Illuminating 4-Hydroxy-2*H*-chromene-2-thione: A Pioneer to the Development of Novel Heterocycles with Potent Biomedical Applications

A Dissertation Submitted to the

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As partial fulfilment for the degree of

DOCTOR OF PHILOSOPHY

By

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2025

DEDICATED TO

My Parents

Whose silent sacrifices and boundless love crafted every step of my life!

With Gratitude & Love

Indian Institute of Technology Guwahati
Department of Chemistry

DECLARATION

I do hereby declare that the matter embodied in this thesis entitled "***Illuminating 4-Hydroxy-2H-chromene-2-thione: A Pioneer to the Development of Novel Heterocycles with Potent Biomedical Applications***" 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, Guwahati, Assam, 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. Anjela Xalxo, Roll Number-196122105, has been working under my guidance since January 2020 as a regular registered PhD student. I am forwarding her thesis entitled "***Illuminating 4-Hydroxy-2H-chromene-2-thione: A Pioneer to the Development of Novel Heterocycles with Potent Biomedical Applications***," *being submitted for the PhD (Science) Degree from this institute*. I also certify that she has fulfilled all the requirements according to the rules & regulations of this institute regarding the investigations embodied in her thesis, and this work has not been submitted elsewhere for any other degree.

IIT Guwahati
25th July, 2025

Prof. Abu Taleb Khan
(Thesis Supervisor)

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Above all, I express my deepest gratitude to the Almighty for blessing me with such wonderful people in my life and for granting me the strength, resilience, and patience to overcome challenges and accomplish this milestone.

Anjela Xalxo

Anjela Xalxo

GENERAL REMARKS

The present investigations were carried out at the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam, India, during the period from December 2019 to July 2025 as a doctoral student under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50 °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.

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 a Perkin-Elmer Spectrum Two Instrument. $CDCl_3$ and DMSO-d_6 were used for recording NMR spectrum.

^1H spectra were recorded on Bruker 400MHz, 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 spectrometers, TMS as the internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^1H 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.

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ABBREVIATION

Aq.	Aqueous
ACN	Acetonirtile
AR	Aldose reductase
t-BuOK	Potassium tert-butoxide
t-Bu	Butyl
BHT	Butylated hydroxytoluene
CCDC	Cambridge crystallographic data centre
CDC	Cross dehydrogenative coupling
°C	Degree Celcius
$CDCl_3$	Deuterated chloroform
COX	Cyclooxygenase
$CuBr_2$	Copper (II) Bromide
CH_3CN	Acetonitrile
CDC	Cross dehydrogenative coupling
DCM	Dichloromethane
DFT	Discrete Fourier transform
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DABCO	1,4-Diazabicyclo[2.2.2]octane
DPDME	Dipropylene glycol dimethyl ether
DNA	Deoxyribonucleic acid
h	hour

ABBREVIATION

HL-60	Human leukemia cell line
HEK-293	Human Embryonic Kidney 293 cells
HIV	Human immunodeficiency virus
HRMS	High-resolution Mass Spectrometry
HBr	Hydrogen Bromide
H_2SO_4	Sulfuric acid
ITC	Isothermal titration calorimetry
IC50	Half maximal inhibitory concentration
Int-A	Intermediate A
IR	Infrared
$K_2S_2O_8$	Potassium Persulfate
LPG	Liquefied petroleum gas
m-CPBA	meta-Chloroperoxybenzoic acid
MCR	Multicomponent reaction
MCF-7	Michigan Cancer Foundation-7
mp	Melting point
mg	Milligram
MBH	o-methoxybenzaldehyde benzoylhydrazone
MeOH	Methanol
MTT	(3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide)
NBS	N-Bromosuccinimide
NCI	National Cancer Institute

ABBREVIATION

NaOAc	Sodium acetate
$NaNO_2$	Sodium nitrite
NR	No Reaction
N_2BF_4	2-(λ1-boraneyl)-1,1,1,1-tetrafluoro-1λ6-diazene
NMR	Nuclear magnetic resonance
ORTEP	Oak ridge thermal ellipsoid program
ppm	Parts per million
$Pd(OAc)_2$	Palladium (II) acetate
PPh_3	TriphenylPhosphine
$PhI(OAc)_2$	Iodobenzene diacetate
ROS	Reactive Oxygen Species
rt	Room temperature
TEMPO	2,2,6,6-tetramethylpiperidine-*N*-oxide
TRIM24	Tripartite Motif-containing protein 24
TBAI	Tetra-*n*-butylammonium iodide
TBAB	Tetrabutylammonium bromide
TBHP	*tert*-Butyl hydroperoxide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
XRD	X-ray diffraction

CHAPTER I

Introduction

1.1 Background
The origin of the thesis work

1.2 Rationale
A fascinating analogue that opens new avenues in heterocyclic chemistry and bioactive molecule design

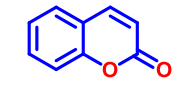
1.3 Overview
A brief preface to the chapters

1.4. Utilization of 4-hydroxy-2H-chromene-2-thione in different types of reaction

1.5. References

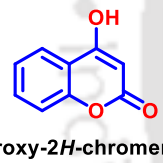
1.1. Background:

Coumarin, or **2*H*-chromen-2-one,** is a naturally occurring aromatic organic compound that bears a fused benzene ring with aα-pyrone ring forming a lactone system. It was first isolated from Tonka beans in 1820 by A. Vogel of Munich. It is found in sweet clover, cinnamon and lavender, contributing to its sweet flavour.[1] Coumarin can be prepared in the laboratory by various experimental techniques, particularly from the Pechmann condensation, which involves the acid-catalyzed reaction between phenols and β-keto esters.[2] Other alternative synthetic approaches include the Perkin and Knoevenagel condensations.[3]It alsoplays an important role in organic synthesis due to its significance in medicinal chemistry, owing to its extensive range of biological activities, such as antioxidant, antiviral, and enzyme inhibitory effects.[4]

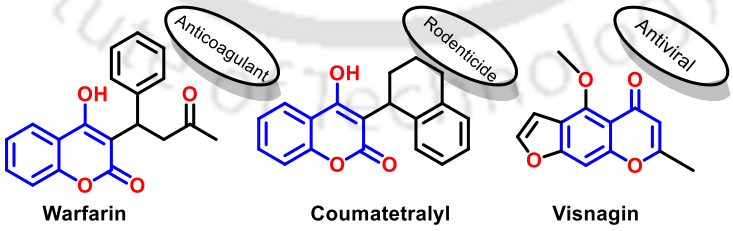


2*H*-chromen-2-one

4-Hydroxy-2*H*-chromen-2-one, or **4-Hydroxycoumarin**(**A**),isa naturally occurring compound and a versatile key structural derivative of coumarin. It is renowned for its contribution as a building blockin the synthesis of anticoagulant drugs such as warfarin, coumatetralyl, and dicoumarol. These compounds prevens the formation of blood clots, particularly by inhibiting vitamin K epoxide reductase. In addition to these, 4-hydroxycoumarin is found to exhibit antimicrobial, anti-inflammatory, antioxidant, and anticancer activities. Therefore, this compound is crucial in both medicinal chemistry and drug discovery.[5]



4-Hydroxy-2*H*-chromen-2-one



Warfarin Coumatetralyl Visnagin

Figure 1. Bioactive 4-Hydroxycoumrain and Chromene derivatives

1.2. Rationale for the Study:

Looking at the scenario in the wide diversity of the profound biological and pharmacological importance of the coumarin scaffold, our research focused on structural alteration to enrich its pursuit and investigate new chemical entities. Based on this, we focused on investigating the effect of sulfur substitution in the coumarin moiety. To begin with, we replaced both oxygen atoms in the coumarin ring with sulfur to study the resulting 4-Hydroxydithiocoumarin derivatives (**B**), a project currently ongoing in our laboratory. Developing this idea, we intend to create and synthesize a mono analogue of thio by replacing one of the oxygen atoms with sulfur, resulting in 4-hydroxy-2*H*-chromene-2-thione(**C**). As this compound remains relatively unexplored in the literature, we sought to investigate its synthetic utility and potential biological significance through our detailed investigation.

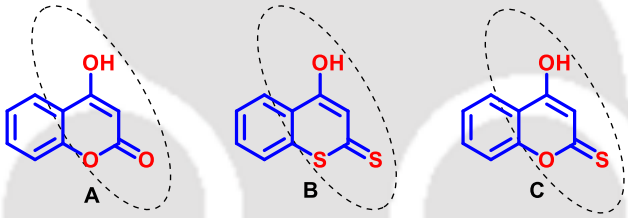


Figure 2. Structural Co-relation

Why Sulfur? A Strategic Element in Coumarin Modification

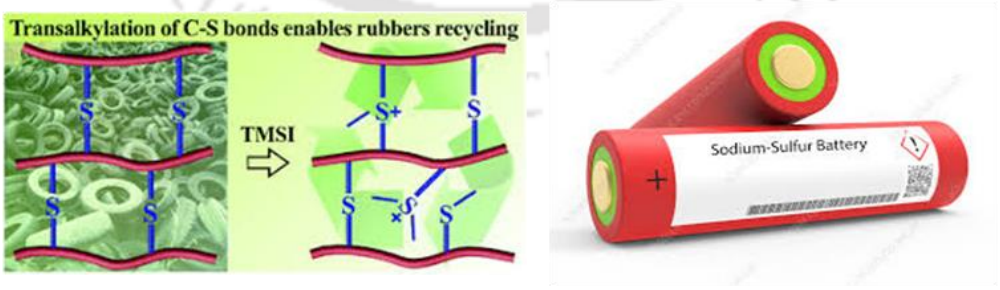


Figure3. Role of sulfur in rubber manufacturing and battery systems

The resourcefulness, utility, and abundance that sulfur has make it vital for its contribution to modern materials science.[6] Its elevation comprises its applicability in the recycling of rubber,[7] in the high-performance lithium/sodium-sulfur batteries,[8]etc. Coupling reactions incorporating sulfur are widely utilized in catalysis,[9]as well as in surface chemistry.[10]In addition to this, the compounds built upon sulfur compounds also tend to contribute as a remarkable core in electronics[11] as well as in biological applications such as DNA sensing or cancer-related activity.[12] While other chalcogens like tellurium and selenium offer parallel applications yet sulfur persists to be predominant in research and in deployment. Sulfur, vital for survival, gets involved in various biological system such as its metabolism in the colon; particularly in the formation of hydrogen sulfide which is revealed to may have affect gut health and other health related diseases such as IBD and colon cancer.[13] A distinguished sulfur compound, taurine, acts as an insulator in humans.[14]

In the sectors of oil, particularly in petroleum, based on geochemical analysis, sulfur compounds are most prominent, and it is one of the major co-products of petroleum refining and is broadly applied in the industrial preparation of sulfuric acid.[15] They originate from sulfate by bacterial sulfate reduction in sedimentary environments and then react with organic matter. Change in their structures and abundance leads to more condensed aromatic sulfur compounds during thermal maturation and high-temperature thermochemical reactions. During refining, particularly due to steric hindrance and their polar nature, the compounds featuring thiophenes, sulfides, thiols, sulfoxides, and sulfones often illustrate fragile chemical stability that is hard to eliminate. Progressive analytical techniques like high-resolution mass spectrometry have proven to enhance their characterization; however, a thorough understanding of their structures and transformation mechanisms is limited, which necessitates future research.

Latest review calls attention to sulfur-containing bioactive compounds that contribute to the positive aspects of health, wellness, and unique essences through vegetables containing isothiocyanates, thiols, and polysulfides, which are prominent in mushrooms.[16] Hydrogen sulfide and thiols tend to provide an unpleasant odor. Nevertheless, the utilization of ethanethiol in LPG cylinders is used to monitor the spillage of the gas. Besides this, the authors Isabella *et al.*, lately described a case where a person tried inhaling liquefied petroleum gas in which

ethanethiol was contained that sealed his fate. This emphasizes the toxicity of butane and ethanethiol. They also highlighted the chemical properties of ethanethiol as life-threatening.[17]

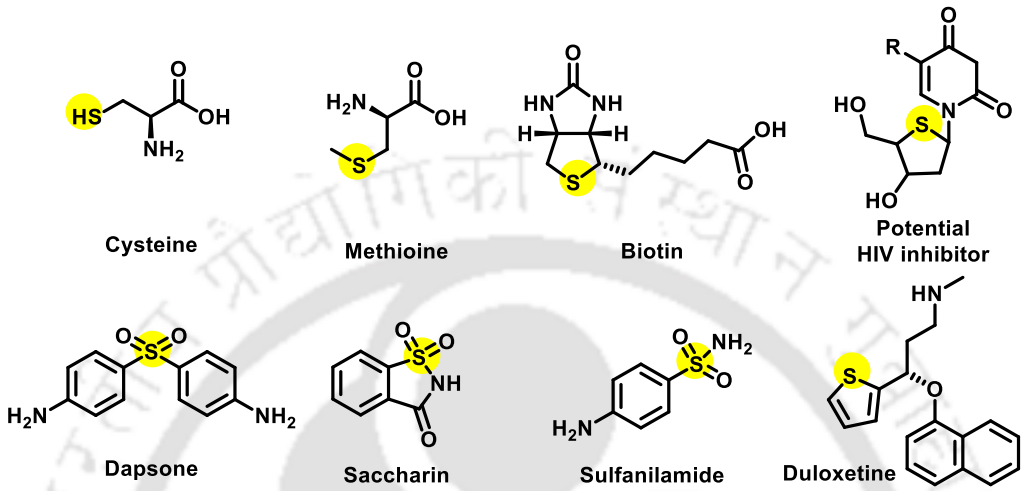
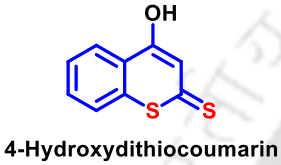


Figure 4. Prominent organosulfur compounds

Organosulfur compounds are known to be rich in their chemical properties, offering both biological and industrial significance. Essential naturally occurring organosulfur compounds are cysteine, methionine, and biotin, which also contribute to the aroma of garlic and onion. By impacting specific signaling pathways, these compounds are also observed to assist in the reduction of inflammation and defend against chronic illness.[18]Their therapeutic usage can be proven through ongoing *in vivo and in vitro* research. Furthermore, owing to their wide range of biological and industrial applications, these compounds are pivotal in pharmaceuticals,[19] agrochemicals,[20] dyestuffs,[21] and synthetic chemistry.[22]The drugs that are composed of sulfur are penicillin, cephalosporin, and monobactam, which are effective against bacterial infections.[23] These compounds also exhibit antimutagenic and anticarcinogenic properties. In umpolung strategies, organosulfur compounds are essential in asymmetric synthesis, with reagents like 1,3-propane dithiol, which is used for the protection of carbonyl.[24]Over and above this, they are present in fungicides, insecticides, dyes, and food additives, and are fundamental to detergents through long-chain sulfonic acids.[25] Solvents like DMSO and CS_2 are also crucial in laboratories.

In summary, organosulfur compounds have found their significance in both the fields of chemistry, such as synthetic organic and materials chemistry. By means of the efficient construction of novel organosulfur compounds and bioactive chiral molecules, organocatalysis, too, has substantially evolved in C–S bond formation. Follow-up research should further explore the establishment of novel organocatalysts with innovative stimulation approaches to extend their usefulness.

A sulfur-containing analogue of 4-hydroxycoumarin, in which the oxygen atom in the lactone ring is replaced by a sulfur atom, forming a thiolactone structure, **4-Hydroxydithiocoumarin**(**B**).



4-Hydroxydithiocoumarin

Andersonmckay and Liepa first synthesized 4-hydroxydithiocoumarin from 2′-chloroacetophenone and carbon disulfide using sodium hydride as a base.[26]Substantialendeavours in the regime of the reactivity of 4-hydroxydithiocoumarin, with several other nucleophiles, have unmasked the unusual reactivity of 4-hydroxydithiocoumarin, which is being explored in our laboratory. Although significant progress has been made in utilizing 4-hydroxydithiocoumarin as an invaluable precursor for accessing various molecules of interest, efforts are still made in the arena of *in vitro* analysis of this moiety.

1.3. Literature reviews on 4-hydroxy-2*H*-chromene-2-thione

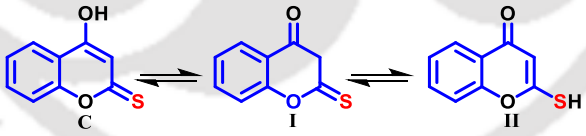
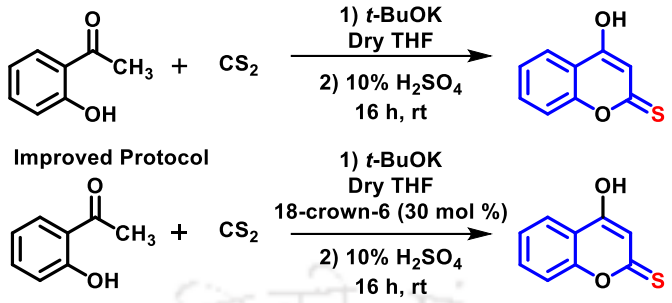


Figure 5. Tautomeric Forms: Keto and Enol Structures

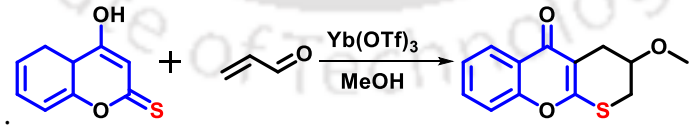
In 2021, L. Costantino[27] and his co-worker established the synthesis of 4-Hydroxy-2*H*-chromene-2-thione, and we have slightly modified it for its higher yield.[28] Potassium *tertiary* butoxide (15 mmol) and 18-crown-6 ether (1.5 mmol) were taken in 7 mL of anhydrous THF in an oven-dried round-bottomed flask. The mixture is purged with N_2 and cooled to 0 °C in an ice bath. Then, 2'-hydroxyacetophenone (5 mmol) is added dropwise to the above solution,



Scheme 1. Adaptation and modification of the reported synthesis of 4-Hydroxy-2*H*-Chromene-2-Thione

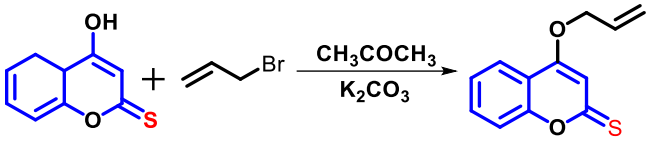
followed by adding carbon disulfide (5 mmol) to the reaction mixture, forming a thick yellow precipitate. The reaction is stirred at 0-15 °C for 1 h, then brought to room temperature and continued stirring at this temperature for 16 h. The reaction was quenched by adding 5 mL of water, and then the water layer was washed with ethyl acetate (2 × 5 mL). The aqueous layer was then acidified with 10% H_2SO_4 until pH was adjusted to 4-5, and the mixture was stirred for another 16 h. A yellow precipitate is formed, collected by vacuum filtration, and washed with petroleum ether several times to obtain the desired product, which is a yellow solid.

G. Palmisano *et al.*, in the year 2007, synthesized several sulfurisosters to see the antitubercular activity of the naturally occurring compounds that may be dissociated from their antithrombin activity. A linear adduct was formed when 4-hydroxy-2-deoxy-2-thiocoumarin was reacted with farnesal and otherα,β-unsaturated aldehydes, causing a regiochemical inversion in the Knoevenagel-electrocyclic reaction.[29]



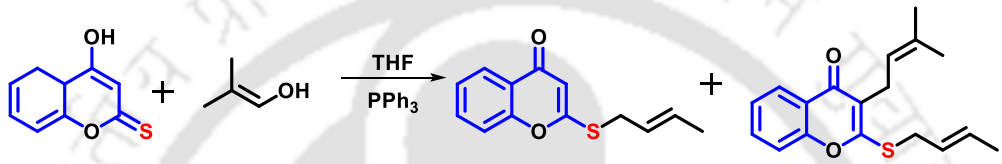
Scheme 2. Synthesis of thiopyrano-chromenone derivatives

A. A. Avetisyan and A.G. Alvandzhyan in 2004, continuing the studies of the chemical transformations of new coumarin derivatives, reacted 4-hydroxy-2*H*-chromene-2-thione with allyl bromide to give corresponding ethers, which were further oxidised.[30]



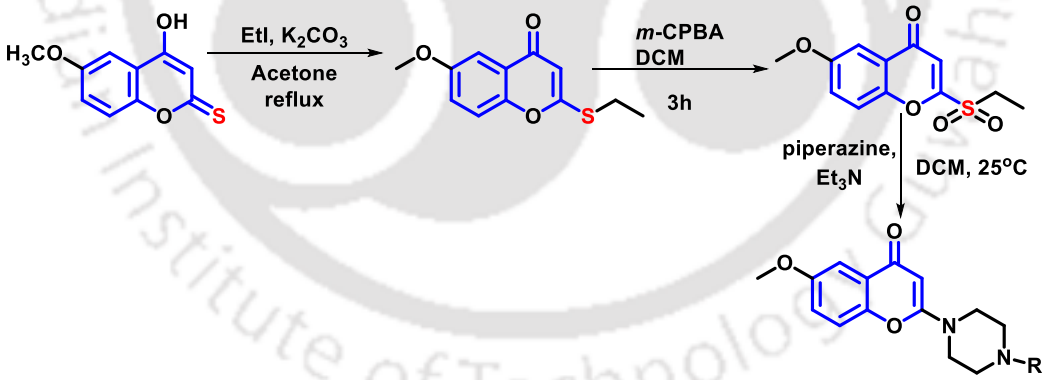
Scheme 3. Synthesis of chromene-thionederivatives

In the Mitsunobu reaction in the year 2003, G. Cravotto*et al*., led to the formation of a new C-C bond through one-pot synthesis with allyl alcohol.[31]



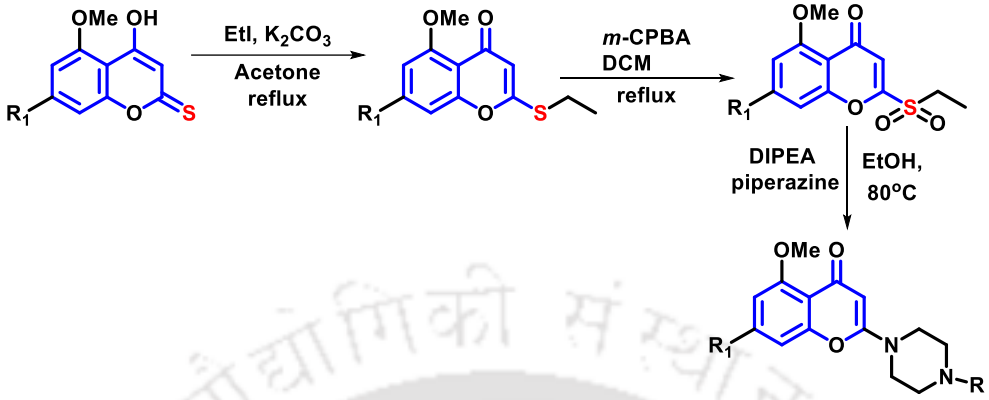
Scheme 4. Synthesis of thiochromenone derivatives

Anti-inflammatory (TNF-α, IL-6 inhibition) and antimicrobial activity were studied by D. Hatnapure*et al*., where they synthesized two series of flavones piperazine derivatives from 4-hydroxy-2*H*-chromene-2-thione.[32]



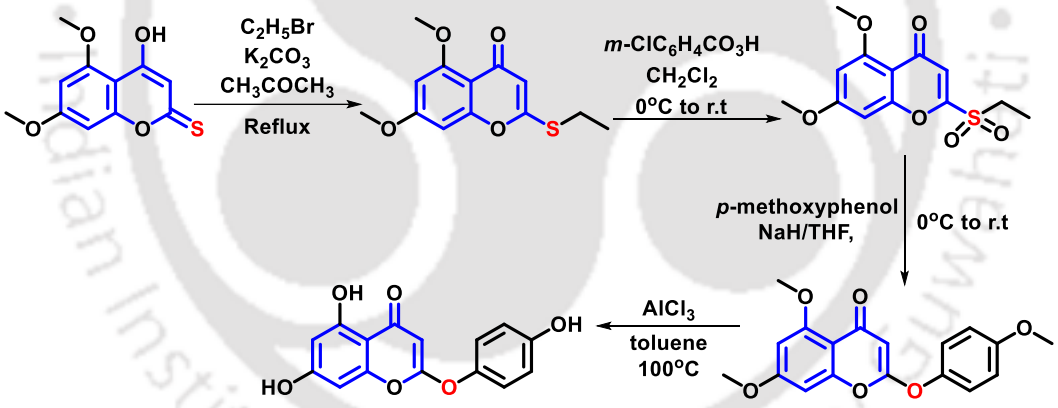
Scheme 5. Synthesis of flavone–piperazine derivatives

In 2016, J. E. O. Balboa and his co-workers synthesized a series of chromones which can revert the chemo-resistance of ABCC1 overexpressing cells and are expected to be of potential value as pharmacological tools for the investigation of the physiological role of the ABCC1 transporter.[33]



Scheme 6. Synthesis of chromones

Capillarisin, a naturally occurring chromone originally isolated from traditional Chinese Capillary wormwood herb, Y. F. Tong and his co-workers in 2007, developed a convenient way for its synthesis and further study its role of functioning as inhibiting aldose reductase (AR).[34]



Scheme 7. Synthesis of Capillarisin

Final Observations on the divergent Reactivity of 4-hydroxy-2*H*-chromene-2-thione

We may conclude from the reactions above that 4-hydroxy-2*H*-chromene-2-thionedoes not give similar kinds of products and its reactivity varies from reaction to reaction owing to its different reactive sites, as shown for the resonating structures in **Figure 5**, as well as shown in **Figure 6**.

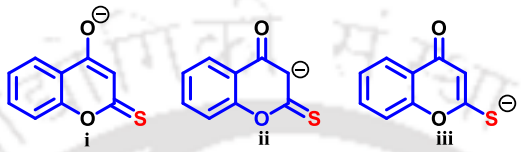


Figure 6. Reactive Sites of 4-hydroxy-2*H*-chromene-2-thione

Hence, the conclusion draws that 4-hydroxy-2*H*-chromene-2-thione, consisting of hydroxyl and thione functional groups, has proven to be a versatile heterocyclic compound on the coumarin scaffold, making it a fundamental feature towards a range of organic transformations. Its usefulness spans across wide range of reactions types, especially in heterocyclic synthetic methodology and C–C/C–X bond forming reactions.

1.4. Utilization of 4-hydroxy-2*H*-chromene-2-thionein different types of reaction

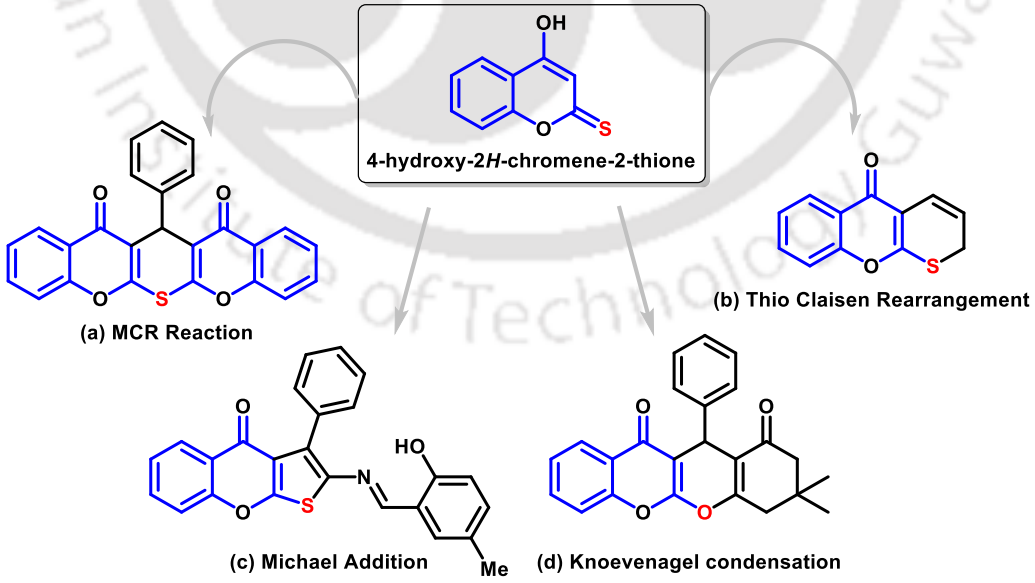
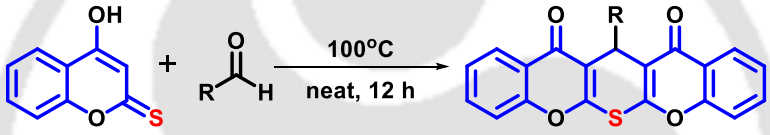


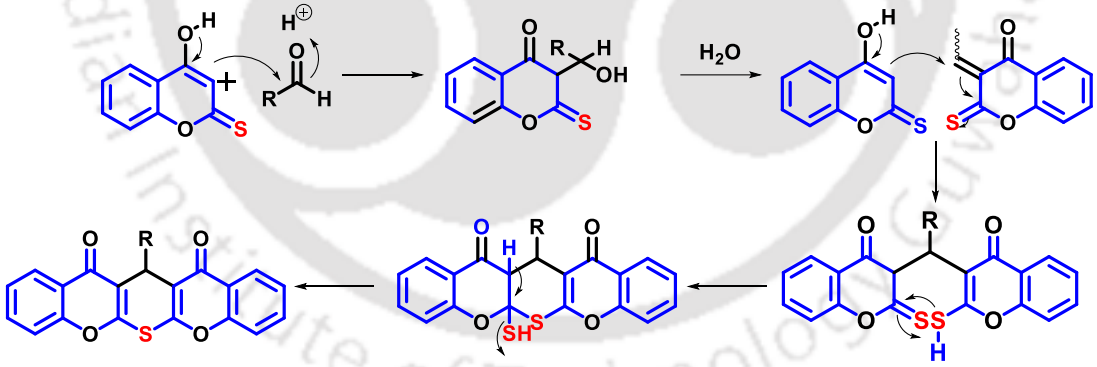
Figure 7. Application of 4-hydroxy-2*H*-chromene-2-thione in different reactions

1.4a. MCR Reaction

In 2023, to explore the chemistry of 4-hydroxy-2*H*-chromene-2-thione, under mild heating**,** we have reported a catalyst and solvent-free one-pot synthesis of pentacyclic-dione motifs from4-hydroxy-2*H*-chromene-2-thione and aromatic aldehydes **Scheme 8.** The reaction proceeds through Knoevenagel condensation, followed by oxa-Michael cyclization, forming fused chromeno-thiophene (thiopyran) derivatives. This protocol offers short reaction times with good to excellent yields without needing any metal catalysts or organic solvents, tolerating a small library of pentacyclic systems, broadcasting its usefulness in medicinal chemistry[35] as shown in **Scheme 9.**



Scheme 8. Reaction between4-hydroxy-2*H*-chromene-2-thione and aromatic aldehydes

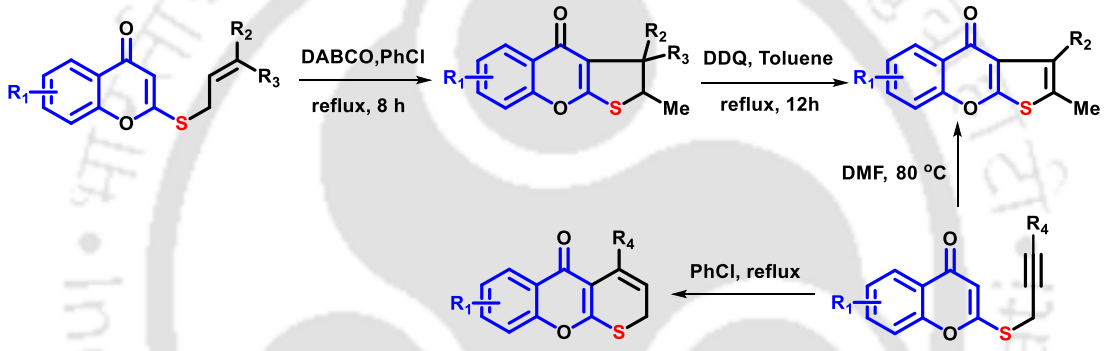


Scheme 9. Proposed mechanism of the pseudo-three-component reaction

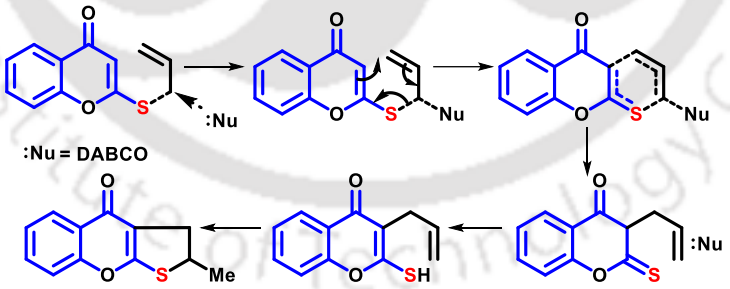
1.4b. Thio Claisen Rearrangement Reaction

In addition to the previous work, in 2024, we reported a solvent-influenced synthetic methodology from 4-hydroxy-2*H*-chromene-2-thione and its derivatives **Scheme 10.** Initially, on

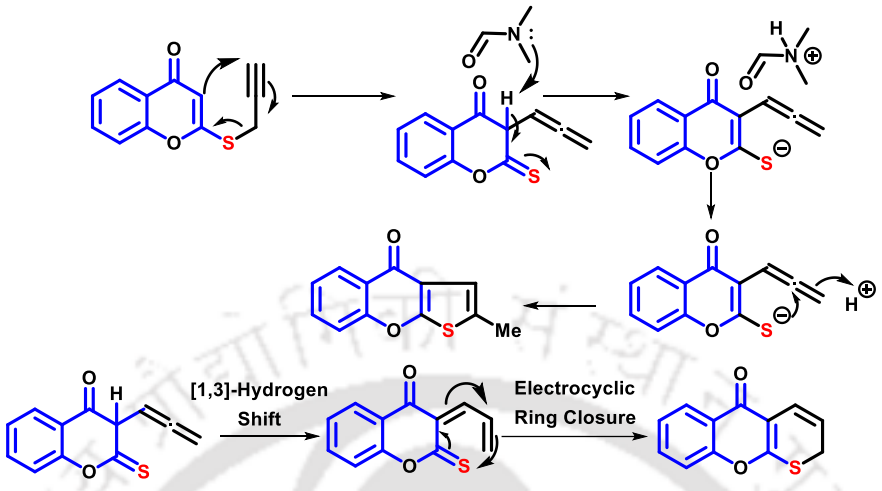
reacting with allyl or propargyl bromide, we received *S*-alkylated ethers. Then continuing with the obtained *S*-alkylated ethers, a thio-Claisen rearrangement turns them into fused heterocycles comprising of chromono thiophene-thiopyran derivatives. Next, the *S*-propargyl ethers lead us to solvent-dependent, distinctive cyclized products, showcasing their selectivity. Additionally, a single-step reaction with nitromethane and *p*-TSA formed a cyclized product with 2-methylbut-3-yn-2-ol, as shown in **Schemes 11**, **12**, and **13**. Theoretical calculations prove the synthetic route for the formation of the product, along with its regioselectivity and the solvent effects. Overall, this protocol offers excellent regioselectivity with high yields and high atom economy.[36]



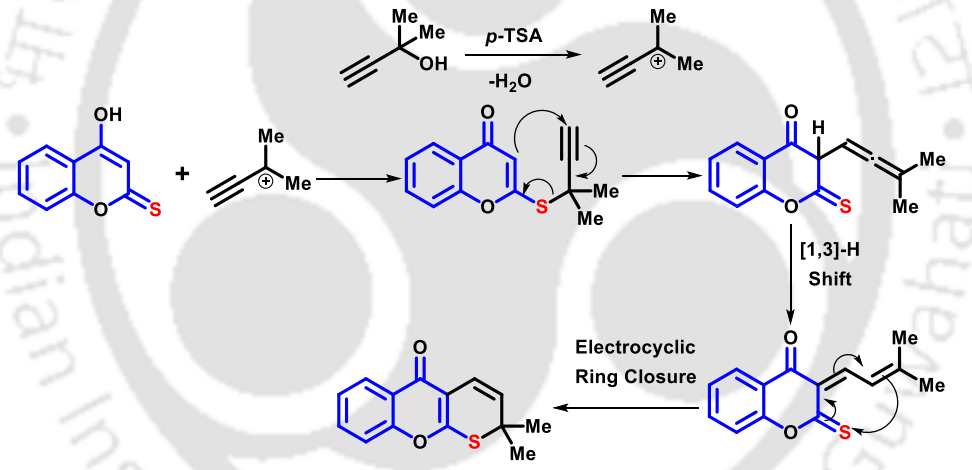
Scheme 10. A two-step synthetic route utilizing 4-hydroxy-2*H*-chromene-2-thione



Scheme 11. Proposed mechanism for the synthesis of fused chromonothiophene derivatives



Scheme 12. Proposed mechanism for the synthesis of fused chromone derivatives

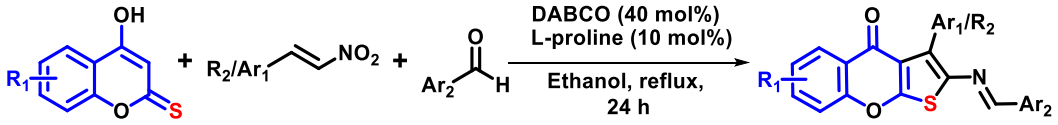


Scheme 13. Proposed mechanism for the synthesis of fused chromono-2,2-dimethyl-thiopyran derivatives

1.4c. Michael Addition Reaction

Subsequently, we demonstrated a one-pot three-component coupling reaction by reacting 4-hydroxy-2*H*-chromene-2-thione with aryl/salicylaldehyde, and trans-*β*-nitrostyrene under basic reaction conditions, **Scheme 14**. This reaction pathway proceeds *via* Michael addition of the 4-hydroxy-2*H*-chromene-2-thione to nitrostyrene, followed by intramolecular cyclization, and then the formation of Schiff base takes place. This protocol offers an alternative route to form new

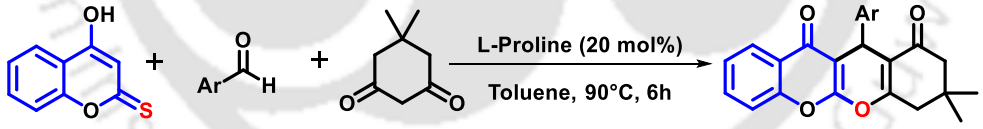
bonds that with high regioselectivity and excellent yields,[37]as shown in **Scheme 15.**



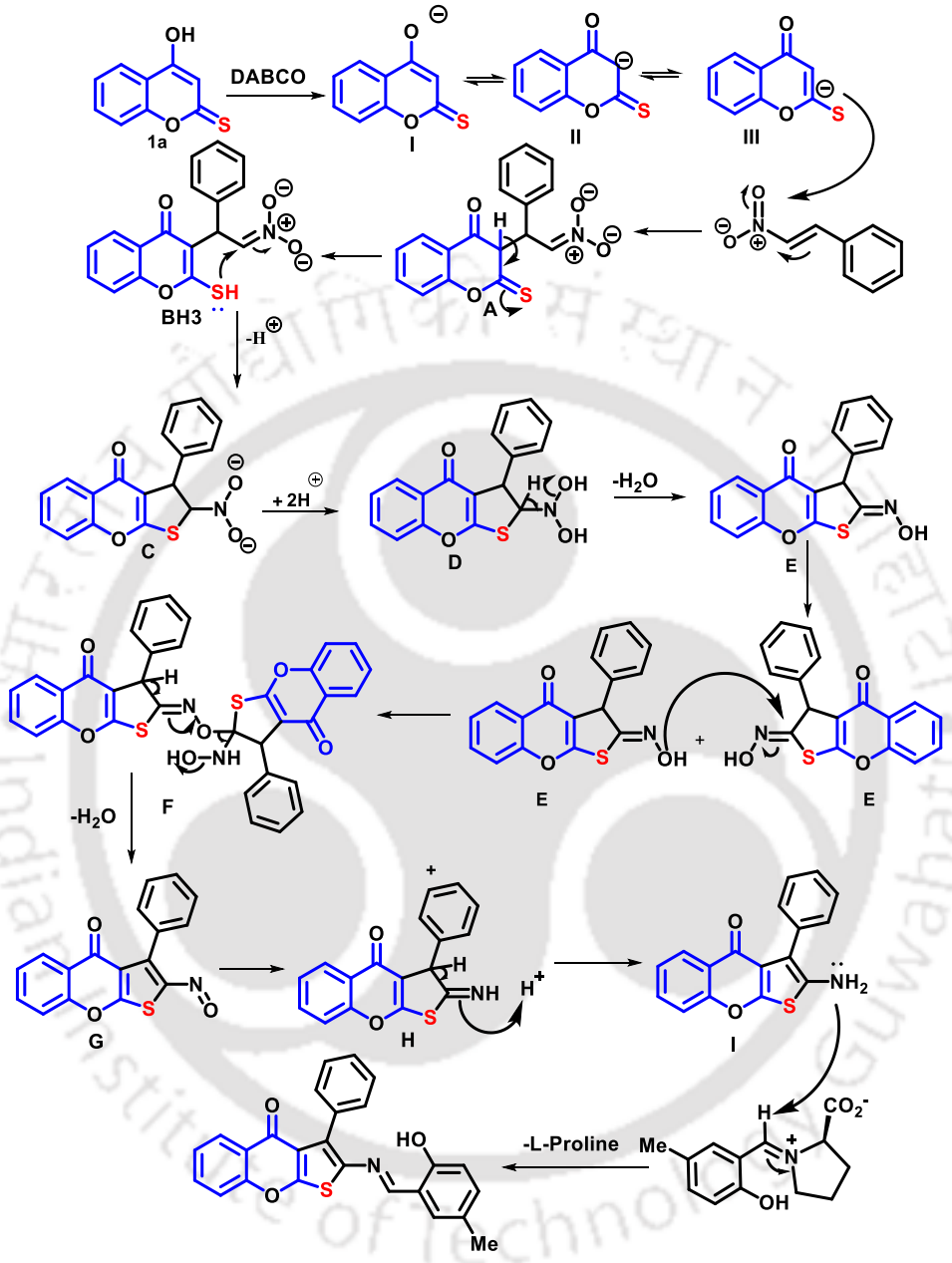
Scheme 14. Reaction between 4-hydroxy-2*H*-chromene-2-thioneand aryl/salicylaldehyde, and *trans*-β-nitrostyrene

1.4d. Knoevenagel condensation

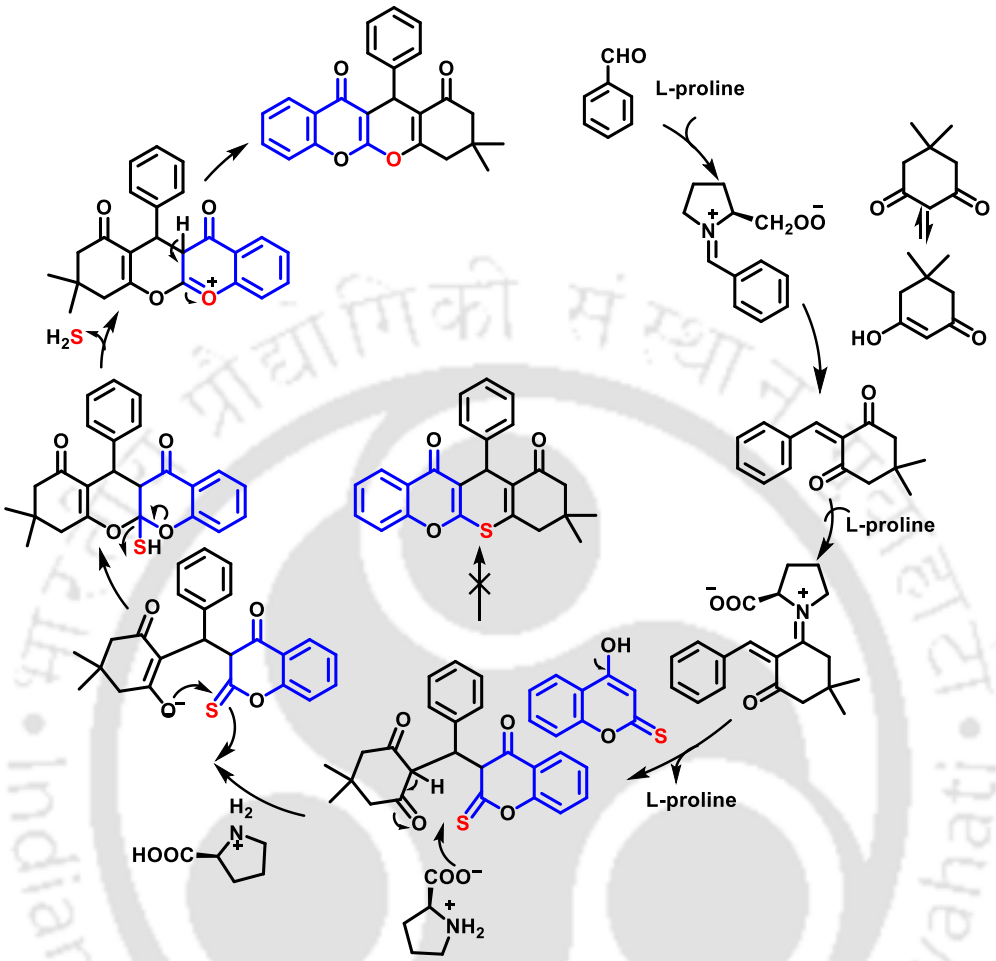
Upon further exploring the reactivity pattern of 4-hydroxy-2*H*-chromene-2-thione, Mandal *et al*., developed a new class of fused chromene employing L-proline-catalyzed, multicomponent approach through 4-hydroxy-2*H*-chromene-2-thione, aromatic aldehydes, and dimedone **Scheme 16**.Contradicting prior assumptions, for the formation of expected angular or linear sulfur-containing products, the reaction persistently produced a new class of fused chromene in good to excellent yields by means of Knoevenagel condensation followed by Michael addition reaction **Scheme 17**.Several derivatives that were formed tend to exhibit anti-proliferative activity against MCF-7 breast cancer cells, and molecular docking and biological assays were conducted.[38]



Scheme 16. Reaction between4-hydroxy-2*H*-chromene-2-thione, aromatic aldehydes, and dimedone



Scheme 15. Aplausible mechanism for the formation of (*E*)-2-((2-hydroxy-5-methylbenzylidene)amino)-3-phenyl-4*H*-thieno[2,3-*b*]chromen-4-one



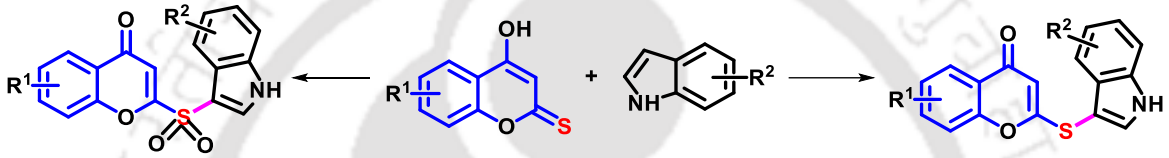
Scheme 17. Plausible mechanism for the formation of chromenes

1.5.An Overview of the Present Investigation on 4-hydroxy-2*H*-chromene-2-thione

This thesis primarily focuses on the development of 4-hydroxy-2*H*-chromene-2-thione for the construction of synthetic methodologies of bioactive molecules. Given the diverse reactive sites present in 4-hydroxy-2*H*-chromene-2-thione, we selected a range of electrophiles and nucleophiles comprising indoles, aniline, aldehydes, enaminones, and benzyl bromide to design and synthesize our target molecules. A relatively smaller portion of the thesis is dedicated to exploring the biological significance of these newly synthesized compounds. The experimental findings and results are organized into five chapters, followed by a summary and discussion of future perspectives. A brief outline of each chapter is provided below.

1.5a. 3-Sulfenylindole

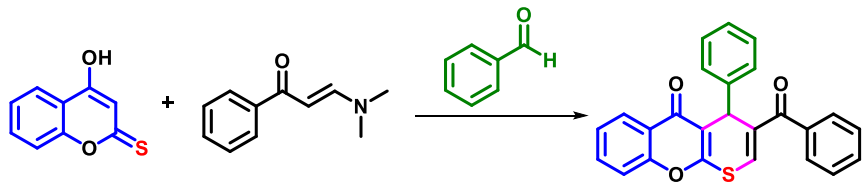
Known for their diverse and promising biomedical applications,3-Sulfenylindole derivatives were synthesized by coupling 4-hydroxy-2*H*-chromene-2-thione with indole through an oxidative cross-dehydrogenative coupling. Computational predictions and molecular docking studies were carried out to prove the reaction pathway that leads to 3-sulfenylindoles. The development of such new scaffolds was proven to be a novel bioactive compound through molecular docking and MTT assay.



Scheme 18. Synthesis of 3-Sulfenylindole

1.5b.Thiopyran

Holding a prestigious importance in the sulfur industry, a six-membered heterocyclic system, thiopyran, is widely studied all around the globe. Its utility expands in the field of pharmaceuticals, chemicals, and agrochemicals. In this 3rd chapter, the derivatives exhibiting 4-hydroxy-2*H*-chromene-2-thione as a core molecule were synthesized, which can further be explored for developing sulfur-loaded materials, including dyes and polymers. The existence of sulfur in the thiopyran systems confers properties such as electron-donating, converting it into a beneficial moiety in engineering complex molecules. Besides this, thiopyran derivatives are utilized as intermediates in organic synthesis that lead to a library of heterocyclic molecules which can be used as a drug. In this protocol presented, the formation of fused thiopyran ring.

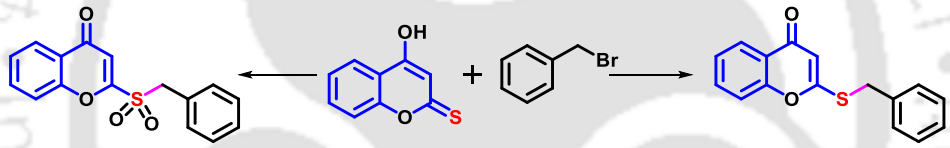


Scheme 19. Synthesis of thiopyrano derivatives

under mild, water-based conditions highlights its role in forming heterocyclic frameworks efficiently and sustainably.

1.5c. Heteroarenes

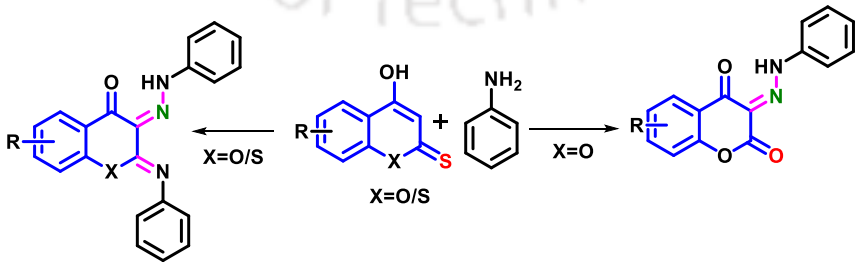
Serving as a biologically active core, heteroarenes lend their functionalityin the world of pharmaceuticals and agrochemicals. The diversity in its structural core makes it more effective in natural product synthesis. As discussed earlier in this chapter, organosulfur, another type of heteroarene, shows its unique reactivity and ability to form new bonds that are stable, which makes it a versatile building block in synthetic organic chemistry. Keeping this in our mind, we have designed in chapter 4, 2-(benzylthio)-4*H*-chromen-4-one derivatives from 4-hydroxy-2*H*-chromene-2-thione, and benzyl bromide. Further analysis of its bioactivityis also aimed at.



Scheme 20. Synthesis of 2-(benzylthio)-4*H*-chromen-4-one derivatives

1.5d. Hydrazones

Condensing a carbonyl with a hydrazine or an aryl hydrazine forms a hydrazone, a versatile synthetic compound. The second chapter outlines the reaction of 4-hydroxy-2*H*-chromene-2-thione with aniline to synthesize hydrazonechromene scaffolds. Mechanistic investigations



Scheme 21. Synthesis of hydrazone derivatives

revealed the reactivity pattern of our thio-moiety, 4-hydroxy-2*H*-chromene-2-thione, showing that it parallels the pattern of 4-hydroxycoumarin under certain reaction conditions, yet sometimes it diverges.

1.5. References

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CHAPTER II

Synthesis of 3-Sulfenylindole derivatives from 4-hydroxy-2*H*-chromene-2-thione and indole using oxidative cross-dehydrogenative coupling reaction and anti-proliferative activity study of some of their sulfone derivatives

2.1. Preparation of 4-hydroxy-2*H*-chromene-2-thione

2.2. Introduction to 3-sulfenylindole

2. 2a. Synthesis of 3-sulfenylindole derivatives

2.3. Results and Discussions

2.4. Biological Applications

2.5. Conclusions

2.6. Experimental Sections

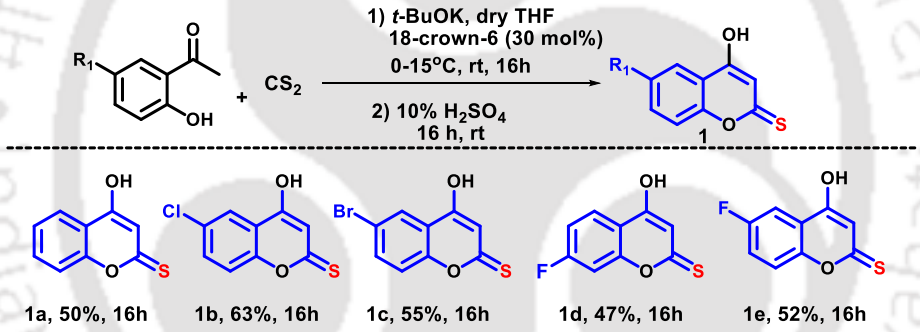
2.7. References

2.1 Preparation of 4-hydroxy-2*H*-chromene-2-thione

To examine the reaction behaviour of 4-hydroxy-2*H*-chromene-2-thione, firstly, they were prepared from the corresponding 2′-hydroxyacetophenone derivatives and carbon disulfide in the presence of a base, potassium *tert*-butoxide in dry THF.[1]To enhance the yield of the product, the procedure was slightly modified by adding 18-crown-6-ether.

It was noted that the yield was increased a little bit due to the formation of [K(18-C-6)(O^{t}Bu)] complex *in situ*, which in turn enhanced the basicity of the O^{t}Bu$^-$ anion.[2] Various 4-hydroxy-2*H*-chromene-2-thione (**1a-e**) were prepared as shown in **Table 1** and characterized using ^{1}H-NMR and^{13}C-NMR spectra.

Table 1. Preparation of 4-hydroxy-2*H*-chromene-2-thione derivatives[a,b]



[a]All the reactions were carried out using 2′-hydroxyacetophenone (5 mmol) carbon disulfide (5mmol) with 3 equivalents of *t*-BuOK in dry THF, along with 30 mol% 18-crown-6 at room temperature. [b]Isolated yield.

The reactivity of 4-hydroxy-2*H*-chromene-2-thione (**1**), the thio-analogue of 4-hydroxy-2*H*-chromene-2-one, is less explored in organic synthesis due to its commercial non-availability[3]. The three possible resonating structures of 4-hydroxy-2*H*-chromene-2-thione are displayed in **Chapter I**, **Figure 5**. In the past few years, our research group has explored the chemistry of 4-hydroxydithiocoumarin, another thio-analogue of 4-hydroxy-2*H*-chromene-2-one with two sulfur atoms, for synthesizing various new chemical entities, and it has been reviewed recently. The present study aims to investigate the reaction behaviour of 4-hydroxy-2*H*-chromene-2-thione with indole, which may lead to

the formation of a new class of 3-sulfenylindole derivatives. In addition, these 3-sulfenyl indole derivatives can be oxidized to sulfones for biological study.

2.2. Introduction to 3-sulfenylindole

The development of organosulfur compounds has immense importance in pharmaceutical and medicinal chemistry,[5]as some are used as marketed drugs, namely Dapsone **Figure 1.**The sulfur-containing compounds, which exhibit biological activity, are also present in vegetables such as garlic, onion, and many more. Moreover, among various sulfur derivatives, sulfides, sulfones, and sulfoxides are used in organic synthesis for C-C bond[6a] formation reactions. The sulfoxide, dimethylsulfoxide, is used extensively as a solvent[6b] and reagent.[6c]

Likewise, the indole nucleus behaves like the core structure in various naturally occurring compounds prone to medicinal and material science.[7a]The biological activity of indole moiety is credited to its C-3 functionalization,[7b] which involves antiviral activity,[7c]HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors[7d] etc (**Figure 1**).

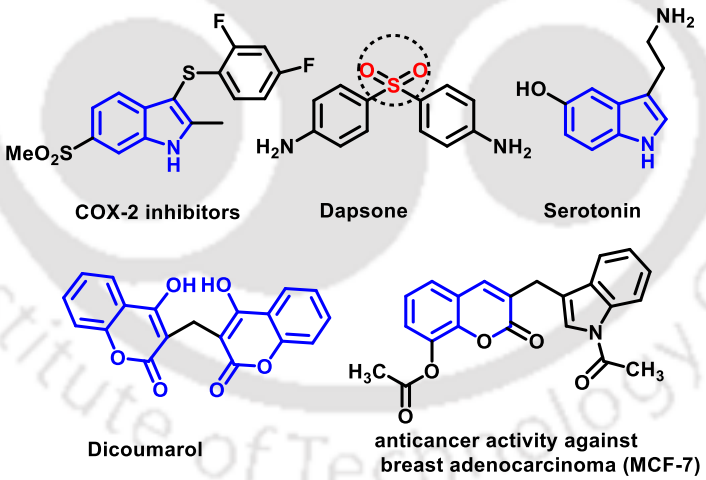


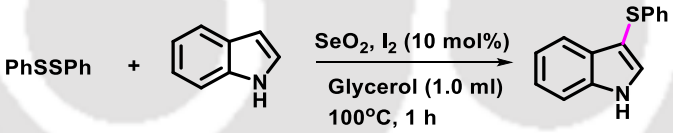
Figure 1. Bioactive molecules based on sulphur, indole and 4-hydroxycoumarin

Coumarin displays a remarkable array of biochemical and pharmacological activities.[8] The substituted coumarin derivative, such as 4-hydroxy-2*H*-chromene-2-one, makes them more significant for effective bioactivity, for example, Dicumarol, Warfarin, etc. (**Figure 1**).

Recently, indoles incorporated with coumarin have been reported to possess anticancer activity.[9] Besides these, molecules have been shown to exhibit significant spectra of biological and pharmaceutical activities,[10a] such as anticancer,[10b] anti-HIV-1 activity,[10c]allergies,[10d] etc. In literature, different approaches have been explored to synthesize 3-sulfenylindole, a hybrid molecule,using numerous sulfenylating reagents such as sulfenyl halides,[11a] thiols,[11b] disulfides,[11c] aryl sulfonyl hydrazides,[11d] aryl sulfonyl chlorides[11e] and sulfinic acids.[11f]Hence, at this border, we decided to build a hybrid structure combining thio-analogues of 4-hydroxy-2*H*-chromene-2-one and indole. For this purpose, oxidative cross-dehydrogenative coupling is the preferred method.

2. 2a. Synthesis of 3-sulfenylindole derivatives

A simple and rapid method has been developed by Thurow and his co-workers[12] for synthesizing 3-sulfenylindoles using I_2/SeO_2 as catalyst/oxidant in glycerol. This protocol enables efficient S–S bond cleavage and S–C sp^2 bond formation, yielding products in minutes with good selectivity and broad substrate scope.

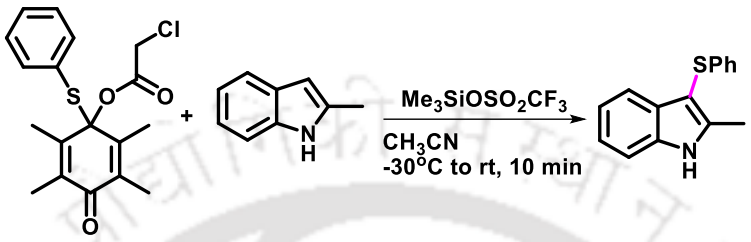


Scheme 1. Synthesis of 3-sulfenylindole

A metal-free and efficient synthesis of sulfenylated chromones and indoles has been achieved *via* C–H functionalization by Sorabad*et.al*., using aqueous HBr and DMSO as an oxidizing system. This method offers excellent yields, avoids hazardous molecular bromine, and delivers various substituted products in a short time.[13]

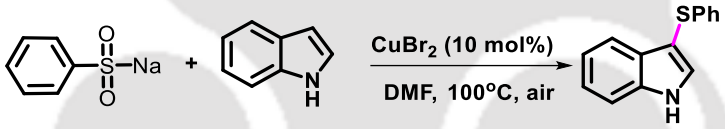
Scheme 2. Synthesis of 3-sulfenylindole

Matsugi*et al*., reported a method for the construction of 3-sulfenylindoles using quinone mono-*O,S*-acetals and indoles, where sulfenylation occurs *via* aromatization of the acetals under nearly neutral conditions.[14]



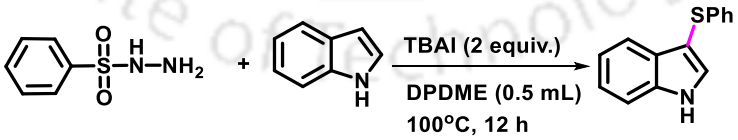
Scheme 3. Synthesis of 3-sulfenylindole

Luo *et al.*, developed a method for the advancement of 3-sulfenylindoles from indole and sodium sulfinate using a Cu/DMF system, where sodium sulfinates serve as sulfenylating agents and DMF functions both as a solvent and a reductant.[15]



Scheme 4. Synthesis of 3-sulfenylindole

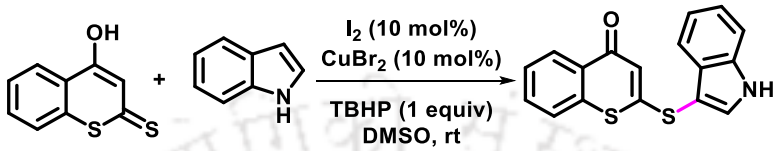
Yueting*et al*., reported a TBAI-mediated C–H sulfenylation of indoles and other electron-rich arenes using sulfonyl hydrazides in DPDME. This method offers excellent functional group tolerance and operates under mild conditions, yielding diverse aryl sulfides efficiently.[16]



Scheme 5. Synthesis of 3-sulfenylindole

A sulfenylation reaction of indole with 4-hydroxydithiocoumarin was developed by Santa and her co-workers using I_2, $CuBr_2$, and TBHP in DMSO under mild conditions, where $CuBr_2$ is key to product formation. The resulting 3-sulfenylindoles were further oxidized to biologically active

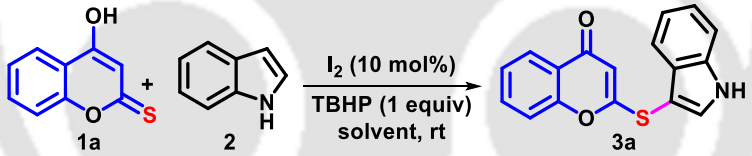
sulfones. The method offers a broad substrate scope, short reaction time, and promising anti-cancer potential as shown by molecular docking and anti-proliferative studies against MCF7 breast cancer cells.[17]



Scheme 6. Synthesis of 3-sulfenylindole

2.3. Results and discussions

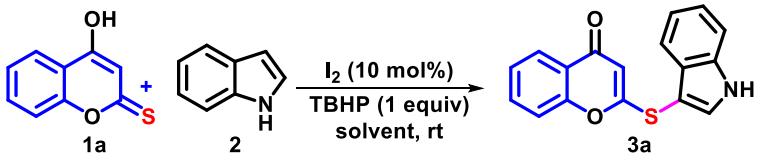
This chapter presents the synthetic method for oxidative cross-dehydrogenative coupling reaction between 4-hydroxy-2*H*-chromene-2-thione and indole at the C-3 position regioselectively using a combination of 10 mol% of molecular iodine and TBHP in the at room temperature.



Scheme 7. Synthesis of 3-sulfenylindole derivatives

After synthesizing the starting material, to find out the optimum reaction conditions, 4-hydroxy-2*H*-chromene-2-thione (**1a**) and indole (**2**) were chosen as the model substrates. We commenced our investigation with a model reaction using 4-hydroxy-2*H*-chromene-2-thione (**1a**, 0.25 mmol) and indole (**2**, 0.25 mmol) without any solvent, catalyst and oxidant. The reaction did not proceed at room temperature, nor did it upon heating. (**Table 2, entries 1** and **2**). However, upon adding 5 mol% iodine and 1 equivalent of TBHP, the reaction proceeded slowly as monitored by TLC to obtain brownish yellow-coloured solid product **3a** in 20% yield (**Table 2, entry 3**). The isolated product **3a** was characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra. Due to the disappearance of

Table 2. Optimization of the reaction conditions[a,b]



Entry	I_2 (mol%)	Oxidant (1 equiv)	Solvent	Time (h)	%Yield[b]
1	-	-	-	3	NR
2[c]	-	-	-	3	NR
3	I_2(5)	TBHP	DMSO	3	20
4	**I_2(10)**	**TBHP**	**DMSO**	**3**	**79**
5	I_2(20)	TBHP	DMSO	3	56
6	I_2(20)	$K_2S_2O_8$	DMSO	3	19
7	$PhI(OAc)_2$	TBHP	DMSO	3	NR
8	IBr	TBHP	DMSO	3	23
9	ICl	TBHP	DMSO	3	28
10	I_2(10)	TBHP	DMF	3	NR
11	I_2(10)	TBHP	Toluene	3	NR
12	I_2(10)	TBHP	CH_3CN	3	NR

[a]All the reactions were carried out using 4-hydroxy-2*H*-chromene-2-thione (**1a**), indole (**2**) in 1 mL of solvent at room temperature. [b]Isolated yield. [c]Reflux conditions.

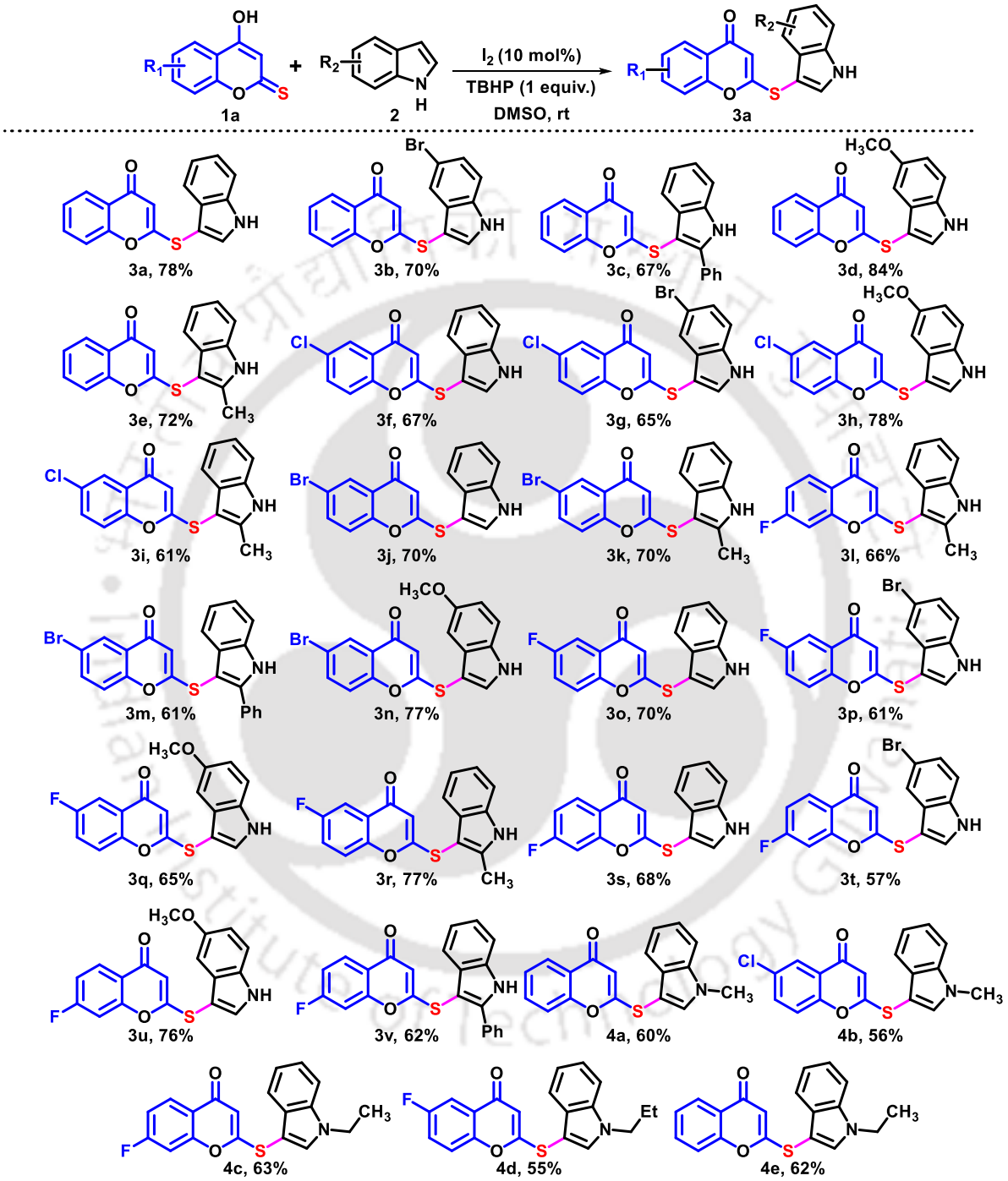
the peak at δ 6.52 for C-3 hydrogen in the ^{1}H NMR spectrum of indole, it was concluded that the coupling reaction took place at the C-3 position of the indole moiety. We focused on increasing the yield of the product **3a**. Upon changing the amount of catalyst from 5 mol% to 10 mol%, the reaction was completed within 3 hours, and the yield significantly increased from 20% to 79% (**Table 2, entry 4**). Further, by increasing the amount of catalyst to 20 mol%, the yield of product **3a** was not increased (**Table 2, entry 5**). To determine the efficacy of other oxidants, the reaction was performed using 1 equivalent of $K_2S_2O_8$, and only a 19% yield of **3a** was obtained

(**Table 2, entry 6**). Next, we also scrutinized the efficacy of various iodine-containing catalysts, such as $PhI(OAc)_2$, IBr, and ICl (**Table 2, entries 7-9**). We noted that I_2 was found to be more efficient as compared to all of these catalysts. Finally, to test the effect of solvents such as DMF, toluene, and CH_3CN, the reaction was performed under similar reaction conditions (**Table 2, entries 10-12**). We noticed that the reaction was incapable of producing product **3a**. Thus, it was concluded from all the above observations that the best reaction conditions are 10 mol% molecular iodine and TBHP (1 equivalent) and DMSO as a solvent in terms of yield and reaction time (**Table 2, entry 4**).

