Exploration of 4-Hydroxydithiocoumarin for the Synthesis of Novel Organosulfur Compounds

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

DOCTOR OF PHILOSOPHY

by

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Dedicated to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "*Exploration of 4-Hydroxydithiocoumarin for the Synthesis of Novel Organosulfur Compounds"* is the result of investigations carried out by me under the supervision of Prof. Abu T. Khan and Dr. Bhubaneswar Mandal in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

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

IIT Guwahati
October 12, 2017

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Professor of Chemistry

CERTIFICATE

This is to certify that Karuna Mahato has been working in my research group since July, 2012 as a regular registered Ph. D. student. I am forwarding her thesis entitled "*Exploration of 4-Hydroxydithiocoumarin for the Synthesis of Novel Organosulfur Compounds"* for submission for the Ph. D. (Science) Degree of this Institute. I certify that she has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

IIT Guwahati
October 12, 2017

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CERTIFICATE

This is to certify that Karuna Mahato has completed her Ph. D. Thesis work from July, 2012 as a regular registered Ph. D. student under my colleague Prof. Abu T. Khan. I have been appointed as a Co-Supervisor when Prof. Khan joined as Vice-Chancellor of Aliah University in West Bengal on deputation from IIT Guwahati. I am forwarding her thesis as a Co-supervisor entitled "*Exploration of 4-Hydroxydithiocoumarin for the Synthesis of Novel Organosulfur Compounds"* for submission for the Ph. D. (Science) Degree of this Institute. I also certify that she has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

IIT Guwahati
October 12, 2017

Dr. Bhubaneswar Mandal
(Thesis Co-Supervisor)

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

Karuna Mahato

Contents of the Thesis

GENERAL REMARKS

The present investigations were carried out at the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam during the period from 23rd July, 2012 to 10th October, 2017 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50 ^{o}C. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) was employed as adsorbent were used. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Büchi R-114V instrument. Melting points were determined on a Büchi melting point apparatus. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 300 MHz, 400 MHz, Bruker 600 MHz and Varian 75 MHz, 100 MHz, Bruker 150 MHz spectrometer; TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in the order: multiplicity, no of protons and coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad singlet). HRMS spectra were recorded using ESI (TOF) mode. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 296 K.

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Bn	benzyl
Bu	butyl
^{t}Bu	*tert*-Butyl
Bz	benzoyl
CCDC	cambridge crystallographic data centre
COSY	correlation spectroscopy
DCM	dichloromethane
DHF	2,3-dihydrofuran
DHP	3,4-dihydropyran
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
Et_3N	triethyl amine
g	gram
h	hour
HRMS	High-resolution Mass Spectrometry
IR	infrared
MCR	Multicomponent reaction
M.p	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid program
Ph	phenyl
Pr	propyl
i-Pr	isopropyl
ppm	parts per million
Py	pyridine

p-TSA	*p*-toluenesulfonic acid
rt	room temperature
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TfOH	Triflic acid
t-BHP	tert-Butyl hydroperoxide
w	weight
XRD	x-ray diffraction

Chapter I

Introduction to Organosulfur Compounds: 4-hydroxydithiocoumarin, 1,3 thiazines, thiophenes, thiopyrans, 1,2-dithioles, sulfenamides, di-sulfides, sulfanes

Review

1.1 Introduction

Organosulfur compounds are widely distributed in nature and they play an eye-catching role in the efficient functioning of the living system.[1] These are found in different locations stretching from interstellar space to inside hot acidic volcanoes to deep inside the oceans. Organosulfur compounds are cherished not only for their rich and varied chemistry, but also for their substantial biological properties.[2] Some of the important naturally occurring organosulfur compounds include Coenzyme A (CoA), biotin, thiamine chloride (vitamin B_1), α-lipoic acid, insulin, oxytocin, sulfated polysaccharides, and the nitrogen-fixing nitrogenase enzymes.[3] In addition, they are associated to foul odors linked to polluted air, water and sulfur-rich fossil fuels. Volatile sulfur compounds are key sponsors to the distinguishing flavors and off-flavors of many foods.[4] Sulfur compounds enrich enzymatically-derived flavors in the cruciform families (broccoli, brussels sprouts, cabbage), allium species (garlic, onion, chive) and are also responsible for thermally-generated flavors such as coffee, roasted meat, seafood etc. Volatile sulfur compounds play vital role in the aromas of bread, popcorn, chocolate, nuts, cheddar cheese wine and tropical fruit flavors.[5] The compound allicin is responsible for the typical odor of garlic whereas onions contain S-propenylcysteine sulfoxide, S-propylcysteine sulfoxide and S-methyl cysteine sulfoxide. N-acetyl-S-allylcysteine and N-acetyl-S-(2-carboxylpropyl)-cysteine are found in the urine from healthy persons consuming garlic or onions.[6] After ingestion of garlic the presence of allylmercaptane and diallyldisulfide in human breath has been revealed by literature reports.[7] The compound lenthionine is accountable for the flavor of shiitake mushrooms and it also inhibits platelet aggregation.[8] Moreover, the sulfur-containing organic molecules are important modules in synthetic drugs, pharmaceutical industry, bioactive natural products, enzyme-mimics, in materials science and synthetic equivalents for asymmetric synthesis.[9] A large number of synthetic drugs containing a sulfur atom are used for treatment of various diseases.[10] Many naturally occurring sulfur based compounds exhibit anticancer activity.[11] These compounds are also known to exhibit remarkable pharmacological activities such as diuretic and HIV protease inhibitory activities.[12] Penicillins antibiotics are effective against syphilis, bacterial infections caused by staphylococci and streptococci. AZD4407 is used as an anti-allergy and anti-asthmatic agent for the treatment of chronic obstructive pulmonary diseases.[13] Nelfinavir is used to treat human immunodeficiency virus (HIV) infection.[14] Prevacid, a proton-pump inhibitor (PPI) constrains gastric acids produced in the stomach.[15] The anti-hyperlipidemic drug, probucol is used for the treatment of coronary artery disease, whereas quetiapine serves

as an antipsychotic drug.[16] Some of biologically active organosulfur compounds are shown in figure 1.

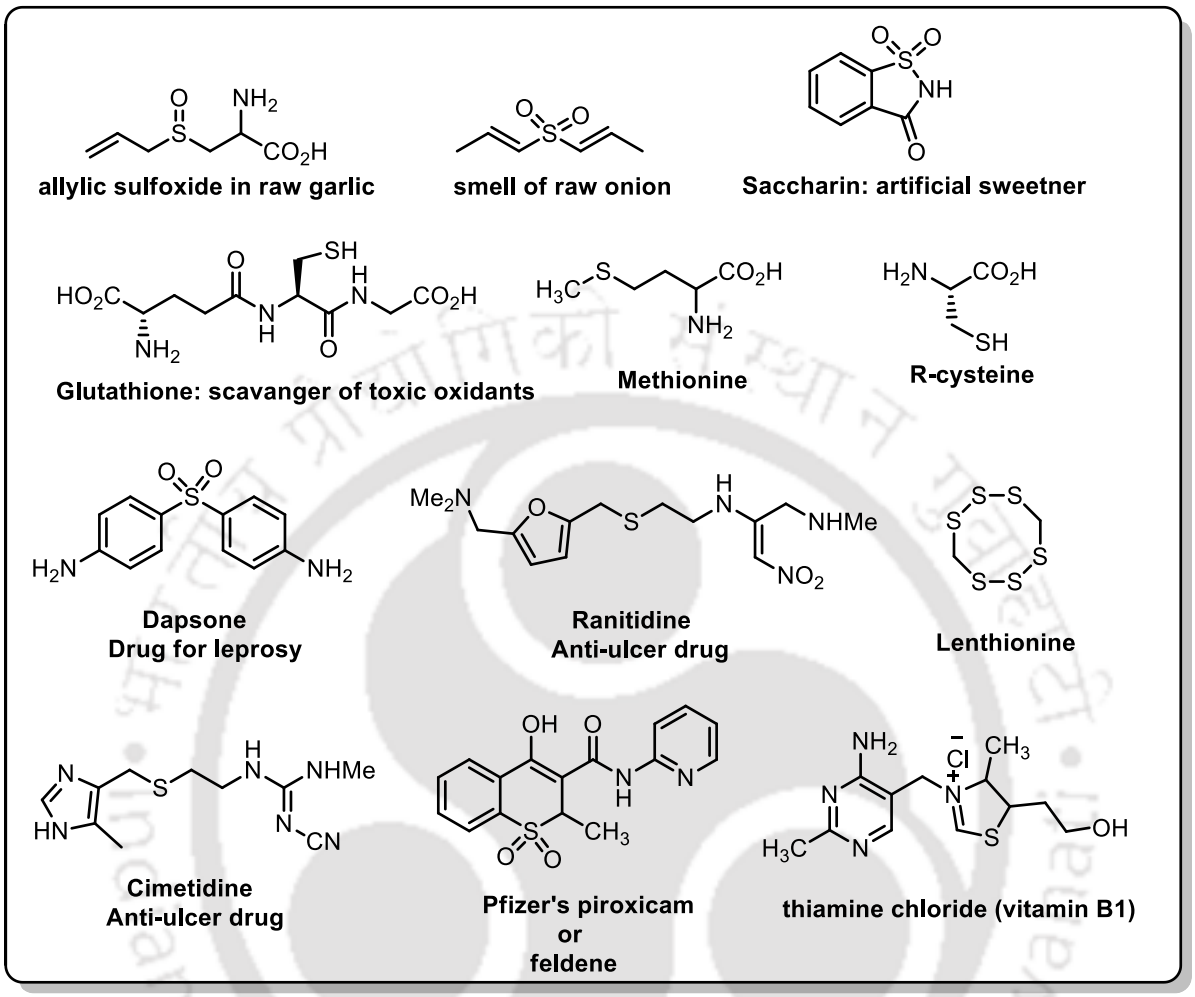


Figure 1: Biologically active organosulfur compounds present in nature and drugs

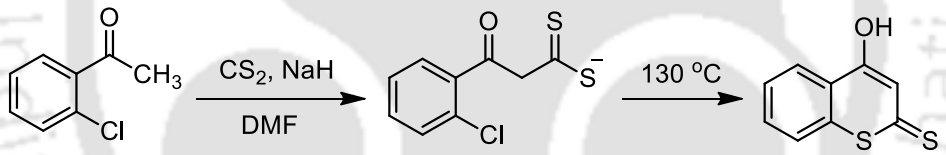
Synthetic organosulfur compounds are also known for numerous material based applications. Organic polysulfanes find its role as additives to high-pressure lubricants to prevent metals from welding together under extreme pressure (EP).[17] The polysulfone resins are used as wire coatings, for fabricating plumbing items and automotive parts.[18] Polythiophenes holds metal-like ability for conducting electricity.[19] Organosulfur compounds are also the essential constituent of insecticides, agricultural chemicals, food additives, dyes, lubricating oil constituents, and substances used to make rayon.[20] Moreover, organosulfur compounds are also used as important solvents such as CS_2, DMSO etc where as long chain sulfonic or sulfonic acids are used as important detergents.[21] In addition, organosulfur compounds are highly valued as active reaction intermediates in organic synthesis.[22] Thus, it is evident that

the synthesis of new organosulfur compounds are immense importance to synthetic organic and material chemistry.

1.2 History and Synthetic Utility of 4-hydroxydithiocoumarin

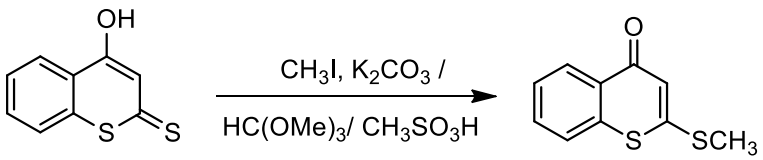
Coumarins and chromones constitute an important class of compound due to their presence as an important constituent of natural products and synthetic organic chemistry.[23] Thiochromone derivatives are also interesting classes of heterocycles due to their broad pharmacological and medicinal importance.[24] The compounds containing a 4-hydroxycoumarin nucleus are known for showing various biological activities such as anticoagulant activity, antibiotic fungicidal, rodenticidal or molluscicidal.[25] The biological activity was also reflected in a series of analogous 4-hydroxythiocoumarins which developed a great curiosity for the further investigation of dithio-analogues thus 4-hydroxydithiocoumarin serves as an attractive candidate to exploit during my research work.

In 1987, Anderson-McKay and his co-worker first established[26] the synthesis of 4-hydroxydithiocoumarin using 2'-chloroacetophenones with carbon disulfide in the presence of sodium hydride as shown in scheme 1.

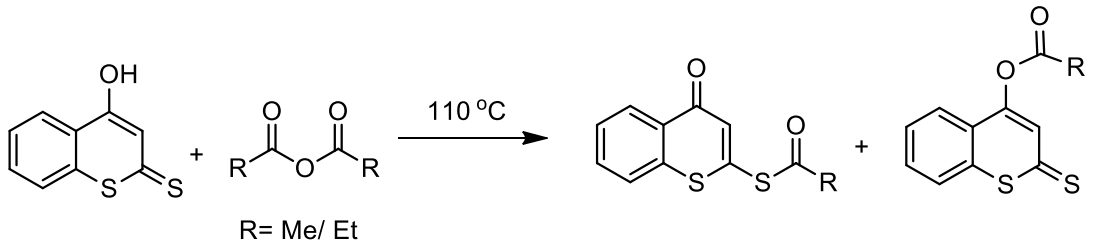


Scheme 1. Synthesis of 4-hydroxydithiocoumarin

After the synthesis of 4-hydroxydithiocoumarin, Anderson-McKay and his co-worker conducted methylation of 4-hydroxydithiocoumarin under both basic (iodomethane/potassium carbonate) and acidic conditions (methylorthoformate/methane sulfonic acid) which took place exclusively on sulfur leading to the isolation of 2-methylthio-1-thiochromone as depicted in Scheme 2a. Whereas, the acylation reaction of 4-hydroxythiocoumarin with acetic and propionic anhydrides at room temperature or with brief warming gave the mixtures of the 0- and S-acyl products as depicted in Scheme 2b.

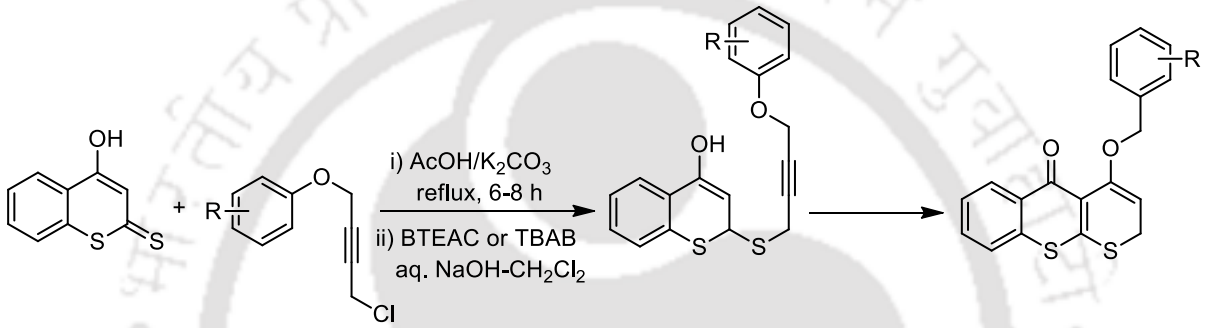


Scheme 2a. Synthesis of 2-methylthio-1-thiochromone



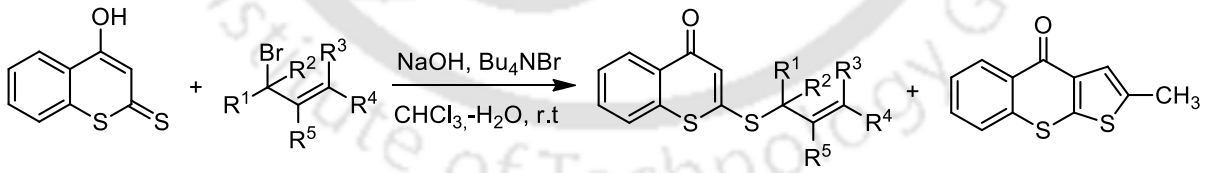
Scheme 2b

In 1992, Majumdar *et al.* described[27] phase transfer catalysed alkylation of 4-hydroxydithiocoumarin with l-aryloxy-4-chloro-but-2-ynes to furnished 4-(aryloxymethyl)thiopyrano[2,3-*b*]benzothiopyran-5(2*H*)-ones as shown in Scheme 3.



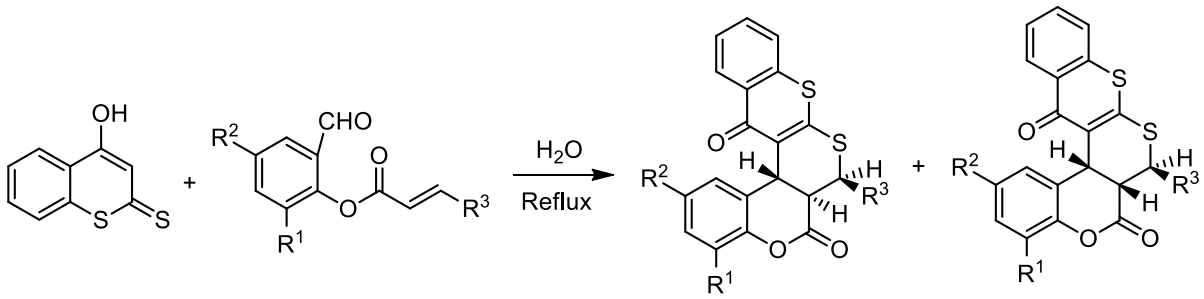
Scheme 3

Majumdar and co-workers reported[28] the synthesis of sulfur heterocycles by thio-Claisen rearrangement reaction of 4-hydroxydithiocoumarin with allylic halides under phase transfer catalysis condition in the presence of TBAB or BTEAC in chloroform-aqueous NaOH (1%) at room temperature as shown in Scheme 4.



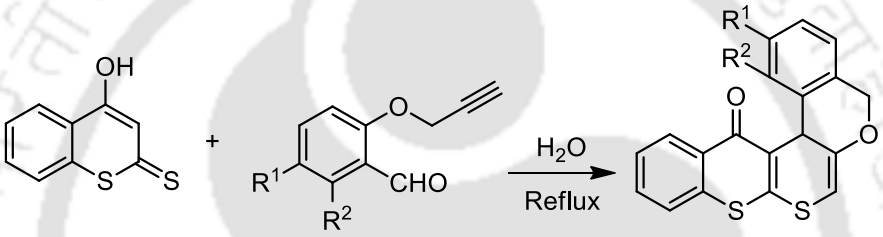
Scheme 4

In 2010, Moghaddam *et al.* accomplished[29] catalyst-free synthesis of novel pentacyclic thiochromone-annulated thiopyranocoumarin derivatives via domino Knoevenagel-hetero-Diels-Alder reaction of 4-hydroxy dithiocoumarin and O-acrylated salicylaldehyde in aqueous medium as shown in Scheme 5.



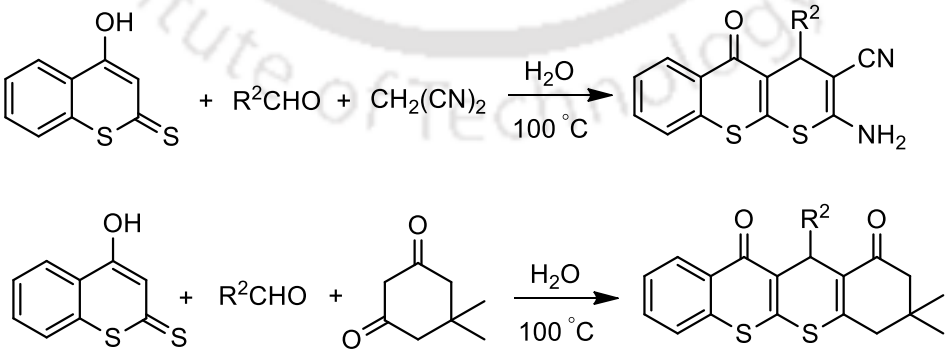
Scheme 5

In the same year Majumdar *et al*. reported[30] a catalyst-free regioselective synthesis of benzopyran-annulated thiopyrano[2,3-*b*]thiochromen-5-(4H)-one derivatives by domino-Knoevenagel-hetero-Diels–Alder reaction of terminal alkynes with 4-hydroxy dithiocoumarin in aqueous medium as shown in Scheme 6.



Scheme 6

Recently, Majumdar *et al*. developed[31] a green one pot three-component methodology for the synthesis of thiopyrano[2,3-*b*]thiochromene-3-carbonitrile and dihydrothiochromeno[2,3-*b*]thiochromene derivatives by the domino reaction of 4-hydroxy-2H-thiochromene-2-thione with aldehyde and malononitrile or dimedone in aqueous medium at 100 °C as shown in Scheme 7.



Scheme 7

We envisaged that it can be further explored for the synthesis new organosulfur compounds. Thus, my thesis is aimed towards the construction of new synthetic protocol for the synthesis

of various novel organosulfur compounds which having 1,3-thiazine, thiophenes, thiopyran, 1,2-dithioles, sulfenamides, sulfanes , di-sulfides moieties from 4-hydroxydithiocoumarin as the key starting material.

1.3 1, 3-Thiazine and its importance

Heterocyclic compounds containing sulfur and nitrogen are pharmacologically potent molecules.[32] Amongst them, 1,3-thiazine structural motifs are of substantial research interest owing to exhibition of a wide range of biological activities spanning from antibacterial, anti-inflammatory, antimicrobial, antitumor, antipyretic, to being the active core of cephalosporin to anabolic agent in medicine.[33] Further, 1,3-thiazine core moieties finds application in various organic synthesis and transformations as reaction intermediates[34a] and it also shows significant potential of anti-radiation agents[34b] and cell growth inhibitors.[34c] Some of the biologically active 1,3-thiazine based organic molecules are displayed in Figure 2.

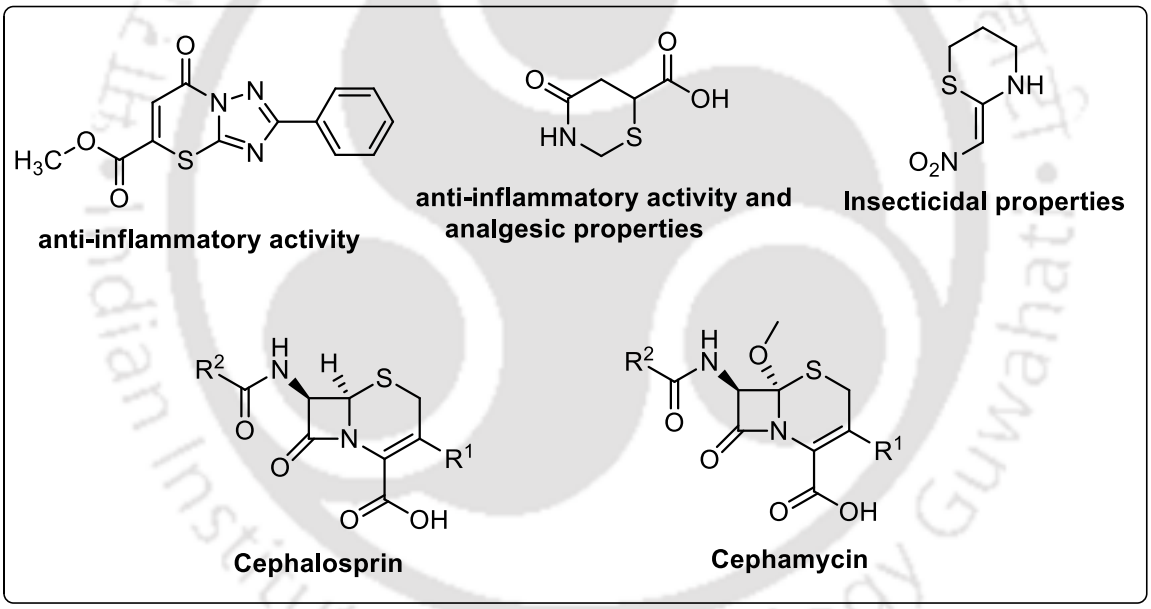
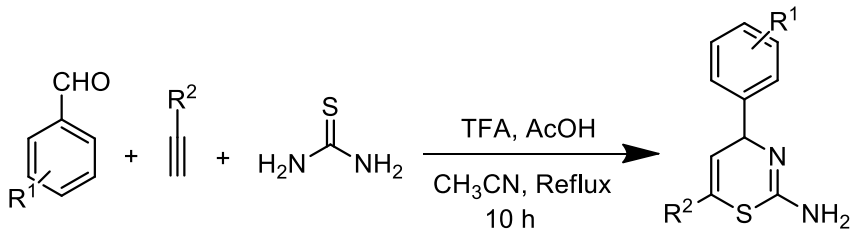


Figure 2: Biologically active compounds containing 1,3-thiazine skeleton

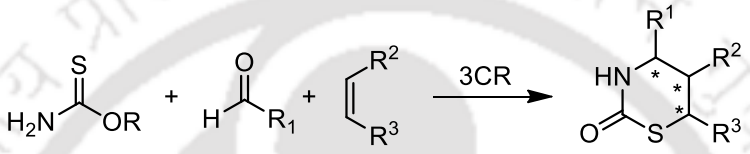
1.3a Synthetic utility of 1,3-Thiazine

1,3-Thiazines beside having synthetic applications, these have also been remarkably known for their various biological activities. Therefore, the development of new efficient and practical strategies for synthesis of 1,3-thiazines skeleton has kindled the interest of synthetic organic chemists. Recently, Wu *et al*. reported[35] one pot reaction of aryl aldehydes and terminal alkyne with thiourea to give 1,3-thiazine derivative in excellent yield as shown in Scheme 8.



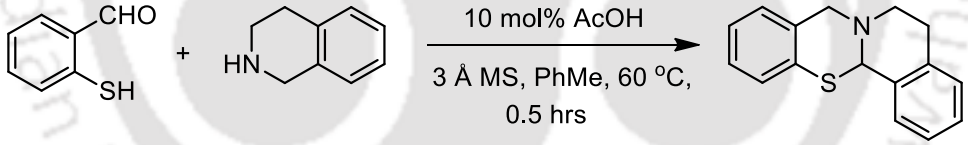
Scheme 8

Reboul *et al*. established[36] a new asymmetric three-component domino process, based on a diastereoselective hetero-Diels Alder reaction involving an aldehyde, alkene and a chiral thio-carbamate leading to enantioenriched 1,3-thiazin-2-ones as shown in Scheme 9.



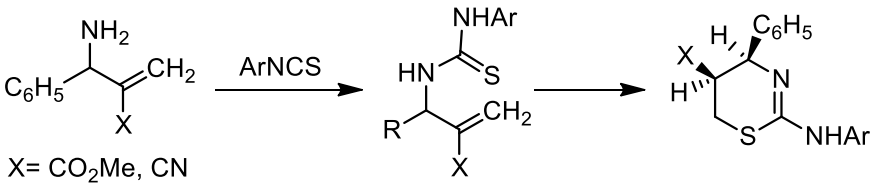
Scheme 9

Recently Seidel *et al*. reported[37] the synthesis of 1,3-thiazine derivatives by the reaction of secondary amines with thiosalicylaldehydes in the presence of catalytic amount of acetic acid as shown in Scheme 10.



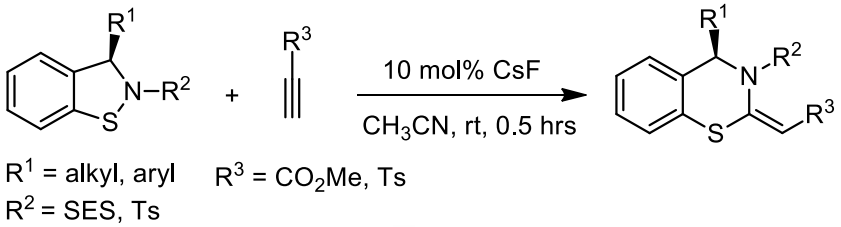
Scheme 10

Recently, Batra *et al*. reported[38] a novel stereo selective one-pot intermolecular cyclized reaction for the synthesis of disusbstituted amino-5,6-dihydro-4H-1,3-thiazines using primary allyl amines and aryl isothiocyanaide as shown in Scheme 11.



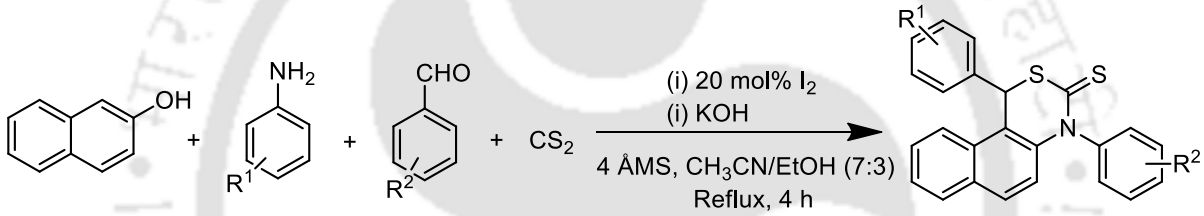
Scheme 11

Spitz *et al*. achieved[39] an efficient synthesis of enantiopure 1,3-benzothiazines by reaction of cyclic sulfenamides and alkylpropiolate or tosylacetylene catalyzed by cesium fluoride as shown in Scheme 12.



Scheme 12

Recently, Sathiyanarayanan *et al*. accomplished[40] the synthesis of 1,3-thiazines using iodine catalyzed four component reaction from *β*-naphthol, aldehydes, amines and carbon disulphide as shown in Scheme 13.



Scheme 13

Over the years, most of the previously reported methods for the synthesis of 1,3-thiazines skeleton involves the employment of thiourea as one of the major reactant where the nitrogen and the sulphur atom of thiourea gets incorporated into the 1,3-thiazine nucleus with different other reactants to produce a variety of 1,3-thiazine derivatives.[41] However, the above methods suffer from the several drawbacks such as harsh reaction conditions, need of expensive and usage of excess amount of catalyst and longer reaction time. Eventually, it creates a space for the development of a new methodologies for the synthesis of 1,3-thiazine scaffolds under mild condition with higher efficiency, operational simplicity, economic viability and high regioselectivity.

1.4 Thiophenes and its importance

Thiophenes are unique sulfur-containing heterocycles that serves as an important building blocks in natural products, pharmacologically active compounds, coal tar distillates and petroleum.[42] Thiophene moieties exhibit remarkable pharmacological activities such as anti-inflammatory activity, these act as serotonin antagonists, finds use in the treatment of

Alzheimer's disease and are widely used as chemotherapeutic agents.[43] Optically active and polyfunctionalized thiophenes are of considerable interest as they are present in biologically important essential coenzyme biotin, acts as potential inhibitors of HIV, leukotriene antagonists, human A3 adenosine receptor ligands and antitumor natural products.[44] Some of the biologically active thiophenes based organic molecules are shown in Figure 3.

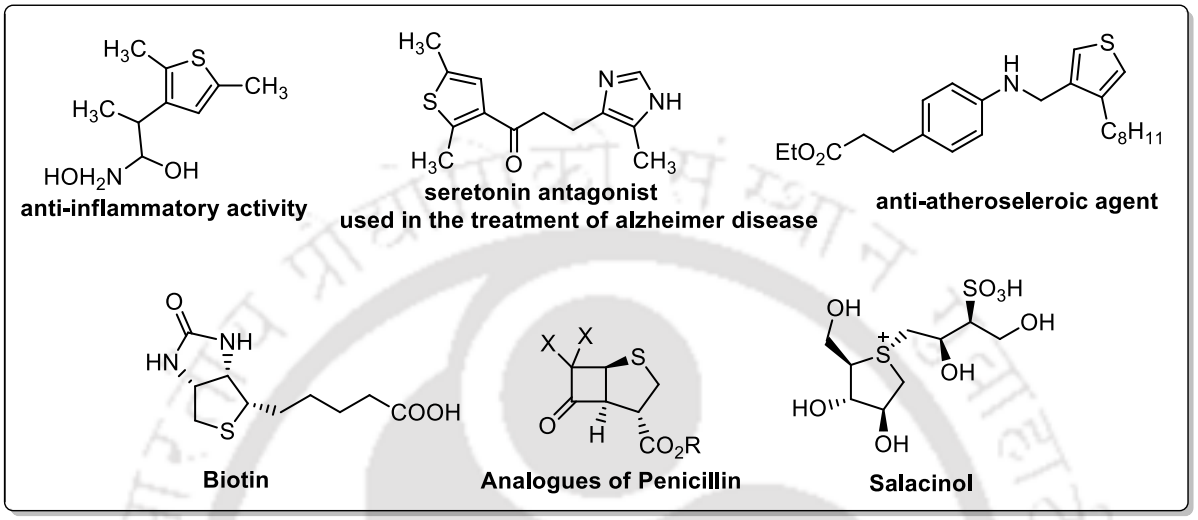
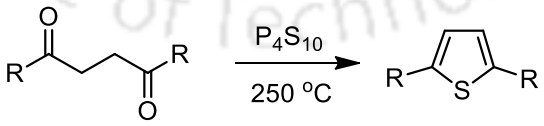


Figure 3: Biologically active thiophenes present in nature and drugs

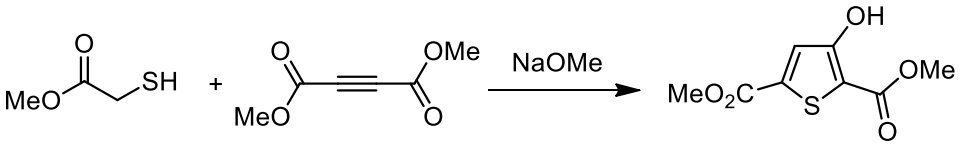
1.4a Synthetic utility of Thiophene

Thiophenes are noted in literature for numerous medicinal and material based applications and hence the syntheses of thiophene derivatives are highly desirable to organic chemists. Well known synthetic procedure for thiophene synthesis includes Paal-Knorr thiophene synthesis, Fiesselmann thiophene synthesis and Gewald amino thiophene synthesis.[45] Paal-Knorr thiophene synthesis[46] allows the formation of thiophenes by condensation of 1,4-dicarbony1 compounds in the presence of an excess of sulfur such as phosphorous Pentasulfide or lawessons's reagent as shown in Scheme 14.



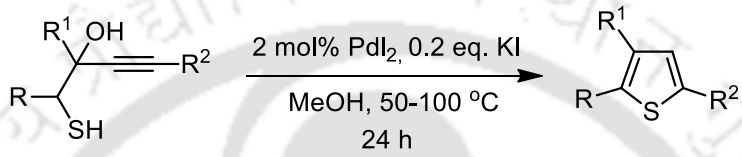
Scheme 14

In 1954, Fiesselmann developed[47] the synthesis of thiophene derivatives from the condensation reaction of thioglycolic acid derivatives with α, β- acetylenic esters, which upon treatment with a base resulted in the formation of 3-hydroxyl-2-thiophenecarboxylic acid derivatives as shown in Scheme 15.



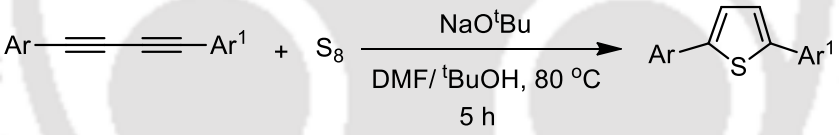
Scheme 15

Recently, Gabriele *et al*. reported[48] palladium-catalyzed heterocyclodehydration reaction of 1-mercapto-3-yn-2-ols in methanol as solvent in the presence of catalytic amounts of PdI_2 along with KI as additive for the construction of substituted thiophenes as shown in Scheme 16.



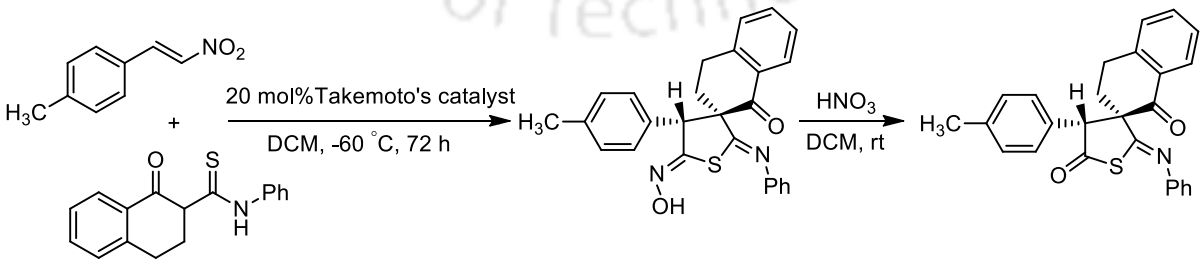
Scheme 16

Recently, Zhang *et al*. established[49] a facile base-promoted single-step protocol for the synthesis of thiophene derivatives using 1,3-diynes via the interaction between elemental sulfur and NaO^tBu as shown in Scheme 17.



Scheme 17

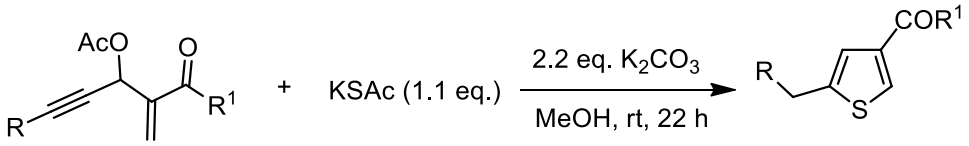
Recently, Zeng *et al*. established[50] an enantioselective route towards the construction of polyfunctionalized spiroannulated dihydrothiophenes via a formal thio [3+2] cyclization using Takemoto's organocatalyst as shown in Scheme 18.



Scheme 18

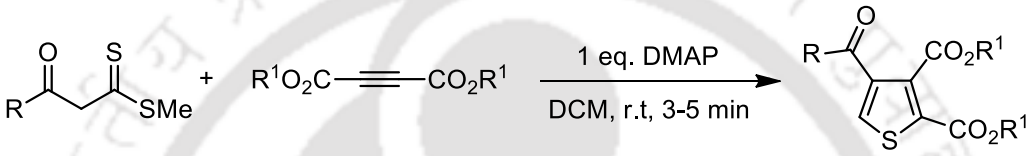
The synthesis of substituted thiophenes via the base-promoted thioannulation of Morita–Baylis–Hillman acetates of acetylenic aldehydes with potassium thioacetate involving a

tandem allylic substitution/deacetylate 5-exo-dig-thiocycloisomerization has recently been reported by Reddy and co-workers[51] as shown in scheme 19.



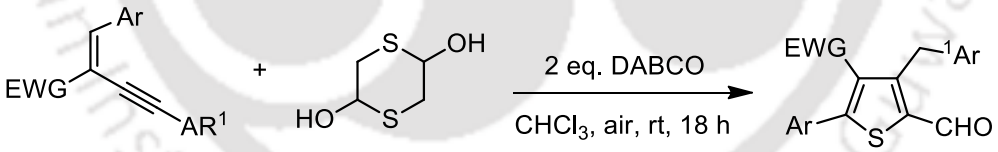
Scheme 19

Recently, Singh *et al*. developed[52] one-pot two-component [3 + 2] cycloaddition/annulation protocol for the synthesis of highly functionalized thiophene derivatives as shown in Scheme 20.



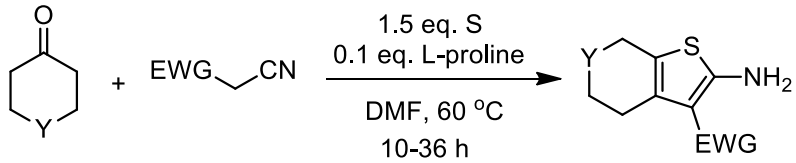
Scheme 20

Punniyamurthy and co-workers reported[53] domino synthesis of tetra substituted thiophenes from 1,3-enynes and mercaptoacetaldehyde in the presence of DABCO at room temperature via a Michael addition, 5-exo-dig carboannulation and oxidation sequence under air as shown in scheme 21.



Scheme 21

Recently, Wang *et al*. reported[54] one-pot procedure for the direct catalytic synthesis of functionalized 2-aminothiophene scaffolds catalyzed by L-proline under mild reaction conditions as shown in Scheme 22.



Scheme 22

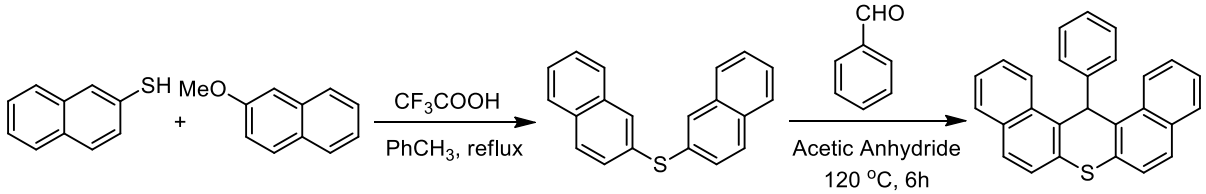
Over the years, a large number of papers have been published for the synthesis of various thiophene derivatives using different metal and nonmetal catalysts.[55] Although, these methods are quite useful but still the major limitations of these established methods lies in poor selectivity, harsh reaction conditions, employment of toxic metal catalysts and longer reaction time. Thus, the scientific fraternities are always on a chase to look for development of alternative new methodologies that employs milder reaction conditions with high stereoselectivity for the synthesis of thiophenes.

1.5 Thiopyran and its importance

Sulphur containing heterocyclic compounds has cached a considerable attention of synthetic chemists over the last few years due to its great medicinal value. In the field of medicinal chemistry thiopyran skeleton acts as vital units and are used as popular building blocks for the synthesis of a wide range of important drugs for psychotic disorder.[56] An extensive literature survey reveals that in the construction of natural products[57a] analogues with various pharmaceutical properties such as anti-hyperplasia,[57b] anti-bacteria,[57c] antiinflammatory[57d] and anticancer activities[58a,b] thiopyran moiety were commonly used as a one of the major constituent. The anticancer activity of thiopyran analogs displayed that they are one of the active anti-proliferative agents against tumor cell lines and have high lipophilicity and might cause insufficient bio-membrane permeability. The substituted thiochromone molecules having thiopyran unit, act as potent inhibitors of deoxyribonucleic acid-protein kinase.[58c]

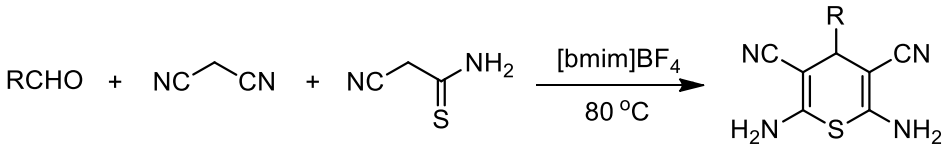
1.5a Synthetic utility of Thiopyran

On account of the immense potentiality of thiopyrans, various research groups have put forward considerable efforts to synthesize these compounds in recent times. Recently, Mullen *et al*. reported[59] an acid-catalyzed ether-sulfide exchange reaction between 2-methoxynaphthalene and naphthalene-2-thiol giving rise to dinaphthalen-2-ylsulfane, which undergoes further condensation with benzaldehyde to provide thiopyran derivatives as depicted in Scheme 23.



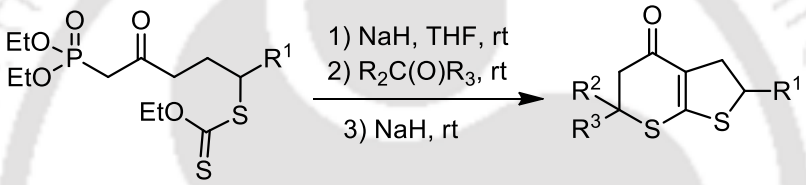
Scheme 23

Zhang *et al*. described[60] ionic liquid promoted preparation of 4H-thiopyran derivatives through one-pot multi-component reaction of thioamide, aldehyde and malononitrile as shown in scheme 24.



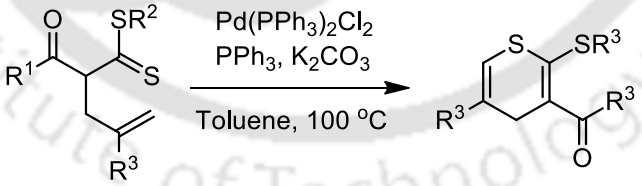
Scheme 24

Corbet and co-workers established[61] one-pot synthesis of various functionalized thieno[2,3 *b*]thiopyran-4-ones from readily available β-keto *ε*-xanthyl phosphonates by combining a Horner-Wadsworth-Emmons olefination with a base-induced intramolecular domino cyclization/thio-Michael addition as shown in scheme 25.



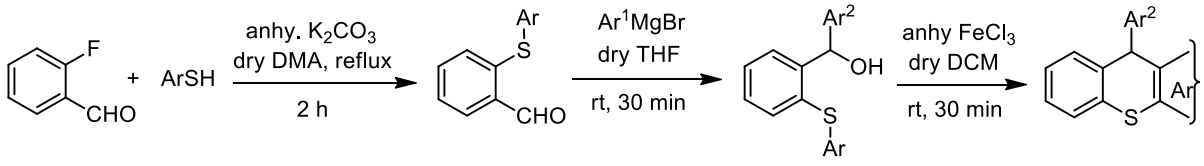
Scheme 25

Recently, Singh *et al*. turned their attention towards[62] palladium catalyzed regioselective synthesis of thiopyran frameworks from intramolecular C_{δ}–S fusion of α-Allyl-β′-oxodithioesters as shown in scheme 26.



Scheme 26

Recently, Panda *et al*. demonstrated[63] a new synthetic route to 9-arylthioxanthenes by $FeCl_3$ catalyzed diaryl methylation of electron-rich arenes. The driving force of reaction is the cationic activation of diaryl carbinols by catalytic amount of $FeCl_3$ as shown in scheme 27.



Scheme 27

Most of the reported methods for synthesis of these compounds suffer from several disadvantages such as the cost of reagents, need of multiple reaction steps, long reaction times, and low yields. Hence, the development of improved methods for the preparation of thiopyran compounds continues to be an interesting goal to both synthetic and medicinal chemists. Therefore, still there exists a scope for upgradation to a new methodology which might be superior in terms of yield, reaction time and substrate scope compatibility employing mild reaction conditions.

1.6 1,2-dithole and its importance

The chemistry of 1,2-dithioles has been less studied as compared to other sulfur heterocycles. Organic skeletons having a cyclic disulphide fused to a benzene ring leaves an indication that these might show unusual redox properties.[64a]

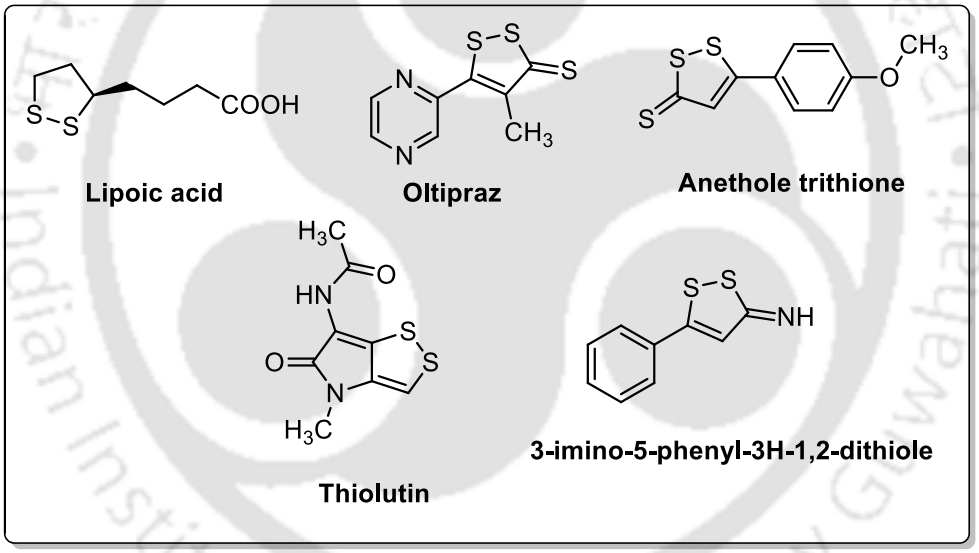


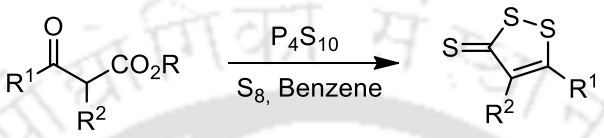
Figure 4. Biologically active 1,2-dithioles present in nature and drugs

These moieties are also biologically active, for example R-lipoic acid is a naturally occurring antioxidant and essential cofactor of four mitochondrial enzyme complexes.[64b-f] The drug Oltipraz containing 1,2-dithiole-3-thione core is potent chemo preventive agent against Schistosoma mansoni and Schistosoma hematobium.[65a,b] The 1,2-dithole based drug, anethole trithione [5-(4-methoxyphenyl)-3H-1,2-dithiole-3-thione] is used as a salivation enhancer for the treatment of dry mouth.[65c,d] In addition, 1,2-dithioles are versatile building blocks that can be employed in many chemical transformations for the synthesis of natural products.[66] Moreover, the 1,2- dithiole derivatives exhibit anti-HIV activities[67a-d] and cytoprotective effects in a variety of cell/tissue types and disease models.[67e] Several other derivatives of 1,2-

dithiole are reported to have a wide range of biological activity as shown in Figure 4. Moreover, 3-imino-5-phenyl-1,2-dithiole (PDTI) inhibit the replication of poliovirus owing to disruption of viral RNA synthesis.[68]

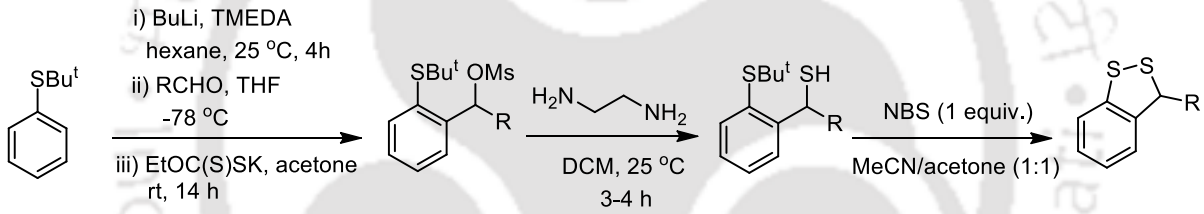
1.6a Synthetic utility of 1,2-dithole

Numerous biological importance of 1,2-dithiole calls for the development of convenient and practical approaches for the preparation of this prized moiety. Traditonally 1,2-dithioles are synthesized[69] using 1,3-ketoesters with mixtures of P_2S_5/S as shown in Scheme 28.



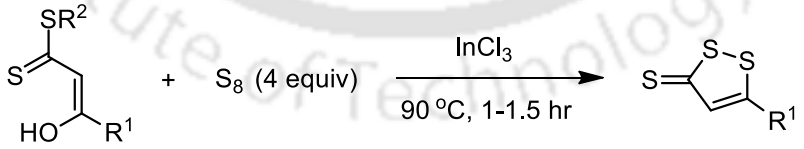
Scheme 28

Recently, Chan *et al*. described[64a] a novel route for the synthesis of 3-substituted-3H-1,2-benzodithioles via oxidative S-dealkylation of tert-butyl aryl sulfides as shown in Scheme 29.



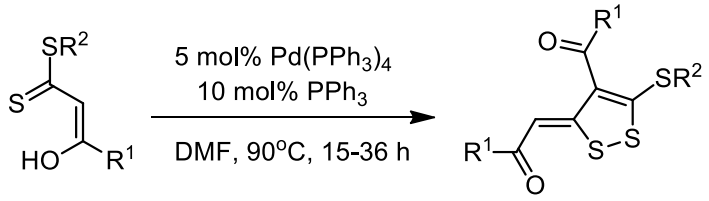
Scheme 29

Koley *et al*. developed[70] a cascade protocol for the construction of 1,2-dithioles derivatives from the reaction of α-enolic dithioesters with elemental sulfur in the presence of $InCl_3$ under solvent-free conditions as shown in Scheme 30.



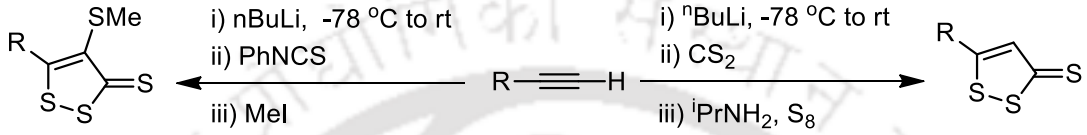
Scheme 30

Chowdhury *et al*. reported[71] a convenient one-pot synthesis for the construction of 3,4,5-trisubstituted 1,2-dithioles via palladium catalyzed self-coupling of R-enolic dithioesters as shown in Scheme 31.



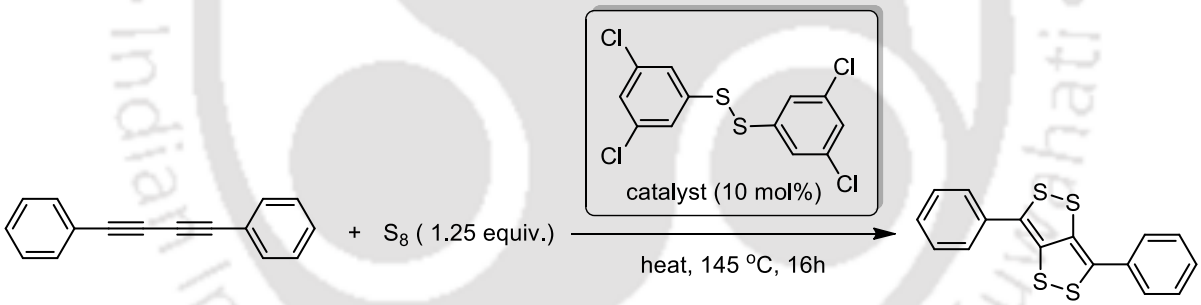
Scheme 31

Adams and co-workers[72] established one-pot synthesis of 1,2-dithiole-3-thiones and 3-imino-1,2-dithioles from terminal alkynes as shown in Scheme 32.



Scheme 32

Recently, Schipper *et al*. have developed[73] the synthesis dithiolodithiole heterocycle which was further used as a new building block for organic electronic materials as shown in Scheme 33.



Scheme 33

From the literature it is evident that the 1,2-dithioles derivatives displays wide range of biological activities. Therefore, the development of new methodologies related to synthesis of 1,2-dithioles derivatives are always a greeting to synthetic organic chemists.

1.7 Sulfenamides, Disulfides, Sulfane and their importances

Organosulfur compounds having S-N, S-S and S-C bonds are known as sulfenamides, disulfides and sulfane respectively. These finds incredible attention of chemical community over the years due to industrial applications, utility as synthetic reagents and interesting pharmaceutical properties.[74] In addition, sulfenamides are also used as load-capacity improvers in lubricants wood preservatives, fungicides, paints, antimicrobial finishes for

textiles and additive to a wood-free thermal recording material.[75] Sulfenamides as a source of sulfur are found to be superior to elemental sulfur as cross-linking agents in the vulcanization of natural and synthetic rubber. Benzo-1,3-thiazole-2-sulfenamides are commonly used as vulcanization accelerator.[76] Compounds containing a disulfide linkage are used for the synthesis of catenanes, macrocycles, carceplexes, dendrimers, rotaxanes and micelles. Organic molecules having sulfane linkage are used in polymer chemistry as well as material science.[77] Some of the biologically active sulfenamides, disulfides and sulfane based organic molecules are shown in Figure 5.

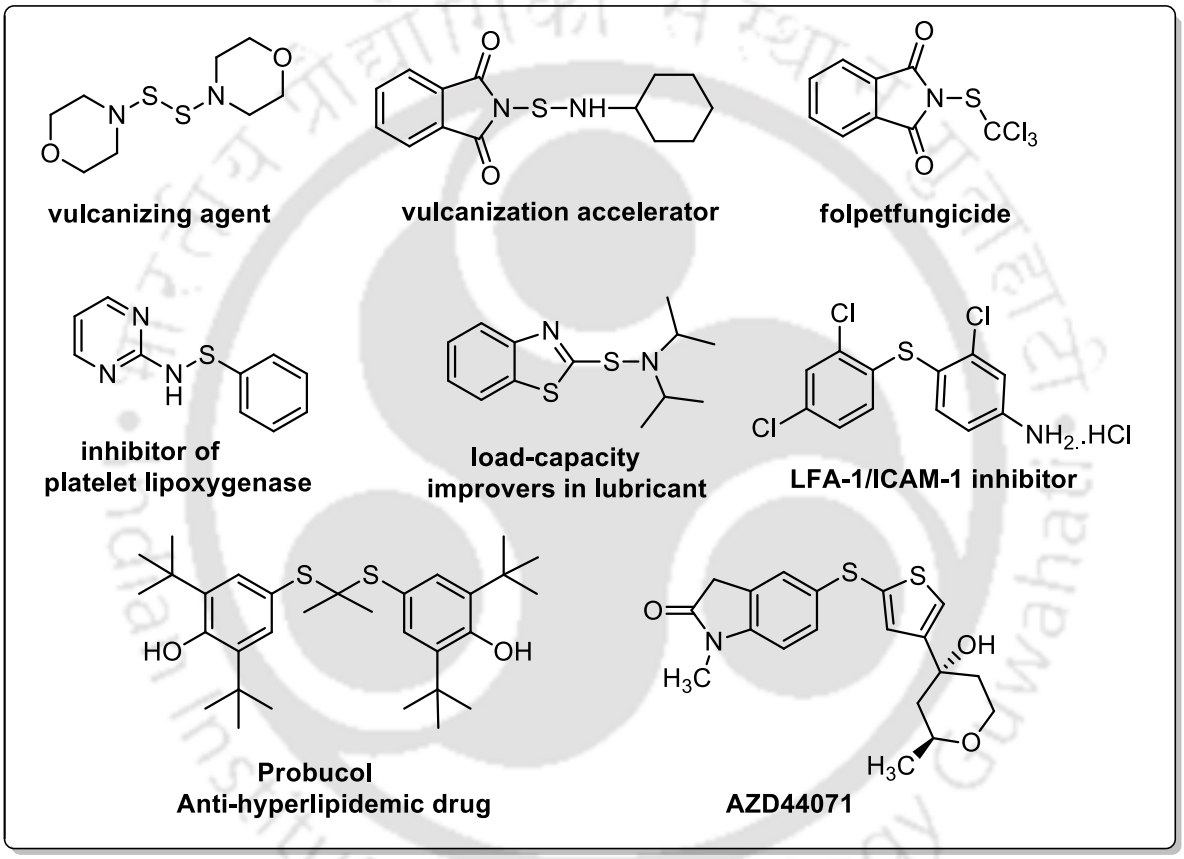
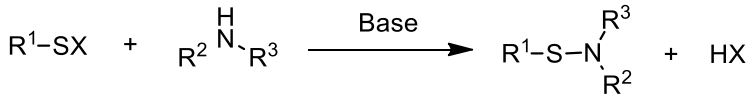


Figure 5: Biologically active sulfenamides, disulfides and sulfanes based organic molecules

1.7a Synthetic utility of Sulfenamides, Disulfides and Sulfane

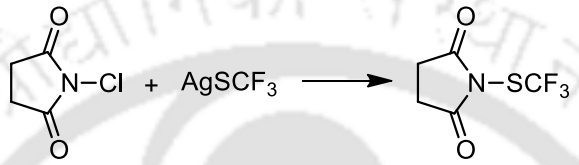
The synthesis of sulfenamides, disulfides and sulfanes based organic molecules are great importance to synthetic organic chemists on account of their unique structure and reactivity. Traditionally the key to sulfenamide preparation involves the condensation of sulfenyl chlorides and amine.[78] The reaction proceeds via nucleophilic attack of the amine on the sulfenyl halide. The acid formed in the reaction is neutralized by the addition of excess base

such as triethylamine, alkali-metal hydroxide, sodium hydride and others as shown in Scheme 34.



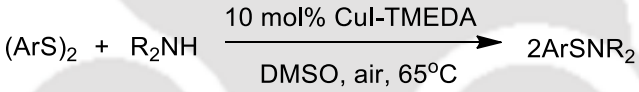
Scheme 34

Recently, Zhu *et al*. reported[79] the reaction of N-chlorosuccinimide with metal thiolates leading to the formation of N-acylsulfenamides as shown in Scheme 35.



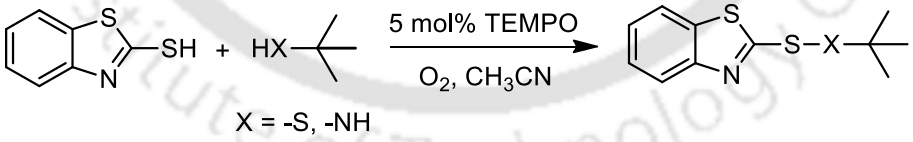
Scheme 35

Taniguchi *et al*. reported[80] copper-catalyzed formation of sulfenamides by dehydrocoupling of aryl thiols with amines under oxygen atmosphere as shown in scheme 36.



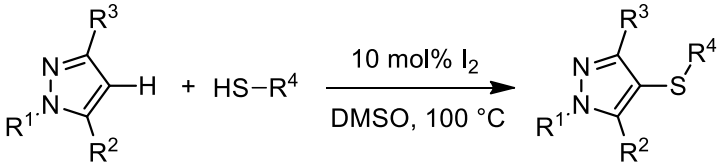
Scheme 36

Recently, Yuan *et al*. developed[81] a new aerobic oxidative coupling method to construct S-N/S-S bonds using TEMPO as the catalyst and O_2 as the oxidant as shown in scheme 37.



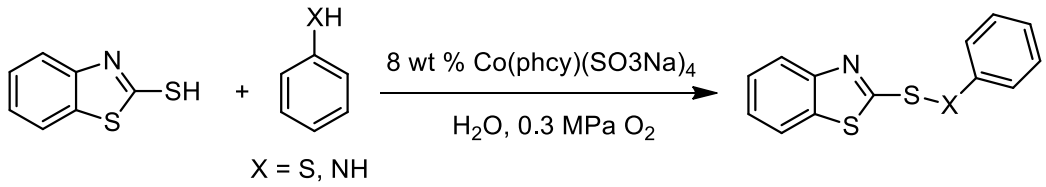
Scheme 37

Wang and co-workers established[82] iodine-catalyzed cross-dehydrogenative C–S coupling method for the synthesis of C-4 sulfenylated pyrazoles as shown in Scheme 38.



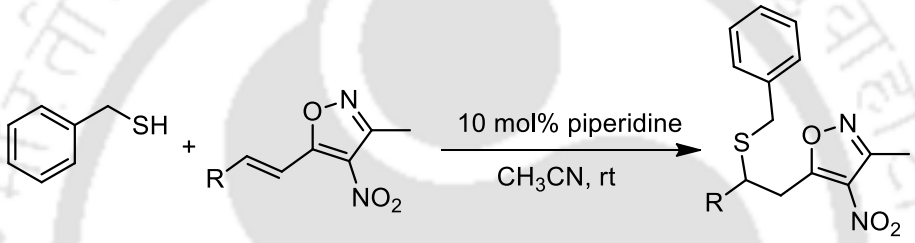
Scheme 38

Further, Yuan *et al*. reported[83] a new aerobic oxidative coupling of thiols in water to construct sulfenamides or disulfides using catalytic amount of cobalt (II) phthalocyanine-tetra-sodium sulfonate and O_2 as the oxidant as shown in Scheme 39.



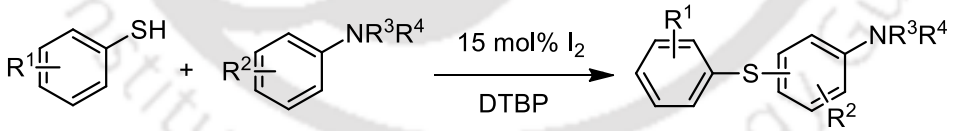
Scheme 39

Adamo and co-workers reported[84] an efficient procedure for synthesis of sulfane from the reactions of benzyl thiol to styrylisoxazoles in the presence of catalytic amount of piperidine as shown in Scheme 40.



