DEVELOPMENT OF METAL-FREE BASED ONE-POT SYNTHETIC PROTOCOL FOR THE FACILE CONSTRUCTIONS OF INDOLE AND COUMARIN BASED FUSED HETEROCYCLES

Ph.D. Thesis

By

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DISCIPLINE OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY INDORE

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DEVELOPMENT OF METAL-FREE BASED ONE-POT SYNTHETIC PROTOCOL FOR THE FACILE CONSTRUCTIONS OF INDOLE AND COUMARIN BASED FUSED HETEROCYCLES

A THESIS

Submitted in partial fulfillment of the
requirements for the award of the degree
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by

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled "**DEVELOPMENT OF METAL-FREE BASED ONE-POT SYNTHETIC PROTOCOL FOR THE FACILE CONSTRUCTIONS OF INDOLE AND COUMARIN BASED FUSED HETEROCYCLES"** in the partial fulfillment of the requirements for the award of the degree of **DOCTOR OF PHILOSOPHY** and submitted in the **DISCIPLINE OF CHEMISTRY, INDIAN INSTITUTE OF TECHNOLOGY INDORE**, is an authentic record of my own work carried out during the time period from JULY 2011 to NOVEMBER 2016 under the supervision of **Dr. SAMPAK SAMANTA**, Associate Professor, Indian Institute of Technology, Indore.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

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This is to certify that the above statement made by the candidate is correct to the best of my/our knowledge.

Signature of Thesis Supervisor with date
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SHIVENDRA SINGH has successfully given his Ph.D. Oral Examination held on ……..

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DEDICATED TO MY PARENTS

AND

MY SUPERVISOR

(Dr. SAMPAK SAMANTA)

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ABSTRACT

This thesis presents research into the development of metal-free based green synthetic methods for the direct access to tetrahydrothiopyrano[2,3-*b*]indoles, furo/pyrano[3,2-*c*]chromen-2-ones and their related heterocyclic scaffolds in a stereoselective manner. We believe that current catalytic/non-catalytic processes will offer new synthetic techniques towards the efficient syntheses of interesting functionalized indole and coumarin derivatives. Moreover, there is a highly scope for more useful chemistry to be originated from this area.

To begin with a general introduction for the syntheses and applications of indole and coumarin heterocycles, with historical perspectives and synthetic methodologies developed for the preparations of annulated indole/coumarin scaffolds through various efficient organic transformations have been discussed in the first chapter.

The next chapter describes an efficient one-pot three component method for the synthesis of biologically attractive 2,3,4-trisubstituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives in good to excellent yields with moderate diastereoselectivities using organocatalysis. Furthermore, the enantioselective synthesis of title compounds was achieved by this methodology.

In the third chapter, one-pot synthesis of 2,9-dihydrothiopyrano[2,3-*b*]indole scaffolds showing large Stokes Shifts has been reported. This chapter unfolds a mild, convenient, practical and general one-pot high yielding method for the synthesis of *N*-Boc-2-aryl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole scaffolds *via* a tandem aromatic nucleophilic thiolation/thio-Michael/Henry reaction of *N*-Boc-2-chloro-3-formylindoles, $NaSH \cdot H_2O$ with aryl-substituted nitroolefins in CH_2Cl_2 at room temperature, followed

by in situ dehydration of resultant tetrahydrothiopyranoindole in the presence of activated molecular sieves.

The fourth chapter demonstrates a remarkable solvent effect on the reaction of 4-hydroxycoumarin with (*E*)-3-aryl-2-nitroprop-2-enol: Facile synthesis of highly substituted furo/pyrano[3,2-*c*]chromenes. This chapter describes a mild, simple, convenient, high yielding procedure for the construction of 2-(hydroxymethyl)-3-aryl-4*H*-furo[3,2-*c*]chromen-4-one scaffolds *via* a one-pot reaction of substituted 4-hydroxycoumarins with (*E*)-3-aryl-2-nitroprop-2-enols in water without using any catalyst in 5-6 hours.

Chapter five describes a catalyst-free facile synthesis of 4-sulfanylcoumarins involving 4-mercaptocoumarin and (*E*)-3-aryl/hetero-aryl-substituted-2-nitroprop-2-enols/MBH acetates of nitroolefins. Here, the nucleophillic substitution reaction between 4-mercaptocoumarin and several (*E*)-3-aryl/hetero-aryl-substituted-2-nitroprop-2-enols/MBH acetates of nitroolefins in DMSO and MeOH respectively at 70 °C under catalyst-free conditions is reported. This operationally simple method delivers mediocre to good yields of a series of novel functionalized α-(4-thiocoumarinyl)-β-nitrostyrenes and (*E*)-dithiocoumarinyl styrene derivatives with excellent stereoselective manner.

The final chapter of this thesis focuses on the conclusion and future outcomes of the current synthetic methodologies accomplished during the entire series of works.

LIST OF PUBLICATIONS

1. **Singh S.**, Srivastava A., Samanta S. (2012), Rapid access of 2,3,4-trisubstituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives *via* one-pot three component reaction using organocatalysis, *Tetrahedron Lett*., 53, 6087-6090 (DOI: 10.1016/j.tetlet.2012.08.125).
2. **Singh S.**, Samanta S. (2015), Efficient one-pot access to 2,9-dihydrothiopyrano[2,3-*b*]indole scaffolds showing large Stokes shifts, *Chin. J. Chem.*, 33, 1244-1250 (DOI: 10.1002/cjoc.201500572).
3. **Singh S.**, Srivastava A., Mobin S. M., Samanta S. (2015), A remarkable solvent effect on the reaction of 4-hydroxycoumarin with (*E*)-3-aryl-2-nitroprop-2-enol: Facile synthesis of highly substituted furo/pyrano[3,2-*c*]chromenes, *RSC Adv*., 5, 5010-5014 (DOI: 10.1039/c4ra10610e).
4. **Singh S.**, Samanta S. (2016), Catalyst-free reaction of 4-mercaptocoumarin with (*E*)-3-aryl/hetero-aryl-substituted-2-nitroprop-2-enols/Morita-Baylis-Hillman acetates of nitroolefins: Facile synthesis of 4-sulfanylcoumarins. (*Manuscript submitted*)
5. Srivastava A., **Singh S.**, Samanta S. (2013), (±)-CSA catalyzed Friedel-Crafts alkylation of indoles with 3-ethoxycarbonyl-3-hydoxyisoindolin-1-one: An easy access of 3-ethoxy carbonyl-3-indolylisoindolin-1-ones bearing a quaternary α-amino acid moiety, *Tetrahedron Lett*., 54, 1444-1448 (DOI: 10.1016/j.tetlet.2013.01.010).
6. Biswas S., Jaiswal P. K., **Singh S.**, Mobin S. M., Samanta S. (2013), L-Proline catalyzed stereoselective synthesis of (*E*)-methyl-α-indol-2-yl-β-aryl/alkyl acrylates: Easy access to substituted carbazoles, γ-carbolines and prenostodione, *Org. Biomol. Chem.*, 11, 7084-7087 (DOI: 10.1039/c3ob41573b).

7. Jaiswal P. K., Biswas S., **Singh S.**, Pathak B., Mobin S. M., Samanta S. (2013), Stereoselective synthesis of highly functionalized tetrahydrocarbazoles through a domino Michael-Henry reaction: An easy access to four contiguous chiral centers, *RSC Adv*., 3, 10644-10649 (DOI: 10.1039/c3ra41409d).
8. Jaiswal P. K., Biswas S., **Singh S.**, Samanta S. (2013), An organocatalytic highly efficient approach to the direct synthesis of substituted carbazoles in water, *Org. Biomol. Chem.*, 11, 8410-8418 (DOI: 10.1039/c3ob42034e).
9. Srivastava A., Biswas S., **Singh S.**, Mobin S. M., Samanta S. (2015), Organocatalyzed Michael addition on arylmethylidenemalonates involving 4-(2-nitrophenyl) acetoacetate: diversity-oriented access to 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one and salicylate scaffolds, *RSC Adv*., 5*,* 26891-26896 (DOI: 10.1039/c5ra01430a).

Conferences

1. "Frontier Lecture Series in Chemistry" organized by Discipline of Chemistry, IIT Indore, Indore, January 30-31, 2014 (Participated).
2. "Laboratory Health and Safety Workshop" organized by Royal Society of Chemistry at IIT Indore, Indore, November 4, 2014 (Participated).
3. "11th *J*-NOST Conference for Research Scholars" at School of Chemical sciences, NISER, Bhubaneswar, December 14-17, 2015 (Poster presented).
4. "Recent Trends in R and D, Quality Control and Marketing in Chemical Industries" organized by Jiwaji University, Gwalior, April 23-25, 2015 (Oral Presentation).
5. "Global Initiative on Academic Network" (GIAN), organized by IIT Indore, in association with Illinois Wesleyan University, USA, June 17-24, 2016 (Participated).

LIST OF ABBREVIATIONS

Acetone-d_6	Deuterated acetone
Ag_2CO_3	Silver carbonate
AIBN	Azobisisobutyronitrile
$ArB(OH)_2$	Arylboronic acid
AcOH	Acetic acid
$AlCl_3$	Aluminium chloride
ACCN	1,1′-Azobis(cyclohexanecarbonitrile)
$AuCl_3$	Gold (III) chloride
$BnEt_3N^+Cl^-$	Benzyltriethylammonium chloride (BTEAC)
Bn	Benzyl
Bz	Benzoyl
Boc	*t*-Butyloxycarbonyl
$B(C_6F_5)_3$	Tris(pentafluorophenyl)borane
Cbz	Carboxybenzyl
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
CH_3NO_2	Nitromethane
$Cu(OTf)_2$	Copper (II) trifluoromethanesulfonate
CBr_4	Carbon tetrabromide
$CeCl_3$	Cerium (III) chloride
Cs_2CO_3	Caesium carbonate
$CDCl_3$	Deuterated chloroform
$Cu(OAc)_2$	Copper (II) acetate

CuI	Copper (I) iodide
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicycloundec-7-ene
DCE	Dichloroethane
DMAP	4-Dimethylaminopyridine
DMSO-d_6	Deuterated dimethyl sulfoxide
DMF	Dimethylformamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
EDDA	Ethylenediaminediacetate
ESI-MS	Electrospray ionization mass spectrometry
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOH	Ethanol
FC	Friedel-Crafts
GABA	γ-Aminobutyric acid
$Gd(OTf)_3$	Gadolinium (III) trifluoromethanesulfonate
HFIP	Hexafluoroisopropanol
Hünig's base	N,N-diisopropylethylamine
IBX	Iodoxybenzoic acid
$InCl_3$	Indium trichloride
*i*PrOH	Isopropyl alcohol
KCN	Potassium cyanide
K_2CO_3	Potassium carbonate
LDA	Lithium diisopropylamide

$LiAlH_4$	Lithium aluminium hydride
LiOAc	Lithium acetate
LiOH	Lithium hydroxide
MCR	Multicomponent reaction
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
MsCl	Methanesulfonyl chloride
MW	Microwave
NaSH	Sodium hydrosulfide
$NaBH_4$	Sodium borohydride
$NiCl_2$	Nickel (II) chloride
NH_4HCO_2	Ammonium formate
NBS	N-Bromosuccinimide
NaN_3	Sodium azide
NaHMDS	Sodium bis(trimethylsilyl)amide
$n Bu_3SnH$	Tributyltin hydride
$PhCO_2H$	Benzoic acid
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium (0)
$Pd(OAc)_2$	Palladium (II) acetate
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium(II)dichloride
PPh_3	Triphenylphosphine
pTSA	*p*-Toluenesulfonic acid
$PhNHNH_2$	Phenylhydrazine
psi	Pounds per square inch
$Pb(OAc)_4$	Lead (IV) acetate

SeO_2	Selenium dioxide
SDS	Sodium dodecyl sulfate
$Sc(OTf)_3$	Scandium (III) trifluoromethanesulfonate
TCA	Trichloroacetic acid
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
TBAB	Tetra-*n*-butylammonium bromide
TOF-MS	Time-of-flight mass spectrometry
$Ti(OEt)_4$	Titanium ethoxide
$Yb(OTf)_3$	Ytterbium (III) trifluoromethanesulfonate
$Zn(OTf)_2$	Zinc (II) trifluoromethanesulfonate

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Chapter 1

General Introduction

Efficient one-pot synthetic protocols for the preparations of a series of biologically as well as synthetically challenging complex heterocyclic molecules like indole and coumarin derivatives have been rapidly growing interest in recent years because these building blocks have enourmous applications in several fields of chemical science.[1] Especially, synthesis of additional rings on indole/coumarin rings is a prime target for synthetic organic and medicinal chemists. The major reason would be that these frameworks constitute many marketable drugs, bioactive natural products, active pharmacophores, functional materials etc. Some of these are as shown in **Figure 1.1**.

In view of the great importance, a large number of classical and modern protocols have been exploited for the efficient access to indole/coumarin fused heterocyclic molecules.[2] This chapter will summarize recent progress towards the syntheses of indole/coumarin based fused heterocyclic systems.

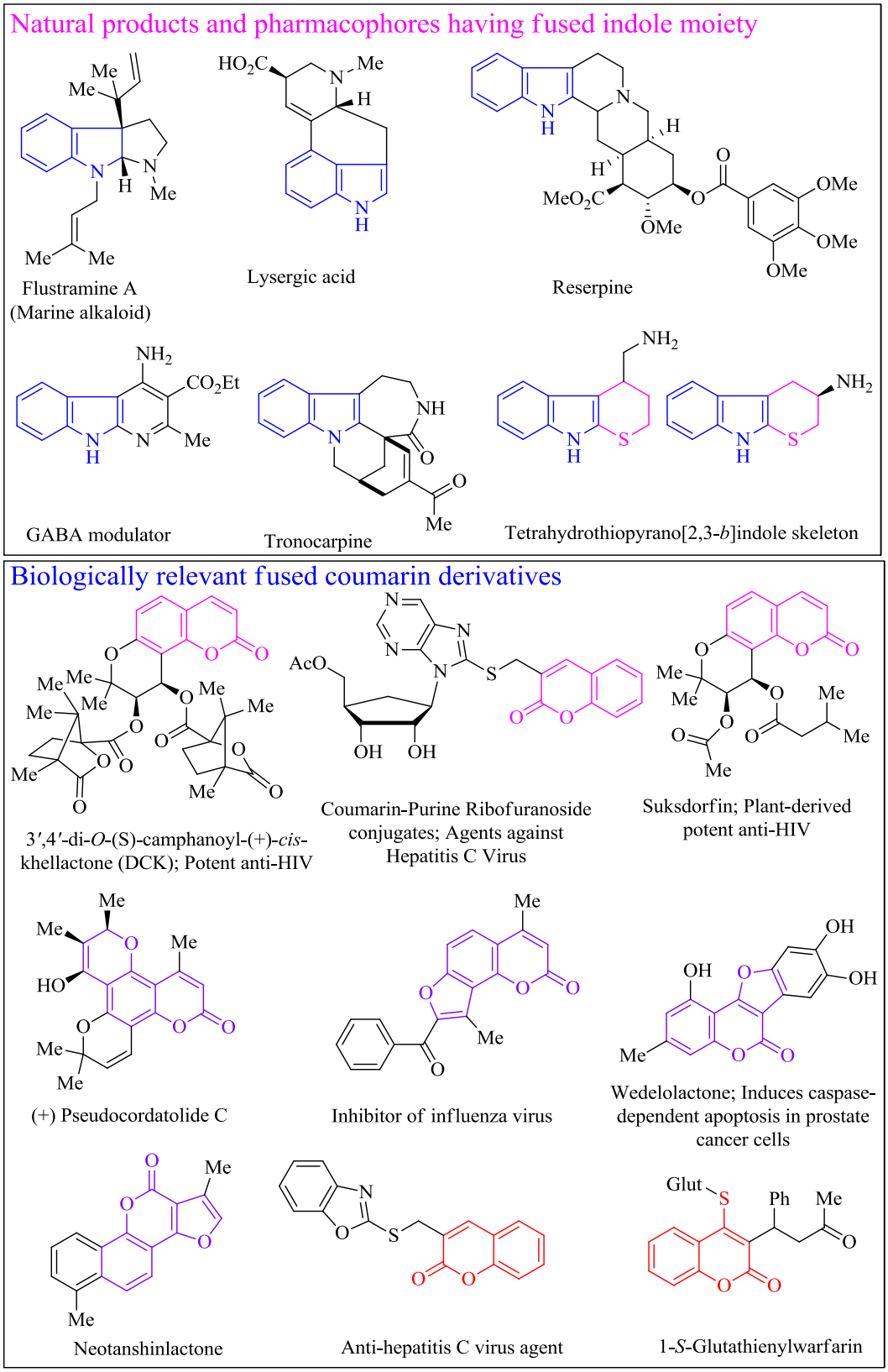


Figure 1.1 Representative indole/coumarin fused heterocycles and their chemical domains of applications.

1.1 Historical background

Indole is an aromatic heterocyclic organic compound (benzopyrrole ring system) having molecular formula C_8H_7N (**Figure 1.2**). In 1866, Adolf von Baeyer reduced oxindole to indole using zinc dust. Later in 1869, he proposed the formula for indole.[3a]

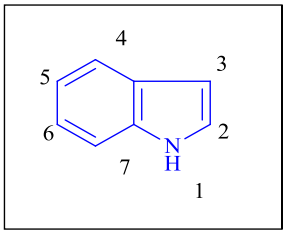


Figure 1.2 Structure of indole ring

On the other hand, coumarin (benzopyrone) is a colourless crystalline substance found in many plants. The isolation of coumarin was first reported by Vogel in 1820 from tonka bean.[3b] The name coumarin originated from a Caribbean word '*coumarou*' for the tonka tree, which was known botanically at one time as *Coumarouna odorata Aubl*. Coumarin is now well accepted trivial name. The IUPAC nomenclature of the coumarin ring system is 2*H*-1-benzopyran-2-one (**Figure 1.3**).

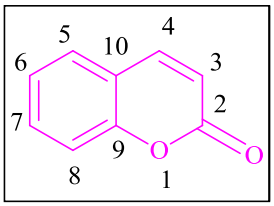


Figure 1.3 Structure of coumarin moiety

1.2 One-pot method

Synthetic organic chemistry deals with the construction of several organic compounds ranging from complex molecules, biologically active natural products to functional materials. Most of the organic reactions progressed through multi-steps, producing a huge amount of waste products during work up and isolation of various intermediates at different steps. Thus, in order to avoid multistep synthesis and to reduce the amount of waste, many organic and medicinal chemists have been devoted towards the development of a simple, cleaner, cheaper and eco-friendly synthetic method.

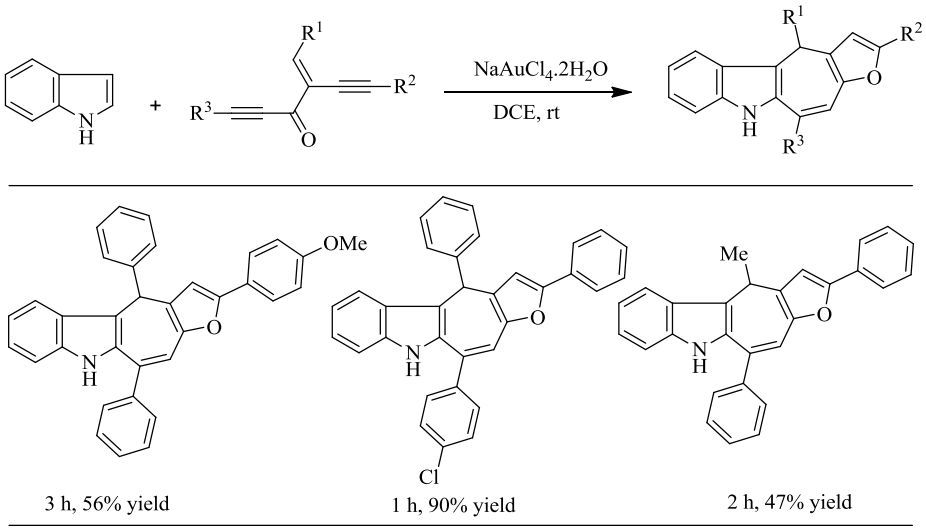
In this regard, scientists have developed one-pot method in which the same reagents/solvents are employed for subsequent transformations and it can be defined as "the strategy to improve the efficiency of a chemical reaction by subjecting all the reactants in a single flask for successive chemical reactions."[4]

A one-pot synthesis saves the time of synthetic chemists and resources by avoiding purification at each step and transferring of materials in vessels during reaction. Thus, one-pot synthesis is not only a useful methodology to adopt for the production of organic molecules, but also a promising green approach to modern synthesis. Furthermore, one-pot method is advantageous in the reactions where the intermediates are unstable or the byproducts can be converted into the desired intermediate or final product. Therefore, the one-pot method is beneficial in terms of reducing manpower, amount of solvents as well as reaction time. Keeping this in mind, varieties of methods are available in the literature towards the syntheses of indole/coumarin based fused heterocyclic systems. Some of them are summarized in the next section.

1.3 One-pot approach to access indole based fused heterocycles

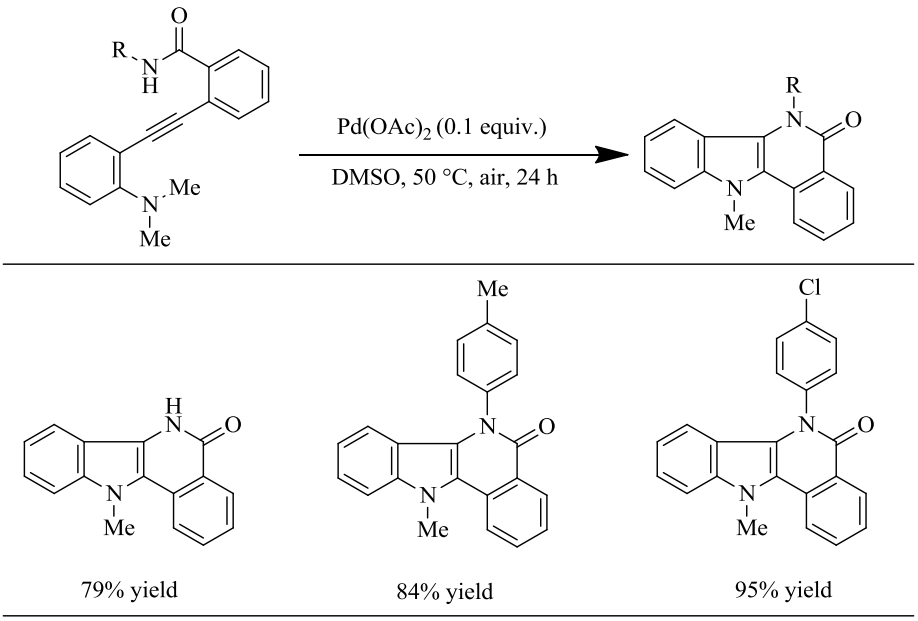
1.3.1 Transition metal-salts mediated reactions

Xie and his associates[5] revealed gold-catalyzed tandem cyclization of several 1,2-*bis*(alkynyl)-2-en-1-ones with indole in DCE at room temperature for 1-3 h to furnish heterocyclic systems fused with indole and furan rings in mediocre to high yields (47-90%) *via* a cascade carbonyl-yne cyclization/Friedel-Crafts/indole-yne cyclization sequences (**Scheme 1.1**).



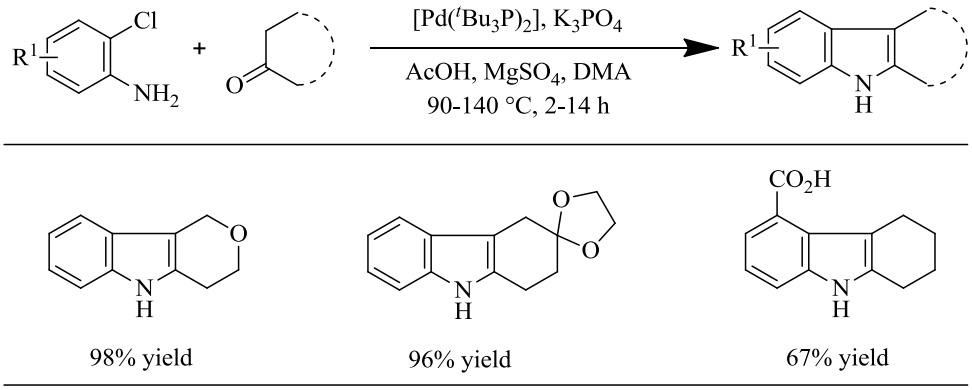
Scheme 1.1 Gold catalyzed synthesis of indole-fused polycyclic systems

Pd-catalyzed cyclization strategy of diarylacetylene to afford several tetracyclic indolo[3,2-*c*]isoquinolinones in good to excellent yields (79-95%) through a sequential amination/N-demethylation/amidation process under oxidative conditions in DMSO at 50 °C for 24 h was unfold by Zhu and his associates as shown in **Scheme 1.2**.[6]



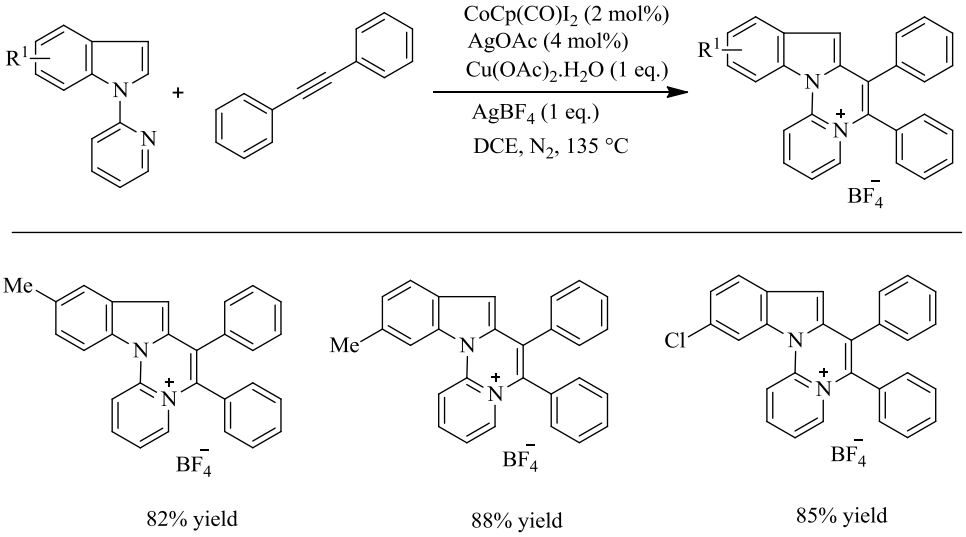
Scheme 1.2 Pd-catalyzed access to indolo[3,2-*c*]isoquinolinones

Nazare *et al.*[7] established one-pot synthesis of fused indoles in good to excellent yields (67-98%) involving several 2-chloroanilines and cyclic ketones under the presence of palladium catalysts,[Pd(^{t}Bu$_3$P)$_2$] (0.1 equiv.) in combination with K_3PO_4 as a base and 0.5 equivalents of $MgSO_4$ as a water-binder in dimethylacetamide (DMA) and acetic acid at 90-140 °C for 2-14 h as shown in the **Scheme 1.3**.



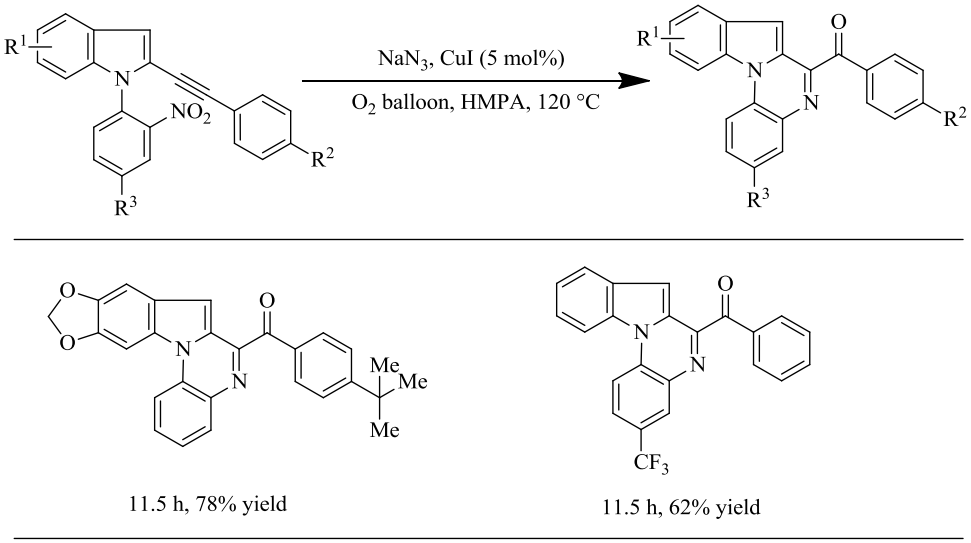
Scheme 1.3 Pd-catalyzed regiospecific synthesis of fused indoles

The cobalt-catalyzed C-2 selective C-H alkenylation/annulations cascade transformation of substituted pyridine-indoles with internal alkynes under nitrogen atmosphere using $Cu(OAc)_2.H_2O$ as the oxidant in the presence of $AgBF_4$ at 135 °C in DCE to afford a series of pyrido-pyrimido-indoles in high yields (82-88%) was established by Yang and his co-workers (**Scheme 1.4**).[8]



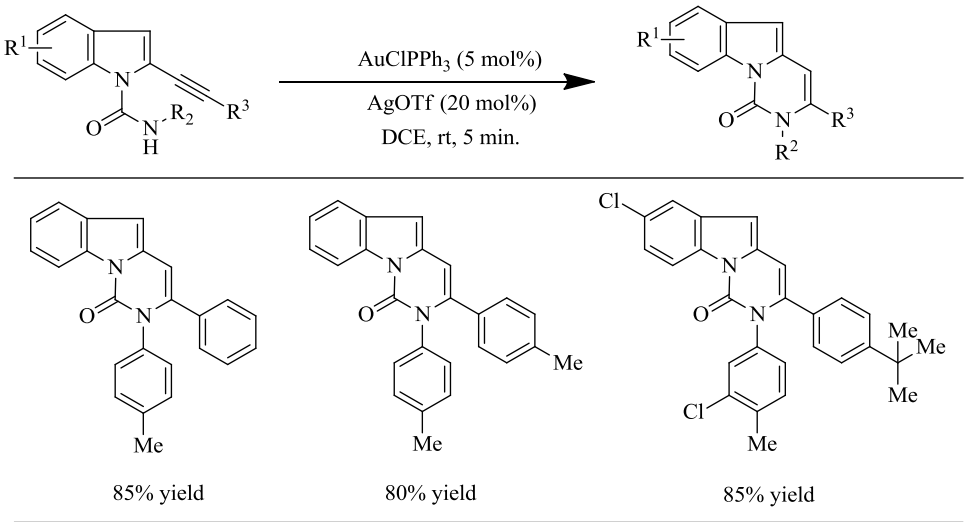
Scheme 1.4 Cobalt-catalysed pyrido-pyrimido-indole synthesis

A similar one-pot cycloaddition protocol for the diversity-oriented synthesis of indole-based annulated ketoindolo-quinoxalines in good yields (62-78%) was presented by Samala *et al.*[9] involving 1-(2-nitroaryl)-2-alkynylindoles and NaN_3 under the presence of 5 mol% CuI as a catalyst and O_2 balloon as a source of oxygen for 11.5 h in hexamethylphosphoramide (HMPA) at 120 °C (**Scheme 1.5**).



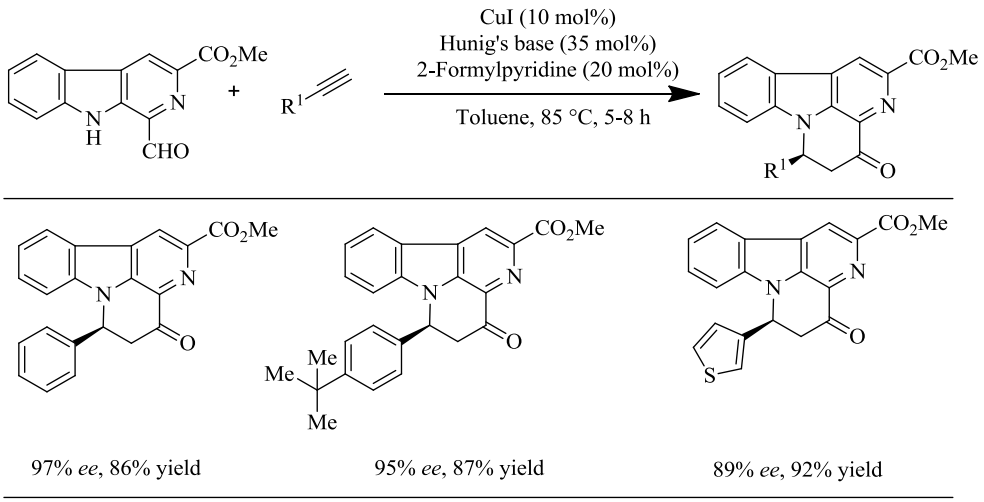
Scheme 1.5 Synthesis of indole-based annulated ketoindoloquinoxalines

Kundu and his coworkers[10] showed the cyclization strategy of several bifunctionalized indoles under the catalytic effect of 5 mol% $AuClPPh_3$ and 20 mol% AgOTf respectively in DCE at room temperature for 5 min. to afford a series of pyrimido[1,6-*a*]indolone derivatives in high yields (80-85%) as shown in the **Scheme 1.6**.



Scheme 1.6 Synthesis of pyrimidoindolone derivatives

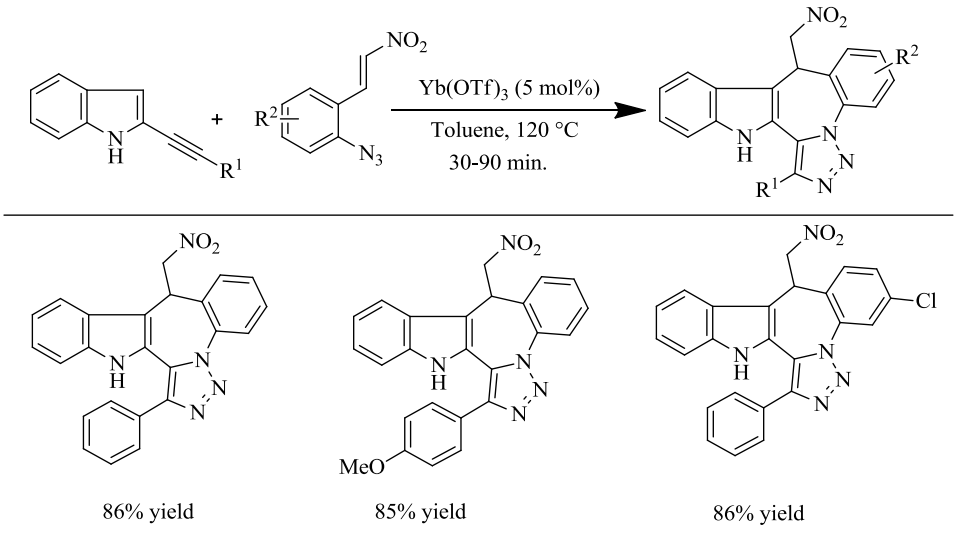
Batra *et al.*[11] illustrated a triple cooperative catalysis-mediated domino reaction between substituted 1-formyl-9*H*-β-carbolines and terminal alkynes under the presence of catalytic amounts of copper iodide (10 mol%), Hünig base (*N*,*N*-diisopropylethylamine) and 2-formylpyridine in toluene at 85 °C for 5-8 h *via* intramolecular aza-Michael addition reaction to afford dihydrocanthin-4-ones in high yields (86-92%) with excellent enantioselectivity (89-97% *ee*) (**Scheme 1.7**).



Scheme 1.7 Enantioselective synthesis of dihydrocanthin-4-ones

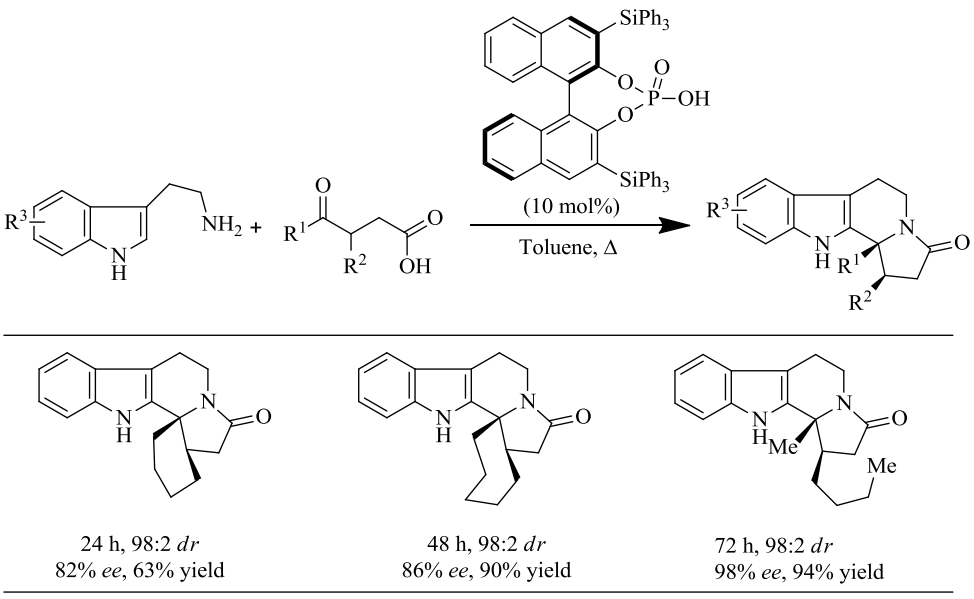
1.3.2 Acid-promoted reactions

Arigela and his associates unfolds a rapid one-pot protocol for the synthesis of annulated tetracyclic indole-derivatives in high yields (85-86%) by using a series of aromatic 2-alkynyl indoles and substituted (*E*)-1-azido-2-(2-nitrovinyl)benzenes in toluene at 120 °C for 30-90 min. *via* a sequential lewis acid (10 mol% $Yb(OTf)_3$) catalyzed intermolecular Michael addition and an intramolecular 1,3-dipolar cycloaddition reaction (**Scheme 1.8**).[12]



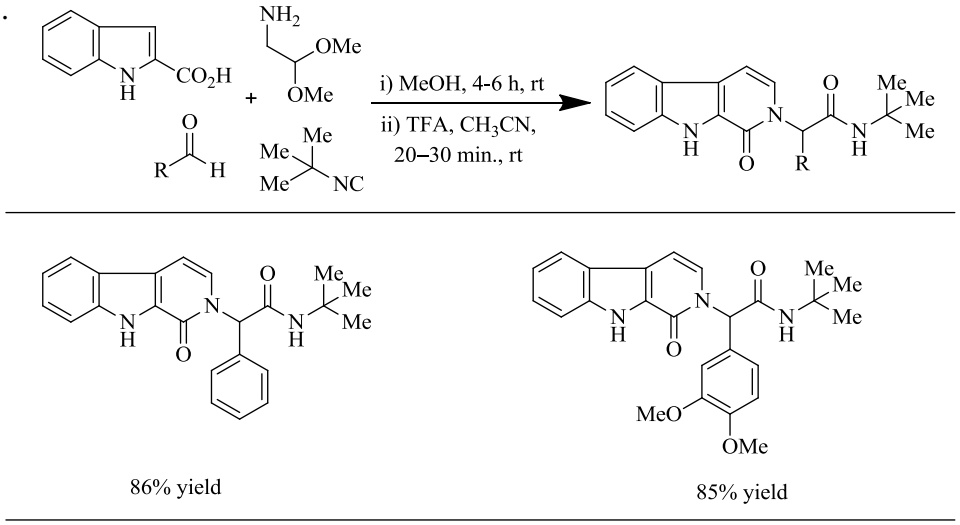
Scheme 1.8 Lewis acid promoted tetracyclic indole-derivatives

Dixon *et al.*[13] described an atom-efficient, enantio- and diastereoselective cyclization strategy to indole fused heterocycles in moderate to high yields (63-94%) under the presence of 10 mol% BINOL derived chiral phosphoric acid in refluxing toluene *via* condensation reaction of tryptamines with ketoacids to afford excellent enantioselectivities (>98% *ee*) and high diastereoselectivities (>98:2) as shown in **Scheme 1.9**.



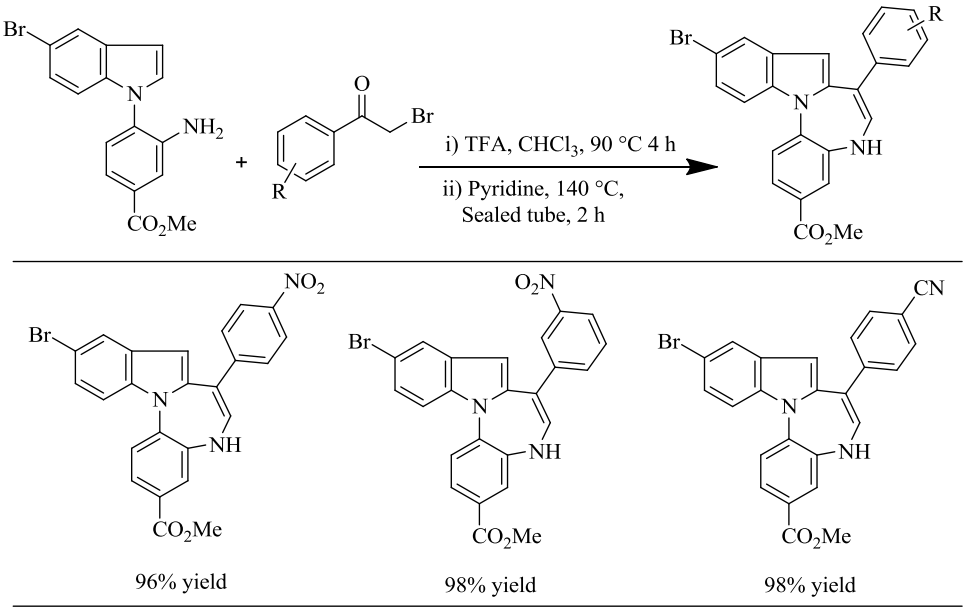
Scheme 1.9 BINOL catalyzed access to fused indole heterocycles

Chauhan and his associates[14] constructed highly functionalized β-carbolinones in high yields (85-86%) *via* one-pot domino Ugi/cyclization approach involving indole-2-carboxylic acid, aryl aldehydes, isocyanide and amines in methanol at room temperature for 4-6 h followed by stirring the reaction under the presence of TFA in acetonitrile at room temperature for 20-30 min. as shown in **Scheme 1.10**



Scheme 1.10 TFA mediated synthesis of functionalized β-carbolinones

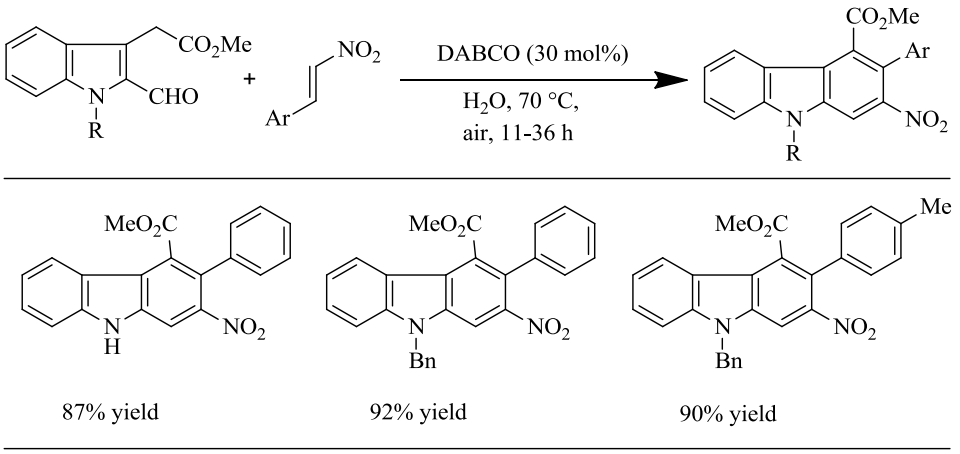
Sun and his colleagues[15] revealed a novel strategy for the synthesis of indole-fused diazocine derivatives in excellent yields (96-98%) by using several methyl-3-amino-(5-bromoindole)benzoates and substituted-bromoacetophenones under the presence of TFA in chloroform at 90 °C for 4 h followed by treatment with pyridine at 140 °C for 2 h in a sealed tube *via* condensation reaction followed by intramolecular cyclization (**Scheme 1.11**).



Scheme 1.11 Synthesis of structurally diverse indole-fused diazocine

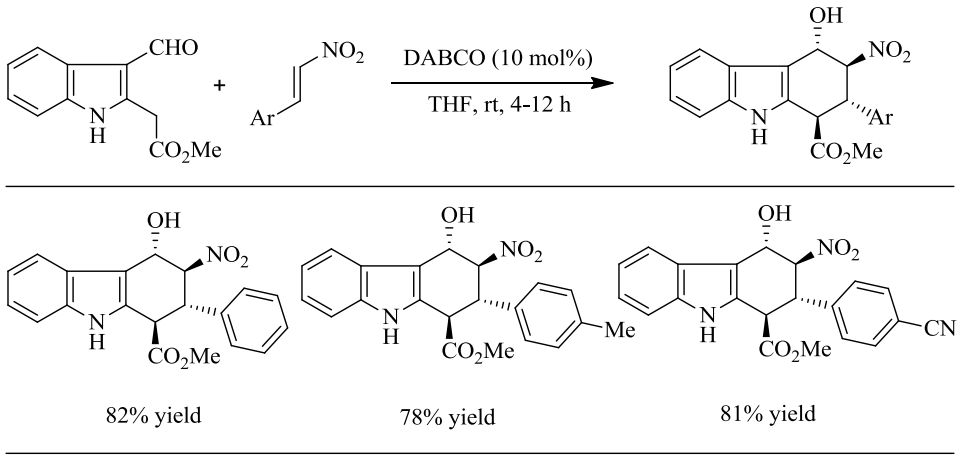
1.3.3 Base-promoted reactions

Samanta *et al.*[16] described a green procedure for the direct access to highly functionalized 3-aryl-4-methoxycarbonyl-2-nitro-9*H*-carbazole derivatives in excellent yields (87-92%) *via* one-pot domino Michael-Henry/aromatization reaction of methyl 2-(3-formyl-1*H*-indol-2-yl)acetates with aryl-substituted β-nitroolefins using 30 mol% DABCO as an organocatalyst under air in aqueous medium at 70 °C for 11-24 h as shown in the **Scheme 1.12**.



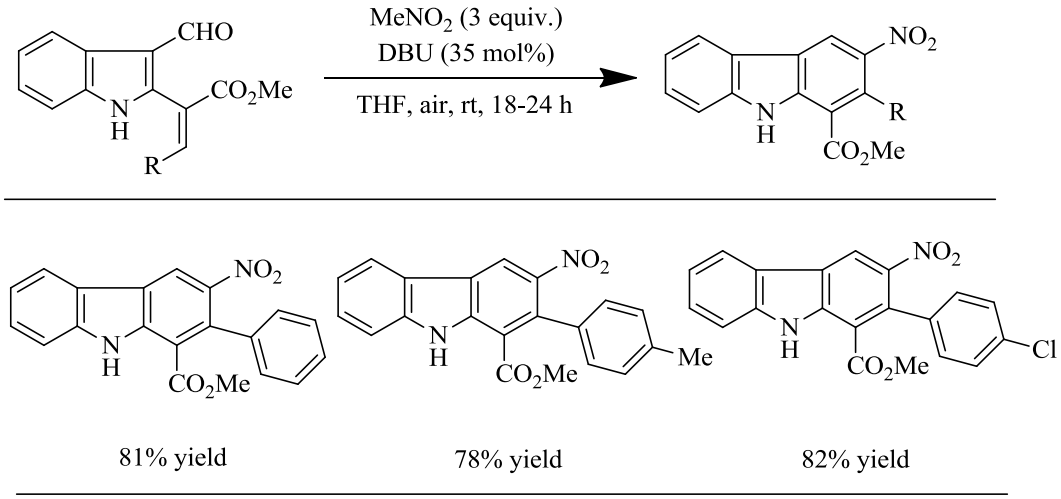
Scheme 1.12 DABCO promoted access to 3-aryl-4-methoxycarbonyl-2-nitro-9*H*-carbazole derivatives

A one-step procedure for the synthesis of functionalized 1-methoxycarbonyl-2-aryl-3-nitro-4-hydroxy-1,2,3,4-tetrahydro-9*H*-carbazole derivatives in high yields (78-82%) was revealed by Samanta *et al.*[17] *via* a domino Michael-Henry reaction of methyl 3-formyl-1*H*-indole-2-acetates with several *trans*-β-nitrostyrenes using 10 mol% DABCO as an organocatalyst in THF at room temperature for 5-7 h as shown in the **Scheme 1.13**.



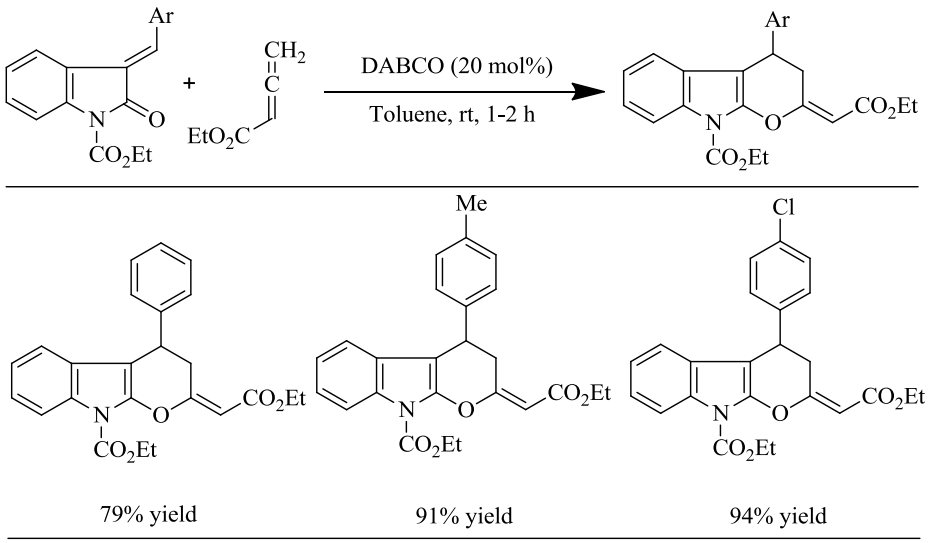
Scheme 1.13 One step synthesis of carbazole derivatives

Samanta *et al.*[18] also established the synthesis of 1-methoxycarbonyl-2-aryl-3-nitro-9*H*-carbazoles in high yields (78-82%) involving several (*E*)-methyl-indol-2-yl-β-aryl-acrylates with 3 equiv. of nitromethane in THF at room temperature for 18-24 h using DBU (35 mol%) as organocatalyst *via* Michael-Henry reaction followed by aerial oxidation (**Scheme 1.14**).



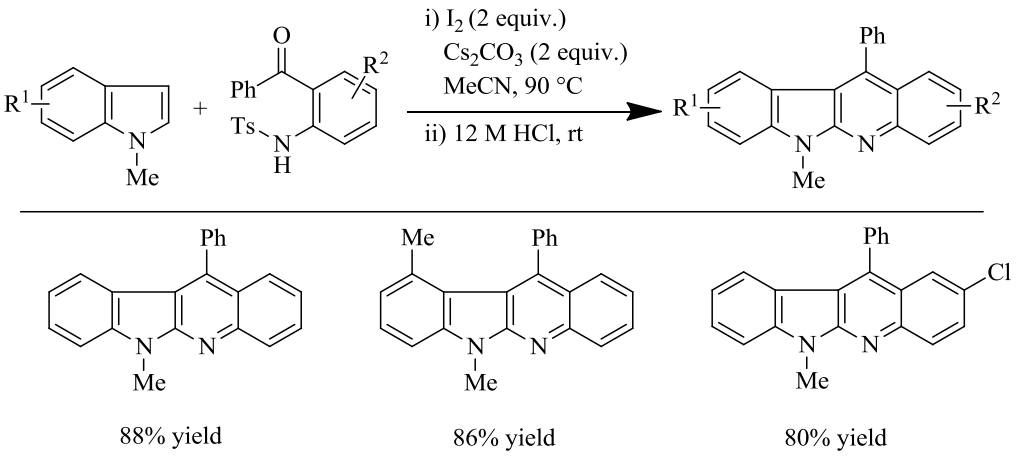
Scheme 1.14 Organobase promoted synthesis of substituted carbazoles

Wang *et al.*[19] unfolds a formal [4+2] cycloaddition of several arylidenoxindoles and allenoates under the presence of 20 mol% DABCO in toluene at room temperature for 1-2 h to afford dihydropyran fused indoles in good to excellent yields (79-94%) with excellent regio- and diastereoselectivities (only *E*-isomer formed) (**Scheme 1.15**).



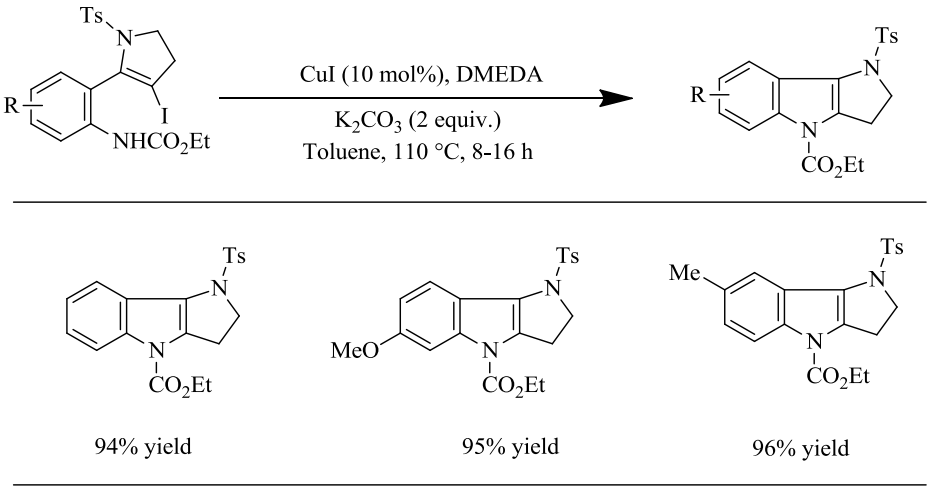
Scheme 1.15 Synthesis of dihydropyran fused indoles

An excellent method for the synthesis of highly substituted indolo[2,3-*b*]quinolines in high yields (80-88%) was reported by Liang and his associates,[20] through the activation at C-2 and C-3 positions of indole in the presence of molecular I_2 and Cs_2CO_3 in acetonitrile at 90 °C followed by the attack of 1-(2-tosylaminophenyl)ketones which was subsequently stirred the reaction mixture in the prsenece 12M HCl for 12 h at room temperature as shown in the **Scheme 1.16**.



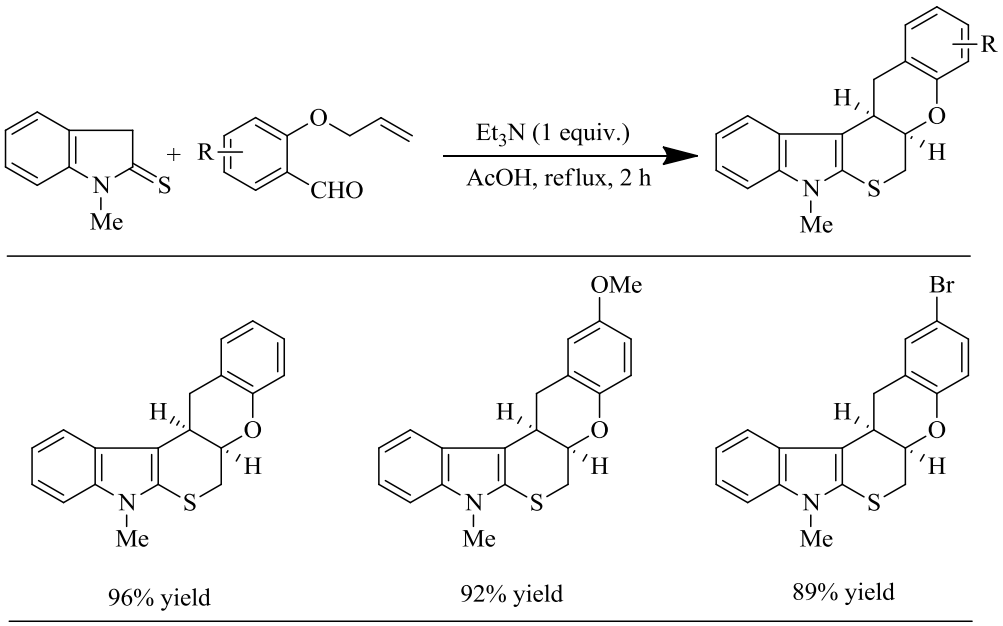
Scheme 1.16 Preparation of indolo[2,3-*b*]quinolones *via* activation at C-2 and C-3 position of indole

Copper catalyzed intramolecular C-N coupling approach to access pyrrolo[3,2-*b*]indoles in excellent yields (94-96%) by treatment of 3-iodo-pyrroloanilne with 10 mol% CuI and *N,N*'-dimethyl ethylenediamine under the presence of potassium carbonate in toluene at 110 °C for 8- 16 h *via* electrophilic iodocyclization was recognized by Likhar *et al.* [21] as shown in **Scheme 1.17**.



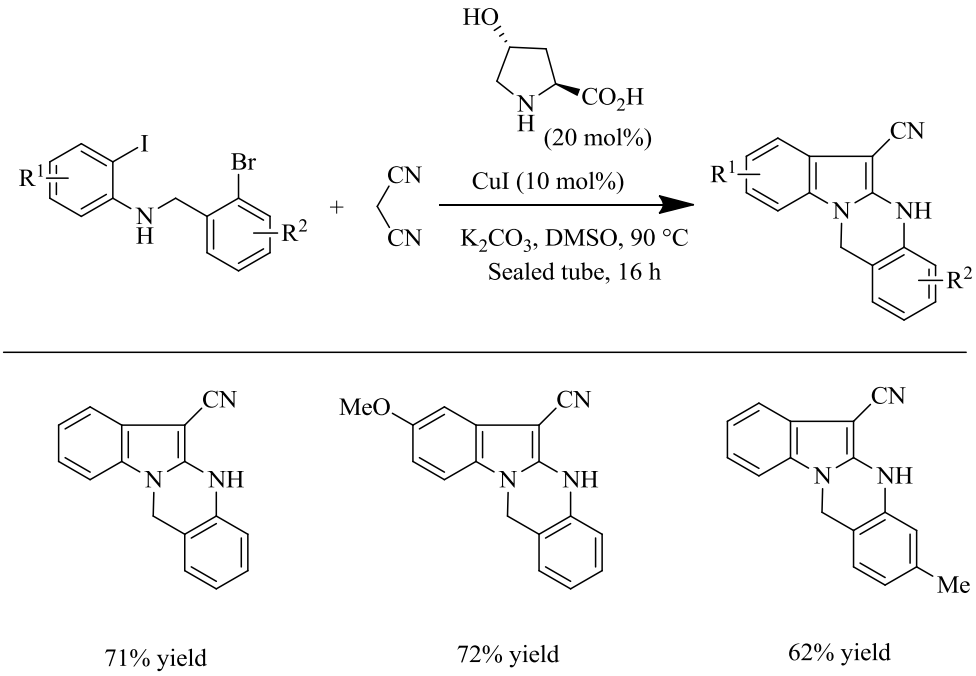
Scheme 1.17 C- N coupling strategy to access pyrrolo[3,2-*b*]indoles

A domino-Knoevenagel-hetero-Diels-Alder reaction strategy for the synthesis of indole annulated-[6,6]-thiopyranobenzopyrans in excellent yields (89-96%) by treating a mixture of 1-methylindoline-2-thione with several O-allyl salicylaldehydes under refluxing conditions in the presence of triehtyl amine in acetic acid for 2 h was reported by Majumdar *et al.*[22] as shown in **Scheme 1.18**.



Scheme 1.18 Domino-Knoevenagel-hetero-Diels-Alder approach to access indole annulated thiopyranobenzopyrans

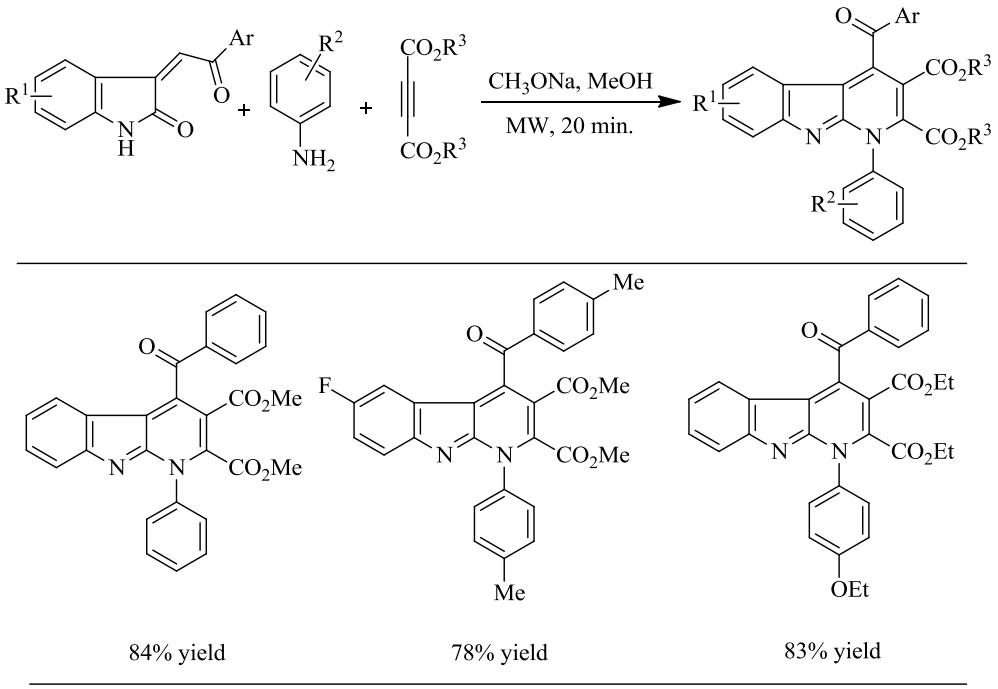
Zhao and his associates[23] discovered a facile and efficient one-pot domino approach to access 5,12-dihydroindolo[2,1-*b*]quinazoline derivatives in high yields (62-72%) *via* copper-catalyzed Ullmann type intermolecular C-C and intramolecular C-N coupling reaction between *N*-(2-bromobenzyl)-2-iodoanilineand malonitrile by using *trans*-4-hydroxy-L-proline (20 mol%) and K_2CO_3 (30 mol%) in DMSO at 90 °C for 16 h in a sealed tube (**Scheme 1.19**).



Scheme 1.19 One-pot access to 5,12-dihydroindolo[2,1-*b*]quinazolines

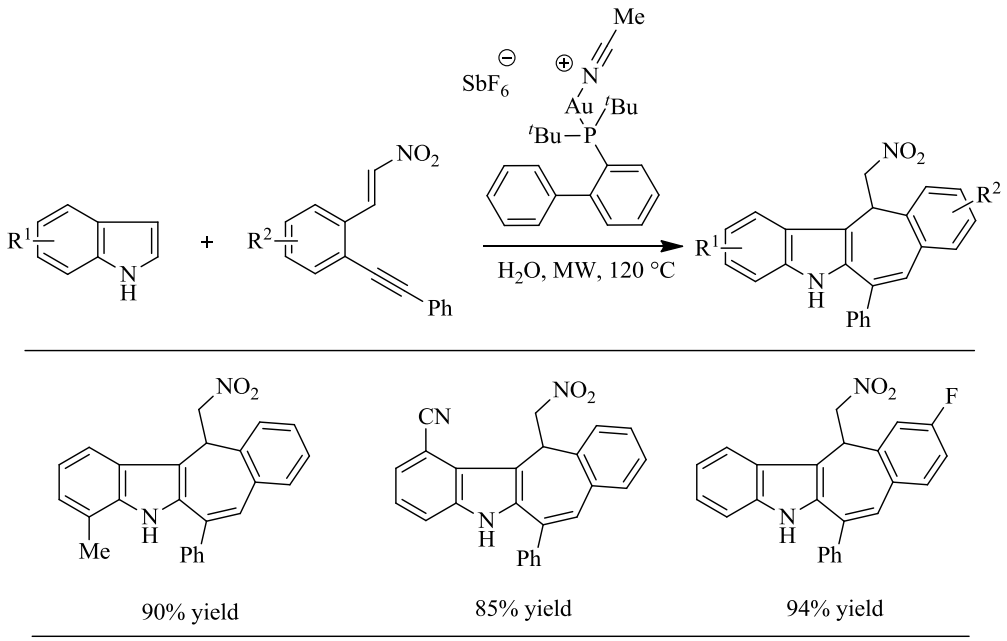
1.3.4 Microwave-promoted reactions

A series of novel polyfunctionalized pyrido[2,3-*b*]indoles were synthesized in high yields (78-84%) by Shi *et al.* by means of a three-component domino approach between 3-benzoylmethylidene-2-oxindoles, substituted anilines and but-2-ynedioates in the presence of catalytic amount of sodium methoxide (10 mol%) in methanol, under microwave irradiation within 20 min. (**Scheme 1.20**).[24]



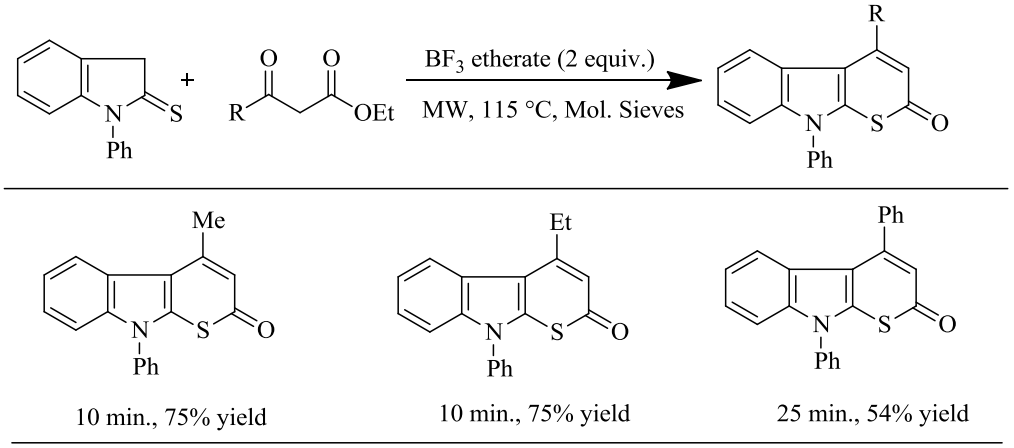
Scheme 1.20 MW assisted access to pyrido[2,3-*b*]indoles

A one-pot, domino, Michael/intramolecular cyclization of orthophenylethylene substituted nitrostyrene with indoles using Au(I) complex and TFA as combined catalyst system was reported by Xu and his associates.[25] This environmental friendly protocol affords a series of tetracyclic indoles with a seven-membered ring in high yield (85-94%) under microwave irradiation at 120 °C in aqueous media (**Scheme 1.21**).



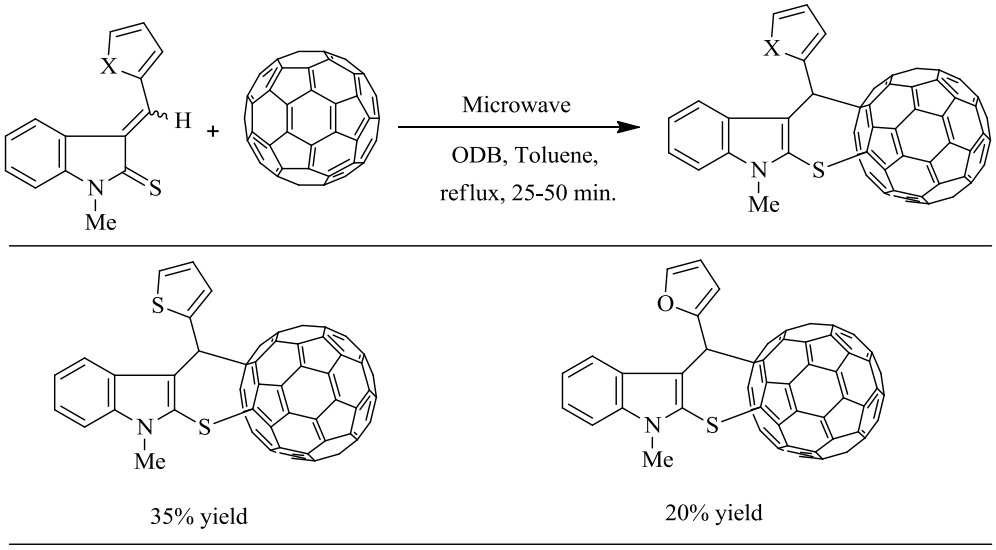
Scheme 1.21 Synthesis of tetracyclic indoles with a seven-membered ring in aqueous media

Jha and his coworkers[26] established a microwave-assisted one-step general synthesis of thiopyrano[2,3-*b*]indol-2-ones in mediocre to good yields (54-75%) from indoline-2-thione and several acetoacetic esters *via* the Pechmann-type condensation reaction in the presence of BF_3 etherate at 115 °C under microwave irradiation for 10-25 minutes as shown in **Scheme 1.22**.



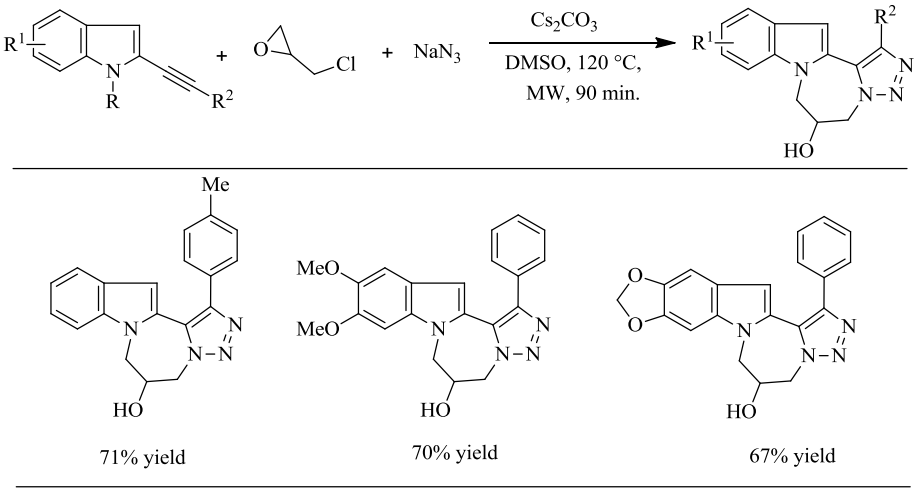
Scheme 1.22 Microwave-assisted access to thiopyrano[2,3-*b*]indol-2-ones

Moghaddam *et al*. established the synthesis of tetrahydrothiopyrano[2,3-*b*]indole [60]fullerene adducts in low yields (20-35%) *via* hetero-Diels-Alder reaction of C_{60} and α,β-unsaturated indole-2-thiones under microwave irradiation in refluxing *O*-dichlorobenzene (ODB) and toluene for 25-50 min. as shown in the **Scheme 1.23**.[27]



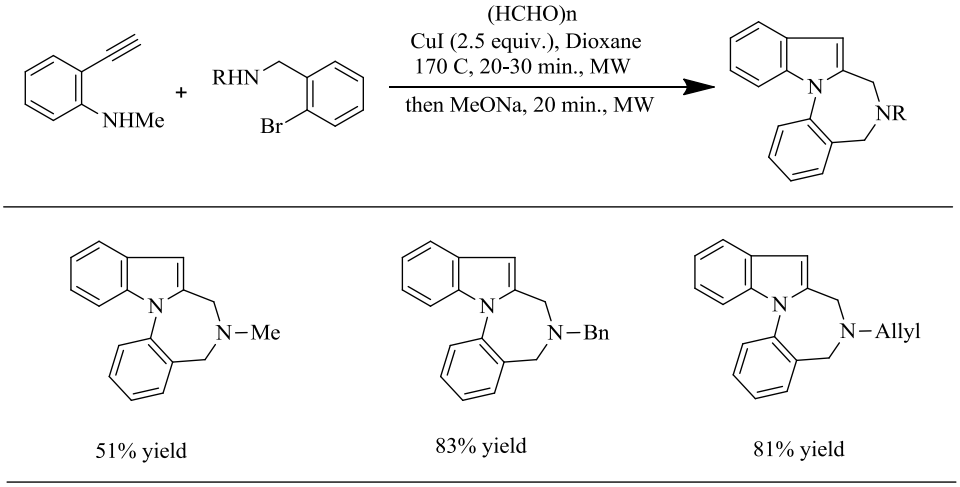
Scheme 1.23 Synthesis of tetrahydrothiopyrano[2,3-*b*]indole[60] fullerene adducts

Arigela *et al*.[28] described a microwave assisted three-component methodology to deliver indolodiazepinotriazoles in good yields (67-71%) by using several 2-alkynylindoles, epichlorohydrin and sodium azide under the presence of 1.5 mmol Cs_2CO_3 in DMSO media at 120 °C for 90 min. *via* *N*-1 alkylation of 2-alkynylindoles followed by 1,3-dipolar cycloaddition domino sequences (**Scheme 1.24**).



Scheme 1.24 Microwave assisted synthesis of indolodiazepinotriazoles

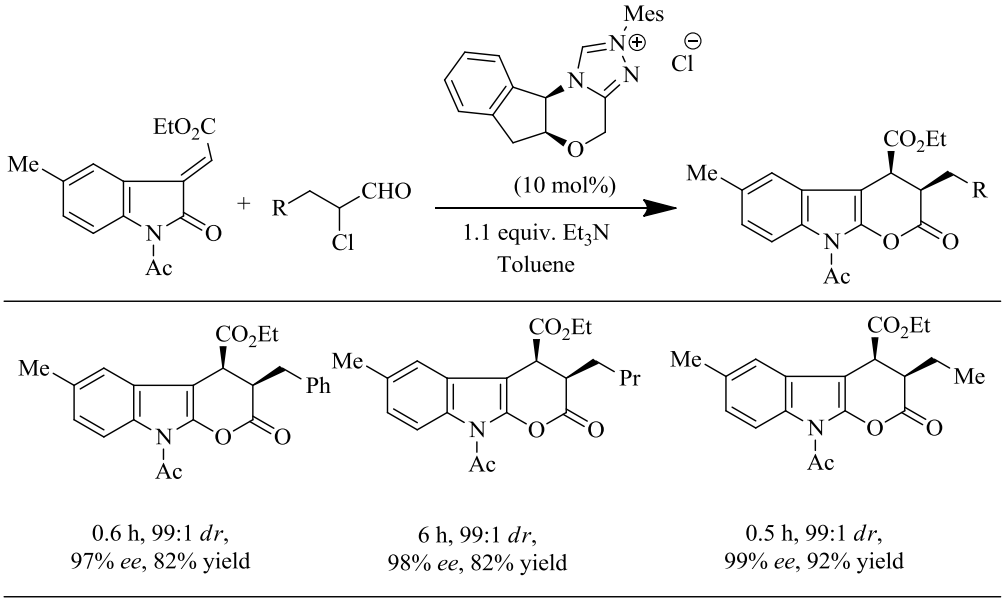
Ohno *et al.*[29] established a novel method for the preparation of fused indoles in moderate to high yields (51-83%) *via* copper-catalyzed domino three component coupling reaction. The methodology involves reaction with *N*-Mesyl-2-ethynylanilines, paraformaldehyde (2 equiv.) and several *O*-bromobenzylamines in the presence of CuI (2.5 mol %) in 1,4-dioxane at 170 °C for 20-30 min. under microwave irradiation followed by addition of 6 equivalents of MeONa and allowing the mixture to heat at 170 °C for 20 min. under microwave irradiation to afford the mentioned compounds as shown in the **Scheme 1.25**.



Scheme 1.25 MW assisted synthesis of fused indoles

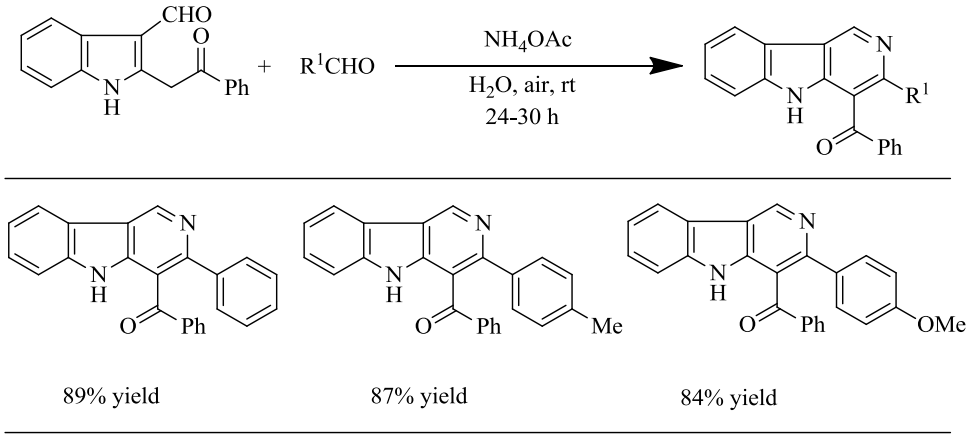
1.3.5 Miscellaneous reactions

Zhong *et al.*[30] established chiral NHC-catalyzed Diels-Alder reaction of 2-oxoindolin-3-ylidenes and several α-chloroaldehydes under the presence of 10 mol% catalyst and triethyl amine in anhydrous toluene to afford fused 3,4-dihydropyrano[2,3-*b*]indol-2(9*H*)-ones in good to excellent yields (82-92%) with high *cis*-diastereoselectivities (>99:1 *dr*) and excellent enantioselectivities (upto 99% *ee*) as shown in the **Scheme 1.26**.



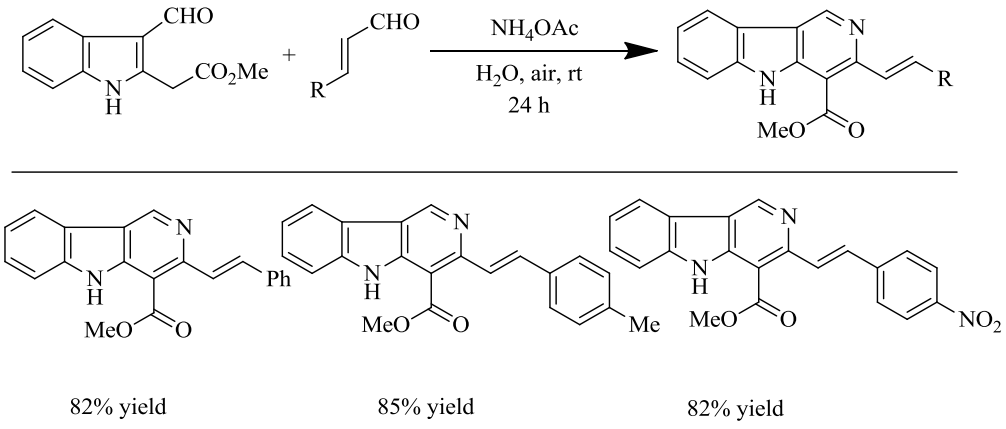
Scheme 1.26 NHC-catalyzed access to 3,4-dihydropyrano[2,3-*b*]indol-2(9*H*)-ones

Samanta *et al.*[31] demonstrated an efficient approach for the construction of functionalized γ-carboline derivatives in excellent yields (84-89%) through a one-pot three-component annulation reaction in aqueous media, involving 3-formyl indole derivatives, several aryl aldehydes and ammonium acetate at room temperature in open air for 24-30 h (**Scheme 1.27**).



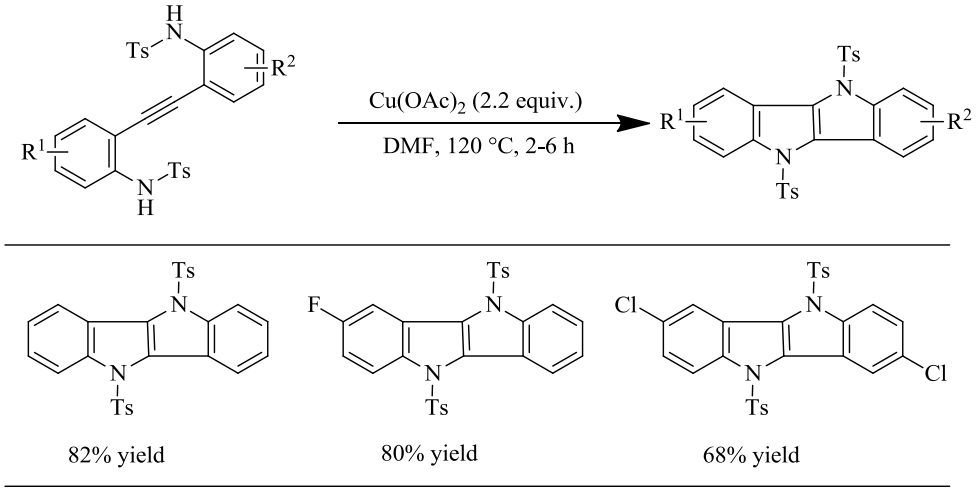
Scheme 1.27 MCR protocol to access functionalized γ-carbolines in water

After successfully employing arylaldehydes as electrophiles in **Scheme 1.27**, Samanta *et al.* further utilized β-substituted acroleins as electrophiles in the one-pot hetero-annulation reaction with 3-formyl indole derivatives under the same conditions to deliver the (*E*)-2-styryl-substituted γ-carbolines in good yields (82-85%, **Scheme 1.28**).[31]



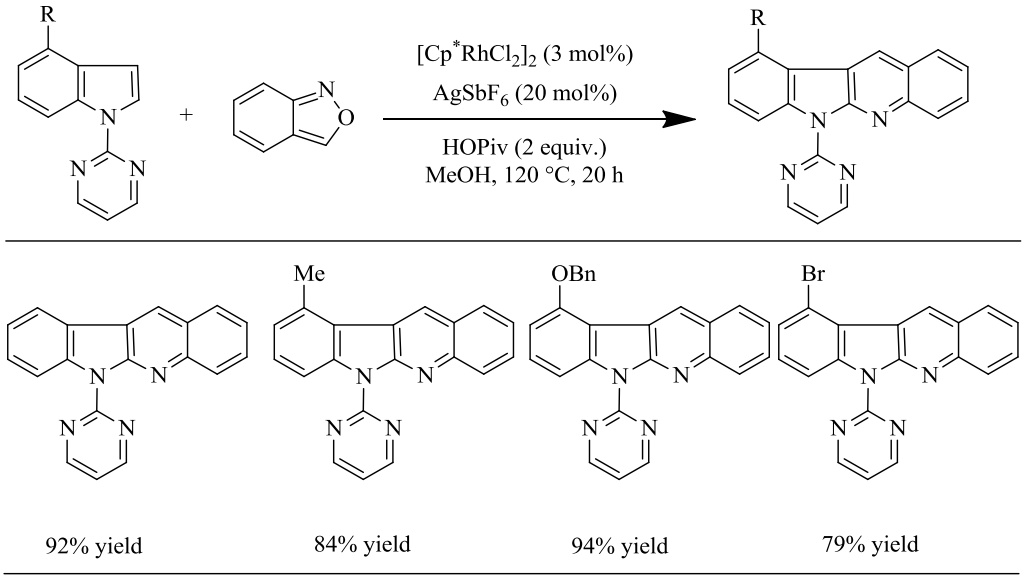
Scheme 1.28 Synthesis of (*E*)-2-styryl substituted γ-carbolines in water

Du *et al.*[32] have discovered a novel cascade reaction for the construction of 5,10-dihydroindolo[3,2-*b*]indoles in high yields (68-82%) through $Cu(OAc)_2$ mediated cascade annulation of internal diaryl alkyne sulfonamides under heating conditions in DMF for 2-6 h as shown in the **Scheme 1.29**.



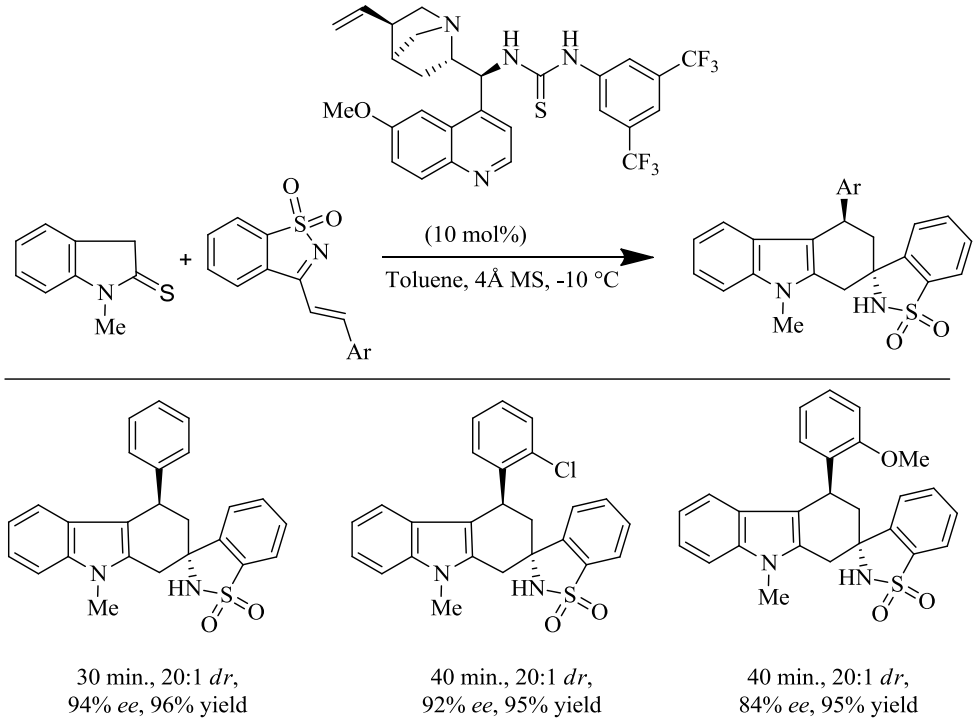
Scheme 1.29 $Cu(OAc)_2$ promoted synthesis of 5,10-dihydroindolo[3,2-*b*]indoles

Li *et al.*[33] revealed a C-H activation/annulations strategy of heteroarenes and functionalization with bifunctional substrates such as anthranils to deliver quinoline-fused heterocycles in good to excellent yields (79-94%) under the presence of $[Cp^*RhCl_2]_2/AgSbF_6$ as a catalys and pivalic acid, $(CH_3)_3CCO_2H$ as an additive in methanol at 120 °C for 20 h as shown in the **Scheme 1.30**.



Scheme 1.30 C-H activation/annulation protocol to access quinoline-fused indole heterocycles

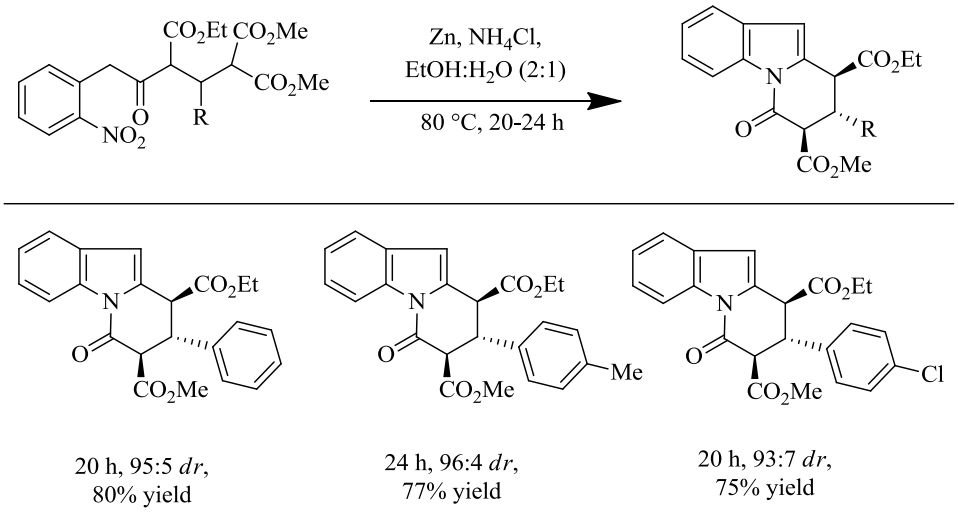
Wang *et al.*[34] described enantioselective formal thio[3+3] spiroannulation reaction of indoline-2-thiones to 1-azadienes under the presence of 10 mol% of quinine-derived bifunctional tertiary amine-thiourea catalyst and 4Å molecular sieves in toluene at -10 °C to furnish spiro[thiopyranoindole-benzoisothiazole] heterocycles with a spiro-stereogenic centers in excellent yields (95-96%) with good to excellent diastereoselectivity (>20:1 *dr*) and high enantioselectivities (upto 94% *ee*) as shown in the **Scheme 1.31**.



Scheme 1.31 Enantioselective synthesis of spiro[thiopyranoindole-benzoisothiazoles]

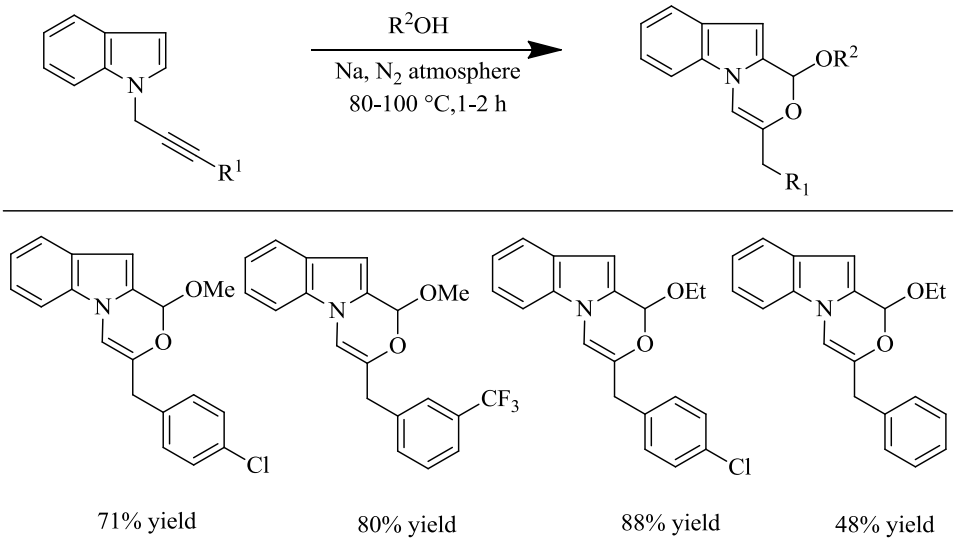
Samanta *et al.*[35] in their continuous interest to develop indole fused heterocycles through domino approach, unfolds an excellent diastereoselective synthesis of functionalized 7,8,9-trisubstituted-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-ones in 75-80% yields by reaction of several 3-ethoxycarbonyl-1,1-dimethoxycarbonyl-5-(2-nitrophenyl) pentan-4-ones using Zn/NH_4Cl as a reducing agent in ethanol/water

mixture at 80 °C for 20-24 h through one-pot reductive cycloaromatization-lactamization sequences (**Scheme 1.32**).



Scheme 1.32 One-pot diastereoselective synthesis of 7,8,9-trisubstituted-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-ones

Abbiati and his coworkers[36] established a domino addition/annulations strategy of δ-alkynylaldehydes and oxygen nucleophiles for the synthesis of oxazino[4,3-*a*]indoles in moderate to high yields (48-88%), by reacting 1-alkynyl-1*H*-indole-2-carbaldehydes and various alcohols in the presence of sodium under nitrogen atmosphere for 1-2 h (**Scheme 1.33**).

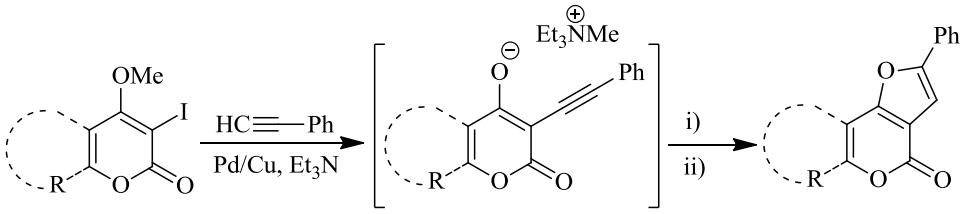


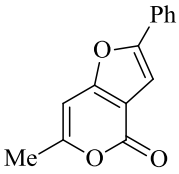
Scheme 1.33 Domino synthesis of [1,4]oxazino[4,3-*a*]indoles

1.4 One-pot method to access coumarin based fused heterocycles

1.4.1 Transition metal salts-mediated reactions

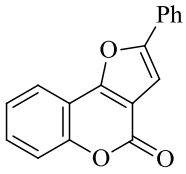
Synthesis of 2-substituted furan-fused coumarin derivatives in good yields (76-82%) from 3-iodo-4-methoxycoumarin by means of an in situ sequential Sonogashira-acetylide coupling and demethylation step induced by Et_3N under heating conditions in acetonitrile was achieved by Conreaux *et al.*[37] (**Scheme 1.34**).





82% yield

i) DMF, 80 °C, 48 h

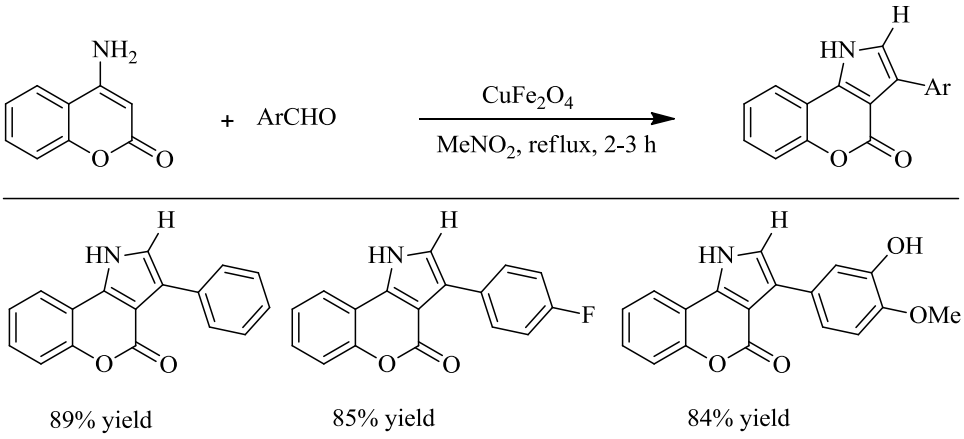


76% yield

ii) MeCN, 60 °C, 15 h

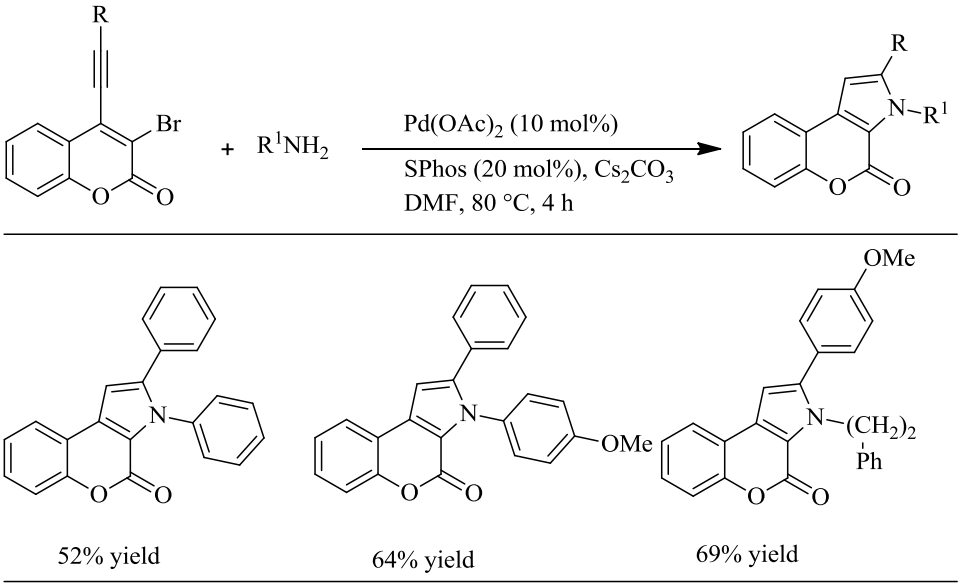
Scheme 1.34 Et_3N induced synthesis of furan-fused heterocycles

Paul and his associates[38] reported a $CuFe_2O_4$ mediated one-pot three-component coupling reaction between 4-aminocoumarin, benzaldehyde and nitromethane under refluxing conditions for 2-3 h to deliver coumarin fused pyrrole derivatives in high yields (84-89%) *via* Knoevenagel condensation followed by Michael addition (**Scheme 1.35**).



Scheme 1.35 $CuFe_2O_4$ catalyzed pyrrole fused coumarin synthesis

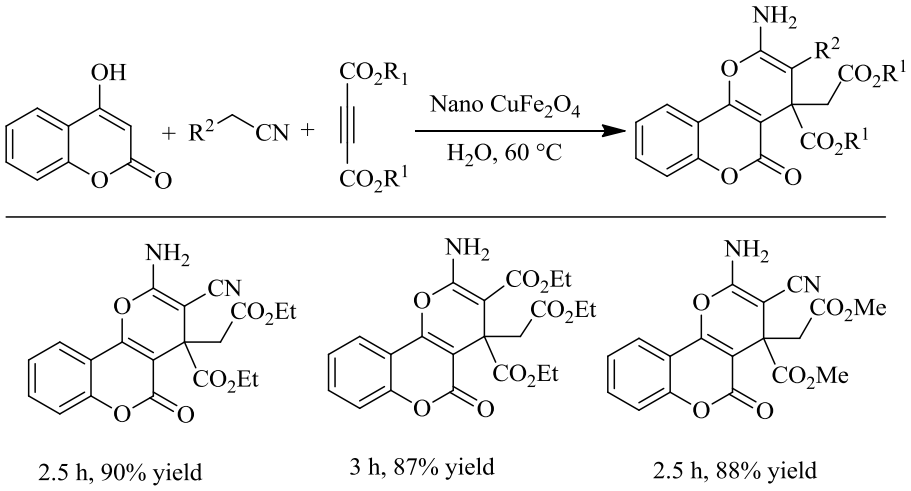
Langer and his coworkers[39] revealed synthesis of a series of pyrrole fused coumarins in high yields (52-69%) under Pd-catalyzed domino C-N coupling/hydroamination reaction involving several 4-alkynated coumarins and aryl amines using Cs_2CO_3 as a base in the presence of 20 mol% SPhos (organophosphorus compound derived from biphenyl) in DMF at 80 °C for 4 h (**Scheme 1.36**).



Scheme 1.36 Pd-catalyzed pyrrolocoumarins synthesis

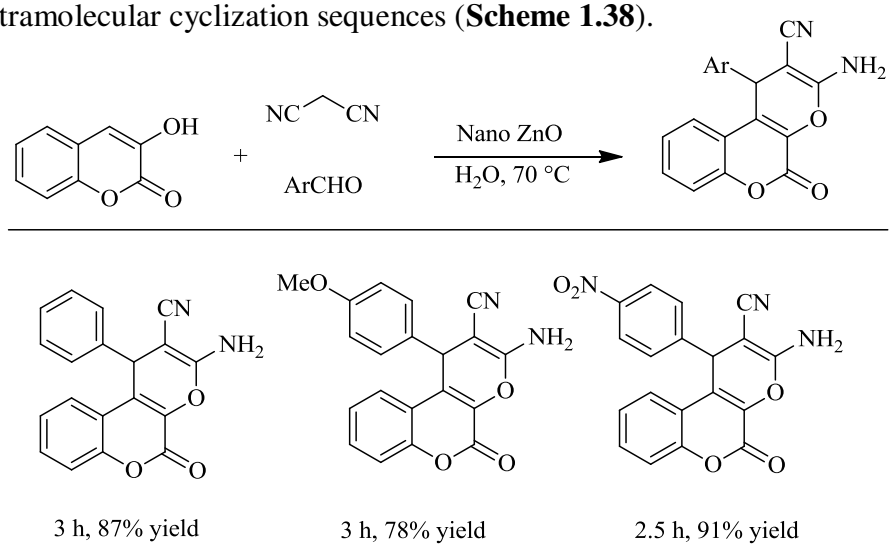
Das group[40] revealed a similar annulation protocol for the synthesis of pyran fused coumarins by utilizing 4-hydroxycoumarin, alkyl nitrile derivatives (malononitrile and ethyl cyanoacetate) and dialkylacetylene dicarboxylates using $CuFe_2O_4$ magnetic nanoparticles as the catalyst under

aqueous conditions at 60 °C for 2.5-3.0 h to afford the dihydropyrano[2,3-*c*]pyrazoles in high yields (87-90%) (**Scheme 1.37**).



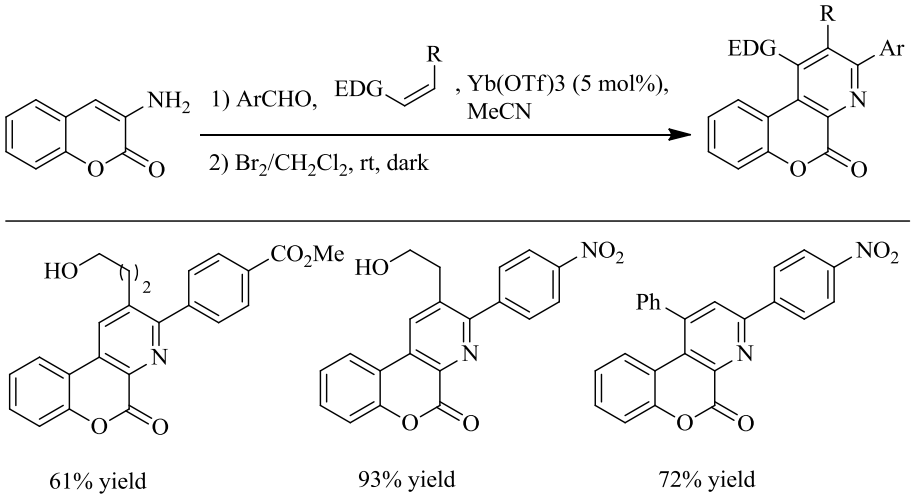
Scheme 1.37 A facile and efficient synthesis of pyrano[3,2-*c*]coumarin

Paul *et al.*[41] established one-pot three component domino approach of 3-hydroxycoumarin, malonitrile and arylaldehydes under the presence of catalytic amount of ZnO in aqueous media at 70 °C for 2.5-3.0 h to afford dihydropyrano[2,3-*c*]chromene derivatives in high yields (78-91%) *via* Knoevenagel condensation followed by Michael addition and then intramolecular cyclization sequences (**Scheme 1.38**).



