Reactivity Studies of 4-Hydroxydithiocoumarin: Design & Synthesis of Novel Bioactive Molecules

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As partial fulfilment for the degree of

DOCTOR OF PHILOSOPHY

by

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DEDICATED TO

MY FAMILY

&

FRIENDS

Indian Institute of Technology Guwahati

Department of Chemistry

DECLARATION

I do hereby declare that the matter embodied in this thesis entitled "*Reactivity Studies of 4-Hydroxydithiocoumarin: Design & Synthesis of Novel Bioactive Molecules"* is the result of investigations carried out by me under the supervision of Prof. Abu T. Khan in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

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

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CERTIFICATE

This is to certify that Ms. Santa Mondal has been working in my research group since January 2018 as a regular registered Ph. D. student. I am forwarding her thesis entitled "*Reactivity Studies of 4-Hydroxydithiocoumarin: Design & Synthesis of Novel Bioactive Molecules"* being submitted for the Ph. D. (Science) Degree from 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
February 25, 2022

Prof. A. T. Khan

(Thesis Supervisor)

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Santa Mondal

Santa Mondal

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 5th February 2018 to 25th February 2022 as a doctoral 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) employed as adsorbent was used. Column chromatography was carried out with silica gel (60-120 mesh, Merck or SRL), for purifications of the reaction mixture. Biotage flash chromatography was also used for purification. After purification, the solvent was usually removed in rotavapor using Büchi R-114V and Büchi R-300 instrument. Melting points were determined on a Büchi melting point apparatus. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. $CDCl_3$ and DMSO-d_6 were used for recording NMR spectrum. ^{1}H spectra were recorded on Bruker 400 MHz, Bruker 500 MHz and Bruker 600 MHz spectrometers using TMS as internal standard. Similarly, ^{13}C NMR spectra recorded on Bruker 100 MHz, Bruker 125 MHz, Bruker 150 MHz spectrometer TMS as the 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), dd (doublet of doublet), dq (doublet of quartet), dt (doublet of triplet) and ddt (doublet of doublet of triplet). HRMS spectra were recorded using ESI (TOF) mode. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 296 K.

Contents of the Thesis

ABBREVIATION

Ac	Acetyl
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
BTEAC	Benzyltriethylammonium chloride
Bu	Butyl
^{t}Bu	*tert*-Butyl
^{t}BuOK	Potassium tert-butoxide
CCDC	Cambridge crystallographic data centre
CDC	Cross dehydrogenative coupling
ChCl	Choline chloride
COD	Cycloocta-1,5-diene
CSA	Camphorsulfonic acid
DABCO	(1,4-Diazabicyclo[2.2.2]octane)
DCE	1,2-Dichloroethene
DCM	Dichloromethane
DFT	Discrete Fourier transform
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DPDME	Dipropylene glycol dimethyl ether
EPC	Electrophilic phosphonium cations
Et	Ethyl
EtBr	Ethidium bromide
Et_3N	Triethylamine
EtOH	Ethanol
g	gram
h	hour
HIV	Human immunodeficiency virus

HRMS	High-resolution Mass Spectrometry
HCl	Hydrochloric acid
$In(OTf)_3$	Indium triflate
IR	Infrared
$LiNTf_2$	Lithium bistrifluoromethanesulfonimide
LPG	Liquefied petroleum gas
m-CPBA	meta-Chloroperoxybenzoic acid
MCR	Multicomponent reaction
MCF-7	Michigan Cancer Foundation-7
Me	Methyl
mg	Milligram
mp	Melting point
ms	Molecular sieves
MTT	(3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide)
MW	Microwave
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
$Ni(acac)_2$	Nickel(II) acetylacetonate
NMR	Nuclear magnetic resonance
OAT	Oxygen atom transfer
ORTEP	Oak ridge thermal ellipsoid program
$Pd(OAc)_2$	Palladium (II) acetate
Ph	Phenyl
PI	Propidium Iodide
Pr	Propyl
ppm	Parts per million
Py	Pyridine
p-TSA	*p*-toluenesulfonic acid
ROS	Reactive Oxygen Species
rt	Room temperature
S_N2	Substitution Nucleophilic Bimolecular
TBAI	Tetra-*n*-butylammonium iodide
TBAB	Tetrabutylammonium bromide
TBHP	*tert*-Butyl hydroperoxide

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TfOH	Triflic acid
w	Weight
XRD	x-ray diffraction

CHAPTER I

Importance of sulfur compounds & Synthetic utility of 4-hydroxydithiocoumarin by exploring its reactivity

1.1. Importance of sulfur compounds

Sulfur is the 10th most abundant element and its natural abundance in the earth's crust is 0.03-0.1%.[1] It is present in minerals and ores as sulfide, namely galena (lead sulfide), pyrite (iron sulfide), and cinnabar (mercury sulfide), as well as sulfate, for example, gypsum (calcium sulfate). In 1777, Lavoisier anticipated to the scientific world that sulfur is an element, not a compound. Elemental sulfur has enormous applications, such as matches, fungicide, and insecticide. It is one of the byproducts of petroleum refining and is extensively used in the contact process for the industrial preparation of sulfuric acid. Sulfuric acid is the key reagent for the industrial synthesis of ammonium sulfate, used as fertilizer. Sulfate derivatives are used as detergent and surfactant (sodium lauryl sulfate). Calcium sulfate and gypsum are used in portland cement. Sulfur is also used as lotions, creams, powders, soaps, and additives for bathing and treating acne and dermatitis.[2] Elemental sulfur is used in the vulcanization of rubber. Disulfide bonds are used to stiffen rubber. It also gives mechanical strength to the protein keratin, found in nails, skin, hair. A potent vesicant, sulfur mustard was used as a blister agent. Sulfur is used to make cellophane and rayon.[3] Some of sulfur compounds give foul smells, such as hydrogen sulfide and thiols. Despite that, ethanethiol is used in the LPG cylinder to detect the leakage of the cylinder.

Organosulfur compounds are an important class of organic compounds having biological and industrial values. Organosulfur compounds are a subclass of organic substances,[4a] and they exhibit rich chemistry in addition to their biological activities.[4b,c] The naturally occurring organosulfur compounds include amino acids (cysteine, methionine), vitamins (biotin, thiamine), and cofactors (glutathione, thioredoxin), which are required for our day-to-day life. The characteristic smell of garlic and onion is produced due to the presence of organosulfur compounds. Some of the naturally occurring organosulfur compounds are shown in Figure 1.1.

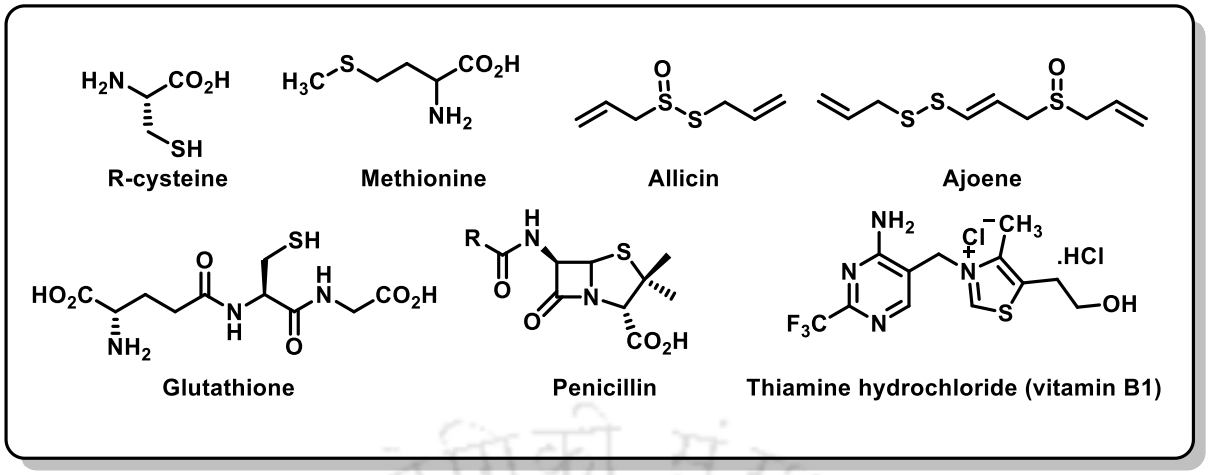


Figure 1.1. Some of the potent naturally occurring organosulfur compounds

Some of the synthesized organosulfur compounds having numerous practical applications are shown in Figure 1.2.

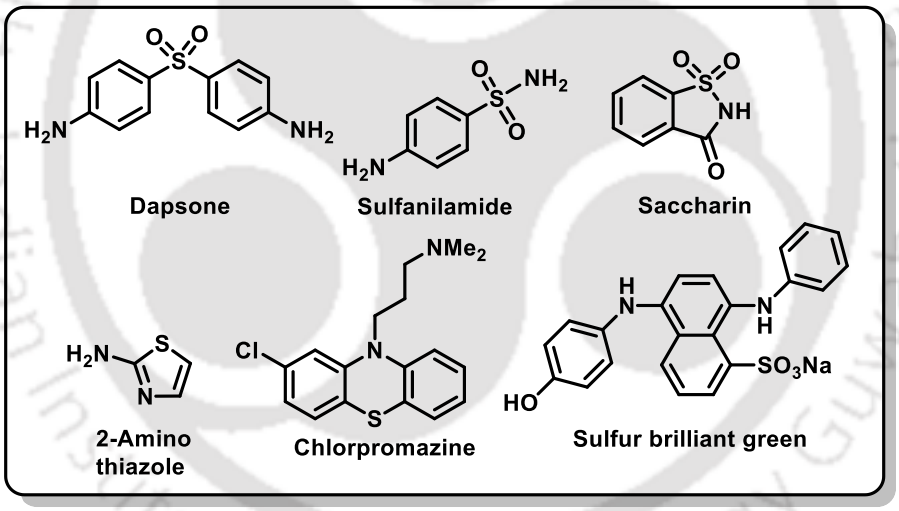


Figure 1.2. Synthetic organosulfur compounds have different biological activities and applications

Organosulfur compounds play an important role in pharmaceuticals, dyestuffs, and agrochemicals. Most sulfur-containing drugs are penicillin, cephalosporin, and monobactam and some of them act against bacteria. Organosulfur compounds have potential as anti-mutagenic and anti-carcinogenic properties. Allicin found in garlic has anticarcinogenic properties were reported first by Weisberger and Pensky.[5] Organosulfur compound plays a vital role in the pharmaceutical industry, bioactive natural products, and synthetic equivalents for asymmetric synthesis.[6] In the Umpolung strategy, 1,3-propane dithiol is extensively used for the protection of the carbonyl group. Sulfur-containing organic molecules play a leading

role in the treatment of tumors,[7] cancer,[8] HIV,[9] allergies,[10] heart disease,[11] and bacterial infections.[12] The antibiotic penicillins are effective against syphilis bacterial infections caused by staphylococci and streptococci. Prevacid is a proton-pump inhibitor (PPI) constraint to produce gastric acids in the stomach. Organosulfur compounds are also a key component of insecticides, fungicides, agricultural chemicals, food additives, dyes.[13] Detergent contains long-chain sulfonic acid.[14] Organosulfur compounds such as dimethyl sulfoxide (DMSO), carbon disulfide (CS_2) are crucial solvents as well as a reagent for an organic laboratory.

As a matter of fact, organosulfur compounds are important for synthetic organic and material chemistry.

1.2. Literature reviews on 4-hydroxydithiocoumarin

Coumarin and chromone are valuable compounds present in natural products and organic molecules.[15] Coumarin was reported as a natural product around 1820. Because of its pleasant odour, coumarin was used as a perfume until 1882. 4-Hydroxythiocoumarin structurally resembles 4-hydroxycoumarin and it is a naturally occurring compound with a wide range of biological activities. From the earlier literature reports, it was shown that 4-hydroxycoumarin containing nucleus has biological activities such as anticoagulant, antifungal, rodenticidal or molluscicidal.[16] The biological activity was also exhibited in a series of similar 4-hydroxythiocoumarins, which got my attention in discovering more about dithio-analogous. As a result, 4-hydroxydithiocoumarin is an attractive prospect to investigate during my research. Analogous structures of 4-hydroxycoumarin are shown in Figure 1.3.

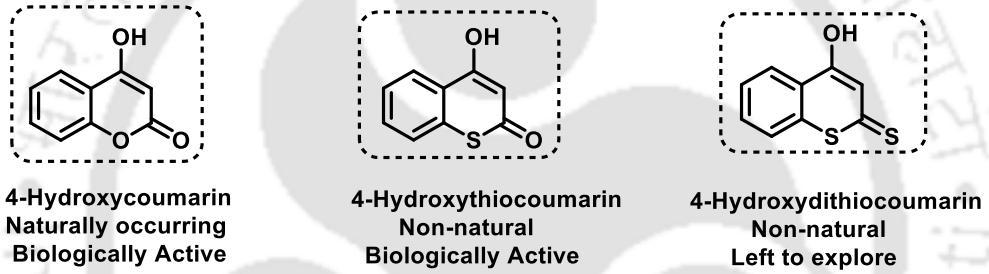
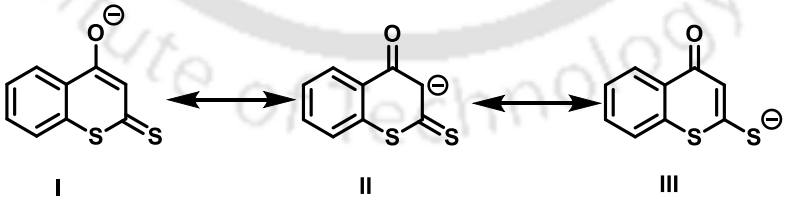


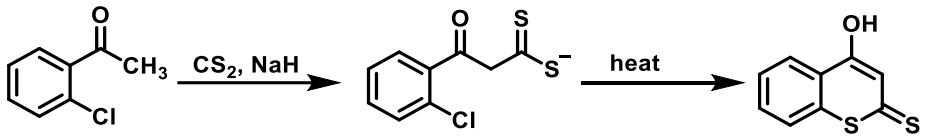
Figure 1.3. Analogous structures of 4-hydroxycoumarin

After deprotonation of 4-hydroxydithiocoumarin, it can exist as three possible resonating structures shown in Scheme 1.1. It has three reactive sites and it can react through oxygen nucleophile, carbon nucleophile, or sulfur nucleophile.



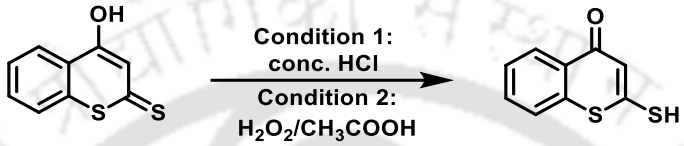
Scheme 1.1. Resonating structures of 4-hydroxydithiocoumarin

The first method to synthesize 4-hydroxydithiocoumarin was reported in 1987 by Anderson-McKay and his co-workers by reacting 2′-chloroacetophenone with carbon disulfide in presence of a strong base sodium hydride,[17] as shown in Scheme 1.2.



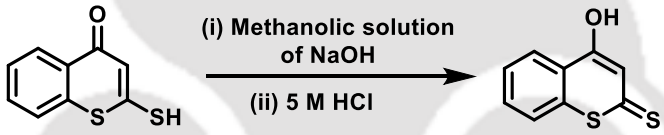
Scheme 1.2. Synthesis of 4-hydroxydithiocoumarin

According to Anderson-McKay and Liepa, 4-hydroxydithiocoumarin can be transformed into thiol form by treating it with either concentrated HCl or acetic acid in combination with hydrogen peroxide.



Scheme 1.3. 4-Hydroxydithiocoumarin in its thiol form

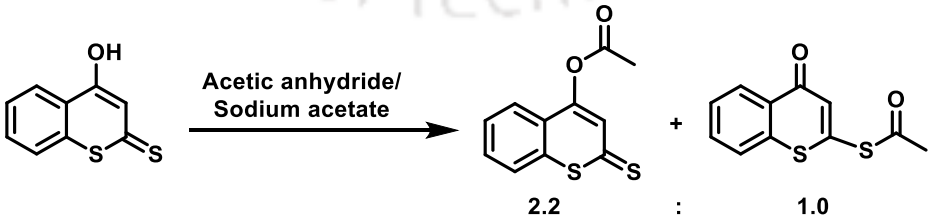
By dissolving in methanolic sodium hydroxide followed by acidification with 5 M HCl, 2-mercapto-1-thiochromone is converted into 4-hydroxydithiocoumarin.



Scheme 1.4. Reconversion from thiol form of 4-Hydroxydithiocoumarin

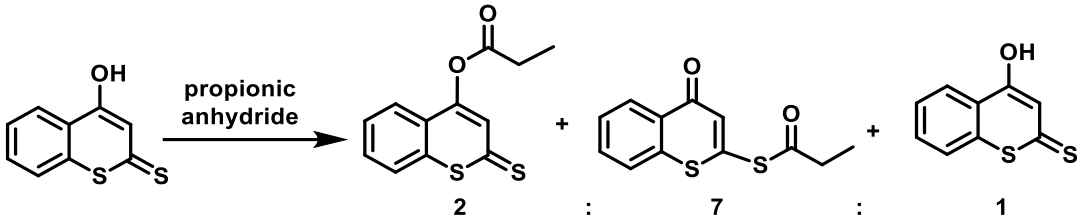
Therefore, the interconversion between 4-hydroxydithiocoumarin and its thiol form is not so easy under neutral conditions.

The same group reported when 4-hydroxydithiocoumarin was acetylated with acetic anhydride in the presence of sodium acetate, it provided a mixture of *O*-acetylated as well as *S*-acetylated products in the ratio 2.2:1.0.



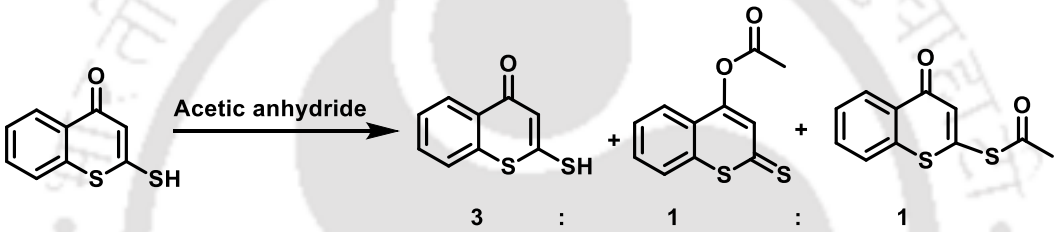
Scheme 1.5. Acylation of 4-hydroxydithiocoumarin

On the other hand, propionic anhydride provided *O*-propionate and *S*-propionate in the different ratios along with unreacted 4-hydroxydithiocoumarin as shown in Scheme 1.6.



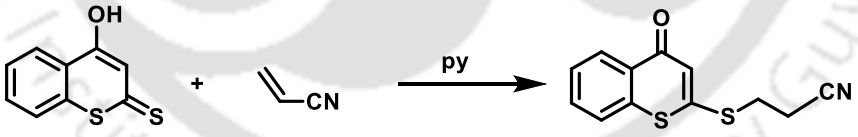
Scheme 1.6. Product ratio obtained on reaction with propionic anhydride

Interestingly, the acetylation of 2-mercapto-1-thiochromone was provided with a 3:1:1 mixture of 2-mercapto-1-thiochromone, *O*-acetylated product, and *S*-acetylated product as shown in Scheme 1.7.



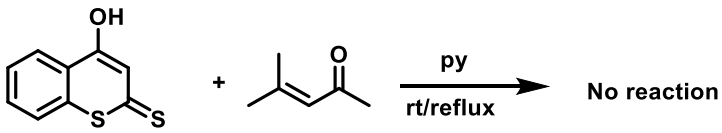
Scheme 1.7. Acylation of 2-mercapto-1-thiochromone

4-Hydroxydithiocoumarin on reaction with acrylonitrile provided thia-Michael addition product in 10% yield as shown in Scheme 1.8.



Scheme 1.8. The reaction between 4-hydroxydithiocoumarin and acrylonitrile

However, the similar thia-Michael addition product is a failure when the reaction was carried out with mesityl oxide.



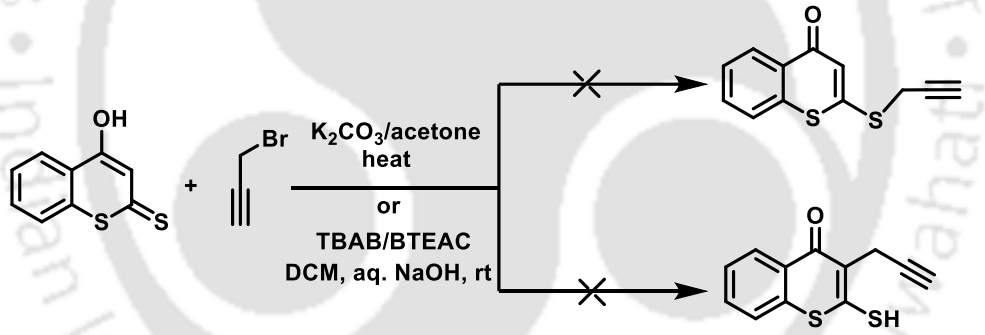
Scheme 1.9. Reaction behaviour of 4-hydroxydithiocoumarin and mesityl oxide

We may conclude from the acetylation reaction, 4-hydroxydithiocoumarin and its resonating structure 2-mercapto-1-thiochromone do not give similar kinds of reaction products. Similarly, 4-hydroxydithiocoumarin has very little reactivity with α,β-unsaturated compounds towards the thia-Michael addition reaction. Therefore, it reveals that 4-hydroxythiocoumarin and its resonating structure 2-mercapto-1-thiochromone are not having identical reaction behaviour.

1.3. Utilization of 4-hydroxydithiocoumarin in different types of reaction

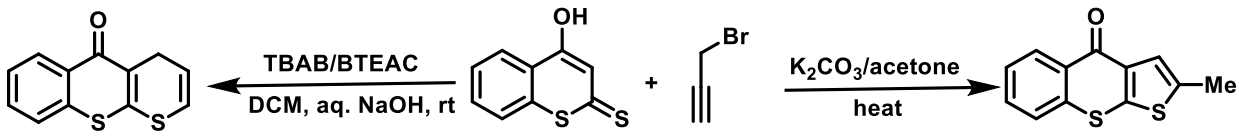
1.3.a. Pericyclic reaction

To explore the chemistry of 4-hydroxydithiocoumarin, Majumdar *et al*. have investigated reactions between 4-hydroxydithiocoumarin and propargyl bromide under classical alkylation using K_2CO_3/acetone as well as phase transfer catalyzed alkylation (TBAB/BTEAC in DCM) and the expected product should have been obtained based on earlier acetylation reaction either *O*-propargylated 4-hydroxydithiocoumarin or *S*-propargylated product as shown in Scheme 1.10.



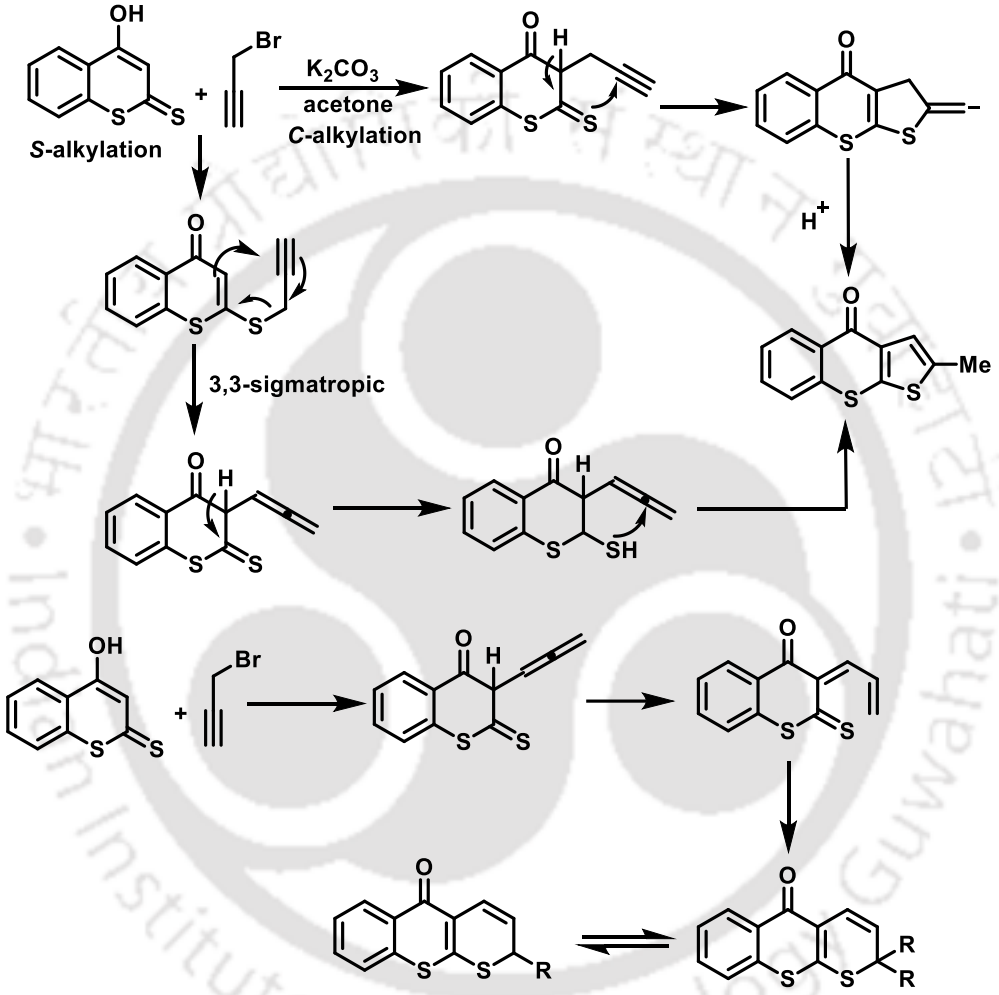
Scheme 1.10. Expected product on reaction with 4-hydroxydithiocoumarin and propargyl bromide

However, they have isolated two products such as 2-methyl-4*H*-thieno[2,3-*b*]thiochromen-4-one under classical condition and 4*H*,5*H*-thiopyrano[2,3-*b*]thiochromen-5-one under phase transfer catalyzed reaction conditions. They have proposed that the product formation goes through the *S*-alkylation followed by cyclization or *C*-alkylation followed by cyclization.



Scheme 1.11. Regioselective propargylation followed by sigmatropic rearrangement of 4-hydroxydithiocoumarin

After first *C*-alkylation, thiophene might result from a [3,3]-sigmatropic rearrangement of traditional cyclization under mild reaction conditions. However, thiopyran is formed from a [1,3-H] shift in an allenyl intermediate following initial *S*-alkylation through S_N2' reaction (Scheme 1.11).[18] From these studies, we may conclude that 4-hydroxydithiocoumarin has more propensity to react either through C=S or C-3 position rather than a hydroxyl group at the 4th position in basic conditions.

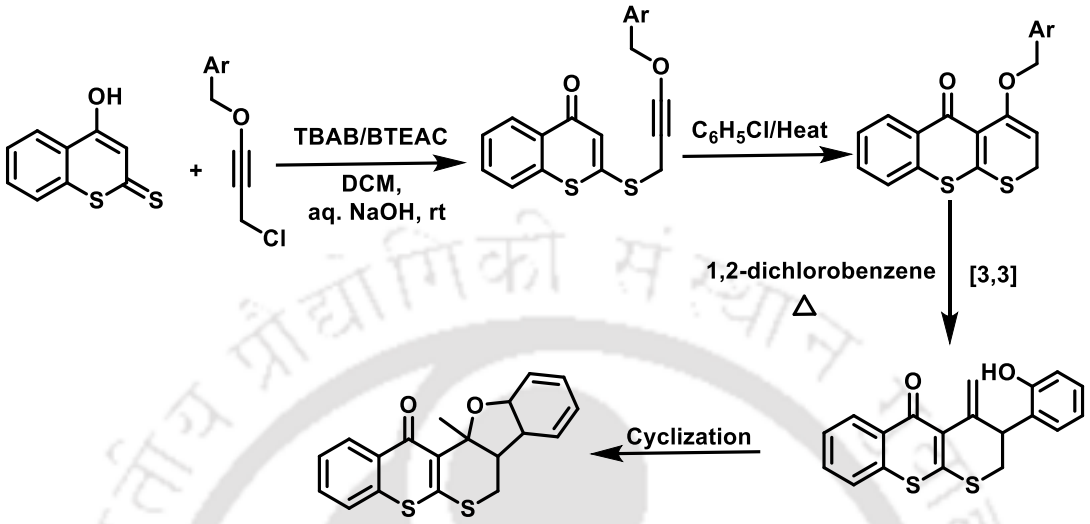


Scheme 1.12. Reaction mechanism for the synthesis of thiopyran and thiophene

Not only that, but also it infers that 4-hydroxydithiocoumarin can exist its resonating structure 2-mercapto-1-thiochromone under basic condition, which contradicts the earlier observation of Anderson and his co-workers mentioned in Scheme 1.4.

Subsequently, Majumdar *et al*. also observed that the phase transfer catalyzed (PTC) *S*-alkylation of 4-hydroxydithiocoumarins by using different 1-aryloxy-4-chloro-but-2-ynes as alkylating reagents. The alkylation step was faster in PTC conditions than simply heating with acetone/K_2CO_3. Then the *S*-alkylated products were converted into 4-(aryloxymethyl)-

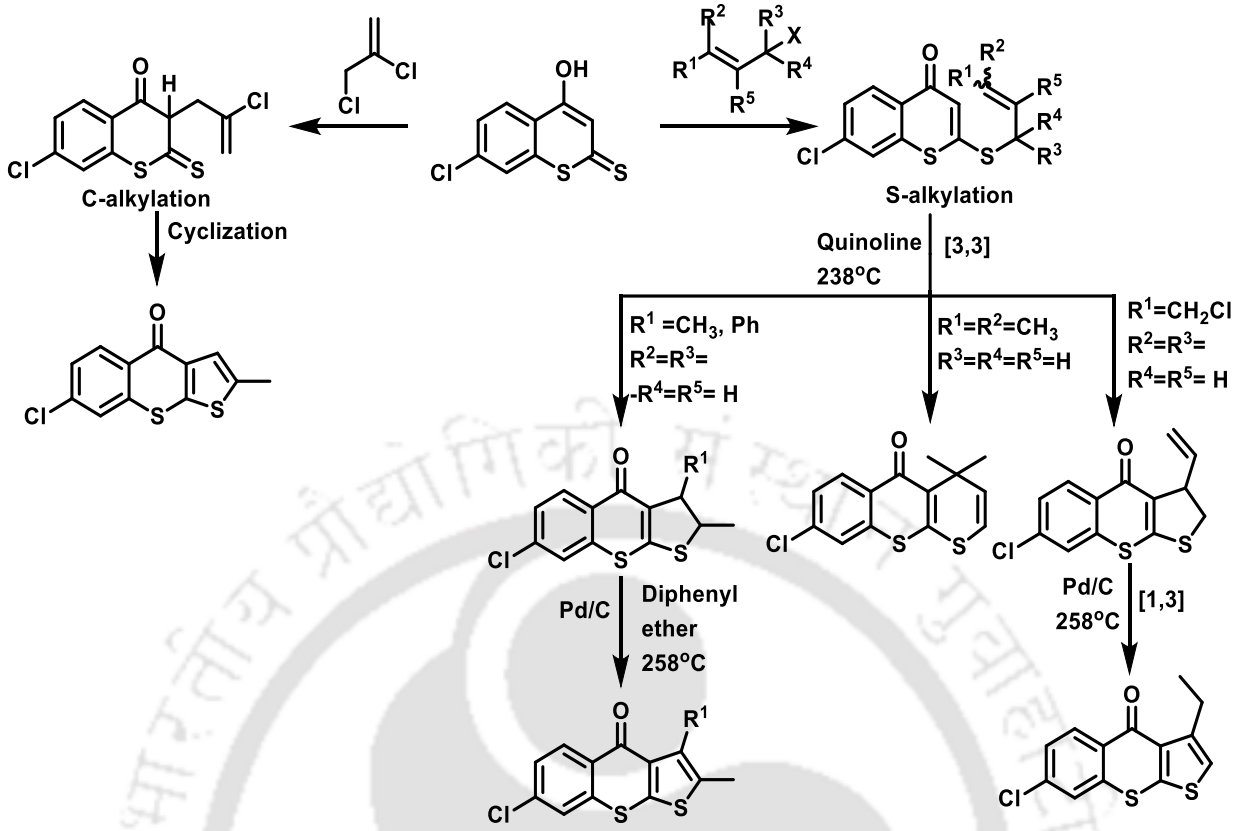
thiopyrano[2,3-*b*]benzothiopyran-5(2*H*)-ones on heating in chlorobenzene as shown in Scheme 1.13. The formation of the product is going through a [3,3] sigmatropic reaction followed by an electrocyclic ring closure reaction.[19]



Scheme 1.13. Thiopyran synthesis *via* a [3,3] sigmatropic reaction

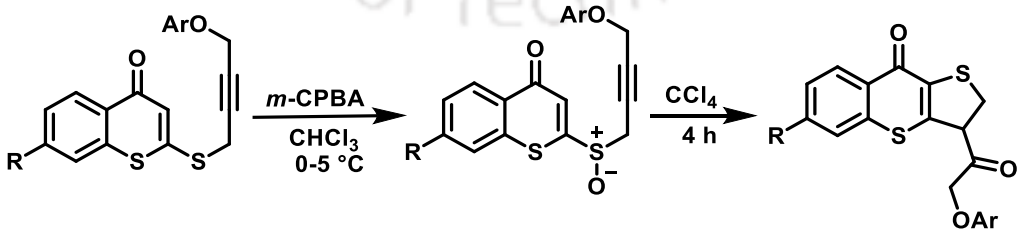
They have demonstrated further a regioselective protocol to access thiocoumarin based pentacyclic compound from 4-(aryloxymethyl)thiopyrano[2,3-*b*]benzothiopyran-5(2*H*)-ones by utilizing sequential [3,3] sigmatropic rearrangements and followed by cyclization (Scheme 1.13).[20] We may conclude from this observation that C=S site in 4-hydroxydithiocoumarin is more reactive as compared to the hydroxyl group at the 4-position.

The reactivity of 4-hydroxydithiocoumarin with different allyl halides under phase transfer catalyzed reaction was testified by Bandopadhyay *et al.* Astonishingly, it was detected that, in the case of 2,3-dichloropropene, *C*-alkylation followed by cyclization was taking place in a single step at room temperature, and directly the cyclized product of 2-methylthieno[2,3-b]thiochromen-4-one was obtained, whereas, in case of other substituted allyl halide, the derivatives of *S*-alkylated thiochromen-4-ones formed initially and succeeding treatment with quinoline it undergoes [3,3] sigmatropic rearrangement, followed by rapid enolization to form allyl-ene-thiols delivered the cyclized products. The products were further oxidized by heating in diphenyl ether at 258 °C, shown in Scheme 1.14.[21]



Scheme 1.14. Synthesis of sulfur heterocycles by thio-Claisen rearrangement

Not only [3,3] sigmatropic rearrangement was studied for *S*-alkylated derivatives of 4-hydroxydithiocoumarin, it also displayed the [2,3] sigmatropic rearrangement, while after chemoselectively converting one sulfur into corresponding sulfoxides, leaving the other reactive centers unreactive. Predominantly, sulfoxides moieties were quite unstable, and underwent intramolecular, [2,3] sigmatropic rearrangement. A [3,3]-sigmatropic rearrangement follows, resulting in an enone intermediate. Finally, the required products were obtained in good to exceptional yields *via* an intramolecular Michael reaction.[22]

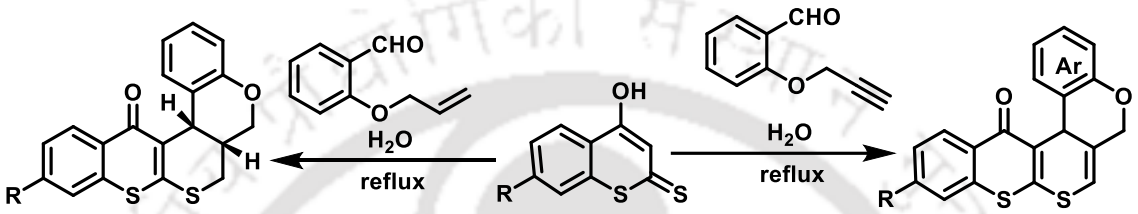


Scheme 1.15. Synthesis of thiocoumarin annulated dihydrothiophenes *via* consecutive [2+3] and [3+3] sigmatropic rearrangement

From all these reactions, it has been noted 4-hydroxydithiocoumarin reacts preferentially at the C=S position with chlorinated alkyl halides.

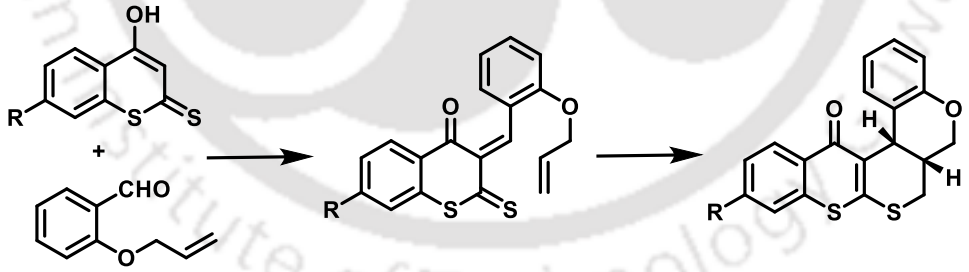
1.3.b. Hetero-Diels-Alder Reactions

In 2010, the same research group demonstrated the synthetic utility of Domino-Knoevenagel-Hetero-Diels-Alder reactions (DKHDA) to synthesize thiocoumarin-based polycyclic structures utilizing 4-hydroxydithiocoumarins and different *O*-allyl/crotyl and *O*-propargyl derivatives of salicylaldehyde in the aqueous medium (Scheme 1.16).[23]



Scheme 1.16. Domino-Knoevenagel-Hetero-Diels-Alder reactions

Since sulfur-containing hetero-dienes are more polarizable than oxygen-containing hetero-dienes, [6,6]-fused thiopyranobenzopyran derivatives were generated over pyranobenzopyran derivatives in a regioselective manner. The authors extended the reaction's substrate scope to include *O*-allylated salicylaldehyde derivatives and a variety of additional *O*-propargylated salicylaldehydes. As evidenced by the cis product formation, the *O*-allylated salicylaldehyde interacts *via* endo selectivity.

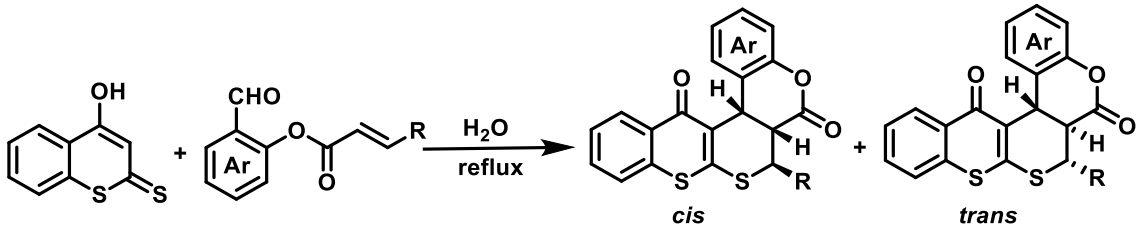


Scheme 1.17. Reaction mechanism for DKHDA reaction

Later on, Moghaddam *et al*. have extended a similar strategy to synthesize the pentacyclic compounds as shown in Scheme 1.18 by employing 4-hydroxydithicoumarins and *O*-acrylated salicylaldehydes.

With a substrate containing an electron-withdrawing group added to them, the *O*-cinnamoylated salicylaldehyde derivatives provided the trans products as the predominant product, yielding more than 90%. Interestingly, the major products of *O*-crotonoylated

salicylaldehyde derivatives were cis isomers. An endo and exo-orientation of the dienophile in the transition state produced the cis and trans isomers (Scheme 1.18).[24]

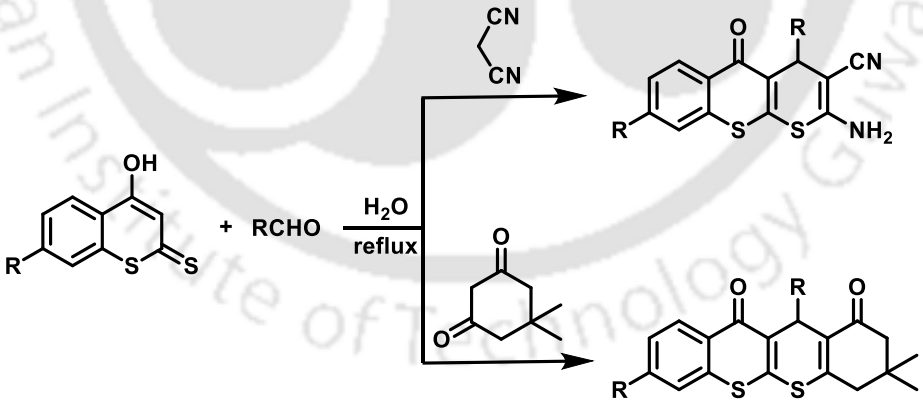


Scheme 1.18. Hetero Diels Alder reaction between *O*-acrylated salicylaldehydes and 4-hydroxydithiocoumarin

From these two investigations, we may say that the C-3 position can react with the aromatic aldehyde to give Knoevenagel product in an aqueous medium under reflux conditions.

1.3.c. Multicomponent reactions

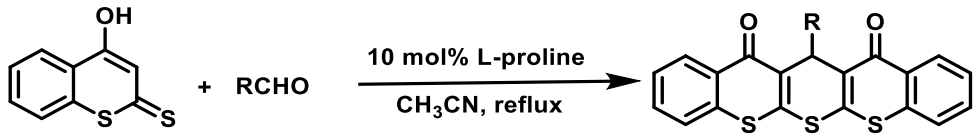
In MCR, 4-hydroxydithiocoumarins have been utilized to make tricyclic and tetracyclic heterocyclic molecules using three-component reactions as shown in Scheme 1.19. Majumdar and colleagues reported a three-component reaction of 4-hydroxydithiocoumarins, aldehydes, and active methylene group-containing compound in water in 2011. Several aldehydes interacted in this reaction, yielding good to excellent products (Scheme 1.19).[25] The reaction is regioselective as *S*- and *C*- the nucleophilic site is more active over *O*- nucleophilic site.



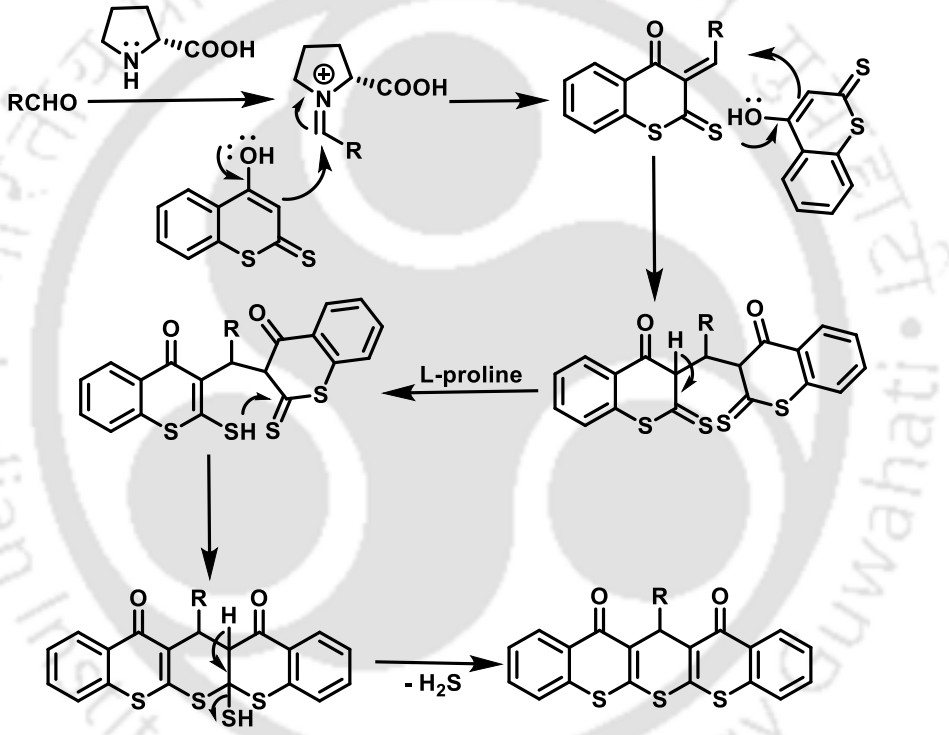
Scheme 1.19. The reaction of aldehydes, 4-hydroxydithiocoumarin and malononitriles/dimedones

For the synthesis of thiocoumarin-annulated thiopyrans, our group developed an L-proline catalyzed pseudo-three-component reaction of 4-hydroxydithiocoumarins and aldehydes in 2014. Several aldehydes, both aromatic and aliphatic, were tolerated well in the reactions, yielding substantial yields of the products (Scheme 1.20).[26] The reaction is catalyzed by L-

proline and involves Knoevenagel reactions of 4-hydroxydithiocoumarin and aldehyde, followed by Michael's attack on the Knoevenagel adduct by another 4-hydroxydithiocoumarin molecule. Finally, cyclization causes H_2S to be released from pentacyclic molecules.



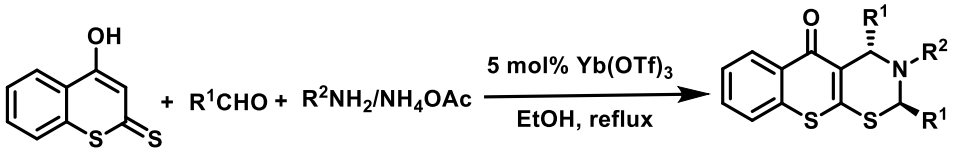
Scheme 1.20. L-proline catalyzed pseudo-three-component reaction of aldehydes and 4-hydroxydithiocoumarin



Scheme 1.21. Reaction mechanism of the pseudo-three-component reaction

Later, employing 4-hydroxydithiocoumarin, aldehydes, and aliphatic amines/ammonium acetate, our group discovered a $Yb(OTf)_3$ catalyzed regioselective pseudo-four-component synthesis.[27] Under mild reaction conditions, several thiocoumarin-based thiazines were synthesized in good yields. This reaction tolerated both electron-rich and electron-deficient aromatic aldehydes, as well as different aliphatic amines (Scheme 1.22). However, aliphatic aldehydes and aromatic amines failed to function, limiting the reaction's synthetic potential. The mechanism of the reaction explores another aspect of 4-hydroxydithiocoumarin reactivity, in which an intermolecular hetero-Diels Alder reaction involving an electron-

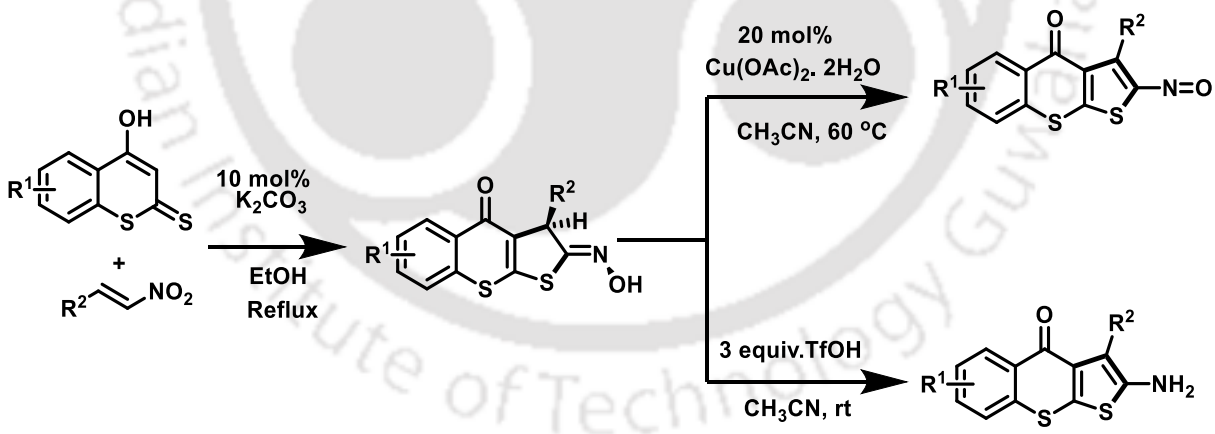
deficient hetero diene and an electron-rich hetero dienophile reacts to produce the desired MCR product with regioselectivity.



Scheme 1.22. A pseudo-four-component reaction of aldehydes and 4-hydroxydithiocoumarin

In 2017, our group succeeded in synthesizing thieno[2,3-*b*]thiochromen-4-one oximes by a thio [3+2] cyclization reaction of 4-hydroxydithiocoumarin and *trans*-β-nitrostyrene with K_2CO_3 catalyst, followed by the synthesis of corresponding amine and nitroso derivatives as shown in Scheme 1.23.[28] In the presence of K_2CO_3, 4-hydroxydithiocoumarin can form an ambident anion. 3-Position of 4-hydroxydithiocoumarin attacks *trans*-β-nitrostyrene and further cyclization followed by water elimination. Here sulfur acts as a better nucleophilic candidate than oxygen due to its large size.

The product is converted to the corresponding amine by treatment with 3 equivalents of TfOH. The product undergoes functional group conversion to yield the corresponding nitroso compound upon treatment with $Cu(OAc)_2$.

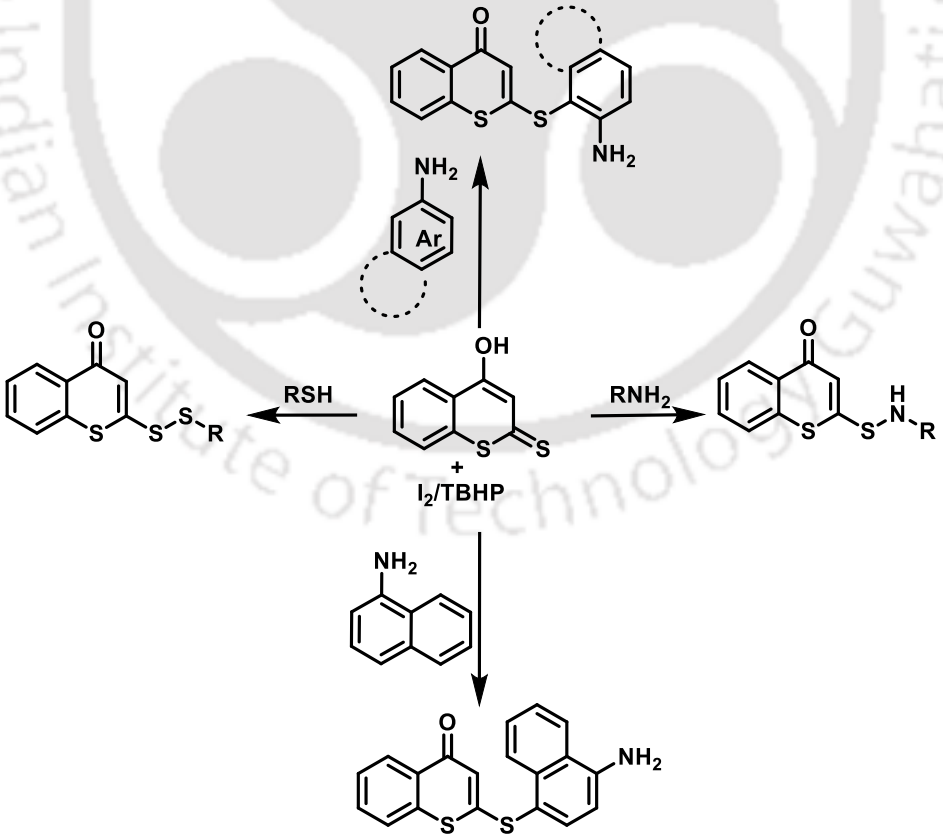


Scheme 1.23. The reaction of 4-hydroxydithiocoumarin and trans-β-nitrostyrene

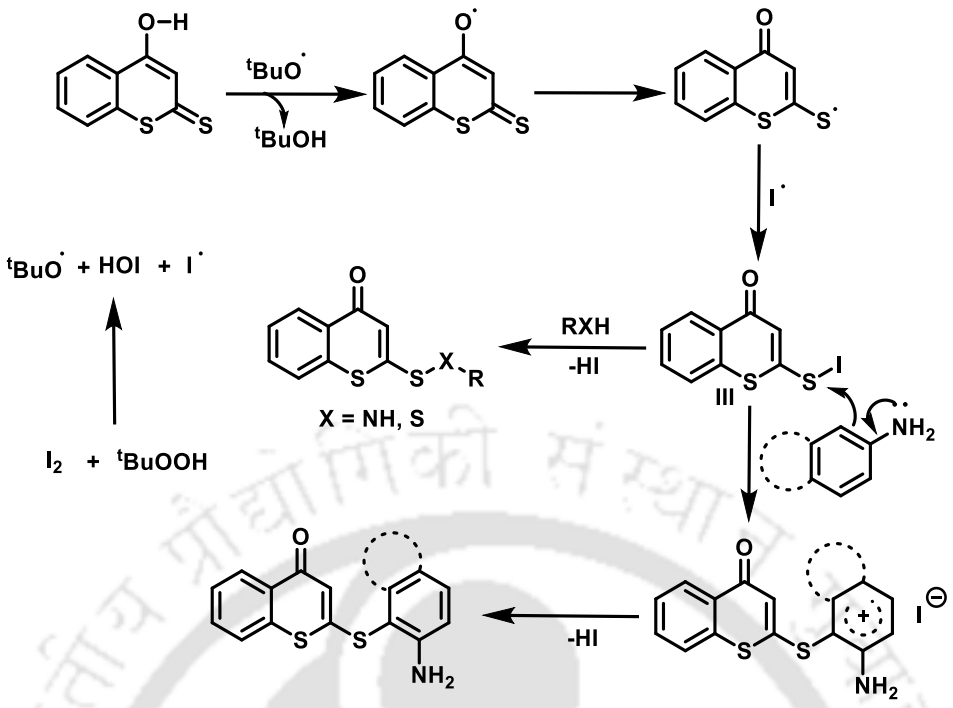
From all these reaction behaviours, it has shown us 4-hydroxydithiocoumarin can react at three possible sites such as 4-OH position, C=S position, and C-3 position which is verified.

1.3.d. Oxidative Cross-coupling reactions

From earlier reaction behaviour, 4-hydroxydithiocoumarin can exist three possible reactive intermediates depending upon the reaction conditions and reagents used. In 2018, motivated by the intriguing formation of bonds through cross-coupling strategy, our group discovered the reactivity of the electron-rich 4-hydroxydithiocoumarin to oxidative coupling reactions with nucleophiles such as amines and thiols. Oxidative cross-coupling with S-H bond of 4-hydroxydithiocoumarin chemoselectively built up *S-N*, *S-C*, and *S-S* bonds depending on the reactivity of the nucleophiles are used in the reactions (Scheme 1.24).[29] As a result, oxidative cross-coupling reactions using aliphatic amines as well as aromatic amines like different anilines as nucleophiles resulted in an effective *S-C*. Strongly electron-rich amines such as anthracylamines, naphthylamines, and 3-aminocoumarins, on the other hand, reacted selectively in the construction of oxidative *S-C* bonds. Another notable aspect of the reaction was that it occurred at the C-4 position of the naphthyl amines instead of the C-2 position with 1-naphthylamine only. Furthermore, some significant *S-S* bonds were achieved under optimal conditions employing thiols.



Scheme 1.24. Oxidative cross-coupling reactions of 4-hydroxydithiocoumarin with a different nucleophile



Scheme 1.25. Mechanism of oxidative cross-coupling reactions

Some of the produced compounds were examined for biological activity and found to have potential anti-proliferative action against the breast cancer cell line MCF7.

From all these reactivity studies from 4-hydroxydithiocoumarin, still there is a scope to synthesize a new molecule from 4-hydroxydithiocoumarin under various reaction conditions.

From the 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 develop new and efficient catalytic routes towards the synthesis of novel organosulfur molecules in an eco-friendly manner with good yields. Thus, the thesis work is designed to employ 4-hydroxydithiocoumarin as an efficient starting material for the synthesis of new organosulfur molecules i.e., 3-sulfenylindole, α-thiocarbonyl, vinyl sulfide, thioether, 1,4-oxathiin, β-hydroxysulfide, β-aminosulfide, 2,3-dihydro-1,4-oxathiin and 2,3-dihydro-1,4-thiazine derivatives *via* fine-tuning of the reaction conditions which will be discussed in the successive chapters of this thesis.

1.4. Origin of our Research problems for the present thesis work

Considering the different reactive sites of 4-hydroxydithiocoumarin, we have chosen different electrophiles and nucleophiles like indoles, acetylenes, styrenes, epoxides, aziridines, and 1,3-dicarbonyl compounds to design our anticipated molecules. The major portion of this thesis deals with the development of a new methodology for the synthesis of new bioactive molecules using 4-hydroxydithiocoumarin as key starting material. The other part, relatively a minor portion, of the thesis is to investigate the biological importance of newly synthesized molecules. The results achieved throughout these syntheses are divided into five chapters. Lastly, a summary and future scopes are presented. A brief outline of all these chapters is discussed below:

1.4.a. 3-Sulfenylindole

3-Sulfenylindole moiety-containing compounds are known to exhibit a variety of potential biomedical applications. Our goal has to incorporate 3-sulfenylindole moiety in the new molecule *via* an oxidative cross dehydrogenative coupling reaction of 4-hydroxydithiocoumarin using the *S*-reactive site with indole. With the help of computational prediction and docking study, 3-sulfenylindole may be especially useful synthons in biomedical applications. The search for new scaffolds might be widening the range of biomedical research. Therefore, it was decided to synthesize novel 3-sulfenylindoles and study their potential in the biological application.

1.4.b. α-thiocarbonyls

1,3-Dicarbonyl compound acts as a crucial starting material in organic synthesis. Many pharmaceutically valuable heterocyclic molecules such as pyrazoles, oxazoles, diazepines, etc. utilize β-diketones as essential building blocks. The sulfenylation of β-diketones, without any deacylation, remains a great challenge. Accepting the challenge, we have tried to construct this moiety with 4-hydroxydithiocoumarin and 1,3-dicarbonyl compounds. Finally, the utility of the reaction was demonstrated by preparing pyrazole and α, α-disubstituted β-diketones.

1.4.c. Vinyl sulfides and thioethers

Vinyl sulfides and thioethers both are highly useful and valuable building blocks for the synthesis of natural products and bio-active molecules. A few of the thioether-containing compounds such as Monatelukast and Neflinavir used to act as the component of medicine for the treatment of asthma and HIV, respectively.

Synthesizing these target molecules will be significant for the study of different areas of synthetic and applied chemistry. As a result, we have decided to synthesize vinyl sulfides/thioethers, starting from 4-hydroxydithiocoumarin and phenylacetylenes/styrenes.

1.4.d. 1,4-Oxathiins

1,4-Oxathiin is a highly demanding structural motif in the agricultural, chemical, and pharmaceutical research fields. For example, carboxin and its sulfone derivative having 1,4-oxathiin moiety exhibit antifungal activity and are used as pesticides. Similarly, another 1,4-oxathiin derivative namely isovanillyl shows an artificial sweetening property. 1,4-Oxathiin is an important class of heterocyclic compounds, which attracts synthetic interest because of their numerous potential activities. Keeping this in our mind, we have designed the 1,4-oxathiins from 4-hydroxydithiocoumarin, phenylacetylene, and DMSO. It was aimed to explore these 1,4-oxathiins for other biological applications.

1.4.e. β-Hydroxysulfides/β-aminosulfides and 2,3-dihydro-1,4-oxathiin/2,3-dihydro-1,4-thiazine

β-Hydroxysulfides and β-aminosulfides serve as a significant building block for the synthesis of valuable biologically active compounds and natural products. These structural subunits are also an integral part of the drugs e.g., diltiazem, naltiazem, and nelfinavir. In this regard, the finding of a new kind of β-hydroxysulfides/β-aminosulfides was developed using 4-hydroxydithiocoumarin and epoxide/tosyl aziridine. 2,3-Dihydro-1,4-oxathiin and 2,3-dihydro-1,4-thiazine moiety-containing compounds are highly demanding structural motifs. Finally, we have designed the molecules 2,3-dihydro-1,4-oxathiin and 2,3-dihydro-1,4-thiazine from β-hydroxysulfides and β-aminosulfide.

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CHAPTER II

Synthesis of 3-sulfenylindole derivatives from 4-hydroxydi-thiocoumarin and indole using an oxidative cross dehydrogenative coupling reaction (OCDCR) and their biological study

Introduction

Results & Discussion

Experimental Section

2.1. Introduction

3-Sulfenylindole exists in small bioactive compounds with a wide range of biological functions.[1] They are utilized to treat tumors,[2] cancer,[3] allergies,[4] heart diseases,[5] and bacterial infections.[6] In addition, some of their sulfone derivatives exhibit anti-HIV properties.[7] Some biologically active compounds with the 3-sulfenylindole structural motif and its sulfone derivative are shown in Figure 2.1.

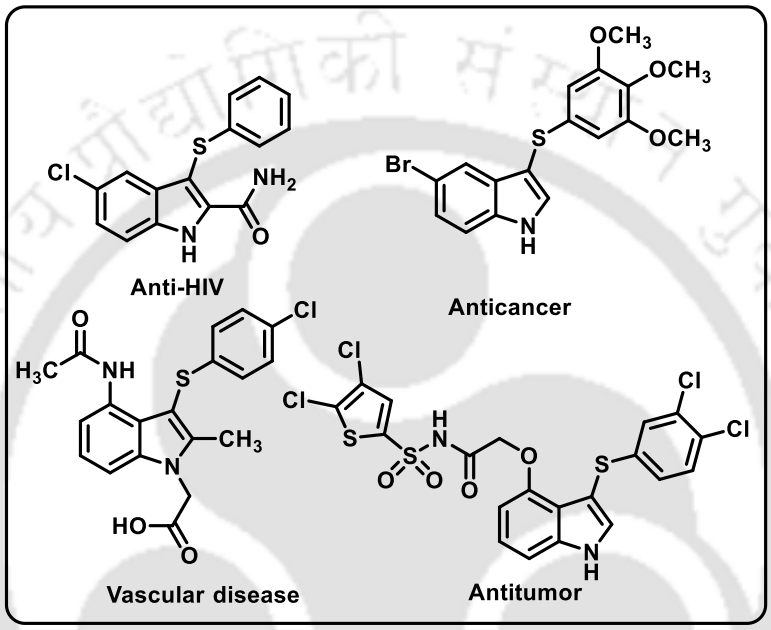


Figure 2.1. Biologically active 3-Sulfenylindole and its Sulfone derivatives

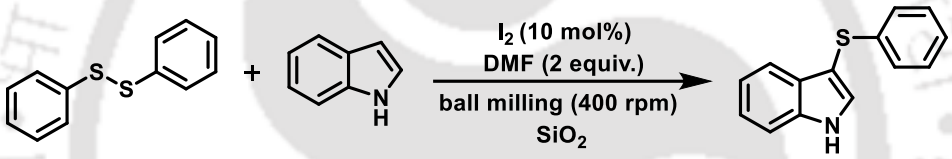
Due to a variety of their usefulness and applications, numerous synthetic strategies have been developed to prepare 3-sulfenylindole derivatives over the years.[8] These methods include the direct sulfenylation of the indole ring by thiols,[9] disulfides,[10] sulfonyl halides,[11] quinone mono-*O*,*S*-acetals,[12] *N*-(arylthio)-succinimides,[13] aryl sulfenyl halide,[14] sulfonyl hydrazide[15] or sodium sulfinates.[16]

2.2. Synthesis of 3-sulfenylindole derivatives

Sorabad *et al.* reported[17] the synthesis of 3-sulfenylindoles from thiols and indoles in the presence of a catalytic amount of 47% aqueous HBr in a 1:1 mixture of DMSO and chloroform at 100 °C as shown in Scheme 2.1.

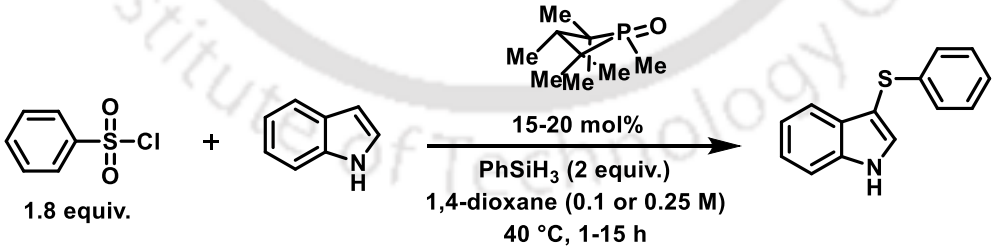
Scheme 2.1. Synthesis of 3-sulfenylindole from thiol and indole

Qin *et al.* described the iodine catalyzed first mechanochemical electrophilic sulfenylation of indoles. Here, mechanical strength provides the driving force to the organic reactions. The electrophilic C−H sulfenylation of indoles with disulfides is reported under the ball milling method, as shown in Scheme 2.2.[18]



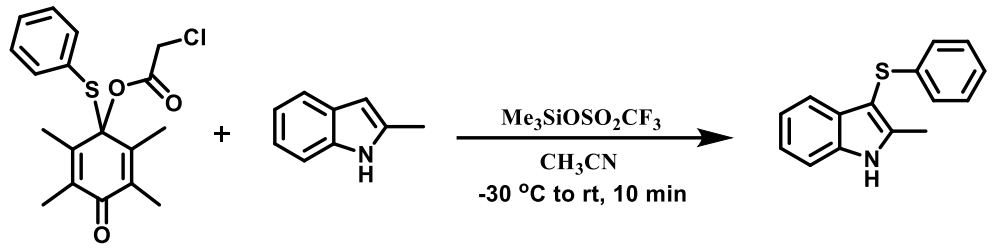
Scheme 2.2. 3-Sulfenylindole synthesis from indole and disulfide

Ghosh *et al.* reported the organophosphorus catalyzed synthesis of 3-sulfenylindoles from sulfonyl chlorides and indole as shown in Scheme 2.3. An advanced method in organophosphorus catalysis is catalytic chemistry motivated by reversible interconversion of phosphines and phosphine oxides.[19]



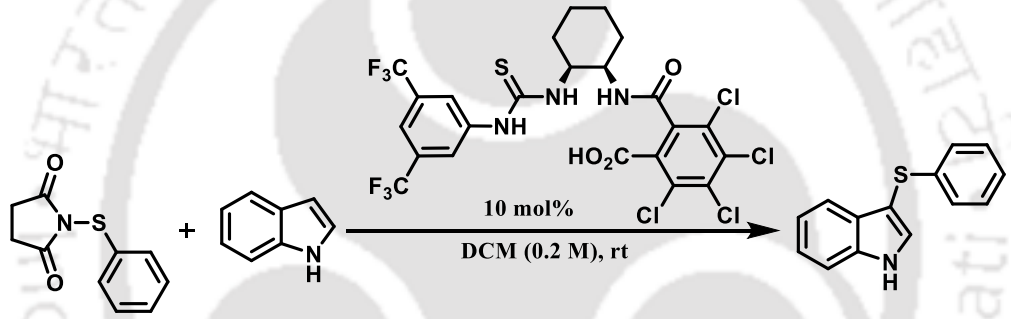
Scheme 2.3. 3-Sulfenylindole synthesis from sulfonyl chloride and indole

Matsugi *et al*. reported the synthesis of 3-sulfenylindole using quinone mono-*O*,*S*-acetal and indole as shown in Scheme 2.4.[20] They have reported the sulfenylation induced by aromatization of quinone mono-*O*,*S*-acetals under almost neutral conditions.



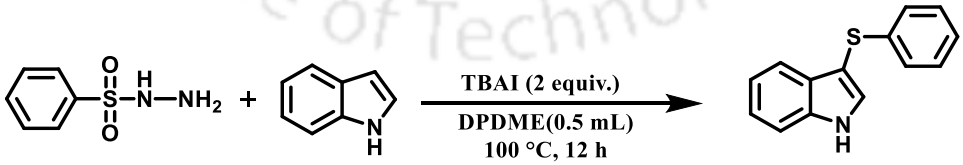
Scheme 2.4. 3-Sulfenylindole synthesis from quinone mono-*O*,*S*-acetal, and indole

Nalbandian *et al.* described the sulfenylation of indole in the presence of thiourea tethered to a carboxylic acid catalyst. Using this Lewis base, they have demonstrated the synthesis of 3-sulfenylindole from *N*-phenylthiol succinamide and indole as shown in Scheme 2.5.[21] They have also reported the substrate scope of the reaction with other *N*-containing heterocycles using similar reaction conditions.



Scheme 2.5. Synthesis of 3-sulfenylindole from *N*-phenyl thiosuccinamide and indole

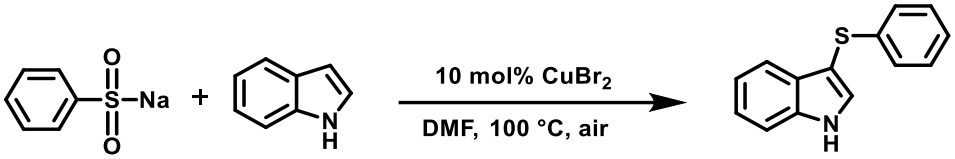
Yueting *et al.* reported TBAI-mediated C-H sulfenylation of indoles with sulfonyl hydrazides in dipropylene glycol dimethyl ether (DPDME).[22] They have also demonstrated the C-H sulfenylation of numerous electron-rich arenes, like naphthylamine, naphthol, aniline, pyrrole. Various aryl sulfides are reported with excellent functional group tolerance and in milder reaction conditions.



Scheme 2.6. Synthesis of 3-sulfenylindole from sulfonyl hydrazides and indoles

Luo *et al.* reported the synthesis of 3-sulfenylindoles from indole and sodium sulfinate in Cu/DMF reaction system as shown in Scheme 2.7.[23] In this reported method, sodium sulfinates

act as sulfenylating agents to afford 3-sulfenylindoles. Here, DMF plays a dual role, it acts as a reductant as well as solvent.



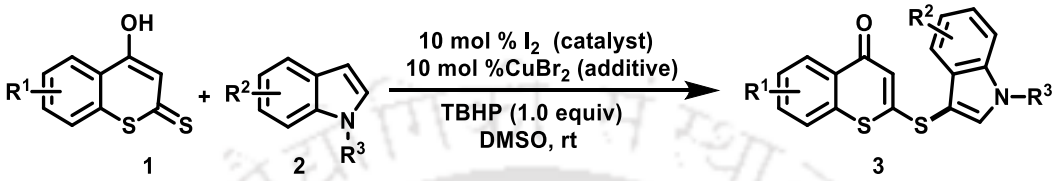
Scheme 2.7. Synthesis of 3-sulfenylindoles from indole and sodium sulfinate

Requirement of excess amount of strong bases, longer reaction time, expensive reagents, and air/water-sensitive reagents are some of the major drawbacks. Though these reagents are quite useful, still there is a further scope to develop a new methodology using a non-conventional sulfenylating source for the synthesis of 3-sulfenylindoles under a mild condition with higher efficiency, operational simplicity, and economic viability.

Inspired by our previous work for the formation of new *S-N*, *S-S,* and *S-C* bonds,[24] we envision that if various indole derivatives are utilized then the corresponding new class of either 3-sulfenyl indole derivatives or *S-N* bond formation products would be generated, which might exhibit interesting biological activity. Herein we report a direct regioselective sulfenylation of indole at the C-3 position with 4-hydroxydithiocoumarin using 10 mol% molecular iodine as a catalyst and 1 equivalent TBHP as well as 10 mol% $CuBr_2$ as additive.

2.3. Results & Discussion

This chapter presents the synthetic method for oxidative cross dehydrogenative coupling reaction between 4-hydroxydithiocoumarin and indole at the C-3 position regio-selectively using a combination of 10 mol% of molecular iodine and TBHP in the presence of 10 mol% $CuBr_2$ as an additive at room temperature.



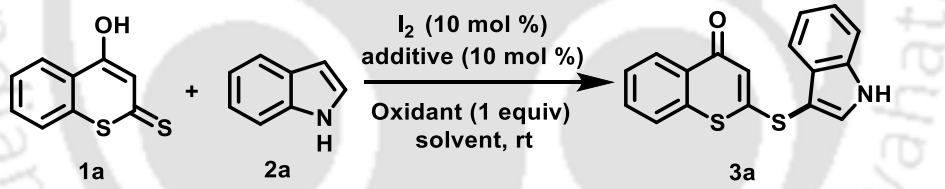
Scheme 2.8. Synthesis of 3-sulfenylindole derivatives

For our present study, various 4-hydroxydithiocoumarin derivatives were prepared from the respective 2′-chloroacetophenones and carbon disulfide in the presence of sodium hydride by the reported procedure.[25]

Taking cues from our earlier observation,[24] the reaction was carried out with 4-hydroxydithiocoumarin (**1a**, 0.5 mmol) and indole (**2a**, 0.5 mmol) in presence of 10 mol% molecular iodine and TBHP (1 equivalent) in DMSO and it gave a brown coloured solid product **3a** in 27% yield (Table 2.1, entry 1). The isolated product **3a** was characterized by IR, ^{1}H, and ^{13}C NMR spectra as well as from HRMS. In the IR spectrum, compound **3a** shows a characteristic peak at 1720 cm^{-1} for the presence of the C=O group. It indicates that the -OH group at the 4th position of the product is converted to C=O during oxidative cross dehydrogenative coupling reaction. In the ^{1}H NMR spectrum, it gives a characteristic signal at δ 6.9 ppm for a single proton for the C-3 hydrogen of 4-hydroxydithiocoumarin. In the ^{13}C NMR spectrum, C-3 of 4-hydroxydithiocoumarin appears at δ 94.16 ppm. Due to the disappearance of the peak at δ 6.52 ppm for C-3 hydrogen of indole in the ^{1}H NMR spectrum, it is concluded that the coupling took place at the C-3 position of indole moiety. To increase the yield of the product, the reaction was executed on a similar scale using a combination of I_2 (10 mol%), $CuBr_2$ (10 mol%), and 1 equivalent amount of TBHP (Table 2.1, entry 2). The yield was increased significantly from 27% to 75% (Table 2.1, entry 2). However, with increasing reaction temperature from room temperature to 120°C, the yield was not increased. The low yield was observed, which may be due to the decomposition of the product (Table 2.1, entry 3). To find out

the efficacy of other oxidants, the reactions were scrutinized using 1 equivalent H_2O_2 and $K_2S_2O_8$ in place of TBHP and it gave only 41% and 43% yield, respectively (Table 2.1, entry 4 & 5). To further improve the yield, the identical reactions were examined with a variety of metal catalysts like $CuCl_2$, $CuSO_4$, and $FeCl_3$ along with 10 mol% I_2 and 1 equivalent of TBHP (Table 2.1, entries 6-8). To verify the requirement of molecular I_2, two more reactions were also examined by employing 5 mol% and 20 mol% of I_2 (Table 2.1, entries 9 & 10), respectively. It provided only 50% yield with 5 mol% whereas the yield was not improved with 20 mol% of iodine as expected. No significant alteration of the yield was noticed while carrying out the reaction by increasing the amount of $CuBr_2$ from 10 mol% to 1 equivalent under similar reaction conditions (Table 2.1, entries 11-13). To find out the suitability of other solvents, the reactions were screened with THF, DCE, CH_3CN, and DMF, respectively and the results are not encouraging (Table 2.1, entries 14-17). From these observations, we may conclude that 10 mol% of $CuBr_2$ along with 10 mol% of I_2 and TBHP (1 equivalent) are the best reaction conditions in terms of best yield and reaction time (Table 2.1, entry 2).

Table 2.1. Optimization of the reaction conditions[a,b]



Entry	I_2 (mol%)	Oxidant (1 equiv)	Catalyst (mol%)	Solvent	Time (h)	% Yield[b]
01	10	TBHP	–	DMSO	5	27
02	**10**	**TBHP**	**$CuBr_2$(10)**	**DMSO**	**0.5**	**75**
03[c]	10	TBHP	$CuBr_2$(10)	DMSO	0.5	50
04	10	H_2O_2	$CuBr_2$(10)	DMSO	5	41
05	10	$K_2S_2O_8$	$CuBr_2$(10)	DMSO	5	43
06	10	TBHP	$CuCl_2$(10)	DMSO	0.75	48
07	10	TBHP	$CuSO_4$(10)	DMSO	0.5	51
08	10	TBHP	$FeCl_3$(10)	DMSO	0.75	39

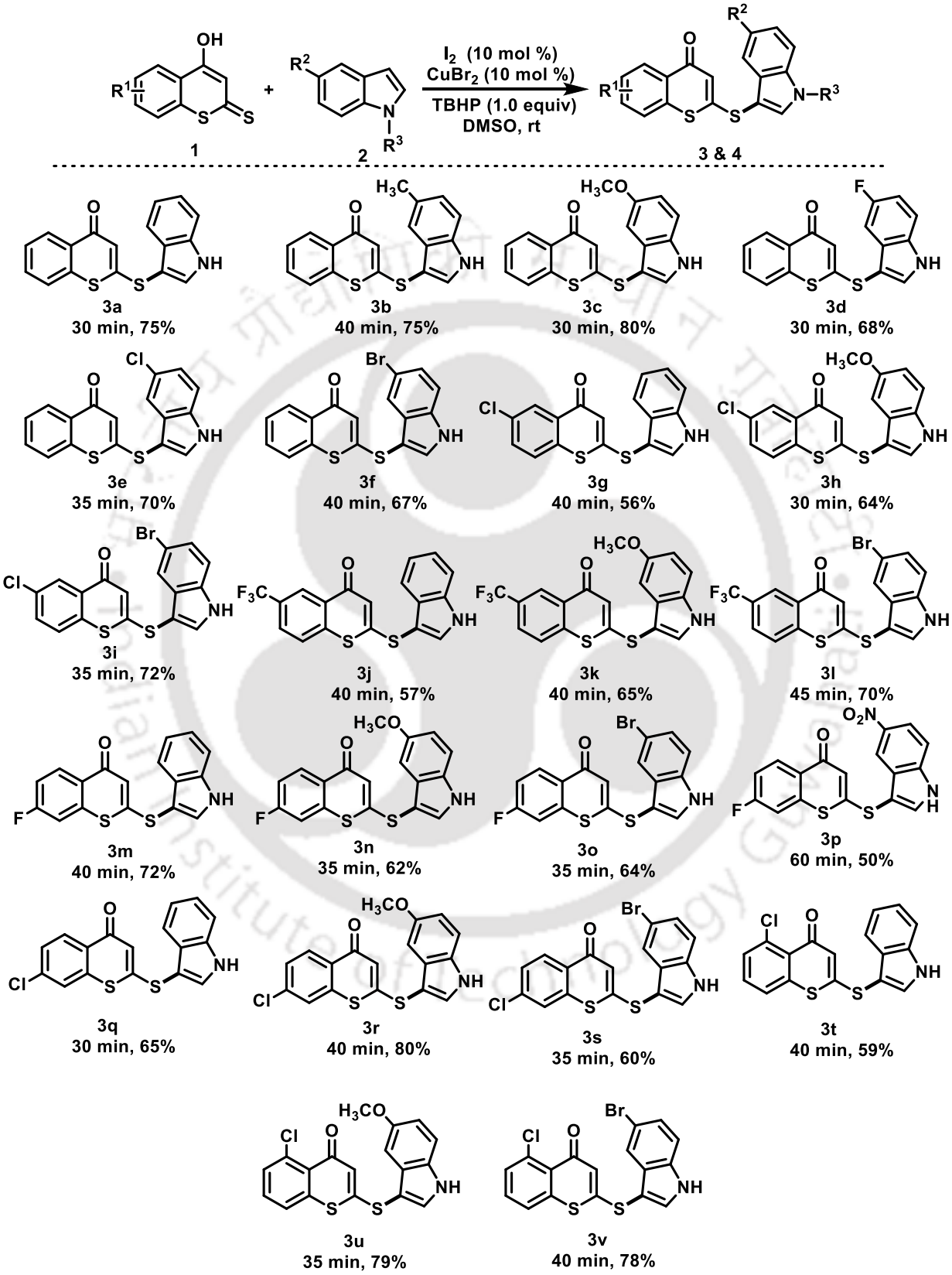
09	05	TBHP	$CuBr_2$(10)	DMSO	0.5	50
10	20	TBHP	$CuBr_2$(10)	DMSO	0.5	70
11	10	TBHP	$CuBr_2$(20)	DMSO	0.5	67
12	10	TBHP	$CuBr_2$(50)	DMSO	0.5	65
13	10	TBHP	$CuBr_2$(1 equiv)	DMSO	0.5	61
14	10	TBHP	$CuBr_2$(10)	THF	3.5	Trace
15	10	TBHP	$CuBr_2$(10)	DCE	3	Trace
16	10	TBHP	$CuBr_2$(10)	CH_3CN	2	36
17	10	TBHP	$CuBr_2$(10)	DMF	0.6	56

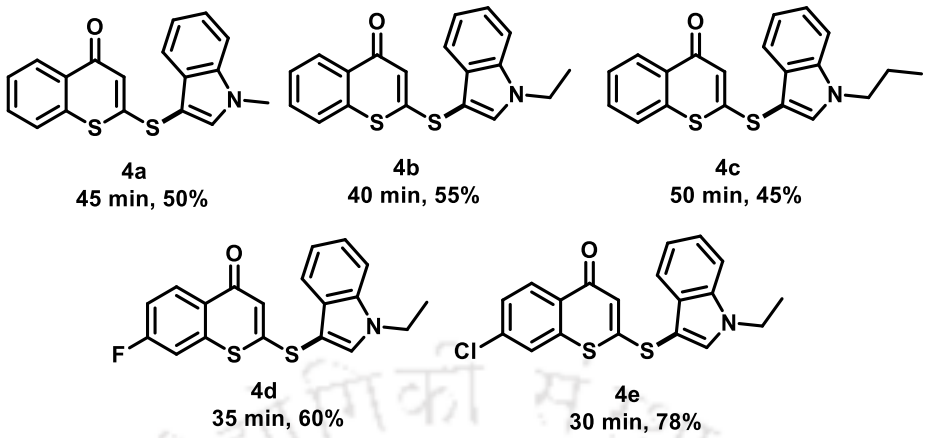
[a]All the reactions were carried out using 4-hydroxydithiocoumarin **1a** (0.5 mmol), indole **2a** (0.5 mmol) in 1 mL of solvent at room temperature. [b]Isolated yield. [c]Heating condition.

With the optimized reaction conditions, the scope and generality of the present procedure were examined with 4-hydroxydithiocoumarin (**1**) and a wide range of substituted indoles, and the results are summarized in Table 2.2.

The reactions were proceeded well with various indole derivatives having substituents such as -Me, -OMe, -F, -Cl, and -Br at the 5 positions of the indole ring and it gave the desired products **3b-f** in 67-80% yields (Table 2.2). The best yield (80%) was obtained when the reaction was carried out with 5-methoxyindole and 4-hydroxydithiocoumarin (**1a**). Further, the diversity of the present protocol was extended by reacting a series of substituted 4-hydroxydithiocoumarins with different substituted indoles. Similarly, the reaction of 6-chloro-4-hydroxydithiocoumarin with various indoles provided 3-sulfenyl indole derivatives **3g-i** in good yields. Likewise, 6-trifluoromethyl-4-hydroxydithiocoumarin on reaction with various substituted indoles afforded the desired products **3j-l** in moderate to good yields under identical reaction conditions. Furthermore, the present protocol was also inspected with 7-fluoro-4-hydroxydithiocoumarin and various indole derivatives having electron-donating and electron-withdrawing groups in the indole ring and it also provided the expected products **3m-p** in moderate to good

Table 2.2. Scope of 3-sulfenylindole derivative in the presence of copper(II)bromide





[a]All reactions were carried out with 4-hydroxydithiocoumarins (0.5 mmol) and indole (0.5 mmol) in the presence of copper(II)bromide & I_2 (10 mol%) and TBHP (1 equiv) in 1 mL DMSO. [b]Isolated yields.

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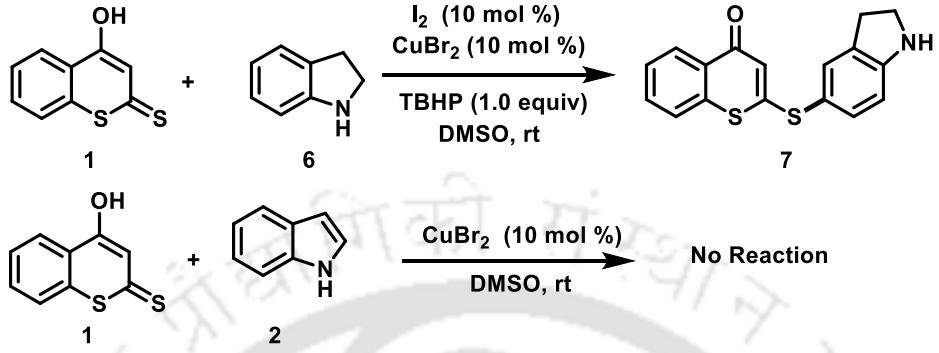
yields. The low yield of the product **3p** might be due to the presence of the -NO_2 group at the 5-position of indole. Once again, the reactions were executed with 5-chloro-4-hydroxydithiocoumarin and 7-chloro-4-hydroxydithiocoumarin with various indole derivatives to provide the desired products **3q-v** in 59-80% yields.

Next, the generality and applicability of the protocol was tested with the *N*-substituted indole derivatives having substituents such as *N*-Me, *N*-Et, and *N*-Pr, and 4-hydroxydithiocoumarin (**1a**) under optimized reaction conditions and it also provided anticipated products **4a-c** in 50-55% yields. The desired products **4d** and **4e** were obtained with 60% and 78% yield when 7-fluoro-4-hydroxydithiocoumarin and 4-chloro-4-hydroxydithiocoumarin were reacted with *N*-ethylindole derivative under identical conditions, respectively. From these successful results, we may conclude that our protocol is also extendable for *N*-alkylated indole derivatives.

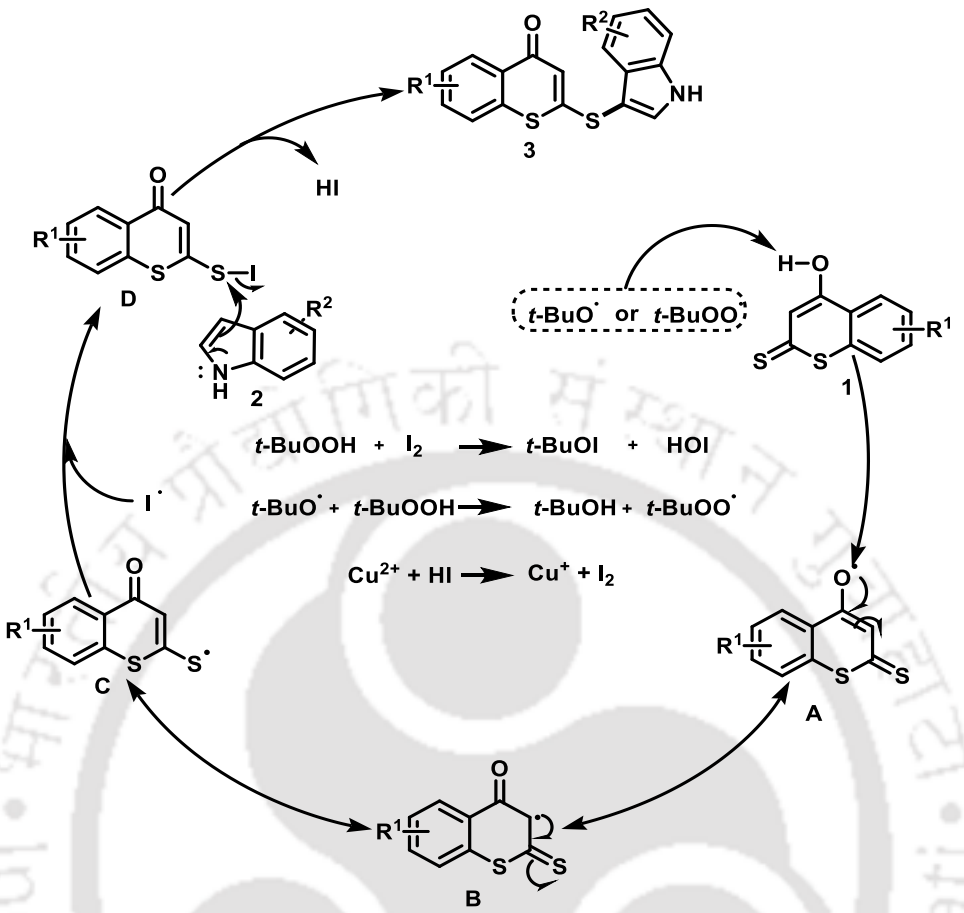
To ascertain the proposed mechanism, we have examined two reactions, which are shown in Scheme 2.9. The first reaction is carried out with 4-hydroxydithiocoumarin and indoline under similar reaction conditions and it provided a product **7** in 45% yield along with an inseparable mixture. The product is obtained through *S-C* bond formation at the 5-position of the indoline through oxidative cross dehydrogenative coupling reaction as there is no feasibility at position 3**.** The second reaction is executed based on the earlier reported procedure[26] for 3-sulfenyl indoles derivatives. Unfortunately, no reaction took

place. We may conclude that a combination of catalytic amount molecular iodine and TBHP has an important role in product formation.

