Synthesis of Sulfur Containing Organic Compounds Using Multicomponent Reactions (MCRs): Their Biological and Photophysical Studies

A Dissertation Submitted to the
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As Partial Fulfillment for the Degree of

DOCTOR OF PHILOSOPHY

by

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November 2015

Dedicated to

My Parents

&

Family

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "*Synthesis of Sulfur Containing Organic Compounds Using Multicomponent Reactions (MCRs): Their Biological and Photophysical Studies"* is the result of investigation carried out by me under the supervision of Prof. Abu T. Khan and co-supervision of Prof. Bhisma K. Patel in the Department of Chemistry, Indian Institute of Technology Guwahati, India

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

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CERTIFICATE

This is to certify that Mr. Ajaz Ahmad Dar has been working in my research group since August 2010 as a regular Institute Research Fellow registered for Ph. D. programme. I am forwarding his thesis entitled *"Synthesis of Sulfur Containing Organic Compounds Using Multicomponent Reactions (MCRs): Their Biological and Photophysical Studies"* being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

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This is to certify that Mr. Ajaz Ahmad Dar has completed his Ph. D. Thesis work from August, 2010 as a regular Institute Research Fellow registered for Ph. D. programme under my colleague Prof. Abu T. Khan. I have been appointed as a Co-supervisor when Prof. Khan joined as Vice-Chancellor of Aliah University in Kolkata, West Bengal on deputation from IIT Guwahati. I am forwarding his thesis as a Co-supervisor entitled "*Synthesis of Sulfur Containing Organic Compounds Using Multicomponent Reactions (MCRs): Their Biological and Photophysical Studies*" for submission for the Ph. D. (Science) Degree of this Institute. I also certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

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November 15, 2015

Prof. B. K. Patel
(Thesis Co-Supervisor)

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Ajaz Ahmad Dar

CONTENTS OF THE THESIS

GENERAL REMARKS

The investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam during the period from August, 2010 to November, 2015 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50ºC for 8 hours. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent were used. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Büchi R-114V instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 243 polarimeter at 25 ºC temperature. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 MHz, Bruker 600 MHz and Bruker 300 MHz spectrometer TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in the order: multiplicity, no. of protons and coupling constant (J value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), brs (broad singlet), dd (doublet of doublet), dq (doublet of quartet), dt (doublet of triplet) and ddt (doublet of doublet of triplet). Mass spectra were collected on Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS and WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. HPLC grade DMSO and Milli-Q water was used in all the experiments. UV-visible absorption spectra were obtained using a Perkin-Elmer Lambda 25 spectrophotometer. Fluorescence emission spectra were recorded on Horiba Fluoromax-4 spectrofluorometer and Flourimeter (VARIAN Cary Eclipse Fluorescence Spectrophotometer) using 10 mm path length quartz cuvette and a slit width of 3 nm at room temperature.

ABBREVIATIONS

Ac	acetyl
BDMS	bromodimethylsulfonium bromide
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	cerium(IV)ammonium nitrate
CCDC	cambridge crystallographic data centre
COSY	correlation spectroscopy
DBU	1,8-diazabicycloundac-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDTA	ethylenediamintetraacetic acid
ee	enantiomeric excess
EPA	Environmental Protection Agency's
ESI-MS	electrospray ionisation mass spectrometry
Et	ethyl
Et_3N	triethylamine
EWG	electron withdrawing group
HRMS	high resolution mass spectrometry
IR	infrared
LOD	limit of detection
MCR	multicomponent reaction
m-CPBA	*m*-chloroperoxybenzoic acid
mp	melting point

MS	molecular sieves
MW	microwave
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
ORTEP	oak ridge thermal ellipsoid program
PDB	Protein data bank
Ph	phenyl
ppm	parts per million
Pr	propyl
p-TsOH	*p*-toluenesulfonic acid
rt	room temperature
SAR	Structure–activity relationship
TBATB	*n*-tetrabutylammonium tribromide
TBAI	*n*-tetrabutylammonium iodide
TBACl	*n*-tetrabutylammonium chloride
TBABr	*n*-tetrabutylammonium bromide
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TryR	Trypanothione reductase
Ts	*p*-toluenesulfonyl
VL	visceral leishmaniasis
XRD	x-ray diffraction

Chapter 1

Brief literature review of sulfur containing organic compounds and their importance

Sulfur in
Present Day
Life

CHAPTER 1: Brief Review

1.1 Introduction

Multicomponent reactions (MCRs) are progressions in which three or more available components in a single chemical operation produce product displaying features of all the involvements and thus offers greater opportunities for molecular diversity with minimum of synthetic liablity and effort.[1]

Multicomponent reactions are found to have high atom economy, efficiency under mild conditions with high convergence/divergence diversity-oriented synthesis (Figure 1.1).[2] Their increasing number of applications are reported in medicinal chemistry and drug discovery programmes,[3] combinatorial chemistry,[4] natural product synthesis,[5] agrochemistry,[6] and polymer chemistry.[7]

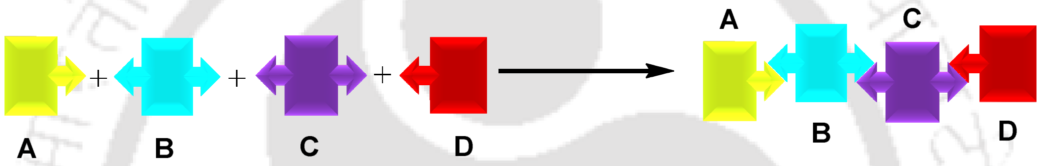


Figure 1.1

First defined by Tietze[8] and most of the known MCRs are *domino reactions*, a sequence of steps in which subsequent transformations are determined by the functionalities produced in the previous step.

MCRs are one-pot reactions and are easier to carry out than multistep syntheses (Figure 1.2). Coupled with high-throughput library screening, an important strategy to develop drug discovery in the context of rapid identification and optimization of biologically active compounds. Libraries of small organic molecule can be considered one of the most desired classes of potential drug candidates. MCRs have become a rapidly evolving field and are now key tools in industrial and academic research.[9]

Multicomponent reactions are used extensively as a tool for rapid generation of small-molecular libraries. However to warrant sufficient molecular diversity and complexity, there is a continuous need for novel reactions. Although serendipity has always played an important role in the discovery of novel multicomponent reactions, rational design approaches have become much more important over the past decade.

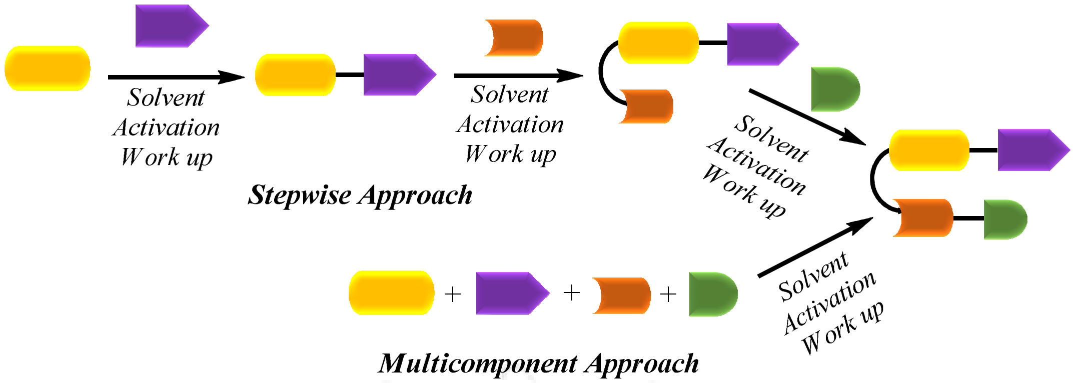


Figure 1.2. *Stepwise vs Multicomponent Approach*

1.2 Development of MCRs

The origin of MCRs dates back to the middle of the 19th century; mainly in 1850 with the publication of the Strecker reaction[10] and was developed through an extensive voyage of Hantzsch,[11] Biginelli[12] and Ugi reactions.[13] However, MCRs emerged as a powerful synthetic strategy only after the discovery of Ugi reaction. MCRs indeed may be labelled as the most promising strategy to reach an outstanding combination of atom economy, competence and sustainability. Enormous interest in MCRs not only lies in their encouraging characteristics but also in the biological properties observed from the synthesized products through multicomponent methodologies. Various MCR adducts have distinct biological activity.

Enantiomerically pure compounds are of importance[14] as each isomers are seen to have distinct activity or potency but for many MCR derivatives, racemic mixtures are seen to have biological activity[15]. All these aforementioned MCR types have already been studied by different approaches and spectroscopic/spectrometric techniques, which allowed for diverse mechanism propositions from the data generated.

From the literature it is apparent that advancement of novel multicomponent reactions is a challenging area in synthetic organic chemistry. Thus, we were inspired to work on this promising field of chemistry. In this part of my research work aimed at the synthesis of sulfur containing compounds. Also, I would like to address their importance as well as some recently developed synthetic methods.

1.3 Brief literature review of sulfur containing organic compounds

The sulfur-containing compounds are present in garlic and onion and are used as herbal medicine. Sulfur based organic compounds have immense potentiality in day-to-day human life be it in organic or inorganic form (Figure 1.3).

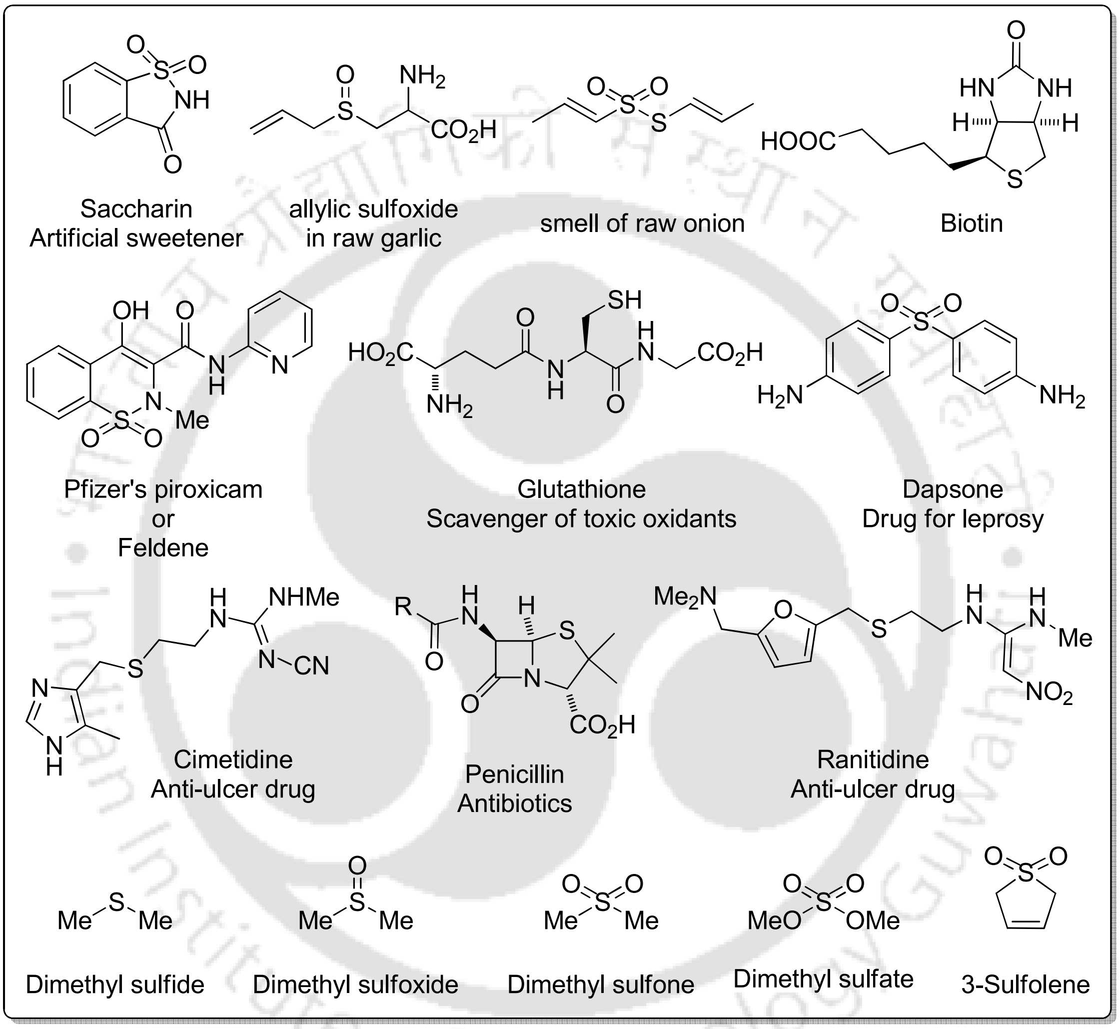


Figure 1.3. Sulfur-containing biologically active compounds present in nature and drugs.

Sulfur-based compounds such as amino acids, peptides as well as protein cross-linking agents, biotin, and ligands in bioinorganic complexes play a vital role in the biochemistry of almost all living entities.[16] They are also used as valuable solvents. Many sulfur containing compounds mostly dithioacetals, oxathioacetal, sulfides, sulfoxide, sulfones and sulfonamides have enormous importance because of their wide synthetic utility in organic synthesis.[17] Moreover sulfides are usually used for generation of α-metallated sulfide, βacylvinyl cation, homoenolate anion, equivalents as stabilized carbanion, extensively used for natural and non-natural product synthesis.[18] They are the key starting material for the synthesis of other sulfur derivatives like sulfoxides and sulfones. The synthesis of unsymmetrical sulfides such as β-mercapto diketones are of great interest. In addition, many naturally occurring sulfur based compounds exhibit anticancer activity.[19] A large number of synthetic drugs containing a sulfur atom are used for treatment of various diseases.[20] These sulfur-containing compounds are important components in synthetic drugs, pharmaceutical industry, bioactive natural products, enzyme-mimics, in materials science and synthetic equivalents for asymmetric synthesis.[21] These compounds are also known to exhibit remarkable pharmacological activities such as diuretic and HIV protease inhibitory activities.[22] Penicillins, a sulfur containing antibiotics, an effective against syphilis or infections caused by staphylococci and streptococci.[23a,b] AZD4407[23c] used as an anti-allergy and anti-asthmatic agent for the treatment of chronic obstructive pulmonary diseases (COPD). Nelfinavir[23d] used to treat human immunodeficiency virus (HIV) infection. Prevacid, a proton-pump inhibitor (PPI) inhibits gastric acids produced in the stomach.[23e] Probucol is an anti-hyperlipidemic drug for the treatment of coronary artery disease. Whereas, quetiapine,[23f] an antipsychotic drug, is used for the treatment of schizophrenia, bipolar disorder, and also as antidepressant to treat major depressive disorders [23g] (Figure 1.4).

Another important class of sulfur-based organic compounds are sulfones with potential applications. Sulfones are key intermediates[24] in organic synthesis. Sulfonyl group is prone to changes in chemical reactivity known as “chemical chameleons”[25] and display interesting chemical properties.[26] The desulfonylation reactions of sulfones gives a sulfinate anion[27] and stabilizes the neighbouring carbanions.[28] The sulfonyl group serves as a possible stereo-inducer, due to lack of inherent asymmetry.[29] Recently, Chi *et al.* developed the enantioselective synthesis of β-sulfonyl ketones and the transformation of γ-ketosulfone into cyclopropane with good enantioselectivity.[30] Benzylic sulfones acts as source for the generation of α-sulfonyl carbanions under different reaction conditions resulting in C-C bond formation.[31] Moreover sulfones play a prominent role in the field of pharmaceuticals,[32] polymers[33] and agrochemicals[34] with an extensive range of biological activities and applications. For instance, sulfone derivatives are potent inhibitors for several enzymes such as HIV-1 reverse transcriptase,[35] γ-secretase,[36] cyclooxygenase-2[37] and matrix metalloproteinase.[38] They are also biologically active agents for drugs used for the treatment of Alzheimer's disease[39] and cancer related diseases.[40]

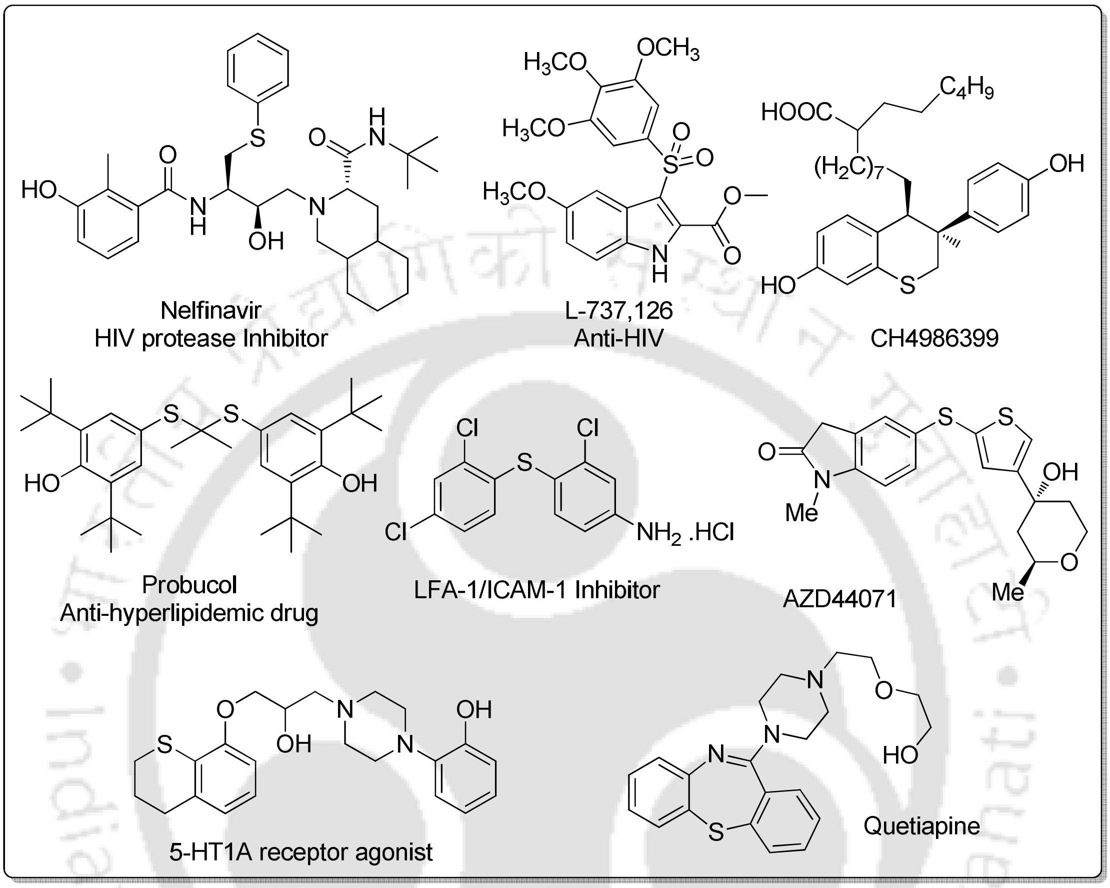


Figure 1.4. Biologically active sulfides used as drugs or drug candidates.

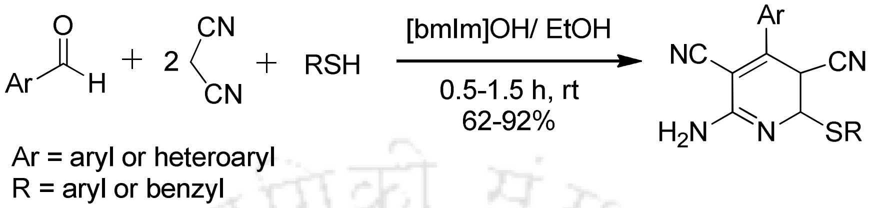
Organosulfur compounds have received considerable attention in the recent years and numerous methods for the construction of C-S bonds are developed. Significant progress for the construction of new C–S bonds, mainly involving addition and substitution strategies have been done. Two strategies are now adopted for: (i) Nucleophilic activation. (ii) Electrophilic activation. For nucleophilic activation, a base is used that abstracts proton from the sulfhydryl group of the thiol to generate thiolate anion which further reacts at the β-carbon of the α,β-unsaturated carbonyl compound. In electrophilic activation, a Lewis acid co-ordinates with the oxygen atom of the carbonyl group of the α,β -unsaturated carbonyl compound rendering it more susceptible to nucleophilic attack at the β-carbon by the sulfur atom of the thiol. Several other organic and inorganic bases have been used for nucleophilic activation of the thiol. The synthesis developed for β-sulfido carbonyl compounds following electrophilic activation strategy includes the use of various Lewis acid as catalysts. The addition of various sulfur nucleophiles to C–C double bonds as well as thiolysis of epoxides, aziridines, and anhydrides represent the most convenient methods for the formation of new C–S bonds. Recently, metal-catalyzed additions of sulfur nucleophiles to the C–C triple bond were performed with excellent selectivity to provide useful vinyl sulfides.[41] Synthesis for the construction of C–S bonds is the sulfenylation reaction involves electrophilic sulfur reagents. The C–S bond formation *via* substitution involves metal-catalyzed cross coupling reactions with aryl or vinyl halides and the direct substitution of leaving groups such as halides, sulfonates, *O*-phosphinite by a sulfur.

The Michael addition (or 1,4-addition) reaction involves sulfur nucleophiles and thiophenolate anions, in particular. Their propensities to react with an activated double bonds results in thioethers. Conjugate 1,4-addition of a thiol nucleophile with an unsaturated acceptor activated by an electron-withdrawing group (e.g., ketone, ester, amide, nitrile, nitro, sulfonate, or phosphonate), the thia-Michael addition constitutes one of the most efficient C–S bond forming strategies in synthetic chemistry.[42] Besides some conventional conjugate additions performed in basic media, a myriad of metal-centered Lewis acid catalysts were developed for potential applications in asymmetric variants.[43]

Addition of a thiol or dithiol nucleophile to an aldehyde or ketone to form a dithioacetal, known the thioacetalization, is a versatile functional group protection tactic.[44] The resultant aldehyde derived dithioacetals serve as masked acyl anion equivalents[45], zwitterion synthons[46] allowing for subsequent reductive desulfurization to the corresponding methylene groups,[47] transformation of carbohydrates to carbocycles,[48] and titanium-alkylidene mediated carbonyl olefination[49] in delicate natural product syntheses.[50] A broad spectrum of dithioacetals in organic syntheses is seen *via* thioacetalization of acetals, ketals, acylals, S,O-acetals, oximes, hydrazones, and enamines.[51] A direct access to dithioacetals without resorting to a conventional deprotection–protection sequence from these compounds can be achieved. Applications of transthioacetalization involving deprotection of acetonide and benzylidene functional groups are also documented.[52] Diversity of the reaction partners, flexibility of the Michael adduct (that can be used as such or easily cleaved, reduced or oxidized) and the potential for asymmetric conjugate addition reactions are the driving forces of interest in this field.

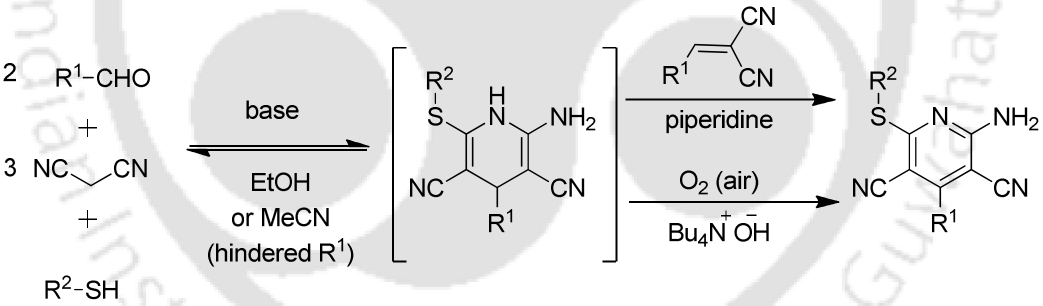
1.4 MCR Based Carbon−Sulfur Bond-Forming Reactions

Ranu *et al.* presented a one-pot, three-component condensation of aldehydes, malononitrile and thiophenols to produce highly substituted pyridines in high yields using a basic ionic liquid, [bmIm]OH, at room temperature (Scheme 1.1).[53]



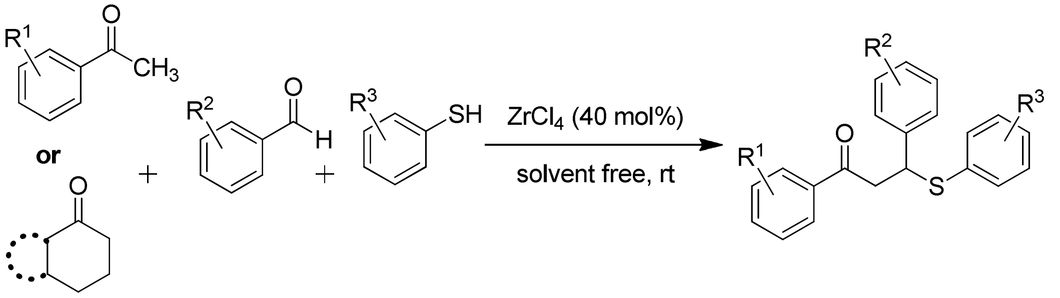
Scheme 1.1

Chen *et al.* investigated effects of an ionic base, tetrabutylammonium-hydroxide, and an amine base, piperidine on the synthesis of pyridine-3,5-dicarbonitriles using multicomponent reaction (MCR) of aldehydes, malononitrile, and thiols. Yields were found similar, when performed with the amine base in ethanol and the ionic base in acetonitrile but the reaction time was shorter in later case. This protocol enables the synthesis of pyridine-3,5-dicarbonitriles *via* the MCR from sterically hindered aldehydes (Scheme 1.2).[54]



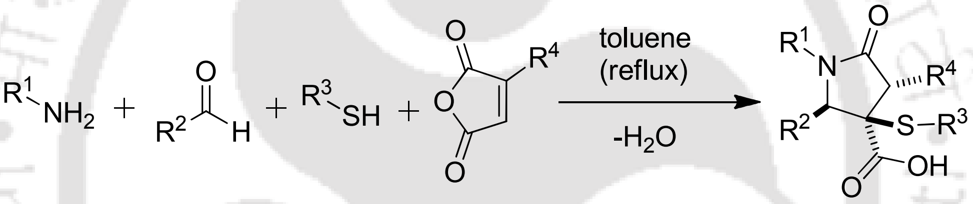
Scheme 1.2

Kumar *et al.* developed the reaction of an aryl aldehyde, cyclic or acyclic enolizable ketones and thiols under solvent-free conditions efficiently. The reaction is catalysed by zirconium chloride at room temperature to afford the corresponding β-aryl-β-mercapto ketones in high yields and short reaction times, *via* a one-pot three-component aldol–Michael addition (Schemes 1.3).[55] However, the reaction of cyclohexanone, benzaldehyde and thiophenol furnished an unexpected bis-aldol as the major product.



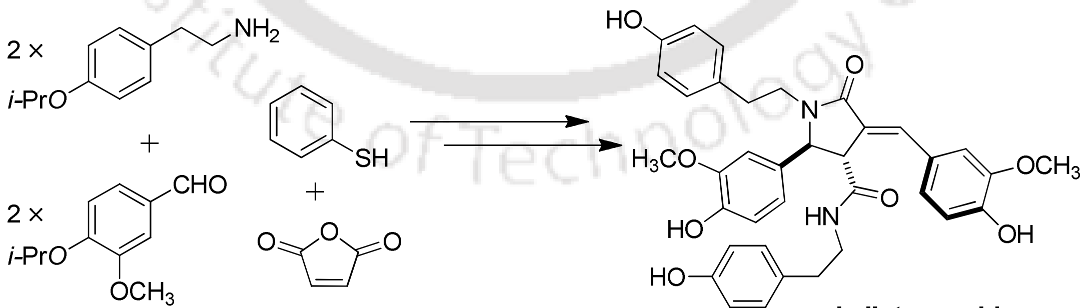
Scheme 1.3

Shaw's group revealed a mechanistically related one-pot four-component reaction (4CR) wherein amines, aldehydes, thiols and maleic anhydrides reacted in high yield and with high diastereoselectivity to form γ-lactams with up to three contiguous stereogenic centers. This 4CR is one of the only new MCRs that uses four independently variable components to form multiple stereogenic centers (Scheme 1.4).[56]



Scheme 1.4

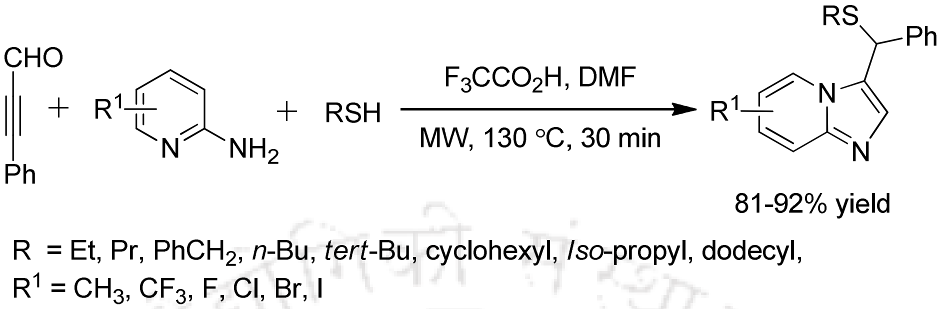
Later on, the same group reported the synthesis of (±)-heliotropamide. The preparation of 2-oxopyrrolidine (γ-lactam), a natural product also relied on a diastereoselective one-pot four-component reaction (4CR) for the assembly of the core structure (Scheme 1.5).[57]



heliotropamide

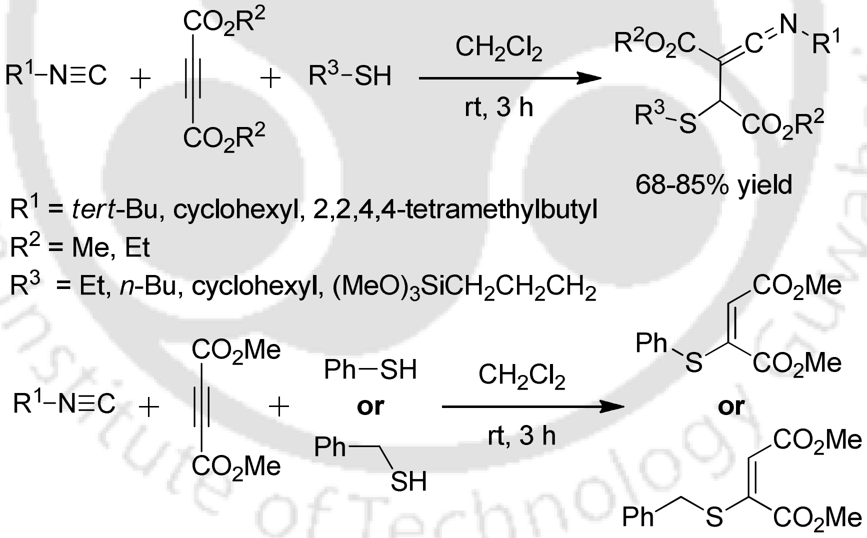
Scheme 1.5

Zhan *et al.* reported an efficient three-component domino sequence for the synthesis of sulfoether-decorated imidazo[1, 2-a]pyridines in good yields. This approach resulted in the formation of C-N and C-S bonds under the microwave irradiation (Scheme 1.6).[58]



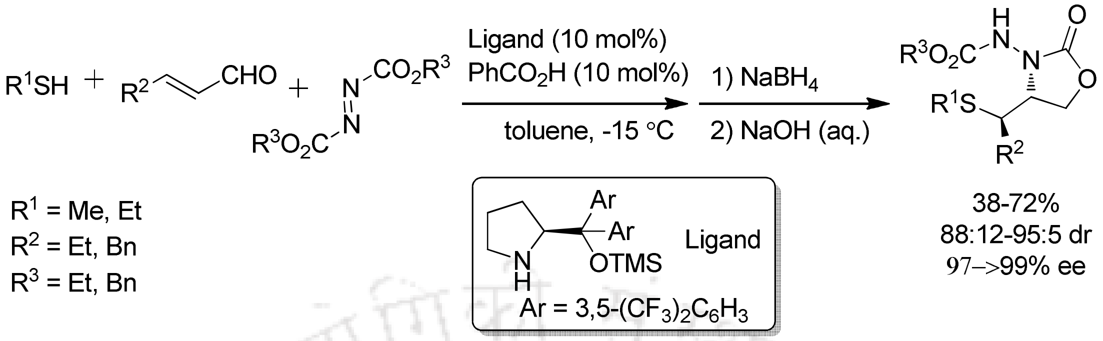
Scheme 1.6

Sarvary et al. described three-component synthesis of stable ketenimines containing a sulfur group based on a zwitterionic intermediate with alkyl mercaptans to afford ketenimines in good yields. However when thiophenol and benzylthiol were used, the expected ketenimines were not obtained, and instead the respective vinyl thioethers were isolated (Scheme 1.7).[59]



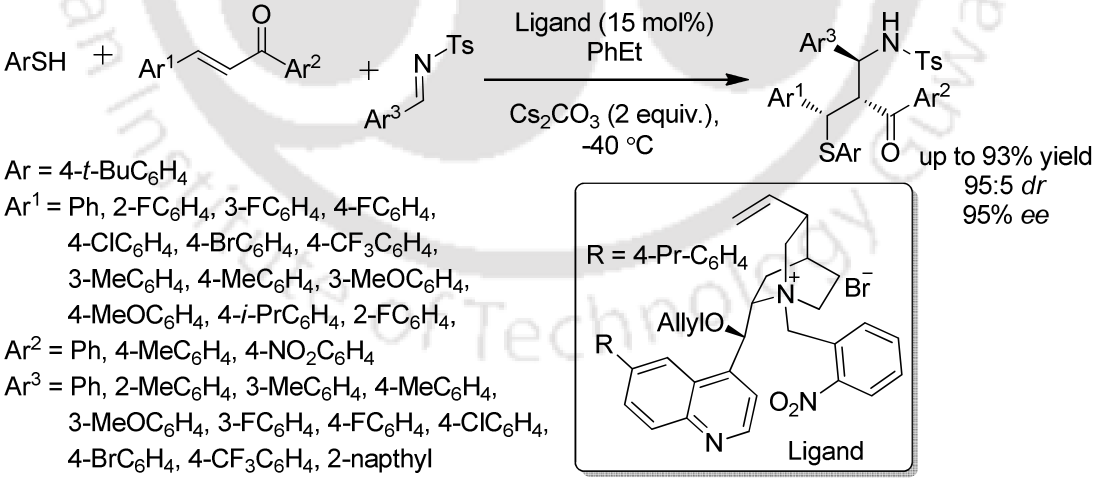
Scheme 1.7

Jørgensen *et al* reported a multicomponent domino sulfa-Michael/amination reaction between alkyl thiols, enals and azodicarboxylates catalyzed by 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]-pyrrolidine. A series of highly functionalized oxazolidinones were synthesized in judicious yields, good to high diastereoselectivities and excellent enantio-selectivities, by reduction of aldehydes and subsequent base-catalyzed cyclization (Scheme 1.8).[60]



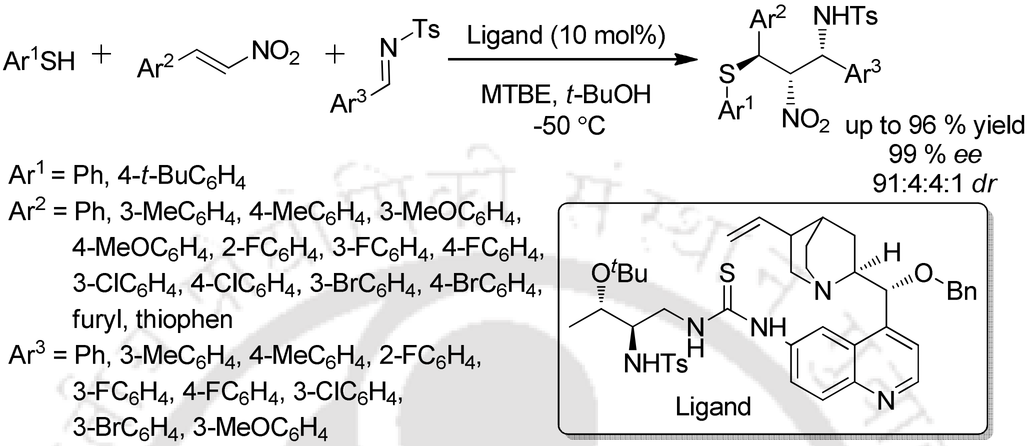
Scheme 1.8

Yungui Peng and co-workers developed an asymmetric sulfur-mediated three-component intermolecular Michael/Mannich domino reaction using chalcones as Michael acceptors. This reaction is catalyzed by chiral quaternary ammonium salts derived from modified quinine and provides facile access to complex sulfur-containing compounds with three contiguous stereogenic centers in excellent yields, good to high diastereoselectivities and enantio-selectivities (Scheme 1.9).[61] These compounds further underwent chiral aza-Morita–Baylis–Hillman reaction involving chalcones and azetidines bearing four chiral centers.



Scheme 1.9

They also established an asymmetric three-component intermolecular sulfa-Michael/Mannich cascade reaction using a chiral multifunctional catalyst. This reaction provides facile access to 1-amino-2-nitro-3-organosulfur compounds bearing three consecutive stereocenters in high yields with good diastereoselectivities and enantioselectivities (Scheme 1.10).[62] Furthermore, the products could be transformed into potentially bioactive 1, 2-diamino-3-organosulfur compounds and 2-nitro allylic amines.

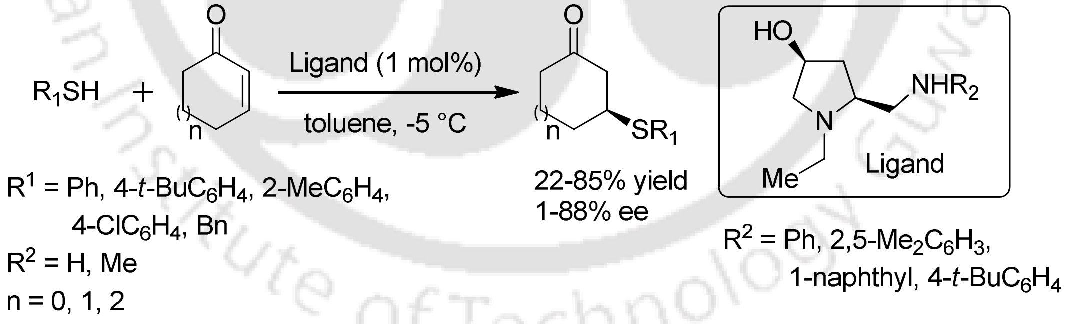


Ar^1 = Ph, 4-*t*-BuC$_6$H$_4$
Ar^2 = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, furyl, thiophen
Ar^3 = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 3-MeOC$_6$H$_4$

Scheme 1.10

1.5 Sulfa-Michael Additions (SMA) of Thiols

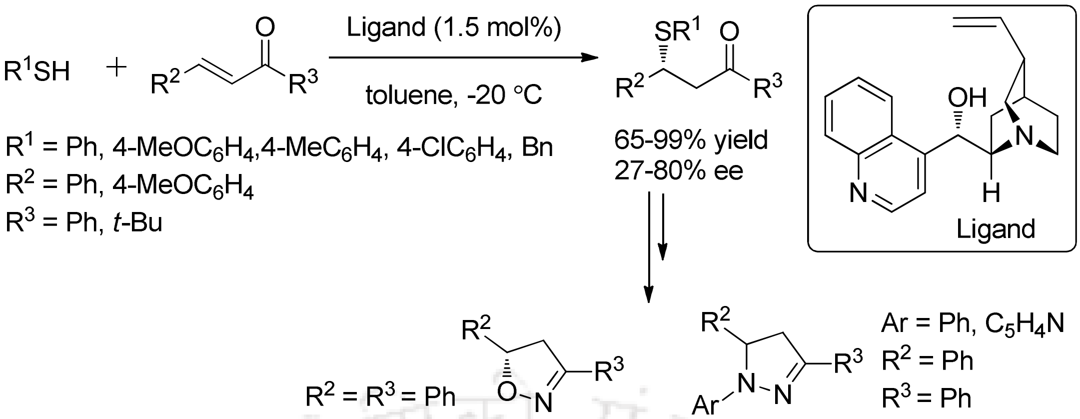
Mukaiyama and co-workers investigated the sulfa-Michael addition (SMA) reaction by using hydroxyproline derivatives and cyclic enones; moderate to high enantioselectivities products were obtained (Scheme 1.11).[63]



R^1 = Ph, 4-*t*-BuC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, Bn
R^2 = H, Me
n = 0, 1, 2
R^2 = Ph, 2,5-Me$_2$C$_6$H$_3$, 1-naphthyl, 4-*t*-BuC$_6$H$_4$

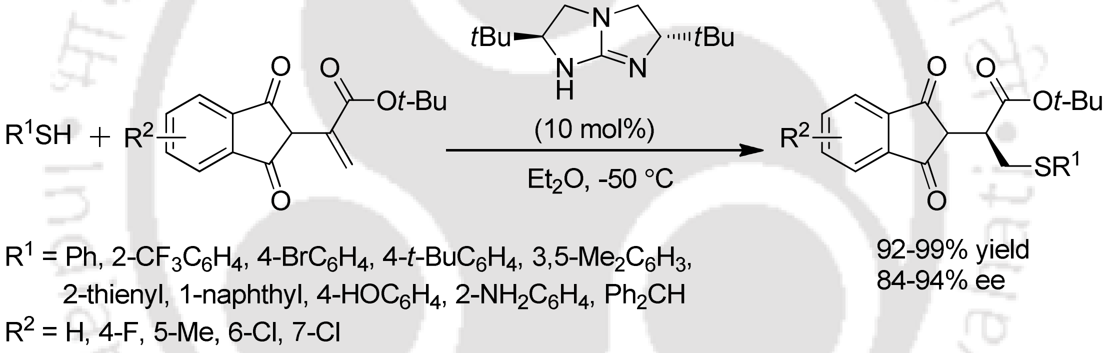
Scheme 1.11

Skarżewski *et al.* reported the addition of thiols to acyclic α,β-unsaturated ketones in the presence of cinchonine catalyst to provide sulfa-Michael adducts in moderate to excellent yields with low to good enantioselectivities. Also the sulfa-Michael adducts can be used to prepare 4,5-dihydroisoxazoles and 4,5-dihydropyrazoles (Scheme 1.12).[64]



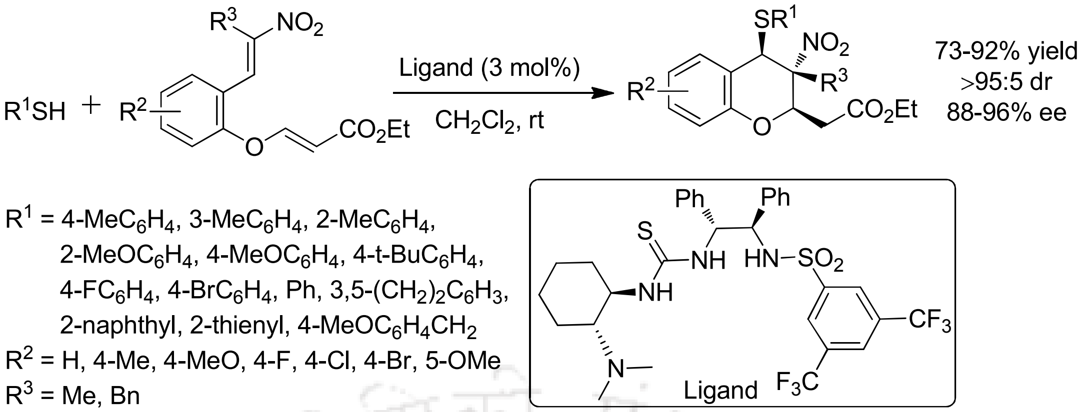
Scheme 1.12

Tan *et al.* described a domino sulfa-Michael/protonation reaction of various thiols with *tert*-butyl 2-phthalimidoacrylates using the chiral bicyclic guanidine organocatalyst. The desired product were obtained in excellent yields and with good enantioselectivities (Scheme 1.13).[65]



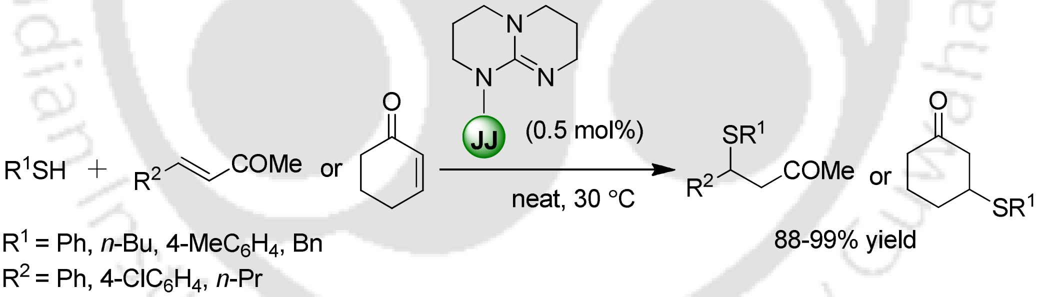
Scheme 1.13

Xiao and co-workers discovered a new domino sulfa-Michael/Michael reaction of thiols with nitroolefin enoates in the presence of multifunctional tertiary amine-thiourea-sulfonamide catalysts. The highly functionalized chromanes bearing a tetrasubstituted stereocenter were efficiently synthesized in good to high yields, high diastereoselectivities, and very good enantioselectivities (Scheme 1.14).[66]



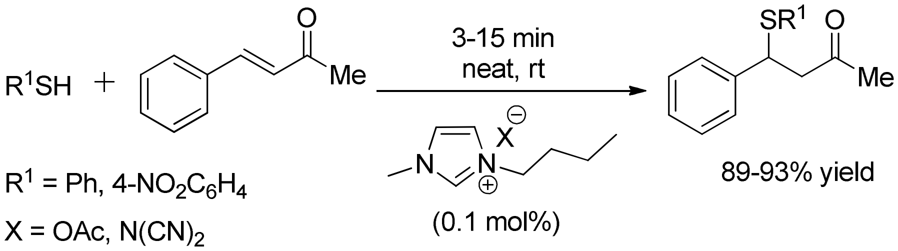
Scheme 1.14

Vaccaro and co-workers established the SMA of thiols with enones catalyzed by a low loading of JandaJel supported TBD, provided the corresponding β-ketosulfides in excellent yield. JandaJel (JJ) was found an efficient support for improving the catalytic efficiency of TBD for carbon–sulfur bond formations under solvent-free conditions. It is assumed that the greater spacing between the linear polymeric chains in JandaJel (compared to that of polystyrene matrixes facilitates), the greater the entry of reactants in the active sites of TBD and without the help of a swelling medium (Scheme 1.15).[67]



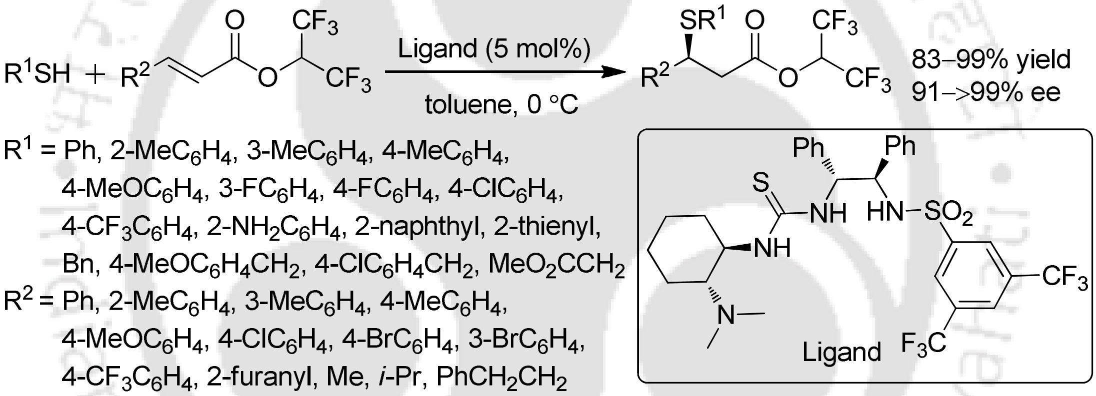
Scheme 1.15

Chakraborti's group established the addition of thiols to α,β-unsaturated carbonyl compounds that is the SMAs of thiophenols to enones, using catalytic amount of 1-butyl-3-methylimidazolium-based ionic liquids. The sulfa-Michael adducts were synthesized in very good yields in short reaction time (Scheme 1.16).[68]



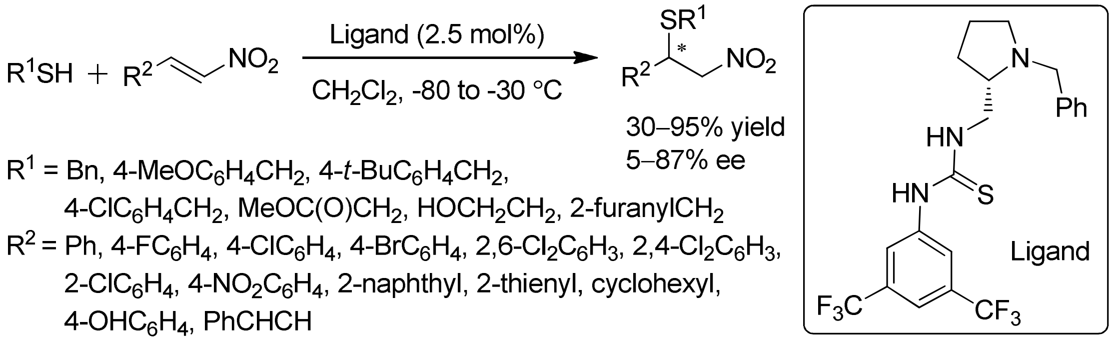
Scheme 1.16

Wang and co-workers developed a highly efficient asymmetric SMA of a wide range of thiols with various hexafluoroisopropyl α,β-unsaturated esters catalyzed by the amine-thiourea-sulfonamide catalyst in high yields and with excellent enantio-selectivities (Scheme 1.17). Its importance was demonstrated by the one-pot three-step synthesis of the antidepressant agent (R)-thiazesim in good yield and high enantio-selectivity .[69]



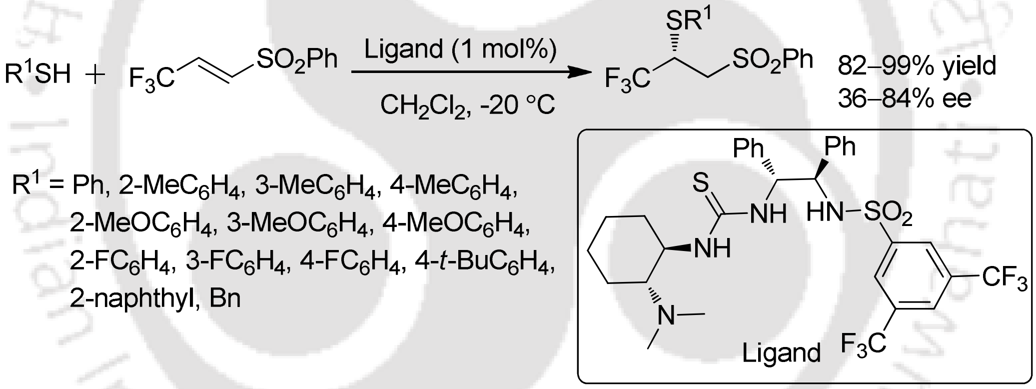
Scheme 1.17

Kowalczyk’s group established asymmetric SMA of aliphatic thiols to nitro-olefins with an effective organocatalyst, N-3,5-bis(trifluoromethyl)phenyl thiourea (Scheme 1.18). The reaction is also extended to the addition with nitrodienes to give the corresponding products in good yields and poor to good enantioselectivities.[70]