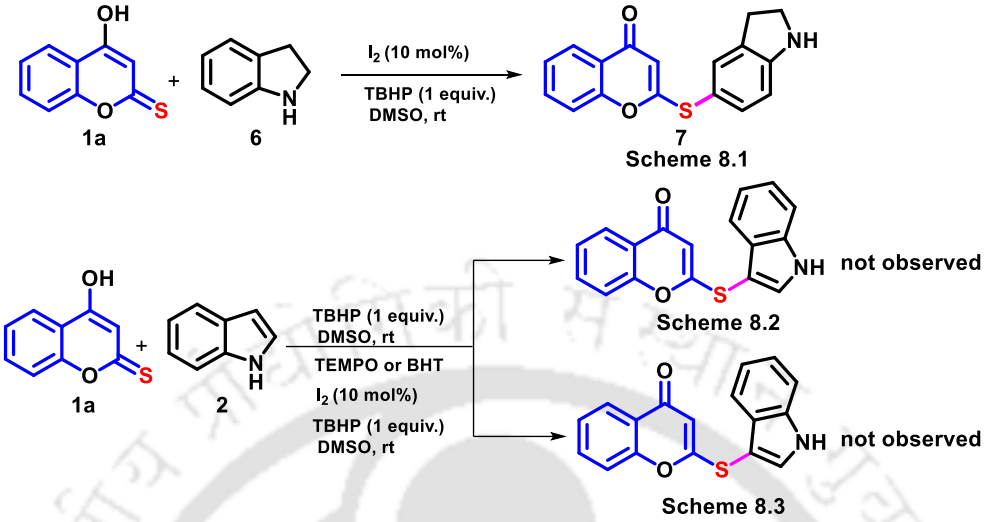
Thus, expanding the scope of reaction with the optimum reaction condition, with various 4-hydroxy-2*H*-chromene-2-thione (**1a**) and indole (**2**) derivatives, the results are summarized in **Table 3**. The reaction proceeded smoothly, with the indoles having electron-donating and electron-withdrawing substituents such as -OMe, -Me, and -Br, providing the products with 78–88% yields. Additionally, with the optimised condition in hand, with a different substituent of indole derivatives, the reaction proceeded with 6-chloro-4-hydroxy-2*H*-chromene-2-thione. The reaction of 4-hydroxy-2*H*-chromene-2- thioneand 5-methoxyindole gave an 84% yield of the product **3d**. 6-chloro-4-hydroxy-2*H*-chromene-2-thione, derivative of 4-hydroxy-2*H*-chromene-2-thione reacted with various indole moieties to yield **3f-3i**, with maximum yield. Further, the derivative of 4-hydroxy-2*H*-chromene-2-thione, 6-bromo-4-hydroxy-2*H*-chromene-2-thione, upon reacting with indole derivatives, afforded the desired product in **3j, 3k, 3m,** and **3n** in good yields. 6-fluoro-4-hydroxy-2*H*-chromene-2-thione reacted with the indole derivatives under similar reaction conditions to afford the products**3o-3r** in good yields. 7-fluoro-4-hydroxy-2*H*-chromene-2-thione with indole substituted derivatives (**3l**, **3s-3v**) gives3-sulfenylindole with 57-76% yields. To extend the applicability of our protocol, the 4-hydroxy-2*H*-chromene-2-thione derivatives reacted with *N*-substituted indole derivatives such as *N*-CH_3, *N*-CH_2CH_3, and *N*-$CH_2CH_2CH_3$, and to our delight, we could afford the anticipated 3-sulfenylindole with **4a-4e** in 55-62% yields.

To understand the mechanism, three control experiments were performed as shown in **Scheme 8**. The first (**Scheme 8.1**) reaction was carried out with 4-hydroxy-2*H*-chromene-

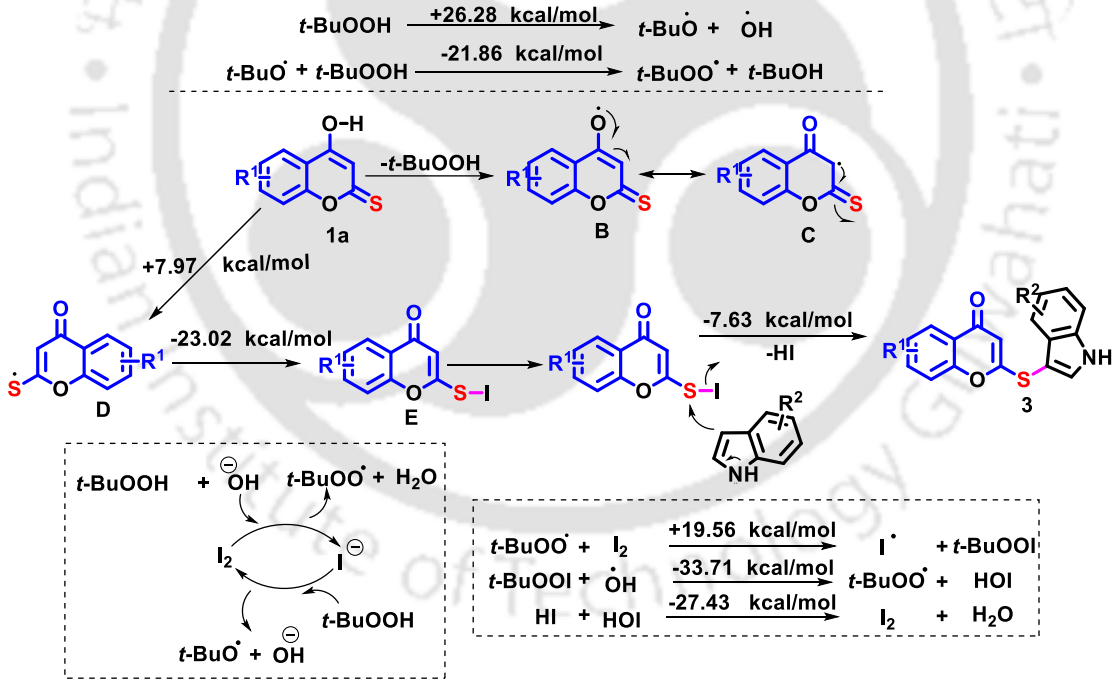
Table 3. Scope of 3-sulfenylindolederivatives[a,b]



[a]All the reactions were carried out using 4-hydroxy-2*H*-chromene-2-thione(**1a**, 0.25 mmol), indole (**2**, 0.25 mmol) in the presence of 10 mol% I_2 in 1 mL of DMSO at room temperature. [b]Isolated yield.



Scheme 8. Control experiments



Scheme 9.A plausible mechanism for the formation of 3-sulfenylindole derivatives

2-thione and indoline under similar reaction conditions, and it provided product **7** with 47% yield. The product was obtained through S-C bond formation at the 5-position of indoline through oxidative cross-dehydrogenative coupling reaction as there is no

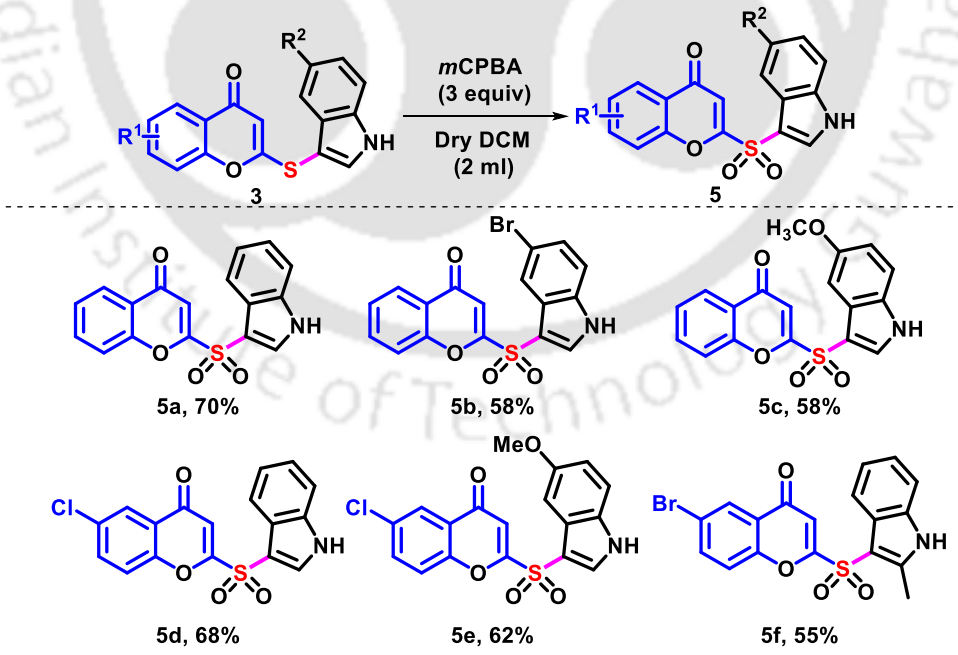
feasibility at the C-3position. The second reaction, (**Scheme 8.2**) was performed without molecular iodine in the presence of 1 equivalent of TBHP and DMSO. Unfortunately, no reaction took place. This shows that a combination of a catalytic amount of molecular iodine and TBHP has an important role in product formation. Thirdly, under standard reaction conditions, 2.0 equiv of 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were introduced into the model reaction mixtures as radical scavengers (**Scheme 8.3**). The desired product **3a** was not obtained. This finding suggested the reaction proceeds through a radical pathway. Following our protocol, based on the control experiment as shown in **Scheme 8** as well as the results summarized in **Table 2**, a plausible mechanism can be drawn for the formation of our isolated product **3a** shown in **Scheme 9**. Initially, TBHP reacts with molecular iodine to generate a *ter*t-butoxy radical and hypoiodous acid. The *tert*-butoxy radical is then reacted with TBHP to give a *tert*-butylperoxy radical.[18] Either the *tert*-butoxy radical or *tert*-butylperoxy radical can abstract hydrogen from the 4-hydroxyl group of 4-hydroxy-2*H*-chromene-2-thione (**1a**) to form radical intermediate **B**, which might also exist as two other possible resonating intermediates, either **C** or **D**. Then, radical intermediate **D** reacts with an iodide radical to give intermediate **E**,[19] which is converted into the desired product **3** after nucleophilic substitution at the C-3 position of indole by eliminating the iodide ion, and hydrogen ion.[20] Subsequently, HI is oxidized to release iodine through the iodine/TBHP system.[21]

To explore the energy profile of the proposed mechanism, quantum chemical analysis of each step of the mechanism shown in **Scheme 9** has been performed using B3LYP/6-31+G(d,p) level. The energy released during this overall reaction is -59.84 kcal/mol, highly exergonic. Starting material **1a** exists in two tautomeric states (**1-t1** and **1-t2**). The energy difference between the two tautomers is very small, 0.28 kcal/mol, implying that the 1,5-H shift in this molecule is a quite favourable process, and the two tautomers exist in equilibrium at room temperature. The spin density analysis of the radical indicates that intermediate **D** is the only option (**B** and **C** structures need to be ignored). According to quantum chemical analysis, the unpaired electron prefers to stay on the sulfur atom; the radical generation is endergonic by 26.28 kcal/mol. However, the immediate next step is

exergonic by 21.86 kcal/mol, exhibiting the formation of ^{t}BuOO• radical requiring only 4.42 kcal/mol and thus considered to be a favourable process. The formation of radical **D** is endergonic by 7.97 kcal/mol, and the formation of iodine radical is endergonic by 19.56 kcal/mol. However, the formation of **E** from iodine radical and **D** radical is exergonic by 23.02kcal/mol. Similarly, many steps along the reaction pathway are associated with exergonic steps, which finally lead to the formation of the product. The energy data obtained from quantum chemical analysis is supporting the proposed mechanistic pathway. Energy of all the steps has been provided in **Table 8.**

Compounds **3a, 3b, 3d, 3f, 3h,** and **3k** were then oxidized into their corresponding sulfones **5a–f** on treating with *m*-CPBA as shown in **Table 4**. The structures of all the products were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectra and by HRMS. Finally, the structures of **3l** and **5d** were also established using single X-ray crystallographic data (**Figure 9**). The study has proven that the sulfonyl compounds regard themselves as potent anti-viral as well as anti-cancer drug.[22]

Table 4. Scope of sulfone derivatives[a,b]



[a]All reactions were carried out with 3-sulfenylindole derivative (0.1 mmol) and *m*CPBA (3 equiv.) in 2 mL dry DCM. [b]Isolated yields.

2.4. Biological Applications

Thereafter, through the lead likeness properties (Molecular weight < 300 Da, octanol-water partition coefficient log P not greater than 3, number of H-bond donor/acceptor < 3) of both compounds **3a** and **5a** were analysed. Among the two, only **5a** passed all three properties of lead likeness, and different functional groups have been added to the **5a** compound to make potential drug molecules. Followed by target prediction, and molecular docking studies were performed.

The SuperPRED server has performed target prediction of lead compound **5a**. The server predicted a total of 117 target proteins with more than a 50 per cent probability of interacting with lead compound **5a**. Out of 117 target proteins, Transcription intermediary factor 1-alpha(TRIM24) has ranked number 1 with a 97% probability of interacting with lead compound **5a.** TRIM24 plays a vital role in breast cancer by activating estrogen-dependent genes associated with tumour development and cellular proliferation. In addition, recently it has been discovered that breast cancer patients' poor overall survival and tumour development are related to TRIM24 overexpression.[23] Different functional groups have been added to the lead molecule **5a** to make a potential drug molecule for the target protein TRIM24.

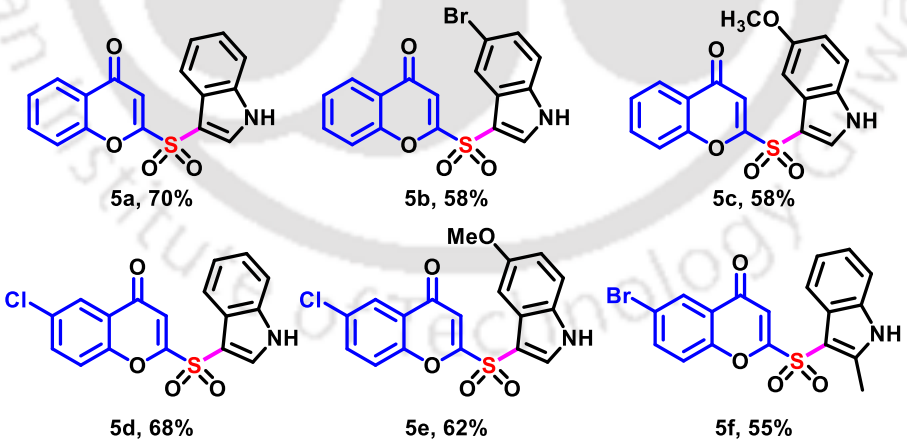


Figure 2. Structural comparison of lead molecule **5a** and modified compounds

It was observed that all the compounds were bound to the bromo domain of TRIM24, which is important to recognize the binding site of TRIM24 in chromatin. The binding scores of the lead (**5a**) and modified lead molecules (**5b**, **5c**, **5d**, **5e**, **5f**) are -8.6, -8.7, -8.6,

-9.2, -8.5, -8.8 kCal/mol respectively. The compounds with a better binding score than lead molecules were selected for further *in-vitro* analysis. The modified structures of the lead molecules are portrayed in **Figure 2**(**5b, 5c, 5d, 5e,** and **5f**).

A molecular docking study showed us the possible interaction of compounds and target proteins in a simulated environment, and also compared it with known inhibitors of TRIM24–C34. Earlier, Bennett, James, *et al.*, reported that the IC_{50} value of C34 (control inhibitor) against TRIM24 by isothermal titration calorimetry (ITC) experiment is 0.43µM. However, they did not find the IC50 of C34, even at very high concentrations, on different cancer cell lines, including MCF-7, in the MTT assay.[24] While in the present study, the synthesized compounds (**5a**, **5d**, **5e**, and **5f)** exhibited IC50 values in the MTT assay, as shown in **Table 5**. The interaction between the synthesised compounds and residues of the target protein is shown in **Figure 3.**MTT assay was used to assess the cytotoxic effect of the compounds on the breast cancer cell line (MCF-7). Treatment of MCF-7 with the compounds **5a, 5d, 5e** and **5f** for 48 h resulted in a dose-dependent reduction in cell viability (**Figure 4**). The obtained data from the MTT assay insinuates that all the derivative compounds exhibited considerable anti-cell proliferative activity, for potential biomedical applications. In addition, biochemical analysis of the compounds using HPLC was carried out (**Figure 6**). The purity of the selected compounds was found to be 99% or more. Therefore, the cytotoxicity exhibited on MCF-7 cells was due to the pure compounds only afterlive-dead cell imaging, it was observed 48 h of treatment with the selected compound caused a substantial increase in propidium Iodide (PI) stained dead cell (red cell) number **(Figure 7**). These findings also portrayed the cell- proliferation inhibitory effect of selected compounds on MCF-7 cells. Whereas, there was no significant alteration in nuclear morphology after 48 h of treatment (**Figure 8**).

Cellular ROS generation was assessed after 6h and 12 h treatment of MCF-7 cells with IC_{50} concentrations of **5a, 5d, 5e**, and **5f**. Treatment with the compounds resulted in the enhancement of intracellular ROS levels on MCF-7 cells. Among all the compounds, **5d** was found to be more effective with ~2-fold increase in ROS after 6 h, and ~1.5-fold increase inROS after 12 h (**Figure 5**). The cell death was therefore likely caused by ROS-mediated cell damage.

Table 5.Binding energy and interaction profile of selected compounds with TRIM24

Sl. No	Compound name	Vina binding score (kCal/mol)	Total number of interactions	Interacting residues		
				H-bond interactions	Pi-interactions	Other interactions
1	**5a**	-8.6	13	LYS 905	ASP 883, LYS 899, PRO 902, ARG 906.	ARG 871, GLU 879, TYR 880, LEU 900, LEU 952, GLU 954, ASP 955, SER 957.
2	**5b**	-8.7	13	LYS 905, ARG 906	ASP 883, LYS 899, PRO 902	ARG 871, PRO876, GLU 879, LEU 900, GLN 953, GLU 954, ASP 955, SER 957.
3	**5c**	-8.6	14	ARG871	PRO 876, LYS 899, PRO 902, LYS 905, ARG 906,	VAL 878, GLU879, TYR 880, ASP 883, LEU 900, GLN 953, GLU 954, ASP 955.
4	**5d**	-9.2	15	LYS899, LEU905	PRO876, ASP 883	ARG 871, VAL878, GLU 879, LEU 900, PRO 902, ARG 906, LEU 952, GLN 953, GLU 954, ASP 955, SER 957.
5	**5e**	-8.5	14	ARG 871	PRO 876, GLU 879, LYS 899, LEU 900, PRO 902, LYS 905, ARG 906,	VAL 878, ASP 883, GLN 953, GLU 954, ASP 955, SER 957.
6	**5f**	-8.8	15	ARG 871	PRO 876, LYS 899, PRO 902, LYS 905, ARG 906,	VAL 878, GLU 879, TYR 880, ASP 883, LEU 900, GLN 953, GLU 954, ASP 955, SER 957.
7	**Control**	-7.5	15	LEU 900, LYS 905	PRO 876, LYS 899, PRO 902, ARG 906	ARG 871, GLU 879, TYR 880, ASP 883, PRO 885GLU 954, ASP 955, SER 957, TYR 959.

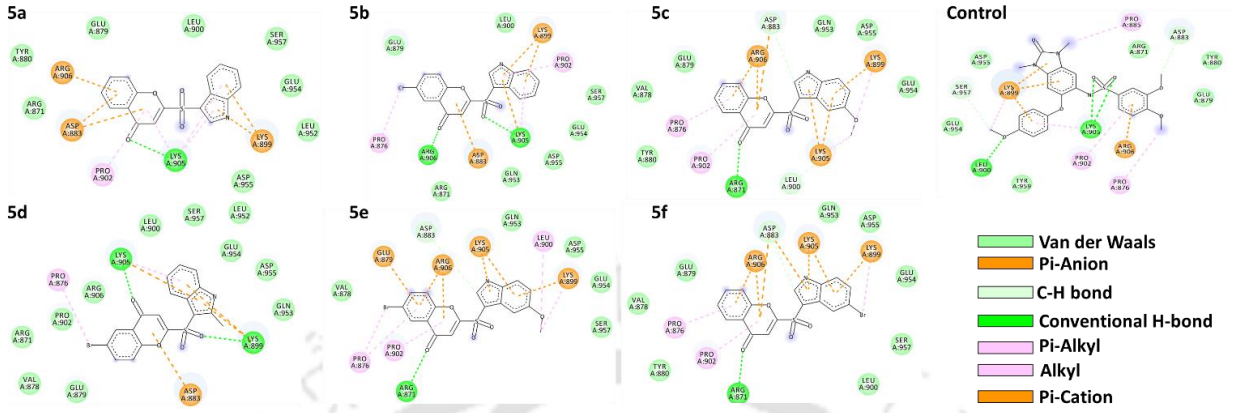


Figure 3.Molecularinteraction of compounds with the residues of TRIM24

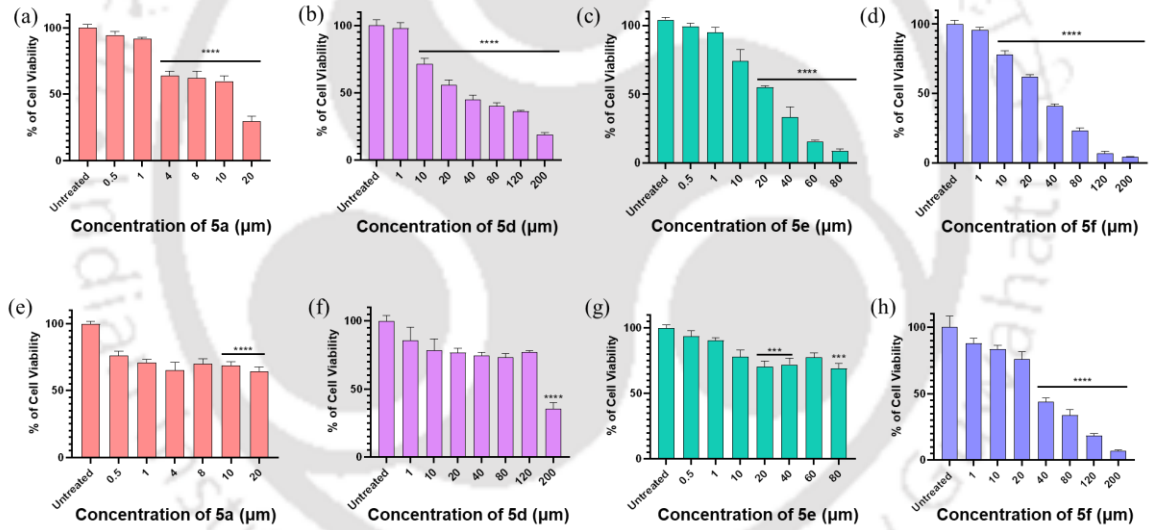


Figure 4. (**a**), (**b**), (**c**) and (**d**) graphically represents the dose-dependent decrease in cell viability in MCF-7 and (**e**), (**f**), (**g**) and (**h**) graphically represents the dose-dependent decrease in cell viability in HEK-293 upon treatment with **5a, 5d, 5f** and **5e** for 48 h. Results are represented as mean±SEM (p-value <0.05 (*), p<0.01 (**), p<0.001 (***) and p<0.0001 (****).

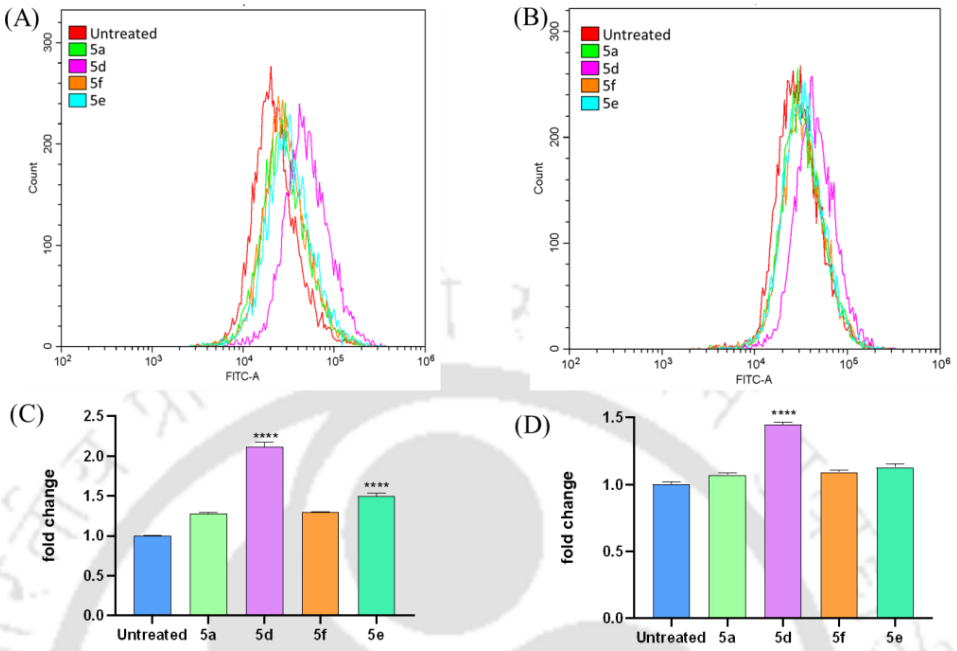


Figure 5. Flow cytometric detection of cellular ROS after (**A**) 6h and (**B**) 12 h of treatment with **5a, 5d, 5f** and **5e**. Graphical representation of the fold change in cellular ROS level on MCF-7 cells following treatment with compounds for (**C**) 6h and (**D**) 12 h.

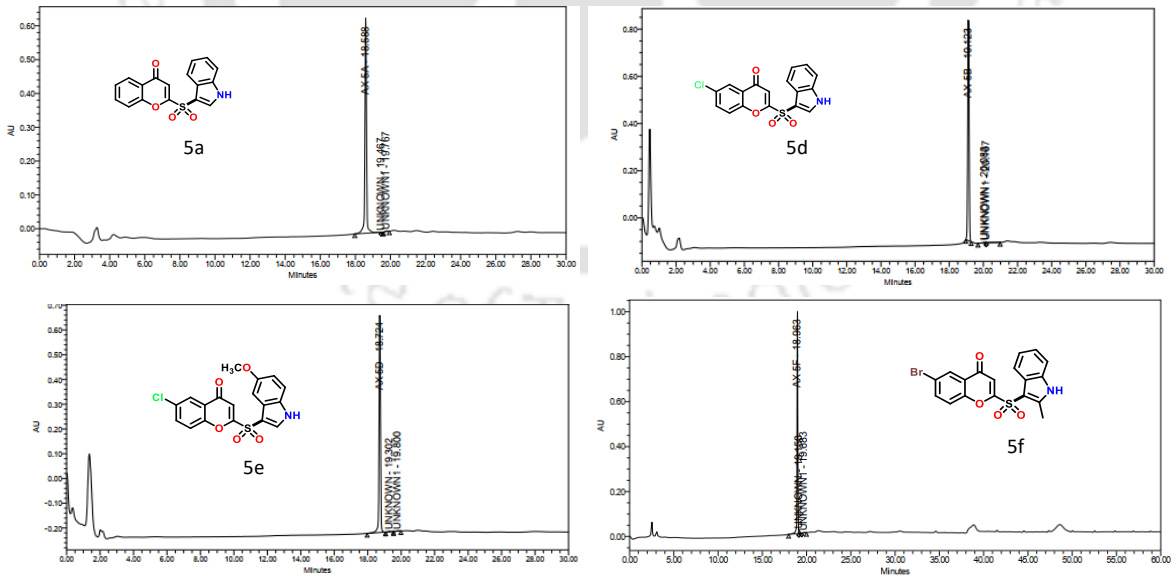


Figure 6. HPLC Spectra for compound: **5a**, **5d**, **5e**, and **5f**

Table 6. IC_{50} values obtained after 48 h treatment with synthesized compounds against MCF-7 and HEK-293 cell line.

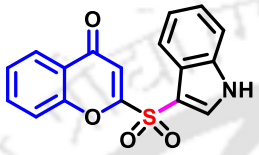
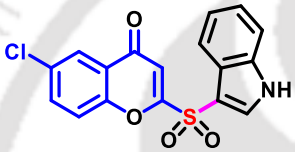
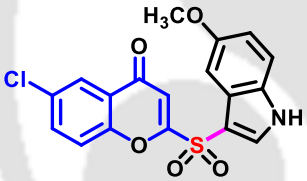
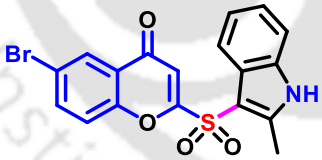
Compound	Structure	IC_{50}(μM) in MCF-7 cells	IC_{50}(μM) in HEK-293 cells
5a		10.83	>20
5d		38.31	153.2
5e		19.58	>80
5f		26.44	37.58

Table 7. The absolute energy values (corrected for free energy changes) of all the species considered in the quantum chemical study.

Sl.No.	Species number as in manuscript	Absolute energywith free energy correction (Hartree)
1	1a	-895.136015
2	2	-363.745763
3	TBHP	-308.726300
4	3	-1257.677546
5	*t*BuOH	-233.595494
6	B	-894.499567
7	D	-895.136015
8	*t*BuOO• radical	-308.102558
9	*t*BuO• radical	-232.936901
10	Iodine	-22.794938
11	Hydroxide anion	-75.811143
12	Iodine radical	-11.488958
13	•OH radical	-75.747513
14	*t*BuOOI	-319.486193
15	HOI	-87.184878
16	HI	-11.996748
17	Int E	-905.916370

Table 8. Step-wise energies

Reaction	Energy in kcal/mol
*t*BuOOH → *t*BuO· + ·OH	+26.28
*t*BuO· + *t*BuOOH → *t*BuOO· + *t*BuOH	-21.86
1*t*1 + *t*BuOO· → D· +TBHP	+7.97
I_2 +*t*BuOO· → I· + *t*BuOOI	+19.56
D· + I· → E	-23.02
E + 2 → 3 + HI	-7.63
*t*BuOOI + ·OH → *t*BuOO· +HOI	-33.71
HI + HOI → I_2 + H_2O	-27.43
Overall energy of reaction	**-59.84**

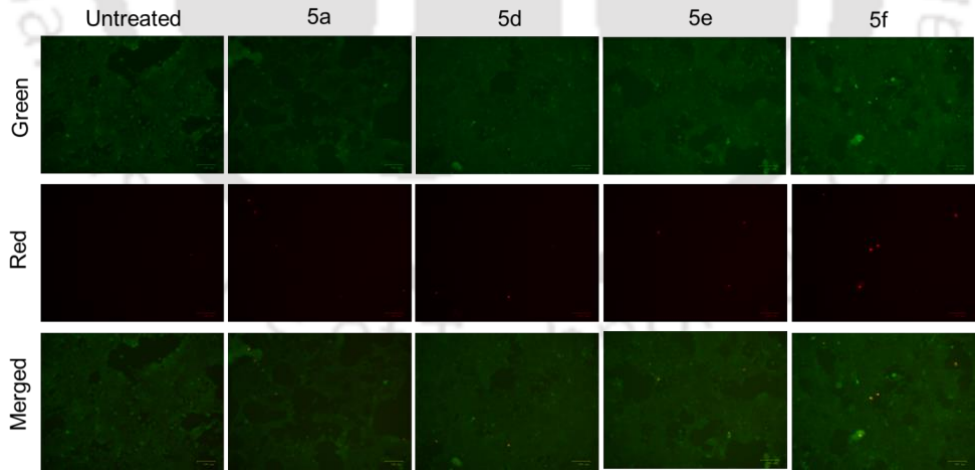


Figure 7. Live/dead cell imaging of MCF-7 cells treated with selected compounds for 48 h(Scale bar, 100 µM)

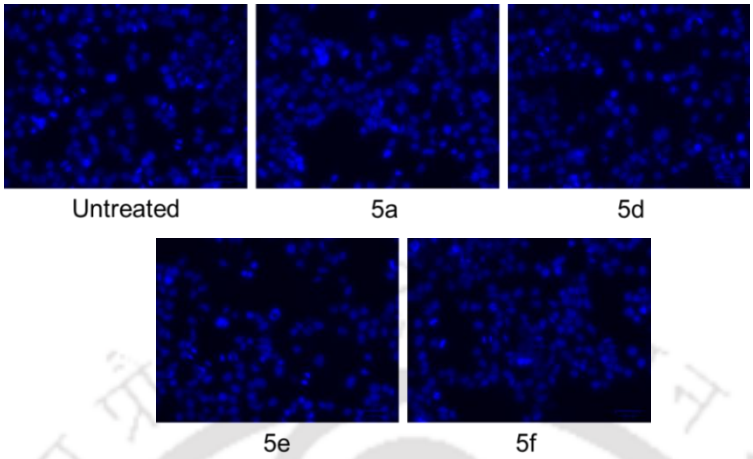


Figure 8. Nuclear morphology study of MCF-7 cells treated with selected compounds for 48 h (Scale bar, 50 µM)

2.5. Conclusions

In conclusion, we demonstrated an efficient and simple method for synthesizing 3-sulfenylindole using 10 mol% molecular iodine and TBHP (1 equiv) in DMSO using 4-hydroxy-2*H*-chromene-2-thione and indole at room temperature. This prominent feature of the reaction is that there is no use of any metal catalysts. Further, the compounds were oxidized to biologically active sulfones. This protocol profits from the efficiency of the reaction yield and substrate scope compatibility, which also includes shorter reaction time and mild reaction conditions. Additionally, *in-silico* and *in-vitro* analyses such as lead likeness, target prediction, molecular docking, cell viability, and ROS generation assay were performed to check the anti-cancer activity of selected compounds in the MCF-7 cell line. Among all the sulfones, such as **5a**, **5d**, **5e**, and **5f**, that possess anti-proliferative activity against breast cancer cells, which gives a scope to analyse them further with biomedical applications.

2.6. Experimental Section

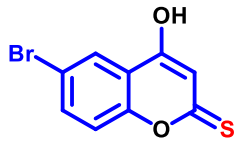
2.6a. Quantum chemical methods

The quantum chemical calculations were carried out using the Gaussian 09 suite of programs.[25] Geometry optimization of compounds was performed by DFT using B3LYP method.[26] The basis set used was 6-31+G(d,p) for C, H, N, O, and LANL2DZ for I. The frequency calculations were carried out on all the structures to verify the character of stationary points (minima v/s saddle points). The NBO[27] charges were estimated to explore the nucleophilicity and electrophilicity of the reacting centers.

2.6b. General procedure for the synthesis of compound 1(a-e)

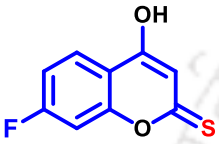
4-hydroxy-2*H*-chromene-2-thione (**1a**) is synthesized following a slightly modified version of the previously reported procedure.[1] Potassium *tertiary* butoxide (15 mmol) and 18-crown-6 ether (1.5 mmol) were taken in 7 mL of anhydrous THF in an oven-dried round-bottomed flask. The mixture is purged with N_2 and cooled to 0^{o}C in an ice bath. Then, 2'-hydroxyacetophenone (5 mmol) is added dropwise to the above solution, followed by the addition of carbon disulfide (5 mmol) to the reaction mixture, resulting in the formation of a thick yellow precipitate. The reaction is stirred at 0-15^{o}C for another 1 hour, then brought to room temperature and continued stirring at this temperature for 16 hours. The reaction is quenched by adding 5 mL of water, and then the water layer is washed with ethyl acetate (2 × 5 mL). The aqueous layer was then acidified with 10% H_2SO_4 until pH was adjusted to 4-5, and the mixture was stirred for another 16 h. A yellow precipitate is formed, collected by vacuum filtration and washed with petroleum ether several times to obtain the desired product as a yellow solid.

4-hydroxy-2*H*-chromene-2-thione (1a). Yellow solid (445 mg, 50%); mp 215–218°C; ^{1}H NMR



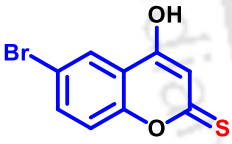
(400 MHz, DMSO) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.37 – 7.32 (m, 1H), 6.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 161.9, 157.5, 132.8, 124.7, 123.4, 117.2, 116.7, 108.9; IR (KBr) ν_{max}/cm^{-1} 3437 (O-H), 1019 (C=S); HRMS (ESI) calculated for $C_9H_7O_2S$ 197.0161 [M + H^+]; found 197.0157.

6-chloro-4-hydroxy-2*H*-chromene-2-thione (1b). Yellow solid (670 mg, 63%); mp 256-



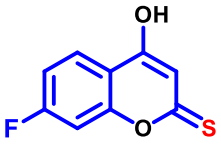
257°C;^{1}H NMR (400 MHz, DMSO) δ 7.82 (d, *J* = 2.5 Hz, 1H), 7.74 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 6.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 196.2, 161.6, 155.6, 133.0, 129.3, 122.6, 119.0, 118.7, 108.6; IR (KBr) ν_{max}/cm^{-1} 3068 (O-H), 1104 (C=S); HRMS (ESI) calculated for $C_9H_6ClO_2S$ 212.9772 [M + H^+]; found 212.9762.

6-Bromo-4-hydroxy-2*H*-chromene-2-thione (1c). Yellow solid (707 mg, 55%); mp 248–



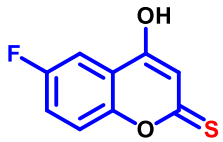
249°C;^{1}H NMR (500 MHz, DMSO) δ 7.95 (d, *J* = 2.4 Hz, 1H), 7.83 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 6.54 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.5, 160.7, 155.9, 135.8, 125.4, 118.9, 118.8, 117.2, 108.5; IR (KBr) ν_{max}/cm^{-1} 3030 (O-H), 1105 (C=S); HRMS (ESI) calculated for $C_9H_6BrO_2S$ 256.9266 [M + H^+]; found 256.9254.

7-fluoro-4-hydroxy-2*H*-chromene-2-thione (1d). Yellowish brown solid (470 mg, 47%), mp



212-214°C; ^{1}H NMR (500 MHz, DMSO) δ 7.93 (dd, *J* = 8.9, 6.2 Hz, 1H), 7.56 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.33 (td, *J* = 8.7, 2.5 Hz, 1H), 6.63 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 196.9, 164.7 (d, *J*=250.6 Hz), 161.1, 158.0 (d, *J*=13.6 Hz), 125.6 (d, *J*=10.5 Hz), 113.9, 113.4 (d, *J*=23.0 Hz), 107.4, 104.0 (d, *J*=25.7 Hz); IR (KBr) ν_{max}/cm^{-1} 3098 (O-H), 1076 (C=S); HRMS (ESI) calculated for $C_9H_6FO_2S$ 197.0067 [M + H^+]; found 197.0062.

6-fluoro-4-hydroxy-2*H*-chromene-2-thione (1e). Yellowish brown solid (519 mg, 52%), mp 218-220°C;



^{1}H NMR (500 MHz, DMSO) δ 7.63 – 7.61 (m, 1H), 7.60 (d, *J* = 3.5 Hz, 1H), 7.58 (d, *J* = 2.9 Hz, 1H), 6.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ196.3, 162.3, 159.6, 157.6, 153.6, 120.9 (d, *J*=26.0 Hz), 119.0, 118.8 (d, *J*=3.4 Hz), 108.7 (d, *J*=24 Hz); IR (KBr)ν_{max}/cm^{-1}3090 (O-H), 1081(C=S);HRMS (ESI) calculated for $C_9H_6FO_2S$ 197.0067 [M + H$^+$]; found 197.0061.

2.6c. General procedure for the synthesis of N-Alkyl indoles

N-Alkyl indoles (**2**) were prepared by the reported method.[28]

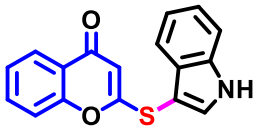
2.6d. General procedure for the synthesis of 3-sulfenylindole derivatives (3a-3v, 4a-4e)

A mixture of 4-hydroxy-2*H*-chromene-2-thione **1a** (0.25 mmol) and indole **2** (0.25 mmol) was taken in DMSO (1 mL) into a 10 mL round-bottomed flask. Then, 10 mol% of I_2 and TBHP (1 equivalent) were added to the above reaction mixture, and it was stirred at room temperature for a period of 3 hours. After the completion of the reaction, as monitored by TLC, the solvent DMSO was removed, and the crude residue was extracted with dichloromethane (10 mL x 1). The organic layer was washed with water (10 mL x 2), and 5 mL of brine solution and dried over anhydrous sodium sulfate. Finally, the solvent was removed in a rotatory evaporator, and the crude residue was purified through silica gel (60–120 mesh) column chromatography to obtain product **3a** in 78% yield. A similar reaction procedure was followed in all other cases.

2.6e. General procedure for the synthesis of compounds 5

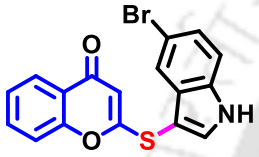
Sulfone derivatives (**5**) were produced by the reported procedure.[29]

2-((1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3a). Brown solid (60 mg, 78%), mp 190-192°C;



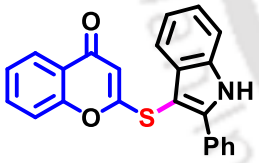
^{1}HNMR (500 MHz, DMSO) δ 12.02 (s, 1H), 7.93 (dd, *J* = 8.2, 4.9 Hz, 2H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 5.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 173.9, 157.0, 136.7, 133.7, 132.4, 128.0, 125.7, 125.5, 123.5, 123.4, 121.4, 118.5, 117.6, 112.4, 106.5, 95.0; IR (KBr) ν_{max}/cm^{-1} 3222, 2929, 1615, 1128; HRMS (ESI) calculated for $C_{17}H_{12}NO_2S$ 294.0583 [M + H^+]; found 294.0633.

2-((5-bromo-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3b). Brown solid (70 mg, 70%), mp



185°C;^{1}H NMR (600 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.22 (d, *J* = 6.2 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.27 – 7.20 (m, 2H), 5.77 (s, 1H);^{13}C NMR (150 MHz, $CDCl_3$) δ139.0 135.2, 119.4, 105.2, 98.1, 95.9, 91.6, 88.28, 87.8, 86.0, 85.1, 83.7, 80.6, 80.0, 73.7, 68.8, 55.2; IR (KBr) ν_{max}/cm^{-1} 3174, 2926, 1614, 1138; HRMS (ESI) calculated for $C_{17}H_{11}BrNO_2S$ 371.9688 [M + H^+]; found 371.9711.

2-((2-phenyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3c). Brown solid (62 mg, 67%), mp



183°C; ^{1}H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 7.93 (d, *J* = 9.7 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 2H), 7.77 – 7.74 (m, 1H), 7.59 (d, *J* = 4.2 Hz, 1H), 7.56 (dd, *J* = 8.4, 3.7 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.47 – 7.45 (m, 2H), 7.30 – 7.27 (m, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 5.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 171.1, 156.3, 143.7, 136.3, 134.2, 130.4, 129.5, 129.2, 128.9, 128.5, 125.8, 125.0, 123.3, 123.0, 121.3, 118.3, 117.8, 112.5, 105.9, 90.4; IR (KBr) ν_{max}/cm^{-1} 3255, 2924, 1617, 1128; HRMS (ESI) calculated for $C_{23}H_{16}NO_2S$ 370.0896 [M + H^+]; found 370.0905**.**

2-((5-methoxy-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3d). Brown solid (68 mg, 84%), mp 180°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.15 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.67 (ddd, *J* = 8.6, 6.9, 1.7 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.24 (s, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.79 (s, 1H), 3.83 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 172.6, 156.9, 155.6, 133.4, 132.3, 131.4, 128.9, 125.8, 125.2, 123.6, 117.5, 114.2, 112.8, 106.7, 100.0, 95.5, 55.7; IR (KBr) ν_{max}/cm^{-1} 3229, 2920, 1613, 1365; HRMS (ESI) calculated for $C_{18}H_{14}NO_3S$ 324.0689 [M + H^+]; found 324.0692.

2-((2-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3e). Brown solid (55 mg, 72%), mp 178°C;^{1}H NMR (500 MHz, DMSO) δ 11.95 (s, 1H), 7.94 (d, *J* = 9.7 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.61(d, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 9.1 Hz, 3H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 5.43 (s, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 174.3, 171.0, 156.2, 143.7, 135.7, 134.0, 128.6, 125.6, 124.9, 122.9, 121.9, 120.5, 117.6, 117.2, 111.7, 105.6, 90.4, 11.5; IR (KBr) ν_{max}/cm^{-1} 3399, 2924, 1613, 1129; HRMS (ESI) calculated for $C_{18}H_{14}NO_2S$ 308.0740 [M + H^+]; found 308.0746.

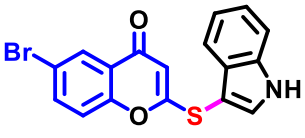
2-((1*H*-indol-3-yl)thio)-6-chloro-4*H*-chromen-4-one (3f). Brown solid (55 mg, 67%), mp 177°C;^{1}H NMR (500 MHz, DMSO) δ 11.18 (s, 1H), 7.11 (d, *J* = 2.9 Hz, 1H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.41 (t, *J* = 7.6 Hz, 1H), 6.31 (t, *J* = 7.5 Hz, 1H), 4.68 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 173.0, 171.9, 154.6, 136.7, 133.9, 133.7, 130.0, 127.6, 124.1, 123.9, 122.6, 120.8, 120.1, 117.9, 112.7, 105.9, 92.8; IR (KBr) ν_{max}/cm^{-1} 3262, 2924, 1627, 1336; HRMS (ESI) calculated for $C_{17}H_{11}ClNO_2S$ 328.0194 [M + H^+]; found 328.0214.

2-((5-bromo-1*H*-indol-3-yl)thio)-6-chloro-4*H*-chromen-4-one (3g). Brown solid (66 mg, 65%), mp 169°C; ^{1}H NMR (500 MHz, DMSO) δ 11.40 (s, 1H), 7.19 (d, *J* = 2.8 Hz, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.98 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.88 (s, 1H), 6.82 (d, *J* = 8.9 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.55 (d, *J* = 8.6 Hz, 1H), 4.72 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 173.4, 171.7, 154.9, 135.7, 135.7, 134.09, 130.2, 129.8, 125.6, 124.3, 124.2, 120.4, 120.4, 115.1, 113.9, 106.2, 92.9; IR (KBr) ν_{max}/cm^{-1} 3279, 2923, 1736, 1106; HRMS (ESI) calculated for $C_{17}H_{10}BrClNO_2S$ 405.9299 [M + H$^+$]; found 405.9290.

6-chloro-2-((5-methoxy-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3h). Brown solid (58 mg, 78%), mp 171°C; ^{1}H NMR (500 MHz, DMSO) δ 11.02 (s, 1H), 7.00 (d, *J* = 2.9 Hz, 1H), 6.81 – 6.77 (m, 1H), 6.76 – 6.72 (m, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 6.10 (d, *J* = 2.6 Hz, 1H), 6.01 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.63 (s, 1H), 2.84 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 172.9, 171.9, 154.6, 154.5, 134.0, 133.6, 131.3, 129.8, 128.3, 124.0, 123.8, 120.0, 113.4, 112.7, 105.6, 99.2, 92.0, 55.2; IR (KBr) ν_{max}/cm^{-1} 3264, 2924, 1626, 1108; HRMS (ESI) calculated for $C_{18}H_{13}ClNO_3S$ 358.0299 [M + H$^+$]; found 358.0297.

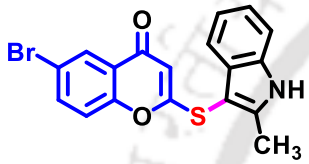
6-chloro-2-((2-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3i). Brown solid (66 mg, 61%), mp 181°C; ^{1}H NMR (500 MHz, DMSO) δ 11.12 (s, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 7.08 (s, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.62 – 6.58 (m, 2H), 6.34 (t, *J* = 7.6 Hz, 1H), 6.27 (t, *J* = 7.5 Hz, 1H), 4.62 (s, 1H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 173.2, 171.9, 155.3, 144.0, 136.7, 135.8, 128.7, 127.2, 124.7, 122.1, 120.8, 120.6, 118.1, 117.4, 111.9, 105.8, 90.3, 11.7; IR (KBr) ν_{max}/cm^{-1} 3224, 2950, 1629, 1333; HRMS (ESI) calculated for $C_{18}H_{13}ClNO_2S$ 342.0350 [M + H$^+$]; found 342.0352.

2-((1*H*-indol-3-yl)thio)-6-bromo-4*H*-chromen-4-one (3j). Brown solid (56 mg, 70%), mp



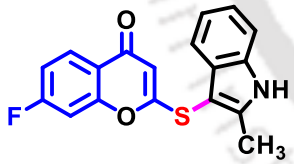
177°C; ^{1}H NMR (500 MHz, DMSO) δ 11.16 (s, 1H), 7.11 (dd, *J* = 11.8, 2.7 Hz, 2H), 7.04 (dd, *J* =8.9, 2.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 2H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.40 (t, *J* = 8.3 Hz, 1H), 6.30 (t, *J* = 7.4 Hz, 1H), 4.67 (s, 1H). ^{13}C NMR (125 MHz, DMSO) δ 173.4, 172.5, 155.6, 137.2, 137.0, 134.4, 128.1, 127.6, 125.0, 123.2, 121.4, 120.8, 118.4, 118.4, 113.3, 106.5, 93.3; IR (KBr) ν_{max}/cm^{-1} 3281, 2924, 1619, 1064; HRMS (ESI) calculated for $C_{17}H_{11}BrNO_2S$ 371.9688 [M + H^+]; found 371.9685.

6-bromo-2-((2-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3k). Brown solid (55 mg,



67%), mp 177°C; ^{1}H NMR (500 MHz, DMSO) δ 11.97 (s, 1H), 7.99 (d, *J* = 2.5 Hz, 1H), 7.93 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.44 (dd, *J* = 11.3, 7.9 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 5.45 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 172.7, 171.7, 155.1, 143.8, 136.5, 135.7, 128.5, 127.0, 124.5, 122.0, 120.6, 120.4, 117.2, 111.7, 105.6, 90.1, 11.5; IR (KBr)ν_{max}/cm^{-1} 3394, 2924, 1634, 1024; HRMS (ESI) calculated for $C_1H_{13}BrNO_2S$ 385.9850 [M + H^+]; found 385.9847.

7-fluoro-2-((2-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3l). Brown solid (63 mg, 66%),



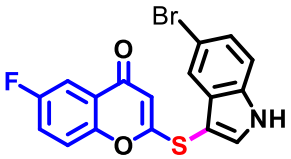
mp 165°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.15 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.25 (d, *J* = 5.3 Hz, 2H), 7.16 – 7.14 (m, 2H), 7.11 (dd, *J* = 8.5, 2.3 Hz, 1H), 5.66 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 173.1, 165.6 (d, *J* = 253.4 Hz), 157.9 (d, *J* = 13.1 Hz), 142.8, 135.8, 129.2, 128.3(d, *J* = 10.5), 122.9, 121.4, 120.6 (d, *J* = 2.4 Hz), 118.2, 114.0 (d, *J* =22.5 Hz), 111.4, 106.5, 104.6 (d, *J* = 25.3 Hz), 92.7, 12.0; IR (KBr) ν_{max}/cm^{-1} 3323, 2923, 1737, 1061; HRMS (ESI) calculated for $C_{18}H_{13}FNO_2S$ 326.0651 [M + H^+]; found 326.0657.

6-bromo-2-((2-phenyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3m). Brown solid (75 mg, 61%), mp 170°C; ^{1}H NMR (500 MHz, DMSO) δ 12.44 (s, 1H), 7.99 (d, *J* = 2.5 Hz, 1H), 7.93 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 2H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.54 (d, *J*= 7.9 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 5.55 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 173.1, 171.8, 155.3, 143.8, 136.7, 136.3, 130.3, 129.4, 129.2, 128.9, 128.6, 128.5, 128.4, 127.1, 124.6, 123.3, 121.3, 120.5, 118.3, 118.1, 112.5, 105.9, 90.1; (KBr) ν_{max}/cm^{-1}3272, 2924, 1631, 1107; HRMS (ESI) calculated for $C_{23}H_{15}BrNO_2S$ 448.0007 [M + H$^+$]; found 448.0002.

6-bromo-2-((5-methoxy-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3n). Brown solid (78 mg, 77%), mp 150°C; ^{1}H NMR (500 MHz, DMSO) δ 11.90 (d, *J* = 2.9 Hz, 1H), 7.99 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.88 (s, 1H), 7.61 (s, 1H), 7.46 (s, 1H), 6.98 (s, 1H), 6.89 (s, 1H), 5.55 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 173.0, 172.1, 155.1, 154.8, 136.6, 134.2, 131.5, 128.5, 127.1, 124.5, 120.4, 117.9, 113.6, 112.9, 105.9, 99.4, 92.2,55.4; IR (KBr) ν_{max}/cm^{-1}3301, 2924, 1738, 1244; HRMS (ESI) calculated for $C_{18}H_{13}BrNO_3S$ 401.9794 [M + H$^+$]; found 401.9793.

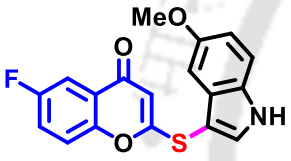
2-((1*H*-indol-3-yl)thio)-6-fluoro-4*H*-chromen-4-one (3o). Brown solid (55 mg, 70%); mp 185°C; ^{1}H NMR (400 MHz, DMSO) δ 12.07 (s, 1H), 8.02 – 7.97 (m, 2H), 7.63 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.56 (dd, *J* = 13.1, 7.9 Hz, 2H), 7.36 (td, *J* = 8.6, 2.4 Hz, 1H), 7.28 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.18 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 5.46 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 173.9 (d, *J*=2.2 Hz), , 173.97, 172.3, 159.2 (d, *J*=243.0 Hz), 152.7, 136.9, 134.1, 127.8, 124.3 (d, *J*=7.2 Hz), 123.0, 122.1 (d, 25.2 Hz), 120.6 (d, *J*=8.4 Hz), 118.1, 113.0, 109.9 (d, *J*=23.7 Hz), 105.6, 93.2; IR (KBr) ν_{max}/cm^{-1} 3318, 2924, 1738, 1062; HRMS (ESI) calculated for $C_{17}H_{11}FNO_2S$ 312.0489 [M + H$^+$]; found 312.0492.

2-((5-bromo-1*H*-indol-3-yl)thio)-6-fluoro-4*H*-chromen-4-one (3p). Brown solid (60 mg, 61%);

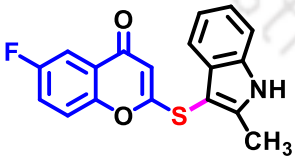


mp 155°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.22 (s, 1H), 8.02 (d, *J* = 2.8 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.67 (t, *J* = 4.2 Hz, 1H), 7.62 (ddd, *J* = 16.5, 8.7, 3.1 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.38 (dd, *J* = 8.6, 2.0 Hz, 1H), 5.54 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ173.6 (d, *J*=2.3 Hz), 171.3, 158.9 (d, *J*=242.9 Hz), 152.5, 135.6, 135.5, 129.7, 125.4, 124.2, 121.8 (d, *J*=25.2 Hz), 120.4, 120.2 (d, *J*=20.9 Hz), 114.8, 113.6, 109.8 (d, *J*=23.7 Hz), 105.4, 92.8; IR (KBr) ν_{max}/cm^{-1} 3321, 2924, 1739, 1246; HRMS (ESI) calculated for $C_{17}H_{10}BrFNO_2S$ 389.9594 [M + H^+]; found 389.9598.

6-fluoro-2-((5-methoxy-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3q). Brown solid (65 mg, 65%); mp 165°C; ^{1}H NMR (500 MHz, DMSO) δ 10.80 (s, 1H), 6.78 (s, 1H), 6.58 (s, 1H), 6.56 (s, 1H), 6.50 (s, 1H), 6.39 (s, 1H), 5.89 (s, 1H), 5.81 (s, 1H), 4.44 (s, 1H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 174.2 (d, *J*=2.2 Hz), 172.7, 159.4 (d, *J*=243.0 Hz), 155.3, 153.0, 134.6, 132.0, 128.9, 124.6 (d, *J*=7.0 Hz), 122.3 (d, *J*=25.1 Hz), 120.8 (d, *J*=8.2 Hz), 114.1, 113.4, 110.2 (d, *J*=23.6 Hz), 105.7, 99.9, 92.9, 55.8; IR (KBr) ν_{max}/cm^{-1} 3301, 2923, 1737, 1247; HRMS (ESI) calculated for $C_{18}H_{13}FNO_3S$ 342.0595 [M + H^+]; found 342.0598.



6-fluoro-2-((2-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3r). Brown solid (65 mg, 77%);



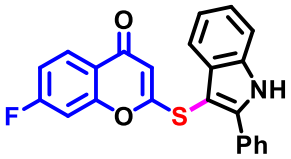
mp 175°C; ^{1}H NMR (500 MHz, DMSO) δ 11.96 (s, 1H), 7.68 (s, 1H), 7.65 – 7.60 (m, 1H), 7.59 (dd, *J* = 8.2, 3.2 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.42 (s, 1H), 7.20 – 7.15 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 5.44 (s, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 173.6 (d, 2.0Hz), 171.7, 159.0 (d, *J*=242.7 Hz), 152.6(d, *J*=1.6 Hz), 143.8, 135.7, 128.6, 124.2 (d, *J*=7.1 Hz), 122.0, 121.8 (d, *J*=25.2 Hz),120.4 (d, *J*=8.2 Hz), 117.2, 111.7, 109.7 (d, *J*=23.7 Hz), 109.65, 105.0, 90.2, 11.5; IR (KBr) ν_{max}/cm^{-1} 3323, 2923, 1737, 1242; HRMS (ESI) calculated for $C_{18}H_{13}FNO_2S$ 326.0646 [M + H^+]; found 326.0648.

2-((1*H*-indol-3-yl)thio)-7-fluoro-4*H*-chromen-4-one (3s). Brown solid (65 mg, 68%); mp 175°C;[1]H NMR (500 MHz, DMSO) δ 11.96 (s, 1H), 7.68 (s, 1H), 7.65 – 7.60 (m, 1H), 7.59 (dd, *J* = 8.2, 3.2 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.42 (s, 1H), 7.20 – 7.15 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 5.44 (s, 1H), 2.50 (s, 3H); [13]C NMR (100 MHz, DMSO) δ173.5, 171.9, 157.1 (d, *J*=13.8Hz), 136.7, 134.0, 127.7 (d, *J*=13.9 Hz), 127.6, 122.8, 121.1, 120.1, 118.0, 114.2 (d, *J*=22.7 Hz), 112.8, 106.1, 105.1, 104.8, 92.9; IR (KBr) ν_{max}/cm^{-1} 3318, 2924, 1738, 1242; HRMS (ESI) calculated for $C_{17}H_{11}FNO_2S$ 312.0489 [M + H^+]; found 312.0492 .

2-((5-bromo-1*H*-indol-3-yl)thio)-7-fluoro-4*H*-chromen-4-one (3t). Brown solid (56 mg, 57%); mp 188°C;[1]H NMR (500 MHz, DMSO) δ 12.24 (s, 1H), 8.05 – 7.96 (m, 2H), 7.71 (s, 1H), 7.60 (d, *J* = 12.2 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.41 – 7.31 (m, 2H), 5.47 (s, 1H); [13]C NMR (125 MHz, DMSO) δ 174.6, 172.4, 165.8 (d, *J*=252.0 Hz), 158.1 (d, *J*=13.9 Hz), 136.4 (d, *J*=10.1Hz), 130.4, 128.5 (d, *J*=10.7 Hz), 126.2, 121.0, 120.8 (d, *J*=2.5 Hz), 114.9, 114.6 (d, *J*=38.9 Hz), 114.4, 106.8, 105.5 (d, *J*=25.4Hz), 104.8 (d, *J*=25.9 Hz), 92.8; IR (KBr) ν_{max}/cm^{-1} 3321, 2924, 1739, 1246; HRMS (ESI) calculated for $C_{17}H_{10}BrFNO_2S$ 389.9594 [M + H^+]; found 389.9598.

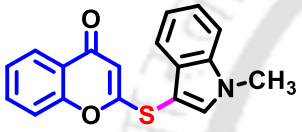
7-fluoro-2-((5-methoxy-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3u). Brown solid (65 mg, 76%); mp 155°C; [1]H NMR (500 MHz, DMSO) δ 11.91 (s, 1H), 7.99 (dd, *J* = 8.9, 6.4 Hz, 1H), 7.89 (d, *J* = 2.9 Hz, 1H), 7.61 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.37 – 7.29 (m, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.89 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.45 (s, 1H), 3.73 (s, 3H); [13]C NMR (125 MHz, DMSO) δ 173.6, 172.0, 164.8 (d, *J*=2.0 Hz),157.1 (d, *J*=13.8 Hz), 154.9, 134.3, 131.6, 128.5, 127.8 (d, *J*=10.8 Hz), 120.1 (d, *J*=2.5 Hz), 114.2 (d, *J*=22.5 Hz), 113.7, 113.0, 106.0, 104.9 (d, *J*=26.0), 99.5, 92.4, 55.5; IR (KBr) ν_{max}/cm^{-1} 3301, 2923, 1737, 1247; HRMS (ESI) calculated for $C_{18}H_{13}FNO_3S$ 342.0595 [M + H^+]; found 342.0598.

7-fluoro-2-((2-phenyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3v). Brown solid (65 mg, 62%);



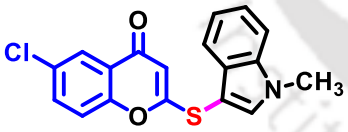
mp 165°C; ^{1}H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 8.01 – 7.94 (m, 1H), 7.85 (d, *J* = 7.7 Hz, 2H), 7.61 – 7.50 (m, 5H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 5.50 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 173.3, 171.2, 165.5, 163.5, 157.0, 156.9, 143.5, 136.0, 130.1, 129.1, 128.5, 128.2, 127.5, 123.0, 121.0, 119.9, 119.9, 127.6 (d, *J*=10.7 Hz), 123.2, 121.2, 120.1 (d, *J*=2.25 Hz), 118.1, 114.1, 113.9, 112.4, 105.9, 104.8 (d, *J*=26.02 Hz), 90.1; IR (KBr) ν_{max}/cm^{-1} 3247, 2924, 1620, 1450; HRMS (ESI) calculated for $C_{23}H_{15}FNO_2S$ 388.0802 [M + H$^+$]; found 388.0807.

2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (4a). Brown solid (60 mg, 60%); mp



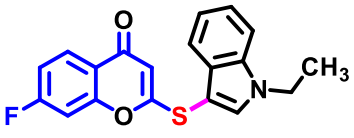
168°C; ^{1}H NMR (500 MHz, DMSO) δ 7.98 (s, 1H), 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.77 (ddd, *J* = 8.8, 7.2, 1.7 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.33 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.24 – 7.17 (m, 1H), 5.54 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 174.6, 171.6, 156.3, 137.6, 137.5, 134.3, 128.3, 125.9, 125.1, 122.9, 121.3, 118.3, 117.9, 116.1, 111.3, 106.2, 92.0, 33.3; IR (KBr) ν_{max}/cm^{-1} 3377, 2924, 1643, 1358; HRMS (ESI) calculated for $C_{18}H_{14}NO_2S$ 308.0740 [M + H$^+$]; found 308.0746.

6-chloro-2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (4b). Brown solid (96 mg,



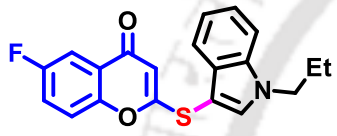
56%); mp 158°C; ^{1}H NMR (500 MHz, DMSO) δ 7.98 (s, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 7.81 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.66 (dd, *J* = 16.4, 8.6 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 5.56 (s, 1H), 3.92 (s, 3H); ^{13}C NMR(125 MHz, DMSO) δ 173.3, 172.1, 154.8, 137.6, 137.5, 134.0, 130.2, 128.1, 124.1, 124.0, 122.9, 121.3, 120.3, 118.2, 111.3, 106.1, 91.7, 33.6; IR (KBr) ν_{max}/cm^{-1} 3417, 2924, 1608, 1106; HRMS (ESI) calculated for $C_{18}H_{13}ClNO_2S$ 342.0350 [M + H$^+$]; found 342.0353.

2-((1-ethyl-1*H*-indol-3-yl)thio)-7-fluoro-4*H*-chromen-4-one (4c). Brown solid (119 mg, 63%);



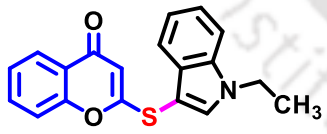
mp 186°C; ^{1}H NMR (500 MHz, DMSO) δ 8.05 (s, 1H), 7.98 (dd, *J* = 8.9, 6.4 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.61 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 5.49 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 173.7, 171.8, 165.8, 163.8, 136.5, 136.1, 128.2,127.8 (d, *J*=10.9Hz), 122.8, 121.2, 120.1, 118.4, 114.3 (d, *J*=22.8Hz), 111.3, 106.1, 105.1, 104.9, 92.0, 41.2, 15.3 ; IR (KBr) ν_{max}/cm^{-1}3306, 2921, 1738, 1063; HRMS (ESI) calculated for $C_{19}H_{15}FNO_2S$ 340.0802 [M + H$^+$]; found 340.0804.

7-fluoro-2-((1-propyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (4d). Brown solid (92 mg, 55%);



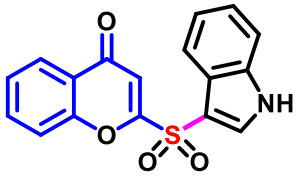
mp 190°C; ^{1}H NMR (500 MHz, DMSO) δ 8.03 (s, 1H), 7.98 (dd, *J* = 8.9, 6.4 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.37 – 7.28 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 5.46 (s, 1H), 4.27 (t, *J* = 7.0 Hz, 2H), 1.85 (q, *J* = 7.2 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 173.5, 171.7, 165.7, 163.7, 157.0 (d, *J*=13.8 Hz), 136.7, 136.7, 128.0, 127.7 (d, *J*= 10.9Hz), 120.0 (d, *J*= 2.01 Hz), 118.3, 114.1 (d, *J* = 22.8), 111.3, 106.0, 105.0, 104.7, 91.8, 47.6, 22.8, 11.0; IR (KBr) ν_{max}/cm^{-1} 3442, 2924, 1734, 1249; HRMS (ESI) calculated for $C_{20}H_{17}FNO_2S$ 354.0959 [M + H$^+$]; found 354.0955.

2-((1-ethyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (4e). Brown solid (60 mg, 62%); mp 186°C;



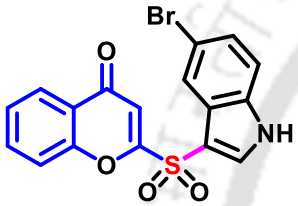
^{1}H NMR (400 MHz, DMSO) δ 7.95 (s, 1H), 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.73 (ddd, *J* = 8.7, 7.1, 1.8 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.45 – 7.38 (m, 1H), 7.29 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.17 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 5.51 (s, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ174.4, 171.3, 156.1, 136.3, 135.7, 133.8, 128.3, 125.5, 124.9, 122.9, 122.6, 120.9, 118.3, 117.6, 110.9, 106.0, 92.3, 41.1, 15.2; IR (KBr) ν_{max}/cm^{-1} 3330, 2924, 1639, 1128; HRMS (ESI) calculated for $C_{19}H_{16}NO_2S$ 322.0896 [M + H$^+$]; found 322.0890.