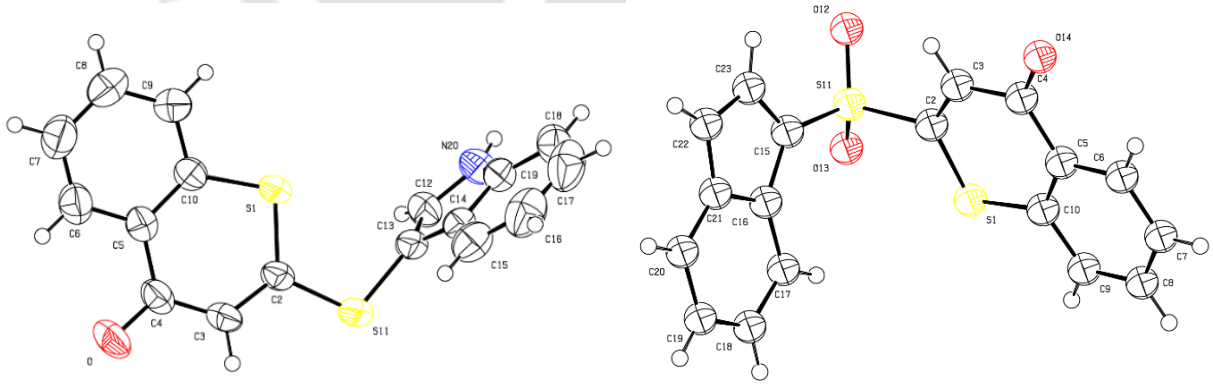


Scheme 2.9. Control experiment

Based on the controlled experiment shown in Scheme 2.9 as well as the results mentioned in Table 2.1 (entry 1), the plausible mechanism can be drawn for the formation of product **3**, as shown in Scheme 2.10. Initially, TBHP reacts with molecular iodine to generate *tert*-butoxy radical and hypoiodous acid. The *tert*-butoxy radical is then reacted with TBHP to give the *tert*-butyl peroxy radical.[27] Either *tert*-butoxy radical or *tert*-butyl peroxy radical can abstract hydrogen from the 4-hydroxyl group of 4-hydroxydithiocoumarin (**1**) to form a radical intermediate **A,**[28] which might also exist in two other possible resonating intermediates either **B** or **C**.[25] Then, the radical intermediate **C** reacts with iodide radical to give intermediate **D**,[24] which is converted into the desired product **3** after nucleophilic substitution at the C-3 position of indole by eliminating iodide ion and hydrogen ion.[9b,10a,16a,29] Subsequently, iodide ion undergoes oxidation in presence of an additive i.e. copper(II)bromide. The released iodine again participated in the catalytic cycle and Cu(I) is reoxidized to Cu(II) in presence of TBHP.[30]



Scheme 2.10. A plausible mechanism for the formation of 3-sulfenylindole derivatives

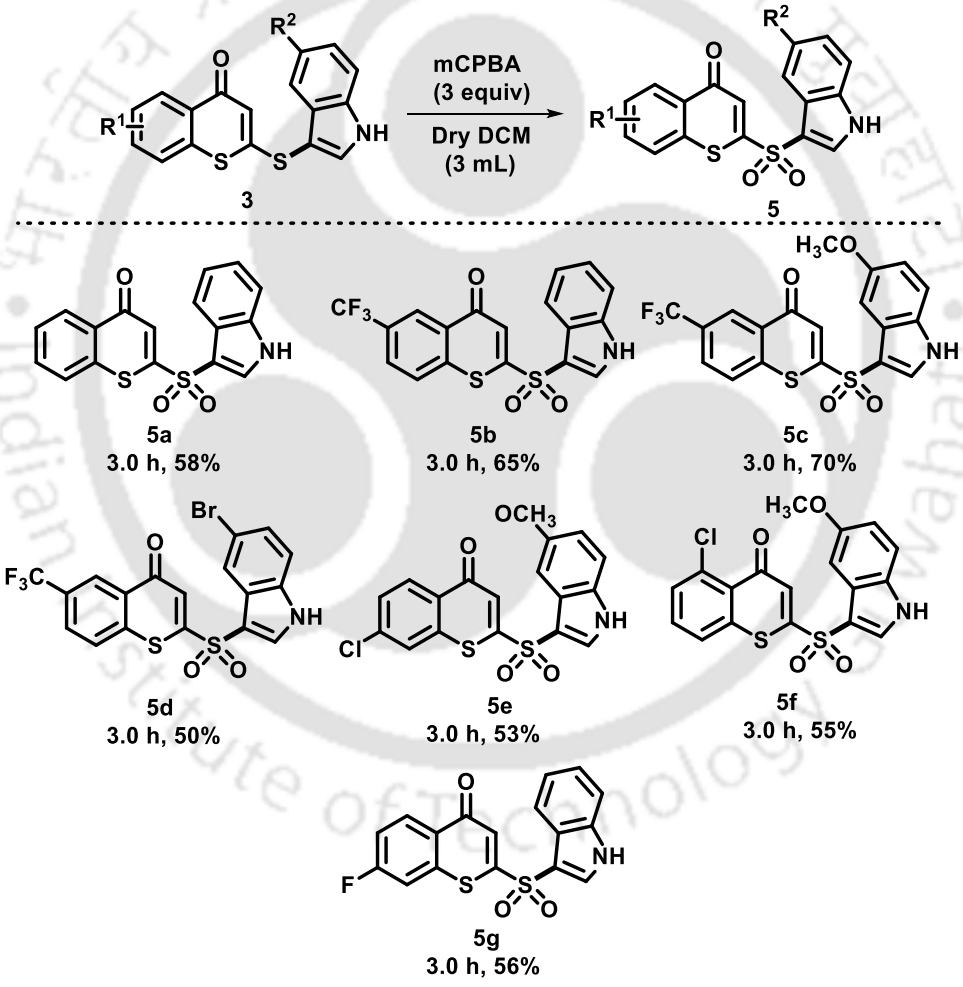


3a **5a**

Figure 2.2. ORTEP diagram of compound **3a** and compound **5a**

Additionally, product **3** can be used as a useful synthetic precursor for further derivatization. The compounds **3a, 3j, 3k, 3l, 3u, 3r,** and **3m** were oxidized to their corresponding sulfones **5a-g** on treating with *m*-CPBA as shown in Table 2.3. Sulfone compounds are also known in the literature for their extraordinary biological activities.[31] Structures of all the products were confirmed by recording IR, ^{1}H NMR, ^{13}C NMR spectra, and their HRMS. Finally, the structures of **3a** and **5a** were also established by single X-ray crystallographic data (Figure 2.2). ^{1}H NMR, ^{13}C NMR, and HRMS of compounds **3a**, **4a**, and **5a** are shown in Figure 2.11, Figure 2.12, and Figure 2.13.

Table 2.3. Scope of Sulfone Derivative



[a]All reactions were carried out with 3-sulfenylindole derivative (0.25 mmol) and *m*-CPBA (3 equiv) in 3 mL dry DCM. [b]Isolated yield.

Additionally, from the molecular docking studies, some of the compound exhibit antiproliferative activity against breast cancer cell line MCF-7.

2.4. Biological application

2.4.a. Molecular Docking Study against DNA

To determine the anti-proliferative activity of the compounds, it was imperative to identify the potential cellular target of the synthesized compounds. DNA holds huge impetus as an important class of target for potential anti-proliferative agents. Anti-proliferative agents targeting DNA have shown significant clinical as well as commercial success.[32,33] Thus, in the present study molecular docking was performed to determine any possible interactions between the sulfone derivatives and DNA. The relative binding energy of the compound-DNA interactions determined by using AutoDockVina was found to be in the range of -6.4 kcal mol^{-1} to -9.3 kcal mol^{-1}, as illustrated in Table 2.4. Based on the binding affinity a total of 11 compounds (namely **3k, 3l, 3m, 3r, 4b, 5a, 5d, 5c, 5d, 5e, 5g**) were selected to further determine their mode of interaction with the DNA. The docking conformation using pymol depicts that the compounds interact with the DNA *via* hydrogen bonds with the guanine (G) or cytosine (C) bases of the DNA (Table 2.5). This shows that the compounds preferentially bind to the GC-rich region of the DNA. Typically, the binding of small aromatic molecules to the GC-rich region of the DNA is indicative of an intercalative mode of binding.[34,35] Thus, the compounds potentially act as DNA intercalators as depicted in Figure 2.3.

Table 2.4. Binding energies of the compound-DNA interaction using AutoDockVina

Sl. No.	Compound Name	Binding Affinity (kcal/mol)
1	3a	-6.7
2	3b	-7.4
3	3c	-7.9
4	3d	-7.7
5	3e	-8.4
6	3f	-8.0
7	3g	-7.3
8	3h	-8.4
9	3i	-7.1
10	3j	-8.5
11	3k	-8.7
12	3l	-9.0
13	3m	-7.8
14	3n	-7.8
15	3o	-7.9
16	3p	-7.9
17	3q	-7.8

continued

18	3r	-8.4
19	3s	-7.6
20	3t	-7.1
21	3u	-8.1
22	3v	-7.0
23	4a	-7.1
24	4b	-7.4
25	4c	-6.5
26	4d	-7.4
27	4e	-6.9
28	5a	-8.2
29	5b	-8.1
30	5c	-8.3
31	5d	-8.1
32	5e	-8.8
33	5f	-7.6
34	5g	-8.6
35	5h	-9.2
36	5i	-9.2
37	5j	-7.5

38	5k	-8.5
39	5l	-9.3
40	5m	-8.3
41	5n	-8.3
42	5o	-8.4
43	5p	-8.0
44	5q	-8.1
45	5r	-8.5
46	5s	-8.3

Table 2.5. Interaction parameters between the compounds and DNA (1BNA)

Sl No	Compound name	From	To	Bond length (A^0)
1	3k	DG-16:H3	3k:O01	2.4
		DG-10:H21	3k:O01	2.1
2	3l	DC-15:02	3l:H03	2.1
		DG-16:H22	3l:O01	2.0
		DC-11:H21	3l:O01	2.5
3	3m	DG-04:O4’	3m:H03	2.1
4	3r	DC-15:02	3R:H03	2.1
		DG-16:H22	3R:O01	2.1
		DG-10:H21	3R:O01	2.5
		DG-10:H3	3R:O01	2.4

continued

		DG-10:H21	3k:O01	2.1
5	4b	DA-5:H3	4B:O01	1.9
6	5a	DG-22:H3	5A:O03	2.5
		DG-4:H22	5A:O03	2.5
7	5b	DC-23:O4’	5B:H03	2.6
8	5c	DC-23:04’	5C:H03	2.3
		DG-4:H22	5C:O02	2.3
		DA-5:H3	5C:O02	2.3
9	5d	DG-4:O4’	5D:H03	2.3
		DG-22:H3	5D:O01	2.0
10	5e	DG-22:H3	5E:O03	2.5
		DG-4:H22	5E:O03	2.5
11	5h	DC-9:O2	5H:O01	2.6
		DG-16:H22	5H:O01	2.1
		DG-10:H3	5H:O01	2.5
12	5l	DC-9:O2	5L:H03	2.4
		DG-10:H3	5L:O01	2.7
		DG-10:H21	5L:O01	2.0
		DG-16:H22	5L:O03	2.1
		DC-9:O2	5L:H03	2.4

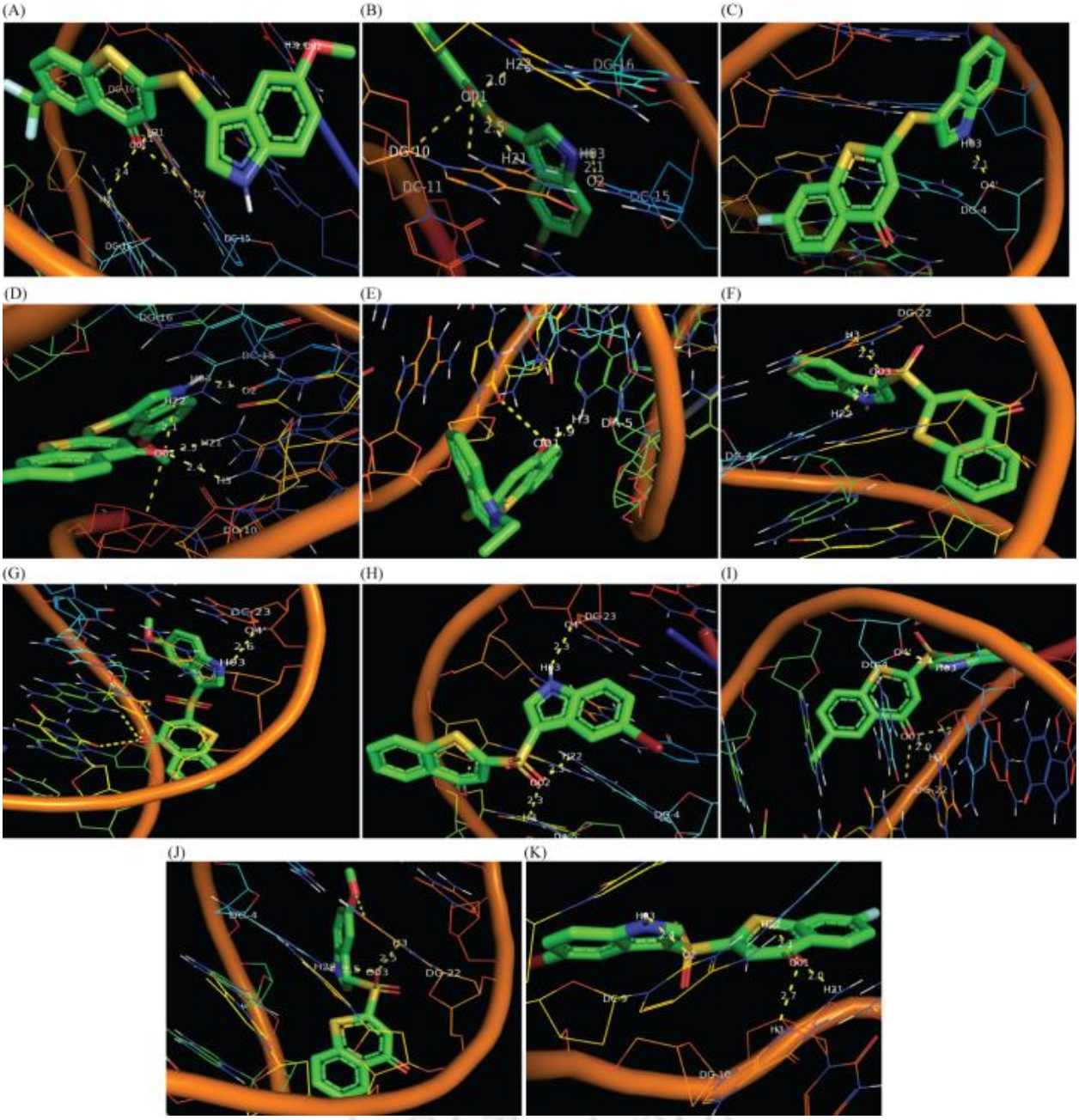


Figure 2.3. (A-K) Molecular docking of the DNA (1BNA) with the compounds 3**k**, **3l**, **3m**, **3r**, **4b**, **5a**, **5b**, **5c**, **5d**, **5e,** and **5g**, respectively. The yellow dotted line depicts the hydrogen bond between the compounds and the GC bases of the DNA.

Based on the interaction of the compounds with DNA as determined by the molecular docking study, a total of 11 different compounds namely **3k** (10-80 μM), **3l**(10-80 μM), **3m** (20-160 μM), **3r** (20-160 μM),**4b** (10-160 μM), **5a** (5-20 μM), **5b** (5-20 μM), **5c** (5-40

μM), **5d** (5-20 μM), **5e** (5-40 μM), **5l** (10-160 μM) were selected to determine their activity on MCF7 cell line. Assessment of cell viability using the MTT assay of the compounds on MCF-7 cells upon treatment for 48 h has been shown in Figure 2.4.

Treatment of MCF-7 with sulfenyl-based compounds (**3k, 3l, 3m,** and **3r**) resulted in the dose-dependent reduction of cell viability and attainment of IC_{50} as illustrated in Table 2.6. Treatment with compound **4b** led to a dose-dependent reduction in cell viability, however, IC_{50} was not achieved till the compound concentration of 160 μM. Treatment with sulfonyl compounds **5a, 5b, 5c, 5d, 5e,** and **5g** also exhibited a dose-dependent reduction in proliferation of MCF-7 cells where IC_{50} was achieved at a lower compound dosage as compared to sulfenyl based compounds. Thus, all the 11 compounds and particularly the sulfonyl compounds **5a, 5b, 5c, 5d,** and **5e** displayed significant anti-proliferative activity providing a strong lead towards further studies and experiments for their potential biomedical applications.

Statistical analysis was performed *via* ANOVA using the Graphpad Prism software with statistical significance denoted by **(p<001), ***(p<0.0001), and ****(p<0.0001), respectively.

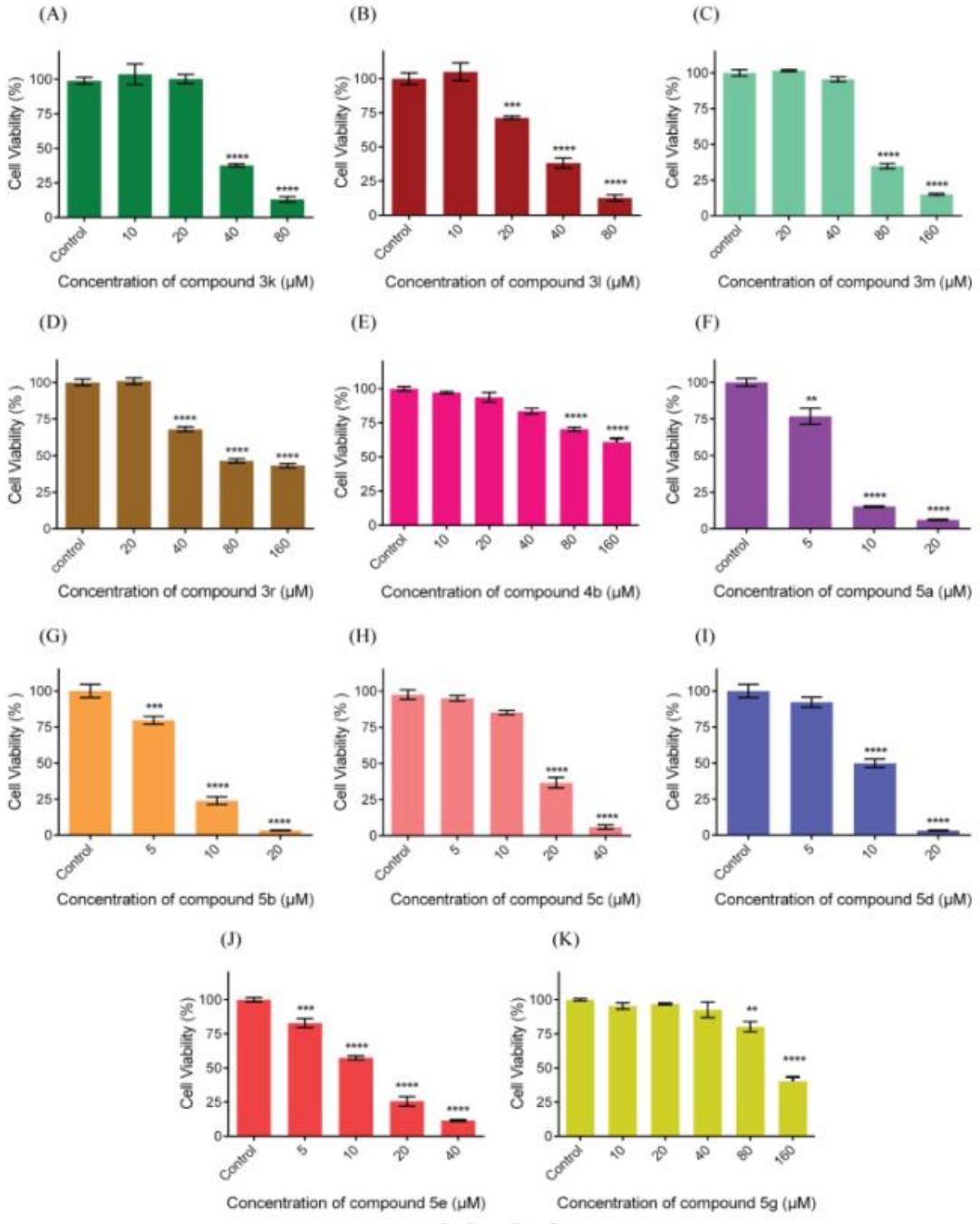


Figure 2.4. (A-K) Assessment of cell viability of MCF-7 cells using MTT assay upon treatment with the compounds **3k**, **3l**, **3m**, **3r**, **4b**, **5a**, **5b**, **5c**, **5d**, **5e,** and **5g** respectively.

Table 2.6. IC_{50} concentration of the compounds on MCF7 cell line

Sl No	Compounds	IC_{50} (μM)
1	**3k**	35.80±1.137
2	**3l**	28.575±1.103
3	**3m**	65.013±1.027
4	**3r**	56.234±1.033
5	**4b**	Not Attained (Till 160 μM)
6	**5a**	6.319±1.053
7	**5b**	7.214±1.030
8	**5c**	17.218±1.040
9	**5d**	10.327±1.043
10	**5e**	10.789±1.051
11	**5g**	80.909±1.252

2.4.b. Molecular Docking Study against DNA PI-based flow cytometry data:

Propidium iodide (PI) is a non-permeable DNA binding dye, which can enter only membrane-compromised cells. Thus, PI is commonly used to distinguish between viable cells and membrane-compromised cells. MCF-7 cells were treated with compounds **3k, 3l, 5a, 5b, 5d,** and **5e** which led to a reduction in cell viability was determined by MTT assay. The probable reason could be the disruption of membrane integrity by the compounds. To determine the same PI-based propidium assay was performed. The experiment was carried out in 6 well plates. Compounds were added at their IC_{50} concentration for 48 hours. Following incubation, the media cell suspension was collected in a microcentrifuge tube. The cell in the plates was washed with PBS and then trypsinized. Following trypsinization, cells were again washed with the media cell suspension that was previously collected. These cells were then further centrifuged at 650 RCF for 10 min and re-suspended in 400 µl PBS. To the cell suspension, 5µl of the 1mg/ml of PI staining solution was added and centrifuged at 650 RCF for 5 min. Cells were again resuspended in 400 µl PBS. PI binds to the double-stranded DNA of the membrane-compromised cells by intercalating between base pairs. PI fluorescence was determined by flow cytometry using Beckman coulter at 488 nm excitation. Treatment with the compounds displayed a significant

increase in the percentage of compromised cells upon 48 h incubation, which indicates that the compounds are biologically active and impart their anti-proliferative activity by inducing membrane damage of the cancer cells (Figure 2.4). Untreated and DMSO treated cells did not show any significant effect as shown in Figure 2.5.

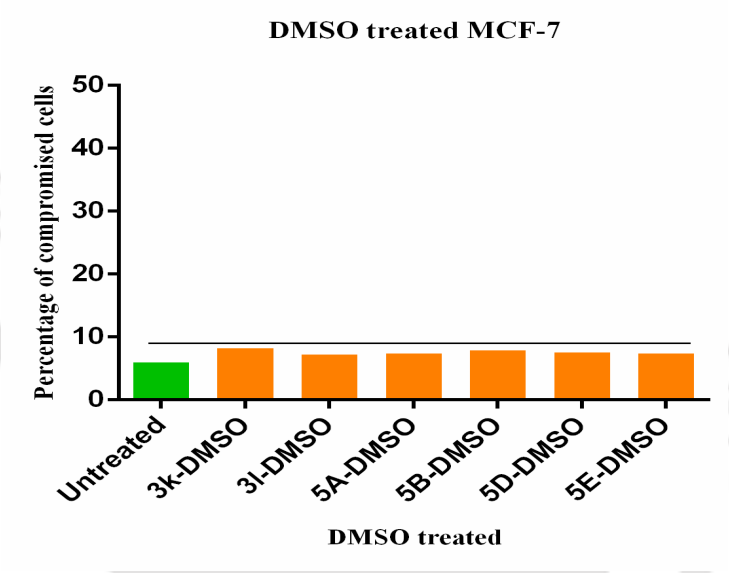


Figure 2.5. Percentage of compromised cells for untreated and DMSO treated MCF 7 cells

Reduction in the cell viability was also confirmed by PI-based flow cytometry data for **3k, 3l, 5a, 5b, 5d,** and **5e** on the MCF-7 cell line (Figure 2.6). Data demonstrated the increment of compromised cells on treatment with IC_{50} concentration of the compounds whereas, in a control experiment, DMSO at the same concentration alone did not show any effect on the cells (Figure 2.5). The percentage of compromised cells and their respective flow cytometry results are presented in Table 2.7 and Figure 2.7, respectively.

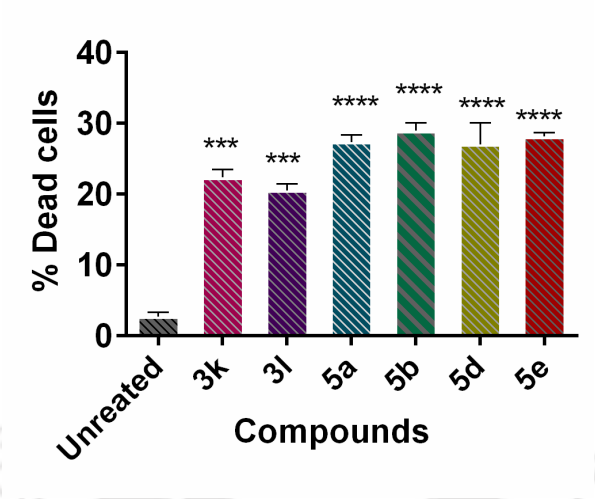


Figure 2.6. Propidium Iodide (PI) based assessment of compromised cells upon treatment IC_{50} concentration of different compounds

Table 2.7. Percentage of compromised cells when treated by IC_{50} concentration of different compounds

Sl No	Compounds	% of Dead cells
1	Control	2.750±0.55
2	3k	22.40±1.105
3	3l	20.54±0.965
4	5a	27.37±0.98
5	5b	28.97±1.1
6	5d	27.04±3.04
7	5e	28.16±0.505

Sl No	DMSO	% of Dead cells
1	Control	5.92
2	3k	7.8
3	3l	7.9
4	5a	7.5
5	5b	7.4
6	5d	8.3
7	5e	7.2

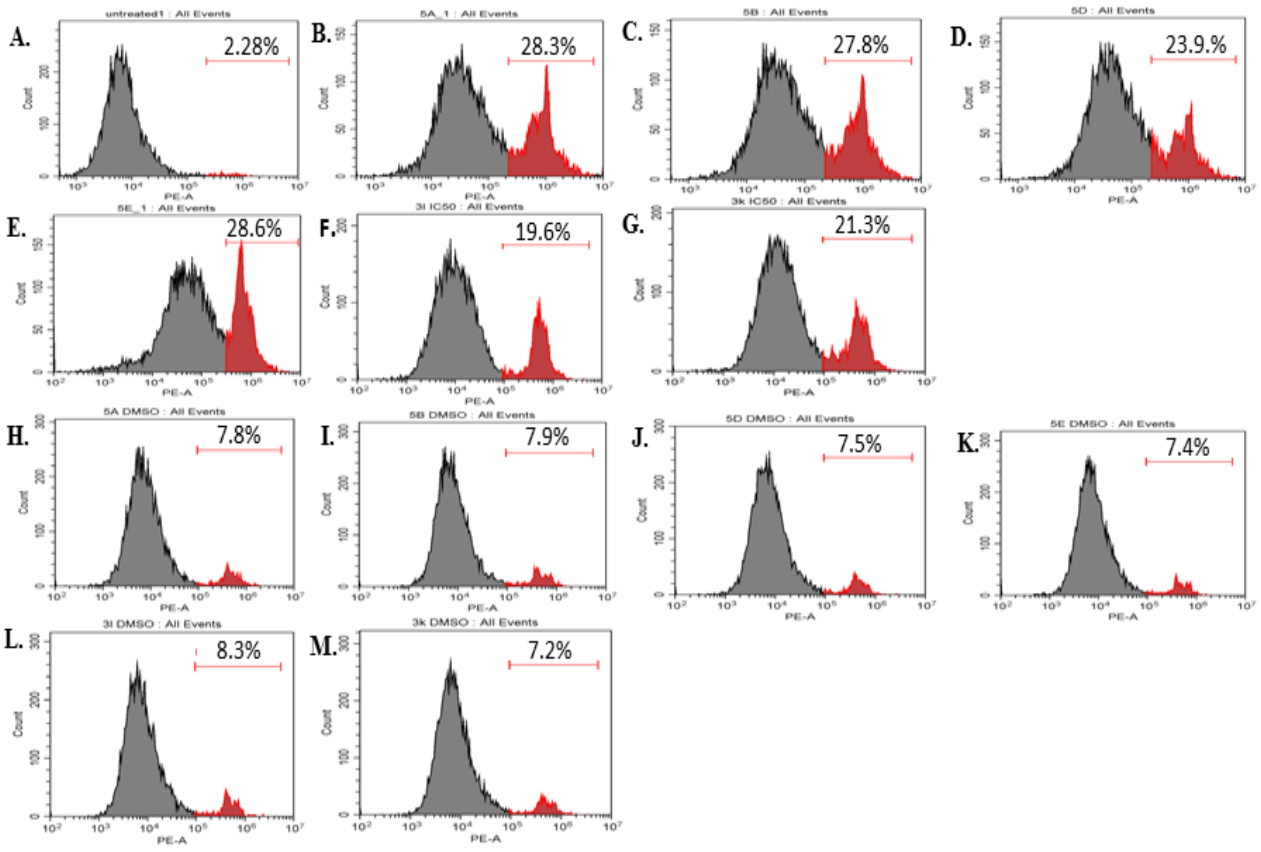


Figure 2.7. PI-based flow cytometry data of (A) Untreated cells (B-G) Upon treatment with compounds **5a, 5b, 5d, 5e, 3l, 3k**, respectively (H-M) DMSO treated cells, corresponding to controls for compounds **5a, 5b, 5d, 5e, 3l, 3k**, respectively

2.4.c. Dual staining with Ethidium bromide (EtBr) and Acridine Orange

MCF-7 cells were seeded in 96 well plates and treated with the compounds by their respective IC_{50} for 24 h. After that cells were washed with 1X PBS pH 7.4 buffer and stained with 4 µM acridine orange for half an hour and then again cell was washed with 1X PBS pH 7.4 buffer and incubated with 2µM EtBr for 15 min. After washing with 1X PBS pH 7.4 buffer cell imaging was done by Zeiss LSM 880 confocal microscope.

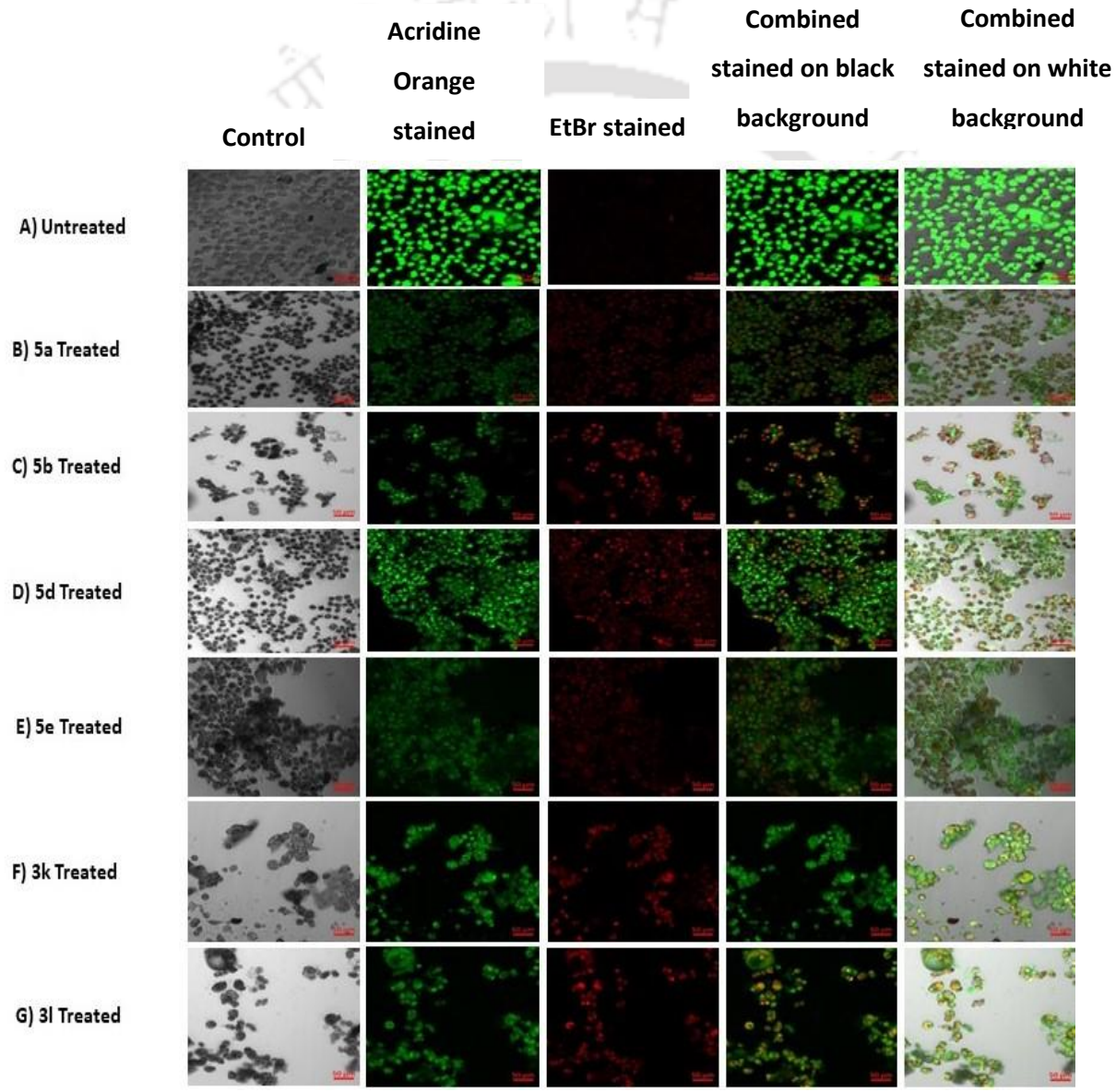
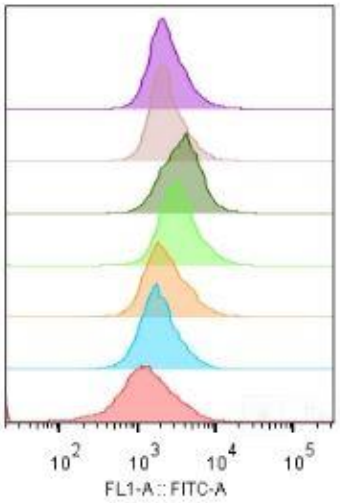


Figure 2.8. Dual staining with EtBr and acridine of MCF-7 cells upon treatment with the compounds

The cell membrane is permeable to acridine orange, but not EtBr. Treatment of the cells with the compounds showed double staining under excitation of green and red laser, emitting slight orange colour, which confirmed the rupture of the cell membrane. However, the untreated control cells did not show double staining or EtBr staining, which conferred membrane integrity.

2.4.d. Cellular Reactive Oxygen Species (ROS) Detection assay

ROS assay was performed using cell-permeant reagent 2',7'-dichlorofluorescein diacetate (DCFDA), a fluorogenic dye that measures hydroxyl, peroxyl, and other ROS activity within the cell. The MCF-7 cells were treated with the IC_{50} concentration of the compounds. After 6 h of treatment, DCF-DA was added and incubated at 37 °C for 30 min. After the incubation, the dye was removed and washed with PBS, and fluorescence was measured using the Cytoflex Beckman coulter instrument. Fluorescence peak shifts were observed upon treatment.



	Sample Name	Subset Name	Count	Mean : FL1-H	Mean : FL1-A
	3l_1.fcs	Ungated	10000	1862	3028
	3k_1.fcs	Ungated	10000	2017	3591
	5e_1.fcs	Ungated	10000	2617	4333
	5d_1.fcs	Ungated	10000	2301	4107
	5b_1.fcs	Ungated	10000	1831	3062
	5a_1.fcs	Ungated	10000	1652	2363
	UNTR_9.fcs	Ungated	10000	1673	2311

Table 2.8: Showing mean value of fluorescence intensity for the respective compounds

Figure 2.9. Fluorescence peak shift in flow cytometry studies

Similarly, dual staining images of the cells treated with acridine orange/ ethidium bromide as recorded by Confocal microscope corroborated with MTT and PI-based flow cytometry results (Figure 2.8). Furthermore, the compounds showed an increase in the levels of reactive oxygen species (ROS) of the treated MCF-7 cells than the untreated cells (Figure 2.10). Hence, it is pertinent that such elevated ROS could cause cell damage leading to cell death.

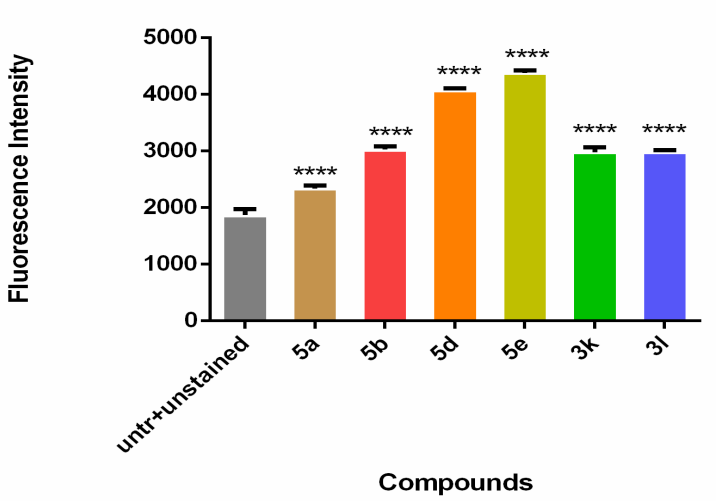


Figure 2.10. Fluorescence quantification of reactive oxygen species after treatment with compounds in MCF-7 cells

2.5. Conclusion

We have demonstrated the sulfenylation reaction of indole with 4-hydroxydithiocoumarin in which sulfur atom in thiolactone acts as sulfenylating reagent under mild reaction conditions using I_2 (10 mol%), $CuBr_2$ (10 mol%), and TBHP (1 equiv) in DMSO as solvent at room temperature. In this reaction, $CuBr_2$ plays a crucial role in the formation of the product. In addition, the synthesized 3-sulfenylindole derivatives were oxidized to the biologically active sulfones. We conclude that the present protocol is a useful one due to shorter reaction time, mild reaction conditions, and a wide substrates scope. Finally, molecular docking studies and anti-proliferative cell-based study of the compounds **3k, 3l, 3m, 3r, 4b, 5a, 5b, 5c, 5d, 5e,** and **5g** against the breast cancer cell line MCF7 opens up a new avenue for future biomedical applications of the synthesized compounds.

2.6. Experimental Section

2.6.a. General procedure for the synthesis of various 4-hydroxydithiocoumarin derivatives (1)[25]

Into a 100 mL round-bottomed flask, a mixture of 2'-chloroacetophenone (10 mmol) and carbon disulfide (20 mmol) was taken in a mixture of DMF: benzene (1:1) at 15-20 ˚C. Sodium hydride was added portion-wise for 20 min and the mixture was stirred over 3 h. Next, 1 mL methanol was added and was stirred for another 30 min. The reaction mixture was heated with stirring at 120 ˚C for 45 min, cooled, and diluted with water. A few drops of acetic acid were added to the diluted reaction mixture. The reaction mixture was extracted with ether and the aqueous layer was collected and acidified with HCl. The yellow coloured precipitate was obtained and it was recrystallized from methanol/dichloroethane to get the 4-hydroxydithiocoumarin as a yellow needle.

2.6.b. General procedure for the synthesis of compounds (2)[36]

To a solution of indole (5 mmol) and potassium hydroxide (25 mmol) in anhydrous DMF (10 mL), alkyl halide was added (10 mmol). The reaction mixture was stirred at room temperature for 20 min. The mixture was then filtered through silica gel, and H_2O was added to the filtrate. The water layer was extracted with CH_2Cl_2 (25 mL × 2). The organic layers were combined and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel chromatography.

2.6.c. General Procedure for the Synthesis of Sulfenyl derivatives (3a-v & 4a-4e) using I_2/TBHP and $CuBr_2$[a,b]

Into a 25 mL round bottom flask, a mixture of 4-hydroxydithiocoumarin (**1**, 0.5 mmol) and indole (**2,** 0.5 mmol) was dissolved in 1mL of DMSO and the resultant solution was kept for stirring at room temperature. Then, 1 equivalent amount of TBHP, 10 mol% I_2, and 10 mol% $CuBr_2$ was added successively to the stirred reaction mixture. The progress of the reaction was monitored by TLC from time to time. After completion of the reaction, it was extracted with DCM (3 x 10 mL) and the organic layer was washed with a saturated solution of $Na_2S_2O_3.5H_2O$ to remove iodine. The organic layer was dried over anhydrous Na_2SO_4 and was concentrated into a rotatory evaporator. The crude residue

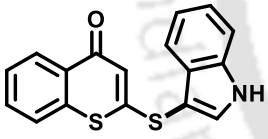
was recrystallized using DCM and CH_3CN to get corresponding sulfenylated compounds **3** and **4**.

2.6.d. General procedure for the synthesis of compounds (5)[31]

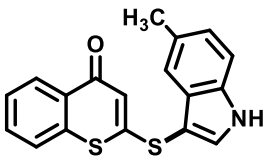
Into a 50 mL round-bottomed flask, 3-sulfenylindole (0.25 mmol) was taken in 3 mL of dichloromethane at ice-bath temperature and the reaction mixture was stirring. After that, *m*-Chloroperoxybenzoic acid (*m*-CPBA, 0.75 mmol) was added in portion for 15 min to a stirred solution of the corresponding 3-sulfenylindole, and stirring was continued for 45 min at the same temperature. Then, the reaction mixture was brought to room temperature slowly and it was stirred for another 2 h. After completion of the reaction, it was extracted by adding 18 mL of dichloromethane, which was washed with 5% aqueous $NaHCO_3$ solution (10 mL) and brine solution (10 mL). Finally, the organic layer was dried over anhydrous Na_2SO_4 and it was concentrated in a rotary evaporator. The desired sulfone was obtained after recrystallization from methanol.

2.7. Characterization

2-((1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3a). Brown solid (116 mg, 75%); mp 202-203 ˚C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.22 (d, *J* = 6.0 Hz, 1H), 7.98 (d, *J* = 2.8 Hz, 1H), 7.65 (d, *J* = 6.0 Hz, 1H), 7.60 (t, *J* = 6.0 Hz, 1H), 7.56-7.52 (m, 3H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.81 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.3, 158.5, 136.8, 136.8, 134.8, 132.0, 129.7, 128.6, 128.2, 127.8, 126.6, 122.9, 121.2, 119.4, 118.1, 112.9, 94.1; IR (KBr)ν_{max} 3434, 3214, 1577, 1550, 1336, 1298, 1127 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}NOS_2$ (M + H$^+$) 310.0355; Found 310.0374.



2-((5-Methyl-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3b). Light brown solid (127 mg,75%); mp 234-235 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.23 (d, *J* = 8 Hz, 1H), 7.91 (d, *J* = 4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8 Hz, 1H), 7.54 (t, *J* = 8 Hz, 1H), 7.44 (d, *J* = 8 Hz, 1H), 7.32 (s, 1H), 7.07 (d, *J* = 8 Hz, 1H), 6.79 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.1, 158.5, 136.7, 134.9, 134.6, 131.8, 129.9, 129.6, 128.8, 128.0, 127.6, 126.4, 124.3, 119.1, 117.4, 112.4, 93.3, 21.1; IR



(KBr)ν_{max} 2922, 2852, 2354, 1652, 1578, 1509, 1331 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}NOS_2$ (M + H^+) 324.0511; Found 324.0512.

2-((5-Methoxy-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3c). Brown solid (130 mg, 80%); mp 220-221 ˚C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.24 (d, *J* = 6.0 Hz, 1H), 7.93 (d, *J* = 6 Hz, 1H), 7.69 (d, *J* = 6Hz, 1H), 7.62 (t, *J* = 6.0 Hz, 1H), 7.55 (t, *J* = 6 Hz, 1H), 7.45 (d, *J* = 12 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 6.89 – 6.87 (m, 1H), 6.82 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.1, 158.6, 154.9, 136.7, 135.1, 131.8, 131.5, 129.6, 129.4, 128.0, 127.6, 126.5, 119.0, 113.6, 112.9, 99.3, 93.3, 55.3; IR (KBr)ν_{max} 3152, 2929, 2833, 1581, 1553, 1509, 1459, 1337, 1289, 1174 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{14}NO_2S_2$ (M + H^+) 340.0460; Found 340.0485.

2-((5-Fluoro-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3d). Light brown solid (116 mg, 68%), mp 239-240 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.23 (d, *J* = 8 Hz, 1H), 8.04 (d, *J* = 4 Hz, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.58 – 7.57 (m, 1H), 7.55 – 7.53 (m, 1H), 7.26 (dd, *J* = 8 Hz, 4 Hz, 1H), 7.10 (t, *J* = 8 Hz, 1H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.3, 159.3, 157.8, 157.0, 136.6, 133.3, 131.9, 129.7, 129.5, 129.4, 128.1, 127.7, 126.5, 119.5, 114.3, 114.2, 111.3, 111.0, 103.1, 102.8, 94.4; IR (KBr)ν_{max} 3423, 2920, 2852, 1638, 1583, 1436, 1100 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}NOS_2F$ (M + H^+) 328.0261; Found 328.0262.

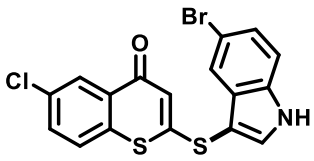
2-((5-Chloro-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3e). Brown solid (135 mg, 70%); mp 234-235 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 4 Hz, 1H), 7.69 (d, *J*= 8.0 Hz, 1H), 7.64 – 7.54 (m, 4H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d^6) δ 177.1, 157.4, 136.6, 136.4, 135.1, 131.8, 129.9, 129.6, 128.0, 127.6, 126.4, 125.8, 122.8, 119.5, 117.1, 114.4, 94.0; IR (KBr)ν_{max} 3440, 2922, 2852, 2089, 1635, 1442, 1335 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}NOS_2Cl$ (M + H^+) 343.9965; Found 343.9966

2-((5-bromo-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3f). Light brown solid (108 mg, 67%); mp 202-203˚C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.23 (d, *J* = 12 Hz, 1H), 8.05 (d, *J* = 6 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.62 – 7.58 (m, 1H), 7.56 – 7.52 (m, 2H), 7.37 (dd, *J* = 12 Hz, 6 Hz, 1H), 6.83 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.1, 157.3, 136.5, 136.3, 135.4, 131.7, 130.5, 129.6, 128.0, 127.6, 126.4, 125.3, 120.1, 119.5, 114.8, 113.7, 93.9; IR (KBr)ν_{max} 3239, 2921, 1584, 1511, 1450, 1406, 1331, 1230, 1130 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}NOS_2Br$ (M + H$^+$) 387.9460; Found 387.9476, 389.9459.

2-((1*H*-indol-3-yl)thio)-6-chloro-4*H*-thiochromen-4-one (3g). Light brown solid (96 mg, 56%); mp 233-234 ˚C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.15 (s, 1H), 8.00 (d, *J* = 6 Hz, 1H), 7.76 (d, *J* = 6 Hz, 1H), 7.68 (d, *J* = 12 Hz, 1H), 7.56 – 7.53 (m, 2H), 7.25 (t, *J* = 6 Hz, 1H), 7.16 (t, *J* = 6 Hz, 1H), 6.88 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 175.9, 159.2, 136.7, 135.4, 134.9, 133.0, 131.7, 131.0, 128.8, 128.5, 126.7, 122.7, 121.1, 119.0, 118.0, 112.8, 93.6; IR (KBr)ν_{max} 3430, 3186, 2920, 2852, 1597, 1510, 1403, 1317, 1093 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}NOS_2Cl$ (M + H$^+$) 343.9965; Found 343.9969.

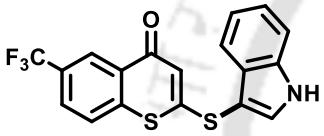
6-chloro-2-((5-methoxy-1*H*-indol-3-yl)thio)-4*H*-thiochromen 4-one (3h). Brown solid (119 mg, 64%); mp 231-232 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.16 (s, 1H), 7.92 (d, *J* = 4 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H), 7.68 (dd, *J* = 8 Hz, 4 Hz, 1H), 7.45 (d, *J* = 8 Hz, 1H), 6.98 (d, *J* = 4 Hz, 1H), 6.90 – 6.87 (m, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.8, 159.3, 154.9, 135.4, 135.0, 132.9, 131.6, 131.4, 131.0, 129.3, 128.7, 126.6, 118.8, 113.6, 112.8, 99.4, 93.1, 55.3; IR (KBr)ν_{max} 3253, 2924 1597, 1578, 1516, 1452, 1317, 1209, 1169 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}NO_2S_2Cl$ (M + H$^+$) 374.0071; Found 374.0090.

2-((5-bromo-1*H*-indol-3-yl)thio)-6-chloro-4*H*-thiochromen-4-one (3i). Brown solid



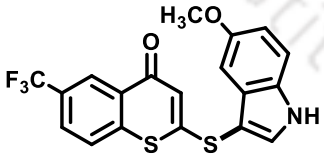
(151 mg, 72%); mp 245- 246 ˚C; 1H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 8.15 (d, J = 4 Hz, 1H), 8.06 (d, J = 4 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.68 (m, 2H), 7.54 (d, J = 8 Hz, 1H), 7.37 (dd, J = 8 Hz, 4 Hz, 1H), 6.89 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.9, 158.3, 136.4, 135.4, 135.3, 133.0, 131.6, 130.9, 130.4, 128.7, 126.6, 125.4, 120.1, 119.2, 114.8, 113.8, 93.6; IR (KBr)ν_{max} 3239, 2920, 1600, 1582, 1512, 1451, 1317, 1142 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}NOS_2ClBr$ (M + H$^+$) 421.9070; Found 421.9076, 423.2506.

2-((1*H*-inol-3-yl)thio)-6-(trifluoromethyl)-4*H*-thiochromen-4-one (3j). Light brown solid



(107 mg, 57%); mp 220-221 ˚C; ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.08 (s, 1H), 8.43 (s, 1H), 8.00 (d, J = 4 Hz, 1H), 7.92 (s, 2H), 7.56 (t, J = 8 Hz, 2H), 7.26 (t, J = 8 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 6.93 (d, J = 4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.1, 159.4, 141.8, 141.0, 136.7, 134.9, 129.8, 128.4, 128.2, 127.5, 124.3, 124.3, 124.2, 122.8, 121.1, 119.3, 118.0, 112.8, 93.5; IR (KBr)ν_{max} 3241, 2918, 2853, 1621, 1591, 1511, 1453, 1290, 1182, 1104 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{11}NOS_2F_3$ (M + H$^+$) 378.0229; Found 378.0229.

2-((5-methoxy-1*H*-indol-3-yl)thio)-6-(trifluoromethyl)-4*H*-thichromen-4-one (3k). Light yellow solid



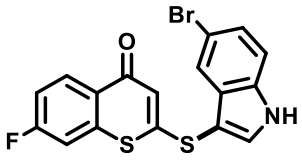
(132 mg, 65%); mp 194-196 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.44 (s, 1H), 7.96 – 7.91 (m, 3H), 7.46 (d, J = 8 Hz, 1H), 6.99 (d, J = 4 Hz, 1H), 6.92 (s, 1H), 6.89 (dd, J = 8 Hz, 4 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.0, 159.6, 154.9, 141.0, 135.1, 131.5, 129.8, 129.3, 128.3, 128.2, 128.0, 127.4, 124.9, 124.2, 122.1, 119.1, 113.6, 112.9, 99.3, 92.9, 55.3; IR (KBr)ν_{max} 3252, 2926, 1620, 1588, 1513, 1291, 1184, 1108 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{13}NO_2S_2F_3$ (M + H$^+$) 408.0334; Found 408.0342.

2-((5-bromo-1*H*-indol-3-yl)thio)-6-(trifluoromethyl)-4*H*-thiochromen-4-one (3l). Off white solid (158 mg, 70%); mp 242-243 ˚C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.28 (s, 1H), 8.44 (s, 1H), 8.08 (d, *J* = 4 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.69 (d, *J* = 4 Hz, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.39- 7.37 (m, 1H), 6.95 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 176.0, 158.6, 136.5, 135.4, 130.4, 129.8, 128.3, 127.5, 127.4, 125.4, 124.3, 124.2, 120.1, 119.6, 114.9, 113.8, 98.4, 93.4; IR (KBr)ν_{max} 3274, 1625, 1594, 1515, 1292, 1133 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{10}NOS_2F_3Br$ (M + H$^+$) 455.9334; Found 455.9343, 457.9290.

2-((1*H*-indol-3-yl)thio)-7-fluoro-4*H*-thiochromen-4-one (3m). Light yellow solid (117 mg, 72%); mp 228-229 ˚C; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 12.08 (s, 1H), 8.29 – 8.26 (m, 1H), 8.00 (d, *J* = 6 Hz, 1H), 7.71 (d, *J* = 6 Hz, 1H), 7.55 (t, *J* = 6 Hz, 2H), 7.40 (t, *J* = 6 Hz, 1H), 7.25 (t, *J* = 6 Hz, 1H), 7.16 (t, *J* = 6 Hz, 1H), 6.84 (s, 1H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ 176.3, 164.0, 162.3, 158.1, 139.1, 139.0, 136.6, 134.9, 130.9, 130.8, 128.5, 126.6, 122.7, 121.0, 119.3, 118.0, 116.4, 116.3, 112.8, 112.8, 112.7, 93.7;IR (KBr)ν_{max} 3209, 2920, 1614, 1586, 1512, 1420, 1319, 1209, 1101 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}NOS_2F$ (M + H$^+$) 328.0261; Found 328.0266.

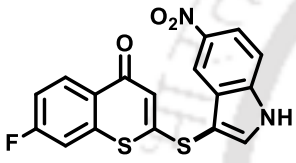
7-fluoro-2-((5-methoxy-1*H*-indol-3yl)thio)-4*H*-thiochromen-4-one (3n). Grey solid (110 mg, 62%); mp 212-213 ˚C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.91 (s, 1H), 8.30 – 8.26 (m, 1H), 7.91 (s, 1H), 7.71 (d, *J* = 4 Hz, 1H), 7.45 (d, *J* = 8 Hz, 1H), 7.40 (t, *J* = 8 Hz, 1H), 6.97 (d, *J* = 4 Hz, 1H), 6.90 – 6.87 (m, 1H), 6.83 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 176.2, 158.3, 154.9, 135.1, 131.5, 130.9, 130.8, 129.4, 126.6, 119.1, 116.3, 116.1, 113.6, 112.8, 112.8, 112.5, 99.4, 93.2, 55.3; IR (KBr)ν_{max} 3189, 2925, 1614, 1588, 1511, 1320, 1213, 1177, 1105 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}NO_2S_2F$ (M + H$^+$) 358.0366; Found 358.0396.

2-((5-bromo-1*H*-indol-3-yl)thio)-7-fluoro-4*H*-thiochromen-4-one (3o). Orange solid



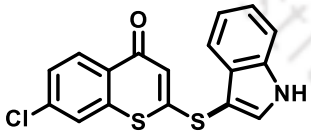
(129 mg, 64%); mp 246-247 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.27 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 8.06 (d, *J* = 4.0 Hz, 1H), 7.71- 7.68 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.30 (m, 2H), 6.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.2, 164.3, 161.8, 157.3, 139.0, 138.9, 136.3, 135.4, 130.9, 130.8, 130.5, 126.5, 125.4, 120.1, 119.5, 116.4, 116.1, 114.8, 113.7, 112.8, 112.5, 93.7; IR (KBr)ν_{max} 3240, 2920, 1612, 1585, 1514, 1452, 1206, 1121 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}NOS_2FBr$ (M + H$^+$) 405.9366; Found 405.9390, 407.9402.

7-fluoro-2-((5-nitro-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3p). Light yellow



solid (93 mg, 50%); mp 284-285 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.70 (s, 1H), 8.41 (s, 1H), 8.28- 8.24 (m, 2H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.76- 7.73 (d, *J* = 12.0 Hz, 1H), 7.65 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 7.38 (td, J = 8.0 Hz, 4.0 Hz, 1H), 6.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.4, 164.4, 161.9, 156.4, 142.3, 139.9, 138.9, 138.8, 131.0, 130.9, 128.3, 126.5, 120.1, 118.1, 116.5, 116.3, 114.6, 113.7, 112.8, 112.6, 97.2; IR (KBr)ν_{max} 3310, 2923, 1620, 1597, 1522, 1468, 1327, 1208, 1123, 1101 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}N_2O_3S_2F$ (M + H$^+$) 373.0111; Found 373.0106.

2-((1*H*-indol-3-yl)thio)-7-chloro-4*H*-thiochromen-4-one (3q). Dark brown solid (111



mg, 65%), mp 235-236 ˚C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.19 (d, *J* = 6.0 Hz, 1H), 8.01 (d, *J* = 6.0 Hz, 1H), 7.94 (d, *J* = 6.0 Hz, 1H), 7.58 – 7.53 (m, 3H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.84 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.4, 158.4, 138.4, 136.9, 136.7, 134.9, 129.6, 128.5, 128.3, 128.3, 125.8, 122.7, 121.0, 119.3, 118.0, 112.8, 93.7; IR (KBr)ν_{max} 3172, 2919, 1596, 1575, 1508, 1421, 1385, 1224, 1133,1103 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}NOS_2Cl$ (M + H$^+$) 343.9965; Found 343.9993.

7-chloro-2-((5-methoxy-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3r). Light brown solid (149 mg, 80%); mp 241-242 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.94 – 7.91 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 6.97 (s, 1H), 6.88 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.83 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.4, 158.7, 154.9, 138.5, 136.8, 135.1, 131.5, 129.6, 129.4, 128.4, 128.3, 125.8, 119.1, 113.6, 112.9, 99.4, 93.1, 55.4; IR (KBr)ν_{max} 3223, 3098, 2991, 2956, 2830, 1597, 1579, 1514, 1381, 1338, 1171, 1105 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}NO_2S_2Cl$ (M + H^+) 374.0071; Found 374.0088.

2-((5-bromo-1*H*-indol-3-yl)thio)-7-chloro-4*H*-thiochromen-4-one (3s). Orange solid (126 mg, 60%), mp 264-265 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 4.0 Hz, 1H), 7.91 (s, 1H), 7.68 (s, 1H), 7.58- 7.52 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.4, 157.6, 138.3, 136.8, 136.4, 135.4, 130.5, 129.5, 128.3, 125.8, 125.4, 120.1, 119.6, 114.9, 113.8, 113.2, 93.6; IR (KBr)ν_{max} 3433, 3205, 3019, 2924, 2850, 1614, 1582, 1522, 1383, 1301, 1101 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}NOS_2ClBr$ (M + H^+) 421.9070; Found 421.9077, 423.9077 .

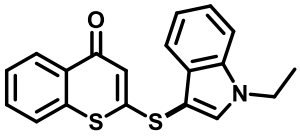
2-((1*H*-indol-3-yl)thio)-5-chloro-4*H*-thiochromen-4-one (3t). Brown solid (100 mg, 59%); mp 220-221 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 4 Hz, 1H), 7.54–7.53 (d, *J* = 4 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.6, 154.8, 139.8, 136.5, 134.7, 134.6, 134.2, 131.5, 128.5, 126.1, 125.9, 122.6, 120.9, 120.8, 117.9, 112.7, 93.8; IR (KBr)ν_{max} 3256, 3101, 1694, 1596, 1519, 1411, 1342, 1274, 1150 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}NOS_2Cl$ (M + H^+) 343.9965; Found 343.9994.

5-chloro-2-((5-methoxy-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3u). Light brown solid (147 mg, 79%); mp 194-195 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 7.90 (s, 1H), 7.62 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 7.54–7.48 (m, 2H), 7.45 (d, *J* = 12.0 Hz, 1H), 6.97 (d, *J* = 4.0 Hz, 1H), 6.89- 6.87 (m, 1H), 6.74 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.7, 155.2, 154.8, 139.9, 135.0, 134.2, 131.5, 131.5, 131.4, 129.4, 126.1, 126.0, 120.6, 113.5, 112.8, 99.4, 93.1, 55.3; IR (KBr)ν_{max} 3168, 2935, 2832, 1609, 1577 1555, 1465, 1288, 1167 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}NO_2S_2Cl$ (M + H$^+$) 374.0071; Found 374.0069.

2-((5-bromo-1*H*-indol-3-yl)thio)-5-chloro-4*H*-thiochromen-4-one (3v). Light yellow solid (mg, 78%); mp 274-275 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.05 (d, *J* = 2.8 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.55 (dd, *J* = 6.0, 1.8 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.37 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.7, 154.2, 139.7, 136.3, 135.3, 134.2, 131.6, 131.5, 130.5, 126.1, 126.0, 125.4, 121.1, 120.1, 114.8, 113.7, 93.6. IR (KBr)ν_{max} 3292, 1607, 1557, 1454, 1300, 1103 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}NOS_2ClBr$ (M + H$^+$) 421.9070; Found 421.9049, 423.9012.

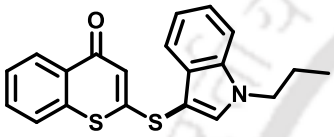
2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (4a). Brown solid (80 mg, 50%), mp 156-157 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 7.68 – 7.60 (m, 3H), 7.55 (t, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.81 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.1, 157.8, 138.0, 137.2, 136.6, 131.8, 129.6, 128.9, 128.0, 127.6, 126.4, 122.7, 121.1, 119.4, 118.2, 111.1, 92.9, 33.1; IR (KBr)ν_{max} 3440, 2922, 2854, 1616, 1517, 1323, 1128 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{14}NOS_2$ (M + H$^+$) 324.0511; Found 324.0521.

2-((1-ethyl-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (4b). Light brown solid (92 mg, 55%); mp 130 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* = 8.0 Hz, 1H), 8.06 (s,

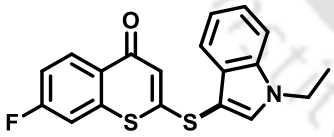


1H), 7.67 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 4.34 (q, *J* = 8.0 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.0, 157.8, 136.6, 136.3, 131.7, 129.6, 129.0, 128.0, 127.6, 126.4, 122.6, 121.1, 119.3, 118.3, 111.1, 93.1, 41.0, 15.2; IR (KBr)ν_{max} 3419, 2255, 2128, 1649, 1029 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{16}NOS_2$ (M + H$^+$) 338.0668; Found 338.0653.

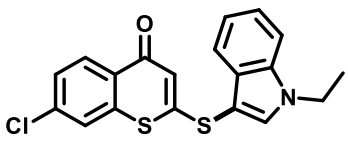
2-((1-Propyl-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (4c). Light yellow solid (87 mg, 50%), mp 139-140 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* = 8.0 Hz, 1H), 8.05 (s, 1H), 7.70- 7.61 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 4.28 (t, *J* = 8.0 Hz, 2H), 1.85 (dd, *J* = 12.1, 8.0 Hz, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.1, 157.9, 137.3, 136.6, 131.8, 129.6, 129.0, 128.0, 127.6, 126.4, 122.6, 121.1, 119.3, 118.3, 111.2, 93.0, 47.6, 22.8, 10.9; IR (KBr)ν_{max} 3442, 3094, 3054, 2962, 2931, 2874, 1615, 1520, 1321, 1129 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{18}NOS_2$ (M + H$^+$) 352.0824; Found 352.0828.



2-((1-ethyl-1*H*-indol-3yl)thio)-7-fluoro-thiochromen-4-one (4d). Light orange solid (106 mg, 60%); mp 134 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.07 (s, 1H), 7.69 (t, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.39 (td, *J* = 8.7, 2.3 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.82 (s, 1H), 4.34 (q, *J* = 8.0 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.2, 157.7, 136.7, 136.3, 130.8, 130.8, 129.0, 126.5, 122.6, 121.1, 119.3, 118.3, 116.3, 116.1, 112.8, 112.5, 111.1, 92.9, 41.0, 15.2; IR (KBr)ν_{max} 3420, 2259, 2132, 1645, 1025 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{15}NOS_2F$ (M + H$^+$) 356.0574; Found 356.0566.

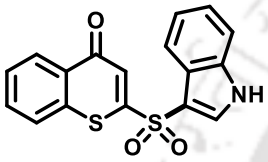


7-chloro-2-((1-ethyl-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (4e). Light brown solid(144 mg, 78%); mp 146 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, *J* = 8.0 Hz,

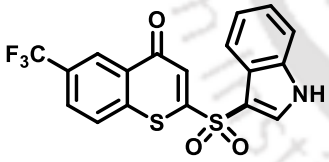


1H), 8.07 (s, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 4.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.82 (s, 1H), 4.34 (q, *J* = 8.0 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.3, 158.1, 138.3, 136.8, 136.7, 136.3, 129.5, 129.0, 128.3, 125.7, 122.7, 121.1, 119.4, 118.3, 111.1, 92.8, 41.0, 15.2; IR (KBr)ν_{max} 3420, 2256, 2129, 1646, 1025 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{15}NOS_2Cl$ (M + H$^+$) 372.0278; Found 372.0250.

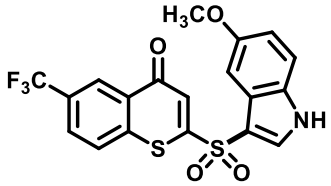
2-((1H-indole-3-yl)sulfonyl)-4H-thiochromen-4-one (5a). Brown solid (49 mg, 58%); mp 266 ˚C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.72 (s, 1H), 8.44 (d, *J* = 3.3 Hz, 1H), 8.28 – 8.26 (m, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.86 – 7.84 (m, 1H), 7.80- 7.77 (m, 1H), 7.66- 7.63 (m, 1H), 7.57 – 7.56 (m, 2H), 7.32 – 7.30 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 179.4, 156.0, 136.6, 135.2, 134.7, 133.2, 129.9, 129.1, 128.2, 127.9, 124.4, 123.8, 123.2, 122.8, 118.6, 113.4, 110.5; IR (KBr)ν_{max} 3423, 2960, 1607, 1419,1330, 1136 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{12}NO_3S_2$ (M + H$^+$) 342.0253; Found 342.0272.



2-((1*H*-indol-3-yl)sulfonyl)-6-(trifluoromethyl)-4*H*-thiochromen-4-one (5b). Brown solid (66 mg, 65%); mp 274 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.44 (s, 1H), 8.01 (d, *J* = 2.8 Hz, 1H), 7.95 (s, 2H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.93 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.1, 159.4, 141.0, 136.7, 134.9, 134.3, 129.8, 128.4, 128.3, 127.5, 124.3, 124.2, 122.8, 122.2, 121.2, 121.1, 119.3, 118.0, 112.8, 93.5; IR (KBr)ν_{max} 3167, 2922, 2855, 1630, 1605, 1504, 1432, 1334,1291, 1180, 1138, 1103, 1080,1022 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{11}NO_3S_2F_3$ (M + H$^+$) 410.0127; Found 410.0151.

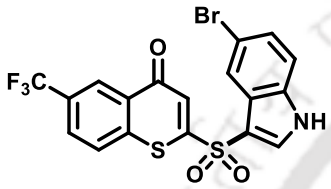


2-((5-methoxy-1*H*-indol-3-yl)sulfonyl)-6-(trifluoromethyl)-4*H*-thiochromen-4-one (5c). Brown solid (76 mg, 70%), mp 210 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.47 (s, 1H), 8.35 (d, *J* = 4.0 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.12 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.63 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 4.0 Hz, 1H), 6.95 (dd, *J* = 8.0



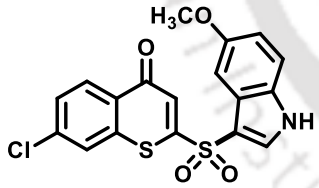
Hz, 4.0 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 178.9, 161.0, 156.5, 155.9, 139.7, 134.7, 131.4, 130.4, 130.1, 129.3, 128.8, 128.8, 124.6, 124.2, 114.4, 113.8, 109.6, 100.9, 100.4, 55.6; IR (KBr)ν_{max} 3358, 3140, 2937, 2834, 1637, 1607, 1586, 1488, 1319, 1248, 1175, 1078,1031 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{13}NO_4S_2F_3$(M + H$^+$) 440.0233; Found 440.0261.

2-((5-bromo-1*H*-indol-3-yl)sulfonyl)-6-(trifluoromethyl)-4*H*-thiochromen-4-one (5d).



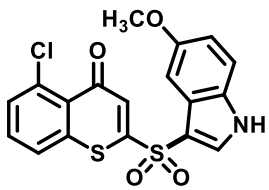
Brown solid (60 mg, 50%); mp 237 ˚C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.91 (s, 1H), 8.51 (d, *J* = 4.0 Hz, 1H), 8.45 (s, 1H), 8.26 (t, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.98 (s, 1H), 7.66 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.46– 7.44 (m, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 178.8, 156.0, 139.6, 136.1, 135.4, 130.3, 130.0, 129.2, 128.9, 128.7, 126.7, 125.0, 124.9, 124.7, 124.5, 124.5, 120.7, 115.5, 109.9; IR (KBr)ν_{max} 3260, 2922, 1625, 1591, 1514, 1451, 1293, 1175, 1132, 1080 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{10}NO_3S_2F_3Br$ (M + H$^+$) 487.9232; Found 487.9256, 489.9263.

7-chloro-2-((5-methoxy-1*H*-indol-3-yl)sulfonyl)-4*H*-thiochromen-4-one (5e). Dark



brown solid (53 mg, 53%); mp 304 ˚C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.58 (s, 1H), 8.33 (d, *J* = 4.0 Hz, 1H), 8.25- 8.22 (m, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 6.95 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 178.7, 156.0, 155.7, 138.1, 137.0, 134.5, 131.3, 129.7, 128.7, 128.5, 127.3, 124.4, 124.0, 114.2, 113.6, 109.7, 100.3, 55.4; IR (KBr)ν_{max} 3354, 2924, 2853, 1611, 1582, 1463, 1382, 1130, 1100, 1033 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}NO_4S_2Cl$ (M + H$^+$) 405.9969; Found 405.9996.

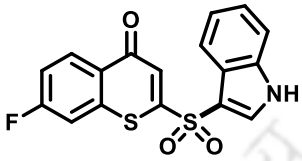
5-chloro-2-((5-methoxy-1*H*-indol-3-yl)sulfonyl)-4*H*-thiochromen-4-one (5f). Brown



solid (55 mg, 55%); mp 245 ˚C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.58 (s, 1H), 8.31 (d, *J* = 4.0 Hz, 1H), 7.93 – 7.91 (m, 1H), 7.66 – 7.64 (m, 2H), 7.47 (t, *J* = 4.4 Hz, 2H), 7.25 (d, *J* = 4.0 Hz, 1H), 6.95

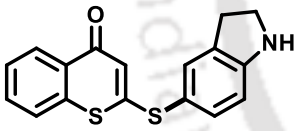
(d, *J* = 8.0 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 178.9, 155.8, 152.9, 138.4, 134.5, 134.4, 132.9, 132.2, 131.3, 127.5, 126.7, 125.7, 124.1, 114.3, 113.7, 109.7, 100.3, 55.5; IR (KBr)ν_{max} 3372, 3123, 3045, 2925, 2834, 1734, 1621, 1577, 1415, 1319, 1297, 1178, 1116, 1036 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}NO_4S_2Cl$ (M + H$^+$) 405.9969; Found 405.9994.

2-((1*H*-indol-3-yl)sulfonyl)-7-fluoro-4*H*-thiochromen-4-one (5g). Light brown solid



(50 mg, 56%); mp 254 ˚C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.71 (s, 1H), 8.42 (d, *J* = 4 Hz, 1H), 8.31-8.35 (m, 1H), 7.99-8.02 (m, 1H), 7.88-7.90 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.32 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 179.3, 166.8, 156.4, 137.0, 135.0, 133.9, 133.3, 131.9, 131.2, 129.3, 128.4, 125.0, 124.6, 123.5, 118.9, 113.9, 110.7; IR (KBr)ν_{max} 3268, 1654, 1049, 1025 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}FNO_3S_2$ (M + H$^+$) 360.0159; Found 360.0158.

2-(indolin-5-ylthio)-4*H*-thiochromen-4-one (7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd,



J = 7.9, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.47–7.43 (m, 2H), 7.27 (s, 1H), 7.24 (d, *J* = 1.7 Hz, 1H), 6.79 (s, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 3.66 (t, *J* = 8.0 Hz, 2H), 3.55 (d, *J* = 5.1 Hz, 1H, 3.07 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 159.6, 154.5, 137.9, 136.7, 132.7, 131.3, 131.2, 130.7, 128.7, 127.6, 125.8, 120.5, 113.2, 109.5, 47.5, 29.3.

Table 2.9. Crystal Data and Structure Refinement for Compounds 3a and 5a

Entry	Identification code	Compound 3a	Compound 5a
01	Empirical formula	C17H11NOS2	C17 H11 N O3 S2
02	Formula weight	309.39	341.39
03	Temperature	293 K	293 K
04	Wavelength	0.71073	0.71073
05	Radiation type	Mo K\a	Mo K\a
06	Radiation source	Fine-focus sealed tube	Fine-focus sealed tube
07	Crystal system	Monoclinic	Orthorhombic
08	Space group	C 2/ c	P 21 21 21
09	Cell length	a 17.5086(10) b 11.7781(8) c 13.9721(9)	a 6.4978(4) b 14.5164(14) c 16.2262(14)
10	Cell Angle	α 90 β 92.716(6) δ 90	α 90 β 90 δ 90
11	Cell Volume	2878.1(3)	1530.5 (2)
12	Density	1.428	1.482
13	Completeness to theta	25°/ 99.7%	25°/ 99.73%
14	Absorption correction	multi-scan	multi-scan
15	Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2
16	Index ranges	-23<=h<=22, -15<=k<=15, -17<=l<=17	-8<=h<=8, -10<=k<=18, -12<=l<=21
17	Reflection number	6700	5606
18	Theta range	2.9190-28.7886	2.8762-28.6975
19	Cell formula units Z	8	4
20	CCDC no	1887551	1887550

Figure 2.11.a. ^{1}H NMR spectra of 2-((1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3a)

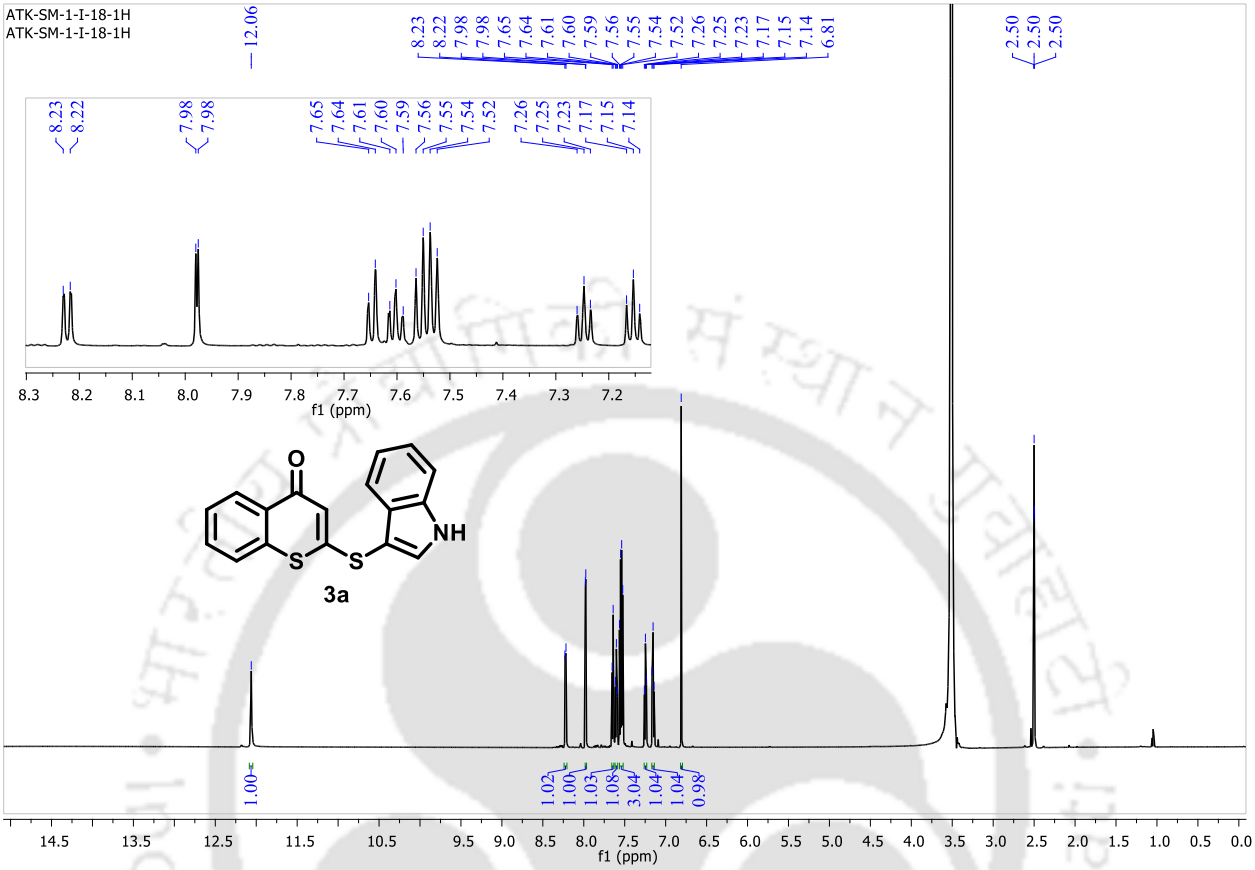


Figure 2.11.b. ^{13}C NMR spectra of 2-((1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3a)

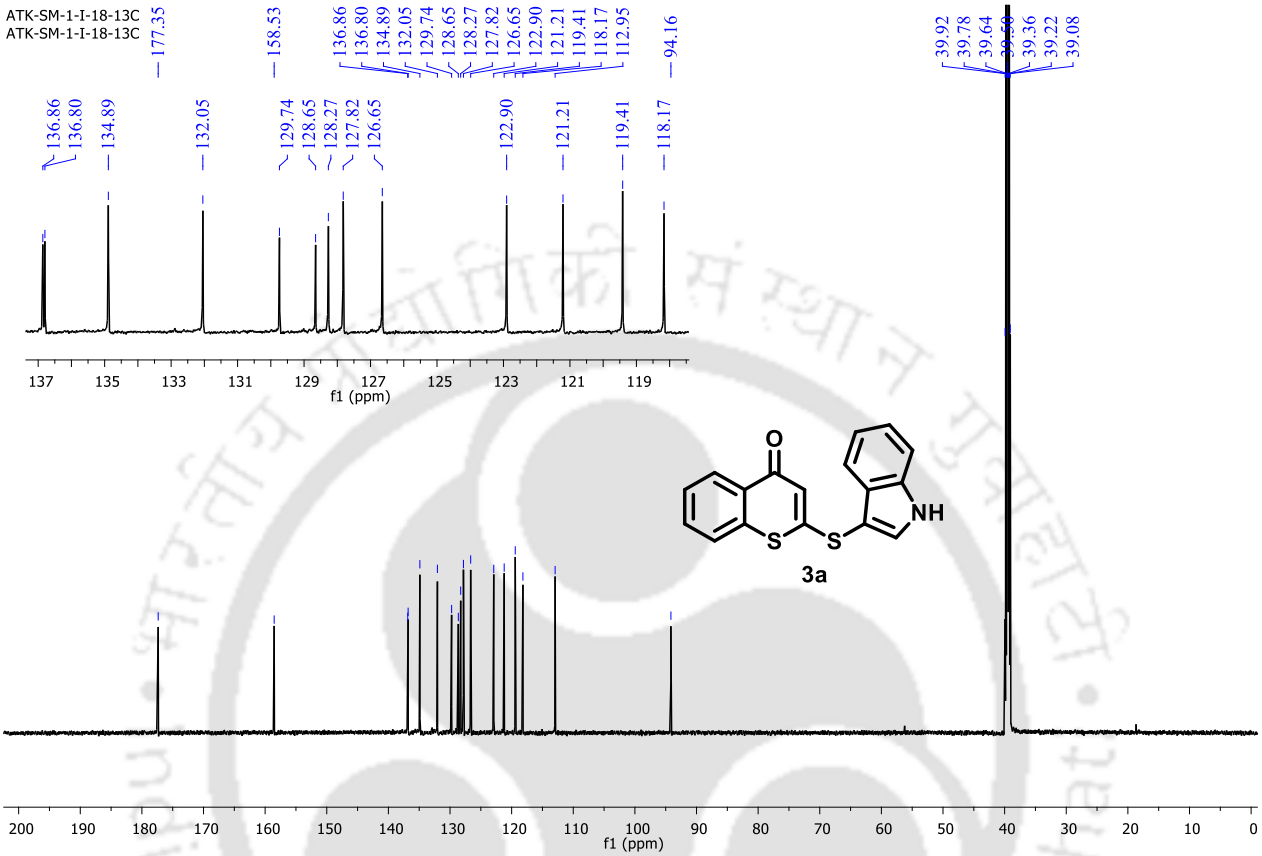


Figure 2.11.c. HRMS spectra of 2-((1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (3a)

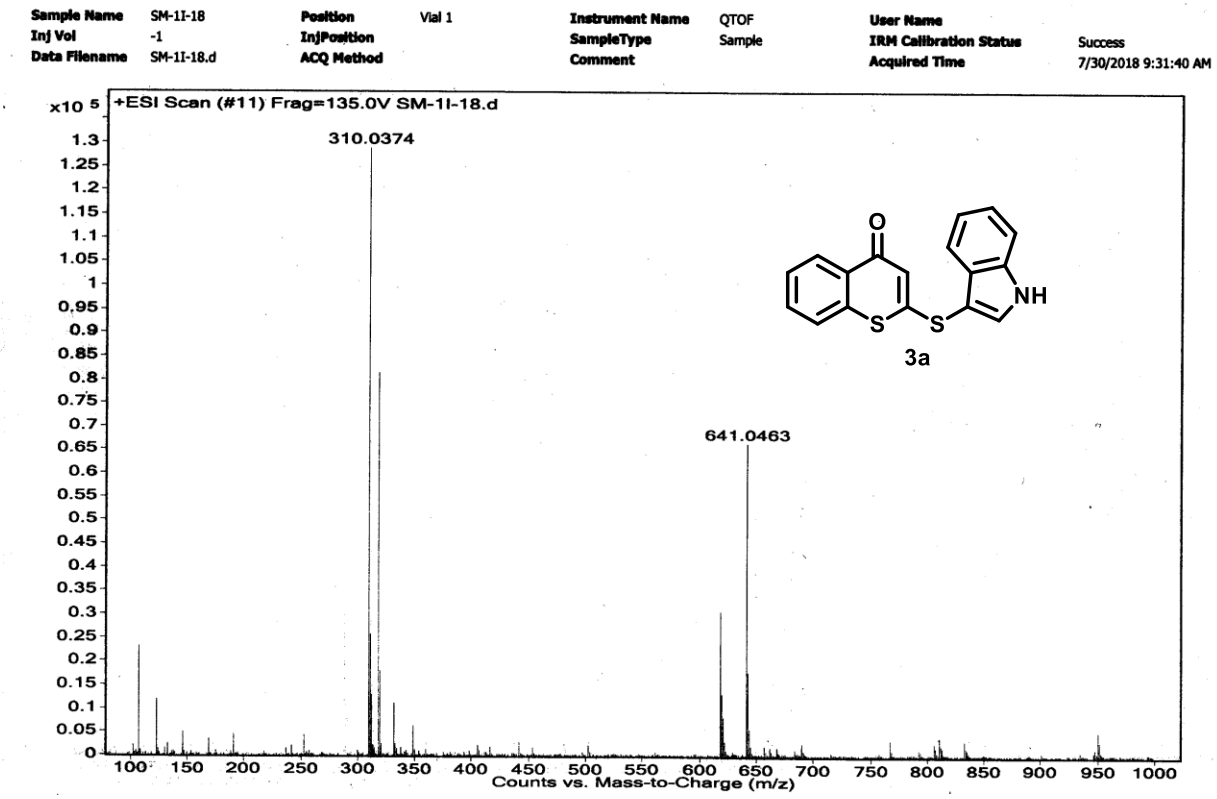


Figure 2.12.a. ^{1}H NMR spectra of 2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (4a)

