time to time. When the reaction was complete, the reaction mixture was worked-up with ethyl acetate and the crude product obtained after evaporating the solvent in rotary evaporator. Finally it was purified by column chromatography with ethyl acetate and hexane mixture (1:9). The pale yellow solid products were obtained, which were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS.

***2-Phenyl-4H-chromeno[3,4-d]thiazol-4-one* (16a):**



16a

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 86% (71.98 mg) **Melting Point:** 164-167 °C

IR (KBr): 2924.97, 2854.00, 1737.29, 1616.79, 1284.21, 1091.91, 1036.64 cm^{-1}.

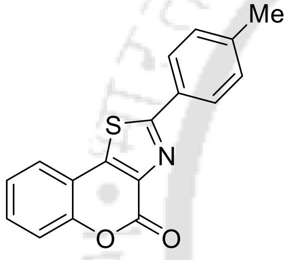
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.12 (d, *J* = 7.2 Hz, 2 H), 7.68 (d, *J* = 8 Hz, 1 H), 7.52 (m, 5 H), 7.38 (t, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 168.7, 155.8, 151.6, 145.0, 140.0, 132.3, 131.9, 131.4, 129.4, 127.6, 125.5, 125.3, 117.8, 116.1 ppm.

HRMS (ESI) calcd for $C_{16}H_9NO_2S$ (M+H$^+$) = 280.0427, found 280.0430.

Elemental Analysis	Calculated	Found
MF $C_{16}H_9NO_2S$	C 68.80	68.93
(279.31)	H 3.25	3.29
	N 5.01	5.10

***2-(p-Tolyl)-4H-chromeno[3,4-d]thiazol-4-one* (16b):**



16b

Reaction Time: 21 h **Colour & State:** pale yellow solid

Yield: 79% (69.44 mg) **Melting Point:** 212-216 °C

IR (KBr): 2956.04, 2924.37, 2853.39, 1743.17, 1602.99, 1182.85, 1088.29, 1033.51 cm^{-1}.

^{1}HNMR (400 MHz, CDCl$_3$): δ 7.98 (d, *J* = 7.6 Hz, 2 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.54 (t, *J* = 8.4 Hz, 1 H), 7.45 (d, *J* = 8 Hz, 1 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.28 (t, *J*= 8 Hz, 2 H), 2.41 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 168.8, 155.8, 151.5, 144.6, 142.5, 139.8, 131.2, 130.0, 129.6, 127.5, 125.4, 125.2, 117.7, 116.1, 21.7 ppm.

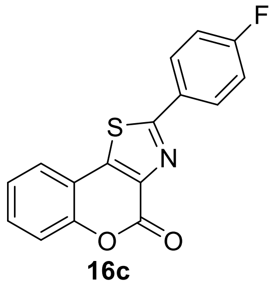
HRMS (ESI) calcd for $C_{17}H_{11}NO_2S$ (M+H$^+$) = 294.0583, found 294.0589.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{11}NO_2S$	C 69.61	69.75
(293.34)	H 3.78	3.73
	N 4.78	4.85

***2-(4-Fluorophenyl)-4H-chromeno[3,4-d]thiazol-4-one* (16c):-**

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 83% (73.95 mg) **Melting Point:** 229-231 °C



16c

IR (KBr): 2923.96, 2853.36, 1754.15, 1602.53, 1266.85, 1159.65, 1091.14, 1034.07 cm^{-1}.

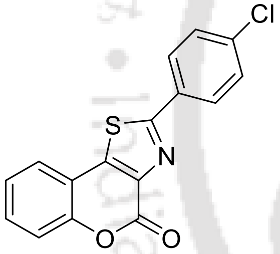
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.13 (dd, *J* = 8.4, 4.8 Hz, 2 H), 7.67(d, *J* = 7.2 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.48 (d, *J* = 8.8 Hz, 1 H), 7.38 (t, *J* = 8 Hz, 1 H), 7.21 (t, *J* = 8.4 Hz, 2 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 167.1, 166.0, 163.5, 155.5, 151.4, 144.8, 139.7, 131.3, 129.6, 129.5, 128.50, 128.47, 125.2, 125.1, 117.7, 116.5, 116.3, 115.7 ppm.

HRMS (ESI) calcd for $C_{16}H_8FNO_2S$ (M+H$^+$) = 298.0333, found 298.0333.

Elemental Analysis	Calculated	Found
MF $C_{16}H_8FNO_2S$	C 64.64	64.78
(297.30)	H 2.71	2.75
	N 4.71	4.66

***2-(4-Chlorophenyl)-4H-chromeno[3,4-d]thiazol-4-one* (16d):**



16d

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 80% (75.29 mg) **Melting Point:** 250-253 °C

IR (KBr): 2923.28, 1753.17, 1604.98, 1266.21, 1087.93, 1034.74 cm^{-1}.

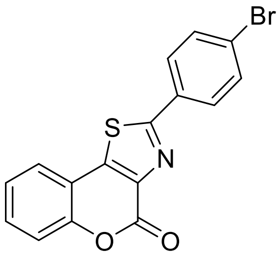
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.98 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 14.4 Hz, 1 H), 7.42 (m, 3 H), 7.31 (t, *J* = 6.8 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 167.3, 155.7, 151.7, 145.2, 140.0, 138.1, 131.6, 130.8, 129.7, 128.8, 125.5, 125.4, 117.9, 115.9 ppm.

HRMS (ESI) calcd for $C_{16}H_8ClNO_2S$ (M+H$^+$) = 314.0037, found 314.0046.

Elemental Analysis	Calculated	Found
MF $C_{16}H_8ClNO_2S$	C 61.25	61.40
(313.76)	H 2.57	2.62
	N 4.46	4.54

***2-(4-Bromophenyl)-4H-chromeno[3,4-d]thiazol-4-*one (16e):**



16e

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 78% (83.77 mg) **Melting Point:** 262-264 °C

IR (KBr): 2923.68, 2852.63, 1760.49, 1604.61, 1265.09, 1085.68, 1033.77 cm^{-1}.

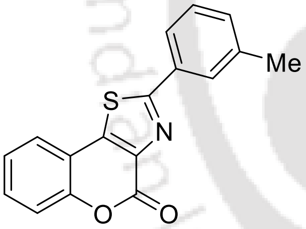
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.97 (d, *J* = 8.4 Hz, 2 H), 7.66 (t, *J* = 5.6 Hz. 3 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.48 (d, 8.4 Hz, 1 H) 7.38 (t, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 167.4, 155.7, 151.7, 145.3, 140.0, 132.7, 131.6, 131.2, 129.0, 126.5, 125.5, 125.4, 125.3, 117.9, 115.9 ppm.

HRMS (ESI) calcd for $C_{16}H_8BrNO_2S$ (M+H$^+$) = 357.9532, found 357.9533.

Elemental Analysis	Calculated	Found
MF $C_{16}H_8BrNO_2S$	C 53.65	53.80
(358.21)	H 2.25	2.19
	N 3.91	3.98

2-(m-Tolyl)-4H-chromeno[3,4-d]thiazol-4-one **(16f):**



16f

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 78% (68.56 mg) **Melting Point:** 193 °C

IR (KBr): 3059.06, 2924.29, 2853.49, 1739.16, 1602.24, 1267.26, 1084.42, 1031.69 cm^{-1}.

^{1}HNMR (600 MHz, CDCl$_3$): δ 7.99 (s, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.56 (t, *J* = 7.8 Hz, 1 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.38 (m, 2 H), 7.34 (d, *J* = 7.2 Hz, 1 H), 2.45 (s, 3 H) ppm.

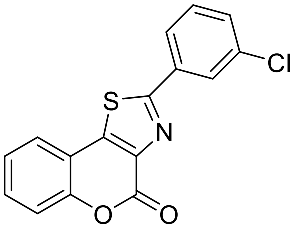
^{13}C NMR (150 MHz, CDCl$_3$): δ 169.0, 155.9, 144.9, 140.0, 139.4, 132.7, 132.3, 131.4, 129.3, 129.0, 128.2, 125.8, 125.3, 124.9, 117.9, 116.1, 21.5 ppm.

HRMS (ESI) calcd for $C_{17}H_{11}NO_2S$ (M+H$^+$) = 294.0583, found 294.0588.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{11}NO_2S$	C 69.61	69.50
(293.34)	H 3.78	3.73

	N 4.78	4.71

***2-(3-Chlorophenyl)-4H-chromeno[3,4-d]thiazol-4-one* (16g):**



16g

Reaction Time: 23 h **Colour & State:** pale yellow solid

Yield: 65% (61.17 mg) **Melting Point:** 180 °C

IR (KBr): 2923.48, 2851.76, 1742.82, 1605.49, 1231.94, 1077.30, 1031.99 cm^{-1}.

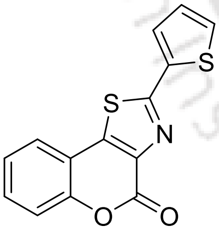
^{1}HNMR (600 MHz, CDCl$_3$): δ 8.15 (t, *J* = 1.2 Hz, 1 H), 7.98 (d, *J* = 7.2, 1 H), 7.68 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.58 (t, *J* = 7.8, 1 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 7.45 (t, *J* = 7.8, 1 H), 7.39 (t, *J* = 7.8, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.9, 155.8, 151.7, 145.4, 135.7, 133.9, 131.8, 131.7, 130.7, 127.5, 125.7, 125.5, 125.4, 118.0, 115.9, 110.2 ppm.

HRMS (ESI) calcd for $C_{16}H_8ClNO_2S$ (M+H$^+$) = 314.0037, found 314.0043.

Elemental Analysis	Calculated	Found
MF $C_{16}H_8ClNO_2S$	C 61.25	61.41
(313.76)	H 2.57	2.61
	N 4.46	4.53

***2-(Thiophen-2-yl)-4H-chromeno[3,4-d]thiazol-4-one* (16h):**



16h

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 66% (56.43 mg) **Melting Point:** 172-175 °C

IR (KBr): 2924.50, 2853.25, 1739.72, 1605.08, 1094.67.43, 1027.29 cm^{-1}.

^{1}HNMR (600 MHz, CDCl$_3$): δ 7.70 (d, *J* = 2.4 Hz, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.55 (m, 2 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.15 (t, *J* = 3.6 Hz, 1 H) ppm.

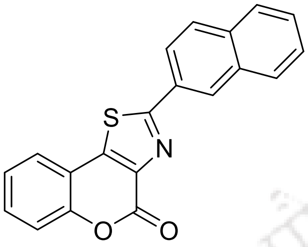
^{13}C NMR (150 MHz, CDCl$_3$): δ 169.0, 162.0, 155.6, 151.6, 144.5, 139.6, 135.9, 131.4, 130.6, 129.3, 128.4, 125.3, 117.9, 115.9 ppm.

HRMS (ESI) calcd for $C_{14}H_7NO_2S_2$ (M+H$^+$) = 285.9991, found 285.9997.

Elemental Analysis	Calculated	Found

MF $C_{14}H_7NO_2S_2$	C 58.93	59.06
(285.34)	H 2.47	2.53
	N 4.91	4.85

***2-(Naphthalen-2-yl)-4H-chromeno[3,4-d]thiazol-4-one* (2i):**



16i

Reaction Time: 16 h **Colour & State:** pale yellow solid

Yield: 89% (87.84 mg) **Melting Point:** 226-228 °C

IR (KBr): 2931.38, 2853.66, 1744.62, 1219.59, 1083.99 cm^{-1}.