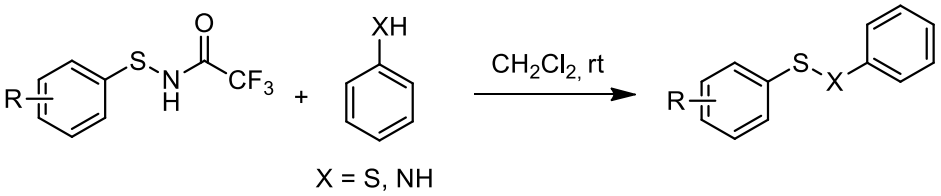
Scheme 40

Wang *et al*. established[85] iodine-catalyzed direct arylthiation of substituted anilines for the synthesis of various diaryl sulfides under metal and solvent-free conditions as shown in Scheme 41.



Scheme 41

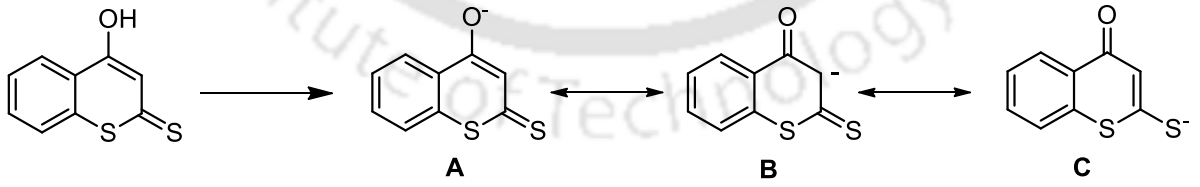
Shimizu *et al*. described[86] an effective method for the synthesis of unsymmetrical disulfides and sulfenamides from the reactions of N-Trifluoroacetyl arenesulfenamides with a variety of aromatic thiols/amines in the presence of dichloromethane at room temperature as shown in Scheme 42.



Scheme 42

Unfortunately, most of the reported methods suffer from one or more shortcomings such as the moisture and thermal sensitivity of the starting material, use of metal catalyst, prolonged reaction times, limited substrate scope reaction, employment of harsh and restricted conditions, such as a high reaction temperature, aerobic conditions or leave a scope for the formation of side products. Due to the increasing demand for sustainable methods in organic synthesis designing a competent and versatile strategy for the synthesis of sulfenamides, disulfides and sulfane based organic molecules is necessary to overcome all these precincts.

From literature, it is worth mentioning that organosulfur compounds have impending application in various pharmacological activities and possess enormous potential for the synthesis of numerous natural products as well. As a consequence, chemists are always on a quest to the develop plethora of new and efficient catalytic route towards the synthesis of novel organosulfur molecules in eco-friendly manner with good yields. Majumdar and co-workers have utilized 4-hydroxydithiocoumarin for the synthesis of numerous organosulfur compounds.[27,28,30,31] It has a unique nature that it can exist in three different resonating structures after deprotonating. Consequently, there are three possible reactive sites that creates a scope for further development of new strategies leading to the formation of new organosulfur compounds.



Thus, the thesis work is designed to employ 4-hydroxydithiocoumarin as an useful starting material for the synthesis of 1,3-thiazine, thiophene, thiopyran, 1,2-dithole, sulfenamides, disulfides and sulfane based new organosulfur molecules through fine tuning of the reaction conditions, which will be discussed in the successive chapters of this thesis.

Reference

1. (a) Ingall, A. H. In Comprehensive Heterocyclic Chemistry II; Boulton, A. S.; McKkillop, A. ed. Pergamon Press: Oxford, **1996**, *5*, 501. (b) Chatgilialoglu, C.; Asmus, K.-D. Sulfur-Centered Reactive Intermediates in Chemistry and Biology, Springer, New York, 1991. (c) Schneller, S. W. *Adv. Heterocycl. Chem*. **1975**, *18*, 59.
2. (a) Fraústo da Silva, J. R.; Williams, R. J. P. The Biological Chemistry of the Elements, Oxford University Press: New York, 2001. (b) Overman, R. S., Stahmann, M. A.; Heubner, C. F.; Sullivan, W. R.; Spero, L.; Doherty, D. C.; Ikawa, M.; Graf, L.; Roseman, S.; Link, K. P. *J. Biol. Chem*. **1944**, *153*, 5.
3. (a) Chatgilialoglu, C.; Asmus, K.-D. Sulfur-Centered Reactive Intermediates in Chemistry and Biology, Springer, New York, 1991. (b) Fluharty, A. L. In The Chemistry of the Thiol Group, part 2, Patai, S., Ed., Wiley: New York, 1974, pp. 589.
4. (a) Burdock, G. A. Fenaroli's Handbook of Flavor Ingredients, 6th ed., CRC Press, Boca Raton, FL, 2010. (b) Bentley, R. *Chem. Rev*. **2006**, *106*, 4099. (c) Escudero, A.; Hernandez-Orte, P.; Cacho, J.; Ferreira, V. *J. Agric. Food Chem*. **2000**, *48*, 4268.
5. (a) Schutte, L.; Teranishi, R. *CRC Crit. Rev. Food Technol.* **1974**, *4*, 457. (b) Kolor, M. G. *J. Agric. Food Chem*. **1983**, *31*, 1125. (c) Waterhouse, A. L.; Ebeler, S. E.; Eds. Chemistry of Wine Flavor; ACS Symposium Series 714; American Chemical Society: Washington, DC, 1998.
6. (a) Smith, R. H. *Vet Res Commun*. **1978**, *2*, 47. (b) de Rooij, B. M.; Boogaard, P. J.; Rijksen, D. A.; Commandeur, J. N.; Vermeulen, N. P. *Arch Toxicol*. **1996**, *70*, 635.
7. (a) de Rooij, B. M.; Boogaard, P. J.; Commandeur, J. N.; van Sittert, N. J.; Vermeulen, N. P. *Occup Environ Med*. **1997**, *54*, 653. (b) Block, E. Garlic and Other Alliums: The Lore and the Science, RSC Publishing, Cambridge, England, 2009.
8. Chen, C.-C.; Ho, C.-T. *J. Agric. Food. Chem*. ***1986***, *34*, 830.
9. (a) Clayden, J.; MacLellan, P. Beilstein. *J. Org. Chem*. **2011**, *7*, 582; (b) Kondo, T.; Mitsudo, T.-A. *Chem. Rev*. **2000**, *100*, 3205. (c) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev*. **2011**, *111*, 1596. (d) Liu, H.; Jiang, X. *Chem. Asian J*. **2013**, *8*, 2546. (e) De Martino, G.; Edler, M. C.; La Regina, G.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem*. **2006**, *49*, 947. (f) Dondoni, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 8995.

10. Singh, R. Synthetic Drugs, Mittal Publication, New Delhi, 2002.

11. (a) Cerella, C.; Kelkel, M.; Viry, E.; Dicato, M.; Jacob, C.; Diederich, M. In Phytochemicals -Bioactivities and Impact on Health, Rasooli, I., Ed.; InTech: New York, USA, 2011, Chapter 1, pp 1-42. DOI: 10.5772/26003. (b) Damani, L. A. Sulfur-Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry, and Toxicology; Ellis Horwood Ltd.: Chichester, UK, 1989; Vol. 1, Part B: Metabolism of Sulfur Functional Groups.

12. (a) Bicking, J. B.; Holtz, W. J.; Watson, L. S.; Cragoe, Jr. E. J. *J. Med. Chem*. **1976**, *19*, 530. (b) Inomata, K.; Barrague, M.; Paquette, L. A. *J. Org. Chem*. **2005**, *70*, 533. (c) Yamauchi, M.; Katayama, S.; Watanabe, T. *Synthesis* **1982**, 935.

13. (a) Garrod, L. P. *Br. Med. J*. **1960**, *1*, 527. (b) Garrod, L. P. *Br. Med. J*. **1960**, *2*, 1695. (c) Alcaraz, M.-L.; Atkinson, S.; Cornwall, P.; Foster, A. C.; Gill, D. M.; Humphries, L. A.; Keegan, P. S.; Kemp, R.; Merifield, E.; Nixon, R. A.; Noble, A. J.; O'Beirne, D.; Patel, Z. M.; Perkins, J.; Rowan, P.; Sadler, P.; Singleton, J. T.; Tornos, J.; Watts, A. J.; Woodland, I. A. *Org. Process Res. Dev*. **2005**, *9*, 555.

14. Raghavan, S.; Sridhar, B. *J. Org. Chem*. **2010**, *75*, 498.

15. Piscitelli, S. C.; Goss, T. F.; Wilton, J. H.; D'Andrea, D. T.; Goldstein, H.; Schentag, J. *Antimicrob. Agents Chemother*. **1991**, *35*, 1765.

16. Bharathi, Ch.; Prabahar, K. J.; Prasad, Ch. S.; Rao, M. S.; Trinadhachary, G. N.; Handa, V. K.; Dandala, R.; Naidu, A. *Pharmazie* **2008**, *63*, 14.

17. Hickner, M. A.; Ghassemi, H.; Kim, Y. S.; Einsla, B. R.; McGrath, J. E. *Chem. Rev*. **2004**, *104*, 4587.

18. Kim, Y. S.; Wang, F.; Hickner, M.; Zawodzinski, T. A.; McGrath, J. E. *J. Membr. Sci*. **2003**, *212*, 263.

19. Savadogo, O. *J. New Mater. Electrochem. Syst*. **1998**, *1*, 47. (a) Roziere, J.; Jones, D. J. *Annu. Rev. Mater. Res*. **2003**, *33*, 503. (b) Alberti, G.; Casciola, M. *Annu. Rev. Mater. Res*. **2003**, *33*, 129.

20. (a) Balandrin, M. F.; Lee, S. M.; Klocke, J. A. *J. Agric. Food Chem*. **1988**, *36*, 1048. (b) Blackburn, R. S.; Harvey, A. *Environ. Sci. Technol*. **2004**, *38*, 4034. (c) Takaki, T.; Yagishita, K.; Tsujimoto, T.; Wakabayashi, T. *Lubricants* **2017**, *5*, 8.

21. (a) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147. (b) Rayner, C. M. *Contemp. Org. Synth*. **1995**, *2*, 409.

22. (a) Simpkins, N. S. Sulfones in Organic Synthesis; Pergamon Press: Oxford, 1993. (b) Block, E. Reaction of OrganosuIfur Compounds; Academic Press: New York, 1978. (c) Liu, Y.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron Lett*. **2011**, *52*, 2935. (d) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y. *Org. Lett*. **2013**, *15*, 1270.

23. (a) Kennedy, R. O.; Thornes, R. D. Coumarins: Biology, Applications and Mode of Action; Wiley: Chichester, UK, 1997. (b) Murray, R. D. H.; Medez, J.; Brown, S. A. The Natural Coumarins: Occurrence, Chemistry, and Biochemistry; Wiley: New York, NY, 1982.

24. (a) Maeda, M. Laser Dyes; Academic: New York, NY, 1984. (b) Peter, H. *Dev. Oncol*. **1984**, *22*, 259.

25. (a) Feuer, G. In Progress in Medicinal Chemistry; Ellis, G. P., West, G. B., Eds.; North-Holland Publishing Co.: New York, 1974. (c) Kostova, I. *Curr. Med. Chem. Anti-Cancer Agents* **2005**, *5*, 29. (d) Wenkert, E.; Buckwalter, B. L. *J. Am. Chem. Soc*. **1972**, *94*, 4367. (e) Deana, A. A. *J. Med. Chem*. **1983**, *26*, 580.

26. Andersonmckay, J. E.; Liepa, A. J. *Aust. J. Chem*. **1987**, *40*, 1179.

27. Majumdar, K. C.; Khan, A. T.; Saha, S. *Synth. Commun*. **1992**, *22*, 901.

28. Majumdar, K. C.; Bandyopadhyay. A. *Monatshefte fur Chemie* **2004**, *135*, 581.

29. Moghaddam, F. M.; Kiamehr, M.; Khodabakhshi, M. R.; Mirjafary, Z.; Fathi, S.; Saeidian, H. *Tetrahedron* **2010**, *66*, 8615.

30. Majumdar, K. C.; Taher, A.; Ponra, S. *Tetrahedron Lett*. **2010**, *51*, 2297.

31. Majumdar, K. C.; Ponra, S.; Ghosh, T. *RSC Adv*. **2012**, *2*, 1144.

32. (a) Lanbach, G. D.; Lombardino, J. G.; McLamore, W. M. Derivatives of thiabenzopyrrocoline, thiabenzopyridocoline and thiazepine. US2985649A, 1961. (b) Sammes, P. G. *Chem. Rev*. **1976**, *76*, 113.

33. (a) Cecchetti, V.; Filipponi, E.; Fravolini, A.; Tabarrini, O.; Xin, T. *Bioorg. Med. Chem.* **1997**, *5*, 1339. (b) Kumar, A.; Rajput, C. S.; Bhati, S. K. *Bioorg. Med. Chem*. **2007**, *15*, 3089. (c) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev*. **2005**, *105*, 395.

34. (a) Hossaini, Z.; Nematpour, M.; Yavari, I. *Monatsh Chem*. **2010**, *141*, 229. (b) Rai, V. K.; Yadav, B. S.; Yadav, L. D. S. *Tetrahedron* **2009**, *65*, 1306. (c) Fodor, L.; Szabó, J.; Bernáth, G.; Sohár, P.; Maclean, D. B.; Smith, R. W.; Ninomiya, I.; Naito, T. *J. Heterocycl. Chem*. **1989**, *26*, 333.

35. Huang, S.; Pan, Y.; Zhu, Y.; Wu. A. *Org. Lett*. **2005**, *7*, 3797.

36. Peudru, F.; Cavelier, F. L.; Lohier, J-F-O.; Gulea, M.; Reboul, V. *Org. Lett*. **2013**, *15*, 5710.

37. Jarvis, C. L.; Richers, M. T.; Breugst, M.; Houk, K. N.; Seidel, D. *Org. Lett*. **2014**, *16*, 3556.

38. Bhowmik, S.; Mishra, A.; Batra, S. *RSC Adv*. **2011**, *1*, 1237.

39. Spitz, C. D.; Lohier, J-F-O.; Reboul, V.; Metzner, P. *Org. Lett*. **2009**, *11*, 2776.

40. Sathishkumar, M.; Sathiyanarayanan, K. I. *RSC Adv*. **2014**, *4*, 8808.

41. Simerpreet.; Damanjit, C. S. *Pharmacophore Rev.* **2013**, *4*, 70.

42. (a) Eicher, T.; Hauptmann, S.; Speicher, A. The Chemistry of Heterocycles; Wiley-VCH: New York, 2003; Chapter 5, section 5.6. (b) Dore, K.; Dubus, S.; Ho, H. A.; Levesque, I.; Brunette, M.; Corbeil, G.; Boissinot, M.; Boivin, G.; Bergeron, M. G.; Boudreau, D.; Leclerc, M. *J. Am. Chem. Soc*. **2004**, *126*, 4240.

43. (a) Zempleni, J.; Wijeratne, S. S. K.; Hassan, Y. I. Bio Factors **2009**, *35*, 36. (b) Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Chem. Rev*. **2012**, *112*, 2129.

44. (a) Haraguchi, K.; Shimada, H.; Tanaka, H.; Hamasaki, T.; Baba, M.; Gullen, E. A.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem*. **2008**, *51*, 1885. (b) El-Aasr, M.; Fujiwara, Y.; Takeya, M.; Ono, M.; Nakano, D.;Okawa, M.; Kinjo, J.; Ikeda, T.; Miyashita, H.; Yoshimitsu, H.; Nohara, T. *Chem. Pharm. Bull*. **2011**, *59*, 1340. (c) Hou, X.; Majik, M. S.; Kim, K.; Pyee, Y.; Lee, Y.; Alexander, V.; Chung, H. J.; Lee, H. W.; Chandra, G.; Lee, J. H.; Park, S. G.; Choi, W. J.; Kim, H. O.; Phan, K.; Gao, Z. G.; Jacobson, K. A.; Choi, S.; Lee, S. K.; Jeong, L. S. *J. Med. Chem*. **2012**, *55*, 342.

45. (a) Gewald, K. *Angew. Chem*. **1961**, *73*, 114. (b) Revelant, G.; Dunand, S.; Hesse, S.; Kirsch, G. *Synthesis* **2011**, 2935.

46. (a) Knorr, L. *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 1635. (b) Paal, C. *Ber. Dtsch. Chem. Ges*. **1885**, *18*, 367. (c) Campaigne, E.; Foye, W. O. *J. Org. Chem*. **1952**, *62*, 1405. (d) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem*. **2005**, 5277.

47. (a) Fiesselmann, H.; Schipprak, P. *Chem. Ber*. **1954**, *87*, 835. (b) Fiesselmann, H.; Schipprak, P.; Zeitler, L. *Chem. Ber*. **1954**, *87*, 841. (c) Fiesselmann, H.; Pfeiffer, G. *Chem. Ber*. **1954**, *87*, 848. (d) Fiesselmann, H.; Thoma, F. *Chem. Ber*.**1956**, *89*, 1907. (e) Fiesselmann, H.; Schipprak, P. *Chem. Ber*. **1956**, *89*, 1897.

48. Gabriele, B.; Mancuso, R.; Veltri, L.; Maltese, V.; Salerno, G. *J. Org. Chem*. **2012**, *77*, 9905.

49. Zhang, G.; Yi, H.; Chen, H.; Bian, C.; Liu, C.; Lei, A. *Org. Lett*. **2014**, *16*, 6156.

50. Zeng, X-M.; Meng, C-Y.; Bao, J-X.; Xu, D-C.; Xie, J-W.; Zhu, W-D. *J. Org. Chem*. **2015**, *80*, 11521.

51. Reddy, C. R.; Valleti, R. R.; Reddy, M. D. *J. Org. Chem*. **2013**, *78*, 6495.

52. Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem*. **2011**, *76*, 8009.

53. Bharathiraja, G.; Sathishkannan, G.; Punniyamurthy.; T. *J. Org. Chem*. **2016**, *81*, 2670.

54. Wang, T.; Huang, X-G.; Liu, J.; Li, B.; Wu, J-J.; Chen, K-X.; Zhu, W-L.; Xiao-Yong Xu, X-Y.; Zeng, B-B. *Synlett* **2010**, *9*, 1351.

55. (a) Fujita, M.; Seki, T.; Ikeda, N. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 1897. (b) Lutjens, H.; Zickgraf, A.; Figler, H.; Linden, J.; Olsson, R. A.; Scammells, P. J. *J. Med. Chem*. **2003**, *46*, 1870. (c) Barnes, D. M.; Haight, A. R.; Hameury, T.; McLaughlin, M. A.; Mei, J. Z.; Tedrow, J. S. J.; Toma, D. R. *Tetrahedron* **2006**, *62*, 11311. (d) Aumann, K. M.; Scammells, P. J.; White, J. M.; Schiesser, C. H. *Org. Biomol. Chem*. **2007**, *5*, 1276. (e) Harza, K.; Saravanan, J.; Mohan, S. *Asian J. Chem*. **2007**, *19*, 3541.

56. El-Subbagh, H. I.; El-Emam, A. A.; El-Ashmawy, M. B.; Shehata, I. A. *Arch. Pharm. Res*. **1990**, *13*, 24. and references cited therein.

57. (a) Murray, R. D. H. *Prog. Chem. Org. Nat. Prod*. **1991**, *58*, 84. (b) Quaglia, W.; Pigini, M.; Piergentili, A.; Giannella, M.; Gentili, F.; Marucci, G.; Carrieri, A.; Carotti, A.; Poggesi, E.; Leonardi, A.; Melchiorre, C. *J. Med. Chem*. **2002**, *45*, 1633. (c) Brown, M. J.; Carter, P. S.; Fenwick, A. E.; Fosberry, A. P., Hamprecht, D. W.; Hibbs, M. J.; Jarvest, R. L.; Mensah, L.; Milner, P. H.; O'Hanlon, P. J.; Pope, A. J.; Richardson, C.

M.; West, A.; Witty, D. R. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 3171. (d) Rogier, D. J. Jr.; Carter, J. S.; Talley, J. J. WO 2001049675, 2001.

58. (a) Berlin, K. D.; Benbrook, D. M.; Nelson, E. C. U.S. Patent, **2003**, 6586460. (b) Sugita, Y.; Hosoya, H.; Terasawa, K.; Yokoe, I.; Fujisawa, S.; Sakagami, H. *Anticancer Res*. **2001**, *21*, 2629. (c) Hollick, J. J.; Golding, B. T.; Hardcastele, I. R.; Martin, N.; Richardson, C.; Rigoreau, L. J.; Smith, G. C.; Girffin, R. *J. Bioorg. Med. Chem. Lett*. **2003**, *13*, 3083.

59. Wu, D.; Pisula, W.; Haberecht, M. C.; Feng, X.; Mullen, K. *Org. Lett*. **2009**, *11*, 5686.

60. Zhang, X.; Li, X.; Fan, X.; Wang, X.; Li, D.; Qu, G.; Wang, J. *Molec. Divers.* **2009**, *13*, 57.

61. Corbet, M.; Zard, S. Z. *Org. Lett*. **2008**, *10*, 2861.

62. Chowdhury, S.; Chanda, T.; Koley, S.; Anand, N.; Singh, M. S. *Org. Lett*. **2014**, *16*, 5536.

63. Das, S. K.; Singh, R.; Panda, G. *Eur. J. Org. Chem*. **2009**, 4757.

64. (a) Chan, M. F.; Garst, M. E. *J. Chem. Soc. Chem. Commun*. **1991**, 540. (b) Fischer, G. *Adv. Heterocycl. Chem*. **2013**, *109*, 1. (c) Pedersen, C. T. *Sulfur Rep*. **1995**, *16*, 173; (d) Pedersen, C. T. *Adv. Heterocycl. Chem*. **1982**, *31*, 63. (e) McKinnon, D. M. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; Vol. 3,. Chapter 11. (f) Landis, P. S. *Chem. Rev*. **1965**, *65*, 237.

65. (a) Clapper, M. L. *Pharmacol. Ther*. **1998**, *78*, 17. (b) Bae, E. J.; Yang, Y. M.; Kim, J. W.; Kim, S. G. *Hepatology* **2007**, *46*, 730. (c) Maxuitenko, Y. Y.; Libby, A. H.; Joyner, H. H.; Curphey, T. J.; Macmillan, D. L.; Kensler, T. W.; Roebuck, B. D. *Carcinogenesis* **1998**, *19*, 1609. (d) Roebuck, B. D.; Curphey, T. J.; Li, Y.; Baumgartner, K. J.; Bodreddigari, S.; Yan, J.; Gange, S. J.; Kensler, T. W.; Sutter, T. R. *Carcinogenesis* **2003**, *24*, 1919.

66. (a) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147. (b) Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. (c) Seebach, D. *Synthesis* **1969**, 17. (d) Bulman Page, P. C.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643. (e) Liang, F.; Zhang, J.; Tan, J.; Liu, Q. *Adv. Synth. Catal*. **2006**, *348*, 1986.

67. (a) Munday, R.; Zhang, Y.; Munday, C. M.; Li, J. *Chem.-Biol. Interact*. **2006**, *160*, 115. (b) Jia, Z.; Zhu, H.; Misra, H. P.; Li, Y. *Brain Res*. **2008**, *1197*, 159. (c) Jia, Z.; Misra, B. R.; Zhu, H.; Li, Y.; Misra, H. P. *NeuroToxicology* **2009**, *30*, 1. (d) Munday, R.; Zhang, Y.; Paonessa, J. D.; Munday, C. M.; Wilkins, A. L.; Babu, J. *J. Med. Chem.* **2010**, *53*, 4761. (e) Nguyen, T.-T.; Gouriou, Y.; Salle, M.; Frere, P.; Jubault, M.; Gorgues, A.; Toupet, L.; Riou, A. *Bull. Soc. Chim. Fr*. **1996**, *133*, 301.

68. Garozzo, A.; Pinizzotto, M. R.; Furneri, P. M.; Baratta, D.; Guerrara, F.; Castro, A.; Tornetta, B.; Geremia, E. *Antiviral Res*. **1990**, *14*, 267.

69. Curphey, T. J. *Tetrahedron Lett*. **2000**, *41*, 9963.

70. Koley, S.; Chanda, T.; Samai, S.; Singh, M. S. *J. Org. Chem*. **2016**, *81*, 11594.

71. Chowdhury, S.; Chanda, T.; Koley, S.; Ramulu, B. J.; Jones, R. C. F.; Singh, M. S. *Org. Lett*. **2013**, *15*, 5386.

72. Adams, H.; Hughes, A. J.; Morris, M. J.; Quenby, S. I. A. *Tetrahedron Lett*. **2014**, *55* 5283.

73. Schipper, D. J.; Moh, L. C. H.; Müller, P.; Swager, T. M. *Angew. Chem., Int. Ed*. **2014**, *53*, 5847.

74. (a) Mandal, B.; Basu, B. *RSC Adv*. **2014**, *4*, 13854. (b) Beletskaya, I.; Moberg, C. *Chem. Rev*. **1999**, *99*, 3435. (c) Ito, S.; Ota, A.; Suhara, H.; Tabashi, K.; Kawashima, Y. *Chem. Pharm. Bull*. **1993**, *41*, 1066. (d) Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem*. **1999**, *64*, 7305. (e) Kitagawa, H.; Mukaiyama, T. *Chem. Pharm. Bull*. **2002**, *50*, 1276.

75. (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev*. **2011**, *111*, 1596. (b) S. S. Mansy, S. S.; Cowan, J. A. *Acc. Chem. Res*. **2004**, *37*, 719.

76. (a) Harpp, D.; Back, T. *J. Org. Chem*. **1971**, *36*, 3828. (b) Craine, L.; Raban, M. *Chem. Rev*. **1989**, *89*, 689. (c) Guarino, V. R.; Karunaratne, V.; Stella, V. J. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4910.

77. Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc*. **1995**, *117*, 2937. (c) Ma, D.; Cai, Q. *Acc. Chem. Res*. **2008**, *41*, 1450.

78. (a) Davis, F. A.; Nadir, U. K. *Org. Prep. Proced. Znt*. **1979**, *11*, 33. (b) Craine, L.; Raban, M. *Chem. Rev*. **1989,** *89*, 689

79. Zhu, S-Q.; Xu, X-H.; Qing, F-L. *Eur. J. Org. Chem*. **2014**, 4453.

80. Taniguchi, N. *Eur. J. Org. Chem.* **2010**, 2670.

81. Yang, L.; Li, S.; Dou, Y.; Zhen, S.; Li, H.; Zhang, P.; Yuan, B.; Yang, G. *Asian J. Org. Chem.* **2017**, *6*, 265.

82. Yang, D.; Sun, P.; Wei, W.; Meng, L.; He, L.; Fang, B.; Jiang, W.; Wang, H. *Org. Chem. Front*. **2016**, *3*, 1457.

83. Dou, Y.; Huang, X.; Wang, H.; Yang, L.; Li, H.; Yuan, B.; Yang, G. *Green Chem.* **2017,** *19*, 2491

84. Bruschi, S.; Moccia, M.; Adamo, M. F. A. *Tetrahedron Lett.* **2011**, *52*, 3602.

85. Yang, D.; Yan, K.; Wei, W.; Zhao, J.; Zhang, M.; Sheng, X.; Li, G.; Lu, S.; Wang, H. *J. Org. Chem.* **2015**, *80*, 6083.

86. Bao, M.; Shimizu, M. *Tetrahedron* **2003**, *59*, 9655.

Chapter II

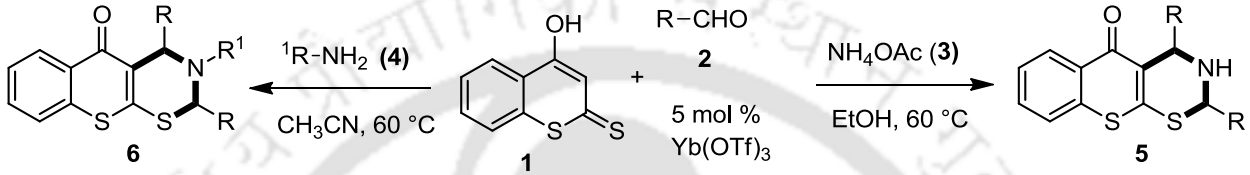
$Yb(OTf)_3$ catalysed regioselective synthesis of unusual di- and tri- substituted 3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one derivatives through a pseudo four-component hetero-Diels-Alder Reaction

Result & Discussion

Experimental Section

Results and Discussion

The synthetic strategies and importance of 1,3-thiazine have already been described in Chapter 1. In this Chapter, we present the synthesis of various 1,3-thiazine derivatives by finding an alternative to thiourea using multicomponent reactions (MCRs). Herein we report the synthesis of hitherto unreported 3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one derivatives through pseudo four component hetero-Diels−Alder reaction involving 4-hydroxydithiocoumarin, ammonium acetate / primary amines and aldehydes in the presence of 5 mol% ytterbium triflate as shown in Scheme 43.



Scheme 43. Synthesis of di- and tri- substituted 3,4-dihydrothiochromeno[3,2-*e*] [1,3]thiazin-5(2*H*)-one derivatives

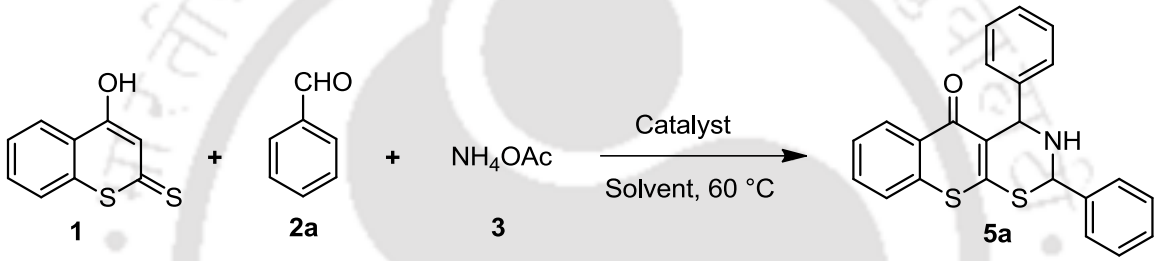
Multicomponent reactions are the convergent approach to synthesize selective final products from three or more starting materials in highly atom economical manner.[1] The MCRs provide a powerful strategy in diversity oriented synthesis of complex molecule with immense biomedical application,[2] a key step for challenging natural product synthesis and it also briefs that intermolecular C-N and C-S bond formation in hetero-Diels-Alder reaction achieve an exclusive role for the synthesis of particularly attractive bimolecular scaffolds.[3] The hetero-Diels-Alder reaction is a influential tool for carbon-carbon and carbon-hetero bond formation laying the foundation of complexity in structural motifs thus finding its application in the synthesis of various asymmetric heterocyclic compounds.[4] The expansion of prominent hetero-Diels−Alder reactions gives a platform to develop new multicomponent reactions which forms a broad area of research interest in modern organic synthesis.

An extensive literature[5] survey divulges that ytterbium triflate catalyzes a wide range of carbon–carbon and carbon–hetero atom bond forming reactions which led us to believe that it can be used to assist hetero-Diels-Alder reaction leading to the synthesis of novel 1,3-thiazine derivatives.

Initially, the reaction was performed with 4-hydroxydithiocoumarin (0.5 mmol), benzaldehyde (1.0 mmol) and ammonium acetate (1.0 mmol) in ethanol solvent as the model

substrates to find out the optimum reaction conditions. At 60 °C temperature in absence of any catalyst the reaction proved futile as it failed to produce any desired product (Table 1, entry 1). To our delight the product **5a** was isolated in 41% yield (Table 1, entry 2) when the same reaction was carried out with acetic acid as catalyst. The isolated product **5a** was characterized by IR, ^{1}H and ^{13}C NMR spectra and HRMS. With an effort to improve the yield, the reaction was again performed both with trifluoromethanesulfonic acid and iodine as catalyst but no significant improvement in yield was observed. However, trifluoromethanesulfonic acid led to the isolation of product **5a** in 52% yield while iodine gave only 38% yield (Table 1, entries 3 and 4). Next, we turned our attention towards metal catalysts.

Table 1. Optimization of the reaction conditions[a,b,c]



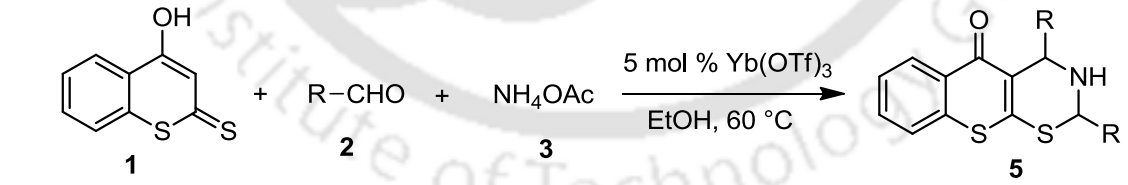
Entry	Catalyst (mol %)	Solvent	Time/h	Yield (%)[c]
01	-	EtOH	12	NR
02	AcOH (05)	EtOH	0.75	41
03	TfOH (05)	EtOH	0.5	52
04	I_2 (05)	EtOH	1	38
05	$In(OTf)_3$ (05)[b]	EtOH	2	trace
06	$In(OTf)_3$ (05)	EtOH	2	22
07	$Yb(OTf)_3$ (2.5)	EtOH	0.5	80
08	**$Yb(OTf)_3$ (05)**	**EtOH**	**0.25**	**86**
09	$Yb(OTf)_3$ (10)	EtOH	0.5	82
10	$Yb(OTf)_3$ (05)	MeOH	1	65
11	$Yb(OTf)_3$ (05)	^{n}BuOH	1.5	56
12	$Yb(OTf)_3$ (05)	CH_3CN	0.5	58

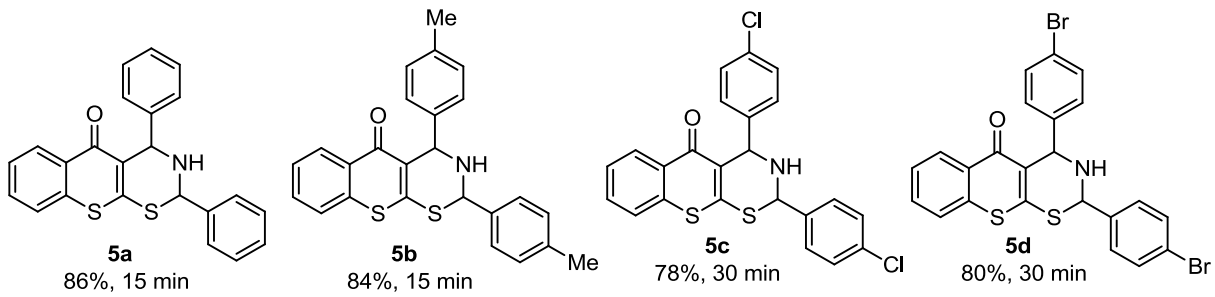
[a]All the reactions were carried out using 4-hydroxy-2*H*-thiochromene-2-thione (0.5 mmol), benzaldehyde (1 mmol) and ammonium acetate (1.0 mmol). [b]Reaction was carried out at room temperature. [c]Isolated yield.

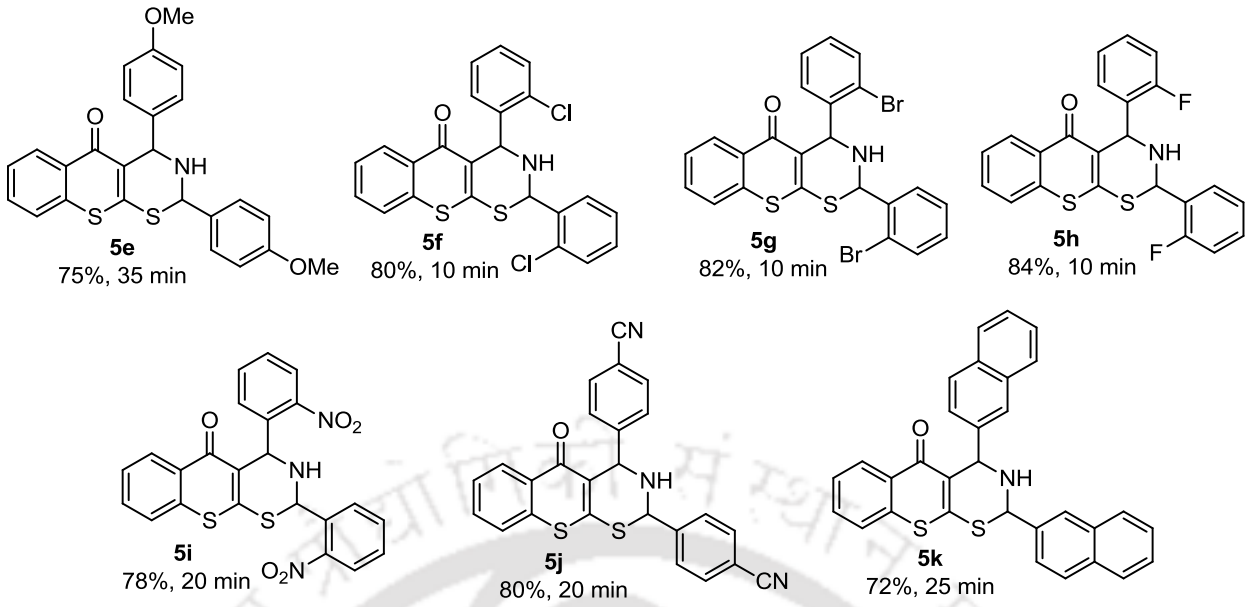
While carrying out the reaction with $In(OTf)_3$ at room temperature it do lead to the formation of trace amount of product **5a**, when the same set of reaction was carried at 60 °C temperature the product **5a** was obtained in only 22% yield (Table 1, entries 5 and 6), but after long time it resulted in multiple spot in TLC which were difficult to isolate. Subsequently the reaction was examined using 2.5 mol% $Yb(OTf)_3$ in ethanol at 60 °C temperature (Table 1, entry 7) and the product was obtained in 80% yield. The yield of the product was increased further when the reaction was executed with 5 mol% $Yb(OTf)_3$ in ethanol at 60 °C and the reaction time was also reduced to 15 min (Table 1, entry 8). This increase could be in accordance with the general trend of a catalyst. In order to obtain more better results, the reaction was scrutinized using 10 mol% catalyst, but the yield was not increased (Table 1, entry 9) which might be due to the deactivation of reactants in the presence of excess catalyst. To check the feasibility of the reaction in other solvents we scrutinized a range of solvents like methanol, butanol, acetonitrile but they also underwent drawbacks of longer reaction time and lower yields (Table 1, entries 9-11). Thus, it was noted that 5 mol % of $Yb(OTf)_3$ in ethanol under heating condition (60 °C) provided the optimum condition for this reaction in terms of yield and reaction time.

After optimization of the reaction condition, the scope of the reaction was investigated with various aromatic aldehydes having substituents on the aromatic ring and the results are summarised in Table 2.

Table 2. Synthesis of 2,4-diphenyl-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one derivatives using ytterbium(III) trifluoromethanesulfonate catalyst[a,b]







[a]All the reactions were carried out using 4-hydroxydithiocoumarin (0.5 mmol), aldehyde (1.0 mmol) and ammonium acetate (1.0 mmol) in ethanol (2 mL). [b]Isolated yield.

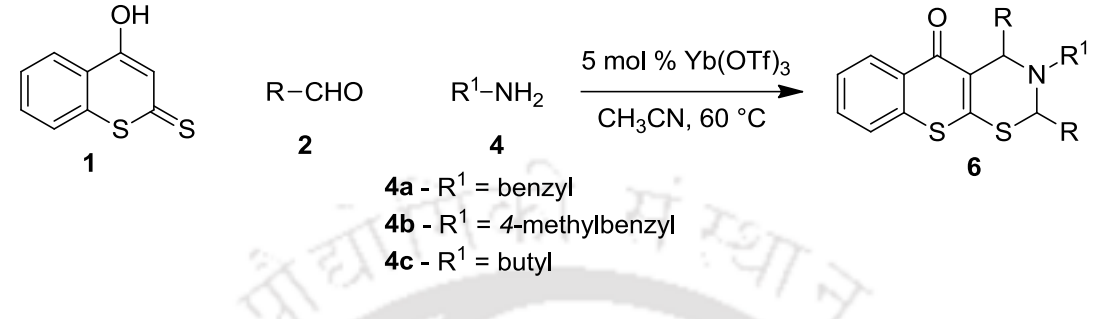
The aromatic aldehydes having substituent on para position such as 4-Me, 4-Cl, 4-Br, 4-OMe gave the product **5b-e** in the 75-84% yield (Table 2) while moving on to aromatic aldehydes having ortho substituents such as Cl, Br, F, NO_2 the reaction proceeded much faster than their para analogues giving the product **5f-i** in 78-84% yield.

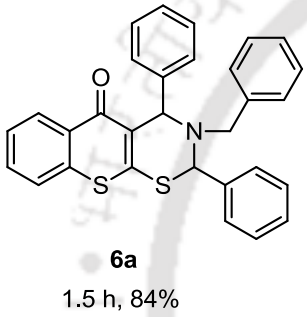
Interestingly the protocol was well applied to 4-CN and 2-naphthaldehyde giving the product **5j** and **5k** in 72-80 % yields. All these products were characterized by IR, ^{1}H and ^{13}C NMR spectra and HRMS. Moreover, the structure of the compound **5f** was confirmed by single-crystal X-ray crystallographic data (Figure 6, **I**). Unfortunately, aliphatic and heteroaromatic aldehydes failed to participate in the reaction.

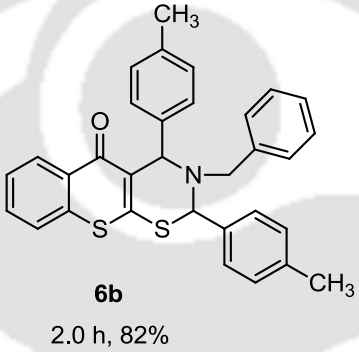
Inspired with the success of the above transformation, we further explored the generality of the reaction with various alkyl/benzyl amines as a substitute of NH_4OAc for the synthesis tri-substituted 3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one derivatives. When the reaction was carried out with 4-hydroxydithiocoumarin (0.5 mmol, **1**), benzaldehyde (1.0 mmol, **2**) and benzyl amine (0.5 mmol, **4a**) under the same set of reaction conditions it furnished the product **6a** with moderate yield (65%) which was characterized by IR, ^{1}H and ^{13}C NMR spectra and HRMS. However, it was observed that the time taken for the completion of the reaction was significantly higher (24 hours) as compared to the above scheme. Therefore, the need to optimize the reaction conditions aroused again. Surprisingly, just changing the solvent from ethanol to acetonitrile worked wonder and the same reaction

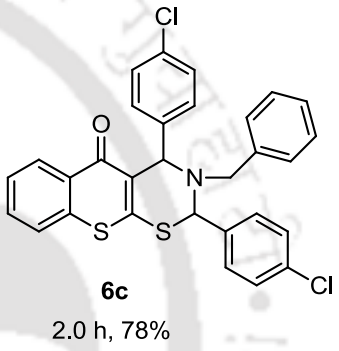
took only 2 hours instead of 24 hours as taken in ethanol medium with the significant improvement in the yield to 84%.

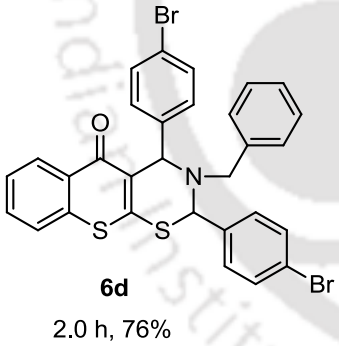
Table 3. Synthesis of 3-alkyl-2,4-diphenyl-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one derivatives using ytterbium(III) trifluoromethanesulfonate catalyst[a,b]

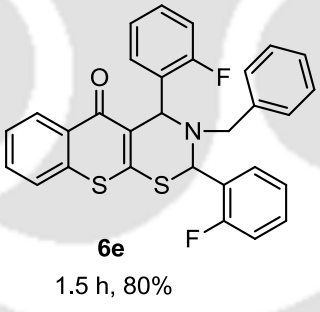


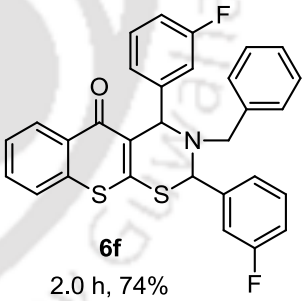


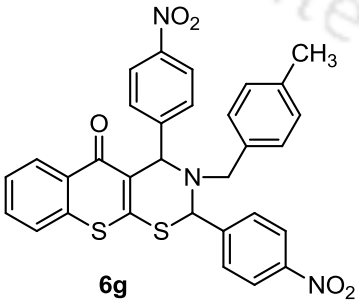


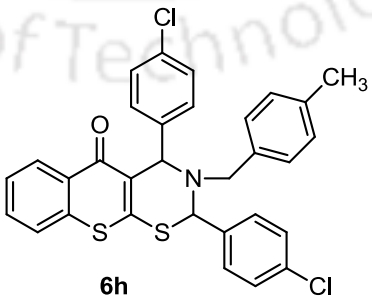


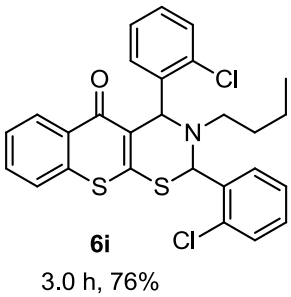


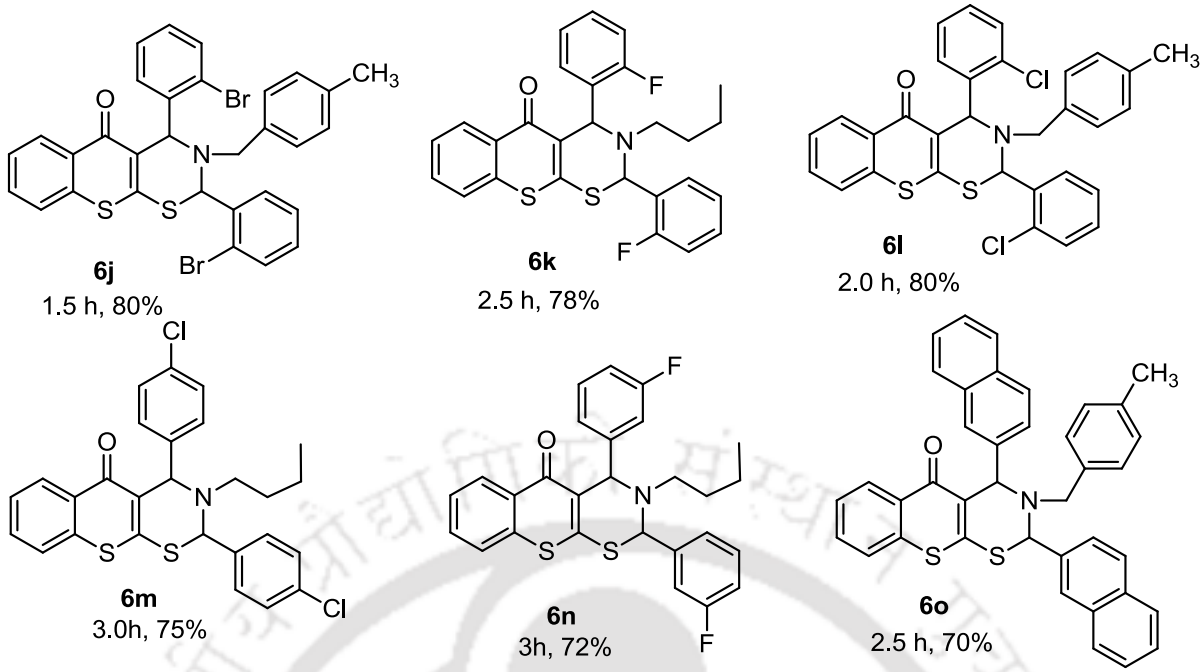












[a]All the reactions were carried out using 4-hydroxydithiocoumarin (0.5 mmol), aldehyde (1.0 mmol) and alkyl amine (0.5 mmol) in acetonitrile (2 mL).[b]Isolated yield.

Next, 4-hydroxydithiocoumarin (0.5 mmol, **1**) participated in the hetero–Diels-Alder reaction with benzyl amine (0.5 mmol, **4a**) and various aromatic aldehydes (1.0 mmol, **2**) showing good tolerance of electron-donating to electron-withdrawing group at ortho, meta and para position on the aromatic ring in presence of 5 mol% of $Yb(OTf)_3$ in acetonitrile at 60 ^oC and the desired products **6b-f** were obtained in 74-82% yields and the results are summarized in table 3. The reaction was further assessed with various other amines such as 4-methyl benzyl amine (**4b**) and butyl amine (**4c**) under identical reaction conditions and the expected products **6g-n** were obtained in good yields. Furthermore, the reaction of 4-hydroxydithiocoumarin with 2-naphthaldehyde and benzyl amine (**4a**) afforded the product **6o** in 70 % yield. All the products were characterized by recording IR, ^1H and ^{13}C NMR spectra as well as from their HRMS. The structure of the compound **6b** was further confirmed by single-crystal X-ray crystallographic data (Figure 6, **II**).

Unfortunately, we were unable to obtain any desired product with aromatic amines, aliphatic and heteroaromatic aldehydes thus somewhat limiting the scope of the reaction.

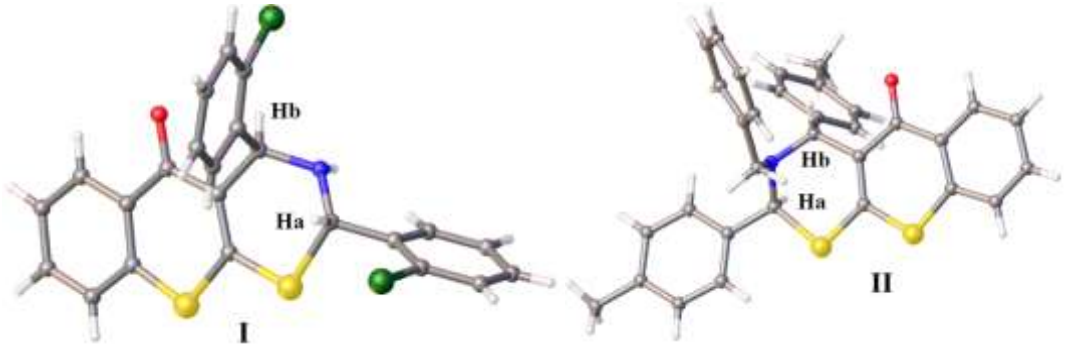


Figure 6. (**I**) XRD structure of **5f** (CCDC no. 1029813) and (**II**) XRD structure of **6b** (CCDC no. 1029814)

In addition, the XRD structure of compounds **5f** and **6b** showed that the position of **Ha** and **Hb** are anti to each other respectively which indicates the formation of single anti-diastereoisomer. The anti-diasteroselectivity was also confirmed through NOEs spectra of compound **6f**, which shows the absence of any cross peak between the (**Ha** & **Hb**) and (**Hb** & **Hc**) region that proves (**Ha** & **Hb**) and (**Hb** & **Hc**) are anti to each other i.e *trans*-orientation respectively, it is also shown that the presence of cross peak in the highlighted region that proves **Hb** and **Hd** are in *cis*-orientation as shown in figure 7.

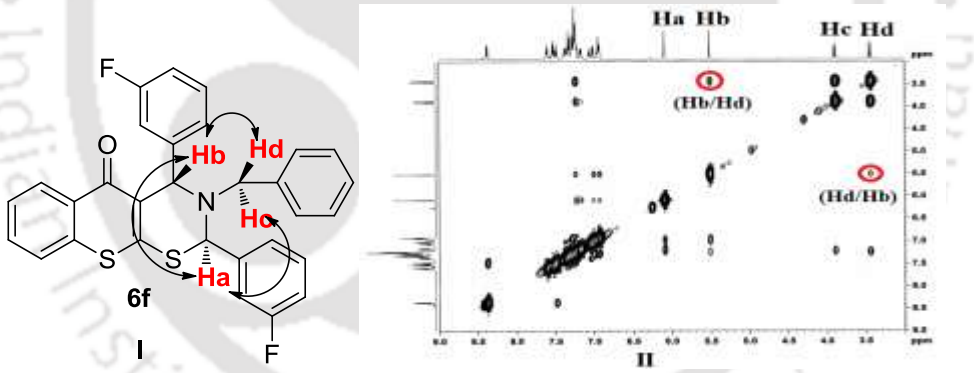
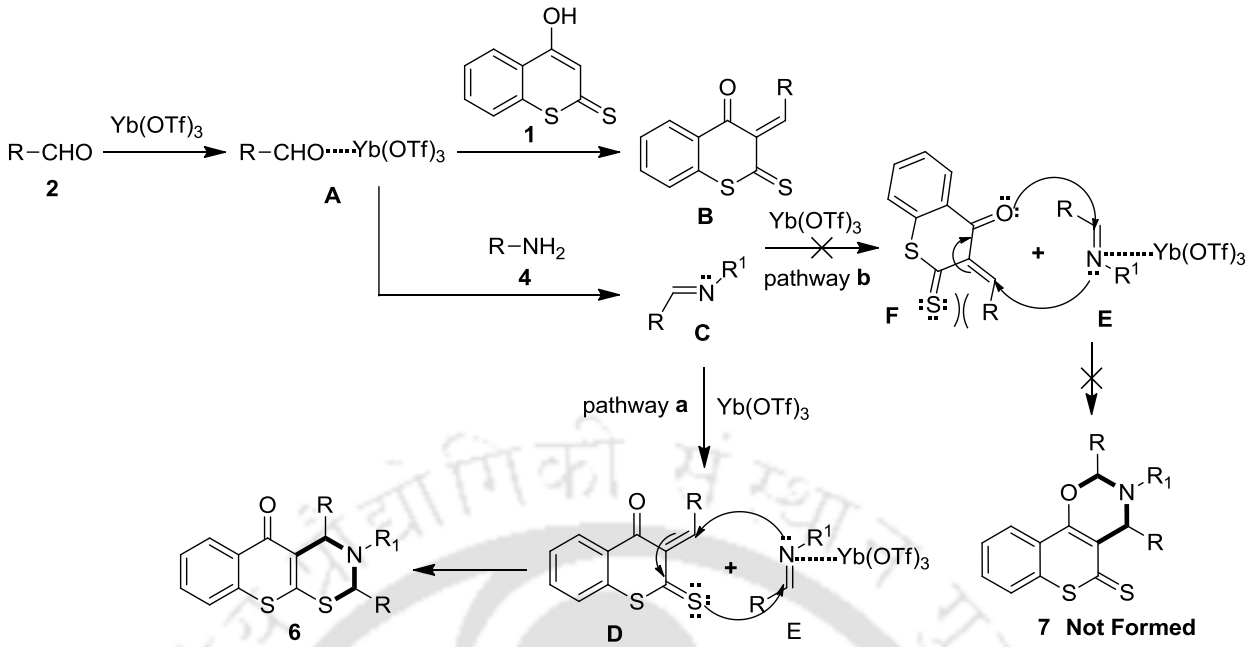


Figure 7. (**I**) Selected NOEs enhancements of compound **6f** and (**II**) Expanded NOEs spectra of compound **6f**

A plausible mechanism for the formation of products **5** and **6** in this unusual ring closure reaction may be drawn as follow (Scheme 44).



Scheme 44. Plausible mechanism for the formation of 3-alkyl-2,4-diphenyl-3,4 dihydrothiochromeno[3,2-e][1,3]thiazin-5(2H)-one derivatives.

Initially, ytterbium triflate reacted with the aldehyde **2** to form active species **A** which further undergoes reaction with 4-hydroxydithiocoumarin **1** to form Knoevenagel product **B** whereas **A** simultaneously reacted with amine **4** to form an imine **C** which was activated in the presence of ytterbium triflate to give dienophile **E**. There are two possibilities which may lead to the formation of two different hetero-Diels-Alder products (products **6** and **7**) via 'pathway a' or 'pathway b'. However, the isolation of only product **6** shows that the reaction proceeds through 'pathway a'. In 'pathway a' the diene **D** undergoes concomitant regioselective cyclization through hetero-Diels-Alder reaction with the dienophile **E** to give the final product **6**. The regioselective formation of product **6** can be rationalized in terms of the following points (i) the presence of soft sulfur atom which decreases HOMO-LUMO gap when the thioester acts as heterodine **D**, (ii) the empty d-ortials in sulfur makes it more polarizable as compared to oxygen thus serving as an efficient reaction core, (iii) the steric hindrance faced by R group with the sulfur of the heterodiene **F** might have also prevented the reaction to proceed via 'pathway b'

Conclusion

In conclusion, we have developed a novel protocol for the synthesis of 3,4-dihydrothiochromeno[3,2-*e*] [1,3]thiazin-5(2*H*)-one derivatives through hetero-Diels-Alder

reaction in high yields with a wide substrates scope. The present protocol is user-friendly, operationally simple, regioselective and shows unusual ring closure leading to the formation of C-C, C-N and C-S bond in a single step reaction. Moreover, these unusual di- and tri-substituted 3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one derivatives were reported first time in the literature from 4-hydroxydithiocoumarin. In addition, the biological activities of these compounds would be reported elsewhere.

Experimental Section

I. General Procedure for the synthesis of the key starting material 4-hydroxydithiocoumarin compound (1)[6]:

To a stirred mixture of 2'-chloroacetophenone (6.5 ml), N,N-dimethylformamide (50 ml), toluene (35 ml) and carbon disulfide (4.2 ml) keep at 15-20°C was added sodium hydride (5.5 g) and the mixture was stirred for over 2.5 h. After an additional 30 emin, methanol (1.5 ml) was added and was stirred again for additional 15 min. Next, the reaction mixture was heated with stirring to let benzene to distil off until the internal temperature reached 125-130°C, kept at 125-130°C for 45 min, cooled and diluted with water (170 ml). After adding of acetic acid (5 ml) followed by extraction with ether (2x 100 ml) the aqueous phase was separated, filtered and acidified with conc. HCl. The obtained precipitate was recrystallized from methanol/ 2-dichloroethane to get the 4-hydroxydithiocoumarin (**1**) as yellow needles (7.1 g, 73%).

II. General Procedure for the synthesis of 2,4-diphenyl-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one derivatives (5):

To a mixture of 4-hydroxydithiocoumarin (0.5 mmol, **1**), aromatic aldehyde (1.0 mmol, **2**) and ammonium acetate (1.0 mmol, **3**) in 2 mL ethanol was added 5 mol% ytterbium triflate (15.5 mg). Then the reaction mixture was kept for stirring in a pre-heated oil-bath at 60°C and the progress of the reaction was monitored by TLC. After a stipulated period of time precipitation was occurred and then the reaction mixture was cooled to room temperature. After that, the precipitate was filter off through a Büchner funnel, washed with EtOH and finally dried over vacuum pump to obtain the pure products **5** in good yields.

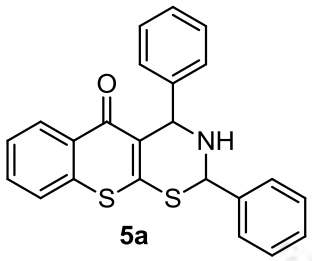
III. General Procedure for the synthesis of 3-alkyl-2,4-diphenyl-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one derivatives (6):

Into an oven dried 25 mL round bottomed flask was taken a mixture 4-hydroxydithiocoumrin (0.5 mmol, **1**), aromatic aldehyde (1.0 mmol, **2**), alkyl amine (0.5 mmol, **4**) in 2 mL of acetonitrile. Then, 5 mol% Ytterbium triflate (15.5 mg) was added into the above reaction mixture and it was kept for stirring at 60°C and the progress of the reaction was monitored by TLC. After the completion of the reaction, it was concentrated under reduced pressure. Then, the obtained residue was extracted with DCM (15 mL x 2), and dried over anhydrous Na_2SO_4 and evaporated in vacuo. After that, the crude residue was purified over a silica gel column

chromatography eluted with 3% ethyl acetate in hexane to afford the desired products **6** in good yields.

Spectra Data of Compounds 5 and 6

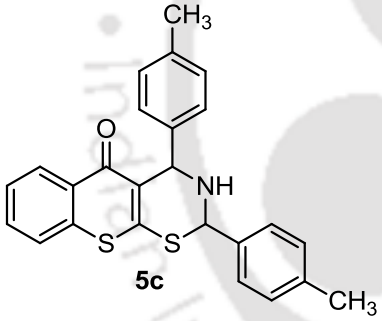
2,4-diphenyl-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5a): White solid



5a

(167 mg, 86% yield), Mp 163-164 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.67 (s, 1H), 5.96 (s, 1H), 7.28-7.29 (m, 1H), 7.33-7.36 (m, 4H), 7.38-7.40 (m, 5H), 7.45-7.48 (m, 2H), 7.54-7.57 (m, 1H), 8.41 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.5, 65.2, 124.3, 124.7, 126.8, 127.1, 127.4, 127.8, 128.5, 128.7, 128.8, 129.1, 129.2, 129.5, 129.9, 131.0, 131.3, 136.9, 137.8, 140.1, 154.1, 175.2; IR (KBr)ν_{max} 1122, 1169, 1229, 1301, 1314, 1346, 1437, 1448, 1479, 1491, 1505, 1557, 1573, 1597, 2852, 2924, 3023, 3061, 3271 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{18}NOS_2$ 388.0825 (M + H^+); Found 388.0825.

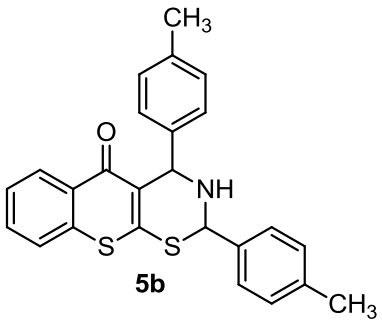
2,4-di-p-tolyl-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5b): White solid



5c

(174 mg, 84% yield), Mp 161-162 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.34 (s, 3H), 5.65 (s, 1H), 5.90 (s, 1H), 7.12-7.18 (m, 4H), 7.24-7.28 (m, 5H), 7.43-7.46 (m, 1H), 7.53-7.56 (m, 1H), 8.39 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 21.4, 56.5, 65.6, 124.6, 124.7, 126.8, 127.4, 128.6, 129.5, 129.6, 129.8, 129.9, 130.0, 131.1, 131.2, 134.9, 137.1, 137.2, 137.4, 139.2, 154.2, 175.1; IR (KBr)ν_{max} 1167, 1241, 1307, 1350, 1404, 1435, 1467, 1489, 1504, 1554, 1583, 1601, 2848, 2922, 3306 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{22}NOS_2$ 416.1138 (M + H^+); Found 416.1139.

2,4-bis(4-chlorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5c):

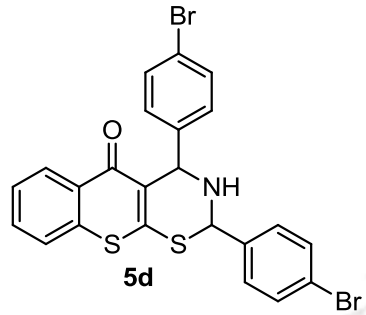


5b

White solid (178 mg, 78% yield), Mp 201-202 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (b s, 1H), 5.55 (s, 1H), 5.87 (s, 1H), 7.30-7.34 (m, 8H), 7.46-7.48 (m, 2H), 7.56-7.58 (m, 1H), 8.40 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.2, 54.4, 121.6, 123.9, 124.7, 124.9, 126.9, 127.1, 127.6, 127.9, 128.4, 129.1, 129.2, 130.1, 130.5, 131.9, 133.4, 133.8, 136.1, 139.5, 140.5, 173.9; IR (KBr)ν_{max} 1121, 1161, 1241, 1285, 1308, 1349, 1401, 1432, 1465, 1489, 1505, 1561, 1582,

1600, 2845, 2923, 3059, 3298 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{16}Cl_2NOS_2$ 456.0045 ($M + H^+$); Found 456.0044.