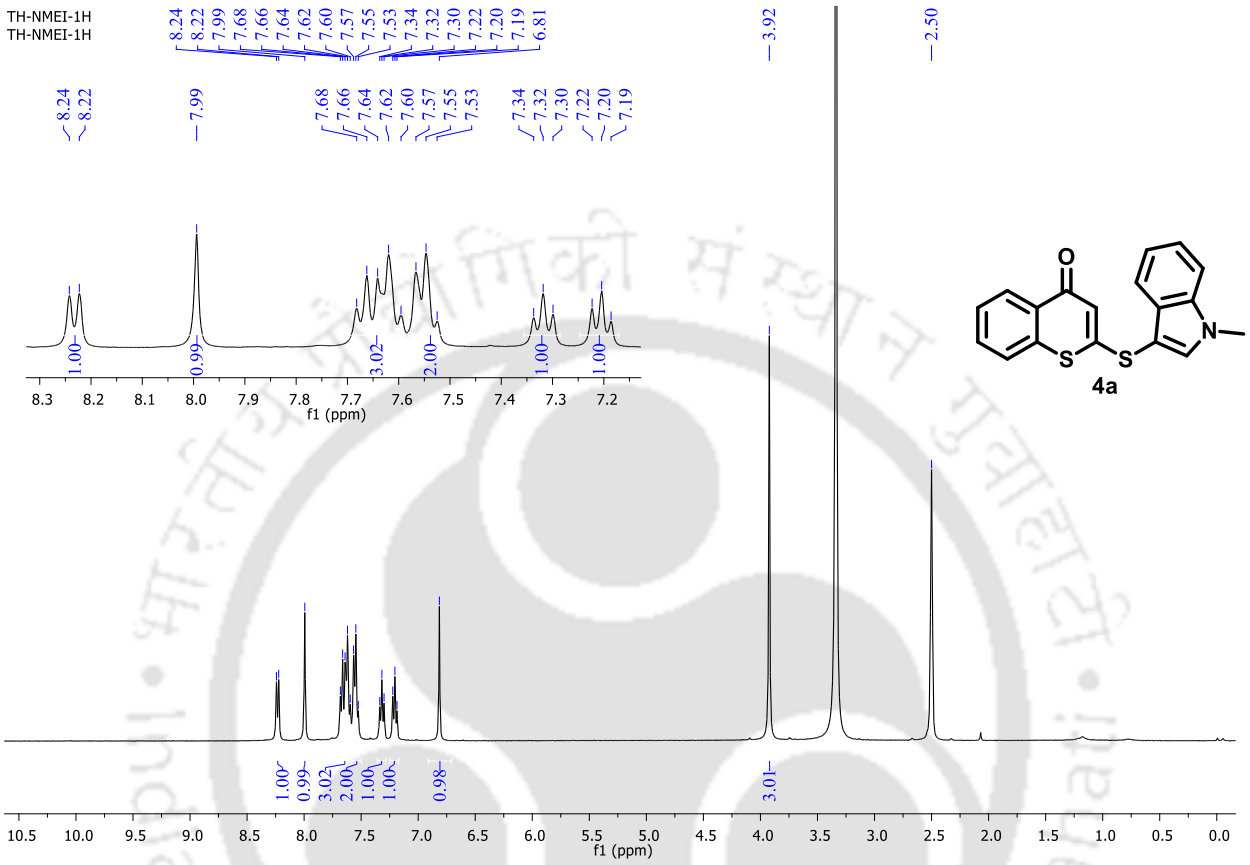


Figure 2.12.b. ^{13}C NMR spectra of 2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (4a)

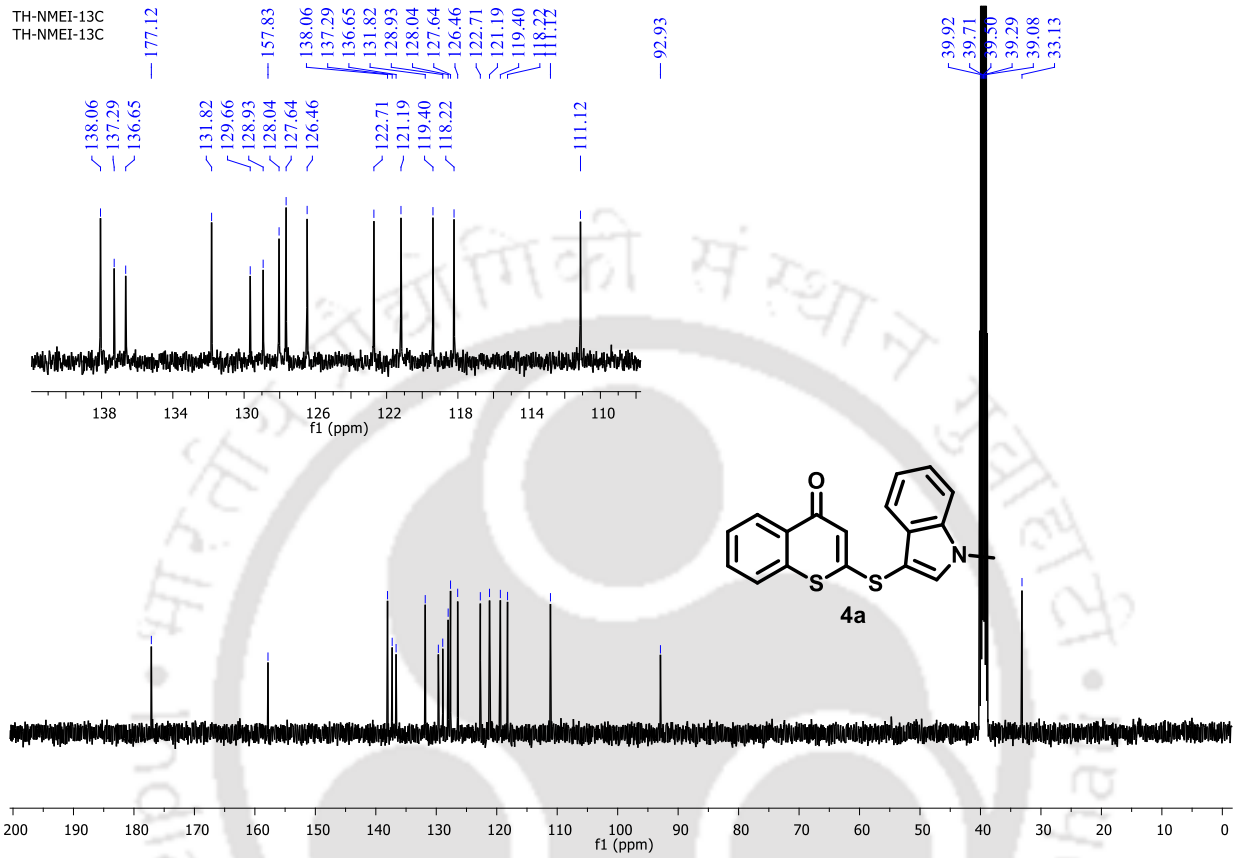


Figure 2.12.c. HRMS spectra of 2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-thiochromen-4-one (4a)

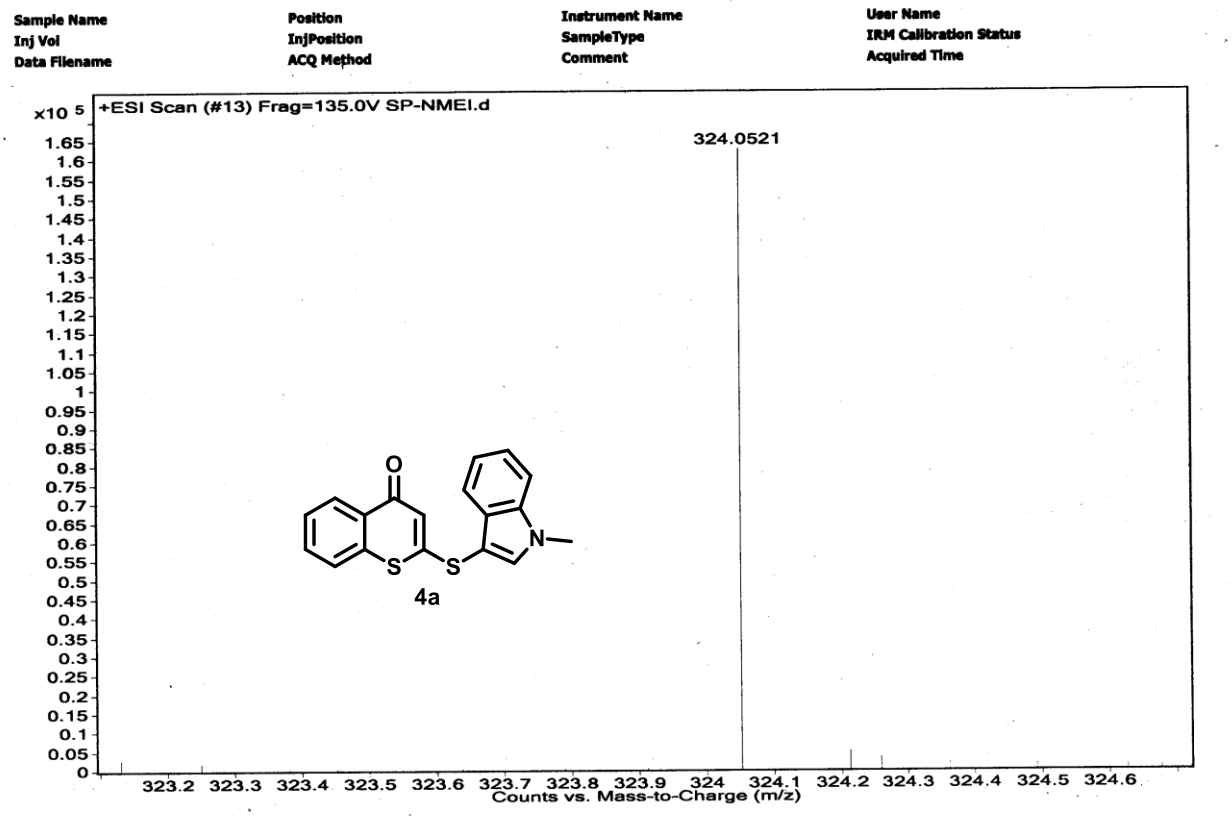


Figure 2.13.a. ^{1}H NMR spectra of 2-((1*H*-indole-3-yl)sulfonyl)-4*H*-thiochromen-4-one (5a)

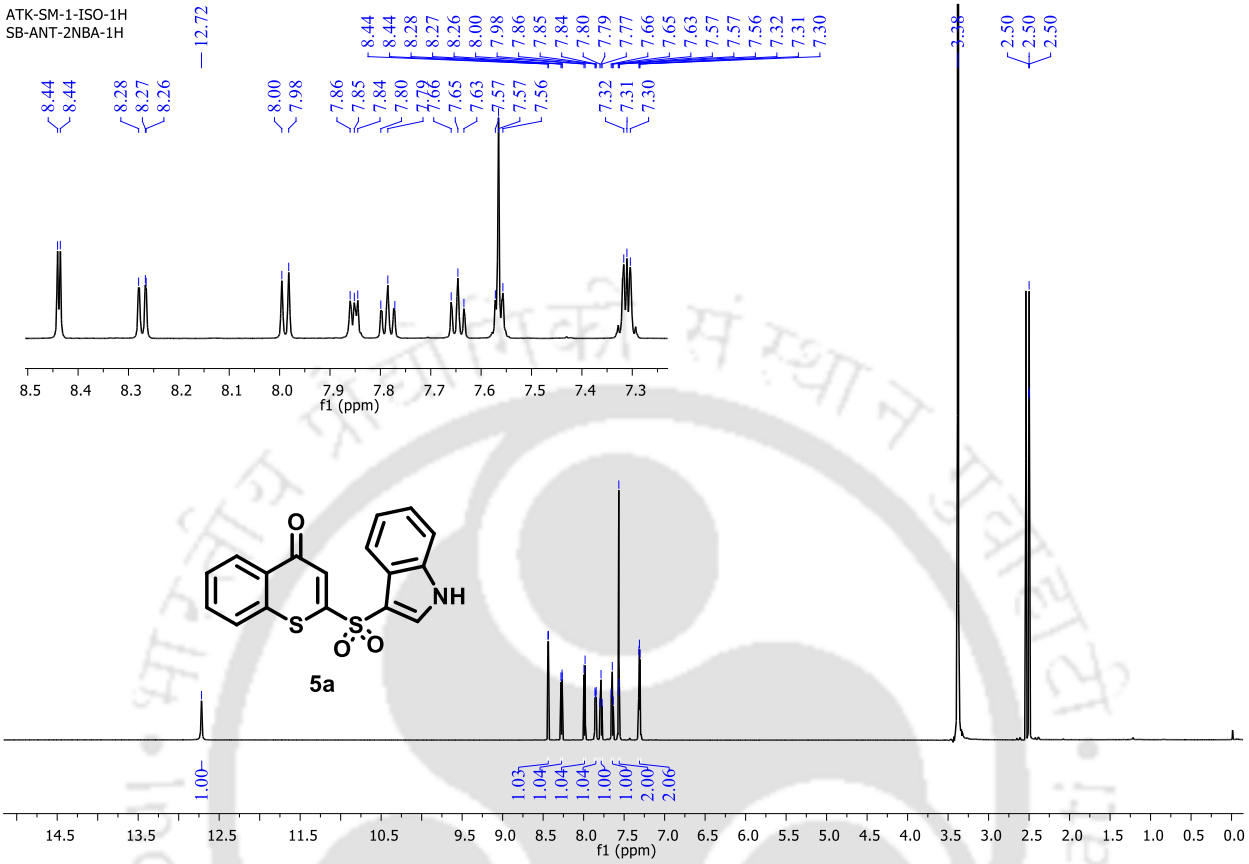


Figure 2.13.b. ^{13}C NMR spectra of 2-((1*H*-indole-3-yl)sulfonyl)-4*H*-thiochromen-4-one (5a)

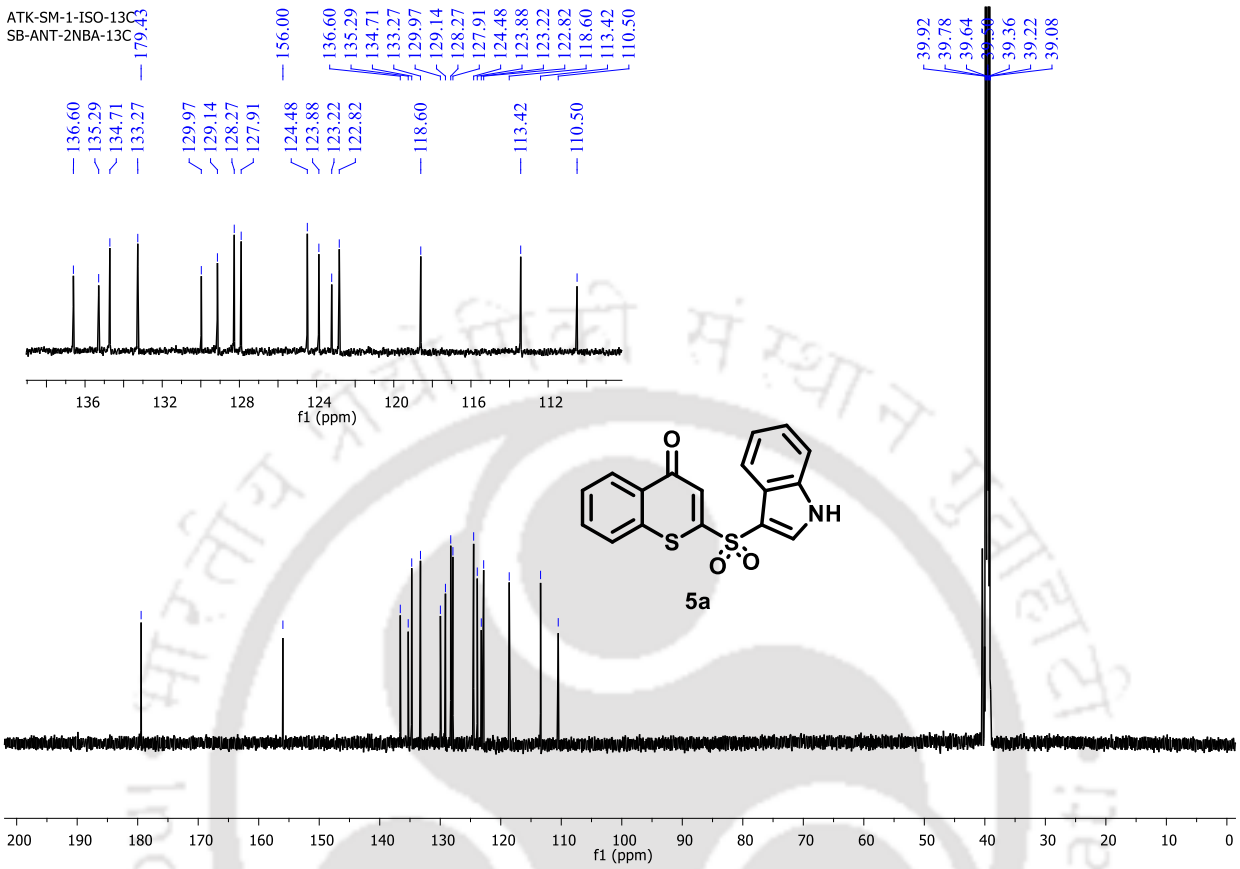
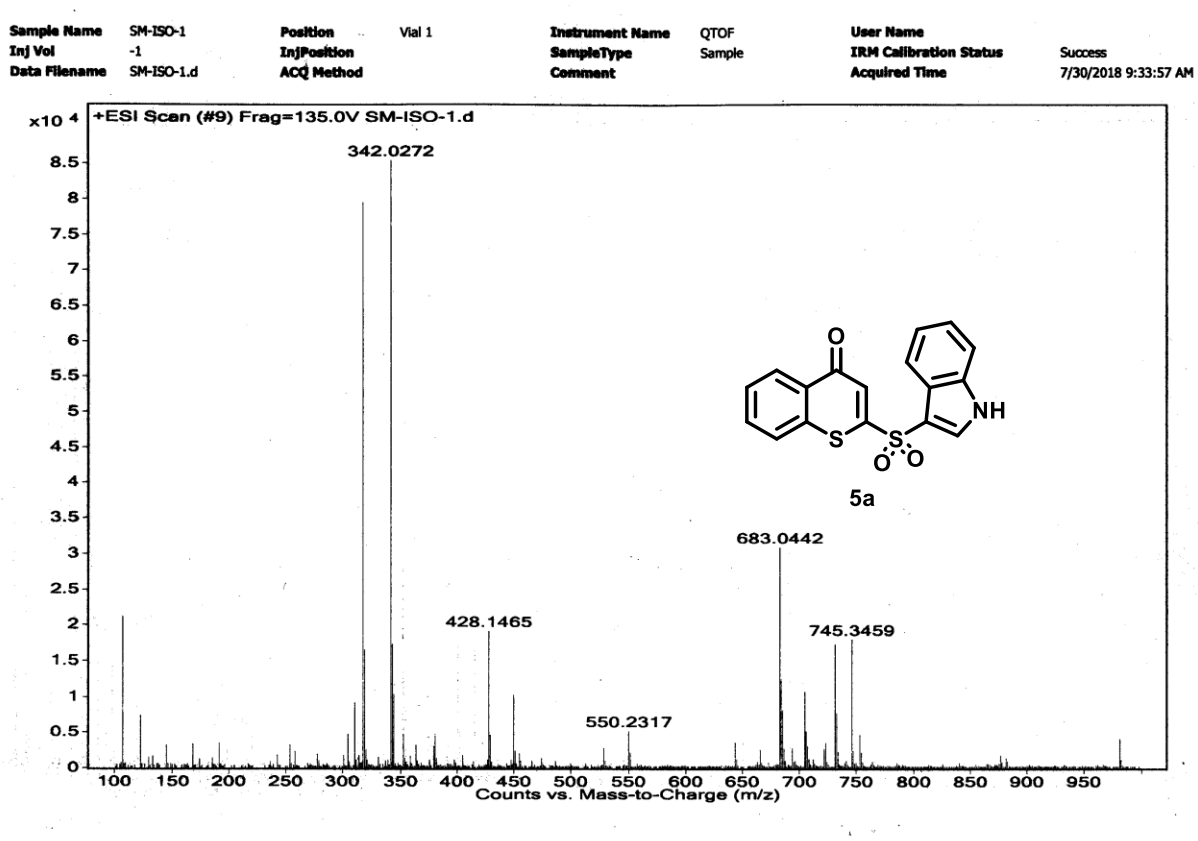


Figure 2.13.c. HRMS spectra of 2-((1*H*-indole-3-yl)sulfonyl)-4*H*-thiochromen-4-one (5a)



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CHAPTER III

KI/TBHP-mediated cross dehydrogenative coupling reaction of 4-hydroxydithiocoumarins and 1,3-dicarbonyl compounds

Introduction

Results & Discussion

Experimental Section

3.1. Introduction

Organosulfur compounds are important intermediates in different chemical syntheses and it has gained a lot of attention in both natural and non-natural product synthesis.[1] The organosulfur compounds, used as medicines, having the *C-S* linkage exhibits antiviral,[2a] antibacterial,[2b] and antiallergic.[2c] As a matter of fact, organic chemists have given much attention to the development of newer processes for *C-S* bond formation reactions. 1,3-Dicarbonyl compounds are valuable starting materials for the synthesis of pyrazoles,[3] oxazoles,[4] and other pharmaceutically[5] significant heterocyclic compounds, as well as, they are an integral part of many naturally occurring compounds.[6] The achievement of hetero-atom substitution of the methylene site of 1,3-dicarbonyl compounds is still an attraction among the scientific community. In this context, α-thiocarbonyl compounds, which have emerged as building blocks in organic synthesis,[7] medicines, and agrochemicals,[8] deserve special consideration. Some of the most effective molecules containing α-thiocarbonyl compounds, such as malathion, gliotoxin, and 2-[(2-methylphenyl)thio]-indane-1,3-dione is depicted in Figure 3.1.[9]

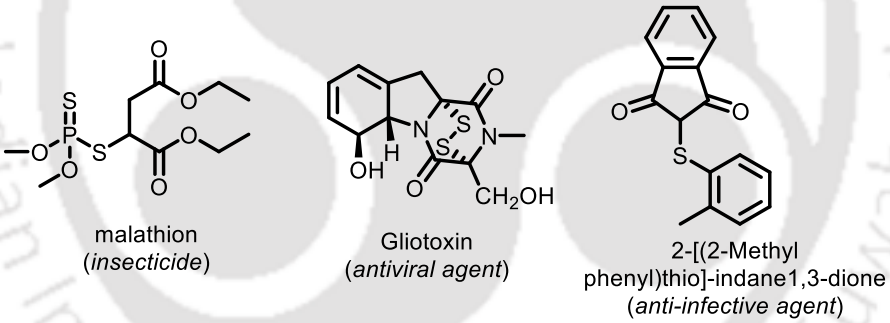
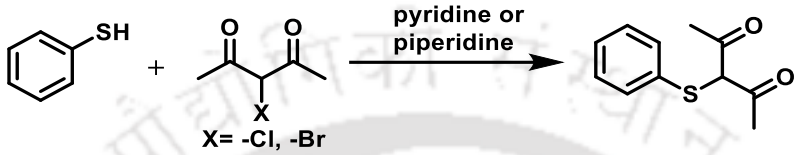


Figure 3.1. Biologically active α-thiocarbonyl compounds

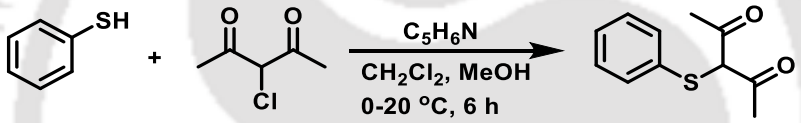
3.2. Synthesis of α-thiocarbonyl derivatives

Yoshida *et al.* reported the synthesis of α-thio-β-dicarbonyl compounds from thiophenol and α-halo-1,3-dicarbonyl compounds using pyridine or piperidine through nucleophilic substitution reaction *via* the traditional method.[10] The incorporation of a thiol-containing group into the α-position of dicarbonyls caused a significant change in the tautomeric equilibrium to the enol group.



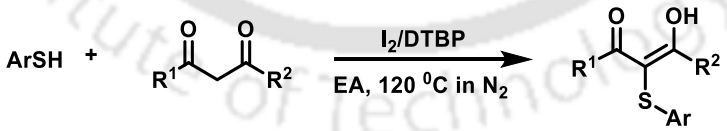
Scheme 3.1. Synthesis of α-thio-β-dicarbonyl compounds

Rashid *et al*. demonstrated the reaction of α-chloroacetoacetate with thiophenol provided α-thio-β-dicarbonyl.[11]



Scheme 3.2. Traditional synthetic route of α-thiocarbonyl compounds

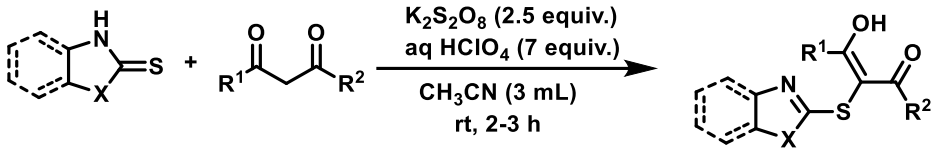
Cao *et al*. displayed the synthesis of β-dicarbonyl thioethers from 1,3-dicarbonyl compounds and thiols using iodine catalyst *via* C–H/S–H oxidative coupling reaction.[12] This approach proved to be straightforward to handle and simple to work up because no base or transition metal was introduced and only stoichiometric diketone was utilized, making it appealing for constructing a biologically active compound.



Scheme 3.3. Synthesis of β-dicarbonyl thioethers from 1,3-dicarbonyl compounds and thiols

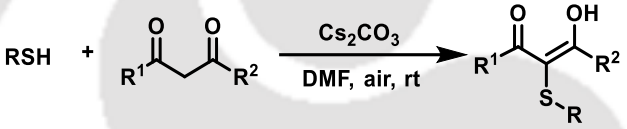
Prabhu *et al*. reported the sulfenylation of β-diketone from thiol and 1,3-dicarbonyl compounds.[13] Sulfenylation of β-diketones is difficult because deacylation occurs following sulfenylation in the reaction media. A cross dehydrogenative coupling (CDC) approach is used to sulfenylate diketones without deacylation under metal-free conditions at room

temperature. The resulting compounds can be further utilized to produce pyrazoles, and α,α-disubstituted-β-diketones.



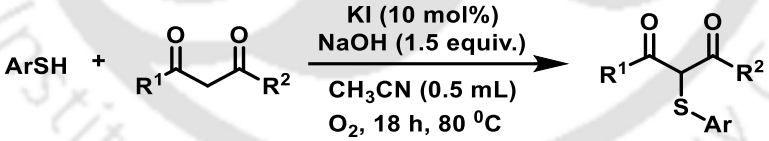
Scheme 3.4. Sulfenylation of β-diketone from thiol and 1,3-dicarbonyl compounds

Chen *et al*. illustrated that halogen-free Cs_2CO_3 promoted synthesis of α-thio-β-carbonyl compounds from thiol and active methylene compounds utilizing air as the oxidant through cross-dehydrogenative coupling (CDC) reaction.[14] This reaction is a simple way to make *C*-*S* bonds with a wide range of functional group compatibility, yielding α-thio-β-carbonyl compounds.



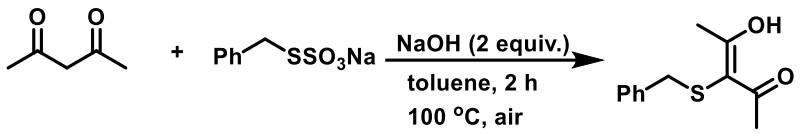
Scheme 3.5. Cs_2CO_3 promoted the synthesis of α-thio-β-dicarbonyl compounds

Jiang *et al*. revealed the synthesis of α-thio-β-dicarbonyl compounds from thiol and symmetrical/unsymmetrical 1,3-dicarbonyl compounds using KI in an alkaline medium under an aerobic atmosphere.[15] This methodology is useful for the modification of the anti-inflammatory drug, butazodine.



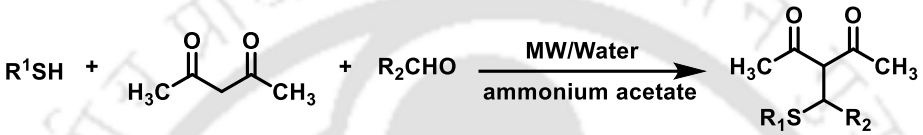
Scheme 3.6. Synthesis of α-thio-β-dicarbonyl compounds from thiol and 1,3-dicarbonyl

Kazmierczak *et al*. reported in their communication that the synthesis of α-thiocarbonyls from β-acetylacetone and sodium *S*-organyl sulfurothioates under basic conditions in toluene as the solvent at 100 °C.[16] Sodium *S*-organyl sulfurothioates acts as a source of sulfur that is free of unpleasant odor and not air-sensitive.



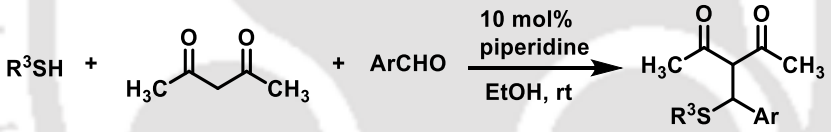
Scheme 3.7. Synthesis of α-organylthio ketones from β-keto esters and sodium *S*-organyl sulfurothioates

Ma *et al*. described the microwave-assisted β-thiodiketone compounds synthesis from mercaptans, aldehydes, and acetylacetone in an aqueous medium using ammonium acetate as a catalyst through a multicomponent pathway as shown in scheme 3.7.[17]



Scheme 3.8. Synthesis β-thiodiketone *via* a multicomponent pathway

Dar *et al*. reported the synthesis of β-thiodiketone 1,3-dicarbonyl compound, thiol, and aldehyde using 10 mol % ethanolic piperidine *via* multicomponent reaction.[18]



Scheme 3.9. Synthesis of β-thiodiketone *via* multicomponent reaction of 1,3-dicarbonyl compound, thiol, and aldehyde.

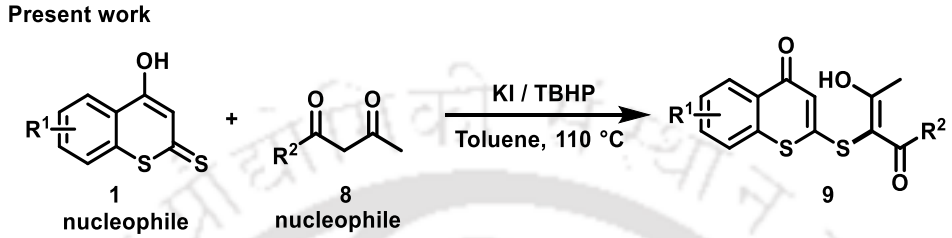
It is difficult to accomplish C–H/S–H oxidative coupling reactions of thiols with 1,3-dicarbonyl compounds due to (i) products might be subsequently oxidized to produce sulfoxides or sulfones; (ii) metal catalysts with high coordination to sulfur atoms are typically poisoned for this process; (iii) deacylation can occur when disulfide or its equivalent is employed in a process;[19] (iv) requirement of inert atmosphere[12] and longer reaction times.[15] Only a few examples of thiocarbonyl being synthesized in one step using 1,3-dicarbonyl compounds and thiophenols as starting materials have been published due to these limitations. Since 1,3-dicarbonyl compounds and thiophenols are both nucleophiles, either of them must be converted to the respective electrophiles before the *C–S* bonds can be generated, hence typical α-thiocarbonyl syntheses are tough and laborious. Exploring a way to directly

synthesize α-thiocarbonyl from thiophenols and 1,3-dicarbonyl compounds is therefore extremely exciting.

Recently our group has shown the reactivity behaviour of 4-hydroxydithiocoumarin for the synthesis of numerous new compounds, which has been reviewed recently.[20] From the reactivity pattern of 4-hydroxydithiocoumarin, it was noted that it can generate one of the intermediate as thiol (2-mercapto-4*H*-thiochromen-4-one)[21] in the reaction medium. The thiol form of 4-hydroxydithiocoumarin acts as a nucleophile and 1,3-dicarbonyl compounds also act as a nucleophile. The cross-coupling reaction between two nucleophiles is a challenging task and using these thiocarbonyl compounds, we can synthesize a new class of pyrazole derivatives.

3.3. Results and Discussion

Herein, we report the synthesis of α-thiocarbonyl compounds from 4-hydroxydithiocoumarin and 1,3-dicarbonyl compounds using 10 mol% KI and 1 equivalent of TBHP in toluene at 110 ˚C as shown in Scheme 3.10.

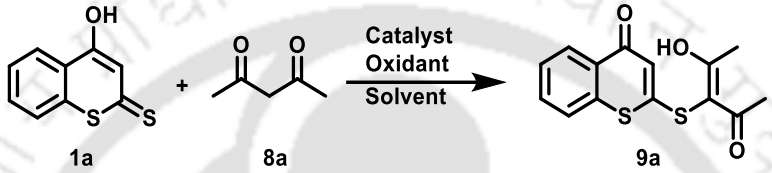


Scheme 3.10. Our approach towards the synthesis of α-thiocarbonyl compounds

We have synthesized various 4-hydroxydithiocoumarin derivatives from 2'-chloroacetophenone and carbon disulfide in the presence of sodium hydride for our present study.[21] 4-Hydroxydithiocoumarin **1a** and acetylacetone **8a** were used as the model substrates to determine a suitable reaction condition, which is summarized in Table 3.1. We began our experiment with 4-hydroxydithiocoumarin and acetylacetone in DMSO at room temperature and 70 °C in the presence of 10 mol% I_2 and 1 equiv of TBHP, no reaction took place and the starting materials were recovered (Table 3.1, entries 1 and 2). Delightfully, product **9a** was observed when we have performed the reaction with 10 mol% I_2 and 1 equiv of TBHP at 100 °C (Table 3.1, entry 3). In the IR spectrum, compound **9a** shows a characteristic peak at 3291 cm^{-1} for the OH group and 1720 cm^{-1} for the presence of the C=O group. This indicates that one of the carbonyls of 1,3-dicarbonyl compounds is converted to the -OH group. In the ^1H NMR spectrum, -OH gives a characteristic singlet at δ 17.47 ppm. In the ^{13}C NMR spectrum, C=O appears at 198.9 ppm and C-3 gives a characteristic peak at 98.3 ppm. From HRMS, we have observed that the molecular mass of **9a** is 293.0302. The structure of the product **9a** was characterized by using IR, ^1H NMR ^{13}C NMR spectroscopy, and HRMS. Furthermore, the reactions were executed with 10 mol% I_2 in DMSO by varying oxidants like DTBP, $K_2S_2O_8$ at 100 ˚C (Table 3.1, entries 4 and 5), but the yields were not improved. During the catalyst screening, we used different Bu_4NI, Bu_4NBr, KBr, CuI, and KI in the presence of TBHP in DMSO at 100°C (Table 3.1, entries 6-10). The yield also did not improve up to the expectation. Moreover, we examined the reaction in presence of 10

mol% KI and 1 equivalent of TBHP by varying solvents like DMF, methanol, CH_3CN, 1,2-dioxane, and toluene (Table 3.1, entries 11-15). We obtained the best yield in toluene at reflux conditions. Finally, we have executed the reactions in toluene with increasing catalyst loading (Table 3.1, entry 16 & 17) and TBHP (Table 3.1, entry 18 & 19). We concluded from all these observations that 10 mol% KI, 1 equivalent TBHP in toluene at 110 ˚C is the best reaction condition to obtain the desired product in maximum yield (Table 3.1, entry 15).

Table 3.1. Optimization for the reaction conditions[a,b]



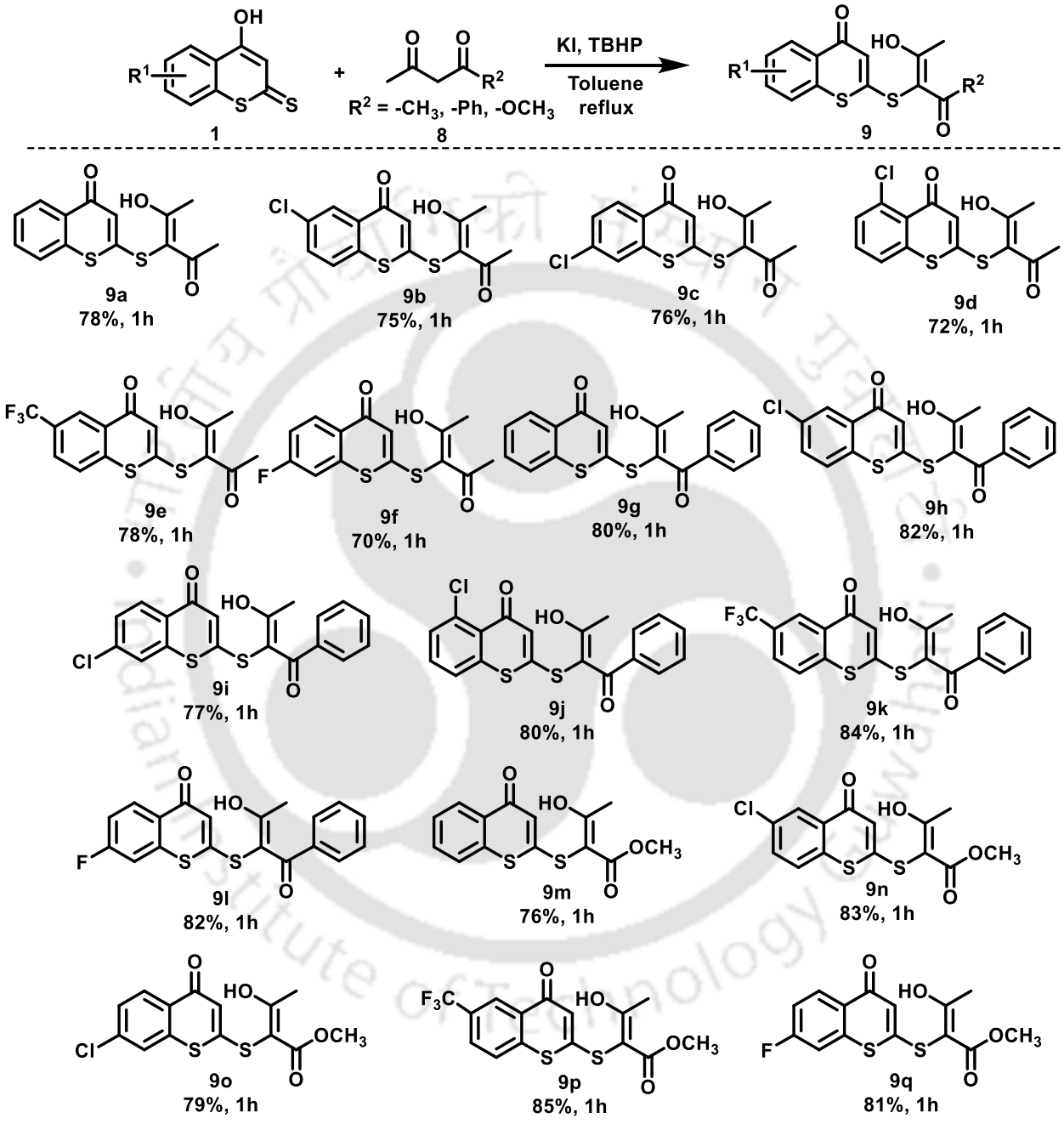
Entry	Oxidant (1 equiv)	Catalyst	Mol (%)	Solvent	Time (h)	Yield (%)
[c]01	TBHP	I_2	10	DMSO	6	-
[d]02	TBHP	I_2	10	DMSO	2	-
[e]03	TBHP	I_2	10	DMSO	2	14
[e]04	DTBP	I_2	10	DMSO	2	12
[e]05	$K_2S_2O_8$	I_2	10	DMSO	2	8
[e]06	TBHP	Bu_4NI	10	DMSO	2	20
[e]07	TBHP	Bu_4NBr	10	DMSO	3	23
[e]08	TBHP	KBr	10	DMSO	2	30
[e]09	TBHP	CuI	10	DMSO	3	40
[e]10	TBHP	KI	10	DMSO	1	48

[e]11	TBHP	KI	10	DMF	3	54
[f]12	TBHP	KI	10	Methanol	2	30
[f]13	TBHP	KI	10	CH_3CN	1	35
[f]14	TBHP	KI	10	1,4-Dioxane	2	32
[f]15	**TBHP**	**KI**	**10**	**Toluene**	**1**	**78**
[f]16	TBHP	KI	20	Toluene	1	80
[f]17	TBHP	KI	50	Toluene	1	79
[f]18	TBHP (2 equiv)	KI	20	Toluene	1	75
[f]19	TBHP (3 equiv)	KI	20	Toluene	1	74

[a]All the reactions were carried out using 4-hydroxydithiocoumarin (0.25 mmol), acetylacetone (0.25 mmol), KI (10 mol%), TBHP (1 equiv) in 1mL of solvent. [c]Room temperature. [d]70 ˚C temperature. [e]100 ˚C temperature. [f]Reflux condition. [b]Isolated yield.

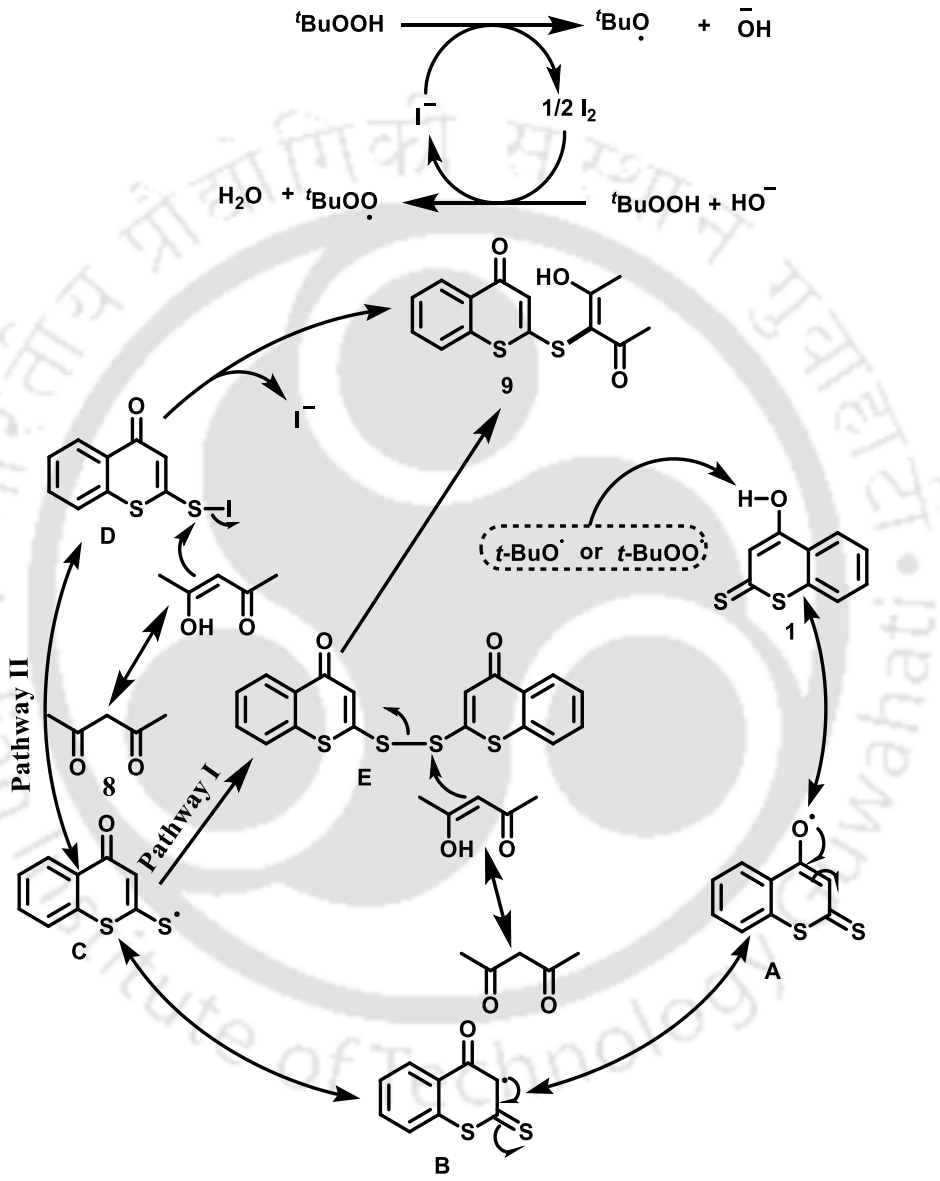
Using this optimized reaction condition, we examined the substrate scope of this transformation with respect to acetylacetone **8a**. Initially, various 4-hydroxydithiocoumarin were investigated. Those substrates having a substituent such as -Cl, -F, -CF_3 in the 4-hydroxydithiocoumarin moiety may be easily converted into the corresponding products (**9b-f**) in moderate to good yields. To study the substrate scope of the reaction, we have performed the reaction of various 4-hydroxydithiocoumarin **1** with 1-phenyl-1,3-butanedione **8b**. When 1-phenyl-1,3-butanedione **8b** was employed, the reaction also proceeded smoothly to afford the product regardless of the nature of the substituent present on the 4-hydroxydithiocoumarin nucleus **9g-l** in 80-84% yield, respectively. Interestingly, the reaction also proceeded well with β-keto ester such as

Table 3.2. Synthesis of α-thiocarbonyl compounds from 4-hydroxydithiocoumarin and 1,3-dicarbonyl compounds.[a,b]



[a]All the reactions were carried out using 4-hydroxydithiocoumarin (0.25 mmol), acetylacetone (0.25 mmol) in presence of 10 mol% KI, 1 equiv TBHP in 1mL of toluene at 110 ˚C. [b]Isolated yield.

methylacetoacetate. On reaction with methyl acetoacetate and various 4-hydroxydithiocoumarin derivatives, it also provided the expected products **9m**–**q** in 76-85% yield. The ^{1}H NMR, ^{13}C NMR, and HRMS of compounds **9a**, **9g**, **9o, 11a** and **13a** are represented in **Figure 3.2, Figure 3.3, Figure 3.4, Figure 3.5 and Figure 3.6.**

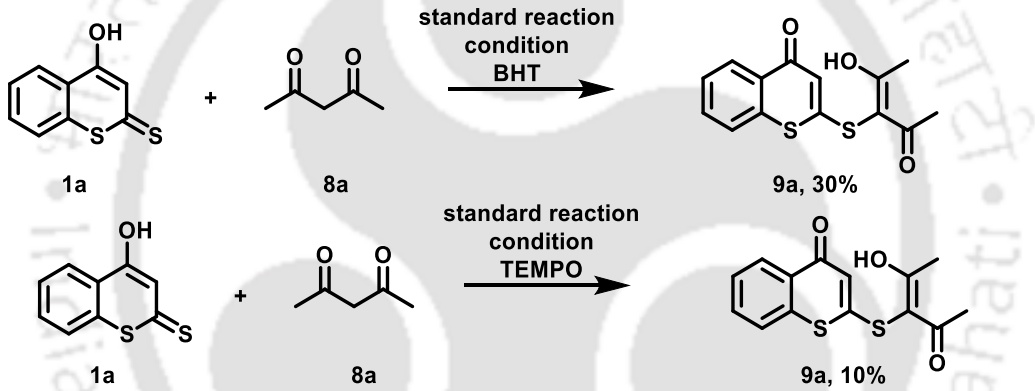


Scheme 3.11. Plausible reaction mechanism

The possible mechanism for the formation of product **9** is illustrated in Scheme 3.11. Initially, TBHP produces a *tert*-butoxy radical and hypoiodous acid when it reacts with iodide. After that, the *tert*-butoxy radical is reacted with TBHP to form the tertbutyl peroxy radical.[22] Furthermore,

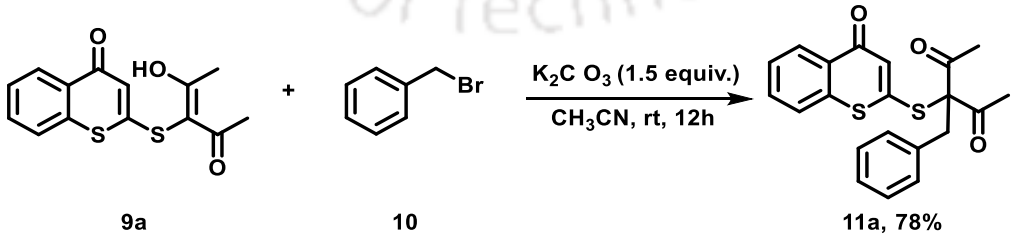
tert-butoxy radicals or *tert*-butyl peroxy radicals can abstract hydrogen from 4-hydroxydithiocoumarin **1** to generate radical intermediate **A**,[23] which could also exist either as **B** or **C**.[21] **Pathway I**: either radical intermediate **C** dimerizes to produce intermediate **E**, which is then converted to product **9**, or **Pathway II**: the intermediate **C** combines with an iodide radical to produce intermediate **D**,[24] which is then converted to product **9** after nucleophilic substitution. After then, the iodide ion is oxidized to iodine.

The control experiments (Scheme 3.12) were carried out to confirm whether the reaction is going through the radical pathway or not. When two reactions were carried out with the radical inhibitors BHT and TEMPO, the yield of the product **9a** was reduced significantly i.e. 30% and 10%, respectively as compared to yield 78%. Based on these two observations, we may predict the reaction is favoured by a radical pathway.



Scheme 3.12. Control reaction

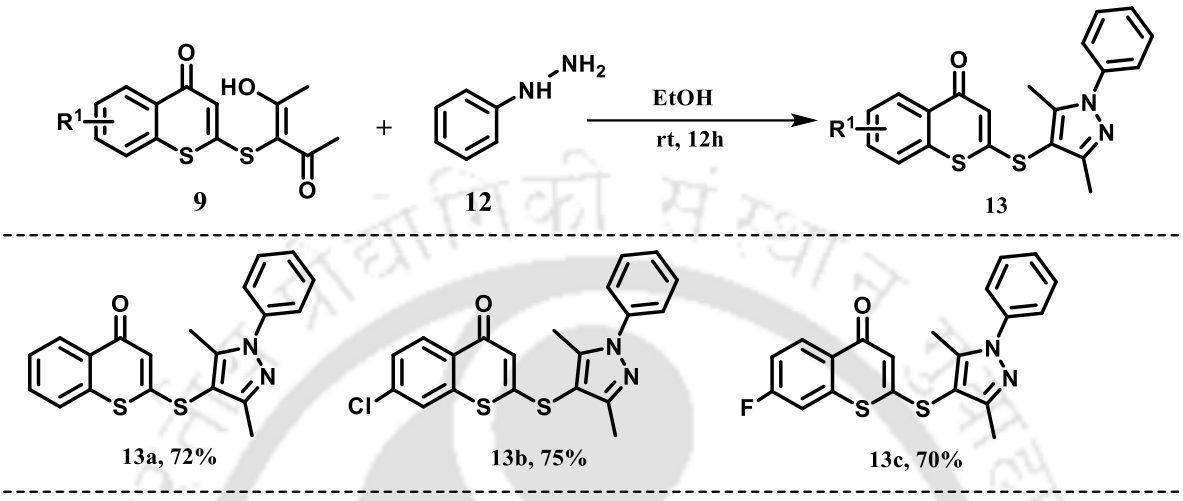
In addition, to demonstrate the utility of this reaction, the active methine carbon of the sulfenylation product, **9a**, was used as a nucleophile with an electrophilic reagent such as benzyl bromide to yield the corresponding quaternary carbon-containing products with good yield (**11a**, 78%).



Scheme 3.13. Synthesis of 3-benzyl-3-((4-oxo-4*H*-thiochromen-2-yl)thio)pentane-2,4-dione

Likewise, **9a** was reacted with phenylhydrazine to obtain derivatives of the **13a-13c** pyrazole heterocycle, with yields ranging from 70% to 75%. (Table 3.3).

Table 3.3. Synthesis of pyrazole derivatives.



3.4. Conclusion

In conclusion, we have demonstrated the new synthesis of α-thiocarbonyl derivatives *via* cross dehydrogenative coupling (CDC) reaction between 4-hydroxydithiocoumarin and 1,3-dicarbonyl compounds by employing 10 mol% KI and TBHP, which is a highly practical and efficient approach. This observation is the first example of the CDC reaction of 4-hydroxydithiocoumarin with 1,3-dicarbonyl compounds that we are aware of it. The current strategy should be applied to the design of libraries with a wide range of features. The reaction is notable for its high yields, mild reaction conditions, and shorter reaction time. Specifically, the α-thiocarbonyl compounds can be used to synthesize pyrazoles, and quaternary carbon-containing α,α-disubstituted-β-diketones. This reaction has potential since it forms an asymmetric quaternary carbon core, which can be used to build enantioselective procedures. Our laboratory is now conducting additional research in this area.

3.5. Experimental Section

3.5.a. General procedure for the synthesis of 4-hydroxydithiocoumarin (1a–f). A wide variety of 4-hydroxydithiocoumarins was prepared by following the previously reported procedure.[21]

3.5.b. General procedure for the synthesis of α-thiocarbonyl compounds (9a-q). Into a 25 mL round bottom flask, a mixture of 4-hydroxydithiocoumarin (**1**, 0.25 mmol) and 1,3-dicarbonyl compounds (**8**, 0.25 mmol) was taken in 1 mL of toluene. Then, 1 equivalent of TBHP and 20 mol% KI were added successively into it. Then the reaction mixture was kept for refluxing in a preheated oil bath with constant stirring. TLC was used to check the reaction's progress from time to time. The reaction mixture was extracted with ethyl acetate (3 x 10 mL) after it was completed. The organic layer was concentrated using a rotary evaporator after drying over anhydrous Na_2SO_4. Silica gel (60–120 mesh) was used to purify the crude residue. The corresponding products **9a-q** were eluted using a mixture of ethyl acetate and hexane in the ratio of 1.5:8.5 during column chromatography.

3.5.c. General procedure for the synthesis of α,α-disubstituted dicarbonyl compound (11). α-Thiocarbonyl compounds (**9a**, 0.5 mmol), benzyl bromide (**10**, 1.5 mmol), and K_2CO_3 (1.5 mmol) were taken in 2 mL acetonitrile into a 25 mL round-bottomed flask and it was kept for stirring at room temperature. The reaction was monitored by checking TLC from time to time. A rotatory evaporator was used to remove acetonitrile after the starting material was consumed. Then the crude residue was extracted with ethyl acetate (2 x10 mL) and dried over anhydrous Na_2SO_4. Finally, the organic layer was concentrated using a rotatory evaporator and the crude residue was purified by using a silica gel column chromatography.

3.5.d. General procedure for the synthesis of pyrazole derivatives (13). Into a 25 mL round-bottomed flask was taken a mixture of α-thiocarbonyl compounds (**9a**, 0.5 mmol) and phenylhydrazine (**12**, 1.5 mmol) in 2 mL of ethanol. The reaction mixture was stirred at room temperature. After the reaction was over, which is confirmed by TLC, the ethanol was removed in a rotatory evaporator. Finally, the crude residue was purified using silica gel column chromatography without any traditional work-up.

3.6. Characterization

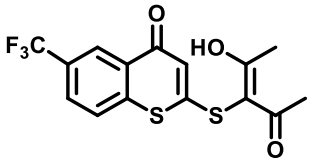
2-((2-Hydroxy-4-oxopent-2-en-3-yl)thio)-4*H*-thiochromen-4-one (9a). Brown solid (78%, 57 mg); mp 150-151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 17.47 (s, 1H), 8.46 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.53 – 7.50 (m, 2H), 6.92 (s, 1H), 2.41 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 178.7, 155.8, 137.0, 131.6, 130.7, 128.9, 128.1, 126.0, 120.4, 98.3, 24.6; IR (KBr)ν_{max} 3291, 1720, 1688 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{13}O_3S_2$ ($M + H^+$) 293.0301; Found 293.0302.

6-Chloro-2-((2-hydroxy-4-oxopent-2-en-3-yl)thio)-4*H*-thiochromen-4-one (9b). Brown liquid (75%, 61 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 17.49 (s, 1H), 8.44 (s, 1H), 7.54 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 6.92 (s, 1H), 2.40 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 177.4, 156.4, 135.1, 134.7, 132.0, 131.9, 128.6, 127.4, 120.2, 98.1, 24.6; IR (KBr)ν_{max} 3302, 1722, 1679 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{12}ClO_3S_2$ ($M + H^+$) 326.9911; Found 326.9911.

7-Chloro-2-((2-hydroxy-4-oxopent-2-en-3-yl)thio)-4*H*-thiochromen-4-one (9c). Brown liquid (76%, 61 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 17.48 (s, 1H), 8.39 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.47 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.90 (s, 1H), 2.41 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 177.8, 155.7, 138.4, 138.3, 130.5, 129.1, 128.8, 125.4, 120.5, 98.1, 24.6; IR (KBr)ν_{max} 3285, 1718, 1684 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{12}ClO_3S_2$ ($M + H^+$) 326.9911; Found 326.9920.

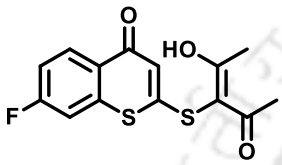
5-Chloro-2-((2-hydroxy-4-oxopent-2-en-3-yl)thio)-4*H*-thiochromen-4-one (9d). Brown liquid (72%, 58 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 17.46 (s, 1H), 7.49 (t, *J* = 4.5 Hz, 1H), 7.40 (d, *J* = 4.8 Hz, 2H), 6.83 (s, 1H), 2.40 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 178.1, 152.4, 139.9, 136.5, 131.9, 130.9, 127.5, 125.1, 122.0, 98.1, 24.6; IR (KBr)ν_{max} 3289, 1716, 1683 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{12}ClO_3S_2$ ($M + H^+$) 326.9911; Found 326.9915.

2-((2-Hydroxy-4-oxopent-2-en-3-yl)thio)-6-(trifluoromethyl)-4*H*-thiochromen-4-one (9e):



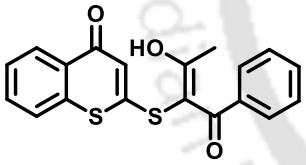
Yellow solid (78%, 70 mg); mp 173-174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 17.50 (s, 1H), 8.74 (s, 1H), 7.84 – 7.77 (m, 1H), 7.63 (d, J = 8.5 Hz, 1H), 6.96 (s, 1H), 2.41 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 177.4, 156.4, 140.3, 130.7, 127.5, 127.5, 127.5, 126.8, 126.3, 126.2, 126.2, 126.2, 120.3, 97.7, 24.5; IR (KBr)ν_{max} 3301, 1724, 1687 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{12}F_3O_3S_2$ ($M + H^+$) 361.0174; Found 361.0174.

7-Fluoro-2-((2-hydroxy-4-oxopent-2-en-3-yl)thio)-4*H*-thiochromen-4-one (9f). Brown liquid



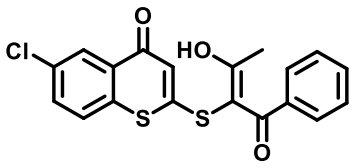
(70%, 54 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 17.50 (s, 1H), 8.48 (dd, *J* = 8.6, 5.9 Hz, 1H), 7.23 – 7.20 (m, 2H), 6.89 (s, 1H), 2.41 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.0, 177.7, 164.9, 163.2, 155.6, 139.1, 139.0, 131.9, 131.9, 127.3, 127.3, 120.4, 116.6, 116.5, 112.2, 112.0, 98.0, 24.6; IR (KBr)ν_{max} 3287, 1720, 1683 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{12}FO_3S_2$ ($M + H^+$) 311.0206; Found 311.0210.

2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-4*H*-thiochromen-4-one (9g). Brown liquid



(80%, 71 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 17.93 (s, 1H), 8.45 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.68 – 7.66 (m, 2H), 7.59 – 7.56 (m, 1H), 7.52 – 7.50 (m, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 6.87 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 192.8, 178.6, 156.6, 137.0, 135.1, 131.9, 131.6, 130.7, 128.9, 128.5, 128.2, 128.1, 126.0, 120.3, 97.5, 25.6; IR (KBr)ν_{max} 3305, 1726, 1680 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{15}O_3S_2$ ($M + H^+$) 355.0457; Found 355.0465.

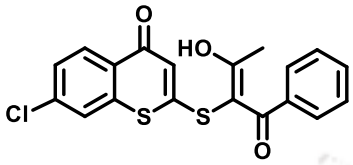
6-Chloro-2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-4*H*-thiochromen-4-one (9h).



Brown liquid (82%, 79 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 17.93 (s, 1H), 8.42 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.53 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.46 (dd, *J* = 11.6, 8.2 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 6.86 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

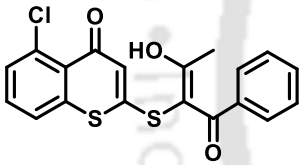
202.3, 193.0, 177.4, 157.1, 135.1, 135.1, 134.7, 131.9, 131.9, 128.5, 128.5, 128.2, 127.4, 120.0, 97.3, 25.6; IR (KBr)ν_{max} 3306, 1727, 1685 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{14}ClO_3S_2$ ($M + H^+$) 389.0067; Found 389.0066.

7-Chloro-2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-4*H*-thiochromen-4-one (9i).



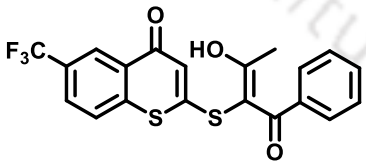
Brown liquid (77%, 74 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 17.92 (s, 1H), 8.36 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.51-7.50 (m, 1H), 7.48 – 7.44 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 6.83 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 193.0, 177.7, 156.4, 138.3, 138.3, 135.1, 131.9, 130.4, 129.1, 128.7, 128.5, 128.2, 125.4, 120.4, 97.3, 25.6; IR (KBr)ν_{max} 3300, 1724, 1688 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{14}ClO_3S_2$ ($M + H^+$) 389.0067; Found 389.0065.

5-Chloro-2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-4*H*-thiochromen-4-one (9j).



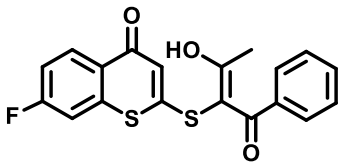
Brown liquid (80%, 77 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 17.90 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.48 – 7.47 (m, 2H), 7.41 – 7.39 (m, 4H), 6.77 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 192.9, 178.0, 153.2, 139.9, 136.5, 135.1, 131.9, 131.9, 130.9, 128.5, 128.2, 127.5, 125.1, 121.8, 97.3, 25.6; IR (KBr)ν_{max} 3292, 1728, 1678 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{14}ClO_3S_2$ ($M + H^+$) 389.0067; Found 389.0113.

2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-6-(trifluoromethyl)-4*H*-thiochromen-4-one (9k).



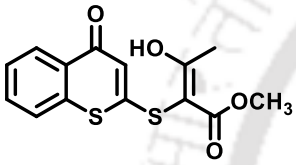
Brown liquid (84%, 88 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 17.94 (s, 1H), 8.72 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.67-7.62 (m, 3H), 7.50-7.47 (m, 1H), 7.41-7.38 (m, 2H), 6.89 (s, 1H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 193.1, 177.4, 157.2, 140.5, 135.0, 132.0, 130.9, 130.4, 128.5, 128.2, 127.7, 127.6, 127.6, 127.6, 126.9, 126.4, 126.4, 126.4, 126.3, 120.4, 97.2, 25.6; IR (KBr)ν_{max} 3304, 1725, 1676 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{14}F_3O_3S_2$ ($M + H^+$) 423.0331; Found 423.0335.

7-Fluoro-2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-4*H*-thiochromen-4-one (9l).



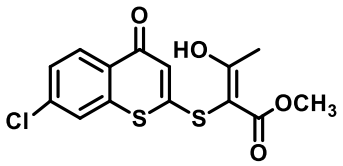
Brown liquid (82%, 76 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 17.92 (s, 1H), 8.46 (dd, *J* = 9.7, 5.8 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.22 – 7.19 (m, 2H), 6.83 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 192.9, 178.0, 153.2, 139.9, 136.5, 135.1, 131.9, 131.9, 130.9, 128.5, 128.2, 127.5, 125.1, 121.8, 97.3, 25.6; IR (KBr)ν_{max} 3298, 1723, 1682 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{14}FO_3S_2$ (M + H^+) 373.0363; Found 373.0362.

Methyl-3-hydroxy-2-((4-oxo-4*H*-thiochromen-2-yl)thio)but-2-enoate (9m). Brown liquid (76%, 58 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.03 (s, 1H), 8.48 – 8.46 (m, 1H), 7.58 – 7.55 (m, 1H), 7.52 – 7.49 (m, 2H), 6.90 (s, 1H), 3.82 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.6, 172.5, 137.3, 131.5, 130.8, 128.9, 127.9, 125.9, 120.5, 88.6, 53.2, 21.2; IR (KBr)ν_{max} 3292, 1791, 1674 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{13}O_4S_2$ (M + H^+) 309.0250; Found 309.0251.



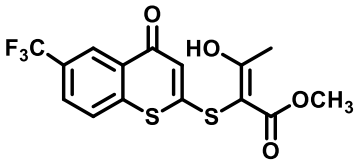
Methyl-2-((6-chloro-4-oxo-4*H*-thiochromen-2-yl)thio)-3-hydroxybut-2-enoate (9n). Brown liquid (83%, 70 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.04 (s, 1H), 8.44 (d, *J* = 2.4 Hz, 1H), 7.52 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.90 (s, 1H), 3.82 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 177.6, 172.4, 156.8, 135.4, 134.5, 132.0, 131.8, 128.5, 127.3, 120.2, 88.3, 53.2, 21.2; IR (KBr)ν_{max} 3295, 1723, 1687 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{12}ClO_4S_2$ (M + H^+) 342.9860; Found 342.9857.

Methyl-2-((7-chloro-4-oxo-4*H*-thiochromen-2-yl)thio)-3-hydroxybut-2-enoate (9o). Light brown solid (79%, 67 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.04 (s, 1H), 8.38 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.87 (s, 1H), 3.82 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 177.9, 172.4, 156.1, 138.6, 138.2,



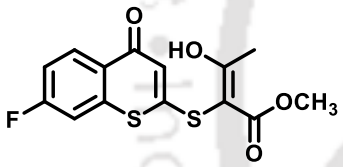
130.4, 129.2, 128.5, 125.3, 120.5, 88.3, 53.2, 21.2; IR (KBr)ν_{max} 3297, 1727, 1682 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{12}ClO_4S_2$ ($M + H^+$) 342.9860; Found 342.9866.

Methyl-3-hydroxy-2-((4-oxo-6-(trifluoromethyl)-4*H*-thiochromen-2-yl)thio)-but-2-enoate

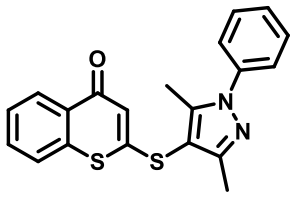


(9p). Light brown solid (85%, 80mg); ^1H NMR (500 MHz, $CDCl_3$) δ 14.06 (s, 1H), 8.73 (s, 1H), 7.77 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 3.82 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8, 177.6, 172.3, 156.9, 140.8, 131.0, 127.5, 127.5, 127.5, 127.4, 126.8, 126.3, 126.3, 126.3, 126.3, 120.5, 88.1, 53.2, 21.3; IR (KBr)ν_{max} 3304, 1725, 1677 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{12}F_3O_4S_2$ ($M + H^+$) 377.0124; Found 377.0135.

Methyl-2-((7-fluoro-4-oxo-4*H*-thiochromen-2-yl)thio)-3-hydroxybut-2-enoate (9q). Light brown solid (81%, 66 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 14.04 (s, 1H), 8.47 (dd, *J* = 9.6, 6.0 Hz, 1H), 7.20 (t, *J* = 8.6 Hz, 2H), 6.86 (s, 1H), 3.82 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 177.8, 172.4, 165.0, 162.9, 155.8, 139.4, 139.3, 131.9, 131.8, 127.4, 120.4, 116.4, 116.2, 112.0, 111.9, 88.3, 53.2, 21.3; IR (KBr)ν_{max} 3297, 1723, 1689 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{12}FO_4S_2$ ($M + H^+$) 327.0156; Found 327.0157.

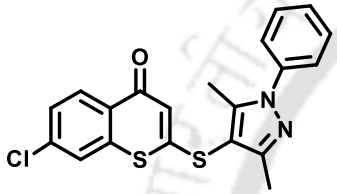


3-Benzyl-3-((4-oxo-4*H*-thiochromen-2-yl)thio)pentane-2,4-dione (11a). Brown liquid (78%, 74 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.9 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.54 (t, *J* = 8.2 Hz, 2H), 7.31 – 7.27 (m, 5H), 7.10 (s, 1H), 3.61 (s, 2H), 2.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 179.5, 145.1, 139.0, 134.3, 133.8, 132.1, 130.8, 130.0, 129.0, 128.7, 128.4, 127.7, 125.8, 80.2, 38.2, 27.8; IR (KBr)ν_{max} 2895, 1722, 1682 cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{19}O_3S_2$ ($M + H^+$) 383.0770; Found 383.0769.



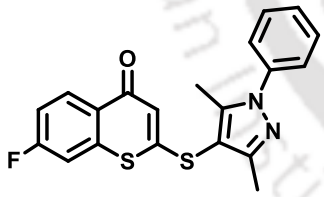
2-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)thio)-4*H*-thiochromen-4-one (13a). Dark brown liquid (72%, 65 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.50 (d, *J* = 2.4 Hz, 4H), 7.49 – 7.43 (m, 2H), 6.90 (s, 1H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 156.9, 153.7, 145.7, 139.5, 137.5, 131.4, 130.7, 129.4, 128.8, 128.5, 127.8, 125.9, 125.0, 120.6, 101.6, 12.2, 11.7; IR (KBr)ν_{max} 1721, 1682 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{17}N_2OS_2$ ($M + H^+$) 365.0777; Found 365.0783.

7-Chloro-2-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)thio)-4*H*-thiochromen-4-one (13b).



Brown liquid (75%, 74 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.6 Hz, 1H), 7.51 (dd, *J* = 13.6, 6.7 Hz, 4H), 7.47 – 7.42 (m, 3H), 6.87 (s, 1H), 2.39 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 156.9, 153.6, 145.7, 139.4, 138.8, 138.1, 130.4, 129.4, 129.1, 128.5, 128.5, 125.2, 125.0, 120.6, 101.3, 12.2, 11.7; IR (KBr)ν_{max} 1723, 1685 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{16}ClN_2OS_2$ ($M + H^+$) 399.0387; Found 399.0389.

2-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)thio)-7-fluoro-4*H*-thiochromen-4-one (13c).



Brown liquid (70%, 67 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 8.9, 5.9 Hz, 1H), 7.54 – 7.47 (m, 4H), 7.46 – 7.42 (m, 1H), 7.22 – 7.14 (m, 2H), 6.87 (s, 1H), 2.39 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 165.2, 162.7, 156.8, 153.6, 145.7, 139.6, 139.5, 139.3, 131.8, 131.8, 129.4, 128.5, 127.3, 127.2, 125.0, 120.8, 120.5, 116.4, 116.2, 115.4, 112.0, 111.8, 101.3, 12.2, 11.7; IR (KBr)ν_{max} 1723, 1685 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{16}FN_2OS_2$ ($M + H^+$) 383.0683; Found 383.0683.

Figure 3.2.a. ^{1}H NMR of 2-((2-Hydroxy-4-oxopent-2-en-3-yl)thio)-4*H*-thiochromen-4-one (9a)

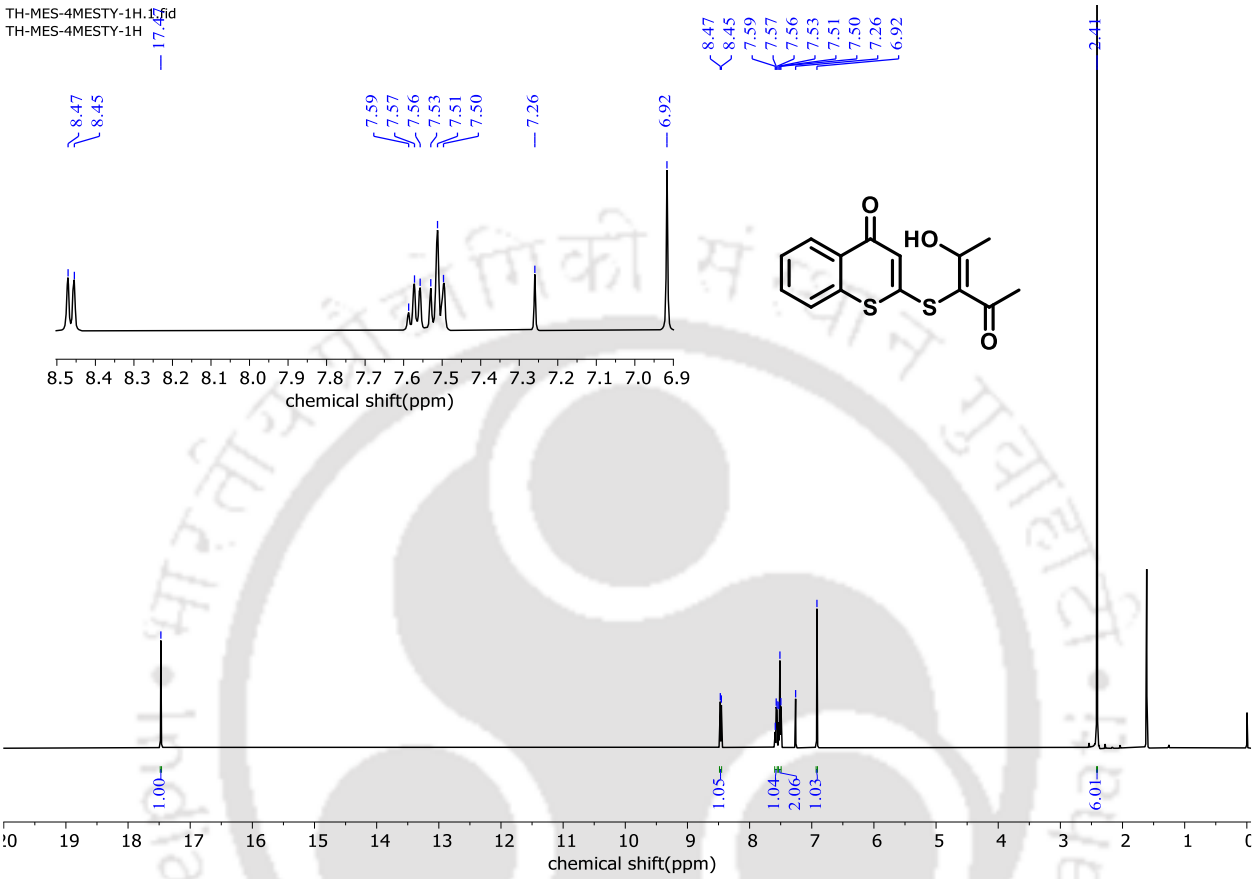


Figure 3.2.b. ^{13}C NMR of 2-((2-Hydroxy-4-oxopent-2-en-3-yl)thio)-4*H*-thiochromen-4-one (9a)

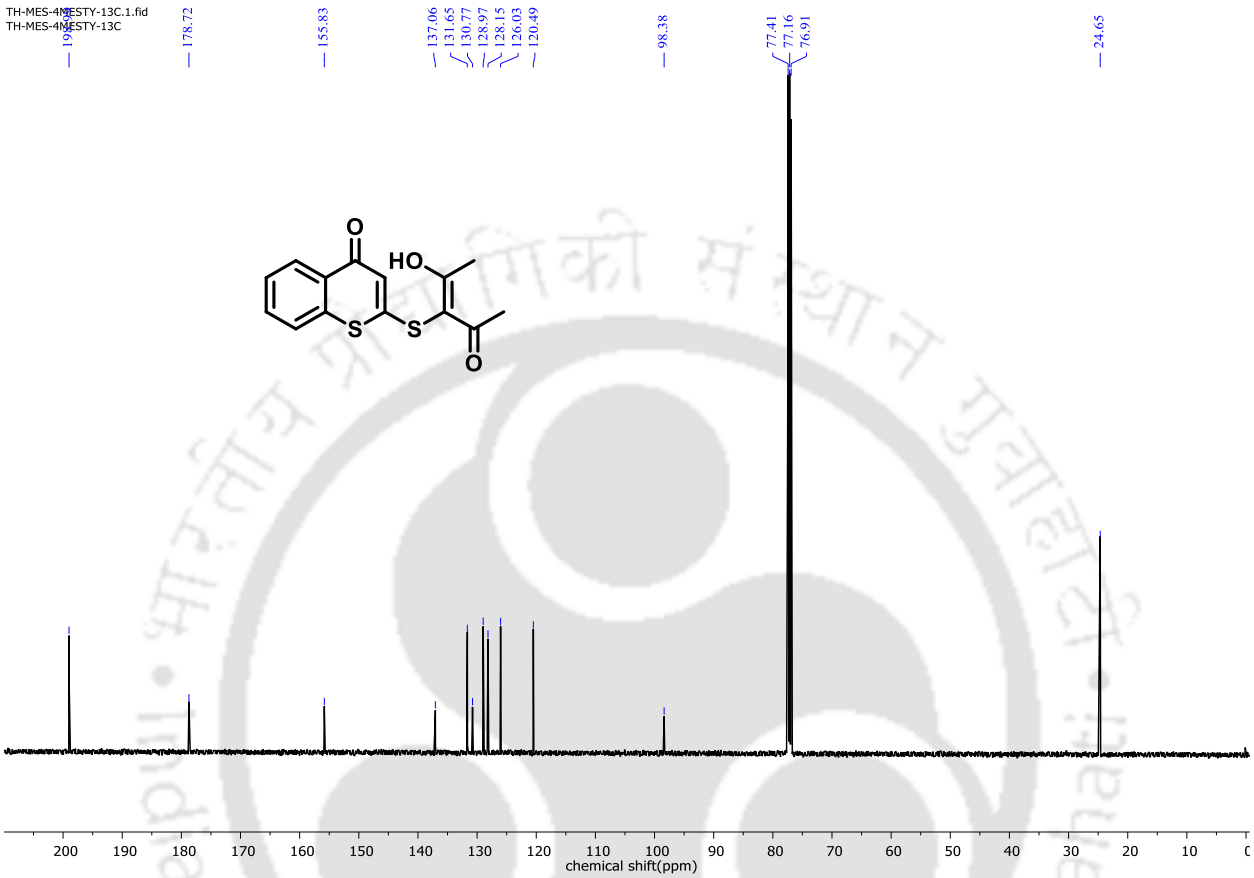


Figure 3.2.c. HRMS of 2-((2-Hydroxy-4-oxopent-2-en-3-yl)thio)-4*H*-thiochromen-4-one (9a)

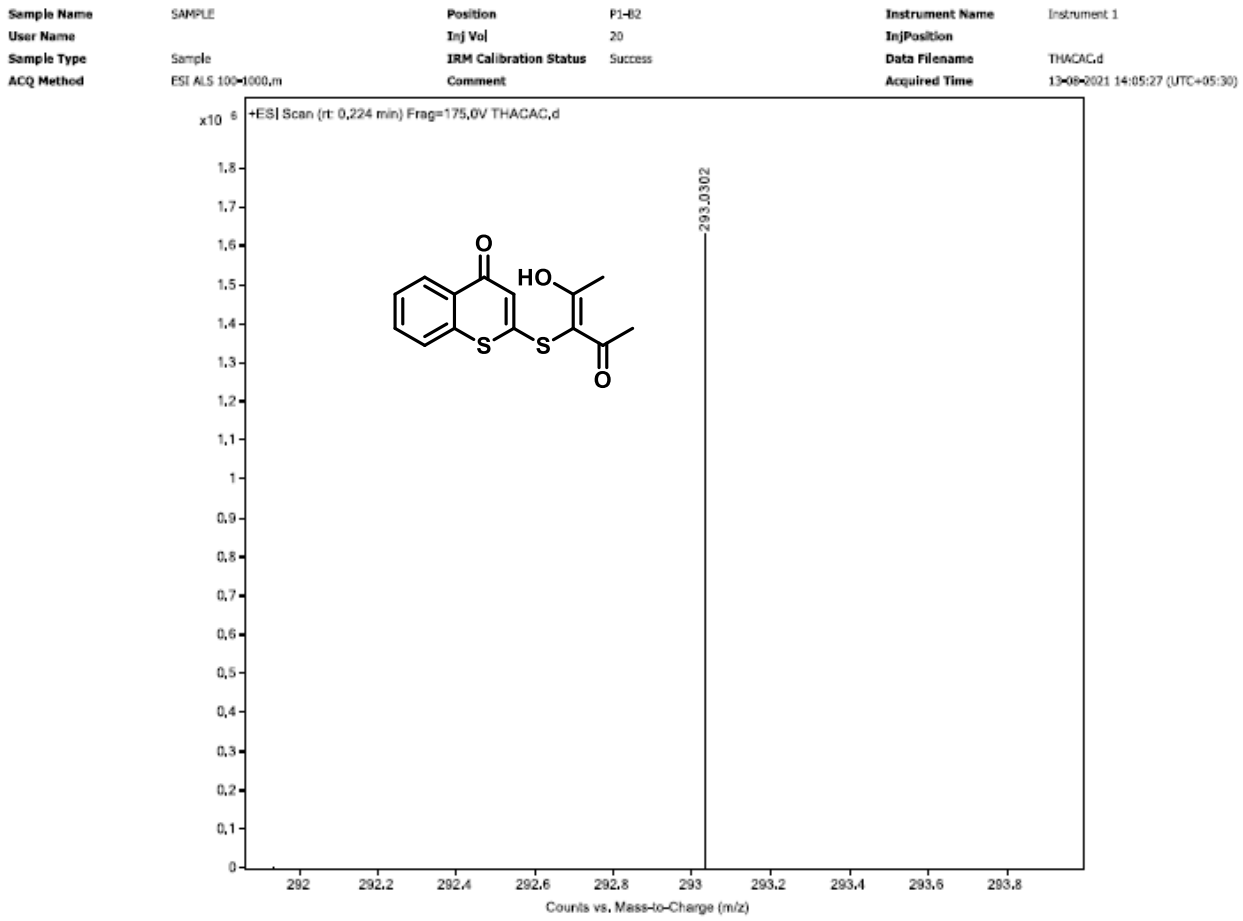


Figure 3.3.a. ^{1}H NMR of 2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-4*H*-thiochromen-4-one (9g)

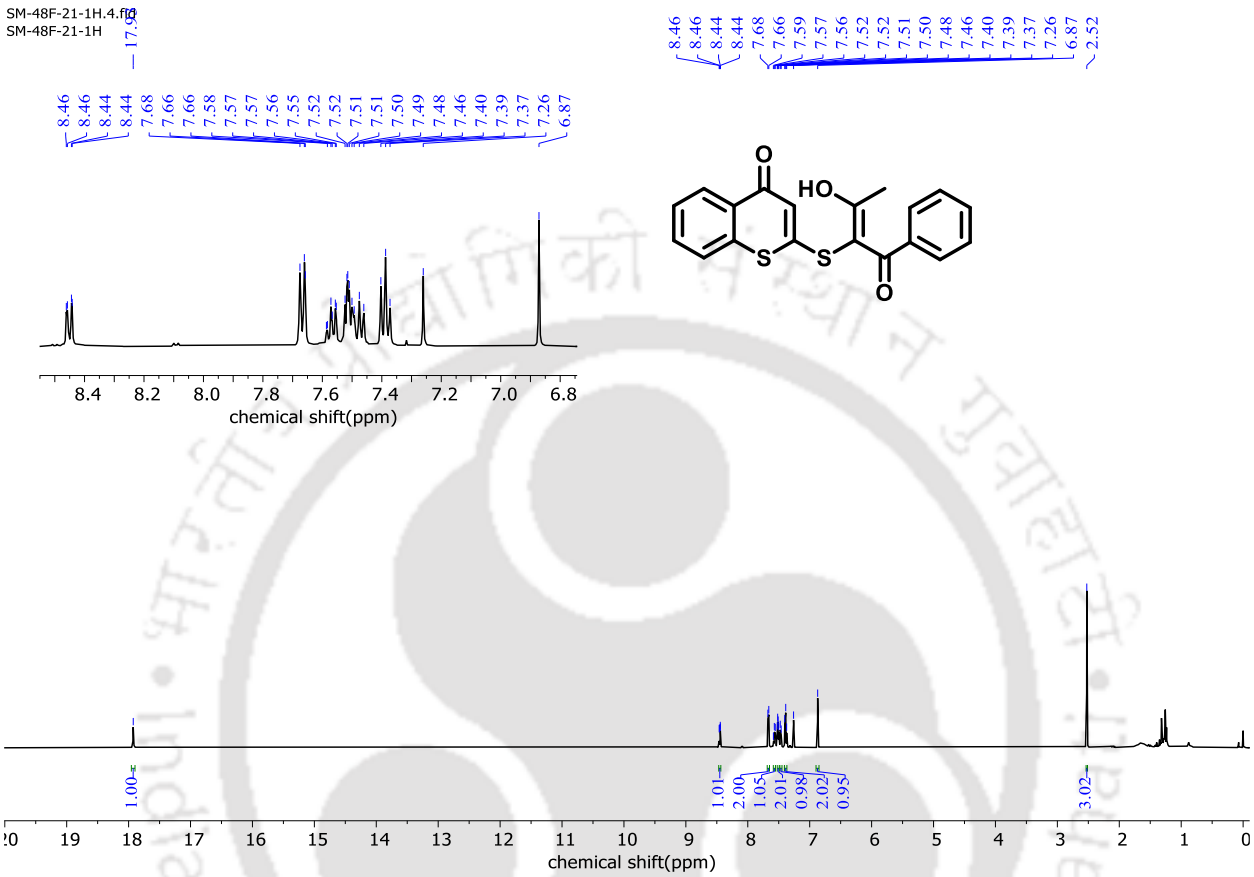


Figure 3.3.b. ^{13}C NMR of 2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-4*H*-thiochromen-4-one (9g)

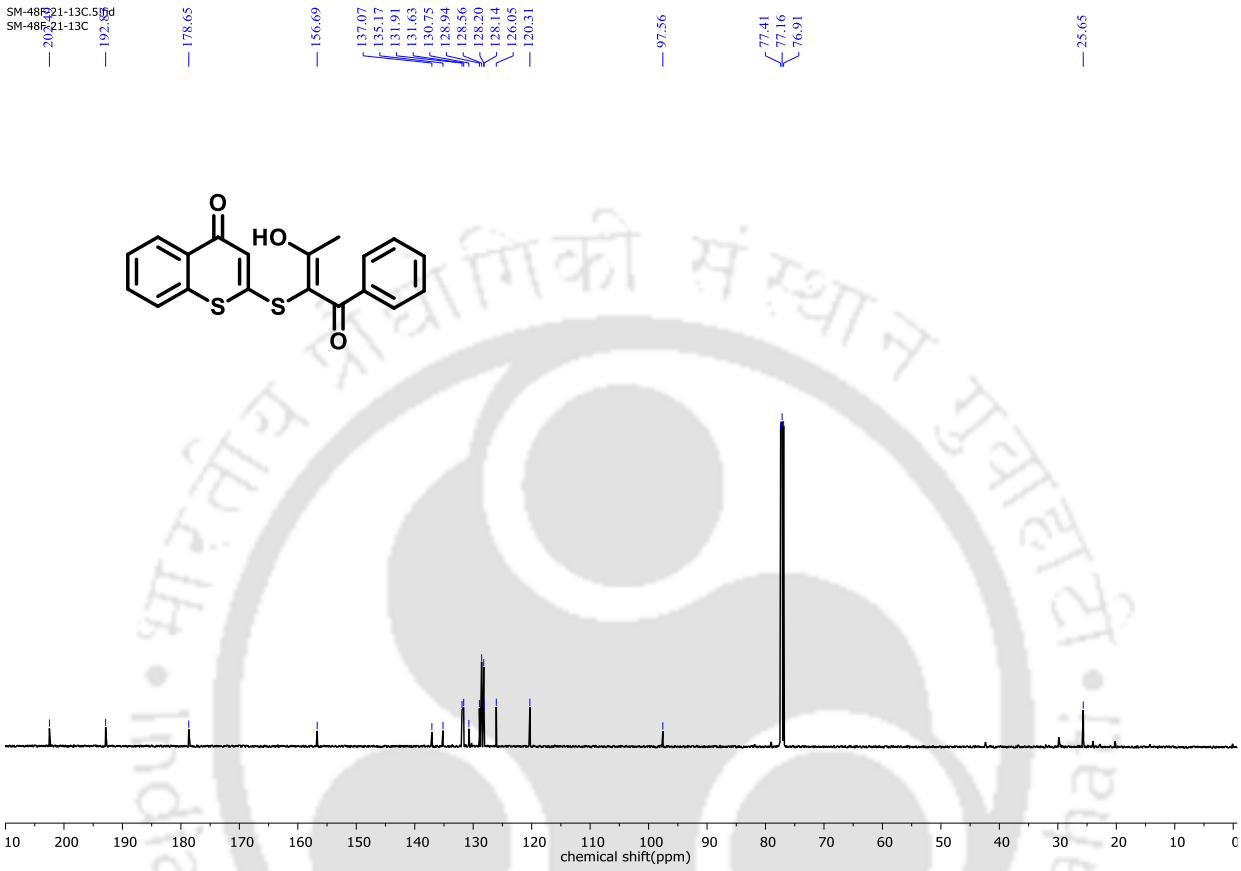


Figure 3.3.c. HRMS of 2-((3-hydroxy-1-oxo-1-phenylbut-2-en-2-yl)thio)-4*H*-thiochromen-4-one (9g)