Scheme 1.18

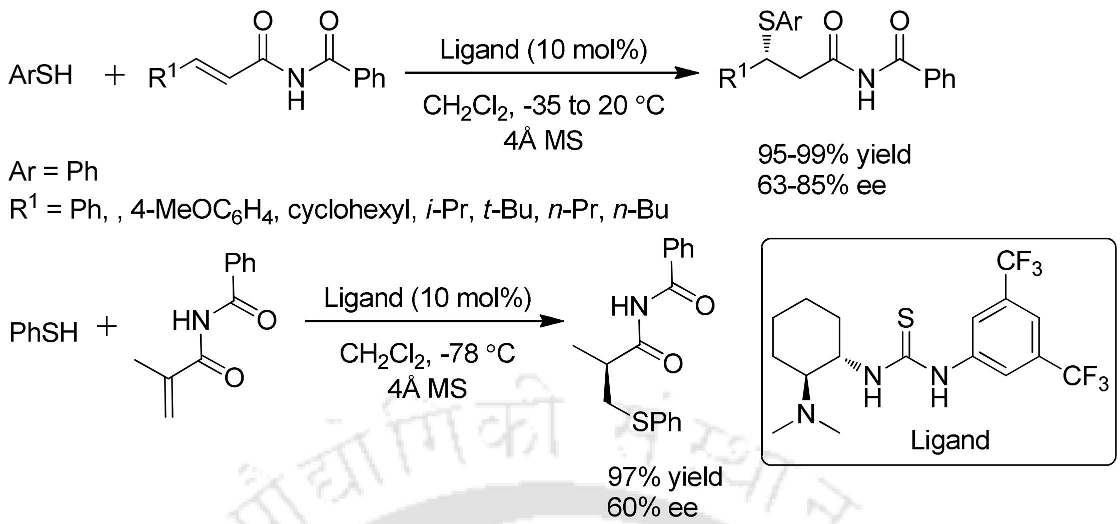
Wang *et al.* reported asymmetric SMA of thiols to (E)-3,3,3-trifluoropropenyl phenyl sulfones catalyzed by a bifunctional amine-thioureasulfonamide at low catalyst loading. A variety of arylthiols as well as benzylthiols were added to the sulfones to provide the desired sulfones bearing a trifluoromethylated stereogenic center in high yields with low to good enantio-selectivities (Scheme 1.19).[71]



Scheme 1.19

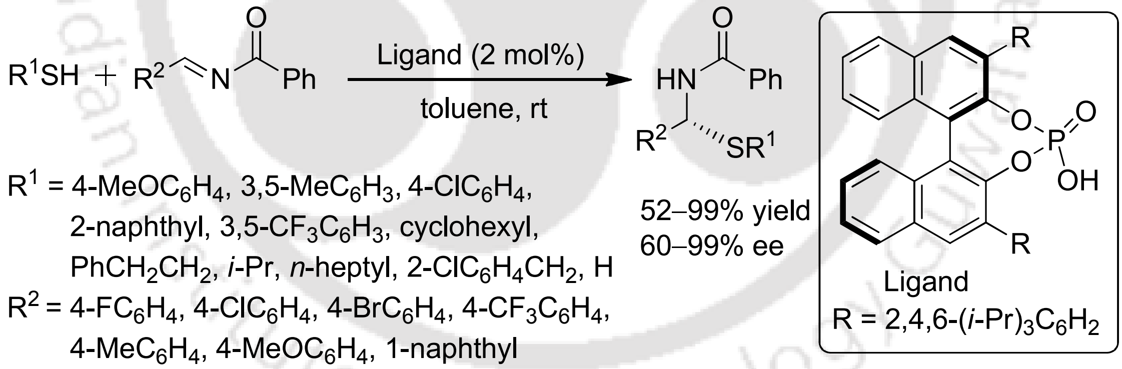
1.6 1,2-, 1,6- and γ-Addition Reactions of Thiols

Chen *et al.* showed the conjugate addition of thiophenols to α,β-unsaturated imides using Takemoto's tertiary amine-thiourea catalyst, offered the product in high yields and moderate enantio-selectivities (Scheme 1.20).[72]



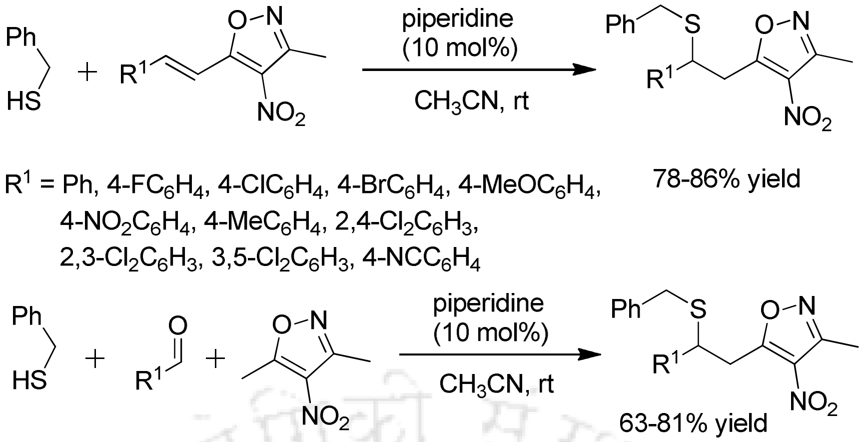
Scheme 1.20

In 2011, Antilla's group reported a catalytic asymmetric 1,2-addition of thiols to imines, by utilizing low amount of the chiral phosphoric acid (TRIP) catalyst. The rapid addition of thiols to N-acyl imines generated enantioenriched N,S-acetals in moderate to excellent yields and enantio-selectivities. A variety of electron-rich and electron-deficient aromatic N-acyl imines as well as a wide range of aliphatic and aromatic thiols were tolerated under the optimized reaction conditions (Scheme 1.21).[73]



Scheme 1.21

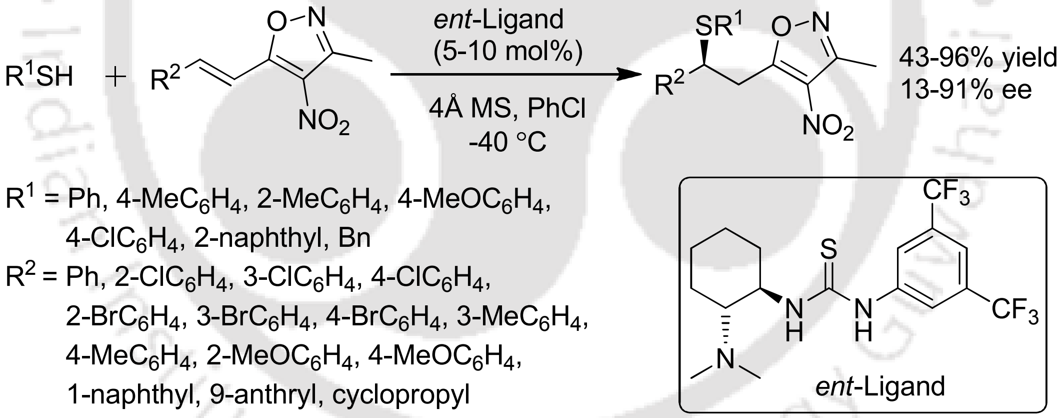
Further, Adamo and co-workers reported an efficient procedure for 1,6-addition reactions of benzyl thiol to styrylisoxazoles catalyzed by piperidine. Under mild reaction conditions, good yields of the corresponding 1,6-adducts were obtained. The three-component reactions between various aldehydes, 3,5-dimethyl-4-nitroisoxazole, and benzyl thiol catalyzed by piperidine were also successfully performed, which involved the *in situ* generation of the styrylisoxazoles (Scheme 1.22).[74]



R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$,
4-$NO_2C_6H_4$, 4-MeC_6H_4, 2,4-$Cl_2C_6H_3$,
2,3-$Cl_2C_6H_3$, 3,5-$Cl_2C_6H_3$, 4-NCC_6H_4

Scheme 1.22

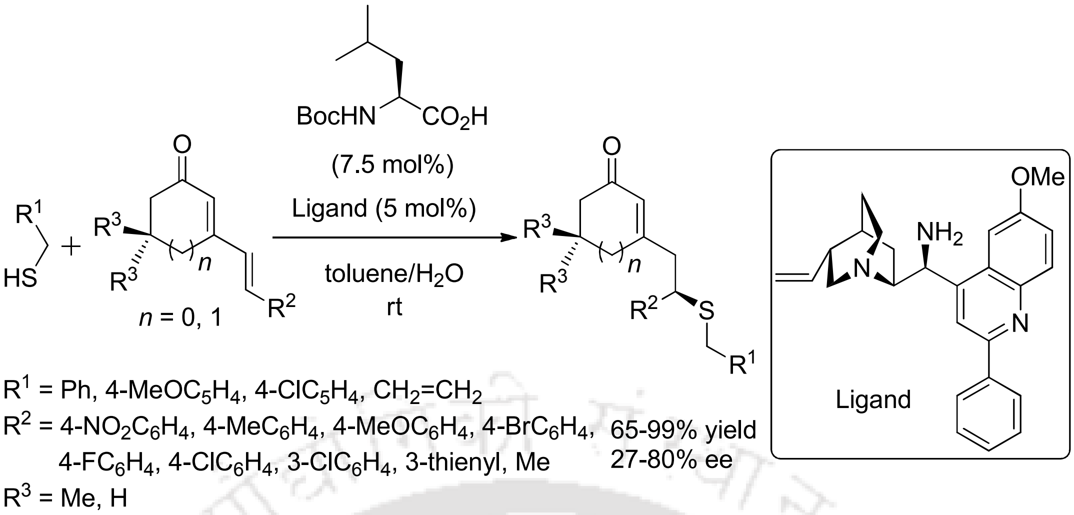
Yuan *et al*. reported an enantioselective organocatalytic 1,6-addition of thiols to various 3-methyl-4-nitro-5-alkenyl-isoxazoles catalyzed by the bi-functional thioureatertiary amine. A series of 1,6-adducts were synthesized from various isoxazoles and aryl thiols in good to high yields and good enantio-selectivities. However, benzyl thiol gave low yields and poor enantioselectivities of the desired products (Scheme 1.23).[75]



R^1 = Ph, 4-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$,
4-ClC_6H_4, 2-naphthyl, Bn
R^2 = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4,
2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 3-MeC_6H_4,
4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$,
1-naphthyl, 9-anthryl, cyclopropyl

Scheme 1.23

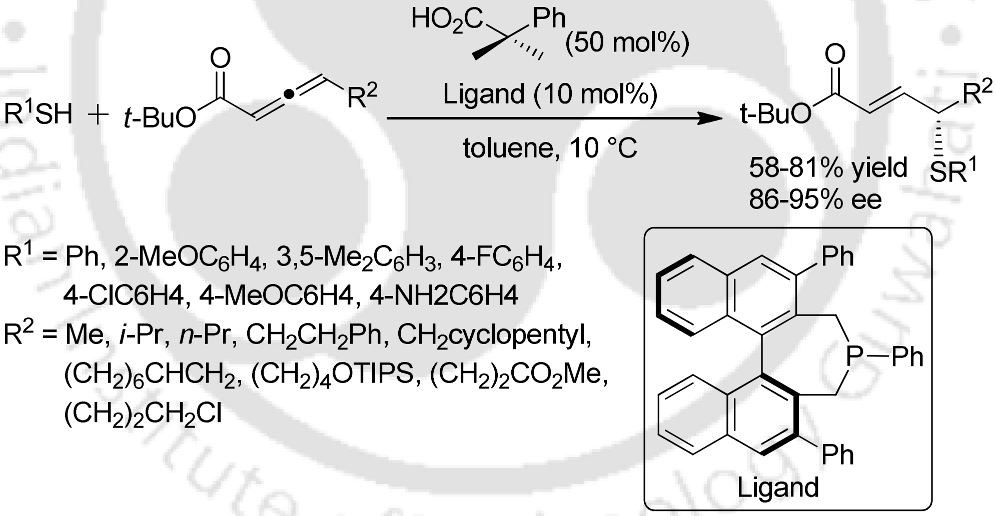
Melchiorre and co-workers developed asymmetric organocatalytic 1,6-addition of thiols to provide corresponding adducts in moderate yields, moderate to good enantio-selectivities, and good 1,6-addition selectivity. It was revealed that the LUMO-lowering activating effect transmitted through the conjugated π-system of 2,4-dienones upon selective condensation with a chiral primary amine catalyst in the presence of a chiral acid resulting in the vinylogous iminium ion (Scheme 1.24).[76]



R^1 = Ph, 4-$MeOC_5H_4$, 4-ClC_5H_4, CH_2=CH_2
R^2 = 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 3-thienyl, Me
R^3 = Me, H

Scheme 1.24

Fu and co-workers reported an effective method for the catalytic enantioselective γ-addition of aryl thiols to allenoates catalyzed by the phosphepine. This process provided an easy access to the γ-thioether substituted enoates in moderate to good yields and very good enantio-selectivities (Scheme 1.25).[77]

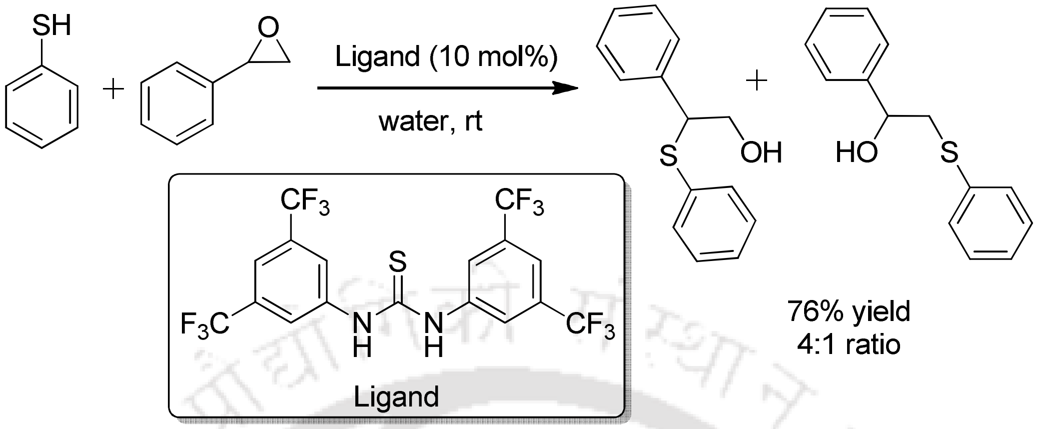


R^1 = Ph, 2-$MeOC_6H_4$, 3,5-$Me_2C_6H_3$, 4-FC_6H_4, 4-ClC6H4, 4-MeOC6H4, 4-NH2C6H4
R^2 = Me, *i*-Pr, *n*-Pr, CH_2CH_2Ph, CH_2cyclopentyl, $(CH_2)_6CHCH_2$, $(CH_2)_4OTIPS$, $(CH_2)_2CO_2Me$, $(CH_2)_2CH_2Cl$

Scheme 1.25

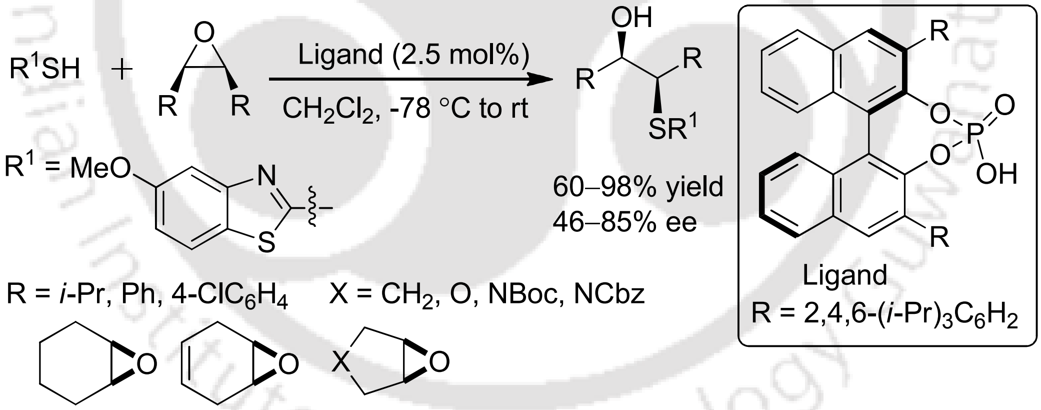
1.7 Ring-Opening of Epoxides, Aziridines, and Azlactones with Thiols

In 2006, Schreiner and Kleiner studied the effects of hydrogen-bonding organocatalysts and water for the rate acceleration of epoxide ring-openings with a variety of nucleophiles. A significant improvement in the reaction rate and yield were observed in the thiourea-catalyzed ring-opening of epoxides with amines, alcohols, and thiophenol in water. The thiourea-catalyzed reaction of thiophenol with styrene oxide gave the desired product in 76% yield with a 4:1 ratio of the regioisomers in favor of the α-addition product (Scheme 1.26).[78]



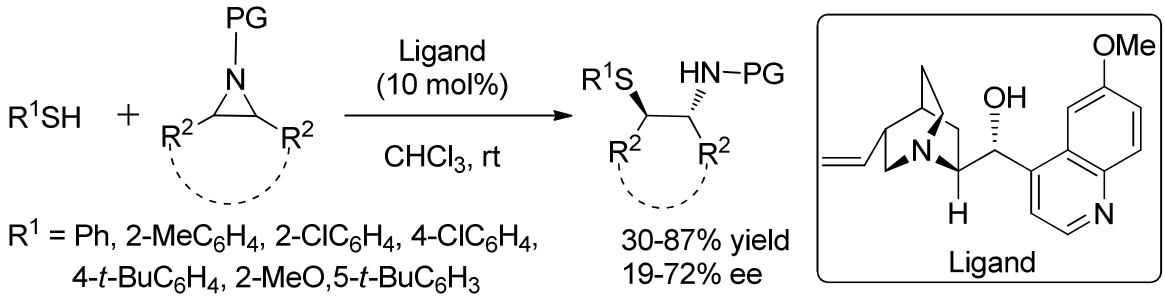
Scheme 1.26

Sun and co-authors reported the desymmetrization by thiolysis of bicyclic and monocyclic *meso*-epoxides in the presence of the phosphoric acid catalyst *via* the asymmetric nucleophilic ring-opening of *meso*-epoxides with thiols to afford the corresponding *β*-hydroxy sulfides in moderate to high yields and moderate to good enantioselectivities (Scheme 1.27).[79]



Scheme 1.27

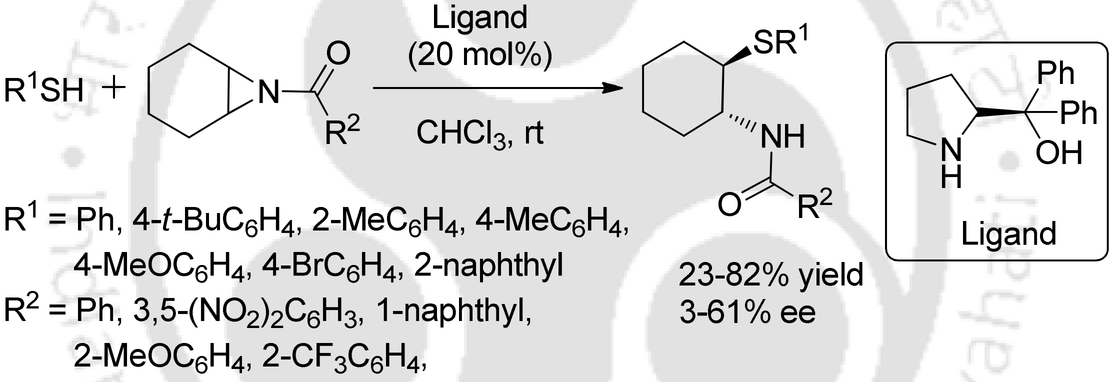
Wu *et al* reported an asymmetric desymmetrization of N-protected *meso*-aziridines with aryl thiols catalyzed by quinine to afford *β*-amino sulfides in low to good yields and low to moderate enantioselectivities as shown in Scheme 1.28.[80]



R^1 = Ph, 2-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$,
4-*t*-BuC$_6$H$_4$, 2-MeO,5-*t*-BuC$_6$H$_3$
R^2 = -CH$_2$CHCHCH$_2$-, -(CH$_2$)$_3$-, -CH$_2$OCH$_2$-, -(CH$_2$)$_4$-
PG = Ts, 3,5-(NO$_2$)$_2$C$_6$H$_3$CO, 4-NO$_2$C$_6$H$_4$CO, 3,5-(CF$_3$)$_2$C$_6$H$_3$CO, Cbz

Scheme 1.28

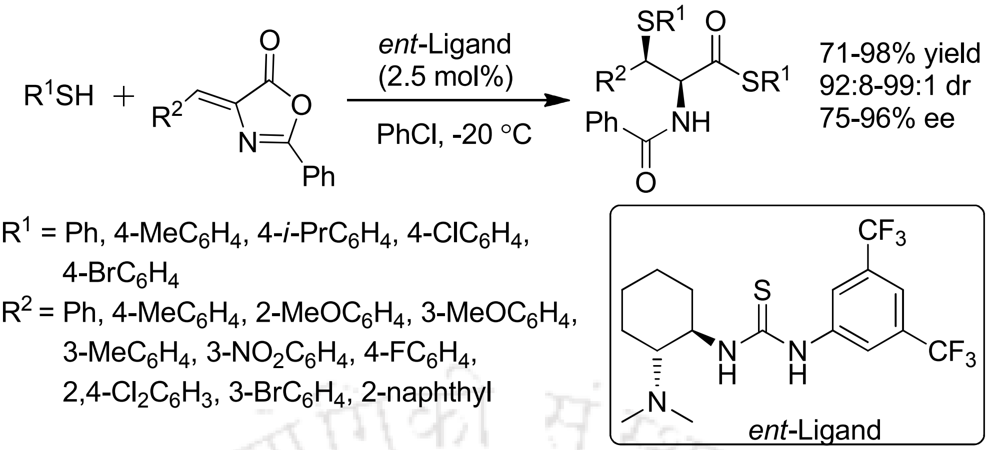
Lattanzi and Sala identified α,α-diphenyl-L-prolinol, an efficient catalyst for the desymmetrization of *meso*-N-acylaziridines with aryl thiols to afford the aminothiols in low to good yields and poor to moderate enantio-selectivities (Scheme 1.29).[81]



R^1 = Ph, 4-*t*-BuC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$,
4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-naphthyl
R^2 = Ph, 3,5-(NO$_2$)$_2$C$_6$H$_3$, 1-naphthyl,
2-MeOC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$,

Scheme 1.29

Wang *et al* reported an elegant organocatalytic domino sulfa-Michael/ring-opening reaction of (Z)-olefinic azlactones with aromatic thiols in the presence of Takemoto's catalyst; the enantioenriched *syn*-*β*-thio-*α*-amino acid derivatives were synthesized in one pot with excellent yields, high levels of diastereoselectivities, and good enantioselectivities. In some cases the desired products (slightly lower yields with a significant improvement in the stereo-selectivities) were obtained by a simple filtration and washing procedure without any purification by column chromatography (Scheme 1.30).[82]



71-98% yield
92:8-99:1 dr
75-96% ee

R^1 = Ph, 4-MeC_6H_4, 4-*i*-PrC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

R^2 = Ph, 4-MeC_6H_4, 2-MeOC_6H_4, 3-MeOC_6H_4, 3-MeC_6H_4, 3-$NO_2C_6H_4$, 4-FC_6H_4, 2,4-$Cl_2C_6H_3$, 3-BrC_6H_4, 2-naphthyl

Scheme 1.30

1.8 References

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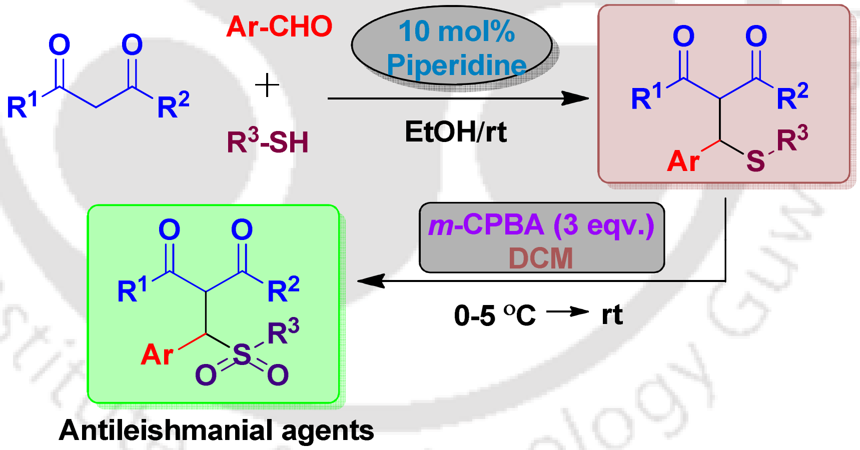
Chapter 2

Synthesis of unsymmetrical sulfides and their oxidation to sulfones to discover potent antileishmanial agents

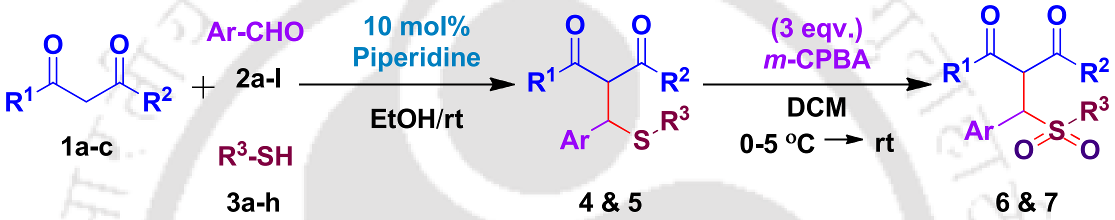


2.1 Results and Discussion

The importance of sulfur containing compounds and their preparation have been discussed in detail in Chapter 1. Literature survey revealed that the thiol based multicomponent reactions (MCRs) are not used widely. Therefore, the scope for development of a practical and efficient method to prepare of sulfur containing compounds through MCR strategies, which would work under mild, neat, environmentally benign conditions.

In this chapter, we have described the synthesis of unsymmetrical sulfides using combinations of 1,3-dicarbonyls, aromatic aldehydes and thiols in presence of 10 mol% ethanolic piperidine. These sulfides derivatives were subsequently converted into corresponding sulfones *via* oxidation in presence of *m*-chloroperoxybenzoic acid (*m*-CPBA) at ice-bath to room temperature. The first reaction was achieved at room temperature through one-pot three-component. The later was obtained in good yields using mild reaction conditions with flexibility in choice from a range of substrates. Further, the antimicrobial properties of the newly synthesized sulfones were investigated against the protozoan parasite, *Leishmania donovani*, a causative agent of visceral leishmaniasis (VL). Nine sulfone derivatives were found to be efficacious and exhibited significant antimicrobial activities. These compounds were non-toxic on murine peritoneal macrophages thus eliminating potential cytoxicity in the host cells. These compounds may be indicated as potential leads in the treatment of visceral leishmaniasis.

Leishmaniasis, one of the world's most neglected diseases, is found to exist in as many as 98 countries with 350 million people at risk of infection.[1] Clinical manifestations include visceral, cutaneous and mucocutaneous forms. Visceral leishmaniasis caused by *L. donovani* is often fatal if left untreated.[2] A limited number of drugs including pentavalent antimonials (still used as first line therapy), amphotericin B, pentamidine and miltefosine (the second line therapies), which are known to show adverse side effects, requirement of long term treatment regimen and emergence of drug resistant parasites.[3] With these issues in mind, there is an urgent need to develop alternative (safer, cheaper and more effective) chemotherapeutic agents with potential antileishmnial activity.[4] Few studies on the activity of sulfonamides and sulfones against *L. major* and *L. donovani* promastigotes and on intracellular amastigotes indicate that these molecules could be promising for the treatment of cutaneous and visceral leishmaniasis, respectively.[5] Dapsone shows effectiveness in the treatment of cutaneous leishmaniasis.[6] In order to improve case management of severe visceral leishmaniasis (VL) and achieve rapid control of outbreaks, the development of an effective antileishmanial drug is highly desirable. Therefore, much attention has been paid to the synthesis of benzylic sulfones that could be useful in developing potential antileishmanial drug. Although several new methods have recently been reported to improve the synthesis of benzylic sulfones, they require expensive reagents or catalysts and/or harsh reaction conditions.[7] However, in this chapter we report a synthesis of highly substituted unsymmetrical sulfides through one-pot piperidine catalyzed three-component reaction using 1,3-dicarbonyl compounds, aromatic aldehydes and thiols followed by the oxidation of sulfides into the corresponding sulfones (Scheme 2.1) and evaluated the activity of sulfones against promastigotes of *L. donovani*.



1a = $R^1 = R^2 = CH_3$
1b = $R^1 = R^2 = Ph$
1c = $R^1 = Ph$, $R^2 = CH_3$

Ar = Ph (2a), 4-MeOPh (2b), 4-MePh (2c), 3,4,5-MeOPh (2d), 4-ClPh (2e), 4-BrPh (2f), 4-OHPh (2g), 4-NO_2Ph (2h), 4-CNPh (2i), 3-NO_2Ph (2j), 3-FPh (2k), 2-Naphthyl (2l), 2-NO_2Ph (2m), 2-OHPh (2n), 2-ClPh (2o), 2-MePh (2p), 2-MeOPh (2q), 2-FPh (2r), 2-BrPh (2s), 2-pryidyl (2t), 2-thiopenyl (2u),

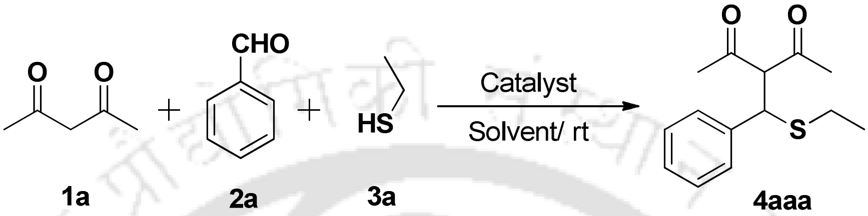
R^3 = Et (3a), Pr (3b), $PhCH_2$ (3c), Ph (3d), 4-MePh (3e), 4-ClPh (3f), 4-BrPh (3g), 2-Naphthyl (3h)

Scheme 2.1. Synthesis of sulfides through MCR strategy and their oxidation into corresponding sulfones.

At the outset, pentane-2,4-dione (**1a**), benzaldehyde (**2a**) and ethanethiol (**3a**) were used as the model substrates to find a suitable reaction condition. A trial reaction was carried out in 3 mL ethanol at room temperature in absence of catalyst and a trace amount of desired product was formed (Table 2.1, entry 1). Then, similar reactions were conducted in presence of 5, 10 and 20 mol% piperidine at room temperature, respectively and the results are summarized (Table 2.1). It was observed that 10 mol% piperidine in ethanol at room temperature gave the best yield (Table 2.1, entry 3). Other catalysts, such as pyridine, pyrrolidine, triethylamine (Et_3N) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in ethanol were also scrutinized

(Table 2.1, entries 9-12). These catalysts provided lower yields and required longer reaction time. Various other solvents were also examined with 10 mol% of piperidine under identical reaction conditions (Table 2.1, entries 5-8) and ethanol proved to be the best solvent as compared to the other tested solvents.

Table 2.1. Optimization of reaction conditions[a]



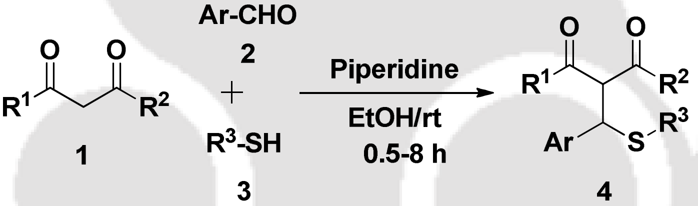
Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	No catalyst (0)	EtOH	24	trace
2	Piperidine (5)	EtOH	5	40
3	**Piperidine (10)**	**EtOH**	**5**	**75**
4	Piperidine (20)	EtOH	5	77
5	Piperidine (10)	DCE	5	64
6	Piperidine (10)	DMF	5	70
7	Piperidine (10)	DCM	5	46
8	Piperidine (10)	CH_3CN	5	50
9	Pyridine (10)	EtOH	12	15
10	Pyrrolidine (10)	EtOH	12	55
11	Et_3N (10)	EtOH	12	40
12	DBU (10)	EtOH	12	35

[a]All the reactions were carried out using **1a** (1 mmol), **2a** (1 mmol) and **3a** (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

The product (**4aaa**) isolated was fully characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra, ESI-MS and by elemental analysis. The signals appears in the ^{1}H NMR spectrum at δ 1.14 (t, J = 7.6 Hz, 3H), 1.88 (s, 3H), 2.27-2.35 (m, 2H), 2.37 (s, 3H), 4.26 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 7.24-7.31 (m, 5H). The signals at δ 4.26 and 4.50 are two doublets for (-CH–CH-) protons clearly indicate the formation of the desired product. Similarly, the various peaks obtained in the ^{13}C NMR spectrum are at δ 14.3, 25.3, 29.5, 30.1, 48.3, 74.8, 128.0, 128.3 (2C), 128.9 (2C), 139.5, 201.6 (2C) and the characteristic peaks at δ 48.3 and 74.8 corresponding to (-CH–CH-) carbon atoms resulting only due to the formation of product.

The optimized protocol was further examined, by carrying out with various aromatic aldehydes (Scheme 2.1) to generalize the scope of this reaction. In case of aromatic aldehydes with both electron donating or withdrawing groups, the desired products were obtained with moderate to good yields, such as Me, OMe, 3,4,5-OMe, OH, Br, Cl, CN, F and NO_2 groups. The reaction between pentane-2,4-dione (**1a**), benzaldehyde (**2a**) with aliphatic or aromatic thiols (**3**) were inspected under optimized reaction conditions. The desired products **4aaa**- **4aae** were obtained in 75 to 83% yields, respectively (Table 2.2, entries 1–5). The reaction between pentane-2,4-dione (**1a**), 4-methoxybenzaldehyde (**2b**) with benzylthiol (**3c**) or 4-methylthiophenol (**3e**) were examined in a similar manner in the presence of the same amount of catalyst. The desired products **4abc** and **4abe** were obtained in 81% and 85% yields, respectively (Table 2.2, entries 6 and 7). The reactions between pentane-2,4-dione (**1a**), aromatic aldehydes with different electron donating or withdrawing substituents in the aromatic ring, and thiophenol (**3d**) were performed under identical conditions, the products **4acd**- **4afd** were obtained in 57-89% yield (Table 2.2, entries 8-11). Also reactions between pentane-2,4-dione (**1a**), aromatic aldehydes with various electron donating or withdrawing substituents in the aromatic ring, and 4-methylthiophenol (**3e**) were examined under similar conditions, the products **4age**- **4aje** were obtained in 57-68% yields (Table 2.2, entries 12-14). Furthermore, we scrutinised the reactions of pentane-2,4-dione (**1a**), 2-napthaldehyde (**2l**) with 4-methylthiophenol (**3e**) and 2-napthalenethiol (**3h**), the reactions proceeded smoothly to give **4ale** and **4alh**, respectively, in good yields (Table 2.2, entries 15 and 16). Due to the steric hindrance at *ortho*-position, 2-NO_2 (**2m**), 2-OH (**2n**) or 2-Cl (**2o**) benzaldehyde with pentane-2,4-dione (**1a**) and 4-methylthiophenol (**3e**) did not give desired product. Although, 2-Me (**2p**), 2-OMe (**2q**), 2-F (**2r**) or 2-Br (**2s**) benzaldehyde with pentane-2,4-dione (**1a**) and 4-methylthiophenol (**3e**) produced the desired product in good yields (Table 2.2, entries 17–20). Likewise, heterocyclic aldehydes 2-pyridinecarboxaldehyde (**2t**) and 2-thiophenecarboxaldehyde (**2u**) also reacted with pentane-2,4-dione (**1a**) and 4-methylthiophenol (**3e**) to produce the desired products **4ate** and **4aue**, in good yield respectively (Table 2.2, entries 21-22). The reactions of 1,3-diphenylpropane-1,3-dione (**1b**), benzaldehyde (**2a**) with benzylthiol (**3c**) or different aromatic thiols (**3**) were examined under optimized reaction condition. The desired products **4bac**- **4bag** were obtained in 61-70% yields (Table 2.2, entries 23–27). Similarly, the reactions of 1,3-diphenylpropane-1,3-dione (**1b**), aromatic aldehydes containing various electron donating or withdrawing substituents at the *para* or *meta*-position on the benzene ring, with varied aromatic thiols (**3**) were also carried out. The desired products **4bbe**- **4bkg** were isolated in good yields (Table 2.2, entries 28–32). By these successful results, we also scrutinized the reactions of unsymmetrical 1,3-dicarbonyl, 1-phenyl-1,3-butanedione (**1c**), benzaldehyde (**2a**), with benzylthiol (**3c**), thiophenol (**3d**) or 4-methylthiophenol (**3e**) by following the same reaction procedure. The desired products **5cac**- **5cae** were isolated in good yields (Table 2.3, entries 1–3). Likewise, the reactions of 1-Phenyl-1,3-butanedione (**1c**), aromatic aldehydes, which have various electron donating or withdrawing substituents in the aromatic ring, and different aromatic thiols (**3**) were examined, the desired products **5cbc**- **5cfe** were obtained in 55-80% yields (Table 2.3, entries 4–9).

Table 2.2. Synthesis of unsymmetrical sulfides from symmetrical diketones[a]

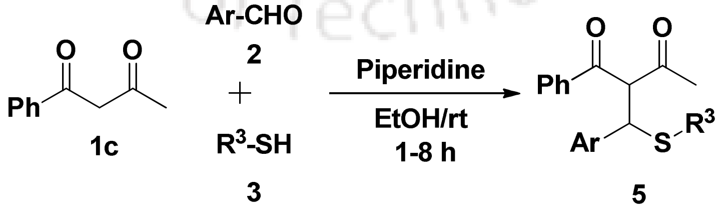


Entry	Diketone	Aldehyde	Thiol	Product	Yield (%)[b]
1	**1a**	**2a**	**3a**	**4aaa**	75
2	**1a**	**2a**	**3b**	**4aab**	80
3	**1a**	**2a**	**3c**	**4aac**	79
4	**1a**	**2a**	**3d**	**4aad**	82
5	**1a**	**2a**	**3e**	**4aae**	83
6	**1a**	**2b**	**3c**	**4abc**	81
7	**1a**	**2b**	**3e**	**4abe**	85
8	**1a**	**2c**	**3d**	**4acd**	83
9	**1a**	**2d**	**3d**	**4add**	89
10	**1a**	**2e**	**3d**	**4aed**	57
11	**1a**	**2f**	**3d**	**4afd**	62

12	**1a**	**2g**	**3e**	**4age**	68
13	**1a**	**2h**	**3e**	**4ahe**	57
14	**1a**	**2j**	**3e**	**4aje**	61
15	**1a**	**2l**	**3e**	**4ale**	78
16	**1a**	**2l**	**3h**	**4alh**	84
17	**1a**	**2p**	**3e**	**4ape**	70
18	**1a**	**2q**	**3e**	**4aqe**	73
19	**1a**	**2r**	**3e**	**4are**	67
20	**1a**	**2s**	**3e**	**4ase**	65
21	**1a**	**2t**	**3e**	**4ate**	64
22	**1a**	**2u**	**3e**	**4aue**	68
23	**1b**	**2a**	**3c**	**4bac**	66
24	**1b**	**2a**	**3d**	**4bad**	68
25	**1b**	**2a**	**3e**	**4bae**	70
26	**1b**	**2a**	**3f**	**4baf**	61
27	**1b**	**2a**	**3g**	**4bag**	63
28	**1b**	**2b**	**3e**	**4bbe**	72
29	**1b**	**2c**	**3d**	**4bcd**	69
30	**1b**	**2c**	**3e**	**4bce**	72
31	**1b**	**2i**	**3f**	**4bif**	58
32	**1b**	**2k**	**3g**	**4bkg**	56

[a]All the reactions were carried out using **1a** or **1b** (1 mmol), **2** (1 mmol) and **3** (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

Table 2.3. Synthesis of unsymmetrical sulfides from unsymmetrical diketone[a]



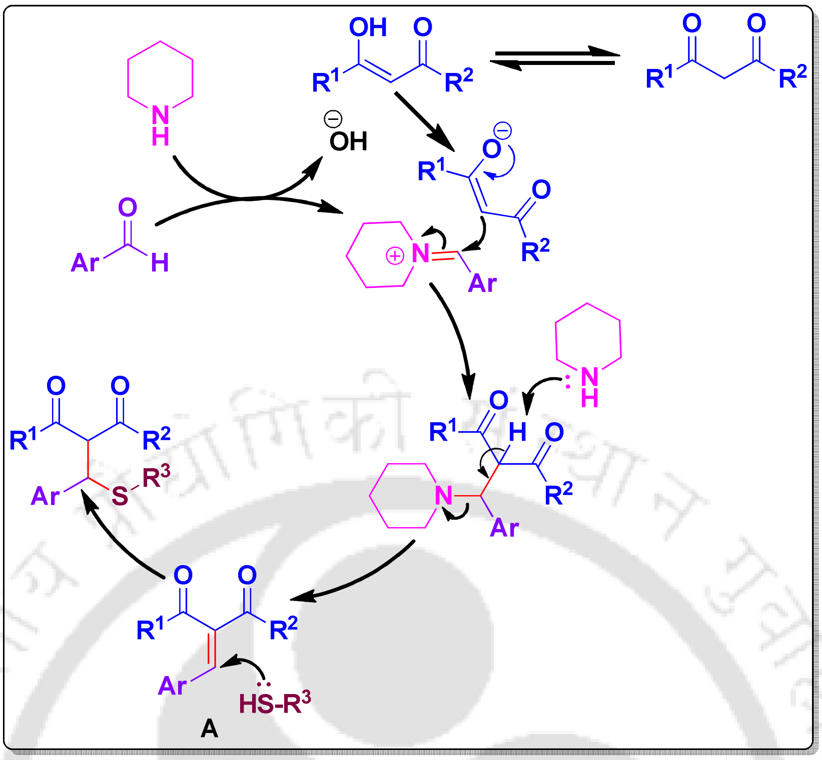
Entry	Diketone	Aldehyde	Thiol	Product	Yield (%)[b]
1	**1c**	**2a**	**3c**	**5cac**	73
2	**1c**	**2a**	**3d**	**5cad**	75

3	**1c**	**2a**	**3e**	**5cae**	77
4	**1c**	**2b**	**3c**	**5cbc**	76
5	**1c**	**2b**	**3e**	**5cbe**	80
6	**1c**	**2c**	**3d**	**5ccd**	76
7	**1c**	**2d**	**3f**	**5cdf**	79
8	**1c**	**2e**	**3g**	**5ceg**	72
9	**1c**	**2f**	**3e**	**5cfe**	55

[a]All the reactions were carried out using **1c** (1 mmol), **2** (1 mmol) and **3** (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

From the above results, the reactions were found to be sensitive to the steric and electronic effects of the R^1 and R^2 groups. Pentane-2,4-dione (**1a**) reacted with benzaldehyde (**2a**) and thiophenol (**3d**) to provide the product **4aad** in 82% yield (Table 2.2, entry 4), while the 1,3-diphenylpropane-1,3-dione (**1b**) and 1-phenyl-1,3-butanedione (**1c**) reacted in similar fashion gave the products **4bad** and **5cad** (68% and 75% yield) respectively (Table 2.2, entry 24 and Table 2.3, entry 2). The aromatic aldehydes bearing electron-donating groups provided better yield along with shorter reaction time as compared to those having electron-withdrawing substituents. It was also observed that the electron donating substituents in thiophenol increased the yield of the products. Furthermore, it was noted that while replacing the pentane-2,4-dione with 1-phenyl-1,3-butanedione or 1,3-diphenylpropane-1,3-dione provided lower yield of the expected product as well as required longer reaction time, these changes were found to be insignificant. This observation can be explained due to the formation of stable Knoevengel intermediate that gives extended conjugation to the system. In addition, when the reaction of unsymmetrical diketone *i.e.* 1-phenyl-1,3-butanedione (**1c**), benzaldehyde (**2a**) or 4-methoxybenzaldehyde (**2b**) and benzylthiol (**3c**), was performed the mixture of two diastereomers were obtained in the ratio of 1:1. The diastereomeric ratio was determined from ^{1}H spectra.

The formation of the product can be explained as follows: Piperidine reacted with the aldehyde (**2**) to form an iminium ion, subsequently attacked by the active methylene group of the 1,3-diketone resulting in the formation Knoevengel intermediate **A**. **A** subsequently undergoes thia-Michael addition reaction with thiol (**3**) to give desired product (Scheme 2.2).



Scheme 2.2. Plausible mechanism for the formation of unsymmetrical sulfide.

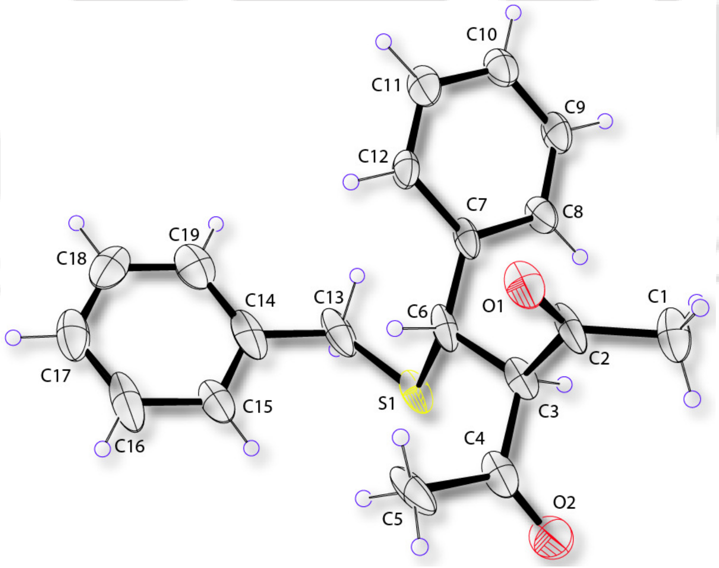


Figure 2.1. X-Ray crystal structure of **4aac**.

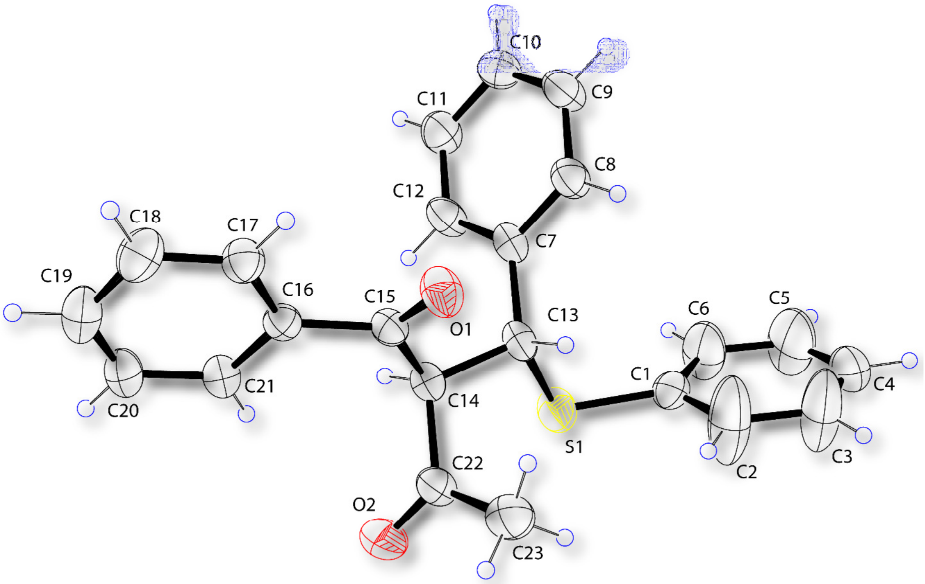


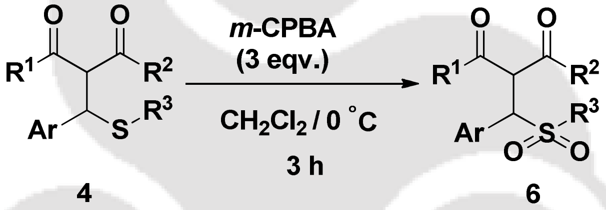
Figure 2.2. X-Ray crystal structure of **5cad**.

All the isolated sulfides were fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, ESI-MS and by elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compounds **4abe, 4ahe, 4bif, 4bce, 5cbc** and **5ceg** are given in the Experimental Section (Figure 2.8, 2.9, 2.10, 2.11, 2.12 and 2.13). The structures of two representative products **4aac** and **5cad**, one each from both the categories, that is symmetrical diketone and unsymmetrical diketone respectively, have been categorically proved by the single-crystal XRD (Figure 2.1 and 2.2).

After the successful synthesis of sulfides, the oxidation of unsymmetrical sulfides to sulfones was carried out using *m*-CPBA as oxidant, because of its outstanding reactivity, availability and ease to handle compared to hydrogen peroxide, peracid and peracetic acids. It was found that a wide variety of dibenzyl, aryl benzyl and alkyl benzyl sulfides were oxidized to their corresponding sulfones in excellent yields in dichloromethane at 0°C to room temperature. The oxidant *m*-chloroperoxybenzoic acid (*m*-CPBA) was used to convert sulfides to sulfones readily under an optimized reaction condition in excellent yields without further purification. All of the reactions occurred with complete selectivity for sulfone formation, no other products such as sulfoxides and Bayer-Villiger products were obtained in the present study. The selectivity of the present method is fairly wide, as other functionalities remained unaffected. Prominent effects of the substituents were not observed in sulfone formation and excellent yields were obtained in all cases (Table 2.4 and Table 2.5).

The product (**6a**) isolated was completely characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra, ESI-MS and by elemental analysis. The signals appear in the ^{1}H NMR spectrum at δ 1.25 (t, J = 7.6 Hz, 3H), 1.85 (s, 3H), 2.42 (s, 3H), 2.64-2.81 (m, 2H), 4.88 (d, J = 11.6 Hz, 1H), 5.16 (d, J = 11.6 Hz, 1H), 7.37 (s, 5H). The signals in the corresponding sulfides at δ 4.26 and 4.50 shows two doublets for (-CH–CH-) protons, got shifted to δ 4.88 and 5.16 clearly indicates the sulfone formation. Similarly, the various peaks obtained in the ^{13}C NMR spectrum are at δ 6.2, 29.0, 30.7, 45.9, 66.8, 66.9, 129.6 (2C), 129.9, 130.2 (2C), 131.1, 199.1, 200.0 and the characteristic peaks in the parent sulfide at δ 48.3 and 74.8 corresponding to (-CH–CH-) carbon atoms, now shifted to δ 66.8 and 66.9 confirming the sulfone formation. Furthermore, the sharp peaks at 1308 and 1134 cm^{-1} corresponding to -SO_2 group in IR spectrum gives clear indication for the formation of sulfone.

Table 2.4. One-pot oxidation of sulfides containing symmetric diketones to sulfones[a]

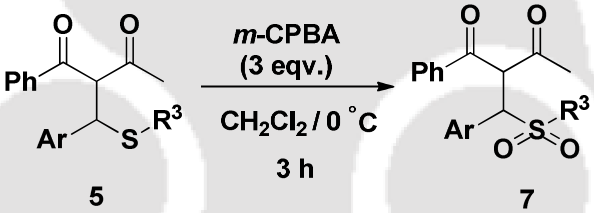


Entry	Substrate	Product	Yield (%)[b]
1	**4aaa**	**6a**	91
2	**4aab**	**6b**	92
3	**4aac**	**6c**	88
4	**4aad**	**6d**	90
5	**4aae**	**6e**	93
6	**4abe**	**6f**	94
7	**4acd**	**6g**	89
8	**4add**	**6h**	95
9	**4aed**	**6i**	87
10	**4afd**	**6j**	90
11	**4age**	**6k**	90
12	**4ahe**	**6l**	86
13	**4aje**	**6m**	88

14	**4ale**	**6n**	88
15	**4alh**	**6o**	88
16	**4aqe**	**6p**	91
17	**4are**	**6q**	89
18	**4aue**	**6r**	87
19	**4bad**	**6s**	85
20	**4bae**	**6t**	88
21	**4baf**	**6u**	83
22	**4bag**	**6v**	85
23	**4bbe**	**6w**	87
24	**4bcd**	**6x**	89
25	**4bce**	**6y**	90

[a]Reaction conditions: substrate (0.5 mmol), *m*-CPBA (3 eqv.), and dichloromethane (3 mL) at 0 °C for 3 h. [b]Isolated yield.

Table 2.5. One-pot oxidation of sulfides containing unsymmetric diketone to sulfones[a]



Entry	Substrate	Product	Yield (%)[b]
1	**5cad**	**7a**	86
2	**5cae**	**7b**	88
3	**5cbe**	**7c**	92
4	**5ccd**	**7d**	87
5	**5cdf**	**7e**	94
6	**5ceg**	**7f**	88
7	**5cfe**	**7g**	87

[a]Reaction conditions: substrate (0.5 mmol), *m*-CPBA (3 eqv.), and dichloromethane (3 mL) at 0 °C for 3 h. [b]Isolated yield.