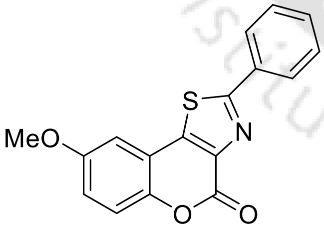
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.59 (s, 1 H), 8.17 (d, *J* = 8.8 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 2 H), 7.86 (d, *J* = 4.8 Hz, 1 H), 7.67 (d, *J* = 8 Hz, 1 H), 7.61 (m, 3 H), 7.46 (d, *J* = 1.2 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 168.6, 155.7, 151.5, 144.9, 139.9, 134.8, 133.1, 131.3, 129.5, 129.2, 129.0, 128.0, 127.7, 127.3, 125.4, 125.2, 124.1, 117.7, 115.9 ppm.

HRMS (ESI) calcd for $C_{20}H_{11}NO_2S$ (M+H$^+$) = 330.0583, found 330.0589.

Elemental Analysis	Calculated	Found
MF $C_{20}H_{11}NO_2S$	C 72.93	73.10
(329.37)	H 3.37	3.33
	N 4.25	4.34

***8-Methoxy-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one* (16j):**



16j

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 85% (78.79 mg) **Melting Point:** 197-200 °C

IR (KBr): 2956.07, 2924.27, 2853.57, 1733.31, 1613.58, 1243.59, 1093.08, 1052.14 cm^{-1}.

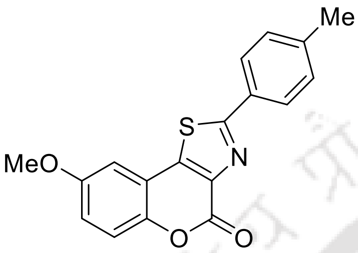
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.11 (m, 2 H), 7.52 (m, 3 H), 7.40 (d, *J* = 8.8 Hz, 1 H), 7.12 (dd, *J* = 9.6, 3.2 Hz, 1 H), 7.05 (d, *J* = 3.2 Hz, 1 H), 3.90 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 168.7, 156.8, 156.0, 146.1, 144.8, 140.3, 132.4, 131.9, 129.4, 127.7, 119.0, 118.8, 116.5, 108.0, 56.2 ppm.

HRMS (ESI) calcd for $C_{17}H_{11}NO_3S$ (M+H$^+$) = 310.0532, found 310.0543.

Elemental Analysis	**Calculated**	**Found**
MF $C_{17}H_{11}NO_3S$	C 66.01	66.20
(309.34)	H 3.58	3.53
	N 4.53	4.46

***8-Methoxy-2-(p-tolyl)-4H-chromeno[3,4-d]thiazol-4-one* (16k):**



16k

Reaction Time: 20 h **Colour & State:** pale yellow solid

Yield: 82% (79.46 mg) **Melting Point:** 218-220 °C

IR (KBr): 2923.91, 2853.23, 1752.78, 1612.11, 1299.66, 1090.87, 1026.53 cm^{-1}.

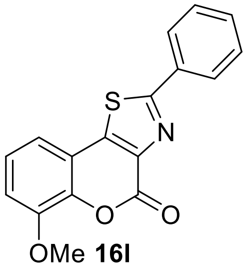
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.99 (d, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 9.6 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.10 (dd, *J* = 8.8, 2.8 Hz, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 3.90 (s, 3 H), 2.42 (s, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 168.8, 156.7, 156.0, 146.0, 144.4, 142.5, 140.1, 130.1, 129.8, 127.6, 118.9, 118.7, 116.5, 108.0, 56.2, 21.8 ppm.

HRMS (ESI): calcd for $C_{18}H_{13}NO_3S$ (M+H$^+$) = 324.0689, found 324.0696.

Elemental Analysis	**Calculated**	**Found**
MF $C_{18}H_{13}NO_3S$	C 66.86	66.74
(323.36)	H 4.05	4.11
	N 4.33	4.24

***6-Methoxy-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one* (16l):**



16l

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 85% (78.79 mg) **Melting Point:** 214-217 °C

IR (KBr): 2956.33, 2924.60, 2853.64, 1738.67, 1605.66, 1270.11, 1094.15, 1013.73 cm^{-1}.

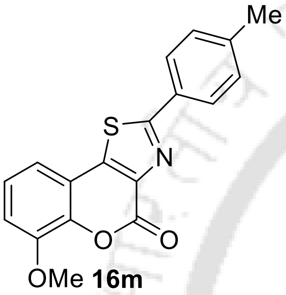
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.10 (d, *J* = 6.8 Hz, 2 H), 7.51 (m, 3 H), 7.28 (m, 2 H), 7.08(d, *J* = 8.4 Hz, 1 H), 3.97 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ, 168.8, 155.5, 148.2, 145.2, 141.6, 140.1, 132.4, 131.8, 129.4, 127.7, 125.4, 116.8, 113.3, 56.6 ppm.

HRMS (ESI) calcd for $C_{17}H_{11}NO_3S$ (M+H$^+$) = 310.0532, found 310.0539.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{11}NO_3S$	C 66.01	66.21
(309.34)	H 3.58	3.53
	N 4.53	4.60

***6-Methoxy-2-(p-tolyl)-4H-chromeno[3,4-d]thiazol-4-one* (16m):**



16m

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 86% (83.33 mg) **Melting Point:** 247-250 °C

IR (KBr): 2924.32, 2853.45, 1737.93, 1607.12, 1272.09, 1098.89, 1016.59 cm^{-1}.

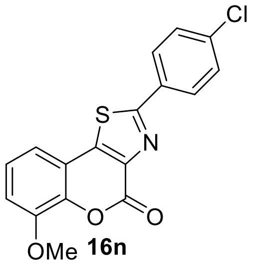
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.98 (d, *J* = 8 Hz, 2 H), 7.29(d, *J* = 8.4 Hz. 3 H), 7.20 (dd, *J* = 7 .6, 1.6 Hz, 1 H), 7.07 (dd, *J* = 7.6, 1.2 Hz, 1 H), 3.40(s, 3 H), 2.42 (s, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 169.0, 155.3, 148.2, 144.8, 142.5, 141.5, 140.0, 130.1, 129.8, 127.6, 125.3, 116.8, 113.2, 56.6, 21.8 ppm.

HRMS (ESI) calcd for $C_{18}H_{13}NO_3S$ (M+H$^+$) = 324.0689, found 324.0687.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{13}NO_3S$	C 66.86	66.97
(323.36)	H 4.05	4.01
	N 4.33	4.23

***2-(4-Chlorophenyl)-6-methoxy-4H-chromeno[3,4-d]thiazol-4-one* (16n):**



16n

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 84% (86.64 mg) **Melting Point:** 209-214 °C

IR (KBr): 2914.91, 2851.04, 1739.32, 1271.85, 1098.82, 1012.97 cm^{-1}.

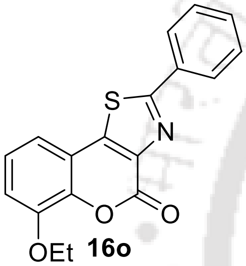
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.97 (d, *J* = 8 Hz, 2 H), 7.41 (d, *J* = 7.6 Hz. 2 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.15 (d, 8 Hz, 1 H) 7.03 (d, *J* = 8 Hz, 1 H), 3.93(s, 3 H),) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 167.4, 155.2, 148.2, 147.9, 145.3, 141.6, 138.0, 130.8, 129.7, 128.8, 125.5, 116.8, 116.6, 113.5, 56.6.ppm.

HRMS (ESI) calcd for $C_{17}H_{10}ClNO_3S$ (M+H$^+$) = 344.0143, found 344.0146.

Elemental Analysis	Calculated	Found
MF $C_{17}H_{10}ClNO_3S$	C 59.39	59.25
(343.78)	H 2.93	2.99
	N 4.07	4.16

6-Ethoxy-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one **(16o):**



16o

Reaction Time: 23 h **Colour & State:** pale yellow solid

Yield: 82%(79.46 mg) **Melting Point:** 205-208 °C

IR (KBr): 2990.00, 2969.05, 2927.46, 1735.89, 1606.16, 1273.88, 1194.97, 1095.46, 1035.45 cm^{-1}.

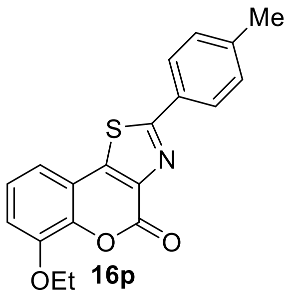
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.10 (m, 1 H), 7.50 (m, 3 H), 7.26 (m, 2 H), 7.22 (d, *J* = 1.6 Hz, 1 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 4.21 (q, *J* = 6.8 Hz, 2 H), 1.51 (t, *J* = 6.8 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 168.7, 155.4, 147.6, 145.3, 141.7, 140.1, 132.4, 131.8, 129.4, 127.7, 125.3, 116.8, 116.7, 114.5, 65.4, 15.0 ppm.

HRMS (ESI) calcd for $C_{18}H_{13}NO_3S$ (M+H$^+$) = 324.0689, found 324.0695.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{13}NO_3S$	C 66.86	66.99
(323.36)	H 4.05	4.01
	N 4.33	4.24

6-Ethoxy-2-(p-tolyl)-4H-chromeno[3,4-d]thiazol-4-one **(16p):**



16p

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 80% (80.88 mg) **Melting Point:** 208-210 °C

IR (KBr): 3071.35, 2911.06, 1738.27, 1273.34, 1183.01, 1081.48, 1034.69 cm^{-1}.

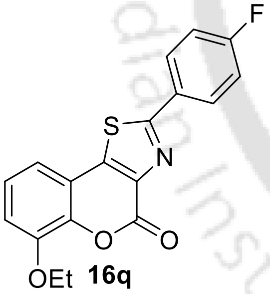
^{1}HNMR (400 MHz, CDCl$_3$): δ 7.99 (d, *J* = 7.6 Hz, 2 H), 7.28 (m, 3 H), 7.20 (d, *J* = 7.6 Hz, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 4.21 (q, *J* =7.2 Hz, 2 H), 2.43 (s, 3 H), 1.52 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 168.9, 155.5, 147.5, 144.9, 142.4, 139.9, 130.0, 129.8, 127.6, 125.3, 116.8, 116.6, 114.3, 65.3, 21.7, 15.0 ppm.

HRMS (ESI) calcd for $C_{19}H_{15}NO_3S$ (M+H$^+$) = 338.0845, found 338.0855.

Elemental Analysis	Calculated	Found
MF $C_{19}H_{15}NO_3S$	C 67.64	67.82
(337.39)	H 4.48	4.53
	N 4.15	4.07

***6-Ethoxy-2-(4-fluorophenyl)-4H-chromeno[3,4-d]thiazol-4-one* (16q):**



16q

Reaction Time: 20 h **Colour & State:** pale yellow solid

Yield: 85% (86.95 mg) **Melting Point:** 193-196 °C

IR (KBr): 2924.18, 2855.07, 1740.43, 1606.15, 1273.67, 1095.69, 1040.43 cm^{-1}.

^{1}HNMR (400 MHz, CDCl$_3$): δ 8.10 (m, 2 H), 7.27 (m, 2 H), 7.19 (m, 2 H), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1 H) ppm.

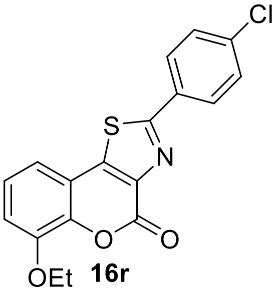
^{13}C NMR (100 MHz, CDCl$_3$): δ 167.3, 166.2, 163.7, 155.4, 147.5, 145.2, 141.6, 140.0, 129.7, 129.6, 128.7, 128.65, 125.4, 116.7, 116.6, 116.5, 114.5, 65.3, 14.9 ppm.

HRMS (ESI) calcd for $C_{18}H_{12}FNO_3S$ (M+H$^+$) = 342.0595, found 342.0599.