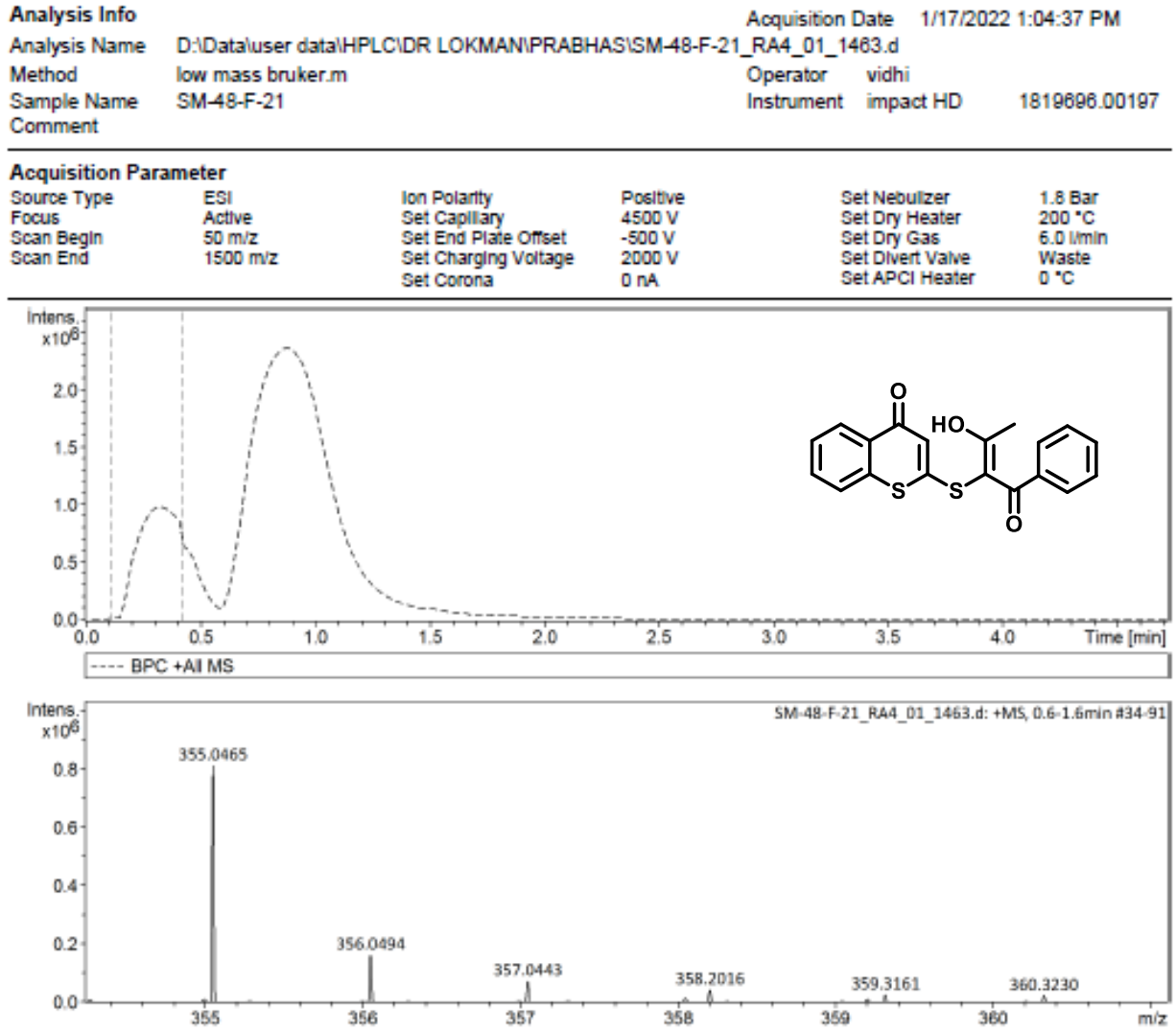


Figure 3.4.a. ^{1}H NMR of Methyl-2-((7-chloro-4-oxo-4*H*-thiochromen-2-yl)thio)-3-hydroxybut-2-enoate (9o)

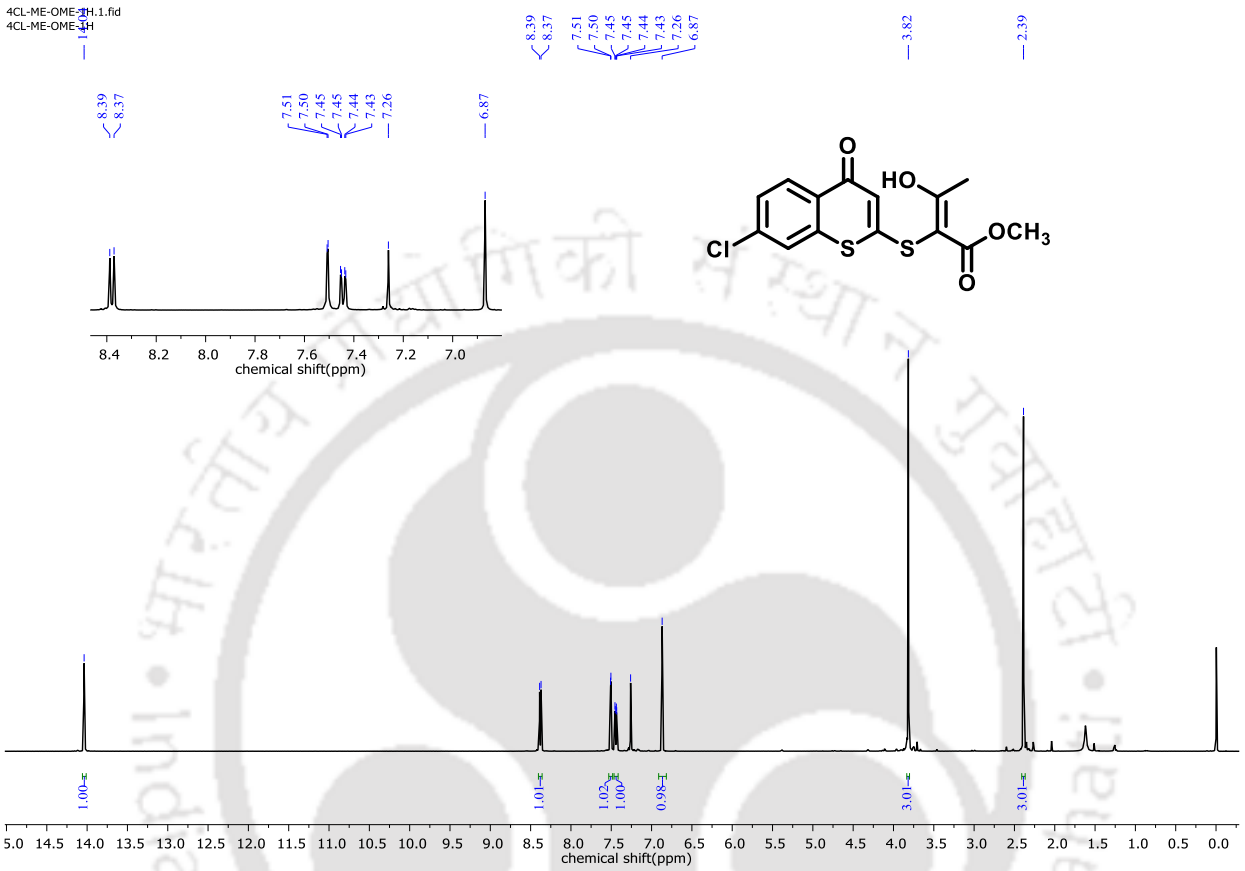


Figure 3.4.b. ^{13}C NMR of Methyl-2-((7-chloro-4-oxo-4 *H* -thiochromen-2-yl)thio)-3-hydroxybut-2-enoate (9o)

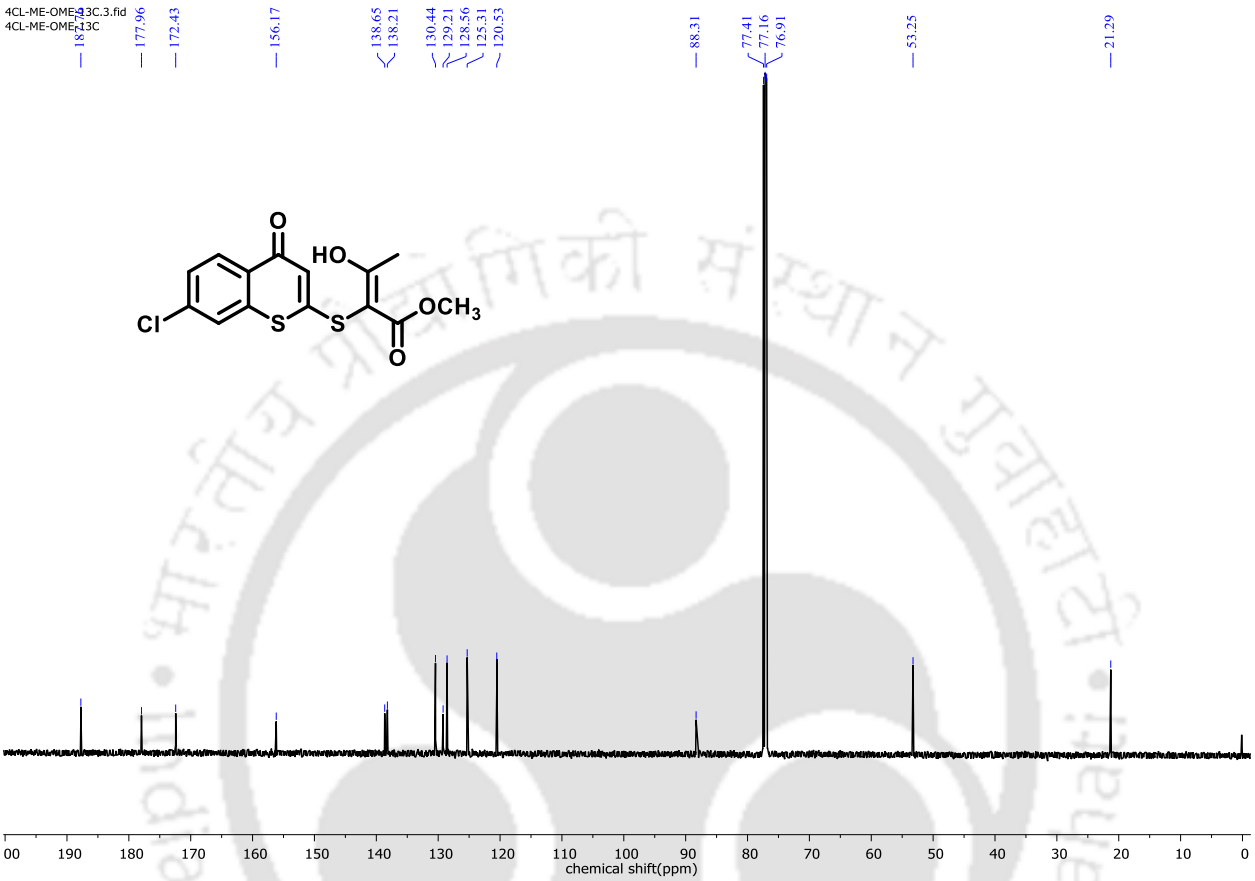


Figure 3.4.c. HRMS of Methyl-2-((7-chloro-4-oxo-4*H*-thiochromen-2-yl)thio)-3-hydroxybut-2-enoate (9o)

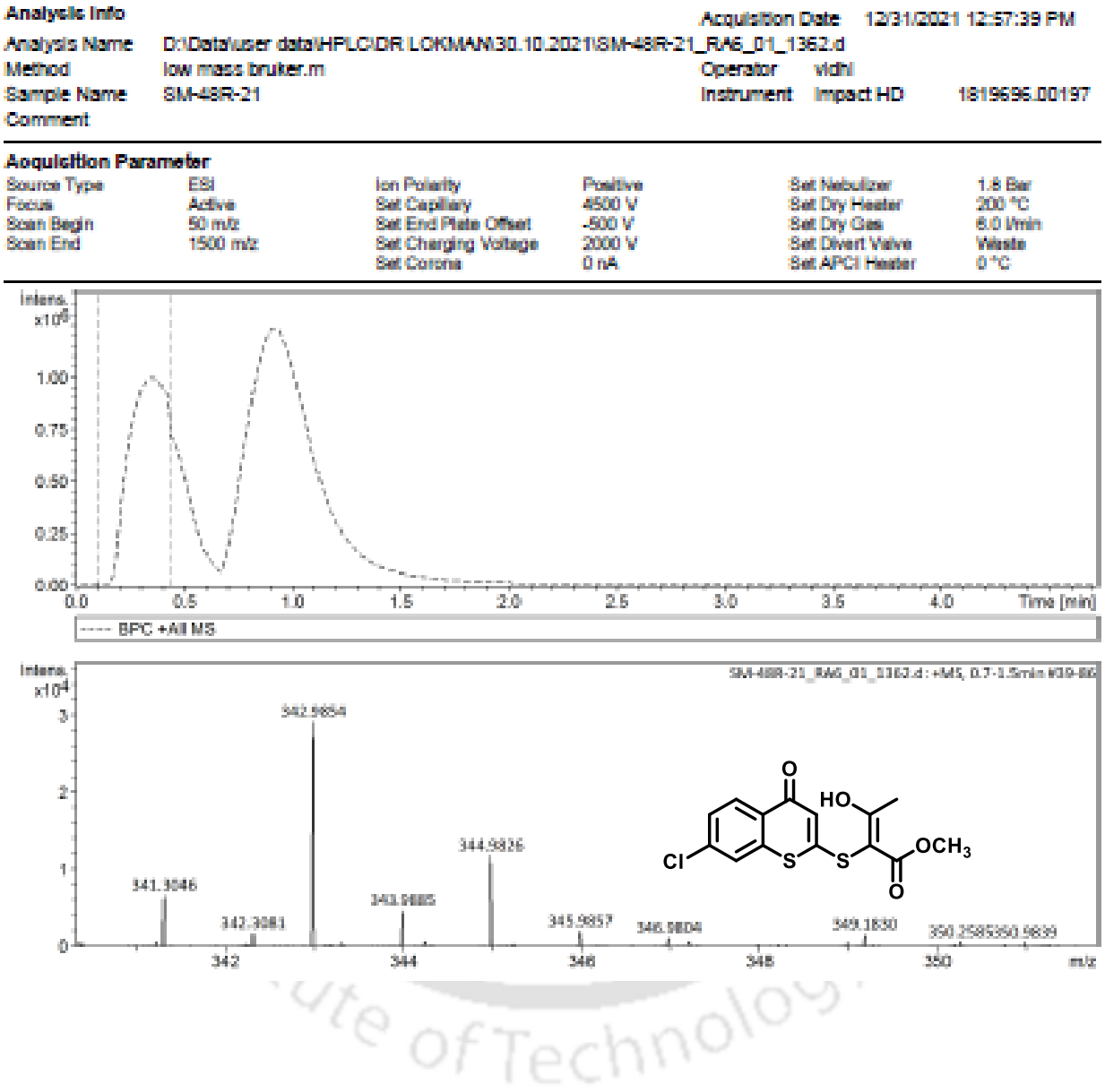


Figure 3.5.a. ^{1}H NMR of 3-Benzyl-3-((4-oxo-4*H*-thiochromen-2-yl)thio)pentane-2,4-dione (11a)

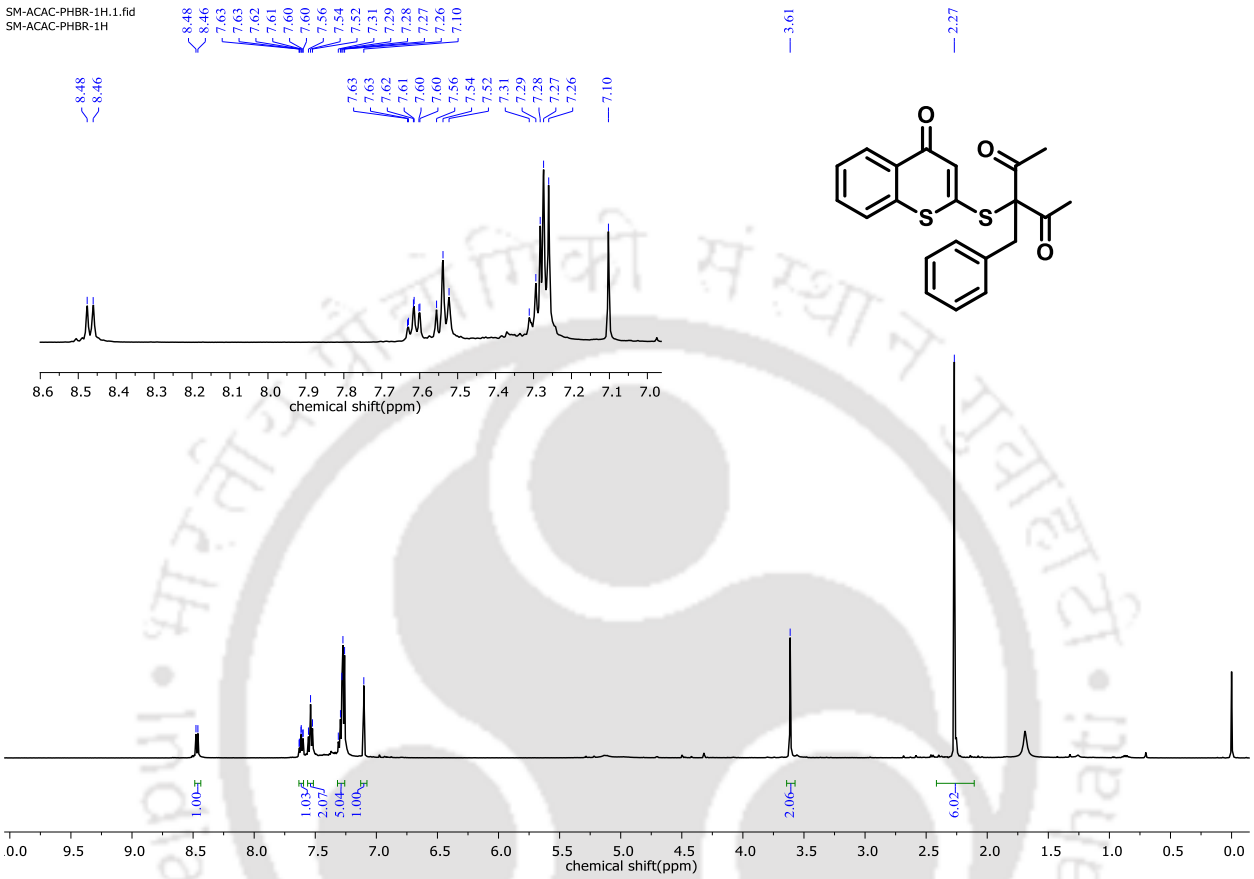


Figure 3.5.b. ^{13}C NMR of 3-Benzyl-3-((4-oxo-4*H*-thiochromen-2-yl)thio)pentane-2,4-dione (11a)

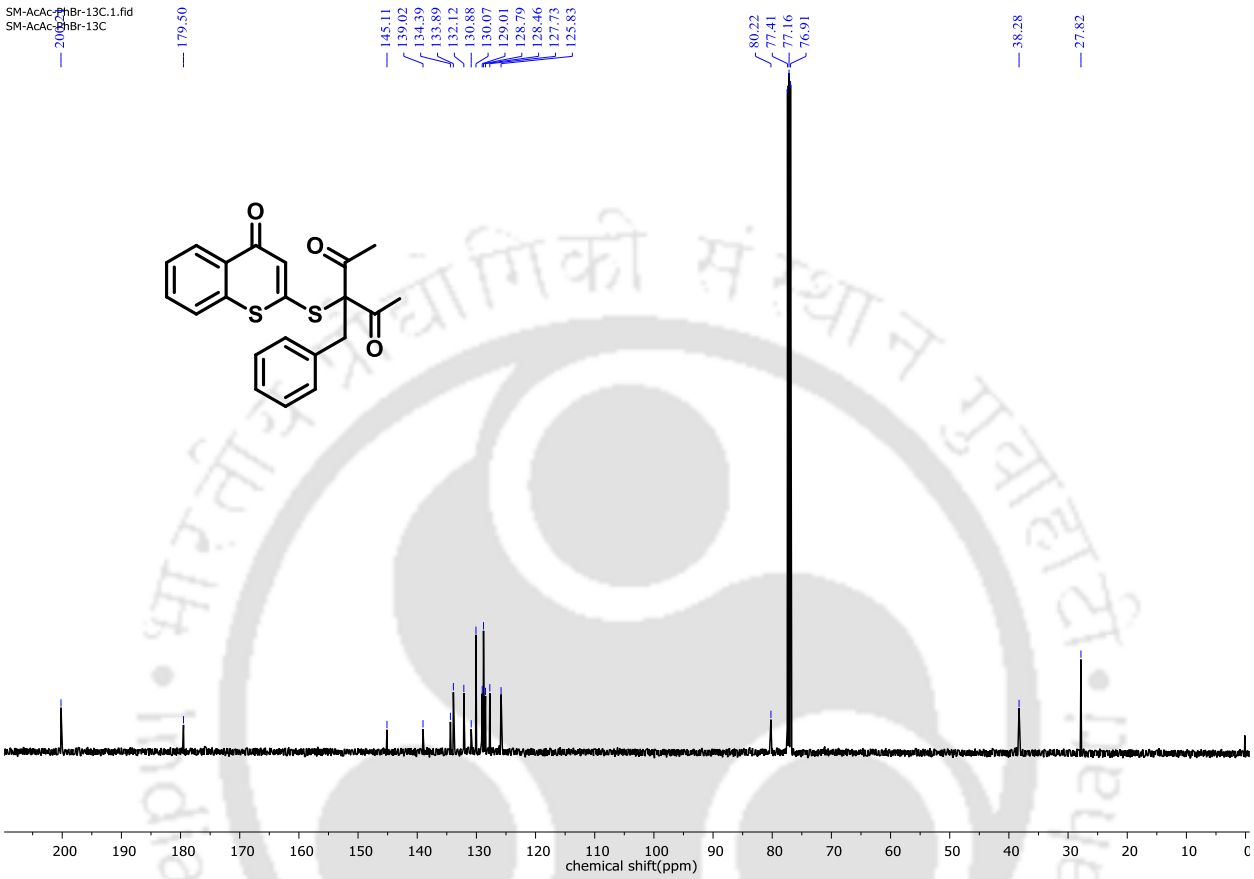


Figure 3.5.c. HRMS of 3-Benzyl-3-((4-oxo-4*H*-thiochromen-2-yl)thio)pentane-2,4-dione (11a)

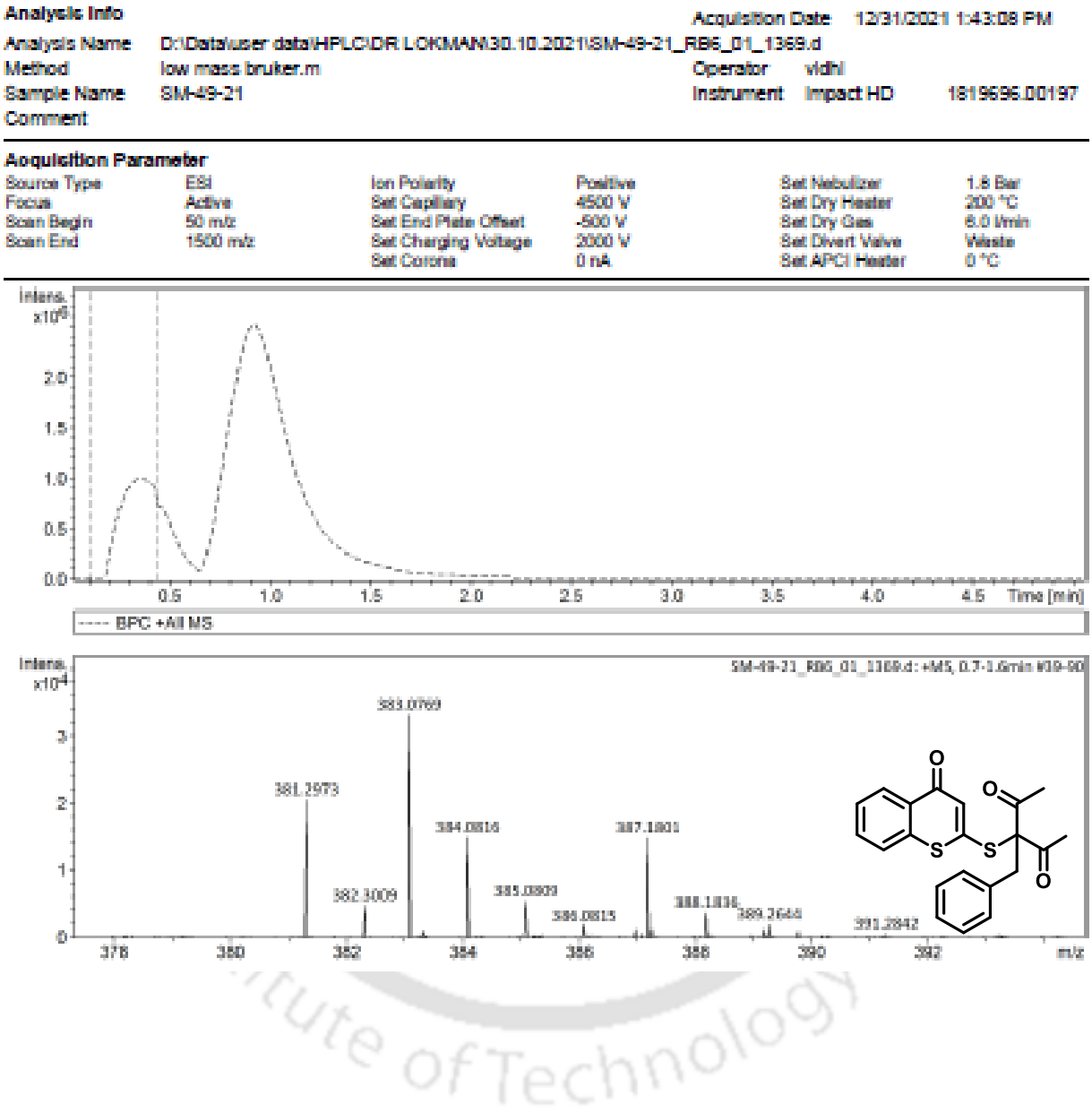


Figure 3.6.a. ^{1}H NMR of 2-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)thio)-4*H*-thiochromen-4-one (13a)

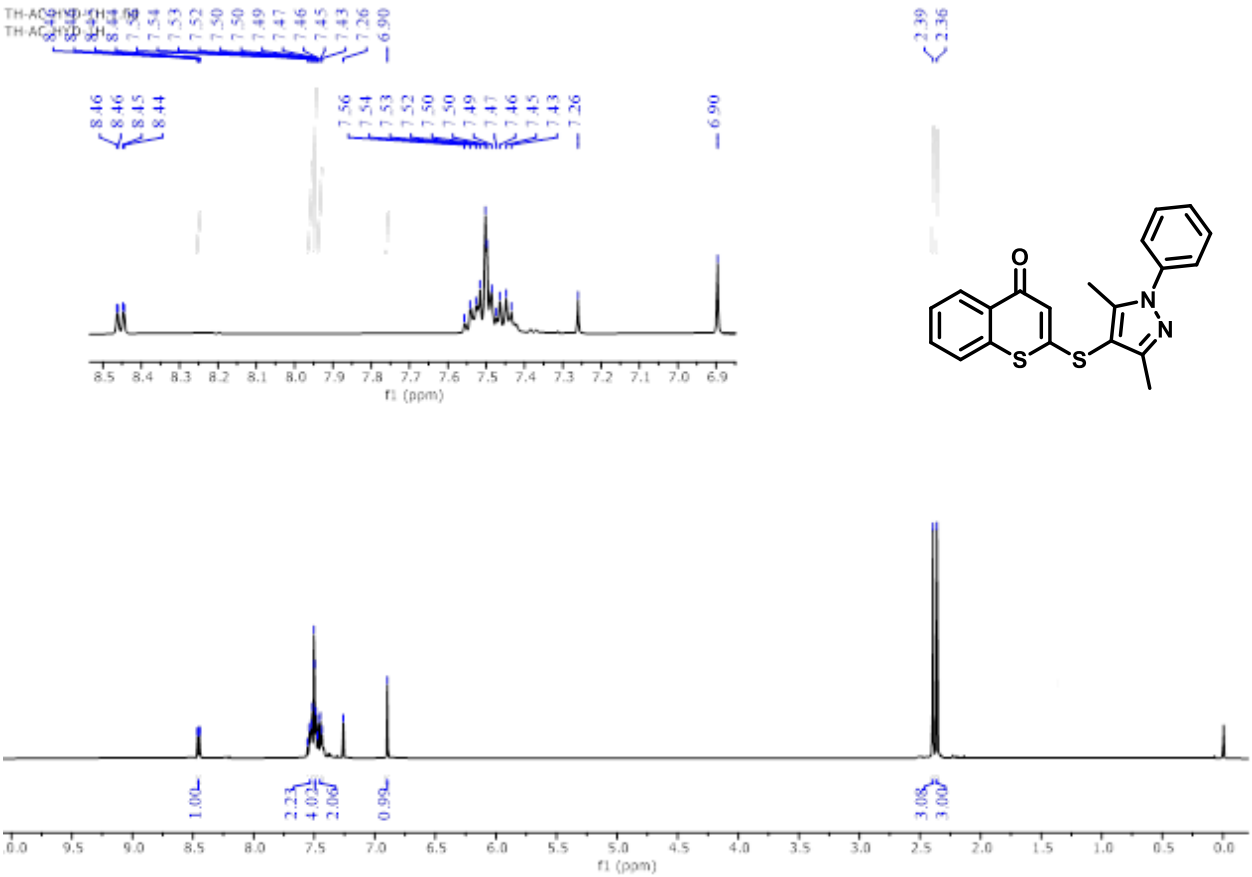


Figure 3.6.b. ^{13}C NMR of 2-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)thio)-4*H*-thiochromen-4-one (13a)

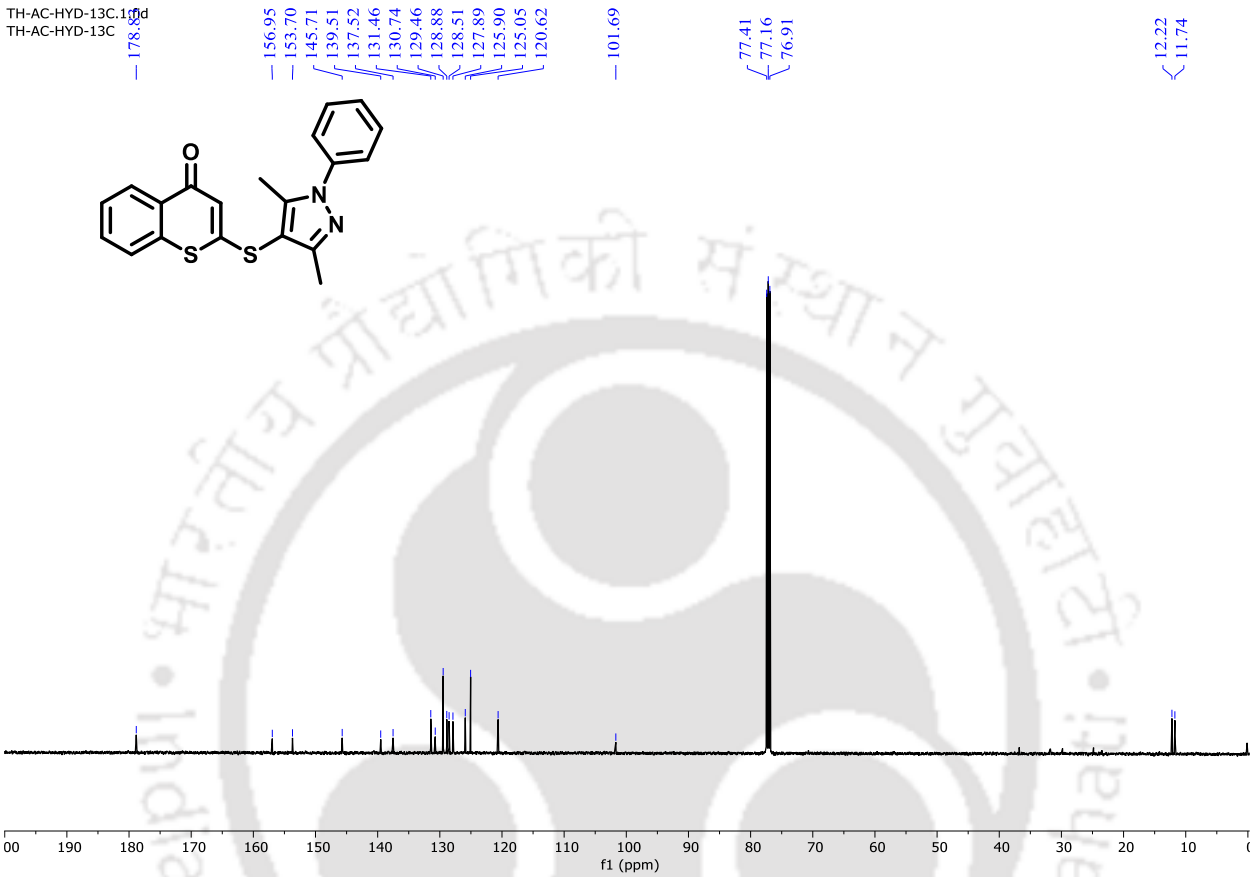
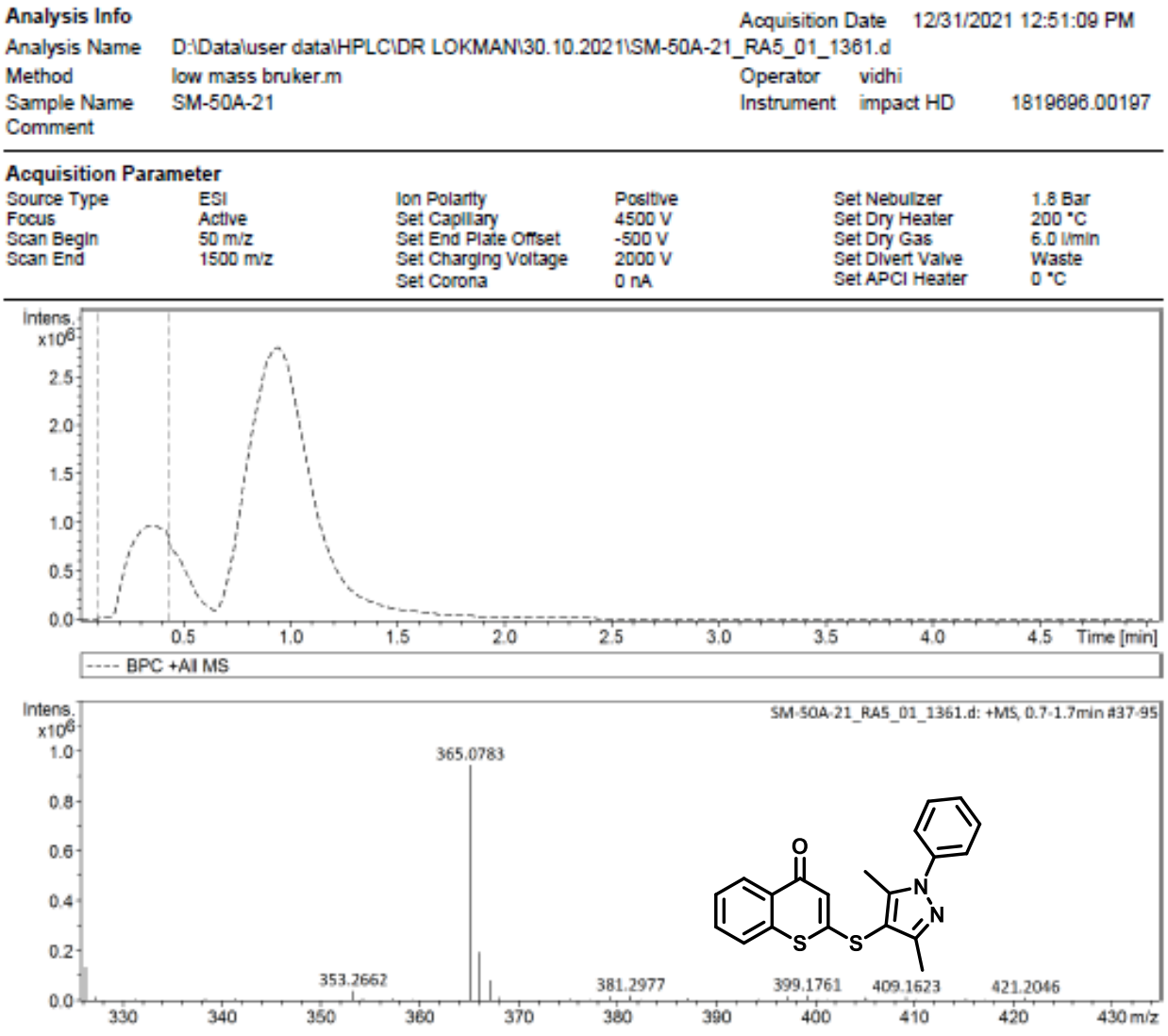


Figure 3.6.c. HRMS of 2-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)thio)-4*H*-thiochromen-4-one (13a)



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CHAPTER IV

Synthesis of vinyl sulfides and thioethers *via* hydrothiolation reaction of 4-hydroxydithiocoumarin and aryl acetylenes/ styrenes

Introduction

Results & Discussion

Experimental Section

4.1. Introduction

In medicinal chemistry, sulfur-containing natural and non-natural compounds are extremely essential.[1] Heterocyclic frameworks[2] with the sulfur atom(s) are versatile favoured scaffolds found in many biologically active compounds and medicines.[3] The synthesis of the carbon-sulfur bond to create vinyl sulfides or thioether derivatives by hydrothiolation of mono-substituted alkyne/alkene is an elegant and atom-efficient method. Vinyl sulfides are extremely important and valuable building blocks in the production of natural products,[4] bioactive compounds,[5] and dendrimers.[6] These classes of compounds are found to display potent pharmacological properties such as anti-melanoma,[7] cysteine protease inhibition,[5b,] and anti-HIV[8] and are used for the treatment of asthma.[9]

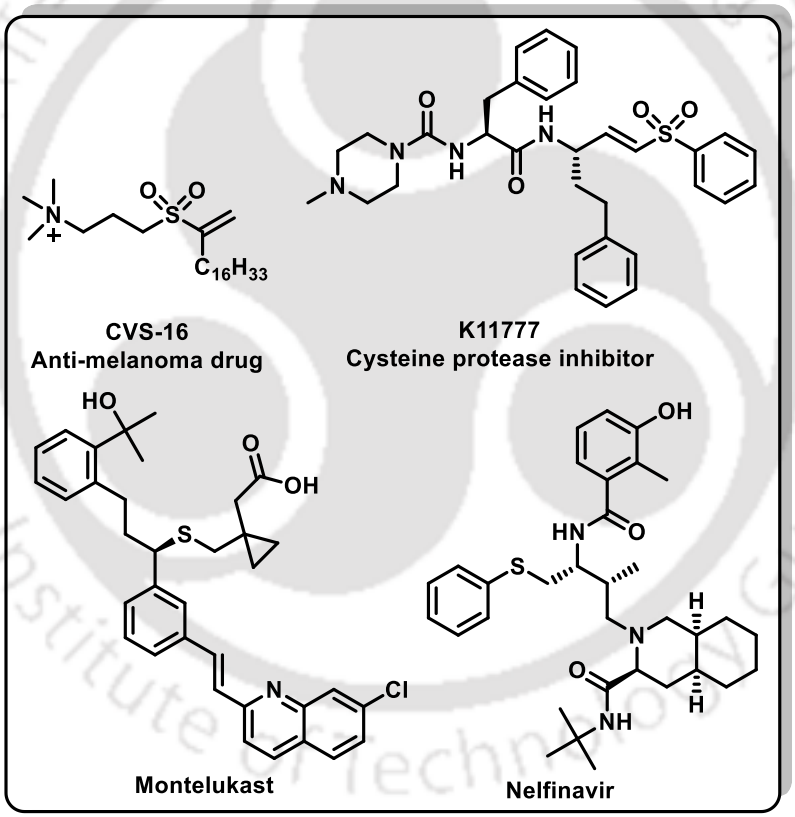


Figure 4.1. Biologically active compounds

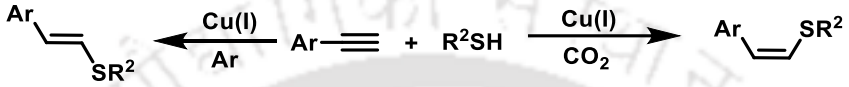
Vinyl sulfides are reported as valuable starting materials, for the synthesis of aldehyde[10a] and ketone.[10b] They are used in Heck reaction,[11a] cycloaddition reaction,[11b] synthesis of polydentate *P,S*-ligands,[11c] and Michael addition reaction.[11d] Due to their practical utility, different research groups have developed numerous methods using transition- or

lanthanide or actinide metal complexes, which are derived mainly from Rh,[12a] Pd,[12b] Ir,[12c] Ni,[12d] Cu,[12e] Co,[12f] Au,[12g] Zr,[12h] U and Th[12i] mediated hydrothiolation of alkynes having electron-rich ligands.

Similarly, the hydrothiolation of an alkene with thiol termed as a thiol-ene reaction,[13] depicts one of the most elegant and atom-economic paths for *C*-*S* bond formation. The hydrothiolation of an alkene can be achieved by exploiting an electrophilic route by using Brönsted acid like H_2SO_4 in AcOH,[14a] $HClO_4$[14b], Lewis acids[14c] or a radical pathway[14d] directing to the α-addition product through Markovnikov pathway or a β-addition product through an anti-Markovnikov pathway.

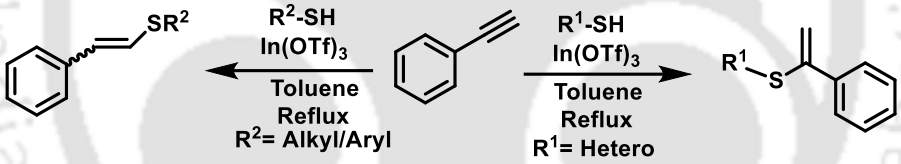
4.2. Synthesis of vinyl sulfide/thioether

Riduan *et al*. reported the Copper(I)-catalyzed stereoselective vinyl sulfides synthesis from thiol and phenylacetylene.[15] The stereoselectivity of vinyl sulfide is decided by the presence or absence of the CO_2 atmosphere. They have reported *Z*-vinyl sulfides and *E*-vinyl sulfides by hydrothiolation reaction of terminal alkynes and thiol in the presence or absence of CO_2 atmosphere, respectively. The crucial step is the formation of cyclic alkene/carboxylate copper complex intermediate in determining the stereoselectivity.



Scheme 4.1. *E*- and *Z*-vinyl sulfide in absence or presence of CO_2 atmosphere

Sarma *et al*. reported the synthesis of exocyclic vinyl sulfide and internal vinyl sulfide using $In(OTf)_3$.[16] They have described that $In(OTf)_3$ can provide both the Markovnikov and anti-Markovnikov hydrothiolated product depending on thiol under similar reaction conditions. It was noted that heteroaromatic thiols selectively react through the Markovnikov addition pathway and aromatic and aliphatic thiols react *via* an anti-Markovnikov pathway.

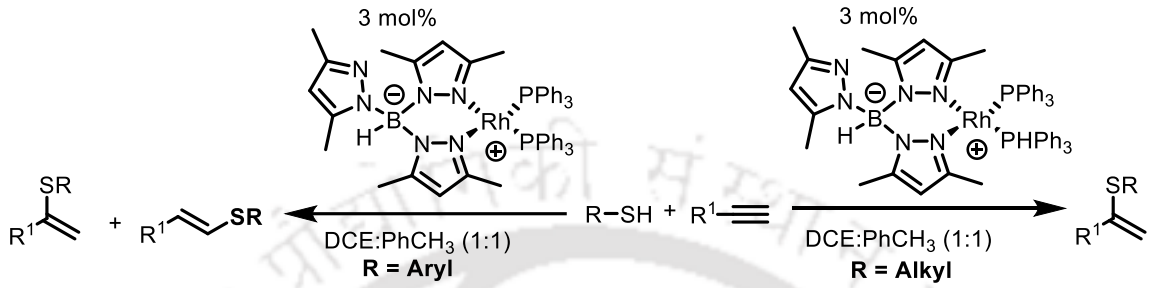


Scheme 4.2. Markovnikov and anti-Markovnikov addition depending on thiols

Fragis *et al*. described the Wittig olefination of aldehydes with phosphonium salt in the presence of ^{t}BuOK.[10b] Due to conflicting redox chemistry with sulfoxides, phosphines were previously unsuitable as Pummerer-type nucleophiles. We get around this obstacle by using a formal phosphine Pummerer reaction, which produces thioalkyl phosphonium salts, which are then used to make various vinyl sulfides *via* Wittig olefinations. From (alkylthioalkyl)triphenylphosphonium salts and aldehydes, vinyl sulfides are synthesized.

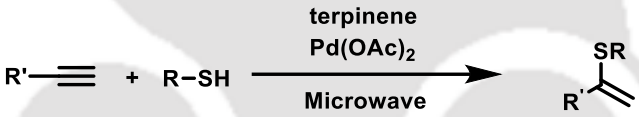
Scheme 4.3. Synthesis of vinyl sulfide from aldehyde and phosphonium salt

They have found exclusively branched vinyl sulfides *via* hydrothiolation reaction of aryl acetylenes and alkyl thiols. But in the case of aryl thiols, they have reported a mixture of linear and branched vinyl sulfides. Vinyl sulfides are synthesized from aryl and alkyl thiol and phenylacetylene using Rhodium complex, reported by Cao *et al*.[12a]



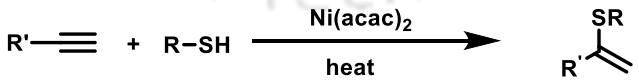
Scheme 4.4. Rh-catalyzed vinyl sulfide synthesis

Pd-Nanoparticle catalyzed vinyl sulfide synthesis is reported by Ananikov *et al*. from thiol and alkyne.[12b] This group reported the synthesis of Pd-nanoparticles with organic ligands. Utilizing these Pd-nanoparticles, Markovnikov addition of alkyl thiol to aliphatic alkynes is reported.



Scheme 4.5. $Pd(OAc)_2$ catalyzed vinyl sulfide synthesis

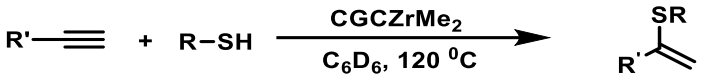
The same group described the synthesis of α-vinyl sulfides from aryl thiols and terminal alkynes using Ni-catalyst under solvent-free conditions. Nickel acetylacetonate is inexpensive and easily available and is used as a precursor of catalyst. Interestingly, we concluded from earlier observation that nickel is a suitable replacement for palladium catalysts. Alkyne insertion into the Ni-S bond is a crucial step for mechanistic studies. Regioselective vinyl sulfide synthesis from thiol and terminal acetylene in presence of $Ni(acac)_2$ is shown in Scheme 4.6.[12d]



Scheme 4.6. Vinyl sulfide synthesis using $Ni(acac)_2$

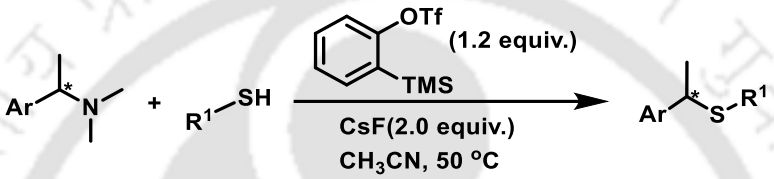
Weiss *et al*. reported the Markovnikov-selective intermolecular hydrothiolation of terminal alkynes using organozirconium complexes as catalysts.[12h] They have displayed the intermolecular hydrothiolation of terminal alkynes by aliphatic, benzylic, and aromatic thiols

using organozirconium(IV) catalysts. Selectively Markovnikov addition products are obtained in this reaction.



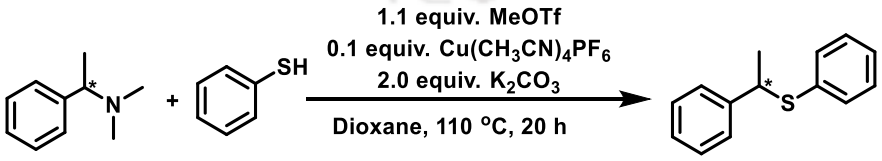
Scheme 4.7. Hydrothiolation reaction of thiol and alkynes in presence of Zr-catalyst

Gui *et al*. described the synthesis of thioethers *via* sequential benzyne activation and nucleophilic substitution of enantioenriched tertiary benzylic amines as shown in Scheme 4.8.[17] A set of reactions were performed with tertiary benzylic amines and nucleophile in the presence of 2-(trimethylsilyl)phenyl triflate and CsF and ranging from good to excellent yield.



Scheme 4.8. Synthesis of thioethers from tertiary benzylic amine and thiol

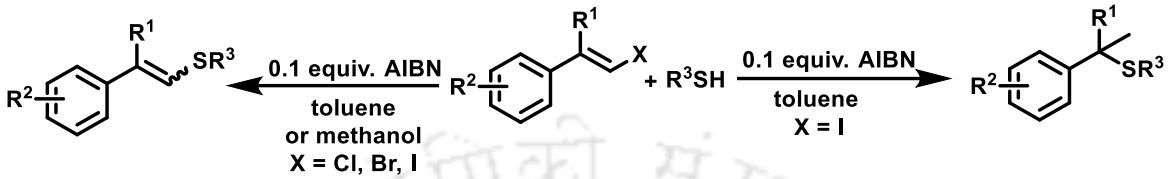
Jiang *et al*. reported in this communication, the synthesis of thioethers, thioacetates, and sulfones from thiols and enantioenriched tertiary benzylic amines in the presence of a copper catalyst. There is no requirement for an additional ligand. Different enantioenriched tertiary benzylic amines, including 1-arylalkylamines, 1-tetrahydronaphthylethylamine, heterocyclic amines (e.g., 1-(thiophen-2-yl)ethanamine), and amino corrosive esters containing a benzylamine moiety, are exceptionally productive substrates, and their chirality is proficiently moved to the items. Various alkene-, arene-, and hetero arene thiols are suitable for this *C−S* coupling *via* this method, at the same time potassium thioacetate and sodium phenyl sulfinate are too. Jiang *et al*. reported that copper-catalyzed stereospecific *C−S* coupling reaction of enantioenriched tertiary benzylic amines *via in-situ* activation with methyl triflate as shown in Scheme 4.9.[18]



Scheme 4.9. Synthesis of thioether from tertiary benzylic amines and thiol

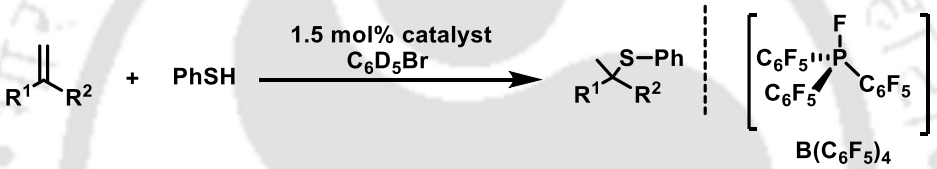
Shi *et al.* demonstrated the construction of the *C-S* bond from vinyl halides and thiols through a radical pathway. The vinyl chloride is yielding vinyl sulfide products. Keeping the same reaction

conditions and tuning the solvent, they obtained vinyl sulfides and thioethers. Vinyl iodide gave vinyl sulfides in protic solvents (methanol) and alkyl sulfides in aprotic solvents (toluene). Shi *et al.* reported the AIBN mediated synthesis of thioethers from vinyl iodides and thiols as displayed in Scheme 4.10.[19]



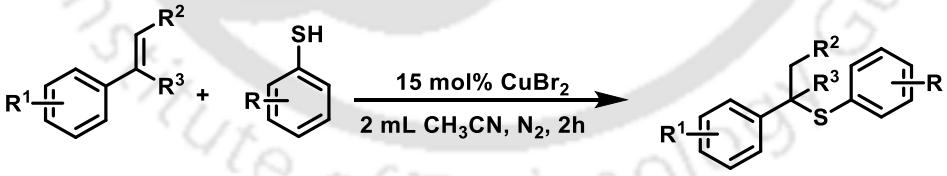
Scheme 4.10. Radical method for the synthesis of thioether and vinyl sulfide

The hydrothiolation reaction of aryl olefins with thiophenols yielding alkyl aryl thioethers in the presence of electrophilic phosphonium cations EPCs. Pe´rez *et al.* reported the phosphonium to catalyze thioethers from hydrothiolation of olefin.[20]



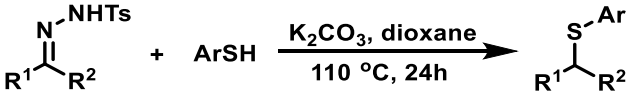
Scheme 4.11. EPC-catalyzed Fridel-Crafts-type reaction

Yi *et al*. reported the Cu(II) catalyzed synthesis of thioether from hydrothiolation reaction of olefin as shown in Scheme 4.12.[21] In this reaction, *in situ* generated Cu^{I} complex plays an important role for the proton transfer in the application of Markovnikov-type hydrothiolation reactions.



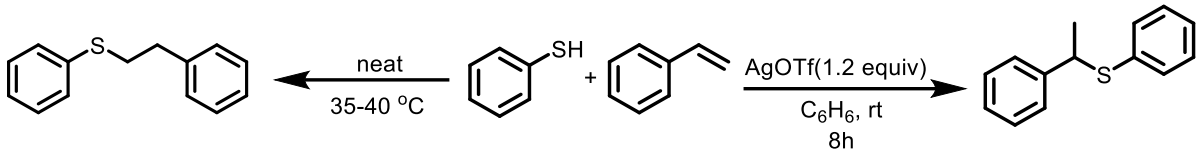
Scheme 4.12. Synthesis of thioether from olefin and thiol

Ding *et al*. reported the synthesis of thioether *via* reductive coupling of tosyl hydrazones with thiols.[22] It is a metal-free base-promoted reductive coupling of tosyl hydrazones with thiols involving the insertion of a carbene into the S–H bond.



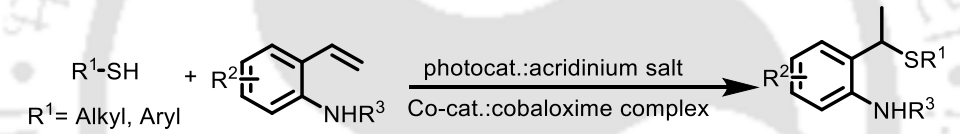
Scheme 4.13. Synthesis of thioether from tosyl hydrazone with thiol

Choudhuri *et al*. reported AgOTf mediated Markovnikov addition of thiols to styrenes to provide α-thioether and they obtained β-thioethers *via* anti-Markovnikov addition in absence of catalyst under the neat condition as shown in Scheme 4.13.[23]



Scheme 4.14. Synthesis of thioether from thiol and styrene

Xiao *et al.* achieved the hydrothiolation of styrenes with thiols by photoredox/cobalt catalysis as shown in Scheme 4.15.[13] Due to the catalyst poisoning of metal catalysts by the way of organosulfur compounds, limited transition-metal catalyzed thiol-ene reactions have been studied. However, in this work, a directing group-assisted hydrothiolation of styrenes with thiols photoredox/cobalt catalysis is observed to continue efficiently to afford Markovnikov-type sulfides with excellent regioselectivity.



Scheme 4.15. Synthesis of thioether from hydrothiolation of styrenes with thiols by photoredox/cobalt catalysis

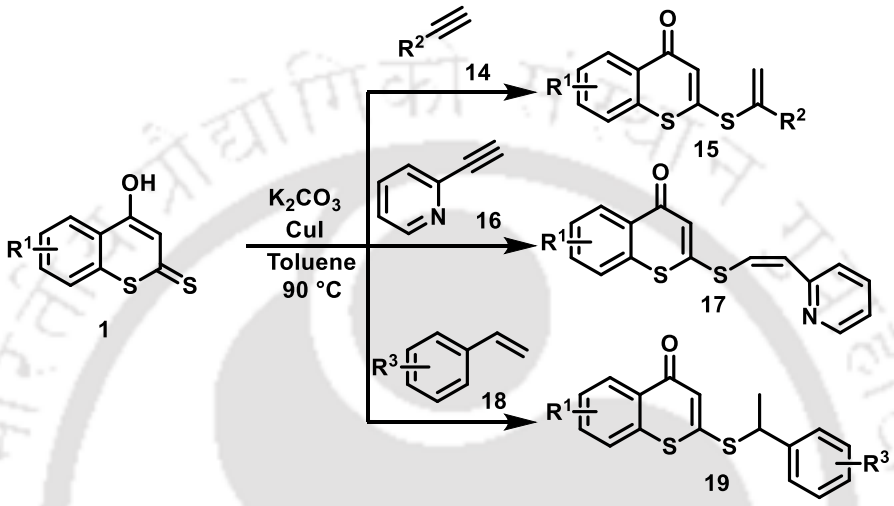
Despite the utility of earlier methods, they require an expensive metal catalyst and ligand. Furthermore, the reported methods require harsh conditions and a longer reaction time. To overcome aforementioned these difficulties, we developed a simple and economical protocol for hydrothiolation of alkynes and alkenes.

Our research group and others have developed the synthesis of new organic molecules[24] from 4-hydroxydithiocoumarin, a key building block by tuning its reactivity site. 4-Hydroxydithiocoumarin has a unique characteristic feature to existing in three possible resonating structures in which one of them has thiol functionality. We have recently reported the method for 1,4-oxathiin derivatives[24c] from 4-hydroxydithiocoumarin, aryl acetylene, and DMSO. Taking clues from hydrothiolation reaction between thiols and aryl acetylene as well as styrene, we conceived that vinyl sulfides and thioethers both can be

easily accessible from 4-hydroxydithiocoumarin and mono-substituted alkynes/alkene by thiol-yne/thiol-ene reaction by tuning the reaction conditions.

4.3. Results and Discussion

Herein, we propose a simple, elegant, and atom economic approach to access newly vinyl sulfides from 4-hydroxydithiocoumarin and aryl alkynes as well as thioethers from alkenes in the presence of 10 mol% copper(I) iodide and K_2CO_3 in toluene at 90 °C as shown in Scheme 4.16.

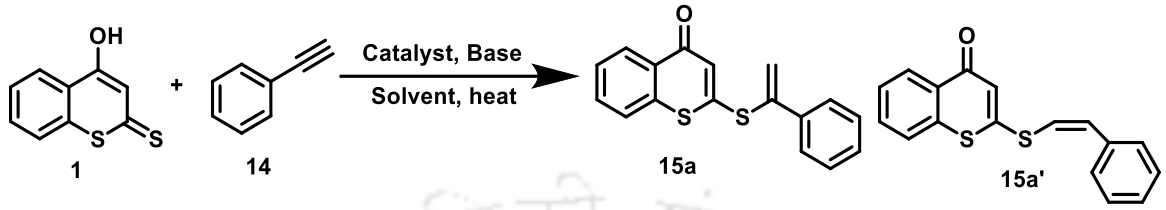


Scheme 4.16. Reaction behavior of 4-hydroxydithiocoumarin with alkynes and alkenes

Our experimental investigation consisted of a variety of 4-hydroxydithiocoumarins, synthesized using an earlier reported procedure.[25] The study was initiated with 4-hydroxydithiocoumarin **1** and phenylacetylene **14** as the model substrates. Initially, the reaction was carried out with 4-hydroxydithiocoumarin (**1,** 0.25 mmol) and phenylacetylene (**14**, 0.25 mmol) at room temperature using 1 equiv K_2CO_3 in presence of 10 mol% copper(I) iodide without any solvent. No reaction occurred at room temperature (Table 4.1, entry 1). However, carrying out the reaction in the presence of 1 equiv of K_2CO_3, 10 mol% CuI at 70 °C resulted in a mixture of approximately 1:1 of the desired product **15a** along with an inseparable mixture of products (Table 4.1, entry 2). Performing the same reaction in the absence of CuI in toluene did not result in the desired product (Table 4.1, entry 3). Further, heating the reaction mixture in presence of 10 mol % Cu(I)I without any solvent resulted in a mixture of (α-vinylsulfide) **15a** and (*Z*-β-vinylsulfide) **15a′** (Table 4.1, entry 4). The yield of **15a** and **15a'** were determined from

the crude ^{1}H NMR spectrum. With an effort to enhance the selectivity and yield of the product **15a**, the reaction

Table 4.1. Optimization of the reaction conditions[a,b,c]



Entry	Base (1 equiv)	Catalyst	Mol (%)	Solvent	Time (min)	% Yield[b] **3a**	% Yield[b] **3a'**
[c]01	K_2CO_3	CuI	10	-	60	-	-
[d]02	K_2CO_3	CuI	10	Toluene	60	30**	-
03	K_2CO_3	-	-	Toluene	60	-	-
04	K_2CO_3	CuI	10	-	60	20	10
05	**K_2CO_3**	**CuI**	**10**	**Toluene**	**20**	**80**	-
06	K_2CO_3	CuI	20	Toluene	20	81	-
07	K_2CO_3	CuI	50	Toluene	20	83	-
08	K_2CO_3	CuCl	10	Toluene	20	40	-
09	K_2CO_3	CuBr	10	Toluene	20	50	-
10	K_2CO_3	$CuSO_4$	10	Toluene	30	40	-
11	K_2CO_3	CuI	10	CH_3CN	60	-	-
12	K_2CO_3	CuI	10	DCM	60	-	-

[a]All the reactions were carried out using 4-hydroxydithiocoumarin (0.25 mmol), phenylacetylene (0.25 mmol), K_2CO_3 (1 equiv) in 1mL of solvent at 90° C. [b]Isolated yield. [C]Room temperature. [d]The reaction was carried out at 70 °C temperature.**Inseparable mixture an equal amount based on crude ^{1}H NMR spectrum.

was performed with 4-hydroxydithiocoumarin and phenylacetylene using 1 equiv K_2CO_3 in 10 mol% Cu(I)I in toluene solvent at 90 °C (Table 4.1, entry 5). The desired vinyl sulfide **15a** could be isolated with 80% yield. Increasing the reaction temperature resulted in higher yields with improved overall selectivity. To ascertain the amount of catalyst

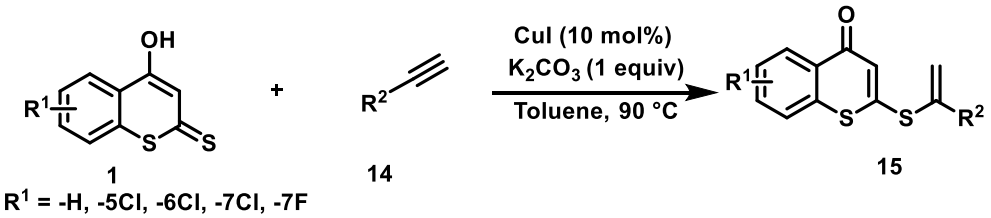
required, two more reactions were also executed by involving 20 mol% and 50 mol% of CuI, respectively (Table 4.1, entries 6 & 7), however, the yield did not improve as expected. In contrast, the metal salts CuI, CuCl, and CuBr showed admirable selectivity towards the β vinyl sulfides within 20 min (Table 4.1, entries 8-9). We observed that the maximum of **15a** yield was 80% by employing CuI (Table 4.1, entry 5). The earlier reaction was carried out again with copper (II) salt, but the yield obtained was poor (Table 4.1, entry 10). To find a suitable solvent, the reactions were scrutinized with CH_3CN and DCM, the results were discouraging (Table 4.1, entries 11-12).

Among the different reactions that were carried out, it was concluded that the best conditions for the reaction are, reacting **1** with **14** in the presence of 10 mol% of CuI and 1.0 equiv of K_2CO_3 in toluene as reaction medium at 90 °C. (Table 4.1, entry 5).

Next, a series of reactions were carried out using various 4-hydroxydithiocoumarin **1** and different substituted aryl acetylenes **14** using the optimized reaction conditions, and the successful results are shown in Table 4.2. Despite their different electronic nature, 4-hydrodithiocoumarin was allowed to react to a wide variety of substituted aryl acetylenes. When 3-ethynyltoluene and 3-ethynylaniline were employed, the corresponding products **15b** and **15c** were obtained in 85% and 70% yield, respectively. Similar results were obtained for 4-ethynylanisole and 4-ethynyltoluene. The reaction of 4-hydroxydithiocoumarin with sterically hindered 4-*tert*-butylphenylacetylene also provided the expected vinyl sulfide **15f** in 82% yield. Subsequently, we have performed the reaction with heteroaryl acetylene, 3-ethynylthiophene and observed the branched vinyl sulfide **15g** in 75% yield. The reaction of 7-chloro substituted 4-hydroxydithiocoumarin with phenylacetylene and 4-*tert*-butylphenylacetylene gave the products **15h** and **15i** in 78% and 82% yield, respectively. The reaction of 6-chloro substituted 4-hydroxydithiocoumarin with 3-ethynyl-toluene and 4-ethynylanisole were also investigated and the desired products **15j** and **15k** were isolated in 84% and 75% yield, respectively. Similarly, aryl acetylene having $–CH_3$ group at *p*-position showed good reactivity with 6-chloro-4-hydroxydithiocoumarin under identical reaction conditions to provide **15l** in 85% yield. The reaction of 7-fluoro-4-hydroxydithiocoumarin with 1,3-ethynylbenzene gave the product *mono*-vinyl sulfide **15m** instead of the expected *bis*-vinyl sulfide.

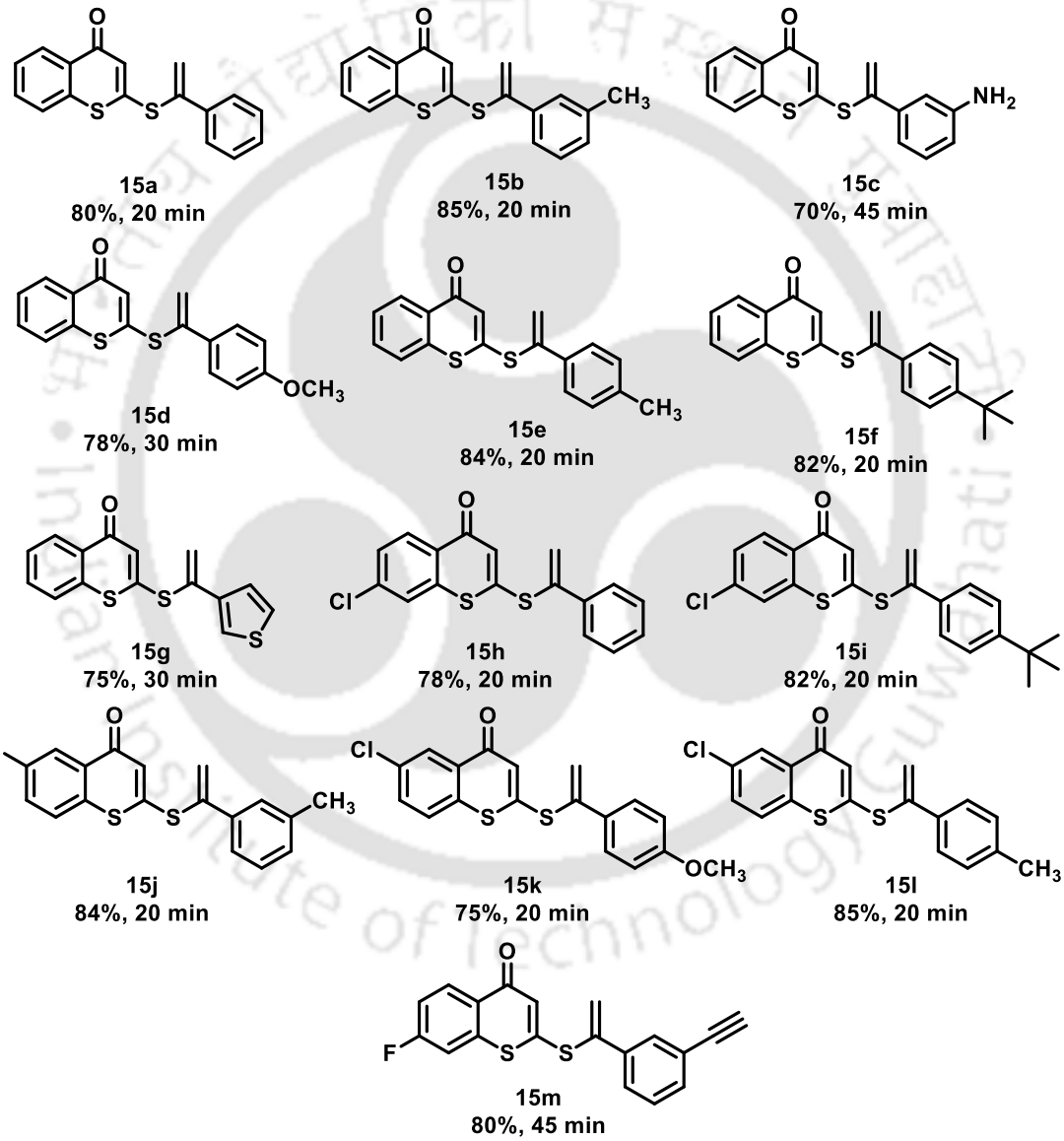
Interestingly, when we did the reaction with 2-ethynylpyridine and 4-hydroxydithiocoumarin under identical conditions, the different product **17a** was obtained, which is confirmed by ^{1}H NMR. We observed two doublets in the ^{1}H NMR spectrum for two protons instead of two singlets for methylene protons. We can conclude from the ^{1}H NMR spectrum, the product is (*Z*)-β-vinyl sulfides instead of α-vinyl sulfides. Likewise -7Cl, -6Cl, -5Cl, -5F, -6CF_3 substituted 4-hydroxydithiocoumarin gave rise to the products **17b-f** in 88–96% yields (Table 4.3).

Table 4.2. Cu-Catalyzed hydrothiolation of various Terminal Alkynes with substituted 4-hydroxydithiocoumarin[a,b]



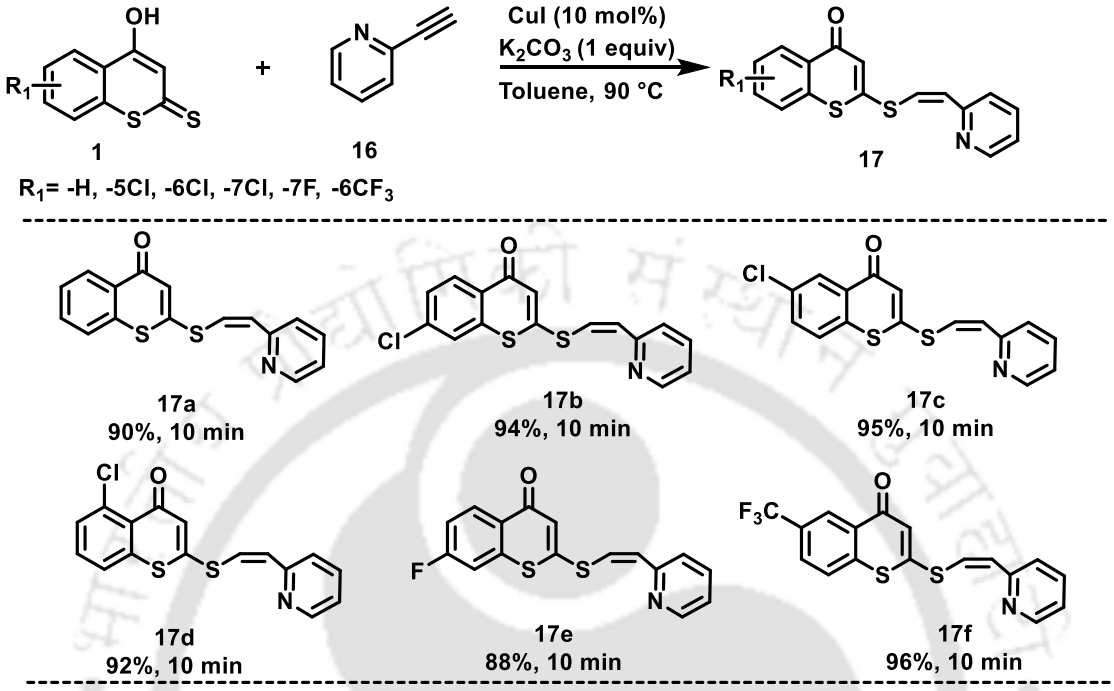
R^1 = -H, -5Cl, -6Cl, -7Cl, -7F

R^2 = -Ph, -3CH_3Ph, -3NH_2Ph, -4OCH_3Ph, -4CH_3Ph, -4^{t}BuPh, -C_4H_3S, -C_8H_5



[a]All reactions were carried out with substituted 4-hydroxydithiocoumarins (0.25 mmol) and substituted phenylacetylene (0.25 mmol) in the presence of copper(I)iodide and K_2CO_3 (1 equiv) in 1 mL toluene at 90 °C. [b]Isolated yields.

Table 4.3. Cu-Catalyzed hydrothiolation of 2-ethynylpyridine with various 4-hydroxydithiocoumarin[a,b]



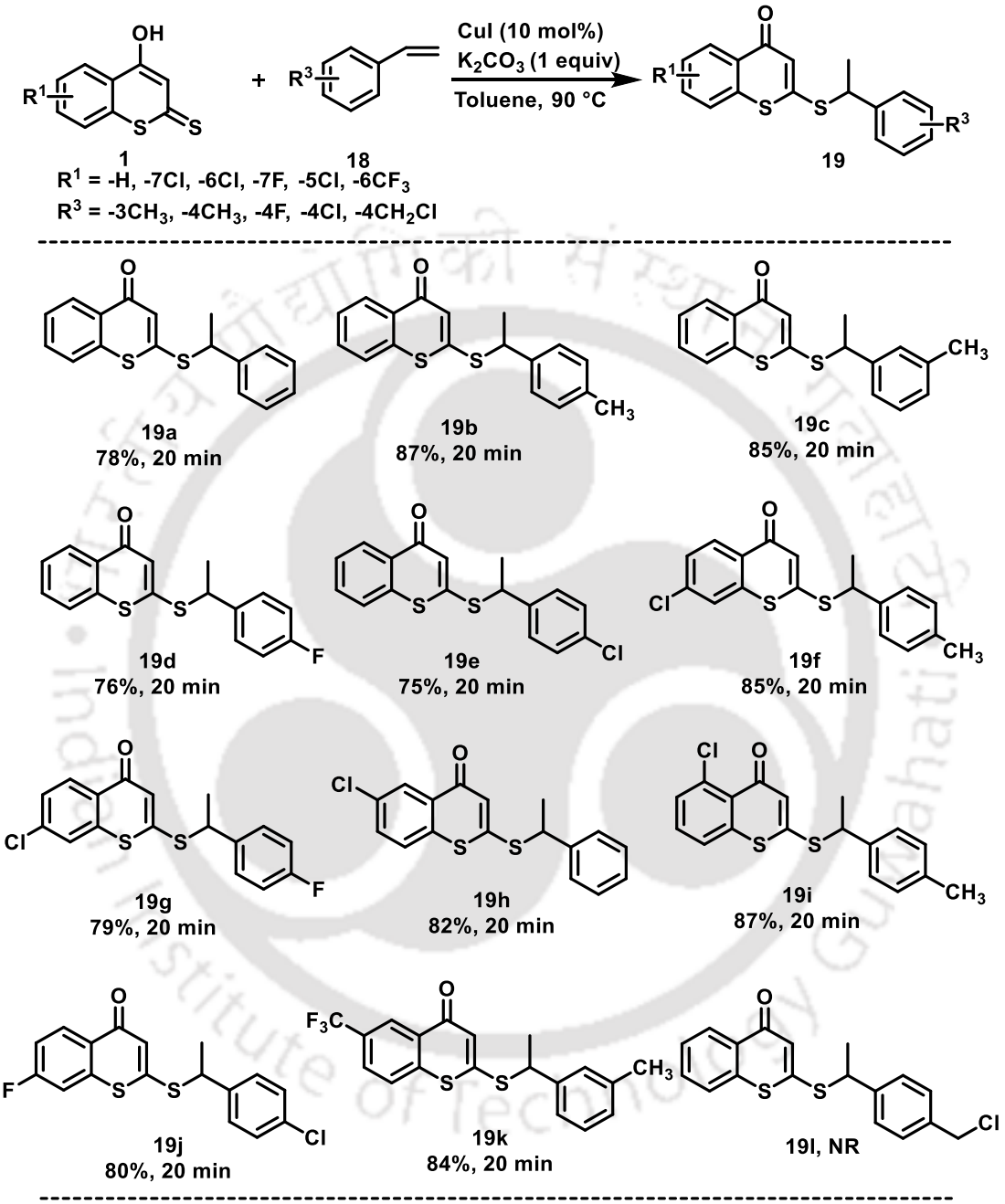
[a]All reactions were carried out with various 4-hydroxydithiocoumarins (0.25 mmol) and 2-ethynylpyridine (0.25 mmol) in the presence of copper(I)iodide and K_2CO_3 (1 equiv) in 1 mL toluene at 90 °C. [b]Isolated yields.

Motivated with the successful regio- and stereoselective reaction, we further investigated the generality of the procedure with various styrenes, and the results are represented in Table 4.4.

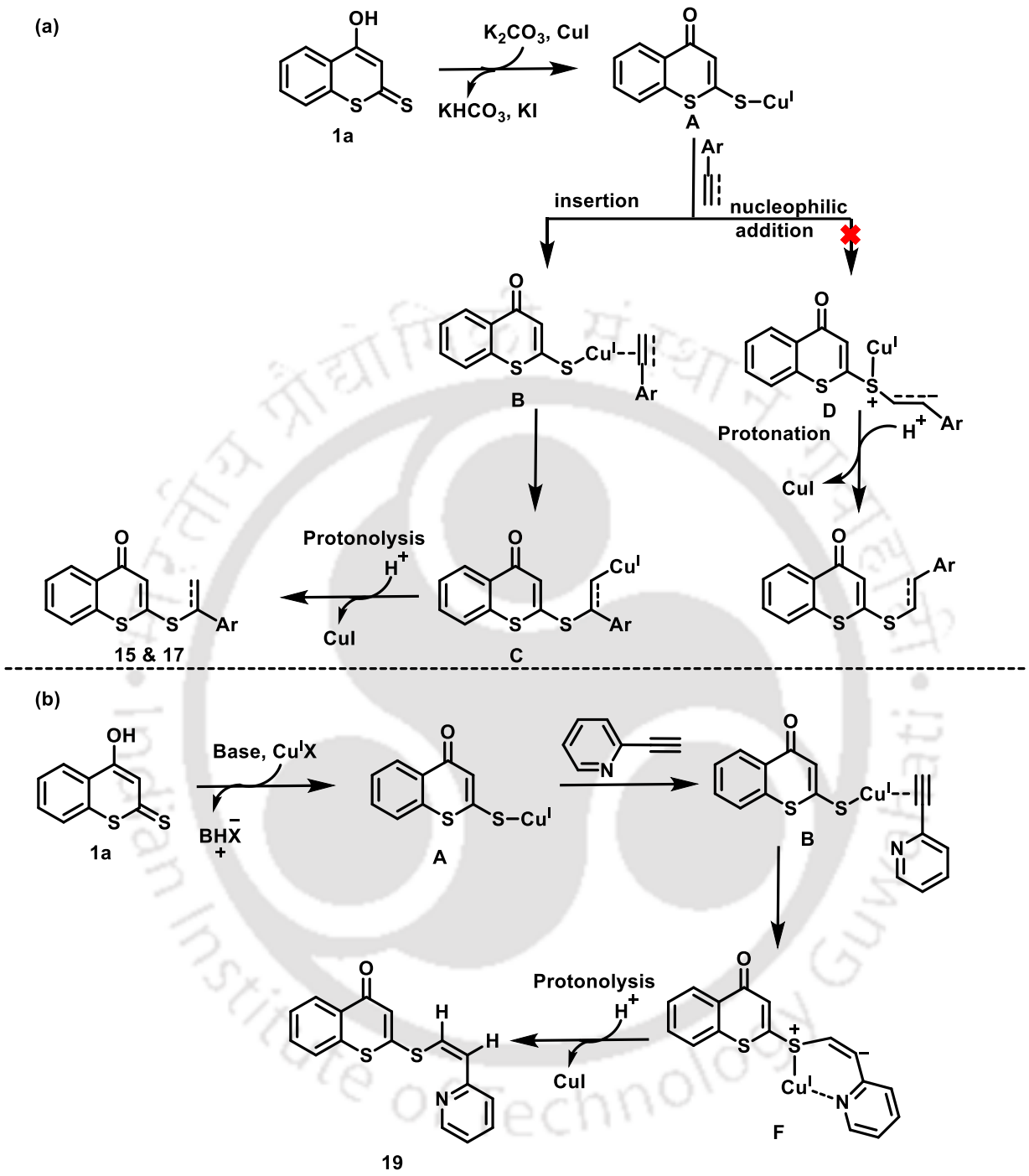
The reaction of 4-hydroxydithiocoumarin with styrene was similar to phenylacetylene and resulted in the product **19a** in 78% yield. Similarly, *p*-CH_3 and *m*-CH_3 substituted styrenes furnished the desired products **19b** and **19c** in 87% and 85% yields, respectively. Thereafter, the reaction of 4-F and 4-Cl styrenes with 4-hydroxydithiocoumarin effectively provided the expected products **19d** and **19e** in 76% and 75% yields, respectively. 7-Chloro substituted 4-hydroxydithiocoumarin also reacted with styrenes having 4-Me or 4-F substituents on the ring to afford the expected products **19f** and **19g,** respectively in good yields. The reaction of 6-Cl substituted 4-hydroxydithiocoumarin with styrene gave rise to **19h** in 82% yield. Electron withdrawing *p*-chlorine containing

styrene was examined with 7-fluoro-4-hydroxydithiocoumarin, the desired product **19j** was isolated in 80% yield. 5-Cl and 6-CF_3 substituted 4-hydroxydithiocoumarin were employed in the reaction with *p*-$CH_3$and *m*-CH_3 substituted styrenes, the desired products **19i** and **19k** were isolated in 87% and 84% yield, respectively. Unfortunately, we did not obtain the expected thioether when the reaction was carried out with 4-vinylbenzyl chloride reacted with 4-hydroxydithiocoumarin under identical reaction conditions. In this reaction, we have obtained a nucleophilic substitution product at the benzylic position.

Table 4.4. Cu-Catalyzed hydrothiolation of substituted styrenes with substituted 4-hydroxydithiocoumarin[a,b]



[a]All reactions were carried out with substituted 4-hydroxydithiocoumarin (0.25 mmol) and substituted styrenes (0.25 mmol) in the presence of copper(I)iodide and K_2CO_3 (1 equiv) in 1 mL toluene at 90 °C. [b]Isolated yields.



Scheme 4.17. A plausible mechanism for the synthesis of vinyl sulfide and thioether derivatives

Based on the isolated products and existing literature survey, a plausible mechanism is proposed in Scheme 4.17. Initially, deprotonation occurs from 4-hydroxydithiocoumarin on reaction with K_2CO_3[26] and form a copper(I) thiolate species (**A**).[27] The reactive intermediate **A** is coordinated with the unsaturated C-C bond in phenylacetylene.[28] In this reaction, the possible product might

form through two possible routes. **Route 1**: ***Nucleophilic addition*** – nucleophilic attack of the thiolate (**A**) at the unsaturated C-C bond gives β-vinyl sulfide. **Route 2**: ***Insertion syn addition*** – insertion of the unsaturated C-C bond into copper thiolate bond to form the species C. Subsequent addition of the proton gives rise to the product **15** & **19** and regenerates the copper(I) iodide. But in case of 2-ethynylpyridine, the Cu center of the copperthiolate species (**A**) approaches the triple bond of 2-ethynylpyridine.[15] The nucleophilic cupration between **A** and 2-ethynylpyridine may occur to form a copper complex intermediate (**F**) is the key step inducing the stereoselectivity. The consequent proton attack on the intermediate (**F**) to the β-carbon generates the *Z*-β-vinyl sulfide (**17**).

4.4. Conclusion

In summary, we have accomplished the synthesis of a new class of vinyl sulfide and thioether derivatives derived from 4-hydroxydithiocoumarin and phenylacetylenes/styrenes, respectively using 10 mol% Cu(I)I at 90 °C. Markovnikov product was observed in presence of CuI instead of anti-Markovnikov product. In the case of 2-ethynylpyridine, we got exclusively (*Z*)-β-vinyl sulfide *via* anti-Markovnikov addition. In addition, we have noted that temperature has a crucial role in the formation of products. Additionally, this method is very practical because of the use of cheaper Cu(I) salt, mild reaction conditions, good yields, regioselectivity, shorter reaction time, and a broad substrates scope. In addition, we are trying to accomplish the asymmetric synthesis of thioethers, which is under investigation and will be reported in due course of time.

4.5. Experimental Section

4.5.a. General procedure for the synthesis of 4-hydroxydithiocoumarin (1a-f)

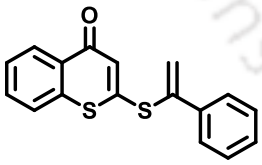
A wide variety of 4-hydroxydithiocoumarin was prepared by following the previously reported literature procedure: J. E. Anderson-McKay, A. J. Liepa, *Aust. J. Chem.*, 1987, **40**, 1179-90.[25]

4.5.b. General Procedure for the Synthesis of vinyl sulfide and thioether derivatives (15, 17 & 19)[a,b]

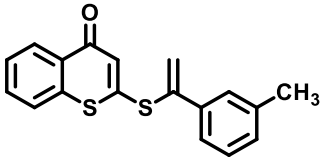
A mixture of 4-hydroxydithiocoumarin (**1**, 0.25 mmol), K_2CO_3 (1 equiv), and CuI (10 mol%) was taken 1 mL of toluene into a 25 mL round-bottomed flask. Subsequently, aryl acetylene/styrene (**14/16/18** 0.25 mmol) was added to it and the reaction mixture was heated in a pre-heated oil bath at 90 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude residue was extracted with ethyl acetate (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and it was concentrated in a rotatory evaporator. The crude residue was purified by using column chromatography to obtain the desired products.

4.6. Characterization

2-((1-phenylvinyl)thio)-4*H*-thiochromen-4-one (15a). Brown liquid (59 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, J = 7.9, 1.6 Hz, 1H), 7.66 – 7.64 (m, 2H), 7.54 – 7.51 (m, 1H), 7.47 – 7.43 (m, 2H), 7.35 – 7.30 (m, 3H), 7.01 (s, 1H), 6.09 (s, 1H), 5.96 (s, 1H);^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 151.6, 139.3, 138.2, 137.4, 131.5, 130.7, 129.3, 128.8, 128.8, 127.8, 127.2, 125.8, 125.7, 125.2; IR $(KBr)_{vmax}$ 3059, 1722 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{12}OS_2$ ($M + H^+$) 297.0402; Found 297.0419.

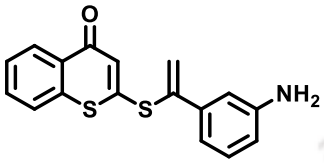


2-((1-(*m*-tolyl)vinyl)thio)-4*H*-thiochromen-4-one (15b). Brown liquid (65 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.0 Hz, 1H), 7.53 (dd, J = 7.6, 5.7 Hz, 1H), 7.48 – 7.44 (m, 4H), 7.22 (t, J = 7.9 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.00 (s, 1H), 6.08 (s, 1H), 5.94 (s, 1H),

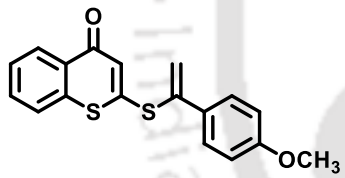


2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 151.9, 139.2, 138.4, 138.2, 137.3, 131.5, 130.7, 130.2, 128.8, 128.6, 127.8, 125.7, 125.6, 125.1, 124.4, 21.5; IR $(KBr)_{vmax}$ 3058, 1726 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{14}OS_2$ $(M + H^+)$ 311.0559; Found 311.0565.