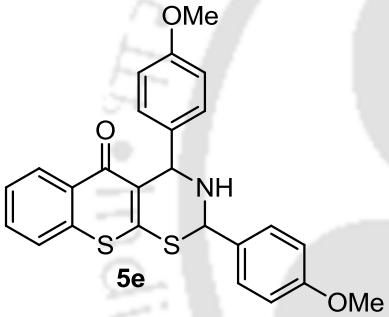
2,4-bis(4-bromophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5d):



5d

White solid (218 mg, 80% yield), Mp 208-209 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 1H), 5.54 (s, 1H), 5.86 (s, 1H), 7.23 (s, 2H), 7.28 (s, 1H), 7.46-7.51 (s, 7H), 7.53-7.58 (s, 1H), 8.40 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.7, 63.5, 122.1, 123.4, 123.9, 124.9, 127.7, 128.6, 129.6, 130.4, 131.1, 131.6, 132.0, 132.4, 136.7, 136.8, 139.2, 153.7, 175.3; IR (KBr)ν_{max} 1162, 1241, 1304, 1350, 1393, 1432, 1465, 1485, 1499, 1581, 1596, 2850, 2923, 2950, 3296 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{16}Br_2NOS_2$ 543.9035 ($M + H^+$); Found 543.9027.

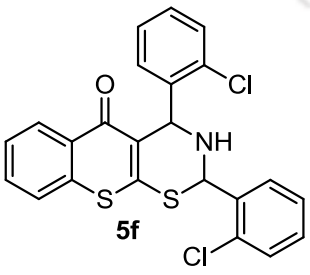
2,4-bis(4-methoxyphenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5e):



5e

White solid (168 mg, 75% yield), Mp 159-160 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.81 (s, 3H), 5.68 (s, 1H), 5.94 (s, 1H), 6.85-6.91 (m, 4H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.35-7.39 (m, 2H), 7.43-7.65 (m, 2H), 7.52-7.56 (m, 1H), 8.39 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.4, 55.6, 56.6, 114.2, 114.5, 124.6, 124.7, 125.6, 127.4, 128.1, 128.4, 129.4, 129.5, 129.8, 129.9, 130.1, 131.2, 131.3, 131.9, 132.3, 137.2, 159.2, 160.4, 175.0; IR (KBr)ν_{max} 1112, 1175, 1245, 1288, 1306, 1437, 1462, 1509, 1581, 1609, 2834, 2933, 3278, 3311 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{22}NO_3S_2$ 448.1036 ($M + H^+$); Found 448.1036.

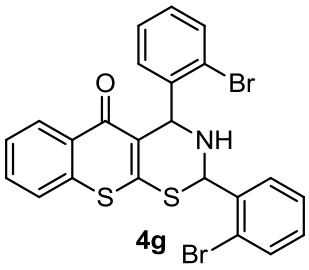
2,4-bis(2-chlorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5f):



5f

White solid (182 mg, 80% yield), Mp 168-169 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.02 (s, 1H), 6.17 (s, 1H), 7.10-7.13 (m, 1H), 7.15-7.18 (m, 3H), 7.19-7.22 (m, 1H), 7.24-7.27 (m, 1H), 7.35-7.39 (m, 3H), 7.45-7.48 (m, 1H), 7.56-7.57 (m, 1H), 8.28 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 54.1, 60.8, 123.7, 124.8, 126.5, 127.6, 127.8, 128.4, 129.2, 129.3, 129.5, 130.3, 130.4, 130.7, 131.2, 131.5, 133.5, 134.9, 136.8, 137.7, 153.6, 175.1 ; IR (KBr)ν_{max} 1128, 1161, 1241, 1301, 1346, 1439, 1458, 1500, 1582, 1600, 2836, 2931 3045, 3325 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{16}Cl_2NOS_2$ 456.0045 ($M + H^+$); Found 456.0045.

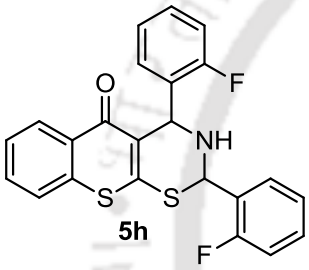
2,4-bis(2-bromophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5g):



4g

White solid (223 mg, 82% yield), Mp 188-189 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (b s, 1H), 6.07 (d, *J* = 11.2 Hz, 1H), 6.18 (s, 1H), 7.17-7.19 (m, 1H), 7.25-7.26 (m, 4H), 7.36-7.40 (m, 1H), 7.44-7.52 (m, 2H), 7.54-7.58 (m, 2H), 7.63-7.68 (m, 2H), 8.38 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 56.1, 63.4, 122.7, 124.3, 124.8, 126.5, 126.9, 127.8, 128.3, 128.4, 128.7, 128.8, 130.1, 130.4, 130.9, 132.7, 133.2, 135.8, 136.1, 138.9, 153.2, 174.2; IR (KBr)$_{vmax}$ 119, 1132, 1159, 1190, 1230, 1288, 1307, 1343, 1435, 1463, 1513, 1560, 1580, 1595, 2844, 2939, 3059, 3313 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{16}Br_2NOS_2$ 543.9035 (M + H$^+$); Found 543.9039.

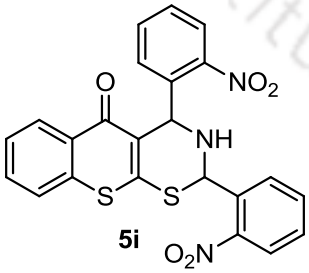
2,4-bis(2-fluorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5h):



5h

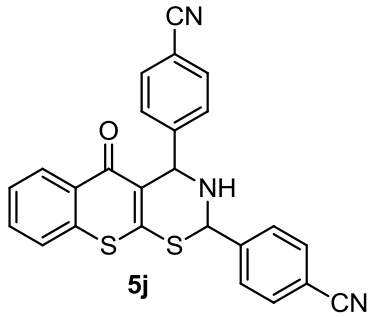
White solid (178 mg, 84% yield), Mp 173-174 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (b s, 1H), 5.92 (d, *J* = 12.0 Hz, 1H), 6.19 (s, 1H), 7.07-7.09 (m, 2H), 7.14-7.21 (m, 3H), 7.31-7.33 (m, 2H), 7.40-7.47 (m, 3H), 7.54-7.55 (m, 1H), 8.37 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.1, 58.4, 115.4, 115.6, 115.7, 122.5, 123.3, 124.1, 124.2, 124.4, 126.9, 127.1, 128.1, 128.5, 128.9, 129.3, 130.4, 130.9, 136.1, 153.2, 158.2, 159.1, 160.7, 161.6, 174.2; IR (KBr)ν_{max} 1146, 1170, 1230, 1276, 1344, 1452, 1488, 1507, 1559, 1576, 1607, 2845, 2925, 2961, 3067, 3109, 3273 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{16}F_2NOS_2$ 424.0636 (M + H$^+$); Found 424.0635.

2,4-bis(2-nitrophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5i): White solid (186 mg, 78% yield), Mp 184-185 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.87 (d, *J* = 8.4 Hz, 1H), 6.15 (d, *J* = 12.0 Hz, 1H), 6.63 (s, 1H), 7.23-7.24 (m, 1H), 7.47-7.54 (m, 5H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 8.41 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ 51.7, 59.9, 122.7, 125.1, 125.5, 125.9, 128.4, 128.9, 129.5, 129.8, 130.4, 130.6, 130.9, 131.1, 132.5, 132.8, 133.5, 134.5, 136.3, 148.0, 149.6, 154.0, 174.5; IR (KBr)ν_{max} 1172, 1239, 1344, 1438, 1475, 1522, 1574, 1599, 2848, 2948, 3059, 3301 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{16}N_3O_5S_2$ 478.0526 (M + H$^+$); Found 478.0526.



5i

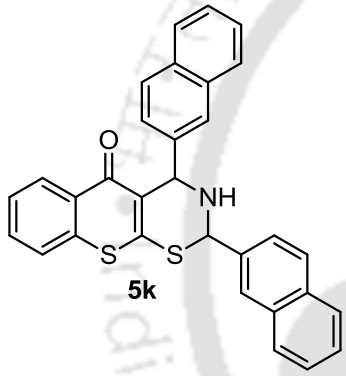
4,4'-(5-oxo-2,3,4,5-tetrahydrothiochromeno[3,2-*e*][1,3]thiazine-2,4-diyl)dibenzonitrile



5j

(5j): White solid (175 mg, 80% yield), Mp 204-205 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (d, *J* = 13.6 Hz, 1H), 5.52 (d, *J* = 13.6 Hz, 1H), 5.93 (s, 1H), 7.48-7.53 (m, 6H), 7.59-7.61 (m, 1H), 7.64-7.66 (m, 2H), 7.69-7.71 (m, 2H), 8.39 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 62.6, 110.1, 112.1, 113.5, 118.2, 118.8, 123.0, 125.1, 127.6, 128.1, 129.6, 130.9, 131.9, 132.8, 133.1, 136.7, 142.3, 145.3, 153.5, 175.4; IR (KBr)ν_{max} 1118, 1235, 1290, 1313, 1348, 1399, 1438, 1468, 1499, 1515, 1554, 1575, 1598, 2227, 2845,2923, 3289 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{16}N_3OS_2$ 438.0730 (M + H^+); Found 438.0728.

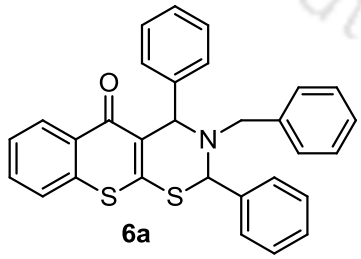
2,4-di(naphthalen-2-yl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (5k):



5k

White solid (175 mg, 72% yield), Mp 144-145 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79 (b s, 1H), 5.83 (s, 1H), 6.15 (s, 1H), 7.45-7.52 (m, 7H), 7.57-7.61 (m, 1H), 7.67-7.71 (m, 2H), 7.78-7.82 (m, 5H), 7.85-7.89 (m, 2H), 8.43 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 56.8, 65.2, 124.2, 124.4, 124.9, 126.1, 126.2, 126.3, 126.9, 127.1, 127.5, 127.6, 127.8, 127.9, 128.3, 128.4, 126.8, 128.9, 129.1, 129.3, 129.6, 131.2, 131.4, 133.3, 133.4, 133.6, 135.0, 137.1, 137.6, 154.4, 175.3; IR (KBr)ν_{max} 1121, 1159, 1205, 1241, 1272, 1291, 1324, 1339, 1360, 1435, 1507, 1525, 1563, 1588, 1613, 2838, 2929, 3046, 3302 cm^{-1}; HRMS (ESI) Calcd For $C_{31}H_{22}NOS_2$ 488.1138 (M + H^+); Found 488.1139.

3-benzyl-2,4-diphenyl-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (6a):

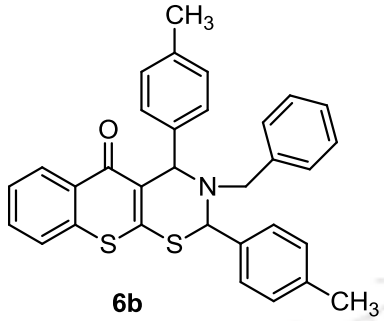


6a

Yellow solid (200 mg, 84% yield), Mp 173-174 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.38 (d, *J* = 13.8 Hz, 1H), 3.87 (d, *J* = 13.8 Hz, 1H), 5.49 (s, 1H), 6.11 (s, 1H), 7.15-7.19 (m, 7H), 7.22-7.26 (m, 4H), 7.29-7.31 (m, 2H), 7.35-7.37 (m, 2H), 7.39-7.40 (m, 1H), 7.43-7.44 (m, 1H), 7.49-7.51 (m, 1H), 8.30 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 50.8, 59.7, 68.9, 121.1, 124.8, 127.5, 127.6, 127.7, 127.9, 128.7, 128.8 (2), 129.0, 129.2, 129.7, 131.2, 131.4, 136.8, 137.0, 137.9, 141.5, 152.7, 176.0; IR (KBr)ν_{max} 1102, 1158, 1235, 1261, 1308, 1333, 1354, 1432, 1449,

1490, 1508, 1560, 1580, 1604, 2853, 2917, 2953, 3017 cm^{-1}; HRMS (ESI) Calcd For $C_{30}H_{24}NOS_2$ 478.1294 ($M + H^+$); Found 478.1294.

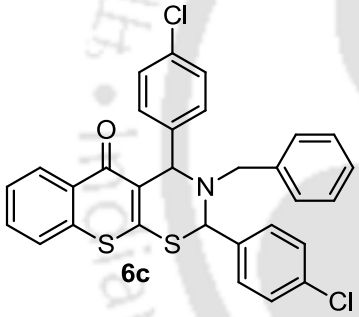
3-benzyl-2,4-di-p-tolyl-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (6b):



6b

Yellow solid (207 mg, 82% yield), Mp 141-142 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.33 (s, 3H), 3.42 (d, *J* = 14.0 Hz, 1H), 3.95 (d, *J* = 14.0 Hz, 1H), 5.50 (s, 1H), 6.19 (s, 1H), 7.12 (s, 3H), 7.16-7.18 (m, 2H), 7.26-7.33 (m, 7H), 7.44-7.51 (m, 3H), 7.55-7.59 (m, 1H), 8.37 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 50.6, 59.4, 68.9, 121.3, 124.7, 127.4, 127.5, 127.8, 128.6, 129.1, 129.4, 129.7, 131.2, 131.4, 133.8, 137.0, 137.2, 138.1, 138.5, 138.8, 152.6, 175.9; IR (KBr)ν_{max} 1113, 1161, 1174, 1232, 1310, 1330, 1402, 1436, 1454, 1510, 1587, 1611, 1646, 2839, 2917, 3028 cm^{-1}; HRMS (ESI) Calcd For $C_{32}H_{28}NOS_2$ 506.1607 ($M + H^+$); Found 506.1611.

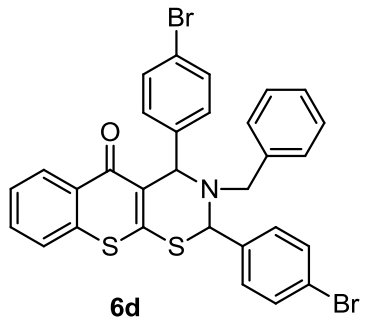
3-benzyl-2,4-bis(4-chlorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one



6c

(6c): Yellow solid (213 mg, 78% yield), Mp 182-183 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (d, *J* = 14.0 Hz, 1H), 3.86 (d, *J* = 14.0 Hz, 1H), 5.48 (s, 1H), 6.05 (s, 1H), 7.14-7.16 (m, 2H), 7.20-7.22 (m, 2H), 7.26-7.34 (m, 6H), 7.36 (s, 3H), 7.47-7.53 (m, 2H), 7.59-7.62 (m, 1H), 8.37 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.7, 59.1, 67.9, 120.5, 124.9, 127.7, 127.9, 128.4, 128.9, 129.0, 129.1, 129.2, 129.3, 129.6, 130.1, 131.0, 131.7, 133.7, 135.0, 135.1, 136.8, 137.4, 139.9, 152.5, 175.9; IR (KBr)ν_{max} 1117, 1161, 1181, 1244, 1314, 1327, 1341, 1400, 1436, 1453, 1487, 1511, 1584, 1607, 2845, 2925, 3024, 3060 cm^{-1}; HRMS (ESI) Calcd For $C_{30}H_{22}Cl_2NOS_2$ 546.0515 ($M + H^+$); Found 546.0515.

3-benzyl-2,4-bis(4-bromophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one

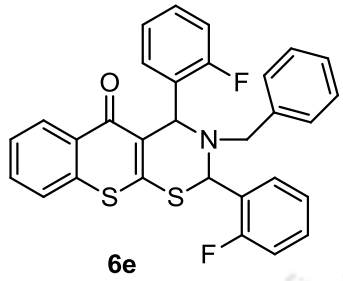


6d

(6d): Yellow solid (241 mg, 76% yield), Mp 172-173 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (d, *J* = 13.6 Hz, 1H), 3.85 (d, *J* = 14.0 Hz, 1H), 5.46 (s, 1H), 6.03 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.26-7.34 (m, 5H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.48 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 3H), 7.60 (t, *J* = 7.2 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.7, 59.2, 67.9, 123.3, 124.9, 127.7, 127.9, 128.8, 128.9, 129.1, 129.2, 129.4, 129.5, 129.6, 129.7, 130.4, 130.5, 131.0, 131.7, 131.9 (2),

132.0, 132.1, 135.5, 136.8, 137.3, 140.5, 152.5, 175.9; IR (KBr)ν_{max} 1162, 1261, 1324, 1396, 1435, 1482, 1511, 1587, 1606, 2853, 2924, 2961, 3059 cm^{-1}; HRMS (ESI) Calcd For $C_{30}H_{22}Br_2NOS_2$ 633.9504 ($M + H^+$); Found 633.9510.

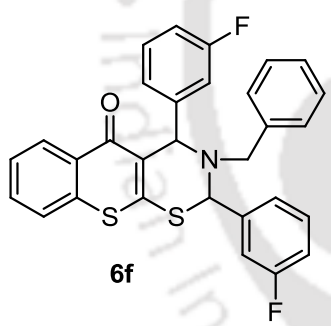
3-benzyl-2,4-bis(2-fluorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one



6e

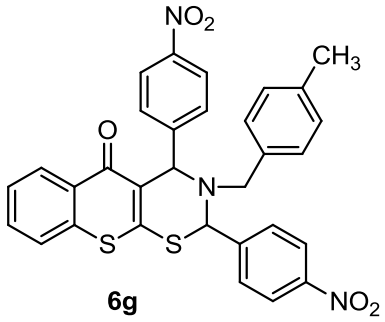
(6e): Yellow solid (205 mg, 80% yield), Mp 126-127 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (d, *J* = 14.0 Hz, 1H), 4.06 (d, *J* = 14.0 Hz, 1H), 5.76 (s, 1H), 6.54 (s, 1H), 6.99-7.05 (m, 2H), 7.09-7.16 (m, 5H), 7.20-7.22 (m, 3H), 7.28 (b s, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.49-7.51 (m, 1H), 7.56-7.62 (m, 1H), 7.64-7.65 (m, 1H), 8.34 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.5, 55.8, 63.8, 116.1, 116.3, 120.2, 123.4, 123.5, 123.6 (2), 123.9, 124.0, 124.8, 127.4, 127.6, 127.7, 127.8, 128.2, 129.1, 129.5, 129.6, 129.8, 129.9, 130.1, 131.1, 131.2, 131.5, 136.9, 137.2, 153.1, 159.6, 160.1, 162.1, 162.6, 175.6; IR (KBr)ν_{max} 1117, 1163, 1232, 1304, 1334, 1452, 1487, 1514, 1614, 2841, 2925, 3063 cm^{-1}; HRMS (ESI) Calcd For $C_{30}H_{22}F_2NOS_2$ 514.1106 ($M + H^+$); Found 514.1107.

3-benzyl-2,4-bis(3-fluorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one



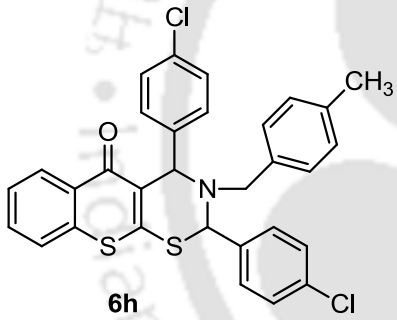
6f

(6f): Yellow solid (190 mg, 74% yield), Mp 70-71 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.44 (d, *J* = 13.8 Hz, 1H), 3.89 (d, *J* = 13.2 Hz, 1H), 5.51 (s, 1H), 6.01 (s, 1H), 6.93-6.96 (m, 2H), 7.01 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 10.2 Hz, 1H), 7.22-7.25 (m, 3H), 7.28-7.30 (m, 2H), 7.32-7.34 (m, 2H), 7.35-7.39 (m, 1H), 7.47-7.50 (m, 1H), 7.52-7.53 (m, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 50.7, 58.9, 67.7, 114.6, 114.8, 114.9, 115.4, 115.6, 115.9, 116.1, 120.3, 123.3, 124.2, 124.7, 127.5, 127.7, 128.7, 129.0, 129.4, 130.1, 130.2, 130.3, 130.4, 130.8, 131.5, 136.6, 137.1, 138.8, 138.9, 143.8, 143.9, 152.4, 161.6, 164.1, 164.2, 175.8; IR (KBr)ν_{max} 1199, 1227, 1260, 1293, 1328, 1340, 1368, 1439, 1484, 1519, 1586, 1611, 2850, 2920, 3017, 3061 cm^{-1}; HRMS (ESI) Calcd For $C_{30}H_{22}F_2NOS_2$ 514.1106 ($M + H^+$); Found 514.1107.

3-(4-methylbenzyl)-2,4-bis(4-nitrophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (6g): 

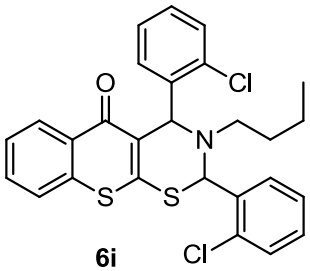
6g

Yellow solid (218 mg, 75% yield), Mp 188-189 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.47 (d, *J* = 13.6 Hz, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 5.57 (s, 1H), 6.03 (s, 1H), 7.09-7.11 (m, 2H), 7.14-7.16 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.52-7.55 (m, 1H), 7.57-7.59 (m, 2H), 7.62-7.66 (m, 2H), 8.17-8.20 (m, 2H), 8.28 (d, *J* = 8.8 Hz, 2H), 8.37 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 50.9, 59.0, 67.5, 119.9, 124.1, 124.3, 124.9, 126.0, 128.0, 128.1, 128.5, 128.7, 129.1, 129.4, 129.6, 129.7, 129.8, 130.8, 132.0, 132.2, 133.2, 136.6, 138.1, 143.3, 147.6, 148.4, 148.7, 152.3, 175.9; IR (KBr)ν_{max} 1119, 1162, 1224, 1319, 1346, 1415, 1437, 1515, 1605, 1624, 2852, 2922, 3015, 3069 cm^{-1}; HRMS (ESI) Calcd For $C_{31}H_{24}N_3O_5S_2$ 582.1152 (M + H^+); Found 582.1130.

2,4-bis(4-chlorophenyl)-3-(4-methylbenzyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (6h): 

6h

Yellow solid (224 mg, 80% yield), Mp 183-184 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 3.30 (d, *J* = 13.6 Hz, 1H), 3.74 (d, *J* = 14.0 Hz, 1H), 5.40 (s, 1H), 5.97 (s, 1H), 7.04-7.08 (m, 7H), 7.19-7.21 (m, 4H), 7.41-7.45 (m, 3H), 7.51-7.53 (m, 1H), 8.29 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 50.4, 58.8, 67.9, 120.6, 124.8, 127.7, 128.9, 129.0, 129.1, 129.2, 129.5, 129.4, 130.1, 131.0, 131.6, 133.6, 134.1, 135.0, 135.1, 136.8, 137.5, 140.1, 152.5, 175.9; IR (KBr)ν_{max} 1119, 1160, 1235, 1260, 1321, 1346, 1397, 1436, 1462, 1488, 1516, 1587, 1611, 2852, 2923, 2958, 3021,3051 cm^{-1}; HRMS (ESI) Calcd For $C_{31}H_{24}Cl_2NOS_2$ 560.0671 (M + H^+); Found 560.0667.

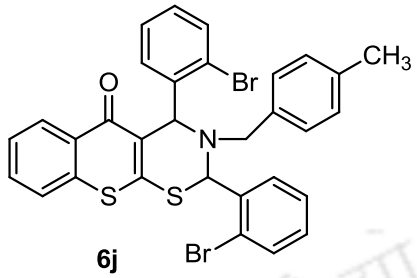
3-butyl-2,4-bis(2-chlorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one (6i): 

6i

Yellow solid (195 mg, 76% yield), Mp 131-132 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.61 (t, *J* = 7.6 Hz, 3H), 0.83-0.89 (m, 2H), 1.42-1.53 (m, 2H), 2.45-2.52 (m, 1H), 2.78-2.83 (m, 1H), 6.04 (s, 1H), 6.48 (s, 1H), 7.15-7.19 (m, 1H), 7.23-7.31 (m, 5H), 7.45-7.48 (m, 3H), 7.53-7.55 (m, 1H), 7.57-7.71 (m, 1H), 8.37 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 13.7, 20.2, 29.6, 47.2, 59.6, 67.6, 121.2, 124.7, 126.3, 126.5, 127.6, 129.3, 129.4, 130.1, 130.2, 130.3, 130.5, 130.7,

131.2, 131.4, 133.3, 135.4, 135.9, 136.9, 137.5, 153.8, 175.7; IR (KBr)ν_{max} 1122, 1161, 1239, 1263, 1299, 1329, 1438, 1468, 1489, 1517, 1588, 1608, 2853, 2925, 2955, 3059 cm^{-1}; HRMS (ESI) Calcd For $C_{27}H_{24}Cl_2NOS_2$ 512.0671 ($M + H^+$); Found 512.0665.

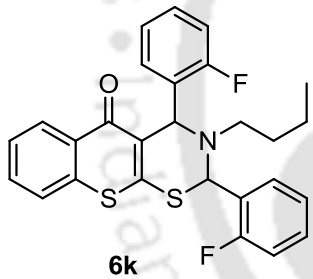
2,4-bis(2-bromophenyl)-3-(4-methylbenzyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin



6j

5(2*H*)-one (6j): Yellow solid (259 mg, 80% yield), Mp 122-123 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.61-3.64 (m, 1H), 4.18-4.21 (m, 1H), 6.02 (s, 1H), 6.69 (s, 1H), 7.06 (s, 4H), 7.35-7.39 (m, 4H), 7.64-7.69 (m, 6H), 7.85 (s, 1H), 8.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 51.9, 61.7, 69.2, 121.4, 124.8, 125.4, 126.8, 127.1, 127.6, 128.6, 129.5, 129.6, 129.8, 129.9, 130.4, 130.6, 130.9, 131.2, 131.5, 133.9, 134.1, 134.2, 134.6, 136.7, 136.9, 138.9, 153.0, 175.5; IR (KBr)ν_{max}1163, 1261, 1302, 1343, 1436, 1466, 1505, 1585, 1603, 2853, 2924, 2963, 3018, 3057 cm^{-1}; HRMS (ESI) Calcd For $C_{31}H_{24}Br_2NOS_2$ 647.9661 ($M + H^+$); Found 647.9661.

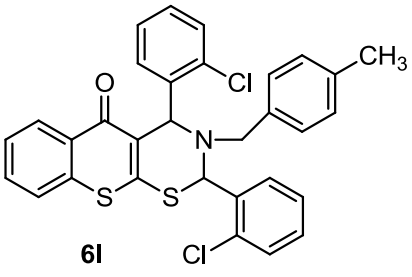
3-butyl-2,4-bis(2-fluorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one



6k

(6k): Yellow semi-solid (187 mg, 78% yield), ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.66 (t, *J* = 7.2 Hz, 3H), 0.92-0.99 (m, 1H), 1.19-1.26 (m, 1H), 1.42-1.45 (m, 1H), 1.52-1.56 (m, 1H), 2.49-2.53 (m, 1H), 2.75-2.80 (m, 1H), 6.00 (s, 1H), 6.44 (s, 1H), 6.97 (t, *J* = 9.0 Hz, 1H), 7.05 (t, *J* = 9.0 Hz, 1H), 7.13-7.18 (m, 3H), 7.29-7.33 (m, 2H), 7.45-7.48 (m, 2H), 7.55-7.58 (m, 1H), 7.60-7.62 (m, 1H), 8.37-8.39 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.7, 20.0, 29.5, 46.6, 55.7, 64.1, 116.0, 116.1, 116.2, 116.3, 120.4, 123.6, 123.9, 124.7, 127.1, 127.6, 129.4, 129.7, 129.8, 130.5, 130.9, 131.0, 131.2, 131.5, 136.9, 153.8, 160.0, 160.5, 161.7, 162.2, 175.8; IR (KBr)ν_{max} 1149, 1202, 1228, 1331, 1455, 1487, 1516, 1610, 2853, 2925, 2961, 3024, 3066 cm^{-1}; HRMS (ESI) Calcd For $C_{27}H_{24}F_2NOS_2$ 480.1262 ($M + H^+$); Found 480.1262.

2,4-bis(2-chlorophenyl)-3-(4-methylbenzyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin

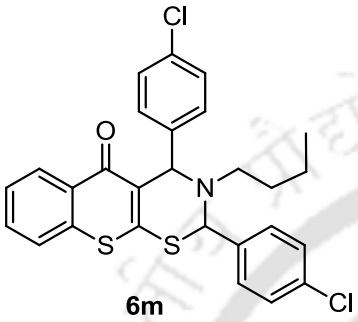


6l

5(2*H*)-one (6l): Yellow solid (224 mg, 80% yield), Mp 173-174 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 3.47 (d, *J* = 13.6 Hz, 1H), 4.03 (d, *J* = 13.6 Hz, 1H), 5.88 (s, 1H), 6.58 (s, 1H), 6.90-6.97 (m, 4H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.20-7.24 (m, 3H), 7.31-7.33 (m, 1H), 7.36-7.38 (m, 1H), 7.45-7.50 (m, 2H), 7.52 (s, 1H), 7.56-7.58

(m, 1H), 7.71-7.73 (m, 1H), 8.37 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 51.4, 58.8, 66.8, 120.7, 124.6, 125.9, 126.4, 127.4, 128.4, 129.0, 129.1, 129.6, 129.9, 130.2, 130.5, 130.9, 131.3, 132.9, 133.7, 134.9, 135.8, 136.5, 136.6, 137.2, 152.9, 175.2; IR (KBr)ν_{max} 1129, 1241, 1302, 1346, 1440, 1500,1583, 1601, 2851, 2919, 2967, 3016, 3058 cm^{-1}; HRMS (ESI) Calcd For $C_{31}H_{24}Cl_2NOS_2$ 560.0671 ($M + H^+$); Found 560.0669.

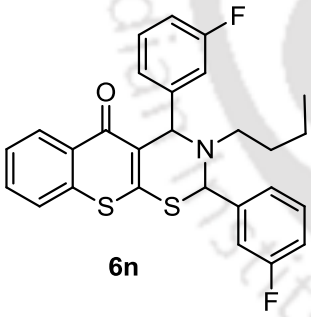
3-butyl-2,4-bis(4-chlorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one



6m

(6m): Yellow solid (192 mg, 75% yield), Mp 138-139 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.70 (t, *J* = 7.2 Hz, 3H), 1.03-1.08 (m, 1H), 1.18-1.24 (m, 1H), 1.44-1.49 (m, 2H), 2.34-2.38 (m, 1H), 2.49-2.55 (m, 1H), 5.64 (s, 1H), 5.85 (s, 1H), 7.16-7.19 (m, 3H), 7.20-7.21 (m, 2H), 7.25-7.26 (m, 3H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.50-7.53 (m, 1H), 8.34 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 20.4, 30.3, 46.1, 59.7, 69.0, 120.9, 124.2, 124.8, 127.7, 128.9, 129.1, 129.2, 129.6, 130.2, 131.0, 131.6, 133.6, 134.8, 135.2, 137.0, 140.1, 153.4, 176.2; IR (KBr)ν_{max} 1101, 1240, 1302, 1330, 1436, 1470, 1518, 1588, 1607, 2856, 2926, 2954, 3021, 3065 cm^{-1}; HRMS (ESI) Calcd For $C_{27}H_{24}Cl_2NOS_2$ 512.0671 ($M + H^+$); Found 512.0674.

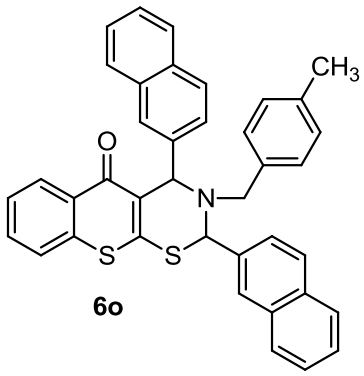
3-butyl-2,4-bis(3-fluorophenyl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one



6n

(6n): Yellow solid (172 mg, 72% yield), Mp 128-129 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.78 (t, *J* = 7.8 Hz, 3H), 1.13-1.19 (m, 1H), 1.28-1.34 (m, 1H), 1.54-1.59 (m, 2H), 2.43-2.47 (m, 1H), 2.60-2.65 (m, 1H), 5.76 (s, 1H), 5.98 (s, 1H), 6.96-6.99 (m, 1H), 7.01-7.07 (m, 3H), 7.11-7.15 (m, 2H), 7.31-7.34 (m, 2H), 7.48-7.51 (m, 2H), 7.58-7.60 (m, 1H), 8.42 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.9, 20.4, 29.9, 46.2, 59.8, 68.9, 114.7, 114.8, 115.0, 115.7, 115.8, 115.9, 120.8, 123.3, 124.5, 124.8, 127.1, 127.5, 127.7, 129.5, 130.3, 130.4, 131.0, 131.6, 136.9, 139.2, 144.2, 153.4, 162.1, 162.5, 163.8, 164.1, 176.2; IR (KBr)ν_{max} 1132, 1241, 1261, 1297, 1328, 1435, 1486, 1513, 1586, 1613, 1650, 1723, 2817, 2955, 3059 cm^{-1}; HRMS (ESI) Calcd For $C_{27}H_{24}F_2NOS_2$ 480.1262 ($M + H^+$); Found 480.1262.

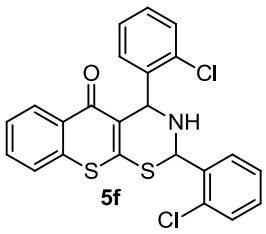
3-benzyl-2,4-di(naphthalen-2-yl)-3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-one

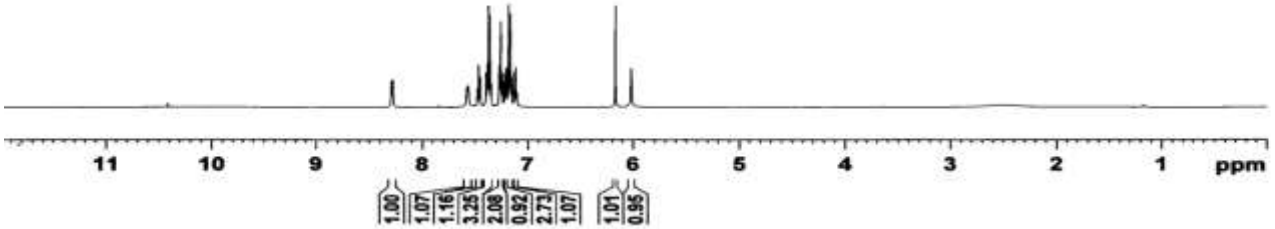


6o

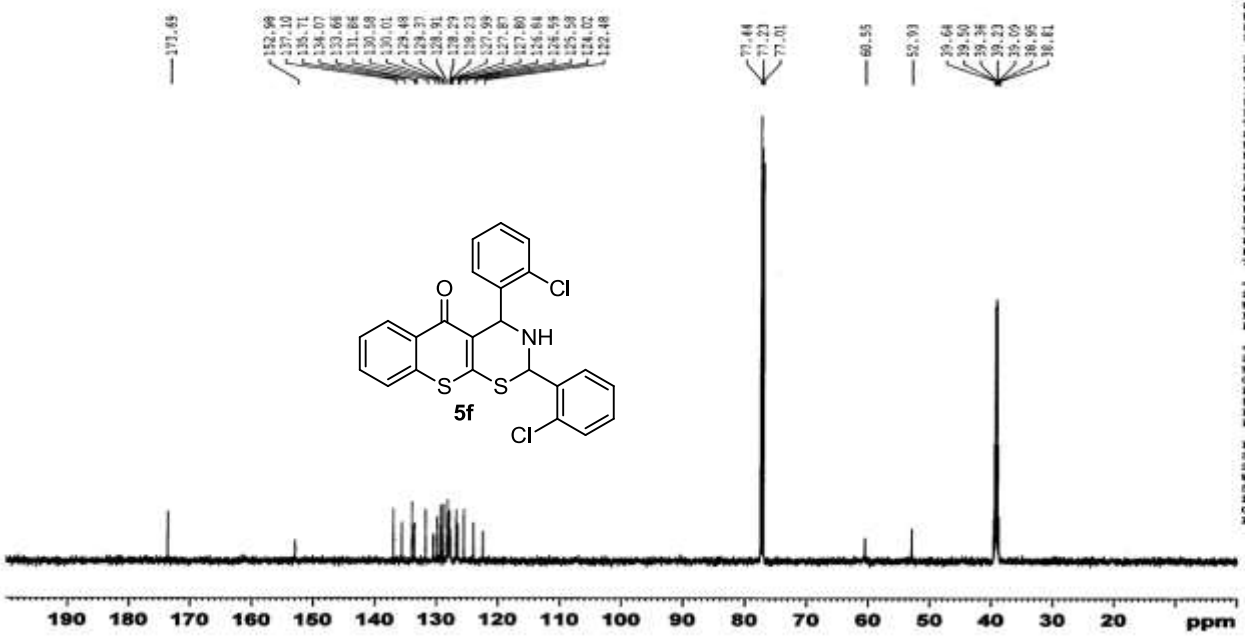
(6o): Yellow solid (202 mg, 70% yield), Mp 110-111˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (d, *J* = 14.4 Hz, 1H), 4.08 (d, *J* = 14.4 Hz, 1H), 5.79 (s, 1H), 6.56 (s, 1H), 6.98-6.99 (m, 1H), 7.02-7.06 (m, 2H), 7.09-7.13 (m, 3H), 7.15-7.20 (m, 3H), 7.22-7.25 (m, 5H), 7.26-7.73 (m, 2H), 7.32-7.46 (m, 1H), 7.46-7.49 (m, 2H), 7.51 (s, 1H), 7.55-7.59 (m, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.8, 59.8, 68.8, 120.9, 124.8, 125.8, 126.1, 126.2, 126.7, 126.9, 127.1, 127.5, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 128.7, 128.9, 129.3, 129.7, 131.2, 131.5, 132.9, 133.2, 133.3, 133.5, 134.0, 137.0, 137.8, 138.9, 152.8, 176.0; IR (KBr)ν_{max} 1162, 1233, 1306, 1343, 1455, 1437, 1510, 1587, 1616, 2851, 2924, 2962, 3067 cm^{-1}; HRMS (ESI) Calcd For $C_{38}H_{28}NOS_2$ 578.1607 ($M + H^+$); Found 578.1613.

[1]HNMR: *2,4-bis(2-chlorophenyl)-3,4-dihydrothiochromeno[3,2-e][1,3]thiazin-5(2H)-one (**5f**)*

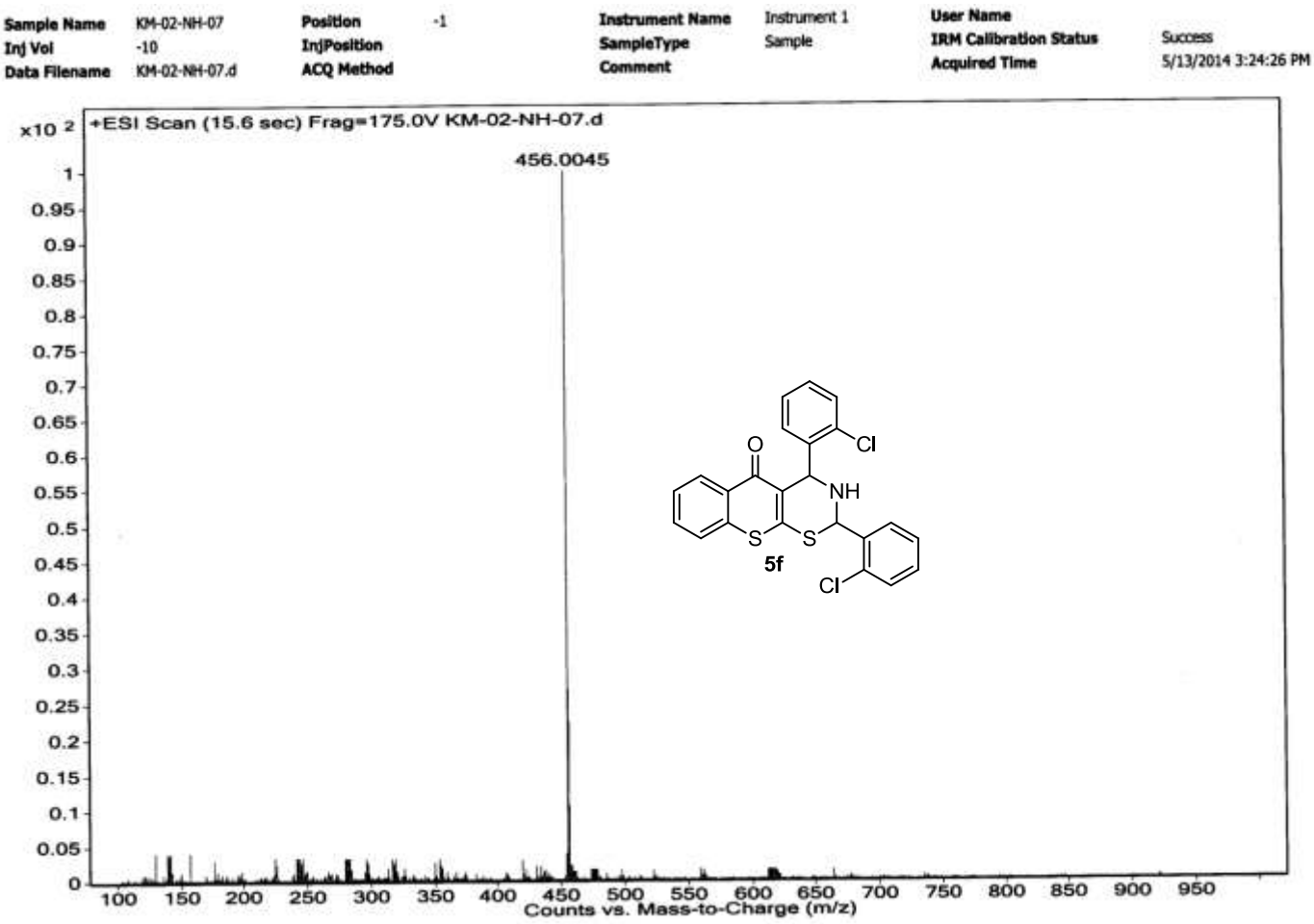




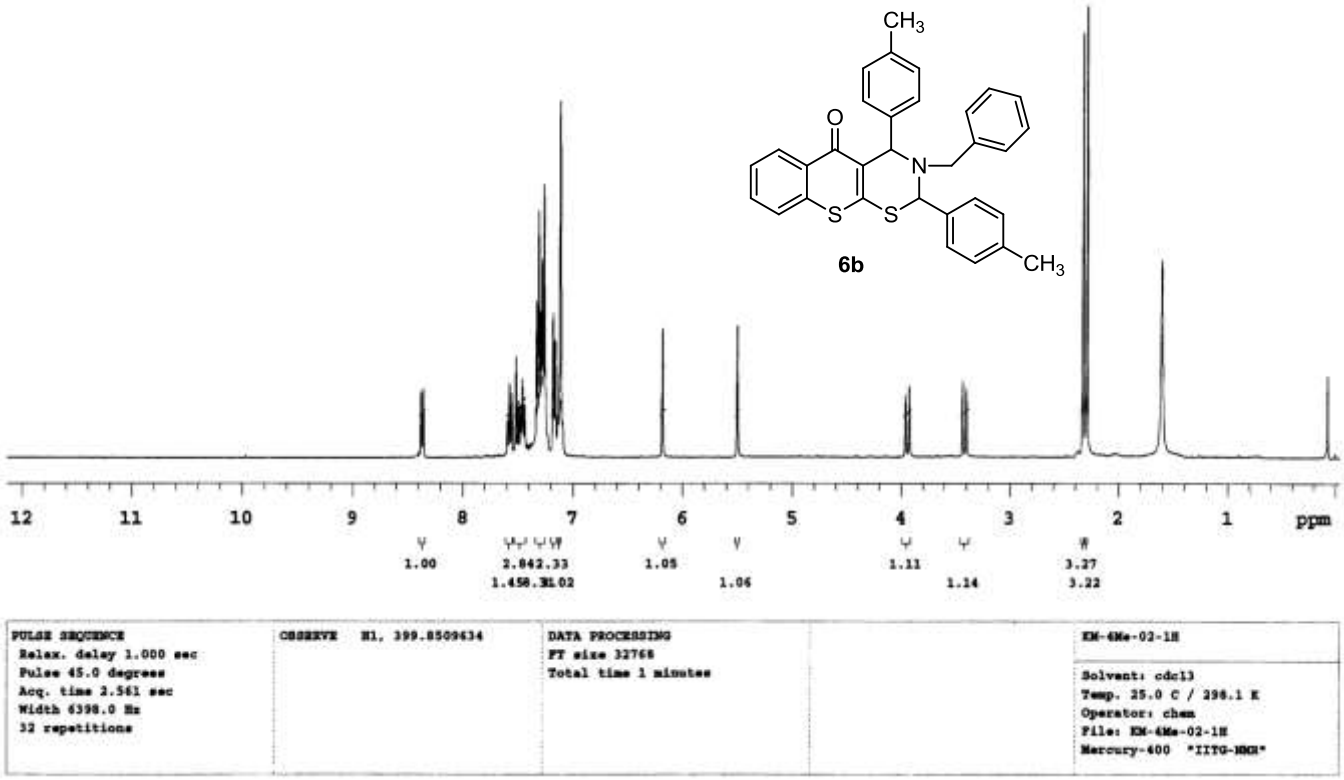
[13]CNMR: *2,4-bis(2-chlorophenyl)-3,4-dihydrothiochromeno[3,2-e][1,3]thiazin-5(2H)-one (**5f**)*



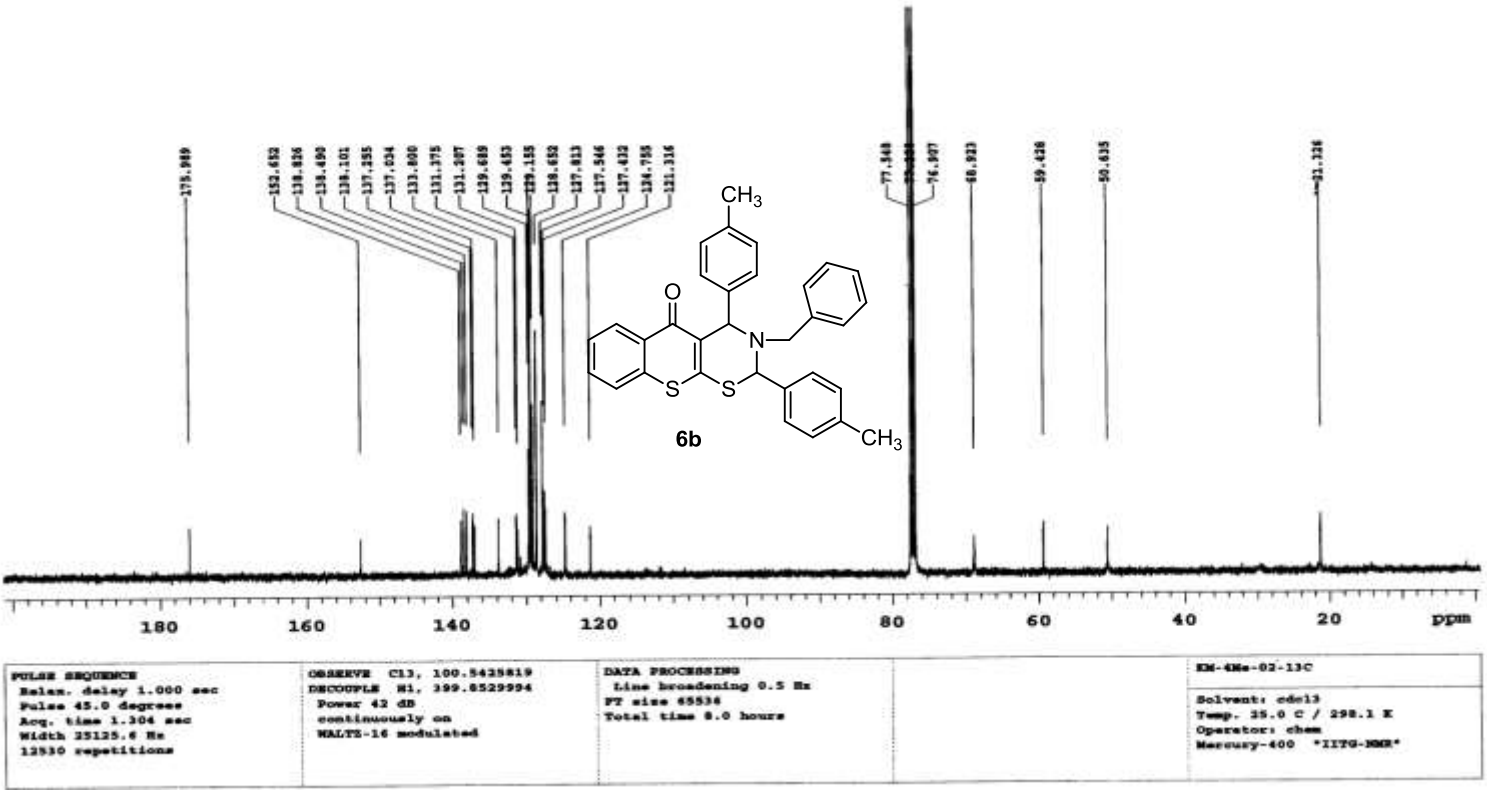
HRMS: *2,4-bis(2-chlorophenyl)-3,4-dihydrothiochromeno[3,2-e][1,3]thiazin-5(2H)-one* (***5f***)



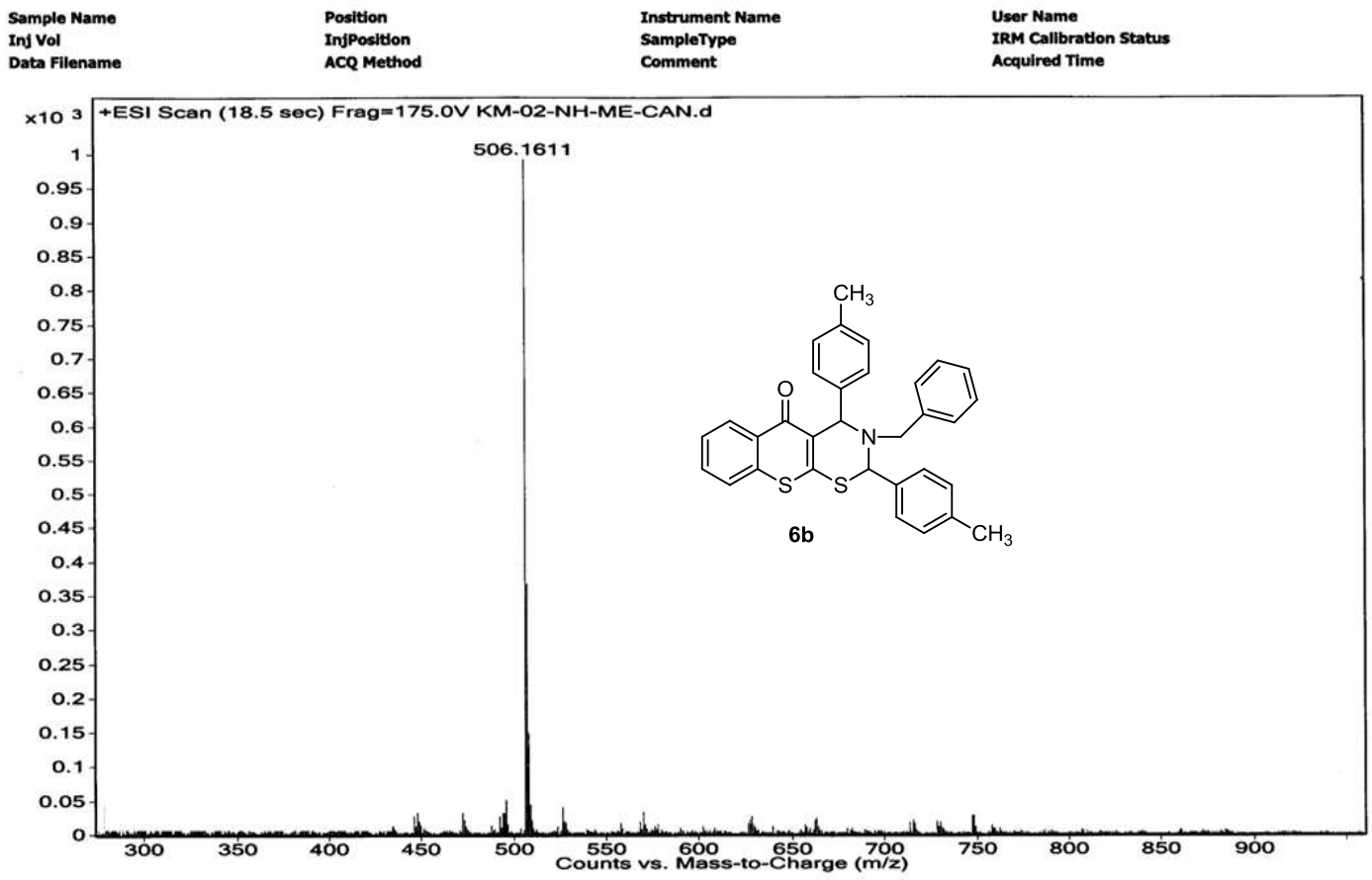
[1]***HNMR:*** *3-benzyl-2,4-di-p-tolyl-3,4-dihydrothiochromeno[3,2-e][1,3]thiazin-5(2H)-one* ***(6b)***



[13]**CNMR:** *3-benzyl-2,4-di-p-tolyl-3,4-dihydrothiochromeno[3,2-e][1,3]thiazin-5(2H)-one* ***(6b)***



HRMS: *3-benzyl-2,4-di-p-tolyl-3,4-dihydrothiochromeno[3,2-e][1,3]thiazin-5(2H)-one* ***(6b)***



Chapter III

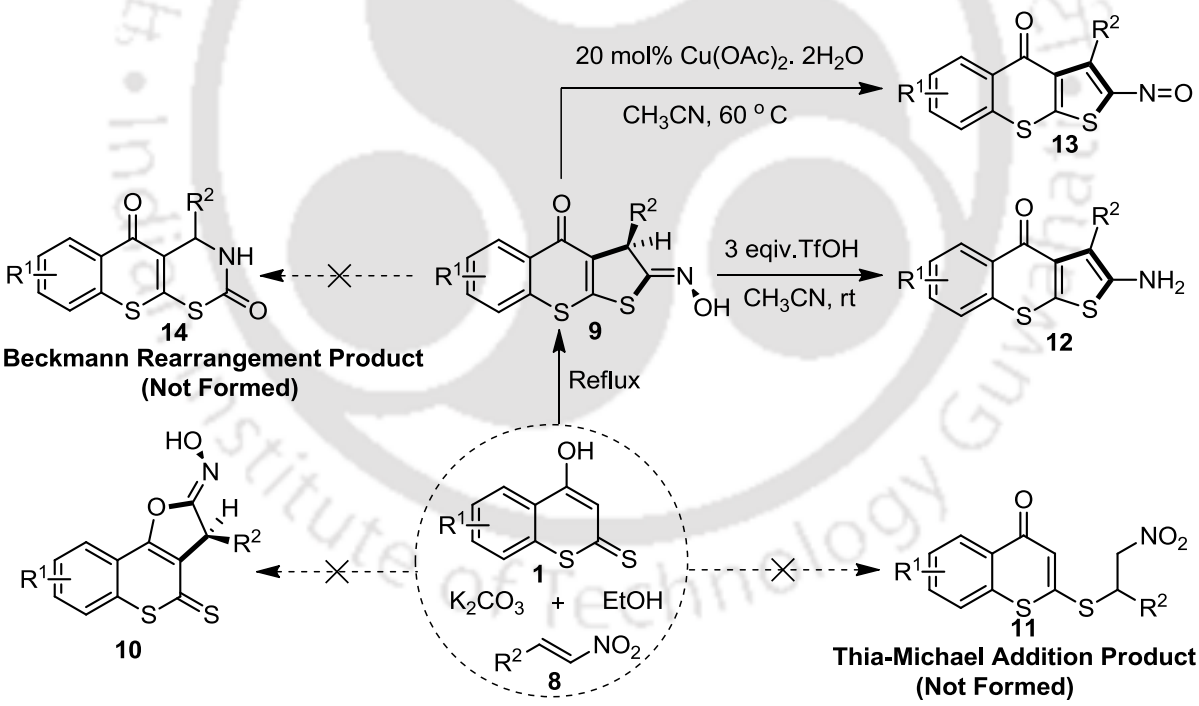
K_2CO_3 catalyzed regioselective synthesis of thieno[2,3-*b*]thiochromen-4-one oximes: Access to the corresponding Amine and Nitroso derivatives

Result & Discussion

Experimental Section

Results and Discussion

The importance of thiophene scaffolds and the various methods of their synthesis have been discussed in Chapter 1. In addition, literature reports reveals that organic molecules having oxime functionality are highly appreciated in the field of biochemistry,[7] polymer chemistry,[8a] fragrances,[8b] fungicides[9] and most importantly as an active reaction intermediate in various organic syntheses thus laying the foundation for the creation molecular diversity.[10] Taking a glance at these reported medicinal and material based applications, the synthesis of thiophenes having oxime functionality is highly desirable to organic chemists. In this chapter we report a convenient synthesis of thieno[2,3-*b*]thiochromen-4-one oxime derivatives via thio[3+2] cyclization reaction of 4-hydroxydithiocoumarins and *trans*-β-nitrostyrene in the presence of 10 mol% K_2CO_3 catalyst in ethanol under reflux condition. Further, these derivatives acted as a valuable synthon for the synthesis of 2-amino thieno[2,3-*b*]thiochromen-4-one and 2-nitroso thieno[2,3-*b*]thiochromen-4-one derivatives using TfOH and $Cu(OAc)_2$ respectively as shown in Scheme 45.



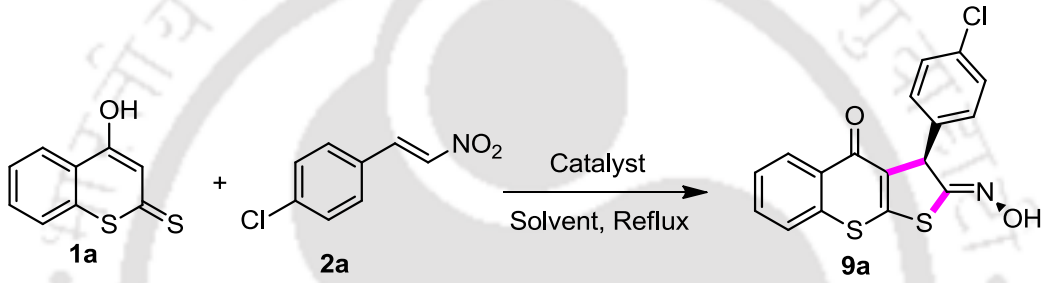
Scheme 45. Synthesis of thiophenes containing oxime functionality

Conventionally, the key ingredients for oxime synthesis are hydroxylamine and aldehydes or ketones[11] or nitrites and compounds containing the active methylene group.[12] The alternative path includes the reduction of α, β-unsaturated / saturated nitro compounds employing expensive catalyst such as Bu_3SnH, $Se/NaBH_4$, $SnCl_2/PhSH$,[13] $Au/TiO_2/H_2$,[14a]

$Ru(bpy)_3Cl_2$[14b], chiral bifunctional thioureas catalyst[14c] and Takemoto organocatalyst.[14d] However, the major restrictions of these recognized approaches lies in poor selectivity, harsh reaction conditions, employment of toxic metal catalysts and longer reaction time.

The optimization studies were initiated with 4-hydroxydithiocoumarin (**1**, 1.0 mmol) and *trans*-4-chloro-β-nitrostyrene (**8**, 1.0 mmol) as the model substrates and the results are summarized in Table 4. Our first attempt of using 1 equiv. NaOH in water under refluxing conditions led to the isolation of product **9a** in 28% yield (Table 4, entry 1). The isolated product **9a** was characterized by IR, ^1H and ^{13}C NMR spectra and HRMS.

Table 4. Optimization of the reaction condition for the synthesis thieno[2,3-*b*]thiochromen-4-one oxime **9a**[a]



Entry	Base	Amount (mol%)	Solvent	Time [h]	Yield[b] (%)
1	NaOH	1 equiv.	H_2O	3.0	28
2	NaOH	10	H_2O	2.0	33
3	NaOH	10	EtOH	1.5	48
4	NaOH	10	CH_3CN	1.5	42
5	KOH	10	EtOH	1.5	52
6	Na_2CO_3	10	EtOH	1.0	60
7	K_2CO_3	5	EtOH	1.5	78
8	**K_2CO_3**	**10**	EtOH	**0.75**	**86**
9	K_2CO_3	15	EtOH	1.0	86
10	K_2CO_3	10	H_2O	2.5	62
11	K_2CO_3	10	MeOH	1.0	70

12	K_2CO_3	10	^tBuOH	1.5	65
13	K_2CO_3	10	CH_3CN	1.5	72
14	Et_3N	10	EtOH	1.0	55
15	Pipyridine	10	EtOH	1.0	68
16	DBU	10	EtOH	1.0	75

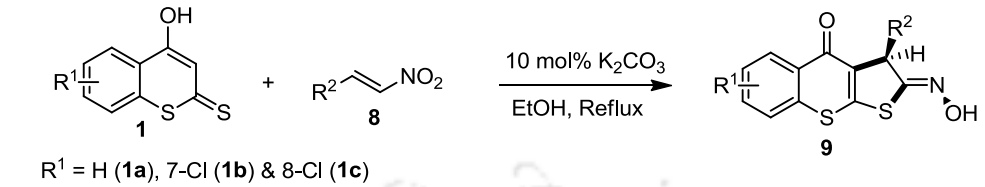
[a]All the reactions were performed in 1.0 mmol scale of 4-hydroxydithiocoumarin (**1**) and *trans*-4-chloro-β-nitrostyrene (**8**) in 2 mL solvent. [b]Isolated yield.

In an effort to increase the yield of the product further, the same set of the reaction was again performed with 10 mol% of NaOH as catalyst under identical reaction condition which resulted in 33% yield of the product **9a**, whereas on changing the solvent to EtOH or CH_3CN, the results were still not satisfactory (Table 4, entries 2-4). With a desire for achieving even better yields, the same reactions were executed with other inorganic bases such as KOH and Na_2CO_3 in 2 mL EtOH giving the product **9a** in 52-60% yields (Table 4, entries 5-6). To our delight, when the same set of reactions were carried out in the presence of 5, 10 and 15 mol% K_2CO_3 catalyst in 2 mL ethanol under similar reaction condition the desired product **9a** was obtained in good yields (Table 4, entries 7–9). Screening the same reaction with other solvents such as water, methanol, butanol and acetonitrile did not show apparent positive effects on the time and yield (Table 4, entries 10-13). Organic bases like Et_3N, piperidine and DBU also gave moderate to good yields (Table 4, entries 14-16). Nevertheless, K_2CO_3 is a commercially cheaper base, and being solid is much easier to handle than liquid organic bases. Thus, it was noted that the optimal condition for this protocol is 10 mol% of K_2CO_3 in EtOH solvent.

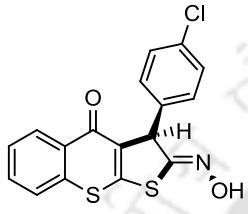
With the optimum conditions in hand, the scope of the reaction was explored with various *trans*-β-nitrostyrenes and the results are summarized in Table 5. The reaction of *trans*-β-nitrostyrene and 4-hydroxydithiocoumarin gave 84% yield of the product **9b**. The reaction proceeded smoothly with the *trans*-β-nitrostyrenes having electron donating to electron withdrawing substituents such as Me, NO_2, Br, F at para position as well as at meta position (Br) providing the products **9c-g** in 78-88% yield. Also, the reaction was well applied for *trans*-2,4-dimethoxy-β-nitrostyrene, *trans*-3,4-dimethoxy-β-nitrostyrene and *trans*-3,4,5-trimethoxy-β-nitrostyrene leading to the isolation of products **9h-j** in 72-78% yield. While employing 4-hydroxydithiocoumarins having substituent on fused benzene ring at 6 and 7 position (Cl) respectively under the same reaction condition we got the products **9k-v** in

moderate to good yields. The reaction was also applicable to alkyl substituted nitro-olefines as 4-hydroxydithiocoumarin reacted with (E)-1-nitrohex-1-ene to give the product **9w** in 68% yield.