2-((1*H*-indol-3-yl)sulfonyl)-4*H*-chromen-4-one (5a). Brown solid (60 mg, 70%); mp 168°C; ^{1}H



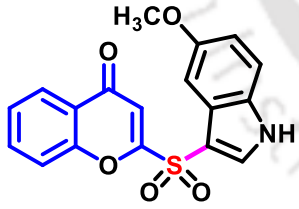
NMR (500 MHz, DMSO) δ 12.70 (s, 1H), 8.42 (s, 1H), 7.94 (dd, *J* = 15.8, 6.6 Hz, 2H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.43 – 7.19 (m, 2H), 7.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 176.6, 162.8, 155.1, 136.6, 135.6, 135.1, 126.6, 125.2, 123.8, 123.6, 123.2, 122.7, 118.8, 118.5, 113.3, 109.3, 108.7; IR (KBr) ν_{max}/cm^{-1} 3346, 1621, 1562, 1187; HRMS (ESI) calculated for $C_{17}H_{12}NO_4S$ 326.0482 [M + H$^+$]; found 326.0512.

2-((5-bromo-1*H*-indol-3-yl)sulfonyl)-4*H*-chromen-4-one (5b). Brown solid (49 mg, 58%); mp



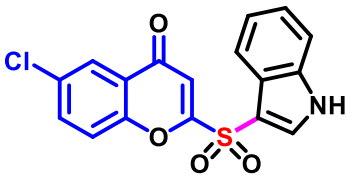
196°C; ^{1}H NMR (400 MHz, DMSO) δ 12.92 (d, *J* = 3.1 Hz, 1H), 8.51 (d, *J* = 3.3 Hz, 1H), 8.07 (d, *J* = 1.9 Hz, 1H), 8.02 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.87 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.62 – 7.50 (m, 3H), 7.48 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 176.6, 162.4, 155.1, 136.4, 135.7, 135.4, 126.7, 126.6, 125.4, 125.3, 123.3, 121.0, 118.4, 115.5, 115.4, 109.5, 108.4; IR (KBr) ν_{max}/cm^{-1} 3391, 2924, 1624, 1023; HRMS (ESI) calculated for $C_{17}H_{11}BrNO_4S$ 403.9587 [M + H$^+$]; found 403.9617.

2-((5-methoxy-1*H*-indol-3-yl)sulfonyl)-4*H*-chromen-4-one (5c). Brown solid (107 mg, 58%);



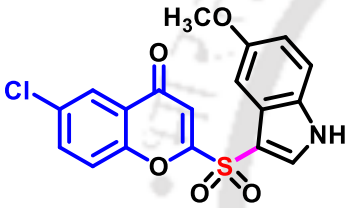
mp 190°C; ^{1}H NMR (400 MHz, DMSO) δ 12.61 (d, *J* = 3.4 Hz, 1H), 8.35 (d, *J* = 3.4 Hz, 1H), 8.02 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.86 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.61 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.57 – 7.44 (m, 2H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.05 (s, 1H), 6.96 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 176.7, 162.8, 155.8, 155.1, 135.7, 135.0, 131.4, 126.6, 125.2, 124.5, 123.2, 118.5, 114.3, 113.9, 109.2, 108.1, 100.2, 55.5; IR (KBr) ν_{max}/cm^{-1} 3215, 2921, 1612, 1128; HRMS (ESI) calculated for $C_{18}H_{14}NO_5S$ 356.0587 [M + H$^+$]; found 356.0596.

2-((1*H*-indol-3-yl)sulfonyl)-6-chloro-4*H*-chromen-4-one (5d). Brown solid (116 mg, 68%); mp



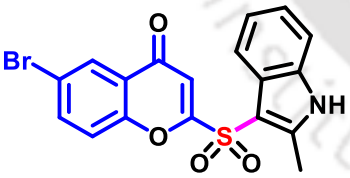
168°C; ^{1}H NMR (400 MHz, DMSO) δ 12.72 (s, 1H), 8.43 (s, 1H), 7.96 – 7.90 (m, 1H), 7.87 (t, *J* = 3.1 Hz, 1H), 7.82 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.59 – 7.49 (m, 1H), 7.34 – 7.27 (m, 2H), 7.05 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 175.7, 136.0, 153.8, 136.7, 135.4, 135.1, 131.1, 124.5, 124.2, 123.9, 123.6, 122.8, 121.0, 118.9, 113.3, 109.3, 108.6; IR(KBr) ν_{max}/cm^{-1} 3380, 1658, 1024; HRMS (ESI) calculated for $C_{17}H_{11}ClNO_4S$ 360.0092 [M + H^+]; found 360.0114.

6-chloro-2-((5-methoxy-1*H*-indol-3-yl)sulfonyl)-4*H*-chromen-4-one (5e). Brown solid (52 mg,



62%); mp 180°C-200°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.61 (d, *J* = 3.5 Hz, 1H), 8.34 (d, *J* = 3.3 Hz, 1H), 7.93 (d, *J* = 2.6 Hz,1H), 7.87 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.32 (s, 1H), 7.08 (s, 1H), 6.95 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 175.8, 163.1, 155.8, 153.8, 135.5, 135.1, 131.4, 131.0, 124.6, 124.5, 124.2, 121.0, 114.3, 113.9, 109.2, 108.0, 100.3, 55.6; IR (KBr) ν_{max}/cm^{-1} 3391, 2931, 1656; HRMS (ESI) calculated for $C_{18}H_{11}ClNO_5S$ 388.0046 [M – H^+]; found 388.0044.

6-bromo-2-((2-methyl-1*H*-indol-3-yl)sulfonyl)-4*H*-chromen-4-one (5f). Brown solid (55 mg,



55%); mp 155°C-160°C; ^{1}H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.48 (d, *J* = 2.6 Hz, 1H), 8.19 (d, *J* = 8.9 Hz, 1H), 8.03 – 7.97 (m, 2H), 7.74 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.66 (d, *J* = 7.5, 7.1, 1.1 Hz, 1H), 5.99 (s, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ173.0, 171.8, 155.2, 143.9, 136.6, 135.7, 128.5, 127.1, 124.6, 122.0, 120.7, 120.5, 118.0, 117.3, 111.8, 105.6, 90.1, 11.2; IR (KBr) ν_{max}/cm^{-1} 3380, 2985, 1658, 1148; HRMS (ESI) calculated for $C_{18}H_{13}BrNO_4S$ 417.9743 [M + H^+]; found 417.9740.

2-(indolin-5-ylthio)-4*H*-chromen-4-one (7). Brown solid (33 mg, 45%); mp 265°C; ^{1}H NMR (400 MHz, DMSO) δ 8.00 (d, *J* = 2.5 Hz, 1H), 7.91 (dd, *J* = 8.9, 2.6 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.25 (d, *J* = 1.6 Hz, 1H), 7.21 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 5.58 (s, 1H), 3.55 (d, *J* = 8.7 Hz, 2H), 2.99 (t, *J* = 8.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 173.8, 173.0, 155.3, 155.1, 136.6, 136.1, 131.6, 131.2, 127.1, 124.5, 120.4, 118.0, 108.7, 108.0, 106.3, 46.4, 28.5; IR (KBr) ν_{max}/cm^{-1}3324, 2924, 1739, 1613, 1260; HRMS (ESI) calculated for $C_{17}H_{14}NO_2S$ 296.0740 [M + H^+]; found 296.0742.

2.5f. X-ray Structure of Compounds 3l and 5d

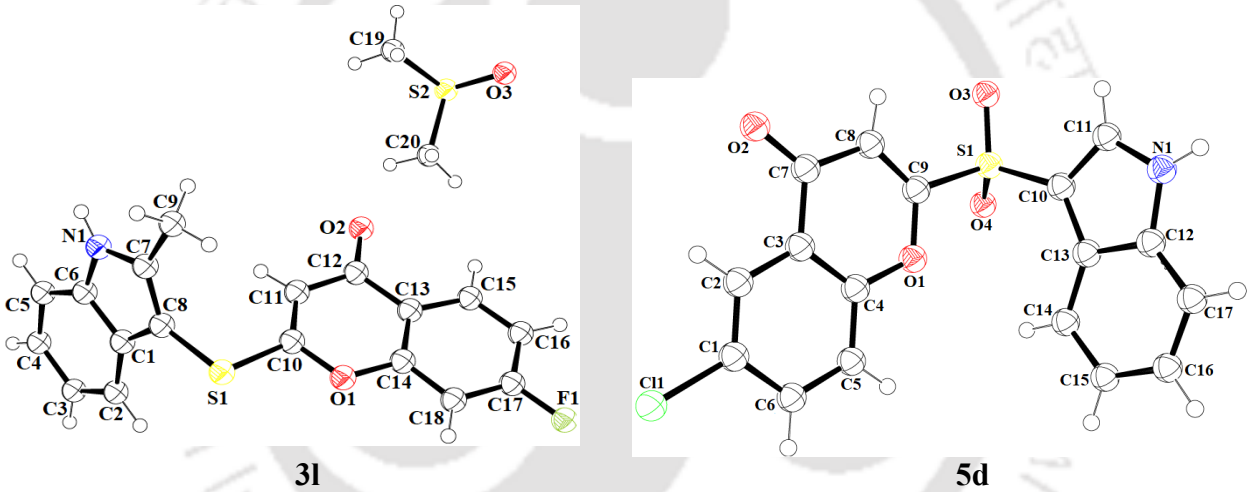


Figure 9. ORTEP diagram of compound **3l** and compound **5d**

Table 7. Crystal data and structure refinement for compound 3l and 5d

Entry	Identification code	Compound (3l)	Compound (5d)
1	Empirical formula	$C_{20}H_{18}FNO_3S_2$	$C_{17}H_{10}ClNO_4S$
2	Formula weight	403.47	359.77
3	Temperature	296K	297K
4	Wavelength	0.71073	0.71073
5	Radiation type	Mo K\a	Mo K\a
6	Radiation source	Fine-focus sealed tube	Fine-focus sealed tube
7	Crystal system	Monoclinic	Monoclinic
8	Space group	P21/n	P2/n
9	Cell length	a10.1055(3) b8.4574(2) c22.9127(6	a7.5732(18) b8.545(2) c23.452(6)
10	Cell Angle	α90 β98.750(1) δ90	α90 β91.048(8) δ90
11	Cell Volume	1935.47(9)	1517.3(6)
12	Density	1.385	1.575
13	Completeness to theta	99.4	99.5
14	Absorption correction	multi-scan	Multi-scan
15	Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2
16	Reflection number	69611	39615
17	R(reflections)	0.0364(3070)	0.0797(1950)
18	wR2(reflections)	0.1135(3403)	0.2112(2664)
19	gooF (S)	1.103	1.076
20	Theta range	27.07	50.468
21	Cell formula units Z	4	4
22	CCDC no	2235875	2235873

Figure 10. ^{1}H NMR spectra of 4-hydroxy-2*H*-chromene-2-thione (1a)

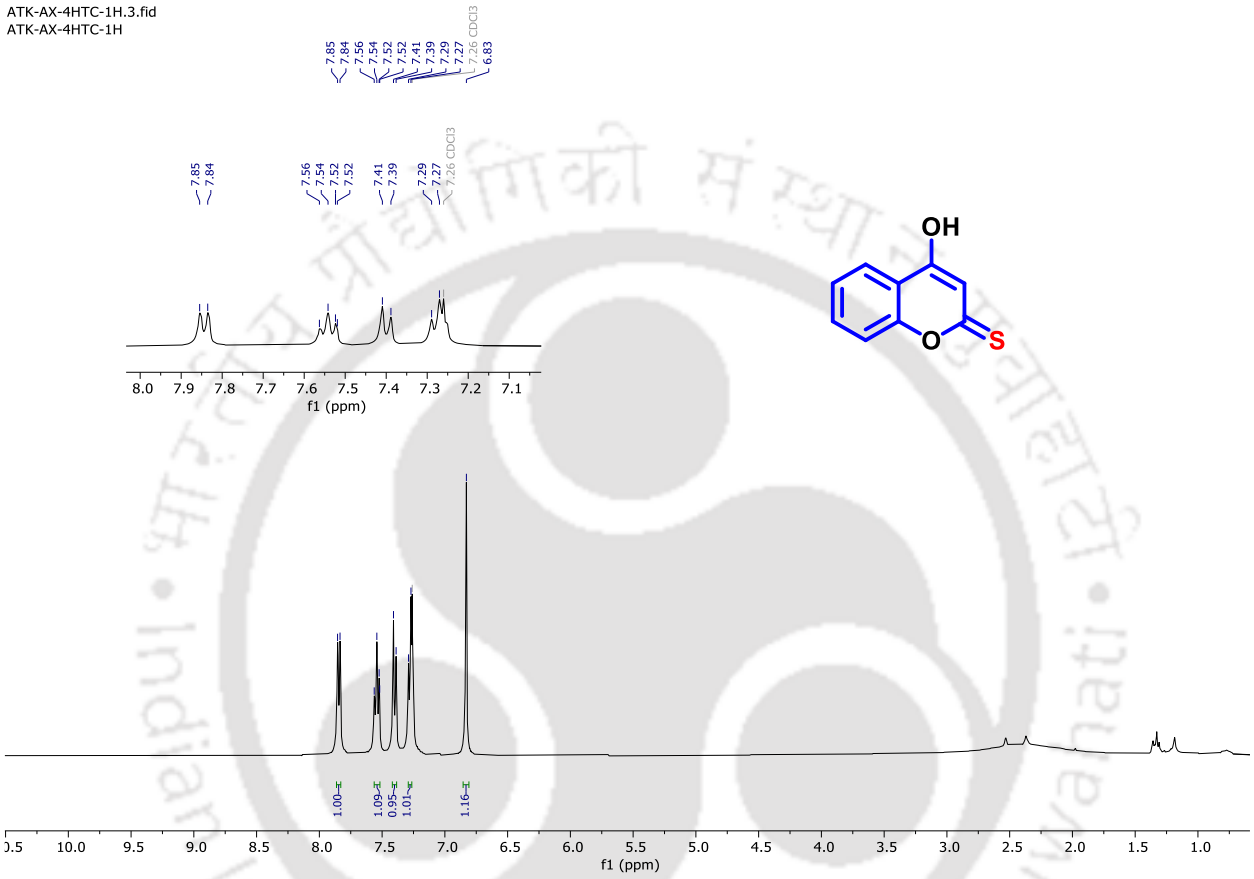


Figure 11. ^{13}C NMR spectra of 4-hydroxy-2*H*-chromene-2-thione (1a)

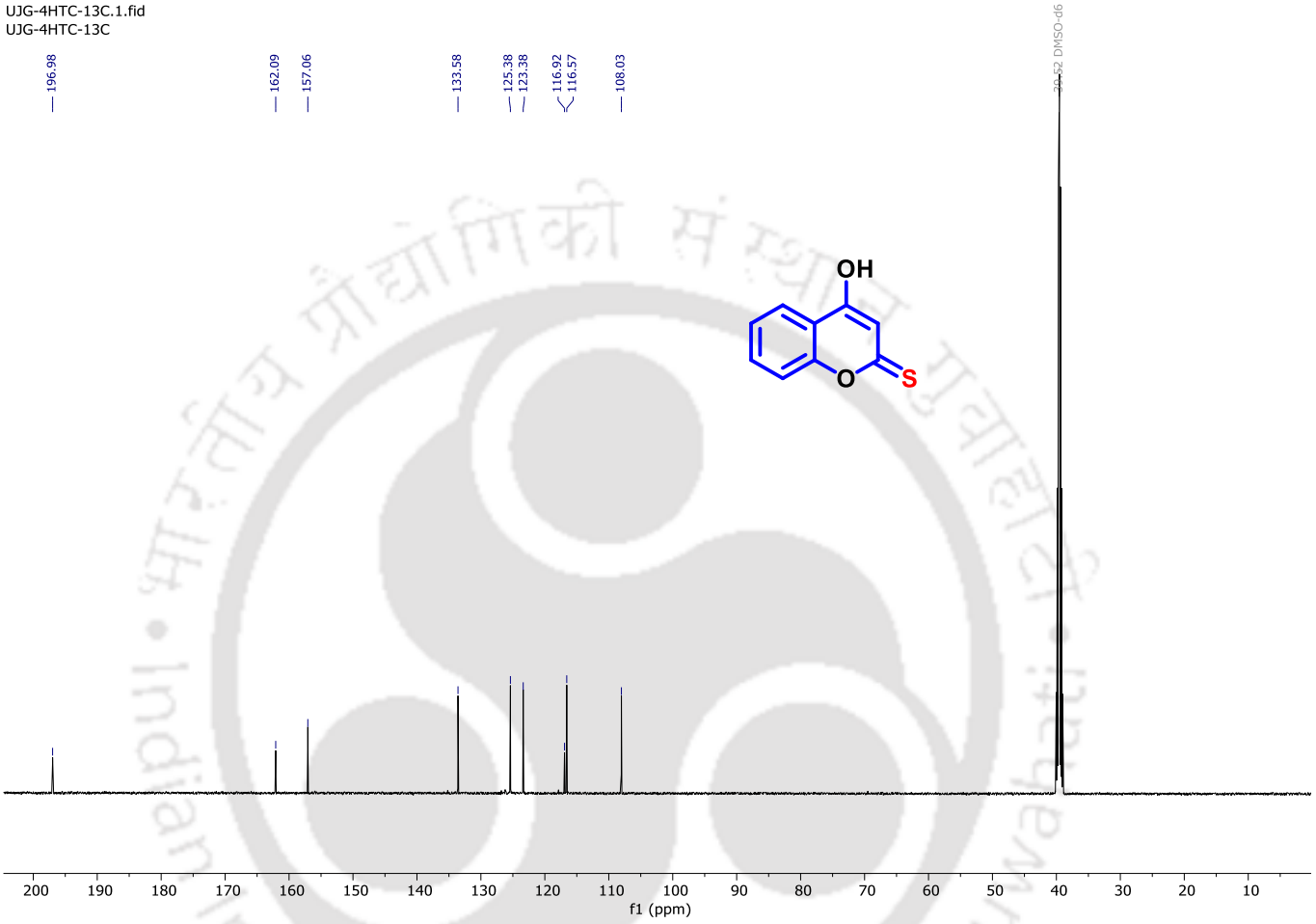


Figure 12. HRMS spectra of (*E*)-3-(2-phenylhydrazineylidene)chromane-2,4-dione (1a)

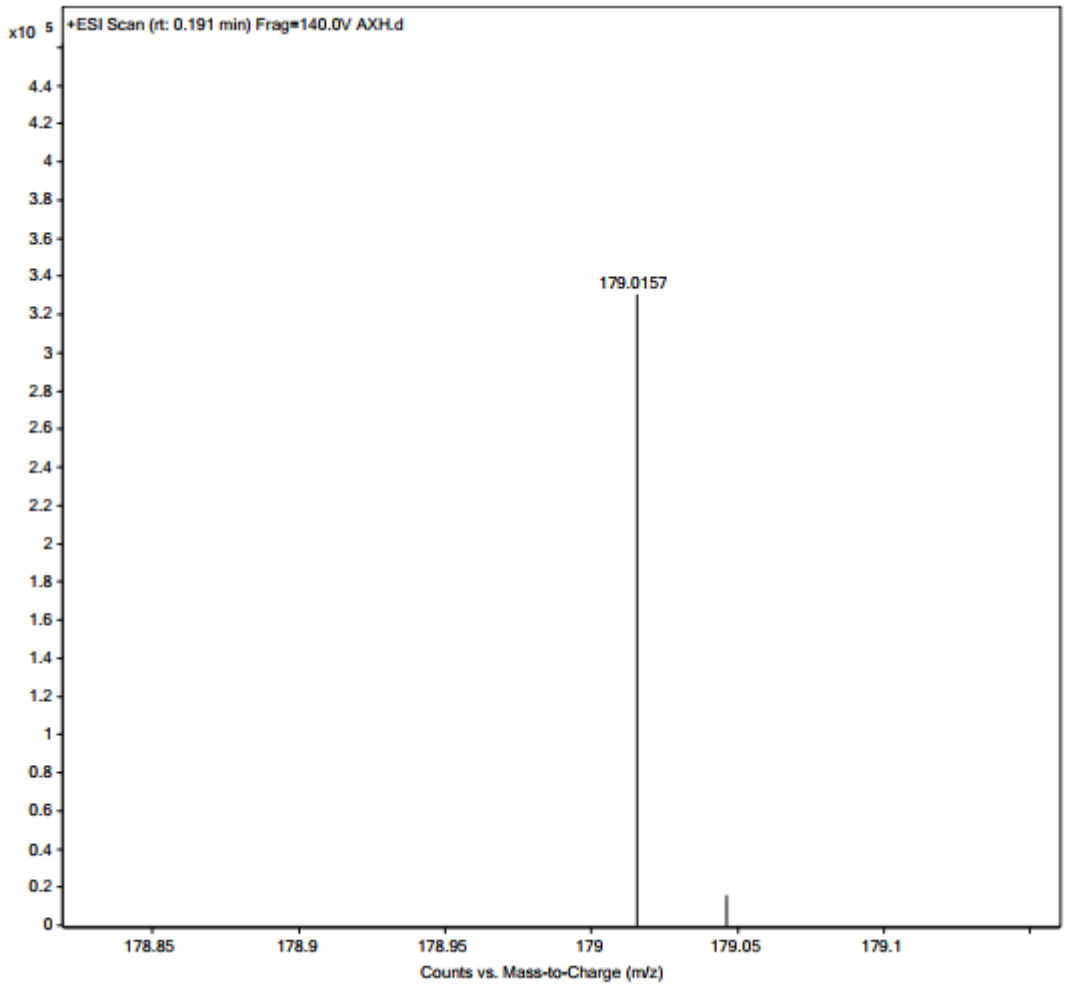


Figure 13. ^{1}H NMR spectra of 2-((1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3aa)

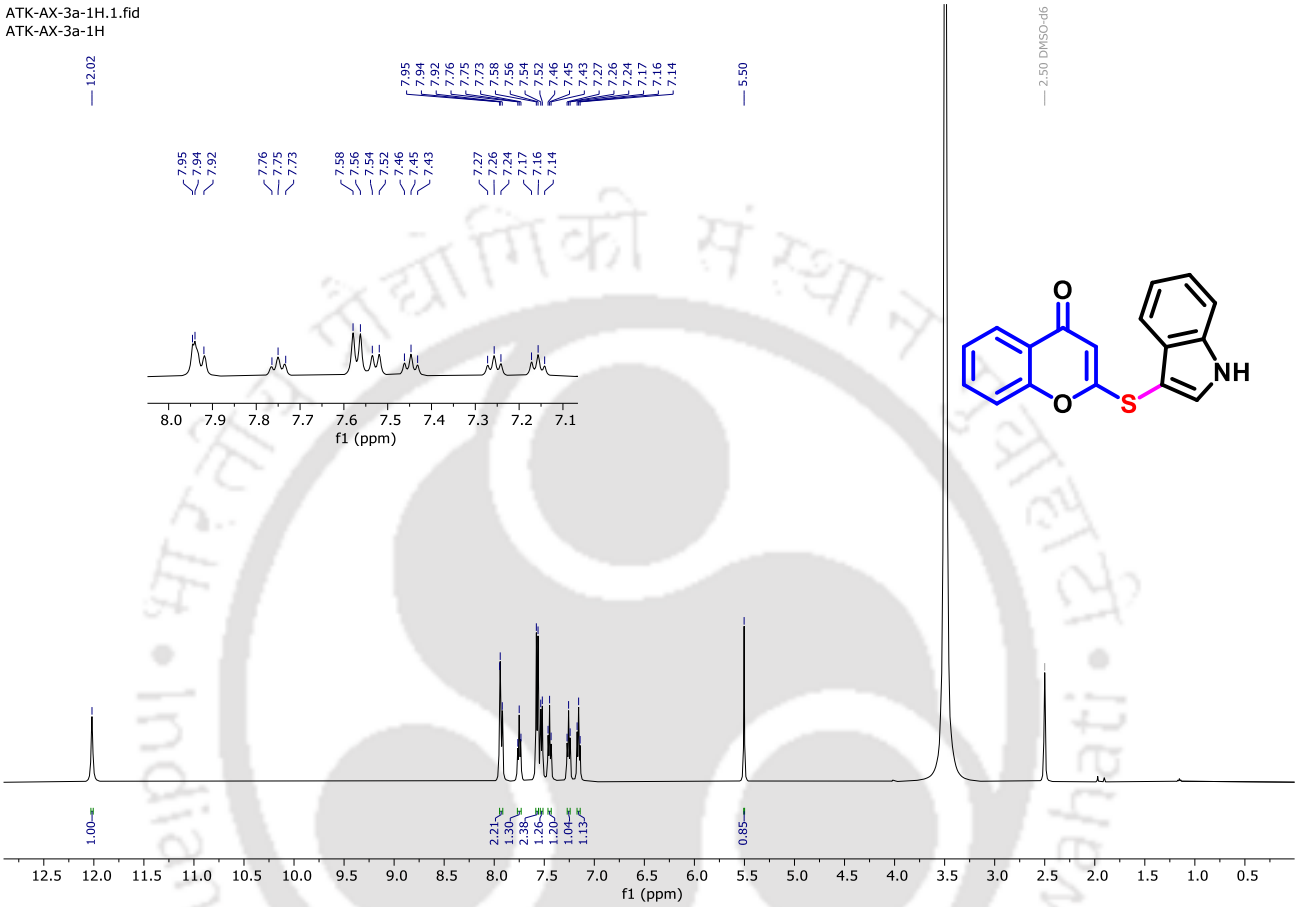


Figure 14. ^{13}C NMR spectra of 2-((1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3aa)

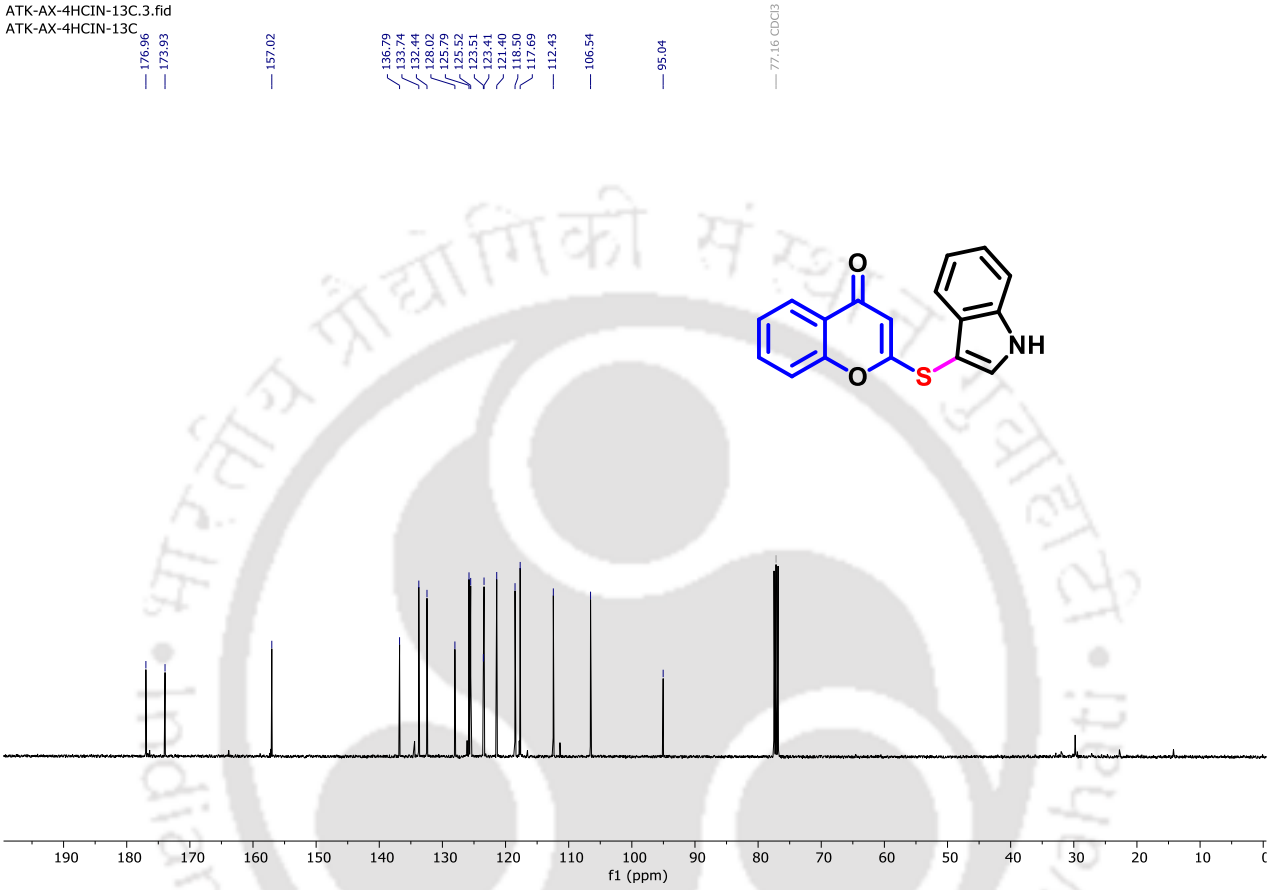


Figure 15. HRMS spectra of 2-((1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (3a)

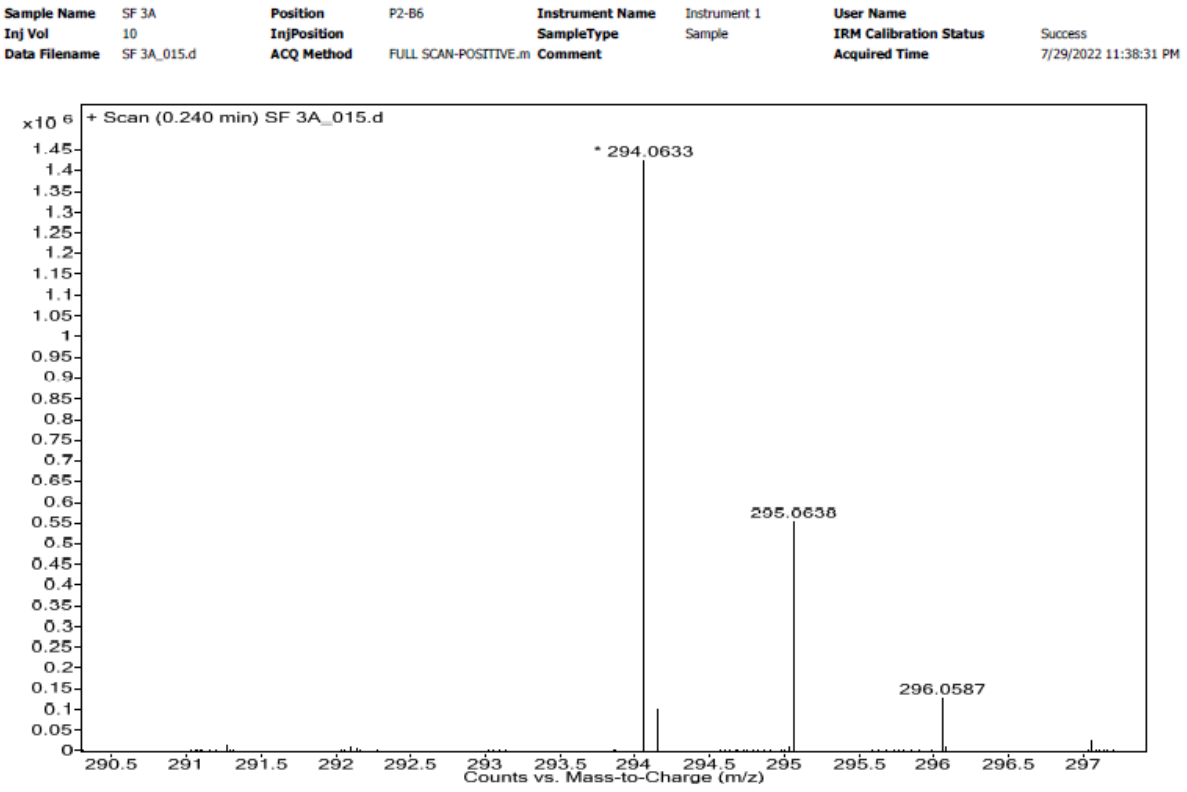


Figure 16. ^{1}H NMR spectra of 2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (4a)

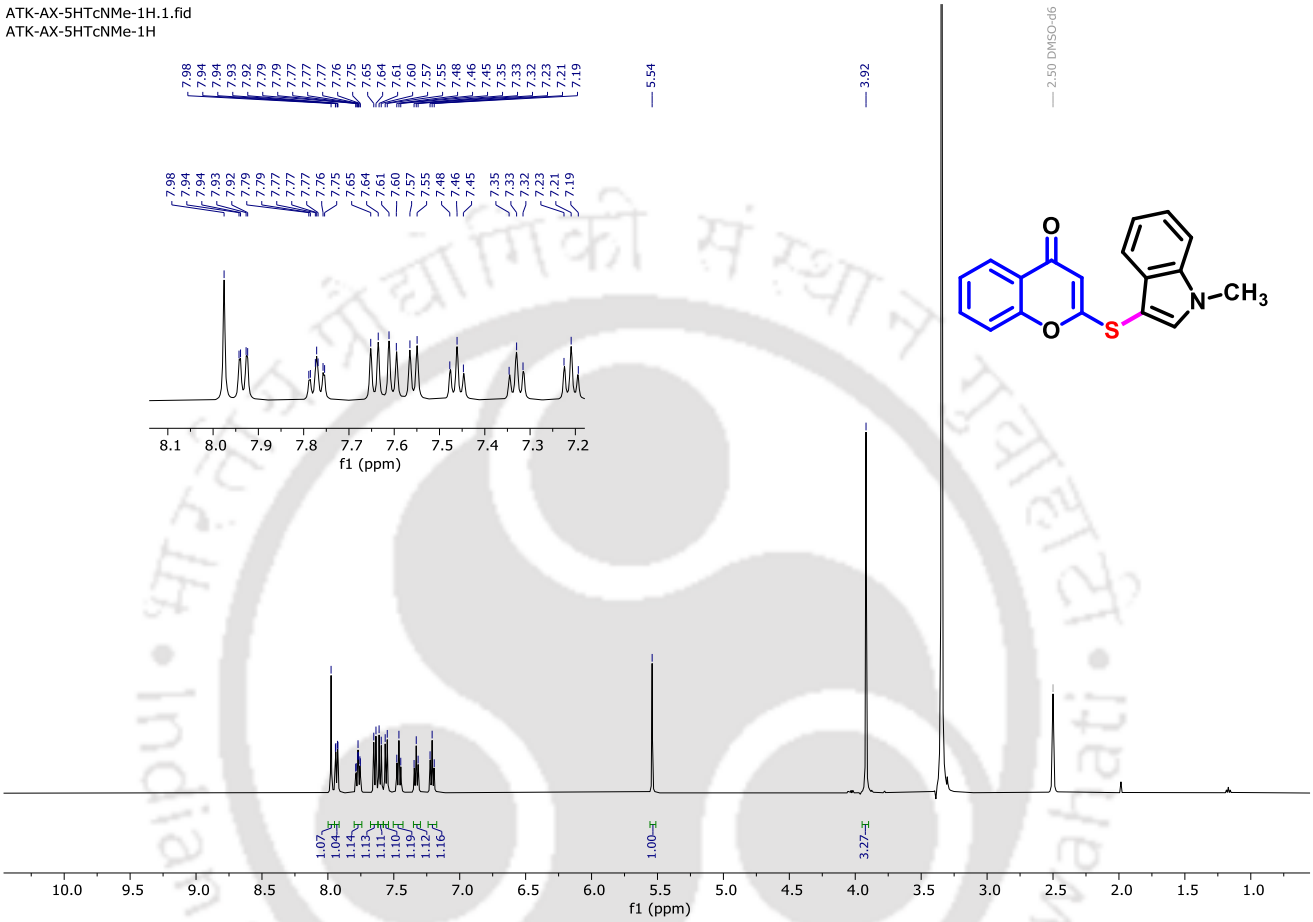


Figure 17. ^{13}C NMR spectra of 2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (4a)

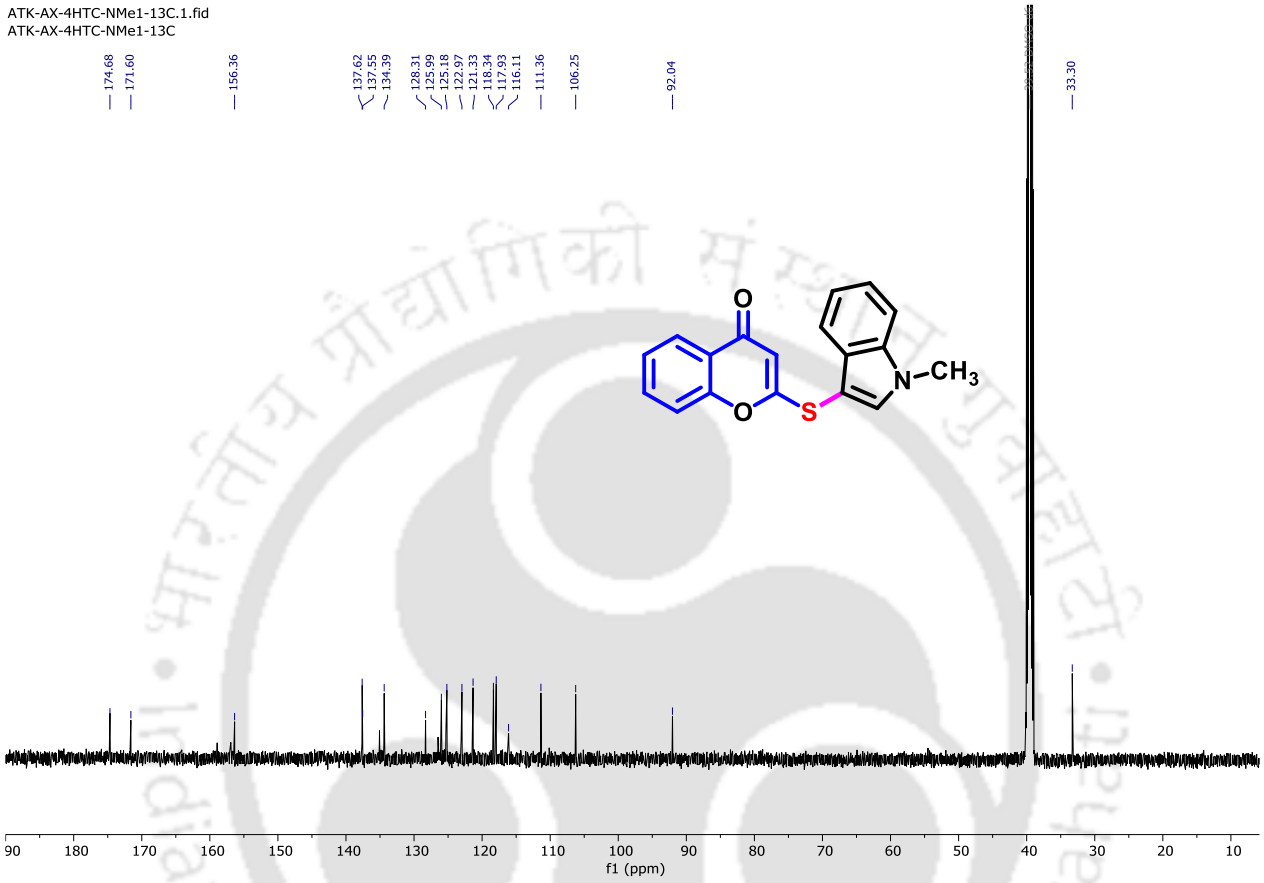


Figure 18. HRMS spectra of 2-((1-methyl-1*H*-indol-3-yl)thio)-4*H*-chromen-4-one (4a)

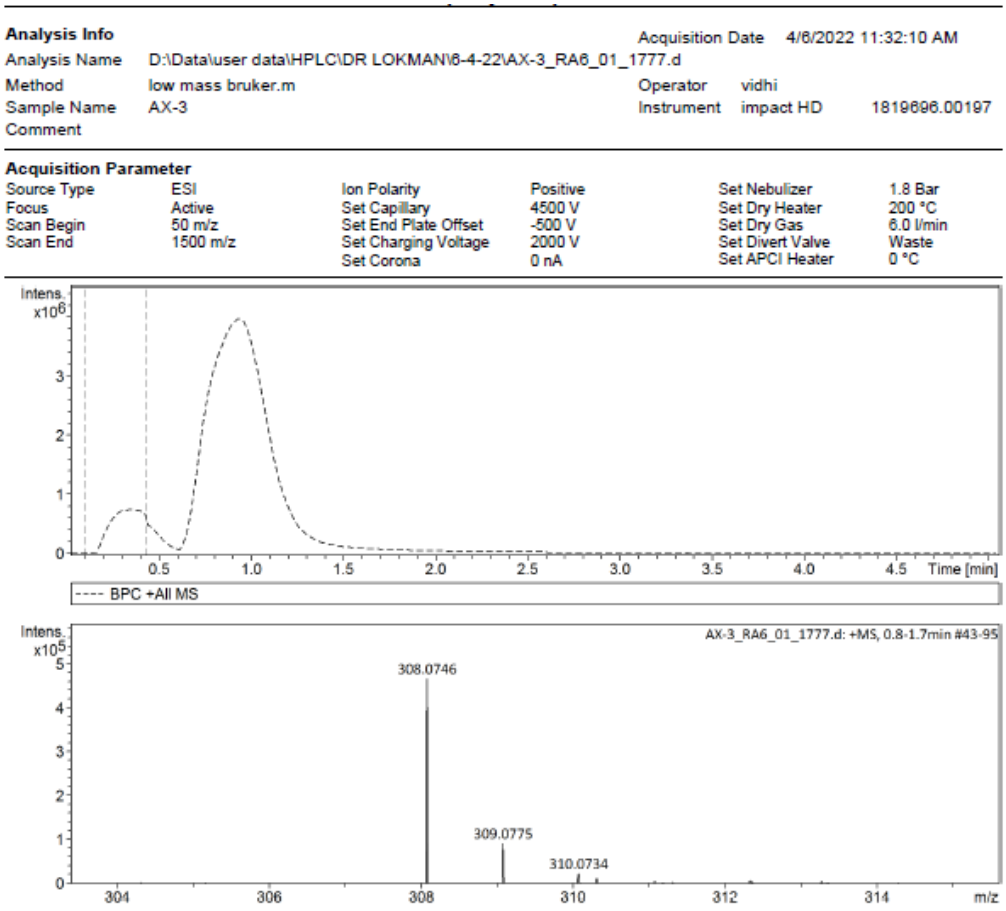


Figure 19. ^{1}H NMR spectra of 2-((1*H*-indol-3-yl)sulfonyl)-4*H*-chromen-4-one (5a)

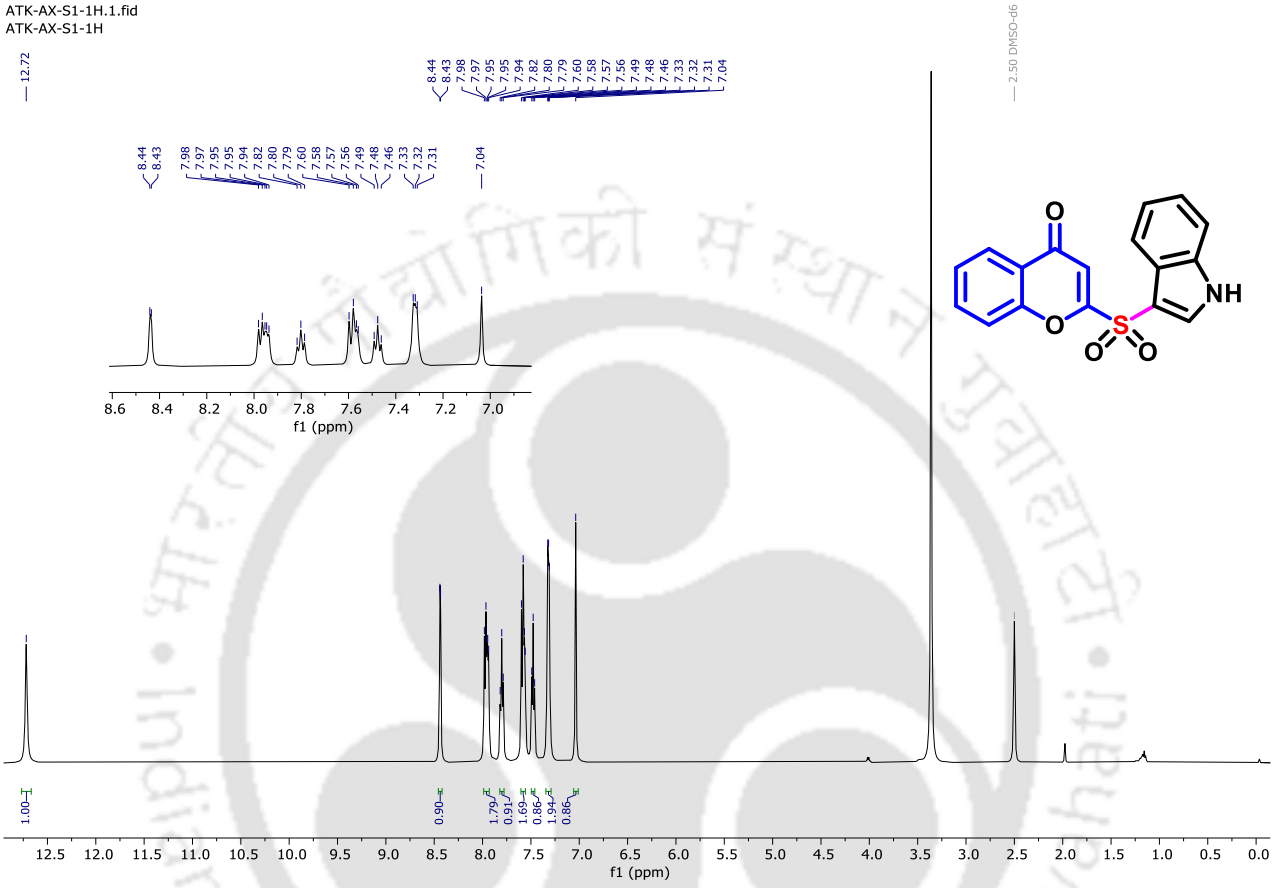


Figure 20. ^{13}C NMR spectra of 2-((1*H*-indol-3-yl)sulfonyl)-4*H*-chromen-4-one (5a)

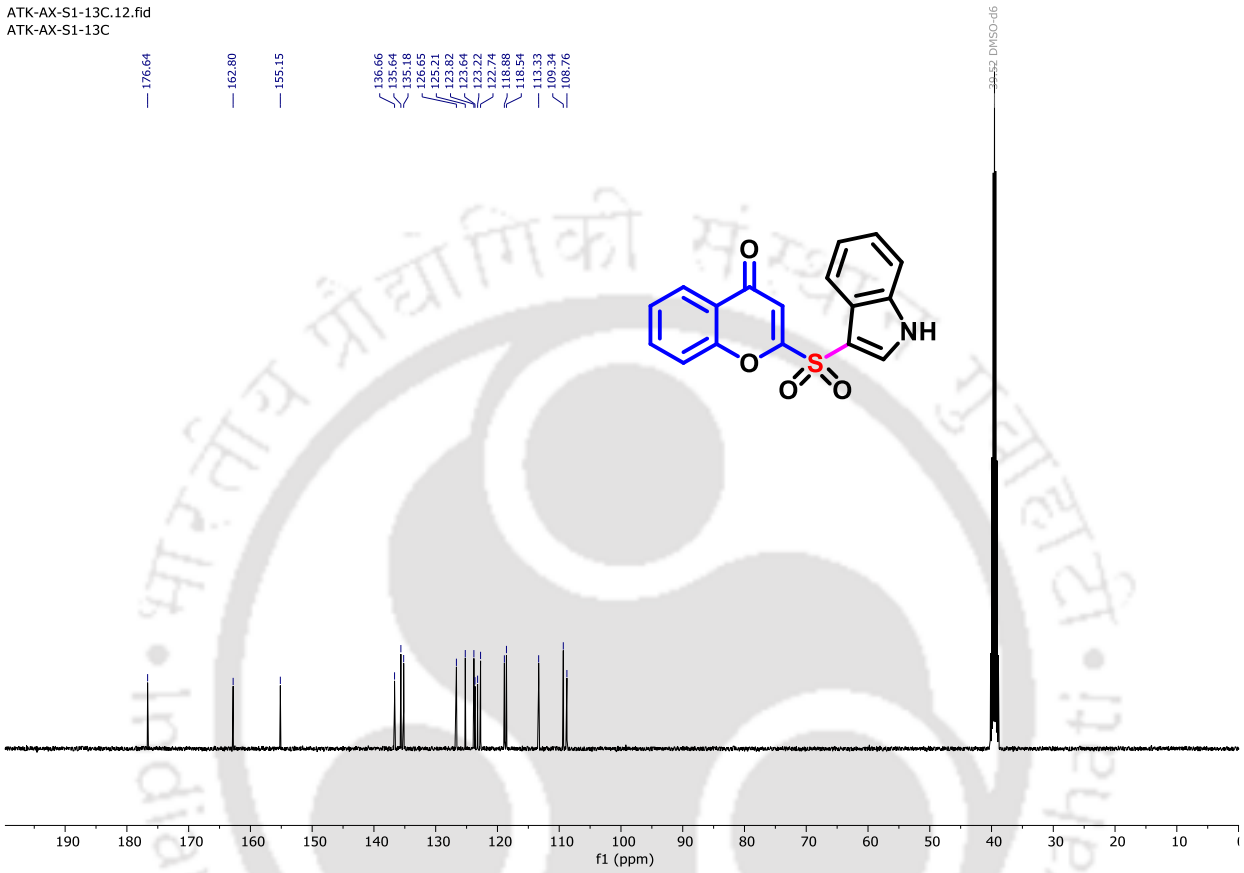


Figure 21. HRMS spectra of 2-((1*H*-indol-3-yl)sulfonyl)-4*H*-chromen-4-one (5a)

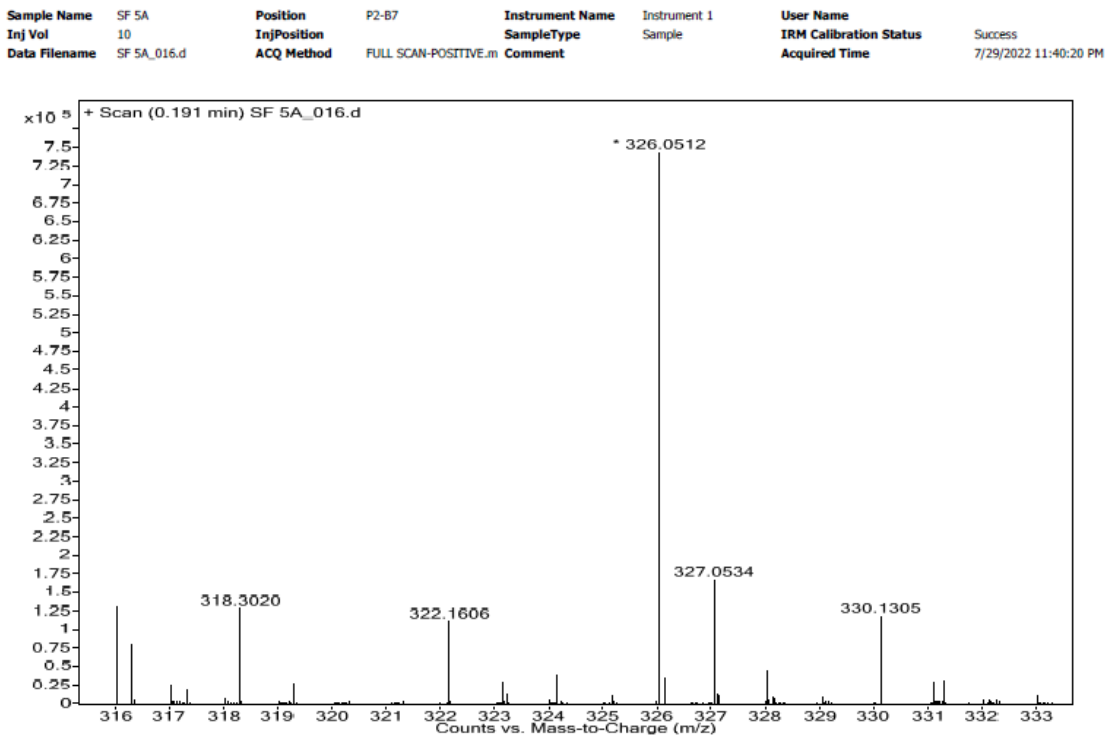


Figure 22. ^{1}H NMR spectra of2-(indolin-5-ylthio)-4*H*-chromen-4-one (7)

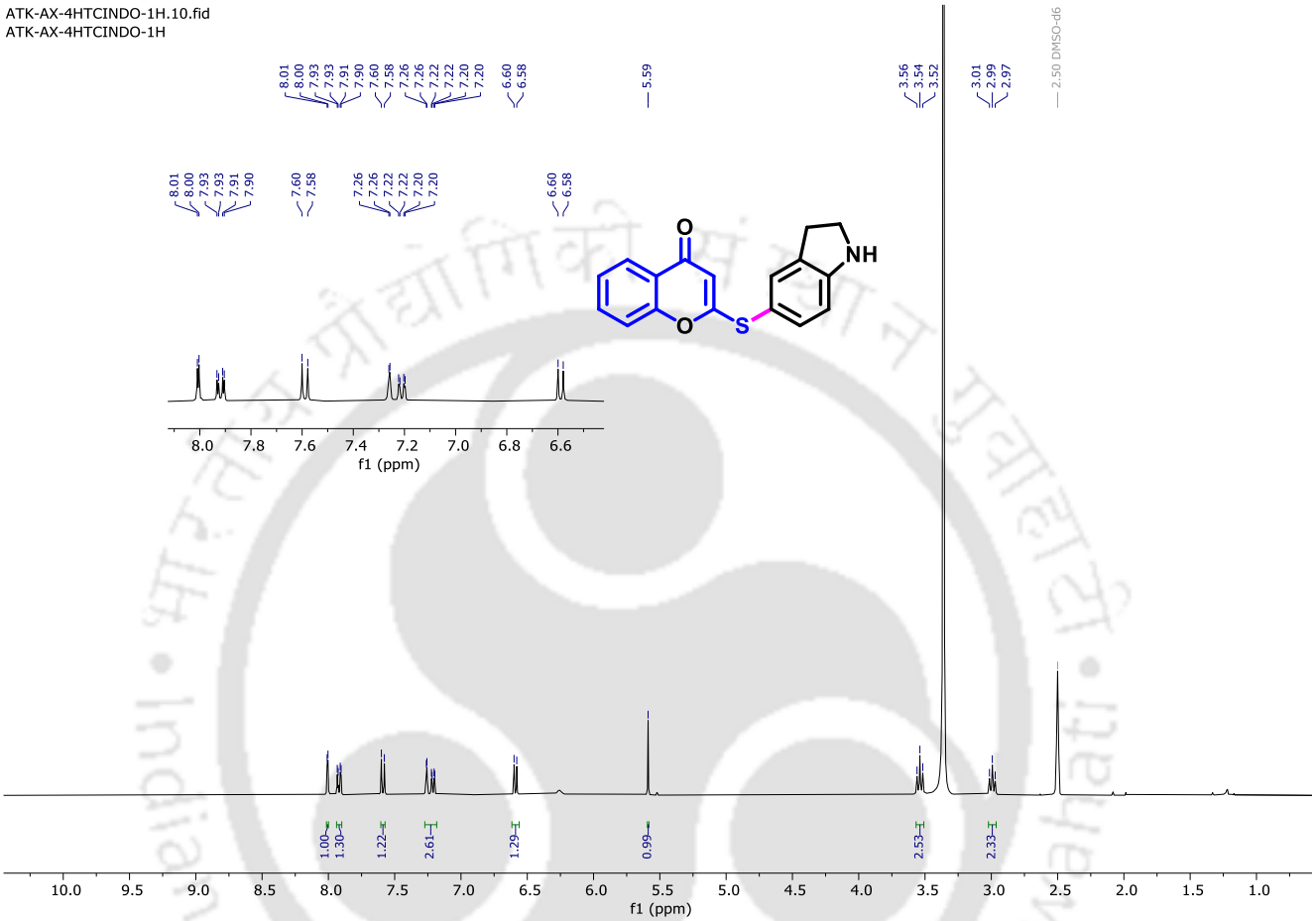


Figure 23. ^{13}C NMR spectra of 2-(indolin-5-ylthio)-4*H*-chromen-4-one (7)

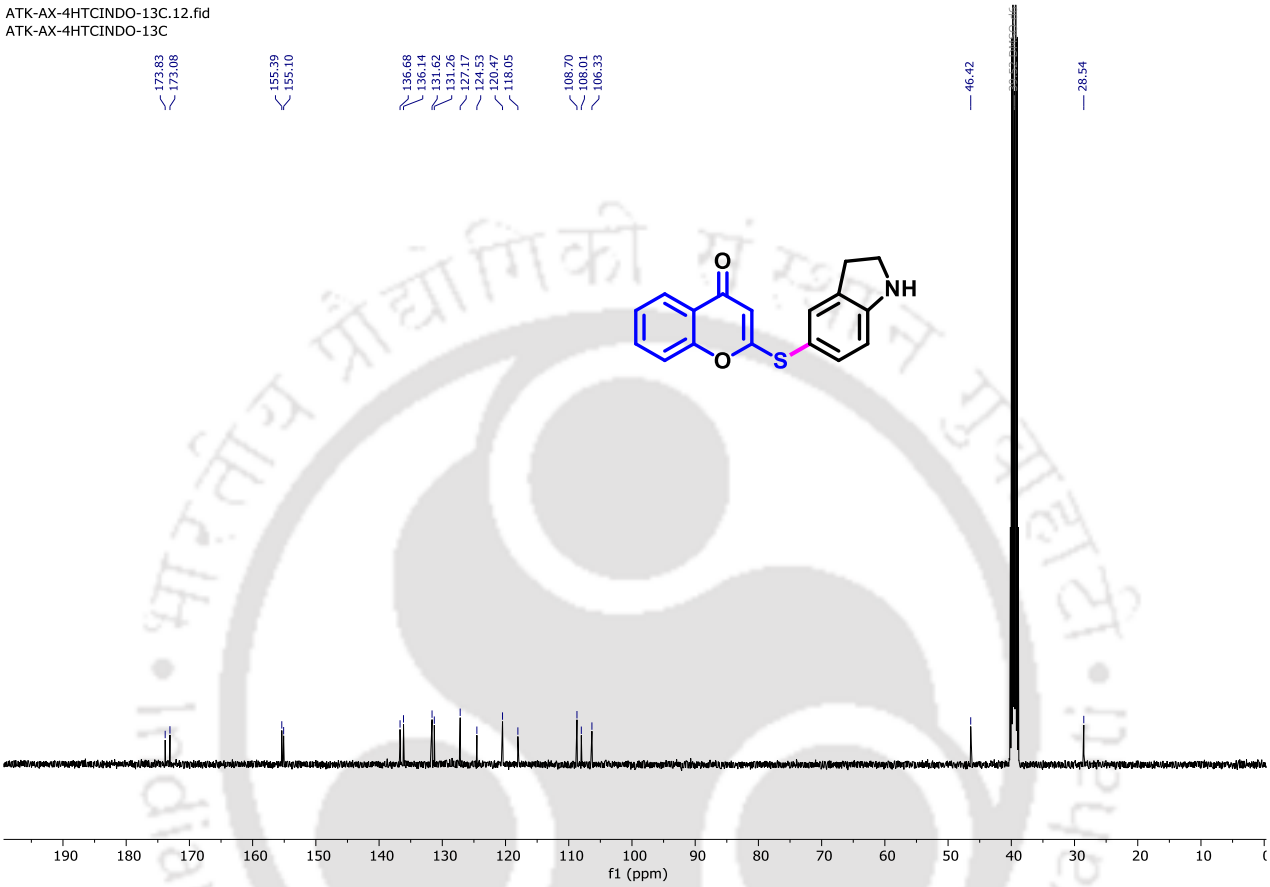
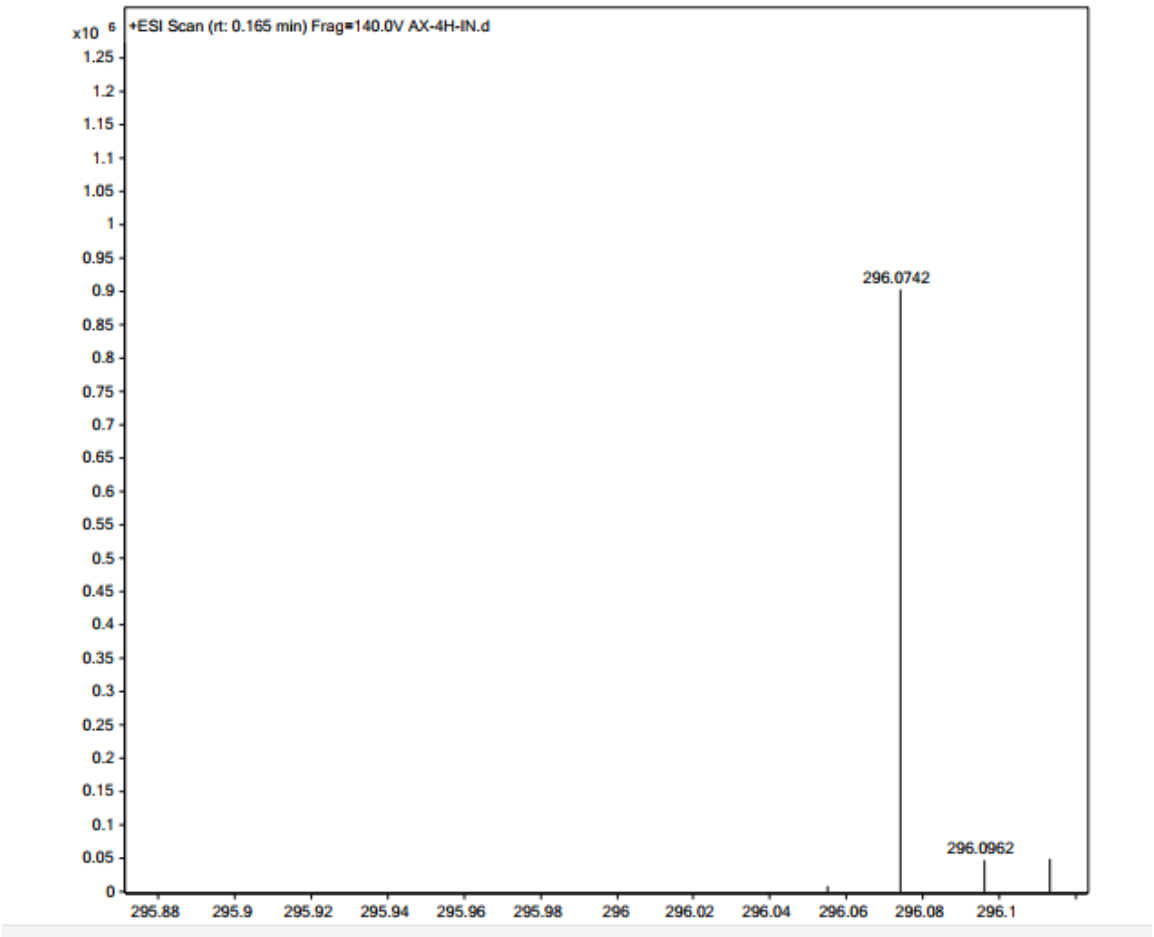


Figure 24. HRMS spectra of 2-(indolin-5-ylthio)-4*H*-chromen-4-one (7)



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CHAPTER III

Reactivity study of 4-hydroxy-2*H*-chromene-2-thione with aromatic aldehyde and β-enaminone: Regioselective synthesis of 3-benzoyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-ones

3.1 Introduction

Thiopyrans and fused thiopyrans, particularly those containing organosulfur compounds, have garnered significant attention from chemists worldwide due to their crucial role in the pharmacological activity of organic molecules.[1] These *S*-heterocycles exhibit various pharmacological activities, including anti-bacterial, anti-cancer, anti-inflammatory, and anti-viral properties, attributed to varied substitutions on the thiopyran nucleus.[2] Combining multiple pharmacophores has emerged as a promising strategy for discovering new potent molecules.[3] Thiopyran-based molecules offer flexible intermediates for organic synthesis, facilitating the development of bioactive molecules targeting diverse therapeutic areas. A comprehensive analysis of the National Cancer Institute's (NCI, USA) registered anticancer drugs revealed a significant presence of heterocyclic systems, including 48 monocyclic and 39 fused heterocyclic systems. The NCI database also contains numerous thiazolidine derivatives, highlighting the potential of heterocyclic compounds in anticancer therapy.[4]

The medicinal industry has recognized α,β-unsaturated carbonyl compounds and enaminones as versatile building blocks for preparing numerous bicyclic compounds of biological interest. Recently, these compounds have been identified as potential anticonvulsant agents.[5a,b] Enaminones, a class of electron-rich olefins, have been exploited to generate a wide variety of heterocycles, including pyrroles, pyrazoles, and isoxazoles.[6] Thiocarbamides[7] and dihydropyridines[8] are synthesized from β-enaminones. However, the synthesis of thiopyrans is not explored from β-enaminones. In this light, we have developed novel thiopyrans through β-enaminones. Recent advances in the field have demonstrated cyclic enaminones as a versatile intermediate to construct a variety of azacyclic frameworks and have been widely used in alkaloid synthesis.[9] Enaminones play a crucial role in organic synthesis, particularly in forming C-S bonds,[10,11] which significantly impact sulfur-containing compounds' physical properties and pharmacological activity.

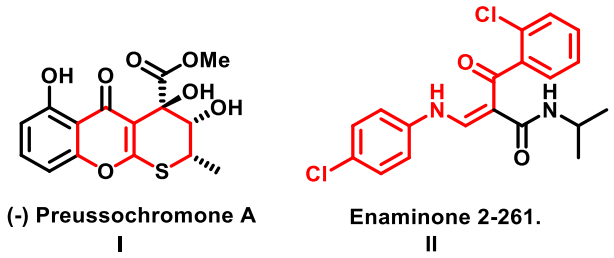
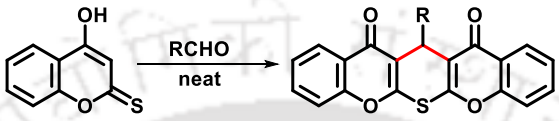


Figure 1. Potential bioactive compounds of thiopyran (**a**) and enaminone (**b)**

Motivated by these findings, we aimed to explore fused chromones and thiopyran derivatives as a novel approach to modelling potential anti-cancer properties of new tetracyclic fused heterocycles. We hypothesise that thiopyrano-chromone derivatives are synthetic precursors to pharmacologically important molecular fragments of biologically active molecules. Therefore, investigating the influence of fusing thiopyrano-chromone scaffolds on the pharmacological profile of these compounds is of significant interest.