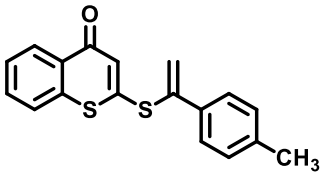
2-((1-(3-aminophenyl)vinyl)thio)-4*H*-thiochromen-4-one (15c). Brown liquid (54 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 8.8 Hz, 2H), 7.11 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 7.00 (s, 1H), 6.95 (s, 1H), 6.62 (d, J = 7.8 Hz, 1H), 6.07 (s, 1H), 5.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 152.2, 146.7, 139.0, 138.4, 138.2, 131.5, 130.6, 129.7, 128.7, 127.8, 125.7, 125.2, 117.6, 116.1, 113.6; IR $(KBr)_{vmax}$ 3350, 3225, 3058, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{13}NOS_2$ $(M + H^+)$ 312.0511; Found 312.0512.



2-((1-(4-methoxyphenyl)vinyl)thio)-4*H*-thiochromen-4-one (15d). Brown liquid (63 mg, 78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 7.1 Hz, 1H), 7.44 (dd, J = 7.7, 5.6 Hz, 2H), 6.99 (s, 1H), 6.84 (d, J = 8.8 Hz, 2H), 5.99 (s, 1H), 5.86 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 160.5, 152.1, 138.5, 138.2, 131.5, 130.7, 129.7, 128.7, 128.6, 127.8, 125.7, 125.5, 123.5, 114.1, 55.4; ; IR $(KBr)_{vmax}$ 3063, 1710 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{14}O_2S_2$ $(M + H^+)$ 327.0508; Found 327.0508.



2-((1-(*p*-tolyl)vinyl)thio)-4*H*-thiochromen-4-one (15e). Brown liquid (65 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, J = 7.8, 1.6 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.47 – 7.42 (m, 3H), 7.13 (d, J = 7.9 Hz, 2H), 6.99 (s, 1H), 6.05 (s, 1H), 5.91 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 152.0, 139.4, 139.0, 138.2, 134.5, 131.5, 130.7, 129.5, 128.7, 127.8, 127.1, 125.7, 125.5, 124.5, 21.3; IR $(KBr)_{vmax}$ 3066, 1718 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{14}OS_2$ $(M + H^+)$ 311.0559; Found 311.0585.



2-((1-(4-(*tert*-butyl)phenyl)vinyl)thio)-4*H*-thiochromen-4-one (15f). Brown liquid (72 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 7.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.53 (t, J= 8.0 Hz, 1H), 7.47 (d, J = 6.9 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.11 (s, 1H), 5.93 (s, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 152.6, 152.3, 138.6, 138.3, 134.3, 131.5, 130.8, 130.7, 130.6, 128.8, 127.8, 126.8, 125.7, 125.2, 125.1, 34.8, 31.3; IR (KBr)$_{\nu max}$ 3063, 1721 cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{20}OS_2$ (M + H^+) 353.1028; Found 353.1039.

2-((1-(thiophen-3-yl)vinyl)thio)-4*H*-thiochromen-4-one (15g). Brown liquid (56 mg, 75%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, J = 8.0, 1.6 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.49 – 7.45 (m, 2H), 7.29 – 7.28 (m, 2H), 7.03 (s, 1H), 6.13 (s, 1H), 5.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 152.0, 139.4, 138.1, 133.1, 131.6, 130.7, 128.8, 127.9, 126.8, 125.8, 125.7, 125.1, 124.7, 124.4; IR (KBr)$_{\nu max}$ 3063, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{10}OS_3$ (M + H^+) 302.9967; Found 302.9980.

7-chloro-2-((1-phenylvinyl)thio)-4*H*-thiochromen-4-one (15h). Brown liquid (64 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.6 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.43 (d, J = 1.5 Hz, 1H), 7.40 (dd, J = 8.7, 1.6 Hz, 1H), 7.33 (q, J = 5.3 Hz, 3H), 6.97 (s, 1H), 6.11 (s, 1H), 5.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 151.7, 139.4, 138.8, 138.3, 137.1, 130.3, 129.4, 129.0, 128.8, 128.5, 127.2, 125.8, 125.6, 125.0; IR (KBr)$_{\nu max}$ 3055, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}ClOS_2$ (M + H^+) 331.0031; Found 331.0006.

2-((1-(4-(*tert*-butyl)phenyl)vinyl)thio)-7-chloro-4*H*-thiochromen-4-one (15i). Brown liquid (79 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 1.4 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 6.97

(s, 1H), 6.12 (s, 1H), 5.94 (s, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 152.7, 152.3, 139.5, 138.3, 138.2, 134.1, 130.3, 129.0, 128.4, 126.8, 125.8, 125.5, 125.1, 125.0, 34.8, 31.3; IR $(KBr)_{vmax}$ 3058, 1721 cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{19}ClOS_2$ ($M + H^+$) 387.0639; Found 387.0639.

6-chloro-2-((1-(*m*-tolyl)vinyl)thio)-4*H*-thiochromen-4-one (15j). Brown liquid (72 mg, 84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 2.3 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.44 (s, 2H), 7.37 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.99 (s, 1H), 6.10 (s, 1H), 5.95 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 152.5, 139.0, 138.5, 137.2, 136.3, 134.4, 131.9, 131.9, 130.3, 128.7, 128.4, 127.8, 127.1, 125.6, 125.1, 124.4, 21.5; IR $(KBr)_{vmax}$ 3063, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}ClOS_2$ ($M + H^+$) 345.0169; Found 345.0170.

6-chloro-2-((1-(4-methoxyphenyl)vinyl)thio)-4*H*-thiochromen-4-one (15k). Brown liquid (67 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.48–7.46 (m, 1H), 7.36 (d, J = 8.6 Hz, 1H), 6.97 (s, 1H), 6.84 (d, J = 8.9 Hz, 2H), 6.00 (s, 1H), 5.87 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 160.5, 152.7, 138.2, 136.3, 134.3, 131.9, 131.8, 129.6, 128.5, 128.4, 127.1, 124.9, 123.9, 114.2, 55.4; IR $(KBr)_{vmax}$ 3074, 1718 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}ClO_2S_2$ ($M + H^+$) 361.0118; Found 361.0117.

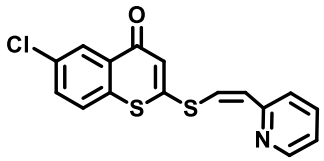
6-chloro-2-((1-(*p*-tolyl)vinyl)thio)-4*H*-thiochromen-4-one (15l). Brown liquid (73 mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 6.96 (s, 1H), 6.06 (s, 1H), 5.92 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 151.9, 139.5, 139.5, 138.7, 138.2, 134.3, 130.3, 129.5, 129.1, 128.4, 127.1, 125.5, 125.0, 124.9, 21.3; IR $(KBr)_{vmax}$ 3063, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}ClOS_2$ ($M + H^+$) 345.0169; Found 345.0186.

2-((1-(3-ethynylphenyl)vinyl)thio)-7-fluoro-4*H*-thiochromen-4-one (15m). Brown liquid (68 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, J = 8.9, 5.9 Hz, 1H), 7.75 (s, 2H), 7.62 (d, J = 8 Hz, 1H), 7.44 – 7.42 (m, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 6.97 (s, 1H), 6.10 (s, 1H), 5.99 (s, 1H), 3.09 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ178.1, 165.1, 163.0, 150.7, 140.2, 140.1, 138.2, 137.6, 132.9, 131.9, 131.8, 130.7, 128.9, 127.6, 126.3, 126.0, 122.9, 116.5, 116.3, 111.9, 111.7, 83.0, 78.1; IR $(KBr)_{vmax}$ 3292, 3061, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{11}FOS_2$ ($M + H^+$) 339.0308; Found 339.0302.

(*Z*)-2-((2-(pyridin-2-yl)vinyl)thio)-4*H*-thiochromen-4-one (17a). Brown liquid (67 mg, 90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.58 (d, J = 13.7 Hz, 2H), 7.52 (s, 1H), 7.25 (d, J = 15.3 Hz, 2H), 7.15 (s, 1H), 6.96 (d, J = 10.3 Hz, 1H), 6.71 (d, J = 10.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 154.5, 154.0, 148.4, 138.1, 136.4, 131.7, 130.9, 128.7, 127.9, 127.3, 126.4, 125.8, 125.3, 123.8, 121.5; IR $(KBr)_{vmax}$ 3055, 1726 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{11}NOS_2$ ($M + H^+$) 298.0355; Found 298.0355.

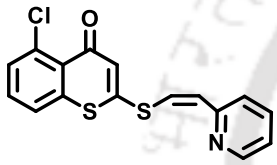
(*Z*)-7-chloro-2-((2-(pyridin-2-yl)vinyl)thio)-4*H*-thiochromen-4-one (17b). Off white solid (77 mg, 94%); mp 143-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 3.8 Hz, 1H), 8.46 (d, J = 8.6 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.52 (dd, J = 8.7, 2.1 Hz, 1H), 7.31 (d, J = 7.4 Hz, 2H), 7.22 (dd, J = 7.6, 4.8 Hz, 1H), 6.98 (d, J = 10.1 Hz, 1H), 6.78 (d, J = 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 154.5, 154.0, 148.5, 139.5, 138.5, 136.6, 130.4, 129.4, 128.7, 127.1, 126.7, 125.6, 125.3, 123.9, 121.7; IR $(KBr)_{vmax}$ 3052, 1726 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}ClNOS_2$ ($M + H^+$) 331.9965; Found 331.9965.

(*Z*)-6-chloro-2-((2-(pyridin-2-yl)vinyl)thio)-4*H*-thiochromen-4-one (17c). Off white solid



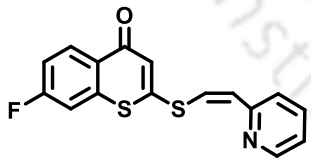
(78 mg, 95%); mp 141-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 4.3 Hz, 1H), 8.49 (d, J = 2.3 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.61 – 7.58 (m, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.30 (s, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.21 – 7.18 (m, 1H), 6.97 (d, J = 10.1 Hz, 1H), 6.76 (d, J = 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 154.6, 154.5, 148.5, 136.6, 136.3, 134.6, 132.2, 132.1, 128.5, 127.3, 127.0, 126.3, 125.6, 123.9, 121.7; IR $(KBr)_{vmax}$ 3053, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}ClNOS_2$ ($M + H^+$) 331.9965; Found 331.9965.

(*Z*)-5-chloro-2-((2-(pyridin-2-yl)vinyl)thio)-4*H*-thiochromen-4-one (17d). Off white solid



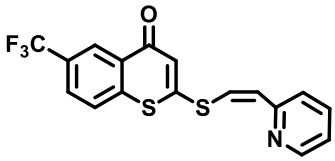
(76 mg, 92%); mp 127-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 4.3 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.51 (td, J = 7.6, 1.8 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.28 (s, 1H), 7.19 – 7.17 (m, 1H), 7.16 (s, 1H), 6.94 (d, J = 10.1 Hz, 1H), 6.73 (d, J = 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 154.5, 150.9, 148.5, 141.1, 136.5, 136.4, 131.8, 131.0, 127.9, 127.9, 127.2, 125.4, 125.0, 123.9, 121.6; IR $(KBr)_{vmax}$ 3055, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}ClNOS_2$ ($M + H^+$) 331.9965; Found 331.9966.

(*Z*)-7-fluoro-2-((2-(pyridin-2-yl)vinyl)thio)-4*H*-thiochromen-4-one (17e). Off white solid



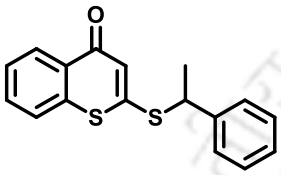
(69 mg, 88%); mp 142-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, J = 4.8, 1.7 Hz, 1H), 8.52 (dd, J = 8.9, 5.8 Hz, 1H), 7.69 (td, J = 7.7, 1.9 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H), 7.24 (dd, J = 8.3, 6.0 Hz, 2H), 7.21 (s, 1H), 7.17 (dd, J = 7.3, 4.5 Hz, 1H), 6.94 (d, J = 10.1 Hz, 1H), 6.73 (d, J = 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 165.5, 162.9, 154.5, 153.8, 148.5, 140.4, 140.3, 136.6, 132.0, 131.9, 127.7, 127.2, 126.8, 125.5, 123.9, 121.7, 116.7, 116.5, 112.0, 111.8; IR $(KBr)_{vmax}$ 3052, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{16}H_{10}FNOS_2$ ($M + H^+$) 316.0261; Found 316.0268.

(*Z*)-2-((2-(pyridin-2-yl)vinyl)thio)-6-(trifluoromethyl)-4*H*-thiochromen-4-one (17f): Off white solid (87 mg, 96%); mp 151-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.70

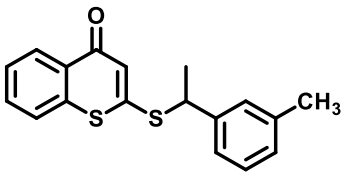


(d, J = 4.5 Hz, 1H), 7.78 (dd, J = 8.4, 2.1 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.24 (s, 2H), 7.16 (dd, J = 7.6, 4.8 Hz, 1H), 6.92 (d, J = 10.1 Hz, 1H), 6.73 (d, J = 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 153.7, 153.2, 147.4, 140.5, 135.4, 130.0, 129.4, 129.1, 126.6, 126.6, 125.7, 125.4, 125.3, 125.2, 125.1, 124.7, 122.8, 120.6; IR $(KBr)_{vmax}$ 3050, 1720 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}F_3NOS_2$ ($M + H^+$) 366.0229; Found 366.0229.

2-((1-phenylethyl)thio)-4*H*-thiochromen-4-one (19a). Brown liquid (58 mg, 78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, J = 8.3, 1.6 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.50 – 7.48 (m, 2H), 7.40 – 7.38 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 1.4 Hz, 1H), 6.98 (s, 1H), 4.69 (q, J = 7.0 Hz, 1H), 1.75 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 151.6, 141.2, 138.5, 131.6, 130.9, 128.9, 128.8, 128.1, 127.9, 127.3, 127.2, 125.6, 48.6, 22.5; IR $(KBr)_{vmax}$ 2969, 2868, 1721 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{14}OS_2$ ($M + H^+$) 299.0559; Found 299.0578.



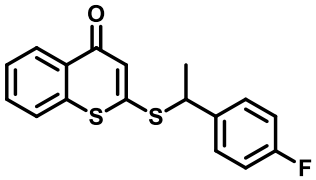
2-((1-(*p*-tolyl)ethyl)thio)-4*H*-thiochromen-4-one (19b). Brown liquid (68 mg, 87%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 8.5 Hz, 1H), 7.57 – 7.54 (m, 1H), 7.50 – 7.47 (m, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 6.98 (s, 1H), 4.68 (q, J = 7.0 Hz, 1H), 2.32 (s, 3H), 1.73 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 152.0, 138.5, 138.1, 137.9, 131.6, 130.8, 129.6, 128.8, 127.8, 127.2, 126.7, 125.6, 48.3, 22.5, 21.2; IR $(KBr)_{vmax}$ 2972, 2859, 1726 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{16}OS_2$ ($M + H^+$) 313.0715; Found 313.0713.



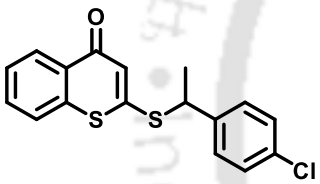
2-((1-(*m*-tolyl)ethyl)thio)-4*H*-thiochromen-4-one (19c). Brown liquid (66 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.43 (m, 1H), 7.55 (dd, J = 7.2, 1.9 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.21 (d, J = 7.2 Hz, 3H), 7.08 (d, J = 6.6 Hz, 1H), 6.99 (s, 1H), 4.68 (q, J = 7.0 Hz, 1H), 2.34 (s, 3H), 1.74 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 151.9, 141.0, 138.7, 138.5, 131.6, 130.9, 130.8,

128.9, 128.8, 128.0, 127.8, 126.8, 125.6, 124.4, 48.5, 22.6, 21.5; IR $(KBr)_{vmax}$ 2961, 2853, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{16}OS_2$ ($M + H^+$) 313.0715; Found 313.0708.

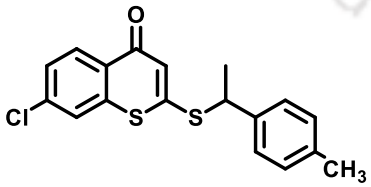
2-((1-(4-fluorophenyl)ethyl)thio)-4*H*-thiochromen-4-one (19d). Brown liquid (60 mg, 76%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.43 (m, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 7.36 (dd, J = 8.6, 5.4 Hz, 2H), 7.03 – 6.98 (m, 3H), 4.68 (q, J = 7.0 Hz, 1H), 1.73 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 163.6, 161.1, 151.1, 138.5, 137.1, 131.7, 129.0, 129.0, 128.9, 127.9, 127.6, 125.6, 116.0, 115.7, 48.0, 22.6; IR $(KBr)_{vmax}$ 2964, 2853, 1722 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{13}FOS_2$ ($M + H^+$) 317.0465; Found 317.0480.



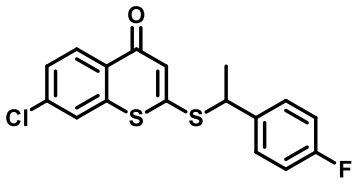
2-((1-(4-chlorophenyl)ethyl)thio)-4*H*-thiochromen-4-one (19e). Brown liquid (62 mg, 75%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 6.98 (s, 1H), 4.65 (q, J = 7.1 Hz, 1H), 1.72 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 150.9, 139.9, 138.4, 133.9, 131.7, 130.9, 129.1, 128.9, 128.7, 128.0, 127.6, 125.6, 48.0, 22.5; IR $(KBr)_{vmax}$ 2961, 2853, 1724 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{13}ClOS_2$ ($M + H^+$) 333.0169; Found 333.0187.



7-chloro-2-((1-(*p*-tolyl)ethyl)thio)-4*H*-thiochromen-4-one (19f). Brown liquid (73 mg, 85%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 8.6 Hz, 1H), 7.47 (s, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 7.7 Hz, 2H), 6.94 (s, 1H), 4.66 (q, J = 7.0 Hz, 1H), 2.32 (s, 3H), 1.72 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 151.8, 139.8, 138.3, 138.0, 137.9, 130.3, 129.6, 129.2, 128.4, 127.2, 126.8, 124.9, 48.5, 22.6, 21.2;IR $(KBr)_{vmax}$2969, 2872, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{15}ClOS_2$ ($M + H^+$) 347.0326; Found 347.0315.

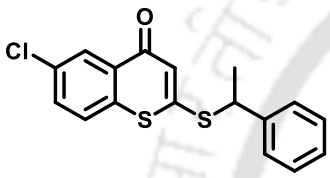


7-chloro-2-((1-(4-fluorophenyl)ethyl)thio)4*H*-thiochromen-4-one (19g). Brown liquid



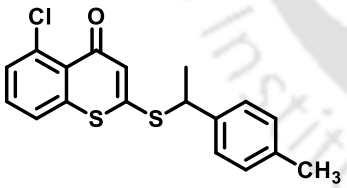
(69 mg, 79%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 8.6 Hz, 1H), 7.47 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 8.3, 5.2 Hz, 2H), 7.01 (t, J = 8.5 Hz, 2H), 6.94 (s, 1H), 4.66 (q, J = 7.0 Hz, 1H), 1.72 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.4, 161.4, 151.0, 139.7, 138.5, 136.9, 136.8, 130.4, 129.2, 129.0, 129.0, 128.9, 128.6, 127.6, 124.9, 116.0, 115.8, 48.1, 22.6; IR $(KBr)_{vmax}$ 2969, 2872, 1721 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{12}ClFOS_2$ ($M + H^+$) 351.0075; Found 351.0059.

6-chloro-2-((1-phenylethyl)thio)4*H*-thiochromen-4-one (19h). Brown liquid (68 mg, 82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 2.4 Hz, 1H), 7.52 (dd, J = 8.6, 2.4 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 7.0 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 6.97 (s, 1H), 4.68 (q, J = 7.0 Hz, 1H), 1.75 (d, J = 7.0 Hz, 3H);

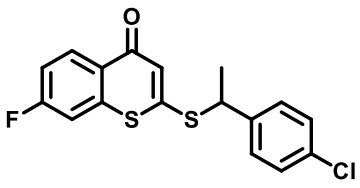


^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 152.1, 141.0, 136.6, 134.4, 132.0, 132.0, 129.0, 128.4, 128.2, 127.3, 127.0, 126.7, 48.8, 22.5; IR $(KBr)_{vmax}$ 2960, 2869, 1722 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{13}ClOS_2$ ($M + H^+$) 333.0169; Found 333.0175.

5-chloro-2-((1-(*p*-tolyl)ethyl)thio)-4*H*-thiochromen-4-one (19i). Brown liquid (75 mg, 87%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 5.2, 3.8 Hz, 1H), 7.38 – 7.37 (m, 2H), 7.27 (d, J = 2.1 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 6.88 (s, 1H), 4.64 (q, J = 7.0 Hz, 1H), 2.32 (s, 3H), 1.72 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 148.7, 141.4, 138.1, 138.0, 136.4, 131.6, 130.9, 129.6, 128.3, 127.8, 127.2, 124.6, 48.3, 22.6, 21.2; IR $(KBr)_{vmax}$ 2968, 2854, 1722 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{15}ClOS_2$ ($M + H^+$) 347.0326; Found 347.0325.

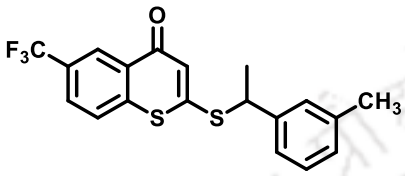


2-((1-(4-chlorophenyl)ethyl)thio)-7-fluoro-4*H*-thiochromen-4-one (19j). Brown liquid (70 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, J = 8.9, 5.8 Hz, 1H), 7.33 – 7.28 (m, 4H), 7.17 (dd, J = 8.4, 6.0 Hz, 2H), 6.93 (s, 1H), 4.63 (q, J = 7.0 Hz, 1H), 1.71 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 165.1, 163.1, 150.6, 140.5, 140.4, 139.7,



133.9, 131.9, 131.8, 129.1, 128.6, 127.6, 116.6, 116.4, 111.7, 111.5, 48.1, 22.4; IR (KBr)$_{vmax}$ 2970, 2852, 1723 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{12}ClFOS_2$ (M + H$^+$) 351.0075; Found 351.0050.

2-((1-(*m*-tolyl)ethyl)thio)-6(trifluoromethyl)-4*H*-4-one (19k). Brown liquid (79 mg, 84%);



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.24 – 7.18 (m, 3H), 7.09 (d, J = 7.3 Hz, 1H), 7.00 (s, 1H), 4.67 (q, J = 7.0 Hz, 1H), 2.34 (s, 3H), 1.74 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 152.7, 141.9, 140.7, 138.7, 130.9, 130.3, 130.0, 129.1, 128.9, 127.9, 127.6, 127.6, 126.5, 126.4, 126.2, 126.2, 124.3, 48.6, 22.6, 21.5; IR (KBr)$_{vmax}$ 2963, 2853, 1718 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{15}F_3OS_2$ (M + H$^+$) 381.0589; Found 381.0590.

Figure 4.2.a. ^{1}H NMR of 2-((1-phenylvinyl)thio)-4*H*-thiochromen-4-one (15a)

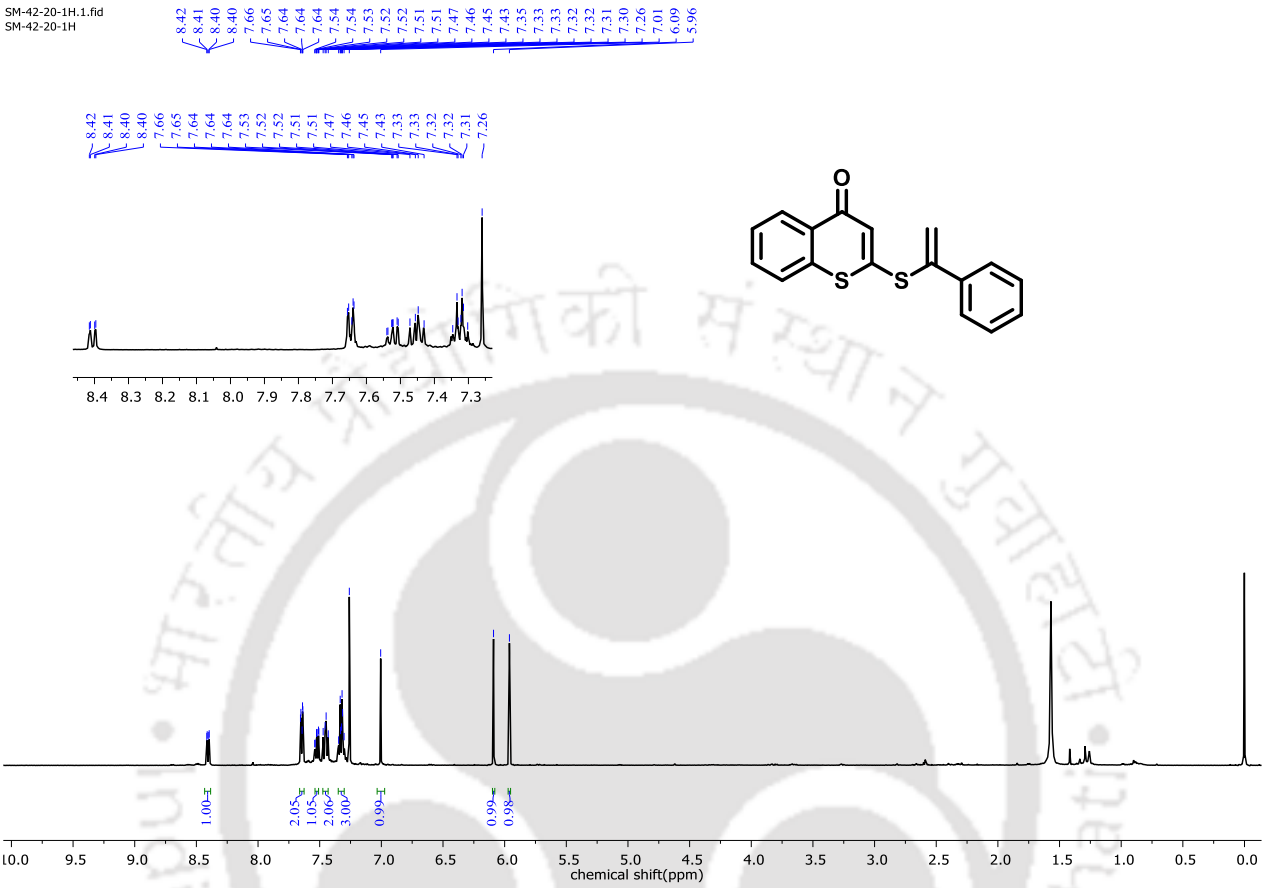


Figure 4.2.b. ^{13}C NMR of 2-((1-phenylvinyl)thio)-4*H*-thiochromen-4-one (15a)

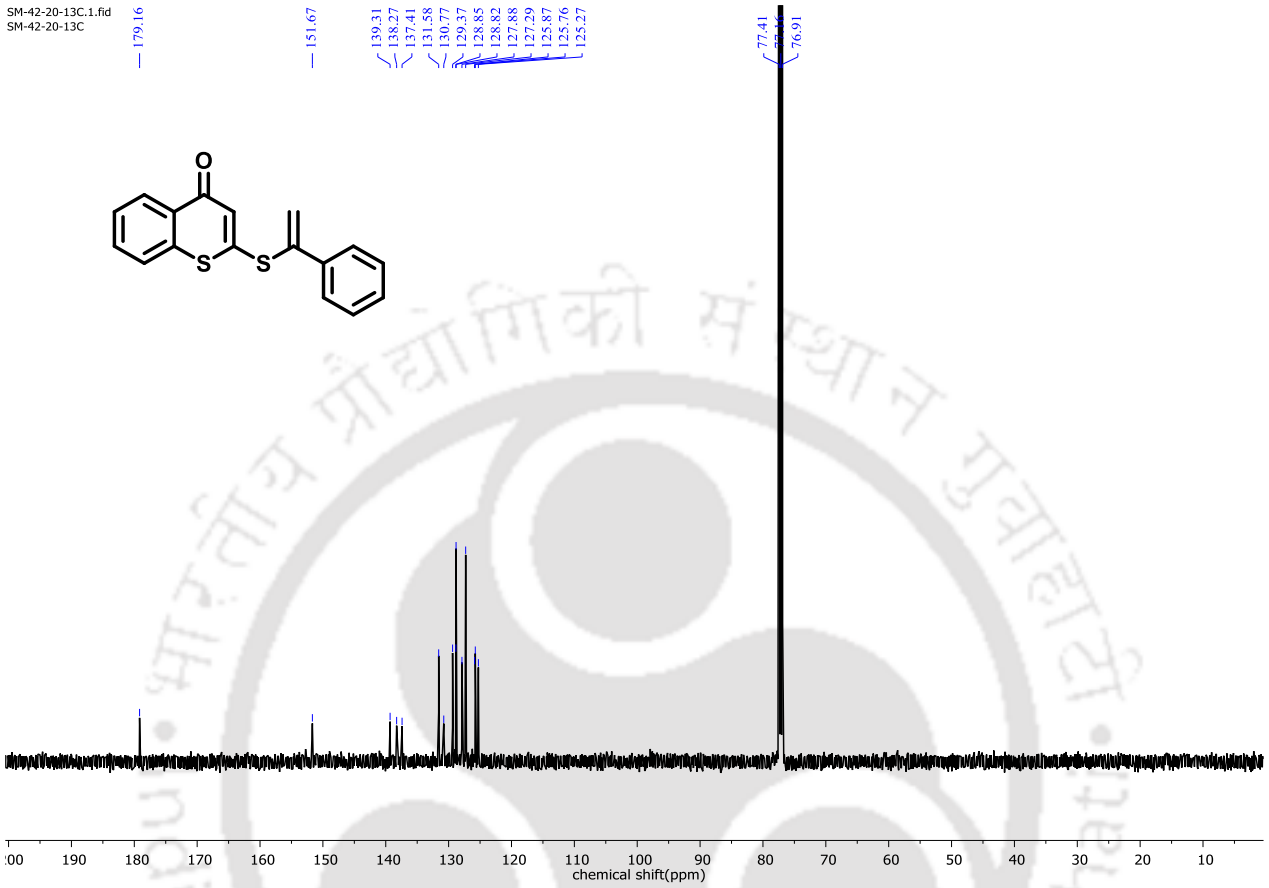


Figure 4.2.c. HRMS of 2-((1-phenylvinyl)thio)-4*H*-thiochromen-4-one (15a)

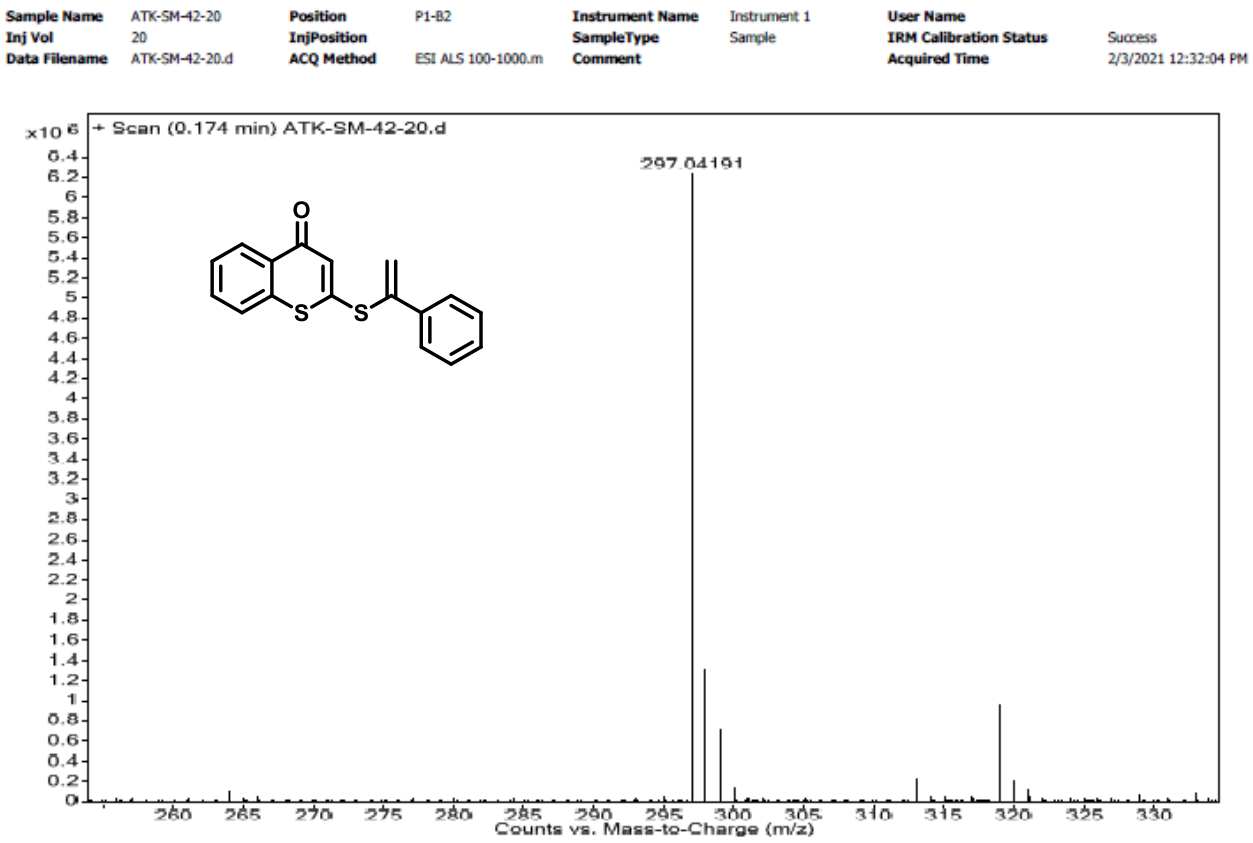


Figure 4.3.a. ^{1}H NMR of 2-((1-(3-ethynylphenyl)vinyl)thio)-7-fluoro-4*H*-thiochromen-4-one (15m)

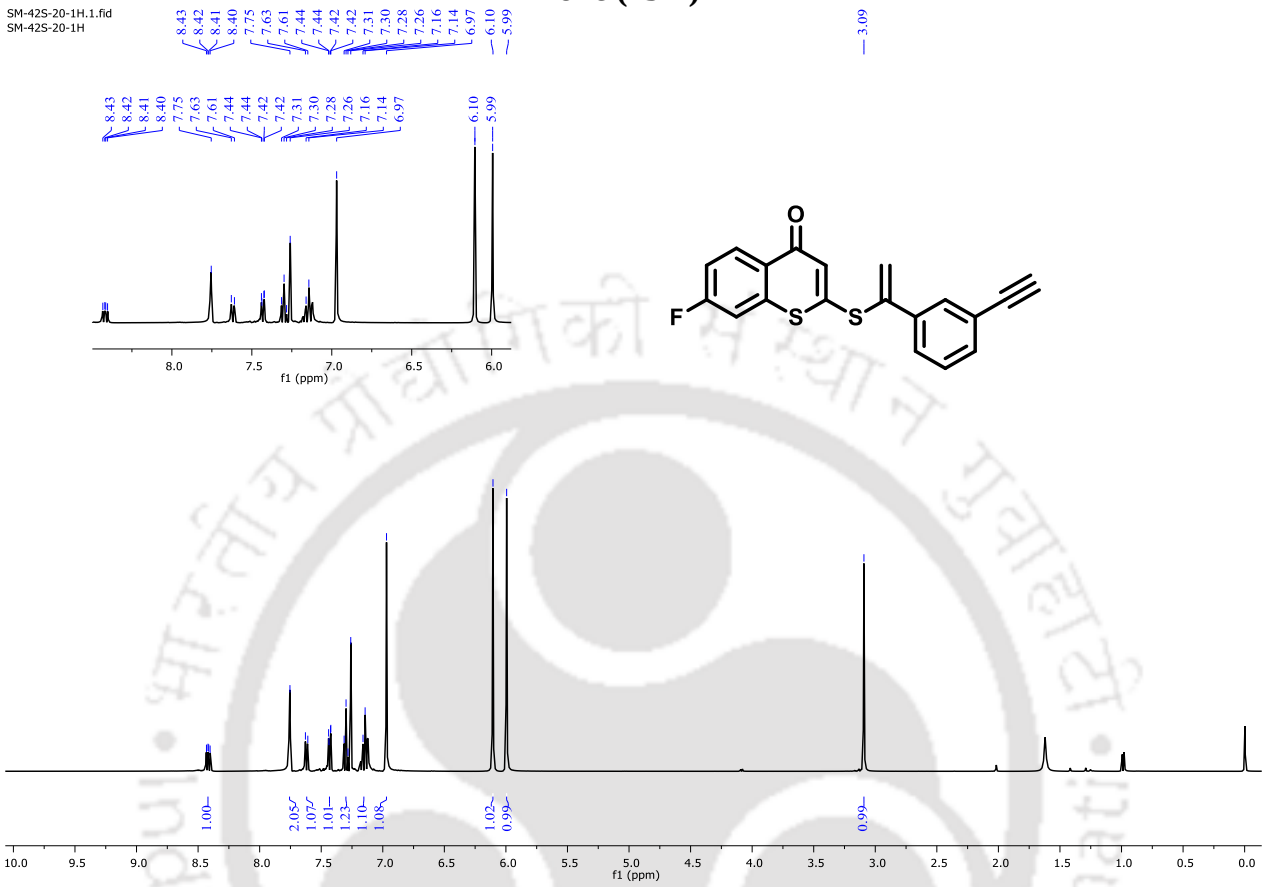


Figure 4.3.b. ^{13}C NMR of 2-((1-(3-ethynylphenyl)vinyl)thio)-7-fluoro-4*H*-thiochromen-4-one (15m)

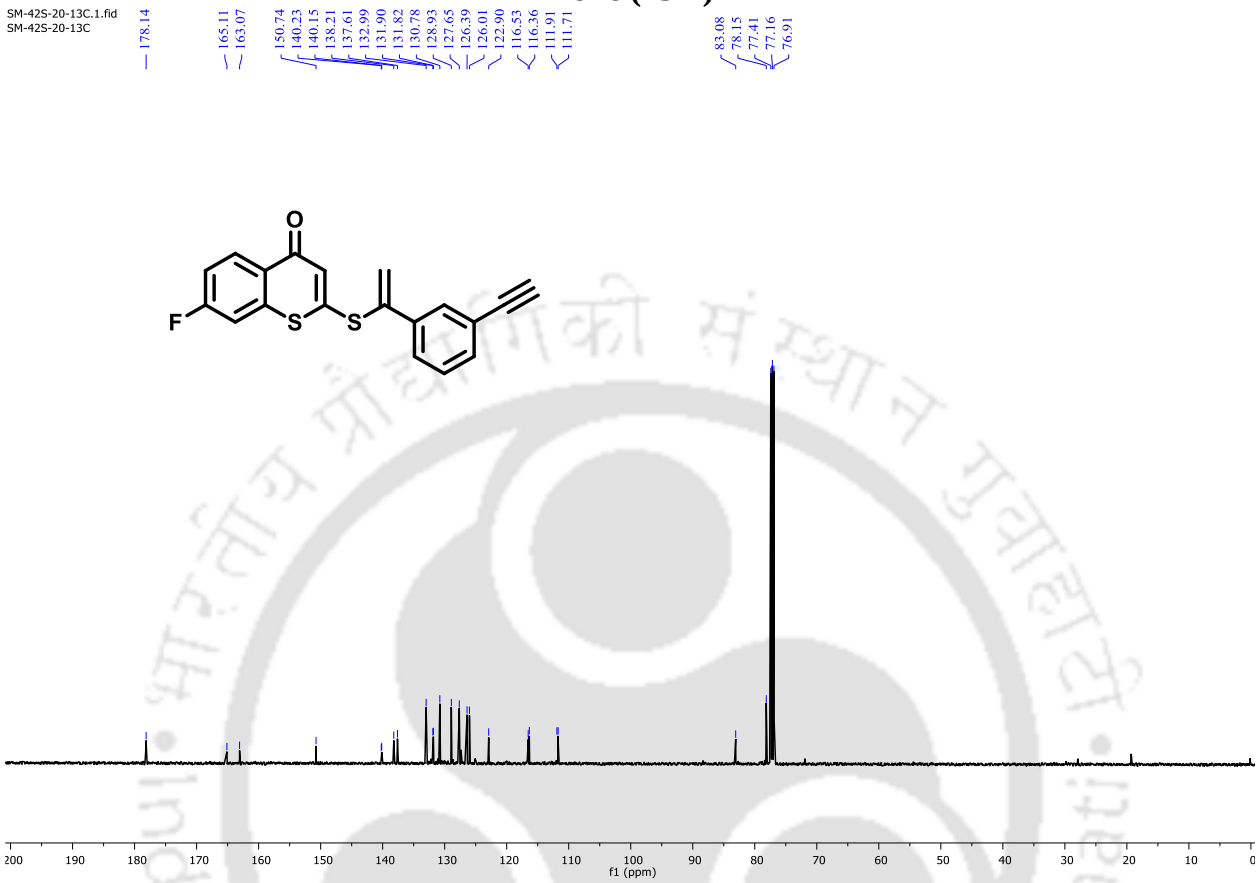


Figure 4.3.c. HRMS of 2-((1-(3-ethynylphenyl)vinyl)thio)-7-fluoro-4*H*-thiochromen-4-one (15m)

Sample Name	SAMPLE 14	**Position**	P2-B5	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	ATK-SM-42S-20.d	**ACQ Method**	ESI ALS 100-1000.m	**Comment**		**Acquired Time**	2/1/2021 7:18:05 PM

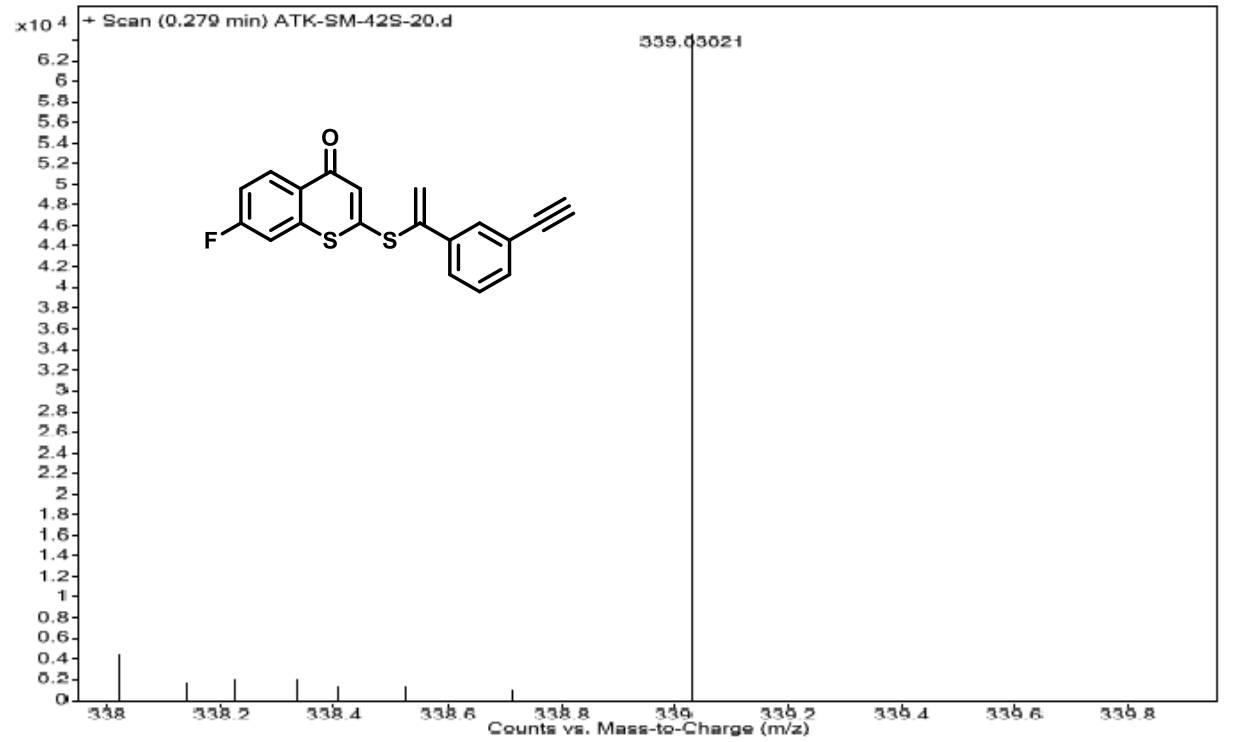


Figure 4.4.a. ^{1}H NMR of (*Z*)-5-chloro-2-((2-(pyridin-2-yl)vinyl)thio)-4*H*-thiochromen-4-one (17d)

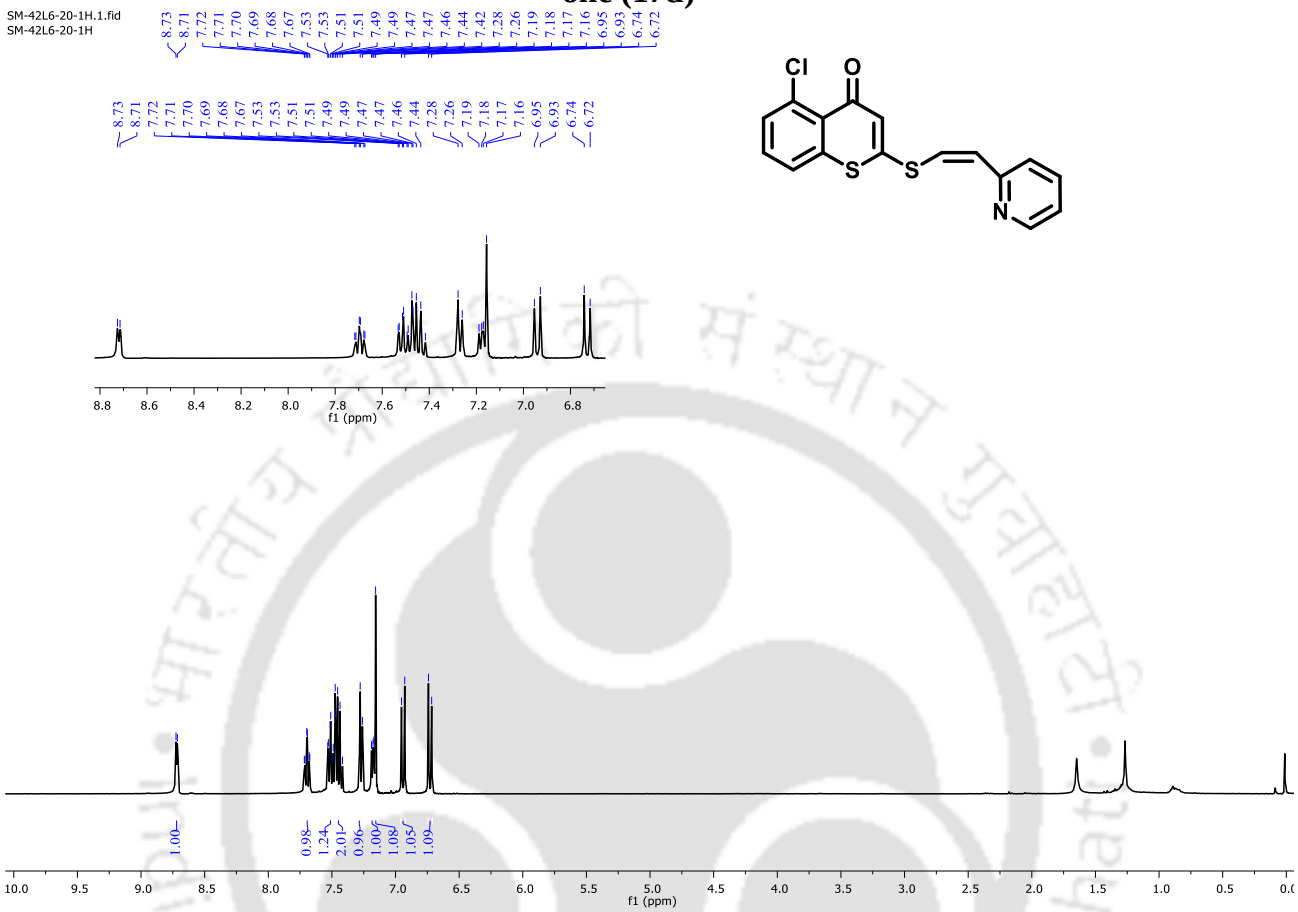


Figure 4.4.b. ^{13}C NMR of (*Z*)-5-chloro-2-((2-(pyridin-2-yl)vinyl)thio)-4*H*-thiochromen-4-one (17d)

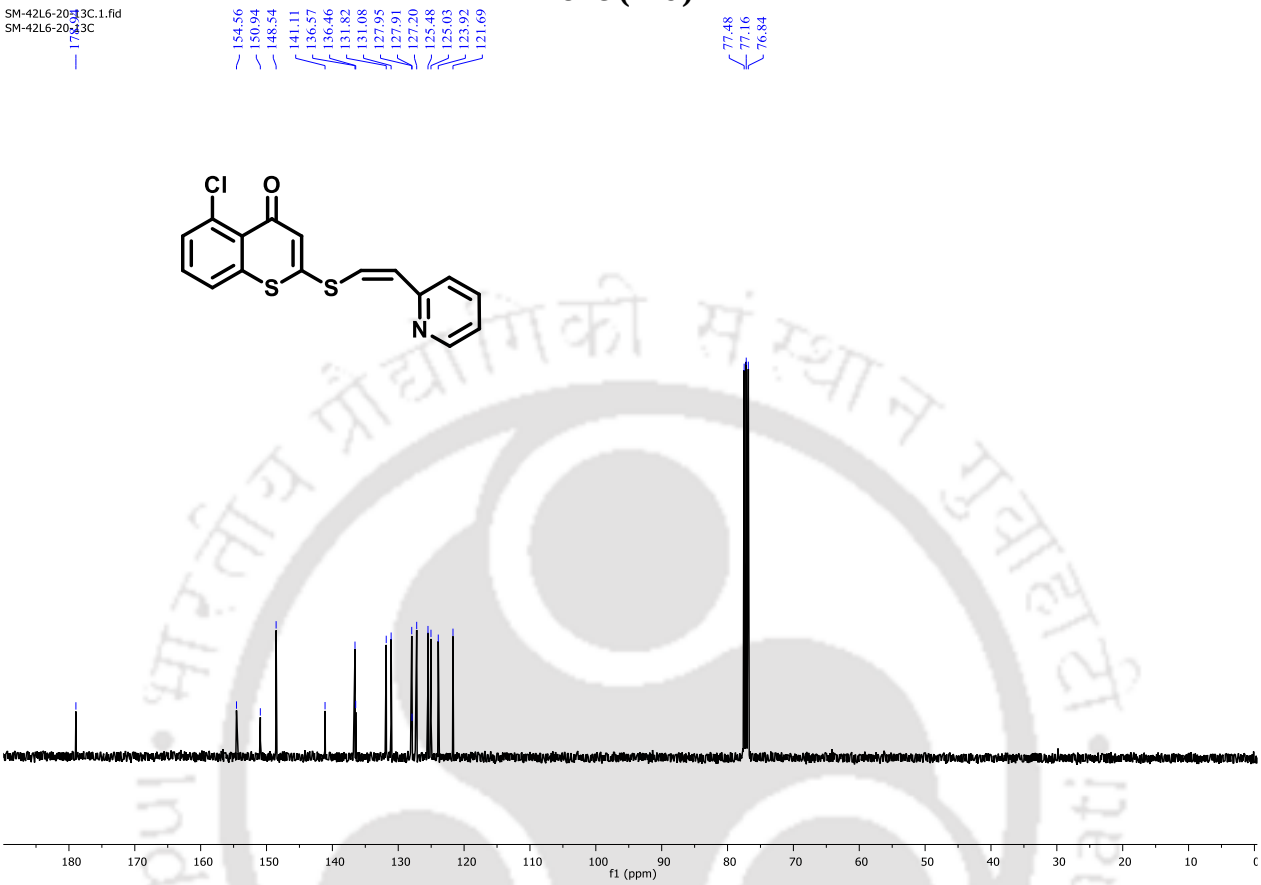


Figure 4.4.c. HRMS of (*Z*)-5-chloro-2-((2-(pyridin-2-yl)vinyl)thio)-4*H*-thiochromen-4-one (17d)

Sample Name	SAMPLE	**Position**	P1-C5	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SM-42L6R-20.d	**ACQ Method**	ESI ALS 100-500.m	**Comment**		**Acquired Time**	2/25/2021 12:23:15 PM

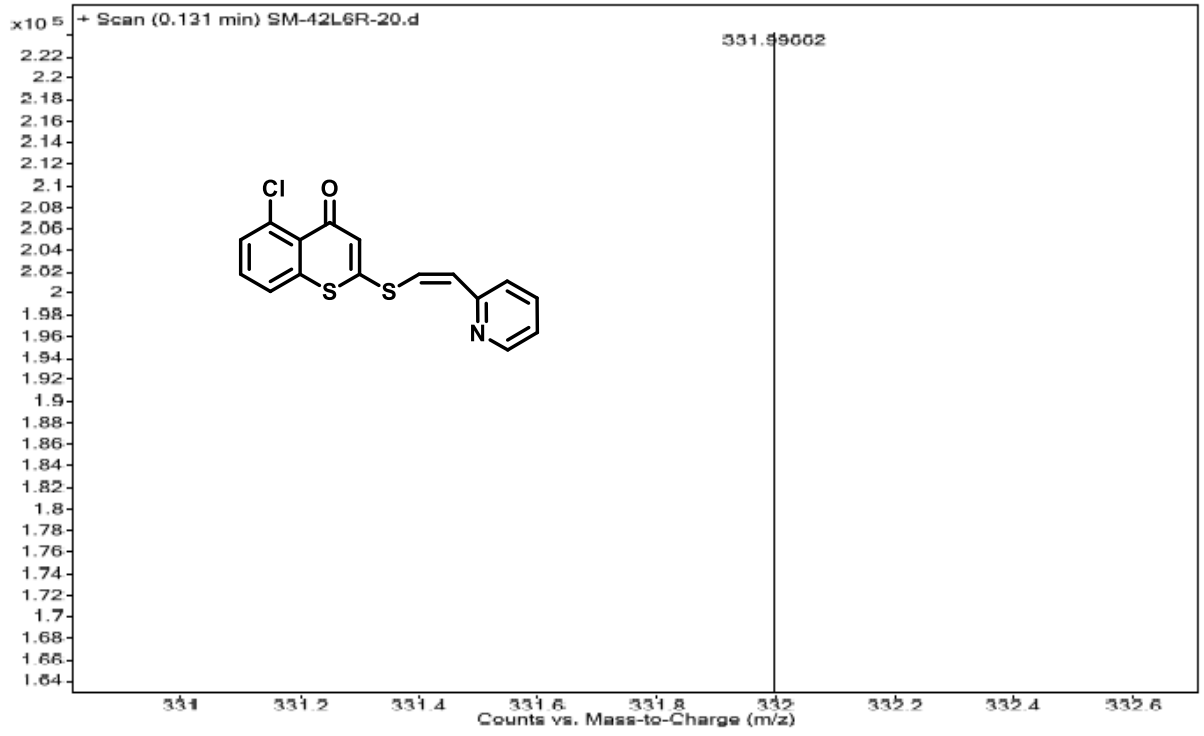


Figure 4.5.a. ^{1}H NMR of 2-((1-phenylethyl)thio)-4*H*-thiochromen-4-one (19a)

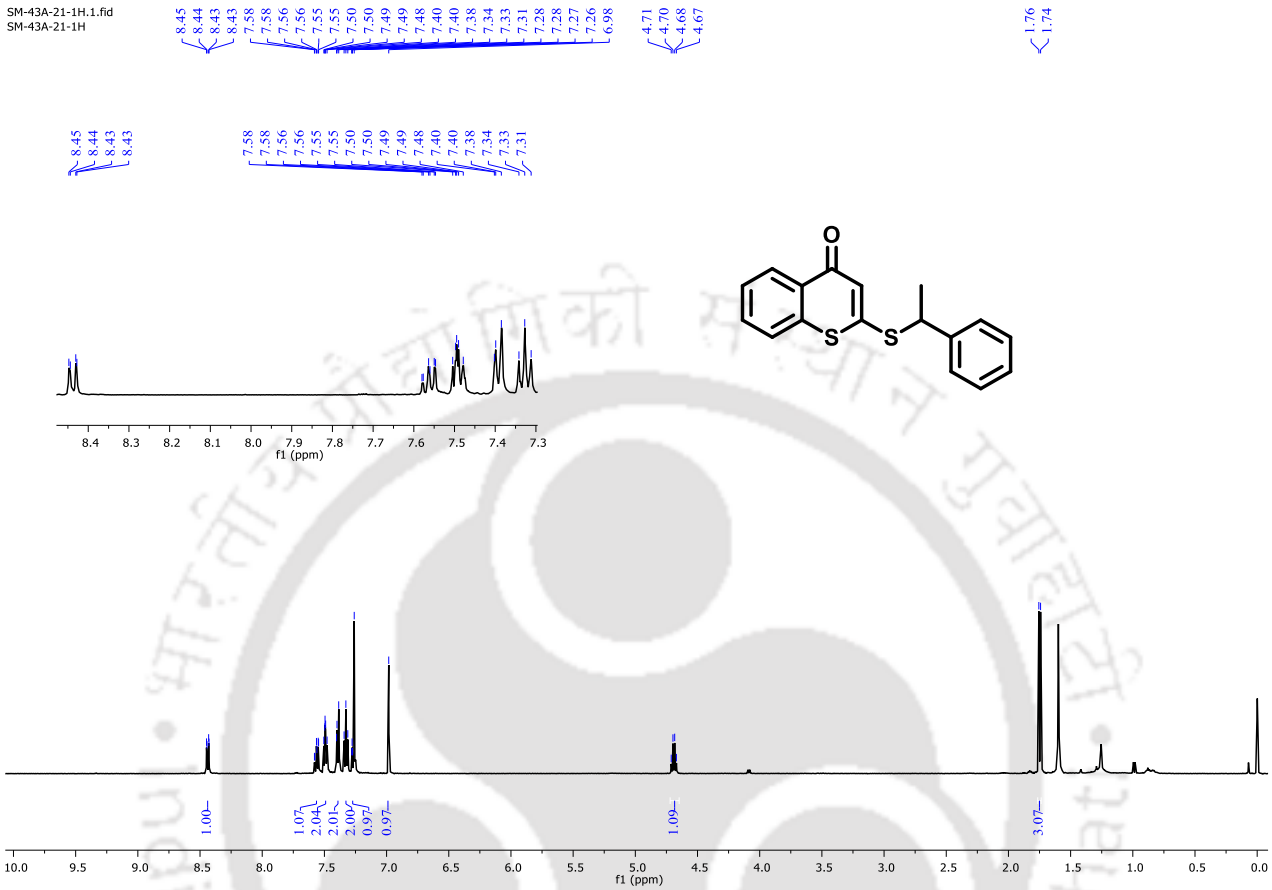


Figure 4.5.b. ^{13}C NMR of 2-((1-phenylethyl)thio)-4*H*-thiochromen-4-one (19a)

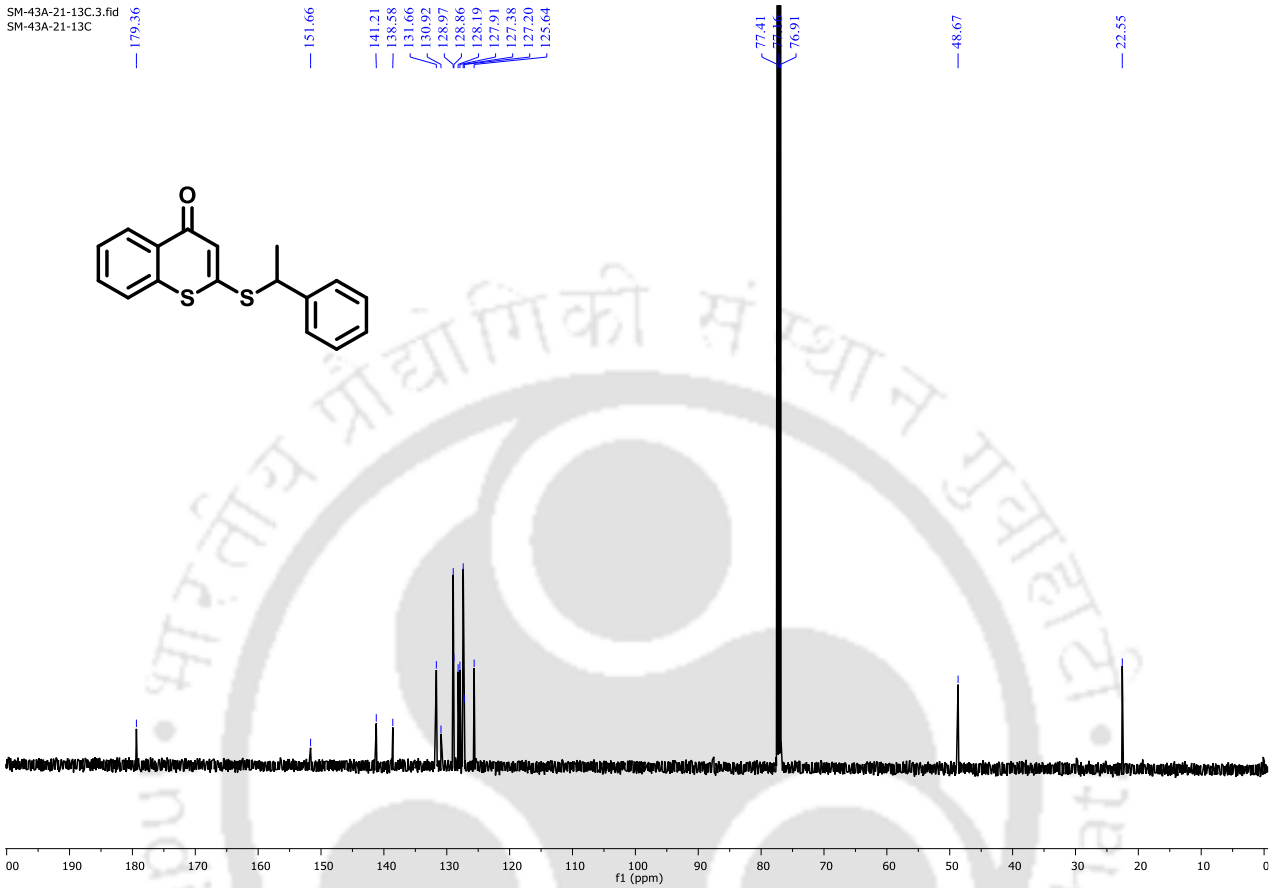
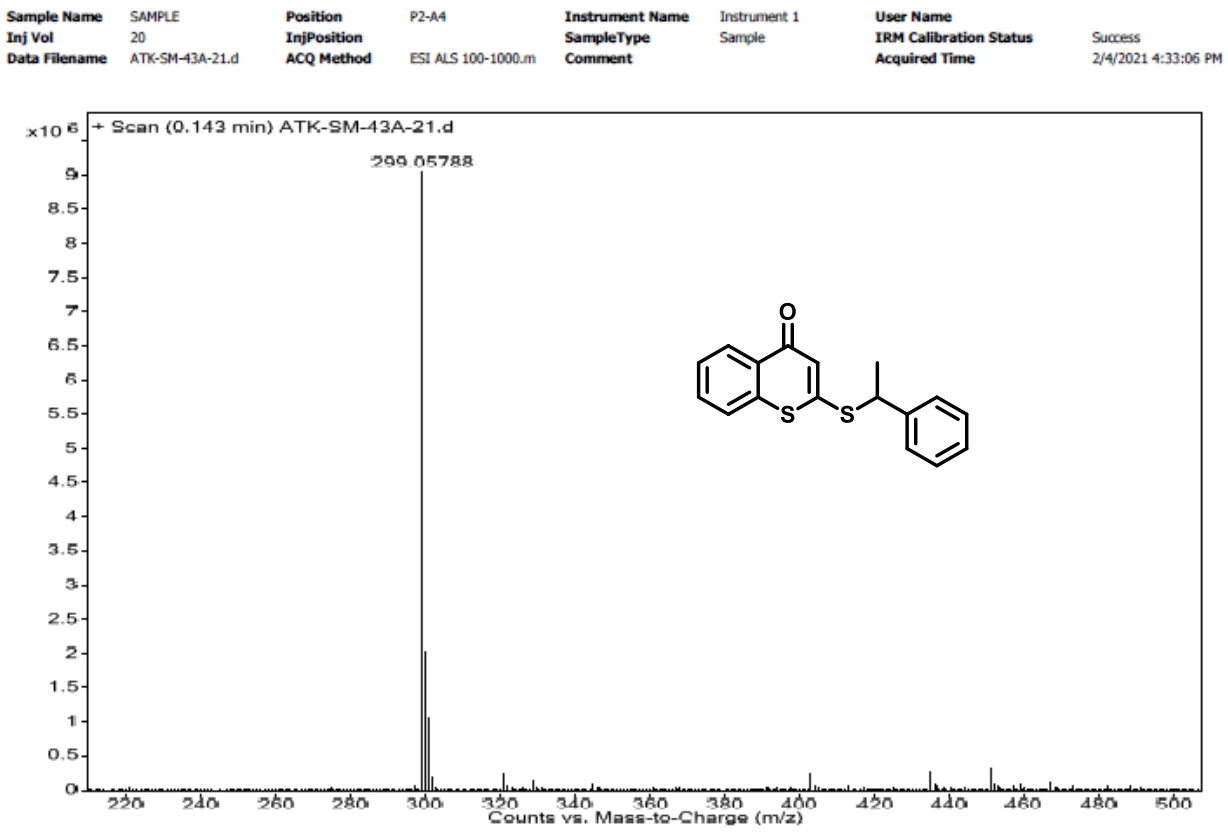


Figure 4.5.c. HRMS of 2-((1-phenylethyl)thio)-4*H*-thiochromen-4-one (19a)



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CHAPTER V

Cu(I)-catalyzed C–H functionalization and cross-dehydrogenative *C–S* coupling reactions of 4-hydroxydithiocoumarins, aryl acetylenes and dimethylsulfoxide and their anticancer activity study

Introduction

Results & Discussion

Experimental Section

5.1. Introduction

1,4-Oxathiin is an important class of heterocyclic compounds, which attracts synthetic interest because of their numerous potential activities. It is a highly demanding structural motif in the agricultural, chemical, and pharmaceutical research fields (Figure 5.1).[1] For example, carboxin and its sulfone derivative having 1,4-oxathiin moiety exhibit antifungal activity and are used as a pesticide,[1a] respectively. Similarly, another 1,4-oxathiin derivative namely isovanillyl shows an artificial sweetening property.[1b] Likewise, phenoxathiin, another fused 1,4-oxathiin derivative, displays antiviral activity[1d] and some of their derivatives are also used in bioimaging.[1e]

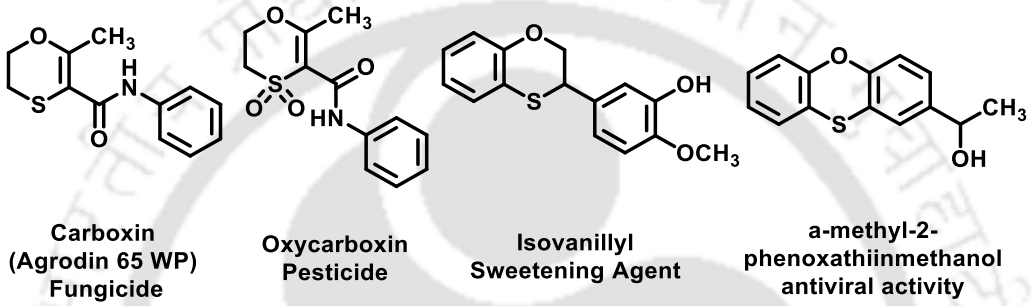
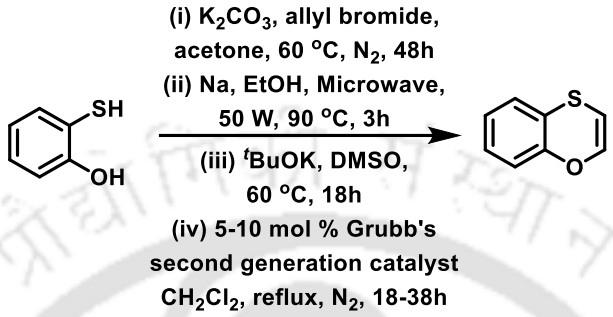


Figure 5.1. Some examples of the biologically active compound having a 1,4-oxathiin skeleton

Therefore, the synthesis of oxathiin derivatives is of significant attention. Generally, 1,4-Oxathiin derivatives have been synthesized typically either by multi-step sequential synthesis[2] or 2-marcaptophenol,[3] as a starting material.

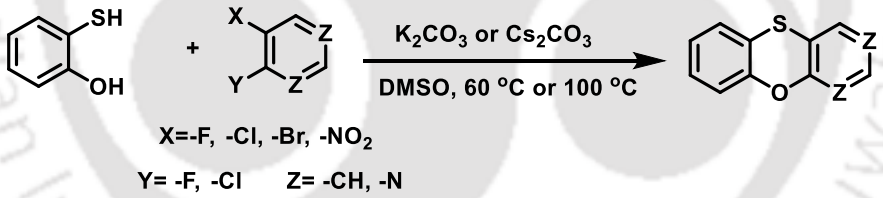
5.2. Synthesis of 1,4-Oxathiin

Morgans *et al.* reported the synthesis of 1,4-oxathiin derivative from 2-mercapto phenol *via* multi-step reaction.[2] 1,4-Oxathiin was synthesized from the corresponding *bis*-allyloxy precursors by way of an initial isomerization to the *bis*-vinyloxy compounds, followed by a ring-closing metathesis using the second-generation Grubbs' catalyst (G2).



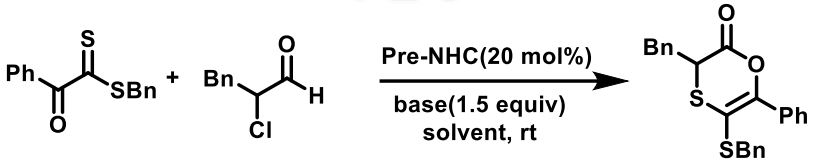
Scheme 5.1. Synthesis of 1,4-oxathiin from 2-mercaptophenol

Ma *et al*. reported the synthesis of phenoxathiine from 2-mercaptophenol under transition metal-free conditions.[3] 2-Marcaptophenol reacted with 1,2-dihaloarenes or 1-halo-2-nitroarenes reacted with to afford phenoxathiine. Interestingly, an electron-withdrawing group containing haloarene plays an important role in nucleophilic substitution, so it is worked for synthesizing the desired product.



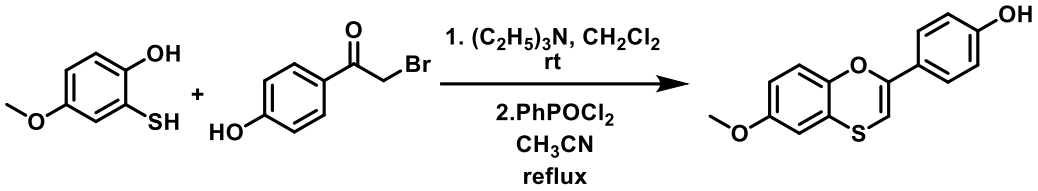
Scheme 5.2. Synthesis of phenoxathiin from 2-mercaptophenol

Wang *et al*. reported the synthesis of 1,4-oxathiin derivatives *via* [4+2] annulations of α-chloroaldehydes and dithioesters.[4] The [4+2] annulation occurred to provide 1,4-oxathiin in the presence of an *N*-heterocyclic carbene (NHC) catalyst.



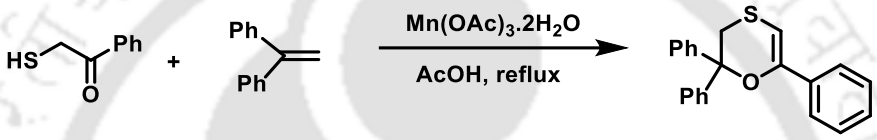
Scheme 5.3. Synthesis of 1,4-oxathiin derivative *via* [4+2] annulations of α-chloroaldehydes and dithioesters

Lai *et al*. reported the synthesis of 1,4-oxathiin from 2-mercaptophenol and 2-bromo acetophenone *via* multistep reaction.[5] In this communication, they focused to compare the capabilities of *O* and *S* atoms to trap radicals and to inhibit DNA oxidation.



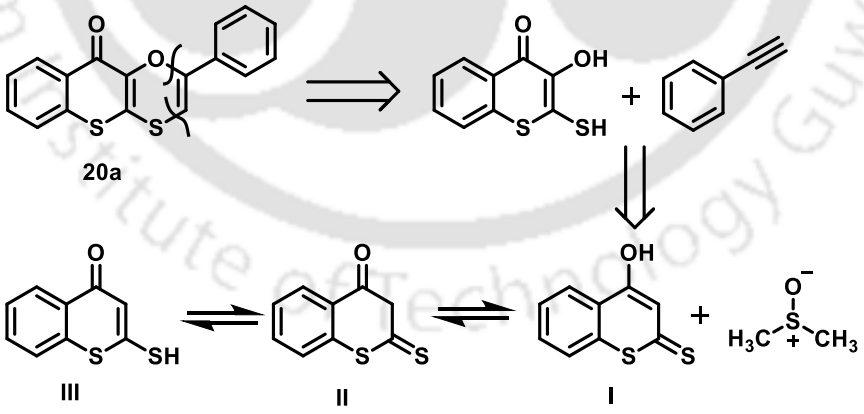
Scheme 5.4. Synthesis of 1,4-oxathiin from 2-mercaptophenol

Nguyen *et al*. demonstrated the synthesis of 1,4-oxathiin from 1,1-diphenylethene and thioglycolic acid using Mn(II)acetate.[6] The reaction might be involved in the formation of a carbocation and followed by cyclization to generate the l,4-oxathiin.



Scheme 5.5. Synthesis of 1,4-oxathiin from 1,1-diphenylethelene and thioglycolic acid

Recently we have achieved the synthesis of numerous biologically active compounds[7] from 4-hydroxydithiocoumarin through cross-dehydrogenative coupling reaction between amines and thiols for the formation of *S-N*, *S-S*, and *S-C* bonds.[7a]



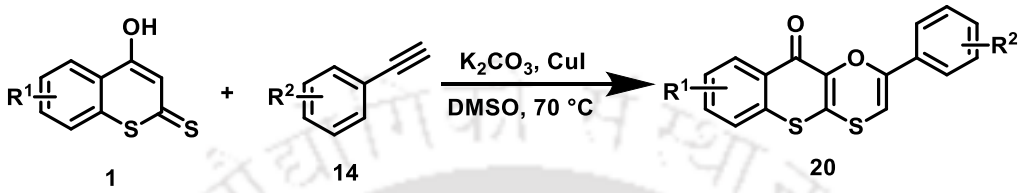
Scheme 5.6. Retrosynthetic analysis of 1,4-oxathiin derivative

4-Hydroxydithiocoumarin is a potent molecule and it can exist in three tautomeric forms I, II (2-thioxothiochroman-4-one), and III (2-mercapto-4*H*-thiochromen-4-one), respectively. Using the reactivity of 4-hydroxydithiocoumarin, Majumdar *et al.* and our research group have demonstrated the synthesis of various new heterocyclic

compounds[8] as well as other bioactive molecules.[7] Conceiving an idea, the synthesis of a new class of 1,4-oxathiin can be achieved in one-pot if 3-position of 4-hydroxydithiocoumarin can be hydroxylated with a suitable reagent, which is not reported earlier, followed by regioselective hydrothiolation with aryl acetylenes and concomitant cyclization. The proposed retrosynthetic analysis is shown in Scheme 5.6. In organic synthesis, the selective hydroxylation of arene is one of the difficult tasks.[9] Nowadays, C-H functionalization has been established by using various noble metals as catalysts.[10] Among various metals, copper salts have been extensively used in C-H functionalization due to its easy availability, economic viability, and less toxicity.[11] Xu and his research group have reported a unique protocol for the hydroxylation at the ortho-position after *S-C* bond formation using thiophenol and aryl iodide in presence of 10 mol% CuI, 10 mol% ligand, and 2 equivalents base in an inert atmosphere.[12a] Similarly, a novel and elegant method for the synthesis of catechol from cyclohexanone was developed by Liang *et al*.[12b] From these two reported reactions, we envisioned that the hydroxyl group might be introduced at the C-3 position of 4-hydroxydithiocoumarin since two possible resonating structures II and III have prerequisite functionalities for the fulfillment of hydroxylation.

5.3. Results and Discussion

Taking cues from the reaction behavior between thiols and terminal alkynes[13-15] and hydroxylation[12] as well as our earlier experience on the reactivity of 4-hydroxydithiocoumarin, we wish to report here the hitherto unreported 1,4-oxathiin derivatives from 4-hydroxydithiocoumarin and aryl acetylenes in the presence of 10 mol% CuI in DMSO (Scheme 5.7).

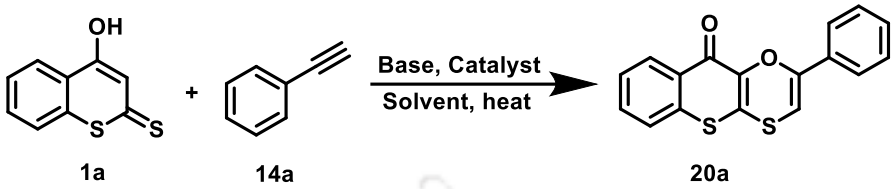


Scheme 5.7. Synthesis of 1,4-oxathiin derivatives from 4-hydroxydithiocoumarin

For our present study, a wide variety of 4-hydroxydithiocoumarins (**1a-f**) was prepared using substituted acetophenones and carbon disulfide by following the reported procedure.[16] For optimization of the reaction conditions, we have chosen 4-hydroxydithiocoumarin **1a** and phenylacetylene **14a** as the model substrates. To find out a suitable reaction condition, a mixture of 4-hydroxydithiocoumarin (0.25 mmol), phenylacetylene (0.25 mmol), potassium carbonate (0.50 mmol), and 5 mol% CuCl was dissolved in 1 mL of DMSO and it was heated with constant stirring in a preheated oil bath at 70 ˚C (Table 5.1, entry 1). After completion of the reaction, usual work-up followed by purification, the product **20a** was isolated in 40% yield along with a trace amount of undesired product 1,4-diphenylbuta-1,3-diyne. In the IR spectrum, the compound **20a** shows a characteristic peak at 1720 cm^{-1} for the presence of the C=O group and no absorption peak at 2100-2200cm^{-1} due to the presence of the C≡C group. This indicates that the product alkynyl sulfide is not formed by a dehydrogenative coupling reaction. In the ^{1}H NMR spectrum, it gives a characteristic signal at δ 5.9 ppm for a single proton instead of the expected signal for the C3 hydrogen of 4-hydroxydithiocoumarin appeared at δ 6.9-7.0 ppm. From this observation, it is clear that C3-H disappeared from the product due to functionalization. From HRMS, we have observed that the molecular mass of **20a** is 311.0194 instead of the expected product for the reductive hydrothiolation product, which is expected at 297.0402. Since the disappearance of C3-H in the ^{1}H NMR spectrum as well as increasing the molar mass of 14 units, we thought C-H functionalization has occurred at C-3 as -OH group. This is possible only for hydroxylation from DMSO. Finally, the

structure of **20a** was ascertained as a 1,4-oxathiine derivative from the ^{1}H NMR, ^{13}C NMR spectrum, and HRMS.

Table 5.1. Optimization of the reaction conditions[a,b]



1a 14a 20a

Entry	Base	Catalyst	Mol (%)	Solvent	Time (h)	% Yield[b]
01	K_2CO_3	CuCl	5	DMSO	1	40
02	K_2CO_3	CuBr	5	DMSO	1	45
03	K_2CO_3	CuI	5	DMSO	0.5	60
04	**K_2CO_3**	**CuI**	**10**	**DMSO**	**0.5**	**85**
05	K_2CO_3	CuI	20	DMSO	0.5	86
[c]06	K_2CO_3	CuI	10	DMSO	0.5	70
07	K_2CO_3	CuI	10	DMF	0.7	30
08	K_2CO_3	CuI	10	CH_3CN	12	-
09	K_2CO_3	CuI	10	Toluene	12	-
10	K_2CO_3	CuI	10	H_2O	12	-
11	Na_2CO_3	CuI	10	DMSO	0.75	35
12	Cs_2CO_3	CuI	10	DMSO	0.75	20
13	Pyridine	CuI	10	DMSO	12	-

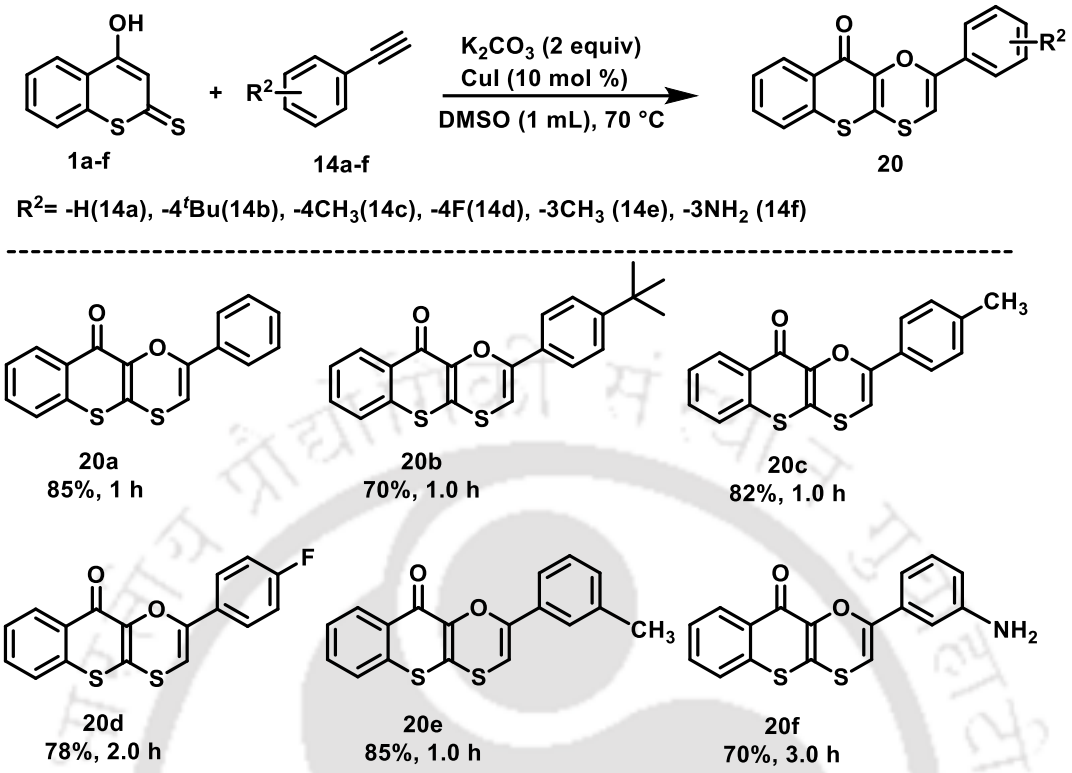
[a]All the reactions were carried out by employing 4-hydroxydithiocoumarin **1a** (0.25 mmol), phenylacetylene **14a** (0.25 mmol) in 1mL of solvent at 70 °C in presence of 2 equivalents of base. [b]Isolated yield and it was calculated based on the phenylacetylene consumed for the formation of the desired product. [C]3 equivalents of the base were used.

As per our anticipation, the product was 1,4-oxathiin instead of the probable cross-dehydrogenative hydrothiolation product.[15] After obtaining the desired product, we are

encouraged further to examine the effectiveness of various Cu(I) salt. Then we have carried out two reactions with CuBr and CuI under similar reaction conditions (Table 5.1, entries 2 and 3). The reaction time is reduced and the yield was increased from 45% to 60% in the case of CuI. To increase the yield further, the reaction is performed with 10 mol% CuI (Table 5.1, entry 4) by keeping all other reactants the same at identical reaction conditions. It was noted that the yield was increased significantly from 60% to 85%, whereas further increasing of catalyst to 20 mol% gave no improvement of the yield (Table 5.1, entry 5). To enhance the yield of the reaction, we have performed one similar reaction with 3 equivalents of K_2CO_3 and 10 mol% CuI, we got the desired product from 85% to 70% (Table 5.1, entry 6). To find out the effectiveness of various solvents, several reactions were examined in DMF, CH_3CN, toluene, and water (Table 5.1, entries 7-10). In DMF, it gave a lower yield whereas no desired product is formed in other solvents. It is accomplished from solvent optimization, DMF,[17] DMSO[18] can donate its oxygen for the reaction. To find out the efficacy of other bases, we also carried out the reaction in the presence of 2 equivalents Na_2CO_3, Cs_2CO_3, and pyridine, respectively under identical reaction conditions (Table 5.1, entries 11-13). Though we have obtained the desired product in lower yield in other carbonate bases, no product is formed while using pyridine as a base. From all these observations, it is clear that the most suitable reaction condition is 10 mol% CuI and 2 equivalents K_2CO_3 in terms of reaction time and yield.

After optimization of reaction conditions, the scope and generality of the reaction procedure were explored with various substituted 4-hydroxydithiocoumarins **1** and aryl acetylenes **14**, which are summarized in Table 5.2 & 5.3. 4-Hydroxydithio-coumarin on reaction with *p*-substituted aryl alkynes having substituents t*ert*-Bu, -CH_3, -F group afforded the desired 1,4-oxathiin derivatives **20b-d** in 70-82% yield. The reaction is well tolerated in the presence of the bulky *tert*-butyl group present in the phenylacetylene. Then the reaction is carried out with 3-ethynyltoluene to give the product **20e** in 85% yield. To examine competitiveness between *S-N* bond formation *versus S-C* bond formation, we have performed the reaction with 3-ethynylaniline and the desired 1,4-oxathiin derivative **20f** was isolated in 70% yield. From this observation, it is noteworthy to mention that *S-C* bond formation is chemoselectively preferred over *S-N* bond formation.