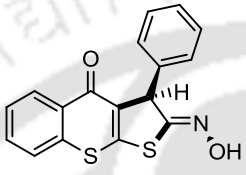
Table 5. Substrate Scope of 2-oxime-3-aryl-2H-thieno[2,3-*b*]thiochromen-4-ones[a,b]



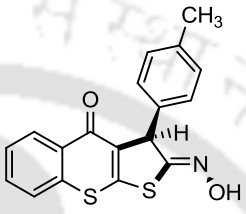
R^1 = H (**1a**), 7-Cl (**1b**) & 8-Cl (**1c**)



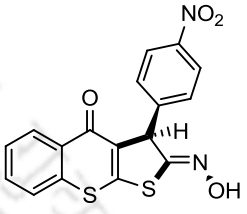
9a, 0.75 h, 86%



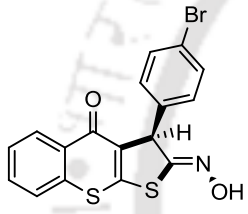
9b, 0.6 h, 84%



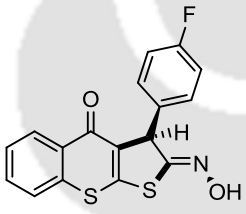
9c, 0.75 h, 88%



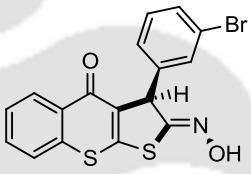
9d, 1.0 h, 78%



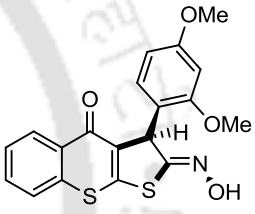
9e, 0.75 h, 85%



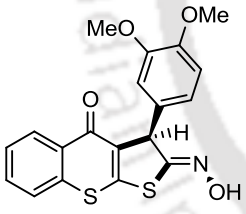
9f, 0.5 h, 88%



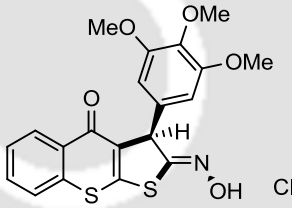
9g, 1.0 h, 80%



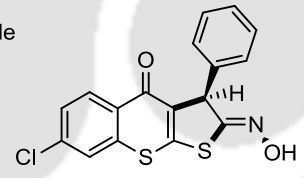
9h, 0.75 h, 78%



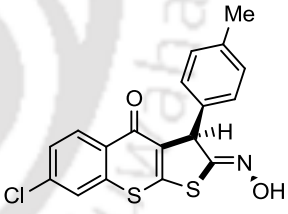
9i, 1.0 h, 72%



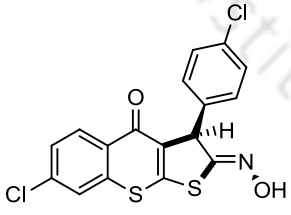
9j, 1.0 h, 75%



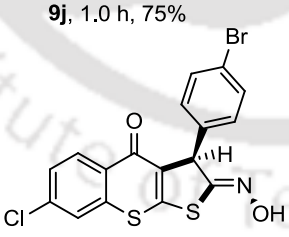
9k, 0.75 h, 84%



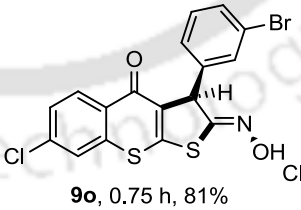
9l, 0.5 h, 86%



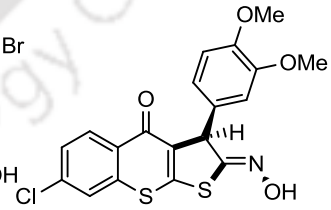
9m, 0.5 h, 88%



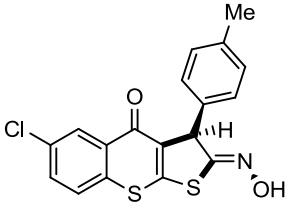
9n, 0.5 h, 86%



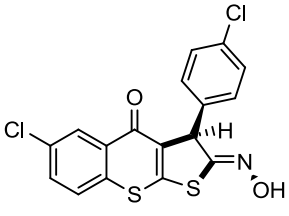
9o, 0.75 h, 81%



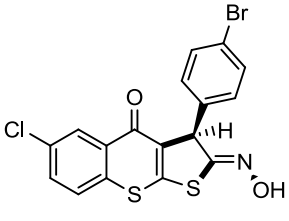
9p, 1.0 h, 78%



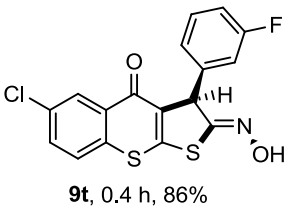
9q, 0.5 h, 82%



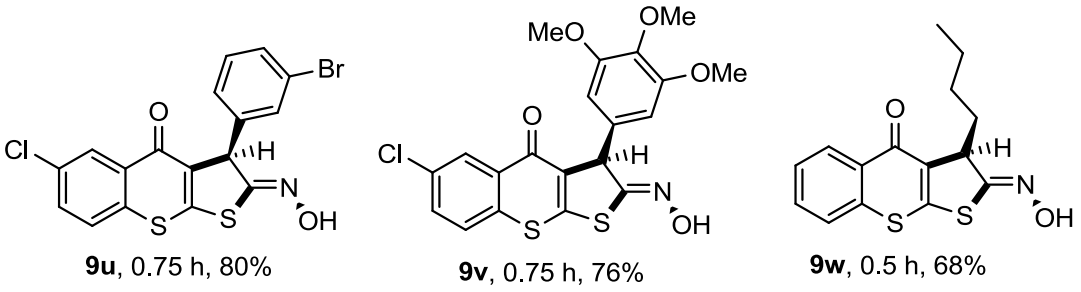
9r, 0.5 h, 84%



9s, 0.5 h, 80%



9t, 0.4 h, 86%



9u, 0.75 h, 80% **9v**, 0.75 h, 76% **9w**, 0.5 h, 68%

[a]All the reactions were performed in 1.0 mmol scale of various 4-hydroxydithiocoumarin (**1**) and *trans*-4-chloro-β-nitrostyrene (**8**) in 2 mL ethanol. [b]Isolated yield.

All of these products **9b-w** were characterized by IR, ^{1}H and ^{13}C NMR spectra and HRMS. In addition, the structure of **9c** was also confirmed through XRD which shows H-8 and the proton of oxime –OH as anti to each other (Figure **8**, I). This is in agreement with the NOESY and COSY spectra of **9q** where the position of H-8 and oxime –OH proton appeared to be anti to each other (Figure **8**, II).

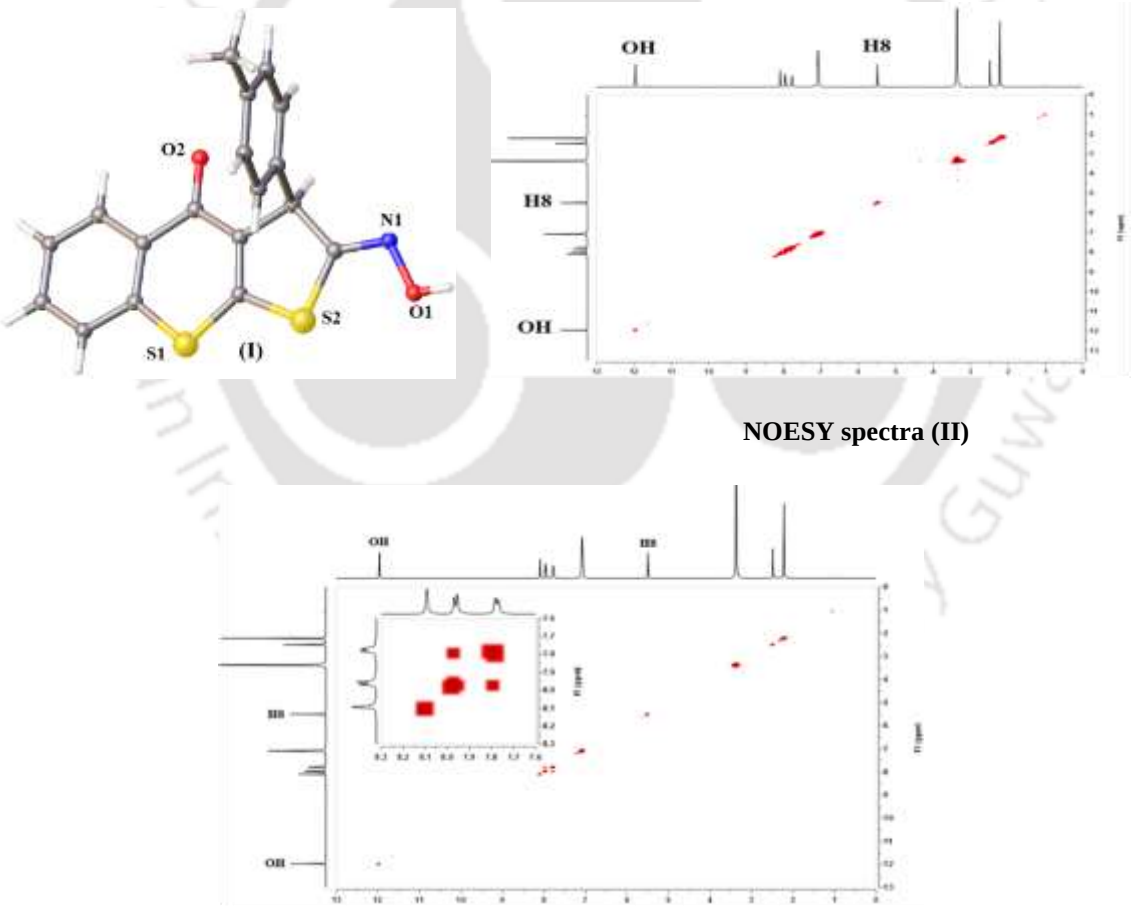
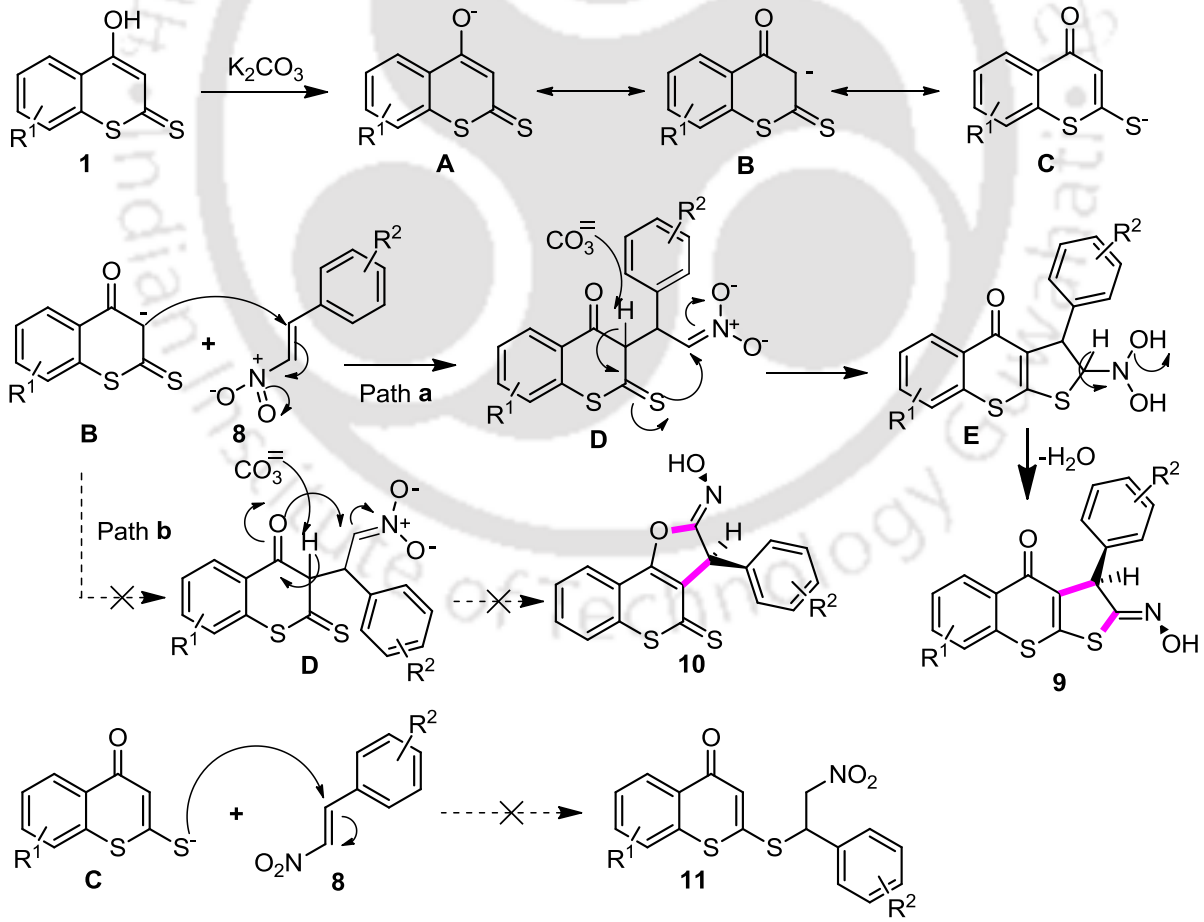


Figure 8. (I) XRD structure of **9c** (CCDC no. 1454211), (**II**) NOESY spectra and (**III**) COSY spectra of **9q**

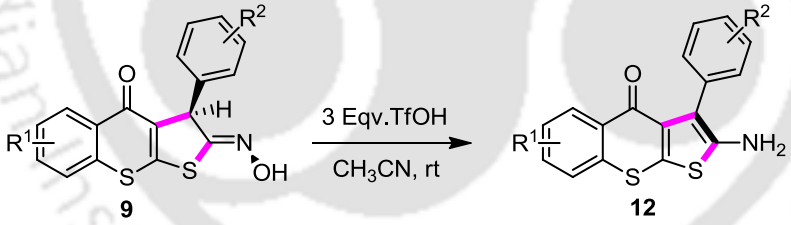
A plausible mechanism can be drawn for the formation of product **9** as shown in Scheme 46. In the presence of base K_2CO_3, 4-hydrodithiocoumarin (**1**) can form an ambident anion with three resonating structures namely **A**, **B** and **C**.[15a,b] The anion **B** further attacks *trans*-nitrostyrene **8** to form an intermediate **D**. There are two possibilities which may lead to the formation of two different products, product **9** via 'path a' or product **10** via 'path b'. However, the selective isolation of product **9** shows that the reaction is compelled via 'path a'. In 'path a' the intermediate **D** undergoes regioselective cyclisation to form an intermediate **E** which finally after the liberation of a water molecule forms the desired product **9**. The key reasons for the regioselective synthesis of product **9** might be[15c] (i) the sulfur atom with its readily accessible lone pair of electrons acts as a better nucleophilic candidate than oxygen counterpart mainly due to its large size and high polarizability (ii) the steric hindrance faced by sulfur with aryl group bars the reaction to proceed via 'path b'. It can be seen here that the 4-hydroxydithiocoumarin **1** attacks *trans*-nitrostyrene **8** exclusively via resonating structure **B** and not **A** and **C** as we might have ended upon having thia-Michael addition product **11**.[15d]

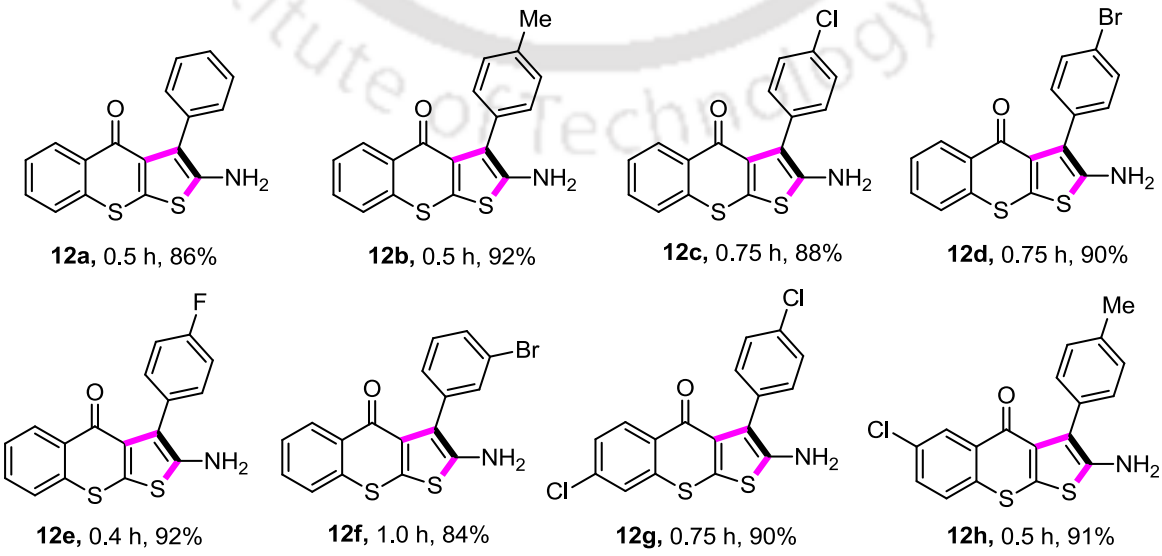


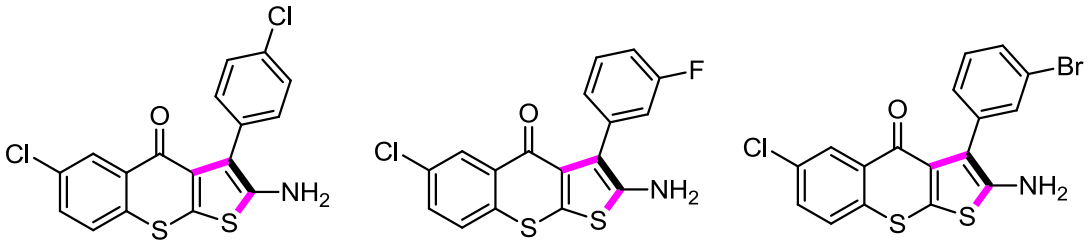
Scheme 46. Mechanism for the formation of 2-Oxime-3-aryl-2H-thieno[2,3-*b*]thiochromen-4-one derivatives (**9**)

The synthesized product **9** was further explored as a valuable synthon in our next phase of study. One of the most hunted reactions of oxime is the Beckmann rearrangement[16] where the oxime is treated with various acids to get amides or lactams. On our pursuit to Beckmann rearrangement we treated the product **9a** with an equiv. amount acetic acid at room temperature but unfortunately no reaction was seen even after 12 hours of stirring. Next, while repeating the same reaction with 3 equiv. of TfOH in CH_3CN at room temperature the reaction proceeded very smoothly without the formation of any side products giving rise to yellow colored solid compound. The yellow solid was characterised through spectroscopic analysis. The IR spectrum of the compound shows two strong characteristic absorption at 3365 and 3454 cm^{-1} which gives an evidence of the presence of $–NH_2$ functional group. Moreover, the peak at δ 3.90 in ^1H NMR also hints the presence of NH_2 group. These observations indicate that the compound **9a** was indeed converted to its corresponding amine **12c**. Thus we can say that Semmler-Wolf[17] type reaction has taken place which lead to the aromatisation of dihydrothiophene ring instead of Beckmann rearrangement. Inspired by these results an array of products **12a-k** was synthesized likewise in good yields (Table 6). Unfortunately, the reaction failed to produce any desired product with alkyl substituted oxime **9w** under identical reaction condition after 12 hrs of stirring.

Table 6. 2-amino-3-aryl-4H-thieno[2,3-*b*]thiochromen-4-one derivatives[a,b]





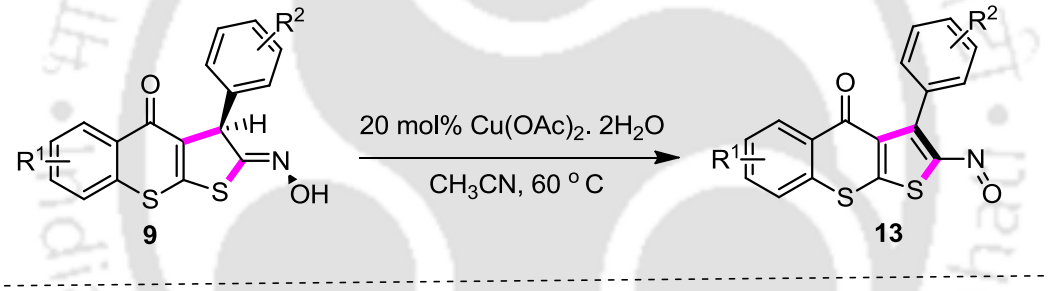


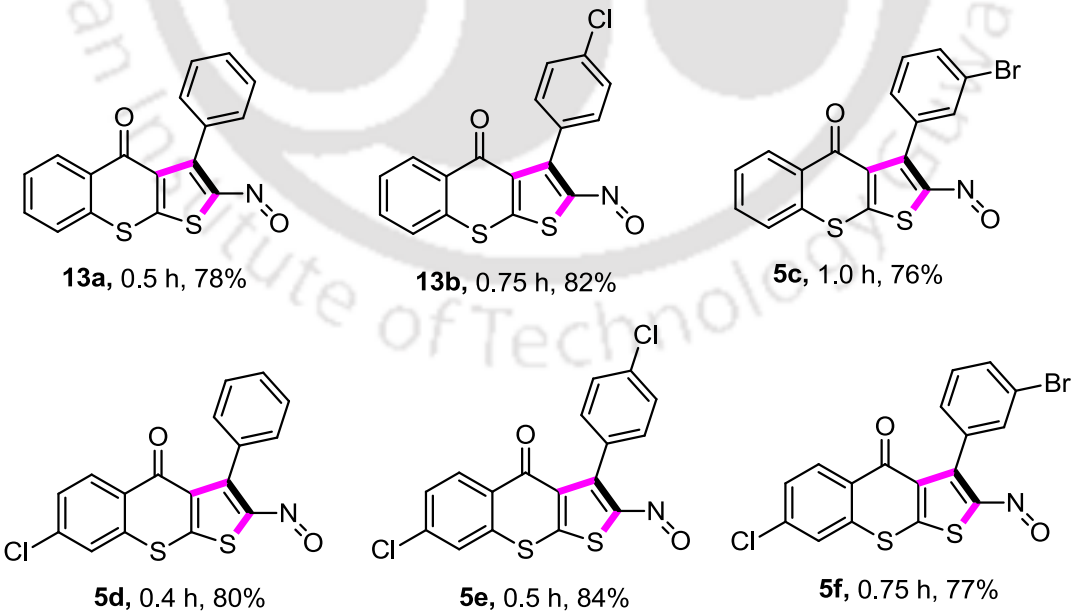
12i, 0.75 h, 90% **12j,** 0.5 h, 88% **12k,** 1.0 h, 82%

[a]All the reactions were performed with 0.5 mmol of 2-oxime-3-aryl-2H-thieno[2,3-*b*]thiochromen-4-one (**9**) and 3 equivalent of trifluoromethanesulfonic acid in 2 mL acetonitrile. [b]Isolated yield.

There are several reports which show Cu could effectively catalyse Beckmann rearrangement.[18] To satisfy our quest for Beckmann rearrangement we treated the product **9a** with the catalyst $Cu(OAc)_2$ (20 mol%) in CH_3CN at 60 °C. After chromatographic separation we isolated a yellow coloured solid.

Table 7. Synthesis of 2-nitroso-3-aryl-4H-thieno[2,3-*b*]thio chromen-4-one derivatives[a,b]





13a, 0.5 h, 78% **13b,** 0.75 h, 82% **5c,** 1.0 h, 76%

5d, 0.4 h, 80% **5e,** 0.5 h, 84% **5f,** 0.75 h, 77%

[a]All the reactions were performed with 0.5 mmol of 2-oxime-3-aryl-2H-thieno[2,3-*b*]thiochromen-4-one (**3**) and 20 mol% of copper(II) acetate in 2 mL acetonitrile. [b]Isolated yield.

After spectroscopic analysis we were delighted to find the yellow solid as unexpected 3-(4-chlorophenyl)-2-nitroso-4H-thieno[2,3-*b*]thiochromen-4-one (**13b**) where the oxime moiety undergoes functional group transformation to nitroso group[19] rather than the conventional Beckmann product. Likewise the products **13a–f** were synthesized in moderate to good yields. However, the reaction proved futile with the oxime **9w** under similar reaction conditions even after overnight stirring. All the products **13a-k** and **13a-f** were characterized by IR, ^{1}H and ^{13}C NMR spectra and HRMS. In addition the structure of compounds **12f** and **13a** was also confirmed through XRD (Figure 9, **I & II**).

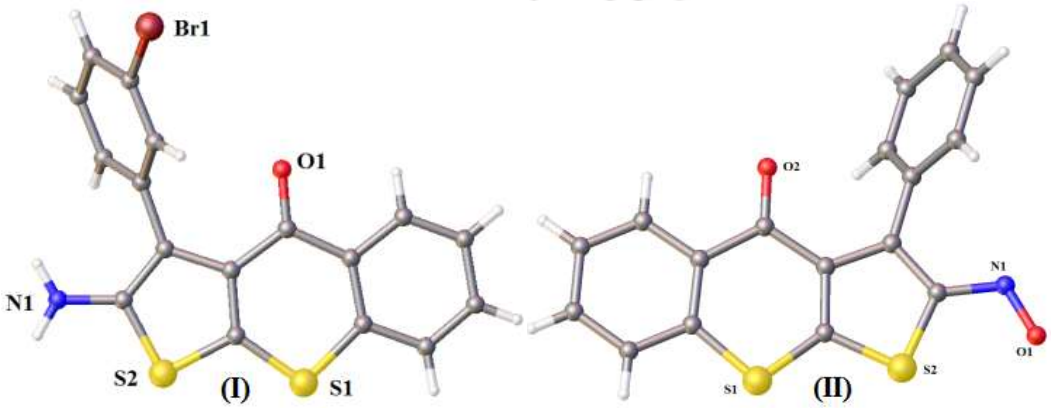


Figure 9. (**I**) XRD structure of **12f** (CCDC no. 1454212) and (**II**) XRD structure of **13a** (CCDC no. 1454213)

Conclusion

In summary, we have developed a rapid and novel method for the synthesis of thieno[2,3-*b*]thiochromen-4-one oximes which were further used in the preparation of 2-amino thieno[2,3-*b*]thiochromen-4-one and 2-nitroso thieno[2,3-*b*]thiochromen-4-one derivatives. The reactions are contrary to traditional methods as the oxime gets functional group transformation rather than conventional Beckmann rearrangement. The unique aspect of this protocol is due to the presence of eye-catching functionality the synthesized 2-amino thieno[2,3-*b*]thiochromen-4-one and 2-nitroso thieno[2,3-*b*]thiochromen-4-one derivatives, may be further used as beneficial synthon in various other synthetic conversions. To the best of our knowledge these oximes, amines and nitroso compounds are reported first time in the literature from 4- hydroxydithiocoumarin. The extensions and applications of this chemistry would be reported elsewhere.

`Experimental Section

I. General procedure for the synthesis of *trans*-β-nitrostyrenes (8)[20]

In a 250-ml round-bottomed flask was taken a mixture of aldehyde (0.20 mol), nitromethane (0.22 mol) and ammonium acetate (0.1 mol) in 50 ml of glacial acid. A reflux condenser was attached and the mixture was refluxed for 4 hours. The solution was then cooled to room temperature and kept overnight at this temperature. The crystals formed were filtered, washed with water and dried under vacuum to afford solid nitrostyrenes (**8**).

II. Synthesis of 2-oxime-3-aryl-2H-thieno[2,3-*b*]thiochromen-4-one derivatives (9a-w)

Into an oven dried 25 mL round bottomed flask was added 4-hydroxydithicoumarin (1.0 mmol, **1**) and *trans*-β-nitrostyrenes (1.0 mmol, **8**) in 2 ml of EtOH along with the catalyst K_2CO_3 (10 mol%, 13.8 mg). The mixture was then subjected to reflux on a pre-heated oil bath. The progress of the reaction was monitored by TLC. After the completion of the reaction, flask was removed from the oil bath and it was brought to room temperature for complete precipitation. The solid precipitate was filtered off through a Büchner funnel, washed with EtOH and finally dried under reduced pressure to get the pure products **9a-w**.

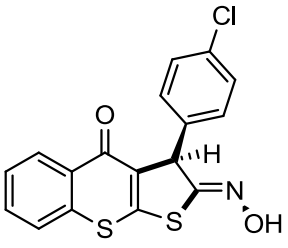
III. Synthesis of 2-amino-3-aryl-4H-thieno[2,3-*b*]thiochromen-4-one derivatives (12a-k)

The synthesized products **9** (0.5 mmol) was added to 2 mL CH_3CN followed by the drop wise addition of 3 equiv. of TfOH. The resultant solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After the completion of the reaction the mixture was concentrated in vacuum and quenched with 3 mL of saturated sodium bicarbonate solution. Finally it was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuum and the residue was purified by silica gel column chromatography to get the pure products **12a-k**.

IV. Synthesis of 2-nitroso-3-aryl-4H-thieno[2,3-*b*]thiochromen-4-one (13a-f)

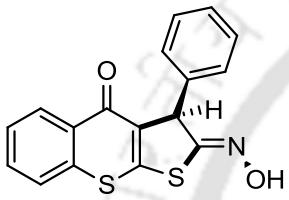
To a stirred mixture of the synthesized products **9** (0.5 mmol) in 2 mL CH_3CN was added $Cu(OAc)_2.2H_2O$ (20 mol%, 0.018 g) and the mixture was refluxed. The progress of the reaction was monitored by TLC. After the completion of the reaction it was concentrated under reduced pressure. Then, the obtained residue was washed with brine solution, extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and evaporated in vacuum. Next, the crude residue was purified over a silica gel column chromatography to afford the desired products **13a-f** in good yields.

(Z)-3-(4-chlorophenyl)-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9a):



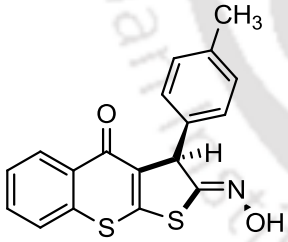
Light brown solid (309 mg, 86% yield), Mp 202-203 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.62 (s, 1H), 7.26-7.28 (m, 2H), 7.34-7.36 (m, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 12.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.5, 126.9, 127.9, 128.4, 128.6, 129.1, 130.1, 130.2, 131.8, 132.0, 135.3, 132.9, 149.4, 152.6, 172.8; IR (KBr)ν_{max} 1165, 1369, 1410, 1438, 1491, 1508, 1561, 1577, 1602, 1630, 2852, 2929, 3056, 3203, 3415 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}ClNO_2S_2$ 359.9914 (M + H$^+$); Found 359.9916.

(Z)-2-(hydroxyimino)-3-phenyl-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9b): White



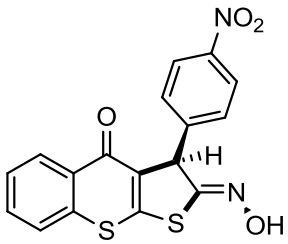
solid (273 mg, 84% yield), Mp 216-217 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.57 (s, 1H), 7.25-7.28 (m, 5H), 7.60 (s, 1H), 7.73 (s, 1H), 7.90 (s, 1H), 8.22 (s, 1H), 11.97 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.2, 126.9, 127.1, 127.9, 128.3, 128.6, 130.1, 130.6, 131.9, 135.2, 140.1, 149.0, 152.9, 172.8; IR (KBr)ν_{max} 1116, 1133, 1165, 1231, 1370, 1435, 1453, 1493, 1513, 1599, 1636, 2830, 2842, 3030, 3059, 3165 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{12}NO_2S_2$ 326.0304 (M + H$^+$); Found 326.0302.

(Z)-2-(hydroxyimino)-3-(p-tolyl)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9c): White



solid (298 mg, 88% yield), Mp 227-228 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 5.53 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.50 (s, 1H), 7.58 (s, 2H), 8.41 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 54.1, 125.7, 126.7, 127.4, 128.2, 128.8, 130.3, 130.5, 130.9, 135.1, 136.4, 136.5, 149.3, 153.1, 173.2; IR (KBr)ν_{max} 1118, 1133, 1162, 1228, 1261, 1367, 1383, 1438, 1510, 1582, 1599, 1631, 2848, 2918, 3061, 3245, 3429 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{14}NO_2S_2$ 340.0461 (M + H$^+$); Found 340.0460.

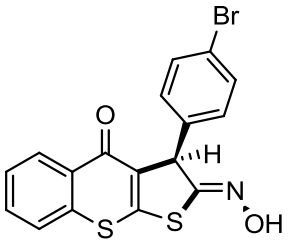
(Z)-2-(hydroxyimino)-3-(4-nitrophenyl)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9d):



Brown solid (288 mg, 78% yield), Mp 193-194 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.82 (s, 1H), 7.54-7.56 (m, 2H), 7.59-7.63 (m, 1H), 7.73-7.77 (m, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.16-8.22 (m, 3H), 12.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.8, 123.8, 126.9, 127.9, 128.4, 128.7, 129.7, 130.0, 132.1, 135.3, 146.6, 147.6, 150.1, 152.0, 172.8; IR (KBr)ν_{max}1112, 1167, 1222, 1261, 1345, 1374, 1438, 1505,

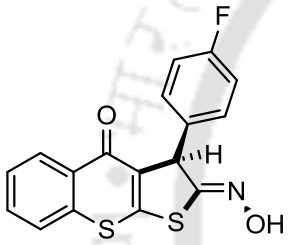
1576, 1596, 1632, 2840, 2926, 3041, 3447 cm^{-1}; HRMS (ESI) Calcd For$C_{17}H_{11}N_2O_4S_2$ 371.0155 ($M + H^+$); Found 371.0146.

(Z)-3-(4-bromophenyl)-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9e):



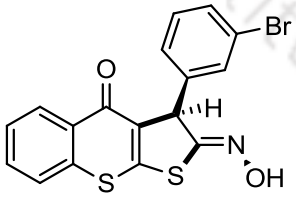
Brown solid (343 mg, 85% yield), Mp 198-199 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.59 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.61 (s, 1H), 7.74 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 12.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.7, 98.1, 127.0, 128.0, 128.5, 129.6, 130.3, 131.6, 132.1, 135.3, 139.7, 149.6, 152.6, 172.9; IR (KBr)ν_{max} 1115, 1162, 1225, 1369, 1405, 1438, 1487, 1508, 2855, 3060, 3182 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}BrNO_2S_2$ 403.9409 ($M + H^+$); Found 403.9408.

(Z)-3-(4-fluorophenyl)-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9f):



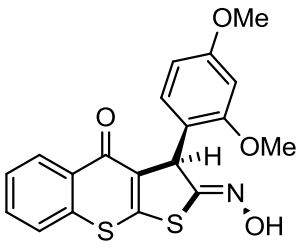
Light brown solid (302 mg, 88% yield), Mp 220-221 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.61 (s, 1H), 7.11 (t, *J* = 12.0 Hz, 2H), 7.28 (s, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 12.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.4, 115.2, 115.4, 126.9, 127.9, 128.3, 129.1, 129.2, 130.1, 130.4, 131.9, 135.2, 136.4, 149.2, 152.8, 160.1, 162.5, 172.8; IR (KBr)ν_{max} 1112, 1161, 1223, 1308, 1366, 1423, 1439, 1509, 1582, 1599, 1632, 2846, 2920, 3038, 3169, 3402 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}FNO_2S_2$ 344.0210 ($M + H^+$); Found 344.0222.

(Z)-3-(3-bromophenyl)-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9g):



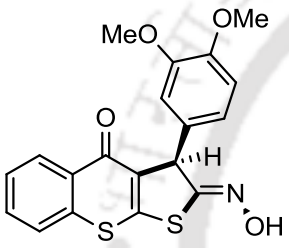
Light brown solid (323 mg, 80% yield) Mp 148-149 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.64 (s, 1H), 7.20-7.21 (m, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.76 (t, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 12.09 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 54.0, 122.0, 125.8, 125.9, 127.7, 128.3, 129.7, 129.9, 130.0, 130.3, 131.3, 135.2, 141.9, 150.2, 152.4, 173.4; IR (KBr)ν_{max} 1117, 1129, 1166, 1261, 1369, 1438, 1473, 1515, 1568, 1586, 1603, 1635, 2851, 2972, 3066 cm^{-1}; HRMS (ESI) Calcd For$C_{17}H_{11}BrNO_2S_2$ 403.9409 ($M + H^+$); Found 403.9411.

(Z)-3-(2,4-dimethoxyphenyl)-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one



(9h): Light brown solid (300 mg, 78% yield), Mp 235-236 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H), 3.74 (s, 3H), 5.72 (s, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 6.55 (s, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 11.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.2, 54.2, 54.9, 98.0, 103.7, 120.1, 125.2, 126.7, 127.3, 127.9, 129.5, 129.7, 130.3, 134.4, 148.2, 152.9, 156.7, 158.9, 172.3; IR (KBr)ν_{max} 1112, 1157, 1210, 1268, 1292, 1370, 1435, 1456, 1509, 1587, 1603, 2834, 2936, 3055, 3206, 3419 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{16}NO_4S_2$ 386.0515 (M + H$^+$); Found 386.0515.

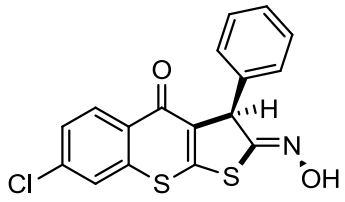
(Z)-3-(3,4-dimethoxyphenyl)-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one



(9i): Light brown solid (277 mg, 72% yield), Mp 205-206 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 3H), 3.71 (s, 3H), 5.51 (s, 1H), 6.66 (s, 1H), 6.81 (s, 1H), 6.92 (s, 1H), 7.59 (s, 1H), 7.72 (s, 1H), 7.87 (s, 1H), 8.22 (s, 1H), 11.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.8, 55.5, 55.6, 111.7, 111.9, 118.6, 126.9, 127.9, 128.3, 130.2, 130.8, 131.9, 132.6, 135.2, 148.1, 148.7, 153.0, 172.8; IR (KBr)ν_{max} 1124, 1155, 1223, 1271, 1364, 1416, 1437, 1463, 1512, 1559, 1578, 1596, 1630, 2853, 2935, 2997, 3220 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{16}NO_4S_2$ 386.0515 (M + H$^+$); Found 386.0514.

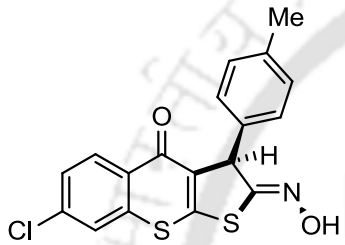
(Z)-2-(hydroxyimino)-3-(3,4,5-trimethoxyphenyl)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9j): Light brown solid (311 mg, 75% yield), Mp 227-228 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.62 (s, 3H), 3.69 (s, 6H), 5.53 (s, 1H), 6.52 (s, 2H), 7.61 (s, 1H), 7.74 (s, 1H), 7.91 (s, 1H), 8.24-8.25 (m, 1H), 11.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.4, 55.9, 59.9, 104.6, 126.9, 127.9, 128.3, 130.2, 130.4, 131.9, 135.2, 135.8, 136.8, 149.1, 152.9, 172.9; IR (KBr)ν_{max} 1107, 1125,1168, 1246, 1333, 1360, 1422, 1460, 1509, 1531, 1593, 1621, 2838, 2938, 2973, 3002, 3264 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{18}NO_5S_2$ 416.0621 (M + H$^+$); Found 416.0620.

(Z)-7-chloro-2-(hydroxyimino)-3-phenyl-2H-thieno[2,3-b]thiochromen-4(3H)-one (9k):



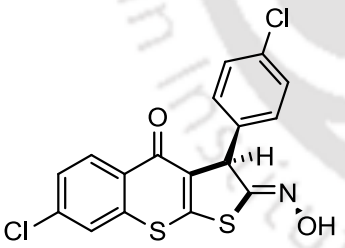
Light brown solid (302 mg, 84% yield), Mp 229-230 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.57 (s, 1H), 7.23-7.25 (m, 3H), 7.28-7.31 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 8.17-8.20 (m, 2H), 12.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.6, 125.2, 127.1, 127.2, 128.3, 128.4, 129.1, 130.1, 130.9, 136.8, 137.7, 139.6, 149.6, 153.0, 172.8; IR (KBr)ν_{max} 1104, 1122, 1357, 1394, 1432, 1451, 1507, 1578, 1596, 1634, 2853, 2927, 3436 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}ClNO_2S_2$ 359.9914 (M + H$^+$); Found 359.9913.

(Z)-7-chloro-2-(hydroxyimino)-3-(p-tolyl)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9l):



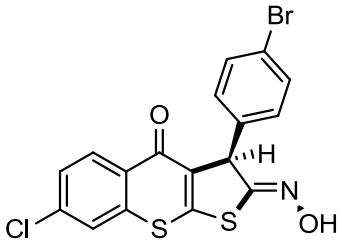
Light brown solid (321 mg, 86% yield), Mp 224-225 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.29 (s, 3H), 5.51 (s, 1H), 7.12 (d, *J* = 6.0 Hz, 2H), 7.21 (d, *J* = 12.0 Hz, 2H), 7.44 (d, *J* = 6.0 Hz, 1H), 7.57 (s, 1H), 8.33 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.8, 54.2, 125.2, 126.9, 128.2, 129.1, 130.1, 130.9, 136.5, 136.7, 136.8, 137.7, 149.4, 153.1, 172.7; IR (KBr)ν_{max} 1103, 1119, 1166, 1354, 1391, 1418,1512, 1579, 1598, 1633, 2814, 2919, 3086, 3189 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}ClNO_2S_2$ 374.0071 (M + H$^+$); Found 374.0060.

(Z)-7-chloro-3-(4-chlorophenyl)-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9m):



Light brown solid (346 mg, 88% yield), Mp 200-201 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.52 (s, 1H), 7.27-7.30 (m, 4H), 7.47 (d, *J* = 12.0 Hz, 1H), 7.58 (s, 1H), 8.33 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 53.7, 125.1, 128.2, 128.3, 128.5, 128.8, 129.9, 130.2, 132.6, 136.6, 137.7, 137.9, 149.8, 152.2, 172.6; IR (KBr)ν_{max} 1107, 1120, 1353, 1392, 1410, 1490, 1510, 1579, 1595, 1633, 2822, 3049, 3092, 3187, 3433 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}Cl_2NO_2S_2$ 393.9525 (M + H$^+$); Found 393.9538.

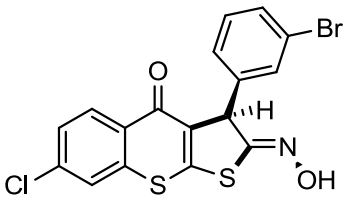
(Z)-3-(4-bromophenyl)-7-chloro-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9n):



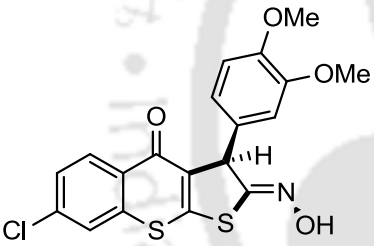
Light brown solid (377 mg, 86% yield), Mp 198-199 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.59 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 8.15-8.18 (m, 2H), 12.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-

d_6): δ 53.5, 120.4, 126.3, 128.7, 128.8, 129.6, 129.8, 130.3, 131.5, 137.1, 139.4, 149.7, 152.4, 172.1; IR (KBr)ν_{max} 1106, 1167, 1354, 1385, 1408, 1487, 1510,1579, 1596,1634, 3438 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}BrClNO_2S_2$ 437.9020 ($M + H^+$); Found 437.9004.

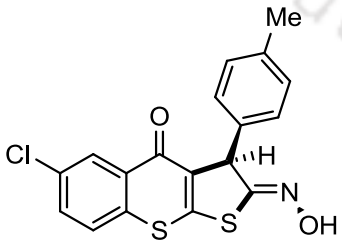
(Z)-3-(3-bromophenyl)-7-chloro-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9o): Light brown solid (355 mg, 81% yield), Mp 206-207 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.65 (s, 1H), 7.22-7.26 (m, 3H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 12.08 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 54.0, 122.2, 125.2, 125.9, 128.3, 128.9, 130.0, 130.1, 130.2, 136.7, 137.8, 141.7, 150.2, 152.2, 172.7; IR (KBr)ν_{max} 1107, 1121, 1356, 1384, 1410, 1426, 1510, 1577, 1594, 1633, 2853, 2927, 2961, 3437 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}BrClNO_2S_2$ 437.9020 ($M + H^+$); Found 437.9026.

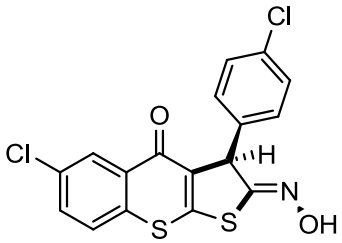


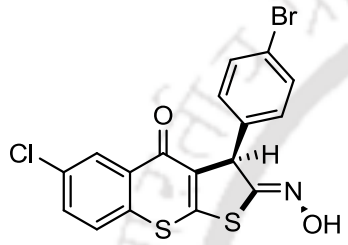
(Z)-7-chloro-3-(3,4-dimethoxyphenyl)-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9p): Light brown solid (327 mg 78% yield), Mp 213-214 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 3H), 3.71 (s, 3H), 5.50 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.90 (s, 1H), 7.64 (d, *J* = 12.0 Hz, 1H), 8.18-8.19 (m, 2H), 11.97 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.7, 55.5, 55.6, 111.6, 111.9, 118.6, 126.3, 128.6, 128.9, 129.9, 130.9, 132.4, 136.9, 137.0, 148.0, 148.6, 149.0, 152.9, 172.1; IR (KBr)ν_{max} 1141, 1168, 1234, 1250, 1272, 1345, 1400, 1423, 1461, 1517, 1560, 1581, 1610, 1517, 2778, 2833, 2932, 2996, 3359 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{15}ClNO_4S_2$ 420.0126 ($M + H^+$); Found 420.0129.

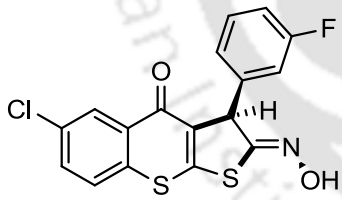


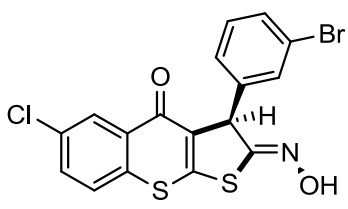
(Z)-6-chloro-2-(hydroxyimino)-3-(p-tolyl)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9q): Light brown solid (306 mg, 82% yield), Mp 228-229 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 5.50 (s, 1H), 7.09 (s, 4H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.08 (s, 1H), 11.99 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.9, 54.3, 127.1, 127.4, 128.3, 129.1, 130.9, 131.5, 132.0, 133.7, 134.1, 136.5, 136.8, 150.1, 153.2, 172.4; IR (KBr)ν_{max} 1124, 1219, 1348, 1410, 1453, 1500, 1579, 1594, 1633, 2852, 2918, 3066, 3086, 3438 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}ClNO_2S_2$ 374.0071 ($M + H^+$); Found 374.0070.



(Z)-6-chloro-3-(4-chlorophenyl)-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9r): 
Light brown solid (331 mg, 84% yield), Mp 208-209 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.53 (s, 1H), 7.27-7.30 (m, 2H), 7.48-7.54 (m, 2H), 7.57-7.58 (m, 1H), 7.72 (s, 1H), 8.38 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 53.9, 127.4, 128.1, 128.5, 128.7, 130.2, 131.6, 131.8, 132.8, 133.6, 134.2, 138.1, 150.6, 152.5, 172.4; IR (KBr)ν_{max} 1116, 1163, 1217, 1247, 1345, 1405, 1455, 1489, 1509, 1582, 1599, 1627, 2844, 3031, 3269 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}Cl_2NO_2S_2$ 393.9525 (M + H$^+$); Found 393.9529.

(Z)-3-(4-bromophenyl)-6-chloro-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9s): 
Light brown solid (350 mg, 80% yield), Mp 208-209 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.62 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.82-7.84 (m, 1H), 8.02 (d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 12.07 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 53.8, 120.8, 127.4, 127.9, 128.9, 129.6, 129.9, 130.9, 131.3, 131.5, 131.6, 133.4, 134.0, 138.5, 150.6, 152.2, 172.2; IR (KBr)ν_{max} 1126, 1162, 1216, 1347, 1412, 1438, 1487, 1502, 1580, 1596, 1634, 2851, 3436 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}BrClNO_2S_2$ 437.9020 (M + H$^+$); Found 437.9024.

(Z)-6-chloro-3-(3-fluorophenyl)-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9t): 
Light brown solid (324 mg, 86% yield), Mp 210-211 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.64 (s, 1H), 7.06-7.13 (m, 3H), 7.31-7.36 (m, 1H), 7.79-7.82 (m, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 4.0 Hz, 1H), 12.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.6, 113.9, 114.2, 114.3, 114.5, 127.0, 129.1, 131.9, 133.4, 142.5, 142.6, 150.5, 152.3, 160.9, 163.4, 171.7; IR (KBr)ν_{max} 1113, 1142, 1228, 1244, 1347, 1406, 1449, 1487, 1511, 1580, 1597, 1613, 1626, 3436 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}ClFNO_2S_2$ 377.9821 (M + H$^+$); Found 377.9822.

(Z)-3-(3-bromophenyl)-6-chloro-2-(hydroxyimino)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9u): 
Light brown solid (350 mg, 80% yield), Mp 218-219 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.63 (s, 1H), 7.20-7.27 (m, 2H), 7.44 (d, J = 4.0 Hz, 1H), 7.49 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 12.11 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.6, 121.7, 126.2, 127.0, 129.1, 129.8, 130.2, 130.3,

130.8, 131.5, 131.9, 133.4, 134.1, 142.5, 150.6, 152.3, 171.7; IR (KBr)ν_{max} 1124, 1160, 1348, 1408, 1505, 1579, 1595, 1633, 2850, 2918, 3069 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}BrClNO_2S_2$ 437.9020 ($M + H^+$); Found 437.9015.

(Z)-6-chloro-2-(hydroxyimino)-3-(3,4,5-trimethoxyphenyl)-2H-thieno[2,3-*b*]thiochromen-4(3H)-one (9v): Light brown solid (341 mg, 76% yield), Mp 222-223 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.61 (s, 3H), 3.68 (s, 6H), 5.53 (s, 1H), 6.51 (s, 2H), 7.80-7.83 (m, 1H), 8.00 (d, *J* = 12.0 Hz, 1H), 8.16 (s, 1H), 12.04 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 54.9, 55.9, 60.5, 104.4, 127.5, 128.4, 130.7, 131.7, 132.0, 133.7, 134.4, 135.2, 137.1, 150.4, 153.1, 172.6; IR (KBr)ν_{max} 1104, 1133, 1246, 1259, 1334, 1404, 1455, 1510, 1527, 1582, 1593, 1625, 2839, 2937, 3002, 3053, 3079, 3278, 3436 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{17}ClNO_5S_2$ 450.0231 ($M + H^+$); Found 450.0227.

(S,Z)-3-butyl-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9w): Light brown solid (207 mg, 68% yield), Mp 186-187˚C, ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.75-0.80 (m, 3H), 1.22-1.24 (m, 4H), 1.91-1.93 (m, 1H), 2.04-2.07 (m, 1H), 4.41-4.43 (m, 1H), 7.61-7.65 (m, 1H), 7.73-7.75 (m, 1H), 7.86-7.89 (m, 1H), 8.34-8.36 (m, 1H), 11.97 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 22.1, 26.4, 31.8, 49.1, 126.8, 128.1, 128.3, 130.0, 130.4, 131.9, 135.2, 148.2, 153.2, 173.4; IR (KBr)ν_{max} 1116, 1142, 1225, 1249, 1265, 1316, 1374, 1420, 1437, 1513, 1557, 1577, 1588, 1630, 2847, 2865, 2886, 2924, 2949, 3054, 3194, 3426 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{16}NO_2S_2$ 306.0617 ($M + H^+$); Found 306.0616

2-amino-3-phenyl-4H-thieno[2,3-*b*]thiochromen-4-one (12a): Yellow solid (133 mg, 86% yield), Mp 200-201 ˚C ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.42-7.49 (m, 3H), 7.52-7.56 (m, 2H), 8.53 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, CDCl3): δ 114.3, 116.1, 120.4, 125.9, 126.7, 127.6, 128.6, 129.8, 130.4, 130.9, 131.1, 135.0, 135.9, 144.8, 174.9; IR (KBr)ν_{max} 1168, 1258, 1319, 1384, 1417, 1629, 2856, 2923, 2959, 3051, 3355, 3437 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{12}NOS_2$ 310.0355 ($M + H^+$); Found 310.0349.

2-amino-3-(p-tolyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12b): Yellow solid (148 mg, 92% yield), Mp 214-215 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.88 (s, 2H), 7.25-7.27 (m, 4H), 7.44 (s, 1H), 7.56 (s, 2H), 8.53 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 120.4, 125.9, 126.7, 129.4, 129.8, 130.2, 130.8, 131.2, 131.9, 133.9, 135.9, 137.2, 144.6, 175.0; IR (KBr)ν_{max} 1178, 1261, 1316, 1376, 1437, 1460, 1509, 1555, 1588, 1626, 1730, 2853, 2923, 2954, 3023, 3057, 3361, 3439 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{14}NOS_2$ 324.0512 (M + H$^+$); Found 324.0515.

2-amino-3-(4-chlorophenyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12c): Yellow solid (151 mg, 88% yield), Mp 167-168˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.90 (s, 2H), 7.29 (d, *J* = 12.0 Hz, 2H), 7.43-7.46 (m, 3H), 7.54-7.58 (m, 2H), 8.51 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.8, 125.9, 126.9, 128.7, 128.8, 129.7, 130.0, 131.0, 131.7, 131.8, 133.4, 133.5, 134.2, 135.9, 145.1, 175.0; IR (KBr)ν_{max} 1165, 1266, 1321, 1384, 1405, 1445, 1462, 1544, 1582, 1621, 2853, 2923, 2963, 3015, 3048, 3365, 3454 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}ClNOS_2$ 343.9965 (M + H$^+$); Found 343.9977.

2-amino-3-(4-bromophenyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12d): Yellow solid (174 mg, 90% yield), Mp 154-155 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 2H), 7.23 (d, *J* = 12.0 Hz, 2H), 7.43-7.47 (m, 1H), 7.55-7.58 (m, 3H), 7.60 (s, 1H), 8.52 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.8, 121.8, 125.9, 126.9, 129.7, 131.0, 131.7, 131.8, 132.1, 133.9, 134.2, 135.9, 145.1, 175.0; IR (KBr)ν_{max} 1161, 1256, 1314, 1387, 1409, 1435, 1468, 1538, 1587, 1628, 2855, 2933, 2973, 3019, 3058, 3365, 3449 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}BrNOS_2$ 387.9460 (M + H$^+$); Found 387.9458.

2-amino-3-(4-fluorophenyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12e): Yellow solid (150 mg, 92% yield), Mp 160-161 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (b s, 2H), 7.16 (t, *J* = 8.0 Hz, 2H), 7.31-7.34 (m, 2H), 7.43-7.47 (m, 1H), 7.53-7.57 (m, 2H), 8.52 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 115.5, 115.7, 119.2, 125.9, 126.9, 129.7, 130.9, 131.1, 131.8, 132.0, 132.1, 134.1, 135.9, 144.9, 161.5, 163.2, 175.1; IR (KBr)ν_{max} 1157, 1225, 1338, 1384, 1437, 1504, 1589, 1626, 2853, 2924, 2955, 3017, 3059, 3352 3439 cm^{-1}; HRMS (ESI) Calcd For$C_{17}H_{11}FNOS_2$ 328.0261 (M + H$^+$); Found 328.0259.

2-amino-3-(3-bromophenyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12f): Yellow solid (163 mg, 84% yield), Mp 222-223 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.93 (s, 2H), 7.29-7.30 (m, 1H), 7.34 (t, *J* = 6.0 Hz, 1H), 7.44-7.47 (m, 1H), 7.51-7.52 (m, 2H), 7.54-7.58 (m, 2H), 8.52 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 118.5, 122.5, 125.9, 126.9, 129.4, 129.7, 130.0, 130.6, 130.9, 131.0, 131.7, 133.1, 134.0, 135.9, 137.2, 145.4, 174.9; IR (KBr)ν_{max} 1203, 1260, 1402, 1447, 1460, 1472, 1541, 1556, 1580, 1614, 2853, 2924, 2961, 3338, 3414 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}BrNOS_2$ 387.9460 (M + H$^+$); Found 387.9452.

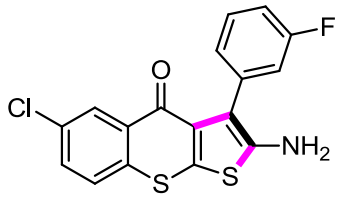
2-amino-6-chloro-3-(4-chlorophenyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12g): Yellow solid (170 mg, 90% yield), Mp 207-208 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.92 (s, 2H), 7.28 (d, *J* = 12.0 Hz, 2H), 7.39-7.41 (m, 1H), 7.43 (d, *J* = 6.0 Hz, 2H), 7.57 (s, 1H), 8.43 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 118.7, 125.2, 127.6, 128.9, 129.4, 131.2, 131.8, 133.2, 133.7, 137.3, 137.7, 145.5, 174.3; IR (KBr)ν_{max} 1188, 1261, 1314, 1384, 1408, 1489, 1454, 1581, 1621, 2853, 2924, 2963, 3298, 3390 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}Cl_2NOS_2$ 377.9576 (M + H$^+$); Found 377.9576.

2-amino-7-chloro-3-(p-tolyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12h): Yellow solid (162 mg, 91% yield), Mp 171-172 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.92 (b s, 2H), 7.22-7.23 (m, 2H), 7.28-7.29 (m, 2H), 7.50 (s, 2H), 8.51 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.6, 120.3, 127.3, 129.4, 130.2, 131.2, 131.6, 131.8, 132.4, 133.1, 133.8, 134.1, 137.4, 145.1, 173.8; IR (KBr)ν_{max}1184, 1261, 1289, 1312, 1454, 1508, 1540, 1580, 1628, 2852, 2923, 2963, 3021, 3278, 3383 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}ClNOS_2$ 358.0122(M + H$^+$); Found 358.0125.

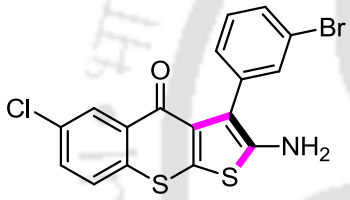
2-amino-6-chloro-3-(4-chlorophenyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12i): Yellow solid (170 mg, 90% yield), Mp 236-237 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27(s, 1H), 7.29 (s, 1H), 7.43 (s, 1H), 7.45 (s, 1H), 7.52 (s, 2H), 8.50 (t, *J* = 4.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 114.3, 118.6, 127.3, 128.9, 129.3, 131.4, 131.5,

131.8, 132.2, 133.1, 133.3, 133.7, 134.0, 139.5, 145.5, 173.8; IR (KBr)νmax 1261, 1314, 1384, 1408, 1454, 1489, 1581, 1621, 1728, 2853, 2924, 2963, 3015, 3298, 3390 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}Cl_2NOS_2$ 377.9576 ($M + H^+$); Found 377.9564.

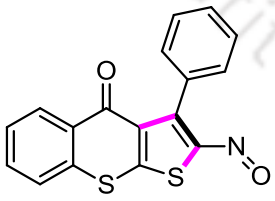
2-amino-6-chloro-3-(3-fluorophenyl)-4H-thieno[2,3-*b*]thiochromen-4-one (12j): Yellow solid (159 mg, 88% yield), Mp 194-195 ˚C, ^1H NMR (600 MHz, $CDCl_3$):δ 3.97 (s, 2H), 7.04-7.07 (m, 1H), 7.09-7.12 (m, 2H), 7.41-7.44 (m, 1H), 7.51 (s, 2H), 8.49 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 114.6, 114.7, 117.3, 117.5, 118.5, 126.1, 126.2, 127.3, 129.3, 129.9, 130.0, 131.3, 131.6, 132.2, 133.3, 133.9, 134.0, 136.8, 136.9, 145.7, 162.1, 162.7, 173.7; IR (KBr)ν_{max} 1182, 1197, 1242, 1262, 1324, 1376, 1451, 1485, 1533, 1578, 1608, 2852, 2923, 2963, 3090, 3189, 3284, 3395 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}ClFNOS_2$ 361.9871 ($M + H^+$); Found 361.9870.



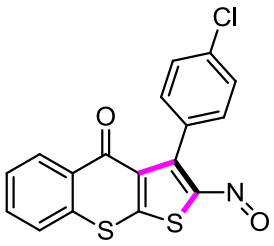
2-amino-3-(3-bromophenyl)-6-chloro-4H-thieno[2,3-*b*]thiochromen-4-one (12k): Yellow solid (173 mg, 82% yield), Mp 208-209 ˚C, ^1H NMR (600 MHz, $CDCl_3$): δ 3.97 (s, 2H), 7.27-7.28 (m, 1H), 7.34 (t, *J* = 6.0 Hz, 1H), 7.50-7.53 (m, 4H), 8.50 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 118.1, 122.5, 127.3, 129.3, 129.4, 130.0, 130.7, 131.3, 132.1, 133.1, 133.3, 134.0, 136.8, 145.9, 173.6; IR (KBr)ν_{max} 1117, 1336, 1403, 1454, 1488, 1505, 1582, 1606, 1620, 2855, 2923, 3085, 3342, 3390 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}BrNOS_2$ 421.9070($M + H^+$); Found 421.9049.



2-nitroso-3-phenyl-4H-thieno[2,3-*b*]thiochromen-4-one (13a): Yellow solid (126 mg, 78% yield), Mp 181-182˚C, ^1H NMR (600 MHz, $CDCl_3$): δ 7.54-7.60 (m, 5H), 7.66-7.70 (m, 1H), 7.82-7.85 (m, 2H), 8.52-8.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.0, 127.5, 128.4, 129.8, 129.9, 130.1, 131.2, 132.0, 132.1, 132.6, 134.1, 153.5, 158.6, 168.1, 176.3; IR (KBr)ν_{max} 1116, 1146, 1203, 1249, 1285, 1271, 1329, 1399, 1435, 1482, 1585, 1646, 2854, 2928, 3054, 3089, cm^{-1}; HRMS (APCI) Calcd For $C_{17}H_{10}NO_2S_2$ 324.0148 ($M + H^+$); Found 324.0148.

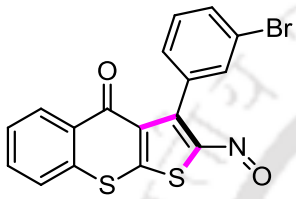


3-(4-chlorophenyl)-2-nitroso-4H-thieno[2,3-*b*]thiochromen-4-one (13b): Yellow solid



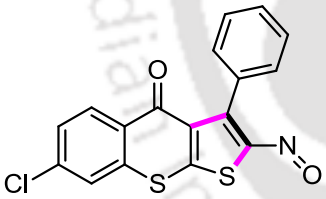
(146 mg, 82% yield), Mp 166-167 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.55 (m, 2H), 7.58-7.62 (m, 2H), 7.68-7.72 (m, 1H), 7.76-7.79 (m, 2H), 8.52-8.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.3, 128.1, 128.7, 130.2, 130.7, 131.9, 132.8, 132.9, 134.3, 136.4, 152.3, 158.9, 168.1, 176.5; IR (KBr)ν_{max} 1259, 1346, 1462, 1491, 1519, 1589, 1629, 2853, 2923, 2955, 3033, 3091 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_9ClNO_2S_2$ 357.9758 (M + H$^+$); Found 357.9759.