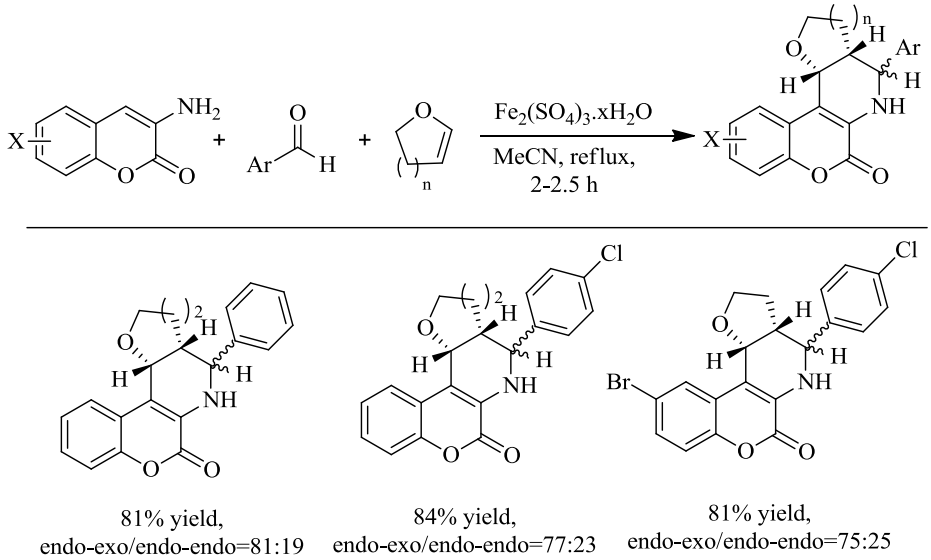
Scheme 1.38 ZnO catalyzed three component synthesis of dihydropyrano[2,3-*c*]chromene derivatives

In 2008, Bodwell and his coworkers[42] demonstrated a three-component Povarov reaction between an in situ formed 2-azadiene component, derived from the condensation of 3-aminocoumarins and aromatic aldehydes, which was further treated with various dienophiles in acetonitrile under the presence of 5 mol% $Yb(OTf)_3$ followed by aromatization of the resulting product on treatmen with Br_2 in CH_2Cl_2 at room temperature in the dark to give the corresponding pyrido[2,3-*c*]coumarins in good to excellent yields (61-93%) (**Scheme 1.39**).



Scheme 1.39 Synthesis of pyrido[2,3-*c*]coumarins *via* Povarov reaction

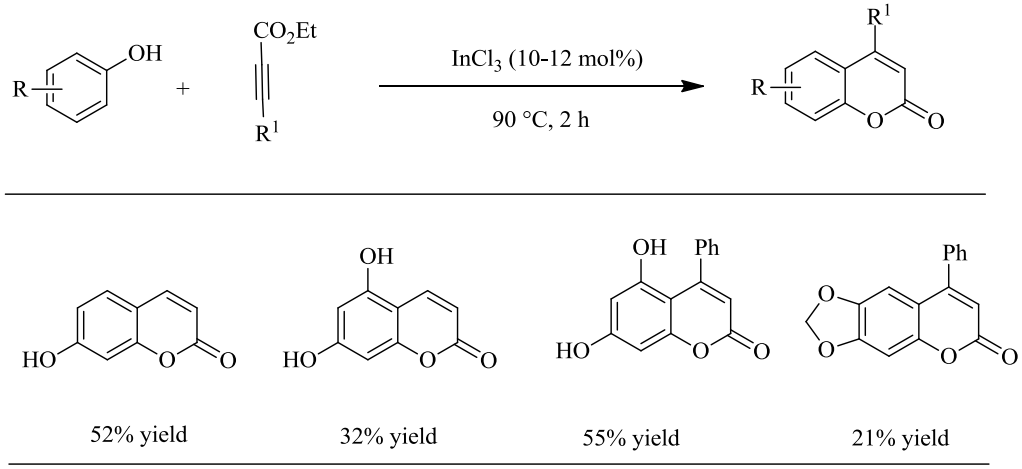
An interesting protocol for the synthesis of tetrahydropyrido[2,3-*c*]coumarin derivatives in high yields (81-84%) and in excellent diastereomeric ratio (>81:19) involving 3-aminocoumarins, aryl aldehydes and cyclic enol ethers in the presence of 10 mol% of hydrated ferric sulphate under refluxing condition in MeCN for 2.0-2.5 h was discovered by Das *et al*. (**Scheme 1.40**).[43]



Scheme 1.40 One-pot synthesis of tetrahydropyrido[2,3-*c*]coumarins

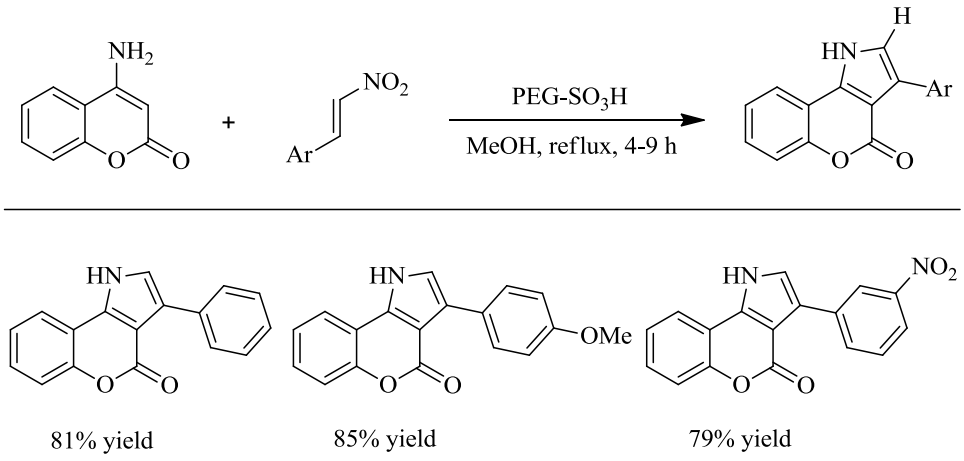
1.4.2 Acid-promoted reactions

A single-step condensation reaction of appropriately oxygen substituted phenols with acetylenic esters in the presence of catalytic amounts of indium chloride (10-12 mol%) under solvent free conditions at 90 °C to afford coumarin derivatives in mediocre yields (21-55%) after 2 h was revealed by Kalyanam and his associates[44] as shown in **Scheme 1.41**.



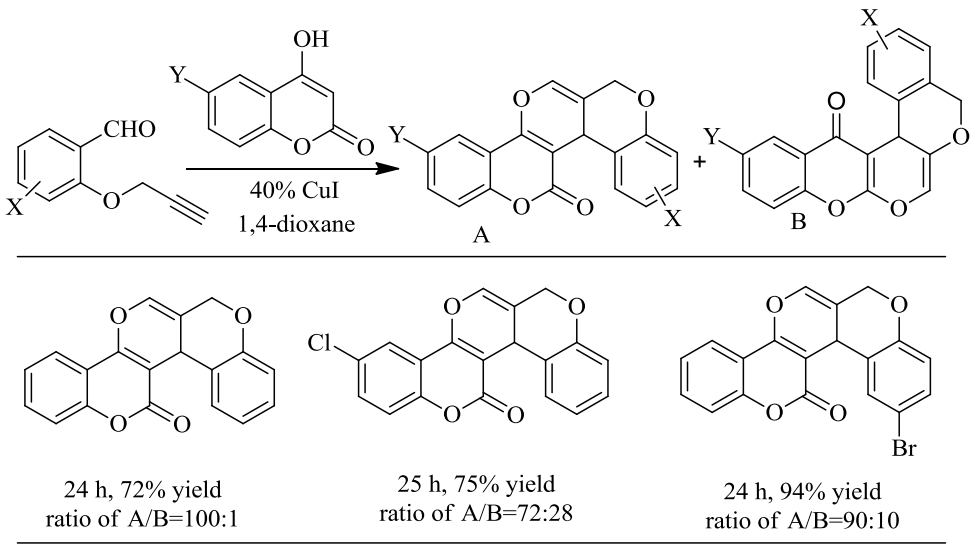
Scheme 1.41 Single-step synthesis of coumarin ring skeletons

Das *et al.*[45] disclosed a similar facile procedure for the synthesis of pyrrole fused coumarins in high yields (79-85%) using 4-aminocoumarin and α,β-unsaturated nitroalkenes in the presence of PEG-SO_3H as a catalyst under refluxing conditions in methanol for 4-9 h *via* Michael addition followed by intramolecular cyclization with the removal of the nitro group (**Scheme 1.42**).



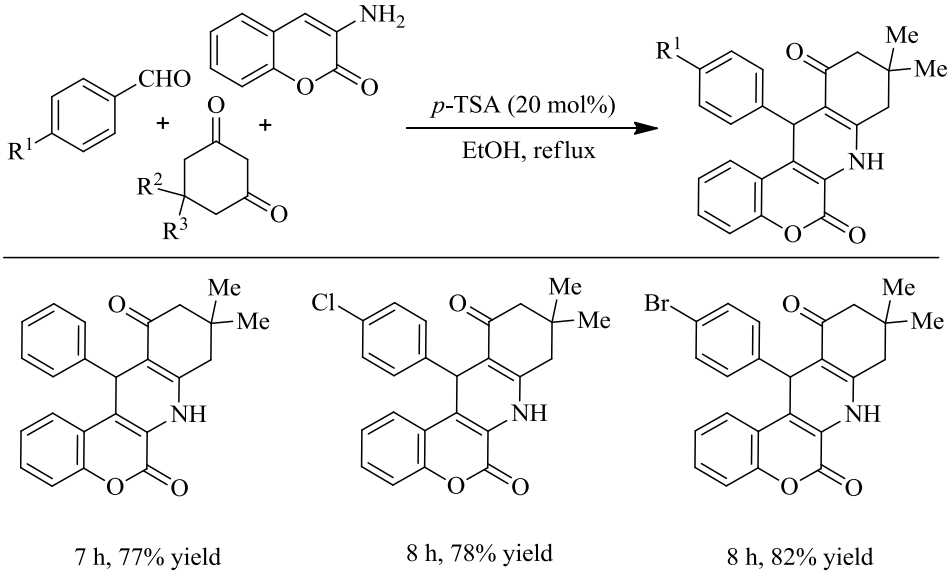
Scheme 1.42 PEG-SO_3H catalyzed pyrrole fused coumarins synthesis

In 2009, Rominger and his coworkers[46] described a domino Knoevenagel hetero-Diels-Alder reaction of *O*-propargylated salicylaldehydes and several 4-hydroxycoumarins under the presence of CuI as a Lewis acid in 1,4-dioxane for 24-25 h that leads to pyrano[2,3-*c*]coumarins (A) and pyrano[2,3-*c*]chromones (B) in high yields (**Scheme 1.43**).



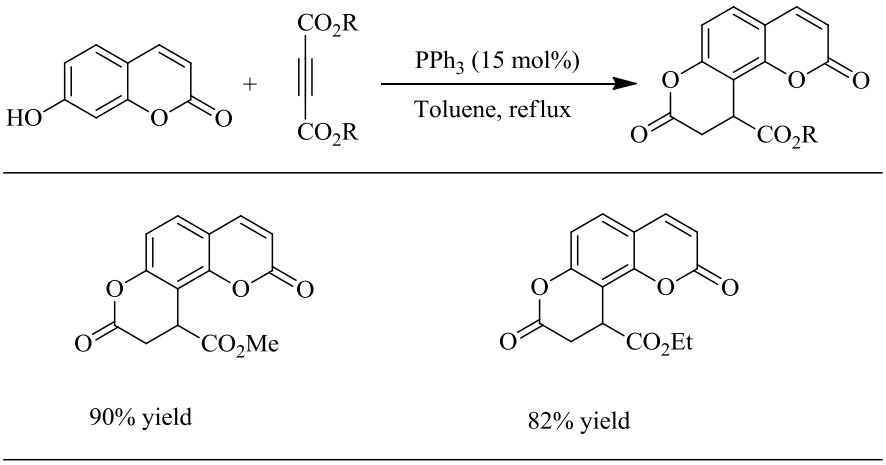
Scheme 1.43 CuI catalyzed pyrano[2,3-*c*]coumarins and pyrano[2,3-*c*]chromones synthesis

Das group[47] revealed one-pot synthesis of chromeno[3,4-*b*]quinoline derivatives in good yields (77-82%) through Michael initiated ring closure (MIRC) by employing three-component condensation of aromatic aldehydes, 3-aminocoumarins and cyclic 1,3-diketones in the presence of catalytic amount of p-toluenesulfonic acid (pTSA) in ethanol for 7-8 h under refluxing condition (**Scheme 1.44**).



Scheme 1.44 Construction of chromeno[3,4-*b*]quinoline derivatives

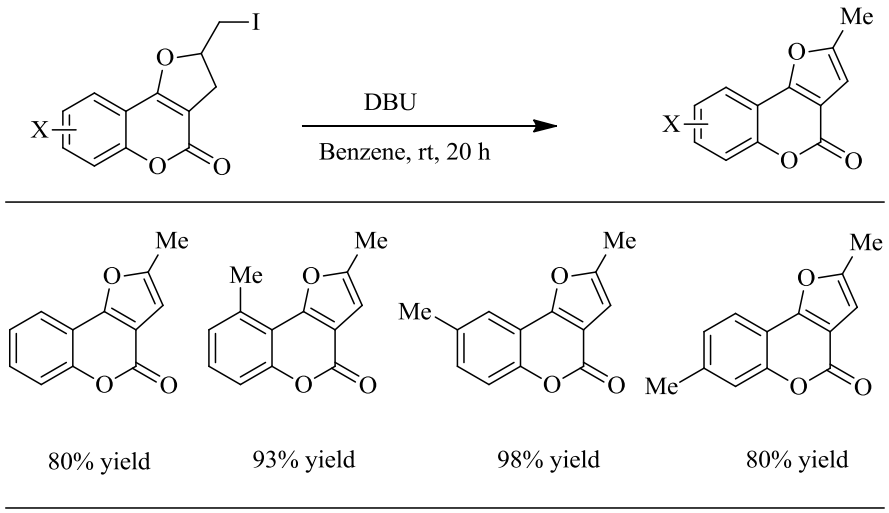
Mohtat and his coworkers[48] discovered the cyclization strategy of 7-hydroxycoumarin with dialkyl acetylene dicarboxylate in the presence of 15 mol% PPh_3 under refluxing toluene resulting in the formation of the methyl-2,8-dioxo-2*H*,8*H*-pyrano[3,2-*g*]chromene-4-carboxylate in high yields (82-90%) as shown in the **Scheme 1.45**.



Scheme 1.45 PPh_3 mediated access to pyrano[3,2-*g*]chromene-4-carboxylate

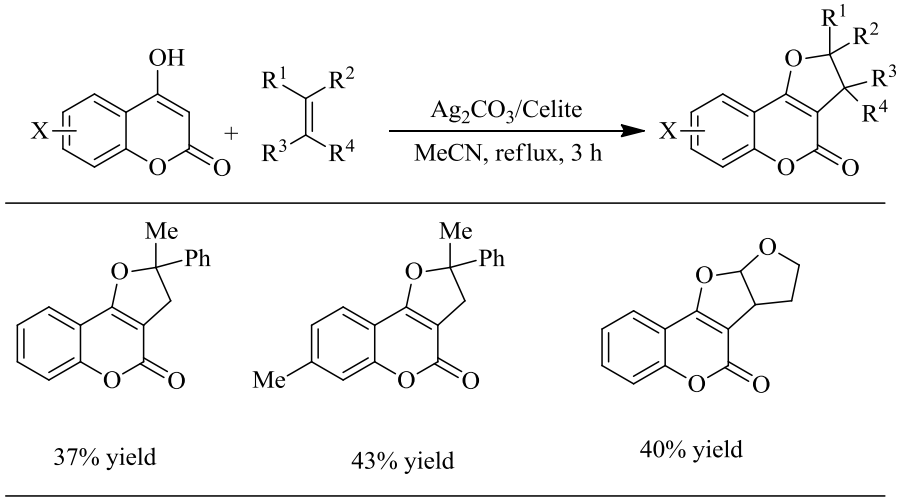
1.4.3 Base-promoted reactions

Suk *et al.*[49] revealed synthesis of furocoumarins in excellent yields (80-98%) from iodomethyl dihydrofurocoumarin derivatives under DBU catalyzed cyclization approach in benzene at room temperature for 20 h as shown in **Scheme 1.46**.



Scheme 1.46 DBU catalyzed synthesis of furocoumarins

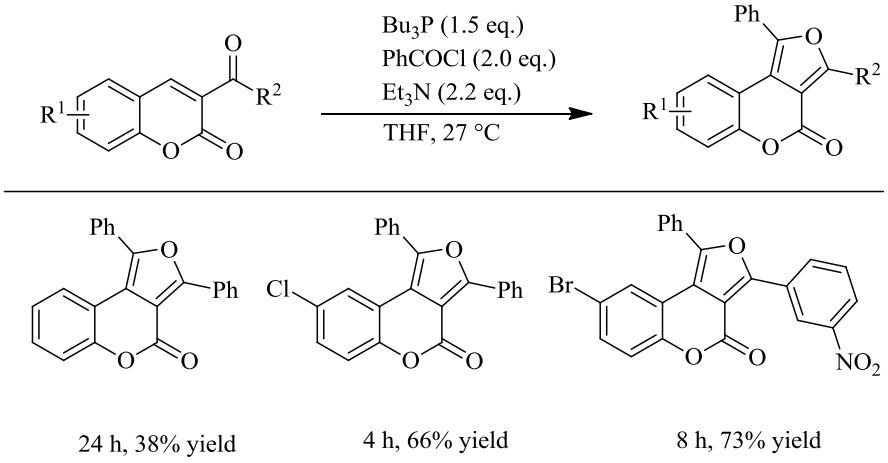
Lee and his coworkers[50] disclosed a facile synthesis of dihydrofuro-coumarins in mediocre yields (37-43%) *via* oxidative cycloaddition approach by using several 4-hydroxycoumarins and 3 equivalents substituted olefins under refluxing conditions in acetonitrile using Ag_2CO_3/celite for 3 h (**Scheme 1.47**).



Scheme 1.47 Silver(I)/Celite promoted synthesis of dihydrofurocoumarins

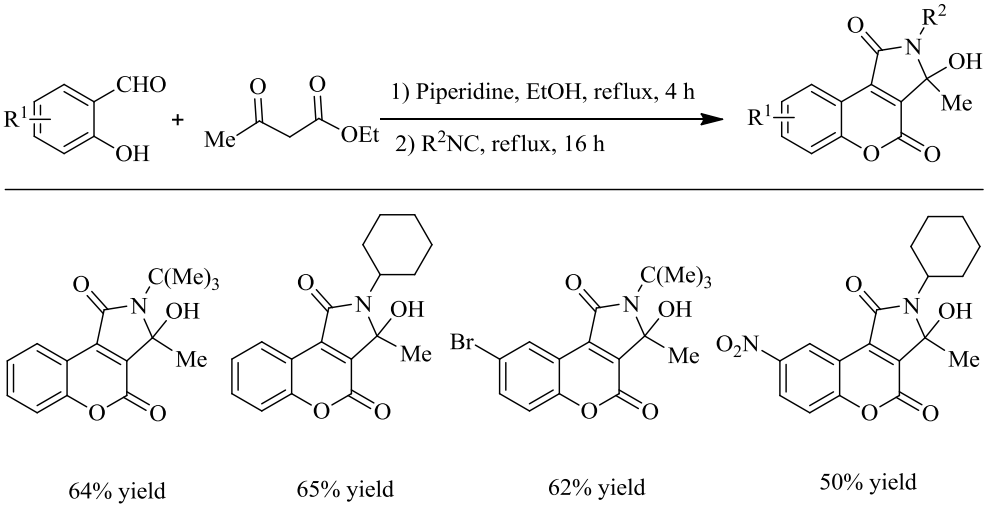
Jang *et al.*[51] revealed a new strategy for the preparation of highly functional furo[3,4-*c*]coumarins and related furylcoumarin derivatives in mediocre to good yields (38-73%) involving α,β-unsaturated ketones, tributylphosphine and acyl chlorides in THF at 27 °C under the presence

of triethyl amine as a base *via* intramolecular Wittig reaction as shown in **Scheme 1.48**.



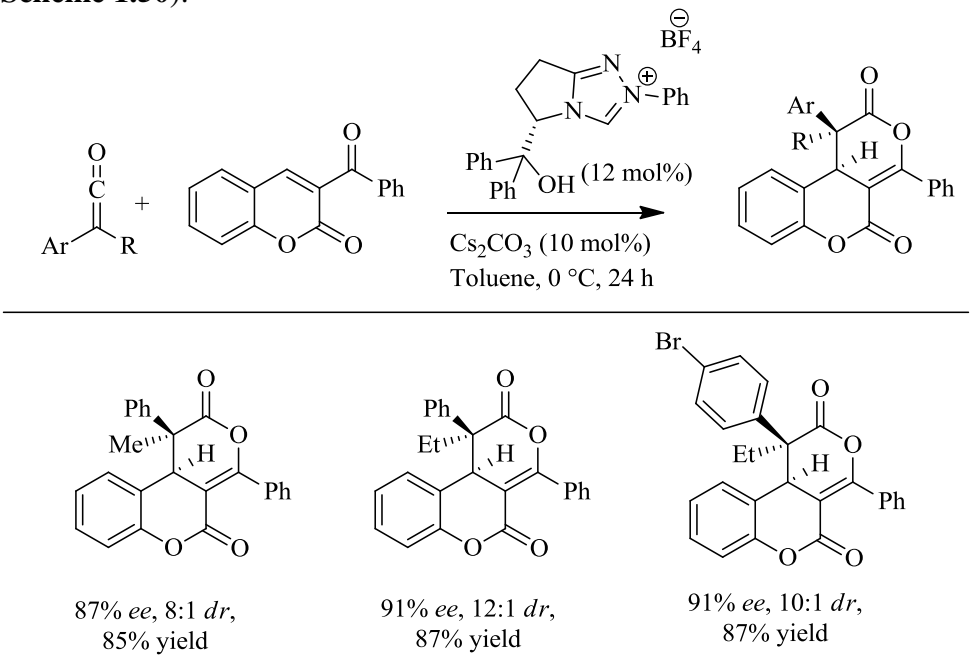
Scheme 1.48 Furo[3,4-*c*]coumarin synthesis *via* intramolecular Wittig reaction

A one-pot three component condensation reaction of 2-hydroxybenzaldehydes, ethyl acetoacetate and several isocyanides in the presence of piperidine under refluxing conditions in ethanol to deliver a number of pyrrole-fused chromanone derivatives in moderate yields (50-65%) was achieved by Ghandi and his coworkers (**Scheme 1.49**).[52]



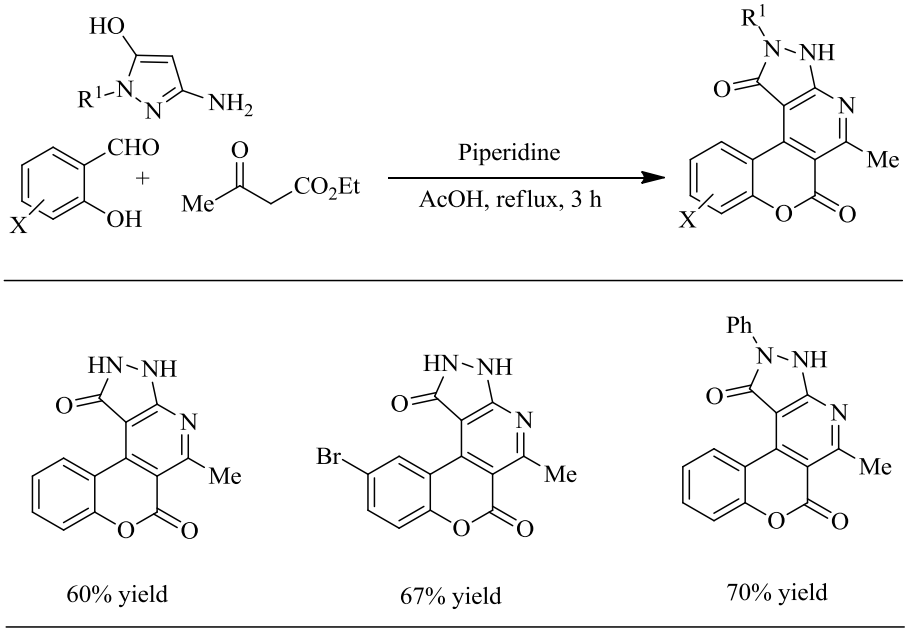
Scheme 1.49 One-pot synthesis of pyrrole fused chromanone derivatives

Jian group[53] described *N*-heterocyclic carbenes catalyzed [4+2] cycloaddition of ketenes and 3-benzoylcoumarins under the presence of 10 mol% Cs_2CO_3 in toluene at 0 °C for 24 h to deliver dihydrocoumarin-fused dihydropyranones in high yields (85-87%) with good to high diastereomeric ratio (>12:1) and excellent enantioselectivity (upto 91%) (**Scheme 1.50**).



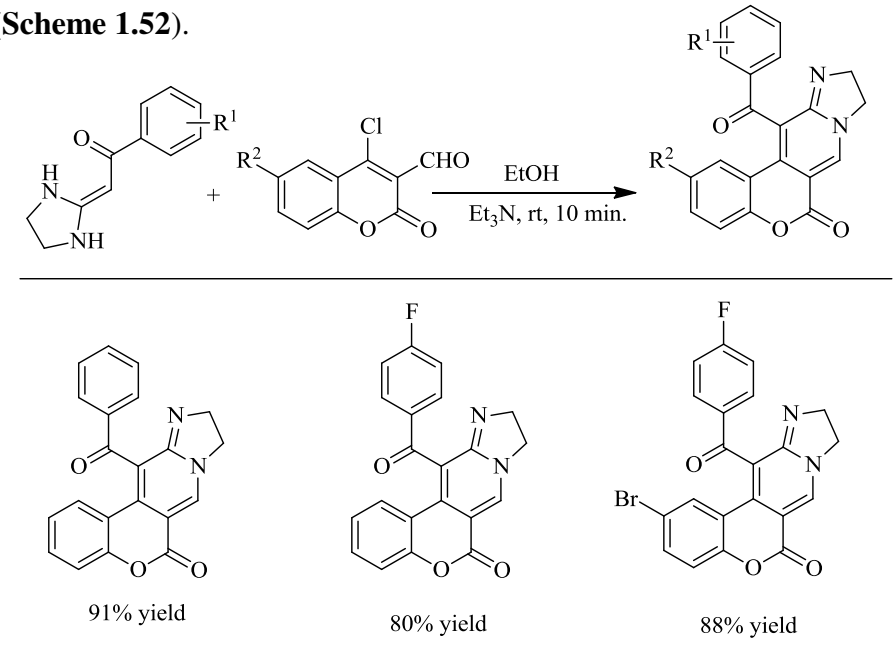
Scheme 1.50 Enantioselective synthesis of dihydrocoumarin-fused dihydropyranones

Efficient three-component reaction between 3-aminopyrazol-5-ones, salicylic aldehydes and acetylacetic ester, involving an in situ formation of 3-acetylcoumarins and subsequent condensation with aminopyrazolones in the presence of piperidine under refluxing conditions for 3 h to furnish dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones in good yields (60-70%) as described by Frolova *et al*. (**Scheme 1.51**).[54]



Scheme 1.51 MCR approach to pyridine fused coumarins

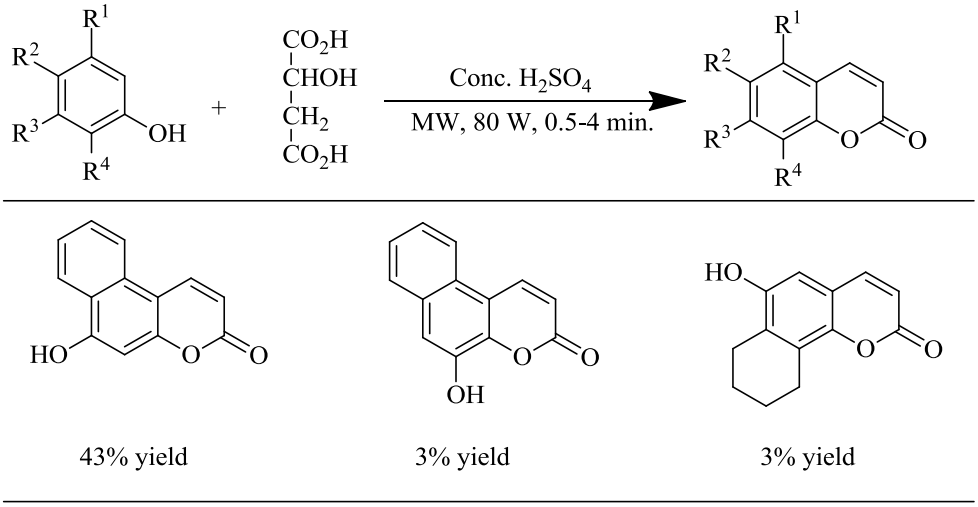
Yu *et al.*[55] unfolds the reaction of heterocyclic ketene aminals (HKAs) with substituted 4-chloro-3-formylcoumarins using Et_3N as a catalyst in EtOH at room temperature for 10 min. to afford dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one derivatives in high yields (80-91%) *via* aza-ene reaction/tautomerization and cyclization sequences (**Scheme 1.52**).



Scheme 1.52 Preparation of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo-[1,2-*a*]pyridin-6-one derivatives

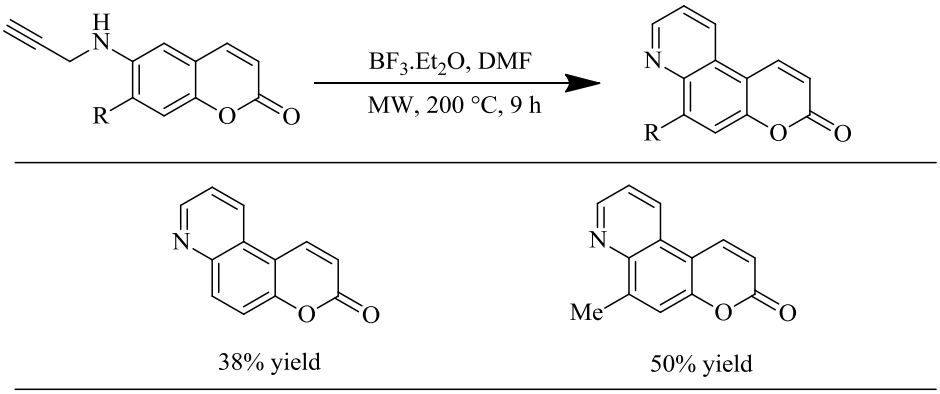
1.4.4 Microwave-promoted reactions

Reaction of equimolar amounts of substituted phenols and malic acid in the presence of a small amount of concentrated H_2SO_4 under microwave irradiation (80 W) for 0.5-4 minutes to afford fused hydroxycoumarin derivatives in low to mediocre yields (3-43%) was revealed by Litinas *et al*. as shown in the **Scheme 1.53**.[56]



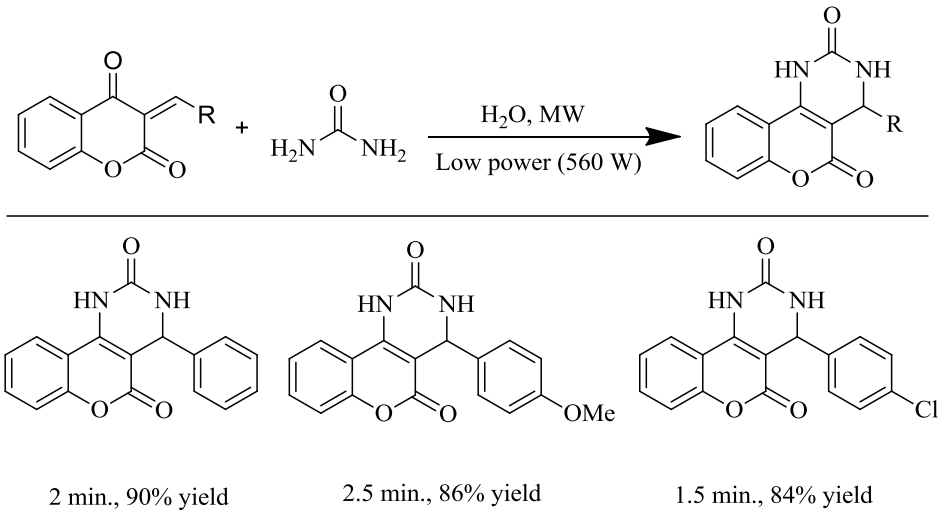
Scheme 1.53 Microwave assisted synthesis of hydroxycoumarins

Litinas and his colleagues[57] also established the synthesis of fused pyridocoumarins in mediocre to good yields (38-50%) using 6-propargyl aminocoumarin with boron trifluoride diethyl etherate in DMF at 200 °C under microwave irradiation for 9 h *via* aza-Claisen rearrangement and subsequent in situ cyclization as shown in the **Scheme 1.54**.



Scheme 1.54 Microwave assisted synthesis of fused pyridocoumarins

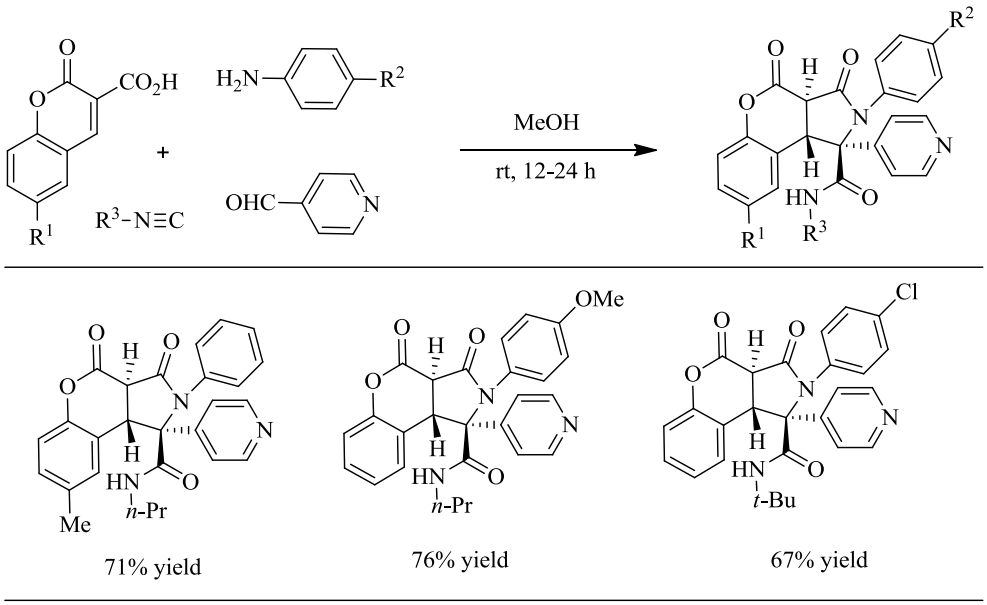
Rastogi *et al.*[58] unfolds a cyclization strategy for the synthesis of tetrahydrobenzopyrano[4,3-*d*]pyrimidine-2,5-diones in good to excellent yields (84-90%) involving 3-arylidenechromane-2,4-diones and a nucleophile (urea) under microwave irradiation in aqueous media for 1.5-2.5 minutes at low power (560 W) as shown in the **Scheme 1.55**.



Scheme 1.55 Microwave accelerated synthesis of tetrahydrobenzopyrano[4,3-*d*]pyrimidine-2,5-diones

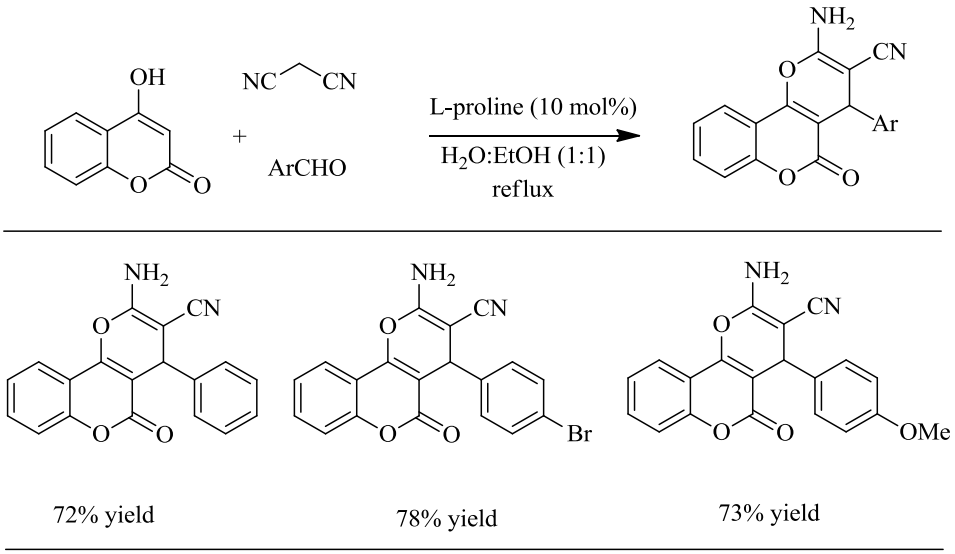
1.4.5 Miscellaneous approaches

Che *et al.*[59] reported a one-pot efficient approach to synthesize substituted chromeno[3,4-*c*]pyrrole-3,4-diones in high yields (67-76%) by using a sequential Ugi reaction and intramolecular Michael addition reaction for 12-24 h from corresponding acids, amines, isocyanides and 4-formyl pyridines at room temperature in methanol (**Scheme 1.56**).



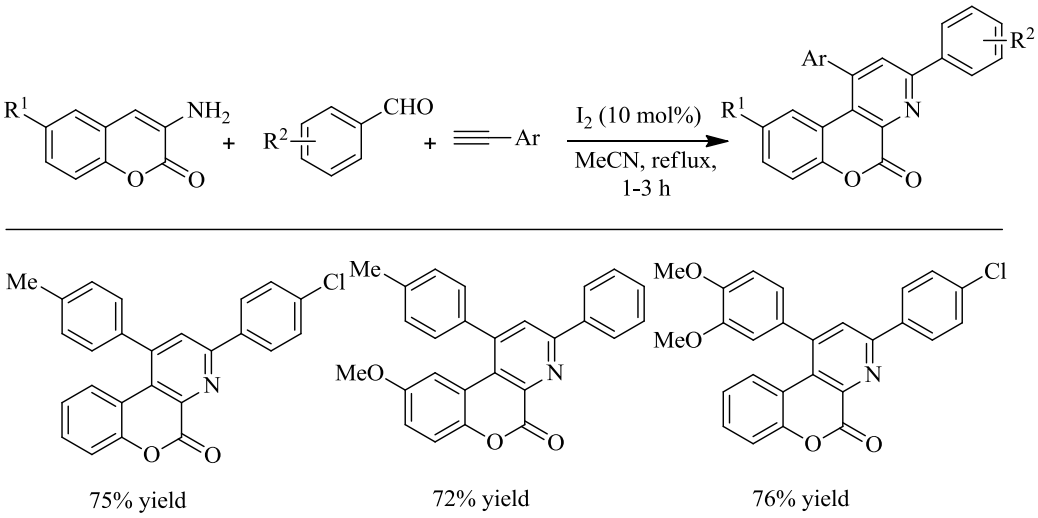
Scheme 1.56 Syntheses of substituted chromeno[3,4-*c*]pyrrole-3,4-diones

Balalaie group[60] revealed a three component reaction between 4-hydroxycoumarin, nitriles and aldehyde in the presence of 10 mol% L-proline under refluxing condition in water/ethanol mixture in 1:1 ratio to afford pyrano[3,2-*c*]coumarin compounds in high yields (72-78%) *via* Knoevenagel condensation followed by cyclization (**Scheme 1.57**).



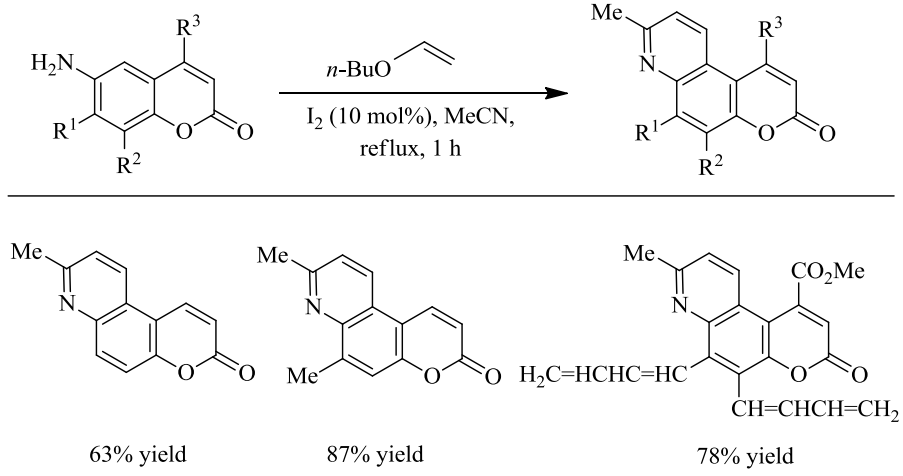
Scheme 1.57 Synthesis of dihydropyranochromenes in aqueous media

A related protocol, for the synthesis of a variety of substituted pyrido[2,3-*c*]coumarin derivatives in high yields (72-76%) was developed by Khan and his co-workers,[61] involving a three-component reaction between substituted 3-aminocoumarins, aromatic aldehydes and alkynes in the presence of 10 mol% molecular iodine in acetonitrile under reflux conditions for 1-3 h through Povarov reaction (**Scheme 1.58**).



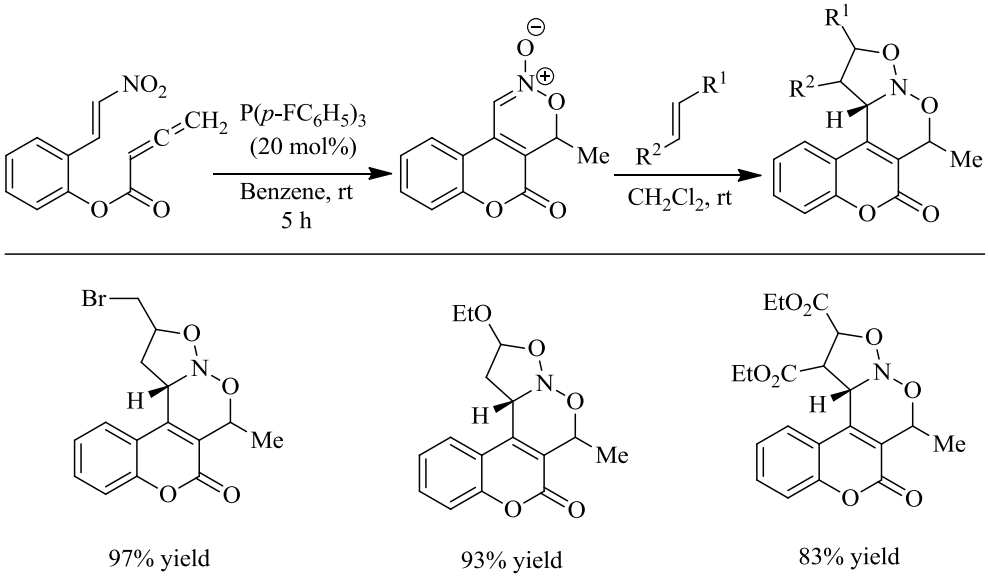
Scheme 1.58 Synthesis of various substituted pyrido[2,3-*c*]coumarin derivatives through Povarov reaction

In 2013, Litinas and his coworkers described the synthesis of fused pyridocoumarins in high yields (63-87%) from three-component reaction between aminocoumarins and two equivalents of *n*-butyl vinyl ether catalysed by 10 mol% iodine under refluxing conditions in acetonitrile through *aza*-Diels-Alder reaction (**Scheme 1.59**).[62]



Scheme 1.59 Iodine-catalyzed synthesis of fused pyridocoumarins

In 2007, Henry *et al.*[63] described the conversion of 2- styrenyl allenoates into nitronate derivatives upon treatment with 20 mol% *tris*(*p*-fluorophenyl)-phosphine in benzene at room temperature for 24 h, which upon further treatment with substituted alkenes in dichloromethane at room temperature furnished corresponding tetracyclic coumarin derivatives in excellent yields (83-97%) as shown in the **Scheme 1.60**.



Scheme 1.60 Phosphine-catalyzed synthesis of functionalized coumarins

Over the intervening years, many classical and modern methods have been exploited for the efficient access to indole and coumarin based fused heterocycles. Despite the rich history on indole/coumarin fused heterocycles, the metal-free one-pot method for the access to a variety of pharmacologically promising molecules such as tetrahydrothiopyrano[2,3-b]indoles, furo/pyrano[3,2-c]chromen-2-ones and their related heterocyclic scaffolds in a stereoselective manner has been less explored.

Therefore, it is ample scope to develop the metal-free based new catalytic systems for the direct synthesis of indole and coumarin based fused heterocycles in an efficient and economical manner.

1.5 References

1. (a) Sashidhara K. V., Kumar A., Chatterjee M., Rao K. B., Singh S., Verma A. K., Palit G. (2011), Discovery and synthesis of novel 3-phenylcoumarin derivatives as antidepressant agents, *Bioorg. Med. Chem. Lett.*, 21, 1937-1941 (DOI: 10.1016/j.bmcl.2011.02.040); (b) Chimenti F., Bizzarri B., Bolasco A., Secci D., Chimenti P., Granese A., Carradori S., Rivanera D., Zicari A., Scaltrito M. M., Sisto F. (2010), Synthesis, selective anti-Helicobacter pylori activity and cytotoxicity of novel N-substituted-2-oxo-2*H*-1-benzopyran-3-carboxamides, *Bioorg. Med. Chem. Lett.*, 20, 4922-4926 (DOI: 10.1016/j.bmcl.2010.06.048); (c) Bansal Y., Sethi P., Bansal G. (2013), Coumarin: A potential nucleus for anti-inflammatory molecules, *Med. Chem. Res.*, 22, 3049-3060 (DOI: 10.1007/s00044-012-0321-6); (d) Barros T. A. A., De Freitas L. A. R., Filho J. M. B., Nunes X. P., Giulietti A. M., De Souza G. E., Santos R. R., Soares M. B. P., Villarreal C. F. (2010), Antinociceptive and anti-inflammatoryproperties of 7-hydroxycoumarin in experimental animal models: Potential therapeutic for the control of inflammatory

chronic pain, *J. Pharm. Pharmacol.*, 62, 205-213 (DOI : 10.1211/jpp/62.02.0008).

2. (a) Majumder S., Bhuyan P. J. (2012), Stereoselective synthesis of novel annulated thiopyranoindole derivatives from simple oxindole *via* intramolecular 1,3-dipolar cycloaddition reactions of nitrone and nitrile oxide, *Tetrahedron Lett.*, 53, 762-764 (DOI:10.1016/j.tetlet.2011.11.136); (b) Moghaddam F. M., Mirjafary Z., Saeidian H., Kiamehr M., Taheri S., Kiamehr M. (2010), Facile entry to polycyclic indolylhydroquinoline skeletons *via* tandem C-alkylation and intramolecular S-alkylation, *Tetrahedron*, 66, 134-138 (DOI: 10.1016/j.tet.2009.11.032).

3. (a) Baeyer A., Emmerling A. (1869), Synthese des Indols, *Berichte der Deutschen Chemischen Gesellschaft*, 2, 679-682 (DOI: 10.1002/cber.186900201268); (b) Gleye C., Lewin G., Laurens A., Jullian J.-C., Loiseau P., Bories C., Hocquemiller R. (2003), Acaricidal activity of tonka bean extracts. Synthesis and structure-activity relationships of bioactive derivatives, *J. Nat. Prod.*, 66, 690-692 (DOI: 10.1021/np020563j).

4. Hayashi Y. (2016), Pot economy and one-pot synthesis, *Chem. Sci.*, 7, 866-880 (DOI: 10.1039/c5sc02913a).

5. Xie X., Du X., Chen Y., Liu Y. (2011), One-pot synthesis of indole-fused scaffolds *via* Gold-catalyzed tandem annulation reactions of 1,2-*bis*(alkynyl)-2-en-1-ones with indoles, *J. Org. Chem.*, 76, 9175-9181 (DOI: 10.1021/jo2017668).

6. Yao X. B., Wang Q., Zhu J. (2012), Palladium(II)-catalyzed intramolecular diamination of alkynes under aerobic oxidative conditions: Catalytic turnover of an iodide ion, *Angew. Chem. Int. Ed.*, 51, 5170-5174 (DOI: 10.1002/anie.201201640).

7. Nazarê M., Schneider C., Lindenschmidt A., Will D. W. (2004), A flexible, palladium-catalyzed indole and aza-indole synthesis by direct annulation of chloroanilines and chloroaminopyridines with ketones, *Angew. Chem. Int. Ed.*, 43, 4526-4528 (DOI: 10.1002/anie.200460122).

8. Yang Y., Li B., Liu W., Zhang R., Yu L., Ma Q.-G., Lv R., Du D., Li T. (2016), Cp^*Co^{III}-catalyzed synthesis of pyrido-[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-iums *via* tandem C-H activation and subsequent annulation from 1-(pyridin-2-yl)-1*H*-indoles and internal alkynes, *J. Org. Chem.*, 81, 11335-11345 (DOI: 10.1021/acs.joc.6b02314).

9. Samala S., Arigela R. K., Kant R., Kundu B. (2014), Diversity-oriented synthesis of ketoindoloquinoxalines and indolotriazolo-quinoxalines from 1-(2-nitroaryl)-2-alkynylindoles, *J. Org. Chem.*, 79, 2491-2500 (DOI: 10.1021/jo402783p).

10. Gupta S., Koley D., Ravikumar K., Kundu B. (2013), Counter ion effect in Au/Ag-catalyzed chemoselective 6-endo-dig *N*- and *O*-cyclizations of enyne-urea system: Diversity-oriented synthesis of annulated indoles, *J. Org. Chem.*, 78, 8624-8633 (DOI:10.1021/jo4013332).

11. Dighe S. U., Mahar R., Shukla S. K., Kant R., Srivastava K., Batra S. (2016), Synthesis of *S*-(-)-5,6-dihydrocanthin-4-ones *via* a triple cooperative catalysis-mediated domino reaction, *J. Org. Chem.*, 81, 4751-4761 (DOI: 10.1021/acs.joc.6b00613).

12. Arigela R. K., Mandadapu A. K., Sharma S. K., Kumar B., Kundu B. (2012), Cascade intermolecular Michael addition-intramolecular azide/internal alkyne 1,3-dipolar cycloaddition reaction in one-pot, *Org. Lett.*, 14, 1804-1807 (DOI : 10.1021/ol300399y).

13. Holloway C. A., Muratore M. E., Storer R., Dixon D. J. (2010), Direct enantioselective brønsted acid catalyzed *N*-acyliminium cyclization cascades of tryptamines and ketoacids, *Org. Lett*., 12, 4720-4723 (DOI: 10.1021/ol101651t).

14. Purohit P., Pandey A. K., Kumar B., Chauhan P. M. S. (2016), Diversity oriented synthesis of β-carbolinone and indolo-pyrazinone analogues based on an Ugi four component reaction and subsequent cyclisation of the resulting indole intermediate, *RSC Adv*., 6, 21165-21186 (DOI: 10.1039/c5ra27090a).

15. Thikekar T. U., Selvaraju M., Sun C.-M. (2016), Skeletally diverse synthesis of indole-fused diazocine and diazepine frameworks by one-pot, two-component cascade reaction, *Org. Lett*., 18, 316-319 (DOI: 10.1021/acs.orglett.5b03481).

16. Jaiswal P. K., Biswas S., Singh S., Samanta S. (2013), An organocatalytic highly efficient approach to the direct synthesis of substituted carbazoles in water, *Org. Biomol. Chem*., 11, 8410-8418 (DOI: 10.1039/c3ob42034e).

17. Jaiswal P. K., Biswas S., Singh S., Pathak B., Mobin S. M., Samanta S. (2013), Stereoselective synthesis of highly functionalized tetrahydrocarbazoles through a domino Michael-Henry reaction: An easy access to four contiguous chiral centers, *RSC Adv*., 3, 10644-10649 (DOI : 10.1039/c3ra41409d).

18. Biswas S., Jaiswal P. K., Singh S., Mobin S. M., Samanta S. (2013), L-Proline catalyzed stereoselective synthesis of (*E*)-methyl-α-indol-2-yl-β-aryl/alkyl acrylates: Easy access to substituted carbazoles, γ-carbolines and prenostodione, *Org. Biomol. Chem*., 11, 7084-7087 (DOI: 10.1039/c3ob41573b).

19. Chen X.-Y., Wen M.-W., Ye S., Wang Z.-X. (2011), Unusual formal [4+2] cycloaddition of ethyl allenoate with arylidenoxindoles: Synthesis of dihydropyran-fused indoles, *Org. Lett*., 13, 1138-1141(DOI: 10.1021/ol103165y).

20. Ali S., Li Y.-X., Anwar S., Yang F., Chen Z.-S., Liang Y.-M. (2012), One-pot access to indolo[2,3-*b*]quinolines by electrophile-triggered cross-amination/Friedel-Crafts alkylation of indoles with 1-(2-tosylaminophenyl)ketones, *J. Org. Chem*., 77, 424-431 (DOI:10.1021/jo202035p).

21. Karkhelikar M. V., Rao V. V., Shinde S. S., Likhar P. R. (2016), A new synthetic approach to pyrrolo[3,2-*b*]indoles *via* regioselective formation of pyrrole and intramolecular C-N coupling, *Tetrahedron Lett*., 57, 4803-4806 (DOI: 10.1016/j.tetlet.2016.09.044).

22. Majumdar K. C., Taher A., Ray K. (2009), Domino-Knoevenagel-hetero-Diels-Alder reactions: An efficient one-step synthesis of indole-annulated thiopyranobenzopyran derivatives, *Tetrahedron Lett*., 50, 3889-3891 (DOI: 10.1016/j.tetlet.2009.04.054).

23. Jiang M., Li J., Wang F., Zhao Y., Zhao F., Dong X., Zhao W. (2012), A facile copper-catalyzed one-pot domino synthesis of 5,12-dihydroindolo[2,1-*b*]quinazolines, *Org. Lett*., 14, 1420-1423 (DOI:10.1021/ol3001624).

24. Hu J.-D., Cao C.-P., Lin W., Hu M.-H., Huang Z.-B., Shi D.-Q., (2014), Selective synthesis of polyfunctionalized pyrido[2,3-*b*]indoles by multicomponent domino reactions, *J. Org. Chem*., 79, 7935-7944 (DOI: 10.1021/jo501049m).

25. Xu S., Zhou Y., Xu J., Jiang H., Liu H. (2013), Gold-catalyzed Michael addition/intramolecular annulation cascade: An effective pathway for the chemoselective- and regioselective synthesis of

tetracyclic indole derivatives in water, *Green Chem*., 15, 718-726, (DOI: 10.1039/c2gc36301a).

26. Jha M., Davis C., Fazzari J., Vitali M. (2014), BF_3 etherate mediated microwave-assisted facile synthesis of thiopyrano[2,3-*b*]indol-2-one, *Tetrahedron Lett*., 55, 7043-7046 (DOI: 10.1016/j.tetlet.2014.10.131).

27. Moghaddam F. M., Ghanbari B., Behzadi M., Baghersad M. H. (2016), Synthesis of tetrahydrothiopyrano[2,3-*b*]indole [60]fullerene derivatives *via* Hetero-Diels-Alder reaction of C60 and α,β-unsaturated indole-2-thiones, *Journal of heterocyclic chemistry* (DOI: 10.1002/jhet.2653).

28. Arigela R. K., Sharma S. K., Kumar B., Kundu B. (2013), Microwave-assisted three-component domino reaction: Synthesis of indolodiazepinotriazoles, *Beilstein J. Org. Chem*., 9, 401-405 (DOI: 10.3762/bjoc.9.41).

29. Ohta Y., Chiba H., Oishi S., Fujii N., Ohno H. (2008), Concise synthesis of indole-fused 1,4-diazepines through copper(I)-catalyzed domino three-component coupling-cyclization-*N*-arylation under microwave irradiation, *Org. Lett*., 10, 3535-3538 (DOI: 10.1021/ol801383b).

30. Yang L., Wang F., Chua P. J., Lv Y., Zhong L.-J., Zhong G. (2012), *N*-Heterocyclic carbene (NHC)-catalyzed highly diastereo- and enantioselective oxo-Diels-Alder reactions for synthesis of fused pyrano[2,3-*b*]indoles, *Org. Lett*., 14, 2894-2897 (DOI: 10.1021/ol301175z).

31. Dagar A., Biswas S., Samanta S. (2015), A catalyst-free, efficient green MCR protocol for access to functionalized γ-carbolines in water, *RSC Adv*., 5, 52497-52507 (DOI : 10.1039/c5ra08422a).

32. Yu J., Zhang-Negrerie D., Du Y. (2016), $Cu(OAc)_2$-Mediated cascade annulation of diarylalkyne sulfonamides through dual C-N bond formation: Synthesis of 5,10-dihydroindolo[3,2-*b*]indoles, *Org. Lett*., 18, 3322-3325 (DOI: 10.1021/acs.orglett.6b01343).

33. Yu S., Li Y., Zhou X., Wang H., Kong L., Li X. (2016), Access to structurally diverse quinoline-fused heterocycles *via* Rhodium(III)-catalyzed C-C/C-N coupling of bifunctional substrates, *Org. Lett*., 18, 2812-2815 (DOI: 10.1021/acs.orglett.6b01032).

34. Chen X., Zhang J.-Q., Yin S.-J., Li H.-Y., Zhou W.- Q., Wang X.-W. (2015), Asymmetric construction of spiro[thiopyranoindole-benzoisothiazole] scaffold *via* a formal [3+3] spiroannulation, *Org. Lett*., 17, 4188-4191 (DOI: 10.1021/acs.orglett.5b01951).

35. Srivastava A., Biswas S., Singh S., Mobin S. M., Samanta S. (2015), Organocatalysed Michael addition on arylmethylidene malonates involving 4-(2-nitrophenyl)acetoacetate: Diversity-oriented access to 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one and salicylate scaffolds, *RSC Adv*., 5, 26891-26896 (DOI: 10.1039/c5ra01430a).

36. Abbiati G., Canevari V., Caimi S., Rossi E. (2005), Domino addition/annulation of δ-alkynylaldehydes and oxygen nucleophiles: A new entry to [1,4]oxazino[4,3-*a*]indoles, *Tetrahedron Lett*., 46, 7117-7120 (DOI: 10.1016/j.tetlet.2005.08.102).

37. Conreaux D., Belot S., Desbordes P., Monteiro N., Balme G. (2008), Et_3N-Induced demethylation-annulation of 3-alkynyl-4-methoxy-2-3-pyridones and structurally related compounds in the synthesis of furan-fused heterocycles, *J. Org. Chem*., 73, 8619-8622 (DOI: 10.1021/jo8014038).

38. Paul S., Pal G., Das A. R. (2013), Three-component synthesis of a polysubstituted pyrrole core containing heterocyclic scaffolds over magnetically separable nanocrystalline copper ferrite, *RSC Adv*., 3, 8637-8644 (DOI: 10.1039/c3ra40571k).

39. Ngo T. N., Akrawi O. A., Dang T. T., Villinger A., Langer P. (2015), Synthesis of pyrrolocoumarins *via* Pd-catalyzed domino C-N coupling/hydroamination reactions, *Tetrahedron Lett*., 56, 86-88 (DOI: 10.1016/j.tetlet.2014.11.007).

40. Pradhan K., Paul S., Das A. R. (2014), Magnetically retrievable nanocrystalline $CuFe_2O_4$ catalyzed multi-component reaction: A facile and efficient synthesis of functionalized dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives in aqueous media, *Catal. Sci. Technol*., 4, 822-831 (DOI: 10.1039/c3cy00901g).

41. Paul S., Bhattacharyya P., Das A. R. (2011), One-pot synthesis of dihydropyrano[2,3-*c*]chromenes *via* a three component coupling of aromatic aldehydes, malononitrile and 3-hydroxycoumarin catalyzed by nano-structured ZnO in water: A green protocol, *Tetrahedron Lett*., 52, 4636-4641 (DOI: 10.1016/j.tetlet.2011.06.101).

42. Kudale A. A., Kendall J., Miller D. O., Collins J. L., Bodwell G. J. (2008), Povarov reactions involving 3-aminocoumarins: Synthesis of 1,2,3,4-tetrahydropyrido[2,3-*c*]coumarins and pyrido[2,3-*c*]coumarins, *J. Org. Chem*., 73, 8437-8447 (DOI: 10.1021/jo801411p).

43. Das D. K., Sarkar S., Khan A. T., Saravanan P., Patra S. (2014), Synthesis of fused tetrahydropyrido[2,3-*c*]coumarin derivatives as potential inhibitors for dopamine d3 receptors, catalyzed by hydrated ferric sulfate, *RSC Adv*., 4, 3581-3590 (DOI: 10.1039/c3ra45174g).

44. Kalyanam N., Nagarajan A., Majeed M. (2004), A single step assembly of coumarin ring skeleton from oxygenated phenols and acetylenic esters by catalytic indium chloride in the absence of solvent, *Synth. Commun*., 34, 1909-1914 (DOI: 10.1081/SCC-120034175).

45. Paul S., Das A. R. (2012), A new application of polymer supported, homogeneous and reusable catalyst PEG-SO_3H in the synthesis of coumarin and uracil fused pyrrole derivatives, *Catal. Sci. Technol*., 2, 1130-1135 (DOI: 10.1039/c2cy20117h).

46. Khoshkholgh M. J., Lotfi M., Balalaie S., Rominger F. (2009), Efficient synthesis of pyrano[2,3-*c*]coumarins *via* intramolecular domino Knoevenagel hetero-Diels-Alder reactions, *Tetrahedron*, 65, 4228-4234 (DOI: 10.1016/j.tet.2009.03.032).

47. Khan A. T., Das D. K. (2012), Michael Initiated Ring Closure (MIRC) reaction on in situ generated benzylidene cyclohexane-1,3-diones for the construction of chromeno[3,4-*b*]quinoline derivatives, *Tetrahedron Lett*., 53, 2345-2351 (DOI: 10.1016/j.tetlet.2012.02.114).

48. Mohtat B., Nahavandian S., Razaghi M., Farsijani S., Djahaniani H. (2013), Triphenylphosphine mediated synthesis of functionalized benzo-fused coumarins from some OH acids and dialkylacetylene dicarboxylate, *Journal of Chemistry*, Article ID 289636, 5 pages (DOI: 10.1155/2013/289636).

49. Lee Y. R., Suk J. Y. (2002), Efficient synthesis of dihydrofurans and furans by rhodium(II)-catalyzed reactions of cyclic diazodicarbonyl compounds, *Tetrahedron*, 58, 2359-2367 (DOI: 10.1016/S0040-4020(02)00118-7).

50. Lee Y. R., Kim B. S., Wang H. C. (1998), Silver(I)/Celite promoted oxidative cycloaddition of 4-hydroxycoumarin to olefins; A facile synthesis of dihydrofurocoumarins and furocoumarins, *Tetrahedron*, 54, 12215-12222 (DOI: 10.1016/S0040-4020(98)00762-5).

51. Jang Y.-J., Syu S., Chen Y.-J., Yang M.-C., Lin W. (2012), Syntheses of furo[3,4-*c*]coumarins and related furylcoumarin derivatives *via* intramolecular Wittig reactions, *Org. Biomol. Chem*., 10, 843-847 (DOI: 10.1039/c1ob06571h).

52. Ghandi M., Ghomi A.-T., Kubicki M. (2013), Synthesis of pyrrole-fused chromanones *via* one-pot multicomponent reactions, *Tetrahedron*, 69, 3054-3060 (DOI: 10.1016/j.tet.2013.01.085).

53. Jian T.-Y., Chen X.-Y., Sun L.-H., Ye S. (2013), *N*-heterocyclic carbene-catalyzed [4+2] cycloaddition of ketenes and 3-aroylcoumarins: Highly enantioselective synthesis of dihydrocoumarin-fused dihydropyranones, *Org. Biomol. Chem*., 11, 158-163 (DOI: 10.1039/c2ob26804c).

54. Frolova L. V., Malik I., Uglinskii P. Y., Rogelj S., Kornienko A., Magedov I. V. (2011), Multicomponent synthesis of 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones: A novel heterocyclic scaffold with antibacterial activity, *Tetrahedron Lett*., 52, 6643-6645 (DOI: 10.1016/j.tetlet.2011.10.012).

55. Yu F.-C., Chen Z.-Q., Hao X.-P., Yan S.-J., Huang R., Lin J. (2014), Regioselective synthesis of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo-[1,2-*a*]pyridin-6-one derivatives, *RSC Adv*., 4, 6110-6115 (DOI: 10.1039/c3ra46428h).

56. Symeonidis T., Chamilos M., Hadjipavlou-Litina D. J., Kallitsakis M., Litinas K. E. (2009), Synthesis of hydroxycoumarins and hydroxybenzo[*f*]-or[*h*]coumarins as lipid peroxidation inhibitors,

Bioorganic & Medicinal Chemistry Letters, 19, 1139-1142 (DOI: 10.1016/j.bmcl.2008.12.098).

57. Symeonidis T. S., Kallitsakis M. G., Litinas K. E. (2011), Synthesis of [5,6]-fused pyridocoumarins through aza-Claisen rearrangement of 6-propargylaminocoumarins, *Tetrahedron Lett*., 52, 5452-5455 (DOI:10.1016/j.tetlet.2011.08.012).

58. Kidwai M., Priya, Rastogi S. (2008), Reaction of coumarin derivatives with nucleophiles in aqueous medium, *Z. Naturforsch*., 63b, 71-76.

59. Che C., Li S., Jiang X., Quan J., Lin S., Yang Z. (2010), One-pot syntheses of chromeno[3,4-*c*]pyrrole-3,4-diones *via* Ugi-4CR and intramolecular Michael addition, *Org. Lett*., 12, 4682-4685 (DOI: 10.1021/ol1020477).

60. Abdolmohammadi S., Balalaie S. (2007), Novel and efficient catalysts for the one-pot synthesis of 3,4-dihydropyrano[*c*]-chromene derivatives in aqueous media, *Tetrahedron Lett*., 48, 3299-3303 (DOI: 10.1016/j.tetlet.2007.02.135).

61. Khan A. T., Das D. K., Islam K., Das P. (2012), A simple and expedient synthesis of functionalized pyrido[2,3-*c*]coumarin derivatives using molecular iodine catalyzed three-component reaction, *Tetrahedron Lett*., 53, 6418-6422 (DOI: 10.1016/j.tetlet.2012.09.051).

62. Symeonidis T. S., Litinas K. E. (2013), Synthesis of methyl substituted [5,6]-and [7,8]-fused pyridocoumarins *via* the iodine-catalyzed reaction of aminocoumarins with *n*-butyl vinyl ether, *Tetrahedron Lett*., 54, 6517-6519 (DOI: 10.1016/j.tetlet.2013.09.089).

63. Henry C. E., Kwon O. (2007), Phosphine-catalyzed synthesis of highly functionalized coumarins, *Org. Lett.*, 9, 3069-3072 (DOI: 10.1021/ol071181d).

Chapter 2

Rapid access to 2,3,4-trisubstituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives *via* one-pot three component reaction using organocatalysis

2.1 Introduction

Highly efficient synthesis of functionalized indole derivatives have attracted significant attention in recent years because this key moiety provides access to a large number of bioactive natural products and pharmacophores.[1-7] Literature survey shows that additional cyclic ring on indole ring also constitutes a large number of biologically active natural compounds.[8] They show a broad spectrum of pharmacological activities including CNS disorders (e.g. Alzheimer's disease), hormone replacement therapy and oxidative stress etc.[9-10] In addition, indole derivatives have been widely used in material science, agrochemicals, polymer, etc.[11-12] Among them, fused indole derivatives possessing tetrahydrothiopyran heterocyclic systems are important privileged structures on account of their application in medicinal fields. For example, tetrahydrothiopyrano[2,3-*b*]indoles (**I-IV**) exhibit analgesic activity[13-14] and salts of some tetrahydrothiopyrano[2,3-*b*]indoles are used as psychoanaleptic and nootropic drugs (**Figure 2.1**).[15]

Thus, efficient one-pot synthesis of mentioned compounds applying multi-component reaction (MCR) strategy is crucial for synthetic organic chemists nowadays, as it eliminates the isolation of intermediates in each step making the procedure more economical and environmental benign. In this direction, several organic and medicinal chemists have been devoted towards the access to tetrahydrothiopyranoindole scaffolds.

Some of the important literature reports have been discussed in the review section **2.2**.

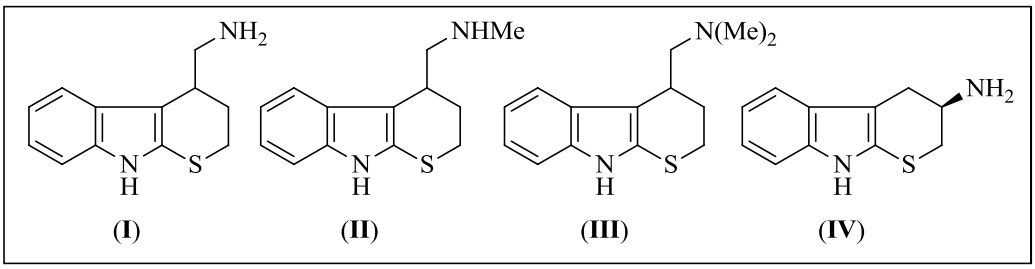
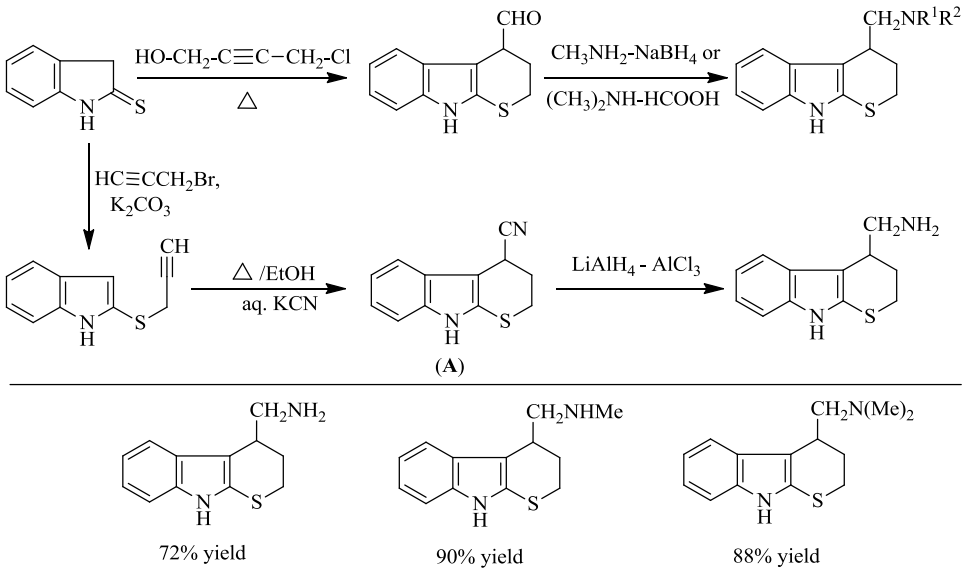


Figure 2.1 Several biologically active molecules containing the tetrahydrothiopyrano[2,3-*b*]indole skeleton

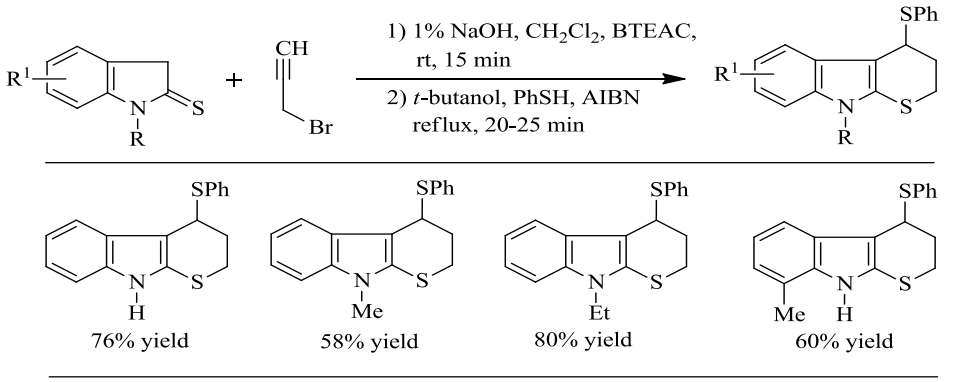
2.2 Review work

In 1984, the first cyclization strategy includes novel synthesis of 4-aminomethyltetrahydrothiopyrano[2,3-*b*]indoles through a thio-Claisen rearrangement revealed by Makisumi *et al*., where they have reported two methods for the preparation of thiopyrano[2,3-*b*]indoles in good yields.[16] Both the methods involve thio-Claisen rearrangement of indol-2-ylpropargyl sulfides as a key step. Here, indol-2-yl propargyl sulfide was prepared in good yield from indoline-2-thione and propargyl bromide using K_2CO_3 as a base. Thermolysis of indol-2-yl propargyl sulfide in refluxing ethanol, followed by treatment with aq. KCN to provide 4-cyanotetrahydrothiopyrano[2,3-*b*]indole (**A**). Further reduction of nitrile (**A**) to 4-aminomethyltetrahydrothiopyrano[2,3-*b*]indoles has been achieved by using a mixture of $LiAlH_4$-$AlCl_3$ as shown in **Scheme 2.1**.



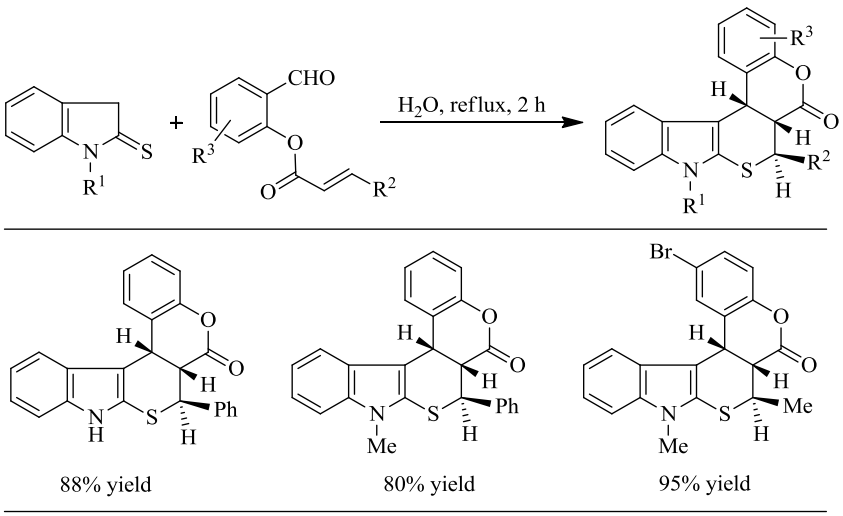
Scheme 2.1 Synthesis of 4-aminomethyltetrahydrothiopyrano[2,3-*b*]indoles through a thio-Claisen rearrangement

In 2007, Majumdar *et al.* also revealed two step synthetic methods for the synthesis of racemic versions of 4-thiophenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles *via* a nucleophilic substitution reaction between indoline-2-thiones and propargyl bromide using phase transfer catalyst (benzene triethyl ammonium chloride) in the presence of NaOH, followed by the addition/cyclization of resultant compound with thiophenol in refluxing *tert*-butanol using AIBN as a radical initiator (**Scheme 2.2**).[17]



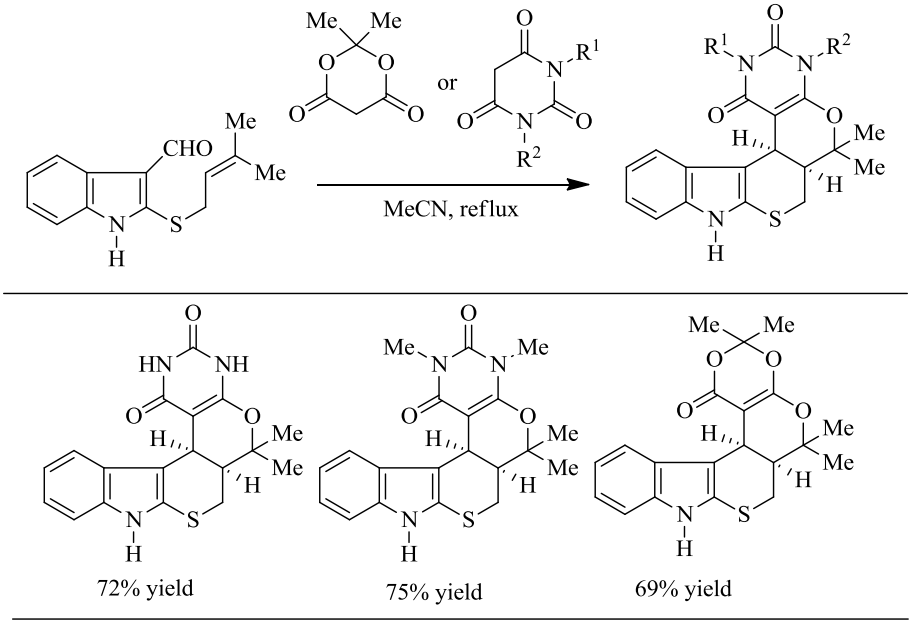
Scheme 2.2 Thiol-mediated radical cyclization of substituted indoline-2-thiones

A closer inspection into the literature also showed that efficient synthesis of dihydrothiopyrano ring annulated with a dihydrocoumarin was achieved *via* domino Knoevenagel-hetero-Diels-Alder reaction of *O*-acrylated salicylaldehyde derivatives with dihydroindole-2-thiones in H_2O as reported by Moghaddam and his associates.[18] The products are formed in good to excellent yields (82-93%) with high regio- and stereoselectivity (always *cis*-fusion), which was determined from the coupling constants of the relevant H-atoms and NOE experiments as shown in **Scheme 2.3**.



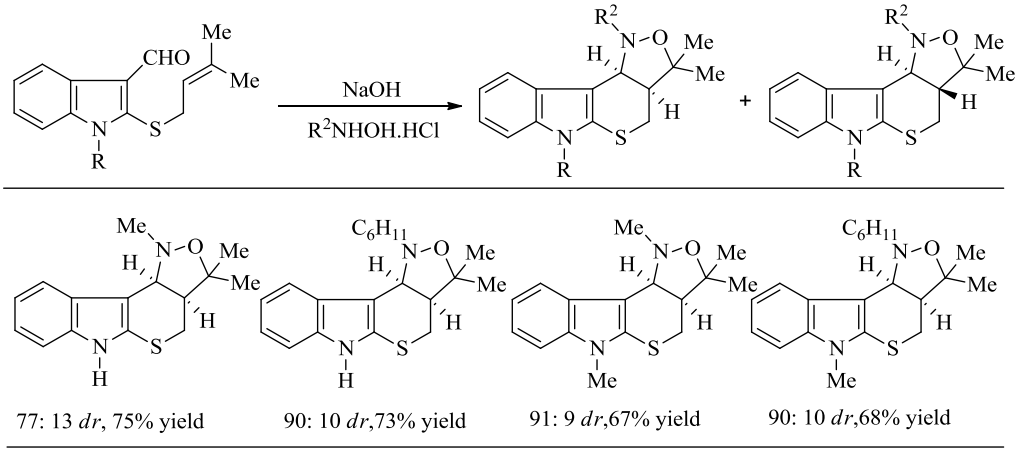
Scheme 2.3 Domino Knoevenagel-hetero-Diels-Alder and multi-component reactions of indoline-2-thione

Majumder *et al.* established a nice intramolecular domino hetero Diels-Alder reactions for the synthesis of novel polycyclic thiopyrano[2,3-*b*]indole derivatives by performing the reaction between 3-formyl-2-S-alkenylindole with *N,N*-dimethylbarbituric acid/Meldrum's acid in refluxing methanol as shown in **Scheme 2.4.**[19]



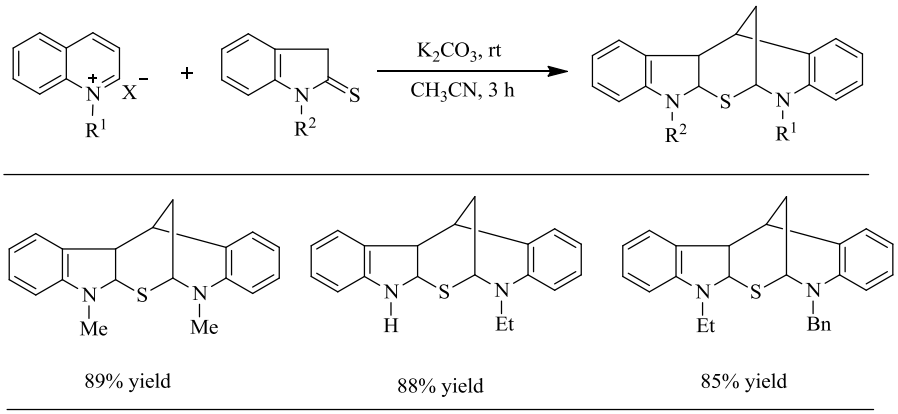
Scheme 2.4 Synthesis of pentacyclic indoles *via* [4+2] hetero Diels-Alder reaction

In 2012, Bhuyan *et al*. disclosed the stereoselective synthesis of a series of novel isoxazolidine/dihydroisoxazole annulated thiopyrano[2,3-*b*]indole derivatives in good yields (67-75%) from simple indolo-S-alkenyl aldehyde *via* 1,3-dipolar cycloaddition reaction with alkylhydroxyl amine in the presence of NaOH (**Scheme 2.5**).[20]



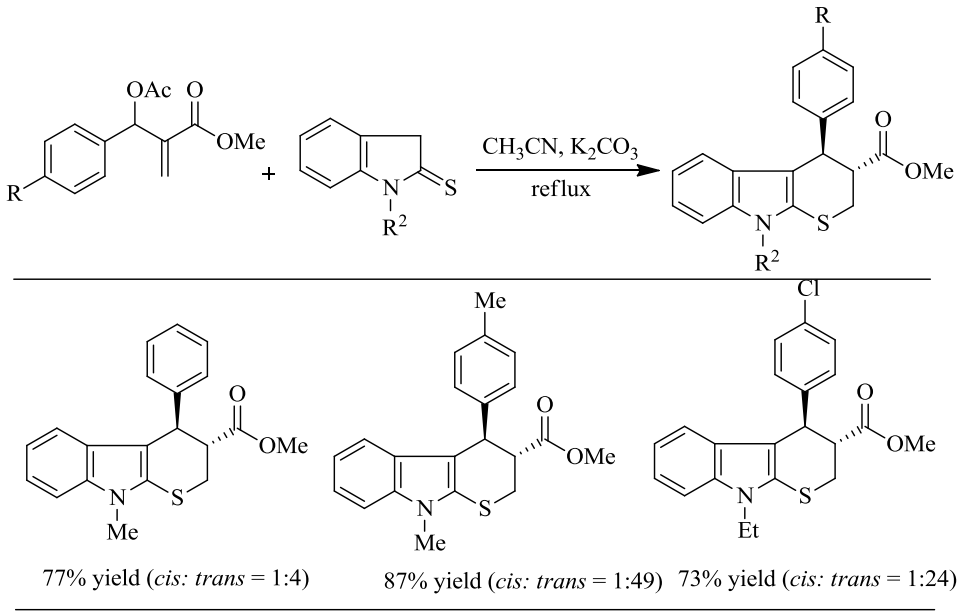
Scheme 2.5 Synthesis of novel tetrahydroisoxazole and dihydroisoxazole fused thiopyrano[2,3-*b*]indole derivatives

Moghaddam and his coworkers also established a one-pot synthesis of indole-annulated pentacyclic indolyl hydroquinolines via a tandem C-alkylation and intramolecular S-alkylation of indolin-2-thiones with N-alkylquinolinium salts in MeCN using K_2CO_3 at room temperature. This reaction provides excellent yields (83-95%) of corresponding pentacyclic compounds with a short span of time as shown in the **Scheme 2.6**.[21]



Scheme 2.6 Tandem alkylation reaction of N-alklylquinolium salts with indoline-2-thiones

Another excellent report on the stereoselective synthesis of tetrahydrothiopyrano[2,3-*b*]indoles *via* a tandem reaction of Baylis-Hillman acetates as 1,3-bielectrophiles with indolin-2-thiones in MeCN promoted by K_2CO_3 under refluxing conditions was developed by Moghaddam and his coworkers.[22] The corresponding products were obtained in high yields (73-87%) with high to excellent distereoselectivities (1:4 to 1:49 *dr*) as shown in **Scheme 2.7**.



Scheme 2.7 The stereoselective synthesis of tetrahydrothiopyrano[2,3-*b*]indole skeletons *via* tandem reaction of indoline-2-thiones

Conclusion

Review work suggested that a quite number of methods have been reported for the preparations of tetrahydrothiopyrano[2,3-*b*]indole skeletons with moderate to high yields and good diastereoselectivities. However, some of the above methods encompass several disadvantages such as harsh reaction conditions, multiple steps, low yields and less substrate scopes. Furthermore, some reports utilize harmful organic solvents like CH_2Cl_2, CH_3CN etc. which produces atrocious effects on environment. Moreover, indoline-2-thiones have been used as starting materials for S-source reagents, which retard the substrate scope. Furthermore, a little attention has been paid for the synthesis of 2,3,4-trisubstituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles. Therefore, it is a great oppourtunity to develop a simple, efficient, organocatalytic one-pot synthetic protocol for the synthesis of both the racemic and enantio-enriched versions of 2-aryl-3-nitro-4-hydroxytetrahydrothiopyrano[2,3-*b*]indoles possessing three contiguous chiral centers from simple starting

materials under mild conditions in a rapid and productive manner as shown in **Figure 2.2**.

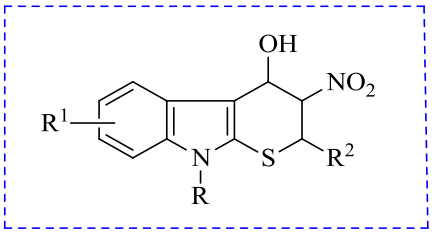


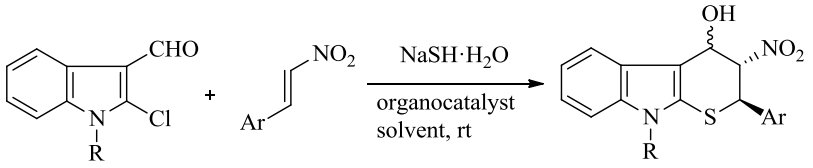
Figure 2.2 Representative structure of 2,3,4-trisubstituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole

2.3 Present work

The efficient synthesis of fused indole derivatives has been rapidly growing interest in synthetic organic chemistry due to their biological importance, which motivates many organic chemists to develop the practical methods for their synthesis. The indoles possessing fused thiopyrane annulated heterocyclic systems are important privileged structures of many biologically active compounds as discussed in the introduction part **2.1**. Owing to their biological activities, several non-asymmetric methods have been documented as mentioned in the review section. Nonetheless, even with considerable progress, organocatalytic non-asymmetric as well as enantioselective method for the synthesis of 2-aryl-3-nitro-4-hydroxytetrahydrothiopyrano[2,3-*b*]indole is still missing. Therefore, it would be highly desirable to synthesize both the racemic and enantio-enriched versions of above-mentioned compound in a more practical and efficient manner.

Nowadays, MCRs have become a traditional strategy for rapid access to the natural products,[23-28] drug discovery, in combinatorial and medicinal chemistry.[29-31] As part of our continued interest in the development of organocatalytic mediated asymmetric/non-asymmetric synthetic

transformations in an environment friendly manner,[32-37] we reported a Henry reaction for enantioselective as well as racemic *β*-nitro-α-hydroxyphosphonates by using quinine derivatives[38] and DABCO[39] as catalysts respectively. There are several reports for organocatalytic enantioselective tandem Michael-Henry reactions. Zhao and other groups reported one-pot catalytic enantioselective tandem thio-Michael-Henry or aldol reactions for the synthesis of thiochromes, where starting material has both a nucleophilic and an electrophilic sites. Therefore, we envisioned that thiopyrane ring can be installed on indole moiety through a nucleophilic thiolation and tandem thio-Michael-Henry involving N-protected-2-chloro-3-formylindoles as bielectrophiles, $NaSH \cdot H_2O$ and nitroolefins in the presence of base. Herein we now disclose an organocatalytic, one-pot three component aromatic nucleophilic thiolation and tandem thio-Michael-Henry reaction involving N-protected-2-chloro-3-formylindole for the stereoselective synthesis of 2-aryl-3-nitro-4-hydroxy-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives using a catalytic amount of DABCO as an organocatalyst (**Scheme 2.8**).



R = H, **1a**
R = Boc, **1b**
R = CO_2Et, **1c**

Scheme 2.8 One-pot three-component tandem aromatic thiolation/ Michael-Henry reaction.

2.4 Results and Discussion

2.4.1 Screening of Solvents and Catalysts

By using 1-Boc-2-chloro-3-formylindole (**1b,** 0.25 mmol), $NaSH \cdot H_2O$ (0.3 mmol) and *trans-β*-nitrostyrene (**2a,** 0.3 mmol) as the model substrates, reaction was carried out in the absence of catalyst in MeOH for 30 min at room temperature. We isolated N-Boc-2-phenyl-3-nitro-4-

hydroxy-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole **3** (**Table 2.1**) in 69% yield with a mixture of only two non-separable (by column chromatography) diastereomers in a ratio of 44:56, even though product bears three contiguous chiral centers. The product was well characterized by its ^{1}H NMR which shows the appearance of characteristic doublets and multiplets in region (δ 5.02-5.78) along with disappearance of characteristic aldehyde peak of **1b** (δ 10.30). The relative configurations of the product **3a** and **4a** were assigned by the coupling constant of the vicinal H-atoms (**Figure 2.3**). For instance, in both the isomers **3a** and **4a**, H_2 and H_3 (J =11.2 Hz) are in *trans*-form, whereas in compound **3a**, H_3 and H_4 (J = 3.5 Hz) are in *cis*-relation. However, in case of compound **4a**, H_3 and H_4 (J = 9.0 Hz) are in *trans*-conformation. Thus, the fate of the diastereomeric ratio depends by the orientation of hydroxyl group. Further, ^{13}C NMR shows appearance of diastereomeric peaks in the aromatic and aliphatic regions with the disappearance of aldehyde peak (δ 185.7). The HRMS spectrum shows the presence of molecular ion peak $[M+Na]^+$ at 449.1143 which corresponds to the molecular weight of the desired product.

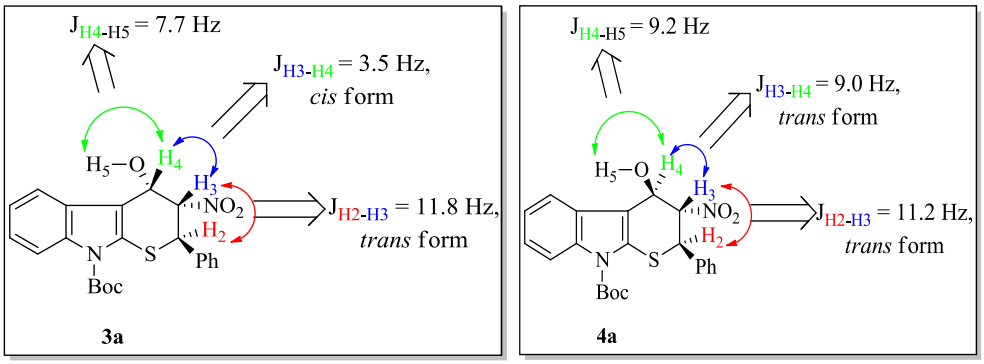
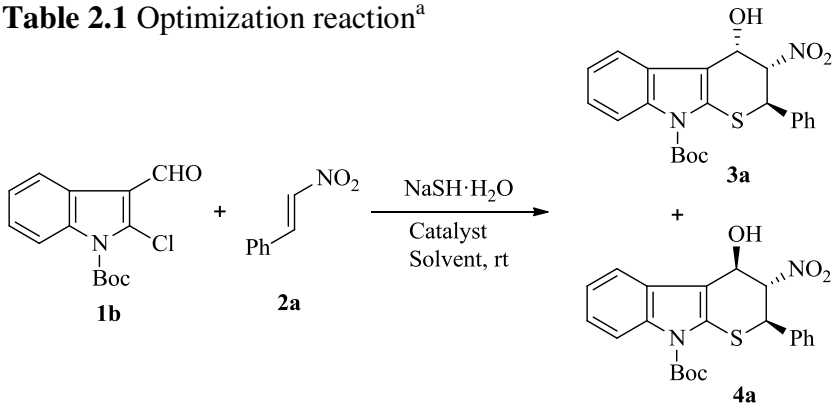


Figure 2.3 Showing coupling constant of **3a** and **4a**

The same phenomenon was also found when the reaction was conducted in EtOH medium. Gratifyingly, the above interesting result motivated us to investigate for this one-pot multi-component reaction in details. In order to evaluate the effects of base on this reaction, we used common organic

bases (5 mol%) as catalysts, namely DABCO, Et_3N, DBU and quiniclidine in EtOH medium. In terms of reactivity, DABCO was the best catalyst for this reaction.

Table 2.1 Optimization reaction[a]



Entry	Catalyst	Solvent	Time (min)	*dr*[b] **3a**:**4a**	Yield[c] (%)
1	Nil	MeOH	30	44:56	69
2	Nil	EtOH	30	47:53	65
3[d]	Nil	H_2O	60	ND	<5
4[d]	DABCO	H_2O	30	ND	<15
5	DABCO	MeOH	10	55:45	89
6	**DABCO**	**EtOH**	**12**	**54:46**	**87**
7	Quiniclidine	EtOH	20	52:48	77
8	DBU	EtOH	20	56:44	81
9	Et_3N	EtOH	20	45:55	75
10	DABCO	THF	30	40:60	40
11	DABCO	Et_2O	140	30:70	71
12	DABCO	CH_3CN	30	55:45	50

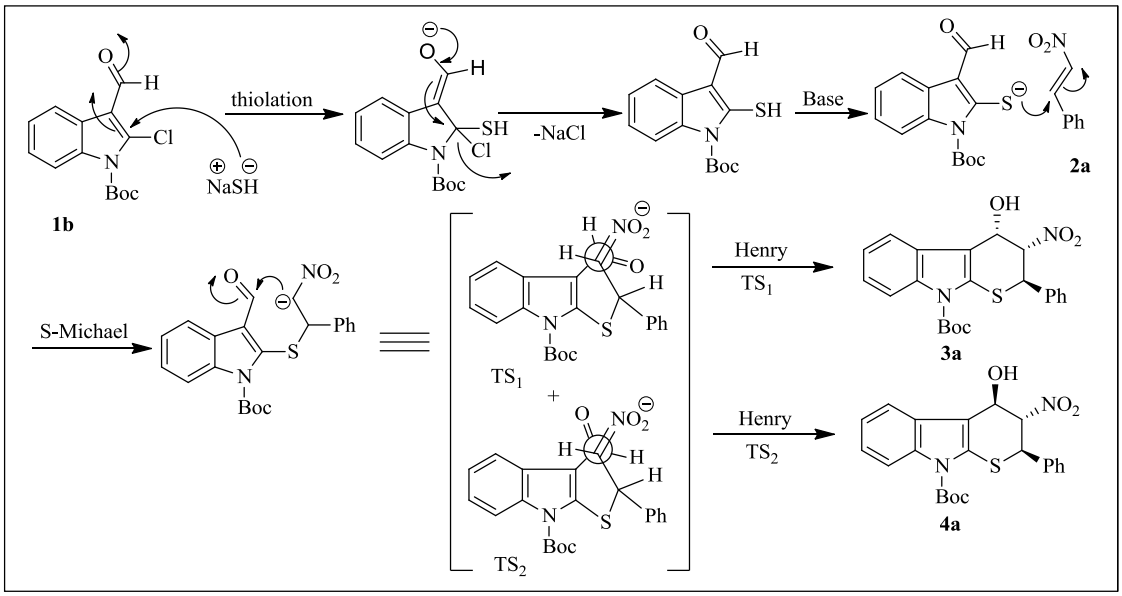
[a]Unless otherwise specified, all reactions were carried out at room temperature with **1b** (0.25 mmol), $NaSH·H_2O$ (0.3 mmol), **2a** (0.3 mmol) and catalyst (5 mol %) in the

specified solvent (2.0 ml). [b]Diastereomeric ratio was determined of the crude product by ^{1}H NMR and their relative configurations of isomers were determined by the coupling constant of the corresponding vicinal H-atoms. [c]Yield of the product was isolated after column chromatography. [d]ND = Not Determined

Next, we investigated the effects of solvents on this reaction. The reaction was witnessed to be much slower in non-protic solvents, such as THF, Et_2O and MeCN. However, reverse configuration of major diastereomer was obtained. In water medium, the reaction was very sluggish. It should be pointed out that the reactivity in MeOH was slightly higher than EtOH. In spite of that EtOH was chosen as the best solvent due to its environmental benign character.

2.4.2 Proposed mechanism

A possible mechanism for the formation of compounds **3a** and **4a** is depicted in **Scheme 2.9**.



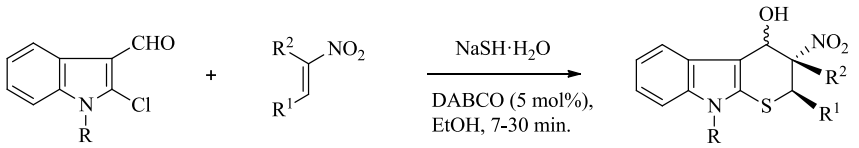
Scheme 2.9 Possible mechanism for one-pot aromatic nucleophilic thiolation/tandem thio-Michael-Henry reaction

At first, 2-mercapto-3-formylindole is generated in situ by the combination of compound **1b** and $NaSH \cdot H_2O$ through aromatic nucleophilic thiolation, which undergoes thio-Michael addition to *β*-nitrostyrene and subsequent intramolecular Henry reaction *via* transition state 1 and 2 (TS_1 and TS_2) to affords **3a** and **4a** respectively from corresponding TS_1 and TS_2 (**Scheme 2.9**).

2.4.3 Substrate scope of this methodology

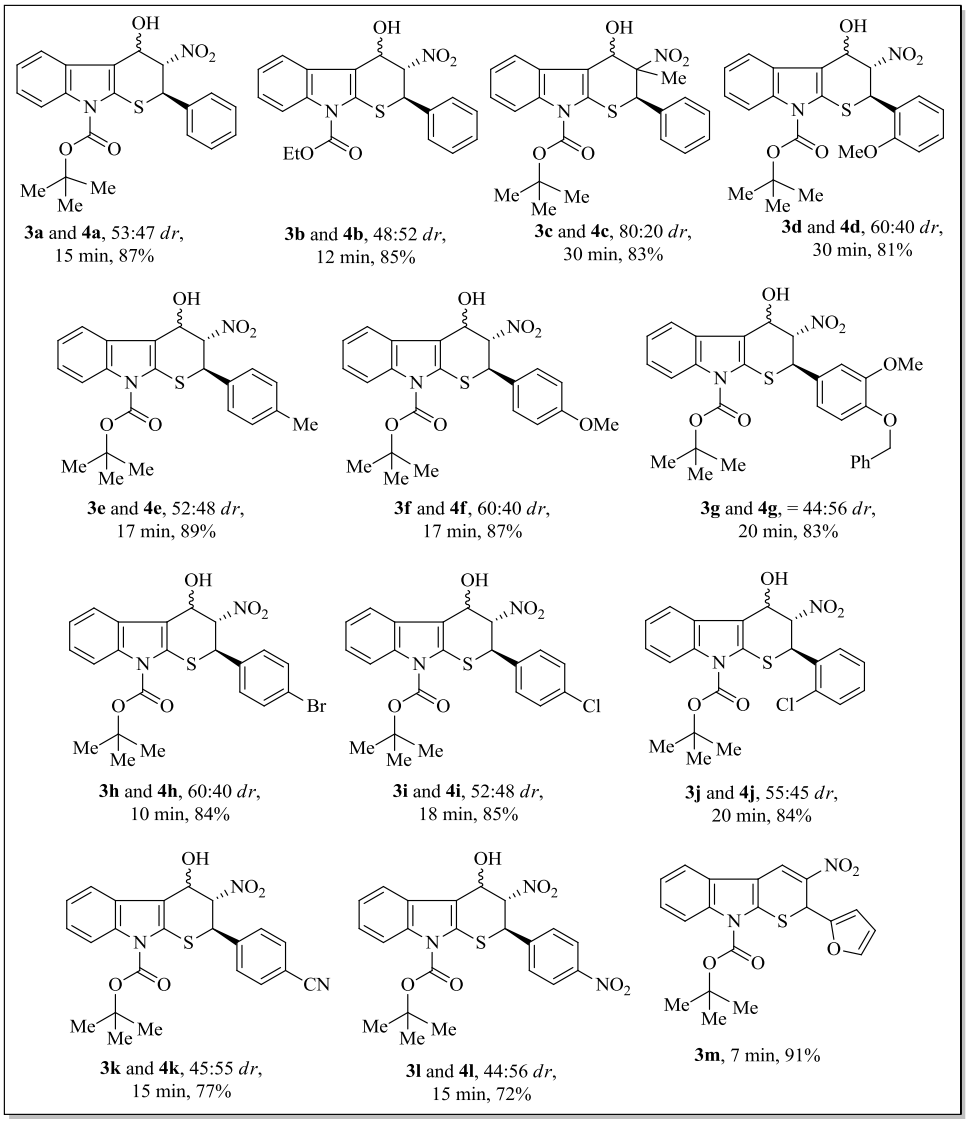
We studied scope and limitation of the one-pot aromatic nucleophile thiolation and tandem thio-Michael-Henry reaction by performing the reaction of a wide range of structurally varied *β*-nitrostyrenes with diverse steric and stereoelectronic environment, $NaSH \cdot H_2O$ and 2-chloro-3-formylindole derivatives **1a-c** using DABCO as a catalyst (5 mol %) at our standard reaction conditions. The results are compiled in **Table 2.2**. As is evident from **Table 2.2**, the unprotected indole derivative **1a** did not participate in this reaction due to very poor electrophilic center at 2-position of indole ring, which retards the thiolation reaction. Therefore, we studied further N-protected indole derivatives **1b-c** with various *β*-nitrostyrenes. All the reactions led to the desired 2-aryl-3-nitro-4-hydroxy-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives in good to excellent yields within short duration of times (12-30 min). Among the series of investigations, only two non-separable diastereomers were generated as calculated by ^1H NMR analyses of the crude products. The relative configurations of major and minor isomers are *trans-cis* and *trans-trans* 'respectively'. It should be noted that *trans*-β-nitrostyrenes with electron withdrawing groups (NO_2 and CN) at the *para*-positions of aryl rings gave the corresponding products with slightly lower yields in comparison with others. It was due to the formation of noticeable amount of dehydrated products (>10%).