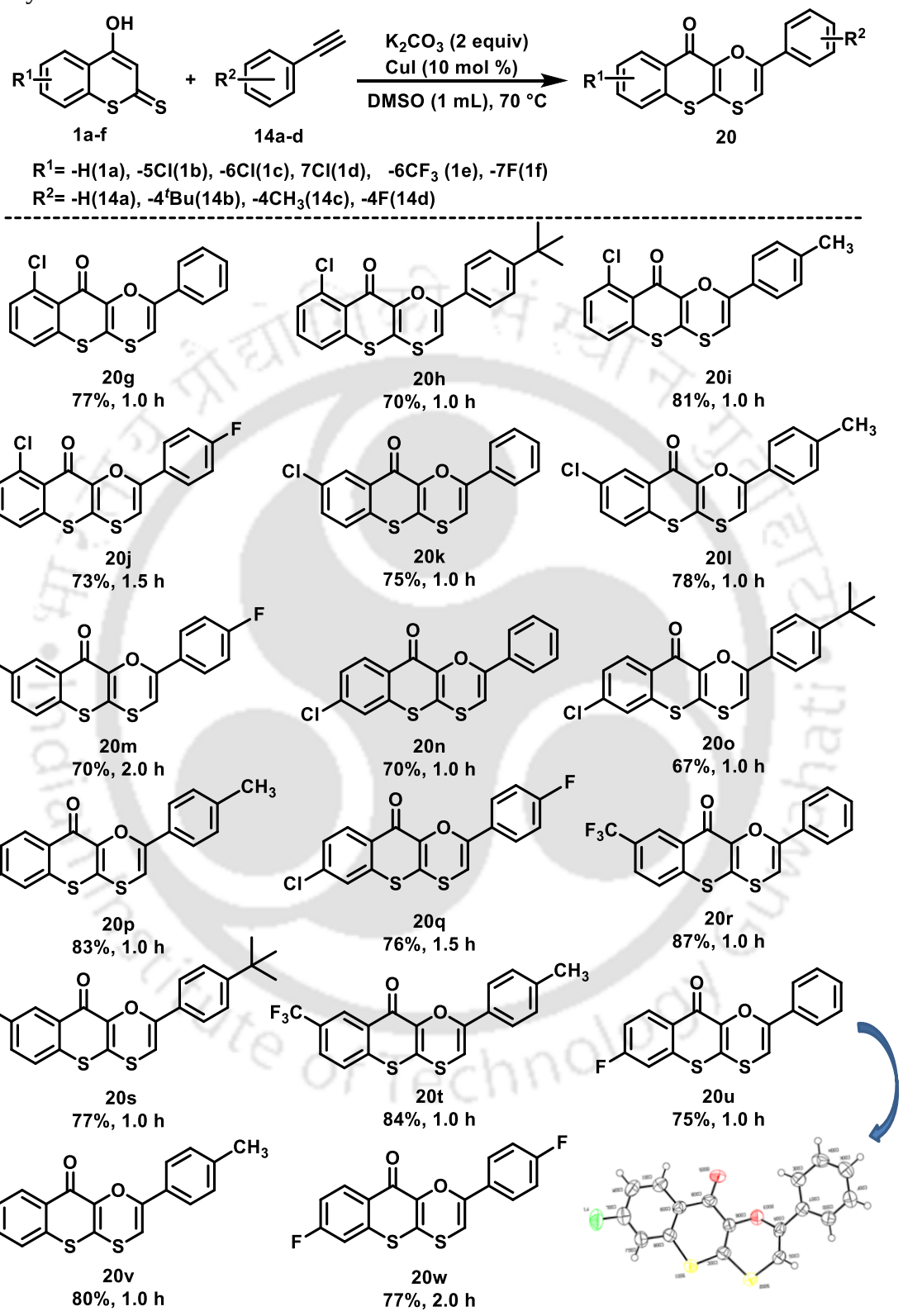
Table 5.2. Reaction of 4-hydroxydithiocoumarin **1a** with various aryl acetylene **14a-f**.[a,b]



[a]All the reactions were carried out using 4-hydroxydithiocoumarins **1a** (0.25 mmol), aryl acetylenes **14** (0.25 mmol) in 1 mL of solvent at 70 °C. [b]Isolated yield.

To extend our protocol further, various reactions were scrutinized with a chloro substituted 4-hydroxydithiocoumarins **1b-d** at positions 5, 6, and 7 and aryl acetylenes **14a-d** to give the desired products **20g-q**. The yield and reaction time are shown in Table 5.3.

Table 5.3. Reaction of substituted 4-hydroxydithiocoumarins **1a-f** with various substituted aryl acetylenes **14a-f**.[a,b]

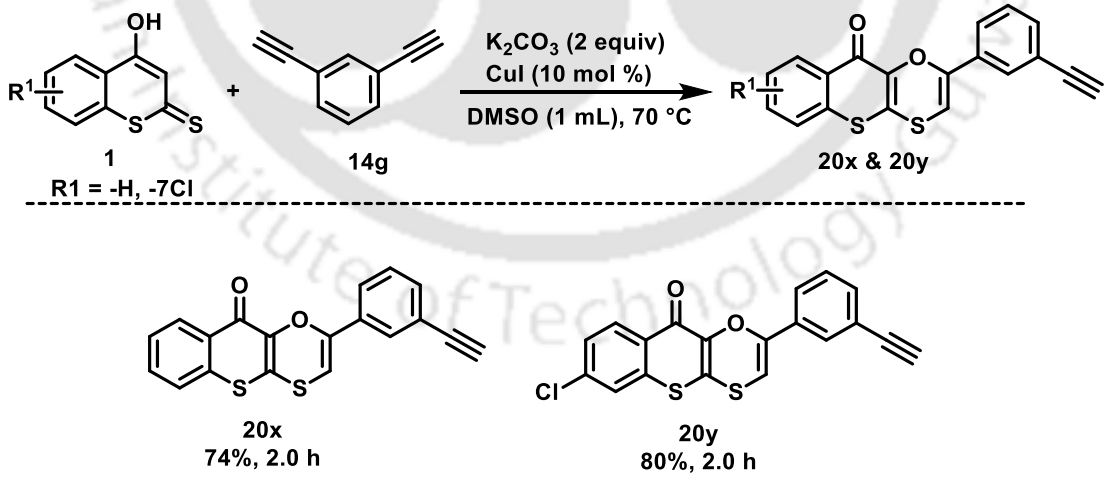


[a]All the reactions were carried out using 4-hydroxydithiocoumarins **1** (0.25 mmol), aryl acetylenes **14** (0.25 mmol) in 1mL of solvent at 70 °C. [b]Isolated yield.

Likewise, the reactions were executed with 6-trifluoromethyl-4-hydroxydithiocoumarin **1e** with various acetylenes **14a-c** provided the desired products **20r-t** in good yields. Furthermore, the reactions were explored with 7-fluoro-4-hydroxydithiocoumarin **1f** with aryl acetylenes to obtain the desired products **20u-w**. The structure of compound **20u** was also confirmed by a single X-Ray diffraction data and the ORTEP diagram is shown above.

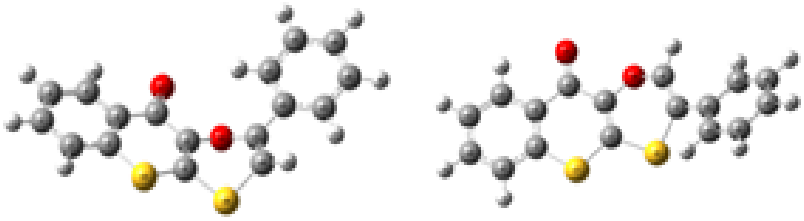
For our curiosity, whether *bis*-1,4-oxathiin derivatives can be formed or not on reaction with 1,3-diethynylbenzene **14g**, we have carried out a reaction under identical reaction conditions with 4-hydroxydithiocoumarions **1a** & **1d** (Table 5.4). Interestingly, we have isolated only mono-1,4-oxathiin derivatives **20x** and **20y**, respectively. From these results, we may conclude that the reaction proceeded well with *m*- and *p*- substituted phenylacetylenes. The reactions underwent smoothly with electron-withdrawing as well as the electron-donating group. It was noted that the reaction took a longer reaction time in the case of the electron-withdrawing group present in the aryl acetylenes. All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectra as well as HRMS.

Table 5.4. Reaction of substituted 4-hydroxydithiocoumarins **1a & 1d** with 1,3-diethynylbenzene **14g**.[a,b]



[a]All the reactions were carried out using 4-hydroxydithiocoumarins **1a & 1d** (0.25 mmol), 1,3-diethynylbenzene **14g** (0.25 mmol) in 1mL of solvent at 70 °C. [b]Isolated yield.

To verify the regioselective product formation, we have done DFT calculation using Gaussian 09 suits of a program* and it was found that ground state energy of 2-aryl-1,4-oxathiin derivative 20a is lower by ~4.22 kcal/mole as a comparison to 3-aryl-1,4-oxathiin derivative 20a′ (Figure 5.2).



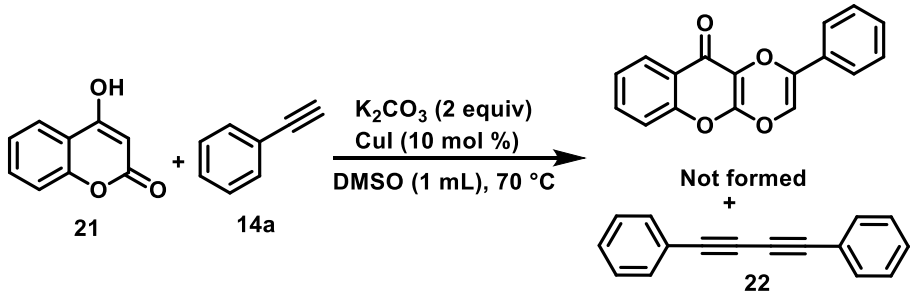
20a **20a'**

Figure 5.2. DFT calculation

Table 5.5. Optimized ground state energy

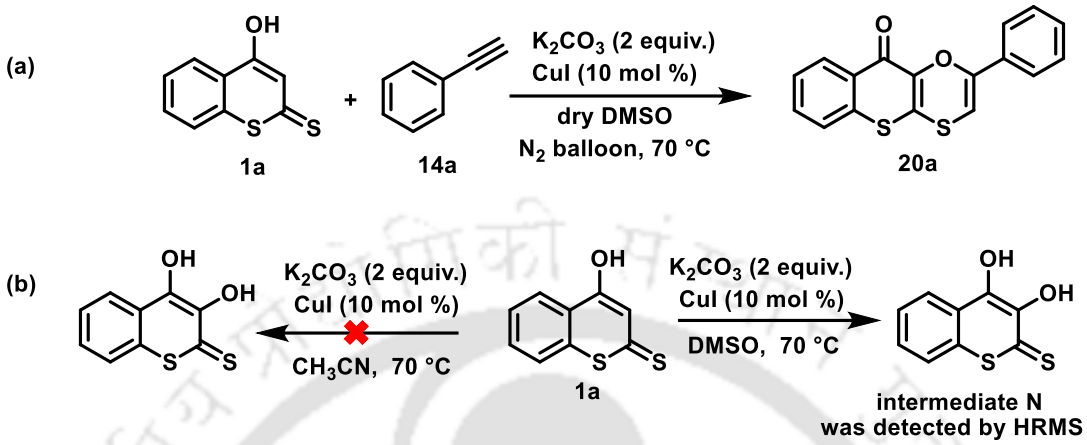
Compound	E (a.u.)	E (kcal/mol)	ΔE(kcal/mol)	Point group	Dipole Moment (Debye)
20a	-1600.65142398	-1004424.1476553	-	C1	3.7955
20a′	-1600.64468617	-1004419.91961479	-4.22804051	C1	4.4642

We are curious to know whether our synthetic strategy can be extended further with structurally similar 4-hydroxycoumarin for C-H functionalization like 4-hydroxydithiocoumarin. In another analogous condition, the reaction was executed with aryl acetylene, but no expected desired product, 2-phenyl-10*H*-[1,4]dioxino[2,3-*b*]chromen-10-one was formed. Therefore, it shows from the reaction behavior of 4-hydroxydithiocoumarin is completely different than 4-hydroxycoumarin (Scheme 5.8).



Scheme 5.8. Reaction between 4-hydroxycoumarin and phenylacetylene

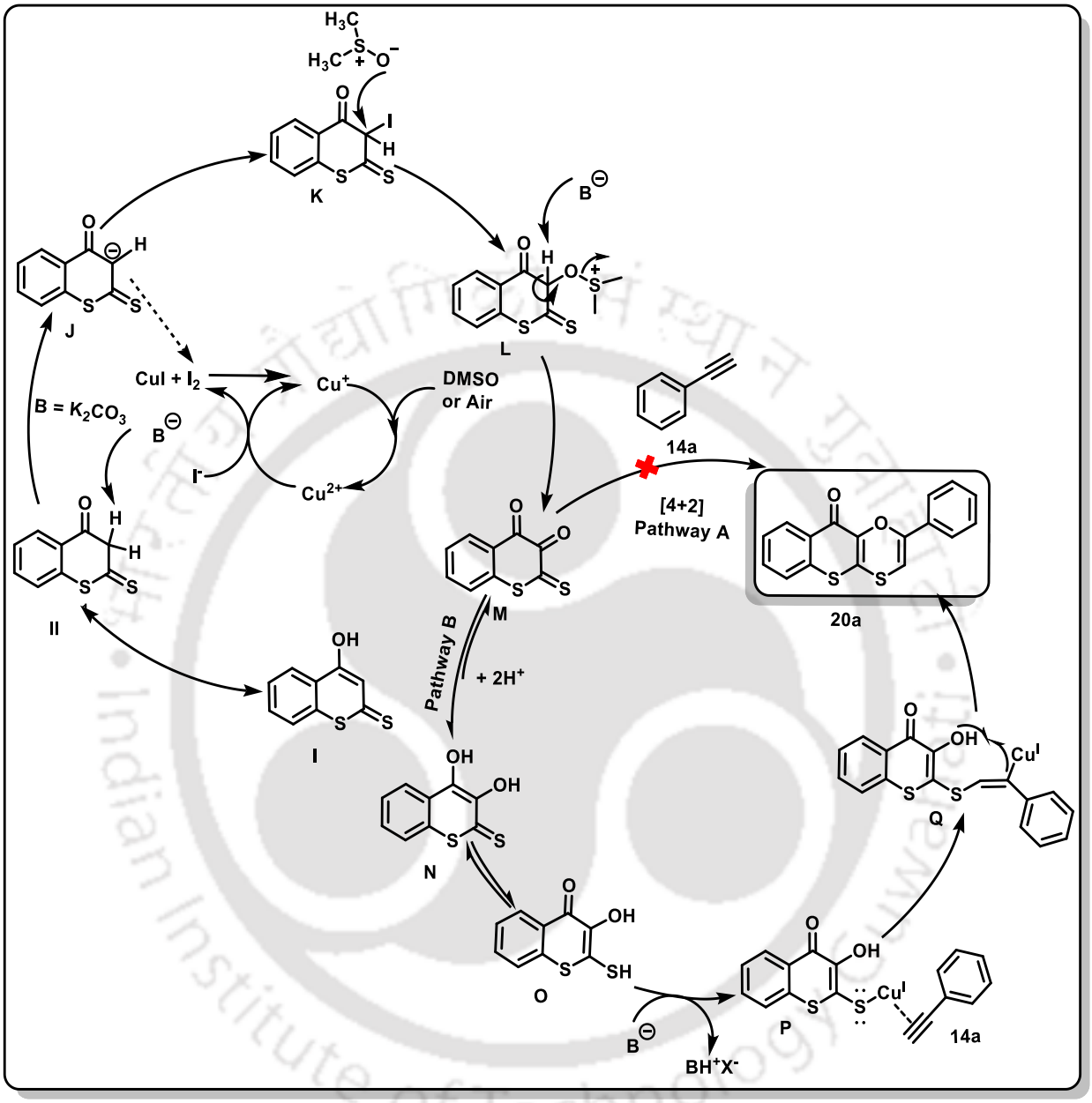
To establish the role of DMSO in the C-H functionalization, the experiment was carried out under an inert atmosphere. We got the desired product **20a** in the same yield, so it shows the oxygen is coming from the DMSO (Scheme 5.9.a).



Scheme 5.9. Preliminary mechanistic studies

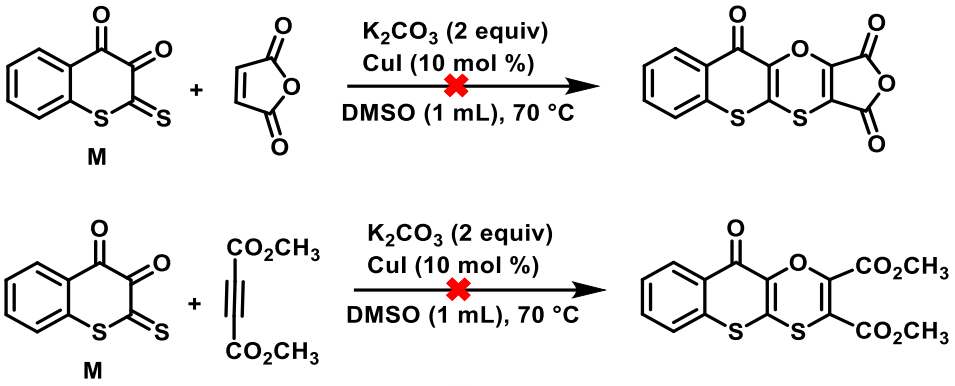
The probable mechanism for the formation of the product may be explained as follows shown in Scheme 5.10. 4-Hydroxydithiocoumarin can exist in three tautomeric structures I, II, and III, respectively, as proposed in retrosynthetic analysis in Scheme 5.6.[16] The tautomeric form II can generate the reactive carbanion intermediate **J** on treatment with potassium carbonate after deprotonation of C-3 hydrogen of 4-hydroxydithiocoumarin.[19] On iodination, the intermediate **J** reacts with in situ generated molecular iodine [Cu(II), which is generated from Cu(I) by oxidation with DMSO to oxidize iodide ion into molecular iodine][20] to provide another reactive intermediate **K**, which undergoes subsequent nucleophilic substitution with DMSO, which acts as a source of oxygen,[18] to give intermediate **M**. The intermediate **M** on hetero-Diels-Alder reaction with aryl acetylene provides the desired product **20** through the Pathway A. Alternatively, the intermediate **M** on protonation can give the intermediate **N**, which can exist in the tautomeric form **O**. The intermediate **N** was confirmed by Mass Spectrometry without adding aryl acetylene. The intermediate copper thiolate **P** reacts with aryl acetylene to generate intermediate **Q**.[13] The intermediate **Q** undergoes cyclization followed by reductive elimination of Cu(I) to give the desired product **20** (Pathway B). To discard the mechanism pathway A, the following experiments were performed as shown in Scheme 5.11. The reactions were

carried out to trap the *in situ* generated diene intermediate **M** with two other different dienophiles.



Scheme 5.10. A plausible mechanism for the formation of the product

Unfortunately, no Diels-Alder product was obtained. In conclusion, the formation of 1,4-oxathiin **20** is going through preferably **pathway B** over **pathway A**.



Scheme 5.11. The reaction between 4-hydroxydithiocoumarin and different dienophile

5.4. Biological application

To study the growth inhibitory effects of newly synthesized compounds of oxathiin derivatives, the cytotoxicity of the compounds was assessed by its effect on the viability of breast cancer cell line, MCF-7, and cervical cancer cell line, HeLa, using MTT mediated cell viability assay. A total of five different compounds, **20a, 20j, 20t, 20u,** and **20w** were selected to check their activity on MCF-7 and HeLa cells. Both the cell lines were treated with various concentrations of **20a** (5-100µM), **20j** (5-100µM), **20t** (5-100µM), **20u** (10-120µM), and **20w** (10-150µM) for 24 hours. Compound **20t** showed dose-dependent inhibition against MCF-7 as well as HeLa, whereas compound **20a** exhibited dose-dependent inhibition against MCF-7 cells only. Treatment with compound **20j** did not show any significant cytotoxicity against MCF-7 as well as HeLa cell lines. In MCF-7, the compounds **20u** and **20w** displayed a slight reduction in cell viability at higher concentrations, with no activity against HeLa cells. The IC_{50} values of the above compounds are listed in Table 5.6.

Table 5.6. Anti-proliferative activity of Oxathiin derivatives against human breast cancer cell line, MCF-7 and human cervical cancer cell line, HeLa.

Sl No	Compound	IC_{50} (µM)	
		MCF-7	**HeLa**
1	**20a**	78.45	Not attained
2	**20j**	Not attained	Not attained
3	**20t**	26.97	49.29
4	**20u**	112.44	Not attained
5	**20w**	104.3	Not attained

MTT mediated cell viability assays of the compounds **20a, 20j, 20t, 20u,** and **20w** on MCF-7 (Figure 5.3 a-e) and HeLa (Figure 5.3 f-j) cell lines, are shown in Figure 5.3. Overall, the results showed that, some of the Oxathiin derivatives have anti-cancer properties and can be utilized for further studies. Statistical analysis was performed *via* ANOVA using the Graphpad Prism6 software with statistical significance denoted by $* (p < 0.5), ** (p < 0.01), *** (p < 0.001), **** (p < 0.0001)$ and ns (not significant).

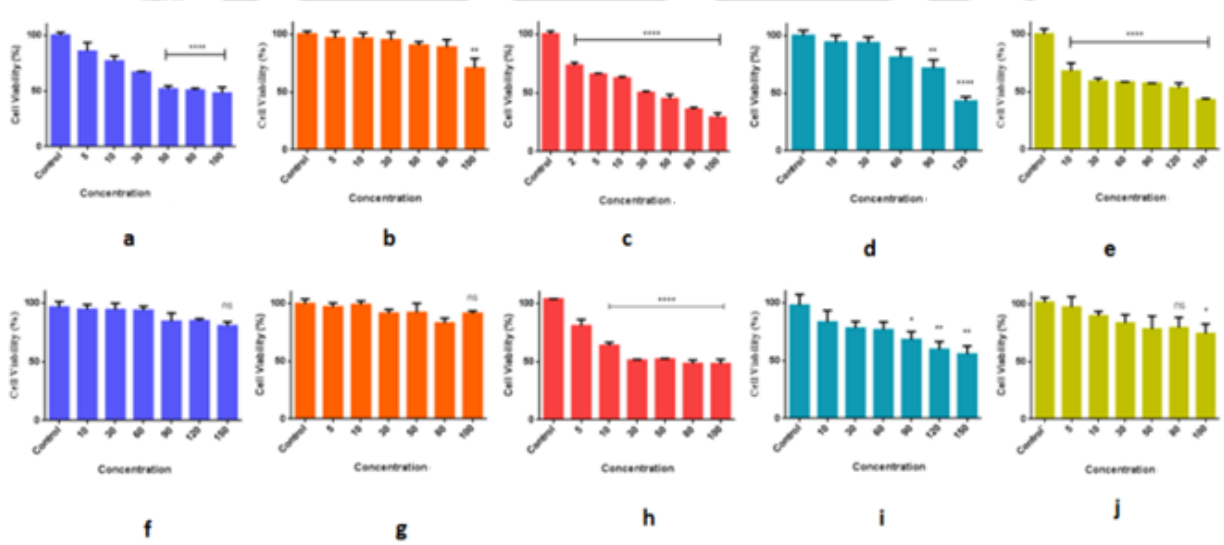


Figure 5.3. Assessment of Cell Viability on MCF-7 cells (**a-e**) and HeLa (**f-j**) using MTT mediated assay upon treating with Oxathiin derivatives **20a, 20j, 20t, 20u,** and **20w**.

5.5. Conclusion

In summary, we have accomplished the synthesis of numerous 1,4-oxathiin derivatives from 4-hydroxydithiocoumarins, aryl acetylenes, and dimethyl sulfoxide in which one *C-S* and two *C-O* bond formation occurs in a single step. The formation of the product is going through three consecutive steps in a single pot i) Cu-catalyzed cross-dehydrogenative coupling reaction between the terminal position of an aryl alkyne and 4-hydroxydithiocoumarin, ii) oxygenation of the C-H bond at the C3-position of 4-hydroxydithiocoumarin, and iii) cyclization. In this reaction, DMSO plays a pivotal role such as it acts as a solvent and the source of oxygen for hydroxylation. It is noteworthy to mention that for the first time C-H functionalization of 4-hydroxydithiocoumarin is reported. In addition to that, the present protocol is very useful because of mild reaction conditions, good yields, shorter reaction time, and a broad substrates scope. Few of the compound exhibit antiproliferative activity against the human breast cancer cell line, MCF-7 and cervical cancer cell line, HeLa. Detailed investigation regarding biological activity is undergoing, which will be disclosed later on.

5.6. Experimental section

I. General procedure for the synthesis of 4-hydroxydithiocoumarin (1a-f)

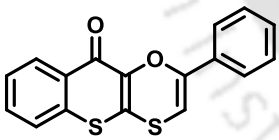
A wide variety of 4-hydroxydithiocoumarins was prepared by following the previously reported procedure: J. E. Anderson-McKay, A. J. Liepa, *Aust. J. Chem.*, 1987, **40**, 1179-90.[16]

II. General procedure for the synthesis of 1,4-oxathiin derivatives (20)[a,b]

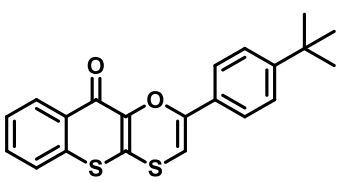
Into a 25 mL round-bottomed flask a mixture of 4-hydroxydithiocoumarin (**1**, 0.25 mmol), K_2CO_3 (1 mmol), and CuI (10 mol%) was taken in 1 mL of DMSO. Subsequently, aryl acetylene (**14**, 0.25 mmol) was added into the above reaction mixture and it was heated at an oil bath at 70°C. The progress of the reaction was monitored by TLC. After completion of the reaction, DMSO was removed, and the crude residue was extracted with DCM (2 x 10 mL) and it was washed with water (1 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and it was concentrated by using a rotatory evaporator. The crude residue was purified by using column chromatography to obtain the desired products.

5.7. Characterization

2-phenyl-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20a). A brown solid (42 mg, 85%); mp 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.89 – 7.87 (m, 2H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 3H), 5.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 155.1, 143.0, 135.9, 132.9, 132.9, 132.2, 131.5, 129.7, 129.6, 128.8, 127.6, 125.5, 125.5, 93.2; IR (KBr)ν_{max} 1737(C=O),1631(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{11}O_2S_2$ ($M + H^+$) 311.0195; Found 311.0194.

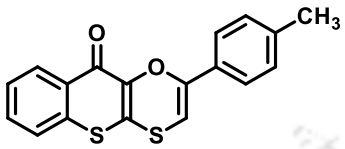


2-(4-(*tert*-butyl)phenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20b). A brown solid (41 mg, 70%); mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 7.3 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.57 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.52 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 5.85 (s, 1H), 1.32 (s, 9H);



^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 155.3, 153.0, 143.1, 135.9, 132.9, 131.4, 129.6, 129.4, 127.5, 125.7, 125.5, 125.3, 92.3, 34.9, 31.3; IR (KBr)ν_{max} 1722(C=O), 1679(C=C)cm^{-1}; HRMS (ESI) CalcdFor $C_{21}H_{19}O_2S_2$ (M + H^+) 367.0821; Found 367.0835.

2-(*p*-tolyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20c). A brown solid (42 mg, 82%); mp 114–116 °C; ^{1}H NMR (400 MHz, CDCl3) δ 8.58 – 8.56 (m, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.59 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.84 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 171.3, 155.4, 143.1, 139.9, 135.9, 133.0, 132.9, 131.5, 129.6, 129.5, 129.5, 127.5, 125.5, 92.0, 21.5; IR (KBr)ν_{max} 1720(C=O), 1676(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}O_2S_2$ (M + H^+) 325.0351; Found 325.0342.



2-(4-fluorophenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20d). A brown solid (41 mg,78%); mp 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.54 (m, 1H), 7.89 – 7.85 (m, 2H), 7.58 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.54 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.10 (t, *J* = 8.7 Hz, 2H), 5.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 164.9, 162.4, 154.3, 142.8, 135.9, 133.1, 132.8, 131.6, 129.5, 128.4, 128.4, 127.7, 127.6, 127.6, 125.5, 116.0, 115.8, 92.9, 92.9; IR (KBr)ν_{max} 1726(C=O), 1627(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}FO_2S_2$ (M + H^+) 329.0101; Found 329.0104.

2-(m-tolyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20e). A brown solid (44 mg, 85%); mp 121–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.68 (s, 2H), 7.58 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.53 (d, *J* = 6.5 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 5.88 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 155.3, 143.0, 138.5, 135.9, 133.0, 132.7, 132.2, 131.5, 130.6, 129.6, 128.7, 127.5, 126.1, 125.5, 122.8, 92.8, 21.6; IR (KBr)ν_{max}1730(C=O), 1621(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{13}O_2S_2$ (M + H^+) 325.0351; Found 325.0351.

2-(3-aminophenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20f). A brown solid (36 mg, 70%); mp 150–152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 6.0 Hz, 1H), 7.60 (dd, *J* = 12.0 , 6.0 Hz, 1H), 7.57–7.52 (m, 2H), 7.31 (s, 1H), 7.16 (dd, *J* = 9.9, 7.8 Hz, 2H), 6.70–6.68 (m, 1H), 5.86 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 155.2, 146.9, 143.0, 135.9, 133.2, 133.0, 132.9, 131.5, 129.6, 129.5, 127.5, 125.5, 116.3, 115.8, 112.0, 93.0; IR (KBr)ν_{max} 3293(N-H), 3246(N-H), 1712(C=O), 1621 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{12}NO_2S_2$ ($M + H^+$) 326.0304; Found 326.0326.

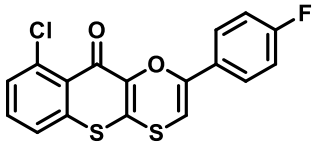
9-chloro-2-phenyl-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20g). A brown solid (42 mg, 77%); mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 6.3 Hz, 1H), 7.53 (d, *J* = 6.2 Hz, 1H), 7.46 – 7.42 (m, 3H), 7.42 – 7.37 (m, 3H), 5.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 155.2, 143.0, 138.9, 137.1, 132.1, 131.5, 130.9, 129.8, 129.0, 128.8, 127.1, 125.7, 124.7, 92.6; IR (KBr)ν_{max}1720(C=O), 1631(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}ClO_2S_2$ ($M + H^+$) 344.9805; Found 344.9823.

2-(4-(*tert*-butyl)phenyl)-9-chloro-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20h). A brown solid (45 mg, 70%); mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.53–7.51 (m, 1H), 7.44 (s, 1H), 7.43 – 7.41 (m, 3H), 5.84 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.3, 153.1, 143.1, 138.9, 137.1, 131.5, 130.9, 129.9, 129.4, 129.1, 126.8, 125.9, 125.7, 125.4, 124.7, 91.7, 34.9, 31.3; IR (KBr)ν_{max} 1722(C=O), 1634(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{18}ClO_2S_2$ ($M + H^+$) 401.0431; Found 401.0431.

9-chloro-2-(*p*-tolyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20i). A brown solid (46 mg, 81%); mp 147–149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 6.6 Hz, 1H), 7.43 (s, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.81 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 155.5, 143.1, 140.0, 138.9, 137.1, 131.5, 130.9, 129.5, 129.5, 129.0, 127.0, 125.6, 124.7, 91.4, 21.5; IR (KBr)ν_{max} 1722(C=O),

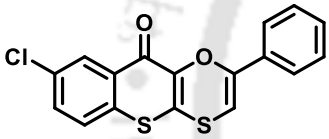
1633(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{12}ClO_2S_2$ (M + H^+) 358.9962; Found 358.9970.

9-chloro-2-(4-fluorophenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20j).



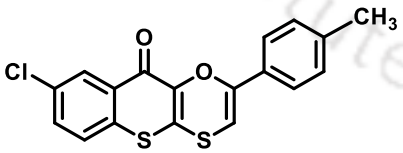
A brown solid (42 mg, 73%); mp 134–136°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.54 (dd, *J* = 5.7, 3.4 Hz, 1H), 7.44 (s, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.09 (t, *J* = 8.8 Hz, 2H), 5.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 164.9, 162.5, 154.4, 142.9, 138.9, 137.1, 131.6, 131.0, 129.1, 128.4, 128.4, 127.8, 127.7, 124.8, 116.0, 115.8, 92.4, 92.3; IR (KBr)ν_{max} 1725(C=O), 1631 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_9ClFO_2S_2$ (M + H^+) 362.9711; Found 362.9711.

8-chloro-2-phenyl-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20k). A brown

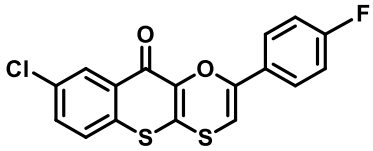


solid (41 mg,75%); mp 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.8 Hz, 1H), 7.87 – 7.85 (m, 2H), 7.59 – 7.54 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.38 (m, 3H), 5.90 (s, 1H);^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 155.2, 143.1, 134.3, 132.0, 131.9, 129.9, 129.1, 129.0, 128.9, 127.1, 127.0, 125.6, 122.6, 93.1; IR (KBr)ν_{max} 1722 (C=O), 1679 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}ClO_2S_2$ (M + H^+) 344.9805; Found 344.9806.

8-chloro-2-(*p*-tolyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20l). A brown

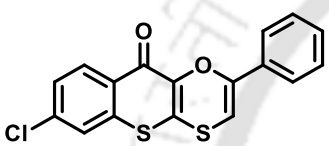


solid (44 mg,78%); mp 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.3 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.55 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.49 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.83 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.4, 143.2, 140.1, 134.3, 134.1, 134.1, 131.9, 129.5, 129.3, 129.1, 127.0, 126.9, 125.5, 91.9, 21.5; IR (KBr)ν_{max}1722 (C=O), 1622 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{12}ClO_2S_2$ (M + H^+) 358.9962; Found 358.9961.

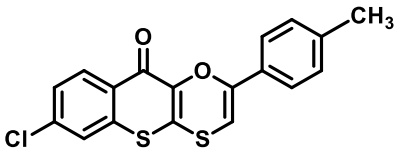


8-chloro-2-(4-fluorophenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20m). A brown solid (40 mg, 70%); mp 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.8 Hz, 1H), 7.85 (dd, *J* = 9.4, 5.6 Hz, 2H), 7.56 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.13 – 7.08 (m, 2H), 5.84 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.1, 165.0, 162.5, 154.4, 143.0, 134.4, 134.1, 134.0, 133.5, 132.0, 129.1, 127.7, 127.6, 127.0, 116.1, 115.8, 92.8, 92.8; IR (KBr)ν_{max} 1720 (C=C), 1621 (C=O) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_9ClFO_2S_2$ (M + H^+) 362.9711; Found 362.9710.

7-chloro-2-phenyl-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20n). A brown solid (38 mg, 70%); mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 12.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.54 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42–7.38 (m, 3H), 5.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.1, 138.4, 137.2, 132.7, 132.0, 131.3, 131.1, 129.8, 128.8, 128.5, 128.3, 125.5, 124.9, 93.1; IR (KBr)ν_{max} 1720 (C=O), 1681 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}ClO_2S_2$ (M + H^+) 344.9805; Found 344.9802.

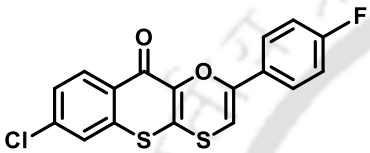


2-(4-(*tert*-butyl)phenyl)-7-chloro-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20o). A brown solid (43 mg, 67%); mp 109–111°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.47 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 5.85 (s, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.3, 153.2, 138.3, 137.1, 132.0, 131.3, 131.1, 129.2, 128.2, 125.8, 125.4, 125.3, 124.8, 92.1, 34.9, 31.3; IR (KBr)ν_{max} 1722 (C=O), 1679 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{18}ClO_2S_2$ (M + H^+) 401.0431; Found 401.0431.



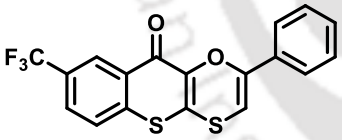
7-chloro-2-(*p*-tolyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20p). A brown solid (47 mg, 83%); mp 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.82 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.4, 143.2, 140.0, 138.3, 137.2, 131.3, 131.1, 129.6, 129.5, 129.3, 128.3, 125.5, 124.8, 91.8, 21.5; IR (KBr)ν_{max}1722(C=O), 1627(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{12}ClO_2S_2$ ($M + H^+$) 358.9962; Found 358.9982.

7-chloro-2-(4-fluorophenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20q).



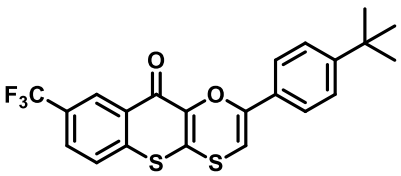
A brown solid (44 mg,76%); mp 177–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.7 Hz, 1H), 7.86 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.10 (t, *J* = 8.6 Hz, 2H), 5.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 154.4, 143.0, 138.5, 137.2, 134.7, 134.6, 131.3, 131.1, 128.4, 127.7, 127.6, 124.9, 116.0, 115.8, 92.8; IR (KBr)ν_{max} 1724(C=O), 1627(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_9ClFO_2S_2$ ($M + H^+$) 362.9711; Found 362.9715.

2-phenyl-8-(trifluoromethyl)-10*H*-thichromeno[3,2-*b*][1,4]oxathiin-10-one (20r).



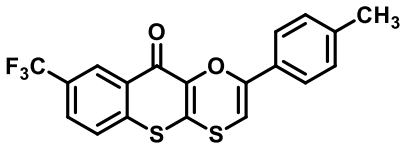
A brown solid (52 mg, 87%); mp 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.87 – 7.85 (m, 2H), 7.79 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.45 – 7.39 (m, 3H), 5.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 155.2, 143.3, 139.4, 133.4, 133.0, 131.9, 129.9, 128.9, 127.6, 127.6, 127.5, 127.5, 127.1, 127.0, 127.0, 126.5, 125.5, 93.0; IR (KBr)ν_{max}1722(C=O), 1634(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{10}F_3O_2S_2$ ($M + H^+$) 379.0069; Found 379.0065.

2-(4-(*tert*-butyl)phenyl)-8-(trifluoromethyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20s). A brown solid (53 mg,77%); mp 124–126°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.79 (d, *J* = 12.0 Hz, 3H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.44 (d, *J* = 6.0 Hz, 2H), 5.86 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ170.2, 155.3, 153.3, 143.4, 139.4, 133.6, 132.9,



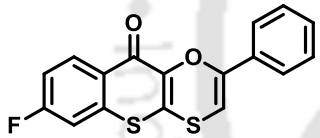
132.3, 129.1, 128.5, 127.5, 127.0, 126.5, 126.0, 125.8, 125.3, 92.0, 34.9, 31.3; IR (KBr)ν_{max}1725(C=O), 1681(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{22}H_{18}F_3O_2S_2$ (M + H^+) 435.0695; Found 435.0698.

2-(*p*-tolyl)-8-(trifluoromethyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one



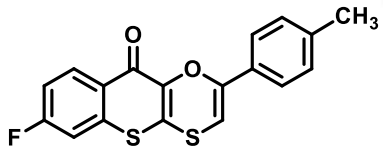
(20t). A brown solid (52 mg, 84%); mp 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.79 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.83 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 155.4, 143.4, 140.2, 139.4, 133.5, 133.0, 130.2, 129.8, 129.6, 129.1, 127.5, 127.5, 127.5, 127.5, 127.0, 127.0, 126.5, 125.5, 91.8, 21.5; IR (KBr)ν_{max} 1720(C=O), 1635 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{12}F_3O_2S_2$ (M + H^+) 393.0225; Found 393.0225.

7-fluoro-2-phenyl-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20u). A brown



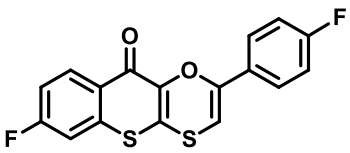
solid (39 mg, 75%); mp 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.86 (d, *J* = 4.0 Hz, 2H), 7.39 (dd, *J* = 12.0, 8.0 Hz, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 165.3, 162.7, 155.2, 143.0, 138.0, 137.9, 134.0, 132.6, 132.5, 132.4, 132.0, 129.8, 128.9, 128.8, 128.6, 128.5, 125.5, 116.4, 116.2, 111.7, 111.4, 93.1; IR (KBr)ν_{max} 1722(C=O), 1683(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{10}FO_2S_2$ (M + H^+) 329.0101; Found 329.0101.

7-fluoro-2-(*p*-tolyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20v). A brown



solid (44 mg, 80%); mp 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 4.0 Hz, 2H), 7.21–7.17 (m, 2H), 5.82 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 165.3, 162.7, 155.4, 143.0, 140.0, 138.0, 132.6, 132.5, 129.6, 129.5, 129.3, 125.5, 116.3, 116.1, 111.6, 111.4, 91.9, 21.5; IR (KBr)ν_{max} 1728 (C=O), 1627 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{12}FO_2S_2$ (M + H^+) 343.0257; Found 343.0271.

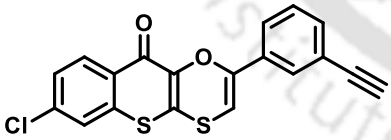
7-fluoro-2-(4-fluorophenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20w).



A brown solid (43 mg, 77%); mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.85 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 2H), 5.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 165.3, 164.9, 162.8, 162.4, 154.4, 142.8, 138.0, 137.9, 132.6, 132.5, 129.5, 128.3, 128.3, 127.7, 127.6, 116.4, 116.2, 116.1, 116.0, 115.9, 115.8, 115.7, 115.4, 111.7, 111.5, 92.8, 92.8; IR (KBr)ν_{max} 1724(C=O), 1631(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_9F_2O_2S_2$ (M + H^+) 347.0007; Found 347.0006.

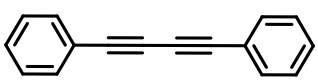
2-(3-ethynylphenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20x). A brown solid (39 mg, 74%); mp 107–109°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.95 – 7.92 (m, 2H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.53 (m, 2H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 5.94 (s, 1H), 3.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 154.0, 142.8, 135.9, 133.2, 132.9, 132.6, 132.5, 131.6, 129.6, 129.1, 129.0, 127.6, 125.9, 125.5, 122.8, 94.2, 83.2, 78.0; IR (KBr)ν_{max} 3293(≡C-H), 2110(C≡C), 1727(C=O), 1619(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{11}O_2S_2$ (M + H^+) 335.0195; Found 335.0198.

7-chloro-2-(3-ethynylphenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20y).



A brown solid (47 mg,80%); mp 119–121 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (d, *J* = 8.8 Hz, 1H), 7.90 (s, 2H), 7.53 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 5.92 (s, 1H), 3.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 154.0, 142.9, 138.5, 137.1, 133.3, 132.3, 131.3, 131.1, 129.1, 129.0, 128.4, 125.9, 124.9, 122.9, 94.1, 83.1, 78.0; IR (KBr)ν_{max} 3293(≡C-H), 2112(C≡C), 1727(C=O), 1625(C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{10}ClO_2S_2$ (M + H^+) 368.9805; Found 368.9805.

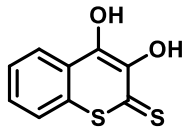
1,4-diphenylbuta-1,3-diyne (22). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (s, 2H), 7.53 (d,



J = 6 Hz, 2H), 7.37 (d, *J* = 6.0 Hz, 2H), 7.35 – 7.33 (m, 4H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 132.6, 129.3, 128.5, 121.9, 81.6, 74.0.

3,4-dihydroxy-2H-thiochromene-2-thione (intermediate N). HRMS (ESI) Calcd For $C_9H_7O_2S_2(M + H^+)$ 210.9982; Found 210.0682.



5.8.3. Crystal Data and Structure Refinement for Compounds 20u

Entry	Identification code	Compound 20u
01	Empirical formula	C17H9FO2S2
02	Formula weight	328.36
03	Temperature	296 K
04	Wavelength	0.71073
05	Radiation type	Mo K\a
06	Radiation source	Fine-focus sealed tube
07	Crystal system	Monoclinic
08	Space group	P 21/ n
09	Cell length	a 14.147(2) b 5.4814(8) c 18.975(3)
10	Cell Angle	α 90 β 109.360(4) δ 90
11	Cell Volume	1388.2(4)
12	Density	1.571
13	Completeness to theta	23°/ 100%
14	Absorption correction	multi-scan
15	Refinement method	Full-matrix least-squares on F2
16	Index ranges	-16<=h<=16, -6<=k<=6, -22<=l<=22
17	Reflection number	8296
18	Theta range	2.38- 23.59
19	Cell formula units Z	1
20	CCDC no	2049895

Figure 5.4.a. ^{1}H NMR of 2-phenyl-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20a)

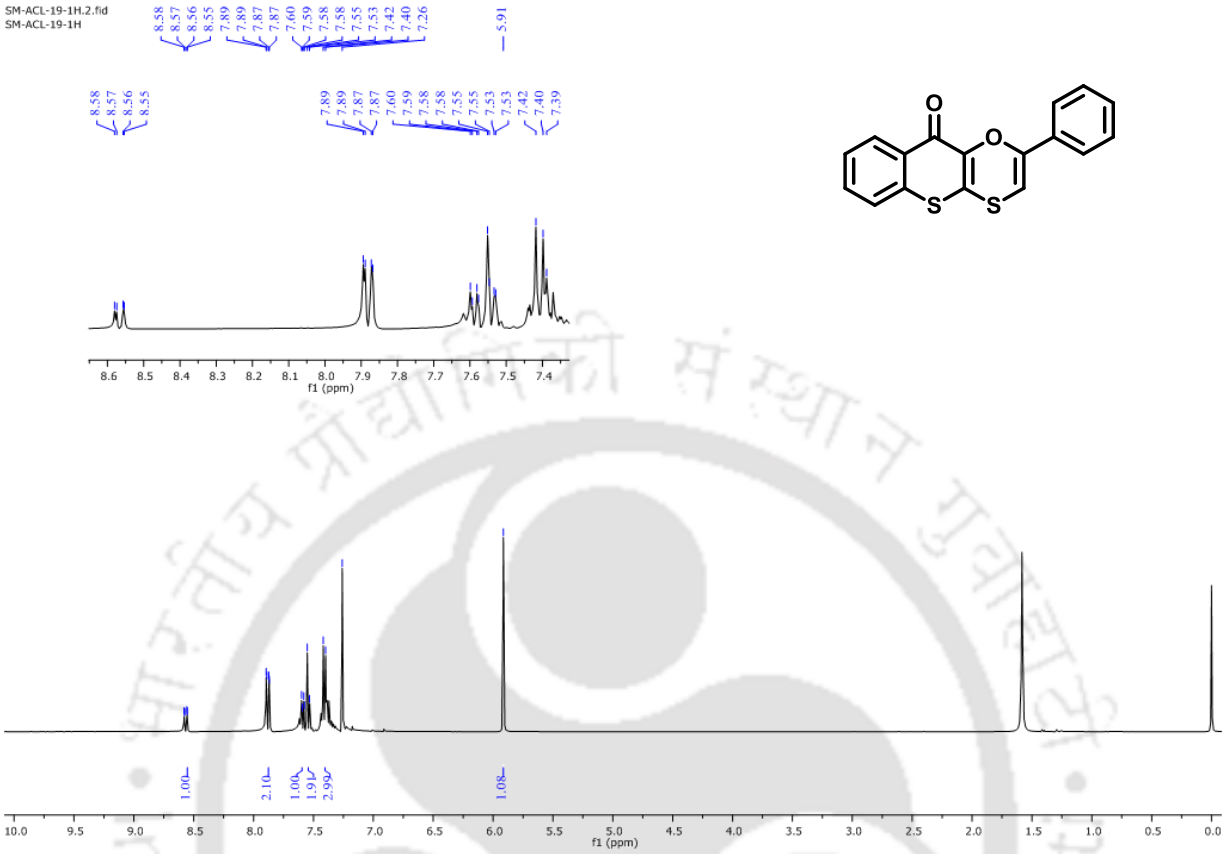


Figure 5.4.b. ^{13}C NMR of 2-phenyl-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20a)

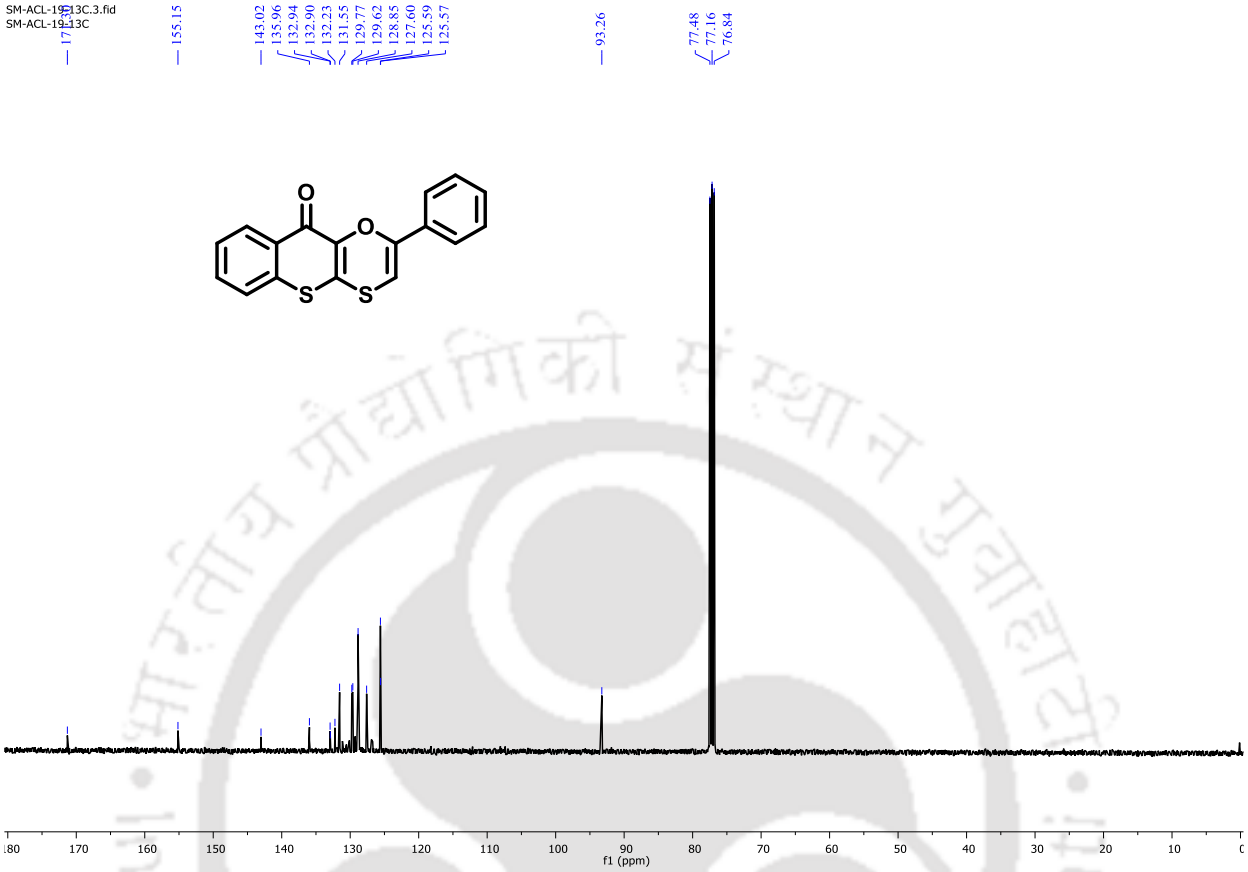


Figure 5.4.c. HRMS of 2-phenyl-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20a)

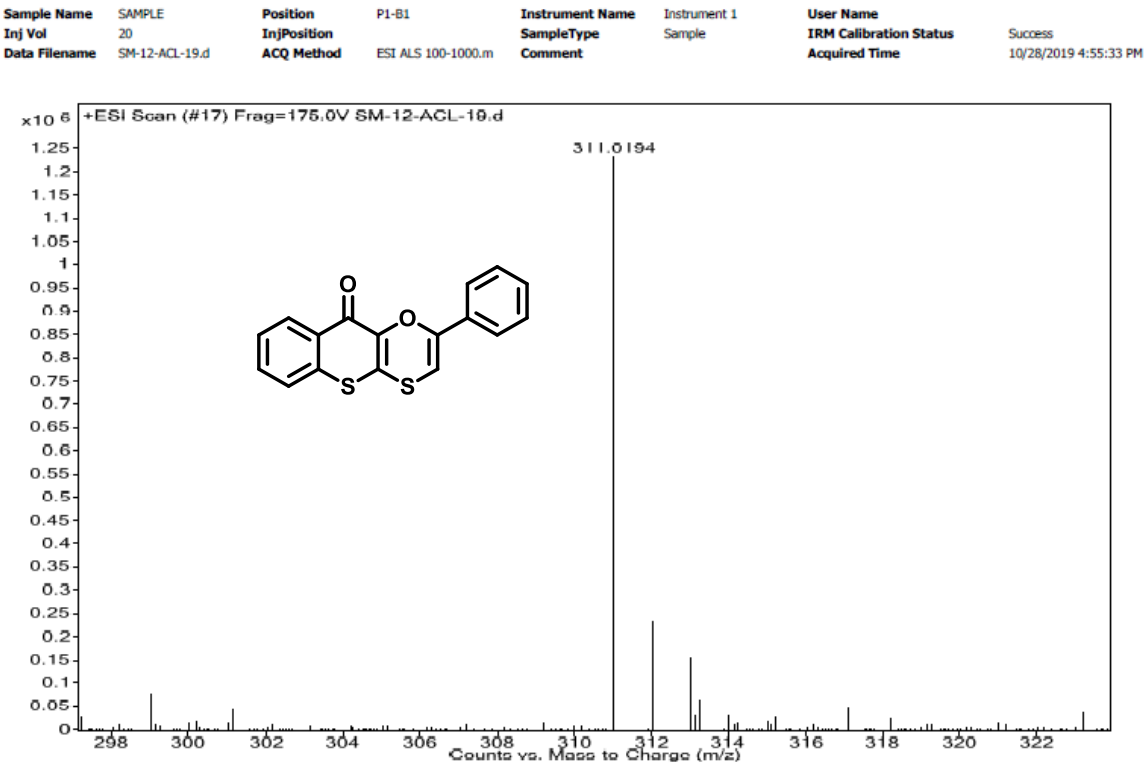


Figure 5.5.a. ^{1}H NMR of 2-(3-ethynylphenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20x)

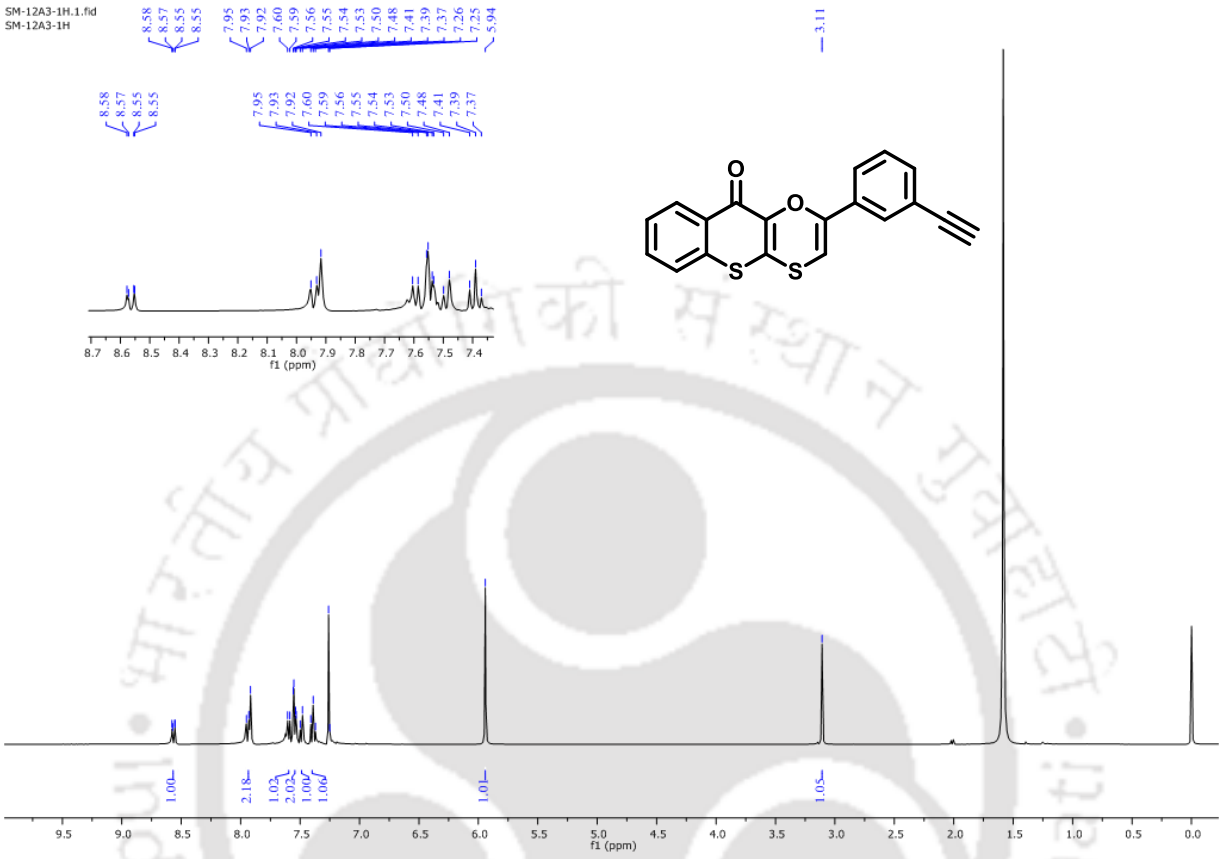


Figure 5.5.b. ^{13}C NMR of 2-(3-ethynylphenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20x)

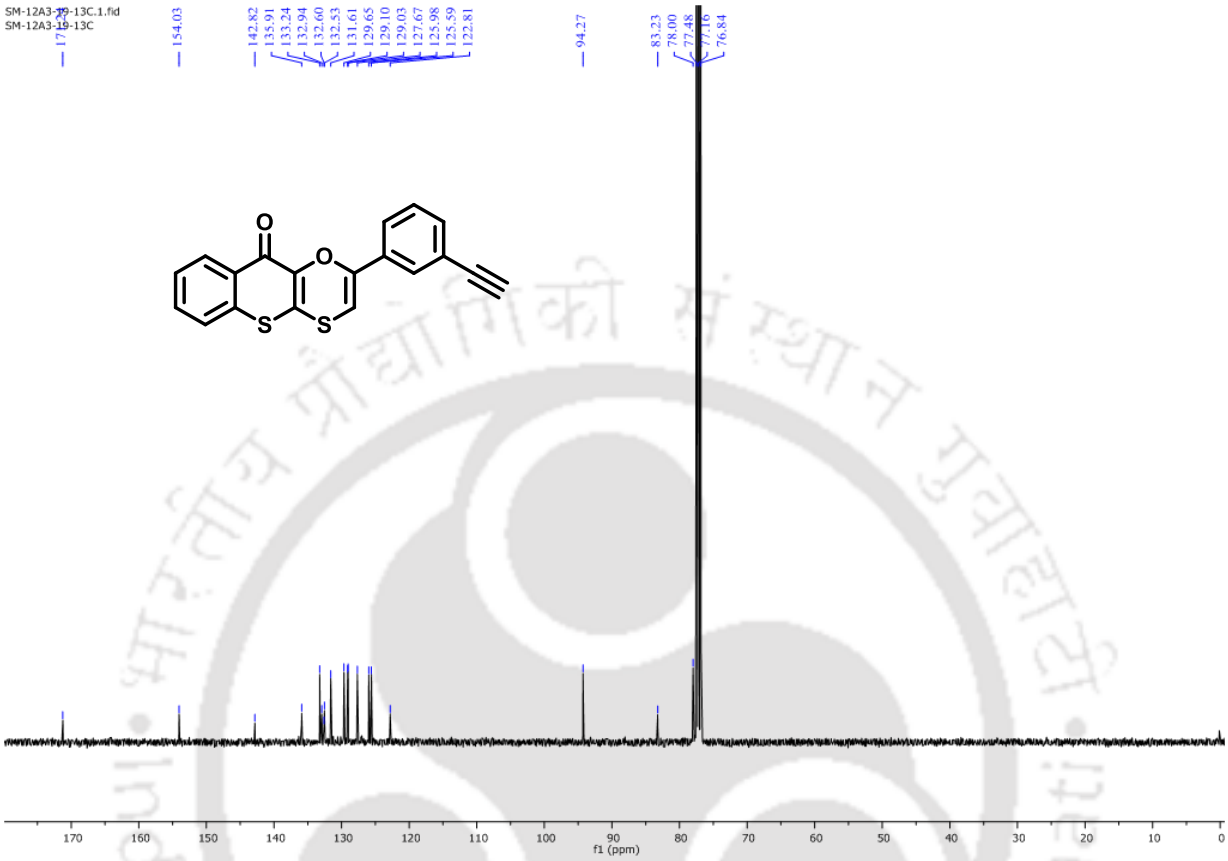


Figure 5.5.c. HRMS of 2-(3-ethynylphenyl)-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (20x)

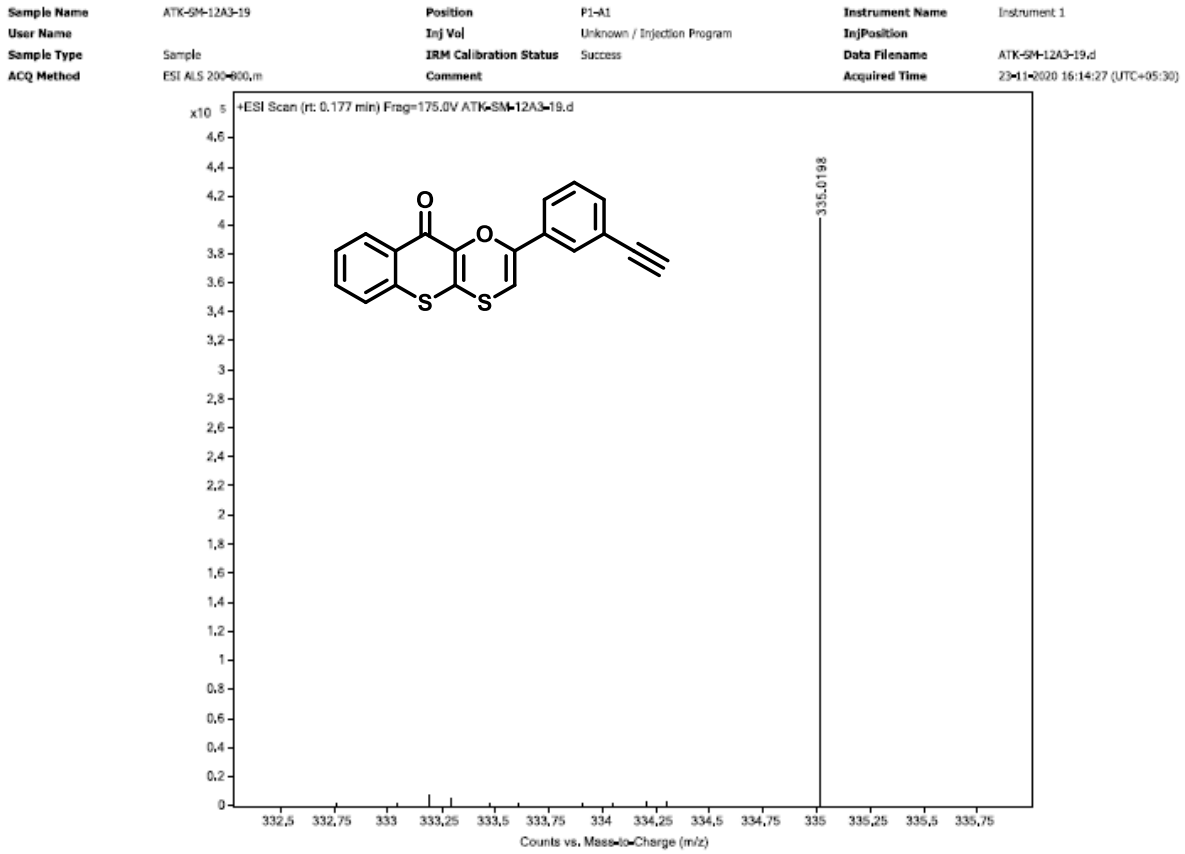


Figure 5.6.a. ^{1}H NMR of Compound 22

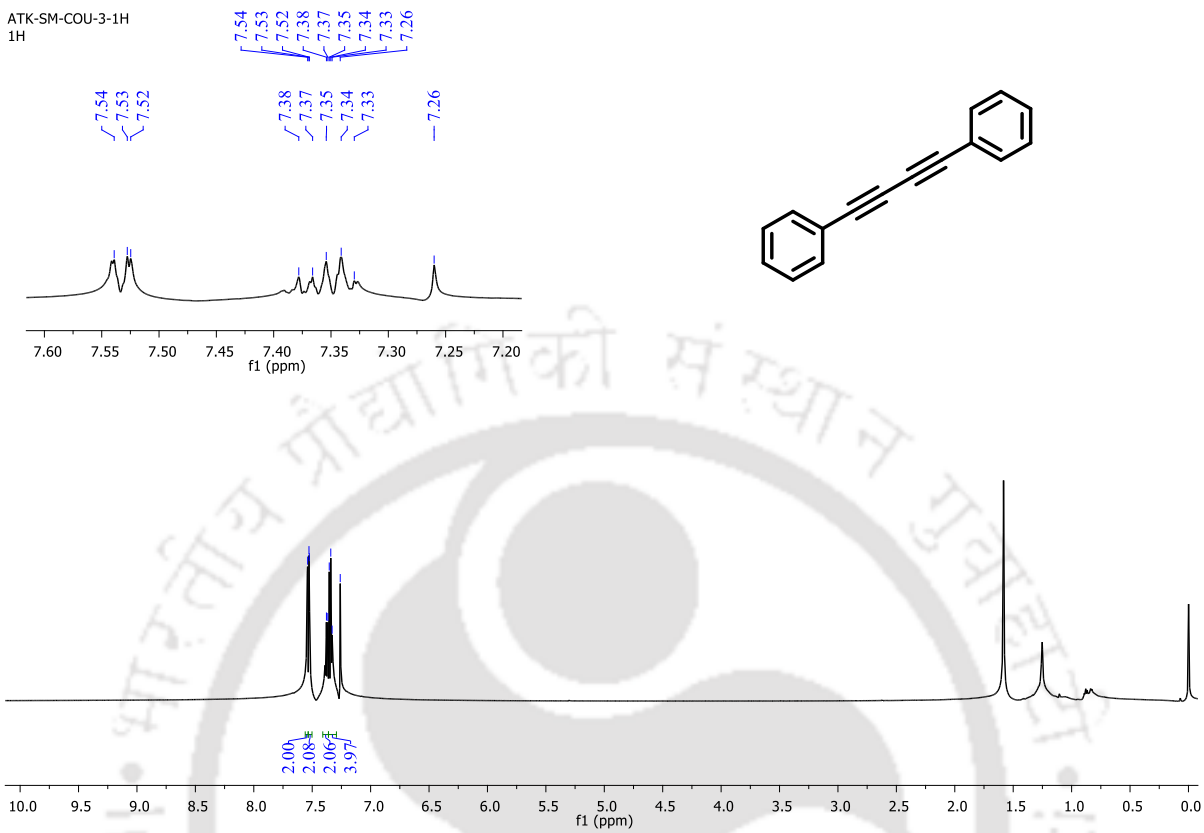


Figure 5.6.b. ^{13}C NMR of Compound 22

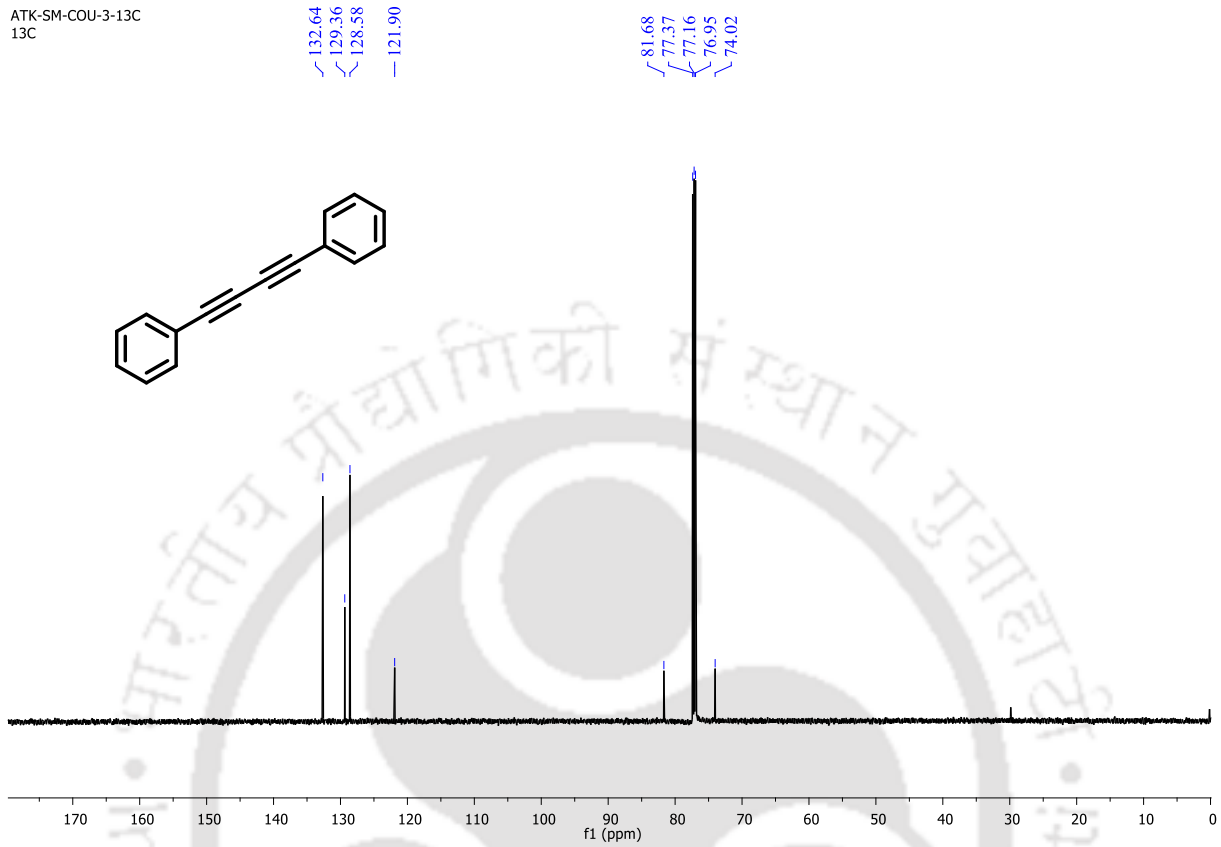
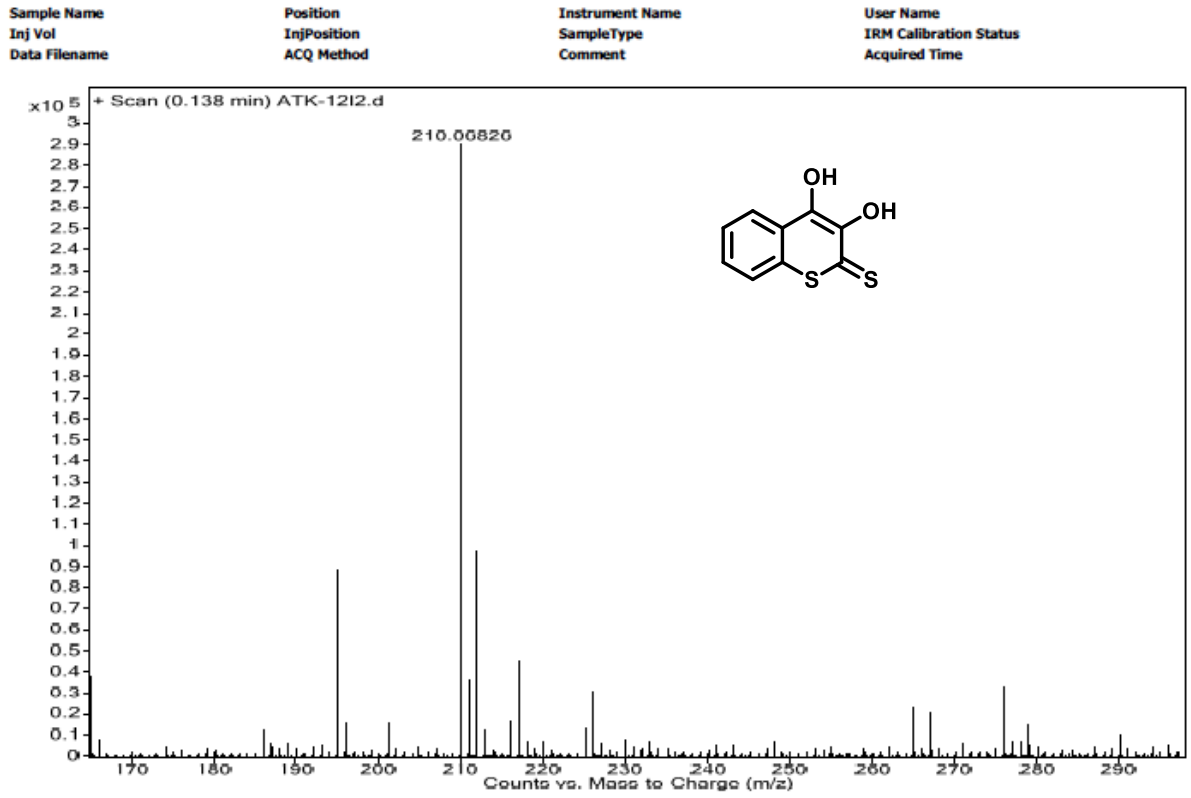


Figure 5.7. HRMS of Compound intermediate N



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CHAPTER VI

Ring-opening reactions of epoxides/tosyl aziridines with 4-hydroxydithiocoumarins and cyclization of the ring-opening product

Introduction

Results & Discussion

Experimental Section

6.1. Introduction

Organosulfur compounds are widely distributed in nature and have immense pharmacological importance for human beings.[1] Sulfur-containing scaffolds are highly desirable in the field of medicinal chemistry.[2] Among a variety of sulfur-containing compounds, β-hydroxysulfides, and β-aminosulfides serve as a significant building block for the synthesis of valuable biologically active compounds[3] and natural products.[4] In addition, these structural subunits are also present in the drugs like diltiazem, naltiazem,[5] and nelfinavir. [6]

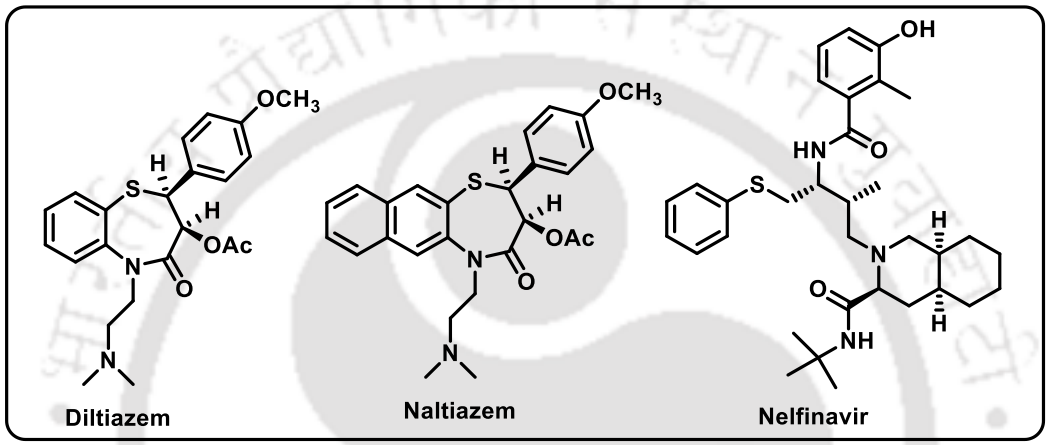


Figure 6.1. Molecules having a structural framework of β-hydroxysulfide and β-aminosulfide

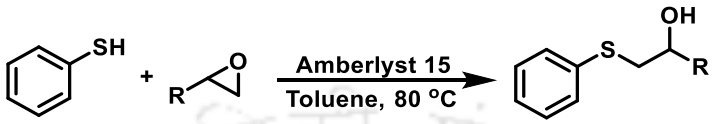
Furthermore, in chemical and pharmaceutical research, 2,3-dihydro-1,4-oxathiin and 2,3-dihydro-1,4-thiazine derivatives have received a lot of attention. The 2,3-dihydrobenzo[1,4]oxathiin is used as an antioxidant, hypertensive drug, adrenoreceptor antagonist, therapeutic drug, and artificial sweetener.[7] Similarly, 1,4-benzothiazines have been intensively investigated due to their biological activities as antifungal agents, the antihypertensive drug, calcium antagonists, antirheumatic agents, adenosine triphosphate-sensitive potassium channel openers, antihistamine agents.[8]

Moreover, the synthetic utilities of β-hydroxysulfides are further explored for the synthesis of benzothiazepines,[5] allylic alcohols,[9a] benzoxathiepines,[9b] and β-hydroxy-sulfoxides.[9c] β-Hydroxy/aminosulfides can be easily accessed by regio- and stereo-selective ring-opening reactions of epoxides and aziridines with thiols.[10] Numerous methods have been developed over the years for the synthesis of β-hydroxysulfides from the reaction of epoxides with thiols in the presence of bases[11] or promoters[12] or Lewis acid and Brønsted acids.[13] Only a few triflates, such as $Ga(OTf)_3$ and $Er(OTf)_3$,

produced ring-opening products at the more hindered sites of styrene oxides, whereas aliphatic epoxides produced ring-opening products at the less hindered sites.[13d,e] Very recently, the asymmetric synthesis of β-hydroxysulfides *via* ring-opening reaction of epoxide with thiol has gained considerable attention in organic synthesis.[14] Similarly, different reaction conditions are needed for the ring-opening reaction of aziridines with different nucleophiles because of their different reactivity and structural complexity.[15] The synthesis of β-aminosulfides was described employing an organocatalyst,[16] Lewis acid,[17] and radical initiator[18] in a regioselective ring-opening reaction of aziridine with thiols. A very few synthetic methods have been developed for the synthesis of 2,3-dihydro-1,4-oxathiins, 2,3-dihydro-1,4-thiazine derivatives. Dong *et al.* reported the synthesis of 2,3-dihydrobenzo-1,4-oxathiin from aryloxymethylthiiranes in dimethyl sulfoxide (DMSO) under microwave conditions *via* the N-bromosuccinimide-mediated ring expansion reactions.[19] Viglianisi *et al.* developed a copper-catalyzed method for the synthesis of 2,3-dihydrobenzo-1,4-oxathiins from O,O'-dihydroxydisulfides.[20] Likewise, some interesting routes are also available for the synthesis of dihydrobenzothiazines. Ghorai *et al.* developed a strategy for the formation of dihydrobenzothiazines through ring-opening of aziridines with 2-halothiophenols.[21] Liu *et al.* demonstrated the synthesis of dihydrobenzothiazines from alkenes with sulfonamides and N-sulfanylsuccinimides.[22]

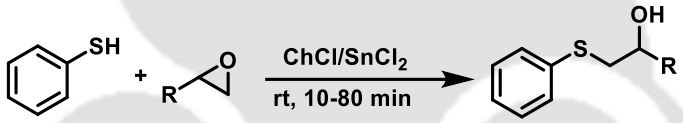
6.2. Synthesis of β-hydroxysulfide and β-aminosulfide

In the presence of Amberlyst 15, Lanke *et al.* reported the synthesis of hydroxysulfide from thiol and epoxide. The catalyst could be recycled up to five times without losing its catalytic activity. A metal-free technique for *C-S* bond formation with excellent atom economy has been designed.[23]



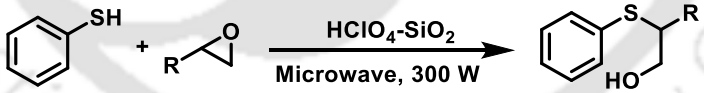
Scheme 6.1. Synthesis of β-hydroxysulfide from thiol and epoxide

Azizi *et al*. reported the synthesis of hydroxysulfide from thiol and epoxide using choline chloride and stannous chloride.[24] Furthermore, the reactions with unsymmetrical epoxides were regioselective, the primary products identified coming from the nucleophile attacking the less hindered carbon atom of the epoxide ring. The compounds produced from the approach on the benzylic position of the epoxide were regioselectively obtained by reacting with thiol and epoxide.



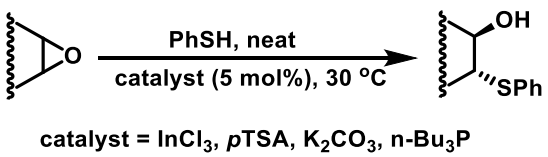
Scheme 6.2. Synthesis of hydroxysulfide from thiol and epoxide

Murthy *et al*. reported the synthesis of microwave-assisted hydroxysulfide *via* ring-opening reaction of epoxide with thiol using silica perchloric acid matrix.[25]



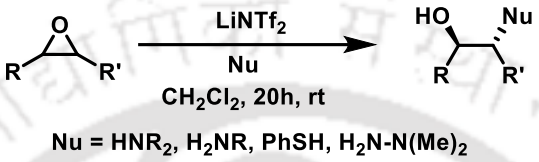
Scheme 6.3. Synthesis of microwave-assisted hydroxysulfide

The thiolysis of 1,2-epoxides by thiophenol under solvent-free conditions was reported by Pizzo *et al*.[11] In the presence of Lewis and Brønsted acid, and base catalysts ($InCl_3$, *p*-TsOH, *n*-Bu_3P, K_2CO_3), thiolysis of alkyl- and aryl-1,2-epoxides was examined. The best results were obtained by using $InCl_3$ and K_2CO_3, and β-hydroxysulfide was isolated in excellent yields.



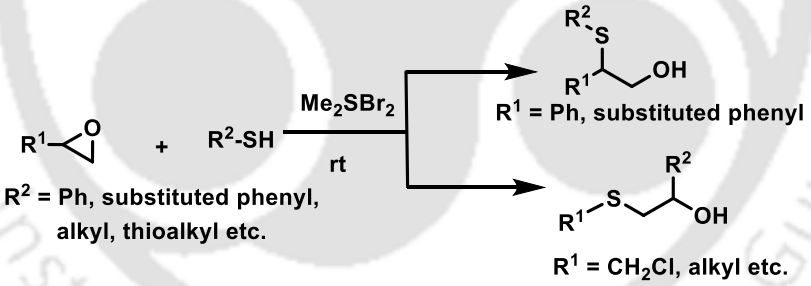
Scheme 6.4. Thiolysis of 1,2-epoxide by thiophenol

Using lithium bistrifluoromethanesulfonimide, Cossy *et al*. described a regioselective ring-opening reaction of epoxides by nucleophiles.[12] When epoxides are treated with nucleophiles including amines, hydrazines, and thiophenol in the presence of $LiNTf_2$, they undergo ring-opening with high regioselectivity and yield. At ambient temperature, in dichloromethane, or even without any solvent, the commercially available inexpensive and non-hazardous lithium salt, $LiNTf_2$, may be used to easily open the rings of epoxides with nucleophiles such as amines, hydrazines, and thiophenol.



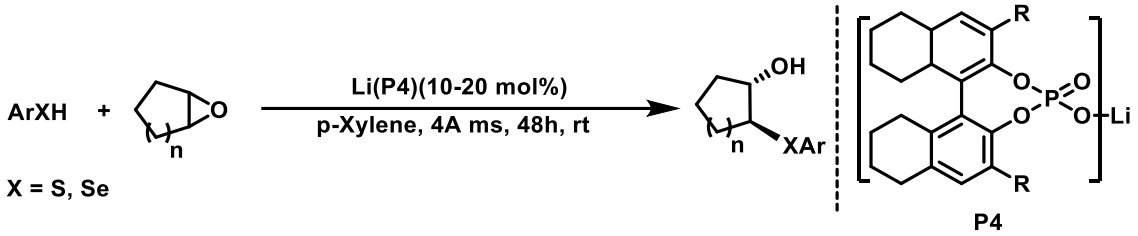
Scheme 6.5. Ring-opening reaction of epoxide by a nucleophile

Shailaja *et al*. demonstrated the ring-opening reaction of an epoxide ring with simple aliphatic and aromatic thiols using (bromodimethyl)sulfonium bromide.[26] It was observed that (bromodimethyl) sulfonium bromide effectively accelerates the thiolysis of epoxides resulting in β-hydroxysulfides in excellent yields and short reaction times. Disulfides and bifunctional thiols might be added to the protocol with success.



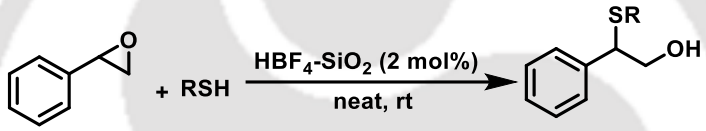
Scheme 6.6. Ring-opening reaction of epoxide ring with simple aliphatic and aromatic thiol

In the presence of Lithium BINOL Phosphate, Ingle *et al*. revealed the formation of β-hydroxyl sulfides from epoxide and aromatic thiol nucleophiles.[14d] The BINOL phosphates have been used to activate epoxides. In terms of epoxide substrates and aromatic thiol nucleophiles, the reaction is versatile. The resultant β-hydroxyl sulfides have a high yield and are enantioselective.



Scheme 6.7. Synthesis of β-hydroxyl sulfides from epoxide and aromatic thiol nucleophile

Bandgar *et al*. revealed the HBF_4-SiO_2 catalyzed regioselective ring-opening of epoxides with thiols.[27] For the first time, high yields of β-hydroxysulfides with outstanding regioselectivity were produced in short reaction durations utilizing a heterogeneous catalyst. Milder reaction conditions, more regioselectivity, a cleaner reaction profile, and excellent yields with minimal experimental effort distinguish the current procedure, making it potentially relevant for industrial applications.

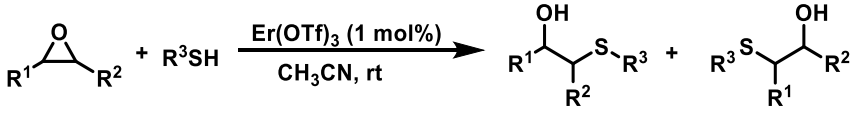


Scheme 6.8. Regioselective ring-opening of epoxides with thiols

Su *et al*. showed remarkable regioselectivity and chemoselectivity in the synthesis of β-hydroxysulfides by ring-opening reaction of epoxides with thiols utilizing gallium(III) triflate.[13d] After the reactions, the catalyst could be easily retrieved and reused with no noticeable loss of activity.

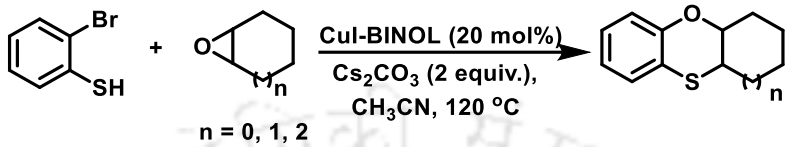
Scheme 6.9. Synthesis of β-hydroxysulfides *via* ring-opening of epoxides with thiol

Dalpozzo *et al.* demonstrated the synthesis of β-hydroxysulfides by ring-opening of epoxides with thiols using mild and efficient Lewis acid catalyst, $Er(OTf)_3$.[13e] The ring-opening reaction of epoxides with erbium(III) triflate are categorized based on chemo- and stereoselectivity. Epoxides can be combined with thiols in the presence of catalytic quantities of Lewis acid under neutral circumstances, yielding high yields of β-hydroxysulfides.



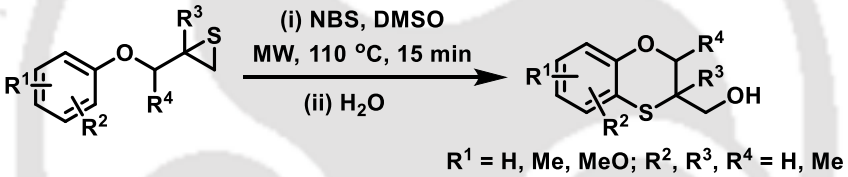
Scheme 6.10. Synthesis of β-hydroxysulfides by ring-opening of epoxides with thiol

Korupalli *et al.* used CuI-BINOL to synthesize 1,4-benzoxathiin from epoxides and *O*-bromothiophenols.[28] With moderate to good yields, 1,4-benzoxathiin moieties can be produced by domino S_N2 ring opening of epoxide with o-halo-thiophenols followed by Ullmann-type coupling cyclization (intramolecular C(aryl)-O bond formation) catalyzed by copper(I)-BINOL.