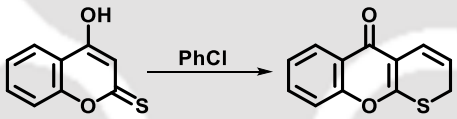
3.2a. Synthesis of thiopyran derivatives

In 2023, Goswami and his co-workers reported the synthesis of pentacyclic-dione derivatives utilizing a pseudo-three-component reaction involving 4-hydroxy-2*H*-chromene-2-thione and a range of aldehydes.[12]



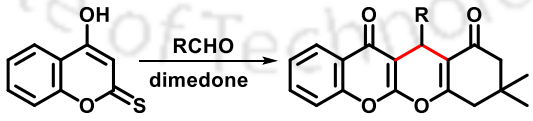
Scheme 1. Synthesis of thiopyrano derivatives

Recently, Goswami and his co-workers demonstrated a simple procedure for the synthesis of fused chromono-2- methylthiophene and fused chromono-thiopyran derivatives from 4-hydroxy-2*H*-chromene-2-thione by simple alkylation followed by [3,3]-sigmatropic rearrangement and ring closure.[13]



Scheme 2. Synthesis of thiopyrano derivatives

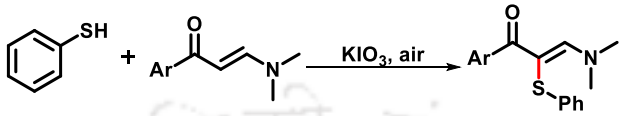
Recently, Mandal*et.al*., synthesised 12-aryl substituted chromeno[2,3-*b*]chromenes using 4-hydroxy-2*H*-chromene-2-thione, dimedone and aromatic aldehyde in good to excellent yields catalysed by L-proline.[14] The reaction involves Knoevenagel condensation between dimedone and an aromatic aldehyde, followed by Michael addition with 4-hydroxy-2*H*-chromene-2-thione



Scheme 3. Synthesis of pyrano derivatives

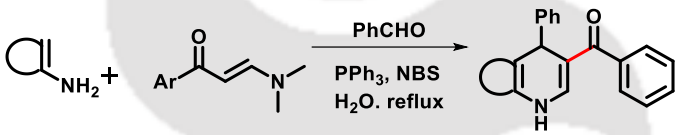
3.2b. Reactions involving β-enaminone

Wan and co-workers developed a sustainable, transition metal-free method using KIO_3 as a catalyst for direct C-H sulfenylation of enaminones and enamines.[15]



Scheme 4. Synthesis of polyfunctionalized alkenes by metal-free C−H sulfenylation

A novel one-pot synthesis was developed by Banda and co-workers for five and six-membered fused dihydropyridines using PPh_3-NBS via a formal [3+2+1] cycloaddition in water. The reaction involves 1,3-bisnucleophiles, β-enaminones and aldehydes through a Michael addition followed by cyclization. This echo-friendly approach offers high compatibility and excellent yields.[16]

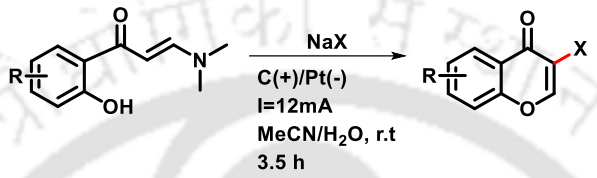


Scheme 5. Synthesis ofdihydropyridines

Sun and his co-workers reacted enamine compounds with disulfides using TBHP and catalytic TBAI to form α-thioenamine derivatives *via* oxidative C(sp^2)–S coupling. Both sulfur atoms from the disulfide are incorporated, making the process atom-efficient.[17]

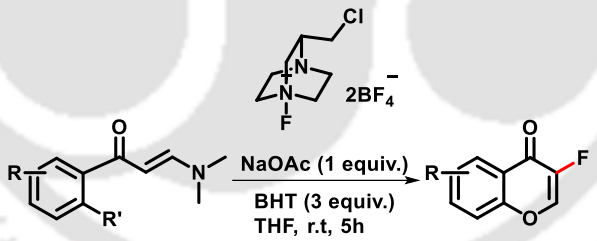
Scheme 6. Synthesis ofα-thioenamine

A simple electrochemical method established by Lin and co-workers to synthesize 3-halochromones and halogenated electron-rich arenes using NaX (X = Cl, Br, I) as the halogen source without external oxidants. This approach operates under mild, room-temperature conditions and is environmentally friendly. It offers a broad substrate scope for both C–H donors and halogen sources.[18]



Scheme 7. Synthesis of electrochemical 3-halochromones

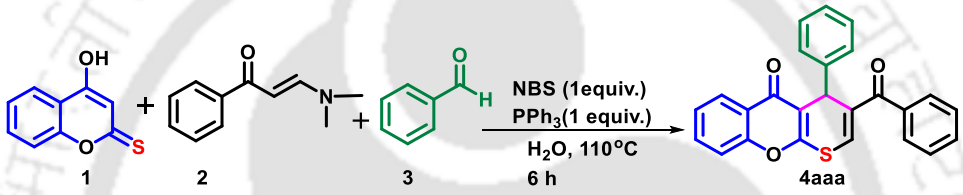
A BHT-regulated, chemoselectivemonofluorination of enaminones using selectfluor under mild conditions has been developed by Zhao and his co-workers. This method efficiently yields monofluorinated chromones with simple operation and good scalability. The fluorinated products could be further transformed into various nitrogen-containing heterocycles, enhancing the protocol's versatility.[19]



Scheme 8. Enaminone-based synthesis of 3-fluorochromones withNaOAc/BHT promotion

3.3. Results and Discussions

We have established a new approach to synthesise fused thiopyran derivatives using 4-hydroxy-2*H*-chromene-2-thione, aldehydes and β-enaminones in water medium (**Scheme 9**). This observation reveals the reactivity patterns of 4-hydroxy-2*H*-chromene-2-thione, a pseudo thiol, and β-enaminones, where bond formation occurs at the β-position of enaminones, yielding thiopyran derivatives. 4-Hydroxy-2*H*-chromene-2-thione can exist in three resonating structures,[20] as shown in **Figure 2**,in which structure **III** can react with β-enaminone to form a C–S bond, followed by cyclization and elimination of dimethylamine to get the desired product.



Scheme 9. Synthesis of 3-benzoyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-ones

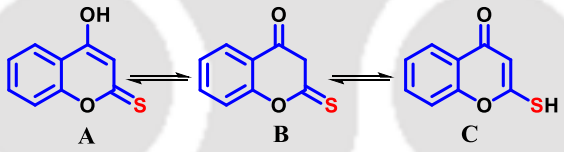
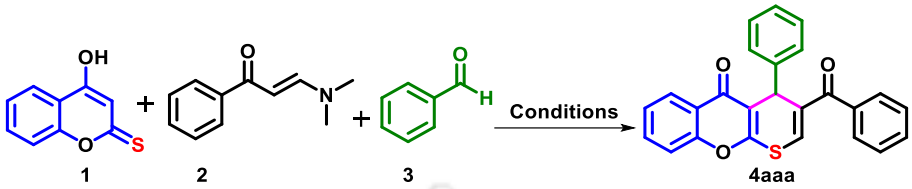


Figure 2. Resonating structure of 4-hydroxy-2*H*-chromene-2-thione.

For our present study, various derivatives of 4-hydroxy-2*H*-chromene-2-thione (**1**) were prepared following the reported procedure.[20] Similarly,β-enaminones (**2**) were prepared following the reported procedure.[21]

A mixture of 4-hydroxy-2*H*-chromene-2-thione (**1**, 0.25 mmol), β-enaminone (**2**, 0.25 mmol) and benzaldehyde (**3**, 0.25 mmol) were taken in a 10 mL round-bottomed flask and stirred at 100° C for 3 hours in the presence of iodine and DABCO to obtain product **4** (**Table 1**, **entry 1-2**).However, the reaction did not proceed, and the starting materials were recovered. Then, along

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

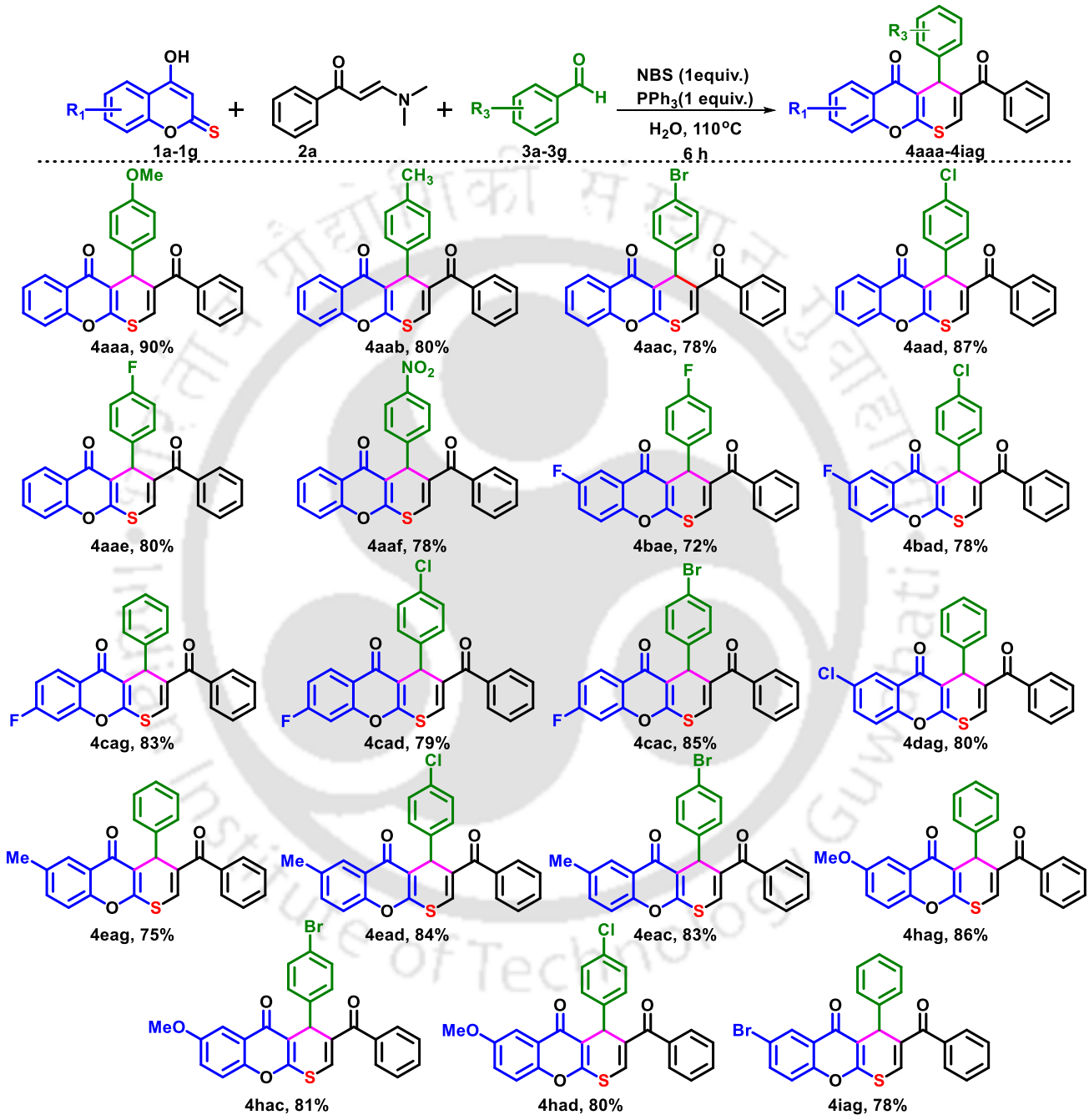


Sl. no	Reagent (equiv.)	PPh_3 (equiv.)	Temp (◦C)	Solvent	Time (h)	Yield (%)
1	I_2 (1)	-	reflux	H_2O	3	-
2	DABCO (1)	-	reflux	H_2O	3	-
3	I_2	1	reflux	H_2O	3	30
4	NBS (1)	1	reflux	H_2O	3	60
5	**NBS (1)**	**1**	**reflux**	**H_2O**	**6**	**90**
6	NBS (1)	1	reflux	H_2O	1	30
7	NBS (1)	1	reflux	H_2O	9	65
8	NBS (1)	1	reflux	H_2O	24	60
9	NBS (1)	1	reflux	DMF	6	55
10	NBS (1)	1	reflux	Toluene	6	32
11	NBS (1)	1	reflux	Methanol	6	57

[a]All the reactions were carried out using 4-hydroxy-2*H*-chromene-2-thione (**1a,** 0.25 mmol), β-enaminone (**2a,** 0.25 ml) and aldehyde (**3a,** 0.25 ml) at 100 °C. [b]Isolated yield.

with the reagent iodine, PPh_3 was introduced into the reaction mixture and heated at 100℃ for 3 hours, which formed the anticipated product **4** by only 30% (**Table 1**, **entry 3**). The isolated product was characterized by IR, ^1H and ^{13}C NMR spectroscopy and HRMS. To enhance the yield of the anticipated product, the model reaction was performed under the same reaction conditions but in the presence of a combination of PPh_3–NBS. Interestingly, the exclusive formation of product **4** was observed in 60% yield (**Table 1**, **entry 4**). Now, upon optimizing the time period of the reaction, we tried to increase the yield of the desired product **4** (**Table 1,**

Table 2. Scope for 3-benzoyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one derivatives.[a,b]



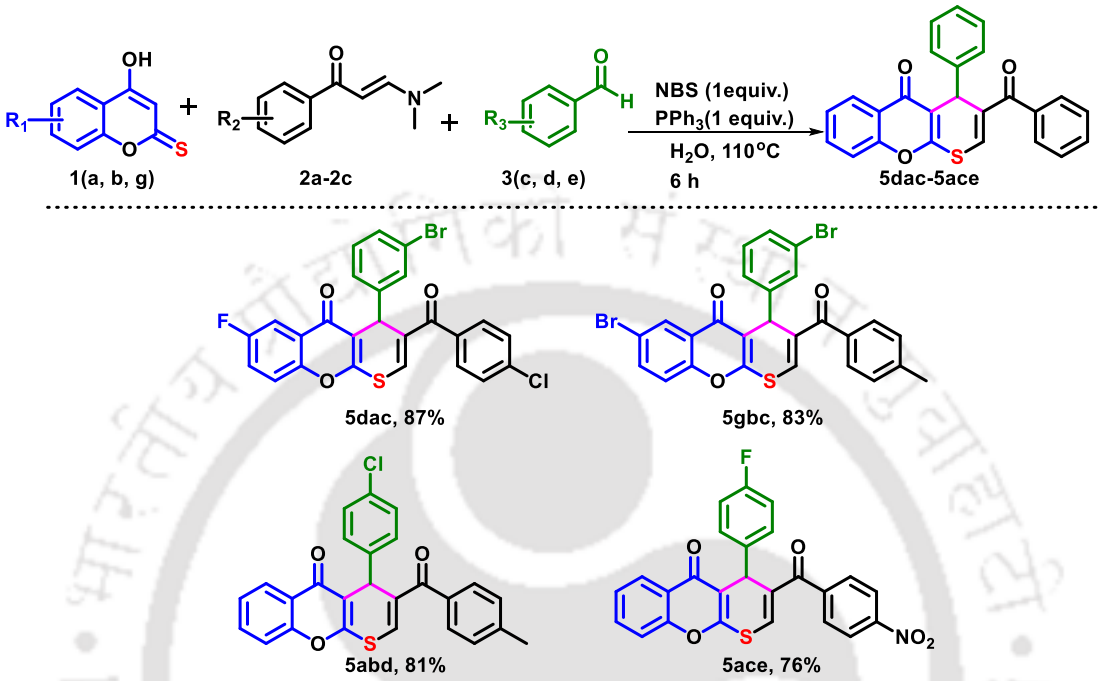
[a]All the reactions were carried out using 4-hydroxy-2*H*-chromene-2-thione (**1a,** 0.25 mmol), β-enaminone (**2a,** 0.25 ml) and aldehyde (**3a,** 0.25 ml) at 100 °C. [b]Isolated yield.

entries 5-8). These observations conclude that reflux at 100°C for 6 hours was the best reaction condition. Next, solvent screening studies were performed, and interestingly, the water-mediated reaction produced the desired product **4** to 32-57% yield (**Table 1**,**entries 9-11**).

With the optimized reaction conditions in hand, the scope and generality of the developed method were explored with different aryl aldehydes **4aaa**–**4iag** (**Table 2**). The reaction of 4-hydroxy-2*H*-chromene-2-thione (**1a**) and β-enaminone (**2a**) with aryl aldehydes containing the -4-OMe and 4-Me groups provided thiopyrano scaffolds **4aaa** and **4aab** in 90% and 80% yields, respectively. Likewise, aryl aldehydes containing electron-withdrawing groups such as -4Br, -4Cl, -4F gave the expected thiopyrano derivatives **4aac**, **4aad** and **4aae** in 78%, 87% and 80% yields, respectively. Fortunately, aryl aldehyde containing strong electron-withdrawing groups, such as $–NO_2$, at the *para* position gave the expectedthiopyarno derivative **4aaf** in 78%yield. Notably, the reaction of 6-fluoro-4-hydroxy-2*H*-chromene-2-thione with β-enaminone and electron-withdrawing groups such as -4F and -4Cl afforded the corresponding thiopyrano scaffolds, **4bae** and **4bad**, in 72% and 78% yields. Similarly, when 7-fluoro-4-hydroxy-2*H*-chromene-2-thione was reacted with β-enaminone and aldehyde, as well as benzaldehydes having -4Cl and -4Br electron-withdrawing groups, the desired products **4cag**, **4cad** and **4cac** were obtained in 83%, 79% and 85% yields, respectively. Additionally, the reaction of benzaldehyde with 6-chloro-4-hydroxy-2*H*-chromene-2-thione and β-enaminone provided **4dag** in 80% yields. Further investigating the reaction with 4-hydroxy-6-methyl-2*H*-chromene-2-thione with benzaldehyde and benzaldehyde containing -4Cl and -4Br groups along with β-enaminone offered the thiopyranoscaffolds **4eag**, **4ead**, **4eac** in 75%, 84%, 83%yields. Gratifyingly, 4-hydroxy-6-methoxy-2*H*-chromene-2-thione with benzaldehyde, -4Br and -4Cl benzaldehydes and β-enaminone gave the corresponding thiopyrano**4hag**, **4hac** and **4had** in 86%, 81% and 80% yields, respectively. Notably, the reaction of 6-bromo-4-hydroxy-2*H*-chromene-2-thione with benzaldehyde and β-enaminone gave the expected product **4iag** in 78% yield.

Inspired by the above-discussed successful results, the scope and generality of the present protocol were extended further using different β-enaminone **5dac**-**5ace**, as well as with the variation of arylaldehydes and 4-hydroxy-2*H*-chromene-2-thione (**Table 3**).

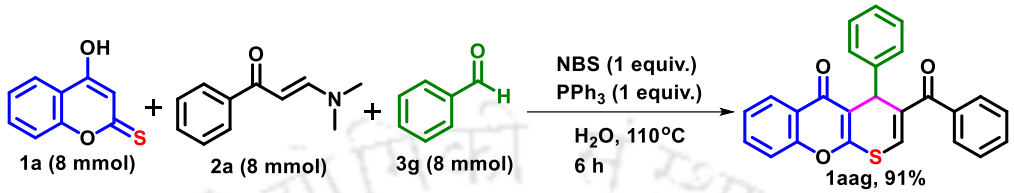
Table 3. Scope for 3-benzoyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one derivatives.[a,b]



[a]All the reactions were carried out using 4-hydroxy-2*H*-chromene-2-thione (**1a,** 0.25 mmol), β-enaminone (**2a,** 0.25 ml) and aldehyde (**3a,** 0.25 ml) at 100 °C. [b]Isolated yield.

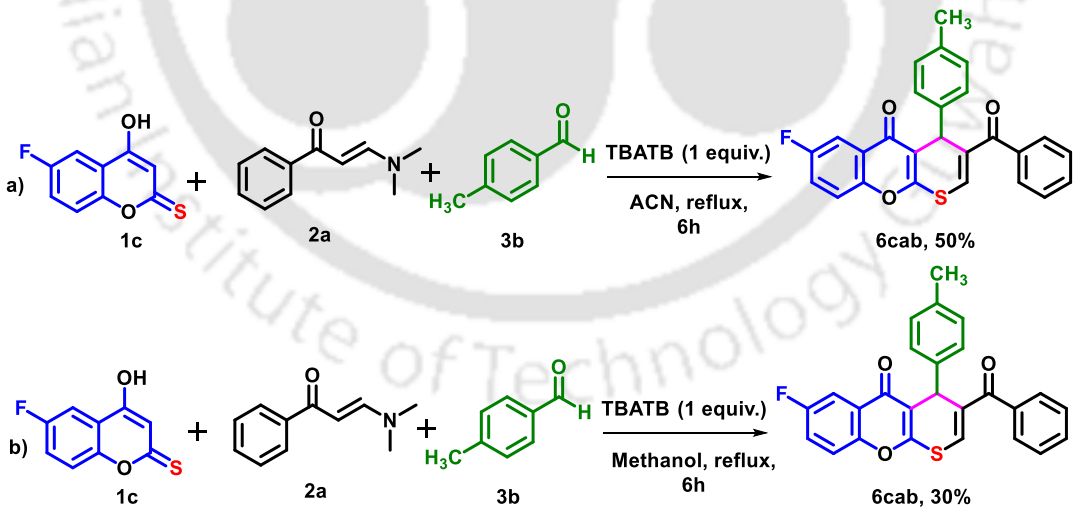
The reaction of 6-fluoro-4-hydroxy-2*H*-chromene-2-thione, 3-bromobenzaldehyde with (*E*)-1-(4-chlorophenyl)-3-(dimethylamino)prop-2-en-1-one under the standard conditions proceeded smoothly and gave the desired thiopyrano**5dac** in 87% yield. Additionally, when 6-bromo-4-hydroxy-2*H*-chromene-2-thione, 3-bromobenzaldehyde with (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one are reacted under the standard reaction conditions yields **5gbc** in 83%. Similarly, 4-hydroxy-2*H*-chromene-2-thione, 4-chlorobenzaldehyde and (*E*)-3-(dimethylamino)-1-(*p*-tolyl)prop-2-en-1-one provided the desired thiopyrano**5abd** in 81% yield. Notably, when 4-hydroxy-2*H*-chromene-2-thione reacted with 4-fluorobenzaldehyde along with (*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one with the same reaction conditions gave the expected product **5ace** in 76% yield.

Finally, a scale up reaction was carried out with 4-hydroxy-2*H*-chromene-2-thione (**1a**, 8.0 mmol), (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2a**, 8.0 mmol) and benzaldehyde(**3g**, 8.0 mmol), the expected product **1aag** was obtained in 78% yield,as shown in **Scheme 10**.



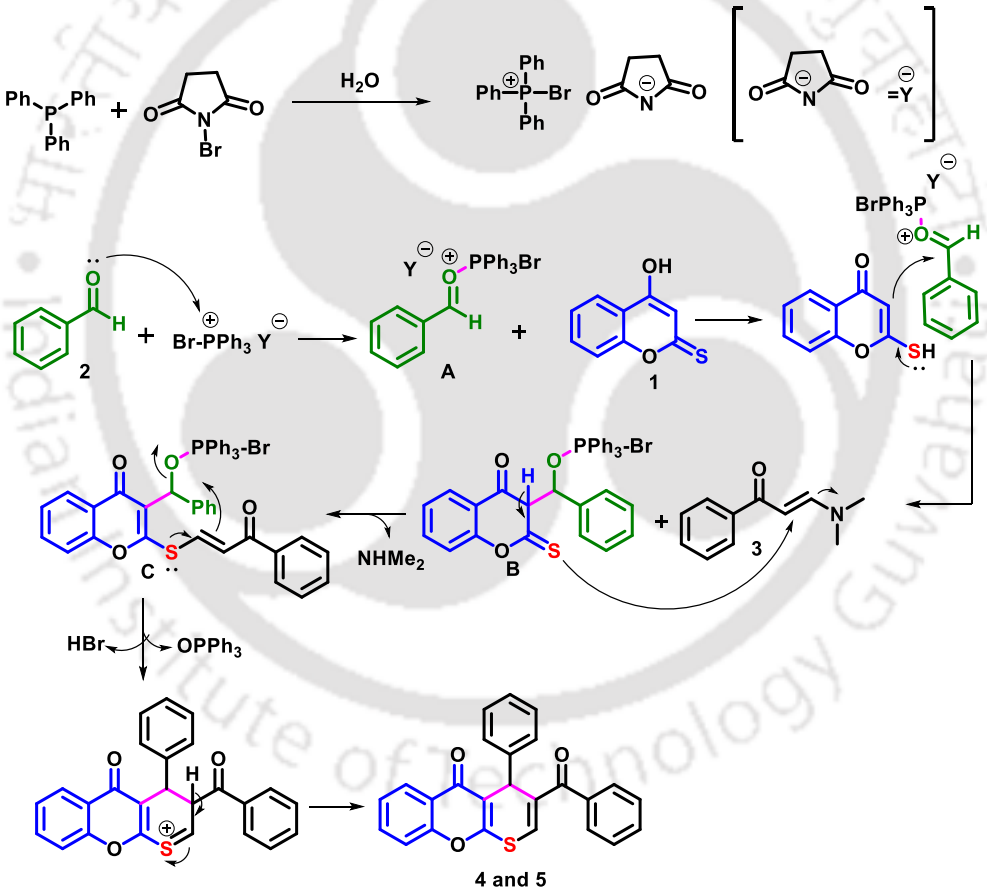
Scheme 10. Gram scale synthesis

Two control experiments were performed, as shown in **Scheme 11**, to understand the reaction mechanism. Both the reactions involved 6-fluoro-4-hydroxy-2*H*-chromene-2-thione (**1a**), 4-methylbenzaldehyde (**3b**) and (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2a**). We performed both reactions without any aid of triphenylphosphine to check if it has any role in the reaction mechanism, only to find out that the desired product **6cab** was only 50% and 30% yield without it. That suggests that triphenylphosphine plays a significant part in the reaction involving NBS due to its ability to facilitate the formation of bromonium ions.



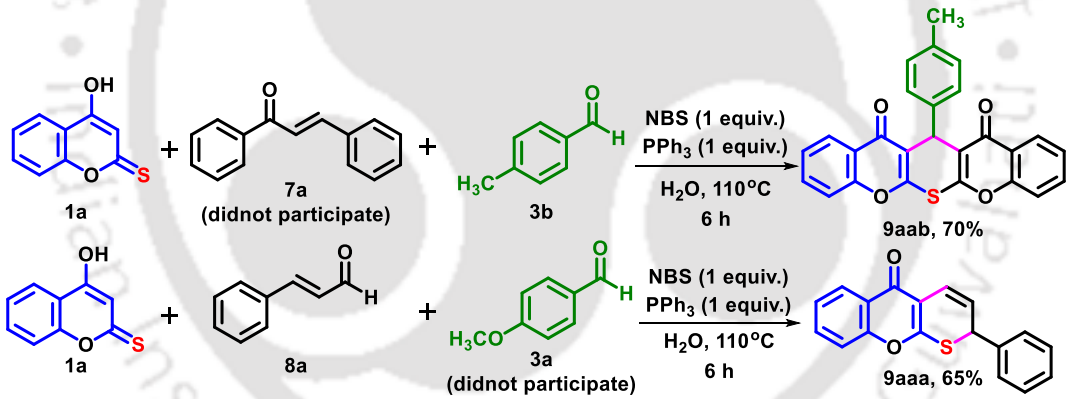
Scheme 11. Control Experiments.

A plausible mechanism was postulated based onliterature,[16] for the formation of products **4** and **5** as shown in **Scheme 12**. Initially, triphenylphosphine (PPh_3) undergoes an oxidative reaction with *N*-bromosuccinimide (NBS) to generate a bromophosphonium ion. This reactive intermediate then reacts *in-situ* with benzaldehyde, activating the carbonyl group by forming anelectron-deficient benzaldehyde species. This activated aldehyde is subsequently attacked by structure **III** from **Figure 2** to form an iminium intermediate (**B**). Next, the iminium intermediate (**B**) reacts with β-enaminones (**3**) *via* a Michael-type addition, followed by the elimination of *N*,*N*-dimethylamine, resulting in the formation of an adduct (**C**).



Scheme 12. Plausible mechanism

Finally, this adduct undergoes intramolecular cyclization, yielding the desired products**4** and **5** along with the liberation of triphenylphosphine oxide ($Ph_3P=O$) and hydrogen bromide (HBr) as by-products. Encouraged by the promising results obtained from the reaction of 4-hydroxy-2*H*-chromene-2-thione with β-enaminone and benzaldehyde, we sought to explore the impact of varying the α,β-unsaturated carbonyl component while maintaining all other reaction conditions. Specifically, we investigated the reactivity of chalcone and cinnamaldehyde as alternative reactants instead of β-enaminone **(Scheme 13)**. Interestingly, when chalcone was employed, it did not participate in the reaction. Instead, two equivalents of 4-hydroxy-2*H*-chromene-2-thione reacted with one equivalent of *p*-tolualdehyde, forming the dimeric product **9aab**. In contrast, when cinnamaldehyde was used with one equivalent of 4-methoxybenzaldehyde, it selectively underwent a sequential Michael addition and cyclization, reacting preferentially over benzaldehyde, to afford the cyclized product **9aaa**.



Scheme 13. The reaction of 4-hydroxy-2*H*-chromene-2-thione (**1a**), with different α,β-unsaturated carbonyl compounds (**7a**, **8a**) and benzaldehydes(**3a-b**) under standard reaction conditions.

3.4 Conclusion

In conclusion, we have developed an efficient and straightforward method for synthesizing 3-benzoyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one derivatives through a one-pot, three-component reaction. This aqueous medium reaction utilizes NBS-PPh_3, where β-enaminone

serves as the electrophile. Key findings indicate that the synergistic combination of NBS and PPh_3 drives the selective formation of brominated compounds. Notably, this protocol offers several advantages, including **a**) Ease of handling, **b**) Use of low-cost starting materials, **c**) Non-requirement for inert atmosphere or dry solvents, and **d**) Broad substrate scope with good to excellent yields. This method provides a convenient and sustainable approach to synthesizing complex heterocyclic compounds. Furthermore, aqueous reaction conditions often facilitate more straightforward and cost-effective experimental procedures, making this approach an alternative option for chemists seeking to develop more environmentally benign synthetic methodologies.

3.5. Experimental Section

3.5a.Procedure for the synthesis of compound 1

4-hydroxy-2*H*-chromene-2-thiones(**1a-1g**) were prepared using the reported method.[20]

3.5b. Procedure for the synthesis of compound 2

β-enaminones (**2a-2c**) were prepared by the reported method.[21]

3.5c. Procedure for the synthesis of 3-benzoyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aaa-4iag, 5dac-5ace)

1 equivalent of NBS and 1 equivalent of triphenylphosphine were allowed to stir at room temperature under an aqueous medium for 30 minutes. Then, 1 equivalent of 4-hydroxy-2*H*-chromene-2-thione (**1a**, 0.25 mmol), 1 equivalent of β-enaminones (**2a**, 0.25 mmol) and 1 equivalent of aryl aldehydes (**3a**, 0.25 mmol) were added to the reaction mixture, and it was stirred under reflux conditions for 6 hours. TLC monitored the completion of the reaction. On completion of the reaction, the crude residue was extracted with dichloromethane (10 mL x 1). The organic layer was washed with water (10 mL x 2) and 5 mL of brine solution and dried over anhydrous sodium sulfate. Finally, the solvent was removed in a rotatory evaporator, and the crude residue was purified through silica gel (60–120 mesh) column chromatography to obtain

products 4 and 5. All the other 3-benzoyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (**4aaa-4iag**, **5dac-5ace**), were synthesized following the same protocol.

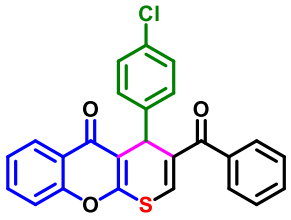
3-benzoyl-4-(4-methoxyphenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aaa). Yellowish brown solid, (95 mg, 90%), mp 200°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.7 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.39 – 7.35 (m, 2H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 11.9 Hz, 2H), 6.72 (dt, *J* = 7.7, 1.7 Hz, 1H), 6.07 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 173.8, 159.8, 156.2, 143.4, 137.6, 136.6, 133.8, 132.3, 129.7, 129.5, 129.2, 128.5, 126.5, 125.5, 123.7, 120.5, 117.4, 117.4, 114.0, 112.7, 55.3, 38.7; IR (KBr) νmax/cm−1 1648 (C=O), 1618 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{26}H_{19}O_4S$ 247.0999 [M + H^+]; found 247.0999.

3-benzoyl-4-(*p*-tolyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aab). Yellowish brown solid, (82 mg, 80%), mp 215°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 6.9 Hz, 1H), 7.57 (d, *J* = 6.8 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.06 (t, *J* = 4.0 Hz, 3H), 6.03 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 173.8, 158.9, 156.2, 139.1, 137.7, 137.1, 136.8, 133.7, 132.2, 129.5, 129.2, 129.2, 128.5, 128.0, 126.5, 125.4, 123.8, 117.7, 117.4, 38.4, 21.2; IR (KBr) νmax/cm−1 1711 (C=O), 1647 (C=O), 1465 (C-O); HRMS (ESI) calculated for $C_{26}H_{19}O_3S$ 411.1055 [M + H^+]; found 411.1040.

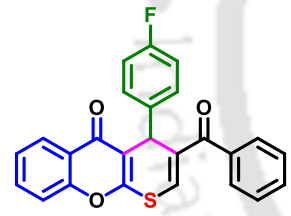
3-benzoyl-4-(4-bromophenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aac). Yellowish brown solid, (93 mg, 78%), mp 225°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.3 Hz, 1H), 7.65 (d, *J* = 11.2 Hz, 2H), 7.56 (d, *J* = 7.0 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.45 – 7.41 (m, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.16 – 7.12 (m, 2H), 6.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 173.8, 159.2, 156.3, 144.3, 137.5, 136.1, 134.0, 132.5, 130.9, 130.8, 130.5, 130.4, 129.2, 128.7, 127.4,

126.6, 125.7, 123.7, 122.9, 117.6, 117.1, 38.6; IR (KBr) νmax/cm−1 1678 (C=O), 1636 (C=O), 1435 (C-O); HRMS (ESI) calculated for $C_{25}H_{16}BrO_3S$ 474.9998 [M + H^+]; found 474.99987.

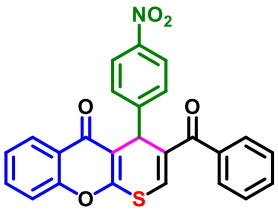
3-benzoyl-4-(4-chlorophenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aad). Yellowish brown solid, (93 mg, 87%), mp 253°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 6.4 Hz, 1H), 7.26 (s, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.08 (s, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.78 (s, 1H), 5.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 173.7, 159.1, 156.2, 145.4, 140.6, 139.9, 136.3, 136.1, 133.9, 133.3, 129.8, 129.6, 129.5, 129.1, 128.9, 128.4, 127.3, 127.3, 126.4, 125.6, 123.7, 117.4, 117.2, 38.4; IR (KBr) νmax/cm−1 1723 (C=O), 1643 (C=O), 1461 (C-O); HRMS (ESI) calculated for $C_{25}H_{16}ClO_3S$ 431.0503 [M + H^+]; found 431.0495.



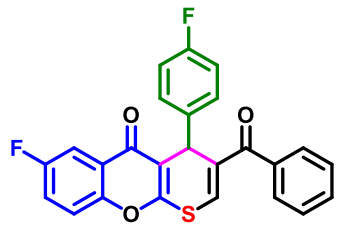
3-benzoyl-4-(4-fluorophenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aae). Yellowish brown solid, (82 mg, 80%), mp 245°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.58 – 7.51 (m, 3H), 7.44 – 7.42 (m, 2H), 7.40 (s, 1H), 7.36 (dd, *J* = 15.4, 7.4 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.13 (s, 1H), 6.87 (td, *J* = 8.5, 1.9 Hz, 1H), 6.08 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 173.7, 162.1 (d, *J* = 246.0 Hz), 158.9, 156.2, 138.0, 137.5, 136.5, 133.9, 132.4, 129.8 (d, J = 8.2 Hz), 129.6, 129.1, 128.6, 126.4, 125.6, 123.7, 117.5, 117.4, 115.6 (d, *J* = 21.5 Hz), 38.1; IR (KBr) νmax/cm−1 1642 (C=O), 1615 (C=O), 1435 (C-O); HRMS (ESI) calculated for $C_{25}H_{16}FO_3S$ 415.0799 [M + H^+]; found 415.0804.



3-benzoyl-4-(4-nitrophenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aaf). Yellowish brown solid, (86 mg, 78%), mp 233°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 4.1 Hz, 1H), 8.14 – 8.11 (m, 2H), 7.74 (d, *J* = 8.9 Hz, 2H), 7.67 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H), 7.56 (d, *J* = 1.4 Hz, 1H), 7.54 (s, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.23 (s, 1H), 6.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 173.6, 156.2, 149.3, 137.2, 135.3, 134.2, 132.6, 131.4, 129.2, 129.1, 128.7, 126.4, 125.8, 124.1, 123.5,117.5, 116.6, 38.9; IR (KBr) νmax/cm−1 1641 (C=O), 1615 (C=O), 1435 (C-O).

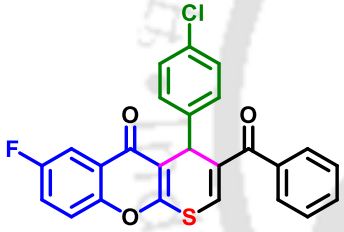


3-benzoyl-7-fluoro-4-(4-fluorophenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4bae).



Yellowish brown solid, (78 mg, 72%), mp 225°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 3.1 Hz, 1H), 7.79 (d, *J* = 3.1 Hz, 1H), 7.59 – 7.57 (m, 2H), 7.56 (s, 1H), 7.46 (d, *J* = 4.1 Hz, 1H), 7.45 (d, *J* = 4.1 Hz, 2H), 7.41 (d, *J* = 3.1 Hz, 1H), 7.39 (d, *J* = 2.8 Hz, 1H), 7.37 (d, *J* = 3.0 Hz, 1H), 6.92 (t, *J* = 8.7 Hz, 2H), 6.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 (d, *J* = 2.2 Hz), 162.2 (d, *J* = 246.0 Hz), 160.8, 158.8, 157.4, 152.6 (d, J = 1.8 Hz), 137.0 (d, *J* = 3.0 Hz), 129.9 (d, *J* = 8.1 Hz), 129.4, 128.9, 128.3, 124.8 (d, *J* = 7.4 Hz), 122.2 (d, *J* = 25.6 Hz), 119.6 (d, *J* = 8.1 Hz), 118.1, 115.5 (d, *J* = 21.5 Hz), 111.6 (d, *J* = 24.1 Hz), 36.7; IR (KBr) νmax/cm−1 1643 (C=O), 1617 (C=O), 1483 (C-O).

3-benzoyl-4-(4-chlorophenyl)-7-fluoro-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4bad).

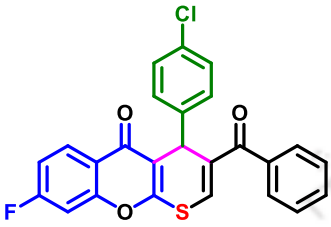


Yellowish brown solid, (88 mg, 78%), mp 202°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.1, 3.0 Hz, 1H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.53 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 4.0 Hz, 1H), 7.36 (td, *J* = 9.3, 8.4, 3.0 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.11 (s, 1H), 6.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 172.8, 160.5, 159.3, 152.2, 140.2, 137.2, 136.0, 133.3, 132.3, 129.6, 129.4, 129.0, 128.8, 128.5, 124.7, 122.0, 121.8, 119.4, 119.4, 116.6, 111.4, 111.2, 38.2; IR (KBr) νmax/cm−1 1644 (C=O), 1617 (C=O), 1483 (C-O); HRMS (ESI) calculated for $C_{25}H_{15}ClFO_3S$ 449.0409 [M + H^+]; found 449.0409.

3-benzoyl-8-fluoro-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4cag). Yellowish brown solid, (86 mg, 83%), mp 215°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 – 8.14 (m, 1H), 7.56 (s, 1H), 7.55 (s, 2H), 7.53 (s, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.28 (s, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 4.3 Hz, 2H), 6.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ192.7, 172.7, 165.50 (d, *J* = 255.0 Hz), 159.2, 156.92 (d, *J* = 13.4 Hz), 141.7, 137.4, 136.6, 132.2, 129.0, 129.0, 128.8 (d, *J* = 10.6 Hz), 128.7, 128.4, 128.0, 127.4, 120.4, 117.5, 114.10 (d, *J* = 22.6 Hz), 104.20 (d, *J* = 25.7 Hz), 38.6; IR (KBr)

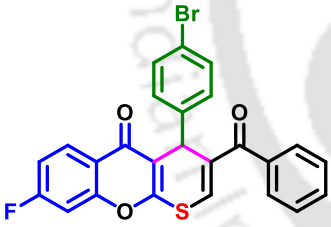
νmax/cm−1; 1727 (C=O), 1649 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{25}H_{16}FO_3S$ 415.0799 [M + H^+]; found 415.0799.

3-benzoyl-4-(4-chlorophenyl)-8-fluoro-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4cad).



Yellowish brown solid, (89 mg, 79%), mp 180°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.14 (m, 1H), 7.57 – 7.53 (m, 3H), 7.48 (d, *J* = 6.5 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.24 (s, 1H), 7.22 (s, 1H), 7.10 (d, *J* = 1.9 Hz, 2H), 7.08 (s, 1H), 6.00 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 172.8, 165.69 (d, *J* = 256.0 Hz), 159.2, 157.03 (d, *J* = 13.3 Hz), 140.4, 137.3, 136.1, 133.4, 132.5, 129.7, 129.6, 129.1, 129.0 128.9 (d, *J* = 8.9 Hz), 128.6, 120.5 (d, *J* = 2.4 Hz),117.3, 114.38 (d, *J* = 22.7 Hz), 104.39 (d, *J* = 25.7 Hz), 38.2; IR (KBr) νmax/cm−1 1723 (C=O), 1601, 1406 (C-O); HRMS (ESI) calculated for $C_{25}H_{15}ClFO_3S$ 449.0409 [M + H^+]; found 449.0409.

3-benzoyl-4-(4-bromophenyl)-8-fluoro-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4cac).



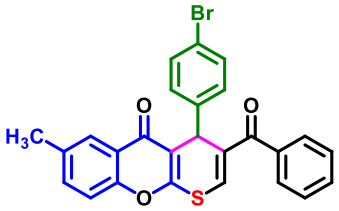
Yellowish brown solid, (105 mg, 85%), mp 220°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (t, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.53 (d, *J* = 11.1 Hz, 2H), 7.44 (s, 2H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.42 (s, 1H), 7.39 (d, *J* = 6.1 Hz, 2H), 7.10 (d, *J* = 7.4 Hz, 3H), 5.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 172.8, 165.70 (d, *J* = 256.0 Hz), 159.2, 157.04 (d, *J* = 13.3 Hz), 140.9, 137.3, 136.0, 132.5, 131.9, 129.9, 129.8, 129.1, 129.00 (d, *J* = 10.8 Hz), 128.6, 121.6, 120.51 (d, *J* = 2.4 Hz), 117.2, 114.40 (d, *J* = 22.8.Hz), δ 104.40(d,*J*=25.8 Hz), 38; IR (KBr) νmax/cm−1 1717 (C=O), 1604 (C=O), 1460 (C-O); HRMS (ESI) calculated for $C_{25}H_{15}BrFO_3S$ 492.9904 [M + H^+]; found 492.9903

3-benzoyl-7-chloro-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4dag). Yellowish brown solid, (85 mg, 80%), mp 215°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 4.6, 2.6 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.57 (t, *J* = 3.1 Hz, 2H), 7.55 (d, *J* = 5.8 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.43 – 7.38 (m, 2H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.24 (s, 1H), 7.19 (q, *J* = 8.1, 7.6 Hz, 1H), 7.07 (s, 1H), 6.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 172.6, 154.5, 141.7, 137.5, 136.7, 133.9, 132.4, 131.4, 129.1, 129.0, 128.8, 128.7, 128.6, 128.2, 128.1, 127.6, 126.1, 125.9, 119.1, 38.8; IR (KBr) νmax/cm−1 1726 (C=O), 1604 (C=O), 1456 (C-O); HRMS (ESI) calculated for $C_{25}H_{16}ClO_3S$ 431.0503 [M + H^+]; found 431.0497.

3-benzoyl-7-methyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4eag). Yellowish brown solid, (77 mg, 75%), mp 235°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.57 (s, 1H), 7.56 (s, 2H), 7.53 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.41 (q, *J* = 8.4, 7.6 Hz, 3H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.08 (s, 1H), 6.07 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 173.9, 158.8, 154.5, 142.1, 137.7, 136.7, 135.4, 134.9, 132.2, 129.6, 129.1, 128.7, 128.5, 128.1, 127.4, 125.8, 123.4, 117.4, 117.1, 38.7, 21.0; IR (KBr) νmax/cm−1 1721 (C=O), 1615 (C=O), 1460 (C-O); HRMS (ESI) calculated for $C_{26}H_{19}O_3S$ 411.1049 [M + H^+]; found 411.1026.

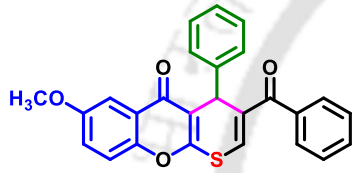
3-benzoyl-4-(4-chlorophenyl)-7-methyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4ead). Yellowish brown solid, (94 mg, 84%), mp 229°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.57 – 7.51 (m, 3H), 7.50 (s, 1H), 7.48 (s, 1H), 7.45 – 7.39 (m, 3H), 7.30 (dd, *J* = 13.5, 8.6 Hz, 1H), 7.20 (dd, *J* = 16.1, 8.5 Hz, 2H), 7.11 (s, 1H), 6.02 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 173.8, 158.7, 154.5, 140.7, 137.4, 136.1, 135.6, 135.1, 133.1, 132.3, 130.2, 129.5, 129.1, 128.8, 128.6, 125.8, 125.7, 123.2, 117.1, 117.0, 21.0; IR (KBr) νmax/cm−1 1715 (C=O), 1613 (C=O), 1456 (C-O); HRMS (ESI) calculated for $C_{26}H_{18}ClO_3S$ 445.0660 [M + H^+]; found 445.0664.

3-benzoyl-4-(4-bromophenyl)-7-methyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4eac).



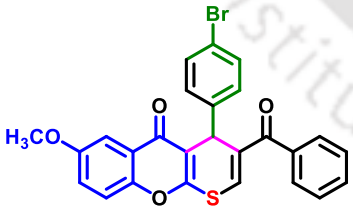
Yellowish brown solid, (101 mg, 83%), mp 220°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.57 – 7.50 (m, 3H), 7.44 (d, *J* = 2.0 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 3H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.12 (s, 1H), 6.01 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 173.8, 158.7, 154.5, 141.2, 137.4, 136.0, 135.6, 135.2, 135.1, 132.3, 131.8, 131.6, 130.3, 130.0, 129.9, 129.1, 128.6, 125.8, 125.7, 123.2, 121.4, 117.1, 116.9, 38.3, 21.0; IR (KBr) νmax/cm−1 1717 (C=O),1603 (C=O), 1462 (C-O).

3-benzoyl-7-methoxy-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4hag).



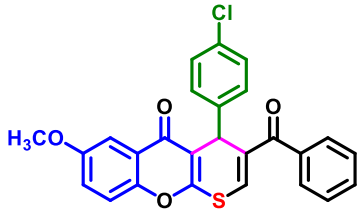
Yellowish brown solid, (91 mg, 86%), mp 213°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.46 (s, 2H), 7.44 – 7.42 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.31 (s, 2H), 7.23 (d, J = 9.1 Hz, 1H), 7.17 (s, 2H), 7.11 (dt, *J* = 7.8, 2.4 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.98 (s, 1H), 5.97 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 173.7, 158.7, 157.1, 151.1, 137.7, 132.2, 129.5, 129.2, 128.8, 128.5, 128.2, 127.4, 123.7, 118.8, 116.9, 105.7, 56.06, 38.9; IR (KBr) νmax/cm−1 1715 (C=O), 1649 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{26}H_{19}O_4S$ 427.0999 [M + H^+]; found 427.0999.

3-benzoyl-4-(4-bromophenyl)-7-methoxy-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4hac).



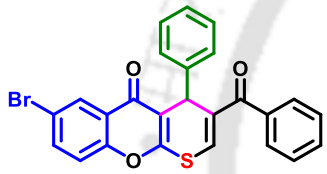
Yellowish brown solid, (102 mg, 81%), mp 185°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 2H), 7.50 (d, *J* = 3.4 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 3H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.21 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.11 (s, 1H), 6.01 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.6, 173.6, 158.6, 157.1, 151.0, 141.2, 137.4, 136.0, 132.3, 131.8, 130.2, 129.9, 129.0, 128.6, 124.2, 123.8, 121.4, 118.8, 116.4, 105.6, 56.0, 38.4; IR (KBr) νmax/cm−1 1727 (C=O), 1601 (C=O), 1463 (C-O); HRMS (ESI) calculated for $C_{26}H_{18}BrO_4S$ 505.0104 [M + H^+]; found 505.0082.

3-benzoyl-4-(4-chlorophenyl)-7-methoxy-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4had).



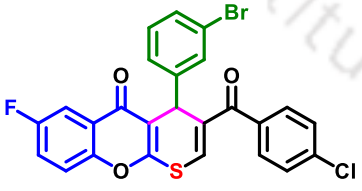
Yellowish brown solid, (92 mg, 80%), mp 229°; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 14.7 Hz, 3H), 7.48 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 9.1 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 3H), 7.11 (s, 1H), 6.02 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.5, 173.5, 158.5, 157.0, 151.0, 140.6, 137.4, 136.0, 133.1, 132.2, 130.0, 129.5, 129.0, 128.8, 128.5, 124.1, 123.7, 118.7, 116.4, 105.5, 55.9, 38.2; IR (KBr) νmax/cm−1 1723 (C=O), 1601 (C=O), 1459 (C-O); HRMS (ESI) calculated for $C_{26}H_{18}ClO_4S$ 461.0609 [M + H^+]; found 461.0605.

3-benzoyl-7-bromo-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4iag).

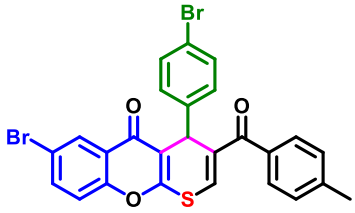


Yellowish brown solid, (93mg, 78%), mp 237°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.25 (m, 1H), 7.70 (ddd, *J* = 11.5, 8.9, 2.5 Hz, 2H), 7.56 (s, 1H), 7.54 (s, 2H), 7.52 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.24 (d, *J* = 3.8 Hz, 1H), 7.17 (t, *J* = 6.6 Hz, 1H), 7.07 (s, 1H), 6.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 172.4, 159.5, 154.9, 141.7, 137.5, 136.9, 136.7, 136.6, 132.3, 129.1, 128.8, 128.5, 128.1, 127.6, 125.0, 124.8, 119.3, 118.8, 117.7, 38.7; IR (KBr) νmax/cm−1 1717 (C=O), 1601 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{25}H_{16}BrO_3S$ 474.9998 [M + H^+]; found 474.9973.

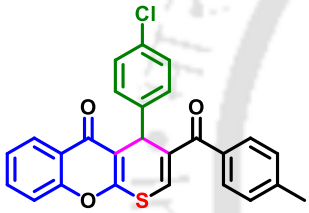
4-(3-bromophenyl)-3-(4-chlorobenzoyl)-7-fluoro-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (5dac).



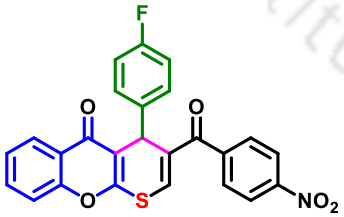
Yellowish brown solid, (114 mg, 87%), mp 245°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.1, 3.0 Hz, 1H), 7.61 (t, *J* = 1.9 Hz, 1H), 7.50 (t, *J* = 8.8 Hz, 3H), 7.44 – 7.37 (m, 4H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.16 – 7.10 (m, 2H), 5.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 191.2, 172.9 (d, *J* = 2.4 Hz), 160.9, 159.4, 158.4, 152.4 (d, *J* = 1.8 Hz), 143.8, 139.0, 135.6 (d, *J* = 21.7 Hz), 130.9, 130.8, 130.5, 130.4, 130.2, 129.0, 127.2, 124.8 (d, *J* = 7.6 Hz), 122.9, 122.1 (d, *J* = 25.6 Hz), 119.6 (d, *J* = 8.1 Hz), 116.4, 111.4 (d, *J* = 24.0 Hz), 38.5; IR (KBr) νmax/cm−1 1726 (C=O), 1604 (C=O), 1465 (C-O); HRMS (ESI) calculated for $C_{25}H_{14}BrClFO_3S$ 526.9514 [M + H^+]; found 526.9509.

7-bromo-4-(3-bromophenyl)-3-(4-methyl benzoyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (5gbc). 

Yellowish brown solid, (117 mg, 83%), mp 255°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 2.4 Hz, 1H), 7.71 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.38 (s, 2H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.07 (s, 1H), 5.97 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 172.4, 159.6, 154.9, 143.4, 140.8, 136.8, 136.1, 134.5, 131.9, 129.9, 129.3, 129.3, 129.0, 128.7, 124.9, 121.5, 118.9, 117.3, 38.5, 21.7; IR (KBr) νmax/cm−1 1646 (C=O), 1607 (C=O), 1464 (C-O); HRMS (ESI) calculated for $C_{26}H_{17}Br_2O_3S$ 566.9260 [M + H^+]; found 566.9260.

4-(4-chlorophenyl)-3-(4-methylbenzoyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (5abd). 

Yellowish brown solid, (90mg, 81%), mp 230°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.62 (m, 1H), 7.49 (s, 2H), 7.47 (s, 1H), 7.41 – 7.35 (m, 3H), 7.22 (d, *J* = 8.4 Hz, 4H), 7.08 (s, 1H), 6.01 (d, *J* = 1.8 Hz, 1H), 2.39 (d, *J* = 1.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 173.7, 159.2, 156.2, 143.3, 140.6, 136.2, 134.6, 133.9, 133.2, 129.6, 129.4, 129.3, 128.9, 128.9, 126.4, 125.6, 123.6, 117.4, 117.2, 38.5, 21.7; IR (KBr) νmax/cm−1 1649 (C=O), 1602 (C=O), 1463 (C-O); HRMS (ESI) calculated for $C_{26}H_{18}ClO_3S$ 455.0660 [M + H^+]; found 455.0664.

4-(4-fluorophenyl)-3-(4-nitrobenzoyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (5ace). 

Yellowish brown solid, (87mg, 76%), mp 240°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.69 – 7.65 (m, 3H), 7.55 – 7.50 (m, 2H), 7.43 – 7.38 (m, 2H), 7.11 (s, 1H), 6.96 (t, *J* = 8.8 Hz, 2H), 6.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 173.5, 163.1, 161.1, 158.1, 157.1, 156.3, 156.1, 149.6, 142.8, 136.0, 133.9, 132.0, 129.7, 129.7, 126.3, 125.6, 123.7, 123.5, 117.3, 117.2, 115.7, 115.5, 37.6; IR (KBr) νmax/cm−1 1726 (C=O), 1649 (C=O), 1460 (C-O); HRMS (ESI) calculated for $C_{25}H_{15}FNO_5S$ 460.0649 [M + H^+]; found 460.0636.

3-benzoyl-7-fluoro-4-(*p*-tolyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (6cab). Yellowish brown solid, mp 255°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.2, 3.0 Hz, 1H), 7.57 (d, *J* = 6.6 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 3.1 Hz, 2H), 7.41 (d, *J* = 3.1 Hz, 2H), 7.40 – 7.38 (m, 1H), 7.37 – 7.31 (m, 1H), 7.07 (d, *J* = 8.2 Hz, 3H), 6.01 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 173.0, 159.4, 158.6, 152.4, 138.9, 137.6, 137.2, 132.3, 129.5, 129.2, 128.9, 128.5, 128.0, 125.0, 121.8 (d, *J* = 25.5 Hz), 119.4 (d, *J* = 8.0 Hz), 117.2, 111.4 (d, *J* = 24.0 Hz), 38.4, 21.2; IR (KBr) νmax/cm−1 1721 (C=O)1649 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{26}H_{18}FO_3S$ 429.0955 [M + H^+]; found 429.0956.

13-(*p*-tolyl)-12*H*,13*H*,14*H*-thiopyrano[2,3-*b*:6,5-*b*']dichromene-12,14-dione (9aab). White solid, (51 mg, 70%), mp 280°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.9 Hz, 2H), 7.64 (t, J = 6.9 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.15 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 157.1, 156.4, 138.6, 137.1, 133.9, 129.3, 128.1, 126.5, 125.6, 123.6, 118.9, 117.4, 36.9, 21.1; IR (KBr) νmax/cm−1 3059 (C=C–H), 2920 (C–H), 1650 (C=O); HRMS (ESI) calculated for $C_{26}H_{17}O_4S$ + 425.0848 [M + H^+]; found 425.0843.

2-phenyl-2*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (9aaa). Yellow solid, (37 mg, 65%), mp 160°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 3H), 7.35 (d, *J* = 3.7 Hz, 2H), 7.32 (d, *J* = 12.0 Hz, 2H), 7.14 (d, *J* = 10.2 Hz, 1H), 5.80 (dd, *J* = 10.1, 5.5 Hz, 1H), 5.14 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 164.3, 156.3, 140.2, 133.4, 129.1, 128.6, 127.9, 126.5, 125.4, 123.6, 122.1, 118.7, 117.6, 115.1, 46.6; IR(KBr) νmax/cm−1 2923, 1600, HRMS (ESI) calculated for $C_{18}H_{13}O_2S$ 293.0636 [M + H^+]; found 293.0637.

3.5d. X-ray Structure of Compounds 4bad

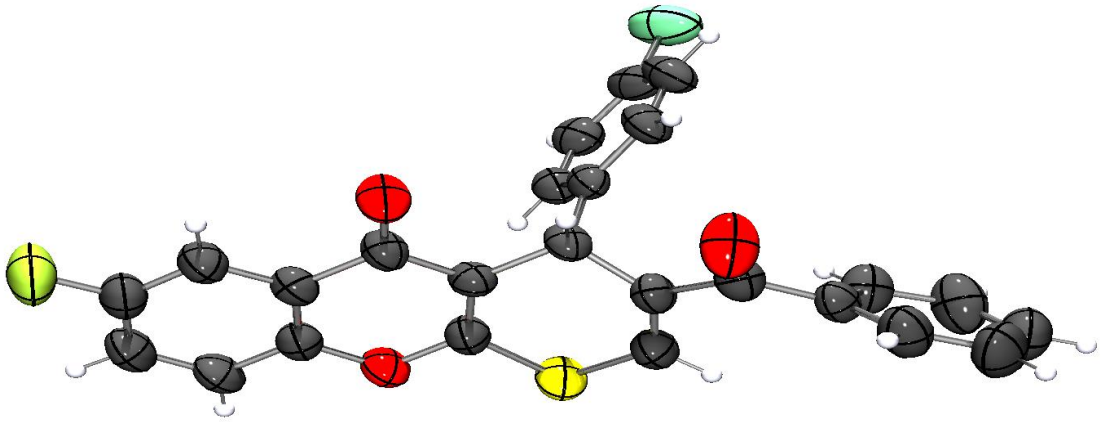


Figure 3. ORTEP diagram of compound **4bad**

Table 4. Crystal data and structure refinement for compound 4bad

Entry	Identification code	Compound (4bad)
1	Empirical formula	$C_{25}H_{14}ClFO_3S$
2	Formula weight	448.87
3	Temperature	295K
4	Wavelength	0.71073
5	Radiation type	Mo K\a
6	Radiation source	Fine-focus sealed tube
7	Crystal system	Orthorhombic
8	Space group	P c a 2_1
9	Cell length	a 38.315(10)
		b5.8431(16)
		c9.177(2)
10	Cell Angle	α90
		β90
		δ90
11	Cell Volume	2054.6 (9)
12	Density	1.451
13	Completeness to theta	99.7
14	Absorption correction	multi-scan
15	Refinement method	Full-matrix least-squares on F2
16	Reflection number	43221
17	R(reflections)	0.0480(2444)
18	wR2(reflections)	0.1068(3601)
19	gooF (S)	1.120
20	Theta range	25.047
21	Cell formula units Z	4
22	CCDC no	2412225

Figure 4. ^{1}H NMR spectra of 3-benzoyl-4-(4-methoxyphenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aa)

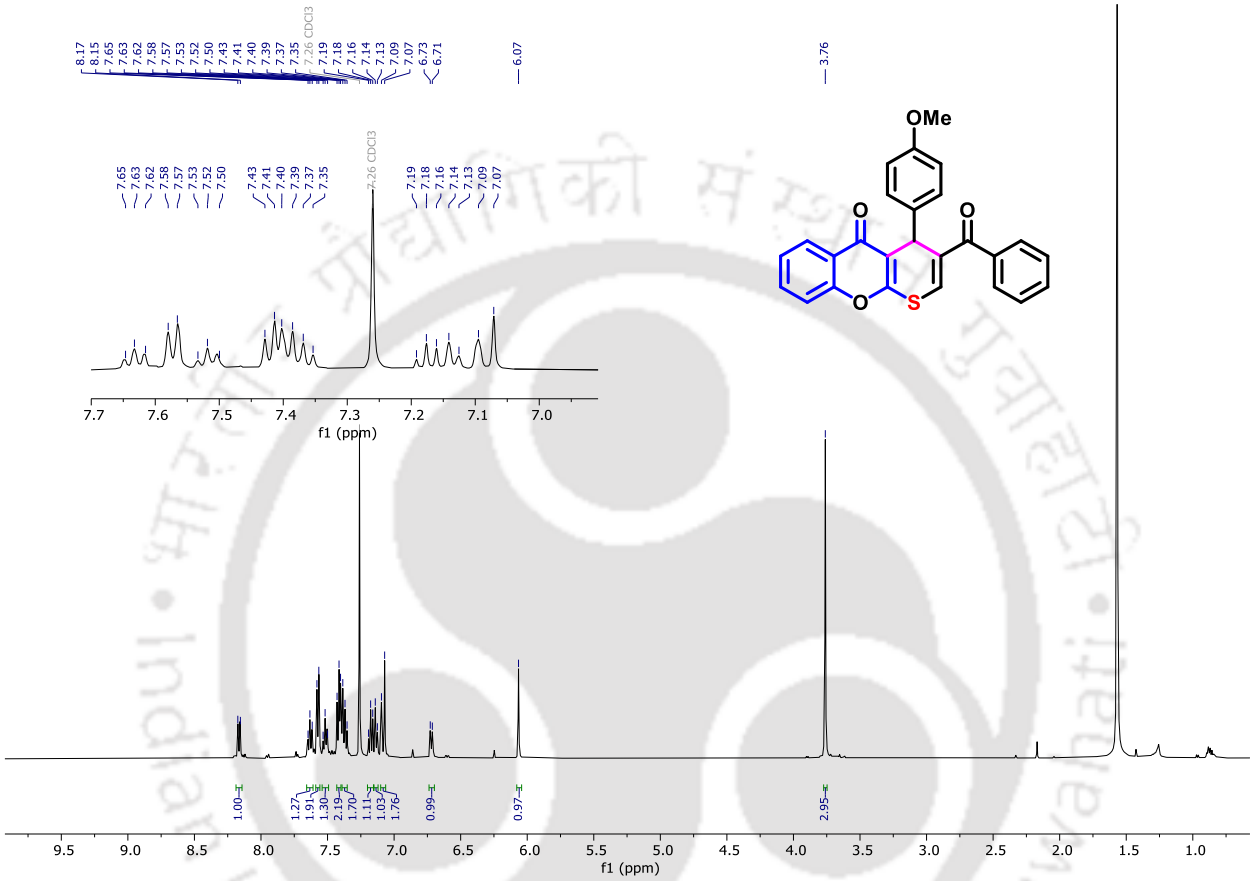


Figure 5. ^{13}C NMR spectra of 3-benzoyl-4-(4-methoxyphenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aa)

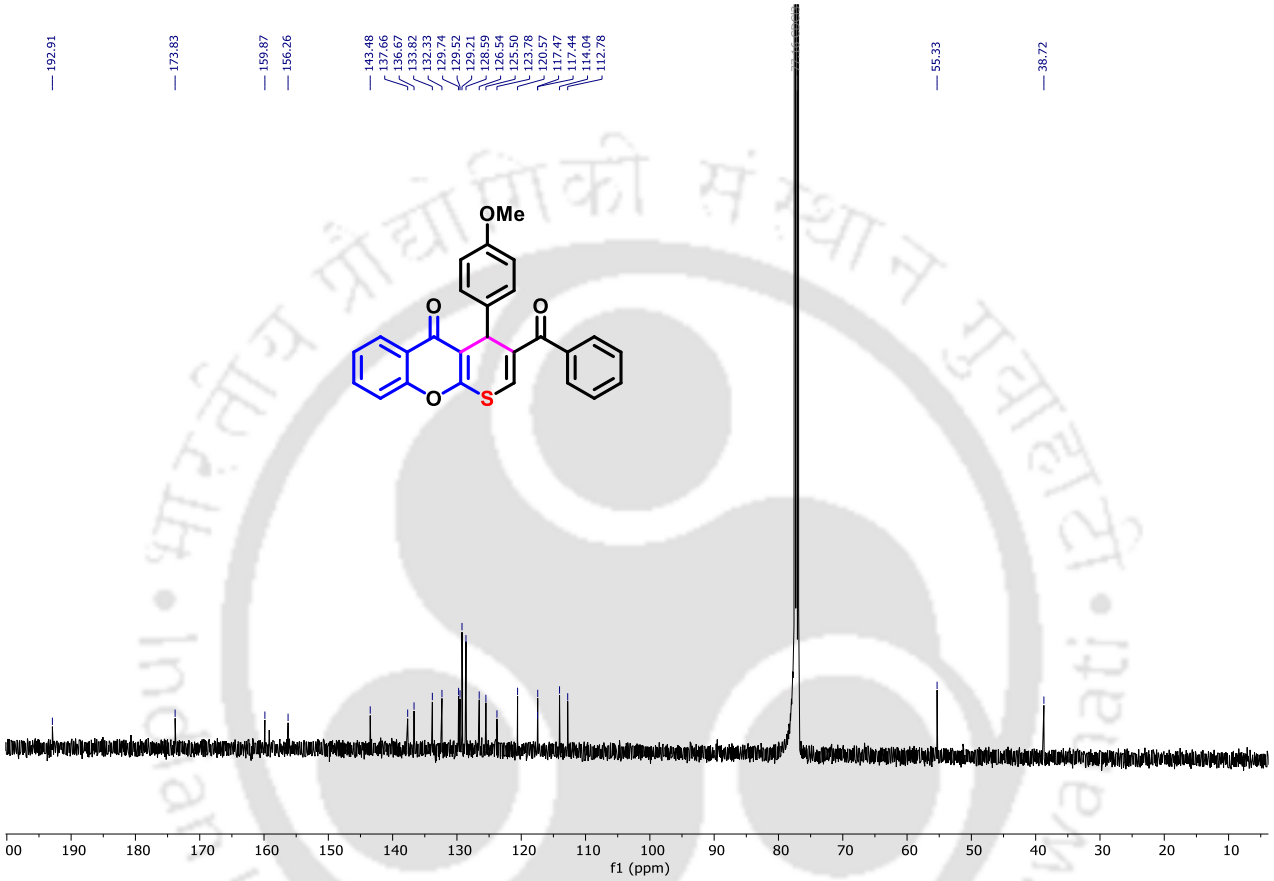


Figure 6. HRMS spectra of 3-benzoyl-4-(4-methoxyphenyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (4aa)

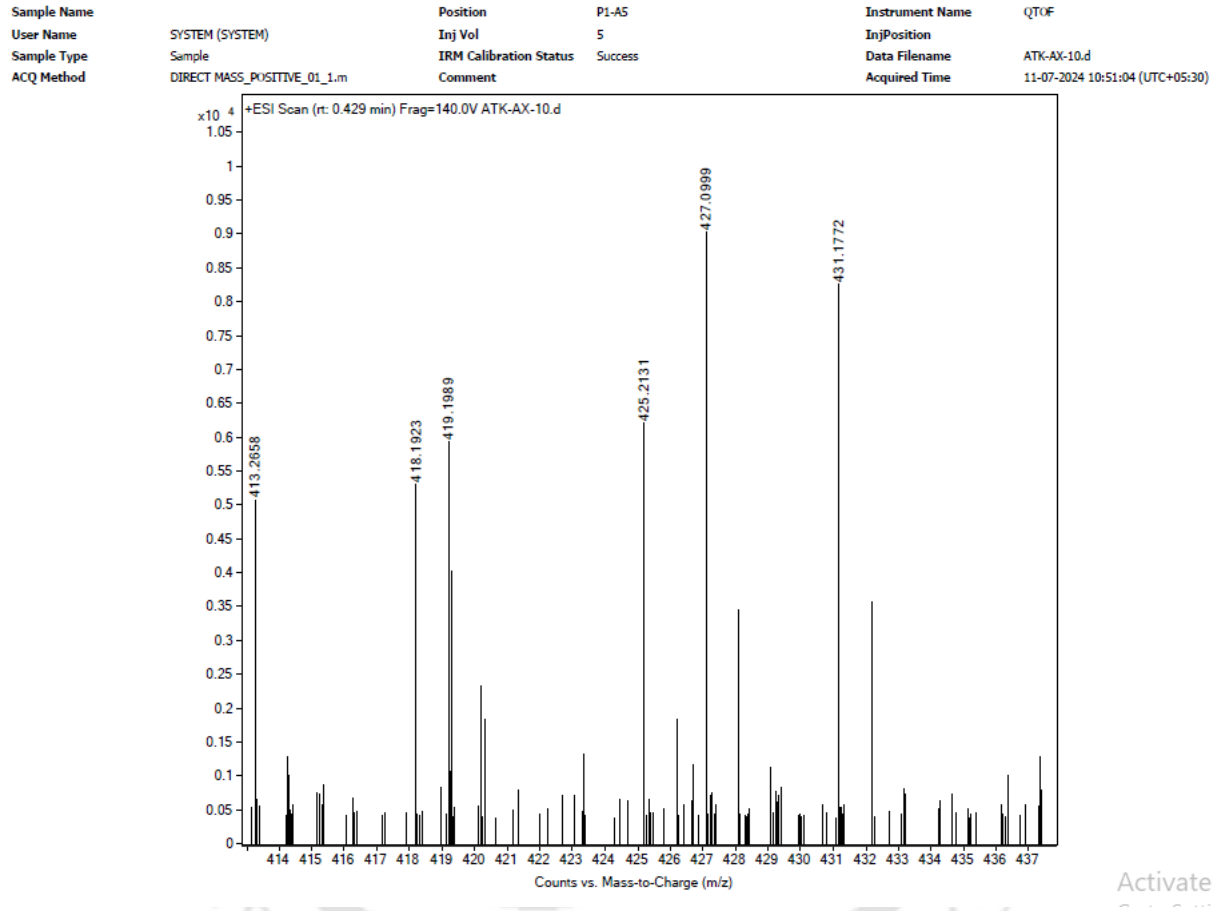


Figure 7. ^{1}H NMR spectra of 4-(3-bromophenyl)-3-(4-chlorobenzoyl)-7-fluoro-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (5dac)