Table 2.2 DABCO catalyzed one-pot synthesis of 2-aryl-3-nitro-4-hydroxy-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives[a]



2a-l **3a-m** + **4a-m**

R = Boc, **1b** **2a** (R^1 = Ph, R^2 = H), **2b** (R^1 = Ph, R^2 = Me),
R = CO_2Et, **1c** **2c** (R^1 = 2-MeOC_6H_4, R^2 = H), **2d** (R^1 = 4-MeC_6H_4, R^2 = H),
2e (R^1 = 4-MeOC_6H_4, R^2 = H), **2f** (R^1 = 3-MeO-4BnOC_6H_3, R^2 = H),
2g (R^1 = 4-BrC_6H_4, R^2 = H), **2h** (R^1 = 4-ClC_6H_4, R^2 = H),
2i (R^1 = 2-ClC_6H_4, R^2 = H), **2j** (R^1 = 4-CNC_6H_4, R^2 = H),
2k (R^1 = 4-$NO_2C_6H_4$, R^2 = H), **2l** (R^1 = 2-furyl, R^2 = H)



3a and **4a**, 53:47 *dr*, 15 min, 87%

3b and **4b**, 48:52 *dr*, 12 min, 85%

3c and **4c**, 80:20 *dr*, 30 min, 83%

3d and **4d**, 60:40 *dr*, 30 min, 81%

3e and **4e**, 52:48 *dr*, 17 min, 89%

3f and **4f**, 60:40 *dr*, 17 min, 87%

3g and **4g**, = 44:56 *dr*, 20 min, 83%

3h and **4h**, 60:40 *dr*, 10 min, 84%

3i and **4i**, 52:48 *dr*, 18 min, 85%

3j and **4j**, 55:45 *dr*, 20 min, 84%

3k and **4k**, 45:55 *dr*, 15 min, 77%

3l and **4l**, 44:56 *dr*, 15 min, 72%

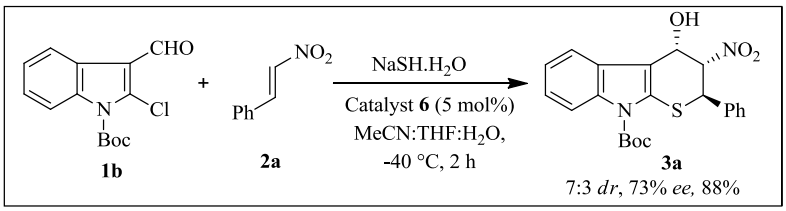
3m, 7 min, 91%

[a]Unless otherwise specified, all reactions were conducted at room temperature with **1b-c** (0.25 mmol), $NaSH \cdot H_2O$ (0.3 mmol), substituted *trans-β*-nitrostyrenes **2a-l** (0.3 mmol) and DABCO (5 mol%) in EtOH (2.0 ml).Diastereomeric ratio was determined of the crude product by ^1H NMR and their relative configurations of isomers were determined by the coupling constant of the corresponding vicinal H-atoms.Yield of the product was isolated after column chromatography.The relative configuration of major isomer was unknown. Product (**3m**) was isolated as a dehydrated form.

Notably, α-methyl-β-nitrostyrene was also a suitable Michael acceptor for this MCR reaction, generating product in high yield (83%) and better diastereoselectivity (80:20). Significantly, the tetrahydrothiopyrane ring possesses one quaternary carbon center at 3-position. Our mild reaction conditions tolerate several sensitive functional groups such as Boc, CO_2Et, furan, MeO, BnO, Br, Cl, CN, NO_2 etc. It should be mentioned that we have isolated the dehydrated product in 91% yield when 2-(2-nitrovinyl) furan was used as a Michael acceptor.

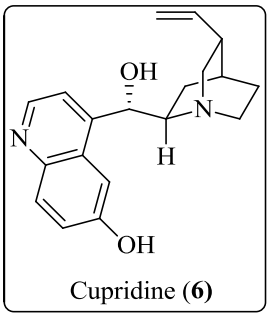
2.4.4 Enantioselective synthesis

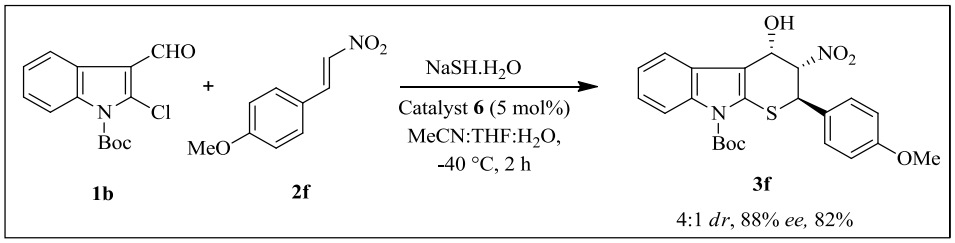
In principle, this reaction may be made enantioselective by using optically active congeners of DABCO such as quinidine or quinine, which are well known H-bonding catalysts for various enantioselective reactions.[40-52] In this direction, we tested several easily available quinidine derivatives as catalysts (catalysts **5**-**8, Figure 2.4**) for enantioselective synthesis of compound **3**. We were pleased to observe that at -40 °C, a mixture of MeCN/THF/H_2O (1:1:0.02) and cupridine (catalyst **6**) were the best conditions for such a reaction. As shown in **Table 2.2**, the reaction with **1b**, $NaSH \cdot H_2O$ and **2a** proceeded smoothly in above mixture of solvents using 5 mol% loading of catalyst **6**. After 2 h, we isolated the desired product **3** in 88% yield with diastereomeric ratio (7:3) and the enantioselectivity of major isomer **3a** was 73%.



Scheme 2.10 Enantioselective synthesis of **3a** using Cupridine (catalyst **6**)

Interestingly, better enantioselectivity (88%) was achieved by using *trans*-β-4-methoxynitrostyrene under similar reaction conditions without compromising the yield and diastereomeric ratio. The absolute configuration of the major diastereomer was not determined.





Scheme 2.11 Enantioselective synthesis of **3f** using Cupridine (catalyst **6**)

2.5 Conclusion

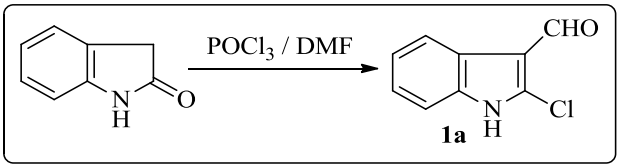
In conclusion, a simple, green and efficient one-pot three component strategy for the both racemic and enantioselective versions of N-protected-2-aryl-3-nitro-4-hydroxy-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives bearing contiguous three chiral centers with good to excellent yields and high enantioselectivities (*ee* >88%) has been achieved by the combination of N-protected-2-chloro-3-formylindoles, sodium hydrosulfide with β-nitrostyrenes at room temperature in ethanol using DABCO as an organo base. This method offers notable advantages such as catalytic, low catalyst loading, fast reaction, clean, mild and broad substrate scope.

2.6 Experimental

General Information

All reactions were carried out under air and monitored by TLC using Merck 60 F_{254} pre coated silica gel plates (0.25 mm thickness) and the products were visualized by UV detection. Flash chromatography was carried out with silica gel (200-300 mesh). FT-IR spectra were recorded on a Bruker Tensor-27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BrukerAvance (III) 400 MHz spectrometer. Data for ^{1}H NMR are reported as a chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constant *J* (Hz), integration and assignment, data for ^{13}C are reported as a chemical shift. High resolutions mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. HPLC analysis was performed on a YL-9100 HPLC, UV detection monitored at appropriate wavelength respectively, using Chiralcel AD-H (0.46 cm x 25 cm) column.

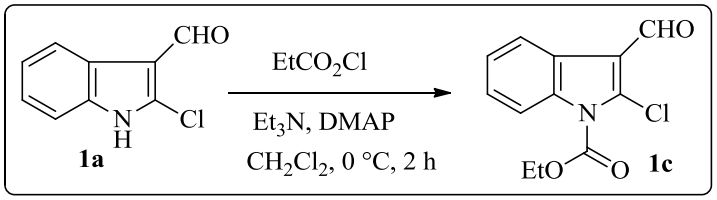
Synthesis of starting materials (1a): The compound 2-chloro-3-formylindole (**1a**) has been synthesized from 2-oxoindole using literature procedure.[53]



Scheme 2.12 Synthesis of 2-chloro-3-formylindole (**1a**)

Synthesis of ethyl 2-chloro-3-formyl-1*H*-indole-1-carboxylate (1c): To a stirred solution of compound 2-chloro-3-formylindole (**1a**, 1.0 mmol), Et_3N (3.0 mmol) and DMAP (0.1 mmol) at 0 ºC in CH_2Cl_2 has added ethyl chloroformate (1.2 mmol) at the same temperature. The stirring was continued for 2 h and then the reaction

mixture was extracted with CH_2Cl_2 before being quenched with water. Evaporation of the solvent left the crude product which was purified by column chromatography over silica-gel to furnish the pure product (184 mg, 73%). The product was characterized by IR, ^{1}H NMR, ^{13}C NMR and MS. **IR** (KBr) ν 1760, 1672, 1526, 1481, 1448 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.30 (s, 1H), 8.32 (m, 1H), 8.07 (m, 1H), 7.41 (m, 2H), 4.63 (q, *J* = 7.2 Hz, 2H), 1.57 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 185.7, 149.8, 135.6, 135.1, 126.1, 125.2, 124.6, 121.19, 117.9, 114.9, 64.8, 14.2; **HRMS** (ESI) m/z calculated for $C_{12}H_{10}NO_3Cl[M+Na]^+$: 274.0241, found 274.0312.



Scheme 2.13 Synthesis of ethyl 2-chloro-3-formyl-1*H*-indole-1-carboxylate (**1c**)

Synthesis of *β*-nitrostyrenes: All *β*-nitrostyrenes either synthesized by literature known procedure or purchased from commercial sources**.**

Synthesis of catalysts: All the catalysts have been synthesized from well known literature procedures.[54]

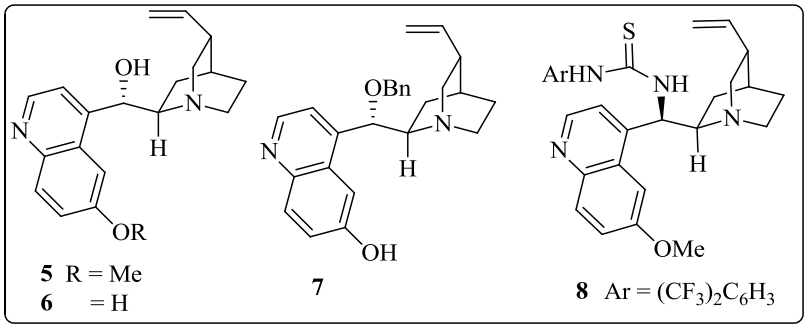
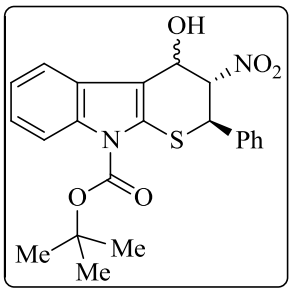


Figure 2.4 Catalysts used to determine enantiomeric excess

General experimental procedure for the synthesis of N-protected-2-aryl-3-nitro-4-hydroxy-2,3,4,9-tetrahydro-thiopyrano[2,3-*b*]indole derivatives:

To a stirred mixture of N-protected-2-chloro-3-formylindole (**1b**, 0.25 mmol), $NaSH \cdot H_2O$ (0.3 mmol) and *trans*-β-nitrostyrenes (**2a**, 0.3 mmol) in EtOH (2 ml) was added catalyst DABCO (5.0 mol%) at room temperature. After completion (monitored by TLC), EtOH was evaporated by rotary evaporator under vacuum. The crude product was extracted with ethyl acetate, washed with water, dried over Na_2SO_4. The evaporation of the organic solvent left the crude product, which was further purified by column chromatography over-silicagel using EtOAc/hexane as solvent mixtures to furnish the pure product. All the products were characterized by their corresponding spectroscopic data (IR, ^1H and ^{13}C NMR, MS). The diastereomeric ratio was determined by ^1H NMR spectrum and relative configurations were determined by coupling constant (*J*) values of the corresponding vicinal H-atoms.

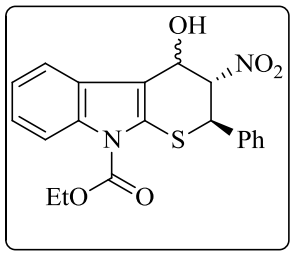
9-(N-*tert*-butoxycarbonyl)-4-hydroxy-3-nitro-2-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3a & 4a): 87% yield; **IR** (KBr) ν



3450, 2981, 2923, 1724, 1635, 1556, 1476, 1450, 1368 cm^{-1}; **^1H NMR (400 MHz, acetone-d_6)** δ (mixture of two diastereomers) 8.01-8.05 (m, 1H), 7.78-7.80 (m, 0.5H), 7.56-7.65 (m, 2.5H), 7.35-7.45 (m, 3H), 7.22-7.29 (m, 2H), 5.79 (dd,J_1= 3.5 Hz,J_2 = 11.8 Hz, 0.53H), 5.64-5.71 (m, 1H), 5.56 (dd,J_1= 9.0 Hz,J_2 = 11.2 Hz, 0.47H), 5.29 (d,J= 9.2 Hz, 0.47H), 5.24 (d,J = 7.7 Hz, 0.53H), 5.19 (d,J = 11.8Hz, 0.53H), 5.02 (d,J = 11.2 Hz, 0.47H), 1.68 (br s, 9H); **^{13}C NMR (100 MHz, acetone-d_6)** δ **(compound 3a)** 150.6, 137.5, 136.5, 131.4, 130.6, 129.8, 129.6(2C), 129.4, 124.6, 124.2, 118.2, 115.9, 114.9, 90.6, 86.6, 64.3, 42.9, 28.2; **^{13}C NMR (100 MHz, acetone-d_6)** δ **(compound 4a)** 150.7, 136.4, 135.4, 134.1, 130.2, 130.1, 129.9(2C), 129.5, 124.9, 124.0, 120.3, 115.8, 115.6,

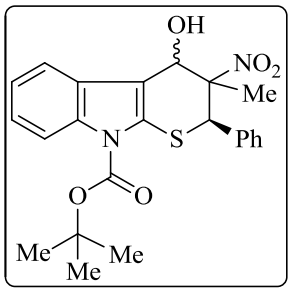
95.7, 86.6, 70.4, 49.6, 28.2; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{22}N_2O_5S$ $[M+Na]^+$: 449.1147, found: 449.1143.

9-(N-ethoxycarbonyl)-4-hydroxy-3-nitro-2-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3b & 4b): 85% yield; **IR** (KBr) ν



3484, 3053, 2982, 1715, 1635, 1554, 1478, 1450, 1405, 1377, 1348, 1318; **^{1}H NMR (400 MHz, acetone-d_6)** δ (mixture of two diastereomers) 8.05-8.09 (m, 1H), 7.78-7.79 (m, 0.5H), 7.56-7.66 (m, 2.5H), 7.42-7.46 (m, 3H), 7.26-7.32 (m, 2H), 5.81 (dd, J_1 = 3.2 Hz, J_2 =12.0 Hz, 0.45), 5.66-5.68 (m, 1H), 5.70 (dd, J_1 = 8.8 Hz, J_2 =11.2 Hz, 0.55H), 5.40-5.44 (br s, 1H), 5.21 (d,J = 12.0 Hz, 0.45H), 5.05 (d,J = 11.2 Hz, 0.55H), 4.52 (q,J = 7.2 Hz, 2H), 1.46 (2t, J = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, acetone-d_6)** δ **(major isomer)** 151.8, 137.2, 134.7, 130.5, 129.8, 129.6 (2C), 129.2, 124.4, 124.2, 118.1, 116.3, 115.7, 115.3, 90.3, 70.0, 64.7, 63.9, 42.7, 14.3; **^{13}C NMR (100 MHz, acetone-d_6)** δ **(minor isomer)** 151.7, 136.1, 136.0, 131.2, 130.4, 129.7, 129.6, 129.4, 124.3, 123.9, 121.1, 116.2, 115.5, 115.1, 95.3, 70.0, 64.7, 49.3, 14.3; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{18}N_2O_5S$ $[M+K]^+$: 437.0563, found: 437.0561.

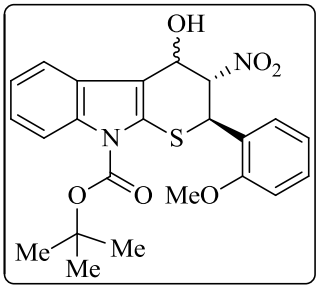
9-(N-*tert*-butoxycarbonyl)-4-hydroxy-3-methyl-3-nitro-2-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3c & 4c): 83% yield; **IR**



(KBr) ν 3501, 2979, 2929, 1719, 1672, 1543, 1477, 1447, 1373, 1357, 1320 cm^{-1}; **^{1}H NMR(400 MHz, $CDCl_3$)** δ (mixture of two diastereomers) 8.02 (m, 1H), 7.83(m, 0.8H), 7.51-7.56 (m, 0.2H), 7.26-7.48 (m, 6H), 6.03 (d, J = 8.8 Hz, 0.8H), 5.60 (s, 0.2H), 5.17 (d, J = 5.6 Hz, 0.2H), 5.0 (s, 0.8H), 2.91 (d, J = 5.6 Hz, 0.2H), 2.28 (d, J = 8.8 Hz, 0.8H), 1.87 (s, 3H), 1.70 (br s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ **(major isomer)** 150.3, 135,6, 132.6, 130.7, 130.1, 129.6, 129.3, 128.9,

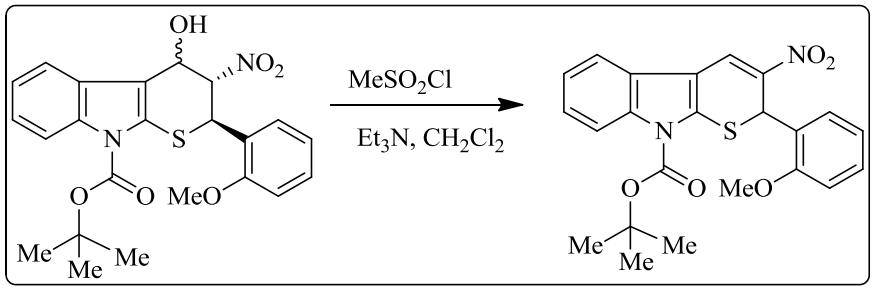
128.5, 123.8, 123.4, 119.3, 114.9, 113.4, 95.0, 86.1, 73.7, 53.4, 28.2, 10.6; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{24}N_2O_5S$ $[M+Na]^+$: 463.1302, found: 463.1306.

9-(N-*tert*-butoxycarbonyl)-4-hydroxy-2-(2-methoxyphenyl)-3-nitro-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3d & 4d): 81% yield; **IR**



(KBr) ν 3492, 1725, 1723, 1600, 1554, 1494, 1450 cm^{-1}; **^{1}H NMR (400 MHz, acetone-d_6)** δ (mixture of two diastereomers) 8.04-8.05 (m, 1H), 7.77-7.80 (m, 0.6H), 7.35-7.53 (m, 1.4H), 7.23-7.26 (m, 3H), 6.99-7.01 (m, 2H), 5.85-5.87 (m, 0.6H), 5.64-5.67 (m, 2.4 H), 5.25-5.28 (m, 1H), 3.91(s, 1.8H), 3.89 (s, 1.2H), 1.66 (s, 9H); **^{13}C NMR (100 MHz, acetone-d_6)** δ **(major isomer)** 159.4, 151.2, 137.1, 132.1, 131.2, 130.8, 130.6 124.7, 124.5, 123.0, 122.3, 120.9, 115.5, 113.5, 113.3, 95.1, 90.8, 87.0, 71.1, 56.9, 28.8; **^{13}C NMR (100 MHz, acetone-d_6)** δ **(minor isomer)** 159.4, 151.3, 136.9, 132.6, 131.2, 130.8, 130.6, 125.8, 124.9 (2C), 122.4, 118.6, 116.4, 116.2, 115.5, 95.1, 90.8, 87.0, 56.9, 28.8; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{24}N_2O_6S$ $[M+Na]^+$: 479.1247, found: 479.1244.

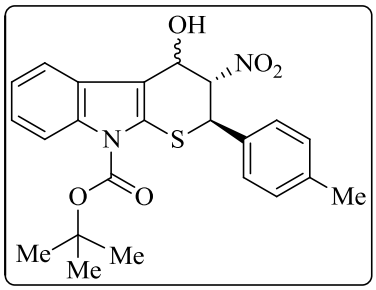
The structure also confirmed dehydrating the desired product:



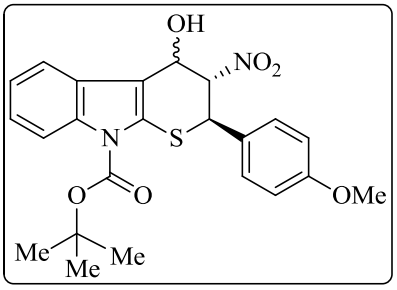
Scheme 2.14 Dehydration of **3d** and **4d**

^{1}H NMR (400 MHz, acetone-d_6) δ 8.73 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 6.8 Hz, 1H), 7.30-7.37 (m, 2H), 7.22-7.26 (m, 1H), 7.05 -7.09 (m, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.19 (s, 1H), 4.00 (s, 3H), 1.67 (s, 9H); **^{13}C NMR (100 MHz, acetone-d_6)** δ 156.9, 150.4, 140.9, 138.2, 135.0, 131.2, 129.3, 129.2, 128.2, 127.8, 126.0, 125.6, 121.8, 119.0, 116.7, 113.5, 113.0, 88.2, 56.9, 37.6, 28.7.

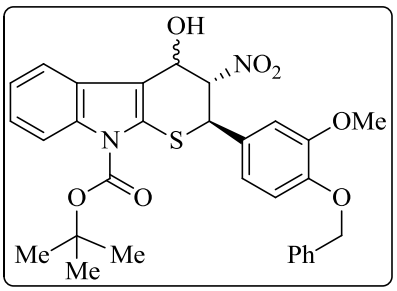
9-(N-*tert*-butoxycarbonyl)-4-hydroxy-3-nitro-2-(4-methylphenyl)-2,3,4,9-tetrahydrothiopyarano[2,3-*b*]indole (3e & 4e): 89% yield; **IR** (KBr) ν 3439, 2979, 2923, 2852, 1727, 1625, 1556, 1513, 1477, 1449 cm^{-1};**^{1}H NMR (400 MHz, acetone-d_6)** δ (mixture of two diastereomers) 8.00-8.03 (m, 1H), 7.75-7.78 (m, 0.5H), 7.60-7.62 (m, 0.5H), 7.47 (d,*J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz), 7.21-7.28 (m, 4H), 5.74 (dd,J_1 = 3.6 Hz,J_2 = 12 Hz, 0.52H), 5.61-5.65 (m, 1H), 5.51 (dd,J_1 = 8.8 Hz,J_2 = 11.2 Hz, 0.48H), 5.35 (br s, 1H), 5.14 (d,*J* =12 Hz, 0.52H), 4.95 (d,*J* = 11.2 Hz, 0.48H), 2.32 (s, 3H), 1.65 (br s, 9H); **^{13}C NMR (100 MHz, acetone-d_6)** δ **(major isomer)** 151.2, 139.9, 136.9, 134.9, 131.0, 130.9, 131.0, 130.7, 125.0, 124.8, 118.7, 116.5, 115.5, 91.4, 87.2, 64.9, 43.2, 28.8, 21.8; **^{13}C NMR (100 MHz, acetone-d_6)** δ **(minor isomer)** 151.3, 140.7, 137.1, 132.5, 132.1, 131.1, 130.7, 129.9, 125.0, 124.5, 120.9, 116.5, 116.2, 94.4, 87.2, 70.9, 50.0, 28.8, 21.7; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{24}N_2O_5S$ $[M+Na]^+$: 463.1306, found: 463.1308.



9-(N-*tert*-butoxycarbonyl)-4-hydroxy-2-(4-methoxyphenyl)-3-nitro-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3f & 4f): 87% yield; **IR** (KBr) ν 3446, 2977, 1717, 1610, 1552, 1321 cm^{-1}; **^{1}H NMR (400 MHz, acetone-d_6)** δ (mixture of two diastereomers) 8.04-8.05 (m, 1H), 7.75-7.78 (m, 0.4 H), 7.60-7.62 (m, 0.6H), 7.50 (d, *J* = 8.8 Hz, 1.2 H), 7.46 (d, *J* = 8.8 Hz, 0.8 H), 7.23-7.28 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.71 (dd, J_1 = 3.28 Hz, J_2 = 12.0Hz, 0.6H), 5.61-5.64 (m, 1H), 5.48 (dd, J_1 = 11.2 Hz, J_2= 9.0 Hz, 0.4H), 5.30 (d, *J* = 9.6 Hz, 0.4 H), 5.23(d, *J* = 7.6 Hz, 0.6H), 5.16 (d, *J* = 12.0 Hz, 0.6H), 4.96 (d, *J* = 11.2 Hz, 0.4H), 3.81 (s, 3H), 1.66 (br s, 9H); **^{13}C NMR (100 MHz, acetone-d_6)** δ **(major isomer)** 161.5, 151.3, 136.9, 132.2, 131.5, 130.7, 129.5, 125.0, 124.8, 118.7, 116.5, 115.8, 115.5, 91.5, 87.1, 64.9, 56.2, 43.0, 28.8; **^{13}C NMR (100 MHz, acetone-d_6)** δ **(minor isomer)** 161.9, 151.2, 137.1, 133.0, 131.3,130.6, 127.1, 125.0, 124.5, 120.9, 116.2, 115.8, 115.4, 96.5, 87.1,71.0, 56.2, 49.7, 28.8; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{24}N_2O_6S$ $[M+Na]^+$: 479.1247, found: 479.1242.

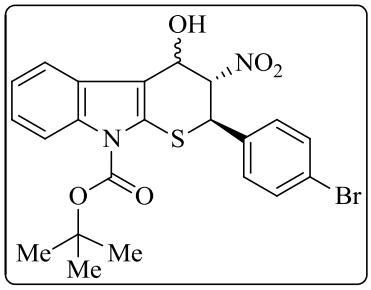


9-(N-*tert*-butoxycarbonyl)-2-(4-benzyloxy-3-methoxyphenyl)-4-hydroxy-3-nitro-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3g & 4g): 83% yield; **IR** (KBr) ν 3441, 3004, 2978, 2931, 1723, 1603, 1555, 1514, 1450, 1422 cm^{-1}; **^{1}H NMR (400 MHz, acetone-d_6)** δ (mixture of two diastereomers) 8.03-8.05 (m, 1H), 7.77-7.79 (m, 0.56H), 7.61-7.63 (m, 0.44H), 7.49 (d, *J* = 14.7 Hz, 2H), 7.39-7.41 (m, 2H), 7.21-7.35 (m, 4H), 7.11-7.14 (m, 0.46H), 7.03-7.08 (m, 1.54H), 5.76 (dd, J_1= 3.52 Hz, J_2 = 11.8 Hz, 0.44H), 5.62-5.69 (m, 1H), 5.56 (dd, J_1 = 8.8 Hz, J_2 = 11.2 Hz, 0.56H), 5.31 (d, *J* = 9.28 Hz, 0.56H), 5.23 (d, *J* = 8.4 Hz, 0.44H), 5.16 (d, *J* = 11.8

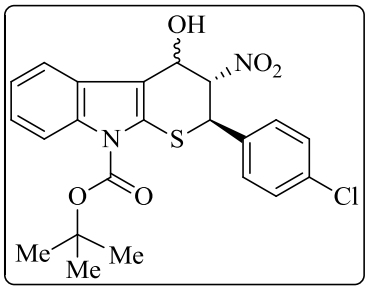


Hz, 0.44H), 5.12 (s, 2H), 4.95 (d, *J* = 11.2 Hz, 0.56H), 3.86 (s, 3H), 1.67 (s, 9H); **^{13}C NMR (100 MHz, acetone-d$_6$)** δ **(major isomer)** 150.9, 150.6, 149.7, 138.3, 136.5, 130.1, 129.9, 129.3, 128.7, 128.6, 127.4, 124.5, 124.0, 122.2, 120.3, 115.8, 115.6, 114.8, 114.6, 113.4, 95.8, 86.5, 71.4, 70.4, 56.4, 49.6, 28.3; **^{13}C NMR (100 MHz, acetone-d$_6$)** δ **(minor isomer)** 151.0, 150.7, 150.2, 138.4, 136.3, 131.7, 130.2, 130.0, 129.3, 128.7, 128.6, 124.4, 124.2, 121.9, 118.1, 115.9, 115.7,114.8, 114.7, 113.5, 90.8, 86.6, 71.3, 64.3, 56.4, 42.8, 28.3; **HRMS** (ESI-TOF) m/z calculated for $C_{30}H_{30}N_2O_7S$ [M-H]: 561.1694, found: 561.1690.

9-(N-*tert*-butoxycarbonyl)-2-(4-Bromophenyl)-4-hydroxy-3-nitro-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3h & 4h): 84% yield; **IR** (KBr) ν 3442, 2925, 1712, 1624, 1552, 1486, 1449 cm^{-1}; **^{1}H NMR (400 MHz, acetone-d$_6$)** δ (mixture of two diastereomers) 8.04-8.06 (m, 1H), 7.78-7.79 (m, 0.4H), 7.53-7.65 (m, 4.6H), 7.25-7.30 (m, 2H), 5.79 (dd,J_1 = 3.28 Hz,J_2 = 11.8 Hz, 0.6H), 5.65-5.70 (m, 1H), 5.54 (dd,J_1 = 3.28 Hz,J_2 = 11.8 Hz, 0.6H), 5.65-5.70 (m, 1H), 5.54 (dd,J_1 = 8.8 Hz,J_2 = 11.2 Hz, 0.4H), 5.35 (d,*J* = 9.28 Hz, 0.4H), 5.31 (d,*J* = 7.5 Hz, 0.66H), 5.19 (d, *J* =11.8 Hz, 0.6H), 5.05 (d,*J* = 11.2 Hz, 0.4 Hz), 1.67 (br s, 1H); **^{13}C NMR (100 MHz, acetone-d$_6$)** δ **(major isomer)** 150.7, 137.0, 134.4, 132.9, 131.7, 130.0, 129.9, 124.6, 124.2, 123.0, 118.2, 115.9, 115.6, 90.5, 86.7, 64.2, 42.4, 28.0; **^{13}C NMR (100 MHz, acetone-d$_6$)** δ **(minor isomer)** 150.6, 136.3, 136.4, 133.1, 131.5, 131.0, 129.5, 124.5, 124.0, 123.8, 120.4, 115.9, 115.0, 95.5, 86.9, 70.2, 48.9, 28.0; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{21}N_2O_5SBr$ [M-H]: 503.0352, found: 503.0356.

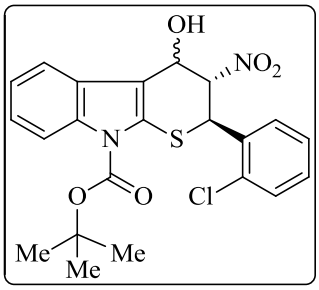


9-(N-*tert*-butoxycarbonyl)-2-(4-chlorophenyl)-4-hydroxy-3-nitro-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3i & 4i): 85% yield; **IR**



(KBr) ν 3449, 2977, 1714, 1629, 1554, 1492, 1449, 1367, 1322 cm^{-1}; **^{1}H NMR (400 MHz, acetone-d_6)** δ (mixture of two diastereomers) 8.01-8.03 (m, 1H), 7.75-7.77 (m, 0.5H), 7.58-7.65 (m, 2.5H), 7.43-7.46 (m, 2H), 7.20-7.28 (m, 2H), 5.77 (dd,J_1 = 3.4 Hz,J_2= 11.9 Hz, 0.52H), 5.62-5.68 (m, 1H), 5.53 (dd,J_1= 8.8 Hz,J_2= 11.2 Hz, 0.48H), 5.35 (d,J = 9.28 Hz, 0.48H), 5.04 (d, J = 7.6 Hz, 0.52H), 5.19 (d, J = 11.9 Hz, 0.52H), 5.04 (d,J = 11.2 Hz, 0.48H), 1.64 (br s, 9H); **^{13}C NMR (100 MHz, acetone-d_6)** δ **(major isomer)** 151.3, 137.1, 136.9, 134.5, 132.0, 131.7, 130.5, 125.1, 124.8, 122.7, 118.8, 116.5, 115.6, , 89.7, 85.8, 69.3, 63.3, 48.0, 27.3; **^{13}C NMR (100 MHz, acetone-d_6)** δ **(minor isomer)** 151.2, 137.1, 136.3, 135.5, 131.8, 130.7, 130.2, 125.2, 124.6, 122.7, 121.0, 116.3, 116.2, 94.7, 85.8, 69.3, 63.2, 41.4, 27.3; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{21}ClN_2O_5S$ $[M+Na]^+$: 483.0757, found: 483.0752.

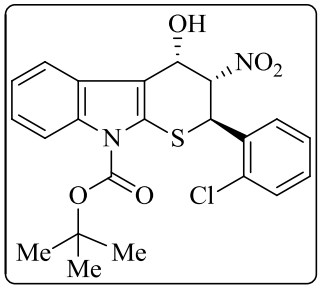
9-(N-*tert*-butoxycarbonyl)-4-hydroxy-2-(2-chlorophenyl)-3-nitro-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3j & 4j): 84% yield; **IR**



(KBr) ν 3491, 1728, 1701, 1558, 1476, 1447, 1367, 1315 cm^{-1}; **^{1}H NMR (400 MHz, acetone-d_6)** δ **(mixture of diastereomers)** 8.00-8.04 (m, 1H), 7.76-7.88 (m, 1.45 H), 7.63-7.65 (m, 0.55H), 7.51-7.56 (m, 1H), 7.36-7.45 (m, 2H), 7.26-7.31 (m, 2H), 5.89-5.93 (m, 0.55H), 5.66-5.80 (m, 2H), 5.58-5.60 (m, 0.45H), 5.48 (d, J = 7.6 Hz, 0.55H), 5.44 (d, J = 9.2 Hz, 0.45 H), 1.67 (s, 9H); **^{13}C NMR (100 MHz, acetone-d_6)** δ **(major isomer)** 150.8, 136.3, 135.4, 135.3, 131.1, 130.9, 130.7, 130.1, 129.1, 128.8, 124.6, 124.3, 118.2, 115.6, 115.1, 90.2, 86.8, 64.1, 38.8, 28.2; **^{13}C NMR (100 MHz, acetone-d_6)** δ **(minor isomer)**

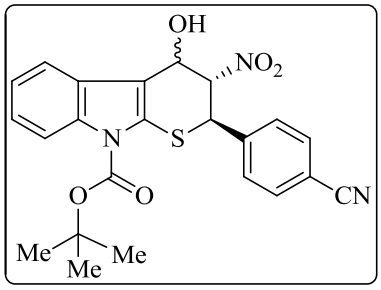
150.8, 136.3, 135.5, 135.1, 132.2, 131.7, 130.9, 130.2, 130.1, 129.9, 124.7, 124.6, 120.4, 116.1, 115.9, 94.5, 86.7, 70.5, 45.1, 28.2; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{21}N_2O_5SCl$ $[M+Na]^+$: 483.0752, found: 483.0751.

The corresponding ***trans-cis*** isomer (**3j**) was separated by crystallization.



^{1}H NMR (400 MHz, acetone-d$_6$) δ 8.02-8.05 (m, 1H), 7.76-7.78 (m, 1H), 7.65-7.67 (m, 1H), 7.53-7.55 (m, 1H), 7.38-7.43 (m, 2H), 7.28-7.30 (m, 2H), 5.89-5.93 (m, 1H), 5.79 (d, J = 11.6 Hz, 1H), 5.70 (dd, J_1= 3.4 Hz, J_2 = 7.6Hz, 1H), 5.46 (d, J = 7.6 Hz, 1H), 1.66 (s, 9H); **^{13}C NMR (100 MHz, acetone-d$_6$)** δ **(*trans-cis*)** 150.8, 136.3, 135.4, 135.3, 131.1, 130.9, 130.7, 130.1, 129.1, 128.8, 124.6, 124.3, 118.2, 115.6, 115.1, 90.2, 86.8, 64.1, 38.8, 28.2; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{21}N_2O_5SCl$ $[M+Na]^+$: 483.0752, found: 483.0746.

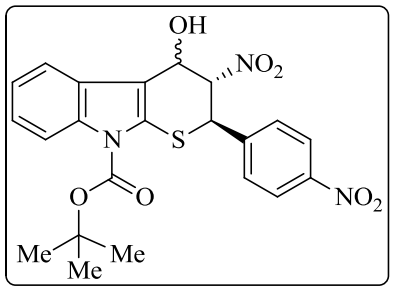
9-(N-*tert*-butoxycarbonyl)-2-(4-cyanophenyl)-4-hydroxy-3-nitro-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3k & 4k): 77% yield; **IR**

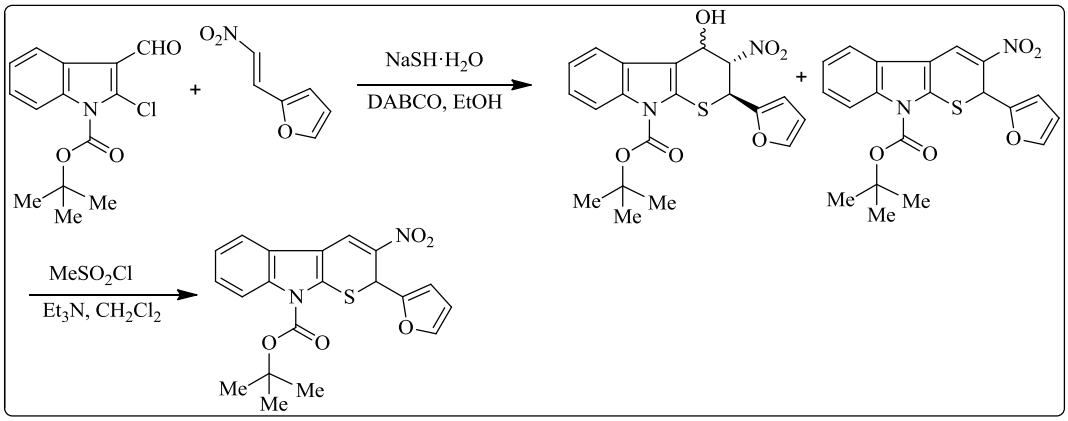


(KBr) ν 3508, 2983, 2228, 1721, 1608, 1555, 1503, 1477, 1449;**^{1}H NMR (400 MHz, acetone-d$_6$)** δ (mixture of two diastereomers) 8.01-8.05 (m, 2H), 7.78-7.90 (m, 4.5H), 7.63-7.68 (m, 0.5H), 7.23-7.30 (m, 2H), 5.87 (dd,J_1 = 3.5 Hz,J_2 = 11.8 Hz, 0.45H), 5.68-5.72 (m, 1H), 5.58-5.63 (m, 1H), 5.41 (dd,J_1 = 8.8 Hz,J_2 = 12 Hz, 0.55H), 5.30 (d,J = 11.8 Hz, 0.45H), 5.17 (d,J = 11.2 Hz, 0.55H), 1.67 (br s, 9H); **^{13}C NMR (100 MHz, acetone-d$_6$)** δ **(major isomer)** 150.7, 140.2, 136.4, 133.8, 133.7, 130.8, 129.8, 124.6, 124.0, 120.4, 118.7, 116.0, 115.6, 114.1, 95.1, 86.8, 70.2, 49.1, 28.2; **^{13}C NMR (100 MHz, acetone-d$_6$)** δ **(minor isomer)** 150.7, 143.1, 137.5, 136.2, 133.7, 133.6, 130.5, 130.0, 124.7, 124.3, 118.9, 118.2, 115.9, 115.0, 113.3,

90.2, 86.8, 64.2, 42.7, 28.2; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{21}N_3O_5S$ $[M+Na]^+$: 474.1134, found: 474.1129.

9-(N-*tert*-butoxycarbonyl)-4-hydroxy-3-nitro-2-(4-nitrophenyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3l & 4l): 72% yield; **IR** (KBr) ν 3443, 2925, 1715, 1621, 1527, 1502, 1488, 1442, 1355, 1320 cm^{-1};**^{1}H NMR (400 MHz, acetone-d_6)** δ (mixture of two diastereomers) 8.29-8.31(m, 2H), 8.03-8.05 (m, 1H), 7.88-7.95 (m, 2H), 7.78-7.80 (m, 0.6H), 7.63-7.66 (m, 0.4H), 7.23-7.30 (m, 2H), 5.89 (dd,J_1 = 3.2 Hz,J_2 = 11.8 Hz, 0.44H), 5.77-5.82 (m, 1H), 5. 63 (dd,J_1 = 8.8 Hz,J_2 = 11.2 Hz, 0.56H), 5.43 (2d,J = 8.4 Hz, 9.2 Hz, 1H), 5.36 (d, J = 11.8 Hz, 0.44 H), 5.23 (d,J = 11.2 Hz, 0.56H), 1.67 (br s, 9H); **^{13}C NMR (100 MHz, acetone-d_6)** δ **(major isomer)** 150.7, 149.1, 145.2, 136.5, 131.3, 130.0, 128.6, 125.1, 124.8, 124.2, 120.6, 116.1, 115.8, 90.3, 86.8, 64.1, 42.4, 28.2; **^{13}C NMR (100 MHz, acetone-d_6)** δ **(minor isomer)** 150.6, 149.6, 142.3, 136.4, 130.9, 130.1, 128.4, 125.0, 124.9, 124.5, 118.4, 116.1, 115.2, 95.1, 86.8, 70.1, 48.7, 28.2; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{21}N_3O_7S$ [M-H]: 470.1022, found: 470.1018.





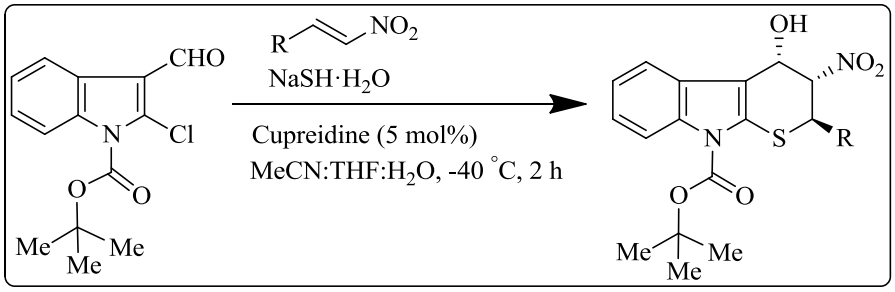
Scheme 2.15 Synthesis of 9-(N-*tert*-Butoxycarbonyl)-2-furyl-3-ene-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (**3m**)

To a stirred mixture of 1-Boc-2-chloro-3-formylindole (**1b**, 0.25 mmol), $NaSH \cdot H_2O$ (0.3 mmol) and 2-(2-nitrovinyl)furan (**2m**, 0.3 mmol) in EtOH (2 ml) was added catalyst DABCO (5 mol%) at room temperature for 7 min. After completion of reaction (monitored by TLC), EtOH was evaporated by rotary evaporator under vacuum. The crude product was extracted with ethyl acetate, washed with water, dried over Na_2SO_4. The evaporation of the organic solvent left the crude product, which was diluted with dry CH_2Cl_2 (5 ml) and followed by addition of Et_3N (1.0 mmol) and $MeSO_2Cl$ (0.5 mmol) respectively at -5 °C. The reaction mixture was stirred for 1h. Then the reaction mixture was extracted with CH_2Cl_2 before being quenched with water. The organic phase was washed with brine, dried using Na_2SO_4. Evaporation of the solvent left the crude product which was purified by column chromatography over silica-gel to furnish the pure product (**3m**). This compound was characterized by corresponding spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR, MS).

9-(N-*tert*-butoxycarbonyl)-2-furyl-3-ene-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3m): 91% yield; **IR** (KBr) ν 3448, 2923, 2852, 1728, 1611, 1579, 1470, 1393, 1359, 1328 cm^{-1}; **^{1}H NMR (400 MHz, acetone-d_6)** δ 8.58 (s, 1H), 8.04-8.06 (m, 1H), 7.91-7.93 (m, 1H), 7.47 (s, 1H), 7.35-7.37 (m, 2H), 6.27 (d, *J* =1.24 Hz, 2H), 6.12 (s,

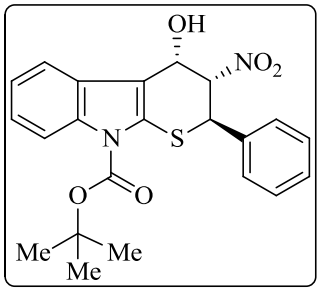
1H), 1.71 (s, 9H); **^{13}C NMR (100 MHz, acetone-d$_6$)** δ152.5, 150.4, 144.9, 139.6, 138.1, 134.2, 129.1, 128.4, 126.1, 125.6, 119.0, 116.6, 114.1, 112.1, 109.5, 88.4, 37.9, 28.7; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{18}N_2O_5S$ $[M+Na]^+$: 421.0834, found: 421.0838.

2.6.4 Catalytic, enantioselective one-pot synthesis of 9-(N-*tert*-butoxycarbonyl)-2-aryl-3-nitro-4-hydroxy-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives.



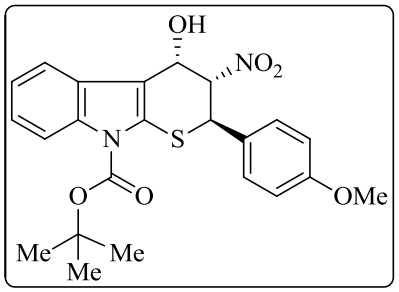
Scheme 2.16 Catalytic, enantioselective one-pot synthesis of **4a** and **4f**

2.6.4.1 Procedure for enantioselective one-pot synthesis of 9-(N-*tert*-butoxycarbonyl)-2-phenyl-3-nitro-4-hydroxy-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole: To a stirred solution of compound 1-Boc-2-chloro-3-formylindole (**1b**, 0.25 mmol) in MeCN:H_2O (1.02 ml, in a ratio of 1:0.02) was added NaSH·H_2O (0.3 mmol) at 0 ºC for 5 min. Phenylnitrostyrene (**2a**, 0.3 mmol) and cupreidine (catalyst **6**, 5 mol%) in THF (1.0 ml) were added to the above reaction mixture at -40 ºC. The stirring was continued for 2 h. After that the reaction mixture was quenched with water and extracted with ethyl acetate, washed with brine, dried over Na_2SO_4. The organic phase was concentrated by rotary evaporator under reduced pressure to leave the crude product which was purified by column chromatography over silica-gel to furnish the pure



product (94 mg, 88% yield). The product was characterized by IR, NMR and MS spectroscopy. The diastereomeric ratio (7:3) was determined by ^{1}H NMR of the crude product and the relative configuration of the major isomer was *trans-cis.* Enantiomers of major isomer were separated by HPLC using a Chiralpak AD-H column (20:80 *i*-PrOH/hexane, UV 220 nm, flow rate 1 mL/min) $T_{R\ (minor)}$ = 19.74 min, $T_{R\ (major)}$ = 20.58 min. Major isomer was obtained in 73% *ee*.

2.6.4.2 Procedure for enantioselective one-pot synthesis of 9-(N-*tert*-butoxycarbonyl)-4-hydroxy-2-(4-methoxyphenyl)-3-nitro-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole: To a stirred solution of compound 1-



Boc-2-chloro-3-formylindole (**1b**, 0.25 mmol) in MeCN:H_2O (1.02 mL, in a ratio of 1:0.02) was added NaSH·H_2O (0.3 mmol) at 0 ºC for 5 min. 4-methoxyphenylnitrostyrene (0.3 mmol) and cupreidine (catalyst **6**, 5 mol%) in THF (1.0 mL) were added to the above reaction mixture at -40 ºC. The stirring was continued for 2 h. After that the reaction mixture was quenched with water and extracted with ethyl acetate, washed with brine, dried over Na_2SO_4. The organic phase was concentrated by rotary evaporator under reduced pressure to leave the crude product which was purified by column chromatography over silica-gel to furnish the pure product (93.5 mg, 82% yield). The product was characterized by IR, NMR and MS spectroscopy. The diastereomeric ratio (4:1) was determined by ^{1}H NMR of the crude product and the relative configuration of the major isomer was *trans-cis.* Enantiomers of major isomer were separated by HPLC using a chiracel AD-H column (10:90 *i*-PrOH/hexane, UV 220 nm, flow rate 1.0 mL/min) $T_{R\ (minor)}$ = 24.40 min, $T_{R\ (major)}$ = 33.23 min. 88% *ee* was obtained of major isomer.

2.7 Copies of ^{1}H and ^{13}C NMR spectra of starting and final compounds

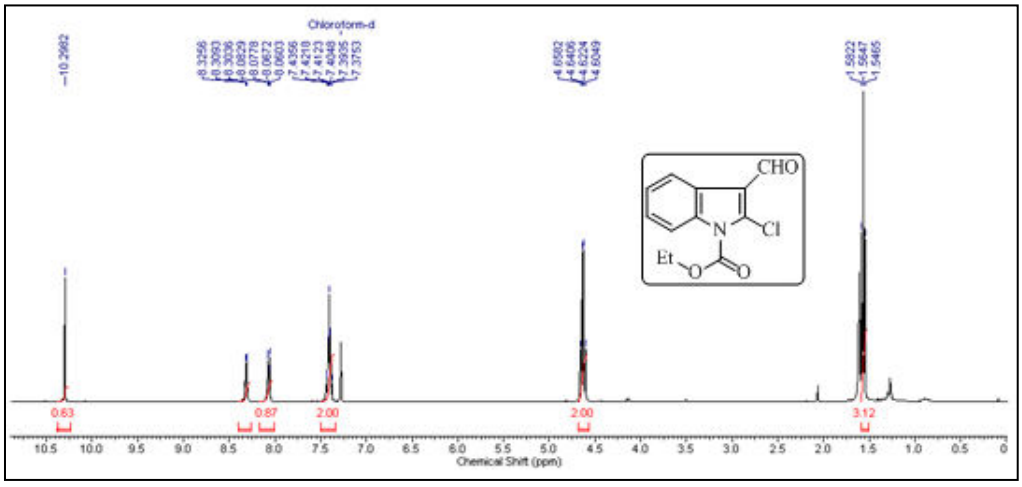


Figure 2.5 400 MHz ^{1}H NMR spectrum of **1c** in $CDCl_3$

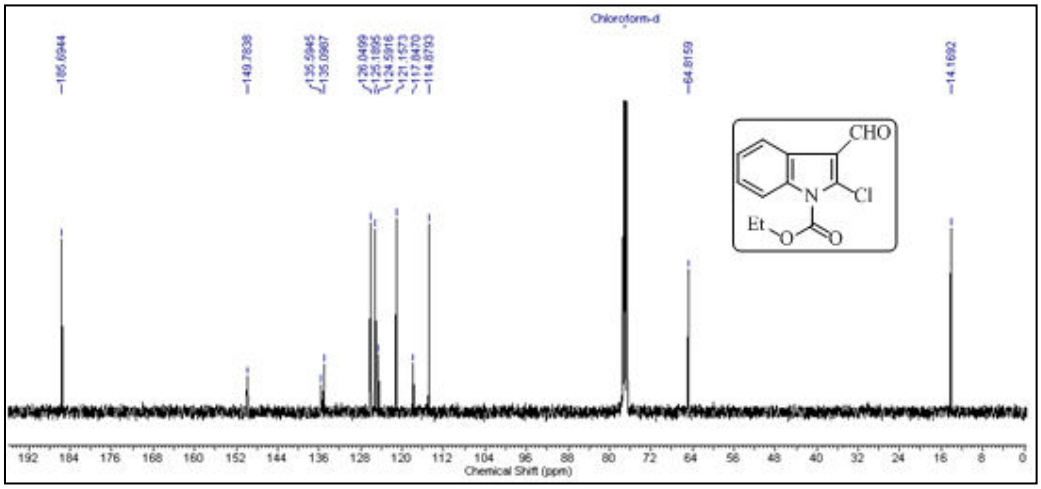


Figure 2.6 100 MHz ^{13}C NMR spectrum of **1c** in $CDCl_3$

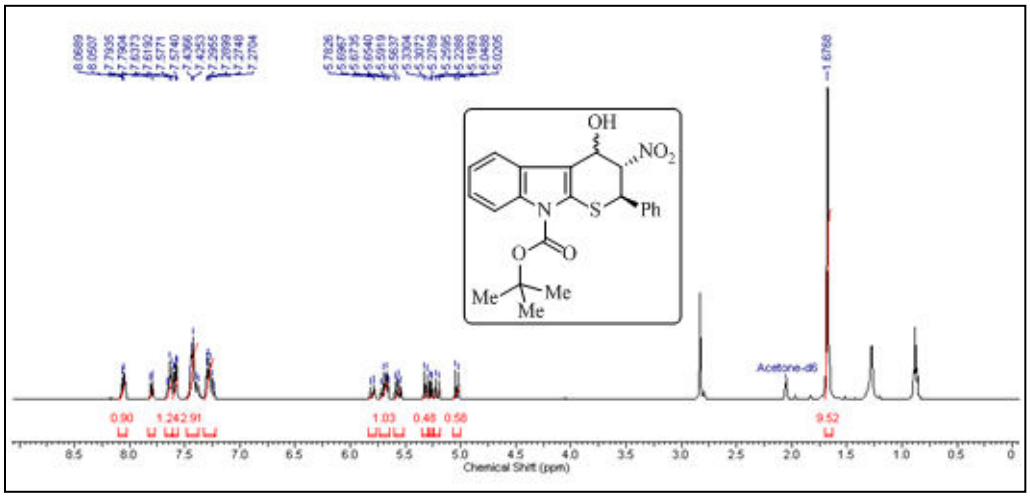


Figure 2.7 400 MHz ^{1}H NMR spectrum of **3a** and **4a** in acetone-d_6

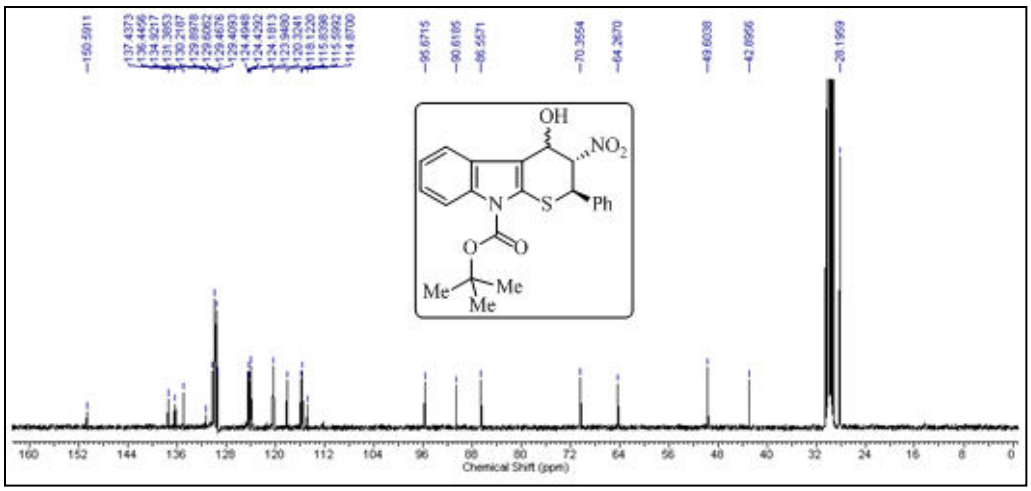


Figure 2.8 100 MHz ^{13}C NMR spectrum of **3a** and **4a** in acetone-d_6

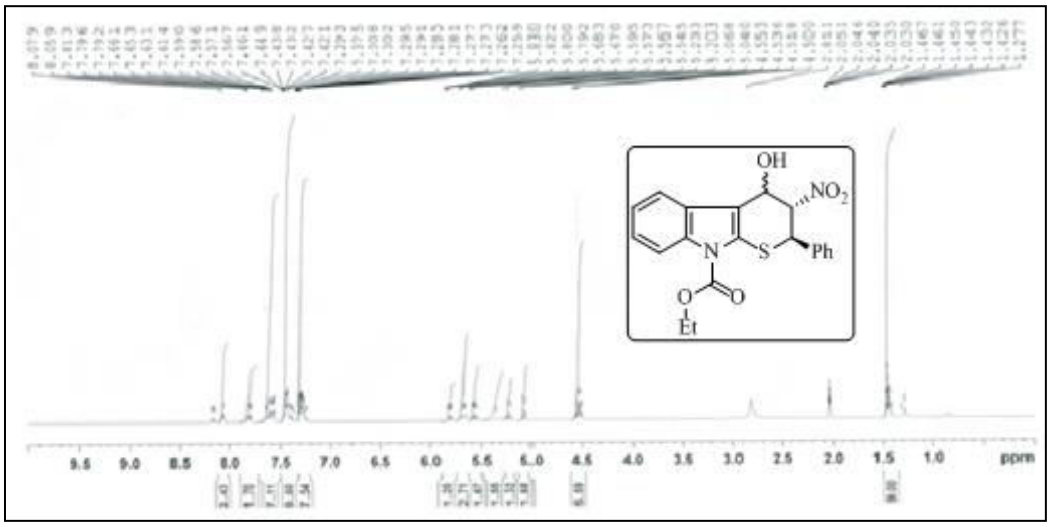


Figure 2.9 400 MHz ^{1}H NMR spectrum of **3b** and **4b** in acetone-d_6

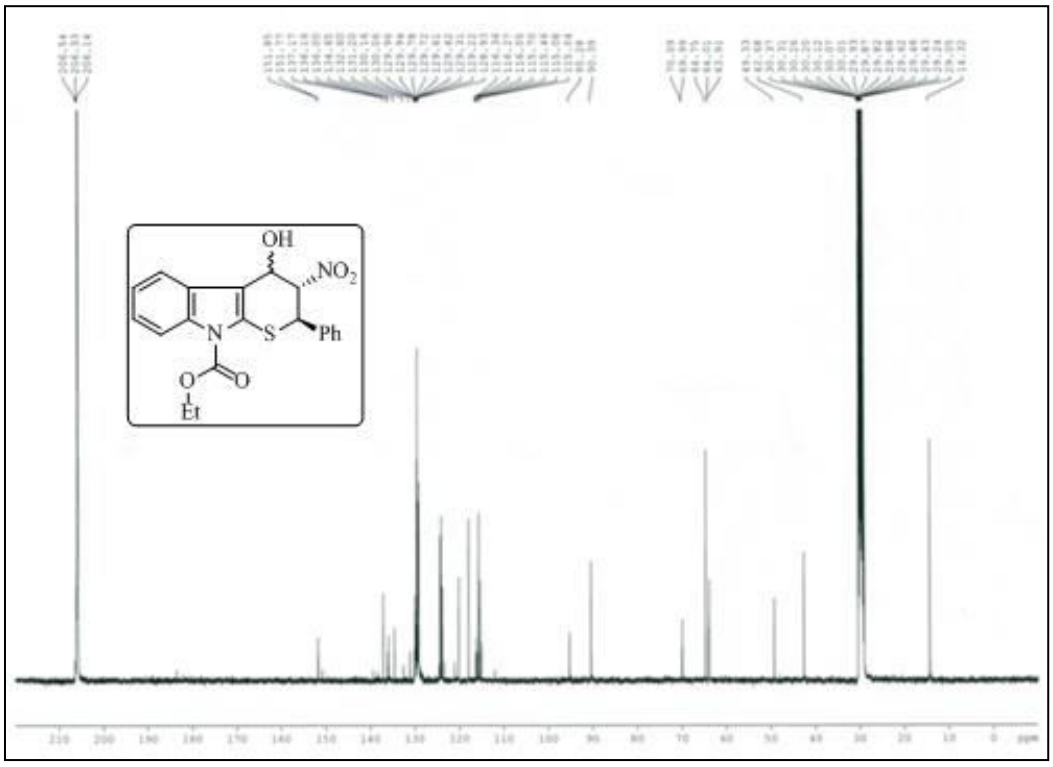


Figure 2.10 100 MHz ^{13}C NMR spectrum of **3b** and **4b** in acetone-d_6

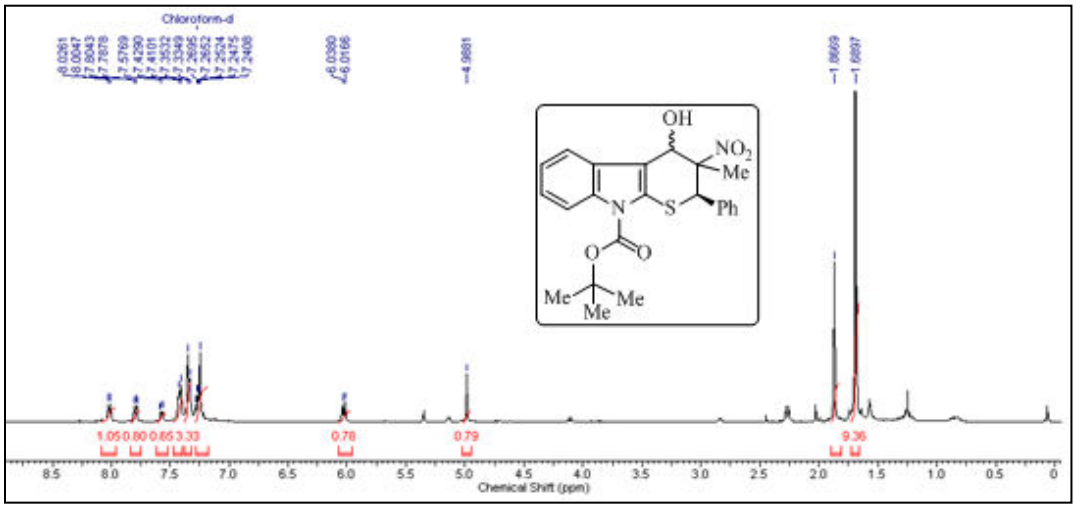


Figure 2.11 400 MHz ^{1}H NMR spectrum of **3c** and **4c** in $CDCl_3$

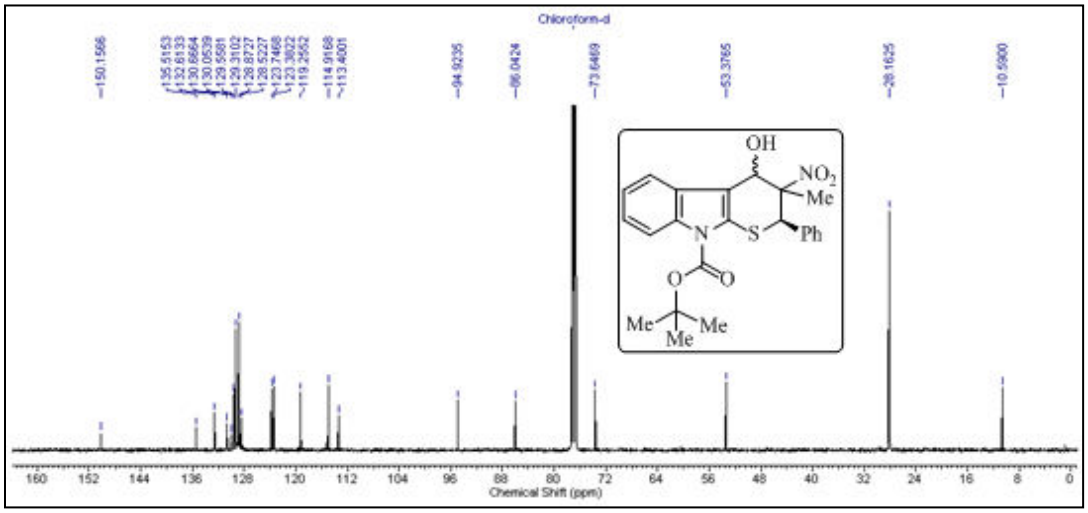


Figure 2.12 100 MHz ^{13}C NMR spectrum of **3c** and **4c** in $CDCl_3$

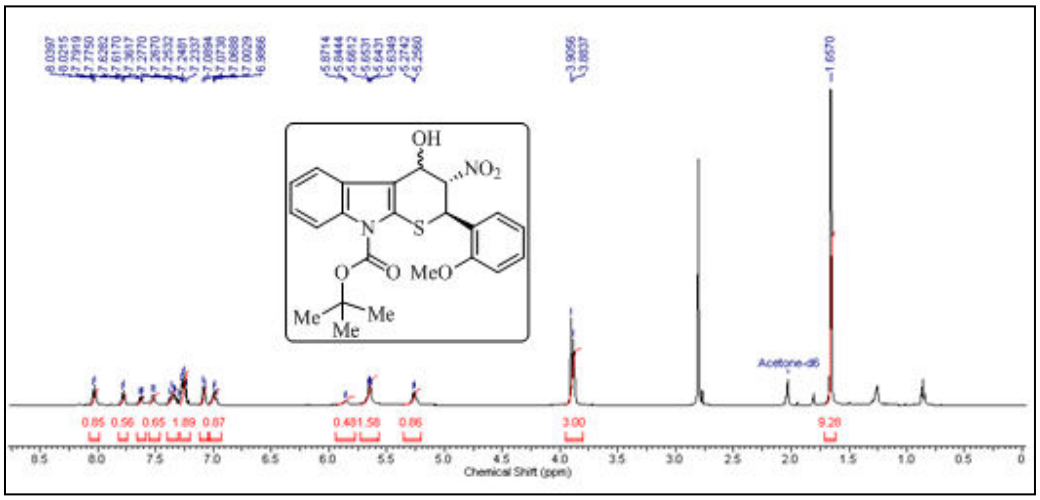


Figure 2.13 400 MHz ^{1}H NMR spectrum of **3d** and **4d** in acetone-d_6

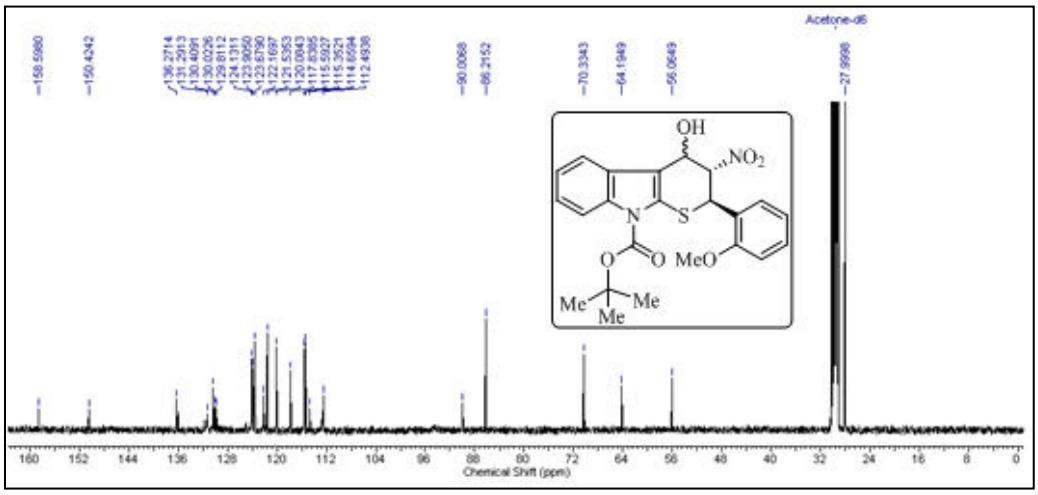


Figure 2.14 100 MHz ^{13}C NMR spectrum of **3d** and **4d** in acetone-d_6

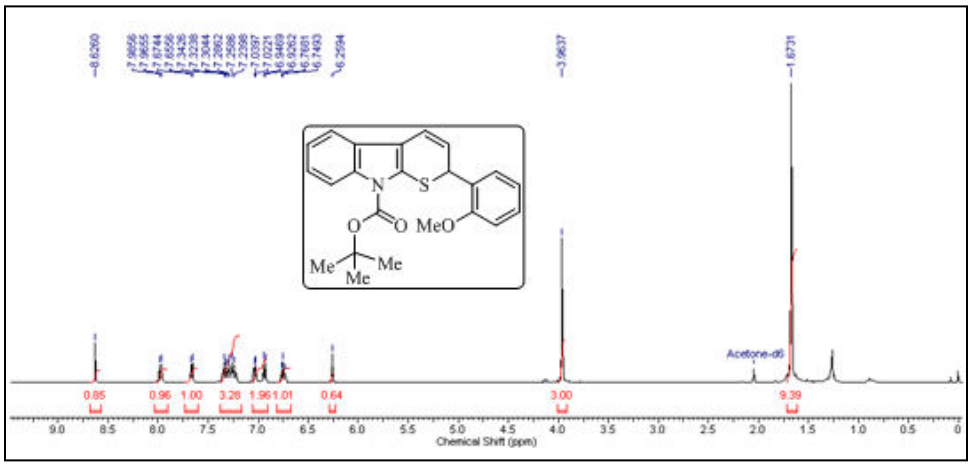


Figure 2.15 400 MHz ^{1}H NMR spectrum of dehydrated **3d** and **4d** in acetone-d_6

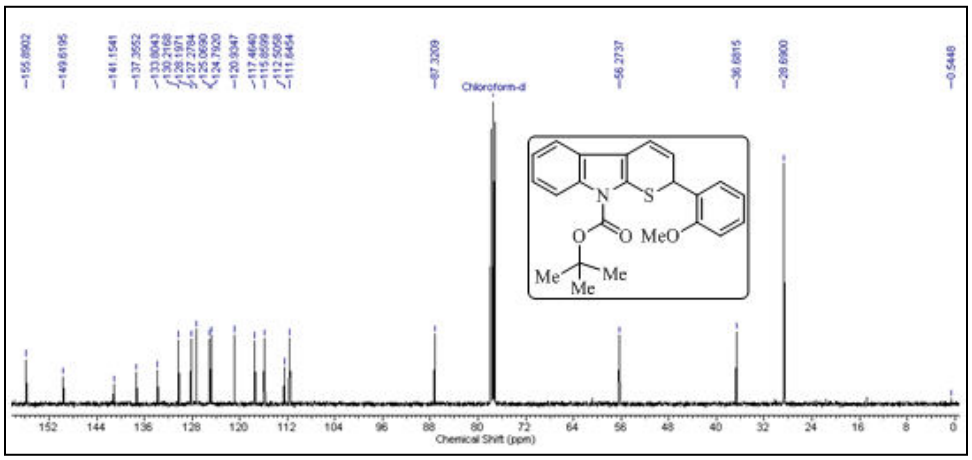


Figure 2.16 100 MHz ^{13}C NMR spectrum of dehydrated **3d** and **4d** in $CDCl_3$

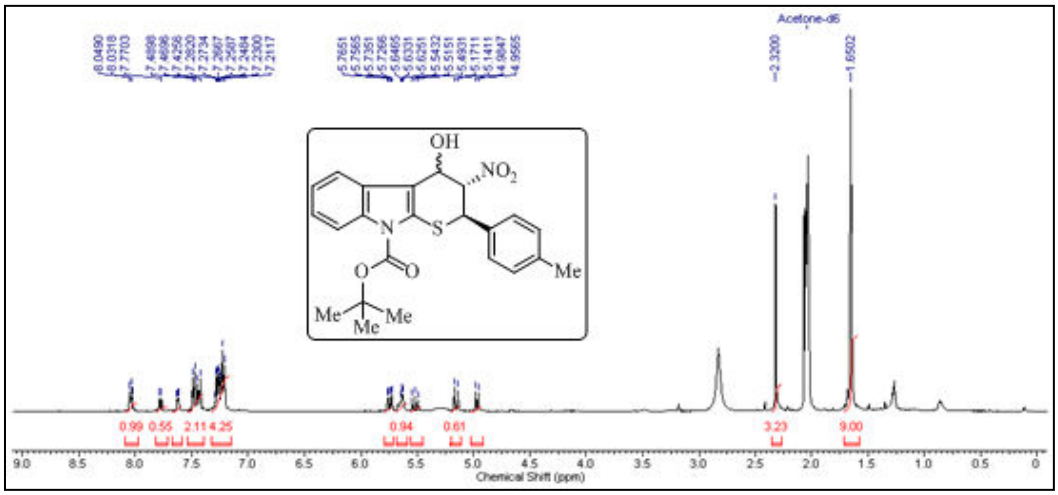


Figure 2.17 400 MHz ^{1}H NMR spectrum of **3e** and **4e** in acetone-d_6

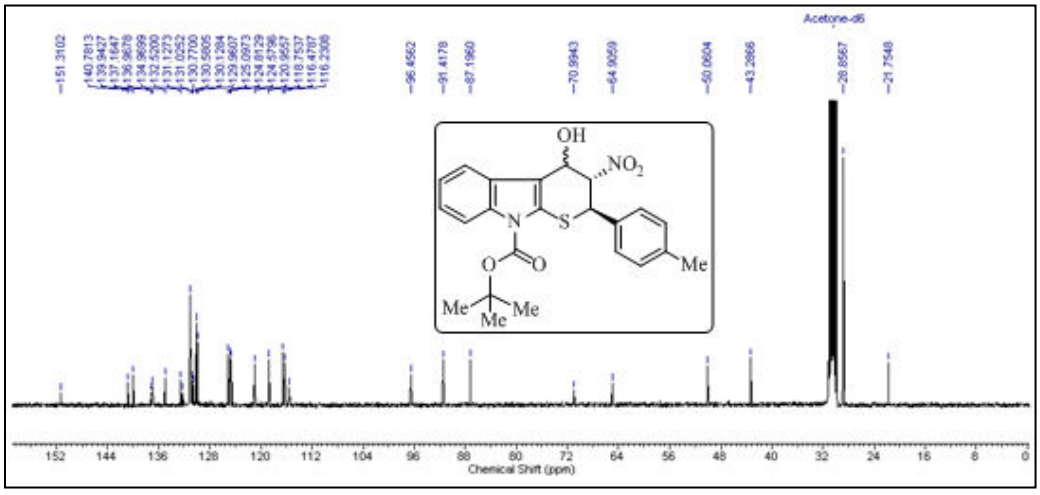


Figure 2.18 100 MHz ^{13}C NMR spectrum of **3e** and **4e** in acetone-d_6

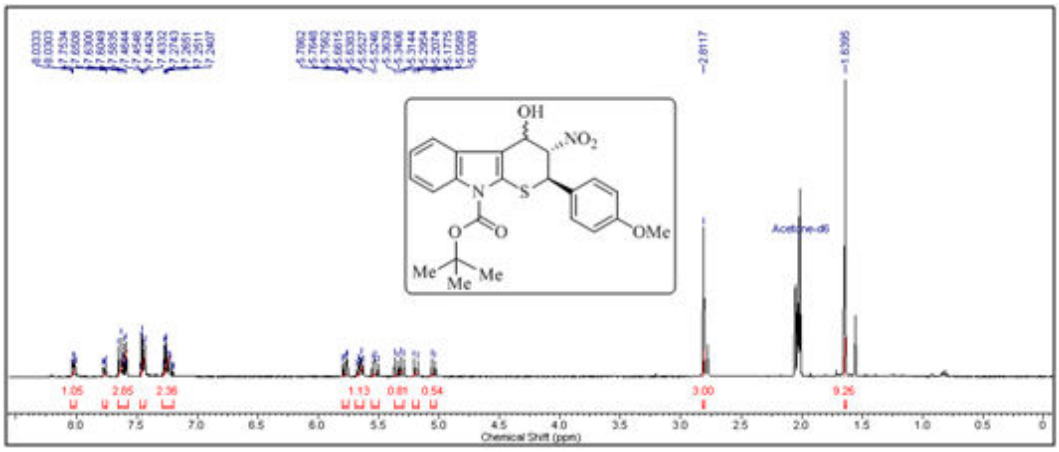


Figure 2.19 400 MHz ^{1}H NMR spectrum of **3f** and **4f** in acetone-d_6

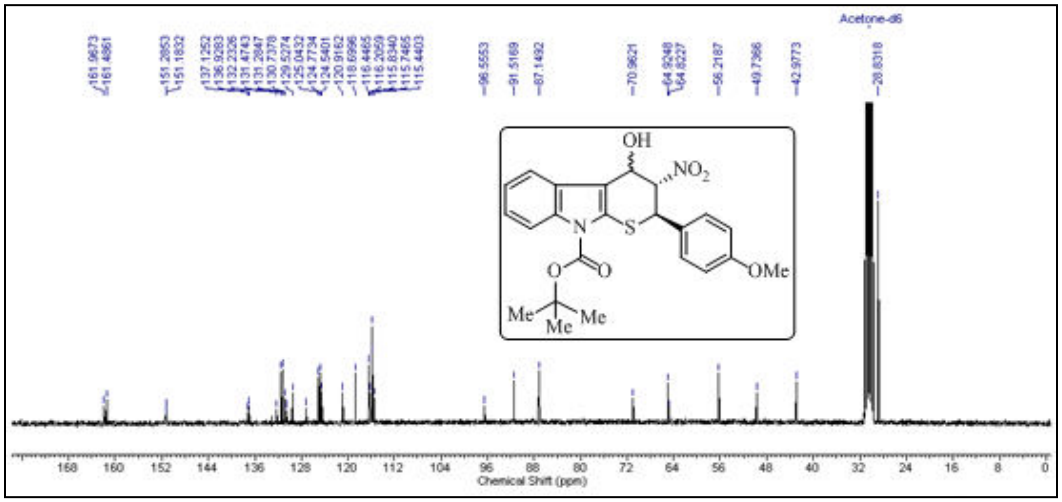


Figure 2.20 100 MHz ^{13}C NMR spectrum of **3f** and **4f** in acetone-d_6

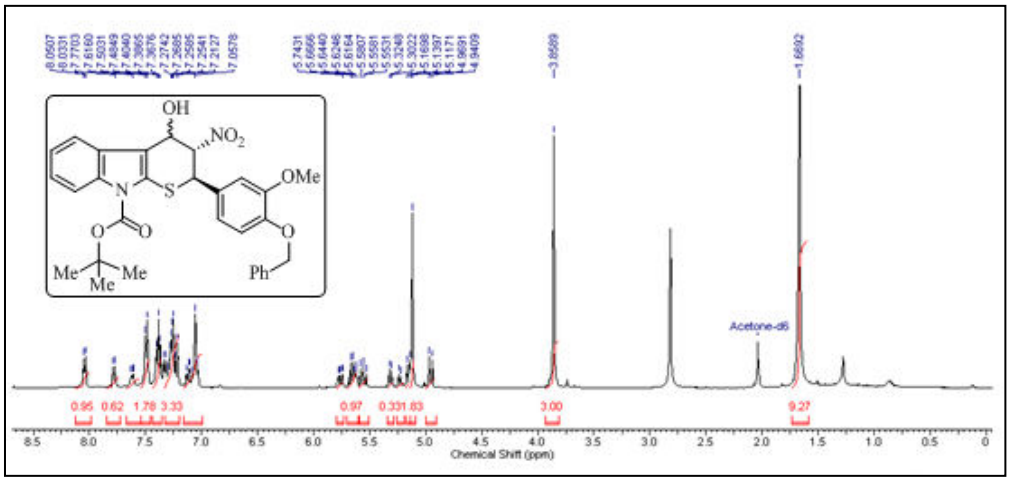


Figure 2.21 400 MHz ^{1}H NMR spectrum of **3g** and **4g** in acetone-d_6

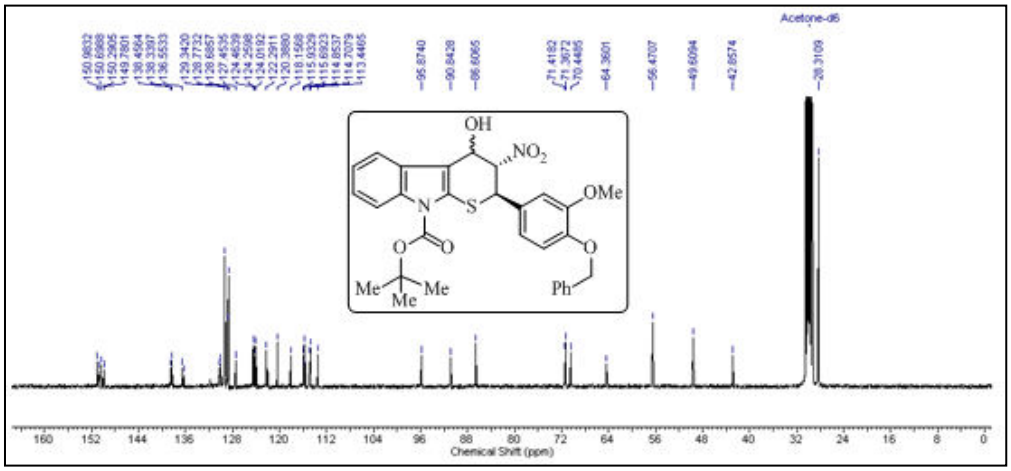


Figure 2.22 100 MHz ^{13}C NMR spectrum of **3g** and **4g** in acetone-d_6

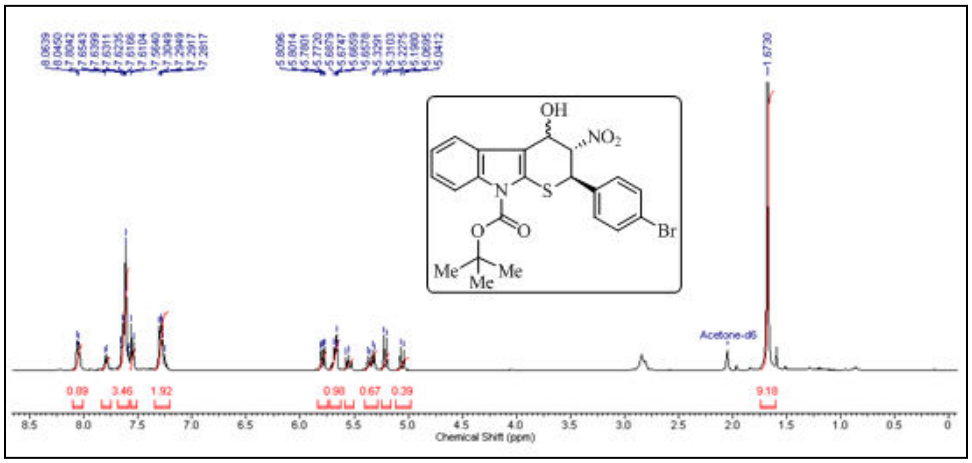


Figure 2.23 400 MHz ^{1}H NMR spectrum of **3h** and **4h** in acetone-d_6

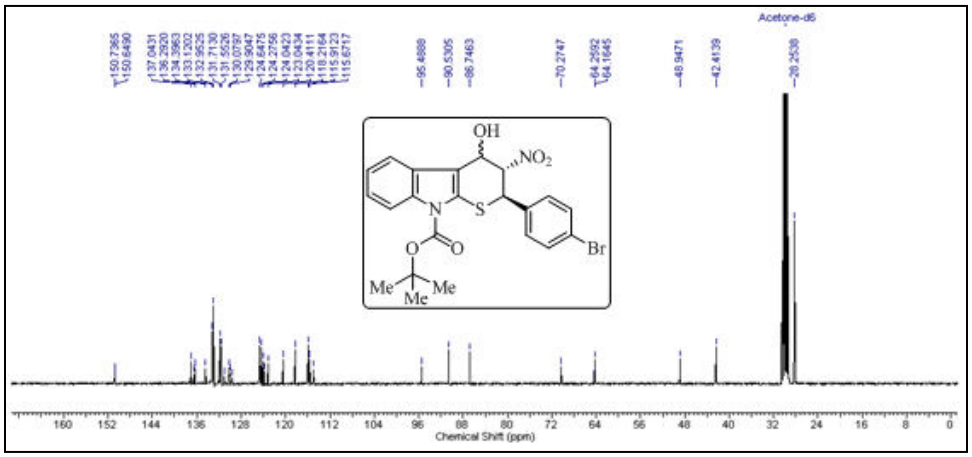


Figure 2.24 100 MHz ^{13}C NMR spectrum of **3h** and **4h** in acetone-d_6

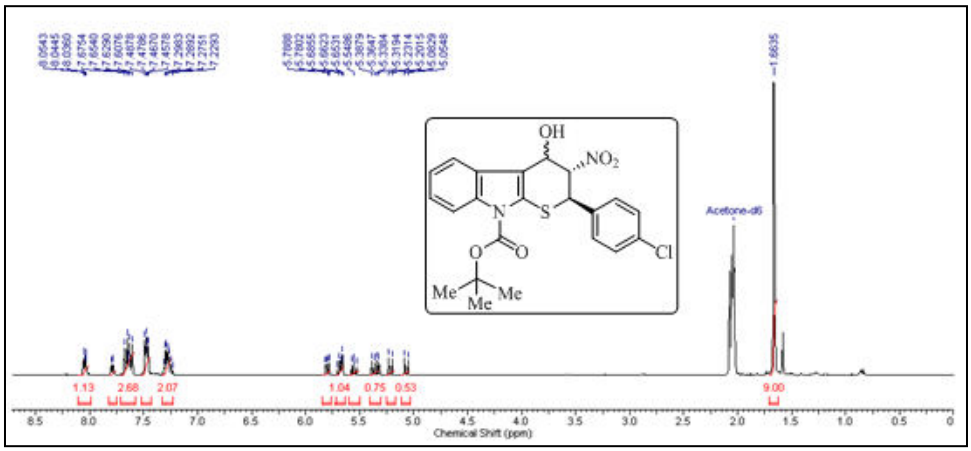


Figure 2.25 400 MHz ^{1}H NMR spectrum of **3i** and **4i** in acetone-d_6

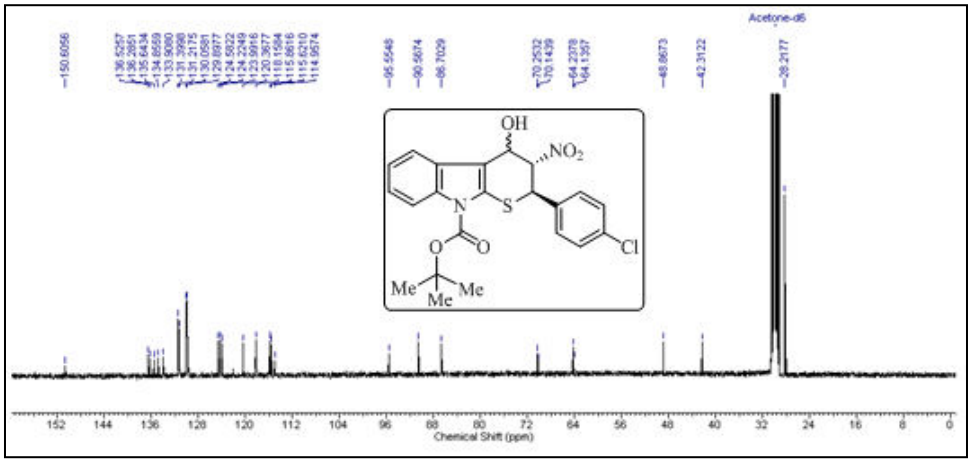


Figure 2.26 100 MHz ^{13}C NMR spectrum of **3i** and **4i** in acetone-d_6

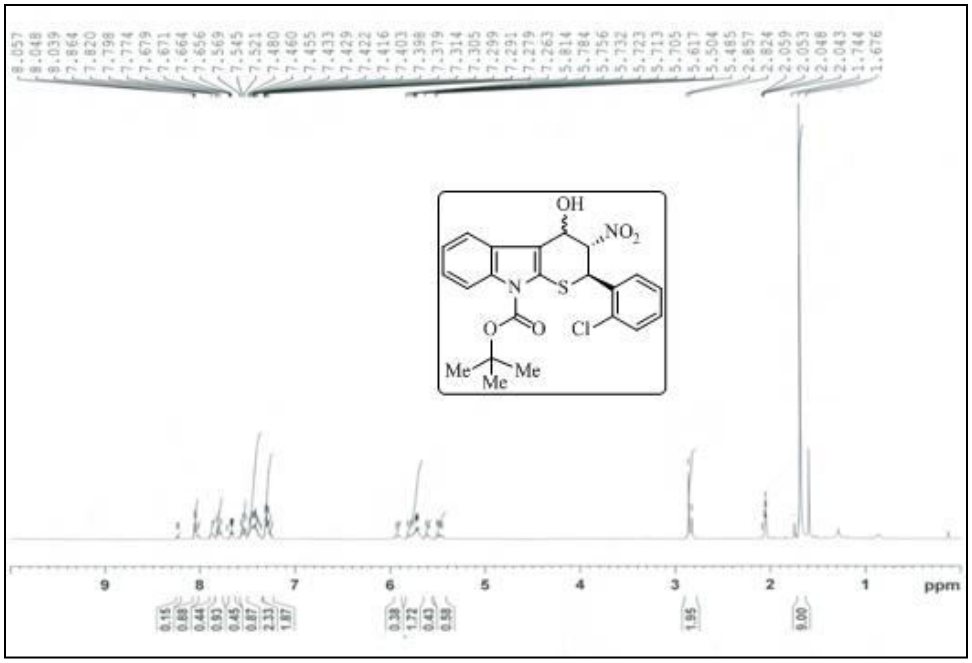


Figure 2.27 400 MHz ^{1}H NMR spectrum of **3j** and **4j** in acetone-d_6

Figure 2.28 100 MHz ^{13}C NMR spectrum of **3j** and **4j** in acetone-d_6

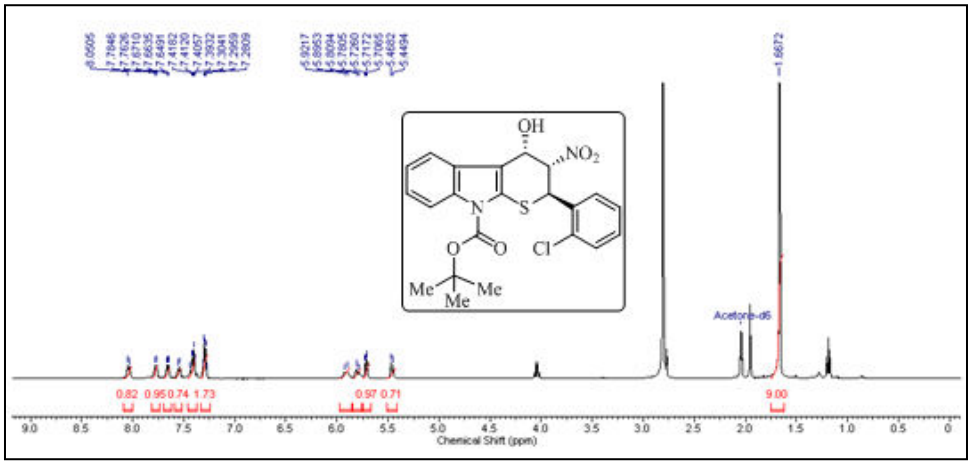


Figure 2.29 400 MHz ^{1}H NMR spectrum of **3j** in acetone-d_6

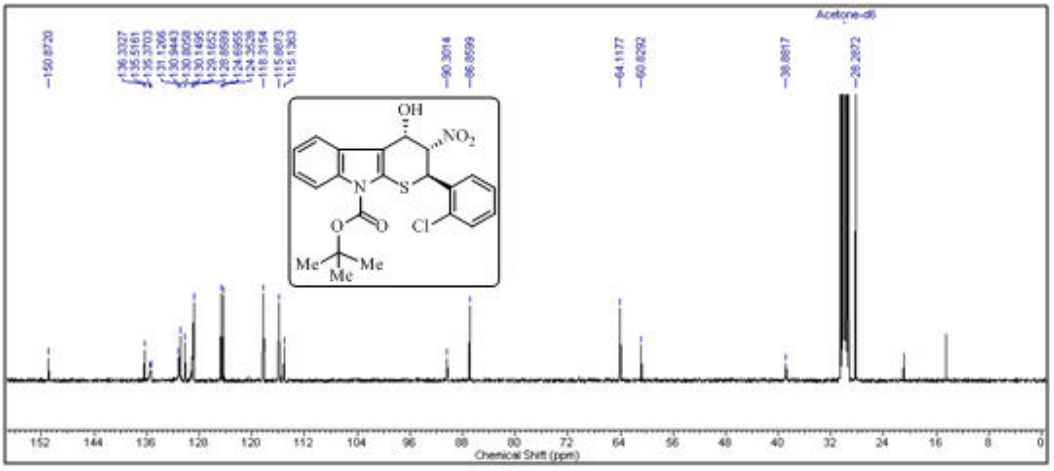


Figure 2.30 100 MHz ^{13}C NMR spectrum of **3j** in acetone-d_6

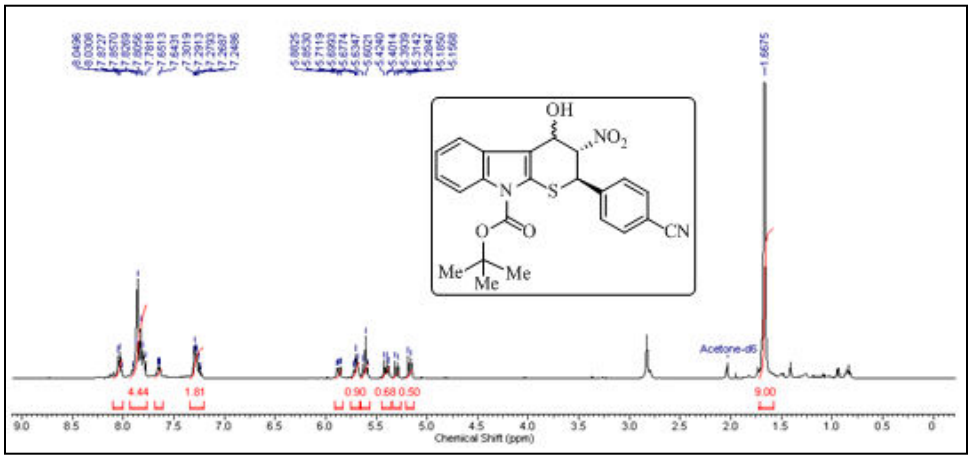


Figure 2.31 400 MHz ^{1}H NMR spectrum of **3k** and **4k** in acetone-d_6

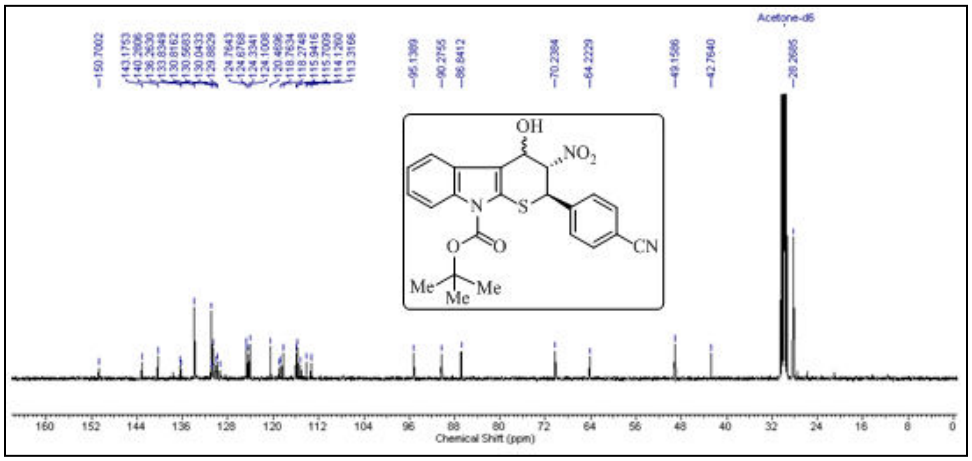


Figure 2.32 100 MHz ^{13}C NMR spectrum of **3k** and **4k** in acetone-d_6

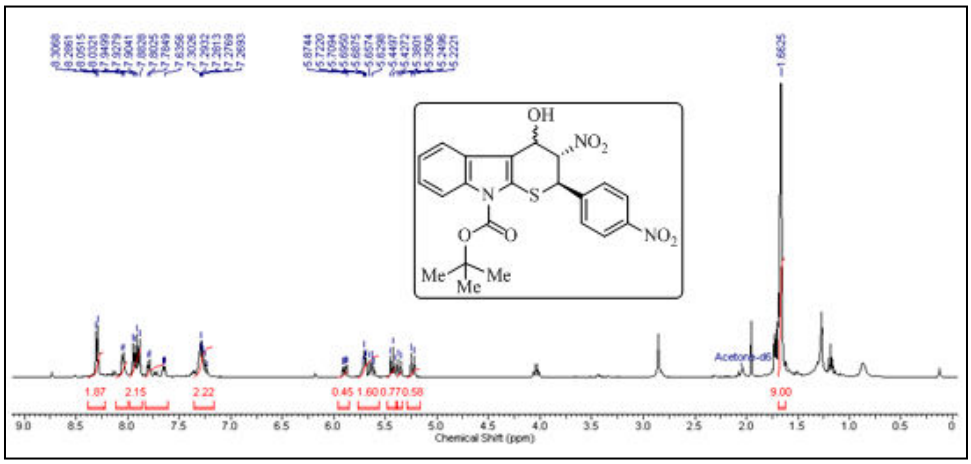


Figure 2.33 400 MHz ^{1}H NMR spectrum of **3l** and **4l** in acetone-d_6

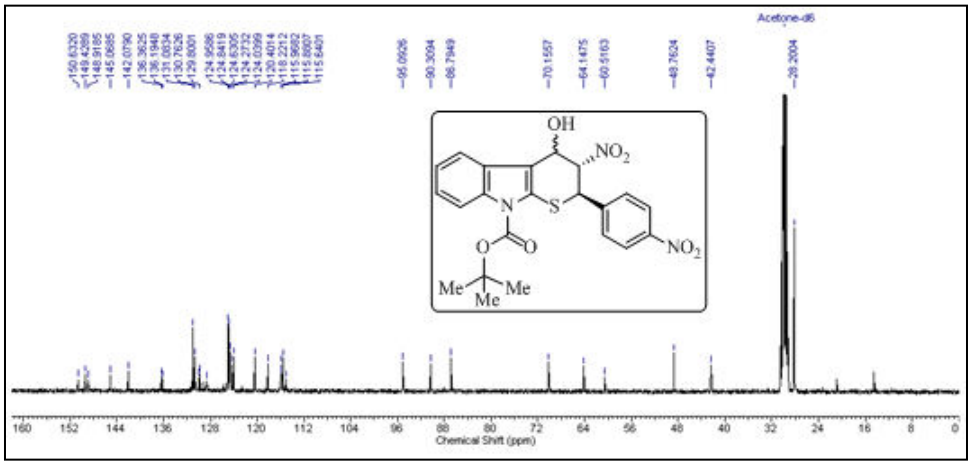


Figure 2.34 100 MHz ^{13}C NMR spectrum of **3l** and **4l** in acetone-d_6

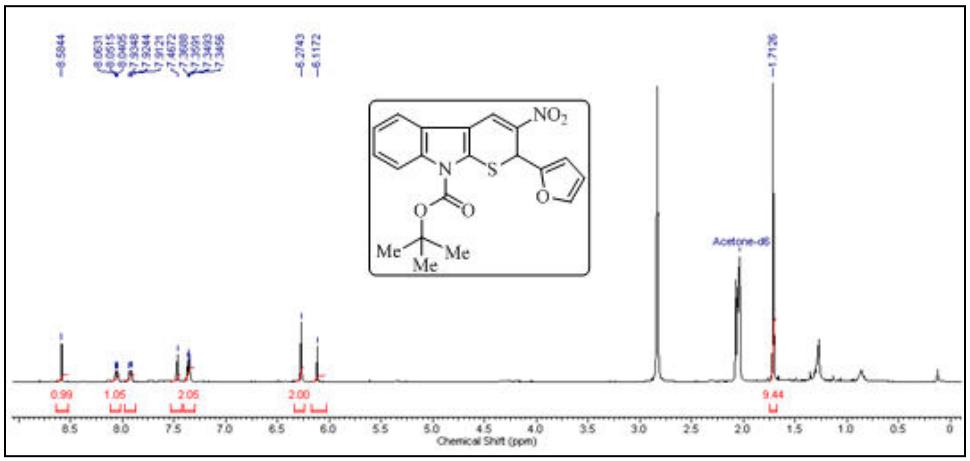


Figure 2.35 400 MHz ^{1}H NMR spectrum of **3m** in acetone-d_6

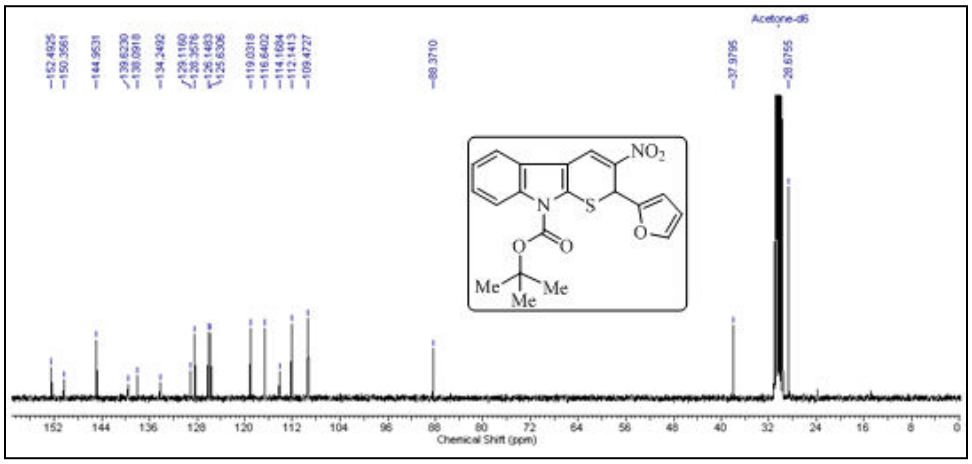


Figure 2.36 100 MHz ^{13}C NMR spectrum of **3m** in acetone-d_6

2.8 COSY and HMQC NMR of 3a and 4a

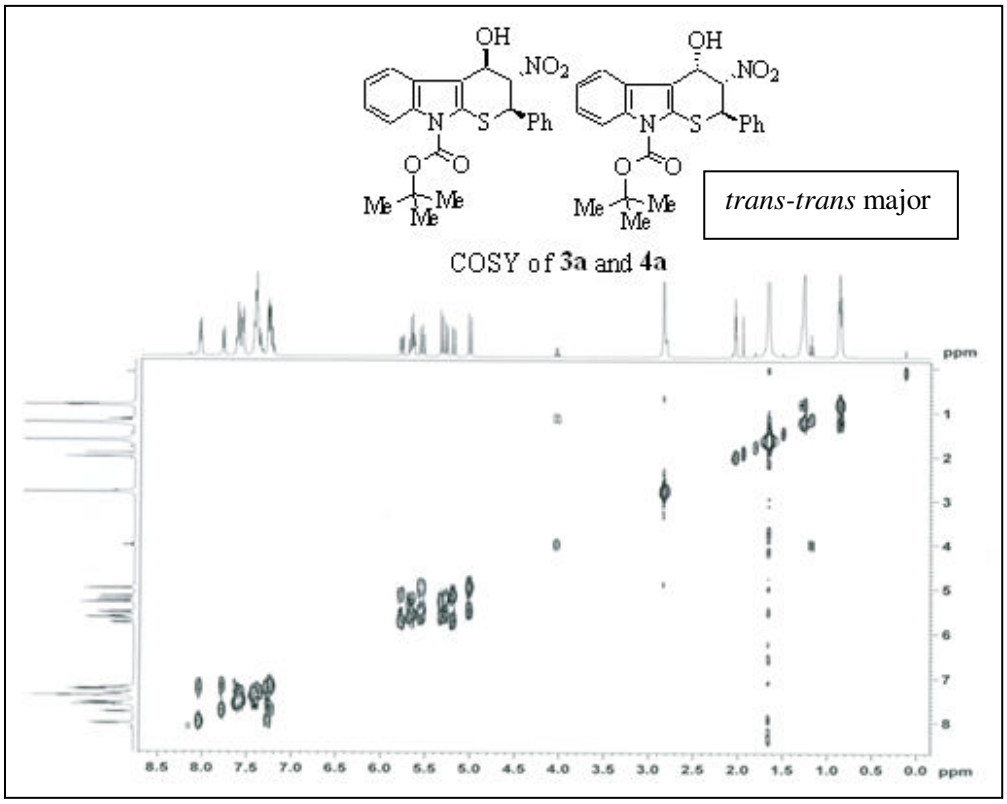


Figure 2.37 COSY NMR spectrum of **3a** and **4a** in acetone-d_6

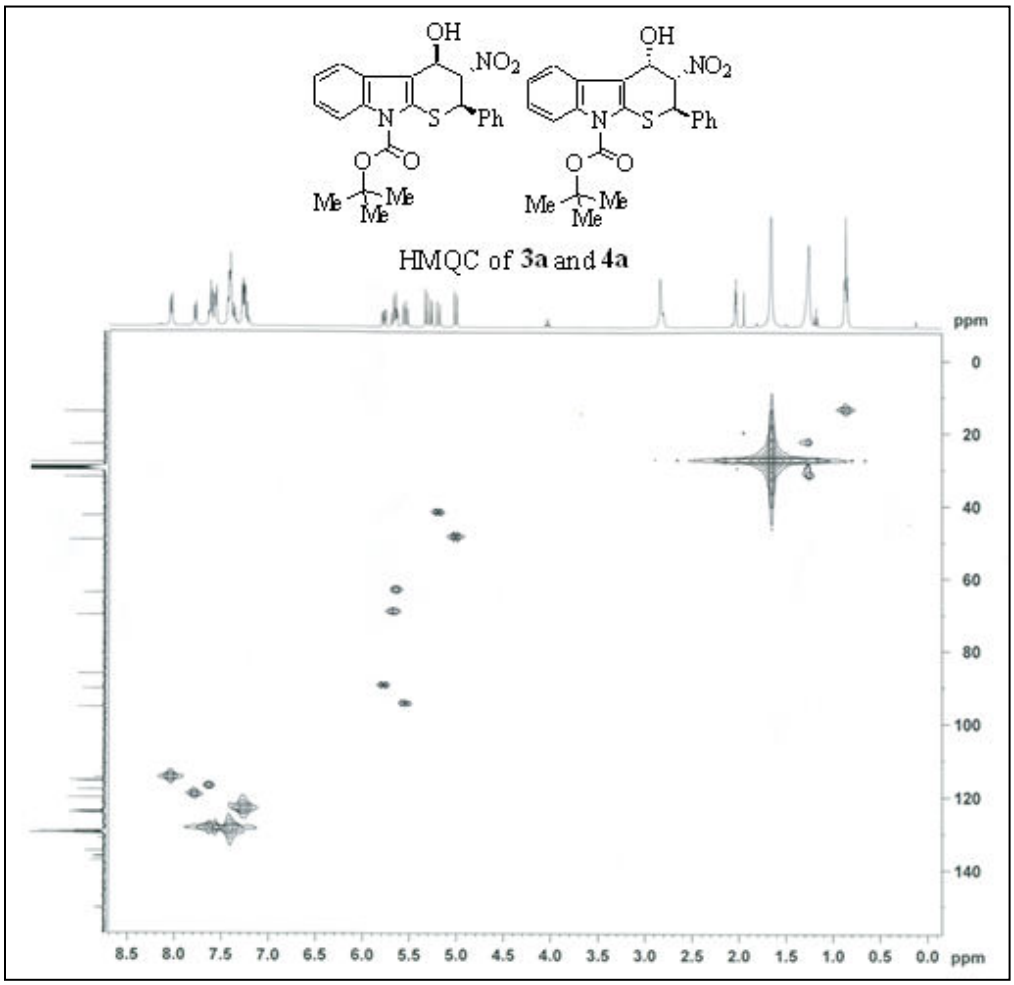
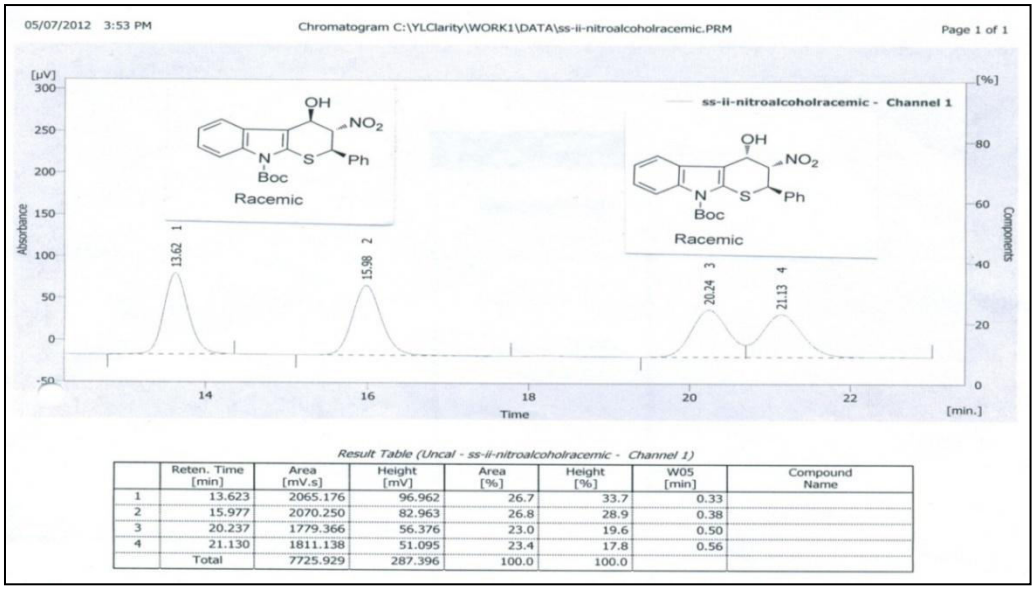