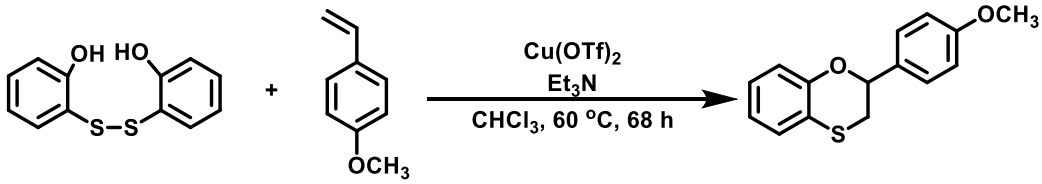
Scheme 6.11. Synthesis of 1,4-benzoxathiin from epoxide and *O*-bromothiophenol

Dong *et al.* demonstrated the synthesis of 3-monosubstituted and 3,3-disubstituted 2,3-dihydrobenzo[*b*][1,4]oxathiins.[19] Microwave-assisted (2,3-Dihydrobenzo[*b*][1,4]oxathiin-3-yl)methanols were synthesized from aryloxymethylthiiranes and *N*-bromosuccinimide (NBS) in DMSO.



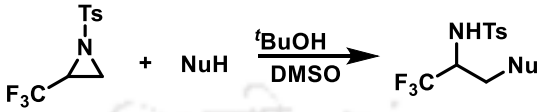
Scheme 6.12. Synthesis of 2,3-dihydro-1,4-benzoxathiin from aryloxymethylthiiranes

Viglianisi et al. devised a copper-catalyzed technique for converting *O,O'*-dihydroxydisulfides into 2,3-dihydrobenzo-1,4-oxathiins. Using a substoichiometric quantity of Cu(II) salts to promote thiolate anion 1,4-elimination at sulphur,[20] *O,O'*-dihydroxydisulfides can be converted to the corresponding *O*-thioquinones. In an inverse electron-demand heterocycle, o-thioquinones are trapped in situ as dienes. Diels–Alder reaction with electron-rich alkenes as dienophiles yields 2,3-dihydrobenzo[*b*][1,4]oxathiin cycloadducts in a single pot.



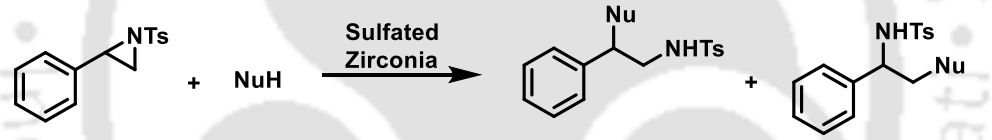
Scheme 6.13. Synthesis of 2,3-dihydro-1,4-benzoxathiins from *O,O'*-dihydroxydisulfides and styrenes

Takehiro *et al.* observed that 2-trifluoromethyl-*N*-tosylaziridine used to have a regioselective ring-opening reaction with various nucleophiles.[29] Under basic circumstances, the ring-opening reaction of 2-trifluoromethyl-*N*-tosyl aziridine with a range of heteroatom- and carbon-centered nucleophiles was accomplished in good yield with remarkable regioselectivity.



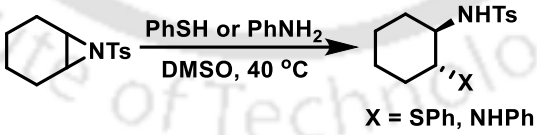
Scheme 6.14. The regioselective ring-opening reaction of 2-trifluoromethyl-*N*-tosyl aziridine with some nucleophiles

Using sulfated zirconia, Llaveria *et al*. reported a regioselective ring-opening reaction of aryl aziridines with alcohols, thiols, amines, and *N*-heteroaromatic compounds.[30] For the regioselective ring-opening of aryl-substituted aziridines, sulfated zirconia is an effective catalyst. This heterogeneous catalyst is compatible with a wide range of acid-sensitive and mildly basic nucleophiles and can be used multiple times without losing activity.



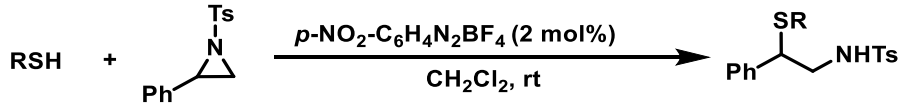
Scheme 6.15. Ring-opening reaction of aryl aziridines with alcohols, thiols, amines, and *N*-heteroaromatic

Wu *et al*. reported the ring-opening of aziridines with various nucleophiles (such as amines, thiols, and silylated nucleophiles) in DMSO under mild circumstances without the use of a catalyst.[31]



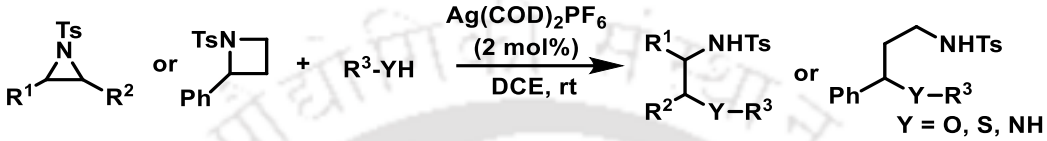
Scheme 6.16. The ring-opening of aziridines with various nucleophiles

Aryldiazonium ion catalyzed *C–N* bond cleavage for the regioselective ring-opening of aziridines was described by Zhang *et al*.[18] The use of aryldiazonium salts to trigger the regioselective cleavage of aziridines for the installation of various functional groups has been demonstrated. At room temperature, the ring-opening mechanism is effective and generic for a variety of nucleophiles. According to the mechanism, a single electron transfer from aziridines to aryldiazonium salts yields a highly reactive amino radical cation.



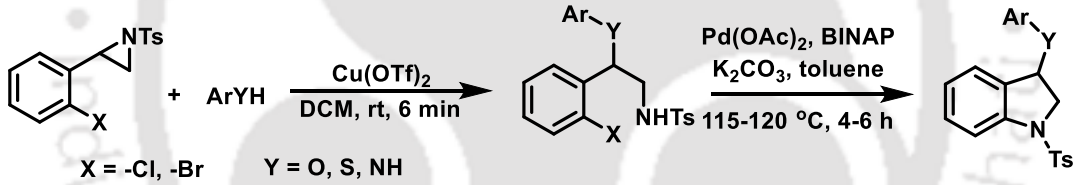
Scheme 6.17. Ring-opening reaction of aziridines with thiol

Bera *et al*. described the regioselective ring-opening of *N*-tosyl aziridine and *N*-tosyl azetidine with *S*-, *O*-, and *N*-nucleophiles and tethered dinucleophiles using $[Ag(COD)_2]PF_6$.[32]



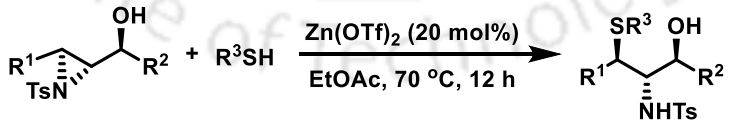
Scheme 6.18. Ring-opening of *N*-tosyl aziridine and N-tosyl azetidine with *S*-, *O*-, and *N*-nucleophiles and tethered dinucleophiles

Ghorai *et al*. revealed the regio- and stereoselective S_N2-type ring-opening of 2-(2-halophenyl)-*N*-tosyl aziridines with heteroatomic nucleophiles, followed by Pd-catalyzed *C*-*N* cyclization.[33] It is one of the useful approaches for the synthesis of indoline.



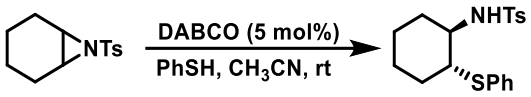
Scheme 6.19. Ring-opening reaction of 2-(2-halophenyl)-*N*-tosyl aziridines with heteroatomic nucleophiles

Liu *et al*. described the Zn-catalyzed ring-opening of sterically unbiased 2,3-aziridinyl alcohols with thiophenols as nucleophiles.[17b] The hydroxyl moiety's directing effect allows for a selective nucleophilic approach on the C-3 position of 2,3-aziridinyl alcohols.



Scheme 6.20. Ring-opening of 2,3-aziridinyl alcohols with thiophenols

Wu *et al*. demonstrated the DABCO catalyzed ring-opening reactions of aziridines with thiols.[16] The use of DABCO as a catalyst, which is air-stable and affordable under mild conditions and with a high degree of operational ease.

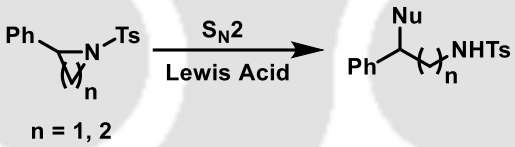


Scheme 6.21. Ring-opening reactions of aziridines with amines or thiols

The $LiClO_4$-catalyzed cleavage of aziridines with thiols to produce β-aminosulfides was reported by Yadav *et al.*[17a] Aziridines to interact effectively with thiols using a catalytic amount of $LiClO_4$ under fundamentally moderate and neutral reaction conditions to give high yields of β-aminosulfides with high regioselectivity.

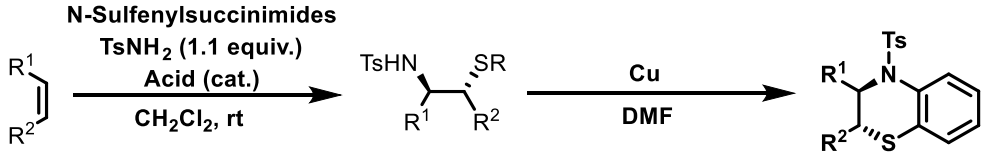
Scheme 6.22. ring-opening reactions of aziridines with thiols

The S_N2-type ring-opening of substituted-*N*-tosyl aziridines with zinc (II) halides was reported by Ghorai *et al.*[34] A highly regioselective ring opening of aziridines with zinc(II) halides to racemic and non-racemic *β*-halo amines in outstanding yield and selectivity is reported using a quaternary ammonium salt. The partial racemization of the starting substrate and the result were efficiently regulated by utilizing quaternary ammonium salts to get the enantioenriched products *via* an S_N2-type pathway.



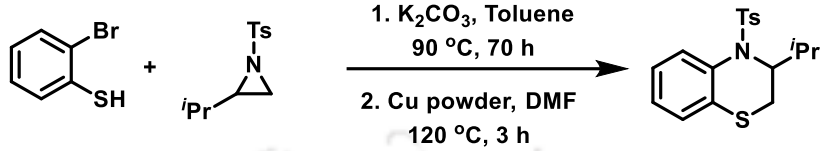
Scheme 6.23. ring opening of substituted-*N*-tosyl aziridines with zinc (II) halides

To obtain β-sulfonylaminosulfides and dihydrobenzothiazines, Liu *et al.* reported intermolecular sulfenoamination of alkenes using sulfonamides and *N*-sulfanylsuccinimides.[22] With sulfonamides as the nitrogen source and *N*-sulfanylsuccinimides as the sulfur source, an acid-catalyzed intermolecular sulfenoamination reaction of alkenes is established. The developed approach was combined with intramolecular *C–N* coupling to obtain dihydrobenzothiazine derivatives.



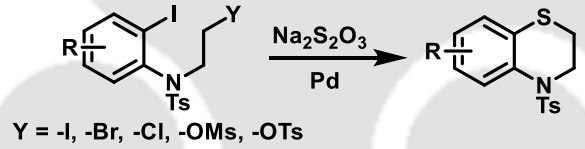
Scheme 6.24. intermolecular sulfenoamination of alkenes with sulfonamides and N-sulfanylsuccinimides

Ghorai *et al.* described a straightforward method for synthesizing dihydro benzothiazines by S_N2-type ring-opening of N-tosyl aziridines with sulfur nucleophiles in a regio- and stereoselective manner followed by intramolecular *C-N* cyclization mediated by copper powder in extremely high yields.[21]



Scheme 6.25. Synthesis of dihydro benzothiazines by S_N2-type ring-opening of *N*-tosyl aziridines

The synthesis of 1,4-benzothiazine was reported by Qiao *et al.* using a palladium catalyst.[35] The development of a unique Pd-catalyzed double *C-S* bond formation coupling reaction has been made. This protocol, which uses $Na_2S_2O_3$ as a sulfurating reagent in metal-catalyzed processes, is an effective way to make substituted 1,4-benzothiazine derivates, which are structural constituents of a variety of bioactivity molecules, making it appealing to both synthetic and medicinal chemistry.



Scheme 6.26. Synthesis 1,4-benzothiazine

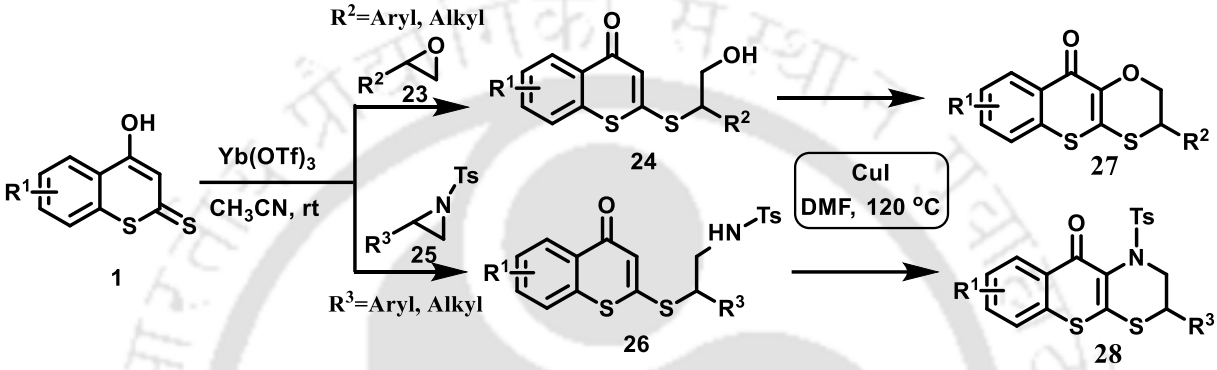
Despite their great utility, many of these methods have drawbacks such as the need for a stoichiometric amount of reagents, harsh reaction conditions, poor regioselectivity, longer reaction times, unsatisfactory yields, and undesirable side products due to oxidation of thiol or rearrangement of epoxide and aziridine. Consequently, there is a further scope to develop a new methodology for ring-opening reaction.

Because of its unique structural properties, 4-hydroxydithiocoumarin has recently been established as a key starting material for the synthesis of novel heterocyclic compounds,[36] and oxidative cross-coupling reactions with suitable electrophiles[37] by our research group and others. In addition, we have also demonstrated recently the synthesis of substituted quinoline derivatives using various epoxides and aromatic amines in the presence of $Yb(OTf)_3$[38] and $Cu(OTf)_2$.[39] Taking the initiative of our earlier results, we hypothesized that β-hydroxysulfides and β-aminosulfides might be

easily accomplished from a ring-opening reaction of epoxide/aziridine with 4-hydroxydithiocoumarin.

6.3. Results and Discussion

Herein, we disclose a simple, elegant, and atom economic approach to access new β-hydroxysulfide derivatives from 4-hydroxydithiocoumarins and epoxides as well as β-aminosulfides from tosyl aziridine by ring-opening reactions in the presence of 2 mol% $Yb(OTf)_3$ in acetonitrile at room temperature. Then, β-hydroxysulfides and β-aminosulfides can further be cyclized to provide 2,3-dihydro-1,4-oxathiin and 2,3-dihydro-1,4-thiazine.

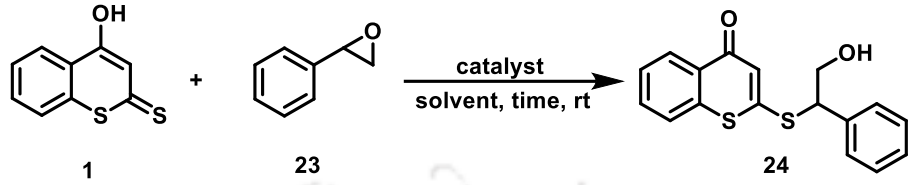


Scheme 6.27. Cyclization of β-hydroxysulfides and β-aminosulfides

For our present study, we have prepared a wide variety of 4-hydroxydithiocoumarins by using the previously reported procedure.[40] To achieve a successful regioselective ring-opening reaction, we have chosen styrene oxide **23** and 4-hydroxydithiocoumarin **1** as the model substrates. Initially, we have carried out a reaction with 4-hydroxydithiocoumarin **1** with the sterically and electronically unbiased epoxide **23** at room temperature in absence of solvent as well as catalyst and no reaction took place (Table 6.1, entry 1). Next, we performed the reaction of epoxide **23** with 4-hydroxydithiocoumarin **1** in CH_3CN at room temperature, and no progress of the reaction was observed (Table 1, entry 2). Next, we have executed the same reaction in the presence of 10 mol% *p*-TSA and the regioselective ring-opening product **24a** isolated in 30% yield (Table 6.1, entry 3). The product **24a** was confirmed by using IR, NMR spectra, and HRMS and are shown in Figure 6.4. In the IR spectrum, -OH gives at 3366 cm^{-1}. In the ^1H NMR spectrum, one broad singlet appears at 5.38 ppm due to the presence of the -OH group. We tried a similar reaction with CSA and $FeCl_3$ to increase the yield of the product, but the yield did not improve appreciably (Table 6.1, entry 4 & 5). Next, we focused our attention to examine the reaction using metal triflates such as copper triflate (1 mol %), and the desired product

24a was obtained in 50% yield within 10 min (Table 6.1, entry 6). By encouraging this result, we switched over our investigation with other metal triflates such as AgOTf, $Bi(OTf)_3$, and $Sc(OTf)_3$, and the outcome of the reactions are shown in

Table 6.1. Optimization of the reaction conditions[a,b]



1 23 24

Entry	Catalyst	Mol (%)	Solvent	Time	Yield[a,b](%)
1	-	-	-	6h	-
2	-	-	CH_3CN	6h	-
3	*p*-TSA	10	CH_3CN	1 h	30
4	CSA	10	CH_3CN	1 h	36
5	$FeCl_3$	10	CH_3CN	1 h	42
6	$Cu(OTf)_2$	1	CH_3CN	10 min	50
7	AgOTf	1	CH_3CN	10 min	40
8	$Bi(OTf)_3$	1	CH_3CN	10 min	45
9	$Sc(OTf)_3$	1	CH_3CN	10 min	35
10	$Yb(OTf)_3$	1	CH_3CN	10 min	70
11	**$Yb(OTf)_3$**	**2**	**CH_3CN**	**10 min**	**83**
12	$Yb(OTf)_3$	5	CH_3CN	10 min	84
13	$Yb(OTf)_3$	10	CH_3CN	10 min	85
14	$Yb(OTf)_3$	2	THF	2 h	20
15	$Yb(OTf)_3$	2	EtOAc	2 h	30
16	$Yb(OTf)_3$	2	$CHCl_3$	2 h	38
17	$Yb(OTf)_3$	2	CH_2Cl_2	2 h	35

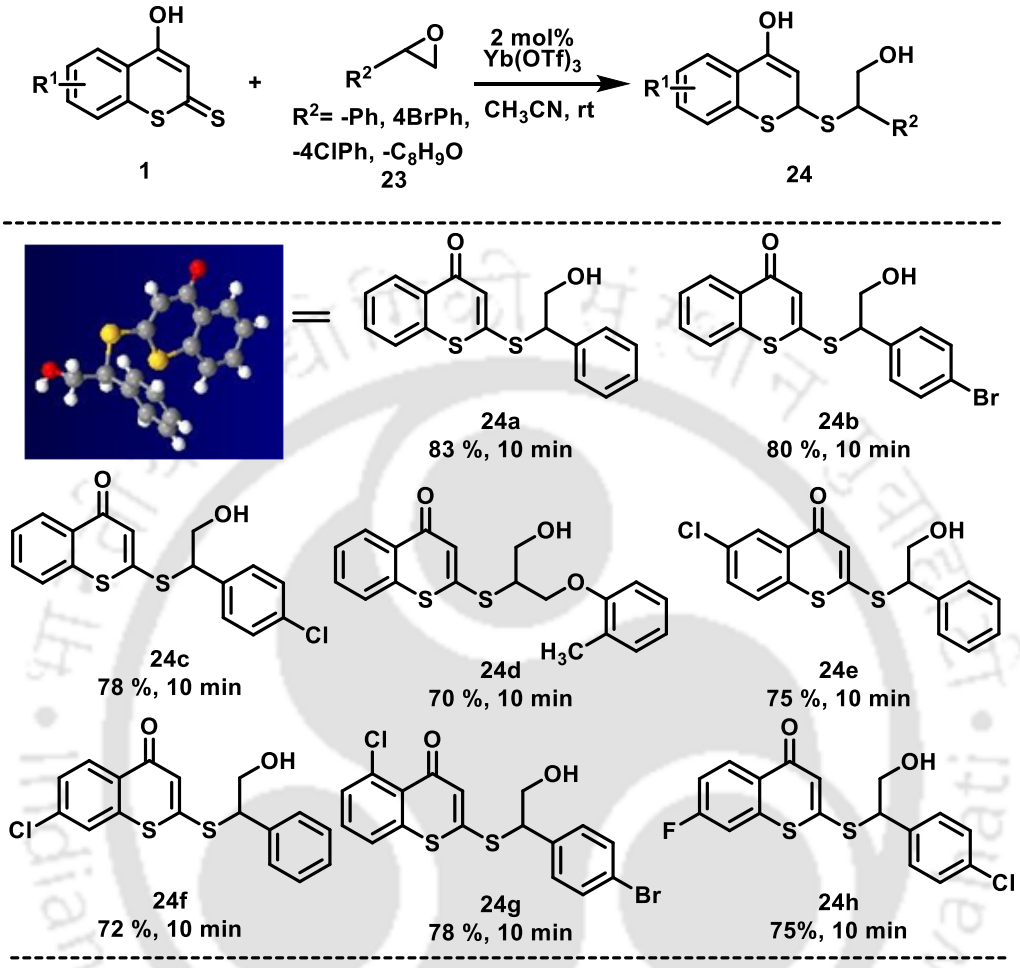
[a]All reactions were carried out with 4-hydroxydithiocoumarins (0.25 mmol) and styrene oxide (0.25 mmol) in the presence of a catalyst in 1 mL solvent at room temperature. [b]Isolated yields.

Table 6.1 (entries 7-9). Interestingly, when the reaction was executed with 1 mol % $Yb(OTf)_3$, it provided the desired product **24a** within 10 min in 70% yield (Table 6.1, entry 10). To find out the requirement of catalyst, we scrutinized the reactions by

increasing the catalyst loading from 2 mol% to 5 mol% to 10 mol% to enhance the yield of the product. From these observations, it was noted that the yield was increased from 70% to 83% yield in 2 mol% $Yb(OTf)_3$ (Table 6.1, entries 11-13). To verify the solvent compatibility, the reactions were also executed in different solvents such as tetrahydrofuran, ethyl acetate, chloroform, and dichloromethane, but the yield of the product **24a** did not improve much after prolonging the reaction time till 2h (Table 6.1, entries 14-17). Based on these findings, we could conclude that 2 mol% $Yb(OTf)_3$ in acetonitrile at room temperature is the optimal reaction condition in terms of reaction time, yield, and selectivity (Table 6.1, entry 11).

With optimal conditions in our hand, we examined the substrate scope of $Yb(OTf)_3$ catalyzed ring-opening reaction by varying the substrates such as 4-hydroxydithiocoumarin **1** and other styrene oxides **23** having different substituents in the phenyl ring (Table 6.2). Then, under identical reaction conditions, 4-hydroxydithiocoumarin was reacted with 2-(4-bromophenyl)oxirane and 2-(4-chlorophenyl)oxirane to obtain the corresponding products **24b** and **24c** in 80 % and 78 % yield, respectively. Moreover, the ether containing epoxide smoothly undergoes the epoxide-opening to furnish the corresponding product **24d** in 70% yield without cleavage of the ether linkage. Various substituted 4-hydroxydithiocoumarins containing substituents such as chloro- and fluoro- at positions 5, 6, and 7 also reacted with different styrene oxides to afford the corresponding β-hydroxysulfide **24e-h** in relatively good yields.

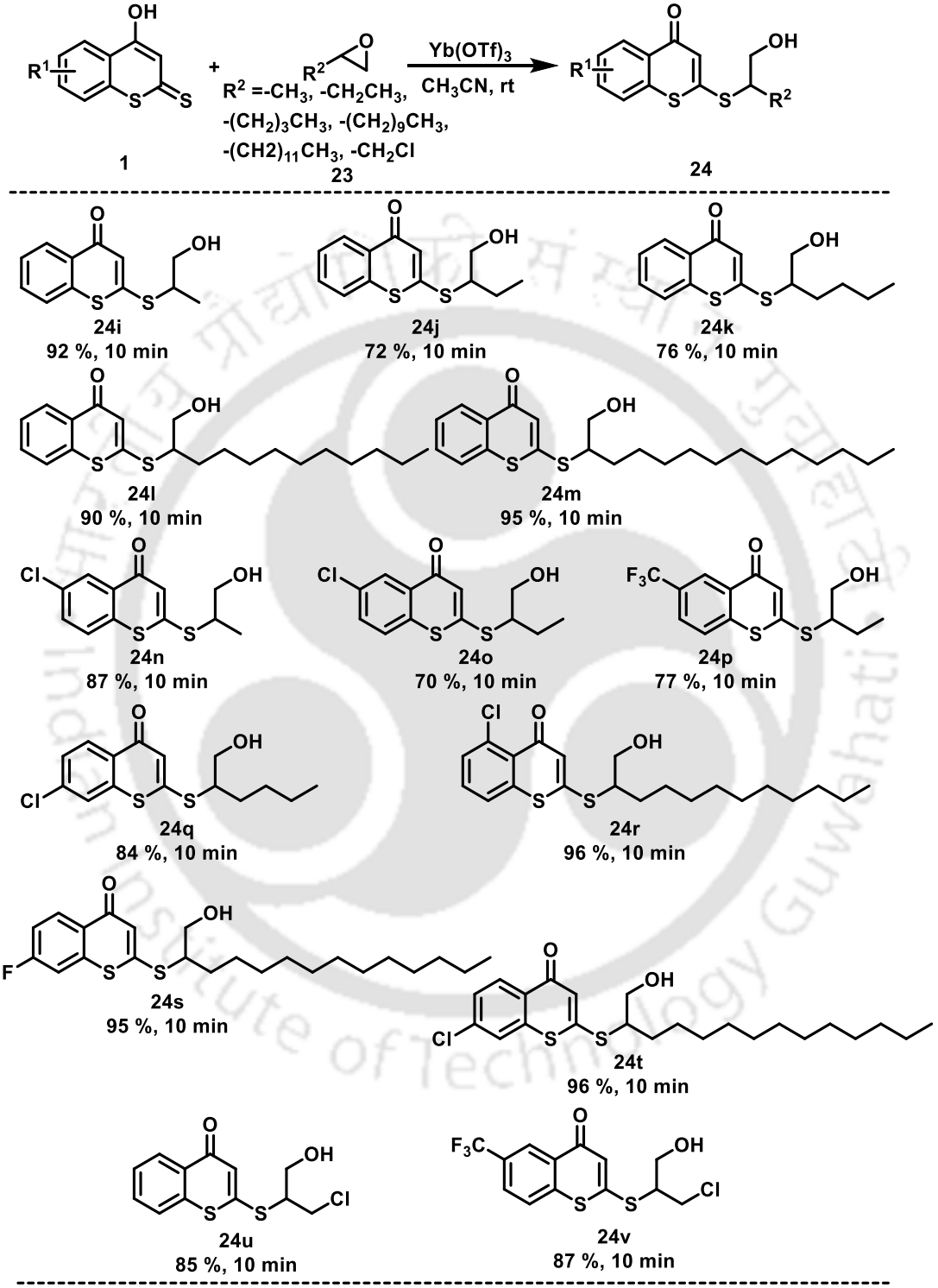
Table 6.2. Ring-opening reaction of various styrene oxides with different 4-hydroxydithiocoumarins



[a]All reactions were carried out with substituted 4-hydroxydithiocoumarins (0.25 mmol) and substituted styrene oxides (0.25 mmol) in the presence of $Yb(OTf)_3$(2 mol%) in 1 mL CH_3CN at room temperature. [b]Isolated yields.

By encouraging these results, we thought whether our synthetic methods could be extended further to aliphatic epoxide or not. Initially, 4-hydroxydithiocoumarin **1** reacted with propylene oxide to give the corresponding product **24i** in excellent yield with the same selectivity. The substrate scope and generality of the protocol were explored with various aliphatic epoxides and a variety of substituted 4-hydroxydithiocoumarins. Next, we have studied the reaction behaviour of 4-hydroxydithiocoumarins with various epoxides such as 1,2-epoxybutane, 1,2-

Table 6.3. Ring opening reaction of various aliphatic epoxide with different 4-hydroxydithiocoumarins

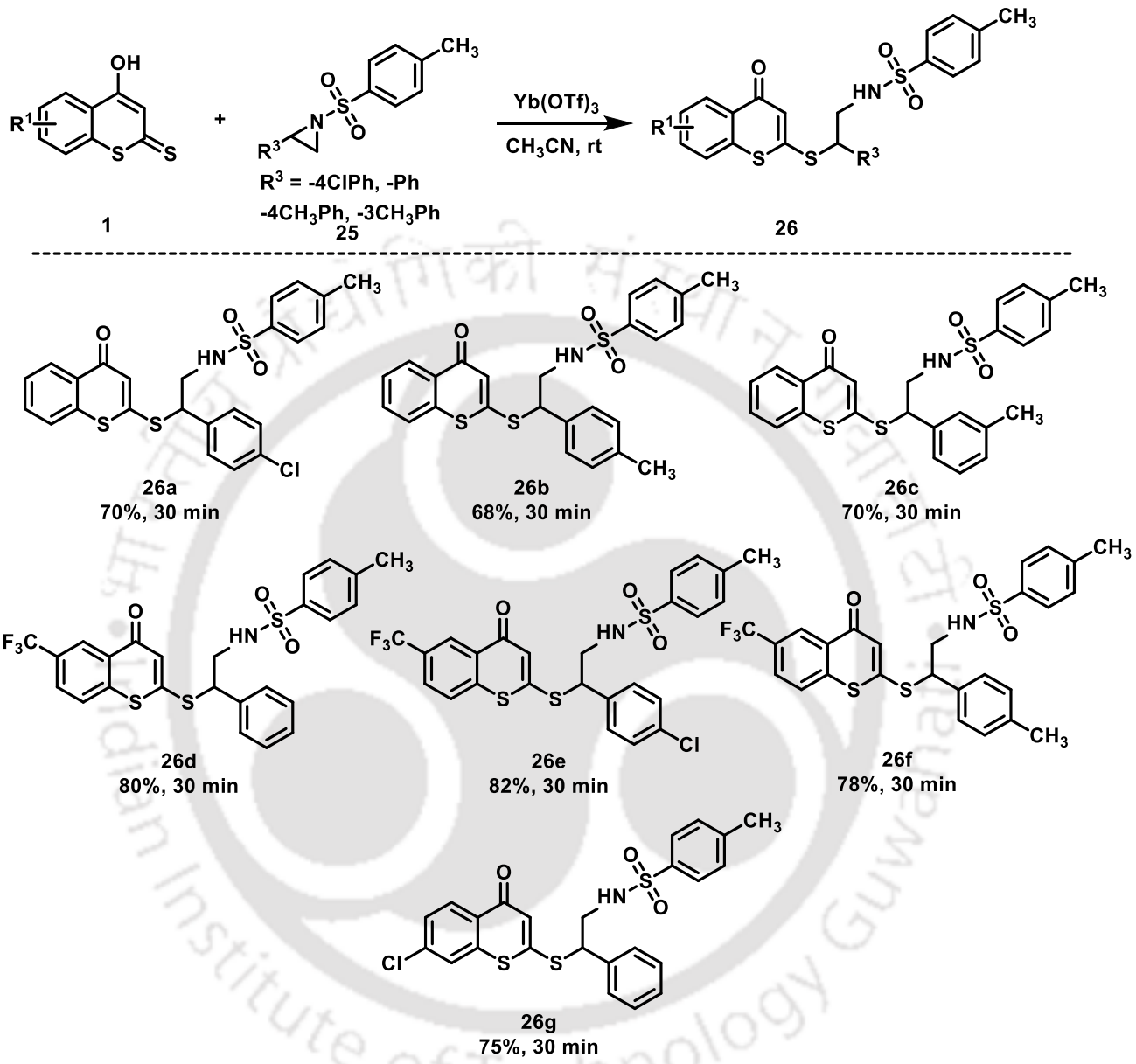


[a]All reactions were carried out with substituted 4-hydroxydithiocoumarins (0.25 mmol) and substituted aliphatic epoxides (0.25 mmol) in the presence of $Yb(OTf)_3$ (2 mol%) in 1 mL CH_3CN at room temperature. [b]Isolated yields.

epoxyhexane, 1,2-epoxydodecane, and 1,2-epoxytetradecane to deliver the β-hydroxysulfides **24j-m** in good to excellent yields. Moreover, we have also investigated the reaction behavior between 6-chloro-4-hydroxydithiocoumarin with propylene oxide as well as 1,2-epoxybutane to give rise to the products **24n** and **24o** with moderate yields. Similarly, the reaction between 6-trifluoro-4-hydroxydithiocoumarin with 1,2-epoxybutane was also examined to afford the desired product **24p** with moderate yield. Likewise, the reaction of 7-chloro-4-hydroxydithiocoumarin with 1,2-epoxyhexane provided the product **24q** in 84% yield. Moreover, the reaction of 5-chloro-4- hydroxydithiocoumarin with 1,2-epoxydodecane gave the desired product **24r** in 96% yield. Thereafter, 7-fluoro and 7-chloro substituted 4-hydroxydithiocoumarin upon reaction with 1,2-epoxytetradecane successfully provided the product **24s** and **24t**, respectively. Subsequently, we have also examined the reaction between 4-hydroxydithiocoumarin and 6-trifluoro-4-hydroxydithiocoumarin with epichlorohydrin, and the expected product **24u** and **24v** were isolated in 85% and 87% yield. From all the studies on this reaction, we can conclude that the procedure applies to both styrene oxides and aliphatic epoxides.

Next, we have put forward our effort for a ring-opening reaction with aziridine to access β-aminosulfides. For this purpose, we have to prepare different tosyl aziridine derivatives by the literature reported method.[41] Motivated with the successful results of ring-opening with 4-hydroxydithiocoumarin and epoxide, we further investigated the generality of the protocol with similar *N*-containing three-membered tosyl aziridine, and results are summarized in Table 6.4. Initially, the reaction of 4-hydroxydithiocoumarin and tosylaziride with -Cl, CH_3 in the *para*- position and -CH_3 in the *meta*- position yielded the products **26a-c** in 68-70% yields. It is noteworthy to mention that the electron-donating as well as electron-withdrawing substituents present on the aromatic ring of tosyl aziridine, were well tolerated. Likewise, 6-trifluoro-4-hydroxydithiocoumarin with simple tosyl aziridine and tosyl aziridine having –Cl and –CH_3 at the *para* position delivered the desired products **26d-f** in moderate yields. Thereafter, the reaction between 7-chloro-4-hydroxydithiocoumarin and tosyl aziridine is examined and the product **26g** was obtained in 75% yield.

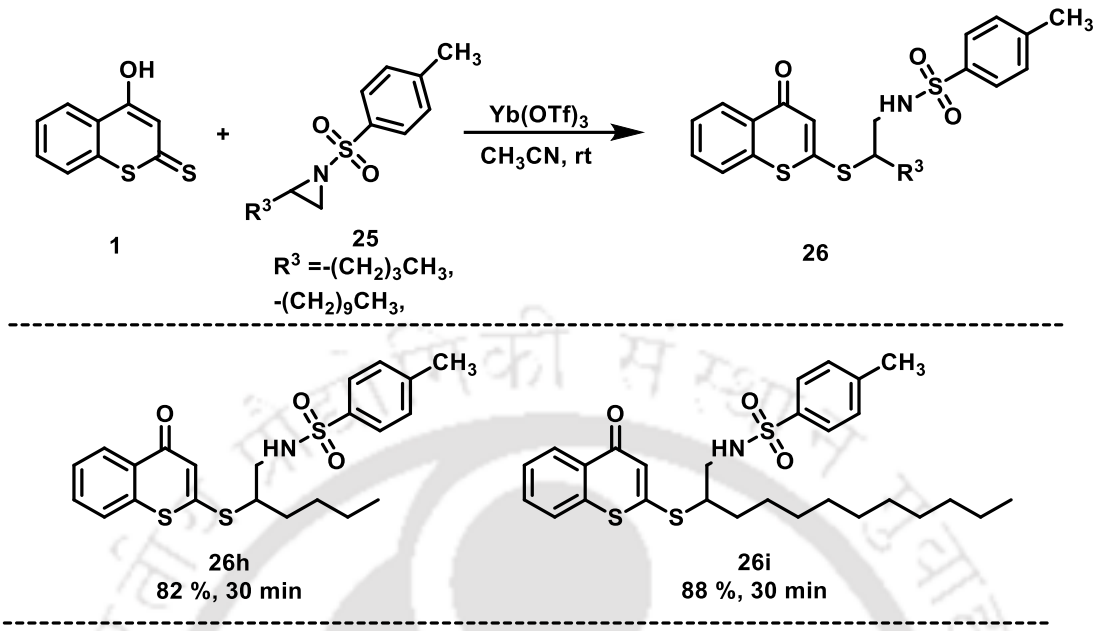
Table 6.4. Ring-opening reaction of various tosyl aziridines with different 4-hydroxydithiocoumarins



[a]All reactions were carried out with substituted 4-hydroxydithiocoumarins (0.25 mmol) and substituted tosyl aziridines (0.25 mmol) in the presence of $Yb(OTf)_3$ (2 mol%) in 1 mL CH_3CN at room temperature. [b]Isolated yields.

We have performed a similar set of reactions with aliphatic tosyl aziridine[42] to extend the substrate scopes. 4-Hydroxydithiocoumarin **1** reacted with tosyl aziridine containing hexyl and dodecyl group to afford the corresponding product **26h** and **26i** in excellent yield with the same selectivity.

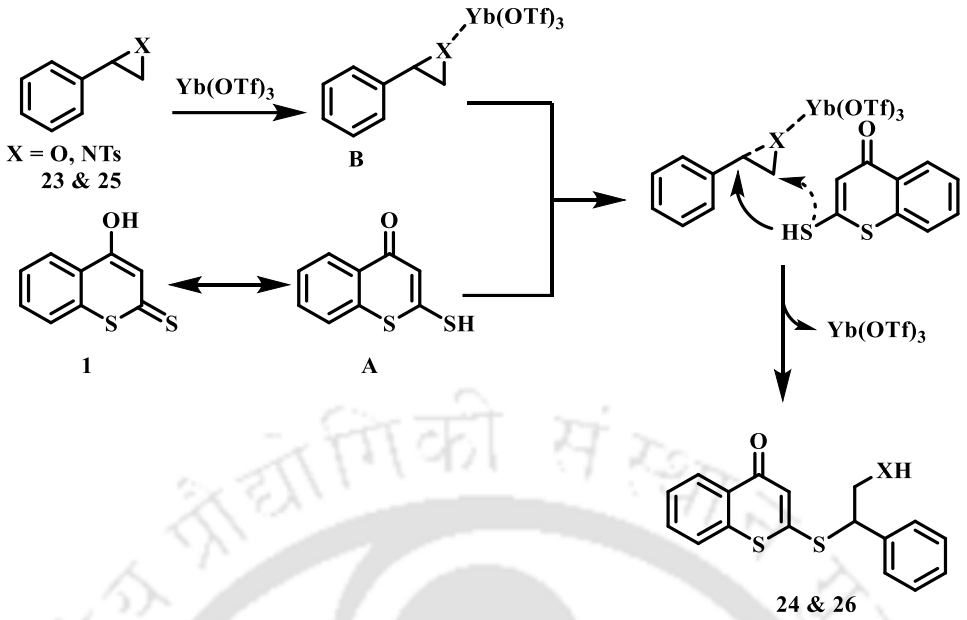
Table 6.5. Ring-opening reaction of aliphatic tosyl aziridines with 4-hydroxydithiocoumarin



[a]All reactions were carried out with 4-hydroxydithiocoumarins (0.25 mmol) and aliphatic tosyl aziridines (0.25 mmol) in the presence of $Yb(OTf)_3$ (2 mol%) in 1 mL CH_3CN at room temperature. [b]Isolated yields

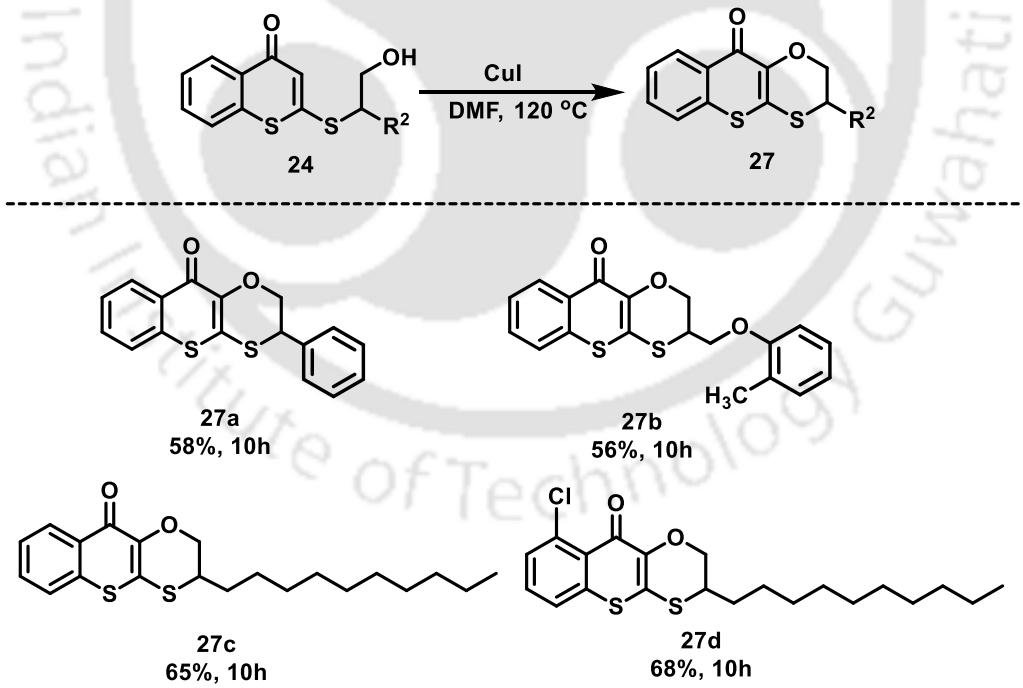
All the synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR spectra, and HRMS analyses. Additionally, the structure of compound **24a** was also ascertained by single X-ray crystallographic data. Some of the represented ^1H NMR spectra, ^{13}C NMR spectra, and HRMS are given in Figure 6.5, Figure 6.6, and Figure 6.7 for compounds **24i**, **26a**, and **26h**.

Based on the isolated product and literature, a plausible mechanism is drawn in Scheme 6.28. Initially, $Yb(OTf)_3$, which acts as a Lewis acid, coordinated with a heteroatom (O, N) of a three-membered ring to give the activated species **B**. Then, the *in situ* generated thiol (**A**) from 4-hydroxydithiocoumarin is reacted with species **B** in a regioselective manner. The regioselective attack of species **B**, possibly due to the benzylic or secondary carbocation character, may occur at the more hindered sites.[11]



Scheme 6.28. Plausible mechanism for ring-opening reaction

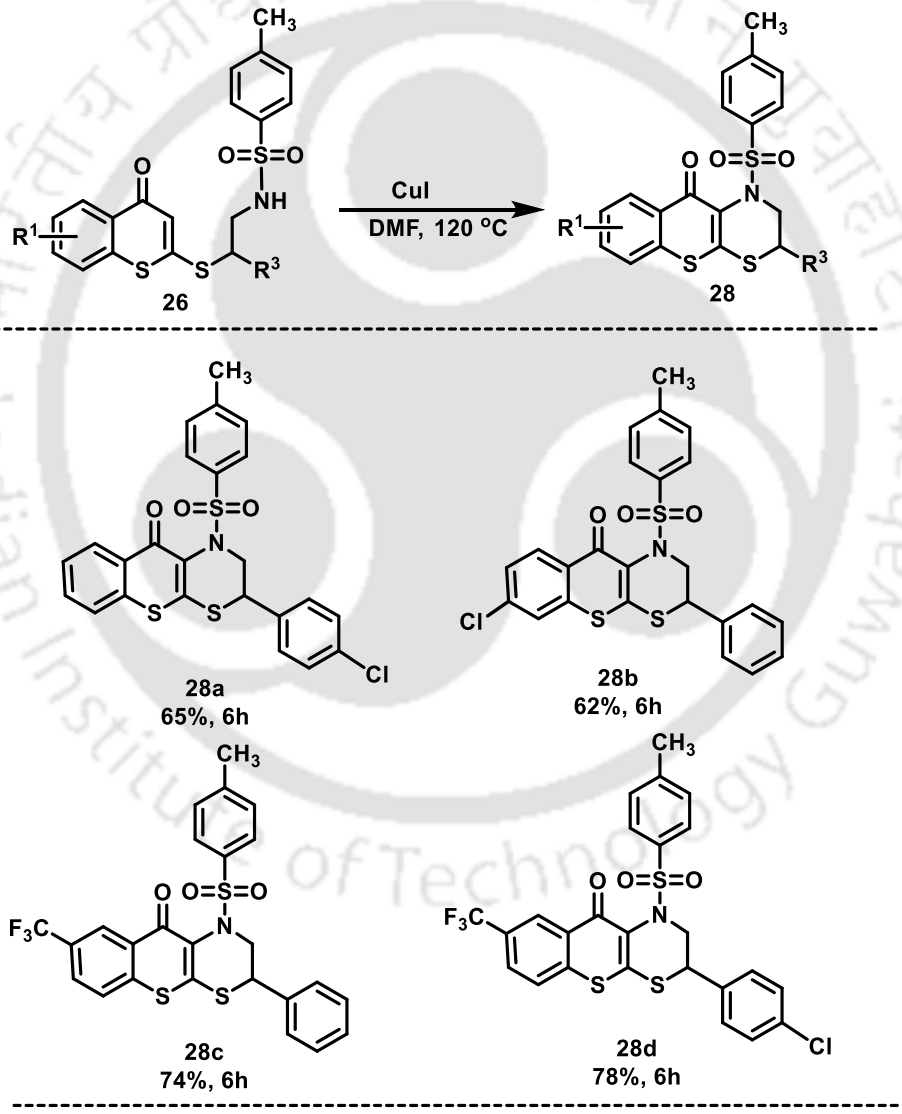
Table 6.6. Synthesis of 1,4-oxathiin derivatives *via* ring-closing reaction of β-hydroxysulfide[a,b]



[a]All reactions were carried out with β-hydroxysulfide (0.10 mmol) in the presence of CuI (10 mol%) in 1 mL DMF at 120 °C. [b]Isolated yields

Taking cues from the copper-catalyzed sp^2 C-H functionalization,[43] we explored our synthetic strategy further for the synthesis of 2,3-dihydro-1,4-oxathiin derivatives **27** and 2,3-dihydro-1,4-thiazine derivatives **28**. We initiated the reaction with β-hydroxysulfide in the presence of CuI in DMF at 120 ˚C and obtained the product 2,3-dihydro-1,4-oxathiin (**27a** to **27d**) in good yield. The structures of the compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS. In the ^{1}H NMR, the disappearance of peaks at 6.98 ppm for C-3 proton and 5.38 ppm for the -OH group indicate the cyclization of the ring-opening product.

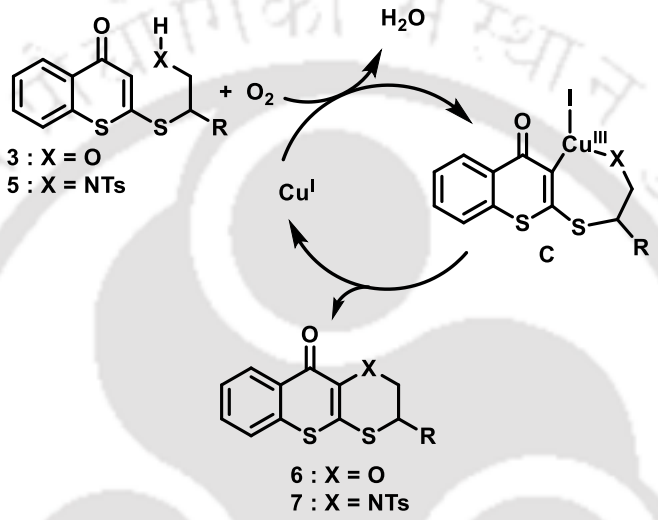
Table 6.7. Synthesis of 1,4-thiazine *via* ring-opening reaction of β-aminosulfide



[a]All reactions were carried out with β-aminosulfide (0.10 mmol) in the presence of CuI (10 mol%) in 1 mL DMF at 120 °C. [b]Isolated yields

A similar synthetic approach was also applied on β-aminosulfides to obtain the product 2,3-dihydro-1,4-thiazine (**28a**-**28d**). The ^{1}H NMR spectra, ^{13}C NMR spectra, and HRMS are shown in Figure 6.8 and Figure 6.9 for the compound **27c** and **28c**, respectively.

At first, Cu(I)iodide and ring-opening product **(24**/**26**) interact with each other in the presence of aerial O_2 and create a reactive Cu(III) intermediate *via* an electrophilic metallation or C–H bond activation.[44] The product is delivered by reductive elimination, and at the same time, Cu(III) is converted to Cu (I) and again participated in the catalytic cycle.



Scheme 6.29. A plausible mechanism for the ring-closing reaction

6.4. Biological Application

6.4.a. Treatment with compounds 24e, 24m, 24i, 26a, and 26e reduces cell viability of breast and cervical cancer cell lines:

Treatment of MCF-7 and HeLa cells with the compounds **24e**, **24m**, **24i**, **26a**, and **26e** for 48 h resulted in a dose-dependent reduction in cell viability. However, in HeLa, the compounds **26a** and **26e** did not attain IC_{50} even at higher concentrations up to 200 μM. The determined IC_{50} values of the respective compounds are listed in Table 6.8.

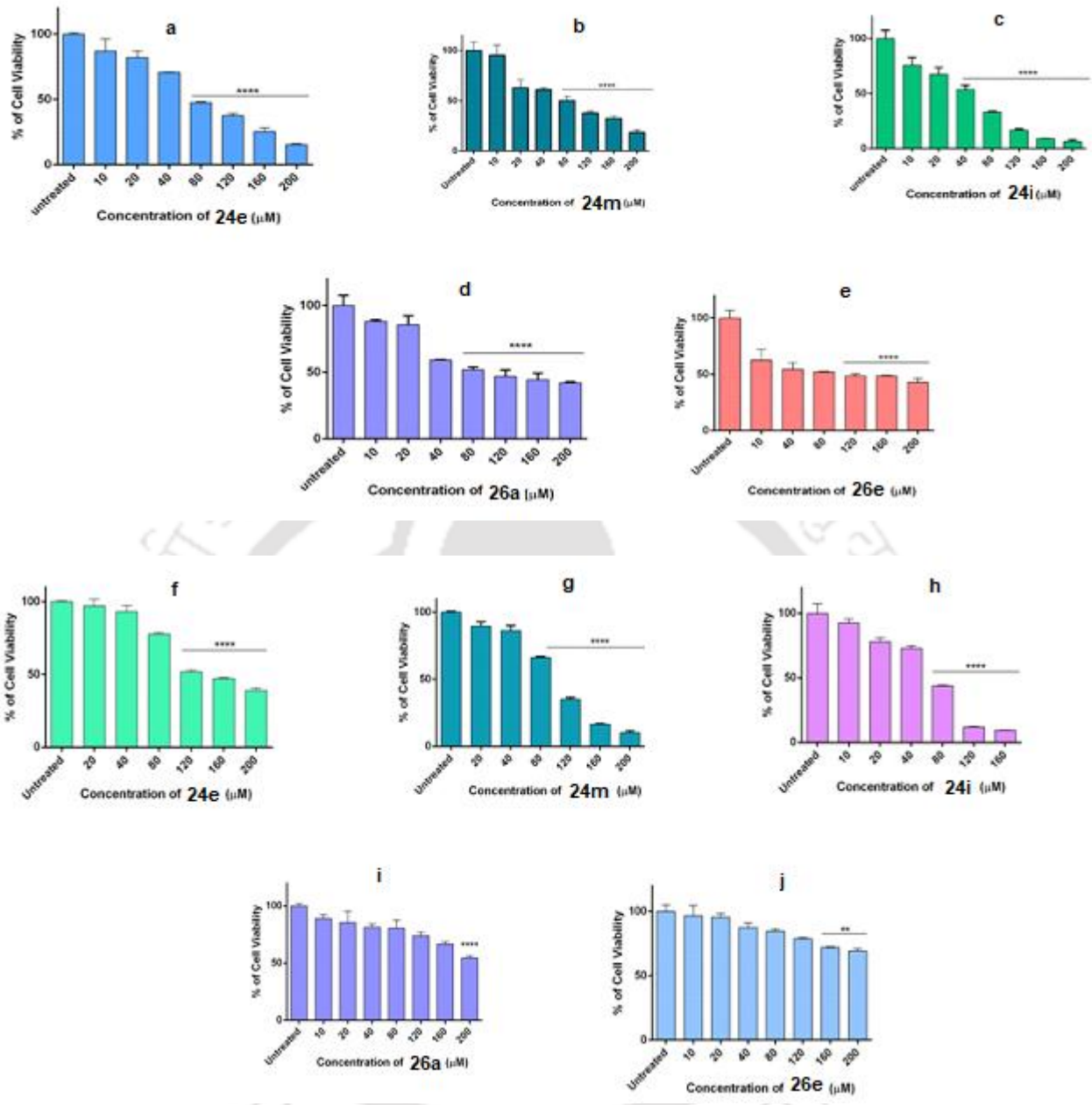


Figure 6.2. (a), (b), (c), (d) and (e) graphically represents the dose-dependent decrease in cell viability upon treatment with **24e, 24m, 24i, 26a, and 26e** in MCF-7. (f), (g), (h), (i) and (j) graphically represents the dose-dependent decrease in cell viability upon treatment with **24e, 24m, 24i, 26a,** and **26e** in HeLa.

The results of cell viability MTT assay insinuates that three compounds, **24e**, **24m**, **24i** possess modest anti-proliferative effect for further structural-activity relationship studies.

Table 6.8. Anti-proliferative activity of synthesized compounds against MCF-7 and HeLa cells

	Compound	IC_{50} (µM)	
Sl. No.		MCF-7	HeLa
1	24m	67.62	171.8
2	24e	65.99	76.79
3	24i	33.92	50.16
4	26a	99.49	Not attained
5	26e	94.66	Not attained

6.4.b. Treatment with compounds 24e, 24m, 24i, 26a, and 26e generates ROS in breast and cervical cancer cells

Treatment with the compounds resulted in the enhancement of cellular ROS levels in both MCF-7 and HeLa cells. The fold change in cellular ROS level due to treatment with the compounds is enlisted in Table 6.9. Therefore, it is anticipated that the cell death was possibly due to ROS-mediated cell damage. Whereas in the case of HeLa, the increase in ROS did not lead to cell death.

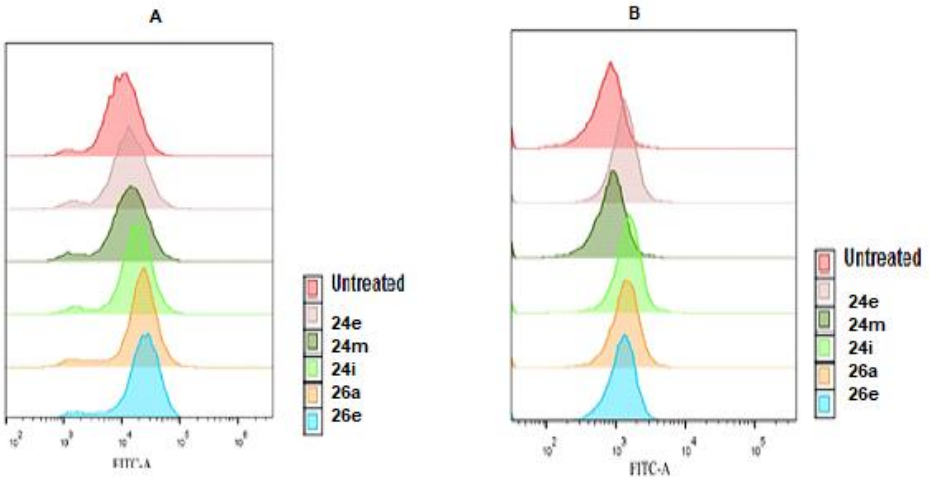


Figure 6.3. Flow cytometric detection of cellular ROS in (A) MCF-7 and (B) HeLa

Table 6.9. Tabular representation of the fold change in cellular ROS level in MCF-7 and HeLa following treatment with compounds.

Compound	MCF-7	HeLa
24e	1.363	1.126
24m	1.334	1.743
24i	1.671	1.985
26a	2.0	1.843
26e	2.17	1.609

6.5. Conclusion

In conclusion, we have synthesized new β-hydroxysulfides and β-aminosulfides derivatives using 2 mol% $Yb(OTf)_3$ catalyst from 4-hydroxydithiocoumarin and epoxides/N-tosyl aziridines, respectively. Moreover, this methodology is useful due to its mild reaction conditions, good yields, high regioselectivity, shorter reaction time, and broad substrates scope. Synthetic uses are also discussed for vinyl sulfide as well as for sulfone derivatives for which the direct method fails. Moreover, a few of those newly reported compounds showed moderate anti-proliferative effects on breast and cervical cancer cell lines with enhanced production of ROS. In addition, β-hydroxysulfide and β-aminosulfide can be easily converted to the 2,3-dihydro-1,4-oxathiin and 2,3-dihydro-1,4-thiazine derivatives, respectively. β-Hydroxysulfide can be used for the synthesis of respective propionic acid derivatives known for their anti-inflammatory activity, such as ibuprofen and naproxen, which is under study and will be published in due course. Moreover, our synthetic strategy is under investigation for the asymmetric ring-opening reaction of epoxide/tosyl aziridine for the synthesis of optically active β-hydroxysulfides and β-aminosulfides and it will be reported after completing the study.

6.6. Experimental Section

6.6.a. General procedure for the synthesis of 4-hydroxydithiocoumarin (1a-f)

Various 4-hydroxydithiocoumarins were synthesized by the previously reported method.[40]

6.6.b. General procedure for the synthesis of aromatic aziridine derivatives.[41]

To a stirred solution of styrene derivatives (1.0 mmol) and benzytriethylammonium chloride (0.05 mmol) in CH_2Cl_2/H_2O (2:1, 10 mL) were added chloramine T (1.1 mmol) and iodine (0.1 mmol) at room temperature under N_2. The stirring was continued for 24 h, then treated with a saturated $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3X10 mL). Drying with anhydrous Na_2SO_4 and evaporation of solvent on rotary evaporator gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as eluent.

6.6.c. General procedure for the synthesis of aliphatic aziridine derivatives.[42]

0.5 mmol of trimethylphenylammonium tribromide was added to a mixture of chloramin T (1.1 mmol) and aliphatic alkene (1.0 mmol) in CH_3CN (5 mL) at ambient temperature. The reaction mixture was stirred for 15 h and concentrated. The residue was dissolved in DCM and filtered through a short column using hexane and ethyl acetate. The solvent was evaporated and dissolved in CH_3CN. 4.0 mmol of K_2CO_3 was added to it and stirred the reaction mixture at 45 ˚C for 2 h. The reaction mixture was cooled to ambient temperature and diluted the reaction mixture with Et_2O. It was filtered through the celite and concentrated. The crude residue was subjected to a column on silica gel using hexane and ethyl acetate as eluent.

6.6.d. General Procedure for the Synthesis of β-hydroxysulfides and β-aminosulfides derivatives (24 and 26)

A mixture of 4-hydroxydithiocoumarin (**1**, 0.25 mmol) and 2 mol % $Yb(OTf)_3$ was taken in 1 mL of acetonitrile into a 25 mL round-bottomed flask. Then, styrene oxide or tosylaziridine (**23** or **25**, 0.25 mmol) was added into the above reaction mixture and kept for stirring at room temperature. The progress of the reaction was monitored by checking

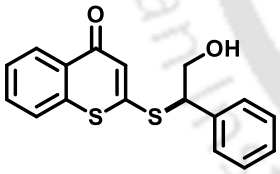
TLC from time to time. After completion of the reaction, acetonitrile was removed in a rotatory evaporator and the crude residue was extracted with ethyl acetate (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4, and it was concentrated in a rotatory evaporator. Finally, the crude residue was purified by using silica gel column chromatography to obtain the desired products. The pure products are eluted with ethyl acetate and hexane mixture (2:8).

6.6.e. General Procedure for the Synthesis of derivatives (27 and 28)

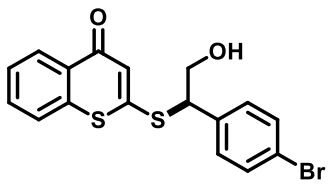
Into a 10 mL round-bottomed flask, 0.10 mmol of β-hydroxysulfide (**24**)/β-aminosulfide (**26**) and 10 mol% CuI was taken in a 1 mL DMF. The reaction mixture was placed on a stirrer at 120 ˚C. The reaction was monitored by using TLC. After completion of the reaction, we kept it for cooling and then extracted it with ethyl acetate (2X10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a rotatory evaporator. At last, the crude residue was purified by using silica gel column chromatography to obtain the products 2,3-dihydro-1,4-oxathiin (**27**) and 2,3-dihydro-1,4-thiazine (**28**).

6.6. Characterization

2-((2-hydroxy-1-phenylethyl)thio)-4*H*-thiochromen-4-one (24a). Brown solid (65 mg, 83%); mp 123-124 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (dd, J = 8.0, 1.1 Hz, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.57 (td, J = 7.6, 7.1, 1.2 Hz, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.29 – 7.25 (m, 1H), 6.98 (s, 1H), 5.38 (bs, 1H), 4.88 (t, J = 6.4 Hz, 1H), 3.91 (dd, J = 11.4, 6.4 Hz, 1H), 3.83 (dd, J = 11.4, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 177.6, 151.8, 138.2, 137.2, 132.1, 129.9, 128.5, 128.2, 127.8, 127.7, 126.1, 124.8, 64.4, 54.8; IR (KBr)ν_{max}3366, 1731, 1582 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{15}O_2S_2$ ($M + H^+$) 315.0508; Found 315.0508.

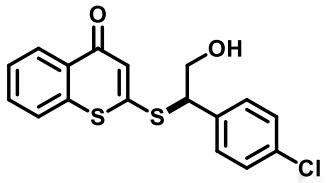


2-((1-(4-bromophenyl)-2-hydroxyethyl)thio)-4*H*-thiochromen-4-one (24b). Brown solid (78 mg, 80%); mp 130-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.52-7.49 (m, 4H), 7.29 (d, J = 8.1 Hz, 2H), 7.03 (s, 1H), 4.65 (t, J = 6.5 Hz, 1H), 4.03 (d, J = 6.6 Hz, 2H); ^{13}C NMR (150



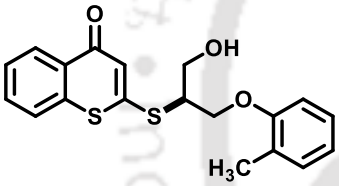
MHz, $CDCl_3$) δ 179.3, 151.0, 138.2, 136.3, 132.3, 131.9, 130.5, 129.9, 128.8, 128.1, 128.1, 126.9, 125.6, 122.6, 65.5, 55.0; IR (KBr)ν_{max}3367, 1737 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{14}BrO_2S_2$ ($M + H^+$) 392.9613; Found 392.9608.

2-((1-(4-chlorophenyl)-2-hydroxyethyl)thio)-4*H*-thiochromen-4-one (24c). White



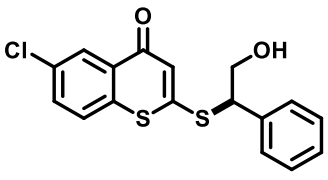
solid (68 mg, 78%); mp 137-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.37 – 7.33 (m, 4H), 7.03 (s, 1H), 4.66 (t, *J* = 6.5 Hz, 1H), 4.04 (d, *J* = 6.6 Hz, 2H), 2.02 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 150.1, 138.2, 135.9, 134.6, 131.8, 130.8, 129.6, 129.4, 128.9, 128.1, 127.8, 125.7, 65.6, 55.3; IR (KBr)ν_{max}3370, 1731 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{14}ClO_2S_2$ ($M + H^+$) 349.0118; Found 349.0120.

2-((1-hydroxy-3-(*o*-tolyloxy)propan-2-yl)thio)-4*H*-thiochromen-4-one (24d). Brown



solid (63 mg, 70%); mp 97-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.42 (m, 1H), 7.57 (td, *J* = 7.8, 1.5 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.3 Hz, 2H), 7.09 (s, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 4.36 – 4.31 (m, 1H), 4.13 – 4.09 (m, 2H), 3.51 (dd, *J* = 13.9, 5.2 Hz, 1H), 3.37 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.63 (bs, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 156.2, 153.2, 137.7, 131.7, 130.9, 128.8, 128.0, 127.0, 126.7, 125.5, 124.2, 121.3, 111.1, 69.9, 69.0, 37.2, 16.4; IR (KBr)ν_{max} 3361, 1732 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{19}O_3S_2$ ($M + H^+$) 359.0770; Found 359.0791.

6-chloro-2-((2-hydroxy-1-phenylethyl)thio)-4*H*-thiochromen-4-one (24e). Brown



solid (65 mg, 75%); mp 138-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.3 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 1.6 Hz, 2H), 7.37 (s, 1H), 7.35 – 7.32 (m, 2H), 7.03 (s, 1H), 4.69 (t, *J* = 6.6 Hz, 1H), 4.07 – 4.04 (m, 2H), 2.11 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 151.4, 137.0, 136.3, 134.6, 132.1, 131.9, 129.3, 128.8, 128.5, 128.2, 127.0, 126.8, 65.8, 55.9;

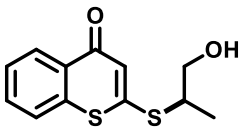
IR(KBr)ν_{max}3420, 1734 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{14}ClO_2S_2$ ($M + H^+$) 349.0118; Found 349.0118.

7-chloro-2-((2-hydroxy-1-phenylethyl)thio)-4*H*-thiochromen-4-one (24f). Brown liquid (63 mg, 72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.6 Hz, 1H), 7.48 (s, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.38 (dd, *J* = 12.8, 5.5 Hz, 4H), 7.33 (d, *J* = 7.1 Hz, 1H), 7.00 (s, 1H), 4.67 (t, *J* = 6.6 Hz, 1H), 4.06 (d, *J* = 7.7 Hz, 2H), 1.93 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 150.6, 139.6, 138.5, 137.0, 130.4, 129.3, 129.2, 128.8, 128.7, 128.2, 127.5, 125.0, 65.8, 56.0; IR(KBr)ν_{max} 3425, 1736 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{14}ClO_2S_2$ ($M + H^+$) 349.0118; Found 349.0118.

2-((1-(4-bromophenyl)-2-hydroxyethyl)thio)-5-chloro-4*H*-thiochromen-4-one (24g). Brown liquid (83 mg, 78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 3H), 7.41 – 7.35 (m, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.93 (s, 1H), 4.61 (t, *J* = 6.5 Hz, 1H), 4.02 (dd, *J* = 6.6, 3.4 Hz, 2H), 2.34 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 147.4, 141.1, 136.4, 136.4, 132.3, 131.8, 131.1, 129.9, 128.8, 127.7, 127.6, 124.7, 122.7, 65.6, 55.2; IR(KBr)ν_{max} 3340,1738 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{13}ClBrO_2S_2$ ($M + H^+$) 426.9223; Found 426.9201.

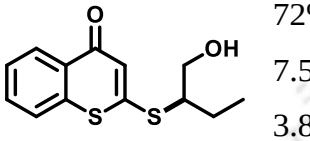
2-((1-(4-chlorophenyl)-2-hydroxyethyl)thio)-7-fluoro-4*H*-thiochromen-4-one (24h). Brown liquid (68 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 9.0, 5.8 Hz, 1H), 7.36- 7.34 (m, 4H), 7.22 – 7.16 (m, 2H), 7.00 (s, 1H), 4.65 (t, *J* = 6.5 Hz, 1H), 4.03 (dd, *J* = 6.5, 3.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 165.2, 163.2, 150.1, 140.4, 140.3, 135.8, 134.6, 132.0, 131.9, 129.6, 129.4, 127.6, 127.6, 127.4, 116.7, 116.5, 111.8, 111.6, 65.6, 55.3; IR(KBr)ν_{max}3383, 1739 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{13}ClFO_2S_2$ ($M + H^+$) 367.0024; Found 367.0023.

2-((1-hydroxypropan-2-yl)thio)-4*H*-thiochromen-4-one (24i). Brown liquid (58 mg, 92%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H),

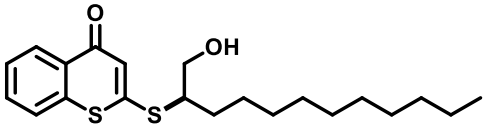


7.46 – 7.42 (m, 2H), 6.99 (s, 1H), 4.13 – 4.07 (m, 1H), 3.22 (dd, *J* = 13.5, 4.7 Hz, 1H), 3.14 (dd, *J* = 13.5, 7.3 Hz, 1H), 2.98 (bs, 1H), 1.33 (d, *J* = 6.2 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 154.1, 137.7, 131.6, 130.6, 128.7, 127.9, 125.4, 123.4, 66.1, 42.2, 22.4; IR(KBr)ν_{max}3359, 1737 cm^{-1}; HRMS (ESI) Calcd For $C_{12}H_{13}O_2S_2$ (M + H$^+$) 253.0351; Found 253.0350.

2-((1-hydroxybutan-2-yl)thio)-4*H*-thiochromen-4-one (24j). Brown liquid (48 mg, 72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.00 (d, *J* = 1.3 Hz, 1H), 3.85 – 3.81 (m, 1H), 3.28 (dd, *J* = 13.4, 4.0 Hz, 1H), 3.11 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.67 (bs, 1H), 1.69 – 1.57 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 154.0, 137.7, 131.6, 130.7, 128.7, 127.9, 125.5, 123.6, 71.2, 40.8, 29.4, 9.9; IR(KBr)ν_{max} 3372, 2925, 1737 cm^{-1}; HRMS (ESI) Calcd For $C_{13}H_{15}O_2S_2$ (M + H$^+$) 267.0508; Found 267.0517.



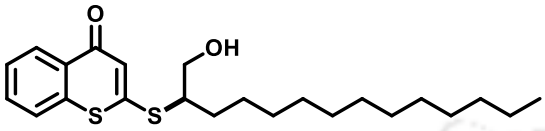
2-((1-hydroxyhexan-2-yl)thio)-4*H*-thiochromen-4-one (24k). Brown liquid (56 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.44 (m, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 6.9 Hz, 2H), 7.03 (s, 1H), 3.92 – 3.86 (m, 1H), 3.30 (dd, *J* = 13.5, 3.8 Hz, 1H), 3.10 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.30 (bs, 1H), 1.60 (dd, *J* = 11.1, 4.9 Hz, 2H), 1.35 (dd, *J* = 9.2, 4.6 Hz, 4H), 0.93 – 0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 153.8, 137.8, 131.7, 130.7, 128.8, 128.0, 125.5, 123.8, 70.0, 41.2, 36.2, 27.8, 22.7, 14.1; IR(KBr)ν_{max} 3400, 2928 2862, 1735 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{19}O_2S_2$ (M + H$^+$) 295.0821; Found 295.0819.



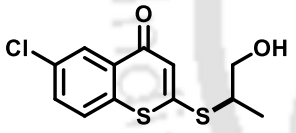
2-((1-hydroxydodecan-2-yl)thio)-4*H*-thiochromen-4-one (24l). Off white solid (85 mg, 90%); mp 83-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.45 (m, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 6.4 Hz, 2H), 7.05 (s, 1H), 3.92 – 3.86 (m, 1H), 3.31 (dd, *J* = 13.5, 3.5 Hz, 1H), 3.10 (dd, *J* = 13.5, 8.1 Hz, 1H), 1.87 (bs, 1H), 1.60 –1.57 (m, 2H), 1.52-1.37 (m, 2H), 1.25 (s, 14H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 153.5, 137.8, 131.7, 130.8, 128.9, 128.0, 125.6, 124.1,

70.1, 41.3, 36.5, 32.0, 29.7, 29.7, 29.6, 29.4, 25.7, 22.8, 14.2; IR(KBr)ν_{max} 3331, 2917, 2848, 1731 cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{31}O_2S_2$ ($M + H^+$) 379.1760; Found 379.1765.

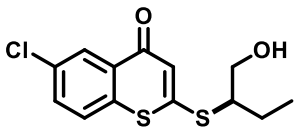
2-((1-hydroxytetradecan-2-yl)thio)-4*H*-thiochromen-4-one (24m). Off white solid (96 mg, 95%); mp 84-86 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.53 – 7.40 (m, 2H), 7.03 (s, 1H), 3.89 (dd, *J* = 8.1, 4.0 Hz, 1H), 3.31 (dd, *J* = 13.6, 3.7 Hz, 1H), 3.12 – 3.07 (m, 1H), 2.14 (d, *J* = 4.5 Hz, 1H), 1.58 (s, 4H), 1.47 (bs, 1H), 1.25 (s, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 153.1, 137.8, 131.7, 130.9, 128.9, 128.0, 125.6, 124.3, 70.1, 41.4, 36.5, 32.0, 29.8, 29.7, 29.7, 29.6, 29.4, 25.7, 22.8, 14.2; IR(KBr)ν_{max} 3345, 2915, 2848, 1731 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{35}O_2S_2$ ($M + H^+$) 407.2073; Found 407.2080.



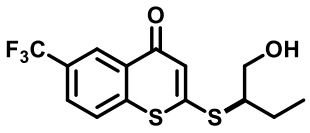
6-chloro-2-((1-hydroxypropan-2-yl)thio)-4*H*-thiochromen-4-one (24n). Brown solid (62 mg, 87%); mp 90-91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 6.99 (s, 1H), 4.13 – 4.07 (m, 1H), 3.25 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.16 – 3.11 (m, 1H), 2.45 (s, 1H), 1.35 (d, *J* = 6.2 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 154.3, 135.8, 134.5, 132.0, 131.8, 128.4, 126.9, 123.3, 66.3, 42.4, 22.5; IR(KBr)ν_{max} 3376, 2928, 1734 cm^{-1}; HRMS (ESI) Calcd For $C_{12}H_{12}ClO_2S_2$ ($M + H^+$) 286.9962; Found 286.9970.



6-chloro-2-((1-hydroxybutan-2-yl)thio)-4*H*-thiochromen-4-one (24o). Brown solid (52 mg, 70%); mp 128-130 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.00 (s, 1H), 3.86 – 3.82 (m, 1H), 3.30 (dd, *J* = 13.5, 3.8 Hz, 1H), 3.11 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.49 (br, 1H), 1.69 – 1.58 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 154.1, 135.8, 134.5, 132.0, 131.9, 128.4, 126.9, 123.5, 71.38, 40.9, 29.4, 9.9; IR(KBr)ν_{max}3408, 2967, 1740 cm^{-1}; HRMS (ESI) Calcd For $C_{13}H_{14}ClO_2S_2$ ($M + H^+$) 301.0118; Found 301.0131.

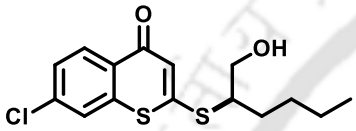


2-((1-hydroxybutan-2-yl)thio)-6-trifluoromethyl)-4*H*-thiochromen-4-one (24p).



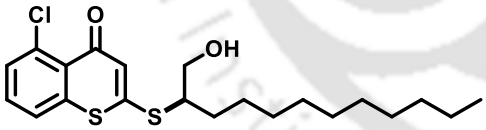
Brown liquid (64 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.78 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H), 3.88 – 3.82 (m, 1H), 3.33 (dd, *J* = 13.5, 3.7 Hz, 1H), 3.13 (dd, *J* = 13.5, 8.1 Hz, 1H), 1.65 – 1.60 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.7, 154.2, 141.2, 127.8, 127.7, 126.4, 126.3, 126.3, 123.7, 71.3, 40.8, 29.5, 10.0; IR(KBr)ν_{max} 3345, 2945, 1742 cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{14}F_3O_2S_2$ (M + H$^+$) 335.0382; Found 335.0387.

7-chloro-2-((1-hydroxyhexane-2-yl)thio)-4*H*-thiochromen-4-one (24q). Light yellow



solid (69 mg, 84%); mp 110-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.6 Hz, 1H), 7.50 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.00 (s, 1H), 3.92 – 3.86 m, 1H), 3.30 (dd, *J* = 13.5, 3.7 Hz, 1H), 3.10 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.15 (bs, 1H), 1.61 – 1.59 (m, 2H), 1.48 – 1.45 (m, 2H), 1.36 – 1.35 (m, 2H), 0.92 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 153.3, 139.1, 138.5, 130.4, 129.2, 128.6, 124.9, 124.2, 70.1, 41.4, 36.2, 27.8, 22.7, 14.0; IR(KBr)ν_{max} 3345, 2953, 2928, 2855, 1726 cm^{-1}; HRMS (ESI) Calcd For $C_{15}H_{18}ClO_2S_2$ (M + H$^+$) 329.0431; Found 329.0446.

5-chloro-2-((1-hydroxydodecan-2-yl)thio)-4*H*-thiochromen-4-one (24r). Off white



solid (99 mg, 96%); mp 86-88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, *J* = 4.5 Hz, 1H), 7.40 (d, *J* = 4.6 Hz, 2H), 6.94 (s, 1H), 3.90 – 3.85 (m, 1H), 3.27 (dd, *J* = 13.5, 3.8 Hz, 1H), 3.07 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.12 (bs, 1H), 1.59 (d, *J* = 5.3 Hz, 3H), 1.48 (dd, *J* = 10.1, 4.5 Hz, 1H), 1.26 (s, 14H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 150.0, 140.7, 136.5, 131.8, 131.0, 127.7, 125.8, 124.6, 70.2, 41.3, 36.5, 32.0, 29.7, 29.7, 29.6, 29.4, 25.7, 22.8, 14.2;IR(KBr)ν_{max}3403, 2922, 2852, 1739 cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{30}ClO_2S_2$ (M + H$^+$) 413.1370; Found 413.1370.

7-fluoro-2-((1-hydroxytetradecan-2-yl)thio)-4*H*-thiochromen-4-one (24s). Yellow solid (100 mg, 95%); mp 103-105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 7.9, 5.5 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.00 (s, 1H), 3.91 – 3.87 (dq, *J* = 8.0, 4.0 Hz, 1H), 3.30 (ddd, *J* = 13.5, 3.7, 1.2 Hz, 1H), 3.10 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.13 (bs, 1H), 1.60 – 1.56 (m, 4H), 1.51 – 1.44 (m, 1H), 1.26 (s, 17H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 165.2, 163.1, 139.9, 139.8, 131.9, 131.9, 127.5, 124.3, 116.5, 116.4, 111.7, 111.5, 70.2, 41.5, 36.5, 32.0, 29.8, 29.7, 29.7, 29.6, 29.4, 25.7, 22.8, 14.2; IR(KBr)ν_{max}3332, 2918, 2849, 1740 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{34}FO_2S_2$ ($M + H^+$) 425.1979; Found 425.1980.

7-chloro-2-((1-hydroxytetradecan-2-yl)thio)-4*H*-thiochromen-4-one (24t). Off white solid (105 mg, 96%); mp 118-119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.7 Hz, 1H), 7.50 – 7.44 (m, 2H),7.00 (s, 1H), 3.89 (s, 1H), 3.30 (d, *J* = 12.6 Hz, 1H), 3.10 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.21 (bs, 1H), 1.60 (s, 4H), 1.48 (s, 1H), 1.25 (s, 17H), 0.88 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 153.3, 139.1, 138.5, 130.4, 129.2, 128.6, 124.9, 124.2, 76.9, 76.8, 70.1, 41.4, 36.5, 32.0, 29.8, 29.7, 29.7, 29.6, 29.4, 25.7, 22.8, 14.2; IR(KBr)ν_{max}3334, 2919, 2849, 1739 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{34}ClO_2S_2$ ($M + H^+$) 441.1683; Found 441.1682.

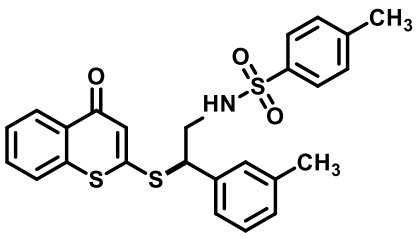
2-((1-chloro-3-hydroxypropan-2-yl)thio)-4*H*-thiochromen-4-one (24u). Off white solid (60 mg, 85%); mp 110-111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.07 (s, 1H), 4.18 – 4.13 (m, 1H), 3.77 – 3.70 (m, 2H), 3.36 (dd, *J* = 14.0, 5.4 Hz, 1H), 3.30 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.86 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 152.1, 137.7, 131.8, 130.8, 128.9, 128.1, 125.6, 125.0, 69.8, 48.0, 37.6; IR (KBr)ν_{max}3259, 2969, 1740 cm^{-1}; HRMS (ESI) Calcd For $C_{12}H_{12}ClO_2S_2$ ($M + H^+$) 286.9962; Found. 286.9950.

2-((1-chloro-3-hydroxypropan-2-yl)thio)-6-trifluoromethyl)-4*H*-thiochromen-4-one (24v). Off white solid (77 mg, 87%); mp 126-128 °C; ^{1}H NMR

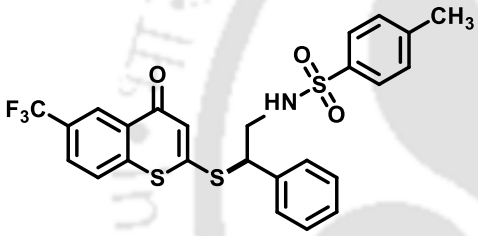
(500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.09 (s, 1H), 4.18 – 4.15 (m, 1H), 3.77 – 3.70 (m, 2H), 3.38 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.31 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.74 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 153.0, 141.1, 130.9, 130.6, 130.4, 127.9, 127.9, 127.8, 127.8, 126.5, 126.4, 126.4, 126.3, 126.3, 124.6, 69.9, 47.9, 37.5; IR(KBr)ν_{max} 3350, 1738 cm^{-1}; HRMS (ESI) Calcd For $C_{13}H_{11}ClF_3O_2S_2$ ($M + H^+$) 354.9836; Found 354.9838.

***N*-(2-(4-chlorophenyl)-2-((4-oxo-4*H*-thiochromen-2-yl)thio)ethyl)-4-methylbenzenesulfonamide (26a).** Brown liquid (87 mg, 70%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.93 (s, 1H), 4.93 (t, *J* = 6.6 Hz, 1H), 4.55 (t, *J* = 7.3 Hz, 1H), 3.54 – 3.48 (m, 1H), 3.46 – 3.39 (m, 1H), 2.39 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 149.0, 144.1, 138.2, 136.9, 135.3, 134.9, 131.9, 130.8, 130.0, 129.5, 129.4, 128.9, 128.3, 128.2, 127.2, 125.7, 52.4, 47.5, 21.6; IR(KBr)ν_{max}3247, 1739 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{21}ClNO_3S_3$ ($M + H^+$) 502.0367; Found 502.0369.

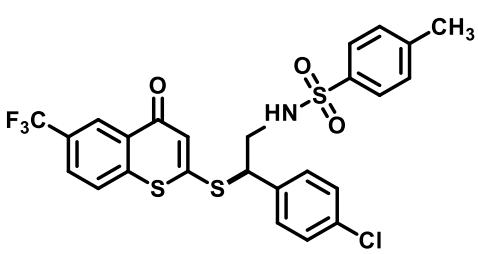
4-methyl-*N*-(2-((4-oxo-4*H*-thiochromen-2-yl)thio)-2-(*p*-tolyl)ethyl)benzenesulfonamide (26b). Brown liquid (81 mg, 68%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.58 (m, 1H), 7.54 – 7.49 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.13 (s, 4H), 6.91 (s, 1H), 4.68 (t, *J* = 6.6 Hz, 1H), 4.49 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.55 – 3.51 (m, 1H), 3.47 - 3.44 (m, 1H), 2.39 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 149.6, 144.0, 139.0, 138.3, 137.0, 133.4, 131.8, 130.8, 130.1, 130.0, 128.9, 128.1, 128.0, 127.9, 127.2, 125.7, 52.5, 47.5, 21.6, 21.2; IR(KBr)ν_{max}3239, 1737 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{24}NO_3S_3$ ($M + H^+$) 482.0913; Found 482.0914.

4-methyl-*N*-(2-((4-oxo-4*H*-thiochromen-2-yl)thio)-2-(*m*-tolyl)ethyl)benzenesulfonamide (26c). 

Light yellow liquid (84 mg, 70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 8.0, 1.6 Hz,1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.57 (m, 1H), 7.53 – 7.48 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 6.7 Hz, 2H), 6.93 (s, 1H), 4.97 (t, *J* = 6.5 Hz, 1H), 4.51 (dd, *J* = 8.3, 6.5 Hz, 1H), 3.55 – 3.51 (m, 1H), 3.48 – 3.46 (m, 1H), 2.37 (s, 3H), 2.30 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 149.8, 143.9, 139.2, 138.3, 137.1, 136.4, 131.8, 130.8, 129.9, 129.8, 129.2, 128.9, 128.7, 128.1, 127.8, 127.2, 125.7, 125.1, 52.7, 47.6, 21.6, 21.5; IR(KBr)ν_{max} 3252, 1734 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{24}NO_3S_3$ ($M + H^+$) 482.0913; Found 482.0917.

4-methyl-*N*-(2-((4-oxo-6-(trifluoromethyl)-4*H*-thiochromen-2-yl)thio)-2-phenylethyl)benzenesulfonamide (26d). 

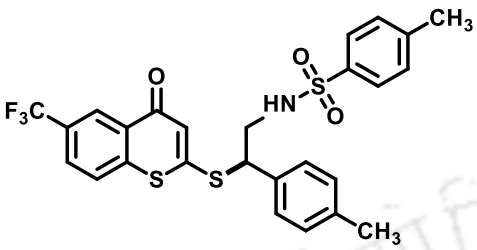
Pale yellow solid (107 mg, 80%); mp 152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.78 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.33 – 7.29 (m, 3H), 7.26 (s, 2H), 7.25 (s, 2H), 6.95 (s, 1H), 4.98 (t, *J* = 6.7 Hz, 1H), 4.61 (t, *J* = 7.4 Hz, 1H), 3.56 – 3.46 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 150.5, 144.0, 141.6, 137.0, 136.4, 130.9, 130.6, 130.3, 130.0, 129.4, 129.1, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 127.2, 126.6, 126.3, 126.3, 126.3, 126.2, 53.0, 47.6, 21.6; IR(KBr)ν_{max}3255, 1738 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{21}F_3NO_3S_3$ ($M + H^+$) 536.0630; Found 536.0642.

***N*-(2-(4-chlorophenyl)-2-((4-oxo-6-(trifluoromethyl)-4*H*-thiochromen-2-yl)thio)ethyl-4-methylbenzenesulfonamide (26e).** 

Yellow solid (116 mg, 82%); mp 165 °C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 1H), 7.25 (s, 2H), 7.22 (t, *J* = 8.0 Hz, 3H), 6.97 (s, 1H), 5.27 (t, *J* = 6.5 Hz, 1H), 4.64 (t, *J* = 7.3 Hz, 1H), 3.50 (q, *J* = 7.0 Hz, 1H), 3.47 – 3.42 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 150.4, 144.1, 141.5, 136.8, 135.1, 134.9, 130.8, 130.0, 129.5, 129.4, 127.9, 127.9, 127.9, 127.8,

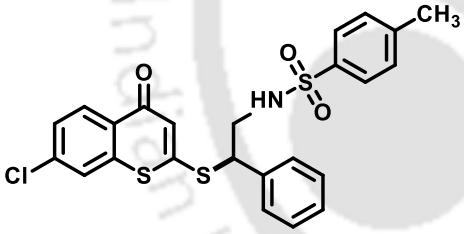
127.5, 127.1, 126.6, 126.3, 126.3, 126.2, 126.2, 52.4, 47.5, 21.6; IR(KBr)ν_{max}3261, 1722 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{20}ClF_3NO_3S_3$ ($M + H^+$) 570.0240; Found 570.0245.