Elemental Analysis	Calculated	Found
MF $C_{18}H_{12}FNO_3S$	C 63.33	63.24
(341.36)	H 3.54	3.50

	N 4.10	4.01

***2-(4-Chlorophenyl)-6-ethoxy-4H-chromeno[3,4-d]thiazol-4-one* (16r):**



16r

Reaction Time: 22 h **Colour & State:** pale yellow solid

Yield: 78% (83.72 mg) **Melting Point:** 204-206 °C

IR (KBr): 2923.05, 2848.11, 1735.13, 1275.51, 1088.12, 1036.74 cm^{-1}.

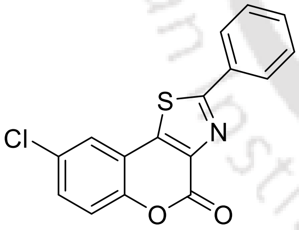
^{1}HNMR (600 MHz, CDCl$_3$): δ 8.03 (d, *J* = 7.8 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.27 (t, *J* = 5.4 Hz, 1 H), 7.20 (d, *J* = 7.8 Hz, 1 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 4.21 (q, *J* = 6.6 Hz, 2 H), 1.53 (t, *J* = 6.6 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 167.3, 155.4, 147.6, 141.7, 140.1, 138.0, 130.9, 129.7, 128.8, 125.4, 116.65, 116.60, 114.6, 65.3, 15.0 ppm.

HRMS (ESI) calcd for $C_{18}H_{12}ClNO_3S$ (M+H$^+$) =358.0299, found 358.0300.

Elemental Analysis	**Calculated**	**Found**
MF $C_{18}H_{12}ClNO_3S$	C 60.42	60.60
(357.81)	H 3.38	3.30
	N 3.91	3.81

***8-Chloro-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one*(16s):**



16s

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 70% (65.73 mg) **Melting Point:** 226 °C

IR (KBr): 2958.46, 2923.42, 2852.10, 1747.32, 1603.59, 1258.19, 1081.96, 1025.50 cm^{-1}.

^{1}HNMR (400 MHz, CDCl$_3$): δ 8.10 (d, *J* = 6.8, 2 H), 7.64 (s, 1 H), 7.51 (m, 4 H), 7.42 (d, *J* = 8.8 Hz, 1 H) ppm.

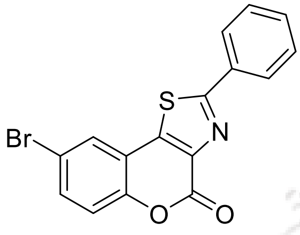
^{13}C NMR (100 MHz, CDCl$_3$): δ 169.5, 155.2, 150.0, 143.6, 140.4, 132.2, 131.3, 130.6, 129.5, 129.1, 127.7, 124.8, 119.3, 117.2 ppm.

HRMS (ESI) calcd for $C_{16}H_8ClNO_2S$ (M+H$^+$) = 314.0037, found 314.0043.

Elemental Analysis	**Calculated**	**Found**

MF $C_{16}H_8ClNO_2S$	C 61.25	61.41
(313.76)	H 2.57	2.61
	N 4.46	4.55

8-Bromo-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one **(16t):**



16t

Reaction Time: 24 h **Colour & State:** pale yellow solid

Yield: 72% (77.33 mg) **Melting Point:** 236 °C

IR (KBr): 2922.61, 2851.76, 1753.56, 1600.71, 1278.36, 1086.66, 1052.63 cm^{-1}.

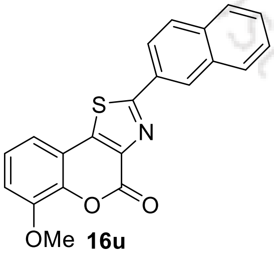
^{1}HNMR (600 MHz, $CDCl_3$): δ 8.10 (d, *J* = 6.6 Hz, 2 H), 7.80 (d, *J* = 1.8 Hz, 1 H), 7.64 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.53 (m, 3 H), 7.36 (d, *J* = 9.0 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 155.2, 150.5, 143.4, 140.4, 134.1, 132.2, 132.1, 129.5, 127.8, 127.7, 119.6, 117.9, 117.7 ppm.

HRMS (ESI) calcd for $C_{16}H_8BrNO_2S$ (M+H$^+$) = 357.9532, found 357.9537.

Elemental Analysis	**Calculated**	**Found**
MF $C_{16}H_8BrNO_2S$	C 53.65	53.79
(358.21)	H 2.25	2.30
	N 3.91	3.81

6-Methoxy-2-(naphthalen-2-yl)-4H-chromeno[3,4-d]thiazol-4-one **(16u):**



16u

Reaction Time: 16 h **Colour & State:** pale yellow solid

Yield: 87% (93.70 mg) **Melting Point:** 223-226 °C

IR (KBr): 2924.34, 2853.58, 1734.86, 1268.44, 1077.43, 1010.71 cm^{-1}.

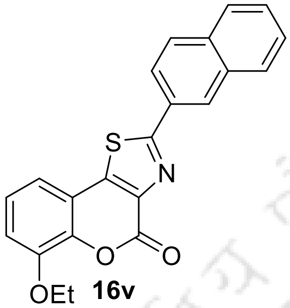
^{1}HNMR (600 MHz, $CDCl_3$): δ 8.61 (s, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 7.8 Hz, 2 H), 7.88 (d, *J* = 6 Hz, 1 H), 7.57 (t, *J* = 4.2 Hz, 2 H), 7.31 (t, *J* = 7.8, Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 4.1 (s, 3 H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.9, 155.4, 153.5, 148.2, 145.2, 141.6, 140.2, 138.5, 135.0, 133.3, 129.7, 129.3, 129.1, 128.1, 127.9, 127.4, 125.4, 124.2, 116.8, 113.3, 56.6 ppm.

HRMS (ESI) calcd for $C_{21}H_{13}NO_3S$ (M+H$^+$) = 360.0689, found 360.0694.

Elemental Analysis	**Calculated**	**Found**
MF $C_{21}H_{13}NO_3S$	C 70.18	70.28
(359.40)	H 3.65	3.70
	N 3.90	3.99

***6-Ethoxy-2-(naphthalen-2-yl)-4H-chromeno[3,4-d]thiazol-4-one* (16v):**



16v

Reaction Time: 18 h **Colour & State:** pale yellow solid

Yield: 85% (95.11 mg) **Melting Point:** 187-190 °C

IR (KBr): 2959.40, 2924.94, 2853.89, 1753.02, 1652.49, 1272.56, 1079.48, 1034.26 cm^{-1}.

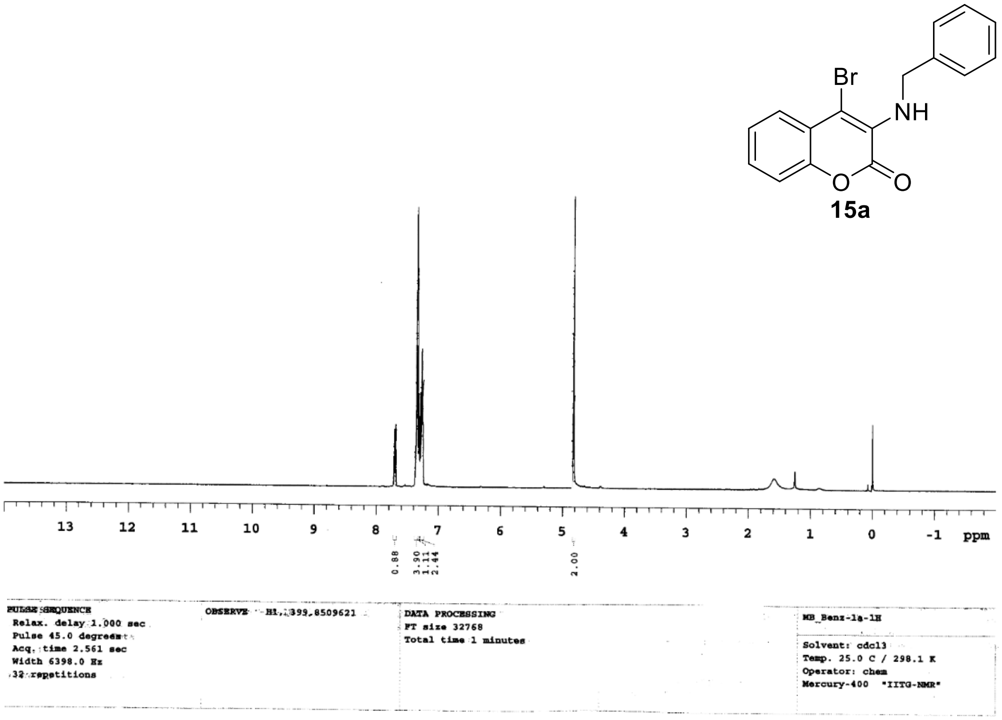
^{1}HNMR (600 MHz, CDCl$_3$): δ 8.58 (d, *J* = 5.4 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 7.94 (t, *J* = 1.8 , 2 H), 7.85 (s, 1 H), 7.55 (d, *J* = 3.6 Hz, 2 H), 7.26 (s, 1 H), 7.21 (d, J = 7.2 Hz, 1 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 1.53 (t, *J* = 6.6 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ 168.8, 155.5, 147.5, 145.2, 141.7, 140.1, 135.0, 133.2, 129.7, 129.2, 129.1, 128.1, 127.8, 127.4, 125.4, 124.2, 116.8, 116.7, 114.4, 65.3, 15.0 ppm.

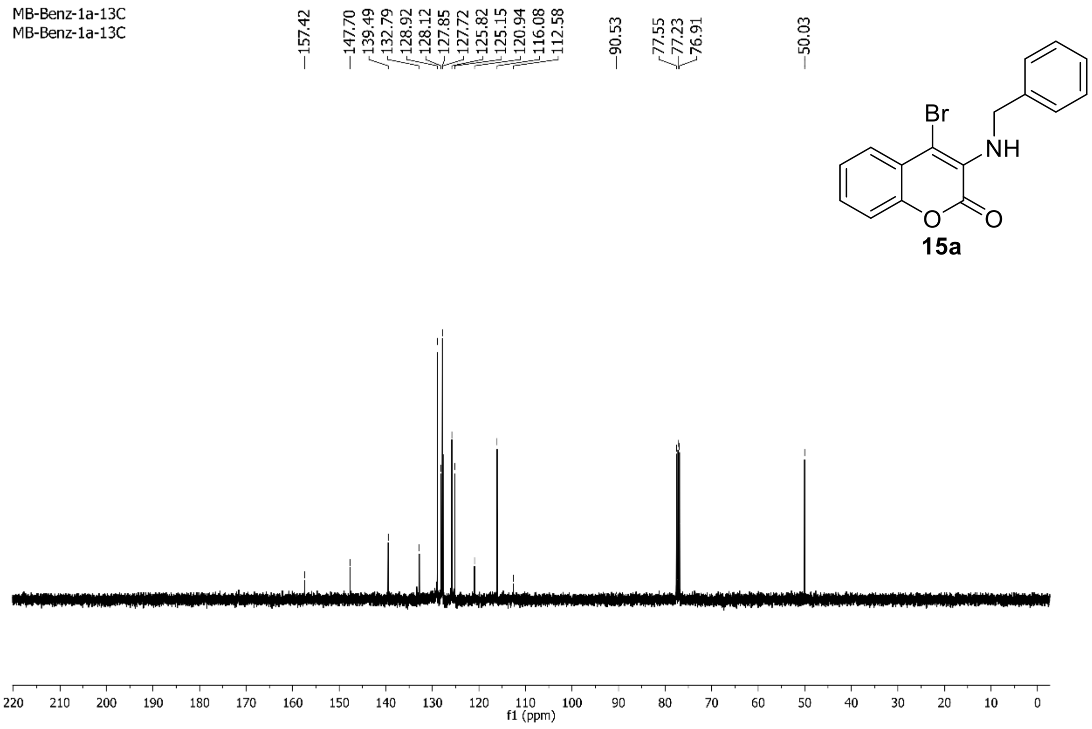
HRMS (ESI) calcd for $C_{22}H_{15}NO_3S$ (M+H$^+$) = 374.0845, found 374.0845.