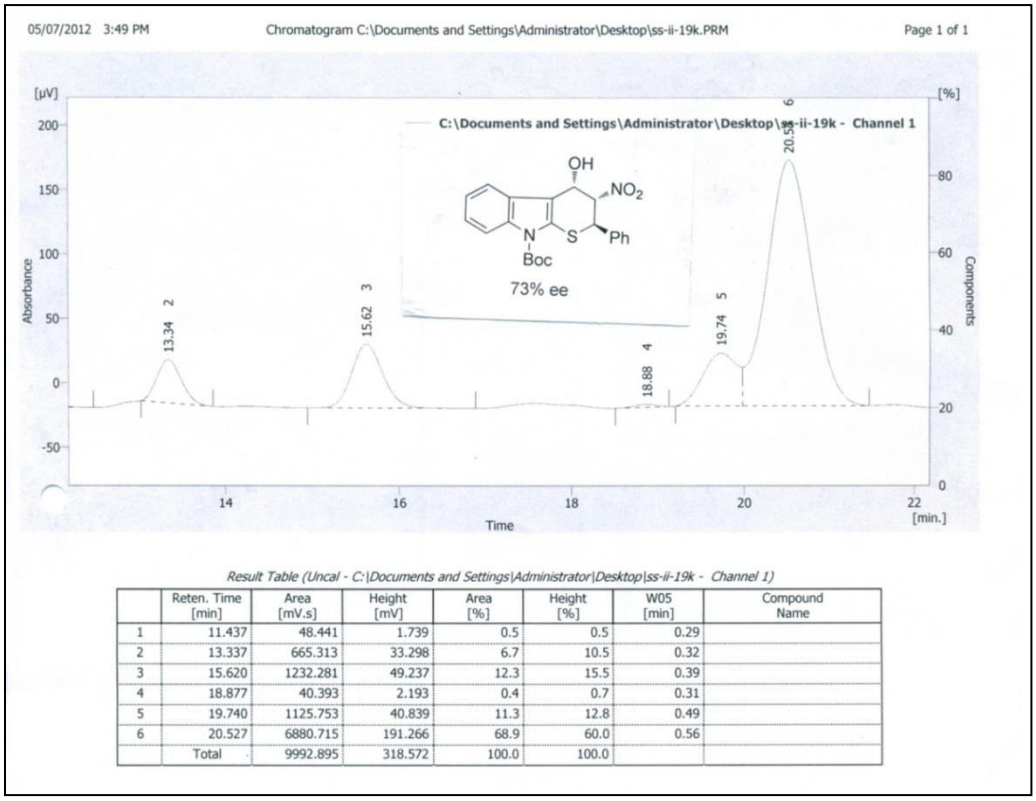
Figure 2.38 HMQC NMR spectrum of **3a** and **4a** in acetone-d_6

2.9 Enantiomeric excess graph



Result Table (Uncal - ss-ii-nitroalcoholracemic - Channel 1)

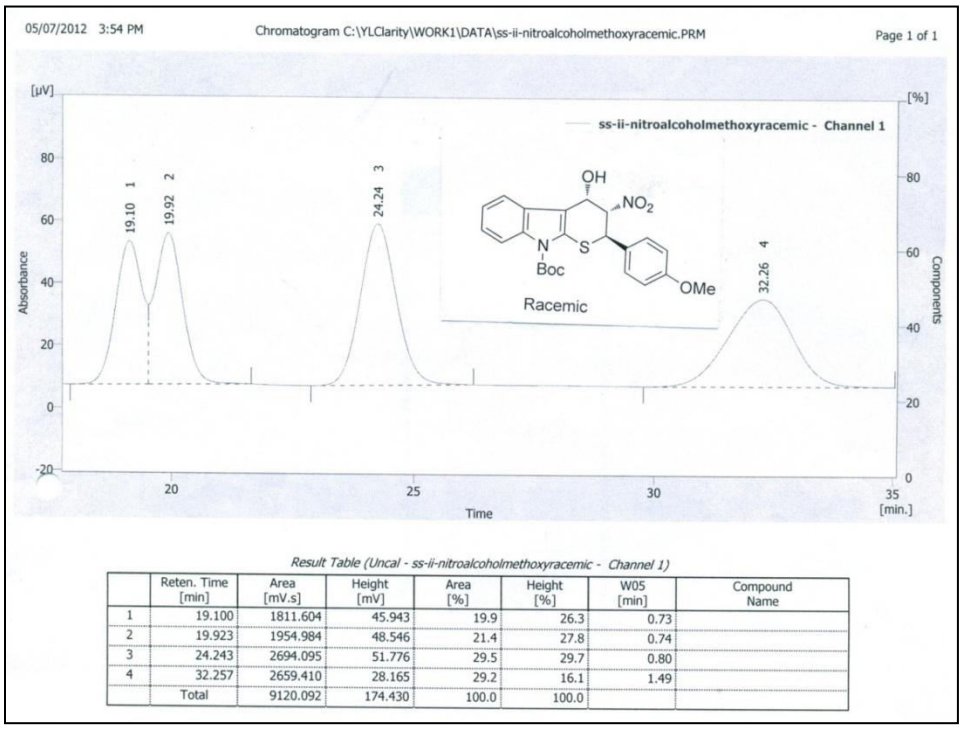
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	13.623	2065.176	96.962	26.7	33.7	0.33	
2	15.977	2070.250	82.963	26.8	28.9	0.38	
3	20.237	1779.366	56.376	23.0	19.6	0.50	
4	21.130	1811.138	51.095	23.4	17.8	0.56	
	Total	7725.929	287.396	100.0	100.0		



Result Table (Uncal - C:\Documents and Settings\Administrator\Desktop\ss-ii-19k - Channel 1)

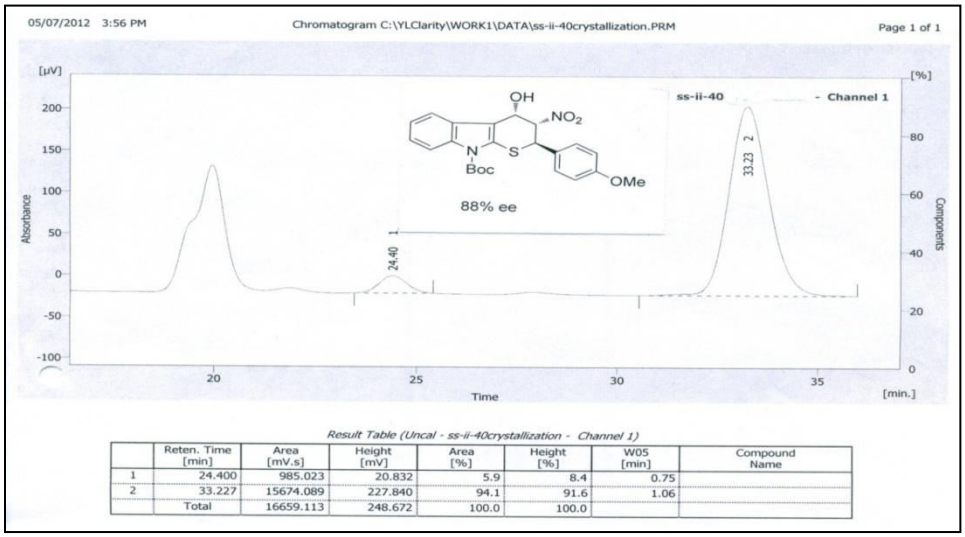
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	11.437	48.441	1.739	0.5	0.5	0.29	
2	13.337	665.313	33.298	6.7	10.5	0.32	
3	15.620	1232.281	49.237	12.3	15.5	0.39	
4	18.877	40.393	2.193	0.4	0.7	0.31	
5	19.740	1125.753	40.839	11.3	12.8	0.49	
6	20.527	6880.715	191.266	68.9	60.0	0.56	
	Total	9992.895	318.572	100.0	100.0		

Figure 2.39 Enantiomeric excess graph of **3a** and **4a**



Result Table (Uncal - ss-ii-nitroalcoholmethoxyracemic - Channel 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	19.100	1811.604	45.943	19.9	26.3	0.73	
2	19.923	1954.984	48.546	21.4	27.8	0.74	
3	24.243	2694.095	51.776	29.5	29.7	0.80	
4	32.257	2659.410	28.165	29.2	16.1	1.49	
	Total	9120.092	174.430	100.0	100.0		



Result Table (Uncal - ss-ii-40crystallization - Channel 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	24.400	985.023	20.832	5.9	8.4	0.75	
2	33.227	15674.089	227.840	94.1	91.6	1.06	
	Total	16659.113	248.672	100.0	100.0		

Figure 2.40 Enantiomericexcess graph of compound **3f** and **4f**

2.10 References

1. Elhag M. A., Gabra A. M., Gabra N. M., Ismail O. B., Mutwakel S. M., Baseer M. A. (2013), Synthesis, characterization, docking studies and bio-efficacy evaluation of novel chalcones, *Journal of Chemical and Pharmaceutical Research*, 5(7), 329-334.

2. Takayama H., Misawa K., Okada N., Ishikawa H., Kitajima M., Hatori Y., Murayama T., Wongseripipatana S., Tashima, K., Matsumoto K., Horie S. (2006), New procedure to mask the 2,3-π bond of the indole nucleus and its application to the preparation of potent opioid receptor agonists with a Corynanthe skeleton, *Org. Lett*., 8, 5705-5708 (DOI: 10.1021/ol062173k).

3. Tietze L. F., Major F. (2006), Synthesis of new water-soluble DNA-binding subunits for analogues of the cytotoxic antibiotic CC-1065 and their prodrugs, *Eur. J. Org. Chem.*, 10, 2314-2321 (DOI: 10.1002/ejoc.200500060).

4. Hopkins C. R., O'Neil S. V., Laufersweiler M. C., Wang Y., Pokross M., Mekel M., Evdokimov A., Walter R., Kontoyianni M., Petrey M. E., Sabatakos G., Roesgen J. T., Richardson E., Demuth T. P. (2006), Design and synthesis of novel N-sulfonyl-2-indole carboxamides as potent PPAR-*c* binding agents with potential application to the treatment of osteoporosis, *Bioorg. Med. Chem. Lett.*, 16, 5659-5663 (DOI: 10.1016/j.bmcl.2006.08.003).

5. Henderson J.L., McDermott S. M., Buchwald S. L. (2010), Palladium-catalyzed amination of unprotected halo-7-azaindoles, *Org.Lett.*, 15, 12, 4438-4441 (DOI: 10.1021/ol101928m).

6. Cacchi S., Fabrizi G. (2005), Synthesis and functionalization of indoles through palladium-catalyzed reactions, *Chem. Rev.*, 105, 2873-2920 (DOI: 10.1021/cr100403z).

7. Humphery G. R., Kuethe J. T. (2006), Practical methodologies for the synthesis of indoles, *Chem. Rev.*, 106, 2875-2911 (DOI: 10.1021/cr0505270).

8. Agarwal S., Caemmerer S., Filali S., Froehner W., Knoell J., Krahl M. P., Reddy K. R., Knoelker H.-J. (2005), Novel routes to pyrroles, indoles and carbazoles- Applications in natural product synthesis, *Current Organic Chemistry*, 15, 1601-1614 (DOI: 10.2174/138527205774370496).

9. Pal R., Gilbert K., Zouhair B., Joachim J., Marc L. B. (2013), Indenoindoles and cyclopentacarbazoles as bioactive compounds: Synthesis and biological applications, *Eur. Jour. of Med. Chem.*, 69, 465-479 (DOI: 10.1016/j.ejmech.2013.08.049).

10. Pereira N. A. L., Sureda F. X., Perez M., Amat M., Santos M. M. M. (2016), Enantiopure indolo[2,3-*a*]quinolizidines: Synthesis and evaluation as NMDA receptor antagonists, *Molecules*, 21, 1027/1-1027/12 (DOI: 10.3390/molecules21081027).

11. Jia W.-b., Wang H.-W., Yang L.-M., Lu H.-B., Kong L., Tian Y.-P., Tao X.-T., Yang J.-X. (2013), Synthesis of two novel indolo[3,2-*b*]carbazole derivatives with aggregation-enhanced emission property, *Jour. of Mater. Chem. C*, 42, 7092-7101 (DOI: 10.1039/c3tc31590h).

12. Granger D. B., Mei Y., Thorley K. J., Parkin S. R., Jurchescu O. D., Anthony J. E. (2016), Synthesis and electrical properties of derivatives of 1,4-*bis*(trialkylsilylethynyl)benzo[2,3-*b*:5,6-*b*']diindolizines, *Org. Lett*., 23, 6050-6053 (DOI: 10.1021/acs.orglett.6b02991).

13. Takada S., Ishizuka N., Sasatani T., Makisumi Y., Jyoyama H., Hatakeyama H., Asanuma F., Hirose K. (1984), Studies on fused indoles II. Structural modifications and analgesic activity of 4-

aminomethyltetrahydrothiopyrano[3,2-*b*]indole, *Chem. Pharm. Bull.*, 32, 877-886.

14. Ishizuka N., Sato T., Makisumi Y. (1990), Indole Grignard reaction III. Synthesis, crystal structure and analgesic activity of (*R*) and (*S*)-3-amino-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles, *Chem. Pharm. Bull.*, 38, 1396-1399.

15. Makisumi Y., Sasatani T. (1990), Tetrahydrothiopyrano[3,2-*b*]indole derivatives, U.S. Patent No. 4,910,318.

16. Takada S., Makisumi Y. (1984), Studies on fused Indole I. Novel synthesis of 4-aminomethyltetrahydrothiopyrano[2,3-*b*]indole through a Thio-Claisen rearrangement, *Chem. Pharm. Bull*., 32, 872-876.

17. Majumdar K. C., Debnath P., Alam S., Maji P. K. (2007), Thiol-mediated radical cyclization: Regioselective formation of indole-annulated sulfur heterocycles by tandem cyclization, *Tetrahedron Lett*., 48, 7031-7033 (DOI: 10.1016/j.tetlet.2007.07.132).

18. Moghaddam F. M., Kiamehr M., Taheri S., Mirjafary Z. (2010), Synthesis of novel polycyclic indole-annulated thiopyranocoumarin derivatives *via* domino Knoevenagel-hetero-Diels-Alder reaction in aqueous media, *Helv. Chim. Acta* , 93, 964-973.

19. Majumder S., Bhuyan P. J. (2012), Synthesis of some novel and complex thiopyranoindole derivatives from simple oxindole *via* intramolecular domino hetero Diels-Alder reactions, *Tetrahedron Lett.*, 53, 137-140 (DOI: 10.1016/j.tetlet.2011.10.133).

20. Majumder S., Bhuyan P. J.(2012), Stereoselective synthesis of novel annulated thiopyranoindole derivatives from simple oxindole via intramolecular 1,3-dipolar cycloaddition reactions of nitrone and nitrile oxide, *Tetrahedron Lett*., 53, 762-764 (DOI: 10.1016/j.tetlet.2011.11.136).

21. Moghaddam F. M., Mirjafary Z., Saeidian H., Kiamehr M., Taheri S., Kiamehr M. (2010), Facile entry to polycyclic indolylhydroquinoline skeletons via tandem C-alkylation and intramolecular S-alkylation, *Tetrahedron*, 66, 134-138 (DOI: 10.1016/j.tet.2009.11.032).

22. Moghaddam F. M., Foroushani B. K., Sobhani M., Masoud N., Khodabakhshi M. R., Weng N. S. (2013), The stereoselective synthesis of tetrahydrothiopyrano[2,3-*b*]indole skeletons *via* tandem reaction of indoline-2-thiones to Baylise-Hillman adduct acetates, *Tetrahedron*, 69, 8169-8173 (DOI: 10.1016/j.tet.2013.07.043).

23. Balme G., Bossharth E., Monteiro N. (2003), Pd-assisted multicomponent synthesis of heterocycles, *Eur. J. Org. Chem.*, 4101-4111 (DOI: 10.1002/ejoc.200300378).

24. Bräse S., Gil C., Knepper K. (2002), The recent impact of solid-phase synthesis on medicinally relevant benzoannelated nitrogen heterocycles, *Bioorg. Med. Chem. Lett.*, 10, 2415-2437 (DOI: 10.1016/S0968-0896(02)00025-1).

25. Dömling A., Ugi I. (2000), Multicomponent reactions with isocyanides, *Angew. Chem. Int. Ed.*, 39, 3168-3210 (DOI: 10.1002/1521-3773(20000915)39).

26. Ishikawa H., Suzuki T., Hayashi Y. (2009), High-yielding synthesis of the anti-influenza neuramidase inhibitor (-)-Oseltamivir by three "one-pot" operations, *Angew. Chem. Int. Ed.*, 48, 1304-1307 (DOI: 10.1002/anie.200804883).

27. Ishikawa H., Honma M., Hayashi Y. (2011), One-pot high-yielding synthesis of the DPP4-selective inhibitor ABT-341 by a four-component coupling mediated by a diphenylprolinolsilyl ether, *Angew. Chem. Int. Ed.*, 50, 2824-2827 (DOI: 10.1002/anie.201006204).

28. Enders D., Huttl M. R. M., Runsink J., Raabe G., Wendt B. (2007), Organocatalytic one-pot asymmetric synthesis of functionalized tricyclic carbon frameworks from a triple-cascade/Diels-Alder sequence, *Angew. Chem. Int. Ed.*, 46, 467-469 (DOI: 10.1002/anie.200603434).

29. Ramón D. J., Yus M. (2005), Asymmetric multicomponent reactions (AMCRs): The new frontier, *Angew. Chem. Int. Ed.*, 44, 1602-1634 (DOI: 10.1002/anie.200460548).

30. Tietze L. F., Brasche G., Gericke K. M. (2006), Domino reaction in organic synthesis; wiley-VCH: Weinheim (DOI: 10.1002/9783527609925.fmatter).

31. Sunderhaus J. D., Dockendroff C., Martin S. F. (2007), Applications of multicomponent reactions for the synthesis of diverse heterocyclic scaffolds, *Org. Lett.*, 9, 4223-4226 (DOI: 10.1021/ol7018357).

32. Samanta S., Perera S., Zhao C.-G. (2010), Organocatalytic enantioselective synthesis of both diastereomers of α-Hydroxyphosphinates, *J. Org. Chem.*, 75, 1101-1106 (DOI: 10.1021/jo9022099).

33. Hayashi Y., Samanta S., Itoh T., Ishikawa H. (2008), Asymmetric, catalytic and direct self-Aldol reaction of acetaldehyde catalyzed by diarylprolinol, *Org. Lett.*, 10, 5581-5583 (DOI: 10.1021/ol802438u).

34. Hayashi Y., Samanta S., Gotoh H., Ishikawa H. (2008), Asymmetric Diels-Alder reactions of α,β-unsaturated aldehydes catalyzed by a diarylprolinolsilyl ether salt in the presence of water, *Angew. Chem., Int. Ed.*, 47, 6634-6637 (DOI: 10.1002/ange.200801408).

35. Samanta S., Krause J., Mandal T., Zhao C.-G. (2007), Inverse-electron-demand hetero-Diels-Alder reaction of *β,γ*-unsaturated α-

ketophosphonates catalyzed by prolinaldithioacetals, *Org. Lett*., 9, 2745-2748 (DOI: 10.1021/ol071097y).

36. Samanta S., Zhao C.-G. (2006), Organocatalytic enantioselective synthesis of α-hydroxyphosphonates, *J. Am. Chem. Soc.*, 128, 7442-7443 (DOI: 10.1021/ja062091r).

37. Samanta S., Liu J., Dodda R., Zhao C.-G. (2005), C_2-Symmetric bisprolinamide as a highly efficient catalyst for direct Aldol reaction, *Org. Lett*., 7, 5321-5323 (DOI: 10.1021/ol052277f).

38. Mandal T., Samanta S., Zhao C.-G. (2007), Organocatalytic highly enantioselective nitroaldol reaction of α-Ketophosphonates and nitromethane, *Org. Lett*., 9, 943-945 (DOI: 10.1021/ol070209i).

39. Samanta S., Zhao C.-G. (2007), Organocatalyzednitroaldol reaction of α-ketophosphonates and nitromethane revisited, *Arkivoc*, 13, 218-226.

40. Song C. E. (2009), Cinchona alkaloids in synthesis and catalysis, ligands, immobilization and organocatalysis; Wiley-VCH.

41. Chauhan P., Chimni S. S. (2012), Recent advances in asymmetric organocatalytic conjugate addition of arenes and hetero-arenes, *RSC Adv*., 2, 6117-6134 (DOI: 10.1039/c2ra20544k).

42. Li H., Wang B., Deng L. (2006), Enantioselective Nitroaldol reaction of α-ketoesters catalyzed by cinchona alkaloids, *J. Am. Chem. Soc*., 128, 732-733 (DOI: 10.1021/ja057237l).

43. Marcelli T., Van der Haas R. N. S., Van Maarseveen J. H., Hiemstra H. (2005), Cinchona derivatives as bifunctional organocatalysts for the direct asymmetric Nitroaldol (Henry) reaction, *Synlett*, 2817-2819 (DOI: 10.1055/s-2005-918935).

44. Corey E. J., Zhang F. Y. (1999), *re*- and *si*-Face-Selective Nitroaldol reactions catalyzed by a rigid chiral quaternary ammonium salt: A

highly stereoselective synthesis of the HIV Protease inhibitor Amprenavir (Vertex 478), *Angew. Chem. Int. Ed.*, 38, 1931-1934 (DOI: 10.1002/(SICI)1521-3773(19990712)38).

45. Ooi T., Maruoka K. (2004), Asymmetric organocatalysis of structurally well-defined chiral quaternary ammonium fluorides, *Acc. Chem. Res.*, 37, 526-533 (DOI: 10.1021/ar030060k).

46. Li H., Wang Y., Tang L., Deng L. (2004), Highly enantioselective conjugate addition of malonate and *β*-ketoester to nitroalkenes: Asymmetric C-C bond formation with new bifunctional organic catalysts based on cinchona alkaloids, *J. Am. Chem. Soc*., 126, 9906-9907 (DOI: 10.1021/ja057237).

47. Li H., Wang Y., Tang L., Wu F., Liu X., Guo C., Foxman B. M., Deng L. (2005), Stereocontrolled creation of adjacent quaternary and tertiary stereocenters by a catalytic conjugate addition, *Angew. Chem. Int. Ed.*, 44, 105-108 (DOI: 10.1002/anie.200461923).

48. Liu X., Li H., Deng L. (2005), Highly enantioselective amination of α-substituted α-cyanoacetates with chiral catalysts accessible from both quinine and quinidine, *Org. Lett.*, 7, 167-169 (DOI: 10.1021/ol048190w).

49. Li H., Song J., Liu X., Deng L. (2005), Catalytic enantioselective C-C bond forming conjugate additions with vinyl sulfones, *J. Am. Chem. Soc*., 127, 8948-8949 (DOI: 10.1021/ja0511063).

50. Bella M., Jorgensen K. A. (2004), Organocatalytic enantioselective conjugate addition to alkynones, *J. Am. Chem. Soc*., 126, 5672-5673 (DOI: 10.1021/ja0493594).

51. Gogoi S., Zhao C.-G. (2009), Organocatalyzed enantioselective synthesis of 6-amino-5-cyanodihydropyrano[2,3-*c*]pyrazoles, *Tetrahedron Lett*., 50, 2252-2255 (DOI: 10.1016/j.tetlet.2009.02.210).

52. Liu Y.-Z., Cheng R.-L., Xu P.-F. (2011), Asymmetric Michael addition of 1-acetylindolin-3-ones to β-nitrostyrenes catalyzed by bifunctional thioureas: A simple access to 2-functionalized indoles, *J. Org. Chem.*, 76, 2884-2887 (DOI: 10.1021/jo102022g).

53. Lu S.-C., Duan X.-Y., Shi Z.-J., Li B., Ren Y.-W., Zhang W., Zhang Y.-H.,Tu Z.-F. (2009), Photoinduced intramolecular addition of 3-acyl-2-haloindoles to alkenes, *Org. Lett.*, *11*, 3902-3905 (DOI: 10.1021/ol901498f).

54. Li H., Wang Y., Liang T., Deng L. (2004), Highly enantioselective conjugate addition of malonate and *β*-ketoester to nitroalkenes: Asymmetric C-C bond formation with new bifunctional organic catalysts based on cinchona alkaloids, *J. Am. Chem. Soc.*, *126*, 9906-9907 (DOI: 10.1021/ja0472811).

Chapter 3

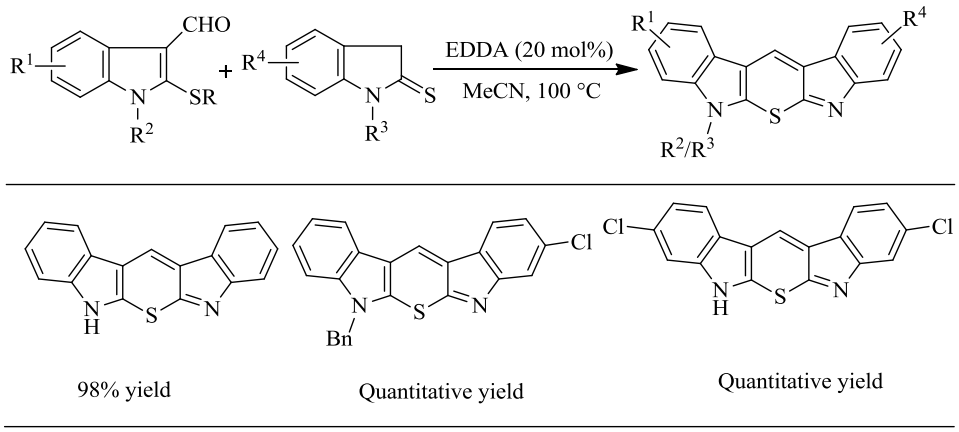
Efficient one-pot access to 2,9-dihydrothiopyrano [2,3-*b*]indole scaffolds showing large Stokes shifts

3.1 Introduction

Highly efficient synthesis of sulfur-containing polycyclic indole derivatives is a subject of growing interest in recent times due to the potential biological activities as well as application in material science, which has been thoroughly discussed in the introduction part of chapter 2. In this regard, a few methods have been developed for the synthesis of 2,9-dihydrothiopyrano[2,3-*b*]indoles as briefly discussed in the review **section 3.2**.

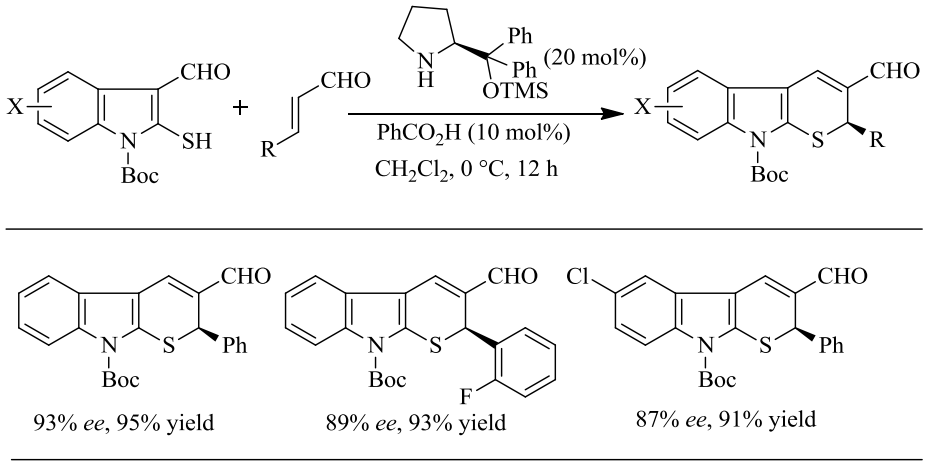
3.2 Review work

A versatile synthesis of symmetrically and unsymmetrically substituted thiopyrano[2,3-*b*:6,5-*b'*]diindoles has been developed by the condensation of 2-(alkylthio)-indole-3-carbaldehydes with indoline-2-thiones in the presence of catalytic amount of ethylenediaminediacetate (EDDA) in **Scheme 3.1**.[1]



Scheme 3.1 Synthesis of symmetrically and unsymmetrically substituted thiopyrano[2,3-*b*:6,5-*b'*]diindoles using EDDA

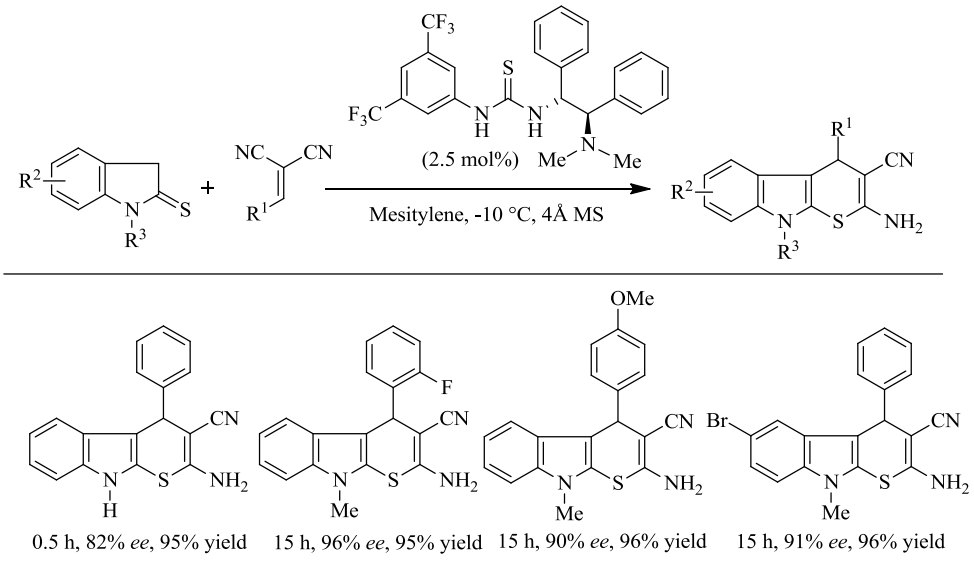
Zhou *et al.*[2] developed an efficient process for the enantioselective construction of dihydrothiopyrano[2,3-*b*]indole skeletons *via* a sulfa-Michael-Aldol reactions between 2-mercaptoindole-3-carbaldehydes and β-aryl-substituted acroleins in CH_2Cl_2 at 0 °C, promoted by chiral diphenyl prolinol TMS ether as catalyst as depicted in **Scheme 3.2**.



Scheme 3.2 Synthesis of enantioenriched version of 3-formyl-2-aryl-2,9-dihydrothiopyrano[2,3-*b*]indoles

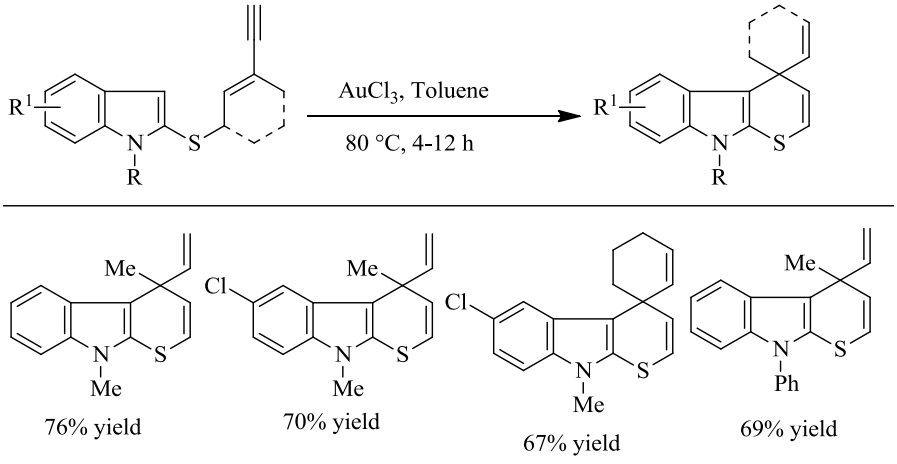
Wang *et al.* revealed that an excellent enantioselective synthesis of 4,9-dihydothiopyrano[2,3-*b*]indole scaffolds in good yields by the combination of indoline-2-thione with 2-benzylidenemalononitrile in the

mesitylene at -10 °C in the presence of molecular sieves using 2.5 mol% chiral thiourea catalyst (**Scheme 3.3**).[3]



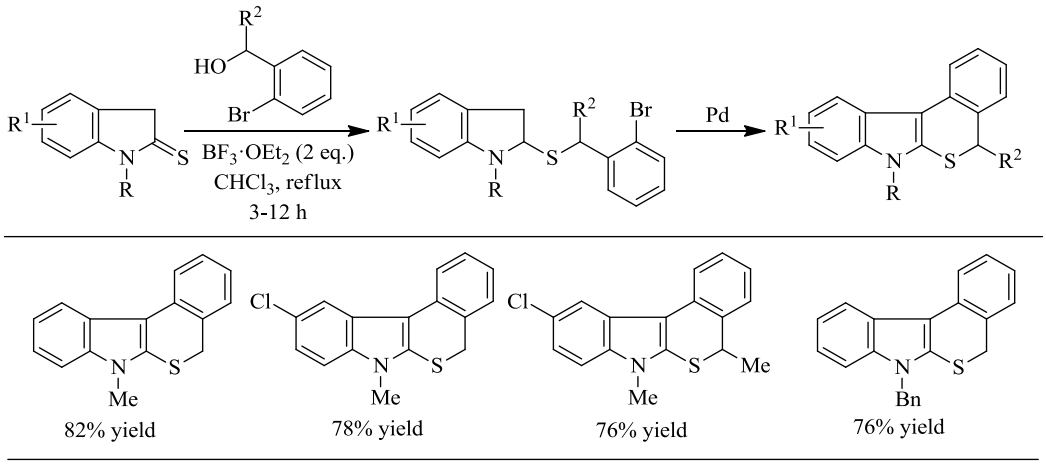
Scheme 3.3 Enantioselective synthesis of 4,9-dihydothiopyrano[2,3-*b*]indole scaffolds

An efficient methodology for the synthesis of indole-fused dihydrothiopyrans has been developed by Jha *et al.*[4] The protocol involves the intramolecular hydroarylation reaction *via* C3-H functionalization of conjugated ene-yne-substituted indole-sulfides in toluene at 80 °C catalyzed by $AuCl_3$ (**Scheme 3.4**).



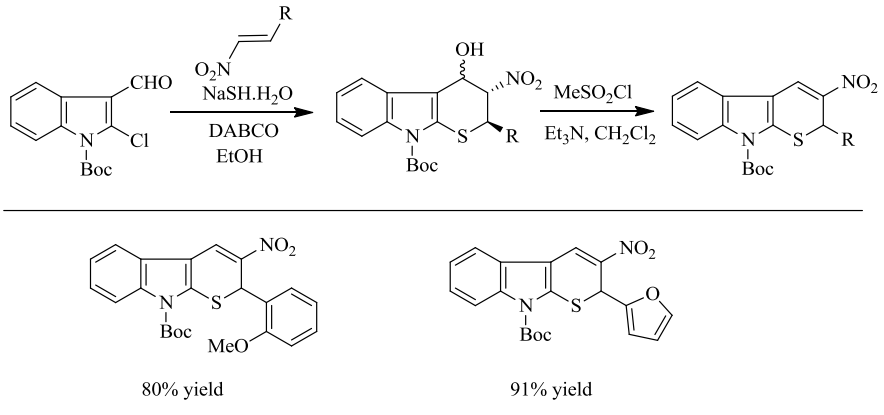
Scheme 3.4 Gold catalysed synthesis of indole-fused dihydrothiopyran

Very recently in 2016, a highly efficient and straightforward approach for the synthesis of 5,7-dihydroisothiochromeno[3,4-*b*]indole derivatives has been reported by Anil *et al. via* the palladium-catalysed direct arylation reaction of 2-(2-bromobenzylthio)-1-methyl-1*H*-indoles (**Scheme 3.5**).[5]



Scheme 3.5 Pd-catalysed access to dihydroisothiochromeno[3,4-*b*]indoles

Finally, Samanta *et al.*[6] also developed a first two-step synthetic method for the synthesis of 2,9-dihydrothiopyrano[2,3-*b*]indole derivative through a three-component reaction between N-Boc-2-chloro-3-formylindole, $NaSH \cdot H_2O$ and arylsubstituted-nitrostyrene in the presence of organic base, and the resulting product was dehydrated by $MeSO_2Cl/Et_3N$ reagent system (**Scheme 3.6**).



Scheme 3.6 Two-step synthetic method for the synthesis of 2,9-dihydrothiopyrano[2,3-*b*]indoles

Conclusion

The above discussed review work indicates that a few strategies are known for the access to dihydrothiopyrano[2,3-*b*]indole. Some methods efficiently give the mentioned derivatives in excellent yields with good to excellent enantioselectivities (*ee* > 96%). However, above method suffers several disadvantages such as harsh reaction conditions, multiple steps, expensive metal-salts used, poor substrate scope etc. Moreover, there is a no one-pot, organocatalytic method for the synthesis of 2,9-dihydrothiopyrano[2,3-*b*]indole derivative involving aryl/heteroary-substitutyed nitroolefins or nitrodienes as electrophiles. Hence, there is a still need a for one-pot high yielding and general protocol towards the synthesis of dihydrothiopyrano[2,3-*b*]indole derivatives.

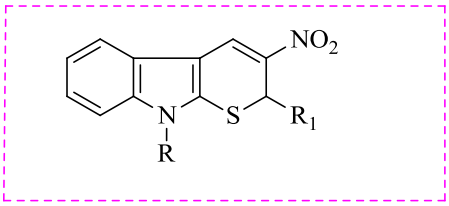
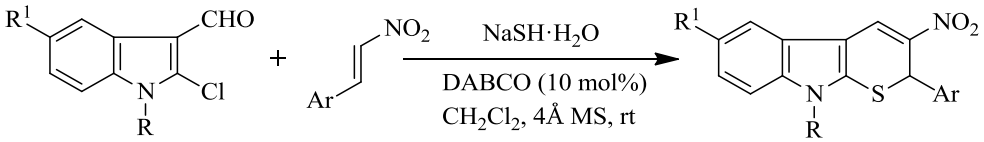


Figure 3.1 Representative structure of dihydrothiopyrano[2,3-*b*]indole derivatives

3.3 Present work

Recently reported a two-step synthetic method for the synthesis of 2,9-dihydrothiopyrano[2,3-*b*]indoles as shown in **Scheme 3.6**. In this regard, we seemed that the dehydration step may perform by using activated molecular sieves (MS) as well known drying agent for the liquids and gases[7-9] as well as promoting various organic transformations[10-12] instead of $MeSO_2Cl/Et_3N$ to produce the corresponding dihydrothiopyrano[2,3-*b*]indole.

As part of our continued interest towards the synthesis of polycyclic indole derivatives,[13-20] herein, we wish to report a mild, convenient, practical and general one-pot method for the synthesis of N-protected-2-aryl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole scaffolds *via* a tandem aromatic nucleophilic thiolation/thio-Michael/Henry reaction of N-protected-2-chloro-3-formylindoles, $NaSH \cdot H_2O$ with substituted nitroolefins/nitrodienes in CH_2Cl_2 at room temperature, followed by in situ dehydration using activated molecular sieves.



Scheme 3.7 One-step synthetic method for the synthesis of 2,9-dihydrothiopyrano[2,3-*b*]indoles

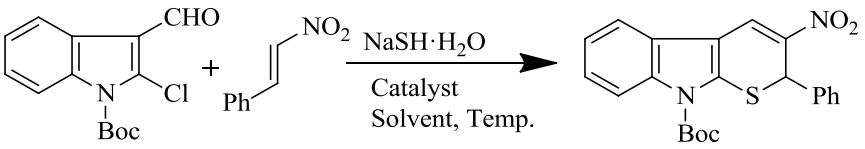
3.4 Results and Discussion

3.4.1 Screening of Solvents and Catalysts

We began a model reaction involving compound **1a**, *β*-nitrostyrene (**2a**) and $NaSH \cdot H_2O$ in methanol at room temperature catalyzed by DABCO as an organo base (**Table 3.1**). Interestingly, a little amount of dihydrothiopyrano[2,3-*b*]indole (**3aa**) was isolated after 24 h. The product was well characterized by its ^1H NMR which shows the appearance of only two peaks in the aliphatic regions at δ 1.67 and 5.78 corresponding to 9 hydrogens of Boc and 1 hydrogen of thiopyran ring while rest of the peaks appears in aromatic region. Further, ^{13}C NMR shows appearance of additional peaks in the aliphatic and aromatic regions. HRMS spectrum of

compound **3aa** shows the presence of molecular ion peak $[M+Na]^+$ at 431.1037 which corresponds to the molecular weight of the desired product. In order to get the better yield of **3aa**, we performed the several reactions in common organic solvents or neat conditions using easily available basic catalysts such as DABCO, DBU, Et_3N, Al_2O_3 and KF-Al_2O_3 at 60 °C.

Table 3.1 Reaction optimization to access 2,9-dihydrothiopyrano[2,3-*b*]indole scaffolds[a]



Entry	Catalyst	Solvent	T(°C)	T/h	Yield (%)[b]
1	DABCO	MeOH	rt	24	18
2	DABCO	MeOH	60	24	21
3	DABCO	EtOH	60	24	24
4	DABCO	THF	60	24	27
5	DBU	EtOH	70	24	31
6	Et_3N	EtOH	60	24	19
7[c]	Al_2O_3	Nil	60	4	32
8[c]	KF-Al_2O_3	Nil	60	4	37
9	DABCO	$CHCl_3$	rt	24	42
10	DABCO	CH_2Cl_2	rt	24	51
11[d]	**DABCO**	**CH_2Cl_2**	**rt**	**4**	**82**

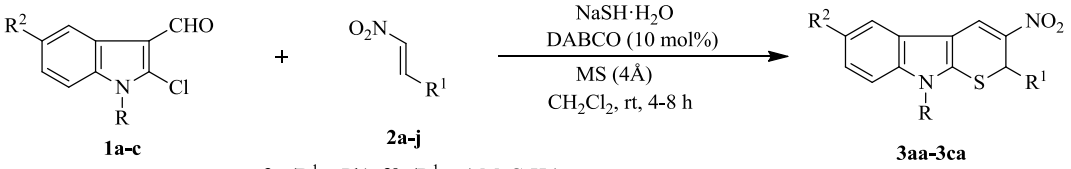
[a]Unless otherwise specified, all reactions were carried out at room temperature with **1a** (0.25 mmol), **2a** (0.3 mmol) and NaSH·H_2O (0.3 mmol) using 10 mol % catalysts in the specified solvent (2.0 mL). [b]Isolated yields after column chromatography. [c]Basic Al_2O_3 (500 mg). [d]Activated molecular sieves (4 Å, 300 mg).

The results indicated that all the cases produced unsatisfactory results. However, using DABCO as a catalyst, the yields of **3aa** were improved when the reaction was carried out in chlorinated solvents (CH_2Cl_2 and $CHCl_3$) at room temperature for 24 h. Gratifyingly, high yield (82%) of **3aa** was obtained in CH_2Cl_2 when the reaction was performed in the presence of activated molecular sieves (4 Å) as dehydrating agent for 4 h.

3.4.2 Generality and substrate scope

Having optimal reaction conditions in hand, a series of 2-aryl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole derivatives were synthesized *via* a one-pot domino reaction of several N-protected-2-chloro-3-formylindoles, $NaSH \cdot H_2O$ with aryl/hetero-aryl-substituted 2-nitroolefins in our established reaction conditions. The obtained results were collected in **Table 3.2**. Several indole derivatives (**1a**-**c**) were annulated smoothly with aryl-substituted-*β*-nitrostyrene possessing electron donating (Me, OMe, OBn) and electron withdrawing (Cl, NO_2, CN) substituents on aryl rings by this procedure. All led to the corresponding N-protected-2-aryl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole derivatives in good to high yields (74%-86%) within 4-8 h. Interestingly, heteroaryl-substituted *β*-nitroolefin (**2j**) was found to be a good thio-Michael-acceptor in our present conditions, resulting in excellent yield (89%) of corresponding product **3aj**. Moreover, several sensitive functional groups such as Cl, OMe, OBn, Boc, CO_2Et, NO_2, CN, furan etc. were unaffected under the present conditions.

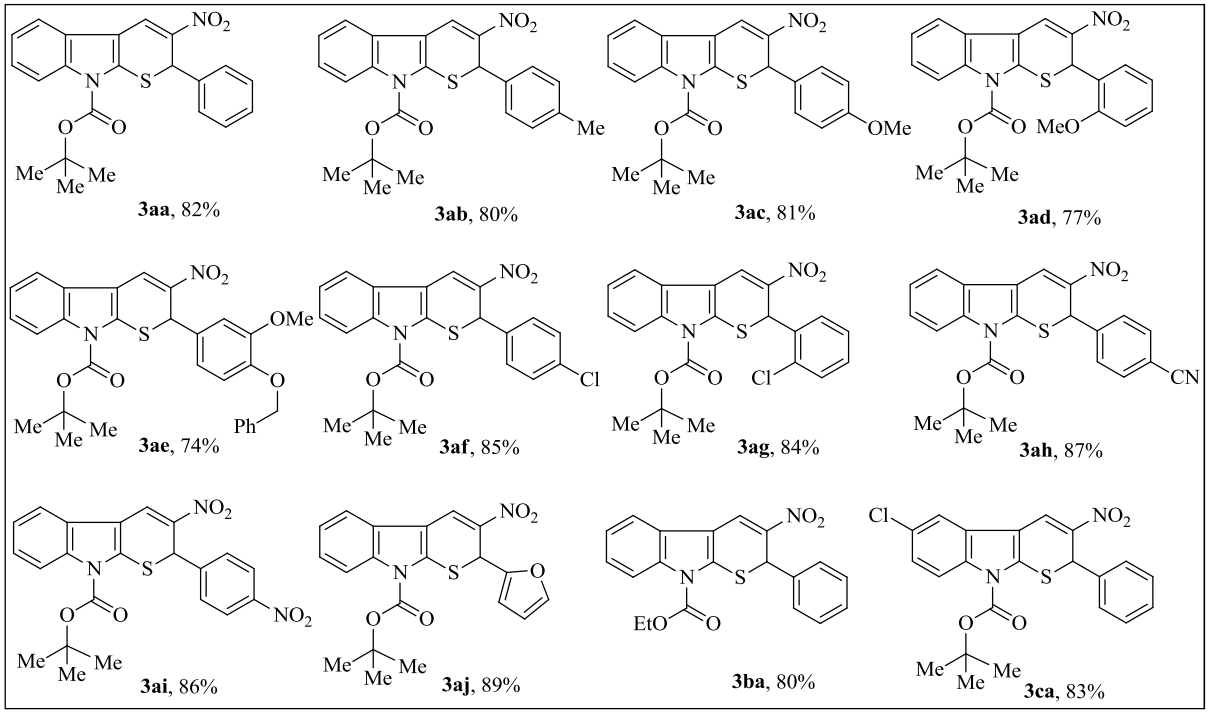
Table 3.2 DABCO catalyzed one-pot access to 2,9-dihydrothiopyrano [2,3-*b*]indole (**3aa-3ca**)[a]



1a-c + **2a-j** → **3aa-3ca**

1a: R = Boc, R^2 = H
1b: R = CO_2Et, R^2 = H
1c: R = Boc, R^2 = Cl

2a (R^1 = Ph), **2b** (R^1 = 4-MeC_6H_4),
2c (R^1 = 4-$MeOC_6H_4$), **2d** (R^1 = 2-$MeOC_6H_4$),
2e (R^1 = 3-MeO-4BnOC_6H_3), **2f** (R^1 = 4-ClC_6H_4),
2g (R^1 = 2-ClC_6H_4), **2h** (R^1 = 4-CNC_6H_4),
2i (R^1 = 4-$NO_2C_6H_4$), **2j** (R^1 = 2-furyl)

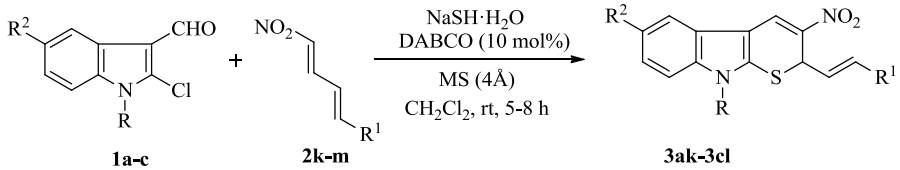


[a]Unless otherwise specified, all reactions were carried out at room temperature with **1a-c** (0.25 mmol), **2a-j** (0.3 mmol) and NaSH·H_2O (0.3 mmol) in the specified solvent (2.0 ml). Isolated yields after column chromatography.

In order to expand towards more substrate possibility, chemically challenging nitrodienes have been used as Michael acceptors in this MCR. As is evident from **Table 3.3**, the thio-Michael reaction between 2-mercapto-3-formylindoles (in situ generated from the reaction between **1a-1c** and NaSH·H_2O) and *δ*-arylsubstituted nitrodienes (**2k-2m**) took place exclusively at the *β*-positions of nitrodienes in our present conditions. As a result, all the reactions led to the corresponding (*E*)-2-styryl-substituted-3-

nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (**3ak** - **3cl**) in good to high (73% - 84%) yields as shown in **Table 3.3**.

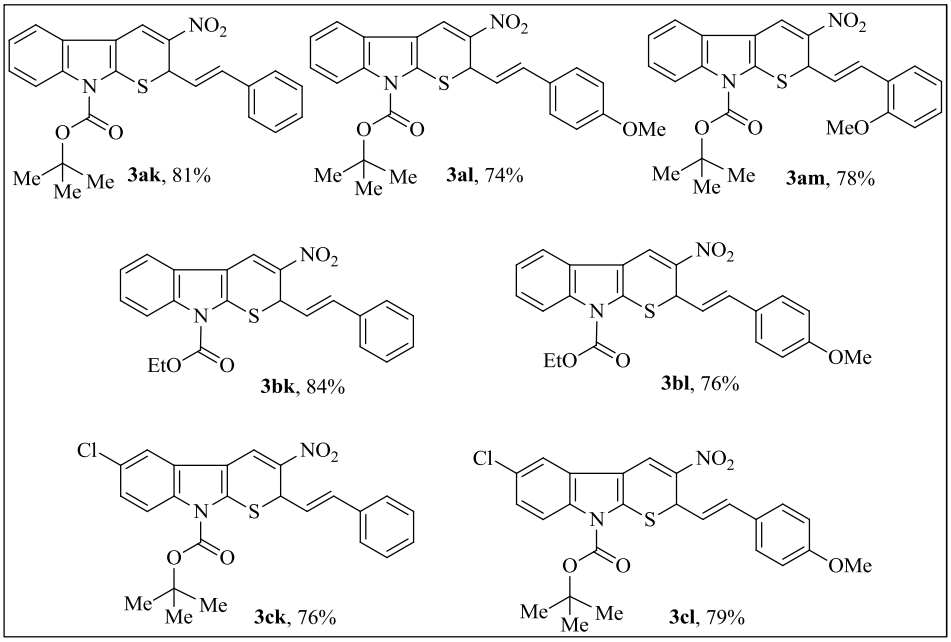
Table 3.3 DABCO catalyzed one-pot synthesis of 2-styrene-3-ene-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indoles (**3ak-3cl**)[a]



1a-c **2k-m** **3ak-3cl**

1a, R = Boc, R^2 = H
1b, R = CO_2Et, R^2 = H
1c, R = Boc, R^2 = Cl

2k: R^1 = Ph
2l: R^1 = 4-MeOPh
2m: R^1 = 2-MeOPh



[a]Unless otherwise specified, all reactions were carried out at room temperature with **1a-c** (0.25 mmol), **2k-m** (0.3 mmol) and NaSH·H_2O (0.3 mmol) in the specified solvent (2.0 ml). Isolated yields after column chromatography.

3.4.3 Spectroscopic properties of 2,9-dihydrothiopyrano [2,3-*b*]indole derivatives:

Physical appearances of all the synthesized compounds are red in color which prompted us to evaluate their spectroscopic properties. In this line, we began to examine the solvatochromic effects of compound **3ai** in

various organic solvents (spectroscopic grade). The results are systematically plotted in **Figure 3.2**. The compound **3ai** shows maximum absorption bands in the visible region at around 460-464 nm (approximately) in THF, ethyl acetate, ethanol and methanol. Whereas, small red shifts (10 - 16 nm) are observed in acetonitrile (λ_{max} 470 nm) and chloroform (λ_{max} 476 nm) solvents.

On the other hand, the emission maxima for **3ai** are strongly influenced by solvent polarity and exhibit bathochromic shifts as well as positive Stokes shifts with increasing polarity of solvents (**Figure 3.2**). For example, in case of non-polar aprotic solvents such as THF, EtOAc, $CHCl_3$ and MeCN, emission bands are shown at 580 nm, 592 nm and 604 nm respectively. The emission bands of **3ai** are further increased to 629 nm and 638 nm when emission spectra are recorded in high polar solvents such as EtOH and MeOH respectively. Thus, it is clearly indicated that the maximum Stokes shift value (5877 cm^{-1} or 174 nm) of compound **3ai** is observed in MeOH as compared to other solvents (4116 - 5841 cm^{-1} or 120 - 169 nm) recorded for this experiment.

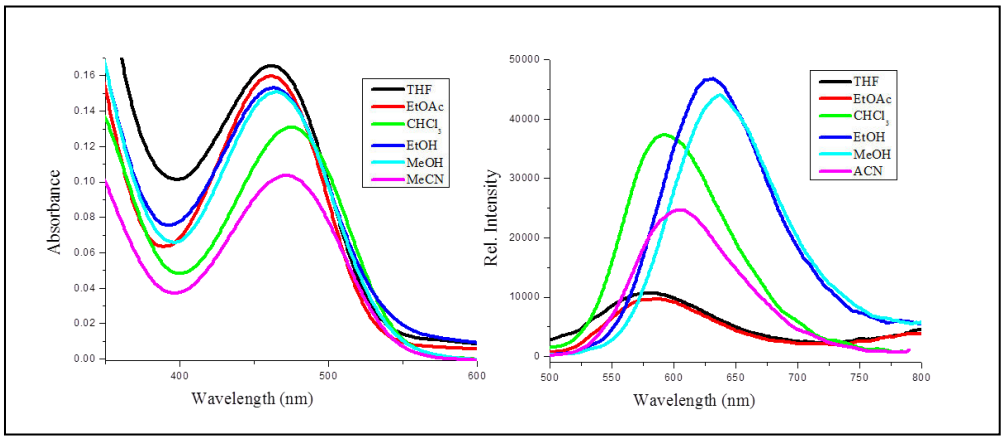


Figure 3.2 UV-Visible and emission spectra of **3ai**

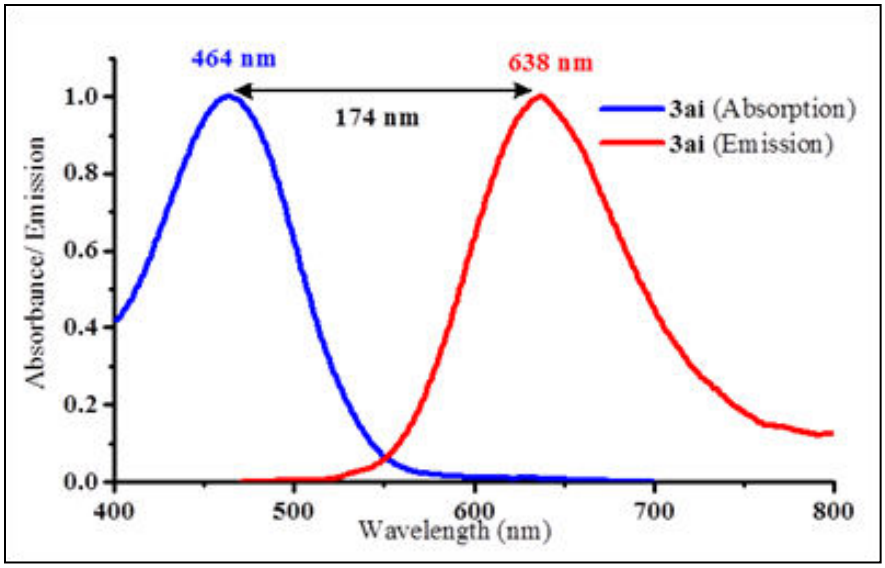


Figure 3.3 Stokes shift of **3ai** in methanol

In order to evaluate the general trends of these photophysical studies, we recorded all the synthesized 2,9-dihydrothiopyrano[2,3-*b*]indole derivatives in MeOH medium under similar conditions (**3aa**-**3cl**). The absorption and emission bands as well as their corresponding Stokes shift values are summarized in **Table 3.4**. As shown in **Table 3.4**, the UV-visible absorption maxima are shown at 456-465 nm which are almost independent nature of substituents and their positions on aryl rings (Entries 1-19, **Table 3.4** and **Figure 3.3**).

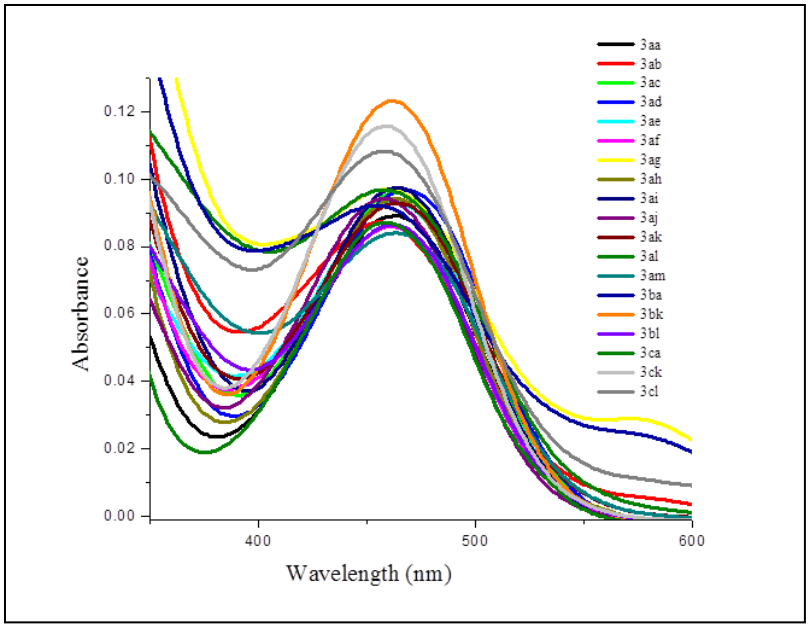


Figure 3.4 UV-Visible spectra of **3aa-3cl**

Similarly, all the compounds emit within the range at 623-641 nm, resulting in large positive Stokes shifts (5632-6081 cm^{-1}, **Table 3.4**). Therefore, the large Stokes shifts of 2,9-dihydrothiopyrano annulated indole derivatives may find out the potential application in material science.[21-24]

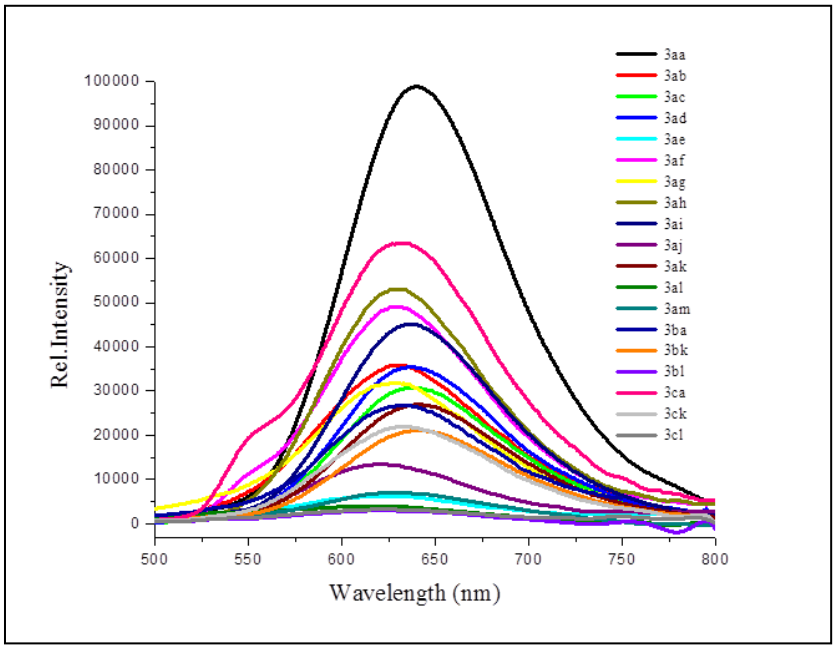


Figure 3.5 Emission spectra of **3aa-3cl**

Table 3.4 Absorption and fluorescence characteristics of derivatives in methanol (**3aa**-**3cl**):

Entry	Product	λ_a(nm)	λ_e(nm)	SS(nm)	SS(cm^{-1})
1	**3aa**	464	641	177	5950
2	**3ab**	456	631	175	6081
3	**3ac**	465	644	179	5977
4	**3ad**	469	643	174	5769
5	**3ae**	460	630	170	5866
6	**3af**	461	630	169	5818
7	**3ag**	465	630	165	5632
8	**3ah**	463	631	168	5750
9	**3ai**	464	638	174	5877
10	**3aj**	458	623	165	5782
11	**3ak**	465	641	176	5904
12	**3al**	458	629	171	5935
13	**3am**	461	631	170	5844
14	**3ba**	460	634	174	5966
15	**3bk**	461	631	170	5844
16	**3bl**	461	630	169	5818
17	**3ca**	461	632	171	5869
18	**3ck**	460	633	173	5941
19	**3cl**	458	631	173	5986

3.5 Conclusion

A one-pot direct method for the construction of unknown functionalized N-protected-2-aryl/styryl-substituted-3-nitro-2,9-dihydro-thiopyrano[2,3-*b*]indoles in CH_2Cl_2 is reported. The reaction proceeds through a tandem

aromatic nucleophilic thiolation/thio-Michael/Henry reaction between N-protected-2-chloro-3-formylindoles, $NaSH \cdot H_2O$ and substituted-nitroolefins/nitrodienes in the presence of DABCO, followed by in situ dehydration using activated molecular sieves (4 Å). The current method has several advantageous points such as mild reaction conditions, high yielding, no toxic by-products, broad substrate scope and construction of three new bonds (C−S, C−C and C=C) by single operation. Moreover, our synthesized compounds have shown the high positive Stokes shift values ($\leq 6081\ cm^{-1}$).

3.6 Experimental

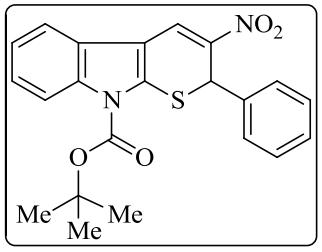
General Information

All reactions were carried out under air and monitoredby TLC using Merck 60 F254 pre coated silica gel plates (0.25 mm thickness) and the products were visualized by UV detection. Flash chromatography was carried out with silica gel (200−300 mesh). FT-IR spectra were recorded on a Bruker Tensor-27 spectrometer. ^{1}HNMR and ^{13}C NMR spectra were recorded on a Bruker Avance (III) 400 MHz spectrometer. Data for ^{1}H NMR are reported as a chemical shift, multiplicity (s=singlet, d=doublet, q=quartet, m=multiplet), coupling constant *J* (Hz), integration and assignment, data for ^{13}Care reported as a chemical shift. High resolutions mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. Absorption spectra were recorded using Varian UV-Vis spectrophotometer (model: cary 100). Emission spectra were recorded in a fluoromax-4p fluorimeter from Horiba Yovin (model: FM-100).

General procedure for the synthesis of 9-(*N-tert*-butoxycarbonyl)-2-phenyl-3-nitro-2,9-dihydrothiopyrano-[2,3-*b*]indole (3aa):

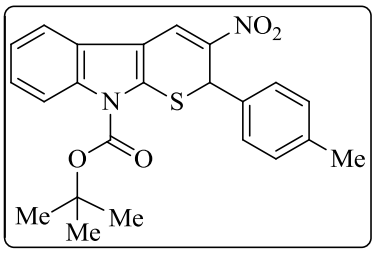
A mixture of N-protected-2-chloro-3-formylindole (**1a**, 0.25 mmol), $NaSH \cdot H_2O$ (0.3 mmol), *β*-nitrostyrenes (**2a**, 0.3 mmol), DABCO (10.0 mol%) and activated molecular sieves (300 mg, 4 Å) was stirred in CH_2Cl_2 (2.0 ml) at room temperature. The reaction mixture was monitored by TLC (Thin Layer Chromatography). Upon completion of the reaction, the product was directly purified by column chromatography over silica gel using EtOAc/hexane as an eluent to afford the corresponding pure product. All the products were synthesized in **Table 3.2** and **Table 3.3** by the above procedure and characterized by their corresponding spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR, HRMS).

9-(*N-tert*-butoxycarbonyl)-2-phenyl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3aa): 82% yield; **m.p.** 150 °C; **IR**

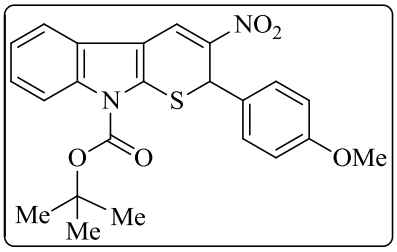


(KBr) ν 3443, 2924, 2852, 1721, 1618, 1495, 1480, 1446, 1402, 1361, 1321 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.54 (s, 1H), 8.00-8.01 (m, 1H), 7.64-7.66 (m, 1H), 7.30-7.36 (m, 4H), 7.24-7.26 (m, 2H), 5.78 (s, 1H), 1.68 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.7, 139.2, 138.2, 136.5, 134.3, 128.6, 128.3, 127.3, 126.2, 126.1, 124.4, 124.0, 111.7, 115.0, 112.3, 86.7, 42.2, 27.8; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{20}N_2O_4S$ $[M+Na]^+$: 431.1036, found: 431.1037.

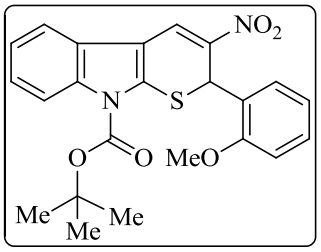
9-(*N-tert*-butoxycarbonyl)-2-(4-methylphenyl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ab): 80% yield; **m.p.** 160 °C; **IR** (KBr) ν 3442, 2961, 2924, 1736, 1626, 1580, 1507, 1491, 1479, 1444, 1400, 1370, 1355, 1315 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.52 (s, 1H), 7.98-8.00 (m, 1H), 7.63-7.65 (m, 1H), 7.29-7.34 (m, 2H), 7.19-7.23 (m, 2H), 7.04-7.06 (m, 2H), 5.75 (s, 1H), 2.27 (s, 3H), 1.69 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.0, 138.6, 136.8, 136.6, 134.7, 129.6, 127.6, 126.4, 126.3, 124.7, 124.3, 117.0, 115.3, 112.5, 86.9, 42.3, 28.1, 21.1; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{22}N_2O_4S$ $[M+Na]^+$: 445.1192, found: 445.1230.



9-(*N-tert*-butoxycarbonyl)-2-(4-methoxyphenyl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ac): 81% yield; **m.p.** 150 °C; **IR** (KBr) ν 3435, 2981, 2836, 1732, 1625, 1609, 1581, 1510, 1479, 1443, 1399, 1371, 1356, 1315 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.51 (s, 1H), 8.00-8.02 (m, 1H), 7.63-7.66 (m, 1H), 7.30-7.34 (m, 2H), 7.22-7.25 (m, 1H), 6.75-6.78 (m, 2H), 5.74 (s, 1H), 3.73 (s, 3H), 1.69 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.8, 149.0, 138.5, 136.8, 134.9, 131.7, 127.7, 127.6, 126.2, 124.7, 124.3, 116.9, 115.3, 114.2, 112.4, 86.9, 55.2, 42.1, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{22}N_2O_5S$ $[M+Na]^+$: 461.1142, found: 461.1087.

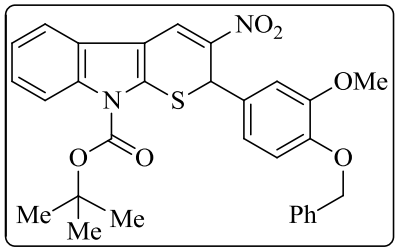


9-(*N-tert*-butoxycarbonyl)-2-(2-methoxyphenyl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ad): 77% yield; **m.p.** 157 °C; **IR** (KBr) ν 3440, 2977, 2928, 1730, 1622, 1598, 1582, 1489, 1445, 1403, 1370, 1357, 1320 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.62 (s,



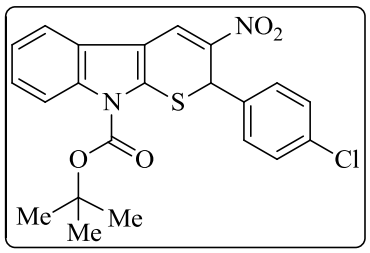
1H), 7.96 (d, J =8.04 Hz, 1H), 7.65 (d, J =7.04 Hz, 1H), 7.28-7.35 (m, 2H), 7.21-7.23 (m, 1H), 7.01-7.03 (m, 1H), 6.91-6.94 (m, 1H), 6.74-6.76 (m, 1H), 6.25 (s, 1H), 3.95 (s, 3H), 1.66 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.3, 149.0, 140.6, 136.8, 133.2, 129.6, 127.7, 127.6, 126.7, 126.6, 124.5, 124.2, 120.3, 116.9, 115.3, 111.9, 111.1, 86.7, 55.7, 36.1, 28.1; **HRMS** (ESI) m/z calcd for $C_{23}H_{22}N_2O_5S$ $[M+Na]^+$: 461.1142, found: 461.1137.

9-(*N-tert*-butoxycarbonyl)-2-(4-benzyloxy-3-methoxyphenyl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ae): 74% yield; **m.p.** 135 °C; **IR**



(KBr) ν 3441, 2925, 2853, 1717, 1620, 1510, 1492, 1481, 1461, 1444, 1400, 1371, 1358, 1320 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.51 (s, 1H), 7.99 (d, J = 7.52 Hz, 1H), 7.62-7.64 (m, 1H), 7.27-7.37 (m, 7H), 6.88-6.89 (m, 1H), 6.72-6.75 (m, 1H), 6.67-6.69 (m, 1H), 5.73 (s, 1H), 5.06 (s, 2H), 3.80 (s, 3H), 1.68 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.7, 149.0, 148.6, 138.6, 136.8, 136.7, 134.8, 132.3, 128.5, 127.8, 127.5, 127.1, 124.7, 124.3, 118.7, 116.9, 115.3, 113.5, 112.5, 110.3, 87.0, 70.8, 56.0, 42.5, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{30}H_{28}N_2O_6S$ $[M+Na]^+$: 567.1560, found: 567.1678.

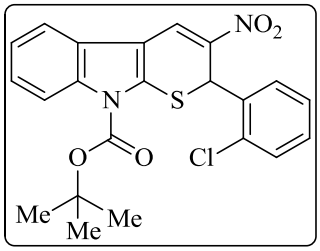
9-(*N-tert*-butoxycarbonyl)-2-(4-chlorophenyl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3af): 85% yield; **m.p.** 155 °C; **IR**



(KBr) ν 3441, 2977, 2924, 1732, 1627, 1581, 1506, 1490, 1443, 1400, 1372, 1356, 1316 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.53 (s, 1H), 8.00-8.02 (m, 1H), 7.64-7.67 (m, 1H), 7.32-7.36 (m, 2H), 7.21-7.27 (m, 3H), 5.75 (s, 1H), 1.69 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.9, 138.2, 138.0, 136.8, 134.5, 134.3, 129.1, 127.8, 127.5, 126.6, 124.9, 124.4,

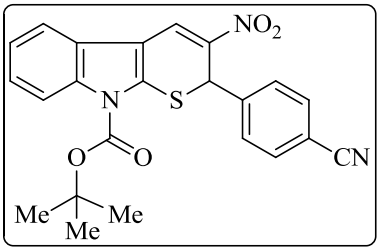
117.1, 115.4, 112.5, 87.2, 41.9, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{19}N_2O_4ClS$ $[M+Na]^+$: 465.0646, found: 465.0687.

9-(*N-tert*-butoxycarbonyl)-2-(2-chlorophenyl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ag): 84% yield; **m.p**. 180 °C; **IR**



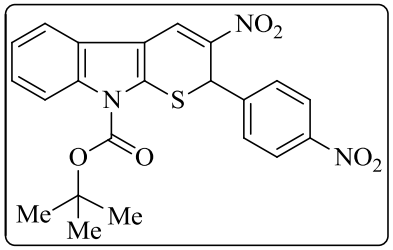
(KBr) ν 3434, 2981, 2930, 1726, 1622, 1581, 1572, 1510, 1496, 1467, 1444, 1397, 1365, 1354 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.65 (s, 1H), 7.99-8.02 (m, 1H), 7.66-7.68 (m, 1H), 7.44-7.46 (m, 1H), 7.33-7.37 (m, 1H), 7.28-7.32 (m, 1H), 7.18-7.22 (m, 1H), 7.11-7.14 (m, 1H), 7.05-7.09 (m, 1H), 6.25 (s, 1H), 1.67 (s, 9H); **^{13}CNMR (100 MHz, $CDCl_3$)** δ 148.8, 139.2, 136.9, 135.7, 133.2, 131.8, 130.5, 129.6, 127.9, 127.4, 127.1, 124.8, 124.4, 116.9, 115.4, 112.0, 87.2, 39.3, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{19}ClN_2O_4S$ $[M+K]^+$: 481.0386, found: 481.0370.

9-(*N-tert*-butoxycarbonyl)-2-(4-cyanophenyl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ah): 87% yield; **m.p.** 158 °C; **IR**

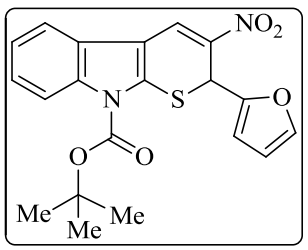


(KBr) ν 3441, 2924, 2853, 2228, 1711, 1620, 1581, 1504, 1479, 1444, 1397, 1370, 1358, 1321 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.55 (s, 1H), 7.97-8.00 (m, 1H), 7.64-7.66 (m, 1H), 7.54-7.56 (m, 2H), 7.42-7.44 (m, 2H), 7.31-7.38 (m, 2H), 5.79 (s, 1H), 1.68 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.9, 144.4, 137.9, 136.8, 133.5, 132.8, 129.9, 127.2, 127.1, 125.1, 124.6, 118.2, 117.2, 115.4, 112.6, 112.5, 87.4, 42.1, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{19}N_3O_4S$ $[M+H]^+$: 434.1169, found: 434.1222.

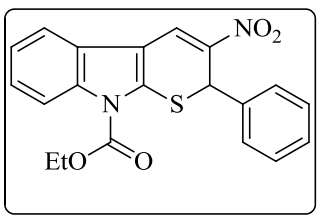
9-(*N-tert*-butoxycarbonyl)-2-(4-nitrophenyl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ai): 86% yield; **m.p.** 155 °C; **IR** (KBr) ν 3440, 2982, 2926, 2854, 1716, 1674, 1622, 1604, 1581, 1528, 1504, 1489, 1443, 1401, 1369, 1355, 1321 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.57 (s, 1H), 8.09-8.12 (m, 2H), 7.98-8.00 (m, 1H), 7.65-7.67 (m, 1H), 7.48-7.50 (m, 2H), 7.31-7.39 (m, 2H), 5.84 (s, 1H), 1.68 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.9, 147.9, 146.2, 137.8, 136.8, 133.5, 127.4, 127.3, 127.2, 125.2, 124.6, 124.2, 117.2, 115.4, 112.6, 87.5, 41.9, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{19}N_3O_6S$ $[M+Na]^+$: 476.0887, found: 476.0878.



9-(*N-tert*-butoxycarbonyl)-2-furyl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3aj): 89% yield; **m.p.** 145 °C; **IR** (KBr) ν 3448, 2923, 2852, 1728, 1611, 1579, 1470, 1393, 1359, 1328 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.44 (s, 1H), 8.01-8.03 (m, 1H), 7.62-7.64 (m, 1H), 7.33-7.36 (m, 1H),7.30-7.33 (m, 2H), 6.20-6.21 (m, 1H), 6.14-6.15 (m, 1H), 5.91 (s, 1H), 1.70 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.4, 149.0, 143.3, 138.5, 136.8, 132.2, 127.6, 126.8, 124.8, 124.3, 117.1, 115.3, 112.7, 110.6, 108.2, 87.1, 36.8, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{18}N_2O_5S$ $[M+Na]^+$: 421.0829, found: 421.0864.

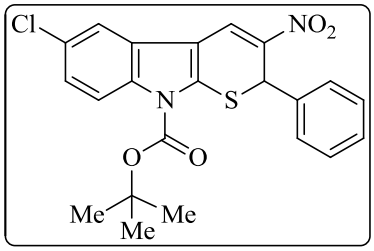


9-(*N*-ethoxycarbonyl)-2-phenyl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ba): 80% yield; **m.p.** 180 °C; **IR** (KBr) ν 3442, 2952, 2924, 1733, 1620, 1581, 1503, 1480, 1445, 1399, 1377, 1346, 1318 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.53 (s, 1H), 8.00-8.02 (m, 1H), 7.64-7.66 (m, 1H), 7.34-7.38 (m, 2H), 7.30-7.32 (m, 3H),7.23-7.24 (m, 2H), 5.80 (s, 1H),

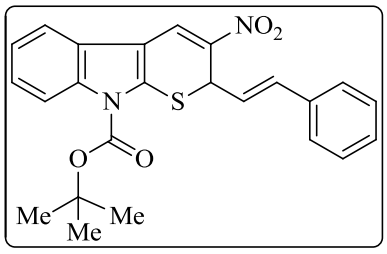


4.53 (q, J = 7.28, 14.16 Hz, 2H), 1.50 (t, J=7.0, 14.28 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.5, 146.1, 139.3, 138.2, 136.6, 134.9, 128.9, 128.6, 127.6, 126.4, 124.9, 124.5, 117.1, 115.4, 112.9, 64.9, 42.5, 14.2; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}N_2O_4S$ $[M+Na]^+$: 403.0723, found: 403.0733.

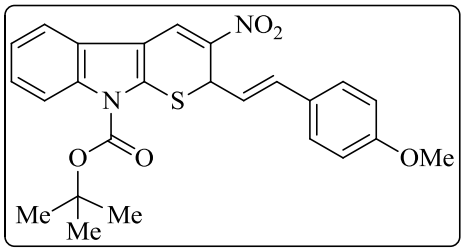
9-(*N-tert*-butoxycarbonyl)-2-phenyl-6-chloro-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ca): 83% yield; **m.p.** 160 °C; **IR** (KBr) ν 3441, 2925, 2854, 1737, 1628, 1507, 1491, 1470, 1454, 1422, 1403, 1372, 1348 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.47 (s, 1H), 8.04-8.05 (m, 1H), 7.54 (d, J=8.28 Hz, 1H), 7.29-7.33 (m, 4H), 7.26-7.27 (m, 2H), 5.78 (s, 1H), 1.68 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.6, 139.3, 138.8, 137.1, 135.0, 130.7, 129.1, 128.9, 128.7, 126.4, 126.0, 124.8, 117.6, 115.8, 112.1, 87.7, 42.4, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{19}ClN_2O_4S$ $[M+Na]^+$: 465.0646, found: 465.0712.



9-(*N-tert*-butoxycarbonyl)-2-styryl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ak): 81% yield; **m.p.** 148 °C; **IR** (KBr) ν 1731, 1619, 1579, 1502, 1489, 1478, 1443, 1398, 1369, 1356, 1318, 1286 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.37 (s, 1H), 8.03-8.04 (m, 1H), 7.61-7.63 (m, 1H), 7.22-7.32 (m, 7H), 6.54 (d, J=15.56 Hz, 1H), 6.24 (dd, J=7.28, 15.4 Hz, 1H), 5.34 (d, J =6.8 Hz, 1H), 1.72 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.1, 138.4, 136.8, 135.7, 133.7, 132.1, 128.5, 128.2, 127.6, 126.8, 125.9, 124.8, 124.3, 123.9, 117.1, 115.4, 112.9, 87.1, 41.2, 28.2; **HRMS** (ESI-TOF) m/z calculated for $C_{24}H_{22}N_2O_4S$ $[M+Na]^+$: 457.1192, found: 457.1196.

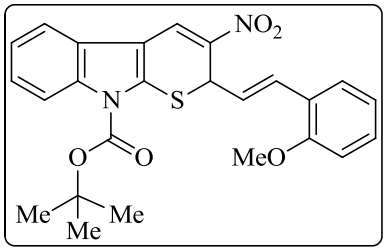


9-(*N-tert*-butoxycarbonyl)-2-(4-methoxystyryl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3al): 74% yield; **m.p.** 150 °C; **IR**



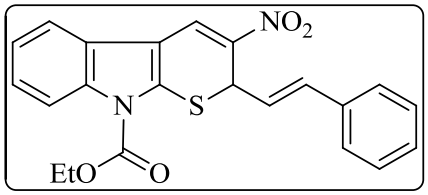
(KBr) ν 1732, 1618, 1606, 1510, 1478, 1445, 1398, 1370, 1355, 1317, 1291 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.36 (s, 1H), 8.02-8.04 (m, 1H), 7.61-7.62 (m, 1H), 7.20-7.35 (m, 4H), 6.75-6.77 (m, 2H), 6.48 (d, *J*=15.56 Hz, 1H), 6.09 (dd, *J*=7.8, 15.68 Hz, 1H), 5.31 (d, *J*=7.52 Hz, 1H), 3.75 (s, 3H), 1.71 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.7, 149.1, 138.5, 136.8, 133.9, 131.6, 128.4, 128.1, 127.7, 125.7, 124.8, 124.3, 121.7, 117.0, 115.4, 113.9, 112.9, 87.0, 55.3, 41.4, 28.2; **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{24}N_2O_5$ $[M+Na]^+$: 487.1298, found: 487.1274.

9-(*N-tert*-butoxycarbonyl)-2-(2-methoxystyryl)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3am): 74% yield; **m.p.** 158 °C; **IR**

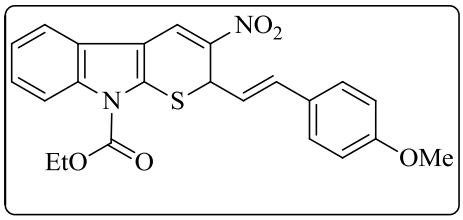


(KBr) ν 1731, 1619, 1598, 1579, 1488, 1464, 1444, 1398, 1371, 1355, 1317, 1292 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.36 (s, 1H), 8.03-8.05 (m, 1H), 7.61-7.63 (m, 1H), 7.29-7.31 (m, 3H), 7.14-7.18 (m, 1H), 6.89 (d, *J*=15.8 Hz, 1H), 6.77-6.83 (m, 2H), 6.26 (dd, *J*=7.52, 15.72 Hz, 1H), 5.34 (d, *J*=7.28 Hz, 1H), 3.74 (s, 3H), 1.71 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.0, 149.0, 138.5, 136.8, 133.9, 129.3, 127.7, 127.2, 126.9,125.8, 124.7, 124.6, 124.3, 123.9, 120.5, 117.0, 115.3, 113.0, 110.9, 86.9, 55.4, 41.8, 28.2; **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{24}N_2O_5S$ $[M+Na]^+$: 487.1298, found: 487.1289.

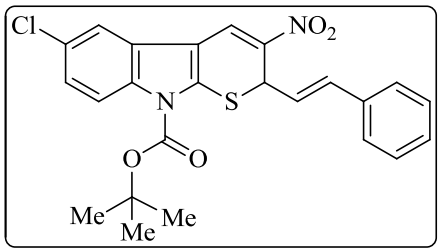
9-(*N*-ethoxycarbonyl)-2-styryl-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3bk): 83% yield; **m.p.** 181 °C; **IR** (KBr) ν1736, 1640, 1610, 1579, 1498, 1485, 1446, 1397, 1376, 1348, 1319, 1298 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.43 (s, H), 8.10-8.12 (m, 1H), 7.68-7.70 (m, 1H), 7.40-7.42 (m, 2H), 7.27-7.35 (m, 5H), 6.60 (d, *J*=15.56 Hz, 1H), 6.29 (dd, *J*=7.28, 15.6 Hz, 1H), 5.42 (d, *J*=7.52 Hz, 1H), 4.64 (q, *J*=7.0, 14.28 Hz, 2H), 1.61 (t, *J*=2.76, 6.28 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.6, 138.2, 136.6, 135.6, 134.0, 132.3, 128.5, 128.3, 127.7, 126.8, 125.7, 124.9, 124.6, 123.7, 117.2, 115.4, 113.3, 64.9, 41.2, 14.3; **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{18}N_2O_4S$ $[M+H]^+$: 407.1060, found: 407.1061.



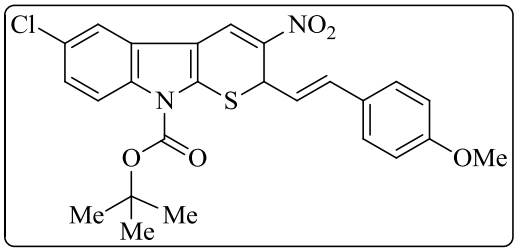
9-(*N*-ethoxycarbonyl)-2-(4-methoxystyrene)-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3bl): 76% yield; **m.p.** 158 °C; **IR** (KBr) ν 1734, 1638, 1606, 1579, 1510, 1490, 1446, 1397, 1375, 1349, 1321, 1291 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.35 (s, 1H), 8.04-8.05 (m, 1H), 7.61-7.63 (m, 1H), 7.33-7.35 (m, 2H), 7.20-7.22 (m, 2H), 6.75-6.77 (m, 2H), 6.48 (d, *J*=15.56 Hz, 1H), 6.08 (dd, *J*=7.80, 15.56 Hz, 1H), 5.32 (d, *J*=7.52 Hz, 1H), 4.57 (q, *J*=7.04, 14.04 Hz, 2H), 3.75 (s, 3H), 1.53 (t, *J*=2.76, 6.28 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.7, 150.6, 138.3, 136.6, 134.2, 131.8, 128.3, 128.1, 127.7, 125.5, 124.9, 124.5, 121.5, 117.1, 115.4, 113.9, 113.3, 64.9, 55.2, 41.4, 14.3; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{20}N_2O_5S$ $[M+Na]^+$: 459.0985, found: 459.0995.



9-(*N-tert*-butoxycarbonyl)-2-styryl-6-chloro-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3ck): 79% yield; **m.p.** 160 °C; **IR** (KBr) ν 1732, 1618, 1490, 1470, 1423, 1395, 1371, 1350, 1313, 1274 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.30 (s, 1H), 8.08 (s, 1H), 7.50-7.52 (m, 1H), 7.19-7.32 (m, 6H), 6.52 (d, *J*=15.56 Hz, 1H), 6.21 (dd, *J*=7.28, 15.56 Hz, 1H), 5.33 (d, *J*=7.28 Hz, 1H), 1.71 (s,9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.6, 138.7, 137.1, 135.5, 134.1, 132.3, 130.7, 128.5, 128.3, 126.8, 126.1, 125.4, 124.8, 123.6, 117.6, 115.8, 112.4, 87.7, 41.2, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{24}H_{21}N_2O_4ClS$ $[M+H]^+$: 469.0983, found: 469.0995.



9-(*N-tert*-butoxycarbonyl)-2-(4-methoxystyryl)-6-chloro-3-nitro-2,9-dihydrothiopyrano[2,3-*b*]indole (3cl): 73% yield; **m.p.** 162 °C; **IR** (KBr) ν 1738, 1621, 1605, 1510, 1490, 1467, 1422, 1401, 1371, 1344, 1296 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.31 (s, 1H), 8.11 (s, 1H), 7.52-7.54 (m, 1H), 7.23-7.34 (m, 3H), 6.78-6.80 (m, 2H), 6.50 (d, *J*=15.32 Hz, 1H), 6.10 (dd, *J*=6.76, 16.20 Hz, 1H), 5.33 (d, *J*=6.28 Hz, 1H), 3.77 (s, 3H), 1.74 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.8, 148.6, 138.8, 137.1, 134.3, 131.8, 130.7, 128.3, 128.1, 126.1, 125.2, 124.8, 121.4, 117.6, 115.8, 113.9, 112.4, 87.6, 55.3, 41.4, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{23}N_2O_5ClS$ $[M+Na]^+$: 521.0908, found: 521.0907.