All these sulfone derivatives were confirmed on the basis of their analytical data (^{1}H NMR, ^{13}C NMR, IR, ESI-MS and by elemental analysis) and physico-chemical data like melting point. The ^{1}H NMR and ^{13}C NMR spectra of compounds **6h, 6t** and **7f** are given in the

Experimental Section (Figure 2.14, 2.15 and 2.16). The structures of compounds **6c** and **7a** were further confirmed by X-ray analysis (Figure 2.3 and 2.4).

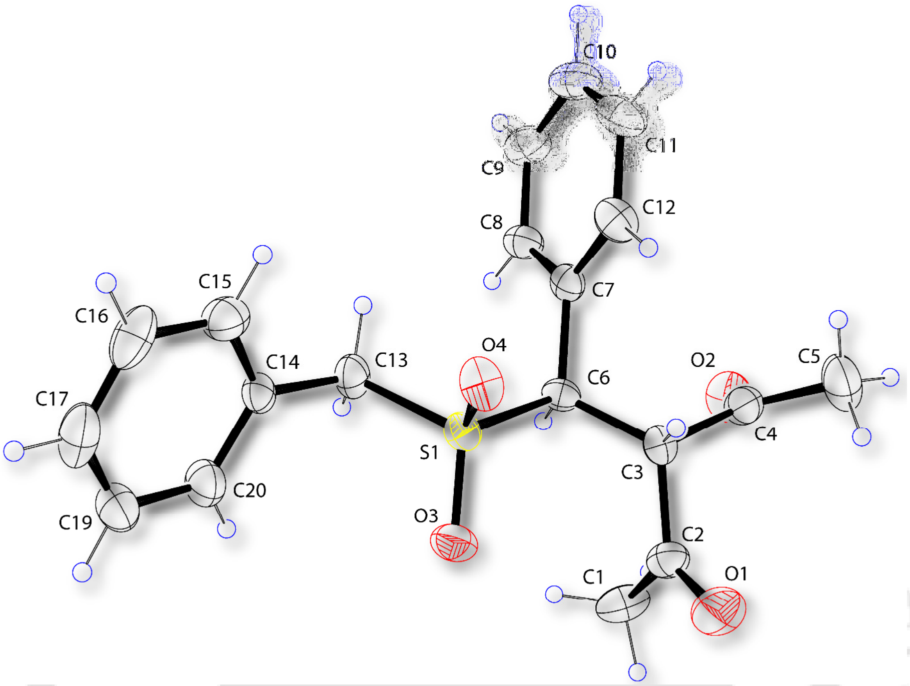


Figure 2.3. X-Ray crystal structure of **6c**.

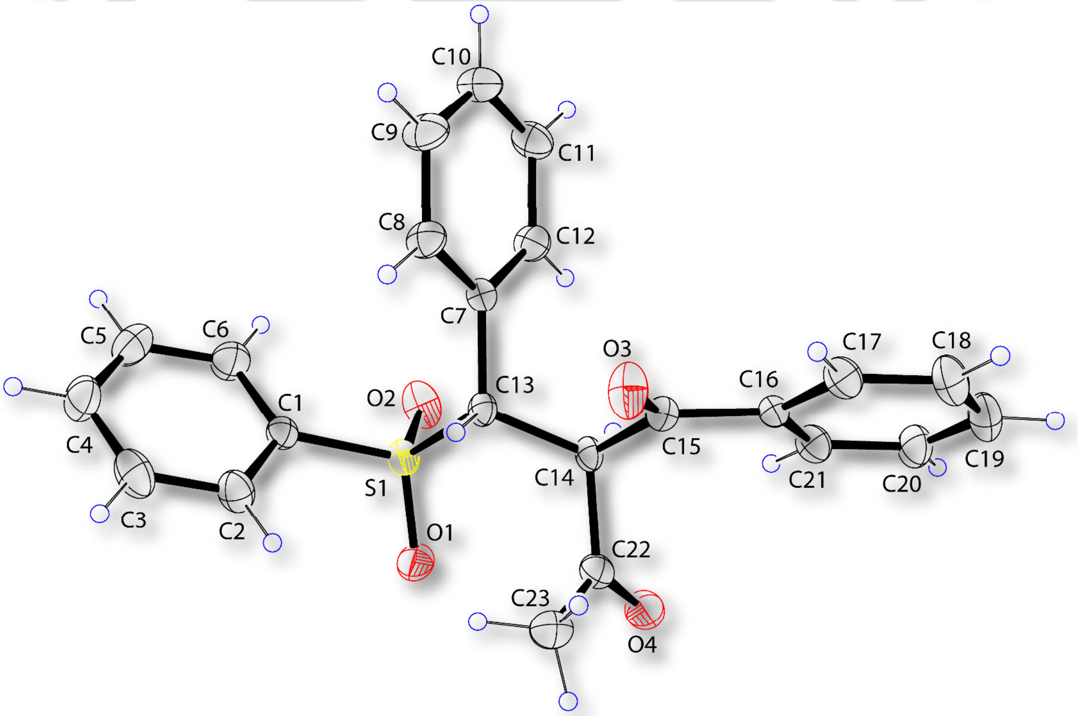
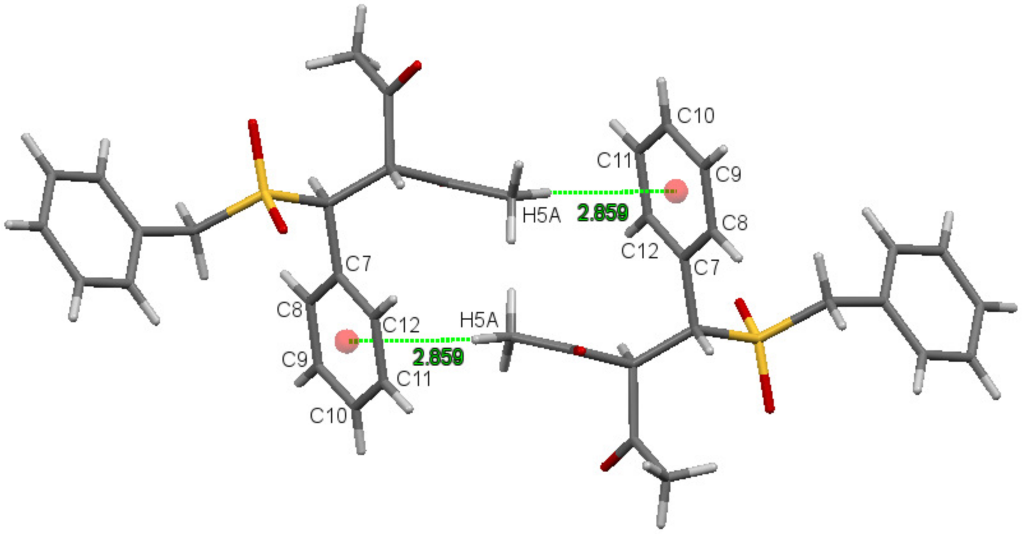
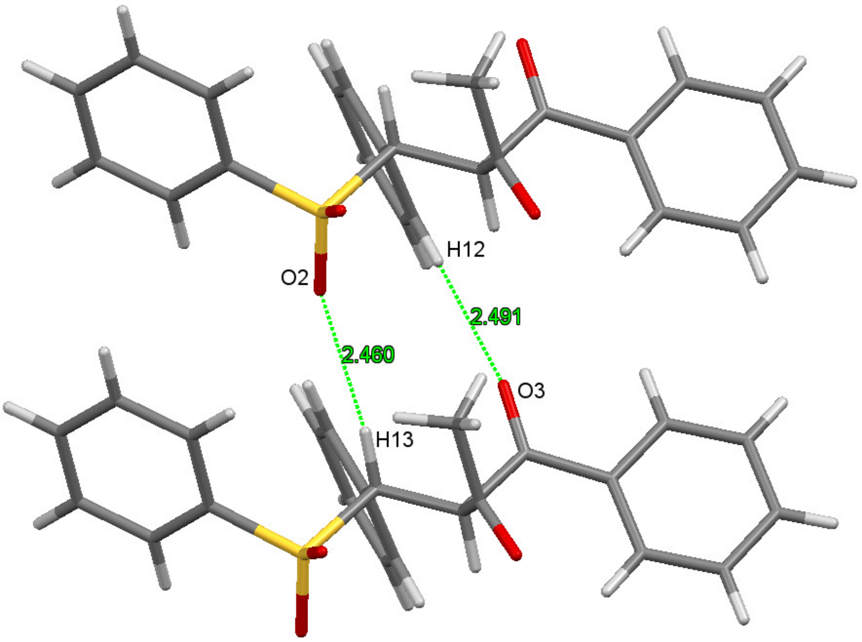


Figure 2.4. X-Ray crystal structure of **7a**.



(**a**) Intermolecular C-H···π interaction in **6c**.



(**b**) Intermolecular O···H interaction in **7a**.

Figure 2.5. (**a**) Intermolecular C-H···π interaction in **6c**. (**b**) Intermolecular O···H interaction in **7a**.

The crystal structure shows that **6c** forms a dimer through non-covalent weak intermolecular C-H···π interactions (C7-C12···H5A = 2.859 Å). Similarly, the crystal structure **7a** also forms a dimer through non-covalent weak intermolecular oxygen-hydrogen interactions (O2···H13 = 2.460 Å, ∠O2···H13-C13 = 167.79° and O3···H12 = 2.491 Å, ∠C15-O3···H12 = 168.15°) (Figure 2.5). In the last few years, these non-covalent interactions involving aromatic rings such as C–H···π, C–H···O–H and C–H···O–S interactions have attracted a great deal of interest among the family of pharmaceutical, optical, functional materials and in biological systems.[8]

We have evaluated the antileishmanial activity of sixteen sulfone derivatives against promastigotes of *L. donovani* and found that most of them displayed significant antileshmanial activity with low cytotoxicity in mammalian cells. Evaluation of *in vitro* antileishmanial activity (Table 2.6) are represented by IC_{50} and IC_{90} values of compounds against promastigotes of *L. donovani*. The cytotoxicity of all compounds were evaluated against murine macrophages. Statistical analysis showed that all these sixteen compounds have no significant difference amongst them in exhibiting activity against the promastigotes of *L. donovani*. This means that all these sulfones possess potent to moderate antileishmanial activities. However, the results showed that out of these, seven compounds namely **7f**, **7a**, **6c**, **6s**, **6d**, **6o** and **6n** displayed toxicity towards the mammalian macrophage cells with IC_{50} values of 7.335±2.652 µg/ml, 8.47±1.499 µg/ml, 8.655±2.708 µg/ml, 8.73±3.168 µg/ml, 10.13±2.949 µg/ml, 11.17±2.249 µg/ml and 11.73±2.157 µg/ml respectively. The IC_{50} values against macrophages were found close to IC_{90} values against promastigotes. Therefore, the efficacy of these compounds is limited due to their toxicity. The compounds **7e**, **6h**, **7b**, **6e**, **6f** and **7c** with IC_{50} values of 4.105±0.7142 µg/ml, 4.325±0.7283 µg/ml, 4.455±0.5445 µg/ml, 4.55±0.8202 µg/ml, 5.59±1.329 µg/ml and 6.435±0.859 µg/ml respectively, could be potent antileishmanial candidates as their toxic effect towards macrophage is negligible at the doses used against the parasite. The compounds **6w**, **6u** and **6v** were found to be most effective against promastigotes with IC_{50} values of 3.645±0.2475 µg/ml, 3.655±0.2051 µg/ml and 3.67±0.1131 µg/ml respectively.

The percent cell viability of *L. donovani* and peritoneal macrophages with increase in concentration from 0.00 to 10.0 mg/mL were also evaluated (Figure 2.6).

Table 2.6. Leishmanicidal activity of compounds against *L. donovani* promastigotes.

	Activity	**Cytotoxicity**
	L. donovani promastigotes	**Macrophages**

Compounds	**$(IC_{50}\mu g/ml\pm SD)^a$**	**$(IC_{90}\mu g/ml\pm SD)^a$**	**$(IC_{50}\mu g/ml\pm SD)^a$**
6c	4.085±0.7283	7.355±1.308	8.655±2.708
6d	4.485±0.9546	8.075±1.718	10.13±2.949
6e	4.55±0.8202	8.395±1.761	16.75±2.56
6f	5.59±1.329	10.08±2.397	19.24±1.648
6h	4.325±0.7283	7.785±1.308	15.02±2.574
6n	3.99±0.297	7.185±0.5303	11.73±2.157
6o	4.095±0.3323	7.365±0.601	11.17±2.249
6s	4.985±1.69	8.975±2.033	8.73±3.168
6u	3.655±0.2051	6.58±0.3677	15.08±1.188
6v	3.67±0.1131	6.61±0.198	22.79±3.663
6w	3.645±0.2475	6.57±0.4525	22.15±4.943
7a	3.855±0.3041	6.94±0.5515	8.47±1.499
7b	4.455±0.5445	8.02±0.9758	17.25±1.435
7c	6.435±0.859	11.59±1.046	23.04±5.317
7e	4.105±0.7142	7.39±1.287	14.78±1.478
7f	4.045±0.5445	7.29±0.9758	7.335±2.652

[a]Mean of two independent determinations

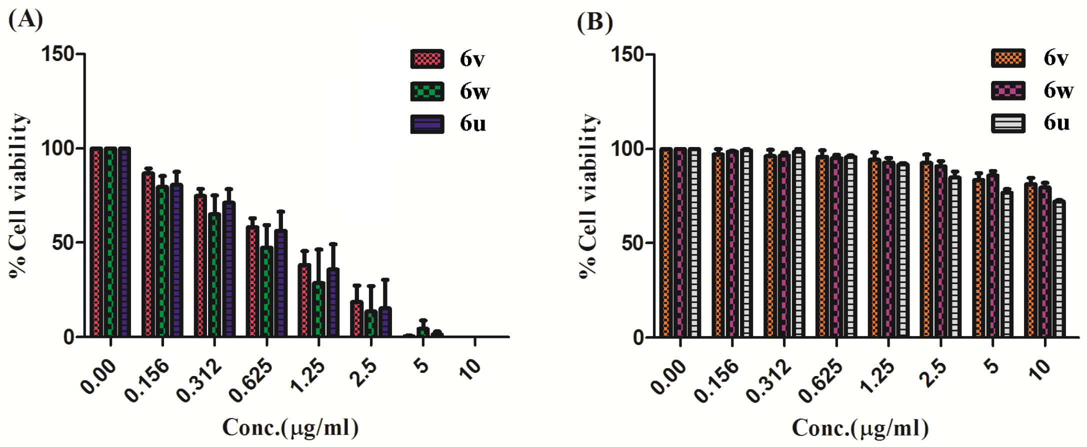
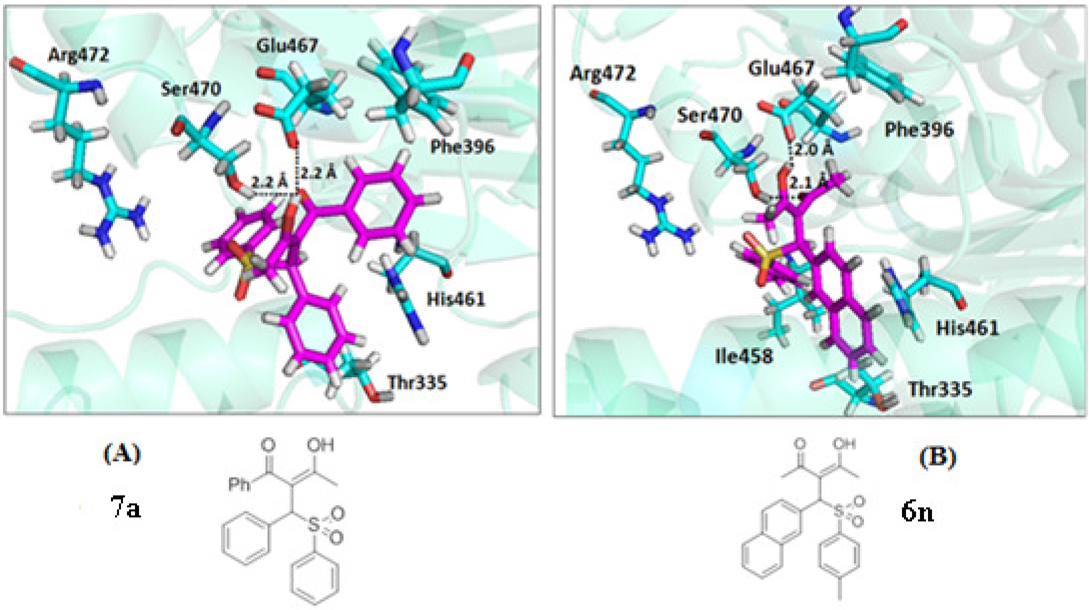


Figure 2.6. Leishmanicidal effect of **6v**, **6w** and **6u** on promastigotes of *L. donovani* and toxic effect on murine peritoneal macrophages. (A) *L. donovani* promastigotes were treated for 24 h with increasing concentrations of three different compounds **6v**, **6w** and **6u** and then cell viability was assessed using alarm blue reagent (as described in material and methods). (B) Similarly, peritoneal macrophages were treated for 24 h with increasing concentrations of these three compounds **6v**, **6w** and **6u** and cell viability was assessed.

Structure–activity relationship (SAR) studies were carried out to identify the structural features in terms of chemical modifications. We found that in all the structures, the dicarbonyl group in its enol form, an interacting moiety, was found necessary for their activity. Moreover, the hydrophobic moiety involved in π-cation interaction significantly contributed to maximize the activity. Although, all these sixteen compounds showed no significant difference amongst them in exhibiting activity against the promastigotes of *L. donovani*, however, SAR studies revealed that the introduction of phenyl rings close to the dicarbonyl group and electron donating groups in the phenyl rings in close proximity to sulfone functionality enhanced the activity of **6w**, **6u** and **6v** when used at low to moderate doses. These compounds or derivatives also exhibited low or negligible cytotoxicity towards normal murine macrophage cells. Furthermore, sulfone derivatives containing electron donating (**7e**, **6h**, **7b**, **6e**, **6f** and **7c**) substituents in the *meta* and/or *para* position in the phenyl moiety displayed promising antileishmanial activity owing to their negligible toxic effect towards macrophages at the doses used against the parasite. In a sharp contrast, the introduction of either electron withdrawing substituents (**7f**) or unsubstituted sulfone derivatives (**7a**, **6c**, **6s**, **6d**, **6o** and **6n**) increased the toxicity towards the mammalian macrophage cells with IC_{50} values close to IC_{90} values against promastigotes.

Trypanothione reductase (TryR) is a key drug target enzyme involved in the redox metabolism of the parasite and inhibition of TryR may disrupt the redox balance of the parasite leading to parasite death. The sulfone derivatives have been designed, which can bind the active site of TryR leading to its inhibition. In order to understand the binding interactions of these sulfones against trypanothione reductase, we have performed the molecular docking study of all the sixteen compounds on *L. infantum* trypanothione.[9] There is no crystal structure available for trypanothione reductase of *L. donovani* and thus we started our molecular docking studies with trypanothione reductase from *Leishmania infantum* as there is 98% sequence similarity between the trypanothione reductase of *L. donovani* and *L. infantum*. The molecular docking study was carried out using X-ray crystal structures of trypanothione reductase from *Leishmania infantum* (PDB code: 2jk6, 2.95 Å).[10] The crystal structure is co-crystallized with cofactor FAD. The enzyme (TryR) is a dimer consisting of two active sites. Active sites are buried at the interface of chains A and B.

The molecular docking study suggested that the sulfone derivatives bind to the trypanothione reductase binding pocket with hydrogen bonds and hydrophobic contacts with the A-chain and B-chain. The molecular docking of sulfone derivatives showed that the most of the interactions are close to Glu 466, Glu 467, Ser 470, Arg 472 indicating that the binding is preferentially happening in γ–Glutamate and new interacting sites. These residues were found around the active site Cys-52 and Cys-57. Interestingly, some of these derivatives show hydrophobic interaction with His 461 which is a part of catalytic triad (Cys-52- His 461-Cys-57). In all the cases, the 1,3-dicarbonyl group in its enol form is interacting with Glu 467, Ser 470. The phenyl/napthyl moiety involved in π-cation interaction with amino acids that includes mainly Arg 472, His 461. All the sixteen compounds were docked into the active site of TryR. A maximum of 10 docking poses per ligand were generated in each case and analyzed further for the binding mode and intermolecular interactions. The two representative examples revealing the mode of interactions are shown in Figure 2.7.



(A)

7a

(B)

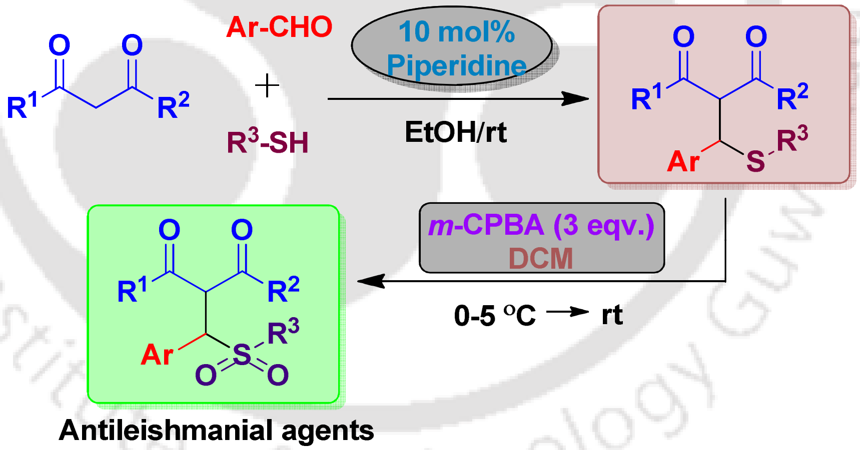
6n

Figure 2.7. Binding modes of ligands at the interface of homodimer. Ligands are shown in stick models (magenta colour). Hydrogen bonding interactions are shown as black dashes and residues involved in hydrogen bonding or hydrophobic interactions (π–π, π–cation) are represented in stick models. (A) Represent the binding mode of **7a** and (B) Represent the binding mode of **6n**.

In conclusion, we have developed an efficient and general method for synthesis of unsymmetrical sulfides, which in turn were transformed into alkyl-benzyl and benzyl-aryl sulfones with various functional groups that can also be extended to the preparation of vinyl sulfones. In synthetic organic chemistry, importance of the sulfone functional group provides significant interest in the development of new methodologies related to the introduction of the sulfone functionality into an organic molecule as well as the further synthetic transformation of the sulfone intermediate, and its eventual elimination from the target when needed. Also based on the evaluation of the biological activity as well as docking analysis at the active site of trypanothione reductase (TryR) enzyme, against visceral leishmaniasis, it may be concluded from the present study, that most of these newly synthesized sulfone derivatives have promising antileishmanial activity and further study on lead optimization through *in vitro* and *in vivo* model of visceral leishmaniasis could allow development of new anitleishmanial drug.

Chapter 2

Synthesis of unsymmetrical sulfides and their oxidation to sulfones to discover potent antileishmanial agents



2.2 Experimental Section

Cell Culture and Parasite. *L. donovani* strain AG83 (MHOM/IN/1983/AG83), originally isolated from an Indian kala-azar patient was maintained by serial passage in hamsters. *L. donovani* amastigotes periodically recovered from the spleens of infected hamsters were transformed into promastigotes through amastigote culture in M199 supplemented with 10% FCS, 2 mM glutamine, penicillin G (100 U/ml), streptomycin sulfate (100 µg/ml) at 22°C. Promastigotes were used at the log phase of growth, approximately 2 to 3 days after subculture. Parasites were kept in culture by weekly passaging.

In vitro antipromastigote activity. Antiparasitic activities of compounds against *L. donovani* (AG83) promastigotes were determined using alamarBlue cytotoxicity assays (Thermofisher). Resazurin (7-Hydroxy-3H-phenoxazin-3-one 10-oxide) is the active ingredient of AlamarBlue reagent and is a non-toxic, non-fluorescent and cell permeable compound that is blue in color. Healthy living mamalian cells maintain a reducing environment within their cytosol. Upon entering cells, the “reducing potential” reduces resazurin to resorufin, which is red in colour and highly fluorescent. Viable cells continuously convert resazurin to resorufin, increasing the overall fluorescence and colour of the culture media.

Assays were performed in sterile 96-well plates using 100 µl of log-phase promastigotes adjusted to 2x10^6 cells/ml. BALB/c mice (8-10 week old) were used for this experiment. Resident peritoneal macrophages were obtained by injecting 5-10 ml RPMI medium supplemented with 10% FCS into the peritoneal cavity of BALB/c mice. The pulled medium containing the peritoneal exudates cells were plated (1x10^5 cells /well) in a 96 well culture plate. Non-adherent cells were washed off after 20 h culture. These cells were incubated in control and in presence of 0.1562 µg/ml, 0.3125 µg/ml, 0.625 µg/ml, 1.25 µg/ml, 2.50 µg/ml, 5.0 µg/ml and 10.0 µg/ml compounds and DMSO for 24 h. Next 10 µl of the resazurin dye (0.01%) were added, and plates were further incubated for 4 h at 37 °C. After incubation, cells were analyzed in a microplate reader (SpectraMax spectrofluorometer, Molecular Devices) at a wavelength of 570 nm, using 600 nm as a reference wavelength (normalized to the 600 nm value). Absorbance in the absence of any inhibitor or solvent was set as the control. Cell viability was evaluated based on a comparison between the untreated control cells, solvent and at inhibitory concentrations of inhibitors necessary to reduce the growth of promastigotes by 50% (IC_{50} values) and 90% (IC_{90} values).

Statistical analysis. Data are expressed as the arithmetic mean±standard deviation values. IC_{50} and IC_{90} values of all sixteen compounds for both promastigotes and macrophages were calculated using dose–response curves in Origin 5.0 software (Microcal Software, Inc., Northampton, MA, USA). These values were compared by 1way ANOVA employing Turkeys multiple comparision test. The p values for all comparisons were determined and $p < 0.05$ was taken as significant difference.

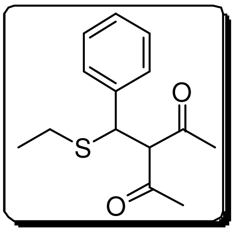
Molecular Docking Study. For the purpose of molecular docking studies, X-ray crystal structure of *L. Infantum* trypanothione redictase was selected (PDB ID: 2jk6, resolution: 2.95 Å). The crystal structure is in dimeric form and it is co-crystalized with cofactor FAD. Both the chains were considered for molecular docking studies because the binding site of trypanothione reductase is at the interface of the chain A and chain B. Protein preparation was done using Maestro. Hydrogen atoms were added during protein preparation wizard. Receptor Grid Generation Panel within Glide suite was used to set up receptor grid for the prepared structures. The grid was defined by 16 Å by considering the amino acids of all the subpockets. Then, this step is followed by restrained minimization using the OPLS 2005 force field to RMSD of 0.3 Å. Three-dimensional structures of these compounds were then prepared using LigPrep module of maestro implementing OPLS_2005 force field and ionic states for the ligands at pH values of 7.0 ± 2.0 were generated. Docking was performed using Glide 5.8 (Grid-based Ligand Docking with Energetics), with the standard precision (SP) mode to estimate protein–ligand binding affinities and static intermolecular interactions.

General procedure for synthesis of compounds (4 and 5). To a stirred solution of 1,3-diketone (1 mmol) in 3 mL of ethanol were added piperidine (0.1 mmol) and aldehyde (1 mmol) successively and the reaction mixture was kept for stirring for 5-10 min at room temperature. Then, thiol (1.2 mmol) was added either directly if it is a solid or drop-wise through a syringe into the reaction mixture. The solid products namely **4aad** to **4aae**, **4abe** to **4alh**, **4are**, **4aue**, **4bad** to **4akg** and **5cad** to **5cae**, **5cbe** to **5cfe** were precipitated out during the reaction after appropriate reaction time. Finally, the products were filtered off through a Büchner funnel and dried. The pure product was obtained after recrystallization from methanol. The following work up procedure was followed for the products such as **4aaa** to **4aac**, **4abc**, **4ape**, **4aqe**, **4ase**, **4ate**, **4bac**, **5cac** and **5cbc** because the solid precipitate did not come out during the reaction time. After completion of reaction as checked by TLC, ethanol was removed in a rotary evaporator and the crude residue was extracted with dichloromethane (2 × 15 mL). The organic layer was washed with water, brine solution (2 x 5 mL) and dried over anhydrous Na_2SO_4. Then, it was concentrated in a rotary evaporator and the crude residue was passed through a silica gel (60-120 mesh) column to get the desired pure product.

General procedure for synthesis of compounds (6 and 7). *m*-Chloroperoxybenzoic acid (*m*-CPBA, 1.5 mmol) was added in portion for a period of 15 min to a stirred solution of corresponding unsymmetrical sulfide (0.5 mmol) in 3 mL of dichloromethane at ice-bath temperature and stirring was continued for 45 min at the same temperature. Then, the reaction mixture was brought to room temperature slowly and it was stirred for another 2 h. After completion of reaction, it was extracted with by adding 18 mL of dichloromethane, which was washed with 5% aqueous $NaHCO_3$ solution (10 mL) and brine solution (10 mL). Finally, the organic layer was dried over anhydrous Na_2SO_4 and it was concentrated in a rotary evaporator. The desired sulfone was obtained after recrystallization from methanol.

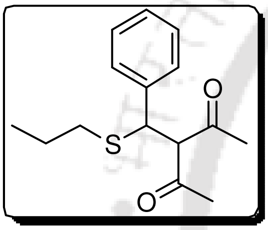
Spectral data of Compounds:

3-((ethylthio)(phenyl)methyl)pentane-2,4-dione (4aaa):



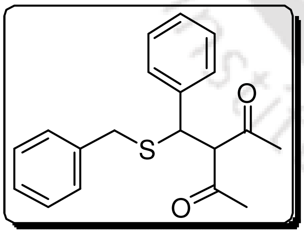
Nature: White solid; mp 73-75 °C; **IR** (KBr): 3396, 3054, 2975, 2956, 1692, 1496, 1454, 1421, 1357, 1270, 1185, 1150, 1099, 717, 700 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 1.14 (t, *J* = 7.6 Hz, 3H), 1.88 (s, 3H), 2.27-2.35 (m, 2H), 2.37 (s, 3H), 4.26 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 7.24-7.31 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 25.3, 29.5, 30.1, 48.3, 74.8, 128.0, 128.3 (2C), 128.9 (2C), 139.5, 201.6 (2C). **ESI-MS** m/z: calcd for $C_{14}H_{18}O_2SNa$: 273.09. Found: 273.15 [M + Na]$^+$. **Anal. Calcd** for $C_{14}H_{18}O_2S$ (250.36): C, 67.16; H, 7.25. Found: C, 67.03; H, 7.16.

3-(phenyl(propylthio)methyl)pentane-2,4-dione (4aab):



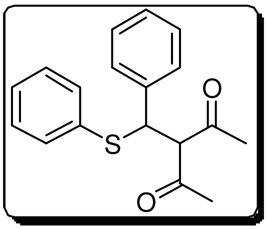
Nature: White solid; mp 70-72 °C; **IR** (KBr): 3390, 2961, 2929, 2868, 1730, 1700, 1494, 1455, 1412, 1355, 1261, 1141, 1099, 955, 885, 781, 724, 707 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.6 Hz, 3H), 1.44-1.53 (m, 2H), 1.87 (s, 3H), 2.19-2.31 (m, 2H), 2.37 (s, 3H), 4.25 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 7.24-7.31 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.4, 22.3, 29.3, 30.0, 33.1, 48.3, 74.5, 127.8, 128.2 (2C), 128.7 (2C), 139.4, 201.2, 201.3. **ESI-MS** m/z: calcd for $C_{15}H_{20}O_2SNa$: 287.12. Found: 287.18 [M + Na]$^+$. **Anal. Calcd** for $C_{15}H_{20}O_2S$ (264.38): C, 68.14; H, 7.62. Found: C, 68.04; H, 7.53.

3-((benzylthio)(phenyl)methyl)pentane-2,4-dione (4aac):



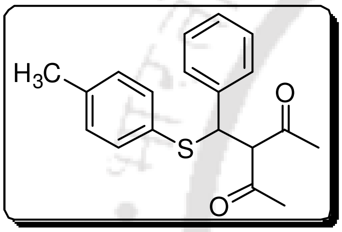
Nature: White solid, mp 71-73 °C; **IR** (KBr): 3399, 3022, 2932, 2903, 1718, 1692, 1597, 1490, 1447, 1419, 1357, 1278, 1244, 1187, 1145, 1069, 1025, 854, 722 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.13 (s, 3H), 3.37 (d, *J* = 13.6 Hz, 1H), 3.53 (d, *J* = 13.6 Hz, 1H), 4.20 (d, *J* = 12.0 Hz, 1H), 4.29 (d, *J* = 12.4 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.26-7.34 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.2, 30.3, 35.3, 47.7, 74.6, 127.3, 127.9, 128.5 (2C), 128.6 (2C), 128.8 (2C), 129.1 (2C), 137.3, 138.9, 201.3 (2C). **ESI-MS** m/z: calcd for $C_{19}H_{20}O_2SNa$: 335.12. Found: 335.22 [M + Na]$^+$. **Anal. Calcd** for $C_{19}H_{20}O_2S$ (312.43): C, 73.04; H, 6.45. Found: C, 72.93; H, 6.37.

3-(phenyl(phenylthio)methyl)pentane-2,4-dione (4aad):



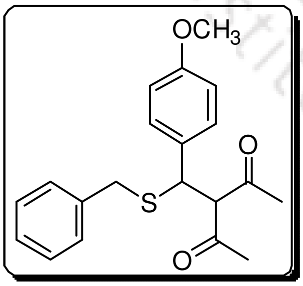
Nature: White solid; mp 107-109 °C; **IR** (KBr): 3397, 3056, 3027, 3006, 1954, 1718, 1693, 1583, 1496, 1473, 1457, 1440, 1419, 1358, 1271, 1243, 1187, 1148, 1068, 1024, 970, 777, 750 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.87 (s, 3H), 2.40 (s, 3H), 4.39 (d, *J* = 12.4 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.14-7.23 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.6, 29.7, 52.9, 74.2, 127.9, 128.2 (2C), 128.6, 128.7 (2C), 129.0 (2C), 132.4, 134.4 (2C), 139.1, 201.4, 201.5. **ESI-MS** m/z: calcd for $C_{18}H_{18}O_2SNa$: 321.09. Found: 321.17 $[M + Na]^+$. **Anal. Calcd** for $C_{18}H_{18}O_2S$ (298.40): C, 72.45; H, 6.08. Found: C, 72.34; H, 5.99.

3-(phenyl(p-tolylthio)methyl)pentane-2,4-dione (4aae):



Nature: White solid; mp 136-137 °C; **IR** (KBr): 3401, 3064, 3031, 2920, 1718, 1694, 1491, 1456, 1419, 1357, 1269, 1180, 1145, 1018, 971, 809, 777, 712, 698 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.85 (s, 3H), 2.27 (s, 3H), 2.38 (s, 3H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 6.98 (t, *J* = 8.4 Hz, 3H), 7.03 (d, *J* = 7.2 Hz, 3H), 7.17 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 29.6, 29.7, 53.1, 74.2, 127.8, 128.2 (2C), 128.6, 128.7 (2C), 129.8 (2C), 134.8 (2C), 138.9, 139.3, 201.5, 201.6. **ESI-MS** m/z: calcd for $C_{19}H_{20}O_2SNa$: 335.11. Found: 335.19 $[M + Na]^+$. **Anal. Calcd** for $C_{19}H_{20}O_2S$ (312.43): C, 73.04; H, 6.45. Found: C, 72.92; H, 6.36.

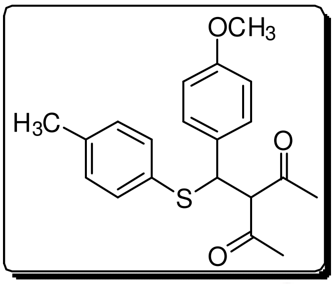
3-((benzylthio)(4-methoxyphenyl)methyl)pentane-2,4-dione (4abc):



Nature: White solid; mp 80-82 °C; **IR** (KBr): 3398, 3067, 3025, 3003, 2954, 2931, 2833, 2359, 2334, 1954, 1904, 1692, 1610, 1584, 1514, 1494, 1454, 1417, 1353, 1318, 1265, 1232, 1177, 1149, 1117, 1068, 1027, 969, 837, 824, 710, 537 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.13 (s, 3H), 3.35 (d, *J* = 13.6 Hz, 1H), 3.51 (d, *J* = 13.6 Hz, 1H), 3.80 (s, 3H), 4.14 (d, *J* = 12.4 Hz, 1H), 4.25 (d, *J* = 12.0 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.17-7.25 (m, 5H), 7.30 (t, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.2, 30.3, 35.2, 47.2, 55.2, 74.7, 114.1 (2C), 127.2, 128.5 (2C), 129.0 (2C), 129.6 (2C), 130.6, 137.4, 159.1, 201.5 (2C). **ESI-MS** m/z: calcd for

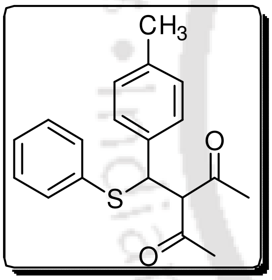
$C_{20}H_{22}O_3SNa$: 365.12. Found: 365.21 $[M + Na]^+$. **Anal. Calcd** for $C_{20}H_{22}O_3S$ (342.45): C, 70.15; H, 6.48. Found: C, 69.99; H, 6.32.

3-((4-methoxyphenyl)(p-tolylthio)methyl)pentane-2,4-dione (4abe):



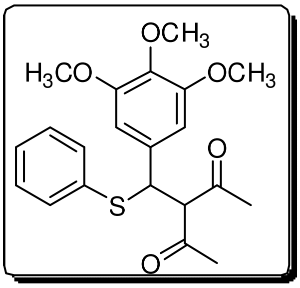
Nature: White solid; mp 130-131 °C; **IR** (KBr): 3390, 3019, 2952, 2837, 1730, 1698, 1611, 1517, 1490, 1447, 1415, 1362, 1303, 1278, 1258, 1204, 1177, 1140, 1110, 1031, 952, 885, 823, 809 cm^{-1}. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.87 (s, 3H), 2.29 (s, 3H), 2.38 (s, 3H), 3.75 (s, 3H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.97-7.04 (m, 6H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.1, 29.4, 29.5, 52.4, 55.1, 74.2, 113.8 (2C), 128.6, 129.2 (2C), 129.6 (2C), 131.0, 134.5 (2C), 138.5, 158.9, 201.3, 201.4. **ESI-MS** m/z: calcd for $C_{20}H_{22}O_3SNa$: 365.12. Found: 365.21 $[M + Na]^+$. **Anal. Calcd** for $C_{20}H_{22}O_3S$ (342.45): C, 70.15; H, 6.48. Found: C, 70.02; H, 6.39.

3-((phenylthio)(p-tolyl)methyl)pentane-2,4-dione (4acd):



Nature: White solid; mp 137-138 °C; **IR** (KBr): 3397, 3028, 2920, 1715, 1694, 1515, 1473, 1441, 1421, 1357, 1274, 1187, 1148, 1068, 1024, 972, 823, 748 cm^{-1}. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.86 (s, 3H), 2.26 (s, 3H), 2.38 (s, 3H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.75 (d, *J* = 12.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 7.15-7.25 (m, 5H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.1, 29.5, 29.6, 52.6, 74.2, 127.9 (2C), 128.3, 128.9 (2C), 129.3 (2C), 132.6, 134.1 (2C), 136.0, 137.5, 201.3, 201.4. **ESI-MS** m/z: calcd for $C_{19}H_{20}O_2SNa$: 335.11. Found: 335.19 $[M + Na]^+$. **Anal. Calcd** for $C_{19}H_{20}O_2S$ (312.43): C, 73.04; H, 6.45. Found: C, 72.89; H, 6.35.

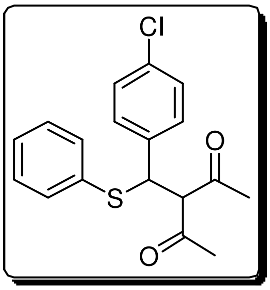
3-((phenylthio)(3,4,5-trimethoxyphenyl)methyl)pentane-2,4-dione (4add):



Nature: White solid; mp 138-140 °C; **IR (KBr):** 3395, 3008, 2962, 2834, 1693, 1590, 1513, 1462, 1425, 1360, 1328, 1278, 1248, 1234, 1183, 1136, 1007, 831, 748 cm^{-1}. ^{1}**H NMR (400 MHz, $CDCl_3$):** δ 1.92 (s, 3H), 2.40 (s, 3H), 3.69 (s, 6H), 3.79 (s, 3H), 4.37 (d, *J* = 12.4 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 6.19 (s, 2H), 7.19-7.26 (m, 5H); ^{13}**C NMR (100 MHz, $CDCl_3$):** δ 29.4, 29.7, 53.0, 56.0, 56.2, 60.9, 73.9, 105.0 (2C), 128.7, 128.9 (2C), 129.1, 132.0, 134.3, 135.0 (2C), 153.0 (2C), 201.2

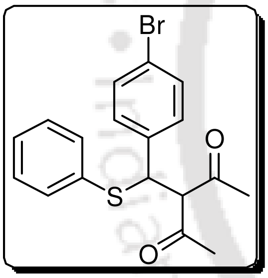
(2C). **ESI-MS m/z:** calcd for $C_{21}H_{24}O_5SNa$: 411.12. Found: 411.12 $[M + Na]^+$. **Anal. Calcd** for $C_{21}H_{24}O_5S$ (388.48): C, 64.93; H, 6.23. Found: C, 64.80; H, 6.14.

3-((4-chlorophenyl)(phenylthio)methyl)pentane-2,4-dione (4aed):



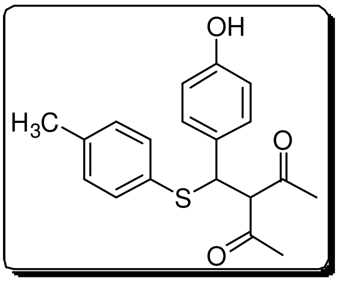
Nature: White solid; mp 109-110 °C; **IR** (KBr): 3446, 3061, 2914, 1730, 1699, 1491, 1475, 1438, 1415, 1358, 1271, 1243, 1159, 1139, 1107, 1089, 1025, 1014, 953, 883, 829, 749 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.40 (s, 3H), 4.32 (d, J = 12.0 Hz, 1H), 4.73 (d, J = 12.4 Hz, 1H), 6.94 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.21 (t, J = 8.0 Hz, 2H), 7.25 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.5, 29.8, 52.1, 73.9, 128.8 (2C), 129.1 (2C), 129.4 (2C), 129.7, 131.7, 131.8, 134.4 (2C), 137.8, 200.8, 201.0. **ESI-MS** m/z: calcd for $C_{18}H_{17}ClO_2SNa$: 355.05. Found: 355.19 $[M + Na]^+$. **Anal. Calcd** for $C_{18}H_{17}ClO_2S$ (332.84): C, 64.95; H, 5.15. Found: C, 64.83; H, 5.07.

3-((4-bromophenyl)(phenylthio)methyl)pentane-2,4-dione (4afd):



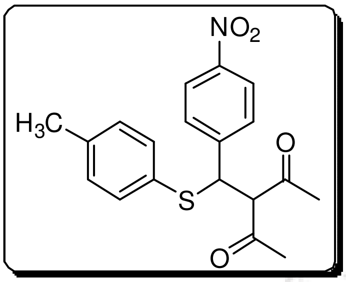
Nature: White solid; mp 117-119 °C; **IR** (KBr): 3386, 3061, 3003, 2956, 2909, 1730, 1698, 1579, 1489, 1474, 1438, 1415, 1357, 1270, 1202, 1158, 1139, 1075, 1024, 1011, 883, 827, 749, 736, 690 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.90 (s, 3H), 2.41 (s, 3H), 4.33 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 7.14-7.25 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.4, 29.7, 52.0, 73.7, 121.5, 128.6, 128.9 (2C), 129.6 (2C), 131.5 (2C), 131.7, 134.2 (2C), 138.2, 200.5, 200.7. **ESI-MS** m/z: calcd for $C_{18}H_{17}BrO_2SNa$: 401.00. Found: 401.17 $[M + Na]^+$. **Anal. Calcd** for $C_{18}H_{17}BrO_2S$ (377.29): C, 57.30; H, 4.54. Found: C, 57.17; H, 4.46.

3-((4-hydroxyphenyl)(p-tolylthio)methyl)pentane-2,4-dione (4age):



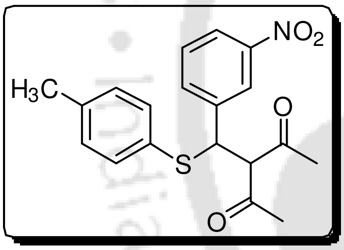
Nature: White solid; mp 149-151 °C; **IR** (KBr): 3347, 3017, 2915, 1718, 1688, 1614, 1593, 1515, 1492, 1445, 1358, 1258, 1215, 1175, 1141, 1106, 1019, 893, 831, 809 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.89 (s, 3H), 2.29 (s, 3H), 2.40 (s, 3H), 4.33 (d, J = 12.0 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 5.68 (s, 1H, OH), 6.62 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.99-7.05 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4, 29.7, 29.9, 52.7, 74.5, 115.6 (2C), 128.6, 129.5 (2C), 129.8 (2C), 130.9, 134.9 (2C), 138.9, 155.5, 202.1, 202.8. **Anal. Calcd** for $C_{19}H_{20}O_3S$ (328.43): C, 69.48; H, 6.14. Found: C, 69.36; H, 6.08.

3-((4-nitrophenyl)(p-tolylthio)methyl)pentane-2,4-dione (4ahe):



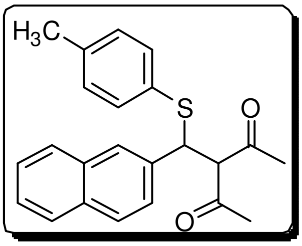
Nature: White solid; mp 149-151 °C; **IR** (KBr): 3395, 3114, 3085, 2923, 2952, 1913, 1718, 1692, 1598, 1513, 1490, 1417, 1350, 1267, 1183, 1145, 1172, 1111, 1015, 970, 851, 813, 717 cm^{-1}. **^{1}H NMR** (400 MHZ, $CDCl_3$): δ 1.94 (s, 3H), 2.30 (s, 3H), 2.44 (s, 3H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 7.01 (s, 4H), 7.19 (d, *J* = 8.0 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 29.5, 29.8, 52.2, 73.5, 123.8 (2C), 127.4, 129.0 (2C), 130.1 (2C), 134.9 (2C), 139.7, 147.0, 147.2, 200.4, 200.5. **ESI-MS** m/z: calcd for $C_{19}H_{19}NO_4SNa$: 380.09. Found: 380.19 $[M + Na]^+$. **Anal. Calcd** for $C_{19}H_{19}NO_4S$ (357.42): C, 63.85; H, 5.36; N, 3.92. Found: C, 63.69; H, 5.26; N, 3.80.

3-((3-nitrophenyl)(p-tolylthio)methyl)pentane-2,4-dione (4aje):



Nature: White solid; mp 132-134 °C; **IR** (KBr): 3396, 3068, 2919, 2867, 1721, 1701, 1529, 1491, 1414, 1349, 1252, 1213, 1182, 1141, 1105, 1077, 1017, 897, 809, 724 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.97 (s, 3H), 2.29 (s, 3H), 2.45 (s, 3H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.81 (d, *J* = 12.4 Hz, 1H), 7.01 (s, 4H), 7.35-7.41 (m, 2H), 7.88 (s, 1H), 8.03-8.06 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 29.5, 29.9, 52.0, 73.4, 122.6, 122.8, 127.3, 129.5, 130.0 (2C), 134.3, 134.9 (2C), 139.6, 141.8, 148.1, 200.4, 200.5. **ESI-MS** m/z: calcd for $C_{19}H_{19}NO_4SNa$: 380.09. Found: 380.33 $[M + Na]^+$. **Anal. Calcd** for $C_{19}H_{19}NO_4S$ (357.42): C, 63.85; H, 5.36; N, 3.92. Found: C, 63.72; H, 5.27; N, 3.82.

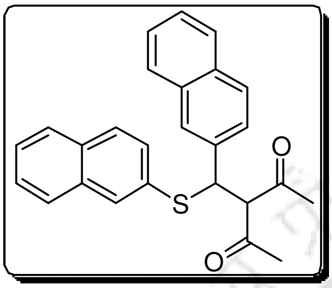
3-(naphthalen-2-yl(p-tolylthio)methyl)pentane-2,4-dione (4ale):



Nature: White solid; mp 139-140 °C; **IR** (KBr): 3393, 3064, 2920, 1896, 1785, 1692, 1597, 1509, 1488, 1419, 1358, 1281, 1212, 1184, 1174, 1147, 1128, 1017, 824, 805, 751 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.86 (s, 3H), 2.25 (s, 3H), 2.44 (s, 3H), 4.47 (d, *J* = 12.4 Hz, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 7.32 (s, 1H), 7.35 (dd, J_1 = 8.8 Hz, J_2 = 8.4 Hz, 1H), 7.41-7.44 (m, 2H), 7.64

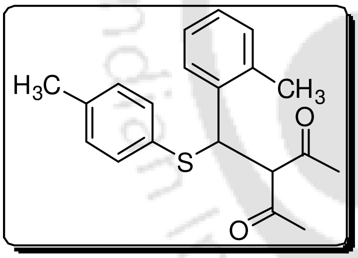
(d, *J* = 7.2 Hz, 1H), 7.74-7.77 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 29.6 (2C), 53.2, 74.0, 125.8, 126.2, 126.3, 127.1, 127.7, 127.9, 128.4, 128.7, 129.7 (2C), 132.8, 132.9, 134.7 (2C), 136.4, 138.8, 201.2, 201.4. **Anal. Calcd** for $C_{23}H_{22}O_2S$ (362.48): C, 76.21; H, 6.12. Found: C, 76.10; H, 6.04.

3-(naphthalen-2-yl(naphthalen-2-ylthio)methyl)pentane-2,4-dione (4alh):



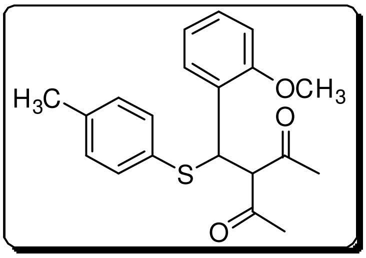
Nature: White solid; mp 126-128 °C; **IR** (KBr): 3400, 3055, 1945, 1914, 1720, 1694, 1599, 1580, 1508, 1498, 1419, 1354, 1275, 1184, 1145, 1018, 958, 948, 889, 856, 827, 813, 752, 738 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.88 (s, 3H), 2.48 (s, 3H), 4.55 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 6H), 7.57-7.77 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.7, 29.8, 53.2, 74.2, 125.8, 126.4, 126.5, 126.6, 126.8, 127.3, 127.8 (3C), 128.0, 128.6, 128.9, 129.1, 129.7, 130.9, 132.9, 133.0, 133.5, 133.7, 136.4, 201.1, 201.3. **ESI-MS** m/z: calcd for $C_{26}H_{22}O_2SNa$: 421.12. Found: 421.27 [M + Na]$^+$. **Anal. Calcd** for $C_{26}H_{22}O_2S$ (398.52): C, 78.36; H, 5.56. Found: C, 78.23; H, 5.47.