Elemental Analysis	**Calculated**	**Found**
MF $C_{22}H_{15}NO_3S$	C 70.76	70.92
(373.43)	H 4.05	3.11
	N 3.75	3.82

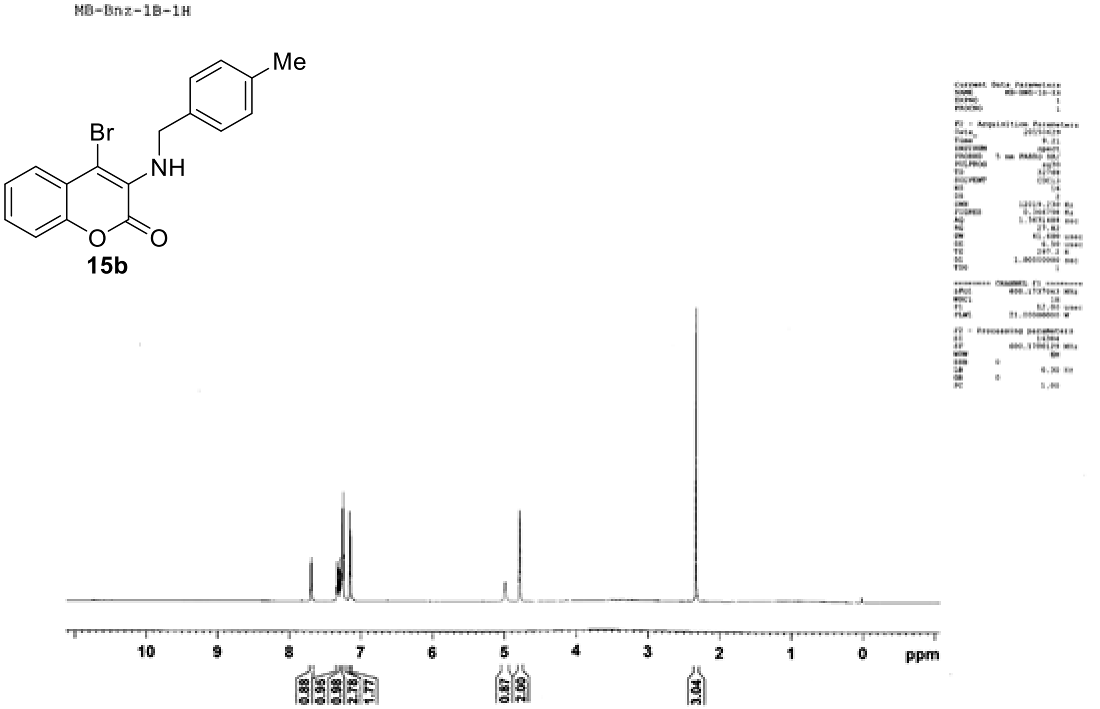
***^{1}HNMR (400 MHz, $CDCl_3$)*: *3-(Benzylamino)-4-bromo-2H-chromen-2-one* (**15a**)



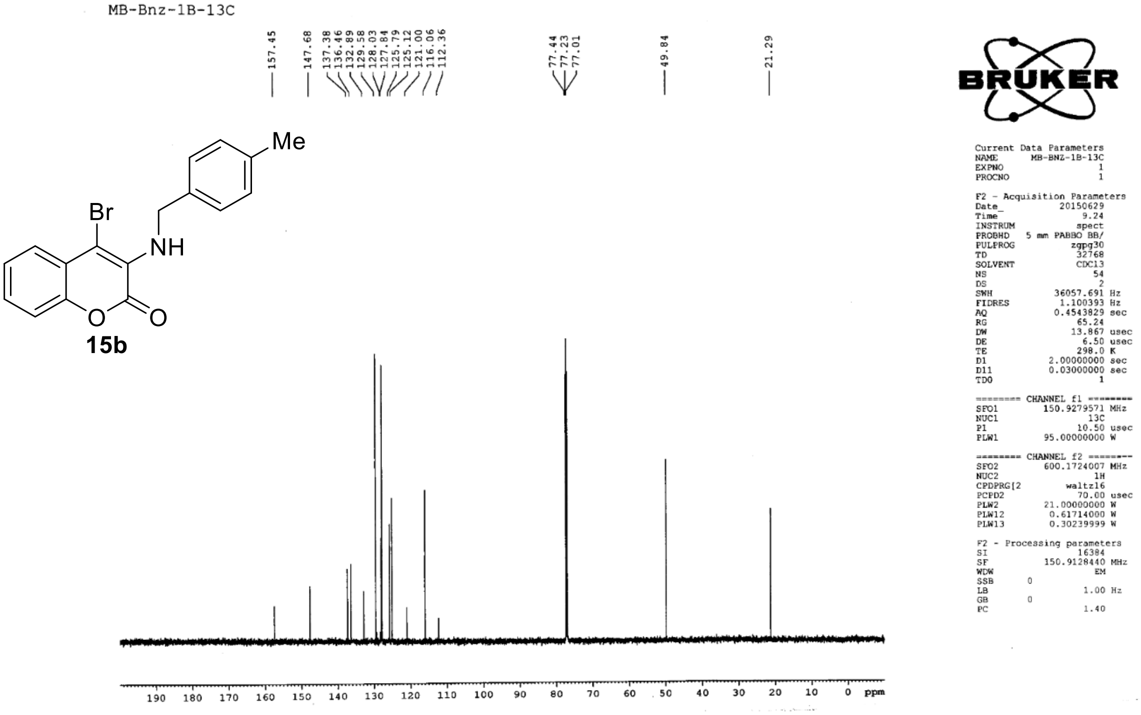
^{13}C NMR (100 MHz, $CDCl_3$): *3-(Benzylamino)-4-bromo-2H-chromen-2-one* (**15a**)



^{1}HNMR (600 MHz, CDCl$_3$): *4-Bromo-3-((4-methylbenzyl)amino)-2H-chromen-2-one* (**15b**)



^{13}C NMR (150 MHz, CDCl$_3$): *4-Bromo-3-((4-methylbenzyl)amino)-2H-chromen-2-one* (**15b**)



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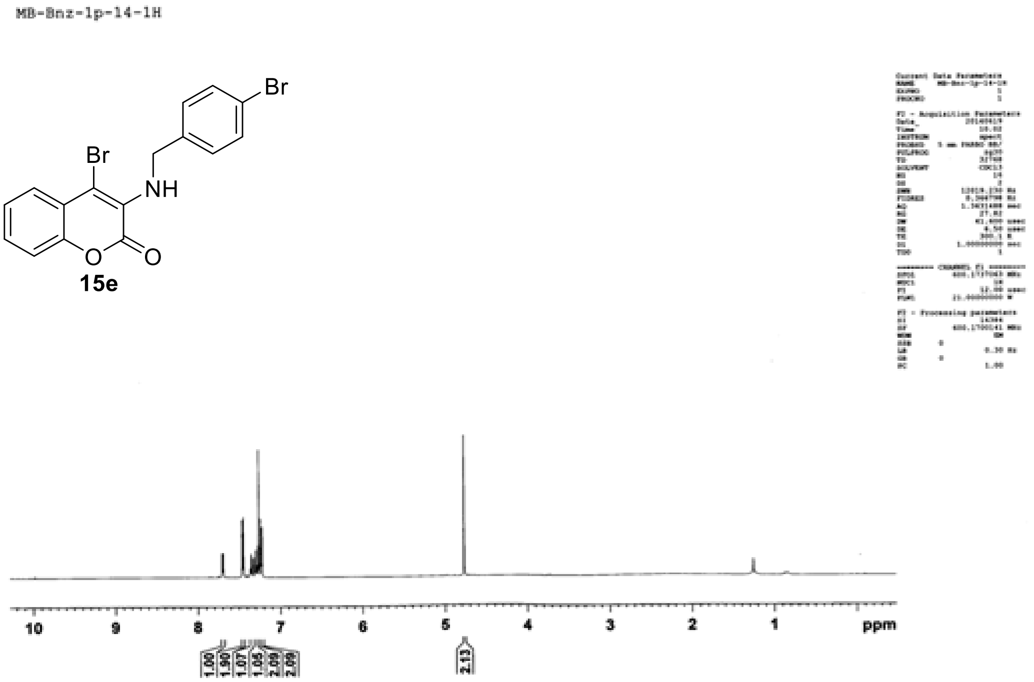
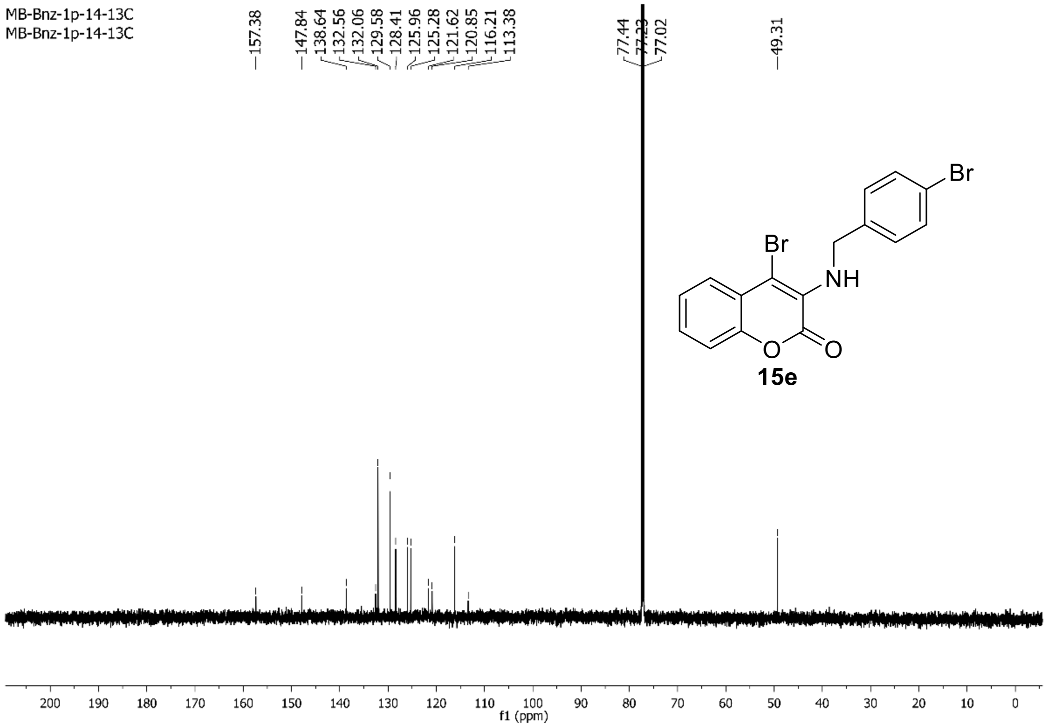
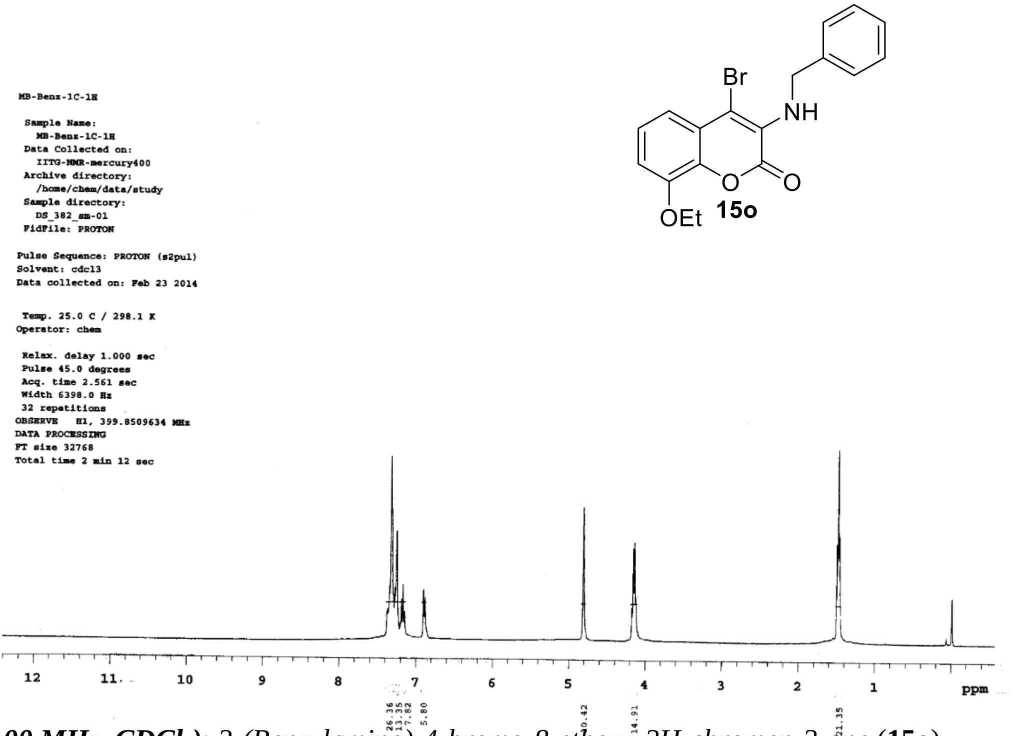
^{1}***HNMR (600 MHz, CDCl$_3$)***: *4-Bromo-3-((4-bromobenzyl)amino)-2H-chromen-2-one* (**15e**)