4-methyl-*N*-(2-((4-oxo-6-(trifluoromethyl)-4*H*-thiochromen-2-yl)thio)-2-(*p*-tolyl)



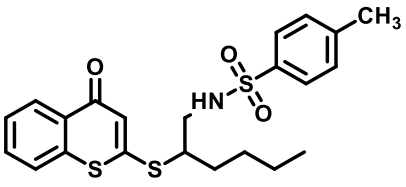
ethyl)benzenesulfonamide (26f). Light yellow liquid (107 mg, 78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.78 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 7.13 (s, 4H), 6.94 (s, 1H), 4.87 (t, *J* = 6.6 Hz, 1H), 4.57 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.56 – 3.53 (m, 1H), 3.47 – 3.41 (m, 1H), 2.39 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 150.7, 144.0, 141.7, 139.1, 137.0, 133.2, 130.9, 130.1, 130.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.4, 127.2, 126.6, 126.3, 126.3, 126.3, 126.2, 52.7, 47.6, 21.6, 21.2; IR(KBr)ν_{max} 3363, 1739 cm^{-1}; HRMS (ESI) Calcd For $C_{26}H_{23}F_3NO_3S_3$ ($M + H^+$) 550.0787; Found 550.0787.

***N*-(2-((7-chloro-4-oxo-4*H*-thiochromen-2-yl)thio)-2-phenylethyl)-4-methylbenzene-**



sulfonamide (26g). Light yellow liquid (93 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 3H), 7.27 (s, 1H), 7.24 (d, *J* = 5.3 Hz, 3H), 6.89 (s, 1H), 4.99 (s, 1H), 4.55 (t, *J* = 7.4 Hz, 1H), 3.55 – 3.46 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 149.6, 144.0, 139.5, 138.6, 137.0, 136.5, 130.4, 130.0, 129.4, 129.1, 129.0, 128.7, 128.0, 128.0, 127.2, 125.0, 53.0, 47.5, 21.6; IR(KBr)ν_{max} 3244, 1731 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{21}ClNO_3S_3$ ($M + H^+$) 502.0367; Found 502.0345.

4-methyl-*N*-(2-((4-oxo-4*H*-thiochromen-2-yl)thio)hexyl)benzenesulfonamide (26h). Off



white liquid (82%, 91 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.51 (q, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 5.02 – 4.92 (m, 1H), 3.55 – 3.48 (m, 1H), 3.25 (dd, *J* = 13.4, 5.1 Hz, 1H), 3.09 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.32 (s, 3H),

1.61 (dd, *J* = 9.7, 4.9 Hz, 1H), 1.50 – 1.44 (m, 1H), 1.25 – 1.11 (m, 4H), 0.77 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 151.5, 142.6, 136.5, 136.4, 130.6, 129.6, 128.7, 127.7, 126.9, 126.0, 124.4, 123.2, 51.8, 37.9, 32.7, 26.3, 21.1, 20.4, 12.7; IR(KBr)ν_{max} 3244, 2801, 1731 cm^{-1}; HRMS (ESI) Calcd For $C_{22}H_{26}NO_3S_3$ (M + H$^+$) 448.1069; Found 448.1067.

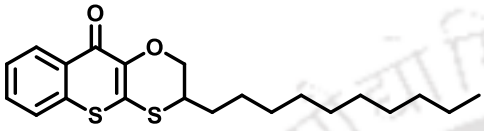
4-methyl-*N*-(2-((4-oxo-4*H*-thiochromen-2-yl)thio)dodecyl)benzenesulfonamide (26i). Off white solid (88%, 117 mg); mp 96-97 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.59 (td, *J* = 7.5, 1.6 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.88 (s, 1H), 4.87 (d, *J* = 7.9 Hz, 1H), 3.52 (ddt, *J* = 7.9, 5.6, 4.1 Hz, 1H), 3.27 (dd, *J* = 13.5, 5.0 Hz, 1H), 3.10 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.32 (s, 3H), 1.59 (dt, *J* = 8.7, 4.6 Hz, 1H), 1.50 – 1.42 (m, 1H), 1.28 – 1.18 (m, 9H), 1.10 (d, *J* = 4.7 Hz, 7H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 152.4, 143.7, 137.6, 137.3, 131.6, 130.6, 129.7, 128.7, 127.9, 127.1, 125.4, 124.4, 52.9, 38.9, 33.9, 31.8, 29.5, 29.4, 29.3, 29.3, 29.0, 25.2, 22.6, 21.4, 14.1; IR(KBr)ν_{max} 3216, 2780, 1735 cm^{-1}; HRMS (ESI) Calcd For $C_{28}H_{38}NO_3S_3$ (M + H$^+$) 532.2008; Found 532.2001.

3-Phenyl-2,3-dihydro-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (27a). Light yellow liquid (58%, 18 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, J = 7.8, 1.1 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.54 – 7.50 (m, 2H), 7.42 – 7.39 (m, 4H), 7.38 – 7.37 (m, 1H), 4.72 (dd, J = 10.8, 2.8 Hz, 1H), 4.47 (dd, J = 9.1, 2.8 Hz, 1H), 4.33 (dd, J = 10.8, 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 157.6, 136.4, 132.9, 131.7, 129.2, 129.0, 128.8, 128.3, 127.3, 125.8, 42.5; IR(KBr)ν_{max} 2923, 1720 cm^{-1}; HRMS (ESI) Calcd For $C_{17}H_{13}O_2S_2$ (M + H$^+$) 313.0351; Found 313.0352.

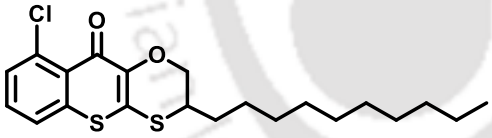
3-((*O*-tolyloxy)methyl)-2,3-dihydro-10*H*-thiochromeno[3,2-*b*][1,4]oxathiin-10-one (27b). Light yellow liquid (56%, 20 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.46 (m, 1H), 7.61 – 7.56 (m, 1H), 7.52 – 7.47 (m, 2H), 7.20 – 7.15 (m, 2H), 6.95 – 6.90 (m, 1H), 6.85 (d, *J* =

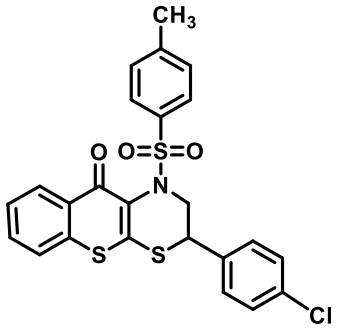
8.4 Hz, 1H), 4.88 – 4.82 (m, 1H), 4.35 (dd, *J* = 10.0, 5.0 Hz, 1H), 4.26 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.37 – 3.25 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 157.7, 156.2, 133.1, 131.6, 131.1, 129.0, 127.9, 127.3, 127.2, 127.0, 125.7, 121.5, 111.3, 110.7, 76.0, 68.4, 26.7, 16.3; IR(KBr)ν_{max} 2925, 2880, 1731, 1569 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{17}O_3S_2$ ($M + H^+$) 357.0614; Found 357.0620.

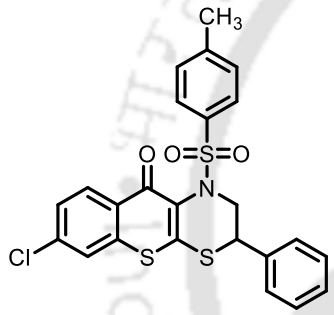
3-decyl-2,3-dihydro-10*H*-thiochromeno[3,2-b][1,4]oxathiin-10-one (27c). Off white liquid (65%, 24 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 – 8.44 (m, 1H), 7.58 – 7.53 (m, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 4.41 (tdd, *J* = 7.7, 5.4, 2.1 Hz, 1H), 3.14 (dd, *J* = 13.5, 2.1 Hz, 1H), 3.00 (dd, *J* = 13.5, 7.8 Hz, 1H), 1.89 (ddt, *J* = 9.9, 4.7, 2.9 Hz, 1H), 1.73 (dq, *J* = 15.0, 5.8, 5.3 Hz, 1H), 1.54 – 1.44 (m, 2H), 1.28 – 1.21 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 158.1, 133.2, 131.4, 128.9, 128.0, 127.1, 125.7, 110.6, 78.4, 34.4, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 25.1, 22.8, 14.2; IR(KBr)ν_{max} 2940, 2880, 2790, 1731, 1558 cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{29}O_2S_2$ ($M + H^+$) 377.1603; Found 377.1608.

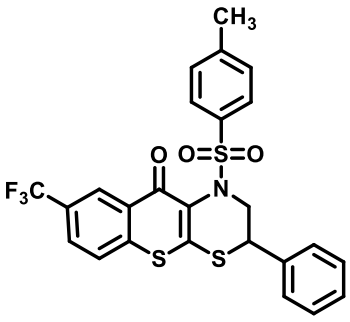


9-chloro-3-decyl-2,3-dihydro-10*H*-thiochromeno[3,2-b][1,4]oxathiin-10-one (27d). Off white liquid (68%, 27mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 5.6, 3.4 Hz, 1H), 7.41 – 7.37 (m, 2H), 4.39 (dt, *J* = 7.7, 2.1 Hz, 1H), 3.12 (dd, *J* = 13.5, 2.1 Hz, 1H), 2.97 (dd, *J* = 13.6, 7.8 Hz, 1H), 1.87 (ddt, *J* = 9.9, 7.2, 4.6 Hz, 1H), 1.78 – 1.69 (m, 1H), 1.53 – 1.43 (m, 2H), 1.27 (s, 15H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 155.4, 136.6, 136.3, 131.2, 130.6, 124.9, 124.6, 112.2, 78.3, 34.3, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8, 14.2; IR(KBr)ν_{max} 2955, 2887, 1738 cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{28}ClO_2S_2$ ($M + H^+$) 411.1214; Found 411.1215.

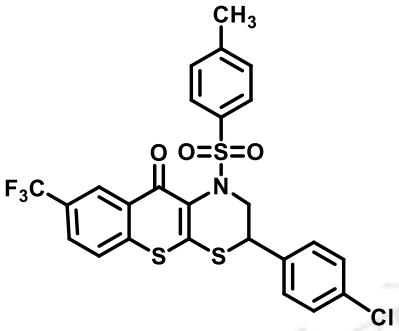


3-(4-Chlorophenyl)-1-tosyl-2,3-dihydro-1*H*, 10*H*-thiochromeno[2,3-*b*][1,4]thiazin-10-one (28a). 
Yellow liquid (65%, 32 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.67 – 7.61 (m, 2H), 7.56 – 7.52 (m, 1H), 7.35 (dd, *J* = 14.9, 8.3 Hz, 4H), 7.24 (d, *J* = 8.5 Hz, 2H), 4.66 – 4.62 (m, 1H), 4.09 – 4.05 (m, 1H), 3.21 – 3.16 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 145.8, 137.9, 136.3, 135.9, 135.9, 135.8, 135.3, 134.8, 132.1, 130.6, 129.5, 129.4, 128.8, 127.6, 125.8, 51.3, 43.3, 21.9; IR(KBr)ν_{max} 2937, 1743, 1630, 1580 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{18}ClNO_3S_3$ (M + H^+) 500.0210; Found 500.0208.

7-Chloro-3-phenyl-1-tosyl-2,3-dihydro-1*H*,10*H*-thiochromeno[2,3-*b*][1,4]-thiazin-10-one (28b). 
Yellow liquid (62%, 31 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.7 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.47 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 3H), 7.35 (s, 2H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.27 (d, *J* = 1.7 Hz, 1H), 4.68 (dd, *J* = 14.4, 3.6 Hz, 1H), 4.04 (dd, *J* = 11.3, 3.6 Hz, 1H), 3.21 (dd, *J* = 14.4, 11.3 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 145.8, 138.8, 137.3, 137.2, 136.5, 135.7, 130.6, 130.4, 129.2, 129.0, 128.3, 128.1, 127.6, 126.6, 125.4, 125.1, 51.3, 43.8, 21.9; IR(KBr)ν_{max} 2952, 1723, 1633, 1590 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{18}ClNO_3S_3$ (M + H^+) 500.0210; Found 500.0228.

3-phenyl-1-tosyl-8-(trifluoromethyl)-2,3-dihydro-1*H*,10*H*-thiochromeno[2,3-*b*][1,4]thiazin-10-one (28c). 
Yellow liquid (74%, 39 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.0 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.81 – 7.78 (m, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.41 – 7.34 (m, 5H), 7.29 – 7.27 (m, 2H), 4.69 (dd, *J* = 14.5, 3.6 Hz, 1H), 4.03 – 3.98 (m, 1H), 3.22 (dd, *J* = 14.4, 11.2 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 146.0, 139.5, 137.5, 136.4, 135.5, 130.7, 129.2, 129.1, 128.1, 127.8, 127.8, 127.6, 126.9, 126.9, 126.8, 126.4, 126.3, 51.3, 43.7, 21.9; IR(KBr)ν_{max} 2949, 1730, 1626, 1576 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{19}F_3NO_3S_3$ (M + H^+) 534.0474; Found 534.0472.

3-(4-chlorophenyl)-1-tosyl-8-(trifluoromethyl)-2,3-dihydro-1*H*, 10*H*-thiochromeno[2,3 *b*][1,4]thiazin-10-one (28d). Yellow liquid (78%, 43 mg);



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.84 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 4.64 (dd, *J* = 14.4, 3.6 Hz, 1H), 4.03 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.18 (dd, *J* = 14.4, 11.2 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 146.1, 139.4, 137.7, 135.5, 135.0, 134.9, 130.7, 129.4, 129.4, 127.9, 127.9, 127.6, 126.9, 126.8, 126.5, 126.4, 126.3, 51.2, 43.3, 21.9; IR(KBr)ν_{max} 2930, 1734, 1625, 1599 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{18}ClF_3NO_3S_3$ ($M + H^+$) 568.0084; Found 568.0063.

Table 6.10. Crystal data and structure refinement for compound **24a**

Entry	Identification code	Compound 24a
01	Empirical formula	C17 H14 O2 S2
02	Formula weight	314.40
03	Temperature	296 K
04	Wavelength	0.71073
05	Radiation type	Mo K\a
06	Radiation source	Fine-focus sealed tube
07	Crystal system	Monoclinic
08	Space group	P 21/n
09	Cell length	a/Å 8.523(2)
		b/Å 19.424(5)
		c/Å 9.964(2)
10	Cell Angle	α/° 90
		β/° 115.165(5)
		γ /°90
11	Cell Volume	1493.1(6)
12	Density	1.399
13	Completeness to theta	23°/ 100% 24.992
14	Absorption correction	multi-scan
15	Refinement method	Full-matrix least-squares on F^2
16	Index ranges	-10<=h<=10,
		-23<=k<=23,
		-11<=l<=11
17	Reflection number	0.0338(2277)
18	Theta range	2.097- 24.992
19	Cell formula units Z	4
20	CCDC no	2102095

Figure 6.4.a. ^{1}H NMR of 2-((2-hydroxy-1-phenylethyl)thio)-4*H*-thiochromen-4-one (24a)

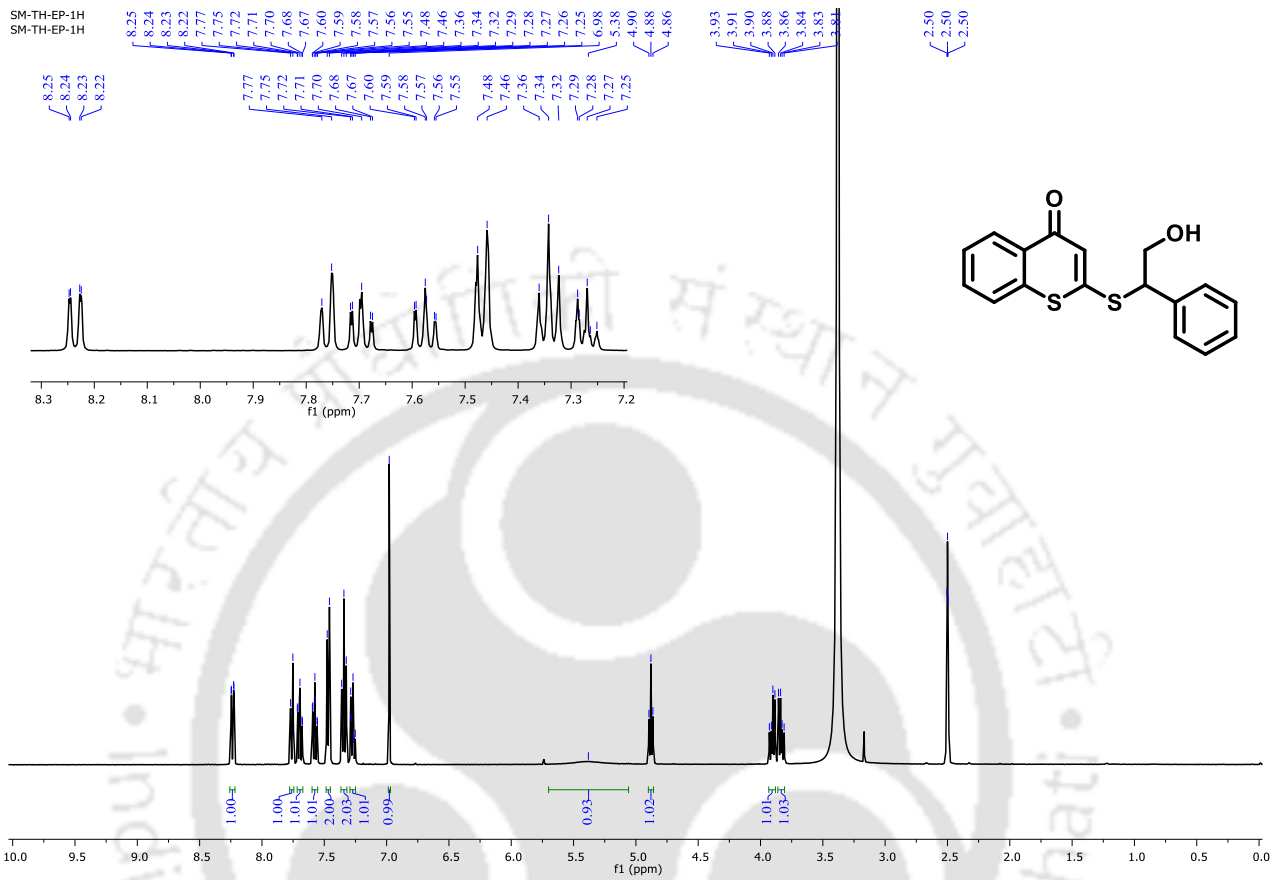


Figure 6.4.b. ^{13}C NMR of 2-((2-hydroxy-1-phenylethyl)thio)-4*H*-thiochromen-4-one (24a)

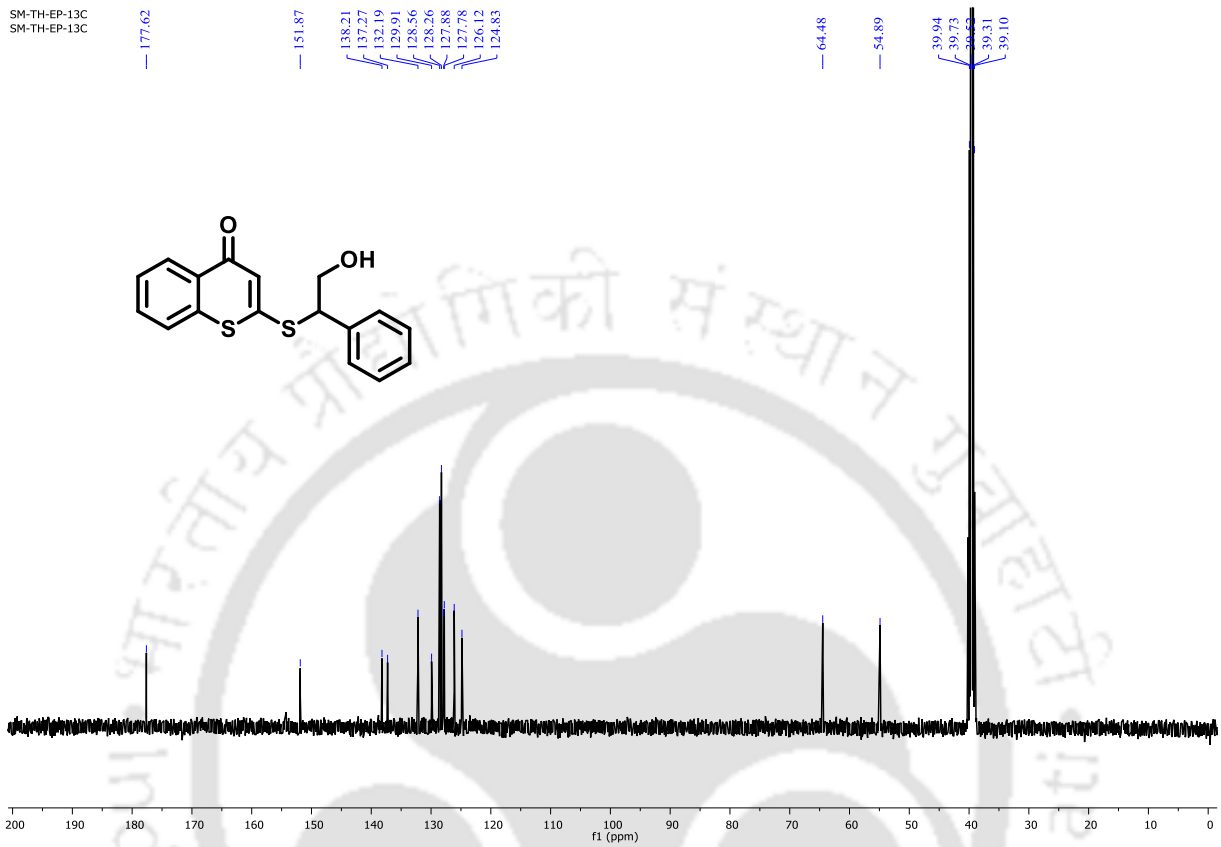


Figure 6.4.c. HRMS of 2-((2-hydroxy-1-phenylethyl)thio)-4*H*-thiochromen-4-one (24a)

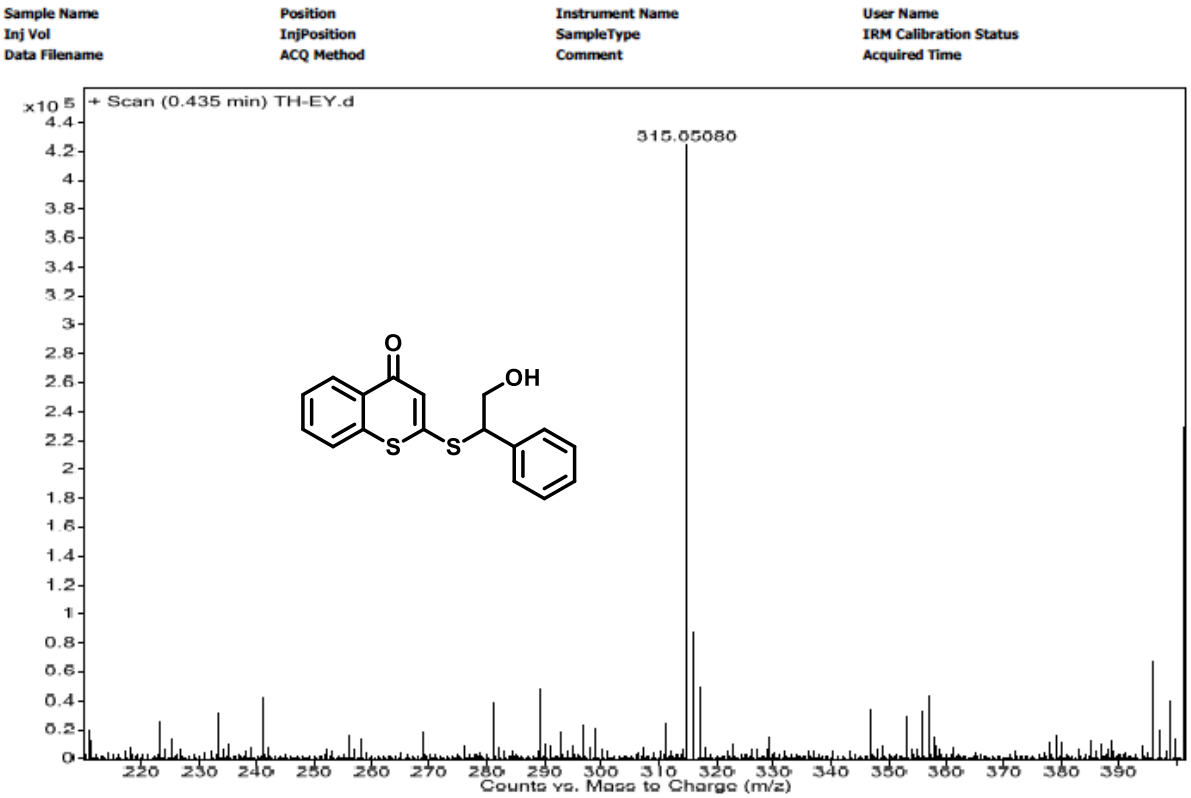


Figure 6.5.a. ^{1}H NMR of 2-((1-hydroxypropan-2-yl)thio)-4*H*-thiochromen-4-one (24i)

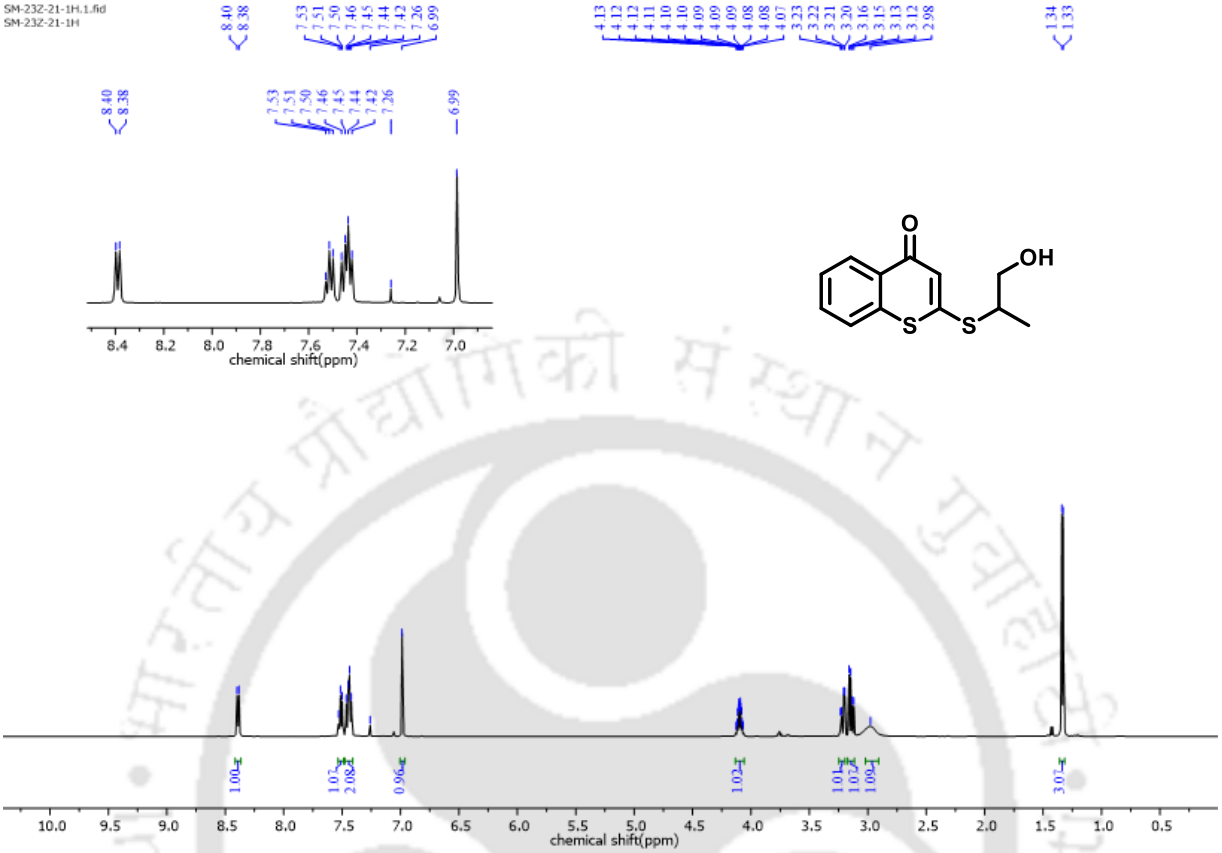


Figure 6.5.b. ^{13}C NMR 2-((1-hydroxypropan-2-yl)thio)-4*H*-thiochromen-4-one (24i)

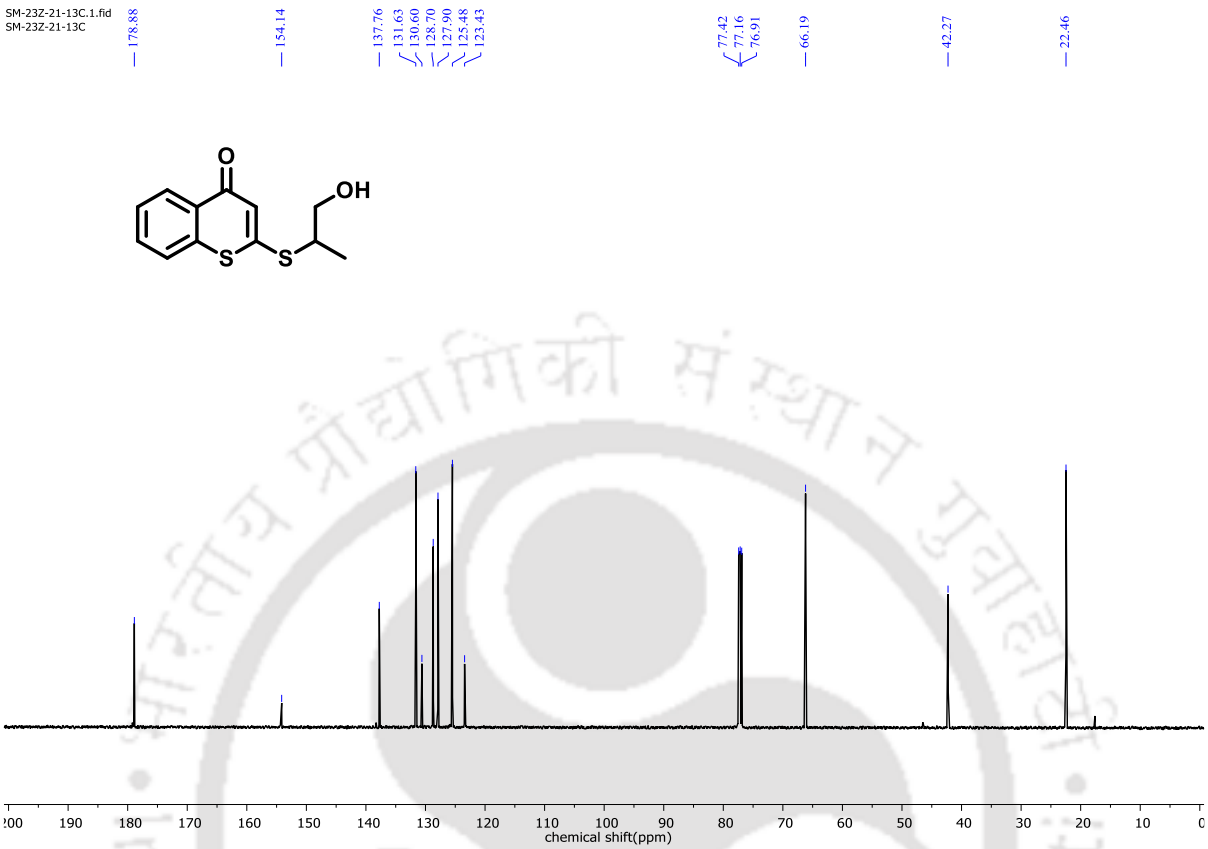


Figure 6.5.c. HRMS of 2-((1-hydroxypropan-2-yl)thio)-4*H*-thiochromen-4-one (24i)

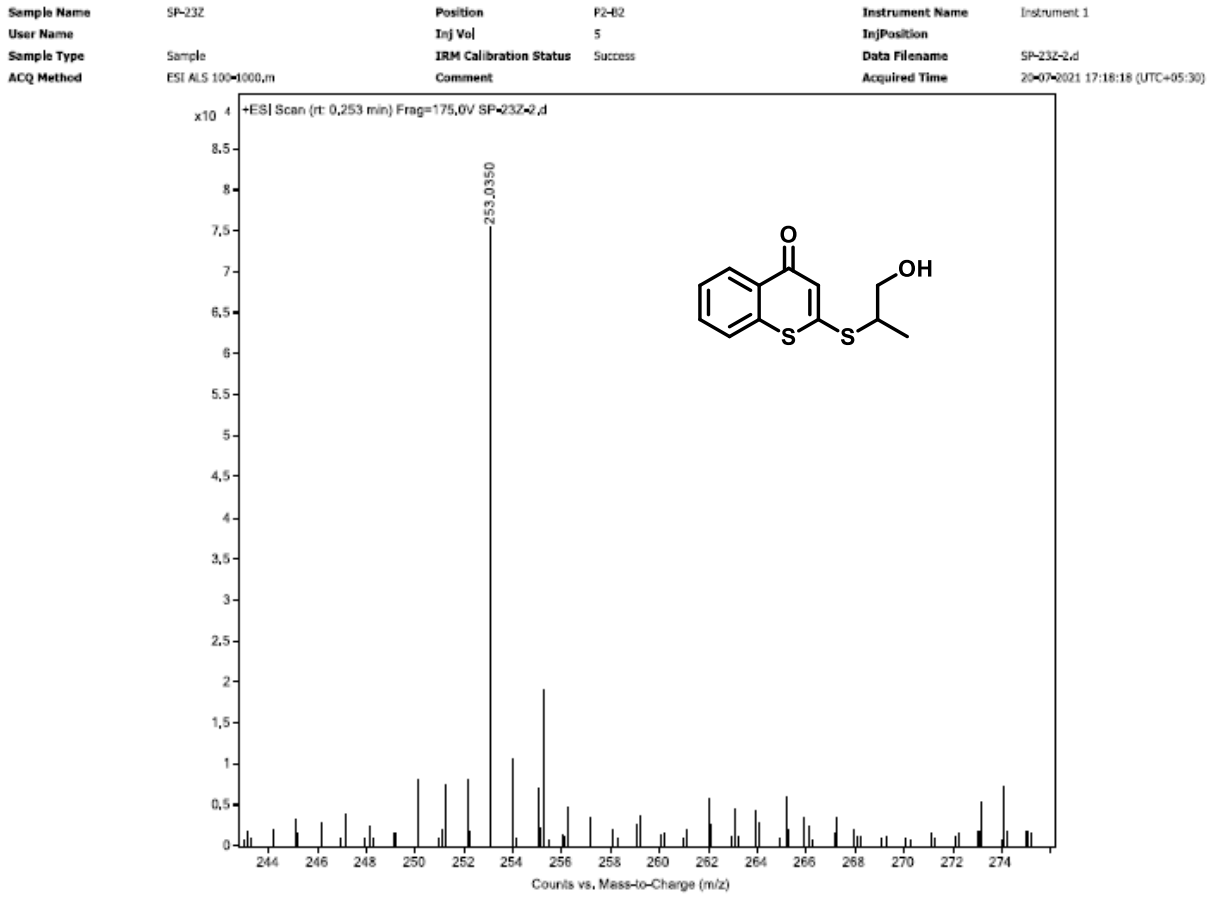


Figure 6.6.a. ^{1}H NMR of *N*-(2-(4-chlorophenyl)-2-((4-oxo-4*H*-thiochromen-2-yl)thio)ethyl)-4-methylbenzenesulfonamide (26a)

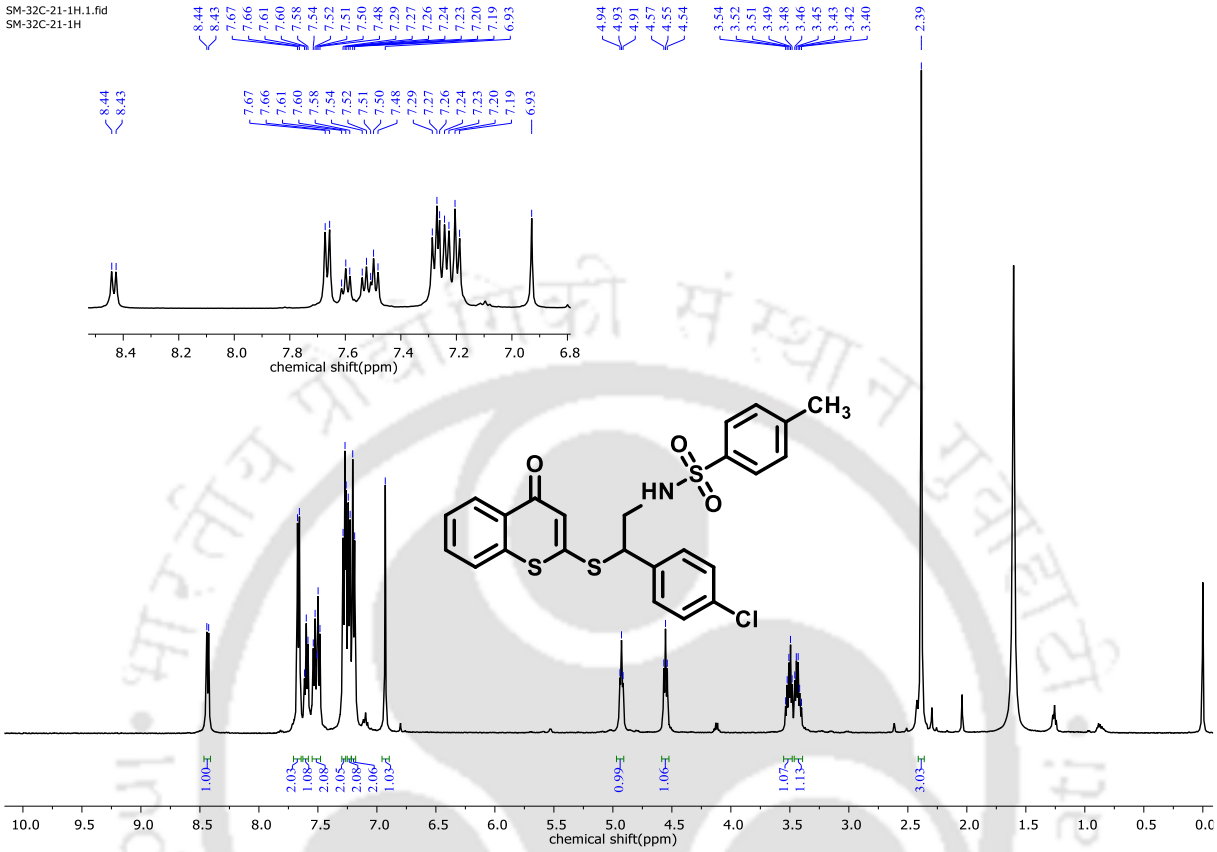


Figure 6.6.b. ^{13}C NMR of *N*-(2-(4-chlorophenyl)-2-((4-oxo-4*H*-thiochromen-2-yl)thio)ethyl)-4-methylbenzenesulfonamide (26a)

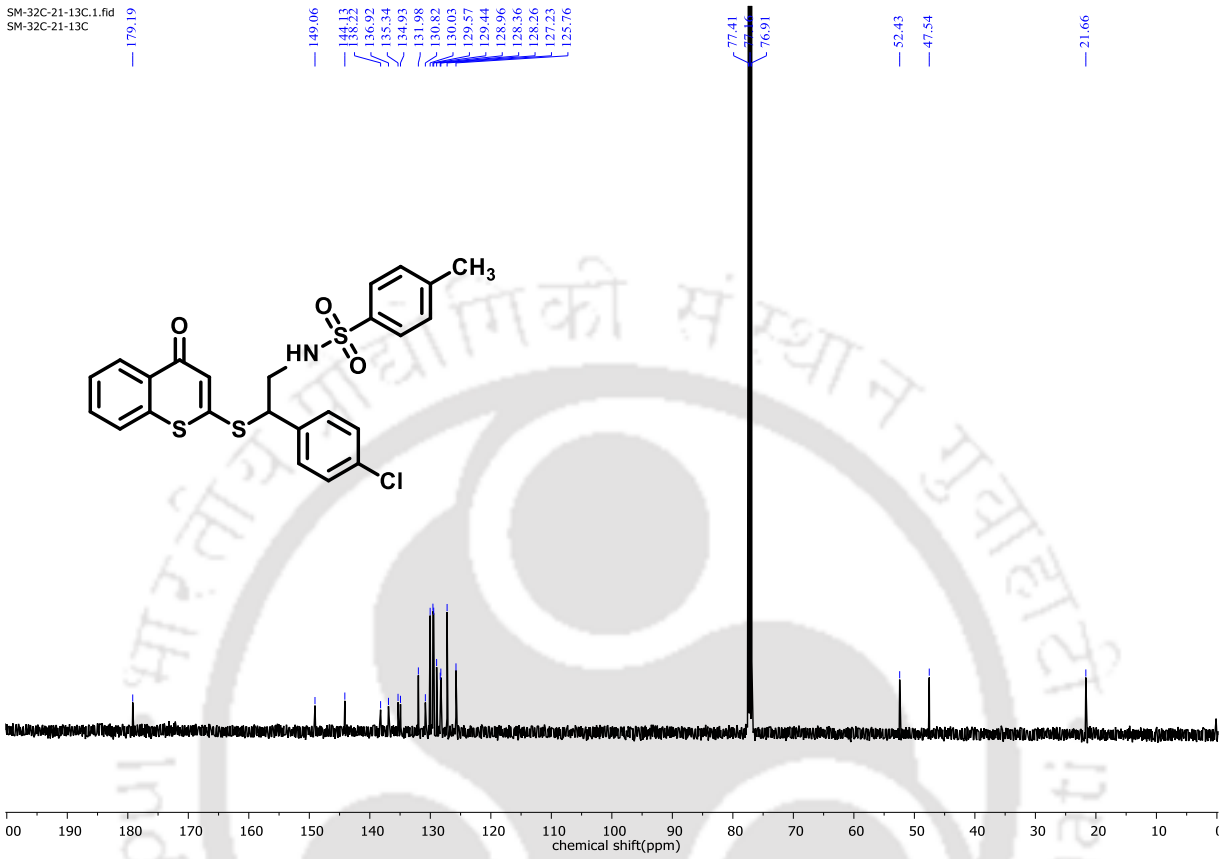


Figure 6.6.c. HRMS of *N*-(2-(4-chlorophenyl)-2-((4-oxo-4*H*-thiochromen-2-yl)thio)ethyl)-4-methylbenzenesulfonamide (26a)

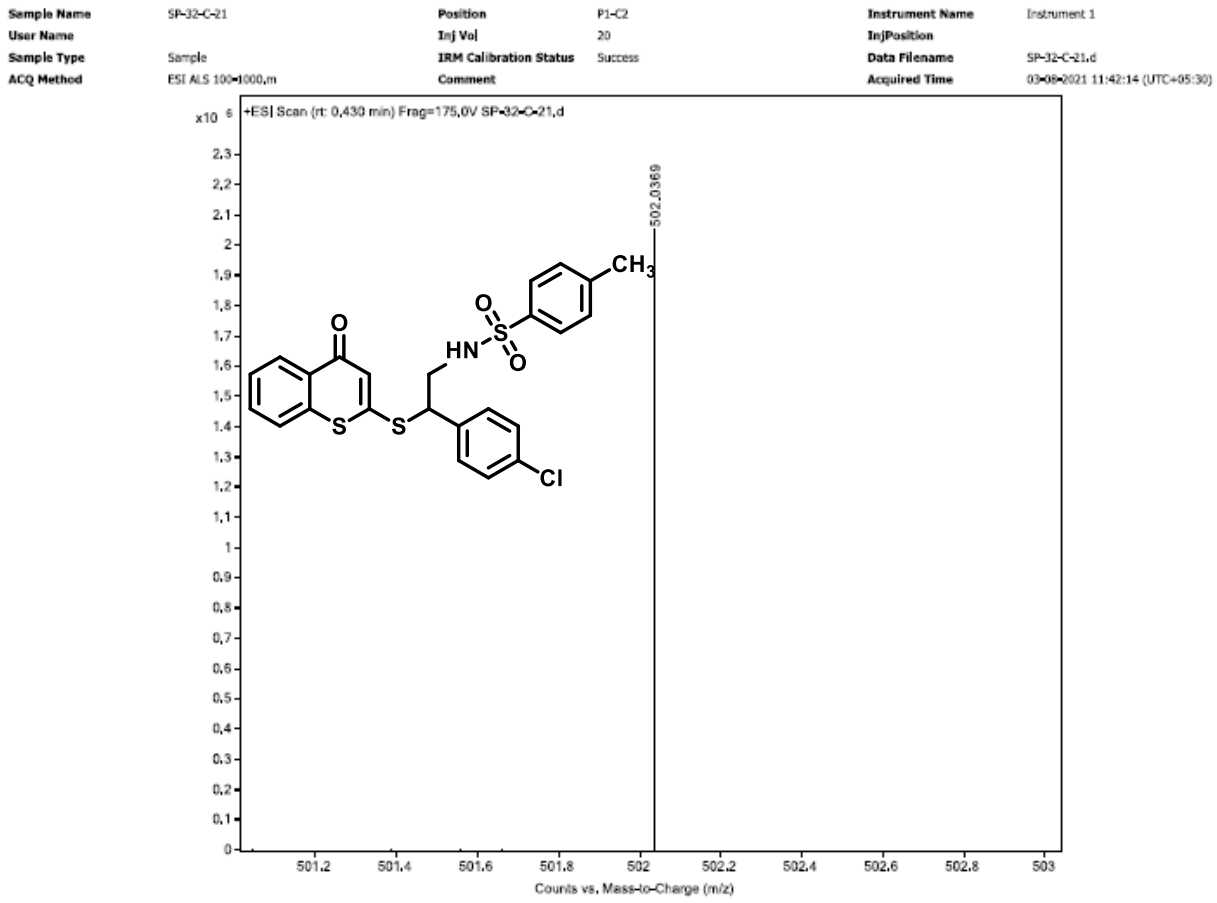


Figure 6.7.a. ^{1}H NMR of 4-methyl-*N*-(2-((4-oxo-4*H*-thiochromen-2-yl)thio)hexyl)benzenesulfonamide (26h)

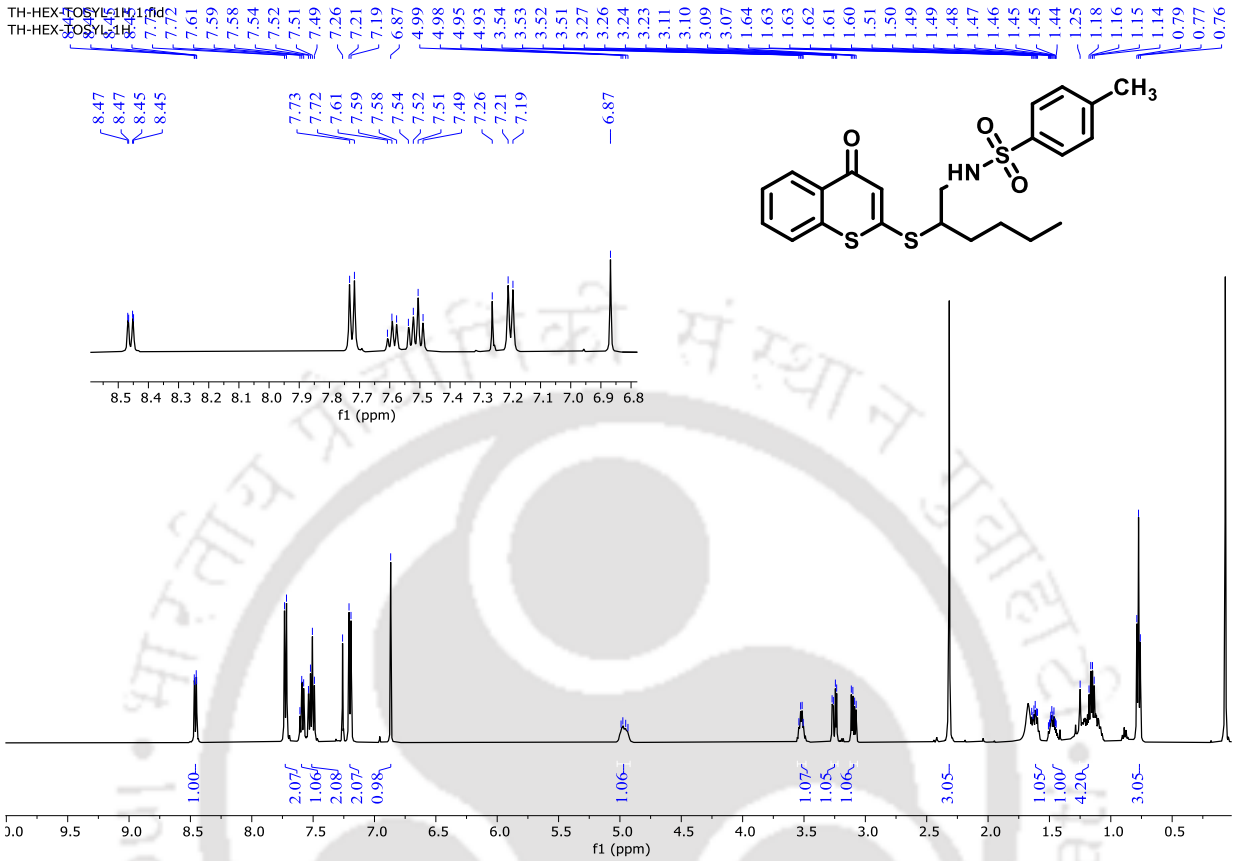


Figure 6.7.b. ^{13}C NMR of 4-methyl-*N*-(2-((4-oxo-4*H*-thiochromen-2-yl)thio)hexyl)benzenesulfonamide (26h)

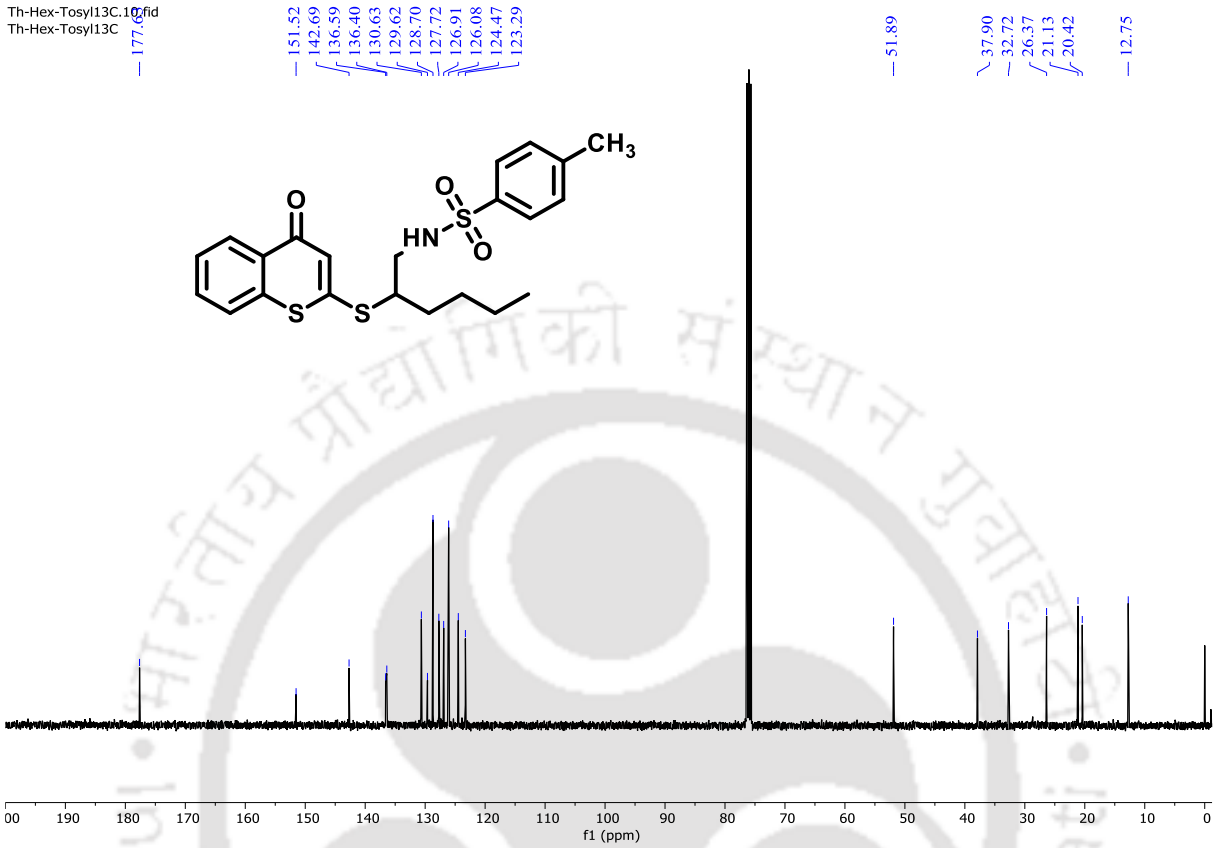


Figure 6.7.c. HRMS of 4-methyl-*N*-(2-((4-oxo-4*H*-thiochromen-2-yl)thio)hexyl)benzenesulfonamide (26h)

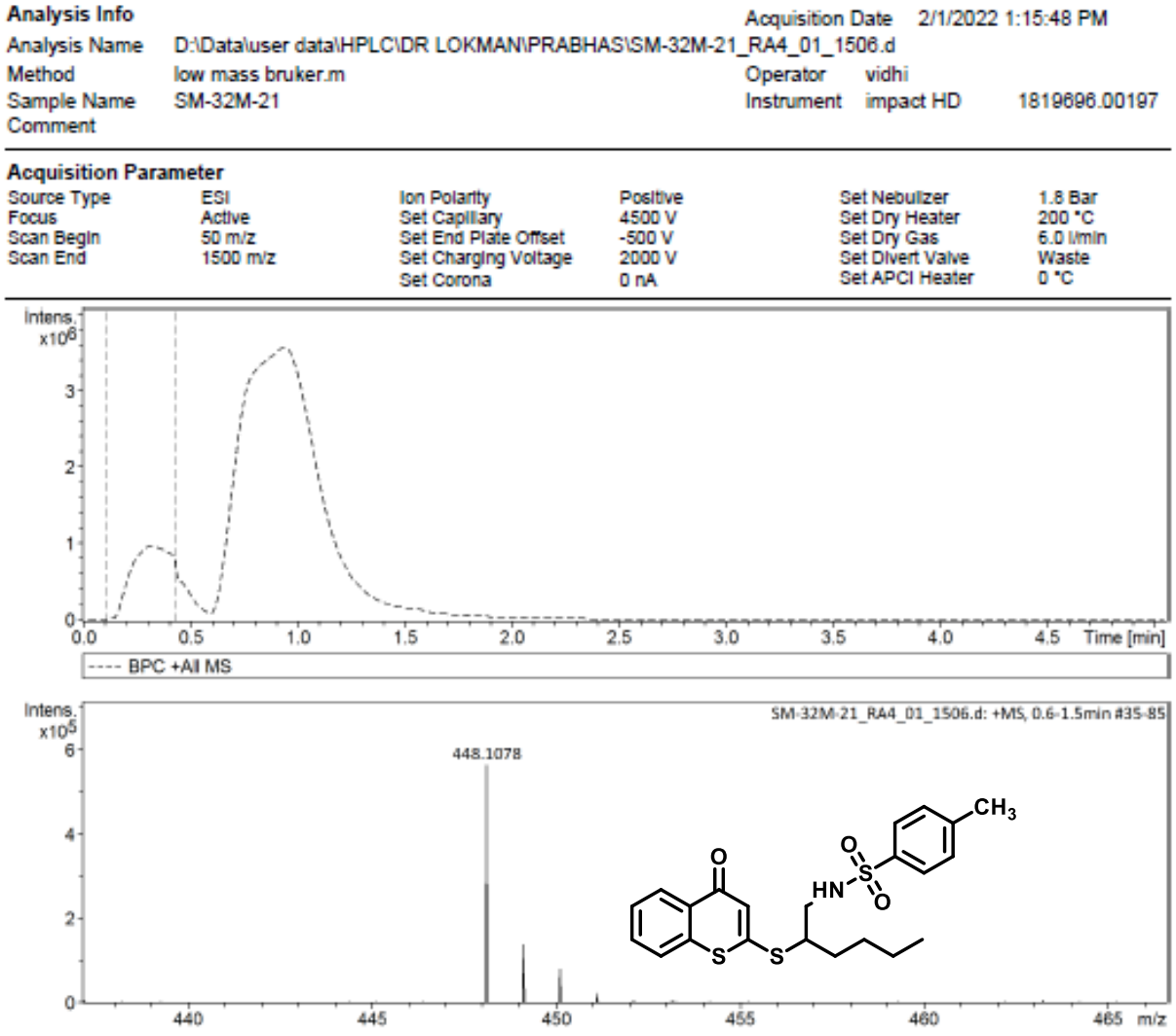


Figure 6.7.a. ^{1}H NMR of 3-decyl-2,3-dihydro-10*H*-thiochromeno[3,2-b][1,4]oxathiin-10-one (27c)

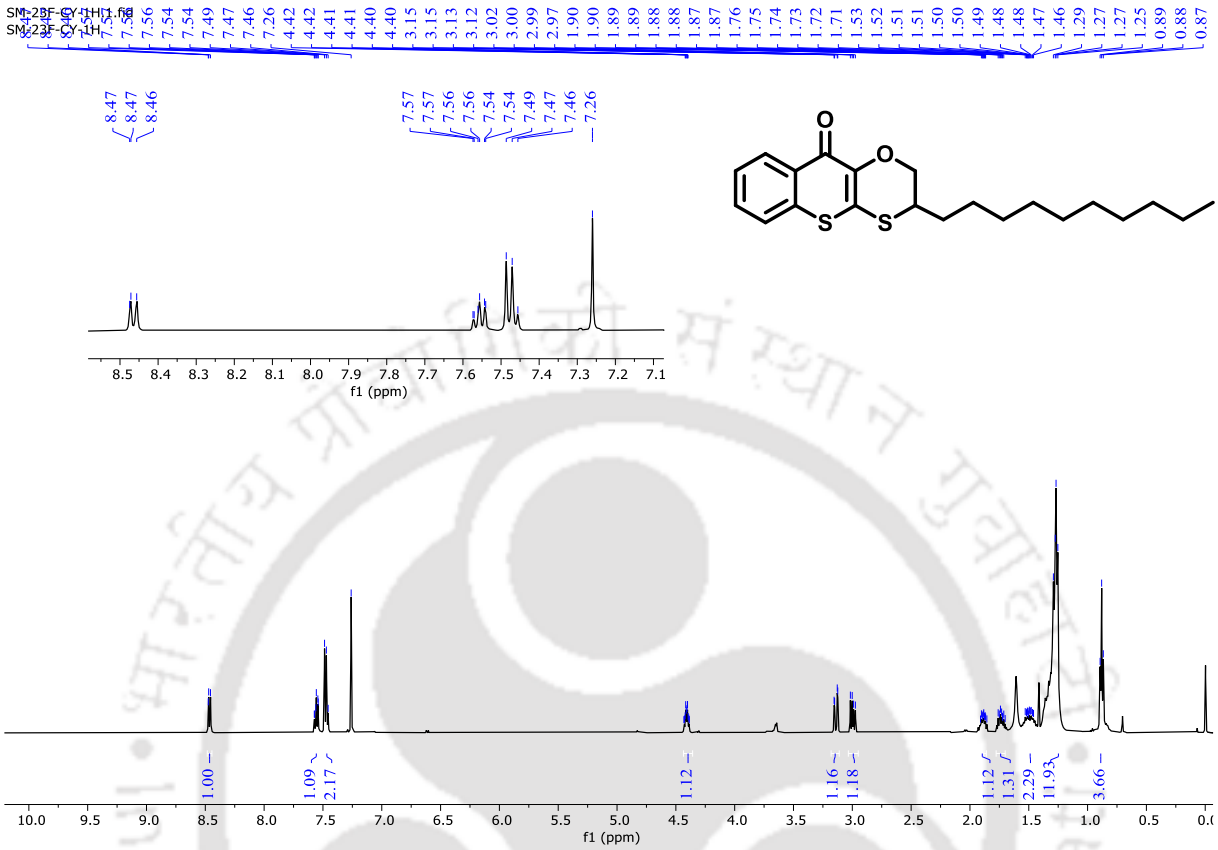


Figure 6.8.b. ^{13}C NMR of 3-decyl-2,3-dihydro-10*H*-thiochromeno[3,2-b][1,4]oxathiin-10-one (27c)

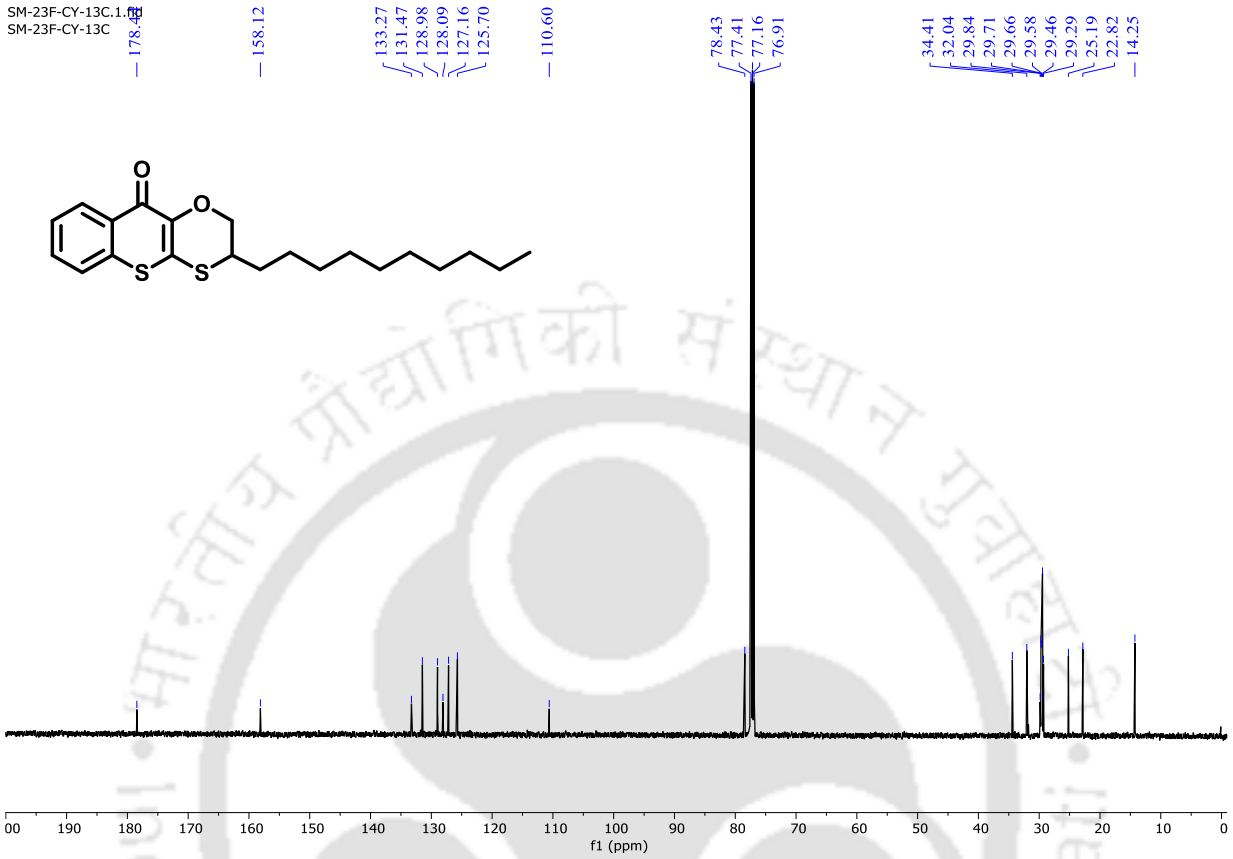


Figure 6.8.c. HRMS of 3-decyl-2,3-dihydro-10*H*-thiochromeno[3,2-b][1,4]oxathiin-10-one (27c)

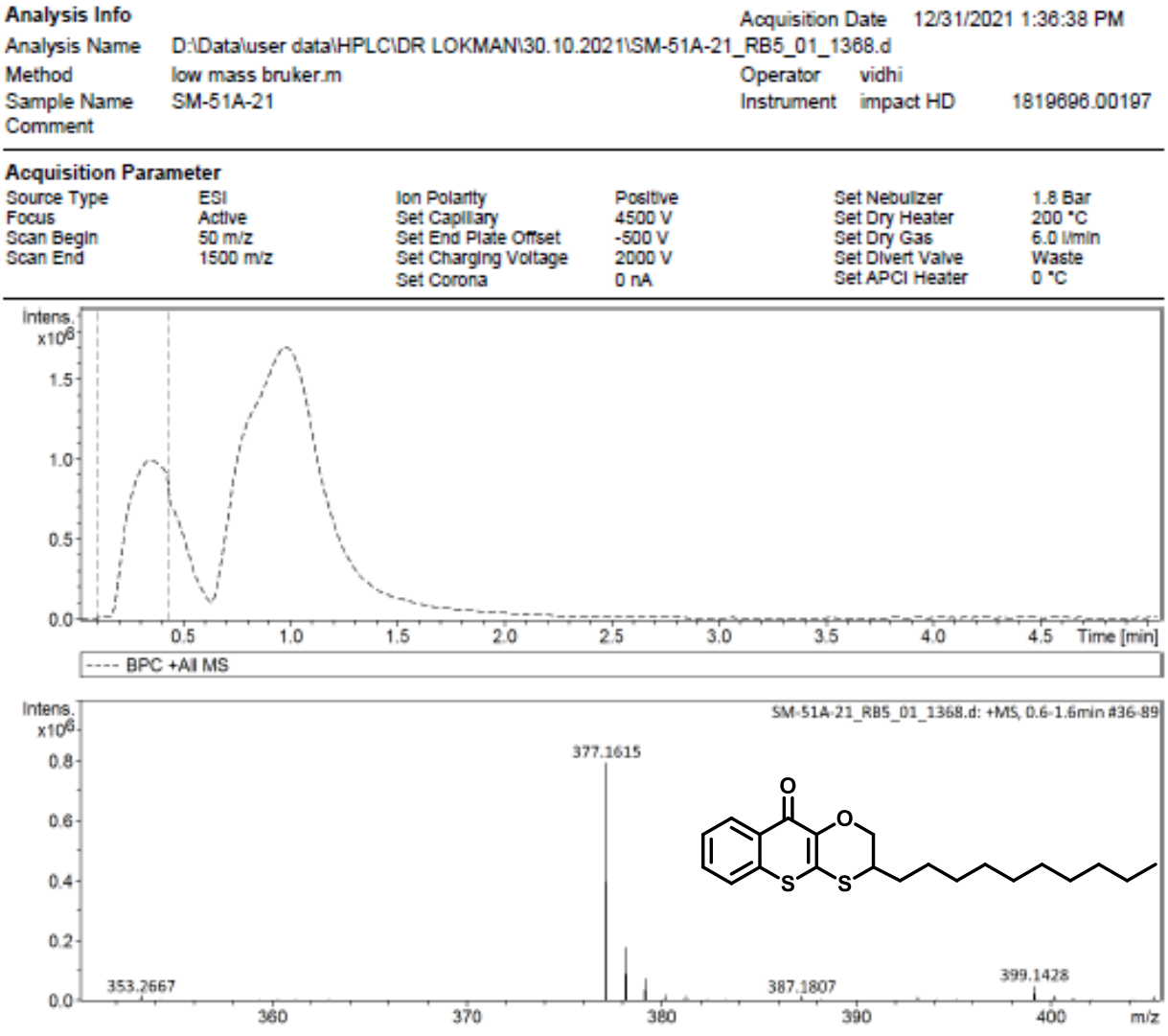


Figure 6.9.a. ^{1}H NMR of 3-phenyl-1-tosyl-8-(trifluoromethyl)-2,3-dihydro-1*H*, 10*H*-thiochromeno[2,3-*b*][1,4]thiazin-10-one (28c)

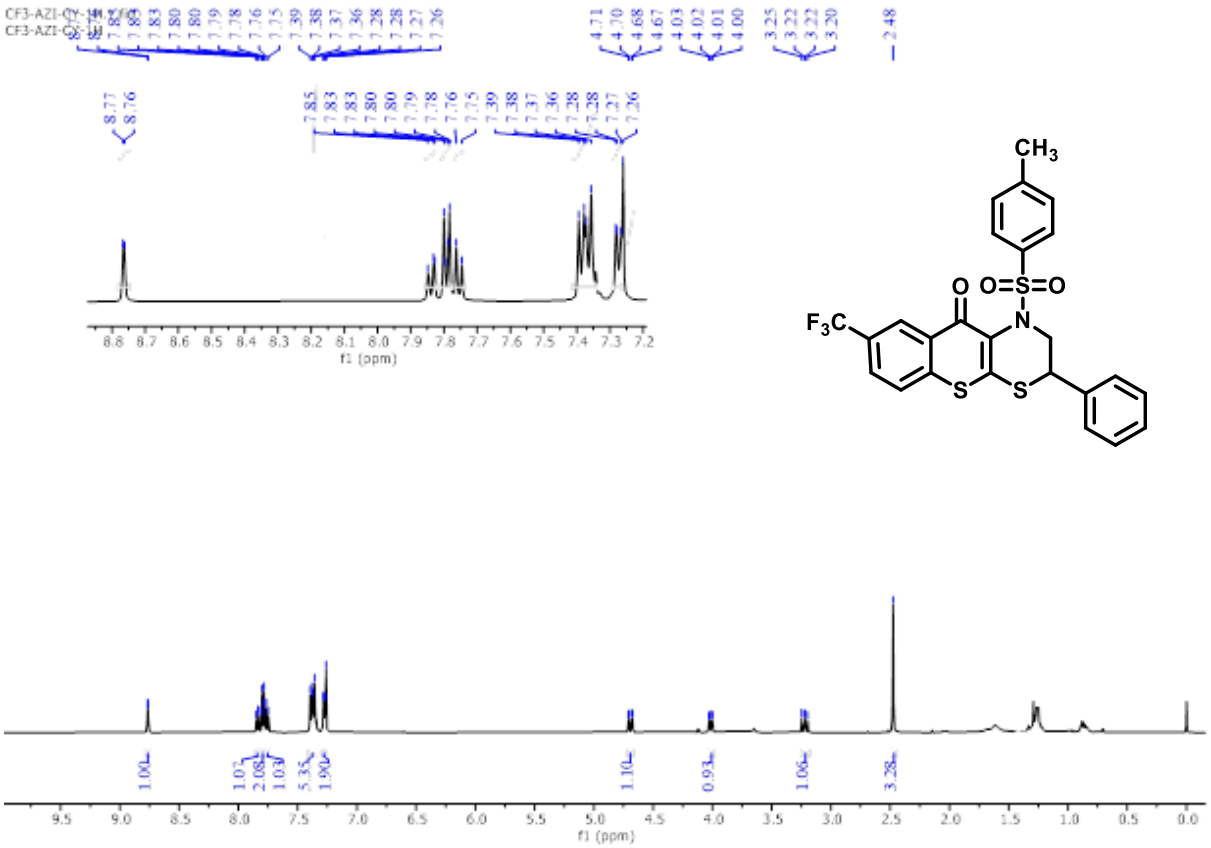


Figure 6.9.b. ^{13}C NMR of 3-phenyl-1-tosyl-8-(trifluoromethyl)-2,3-dihydro-1*H*, 10*H*-thiochromeno[2,3-*b*][1,4]thiazin-10-one (28c)

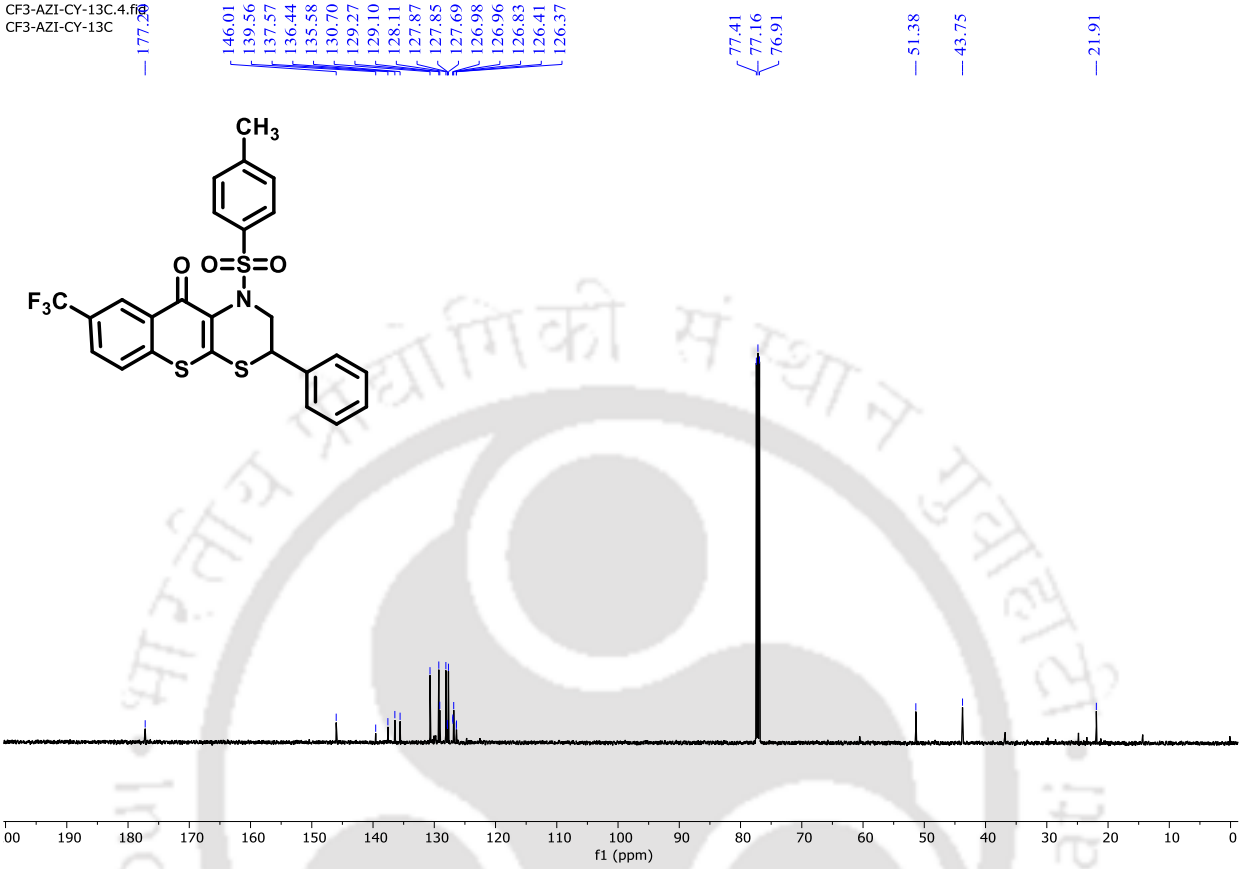
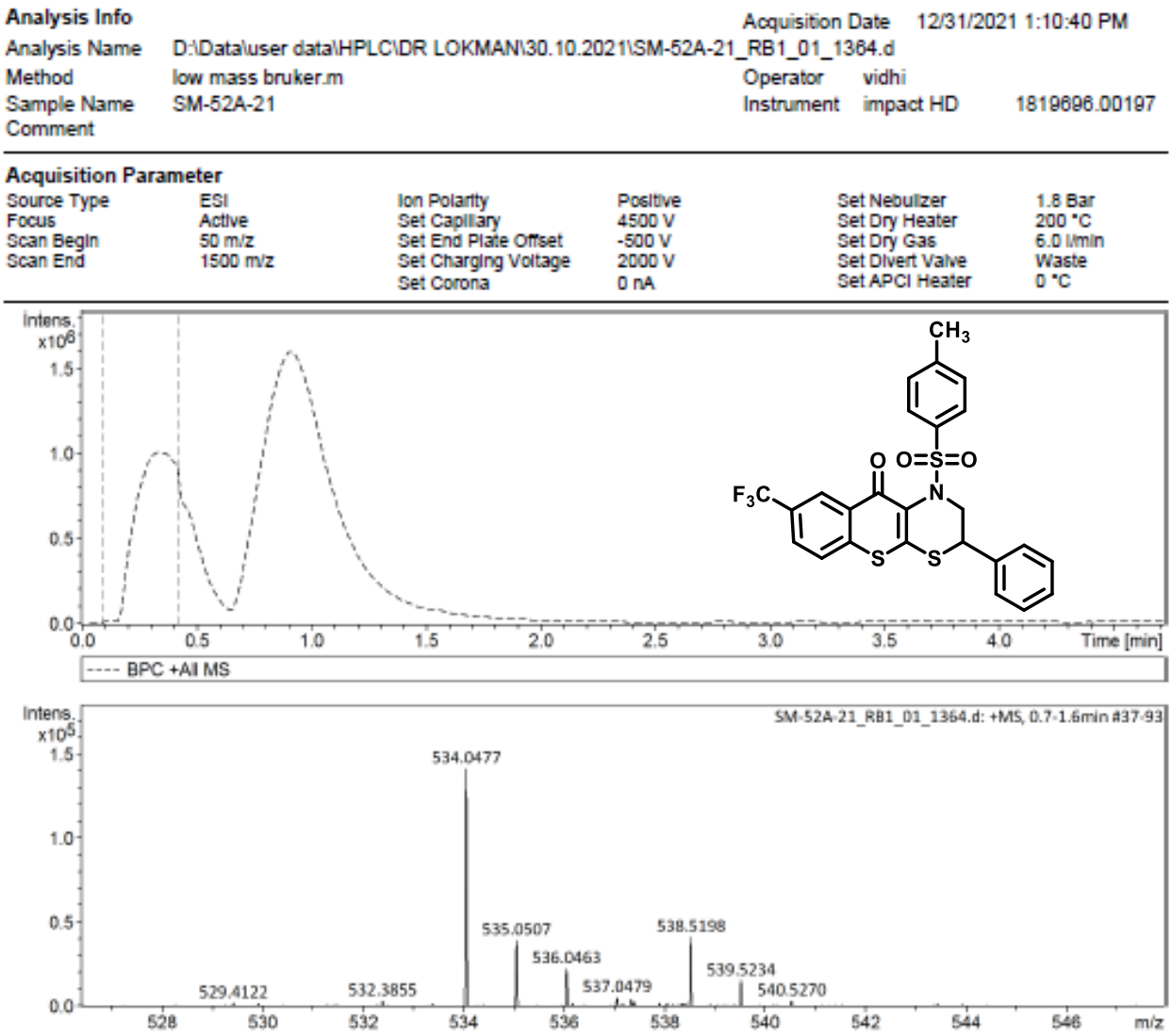


Figure 6.9.c. HRMS of 3-phenyl-1-tosyl-8-(trifluoromethyl)-2,3-dihydro-1*H*, 10*H*-thiochromeno[2,3-*b*][1,4]thiazin-10-one (28c)



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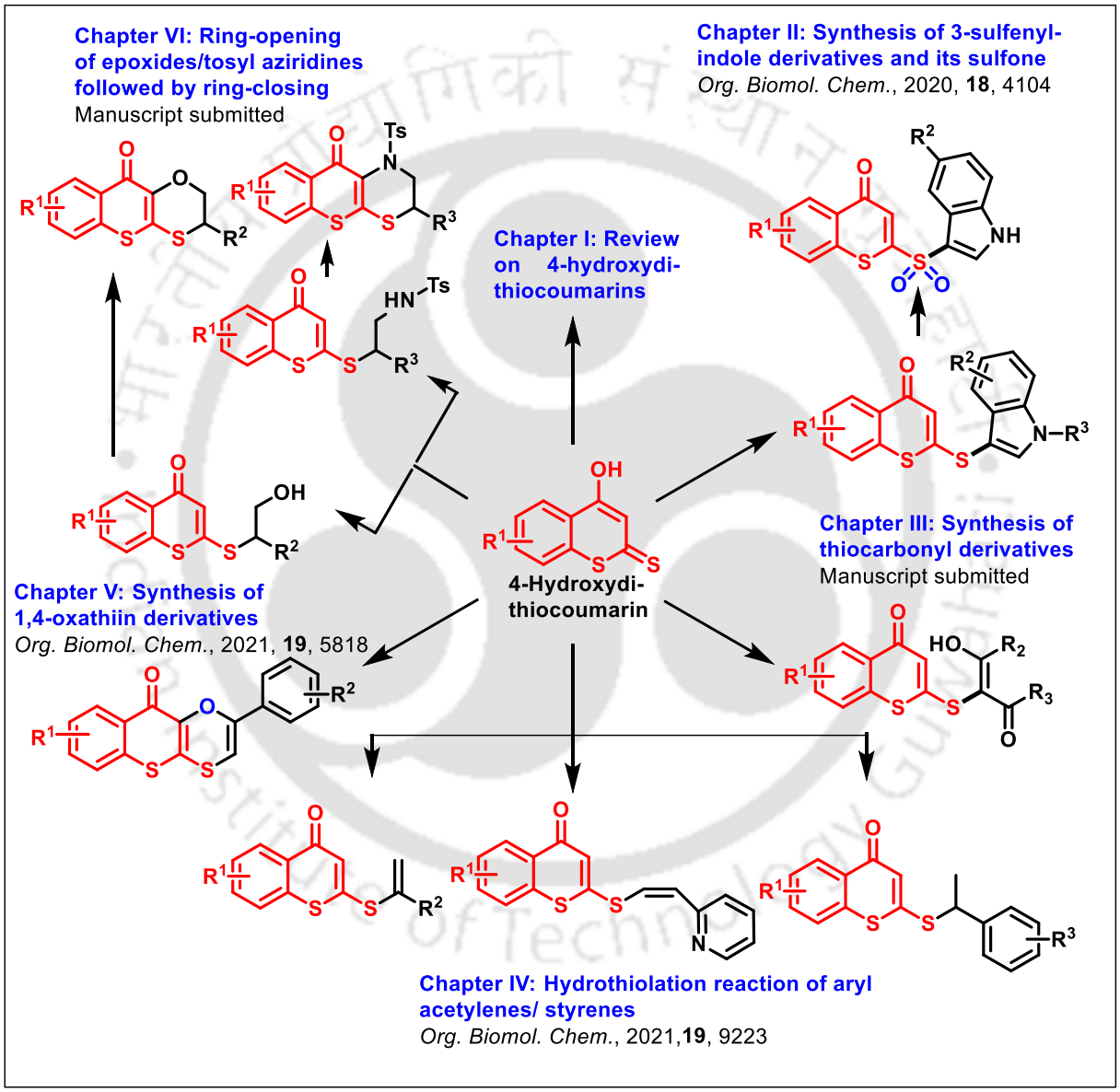
Thesis overview and Future Scope of the Research Works

During my Ph. D. studies, I have focused my research work on synthetic utilities of 4-hydroxydithiocoumarin using its reactive site. The summarised results are represented here schematically.

Thesis overview

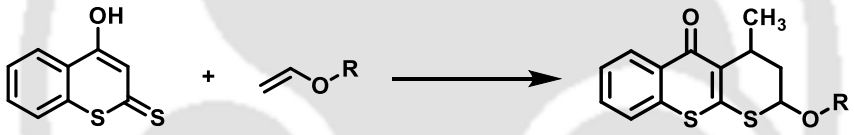


Future Scopes

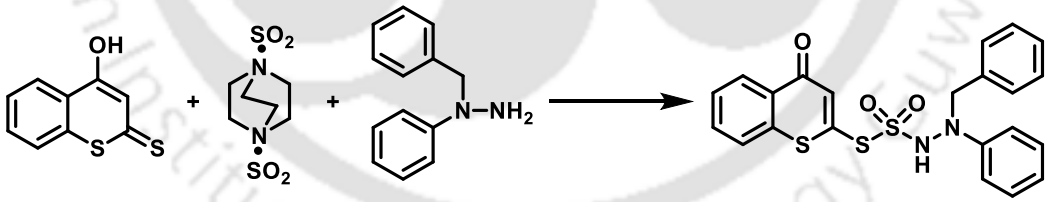
Several new molecules containing thiochromeno moieties have been synthesized and screened for anti-proliferative activity on MCF7 cell-line and Hela-cell as well as antifungal activity. Also, the compounds synthesized in the present work can be structurally modified further to generate a new class of compounds for structure-activity relationship studies. The methodology used for the synthesis of compounds containing styrene can be extended further to accomplish the asymmetric synthesis of thioethers.

In addition, β-hydroxysulfide that can be easily converted to the respective propionic acid derivatives known for their anti-inflammatory activity, such as ibuprofen and naproxen, is under study and will be published in due course. Moreover, our synthetic strategy is under investigation for the asymmetric ring-opening reaction of epoxide/tosylaziridine for the synthesis of optically active β-hydroxy sulfides and β-amino sulfides and it will be reported after completion of the study.

Based on our previously reported research work, the future exploration of the reactivity of 4-hydroxydithiocoumarin as shown below.



Scheme 7.1. Synthesis of dihydrothiopyran derivatives



Scheme 7.2. Synthesis of sulfonamide derivatives

1. **Santa Mondal** and Abu Taleb Khan, "KI/TBHP-mediated cross dehydogenative coupling between 4-hydroxydithiocoumarin and active methylene compound" (Submitted)
2. **Santa Mondal** and Abu Taleb Khan, "Ring opening reactions followed by cyclization of epoxides/tosyl aziridines with 4-hydroxydithio-coumarins" (Manuscript under preparation)
3. **Santa Mondal**, Sabina Yashmin and Abu Taleb Khan, "Synthesis of vinyl sulfides and thioethers *via* a hydrothiolation reaction of 4-hydroxydithiocoumarins and arylacetylenes/styrenes", *Org. Biomol. Chem.*, 2021, **19**, 9223-9230.
4. **Santa Mondal**, Sabina Yashmin, Rashid Ali, R Soundaram, Siddhartha S. Ghosh and Abu Taleb Khan, "Synthesis of biologically active fused 1,4-oxathiin derivatives from 4-hydroxydithiocoumarins, arylacetylenes and dimethyl sulfoxide by Cu(i)-catalyzed C–H functionalization and cross-dehydrogenative C–S coupling reactions", *Org. Biomol. Chem.*, 2021, **19**, 5818-5826.
5. **Santa Mondal**, Karuna Mahato, Neha Arora, Dheerendra Kankane, Umed Pratap Singh, Saghir Ali, Aftab Hossain Khan, Siddhartha S. Ghosh and Abu T. Khan, "Newly synthesized 3-sulfenylindole derivatives from 4-hydroxydithiocoumarin using an oxidative cross dehydrogenative coupling reaction (OCDCR): potential lead molecules for antiproliferative activity", *Org. Biomol. Chem.*, 2020, **18**, 4104-4113.
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7. Sabina Yashmin, **Santa Mondal**, Abu Taleb Khan, "An elegant and unusual regioselective synthetic approach for key precursors of 6-arylbenzo[c]phenanthridin-10-ol derivatives by temperature-dependent multicomponent reaction" (Submitted)
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10. Radhakrishna Gattu, **Santa Mondal**, Saghir Ali and Abu T. Khan, "Iodine monobromide catalysed regioselective synthesis of 3-arylquinolines from α-aminoacetophenones and trans-β-nitrostyrenes", *Org. Biomol. Chem.*, 2019, **17**, 347-353