3-(o-tolyl(p-tolylthio)methyl)pentane-2,4-dione (4ape):



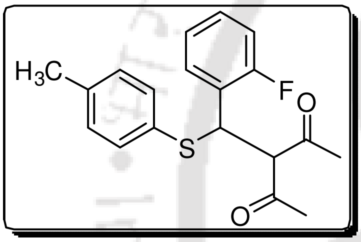
Nature: White solid; mp 66-68 °C; **IR** (KBr): 3022, 2913, 1912, 1699, 1596, 1490, 1462, 1415, 1381, 1353, 1300, 1256, 1240, 1215, 1175, 1139, 1105, 1038, 1018, 967, 949, 875, 861, 835, 814, 772, 734, 705, 620, 549, 540 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.22 (s, 3H), 2.26 (s, 3H), 2.28 (s, 3H), 4.46 (d, *J* = 12.0 Hz, 1H), 5.00 (d, *J* = 12.4 Hz, 1H), 6.81 (d, *J* = 7.2 Hz, 1H), 6.96 (m, 5H), 7.04 (d, *J* = 4.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.4, 21.2, 29.1, 29.6, 47.5, 73.9, 126.0, 127.4 (2C), 129.5 (3C), 130.6, 135.9, 136.2 (2C), 137.0, 139.1, 201.3, 201.6. **ESI-MS** m/z: calcd for $C_{20}H_{22}O_2SNa$: 349.12. Found: 349.12 [M + Na]$^+$. **Anal. Calcd** for $C_{20}H_{22}O_2S$ (326.45): C, 73.58; H, 6.79. Found: C, 73.42; H, 6.67.

3-((2-methoxyphenyl)(p-tolylthio)methyl)pentane-2,4-dione (4aqe):



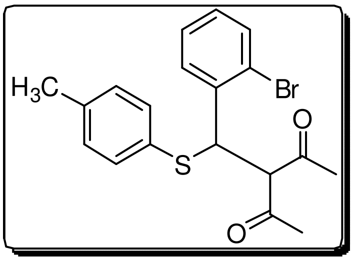
Nature: White solid; mp 84-86 °C; **IR** (KBr): 3005, 2837, 1904, 1712, 1692, 1597, 1496, 1463, 1439, 1414, 1359, 1297, 1272, 1252, 1184, 1146, 1115, 1052, 1028, 972, 940, 870, 857, 810, 765, 751, 701, 615, 602, 571 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.88 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.77 (s, 3H), 4.53 (d, *J* = 12.4 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 6.74-6.82 (m, 3H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.2, 28.5, 30.4, 46.4, 55.6, 73.2, 111.2, 120.5, 127.3, 128.6, 128.8, 129.1, 129.4 (2C), 134.9 (2C), 138.5, 156.6, 201.7, 202.2. **ESI-MS** m/z: calcd for $C_{20}H_{22}O_3SNa$: 365.11. Found: 365.11 [M + Na]$^+$. **Anal. Calcd** for $C_{20}H_{22}O_3S$ (342.45): C, 70.15; H, 6.48. Found: C, 70.00; H, 6.37.

3-((2-fluorophenyl)(p-tolylthio)methyl)pentane-2,4-dione (4are):



Nature: White solid; mp 110-112 °C; **IR** (KBr): 3017, 2917, 1898, 1716, 1697, 1611, 1587, 1491, 1459, 1461, 1357, 1302, 1291, 1268, 1254, 1231, 1181, 1145, 1109, 1075, 1038, 1018, 971, 880, 865, 841, 810, 766, 753, 701, 613, 553 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.94 (s, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 4.48 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 6.89-6.98 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.15-7.20 (m, 1H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.4, 29.0, 30.0, 46.2, 73.1, 115.8, 116.1, 124.2, 124.3, 126.6, 126.7, 128.3, 129.3, 129.4, 129.5, 129.8 (2C), 135.0 (2C), 139.1, 160.0, 161.5, 201.0, 201.4. **ESI-MS** m/z: calcd for $C_{19}H_{19}FO_2SNa$: 353.09. Found: 353.09 [M + Na]$^+$. **Anal. Calcd** for $C_{19}H_{19}FO_2S$ (330.42): C, 69.07; H, 5.80. Found: C, 68.93; H, 5.70.

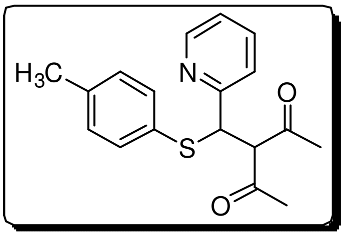
3-((2-bromophenyl)(p-tolylthio)methyl)pentane-2,4-dione (4ase):



Nature: Gummy liquid; **IR** (KBr): 3056, 2920, 1700, 1665, 1593, 1565, 1490, 1467, 1422, 1356, 1239, 1176, 1147, 1022, 967, 952, 880, 810, 767, 739, 707, 668, 598, 534 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.87 (s, 3H), 2.26 (s, 3H), 2.36 (s, 3H), 4.39 (d, *J* = 8.4 Hz, 1H), 5.36 (d, *J* = 9.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.96-7.03 (m, 5H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.3, 28.4, 30.1, 49.7, 73.7, 124.7, 127.4, 129.0 (2C), 129.6 (3C), 133.3, 136.0, 137.8 (2C), 139.3, 200.5, 200.7. **ESI-MS** m/z: calcd for $C_{19}H_{19}BrO_2SH^+$:

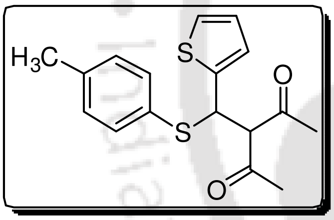
393.03. Found: 393.13 [M + H]$^+$. **Anal. Calcd** for $C_{19}H_{19}BrO_2S$ (391.32): C, 58.32; H, 4.89. Found: C, 58.17; H, 4.78.

3-(pyridin-2-yl(p-tolylthio)methyl)pentane-2,4-dione (4ate):



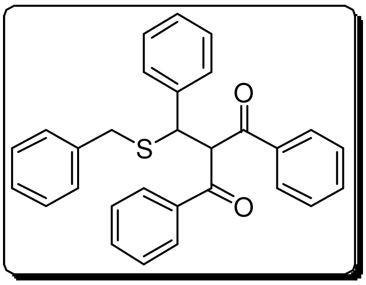
Nature: White solid; mp 71-73 °C; **IR** (KBr): 3382, 3050, 3015, 2956, 2921, 2854, 1957, 1898, 1790, 1724, 1696, 1587, 1568, 1492, 1469, 1434, 1416, 1359, 1314, 1305, 1268, 1252, 1208, 1176, 1140, 1103, 1089, 1048, 1016, 993, 953, 897, 851, 809, 798, 749, 718, 651, 626, 591 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.29 (s, 3H), 2.44 (s, 3H), 4.80 (d, J = 12.0 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 7.01 (s, 4H), 7.07 (t, J = 6.0 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 8.34 (d, J = 4.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.4, 29.8, 30.5, 53.3, 71.1, 122.3, 123.9, 127.7, 129.8 (2C), 135.1 (2C), 136.5, 139.1, 148.7, 158.8, 201.9, 202.0. **ESI-MS** m/z: calcd for $C_{18}H_{19}NO_2SH^+$: 314.12. Found: 314.12 [M + H]$^+$. **Anal. Calcd** for $C_{18}H_{19}NO_2S$ (313.41): C, 68.98; H, 6.11; N, 4.47. Found: C, 68.83; H, 5.99; N, 4.37.

3-(thiophen-2-yl(p-tolylthio)methyl)pentane-2,4-dione (4aue):



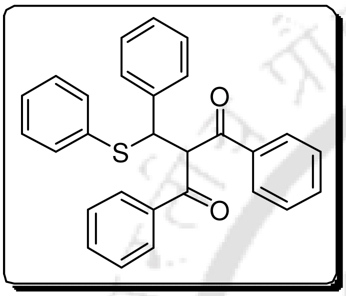
Nature: White solid; mp 96-98 °C; **IR** (KBr): 3401, 3095, 3067, 2959, 2923, 2853, 1897, 1719, 1696, 1595, 1488, 1415, 1385, 1355, 1298, 1281, 1234, 1225, 1209, 1195, 1169, 1155, 1125, 1103, 1045, 1018, 964, 879, 852, 835, 808, 794, 723, 703, 621 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.31 (s, 3H), 2.39 (s, 3H), 4.32 (d, J = 12.0 Hz, 1H), 5.02 (d, J = 12.6 Hz, 1H), 6.53 (s, 1H), 6.76 (t, J = 4.2 Hz, 1H), 7.04 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 4.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.3, 29.4, 29.7, 48.2, 74.9, 125.3, 126.4, 126.6, 128.2, 129.8 (2C), 134.9 (2C), 139.1, 142.9, 201.0, 201.1. **ESI-MS** m/z: calcd for $C_{17}H_{18}O_2S_2$: 318.07. Found: 318.20 [M]. **Anal. Calcd** for $C_{17}H_{18}O_2S_2$ (318.45): C, 64.12; H, 5.70. Found: C, 63.99; H, 5.60.

2-((benzylthio)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione (4bac):



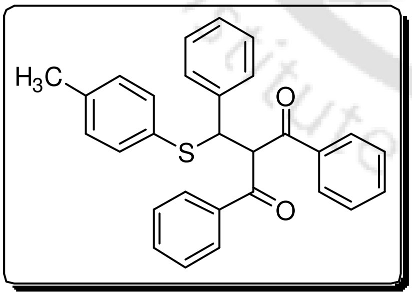
Nature: White solid; mp 91-93 °C; **IR** (KBr): 3058, 3025, 2922, 1687, 1662, 1593, 1577, 1492, 1446, 1354, 1320, 1260, 1230, 1221, 1195, 1177, 1158, 1073, 1030, 1001, 972, 930, 815, 782, 758, 726, 697 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.41 (dd, J_1 = 13.2 Hz, J_2 = 13.2 Hz, 2H), 4.84 (d, J = 11.2 Hz, 1H), 5.87 (d, *J* = 11.2 Hz, 1H), 7.02 (d, *J* = 6.4 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 3H), 7.20 (t, *J* = 7.2 Hz, 3H), 7.35 (t, *J* = 7.6 Hz, 3H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 8.03 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 36.4, 49.6, 63.2, 127.2, 127.6, 128.5 (4C), 128.7 (4C), 128.8 (2C), 128.9 (2C), 129.0 (2C), 129.1 (2C), 133.5, 133.7, 136.5, 137.2, 137.3, 140.1, 192.5, 193.0. **ESI-MS** m/z: calcd for $C_{29}H_{24}O_2SNa$: 459.14. Found: 459.24 $[M + Na]^+$. **Anal. Calcd** for $C_{29}H_{24}O_2S$ (436.56): C, 79.78; H, 5.54. Found: C, 79.62; H, 5.44.

1,3-diphenyl-2-(phenyl(phenylthio)methyl)propane-1,3-dione (4bad):



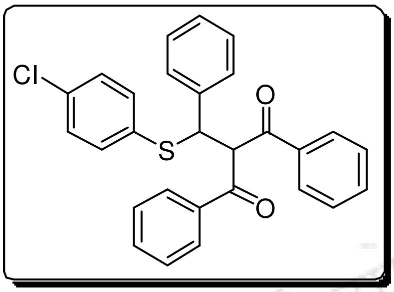
Nature: White solid; mp 112-114 °C; **IR** (KBr): 3432, 3056, 2925, 1959, 1882, 1812, 1686, 1662, 1595, 1576, 1478, 1448, 1357, 1318, 1298, 1262, 1249, 1227, 1178, 1159, 1023, 961, 927, 812, 757, 749 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.32 (d, *J* = 11.6 Hz, 1H), 6.09 (d, *J* = 11.2 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 7.07-7.16 (m, 5H), 7.21-7.32 (m, 3H), 7.37 (d, *J* = 5.6 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 54.6, 62.3, 127.4, 127.9, 128.2 (2C), 128.5 (2C), 128.6 (4C), 128.7 (2C), 128.9 (2C), 129.0 (2C), 129.4, 133.3 (2C), 133.5, 133.7, 136.5, 137.2, 140.0, 192.5, 192.9. **ESI-MS** m/z: calcd for $C_{28}H_{22}O_2SNa$: 445.12. Found: 445.24 $[M + Na]^+$. **Anal. Calcd** for $C_{28}H_{22}O_2S$ (422.54): C, 79.59; H, 5.25. Found: C, 79.48; H, 5.16.

1,3-diphenyl-2-(phenyl(p-tolylthio)methyl)propane-1,3-dione (4bae):



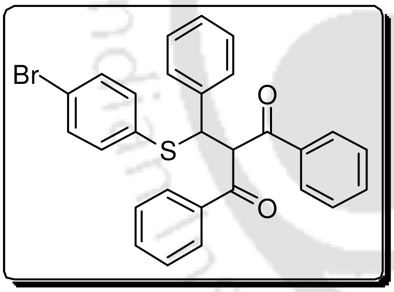
Nature: White solid; mp 133-135 °C; **IR** (KBr): 3445, 3059, 3022, 2917, 1692, 1662, 1594, 1491, 1447, 1360, 1319, 1302, 1266, 1244, 1225, 1181, 1078, 1000, 961, 808, 757, 699, 689 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 5.22 (d, *J* = 11.6 Hz, 1H), 6.03 (d, *J* = 11.2 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 2H), 8.14 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 55.0, 62.8, 127.4, 128.3 (2C), 128.6 (2C), 128.7 (2C), 128.8 (2C), 129.0 (2C), 129.2 (2C), 129.6 (2C), 129.8, 133.5, 133.8, 134.1 (2C), 136.8, 137.5, 138.3, 140.2, 192.7, 193.1. **Anal. Calcd** for $C_{29}H_{24}O_2S$ (436.56): C, 79.78; H, 5.54. Found: C, 79.67; H, 5.47.

2-(((4-chlorophenyl)thio)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione (4baf):



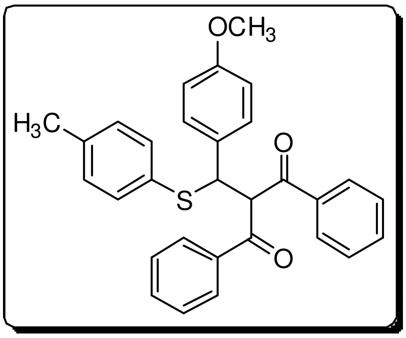
Nature: White solid; mp 160-162 °C; **IR** (KBr): 3420, 3064, 2923, 2847, 1691, 1661, 1594, 1474, 1447, 1266, 1244, 1226, 1181, 1090, 1012, 960, 823, 757, 699, 688 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.25 (d, *J* = 11.2 Hz, 1H), 6.03 (d, *J* = 11.2 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 3H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 3H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 3H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 54.9, 62.5, 127.7, 128.5 (2C), 128.6 (2C), 128.8 (4C), 129.0 (2C), 129.1 (2C), 129.2 (2C), 132.1, 133.6, 133.9, 134.3, 134.9 (2C), 136.6, 137.3, 139.7, 192.4, 192.9. **ESI-MS** m/z: calcd for $C_{28}H_{21}ClO_2SNa$: 479.08. Found: 479.38 $[M + Na]^+$. **Anal. Calcd** for $C_{28}H_{21}ClO_2S$ (456.98): C, 73.59; H, 4.63. Found: C, 73.47; H, 4.56.

2-(((4-bromophenyl)thio)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione (4bag):



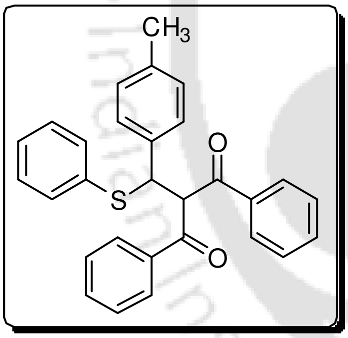
Nature: White solid; mp 175-177 °C; **IR** (KBr): 3441, 3061, 2923, 2852, 1691, 1661, 1594, 1471, 1447, 1319, 1266, 1244, 1225, 1181, 1090, 1066, 1008, 961, 929, 818, 757, 699, 688 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.26 (d, *J* = 11.2 Hz, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 6.4 Hz, 4H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 6.8 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 54.8, 62.6, 122.5, 127.7, 128.5 (2C), 128.7 (2C), 128.8 (4C), 129.1 (2C), 129.2 (2C), 132.0 (2C), 132.8, 133.7, 133.9, 135.0 (2C), 136.6, 137.3, 139.7, 192.5, 192.9. **ESI-MS** m/z: calcd for $C_{28}H_{21}BrO_2SNa$: 525.03. Found: 525.36 $[M + Na]^+$. **Anal. Calcd** for $C_{28}H_{21}BrO_2S$ (501.43): C, 67.07; H, 4.22. Found: C, 66.96; H, 4.14.

2-((4-methoxyphenyl)(p-tolylthio)methyl)-1,3-diphenylpropane-1,3-dione (4bbe):



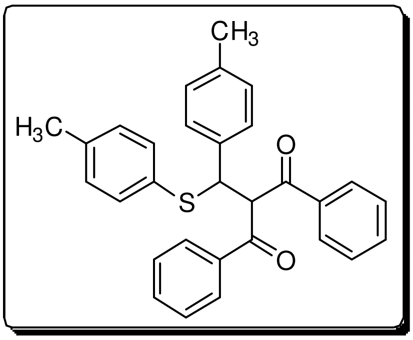
Nature: White solid; mp 168-170 °C; **IR** (KBr): 3444, 2924, 2838, 1695, 1664, 1606, 1594, 1510, 1490, 1447, 1305, 1266, 1248, 1225, 1201, 1180, 1031, 967, 842, 804, 768, 690 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.66 (s, 3H), 5.20 (d, *J* = 11.6 Hz, 1H), 5.97 (d, *J* = 11.6 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 8.12 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 54.4, 55.3, 63.1, 113.7, 128.7 (2C), 128.8 (3C), 129.0 (2C), 129.2 (2C), 129.6 (2C), 129.8 (2C), 129.9, 132.2, 133.5, 133.8, 134.0 (2C), 136.8, 137.5, 138.2, 158.7, 192.8, 193.1. **ESI-MS** m/z: calcd for $C_{30}H_{26}O_3SNa$: 489.15. Found: 489.26 $[M + Na]^+$. **Anal. Calcd** for $C_{30}H_{26}O_3S$ (466.59): C, 77.22; H, 5.62. Found: C, 77.09; H, 5.54.

1,3-diphenyl-2-((phenylthio)(p-tolyl)methyl)propane-1,3-dione (4bcd):



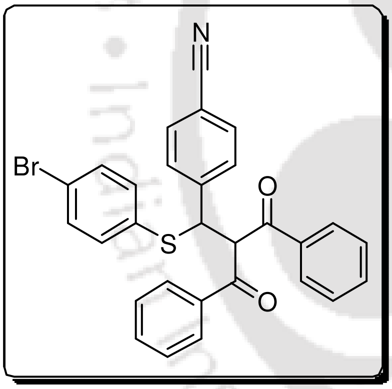
Nature: White solid; mp 151-153 °C; **IR** (KBr): 3429, 3062, 2925, 1959, 1904, 1806, 1687, 1662, 1594, 1577, 1514, 1475, 1446, 1438, 1347, 1323, 1281, 1258, 1225, 1196, 1023, 987, 788, 767, 755, 705, 690 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.17 (s, 3H), 5.27 (d, *J* = 11.2 Hz, 1H), 6.03 (d, *J* = 11.2 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.09-7.16 (m, 7H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 8.13 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 54.4, 62.8, 127.4, 127.7, 127.9, 128.5 (2C), 128.7 (2C), 128.8 (3C), 129.0 (2C), 129.1 (2C), 129.2 (2C), 132.7, 133.4 (2C), 133.5, 133.8, 136.8, 137.1, 137.5, 192.7, 193.1. **ESI-MS** m/z: calcd for $C_{29}H_{24}O_2SNa$: 459.14. Found: 459.42 $[M + Na]^+$. **Anal. Calcd** for $C_{29}H_{24}O_2S$ (436.56): C, 79.78; H, 5.54. Found: C, 79.65; H, 5.46.

1,3-diphenyl-2-(p-tolyl(p-tolylthio)methyl)propane-1,3-dione (4bce):



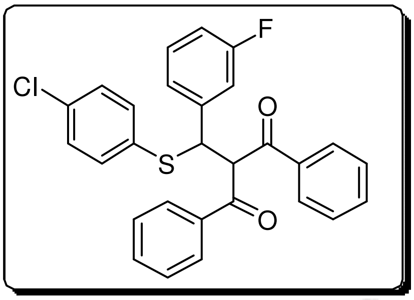
Nature: White solid; mp 163-165 °C; **IR** (KBr): 3066, 2920, 1907, 1688, 1663, 1594, 1577, 1514, 1491, 1449, 1377, 1323, 1315, 1297, 1260, 1227, 1198, 1180, 1162, 1112, 1104, 1064, 1023, 964, 928, 811, 789, 770, 714, 699, 687 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.24 (s, 3H), 5.20 (d, *J* = 11.2 Hz, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 6.92 (s, 4H), 7.01-7.28 (m, 6H), 7.42-7.58 (m, 4H), 7.78 (d, *J* = 6.0 Hz, 2H), 8.13 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 54.7, 62.9, 128.4 (2C), 128.7 (2C), 128.9 (2C), 129.0 (2C), 129.1 (2C), 129.2 (2C), 129.6 (2C), 130.0, 133.5, 133.7, 133.9 (2C), 136.8, 137.0, 137.2, 137.5, 138.1, 192.7, 193.2. **ESI-MS** m/z: calcd for $C_{30}H_{26}O_2SNa$: 473.16. Found: 473.34 [M + Na]$^+$. **Anal. Calcd** for $C_{30}H_{26}O_2S$ (450.59): C, 79.97; H, 5.82. Found: C, 79.85; H, 5.76.

4-(2-benzoyl-1-((4-bromophenyl)thio)-3-oxo-3-phenylpropyl)benzonitrile (4bif):



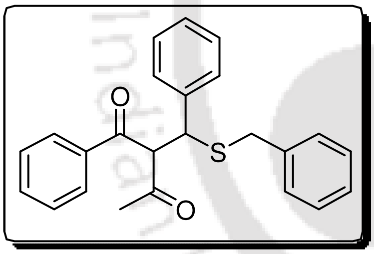
Nature: White solid; mp 176-177 °C; **IR** (KBr): 3062, 2922, 2850, 2224, 1687, 1660, 1594, 1503, 1473, 1447, 1411, 1385, 1351, 1272, 1262, 1223, 1184, 1088, 1073, 1005, 981, 965, 811, 784, 761, 693, 685 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.24 (d, *J* = 11.2 Hz, 1H), 5.97 (d, *J* = 11.2 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.31 (t, *J* = 8.4 Hz, 3H), 7.36 (d, *J* = 8.4 Hz, 3H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 8.13 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 54.6, 61.9, 111.5, 118.6, 123.3, 128.8 (2C), 129.1 (2C), 129.2 (2C), 129.3 (2C), 129.4 (2C), 131.6, 132.3 (2C), 132.4 (2C), 134.2, 134.3, 135.4 (2C), 136.1, 137.0, 145.5, 192.0, 192.4. **ESI-MS** m/z: calcd for $C_{29}H_{20}BrNO_2SNa$: 550.03. Found: 550.27 [M + Na]$^+$. **Anal. Calcd** for $C_{29}H_{20}BrNO_2S$ (526.44): C, 66.16; H, 3.83; N, 2.66. Found: C, 66.02; H, 3.74; N, 2.56.

2-(((4-chlorophenyl)thio)(3-fluorophenyl)methyl)-1,3-diphenylpropane-1,3-dione (4bkg):



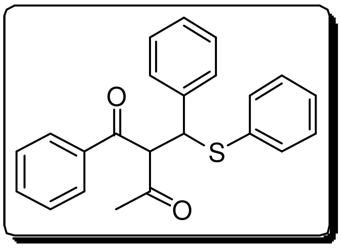
Nature: White solid; mp 151-152 °C; **IR** (KBr): 3442, 3061, 1904, 1691, 1664, 1612, 1593, 1489, 1475, 1448, 1388, 1357, 1299, 1267, 1238, 1182, 1090, 1012, 1000, 973, 957, 930, 822, 785, 770, 744, 704, 693, 688 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.23 (d, *J* = 11.2 Hz, 1H), 5.98 (d, *J* = 10.8 Hz, 1H), 6.79 (t, *J* = 8.8 Hz, 1H), 7.00-7.15 (m, 7H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.2 Hz, 2H), 8.13 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 54.5, 62.2, 114.6, 114.8, 115.4, 115.6, 124.5, 124.6, 128.8, 128.9, 129.1 (2C), 129.2, 129.9, 130.0, 131.6, 133.9, 134.1, 134.7, 135.0, 136.4, 137.2, 142.4, 142.5, 161.5, 164.0, 192.2, 192.6. **ESI-MS** m/z: calcd for $C_{28}H_{20}ClFO_2SNa$: 497.08. Found: 497.27 $[M + Na]^+$. **Anal. Calcd** for $C_{28}H_{20}ClFO_2S$ (474.97): C, 70.80; H, 4.24. Found: C, 70.64; H, 4.16.

2-((benzylthio)(phenyl)methyl)-1-phenylbutane-1,3-dione (5cac):



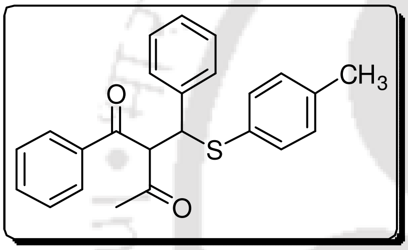
Nature: White solid; mp 118-120 °C; **IR** (KBr): 3415, 3059, 3021, 2929, 1714, 1667, 1595, 1578, 1493, 1450, 1358, 1305, 1278, 1243, 1215, 1176, 1160, 1066, 1000, 971, 763, 709, 702, 684 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.86 (s, 3H), 2.06 (s, 3H), 3.36 (d, *J* = 13.6 Hz, 1H), 3.48 (s, 2H), 3.56 (d, *J* = 13.6 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 5.17 (d, *J* = 11.2 Hz, 1H), 7.09-7.15 (m, 2H), 7.19-7.25 (m, 3H), 7.29-7.34 (m, 5H), 7.48 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.4, 28.2, 35.1, 36.1, 47.9, 48.7, 68.6, 69.5, 127.1, 127.3, 127.6, 127.9, 128.4 (3C), 128.5 (4C), 128.6 (5C), 128.7 (4C), 128.8 (2C), 128.9 (2C), 129.0 (3C), 129.1 (2C), 133.7, 133.8, 136.3, 137.1, 137.4, 139.2, 139.3, 192.9, 193.3, 200.8, 201.2. **ESI-MS** m/z: calcd for $C_{24}H_{22}O_2SNa$: 397.12. Found: 397.27 $[M + Na]^+$. **Anal. Calcd** for $C_{24}H_{22}O_2S$ (374.49): C, 76.97; H, 5.92. Found: C, 76.85; H, 5.84.

1-phenyl-2-(phenyl(phenylthio)methyl)butane-1,3-dione (5cad):



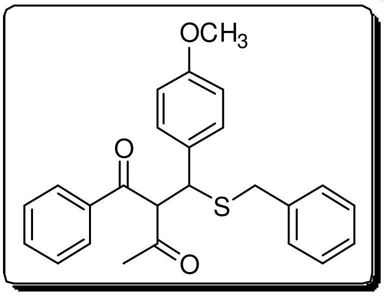
Nature: White solid; mp 140-142 °C; **IR** (KBr): 3440, 3063, 2925, 2853, 1959, 1711, 1667, 1595, 1578, 1496, 1475, 1448, 1438, 1355, 1278, 1216, 1184, 1168, 1065, 1023, 1000, 973, 932, 765, 747, 717, 701, 691 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 5.04 (d, *J* = 12.0 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 7.05-7.12 (m, 5H), 7.19-7.25 (m, 5H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.4, 53.2, 68.9, 127.5, 128.3 (2C) , 128.4 (3C), 128.8 (4C), 128.9 (2C), 132.5, 134.0, 134.1 (2C), 136.5, 139.4, 193.1, 201.4. **ESI-MS** m/z: calcd for $C_{23}H_{20}O_2SNa$: 383.12. Found: 383.22 $[M + Na]^+$. **Anal. Calcd** for $C_{23}H_{20}O_2S$ (360.47): C, 76.64; H, 5.59. Found: C, 76.51; H, 5.49.

1-phenyl-2-(phenyl(p-tolylthio)methyl)butane-1,3-dione (5cae):



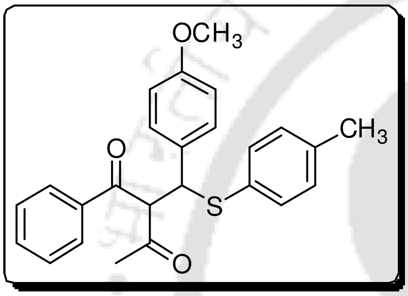
Nature: White solid; mp 149-150 °C; **IR** (KBr): 3403, 3055, 3022, 2973, 2948, 2925, 1906, 1713, 1673, 1596, 1577, 1489, 1447, 1355, 1299, 1268, 1220, 1162, 1077, 1016, 970, 925, 813, 763, 697 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.40 (s, 3H), 4.97 (d, *J* = 12.0 Hz, 1H), 5.20 (d, *J* = 12.0 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.08 (s, 7H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 27.4, 53.4, 68.9, 127.5, 128.2 (2C), 128.3 (2C), 128.6, 128.8 (2C), 128.9 (2C), 129.8 (2C), 133.9, 134.6 (2C), 136.5, 138.7, 139.6, 193.2, 201.6. **ESI-MS** m/z: calcd for $C_{24}H_{22}O_2SNa$: 397.12. Found: 397.23 $[M + Na]^+$. **Anal. Calcd** for $C_{24}H_{22}O_2S$ (374.49): C, 76.97; H, 5.92. Found: C, 76.80 H, 5.82.

2-((benzylthio)(4-methoxyphenyl)methyl)-1-phenylbutane-1,3-dione (5cbc):



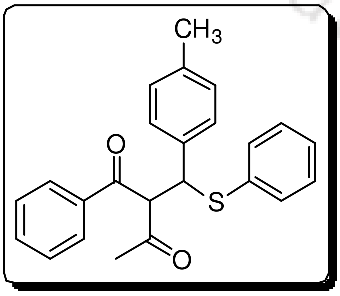
Nature: White solid; mp 116-118 °C; **IR** (KBr): 3005, 2958, 2931, 2833, 1707, 1666, 1610, 1594, 1515, 1463, 1448, 1354, 1326, 1309, 1274, 1263, 1231, 1211, 1182, 1173, 1118, 1035, 1000, 968, 931, 818, 781, 761, 740, 709, 682 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.88 (s, 3H), 2.06 (s, 3H), 3.36 (d, *J* = 13.6 Hz, 1H), 3.48 (s, 2H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.73 (s, 3H), 3.80 (s, 3H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 5.14 (d, *J* = 11.6 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 3H), 6.86 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 2H), 7.22-7.28 (m, 8H), 7.32 (d, *J* = 7.2 Hz, 3H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 3H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 2H), 8.06 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.4, 28.2, 35.0, 36.0, 47.3, 48.2, 55.2, 55.3, 69.0, 69.8, 113.9 (2C), 114.2 (2C), 127.0, 127.1, 127.3 (2C), 128.5 (2C), 128.6 (2C), 128.7 (2C), 128.8 (2C), 128.9 (2C), 129.0 (2C), 129.2 (2C), 129.7 (2C), 129.8 (2C), 130.9, 131.1, 133.8, 133.9, 136.4, 137.1, 137.3, 137.6, 158.9, 159.1, 193.1, 193.4, 201.2, 201.5. **ESI-MS** m/z: calcd for $C_{25}H_{24}O_3SNa$: 427.13. Found: 427.18 $[M + Na]^+$. **Anal. Calcd** for $C_{25}H_{24}O_3S$ (404.52): C, 74.23; H, 5.98. Found: C, 74.10; H, 5.86.

2-((4-methoxyphenyl)(p-tolylthio)methyl)-1-phenylbutane-1,3-dione (5cbe):



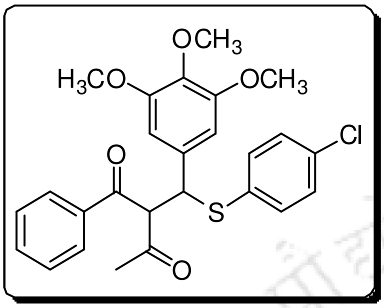
Nature: White solid; mp 147-149 °C; **IR** (KBr): 3416, 3067, 3007, 2927, 2833, 1890, 1713, 1670, 1610, 1597, 1515, 1463, 1451, 1357, 1307, 1279, 1263, 1232, 1216, 1181, 1174, 1112, 1037, 975, 817, 805, 759, 689 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.39 (s, 3H), 3.68 (s, 3H), 4.94 (d, *J* = 12.0 Hz, 1H), 5.15 (d, *J* = 12.0 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 4H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 27.3, 52.9, 55.2, 69.2, 113.7, 128.8 (3C), 128.9 (3C), 129.4 (2C), 129.7 (2C), 131.6, 133.9, 134.5 (2C), 136.6, 138.6, 158.7, 193.3, 201.6. **ESI-MS** m/z: calcd for $C_{25}H_{24}O_3SNa$: 427.13. Found: 427.30 $[M + Na]^+$. **Anal. Calcd** for $C_{25}H_{24}O_3S$ (404.52): C, 74.23; H, 5.98. Found: C, 74.14; H, 5.89.

1-phenyl-2-((phenylthio)(p-tolyl)methyl)butane-1,3-dione (5ccd):



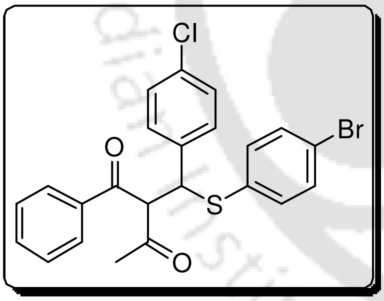
Nature: White solid; mp 121-123 °C; **IR** (KBr): 3403, 3050, 2917, 2856, 1707, 1666, 1595, 1578, 1515, 1474, 1440, 1357, 1326, 1301, 1279, 1223, 1173, 1067, 1023, 975, 925, 810, 775, 749, 693 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 2.36 (s, 3H), 5.00 (d, *J* = 12.0 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 2H), 7.20 (s, 5H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 27.4, 52.9, 69.2, 128.1 (2C), 128.3, 128.9 (2C), 129.0 (5C), 129.1 (2C), 132.8, 134.0 (2C), 136.4, 136.5, 137.2, 193.3, 201.6. **Anal. Calcd** for $C_{24}H_{22}O_2S$ (374.49): C, 76.97; H, 5.92. Found: C, 76.82; H, 5.83.

2-(((4-chlorophenyl)thio)(3,4,5-trimethoxyphenyl)methyl)-1-phenylbutane-1,3-dione (5cdf):



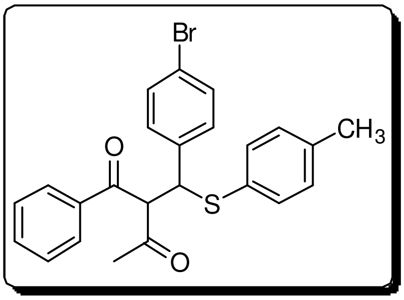
Nature: White solid; mp 169-170 °C; **IR** (KBr): 3071, 2995, 2951, 2935, 2836, 1701, 1670, 1590, 1511, 1475, 1457, 1448, 1429, 1386, 1360, 1328, 1289, 1251, 1232, 1215, 1185, 1154, 1130, 1091, 1012, 1001, 972, 828, 769, 699 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.55 (s, 6H), 3.68 (s, 3H), 4.92 (d, J = 11.6 Hz, 1H), 5.17 (d, J = 12.4 Hz, 1H), 6.19 (s, 2H), 7.16 (dd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, 4H), 7.38 (t, J = 7.6 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.7, 53.7, 55.9 (2C), 60.8, 68.0, 105.2, 128.7 (2C), 128.9 (2C), 129.1 (4C), 130.6, 134.1, 134.2, 135.1, 136.1 (2C), 136.6, 137.2, 152.9, 193.1, 201.1. **ESI-MS** m/z: calcd for $C_{26}H_{25}ClO_5SNa$: 507.10. Found: 507.30 $[M + Na]^+$. **Anal. Calcd** for $C_{26}H_{25}ClO_5S$ (484.99): C, 64.39; H, 5.20. Found: C, 64.24 H, 5.08.

2-(((4-bromophenyl)thio)(4-chlorophenyl)methyl)-1-phenylbutane-1,3-dione (5ceg):



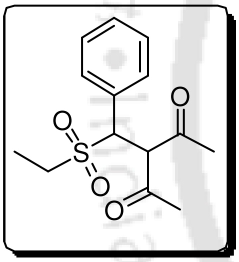
Nature: White solid; mp 144-146 °C; **IR** (KBr): 3062, 2967, 2923, 2850, 1721, 1667, 1596, 1578, 1494, 1469, 1450, 1360, 1313, 1291, 1274, 1216, 1169, 1161, 1108, 1091, 1067, 1009, 973, 827, 810, 760, 733, 693 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 4.98 (d, J = 12.0 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 7.03-7.05 (m, 4H), 7.09 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.6, 52.5, 68.6, 123.3, 128.7 (2C), 128.9 (2C), 129.0 (2C), 129.6 (2C), 131.1, 132.3 (2C), 133.5, 134.3, 135.8 (2C), 136.2, 137.8, 192.7, 200.8. **ESI-MS** m/z: calcd for $C_{23}H_{18}BrClO_2SNa$: 496.98. Found: 497.17 $[M + Na]^+$. **Anal. Calcd** for $C_{23}H_{18}BrClO_2S$ (473.81): C, 58.30; H, 3.83. Found: C, 58.14; H, 3.71.

2-((4-bromophenyl)(p-tolylthio)methyl)-1-phenylbutane-1,3-dione (5cfe):



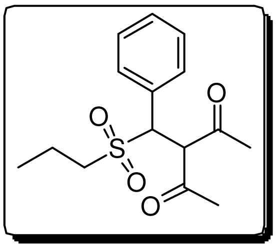
Nature: White solid; mp 158-160 °C; **IR** (KBr): 3448, 3064, 3017, 2967, 2928, 1718, 1665, 1595, 1578, 1489, 1450, 1412, 1358, 1312, 1274, 1216, 1172, 1105, 1076, 1012, 974, 933, 805, 760, 732, 689 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.39 (s, 3H), 4.93 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 7.05 (dd, J_1 = 7.6 Hz, J_2 = 8.0 Hz, 4H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 27.4, 52.7, 68.6, 121.3, 128.2, 128.9 (2C), 129.0 (2C), 129.2, 129.9 (3C), 131.4 (2C), 131.7, 134.1, 134.6 (2C), 136.2, 138.8, 192.9, 201.0. **ESI-MS** m/z: calcd for $C_{24}H_{21}BrO_2SNa$: 477.03. Found: 477.17 $[M + Na]^+$. **Anal. Calcd** for $C_{24}H_{21}BrO_2S$ (453.39): C, 63.58; H, 4.67. Found: C, 63.47; H, 4.59.

3-((ethylsulfonyl)(phenyl)methyl)pentane-2,4-dione (6a):



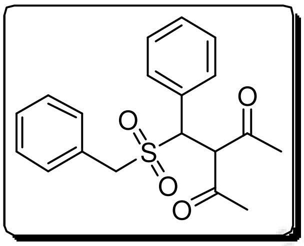
Nature: White solid; mp 140-142 °C; **IR** (KBr): 3395, 3048, 2974, 2944, 2659, 2549, 1965, 1908, 1733, 1701, 1596, 1574, 1452, 1424, 1364, 1335, 1308, 1294, 1260, 1246, 1217, 1169, 1134, 1069, 1051, 1036, 877, 851, 795, 707 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.6 Hz, 3H), 1.85 (s, 3H), 2.42 (s, 3H), 2.64-2.81 (m, 2H), 4.88 (d, *J* = 11.6 Hz, 1H), 5.16 (d, *J* = 11.6 Hz, 1H), 7.37 (s, 5H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 6.2, 29.0, 30.7, 45.9, 66.8, 66.9, 129.6 (2C), 129.9, 130.2 (2C), 131.1, 199.1, 200.0. **ESI-MS** m/z: calcd for $C_{14}H_{18}O_4SNa$: 305.08. Found: 305.16 $[M + Na]^+$. **Anal. Calcd** for $C_{14}H_{18}O_4S$ (282.35): C, 59.55; H, 6.43. Found: C, 59.43; H, 6.35.

3-(phenyl(propylsulfonyl)methyl)pentane-2,4-dione (6b):



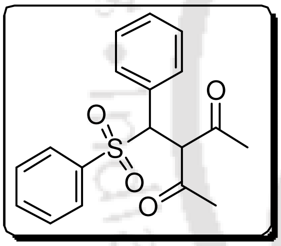
Nature: White solid; mp 118-119 °C; **IR** (KBr): 3406, 3073, 2969, 2939, 2881, 2657, 2549, 1909, 1698, 1596, 1574, 1499, 1459, 1417, 1359, 1308, 1282, 1263, 1242, 1181, 1147, 1132, 1113, 1086, 912, 898, 850, 838, 801, 786, 750, 703 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.6 Hz, 3H), 1.71-1.82 (m, 2H), 1.87 (s, 3H), 2.45 (s, 3H), 2.62-2.80 (m, 2H), 4.90 (d, *J* = 11.6 Hz, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 7.40 (s, 5H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.2, 15.4, 29.0, 30.7, 53.0, 66.9, 67.5, 129.6 (2C), 130.0, 130.2 (2C), 131.1, 199.2, 200.1. **ESI-MS** m/z: calcd for $C_{15}H_{20}O_4SNa$: 319.10. Found: 319.16 $[M + Na]^+$. **Anal. Calcd** for $C_{15}H_{20}O_4S$ (296.38): C, 60.79; H, 6.80. Found: C, 60.67; H, 6.71.

3-((benzylsulfonyl)(phenyl)methyl)pentane-2,4-dione (6c):



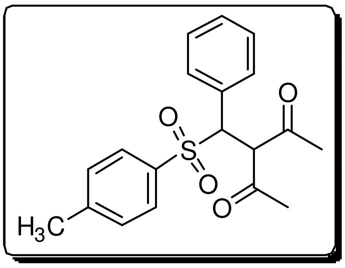
Nature: White solid; mp 148-150 °C; **IR** (KBr): 3063, 2968, 2359, 1719, 1698, 1495, 1455, 1360, 1330, 1305, 1294, 1259, 1178, 1145, 1130, 1120, 974, 783, 773, 703 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.85 (s, 3H), 2.39 (s, 3H), 4.04 (dd, J_1 = 13.6 Hz, J_2 = 13.6 Hz, 2H), 4.90 (d, J = 11.6 Hz, 1H), 5.18 (d, J = 11.6 Hz, 1H), 7.26-7.33 (m, 4H), 7.35-7.42 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 29.2, 30.5, 58.2, 66.7, 67.4, 126.5, 129.1 (2C), 129.3, 129.4 (2C), 129.8, 130.4 (2C), 130.9, 131.3 (2C), 199.1, 200.1. **ESI-MS** m/z: calcd for $C_{19}H_{20}O_4SNa$: 367.10. Found: 367.21 $[M + Na]^+$. **Anal. Calcd** for $C_{19}H_{20}O_4S$ (344.42): C, 66.26; H, 5.85. Found: C, 66.14; H, 5.77.

3-(phenyl(phenylsulfonyl)methyl)pentane-2,4-dione (6d):



Nature: White solid; mp 177-179 °C; **IR** (KBr): 3407, 3061, 2961, 2925, 1695, 1497, 1449, 1420, 1358, 1310, 1298, 1262, 1178, 1149, 1086, 800, 758, 712, 700, 686 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74 (s, 3H), 2.44 (s, 3H), 4.87 (d, J = 11.6 Hz, 1H), 5.11 (d, J = 11.6 Hz, 1H), 6.91 (d, J = 6.0 Hz, 2H), 7.12 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 7.6 Hz, 1H), 7.29-7.36 (m, 4H), 7.50 (t, J = 7.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 28.4, 30.7, 67.5, 70.5, 128.9 (2C), 129.0 (2C), 129.3 (2C), 129.5, 130.4, 130.7, 134.2 (2C), 136.6, 199.3, 200.2. **ESI-MS** m/z: calcd for $C_{18}H_{18}O_4SNa$: 353.08. Found: 353.17 $[M + Na]^+$. **Anal. Calcd** for $C_{18}H_{18}O_4S$ (330.40): C, 65.43; H, 5.49. Found: C, 65.32; H, 5.40.

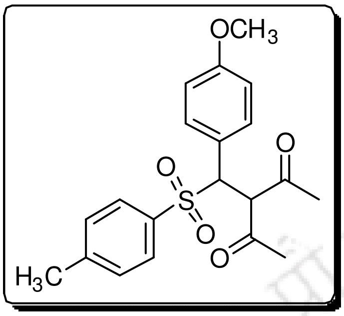
3-(phenyl(tosyl)methyl)pentane-2,4-dione (6e):



Nature: White solid; mp 171-173 °C; **IR** (KBr): 3052, 2959, 2915, 1718, 1695, 1596, 1492, 1455, 1413, 1357, 1314, 1304, 1287, 1254, 1175, 1145, 1130, 1085, 1039, 1018, 975, 814, 780, 725, 703, 697, 663 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.73 (s, 3H), 2.32 (s, 3H), 2.44 (s, 3H), 4.85 (d, J = 12.0 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 6.92 (d, J = 6.0 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 9.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ

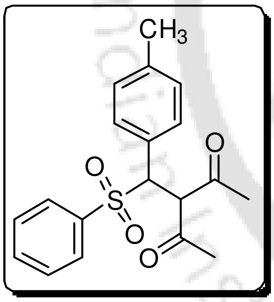
21.8, 28.4, 30.7, 67.6, 70.6, 128.9 (2C), 129.3 (2C), 129.5, 129.6 (3C), 130.4, 130.8, 133.6, 145.4, 199.4, 200.3. **ESI-MS** m/z: calcd for $C_{19}H_{20}O_4SNa$: 367.10. Found: 367.19 $[M + Na]^+$. **Anal. Calcd** for $C_{19}H_{20}O_4S$ (344.42): C, 66.26; H, 5.85. Found: C, 66.10; H, 5.73.

3-((4-methoxyphenyl)(tosyl)methyl)pentane-2,4-dione (6f):



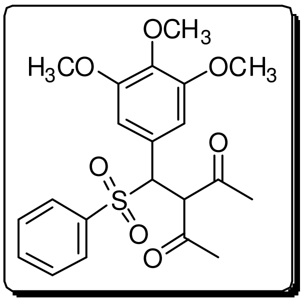
Nature: White solid; mp 144-146 °C; **IR** (KBr): 3460, 3075, 3011, 2959, 2925, 2835, 2662, 2598, 2549, 1695, 1614, 1596, 1574, 1518, 1465, 1426, 1417, 1358, 1304, 1263, 1180, 1149, 1085, 1036, 898, 849, 817, 761, 750, 718 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80 (s, 3H), 2.40 (s, 3H), 2.49 (s, 3H), 3.77 (s, 3H), 4.86 (d, *J* = 11.6 Hz, 1H), 5.10 (d, *J* = 11.6 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.9, 28.2, 30.7, 55.4, 67.8, 69.9, 114.3 (2C), 122.5, 129.4 (2C), 129.7 (3C), 131.7, 133.8, 145.3, 160.4, 199.7, 200.5. **ESI-MS** m/z: calcd for $C_{20}H_{22}O_5SNa$: 397.11. Found: 397.21 $[M + Na]^+$. **Anal. Calcd** for $C_{20}H_{22}O_5S$ (374.45): C, 64.15; H, 5.92. Found: C, 64.04; H, 5.84.

3-((phenylsulfonyl)(p-tolyl)methyl)pentane-2,4-dione (6g):



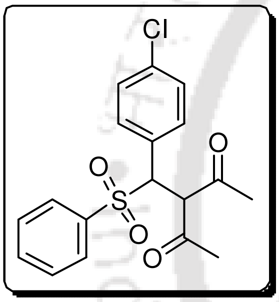
Nature: White solid; mp 170-173 °C; **IR** (KBr): 3439, 3071, 2962, 2920, 2540, 1696, 1573, 1517, 1477, 1449, 1426, 1361, 1309, 1297, 1263, 1180, 1150, 1085, 1074, 909, 851, 828, 760, 721 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80 (s, 3H), 2.29 (s, 3H), 2.50 (s, 3H), 4.90 (d, *J* = 11.6 Hz, 1H), 5.14 (d, *J* = 11.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 7.38-7.46 (m, 4H), 7.57-7.61 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.4, 28.3, 30.7, 67.7, 70.3, 127.5, 129.0 (2C), 129.4 (3C), 129.7 (2C), 130.3, 134.2, 136.8, 139.7, 199.5, 200.4. **ESI-MS** m/z: calcd for $C_{19}H_{20}O_4SNa$: 367.10. Found: 367.19 $[M + Na]^+$. **Anal. Calcd** for $C_{19}H_{20}O_4S$ (344.42): C, 66.26; H, 5.85. Found: C, 66.14; H, 5.77.

3-((phenylsulfonyl)(3,4,5-trimethoxyphenyl)methyl)pentane-2,4-dione (6h):



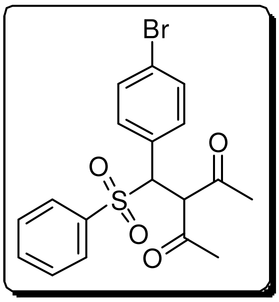
Nature: White solid; mp 189-191 °C; **IR** (KBr): 3408, 2999, 2966, 2833, 1721, 1698, 1588, 1510, 1465, 1451, 1425, 1363, 1328, 1300, 1270, 1248, 1231, 1177, 1145, 1132, 1084, 1000, 956, 842, 833, 776, 754, 716, 688, 631 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.84 (s, 3H), 2.51 (s, 3H), 3.62 (s, 6H), 3.79 (s, 3H), 4.89 (d, *J* = 11.2 Hz, 1H), 5.10 (d, *J* = 11.2 Hz, 1H), 6.10 (s, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.1, 30.6, 56.1 (2C), 61.0, 67.3, 70.5, 107.4, 125.7, 128.9 (3C), 129.3 (3C), 134.1, 136.4, 138.7, 153.2, 199.4, 200.0. **ESI-MS** m/z: calcd for $C_{21}H_{24}O_7SNa$: 443.11. Found: 443.13 [M + Na]$^+$. **Anal. Calcd** for $C_{21}H_{24}O_7S$ (420.47): C, 59.99; H, 5.75. Found: C, 59.85; H, 5.66.

3-((4-chlorophenyl)(phenylsulfonyl)methyl)pentane-2,4-dione (6i):



Nature: White solid; mp 175-176 °C; **IR** (KBr): 3397, 3070, 3059, 2965, 2920, 1962, 1904, 1696, 1587, 1555, 1492, 1448, 1414, 1388, 1319, 1307, 1299, 1263, 1203, 1178, 1149, 1083, 1071, 896, 863, 833, 793, 761, 738, 722 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.84 (s, 3H), 2.51 (s, 3H), 4.89 (d, *J* = 11.6 Hz, 1H), 5.14 (dd, J_1 = 11.2 Hz, J_2 = 11.6 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.41-7.47 (m, 4H), 7.59-7.63 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 28.6, 30.7, 67.5, 69.9, 129.2 (5C), 131.7, 131.9, 132.2, 134.5 (2C), 135.9, 136.5, 199.0, 199.9. **ESI-MS** m/z: calcd for $C_{18}H_{17}ClO_4SNa$: 387.04. Found: 387.04 [M + Na]$^+$. **Anal. Calcd** for $C_{18}H_{17}ClO_4S$ (364.84): C, 59.26; H, 4.70. Found: C, 59.14; H, 4.62.

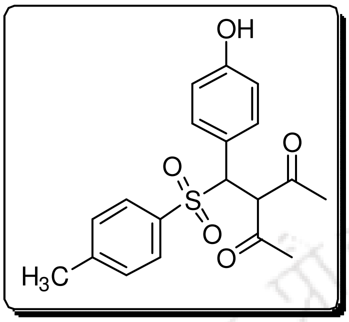
3-((4-bromophenyl)(phenylsulfonyl)methyl)pentane-2,4-dione (6j):



Nature: White solid; mp 162-164 °C; **IR** (KBr): 3403, 3058, 3000, 2965, 2653, 2595, 2545, 1695, 1595, 1573, 1557, 1489, 1448, 1426, 1361, 1318, 1307, 1262, 1181, 1149, 1083, 1013, 897, 849, 831, 760, 749, 721 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.84 (s, 3H), 2.51 (s, 3H), 4.89 (d, *J* = 11.6 Hz, 1H), 5.14 (d, *J* = 11.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.41-7.47 (m, 4H), 7.59-7.63 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 28.6, 30.7, 67.4, 70.0, 124.1, 129.2 (2C), 129.3

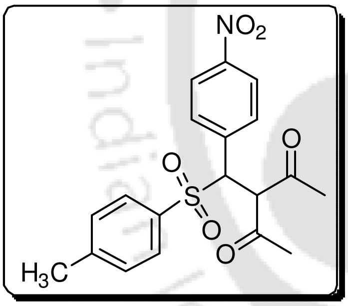
(2C), 129.9, 131.9, 132.2 (2C), 134.5 (2C), 136.5, 199.0, 199.8. **ESI-MS** m/z: calcd for $C_{18}H_{17}BrO_4SNa$: 432.99. Found: 432.95 $[M + Na]^+$. **Anal. Calcd** for $C_{18}H_{17}BrO_4S$ (409.29): C, 52.82; H, 4.19. Found: C, 52.70; H, 4.11.