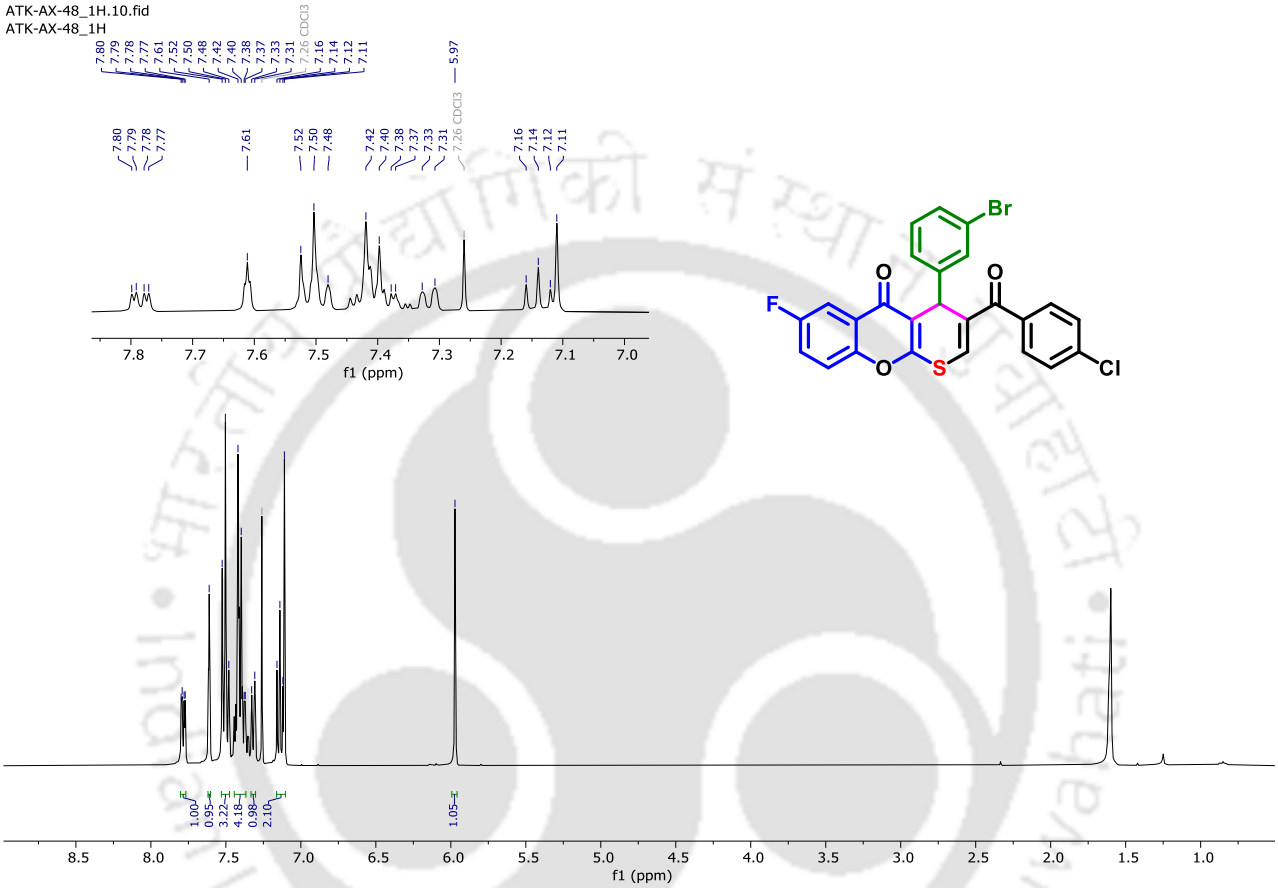


Figure 8. ^{13}C NMR spectra of 4-(3-bromophenyl)-3-(4-chlorobenzoyl)-7-fluoro-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (5dac)

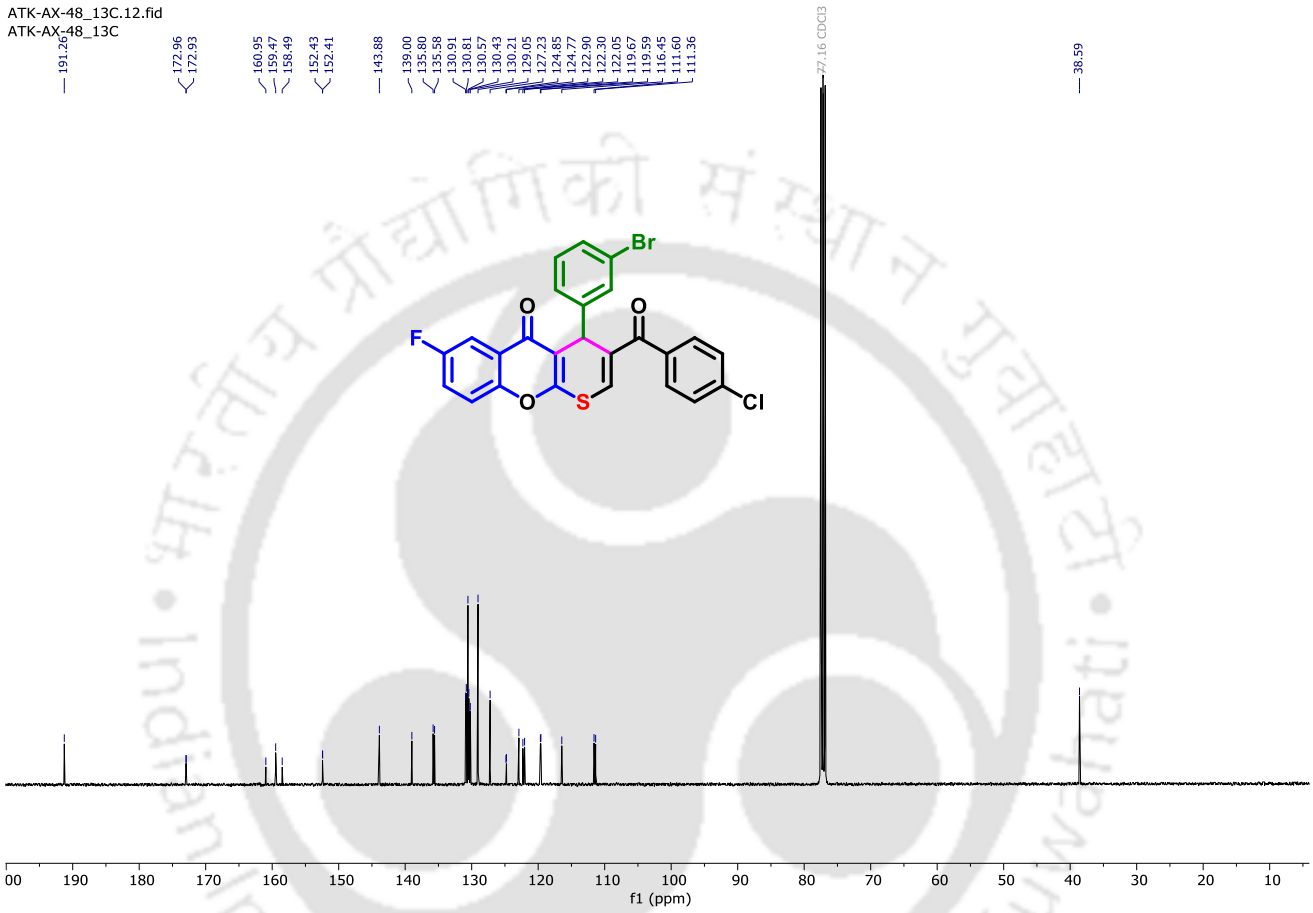


Figure 9. HRMS spectra of 4-(3-bromophenyl)-3-(4-chlorobenzoyl)-7-fluoro-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (5dac)

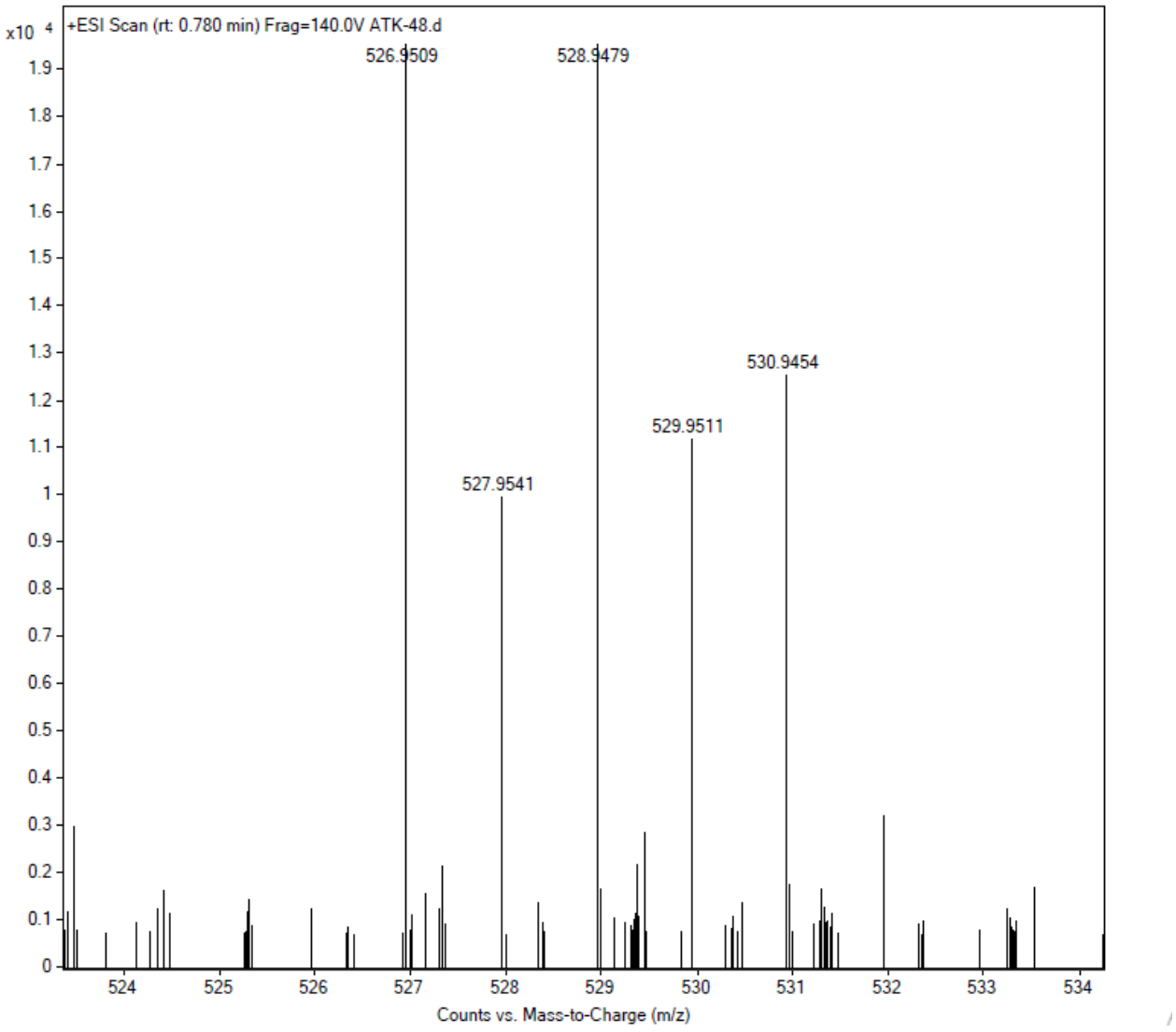


Figure 10. ^{1}H NMR spectra of 3-benzoyl-7-fluoro-4-(*p*-tolyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (6cab)

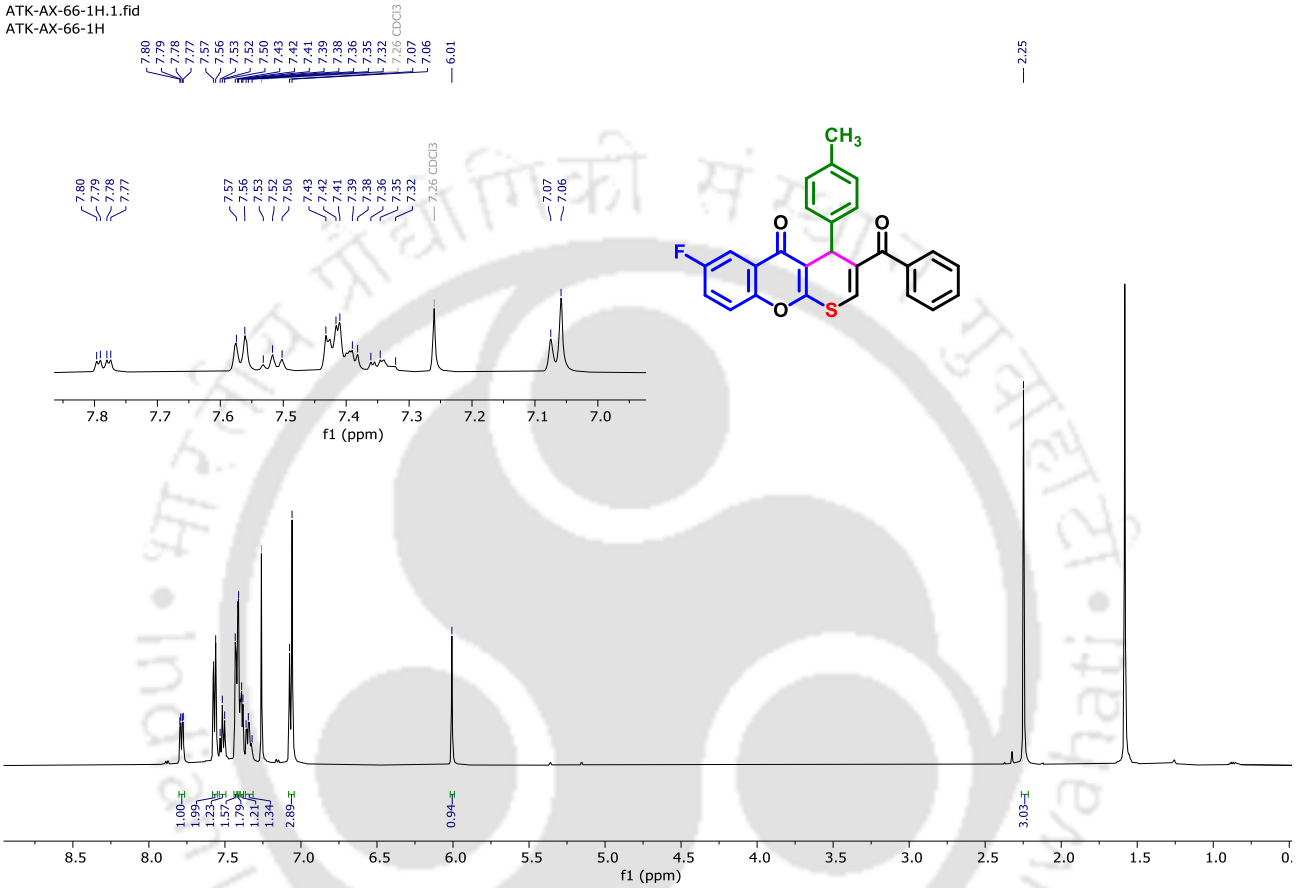


Figure 11. ^{13}C NMR spectra of 3-benzoyl-7-fluoro-4-(*p*-tolyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (6cab)

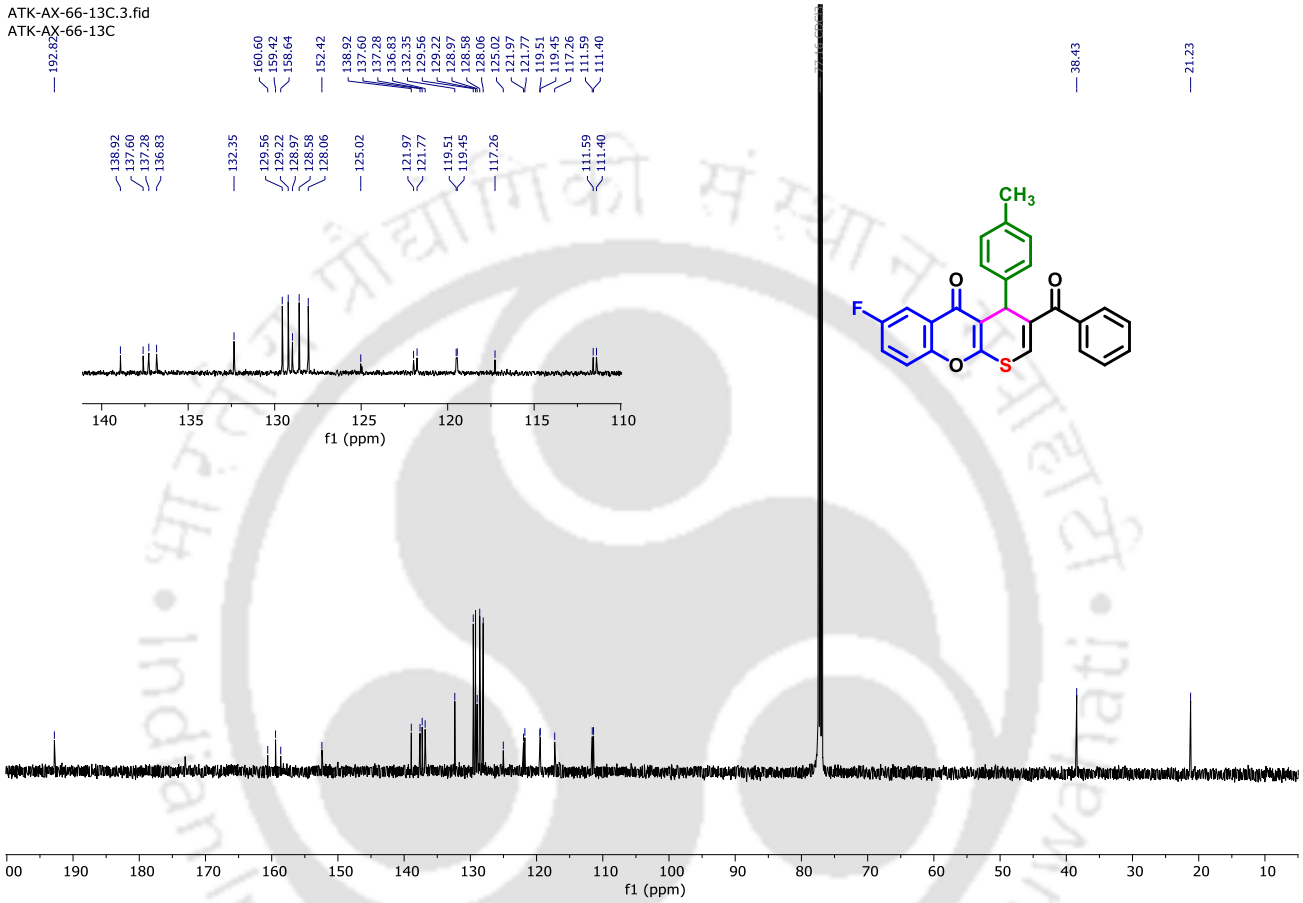


Figure 12. HMRS spectra of 3-benzoyl-7-fluoro-4-(*p*-tolyl)-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (6cab)

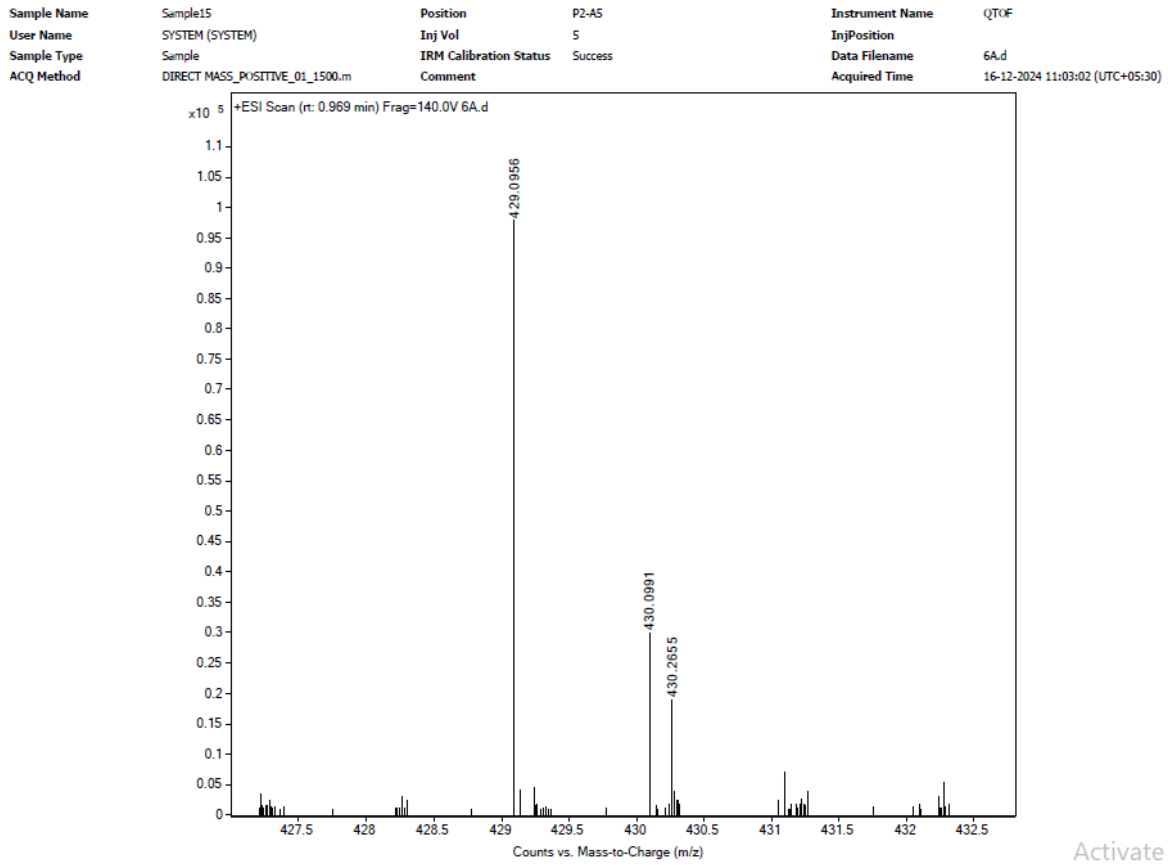


Figure 13. ^{1}H NMR spectra of 13-(*p*-tolyl)-12*H*,13*H*,14*H*-thiopyrano[2,3-*b*:6,5-*b*']dichromene-12,14-dione (9aab)

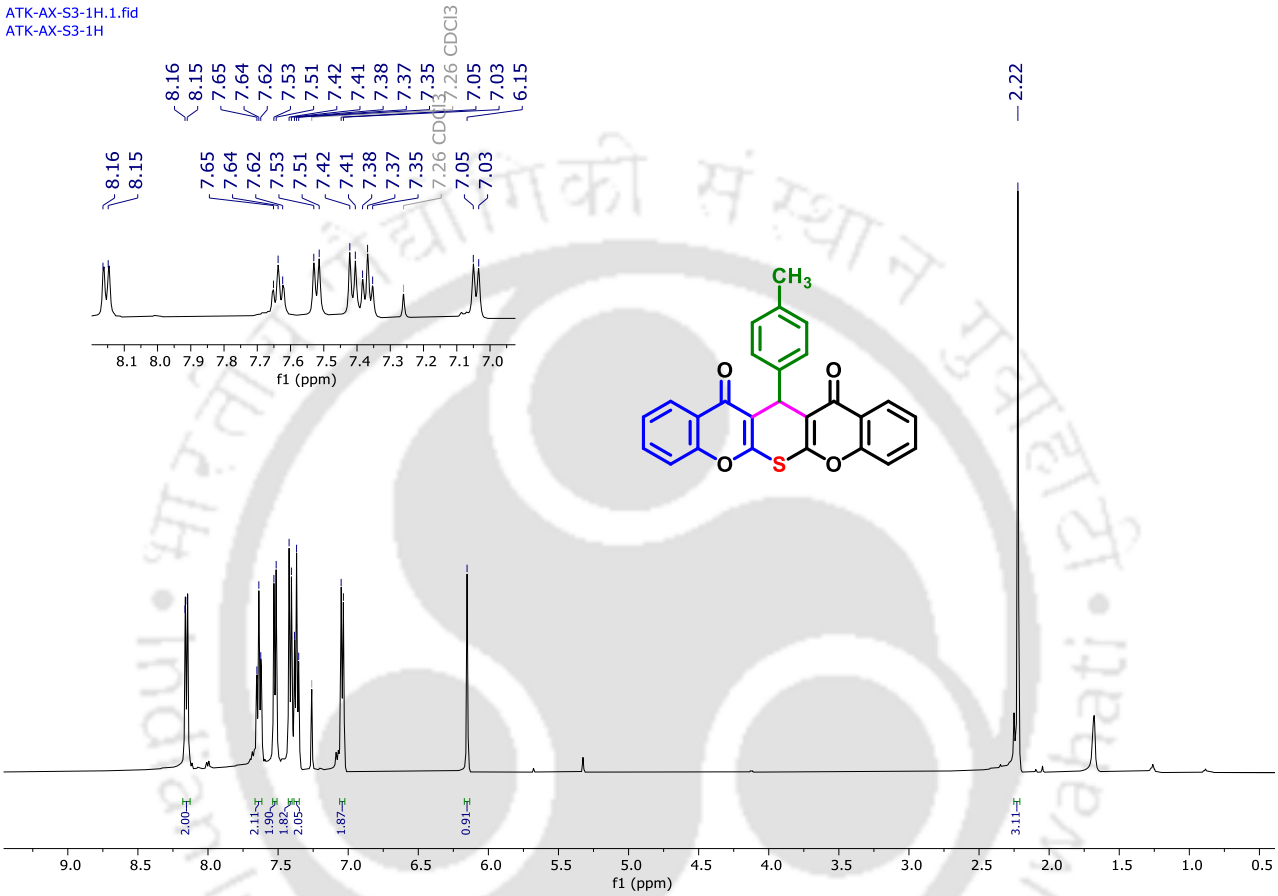


Figure 14. ^{13}C NMR spectra of 13-(*p*-tolyl)-12*H*,13*H*,14*H*-thiopyrano[2,3-*b*:6,5-*b*']dichromene-12,14-dione (9aab)

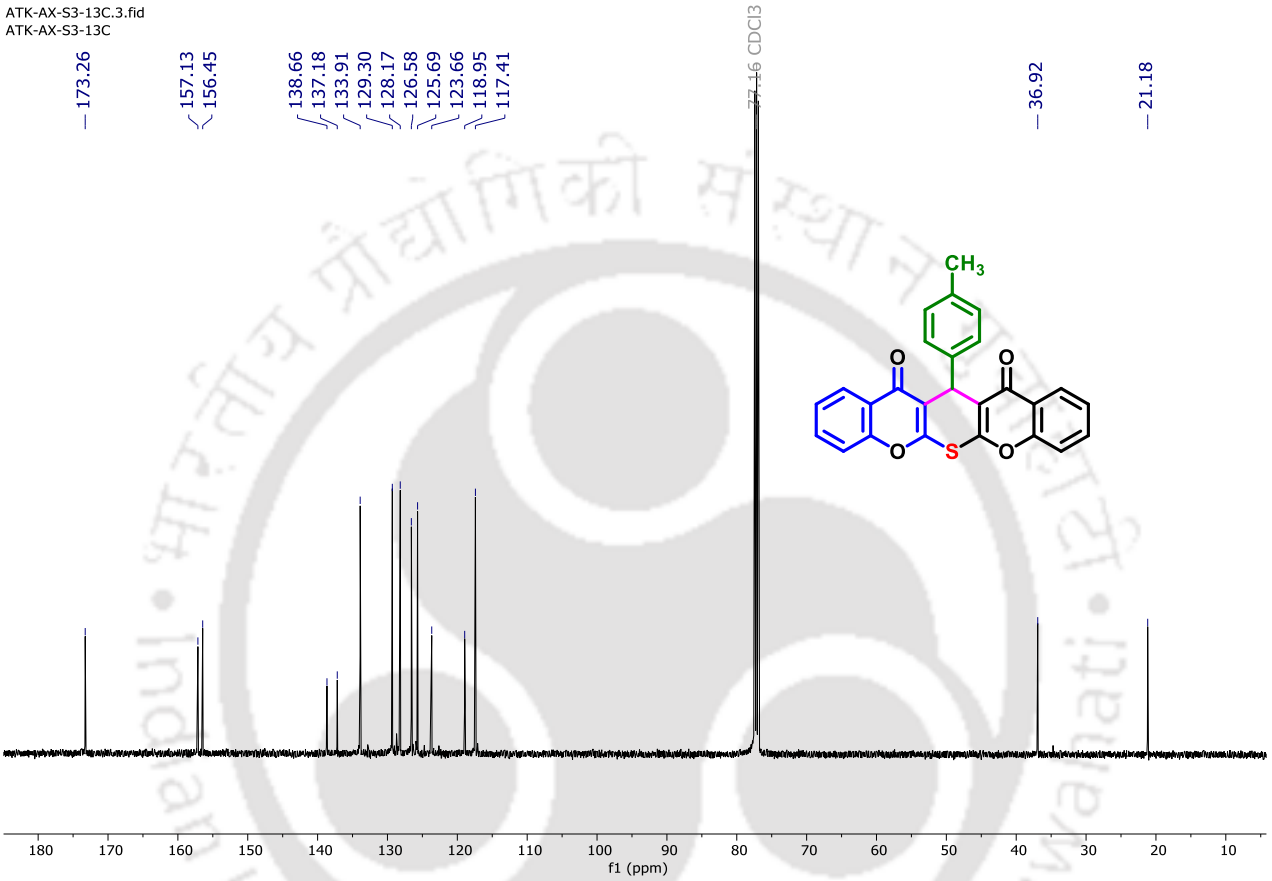


Figure 15. HRMS spectra of 13-(*p*-tolyl)-12*H*,13*H*,14*H*-thiopyrano[2,3-*b*:6,5-*b*']dichromene-12,14-dione (9aab)

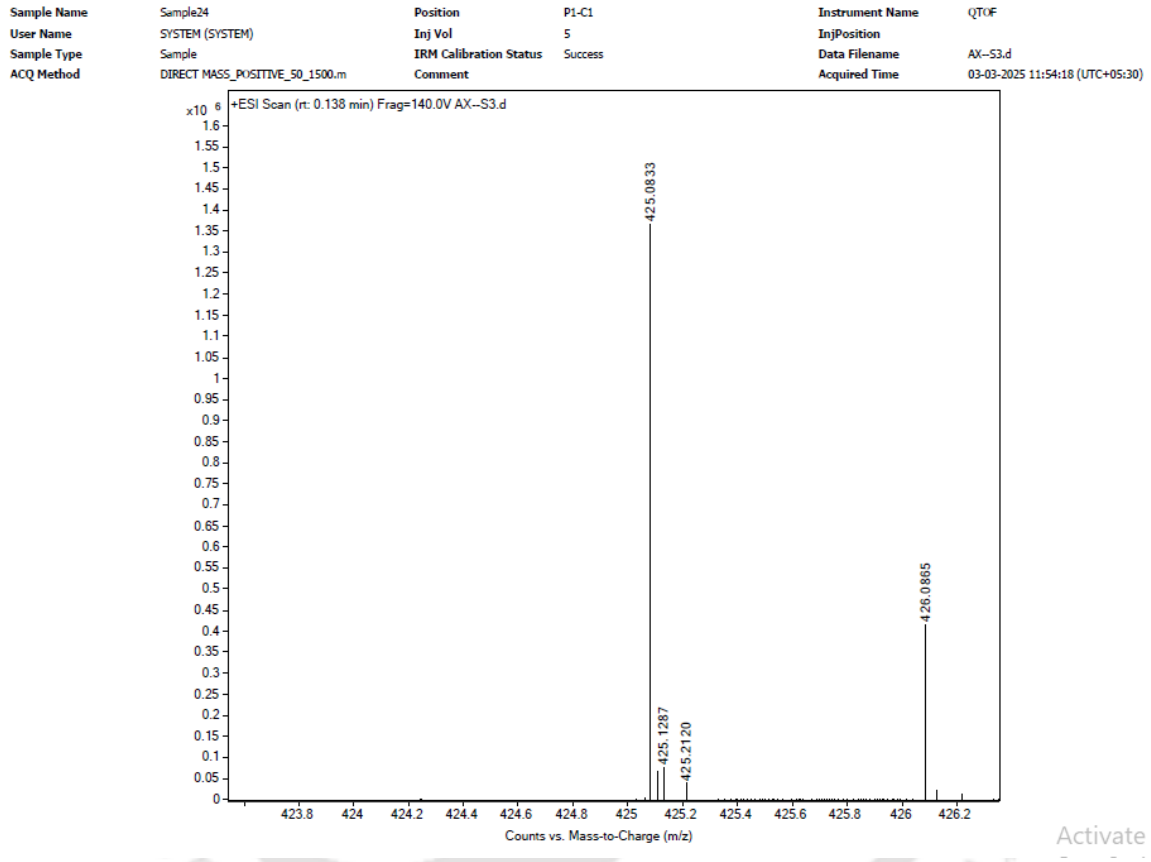


Figure 16. ^{1}H NMR spectra of 2-phenyl-2*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (9aaa)

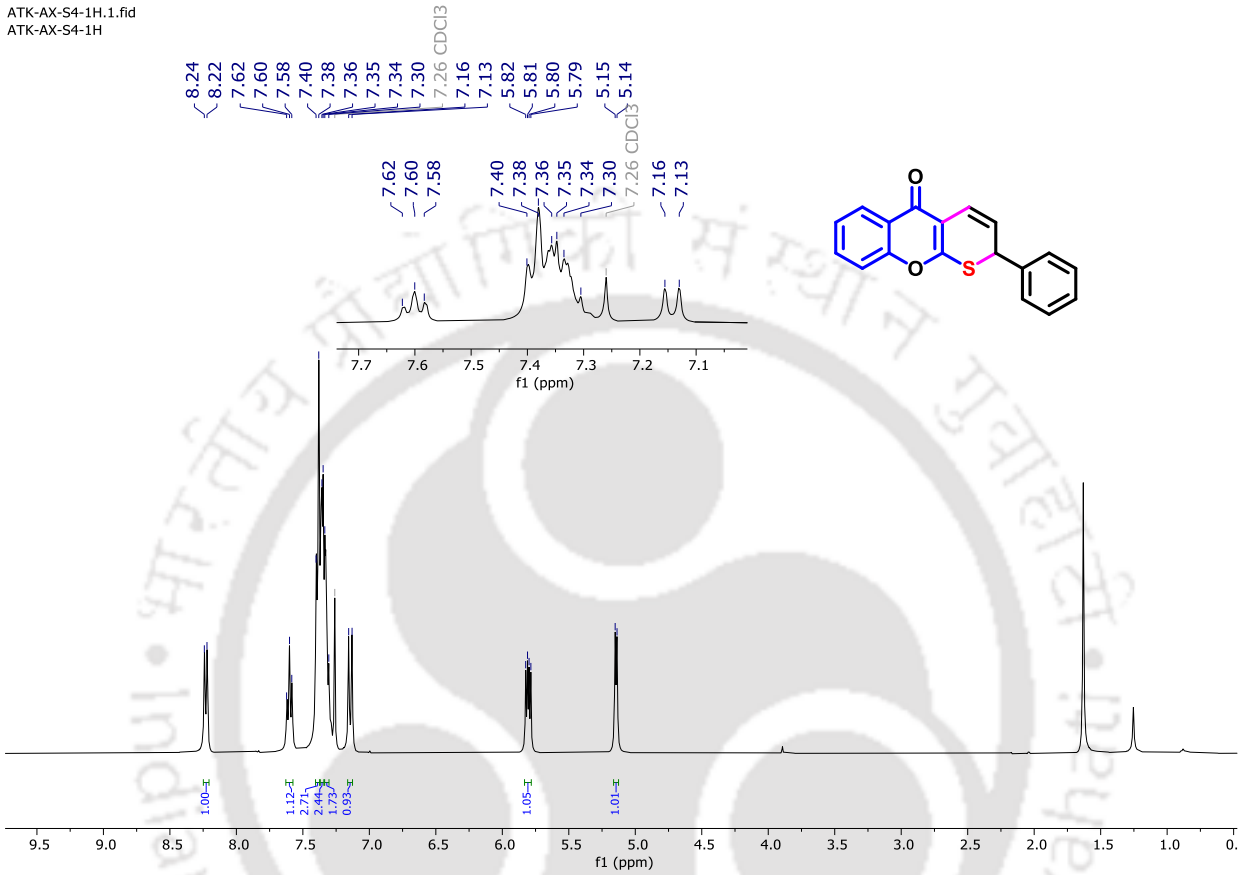


Figure 17. ^{13}C NMR spectra of 2-phenyl-2*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (9aaa)

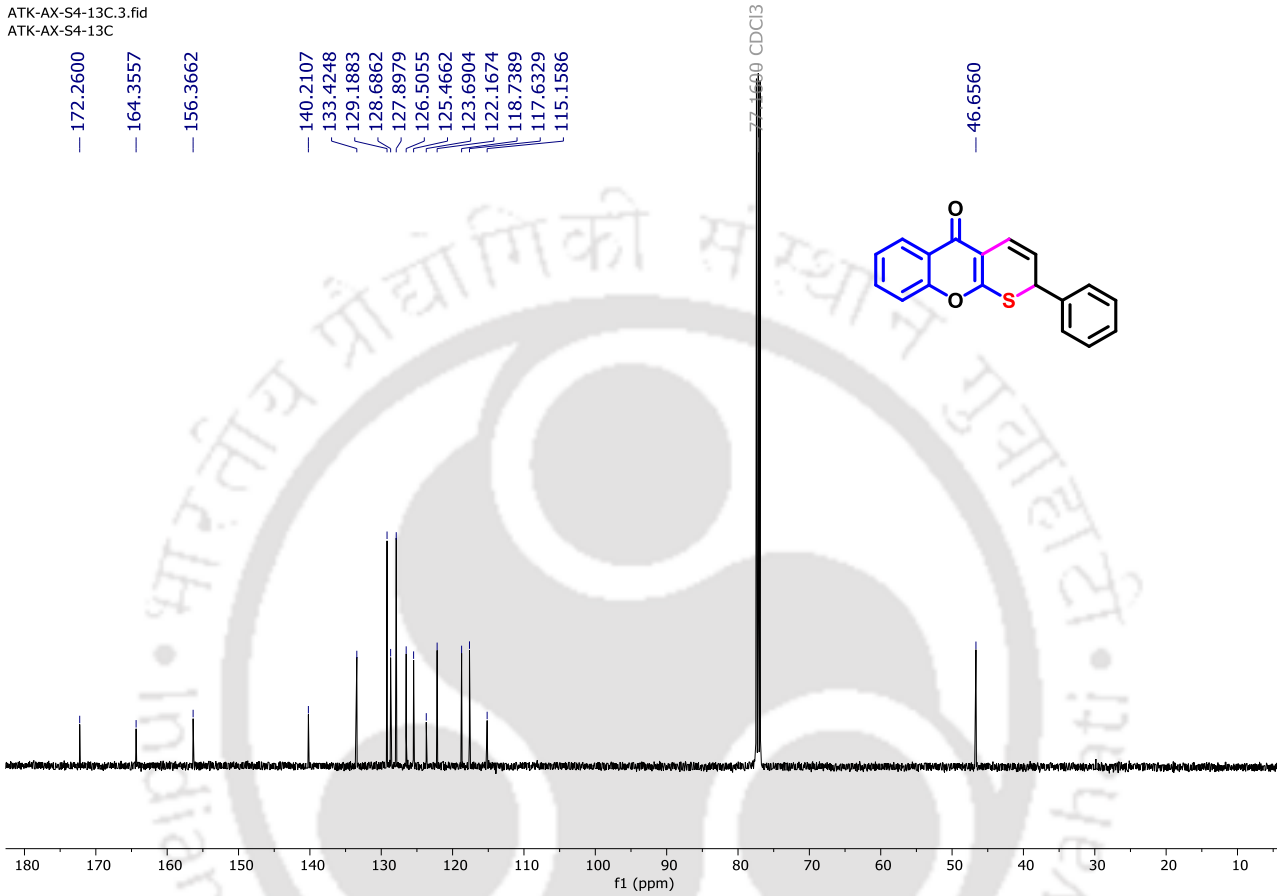
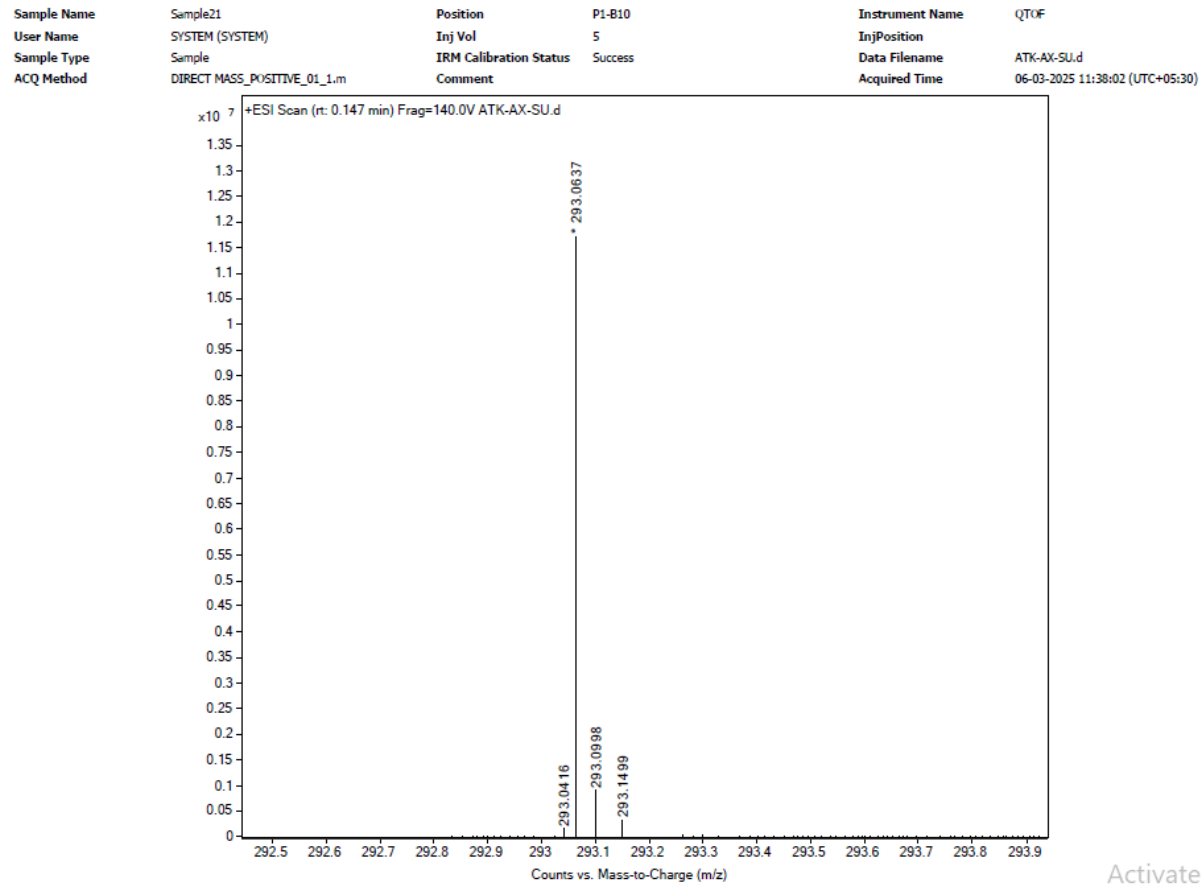


Figure 18. HRMS spectra of 2-phenyl-2*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one (9aaa)



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CHAPTER IV

Development of sulfur-rich heterocycles *via* Thioalkylation of 4-hydroxy-2*H*-chromene-2-thione: One-pot approach and *in-vitro* evaluation of Sulfone derivatives for antiproliferative activity

4.1a. Introduction to heteroarenes

In organic synthetic protocols, heteroarenes are considered to be a prominent factor *via* their alkylation due to their diverse biological activities1 as well as their usefulness in C-C[2] and C-S bond construction.[3] Focusing on the diverse bioactivities of (het)arenes, a review on the synthetic methodology as well as their potential on antidiabetic property, C-glycopyranosylarenes and hetarenes were explored.[4] Another review based on direct (hetero)arylation reactions was published, showcasing its transition metal-catalyzed C–H activation to construct biaryl and heterobiaryl scaffolds.[1]In 2023, Liu and his co-workers examined the novel area of research through carbene chemistry, i.e. skeletal editing of (hetero)arenes.[5] In addition to these, they also evaluated collectively its capability as well as its obstacles in implementing these procedures for widening its scope in the development of drugs and in material science. As discussed in **Chapter I**, organosulfur compounds turn out to be the core in numerous drugs as well as in natural alkaloids that are widely used in the medicinal field and also in dyes. Also, they can be utilized as tuberculostatic and as receptor antagonists, as shown in **Figure 1**. Various synthetic methods have been implemented to produce heteroarenes, namely through activation methods such as electrochemical, together with photochemical processes, and subsequently being subjected to nucleophilic attack.[6]

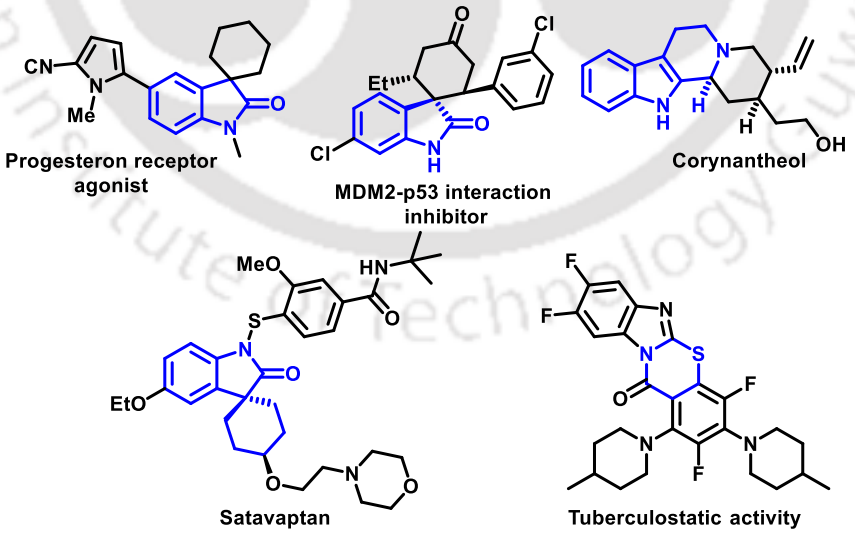


Figure 1. Biologically active *N* and *S*heteroarenes

4.1b. Introduction to thioalkylation

The thioalkyl group (-SCH_2R) is well-researched and recognized to be broadly applicablewithin the realm of organic chemistry. Empowering the formation of thioethers, this category moves forward through Mannich-type reaction, incorporating carbonyl compounds, thiols, as well as methylene donors.[7] It uncovers its widerelevance with diverse substrates,specifically with amines, amides, aromatics, and activated methylene derivatives.[8]Furthermore, thioalkylatedanalogues can be observed to remain prominent in pharmaceuticals[9] along with their applications in the domain of agrochemicals[10] and evolved materials.[11] The reaction functionality is assessedthrough acids, bases,[8]together witha transition metal catalyst.[12]Additionally, to enhanceits durability in organic chemistry,moderninnovationshave been made focusing primarily on greener protocols. Summing up, thioalkylation functions as the fundamentalframeworktowards incorporating sulfur in several chemical entities.

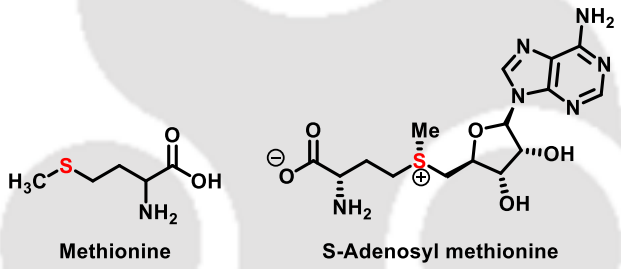
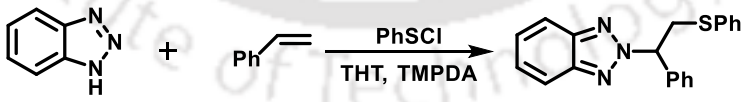


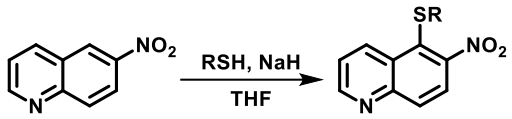
Figure 2. Biologically relevant molecules that contain thioalkyl groups

Subjected under metal-free reaction conditions, a stereospecific approach for β-thioalkylation of benzotriazoles was accomplished with N_2 selectivity.[13]



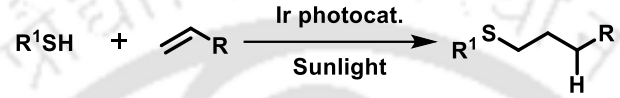
Scheme 1. β-thioalkylation of benzotriazoles

Thioalkylation of nitroquinolines was carried out with alkane thiols mediated by THF, which led to the substitution of a hydrogen atom. This protocol aimed to synthesize a sequence of thioalkylated products in good to excellent amounts.[14]



Scheme 2. Thioalkylation of nitroquinolines

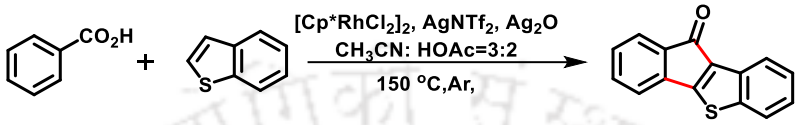
Under the pretext of photochemistry, olefins were thioalkylated with the aid of iridium catalyst towards oxidation of alkyl and aryl-thioalkyltrifluoroborates.[15]



Scheme 3. Thioalkylation of Olefins.

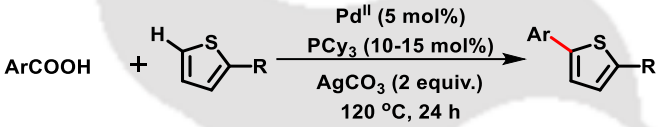
4.2. Synthesis of heteroarenes and display of some variant structures

A one-pot strategy was developed by Li and his co-workers to synthesized planar sulfur-containing heteroarenes by means of the cyclizing aromatic acids with benzothiophenes with Rhodium as a catalyst, which was further analyzed in biological imaging.[16]



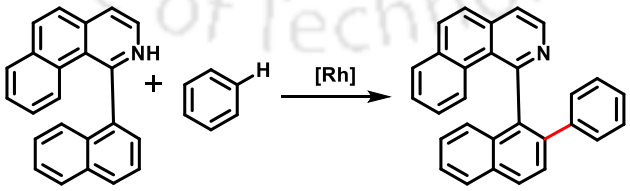
Scheme 4. Synthesis of Sulfur-Containing Polycyclic Heteroarenes

In combination with $AgCO_3$, Hu and his co-workers proved that PCy_3 /$Pd(OAc)_2$ or $Pd(TFA)_2$ systems effectively enhanced the decarboxylative C-H bond arylation of thiophenes, together with economical and easily accessible benzoic acids.[17]



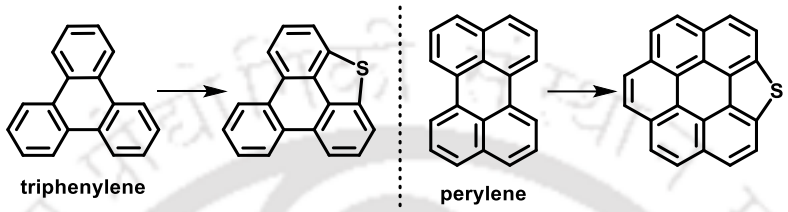
Scheme 5. C-H bond arylation of Thiophenes

Atroposelective C−H arylation through rhodium (III) catalysed cross-coupling reaction was performed between 1-Aryl Isoquinoline derivatives and electron-rich heteroarenes by Wang and his co-workers. Expanding this investigation, it showed that the use of this oxidative cross-coupling reaction can be further applied for the construction of various other categories of atropisomeric entities.[18]



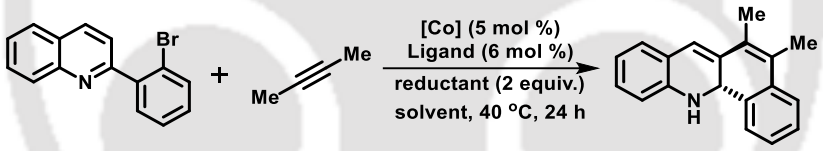
Scheme 6. C−H/C−H Cross-Coupling Reaction

In the form of fused aromatic rings, chalcogens and nitrogens containing heteroarenes were found to serve as a potential semiconductor resource, in their review, by Jiang and his co-workers, towards their utilisation in anarray of electronic devices on account of their extraordinary optoelectronic properties.[19]



Scheme 7. Chemical structures of heteroatom annulated triphenylenes and perylene

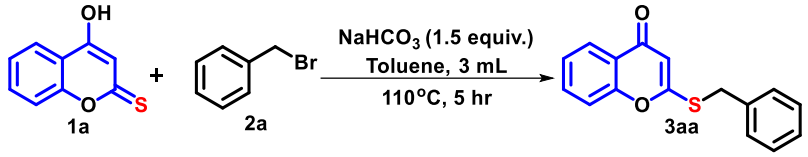
A straightforwardenantioselective umpolung annulation of *N*-heteroarenes with alkynes was carried out by Yang and his co-workers, *via*a cobalt-catalyzed strategy in the presence of a ligand and a reductant to furnish *N*-spiroheterocyclic scaffolds.[20]



Scheme 8. Umpolung annulation of N-heteroarenes

4.3. Results and Discussions

4-hydroxycoumarin, as well as coumarin scaffolds, is widely utilized in the pharmaceutical industry. Therefore, in continuation with **Chapter II**, we sought to investigate the significance of thioalkylation of 4-hydroxy-2*H*-chromene-2-thione.In this protocol, an efficient and elegant approach has been implemented to thioalkylate4-hydroxy-2*H*-chromene-2-thione to obtain heteroarenes through benzyl bromide under basic reaction conditions.

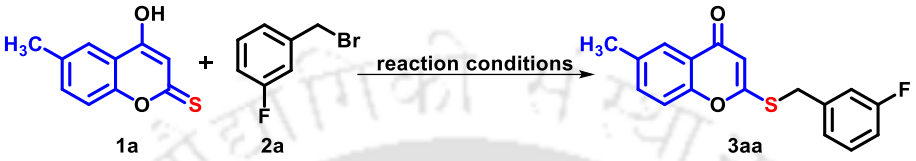


Scheme 9. Synthesis of 2-(benzylthio)-4*H*-chromen-4-one derivatives

After synthesizing the starting material (**1a**), to find out the optimum reaction conditions, 4-hydroxy-6-methyl-2*H*-chromene-2-thione (**1a**) and 1-(bromomethyl)-3-fluorobenzene (**2a**) were chosen as the model substrates. We commenced our investigation with a model reaction using 4-hydroxy-6-methyl-2*H*-chromene-2-thione(**1a**, 1 equiv.) and 1-(bromomethyl)-3-fluorobenzene (**2a**, 2 equiv.). The optimisation **Table 1** outlines the screening of several catalytic approaches for the reaction of 4-hydroxy-6-methyl-2H-chromene-2-thione with 1-(bromomethyl)-3-fluorobenzene with the application of $NaHCO_3$ (1.5 equiv.) at 110 °C to synthesize 2-(benzylthio)-4*H*-chromen-4-one derivatives. Preliminaryefforts were performed by employingCuI and CuCl (7.5 mol%) together with 1, 10-phenanthroline (10 mol%) in DCE as solvent,which ended in moderate yields of 38% and 50%, respectively. Notably, when the reaction was carried out without any metal catalyst or ligand but only in toluene as solvent, a prominent increase in the yield of 90% was observed. (**Table 1**, **entry 3**). This reveals that the reaction advanceswith ease under metal-free conditions. Additionally, exploring with other copper catalysts such as $Cu(acac)_2$ and $Cu(OTf)_2$ in toluene (**Table 1**, **entries 4** and **5**), provided moderate yields of 52% and 50% respectively. These findingsemphasize that the most effective criteria include merely by means of a base, $NaHCO_3$ in toluene at enhanced temperature in the absence of therequirement for any metal catalyst or ligand.

Thus, it was concluded from all the above observations that the best reaction conditions are $NaHCO_3$ (1.5 equivalent) in toluene as a solvent in terms of yield and reaction time (**Table 1, entry 3**).

Table 1. Optimization of the reactionconditions[a,b]



Entry	Catalyst (mol %)	Additive (equiv.)	Ligand (mol %)	Time (h)	Solvent	Yield[a,b] (%)
1	CuI (7.5)	$NaHCO_3$ (1.5)	Phen (10)	5	DCE	38
2	CuCl (7.5)	$NaHCO_3$ (1.5)	Phen (10)	5	DCE	50
3	**-**	**$NaHCO_3$ (1.5)**	**-**	**5**	**Toluene**	**90**
4	$Cu(acac)_2$ (7.5)	$NaHCO_3$ (1.5)	-	5	Toluene	52
5	$Cu(OTf)_2$ (7.5)	$NaHCO_3$ (1.5)	-	5	Toluene	50

[a]All the reactions were carried out using 4-hydroxy-6-methyl-2*H*-chromene-2-thione(**1a**), 1-(bromomethyl)-3-fluorobenzene (**2a**) was reacted in the presence of base in toluene at 110 °C. [b]Isolated yield.

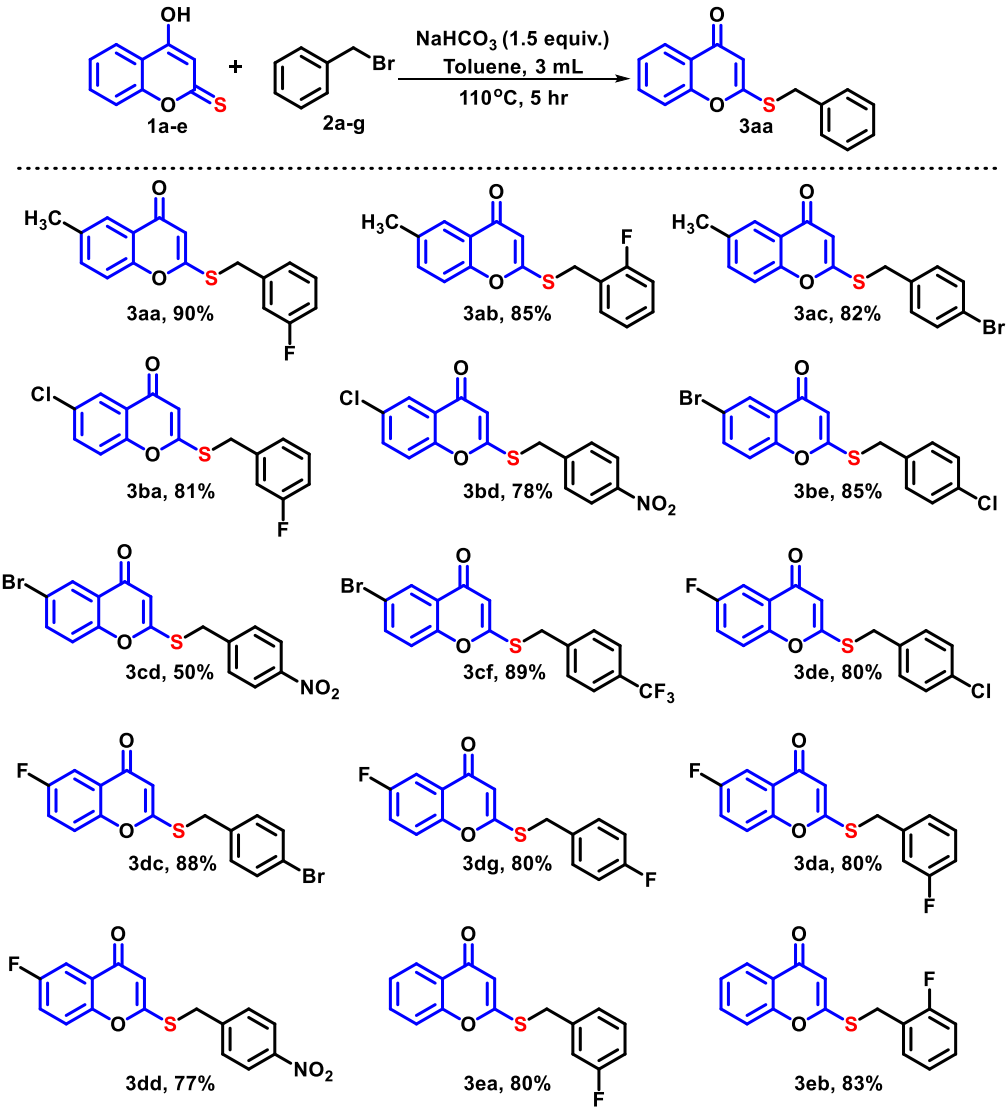
Thus, expanding the scope of reaction with the optimum reaction condition, with various 4-hydroxy-2*H*-chromene-2-thione (**1a**) and(bromomethyl)benzene (**2a**) derivatives, the results are summarized in **Table 3**. The reaction proceeds smoothly with methyl substituted 4-Hydroxy-2*H*-chromene-2-thione with 3-fluoro, 2-fluoro benzylbromide, 4-bromo benzylbromide derivatives yielding 90%, 85% and 82% of the desired product **3aa**, **3ab**and **3ac**. **3ba** and **3bd**, shows the *S*-alkylation of 6-chloro-4-hydroxy-2*H*-chromene-2-thione with various substituted benzylbromides. **3ba,** which contains a 3-fluorobenzylbromide group, yields 81% of the product,

and **3bd**, which contains a 4-nitrobenzylbromide group**,** yields 78% of the product.Then continuing with 6-bromo-4-hydroxy-2*H*-chromene-2-thione derivatives of 4-hydroxy-2*H*-chromene-2-thione with 4-chlorobenzylbromide, 4-nitrobenzybromide as well as with 4–CF_3 bromide group yields 85%, 50% and 89% of the anticipated products**3be**, **3cd** and **3cf**. A series of thioalkylated 4-Hydroxy-2*H*-chromene-2-thione derivatives (compounds **3de**, **3dc**, **3dg**, **3da** and **3dd**), each featuring 6-fluoro-4-hydroxy-2*H*-chromene-2-thione were accomplished. These include 4-chlorobenzyl bromide (**3de**, 80% yield), 4-bromobenzyl bromide (**3dc**, 88% yield), 4-fluorobenzylbenzylbromide (**3dg**, 80% yield), 3-fluorobenzylbromide (**3da**, 80% yield) and 4-nitrobenzylbromide (**3dd**, 77% yield). Expanding our protocol, the 4-hydroxy-2*H*-chromene-2-thione reacted with the benzyl derivatives of 3-fluoro and 2-fluoro benzyl derivatives under similar reaction conditions to afford the products**3ea** and **3eb** in good yields (80%-83% yields).

Compounds **3ab** and **3dh** were then oxidized into their corresponding sulfones **4ab** and **4da** on treating with *m*-CPBA as shown in **Table 4**. The structures of all the products were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectra. The study has proven that the sulfonyl compounds regard themselves as potent anti-viral as well as anti-cancer drug.[21]

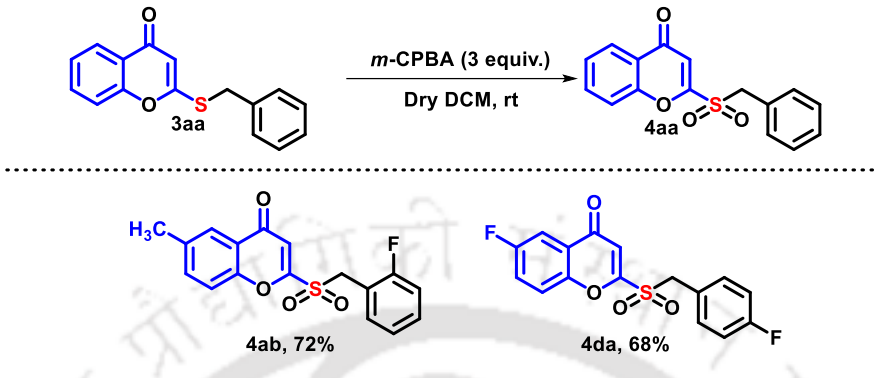
A very simple mechanism can be depicted as shown in **Scheme 10**. It entails the base-mediated thioalkylation of 4-hydroxy-2*H*-chromene-2-thione (**1a)**under the influence of a base, $NaHCO_3$. As a first step, deprotonation of thione (**1a**) takes place, which generates two tautomeric structures in keto-enol form. This intermediate then participates in the reaction with benzylbromide (**2a**) *via*the route of *S*-alkylation, resultingin the production of the anticipated product **3aa**. This mechanism emphasizes the nucleophilic attack on the C-2 of the sulphur centre of **1a**, generating a new C-S bond and therefore establishing a simple and user-friendlythioalkylationconversionwith mild basic reaction conditions.

Table 2. Substrate scope 2-(benzylthio)-4*H*-chromen-4-one derivatives[a,b]

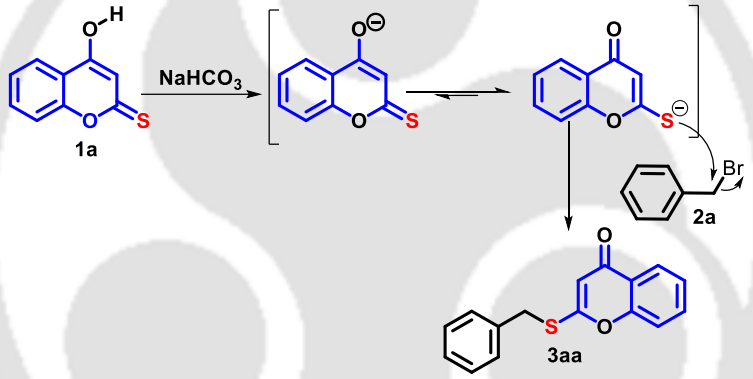


[a]All the reactions were carried out using 4-Hydroxy-2*H*-chromene-2-thione (**1a**), benzyl bromide (**2a**) was reacted in presence of base in Toluene at 110 °C. [b]Isolated yield

Table 3. Substrate scope 2-(benzylsulfonyl)-4*H*-chromen-4-one derivatives[a,b]



[a]All the reactions were carried out using 2-(benzylthio)-4*H*-chromen-4-one derivatives (**3aa**) with *m*-CPBA (3 equiv) in 2 mL of dry DCM at room temperature. [b]Isolated yield



Scheme 10. Plausible mechanism

4.4. Biological Applications

4.4a. Target Prediction and Bioinformatic analysis:

Swiss Target Prediction was used to identify potential protein targets for the parent compounds **3aa** and **4ab** based on structural similarity to known bioactive molecules. Both compounds shared equal probability scores for their top predicted targets. Expression analysis using UALCAN revealed that PARP1, a key DNA repair enzyme, was upregulated in lung cancer for compound **3aa**, while CDC25B, a cell cycle regulator, was upregulated for compound **4ab**. PARP1 supports cancer cell survival through DNA repair and is linked to drug resistance,

making it a therapeutic target. Similarly, CDC25B overexpression promotes unchecked cell division and genomic instability, contributing to lung cancer progression and poor prognosis.