3-(3-bromophenyl)-2-nitroso-4H-thieno[2,3-*b*]thiochromen-4-one (13c): Yellow solid



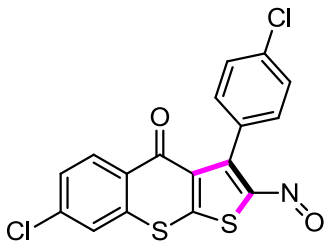
(152 mg, 76% yield), Mp 193-194 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, *J* = 8.0 Hz, 1H), 7.57-7.61 (m, 2H), 7.67-7.76 (m, 3H), 7.96 (s, 1H), 8.53-8.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.8, 126.3, 129.2, 129.9, 130.2, 132.9, 134.1, 134.3, 139.6, 151.6, 158.5, 168.1, 176.3; IR (KBr)ν_{max} 1260, 1345, 1437, 1466, 1521, 1589, 1627, 2852, 2923, 3043 3087 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_9BrNO_2S_2$ 401.9253 (M + H$^+$); Found 401.9266.

7-chloro-2-nitroso-3-phenyl-4H-thieno[2,3-*b*]thiochromen-4-one (13d): Yellow solid (143



mg, 80% yield), Mp 194-195 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.59 (m, 5H), 7.82-7.83 (m, 2H), 8.46 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.6, 127.8, 128.7, 129.2, 130.1, 131.5, 131.7, 132.1, 132.3, 135.7, 139.7, 153.4, 157.9, 168.3, 175.6; IR (KBr)ν_{max} 1107, 1204. 1266, 1325, 1384, 1409, 1604, 2852, 2923, 2963, 3036 3089 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_9ClNO_2S_2$ 357.9758 (M + H$^+$); Found 357.9759.

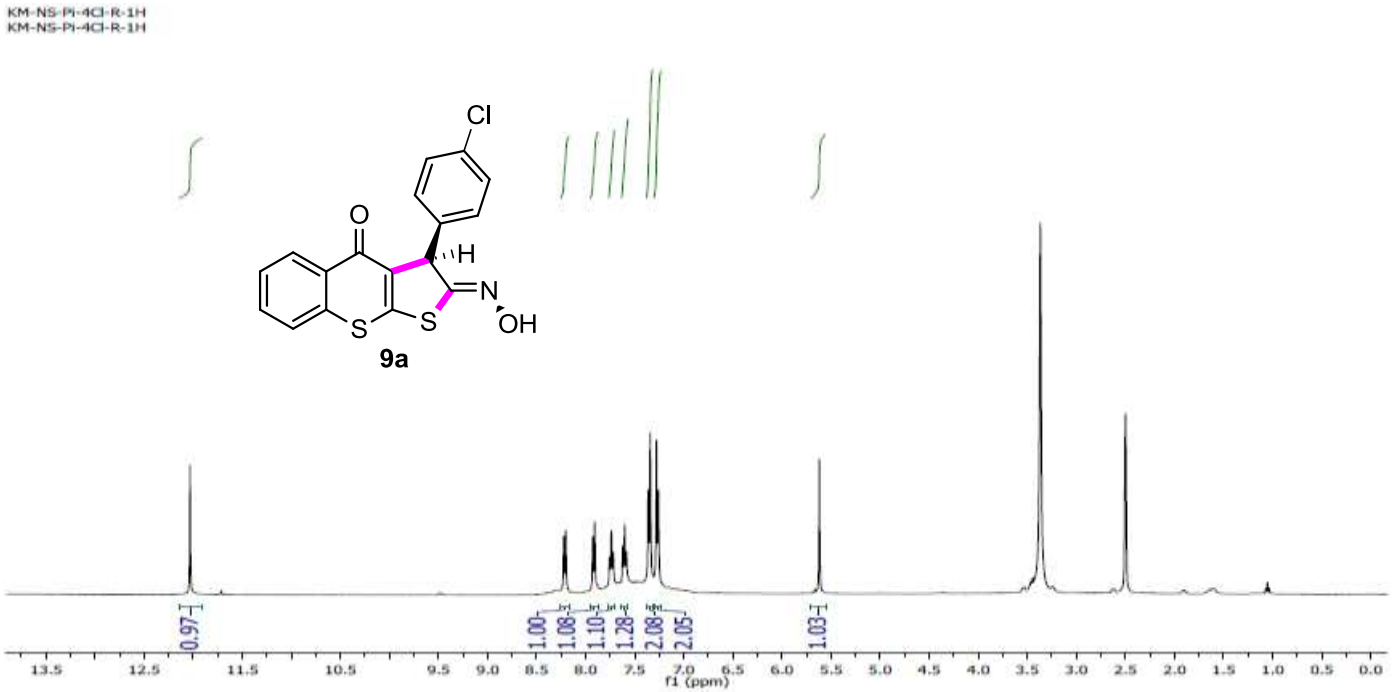
7-chloro-3-(4-chlorophenyl)-2-nitroso-4H-thieno[2,3-*b*]thiochromen-4-one (13e): Yellow



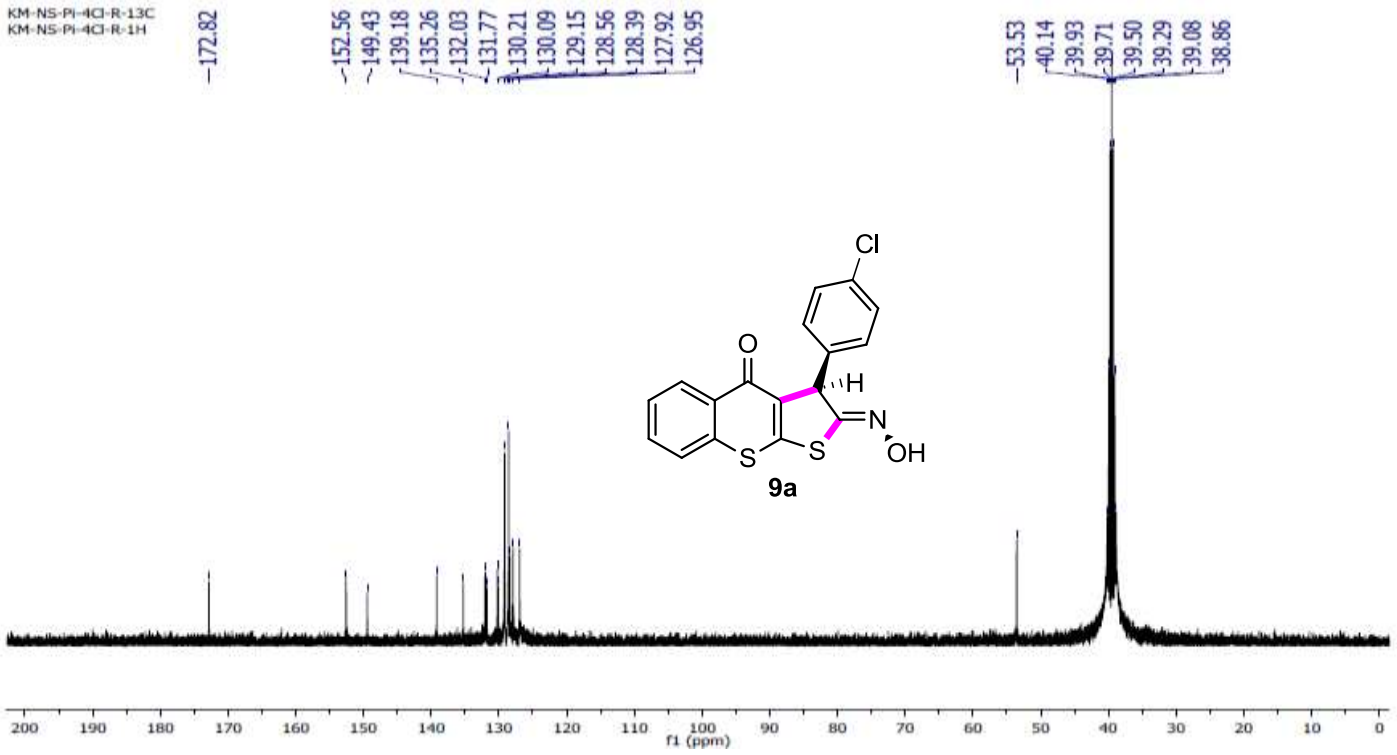
solid (164 mg, 84% yield), Mp 188-189 ˚C, ^{1}H NMR (400 MHz, CDCl3): δ 7.52-7.55 (m, 3H), 7.59 (d, *J* = 4.0 Hz, 1H), 7.76-7.78 (m, 2H), 8.45 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 125.6, 128.1, 128.6, 129.3, 130.5, 131.6, 132.1, 132.9, 135.7, 136.6, 139.8, 151.9, 157.9, 168.2, 175.7; IR (KBr)ν_{max} 1262,1334, 1383, 1400, 1461,1489, 1522, 1555, 1584, 1634, 1679, 2851, 2922, 3081, 3112 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_8Cl_2NO_2S_2$ 391.9368 (M + H$^+$); Found 391.9364.

3-(3-bromophenyl)-7-chloro-2-nitroso-4H-thieno[2,3-b]thiochromen-4-one (13f): Yellow solid (168 mg, 77% yield), Mp 169-170 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.45 (m, 1H), 7.53-7.55 (m, 1H), 7.60 (s, 1H), 7.71-7.75 (m, 2H), 7.95-7.96 (m, 1H), 8.46 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 121.9, 125.7, 128.6, 129.2, 129.3, 129.9, 131.7, 132.2, 132.9, 134.1, 134.2, 135.7, 139.8, 151.4, 157.7, 168.3, 175.5; IR (KBr)ν_{max} 1102, 1261, 1336, 1383, 1462, 1522, 1583, 1633, 2850, 2921, 3073, 3115 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_8BrClNO_2S_2$ 435.8863 (M + H^+); Found 435.8840.

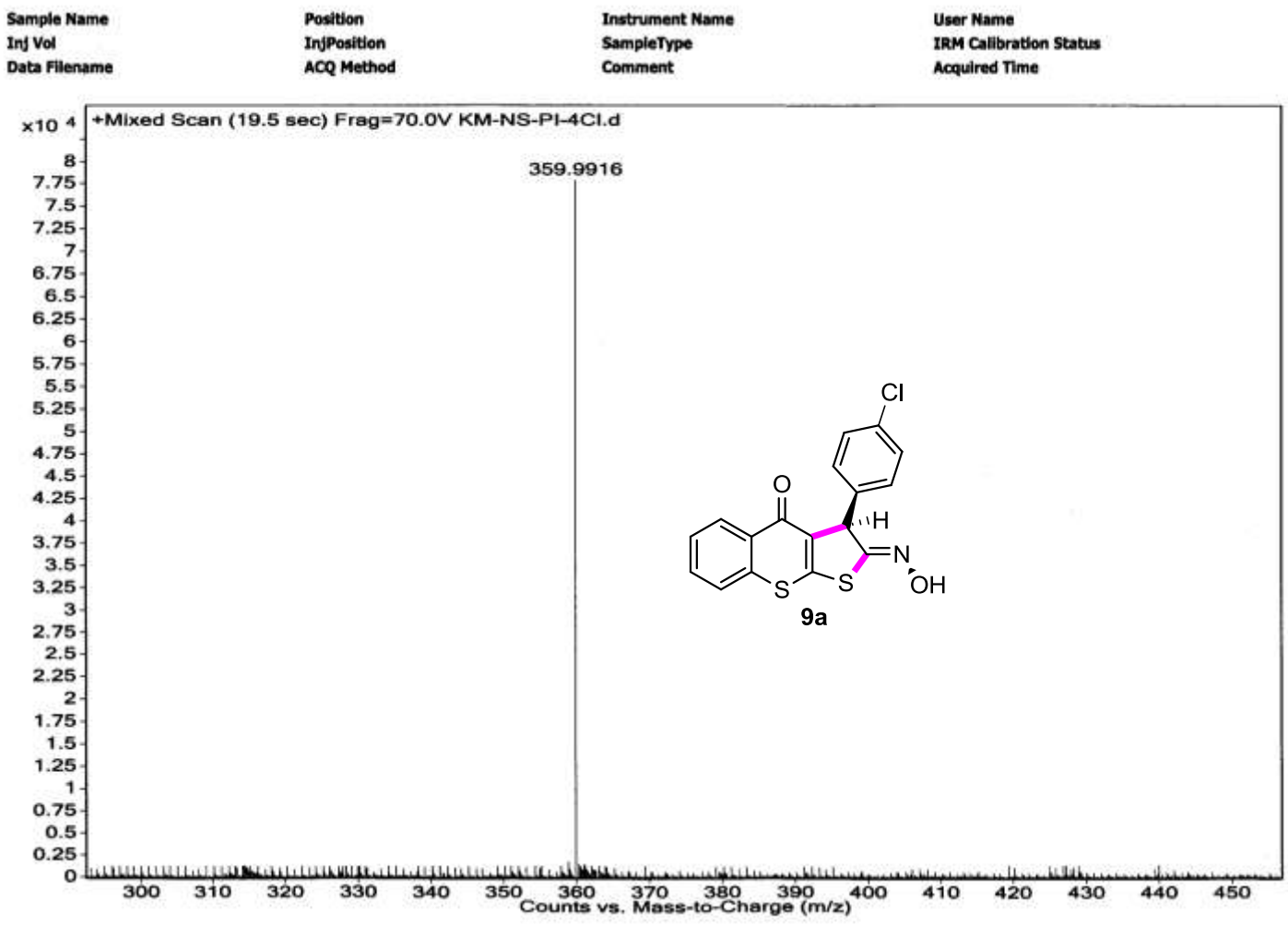
[1]HNMR: *(Z)-3-(4-chlorophenyl)-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (**9a**)*



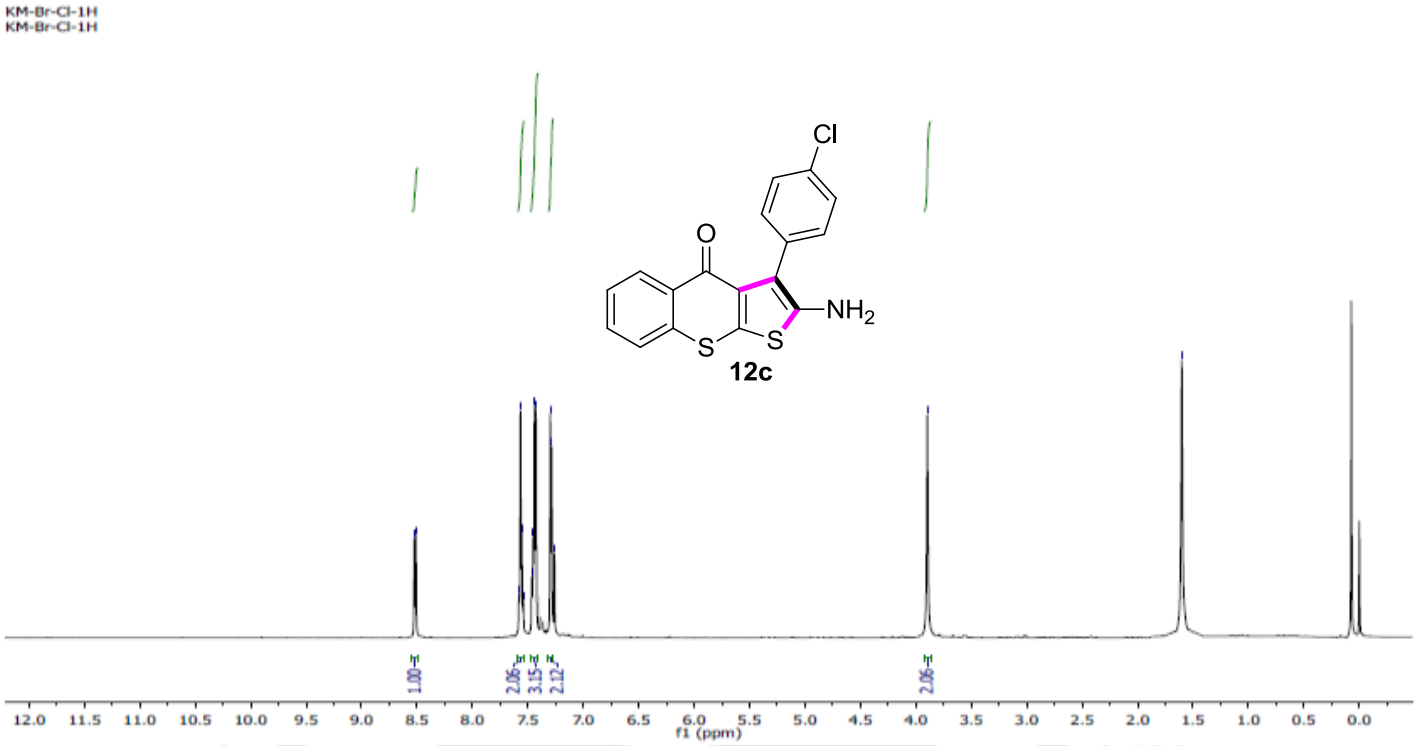
[13]CNMR: *(Z)-3-(4-chlorophenyl)-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (**9a**)*



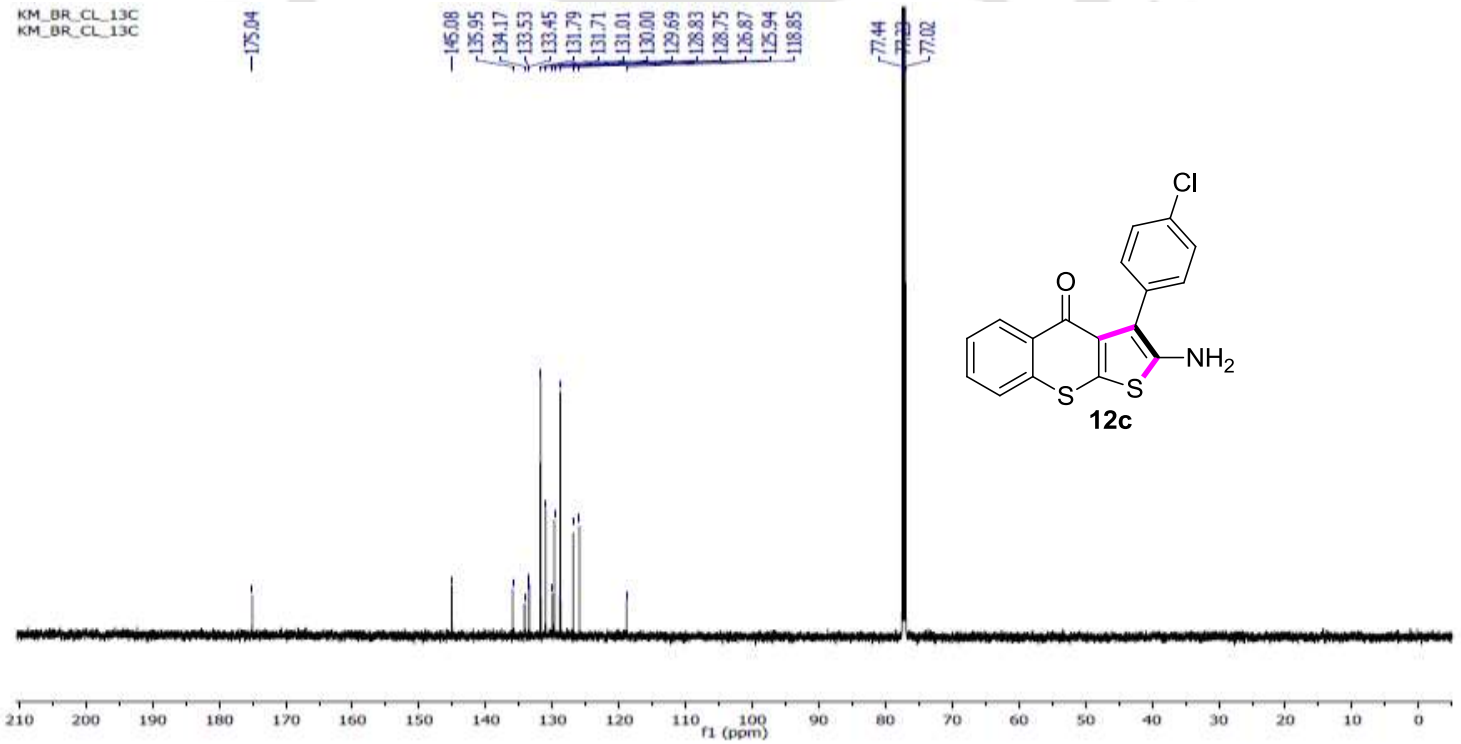
HRMS: *(Z)-3-(4-chlorophenyl)-2-(hydroxyimino)-2H-thieno[2,3-b]thiochromen-4(3H)-one (9a)*



[1]HNMR: *2-amino-3-(4-chlorophenyl)-4H-thieno[2,3-b]thiochromen-4-one (**12c**)*

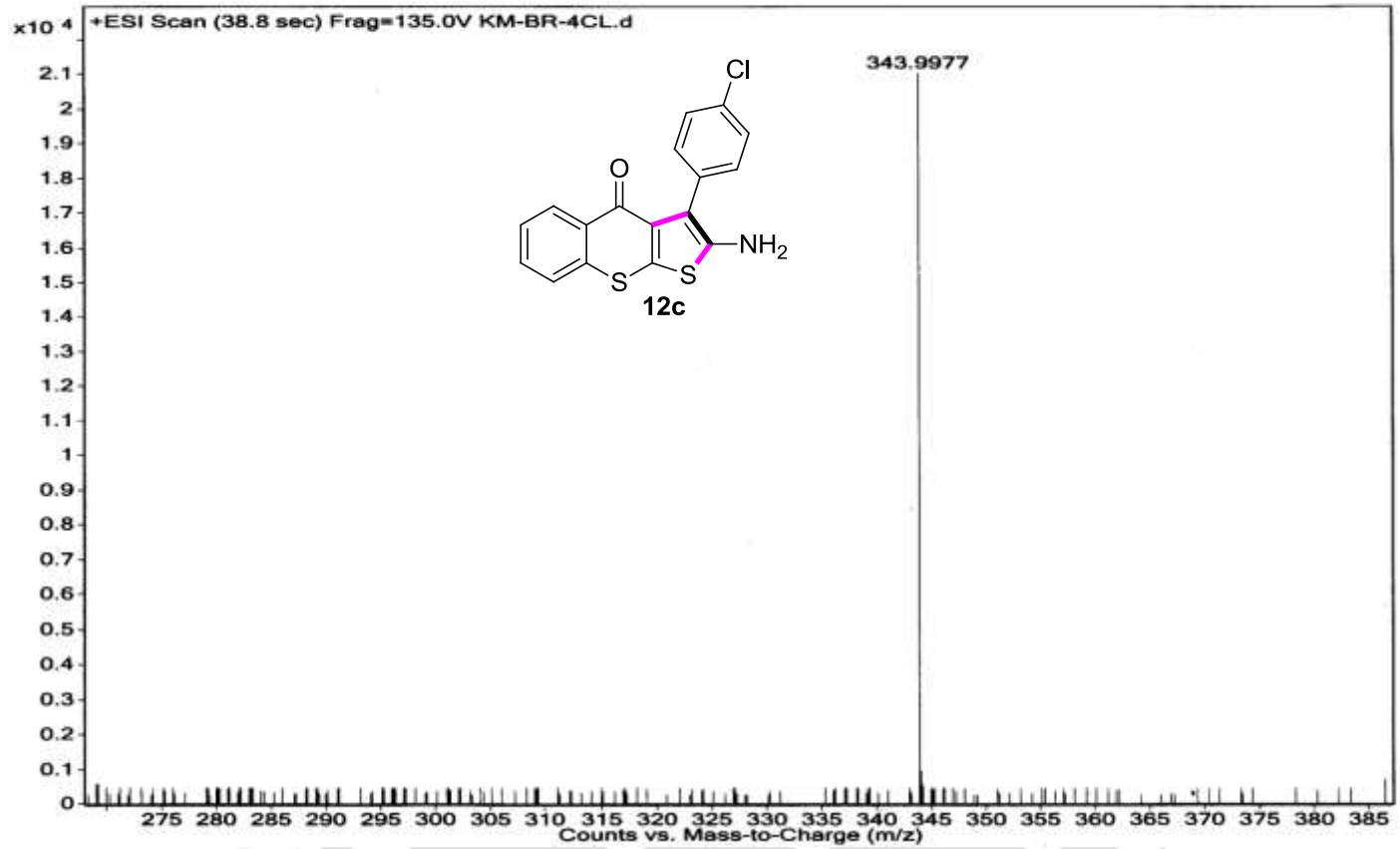


[13]CNMR: *2-amino-3-(4-chlorophenyl)-4H-thieno[2,3-b]thiochromen-4-one (**12c**)*

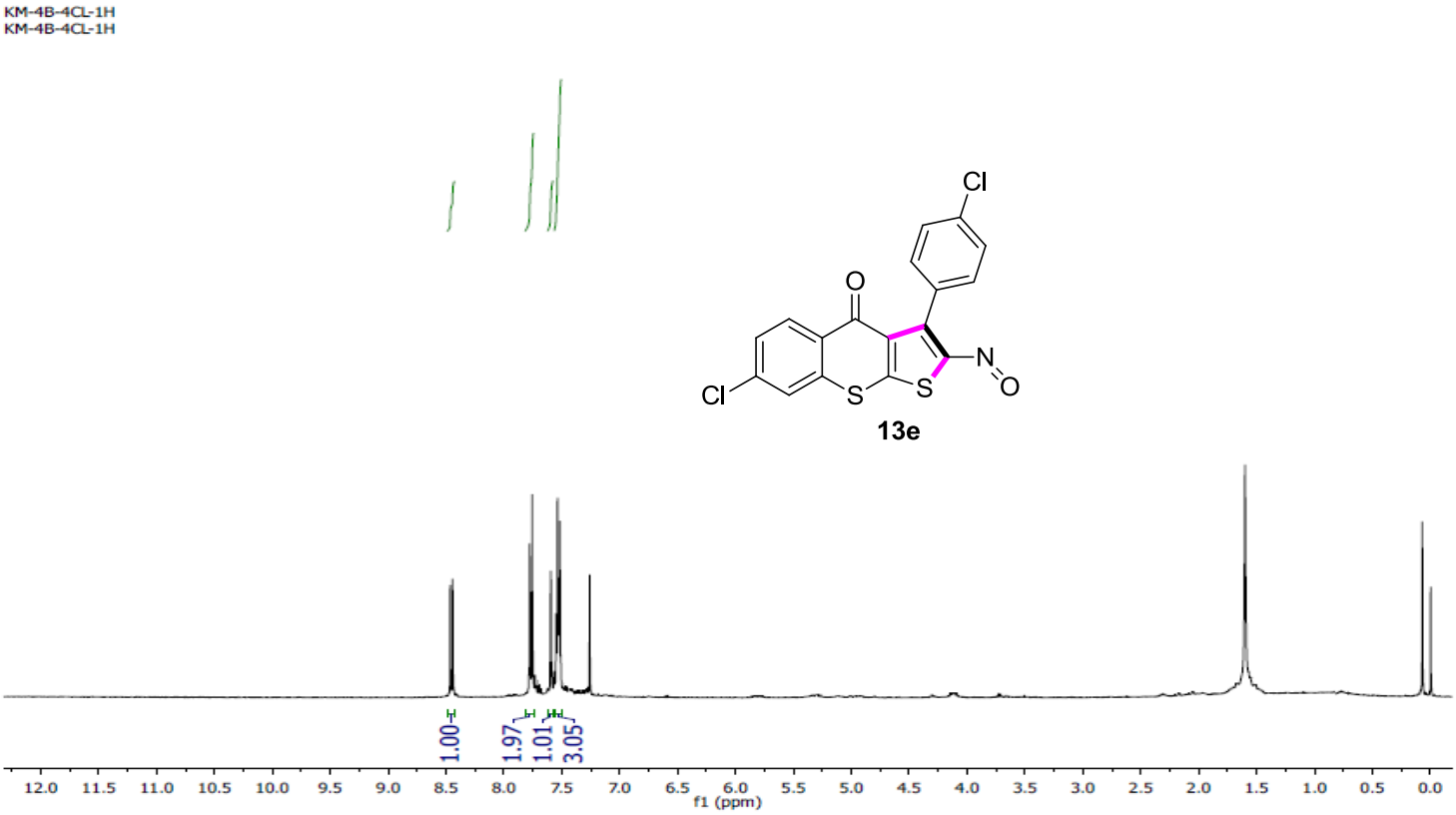


HRMS: *2-amino-3-(4-chlorophenyl)-4H-thieno[2,3-b]thiochromen-4-one (**12c**)*

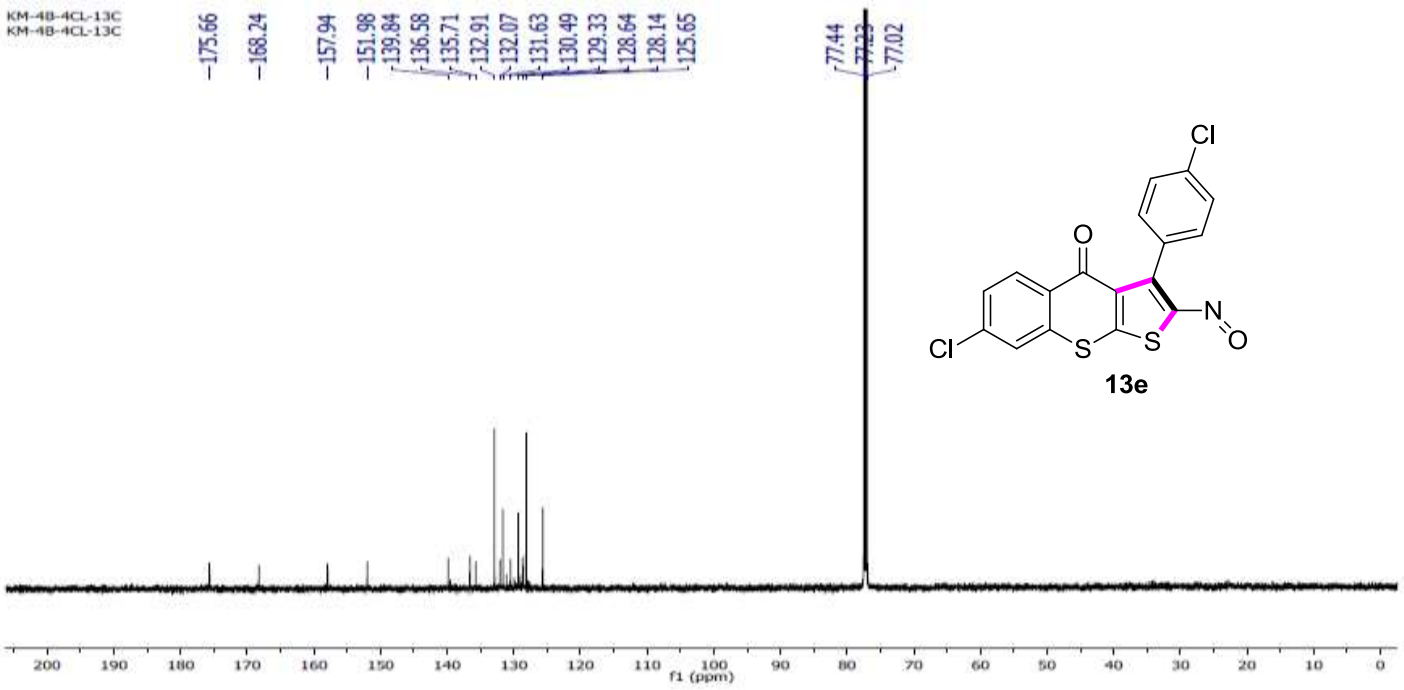
Sample Name	KM-BR-4CL	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	KM-BR-4CL.d	**ACQ Method**		**Comment**		**Acquired Time**	2/3/2016 11:25:30 AM



[1]HNMR: *7-chloro-3-(4-chlorophenyl)-2-nitroso-4H-thieno[2,3-b]thiochromen-4-one* ***(13e)***

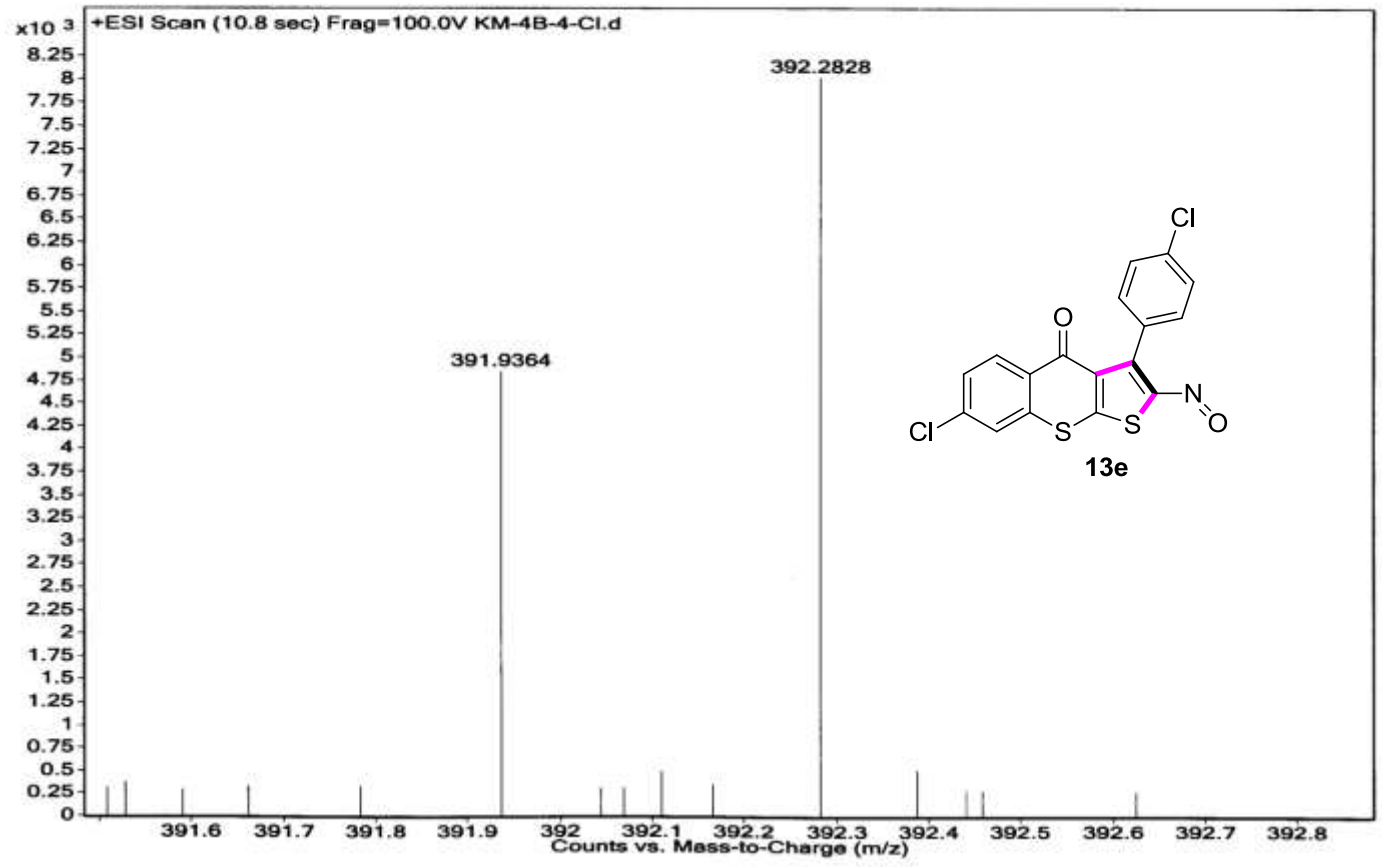


[13]CNMR: *7-chloro-3-(4-chlorophenyl)-2-nitroso-4H-thieno[2,3-b]thiochromen-4-one* ***(13e)***



HRMS: *7-chloro-3-(4-chlorophenyl)-2-nitroso-4H-thieno[2,3-b]thiochromen-4-one* ***(13e)***

Sample Name	KM-4B-4-Cl	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Some Ions Missed
Data Filename	KM-4B-4-Cl.d	**ACQ Method**		**Comment**		**Acquired Time**	2/16/2016 10:59:54 AM



Chapter IV

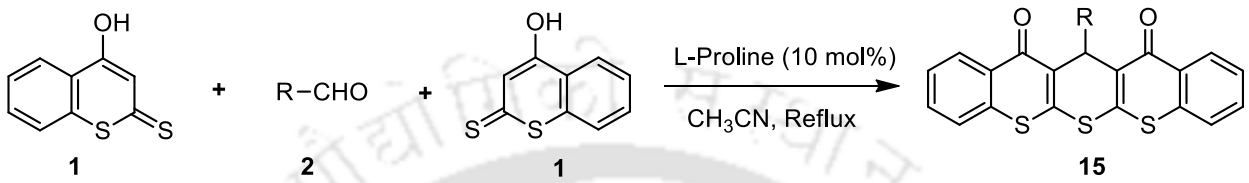
L-Proline catalyzed unusual product formation from the reaction of 4-hydroxydithiocoumarin and aldehydes through a pseudo three-component reaction

Result & Discussion

Experimental Section

Introduction

The importance and synthetic approaches of thiopyran has have already been described in Chapter I. In this chapter a favorable method was worked out for the synthesis of unreported thiopyrano[2,3-b:6,5-b′]bis(thiochromene)-12,14(13H)-dione derivatives through a one-pot, pseudo-three-component domino Knoevenagel–Michael reaction of 4-hydroxydithio-coumarin and aldehydes using L-proline as catalyst as shown in Scheme **47**.

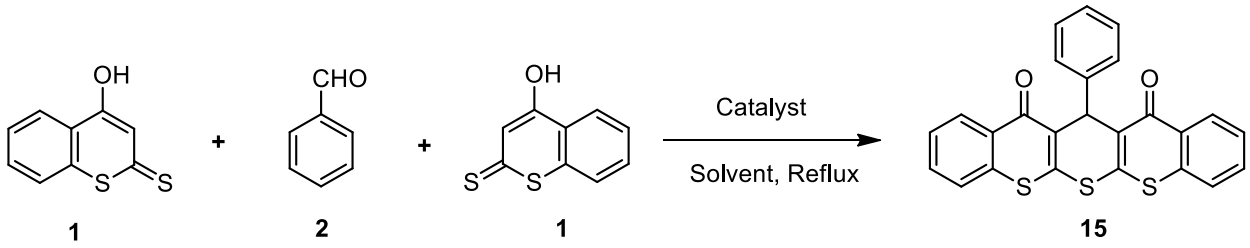


Scheme 47. L-Proline catalyzed synthesis of thiopyrano[2,3-b:6,5-b']bis(thiochromene)-12,14(13H)-dione derivatives

Recently, various research groups have exploited the utility of L-proline as catalyst for numerous organic transformations.[21] The synthesis of 4-hydroxydithiocoumarin has been described previously in Chapter 2. Initially, the condensation was performed with two equivalents of 4-hydroxydithiocoumarin and one equivalent of benzaldehyde as model substrates to optimize the reaction conditions for the synthesis of 13-phenyl-12*H*thiopyrano[2,3-*b*:6,5-*b*′]bis(thiochromene)-12,14(13*H*)-dione derivative **15a**. A control reaction in the absence of catalyst in 2 mL acetonitrile under refluxing conditions gave only 22% yield of product after 12 hours (Table 8, entry 1). The isolated product **15a** was characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopic and elemental analysis. Product **15a** showed a singlet at δ = 7.03 ppm in the ^{1}H NMR spectrum and a resonance at δ = 39.7 ppm in ^{13}CNMR spectrum, respectively, corresponding to Ph–CH (19-C and 19-H) and these two signals were correlated to each other through HMQC as shown in experimental section page no. **95**. In order to optimize the yield, the reaction was performed with a wide range of catalysts such as iodine, ammonium chloride, and PTSA under similar reaction conditions but these modifications led not only lower yields but also longer reaction time (Table 8, entries 2–4).

Interestingly, when the same set of conditions was applied out in the presence of 5, 10, and 15 mol% L-proline catalyst the desired product **15a** was obtained in good yields (Table 8, entries 5–7).

Table 8. Optimization of the reaction conditions[a,b]



1 2 1 15

Entry	Catalyst (mol %)	Solvent	Time/h	Yield (%)[b]
01	-	CH_3CN	12	22
02	I_2 (10)	CH_3CN	12	28
03	NH_4Cl (10)	CH_3CN	8	50
04	PTSA (10)	CH_3CN	12	22
05	L-Proline (5)	CH_3CN	0.75	75
06	**L-Proline (10)**	**CH_3CN**	**0.25**	**85**
07	L-Proline (15)	CH_3CN	0.75	82
08	L-Proline (10)	EtOH	1.5	65
09	L-Proline (10)	THF	12	48
10	L-Proline (10)	H_2O	12	56

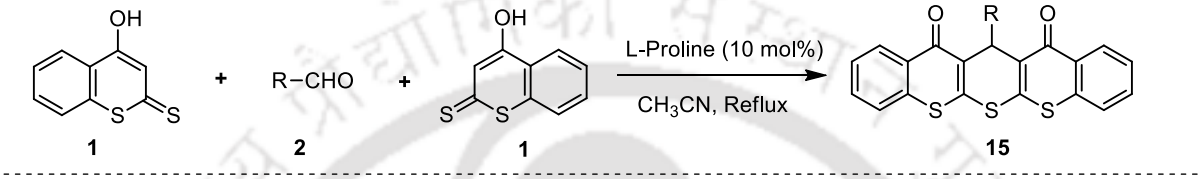
[a]All the reactions were carried out using (2 mmol) 4-hydroxydithiocoumarin (2 mmol) and aldehyde (1 mmol) .[b]Isolated yield.

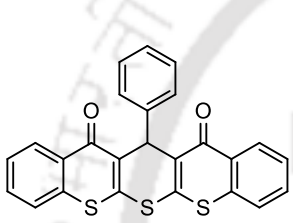
The reaction was also examined using different solvents such as EtOH, THF, and H_2O under similar reaction conditions (Table 8, entries 8–10) and it was observed that MeCN proved to be the most efficient solvent. Therefore, it was concluded that 10 mol% L-proline in 2 mL acetonitrile under refluxing conditions provided the optimum conditions in terms of yield and reaction time.

Thus, the scope of the reaction was expanded to various aromatic aldehydes and the results are summarized in table 8. The aldehydes having substituents on the aromatic ring such as 4-Me, 4-MeO, 2,4-di-MeO, and 4-NO_2 afforded the desired products **15b**–**e** in 78–88% yields. The reactions of various aromatic aldehydes were also examined with 4-hydroxydithiocoumarin under identical reaction conditions, and products **15f**–**i** were isolated in 78–82% yields. Furthermore, the reaction of 2-napthaldehyde with 4-

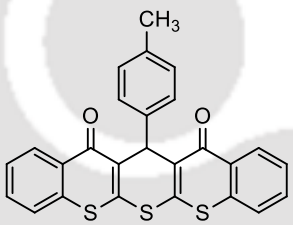
hydroxydithiocoumarin gave product **15j** in 75% yield. When the protocol was applied to different hetero aromatic aldehydes, such as 2-furfural, 2-thiophenylcarboxaldehyde and 3-formylindole, this led to formation of products **15k**–**m**. Finally, the reaction was assessed with a range of aliphatic aldehydes, and the expected products **15n**–**p** were isolated in good yields. All the products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis.

Table 9. Synthesis of Synthesis of Thiopyrano[2,3-*b*:6,5-*b*′]bis(thiochromene)-12,14(13*H*)-dione Derivatives Using as L-Proline a Catalyst[a,b]

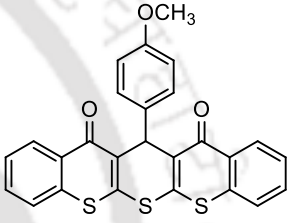




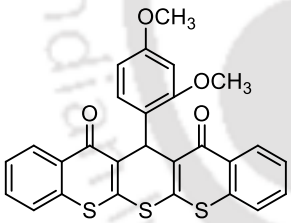
15a
85%, 15 min



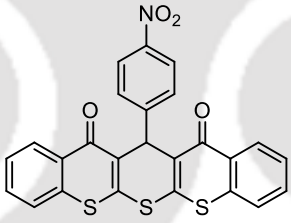
15b
88%, 15 min



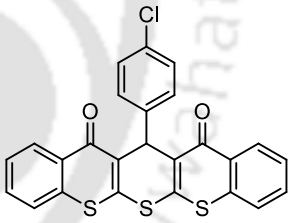
15c
82%, 30 min



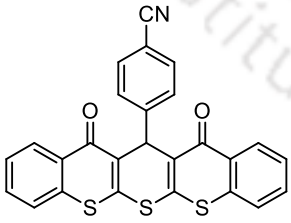
15d
76%, 40 min



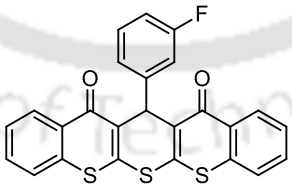
15e
78%, 30 min



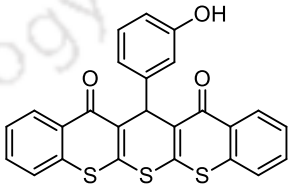
15f
82%, 25 min



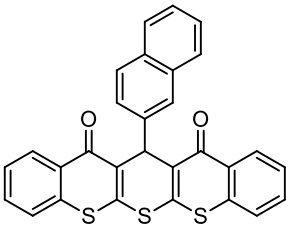
15g
80%, 20 min



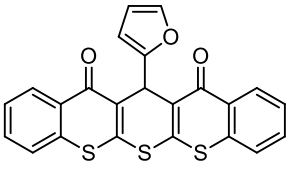
15h
78%, 15 min



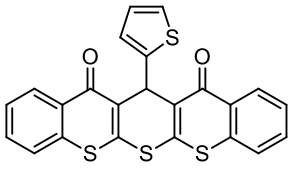
15i
72%, 20 min



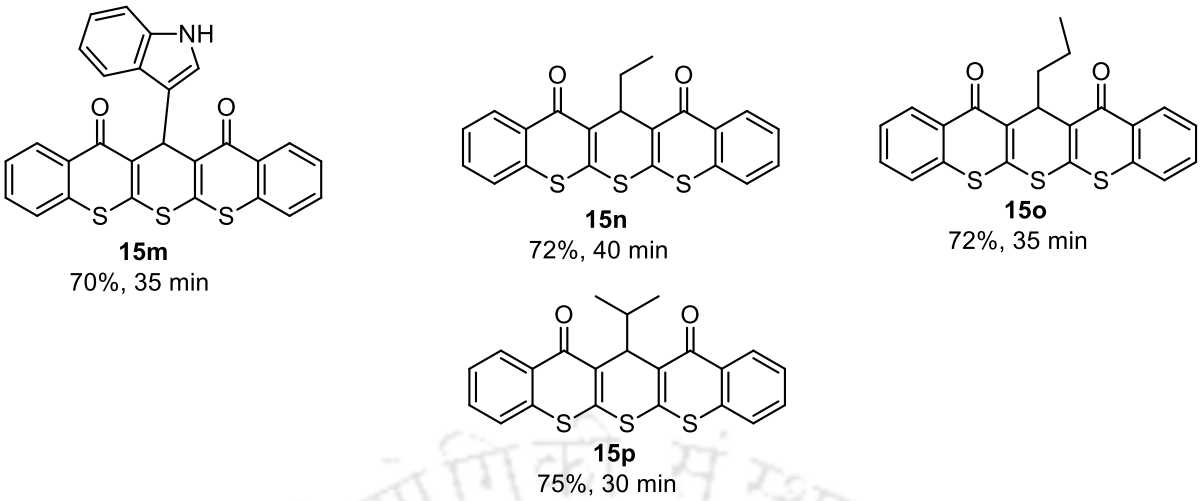
15j
75%, 25 min



15k
78%, 30 min



15l
77%, 25 min



[a]All the reactions were performed with 4-hydroxydithiocoumarin (2 mmol) and aldehyde (1mmol) in 2 mL acetonitrile. [b]Isolated yield.

Moreover, the structure of the compound **15a** was confirmed by single-crystal X-ray crystallographic analysis (Figure **10**, **A**); it was shown to have an unexpected infinite layered arrangement via C–S···π interactions. Analysis of the crystal structure of **15a** revealed that it forms a dimer through C–S···π interactions involving one molecule of S-2 with C-10 of a second molecule as shown in Figure **10**, **B**. This interaction leads the molecule to undergo complete assembly in the solid state thereby forming a layered structure shown in Figure **10**, **C**.

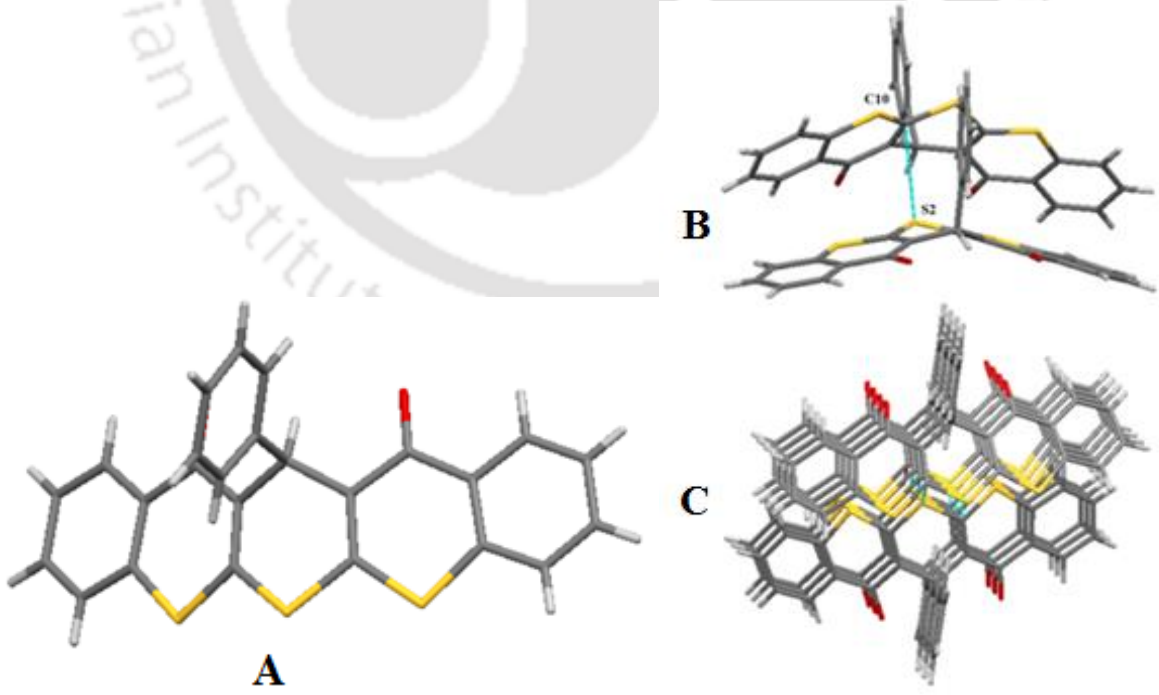
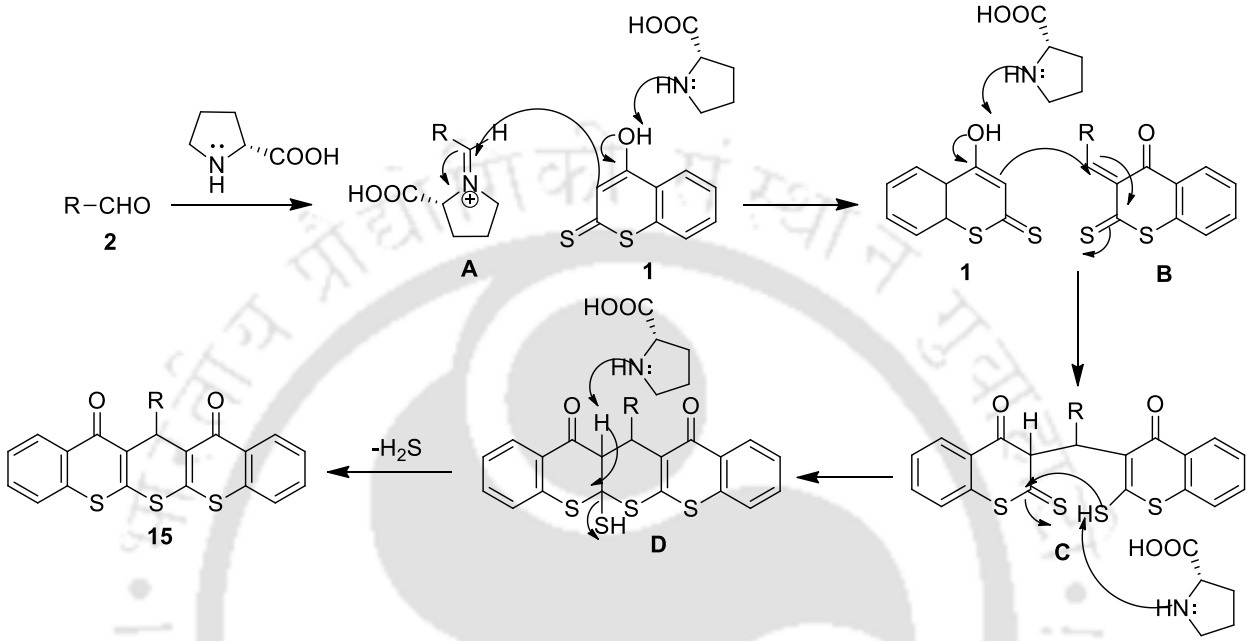


Figure 10. (**A**) XRD structure of **15a**, (**B**) Intermolecular C10-S2 short contact (**C**) Layered-Structure of Intermolecular C10-S2 short contact **15a**

Formation of product **15** may be rationalized by aldehyde **2** reacting with L-proline to form enamine A, followed by reaction of 4-hydroxydithiocoumarin **1** with A to form the Knoevenagel product B that reacts with another 4-hydroxydithiocoumarin to form Michael adduct C. This, on cyclization and elimination of H_2S gas, leads to the final product **15** (Scheme **48**).



Scheme 48. Plausible mechanism for the formation of thiopyrano[2,3-*b*:6,5-*b*′]bis(thiochromene)-12,14(13*H*)-dione derivatives

Conclusion

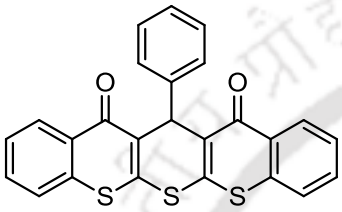
In conclusion, we have developed an interesting pseudo three-component reaction of 4-hydroxydithiocoumarin and aldehydes to generate novel thiopyrano[2,3-*b*:6,5-*b*′]bis(thiochromene)-12,14(13*H*)-dione derivatives in high yield with good substrate scope. The reaction profits from the efficiency of sulfur as a nucleophile as well as a leaving group. The protocol involves a simple workup procedure involving filtration and washing the precipitate with acetonitrile to afford the desired products. Finally, the compound **15a** was found to demonstrate C–S···π interactions, leading to assembly into a layered structure.

Experimental Section

General Procedure for the synthesis of thiopyrano[2,3-b:6,5-b']bis(thiochromene)-12,14(13H)-dione derivatives

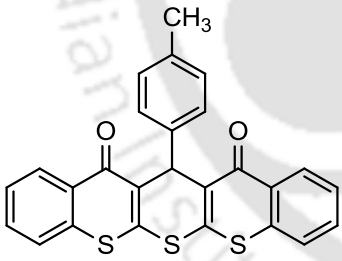
A mixture of 4-hydroxydithiocoumarin (2 mmol, **1**), aldehyde (1 mmol, **2**), and L-proline (0.012 mg, 10 mol%) was dissolved in MeCN (2 mL) into an oven-dried 25 mL round-bottomed flask and heated to reflux with stirring, progress of reaction being monitored by TLC. The precipitate was filtered off and washed with MeCN to furnish the pure product **15**.

13-phenyl-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15a):



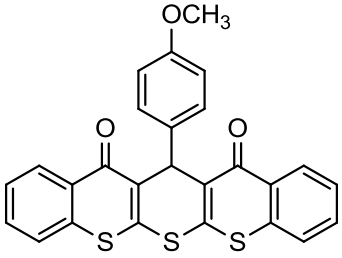
White solid (188 mg, 85% yield), mp 306-307 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 1H), 7.13-7.15 (m, 1H), 7.16-7.20 (m, 2H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 4H), 7.58-7.62 (m, 2H), 8.54 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.5, 125.4, 127.1, 127.9, 128.1, 128.4, 129.9, 130.7, 131.8, 132.3, 135.5, 139.6, 142.1, 176.1; IR (KBr)ν_{max} 1146, 1155, 1233, 1277, 1325, 1340, 1435, 1454, 1491, 1547, 1572, 1588, 1616, 2848, 2925, 3059 cm^{-1}; Anal. calcd for $C_{25}H_{14}O_2S_3$: C, 67.85; H, 3.19. found C, 67.73; H, 3.10.

13-(p-tolyl)-12H-thiopyrano[2,3-b:6,5-b']bis(thiochromene)-12,14(13H)-dione (15b):



White solid (200 mg, 88% yield), mp 290-291 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.19 (s, 3H), 6.97 (d, *J* = 6.0 Hz, 3H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.49-7.52 (m, 4H), 7.56-7.59 (m, 2H), 8.51-8.53 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.2, 39.3, 125.6, 128.1, 128.2, 129.3, 130.1, 131.0, 131.9, 132.6, 135.7, 136.8, 136.9, 141.9, 176.2; IR (KBr)ν_{max} 1112, 1144, 1155, 1232, 1274, 1297, 1322, 1344, 1434, 1460, 1509, 1523, 1546, 1587, 1618, 2852, 2922 cm^{-1}; Anal. calcd for: $C_{26}H_{16}O_2S_3$: C, 68.39; H, 3.53. found C, 68.28; H, 3.45.

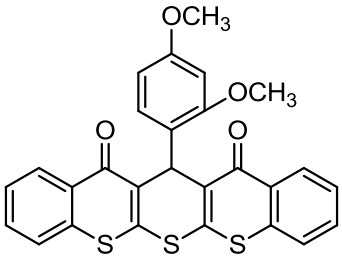
13-(4-methoxyphenyl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15c):



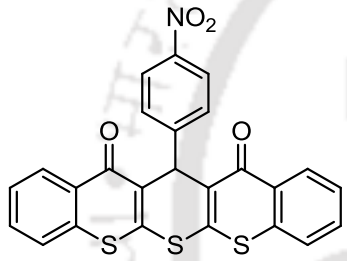
White solid (193 mg, 82% yield), mp 289-290 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.93 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.50-7.54 (m, 4H), 7.57-7.61 (m, 2H), 8.53 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.9, 55.4, 114.0, 125.6, 128.2, 129.4, 130.1, 131.0, 131.9, 132.1, 132.6, 135.7, 141.9, 176.3; IR (KBr)ν_{max} 1147, 1156, 1177, 1234, 1265,

1276, 1323, 1346, 1435, 1454, 1507, 1546, 1570, 1588, 1617, 2817, 2850, 2921, 2987, 3063 cm^{-1}; Anal. calcd for $C_{26}H_{16}O_3S_3$: C, 66.08; H, 3.41. found C, 65.97; H, 3.32.

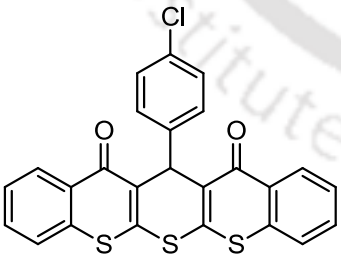
13-(2,4-dimethoxyphenyl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15d): White solid (190 mg, 76% yield), mp 275-276 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.70 (s, 3H), 6.31-6.36 (m, 2H), 6.86 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 4H), 7.55-7.59 (m, 2H), 8.48-8.50 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 37.3, 55.3, 55.4, 99.1, 103.8, 125.4, 127.9, 129.9, 131.4, 131.6, 131.7, 135.4, 141.9, 159.4, 160.0, 176.5; IR (KBr)ν_{max} 1143, 1156, 1183, 1213, 1232, 1273, 1296, 1335, 1459, 1503, 1546, 1587, 1619, 2828, 2923, 2947 cm^{-1}; Anal. calcd for $C_{27}H_{18}O_4S_3$: C, 64.52; H, 3.61. found C, 64.40; H, 3.52.

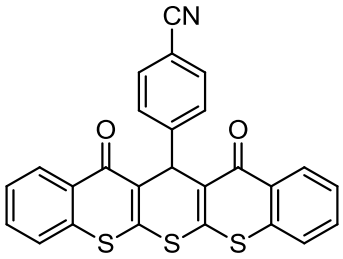


13-(4-nitrophenyl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15e): White solid (183 mg, 80% yield), mp 264-265 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (s, 1H), 7.52-7.56 (m, 4H), 7.57-7.64 (m, 4H), 8.01-8.04 (m, 2H), 8.51-8.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.5, 122.5, 124.9, 127.3, 127.7, 128.3, 129.1, 129.7, 131.3, 134.4, 142.6, 145.8, 174.8; IR (KBr)ν_{max} 1110, 1157, 1231, 1275, 1345, 1434, 1460, 1504, 1546, 1587, 1613, 2922, 2958 cm^{-1}; Anal. calcd for $C_{25}H_{13}NO_4S_3$: C, 61.58; H, 2.69; N, 2.87. found C, 61.46; H, 2.61; N, 2.78.

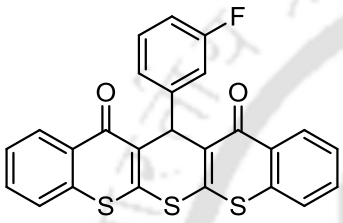


13-(4-chlorophenyl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15f): White solid (190 mg, 80% yield), mp 330-331 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (s, 1H), 7.11-7.13 (m, 2H), 7.38-7.40 (m, 3H), 7.50-7.54 (m, 3H), 7.58-7.62 (m, 2H), 8.51-8.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.4, 122.1, 124.7 , 127.0, 127.3, 127.8, 128.7, 129.3, 131.0, 133.9, 142.3, 145.3, 174.3; IR (KBr)ν_{max} 1155, 1275, 1324, 1346, 1407, 1436, 1485, 1547, 1587, 1617, 2877, 2917 cm^{-1}; Anal. calcd for $C_{25}H_{13}ClO_2S_3$: C, 62.95; H, 2.75. found C, 66.83; H, 2.68.

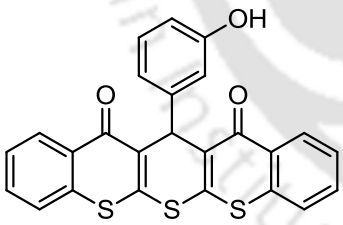


4-(12,14-dioxo-13,14-dihydro-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-13-yl) benzonitrile (15g): 

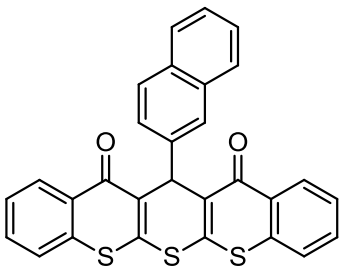
White solid (191 mg, 82% yield), mp 250-251 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.95 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.46-7.49 (m, 4H), 7.50-7.52 (m, 2H), 7.55-7.57 (m, 2H) , 8.46 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 39.9, 111.1, 119.0, 125.7, 128.5, 129.2, 130.1, 130.8, 131.4, 132.3, 132.5, 135.6, 143.0, 145.4, 176.2; IR (KBr)ν_{max} 1154, 1323, 1548, 1588, 1619, 2223, 2844, 2924 cm^{-1}; Anal. calcd for $C_{26}H_{13}NO_2S_3$: C, 66.79; H, 2.80; N, 3.00. found C, 66.67; H, 2.72; N, 2.90.