3-((4-hydroxyphenyl)(tosyl)methyl)pentane-2,4-dione (6k):



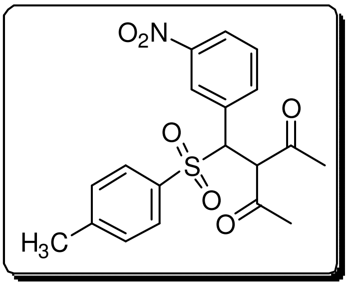
Nature: White solid; mp 174-176 °C; **IR** (KBr): 3416, 3071, 2967, 2923, 2656, 2545, 2340, 1698, 1613, 1596, 1573, 1518, 1475, 1426, 1360, 1283, 1262, 1222, 1175, 1139, 1074, 1035, 909, 850, 834, 813, 759, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.41 (s, 3H), 2.49 (s, 3H), 4.84 (d, J = 11.6 Hz, 1H), 5.09 (d, J = 11.6 Hz, 1H), 6.65 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.9, 28.3, 30.8, 67.8, 69.9, 115.9 (2C), 129.4 (3C), 129.7 (2C), 130.6, 131.7, 133.8, 145.4, 156.7, 199.9, 200.4. **Anal. Calcd** for $C_{19}H_{20}O_5S$ (360.42): C, 63.32; H, 5.59. Found: C, 63.21; H, 5.51.

3-((4-nitrophenyl)(tosyl)methyl)pentane-2,4-dione (6l):



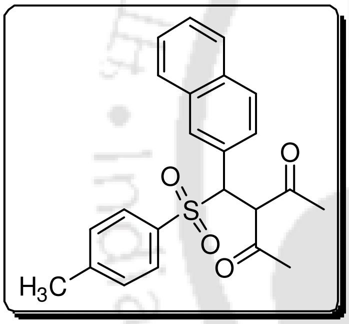
Nature: White solid; mp 170-173 °C; **IR** (KBr): 3413, 3070, 2973, 2920, 2859, 1697, 1595, 1558, 1521, 1426, 1382, 1349, 1316, 1297, 1261, 1176, 1144, 1083, 1074, 1042, 1015, 909, 864, 850, 813, 760, 737, 721 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.43 (s, 3H), 2.55 (s, 3H), 4.99 (d, J = 11.2 Hz, 1H), 5.27 (d, J = 11.6 Hz, 1H), 7.21-7.24 (m, 4H), 7.33 (d, J = 6.8 Hz, 2H), 8.07 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.9, 29.2, 30.8, 67.2, 70.1, 123.8 (2C), 129.1 (2C), 130.0 (3C), 131.3, 133.3, 138.5, 146.2, 148.3, 198.5, 199.2. **ESI-MS** m/z: calcd for $C_{19}H_{19}NO_6SNH_4^+$: 407.13. Found: 407.24 $[M + NH_4]^+$. **Anal. Calcd** for $C_{19}H_{19}NO_6S$ (389.42): C, 58.60; H, 4.92; N, 3.60. Found: C, 58.44; H, 4.82; N, 3.50.

3-((3-nitrophenyl)(tosyl)methyl)pentane-2,4-dione (6m):



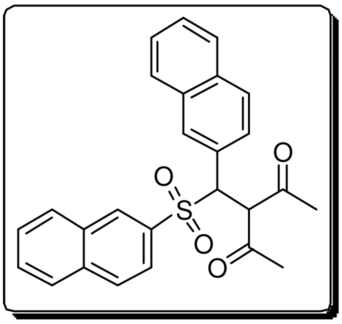
Nature: White solid; mp 181-183 °C; **IR** (KBr): 3088, 2973, 2925, 2706, 2657, 2595, 2547, 1699, 1596, 1574, 1532, 1481, 1426, 1415, 1349, 1317, 1302, 1262, 1171, 1146, 1083, 917, 898, 850, 816, 750, 719, 706 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.41 (s, 3H), 2.55 (s, 3H), 4.99 (d, *J* = 11.6 Hz, 1H), 5.26 (d, *J* = 11.2 Hz, 1H), 7.22 (d, *J* = 6.8 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.76 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.9, 29.4, 30.7, 67.2, 70.0, 124.3, 129.2 (2C), 130.0, 130.1 (3C), 133.2, 133.6, 136.2, 146.3, 148.2, 198.6, 199.2. **ESI-MS** m/z: calcd for $C_{19}H_{19}NO_6SNa$: 412.08. Found: 412.16 $[M + Na]^+$. **Anal. Calcd** for $C_{19}H_{19}NO_6S$ (389.42): C, 58.60; H, 4.92; N, 3.60. Found: C, 58.48; H, 4.85; N, 3.52.

3-(naphthalen-2-yl(tosyl)methyl)pentane-2,4-dione (6n):



Nature: White solid; mp 162-164 °C; **IR** (KBr): 3405, 3067, 2963, 2920, 1694, 1596, 1573, 1508, 1426, 1357, 1310, 1300, 1263, 1181, 1145, 1084, 1018, 974, 949, 898, 865, 850, 827, 813, 760, 739, 721 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.79 (s, 3H), 2.36 (s, 3H), 2.54 (s, 3H), 5.03 (d, *J* = 11.6 Hz, 1H), 5.33 (d, *J* = 11.6 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.45-7.52 (m, 4H), 7.68 (t, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.8, 28.4, 30.7, 67.9, 70.7, 126.8, 127.3, 127.8, 128.2, 128.3, 128.7, 129.3 (2C), 129.6 (4C), 133.0, 133.4, 133.6, 145.4, 199.4, 200.3. **ESI-MS** m/z: calcd for $C_{23}H_{22}O_4SNa$: 417.11. Found: 417.12 $[M + Na]^+$. **Anal. Calcd** for $C_{23}H_{22}O_4S$ (394.48): C, 70.03; H, 5.62. Found: C, 69.94; H, 5.55.

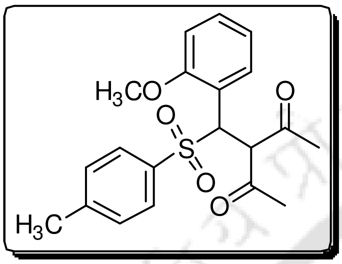
3-(naphthalen-2-yl(naphthalen-2-ylsulfonyl)methyl)pentane-2,4-dione (6o):



Nature: White solid; mp 159-161 °C; **IR** (KBr): 3051, 2949, 2917, 2656, 2548, 1731, 1702, 1596, 1574, 1504, 1418, 1363, 1347, 1310, 1262, 1210, 1144, 1126, 1071, 954, 900, 858, 819, 752, 735, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80 (s, 3H), 2.58 (s, 3H), 5.10 (d, *J* = 11.6 Hz, 1H), 5.44 (d, *J* = 11.6 Hz, 1H), 7.06 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.41-7.50 (m, 3H), 7.55

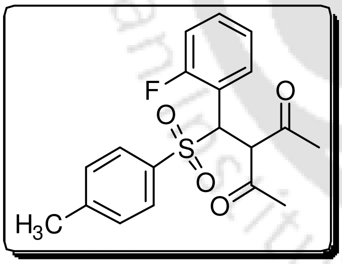
(d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.71-7.77 (m, 3H), 7.85 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 28.4, 30.8, 67.9, 70.8, 123.7, 126.9 (2C), 127.3, 127.8, 127.9 (2C), 128.1 (2C), 128.3, 128.8, 129.1, 129.6, 129.7, 131.5, 132.0, 133.0, 133.5, 133.6, 135.6, 199.3, 200.3. **ESI-MS** m/z: calcd for $C_{26}H_{22}O_4SNa$: 453.11. Found: 453.09 $[M + Na]^+$. **Anal. Calcd** for $C_{26}H_{22}O_4S$ (430.51): C, 72.54; H, 5.15. Found: C, 72.42; H, 5.07.

3-((2-methoxyphenyl)(tosyl)methyl)pentane-2,4-dione (6p):



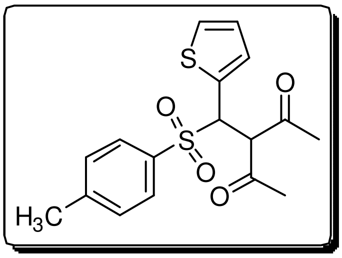
Nature: White solid; mp 158-160 °C; **IR** (KBr): 2970, 2839, 1726, 1700, 1602, 1594, 1497, 1467, 1444, 1415, 1361, 1319, 1309, 1297, 1289, 1255, 1180, 1143, 1118, 1083, 1054, 1023, 956, 823, 802, 780, 770, 756, 722, 662, 619, 581 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.77 (s, 3H), 2.38 (s, 3H), 2.52 (s, 3H), 3.27 (s, 3H), 4.90 (d, *J* = 12.0 Hz, 1H), 5.91 (d, *J* = 12.0 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.7, 27.1, 31.1, 55.1, 61.3, 67.2, 110.4, 119.0, 121.1, 129.0 (2C), 129.3 (2C), 130.4, 130.8, 134.6, 144.8, 157.1, 199.7, 200.8. **ESI-MS** m/z: calcd for $C_{20}H_{22}O_5SH^+$: 375.12. Found: 375.12 $[M + H]^+$. **Anal. Calcd** for $C_{20}H_{22}O_5S$ (374.45): C, 64.15; H, 5.92. Found: C, 64.01; H, 5.82.

3-((2-fluorophenyl)(tosyl)methyl)pentane-2,4-dione (6q):



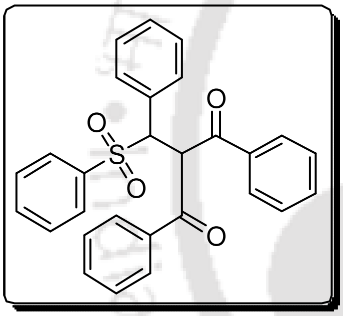
Nature: White solid; mp 146-148 °C; **IR** (KBr): 3075, 3045, 2958, 1926, 1700, 1614, 1597, 1492, 1457, 1415, 1363, 1314, 1300, 1265, 1250, 1231, 1191, 1177, 1146, 1105, 1084, 1034, 1018, 978, 960, 877, 863, 846, 816, 802, 783, 773, 759, 716, 661, 617, 577, 557 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.87 (s, 3H), 2.40 (s, 3H), 2.52 (s, 3H), 4.96 (s, 1H), 5.62 (s, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.8, 27.9, 30.6, 61.3, 67.0, 115.7, 118.4, 118.5, 124.8, 129.0 (2C), 129.6 (2C), 130.5, 131.3, 131.4, 133.8, 145.5, 159.6, 162.1, 198.9, 199.9. **ESI-MS** m/z: calcd for $C_{19}H_{19}FO_4SH^+$: 363.10. Found: 363.10 $[M + H]^+$. **Anal. Calcd** for $C_{19}H_{19}FO_4S$ (362.42): C, 62.97; H, 5.28. Found: C, 62.81; H, 5.18.

3-(thiophen-2-yl(tosyl)methyl)pentane-2,4-dione (6r):



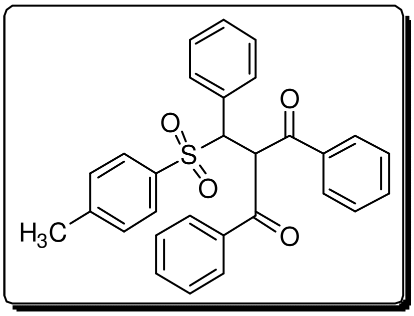
Nature: White solid; mp 151-153 °C; **IR** (KBr): 3414, 3078, 2950, 2920, 2850, 1923, 1818, 1701, 1597, 1494, 1427, 1383, 1361, 1308, 1302, 1280, 1258, 1240, 1190, 1183, 1177, 1145, 1127, 1083, 1018, 973, 854, 846, 816, 760, 726, 660, 622, 586, 570 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.40 (s, 3H), 2.48 (s, 3H), 4.83 (d, *J* = 11.4 Hz, 1H), 5.42 (d, *J* = 11.4 Hz, 1H), 6.78 (s, 1H), 6.87 (t, *J* = 4.2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 4.8 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.9, 28.8, 30.4, 66.0, 68.4, 127.3, 127.9, 129.3 (2C), 129.7 (2C), 130.4, 132.2, 133.3, 145.6, 199.1, 199.7. **ESI-MS** m/z: calcd for $C_{17}H_{18}O_4S_2NH_4^+$: 368.09. Found: 368.10 $[M + NH_4]^+$. **Anal. Calcd** for $C_{17}H_{18}O_4S_2$ (350.45): C, 58.26; H, 5.18. Found: C, 58.12; H, 5.07.

1,3-diphenyl-2-(phenyl(phenylsulfonyl)methyl)propane-1,3-dione (6s):



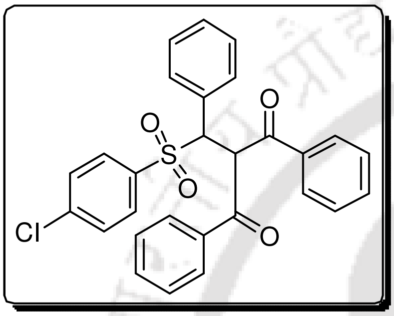
Nature: White solid; mp 203-205 °C; **IR** (KBr): 3058, 2935, 2653, 2592, 2547, 1696, 1595, 1575, 1447, 1426, 1417, 1305, 1261, 1193, 1145, 1083, 1028, 1002, 968, 957, 926, 789, 771, 752, 736, 719, 703 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.64 (d, *J* = 10.8 Hz, 1H), 6.76 (d, *J* = 10.4 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 4H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 8.4 Hz, 4H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 8.19 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 55.4, 71.9, 128.5 (2C), 128.8 (5C), 128.9 (4C), 129.0 (2C), 129.1 (2C), 129.5 (2C), 131.2, 133.9 (2C), 134.0, 136.6, 136.8, 137.3, 191.1, 191.9. **ESI-MS** m/z: calcd for $C_{28}H_{22}O_4SH^+$: 455.13. Found: 455.12 $[M + H]^+$. **Anal. Calcd** for $C_{28}H_{22}O_4S$ (454.53): C, 73.99; H, 4.88. Found: C, 73.87; H, 4.80.

1,3-diphenyl-2-(phenyl(tosyl)methyl)propane-1,3-dione (6t):



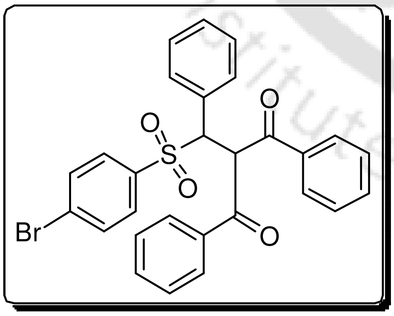
Nature: White solid; mp 227-228 °C; **IR** (KBr): 3411, 3061, 2939, 1697, 1670, 1596, 1579, 1493, 1448, 1312, 1302, 1288, 1263, 1248, 1236, 1187, 1143, 1084, 999, 969, 955, 930, 813, 786, 771, 758, 730, 701 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 5.62 (d, *J* = 10.8 Hz, 1H), 6.75 (d, *J* = 10.8 Hz, 1H), 7.04-7.15 (m, 7H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 8.20 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.8, 55.4, 71.9, 128.5 (2C), 128.8 (2C), 128.9, 129.0 (3C), 129.1 (2C), 129.2 (3C), 129.5 (4C), 131.3, 133.8, 133.9, 134.3, 136.6, 136.8, 145.1, 191.2, 191.9. **ESI-MS** m/z: calcd for $C_{29}H_{24}O_4SNa$: 491.13. Found: 491.19 [M + Na]$^+$. **Anal. Calcd** for $C_{29}H_{24}O_4S$ (468.56): C, 74.34; H, 5.16. Found: C, 74.18; H, 5.05.

2-(((4-chlorophenyl)sulfonyl)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione (6u):



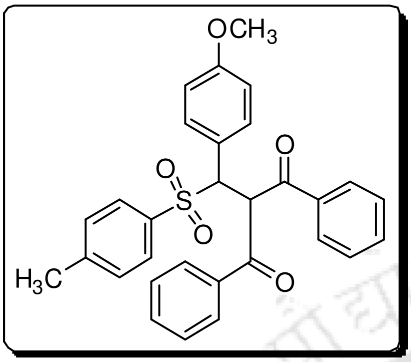
Nature: White solid; mp 227-229 °C; **IR** (KBr): 3061, 3006, 2989, 1696, 1665, 1595, 1576, 1475, 1448, 1395, 1315, 1275, 1267, 1260, 1179, 1147, 1086, 1014, 962, 824, 764, 750, 702 cm^{-1}. **^{1}H NMR** (600 MHz, CDCl$_3$): δ 5.57 (d, *J* = 10.8 Hz, 1H), 6.68 (d, *J* = 10.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.18-7.23 (m, 6H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 8.12 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 55.3, 72.0, 128.6 (2C), 128.8 (2C), 128.9 (3C), 129.0 (3C), 129.1, 129.2 (2C), 129.5, 130.6 (3C), 130.9, 133.9 (2C), 135.8, 136.5, 136.6, 140.9, 190.9, 191.7. **ESI-MS** m/z: calcd for $C_{28}H_{21}ClO_4SNa$: 511.07. Found: 511.12 [M + Na]$^+$. **Anal. Calcd** for $C_{28}H_{21}ClO_4S$ (488.98): C, 68.78; H, 4.33. Found: C, 68.60; H, 4.21.

2-(((4-bromophenyl)sulfonyl)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione (6v):



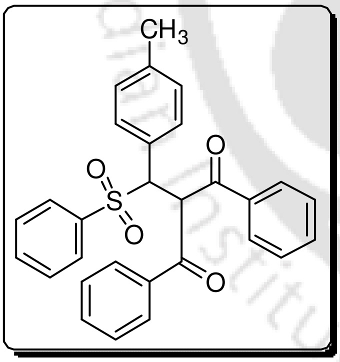
Nature: White solid; mp 230-232 °C; **IR** (KBr): 3412, 3062, 2962, 2925, 2850, 1696, 1595, 1573, 1495, 1468, 1448, 1389, 1314, 1260, 1179, 1146, 1082, 1067, 1011, 963, 819, 758, 746, 701, 687 cm^{-1}. **^{1}H NMR** (600 MHz, CDCl$_3$): δ 5.65 (d, *J* = 10.8 Hz, 1H), 6.74 (d, *J* = 10.8 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.28-7.33 (m, 5H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 2H), 8.20 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 55.3, 72.0, 128.7 (2C), 128.8 (2C), 128.9 (3C), 129.1 (2C), 129.2, 129.5 (2C), 129.6, 130.6 (3C), 130.9, 132.2 (2C), 134.0 (2C), 136.4, 136.5, 136.6, 190.9, 191.8. **ESI-MS** m/z: calcd for $C_{28}H_{21}BrO_4SNa$: 557.02. Found: 557.10 $[M + Na]^+$. **Anal. Calcd** for $C_{28}H_{21}BrO_4S$ (533.43): C, 63.04; H, 3.97. Found: C, 62.89; H, 3.86.

2-((4-methoxyphenyl)(tosyl)methyl)-1,3-diphenylpropane-1,3-dione (6w):



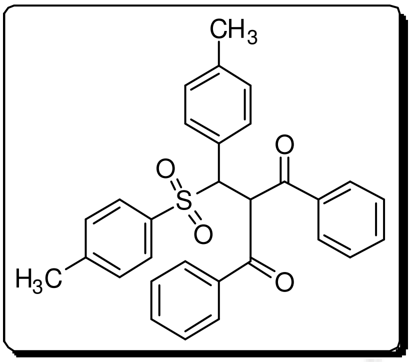
Nature: White solid; mp 213-214 °C; **IR** (KBr): 3440, 3056, 2956, 2925, 2848, 1698, 1674, 1612, 1598, 1515, 1447, 1289, 1269, 1249, 1192, 1177, 1146, 1086, 1032, 956, 816, 769, 748, 720, 690, 673, 668 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.68 (s, 3H), 5.58 (d, *J* = 11.2 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 10.4 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 3H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 6.8 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 3H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.8, 55.3, 55.5, 71.2, 113.9 (2C), 123.0, 128.9 (2C), 129.0 (4C), 129.2 (3C), 129.4 (3C), 129.5 (2C), 133.8, 133.9, 134.4, 136.6, 136.8, 145.0, 159.9, 191.3, 191.9. **ESI-MS** m/z: calcd for $C_{30}H_{26}O_5SNa$: 521.14. Found 521.20 $[M + Na]^+$. **Anal. Calcd** for $C_{30}H_{26}O_5S$ (498.58): C, 72.27; H, 5.26. Found: C, 72.12; H, 5.13.

1,3-diphenyl-2-((phenylsulfonyl)(p-tolyl)methyl)propane-1,3-dione (6x):



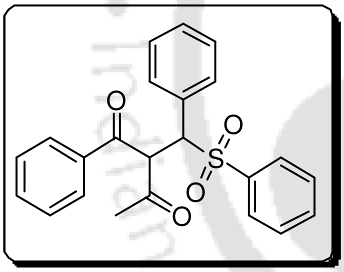
Nature: White solid; mp 215-217 °C; **IR** (KBr): 3438, 3063, 2934, 2923, 2845, 2662, 2598, 2545, 1697, 1596, 1578, 1513, 1447, 1320, 1306, 1293, 1260, 1235, 1180, 1147, 1083, 958, 811, 768, 748, 720, 690 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.11 (s, 3H), 5.56 (d, *J* = 10.8 Hz, 1H), 6.68 (d, *J* = 10.8 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 2H), 6.94 (s, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.36-7.52 (m, 7H), 7.36 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.3, 55.4, 71.7, 128.0, 128.9 (4C), 129.0 (5C), 129.1 (3C), 129.2 (2C), 129.5 (2C), 133.8, 133.9, 134.0, 136.6, 136.8, 137.4, 138.9, 191.2, 191.9. **ESI-MS** m/z: calcd for $C_{29}H_{24}O_4SH^+$: 469.14. Found: 469.14 $[M + H]^+$. **Anal. Calcd** for $C_{29}H_{24}O_4S$ (468.56): C, 74.34; H, 5.16. Found: C, 74.22; H, 5.07.

1,3-diphenyl-2-(p-tolyl(tosyl)methyl)propane-1,3-dione (6y):



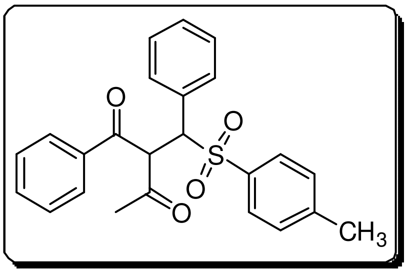
Nature: White solid; mp 212-213 °C; **IR** (KBr): 3442, 3060, 2922, 2853, 1697, 1668, 1595, 1580, 1514, 1448, 1300, 1290, 1261, 1231, 1196, 1146, 1086, 1016, 959, 812, 789, 771, 748, 716, 688, 673 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.37 (s, 3H), 5.59 (d, J = 10.8 Hz, 1H), 6.75 (d, J = 10.4 Hz, 1H), 6.88 (d, J = 7.6 Hz, 2H), 7.03 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.36 (d, J = 6.8 Hz, 2H), 7.45 (d, J = 7.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 3H), 7.57 (d, J = 6.4 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H), 8.19 (d, J = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 21.9, 55.5, 71.7, 128.2, 128.8 (2C), 129.0 (3C), 129.1 (3C), 129.2 (2C), 129.3 (3C), 129.5 (3C), 133.8, 133.9, 134.5, 136.7, 136.9, 138.9, 145.0, 191.3, 192.0. **ESI-MS** m/z: calcd for $C_{30}H_{26}O_4SNa$: 505.14. Found: 505.19 [M + Na]$^+$. **Anal. Calcd** for $C_{30}H_{26}O_4S$ (482.59): C, 74.66; H, 5.43. Found: C, 74.49; H, 5.30.

1-phenyl-2-(phenyl(phenylsulfonyl)methyl)butane-1,3-dione (7a):



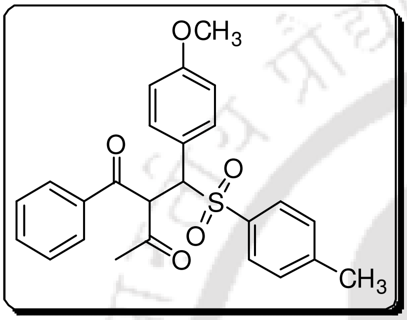
Nature: White solid; mp 178-181 °C; **IR** (KBr): 3072, 2984, 2882, 2658, 2549, 1696, 1596, 1574, 1426, 1417, 1304, 1263, 1145, 1085, 1074, 962, 910, 898, 851, 807, 780, 759, 750, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 5.36 (d, J = 11.2 Hz, 1H), 5.90 (d, J = 11.2 Hz, 1H), 6.97 (s, 2H), 7.04 (t, J = 7.2 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 8.0 Hz, 2H), 7.43-7.48 (m, 4H), 7.55-7.60 (m, 2H), 7.92 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 29.7, 61.1, 71.5, 128.6 (2C), 128.9 (3C), 129.0 (3C), 129.2 (3C), 129.3 (2C), 131.1, 134.2, 134.4, 136.4, 136.9, 191.5, 199.1. **ESI-MS** m/z: calcd for $C_{23}H_{20}O_4SNa$: 415.10. Found: 415.20 [M + Na]$^+$. **Anal. Calcd** for $C_{23}H_{20}O_4S$ (392.46): C, 70.39; H, 5.14. Found: C, 70.26; H, 5.06.

1-phenyl-2-(phenyl(tosyl)methyl)butane-1,3-dione (7b):



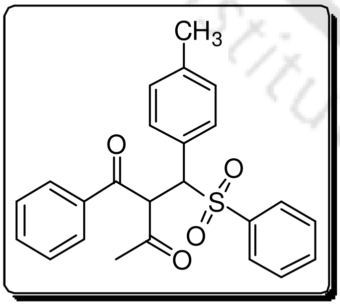
Nature: White solid; mp 193-195 °C; **IR** (KBr): 3453, 3073, 2961, 2923, 2881, 2657, 2592, 2549, 1696, 1671, 1595, 1575, 1426, 1417, 1358, 1302, 1263, 1216, 1182, 1168, 1145, 1083, 964, 898, 850, 810, 774, 762, 750, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.50 (s, 3H), 5.33 (d, J = 11.2 Hz, 1H), 5.88 (d, J = 11.2 Hz, 1H), 6.99 (s, 2H), 7.05 (t, J = 8.0 Hz, 2H), 7.13 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 8.0 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.92 (d, J = 7.2 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.9, 29.6, 61.3, 71.6, 128.5 (2C), 129.0 (3C), 129.2 (3C), 129.3 (2C), 129.6 (3C), 131.3, 134.0, 134.3, 136.4, 145.3, 191.6, 199.2. **ESI-MS** m/z: calcd for $C_{24}H_{22}O_4SNa$: 429.11. Found: 429.22 $[M + Na]^+$. **Anal. Calcd** for $C_{24}H_{22}O_4S$ (406.49): C, 70.91; H, 5.46. Found: C, 70.80 H, 5.38.

2-((4-methoxyphenyl)(tosyl)methyl)-1-phenylbutane-1,3-dione (7c):



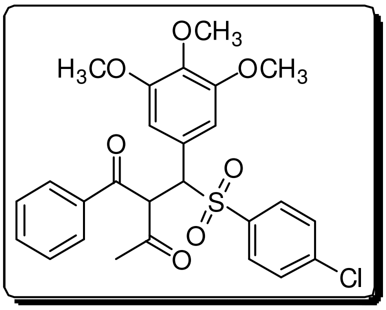
Nature: White solid; mp 162-164 °C; **IR** (KBr): 3467, 3068, 2959, 2930, 2837, 1715, 1670, 1611, 1595, 1556, 1516, 1426, 1384, 1286, 1263, 1237, 1181, 1140, 1082, 1031, 965, 814, 760, 737, 719 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.48 (s, 3H), 3.66 (s, 3H), 5.30 (d, J = 11.2 Hz, 1H), 5.84 (d, J = 11.2 Hz, 1H), 6.57 (d, J = 8.4 Hz, 2H), 6.90 (s, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.92 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.8, 29.6, 55.3, 61.4, 70.9, 113.9, 123.1, 129.0 (3C), 129.1 (2C), 129.3 (3C), 129.6 (3C), 134.1, 134.3, 136.4, 145.2, 160.0, 191.6, 199.3. **ESI-MS** m/z: calcd for $C_{25}H_{24}O_5SNa$: 459.12. Found: 459.13 $[M + Na]^+$. **Anal. Calcd** for $C_{25}H_{24}O_5S$ (436.52): C, 68.79; H, 5.54. Found: C, 68.67; H, 5.45.

1-phenyl-2-((phenylsulfonyl)(p-tolyl)methyl)butane-1,3-dione (7d):



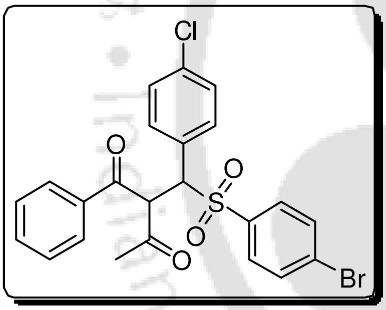
Nature: White solid; mp 169-171 °C; **IR** (KBr): 3420, 3070, 3036, 2951, 2921, 2859, 1715, 1671, 1596, 1582, 1517, 1449, 1360, 1311, 1296, 1265, 1215, 1185, 1150, 1072, 1085, 1024, 997, 964, 808, 753, 721, 706 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 2.46 (s, 3H), 5.31 (d, J = 11.2 Hz, 1H), 5.86 (d, J = 11.2 Hz, 1H), 6.82 (s, 4H), 7.37 (t, J = 8.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.46 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.6 Hz, 2H), 7.91 (d, J = 7.2 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.3, 29.6, 61.2, 71.3, 128.0, 128.9 (3C), 129.0 (2C), 129.1 (2C), 129.2 (2C), 129.3 (3C), 134.1, 134.3, 136.4, 137.0, 139.0, 191.5, 199.2. **ESI-MS** m/z: calcd for $C_{24}H_{22}O_4SH^+$: 407.13. Found: 407.12 $[M + H]^+$. **Anal. Calcd** for $C_{24}H_{22}O_4S$ (406.49): C, 70.91; H, 5.46. Found: C, 70.79; H, 5.37.

2-(((4-chlorophenyl)sulfonyl)(3,4,5-trimethoxyphenyl)methyl)-1-phenylbutane-1,3-dione (7e):



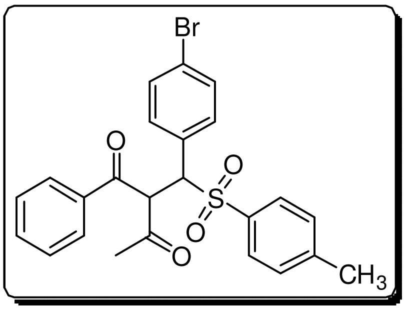
Nature: White solid; mp 211-213 °C; **IR** (KBr): 3435, 3085, 2995, 2959, 2935, 2839, 1714, 1672, 1592, 1512, 1476, 1464, 1448, 1428, 1396, 1360, 1317, 1280, 1149, 1129, 1039, 1014, 999, 956, 834, 765 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.45 (s, 6H), 3.71 (s, 3H), 5.27 (d, *J* = 10.8 Hz, 1H), 5.88 (d, *J* = 11.2 Hz, 1H), 6.04 (s, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.45 (s, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.9, 55.9 (2C), 59.9, 61.0, 71.5, 125.8, 128.9 (3C), 129.2 (3C), 129.3 (2C), 130.8 (3C), 134.5, 135.4, 136.5, 138.5, 141.1, 153.0, 191.3, 198.5. **ESI-MS** m/z: calcd for $C_{26}H_{25}ClO_7SNa$: 539.09. Found: 539.15 $[M + Na]^+$. **Anal. Calcd** for $C_{26}H_{25}ClO_7S$ (516.99): C, 60.40; H, 4.87. Found: C, 60.26; H, 4.75.

2-(((4-bromophenyl)sulfonyl)(4-chlorophenyl)methyl)-1-phenylbutane-1,3-dione (7f):



Nature: White solid; mp 201-203 °C; **IR** (KBr): 3428, 3089, 3067, 2955, 2924, 2853, 1716, 1667, 1595, 1573, 1494, 1470, 1449, 1416, 1389, 1360, 1318, 1310, 1272, 1169, 1151, 1091, 1083, 1067, 1016, 1009, 963, 819, 760, 735, 712, 703 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 5.34 (d, *J* = 11.2 Hz, 1H), 5.83 (d, *J* = 11.2 Hz, 1H), 6.95 (s, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.8, 60.8, 70.8, 128.9 (3C), 129.0 (2C), 129.3 (2C), 129.6, 130.0, 130.7 (3C), 132.5 (2C), 134.6, 135.4, 135.9, 136.2, 191.1, 198.5. **ESI-MS** m/z: calcd for $C_{23}H_{18}BrClO_4SNa$: 528.97. Found: 529.02 $[M + Na]^+$. **Anal. Calcd** for $C_{23}H_{18}BrClO_4S$ (505.80): C, 54.61; H, 3.59. Found: C, 54.43; H, 3.47.

2-((4-bromophenyl)(tosyl)methyl)-1-phenylbutane-1,3-dione (7g):



Nature: White solid; mp 178-180 °C; **IR** (KBr): 3424, 3058, 2968, 2925, 1714, 1670, 1595, 1557, 1489, 1447, 1426, 1386, 1317, 1304, 1286, 1262, 1186, 1151, 1086, 1073, 1012, 962, 814, 760, 738, 720 cm^{-1}. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 2.47 (s, 3H), 5.32 (d, *J* = 11.2 Hz, 1H), 5.86 (d, *J* = 10.8 Hz, 1H), 6.87 (s, 2H), 7.21 (t, *J* = 7.6 Hz, 4H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H); ^{13}**C NMR** (150 MHz, $CDCl_3$): δ 21.9, 29.8, 61.0, 70.9, 123.4, 129.1 (2C), 129.3 (5C), 129.8 (2C), 130.6, 131.8 (3C), 133.8, 134.6, 136.2, 145.6, 191.3, 198.7. **ESI-MS** m/z: calcd for $C_{24}H_{21}BrO_4SNa$: 509.02. Found: 509.16 $[M + Na]^+$. **Anal. Calcd** for $C_{24}H_{21}BrO_4S$ (485.39): C, 59.39; H, 4.36. Found: C, 59.28; H, 4.27.

Crystallographic description:

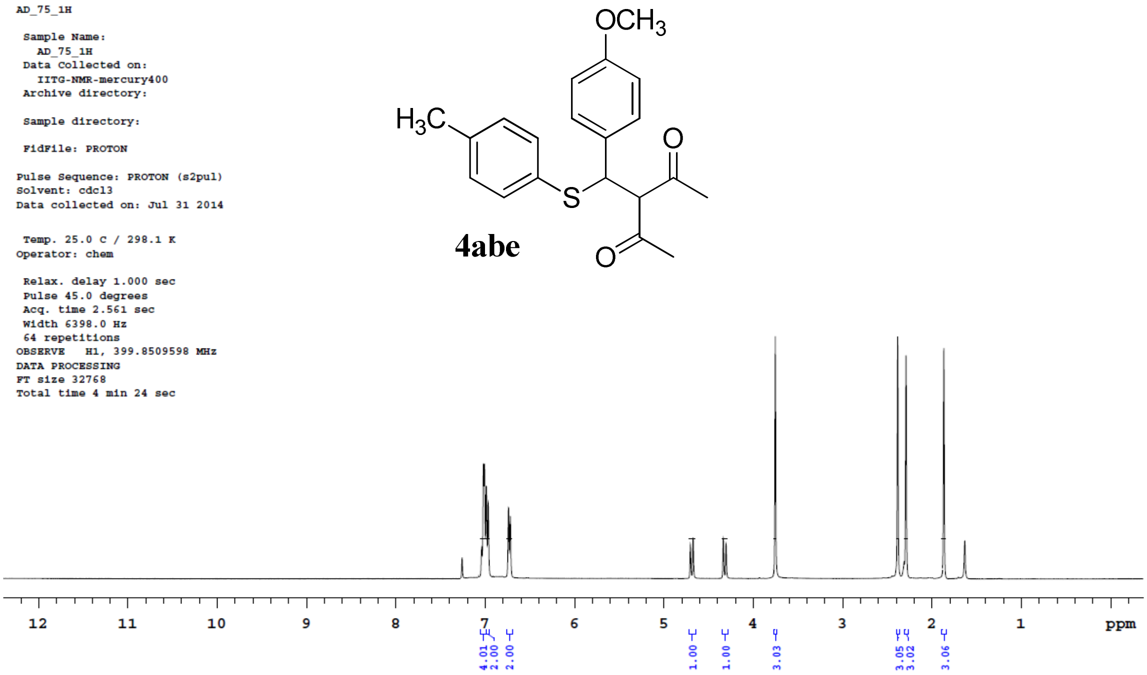
Complete crystallographic data of **4aac**, **5cad**, **6c** and **7a** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1019727, 958054, 930603 and 958055 respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 2.7. Crystal data and structures refinement for **4aac, 5cad, 6c** and **7a**. For atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check the CIF.

Compound reference	**4aac**	**5cad**	**6c**	**7a**
Chemical formula	$C_{19}H_{20}O_2S_1$	$C_{23}H_{20}O_2S_1$	$C_{19}H_{20}O_4S_1$	$C_{23}H_{22}O_4S_1$
Formula Mass	312.41	360.45	344.41	392.45
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
a/Å	16.054 (3)	5.5396(7)	5.4460 (4)	5.614 (2)
b/Å	5.3498 (6)	10.8167(13)	16.8784 (17)	32.096 (12)
c/Å	20.105 (3)	17.091(2)	19.1283 (14)	11.011 (2)
α/°	90.00	72.010(6)	90.00	90.00
β/°	106.442 (15)	81.369(6)	91.083 (7)	101.47(3)
γ/°	90.00	78.119(6)	90.00	90.00

Unit cell volume/Å^3	1656.1 (4)	949.0(2)	1757.9 (3)	1944.6 (12)
Temperature/K	293 K	296 K	293 K	293 K
Space group	P2(1)/c	P-1	P2(1)/c	P2(1)/a
No. of formula units per unit cell, Z	4	2	4	4
Radiation type	Mo K\a	Mo K\a	Mo K\a	Mo K\a
Absorption coefficient, μ/mm^{-1}	0.200	0.184	0.203	0.193
No. of reflections measured	2892	3276	3095	3428
No. of independent reflections	1321	1744	1432	2453
R_{int}	0.1347	0.1192	0.0646	0.0551
Final R_1 values ($I > 2\sigma(I)$)	0.1746	0.0703	0.0730	0.0671
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.4331	0.2114	0.0999	0.1422
Final R_1 values (all data)	0.2699	0.1117	0.1683	0.0974
Final $wR(F^2)$ values (all data)	0.5445	0.2258	0.1413	0.1654
Goodness of fit on F^2	1.630	1.007	1.049	1.050
CCDC number	1019727	958054	930603	958055

^{1}***H NMR (400 MHz, CDCl$_3$):*** *3-((4-methoxyphenyl)(p-tolylthio)methyl)pentane-2,4-dione* (**4abe**)



AD_75_1H

Sample Name:
AD_75_1H
Data Collected on:
IITG-NMR-mercury400
Archive directory:

Sample directory:

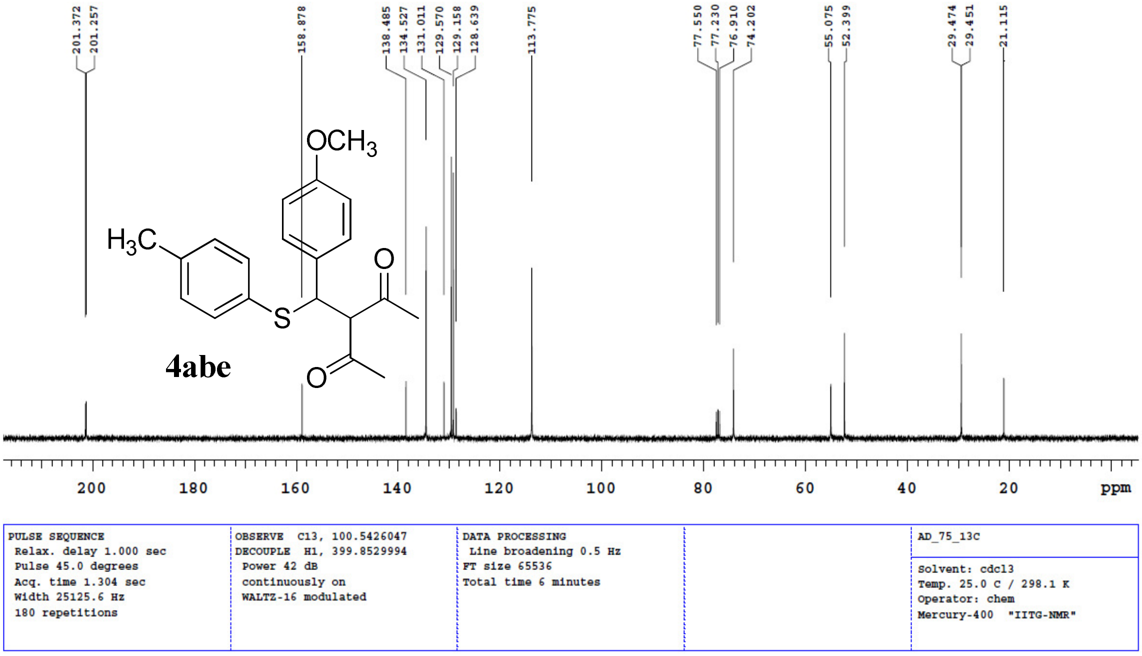
FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 31 2014

Temp. 25.0 C / 298.1 K
Operator: chem

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
64 repetitions
OBSERVE H1, 399.8509598 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec

^{13}***C NMR (100 MHz, CDCl$_3$):*** *3-((4-methoxyphenyl)(p-tolylthio)methyl)pentane-2,4-dione* (**4abe**)



PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
180 repetitions

OBSERVE C13, 100.5426047
DECOUPLE H1, 399.8529994
Power 42 dB
continuously on
WALTZ-16 modulated

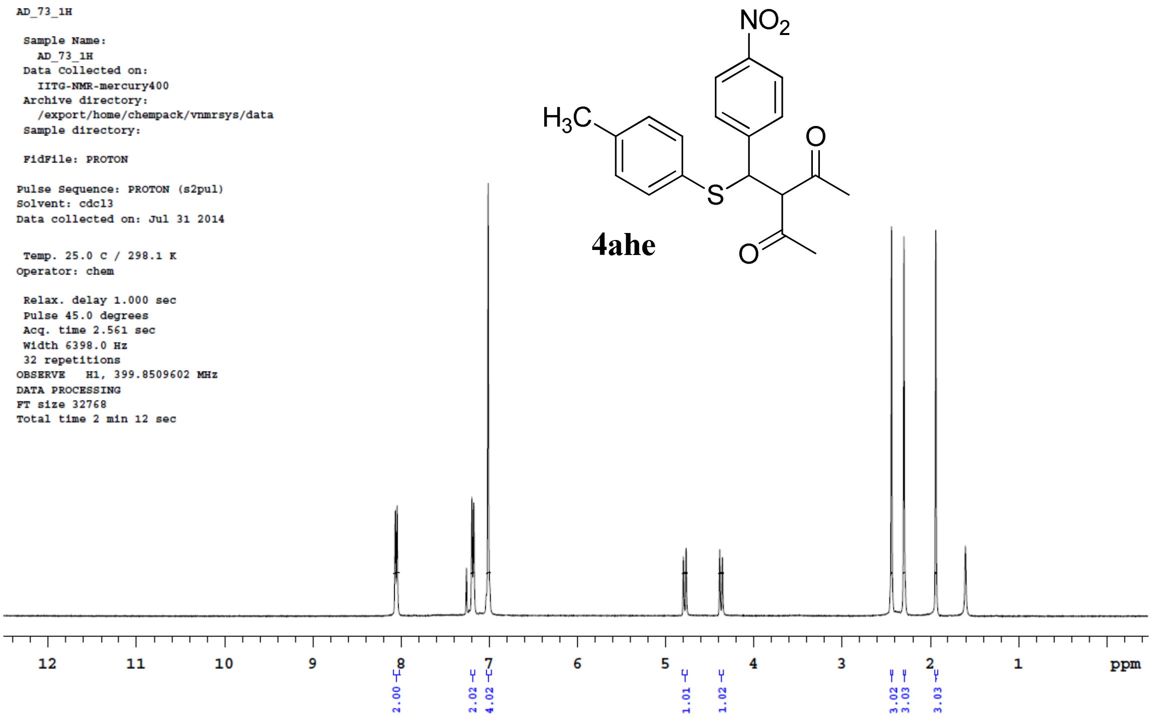
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 6 minutes

AD_75_13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400 "IITG-NMR"

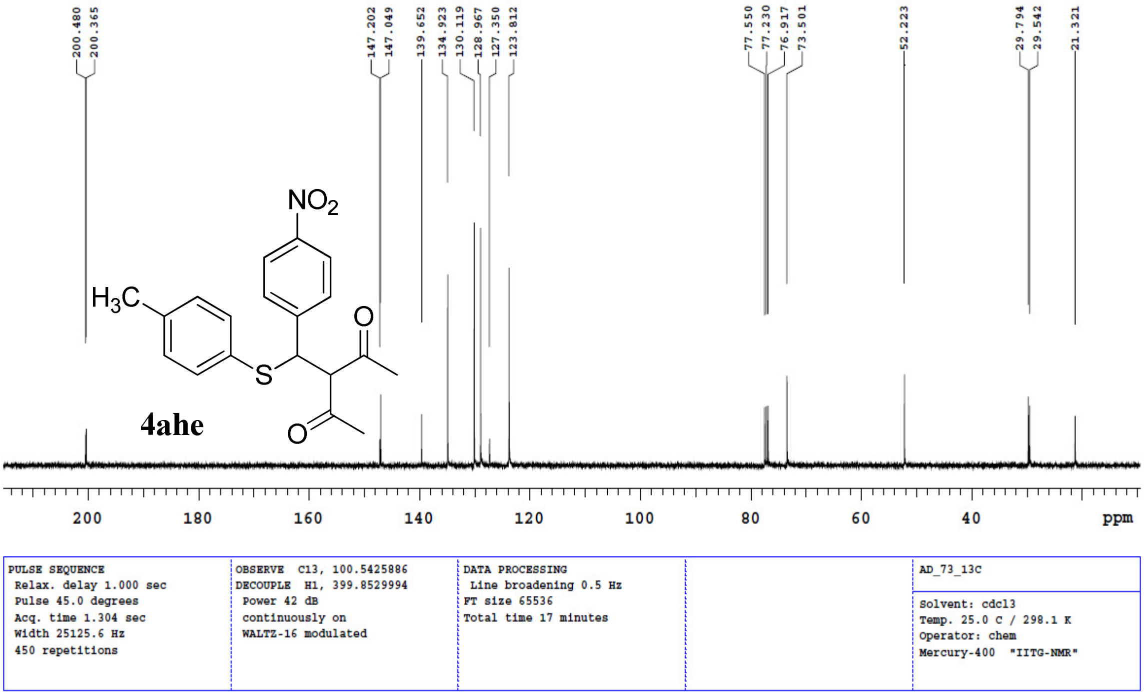
Figure 2.8

***^{1}H NMR (400 MHz, CDCl$_3$)**: 3-((4-nitrophenyl)(p-tolylthio)methyl)pentane-2,4-dione* (**4ahe**)



```
AD_73_1H

 Sample Name:
   AD_73_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 31 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions
OBSERVE   H1, 399.8509602 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 12 sec
```

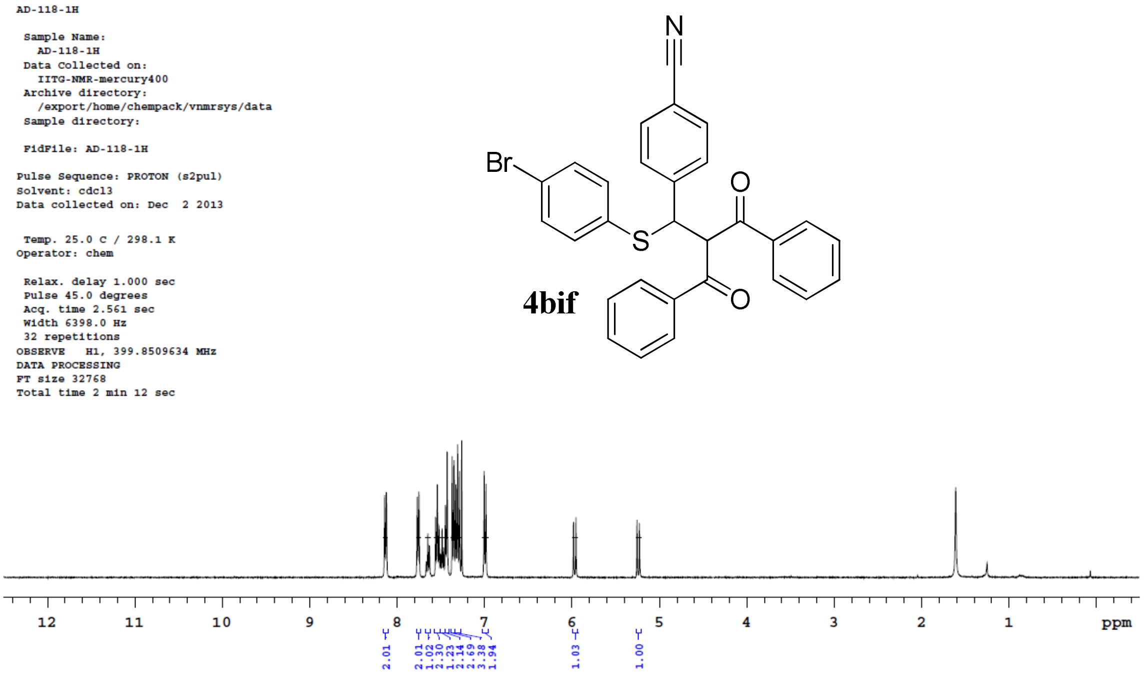
***^{13}C NMR (100 MHz, CDCl$_3$)**: 3-((4-nitrophenyl)(p-tolylthio)methyl)pentane-2,4-dione* (**4ahe**)



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 450 repetitions

OBSERVE  C13, 100.5425886
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 17 minutes