Table 4: Top 10 predicted targets of Compound **3aa**

Target	Common name	Uniprot ID	Probability
Metabotropic glutamate receptor 5	GRM5	P41594	0.112041901
Carbonic anhydrase II	CA2	P00918	0.112041901
AdenosineA1 receptor	ADORA1	P30542	0.112041901
Adenosine A2a receptor	ADORA2A	P29274	0.112041901
Carbonic anhydrase I	CA1	P00915	0.112041901
Poly [ADP-ribose] polymerase-1	PARP1	P09874	0.112041901
Carbonic anhydrase XII	CA12	O43570	0.112041901
Carbonic anhydrase IX	CA9	Q16790	0.112041901
Tankyrase-2	TNKS2	Q9H2K2	0.112041901
Tankyrase-1	TNKS	O95271	0.112041901

Table 5: Top 10 predicted targets of Compound **4ab**

Target	Common name	Uniprot ID	Probability
Dual specificity phosphatase Cdc25B	CDC25B	P30305	0.097874534
Monoamine oxidase B	MAOB	P27338	0.097874534
P2X purinoceptor 7	P2RX7	Q99572	0.097874534
c-Jun N-terminal kinase 1	MAPK8	P45983	0.097874534
Glycogen synthase kinase-3 beta	GSK3B	P49841	0.097874534
Hexokinase type IV	GCK	P35557	0.097874534
Protein kinase C gamma	PRKCG	P05129	0.097874534
Protein kinase C alpha	PRKCA	P17252	0.097874534
Dual specificity mitogen-activated protein kinase kinase 1	MAP2K1	Q02750	0.097874534
CDK8/Cyclin C	CCNC CDK8	P24863 P49336	0.097874534

4.4b. Cell Viability Assay:

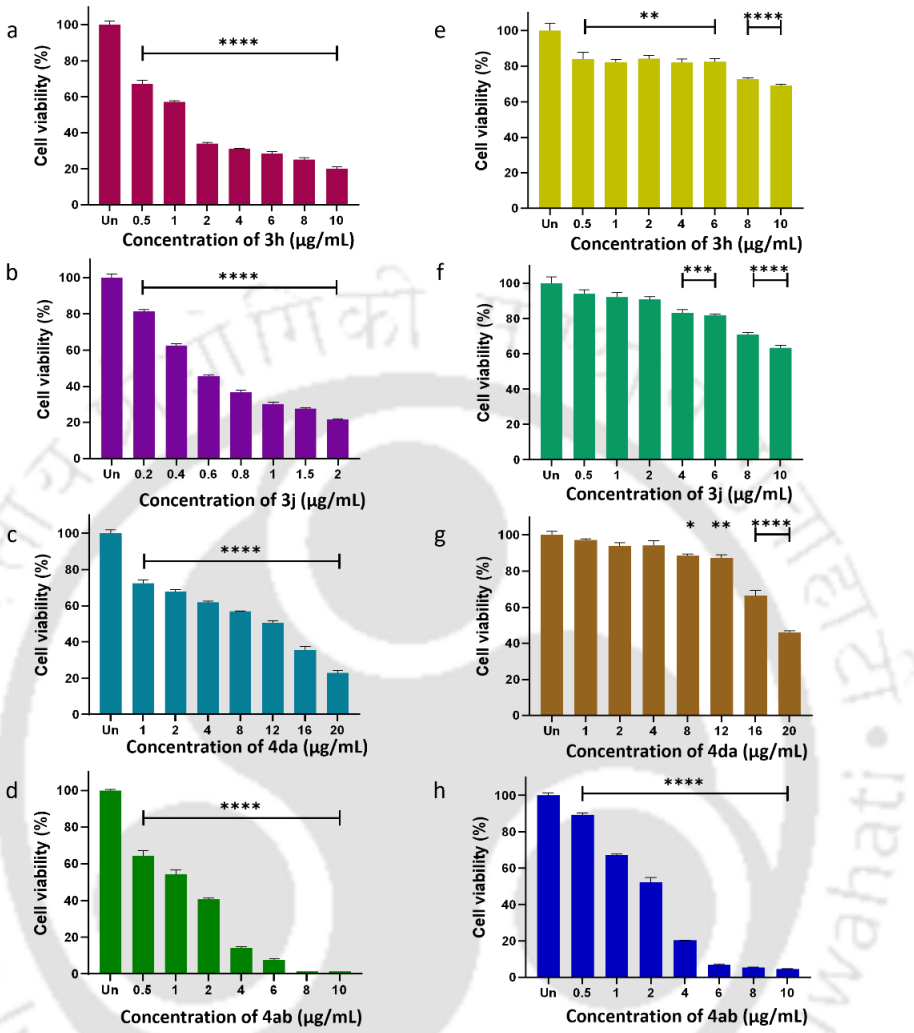
The MTT assay demonstrated that all four compounds reduced A549 lung cancer cell viability in a dose-dependent manner, with notably lower IC_{50} values compared to HEK-293T normal cells. **3j** showed the highest selectivity (IC_{50}: 0.57 µg/mL in A549 vs. 20.60 µg/mL in HEK-293T), followed by **3h**, **4da**, and **4ab**. While **4ab** was effective against both cell lines, the others exhibited greater selectivity toward cancer cells. These results suggest that the compounds, particularly **3j** and **3h**, may possess promising anticancer potential with limited toxicity to normal cells, warranting further investigation.

4.4c. Live Dead Cell Imaging:

Live-dead cell imaging of A549 cells treated with compounds at their IC_{50} concentrations showed a notable increase in propidium iodide (PI)-stained dead cells after 48 hours, indicating enhanced cell death compared to untreated controls. Dual staining with Calcein AM and PI revealed significant red fluorescence in treated samples, particularly with **4da** and **4ab** compounds, highlighting their strong anti-proliferative and anti-cancer efficacy.

4.4d. Detection of ROS and analysis of Nuclear Morphology:

The study assessed ROS generation and nuclear morphology in A549 cells treated with the selected compounds at their IC_{50} concentrations. ROS levels increased significantly, with **4ab** showing the highest upregulation (2.2-fold), followed by **3h** (1.4-fold), **3j** (1.3-fold), and **4da**(1.2-fold), supporting their antiproliferative and cytotoxic effects observed in earlier assays. Additionally, nuclear morphology analysis after 48 hours revealed DNA damage indicators, such as distorted or fragmented nuclei, in cells treated with **3h**, **3j**, and especially **4da** while **4ab** showed no significant nuclear changes.



Name of the Compound	IC50 on A549 Cell line (µg/mL)	Name of the Compound	IC50 on HEK-293 Cell line (µg/mL)
3h	1.27	3h	Undefined upto 10 µg/mL
3j	0.57	3j	20.6
4da	7.38	4da	19.45
4ab	1.05	4ab	1.79

Figure 3: Graphical representations of the dose-dependent decrease in cell viability of A549 following treatment with (a) 3h, (b) 3j, (c) 4da, (d) 4ab and dose-dependent decrease in cell viability of HEK-293T following treatment with (e) 3h, (f) 3j, (g) 4da, (h) 4ab for 48 h.The results are expressed as the mean ± SEM. The statistical significance was assessed in comparison to the untreated cells. The significance level was set at $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***), $p < 0.0001$ (****).

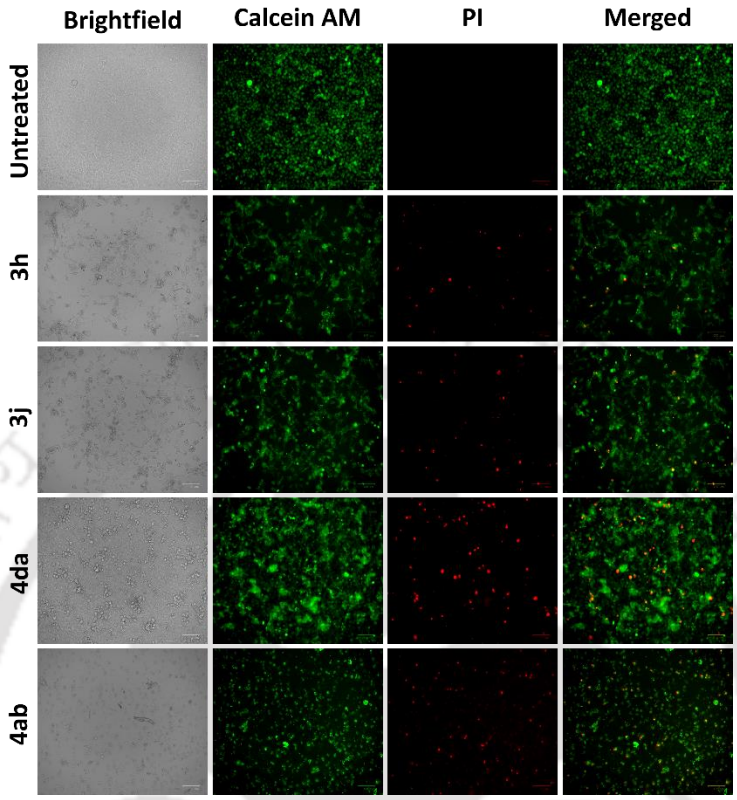
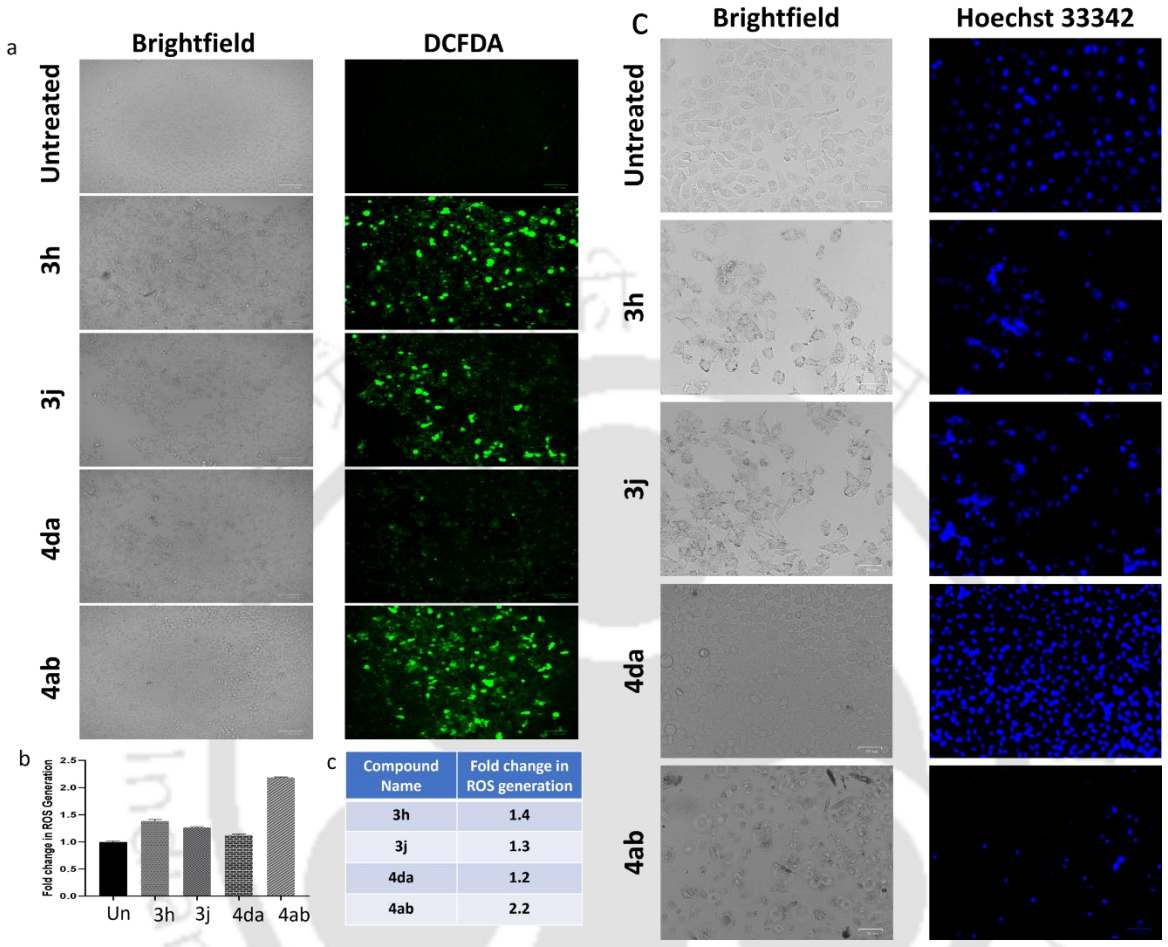


Figure 4: Live/dead cell imaging of A549 cells treated with compounds for 48 h using Calcein-AM and propidium iodide (PI) dual staining. Scale Bar represents 100µM.



Compound Name	Fold change in ROS generation
3h	1.4
3j	1.3
4da	1.2
4ab	2.2

Figure 5: (a) Fluorescence imaging and graphical representation of cellular ROS generation by DCFDA staining on A549 cells upon treatment with compounds for 12 h. (Scale bar, 100 µM). (c) Nuclear morphology study of A549 cells treated with selected compounds for 48 h and stained with Hoechst 33342 (Blue) (Scale bar, 50 µM).

4.5. Conclusion

Concluding this work, we have accomplished the synthesis of 2-(benzylthio)-4*H*-chromen-4-one derivatives from 4-hydroxy-2*H*-chromene-2-thione and benzyl bromide *via* base-catalyzed reaction. The features of this protocol are good yields, shorter reaction time, and broad substrate scope. Further, sulfones have been studied for their anti-proliferative activity.

4.6. Experimental Section

4.6a.General procedure for the synthesis of compound 1(a-e)

4-hydroxy-2*H*-chromene-2-thione (**1a**) is synthesized following a slightly modified version of the previously reported procedure.[23] Potassium *tertiary* butoxide (15 mmol) and 18-crown-6 ether (1.5 mmol) were taken in 7 mL of anhydrous THF in an oven-dried round-bottomed flask. The mixture is purged with N_2 and cooled to 0°C in an ice bath. Then, 2'-hydroxyacetophenone (5 mmol) is added dropwise to the above solution, followed by the addition of carbon disulfide (5 mmol) to the reaction mixture, resulting in the formation of a thick yellow precipitate. The reaction is stirred at 0-15 °C for another 1 hour, then brought to room temperature and continued stirring at this temperature for 16 hours. The reaction is quenched by adding 5 mL of water, and then the water layer is washed with ethyl acetate (2 × 5 mL). The aqueous layer was then acidified with 10% H_2SO_4 until pH was adjusted to 4-5, and the mixture was stirred for another 16 h. A yellow precipitate is formed, collected by vacuum filtration and washed with petroleum ether several times to obtain the desired product as a yellow solid.[24]

4.6b. General procedure for the synthesis of 2-(benzylthio)-4*H*-chromen-4-one derivatives (3aa-3eg)

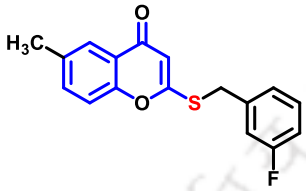
A mixture of 4-hydroxy-2*H*-chromene-2-thione **1a** (0.25 mmol) and benzyl bromide **2a** (2 equiv) was taken into toluene (3 mL) in a 10 mL round-bottomed flask. Then 1.5 equivalent of $NaHCO_3$ was added to the reaction mixture, and it was refluxed at 110 °C for a period of 5 hours. After the completion of the reaction, as monitored by TLC, the solvent was removed, and the crude residue was extracted with dichloromethane (10 mL x 1). The organic layer was washed with water (10 mL x 2) and 5 mL of brine solution and dried over anhydrous sodium sulfate. Finally, the solvent was removed in a rotatory evaporator, and the crude residue was purified through silica gel (60–120 mesh) column

chromatography to obtain product 3aa in 78% yield. A similar reaction procedure was followed in all other cases.

4.6c. General procedure for the synthesis of compounds 4

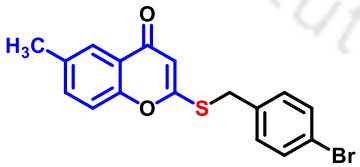
Sulfone derivatives (**4**) were produced by the reported procedure.[24]

2-((3-fluorobenzyl)thio)-6-methyl-4*H*-chromen-4-one (3aa). White solid (68 mg, 90%, mp118°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 9.7 Hz, 1H), 6.98 (t, *J* = 8.6 Hz, 1H), 6.26 (d, *J* = 2.8 Hz, 1H), 4.26 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 166.5, 163.0 (d, *J* = 247.2 Hz), 155.3, 138.0 (d, *J* = 7.5 Hz), 135.6, 134.8, 130.5 (d, *J* = 8.4 Hz), 125.5, 124.5 (d, *J* = 2.8 Hz), 123.3, 117.0, 115.8 (d, *J* = 22.2 Hz), 115.1 (d, *J* = 21.1 Hz), 109.9, 35.2, 21.0.

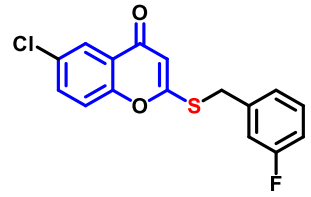


2-((2-fluorobenzyl)thio)-6-methyl-4*H*-chromen-4-one (3ab). White solid (64 mg, 86%, mp125°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 10.8 Hz, 1H), 7.11 – 7.03 (m, 2H), 6.30 – 6.26 (m, 1H), 4.32 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 166.4, 160.8 (d, *J* = 247.8 Hz), 155.3, 135.5, 134.7, 130.8 (d, *J* = 3.3 Hz), 129.9 (d, *J* = 8.2 Hz), 125.3, 124.61 (d, *J* = 3.7 Hz), 123.3, 123.1 (d, *J* = 14.4 Hz), 117.1, 115.8 (d, *J* = 21.5 Hz), 110.0, 28.7, 21.0.

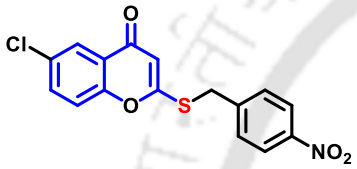
2-((4-bromobenzyl)thio)-6-methyl-4*H*-chromen-4-one (3ac). White solid (74 mg, 82%, mp120°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.33 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.27 (s, 2H), 7.22 (d, *J* = 9.1 Hz, 1H), 6.26 (s, 1H), 4.23 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 166.4, 157.2, 151.8, 134.6, 132.1, 130.5, 124.3, 123.4, 122.1, 118.7, 109.4, 105.4, 56.1, 35.1.



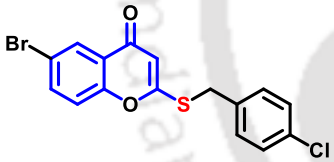
6-chloro-2-((3-fluorobenzyl)thio)-4*H*-chromen-4-one (3ba). White solid (65 mg, 81%, mp115°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 9.5 Hz, 1H), 7.00 (t, *J* = 8.4 Hz, 1H), 6.27 (s, 1H), 4.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 167.4, 163.0 (d, *J* = 247.7 Hz), 155.2, 137.6 (d, *J* = 7.4 Hz), 133.8, 131.6, 130.6 (d, *J* = 8.3 Hz), 125.6, 125.14, 123.4, 119.0, 115.8 (d, *J* = 22.1 Hz), 115.3 (d, *J* = 21.1 Hz), 109.7, 35.3 (d, *J* = 2.2 Hz).



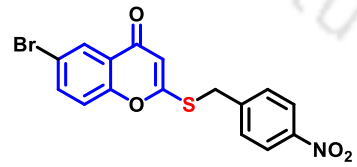
6-chloro-2-((4-nitrobenzyl)thio)-4*H*-chromen-4-one (3bd). White solid (67 mg, 78%, mp120°C); ^{1}H NMR (500 MHz, CDCl3) δ 8.21 (d, J = 8.3 Hz, 2H), 8.11 (s, 1H), 7.58 (d, J = 8.5 Hz, 3H), 7.33 (d, J = 8.9 Hz, 1H), 6.28 (s, 1H), 4.36 (s, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 174.5, 166.2, 155.2, 147.8, 142.9, 134.0, 131.8, 129.7, 125.7, 124.7, 124.3, 118.9, 110.3, 35.0.



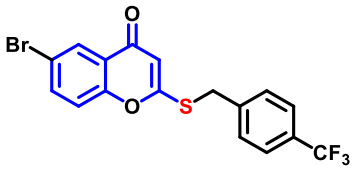
6-bromo-2-((4-chlorobenzyl)thio)-4*H*-chromen-4-one (3be). White solid (81 mg, 85%, mp127°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.9 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 6.1 Hz, 2H), 7.24 (d, *J* = 6.5 Hz, 3H), 6.24 (d, *J* = 2.4 Hz, 1H), 4.20 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 167.4, 155.6, 136.6, 134.1, 132.2, 130.5, 128.8, 125.0, 122.3, 119.2, 119.0, 109.8, 35.2.



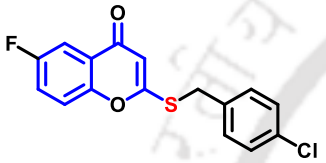
6-bromo-2-((4-nitrobenzyl)thio)-4*H*-chromen-4-one (3cd). White solid (49 mg, 50%, mp125°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.24 (s, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 8.00 (s, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.19 (s, 1H), 5.44 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 164.4, 151.2, 150.9, 142.4, 140.1, 131.0, 130.6, 128.8, 124.4, 124.1, 123.8, 66.2.



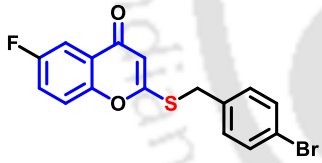
6-bromo-2-((4-(trifluoromethyl)benzyl)thio)-4*H*-chromen-4-one (3cf). White solid (mg, 93%, mp127°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 9.8 Hz, 1H), 6.21 (s, 1H), 4.25 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 167.0, 155.6, 139.4, 136.6, 130.4, 129.2, 128.8, 126.1 (*J* = 3.8 Hz), 125.0, 119.2, 119.1, 110.0, 35.2.



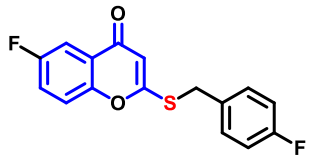
2-((4-chlorobenzyl)thio)-6-fluoro-4*H*-chromen-4-one (3de). White solid (64 mg, 80%, mp128°C);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.35 (d, *J* = 10.2 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 4H), 6.25 (s, 1H), 4.25 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 167.4, 159.7 (d, *J* = 247.3 Hz), 153.1, 134.1, 133.7, 130.1, 129.2, 125.0 (d, *J* = 7.4 Hz), 121.6 (d, *J* = 25.7 Hz), 119.3, 111.1 (d, *J* = 23.9 Hz), 109.2, 35.1.



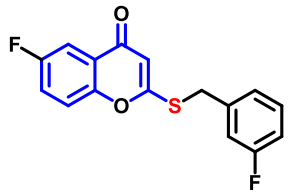
2-((4-bromobenzyl)thio)-6-fluoro-4*H*-chromen-4-one (3dc). White solid (80 mg, 88%, mp124°C);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 5.1 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.33 (m, 2H), 7.27 (d, *J* = 5.6 Hz, 2H), 6.26 (s, 1H), 4.24 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 167.3, 159.7 (d, *J* = 247.4 Hz), 153.1 (d, *J* = 1.8 Hz), 134.3, 132.2, 130.5, 125.0 (d, *J* = 7.3 Hz), 122.2, 121.6 (d, *J* = 25.6 Hz), 119.3 (d, *J* = 8.1 Hz), 111.1 (d, *J* = 23.8 Hz), 109.2, 35.2.



6-fluoro-2-((4-fluorobenzyl)thio)-4*H*-chromen-4-one (3dg). White solid (61 mg, 80%, mp118°C);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 16.4 Hz, 4H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.26 (s, 1H), 4.26 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 167.7, 162.5 (d, *J* = 247.5 Hz), 159.7 (d, *J* = 247.3 Hz), 153.1, 130.8 (d, *J* = 3.5 Hz), 130.6 (d, *J* = 8.3 Hz), 125.0 (d, *J* = 7.6 Hz), 121.6 (d, *J* = 25.4 Hz), 119.3 (d, *J* = 8.0 Hz), 116.0 (d, *J* = 21.8 Hz), 111.1 (d, *J* = 23.9 Hz), 109.1, 35.1.

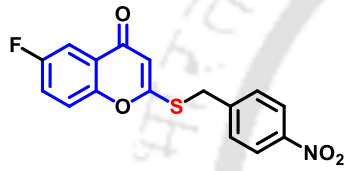


6-fluoro-2-((3-fluorobenzyl)thio)-4*H*-chromen-4-one (3da). White solid (61 mg, 80%, mp120°C);



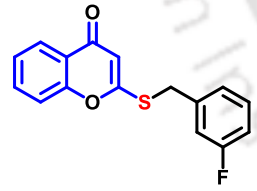
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.41 – 7.27 (m, 3H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.99 (t, *J* = 8.7 Hz, 1H), 6.26 (d, *J* = 1.9 Hz, 1H), 4.27 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 167.3, 163.0 (d, *J* = 247.3 Hz), 159.7 (d, *J* = 247.3 Hz), 153.1, 137.7 (d, *J* = 7.5 Hz), 130.6 (d, *J* = 8.4 Hz), 124.9 (d, *J* = 7.4 Hz), 124.5, 121.6 (d, *J* = 25.6 Hz), 119.3 (d, *J* = 7.9 Hz), 115.8 (d, *J* = 22.3 Hz), 115.2 (d, *J* = 21.1 Hz), 111.1 (d, *J* = 24.0 Hz), 109.1, 35.2.

6-fluoro-2-((4-nitrobenzyl)thio)-4*H*-chromen-4-one (3dd). White solid (63 mg, 77%, mp127°C);



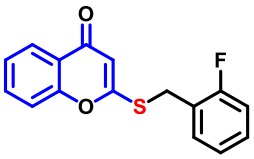
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 6.8 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.0 Hz, 2H), 7.37 (d, *J* = 2.5 Hz, 2H), 6.26 (s, 1H), 4.36 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 166.1, 159.8 (d, *J* = 247.8 Hz), 153.0, 147.7, 143.0, 129.7, 124.9 (d, *J* = 7.4 Hz), 124.2, 121.8 (d, *J* = 25.4 Hz), 119.3 (d, *J* = 8.2 Hz), 111.2 (d, *J* = 23.8 Hz), 109.7, 34.9.

2-((3-fluorobenzyl)thio)-4*H*-chromen-4-one (3ea). White solid (57 mg, 80%, mp123°C); ^{1}H

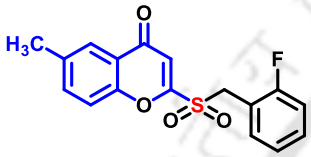


NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.9 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.30 (q, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 9.6 Hz, 1H), 6.99 (t, *J* = 8.5 Hz, 1H), 6.28 (s, 1H), 4.28 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 166.8, 164.0, 162.0, 156.9, 138.0, 133.6, 130.6 (d, *J* = 8.3 Hz), 125.8 (d, *J* = 60.8 Hz), 124.5, 123.7, 117.3, 115.8 (d, *J* = 22.3 Hz), 115.2 (d, *J* = 21.1 Hz), 110.0, 35.2.

2-((2-fluorobenzyl)thio)-4*H*-chromen-4-one (3eb). White solid (59 mg, 83%, mp 128°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.6 Hz, 1H), 7.58 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.34 (s, 2H), 7.03 (t, *J* = 8.6 Hz, 2H), 6.27 (s, 1H), 4.26 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 167.7, 155.2, 133.8, 131.5, 130.6 (d, *J* = 8.2 Hz), 125.6, 124.7, 119.0, 116.1 (d, *J* = 21.8 Hz), 109.7, 35.2.



2-((2-fluorobenzyl)sulfonyl)-6-methyl-4*H*-chromen-4-one (4ab). White solid (60 mg, 72%, mp155°C);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.99 (s, 2H), 7.58 (s, 1H), 7.34 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 9.4 Hz, 1H), 6.81 (s, 1H), 4.66 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 170.5, 159.1, 154.2, 137.1, 136.7, 134.8, 133.9, 131.9, 130.3, 129.9, 128.4, 125.6, 115.8, 113.9, 53.0, 21.1.



6-fluoro-2-((4-fluorobenzyl)sulfonyl)-4*H*-chromen-4-one (4da). White solid (57 mg, 68%, mp145°C);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 9.8 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 3H), 6.87 (s, 1H), 4.56 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 159.6, 130.9 (d, *J* = 8.2 Hz), 130.5 (d, *J* = 8.3 Hz), 123.8 (d, *J* = 25.6 Hz), 120.7 (d, *J* = 8.3 Hz), 118.0, 117.8 (d, *J* = 8.1 Hz), 117.6, 117.0 (d, *J* = 21.0 Hz), 115.7 (d, *J* = 21.1 Hz), 113.3, 111.5 (d, *J* = 24.2 Hz), 59.3.

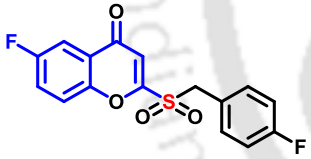


Figure 3. ^{1}H NMR spectra of 2-((3-fluorobenzyl)thio)-6-methyl-4*H*-chromen-4-one (3aa)

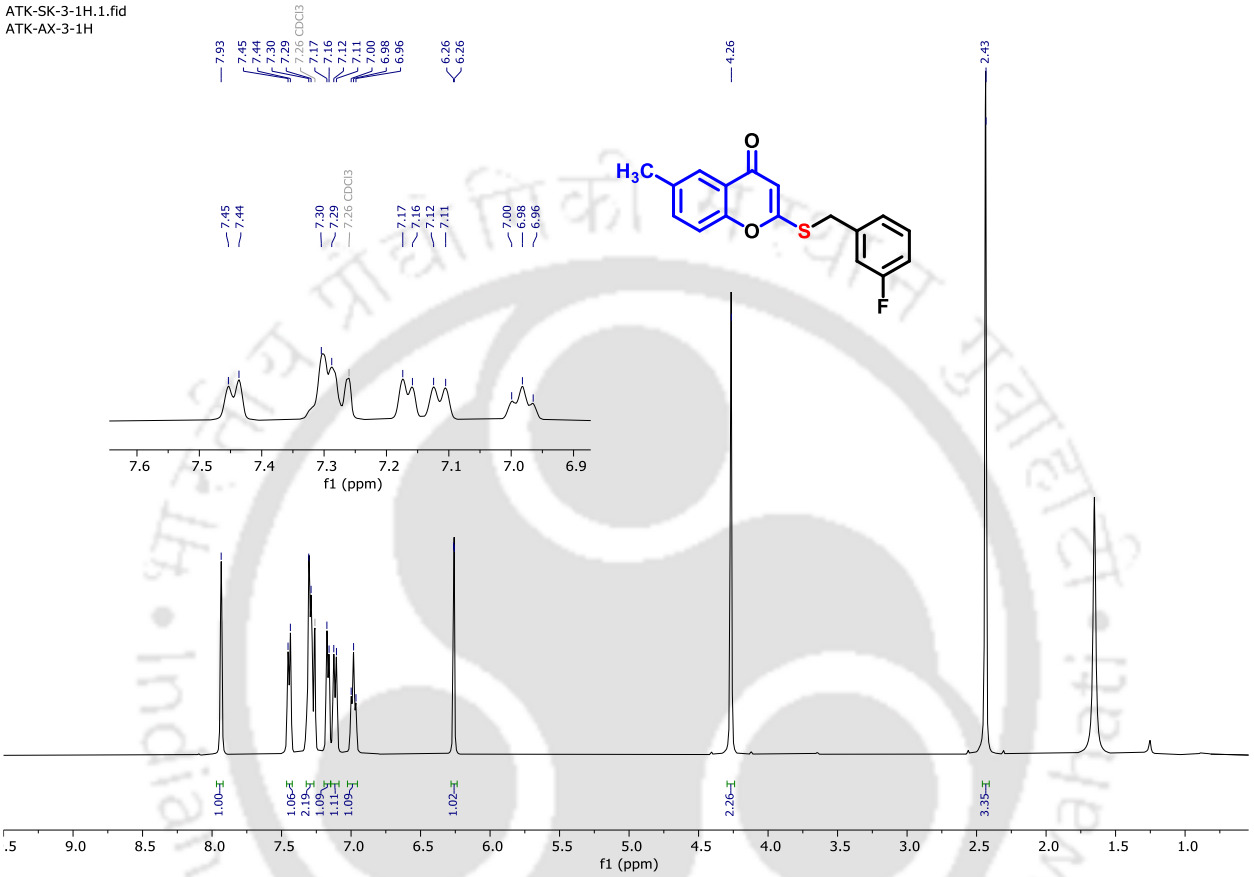


Figure 4. ^{13}C NMR spectra of 2-((3-fluorobenzyl)thio)-6-methyl-4*H*-chromen-4-one (3aa)

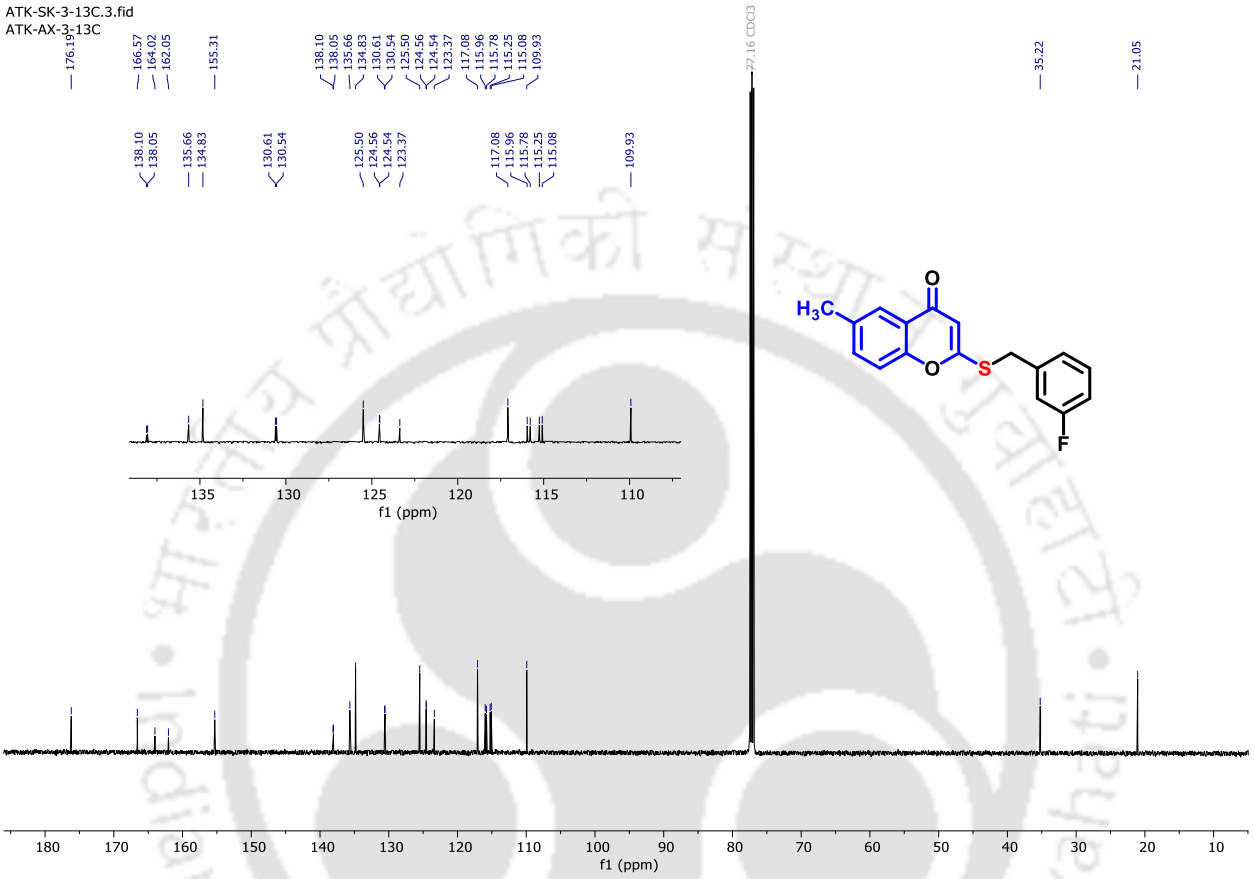


Figure 5. ^{1}H NMR spectra of 2-((2-fluorobenzyl)sulfonyl)-6-methyl-4*H*-chromen-4-one (4ab)

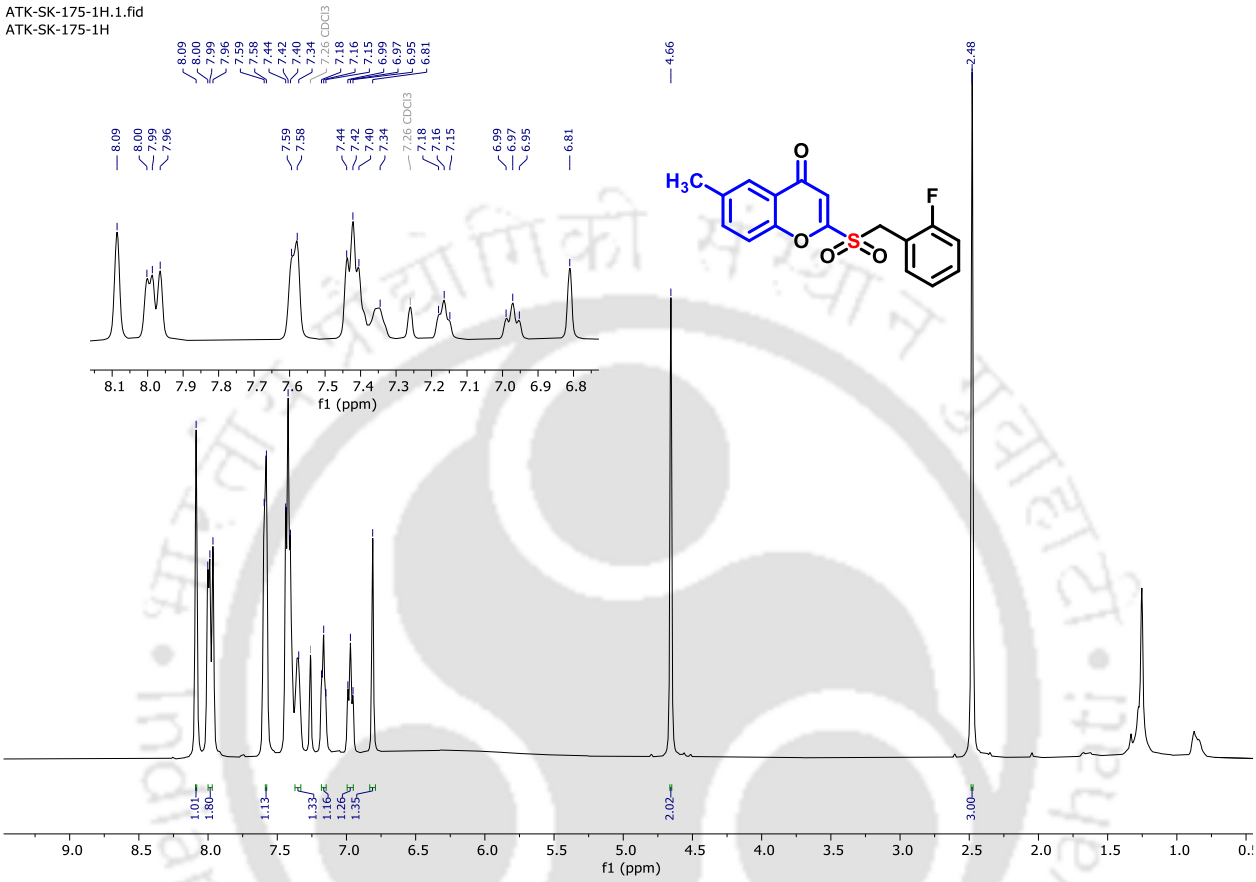
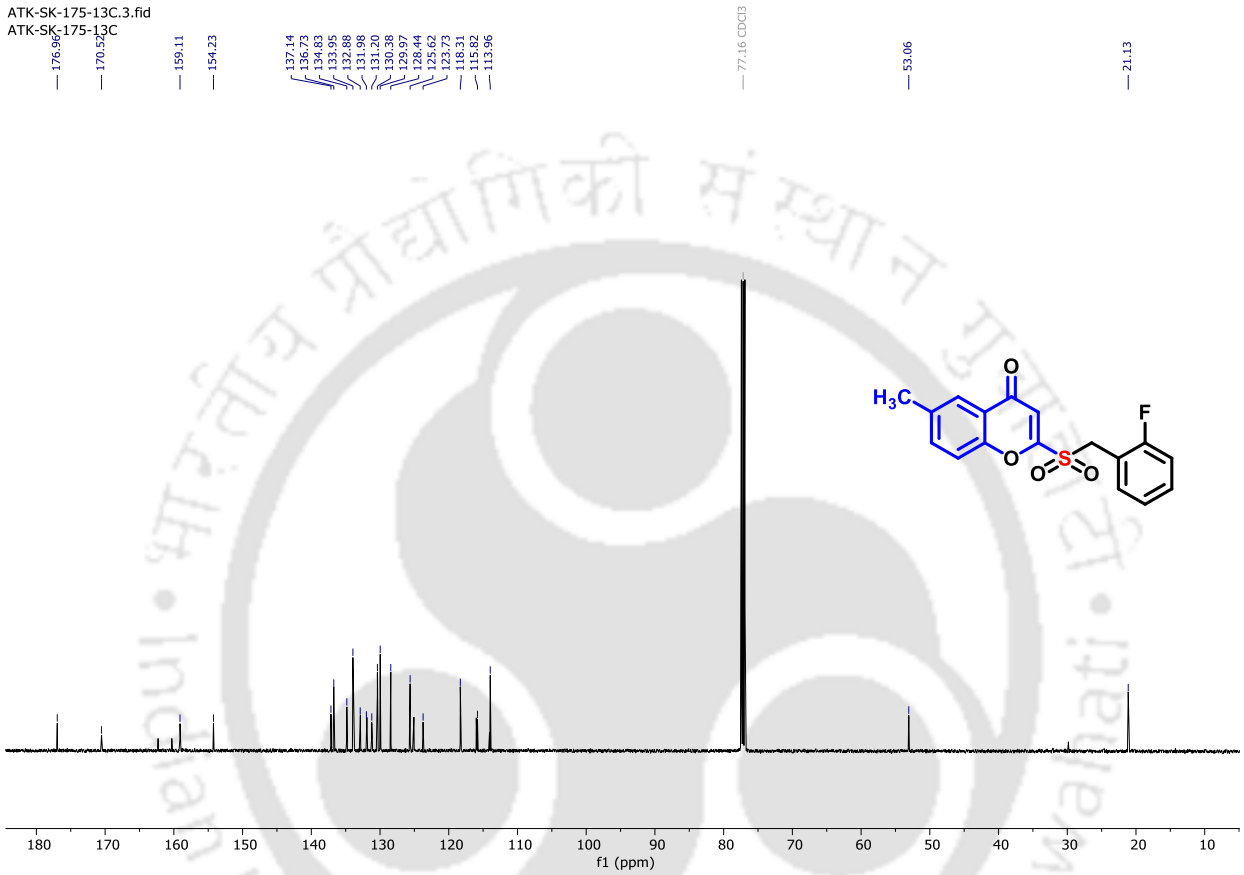


Figure 6. ^{13}C NMR spectra of 2-((2-fluorobenzyl)sulfonyl)-6-methyl-4*H*-chromen-4-one (4ab)



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CHAPTER V-A

Reactivity study of 4-hydroxy-2*H*-chromene-2-thione and 4-hydroxy-2*H*-thiochromene-2-thione with *tertiary* butyl nitrite and aromatic amines: Environmentally benign synthesis of new hydrazone derivatives

5a.1 Introduction

The coumarin and its derivatives are naturally occurring compounds and possess pharmacological effects such as analgesic[1], anti-arthritis[2], anti-inflammatory[3], anti-pyretic[4], anti-bacterial[5], anti-viral[6], and anti-cancer[7] properties. For Example, 4-hydroxycoumarin and its derivatives have been effectively used as anticoagulants[8] for treating disorders with excessive or undesirable clotting, such as thrombophlebitis, pulmonary embolism, and certain cardiac conditions. Numerous comparative pharmacological investigations of the 4-hydroxycoumarin derivatives have shown good anticoagulant activity[9]combined with low side effects and less toxicity (**Figure 1**).

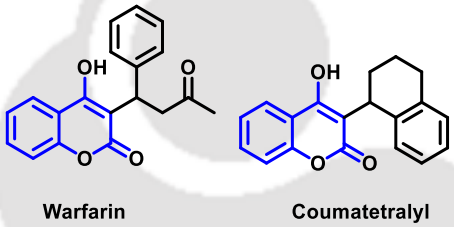


Figure 1. Structures of some biologically active compounds derived from 4-Hydroxycoumarin

The chemical synthesis, structural modification, and a wide variety of biological activities of 4-hydroxycoumarins have been reported in many papers. By exploring the reactivity of 4-hydroxy-2*H*-chromene-2-thione and 4-hydroxydithiocoumarin, we have synthesized various new molecules owing to their reactivity and biological activity[10].

Our group has explored the chemistry of 4-hydroxydithiocoumarin for the synthesis of various new entities, which was reviewed recently[11]. We have also shown the unprecedented S–C bond formation in addition to S–N and S–S bonds in the reaction of aniline with 4-hydroxydithiocoumarin[12]. So, bearing that in mind, to examine the reactivity pattern of 4-hydroxy-2*H*-chromene-2-thione, in case it forms S–N bond with aniline or it will react with NO^+ which generates from *tertiary* butyl nitrite to give S–N or C–N bond at its C-2 position. Interestingly, for the present study, we have noted that it reacts with in situ generated NO^+ followed by reaction with aniline to give hydrazone derivatives at C-2 position rather than

expected S–N bond formation. Thus, we anticipate this method will be highly useful, particularly in light ofits simplicity, shorter reaction time, non-toxic metal-free reaction conditions and broad scope. Owing to theseadvantages ofhydrazones,combining them with other functional groups may lead to interesting and unique chemical as well as physical behavior (**Figure 2**). The incorporation of the thiol group into coumarin results in thiocoumarin, which has been relatively less extensively studied and has emerged as a promising bioactive[13] compounds that inhibit inducible nitric oxide synthase and have a strong antimicrobial action on Mycobacterium tuberculosis. Their chemistry and bioactivity appear to be interesting. This functionalization of coumarin gives a special reactivity because of the implication of the thiol group indifferent types of organic reactions, which facilitates numerous series of derivatives that may have special applications or biological activities.

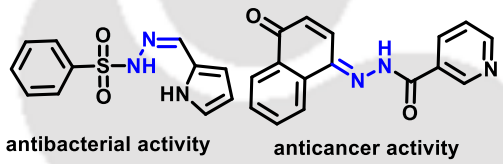
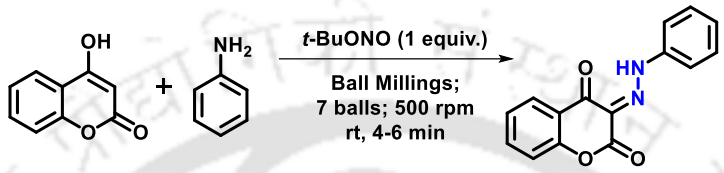


Figure 2. Structure of some biologically active hydrazone derivatives

As oxidation aids towards the instability of thiocarbonyl compounds, it is of great concern to those who explore the chemical behaviour of such compounds. Since the 19th century, the conversion of thioketones to carbonyl compounds has attracted researchers all over the globe,[14] basically for the quantitative determination of compounds containing the thiocarbonyl moiety and synthetic and mechanistic aspects involving both inorganic and organic oxidizing agents and hydrolytic procedures catalysed by metal ions.

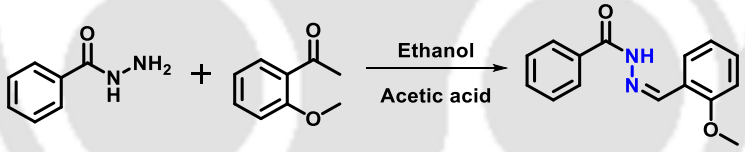
5a. 2. Synthesis of hydrazone derivatives

Brahmachari*et al.*,reported[15] the synthesis of (*E*)-3-(2-arylhydrazono)chromane-2,4-diones from one-pot three-component reaction between 4-hydrocoumarins, primary aromatic amines and *tert*-butyl nitrite through a mechano-chemistry employing under ball-milling reaction conditions.



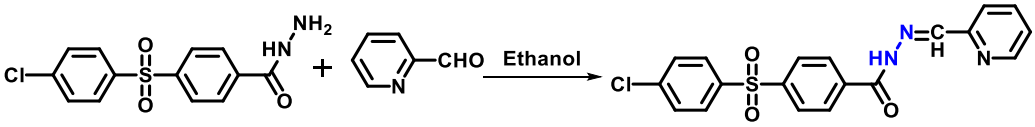
Scheme 1. Synthesis of hydrazone from 4-hydrocoumarins and aniline

Wahab *et al.*,reported[16] Cu and Ni complexes of hydrazone Schiff base ligand, namely *O*-methoxybenzaldehydebenzoylhydrazone (MBH) derived from condensation of benzoylhydrazide and *O*-methoxybenzaldehyde. The MBH ligand and its metal complexes were incorporated physically into a polyurethane coating to study their antimicrobial and flame-retardant properties.



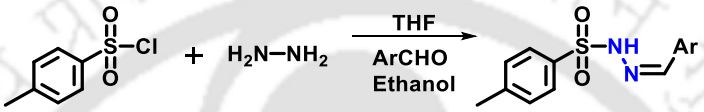
Scheme 2. Synthesis of *O*-methoxybenzaldeyhdebenzoylhydrazone (MBH) ligand

Angelusiu*et al.*,reported[17] synthesis of Cu(II), Co(II), Ni(II) ligand formed by the condensation of 4-(4-chloro-phenylsulfonyl)benzohydrazide with 2-pyridinecarbaldehyde which behaves as mononegative bidentate/tridentate with NO/NON donor sequence in *E* isomeric form towards the metal ions.



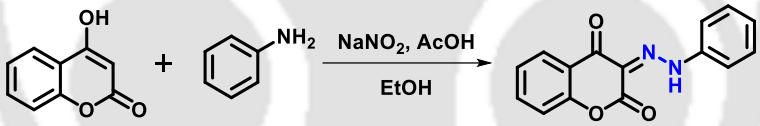
Scheme 3. Synthesis of hydrazone (Ligand) complexes.

Senkardes*et al.*,reported[18] synthesis of a series of sulfonylhydrazones and were investigated for their cytotoxic and apoptotic effects on PC3 and MCF-7 cell lines besides COXs activities.



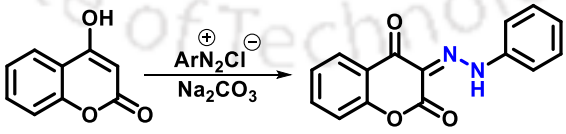
Scheme 4. Synthesis of sulfonylhydrazone

Lung targeting was developed by synthesisinghydrazone derivatives under solvent-free and thermal conditions by reacting azo coumarins with hydrazines using maltose as a biodegradable catalyst by Abdou *et al.*,[19]



Scheme 5. Synthesis of hydrazone

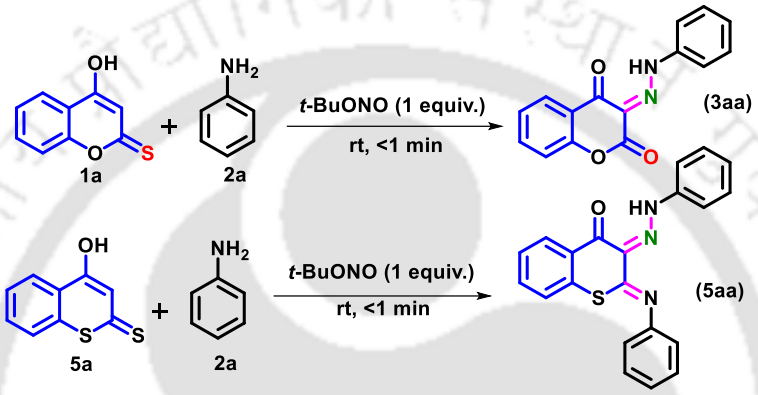
Metwally*et al.*,reported[20] the synthesis of novel azo disperse dyes with better dyeing properties *via* the reaction of hydrazine hydrate with 2,3,4-chromantrione-3-arylhydrazones.



Scheme 6. Synthesis of hydrazone

5a. 3. Results and Discussions

This chapter presents the synthetic method solvent-free synthesis for a series of diversely functionalized (*E*)-3-(2-arylhydrazineylidene)chromane-2,4-dione from 4-hydroxy-2*H*-chromene-2-thione and 4-hydroxydithiocoumarin with aniline and *tertiary* butyl nitrite under solvent- and catalyst-free conditions in 76-86% yields.



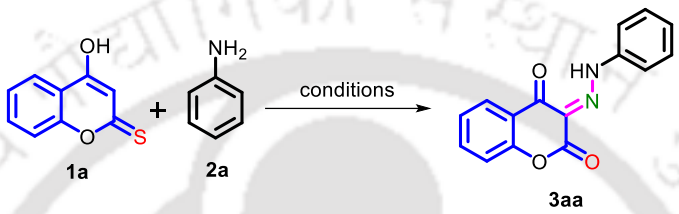
Scheme 7. Synthesis of (*E*)-3-(2-arylhydrazineylidene)chromane-2,4-dione derivatives

For our present study, various derivatives of 4-hydroxy-2*H*-chromene-2-thione (**1a**) and 4-hydroxydithiocoumarin (**5a**) were prepared following the reported procedure.[10, 21]

A mixture of 4-hydroxy-2*H*-chromene-2-thione (**1a**, 0.25 mmol), aniline (**2a**, 0.25 mmol) and *tert*-butyl nitrite (0.25 mmol) was taken in a 10 mL round-bottomed flask and stirred at room temperature for less than one minute to obtain **3aa** in 86% yield (**Table 5a.1, entry 1)**. The isolated product was characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and HRMS. Due to the disappearance of the peak at δ = 6.90 ppm for C-2 hydrogen in the ^{1}H NMR spectrum, it is concluded that the coupling took place at the C-2 position of 4-hydroxythiocoumarin. In addition, the peak emerged at 13.03 as a singlet for the N–H proton.To enhance the yield of the anticipated product, the model reaction was performed under the same reaction condition in the presence of solvents such as acetonitrile and DMSO (**Table1, entries 2** and **3**). However, no

improvement in the yield of **3aa** took place. To overcome these, we tried to increase the reaction timeinvolvement in the reaction(**Table1, entry 4**), which yielded product **3aa** to only 26%. Next, we tried withanother nitriteagent, sodium nitrite, along with acetonitrile as a solvent, with increasing the time as well (**Table1, entries 5**, **6 and 7**), and the anticipated product was only

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



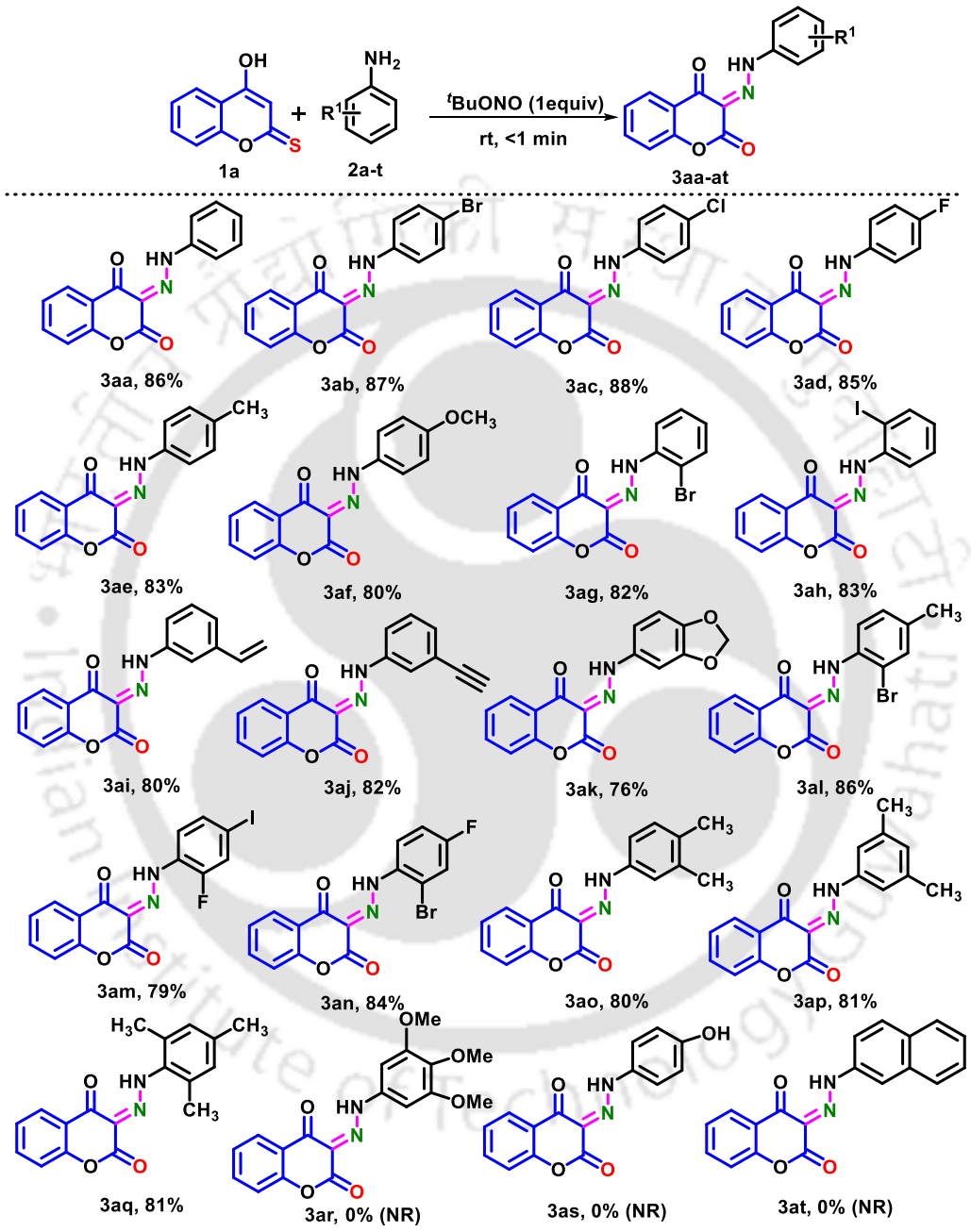
Sl. No.	Solvent	Nitrite Reagent (1 equiv.)	Time (sec)	Yield[a,b] (%)
1	**-**	**^{t}BuONO**	**<1**	**86**
2	CH_3CN	^{t}BuONO	5	12
3	DMSO	^{t}BuONO	5	10
4	-	^{t}BuONO	1 min	26
5	-	$NaNO_2$	5	trace
6	-	$NaNO_2$	1 min	trace
7	CH_3CN	$NaNO_2$	5	-

[a]All the reactions were carried out using 4-hydroxy-2*H*-chromene-2-thione (**1a**), primary aniline (**2a**) was reacted with *tert*-butyl nitrite (1 equivalent) or sodium nitrite (1 equivalent) in absence of any catalysts or solvents at room temperature. [b]Isolated yield.

seen in trace amount on TLC and with solvent left no trace of the desired product. Therefore, the optimal conditions were established as follows: 1 equivalent of *tert*-butyl nitrite with 0.25 mmol of 4-hydroxy-2*H*-chromene-2-thione and 0.25 mmol of primary amine at room temperature for 5 seconds (**Table1, entry 1**). Having established the optimized reaction conditions, the scope of the substrate towards aza coupling was investigated (**Table2**). A wide range of primary aromatic amines were well tolerated, affording the corresponding phenylhydrazineylidene) chromane-2,4-dione derivatives **3aa**-**3aq**in 75-86% yields. Aromatic amine derivatives bearing halogen groups, such as Br, Cl, F, and I, afforded the corresponding products **3aa**-**3ad**, **3ag**, and **3ah** yields of 82-88%. Differently substituted primary aromatic amines having both electron-donating and electron-withdrawing groups, such as methyl, methoxy, dimethyl, and trimethyl, obtained the anticipated product **3ae**-**3af** with 83-80% yields. Using 4-vinlyaniline, **3ai** and 4-ethynylaniline, **3aj** as substrates contributed to 80-82% yield to this reaction.Benzo[*d*][1,3]dioxol-5-amine on reacting with 4-hydroxy-2*H*-chromene-2-thione afforded the desired product **3ak** in 76% yields.Aromatic primary amines with disubstituted and trisubstituted halogen contributed to this reaction with the desired product **3al-3aq**in 79-86% yields. Unfortunately, the reactions of **1a** with aryl amines **2r** and **2s** did not provide the desired products **3ar** and **3as** under identical conditions. Similarly, the reaction was failure with 2-naphthylamine to get the expected product **3at.**

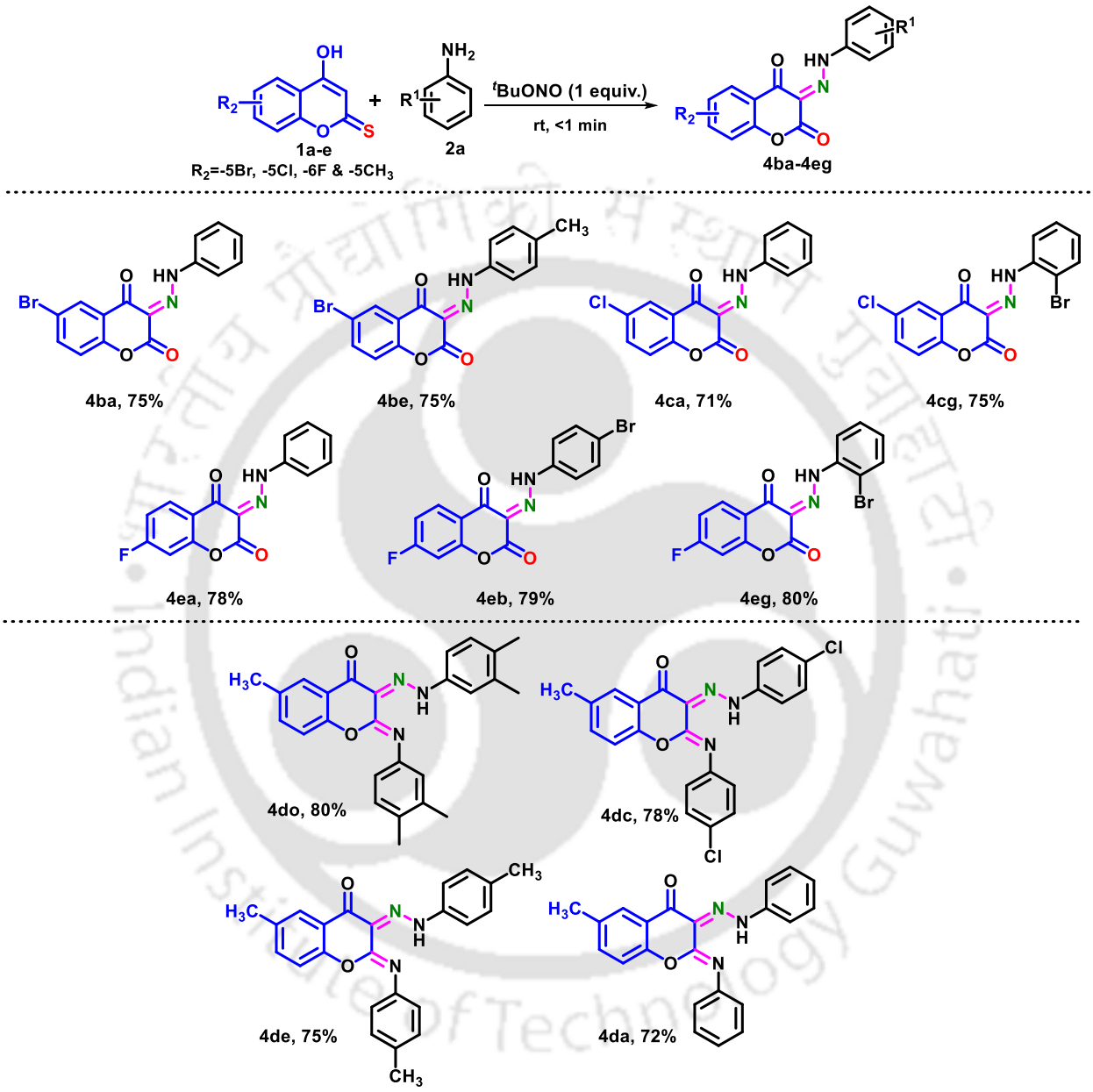
Motivated by the above-discussed successful results, we further investigated the scope and generality of the developed protocol with substituted 4-hydroxy-2*H*-chromene-2-thione (**1a**) and different aromatic primary amines (**2a**) **4a-k,** and results are shown in **Table 3**. It was observed that when the reaction was performed between 6-bromo-4-hydroxy-2*H*-chromene-2-thione and aniline derivatives under the optimized reaction conditions, the expected product **4ba-4be** was obtained in 75 % yields. Similarly, we carried out the reaction with 6-chloro-4-hydroxy-2*H*-chromene-2-thione and aniline as well as with 2-bromo aniline to provide the desired products **4ca-4cg** in 71 and 75% yields, respectively.Furthermore, we also examined the reaction of 7-fluoro-4-hydroxy-2*H*-chromene-2-thione with aniline, 4-bromoaniline and 2-bromoaniline; the reaction proceeded smoothly to provide the expected products **4ea-4eg** in 78-80 % yields.

Table 2. Scope of (*E*)-3-(2-phenylhydrazineylidene)chromane-2,4-dione derivatives[a,b]



[a]All the reactions were carried out using 4-hydroxy-2*H*-chromene-2-thione (**1a**), aniline (**2a**) and *tert*-butyl nitrite (1 equivalent) at room temperature. [b]Isolated yield is shown. NR= No Reaction

Table 3. Scope of (*E*)-3-(2-phenylhydrazineylidene)chromane-2,4-dione derivatives[a,b]

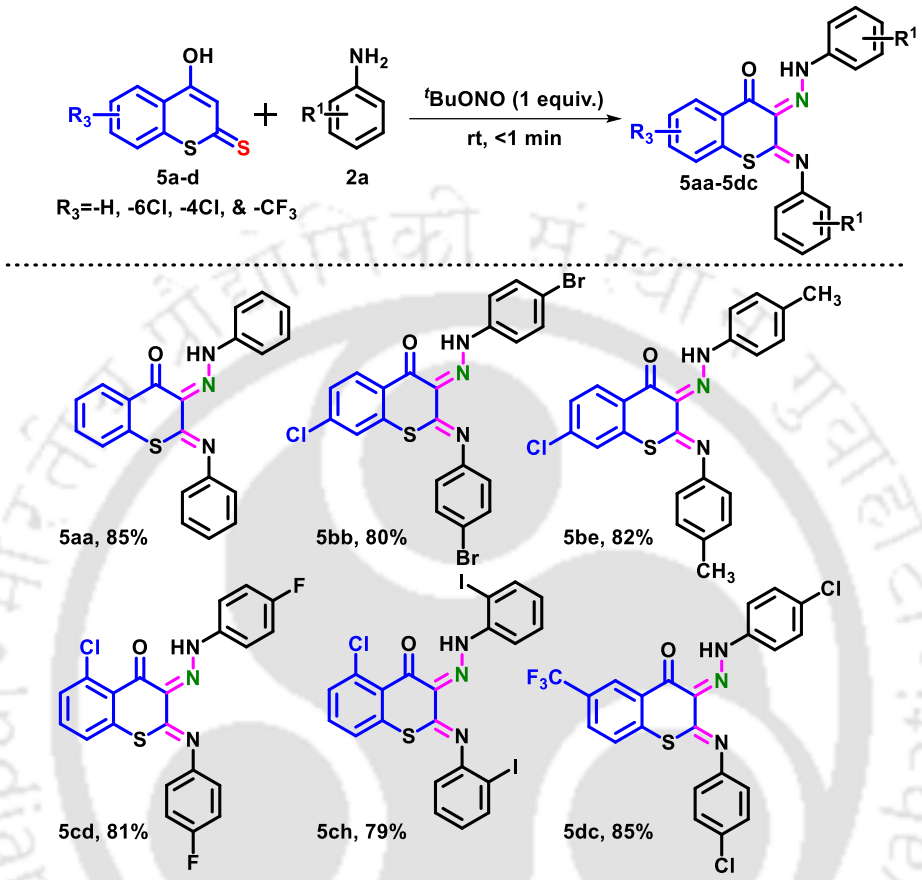


[a]All the reactions were carried out using 4-hydroxy-2*H*-chromene-2-thione (**1a**), aniline (**2a**) and *tert*-butyl nitrite (1 equivalent) at room temperature. [b]Isolated yield is shown.