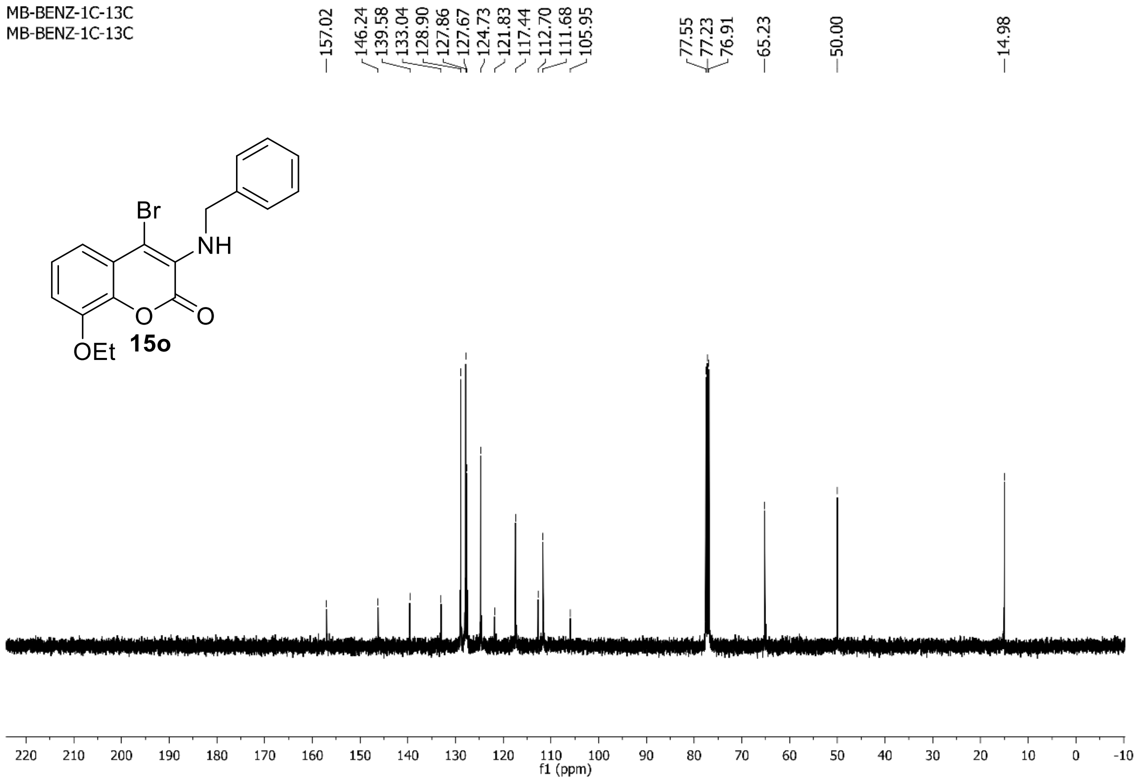
^{13}***C NMR (100 MHz, CDCl$_3$)***: *4-Bromo-3-((4-bromobenzyl)amino)-2H-chromen-2-one* (**15e**)



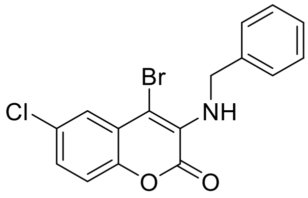
^{1}HNMR (400 MHz, CDCl$_3$): *3-(Benzylamino)-4-bromo-8-ethoxy-2H-chromen-2-one* (**15o**)



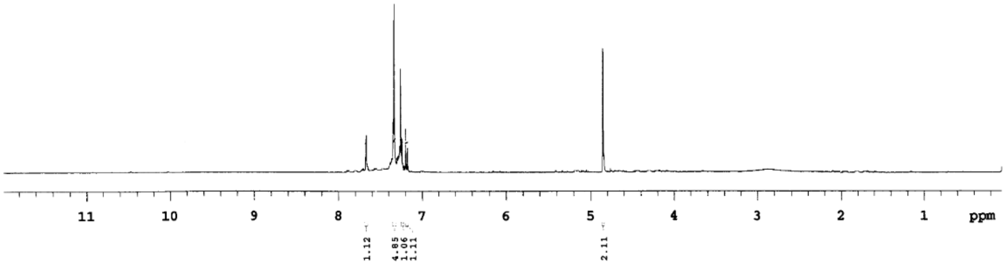
^{13}C NMR (100 MHz, CDCl$_3$): *3-(Benzylamino)-4-bromo-8-ethoxy-2H-chromen-2-one* (**15o**)



^{1}HNMR (400 MHz, CDCl$_3$): *3-(Benzylamino)-4-bromo-6-chloro-2H-chromen-2-one* (**15s**)



15s



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Total time 1 minutes

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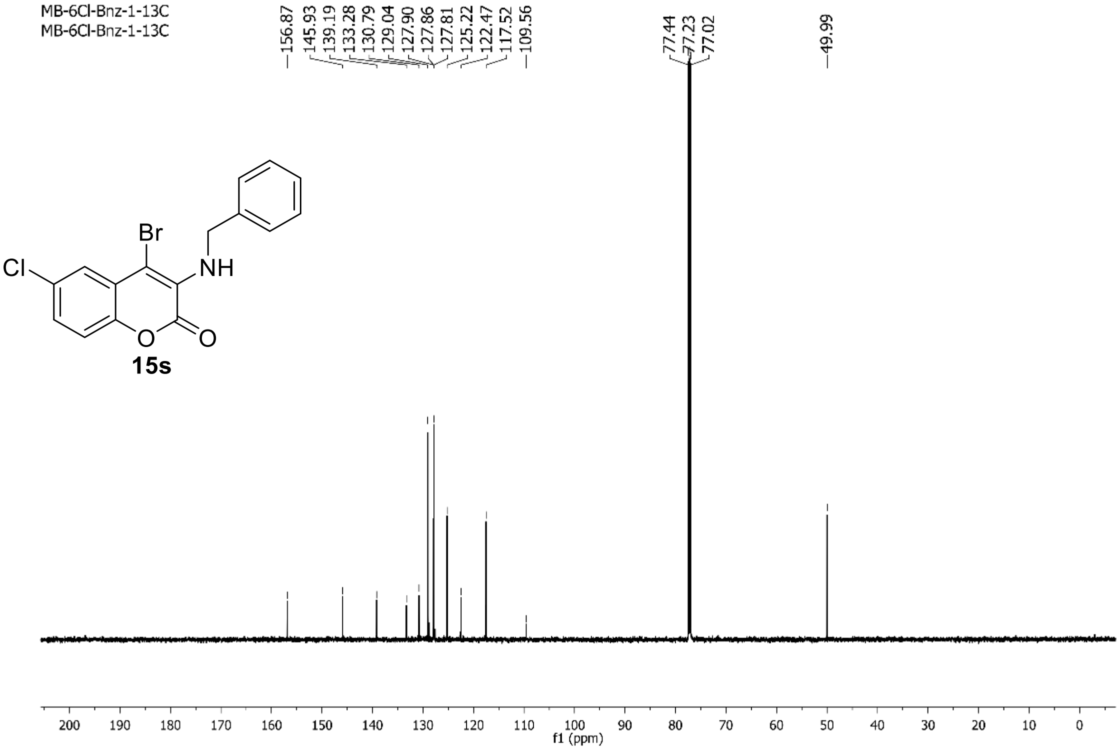
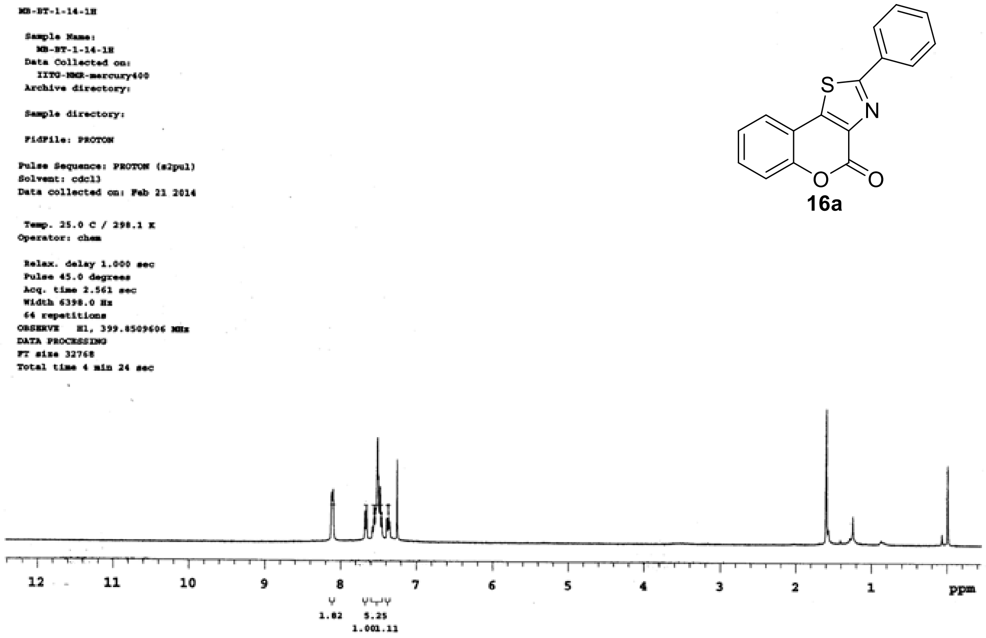
Temp. 25.0 C / 298.1 K
Operator: chem
File: MB-6-Cl-Bnz-1-1H
Mercury-400 "IITG-NMR"