13-(3-fluorophenyl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15h): 

White solid (179 mg, 78% yield), mp 269-270 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80-6.85 (m, 1H), 7.04 (s, 1H), 7.11-7.17 (m, 2H), 7.52-7.57 (m, 5H), 7.60-7.64 (m, 2H), 8.55 (d, *J* = 8.4 Hz, 2H) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ 39.4, 114.2, 114.3, 115.1, 115.2, 124.0, 125.7, 128.3, 129.9, 130.0, 130.2, 130.9, 132.0, 132.1, 135.7, 142.0, 142.1, 142.7, 163.8, 176.2; IR (KBr)ν_{max} 1021, 1143, 1156, 1230, 1272, 1297, 1342, 1435, 1454, 1484, 1544, 1587, 1618, 2850, 2921, 2954 cm^{-1}; Anal. calcd for: $C_{25}H_{13}FO_2S_3$ C, 65.20; H, 2.85. found C 65.07; H, 2.78.

13-(3-hydroxyphenyl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15i): 

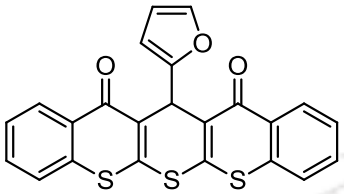
White solid (165 mg, 72% yield), mp 331-332 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.53 (br s, 1H), 6.61 (br s, 2H), 6.89 (br s, 1H), 6.97 (br s, 1H), 7.69 (br s, 2H), 7.81 (br s, 2H), 7.93 (br s, 2H), 8.43 (br s, 2H), 9.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.7, 112.8, 116.2, 124.6, 126.7, 127.5, 128.4, 130.2, 130.7, 133.6, 138.4, 141.1, 155.8, 165.6, 174.0 ; IR (KBr) ν_{max} 1156, 1240, 1289, 1347, 1435, 1548, 1621, 2842, 2928, 2967, 3410; Anal. calcd for: $C_{25}H_{14}O_3S_3$: C, 65.48; H, 3.08. found C, 65.36; H, 3.01.

13-(naphthalen-2-yl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15j): 

White solid (184 mg, 75% yield), mp 272-273 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H), 7.35-7.36 (m, 2H), 7.52-7.54 (m, 4H), 7.59-7.63 (m, 2H), 7.68-7.70 (m, 4H), 7.81 (s, 1H), 8.55 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz,

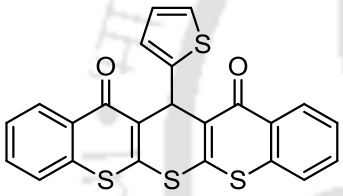
$CDCl_3$): δ 39.9, 125.6, 125.8, 125.9, 126.5, 127.0, 127.6, 128.2, 128.4, 130.2, 131.0, 131.9, 132.4, 133.4, 135.7, 137.2, 142.4, 176.3; IR (KBr)ν_{max} 1154, 1232, 1275, 1326, 1340, 1370, 1434, 1460, 1505, 1545, 1571, 1588, 1615, 1724, 2853, 2923, 3052 cm^{-1}; Anal. calcd for $C_{29}H_{16}O_2S_3$: C, 70.70; H, 3.27. found C, 70.57; H, 3.19.

13-(furan-2-yl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15k):



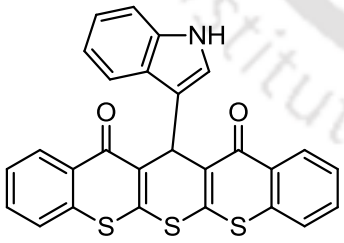
White solid (166 mg, 77% yield), mp 275-276 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.03-6.09 (m, 2H), 7.10 (d, *J* = 12 Hz, 2H), 7.44-7.49 (m, 3H), 7.53-7.55 (m, 3H), 8.50 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 34.2, 107.1, 110.3, 125.6, 128.2, 129.8, 130.2, 130.9, 132.0, 135.7, 142.1, 143.4, 151.5, 175.9; IR (KBr)ν_{max} 1138, 1231, 1269, 1332, 1402, 1435, 1546, 1588, 1625, 2847, 2918, 3131 cm^{-1}; Anal. calcd for $C_{23}H_{12}O_3S_3$: C, 63.87; H, 2.80. found C, 63.75; H, 2.72.

13-(thiophen-2-yl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione



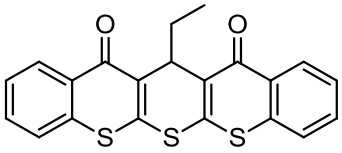
(15l): White solid (174 mg, 78% yield), mp 272-273 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.72 (s, 1H), 6.92 (d, *J* = 14.4 Hz, 2H), 7.19 (s, 1H), 7.45-7.54 (m, 6H), 8.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.3, 124.2, 125.6, 125.7, 126.6, 128.3, 130.2, 130.9, 131.9, 132.1, 135.7, 141.9, 142.7, 175.9; IR (KBr)ν_{max} 1146, 1158, 1228, 1274, 1341, 1437, 1548, 1572, 1588, 1614, 2861, 2918, 3060 cm^{-1}; Anal. calcd for $C_{23}H_{12}O_2S_4$: C, 61.58; H, 2.70. found C, 61.47; H, 2.63.

13-(1*H*-indol-3-yl)-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione



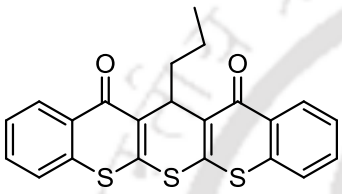
(15m): White solid (168 mg, 70% yield), mp 290-291 ˚C, ^{1}H NMR (400 MHz, DMSO): δ 6.93 (t, *J* = 7.6 Hz, 1H), 6.97-7.01 (m, 2H), 7.19 (s, 1H), 7.25 (d, *J* = 8 .0 Hz, 1H), 7.64-7.67 (m, 2H), 7.76-7.79 (m, 3H), 7.90 (d, *J* = 8.4 Hz, 2H), 8.43 (d, *J* = 8.0 Hz, 2H), 10.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 31.4, 111.4, 111.9, 119.1, 119.9, 121.5, 123.8, 126.5, 126.7, 128.8, 129.3, 130.4, 132.5, 132.8, 135.5, 136.8, 142.7, 175.9; IR (KBr)ν_{max} 1107, 1157, 1227, 1272, 1337, 1459, 1567, 1587, 1618, 2853, 2925, 3056, 3117, 3412 cm^{-1}; Anal. calcd for $C_{27}H_{15}NO_2S_3$: C, 67.33; H, 3.14; N, 2.91. found C, 67.21; H, 3.06; N, 2.80.

13-propyl-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15n):

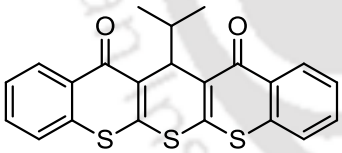


White solid (142 mg, 72% yield), mp 222-223 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.82 (t, *J* = 7.8 Hz, 3H), 1.24-1.30 (m, 2H), 1.55-1.59 (m, 2H), 5.86 (t, *J* = 7.8 Hz, 1H), 7.48-7.52 (m, 4H), 7.56-7.58 (m, 2H), 8.53 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.4, 20.9, 32.6, 35.2, 125.6, 128.1, 130.1, 130.9, 131.8, 133.9, 135.9, 141.3, 176.5; IR (KBr)ν_{max} 1105, 1153, 1228, 1281, 1312, 1330, 1352, 1434, 1460, 1515, 1541, 1587, 1618, 2852, 2954 cm^{-1}; Anal. calcd for: $C_{22}H_{16}O_2S_3$ C, 64.68; H, 3.95. found C, 64.54; H, 3.88.

13-butyl-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15o): White solid (147 mg, 72% yield), mp 217-218 ˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.75-0.77 (m, 3H), 1.21-1.23 (m, 4H), 1.57-1.60 (m, 2H), 5.85 (t, *J* = 7.8 Hz, 1H), 7.48-7.52 (m, 4H), 7.56-7.58 (m, 2H), 8.53 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0, 22.9, 29.4, 29.9, 35.1, 125.5, 127.9, 129.9, 130.8, 131.7, 133.7, 135.7, 141.1, 176.3; IR (KBr)ν_{max} 1153, 1228, 1281, 1312, 1330, 1352, 1434, 1460, 1515, 1587, 1618, 2852, 2954 cm^{-1}; Anal. calcd for $C_{23}H_{18}O_2S_3$: C, 65.37; H, 4.29. found C, 65.24; H, 4.20.

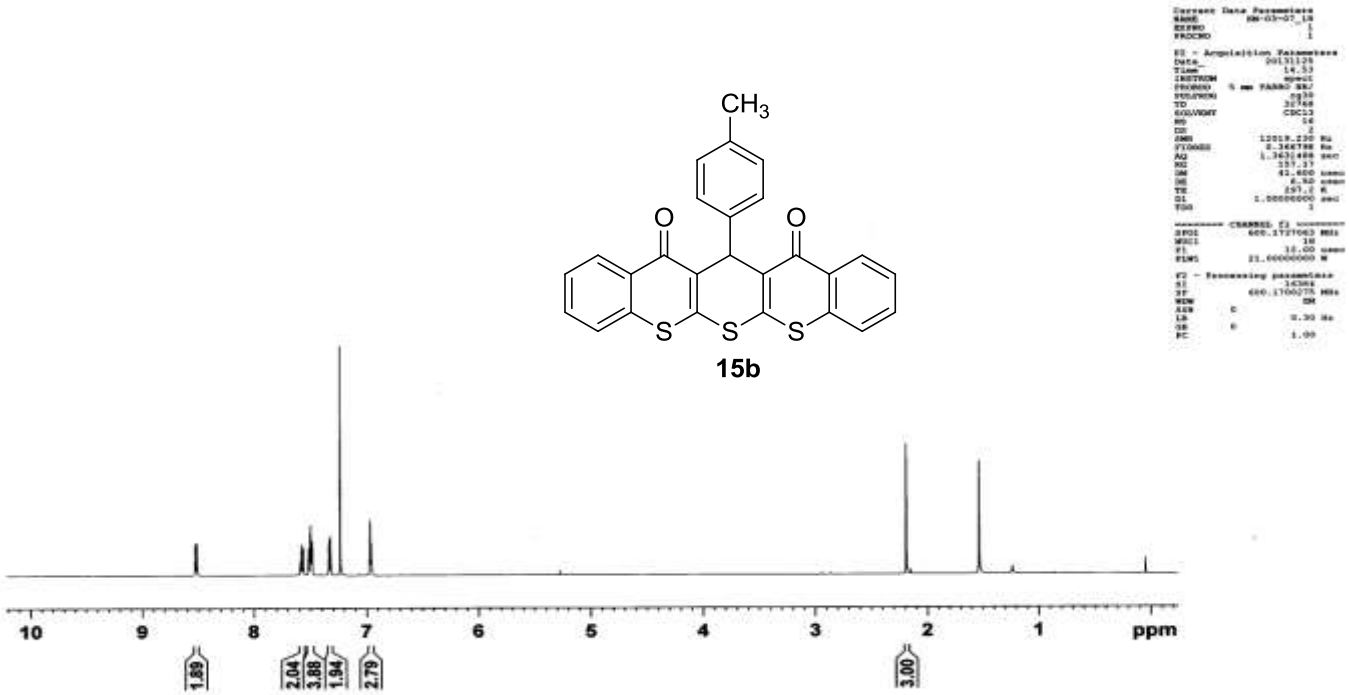


13-isobutyl-12*H*-thiopyrano[2,3-*b*:6,5-*b*']bis(thiochromene)-12,14(13*H*)-dione (15p):

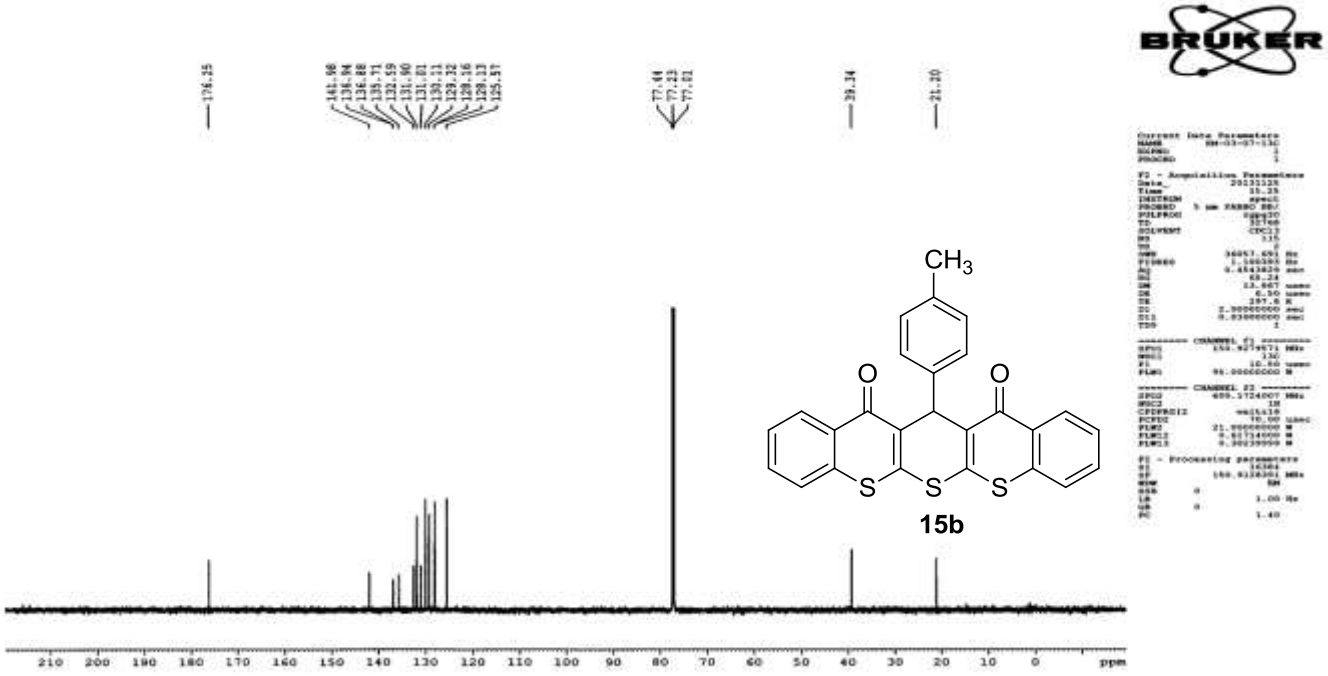


White solid (153 mg, 75% yield), mp 193-194 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H), 0.99 (s, 3H), 1.28-1.35 (m, 1H), 1.45 (t, *J* = 7.2 Hz, 2H), 5.99 (t, *J* = 7.6 Hz, 1H), 7.51-7.57 (m, 4H), 7.59-7.63 (m, 2H), 8.56 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 26.1, 33.4, 39.1, 125.6, 128.0, 129.9, 130.9, 131.8, 134.3, 135.8, 141.3, 176.3; IR (KBr)ν_{max} 1154, 1231, 1266, 1287, 1331, 1385, 1461, 1542, 1587, 1616, 2864, 2926, 2948 cm^{-1}; Anal. calcd for $C_{23}H_{18}O_2S_3$: C, 65.37; H, 4.29. found C, 65.25; H, 4.21.

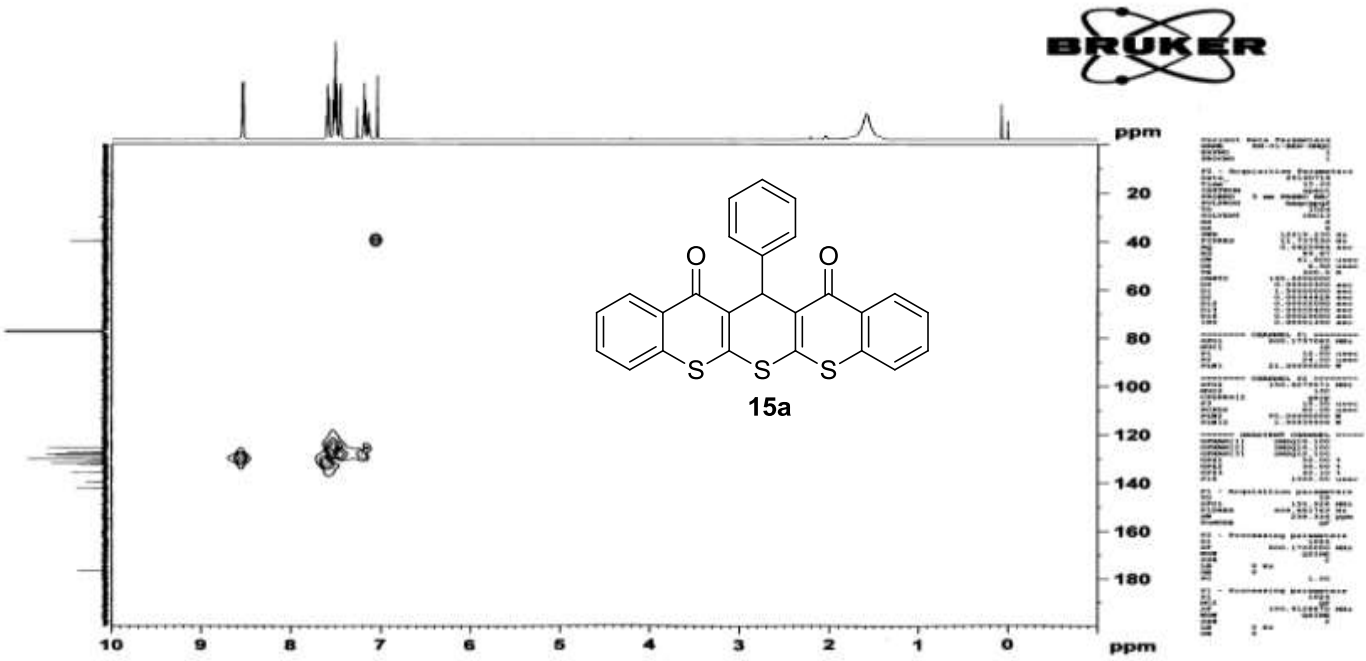
^{1}H NMR: *13-(p-tolyl)-12H-thiopyrano[2,3-b:6,5-b']bis(thiochromene)-12,14(13H)-dione* ***(15b)***



^{13}C NMR: *13-(p-tolyl)-12H-thiopyrano[2,3-b:6,5-b']bis(thiochromene)-12,14(13H)-dione* ***(15b)***



HMQC NMR: *13-phenyl-12H-thiopyrano[2,3-b:6,5-b']bis(thiochromene)-12,14(13H)-dione* ***(15a)***



Chapter V

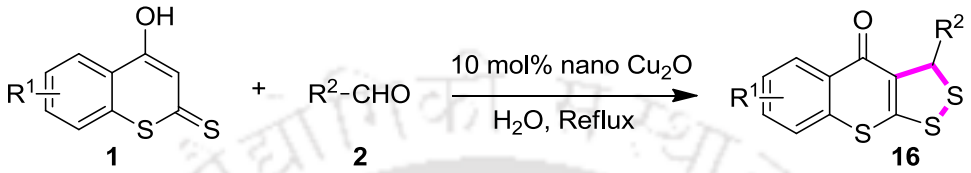
Cuprous Oxide Nanoparticles catalyzed synthesis of 3-alkyl-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-ones from the reaction of 4-hydroxydithiocoumarin and aldehydes in aqueous media

Result & Discussion

Experimental Section

Results and Discussion

The synthetic strategies and the importance of 1,2-dithioles have already been described in Chapter 1. In this Chapter, we present the synthesis of 3-phenyl-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-ones from the reaction of 4-hydroxydithiocoumarin and aldehydes in the presence of Cu_2O nanoparticle in aqueous medium under refluxing conditions as shown in Scheme 49.

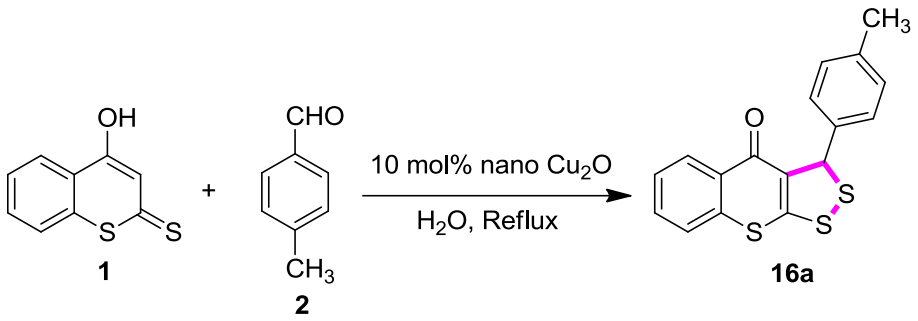


Scheme 49. Synthesis of [1,2]dithiolo[3,4-*b*]thiochromen-4(3H)-one derivatives

Transition metal based nanoparticles are found to be an efficient heterogeneous catalyst with distinct active sites[22] which crafts its own identity in the field of environment protection to overcome the problems of homogeneous catalysis. Thus, the engagement of heterogeneous copper oxide nanoparticles catalyst serves as an attractive contender for the synthesis of cyclic 1,2-dithiole based molecules that leads to the recovery as well as recyclability of the catalyst without any substantial loss of activity.

Our synthetic attempt began with the search for optimal reaction conditions for the synthesis of 1,2-dithiole, we investigated the reaction of with 4-hydroxydithiocoumarin (**1**, 1.0 mmol) and 4-Methyl benzaldehyde (1.0 mmol) as the model substrates and the results are summarized in Table 10. Initially, conducting the reaction without the aid of any catalyst in aqueous medium under refluxing conditions went in vain as we were unable to isolate any desired product (Table 10, entry 1). To our delight, performing the reaction with 10 mol% of CuI as catalyst in aqueous medium led to the isolation of the desired product **16a** in 35% yield (Table 10, entry 2). The isolated product **16a** was characterized by IR, ^{1}H and ^{13}C NMR spectra and HRMS. Next switching on to other copper sources such CuBr and CuCl didn't help much to improve the yield of product **16a** (Table 10, entries 3-4). In order to improve the yield of the product the reaction was performed with 5 mol%, 10 mol% and 15 mol% of Cu_2ONPs individually under similar reaction conditions and it was found that 10 mol% Cu_2ONPs gave the best yield amongst them (Table 10, entries 5-7).

Table 10. Optimization of the reaction conditions[a,b]



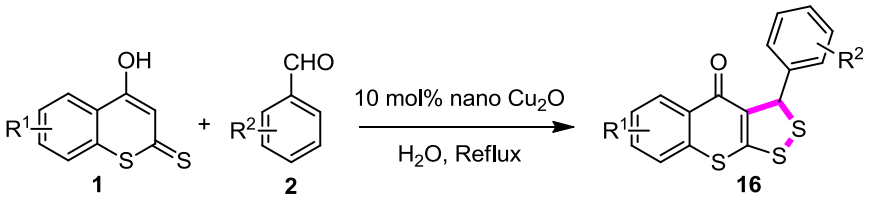
Sl No	Catalyst (mol %)	Solvent	Time	Yield
1	-	H_2O	48	NR
2	CuI (10)	H_2O	24	35
3	CuBr (10)	H_2O	24	30
4	CuCl (10)	H_2O	24	36
5	Cu_2ONPs (5)	H_2O	12	40
6	**Cu_2ONPs (10)**	**H_2O**	**6**	**65**
7	Cu_2ONPs (15)	H_2O	8	65
8	Cu_2ONPs (10)	EtOH	12	30
9	Cu_2ONPs (10)	MeOH	24	25
10	Cu_2ONPs (10)	^{n}BuOH	24	15
11	Cu_2ONPs (10)	^{n}BuOH	24	10

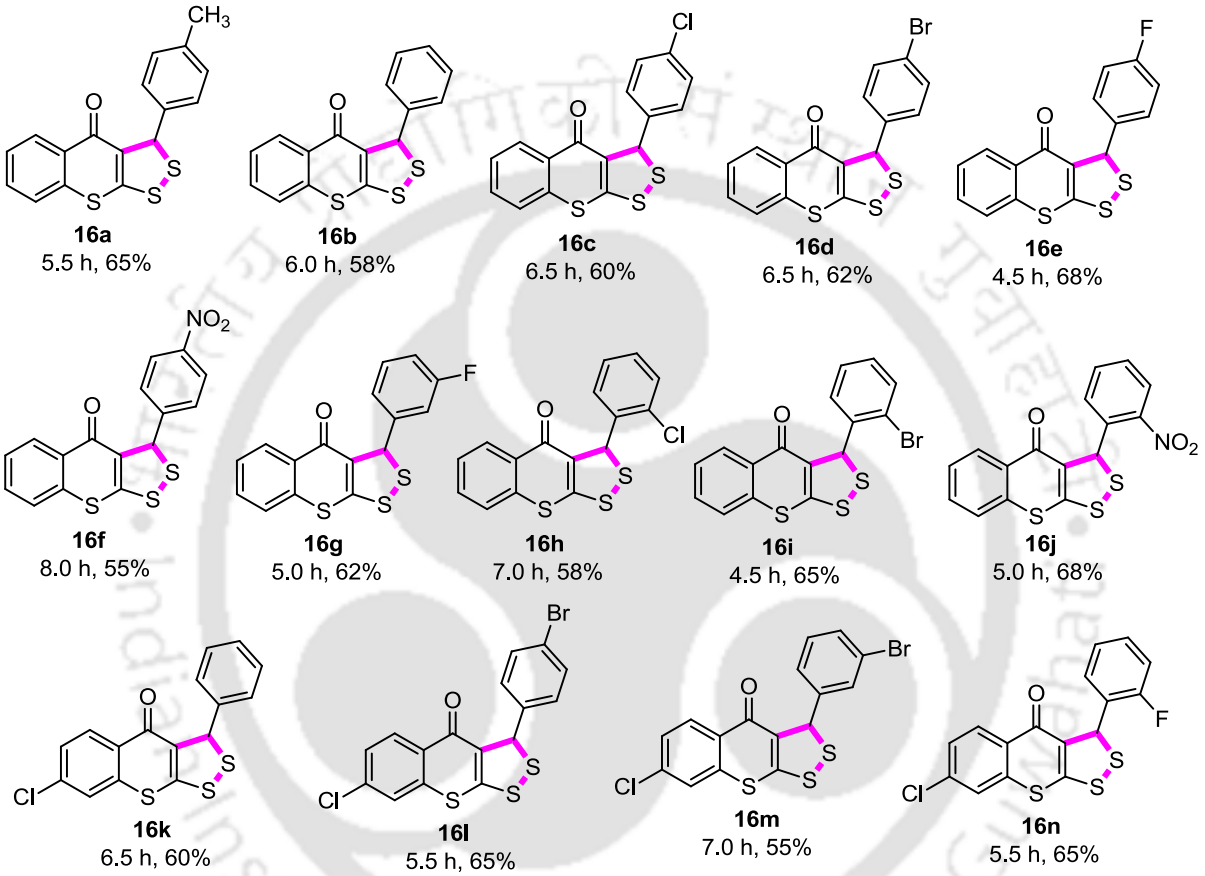
[a]All the reactions were carried out using 4-hydroxy-2H-thiochromene-2-thione (0.5 mmol), benzaldehyde (1 mmol) and ammonium acetate (1.0 mmol). [b]Isolated yield.

Screening the same reaction with organic solvents such as EtOH, MeOH, ^{n}BuOH, ^{n}BuOH did not improve the isolated yield rather the yield was decreased (Table 10, entries 8-11). Therefore, the optimized conditions for this coupling reaction are 10 mol% Cu_2ONPs as catalyst in aqueous medium under refluxing conditions.

With the above optimized reaction conditions in hand, we commenced to explore the substrate scope, and the results are summarized in Table 11. Benzaldehyde reacted with 4-hydroxydithiocoumarin to afford the product **16b** in 58% yield. The reaction was feasible with aromatic aldehydes having electron withdrawing group such as 4-Cl, 4-Br, 4-F and 4-NO_2 at the para position giving rise to the products **16c-f** in 55-68% yield. 3-F benzaldehyde gave the product **16g** in 62% yield.

Table 11. Synthesis of [1,2]dithiolo[3,4-*b*]thiochromen-4(3H)-one derivatives using copper oxide nanoparticle[a,b]





[a]All the reactions were carried out using 4-hydroxydithiocoumarin (1.0 mmol), aldehyde (1.0 mmol) in water (2 mL). [b]Isolated yield.

The reaction worked well with the aromatic aldehydes having ortho-substituents such as 2-Cl, 2-Br and 2-NO_2 on the ring to give the product **16h-i** in 58-68% yield. Next we performed the reaction with 6-Cl substituted 4-hydroxydithiocoumarin with various aldehydes under the similar reaction condition leading to the isolation of the product **16k-n** in 55-65% yield.

In addition, the recyclability of the catalyst was tested with **16a**. The reactions were carried out with 4 mmol scale of 4-hydroxydithiocoumarin (**1**) and 4-Me benzaldehyde in the presence of 10 mol% of Cu_2O nanoparticle in water. The yield of the product **16a** is shown (Table 12 and Figure 13A) after each cycle. Thus, it is concluded from

the table 12 that even after four cycles our expected [1,2]dithiolo[3,4-*b*]thiochromen-4(3H)-one derivatives formation could be achieved which shows the catalyst Cu_2O nanoparticle is recyclable.

Table 12. Recyclability of the catalyst[a] in **16a**

Entry	mmol scale	Amount of catalyst	Recovered catalyst	Time (h)	Yield (%)
01	04	32	28	5.5	65
02	3.5	28	24	8.0	55
03	3	24	20	12	48
04	2.5	20	15	16	42

[a]*The Cu_2O nanoparticle was reused as follows: it was filtered off, washed with dichloromethane and finally dried before use for next cycle.*

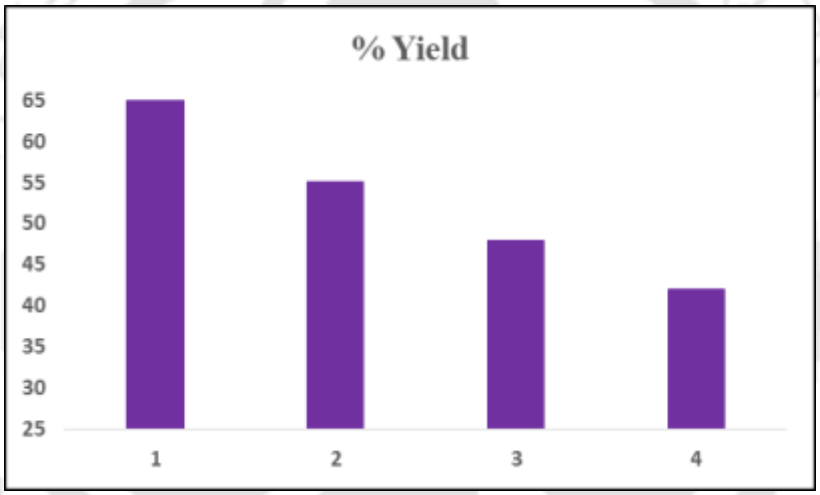


Figure 13A. Recyclability of cuprous oxide nanoparticle of **16a**

All the products were characterized by recording IR, ^{1}H and ^{13}C NMR spectra as well as from their HRMS. In addition the structure of compounds **16d** was also confirmed through XRD (Figure **13B**).

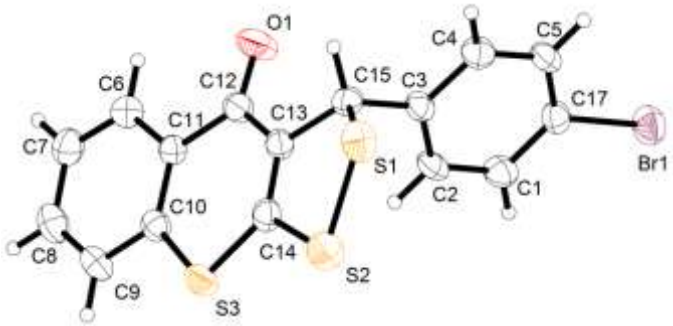
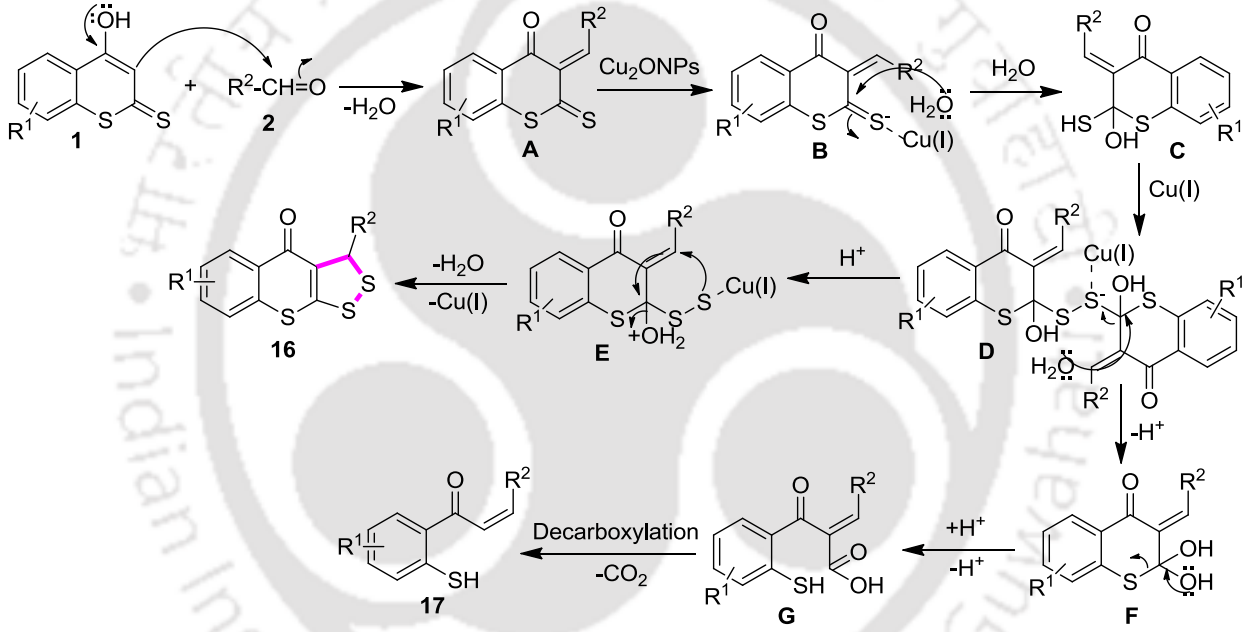


Figure 13B. Ortep view of the compound **16d**

A plausible mechanism can be drawn for the formation of product **16** as shown in Scheme 50. The 4-hydroxydithiocoumarin **1** attacks aldehyde to form a Knoevenagel product **A** which in presence of Cu_2ONPS forms an intermediate **B**. The formation of this intermediate **B** was confirmed through mass spectra (when R^2= C_6H_5, R^1= H). The solvent water attacks **B** to form **C** which dimerizes in the presence of catalyst to form **D**. This product **D** breaks in the presence of water to give **E** (confirmed through mass spectra when R^2= C_6H_5, R^1= H) and ultimately after cyclization gives way to our desired product **16**. The intermediate **D** also breaks to give the species **F** which after protonation/deprotonation gives **G** which undergoes de-carboxylation to give **17** (confirmed through mass spectra when R^2= 4-Me-C_6H_4, R^1= H as shown in the experiment section).



Scheme 50. Plausible mechanism for the formation of [1,2]dithiolo[3,4-*b*]thiochromen-4(3H)-one derivatives.

Conclusion

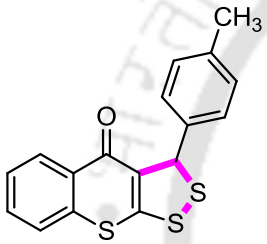
In summary, we have developed a simple and efficient protocol for the synthesis of [1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one derivatives using 10 mol% Cu_2ONPS in water using 4-hydroxydithiocoumarin and aldehydes. The main features of the protocol are the mild reaction conditions, the easy reaction procedure, and unexpected ring closure leading to S-S bond formation, commercially available and recyclable nano catalyst and substrate scope compatibility.

Experimental Section

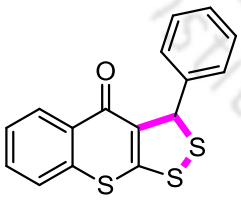
General Procedure for the synthesis of [1,2]dithiolo[3,4-b]thiochromen-4(3H)-one derivatives 16

Into an oven dried 25 mL round bottomed flask was taken a mixture of 4-hydroxydithiocoumarin (1.0 mmol) and aldehyde (1.0 mmol) in 2mL of water. Then, Cu_2O nanoparticle (14 mg, 10 mol%) was added into it and the reaction mixture was refluxed in a pre-heated oil-bath. After completion of the reaction, as indicated by TLC the reaction mixture was cooled and extracted with DCM (15 mL x 2), dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude residue was purified through a silica gel column chromatography to obtain the desired product **16**.

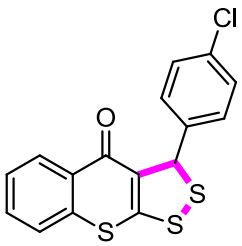
3-(p-tolyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16a): Yellow solid (213 mg, 65% yield), Mp 149-150˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.30 (s, 3H), 6.28 (s, 1H), 7.11 (d, *J* = 6.0 Hz, 2H), 7.33 (d, *J* = 12.0 Hz, 2H), 7.48-7.51 (m, 1H), 7.53-7.54 (m, 1H), 7.57-7.60 (m, 1H), 8.40-8.42 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 62.3, 125.9, 126.9, 128.1, 129.5, 129.7, 130.8, 131.9, 134.3, 135.7, 137.5, 138.5, 153.6, 175.4; IR $(KBr)_{vmax}$ 1110, 1126, 1332, 1384, 1434, 1458, 1522, 1560, 1584, 1607, 2853, 2923, 2956, 3056, 3093 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{12}OS_3$ 329.0123 (M + H$^+$); Found 329.0124.



3-phenyl-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16b): Yellow solid (182 mg, 58% yield), Mp 137-138˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.29 (s, 1H), 7.27-7.28 (m, 1H), 7.31 (t, *J* = 6.0 Hz, 2H), 7.44-7.45 (m, 2H), 7.50 (t, *J* = 6.0 Hz, 1H), 7.54-7.55 (m, 1H), 7.58-7.61 (m, 1H), 8.41 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 62.3, 125.9, 126.9, 128.2, 128.6, 129.0, 129.5, 130.7, 131.9, 134.3, 135.7, 140.4, 153.8, 175.4; IR $(KBr)_{vmax}$ 1105, 1148, 1356, 1400, 1451, 1458, 1561, 1575, 1592, 1610, 2843, 2930, 2976, 3036, 3075 cm^{-1}; HRMS (ESI) Calcd For 314.9967 (M + H$^+$); Found 314.9970.

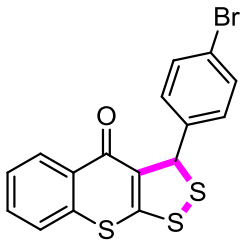


3-(4-chlorophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16c): Yellow solid (208 mg, 60% yield), Mp 203-204˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.23 (s, 1H), 7.24 (s, 2H), 7.36-7.38 (m, 2H), 7.49-7.54 (m, 2H), 7.57-7.58 (m, 1H), 8.39 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.6, 125.9, 128.3, 128.4, 129.2, 129.4, 130.6, 132.0, 133.9, 134.4,

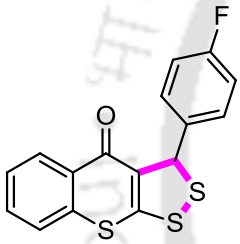


135.7, 138.9, 153.9, 175.4; IR $(KBr)_{vmax}$ 1126, 1180, 1332, 1384, 1434, 1458, 1522, 1560, 1584, 1607, 2853, 2923, 2958, 3056, 3091 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}ClOS_3$ 348.9577 $(M + H^+)$; Found 348.9576.

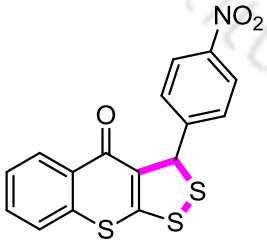
3-(4-bromophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16d): Yellow solid (267 mg, 68% yield), Mp 210-211˚C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.23 (s, 1H), 7.33-7.35 (m, 2H), 7.42-7.44 (m, 2H), 7.49-7.56 (m, 2H), 7.58-7.62 (m, 1H), 8.41 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.6, 122.6, 125.9, 128.3, 128.7, 129.4, 130.5, 132.0, 132.1, 133.8, 135.6, 139.4, 154.0, 175.4; IR $(KBr)_{vmax}$ 1107, 1127, 1162, 1182, 1227, 1261, 1341, 1383, 1399, 1437, 1460, 1481, 1515, 1587, 1611, 1734, 2853, 2924, 2956, 3060, 3083 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}BrOS_3$ 392.9073 $(M + H^+)$; Found 392.9080.



3-(4-fluorophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16e): Yellow solid (226 mg, 68% yield), Mp 140-141˚C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.27 (s, 1H), 6.96-7.01 (m, 2H), 7.42-7.45 (m, 2H), 7.48-7.55 (m, 2H), 7.57-7.61 (m, 1H), 8.39-8.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.6, 115.8, 116.0, 125.9, 128.3, 128.7, 128.8, 129.4, 130.7, 131.9, 134.2, 135.7, 136.3, 136.4, 153.0, 161.6, 164.0, 175.4; IR $(KBr)_{vmax}$ 1130, 1156, 1192, 1225, 1261, 1314, 1341, 1384, 1436, 1464, 1507, 1516, 1525, 1562, 1586, 1599, 1615, 2853, 2923, 2958, 3064 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}FOS_3$ 332.9873 $(M + H^+)$; Found 332.9873.



3-(4-nitrophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16f): Yellow solid (197 mg, 55% yield), Mp 195-196˚C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.32 (s, 1H), 7.52-7.58 (m, 2H), 7.61-7.66 (m, 3H), 8.17-8.19 (m, 2H), 8.40 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.2, 124.3, 126.1, 128.0, 128.5, 129.4, 130.5, 132.3, 133.4, 135.6, 147.4, 154.6, 175.4; IR $(KBr)_{vmax}$ 1109, 1131, 1194, 1310, 1344, 1384, 1437, 1458, 1516, 1587, 1604, 2852, 2919, 3075, 3113 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}NO_3S_3$ 359.9818 $(M + H^+)$; Found 359.9819.



3-(3-fluorophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16g): Yellow solid (206 mg, 62% yield), Mp 148-149˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (s, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.22-7.24 (m, 1H), 7.27-7.31 (m, 1H), 7.49-7.56 (m, 2H), 7.59-7.62 (m, 1H), 8.42 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 61.6, 113.9, 114.0, 114.3, 115.5, 115.6, 122.7, 122.8, 126.0, 128.3, 129.4, 130.4, 130.5, 130.6, 132.0, 133.8, 135.7, 139.5, 142.7, 154.2, 162.3, 163.9, 175.4; IR $(KBr)_{vmax}$ 1100, 1106, 1182, 1252, 1298, 1332, 1398, 1426, 1464, 1503, 1520, 1530, 1582, 1596, 1602, 1615, 2843, 2913, 2955, 3064 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}FOS_3$ 332.9873 ($M + H^+$); Found 332.9874.

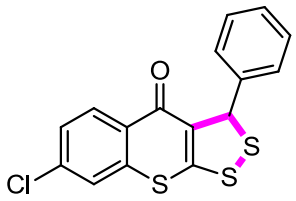
3-(2-chlorophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16h): Yellow solid (202 mg, 58% yield), Mp 180-181 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 6.97-7.00 (m, 1H), 7.12-7.16 (m, 1H), 7.46-7.48 (m, 1H), 7.53-7.64 (m, 4H), 8.42-8.44 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 58.4, 125.4, 127.1, 127.3, 129.0, 129.7, 130.4, 130.9, 132.8, 133.1, 136.1, 137.1, 138.9, 155.8, 174.5; IR $(KBr)_{vmax}$ 1126, 1180, 1332, 1384, 1458, 1522, 1560, 1584, 1607, 2853, 2923, 2958, 3056, 3091 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}ClOS_3$ 348.9577 ($M + H^+$); Found 348.9570.

3-(2-bromophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16i): Yellow solid (225 mg, 65% yield), Mp 155-156 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (s, 1H), 6.96-6.97 (m, 1H), 7.13-7.19 (m, 2H), 7.52-7.54 (m, 1H), 7.57-7.59 (m, 1H), 7.61-7.66 (m, 2H), 8.42-8.43 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 61.5, 123.9, 126.0, 127.2, 127.9, 128.3, 129.5, 129.8, 130.5, 132.1, 132.6, 133.6, 135.7, 137.8, 156.2, 175.3; IR $(KBr)_{vmax}$ 1131, 1165, 1350, 1385, 1496, 1530, 1598, 1610, 2851, 2929, 3098 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}BrOS_3$ 392.9073 ($M + H^+$); Found 392.9068.

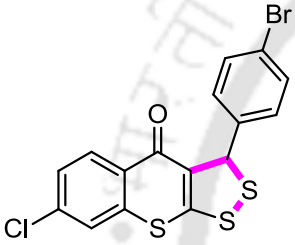
3-(2-nitrophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16j): Yellow solid (244 mg, 68% yield), Mp 174-175˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 1H), 7.17-7.20 (m, 1H), 7.43-7.47 (m, 1H), 7.51-7.54 (m, 2H), 7.57-7.65 (m, 2H), 8.17-8.19 (m, 1H), 8.37 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.3, 126.0, 126.3, 127.9, 128.4,

129.2, 129.3, 130.3, 131.5, 132.2, 134.4, 135.0, 135.8, 146.4, 156.7, 175.3; IR $(KBr)_{vmax}$ 1115, 1145, 1350, 1365, 1391, 1445, 1468, 1516, 1590, 1613, 2842, 2938, 3070 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}NO_3S_3$ 359.9818 $(M + H^+)$; Found 359.9817.

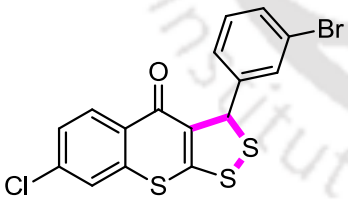
7-chloro-3-phenyl-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16k): Yellow solid (209 mg, 60% yield), Mp 191-192˚C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.23 (s, 1H), 7.21-7.29 (m, 3H), 7.39 (s, 3H), 7.49 (s, 1H), 8.23-8.30 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 61.2, 114.3, 125.3, 126.9, 128.7, 128.8, 129.1, 130.9, 137.1, 138.7, 140.2, 153.6, 174.6; IR $(KBr)_{vmax}$ cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}ClOS_3$ 348.9577 $(M + H^+)$; Found 348.9576.



3-(4-bromophenyl)-7-chloro-[1,2]dithiolo[3,4-b]thiochromen-4(3*H*)-one (16l): Yellow solid (278 mg, 65% yield), Mp 181-182˚C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.21 (s, 1H), 7.31-7.33 (m, 2H), 7.42-7.46 (m, 3H), 7.54 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 61.5, 122.7, 125.3, 128.7, 128.9, 129.1, 130.9, 132.2, 134.0, 137.0, 138.9, 139.3, 153.8, 174.6; IR $(KBr)_{vmax}$ 1107, 1127, 1162, 1182, 1227, 1261, 1341, 1383, 1399, 1437, 1460, 1481, 1515, 1587, 1611, 1734, 2853, 2924, 2956, 3060, 3083 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_9BrClOS_3$ 426.8682 $(M + H^+)$; Found 426.8690.

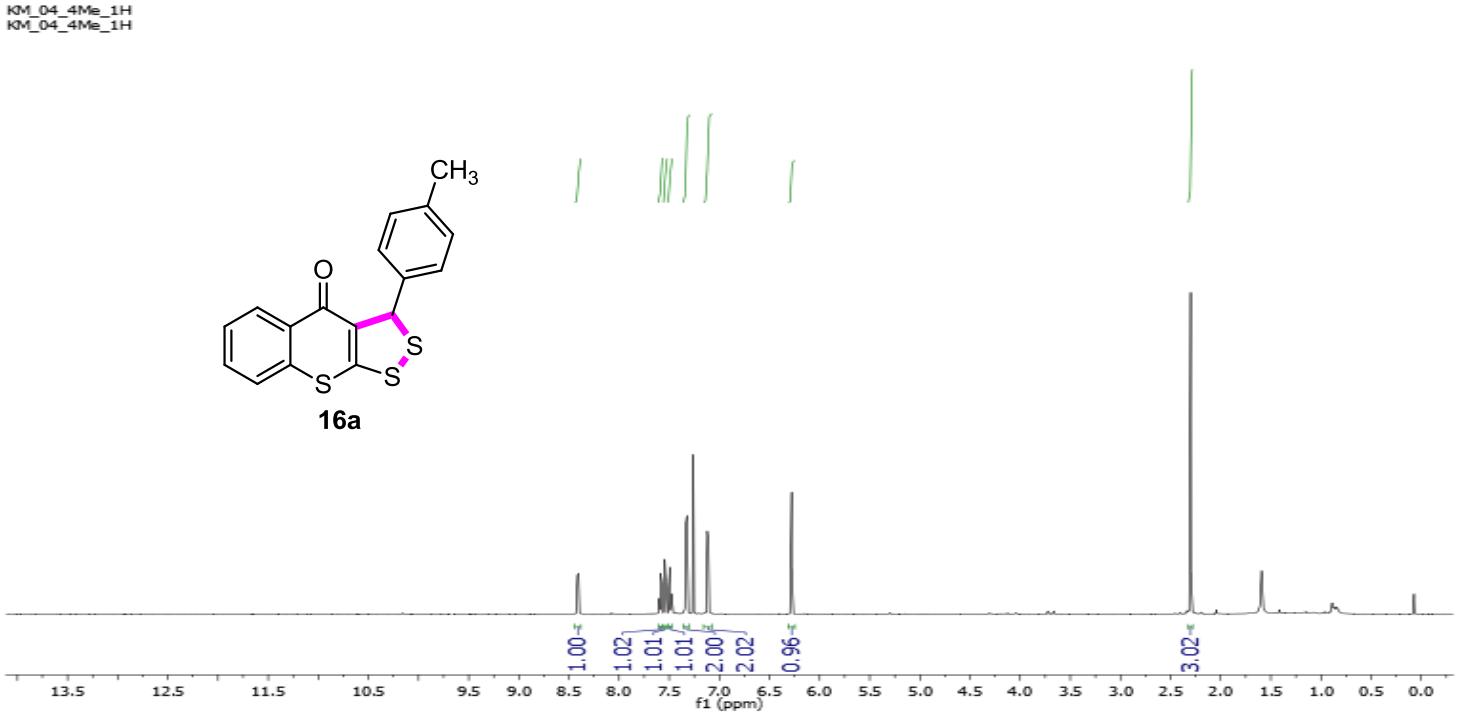


3-(3-bromophenyl)-7-chloro-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16m): Yellow solid (235 mg, 55% yield), Mp 235-236˚C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.20 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.45-7.47 (m, 1H), 7.55 (s, 1H), 7.59 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 61.4, 123.1, 125.3, 125.7, 128.9, 129.1, 129.9, 130.6, 130.9, 131.8, 133.9, 137.0, 138.9, 142.4, 154.0, 174.6; IR $(KBr)_{vmax}$ 1103, 1110, 1315, 1345, 1391, 1475, 1520, 1586, 1603, 1610, 2843, 2935, 3072 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_9BrClOS_3$ 426.8682 $(M + H^+)$; Found 426.8675.

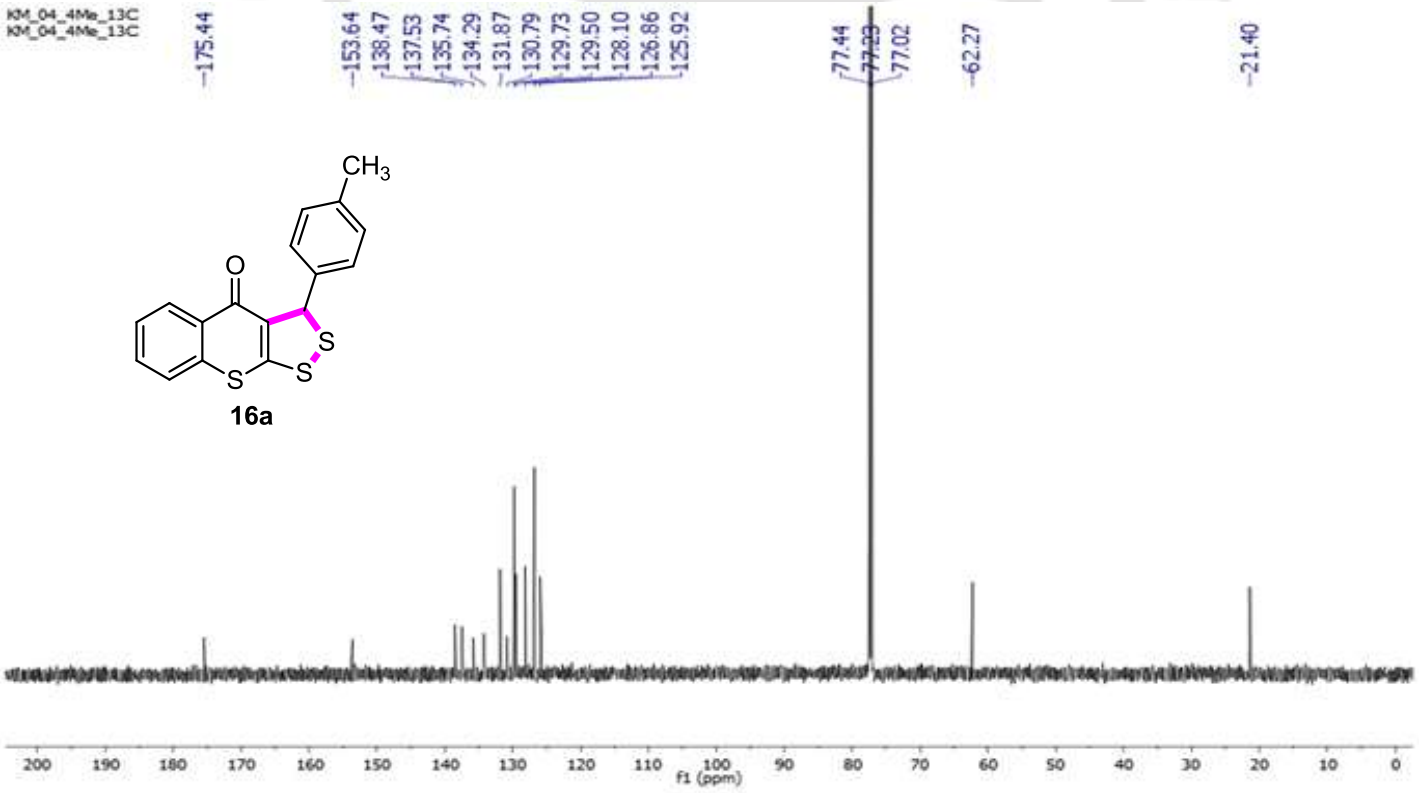


7-chloro-3-(2-fluorophenyl)-[1,2]dithiolo[3,4-*b*]thiochromen-4(3*H*)-one (16n): Yellow solid (238 mg, 65% yield), Mp 181-182˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.53 (s, 1H), 7.02-7.14 (m, 3H), 7.28 (s, 1H), 7.46 (d, *J* = 12.0 Hz, 1H), 7.57 (s, 1H), 8.33 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 54.4, 116.0, 116.2, 124.5, 125.3, 127.5, 128.9, 129.0, 130.2, 130.3, 132.8, 137.0, 138.9, 154.9, 158.7, 160.4, 174.5; IR $(KBr)_{vmax}$ 1103, 1198, 1261, 1300, 1345, 1378, 1435, 1478, 1500, 1535, 1591, 1596, 1619, 2828, 2932, 2960, 3062 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_9ClFOS_3$ 366.9483 (M + H^+); Found 366.9466.

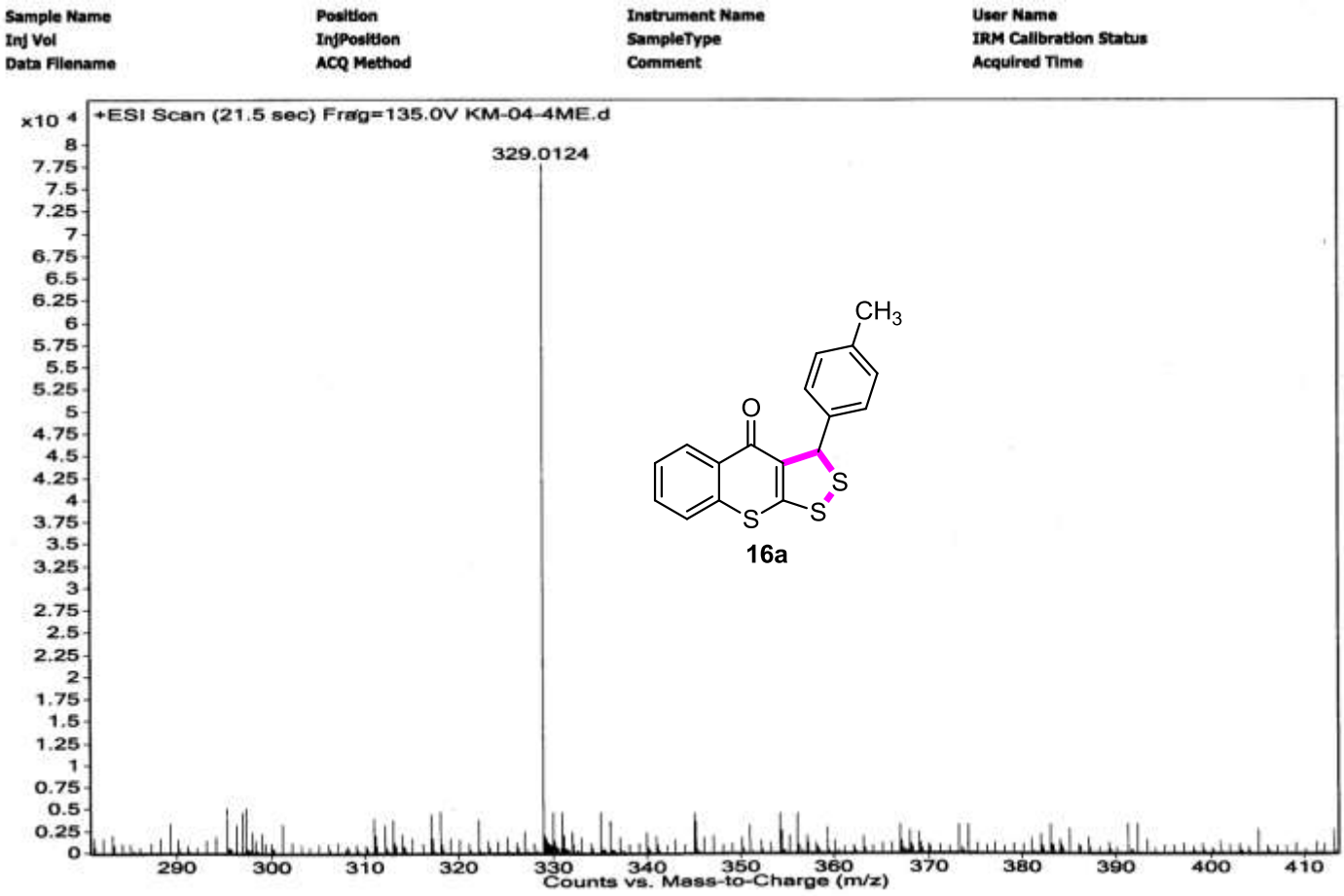
[1]HNMR: *3-(p-tolyl)-[1,2]dithiolo[3,4-b]thiochromen-4(3H)-one* ***(16a)***



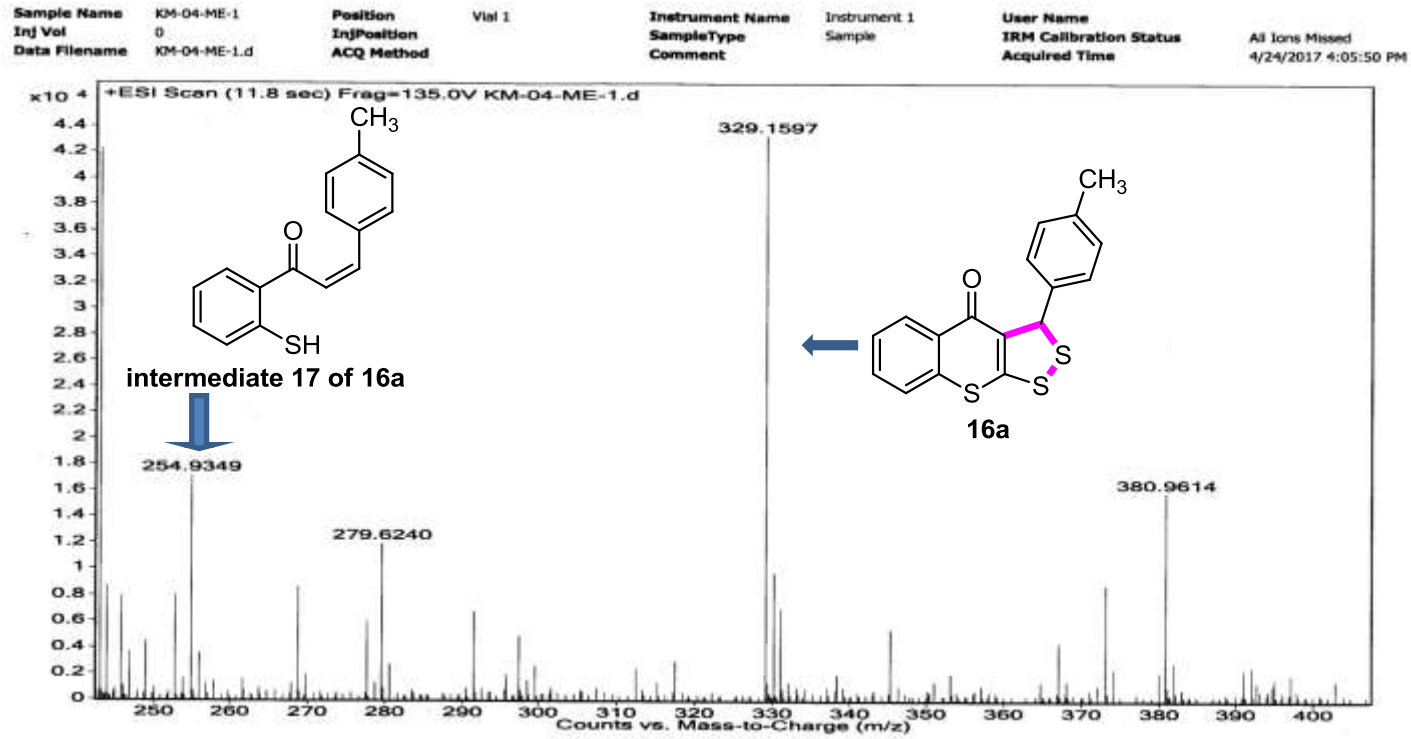
[13]CNMR: *3-(p-tolyl)-[1,2]dithiolo[3,4-b]thiochromen-4(3H)-one* ***(16a)***



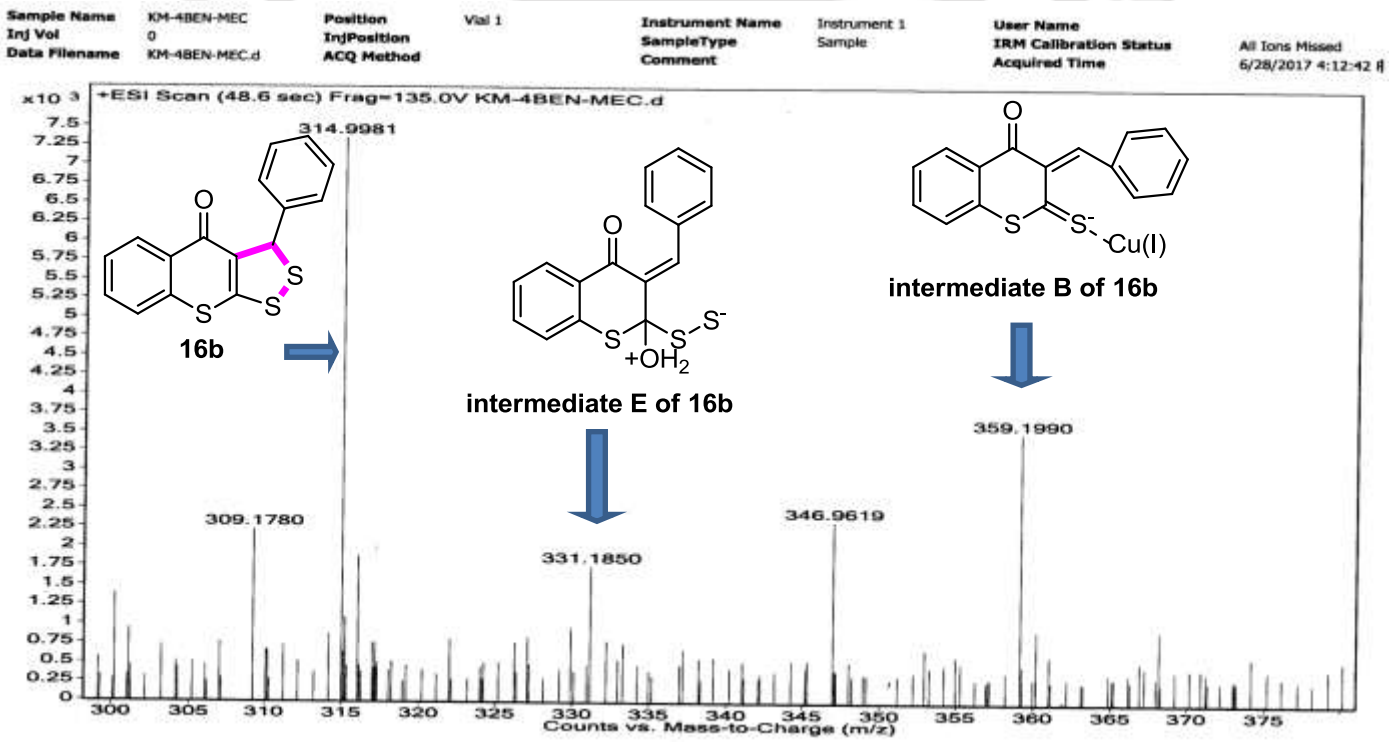
HRMS: *3-(p-tolyl)-[1,2]dithiolo[3,4-b]thiochromen-4(3H)-one* ***(16a)***



Mass analysis of crude mixture of the compound 16a



Mass analysis of crude mixture of the compound 16b



Chapter VI

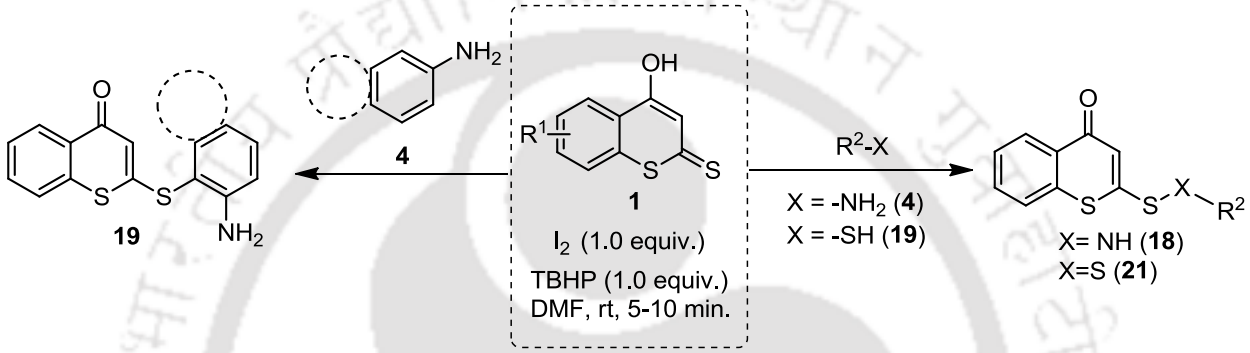
Metal free I_2/TBHP induced construction of S-N/ S-C/ S-N bond by coupling of 4-hydroxydithiocoumarin and amines/thiols

Result & Discussion

Experimental Section

Results and Discussion

The importance, synthetic utility and some of the recent strategies for the synthesis of sulfenamides, disulfides and sulfane have already been discussed in previous Chapter 1. In continuation of our endeavour to explore the application of 4-hydroxydithiocoumarin for the synthesis of new organosulfur compounds, in this chapter we present metal-free I_2/TBHP induced, atom-economic, and operationally simple method for direct S-N, S-C and S-S bond formation from the coupling of 4-hydroxydithiocoumarin and amines/thiols as shown in Scheme 51.