Then, the reaction screening was performed with 4-hydroxy-6-methyl-2*H*-chromene-2-thione (**1d**). Then, the reaction screening was performed with 4-hydroxy-6-methyl-2*H*-chromene-2-thione (**1d**), another methyl derivative of 4-hydroxy-2*H*-chromene-2-thione. There were five signals in the ^{13}C spectra of **4do**, which left us in commotion as to what the product might be. HRMS confirmed that two aniline molecules took part in the reaction, forming an imine moiety. Such classes of products were only formed when we performed the reaction with 4-hydroxy-6-methyl-2*H*-chromene-2-thione and substrates with diverse substituents of aniline yielded the corresponding products (**4da-4do**) in moderate to good yields.Next, a series of reactions were carried out using 4-hydroxydithiocoumarin (**5a**), prepared by the reported procedure,[21] primary aniline (**2a**) and *tert*-butyl nitrite using the optimized reaction conditions and the results are summarized in **Table 4**. Interestingly, a different product, **5aa,** was obtained, confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and single crystal XRD. We observed two singlets in the ^{1}H NMR spectrum for six protons instead of one singlet for methyl protons of para-toluidine. In ^{13}C, we obtained two peaks at the up-field shift. We can conclude from the data that two aniline molecules are being incorporated in the reaction. Hence, single X-ray crystallographic data confirmed the product **5aa**. The reaction proceeded smoothly to provide the expected products **5aa**–**5dc** in 79-85% yields with different derivatives of 4-hydroxydithiocoumarin and aryl amine derivatives reactions under similar reaction conditions. Likewise, when -5Cl, -7Cl and -6CF_3 substituted 4-hydroxydithiocoumarin reacted with substituted electron-donating and electron-withdrawing groups of primary aniline gave rise to the products 5ab-5dc in 79-85% yields (**Table 4**).

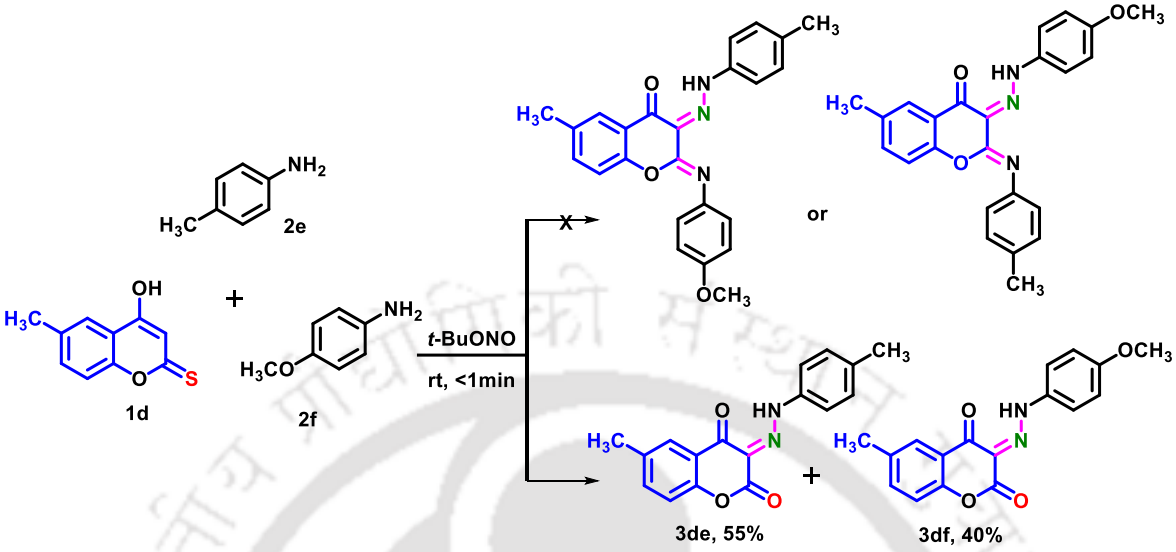
Next, when using 4-hydroxy-6-methyl-2*H*-chromene-2-thione (**1d**) as substrates to check whether the addition of different anilines to the system results in cross-substitution products, **Scheme 8** was performed under the same reaction conditions using 4-methyl aniline (**2e**) and 4-methoxy aniline (**2f**) as the substrate. To our surprise, it was found that instead of the cross-substitution products, two products were obtained, **3de** and **3df**, with 55% and 40% yield, where each aniline reacted differently with 4-hydroxy-6-methyl-2*H*-chromene-2-thione (**1d**). This proves that having two different anilines wouldn't form any cross-substitution products.

Table 4. Scope of (*E*)-3-(2-phenylhydrazineylidene)chromane-2,4-dione derivatives[a,b]

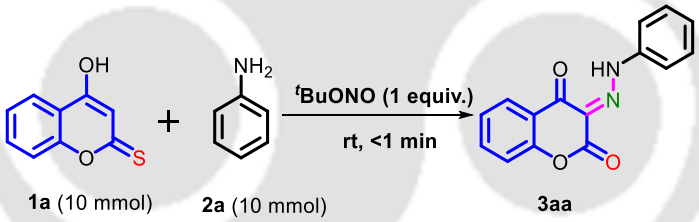


[a]All the reactions were carried out using 4-hydroxydithiocoumarin (**1a**), aniline (**2a**) and *tert*-butyl nitrite (1 equivalent) at room temperature. [b]Isolated yield is shown.

In order to check the efficacy of the present protocol, we carried out a scale-up reaction using 4-4-hydroxy-2*H*-chromene-2-thione (**1a**, 1.78 g, 10 mmol), aniline (**2a**, 0.930 g, 10 mmol) and *tertiary* butyl nitrite under similar reaction conditions as presented in **Scheme 9**. The reaction proceeded smoothly and provided 2.35 g of the expected product **3aa**, in 87% yield.To explore the energy profile of the proposed mechanism, quantum chemical analysis of eachstep of the mechanism shown in **Scheme 10** and **Scheme 11** has been performed using the

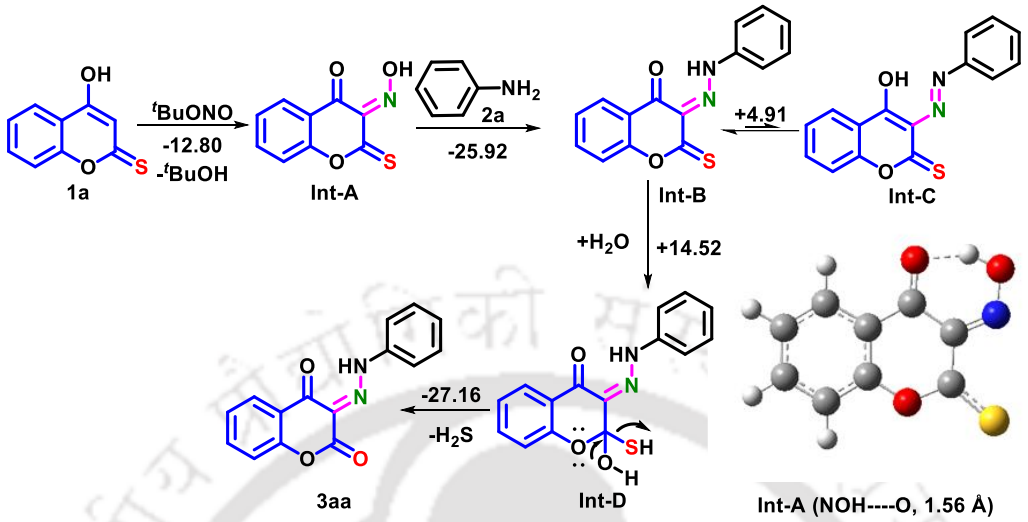


Scheme 8. All the reactions were carried out using 4-hydroxy-6-methyl-2*H*-chromene-2-thione (**1d**), *p*-toluidine (**2e**), 4-methoxyaniline (**2f**) and *tert*-butyl nitrite (1 equivalent) at room temperature.



Scheme 9. Gram Scale Synthesis

B3LYP/6-31+G(d,p) level.The energy released during this reaction is -51.36 kcal/mol, highly exergonic. Starting material 4-hydroxy-2*H*-chromene-2-thione (**1a**) reacts with *tertiary* butyl nitrite to give **Int-A** and tertiary butanol; the step is exergonic by 12.8 kcal/mol. **Int-A** is stabilized by intramolecular H-bonding. **Int-A** reacts with aniline to give **Int-B**, releasing water molecule, exergonic 25.92 by kcal/mol. **Int-B** can undergo a 1,5-*H* shift to give **Int-C**, although the process is endergonic by 4.9 kcal/mol, proving the preferable existence and participation of **Int-B** in the reaction mechanism. Adding water to **Int-B** leads to **Int-D**, an endergonic process of



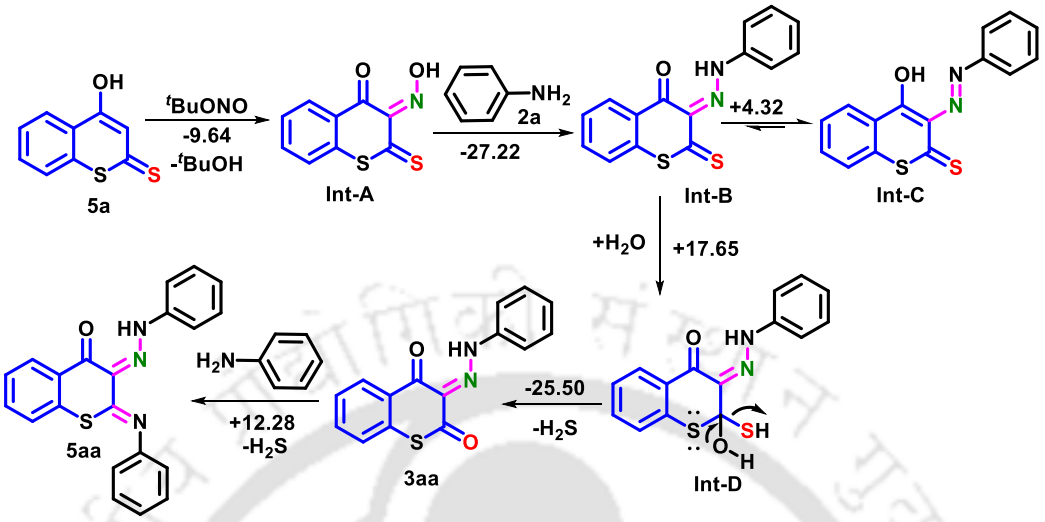
Scheme 10. Plausible mechanism for the formation of 3aa and energy change at every reaction step obtained from quantum chemical analysis. All the energy values are in kcal/mol.

14.92 kcal/mol. **Int-D** forms **3a** by releasing hydrogen sulphide, exergonic by 27.16 kcal/mol. The energy data from quantum chemical analysis clearly supports the proposed mechanistic pathway.

The quantum chemical calculations were carried out using the Gaussian 16 suite of programs.[22] Geometry optimization of compounds was performed by DFT using the B3LYP method.[23] The basis set used was 6-31+G(d,p) for C, H, N, O and S. The frequency calculations were carried out on all the structures to verify the character of stationary points (minima v/s saddle point).[24] The NBO charges were estimated to explore the nucleophilicity and electrophilicity of the reacting centres.

5a. 4. Conclusion

We have accomplished efficient solvent-free synthesis for a series of diversely functionalized (*E*)-3-(2-arylhydrazineylidene)chromane-2,4-dione from 4-hydroxy-2*H*-chromene-2-thione (**1a**) and 4-hydroxydithiocoumarin (**5a**) with aniline (**2a**) and *tertiary* butyl nitrite. Herein, thereactivity of 4-hydroxy-2*H*-chromene-2-thione (**1a**) and 4-hydroxydithiocoumarin (**5a**) follows selective pathways for the formation of the desired product. This protocol



Scheme 11. Plausible mechanism for the formation of 5aa and energy change at every reaction step obtained from quantum chemical analysis. All the energy values are in kcal/mol.

Offers simplicity in the reaction condition, (**a**) without aiding any harsh reaction conditions, (**b**) use of commercially available low-cost starting materials with broad substrate scope and (**c**) high yields of products at short reaction time.

5a.5. Experimental Section

5a.5a. Procedure for the synthesis of 4-hydroxy-2*H*-chromene-2-thione derivatives (1a-e)[10]

A wide variety of 4-hydroxy-2*H*-chromene-2-thione(**1a-e**) was prepared by following the previouslyreported literature procedure.

5a.5b. Procedure for the synthesis of 4-hydroxydithiocoumarin (5a-d)[21]

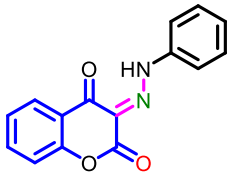
Into a 100 mL round-bottomed flask, a mixture of 2'-chloroacetophenone (10 mmol) and carbon disulfide (20 mmol) was taken in a mixture of DMFat 15-20 ˚C. Sodium hydride was added portion-wise for 20 min and the mixture was stirred over 3 h. Next, 1 mL methanol was added and was stirred for another 30 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 wasextracted

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.

5a.5c. Procedure for the synthesis of (*E*)-3-(2-arylhydrazineylidene)- chromane-2,4-dione derivatives (3aa-3at, 4ea-4da, 5aa-5dc)

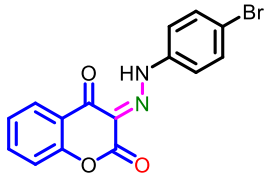
A mixture of 4-hydroxy-2*H*-chromene-2-thione (**1a**, 0.25 mmol), or 4-hydroxydithiocoumarin (**5a**), aromatic primary amine (**2a**, 0.25 mmol) and *tert*-butyl nitrite (0.25 mmol) was taken in 10 mL round-bottomed flask and stirred at room temperature. The reaction mixture becomes red, indicating that the reaction took place. After stirring, effervescence was observed. The completion of the reaction was monitored by TLC, which gave a yellow-coloured spot on TLC. On completion of the reaction, the crude residue was extracted with dichloromethane (10 mL x 1). The organic layer was washed with water (10 mL x 2) and 5 mL of brine solution and dried over anhydrous sodium sulfate. Finally, the solvent was removed in a rotatory evaporator, and

the crude residue was purified through a silica gel (60–120 mesh) column chromatography to obtain products **3aa**, **4ba** and **5aa**. All the other were (*E*)-3-(2-arylhydrazineylidene)chromane-2,4-dione derivatives (**3aa-3at**, **4ba-4da**, **5aa-5dc**) were synthesized following the same protocol.



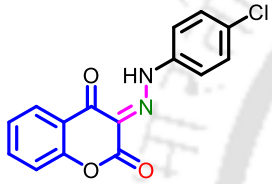
(*E*)-3-(2-phenylhydrazineylidene)chromane-2,4-dione (3aa). Yellowish brown solid (57 mg, 86%), mp 165°C-166°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.40 (s, 1H), 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.70 (s, 1H), 7.68 (s, 1H), 7.66 (d, *J* = 6.6 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 5.2 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.7, 159.2, 154.6, 140.6, 136.4, 130.0, 128.7, 126.97, 124.8, 122.4, 120.4, 118.2, 117.8; IR (KBr) ν_{max}/cm^{-1}3069 (NH), 1649 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{15}H_{11}N_2O_3$ 267.0764 [M + H$^+$]; found 267.0764.

(*E*)-3-(2-(4-bromophenyl)hydrazineylidene)chromane-2,4-dione (3ab). Yellowish brown solid



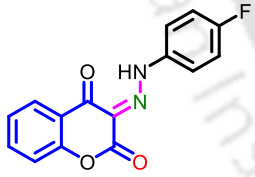
(74 mg, 87%), mp 245°C-247°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.36 (s, 1H), 8.20 (d, *J* = 2.5 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.53 – 7.48 (m, 2H), 7.39 (tt, *J* = 6.9, 1.2 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 159.0, 154.7, 139.7, 136.6, 133.2, 127.0, 124.9, 122.8, 122.1, 120.3, 119.5, 117.8; IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1629 (C=O), 1481 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}BrN_2O_3$ 344.9869 [M + H^+]; found 344.9869.

***(E)*-3-(2-(4-chlorophenyl)hydrazineylidene)chromane-2,4-dione (3ac).** Yellowish brown solid



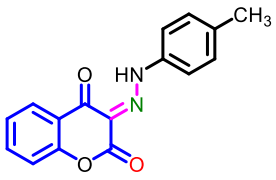
(65 mg, 86%), mp 162°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.35 (s, 1H), 8.08 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.63 – 7.61 (m, 2H), 7.46 – 7.44 (m, 2H), 7.34 – 7.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 174.8, 168.2, 166.5, 157.8, 140.9, 131.4, 130.2, 129.2, 119.5, 118.8, 118.1, 113.7, 104.7; IR (KBr) ν_{max}/cm^{-1} 3068 (NH), 1740 (C=O), 1466 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}ClN_2O_3$ 301.0374 [M + H^+]; found 301.0378.

(*E*)-3-(2-(4-fluorophenyl)hydrazineylidene)chromane-2,4-dione (3ad). Yellowish brown solid

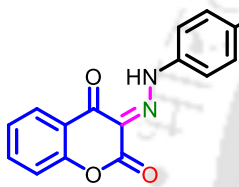


(60 mg, 85%), mp 218°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.47 (s, 1H), 8.08 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.69 – 7.65 (m, 3H), 7.34 – 7.28 (m, 2H), 7.18 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 162.4 (d, *J* = 250.3 Hz), 159.1, 154.6, 137.0 (d, *J* = 2.7 Hz), 136.4, 126.9, 124.8, 122.4, 120.3,119.9 (d, *J* = 8.7 Hz), 117.8, 117.1 (d, *J* = 23.4 Hz); IR (KBr) ν_{max}/cm^{-1} 3068 (NH), 1603 (C=O), 1466 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}FN_2O_3$ 285.0670 [M + H^+]; found 285.0671.

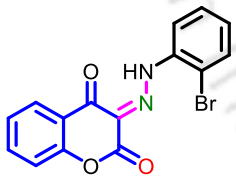
(*E*)-3-(2-(*p*-tolyl)hydrazineylidene)chromane-2,4-dione (3ae). Yellowish brown solid (57 mg, 83%), mp 178°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.51 (s, 1H), 8.08 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.66 (td, *J* = 8.3, 7.9, 1.7 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.30 – 7.28 (m, 2H), 7.27 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 159.4, 154.5, 139.3, 138.4, 136.1, 130.6, 126.8, 124.7, 122.0, 120.4, 118.2, 117.7, 21.4; IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1644 (C=O), 1492 (C-O); HRMS (ESI) calculated for $C_{16}H_{13}N_2O_3$ 281.0921 [M + H^+]; found 281.0920.



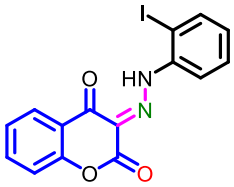
(*E*)-3-(2-(4-methoxyphenyl)hydrazineylidene)chromane-2,4-dione (3af). Yellowish brown solid (58 mg, 80%), mp 180°C-186°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.75 (s, 1H), 8.09 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.65 (dd, *J* = 7.9, 5.6 Hz, 3H), 7.34 – 7.29 (m, 2H), 7.00 (d, *J* = 9.1 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 160.4, 159.6, 154.5, 136.0, 134.2, 126.7, 124.6, 121.7, 120.5, 120.0, 117.7, 115.3, 55.8; IR (KBr) ν_{max}/cm^{-1} 3080 (NH), 1607 (C=O), 1465 (C-O); HRMS (ESI) calculated for $C_{16}H_{13}N_2O_4$ 297.0870 [M + H^+]; found 297.0869.



(*E*)-3-(2-(2-bromophenyl)hydrazineylidene)chromane-2,4-dione (3ag). Yellowish brown solid (70 mg, 82%), mp 235°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.33 (s, 1H), 8.14 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.70 – 7.66 (m, 1H), 7.64 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.21 (td, *J* = 7.7, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 158.9, 154.6, 139.0, 136.7, 133.2, 129.2, 129.1, 127.2, 124.9, 123.6, 120.3, 118.9, 117.8, 113.2; IR (KBr) ν_{max}/cm^{-1} 3072 (NH), 1629 (C=O), 1480 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}BrN_2O_3$ 344.9869 [M + H^+]; found 344.9869.

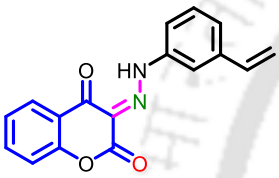


(*E*)-3-(2-(2-iodophenyl)hydrazineylidene)chromane-2,4-dione (3ah). Yellowish brown solid



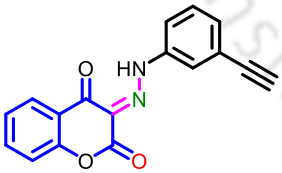
(81 mg, 83%), mp 170°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.19 (s, 1H), 8.16 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.88 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.69 (td, *J* = 7.9, 7.2, 1.7 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 13.3, 5.7 Hz, 2H), 7.07 (td, *J* = 7.6, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 159.0, 154.7, 141.8, 139.8, 139.8, 136.7, 130.0, 129.5, 127.3, 124.9, 120.4, 119.1, 117.8, 87.1; IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1650 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}IN_2O_3$ 392.9731 [M + H^+]; found 392.9731.

(*E*)-3-(2-(3-vinylphenyl)hydrazineylidene)chromane-2,4-dione (3ai). Yellowish brown solid



(57 mg, 80%), mp 175°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.42 (s, 1H), 8.10 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.57 – 7.55 (m, 1H), 7.44 (s, 1H), 7.41 – 7.37 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.79 – 6.72 (m, 1H), 5.87 (d, *J* = 17.5 Hz, 1H), 5.39 (d, *J* = 10.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 159.2, 154.6, 140.9, 139.7, 136.4, 135.6, 130.1, 126.9, 126.4, 124.8, 122.4, 120.4, 117.8, 117.5, 116.2, 115.7; IR (KBr) ν_{max}/cm^{-1} 3078 (NH), 1650 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{17}H_{13}N_2O_3$ 293.0921 [M + H^+]; found 293.0919.

(*E*)-3-(2-(3-ethynylphenyl)hydrazineylidene)chromane-2,4-dione (3aj). Yellowish brown



solid (59 mg, 82%), mp 219°C-222°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.28 (s, 1H), 8.09 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.81 (s, 1H), 7.70 – 7.64 (m, 2H), 7.44 (d, *J* = 7.0 Hz, 2H), 7.35 – 7.29 (m, 2H), 3.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 158.9, 154.7, 140.8, 136.6, 131.9, 130.0, 127.1, 124.8, 124.3, 122.9, 121.4, 120.3, 118.4, 117.8, 82.2; IR (KBr) ν_{max}/cm^{-1} 3002 (NH), 1649 (C=O), 1441 (C-O); HRMS (ESI) calculated for $C_{17}H_{11}N_2O_3$ 291.0764 [M + H^+]; found 291.0763.

(*E*)-3-(2-(benzo[*d*][1,3]dioxol-5-yl)hydrazineylidene)chromane-2,4-dione (3ak). Yellowish brown solid (58 mg, 76%), mp 225°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.70 (s, 1H), 8.08 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.02 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.07 (d, *J* = 1.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 159.4, 154.5, 149.7, 148.6, 136.1, 135.8, 126.7, 124.7, 120.4, 117.7, 113.4, 108.7, 102.4, 98.9; IR (KBr) ν_{max}/cm^{-1} 3069 (NH), 1736 (C=O), 1469 (C-O); HRMS (ESI) calculated for $C_{16}H_{11}N_2O_5$ 311.0662 [M + H^+]; found 311.0666.

(*E*)-3-(2-(2-bromo-4-methylphenyl)hydrazineylidene)chromane-2,4-dione (3al). Yellowish brown solid (76 mg, 86%), mp 215°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.35 (s, 1H), 8.14 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.70 – 7.67 (m, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.02 (dd, *J* = 8.2, 2.1 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 159.1, 154.6, 139.9, 138.5, 136.6, 132.9, 130.3, 127.2, 124.9, 123.5, 120.4, 119.1, 117.8, 110.1, 21.3; IR (KBr) ν_{max}/cm^{-1} 3069 (NH), 1649 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{16}H_{12}N_2O_3Br$ 359.0026 [M + H^+]; found 359.0026.

(*E*)-3-(2-(2-fluoro-4-iodophenyl)hydrazineylidene)chromane-2,4-dione (3am). Yellowish brown solid (80 mg, 79%), mp 218°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.28 (s, 1H), 8.11 (dd, *J* =7.9, 1.7 Hz, 1H), 7.82 (t, *J* = 8.2 Hz, 1H), 7.69 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 7.63 – 7.59 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 158.7, 154.7, 152.1 (d, *J* = 255.4 Hz), 136.9, 135.1 (d, *J* = 3.8 Hz), 129.3 (d, *J* = 8.4 Hz), 127.2, 125.5 (d, *J* = 19.9 Hz), 125.0, 124.2, 120.2, 119.5, 117.8, 91.5 (d, *J* = 7.4 Hz); IR (KBr) ν_{max}/cm^{-1} 3081 (NH), 1638 (C=O), 1450 (C-O); HRMS (ESI) calculated for $C_{15}H_9N_2O_3FI$ 410.9636 [M + H^+]; found 410.9628.

(*E*)-3-(2-(2-bromo-4-fluorophenyl)hydrazineylidene)chromane-2,4-dione (3an). Yellowish brown solid (75 mg, 84%), mp 220°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.40 (s, 1H), 8.16 – 8.12 (m, 2H), 7.69 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 7.41 (dd, *J* = 7.6, 2.7 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.31 (dd, *J* = 9.0, 4.1 Hz, 1H), 7.20 (td, *J* = 7.2, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 161.4 (d, *J* = 254.0 Hz), 158.9, 154.6, 136.7, 135.7 (d, *J* = 3.3 Hz), 127.2, 124.9, 123.6, 120.3 (d, *J* = 22.0 Hz), 120.2, 120.2 (d, *J* = 8.6 Hz), 117.8, 116.8 (d, *J* = 22.9 Hz), 113.3 (d, *J* = 9.8 Hz); IR (KBr) ν_{max}/cm^{-1} 3067 (NH), 1645 (C=O), 1460 (C-O); HRMS (ESI) calculated for $C_{15}H_9N_2O_3BrFN_2O_3$ 362.9775 [M + H^+]; found 410.9628.

***(E)*-3-(2-(3,4-dimethylphenyl)hydrazineylidene)chromane-2,4-dione (3ao).** Yellowish brown solid (58 mg, 80%), mp 160°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.52 (s, 1H), 8.08 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.22 (d, *J* = 8.1 Hz, 1H), 2.33 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 159.5, 154.5, 138.9, 138.6, 136.0, 131.0, 131.0, 126.8, 124.6, 121.9, 120.5, 119.1, 117.7, 116.0, 19.9, 19.8; IR (KBr) ν_{max}/cm^{-1} 3071 (NH), 1666 (C=O), 1466 (C-O); HRMS (ESI) calculated for $C_{17}H_{15}N_2O_3$ 295.1077 [M + H^+]; found 295.1077.

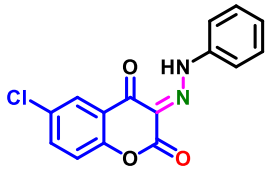
(*E*)-3-(2-(3,5-dimethylphenyl)hydrazineylidene)chromane-2,4-dione (3ap). Yellowish brown solid (59 mg, 81%), mp 206°C-210°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.41 (s, 1H), 8.09 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.38 – 7.33 (m, 1H), 7.31 (d, *J* = 2.0 Hz, 2H), 7.28 (d, *J* = 1.1 Hz, 1H), 6.99 (s, 1H), 2.38 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 159.4, 154.5, 140.6, 140.1, 136.2, 130.7, 126.9, 124.7, 122.1, 120.5, 117.7, 116.1, 21.4; IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1665 (C=O), 1468 (C-O); HRMS (ESI) calculated for $C_{17}H_{15}N_2O_3$ 295.1077 [M + H^+]; found 295.1074.

(*E*)-3-(2-mesitylhydrazineylidene)chromane-2,4-dione (3aq). Yellowish brown solid (62 mg, 81%), mp 214°C-218°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.51 (s, 1H), 8.11 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.65 (ddd, *J* = 8.4, 7.3, 1.8 Hz, 1H), 7.34 – 7.29 (m, 2H), 6.97 (d, *J* = 4.2 Hz, 2H), 2.52 (d, *J* = 16.3 Hz, 6H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 159.5, 154.5, 138.6, 135.9, 135.2, 130.9, 130.9, 130.8, 126.8, 124.5, 122.3, 120.5, 117.7, 21.2, 19.7, 19.4; IR (KBr) ν_{max}/cm^{-1} 3072 (NH), 1649 (C=O), 1465 (C-O); HRMS (ESI) calculated for $C_{18}H_{17}N_2O_3Na$ 309.1234 [M + Na^+]; found 331.1053.

(*E*)-6-bromo-3-(2-phenylhydrazineylidene)chromane-2,4-dione (4ba). Yellowish brown solid (65 mg, 75%), mp 220°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.35 (s, 1H), 8.19 (d, *J* = 2.5 Hz, 1H), 7.74 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.28, 158.73, 153.49, 140.52, 139.03, 130.13, 129.44, 129.11, 122.05, 121.83, 119.71, 118.48, 117.75; IR (KBr) ν_{max}/cm^{-1} 3083 (NH), 1621 (C=O), 1464 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}N_2O_3Br$ 344.9869 [M + H^+]; found 344.9873.

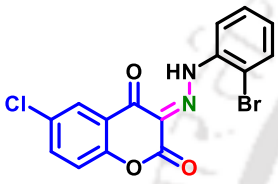
(*E*)-6-bromo-3-(2-(*p*-tolyl)hydrazineylidene)chromane-2,4-dione (4be). Yellowish brown solid (67 mg, 75%), mp 218°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.46 (s, 1H), 8.17 (d, *J* = 2.5 Hz, 1H), 7.72 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 3H), 7.18 (d, *J* = 8.7 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 158.9, 153.4, 139.8, 138.8, 138.2, 130.7, 129.3, 121.8, 121.6, 119.6, 118.4, 117.6, 21.4; IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1650 (C=O), 1480 (C-O); HRMS (ESI) calculated for $C_{16}H_{12}N_2O_3Br$ 359.0026 [M + H^+]; found 359.0025.

(*E*)-6-chloro-3-(2-phenylhydrazineylidene)chromane-2,4-dione (4ca). Yellowish brown solid



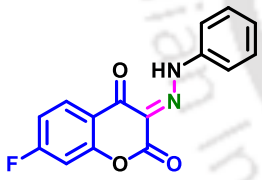
(69 mg, 71%), mp 211°C; ^{1}H NMR (500 MHz, CDCl3) δ 16.36 (s, 1H), 8.40 – 8.16 (m, 1H), 8.03 (s, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.59 (s, 1H), 7.50 (s, 1H), 7.38 (s, 1H), 7.24 (s, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 177.3, 158.7, 153.5, 140.5, 139.0, 130.1, 129.4, 129.1, 122.1, 121.8, 119.7, 118.5, 117.7; IR (KBr) ν_{max}/cm^{-1} 3069 (NH), 1649 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}N_2O_3Cl$ 301.3074 [M + H^+]; found 301.0374.

***(E)*-3-(2-(2-bromophenyl)hydrazineylidene)-6-chlorochromane-2,4-dione (4cg).** Yellowish



brown solid (71 mg, 75%), mp 218°C; ^{1}H NMR (500 MHz, CDCl3) δ 16.30 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 2.6 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.47 (s, 1H), 7.25 – 7.21 (m, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 177.2, 158.4, 153.0, 138.8, 136.5, 133.3, 133.3, 130.7, 129.4, 129.3, 126.6, 121.3, 119.4, 119.1, 113.5; IR (KBr) ν_{max}/cm^{-1} 3065 (NH), 1645 (C=O), 1462 (C-O.

(*E*)-7-fluoro-3-(2-phenylhydrazineylidene)chromane-2,4-dione (4ea). Yellowish brown solid



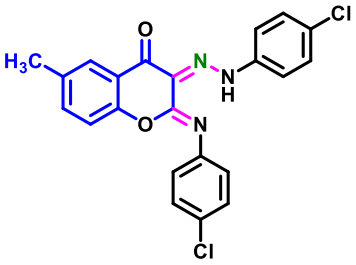
(55 mg, 78%), mp 215°C; ^{1}H NMR (500 MHz, CDCl3) δ 16.35 (s, 1H), 8.11 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.69 – 7.67 (m, 2H), 7.50 (dd, *J* = 7.1, 1.6 Hz, 2H), 7.39 – 7.35 (m, 1H), 7.05 (ddd, *J* = 8.7, 7.9, 2.4 Hz, 1H), 7.00 (dd, *J* = 9.0, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 177.6, 167.4 (*J*= 257.0 Hz), 158.8, 156.0 (*J*= 13.3 Hz), 140.6, 130.0, 129.4 (*J*= 10.95 Hz), 128.8, 121.8, 118.3, 117.1 (*J*= 2.7 Hz), 113.1 (*J*= 22.7 Hz), 105.1 (*J*= 25.7 Hz) ; IR (KBr) ν_{max}/cm^{-1} 3069 (NH), 1649 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}N_2O_3F$ 285.0670 [M + H^+]; found 285.0670.

(*E*)-3-(2-(4-bromophenyl)hydrazineylidene)-7-fluorochromane-2,4-dione (4eb). Yellowish brown solid (71 mg, 79%), mp 222°C; ^{1}H NMR (500 MHz, CDCl3) δ 16.22 (s, 1H), 7.98 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.51 (s, 1H), 7.45 (d, *J* = 8.9 Hz, 2H), 7.25 – 7.18 (m, 2H); ^{13C} NMR (125 MHz, CDCl3) δ 178.9, 159.0, 154.6, 139.7, 136.6, 133.1, 127.7, 127.0, 125.4, 124.9, 122.8, 122.0, 120.3, 119.5, 117.8; IR (KBr) ν_{max}/cm^{-1} 3072 (NH), 1651 (C=O), 1449 (C-O); HRMS (ESI) calculated for $C_{15}H_9N_2O_3BrF$ 362.9775 [M + H^+]; found 362.9773.

(*E*)-3-(2-(2-bromophenyl)hydrazineylidene)-7-fluorochromane-2,4-dione (4eg). Yellowish brown solid (72 mg, 80%), mp 223°C; ^{1}H NMR (400 MHz, CDCl3) δ 16.30 (s, 1H), 8.16 (td, *J* = 9.8, 9.3, 6.9 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.04 (ddd, *J* = 17.7, 8.6, 6.2 Hz, 2H); ^{13}C NMR (150 MHz, CDCl3) δ 177.4, 167.6 (d, *J* = 259.3 Hz), 158.5, 156.1 (d, *J* = 13.4 Hz), 138.9, 133.3, 129.8 (d, *J* = 11.1 Hz), 129.2 (d, *J* = 5.0 Hz), 123.1, 118.9, 117.1 (d, *J* = 2.4 Hz), 113.3 (d, *J* = 12.1 Hz), 113.2, 105.2 (d, *J* = 25.7 Hz); IR (KBr) ν_{max}/cm^{-1} 3072 (NH), 1650 (C=O), 1463 (C-O); HRMS (ESI) calculated for $C_{15}H_9N_2O_3BrF$ 362.9775 [M + H^+]; found 362.9773.

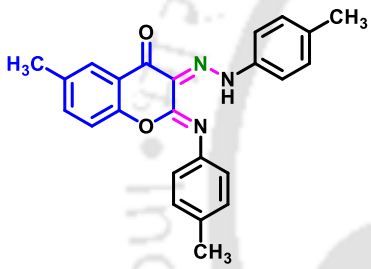
(2*Z*,3*E*)-3-(2-(3,4-dimethylphenyl)hydrazineylidene)-2-((3,4-dimethylphenyl)imino)-6-methylchroman-4-one (4do). Yellowish brown solid (82 mg, 80%), mp 217°C; ^{1}H NMR (500 MHz, CDCl3) δ 15.56 (s, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.45 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.26 (s, 1H), 7.21 (d, *J* = 3.2 Hz, 4H), 2.34 (s, 3H), 2.33 (s, 8H), 2.29 (s, 4H); ^{13}C NMR (125 MHz, CDCl3) δ 175.17, 151.7, 151.0, 144.3, 138.0, 137.6, 137.5, 136.9, 135.2, 134.7, 134.4, 130.5, 130.4, 126.9, 124.9, 122.2, 121.0, 120.1, 119.8, 117.5, 116.5, 20.9, 20.1, 19.9, 19.7, 19.5; IR (KBr) ν_{max}/cm^{-1} 3069 (NH), 1659 (C=O), 1456 (C-O); HRMS (ESI) calculated for $C_{26}H_{26}N_3O_2$ 412.2020 [M + H^+]; found 412.2027.

(2*Z*,3*E*)-3-(2-(4-chlorophenyl)hydrazineylidene)-2-((4-chlorophenyl)imino)-6-methylchroman-4-one (4dc).



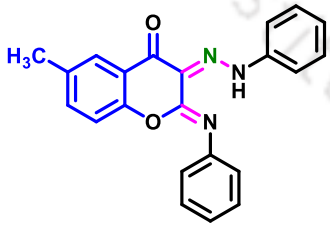
Yellowish brown solid (83 mg, 78%), mp 218°C; ^{1}H NMR (500 MHz, CDCl3) δ 16.34 (s, 1H), 8.02 (d, *J* = 30.2 Hz, 1H), 7.84 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 3H), 7.44 (q, *J* = 10.1, 7.6 Hz, 5H), 7.18 (d, *J* = 8.4 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 159.2, 152.8, 139.3, 137.7, 134.7, 134.0, 130.2, 129.8, 129.4, 126.5, 125.0, 122.8, 120.1, 119.9, 119.2, 117.6, 20.8; IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1650 (C=O), 1463 (C-O); HRMS (ESI) calculated for $C_{22}H_{16}ClN_3O_2$ 424.0614 [M + H^+]; found 424.0618.

(2*Z*,3*E*)-6-methyl-3-(2-(*p*-tolyl)hydrazineylidene)-2-(p-tolylimino)chroman-4-one (4de).



Yellowish brown solid (72 mg, 75%), mp 220°C; ^{1}H NMR (500 MHz, CDCl3) δ 15.58 (s, 1H), 8.08 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.39 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.27 (s, 1H), 7.24 (d, *J* = 7.9 Hz, 3H), 7.11 (d, *J* = 8.4 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)δ 175.1, 151.6, 151.0, 144.2, 138.2, 137.0, 135.8, 135.3, 134.8, 130.1, 129.9, 126.9, 123.6, 122.1, 119.8, 119.5, 116.5, 21.4, 21.2, 20.9.; IR (KBr) ν_{max}/cm^{-1} 3069 (NH), 1650 (C=O), 1461 (C-O); HRMS (ESI) calculated for $C_{24}H_{22}N_3O_2$ 384.1707 [M + H^+]; found 384.1710.

(2*Z*,3*E*)-6-methyl-3-(2-phenylhydrazineylidene)-2-(phenylimino)chroman-4-one (4da).

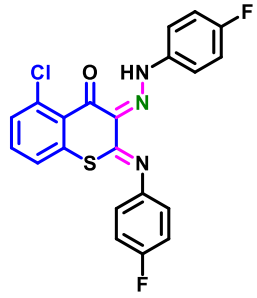


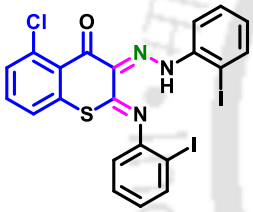
Yellowish brown solid (64 mg, 72%), mp 210°C; ^{1}H NMR (500 MHz, CDCl3) δ 15.70 (s, 1H), 8.08 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 4H), 7.43 – 7.40 (m, 3H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 175.4, 151.8, 150.6, 145.2, 140.6, 135.7, 134.8, 129.6, 129.3, 127.7, 127.0, 125.9, 123.7, 121.9, 120.6, 119.2, 116.6, 20.9; IR (KBr) ν_{max}/cm^{-1} 3072 (NH), 1659 (C=O), 1460 (C-O); HRMS (ESI) calculated for $C_{22}H_{18}N_3O_2$ 356.1394 [M + H^+]; found 356.1399.

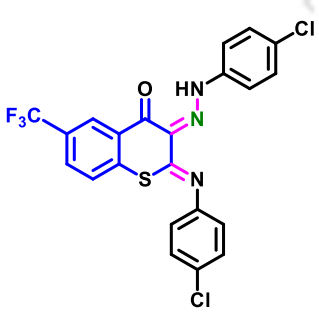
(2*E*,3*E*)-3-(2-phenylhydrazineylidene)-2-(phenylimino)thio-chroman-4-one (5aa). Yellowish brown solid (75 mg, 85%), mp 224°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 16.29 (s, 1H), 8.43 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.51 – 7.45 (m, 3H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.13 (dd, *J* = 11.4, 7.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 157.1, 145.9, 143.1, 133.2, 133.0, 130.4, 130.0, 129.7, 129.6, 126.9, 126.8, 126.2, 126.1, 125.6, 121.6, 118.1; IR (KBr) ν_{max}/cm^{-1} 3068 (NH), 1654 (C=O), 1469 (C-O); HRMS (ESI) calculated for $C_{21}H_{18}N_3OS$ 358.1009 [M + H^+]; found 358.1006.

(2*E*,3*E*)-3-(2-(4-bromophenyl)hydrazineylidene)-2-((4-bromo-phenyl)imino)-7-chlorothiochroman-4-one (5bb). Yellowish brown solid (111 mg, 80%), mp 215°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 16.07 (s, 1H), 8.37 – 8.33 (m, 1H), 7.61 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.50 – 7.47 (m, 2H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.15 (t, *J* = 1.9 Hz, 1H), 6.99 – 6.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 144.6, 141.6, 139.7, 134.3, 132.8, 132.7, 131.8, 127.4, 125.1, 123.0, 119.3; IR (KBr) ν_{max}/cm^{-1} 3063 (NH), 1651 (C=O), 1460 (C-O); HRMS (ESI) calculated for $C_{21}H_{13}Br_2ClN_3OS$ 547.8829 [M + H^+]; found 547.8843.

(2*E*,3*E*)-7-chloro-3-(2-(*p*-tolyl)hydrazineylidene)-2-(p-tolylimino)thiochroman-4-one (5be). Yellowish brown solid (85 mg, 82%), mp 218°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 16.32 (s, 1H), 8.37 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.28 (m, 3H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 1.7 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 2H), 2.43 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 156.0, 142.6, 141.3, 139.2, 137.5, 136.4, 134.8, 131.7, 130.3, 130.2, 128.5,127.2, 125.4, 125.1, 121.8, 118.4, 21.3, 21.2; IR (KBr) ν_{max}/cm^{-1} 3066 (NH), 1651 (C=O), 1461(C-O); HRMS (ESI) calculated for $C_{23}H_{19}ClN_3OS$ 420.0932 [M + H^+]; found 420.0932.

(2*Z*,3*E*)-5-chloro-3-(2-(4-fluorophenyl)hydrazineylidene)-2-((4-fluorophenyl)imino)thiochroman-4-one (5cd).  Yellowish brown solid (85 mg, 81%), mp 234°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 15.83 (s, 1H), 7.59 – 7.53 (m, 2H), 7.42 – 7.38 (m, 1H), 7.32 – 7.29 (m, 1H), 7.25 (s, 1H), 7.19 – 7.14 (m, 2H), 7.11 – 7.07 (m, 2H), 7.06 – 7.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 162.3, 162.1, 160.4, 160.1, 155.8, 141.8, 141.8, 139.3, 139.3, 136.5, 135.0, 132.1, 131.0, 128.0, 127.6, 124.9, 123.3, 123.2, 119.4, 119.3, 116.7, 116.7, 116.5, 116.5; IR (KBr) ν_{max}/cm^{-1} 3065 (NH), 1650 (C=O), 1465 (C-O); HRMS (ESI) calculated for $C_{21}H_{13}F_2ClN_3OS$ 428. .0430 [M + H^+]; found 428.0430.

(2*E*,3*E*)-5-chloro-3-(2-(2-iodophenyl)hydrazineylidene)-2-((2-iodophenyl)imino)thiochroman-4-one (5ch).  Yellowish brown solid (126 mg, 79%), mp 220°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 15.86 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 7.8, 2.1 Hz, 2H), 7.01 (t, *J* = 6.9 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 155.9, 148.9, 143.8, 139.9, 139.4, 136.7, 135.2, 132.3, 131.0, 129.6, 129.4, 128.5, 127.9, 127.7, 127.4, 125.0, 121.1, 118.5, 91.1, 86.9; IR (KBr) ν_{max}/cm^{-1} 3063 (NH), 1649 (C=O), 1466 (C-O); HRMS (ESI) calculated for $C_{21}H_{13}I_2ClN_3OS$ 643.8552 [M + H^+]; found 643.8570.

(2*E*,3*E*)-3-(2-(4-chlorophenyl)hydrazineylidene)-2-((4-chlorophenyl)imino)-6-(trifluoromethyl)thiochroman-4-one (5dc).  Yellowish brown solid (104 mg, 85%), mp 228°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 16.14 (s, 1H), 8.67 (s, 1H), 7.97 – 7.94 (m, 1H), 7.77 (t, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.65 – 7.61 (m, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 6.7 Hz, 2H), 7.40 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 156.7, 150.4, 143.9, 141.3, 137.7, 136.9, 132.9, 132.2, 130.4, 130.3, 130.0, 129.9 (q, *J* = 3.5 Hz), 129.6, 129.2, 127.6 (q, *J* = 3.9 Hz), 127.5, 126.6, 126.5, 126.2, 125.8, 124.4, 123.0, 119.9, 119.4; IR (KBr) ν_{max}/cm^{-1} 3065 (NH),

1659 (C=O), 1460 (C-O); HRMS (ESI) calculated for $C_{22}H_{13}Cl_2F_3N_3OS$ 494.0103 [M + H^+]; found 494.0109.

(*E*)-6-methyl-3-(2-(*p*-tolyl)hydrazineylidene)chromane-2,4-dione (3de). Yellowish brown solid (40 mg), mp 222-223°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.49 (s, 1H), 7.84 (d, *J* = 2.2 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 3H), 7.45 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.28 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 159.6, 152.7, 139.2, 138.4, 137.2, 134.5, 130.6, 126.3, 122.1, 120.0, 118.2, 117.5, 21.4, 20.8; (KBr) ν_{max}/cm^{-1} 3042 (NH), 1620 (C=O), 1438 (C-O); HRMS (ESI) calculated for $C_{17}H_{15}N_2O_3$ 295.1077 [M + H^+]; found 295.1068.

(*E*)-3-(2-(4-methoxyphenyl)hydrazineylidene)-6-methylchromane-2,4-dione (3df). Red solid (34 mg), mp 224°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.74 (s, 1H), 7.85 (d, *J* = 1.3 Hz, 1H), 7.66 – 7.63 (m, 2H), 7.45 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.02 – 6.97 (m, 2H), 3.87 (d, *J* = 1.6 Hz, 3H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 159.4, 152.5, 139.0, 137.1, 134.4, 130.4, 126.2, 121.9, 119.9, 118.1, 117.3, 117.1, 21.2, 20.7; (KBr) ν_{max}/cm^{-1} 3040 (NH),1605 (C=O), 1440 (C-O); HRMS (ESI) calculated for $C_{17}H_{15}N_2O_4$ 311.1026 [M + H^+]; found 311.0998.

(*E*)-3-(hydroxyimino)-6-methyl-2-thioxochroman-4-one (Int-A). White solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.95 (m, 1H), 7.48 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 6.71 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 163.5, 155.5, 136.2, 135.5, 125.5, 123.3, 117.6, 111.3, 21.0.

5a.6b. X-ray Structure of Compounds 5be

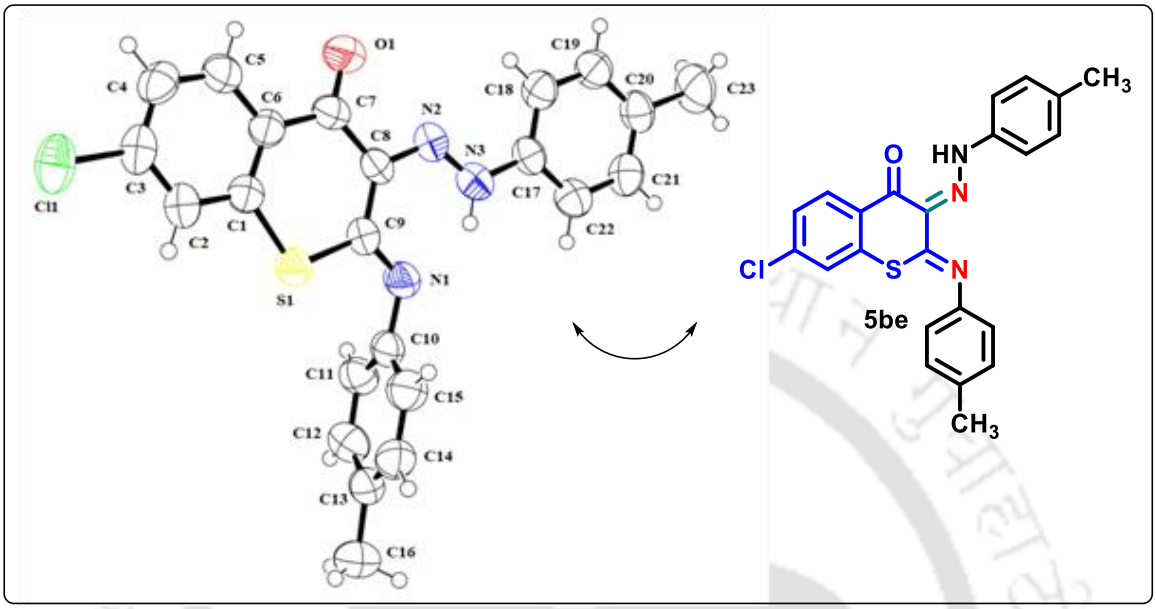


Figure 3. ORTEP diagram of compound **5be**

Table 5. Crystal data and structure refinement for compound 5be

Entry	Identification code	Compound (5be)
1	Empirical formula	$C_{23}H_{18}ClN_3OS$
2	Formula weight	419.91
3	Temperature	297K
4	Wavelength	0.71073
5	Radiation type	Mo K\a
6	Radiation source	Fine-focus sealed tube
7	Crystal system	Triclinic
8	Space group	P -1
9	Cell length	a 10.061(1) b10.6050(11) c11.1053(11)
10	Cell Angle	α101.430 (3) β113.060 (3) δ95.773 (3)
11	Cell Volume	1047.53 (19)
12	Density	1.331
13	Completeness to theta	99.2
14	Absorption correction	multi-scan
15	Refinement method	Full-matrix least-squares on F2
16	Reflection number	22331
17	R(reflections)	0.0872(2162)
18	wR2(reflections)	0.1990(3631)
19	gooF (S)	1.125
20	Theta range	24.943
21	Cell formula units Z	2
22	CCDC no	2359847

Figure 4. ^{1}H NMR spectra of (*E*)-3-(2-(2-bromo-4-methylphenyl)hydrazineylidene)chromane-2,4-dione (3al)

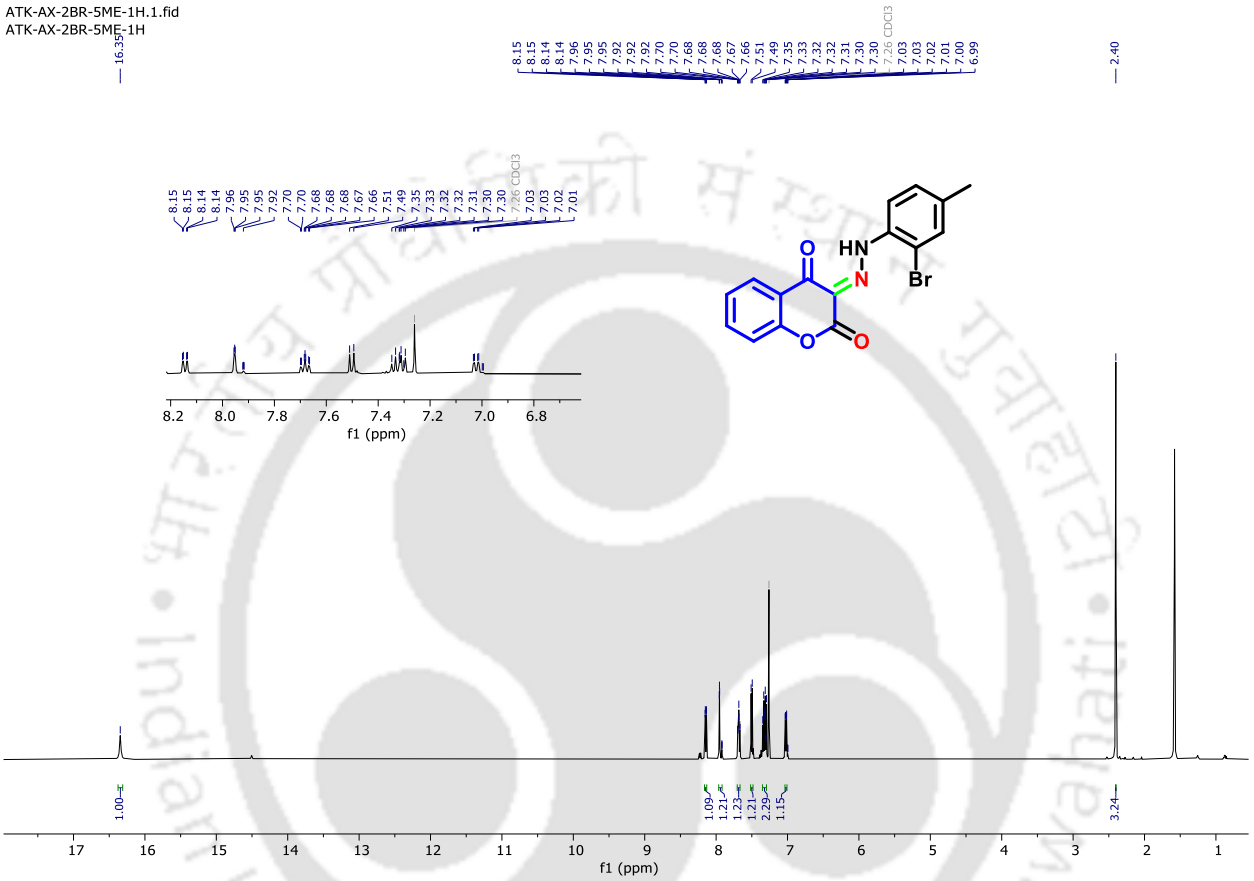


Figure 5. ^{13}C NMR spectra of (*E*)-3-(2-(2-bromo-4-methylphenyl)hydrazineylidene) chroman-2,4-dione (3al)

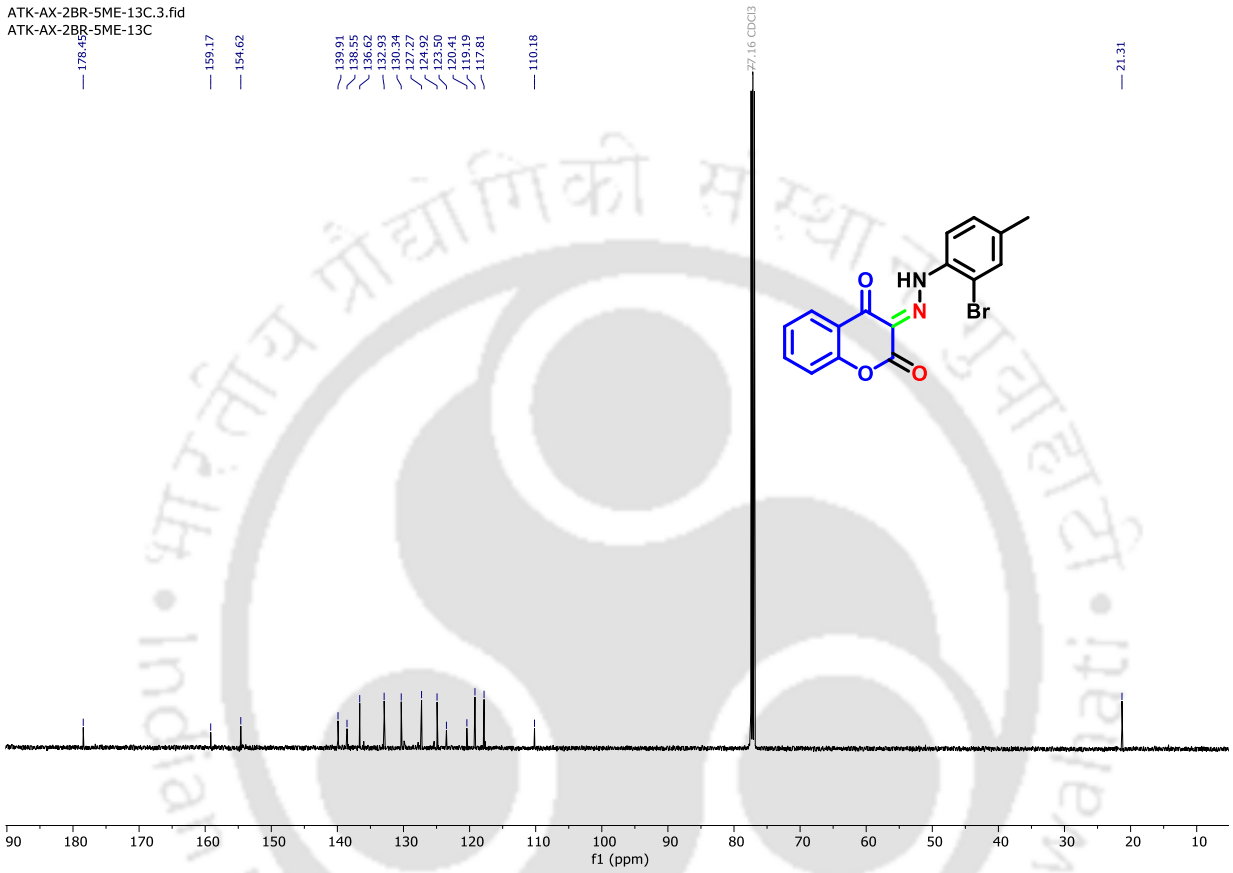


Figure 6. HRMS spectra of (*E*)-3-(2-(2-bromo-4-methylphenyl)hydrazineylidene)chromane-2,4-dione (3al)

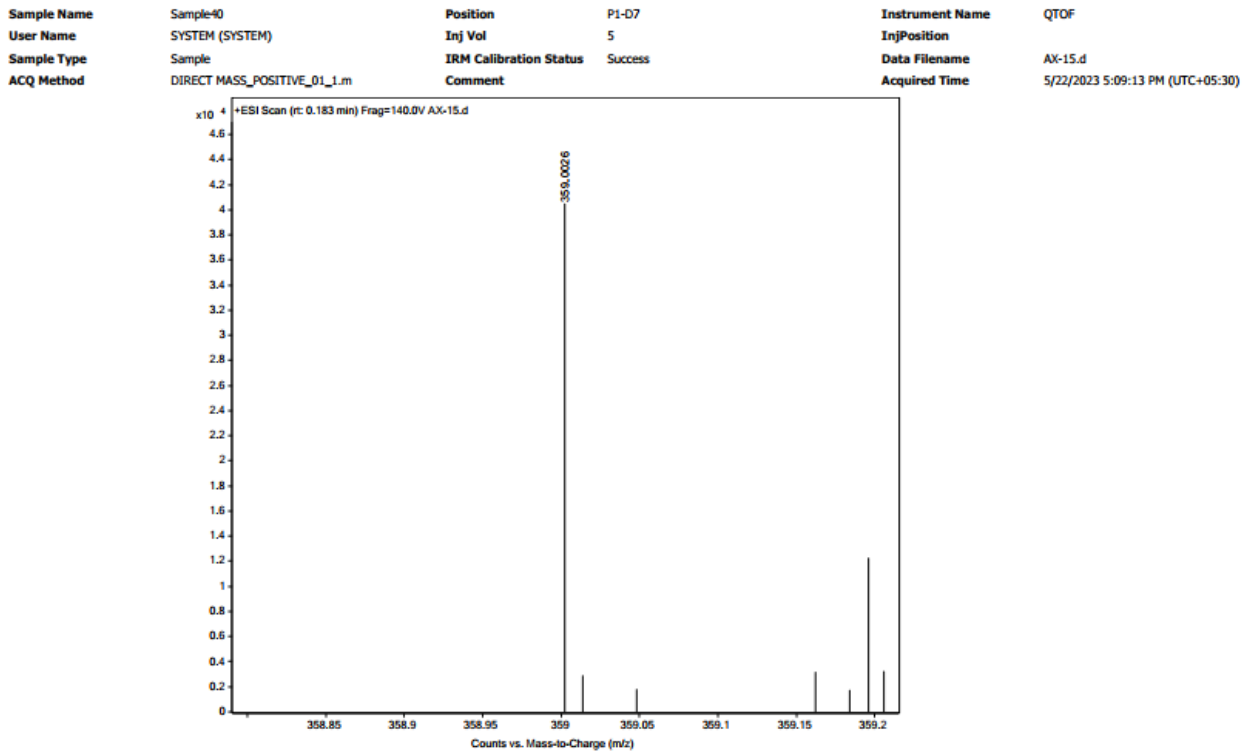


Figure 7. ^{1}H NMR spectra of (*E*)-6-bromo-3-(2-phenylhydrazineylidene)chromane-2,4-dione (4ba)

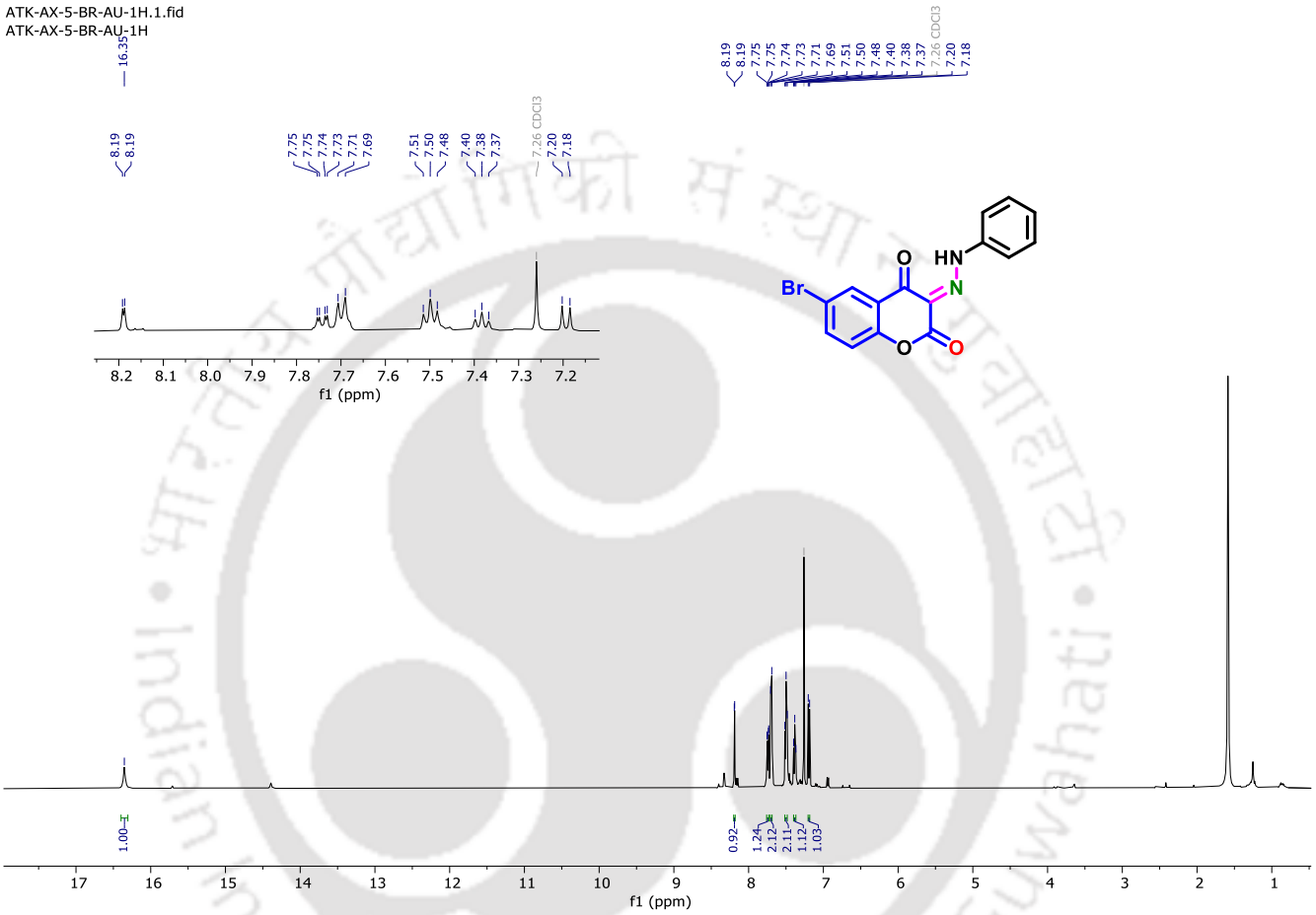


Figure 8. ^{13}C NMR spectra of (*E*)-6-bromo-3-(2-phenylhydrazineylidene)chromane-2,4-dione(4ba)

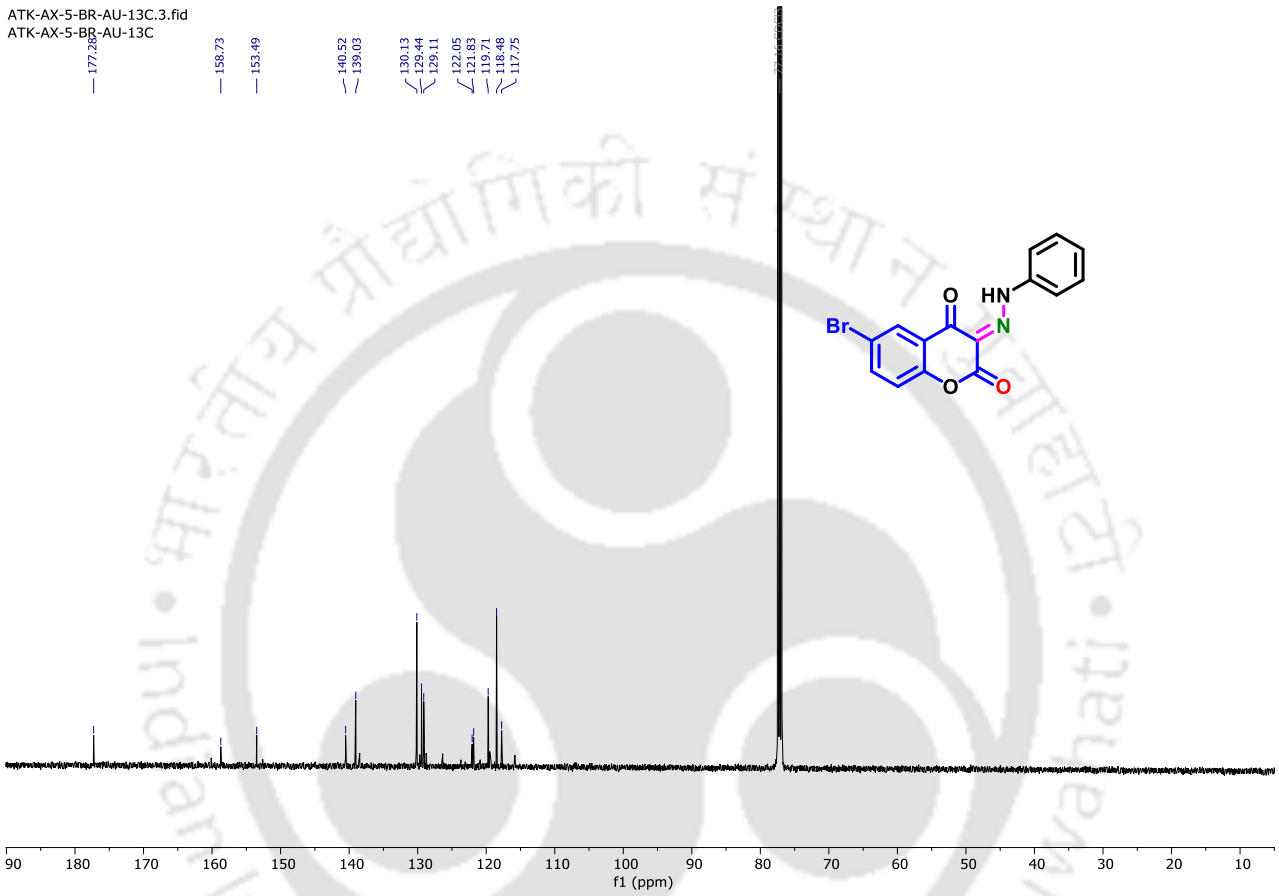


Figure 9. HRMS spectra of (*E*)-6-bromo-3-(2-phenylhydrazineylidene)chromane-2,4-dione (4ba)