^{13}C NMR (100 MHz, CDCl$_3$): *3-(Benzylamino)-4-bromo-6-chloro-2H-chromen-2-one* (**15s**)



^{1}HNMR (400 MHz, CDCl$_3$): *2-Phenyl-4H-chromeno[3,4-d]thiazol-4-one* (**16a**)



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 Archive directory:

 Sample directory:

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Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Feb 21 2014

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Operator: chem

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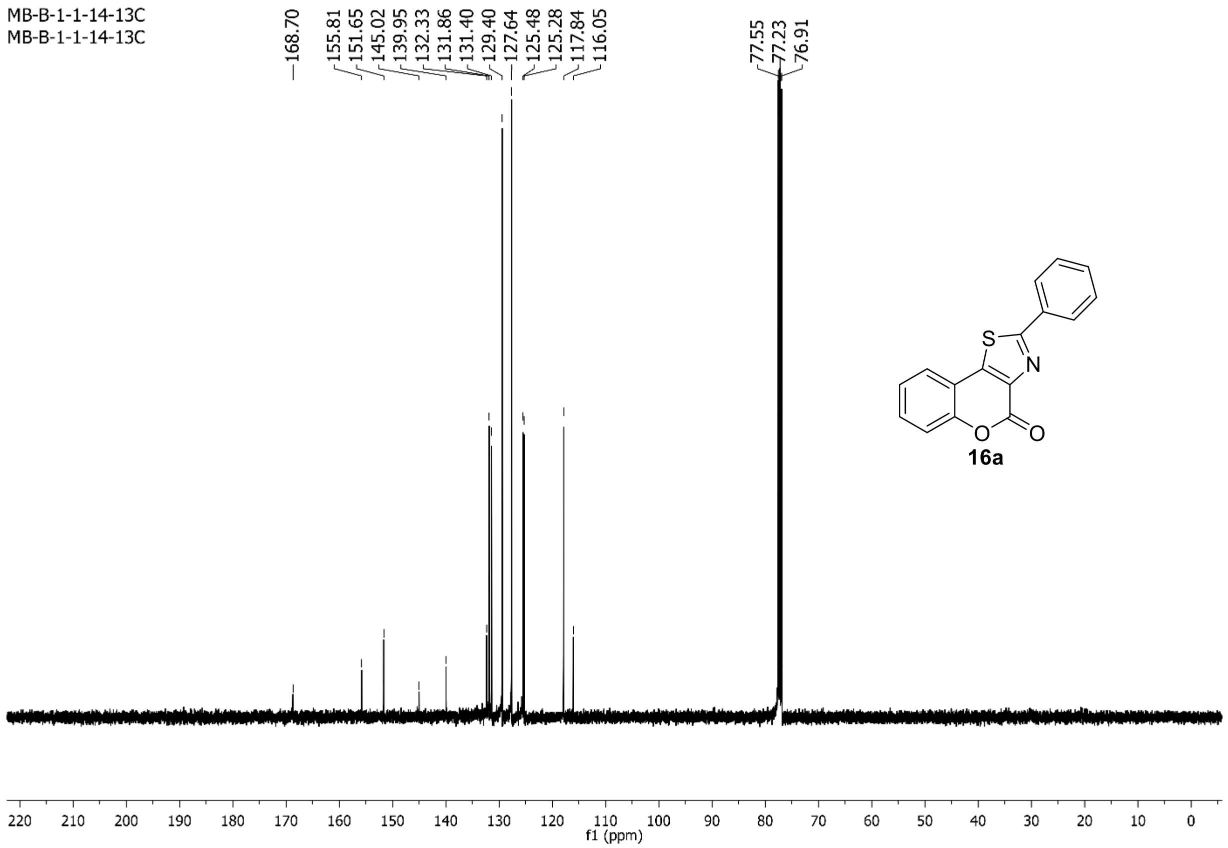
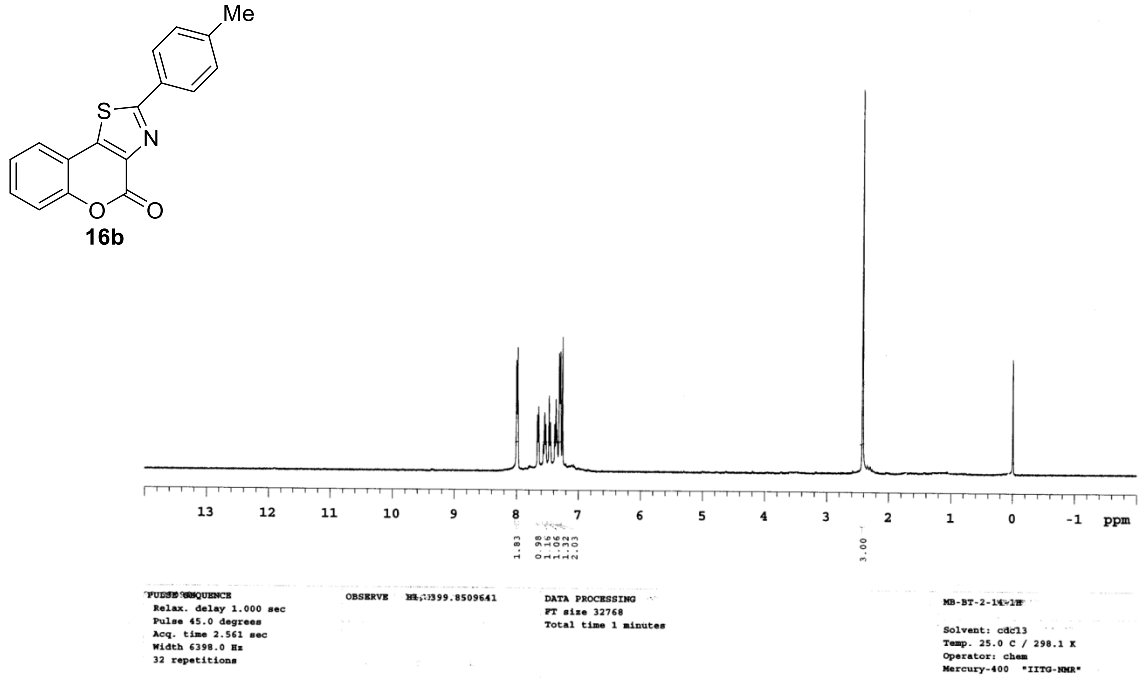
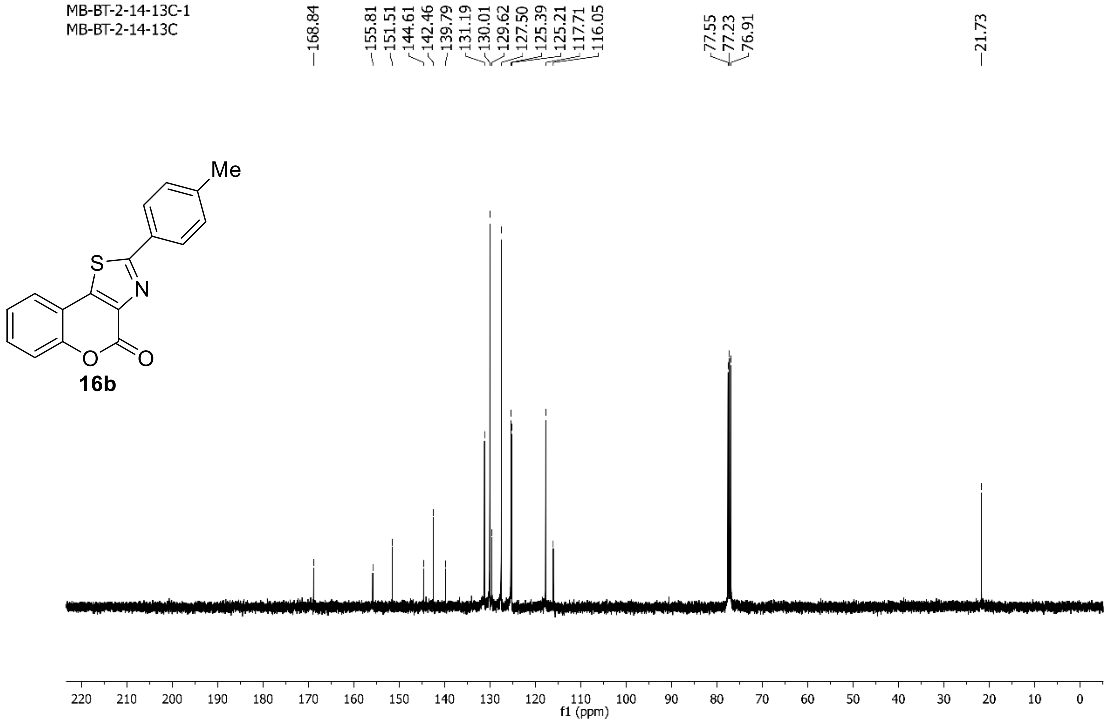
^{13}C NMR (100 MHz, CDCl$_3$): *2-Phenyl-4H-chromeno[3,4-d]thiazol-4-one* (**16a**)



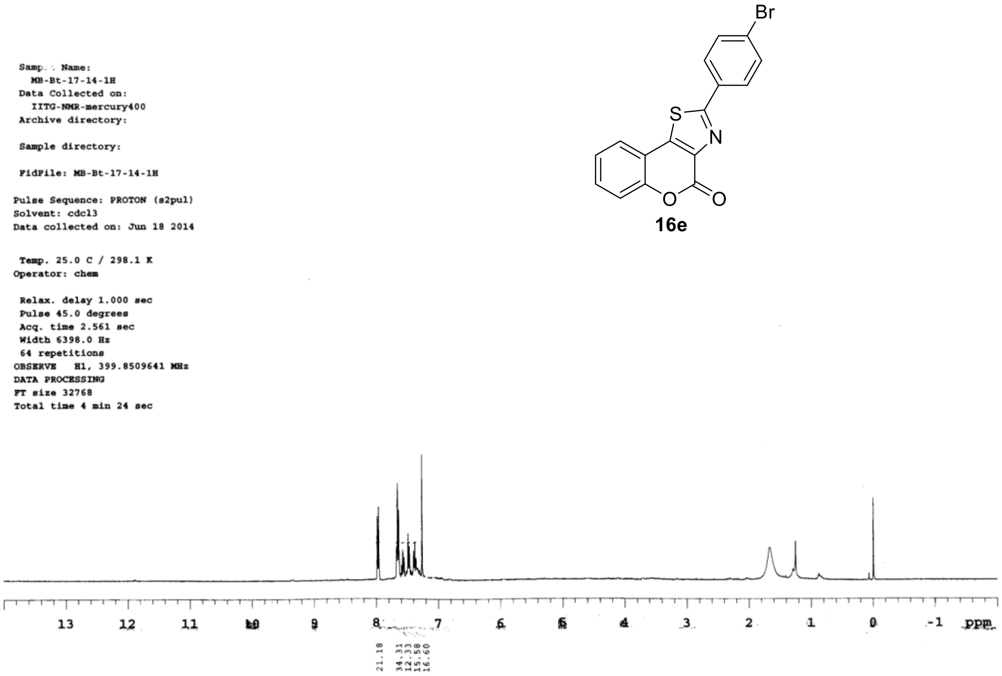
^{1}HNMR (400 MHz, CDCl$_3$): *2-(p-Tolyl)-4H-chromeno[3,4-d]thiazol-4-one* (**16b***)*



^{13}C NMR (100 MHz, CDCl$_3$): *2-(p-Tolyl)-4H-chromeno[3,4-d]thiazol-4-one* (**16b**)



^{1}HNMR (400 MHz, CDCl$_3$): *2-(4-Bromophenyl)-4H-chromeno[3,4-d]thiazol-4-one* (**16e**)