AD_73_13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

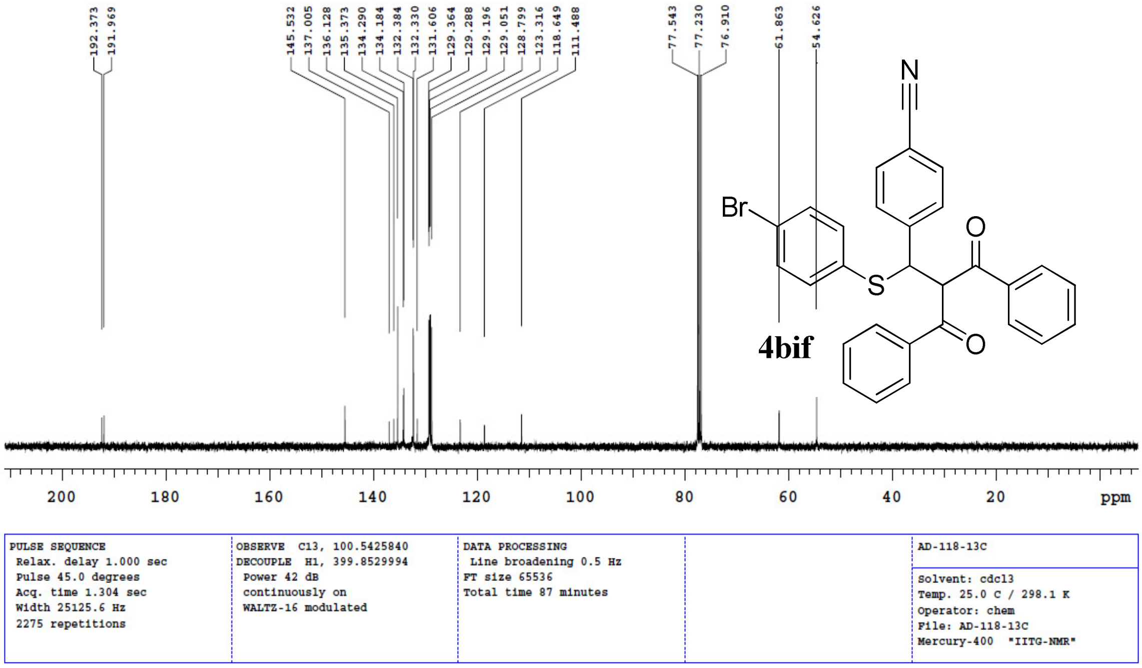
Figure 2.9

^{1}H NMR (400 MHz, CDCl$_3$): *4-(2-benzoyl-1-((4-bromophenyl)thio)-3-oxo-3-phenylpropyl)benzonitrile* (**4bif**)



```
AD-118-1H

 Sample Name:
   AD-118-1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: AD-118-1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec  2 2013


 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 12 sec
```

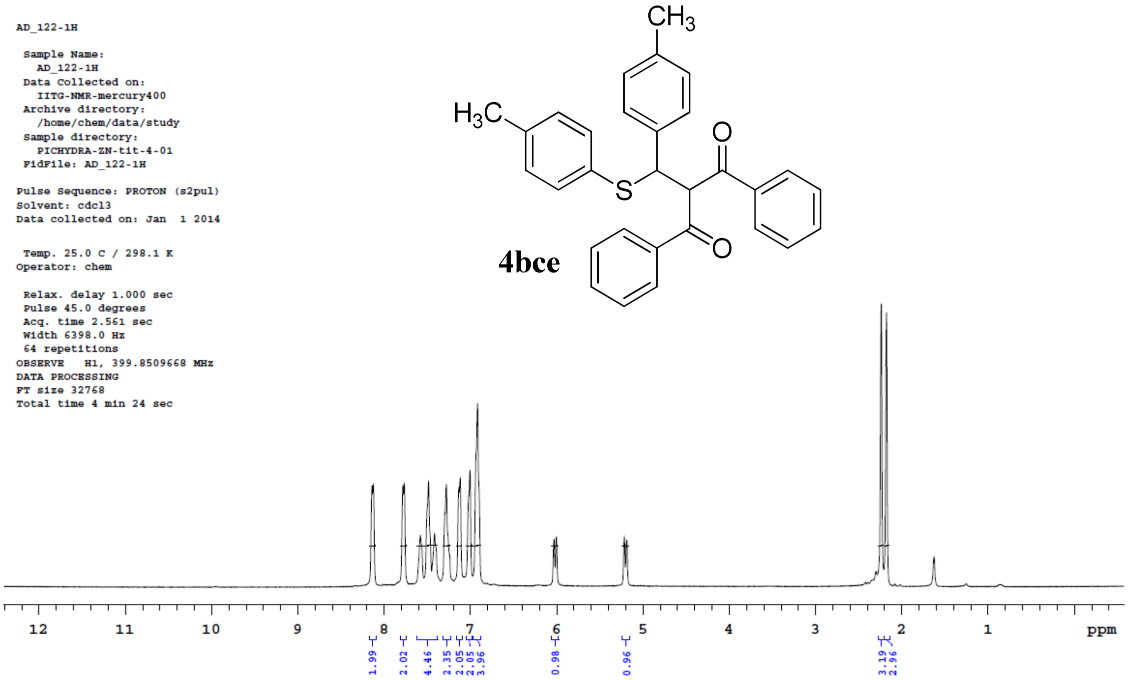
^{13}C NMR (100 MHz, CDCl$_3$): *4-(2-benzoyl-1-((4-bromophenyl)thio)-3-oxo-3-phenylpropyl)benzonitrile* (**4bif**)



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 2275 repetitions

OBSERVE  C13, 100.5425840
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 87 minutes

AD-118-13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: AD-118-13C
Mercury-400  "IITG-NMR"
```

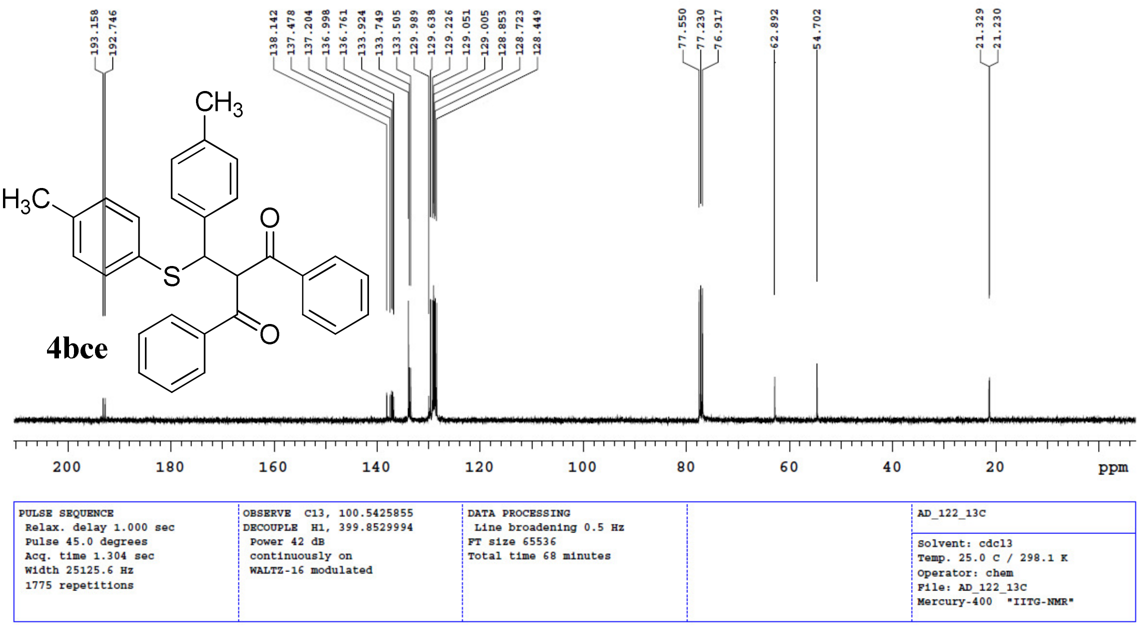
Figure 2.10

^{1}H NMR (400 MHz, CDCl$_3$): *1,3-diphenyl-2-(p-tolyl(p-tolylthio)methyl)propane-1,3-dione* (**4bce**)



```
AD_122-1H

 Sample Name:
   AD_122-1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /home/chem/data/study
 Sample directory:
   PICHYDRA-ZN-tit-4-01
 FidFile: AD_122-1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan  1 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509668 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```

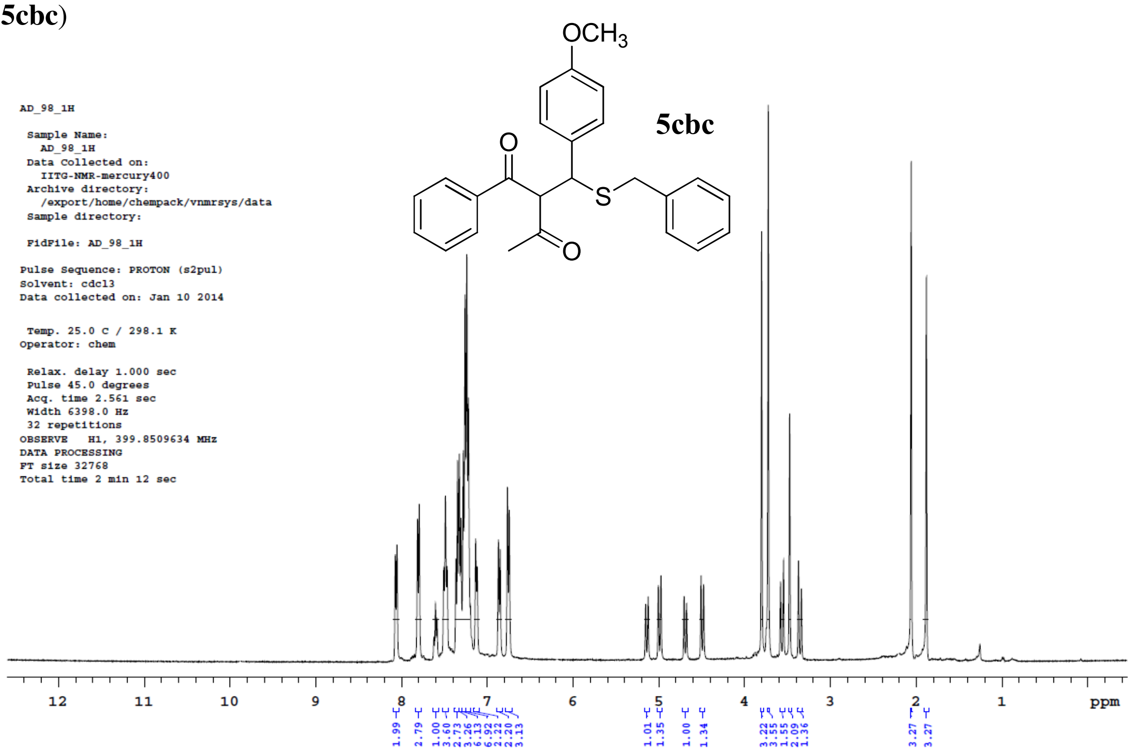
^{13}C NMR (100 MHz, CDCl$_3$): *1,3-diphenyl-2-(p-tolyl(p-tolylthio)methyl)propane-1,3-dione* (**4bce**)



```
PULSE SEQUENCE            OBSERVE  C13, 100.5425855   DATA PROCESSING            AD_122_13C
 Relax. delay 1.000 sec   DECOUPLE  H1, 399.8529994    Line broadening 0.5 Hz
 Pulse 45.0 degrees        Power 42 dB               FT size 65536              Solvent: cdcl3
 Acq. time 1.304 sec       continuously on           Total time 68 minutes      Temp. 25.0 C / 298.1 K
 Width 25125.6 Hz          WALTZ-16 modulated                                   Operator: chem
 1775 repetitions                                                               File: AD_122_13C
                                                                                Mercury-400  "IITG-NMR"
```

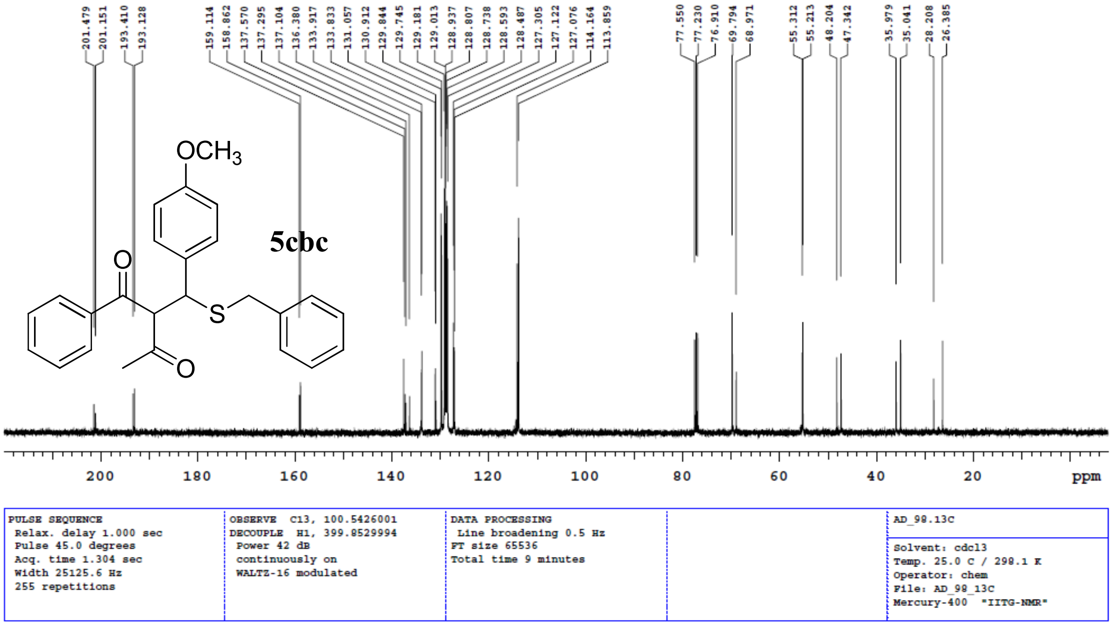
Figure 2.11

***^{1}H NMR (400 MHz, CDCl$_3$)**: 2-((benzylthio)(4-methoxyphenyl)methyl)-1-phenylbutane-1,3-dione* (**5cbc**)



```
AD_98_1H

 Sample Name:
   AD_98_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: AD_98_1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 10 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 12 sec
```

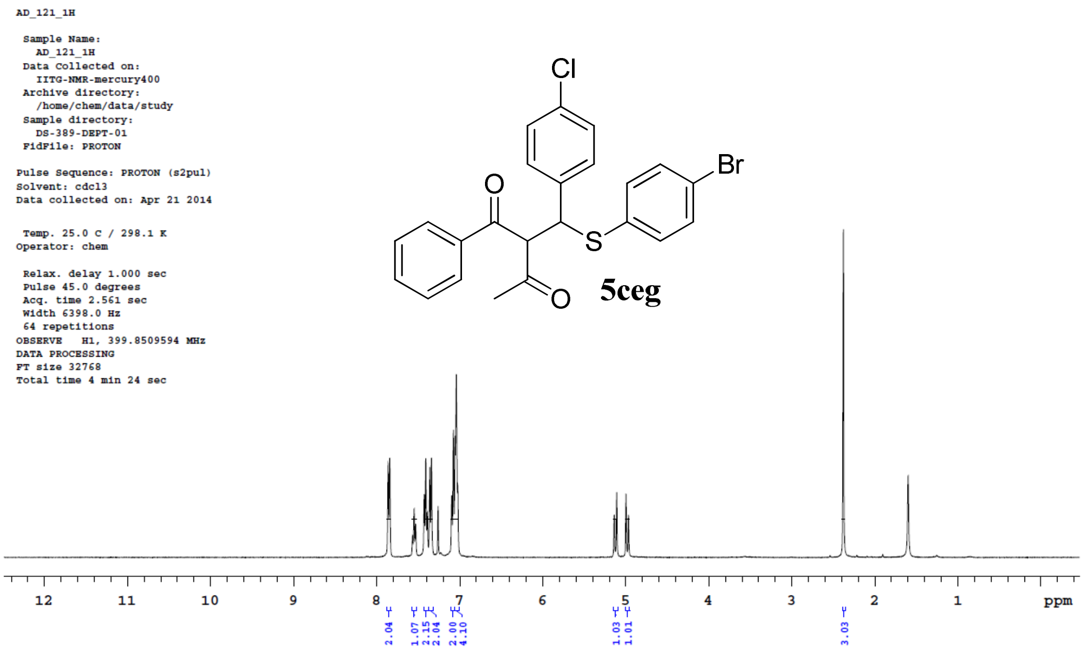
***^{13}C NMR (100 MHz, CDCl$_3$)**: 2-((benzylthio)(4-methoxyphenyl)methyl)-1-phenylbutane-1,3-dione* (**5cbc**)



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 255 repetitions

OBSERVE  C13, 100.5426001
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 9 minutes

AD_98.13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: AD_98_13C
Mercury-400  "IITG-NMR"
```

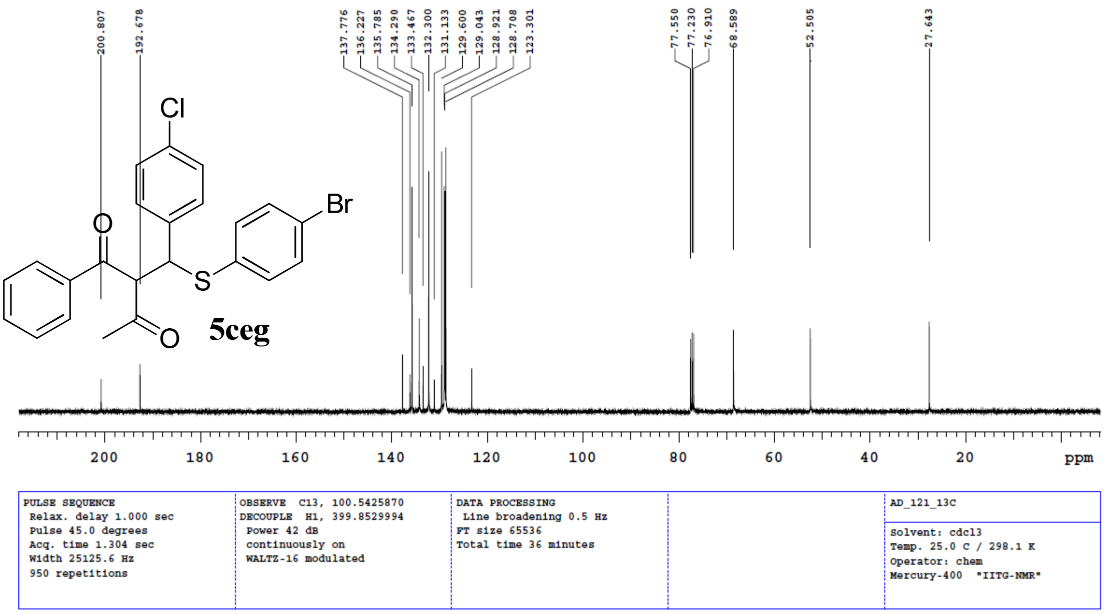
Figure 2.12

^{1}H NMR (400 MHz, CDCl$_3$)*: 2-(((4-bromophenyl)thio)(4-chlorophenyl)methyl)-1-phenylbutane-1,3-dione* (**5ceg**)



```
AD_121_1H

 Sample Name:
   AD_121_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /home/chem/data/study
 Sample directory:
   DS-389-DEPT-01
 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 21 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509594 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```

^{13}C NMR (100 MHz, CDCl$_3$)*: 2-(((4-bromophenyl)thio)(4-chlorophenyl)methyl)-1-phenylbutane-1,3-dione* (**5ceg**)



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 950 repetitions
```

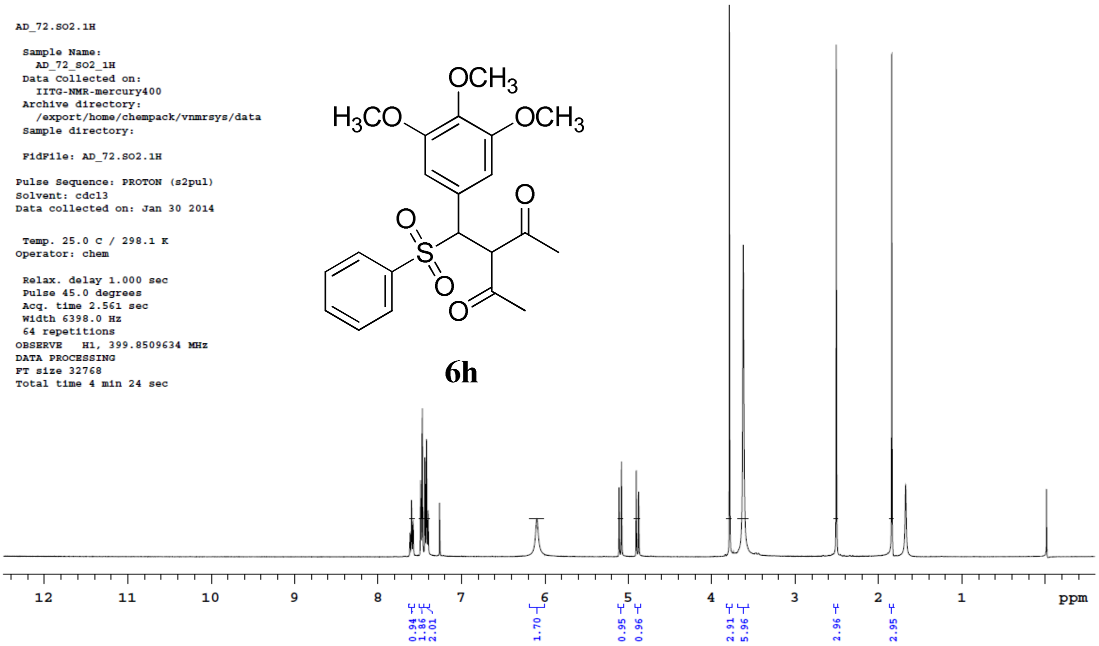
```
OBSERVE  C13, 100.5425870
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated
```

```
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 36 minutes
```

```
AD_121_13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

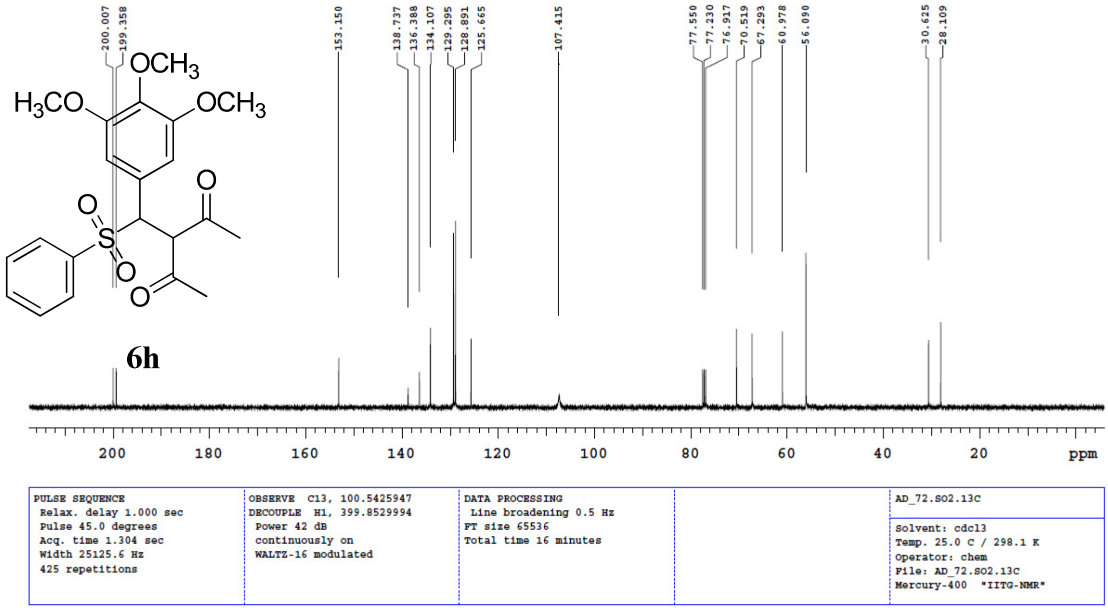
Figure 2.13

^{1}H NMR (400 MHz, CDCl$_3$): *3-((phenylsulfonyl)(3,4,5-trimethoxyphenyl)methyl)pentane-2,4-dione* (**6h**)



```
AD_72.SO2.1H

 Sample Name:
   AD_72_SO2_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: AD_72.SO2.1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 30 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```

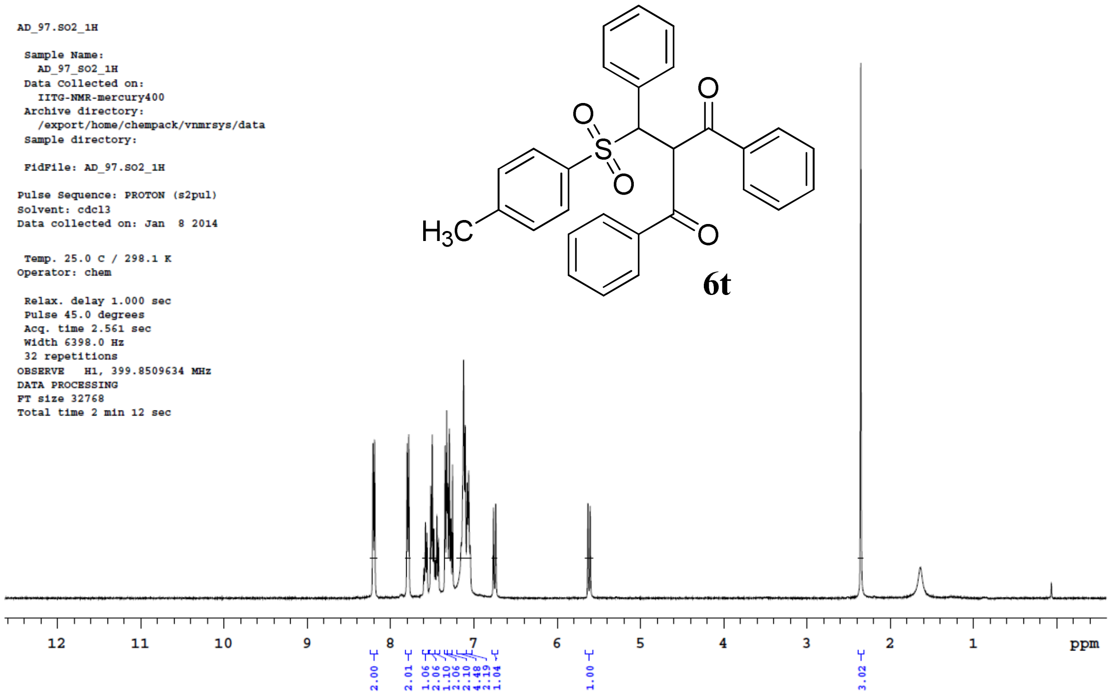
^{13}C NMR (100 MHz, CDCl$_3$): *3-((phenylsulfonyl)(3,4,5-trimethoxyphenyl)methyl)pentane-2,4-dione* (**6h**)



```
PULSE SEQUENCE              OBSERVE  C13, 100.5425947   DATA PROCESSING                AD_72.SO2.13C
 Relax. delay 1.000 sec     DECOUPLE  H1, 399.8529994    Line broadening 0.5 Hz
 Pulse 45.0 degrees          Power 42 dB               FT size 65536                  Solvent: cdcl3
 Acq. time 1.304 sec         continuously on           Total time 16 minutes          Temp. 25.0 C / 298.1 K
 Width 25125.6 Hz            WALTZ-16 modulated                                       Operator: chem
 425 repetitions                                                                      File: AD_72.SO2.13C
                                                                                      Mercury-400  "IITG-NMR"
```

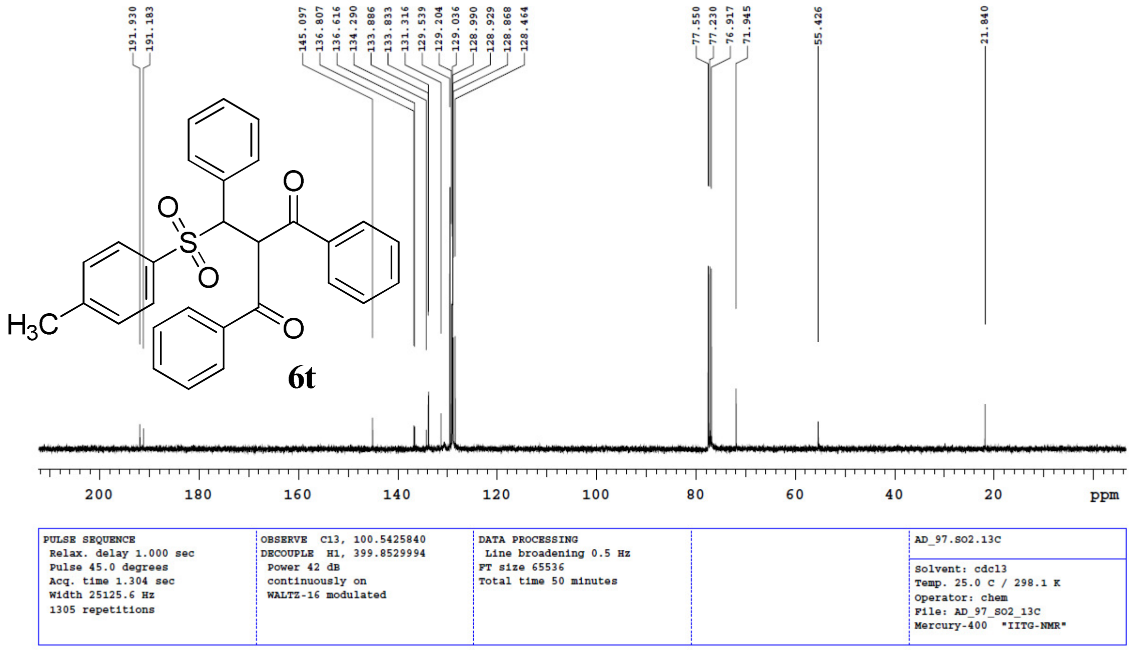
Figure 2.14

^{1}H NMR (400 MHz, CDCl$_3$): *1,3-diphenyl-2-(phenyl(tosyl)methyl)propane-1,3-dione* (**6t**)



```
AD_97.SO2_1H

 Sample Name:
   AD_97_SO2_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: AD_97.SO2_1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan  8 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 12 sec
```

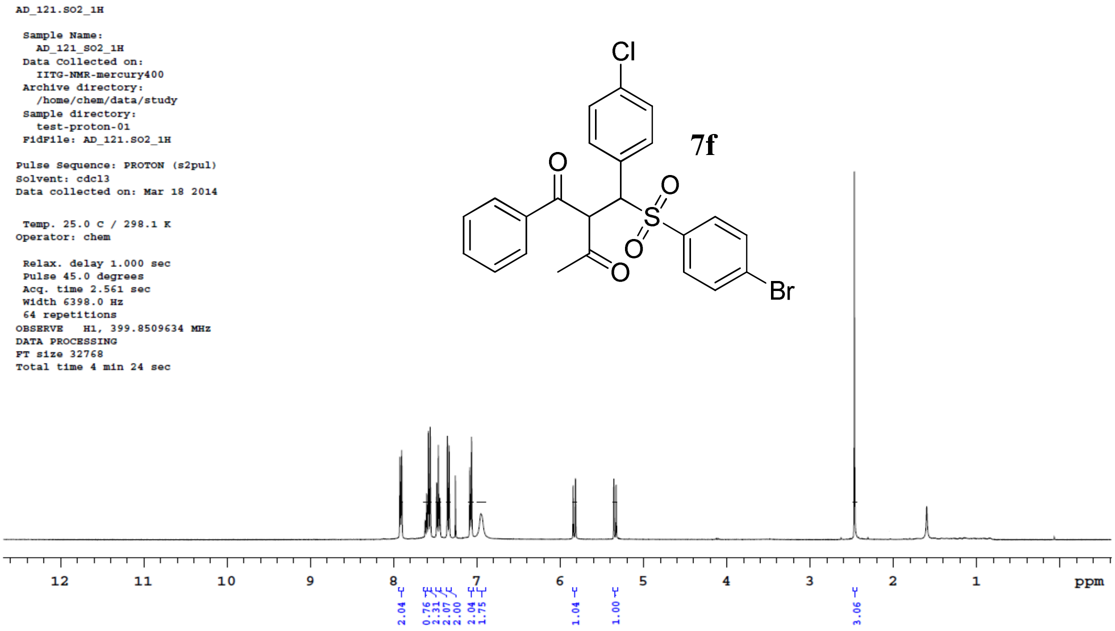
^{13}C NMR (100 MHz, CDCl$_3$): *1,3-diphenyl-2-(phenyl(tosyl)methyl)propane-1,3-dione* (**6t**)



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 1305 repetitions

OBSERVE  C13, 100.5425840
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 50 minutes

AD_97.SO2.13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: AD_97_SO2_13C
Mercury-400  "IITG-NMR"
```