3.7 Copies of ^{1}H and ^{13}C NMR of final compounds

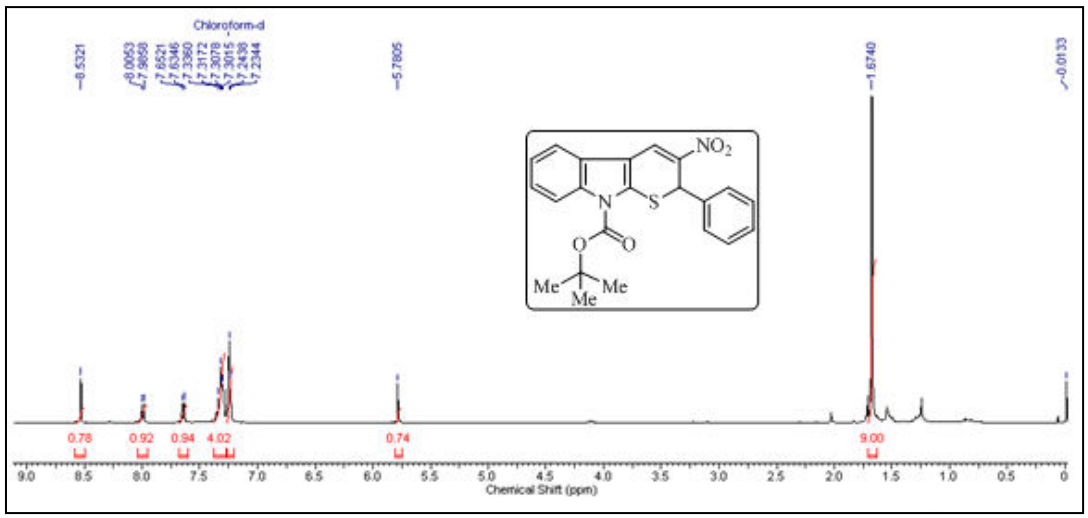


Figure 3.6 400 MHz ^{1}H NMR spectrum of **3aa** in $CDCl_3$

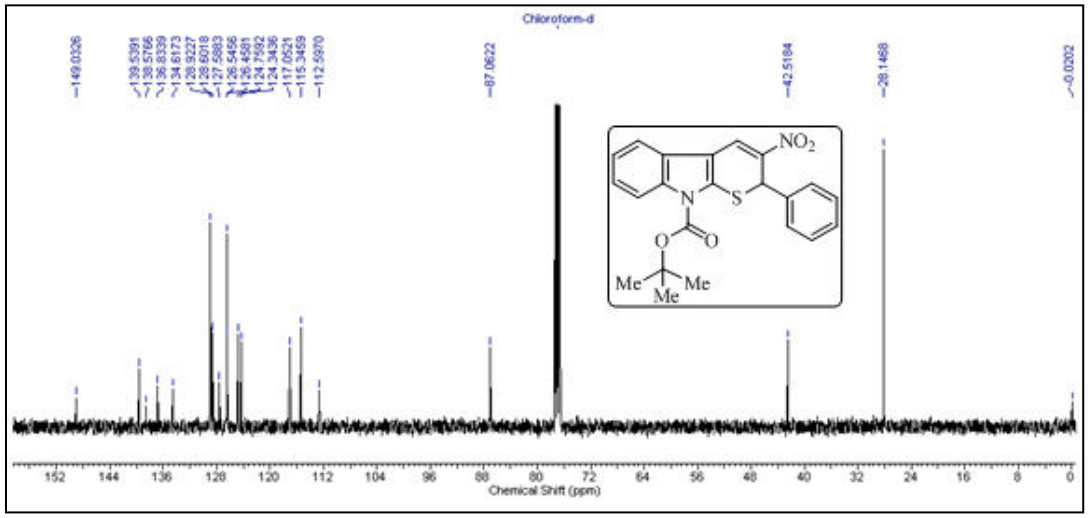


Figure 3.7 100 MHz ^{13}C NMR spectrum of **3aa** in $CDCl_3$

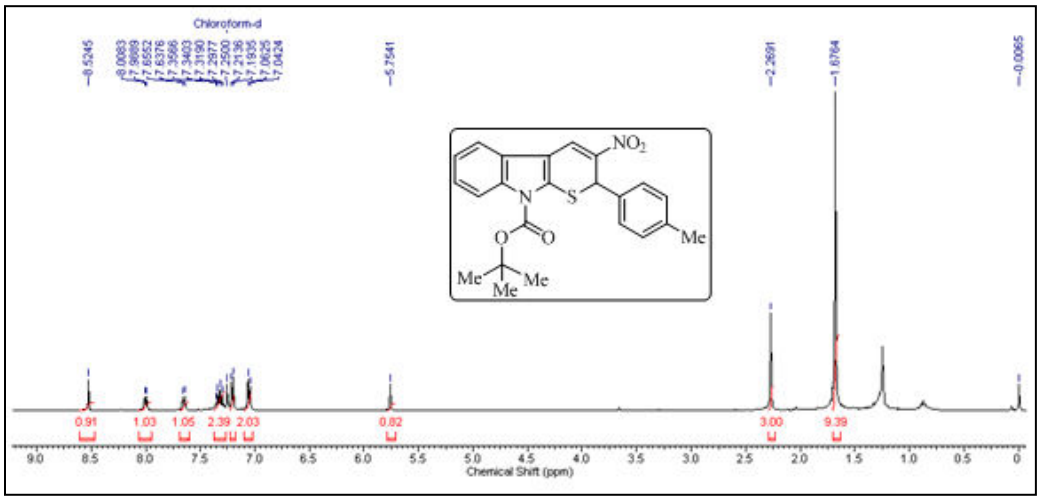


Figure 3.8 400 MHz ^{1}H NMR spectrum of **3ab** in $CDCl_3$

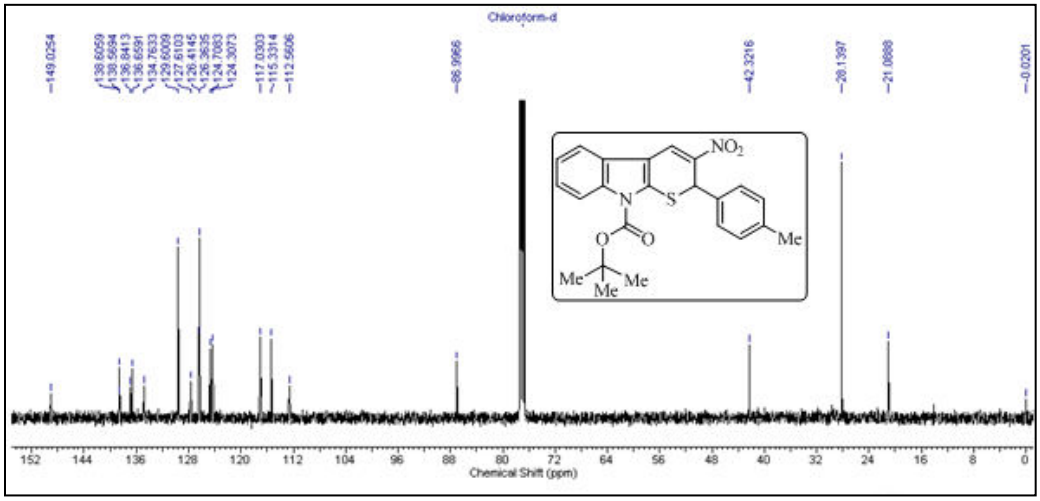


Figure 3.9 100 MHz ^{13}C NMR spectrum of **3ab** in $CDCl_3$

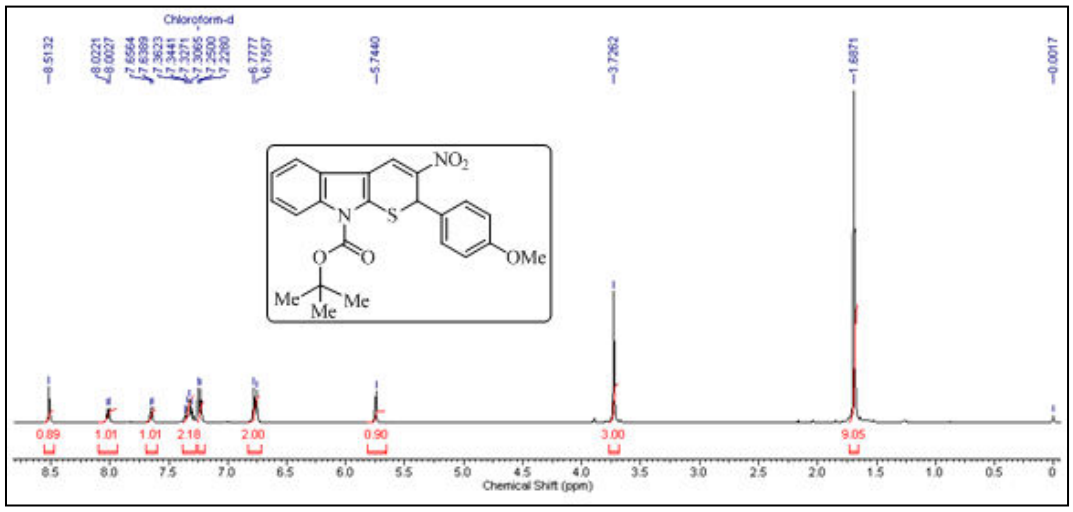


Figure 3.10 400 MHz ^{1}H NMR spectrum of **3ac** in $CDCl_3$

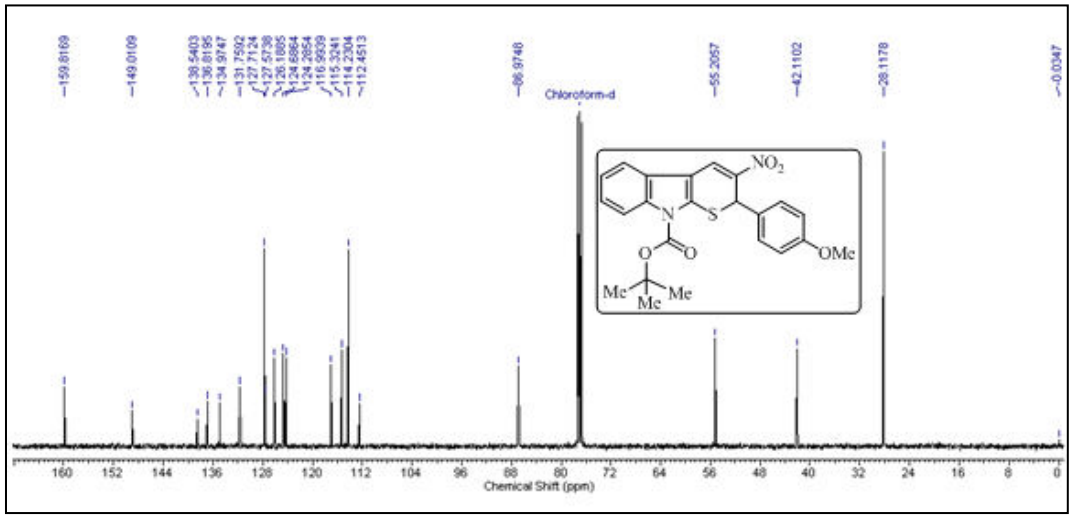


Figure 3.11 100 MHz ^{13}C NMR spectrum of **3ac** in $CDCl_3$

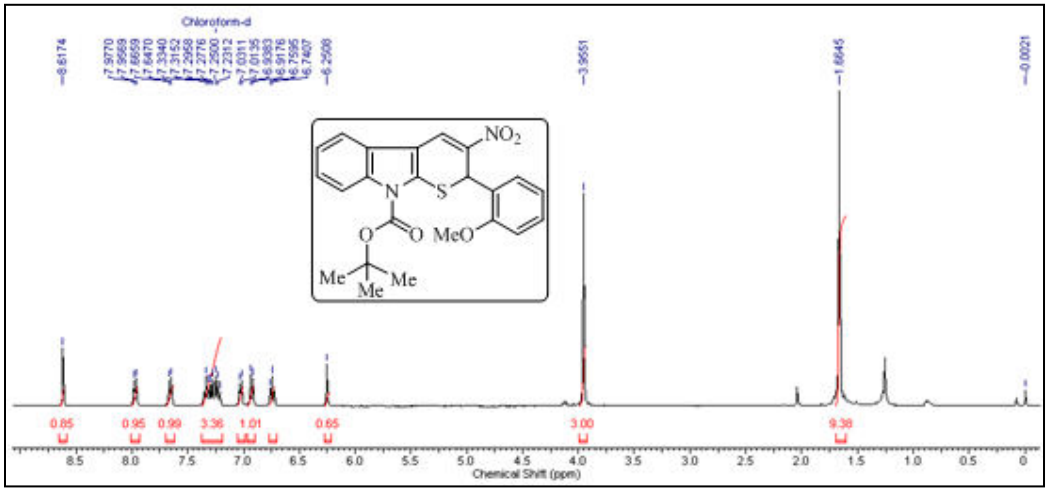


Figure 3.12 400 MHz ^{1}H NMR spectrum of **3ad** in $CDCl_3$

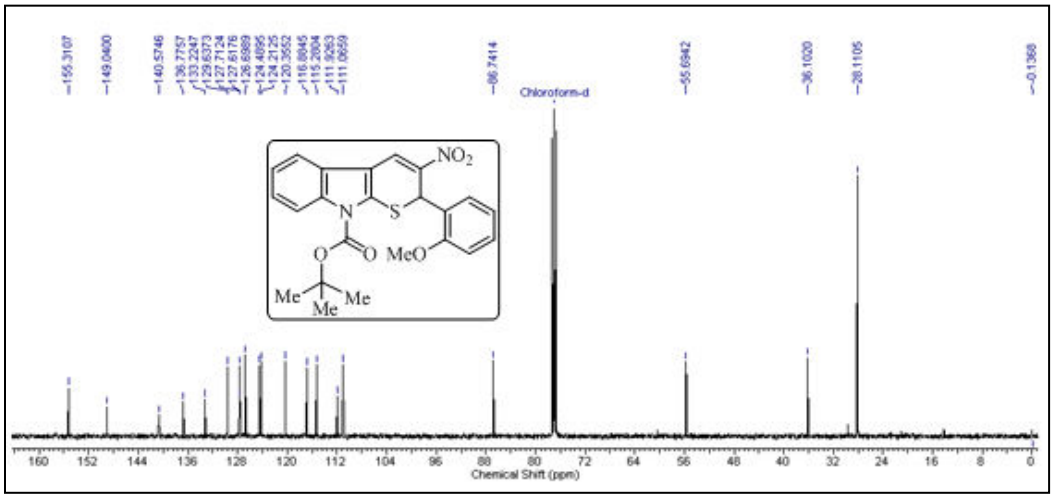


Figure 3.13 100 MHz ^{13}C NMR spectrum of **3ad** in $CDCl_3$

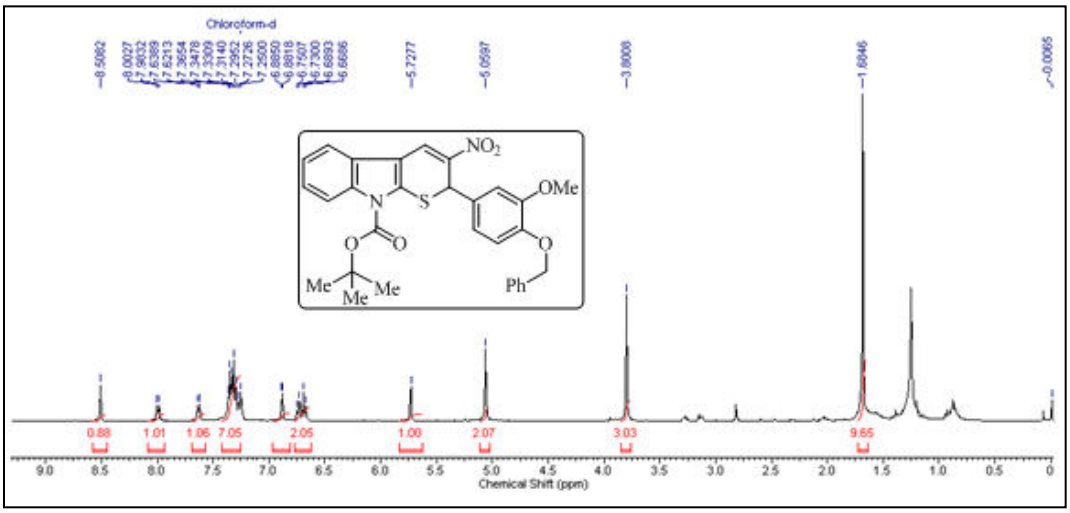


Figure 3.14 400 MHz ^{1}H NMR spectrum of **3ae** in $CDCl_3$

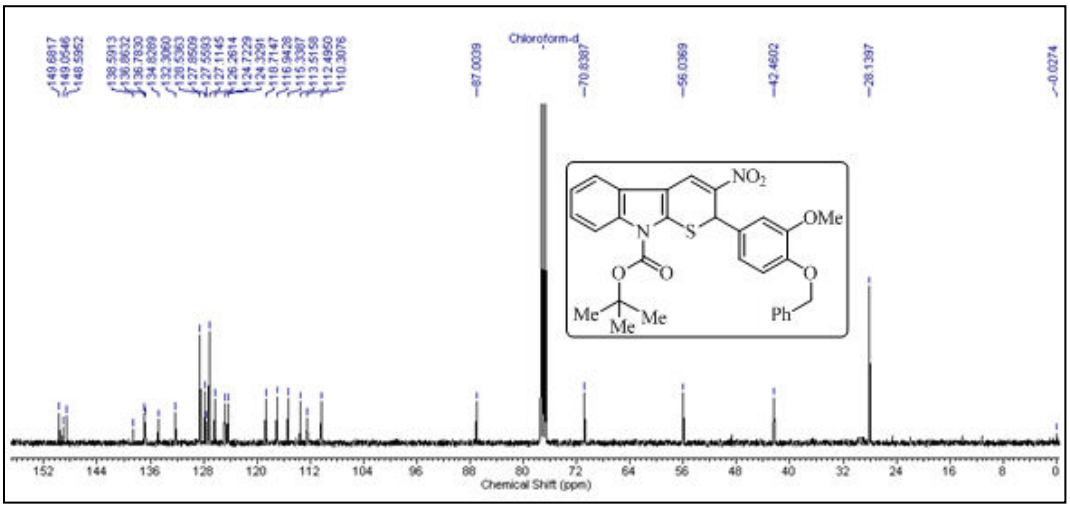


Figure 3.15 100 MHz ^{13}C NMR spectrum of **3ae** in $CDCl_3$

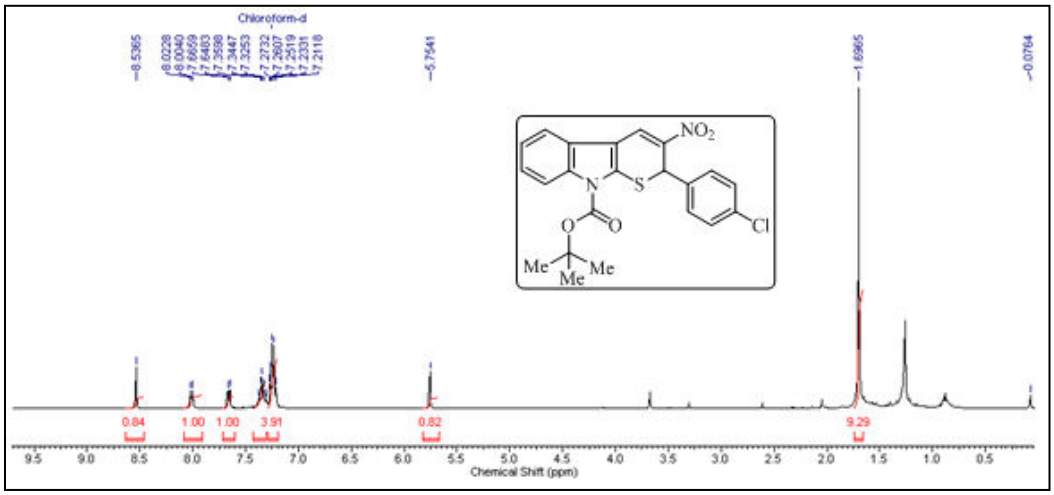


Figure 3.16 400 MHz ^{1}H NMR spectrum of **3af** in $CDCl_3$

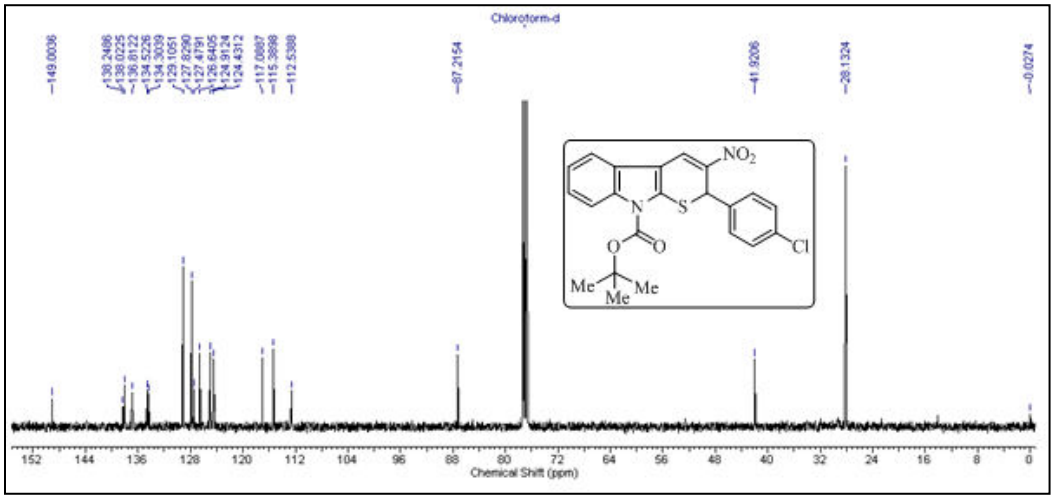


Figure 3.17 100 MHz ^{13}C NMR spectrum of **3af** in $CDCl_3$

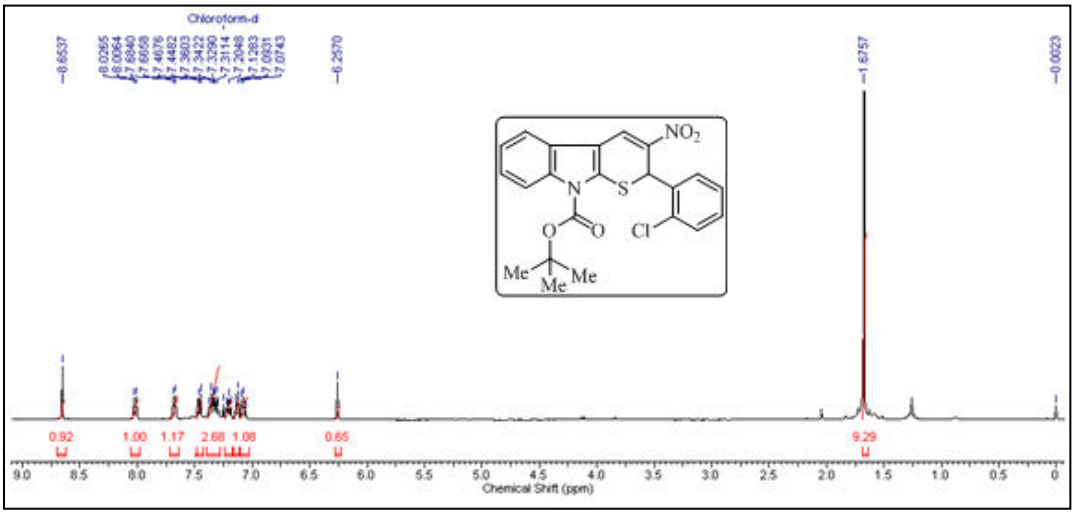


Figure 3.18 400 MHz ^{1}H NMR spectrum of **3ag** in $CDCl_3$

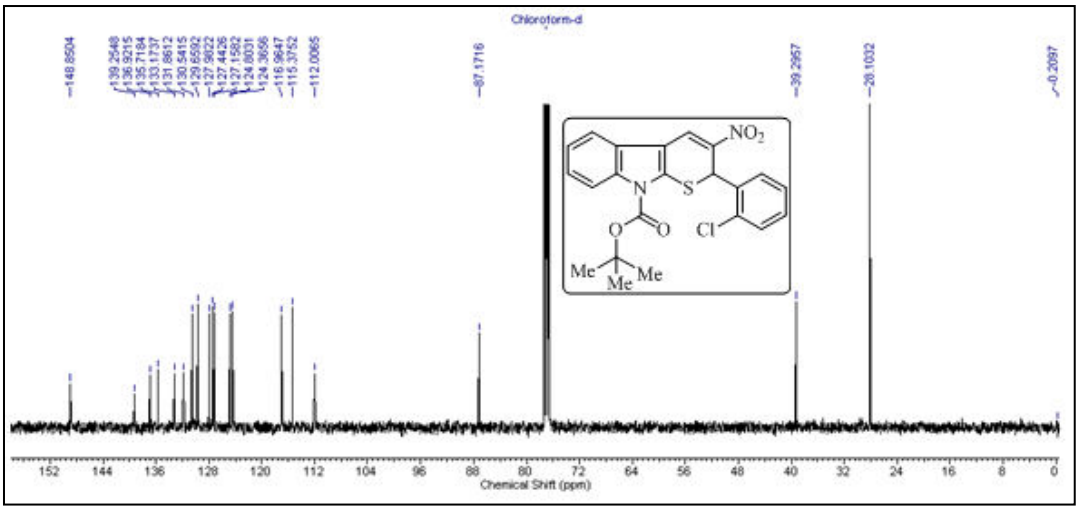


Figure 3.19 100 MHz ^{13}C NMR spectrum of **3ag** in $CDCl_3$

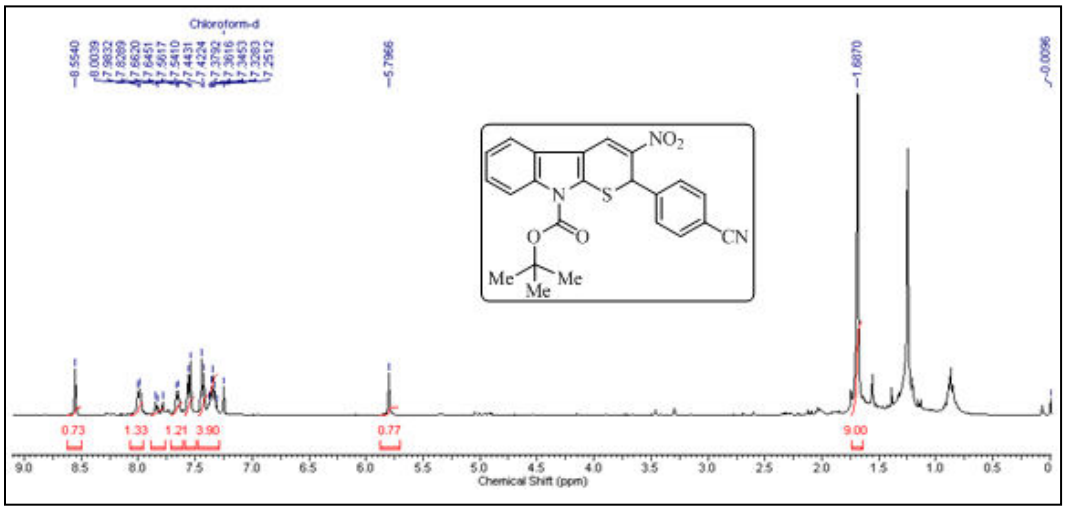


Figure 3.20 400 MHz ^{1}H NMR spectrum of **3ah** in $CDCl_3$

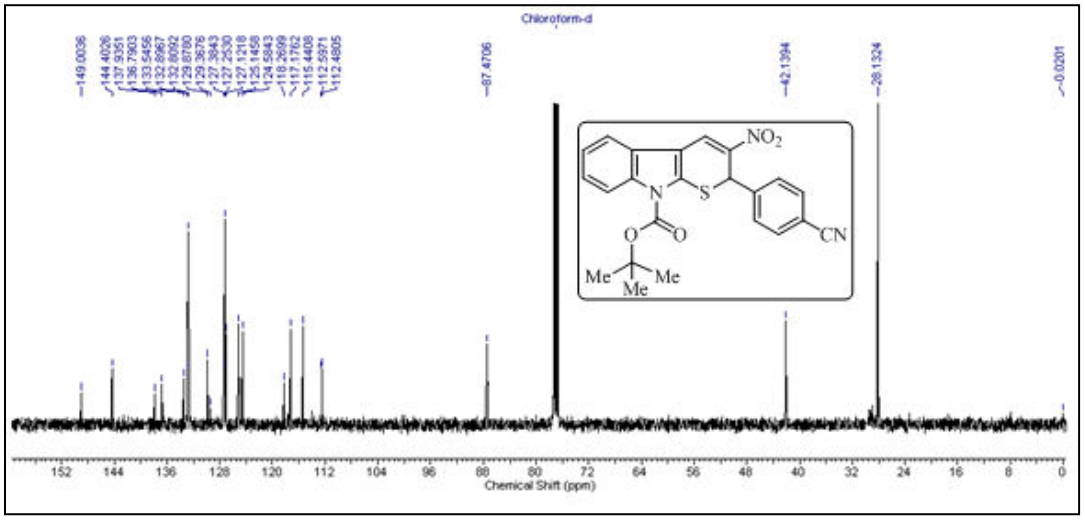


Figure 3.21 100 MHz ^{13}C NMR spectrum of **3ah** in $CDCl_3$

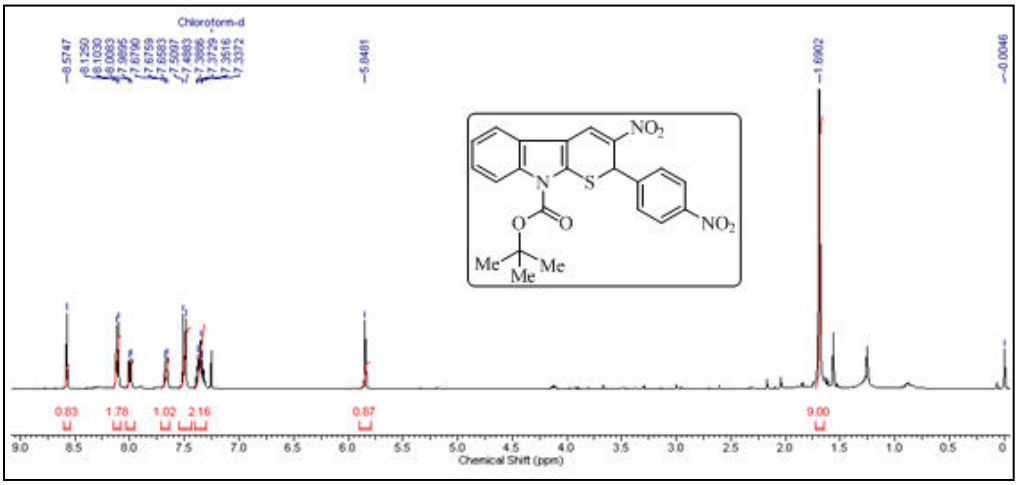


Figure 3.22 400 MHz ^{1}H NMR spectrum of **3ai** in $CDCl_3$

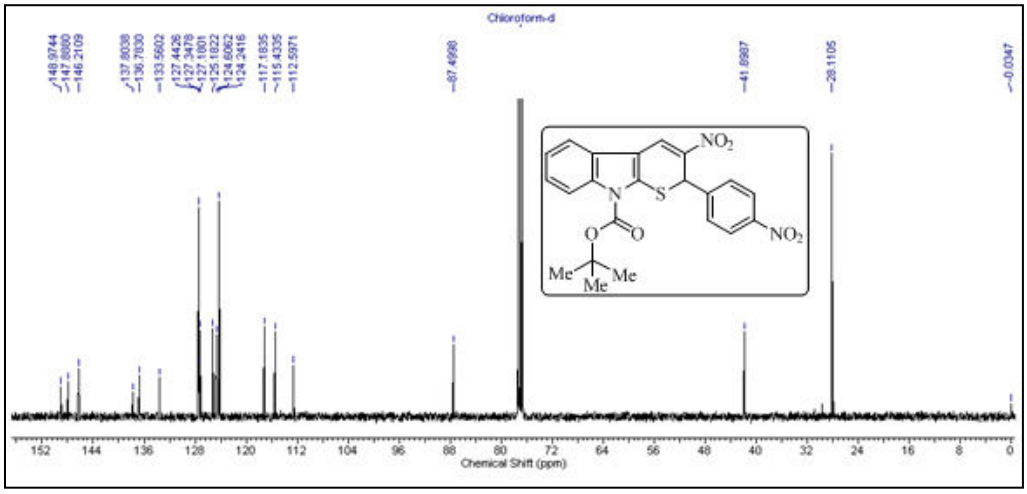


Figure 3.23 100 MHz ^{13}C NMR spectrum of **3ai** in $CDCl_3$

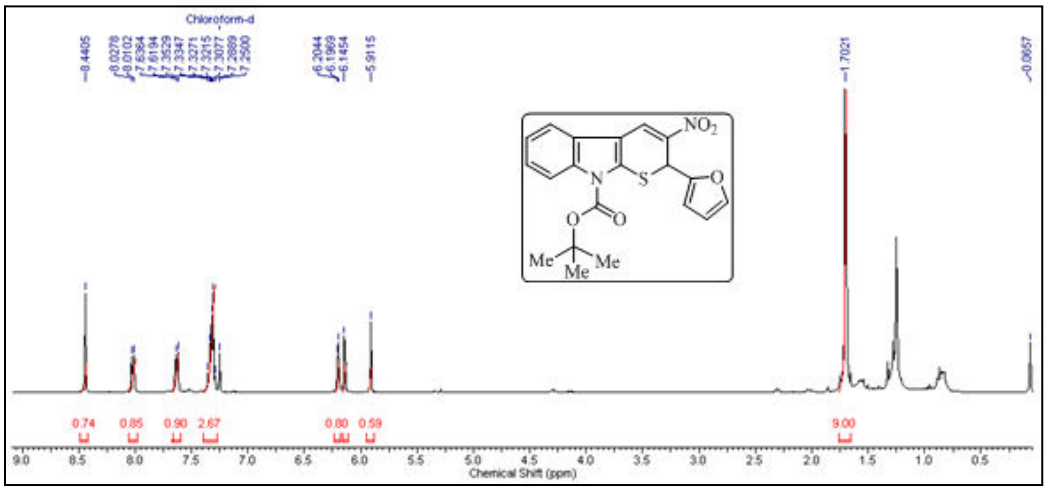


Figure 3.24 400 MHz ^{1}H NMR spectrum of **3aj** in $CDCl_3$

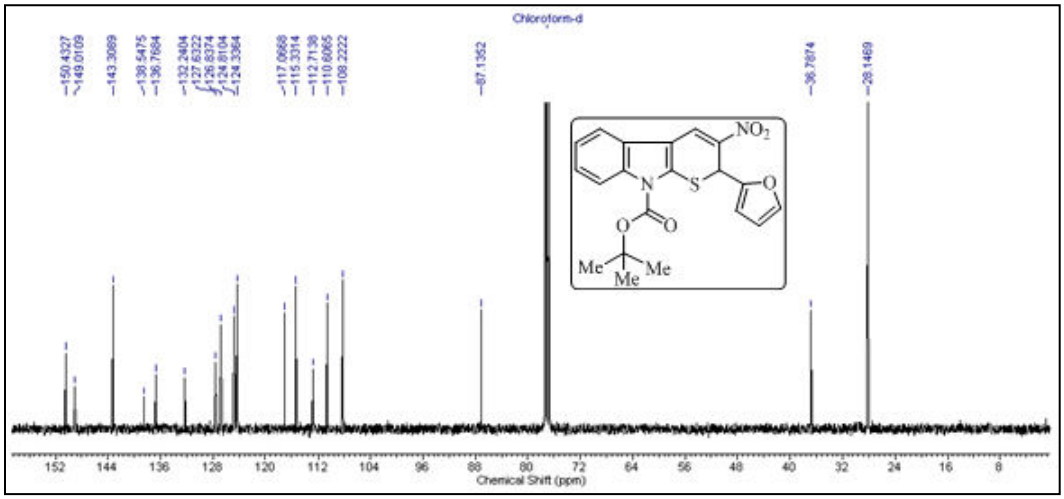


Figure 3.25 100 MHz ^{13}C NMR spectrum of **3aj** in $CDCl_3$

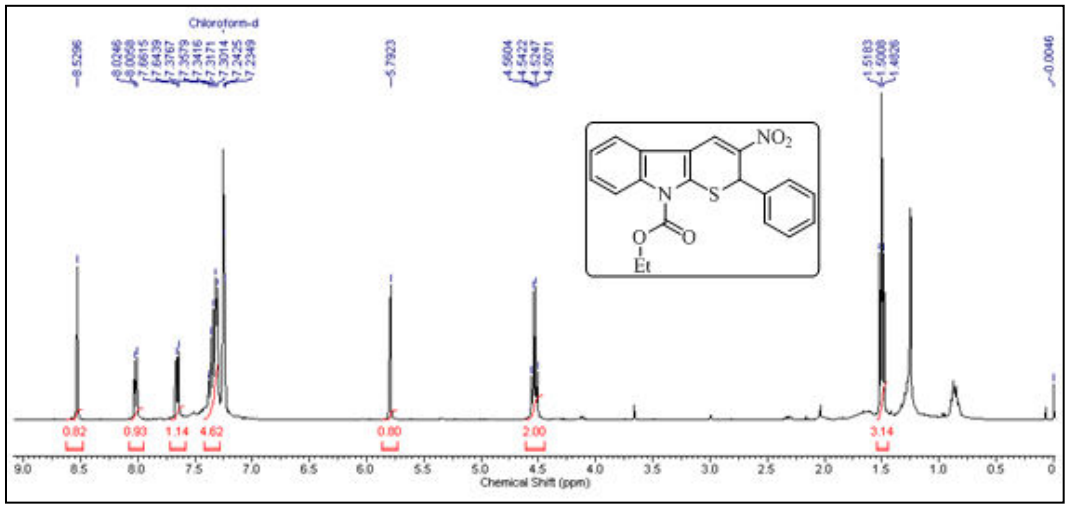


Figure 3.26 400 MHz ^{1}H NMR spectrum of **3ba** in $CDCl_3$

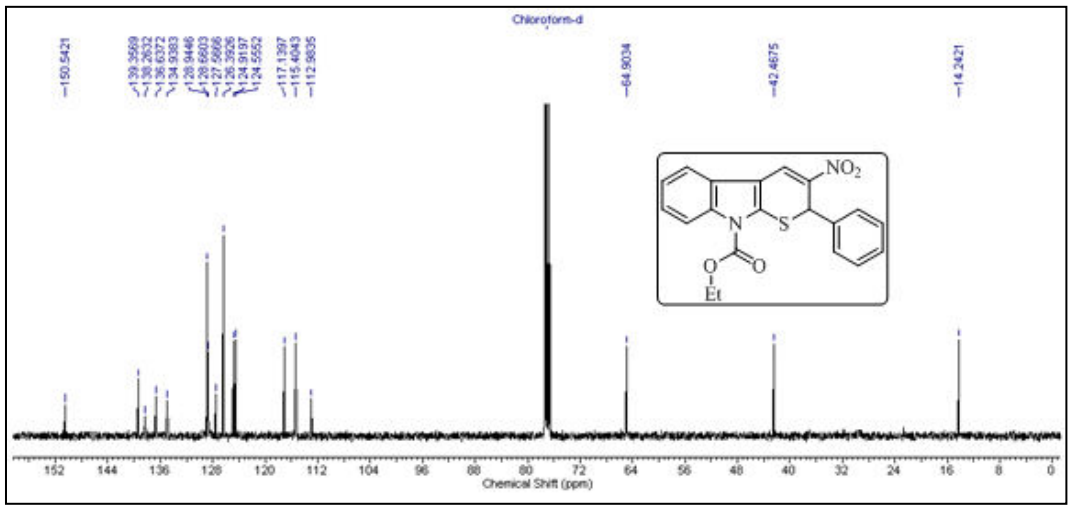


Figure 3.27 100 MHz ^{13}C NMR spectrum of **3ba** in $CDCl_3$

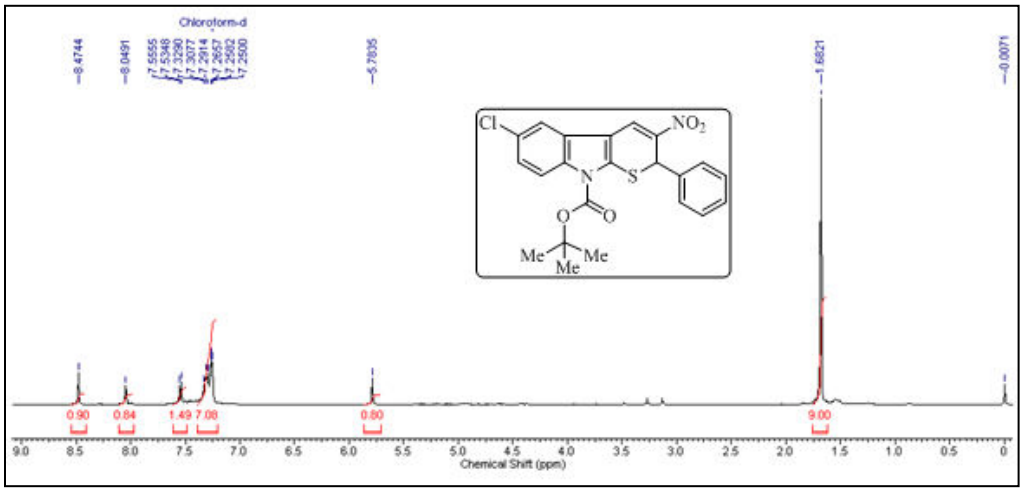


Figure 3.28 400 MHz ^{1}H NMR spectrum of **3ca** in $CDCl_3$

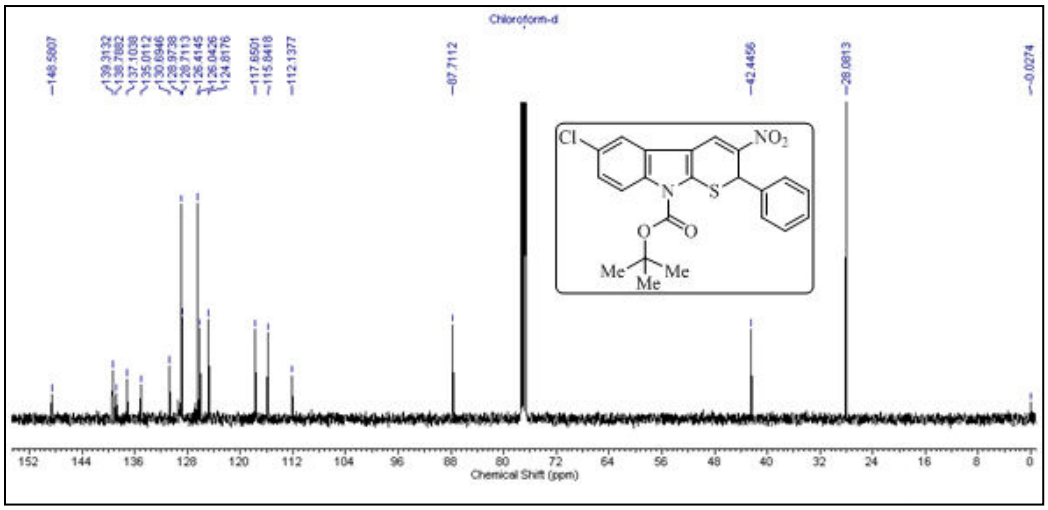


Figure 3.29 100 MHz ^{13}C NMR spectrum of **3ca** in $CDCl_3$

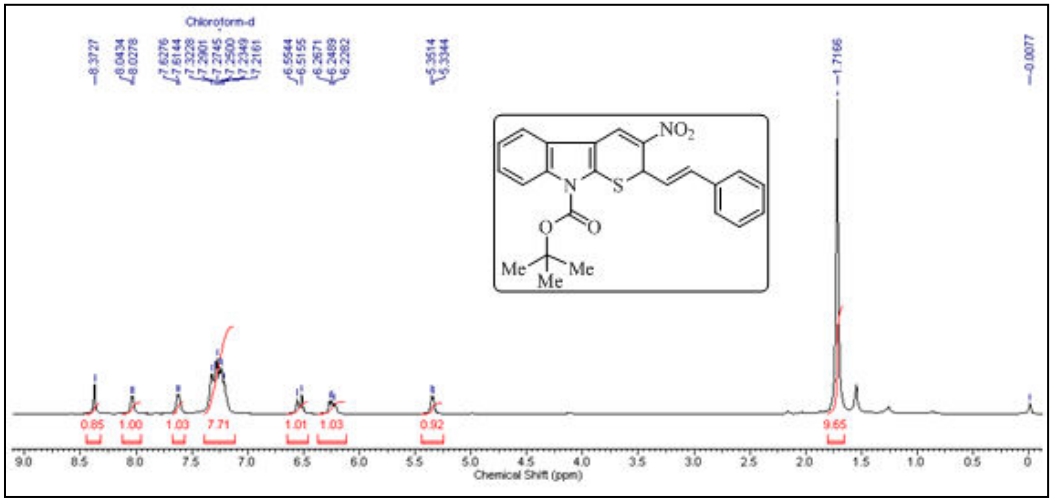


Figure 3.30 400 MHz ^{1}H NMR spectrum of **3ak** in $CDCl_3$

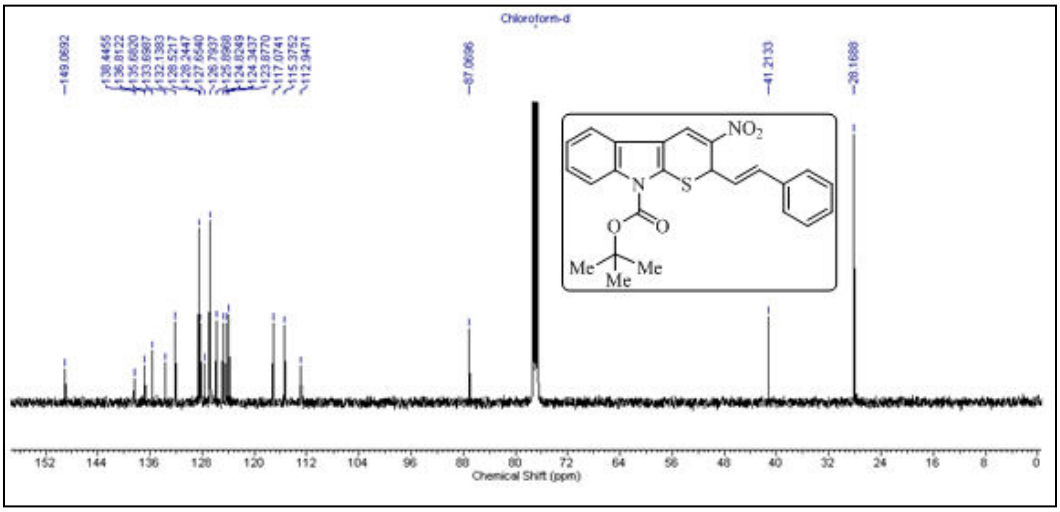


Figure 3.31 100 MHz ^{13}C NMR spectrum of **3ak** in $CDCl_3$

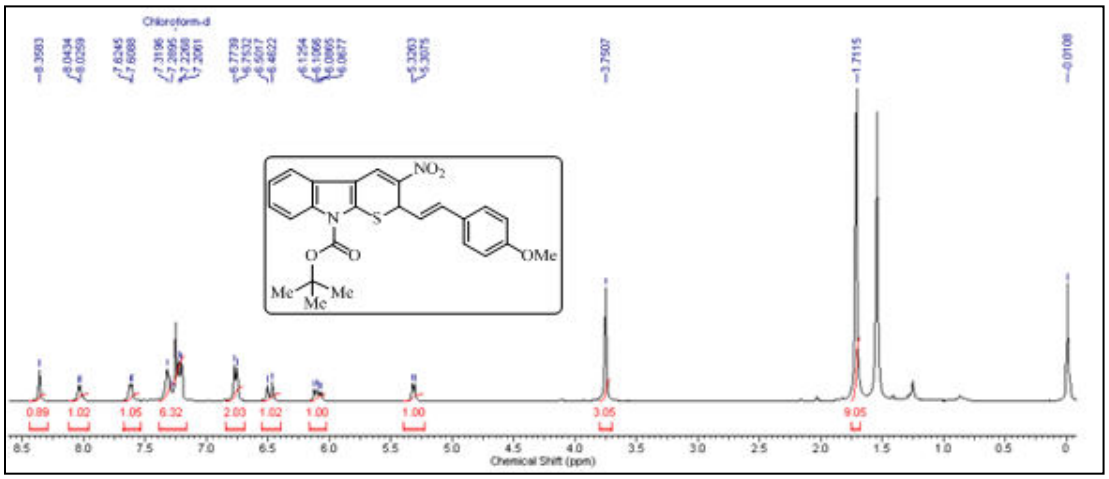


Figure 3.32 400 MHz ^{1}H NMR spectrum of **3al** in $CDCl_3$

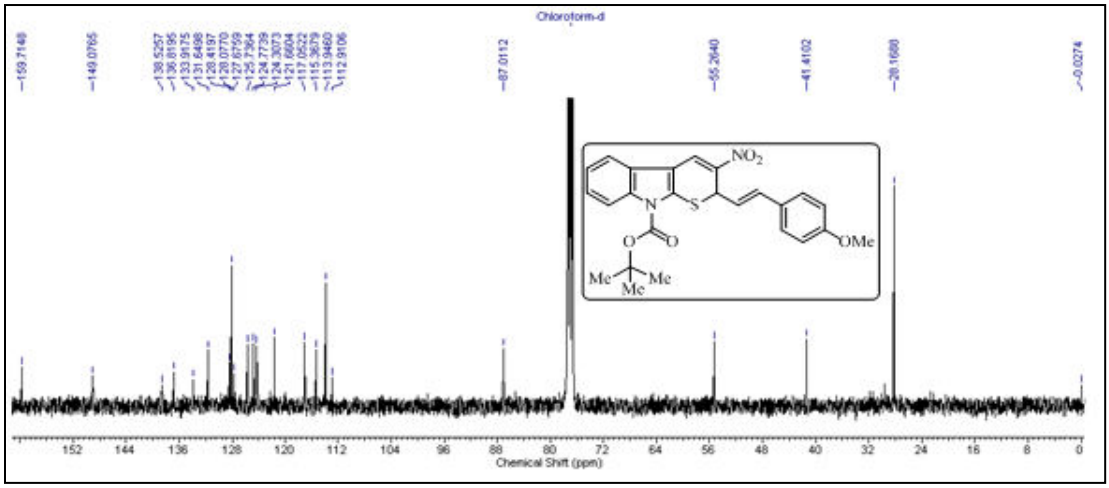


Figure 3.33 100 MHz ^{13}C NMR spectrum of **3al** in $CDCl_3$

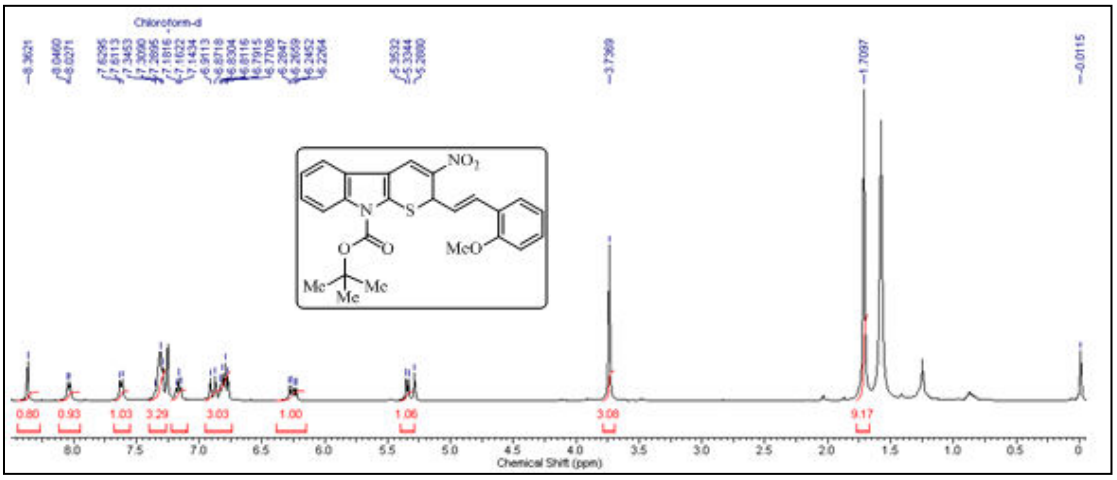


Figure 3.34 400 MHz ^{1}H NMR spectrum of **3am** in $CDCl_3$

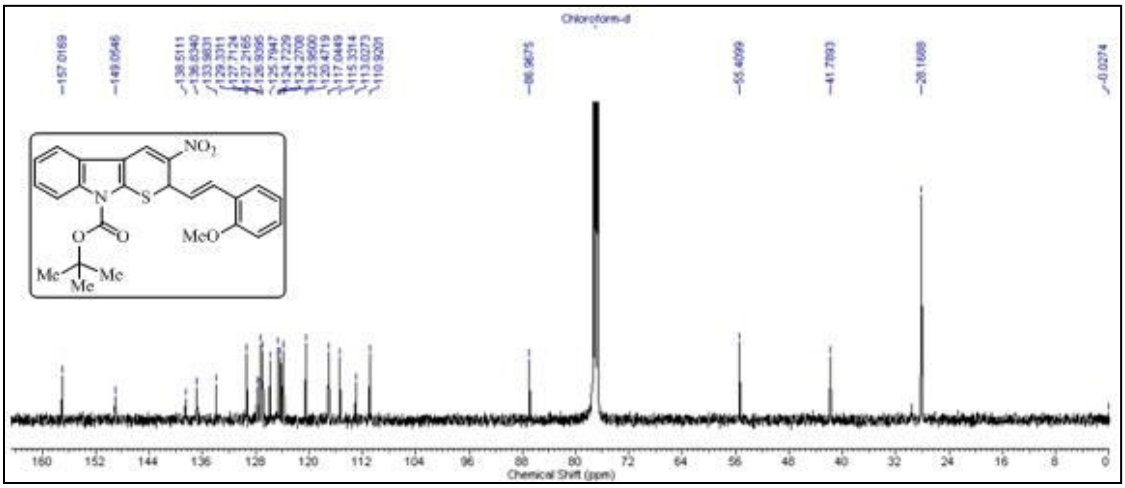


Figure 3.35 100 MHz ^{13}C NMR spectrum of **3am** in $CDCl_3$

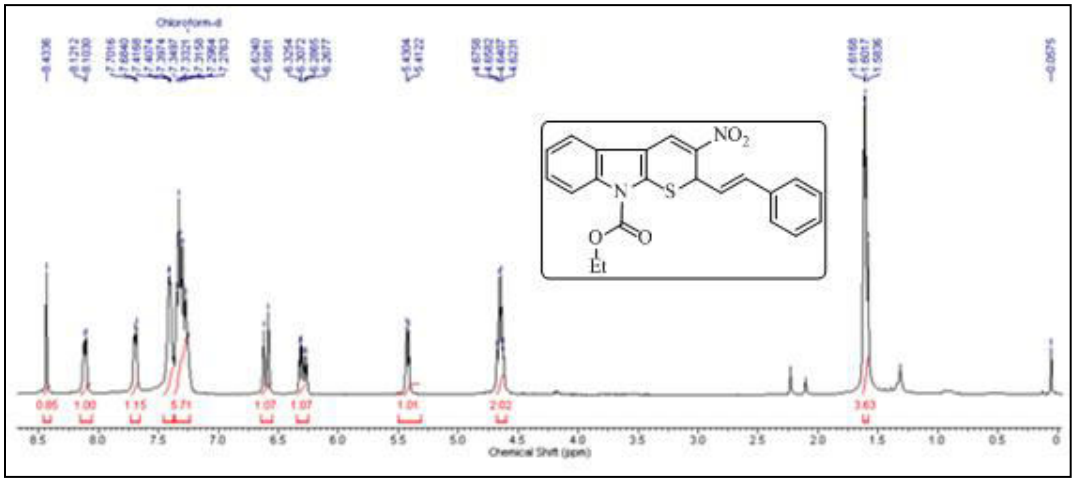


Figure 3.36 400 MHz ^{1}H NMR spectrum of **3bk** in $CDCl_3$

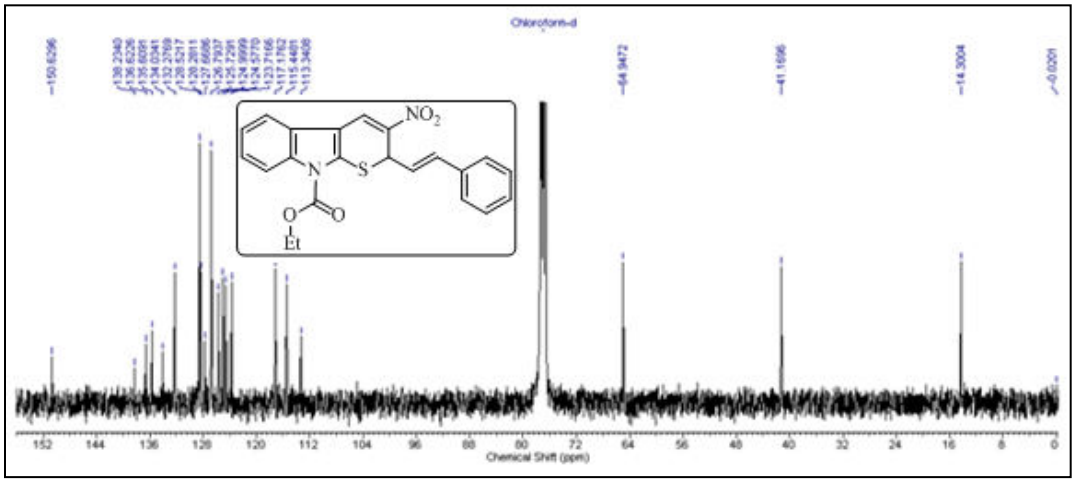


Figure 3.37 100 MHz ^{13}C NMR spectrum of **3bk** in $CDCl_3$

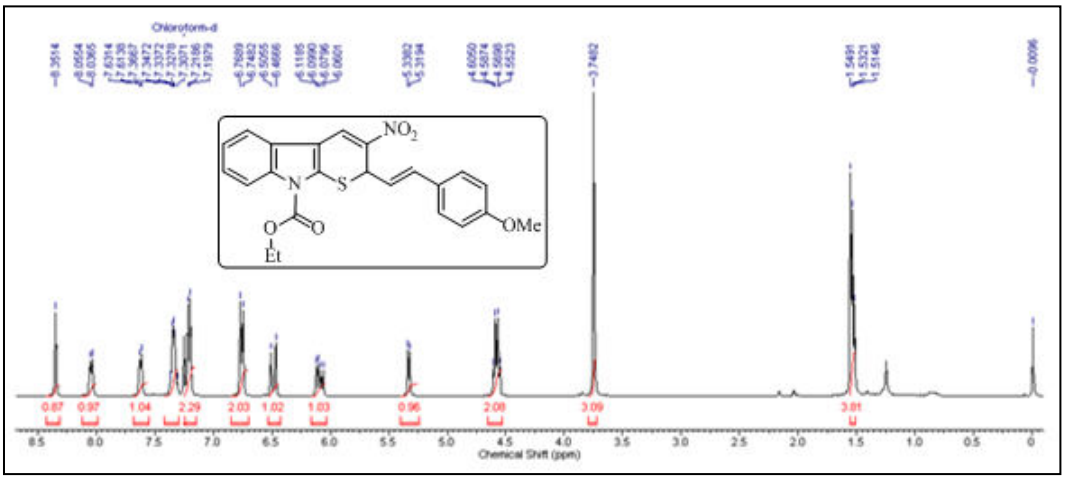


Figure 3.38 400 MHz ^{1}H NMR spectrum of **3bl** in $CDCl_3$

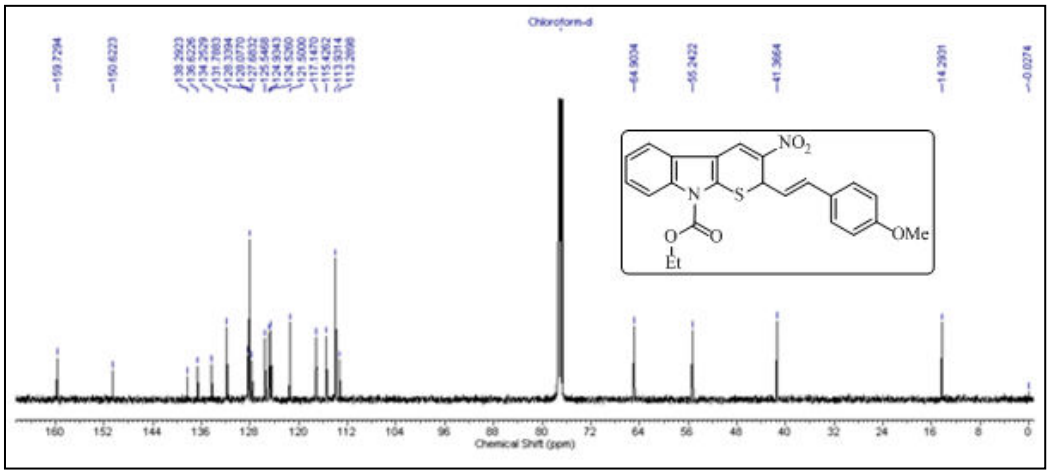


Figure 3.39 100 MHz ^{13}C NMR spectrum of **3bl** in $CDCl_3$

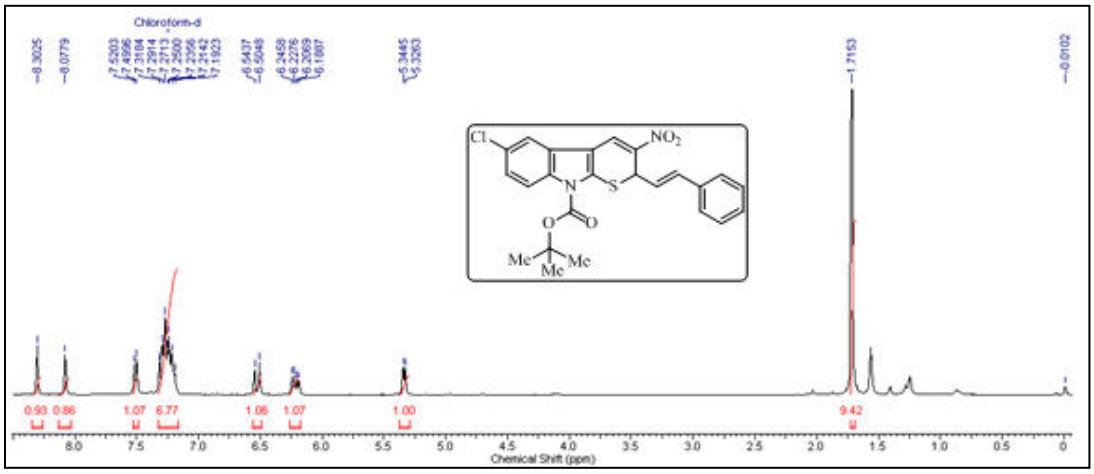


Figure 3.40 400 MHz ^{1}H NMR spectrum of **3ck** in $CDCl_3$

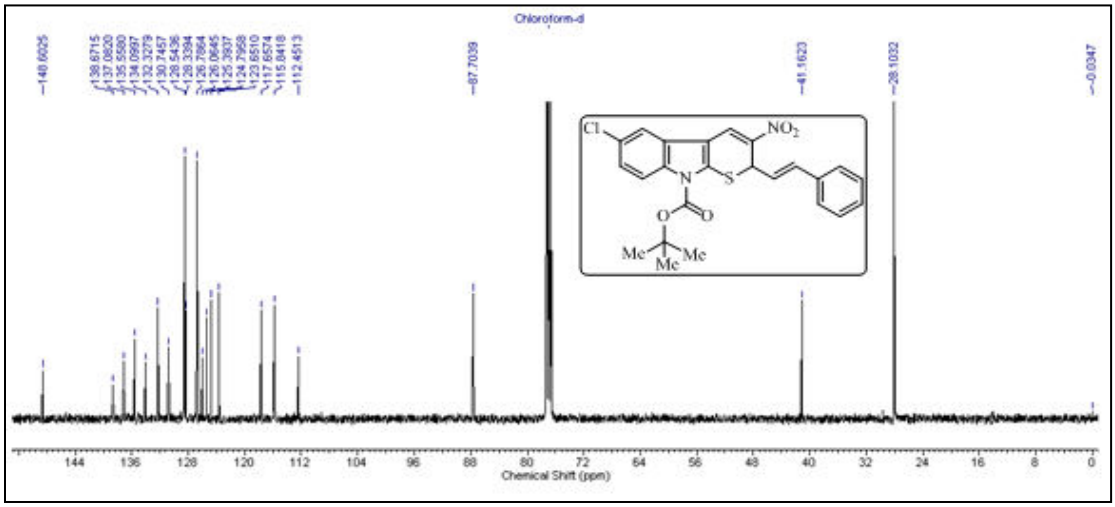


Figure 3.41 100 MHz ^{13}C NMR spectrum of **3ck** in $CDCl_3$

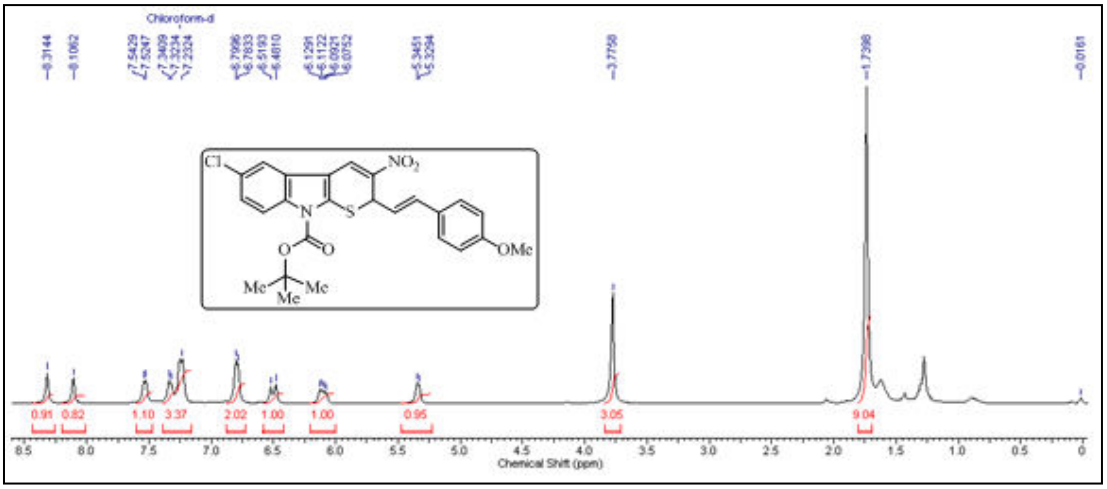


Figure 3.42 400 MHz ^{1}H NMR spectrum of **3cl** in $CDCl_3$

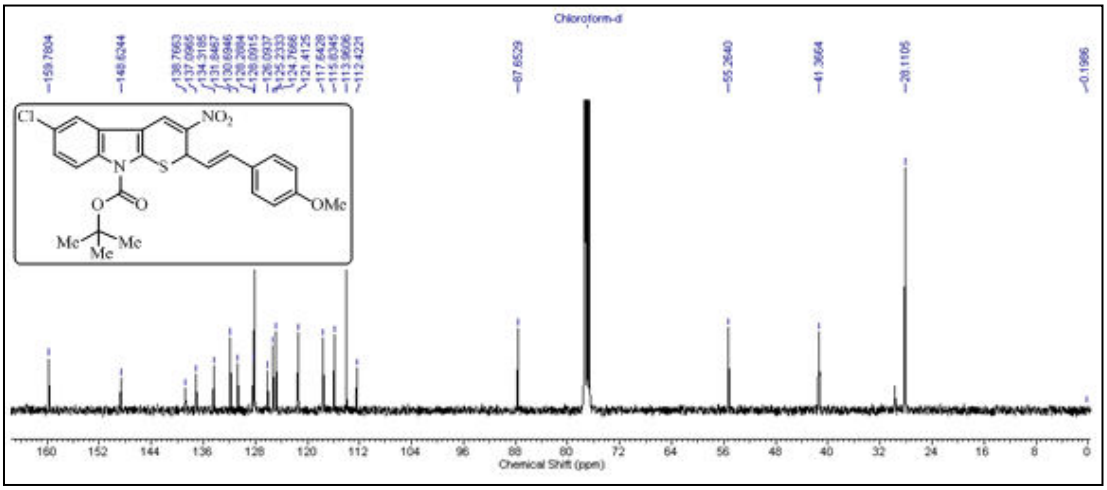


Figure 3.43 100 MHz ^{13}C NMR spectrum of **3cl** in $CDCl_3$

3.8 References

1. Jha M., Edmunds M., Lund K.-I., Ryan A. (2014), A new route to the versatile synthesis of thiopyrano[2,3-*b*:6,5-*b*']diindoles *via* 2-(alkylthio)-indole-3-carbaldehydes, *Tetrahedron Lett*., 55, 5691-5694 (DOI: 10.1016/j.tetlet.2014.08.100).

2. Wu L., Wang Y., Zhou Z. (2014), Stereocontrolled construction of the dihydrothiopyrano[2,3-*b*]indole skeleton *via* an organocatalyzed asymmetric cascade sulfa-Michael-Aldol reaction, *Tetrahedron: Asymmetry*, 25, 1389-1395 (DOI: 10.1016/j.tetasy.2014.09.005).

3. Chen X., Qi Z.-H., Zhang S.-Y., Kong L.-P., Wang Y., Wang X.-W. (2015), Enantioselective construction of functionalized thiopyrano-indole annulated heterocycles *via* a formal thio[3+3]cyclization, *Org. Lett*., 17, 42-45 (DOI: 10.1021/ol503210q).

4. Jha M., Shelke G. M., Cameron T. S., Kumar A. (2015), Access to substituted dihydrothiopyrano[2,3-*b*]indoles *via* sequential rearrangements during *S*-alkylation and Au-catalyzed hydroarylation on indoline-2-thiones, *J. Org. Chem.*, 80, 5272-5278 (DOI: 10.1021/jo5025943).

5. Shelke G. M., Jha M., Kumar A. (2016), Synthesis of indole-annulated sulfur heterocycles using copper-catalysed C-N coupling and palladium-catalysed direct arylation, *Org. Biomol. Chem.*, 14, 3450-3458 (DOI: 10.1039/c6ob00117c).

6. Singh S., Srivastava A., Samanta S. (2012), Rapid access of 2,3,4-trisubstituted-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives via one-pot three component reaction using organocatalysis, *Tetrahedron Lett*., 53, 6087-6090 (DOI: 10.1016/j.tetlet.2012.08.125).

7. Okachi T., Fujimoto K., Onaka M. (2002), Practical carbonyl-Ene reactions of α-methylstyrenes with paraformaldehyde promoted by a combined system of boron trifluoride and molecular sieves 4Å, *Org. Lett.*, 4, 1667-1669 (DOI: 10.1021/ol025719).

8. Pérez-Serrano L., Casarrubios L., Domínguez G., Pérez-Castells J. (1999), Pauson-Khand reaction induced by molecular sieves, *Org. Lett.*, 1, 1187-1188 (DOI: 10.1021/ol990856c).

9. Grassot J. M., Masson G., Zhu J. P. (2008), Synthesis of α-ketoamides by a molecular-sieves-promoted formal oxidative coupling of aliphatic aldehydes with isocyanides, *Angew. Chem. Int. Ed.*, 47, 947-950 (DOI: 10.1002/anie.200704840).

10. Löwenberg P. (1959), Molecular sieves in organic chemistry, *J. Appl. Chem.*, 9, 417-420 (DOI: 10.1002/jctb.5010090806).

11. Burfield D. R., Lee K.-H., Smithers R. H. (1977), Dessicant efficiency in solvent drying. A reappraisal by application of a novel method for solvent water assay, *J. Org. Chem.*, 42, 3060-3065 (DOI: 10.1021/jo00438a024).

12. Williams D. B. G., Lawton M. (2010), Drying of organic solvents: Quantitative evaluation of the efficiency of several desiccants, *J. Org. Chem.*, 75, 8351-8354 (DOI: 10.1021/jo101589h).

13. Srivastava A., Singh S., Samanta S. (2013), (±)-CSA catalyzed Friedel-Crafts alkylation of indoles with 3-ethoxycarbonyl-3-hydoxyisoindolin-1-one: An easy access of 3-ethoxycarbonyl-3-indolylisoindolin-1-ones bearing a quaternary α-amino acid moiety, *Tetrahedron Lett.*, 54, 1444-1448 (DOI: 10.1016/j.tetlet.2013.01.010).

14. Jaiswal P. K., Biswas S., Singh S., Pathak B., Mobin S. M., Samanta S. (2013), Stereoselective synthesis of highly functionalized tetrahydrocarbazoles through a domino Michael-Henry reaction: An

easy access to four contiguous chiral centers, *RSC Adv*., 3, 10644-10649 (DOI: 10.1039/c3ra41409d).

15. Jaiswal P. K., Biswas S., Singh S., Samanta S. (2013), An organocatalytic highly efficient approach to the direct synthesis of substituted carbazoles in water, *Org. Biomol. Chem*., 11, 8410-8418 (DOI: 10.1039/c3ob42034e).

16. Biswas S., Jaiswal P. K., Singh S., Mobin S. M., Samanta S. (2013), L-Proline catalyzed stereoselective synthesis of (*E*)-methyl-α-indol-2-yl-β-aryl/alkyl acrylates: Easy access to substituted carbazoles, γ-carbolines and prenostodione, *Org. Biomol. Chem*., 11, 7084-7087 (DOI: 10.1039/c3ob41573b).

17. Biswas S., Majee D., Dagar A., Samanta S. (2014), Metal-free one-pot protocol for the preparation of unexpected carbazole derivative in water: Easy access to pyrimidocarbazole and pyridocarbazolone derivatives, *Synlett*, 25, 2115-2120 (DOI: 10.1055/s-0034-1378446).

18. Srivastava A., Biswas S., Singh S., Mobin S. M., Samanta S. (2015), Organocatalysed Michael addition on arylmethylidene malonates involving 4-(2-nitrophenyl)acetoacetate: Diversity-oriented access to 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one and salicylate scaffolds, *RSC Adv*., 5, 26891-26896 (DOI: 10.1039/c5ra01430a).

19. Dagar A., Biswas S., Samanta S. (2015), A catalyst-free, efficient green MCR protocol for access to functionalized γ-carbolines in water, *RSC Adv*., 5, 52497-52507 (DOI: 10.1039/c5ra08422a).

20. Biswas S., Dagar A., Srivastava A., Samanta S. (2015), Access to substituted carbazoles in water by a one-pot sequential reaction of α, *β*-substituted nitro olefins with 2-(3-formyl-1*H*-indol-2-yl)acetates, *Eur. J. Org. Chem*., 4493-4503 (DOI: 10.1002/ejoc.201500470).

21. (a) Lakowicz J. R. (2006), Principles of fluorescence spectroscopy, 3rd edition, Springer science, Singapore; (b) Valeur B. (2002), Molecular fluorescence, Wiley-VCH GmbH, Germany; (c) Iliashenko R. Y., Gorobets N. Y., Doroshenko A. O. (2011), New and efficient high Stokes shift fluorescent compounds: Unsymmetrically substituted 1,2-*bis*-(5-phenyloxazol-2-yl)benzenes *via* microwave-assisted nucleophilic substitution of fluorine, *Tetrahedron Lett*., 52, 5086-5089 (DOI: 10.1016/j.tetlet.2011.07.100).

22. Liu D., Duan Y.-H. (2013), Synthesis of novel thieno[3,4-*b*]pyrazine-cored molecules as red fluorescent materials, *Chin. Chem. Lett*., 24, 809-812 (DOI: 10.1016/j.cclet.2013.05.024).

23. Chen S., Qiao X., Li H., Li H. (2015), Acceptor-Donor-Acceptor type small molecular low band gap organic semiconductors containing 2-dicyanomethylen-3-cyano-4,5,5-trimethyldihydrofuran, *Chin. J. Chem*., 33, 934-938 (DOI: 10.1002/cjoc.201400811).

24. Li M., Ni W., Feng H., Kan B., Wan X., Zhang Y., Yang X., Chen Y. (2015), Dithienopyrrole based small molecule with low band gap for organic solar cells, *Chin. J. Chem*., 33, 852-858 (DOI: 10.1002/cjoc.201500170).

Chapter 4

A remarkable solvent effect on the reaction of 4-hydroxycoumarin with (*E*)-3-aryl-2-nitroprop-2-enol: Facile synthesis of highly substituted furo/pyrano[3,2-*c*]chromenes

4.1 Introduction

Coumarin nucleus represents an important class of heterocycle molecule which was found in a variety of natural products and pharmacophores.[1-4] Several coumarin based fused heterocycles have been attributed to a variety of medicinally privileged compounds. They used in pharmaceuticals, material science, polymers etc.[5-6] Among them, furo/pyrano based fused coumarins are of considerable interest in recent years due to their applications in a variety fields.[7-9] For instance, Psoralens (**I**), 5-methoxypsoralen (5-MOP or bergapten) (**II**), 8-methoxypsoralen (**III**), Angelicin (IV), 4,6,4-trimethylangelicin (**V**), neo-tanshinlactone (**VI**), coumestrol (**VII**), Wedelolactone (**VIII**), Heraclenin (**IX**) and Nuclear factor kappaB (**X**) having several biological activities as shown in **Figure 4.1**.[10-47]

In addition to furocoumarins, pyranocoumarins like (+)-pseudocordatolide C (**XI**), alloxanthoxyletin (**XII**) and (**XIII-XV**) possess other interesting biological properties are also mentioned in **Figure 4.1**.[48-52]

Thus, the development of efficient protocol for the straightforward synthesis of functionalized furo/pyranocoumarins from simple raw material is a key research area in synthetic organic chemistry and drug discovery programme.

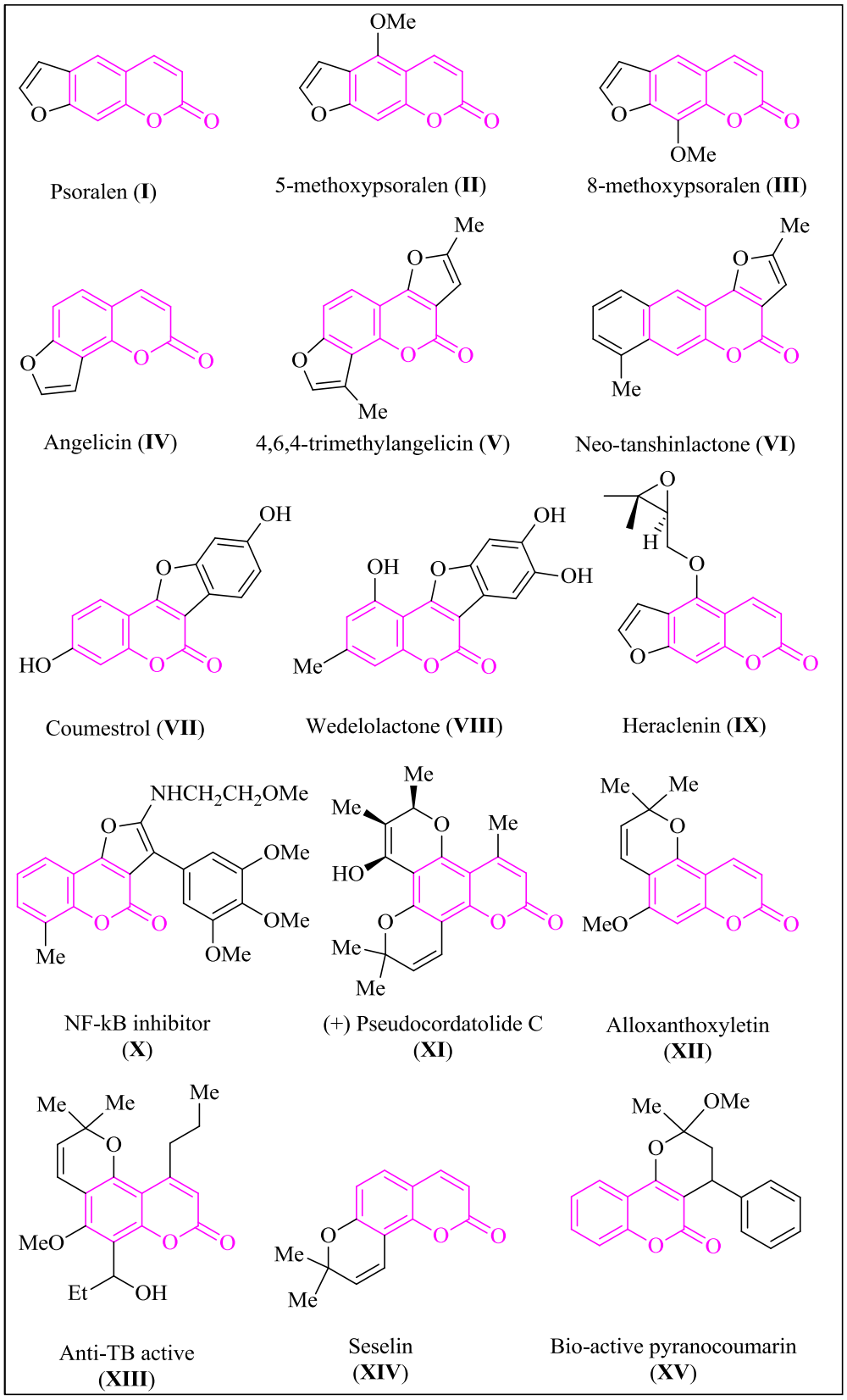


Figure 4.1 Natural products and biologically active compounds that have furo/pyranocoumarins

Owing to the importance of these bioactive fused-coumarin derivatives, several powerful protocols have been devoted for the constructions of furo/pyrano[3,2-*c*]coumarins. Some of the important literature reports to access the mentioned compounds have been discussed in the review section **4.2**.

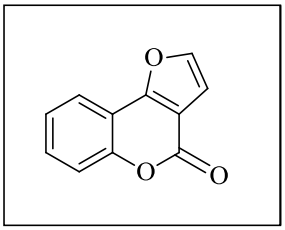
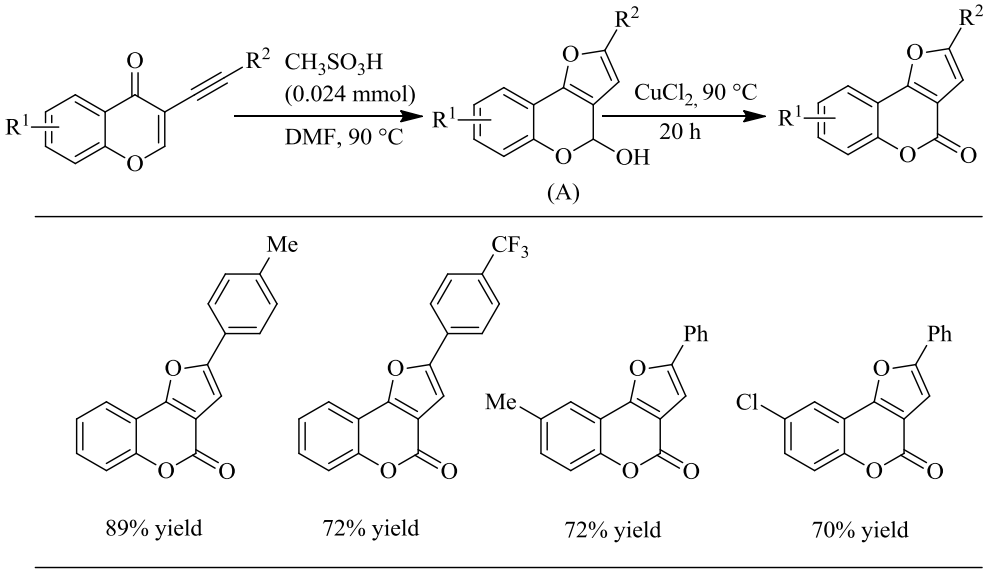


Figure 4.2 Representative structure of furo[3,2-*c*]coumarin

4.2 Review work

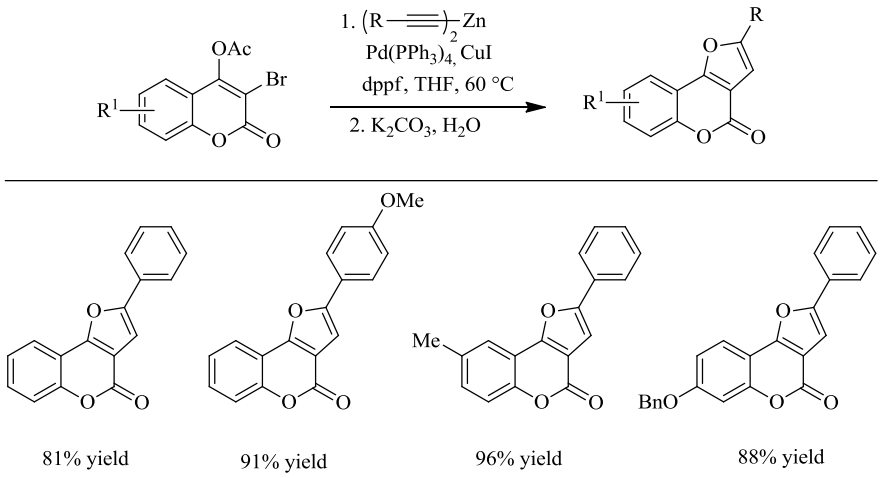
Due to various applications in different fields, researchers all over the world are giving their enormous efforts to make furocoumarins in different possible ways. Some important reviews to access furo[3,2-*c*]coumarins are discussed below.

A sequential one-pot cascade addition-cyclization-oxidation for the regioselective synthesis of furo[3,2-*c*]coumarins was developed by Cheng *et al*. in 2007.[53] The reaction has been performed by using substituted 2-(1-alkynyl)-2-alken-1-ones in DMF at 90 °C in the presence of a catalytic amount of CH_3SO_3H to provide cyclic hemiacetal (A) which is subsequently oxidized by $CuCl_2$ at 90 °C for 20 h (**Scheme 4.1**).



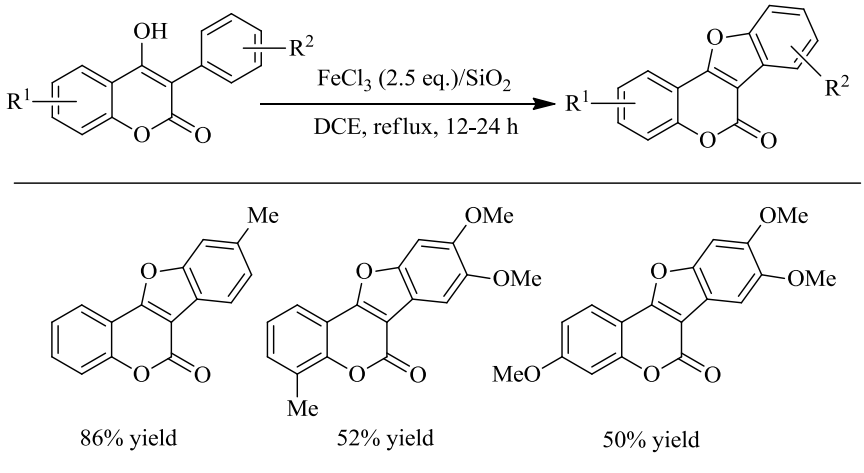
Scheme 4.1 Regioselective synthesis of furo[3,2-*c*]coumarins

In 2010, Xu *et al.* successfully achieved in the rapid synthesis of furocoumarins through a one-pot sequential coupling/cyclization strategy by utilizing 3-bromo-4-acetoxycoumarins and terminal alkynes.[54] The reaction involves Pd/Cu-catalyzed alkynylation with in situ generated dialkynylzincs in THF at 60 °C in the presence of 1,1′-bis(diphenylphosphino)ferrocene (dppf) as an additive, which is further followed by intramolecular hydroalkoxylation using aq. K_2CO_3 (**Scheme 4.2**). The resulting method affords high to excellent yields (81-96%) of functionalized furocoumarins.



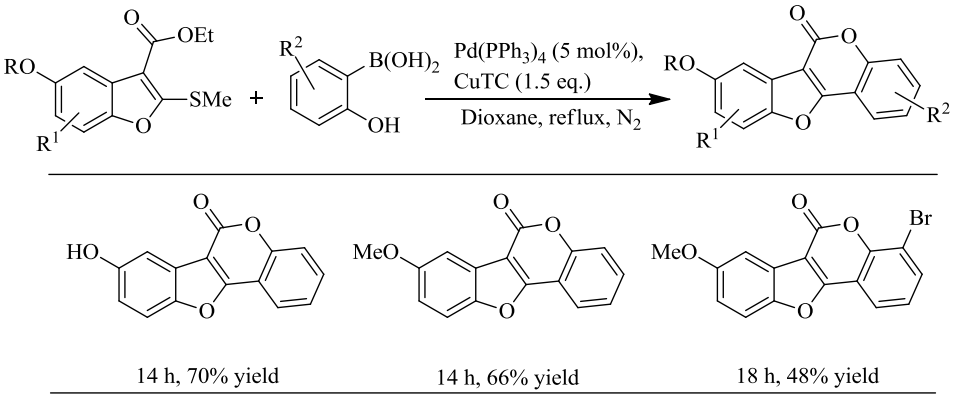
Scheme 4.2 One-pot sequential coupling/cyclization strategy for furocoumarins

To develop more efficient approach for the syntheses of furocoumarin analogues, $FeCl_3/SiO_2$-mediated direct intramolecular oxidative annellation reaction of 4-hydroxy-3-aryl-2*H*-chromen-2-one derivatives has been done in DCE under refluxing conditions for 12-24 h by Zhao *et al.*[55] Applying this methodology, a variety of coumestan derivatives were synthesized in mediocre to high chemical yields from readily available 4-hydroxycoumarins derivatives (**Scheme 4.3**).



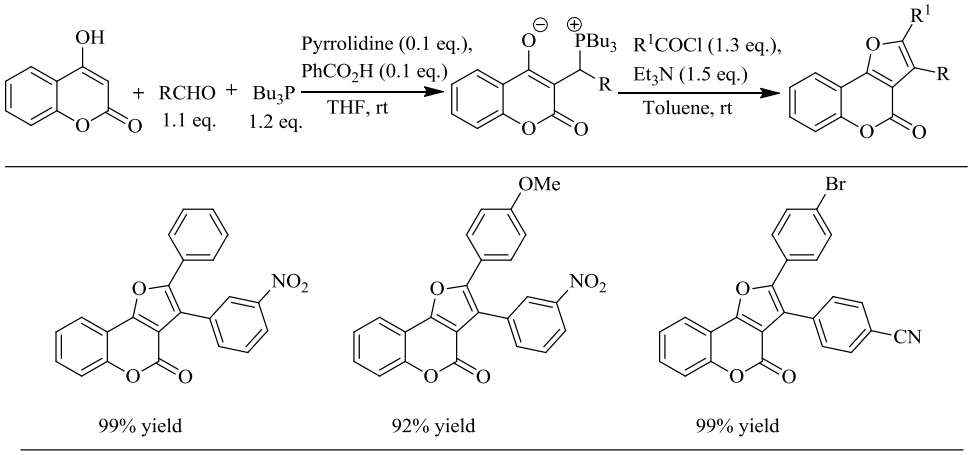
Scheme 4.3 $FeCl_3$-mediated direct intramolecular oxidative annellation

The sequential cross-coupling and trans esterification reactions of (2-methylthio-3-ester)benzofurans with 2-hydroxyphenylboronic acids have been performed in dioxane by using a catalytic amount of $Pd(PPh_3)_4$ and Copper(I)thiophene-2-carboxylate (CuTC) reagent system to provide coumestane derivatives in 48-70% yields after 14 h as reported by Wang and his coworkers (**Scheme 4.4**).[56]



Scheme 4.4 Cross-coupling of (2-methylthio-3-ester)benzofurans with 2-hydroxyphenylboronic acids

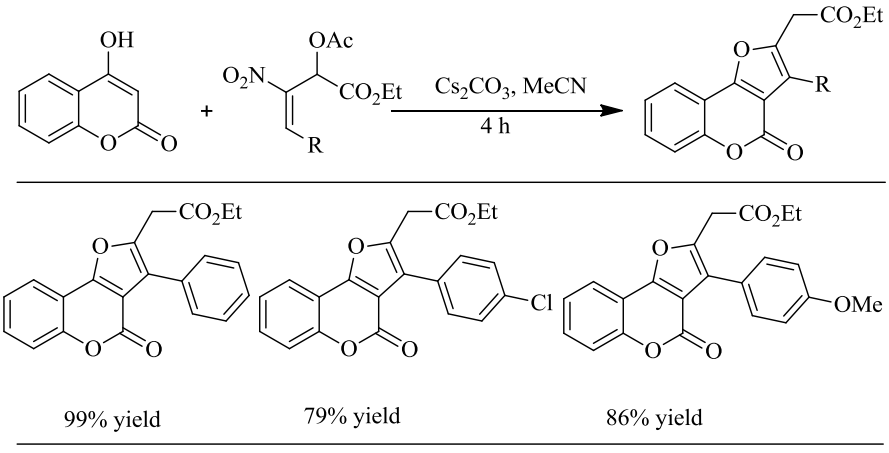
Lin *et al.* reported a general preparation of highly functional phosphorus zwitter ions *via* tandem three-component reactions using the corresponding 4-hydroxycoumarins, aldehydes (1.1 eq.) and Bu_3P (1.2 eq.) in the presence of pyrollidine/benzoic acid reagent system which was further utilized for the synthesis of furo[3,2-*c*]coumarin scaffolds (92-99% yields) by using acid chlorides under the presence of base at room temperature (**Scheme 4.5**).[57]



Scheme 4.5 Furocoumarins access *via* highly functional phosphorus zwitter ions

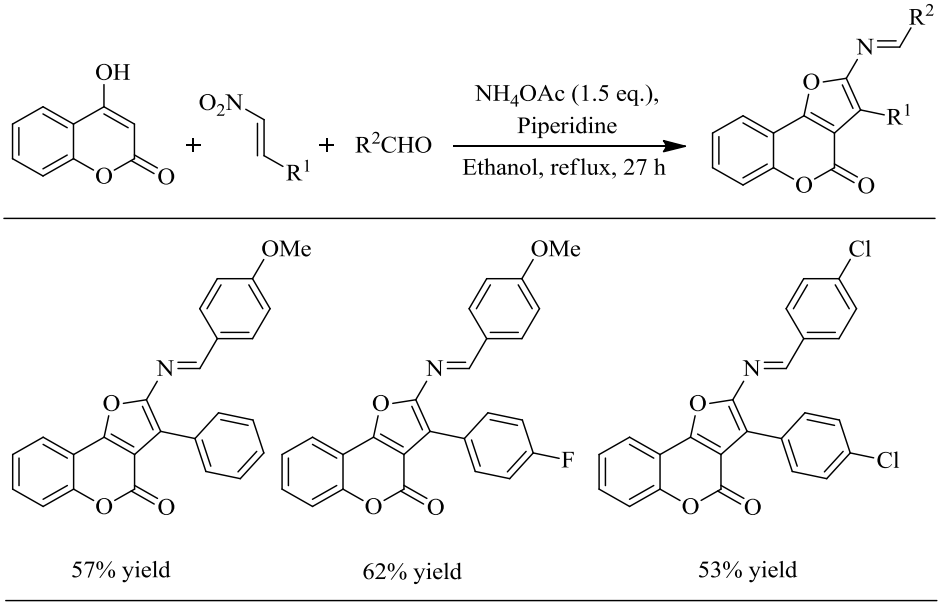
Besides, the great success of transition metal catalysts, a few examples of metal-free mediated one-pot synthesis of substituted furocoumarin derivatives have been well documented as some of these works were published very recently.

Feist-Benary/addition-elimination reaction of 4-hydroxycoumarin with nitroallyl acetate under basic conditions has been realized by Chen and his associates in 2012.[58] This procedure gives tetrasubstituted furans in good to excellent yield (79-99%) in **Scheme 4.6**.



Scheme 4.6 Feist-Benary/addition-elimination reaction of 4-hydroxycoumarin with nitroallyl acetate

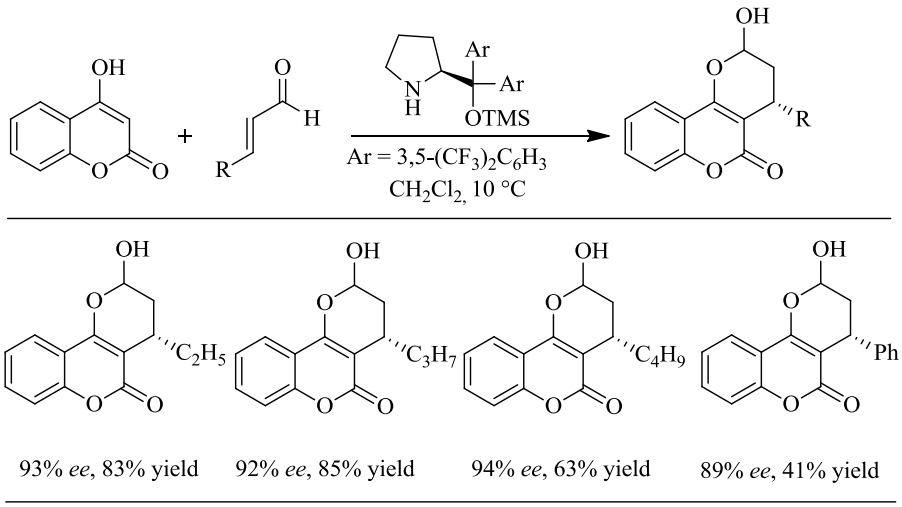
Wang and his co-workers also established an efficient and attractive synthetic strategy involving a four-component reaction between substituted-nitrostyrenes, aromatic aldehyde, 4-hydroxycoumarin and ammonium acetate under refluxing ethanol for 27 h to afford 2-alkylamino-3-aryl-4*H*-furo[3,2-*c*]chromen-4-ones in good yields (53-62%).[59] This process involves sequential Michael addition, aza-nucleophilic addition of imine to the double bond, which is further followed by intermolecular nucleophilic addition and dehydration (**Scheme 4.7**).



Scheme 4.7 Four-component reaction to access furocoumarins

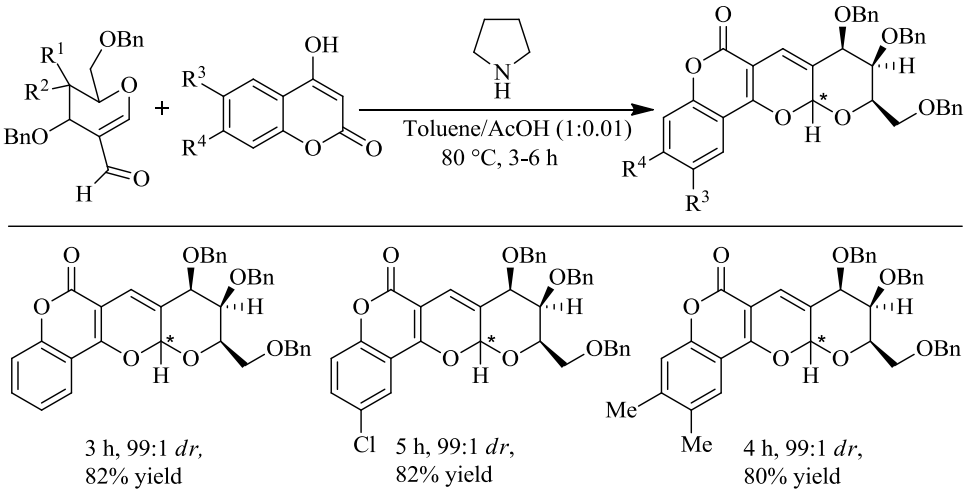
Besides these attractive protocols for the synthesis of furo-coumarins, there are some efficient procedures to access pyrano-coumarins. Some of them are discussed as below the section.

Rueping *et al*. has developed an efficient, organocatalytic and enantioselective addition-cyclization strategy of cyclic 1,3-dicarbonyl compounds with different α,β-unsaturated aldehydes in CH_2Cl_2 at 10 °C.[60] They utilizes diarylprolinol silyl ether catalyst to achieve a variety of optically active pyrano[3,2-*c*]chromenes in excellent enantioselectivity (upto 94% *ee*) with poor to high yields (41-85%) as shown in **Scheme 4.8**.



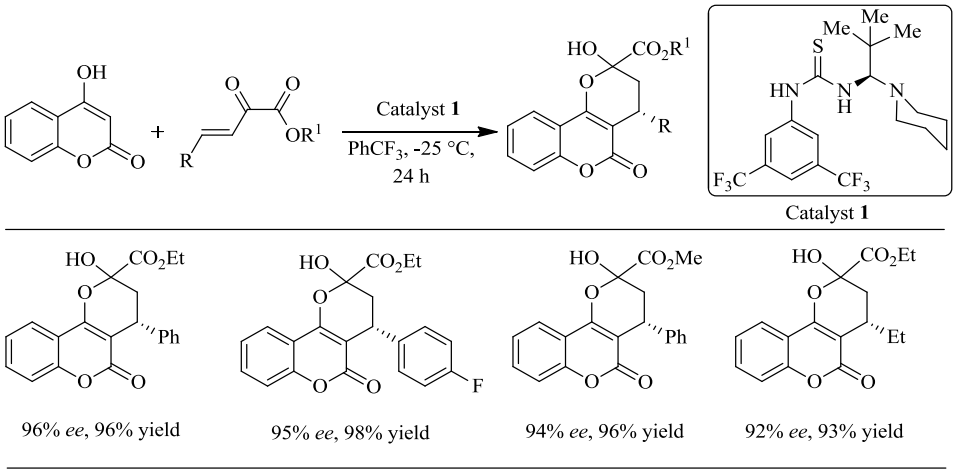
Scheme 4.8 The diarylprolinol ether-catalyzed cascade reaction

A facile, efficient and one-pot diastereoselective approach to polycyclic acetal-fused pyrano[3,2-*c*]pyrane-5(2*H*)-one was reported by Park and his coworkers in 2008. The method involves annulation reaction of 2-*C*-formyl galactals with various substituted 4-hydroxycoumarins in toluene/AcOH at 80 °C for 3-6 h using pyrrolidine as a base (**Scheme 4.9**).[61] A series of tetracyclic fused coumarins were obtained in high yields (80-82%) with excellent diastereoselectivities (*dr* > 99:1).



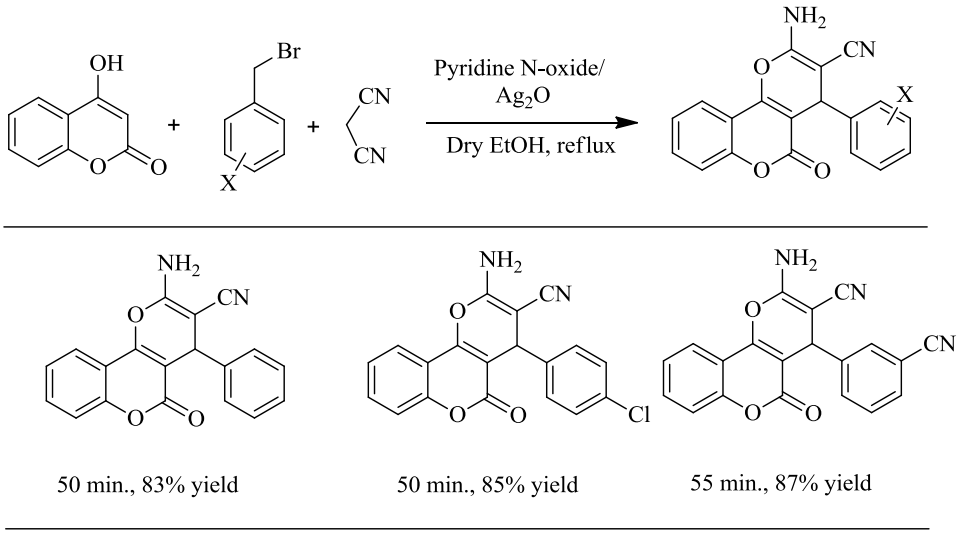
Scheme 4.9 Diastereoselective one-pot access of polycyclic acetal-fused pyrano[3,2-*c*]pyrane-5(2*H*)-one

Wang *et al.* reported an efficient and convenient enantioselective Michael addition reaction between 4-hydroxycoumarin and β,γ-unsaturated α-ketoesters as highly reactive Michael acceptors catalyzed by thio-urea based H-bonding catalyst to afford pyranocoumarins in excellent chemical yields (93-98%) with excellent enanantioselectivity (up to 96% *ee*) after 24 h (**Scheme 4.10**).[62]



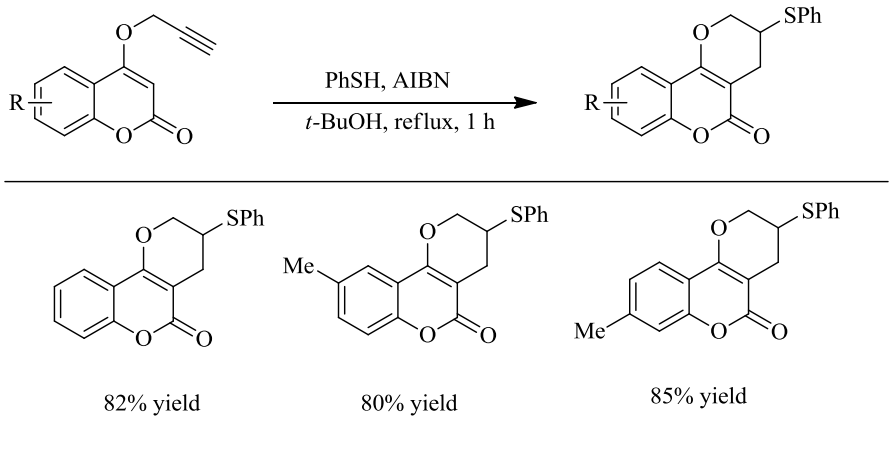
Scheme 4.10 Enantioselective Michael addition reaction between coumarin and highly reactive electrophile β,γ-unsaturated α-ketoester

Beerappa *et al*. reported one-pot three-component strategy involving 4-hydroxy coumarin, benzyl halides and malanonitrile under the presence of pyridine N-oxide/silver oxide as catalyst in refluxing ethanol to deliver corresponding pyran fused coumarin analogues in high yields (83-87%) in a short span of time (50-55 min.) (**Scheme 4.11**).[63]



Scheme 4.11 One-pot synthesis of pyran-based heterocycles from benzyl halides

Majumdar and his co-workers described a regioselective synthesis of dihydropyranocoumarins in high yields (80-85%) *via* a thiol-mediated radical reaction involving propargylcoumarin derivatives and thiophenol (2 equiv.) under refluxing conditions in dry *t*-butanol for 1 h (**Scheme 4.12**).*[64]*



Scheme 4.12 Thiol-mediated synthesis of dihydropyranocoumarins

Conclusion

There are several reports in the literature for facile synthesis of highly substituted furo/pyrano[3,2-*c*]chromenes in good to excellent yield as discussed in the review section. However, many of these reported protocols involve toxic/expensive metal catalysts, toxic reagents and harmful/hazardous organic solvents which are not much appreciable from environmental and economic stand points of view.

Even with a noticeable progress, there is no successful report on catalyst-free one-pot synthesis of furo[3,2-*c*]chromen-4-one derivatives in water medium.[65-66] Similarly, the synthesis of 2-aryl-3-nitropyrano[3,2-*c*]chromenones has been overlooked in the literature. Thus, it is necessary to devise an alternative practical, cost-effective and metal-free green protocol for the preparation of a pharmacologically attractive functionalized furo/pyranocoumarin scaffolds involving simple substances that lead to better yields under aqueous conditions.

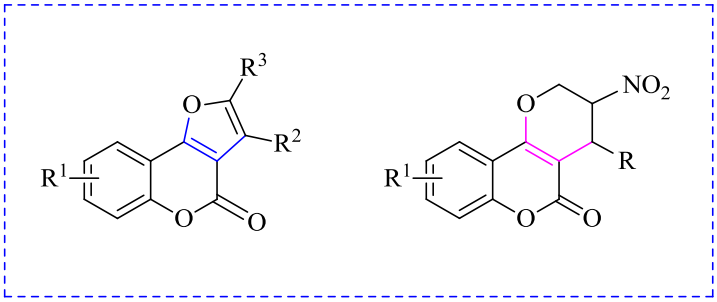
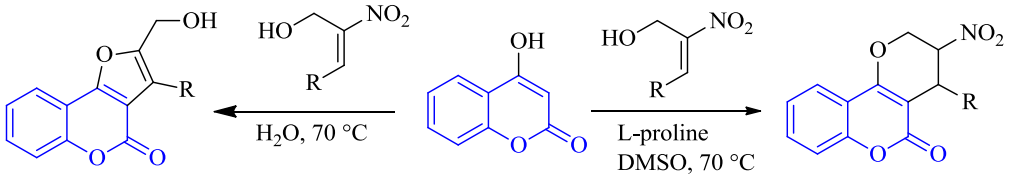


Figure 4.3 Representative structures of furo/pyro[3,2-*c*]coumarins

4.3 Present work

The facile and atom economical strategy to synthesize furo/pyrano[3,2-*c*]chromene derivatives under green reaction conditions is a lightning attraction in the field of synthetic as well as medicinal chemistry. As these furo/pyrano[3,2-*c*]coumarin rings are important privileged structures in many biologically active compounds as discussed in the introduction part

4.1. Here, we wish to report a mild, simple, convenient, high yielding procedure for the construction of furo/pyrano[3,2-*c*]coumarins *via* a one-pot reaction of substituted 4-hydroxycoumarins with (*E*)-3-aryl-2-nitroprop-2-enols in water/DMSO medium respectively under metal-free conditions.