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 Samp.. Name:
   MB-Bt-17-14-1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:

 Sample directory:

 FidFile: MB-Bt-17-14-1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 18 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509641 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```
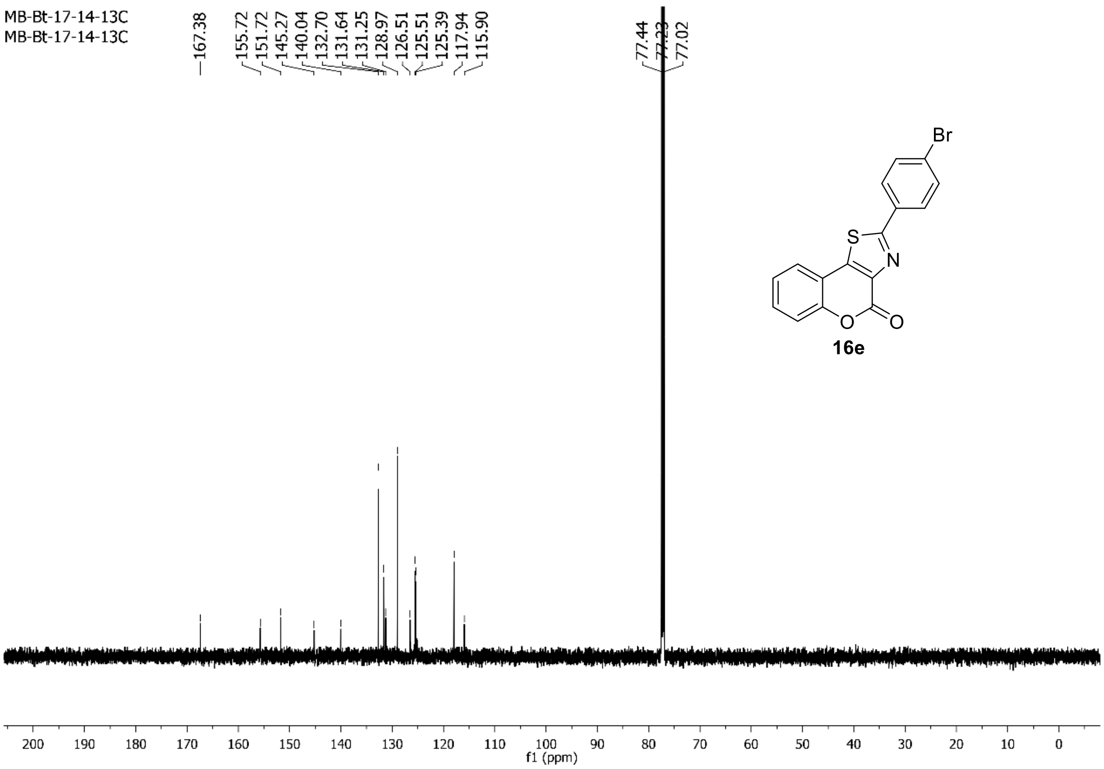
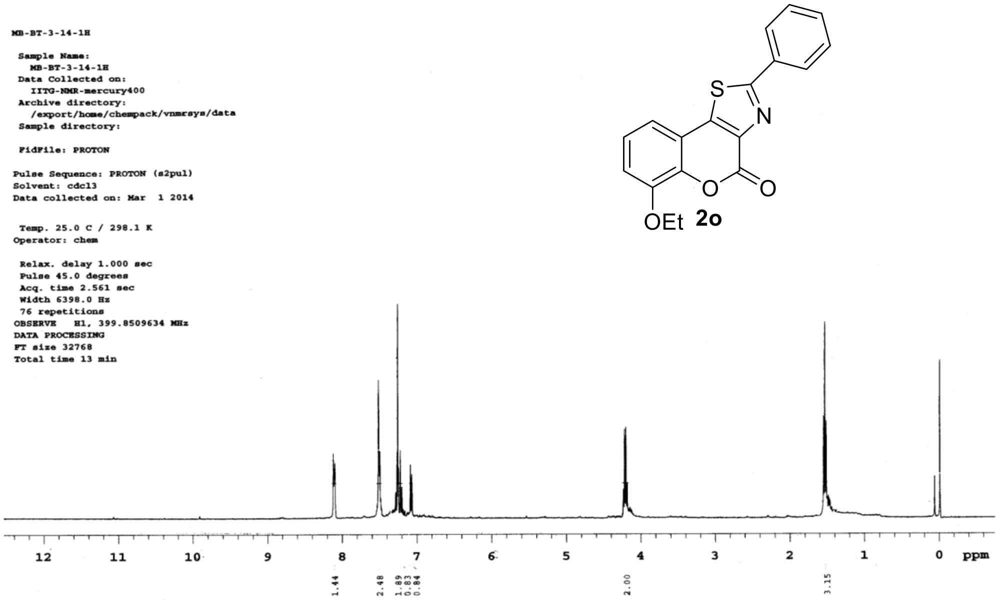

^{13}C NMR (150 MHz, CDCl$_3$): *2-(4-Bromophenyl)-4H-chromeno[3,4-d]thiazol-4-one* (**16e**)

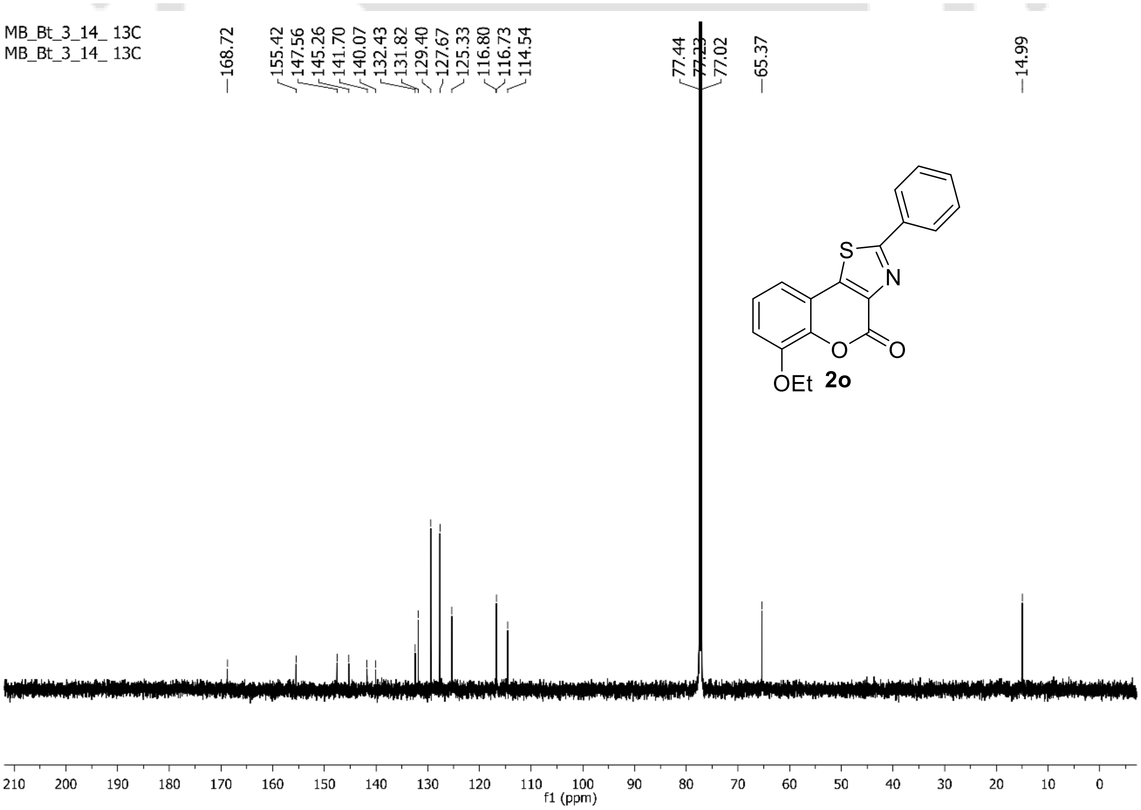


^{1}HNMR (400 MHz, CDCl$_3$): *6-Ethoxy-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one* (**16o**)

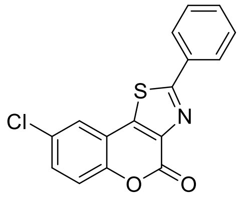


```
MB-BT-3-14-1H

 Sample Name:
   MB-BT-3-14-1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar  1 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 76 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 13 min
```

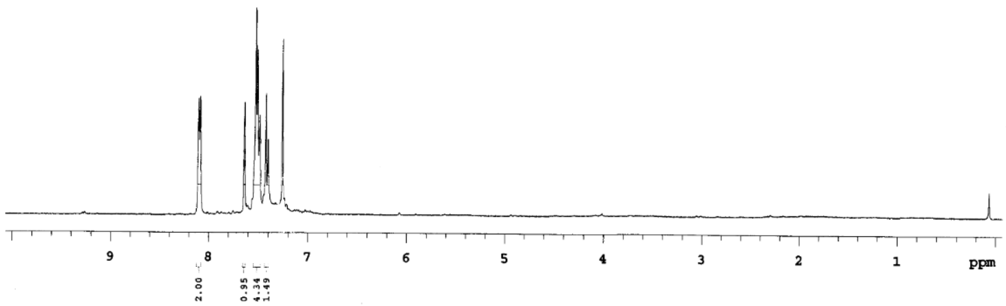
^{13}C NMR (150 MHz, CDCl$_3$): *6-Ethoxy-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one* (**16o**)



^{1}*HNMR (400 MHz, CDCl$_3$)*: *8-Chloro-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one* (**16s**)



16s



PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions

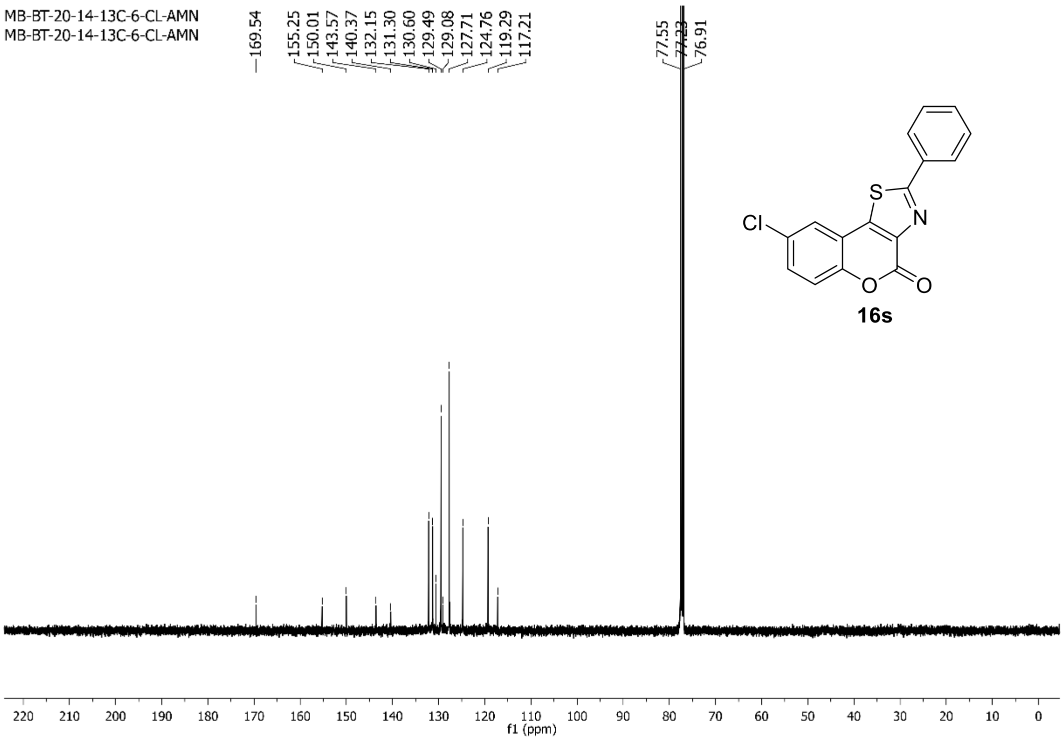
OBSERVE H1, 399.8509637

DATA PROCESSING
FT size 32768
Total time 1 minutes

MB-Bt-20-14-1H-6-Cl-amn

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: MB-Bt-20-14-1H-6-Cl-amn
Mercury-400 "IITG-NMR"

^{13}*C NMR (100 MHz, CDCl$_3$)*: *8-Chloro-2-phenyl-4H-chromeno[3,4-d]thiazol-4-one* (**16s**)



Crystallographic Description: Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

Table 16. Crystal data and structure refinements of compounds **16a**. For atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check CIF.