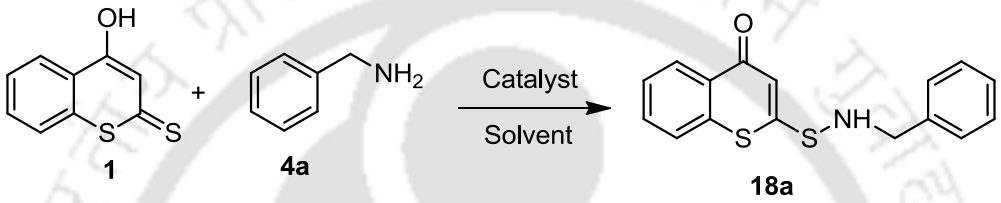
Scheme 51. Formation of S-N, S-S and S-C bond from the 4-hydroxydithiocoumarin using I_2/TBHP

Recently, there are cumulative demands in metal-free transformations as trace-metal impurities might be eluded in the target molecules.[23] In recent years, molecular iodine has received considerable atten*tion since it is a nontoxic, inexpensive and environmentally benign reagent effecting various organic transformations.[24]

Initially the reaction was performed with 4-hydroxydithiocoumarin (1.0 mmol) and 4-methyl benzylamine (1.0 mmol) in DMF solvent at room temperature as the model substrates to find the suitable reaction conditions, and the results are summarized in Table 13. It was seen that merely the use of the reactants in DMF solvent failed to initiate any reaction (Table 13, entry 1). Unfortunately, performing the same reaction in the presence of 0.3 equiv. of iodine and 1 equiv aq. TBHP we failed to obtain any desired product (Table 13, entry 2). Increasing the amount of iodine to 0.5 equiv, the anticipated product **18a** was isolated in 50% yield after 30 min (Table 13, entry 3). To improve the reaction efficiency, amount of iodine was further increased to 1 equiv. and to our delight the product **18a** was obtained in 95% within 5 min whereas increasing the iodine amount further had no apparent positive effect on the yield

(Table 13, entries 5-6). Change of other solvents such as DMSO, CH_3CN, EtOH, MeOH, DCE, and THF or to aqueous medium had a negative influence on the yield of the product (Table 13, entries 7-13). It was also noted that the transformation failed to proceed exclusively in presence of iodine or TBHP alone (Table 13, entries 14-15). Thus, the optimum reaction conditions for the synthesis of 2-((benzylamino)thio)-4*H*-thiochromen-4-one is achieved by employing 4-hydroxydithiocoumarin **1** (0.5 mmol) and 4-methyl benzylamine **4a** (0.5 mmol) in the presence of 1 equiv. each of iodine and aq. TBHP in 1 ml of DMF at room temperature.

Table 13. Optimization of the reaction conditions[a,b]

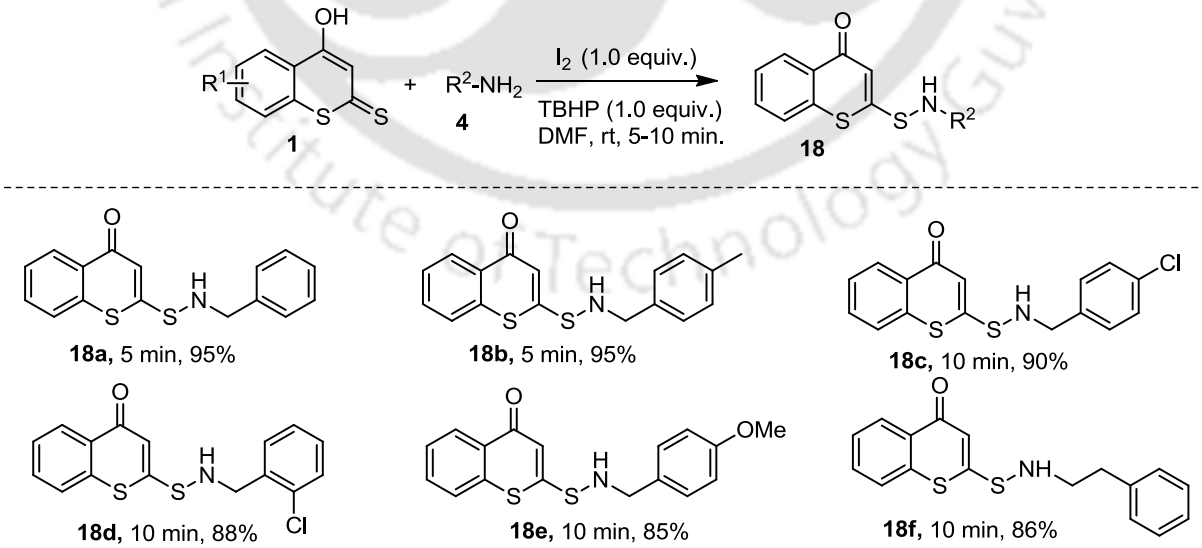


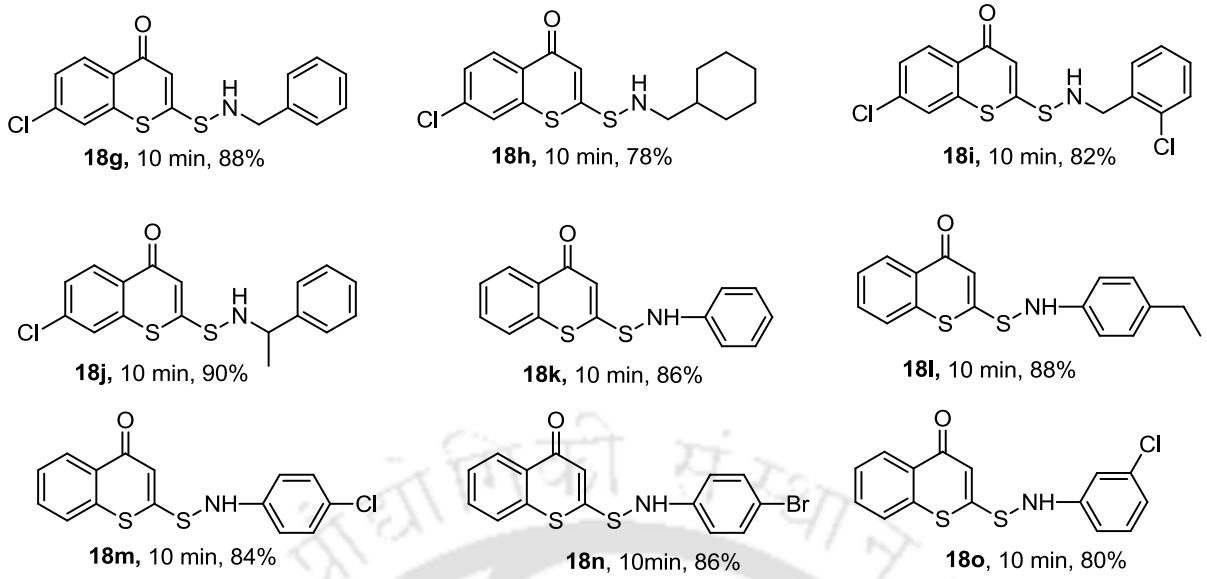
Entry	I_2 (equiv.)	aq. TBHP (equiv.)	Solvent	Time/min	Yield (%)[b]
01	-	-	DMF	24 hrs	NR
02	0.3	1	DMF	2.0 hrs	NR
03	0.5	1	DMF	30	50
04	**1**	**1**	**DMF**	**05**	**95**
05	1.5	1	DMF	15	90
06	2	2	DMF	20	85
07	1	1	DMSO	40	81
08	1	1	CH_3CN	50	70
09	1	1	EtOH	50	68
10	1	1	MeOH	60	65
11	1	1	DCE	40	72
12	1	1	H_2O	8.0 hrs	20
13	1	1	THF	6.0 hrs	40
14	1	-	DMF	24 hrs	NR
15	-	1	DMF	24 hrs	NR

[a]All the reactions were carried out using 4-hydroxydithiocoumarin **1** (1.0 mmol), amines **4** (1.0 mmol) in 1ml of solvent at room temperature. [b]Isolated yield.

With the above optimized reaction conditions in hand, we commenced to explore the scope of the reaction, and the results are summarized in the Table 14. As it can be seen clearly from table 13, all of the heterocoupling reactions proceeded smoothly to the give corresponding products **18** in excellent yields within a short span of time. The reactions were well tolerated for benzylamines having electron-donating group (4-Me) to electron withdrawing group on the aromatic ring (4-Cl, 2-Cl) to give the desired product **18b-d** in 88-95% yield. The reaction was also compatible with 4-OMe benzyl amine to give the product **18e** in 85% yield. With ethyl benzyl amine it resulted in the isolation of the products **18f** in 86% yield. The reaction of 4-hydroxydithiocoumarin having 6-chloro substituent on the fused ring with worked well under similar reaction conditions as it reacted with different benzyl amines, cyclohexyl amine and ethyl benzyl amine to afford the desired product **18g-j** in good yields. Moving on next to the reaction of 4- hydroxydithiocoumarin **1** with aniline, it leads to the isolation of the product **18m** in the 86% yield. It was observed that the reaction holds good for both electron-donating groups (4-Me) as well as electron-withdrawing (4-Cl, 4 Br, -3Cl) on the aromatic ring of the anilines giving the products **18l-o** in 80-88% yields. All the products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and HRMS. Moreover, the structure of the compound **18m** was also confirmed by single-crystal X-ray crystallographic data (Figure 14, I).

Table 14. Synthesis of 2-((benzylamino)thio)-4*H*-thiochromen-4-one derivatives using I_2/TBHP[a,b]

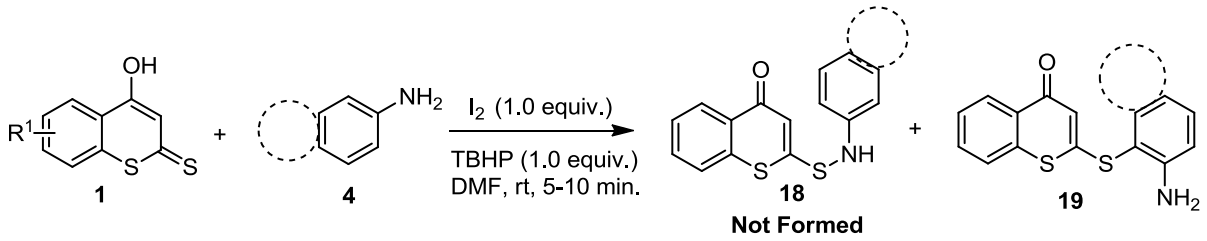


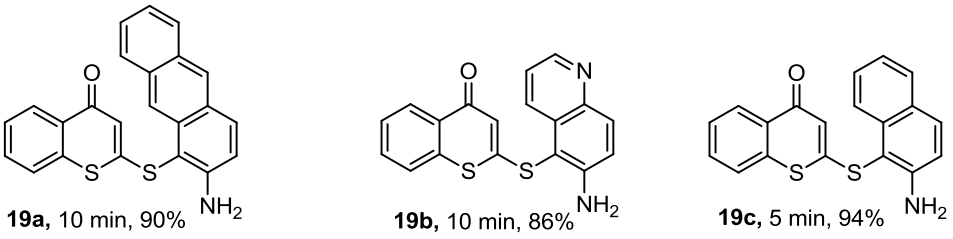


[a]All the reactions were carried out using various 4-hydroxydithiocoumarin (1.0 mmol), amines (1.0 mmol) in DMF (1 mL). [b]Isolated yield.

Interestingly, when we treated 4-hydroxydithiocoumarin with 2-aminoanthracene under the same reaction condition no sulfenamides were obtained but after chromatographic purification a yellow coloured solid product **19a** was isolated in 90% yield which showed discrepancy with spectroscopic analysis of the previous compounds i.e. **18**. The IR spectrum showed two characteristic strong absorptions at 3302 and 3461 cm^{-1} which gives a hint of the occurrence of free $–NH_2$ group, ^{1}HNMR pattern shows the presence of a single at δ 4.97 for two protons. These observations indicates that the final product so obtained was unprecedented 2-((3-aminoanthracen-2-yl)thio)-4*H*-thiochromen-4-one which shows the formation of S–C bond rather than anticipated S-N bond. Likewise 6-aminoanthraquinoline and 2-naphthylamine gave rise to the product **19b** and **19c** in 86 and 94% yield (Table 15). All the products **19** were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and HRMS. Moreover the structure of **19a** was also confirmed through single-crystal X-ray crystallographic data (Figure 14, II). Thus this protocol also gave a route to an efficient, economical, and practical method for direct arylthiation as well.

Table 15. Synthesis of 2-((2-aminophenyl)thio)-4*H*-thiochromen-4-one derivatives[a,b]

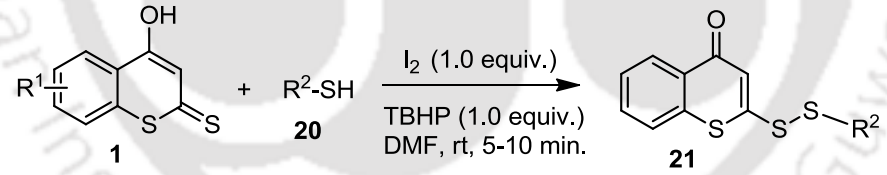


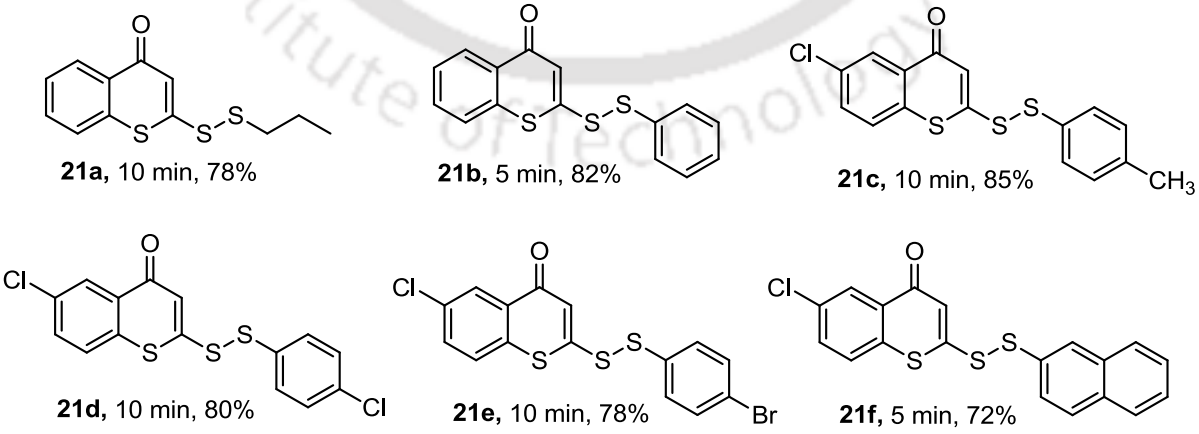


[a]All the reactions were carried out using 4-hydroxydithiocoumarin (1.0 mmol), amines (1.0 mmol) in DMF (1 mL). [b]Isolated yield.

Enthused with the success of the above transformation, we further explored the generality of the protocol with various thiols and the results are summarized in the Table 16. 4-hydroxydithiocoumarin **1** reacted smoothly with aliphatic thiol i.e, propanethiol leading to the isolation of the product **21a** in 78% yield whereas the reaction with thiophenol led to the formation of the product **21b** in 82 % yield. The reaction was well tolerated for substituted 4-hydroxydithiocoumarin having 7-Cl on the ring as it reacted with various aromatic thiols having 4-Me, 4-Cl, 4-Br substituent on the ring to give the anticipated product **21c**-**e** in good yields and also the reaction is feasible for 2-naphthylthiol as well. It is worth mentioning that the reaction gives only the desired unsymmetrical disulfides as the sole product. All the products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and HRMS.

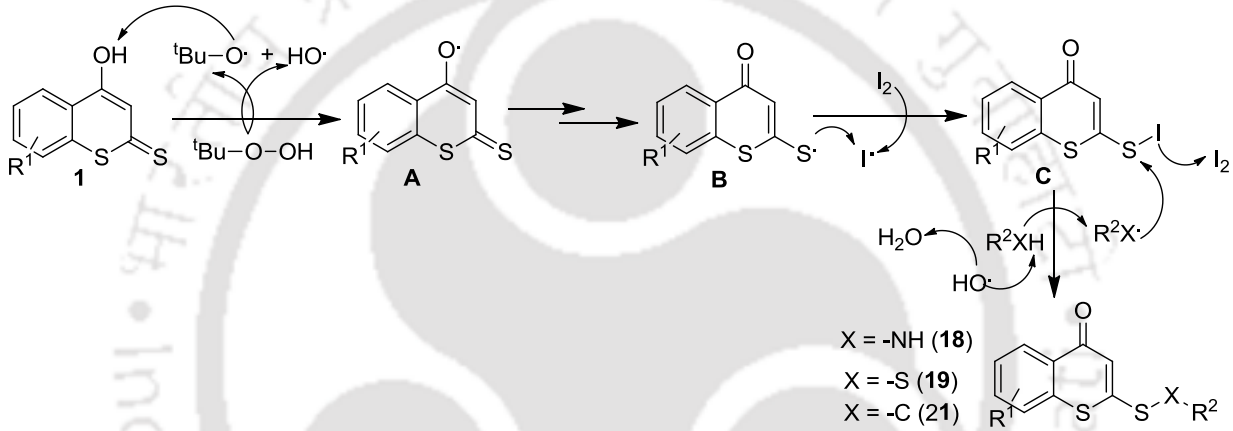
Table 16. Synthesis of 2-(phenyldisulfanyl)-4*H*-thiochromen-4-one derivatives[a,b]





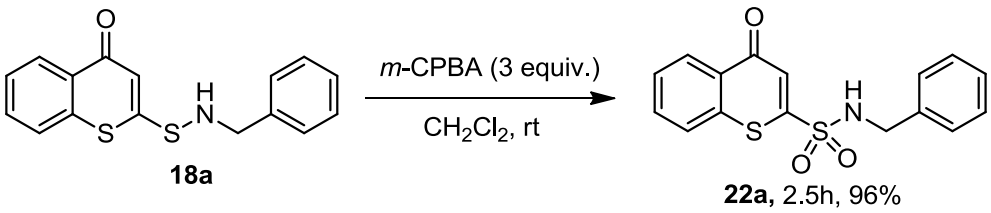
[a]All the reactions were carried out using various 4-hydroxydithiocoumarin (1.0 mmol), thiols (1.0 mmol) in DMF (1 mL). [b]Isolated yield

A plausible mechanism can be drawn for the formation of product **18, 19** and **21** as shown in Scheme 52. Initially, TBHP undergoes cleavage to generate tert butoxyl radical and hydroxyl radical. This tert butoxyl radical abstracts proton from 4-hydroxydithiocoumarin **1** to generate a radical species A which quickly rearranges to B. Now this radical B forces I_2 to undergo homolytic cleavage to form C. In the mean-time the hydroxyl radical abstracts a proton from R^2XH to a form a radical species $R^2X^{\cdot}$ which undergoes reaction with C along with the liberation of iodine to finally give the product **18**, **19** and **21**. S-N vs S-C bond formation depends upon the amine reactivity. The conjugated amines have more reactivity at α position which leads to the formation of S-C bond rather than S-N bond. 1-naphthylamine failed to take part in the reaction.



Scheme 52. Proposed reaction mechanism for the formation of 2-((benzylamino)thio)-4*H*-thiochromen-4-one, 2-((2-aminophenyl)thio)-4*H*-thiochromen-4-one and 2-(phenyldisulfanyl)-4*H*-thiochromen-4-one derivatives

In addition, the product **18** served as a useful building block for further functionalization. The product **18a** was oxidized to its corresponding sulfonamide **22a** on treating it with m-CPBA[25] as shown in the Scheme 53.



Scheme 53. Oxidation of 2-((benzylamino)thio)-4*H*-thiochromen-4-one derivatives to N-benzyl-4-oxo-4*H*-thiochromene-2-sulfonamide

Sulfonamides are a diverse group of compounds of considerable medical importance.[26] Sulfonamides also known as sulfa are well renowned in literature for their incredible antibacterial activity.[27] The product **22a** was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, HRMS and also was confirmed by single-crystal X-ray crystallographic data (Figure 14, III).

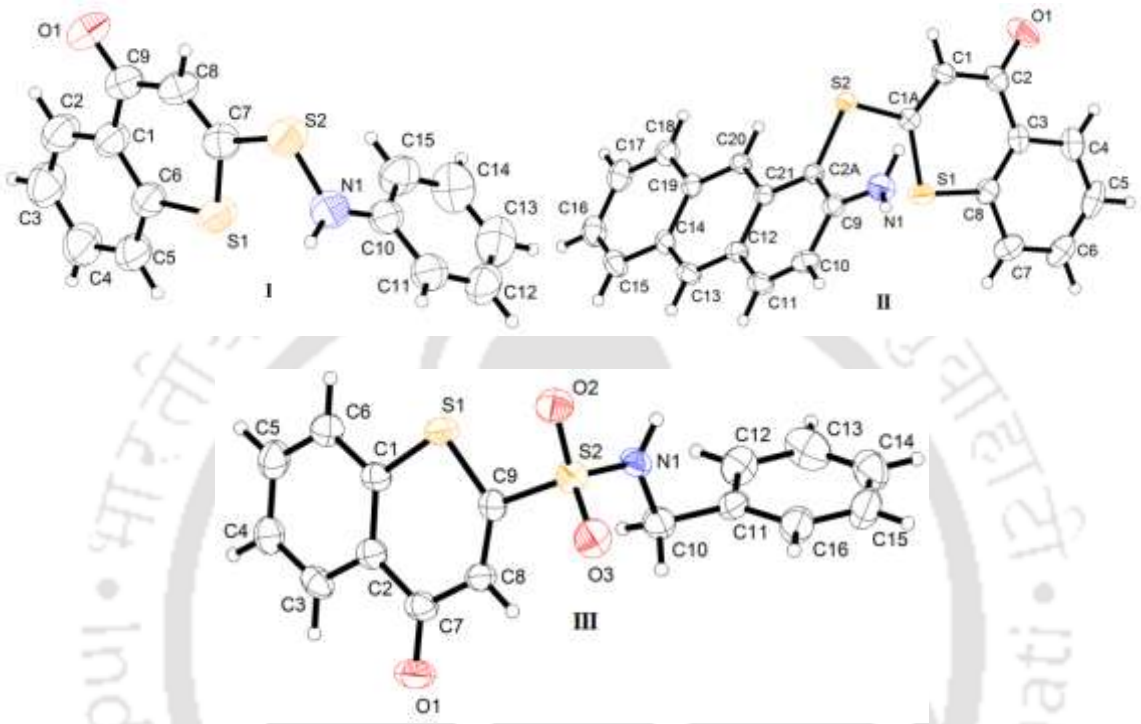


Figure 14. Ortep view of **18k** (I), **19a** (II) and **22a** (III)

Further, to study biological implication of the synthesized compounds, the effect of the compounds on viability of breast cancer cell line MCF7 was determined. A total of 6 different compounds **18k**, **19b**, **19c**, **21c**, **21e** and **22a** were selected to determine their activity on MCF7 cells. MCF7 cells were treated with various concentrations of **18k** (3-22 μM), **19b** (6-45 μM), **19c** (3-48 μM), **21c** (1.4-56 μM), **21e** (1.4-56 μM) and **22a** (3-22 μM) for 48 hrs. Compounds **18k**, **22a**, **21c** and **21e** exhibited dose dependent inhibition of cell viability as evaluated by MTT based assay. Treatment with compounds **19b** and **19c** lead to slight reduction in viability of the cells, however there was no dose dependent reduction and IC_{50} was not achieved. The IC_{50} value of the compounds is in listed in Table 17. Assessment of Cell viability by MTT assay of compounds **18k**, **19b**, **19c**, **22a**, **22e** and **21c** on MCF7 cells upon treatment for 48 hrs are shown in figure 15.

Table 17. Anti-proliferative activity of compounds against breast cancer cell line MCF7

Sl. No	Compound	IC_{50} (µM)
1	**18k**	35
2	**19b**	Not Attained
3	**19c**	Not Attained
4	**21c**	11.2
5	**21e**	20
6	**22a**	10

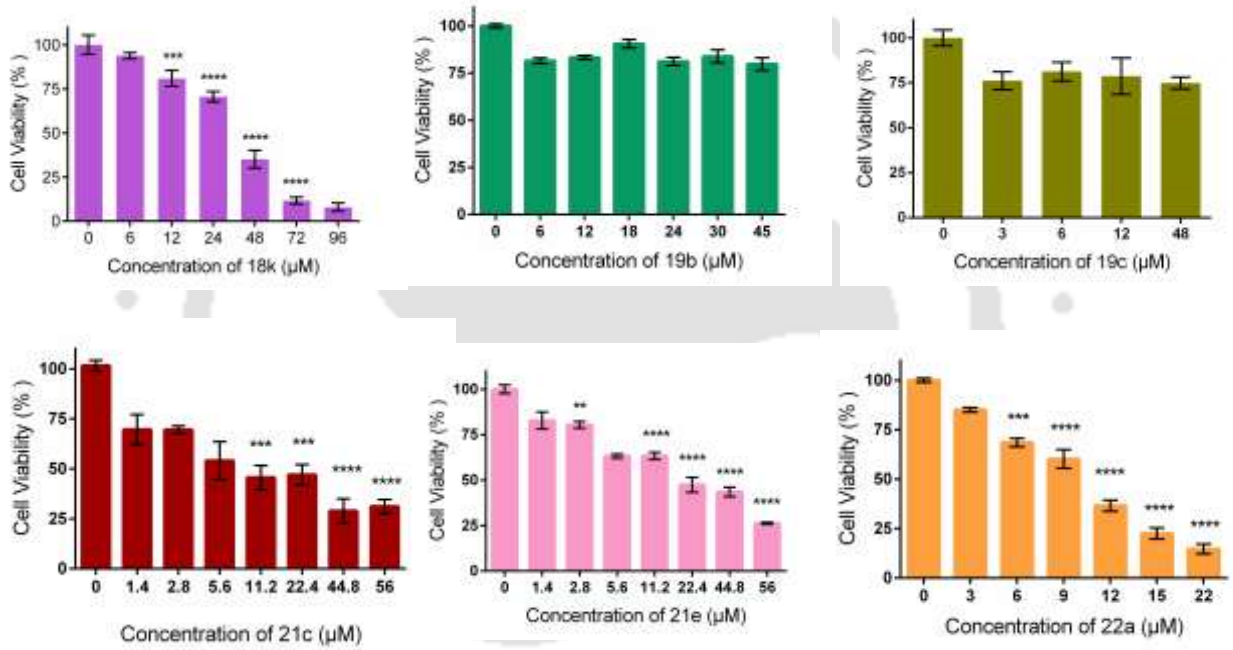


Figure 15. Assessment of Cell viability by MTT assay of compounds **18k**, **19b**, **19c**, **21c**, **21e** and **22a** on MCF7 cells upon treatment for 48 hrs.

The significant anti-proliferative activity of the four compounds namely **18k**, **21c**, **22e** and **22a** provides a strong foundation for future studies and experiments for their potential biomedical applications. Statistical analysis was performed by ANOVA using Graphpad Prism software with statistical significance denoted by *(p<0.5), **(p<0,01), ***(p<0.001) and ****(p<0.0001).

Conclusion

In conclusion, an unprecedented, versatile iodine-TBHP catalysed synthesis of some novel S-N/S-C/ S-S bonds has been uncovered. This catalyst system was found to be very effective

and compatible with a wide range of amines/thiols. In addition the product **18a** was oxidized to its corresponding sulfone. Nontoxic metal-free reaction conditions, broad substrate scope, good functional group tolerance and significant anti-proliferative activity of the four compounds namely **18k**, **21c**, **22e** and **22a** makes this approach highly viable for future applications. To the best of our knowledge these sulfenamides, sulfanes and di-sulfides are reported for the first time in the literature from 4-hydroxydithiocoumarin.

Experimental

General Procedure for the Synthesis of 2-((benzylamino)thio)-4*H*-thiochromen-4-one (18)

To a stirred solution of 4-hydroxydithiocoumarin (1.0 equiv, **1**) and amine (1.0 equiv, **4**) in DMF (1 mL) at room temperature was added 1.0 equiv. of I_2 along with 1.0 equiv. of aq. TBHP. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC analysis. The completion of the reaction (marked by the disappearance of starting material and formation of new spot) was observed by TLC of ethyl acetate and hexane (1:10). After completion of the reaction, I_2 was quenched with a saturated aqueous solution of $Na_2S_2O_3.6H_2O$ and followed by the extraction with ethyl acetate. The organic phase was separated, dried over anhydrous Na_2SO_4, and evaporated to give a crude residue. It was purified by the silica gel column chromatography using hexane and ethyl acetate as eluent to give the desired product **18**.

General Procedure for the Synthesis of 2-((2-aminophenyl)thio)-4*H*-thiochromen-4-one derivatives (19)

In a dried 25 mL round-bottomed flask a mixture of 4-hydroxydithiocoumarin (1.0 equiv, **1**) and conjugated-amine (1.0 equiv, **4**) was taken in DMF (1 mL). Then, 1.0 equiv of I_2 along with aq. TBHP was added into it and the reaction mixture was kept for stirring at room temperature. The progress of the reaction was supervised through TLC time to time. After completion of the reaction, I_2 was quenched with a saturated aqueous solution of $Na_2S_2O_3.6H_2O$ and was extracted with ethylacetate. The organic phase was separated, dried over anhydrous Na_2SO_4, and was concentrated in vacuo. The desired products (**19a-c**) were obtained in 86-94% yield after purification through column chromatography using ethylacetate/hexane as eluent.

General Procedure for the Synthesis of 2-(phenyldisulfanyl)-4*H*-thiochromen-4-one derivatives (21)

In a dried 25 mL round-bottomed flask a mixture of 4-hydroxydithiocoumarin (1.0 equiv, **1**) and requisite thiol (1.0 equiv, **20**) was taken in DMF (1 mL) as solvent. Then, 1.0 equiv of I_2 along with aq. TBHP was added to it and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, I_2 was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and was extracted with ethylacetate. The organic phase was separated, dried over anhydrous Na_2SO_4,

and evaporated to give a crude residue. It was purified by the silica gel column chromatography using hexane and ethyl acetate as eluent to give the desired product **21**.

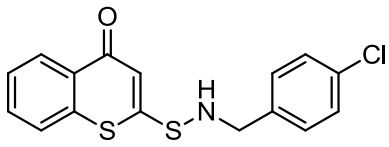
General Procedure for the Synthesis of N-benzyl-4-oxo-4*H*-thiochromene-2-sulfonamides (22a)

This reaction was conducted maintaining the procedure mentioned in the following paper, Dar, Ajaz A.; Enjamuri, N.; Shadab, M; Ali, N; Khan, A.T. *ACS Comb. Sci*. **2015**, *17*, 671. To a stirred solution of (0.5 mmol, **18a**) in 3 mL of dichloromethane at ice-bath temperature was added m-chloroperoxybenzoic acid (m-CPBA, 1.5 mmol) in portion for a period of 15 min and stirred for another 45 min at the same temperature. Next, the reaction mixture was brought to room temperature slowly and it was stirred for additional 2 h. After completion of reaction 5% aqueous $NaHCO_3$ solution was added and extracted with dichloromethane. Finally, the organic layer was dried over anhydrous Na_2SO4 and was concentrated in a rotary evaporator. The desired product **22a** was obtained after recrystallization from methanol.

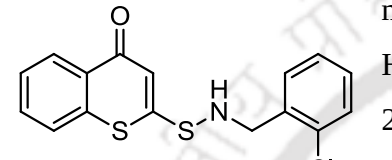
2-((benzylamino)thio)-4*H*-thiochromen-4-one (18a): Yellow semi-solid (284 mg, 95% yield), ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.32-3.34 (m, 1H), 4.19 (d, *J* = 6.0 Hz, 2H), 6.87 (s, 1H), 7.30-7.34 (m, 1H), 7.37-7.39 (m, 4H), 7.49-7.51 (m, 1H), 7.54-7.58 (m, 2H), 8.46 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 57.0, 116.4, 126.4, 127.8, 128.2, 128.5, 128.6, 128.9, 129.1, 131.2, 131.3, 137.6, 138.4, 162.8, 178.7; IR $(KBr)_{vmax}$ 1120, 1145, 1267, 1320, 1325, 1450, 1459, 1514, 1579, 2856, 2928, 2969, 3012, 3069, 3321 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{14}NOS_2$ 300.0512 ($M + H^+$); Found 300.0509.

2-(((4-methylbenzyl)amino)thio)-4*H*-thiochromen-4-one (18b): Yellow solid (297 mg, 95% yield), Mp 80-81˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.37 (t, *J* = 6.0 Hz, 1H), 4.10 (d, *J* = 6.0 Hz, 2H), 6.81 (s, 1H), 7.12 (d, *J* = 6.0 Hz, 2H), 7.20-7.22 (m, 2H), 7.43-7.46 (m, 1H), 7.50-7.52 (m, 2H), 8.41 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.3, 56.7, 116.3, 126.3, 126.3, 127.8, 128.4, 128.8, 129.6, 131.1, 131.3, 135.4, 137.6, 137.9, 162.9, 178.6; IR $(KBr)_{vmax}$ 1131, 1166, 1237, 1317, 1338, 1436, 1458, 1514, 1586, 2853, 2923, 2967, 3012, 3050, 3356 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{16}NOS_2$ 314.0668 ($M + H^+$); Found 314.0675.

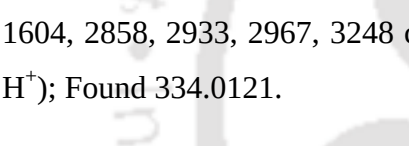
2-(((4-chlorobenzyl)amino)thio)-4*H*-thiochromen-4-one (18c): Yellow solid (300 mg, 90% yield), Mp 70-71˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.37-3.38 (m, 1H), 4.16 (d, *J* = 6.0 Hz, 2H), 6.86 (s, 1H), 7.29-7.30 (m, 2H), 7.32-7.34 (m, 2H), 7.49-7.52 (m, 1H), 7.56-7.57 (m, 2H), 8.45 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 56.1, 116.6, 126.4, 127.9, 128.9, 129.1, 129.9, 131.1, 131.4, 136.8, 137.5, 162.2, 178.7; IR $(KBr)_{vmax}$ 1110, 1125, 1245, 1370, 1460, 1489, 1524, 1589, 2865, 2930, 2974, 3198 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{13}ClNOS_2$ 334.0122 (M + H^+); Found 334.0129.



2-(((2-chlorobenzyl)amino)thio)-4*H*-thiochromen-4-one (18d): Yellow semi-solid (293 mg, 88% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (t, *J* = 4.0 Hz, 1H), 4.28 (d, *J* = 4.0 Hz, 2H), 6.85 (s, 1H), 7.24-7.25 (m, 2H), 7.36-7.40 (m, 2H), 7.46-7.51 (m, 1H), 7.53-7.54 (m, 2H), 8.44 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.8, 115.4, 116.9, 126.8, 127.3, 127.7, 128.3, 128.7, 128.9, 129.2, 130.1, 130.2, 130.5, 131.0, 137.6, 162.9, 178.6; IR $(KBr)_{vmax}$ 1121, 1141, 1281, 1356, 1385, 1447, 1488, 1567, 1589, 1604, 2858, 2933, 2967, 3248 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{13}ClNOS_2$ 334.0122 (M + H^+); Found 334.0121.



2-(((4-methoxybenzyl)amino)thio)-4*H*-thiochromen-4-one (18e): Yellow semi-solid (280 mg, 85% yield), ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.26 (s, 1H), 3.80 (s, 3H), 4.11 (d, *J* = 6.0 Hz, 2H), 6.86 (s, 1H), 6.88 (s, 1H), 6.89 (s, 1H), 7.28 (d, *J* = 6.0 Hz, 1H), 7.48-7.51 (m, 1H), 7.54-7.57 (m, 2H), 8.46 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.5, 56.4, 114.3, 116.3, 126.4, 127.8, 128.8, 129.9, 130.5, 131.2, 131.3, 137.6, 159.6, 162.9, 178.7; IR $(KBr)_{vmax}$ 1101, 1176, 1249, 1323, 1339, 1383, 1436, 1460, 1512, 1587, 1609, 2854, 2925, 2959, 3050, 3212 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{16}NO_2S_2$ 330.0617 (M + H^+); Found 330.0615



2-((phenethylamino)thio)-4*H*-thiochromen-4-one (18f): Yellow semi-solid (269 mg, 86 % yield), ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.91 (t, *J* = 6.0 Hz, 2H), 2.95 (t, *J* = 6.0 Hz, 1H), 3.31-3.34 (m, 2H), 6.82 (s, 1H), 7.21-7.22 (m, 2H), 7.23-7.25 (m, 1H), 7.30-7.34 (m, 2H), 7.48-7.57 (m, 2H), 8.44-8.45 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.0, 36.9, 54.1, 116.0, 124.3, 126.4, 126.9, 127.6, 127.8, 128.6, 128.8, 128.9, 129.1, 129.2, 131.2, 132.5, 137.6, 138.5, 163.3, 178.6; IR $(KBr)_{vmax}$ 1165, 1333,

1403, 1455, 1503, 1610, 2870, 2930, 2955, 3246 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{16}NOS_2$ 314.0668 ($M + H^+$); Found 314.0670.

2-((benzylamino)thio)-7-chloro-4*H*-thiochromen-4-one (18g):Yellow semi-solid (293 mg, 88% yield), ^1H NMR (600 MHz, $CDCl_3$): δ 3.26 (t, *J* = 6.0 Hz, 1H), 4.20 (d, *J* = 6.0 Hz, 1H), 6.84 (s, 1H), 7.32-7.35 (m, 1H), 7.36-7.40 (m, 4H), 7.44-7.46 (m, 1H), 7.58 (s, 1H), 8.39 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 57.1, 114.3, 116.4, 125.8, 128.4, 128.5, 129.0, 129.6, 130.5, 138.0, 138.3, 138.9, 162.9, 177.8; IR $(KBr)_{vmax}$ 1120, 1167, 1398, 1325, 1459, 1586, 1598, 2856, 2928, 2969, 3221 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{13}ClNOS_2$ 334.0122 ($M + H^+$); Found 334.0119.

7-chloro-2-(((cyclohexylmethyl)amino)thio)-4*H*-thiochromen-4-one (18h): Yellow semi-solid (264 mg, 78% yield), ^1H NMR (600 MHz, $CDCl_3$): δ 1.13-1.31 (m, 7H), 1.60-1.63 (m, 1H), 1.75-1.78 (m, 2H), 2.04-2.06 (m, 2H), 2.79-2.83 (m, 1H), 2.88-2.89 (m, 1H), 6.83 (s, 1H), 7.42-7.44 (m, 1H), 7.56 (s, 1H), 8.37 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.0, 25.8, 33.7, 60.4, 115.6, 125.8, 128.3, 129.6, 130.4, 137.8, 139.1, 164.8, 177.8; IR $(KBr)_{vmax}$ 1153, 1348, 1475, 1589, 1609, 2845, 2952, 2974 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{19}ClNOS_2$ 340.0591 ($M + H^+$); Found 340.0598.

7-chloro-2-(((2-chlorobenzyl)amino)thio)-4*H*-thiochromen-4-one (18i): Yellow solid (300 mg, 82% yield), Mp 104-105˚C, ^1H NMR (600 MHz, $CDCl_3$): δ 3.54 (t, *J* = 6.0 Hz, 1H), 4.26 (d, *J* = 6.0 Hz, 2H), 6.79 (s, 1H), 7.24-7.25 (m, 2H), 7.35-7.38 (m, 2H), 7.40-7.42 (m, 1H), 7.51 (s, 1H), 8.34 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 54.9, 116.2, 125.7, 127.3, 128.4, 129.5, 129.8, 130.0, 130.4, 130.9, 134.1, 135.9, 137.9, 138.9, 162.9, 177.8; IR $(KBr)_{vmax}$ 1145, 1232, 1251, 1435, 1460, 1589, 1610, 2852, 2920, 2952, 3175 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{12}C_{l2}NOS_2$ 367.9792 ($M + H^+$); Found 367.9791.

7-chloro-2-(((1-phenylethyl)amino)thio)-4*H*-thiochromen-4-one (18j): Yellow semi-solid (312 mg, 90% yield), ^1H NMR (600 MHz, $CDCl_3$): δ 1.54 (d, *J* = 6.0 Hz, 3H), 3.47 (d, *J* = 6.0 Hz, 1H), 4.14-4.18 (m, 1H), 6.80 (s, 1H), 7.28-7.31 (m, 1H), 7.33-7.38 (m, 4H), 7.40-7.42 (m, 1H), 7.54 (s, 1H), 8.35 (d, *J* = 6.0 Hz, 1H);

^{13}C NMR (150 MHz, $CDCl_3$): δ 22.5, 61.0, 116.1, 125.7, 126.7, 126.8, 128.1, 128.3, 128.9, 129.4, 130.3, 137.8, 138.9, 143.4, 163.5, 177.7; IR $(KBr)_{vmax}$ 1108, 1231, 1282, 1347, 1354, 1487, 1530, 1571, 1589, 2873, 2954, 2965, 3235 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{15}ClNOS_2$ 348.0278 ($M + H^+$); Found 348.0279.

2-((phenylamino)thio)-4*H*-thiochromen-4-one (18k): Yellow solid (245 mg, 86% yield), Mp 190-191˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.37 (s, 1H), 6.93 (s,1H), 6.96-6.99 (m, 1H), 7.08 (d, *J* = 12.0 Hz, 1H), 7.27-7.30 (m, 2H), 7.47-7.55 (m, 4H), 8.46 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 115.3, 116.6, 122.1, 126.4, 128.0, 128.9, 129.7, 131.1, 131.5, 137.2, 145.2, 161.6, 178.7; IR $(KBr)_{vmax}$ 1103, 1132, 1174, 1225, 1284, 1336, 1384, 1419, 1437, 1494, 1518, 1557, 1583, 1597, 2853, 2922, 2959, 3184 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{12}NOS_2$ 286.0355 ($M + H^+$); Found 286.0356.

2-(((4-ethylphenyl)amino)thio)-4*H*-thiochromen-4-one (18l): Brown semi-solid (275 mg, 88% yield), ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.20 (t, *J* = 12.0 Hz, 3H), 2.57-2.61 (m, 2H), 5.20 (s, 1H), 6.92 (s, 1H), 7.00 (d, *J* = 12.0 Hz, 2H), 7.11 (d, *J* = 12.0 Hz, 2H), 7.48-7.51 (m, 2H), 7.52-7.55 (m, 1H), 8.45-8.47 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.9, 28.2, 114.3, 115.3, 116.4, 126.4, 127.9, 128.8, 128.9, 131.1, 131.4, 137.3, 138.1, 142.9, 162.2, 178.7; IR $(KBr)_{vmax}$ 1101, 1128, 1229, 1331, 1377, 1438, 1462, 1509, 1525, 1561, 1586, 1607, 2955, 2924, 2955, 3191 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{16}NOS_2$ 314.0668 ($M + H^+$); Found 314.0668.

2-(((4-chlorophenyl)amino)thio)-4*H*-thiochromen-4-one (18m): Brown solid (268 mg, 84% yield), Mp 70-71˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.59 (s, 1H), 6.90 (s, 1H), 7.00-7.02 (d, *J* = 12.0 Hz, 2H), 7.22 (d, *J* = 6.0 Hz, 1H), 7.47-7.5 (m, 2H), 7.53-7.56 (m, 1H), 8.45 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 116.5, 116.8, 126.4, 128.1, 128.9, 131.1, 129.6, 131.6, 137.0, 143.9, 160.7, 178.6; IR $(KBr)_{vmax}$ 1131, 1171, 1231, 1281, 1326, 1382, 1437, 1466, 1488, 1527, 1559, 1584, 1604, 2853, 2923, 2957, 3054, 3198 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{11}ClNOS_2$ 319.9965 ($M + H^+$); Found 319.9964.

2-(((4-bromophenyl)amino)thio)-4*H*-thiochromen-4-one (18n): Yellow solid (312 mg, 86% yield), Mp 105-106˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.71 (s, 1H), 6.90 (s, 1H), 6.96 (d, *J* = 12.0 Hz, 2H), 7.34 (d, *J* = 12.0 Hz, 2H), 7.46-7.54 (m, 3H), 8.45-8.46 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 114.3, 116.8, 116.9, 126.4, 128.1, 128.9, 131.1, 131.6, 132.5, 137.0, 144.4, 160.8, 178.7; IR $(KBr)_{vmax}$ 129, 1221, 12832, 1334, 1384, 1437, 1466, 1520, 1557, 1587, 2853, 2924, 2955, 3066, 3199 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{11}BrNOS_2$ 363.9460 ($M + H^+$); Found 363.9452.

2-(((3-chlorophenyl)amino)thio)-4*H*-thiochromen-4-one (18o): Yellow solid (255 mg, 80% yield), Mp 158-159˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.78 (s, 1H), 6.91 (s, 1H), 6.93-6.96 (m, 1H), 7.08 (s, 1H), 7.17 (t, *J* = 6.0 Hz, 1H), 7.47-7.55 (m, 3H), 8.45-8.47 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 113.5, 115.3, 116.7, 122.2, 126.4, 128.1, 128.9, 130.7, 131.1, 131.6, 135.5, 137.0, 146.6, 160.8, 178.7; IR $(KBr)_{vmax}$ 1129, 1221, 12832, 1334, 1384, 1437, 1466, 1520, 1557, 1587, 2853, 2924, 2955, 3066, 3199 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{11}ClNOS_2$ 319.9965 ($M + H^+$); Found 319.9959.

2-((2-aminoanthracen-1-yl)thio)-4*H*-thiochromen-4-one (19a): Yellow solid (346 mg, 90% yield), Mp 118-119˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.97 (s, 2H), 6.99 (s, 1H), 7.07 (d, *J* = 12.0 Hz, 1H), 7.29-7.31 (m, 1H), 7.38-7.46 (m, 4H), 7.94 (t, *J* = 6.0 Hz, 2H), 8.01 (d, *J* = 12.0 Hz, 1H), 8.33 (s, 1H), 8.40-8.42 (m, 1H), 8.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 119.1, 121.1, 121.7, 124.9, 125.9, 126.5, 127.8, 128.0, 128.2, 128.3, 128.9, 131.3, 134.5, 137.8, 149.8, 149.9, 155.4, 178.9; IR $(KBr)_{vmax}$ 1101, 1134, 1169, 1237, 1277, 1325, 1342, 1384, 1436, 1462, 1478, 1505, 1544, 1568, 1579, 1630, 2853, 2924, 3049, 3302, 3461 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{16}NOS_2$ 386.0668 ($M + H^+$); Found 386.0667.

2-((6-aminoquinolin-5-yl)thio)-4*H*-thiochromen-4-one (19b): Brown solid (289 mg, 86% yield), Mp 142-143˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.11 (s, 2H), 6.84 (s, 1H), 7.28 (s, 1H), 7.34-7.39 (m, 2H), 8.06 (d, *J* = 6.0 Hz, 1H), 8.29 (d, *J* = 6.0 Hz, 1H), 8.42 (d, *J* = 6.0 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 121.2, 121.8, 123.2, 125.9, 128.0,

128.9, 130.7, 131.6, 131.5, 132.3, 135.2, 137.7, 147.1, 150.2, 154.6, 178.9; IR $(KBr)_{vmax}$ 1245, 1370, 1520, 1590, 2845, 2930, 3025, 3325, 3482 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{12}ClN_2OS_2$ 337.0464 ($M + H^+$); Found 337.0461.

2-((2-aminonaphthalen-1-yl)thio)-4*H*-thiochromen-4-one (19c): Off-white solid (315 mg, 94% yield), Mp 145-146˚C, ^1H NMR (400 MHz, $CDCl_3$): δ 4.83 (s, 2H), 6.86-6.87 (m, 1H), 7.01-7.03 (m, 1H), 7.24-7.30 (m, 2H), 7.41-7.47 (m, 3H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 12.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.37-8.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 117.8, 121.3, 123.2, 123.4, 125.8, 127.8, 128.4, 128.6, 128.7, 128.8, 130.8, 131.3, 133.9, 136.6, 137.9, 149.9, 155.7, 178.9; IR $(KBr)_{vmax}$ 1102, 1127, 1210, 1328, 1384, 1403, 1428, 1469, 1512, 1554, 1581, 1605, 2855, 2923, 2954, 3054, 3374, 3468 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{14}NOS_2$ 336.0512 ($M + H^+$); Found 336.0516.

2-(propyldisulfanyl)-4*H*-thiochromen-4-one (21a): Yellow semi-solid (209 mg, 78% yield), ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 8.0 Hz, 3H), 1.70-1.79 (m, 2H), 2.38 (t, *J* = 8.0 Hz, 2H), 7.16 (s, 1H), 7.47-7.52 (m, 1H), 7.54-7.57 (m, 2H), 8.44 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 22.3, 41.9, 113.3, 122.3, 126.2, 127.9, 128.9, 131.6, 137.7, 178.9; IR $(KBr)_{vmax}$ 1123, 1225, 1261, 1324, 1379, 1423, 1451, 1464, 1551, 1574, 1590, 1618, 2853, 2923, 2957 cm^{-1}; HRMS (ESI) Calcd For $C_{12}H_{13}OS_3$ 269.0123 ($M + H^+$); Found 269.0125.

2-(phenyldisulfanyl)-4*H*-thiochromen-4-one (21b): Yellow semi-solid (247 mg, 82% yield), ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 7.20-7.33 (m, 3H), 7.38-7.48 (m, 5H), 8.36 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.7, 123.3, 126.2, 128.1, 128.8, 128.9, 129.4, 129.6, 130.8, 131.7, 178.8; IR $(KBr)_{vmax}$ 1136, 1189, 1268, 1289, 1369, 1384, 1400, 1468, 1510, 1538, 1572, 1610, 2850, 2967 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{11}OS_3$ 302.9967 ($M + H^+$); Found 302.9969.

6-chloro-2-(p-tolyldisulfanyl)-4*H*-thiochromen-4-one (21c): Yellow solid (298 mg, 85% yield), Mp 120-121˚C, ^1H NMR (600 MHz, $CDCl_3$): δ 2.34 (s, 3H), 7.15-7.17 (m, 3H), 7.46-7.47 (m, 2H), 7.50-7.51 (m, 1H), 7.53-7.55 (m, 1H), 8.42 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 123.0,

127.7, 128.6, 130.4, 130.5, 132.1, 134.7, 135.9, 139.7, 177.7; IR (KBr)$_{vmax}$ 1104, 1142, 1181, 1260, 1281, 1312, 1384, 1397, 1451, 1490, 1507, 1527, 1582, 1610, 2853, 2923, 2955, 3024, 3086 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{12}ClOS_3$ 350.9734 (M + H$^+$); Found 350.9733.

6-chloro-2-((4-chlorophenyl)disulfanyl)-4*H*-thiochromen-4-one (21d): Yellow solid (289 mg, 78% yield), Mp 101-102˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.49-7.57 (m, 4H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.6, 127.3, 128.2, 128.5, 128.3, 129.6, 130.2, 130.4, 131.8, 131.9, 134.9, 135.6, 154.7, 177.7; IR (KBr)$_{vmax}$ 1146, 1263, 1286, 1314, 1377, 1401, 1463, 1522, 1583, 1618, 2853, 2924, 2955 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_9Cl_2OS_3$ 370.9187 (M + H$^+$); Found 370.9190.

2-((4-bromophenyl)disulfanyl)-6-chloro-4*H*-thiochromen-4-one (21e): Yellow solid (324 mg, 78% yield), Mp 141-142˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.13 (s, 1H), 7.40-7.41 (m, 2H), 7.45-7.47 (m, 3H), 7.51-7.53 (m, 1H), 8.38 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.8, 123.2, 127.7, 128.5, 130.8, 131.6, 132.2, 132.7, 134.1, 134.7, 135.5, 154.6, 177.5; IR (KBr)$_{vmax}$ 1105, 1142, 1175, 1260, 1282, 1312, 1284, 1397, 1451, 1470, 1508, 1583, 1610, 1682, 1900, 2853, 2923, 2897, 3024, 3080 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_9BrClOS_3$ 414.8682 (M + H$^+$); Found 414.8684.

6-chloro-2-(naphthalen-2-yldisulfanyl)-4*H*-thiochromen-4-one (21f): Yellow semi-solid (278 mg, 72% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (s,1H), 7.40-7.53 (m, 4H), 7.60-7.66 (m, 1H), 7.78-7.84 (m, 3H), 8.03-8.04 (m, 1H), 8.41 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.3, 122.8, 126.3, 127.2, 127.3, 127.7, 127.9, 127.9, 128.1, 128.6, 128.7, 129.8, 132.1, 133.5, 134.7, 135.8, 155.5, 177.7; IR (KBr)$_{vmax}$ 1108, 1235, 1260, 1320, 1380, 1445, 1532, 1575, 1610, 2843, 2935, 2965 cm^{-1}; HRMS (ESI) Calcd For 386.9734 (M + H$^+$); Found 386.9733.

N-benzyl-4-oxo-4*H*-thiochromene-2-sulfonamide (22a): White solid (318 mg, 96% yield), Mp 175-176˚C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.05 (d, *J* = 6.0 Hz, 2H), 6.96-6.98 (m, 1H), 7.03 (d, *J* = 6.0 Hz, 2H), 7.09-7.11 (m, 2H), 7.23-7.24 (m, 1H), 7.40 (t, *J* = 6.0 Hz, 1H), 7.47-7.52

(m, 2H), 8.24 (d, *J* = 12.0 Hz, 1H), 8.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.3, 125.6, 127.1, 127.6, 127.8, 128.2, 128.3, 128.4, 132.3, 136.2, 153.6, 180.0; IR $(KBr)_{vmax}$ 1120, 1145, 1267, 1320, 1325, 1450, 1459, 1514, 1579, 1616, 2875, 2935, 2968, 3257 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{14}NO_3S_2$ 332.0410 $(M + H^+)$; Found 332.0419.

Materials

Dulbecco's Modified Eagle's medium (DMEM) from Sigma-Aldrich, Fetal Bovine Serum (FBS) from Gibco ThermoFisher Scientific, (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium bromide) (MTT) from Himedia, Tissue culture dishes from Eppendorf, MCF7 cell line was procured from National Centre for Cell Science (NCCS), Pune, India.