Scheme 4.13 Facile synthesis of highly substituted furo/pyrano[3,2-*c*]chromenes

4.4 Results and Discussion

4.4.1 Screening of solvents and catalysts

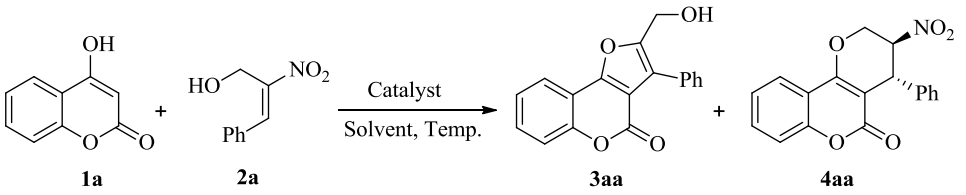
We chose a model reaction between 4-hydroxycoumarin (**1a**) and (*E*)-3-phenyl-2-nitropro-2-enol (**2a**) in the absence of catalyst in $CHCl_3$ at 50 °C for 24 h. Interestingly, a very little amount of unexpected 2-(hydroxymethyl)-3-phenyl-4*H*-furo[3,2-*c*]chromen-4-one (**3aa**) along with *trans*-3-nitro-4-phenyl-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one (**4aa**) were obtained in 12% and 3% yields respectively (**Table 4.1**). Both the products are well characterized by their spectroscopic data (^{1}H NMR and ^{13}C NMR, HRMS). For example, ^{1}H NMR spectrum of **3aa** shows the one broad singlet at δ 5.68 corresponds to OH and one singlet at δ 4.53 corresponds to CH_2. ^{13}C NMR spectrum shows appearance of 4 peaks at δ 157.6, 157.4, 152.7 and 152.4 characteristics of oxygen attached with aromatic ring. Further, 135° DEPT shows the presence of single opposite phase peak at δ 55.6 corresponds to CH_2 group. The HRMS spectrum indicates the presence of molecular ion peak $[M+Na]^+$ at 315.0623 which corresponds to the molecular weight of the desired product (292.0736).

Similarly ^{1}H NMR spectrum of **4aa** shows doublets and multiplets in the region δ 4.39-5.12 corresponds to aliphatic hydrogens. ^{13}C NMR spectrum shows presence of peaks at δ 39.2, 62.8, 82.2 and at 89.2 corresponding aliphatic region. 135° DEPT shows the presence of single opposite phase peak at δ 62.8 corresponds to CH_2 group while two positive phase peaks appears at δ 82.2 and at 38.3. The HRMS spectrum shows the presence of molecular ion peak $[M+Na]^+$ at 346.0687 which corresponds to the molecular weight of the desired product (323.0794).

In order to get the best reaction condition we tried the same reaction in different conditions. Interestingly, when the same reaction was carried out at elevated temperature 70 °C, slight improvements of results were recorded in terms of reaction time (24 h to 15 h) and yield (**3aa**, 12% to 25%). As we are aware that the reaction of 4-hydroxycoumarin with *β*-nitrostyrene derivatives highly depends on the polarity of the solvents.[67-68] In this regard, we tested this reaction in several common organic solvents namely EtOH, DMSO, DMF, $CHCl_3$, 1,2-dichloroethane (DCE), toluene, MeCN at 70 °C. Pleasantly, we found that polar solvents like EtOH, DMF and DMSO favoured the formation of **4aa** in good to high yields (42-85%) and non-polar solvents ($CHCl_3$, DCE, toluene and MeCN) resulted in low yield (21-42%) of furocoumarin **3aa**.

Screening of several catalysts (L-proline, DABCO and DMAP) revealed that they have almost no influence on product selectivity. However, they enhanced the rate of the reaction (5-10 h vs 15 h), resulting in higher yields of **3aa** (69-76%) and **4aa** (51-88%). In order to make this reaction conditions in an environmentally friendly manner, we did this reaction in water instead of harmful organic solvent. Surprisingly, after 5 h, in the absence of catalyst, the reaction proceeded very smoothly at 70 °C, leading to the high yield of major product **3aa** (83%).

Table 4.1 Catalyst screening and optimization of conditions[a]



Entry	Catalyst	Solvent	T(°C)	T/h	Yield(%)[c]	
					3aa	**4aa**[d]
1[b]	Nil	$CHCl_3$	50	24	12	<3
2[b]	Nil	$CHCl_3$	70	15	25	<5
3[b]	Nil	DCE	70	15	21	<7
4[b]	Nil	Toluene	70	15	41	8
5[b]	Nil	MeCN	70	15	29	<7
6[b]	Nil	EtOH	70	15	19	42
7[b]	Nil	DMSO	70	15	6	85
8[b]	Nil	DMF	70	15	11	81
9	L-proline	$CHCl_3$	70	10	74	9
10	L-proline	DCE	70	10	76	<8
11	L-proline	Toluene	70	10	72	11
12	L-proline	MeCN	70	10	69	7
13	**L-proline**	**DMSO**	**70**	**5**	**7**	**88**
14	L-proline	DMF	70	7	10	83
15	L-proline	EtOH	70	7	29	51
16	DABCO	DMSO	70	5	9	81
17	DMAP	DMSO	70	5	12	83
18	DABCO	DMF	70	7	13	77
19[b]	**Nil**	**H_2O**	**70**	**5**	**83**	**<6**
20	L-proline	H_2O	70	5	86	8
21	DABCO	H_2O	70	5	83	9
22	DMAP	H_2O	70	5	84	<7

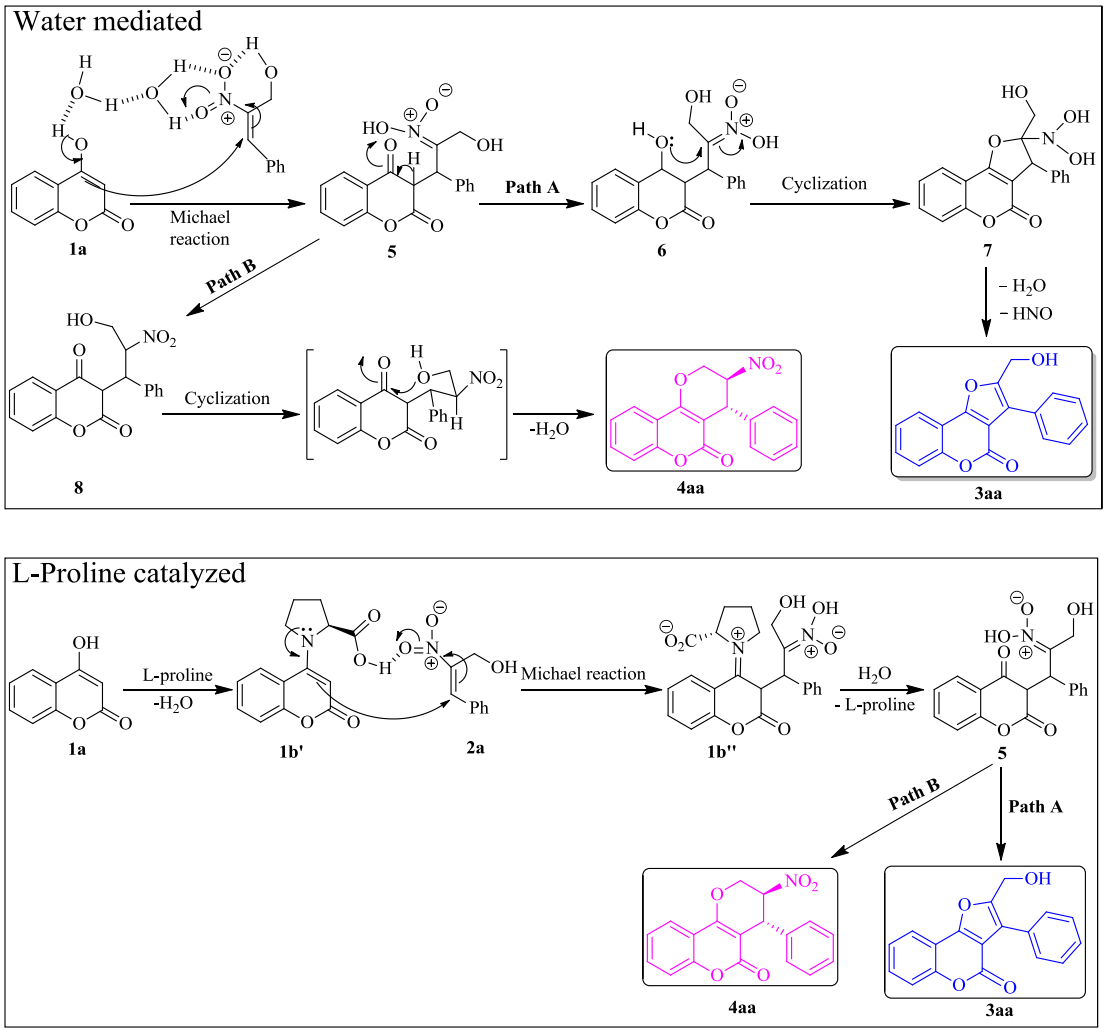
[a]Unless otherwise specified, all the reactions were performed with compound **1a** (0.25 mmol), **2a** (0.3 mmol) and catalyst (0.05 mmol, 20 mol%) in specified solvent (0.6 ml) and temperature. [b]Nil indicates no catalyst. [c]Yield of isolated product after column chromatography. [d]Diastereomeric ratio (99:1) of the crude product recorded by ^{1}H NMR.

In particular, there was no significant improvement of result in terms of yield, selectivity or time when the reaction was carried out in the presence of catalyst (L-proline, DABCO and DMAP) under identical conditions. From the various reaction conditions as shown in **Table 4.1**, it was obvious that best result was obtained for **3aa** at condition mentioned in 83% yield.

4.4.2 Proposed mechanism

Herein we present the following probable mechanism for the formations of compounds **3aa** and **4aa** under present reaction conditions as shown in **Scheme 4.11**. In case of water medium, we assume that water plays a crucial role in this reaction by acting as an amphiphilic dual-catalyst.[69-70] It may activate both the substrates **1a** and **2a** through intermolecular H-bonding which increases rate of the Michael addition reaction between **1a** and **2a**, resulting in formation of nitronic acid intermediate **5**. Afterwards, the intermediate **6** is generated from **5** *via* a tautomerization process which undergoes in turn intramolecular cyclization, subsequent dehydration and elimination of hyponitrous acid (HNO) to give the final compound **3aa** (**Path A**).

On the other hand, the intermediate **5** instead tend to form an intermediate **8** under this condition *via* a tautomerization process, which is followed by intramolecular cyclization-dehydration, leading to the pyranocoumarin **4aa** (**Path B**).



Scheme 4.14 Mechanism for synthesis of highly substituted furo/pyrano[3,2-*c*]chromenes

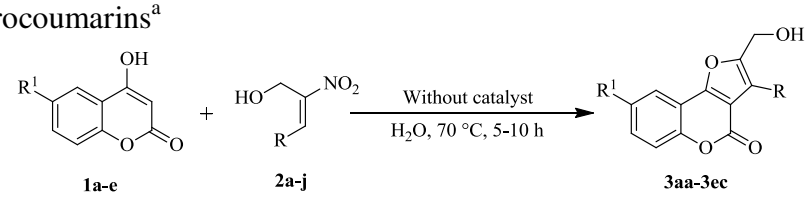
In case of L-proline, we think at this point that Michael reaction may take place through an enamine intermediate **1b′** to form **1b″** which upon reaction with water and followed by elimination of L-proline furnishes intermediate **5**. Finally products **3aa** and **4aa** are generated from **5** by following **path A** and **path B** respectively. However, additional work is necessary for understanding the detailed mechanism of this reaction.

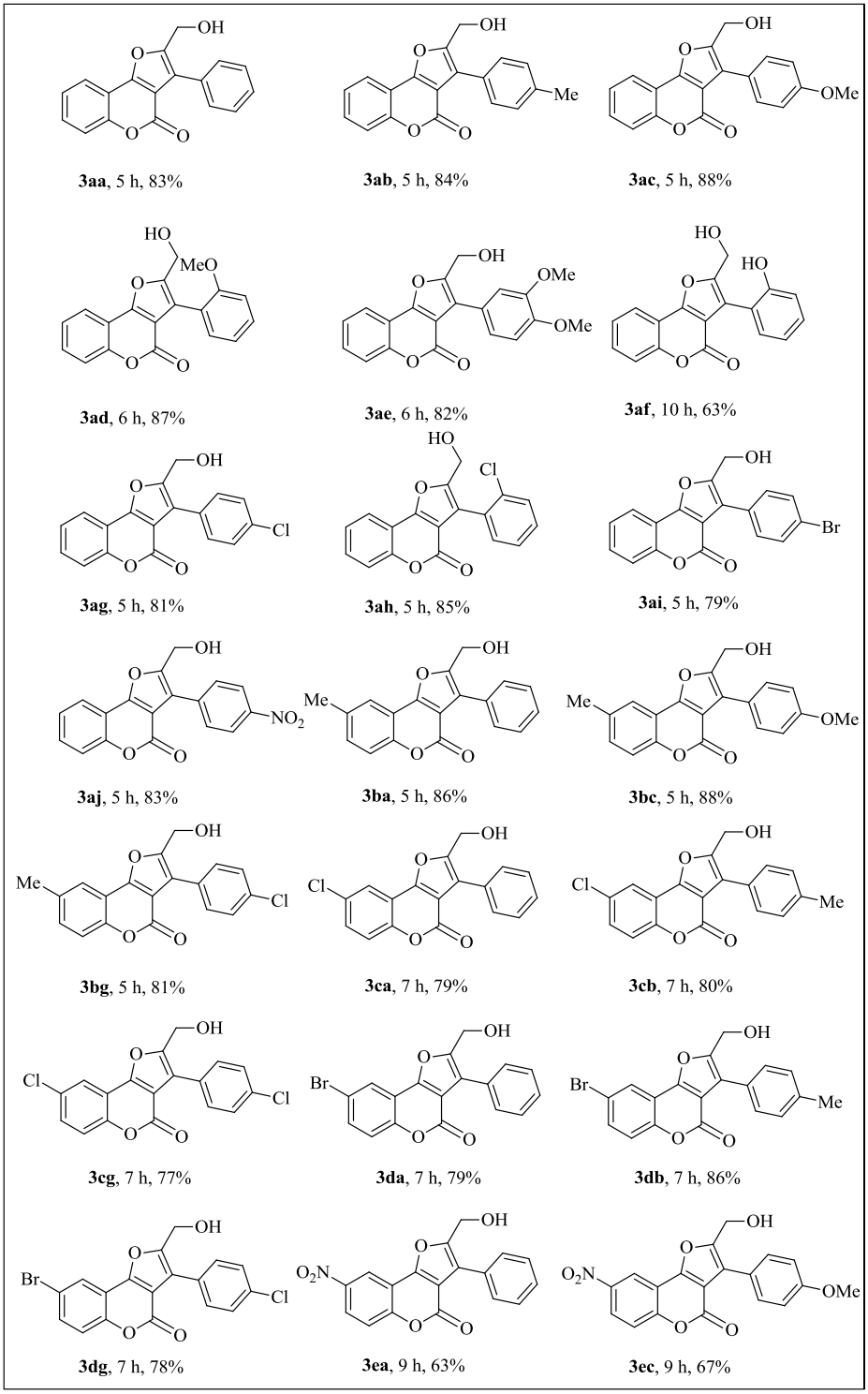
4.4.3 Substrate scope

With the optimum reaction conditions in hand, various substituted (*E*)-3-aryl-substituted-2-nitroprop-2-enols and 4-hydroxycoumarin derivatives were examined to understand the generality and scope of this reaction. The outcomes are compiled in **Table 4.2**. It is noteworthy that both electron-donating (Me, MeO and OH) and electron-withdrawing (Cl, Br, and NO_2) groups on the aromatic rings of 3-aryl-substitited-2-nitroprop-2-enols annulated smoothly with substrate (**1a**), resulting in good to high yields (63-88%) of corresponding furo[3,2-*c*]chromenes. Similarly, incorporation of several functionalities such as mild electron rich (Me) and electron poor groups (Cl, Br and NO_2) on aryl rings of 4-hydroxycoumarins (**1b**-**e**) did not make any difficulty with (*E*)-3-aryl-substituted-2-nitroprop-2-enols (**2a**-**c** and **2g**) by this procedure and resulted in clean and complete Michael/cyclization-elimination reactions, providing the corresponding annulated products (**3ba**-**3ec**) in good to high yields (63-88%). It should be noted that 4-hydroxycoumarins (**1c**-**e**) possessing electron-withdrawing substituents are slightly less reactive than its unsubstituted version **1a** towards Michael acceptors under identical conditions (e.g. 5 h vs 9 h).

Importantly, our present conditions are mild enough to retain several functional groups such as OMe, OH, Cl, Br, NO_2, CH_2OH etc. Besides, the bench scale preparation of compound **3aa** was investigated in our imposed conditions. A heterogeneous mixture of compound **1a** (1.62 gm, 10.0 mmol) and **2a** (12.0 mmol) in water (6.0 mL) was heated at 70 °C for 6 h. Afterwards, water was decanted carefully from the reaction mixture to give the gummy residue which was directly purified by column chromatography technique, leading to the pure product **3aa** in 76% yield. This interesting result reveals that our optimal condition can be used for milligram to gram scale synthesis.

Table 4.2 Generality of this one pot domino reaction to access furocoumarins[a]



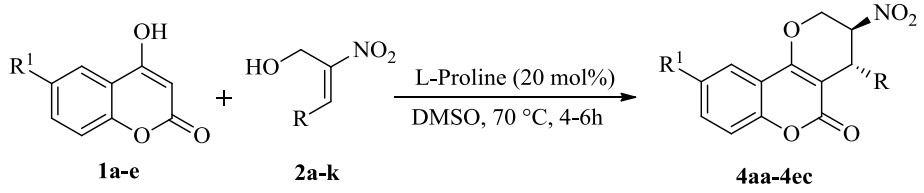


[a]All the reactions were done with 4-hydroxycoumarin derivative (**1a-e**, 0.25 mmol), (*E*)-3-aryl-2-nitropro-2-enols (**2a-j**, 0.3 mmol) in water (0.6 mL) at 70 °C. Isolated yield after column chromatography.

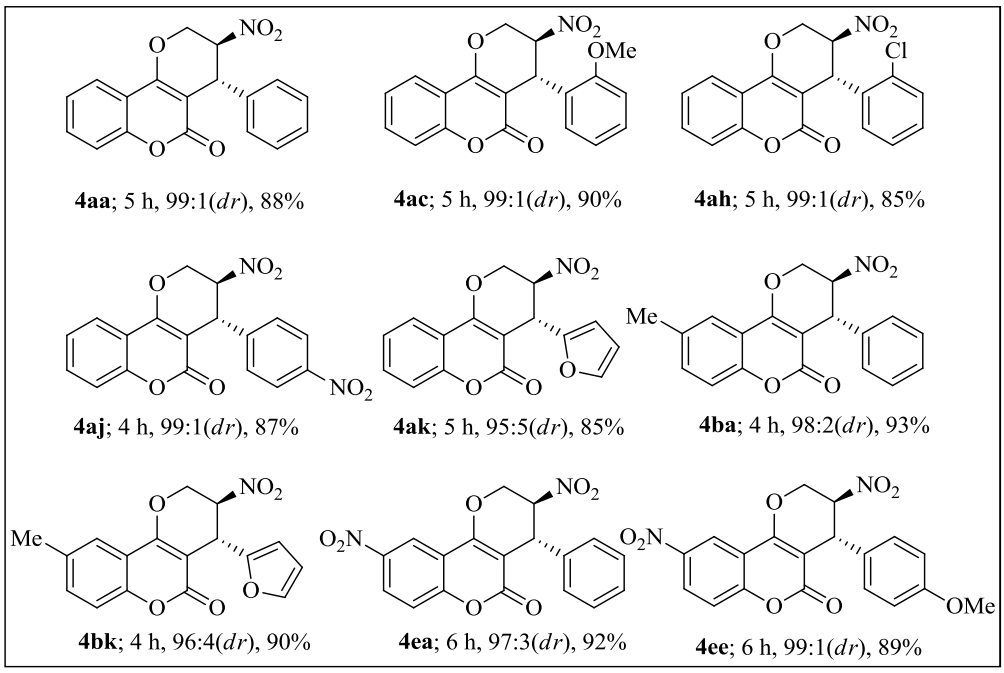
Next, we turned our attention towards the facile synthesis of functionalized pyranocoumarin derivative as this motif is frequently existed in a variety of bioactive natural products and pharmacophores.[71-75] Literature survey shows that several practical and efficient techniques are available for the syntheses of both the racemic and enantio-enriched versions of dihydropyrano[3,2-*c*]chromen derivatives.[76]

Towards our investigations, various functionalized 4-hydroxycoumarin derivatives (**1a-b**, **1e**) were reacted with several aryl/hetero-aryl substituted nitroallylic alcohols in DMSO medium at 70 °C in the presence of L-proline (20 mol%).

Table 4.3 Generality of this one pot domino reaction to access pyranocoumarins[a]



1a-e **2a-k** **4aa-4ec**



4aa; 5 h, 99:1(*dr*), 88% **4ac**; 5 h, 99:1(*dr*), 90% **4ah**; 5 h, 99:1(*dr*), 85%

4aj; 4 h, 99:1(*dr*), 87% **4ak**; 5 h, 95:5(*dr*), 85% **4ba**; 4 h, 98:2(*dr*), 93%

4bk; 4 h, 96:4(*dr*), 90% **4ea**; 6 h, 97:3(*dr*), 92% **4ee**; 6 h, 99:1(*dr*), 89%

[a]All the reactions were done with 4-hydroxycoumarin derivative (**1a-e**, 0.25 mmol), (*E*)-3-aryl-2-nitropro-2-enols (**2a**-**k**, 0.3 mmol) in DMSO (0.6 mL) by using L-proline (0.05 mmol) at 70 ºC. Isolated yield after column chromatography. The diastereomeric ratio of the crude product was determined by ^{1}H NMR spectrum.

The results are summarized in **Table 4.3**. To our delight, all the reactions took place easily by this procedure to give the corresponding previously unknown class of substituted *trans*-3-nitro-4-aryl-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one derivatives in high to excellent yields (85-93%, **4aa**-**4ec**) with excellent diastereoselectivities (up to ≤99:1 dr).

It should be noted that relative stereochemistry of major diastereomer **4ah** was unanimously confirmed by its single crystal X-ray diffraction data (**Figure 4.2**) indicating aryl group in *trans*-orientation with NO_2. Similarly, several sensitive functional groups namely NO_2, OMe, furan, Me and Cl are tolerable in our present conditions.

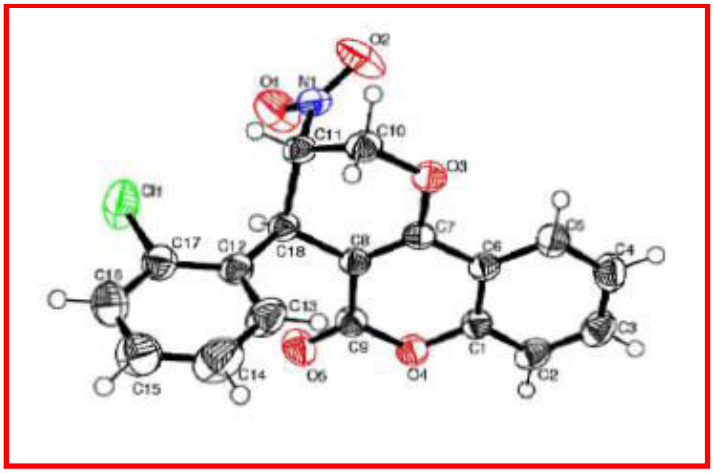


Figure 4.4 ORTEP diagram of **4ah.**

4.5 Conclusion

In this chapter, a remarkable solvent effect on one-pot reaction of 4-hydroxycoumarin derivatives with (*E*)-3-aryl-substituted-2-nitroprop-2-enols has been observed which was employed for the convenient synthesis of highly substituted furo/pyrano[3,2-*c*]chromen-5(2*H*)-ones, by performing the reaction in water or DMSO respectively. Moreover, water shows not only positive roles on the rate and selectivity (product) of this reaction but also beneficial features in terms of safety, health, cost-effectiveness and environmental standpoints of view. Furthermore, our current procedure avoids the use of toxic metals and their salts, harmful/volatile organic solvents, any need for dry conditions or inert-atmosphere, multi-step, etc. Importantly, in comparison to the reported methods, our protocols are advantageous since they are operationally simple, easy to work-up, applicable for gram-scale synthesis, as well as offer good to excellent yields (63-93%), excellent diastereoselectivities (upto $\leq$ 99:1 *dr*) and good substrate scope.

4.6 Experimental

General Information

All the reactions were performed under air and their progress was monitored by TLC using Merck 60 F_{254} pre coated silica gel plates (0.25 mm thickness) and the products were visualized by UV detection. The purification of the desired products was carried out using Flash chromatography with silica gel (200-300 mesh). FT-IR spectra were recorded on a Bruker Tensor-27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BrukerAvance (III) 400 MHz spectrometer. Data for ^{1}H NMR are reported as a chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constant *J* (Hz), integration, and assignment, data for ^{13}C are reported as a chemical shift.

The deuterated solvents used for NMR include $CDCl_3$ and DMSO-d_6. High resolution mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. The starting materials were either purchased or synthesized using literature known procedure.

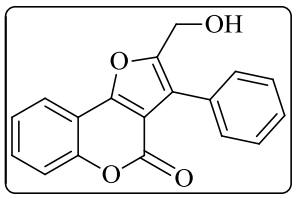
Synthesis of (*E*)-3-(2-chlorophenyl)-2-nitropro-2-enol (2h): 2-Chloro-*trans*-β-nitrostyrene (1.5 mmol, 274 mg) and imidazole (1.5 mmol, 102 mg) was stirred in THF (5.0 mL) at room temperature. HCHO (2 mL) was added in the reaction mixture, which is further allowed to stirr for 24 h (monitored by TLC). The solvent was removed by rotary evaporator under reduced pressure to leave the crude product which was obtained (89% yield) in a pure form through column chromatography purification over silica-gel and the product (**2h**) was characterized by ^{1}H NMR spectrum.

(*E*)-3-(2-chlorophenyl)-2-nitropro-2-enol (2h): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.35 (s, 1H), 7.58-7.60 (m, 1H), 7.47-7.59 (m, 1H), 7.35-7.43 (m, 2H), 4.59-4.61 (m, 2H).

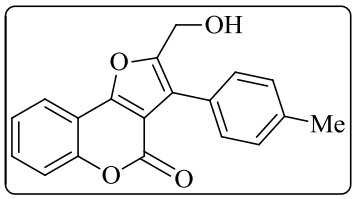
4.6.1 General Procedure for the Synthesis of Furocoumarin Derivatives (3aa-3ec):

A heterogenous mixture of substituted 4-hydroxycoumarin (**1a-e**, 0.25 mmol) and (*E*)-3-aryl-2-nitroprop-2-enol (**2a-j**, 0.3 mmol) in water (0.6 mL) was heated at 70 ºC for 5-10h (monitored by TLC). After completion of the reaction, water was decanted or removed by rotary evaporator under reduced pressure to give the gummy residue which was purified by column chromatography over silica gel (eluent: EtOAc/hexane = 1:9 to 1:4) to furnish the pure product **3aa-3ec**. All the products were characterized by their spectroscopic data (IR, ^{1}H and ^{13}C NMR, HRMS).

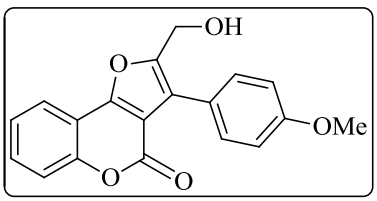
2-(Hydroxymethyl)-3-phenyl-4*H*-furo[3,2-*c*]chromen-4-one (3aa): 83% yield; **IR** (KBr) ν 3509, 3048, 2924, 2853, 1743, 1631, 1558, 1502, 1452, 1426, 1373, 1324, 1277 cm^{-1}; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.97-7.99 (m, 1H), 7.64-7.68 (m, 1H), 7.55-7.60 (m, 3H), 7.47-7.50 (m, 2H), 7.40-7.46 (m, 2H), 5.68 (br s, 1H), 4.53 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.6, 157.4, 152.7, 152.4, 131.0, 129.9, 128.9, 128.4, 128.4, 124.4, 123.9, 121.0, 117.2, 112.6, 109.4, 55.6; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{12}O_4$ $[M+Na]^+$: 315.0628, found: 315.0623.



2-(Hydroxymethyl)-3-(4-methylphenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3ab): 84% yield; **IR** (KBr) ν 3417, 2924, 2855, 1750, 1630, 1556, 1516, 1497, 1452, 1428, 1372, 1321, 1277, 1217 cm^{-1}; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.97-7.99 (m, 1H), 7.63-7.67 (m, 1H), 7.54-7.56 (m, 1H), 7.45-7.49 (m, 3H), 7.27-7.29 (m, 2H), 5.65 (t, J_1 = 5.76 Hz, J_2 = 11.04 Hz, 1H), 4.52 (d, J = 5.52 Hz, 2H), 2.36 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.6, 157.4, 152.7, 152.2, 138.4, 130.9, 129.8, 129.1, 125.9, 124.4, 123.9, 121.0, 117.2, 112.6, 109.4, 55.7, 21.3; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{14}O_4$ $[M+Na]^+$: 329.0784, found: 329.0785.

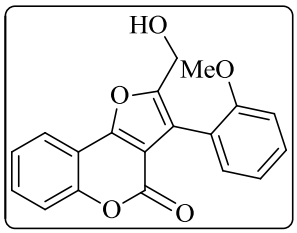


2-(Hydroxymethyl)-3-(4-methoxyphenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3ac): 88% yield; **IR** (KBr) ν 3465, 3069, 2935, 2837, 1746, 1649, 1628, 1599, 1570, 1516, 1452, 1429, 1408, 1373, 1349, 1309, 1292, 1276 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89-7.91 (m, 1H), 7.49-7.53 (m, 2H), 7.41-7.43 (m, 1H), 7.32-7.37 (m, 2H), 6.97-7.60 (m, 2H), 4.76 (s, 2H), 3.84 (s, 3H), 2.03 (br s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.8, 157.8, 157.4, 152.8, 152.0, 131.2, 131.0, 124.5, 123.7, 121.2, 121.0, 117.2, 113.9, 112.7, 109.5,

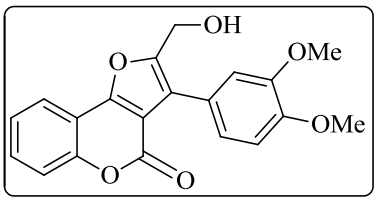


55.7, 55.3; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{14}O_5$ $[M+Na]^+$: 345.0733, found: 345.0732.

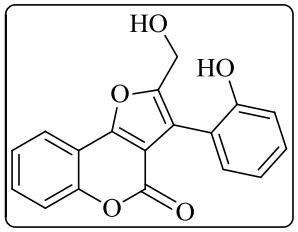
2-(Hydroxymethyl)-3-(2-methoxyphenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3ad): 87% yield; **IR** (KBr) ν 3432, 2956, 2922, 2852, 1721, 1630, 1597, 1559, 1493, 1463, 1436, 1374, 1320, 1276, 1247, 1214 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92-7.95 (m, 1H), 7.50-7.54 (m, 1H), 7.41-7.44 (m, 2H), 7.30-7.40 (m, 3H), 7.02-7.10 (m, 2H), 4.63 (s, 2H), 3.83 (s, 3H), 2.16 (br s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.4, 157.3, 156.9, 153.1, 152.7, 132.2, 130.7, 130.2, 124.4, 121.0, 120.9, 118.9, 118.0, 117.2, 112.8, 111.5, 110.4, 56.2, 55.9; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{14}O_5$ $[M+Na]^+$: 345.0733, found: 345.0738.



2-(Hydroxymethyl)-3-(3,4-dimethoxyphenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3ae): 82% yield; **IR** (KBr) ν 3493, 2944, 2916, 2834, 1760, 1629, 1587, 1556, 1518, 1470, 1451, 1423, 1413, 1379, 1359, 1322, 1272 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93-7.96 (m, 1H), 7.55-7.59 (m, 1H), 7.37-7.49 (m, 2H), 7.26-7.31 (m, 1H), 7.16-7.20 (m, 1H), 6.97-7.00 (m, 1H), 4.82 (s, 2H), 3.96 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.8, 157.3, 152.7, 152.1, 149.2, 148.6, 130.9, 124.4, 123.9, 122.3, 121.4, 121.0, 117.1, 113.5, 112.6, 110.9, 109.3, 55.9, 55.8, 55.7; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}O_6$ $[M+Na]^+$: 375.0839, found: 375.0859.

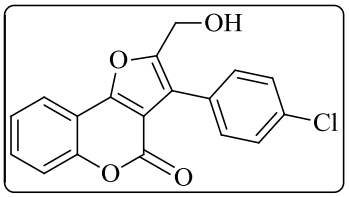


2-(Hydroxymethyl)-3-(2-hydroxyphenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3af): 63% yield; **IR** (KBr) ν 3423, 2924, 2854, 1720, 1628, 1600, 1560, 1503, 1450, 1424, 1377, 1321, 1288, 1237 cm^{-1}; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 9.55 (br s, 1H), 7.95-7.97 (m, 1H), 7.61-7.65 (m, 1H),

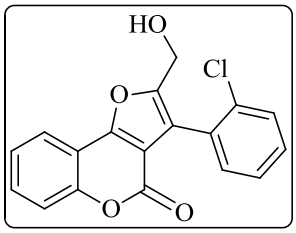


7.44-7.54 (m, 2H), 7.21-7.26 (m, 2H), 6.85-6.92 (m, 2H), 4.44 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.3, 157.9, 153.6, 153.4, 152.5, 132.2, 131.2, 130.5, 124.8, 121.6, 121.2, 119.1, 118.5, 117.6, 117.3, 112.6, 110.4, 55.8; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{12}O_5$ $[M+Na]^+$: 331.0577, found: 331.0578.

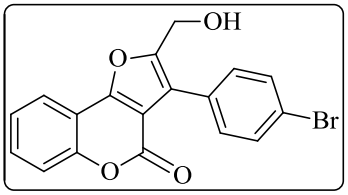
2-(Hydroxymethyl)-3-(4-chlorophenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3ag): 81% yield; **IR** (KBr) ν 3529, 3444, 2956, 2924, 2853, 1883, 1733, 1628, 1556, 1499, 1451, 1423, 1400, 1323, 1275, 1214 cm^{-1}; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.98-7.99 (m, 1H), 7.64-7.69 (m, 1H), 7.60-7.63 (m, 2H), 7.54-7.58 (m, 3H), 7.46-7.50 (m, 1H), 5.71 (t, *J*= 5.52 Hz, 1H), 4.53 (d, *J* = 5.52 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.6, 157.5, 152.8, 152.5, 134.7, 131.3, 131.2, 128.6, 127.4, 124.6, 122.9, 121.1, 117.3, 112.5, 109.2, 55.6; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{11}ClO_4$ $[M+Na]^+$: 349.0238, found: 349.0241.



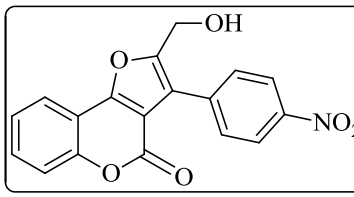
2-(Hydroxymethyl)-3-(2-chlorophenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3ah): 85% Yield; **IR** (KBr) ν 3444, 2957, 2924, 2853, 1720, 1630, 1514, 1502, 1452, 1422, 1379, 1320, 1258, 1213 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95-7.97 (m, 1H), 7.52-7.57 (m, 2H), 7.35-7.46 (m, 5H), 4.59-4.74 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.4, 157.2, 153.2, 152.9, 134.2, 132.2, 131.1, 130.2, 129.8, 128.4, 126.8, 124.5, 121.1, 120.2, 117.3, 112.7, 110.4, 55.8; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{11}ClO_4$ $[M+Na]^+$: 349.0238, Found: 349.0239.



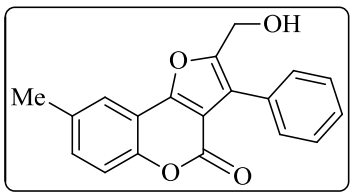
2-(Hydroxymethyl)-3-(4-bromophenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3ai): 79% yield; **IR** (KBr) ν 3433, 2924, 2854, 1733, 1629, 1597, 1559, 1501, 1450, 1425, 1394, 1366, 1321, 1276, 1261, 1234 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.91-7.93 (m, 1H), 7.58-7.60 (m, 2H), 7.52-7.55 (m, 1H), 7.43-7.48 (m, 3H), 7.34-7.38 (m, 1H), 6.99 (br s, 1H), 4.75 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.6, 152.7, 152.4, 135.9, 131.6, 131.5, 131.2, 127.9, 124.8, 124.6, 122.9, 121.1, 117.3, 112.4, 109.1, 55.5; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{11}BrO_4$ $[M+Na]^+$: 392.9733, found: 392.9732.



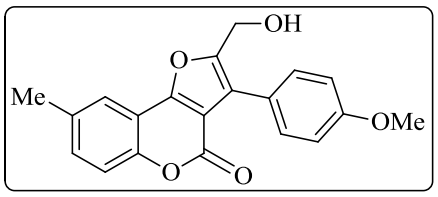
2-(Hydroxymethyl)-3-(4-nitrophenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3aj): 83% yield; **IR** (KBr) ν 3502, 3102, 2917, 1738, 1630, 1596, 1508, 1449, 1425, 1396, 1344, 1214 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.33-8.35 (m, 2H), 7.94-7.96 (m, 1H), 7.80-7.82 (m, 2H), 7.56-7.61 (m, 1H), 7.47-7.49 (m, 1H), 7.38-7.42 (m, 1H), 4.79 (s, 2H); **^{13}C NMR (100 MHz, DMSO-D_6)** δ 156.7, 155.3, 153.0, 152.1, 147.0, 136.2, 131.6, 131.2, 125.1, 123.2, 120.9, 119.9, 117.0, 111.8, 108.7, 53.8; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{11}NO_6$ $[M+H]^+$: 388.0659, found: 388.0659.



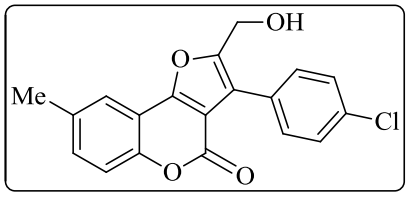
2-(Hydroxymethyl)-8-methyl-3-phenyl-4*H*-furo[3,2-*c*]chromen-4-one (3ba): 86% yield; **IR** (KBr) ν 3430, 2924, 2854, 2362, 2342, 1719, 1652, 1629, 1570, 1497, 1451, 1433, 1389, 1313, 1277 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69-7.72 (m, 1H), 7.56-7.58 (m, 2H), 7.41-7.48 (m, 3H), 7.32-7.33 (m, 2H), 4,76 (s, 2H), 2.45 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.8, 157.5, 152.2, 150.9, 134.3, 132.1, 129.9, 129.0, 128.4, 128.3, 123.8, 120.7, 116.9, 112.2, 109.2, 55.6, 20.9; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{14}O_4$ $[M+Na]^+$: 329.0784, found: 329.0780.



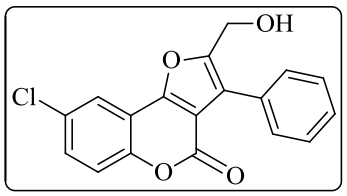
2-(Hydroxymethyl)-8-methyl-3-(4-methoxyphenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3bc): 88% yield; **IR** (KBr) ν 3439, 2945, 2918, 2837, 2360, 2339, 1828, 1707, 1656, 1616, 1593, 1566, 1515, 1458, 1435, 1413, 1359, 1316, 1293 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 (br s, 1H), 7.50-7.53 (m, 2H), 7.32-7.33 (m, 2H), 6.98-7.01 (m, 2H), 4.76 (s, 2H), 3.85 (s, 3H), 2.45 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.8, 159.7, 157.9, 157.4, 151.8, 150.9, 134.3, 132.0, 131.2, 123.7, 121.2, 120.7, 116.9, 113.9, 112.3, 55.7, 55.3, 20.9; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}O_5$ $[M+H]^+$: 337.1071, found: 337.1074.



2-(Hydroxymethyl)-8-methyl-3-(4-chlorophenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3bg): 81% yield; **IR** (KBr) ν 3561, 3428, 2956, 2925, 2854, 2360, 1729, 1632, 1571, 1505, 1493, 1463, 1431, 1407, 1362, 1314, 1276 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 (br s, 1H), 7.51-7.54 (m, 2H), 7.42-7.45 (m, 2H), 7.32-7.34 (m, 2H), 4.74 (s, 2H), 2.46 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.8, 157.6, 152.3, 150.9, 134.6, 134.4, 132.3, 131.3, 128.6, 127.5, 122.9, 120.8, 116.9, 112.1, 109.1, 55.6, 20.9; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{13}ClO_4$ $[M+H]^+$: 341.0575, found: 341.0608.

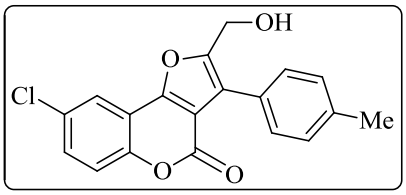


2-(Hydroxymethyl)-8-chloro-3-phenyl-4*H*-furo[3,2-*c*]chromen-4-one (3ca): 79% yield; **IR** (KBr) ν 3555, 3063, 2925, 2360, 2340, 1747, 1632, 1556, 1502, 1447, 1419, 1362, 1307, 1262, 1241 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.91-7.92 (m, 1H), 7.55-7.57 (m, 2H), 7.42-7.49 (m, 4H), 7.37-7.39 (m, 1H), 4.78 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.6, 156.8, 156.1, 153.0, 149.6, 138.1, 130.9, 130.0, 129.9, 128.6, 128.4, 121.3, 120.6, 118.7, 113.6, 55.6;



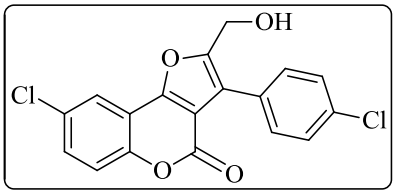
HRMS (ESI-TOF) m/z calculated for $C_{18}H_{11}ClO_4$ $[M+Na]^+$: 349.0238, found: 349.0234.

2-(Hydroxymethyl)-8-chloro-3-(4-methylphenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3cb): 80% yield; **IR** (KBr) ν 3432, 2922, 2855, 1755,



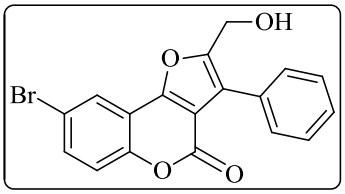
1630, 1555, 1514, 1492, 1420, 1355, 1309, 1258, 1214 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89-7.92 (m, 1H), 7.43-7.49 (m, 3H), 7.36-7.39 (m, 1H), 7.26-7.29 (m, 2H), 4.76 (s, 2H), 2.41 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.0, 156.0, 152.8, 150.9, 138.6, 130.9, 130.0, 129.9, 129.8, 129.2, 125.6, 124.0, 120.6, 118.7, 113.7, 55.6, 21.3; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{13}ClO_4$ $[M+Na]^+$: 363.0395, found: 363.0396.

2-(Hydroxymethyl)-8-chloro-3-(4-chlorophenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3cg): 77% yield; **IR** (KBr) ν 3429, 2924, 2853, 1750,



1629, 1555, 1494, 1465, 1421, 1355, 1369, 1259 cm^{-1}; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.96-7.97 (m, 1H), 7.66-7.68 (m, 1H), 7.57-7.61 (m, 3H), 7.53-7.56 (m, 2H), 5.70 (t, *J* = 5.52 Hz, 1H), 4.52 (d, *J* = 5.52 Hz, 2H); **^{13}C NMR (100 MHz, DMSO-d_6)** δ 156.3, 155.0, 150.6, 133.1, 131.7, 130.9, 128.9, 128.2, 128.2, 127.8, 120.7, 120.0, 118.9, 113.3, 109.5, 53.7; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{10}Cl_2O_4$[M+Na]$^+$: 382.9848, found: 382.9816.

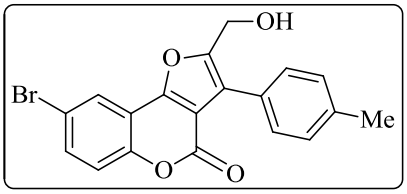
2-(Hydroxymethyl)-8-bromo-3-phenyl-4*H*-furo[3,2-*c*]chromen-4-one (3da): 79% yield; **IR** (KBr) ν 3560, 3443, 3062, 2853, 1747, 1630, 1584,



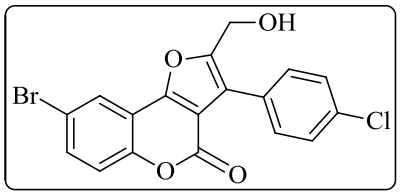
1552, 1499, 1446, 1417, 1359, 1305, 1263 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05-8.06 (m, 1H), 7.59-7.62 (m, 1H), 7.54-7.57 (m, 2H), 7.39-7.49 (m, 3H), 7.31-7.33 (m, 1H), 4.77 (s, 2H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.9, 155.9, 153.0,

151.5, 133.8, 129.9, 128.6, 128.4, 124.0, 123.6, 123.6, 118.9, 117.3, 114.1, 110.1, 55.6; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{11}BrO_4$ $[M+Na]^+$: 392.9733, found: 392.9704.

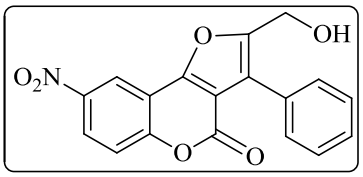
2-(Hydroxymethyl)-8-bromo-3-(4-methylphenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3db): 86% yield; **IR** (KBr) ν 3431, 2921, 2855, 2360, 2340, 1747, 1626, 1550, 1514, 1491, 1422, 1409, 1355, 1306, 1259 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05-8.06 (m, 1H), 7.60-7.62 (m, 1H), 7.43-7.45 (m, 2H), 7.30-7.33 (m, 1H), 7.27-7.29 (m, 2H), 4.76 (s, 2H), 2.40 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.9, 155.9, 152.8, 151.5, 138.6, 133.7, 132.9, 129.8, 129.2, 125.6, 124.0, 123.6, 118.9, 117.3, 114.2, 55.6, 21.3; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{13}BrO_4$ $[M+Na]^+$: 406.9889, found: 406.9839.



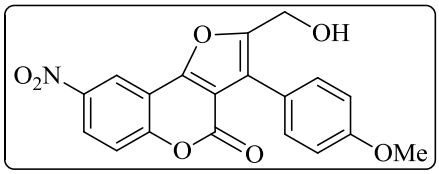
2-(Hydroxymethyl)-8-bromo-3-(4-chlorophenyl)-4*H*-furo[3,2-*c*]chromen-4-one (3dg); 78% yield; **IR** (KBr) ν 3439, 2923, 2853, 2360, 2339, 1747, 1627, 1567, 1551, 1492, 1463, 1420, 1353, 1306, 1261 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07-8.08 (m, 1H), 7.61-7.64 (m, 1H), 7.50-7.53 (m, 2H), 7.43-7.46 (m, 2H), 7.32-7.34 (m, 1H), 4.75 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.9, 153.1, 151.5, 139.3, 134.8, 133.9, 131.3, 129.8, 128.7, 125.9, 123.6, 119.0, 117.4, 113.9, 109.9, 55.5; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{10}ClO_4Br$ $[M+Na]^+$: 426.9343, found: 426.9319.



2-(Hydroxymethyl)-8-nitro-3-phenyl-4H-furo[3,2-*c*]chromen-4-one (3ea): 63% yield; **IR** (KBr) ν 3450, 1765, 1745, 1633, 1615, 1524, 1503, 1499, 1422, 1399, 1336, 1254 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.86-8.87 (m, 1H), 8.39-8.42 (m, 1H), 7.56-7.59 (m, 3H), 7.46-7.53 (m, 3H), 4.82 (br s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.0, 155.8, 155.7, 153.9, 144.1, 129.9, 128.9, 128.6, 128.3, 125.7, 124.2, 118.4, 117.4, 113.0, 110.8, 55.6; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{11}NO_6$ $[M+Na]^+$: 360.0479, found: 360.0544.



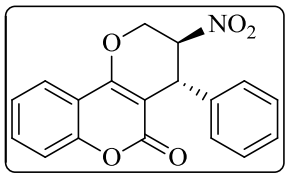
2-(Hydroxymethyl)-8-nitro-3-(4-methoxyphenyl)-4H-furo[3,2-*c*]chromen-4-one (3ec): 67% yield; **IR** (KBr) ν 3458, 3086, 2360, 1769, 1633, 1614, 1516, 1496, 1351, 1339, 1293, 1254 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.83-8.84 (m, 1H), 8.37-8.40 (m, 1H), 7.55- 7.58 (m, 1H), 7.49-7.52 (m, 2H), 7.00-7.03 (m, 2H), 4.80 (br s, 2H), 3.86 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 160.1, 156.1, 155.7, 155.5, 153.5, 144.1, 131.2, 125.5, 123.9, 120.4, 118.3, 117.3, 114.0, 113.0, 110.7, 55.5, 55.3; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{13}NO_7$ $[M+Na]^+$: 390.0584, found: 390.0588.



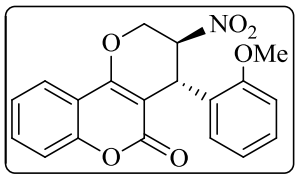
4.6.2 General procedure for the synthesis of dihydropyrano[3,2-*c*]chromene derivatives (4aa-4ec): To a stirred solution of 4-hydroxycoumarin (**1a**, 40.5 mg, 0.25 mmol) and (*E*)-3-aryl-2-nitroprop-2-enol (**2a-k**, 0.3 mmol) in DMSO (0.6 mL) was added L-proline (5.75 mg, 0.05 mmol) at 70 ºC for 4-6 h (monitored by TLC). After completion of the reaction, the mixture was extracted with ethyl acetate (3 × 10 mL), washed with water and dried with Na_2SO_4. The combined organic phase was concentrated under reduced pressure to afford the crude residue which was purified by column chromatography

over silica-gel (eluent: EtOAc/hexane = 1:19) to give the pure products **4aa-4ec**. The products were characterized by their corresponding spectroscopic data (IR, ^{1}H and ^{13}C NMR, HRMS). The diastereomeric ratio of the crude product was determined by ^{1}H NMR spectrum.

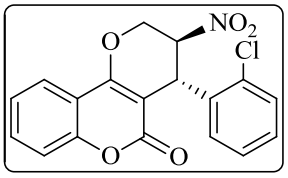
***Trans*-3-nitro-4-phenyl-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one** (**4aa**): 88% yield; **IR** (KBr) ν 3441, 2924, 1711, 1631, 1612, 1575, 1554, 1494, 1453, 1404, 1375, 1325, 1271 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.82-7.84 (m, 1H), 7.57-7.61 (m, 1H), 7.31-7.39 (m, 5H), 7.27-7.28 (m, 2H), 5.10 (dt, J_1 = 13.04 Hz, J_2 = 2.28 Hz, 1H), 5.01 (br s, 1H), 4.83-4.84 (m, 1H), 4.40 (dd, J_1 = 13.04 Hz, J_2 = 2.24 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.1, 159.7, 152.7, 138.9, 132.5, 129.4, 128.3, 127.9, 124.2, 122.8, 116.9, 114.4, 99.1, 82.2, 62.8, 38.2; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{13}NO_5$ $[M+Na]^+$: 346.0686, found: 346.0687.



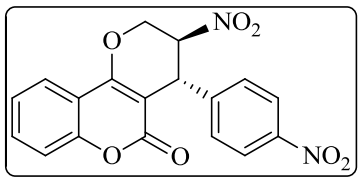
***Trans*-3-nitro-4-(2-methoxyphenyl)-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one** (**4ad**)**:** 90% yield; **IR** (KBr) ν 3446, 2923, 2852, 1710, 1628, 1577, 1550, 1491, 1460, 1437, 1407, 1377, 1357, 1315, 1286, 1271 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79-7.82 (m, 1H), 7.56-7.60 (m, 1H), 7.34-7.37 (m, 1H), 7.27-7.32 (m, 2H), 6.86-6.96 (m, 3H), 5.28 (br s, 1H), 5.05 (dd, J_1 = 12.56 Hz, J_2 = 2.28 Hz, 1H), 4.96 (m, 1H), 4.28-4.31 (m, 1H), 3.93 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.2, 160.2, 156.4, 152.7, 132.4, 129.5, 128.6, 126.3, 124.1, 122.7, 120.9, 116.8, 110.8, 99.2, 79.9, 63.6, 55.6, 32.9; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{15}NO_6$ $[M+H]^+$: 354.0972, found: 354.0975.



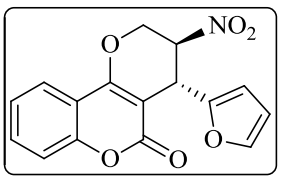
***Trans*-3-nitro-4-(2-chlorophenyl)-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one** (**4ah**): 85% yield; **IR** (KBr) ν 3434, 2924, 2853, 1710, 1627, 1611, 1573, 1552, 1493, 1456, 1439, 1405, 1373, 1358, 1314, 1275 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82-7.84 (m, 1H), 7.59-7.63 (m, 1H), 7.49-7.51 (m, 1H), 7.28-7.39 (m, 2H), 7.22-7.26 (m, 1H), 7.05-7.07 (m, 1H), 5.37 (br s, 1H), 5.12 (dd, J_1 = 12.8 Hz, J_2 = 2.28 Hz, 1H), 4.95 (m, 1H), 4.29-4.33 (m, 1H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 160.9, 160.4, 152.7, 135.8, 133.8, 132.7, 130.7, 129.7, 129.3, 127.6, 124.3, 122.8, 116.9, 114.3, 98.7, 79.8, 63.2, 35.8; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{12}ClNO_5$ $[M+Na]^+$: 380.0296, found: 380.0296.



***Trans*-3-nitro-4-(4-nitrophenyl)-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one** (**4aj**): 87% yield; **IR** (KBr) ν 3439, 2925, 2853, 2360, 1710, 1629, 1576, 1553, 1518, 1494, 1454, 1411, 1376, 1350, 1321, 1273 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23-8.27 (m, 2H), 7.84-7.87 (m, 1H), 7.61-7.66 (m, 1H), 7.49-7.52 (m, 2H), 7.35-7.39 (m, 2H), 5.12-5.20 (m, 2H), 4.85-4.87 (m, 1H), 4.36-4.40 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.0, 160.4, 152.8, 147.8, 146.0, 133.1, 129.0, 124.6, 124.5, 123.0, 117.0, 114.1, 98.3, 81.6, 62.8, 38.3; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{12}N_2O_7$ $[M+H]^+$: 369.0717, found: 369.0726.

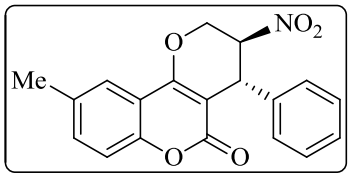


***Trans*-3-nitro-4-(2-furyl)-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one** (**4ak**): 85% yield; **IR** (KBr) ν 3433, 2924, 2853, 1718, 1631, 1556, 1495, 1456, 1410, 1377, 1359, 1321, 1274 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79-7.81 (m, 1H), 7.55-7.60 (m, 1H), 7.29-7.38 (m, 3H), 6.26-6.35 (m, 2H), 5.20 (dd, J_1= 12.8 Hz, J_2 =3.2 Hz, 1H), 5.06-5.07 (m, 2H), 4.58-4.62 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ

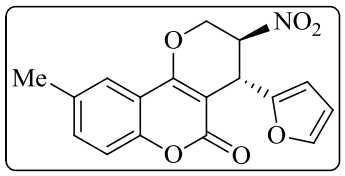


161.1, 159.5, 152.6, 150.5, 143.0, 132.7, 124.2, 122.9, 116.8, 114.5, 111.0, 109.4, 97.9, 79.0, 64.1, 32.3; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}NO_6$ $[M+H]^+$: 314.0659, found: 314.0603.

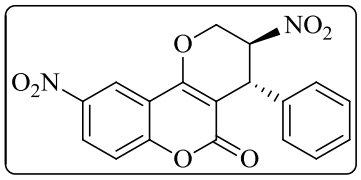
***Trans*-3-nitro-4-phenyl-9-methyl-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one** (**4ba**): 71% yield; **IR** (KBr) ν 3441, 2924, 2853, 2360, 1710, 1634, 1586, 1552, 1494, 1454, 1425, 1397, 1373, 1355, 1306, 1270 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.62-7.63 (m, 1H), 7.35-7.40 (m, 3H), 7.30-7.33 (m, 1H), 7.23-7.29 (m, 3H), 5.09 (dt, J_1 = 12.8 Hz, J_2 = 2.28 Hz, 1H), 5.00 (br s, 1H), 4.83 (q, J_1 = 2.04 Hz, J_2 = 4.28 Hz, 1H), 4.38 (dd, J_1 = 1.76 Hz, J_2 = 2.52 Hz, 1H), 2.43 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.3, 159.7, 150.9, 138.9, 134.0, 133.5, 129.4, 128.2, 127.9, 122.5, 116.6, 114.0, 98.9, 82.2, 62.7, 38.3, 20.9; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{15}NO_5$ $[M+Na]^+$: 360.0842, found: 360.0843.



***Trans*-3-nitro-4-(2-furyl)-9-methyl-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one** (**4bk**)**:** 90% yield; **IR** (KBr) ν 3434, 2924, 2853, 1714, 1635, 1586, 1554, 1498, 1455, 1427, 1401, 1374, 1357, 1307, 1277 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59-7.60 (m, 1H), 7.36-7.39 (m, 2H), 7.22- 7.25 (m, 1H), 6.25-6.35 (m, 2H), 5.19 (dd, J_1 = 12.8 Hz, J_2 = 2.28 Hz, 1H), 5.05-5.06 (m, 2H), 4.56 (dd, J_1 = 12.8 Hz, J_2 = 3.2 Hz, 1H), 2.42 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.3, 159.5, 150.8, 150.6, 142.9, 134.1, 133.7, 122.6, 116.6, 114.1, 111.0, 109.3, 97.7, 79.0, 64.0, 32.4, 20.9; **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{13}NO_6$ $[M+Na]^+$: 350.0635, found: 350.0642.



***Trans*-3,9-dinitro-4-phenyl-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one (4ea):** 92% yield; **IR** (KBr) ν 3464, 1742, 1556, 1527, 1488, 1455, 1401, 1343, 1308, 1258, 1212 cm^{-1};**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.76-8.77 (m, 1H), 8.44-8.47 (m, 1H), 7.48-7.51 (m, 1H), 7.34-7.43 (m, 4H), 7.27-7.28 (m, 1H), 5.20 (dd, J_1 = 12.8 Hz, J_2 = 3.6 Hz, 1H), 5.00- 5.01 (m, 1H), 4.89-4.90 (m, 1H), 4.46-4.50 (m, 1H);**^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.6, 158.4, 156.1, 144.1, 138.1, 129.7, 128.7, 127.8, 127.3, 119.5, 118.2, 114.9, 101.0, 81.9, 63.3, 38.3; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{12}N_2O_7$ $[M+Na]^+$: 391.0537, found: 391.0545.



***Trans*-3,9-dinitro-4-phenyl-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one (4ec):** 89% yield; **IR** (KBr) ν 3456, 2360, 1737, 1643, 1625, 1610, 1557, 1527, 1513, 1487, 1455, 1400, 1341, 1257 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.75-8.76 (m, 1H), 8.43-8.46 (m, 1H), 7.48-7.50 (m, 1H), 7.16-7.19 (m, 2H), 6.90-6.93 (m, 2H), 5.17 (dd, J_1 = 12.8 Hz, J_2 = 2.0 Hz, 1H), 4.85-4.94 (m, 2H), 4.46-4.50 (m, 1H), 3.80 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.7, 159.6, 158.2, 156.0, 144.1, 129.9, 128.9, 127.2, 119.5, 118.1, 115.0, 114.9, 101.3, 82.0, 63.3, 55.4, 37.6; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{14}N_2O_8$ $[M+Na]^+$: 421.0642, found: 421.0650.

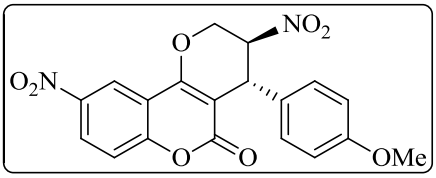


Table 4.4 Crystal data of compound **4ah.**

Compound	Compound **4ah**
Empirical formula	$C_{18}H_{12}ClNO_5$
Molecular weight	357.74
Temperature	150(2) K
Wavelength (Å)	0.7107A
Crystal system, space group	monoclinic, P 21/c
a (Å)	a = 14.7809(9)
b (Å)	b = 8.0602(3)
c (Å)	c = 14.9746(8)
α (^{o})	alpha = 90
β (^{o})	beta =116.158(7)
γ (^{o})	gamma = 90
Volume (Å^3)	1601.31(14)
Z, Calculated density (mg/m^3)	4, 1.484
Absorption coefficient (mm^{-1})	0.268
F(000)	736
Crystal size (mm)	0.15 x 0.11 x 0.05
θ range (deg)	2.95 to 25.00
Limiting indices	-17<=h<=17,-9<=k<=9,-17<=l<=16
Reflections collected / unique	12705 / 2809 [R(int) = 0.0511]
Completeness to θ = 25	99.9 %
Max. and min. transmission	0.9867 and 0.9608
Data / restraints / parameters	2809 / 0 / 226
Goodness-of-fit on F^2	1.072
Final R indices [I>2sigma(I)]	R1 = 0.0579, wR2 = 0.1461
R indices (all data)	R1 = 0.0664, wR2 = 0.1517
Largest diff. peak and hole (e.A$^{-3)}$	0.281 and -0.313
CCDC	1011395