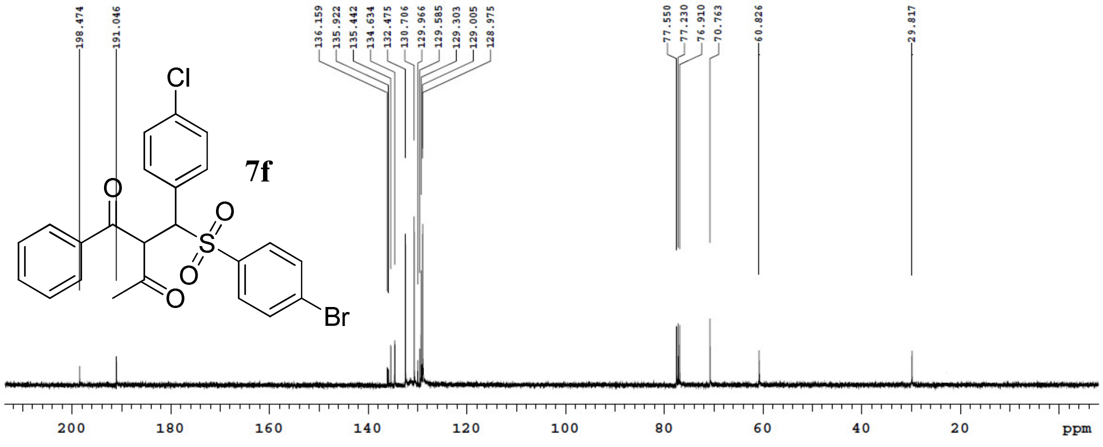
Figure 2.15

^{1}H NMR (400 MHz, CDCl$_3$): *2-(((4-bromophenyl)sulfonyl)(4-chlorophenyl)methyl)-1-phenylbutane-1,3-dione* (**7f**)



```
AD_121.SO2_1H

 Sample Name:
   AD_121_SO2_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /home/chem/data/study
 Sample directory:
   test-proton-01
 FidFile: AD_121.SO2_1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 18 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```

^{13}C NMR (100 MHz, CDCl$_3$): *2-(((4-bromophenyl)sulfonyl)(4-chlorophenyl)methyl)-1-phenylbutane-1,3-dione* (**7f**)



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 408 repetitions

OBSERVE  C13, 100.5425855
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
Total time 15 minutes

AD-121_SO2-13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

Figure 2.16

2.3 References

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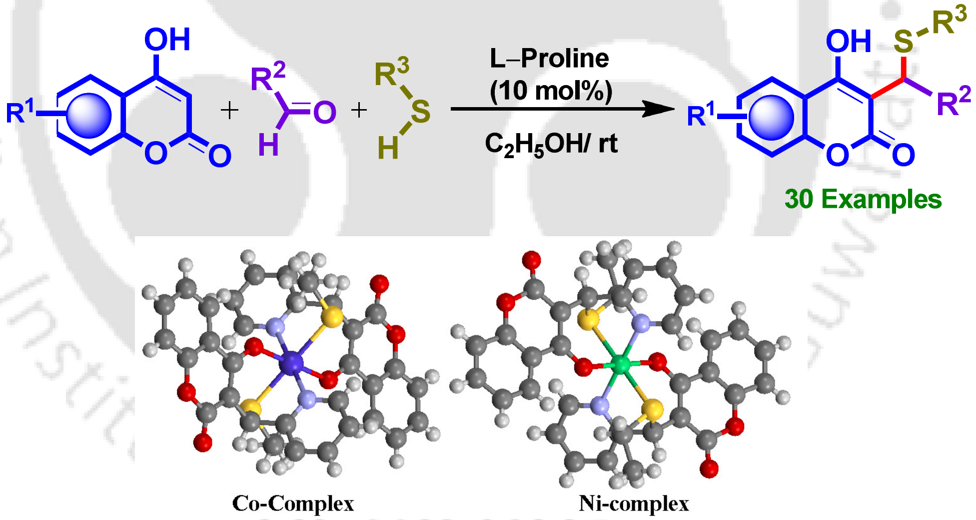
Chapter 3

One-pot synthesis of functionalized 4-hydroxy-3-thiomethylcoumarins: Detection and discrimination of Co^{2+} and Ni^{2+} ions



CHAPTER 3: Results and Discussion

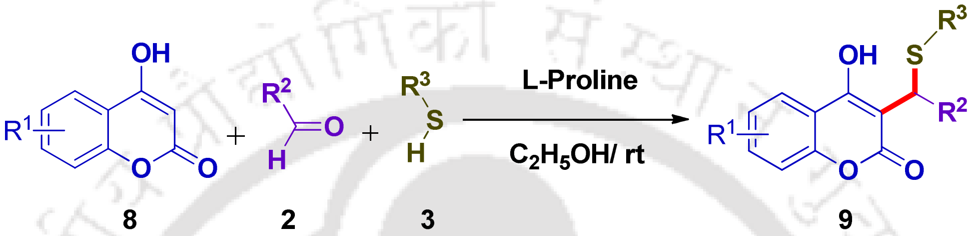
3.1 Results and Discussion

Among various substituted coumarins, 3-substituted 4-hydroxycoumarin is one of the active classes of compounds possessing a wide spectrum of biological activity.[1] 3-Benzyl substituted 4-hydroxycoumarin derivatives are constituents of natural products like warfarin, phenprocoumon, coumatetralyl and bromadialone. 4-Hydroxycoumarin derivatives have been widely used for curing myocardial infarction, strokes and venous thromboembolism.[2] These compounds are recognized to possess anti-inflammatory, antithrombotic, anticoagulant, antioxidant, antibacterial, anthelminthic and anti-HIV activities.[3] 4-Hydroxycoumarin derivatives are potent inhibitors of NAD(P)H, Quinone Oxidoreductase-1 (NQO1)[4] and metalloenzyme carbonic anhydrase (CA).[5] They have potential anti-acetylcholinesterase (AChE) inhibitors as therapeutics for Alzheimer's disease.[6]

In the present chapter, we have shown the synthesis of a wide variety of 4-hydroxy-3-thiomethylcoumarin derivatives. Photophysical studies of 4-hydroxy-3-thiomethyl-coumarin derivative revealed as fluorescence probe that displays remarkable changes in its optical properties in presence of cobalt and nickel ions in aqueous based media. Coumarin derived molecules also act as promising fluorescent probes[7] due to their excellent photophysical properties.[8] The compound **9ata** displays a remarkable change in its optical properties only in the presence of cobalt and nickel in aqueous based media. The probe is based on fluorescence "turn-off" strategy and the binding of these two metals with compound **9ata** forms non-fluorescent complexes, confirmed *via* single crystal X-ray structures. Moreover, the two metals can be distinguished by EDTA induced fluorescence recovery that was only possible towards cobalt (II) complex. This unique yet simple strategy for metal detection is rare and serves as an efficient probe for the detection and discrimination of cobalt and nickel metals.

Cobalt is found in cobalamins[9] and acts as a cofactor in Vitamin B_{12}. Apart from its biological importance in metabolisms, its exposure at high levels can cause severe health problems[10] *viz.* mutagenesis, cardio-toxicity, asthma, lung-fibrosis, elevation of blood cells and allergic contact dermatitis. Nickel has applications in Ni-Cd batteries, electroplating, pigments for paints, ceramics, catalysts for hydrogenation and in electronic industries. In excess, it is also responsible for several diseases[11] related to the respiratory and central nervous system. These metal ions can be easily contaminated in the environment[12] *via* burning of coal and oil, truck and aircraft exhausts, diamond polishing, porcelain, volcanic eruptions and chemical industries. Thus, the development of highly sensitive probes to monitor the presence of these metals in industrial, environmental and food samples for maintaining good human health is of immense significance.

We have developed a selective C-3 alkylation based on a three-component strategy involved *via* a domino process comprising a Knoevenagel type condensation between 4-hydroxycoumarin and aldehyde, followed by a thia-Michael addition onto the resulting unsaturated ketone and generation of 4-hydroxy-3-thiomethylcoumarin derivatives (Scheme 3.1).



R^1 = H (8a)

R^2 = Ph (2a), 4-MeOPh (2b), 4-MePh (2c), 4-ClPh (2e), 4-BrPh (2f), 4-OHPh (2g), 4-NO_2Ph (2h), 4-CNPh (2i), 2-Naphthyl (2l), 2-NO_2Ph (2m), 2-ClPh (2o), 2-BrPh (2s), 2-pryidyl (2t), 2-thiopenyl (2u), 4-FPh (2v), 2,4-MeOPh (2w), cyclohexyl (2x), propylene (2y)

R^3 = Et (3a), Pr (3b), $PhCH_2$ (3c), Ph (3d), 4-MePh (3e), 4-ClPh (3f), 4-BrPh (3g), 2-Naphthyl (3h), 4-MeOPh (3i), 2-$ClPhCH_2$ (3j), 2-ClPh (3k), 2-BrPh (3l), $HOCH_2CH_2$ (3m)

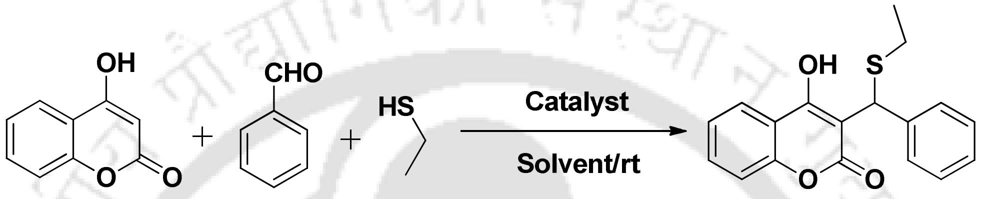
Scheme 3.1. Synthesis of 3-(alkyl/aryl(alkyl/arylthio)methyl) substituted 4-hydroxy coumarins.

4-hydroxy-3-thiomethylcoumarin derivative were synthesized in a one-pot reaction with 4-hydroxycoumarin, benzaldehyde and ethanethiol in 3 mL of ethanol at room temperature (Table 3.1). The reaction was carried out with L-proline as catalyst with different catalyst loading as shown in Table 3.1 (Entries 2-5). It was found that 10 mol% of the catalyst provided 83% yield (Table 3.1, entry 3). Further increase in the catalyst loading did not improve the yield of product significantly.

Other catalysts such as triethylamine (Et_3N), *p*-toluenesulfonic acid (*p*-TsOH), ferric sulfate ($Fe_2(SO_4)_3$), iodine (I_2), and tetrabutylammonium bromide (TBAB) resulted in lower yield (Table 3.1, entries 6-10). Different solvents like acetonitrile, methanol, dichloroethane, dicholoromethane and dimethylsulfoxide, using 10 mol% of L-proline (Table 3.1, entries 11-15) resulted in no increment in the yield.

The isolated product (**9aaa)** was fully characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and by HRMS. The signals appear in the ^{1}H NMR spectrum at δ 1.34 (t, J = 6.8 Hz, 3H), 7.58-7.72 (m, 2H), 5.77 (s, 1H), 7.25-7.30 (m, 5H), 7.44 (d, J = 6.0 Hz, 2H), 7.53 (t, J = 6.4 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 10.85 (s, 1H, OH). The signals at δ 5.77 for methine proton and 10.85 for OH group clearly indicate the formation of the desired product. Similarly, the various peaks obtained in the ^{13}C NMR spectrum are at δ 14.0, 26.8, 45.4, 101.3, 116.0, 116.5, 123.5, 124.2, 127.8 (2C), 128.1, 129.0 (2C), 132.6, 137.9, 152.9, 162.9, 163.6 and the characteristic peak at δ 45.4 resulting only due to the formation of product.

Table 3.1. Optimization of reaction conditions[a]



8a 2a 3a 9aaa

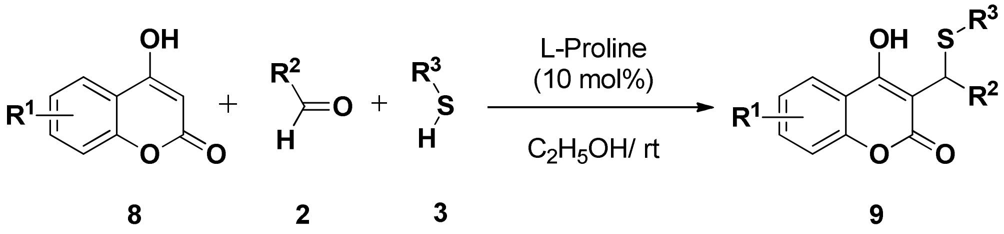
Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	No catalyst	C_2H_5OH	12	--[c]
2	Proline (5)	C_2H_5OH	7.0	40
3	**Proline (10)**	**C_2H_5OH**	**3.0**	**83**
4	Proline (15)	C_2H_5OH	3.0	84
5	Proline (20)	C_2H_5OH	3.0	86
6	Et_3N (10)	C_2H_5OH	6.0	35
7	*p*-TsOH (10)	C_2H_5OH	5.0	45
8	$Fe_2(SO_4)_3$(10)	C_2H_5OH	5.0	40
9	I_2(10)	C_2H_5OH	6.0	42
10	TBAB (10)	C_2H_5OH	7.0	38
11	Proline (10)	CH_3CN	3.0	69
12	Proline (10)	CH_3OH	3.0	73
13	Proline (10)	$C_2H_4Cl_2$	3.0	65
14	Proline (10)	CH_2Cl_2	3.0	60
15	Proline (10)	DMSO	3.0	67

[a]Reaction conditions: 4-Hydroxycoumarin (1 mmol), benzaldehyde (1 mmol), ethanethiol (1.2 mmol), at room temperature. [b]Isolated yield. [c]No product was formed.

It is noteworthy to mention that the sequence of addition of the aldehyde, catalyst and coumarin, as well as the subsequent addition of thiol to the reaction mixture is very important as coumarin has a tendency to form biscoumarin derivatives in the presence of aldehyde.

Having the optimized reaction condition, the substrate scope of the protocol was examined (Table 3.2). Initially 4-hydroxycoumarin (**8a**) and benzaldehyde (**2a**) were treated with a series of aliphatic thiols (**3**) to observe the reactivity of different thiols (Table 3.2, entries 1-5). Ethanethiol, propanethiol, benzylthiol and 2-chlorobenzylthiol produced the desired products in comparable yields (**9aaa-9aaj**), however, the yield decreased in case of 2-mercaptoethanol. After examining the aliphatic thiols, we turned our attention towards aromatic thiols keeping all other reactants unaltered. Similar yields were obtained, however, thiol with electron donating functionality reacts slight faster than the electron-withdrawing counterparts (Table 3.2, entries 6-10). 2-naphthalenethiol also underwent the transformation smoothly to produce the expected product (**9aah**) in good yield (Table 3.2, entry 11). After observing the effect of different thiols, we focused towards examining the effect of substituents on the aldehyde. Thiophenol and various aromatic and aliphatic aldehydes (Table 3.2, entries 12-15) were studied. Aromatic aldehydes produced better yields than the aliphatic aldehydes owing to the relative instability of aliphatic aldehydes. It was observed that the electronic factor of the substituents on the aldehyde did not play prominent role, however, the steric factor did. *Para*-substituted derivatives produced much better yields (**9aae-9ahe**) than the *ortho*-substituted derivatives (**9aoe** and **9ame**). Moreover, it was found that 2,4-dimethoxybenzaldehyde also produced the desired product with good yield (**9awe**). Notably, 2-napthyldehyde also reacted smoothly to produce the desired product (**9ale**) in good yield (Table 3.2, entry 26). In the presence of 4-halo substituted thiols, 4-methoxybenzaldehyde and 4-cyanobenzaldehyde reacted with similar efficiency (**9abg** and **9aif**), although the yield was slightly higher in the latter case (Table 3.2, entries 27-28). Heterocyclic aldehydes also worked well to produce the desired products (**9auc** and **9ata**) in good yield (Table 3.2, entries 29-30).

Table 3.2. Synthesis of 4-hydroxy-3-thiomethylcoumarins[a,b]

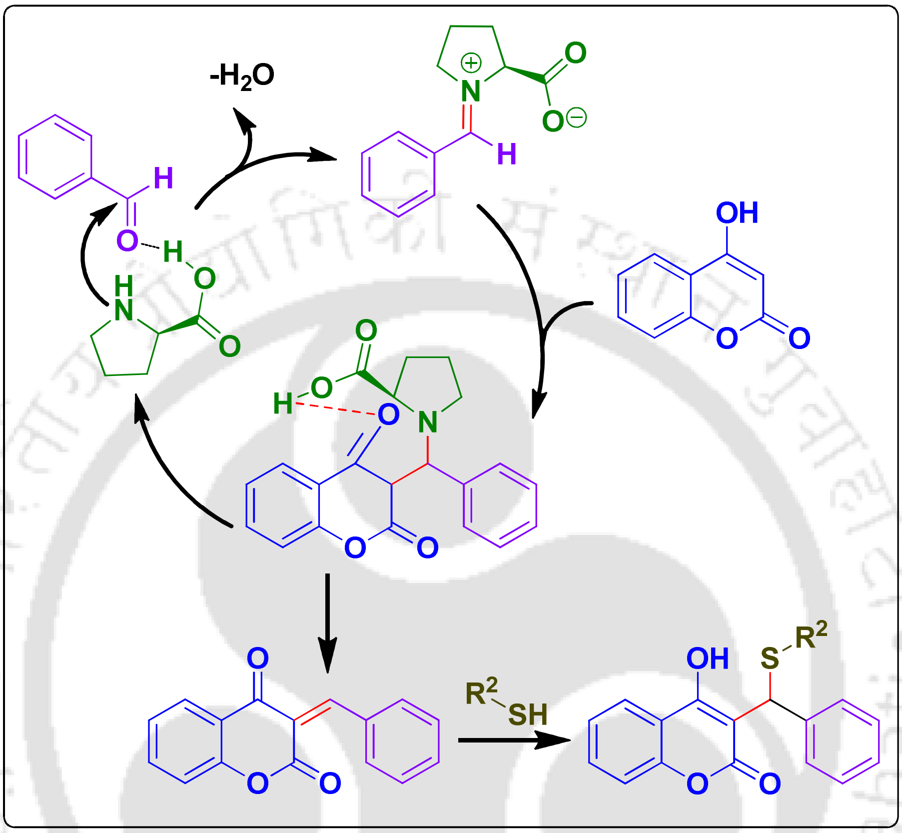


Entry	4-Hydroxycoumarin	Aldehyde	Thiol	Product	Yield (%)[b]
1	**8a**	**2a**	**3a**	**9aaa**	83

2	**8a**	**2a**	**3b**	**9aab**	85
3	**8a**	**2a**	**3c**	**9aac**	76
4	**8a**	**2a**	**3j**	**9aaj**	78
5	**8a**	**2a**	**3m**	**9aam**	60
6	**8a**	**2a**	**3d**	**9aad**	69
7	**8a**	**2a**	**3i**	**9aai**	77
8	**8a**	**2a**	**3f**	**9aaf**	75
9	**8a**	**2a**	**3k**	**9aak**	71
10	**8a**	**2a**	**3l**	**9aal**	73
11	**8a**	**2a**	**3h**	**9aah**	76
12	**8a**	**2g**	**3d**	**9agd**	72
13	**8a**	**2c**	**3d**	**9acd**	67
14	**8a**	**2x**	**3d**	**9axd**	53
15	**8a**	**2y**	**3d**	**9ayd**	50
16	**8a**	**2a**	**3e**	**9aae**	72
17	**8a**	**2g**	**3e**	**9age**	76
18	**8a**	**2b**	**3e**	**9abe**	74
19	**8a**	**2e**	**3e**	**9aee**	77
20	**8a**	**2f**	**3e**	**9afe**	79
21	**8a**	**2v**	**3e**	**9ave**	69
22	**8a**	**2h**	**3e**	**9ahe**	81
23	**8a**	**2o**	**3e**	**9aoe**	62
24	**8a**	**2m**	**3e**	**9ame**	65
25	**8a**	**2w**	**3e**	**9awe**	70
26	**8a**	**2l**	**3e**	**9ale**	79
27	**8a**	**2b**	**3g**	**9abg**	71
28	**8a**	**2i**	**3f**	**9aif**	78
29	**8a**	**2u**	**3c**	**9auc**	73
30	**8a**	**2t**	**3a**	**9ata**	75

[a]Reaction conditions: 4-hydroxycoumarin (1 mmol), aldehyde (1 mmol), thiol (1.2 mmol), using L-proline as a catalyst in ethanol (3 mL) at room temperature. [b]Isolated yield.

The reaction of 4-hydroxycoumarin with aromatic aldehyde gave Knoevenagel intermediate in presence of L-proline catalyst. We believe that L-proline activates the aromatic aldehyde, which can assist the formation of Knoevenagel intermediate with the 4-hydroxycoumarin through condensation. The nucleophilic addition to Knoevenagel intermediate *via* conjugate addition to α,β-unsaturated carbonyl group by substituted thiols provides the final product (Scheme 3.2).



Scheme 3.2. A Plausible Reaction Mechanism.

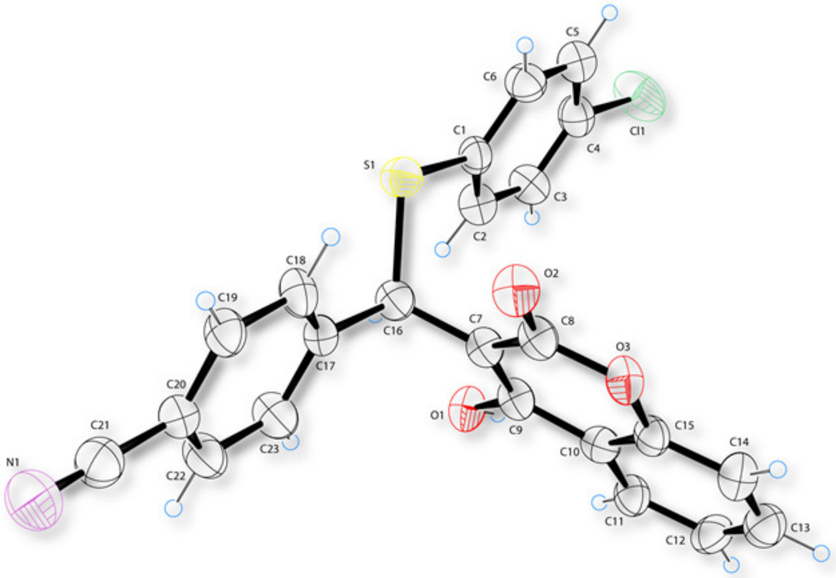
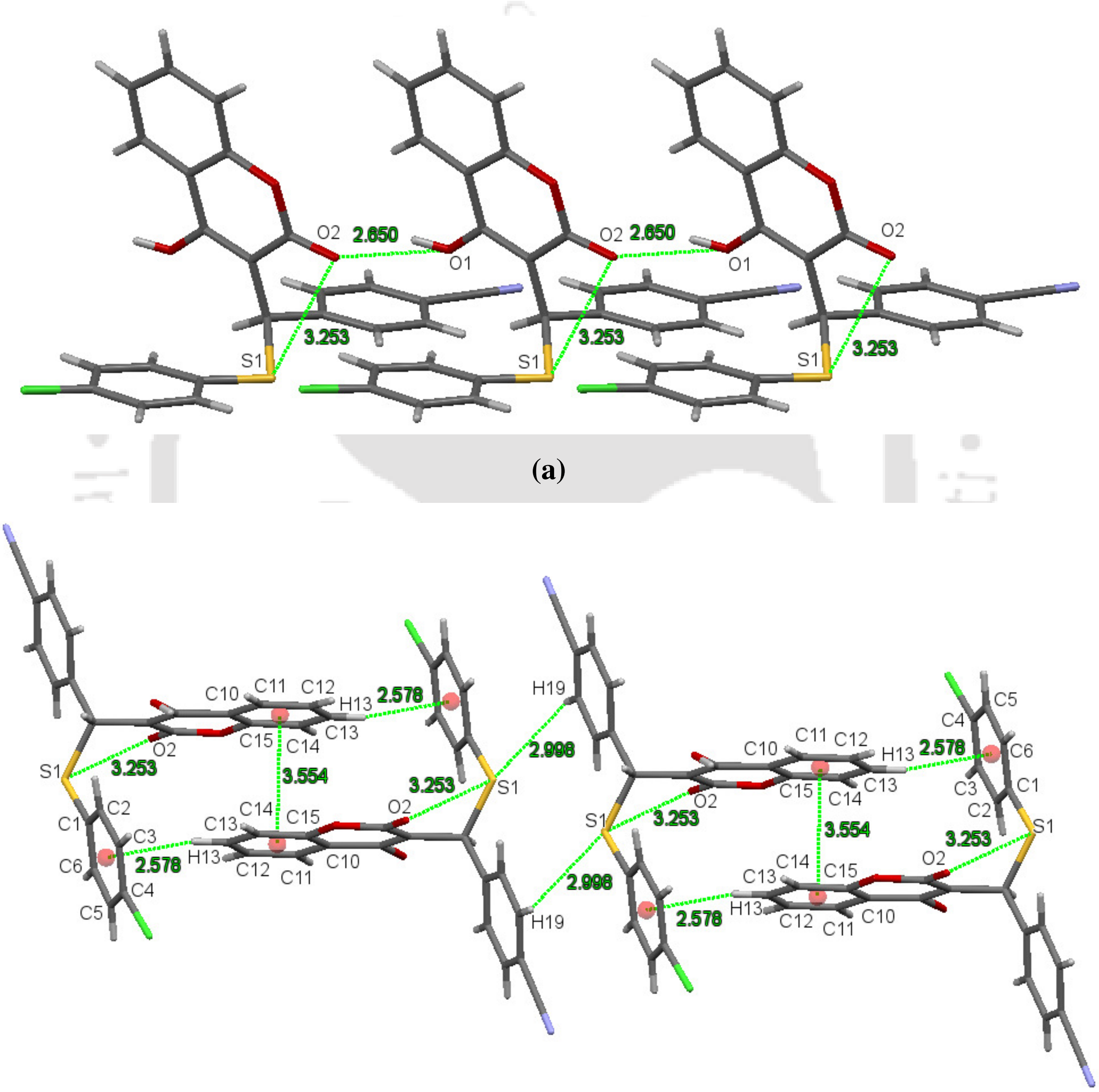


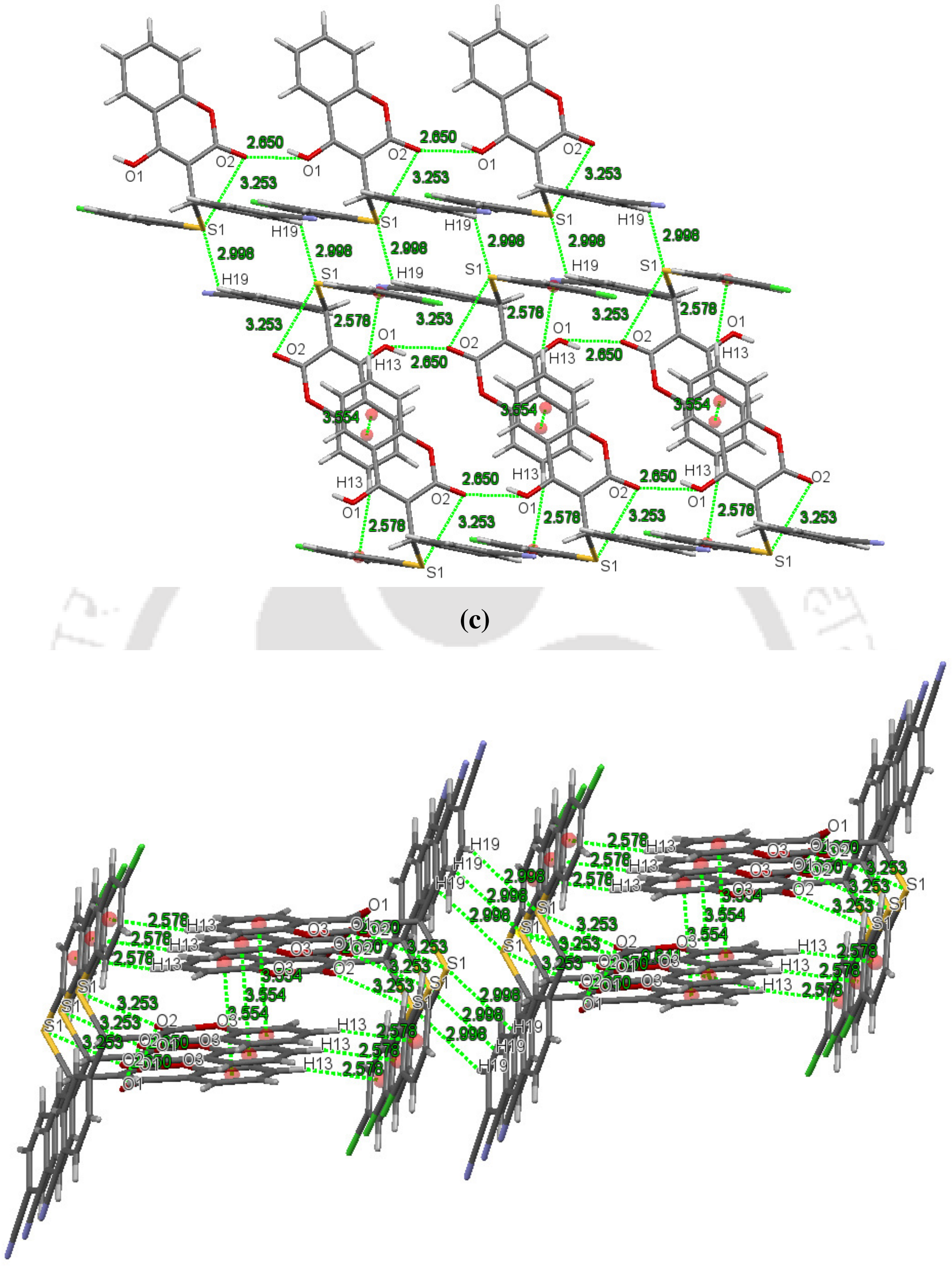
Figure 3.1. Single-crystal X-ray structure of **9aif**.

The present protocol worked with a variety of thiols as well as with different aliphatic and aromatic aldehydes. All the isolated products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and by HRMS. The ^{1}H NMR and ^{13}C NMR spectra of compounds **9aac, 9aal, 9aee** and **9ata** are given in the Experimental Section (Figure 3.13, 3.14, 3.15, and 3.16). Moreover, the structure of compound **9aif** was further confirmed by the X-ray crystallographic analysis (Figure 3.1).



(a)

(b)



(c)

(d)

Figure 3.2. (a) Intra-hetero-atomic and intermolecular interaction to form the long chain structure along c-axis. (b) Packing diagram of **9aif** forming a 2D sheet viewed along c-axis. (c) Top view (d) Side view of collectively presentation of interactions resulting in the formation of a molecular ladder.

The packing diagram of **9aif** exhibits short S1···O2 (3.253Å) intra-hetero-atomic contacts within the molecule and intermolecular interaction between O1···O2 (2.650Å) to form the long chain structure (Figure 3.2a). The packing diagram of **9aif** also showed π-π stacking interaction C10–C15···C10–C15 (3.554Å) between the aromatic rings of two polymeric chain units running anti-parallel to each other, leading to the formation of ladder like structure. These polymeric chains are interlinked in *anti*-fashion *via* intermolecular C–H···π interaction C13H13···C1–C6 (2.578Å) to form 2D double stranded sheet structure. Furthermore, the two separate 2D double stranded sheet structures are interlinked by intermolecular interaction between S1···H19 (2.998Å) (Figure 3.2b). For clarity, the above interactions are presented collectively (Figure 3.2c & 3.2d). In the last few years, these non-covalent interactions involving aromatic rings such as π-π, C–H···π interactions have lured researchers from the field of pharmaceutical, optical, and functional materials.[13] It can also find a wide application in biological systems.[14]

Unlike other compounds, ligand **9ata** was chosen as model compound for sensing studies due to the presence of electron donating nitrogen atom (pyridine ring). The photophysical properties of **9ata** was studied in DMSO/HEPES buffer (9:1, pH=7.4) mixture due to limited water solubility *via* UV-vis and fluorescence spectroscopy. The ligand showed two characteristic bands at 254 nm and 313 nm in UV-vis spectrum with an emission maximum at 401 nm (320 nm excitation), respectively. Fluorescence quenching experiment was performed by adding aliquots of Co^{2+} and Ni^{2+} separately to the solution of **9ata** (25 μM) in DMSO/HEPES buffer (9:1, pH=7.4). The gradual decrease in the fluorescence intensity with the increasing concentration of Co^{2+} and Ni^{2+}, ~80% and ~85% fluorescence quenching was observed at concentration of 16.6 μM Co^{2+} and 10 μM Ni^{2+}, respectively (Figure 3.3a & 3.3b). The quenching constant values obtained *via* linear fitting of S-V plot for Co^{2+} and Ni^{2+} were found to be 1×10^5 M^{-1} and 2.4×10^5 M^{-1} respectively, (Figure 3.4a and 3.4b) indicating very high quenching efficiencies. The LOD value was observed to be as low as 0.22 and 0.13 μM for Co^{2+} and Ni^{2+} (Figure 3.5a and 3.5b) confirming the practicability of the system for real sample analysis.

The quenching of fluorescence can be attributed to the deprotonation of hydroxyl group attached to the ligand (**9ata**) on addition of Co^{2+} or Ni^{2+} that consequently affects the electronic properties of the fluorophore *via* intermolecular charge transfer (ICT) between the metal and the ligand. To evaluate the selectivity, ligand (**9ata)** was treated with various common metal ions including alkali and transition metal ions *viz.* Na^+, Ca^{2+}, K^+, Pb^{2+}, Ag^+, Mn^{2+}, Cr^{3+}, Al^{3+}, Fe^{3+}, Fe^{2+} and Hg^{2+} (Figure 3.6).

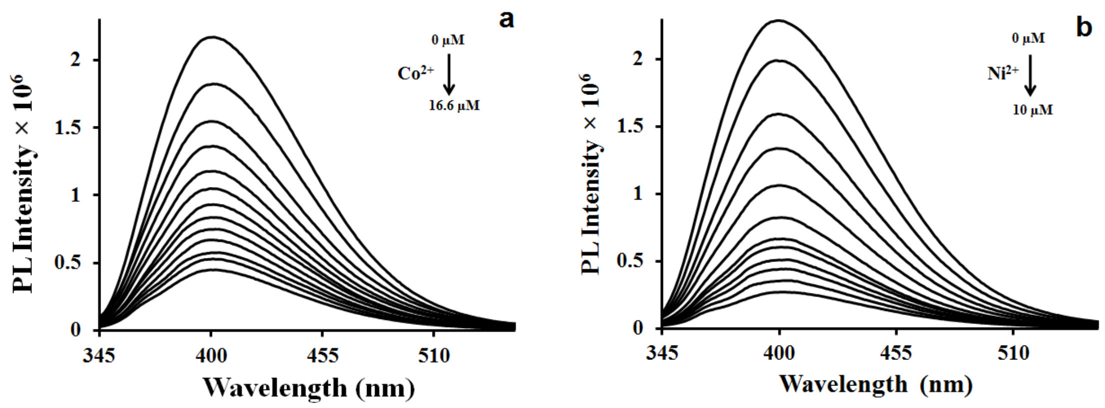


Figure 3.3. Emission spectra of **9ata** (25 µM) with varying concentrations of **(a)** Co^{2+} and **(b)** Ni^{2+} in DMSO/HEPES buffer (9:1, pH=7.4) at room temperature.

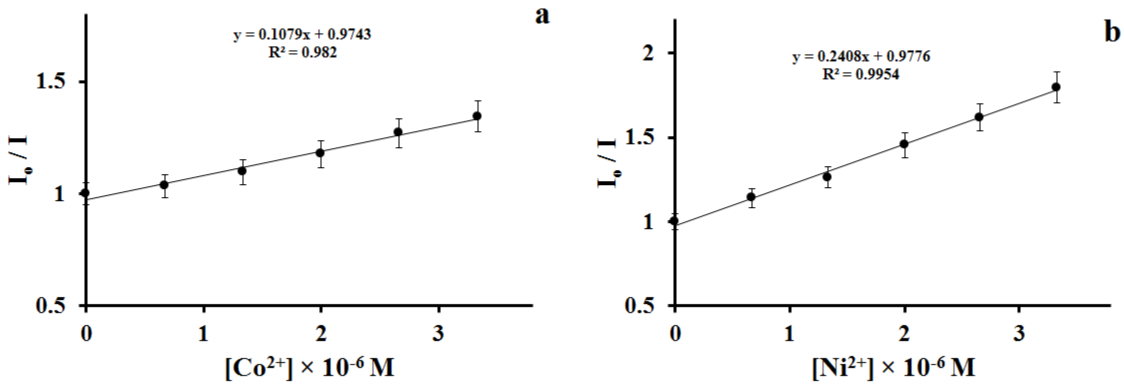


Figure 3.4. Stern-Volmer plots of ligand **9ata** (25 µM) upon addition of (a) Co^{2+} and (b) Ni^{2+} in DMSO/HEPES buffer (9:1, pH=7.4) at room temperature.

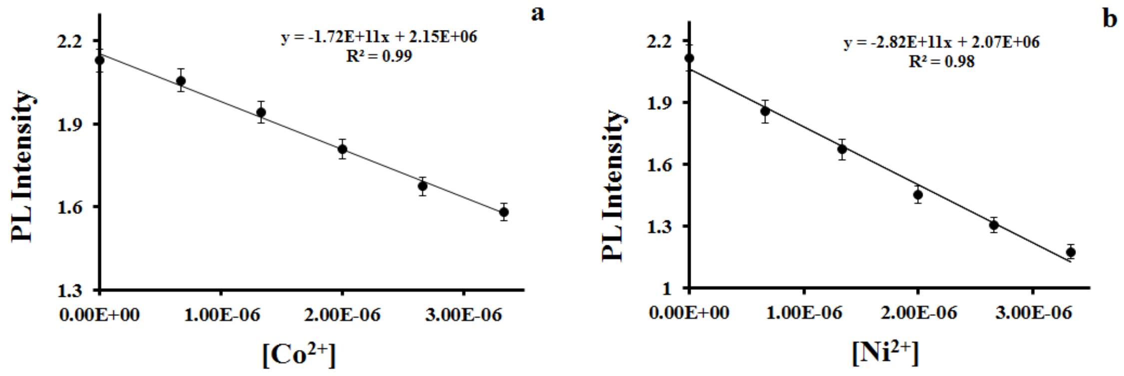


Figure 3.5. Detection limit plot for (a) Co^{2+} and (b) Ni^{2+} in DMSO/HEPES buffer (9:1, pH=7.4) at room temperature.

LOD for $Co^{2+} = 3\times2421.5/\ 1.72\times10^{11}$

$= 0.22\mu M$

LOD for $Ni^{2+} = 3\times12154.2/\ 2.82\times10^{11}$

$= 0.13\mu M$

Interestingly, these metal ions did not affect the fluorescence spectra of **9ata** when excited at 320 nm. Thus, the probe was found to be highly selective and sensitive towards Co^{2+} and Ni^{2+} ions only.

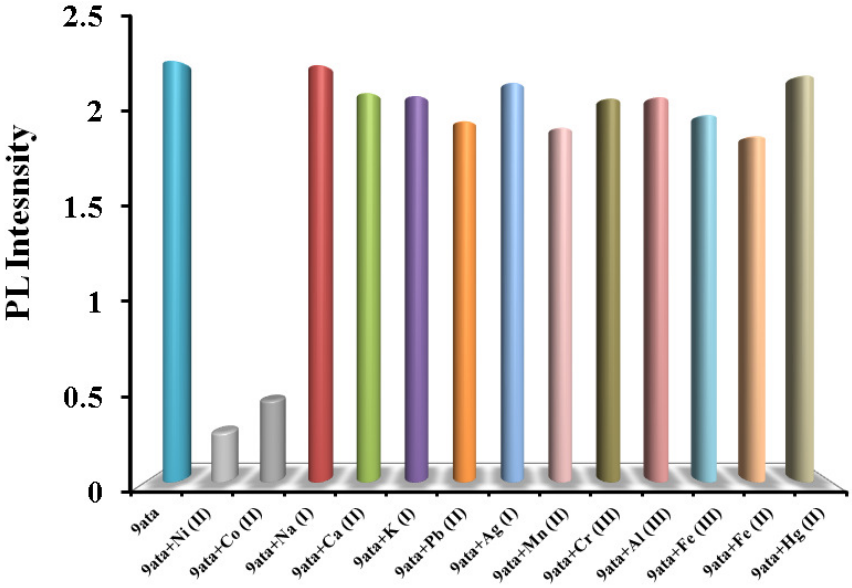


Figure 3.6. Effect of various metal ions on emission of **9ata** in DMSO/HEPES buffer (9:1, pH=7.4). Concentration of **9ata** and metal ions were 25 µM and 20 µM, respectively.

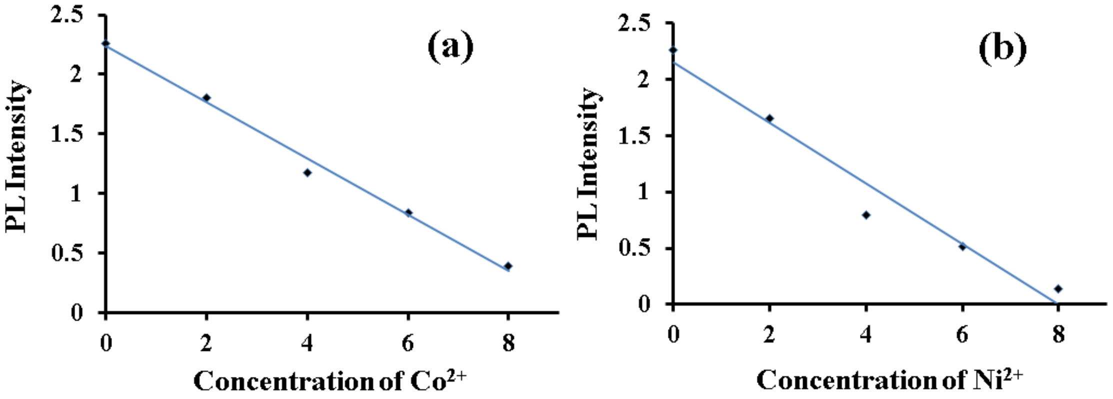


Figure 3.7. Job's plot analysis of the stoichiometry of ligand **9ata** with **(a)** [Co^{2+}] and **(b)** [Ni^{2+}] in DMSO/HEPES buffer (9:1, pH=7.4) (excited at 320 nm).

Job's Plot[9] analysis confirmed a 2:1 stoichiometry for the host-guest complexation. The summation of the concentration of ligand **9ata** and Co^{2+} was kept constant as 25 µM, and the fluorescence intensity of ligand **9ata** with Co^{2+} in four different concentrations (2 µM, 4 µM, 6 µM, 8 µM) was observed (Figure 3.7a). The linear fitting analysis demonstrated that the concentration of Co^{2+} was ~8 µM when the fluorescence of ligand was almost quenched, suggesting the probable binding for ligand-metal as 2:1 stoichiometry. Similar binding ratio was also observed for ligand **9ata** and Ni^{2+} suggesting 2:1 stoichiometry (Figure 3.7b).

The High Resolution Mass spectroscopy (HRMS) spectra of a mixture of ligand **9ata** with Ni^{2+}/Co^{2+} also justify the formation of a 2:1 ligand-metal complex with a major signal at *m/z* = 684.0793 for **9ata**-Co^{2+} and *m/z* = 683.0815 for **9ata**-Ni^{2+}. The binding constant of ligand **9ata** for cobalt and nickel *via* nonlinear least squares analysis was observed to be 9.3×10^4 M^{-1} and 2.07×10^5 M^{-1}, respectively (Figure 3.8a and 3.8b).

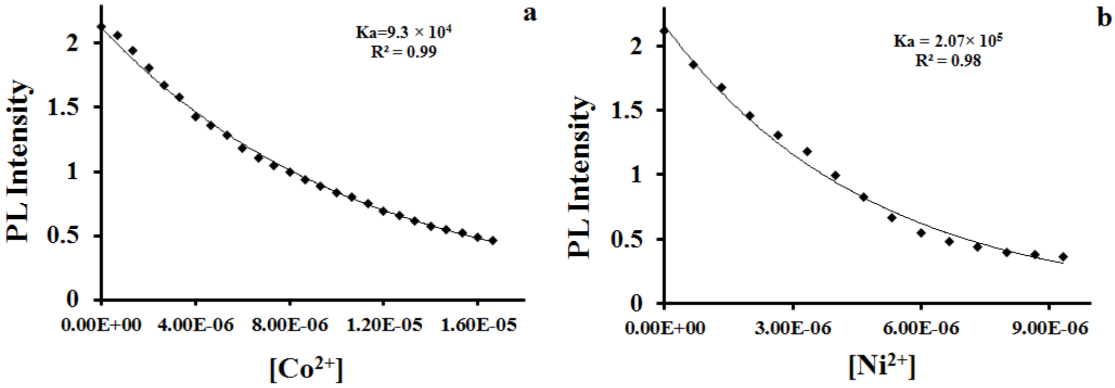


Figure 3.8. Plot of emission of ligand **9ata** *vs* concentration of (a) Co^{2+} and (b) Ni^{2+} in DMSO/HEPES buffer (9:1, pH=7.4).

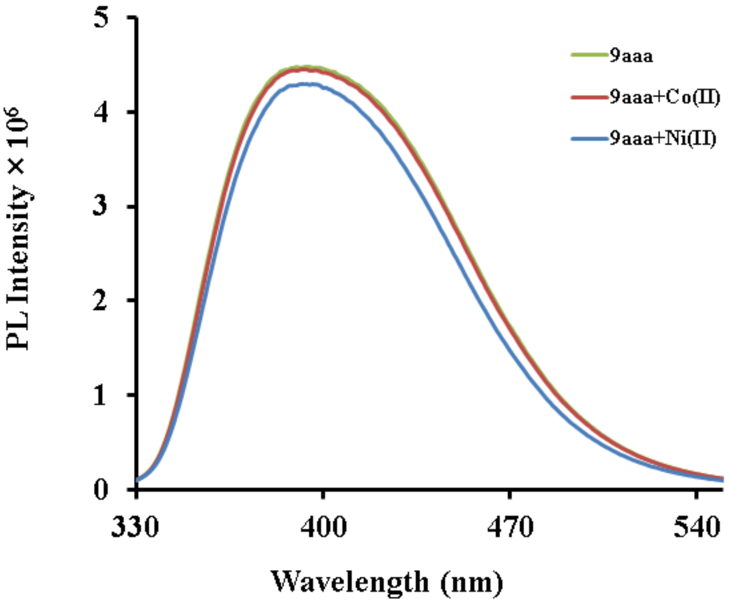


Figure 3.9. PL Spectra showing the effect of Co^{2+}/Ni^{2+} on the fluorescence emission of ligand **9aaa** in DMSO/HEPES buffer (9:1, pH=7.4) at room temperature.

A control study using compound **9aaa** was performed to confirm whether the presence of adjacent pyridinium nitrogen in **9ata** is necessary to form a complex with cobalt or nickel. Fluorescence titration experiment of **9aaa** with Co^{2+} or Ni^{2+} showed no change in fluorescence emission (Figure 3.9). It can be concluded that nitrogen present on adjacent group actively takes part in complexation process *viz-a-viz* quenching process.

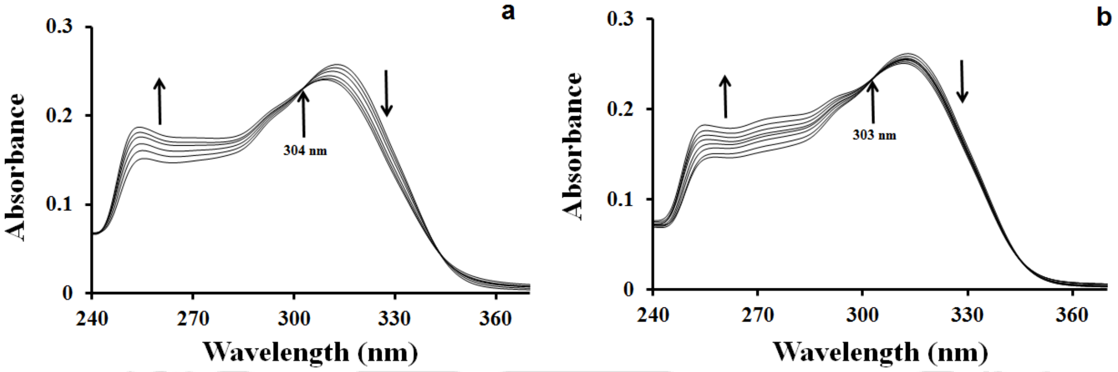
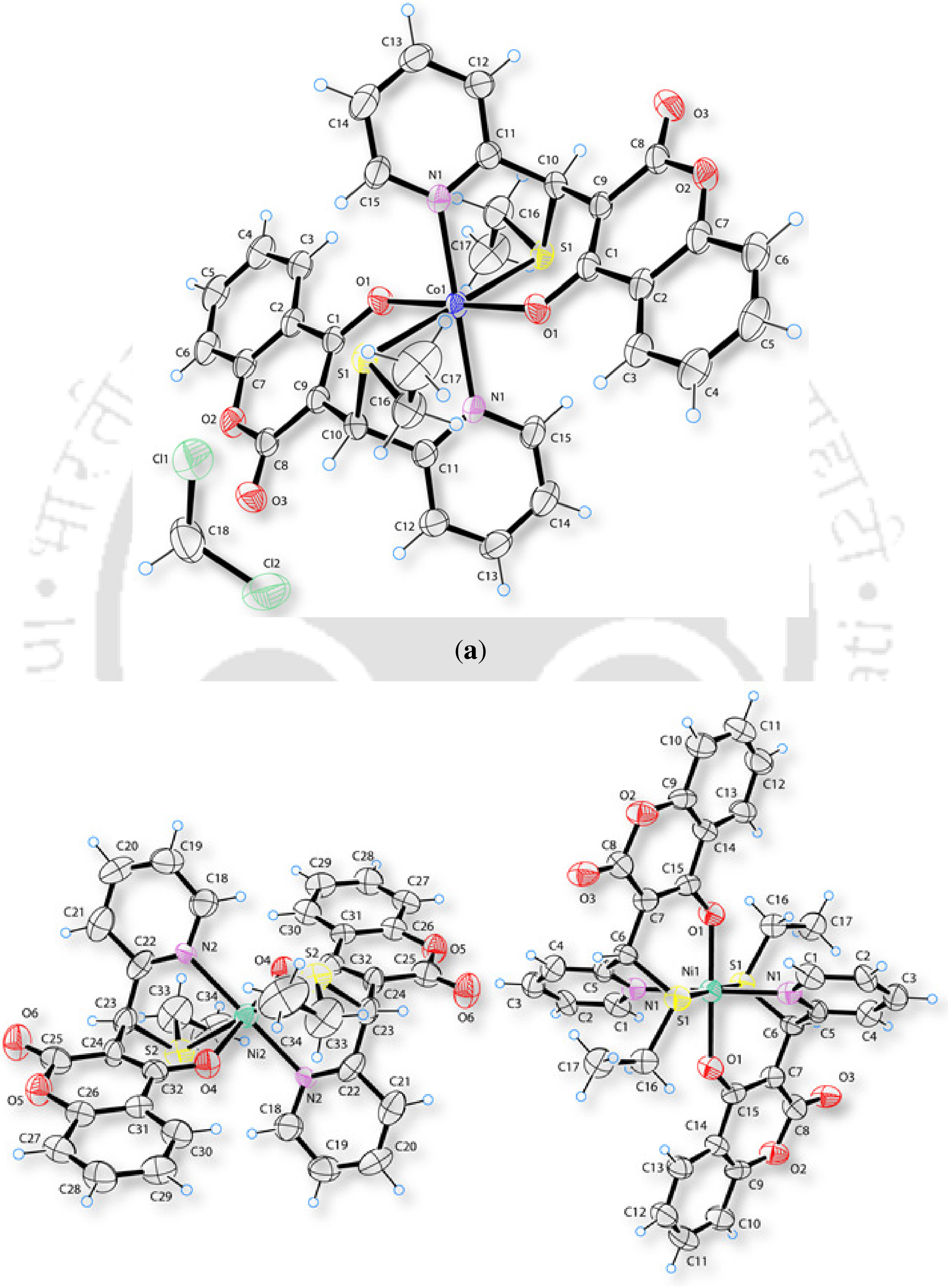


Figure 3.10. UV-visible titration spectra of **9ata** (25 μM) against various concentration of **(a)** Co^{2+} (5 μM) and **(b)** Ni^{2+} (3 μM) in DMSO/HEPES buffer (9:1, pH=7.4) at room temperature.

Titration of **9ata** with Co^{2+} and Ni^{2+} was also observed by UV-vis spectroscopy (Figure 3.10a & 3.10b). On adding Co^{2+} to the solution of **9ata** (25 μM) in 9:1 DMSO/HEPES, the absorption maximum peak of **9ata** at 313 nm significantly decreased and the peak at 254 nm was enhanced with the clear formation of an isosbestic point at around 304 nm. Similar observation was observed on adding Ni^{2+} to the solution of **9ata** with an isosbestic point at 303 nm. Changes in absorbance and formation of isosbestic points are strong evidence for the formation of stable complex between the ligand and these metals.

Finally, the predicted binding mode of ligand **9ata** with cobalt and nickel was confirmed by single crystal X-ray structure of the complexes (Figure 3.11a & 3.11b) obtained in dichloromethane-methanol solution as determined by the X-ray diffraction method. It was observed that two ligand units bind with single Co^{2+}/Ni^{2+} atom *via* six coordination bonds.

In order to differentiate cobalt and nickel, a strong chelating agent disodium salt of ethylenediamintetraacetic acid (EDTA) was employed[15] that has good affinity for Co^{2+} compared to Ni^{2+}. The cobalt (II) complex displayed "turn-on" florescence response towards EDTA due to the displacement of metal from the complex with the total fluorescence recovery of ~80% on addition of total 1.1 eq. EDTA (Figure 3.12a). However, nickel (II) complex did not show any significant change (Figure 3.12b) in fluorescence on adding EDTA even after prolonged time of 30 minutes. These results demonstrate the method as simple and rapid to discriminate Co^{2+} from Ni^{2+} using displacement mechanism.



(**b**)

Figure 3.11. The X-ray crystal structures of **(a)** cobalt (II) complex and **(b)** nickel (II) complex.

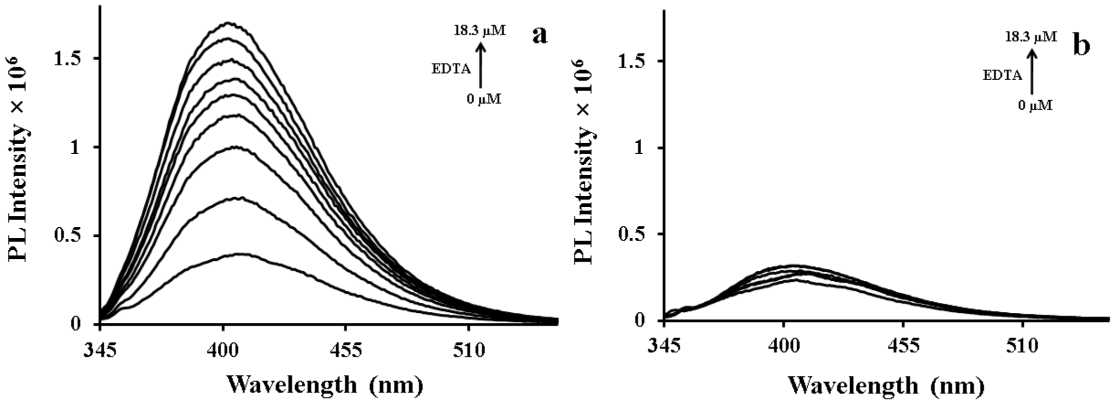
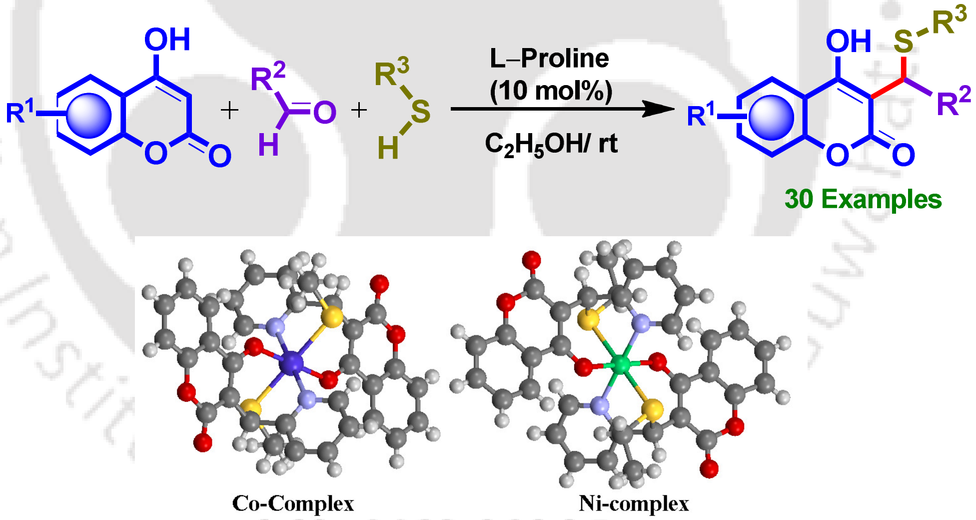


Figure 3.12. Photoluminescence spectra of **(a)** cobalt (II) complex and **(b)** nickel (II) complex on addition of EDTA.

In conclusion, a convenient and environmentally green methodology for the synthesis of 3-(alkyl/aryl(alkyl/arylthio)-methyl) substituted 4-hydroxycoumarin derivatives *via* the three-component reactions of 4-hydroxycoumarin, aldehydes, and thiols by using L-proline as an efficient catalyst at room temperature was developed. The attractive features of this protocol are simple reaction procedure, short reaction time, high yield and easy isolation technique of the product, its flexibility for the synthesis of a broad range of 3-(alkyl/aryl(alkyl/arylthio)methyl) substituted 4-hydroxycoumar-in derivatives in moderate to high yields. Additionally, the demonstration of **9aif** crystal structure, towards non-covalent interactions is expected to make a significant impact among the researchers working in the area of supra-molecular chemistry, sensing applications for environmental contaminants and biologically relevant ions. Furthermore, sensing studies performed using model compound **9ata** suggest that the ligand can be used as an effective fluorescence tool to monitor and distinguish traces of both cobalt and nickel in the competent environment.

Chapter 3

One-pot synthesis of functionalized 4-hydroxy-3-thiomethylcoumarins: Detection and discrimination of Co^{2+} and Ni^{2+} ions



CHAPTER 3: Experimental Section

3.2 Experimental Section

UV-Vis and fluorescence titration

Stock solution of **9ata** (5 mM) and several other metal ions (1×10^{-3} M) were prepared in DMSO and Milli-Q water, respectively. The absorption or fluorescence spectra were recorded by adding small fractions of different metal ions to 3 mL of 9:1 DMSO/ HEPES buffer (pH=7.4, 10 mM) solution containing 25 µM **9ata** in a quartz cuvette (1 cm × 1 cm) with time interval of 1 min at room temperature.

Determination of quenching constant

The quenching constant (K_{sv}) values for Co^{2+} and Ni^{2+} were obtained by plotting a Stern-Volmer plot (I_0/I vs [Q], where I_0 represents the initial fluorescence intensity of ligand **9ata**, I denotes fluorescence intensity of **9ata** after adding given concentration of quencher [Q], and $[Q] = [Co^{2+}]$ or $[Ni^{2+}]$).

Determination of detection limit

The limit of detection (LOD) was calculated using the following equation[16]

$LOD = 3\sigma/K$

Where, 'σ' denotes the standard deviation for the intensity of ligand **9ata** solution in the absence of Co^{2+}/Ni^{2+} and 'K' represents the slope of the curve.

Method of drawing Job Plot using fluorescence

Job's plot analysis[9] was performed to determine the stoichiometry between ligand **9ata** and Co^{2+}/Ni^{2+}. The summation of the concentration of ligand **9ata** and Co^{2+} was kept as constant *c*. Assuming the complex as non-fluorescent, the fluorescence intensity of **9ata** (*F*) can be calculated from the equation below:

$$F = [\mathbf{9ata}] - \frac{1}{a}[Co^{2+}]$$

Where [**9ata**] and $[Co^{2+}]$ denotes the concentration of ligand and Co^{2+} respectively and '*a*' represents the complex ratio of ligand **9ata** and Co^{2+}. Since summation of the concentration of ligand and Co^{2+} was kept as constant 'c', the above equation above could be modified as:

$$F = c - [Co^{2+}] - \frac{1}{a}[Co^{2+}] = c - \frac{a+1}{a}[Co^{2+}]$$

When the fluorescence of ligand is almost quenched by Co^{2+}, *i.e.* F=0, the complex ratio '*a*' could be evaluated from the concentration of Co^{2+}. Similar method can be used to calculate the complex ratio '*a*' for ligand **9ata** and Ni^{2+}.

General procedure for synthesis of compounds (9)

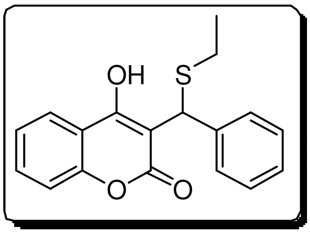
In 10 mL round bottomed flask, a mixture of aldehyde (1 mmol) and L-proline (0.1 mmol) was dissolved in 3 mL of ethanol and stirred at room temperature. After 10 min of stirring, 4-hydroxycoumarin (1 mmol) and thiol (1.2 mmol) were added either directly if it is a solid or drop-wise through a syringe, in quick succession. The solid products were precipitated out during the reaction after appropriate reaction time. Finally, the solid products were filtered off through a Büchner funnel, thoroughly washed with the mixture of ethanol and hexane (2:8) to remove unreacted starting material and recrystallized in 9:1 mixture of ethanol and chloroform. The following work up procedure was followed for the products in case the solid precipitate did not come out during the reaction time. After completion of reaction as checked by TLC, ethanol was removed under reduced pressure via a rotary evaporator and the crude residue was extracted with dichloromethane (2 × 15 mL). The organic layer was washed with water, brine solution (2 x 5 mL) and dried over anhydrous Na_2SO_4. Then, it was concentrated under reduced pressure and the crude residue was passed through a silica gel (60-120 mesh) column with gradient eluents of petroleum ether and ethyl acetate to get the desired pure product.

Synthesis of Cobalt and Nickel complexes:

$Co(ClO_4)_2.6H_2O$ or $Ni(ClO_4)_2.6H_2O$ (0.05 mmol) dissolved in 2 ml of methanol was added to a solution of ligand (0.10 mmol) in dichloromethane (2 ml) with stirring under atmosphere oxygen. The resulting solution was allowed to stir for 10 min at room temperature and then filtered. The filtrate obtained were the desired complexes and dried under vacuum. These complexes were characterized by High Resolution Mass spectroscopy (HRMS). For **9ata-Co^{2+}** HRMS (ESI): calcd for $C_{34}H_{28}N_2CoO_6S_2$ $[M + H]^+$: 684.0794; Found: 684.0793. For **9ata-Ni^{2+}** HRMS (ESI): calcd for $C_{34}H_{28}N_2NiO_6S_2$ $[M + H]^+$: 683.0815; Found: 683.0815.

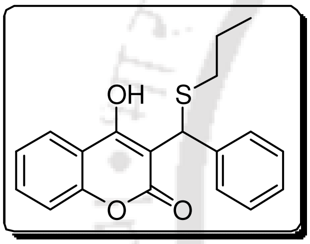
Spectral data of Compounds:

3-((ethylthio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one (9aaa):



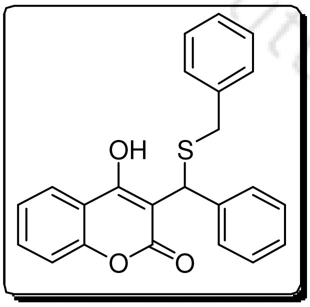
Nature: Semi-solid; **IR** (KBr): 3428, 3070, 3030, 2973, 2928, 1707, 1665, 1624, 1572, 1494, 1453, 1404, 1332, 1288, 1250, 1210, 1164, 1107, 1035, 1002, 933, 896, 835, 757, 697 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.34 (t, J = 6.8 Hz, 3H), 7.58-7.72 (m, 2H), 5.77 (s, 1H), 7.25-7.30 (m, 5H), 7.44 (d, J = 6.0 Hz, 2H), 7.53 (t, J = 6.4 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 10.85 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.0, 26.8, 45.4, 101.3, 116.0, 116.5, 123.5, 124.2, 127.8 (2C), 128.1, 129.0 (2C), 132.6, 137.9, 152.9, 162.9, 163.6. **HRMS** (ESI): calcd for C$_{18}$H$_{16}$O$_3$S [M + H]$^+$: 313.0893. Found: 313.0912.

4-hydroxy-3-(phenyl(propylthio)methyl)-2H-chromen-2-one (9aab):



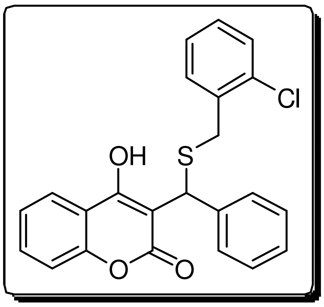
Nature: White solid; mp 90-92 °C; **IR** (KBr): 3455, 3059, 3028, 2964, 2931, 2875, 1707, 1666, 1625, 1572, 1494, 1453, 1404, 1349, 1332, 1281, 1265, 1250, 1209, 1164, 1108, 1035, 933, 896, 834, 798, 757, 736, 697 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.02 (t, J = 7.6 Hz, 3H), 1.64-1.74 (m, 2H), 2.52-2.59 (m, 1H), 2.69-2.75 (m, 1H), 5.71 (s, 1H), 7.28-7.36 (m, 5H), 7.43 (d, J = 6.8 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 10.99 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 13.5, 22.1, 34.7, 45.7, 101.3, 116.1, 116.5, 123.5, 124.1, 127.8 (2C), 128.1, 129.1 (2C), 132.5, 138.1, 153.1, 162.7, 163.5. **HRMS** (ESI): calcd for C$_{19}$H$_{18}$O$_3$S [M + H]$^+$: 327.1049. Found: 327.1060.

3-((benzylthio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one (9aac):



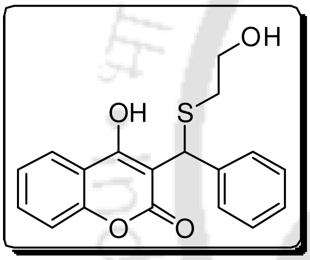
Nature: White crystalline solid; mp 110-112 °C. **IR** (KBr): 3086, 3059, 3026, 3000, 1700, 1623, 1570, 1494, 1454, 1385, 1332, 1281, 1243, 1210, 1180, 1164, 1103, 1071, 1036, 1001, 950, 933, 911, 896, 836, 797, 777, 764, 752, 729, 712, 696, 671 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.86 (s, 2H), 5.60 (s, 1H), 7.17 (s, 1H), 7.26-7.37 (m, 11H), 7.57 (t, J = 7.6 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 10.63 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 37.7, 46.0, 101.5, 116.1, 116.5, 123.6, 124.1, 127.7, 127.9 (2C), 128.2, 128.8 (2C), 128.9 (2C), 129.0 (2C), 132.5, 136.0, 137.6, 153.0, 162.5, 163.3. **HRMS** (APCI): calcd for C$_{23}$H$_{18}$O$_3$S [M + H]$^+$: 375.1049. Found: 375.1049.

3-(((2-chlorobenzyl)thio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one (9aaj):



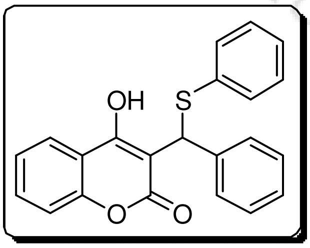
Nature: White solid; mp 146-148 °C. **IR** (KBr): 3445, 3062, 2952, 1817, 1684, 1622, 1611, 1572, 1495, 1472, 1442, 1416, 1384, 1331, 1278, 1250, 1237, 1205, 1165, 1146, 1108, 1054, 1038, 1001, 933, 896, 831, 759, 738, 707, 693, 668 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.00 (dd, J_1 = 13.2 Hz & J_2 = 13.2 Hz, 2H), 5.66 (s, 1H), 7.06 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 2H), 7.28-7.33 (m, 5H), 7.36 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 10.53 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 35.7, 46.4, 101.7, 116.1, 116.5, 123.6, 124.1, 127.1, 128.0 (2C), 128.3, 129.0 (2C), 129.2, 130.0, 131.0, 132.5, 133.9, 134.1, 137.5, 152.9, 162.6, 163.4 . **HRMS** (ESI): calcd for $C_{23}H_{17}ClO_3S$ [M + H]$^+$: 409.0660. Found: 409.0662.

4-hydroxy-3-(((2-hydroxyethyl)thio)(phenyl)methyl)-2H-chromen-2-one (9aam):



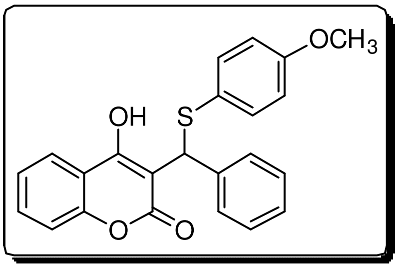
Nature: White solid; mp 126-128 °C. **IR** (KBr): 3448, 2929, 2865, 2589, 1670, 1621, 1610, 1569, 1495, 1453, 1426, 1409, 1334, 1309, 1277, 1250, 1206, 1166, 1103, 1071, 1047, 1002, 936, 897, 863, 800, 760, 735, 696 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.35 (s, 1H, OH), 2.77-2.89 (m, 2H), 3.89 (s, 2H), 5.82 (s, 1H), 7.28-7.31 (m, 5H), 7.44 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 8.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 10.48 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 35.2, 45.7, 60.9, 101.7, 116.1, 116.7, 123.7, 124.3, 127.9 (2C), 128.4, 129.1 (2C), 132.8, 137.8, 153.0, 163.0, 163.6. **HRMS** (ESI): calcd for $C_{18}H_{16}O_4S$ [M + Na]$^+$: 351.0662. Found: 351.0664.

4-hydroxy-3-(phenyl(phenylthio)methyl)-2H-chromen-2-one (9aad):



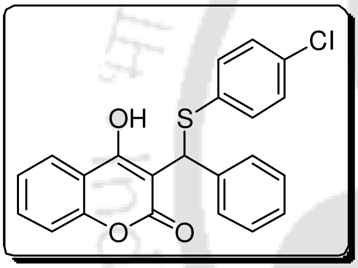
Nature: White solid; mp 160-161 °C. **IR** (KBr): 3449, 3050, 3023, 2978, 1652, 1611, 1596, 1561, 1537, 1491, 1479, 1450, 1437, 1420, 1347, 1261, 1230, 1204, 1167, 1155, 1103, 1084, 1027, 997, 925, 848, 756, 740, 720, 690, 666 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.18 (s, 1H), 7.23-7.32 (m, 6H), 7.36 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 7.2 Hz, 3H), 7.91 (d, J = 8.4 Hz, 1H), 10.32 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 49.6, 102.3, 116.0, 116.6, 123.6, 124.1, 128.1 (2C), 128.5, 128.6, 129.2 (2C), 129.6 (2C), 130.9 (2C), 132.1, 132.6, 136.9, 152.8, 162.7, 163.1. **HRMS** (ESI): calcd for $C_{22}H_{16}O_3S$ [M + H]$^+$: 361.0893. Found: 361.0905.

4-hydroxy-3-(((4-methoxyphenyl)thio)(phenyl)methyl)-2H-chromen-2-one (9aai):



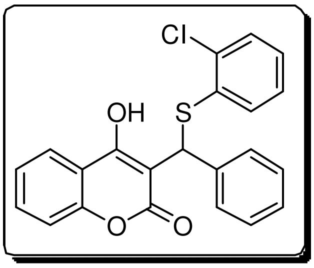
Nature: White solid; mp 126-127 °C. **IR** (KBr): 3434, 3063, 2932, 1686, 1624, 1610, 1590, 1572, 1494, 1453, 1439, 1390, 1330, 1291, 1249, 1210, 1179, 1166, 1110, 1029, 932, 896, 847, 832, 817, 799, 757, 731, 711, 702, 669 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.74 (s, 3H), 6.02 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 9.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 10.48 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$)**:** δ 51.4, 55.4, 102.4, 115.3 (2C), 116.2, 116.6, 122.2, 123.6, 124.2, 128.1 (2C), 128.4, 129.2 (2C), 132.5, 134.2 (2C), 137.2, 152.9, 160.4, 162.7, 163.0. **HRMS** (APCI): calcd for $C_{23}H_{18}O_4S$ [M + H]$^+$: 391.0999. Found: 391.0994.

3-(((4-chlorophenyl)thio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one (9aaf):



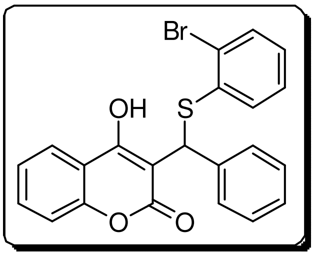
Nature: White solid; mp 167-169 °C. **IR** (KBr): 3084, 3022, 2973, 1653, 1611, 1596, 1559, 1540, 1491, 1476, 1451, 1418, 1391, 1341, 1318, 1286, 1229, 1196, 1166, 1152, 1103, 1095, 1080, 1030, 1010, 950, 923, 860, 847, 832, 820, 787, 754, 720, 698, 664 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 6.18 (s, 1H), 7.26 (s, 4H), 7.31-7.37 (m, 3H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.50-7.55 (m, 3H), 7.90 (d, *J* = 6.4 Hz, 1H), 10.04 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 49.7, 102.1, 115.9, 116.7, 123.6, 124.3, 128.1 (2C), 128.7, 129.3 (2C), 129.9 (2C), 130.6, 132.3 (2C), 132.8, 134.8, 136.5, 152.9, 162.8, 163.1. **HRMS** (ESI): calcd for $C_{22}H_{15}ClO_3S$ [M + H]$^+$: 395.0503. Found: 395.0512.

3-(((2-chlorophenyl)thio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one (9aak):



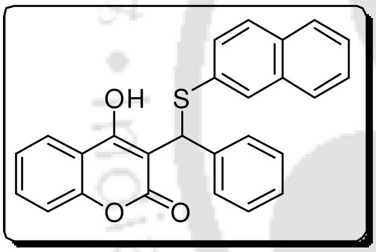
Nature: White solid; mp 179-180 °C. **IR** (KBr): 3312, 3064, 1676, 1621, 1568, 1496, 1450, 1431, 1396, 1335, 1299, 1273, 1220, 1191, 1169, 1147, 1105, 1070, 1033, 949, 912, 892, 854, 784, 757, 748, 734, 718, 678 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 6.32 (s, 1H), 7.18 (t, *J* = 4.0 Hz, 2H), 7.25-7.33 (m, 3H), 7.35 (d, *J* = 5.2 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 3H), 7.90 (d, *J* = 7.6 Hz, 1H), 9.97 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 47.5, 101.9, 116.0, 116.6, 123.8, 124.3, 127.9, 128.3 (2C), 128.8, 129.0, 129.4 (2C), 130.4, 130.7, 131.8, 132.7, 134.6, 136.3, 152.9, 162.7, 163.4. **HRMS** (ESI): calcd for $C_{22}H_{15}ClO_3S$ [M + K]$^+$: 433.0062. Found: 433.0053.

3-(((2-bromophenyl)thio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one (9aal):



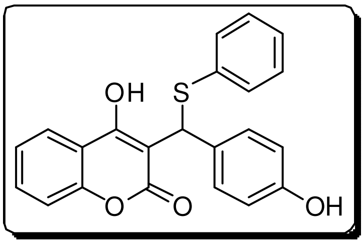
Nature: White solid; mp 181-183 °C. **IR** (KBr): 3321, 3070, 1676, 1622, 1568, 1496, 1449, 1427, 1395, 1335, 1298, 1271, 1220, 1189, 1173, 1147, 1105, 1070, 1017, 911, 891, 853, 784, 756, 732, 719, 678, 647 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.33 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.32-7.36 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 5H), 7.91 (d, *J* = 7.6 Hz, 1H), 9.94 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 47.7, 101.8, 115.9, 116.6, 123.8, 124.2, 124.3, 128.3 (2C), 128.5, 128.8, 128.9, 129.3 (2C), 130.2, 132.7, 133.6, 133.9, 136.2, 152.8, 162.8, 163.4. **HRMS** (ESI): calcd for $C_{22}H_{15}BrO_3S$ [M + H]$^+$: 440.9979. Found: 441.0000.

4-hydroxy-3-((naphthalen-2-ylthio)(phenyl)methyl)-2H-chromen-2-one (9aah):



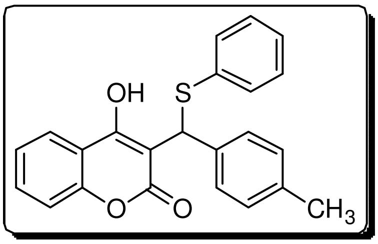
Nature: White solid; mp 153-155 °C. **IR** (KBr): 3078, 3052, 1683, 1662, 1622, 1607, 1593, 1567, 1494, 1446, 1399, 1340, 1281, 1228, 1194, 1165, 1148, 1108, 1080, 1029, 943, 916, 894, 860, 850, 839, 813, 777, 758, 738, 717, 697, 647 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.35 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.33-7.38 (m, 3H), 7.45-7.49 (m, 3H), 7.56-7.57 (m, 3H), 7.76-7.78 (m, 4H), 7.90 (d, *J* = 6.4 Hz, 1H), 7.95 (s, 1H) 10.34 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 49.3, 102.3, 116.0, 116.6, 123.6, 124.1, 126.9, 127.0, 127.4, 127.7, 127.8, 127.9, 128.2 (2C), 128.6, 129.3 (2C), 129.5, 129.9, 132.6, 132.8, 133.7, 136.8, 152.8, 162.8, 163.2. **HRMS** (ESI): calcd for $C_{26}H_{18}O_3S$ [M]$^+$: 410.0977. Found: 410.0983.

4-hydroxy-3-((4-hydroxyphenyl)(phenylthio)methyl)-2H-chromen-2-one (9agd):



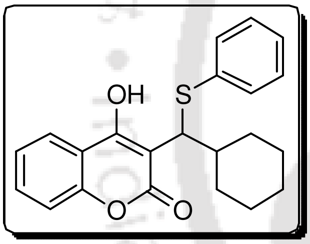
Nature: White solid; mp 115-117 °C. **IR** (KBr): 3068, 2606, 2360, 2256, 2126, 1657, 1601, 1566, 1514, 1474, 1452, 1437, 1354, 1311, 1271, 1253, 1217, 1182, 1160, 1114, 1097, 1048, 1024, 995, 907, 841, 791, 764, 740, 688, 675 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.63 (s, 1H, OH), 6.03 (s, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 7.16-7.24 (m, 7H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 10.34 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$/DMSO): δ 46.7, 105.5, 114.4 (2C), 115.2, 115.4, 123.0, 125.7, 128.1 (3C), 128.2 (2C), 129.1 (2C), 129.2, 131.2, 135.9, 151.5, 155.7, 160.0, 161.3. **HRMS** (ESI): calcd for $C_{22}H_{16}O_4S$ $[M + K]^+$: 415.0401. Found: 415.0393.

4-hydroxy-3-((phenylthio)(p-tolyl)methyl)-2H-chromen-2-one (9acd):



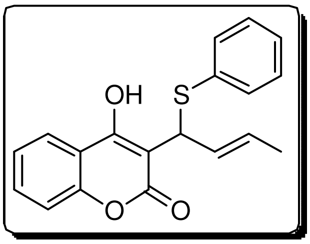
Nature: White solid; mp 134-136 °C. **IR** (KBr): 3089, 2919, 2850, 2362, 1695, 1625, 1572, 1514, 1495, 1455, 1439, 1279, 1250, 1205, 1159, 1109, 1037, 931, 897, 762, 756, 748, 711, 692 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 6.17 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.23-7.31 (m, 5H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 10.30 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 49.3, 102.5, 116.0, 116.5, 123.6, 124.1, 128.0 (2C), 128.4, 129.6 (2C), 129.9 (2C), 130.8 (2C), 132.3, 132.5, 133.9, 138.4, 152.8, 162.7, 163.0. **HRMS** (ESI): calcd for $C_{23}H_{18}O_3S$ $[M + H]^+$: 375.1049. Found: 375.1057.

3-(cyclohexyl(phenylthio)methyl)-4-hydroxy-2H-chromen-2-one (9axd):



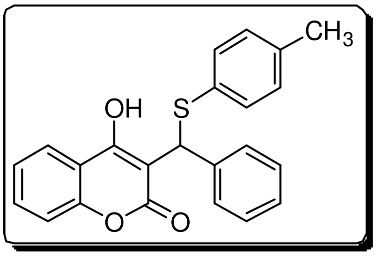
Nature: Dark brown semi-solid; **IR** (KBr): 3418, 2927, 2851, 1704, 1666, 1622, 1570, 1495, 1480, 1449, 1439, 1385, 1330, 1282, 1202, 1170, 1106, 1068, 1025, 959, 897, 760, 689 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43-1.25 (m, 4H), 1.37-1.45 (m, 1H), 1.59-1.79 (m, 4H), 1.96-2.08 (m, 2H), 4.89 (d, *J* = 6.4 Hz, 1H), 7.15-7.27 (m, 5H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 9.98 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.0, 26.2, 26.3, 31.0, 31.1, 42.5, 51.7, 102.7, 116.0, 116.3, 123.3, 123.9, 127.8, 129.3 (2C), 130.7 (2C), 131.8, 132.1, 152.6, 162.5, 163.4. **HRMS** (ESI): calcd for $C_{22}H_{22}O_3S$ $[M + H]^+$: 367.1362. Found: 367.1383.

(E)-4-hydroxy-3-(1-(phenylthio)but-2-en-1-yl)-2H-chromen-2-one (9ayd):



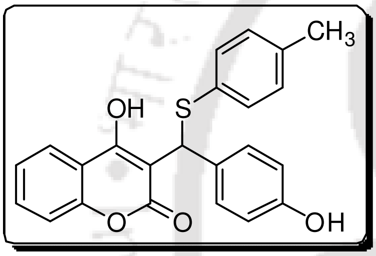
Nature: Dark brown semi-solid; **IR** (KBr): 3419, 2978, 2924, 2853, 1711, 1627, 1609, 1573, 1493, 1454, 1438, 1415, 1382, 1327, 1276, 1213, 1187, 1112, 1036, 906, 757, 691, 666 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.47 (d, *J* = 6.8 Hz, 3H), 5.21-5.22 (m, 1H), 5.50 (d, *J* = 9.6 Hz, 1H), 6.49 (d, *J* = 10.0 Hz, 1H), 7.14-7.23 (m, 6H), 7.43 (dd, J_1 = 7.2 Hz & J_2 = 7.6 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.0, 74.6, 101.0, 115.4, 116.9 (2C), 118.2, 122.4, 122.9, 124.2, 127.3, 127.7, 129.2, 129.4, 132.3 (2C), 153.3, 159.5, 161.0. **HRMS** (ESI): calcd for $C_{19}H_{16}O_3S$ $[M + H]^+$: 325.0893. Found: 325.0896.

4-hydroxy-3-(phenyl(p-tolylthio)methyl)-2H-chromen-2-one (9aae):



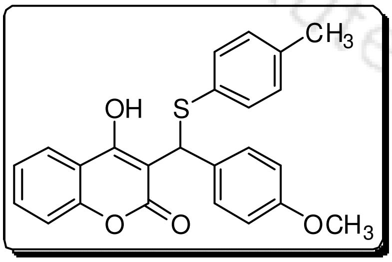
Nature: White solid; mp 134-135 °C. **IR** (KBr): 3446, 3063, 2920, 1686, 1654, 1620, 1611, 1572, 1561, 1535, 1492, 1453, 1390, 1279, 1229, 1202, 1166, 1103, 1087, 1036, 931, 848, 821, 805, 753, 724, 700 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 2.27 (s, 3H), 6.10 (s, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 3H), 7.50-7.53 (m, 3H), 7.93 (d, *J* = 8.0 Hz, 1H), 10.45 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 50.3, 102.4, 116.2, 116.6, 123.6, 124.2, 128.1 (2C), 128.4, 128.5, 129.2 (2C), 130.5 (2C), 131.5 (2C), 132.5, 137.1, 139.0, 152.9, 162.7, 163.1. **HRMS** (APCI): calcd for $C_{23}H_{18}O_3S$ $[M + H]^+$: 375.1049. Found: 375.1048.

4-hydroxy-3-((4-hydroxyphenyl)(p-tolylthio)methyl)-2H-chromen-2-one (9age):



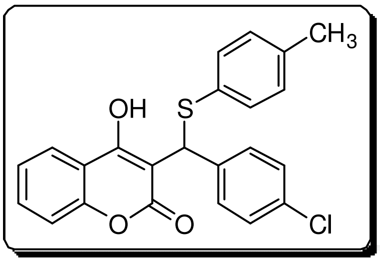
Nature: White solid; mp 144-145 °C. **IR** (KBr): 3313, 3124, 1665, 1610, 1591, 1571, 1512, 1496, 1455, 1438, 1284, 1272, 1253, 1225, 1177, 1159, 1107, 1059, 1030, 1017, 845, 838, 802, 763, 750, 669 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 6.02 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 7.2 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 3H), 7.36 (s, *J* = 7.2 Hz, 3H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 10.57 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 50.0, 102.6, 116.1, 116.2 (2C), 116.3, 116.6, 123.7, 124.4, 128.2, 128.5, 129.4 (2C), 130.4 (2C), 131.4 (2C), 132.6, 138.9, 152.7, 156.5, 163.5. **HRMS** (APCI): calcd for $C_{23}H_{18}O_4S$ $[M + H]^+$: 391.0999. Found: 391.0998.

4-hydroxy-3-((4-methoxyphenyl)(p-tolylthio)methyl)-2H-chromen-2-one (9abe):



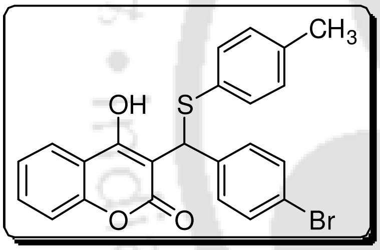
Nature: White solid; mp 142-144 °C. **IR** (KBr): 3078, 2959, 2837, 1693, 1629, 1604, 1573, 1510, 1493, 1453, 1443, 1364, 1334, 1306, 1279, 1257, 1213, 1180, 1164, 1148, 1111, 1091, 1044, 1033, 936, 896, 837, 817, 807, 792, 765, 749, 739, 701, 690, 671 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.80 (s, 3H), 6.07 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 10.46 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 49.7, 55.4, 102.6, 114.5 (2C), 116.1, 116.5, 123.5, 124.1, 128.5, 128.9, 129.3 (2C), 130.4 (2C), 131.4 (2C), 132.4, 138.8, 152.8, 159.6, 162.7, 162.9. **HRMS** (APCI): calcd for $C_{24}H_{20}O_4S$ [M + K]$^+$: 443.0714. Found: 443.0725.

3-((4-chlorophenyl)(p-tolylthio)methyl)-4-hydroxy-2H-chromen-2-one (9aee):



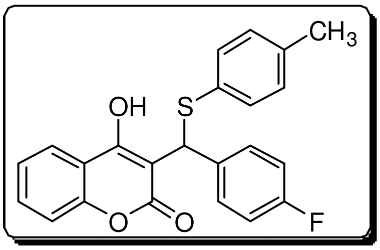
Nature: White solid; mp 138-140 °C. **IR** (KBr): 3155, 2922, 1892, 1682, 1619, 1567, 1492, 1450, 1393, 1340, 1282, 1199, 1161, 1146, 1108, 1088, 1061, 1013, 896, 815, 804, 765, 754, 733, 680 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 6.04 (s, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 3H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 10.42 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 49.8, 102.1, 116.0, 116.7, 123.7, 124.2, 128.0, 129.4 (2C), 129.5 (2C), 130.5 (2C), 131.6 (2C), 132.7, 134.4, 135.7, 139.2, 152.9, 162.6, 163.2. **HRMS** (APCI): calcd for $C_{23}H_{17}ClO_3S$ [M + K]$^+$: 447.0219. Found: 447.0221.

3-((4-bromophenyl)(p-tolylthio)methyl)-4-hydroxy-2H-chromen-2-one (9afe):



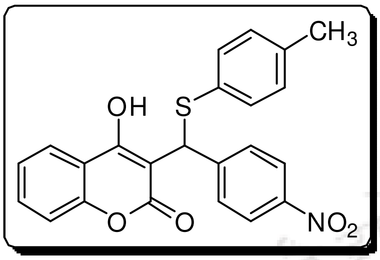
Nature: White solid; mp 143-145 °C. **IR** (KBr): 3493, 3160, 2961, 2919, 2852, 1682, 1619, 1566, 1493, 1449, 1395, 1339, 1281, 1198, 1161, 1145, 1108, 1061, 1009, 896, 804, 764, 754, 731, 684, 668 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 6.03 (s, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 4H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 10.42 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 49.7, 102.0, 115.9, 116.5, 122.4, 123.5, 124.2, 128.0, 129.7 (2C), 130.4 (2C), 131.5 (2C), 132.2 (2C), 132.6, 136.2, 139.1, 152.8, 162.6, 163.1. **HRMS** (ESI): calcd for $C_{23}H_{17}BrO_3S$ [M + H]$^+$: 455.0136. Found: 455.0144.

3-((4-fluorophenyl)(p-tolylthio)methyl)-4-hydroxy-2H-chromen-2-one (9ave):



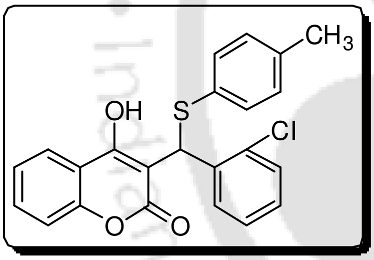
Nature: White solid; mp 79-80 °C. **IR** (KBr): 3447, 3071, 2953, 2922, 2858, 1925, 1686, 1624, 1573, 1507, 1494, 1454, 1381, 1279, 1250, 1234, 1211, 1160, 1108, 1040, 1015, 942, 929, 896, 853, 819, 799, 767, 751, 716, 671 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 6.06 (s, 1H), 7.03 (t, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 9.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.48 (dd, J_1 = 8.4 Hz & J_2 = 8.8 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 10.47 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 49.6, 102.3, 115.9, 116.0, 116.2, 116.6, 123.6, 124.2, 128.1, 129.8, 129.9, 130.4, 131.5, 132.6, 132.9, 133.0, 139.1, 152.8, 161.3, 162.6, 163.1, 163.8. **HRMS** (APCI): calcd for $C_{23}H_{17}FO_3S$ $[M + K]^+$: 431.0514. Found: 431.0518.

4-hydroxy-3-((4-nitrophenyl)(p-tolylthio)methyl)-2H-chromen-2-one (9ahe):



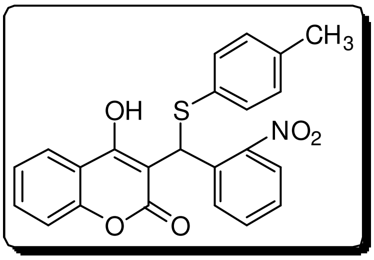
Nature: White solid; mp 201-203 °C. **IR** (KBr): 3471, 3162, 2919, 2847, 1678, 1620, 1566, 1518, 1495, 1451, 1401, 1344, 1280, 1220, 1190, 1166, 1148, 1109, 1072, 1012, 897, 854, 827, 806, 767, 759, 715, 673 cm^{-1}. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 6.11 (s, 1H), 7.11 (d, J = 7.2 Hz, 2H), 7.26 (d, J = 3.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 2H), 10.45 (s, 1H, OH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.3, 50.0, 101.4, 115.9, 116.7, 123.7, 124.3 (2C), 124.4, 127.4, 129.2 (2C), 130.7 (2C), 131.9 (2C), 133.0, 139.7, 144.7, 147.8, 152.9, 162.6, 163.5. **HRMS** (APCI): calcd for $C_{23}H_{17}NO_5S$ $[M + H]^+$: 420.0900. Found: 420.0901.

3-((2-chlorophenyl)(p-tolylthio)methyl)-4-hydroxy-2H-chromen-2-one (9aoe):



Nature: White solid; mp 197-199 °C. **IR** (KBr): 3173, 2964, 2919, 2855, 1668, 1627, 1568, 1496, 1465, 1452, 1437, 1404, 1343, 1292, 1269, 1231, 1192, 1163, 1151, 1114, 1058, 1046, 1034, 1017, 955, 939, 896, 867, 850, 807, 764, 750, 738, 697, 682, 643 cm^{-1}. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 6.29 (s, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.25-7.27 (m, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.46-7.49 (m, 3H), 7.58 (t, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 11.06 (s, 1H, OH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.3, 49.2, 101.5, 116.2, 116.7, 123.7, 124.2, 127.5, 128.3, 128.7, 129.9, 130.6 (2C), 130.7, 132.0 (2C), 132.7, 134.7, 134.8, 139.5, 153.0, 162.3, 163.8. **HRMS** (ESI): calcd for $C_{23}H_{17}ClO_3S$ $[M + H]^+$: 409.0660. Found: 409.0667.

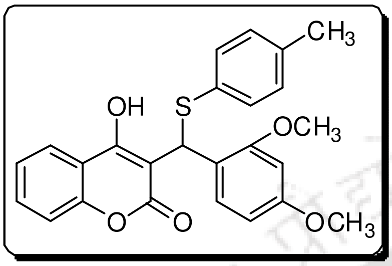
4-hydroxy-3-((2-nitrophenyl)(p-tolylthio)methyl)-2H-chromen-2-one (9ame):



Nature: White solid; mp 170-172 °C. **IR** (KBr): 3174, 2919, 2861, 1667, 1630, 1619, 1565, 1525, 1497, 1475, 1451, 1404, 1349, 1292, 1267, 1231, 1212, 1190, 1164, 1150, 1113, 1081, 1059, 1033, 1017, 941, 921, 897, 878, 858, 828, 808, 788, 761, 749, 735, 716, 678 cm^{-1}. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 6.60 (s, 1H), 7.06 (d, J = 7.6 Hz, 2H), 7.18 (d, J = 7.2 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 7.38-7.45 (m, 4H), 7.49 (t, J = 8.0 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.0

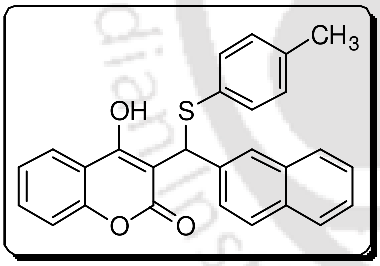
Hz, 1H), 11.09 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.4, 47.6, 101.3, 116.0, 116.7, 123.8, 124.3, 126.0, 127.5, 129.4, 129.5, 130.7 (2C), 132.5 (2C), 132.6, 132.9, 133.7, 140.0, 148.8, 153.1, 162.2, 163.9. **HRMS** (ESI): calcd for $C_{23}H_{17}NO_5S$ [M + H]$^+$: 420.0900. Found: 420.0904.

3-((2,4-dimethoxyphenyl)(p-tolylthio)methyl)-4-hydroxy-2H-chromen-2-one (9awe):



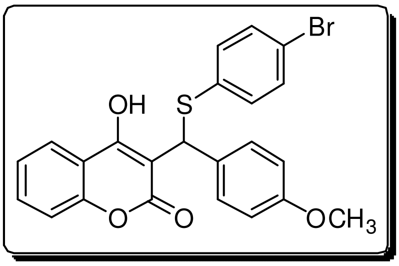
Nature: White solid; mp 122-123 °C. **IR** (KBr)**:** 3213, 2919, 2836, 2359, 2332, 1671, 1621, 1606, 1567, 1495, 1457, 1438, 1399, 1345, 1293, 1204, 1191, 1178, 1163, 1102, 1074, 1031, 938, 917, 894, 840, 820, 757, 680 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.27 (s, 3H), 3.79 (s, 3H), 3.95 (s, 3H), 6.16 (s, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.22-7.32 (m, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 10.77 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.1, 46.0, 55.4, 55.9, 99.3, 102.5, 104.8, 116.3, 118.1, 123.5, 123.9, 129.7, 129.8, 130.1 (2C), 131.3 (2C), 132.1, 132.4, 138.3, 152.6, 158.0, 161.1, 162.5, 162.7. **HRMS** (ESI): calcd for $C_{25}H_{22}O_5S$ [M + K]$^+$: 473.0820. Found: 473.0827.

4-hydroxy-3-(naphthalen-2-yl(p-tolylthio)methyl)-2H-chromen-2-one (9ale):



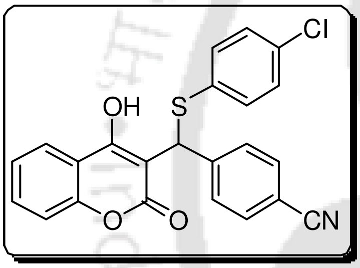
Nature: White solid; mp 114-116 °C. **IR** (KBr): 3445, 3052, 2921, 2854, 1693, 1662, 1621, 1567, 1492, 1453, 1395, 1331, 1281, 1207, 1105, 1037, 896, 858, 808, 761, 669 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.28 (s, 3H), 6.26 (s, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.25 (s, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.46-7.47 (m, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.80-7.86 (m, 3H), 7.89 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 10.47 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.3, 50.6, 102.4, 116.2, 116.6, 123.7, 124.2, 126.2, 126.5, 126.6, 126.8, 127.8, 128.2, 128.4, 129.1, 130.5 (2C), 131.6 (2C), 132.6, 133.2, 133.5, 134.5, 139.0, 152.9, 162.8, 163.2. **HRMS** (APCI): calcd for $C_{27}H_{20}O_3S$ [M + K]$^+$: 463.0765. Found: 463.0755.

3-(((4-bromophenyl)thio)(4-methoxyphenyl)methyl)-4-hydroxy-2H-chromen-2-one (9abg):



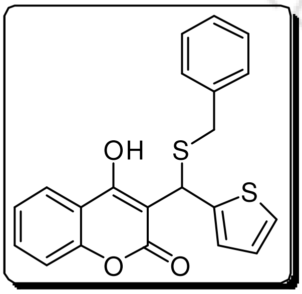
Nature: White solid; mp 230-232 °C. **IR** (KBr): 3438, 3074, 2837, 2734, 2616, 1670, 1615, 1604, 1564, 1510, 1453, 1353, 1308, 1280, 1258, 1219, 1178, 1162, 1093, 1053, 1034, 1009, 960, 920, 906, 895, 827, 811, 798, 787, 769, 674 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.15 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.25-7.28 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 3H), 7.41 (t, *J* = 9.2 Hz, 4H), 7.55 (t, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 10.03 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 48.9, 55.5, 102.3, 114.7 (2C), 115.9, 116.7, 122.6, 123.6, 124.3, 128.2, 129.4 (2C), 131.5, 132.2 (3C), 132.7 (2C), 152.8, 159.8, 162.7, 162.9. **HRMS** (ESI): calcd for $C_{23}H_{17}BrO_4S$ [M + K]$^+$: 508.9644. Found: 508.9628.

4-(((4-chlorophenyl)thio)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)benzonitrile (9aif):



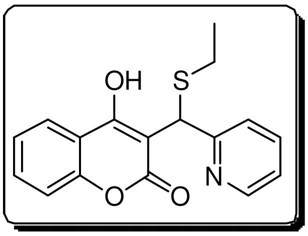
Nature: White solid; mp 110-112 °C. **IR** (KBr): 3157, 2229, 1678, 1621, 1607, 1566, 1498, 1476, 1451, 1395, 1345, 1279, 1221, 1198, 1167, 1149, 1108, 1093, 1076, 1023, 1011, 952, 922, 897, 860, 827, 820, 789, 770, 757, 743, 690 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.11 (s, 1H), 7.21-7.23 (m, 3H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.54 (t, *J* = 8.4 Hz, 1H), 7.60 (s, 3H), 7.90 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$/DMSO): δ 47.1, 104.7, 109.3, 115.1, 115.4, 117.8, 122.9, 128.0 (5C), 130.7 (3C), 130.8 (2C), 131.4, 134.5, 145.0, 151.6, 160.6, 160.9. **HRMS** (ESI): calcd for $C_{23}H_{14}ClNO_3S$ [M + K]$^+$: 458.0015. Found: 458.0015.

3-((benzylthio)(thiophen-2-yl)methyl)-4-hydroxy-2H-chromen-2-one (9auc):



Nature: Light green solid; mp 178-180 °C. **IR** (KBr): 3235, 3070, 2924, 2854, 1723, 1679, 1664, 1621, 1609, 1551, 1495, 1463, 1450, 1401, 1387, 1339, 1306, 1249, 1212, 1193, 1164, 1110, 1068, 1028, 892, 863, 804, 763, 747, 698 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.86 (s, 2H), 5.90 (s, 1H), 6.88 (t, *J* = 4.0 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 5.6 Hz, 1H), 7.20 (d, *J* = 4.8 Hz, 1H), 7.24 (t, *J* = 6.0 Hz, 3H), 7.31 (t, *J* = 7.6 Hz, 3H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 10.03 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 37.5, 40.8, 102.2, 115.8, 116.4, 123.5, 124.1, 125.7, 126.2, 126.9, 127.6, 128.7 (2C), 128.8 (2C), 132.6, 135.8, 140.6, 152.8, 162.2, 162.9. **HRMS** (ESI): calcd for $C_{21}H_{16}O_3S_2$ [M + K]$^+$: 419.0172. Found: 419.0172.

3-((ethylthio)(pyridin-2-yl)methyl)-4-hydroxy-2H-chromen-2-one (9ata):



Nature: White solid; mp 97-99 °C. **IR** (KBr): 3446, 3067, 2980, 2970, 2930, 2919, 2872, 2853, 1684, 1630, 1613, 1596, 1578, 1488, 1453, 1434, 1382, 1368, 1329, 1298, 1278, 1263, 1199, 1186, 1165, 1108, 1052, 1034, 1012, 944, 901, 864, 805, 779, 769, 760, 705, 675 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.6 Hz, 3H), 2.52-2.57 (m, 2H), 5.87 (s, 1H), 7.26 (d, *J* = 5.6 Hz, 2H), 7.39 (s, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.89 (t, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 8.53 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 26.9, 46.3, 101.9, 116.4, 118.0, 123.7, 124.0, 124.4, 124.5, 132.4, 140.2, 146.2, 152.9, 159.5, 164.1, 165.7. **HRMS** (ESI): calcd for $C_{17}H_{15}NO_3S$ [M + H]$^+$: 314.0845. Found: 314.0845.

Crystallographic description:

The X-ray crystal structures were determined using a single XRD diffractometer. Complete crystallographic data of **9aif**, **Co-Complex** and **Ni-Complex** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1038726, 1038805 and 1038804 respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 3.3. Crystal data and structures refinement for the compound **9aif** for atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**Compound 9aif**
Empirical Formula	$C_{23}H_{14}ClNO_3S$
Formula weight	419.86
Temperature	296 K
Wavelength	0.71073 (Å)
Crystal system	Triclinic
Space group	*P*-1
Radiation source	'fine-focus sealed tube'
Unit cell dimensions	*a* = 6.8647(11) (Å), α = 112.561(8)°

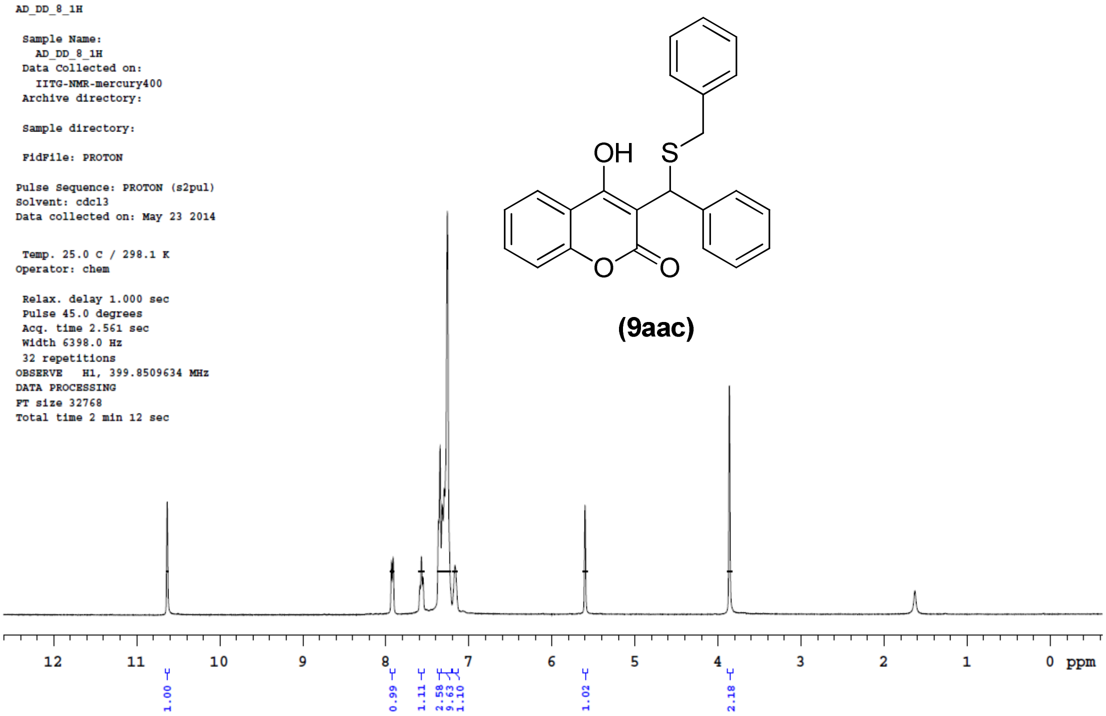
	b = 10.9002(13) (Å), β = 93.159(14)°
	c = 14.125(2) (Å), γ = 92.253(10)°
Unit cell volume	972.5(3) $Å^3$
Z	2
Density	1.434 g/cm^3
Reflections collected	7641
Independent reflections	3138 [R(int) = 0.0558]
Final R_1 values ($I > 2\sigma(I)$)	0.1338
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.3299
Final R_1 values (all data)	0.2072
Final $wR(F2)$ values (all data)	0.3775
Absorption coefficient, μ/mm	0.329
Radiation type	Mo K\a
Goodness of fit on F^2	1.075
F(0 0 0)	432.0
Theta range for data collection	2.03 to 24.99°
Index ranges	$-8 \leq h \leq 8$, $-12 \leq k \leq 12$, $-16 \leq l \leq 14$
Completeness to theta	24.99° 91.8 %
Number of parameters	263
Number of restraints	0
Refinement method	Full-matrix least-squares on F^2
CCDC number	1038726

Table 3.4. Crystal data and structures refinement for **Co-Complex** and **Ni-Complex.** For atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**Co Complex**	**Ni Complex**
Empirical Formula	$C_{34}H_{28}N_2O_6S_2Co{\bullet}2CH_2Cl_2$	$C_{34}H_{28}N_2O_6S_2Ni$
Formula weight	853.49	683.427
Temperature	296 K	296 K
Wavelength	0.71073 (Å)	0.71073 (Å)
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
Radiation source	'fine-focus sealed tube'	'fine-focus sealed tube'

Unit cell dimensions	a = 8.3365(6) (Å), α = 82.838(5)°	a = 8.1460(16) (Å), α = 76.635(17)°
	b = 11.1277(8) (Å), β = 69.409(4)°	b = 11.425(2) (Å), β = 83.429(17)°
	c = 11.2945(8) (Å), γ = 73.262(4)°	c = 17.576(4) (Å), γ = 72.903(17)°
Unit cell volume	938.94(12) Å^3	1519.3(5) Å^3
Z	1	2
Density	1.509 g/cm^3	1.494 g/cm^3
Reflections collected	13358	10908
Independent reflections	3333 [R(int) = 0.0254]	5482 [R(int) = 0.1085]
Final R_1 values ($I > 2\sigma(I)$)	0.0491	0.1013
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1421	0.1476
Final R_1 values (all data)	0.0615	0.2339
Final $wR(F2)$ values (all data)	0.1553	0.2041
Absorption coefficient, μ/mm	0.900	0.826
Radiation type	Mo K\a	Mo K\a
Goodness-of-fit (GOF) on F^2	0.987	1.102
F(0 0 0)	437.0	708.0
Theta range for data collection	1.91 to 25.25°	2.93 to 25.25°
Index ranges	$-10 \leq h \leq 10$, $-13 \leq k \leq 13$, $-13 \leq l \leq 13$	$-9 \leq h \leq 9$, $-13 \leq k \leq 13$, $-21 \leq l \leq 18$
Completeness to theta	25.25° 98.1 %	25.25° 99.5 %
Number of parameters	233	411
Number of restraints	0	0
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
CCDC number	1038805	1038804

***^{1}H NMR (400 MHz, CDCl$_3$)**: 3-((benzylthio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one* **(9aac)**



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AD_DD_8_1H

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   AD_DD_8_1H
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   IITG-NMR-mercury400
 Archive directory:

 Sample directory:

 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 23 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 12 sec
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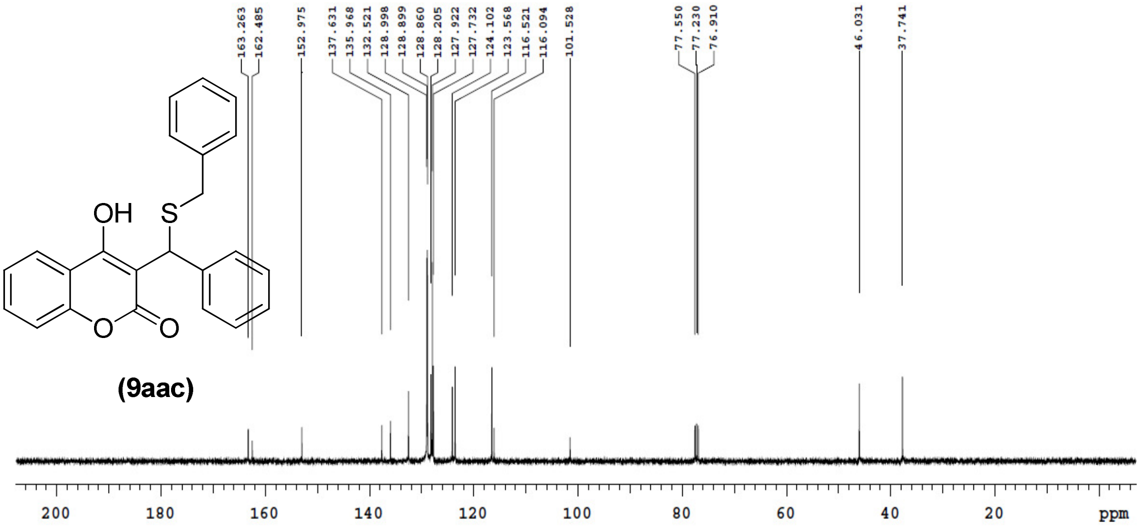
***^{13}C NMR (100 MHz, CDCl$_3$)**: 3-((benzylthio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one* **(9aac)**



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PULSE SEQUENCE          OBSERVE  C13, 100.5426001   DATA PROCESSING                 AD_DD_8_13C
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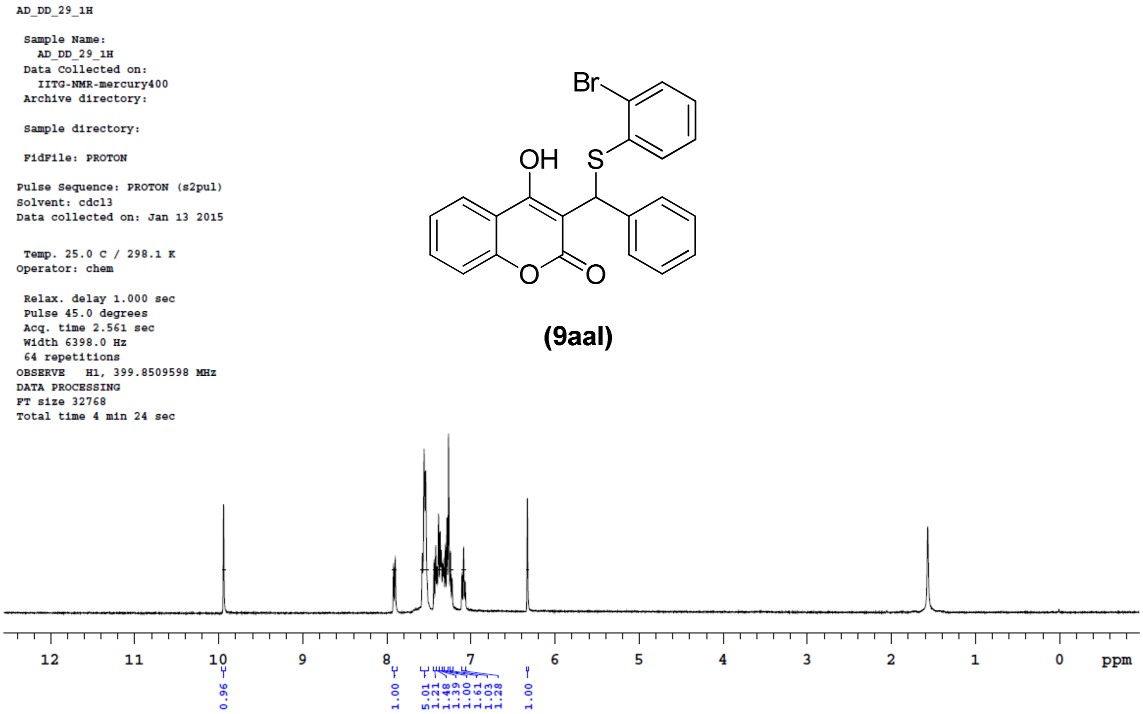
 Pulse 45.0 degrees      Power 42 dB                FT size 65536                   Solvent: cdcl3
 Acq. time 1.304 sec     continuously on            Total time 16 minutes           Temp. 25.0 C / 298.1 K
 Width 25125.6 Hz        WALTZ-16 modulated                                         Operator: chem
 425 repetitions                                                                    Mercury-400  "IITG-NMR"
```