Method

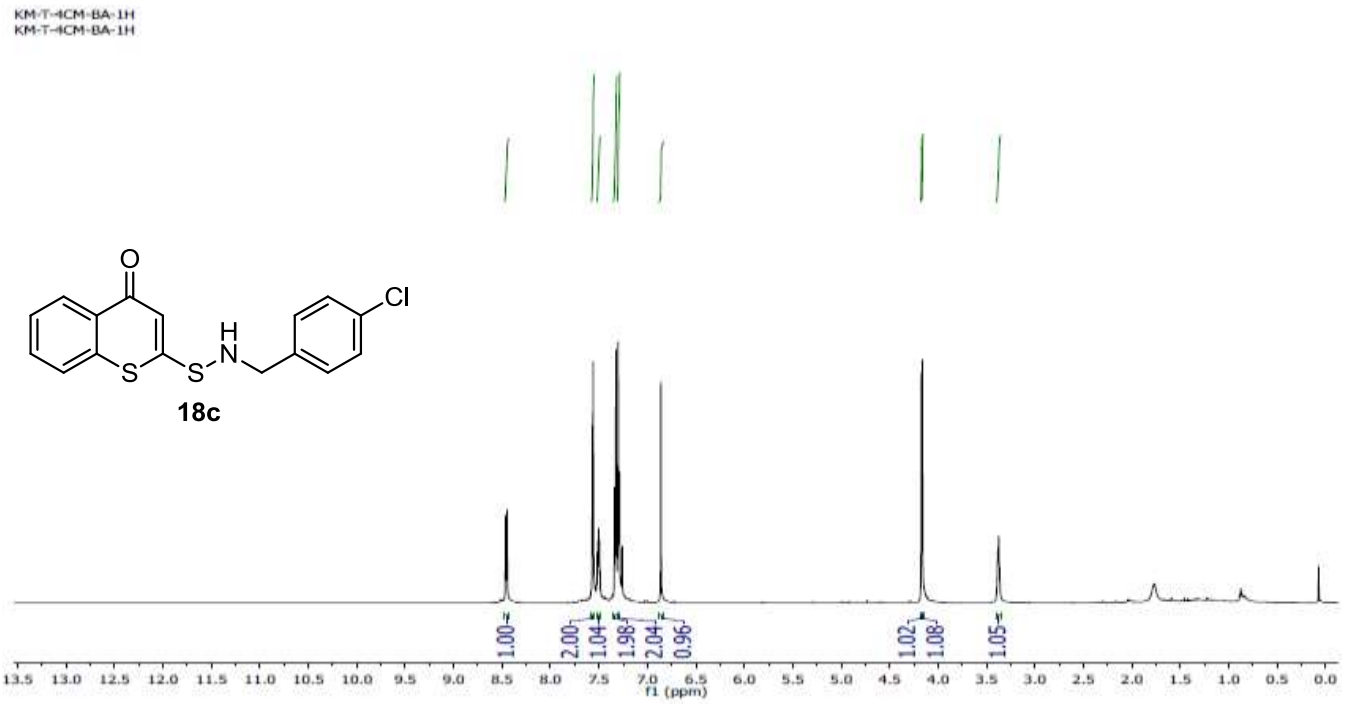
Cell Viability Assay

Breast cancer cell line MCF7 seeded in 96 well plates at a density of 7000 cells per well in DMEM media supplemented with 10% FBS was allowed to attach overnight in CO_2 incubator maintained at 37˚C supplied with 5% CO_2. Following attachment, media was discarded and fresh serum media containing varying concentrations of the compounds were added to the seeded cells. After 48 h incubation, serum media containing 5 µl of 5 mg/ml MTT solution was added to each well and the plates were incubated in the CO_2 incubator. MTT is converted to purple formazan crystals by dehydrogenase enzyme in the mitochondria of the viable cells. Subsequently, the media was discarded and DMSO was added to dissolve the formazan crystals formed by enzymatic conversion by the live cells. The product was measured by absorbance at 570 nm along with background measurement at 690 nm using multiplate reader (Tecan, Infinite M200PRO). The experiment was also performed with DMSO as control to eliminate any possibility of its effect in cell viability. Cell viability (%) relative to the control untreated cells was calculated using the following formula:

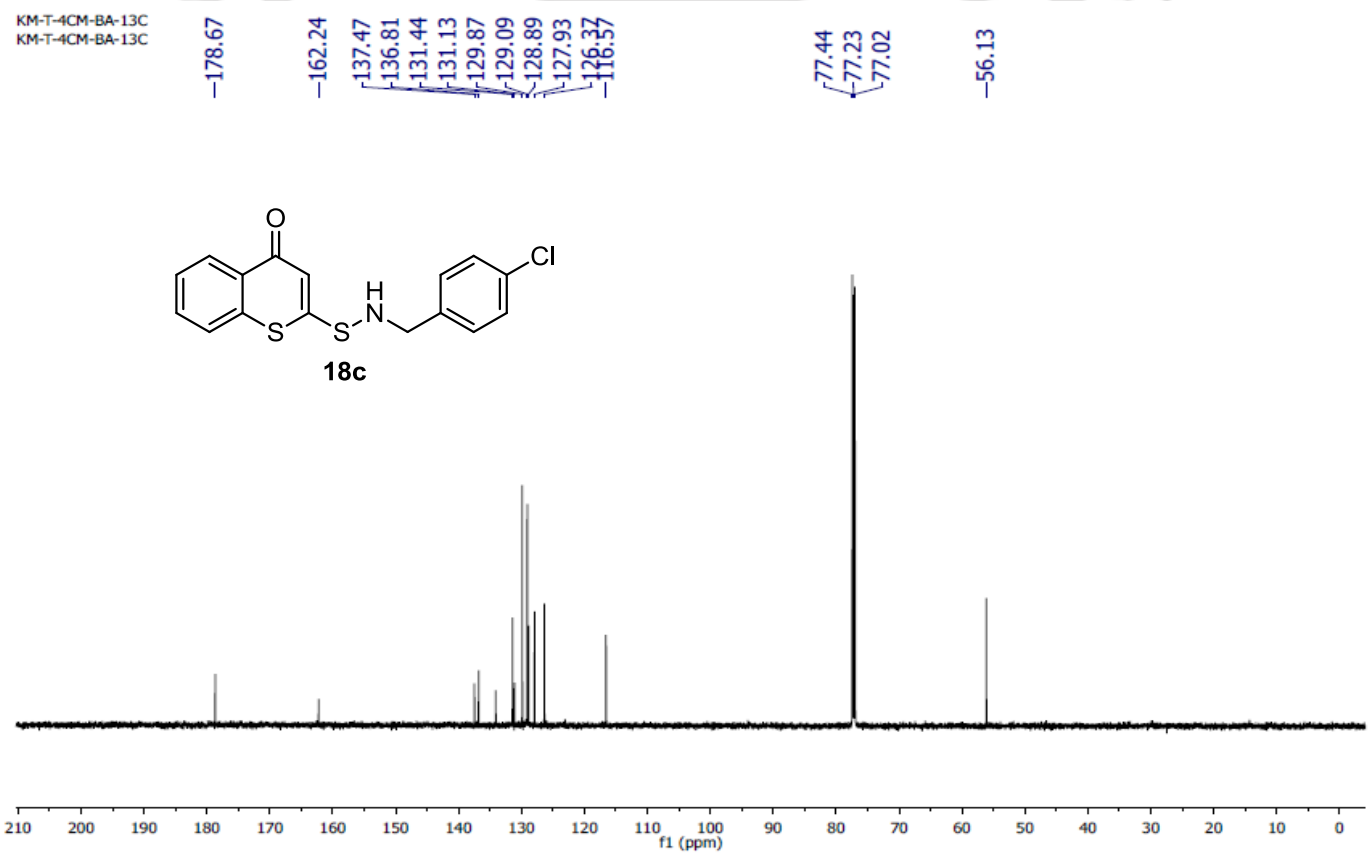
$$Cell\ viability\ (\%) = \frac{(Abs\ 570 - Abs\ 690)\ Sample}{(Abs\ 570 - Abs\ 690)\ Control} X\ 100$$

Where, Abs570 is the absorbance of formazan at 570 nm and Abs690 is the background absorbance which is subtracted from all treated and untreated samples

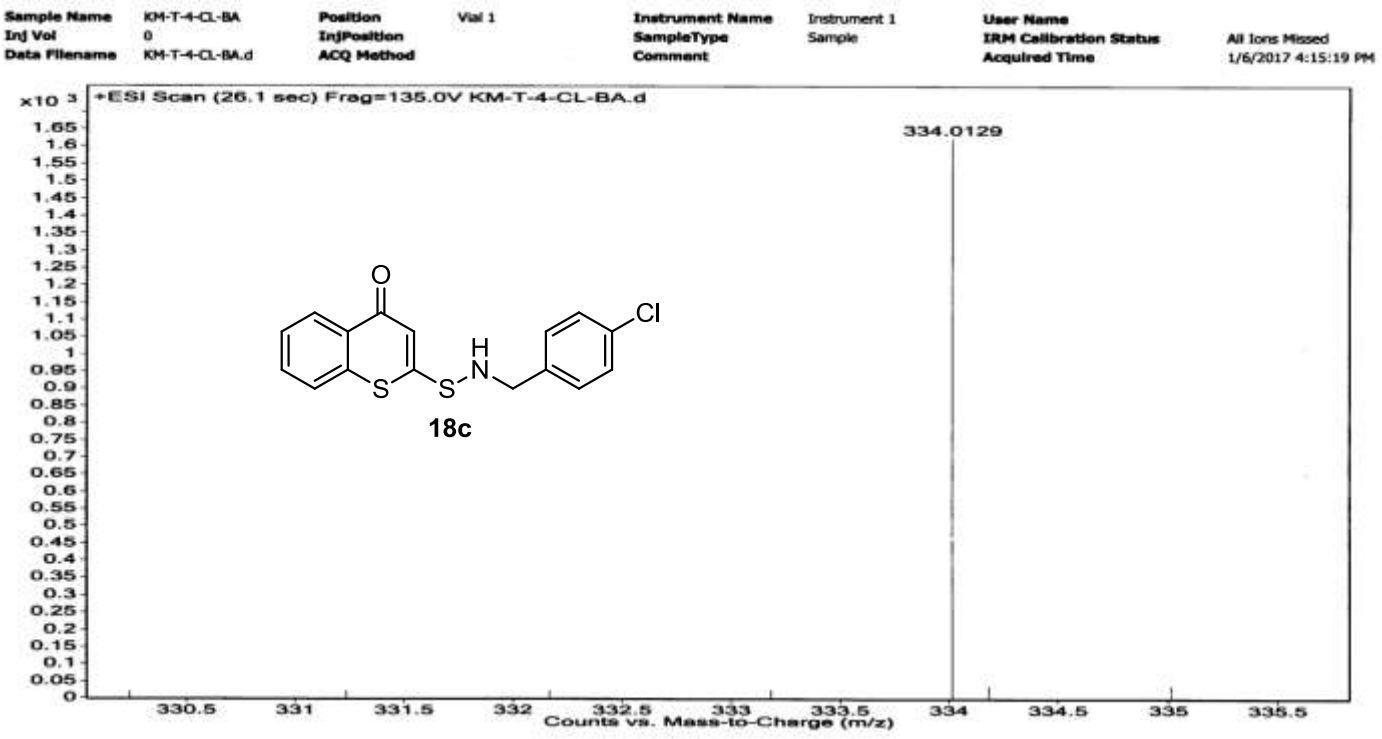
[1]HNMR: *12-(((4-chlorobenzyl)amino)thio)-4H-thiochromen-4-one* ***(18c)***



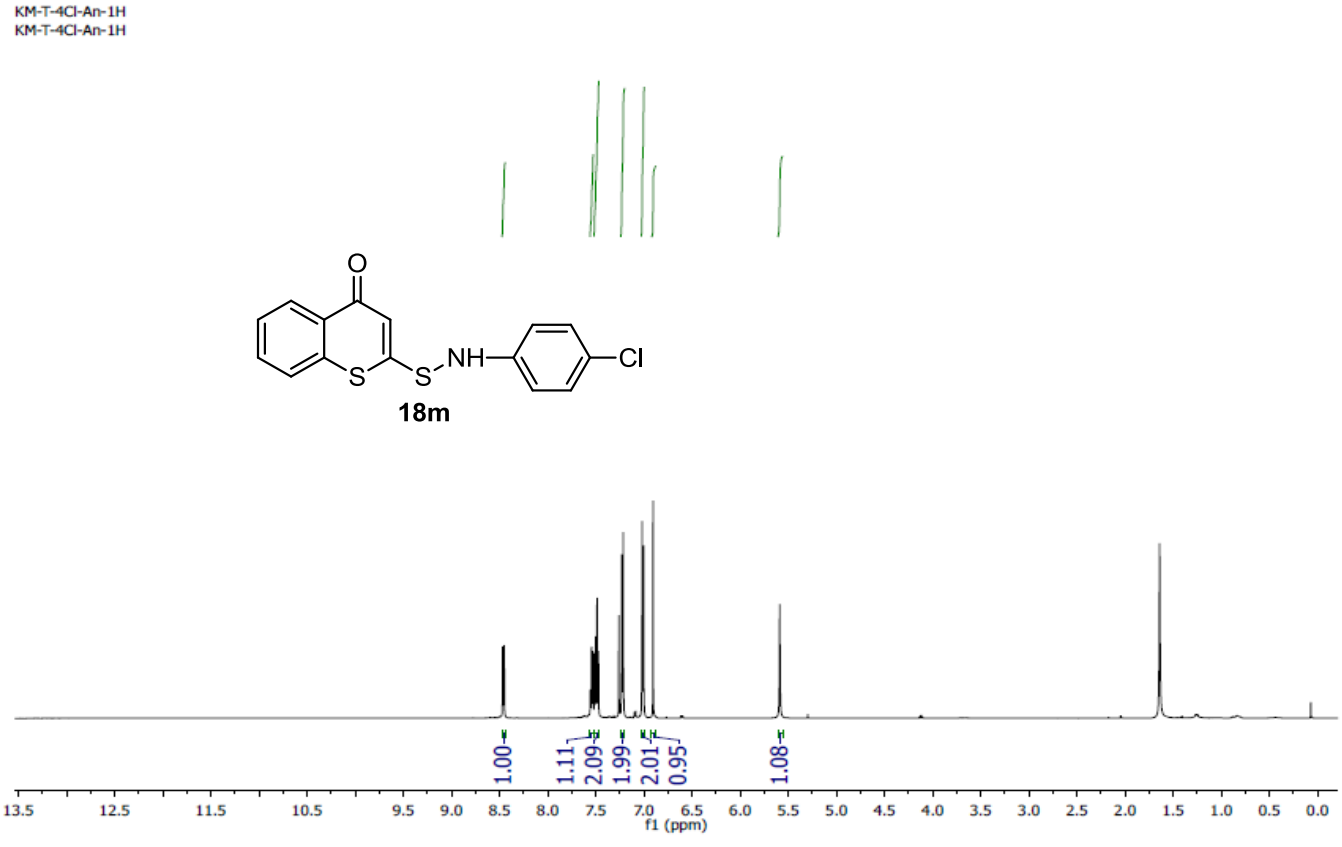
[13]CNMR: *2-(((4-chlorobenzyl)amino)thio)-4H-thiochromen-4-one* ***(18c)***



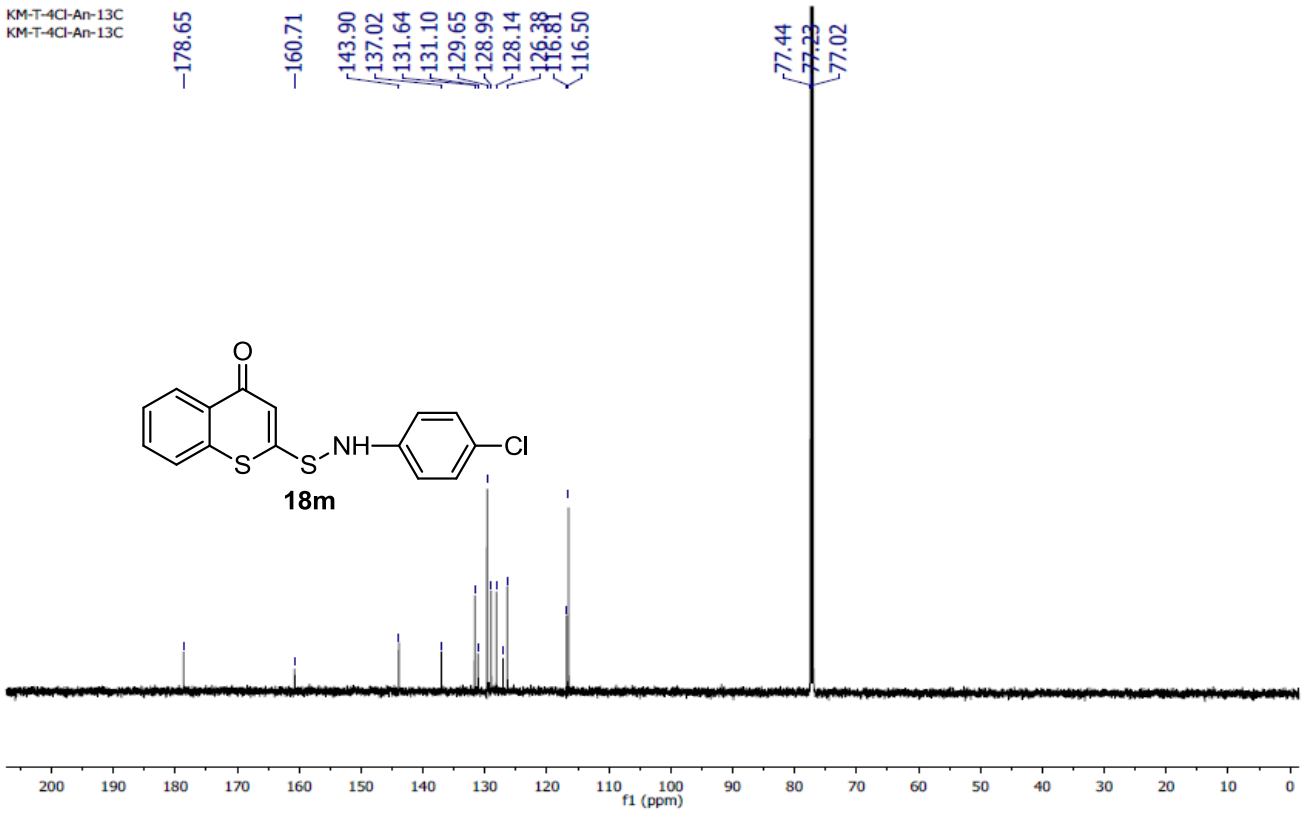
HRMS: *2-(((4-chlorobenzyl)amino)thio)-4H-thiochromen-4-one* ***(18c)***



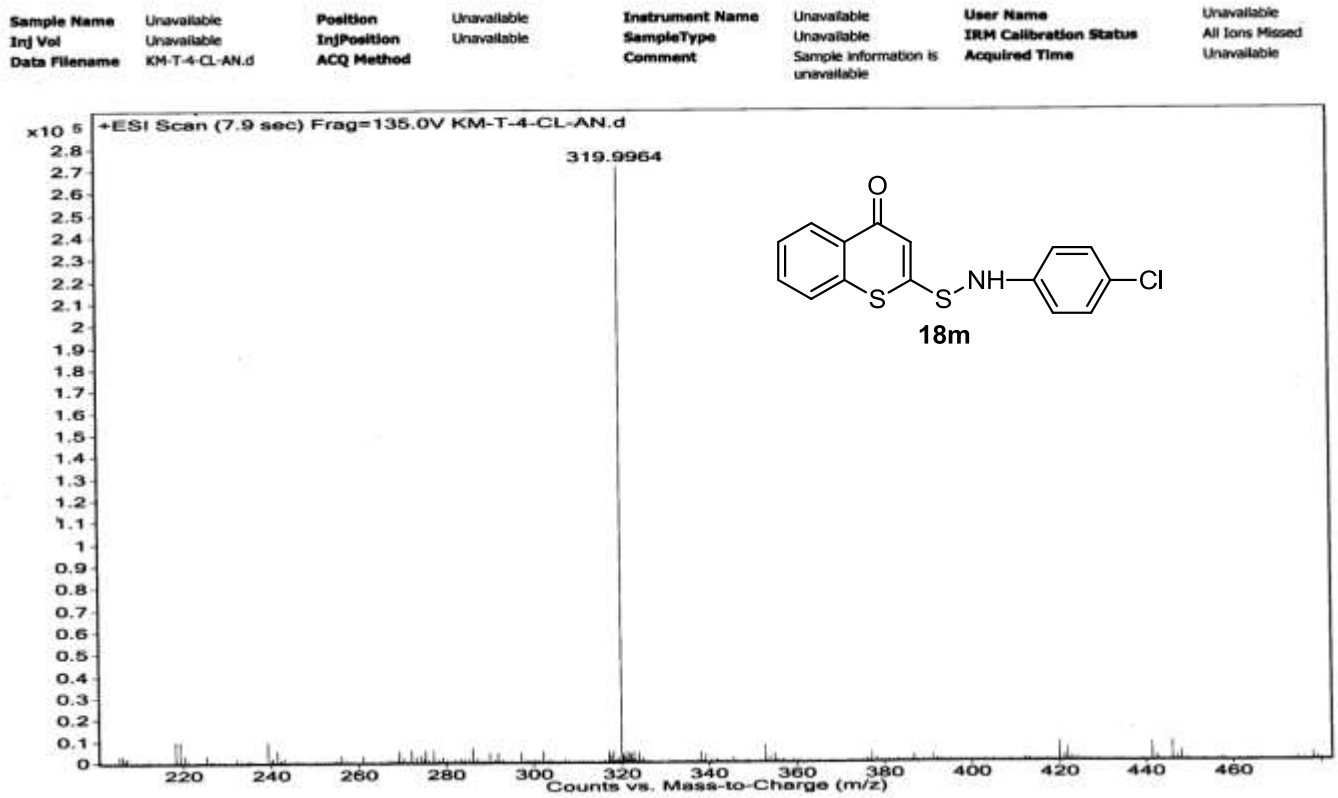
[1]HNMR: *2-(((4-chlorophenyl)amino)thio)-4H-thiochromen-4-one* ***(18m)***



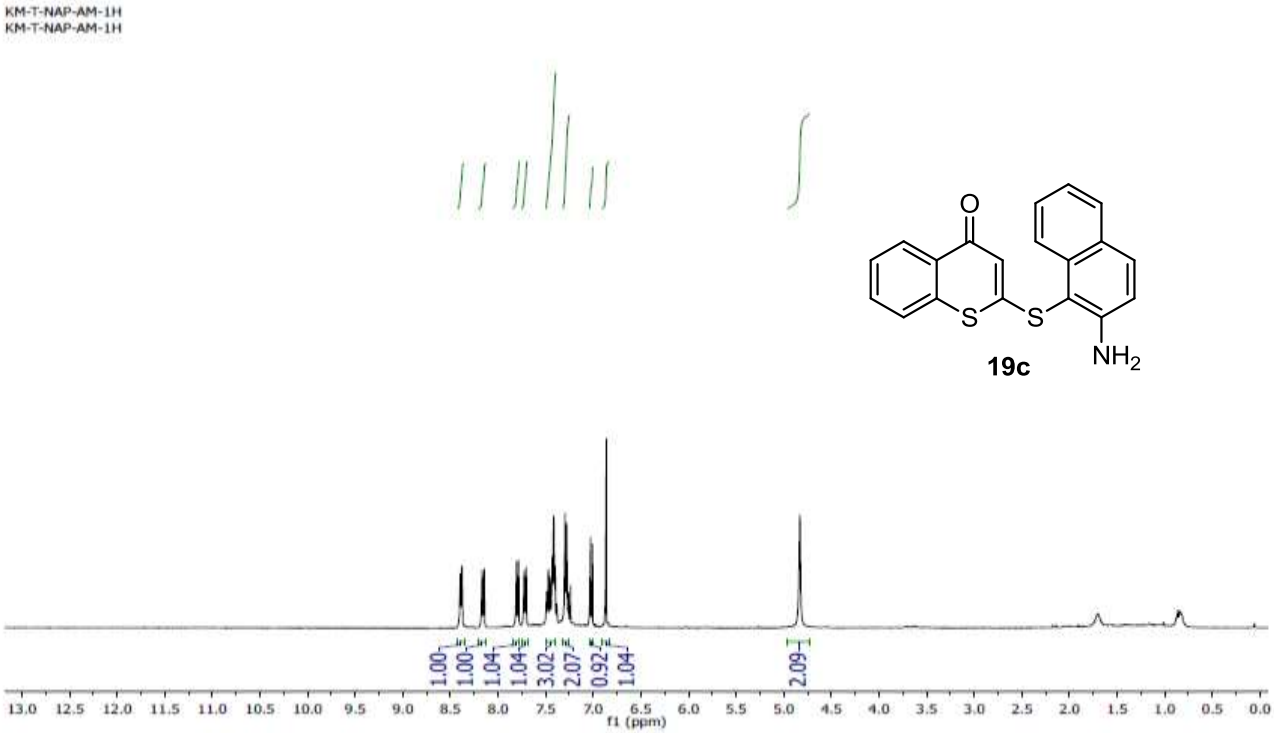
^{13}CNMR: *2-(((4-chlorophenyl)amino)thio)-4H-thiochromen-4-one* ***(18m)***



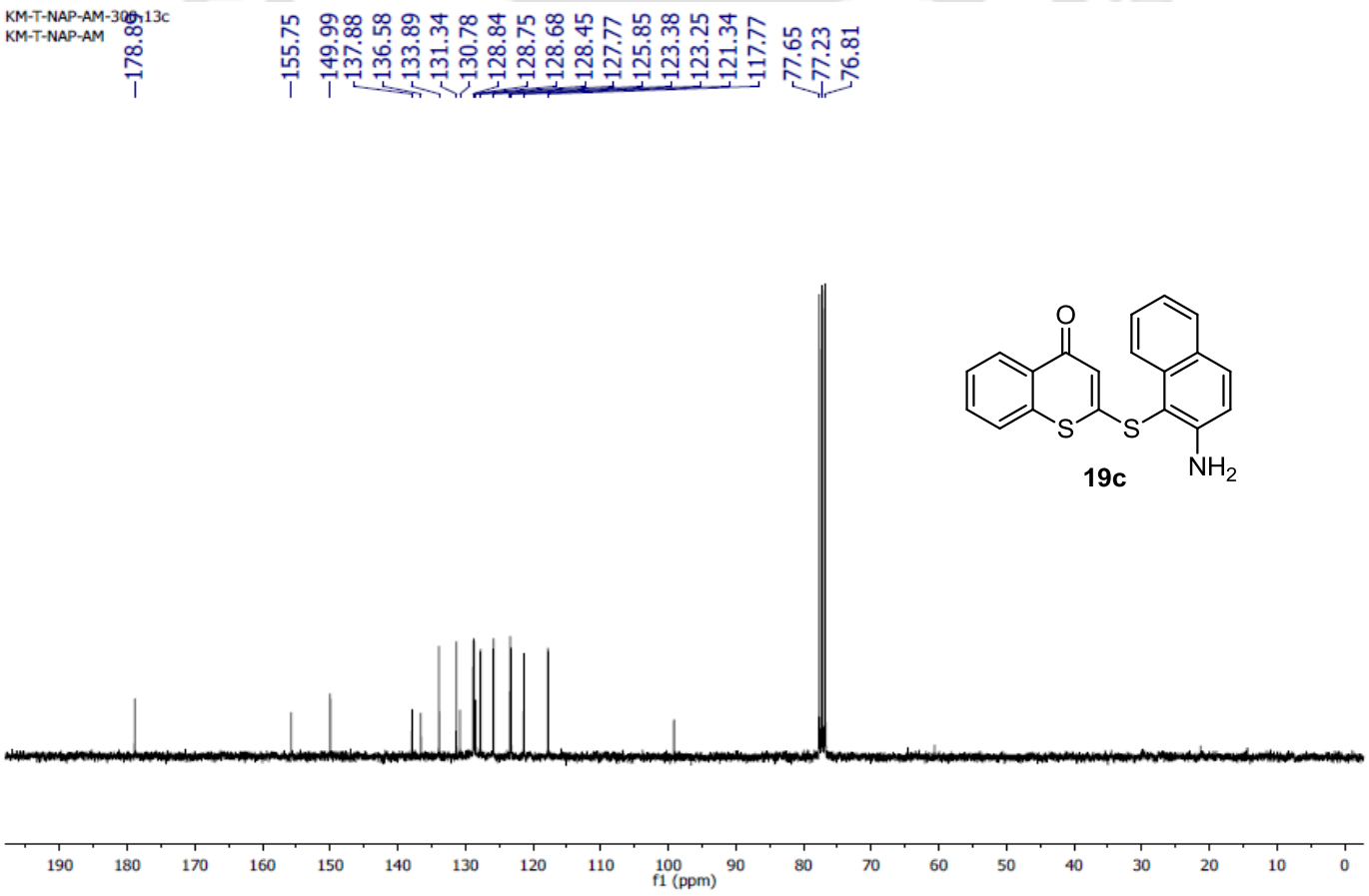
HRMS: *2-(((4-chlorophenyl)amino)thio)-4H-thiochromen-4-one* ***(18m)***



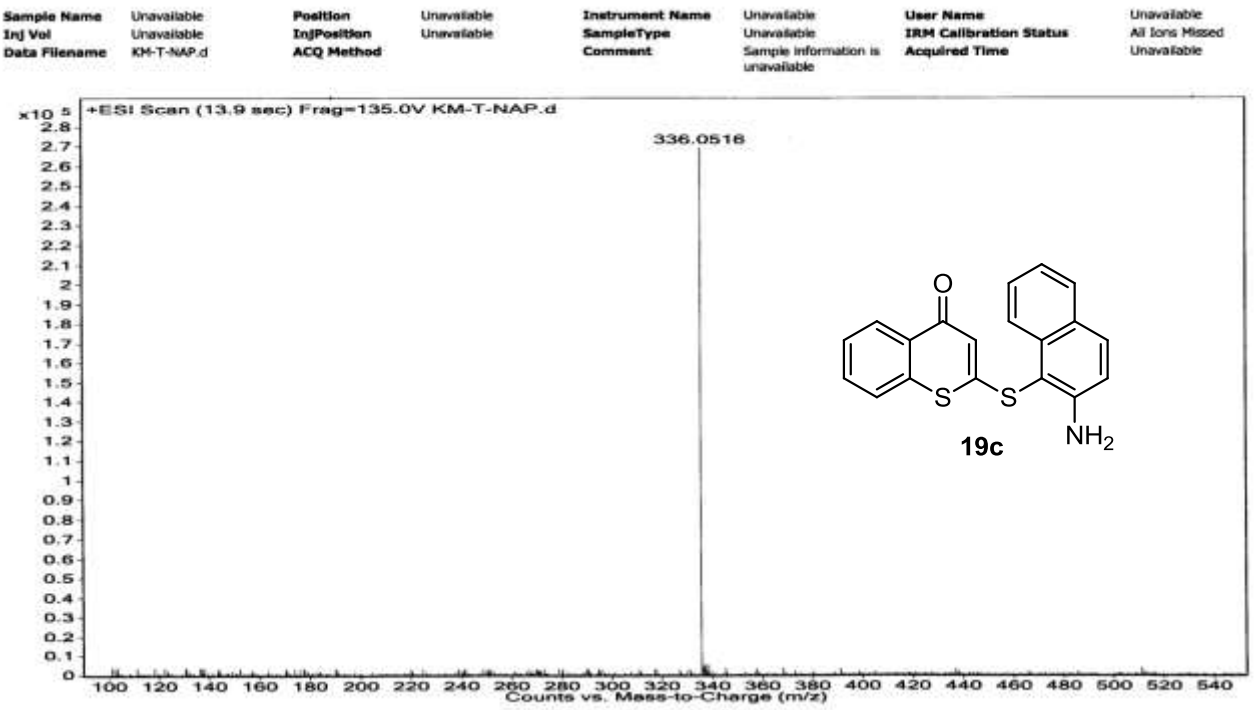
[1]HNMR: *2-((2-aminonaphthalen-1-yl)thio)-4H-thiochromen-4-one* ***(19c)***



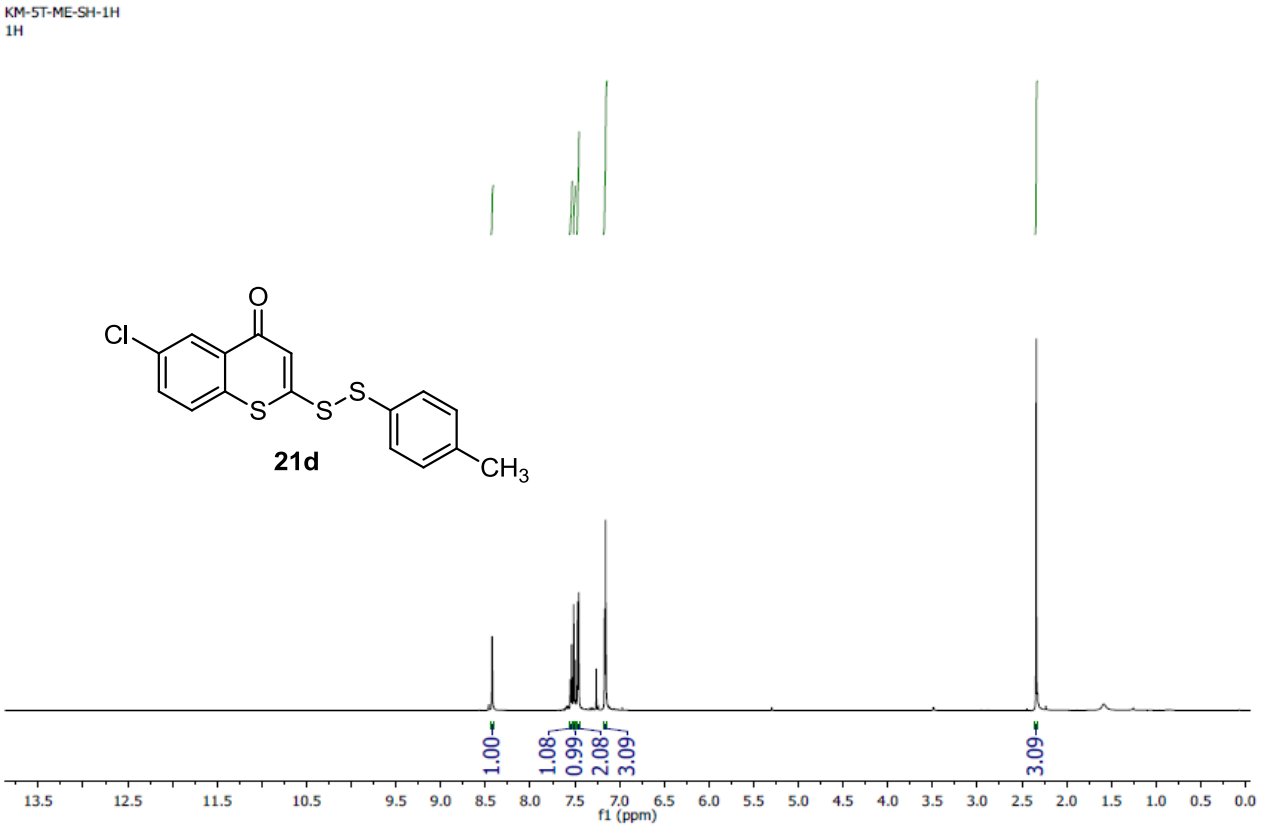
[13]CNMR: *2-((2-aminonaphthalen-1-yl)thio)-4H-thiochromen-4-one* ***(19c)***



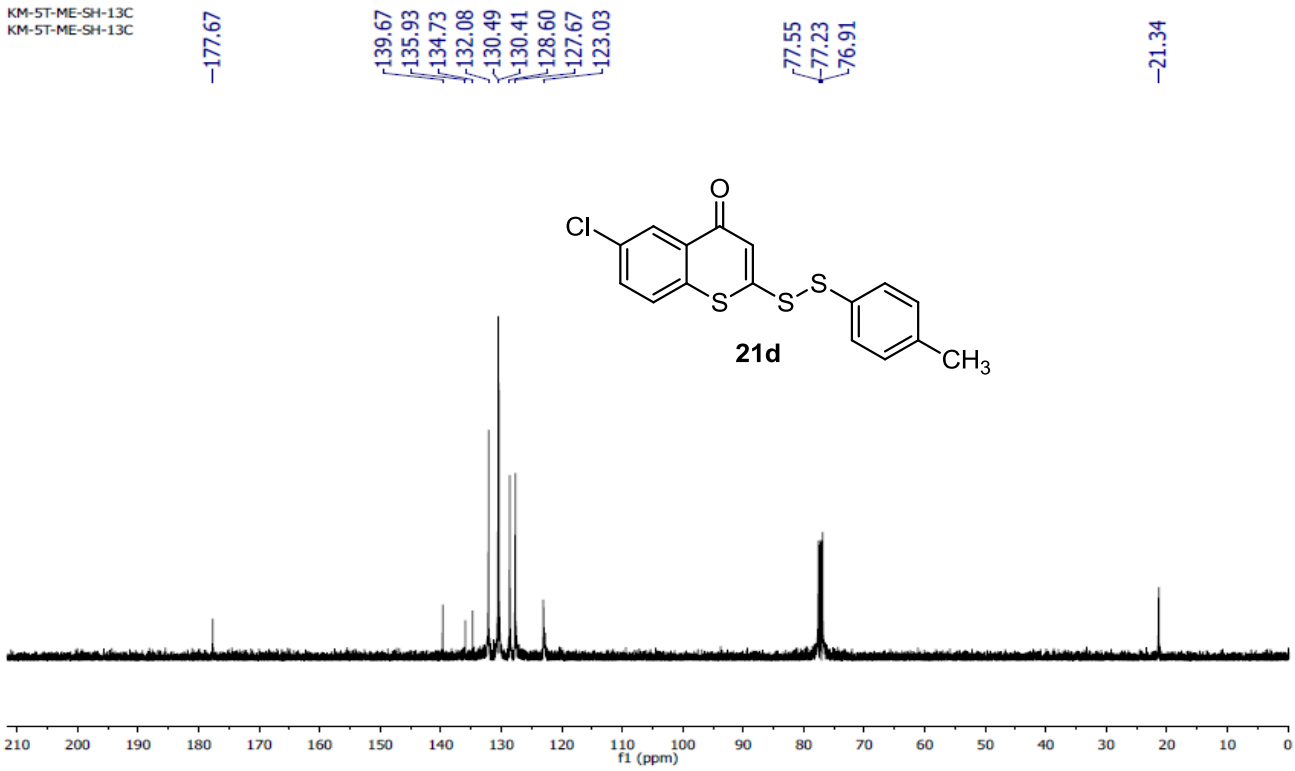
HRMS : *2-((2-aminonaphthalen-1-yl)thio)-4H-thiochromen-4-one* ***(19c)***



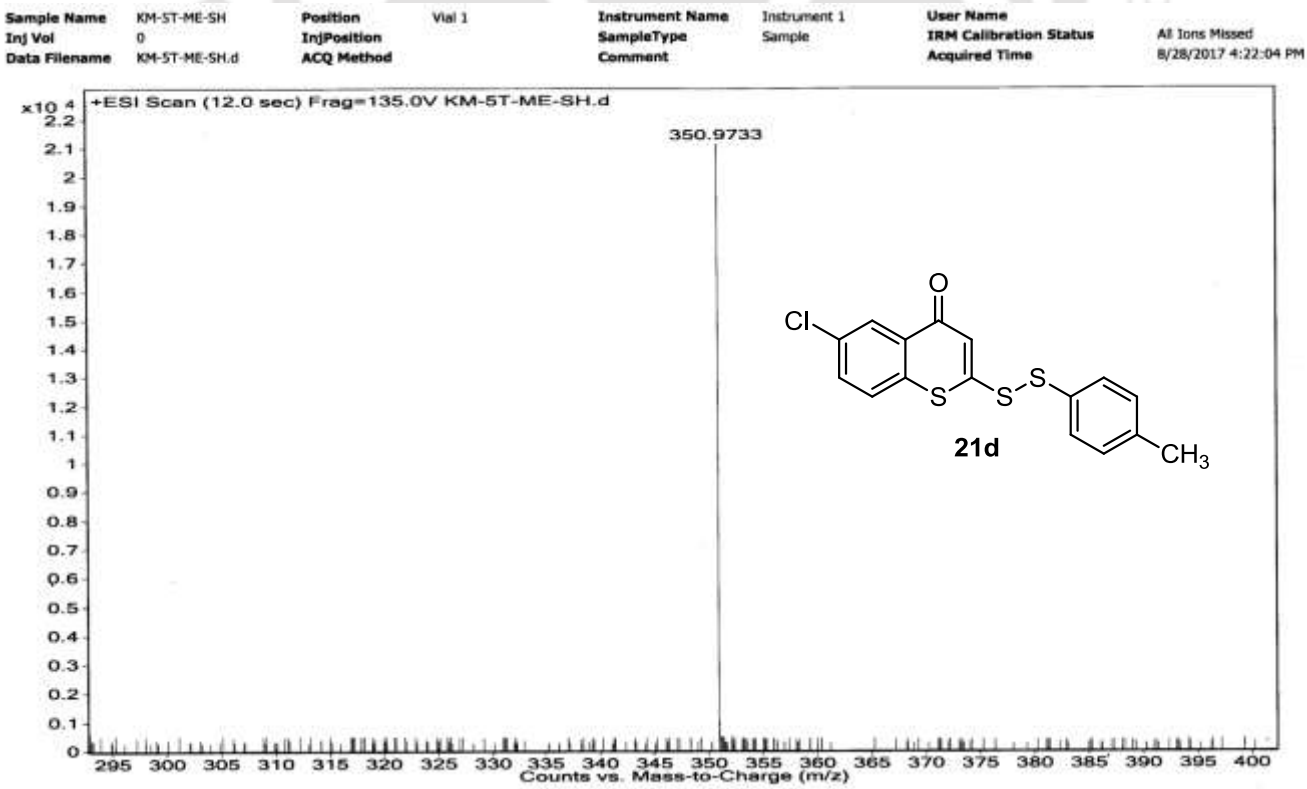
^{1}HNMR : *6-chloro-2-(p-tolyldisulfanyl)-4H-thiochromen-4-one* ***(21d)***



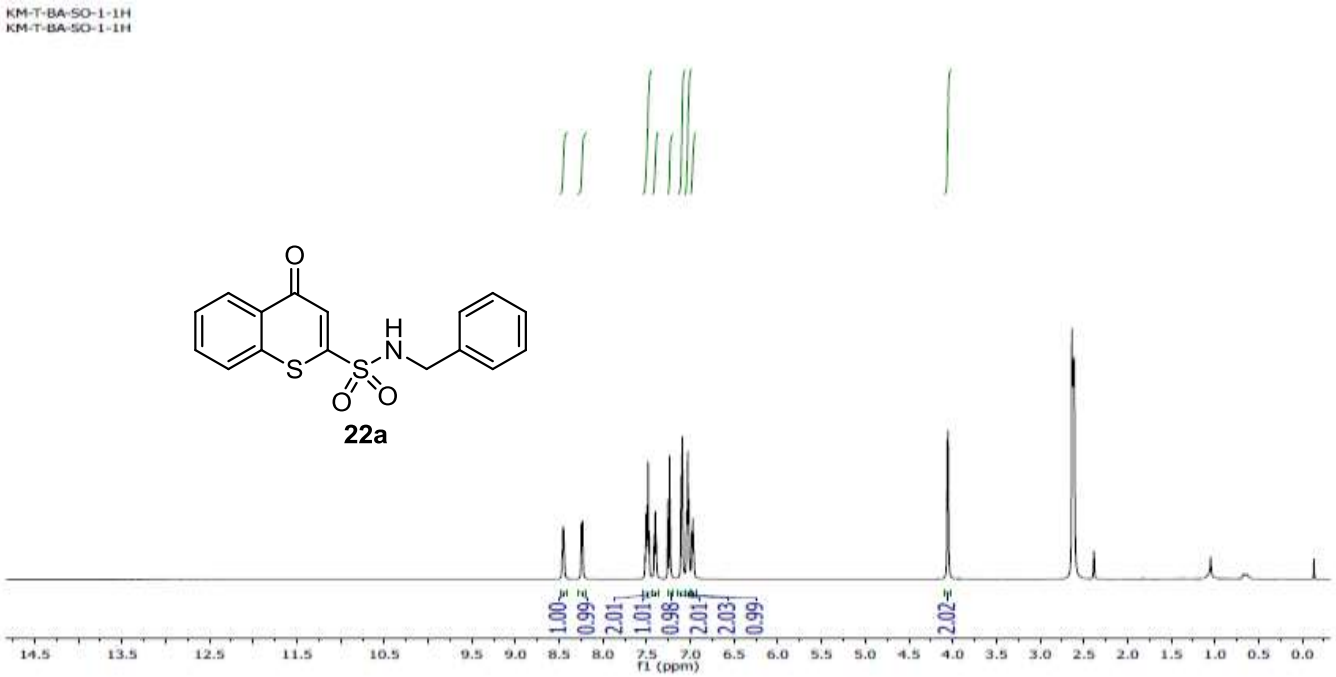
^{13}CNMR: *6-chloro-2-(p-tolyldisulfanyl)-4H-thiochromen-4-one* ***(21d)***



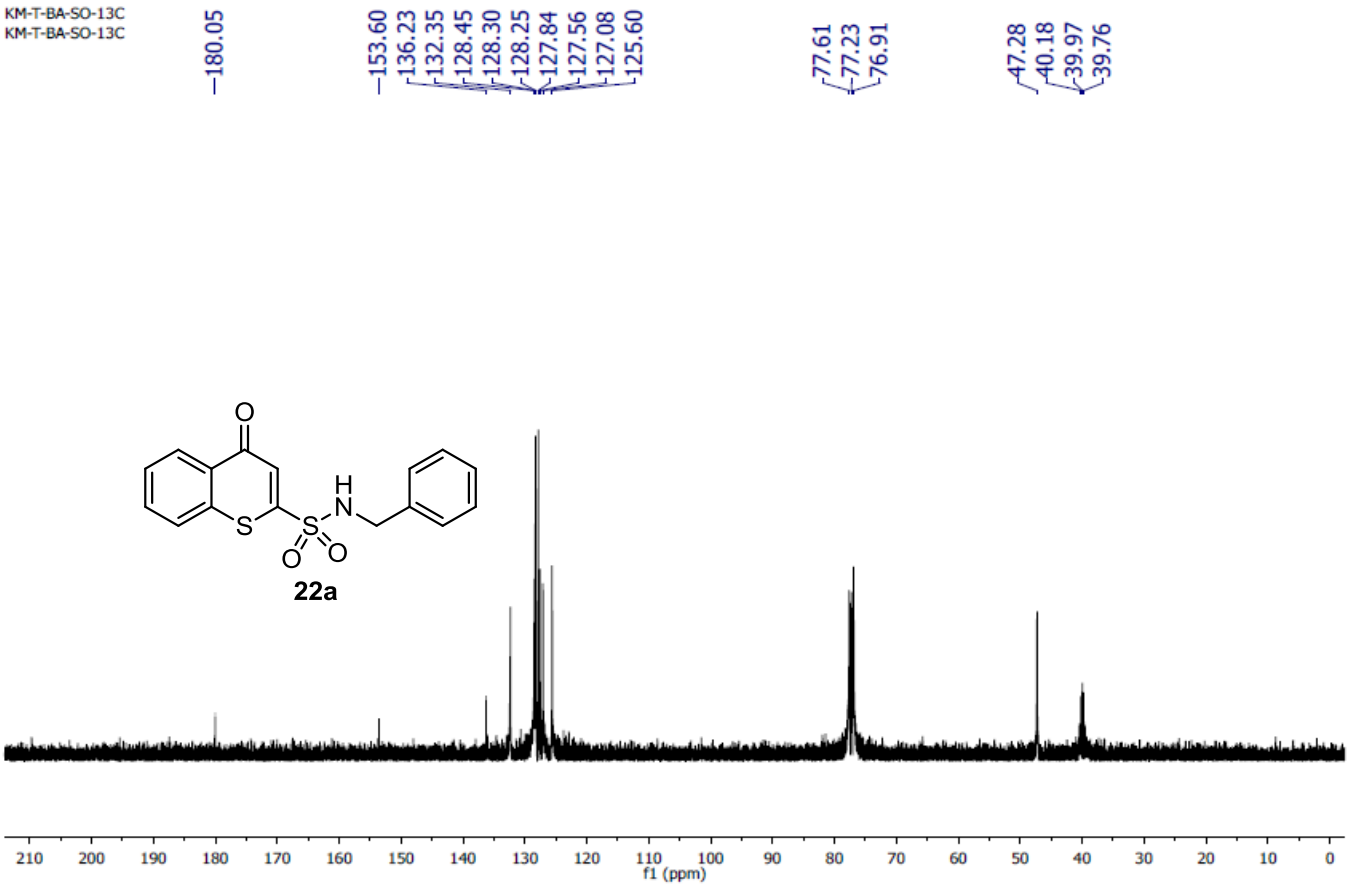
HRMS: *6-chloro-2-(p-tolyldisulfanyl)-4H-thiochromen-4-one* ***(21d)***



[1]HNMR: *N-benzyl-4-oxo-4H-thiochromene-2-sulfonamide* ***(22a)***

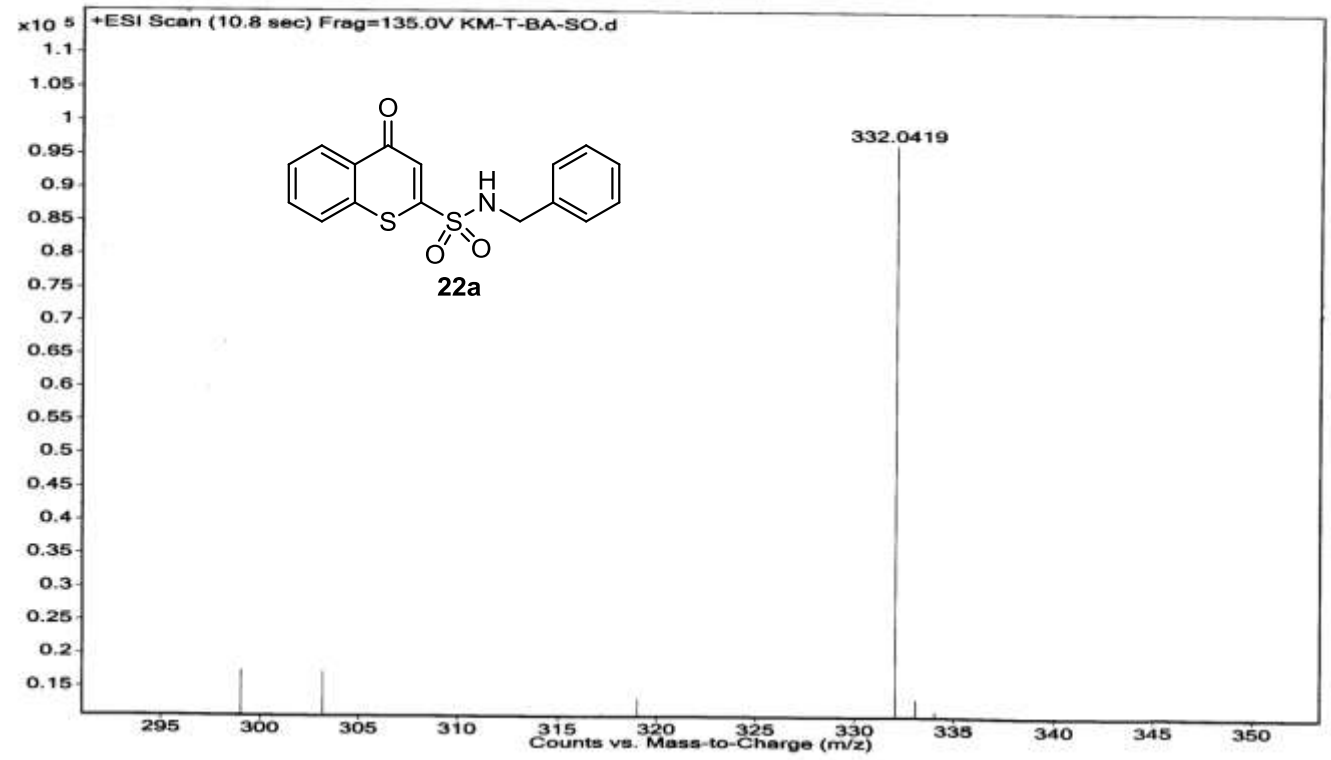


[13]CNMR: *N-benzyl-4-oxo-4H-thiochromene-2-sulfonamide* ***(22a)***



HRMS: *N-benzyl-4-oxo-4H-thiochromene-2-sulfonamide* ***(22a)***

Sample Name	Unavailable	**Position**	Unavailable	**Instrument Name**	Unavailable	**User Name**	Unavailable
Inj Vol	Unavailable	**InjPosition**	Unavailable	**SampleType**	Unavailable	**IRM Calibration Status**	All Ions Missed
Data Filename	KM-T-BA-SO.d	**ACQ Method**		**Comment**	Sample information is unavailable	**Acquired Time**	Unavailable



22a

1. (a) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev*. **2012**, *112*, 3083. (b) Domling, A. *Chem. Rev*. **2006**, *106*, 17.
2. Toure´, B. B.; Hall, D. G. *Chem. Rev*. **2009**, *109*, 4439.
3. (a) Jiang, X.; Wang, R. *Chem. Rev*. **2013**, *113*, 5515. (b) Casiraghi, G.; Zanardi, F. *Chem. Rev*. **2000**, *100*, 1929.
4. (a) Majumdar, K. C.; Taher, A.; Ponra, S. *Tetrahedron Lett*. **2010**, *51*, 2297. (b) Moghaddam, F. M.; Kiamehr, M.; Khodabakhshi, M. R.; Mirjafary, Z.; Fathi, S.; Saeidian, H. *Tetrahedron* **2010**, *66*, 8615.
5. (a) Ruano, J-L. G.; Ferna´ndez-Iba´n˜ez, M. A.; Maestro, M. C. *J. Org. Chem*. **2006**, *71*, 7683. (b) Genovese, S.; Epifano, F.; Pelucchini, C.; Procopio, A.; Curini, M. *Tetrahedron Lett*. **2010**, *51*, 5992. (c) Hua, L.; Yao, Z.; Xu, F.; Shen, O. *RSC Adv*. **2014**, *4*, 3113.
6. Andersonmckay, J. E.; Liepa, A. J. *Aust. J. Chem*. **1987**, *40*, 1179.
7. (a) Park, J.; Pei, D. Biochemistry **2000**, *43*, 15014. (b) Gergely, A.; Gyimesi-Forras, K.; Horvath, P.; Hosztafi, S.; Koekoesi, J.; Nagy, P. I.; Szasz, Gy.; Szentesi, A. *Curr. Med. Chem*. **2004**, *11*, 2555.
8. (a) Mokaya, R.; Poliakoff, M. *Nature* **2005**, *437*, 1243. (b) Fehr, C.; Delay, *F. Firmenich & Cie*. *U.S. Patent* US5521151, **1996**.
9. Fawcett, C. H. *Nature* **1964**, *204*, 1200.
10. (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, Vol. A, 5th ed.; Springer: New York, 2008; pp 650. (b) Blatt, A. H. *Chem. Rev*. **1933**, *12*, 215. (c) Freeman, J. P. *Chem. Rev*. **1973**, *73*, 283. (d) Subiros-Funósas, R.; Khattab, S. N.; Nieto-Rodríguez, L.; El-Faham, A.; Albericio, F. *Aldrichimica Acta* **2013**, *46*, 21.
11. (a) Sanford, J. K.; Blair, F. T.; Arroya, J.; Sherk, K. W. *J. Am. Chem. Soc*. **1945**, *67*, 1941. (b) Smith, P. A. S. *J. Am. Chem. Soc*. **1948**, *70*, 323. (c) Baczynskyj, L.; Mizsak, S.; Szmuszkovicz, J. *J. Org. Chem*. **1972**, *37*, 4104. (d) Armor, J. N. *J. Am. Chem. Soc*. **1980**, *102*, 1453.
12. Ferris, J. P.; Sanchez, R. A.; Mancuso, R. W. *Org. Synth*. **1973**, Coll. Vol. 5, 32. and references cited therein.

13. (a) Braun, V. J.; Sobecki, W. *Ber. Dtsch. Chem. Ges*. **1911**, *44*, 2526. (b) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed*. **2002**, *41*, 4556. (c) Wang, K. W.; Qian, X. H.; Cui, J. N. *Tetrahedron* **2009**, *65*, 10377. (d) Albanese, D.; Landini, D.; Penseo, M. *Synthesis* **1990**, 333. (e) Barton, D. H. R.; Fernandez, I.; Richard, C. S.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 551. (f) Grundmann, C. *Angew. Chem.* **1950**, *62*, 558.

14. (a) Corma, A.; Serna, P.; Garcı´a, H. *J. Am. Chem. Soc*. **2007**, *129*, 6358. (b) Cai, S.; Zhang, S.; Zhao, Y.; Wang, D. Z. *Org. Lett*. **2013**, *15*, 2660. (c) Mei, R-Q.; Xu, X-Y.; Peng, L.; Wang, F.; Tian, F.; Wang, L-X. *Org. Biomol. Chem*. **2013**, *11*, 1286 (d) Zeng, M-X.; Meng, Y-C.; Bao, X-J.; Xu, C-D.; Xie, W-J.; Zhu, W-D. *J. Org. Chem*. **2015**, *80*, 11521.

15. (a) Majumdar, K. C.; Khan, A. T.; Saha, S. *Synlett* **1991**, 595. (b) Majumdar, K. C.; Saha, S.; Khan, A. T. *Indian. J. Chem*. **1994**, *33B*, 216.

16. Yamabe, S.; Tsuchida, N.; Yamazaki, S. *J. Org. Chem*. **2005**, *70*, 10638.

17. Horning, E. C.; Stromberg, V. L.; Lloyd, H. A. *J. Am. Chem. Soc*. **1952**, *74*, 5153.

18. Sharma, S. K.; Bishopp, S. D.; Allen, C. L.; Lawrence, R.; Bamford, M. J.; Lapkin, A. A.; Plucinski, P.; Watson, R. J.; Williams, J. M. J. *Tetrahedron Lett*. **2011**, *52*, 4252.

19. (a) Kumar, V.; Kaushik, M. P. *Tetrahedron Lett*. **2005**, *46*, 8121. (b) Sha, X.; Isbell, T. S.; Patel, R. P.; Day, C. S.; King, S. B. *J. Am. Chem. Soc*. **2006**, *128*, 9687. (c) Banerjee, R.; King, S. B. *Org. Lett*. **2009**, *11*, 4580 and references therein.

20. Liu, J-T.; Yao, C-F. *Tetrahedron Lett*. **2001**, *42*, 6147.

21. (a) Chandrasekhar, S.; Reddy, N. S.; Sultana, S. S.; Narsihmulu, C.; Reddy, K. V. *Tetrahedron* **2006**, *62*, 338. (b) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc*. **2006**, *128*, 732. (c) Gunasekaran, P.; Prasanna, P.; Perumal, S. *Tetrahedron Lett*. **2014**, *55*, 329 and references therein.

22. (a) Bell, A. T. *Science* **2003**, *299*, 1688. (b) Schlogl, R.; Abd Hamid, S. B. *Angew. Chem., Int. Ed*. **2004**, *43*, 1628.

23. (a) Thome, I.; Besson, C.; Kleine, T.; Bolm, C. *Angew. Chem., Int. Ed*. **2013**, *52*, 7509. (b) Kano, T.; Shirozu, F.; Maruoka, K. *J. Am. Chem. Soc*. **2013**, *135*, 18036. (c) Sun, C.-L.; Shi, Z.-J. *Chem. Rev*. **2014**, *114*, 9219.

24. (a) Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *Org. Lett*. **2006**, *8*, 2491. (b) Nobuta, T.; Tada, N.; Fujiya, A.; Kariya, A.; Miura, T.; Itoh, A. *Org. Lett*. **2013**, *15*, 574. (c) Pan, X.; Boussonnière, A.; Curran, D. P. *J. Am. Chem. Soc*. **2013**, *135*, 14433. (d) Humne, V.; Dangat, Y.; Vank, K.; Lokhande, P. *Org. Biomol. Chem*. **2014**, *12*, 4832.

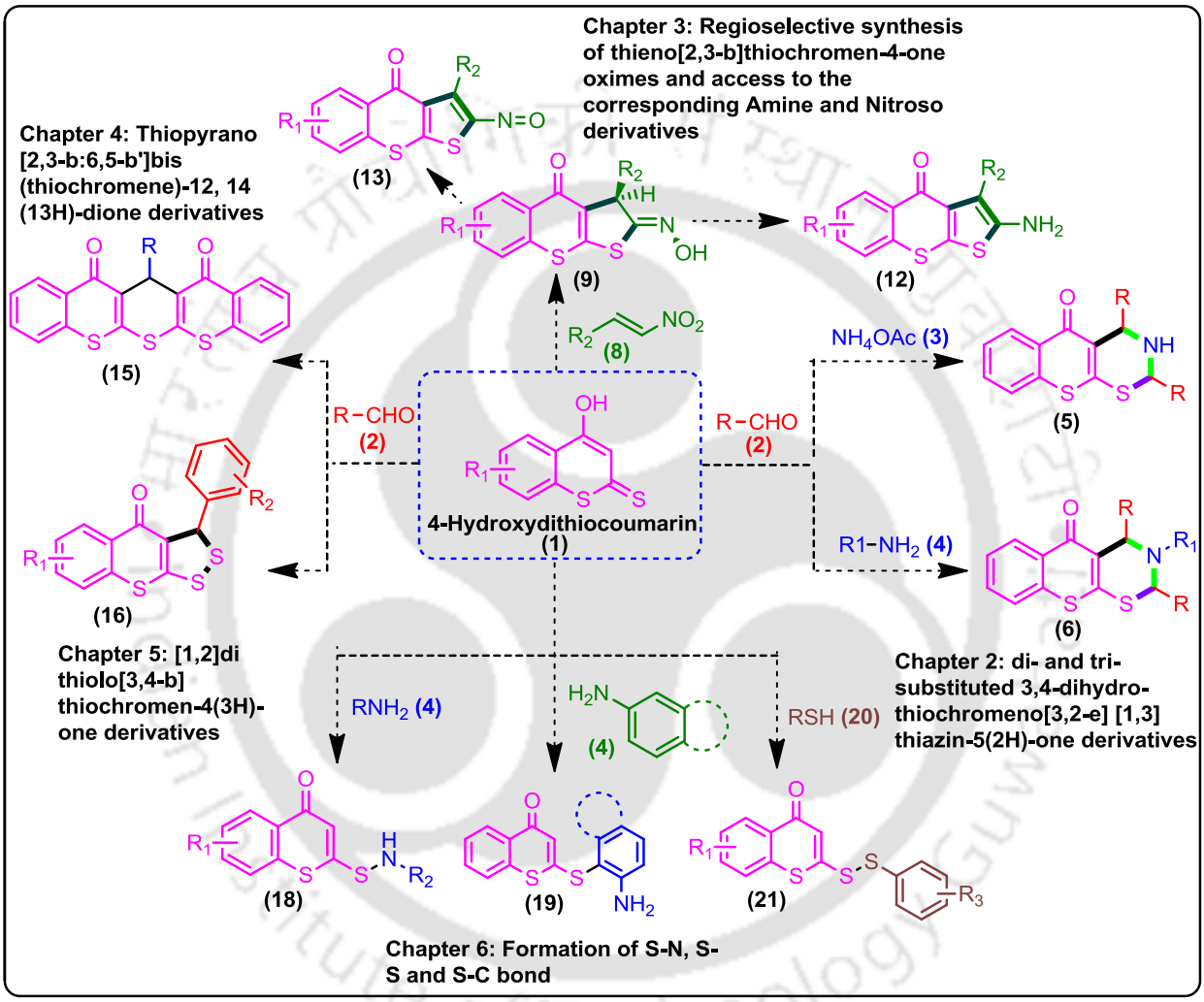
25. Dar, Ajaz A.; Enjamuri, N.; Shadab, M; Ali, N; Khan, A.T. *ACS Comb. Sci*. **2015**, 17, 671.

26. *Pharmaceutical Substances, Syntheses, Patents, Applications*; Kleemann, A., Engel, J., Kutscher, B., Reichert, D., Eds.; Thieme: Stuttgart, 1999.

27. (a) Harter, W. G.; Albrect, H.; Brady, K.; Caprathe, B.; Dunbar, J.; Gilmore, J.; Hays, S.; Kostlan, C. R.; Lunney, B.; Walker, N. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 809. (b) Reddy, N. S.; Mallireddigari, M. R.; Cosenza, K. G.; Bell, S. C.; Reddy, E. P.; Reddy, M. V. R. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 4093. (c) Stranix, B. R.; Lavallee, J.-F.; Sevigny, G.; Yelle, J.; Perron, V.; Leberre, N.; Herbart, D.; Wu, J. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3459. (d) Purushottamachar, P.; Khandelwal, A.; Vasaitis, T. S.; Bruno, R. D.; Gediya, L. K.; Njar, V. C. O. *Bioorg. Med. Chem*. **2008**, *16*, 3519. (e) Wu, C.; Decker, E. R.; Holland, G. W.; Brown, F. D.; Stavros, F. D.; Brock, T. A.; Dixon, R. A. C. *Drugs Today* **2001**, *37*, 441.

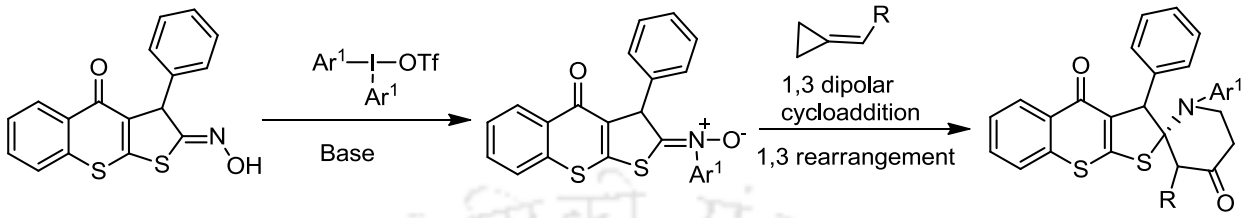
CONCLUSION AND FUTURE PERSPECTIVES

During the tenure of my PhD, I have focused my research work mainly on the utility of 4-hydroxydithiocoumarin in the synthesis of 1,3-thiazine, thiophenes, thiopyran, 1,2-dithole, sulfenamides, disulfides and sulfanes. The summarized results are shown below schematically.



In future, we believe that synthesized novel organosulfur compounds i.e, 1,3-thiazine, thiophenes, thiopyran and 1,2-dithole, are useful classes of compounds which could be further studied for their potent biological activities in collaboration with other research groups. The synthesized product 2-oxime-3-aryl-2H-thieno[2,3-*b*]thiochromen-4-ones could be used for the synthesis of (E)-N-(4-oxo-3-phenyl-3,4-dihydro-2H-thieno[2,3-b]thiochromen-2-ylidene)aniline oxides through a metal-free selective N- Arylation process and the corresponding cycloaddition

of with methylenecyclopropanes and sequential 1,3-Rearrangement could give an entry towards (2S)-3-(hydroxymethyl)-1,3'-diphenylspiro[piperidine-2,2'-thieno[2,3-b]thiochromene]-4,4'(3'H)-diones (R= CH_2OH) as shown in scheme 1.



Scheme 1

LIST OF PUBLICATIONS AND COMMUNICATIONS

- L-Proline catalysed unusual product formation from the reaction of 4-hydroxydithiocoumarin and aldehydes through a pseudo three-component reaction' **Karuna Mahato**, Prasanta Ray Bagdi, Abu T. Khan, *Synlett*. **2014**, 25, 2438.
- 'Yb$(OTf)_3$ catalysed regioselective synthesis of unusual di- and tri- subsituted 3,4-dihydrothiochromeno[3,2-e][1,3]thiazin-5(2H)-one through a pseudo four-component hetero-Diels-Alder reaction' **Karuna Mahato**, Prasanta Ray Bagdi, Abu T. Khan, *RSC Adv*. **2015**, 5, 48104.
- 'K_2CO_3 Catalysed unprecedented regioselective synthesis of thieno[2,3-b]thiochromen-4-one oximes as a valuable synthon: Facile route to the corresponding Amine and Nitroso derivatives' **Karuna Mahato**, Prasanta Ray Bagdi, Abu T. Khan, *Org. Biomol. Chem*. **2017**, 15, 5625.
- Copper Oxide nanoparticles catalyzed synthesis of unusual [1,2]dithiolo[3,4-b]thiochromen-4(3H)-one derivatives from 4-hydroxydithiocoumarin and aldehydes (Communicated)
- Metal free I_2/TBHP induced construction of S-N/ S-S/ S-C bond by coupling of 4-hydroxydithiocoumarin and amines/thiols (Communicated)