4.7 Copies of ^{1}H and ^{13}C NMR spectra of final compounds

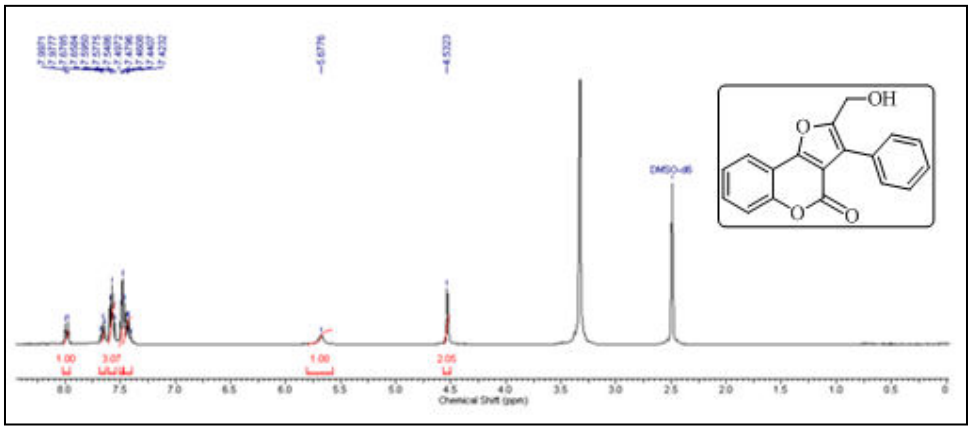


Figure 4.5 400 MHz ^{1}H NMR spectrum of **3aa** in DMSO-d_6

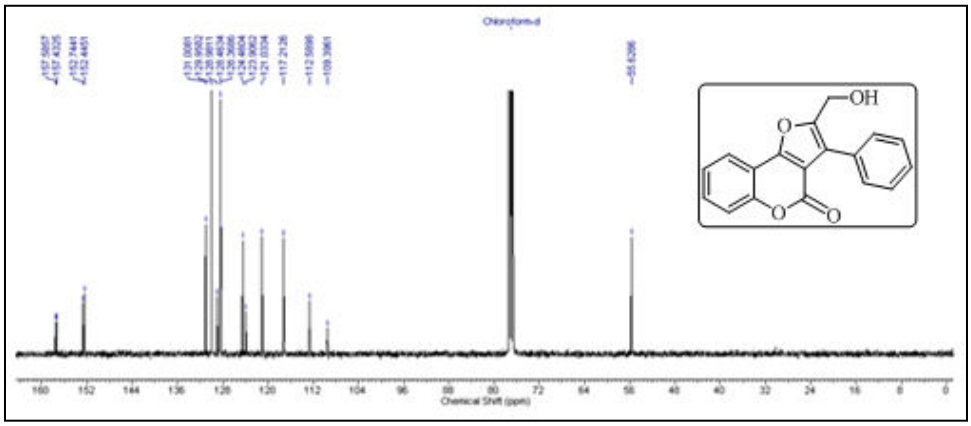


Figure 4.6 100 MHz ^{13}C NMR spectrum of **3aa** in $CDCl_3$

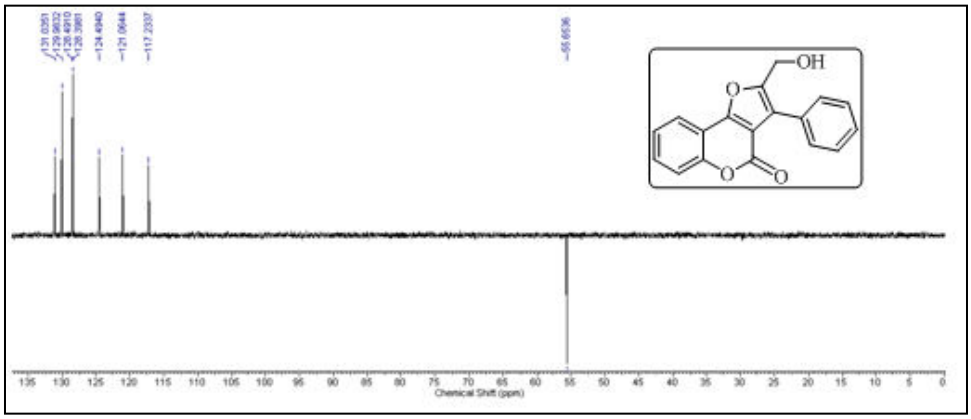


Figure 4.7 135° DEPT NMR spectrum of **3aa** in $CDCl_3$

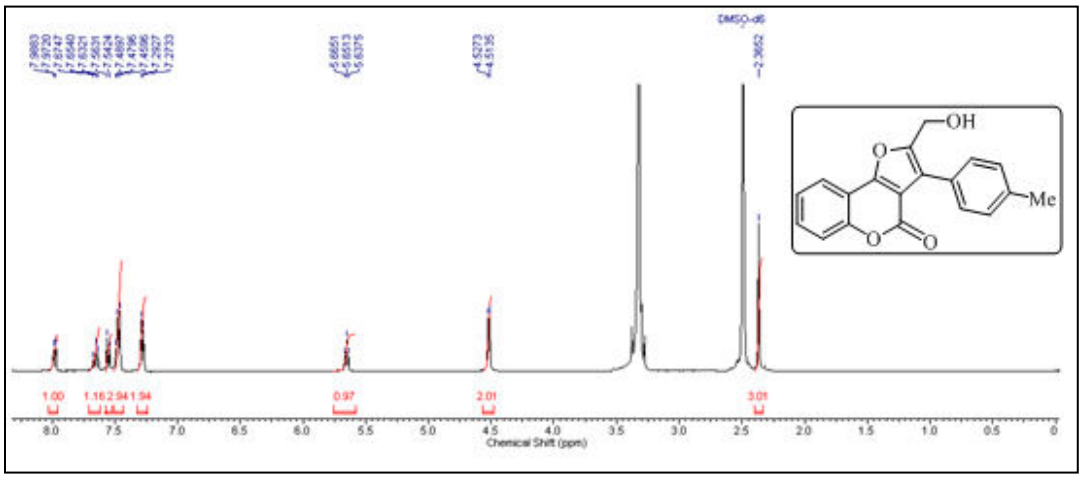


Figure 4.8 400 MHz ^{1}H NMR spectrum of **3ab** in DMSO-d_6

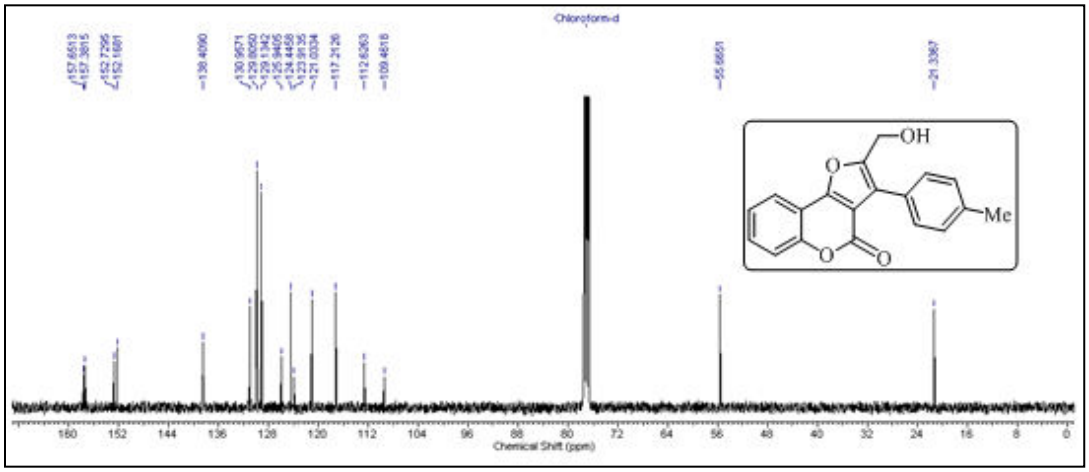


Figure 4.9 100 MHz ^{13}C NMR spectrum of **3ab** in $CDCl_3$

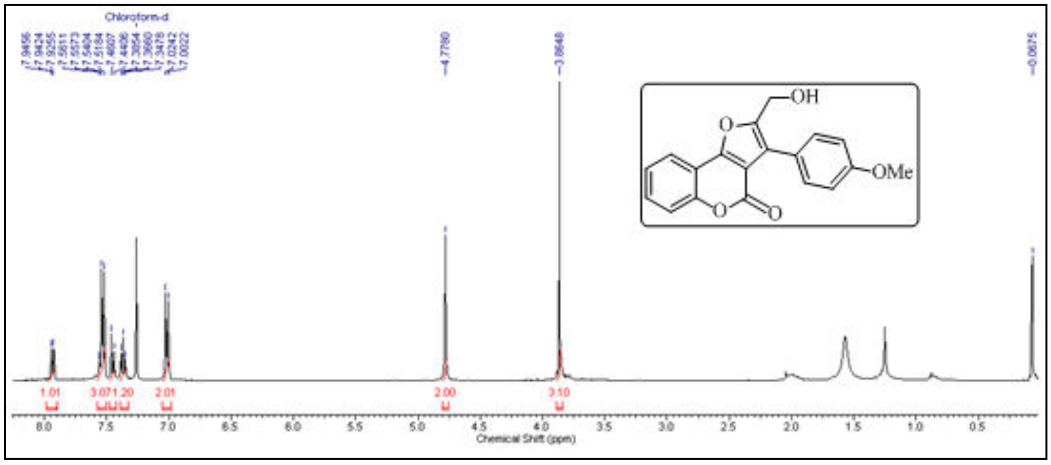


Figure 4.10 400 MHz ^{1}H NMR spectrum of **3ac** in $CDCl_3$

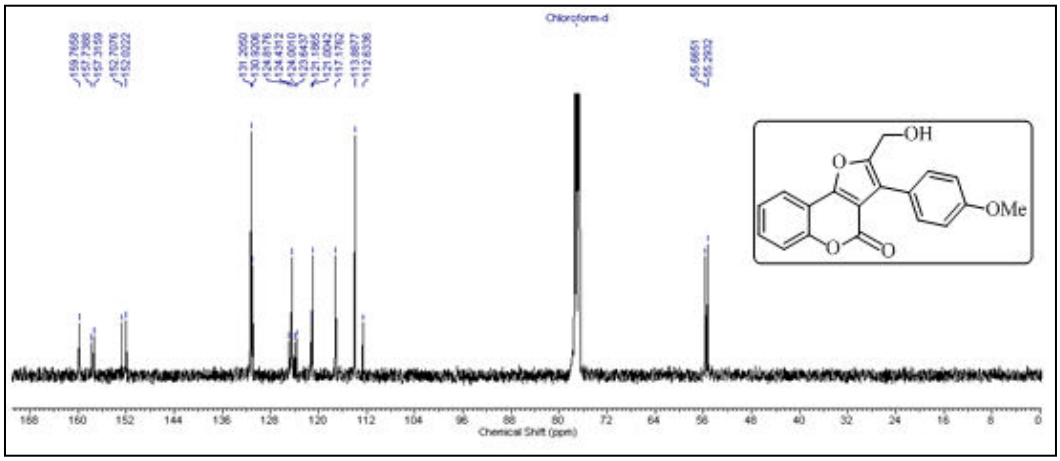


Figure 4.11 100 MHz ^{13}C NMR spectrum of **3ac** in $CDCl_3$

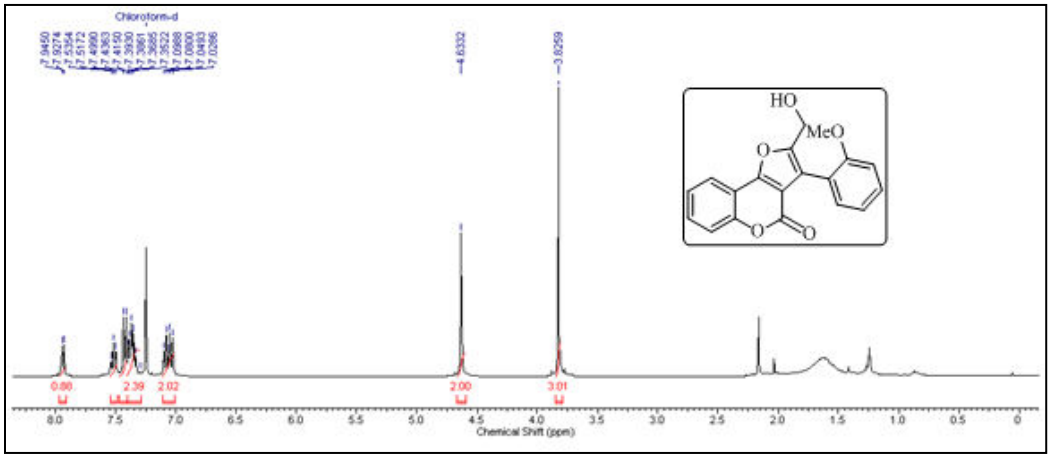


Figure 4.12 400 MHz ^{1}H NMR spectrum of **3ad** in $CDCl_3$

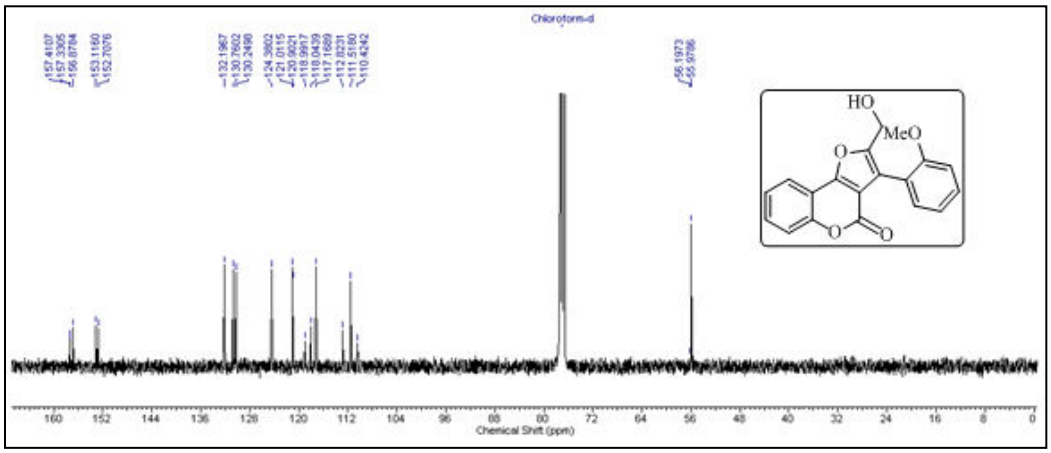


Figure 4.13 100 MHz ^{13}C NMR spectrum of **3ad** in $CDCl_3$

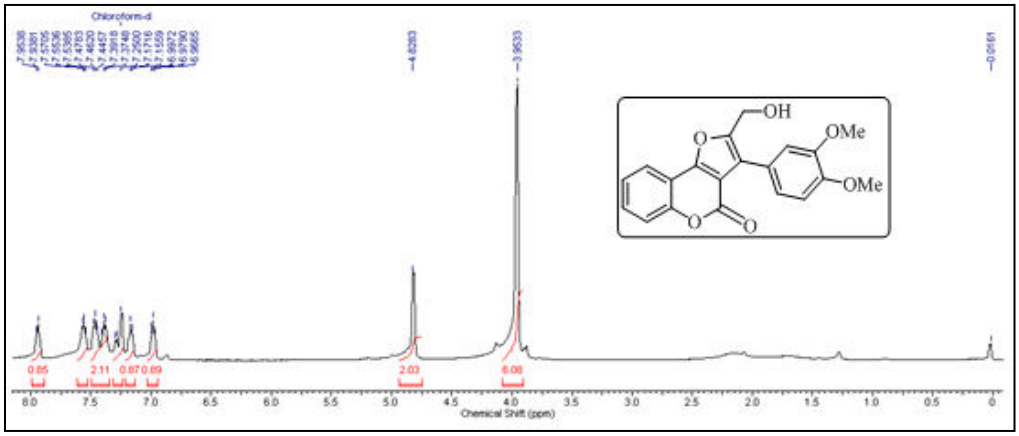


Figure 4.14 400 MHz ^{1}H NMR spectrum of **3ae** in $CDCl_3$

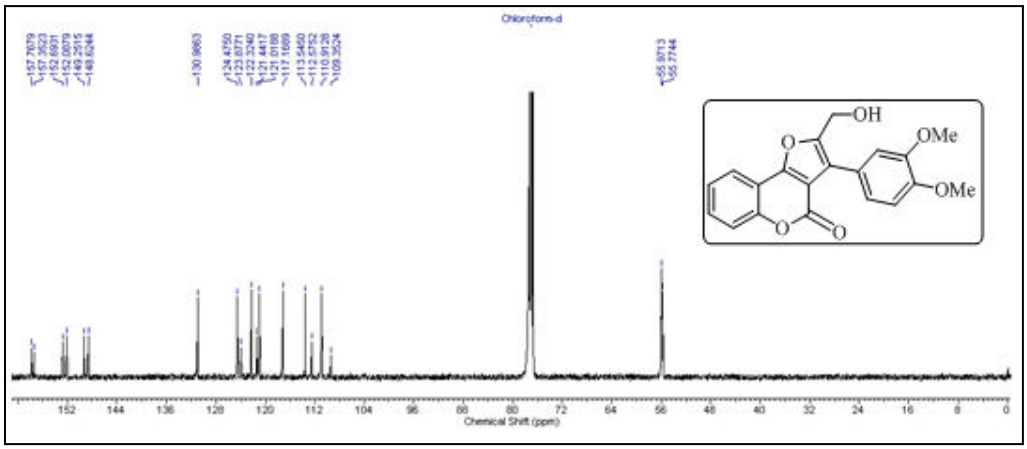


Figure 4.15 100 MHz ^{13}C NMR spectrum of **3ae** in $CDCl_3$

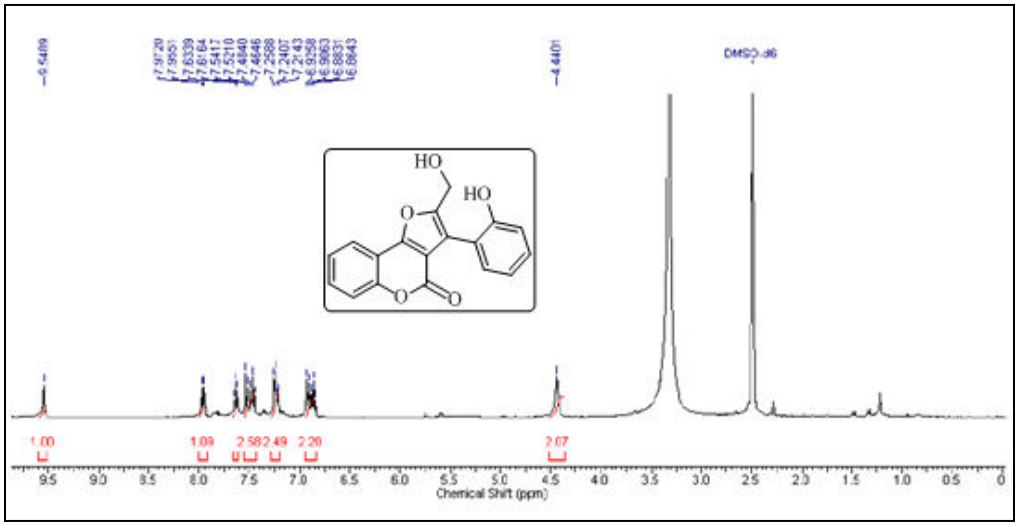


Figure 4.16 400 MHz ^{1}H NMR spectrum of **3af** in DMSO-d_6

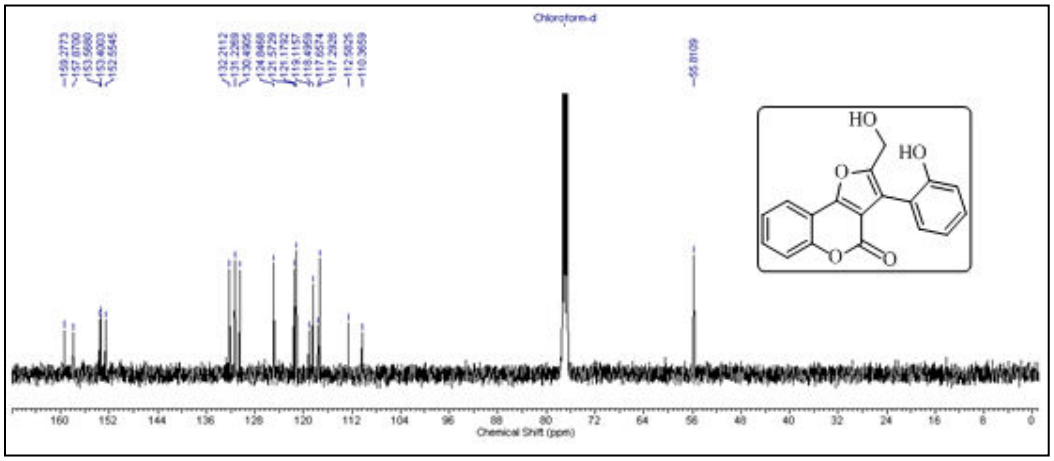


Figure 4.17 100 MHz ^{13}C NMR spectrum of **3af** in $CDCl_3$

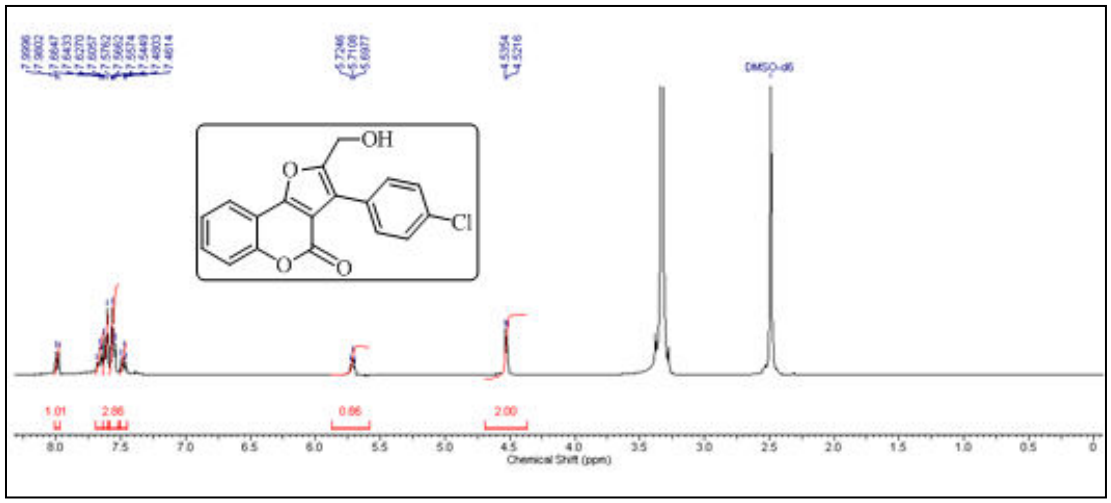


Figure 4.18 400 MHz ^{1}H NMR spectrum of **3ag** in DMSO-d_6

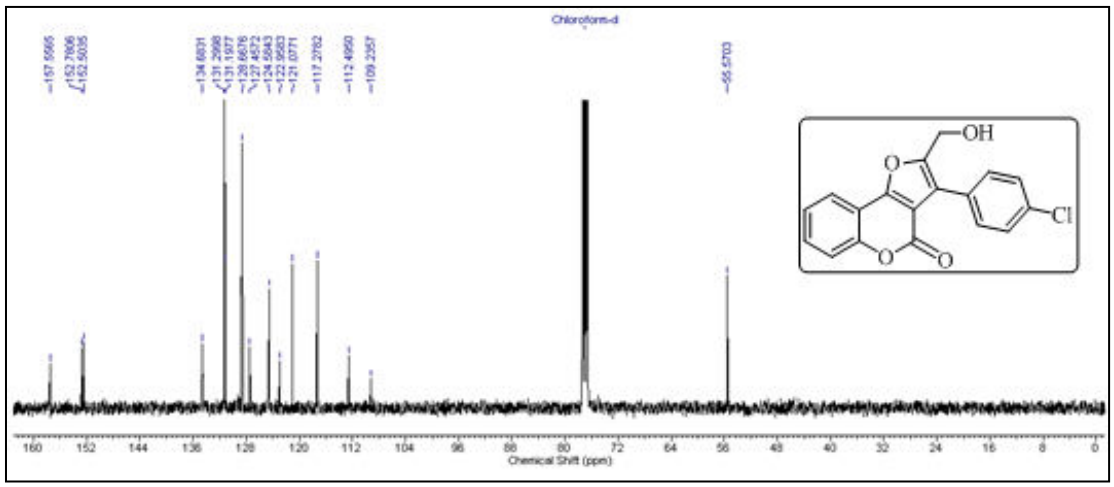


Figure 4.19 100 MHz ^{13}C NMR spectrum of **3ag** in $CDCl_3$

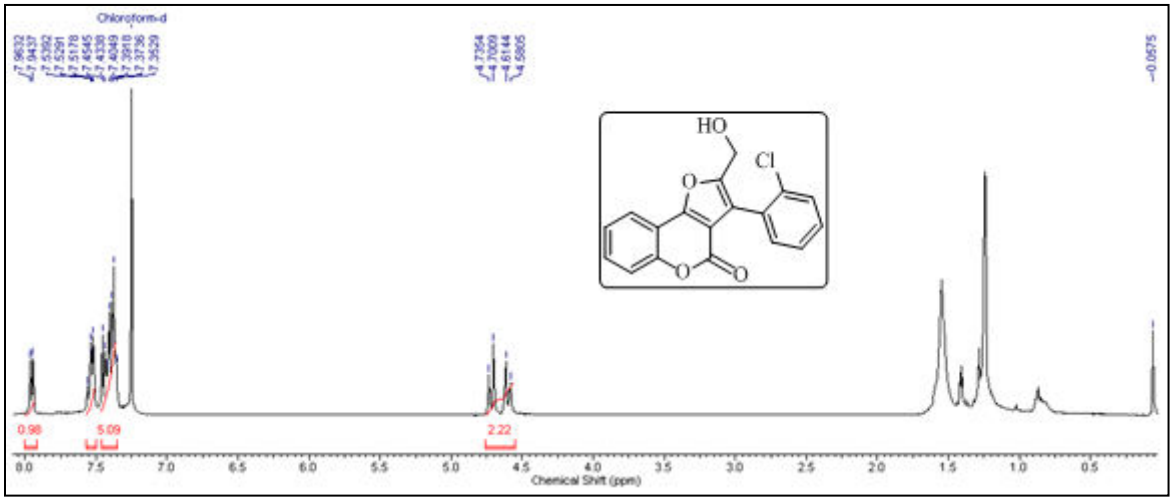


Figure 4.20 400 MHz ^{1}H NMR spectrum of **3ah** in $CDCl_3$

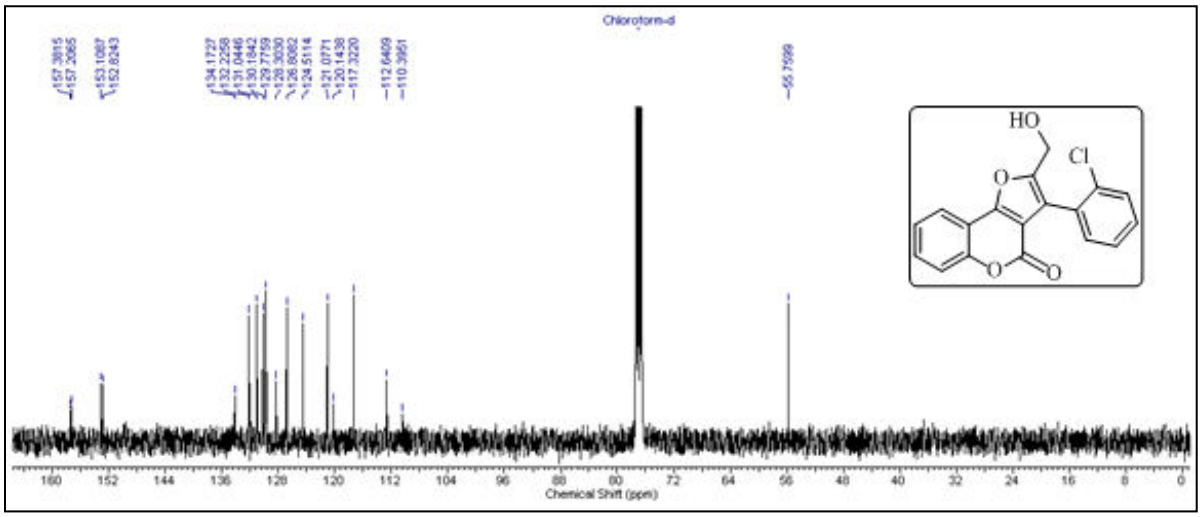


Figure 4.21 100 MHz ^{13}C NMR spectrum of **3ah** in $CDCl_3$

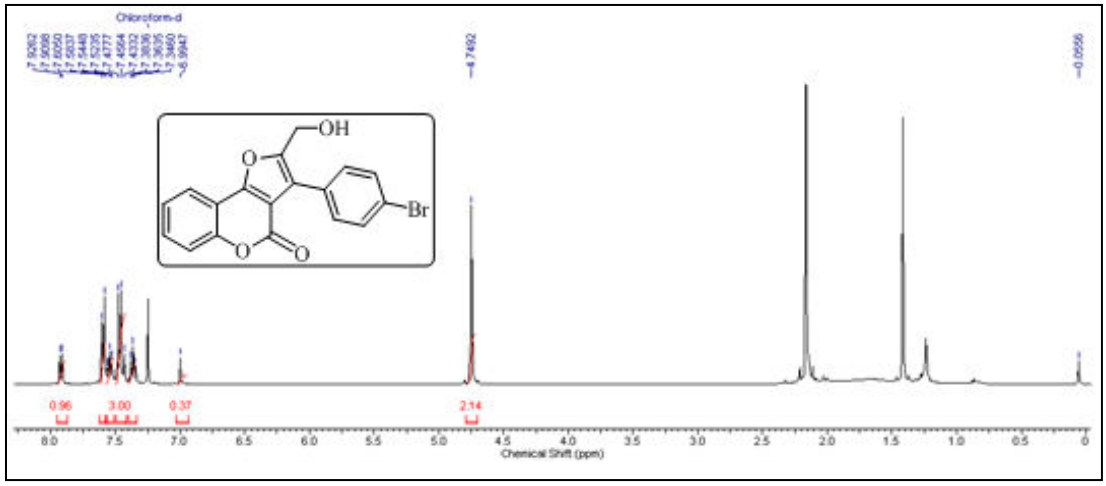


Figure 4.22 400 MHz ^{1}H NMR spectrum of **3ai** in $CDCl_3$

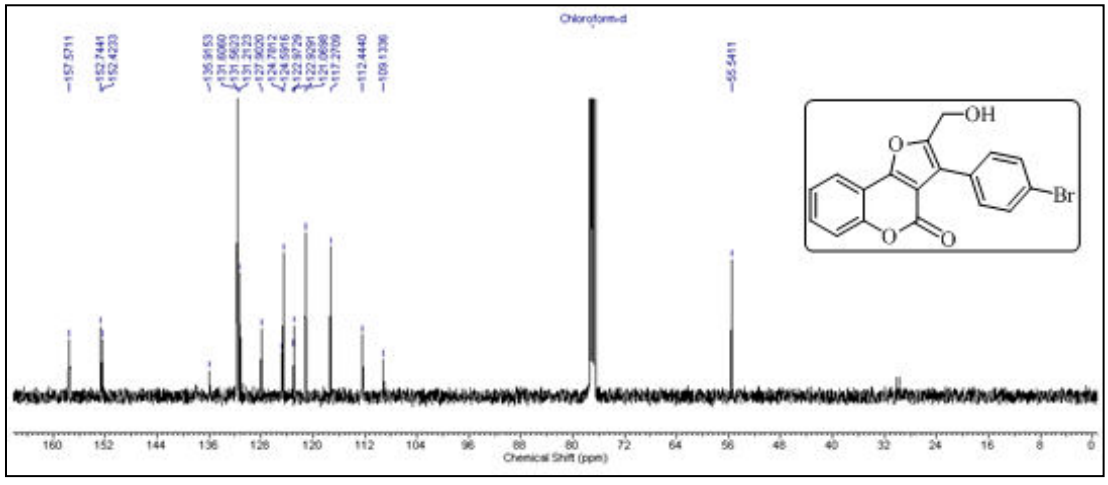


Figure 4.23 100 MHz ^{13}C NMR spectrum of **3ai** in $CDCl_3$

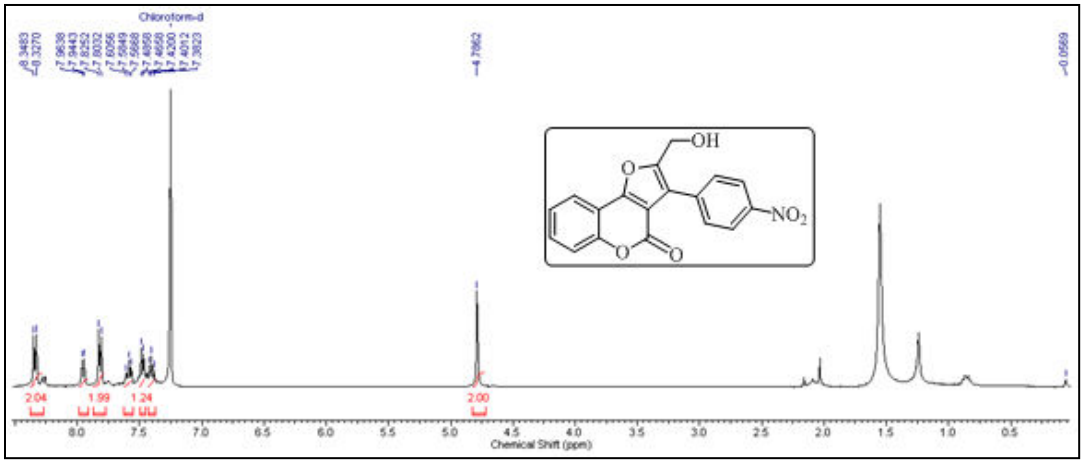


Figure 4.24 400 MHz ^{1}H NMR spectrum of **3aj** in $CDCl_3$

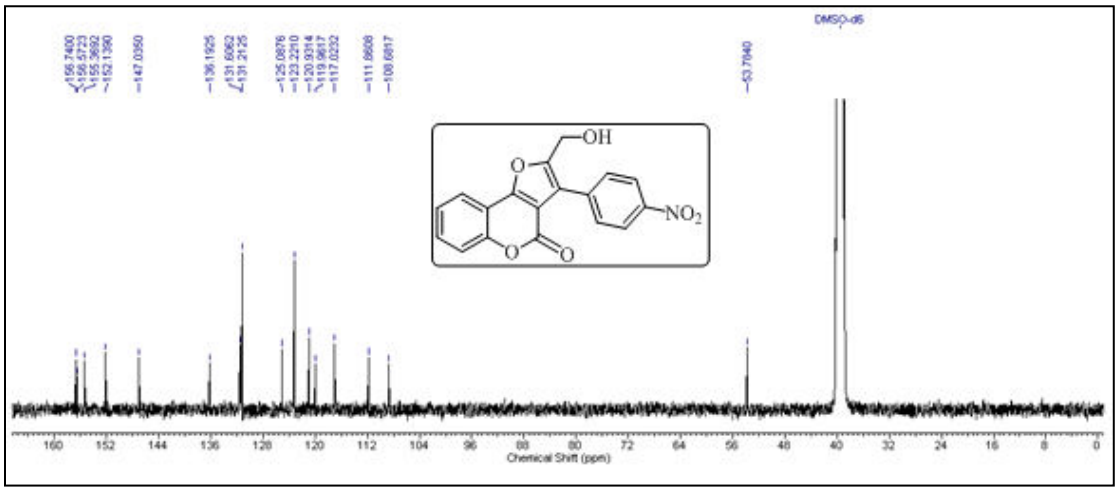


Figure 4.25 100 MHz ^{13}C NMR spectrum of **3aj** in DMSO-d_6

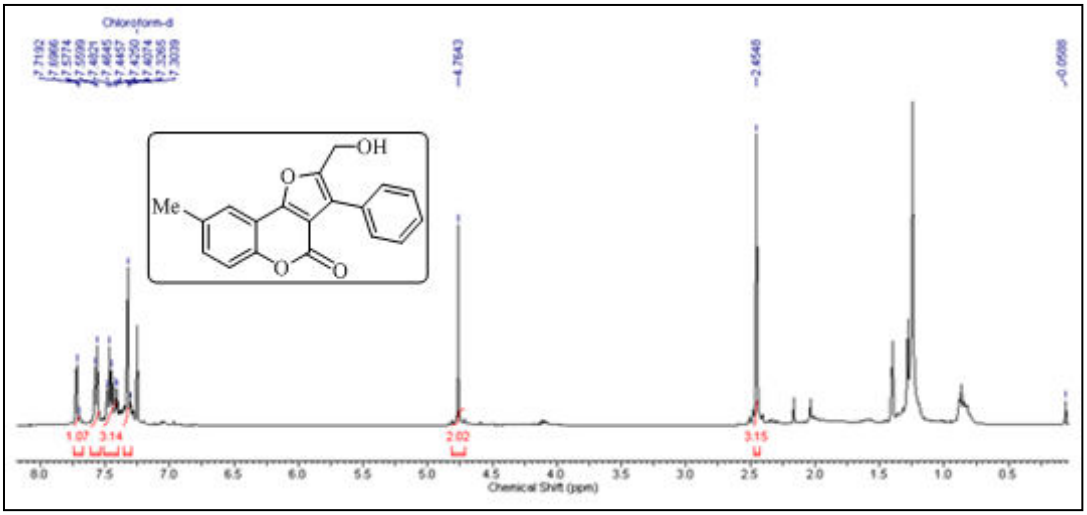


Figure 4.26 400 MHz ^{1}H NMR spectrum of **3ba** in $CDCl_3$

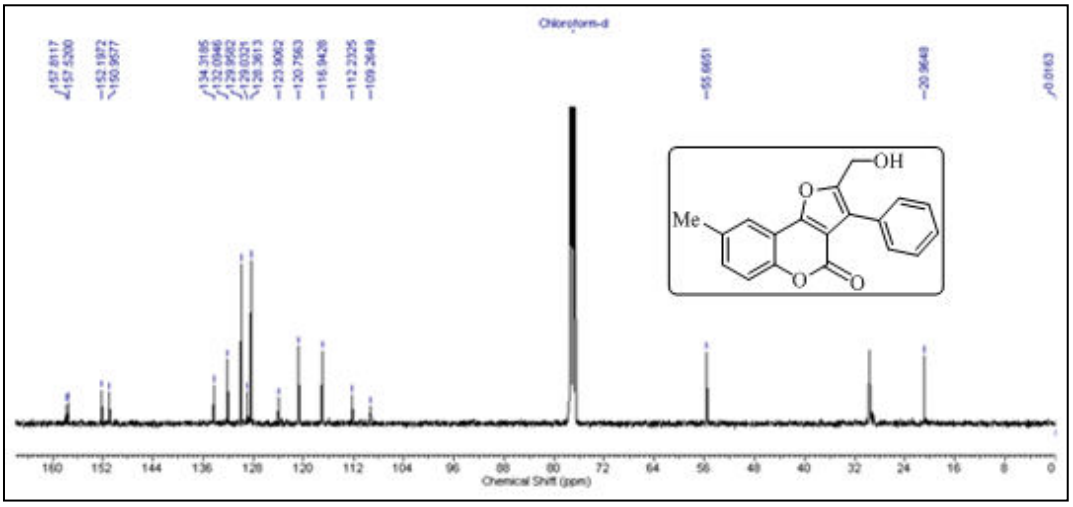


Figure 4.27 100 MHz ^{13}C NMR spectrum of **3ba** in $CDCl_3$

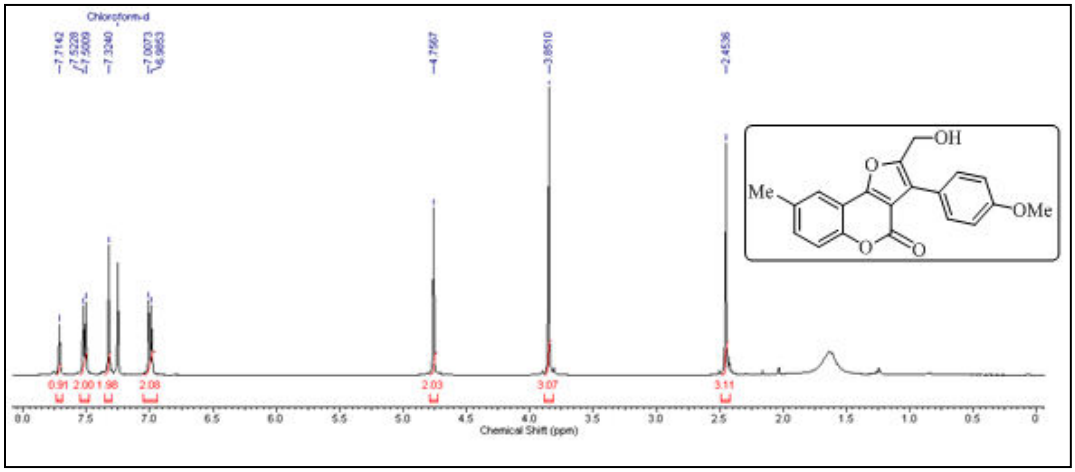


Figure 4.28 400 MHz ^{1}H NMR spectrum of **3bc** in $CDCl_3$

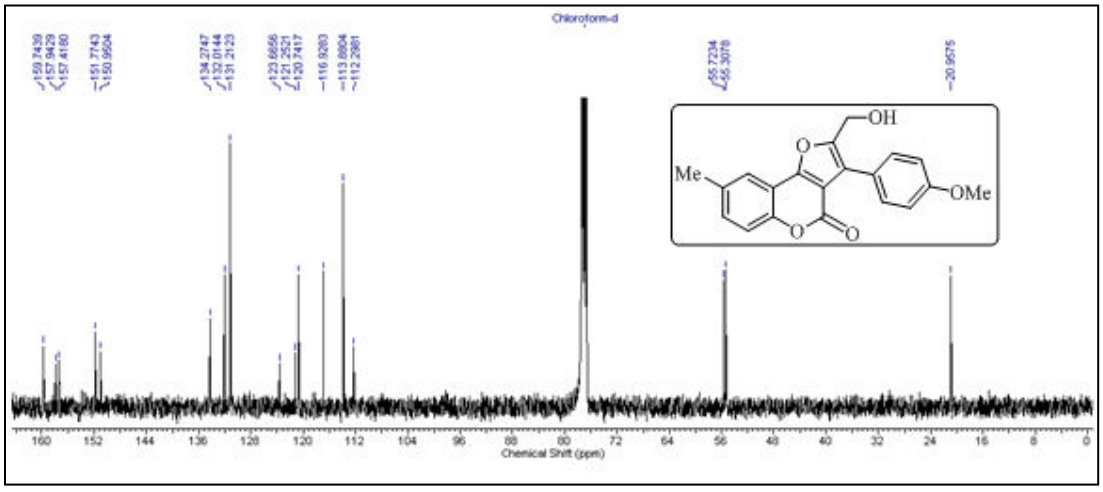


Figure 4.29 100 MHz ^{13}C NMR spectrum of **3bc** in $CDCl_3$

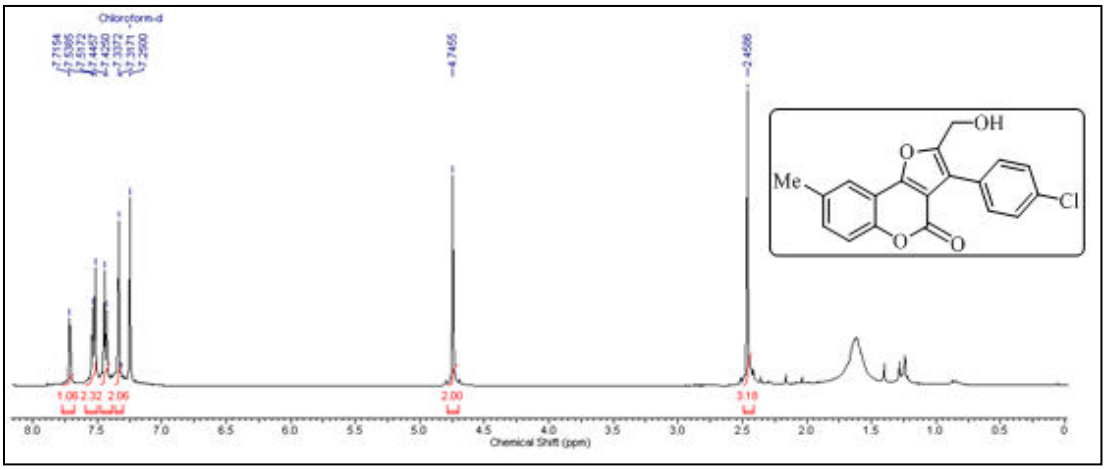


Figure 4.30 400 MHz ^{1}H NMR spectrum of **3bg** in $CDCl_3$

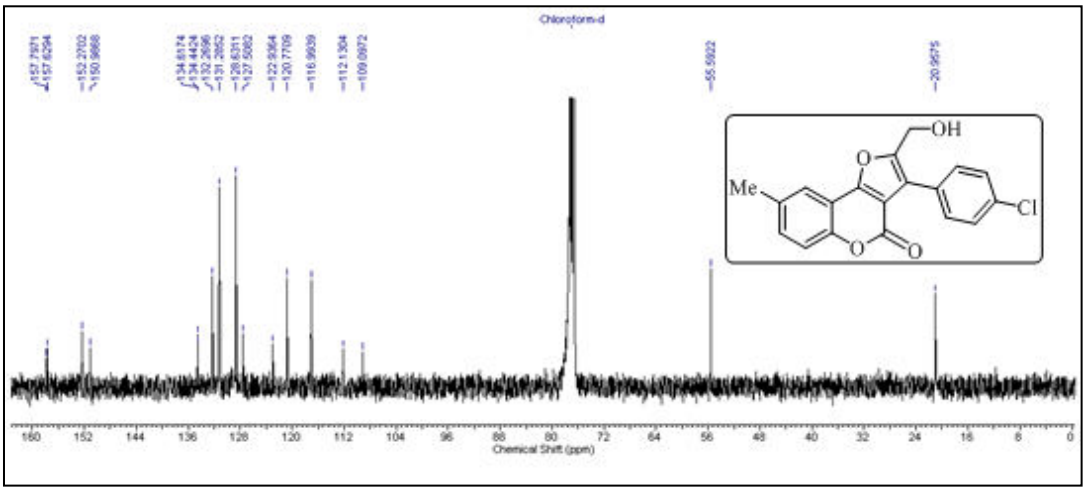


Figure 4.31 100 MHz ^{13}C NMR spectrum of **3bg** in $CDCl_3$

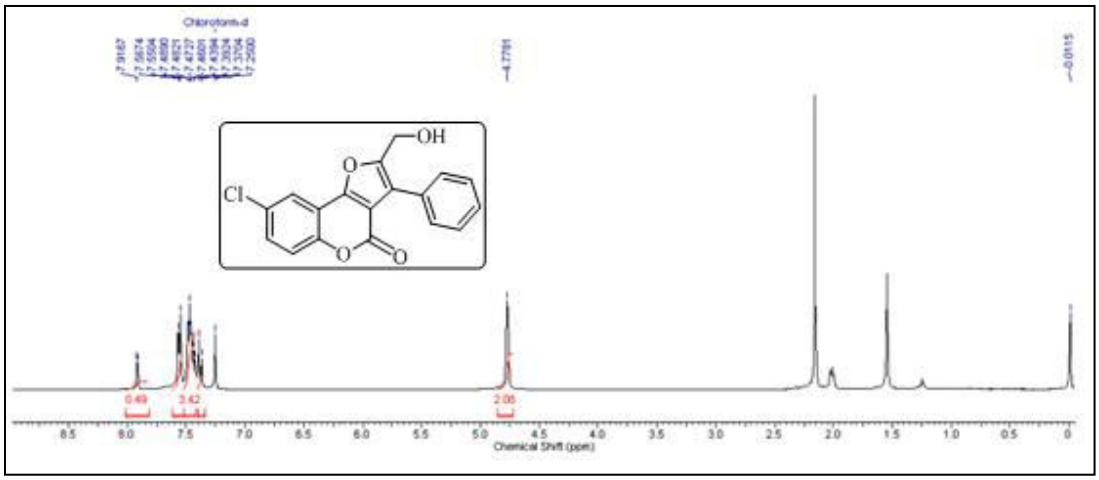


Figure 4.32 400 MHz ^{1}H NMR spectrum of **3ca** in $CDCl_3$

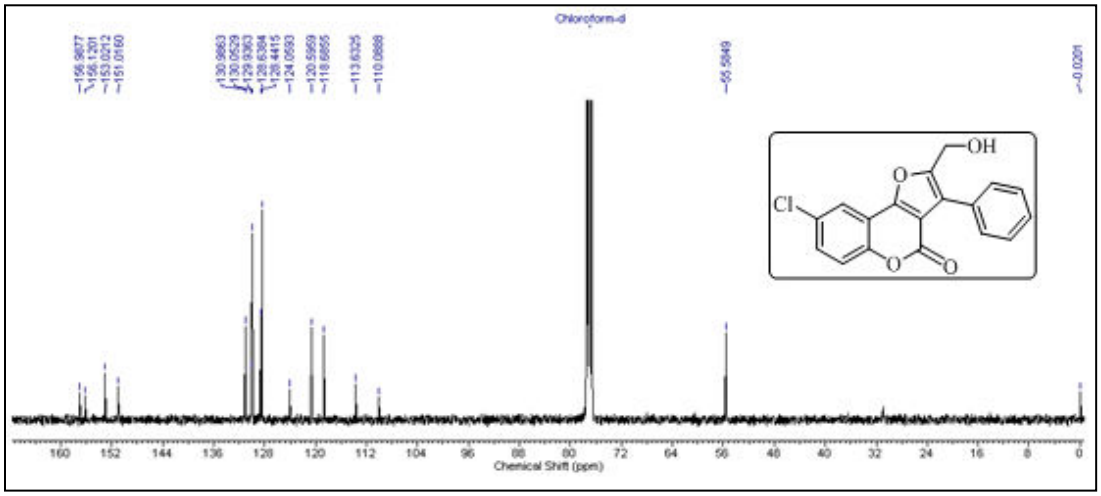


Figure 4.33 100 MHz ^{13}C NMR spectrum of **3ca** in $CDCl_3$

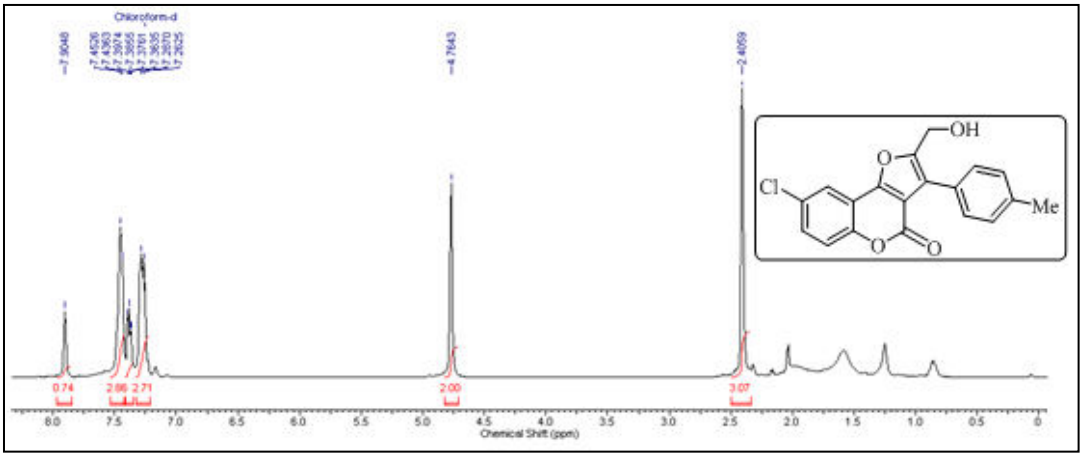


Figure 4.34 400 MHz ^{1}H NMR spectrum of **3cb** in $CDCl_3$

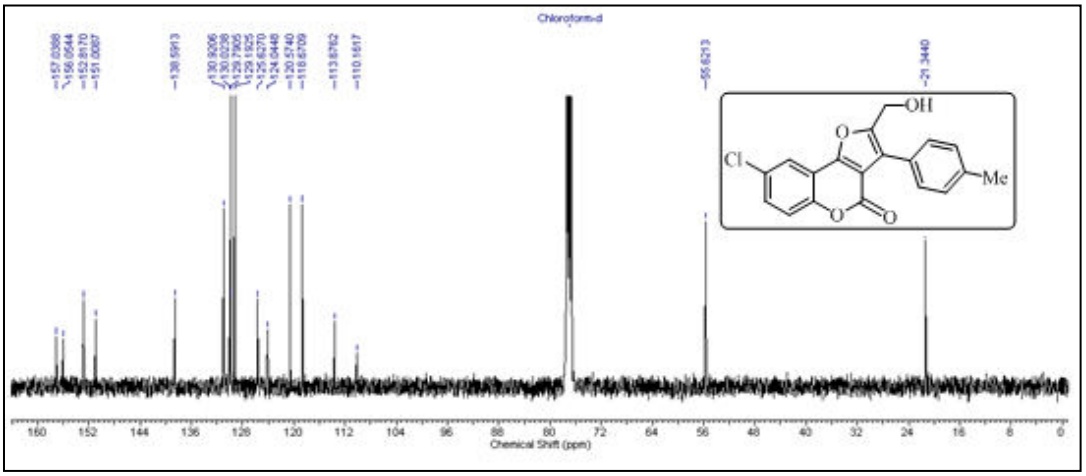


Figure 4.35 100 MHz ^{13}C NMR spectrum of **3cb** in $CDCl_3$

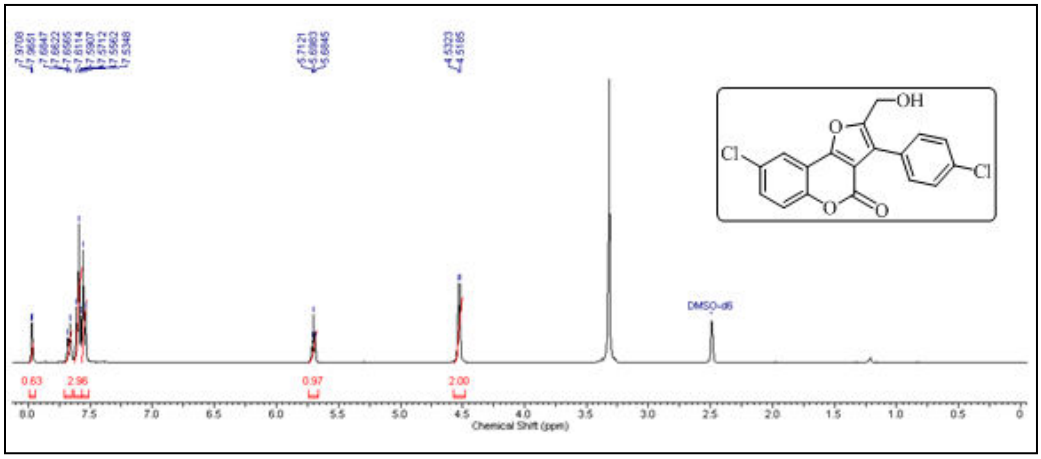


Figure 4.36 400 MHz ^{1}H NMR spectrum of **3cg** in DMSO-d_6

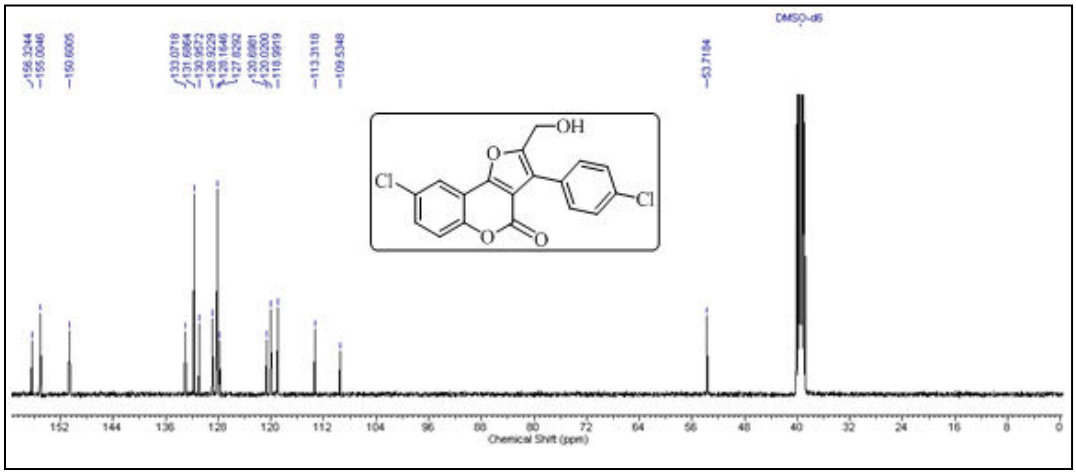


Figure 4.37 100 MHz ^{13}C NMR spectrum of **3cg** in DMSO-d_6

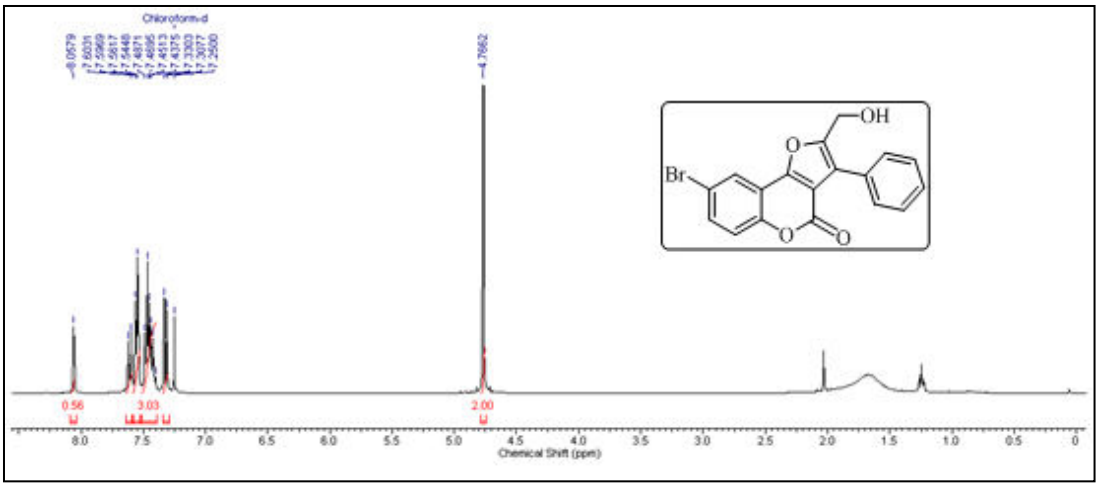


Figure 4.38 400 MHz ^{1}H NMR spectrum of **3da** in $CDCl_3$

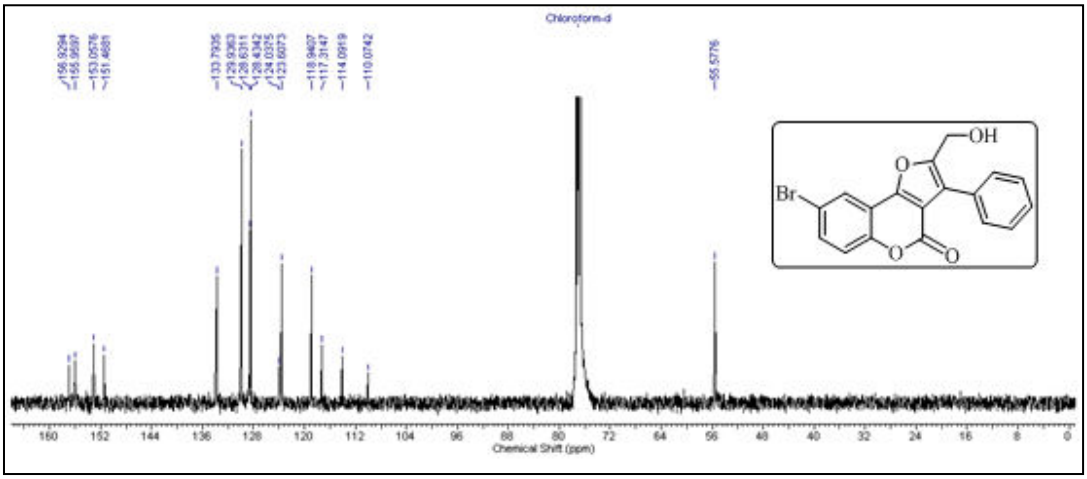


Figure 4.39 100 MHz ^{13}C NMR spectrum of **3da** in $CDCl_3$

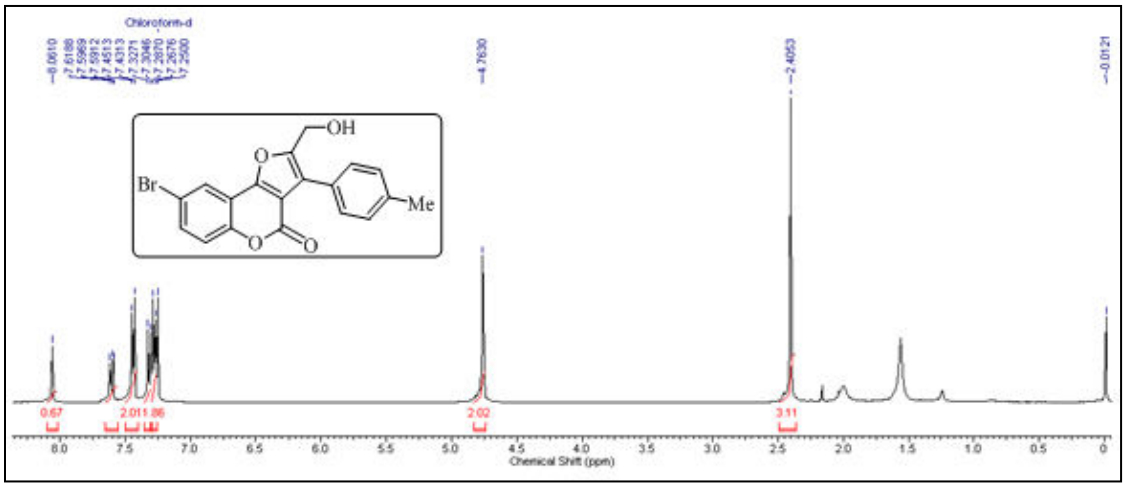


Figure 4.40 400 MHz ^{1}H NMR spectrum of **3db** in $CDCl_3$

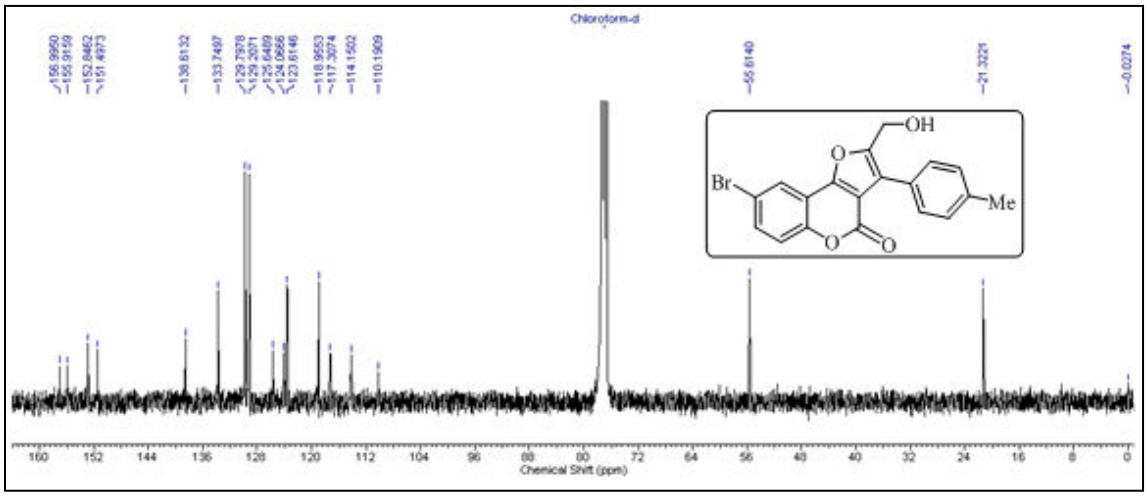


Figure 4.41 100 MHz ^{13}C NMR spectrum of **3db** in $CDCl_3$

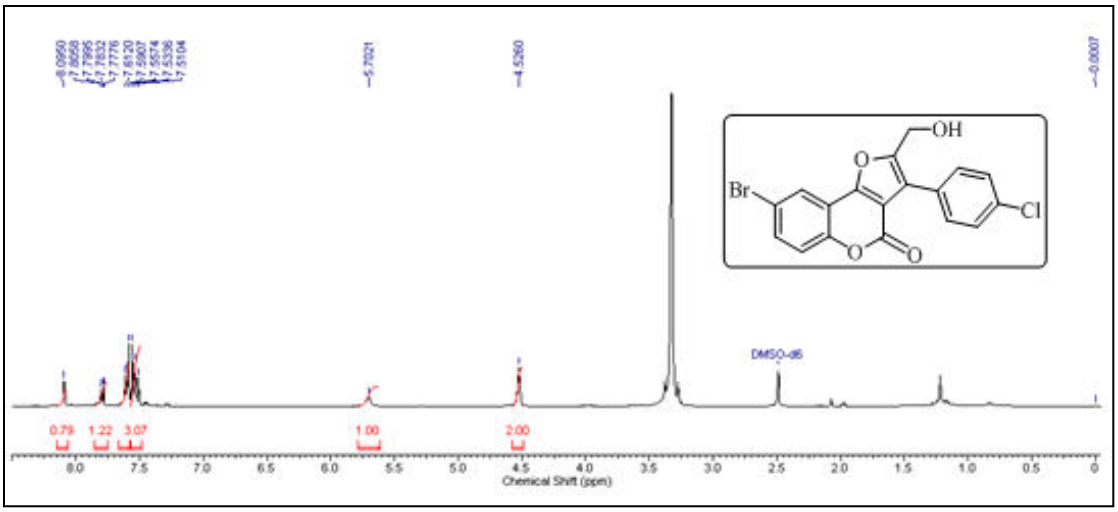


Figure 4.42 400 MHz ^{1}H NMR spectrum of **3dg** in DMSO-d_6

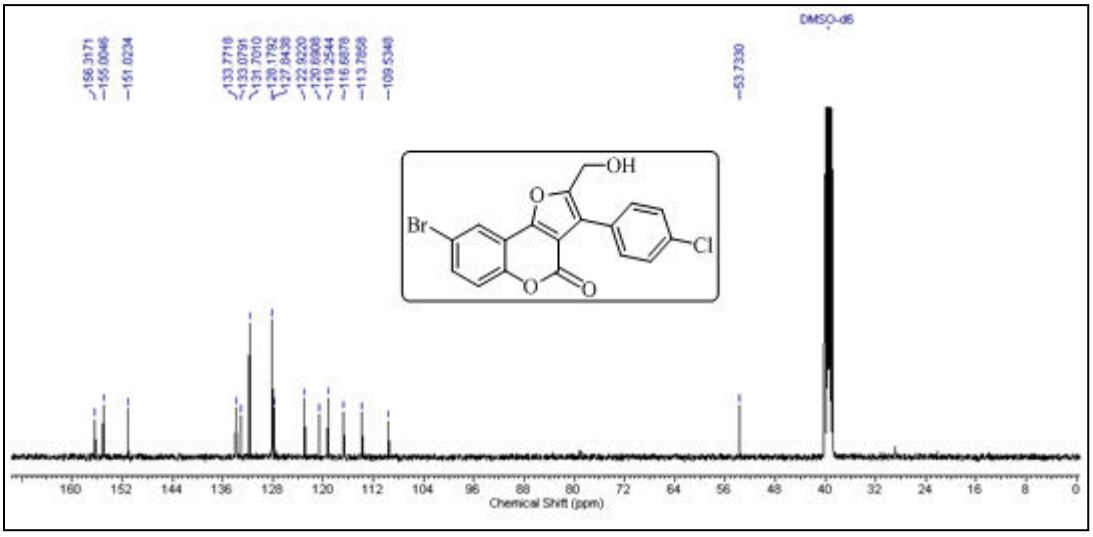


Figure 4.43 100 MHz ^{13}C NMR spectrum of **3dg** in DMSO-d_6

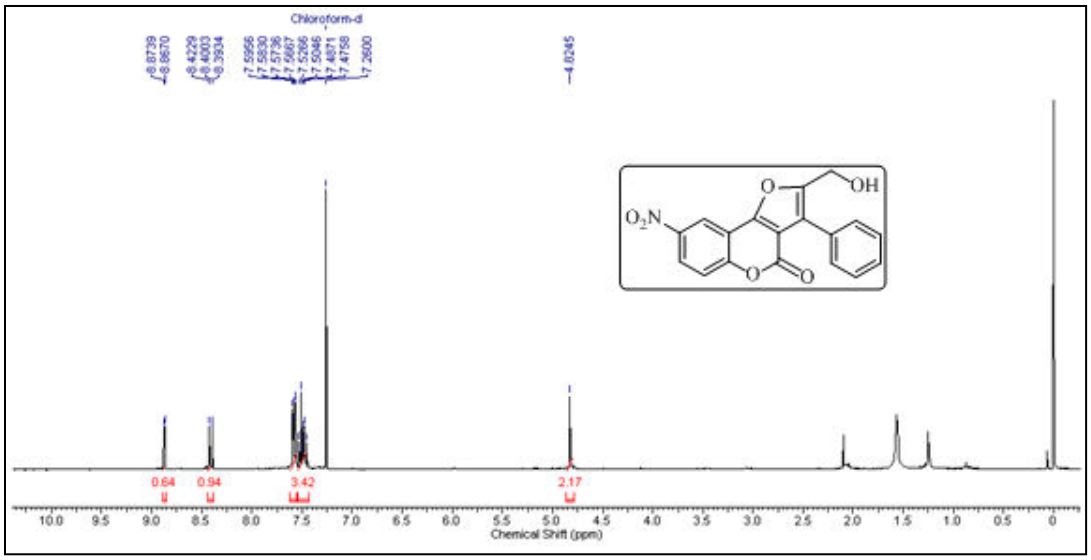


Figure 4.44 400 MHz ^{1}H NMR spectrum of **3ea** in $CDCl_3$

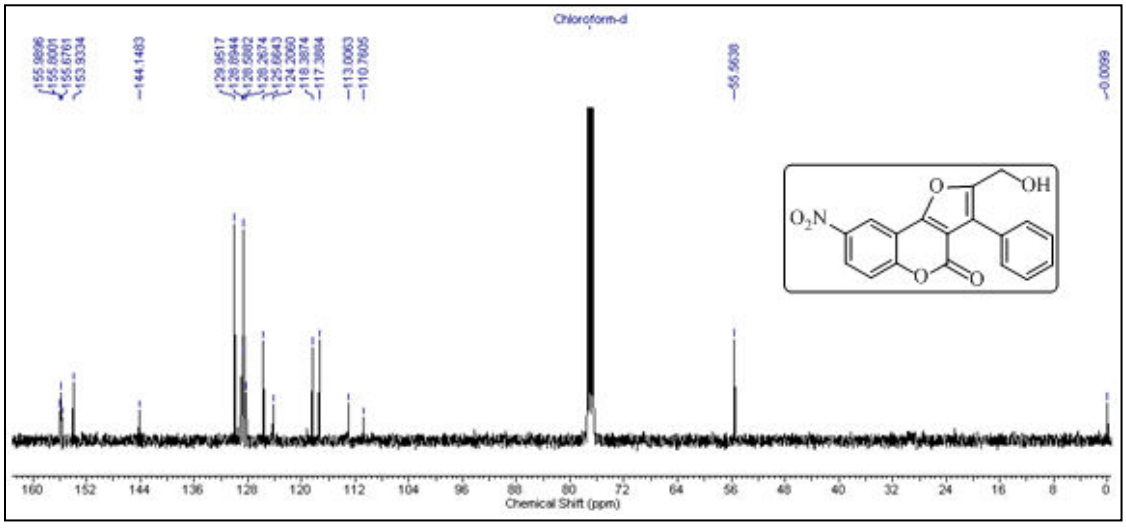


Figure 4.45 100 MHz ^{13}C NMR spectrum of **3ea** in $CDCl_3$

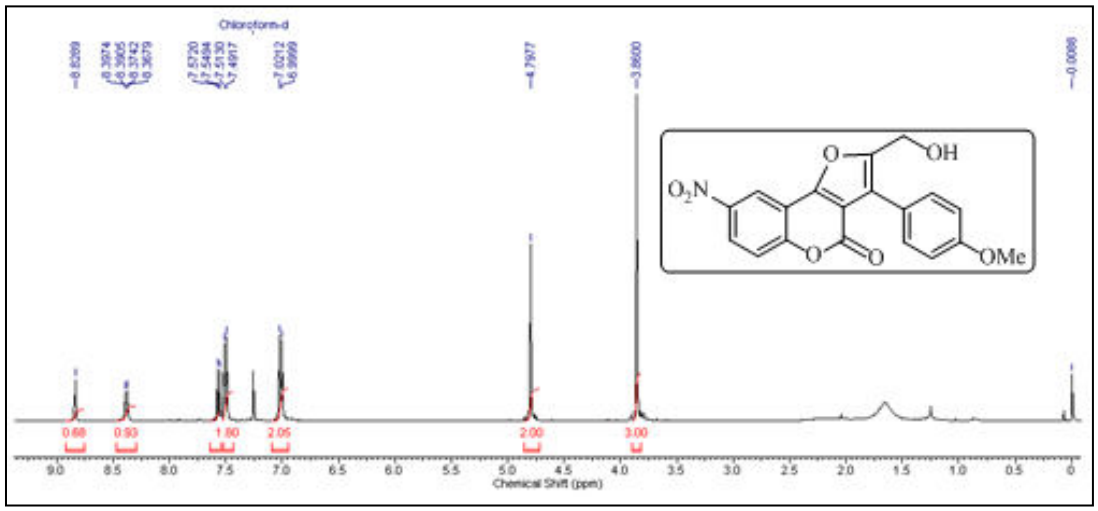


Figure 4.46 400 MHz ^{1}H NMR spectrum of **3ec** in $CDCl_3$

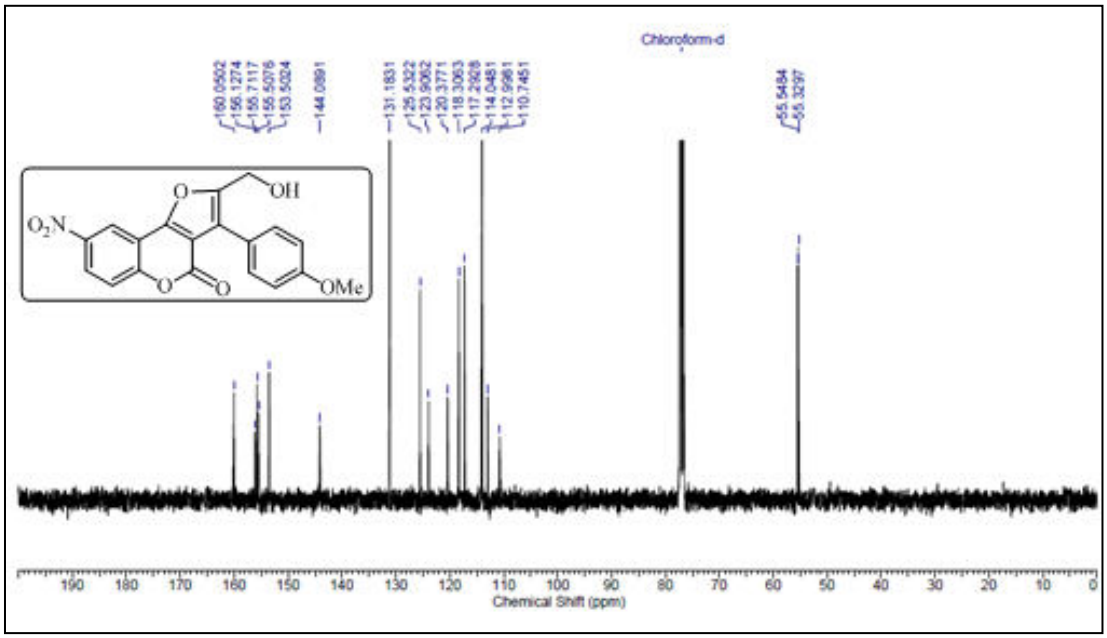


Figure 4.47 100 MHz ^{13}C NMR spectrum of **3ec** in $CDCl_3$

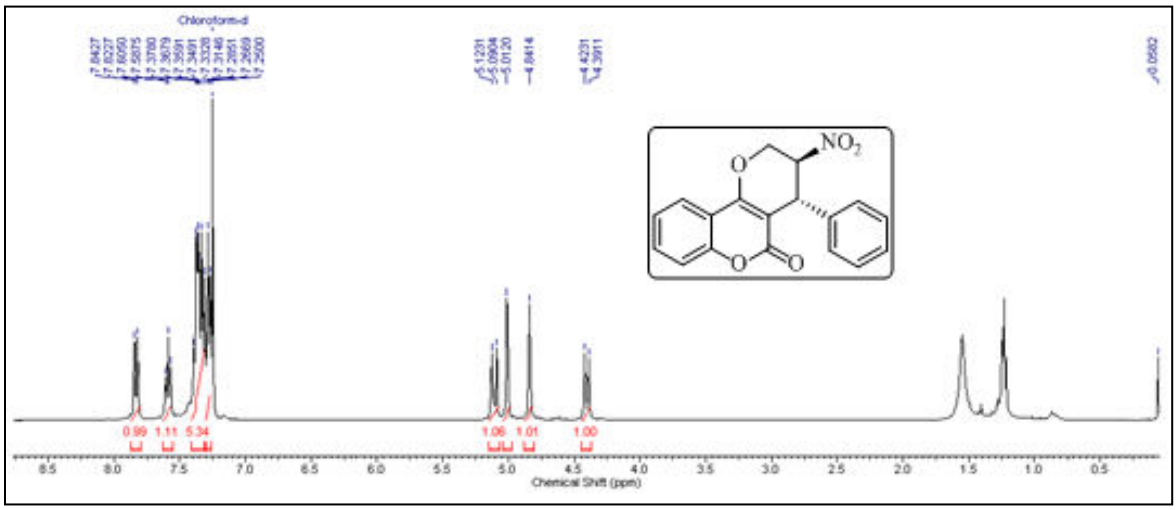


Figure 4.48 400 MHz ^{1}H NMR spectrum of **4aa** in $CDCl_3$

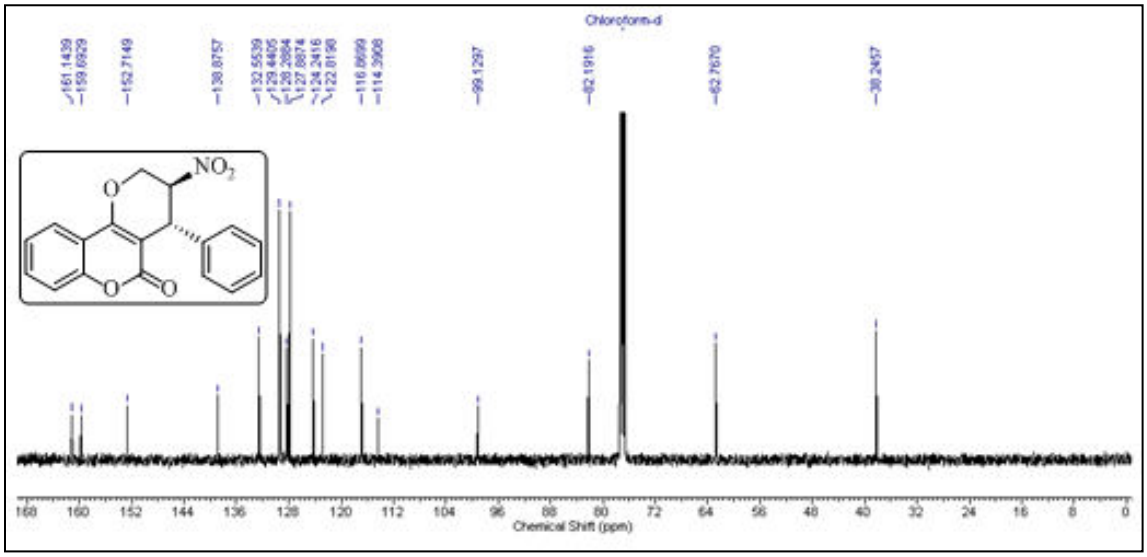


Figure 4.49 100 MHz ^{13}C NMR spectrum of **4aa** in $CDCl_3$

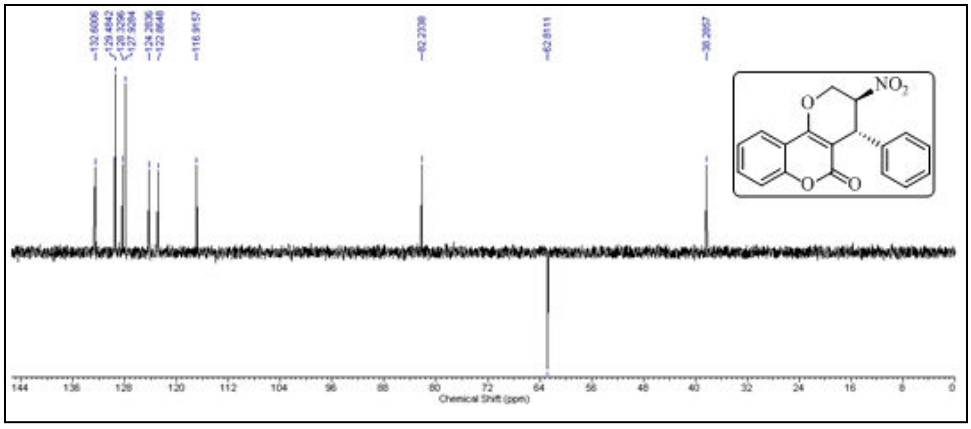


Figure 4.50 135°DEPT-NMR spectrum of **4aa** in $CDCl_3$

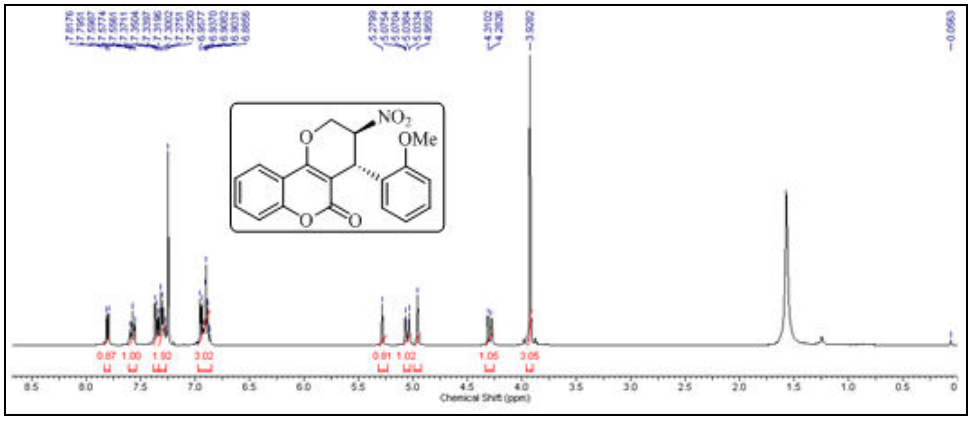


Figure 4.51 400 MHz ^{1}H NMR spectrum of **4ac** in $CDCl_3$

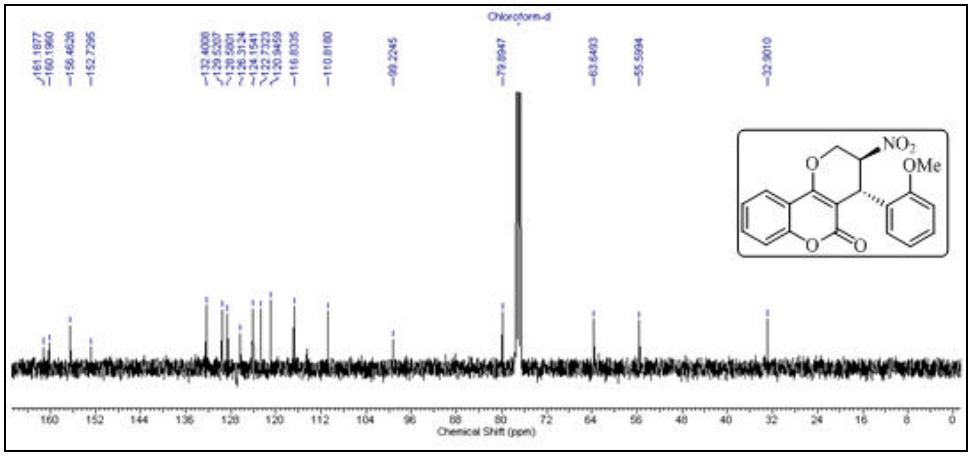


Figure 4.52 100 MHz ^{13}C NMR spectrum of **4ac** in $CDCl_3$

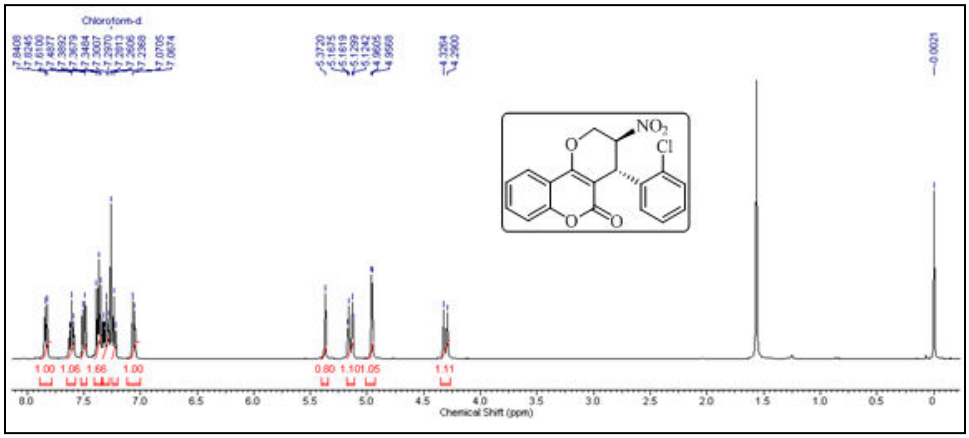


Figure 4.53 400 MHz ^{1}H NMR spectrum of **4ah** in $CDCl_3$

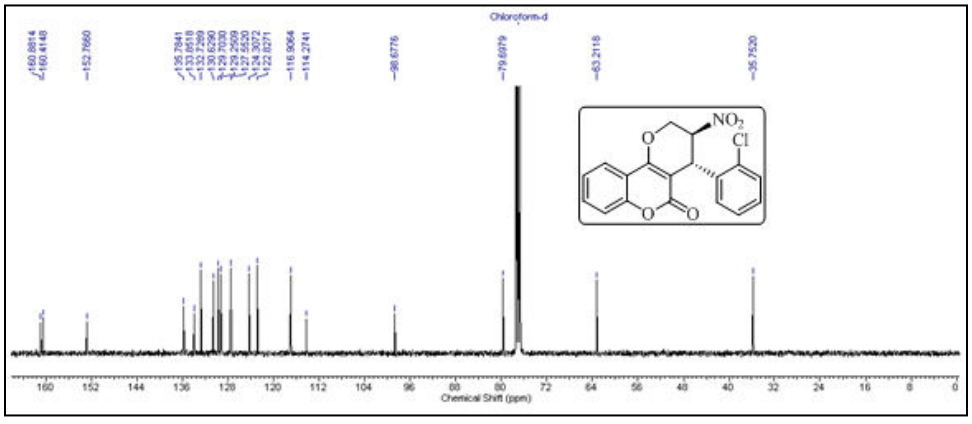


Figure 4.54 100 MHz ^{13}C NMR spectrum of **4ah** in $CDCl_3$

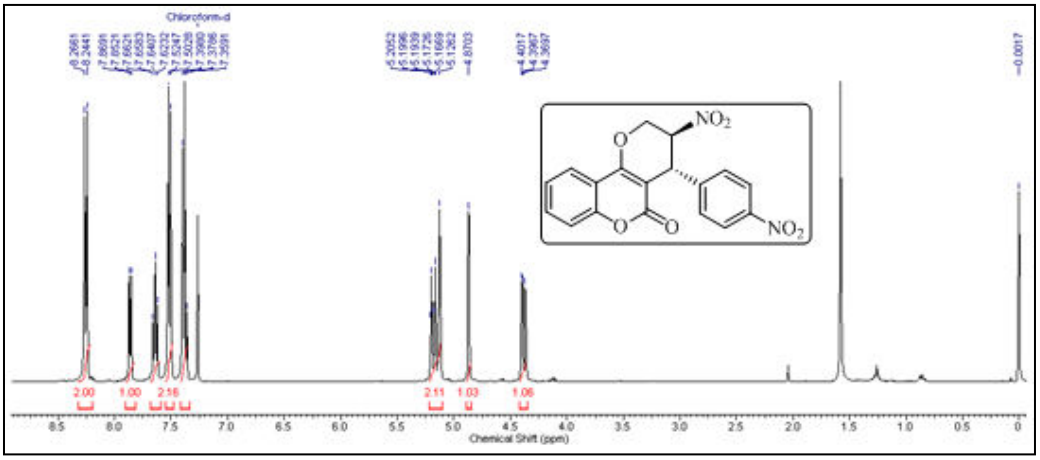


Figure 4.55 400 MHz ^{1}H NMR spectrum of **4aj** in $CDCl_3$

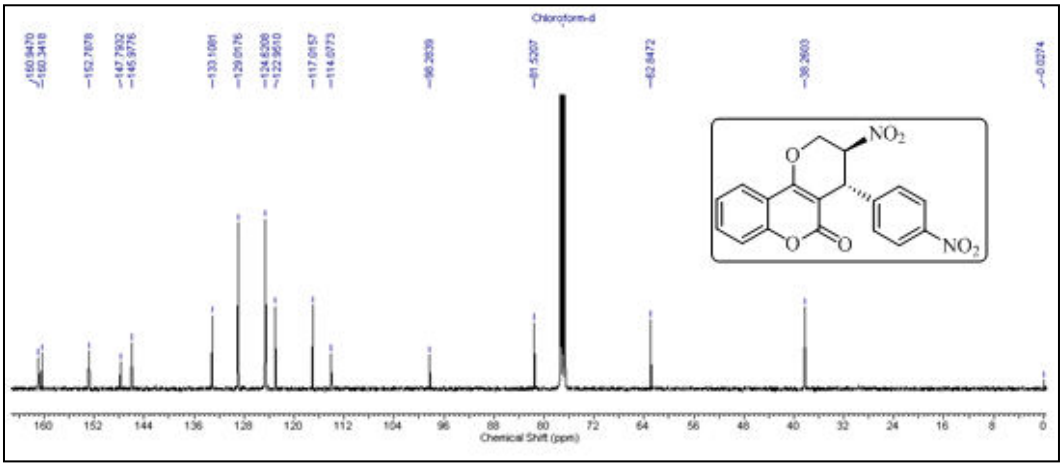


Figure 4.56 100 MHz ^{13}C NMR spectrum of **4aj** in $CDCl_3$

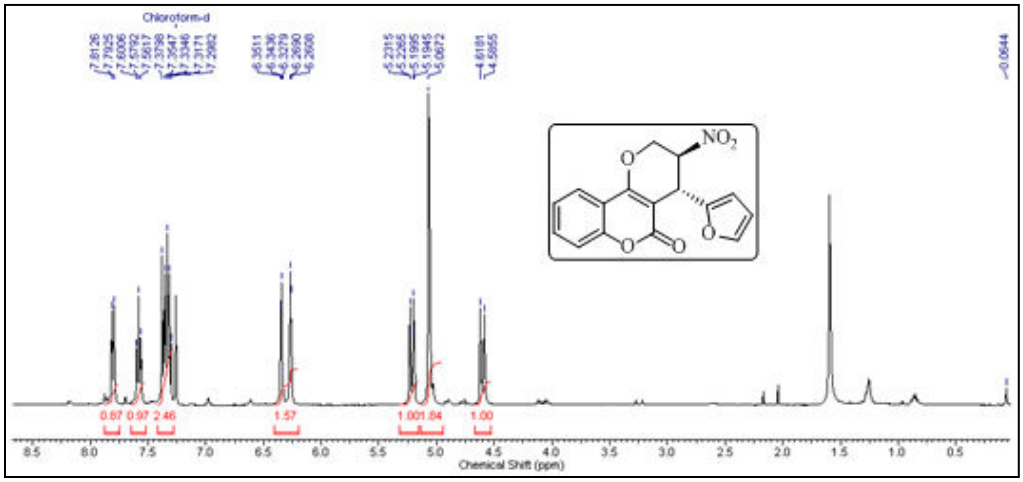


Figure 4.57 400 MHz ^{1}H NMR spectrum of **4ak** in $CDCl_3$

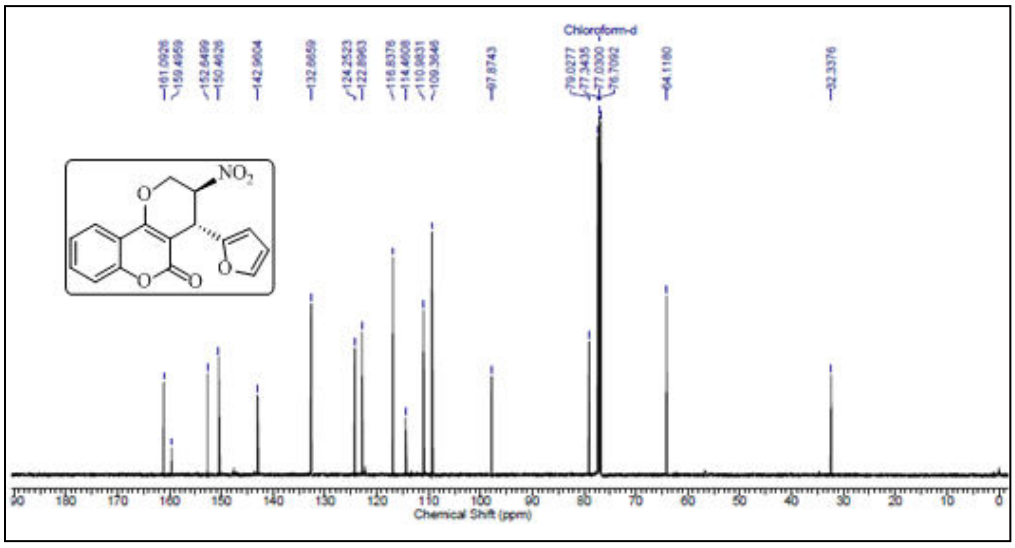


Figure 4.58 100 MHz ^{13}C NMR spectrum of **4ak** in $CDCl_3$

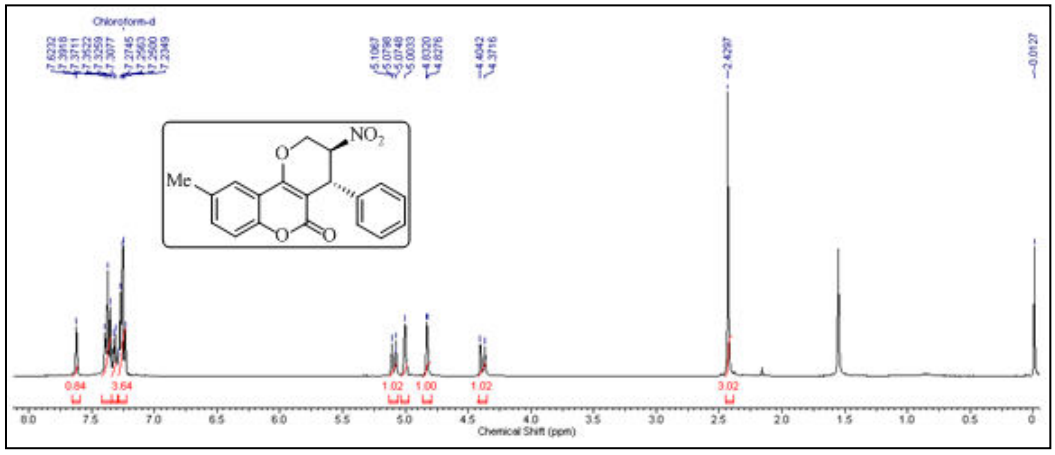


Figure 4.59 400 MHz ^{1}H NMR spectrum of **4ba** in $CDCl_3$

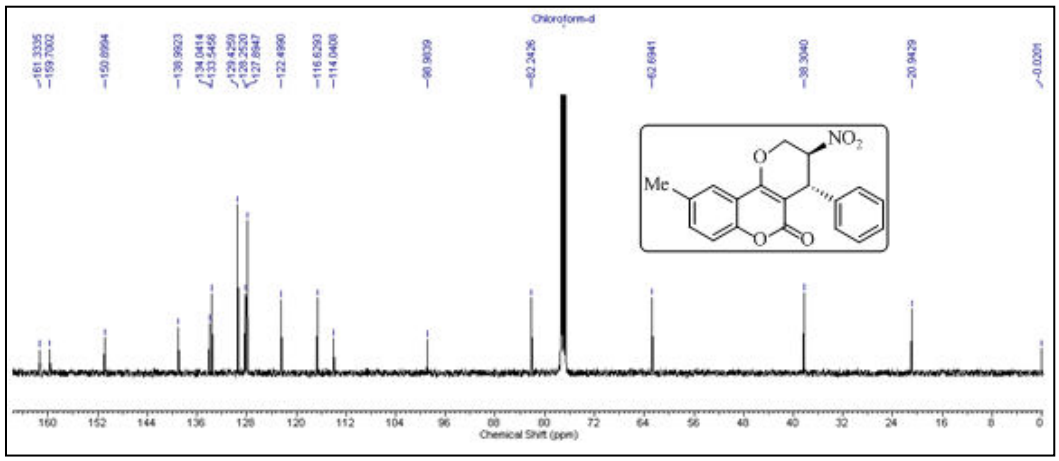


Figure 4.60 100 MHz ^{13}C NMR spectrum of **4ba** in $CDCl_3$

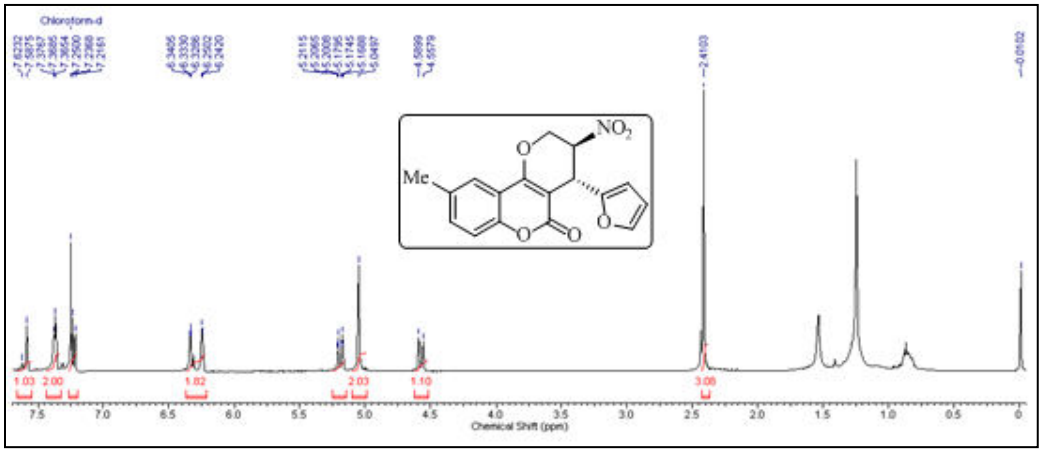


Figure 4.61 400 MHz ^{1}H NMR spectrum of **4bk** in $CDCl_3$

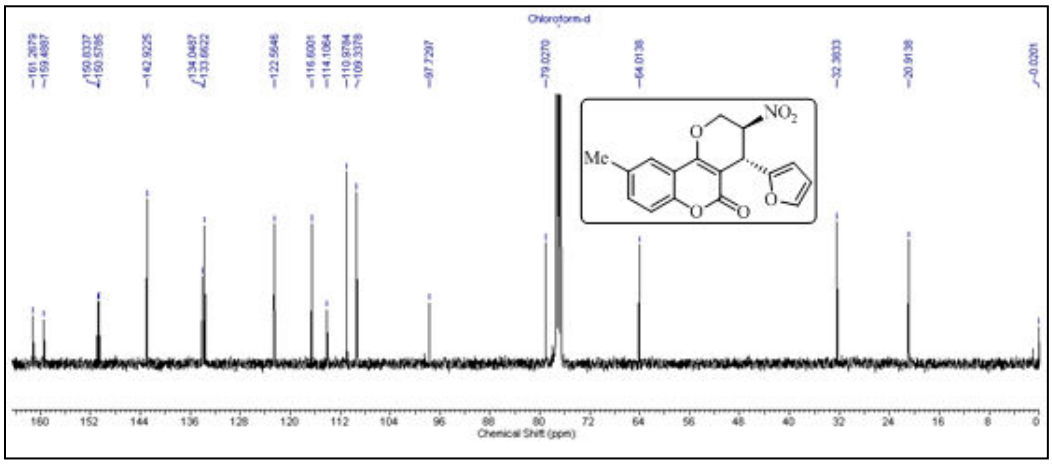


Figure 4.62 100 MHz ^{13}C NMR spectrum of **4bk** in $CDCl_3$

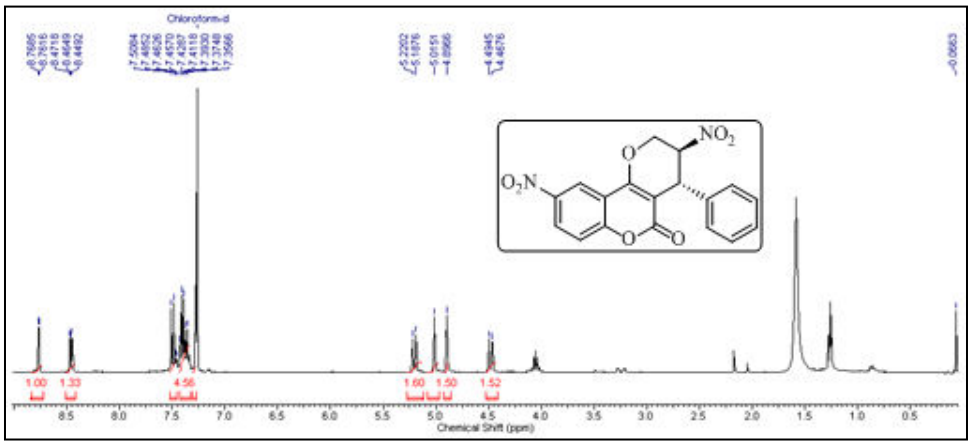


Figure 4.63 400 MHz ^{1}H NMR spectrum of **4ea** in $CDCl_3$

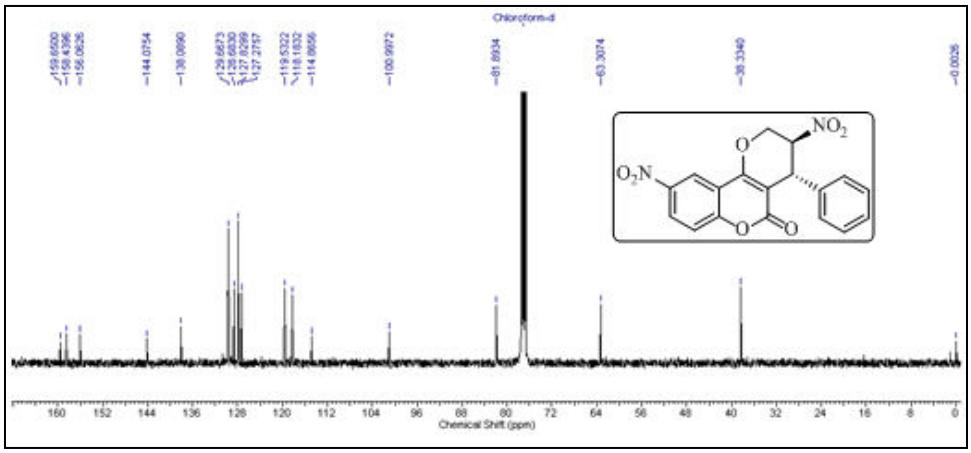


Figure 4.64 100 MHz ^{13}C NMR spectrum of **4ea** in $CDCl_3$

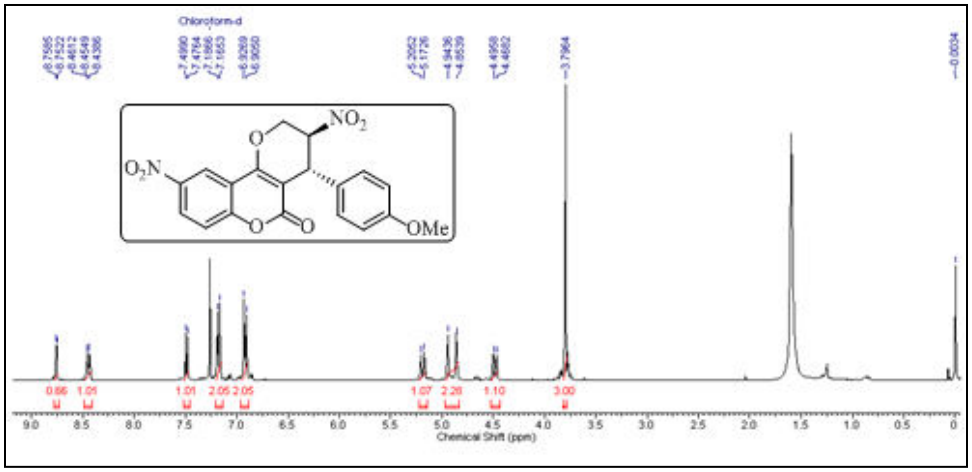


Figure 4.65 400 MHz ^{1}H NMR spectrum of **4ec** in $CDCl_3$

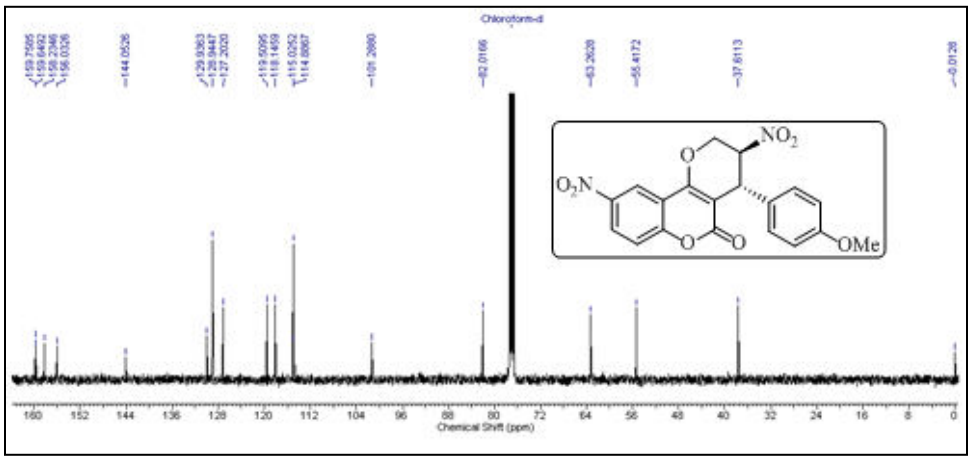


Figure 4.66 100 MHz ^{13}C NMR spectrum of **4ec** in $CDCl_3$

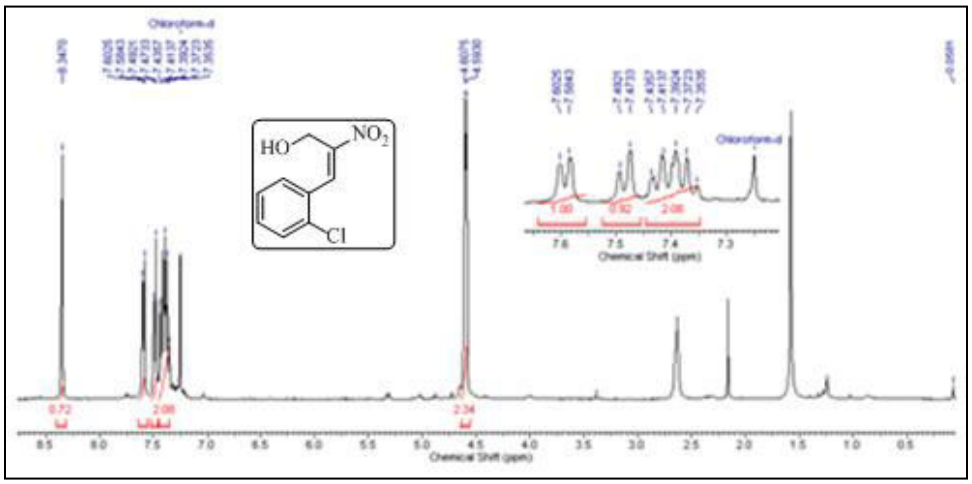


Figure 4.67 400 MHz ^{1}H NMR spectrum of **2h** in $CDCl_3$

4.8 References

1. Parrish J. A., Stern R. S., Pathak M. A., Fitzpatrick T.B. (1982), *Science of Photomedicine*; NATO Conference Series, Regan JD, Parrish JA. Eds. New York: Plenum Press; 595-624.

2. Gasparro F. P. (1994), Extracorporeal photochemotherapy: Clinical aspects and the molecular basis for efficacy. Georgetown, TX: Landes Press.

3. ÒKennedy R., Thornes R. D. (1997), Coumarins-biology, applications and mode of action, John Wiley & Sons Ltd.: Chichester.

4. Simões C.M.O., Schenkel E.P., Gosmann G., Mello J.C.P., Mentz L.A., Petrovick P.R. Eds. (2002), Farmacognosia: Da planta ao medicamento, 4th ed., editora da UFSC: Florianópolis, SC; editora da UFRS: Porto Alegre, RS.

5. Santana L., Uriarte E., Roleira F., Milhazes N., Borges F. (2004), Furocoumarins in medicinal chemistry: Synthesis, natural occurrence and biological activity, *Curr. Med. Chem.*, 11, 3239-3261 (DOI: 10.2174/0929867043363721).

6. Gambari R., Lampronti I., Bianchi N., Zuccato C., Viola G., Vedaldi D., DallaAcqua F. (2007), Structure and biological activity of furocoumarins, *Top. Heterocycl. Chem.*, 9, 265-276 (DOI: 10.1007/7081_2007_089).

7. Conforti F., Marrelli M., Menichini F., Bonesi M., Statti G., Provenzano E., Menichini F. (2009), Natural and synthetic furanocoumarins as treatment for vitiligo and psoriasis, *Curr. Drug Ther.*, 4, 38-58 (DOI: 10.2174/157488509787081886).

8. Marzaro G., Guiotto A., Borgatti M., Finotti A., Gambari R., Breveglieri G., Chilin A. (2013), Psoralen derivatives as inhibitors of

NF-κB/DNA interaction: Synthesis, molecular modeling, 3D-QSAR and biological evaluation, *J. Med. Chem*., 56, 1830-1842 (DOI: 10.1021/jm3009647).

9. Li C. C., Xie Z. X., Zhang Y. D., Chen J. H., Yang Z. (2003), Total synthesis of Wedelolactone, *J. Org. Chem*., 68, 8500-8504 (DOI: 10.1021/jo030228f).

10. Gambari R., Fibach E. (2007), Medicinal chemistry of fetal hemoglobin inducers for treatment of β-Thalassemia, *Curr. Med. Chem.,* 14, 199-214 (DOI: 10.2174/092986707779313318).

11. Perrine S. P., Ginder G. D., Faller D. V., Dover G. H., Ikuta T., Witkowska H. E., Cai S. P., Vichinsky E. P., Olivieri N. F. (1993), A short-term trial of butyrate to stimulate fetal-globin-gene expression in the beta-globin disorders, *N. Engl. J. Med.,* 328, 81-86 (DOI: 10.1056/NEJM199301143280202).

12. Rodgers G. P., Dover G. J., Uyesaka N., Noguchi C. T., Schechter A. N., Nienhuis A. W. (1993), Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle cell disease, *N. Engl. J. Med.*, 328, 73-80 (DOI: 10.1056/NEJM199301143280201).

13. Rodgers G. P., Rachmilewitz E. A. (1995), Novel treatment options in the severe β-globin disorders, *Br. J. Haematol.*, 91, 263-268 (DOI: 10.1111/j.1365-2141.1995.tb05288.x).

14. Steinberg M. H, Lu L. Z., Barton F. B., Terrin M. L., Charache S., Dover G. J. (1997), Fetal hemoglobin in sickle cell anemia: Determinants of response to hydroxyurea. Multicenter study of hydroxyurea, *Blood*, 89, 1078-1088.

15. Piccagli L., Borgatti M., Nicolis E., Bianchi N., Mancini I., Lampronti I., Vevaldi D., Dall'Acqua F., Cabrini G., Gambari R. (2010), Virtual screening against nuclear factor κB (NF-κB) of a focus library:

Identification of bioactive furocoumarin derivatives inhibiting NF-κB dependent biological functions involved in cystic fibrosis, *Bioorg. Med. Chem.*, 18, 8341-8349 (DOI: 10.1016/j.bmc.2010.09.063).

16. Al-Sehemi A. G., El-Gogary S. R. (2012), Synthesis and photooxygenation of furo[3,2-*c*]coumarin derivatives as antibacterial and DNA intercalating agent, *Chin. J. Chem.*, 30, 316-320 (DOI: 10.1002/cjoc.2011080483).

17. Borgatti M., Chilin A., Piccagli L., Lampronti I., Bianchi N., Mancini I., Marzaro G., dall'Acqua F., Guiotto A., Gambari R. (2011), Development of a novel furocoumarin derivative inhibiting NF-κB dependent biological functions: Design, synthesis and biological effects, *Eur. J. Med. Chem.*, 46, 4870-4877 (DOI: 10.1016/j.ejmech.2011.07.032).

18. Stolk L. M., Siddiqui A. H. (1988), Biopharmaceutics, pharmacokinetics and pharmacology of psoralens, *Gen Pharmacol*, 19, 649-653 (DOI:10.1016/0306-3623(88)90122-X).

19. Dalla Via L., Gia O., Marciani Magno S., Santana L., Teijeira M., Uriarte E. (1999), New tetracyclic analogues of photochemotherapeutic drugs 5-MOP and 8-MOP: Synthesis, DNA interaction and antiproliferative activity, *J. Med. Chem.*, 42, 4405-4413 (DOI: 10.1021/jm9910829).

20. Gia O., Anselmo A., Conconi M. T., Antonello C., Uriarte E., Caffieri S. (1996), 4′-Methyl derivatives of 5-MOP and 5-MOA: Synthesis, photoreactivity and photobiological activity, *J. Med. Chem.*, 39, 4489-4496 (DOI: 10.1021/jm960117r).

21. Anselmino C., Averbeck D., Cadet J. (1995), Photoreaction of 5-methoxypsoralen with thymidine and the thymine moiety of isolated and *Saccharomyces cerevisiae* DNA. Characterization and

measurement of the two *cis-syn* furan-side monocycloadducts, *Photochem. Photobiol.,* 62, 997-1004 (DOI: 10.1111/j.1751-1097.1995.tb02399.x).

22. Engin B., Oguz O. (2005), Evaluation of time-dependent response to psoralen plus UVA (PUVA) treatment with topical 8-methoxypsoralen (8-MOP) gel in palmoplantar dermatoses, *Int. J. Dermatol.*, 44, 337-339 (DOI: 10.1111/j.1365-4632.2004.02153.x).

23. McGinnis K. S., Shapiro M., Vittorio C. C., Rook A. H., Junkins-Hopkins J. M. (2003), Psoralen plus long-wave UV-A (PUVA) and bexarotene therapy: An effective and synergistic combined adjunct to therapy for patients with advanced cutaneous T-cell lymphoma, *Arch Dermatol*, 139, 771-775 (DOI: 10.1001/archderm.139.6.771).

24. Zane C., Venturini M., Sala R., Calzavara-Pinton P. (2006), Photodynamic therapy with methylaminolevulinate as a valuable treatment option for unilesional cutaneous T-cell lymphoma, *Photodermatol. Photoimmunol. Photomed.*, 22, 254-258 (DOI: 10.1111/j.1600-0781.2006.00246.x).

25. Cho H.-J., Jeong S.-G., Park J.-E., Han J.-A., Kang H.-R., Lee D., Song M. J. (2013), Antiviral activity of angelicin against gamma herpesviruses, *Antiviral research*, 1, 75-83 (DOI: 10.1016/j.antiviral.2013.07.009).

26. Cabrini G., Casavola V., Gambari R. (2012), Trimethylangelicin as CFTR (Cystic Fibrosis Transmembrane conductance Regulator) corrector in bronchial epithelial cells, WO 2012171954 A1.

27. Wang X., Nakagawa-Goto K., Baston K. F., Don M.-J., Lin Y.-L., Wu T.-S., Lee K.-H. (2006), Antitumor agents. 254. Synthesis and biological evaluation of novel Neo-tanshinlactone analogues as potent

anti-breast cancer agents, *J. Med. Chem*., 49, 5631-5634 (DOI: 10.1021/jm060184d).

28. Jacob D. A., Temple J. L., Patisaul H. B., Young L. J., Rissman E. F. (2001), Coumestrol antagonizes neuroendocrine actions of estrogen via the estrogen receptor alpha, *Exp. Biol. Med*., 226, 301-306.

29. Wagner H., Fessler B. (1986), *In-Vitro*-5-Lipoxygenasehemmung durch *Eclipta alba* extrakte und das Coumestan-derivat Wedelolacton *Planta Med*., 52, 374-377 (DOI: 10.1055/s-2007-969189).

30. Sarveswaran S., Gautam S. C., Ghosh J. (2012), Wedelolactone, a medicinal plant-derived coumestan, induces caspase-dependent apoptosis in prostate cancer cells via downregulation of PKCε without inhibiting Akt, *Int. J. Oncol.*, 41, 2191-2199 (DOI: 10.3892/ijo.2012.1664).

31. Joyce D., Albanese C., Steer J., Fu M., Bouzahzah B., Pestell R.G. (2001), NF-kappaB and cell-cycle regulation: the cyclin connection, *Cytokine Growth Factor Rev.*, 12, 73-90 (DOI:10.1016/S1359-6101(00)00018-6).

32. Chen F., Castranova V., Shi X. (2001), New insights into the role of nuclear factor kappaB in cell growth regulation, *Am. J. Pathol.*, 59, 387-397 (DOI:10.1016/S0002-9440(10)61708-7).

33. Hinz M., Krappmann D., Eichten A., Heder A., Scheidereit C., Strauss M. (1999), NF-kappaB function in growth control: regulation of cyclin D1 expression and G_0/G_1-to-S-phase transition, *Mol. Cell. Biol.*, 19, 2690-2698 (DOI: 10.1128/MCB.19.4.2690).

34. Mosialos G. (1997), The role of Rel/NF-kappa B proteins in viral oncogenesis and the regulation of viral transcription, *Semin. Cancer Biol.*, 8, 121-129 (DOI: 10.1006/scbi.1997.0063).

35. Hinz M., Loser P., Mathas S., Krappmann D., Dorken B., Scheidereit C. (2001), Constitutive NF-kappaB maintains high expression of a characteristic gene network, including CD40, CD86, and a set of antiapoptotic genes in Hodgkin/Reed-Sternberg cells, *Blood*, 97, 2798-2807 (DOI: 10.1182/blood.V97.9.2798).

36. Finco T. S., Westwick J. K., Norris J. L., Beg A. A., Der C. J., Baldwin Jr. A. S. (1997), Oncogenic Ha-Ras-induced signaling activates NF-kappaB transcriptional activity, which is required for cellular transformation, *J. Biol. Chem.*, 272, 24113-24116 (DOI: 10.1074/jbc.272.39.24113).

37. Guttridge D. C., Albanese C., Reuther J. Y., Pestell R. G., Baldwin Jr. A. S. (1999), NF-kappaB controls cell growth and differentiation through transcriptional regulation of cyclin D1, *Mol. Cell. Biol.*, 19, 5785-5799 (DOI: doi: 10.1128/MCB.19.8.5785).

38. Griffith T. S., Chin W. A., Jackson G. C., Lynch D. H., Kubin M. Z. (1998), Intracellular regulation of TRAIL-induced apoptosis in human melanoma cells, *J. Immunol.*, 161, 2833-2840.

39. Vasudevan K. M., Gurumurthy S., Rangnekar V. M. (2004), Suppression of PTEN expression by NF-kappa B prevents apoptosis, *Mol. Cell Biol.*, 24, 1007-1021 (DOI: 10.1128/MCB.24.3.1007-1021.2004).

40. Wang C. Y., Mayo M. W., Korneluk R. G., Goeddel D. V., Baldwin Jr. A. S. (1998), NF-kappaB antiapoptosis: Induction of TRAF1 and TRAF2 and c-IAP1 and c-IAP2 to suppress caspase-8 activation, *Science*, 281, 1680-1683 (DOI: 10.1126/science.281.5383.1680).

41. Piva R., Penolazzi L., Borgatti M., Lampronti I., Lambertini E., Torreggiani E., Gambari R. (2009), Apoptosis of human primary osteoclasts treated with molecules targeting nuclear factor-kappaB,

Ann. N.Y. Acad. Sci., 1171, 448-456 (DOI: 10.1111/j.1749-6632.2009.04906.x).

42. Boyce B. F., Yao Z., Xing L. (2010), Functions of nuclear factor kappaB in bone, *Ann. N.Y. Acad. Sci.*, 1192, 367-375 (DOI: 10.1111/j.1749-6632.2009.05315.x).

43. Atkinson G. P., Nozell S. E., Benveniste E. T. (2010), NF-kappaB and STAT3 signaling in glioma: Targets for future therapies, *Expert Rev. Neurother*, 10, 575-586 (DOI: 10.1586/ern.10.21).

44. Wong K. K., Jacks T., Dranoff G. (2010), NF-kappaB fans the flames of lung carcinogenesis, *Cancer Prev. Res.*, 3, 403-405 (DOI: 10.1158/1940-6207.CAPR-10-0042).

45. Abel G., Schimmer O. (1986), Chromosome-damaging effects of heraclenin in human lymphocytes in vitro, *Mutation Research/Genetic Toxicology*, 169, 51-54 (DOI: 10.1016/0165-1218(86)90018-2).

46. Banday J. A., Bhat G. M., Mir F. A., Qurishi M. A., Koul S., Razdan T. K. (2013), Heraclenin: A potential optoelectronic device material from *Prangos pabularia*, *Journal of Electronic Materials*, 42, 2498-2503 (DOI: 10.1007/s11664-013-2596-x).

47. Moon T. C., Jin M., Son J. K., Chang H. W. (2008), The effects of isoimperatorin isolated from Angelicae dahuricae on cyclooxygenase-2 and 5-lipoxygenase in mouse bone marrow-derived mast cells, *Arch Pharm Res.*, 31, 210-215.

48. Srinivasan S., Sarada D. V. L. (2012), Antifungal activity of phenyl derivative of pyranocoumarin from Psoralea corylifolia L. seeds by inhibition of acetylation activity of Trichothecene 3-O-acetyltransferase (Tri101), *Journal of Biomedicine and Biotechnology*, Article ID 310850, 1-8 (DOI:10.1155/2012/310850).

49. Xu Z.-Q., Pupek K., Suling W. J., Enache L., Flavin M. T. (2006), Pyranocoumarin, a novel anti-TB pharmacophore: Synthesis and biological evaluation against *Mycobacterium tuberculosis*, *Bioorganic and Medicinal Chemistry*, 14, 4610-4626 (DOI: 10.1016/j.bmc.2006.02.017).

50. Mao W.-W., Wang T.-T., Zeng H.-P., Wang Z.-Y., Chen J.-P., Shen J.-G. (2009), Synthesis and evaluation of novel substituted 5-hydroxycoumarin and pyranocoumarin derivatives exhibiting significant antiproliferative activity against breast cancer cell lines, *Bioorganic & Medicinal Chemistry Letters*, 19, 4570-4573 (DOI: 10.1016/j.bmcl.2009.06.098A).

51. Xu Z.-Q., Barrow W. W., Suling W. J., Westbrook L., Barrow E., Lin Y.-M., Flavin M. T. (2004), Anti-HIV natural product (+)-calanolide A is active against both drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis*, *Bioorganic and Medicinal Chemistry*, 12, 1199-1207 (DOI: 10.1016/j.bmc.2003.11.012).

52. Su C.-R., Yeh S. F., Liu C. M., Damu A. G., Kuo T.-H., Chiang P.-C., Bastow K. F., Lee K.-H., Wu T.-S. (2009), Anti-HBV and cytotoxic activities of pyranocoumarin derivatives, *Bioorganic & Medicinal Chemistry*, 17, 6137-6143 (DOI: 10.1016/j.bmc.2008.12.007).

53. Cheng G., Hu Y. (2007), One-pot synthesis of furocoumarins through cascade addition-cyclization-oxidation, *Chem. Commun*., 3285-3287 (DOI: 10.1039/b705315k).

54. Chen L., Li Y., Xu M.-H. (2010), One-pot synthesis of furocoumarins *via* sequential Pd/Cu-catalyzed alkynylation and intramolecular hydroalkoxylation, *Org. Biomol. Chem*., 8, 3073-3077 (DOI: 10.1039/c004233a).

55. Tang L., Pang Y., Yan Q., Shi L., Huang J., Du Y., Zhao K. (2011), Synthesis of coumestan derivatives *via* $FeCl_3$-mediated oxidative ring closure of 4-hydroxy coumarins, *J. Org. Chem.*, 76, 2744-2752 (DOI: 10.1021/jo2000644).

56. Liu J., Liu Y., Du W., Dong Y., Liu J., Wang M. (2013), Pd-catalyzed C-S activation for [3+3]annulation of 2-(methylthio)benzofuran-3-carboxylates and 2-hydroxyphenylboronic acids: Synthesis of coumestan derivatives, *J. Org. Chem.*, 78, 7293-7297 (DOI: 10.1021/jo400984h).

57. Lee C.-J., Jang Y.-J., Wu Z.-Z., Lin W. (2012), Preparation of functional phosphorus zwitterions from activated alkanes, aldehydes and tributylphosphine: Synthesis of polysubstituted furo[3,2-*c*]coumarins, *Org. Lett.*, 14, 1906-1909 (DOI: 10.1021/ol3005479).

58. Huang W.-Y., Chen Y.-C., Chen K. (2012), Efficient synthesis of tetrasubstituted furans from nitroallylic acetates and 1,3-Dicarbonyl/α-activating ketones by Feist-Bénary addition-elimination, *Chem. Asian J.*, 7, 688-691 (DOI: 10.1002/asia.201100988).

59. Zhou Z., Liu H., Li Y., Liu J., Li Y., Liu J., Yao J., Wang C. (2013), Novel synthesis of substituted furo[3,2-*c*]chromen-4-ones *via* four component reaction from substituted nitrostyrenes, aromatic aldehydes, coumarins and ammonium acetate, *ACS Comb. Sci.*, 15, 363-369 (DOI: 10.1021/co4000419).

60. Rueping M., Merino E., Sugiono E. (2008), Enantioselective organocatalytic reactions of 4-hydroxy-coumarin and 4-hydroxypyrone with α,*β*-unsaturated aldehydes: An efficient Michael addition-acetalization cascade to chromenones, quinolinones and pyranones, *Adv. Synth. Catal.*, 350, 2127-2131 (DOI: 10.1002/adsc.200800340).

61. Sagar R., Park J., Koh M., Park S. B. (2009), Diastereoselective synthesis of polycyclic acetal-fused pyrano[3,2-*c*]pyran-5(2*H*)-one derivatives, *J. Org. Chem.*, 74, 2171-2174 (DOI: 10.1021/jo8023889).

62. Gao Y., Ren Q., Wang L., Wang J. (2010), Enantioselective synthesis of coumarins catalyzed by a bifunctional amine-thiourea catalyst, *Chem.-Eur. J.*, 16, 13068-13071 (DOI: 10.1002/chem.201002202).

63. Beerappa M., Shivashankar K. (2015), One pot synthesis of pyran-based heterocycles from benzyl halides as key reagents, *RSC Adv*., 5, 30364-30371 (DOI: 10.1039/c4ra17219a).

64. Majumdar K. C., Debnath P., Maji P. K. (2007), Thiophenol-catalyzed Claisen rearrangement and radical cyclization: Formation of furo- and pyrano-coumarin derivatives, *Tetrahedron Lett*., 48, 5265-5268 (DOI: 10.1016/j.tetlet.2007.05.133).

65. Gawande M. B., Bonifåcio V. D. B., Luque R., Branco P. S., Varma R. S. (2013), Benign by design: Catalyst-free in-water, on-water green chemical methodologies in organic synthesis, *Chem. Soc. Rev.*, 42, 5522-5551 (DOI: 10.1039/c3cs60025d).

66. Chakraborti A. K., Rudrawar S., Jadhav K. B., Kaur G., Chaneshwara S. V. (2007), ‘‘On water’’ organic synthesis: A highly efficient and clean synthesis of 2-aryl/heteroaryl/styryl benzothiazoles and 2-alkyl/aryl alkyl benzothiazolines*, Green Chem.*, 9, 1335-1340 (DOI: 10.1039/b710414f).

67. Ghabraie E., Bararjanian M., Balalaie S., Rominger F., Bijanzadeh H. R. (2011), Efficient synthesis of (3*E*)-3-[amino(aryl)methylidene] chromane-2,4-diones(=(3*E*)-3-[amino(aryl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-diones) *via* a three-component reaction, *Helv. Chim. Acta*, 94, 1440-1447 (DOI: 10.1002/hlca.201100001).

68. Zanwar M. R., Raihan M. J., Gawande S. D., Kavala V., Janreddy D., Kuo C.-W., Ambre R., Yao C.-F. (2012), Alcohol mediated synthesis of 4-oxo-2-aryl-4*H*-chromene-3-carboxylate derivatives from 4-hydroxy-coumarins, *J. Org. Chem.*, 75, 6495-6504 (DOI: 10.1021/jo301044y).

69. Barange D. K., Kavala V., Raju B. R., Kuo C.-W., Tseng C., Tu Y.-C., Yao C.-F. (2009), Facile and highly efficient method for the C-alkylation of 2-hydroxy-1,4-naphthoquinone to nitroalkenes under catalyst-free 'on water' conditions, *Tetrahedron Lett.*, 50, 5116-5119 (DOI: 10.1016/j.tetlet.2009.06.107).

70. Barange D. K., Kavala V., Kuo C.-W., Lei P.-M., Yao C.-F. (2011), Synthesis of *C*3-nitroalkylated-4-hydroxycoumarin and hydroxyimino-dihydrofuroquinolinone derivatives *via* the Michael addition of cyclic 1,3-dicarbonyl compounds to *β*-nitrostyrenes, *Tetrahedron*, 67, 2870-2877 (DOI: 10.1016/j.tet.2011.02.062).

71. Murray R. D. H., Medez J., Brown S. A. (1982), The natural coumarins: Occurrence, chemistry and biochemistry, Wiley, New York.

72. Emmadi N. R., Atmakur K., Chityal G. K., Pombala S., Nanubolu J. B. (2012), Synthesis and cytotoxicity evaluation of highly functionalized pyranochromenes and pyranopyrans, *Bioorg. Med. Chem. Lett.*, 22, 7261-7264 (DOI: 10.1016/j.bmcl.2012.09.018).

73. Ishikawa T. (2000), Anti HIV-1 active Calophyllum coumarins: Distribution, chemistry and activity, *Heterocycles*, 53, 453-474 (DOI: 10.3987/REV-99-526).

74. Melliou E., Magiatis P., Mitaku S., Skaltsounis A.-L., Chinou E., Chinou I. (2005), Natural and synthetic 2,2-dimethylpyranocoumarins

with antibacterial activity, *J. Nat. Prod.*, 68, 78-82 (DOI: 10.1021/np0497447).

75. Xu Z.-Q., Pupek K., Suling W. J., Enache L., Flavin M. T. (2006), Pyranocoumarin, a novel anti-TB pharmacophore: Synthesis and biological evaluation against Mycobacterium tuberculosis, *Bioorg. Med. Chem.*, 14, 4610-4626 (DOI: 10.1016/j.bmc.2006.02.017).

76. Zhu X., Lin A., Shi Y., Guo J., Zhu C., Cheng Y. (2011), Enantioselective synthesis of polycyclic coumarin derivatives catalyzed by an in situ formed primary amine-imine catalyst, *Org. Lett.*, 13, 4382-4385 (DOI: 10.1021/ol201715h).

Chapter 5

Catalyst-free reaction of 4-mercaptocoumarin with (*E*)-3-aryl/hetero-aryl-substituted-2-nitroprop-2 enols/Morita-Baylis-Hillman acetates of nitroolefins: facile synthesis of 4-sulfanylcoumarins

5.1 Introduction

Coumarin is one of the most important heterocycles, widely found in a variety of biologically active natural products and pharmacophores as discussed in previous chapter.[1] Thus, many synthetic organic and medicinal chemists have been devoted towards the synthesis of functionalized coumarin derivatives.[2-3] On the other hand, substituted thiocoumarin having S-atom at C-4 position has also continuously receiving widespread attention due to their significant biological activities.[4] Thus, it is crucial to develop new synthetic pathway to make 4-sulfanylcoumarin derivatives as synthetic point of view (**Figure 5.1**).

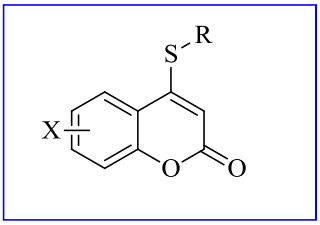
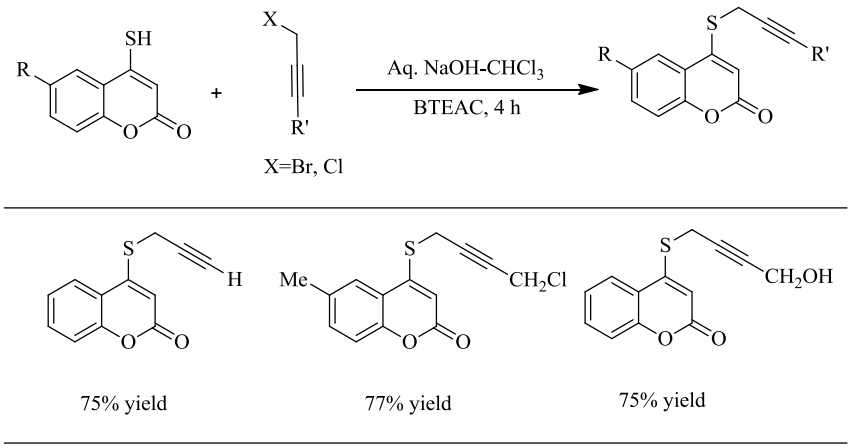


Figure 5.1 Representative structures of substituted 4- sulfanylcoumarins

Owing to the importance of the 4-sulfanylcoumarin derivatives, several reports have been revealed for their synthesis. Some of the important literature reports have been summarized below in the review **section 5.2**.

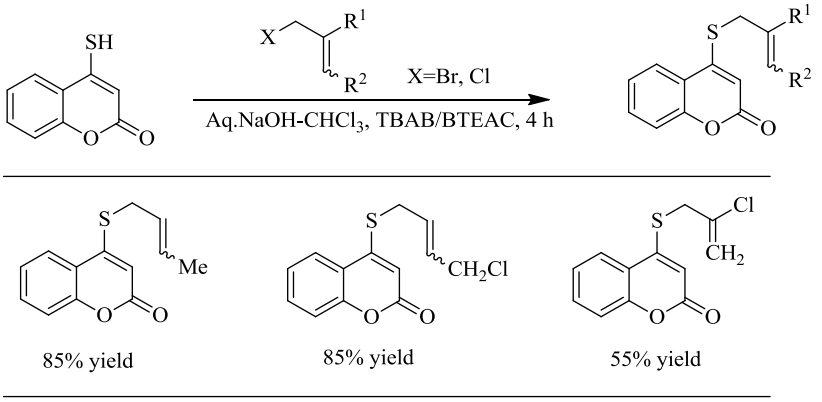
5.2 Review work

In 2002, Majumdar *et al.* reported the synthesis of 4-propargylthiocoumarins by performing the reaction in a two-phase mixture of propargyl halides, chloroform and 1% aqueous sodium hydroxide with substituted 4-mercaptocoumarin in the presence of benzyltriethylammonium chloride (BTEAC) as phase transfer catalyst at room temperature after 4 h in good yields (75-77%) (**Scheme 5.1**).[5]



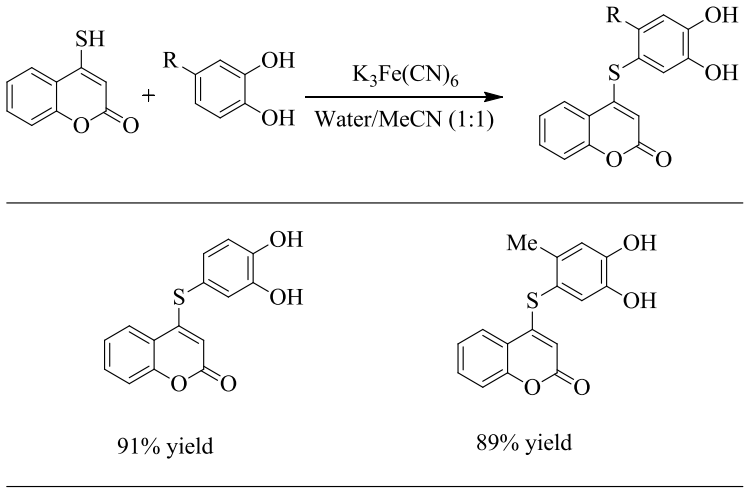
Scheme 5.1 Base catalyzed synthesis of S-alkylated coumarins

In 2004, Majumdar *et al.* further investigated the nucleophilic reaction between 4-mercaptocoumarin and several allylic halides in chloroform-aqueous sodium hydroxide (1%) solution at room temperature catalyzed by tetrabutyl-ammoniumbromide (TBAB) or benzyltriethyl-ammoniumchloride (BTEAC) for 4 h to give 4-*S*-allylic-substituted coumarins in mediocre to good yields (55-85%) (**Scheme 5.2**).[6]



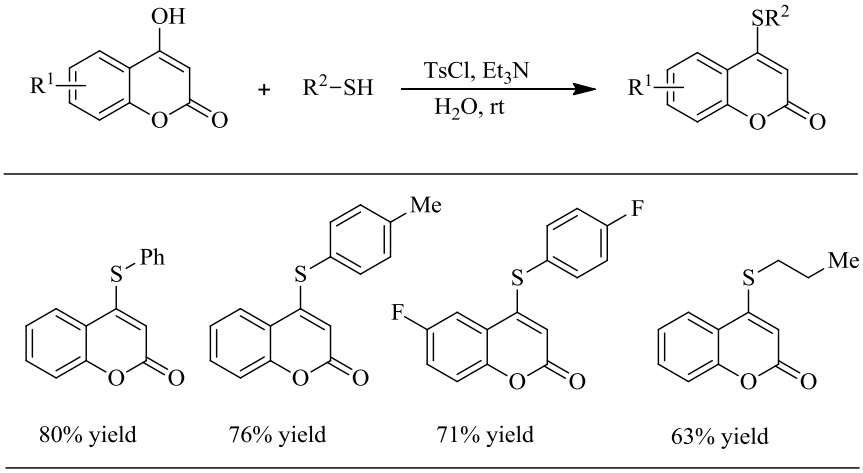
Scheme 5.2 Phase transfer mediated synthesis of 4-S-alkylated coumarins

A high yielding one-pot method for the synthesis of 4-arylthiocoumarins *via* a Michael reaction of 4-mercaptocoumarin as a nucleophile with in situ generated *o*-quinones from catechols by using $K_3Fe(CN)_6$ as a oxidizing agent in water/acetonitrile solution was established by Nematollahi *et al.* (**Scheme 5.3**).[7]



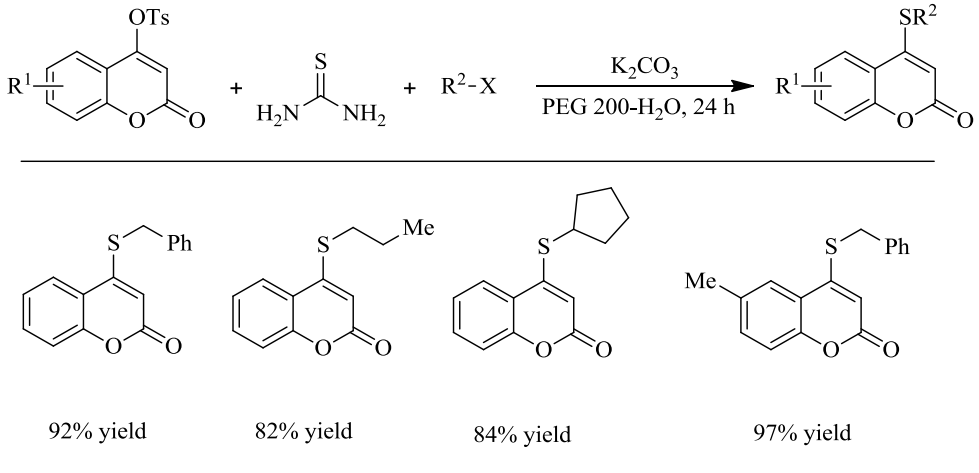
Scheme 5.3 Electrochemical synthesis of 4-arylthiocoumarins

Peng and his coworkers[8] also developed a green approach to form 4-sufanylcoumarins in good yields (71-80%) from several 4-hydroxycoumarins *via* a tosylation reaction using $TsCl/Et_3N$, followed by thiolation reaction using several aryl/alkylthiols (**Scheme 5.4**).



Scheme 5.4 Sulfanylation of 4-hydroxycoumarins with thiols in water

In 2013, Yin and his coworkers[9] disclosed an alternative environmental benign method for the synthesis of 4-alkylthiocoumarins (82-97% yields) by involving the three-component reaction between 4-tosylcoumarin, thiourea and alkylhalides performed in polyethylene glycol 200-water mixture at room temperature in the presence of K_2CO_3 (**Scheme 5.5**).



Scheme 5.5 Synthesis of 4-sulfanylcoumarins in polyethylene glycol-water

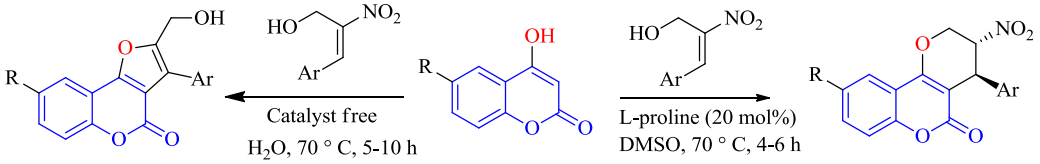
Conclusion

The above review concluded that only few synthetic methods have been developed for the preparations of 4-sulfanylcoumarins with moderate to high yields under different conditions. Some of the reported protocols involve toxic reagents and tedious procedures which are not much appreciable from synthetic points of view.

Even with these noticeable progresses, the synthesis of substituted thiocoumarins having S-atom at C-4 position has been less explored[10] despite its potential application in medicinal chemistry.[11] Moreover, the nucleophilic substitution reaction between 4-mercaptocoumarin and α, β-disubstituted nitroolefins as electrophiles has not been studied in the literature. Therefore, it is necessary to develop a simple and convenient method for the preparation of 4-sufanylcoumarins involving α, β-difunctionalized nitroolefins as acceptors under catalyst-free conditions.