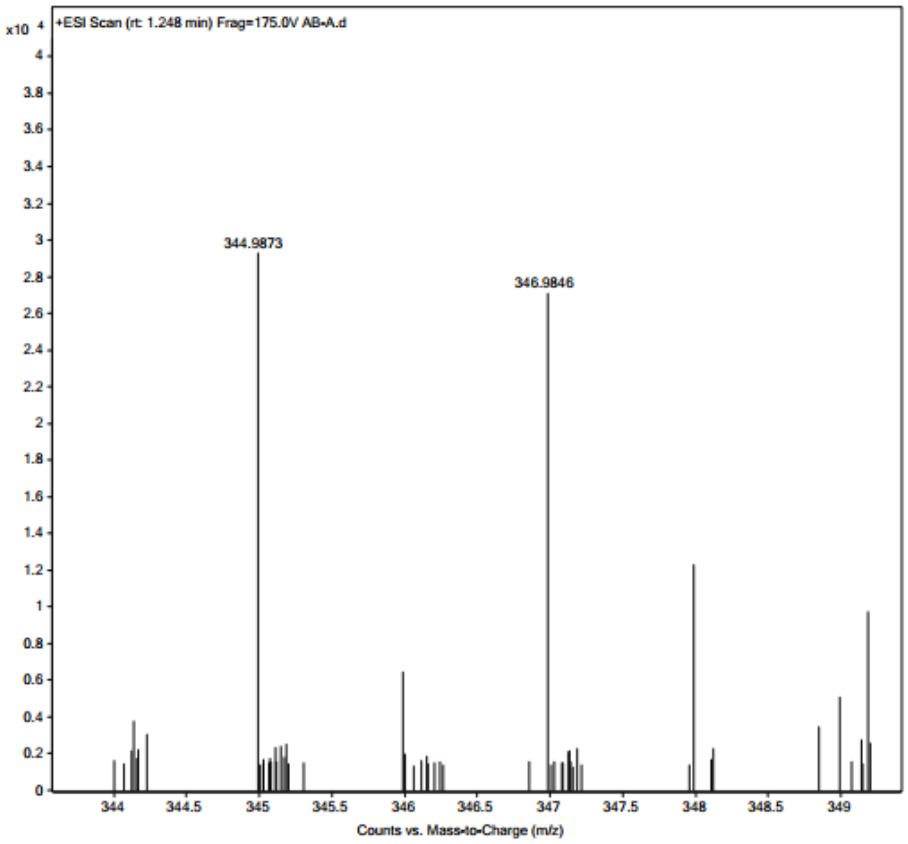


Figure 10. ^{1}H NMR spectra of (2*E*,3*E*)-3-(2-phenylhydrazineylidene)-2-(phenylimino)thiochroman-4-one (5aa)

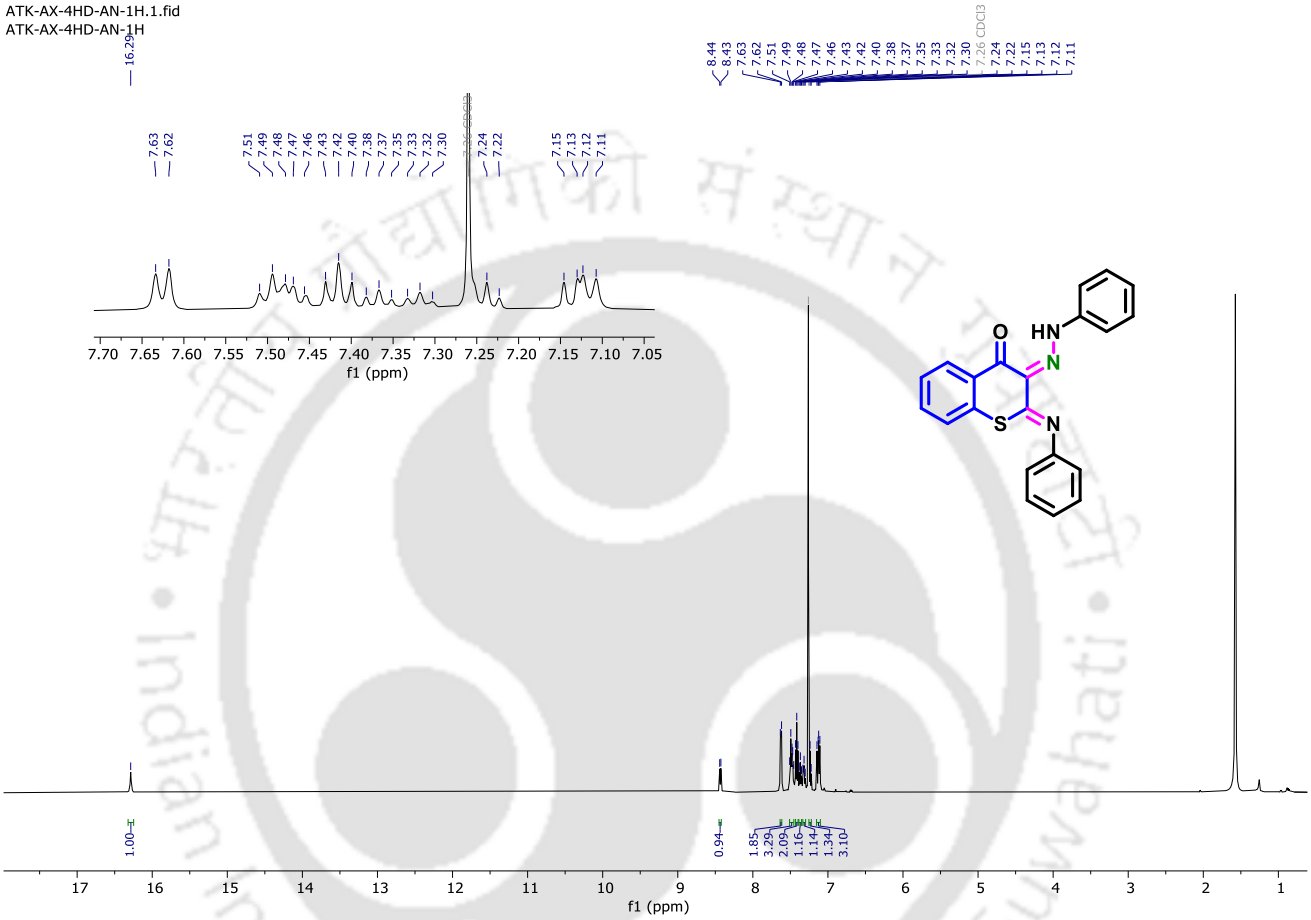


Figure 11.^{13}C NMR spectra of (2*E*,3*E*)-3-(2-phenylhydrazineylidene)-2-(phenylimino)thiochroman-4-one (5aa)

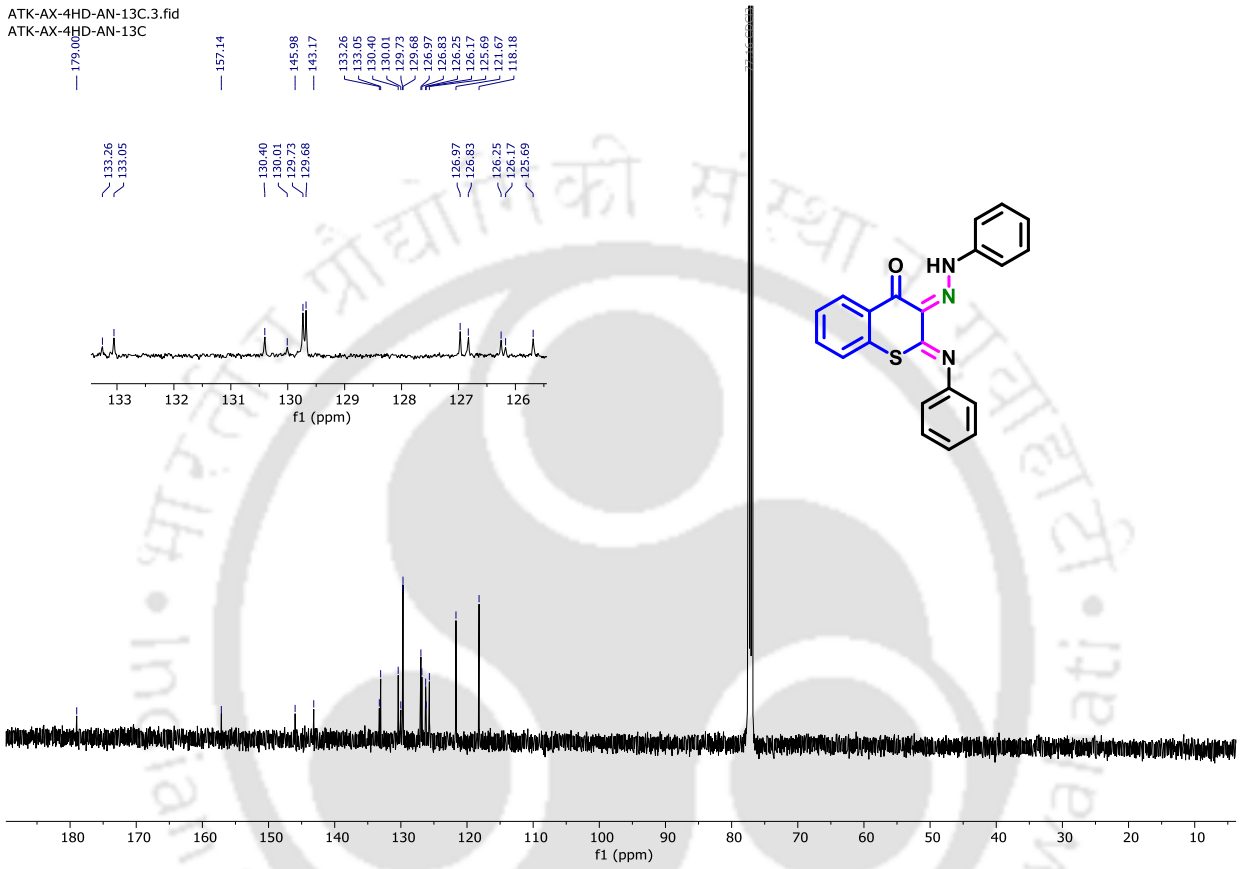
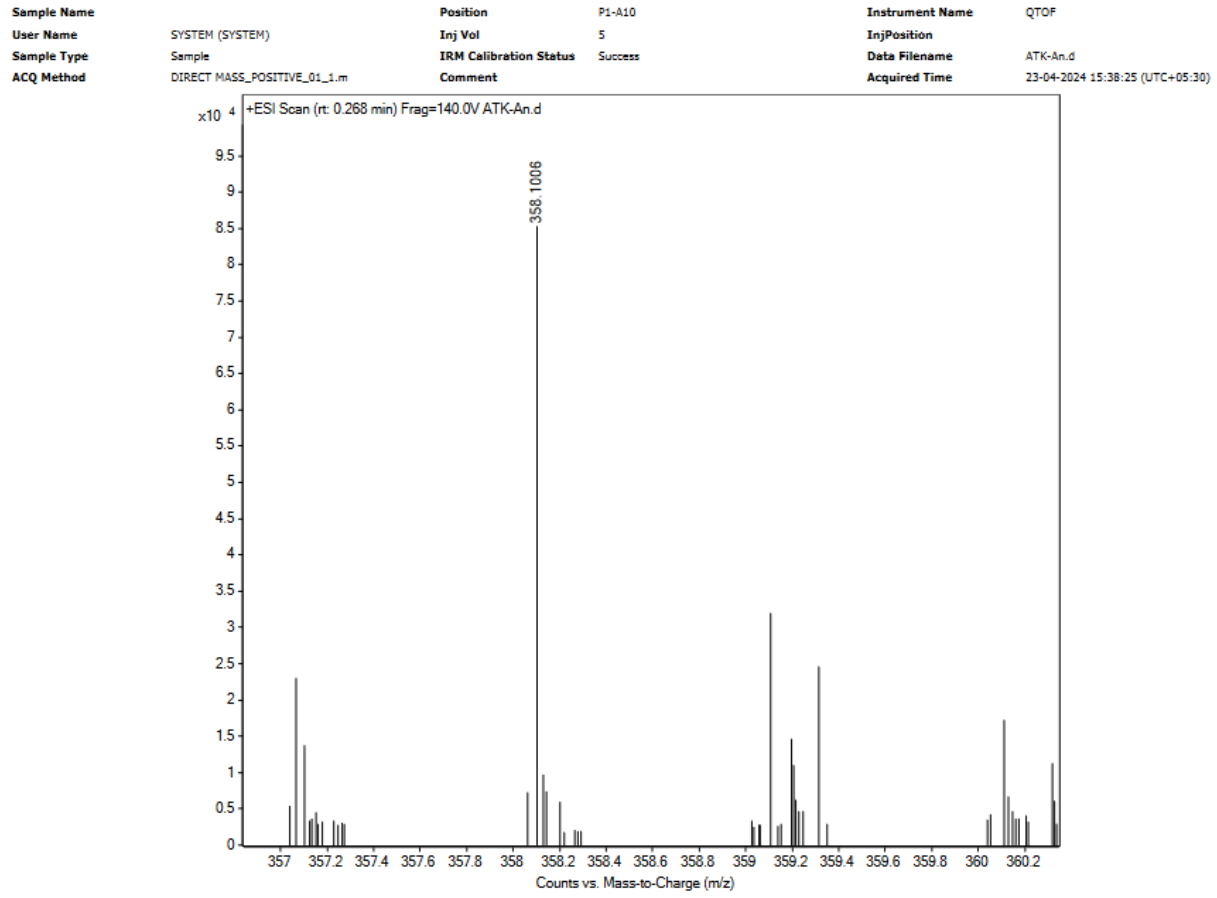


Figure 12. HRMS spectra of (2*E*,3*E*)-3-(2-phenylhydrazineylidene)-2-(phenylimino)thiochroman-4-one (5aa)



5a.6. References

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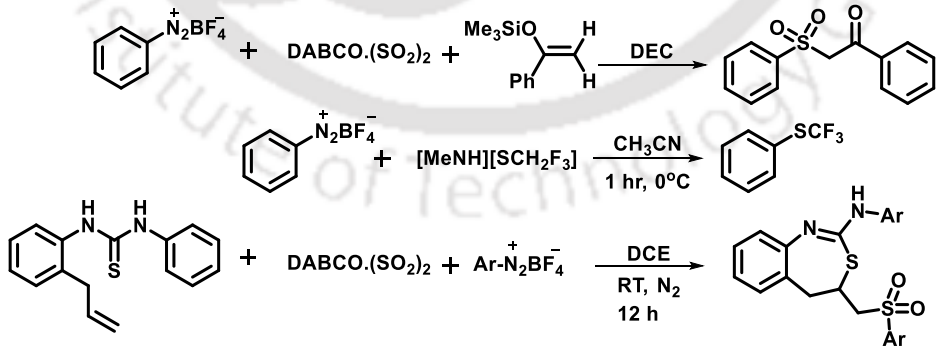
CHAPTER V-B

Aryl $N_2^+BF_4^-$ driven synthesis of (*Z*)-3-(2-phenylhydrazineylidene)-chromane-2,4-dione derivatives from 4-hydroxycoumarin and aniline

5b.1 Introduction

Aryl diazonium salts, first discovered by Johann Peter Griess[1] in the mid-19th century, have profoundly impacted the synthesis of organic compounds. They have found extensive applications as precursors in the production of azo-dye[2] and as versatile intermediates in various synthetic processes[3]. Aryl diazonium salts are versatile reagents that extend their utility to various cross-coupling reactions, notably: Sandmeyer reaction,[4]Meerwein arylation,[5] Suzuki-Miyaura[6]and other coupling reaction. In recent years, aryl diazonium salt has seen a significant focus on transformations involving radical intermediates generated through thermal, photochemical and electrochemical activation modes.[7]

In addition, aryl diazonium salts have experienced a resurgence of interest within the synthetic community, driven primarily by their catalytic cross-couplings and C−H bond activation/functionalization applications. Recent examples are by Liu and his coworkers in 2017, who synthesized β-keto sulfones through a reaction of aryldiazonium tetrafluoroborates, sulfur dioxide, and silyl enol ether. In 2018, Bertoli*et al.* exploited arene diazonium salts for the synthesis of significant pharmaceutical trifluoromethyl thioesters.[9] In the same year, Wu and his co-workers developed a three-component thiosulfonylation reaction, synthesizing sulfonated [3,1]-benzothiazepines from 1-(2-allylaryl)thioureas and aryldiazonium tetrafluoroborates utilizing *in situ* generated arylsulfonyl radicals from DABSO.[10]



Scheme 1. Reactions involvingaryldiazonium tetrafluoroborates

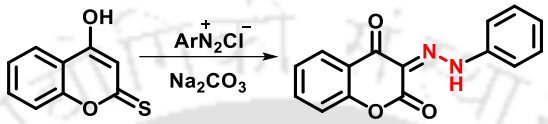
Despite the common use of aryl halides or aryl boronic acids, aryl diazonium salts offer unique advantages in the functionalization of nanomaterials[11] and coupling reactions[12], which includes

their accessibility as they are synthesized from widely available and inexpensive aryl amines. They are also used as protecting and deprotecting groups for amines in the late-stage modification for drug and natural product synthesis[13].

Of great industrial interest, coumarin, a naturally occurring compound, has profound distribution in biological and pharmacological applications for their distinctive structural scales as it has been discussed in **Chapter I**, **Chapter II** as well as in **Chapter V-A**. Research has revealed that the hydrazone moiety is promising for creating novel therapeutic agents. Furthermore, the importance of hydrazones is already been discussed in **Chapter V-A**.

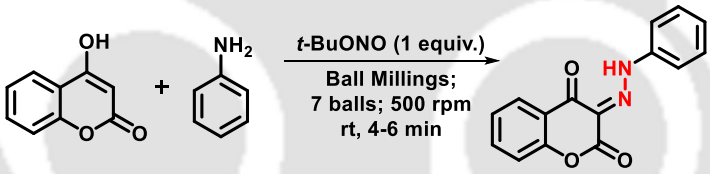
5b.2. Synthesis of hydrazone derivatives

A series of novel azopyrazolin-5-one dyes were synthesized by Metwally and his co-workers[14]*via* regioselective reactions and characterized. The dyes exhibited effective dyeing properties on polyester fabrics and demonstrated antimicrobial activity.



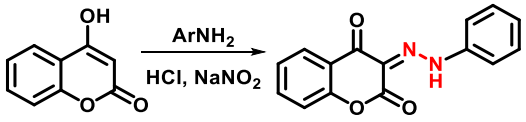
Scheme 2. Synthesis of hydrazone

Brahmachari*et al*., reported the synthesis of (*E*)-3-(2-arylhydrazono)chromane-2,4-diones via a one-pot, three-component reaction of 4-hydroxycoumarins, aromatic amines, and *tert*-butyl nitrite. The reaction was carried out using a solvent-free, mechanochemical approach under ball-milling conditions.[15]



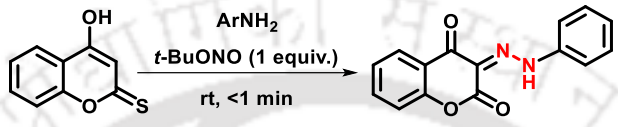
Scheme 3. Synthesis of hydrazone from 4-hydrocoumarins and aniline

Hisam*et al.*,reported[16] developed translucent PMMA-based coatings on glass enhanced with PMVEMA-ES for improved adhesion and CAD dyes for coloration from 4-hydroxycoumarin and aniline. The coatings showed high glossiness, strong adhesion, and excellent light transmittance (>90%) beyond 500 nm, making them ideal for decorative and protective glass applications.



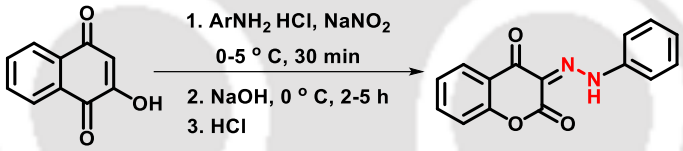
Scheme 4. Synthesis of hydrazine

We reported[17] biologically active coumarin-based hydrazone derivatives were *via* efficient one-pot, solvent- and catalyst-free multi-component reactions between 4-hydroxy-2*H*-chromene-2-thiones with aniline and *tertiary* butyl nitrite as well as with 4-hydroxydithiocoumarin. The reactions showed distinct pathways based on starting materials, were exergonic, and offered broad substrate scope with high functional group tolerance.



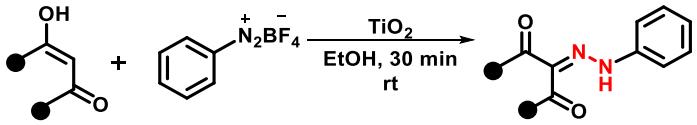
Scheme 5. Synthesis of hydrazone

DFT calculations we done by Francisco *et.al.*, that keto-hydrazone forms of 3-(2-phenylhydrazone)-naphthalene-1,2,4-trione were more stable than their enol-azo counterparts and the synthesized compounds were studied further for their antibacterial activity, that enhanced cytotoxicity, showing moderate activity against HL-60 leukemia cells.[18]



Scheme 6. Synthesis of hydrazone

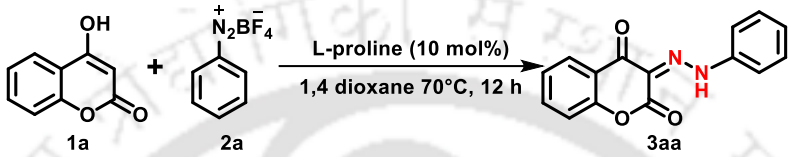
A simple and eco-friendly method for diazenylation of 1,3-dicarbonyl compounds using a reusable TiO_2catalyst was developed by Evangelista *et al*., yielding stable *E*-azo-keto products under mild conditions. This approach enables efficient synthesis of diverse compounds with broad substrate compatibility and high yields.[19]



Scheme 7. Synthesis of hydrazone

5b.1. Results and Discussions

Herein, we propose a simple, elegant, and atom economic approach to access (*E*)-3-(2-arylhydrazineylidene)chromane-2,4-dione from 4-hydroxycoumarin and aryl diazonium tetrafluoroborate in the presence of 10 mol% L-Proline in 1,4-dioxane at 70 °C as shown in **Scheme 5b.3a**.



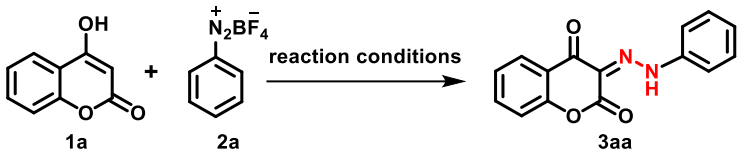
Scheme 8. Synthesis of (*E*)-3-(2-arylhydrazineylidene)chromane-2,4-dione derivatives

Our experimental investigation consisted of various 4-hydroxycoumarins, aryl diazonium salt synthesized using a previously reported procedure.[20]

The optimization study was conducted to identify the most effective reaction conditions for the synthesis of compound **3aa** from 4-hydroxycoumarin (**1a**) and phenyl diazonium tetrafluoroborate (**2a**). Initially, in the absence of any catalyst (**Table 1, Entry 1**), no product formation was observed even after 36 hours at room temperature in acetonitrile. Introduction of L-Proline as a catalyst under gradually increasing temperature from room temperature to 60 °C (**Table 1**, **Entry 2**) or at a constant 60 °C (**Table 1**, **Entry 3**) in acetonitrile also resulted in no reaction. Similarly, the use of palladium acetate under a nitrogen atmosphere in methanol (**Table 1**, **Entry 4**) failed to yield the desired product. In contrast, the application of photoredox catalysis using Eosin Y under white LED light and nitrogen atmosphere (**Table 1**, **Entries 5** and **6**) led to product formation, with yields improving from 36% in acetonitrile to 51% in 1,4-dioxane upon increasing the catalyst loading from 10 mol% to 20 mol%. A significant breakthrough was observed in (**Table 1**, **Entry 7**), where the use of L-Proline (20 mol%) as the catalyst in 1,4-dioxane at 70 °C for 12 hours afforded the target product in an excellent yield of 87%, marking this as the optimized condition. Prolonging the reaction time to 16 hours under the same conditions (**Table 1**, **Entry 8**) led to a reduced yield of 45%, indicating possible degradation or side reactions. (**Table 1**, **Entry 9**), where reaction conditions were similar but solvent details are unclear or altered, resulted in no reaction, reinforcing the critical role of 1,4-

dioxane as a solvent. Lastly, using K_2CO_3 as a base catalyst (**Table 1**, **Entry 10**) gave only a 17% yield, further highlighting that L-Proline is the most effective catalyst for this transformation. Thus, the optimized condition was established as L-Proline (20 mol%) in 1,4-dioxane at 70 °C for 12 hours.Having established the optimal reaction conditions, we presented **Table 2** which outlines a highly efficient L-proline-catalyzed synthesis of tricyclic fused heterocycles via the reaction between 4-hydroxycoumarin derivatives (**1a**–**1f**) and various aryl diazonium tetrafluoroborate salts (**2a**–**2j**). The reaction was carried out in 1,4-dioxane at 70 °C for 12 hours using 10 mol% of L-proline as an organocatalyst. The transformation led to the formation of a series of diazenylated fused products (**3aa**–**3ej**) in good to excellent yields ranging from 70% to 87%. The scope of the reaction was extensively explored by varying both the 4-hydroxycoumarin core and the aryl diazonium salts. Electron-donating (e.g., CH_3, OCH_3) and electron-withdrawing groups (e.g., F, Cl, Br) on the aryl diazonium salts were well tolerated, yielding products such as **3aa** (87%), **3ab** (85%), **3ac** (80%), **3ad** (78%), and **3ae** (72%). Similarly, substitutions on the 4-hydroxycoumarin ring, including methoxy, halogen, and fused aryl groups, showed no significant hindrance to the reaction, as demonstrated by the consistent yields of products like **3ba** (83%), **3bd** (85%), **3cd** (80%), **3dd** (83%), and **3ej** (83%). The results indicate that this protocol accommodates a broad range of electronic and steric environments, making it a valuable and green synthetic approach for constructing structurally diverse coumarin-based tricyclic diazenyl heterocycles under mild conditions

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

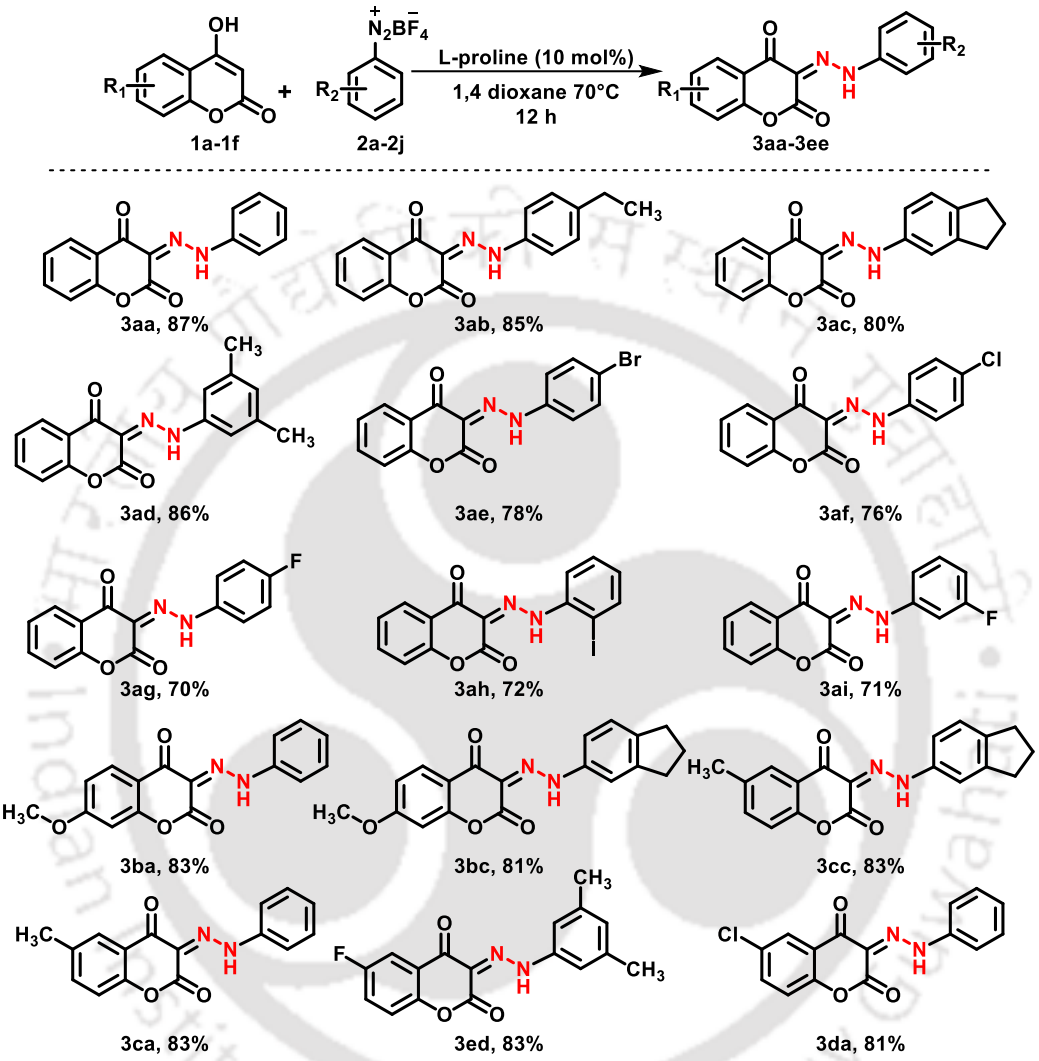


Sl. No.	Catalyst	Mol %	Temp (°C)	Solvent	Time (h)	Yield[b] (%)
1	-	-	RT	ACN	36 h	NR
2	L-Proline	-	RT to 60°C	ACN	3 h to 12 h	NR
3	L-Proline	33	60°C	ACN	12	NR
4	$Pd(OAc)_2$, N_2	33	RT	MeOH	16 h	NR
5	Eosin Y (white LED), N_2	10	RT	ACN	4 h	36
6	Eosin Y (white LED), N_2	20	RT	1,4 dioxane	12 h	51
7	**L-Proline**	**20**	**70°C**	**1,4 dioxane**	**12 h**	**87**
8	L-Proline	33	70°C	1,4 dioxane	16 h	45
9	L-Proline	20	70°C	-	12 h	
10	K_2CO_3 (2 equiv.)	33	70°C	1,4 dioxane	12 h	NR

[a]All the reactions were carried out using 4-hydroxycoumarin (**1a**), phenyl diazonium tetrafluoroborate (**2a**) was reacted with L-Proline (10 mol %) in 1,4-dioxane at 70 °C for 12 h. [b]Isolated yield.

Also, aryl diazoniumsalt with di-substituted methyl groups gave the anticipated product **3ad** in 86% yield. Meanwhile,the reaction of aryl diazonium tetrafluoroborate saltscontaining halogensubstituents (bromo, chloro, fluoro and iodo) afforded the corresponding products, **3ae**, **3af**, **3ag**,

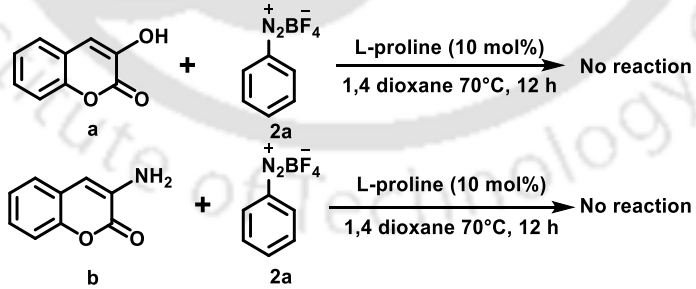
Table 2. Scope of (*E*)-3-(2-phenylhydrazineylidene)chromane-2,4-dione derivatives[a,b]



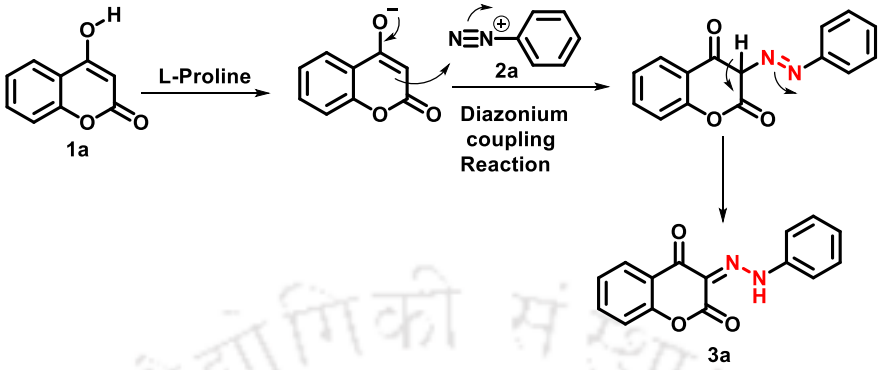
[a]All the reactions were carried out using 4-hydroxycoumarin (**1a**), phenyl diazonium tetrafluoroborate (**2a**) was reacted with L-Proline (10 mol %) in 1,4-dioxane at 70 °C for 12 h. [b]Isolated yield.

3ah, **3ai** ingood yields (70–78%).Gratifyingly, the electron-donating and electron-withdrawing groups present at the C-7 and C-6position of 4-hydroxycoumarins **1b** and **1c** were also tolerated and provided the corresponding hydrazones derivatives **3ba**, **3bc** and **3cc** in 81–83% yield in reaction with phenyl diazonium tetrafluoroborate and also salts containing dihydro substituent, and dimethyl substituents. Likewise, halogen substituents at the C-7 position of 4-hydroxycoumarin yielded the anticipated product **3ed** and**3da** with 83-81% yield.

Scheme 9shows two attempted reactions involving aryl diazonium tetrafluoroborate salts (**2a**) with different chromen-2-one derivatives, catalyzed by L-proline under identical conditions, specifically, 10 mol% of L-proline in 1,4-dioxane at 70 °C for 12 hours. In the first case, compound 3-hydroxy-2*H*-chromen-2-one (**a**), was reacted with the diazonium salt. Despite the presence of a hydroxyl group at position 3, which could potentially act as a nucleophile, no product formation was observed, indicating no reaction occurred under these conditions. Similarly, in the second reaction, 3-amino-2*H*-chromen-2-one (**b**), was used. The amino group is generally more nucleophilic than the hydroxyl group; however, even this substrate did not react with the diazonium salt under the same reaction setup. These results suggest that L-proline, under these mild conditions, is not sufficient to promote the desired transformation, and that either the reaction pathway requires different activation or the substrates are not reactive enough under the given conditions.



Scheme 9. Reaction of aryl tetrafluoroborate with3-hydroxy-2*H*-chromen-2-one (**a**) and 3-amino-2*H*-chromen-2-one (**b**)



Scheme 10. Plausible mechanism

Therefore, the use of 3-hydroxy or 3-amino chromen-2-one alone with aryl diazonium tetrafluoroborates in the presence of L-proline does not yield the expected product, highlighting the need for optimized catalysts or reaction conditions.

A simple plausible mechanism was proposed for the formation of hydrazine **Scheme 10**. In presence of L-proline, the enol form of 4-hydroxycoumarin forms an activated enamine-like intermediate. Diazonium salt **2a**, reacts with the intermediate which results in the formation of a C-N=N-Ar linkage, forming an azo-coupled product which is our desired product **3a**.

5b. 4. Conclusion

In summary, we present a smooth and operationally simple direct diazenylation of 4-hydroxycoumarin using an accessible aryltetrafuloroborate with L-proline as a catalyst. This efficient synthetic approach for diazenylationof 4-hydroxycoumarin opens up new avenues for the development of hydrazone libraries.

5b.5. Experimental Section

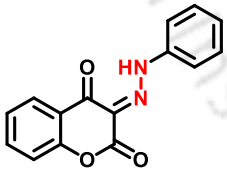
5b.5a.Procedure for the synthesis of (*E*)-3-(2-arylhydrazineylidene)- chromane-2,4-dione derivatives (3aa-3ee)

A mixture of 4-hydroxycoumarin (**1a**, 0.25 mmol), aryl tetrafluoroborate (**2a**, 0.25 mmol) and L-proline (10 mol %) was taken in 10 mL round-bottomed flask in 1,4-dioxane kept under reflux at 70°C temperature. 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.

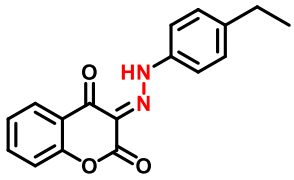
5b.5b.Procedure for the synthesis of aryl diazonium salt (2a-2j)

A wide variety of aryl diazonium salts (**2a-2j**) was prepared by following the previouslyreported literature procedure.[20]

(*E*)-3-(2-phenylhydrazineylidene)chromane-2,4-dione (3aa). Yellowish brown solid (57 mg, 87%), mp 165°C-166°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.40 (s, 1H), 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.70 (s, 1H), 7.68 (s, 1H), 7.66 (d, *J* = 6.6 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 5.2 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.7, 159.2, 154.6, 140.6, 136.4, 130.0, 128.7, 126.97, 124.8, 122.4, 120.4, 118.2, 117.8; IR (KBr) ν_{max}/cm^{-1}3069 (NH), 1649 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{15}H_{11}N_2O_3$ 267.0764 [M + H$^+$]; found 267.0764.

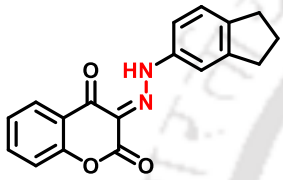


(*Z*)-3-(2-(4-ethylphenyl)hydrazineylidene)chromane-2,4-dione (3ab). Yellowish brown solid



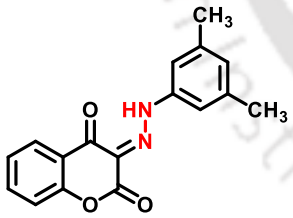
(62 mg, 85%), mp 160°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.53 (s, 1H), 8.09 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.31 (dt, *J* = 8.7, 5.1 Hz, 4H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 159.4, 154.5, 145.6, 138.5, 136.1, 129.4, 126.8, 124.7, 122.0, 120.4, 118.3, 118.3, 117.7, 28.7, 15.4; HRMS (ESI) calculated for $C_{17}H_{15}N_2O_3$ 295.1077 [M + H^+]; found 295.1088

(*Z*)-3-(2-(2,3-dihydro-1*H*-inden-5-yl)hydrazineylidene)chromane-2,4-dione (3ac).Yellowish brown solid



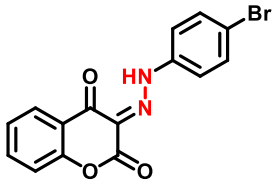
(61 mg, 80%), mp 166°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.54 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.30 (dd, *J* = 18.2, 7.9 Hz, 3H), 2.94 (dt, *J* = 14.2, 7.4 Hz, 5H), 2.12 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 159.5, 154.5, 146.7, 146.0, 139.2, 136.0, 127.6, 126.7, 125.4, 125.1, 124.6, 121.8, 120.4, 117.6, 117.4, 116.9, 116.8, 114.0, 32.8, 32.7, 25.5; HRMS (ESI) calculated for $C_{18}H_{15}N_2O_3$ 307.1077 [M + H^+]; found 307.1062.

(*E*)-3-(2-(3,5-dimethylphenyl)hydrazineylidene)chromane-2,4-dione (3ad). Yellowish brown solid



(63 mg, 86%), mp 200°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.41 (s, 1H), 8.09 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.38 – 7.33 (m, 1H), 7.31 (d, *J* = 2.0 Hz, 2H), 7.28 (d, *J* = 1.1 Hz, 1H), 6.99 (s, 1H), 2.38 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 159.4, 154.5, 140.6, 140.1, 136.2, 130.7, 126.9, 124.7, 122.1, 120.5, 117.7, 116.1, 21.4; IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1665 (C=O), 1468 (C-O); HRMS (ESI) calculated for $C_{17}H_{15}N_2O_3$ 295.1077 [M + H^+]; found 295.1074.

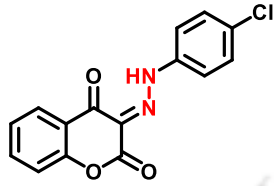
(*E*)-3-(2-(4-bromophenyl)hydrazineylidene)chromane-2,4-dione (3ae). Yellowish brown solid



(67 mg, 78%), mp 162°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.36 (s, 1H), 8.20 (d, *J* = 2.5 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.53 – 7.48 (m, 2H), 7.39 (tt, *J* = 6.9, 1.2 Hz, 1H), 7.20 (d, *J* = 8.7,

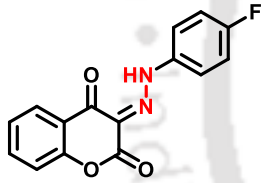
Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 159.0, 154.7, 139.7, 136.6, 132.2, 127.0, 124.9, 122.8, 122.1, 120.3, 119.5, 117.8, IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1629 (C=O), 1481 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}BrN_2O_3$ 344.9869 [M + H^+]; found 344.9869.

***E*)-3-(2-(4-chlorophenyl)hydrazineylidene)chromane-2,4-dione (3af).** Yellowish brown solid



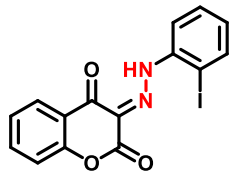
(57 mg, 76%), mp 162°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.35 (s, 1H), 8.08 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.63 – 7.61 (m, 2H), 7.46 – 7.44 (m, 2H), 7.34 – 7.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 174.8, 168.2, 166.5, 157.8, 140.9, 131.4, 130.2, 129.2, 119.5, 118.8, 118.1, 113.7, 104.7; IR (KBr) ν_{max}/cm^{-1} 3068 (NH), 1740 (C=O), 1466 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}ClN_2O_3$ 301.0374 [M + H^+]; found 301.0378.

(*E*)-3-(2-(4-fluorophenyl)hydrazineylidene)chromane-2,4-dione (3ag). Yellowish brown solid



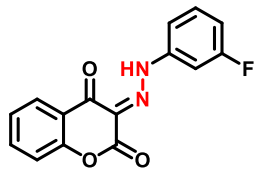
(50 mg, 70%), mp 160°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.47 (s, 1H), 8.08 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.69 – 7.65 (m, 3H), 7.34 – 7.28 (m, 2H), 7.18 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 162.4 (d, *J* = 250.3 Hz), 159.1, 154.6, 137.0 (d, *J* = 2.7 Hz), 136.4, 126.9, 124.8, 122.4, 120.3,119.9 (d, *J* = 8.7 Hz), 117.8, 117.1 (d, *J* = 23.4 Hz); IR (KBr) ν_{max}/cm^{-1} 3068 (NH), 1603 (C=O), 1466 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}FN_2O_3$ 285.0670 [M + H^+]; found 285.0671.

(*E*)-3-(2-(2-iodophenyl)hydrazineylidene)chromane-2,4-dione (3ah). Yellowish brown solid



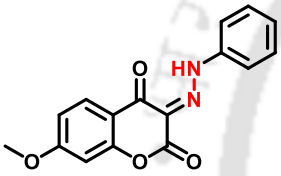
(71 mg, 72%), mp 166°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.19 (s, 1H), 8.16 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.88 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.69 (td, *J* = 7.9, 7.2, 1.7 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 13.3, 5.7 Hz, 2H), 7.07 (td, *J* = 7.6, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 159.0, 154.7, 141.8, 139.8, 139.8, 136.7, 130.0, 129.5, 127.3, 124.9, 120.4, 119.1, 117.8, 87.1; IR (KBr) ν_{max}/cm^{-1} 3070 (NH), 1650 (C=O), 1462 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}IN_2O_3$ 392.9731 [M + H^+]; found 392.9731.

(*Z*)-3-(2-(3-fluorophenyl)hydrazineylidene)chromane-2,4-dione (3ai). Yellowish brown solid



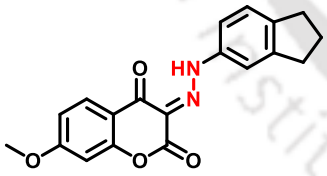
(50 mg, 71%), mp 165°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 16.21 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.03 (t, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.93, 176.29, 164.74, 162.77, 160.35, 158.82, 154.66, 153.72, 142.33, 142.25, 136.74, 136.01, 131.38, 131.35, 131.31, 131.28, 127.77, 127.08, 125.46, 124.90, 122.91, 121.81, 121.52, 120.24, 117.83, 117.56, 115.44, 115.27, 114.05, 114.02, 105.43, 105.22; IR (KBr) ν_{max}/cm^{-1} 3068 (NH), 1603 (C=O), 1466 (C-O); HRMS (ESI) calculated for $C_{15}H_{10}FN_2O_3$ 285.0670 [M + H^+]; found 285.0671.

(*Z*)-7-methoxy-3-(2-phenylhydrazineylidene)chromane-2,4-dione (3ba). Yellowish brown



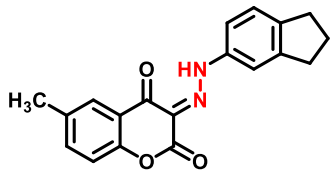
solid (61 mg, 83%), mp 170°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.31 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.35 – 7.29 (m, 1H), 6.85 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.71 (d, *J* = 2.5 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 166.4, 159.4, 156.5, 140.8, 129.9, 128.5, 128.2, 122.0, 117.9, 113.8, 113.1, 101.2, 101.1, 56.1, 56.1; HRMS (ESI) calculated for $C_{16}H_{13}N_2O_4$ 297.0870 [M + H^+]; found 297.0850.

(*Z*)-3-(2-(2,3-dihydro-1*H*-inden-5-yl)hydrazineylidene)-7-methoxychromane-2,4-dione



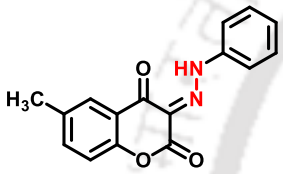
(3bc). Yellowish brown solid (68 mg, 81%), mp 167°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.45 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.60 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.27 (s, 1H), 6.84 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 3.90 (s, 3H), 2.93 (dd, *J* = 12.2, 7.4 Hz, 4H), 2.15 – 2.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 166.2, 159.7, 156.4, 146.6, 145.4, 139.4, 128.3, 125.4, 121.4, 116.7, 113.9, 113.8, 112.9, 101.0, 56.1, 55.9, 32.9, 32.7, 25.6; HRMS (ESI) calculated for $C_{19}H_{17}N_2O_4$ 337.1183 [M + H^+]; found 337.1176.

(*Z*)-3-(2-(2,3-dihydro-1*H*-inden-5-yl)hydrazineylidene)-6-methylchromane-2,4-dione (3cc).



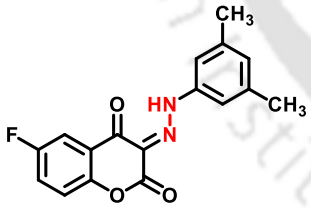
Yellow solid (66 mg, 83%), mp 160°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.51 (s, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 2.2 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.36 (d, *J* = 5.7 Hz, 1H), 7.28 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 2.93 (dt, *J* = 14.4, 7.4 Hz, 4H), 2.41 (s, 3H), 2.13 (q, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 159.7, 152.6, 146.7, 145.8, 139.2, 137.0, 134.4, 126.2, 125.4, 125.4, 121.8, 120.0, 117.4, 116.9, 113.9, 32.8, 32.7, 25.5, 20.8.

(*Z*)-6-methyl-3-(2-phenylhydrazineylidene)chromane-2,4-dione (3ca). Yellow solid (58 mg, 83%), mp 161°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.35 (s, 1H), 7.83 (s, 1H), 7.66 (d, *J* = 7.5 Hz,



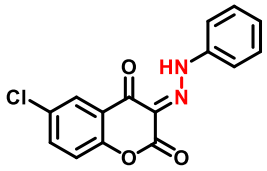
2H), 7.49 – 7.43 (m, 3H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 2.41 (s, 3H); 13C NMR (125 MHz, $CDCl_3$) δ 178.7, 159.3, 152.7, 140.7, 137.4, 134.6, 129.9, 128.5, 126.4, 122.5, 120.0, 118.2, 117.5, 20.8; HRMS (ESI) calculated for $C_{16}H_{13}N_2O_3$ 281.0921 [M + H^+]; found 281.0904.

(*Z*)-3-(2-(3,5-dimethylphenyl)hydrazineylidene)-6-fluorochromane-2,4-dione (3ed). Yellow solid (65 mg, 83%), mp 164°C; ^{1}H NMR (500 MHz, DMSO) δ 16.35 (s, 1H), 7.71 (dd, *J* = 7.8,



3.1 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.31 (s, 3H), 6.99 (s, 1H), 2.37 (s, 6H); ^{13}C NMR (125 MHz, DMSO) δ 177.4, 177.3, 159.0, 158.2, 150.7, 150.7, 140.4, 140.2, 131.1, 130.6, 123.7, 123.5, 121.7, 121.5, 121.4, 119.6, 119.5, 116.2, 112.2, 112.0, 21.3.

(*Z*)-6-chloro-3-(2-phenylhydrazineylidene)chromane-2,4-dione (3da). Yellow solid (60 mg, 81%), mp 165°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.35 (s, 1H), 8.03 (s, 1H), 7.70 (d, *J* = 7.9 Hz,



2H), 7.60 (d, *J* = 8.9 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 158.7, 153.0, 140.5, 136.2, 130.5, 130.1, 129.1, 126.3, 122.0, 121.4, 119.4, 118.4.21.3.

Figure 1. ^{1}H NMR spectra of (*Z*)-3-(2-(4-ethylphenyl)hydrazineylidene)chromane-2,4-dione (3ab)

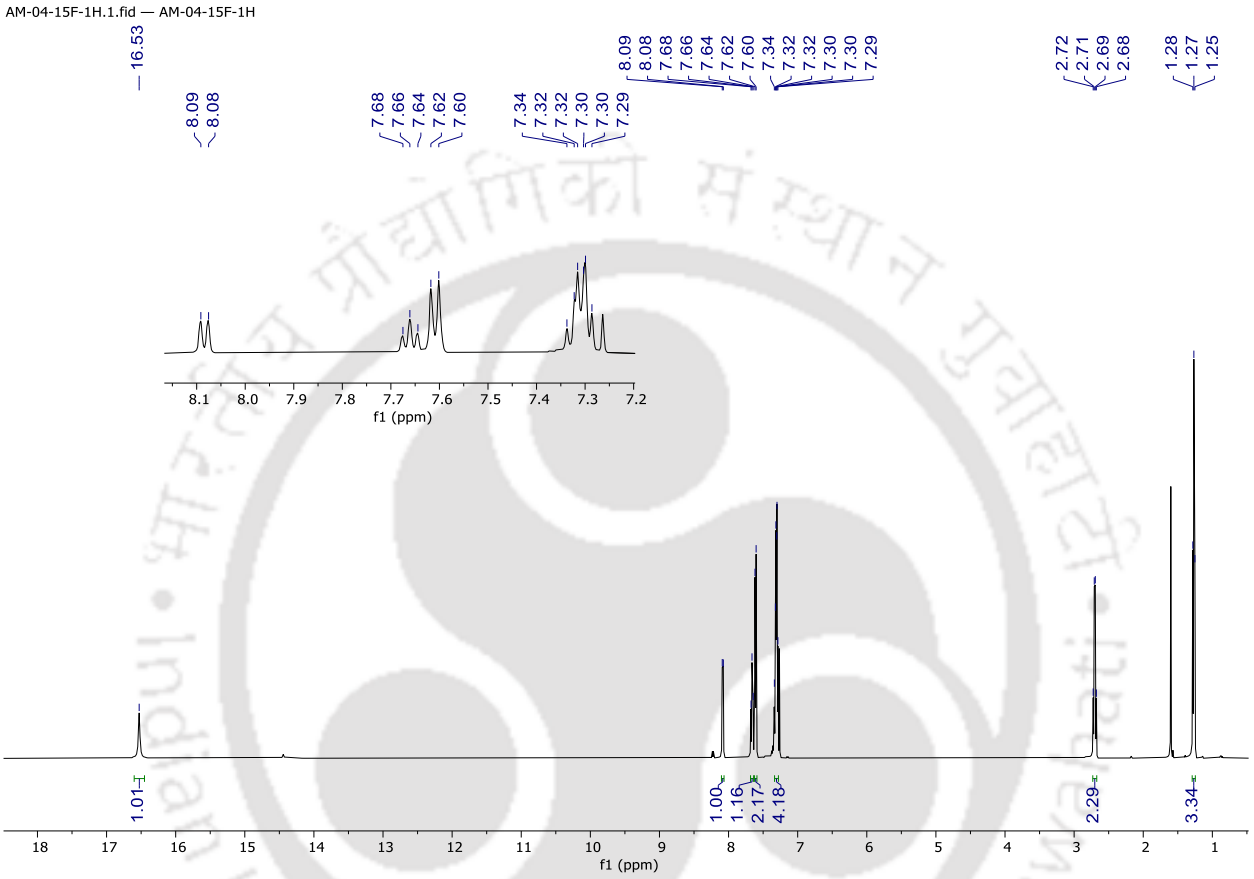


Figure 2. ^{13}C NMR spectra of (*Z*)-3-(2-(4-ethylphenyl)hydrazineylidene)chromane-2,4-dione (3ab)

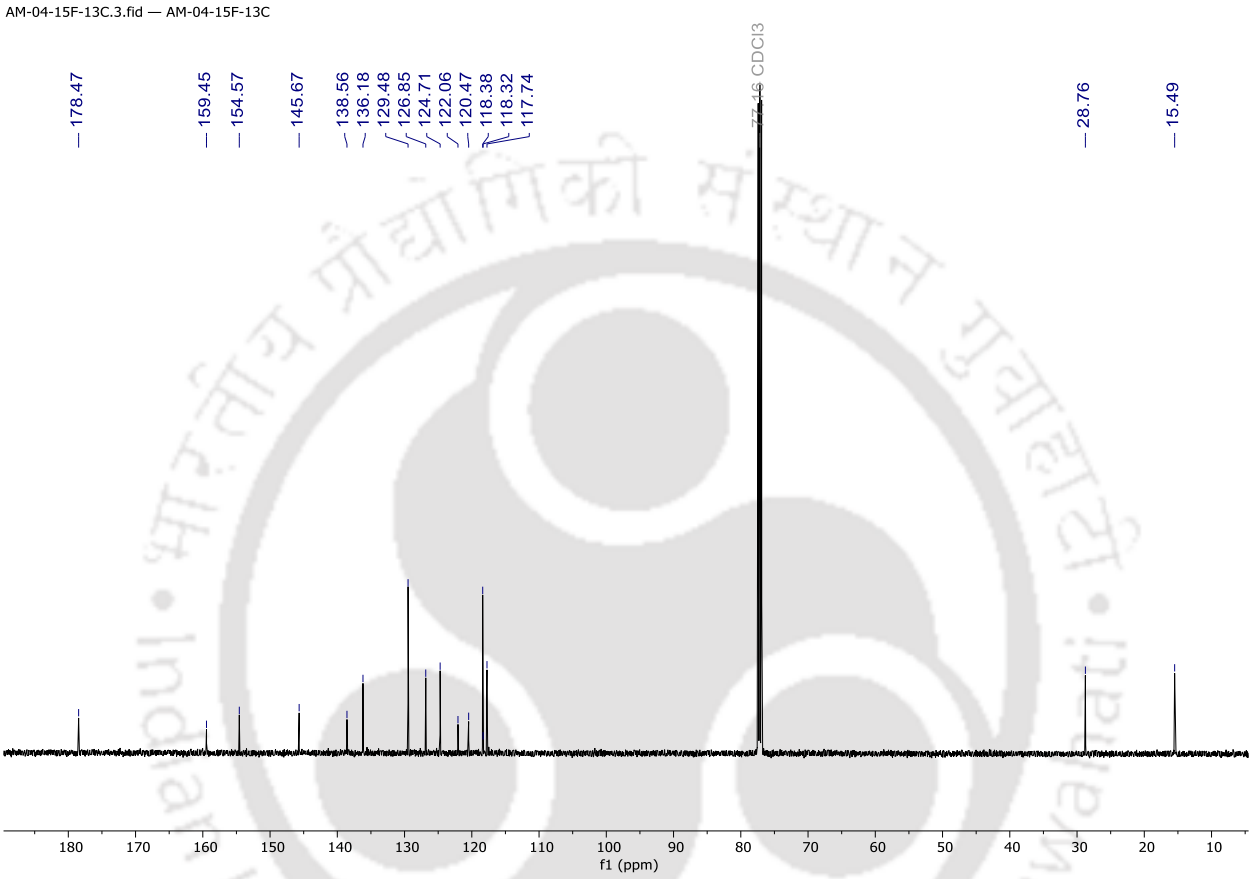
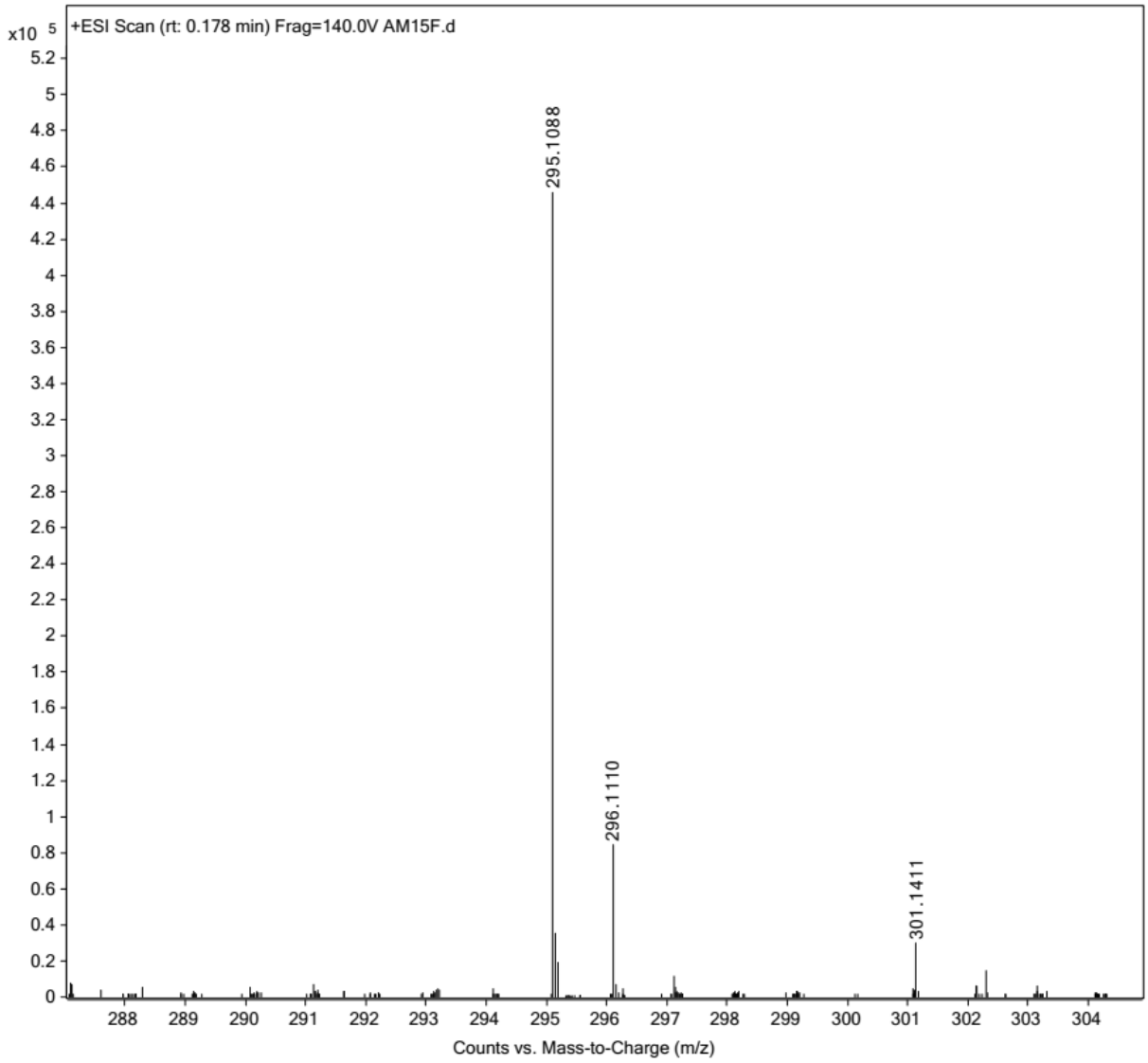


Figure 3.HRMSof (*Z*)-3-(2-(4-ethylphenyl)hydrazineylidene)chromane-2,4-dione (3ab)



5b.6. References

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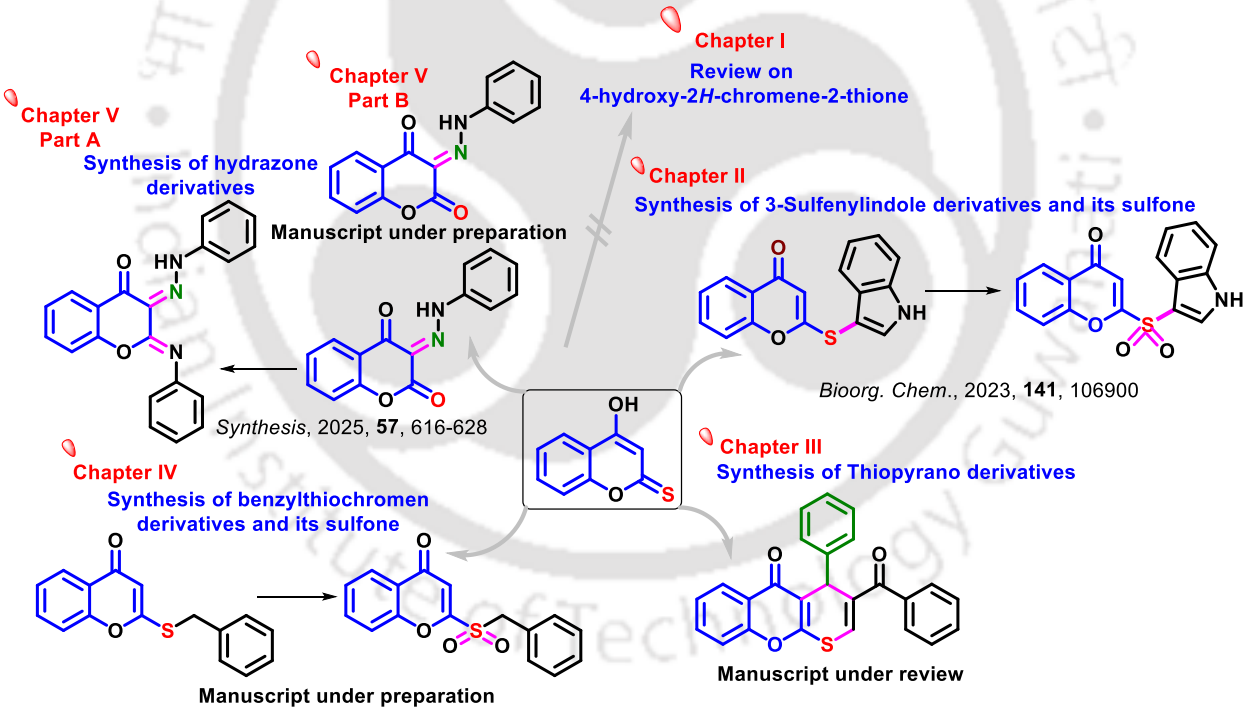
CHAPTER VI

Research Synopsis and Scope for Future Exploration

During my Ph.D. studies, my research focused on exploring the synthetic utility of 4-hydroxy-2*H*-chromene-2-thione through its reactive sites. The summarized findings are presented schematically below.

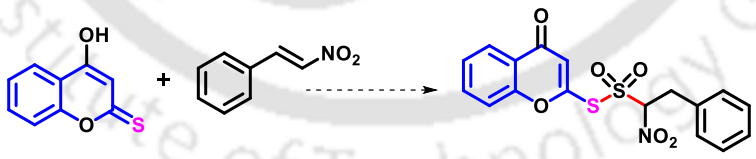
Thesis at a Glance



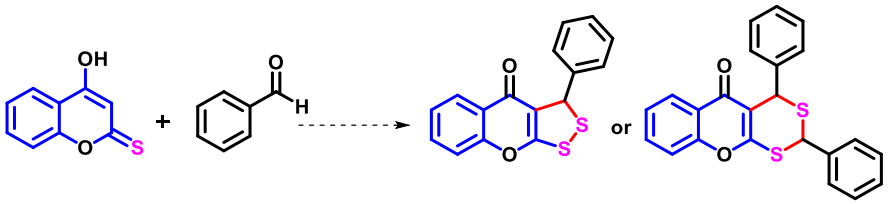
Future Prospects

A number of unprecedented assemblies bearing thiochromeno fragments have been developed and considered for their anti-proliferative activity against MCF-7 and HeLa cell lines, together with their antifungal potential. The developed compounds carrypotential for expanded structural modifications, promoting the implementation of novel analogues for structure–activity relationship (SAR) studies. Furthermore, the thiopyrano derivatives synthesized herein, demonstrate notable possibility for biological screening. Their distinctive sulfur-containing framework enhances their value for further synthetic transformations. Owing to their photophysical and electronic characteristics, they may also find applications in materials science and molecular sensors. Additionally, an ongoing study involves the thioalkylation of 4-hydroxy-2*H*-chromene-2-thione with benzyl bromide, followed by oxidation to the corresponding sulfone derivative. The anti-proliferative activity of this compound is currently under investigation and will be reported upon completion of the study. The synthetic methodology applied for hydrazone-based compounds can be extended and explored for a broader range of biological investigations, including potential applications in fluorescence and molecular sensing. These compounds also show promise as dye candidates.

In continuation of our prior research, the potential directions for further investigation into the reactivity of 4-hydroxy-2*H*-chromene-2-thione are depicted below.



Scheme 1. Synthesis of sulfonothioate derivatives



Scheme 2. Synthesis of dithiolochromene derivatives

Appendix

Publications & Conferences Attended

Publications Included in Thesis

1.**A. Xalxo**, U. J. Goswami, S. Sarkar, T. Kandasamy, K. Mehta, S. S. Ghosh, P. V. Bharatam, and A. T. Khan, "Synthesis of 3-Sulfenylindole derivatives from 4-Hydroxy-2*H*-chromene-2-thione and indole using oxidative cross-dehydrogenative coupling reaction and antiproliferative activity study of some of their sulfone derivatives", *Bioorg. Chem.,* 2023, **141**, 106900.

2.**A. Xalxo**, U. J. Goswami, C. Das, K. Mehta, P. V. Bharatam and A. T. Khan, "A Reactivity Study of 4-Hydroxy-2*H*-chromene-2-thione and 4-Hydroxy-2*H*-thiochromene-2-thione with *tert*-Butyl Nitrite and Aromatic Amines: An Environmentally Benign Synthesis of New Hydrazone Derivatives", *Synthesis,* 2025, **57**, 616.

3. **A. Xalxo**, U. J. Goswami and A. T Khan,"Reactivity study of 4-Hydroxy-2*H*-chromene-2-thione: A Regioselective approach to 3-benzoyl-4-phenyl-4*H*,5*H*-thiopyrano[2,3-*b*]chromen-5-one derivatives through one pot domino reaction with aromatic aldehyde and β-enaminone." *Eur. J. Org*., 2025, **00**, 0000.

4. **A. Xalxo**, A. Mandal, V. M. Bharatbhai and A. T. Khan, "Aryl-N_2BF_4 driven synthesis of (*Z*)-3-(2-phenylhydrazineylidene)chromane-2,4-dione derivatives from 4-Hydroxycoumarin and aniline." (Manuscript under preparation)

5. **A. Xalxo,** B. Ghosh, S. S. Ghosh and A. T. Khan, "Efficient one pot access to Sulfur containing heteroarenes *via* copper catalysed alkylation of 4-Hydroxy-2*H*-chromene-2-thione." (Manuscript under preparation)

Publications Not Included in Thesis

1. U. J. Goswami, **A. Xalxo**, and A. T. Khan, "Catalyst and Solvent Free Synthesis of Pentacyclic-dione Derivatives from 4-Hydroxythiocoumarin and Aldehyde Using Pseudo-Three-Component Reaction", *ChemistrySelect, 2023,* e202302520.

2. U. J. Goswami, **A. Xalxo**, Kusum, M. Basumatary, K. Soni, K. Bhattacharyya and A. T. Khan, "Reactivity study of 4-Hydroxythiocoumarin: a novel synthetic route to fused chromono-thiophene and -thiopyran derivatives through solvent-dependent thio-Claisen rearrangement," *New J. Chem.,* 2024, **48**, 14697.

3. U. J. Goswami, **A. Xalxo** and A. T. Khan. "A regioselective and sustainable approach for the synthesis of substituted thieno[2,3-*b*]chromen-4-ones with pendant imine groups *via* a base-promoted multicomponent reaction", *Org. Chem. Front., 2025,* **12**, 3215**.**

Conferences Attended

1. The Poster was presented at the conference **Frontiers in Chemical Sciences (FICS 2022)** from 2nd-4th December 2022, which was organized by the Department of Chemistry at IIT Guwahati, Guwahati, Assam.

2. The Poster was presented at the conference **Emerging Trends in Chemistry (ICETC 2023)** from 16th-17th March 2023, which was organized by the Department of Chemistry at Assam Don Bosco University Tapesia, Guwahati, Assam. (Best Poster Award)

3. The Poster was presented at the **Emerging Trends in Catalysis & Synthesis 2024 (ETCS 2024)** from 7th-9th March 2024, which is organized by the Department of Chemistry at IIT Kharagpur, West Bengal.

4. The Poster was presented at the conference **Innovation and Advances in Chemical Sciences (IACS 2025)** on 24th-25th January 2025, which was organized by the Department of Chemistry at Cotton University, Guwahati, Assam. (Best Poster Award)