Parameters	**Compound 16a**
Empirical Formula	$C_{16}H_9NO_2S$
Formula Weight	279.30
Temperature	296(2) K
CCDC No.	1013314
Wavelength (A^o)	0.71073
Crystal System	monoclinic
Space group	P-1
Radiation type	MoK\a
Radiation source	fine-focus sealed tube
a (A^o)	8.2110 (2)
b (A^o)	8.9277 (2)
c (A^o)	9.0926 (2)
α (^{o})	89.3770 (10)
β (^{o})	82.5790 (10)
γ (^{o})	80.8590 (10)
Cell Voloume	652.53 (3)
z	2
Density	1.422
F (0 0 0)	288
Theta ranges	2.26 to 24.99

Index ranges	-9 ≤ h ≤ 9, -10 ≤ k ≤ 10, -10 ≤ l ≤ 10
Reflection collected	6773
Independent reflections	2174
Completeness to theta	0.946
Number of parameters	181
Number of restraints	0
Godness of fit (GOF)on F^2	1.049
Refinement method	Full-matrix least square on F2

REFERENCES
CHAPTER (I-VI)

REFERENCES

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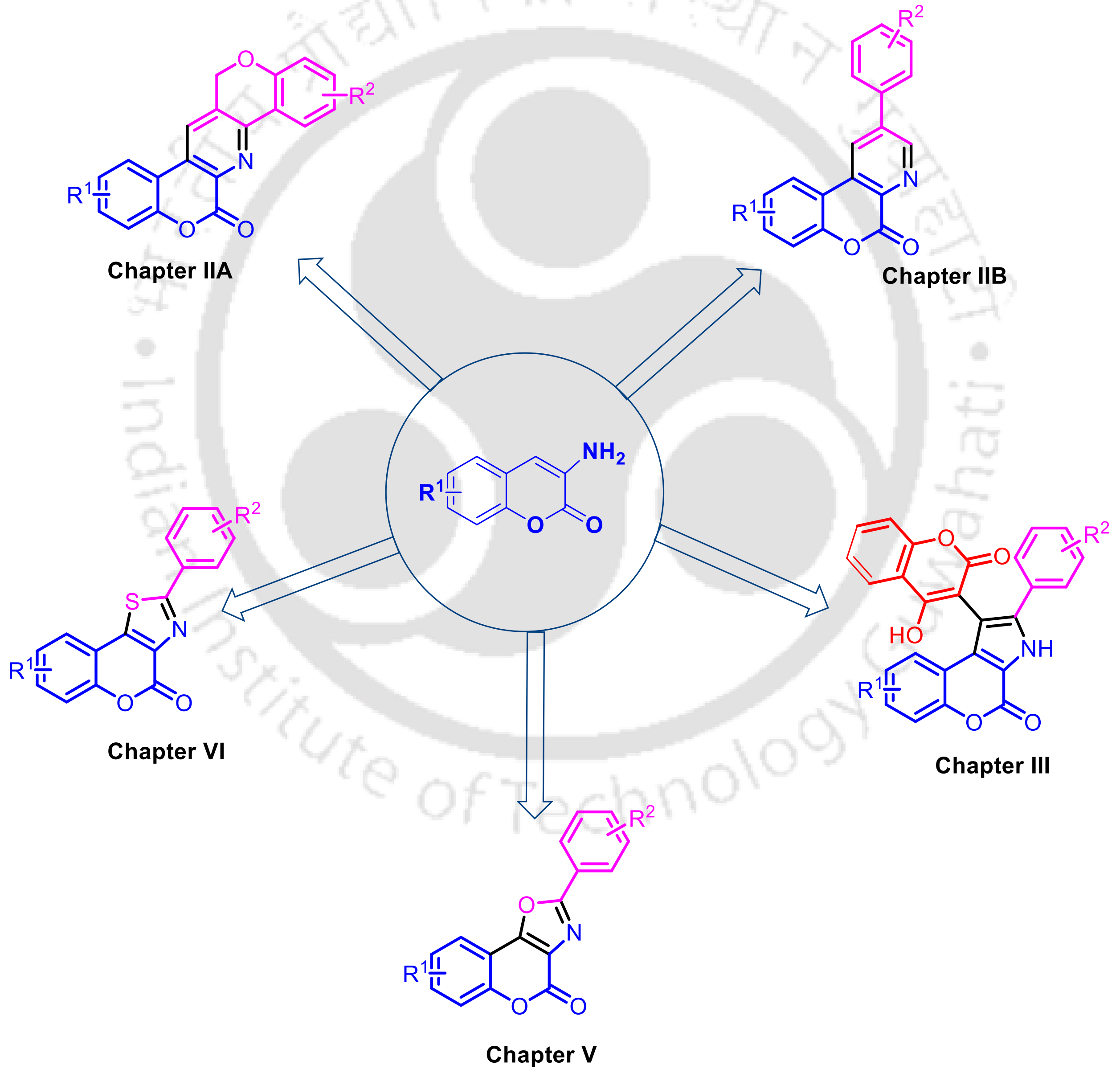
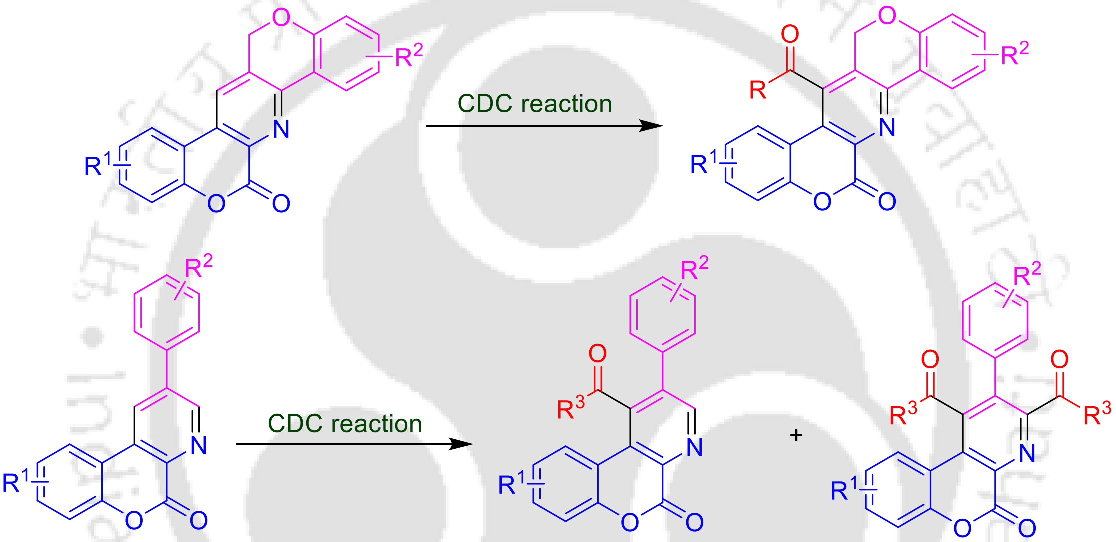
Conclusion and the Thesis Overview

In conclusion, the thesis demonstrates the synthesis of various coumarin fused heterocyclic compounds exploring 3-aminocoumarin moiety. A large number of different pyridocoumarins have been achieved using protic acid as catalysts with simple reaction procedures. Moreover, using multicomponent approach and iodine as a catalyst, substituted pyrrole fused coumarin derivatives were obtained with good to excellent yields. Further, oxidative C-H bond functionalizationhas been used to accomplish various fused oxazole and thiazole derivatives of coumarin.



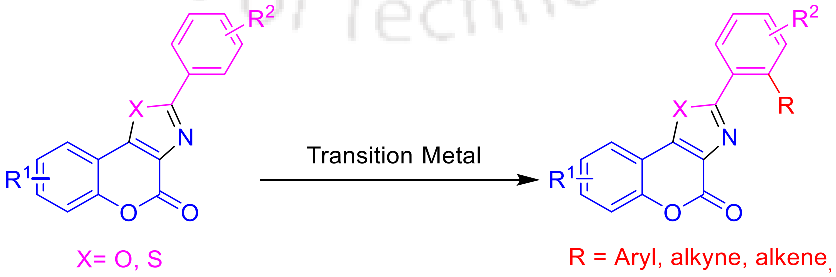
Future Perspective

Coumarin fused heterocyclic compounds exhibit important biological activities. Thus, the synthesized compounds can be explored for their biological evaluation. Acylation of electron deficient pyridine rings is a very challenging but recently cross dehydrogenative coupling (CDC) reactions have been used to overcome this difficulty. The acylation of the pyridocoumarins moieties can be achieved via CDC reactions to synthesize the respective acylated pyridocoumarin derivatives which may have valuable biological properties as acylated heterocycles are parts of many naturally occurring compounds (Scheme I).



Scheme I. CDC reaction for acylation of pyrido(2,3-c)coumarins

Further, the synthesized oxazole and thiazole derivatives can be explored further for C-H activation where the thiazole and oxazole moieties can act as directing groups and this can lead to the development of new organic molecules of biological importance (Scheme II).



Scheme II.Thiazole and oxazole moieties as directing groups

Publications

- **Md. Belal** and Abu T. Khan; Synthesis of fused oxazole-containing coumarin derivatives via oxidative cross coupling reaction using a combination of $CuCl_2$ and TBHP *RSC Advances* **2016**, *6*, 18891-18894.

- **Md. Belal** and Abu T. Khan; Oxidative cross coupling reaction mediated by I_2/H_2O_2: a novel approach for the construction of fused thiazole containing coumarin derivatives *RSC Advance*, **2015**, *5*, 104155-104163.

- **Md. Belal**, Deb K. Das and Abu T. Khan; Synthesis of Pyrido(2,3-*c*)coumarin Derivatives by an Intramolecular Povarov Reaction *Synthesis* **2015**, *47*, 1109-1116.

- Deb K. Das , Satavisha Sarkar , Musawwer Khan , **Md. Belal** and Abu T. Khan; A mild and efficient method for large scale synthesis of 3-aminocoumarins and its further application for the preparation of 4-bromo-3-aminocoumarins *Tetrahedron Lett*. **2014,** *55*, 4869–4874.

- **Md. Belal** and Abu T. Khan; PSTA$\cdot H_2O$ catalyzed reaction of 3-aminocoumarin and phenylacetaldehyde derivatives: A route to access various Pyrido(2,3-*c*)coumarin derivatives (Manuscript communicated).

- **Md. Belal** and Abu T. Khan Iodine catalyzed multicomponent approach to access various Pyrrolo(2,3-*c*)coumarin derivatives using 3-aminocoumarins, acetophenone derivatives and 4-hydroxycoumarin (Manuscript communicated).