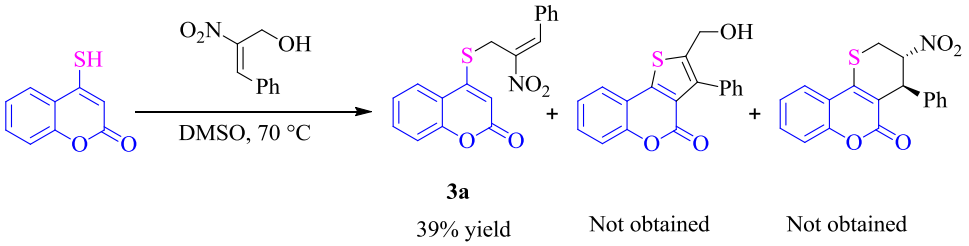
5.3 Present work

A facile and catalyst free approach for the synthesis of 4-sulfanyl coumarin derivatives is a challenging task in the field of synthetic organic chemistry because of several 4-sulfanyl coumarin derivatives are part of some important biologically attractive compounds. In our previous work, we established one-pot method for the construction of furo/pyrano[3,2-*c*]chromenes in water and DMSO medium respectively involving 4-hydroxycoumarin and (*E*)-3-aryl-2-nitroprop-2-enols as starting materials as described in chapter 4 (**Scheme 5.6**).[12]



Scheme 5.6 Synthesis of furo/pyrano[3,2-*c*]chromenes in water and DMSO medium respectively

We envisaged that replacing 4-hydroxycoumarin by 4-mercaptocoumarin as a nucleophile may react with nitroallylic alcohol in a similar fashion. To check the hypothesis, we performed the reaction of freshly prepared 4-mercaptocoumarin with (*E*)-3-phenyl-2-nitroprop-2-enol under heating conditions in DMSO for 5 h.



Scheme 5.7 Synthesis of 4-sulfanylcoumarin

Surprisingly, we isolated only 4-sufanylcoumarin (**3aa**) in mediocre yield instead of thiocoumestan/thiopyranocoumarin adducts as shown in **Scheme 5.7**. Herein we wish to report a two-step metal-free synthesis of 4-sulfanylcoumarins by reacting 4-mercaptocoumarin with (*E*)-3-aryl/hetero-aryl-substituted-2-nitroprop-2-enols under heating conditions.

5.4 Results and Discussion

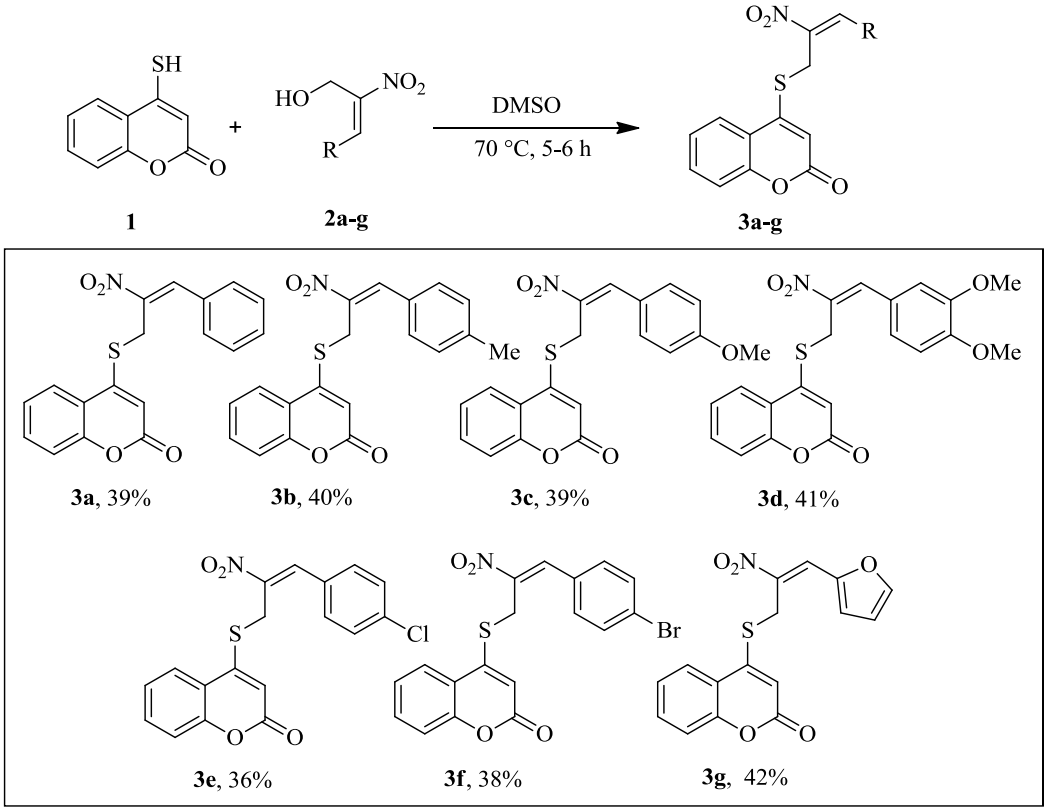
5.4.1 Synthesis of (*E*)-3-aryl-substituted-2-nitropropo-2-enols (3a-3g)

We performed the reaction between freshly prepared 4-mercaptocoumarin (**1**, 0.3 mmol) and (*E*)-3-phenyl-2-nitroprop-2-enol (**2a**, 0.2 mmol) in dry DMSO (at 70 °C) for 5 h. Surprisingly, we got 4-sufanylcoumarin **3a** in a mediocre yield (39%). The product **3a** was further characterized by various spectroscopic techniques (^{1}H NMR, ^{13}C NMR, FT-IR and HRMS). The ^{1}H NMR shows the appearance of characteristic singlets at δ 8.03 corresponds to alkenyl hydrogen adjacent to nitro group and singlet at δ 4.44 characteristic of methylene (-CH_2-) peak. Further, ^{13}C NMR shows appearance of three peaks in the region of δ 158.7, 154.4 and 152.1 corresponds to carbons attached with oxygen and sulfur atoms. Also, only one peak at δ 28.4 shows the presence of methylene carbon in the aliphatic region. The HRMS shows the presence of molecular ion peak $[M+H]^+$ at 340.0637 which corresponds to the desired product.

The above promising result promoted us to investigate scope of this nucleophilic substitution reaction in more details. In this regard, several β-aryl-substituted nitroallylic alcohols possessing electron donating (Me, MeO) and electron withdrawing (Cl, Br) substituents on aryl rings have been reacted with 4-mercaptocoumarin under catalyst-free conditions at 70 °C in DMSO. All the reactions led to corresponding (*E*)-4-[(2-nitro-3-arylallyl)thio]-2*H*-chromen-2-ones in similar yields (34-41%, **3b-3f**).

Similarly, β-heteroaryl-substituted nitroallylic alcohol (**2g**) is found to be good substrate for this substitution reaction, resulting in 42% yield of desired product **3g** (**Table 5.1**).

Table 5.1 Scope of (*E*)-3-aryl-substituted-2-nitropropo-2-enols[a]



[a]All the reactions were performed using a 4-mercaptocoumarin (**1**, 0.3 mmol, freshly prepared) and nitroallylic alcohols (**2a-g**, 0.2 mmol) in dry DMSO (1 ml) at 70 °C for 5-6 h. Isolated yield (after column chromatography) was calculated with respect to nitroallylic alcohols.

Despite the yields of the reactions were mediocre, the present catalyst-free conditions are enough mild to retain several functionalities such as Me, OMe, Cl, Br, NO_2, furan, coumarin etc.

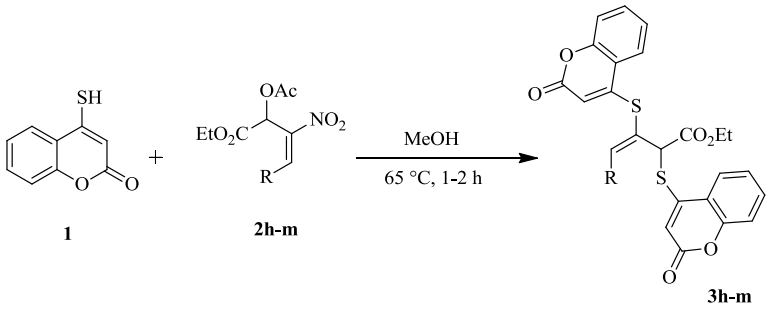
5.4.2 Synthesis of (*E*)-dithiocoumarinyl styrenes (3h-3m):

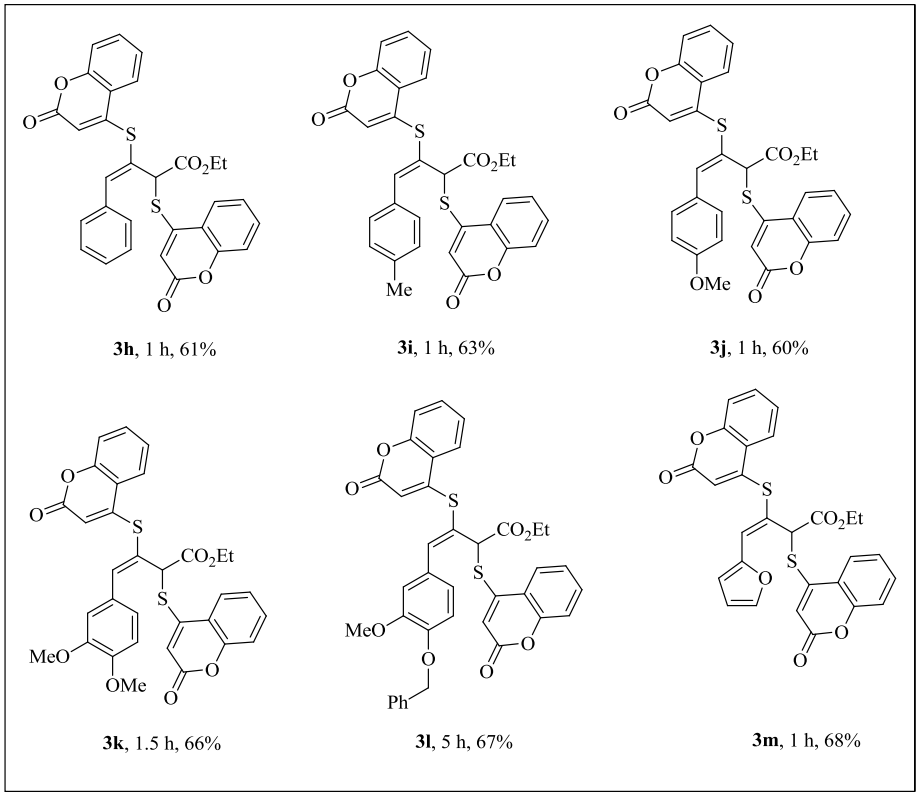
By further extension of this methodology, Morita-Baylis-Hillman acetate (**2h**) (well-known 1,3-bielectrophile)[13-17] derived from nitroolefin (**2a**) has been reacted with 4-mercaptocoumarin in MeOH at 65 °C.

Surprisingly, after 1 h, unexpected (*E*)-dithiocoumarinyl styrene derivative (**3h)** was obtained in pretty good yield (61%) with excellent stereoselectivity (*E:Z* = 100:0) under catalyst-free condition (**Table 5.2**). The product **3h** was further characterized by various spectroscopic techniques (^{1}H NMR, ^{13}C NMR, FT-IR and HRMS). ^{1}H NMR shows the appearance of characteristic singlets at δ 6.53, 5.69 and at 5.67 corresponds to benzylic hydrogen and hydrogens adjacent to carbonyl group in coumarin rings. Further, ^{13}C NMR shows appearance of seven peaks in the region of δ 151.0 to 166.6 corresponds to carbons attached with oxygen and sulfur atoms and carbonyl carbon of ester group. Also, only three peaks at δ 63.8, 51.8 and at 13.9 in ^{13}C NMR shows the presence of three carbons in the aliphatic region. The HRMS shows the presence of molecular ion peak $[M+Na]^+$ at 565.0746 which indicates the molecular weight of the desired product. In order to increase the yield of our desired product (**3h**), reactions were also carried out in toluene, THF and ethanol but yields of the products obtained were 55%, 48% and 56% respectively in the given solvents. It was also found that, in DMSO the desired product was not formed.

Using this methodology, several substituents such as Me, OMe and OBn on aryl-rings of MBH acetates (**2h-2l**) underwent reaction with two molecules of 4-mercaptocoumarin. Consequently, after 1-2 h, all the reactions produced a series of unexpected (*E*)-dithiocoumarinyl styrene derivatives (**3h-3l)** in pretty good yields (60-67%) with excellent stereoselectivity (*E:Z* = 100:0) under present conditions. Furthermore, hetero-aryl-substituted MBH acetates (**2m**) was witnessed to be suitable substrates for this type of substitution reaction and resulted in good yield (68%) of corresponding products **3m** after 1 h.

Table 5.2 Substrate scope of MBH acetates and nitroolefins[a]





[a]Unless otherwise noted, all the reactions were carried out with MBH acetates (**2h-2m**, 0.12 mmol) and 4-mercaptocoumarin (**1**, 0.36 mmol) in MeOH (2.0 ml) at 65 °C. Isolated yields after column chromatography.

All the products were characterized by their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and HRMS). The double bond geometry (*E*-configuration) was assigned by based on the single crystal X-ray diffraction data of compound **3j** (**Figure 5.3**).

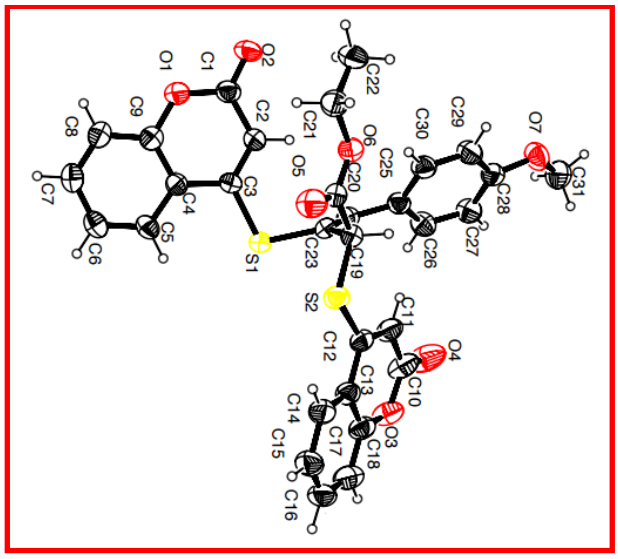
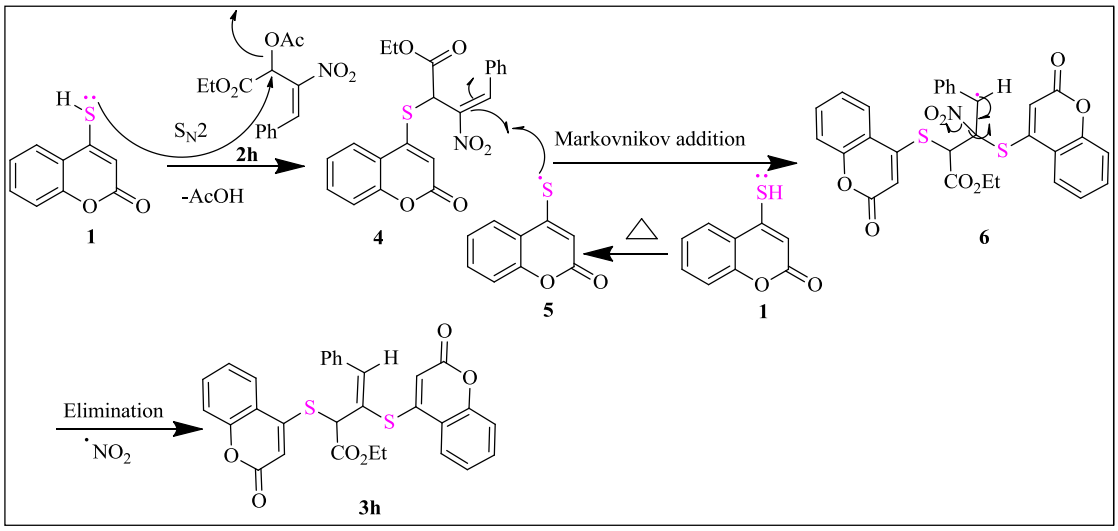


Figure 5.2 ORTEP diagram of 3j

5.4.3 Proposed mechanism for (*E*)-dithiocoumarinyl styrene synthesis:

The detailed mechanism of this reaction is not clear to us. However, a probable mechanism for the formation of compound **3h** is presented in **Scheme 5.8**. At first, the lone pair electrons on nucleophilic S-atom of 4-mercaptocoumarin attacks C-3 position of MBH acetate **2h** to form 4-thiocoumaryl nitrostyrene derivative **4.** On the other hand**,** the S-H bond of 4-mercaptocoumarin dissociate into 4-sufanylcoumarin radical **5** under thermal conditions[18-20] which undergoes addition at the α-position of nitroolefinic bond to form a more stable benzylic radical **6.** Finally, the product **3h** is formed *via* an elimination of $^{\cdot}NO_2$ radical. It should be noted that the reaction did not happen at all in the presence of a radical scavenger like TEMPO which indicates reaction may proceed through a thiyl radical pathway.



Scheme 5.8 Probable mechanism of substitution reaction

5.5 Conclusion

In the current chapter, we have established first catalyst-free nucleophilic substitution reaction of 4-mercaptocoumarin with a several (*E*)-3-aryl/hetero-aryl-substituted-2-nitroprop-2-enols/MBH acetates of nitroolefins in DMSO and MeOH medium respectively. This operationally simple method delivers a novel series of interesting functionalized mono and *bis*-4-sulfanylcoumarin derivatives in mediocre to good yields with excellent stereoselectivity.

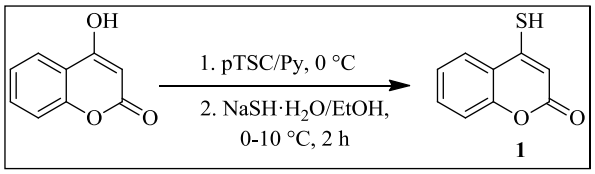
5.6 Experimental

General informations:

All reactions were carried out under air and monitored by TLC using Merck 60 F_{254} pre-coated silica gel plates (0.25 mm thickness) and the products were visualized by UV detection. Flash chromatography was

carried out with silica gel (200-300 mesh). FT-IR spectra were recorded on a Bruker Tensor-27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance (III) 400 MHz spectrometer. Data for ^{1}H NMR are reported as a chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constant *J* (Hz), integration, and assignment of data for ^{13}C are reported as a chemical shift. High resolutions mass spectral analyses (HRMS) were carried out using ESI-TOF-MS.

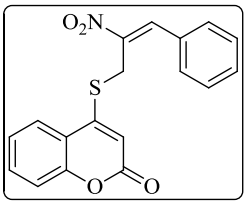
Synthesis of starting material (1): The tosyl derivative of 4-hydroxycoumarin was prepared by dissolving 4-hydroxycoumarin in pyridine, followed by the addition of *p*-toluenesulfonyl chloride with constant stirring at 0 °C temperature (**Scheme 5.9**). This tosyl derivative, on treatment with $NaSH{\cdot}H_2O$ in ethanol at 0-10 °C with vigorous stirring for 2 h furnished the 4-mercaptocoumarin (**1**).



Scheme 5.9 Synthesis of 4-mercaptocoumarin

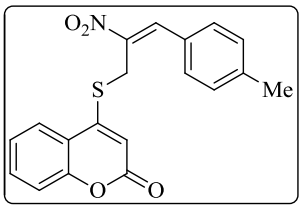
General procedure for the synthesis of (*E*)-4-[(2-nitro-3-arylallyl)thio]-2*H*-chromen-2-ones (3a-3g): The 4-mercaptocoumarin (**1,** 0.3 mmol, freshly prepared) and (*E*)-3-aryl-2-nitroprop-2-enol (**2a-g,** 0.2 mmol) in DMSO (1.0 ml) were heated at 70 °C for 5 h. Afterwards, the reaction mixture was extracted with ethyl acetate (3 × 10 ml), washed with brine and dried over Na_2SO_4. The combined organic solvents were evaporated by rotary evaporator under reduced pressure to leave the crude mass. Product was purified by column chromatography over silica-gel using EtOAc/hexane as an eluent and characterized by spectroscopic data (IR, ^{1}H and ^{13}C NMR, HRMS).

(*E*)-4-[(2-Nitro-3-phenylallyl)thio]-2*H*-chromen-2-one (3a): 39% yield;



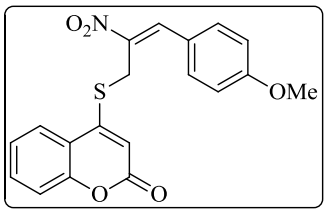
m.p. 154-156 °C; **IR** (KBr) ν 1715, 1606, 1595, 1551, 1524, 1486, 1446, 1419, 1349, 1319, 1267 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.39 (s, 1H), 7.71-7.72 (m, 1H), 7.51-7.59 (m, 6H), 7.29-7.36 (m, 2H), 6.07 (s, 1H), 4.44 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.7, 154.4, 152.1, 143.5, 138.9, 132.5, 131.6, 130.8, 130.0, 129.6, 124.3, 123.8, 117.6, 117.3, 108.1, 18.4; **HRMS**(ESI-TOF) m/z calculated for $C_{18}H_{13}O_4NS$ $[M+H]^+$: 340.0638, found 340.0637.

(*E*)-4-[(2-Nitro-3-(4-methylphenyl)allyl)thio]-2*H*-chromen-2-one (3b):



40% yield; **m.p.** 170-172 °C; **IR** (KBr) ν 1715, 1644, 1605, 1595, 1551, 1521, 1486, 1447, 1423, 1351, 1320, 1267 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.37 (s, 1H), 7.70-7.72 (m, 1H), 7.55-7.58 (m, 1H), 7.41-7.43 (m, 3H), 7.34-7.35 (m, 1H), 7.28-7.30 (m, 2H), 6.10 (s, 1H), 4.45 (s, 2H), 2.40 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.8, 154.7, 152.1, 142.6, 142.5, 139.2, 132.5, 130.4, 130.2, 127.9, 124.3, 123.9, 117.7, 117.3, 108.1, 28.7, 21.6; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{15}O_4NS$ $[M+Na]^+$: 376.0614, found 376.0618.

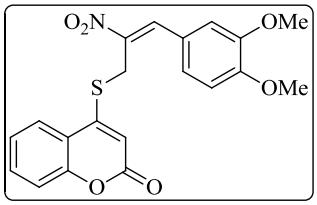
(*E*)-4-[(3-(4-Methoxyphenyl)-2-nitro-allyl)thio]-2*H*-chromen-2-one



(3c): 39% yield; **m.p.** 165-167 °C; **IR** (KBr) ν 1715, 1633, 1601, 1551, 1519, 1505, 1446, 1427, 1416, 1350, 1311 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.38 (s, 1H), 7.71-7.72 (m, 1H), 7.51-7.60 (m, 3H), 7.34-7.36 (m, 1H), 7.27-7.31 (m, 1H), 6.99-7.01 (m, 2H), 6.15 (s, 1H), 4.48 (s, 2H), 3.86 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.5, 158.8, 154.9, 152.1, 140.8, 139.1, 132.7, 132.6, 124.3, 123.9, 123.0, 117.7, 117.3, 115.3, 107.9, 55.6,

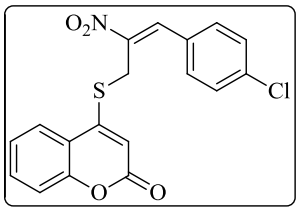
28.9; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{15}O_5NS$ $[M+Na]^+$: 392.0563, found 392.0567.

(*E*)-4-[(3-(3,4-Dimethoxyphenyl)-2-nitro-allyl)thio]-2*H*-chromen-2-one



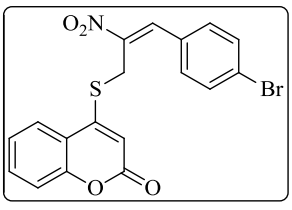
(3d): 41% yield; **m.p.** 168-169 °C; **IR** (KBr) ν 1724,1634, 1595, 1554, 1524, 1508, 1488, 1463, 1448, 1438, 1427, 1351 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.36 (s, 1H), 7.56-7.71 (m, 2H), 7.18-7.35 (m, 3H), 6.94-7.07 (m, 2H), 6.16 (s, 1H), 4.50 (s, 2H), 3.92 (s, 3H), 3.79 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.7, 154.9, 152.2, 152.1, 149.6, 140.9, 139.4, 132.6, 124.9, 124.3, 123.8, 123.3, 117.6, 117.3, 112.8, 111.7, 108.1, 56.1, 55.8, 29.2; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{17}O_6NS$ $[M+Na]^+$: 422.0699, found 422.0699.

(*E*)-4-[(3-(4-Chlorophenyl)-2-nitro-allyl)thio]-2*H*-chromen-2-one (3e):



36% yield; **m.p.** 166-168 °C; **IR** (KBr) ν 1713, 1638, 1604, 1591, 1551, 1520, 1490, 1448, 1425, 1351, 1317, 1267 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.34 (s, 1H), 7.69-7.71 (m, 1H), 7.56-7.60 (m, 1H), 7.46-7.47 (m, 4H), 7.29-7.37 (m, 2H), 6.11 (s, 1H), 4.41 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.7, 154.2, 152.2, 143.8, 138.0, 137.6, 132.7, 131.2, 130.0, 129.7, 129.2, 124.3, 123.8, 117.4, 108.4, 28.4; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{12}ClO_4NS$ $[M+Na]^+$: 396.0068, found 396.0074.

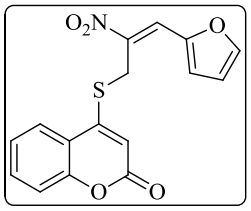
(*E*)-4-[(3-(4-Bromophenyl)-2-nitro-allyl)thio]-2*H*-chromen-2-one (3f):



38% yield; **m.p.** 168-170 °C; **IR** (KBr) ν 1713, 1638, 1604, 1594, 1583, 1551, 1520, 1487, 1448, 1400, 1351, 1321, 1268 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.31 (s, 1H), 7.68-7.70 (m, 1H), 7.62-7.64 (m, 2H), 7.54-7.58 (m, 1H), 7.34-7.39 (m, 3H), 7.29-7.31 (m,

1H), 6.09 (s, 1H), 4.39 (s, 2H); **^{13}C NMR (100 MHz, DMSO-d_6)** δ 157.8, 153.7, 151.6, 144.4, 137.5, 132.9, 132.5, 131.3, 130.8, 130.0, 129.2, 124.7, 123.9, 117.0, 108.7, 28.1; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{12}BrO_4NS$ $[M+K]^+$: 455.9302, found 455.9306.

(*E*)-4-[(3-Furyl)-2-nitro-allyl)thio]-2*H*-chromen-2-one (3g): 42% yield;

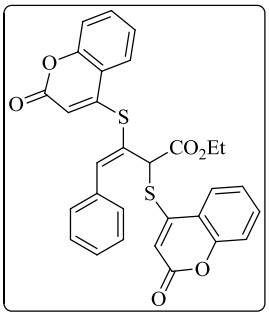


m.p. 166-168 °C; **IR** (KBr) ν 1720, 1638, 1595, 1551, 1518, 1506, 1466, 1445, 1414, 1386, 1348, 1307, 1279 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 (s, 1H), 7.67-7.71 (m, 2H), 7.52-7.33 (m, 1H), 7.31-7.33 (m, 1H), 7.24-7.27 (m, 1H), 7.03 (s, 1H), 6.65 (s, 1H), 6.36 (s, 1H), 4.75 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.1, 155.2, 152.1, 148.4, 146.4, 140.0, 132.4, 124.2, 123.9, 123.6, 123.3, 117.9, 117.2, 113.8, 108.3, 28.3; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}O_4NS$ $[M+Na]^+$: 352.0250, found 352.0256.

General procedure for the synthesis of (*E*)-dithiocoumarinyl styrene derivatives (3h-3m):

To a stirred solution of 4-mercaptocoumarin (**1,** 0.36 mmol) in MeOH (2.0 ml) was added in MBH acetate of nitroolefin (**2h-2m,** 0.12 mmol) at 65 °C for 1-2 h (monitored by TLC). Then the reaction mixture was concentrated under reduced pressure to leave the residual mass which was extracted with ethyl acetate, washed with water and dried over Na_2SO_4. The evaporation of the organic solvent left the crude product which was further purified by column chromatography over-silica gel using a mixture of solvent EtOAc/hexane to furnish the pure product. All the products were characterized by their corresponding spectroscopic data (IR, ^{1}H and ^{13}C NMR, HRMS).

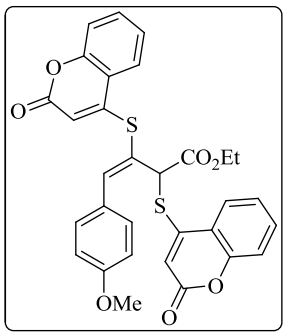
(*E*)-Ethyl-2,3-bis[(2-oxo-2*H*-chromen-4-yl)thio]-4-phenylbut-3-enoate



(3h): 61% yield; **m.p.** 151-153 °C; **IR** (KBr) ν 1717, 1594, 1551, 1484, 1446, 1339, 1318, 1263, 1182 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81-7.83 (m, 1H), 7.71-7.73 (m, 1H), 7.49-7.7.60 (m, 8H), 7.27-7.35 (m, 3H), 7.21-7.23 (m, 1H), 6.53 (s, 1H), 5.69 (s, 1H), 5.67 (s, 1H), 4.21-4.33 (m, 2H), 1.34 (t, *J* = 6.76 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.6, 159.2, 158.3, 155.9, 152.3, 152.2, 151.8, 151.0, 133.7, 132.6, 132.5, 130.3, 129.5, 128.6, 124.3, 124.2, 124.0, 123.9, 122.8, 117.7, 117.6, 117.3, 117.2, 110.6, 108.7, 63.8, 51.8, 13.9; **HRMS** (ESI-TOF) m/z calculated for $C_{30}H_{22}O_6S_2$ $[M+Na]^+$: 565.0750, found 565.0746.

(*E*)-Ethyl-2,3-bis[(2-oxo-2*H*-chromen-4-yl)thio]-4-(4-methylphenyl) but-3-enoate (3i): 63% yield; **m.p.** 155-157 °C; **IR** (KBr) ν 1716, 1603, 1594, 1552, 1485, 1446, 1340, 1319, 1266, 1250, 1184 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.51-7.60 (m, 3H), 7.42-7.44 (m, 2H), 7.28-7.36 (m, 4H), 7.21-7.25 (m, 1H), 6.52 (s, 1H), 5.74 (s, 1H), 5.70 (s, 1H), 4.20-4.34 (m, 2H), 2.42 (s, 3H), 1.34 (t, *J* = 7.04 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.7, 159.2, 158.4, 156.1, 152.3, 152.2, 152.0, 151.4, 140.7, 132.5, 132.4, 130.9, 130.2, 128.6, 124.2, 124.2, 124.1, 124.0, 121.5, 117.7, 117.6, 117.3, 117.2, 110.6, 108.5, 63.7, 51.8, 21.5, 13.9; **HRMS** (ESI-TOF) m/z calculated for $C_{31}H_{24}O_6S_2$ $[M+Na]^+$: 579.0907, found 579.0905.

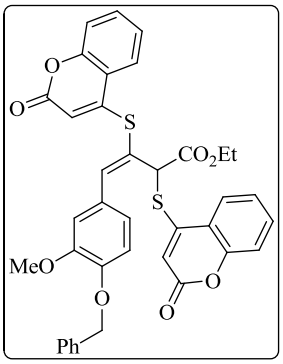
(*E*)-Ethyl-4-(4-methoxyphenyl)-2,3-bis[(2-oxo-2*H*-chromen-4-yl)thio]



but-3-enoate (3j): 60% yield; **m.p.** 175-176 °C; **IR** (KBr) ν 1731, 1705, 1604, 1594, 1551, 1509, 1447, 1339, 1320, 1250, 1181 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80-7.82 (m, 1H), 7.72-7.73 (m, 1H), 7.47-7.59 (m, 5H), 7.21-7.34 (m, 3H), 7.00-7.02 (m, 2H), 6.49 (s, 1H), 5.72 (s, 1H), 5.70 (s, 1H), 4.20-4.33 (m, 2H), 3.87 (s, 3H), 1.33 (t, *J* = 7.04 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.8, 161.1, 159.3, 158.4, 156.3, 152.3, 152.2, 152.1, 151.3, 132.5, 132.4, 130.5, 126.2, 124.2, 124.0, 123.9, 119.8, 117.7, 117.6, 117.3, 117.2, 114.9, 110.3, 108.3, 63.7, 55.4, 51.9, 13.9; **HRMS** (ESI-TOF) m/z calculated for $C_{31}H_{24}O_7S_2$ $[M+Na]^+$:595.0856, found 595.0852.

(*E*)-Ethyl-4-(3,4-dimethoxyphenyl)-2,3-bis[(2-oxo-2*H*-chromen-4-yl) thio]but-3-enoate (3k): 66% yield; **m.p.** 162-164 °C; **IR** (KBr) ν 1720, 1704, 1603, 1594, 1550, 1514, 1447, 1340, 1300, 1263, 1182 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80-7.82 (m, 1H), 7.72-7.74 (m, 1H), 7.49-7.59 (m, 3H), 7.26-7.34 (m, 3H), 7.19-7.23 (m, 2H), 7.07 (s, 1H), 6.95-6.97 (m, 1H), 6.50 (s, 1H), 5.75 (s, 1H), 5.72 (s, 1H), 4.20-4.33 (m, 2H), 3.95 (s, 6H), 1.32 (t, *J* = 7.28 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.7, 159.3, 158.4, 156.3, 152.3, 152.2, 151.9, 151.5, 150.8, 149.5, 132.5, 132.4, 126.4, 124.2, 124.1, 124.0, 123.9, 122.1, 120.3, 117.7, 117.6, 117.3, 117.2, 111.6, 111.5, 110.8, 108.4, 63.8, 56.0, 52.1, 13.9; **HRMS** (ESI-TOF) m/z calculated for $C_{32}H_{26}O_8S_2$ $[M+Na]^+$: 625.0961, found 625.0985.

(*E*)-Ethyl-4-(4-(benzyloxy)-3-methoxyphenyl)-2,3-bis[(2-oxo-2*H*-chromen-4-yl)thio]but-3-enoate (**3l**): 67% yield; **m.p.** 177-179 °C; **IR** (KBr) ν 1718, 1603, 1594, 1552, 1510, 1448, 1415, 1339, 1318, 1263, 1183 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80-7.82 (m, 1H), 7.72-7.74 (m, 1H), 7.46-7.59 (m, 5H), 7.27-7.41 (m, 6H), 7.21-7.26 (m, 1H), 7.12-7.14 (m, 1H), 7.08 (s, 1H), 6.96-6.99 (m, 1H), 6.50 (s, 1H), 5.74 (s, 1H), 5.73 (s, 1H), 5.23 (s, 2H), 4.19-4.33 (m, 2H), 3.96 (s, 3H), 1.32 (t, *J* = 7.00 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.7, 159.2, 158.4, 156.3, 152.3, 152.2, 151.9, 151.4, 150.1, 149.9, 136.4, 132.5, 132.4, 128.6, 128.0, 127.3, 126.8, 124.2, 124.2, 124.0, 123.9, 121.9, 120.4, 117.7, 117.6, 117.3, 117.2, 113.9, 112.1, 110.7, 108.4, 70.9, 63.8, 56.1, 52.1, 13.9; **HRMS** (ESI-TOF) m/z calculated for $C_{38}H_{30}O_8S_2$ $[M+Na]^+$: 701.1274, found 701.1264.



(*E*)-Ethyl-4-(furan-2-yl)-2,3-bis[(2-oxo-2*H*-chromen-4-yl)thio]but-3-enoate (**3m**): 68% yield; **m.p.** 166-167 °C; **IR** (KBr) ν 1718, 1603, 1595, 1551, 1483, 1459, 1447, 1341, 1318, 1264, 1183 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78-7.80 (m, 1H), 7.72-7.74 (m, 1H), 7.51-7.63 (m, 3H), 7.22-7.37 (m, 4H), 7.04 (s, 1H), 6.70-6.71 (m, 1H), 6.57 (s, 1H), 6.46 (s, 1H), 6.34 (s, 1H), 6.28 (s, 1H), 4.17-4.33 (m, 2H), 1.27 (t, *J* = 7.00 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.1, 159.3, 158.9, 156.0, 153.2, 152.6, 152.3, 152.2, 149.1, 145.7, 135.4, 132.5, 132.4, 124.3, 124.2, 124.1, 123.9, 117.9, 117.8, 117.6, 117.2, 117.0, 112.6, 110.1, 109.0, 63.4, 52.4, 13.9; **HRMS** (ESI-TOF) m/z calculated for $C_{28}H_{20}O_7S_2$ $[M+Na]^+$: 555.0543, found 555.0547.

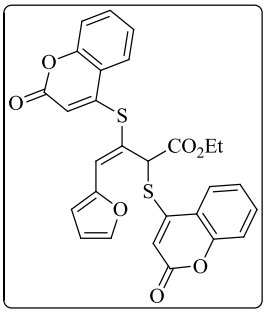


Table 5.3 Crystal data for compound 3j.

Compound	Compound **3j**
Empirical formula	$C_{62}H_{48}S_4O_{14}$
Molecular weight	1144.23
Temperature	293(2) K
Wavelength (Å)	1.54184A
Crystal system, space group	monoclinic, P 21/c
a (Å)	a = 14.6840(4)
b (Å)	b = 23.9808(10)
c (Å)	c = 15.5079(6)
α (^{o})	alpha = 90
β (^{o})	beta = 90.972(3)
γ (^{o})	gamma = 90
Volume ($Å^3$)	5460.1(3)
Z, Calculated density (mg/m^3)	4,1.392
Absorption coefficient (mm^{-1})	2.179
F(000)	2380
Crystal size (mm)	0.360 x 0.320 x 0.280
θ range (deg)	3.010 to 71.521
Limiting indices	-18<=h<=12,-27<=k<=29,-19<=l<=18
Reflections collected / unique	38905 / 10505 [R(int) = 0.0731]
Completeness to θ = 67.684	100.0 %
Max. and min. transmission	1.00000 and 0.56377
Data / restraints / parameters	10505 / 9 / 726
Goodness-of-fit on F^2	1.22
Final R indices [I>2sigma(I)]	R1 = 0.1189, wR2 = 0.3613
R indices (all data)	R1 = 0.1544, wR2 = 0.3980
Extinction coefficient	0.0006(2)
Largest diff. peak and hole ($e.A^{-3)}$	0.789 and -0.530

5.7 Copies of ^{1}H and ^{13}C NMR spectra of final compounds

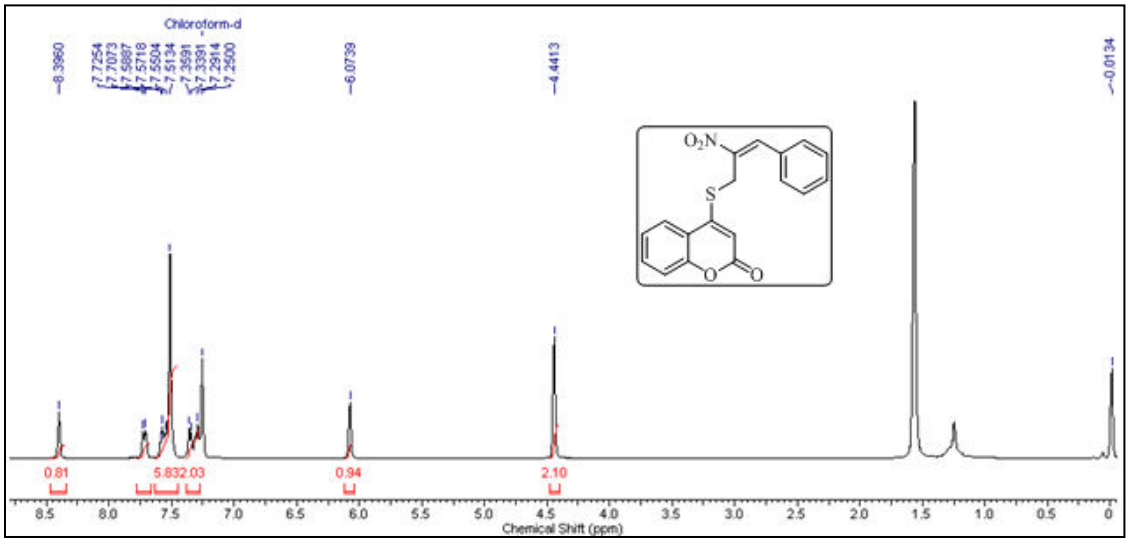


Figure 5.3 400 MHz ^{1}H NMR spectrum of **3a** in $CDCl_3$

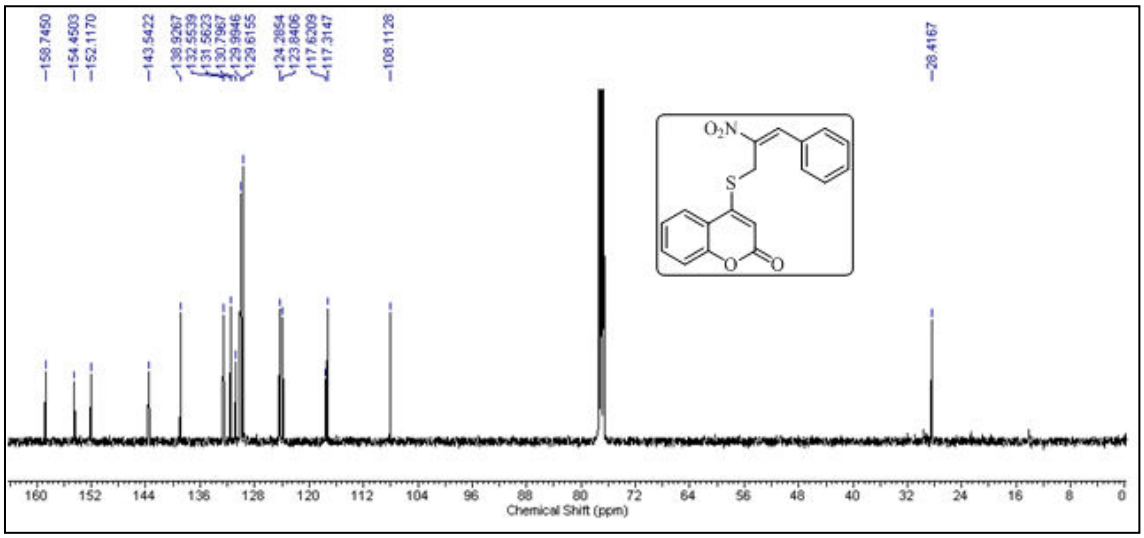


Figure 5.4 100 MHz ^{13}C NMR spectrum of **3a** in $CDCl_3$

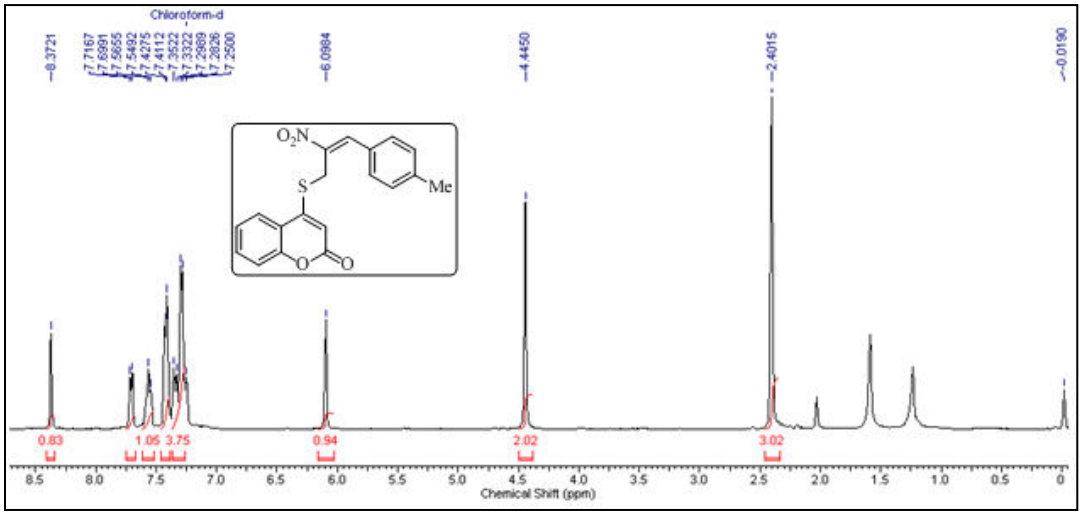


Figure 5.5 400 MHz ^{1}H NMR spectrum of **3b** in $CDCl_3$

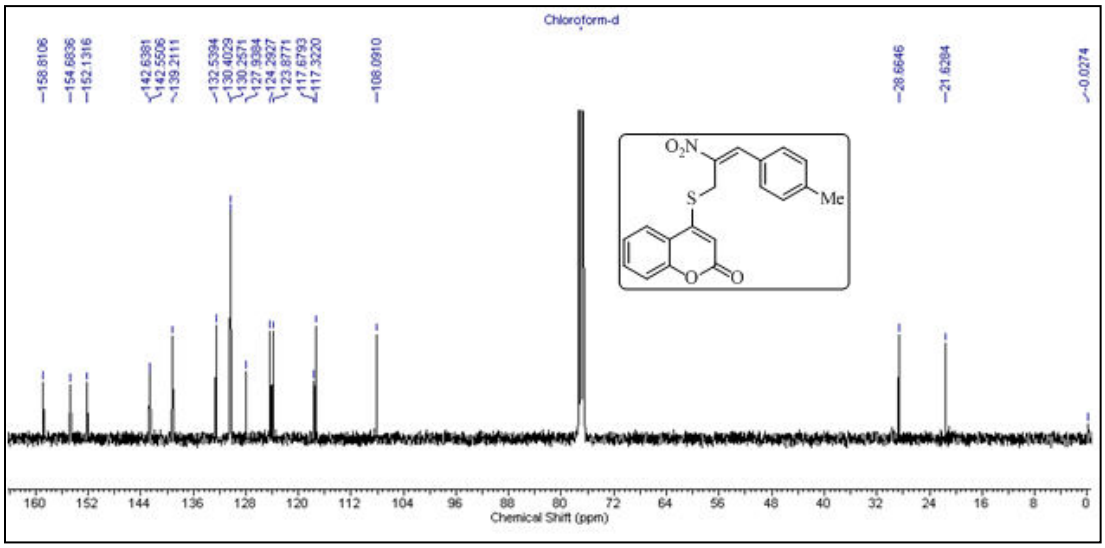


Figure 5.6 100 MHz ^{13}C NMR spectrum of **3b** in $CDCl_3$

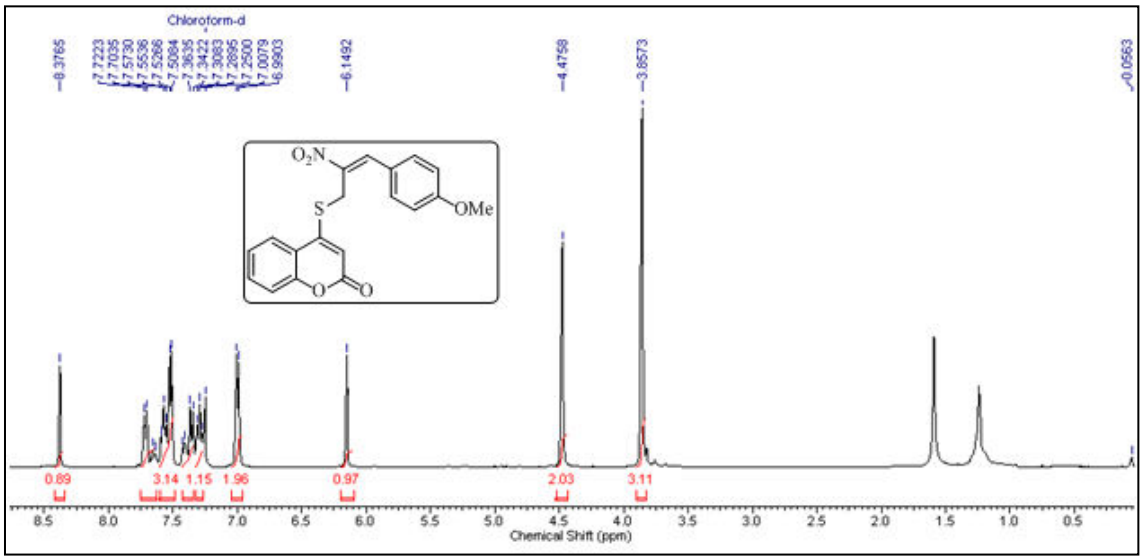


Figure 5.7 400 MHz ^{1}H NMR spectrum of **3c** in $CDCl_3$

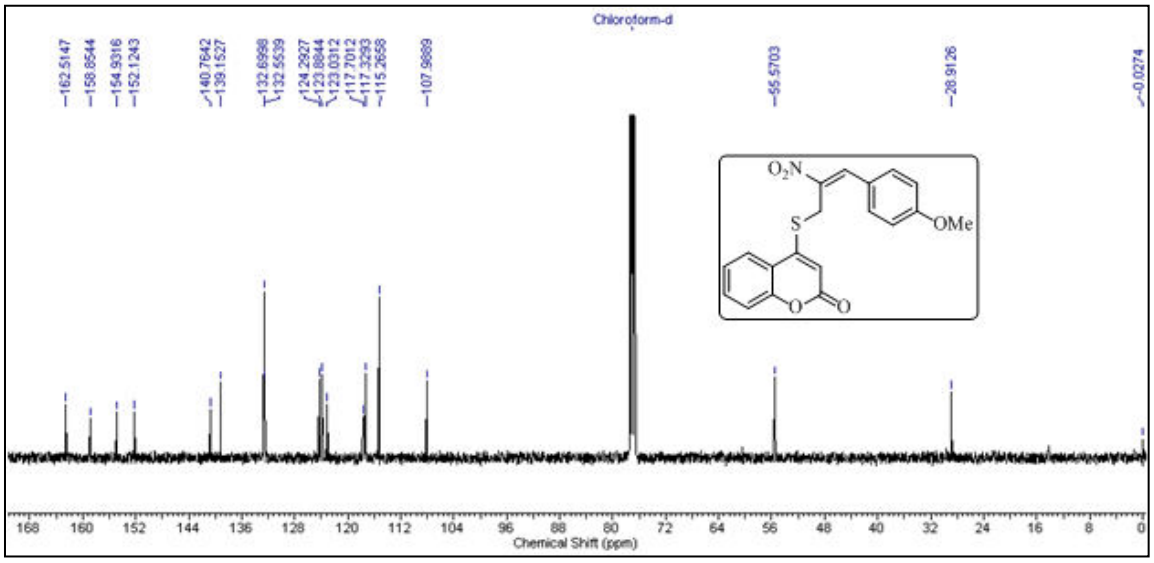


Figure 5.8 100 MHz ^{13}C NMR spectrum of **3c** in $CDCl_3$

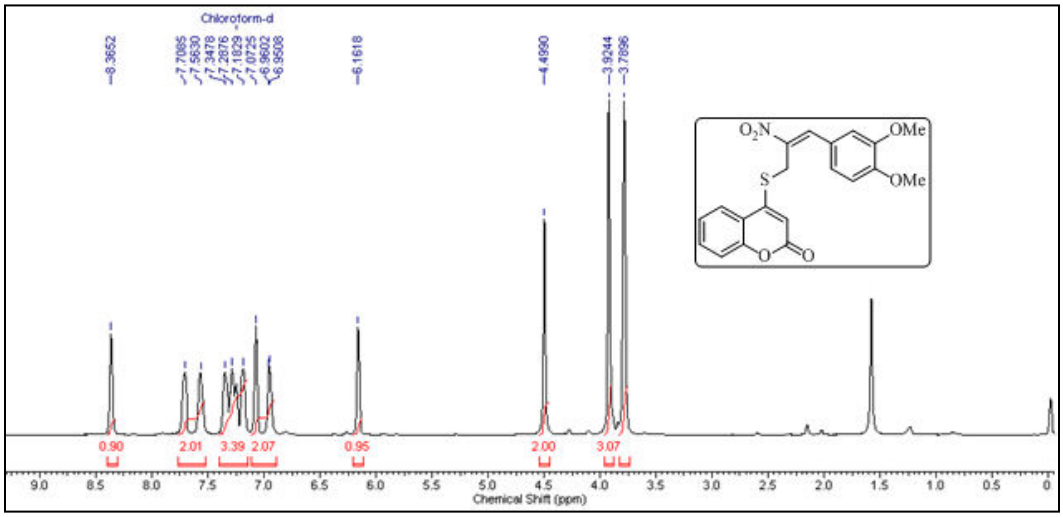


Figure 5.9 400 MHz ^{1}H NMR spectrum of **3d** in $CDCl_3$

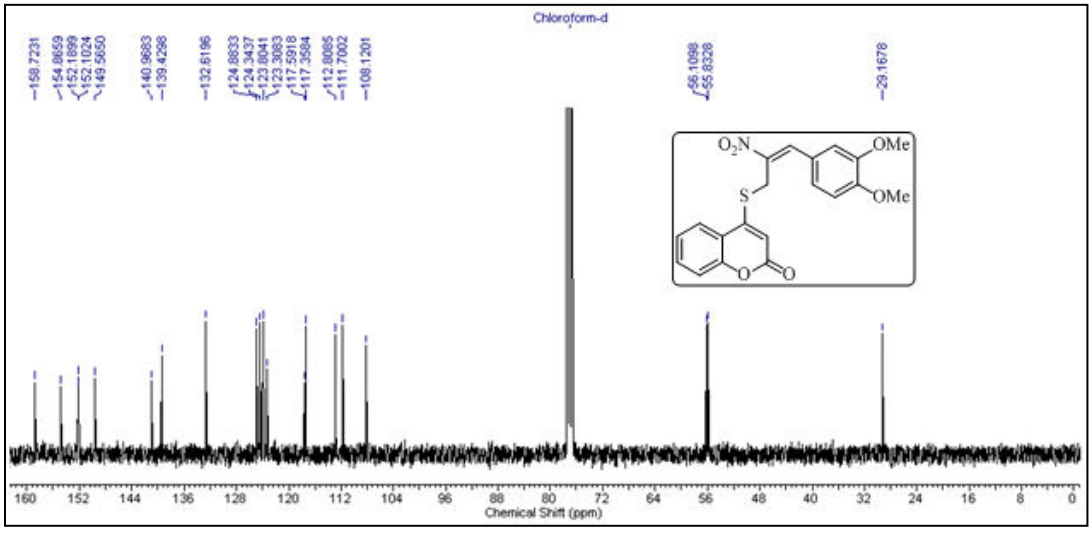


Figure 5.10 100 MHz ^{13}C NMR spectrum of **3d** in $CDCl_3$

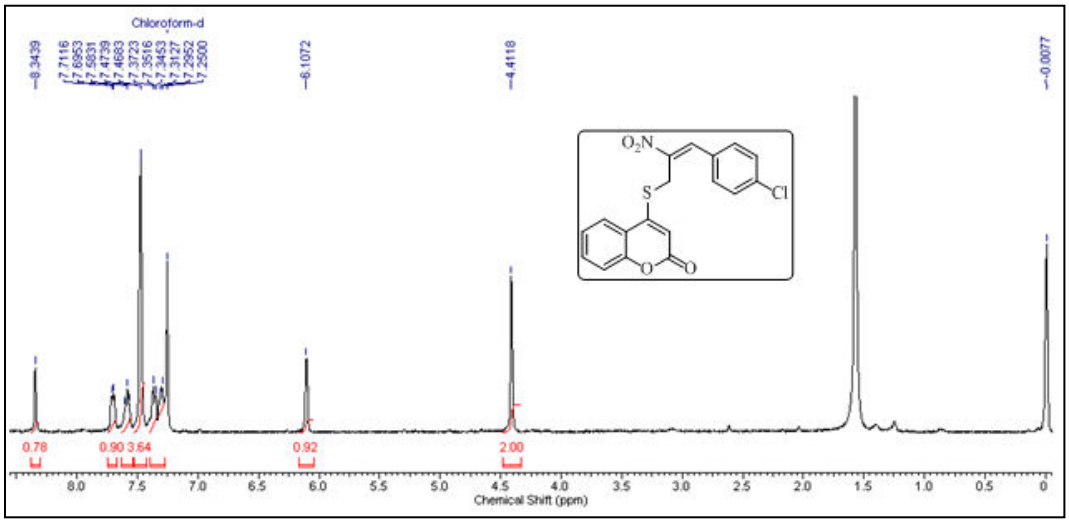


Figure 5.11 400 MHz ^{1}H NMR spectrum of **3e** in $CDCl_3$

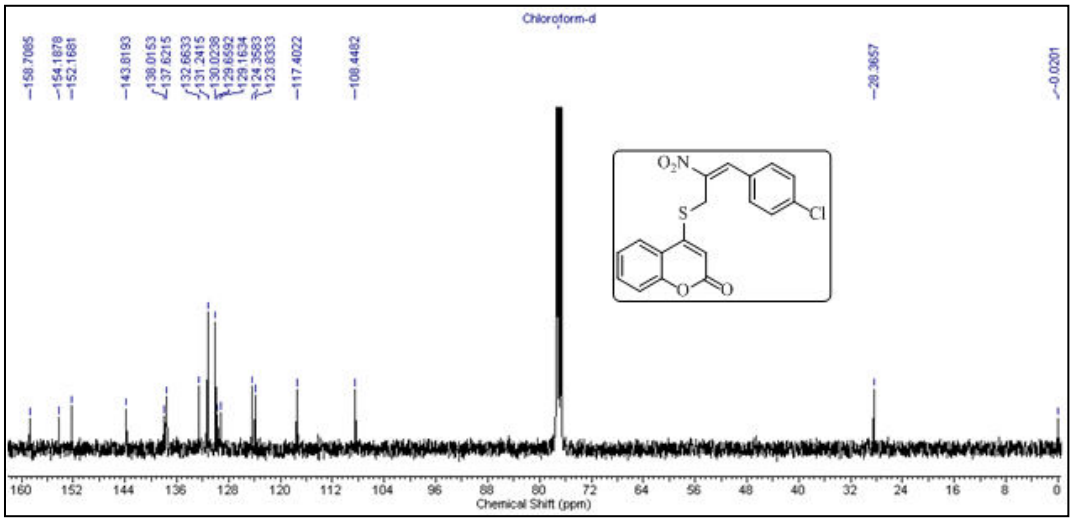


Figure 5.12 100 MHz ^{13}C NMR spectrum of **3e** in $CDCl_3$

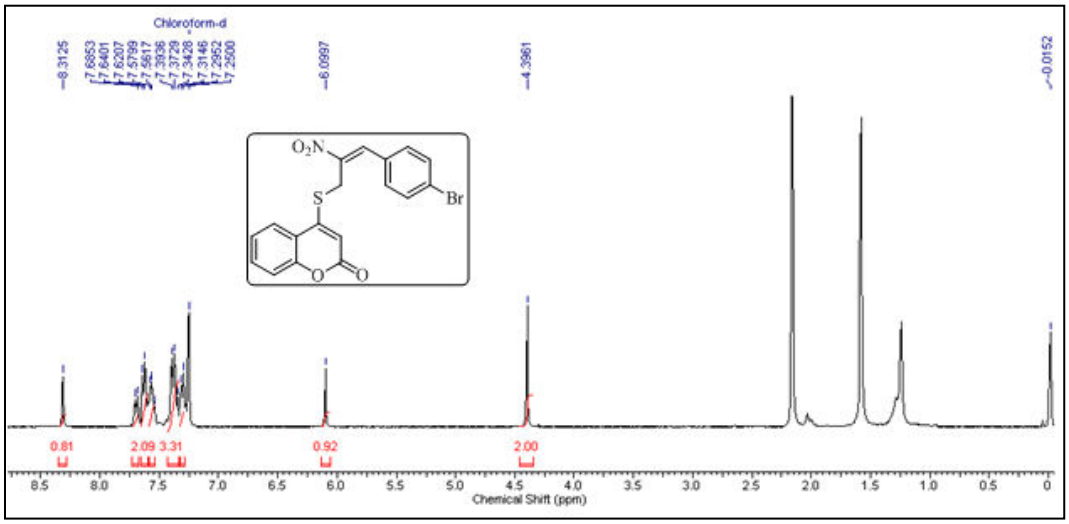


Figure 5.13 400 MHz ^{1}H NMR spectrum of **3f** in $CDCl_3$

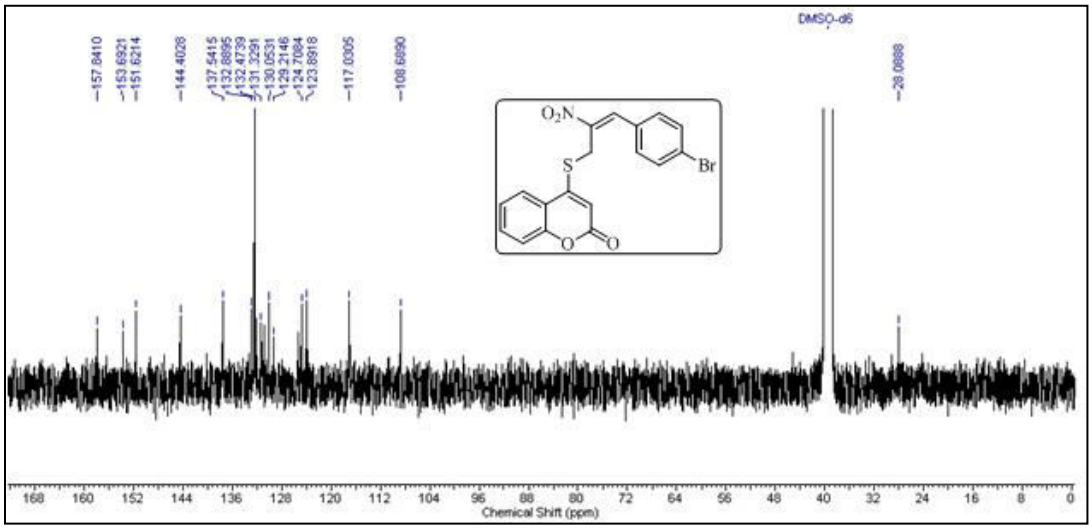


Figure 5.14 100 MHz ^{13}C NMR spectrum of **3f** in DMSO-d_6

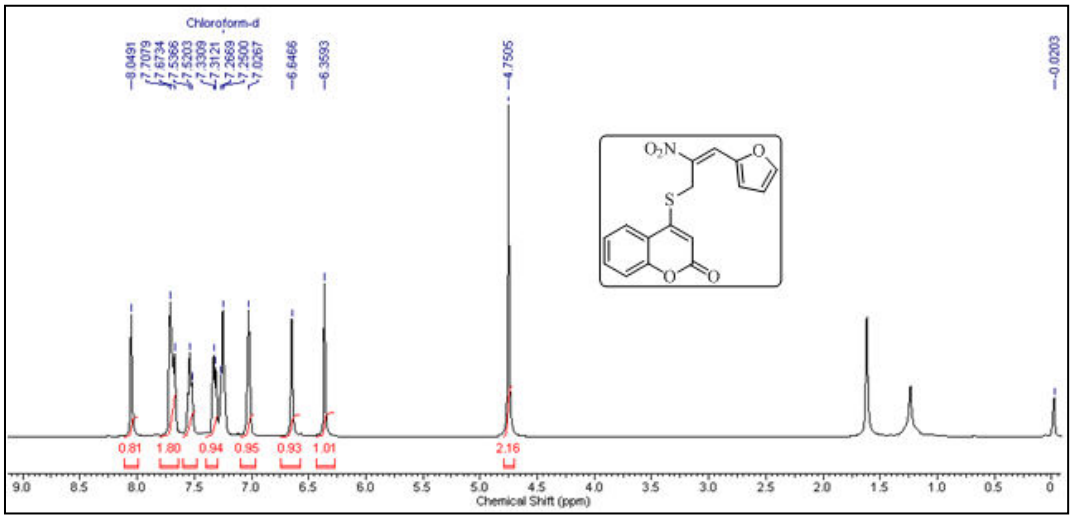


Figure 5.15 400 MHz ^{1}H NMR spectrum of **3g** in $CDCl_3$

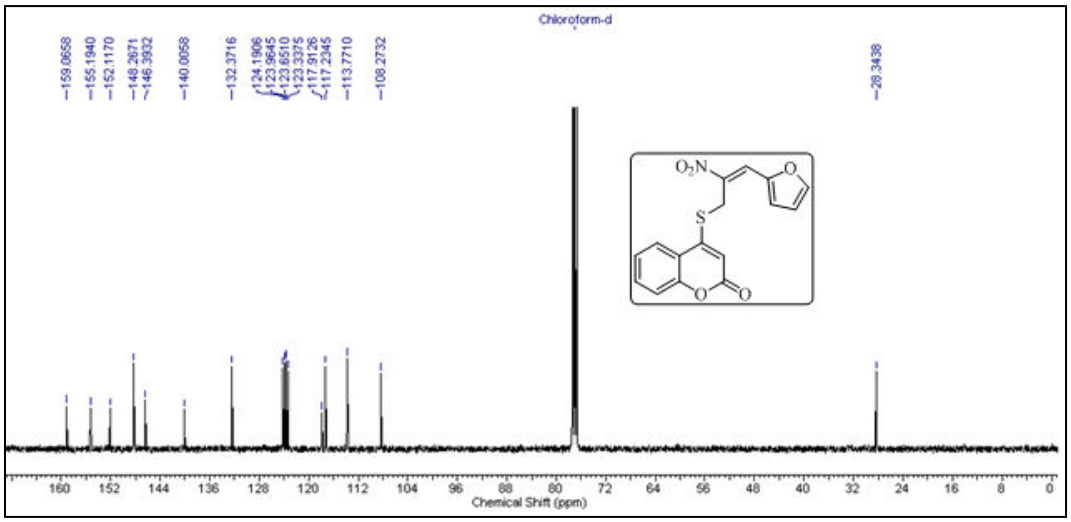


Figure 5.16 100 MHz ^{13}C NMR spectrum of **3g** in $CDCl_3$

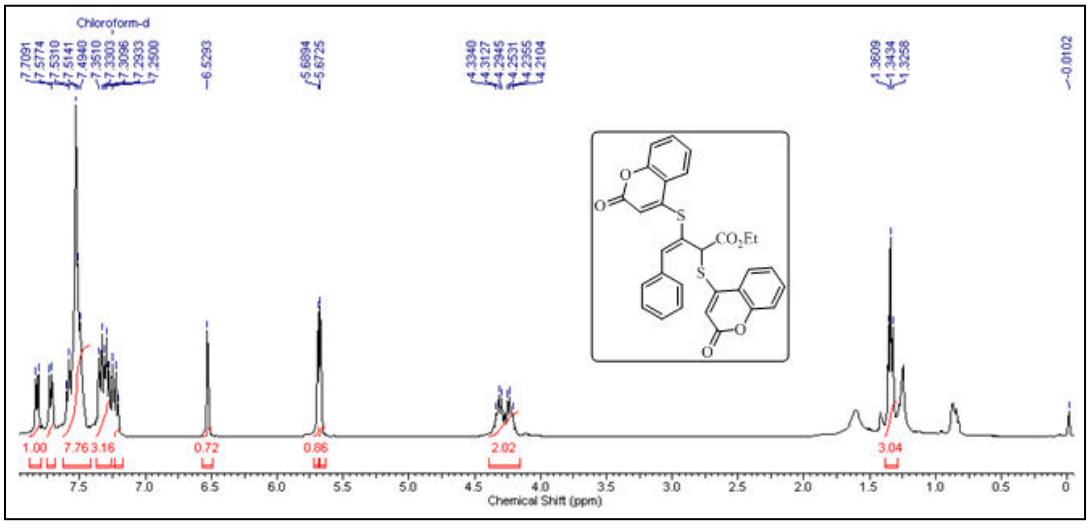


Figure 5.17 400 MHz ^{1}H NMR spectrum of **3h** in $CDCl_3$

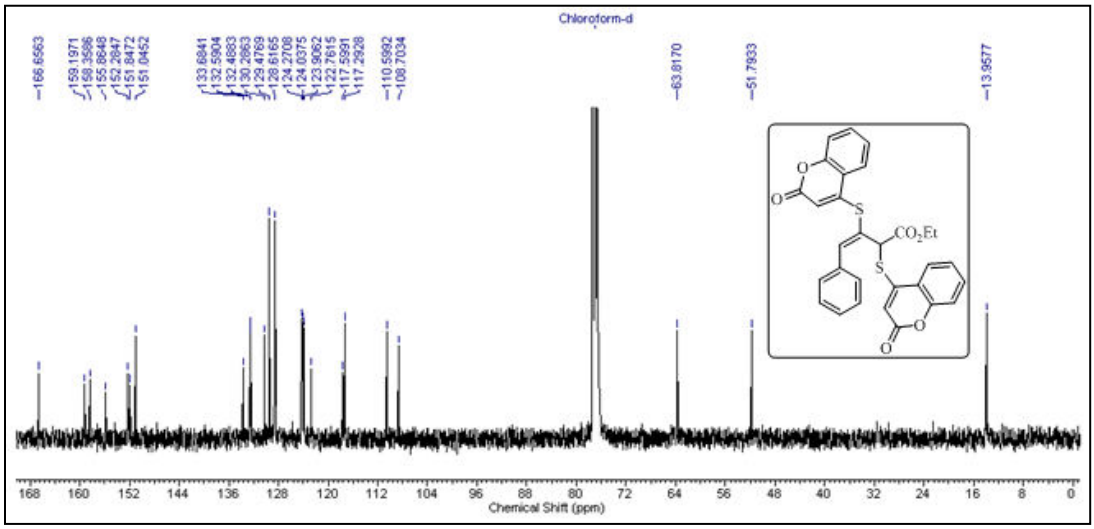


Figure 5.18 100 MHz ^{13}C NMR spectrum of **3h** in $CDCl_3$

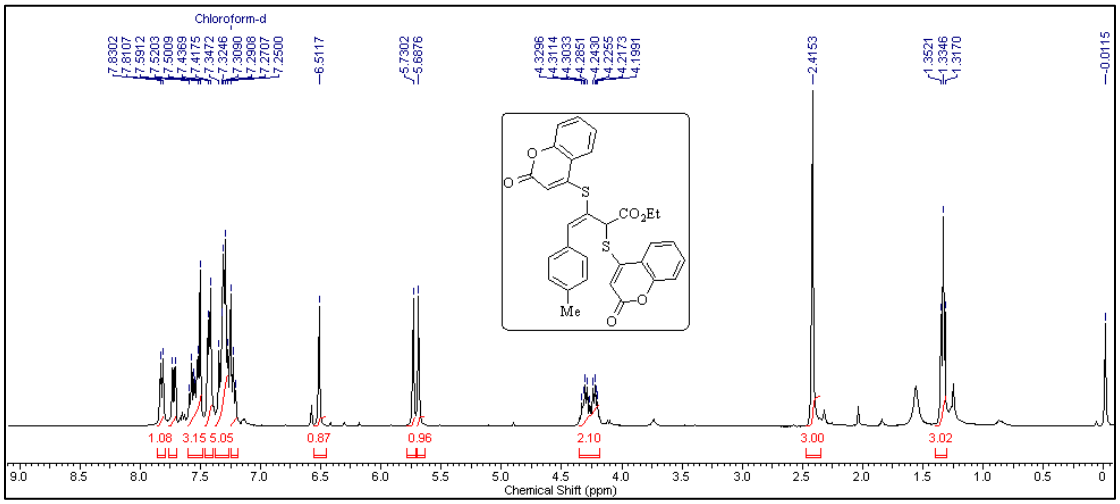


Figure 5.19 400 MHz ^{1}H NMR spectrum of **3i** in $CDCl_3$

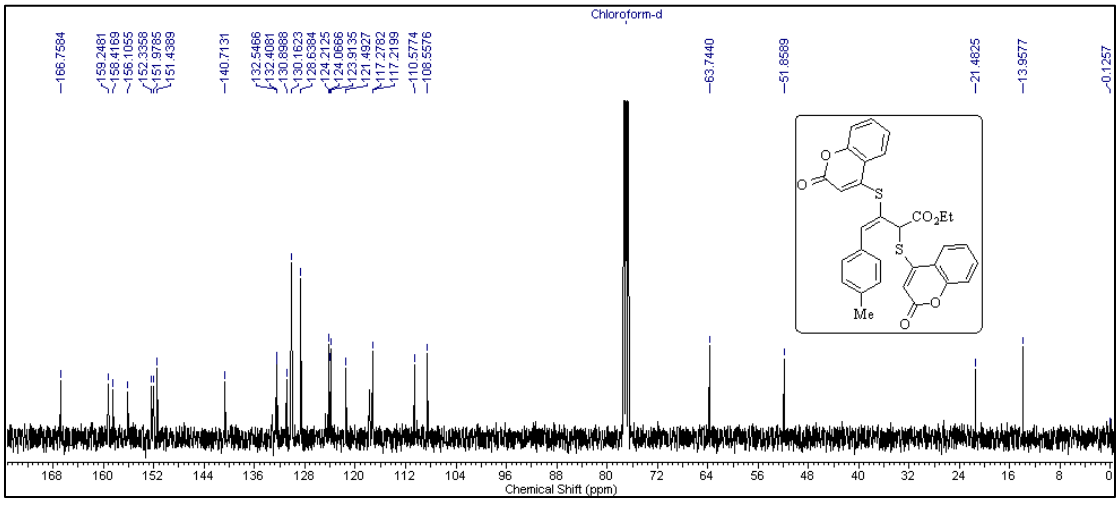


Figure 5.20 100 MHz ^{13}C NMR spectrum of **3i** in $CDCl_3$

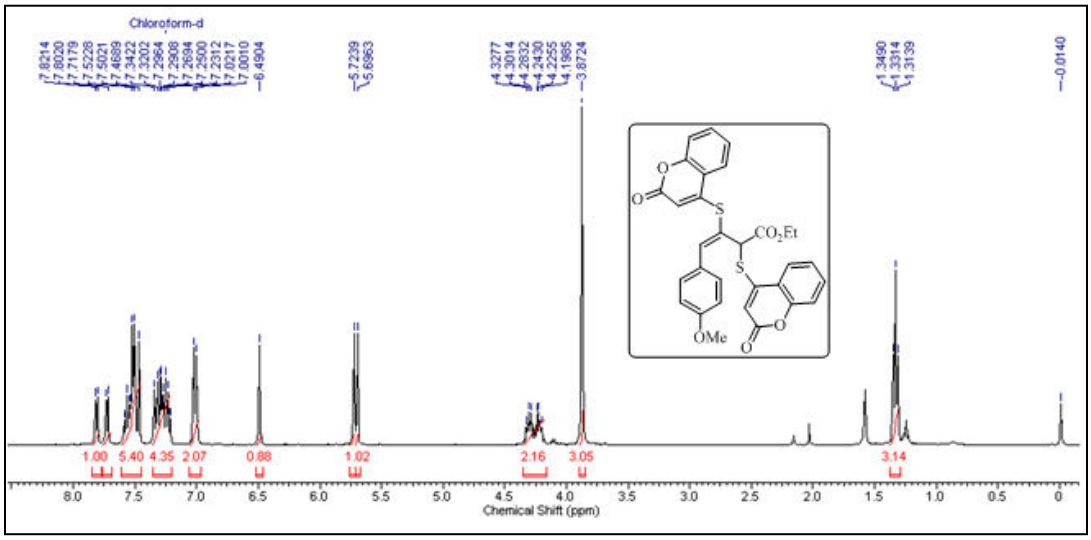


Figure 5.21 400 MHz ^{1}H NMR spectrum of **3j** in $CDCl_3$

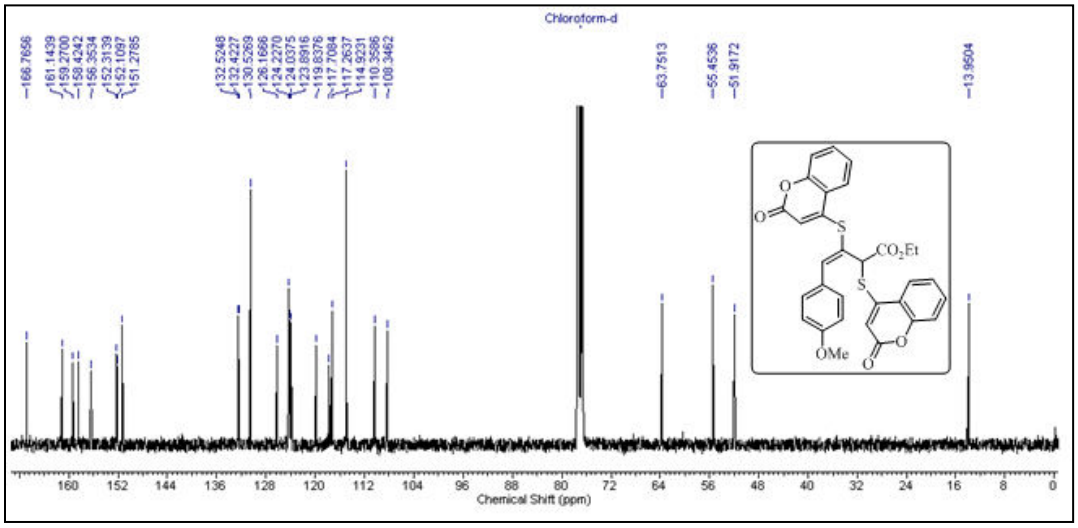


Figure 5.22 100 MHz ^{13}C NMR spectrum of **3j** in $CDCl_3$

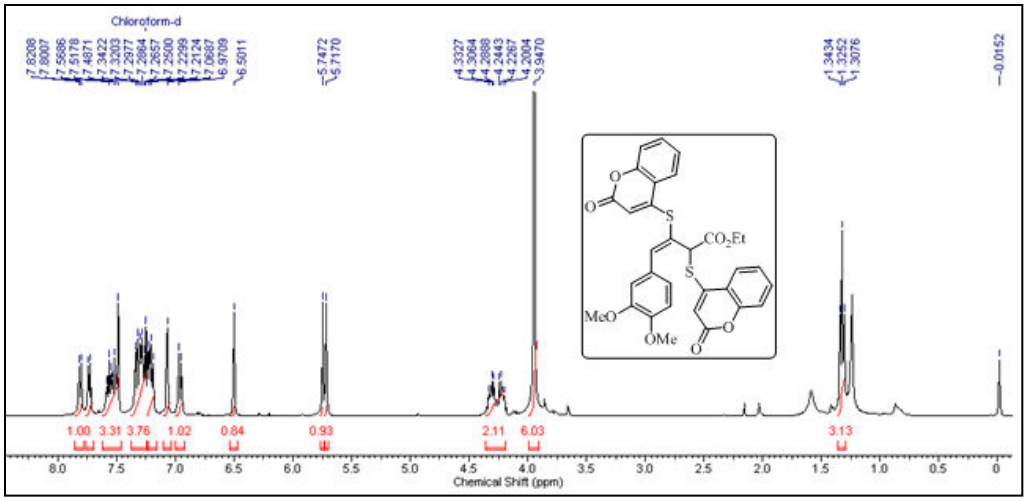


Figure 5.23 400 MHz ^{1}H NMR spectrum of **3k** in $CDCl_3$

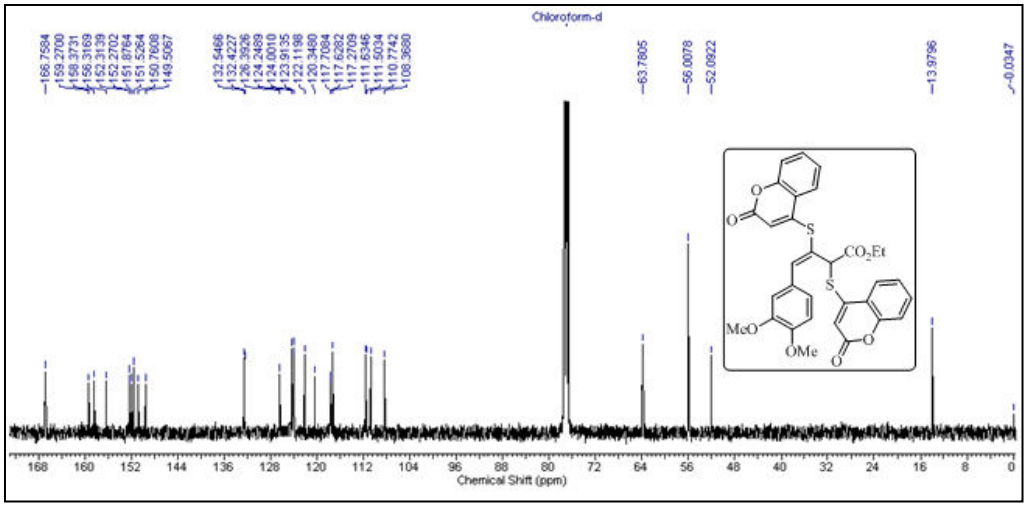


Figure 5.24 100 MHz ^{13}C NMR spectrum of **3k** in $CDCl_3$

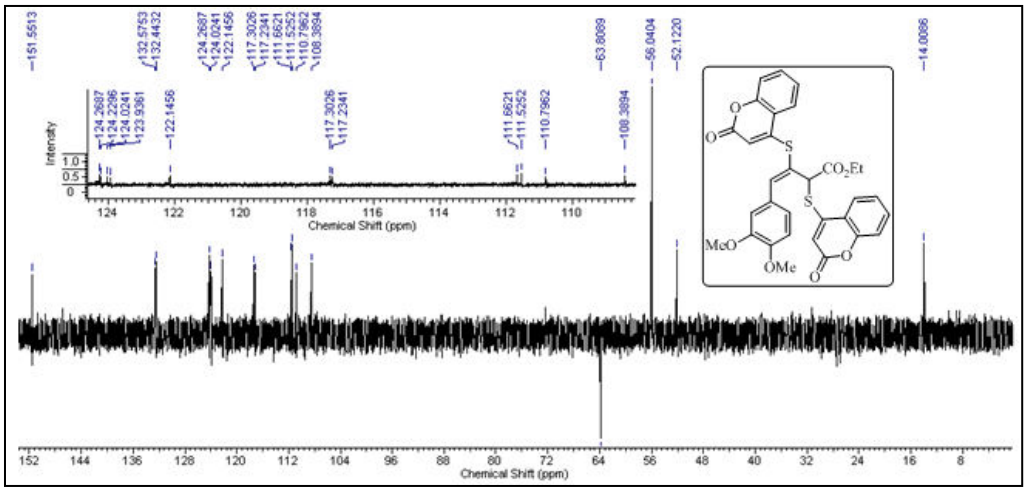


Figure 5.25 100 MHz ^{13}C NMR spectrum of **3k** in $CDCl_3$

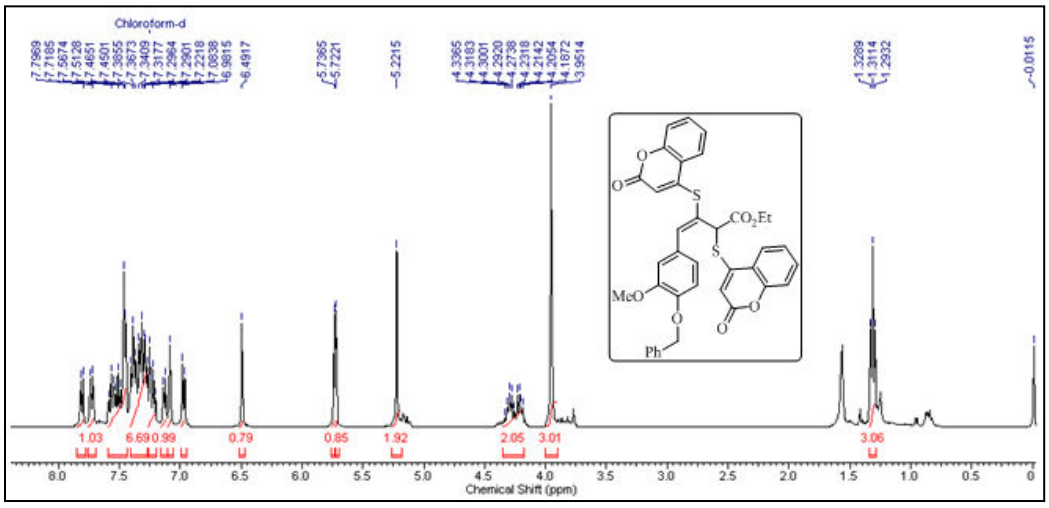


Figure 5.26 400 MHz ^{1}H NMR spectrum of **3l** in $CDCl_3$

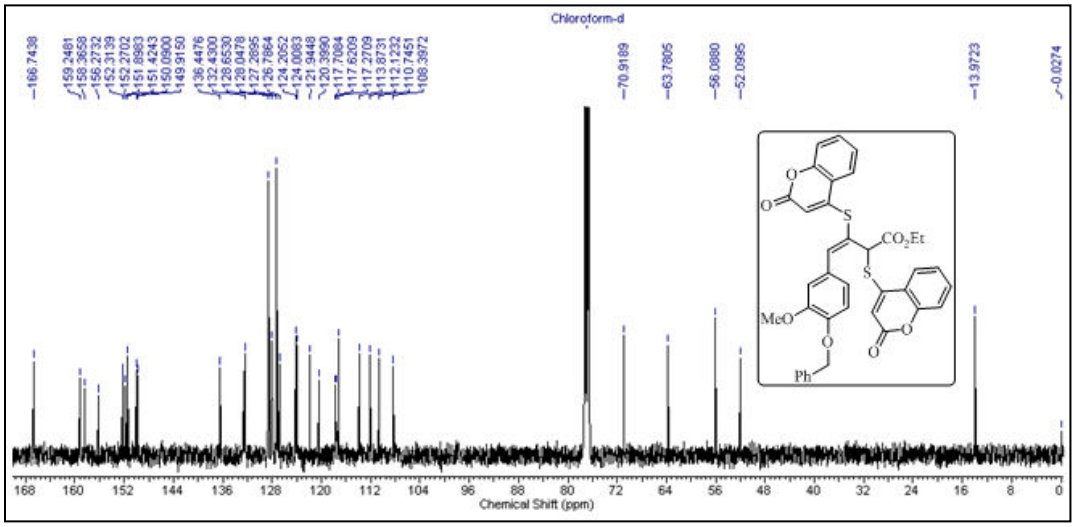


Figure 5.27 100 MHz ^{13}C NMR spectrum of **3l** in $CDCl_3$

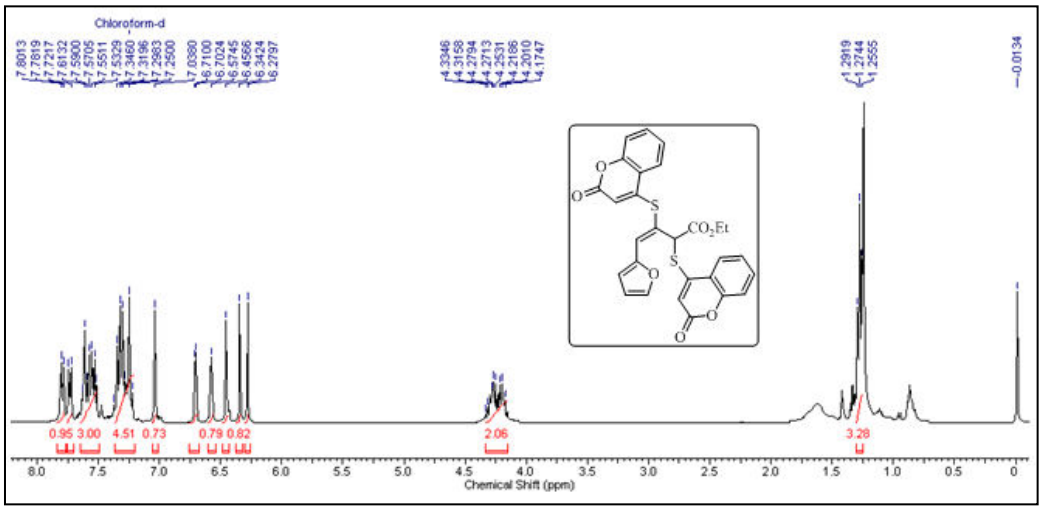


Figure 5.28 400 MHz ^{1}H NMR spectrum of **3m** in $CDCl_3$

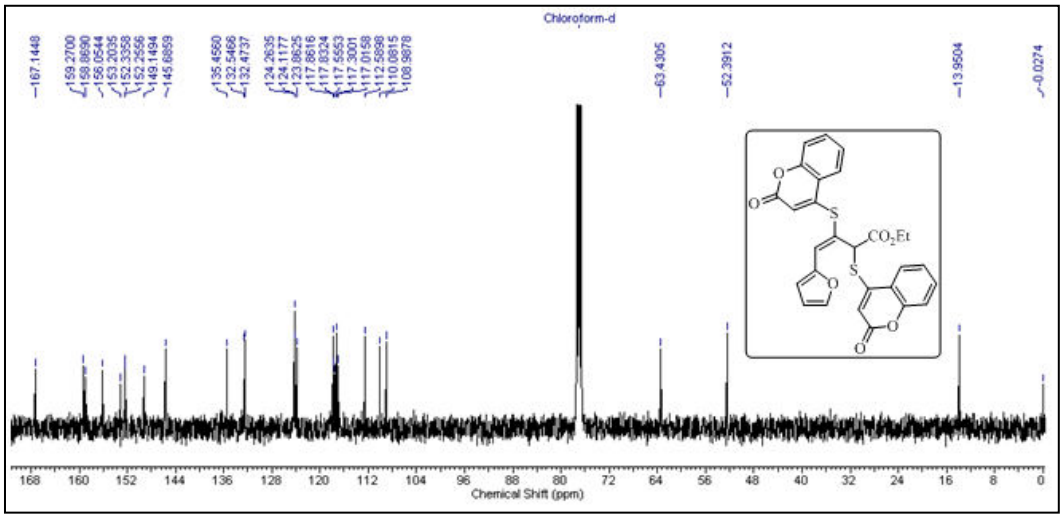


Figure 5.29 100 MHz ^{13}C NMR spectrum of **3m** in $CDCl_3$

5.8 References

1. (a) Murray R. D. H., Mendez J., Brown S. A. (1982), The Natural coumarins: Occurrence, chemistry, and biochemistry, John Wiley & sons, New York, NY, USA; (b) Kennedy R. O., Thornes R. D. (1997), Coumarins: Biology, applications and mode of action; Wiley; (c) Fylaktakidou K. C., Hadjipavlou-Litina D. J., Litinas K. E., Nicolaides D. N. (2004), Natural and synthetic coumarin derivatives with anti-Inflammatory/antioxidant activities, *Curr. Pharm. Des.*, 10, 3813-3833. (DOI: 10.2174/1381612043382710).

2. (a) Yu D., Suzuki M., Xie L., Morris-Natschke S. L., Lee K.-H. (2003), Recent progress in the development of coumarin derivatives as potent anti-HIV agents, *Med. Res. Rev.*, 23, 322-345 (DOI: 10.1002/med.10034); (b) Borges F., Roleira F., Mihazes N., Santana L., Uriarte E. (2005), Simple coumarins and analogues in medicinal chemistry: Occurrence, synthesis and biological activity, *Curr. Med. Chem.*, 12, 887-916 (DOI: 10.2174/0929867053507315); (c) Kulkarni M. V., Kulkarni G. M., Lin C.-H., Sun C.-M. (2006), Recent advances in coumarins and 1-azacoumarins as versatile biodynamic agents, *Curr. Med. Chem.*, 13, 2795-2818 (DOI: 10.2174/092986706778521968); (d) Wu L., Wang X., Xu W., Farzaneh F., Xu R. (2009), The structure and pharmacological functions of coumarins and their derivatives, *Curr. Med. Chem.*, 16, 4236-4260 (DOI: 10.2174/092986709789578187); (e) Conforti F., Marrelli M., Menichini F., Bonesi M., Statti G., Provenzano E., Menichini F. (2009), Natural and synthetic furanocoumarins as treatment for vitiligo and psoriasis, *Curr. Drug Ther.*, 4, 38-58 (DOI: 10.2174/157488509787081886).

3. (a) Medina F. G., Marrero J. G., Macías-Alonso M., Gonzalez M. C., Córdova-Guerrero I., García A. G. T., Osegueda-Robles S. (2015),

Coumarin heterocyclic derivatives: Chemical synthesis and biological activity, *Nat. Prod. Rep.*, 32, 1472-1507 (DOI: 10.1039/c4np00162a); (b) Vekariya R. H., Patel H. D. (2014), Recent advances in the synthesis of coumarin derivatives *via* Knoevenagel condensation: A review, *Synth. Commun.*, 44, 2756-2788 (DOI: 10.1080/00397911.2014.926374); (c) El-Ansary S. L., Aly E. I., Halem M. A. (1992), New coumarin derivatives as antibacterial agents, *Egypt. J. Pharm. Sci.*, 33, 379-390; (d) Zhao H., Neamati N., Hong H., Mazumder A., Wang S., Sunder S., Milne G. W. A., Pommier Y. Jr., Burke T. R. (1997), Coumarin-based inhibitors of HIV Integrase, *J. Med. Chem.*, 40, 242-249 (DOI: 10.1021/jm960450v); (e) Xie L., Takeuchi Y., Cosentino L. M., Lee K. (1999), Anti-AIDS agents. 37. Synthesis and structure-activity relationships of (3′*R*, 4′*R*)(+)-*cis*-Khellactone derivatives as novel potent anti-HIV agents, *J. Med. Chem.*, 42, 2662-2672 (DOI: 10.1021/jm9900624).

4. (a) Flynn B. L., Verdier-Pinard P., Hamel E. (2001), A novel Palladium-mediated coupling approach to 2,3-disubstituted benzo[*b*]thiophenes and its application to the synthesis of tubulin binding agents, *Org. Lett.*, 3, 651-654 (DOI: 10.1021/ol0067179); (b) Zhang T. Y., O'Toole J., Proctor C. S. (1999), Recent advances in the synthesis and applications of benzo[*b*]thiophenes, *Sulfur Rep.*, 22, 1-47 (DOI: 10.1080/01961779908047953); (c) Zlotin S. G., Kislitsin P. G., Samet A. V., Serebryakov E. A., Konyushkin L. D., Semenov V. V., Buchanan A. C., III; Gakh, A. A. (2000), Synthetic utilization of polynitroaromatic compounds. 1. S-derivatization of 1-substituted 2,4,6-trinitrobenzenes with thiols, *J. Org. Chem.*, 65, 8430-8438 (DOI: 10.1021/jo000479d); (d) Silvestri M. G., Wong C.-H. (2001), Opening of Thiiranes: Preparation of orthogonal protected 2-thioglyceraldehyde, *J. Org. Chem.*, 66, 910-914 (DOI: 10.1021/jo001392v); (e) Gebauer M. (2007), Synthesis and structure-

activity relationships of novel warfarin derivatives, *Bioorganic & Medicinal Chemistry*, 15, 2414-2420 (DOI: 10.1016/j.bmc.2007.01.014).

5. Majumdar K. C., Ghosh S. K. (2002), Studies of bioactive heterocycles: Facile thio-Claisen rearrangement of propargylthio[1]benzopyran-2-ones, *Tetrahedron Lett.*, 43, 2115-2117 (DOI: 10.1016/S0040-4039(02)00195-8).

6. Majumdar K. C., Biswas A. (2004), Regioselective Synthesis of thieno[3,2-*c*][1]benzopyran-4-ones by thio-Claisen Rearrangement, *Monatshefte für Chemie*, 135, 1001-1007 (DOI 10.1007/s00706-003-0164-4).

7. Nematollahi D., Azizian J., Sargordan-Arani M., Hesari M., Jameh-Bozorghi S., Alizadeh A., Fotouhil., Mirza B. (2008), Electrochemical synthesis of 4-(Dihydroxyphenylthio)-2*H*-chromen-2-one derivatives, *Chem. Pharm. Bull.*, 56, 1562-1566 (DOI: 10.1248/cpb.56.1562).

8. Peng Y.-Y., Wen Y., Mao X., Qiu G. (2009), Direct sulfanylation of 4-hydroxycoumarins with thiols in water, *Tetrahedron Lett.*, 50, 2405-2406 (DOI: 10.1016/j.tetlet.2009.03.004).

9. Yin Z., Wang Y., Yang Q., Wang Y., Xu J., Deng Z., Peng Y. (2013), Synthesis of 4-sulfanylcoumarins using thiourea and alkyl halides as the sulfanylation agent in polyethylene glycol-water, *Synthesis*, 45, 759-766 (DOI: 10.1055/s-0032-1318139).

10. (a) Wu J., Yang Z., Fathi R., Zhu Q., Wang L. (2004), 4-Thiocoumarins, US Patent 6703514B2; (b) Wang G., Chen L., Xian T., Liang Y., Zhang X., Yang Z., Luo M. (2014), Discovery and SAR study of piperidine-based derivatives as novel influenza virus inhibitors, *Org. Biomol. Chem.*, 12, 8048-8060 (DOI: 10.1039/c4ob01079e); (c) Wittine K., Ratkaj I., Benci K., Suhina T.,

Mandić L., Ilić N., Pavelić S. K., Pavelić K., Mintas M. (2016), The novel coumarin[3,2-*c*]thiophene and its hydroxamic acid and ureido derivatives: Synthesis and cytostatic activity evaluations, *Med. Chem. Res.*, 25, 728-737 (DOI 10.1007/s00044-016-1523-0); (d) Goel A., Prasad A. K., Parmar V. S., Ghosh B., Saini N. (2009), Apoptogenic effect of 7,8-diacetoxy-4-methylcoumarin and 7,8-diacetoxy-4-methylthiocoumarin in human lung adenocarcinoma cell line: Role of NF-κB, Akt, ROS and MAP kinase pathway, *Chem. Biol. Interact.*, 179, 363-374 (DOI: 10.1016/j.cbi.2008.10.060).

11. (a) Yin Z., Wang Y., Yang Q., Wang Y., Xu J., Deng Z., Peng Y.-Y. (2013), Synthesis of 4-sulfanylcoumarins using thiourea and alkyl halides as the sulfanylation agent in polyethylene glycol-water, *Synthesis*, 2013, 45, 759-766 (DOI: 10.1055/s-0032-1318139); (b) Wang W., Ding Q., Fan R., Wu J. (2007), A general and efficient route to 3-amino-4-sulfanylcoumarins *via* substitution and palladium-catalyzed amination of 3-bromo-4-tosyloxycoumarins, *Tetrahedron Lett.*, 48, 3647-3649 (DOI: 10.1016/j.tetlet.2007.03.142).

12. Singh S., Srivastava A., Mobin S. M., Samanta S. (2015), A remarkable solvent effect on the reaction of 4-hydroxycoumarin with (*E*)-3-aryl-2-nitroprop-2-enol: Facile synthesis of highly substituted furo/pyrano[3,2-*c*]chromenes, *RSC Adv.*, 5, 5010-5014 (DOI: 10.1039/C4RA10610E).

13. Nair D. K., Menna-Barreto R. F. S., da Silva Júnior E. N., Mobin S. M., Namboothiri I. N. N. (2014), Chiral squaramide-catalyzed asymmetric synthesis of pyranones and pyranonaphthoquinones *via* cascade reactions of 1,3-dicarbonyls with Morita-Baylis-Hillman acetates of nitroalkenes, *Chem. Commun.*, 50, 6973-6976 (DOI: 10.1039/c4cc02279c).

14. Nair D. K., Mobin S. M., Namboothiri I. N. N. (2012), Synthesis of imidazopyridines from the Morita-Baylis-Hillman acetates of nitroalkenes and convenient access to Alpidem and Zolpidem, *Org. Lett.*, 14, 4580-4583 (DOI: 10.1021/ol3020418).

15. Gopi E., Kumar T., Menna-Barreto R. F. S., Valença W. O., da Silva Júnior E. N., Namboothiri I. N. N. (2015), Imidazoles from nitroallylic acetates and α-bromonitroalkenes with amidines: Synthesis and trypanocidal activity studies, *Org. Biomol. Chem.*, 13, 9862-9871 (DOI: 10.1039/c5ob01444a).

16. Nair D. K., Mobin S. M., Namboothiri I. N. N. (2012), Synthesis of functionalized and fused furans and pyrans from the Morita-Baylis-Hillman acetates of nitroalkenes, *Tetrahedron Lett.*, 53, 3349-3352 (DOI: 10.1016/j.tetlet.2012.04.084).

17. Majee D., Biswas S., Mobin S. M., Samanta S. (2016), Access to 4,6-diarylpicolinates *via* a domino reaction of cyclic sulfamidate imines with Morita-Baylis-Hillman acetates of nitroolefins/nitrodienes, *J. Org. Chem.*, 81, 4378-4385 (DOI: 10.1021/acs.joc.6b00472).

18. Majumdar K. C., Sarkar S., Pal P., Muhuri S. (2009), C-C bond formation by radical cyclization: Facile syntheses of [6,6]pyranothiopyrans and [6,6]pyridothiopyrans, *J. Heterocyclic Chem.*, 46, 1324-1330 (DOI: 10.1002/jhet.220).

19. Yao C.-F., Chu C.-M., Liu J.-T. (1998), Free-radical reactions of trialkylboranes with *β*-nitrostyrenes to generate alkenes, *J. Org. Chem.*, 63, 719-722 (DOI: 10.1021/jo9716901).

20. Chu C.-M., Tu Z., Wu P., Wang C.-C., Liu J.-T., Kuo C.-W., Shin Y.-H., Yao C.-F. (2009), Straightforward and highly efficient catalyst-free regioselective reaction of thiol to β-nitrostyrene: A concise synthesis

of vinyl sulfide and nitro sulfide, *Tetrahedron*, 65, 3878-3885 (DOI: 10.1016/j.tet.2009.02.074).

Chapter 6

Conclusion and Future Outlook

The developments of atom-economical, cost-effective, efficient, metal-free based and green synthetic protocols for the preparations of highly functionalized thiopyrano annulated indoles, furo/pyranocoumarins and related heterocyclic frameworks such as α-(4-thiocoumarinyl)-β-nitrostyrene derivatives and (*E*)-dithiocoumarinyl styrene derivatives by involving simple raw materials are included in this thesis. The current methodologies provide good to excellent yields of the corresponding thiopyranoindoles and furo/pyranocoumarin derivatives with high to excellent stereoselectivities and tolerate a wide range of synthetically valuable functional groups under optimal reaction conditions. Moreover, enantiomeric excess of biologically attractive compounds such as tetrahydrothiopyrano[2,3-*b*]indoles have been successfully achieved by using quinidine type of catalyst. Furthermore, a variety of commercially available acids/bases such as DABCO, DBU, L-proline etc. have been proven as efficient catalysts for above one-pot reactions.

It should be noted that all the aforementioned procedures avoid the use of costly metals or their salts, minimize the use of organic solvents, prevent a tedious workup, offer the possible advantage of significant lower costs and mitigate the environmental burden of their manufacturing process. Therefore, we believe that all the described methods in this thesis will offer great importance in synthetic organic as well as medicinal chemistry as powerful tactics for the efficient access to the aforesaid heterocyclic compounds in an environmentally friendly manner.