Figure 3.13

***^{1}H NMR (400 MHz, $CDCl_3$)**: 3-(((2-bromophenyl)thio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one* (**9aal**)



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AD_DD_29_1H

 Sample Name:
   AD_DD_29_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:

 Sample directory:

 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 13 2015

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509598 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```
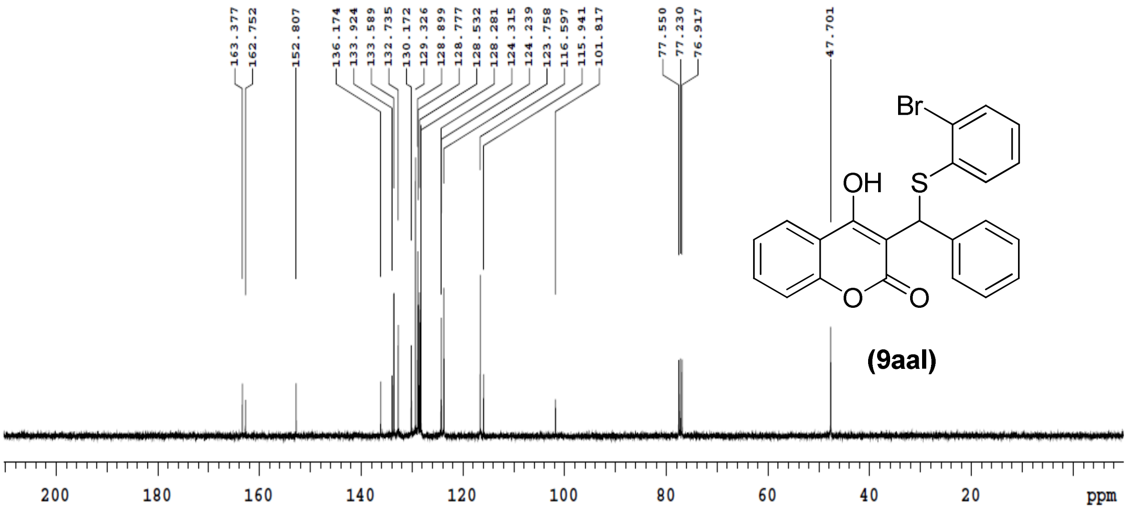

(9aal)

***^{13}C NMR (100 MHz, $CDCl_3$)**: 3-(((2-bromophenyl)thio)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one* (**9aal**)

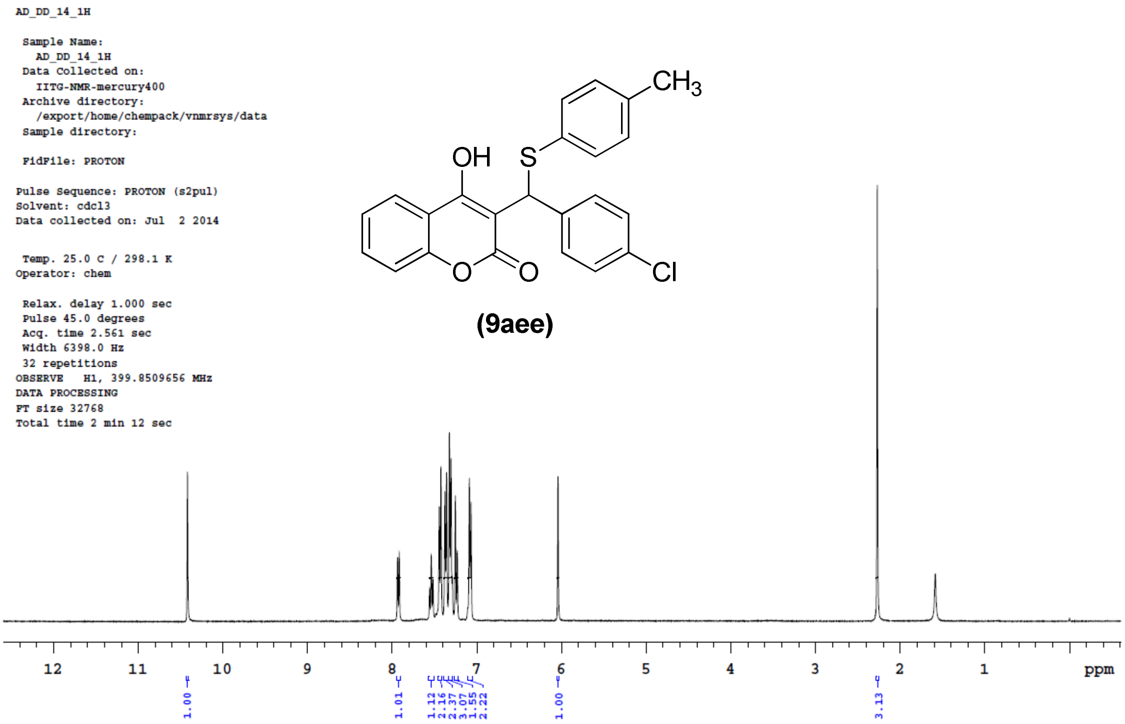


(9aal)

```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 68 repetitions

OBSERVE  C13, 100.5425939
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 2 minutes

AD_DD_29_13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

Figure 3.14

^{1}**H NMR (400 MHz, CDCl$_3$)**: *3-((4-chlorophenyl)(p-tolylthio)methyl)-4-hydroxy-2H-chromen-2-one* (**9aee**)



^{13}**C NMR (100 MHz, CDCl$_3$)**: *3-((4-chlorophenyl)(p-tolylthio)methyl)-4-hydroxy-2H-chromen-2-one* (**9aee**)

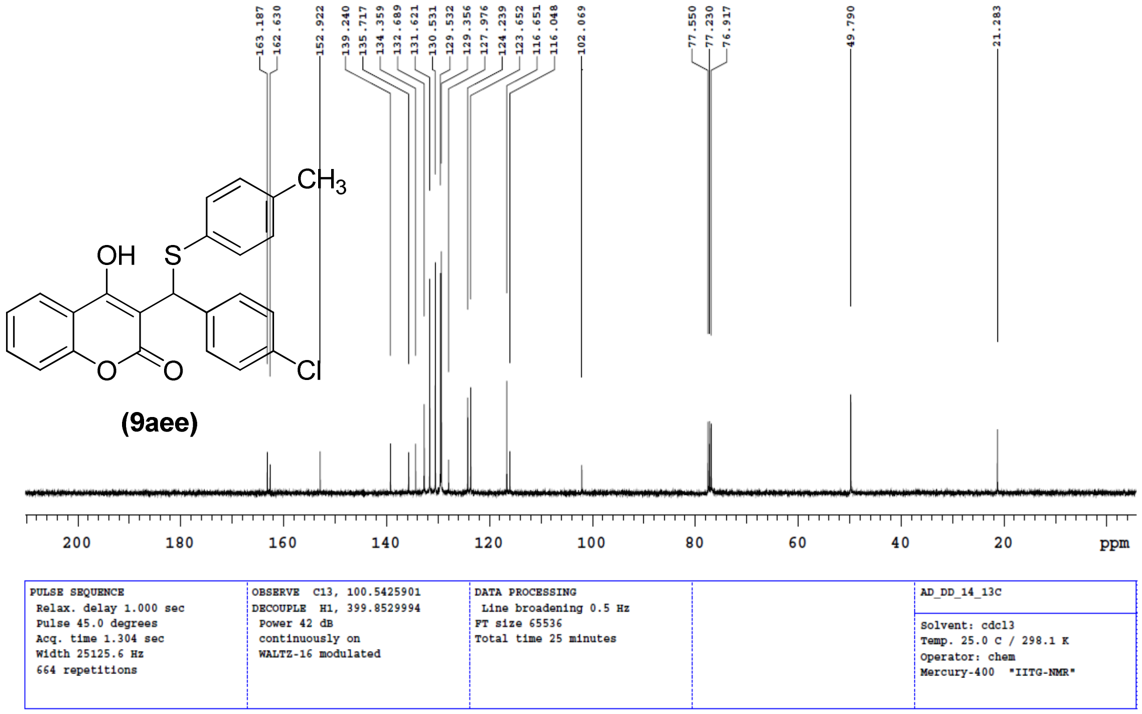
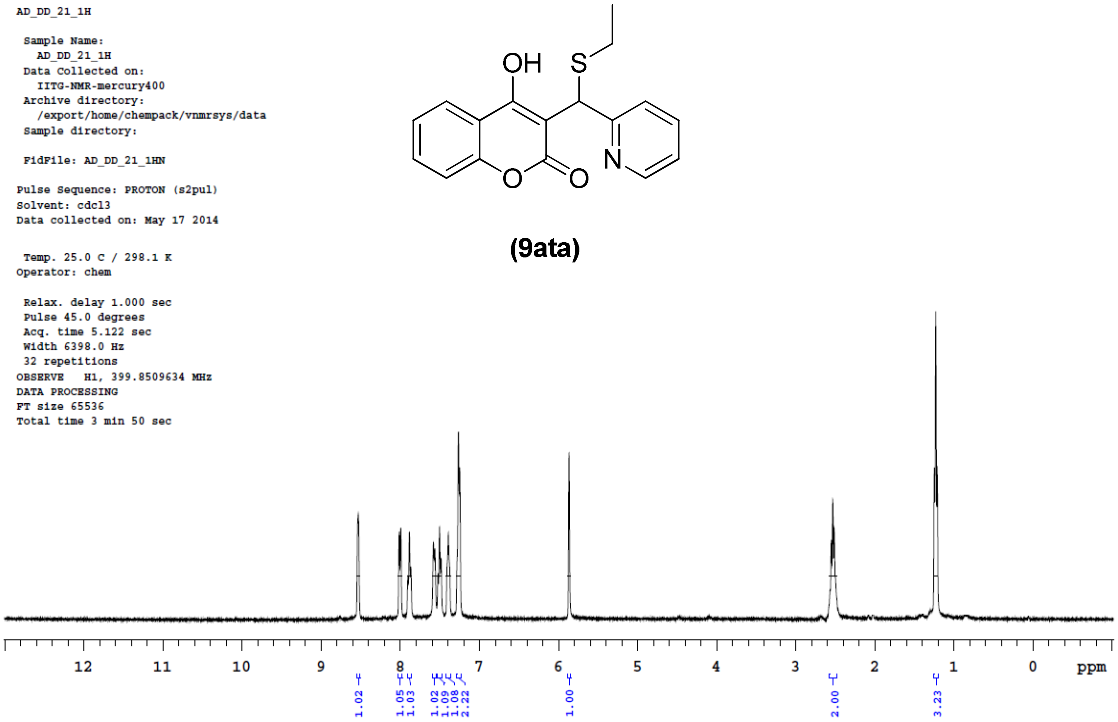


Figure 3.15

^{1}H NMR (400 MHz, CDCl$_3$): *3-((ethylthio)(pyridin-2-yl)methyl)-4-hydroxy-2H-chromen-2-one* (**9ata**)



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AD_DD_21_1H

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   AD_DD_21_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: AD_DD_21_1HN

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 17 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 5.122 sec
 Width 6398.0 Hz
 32 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
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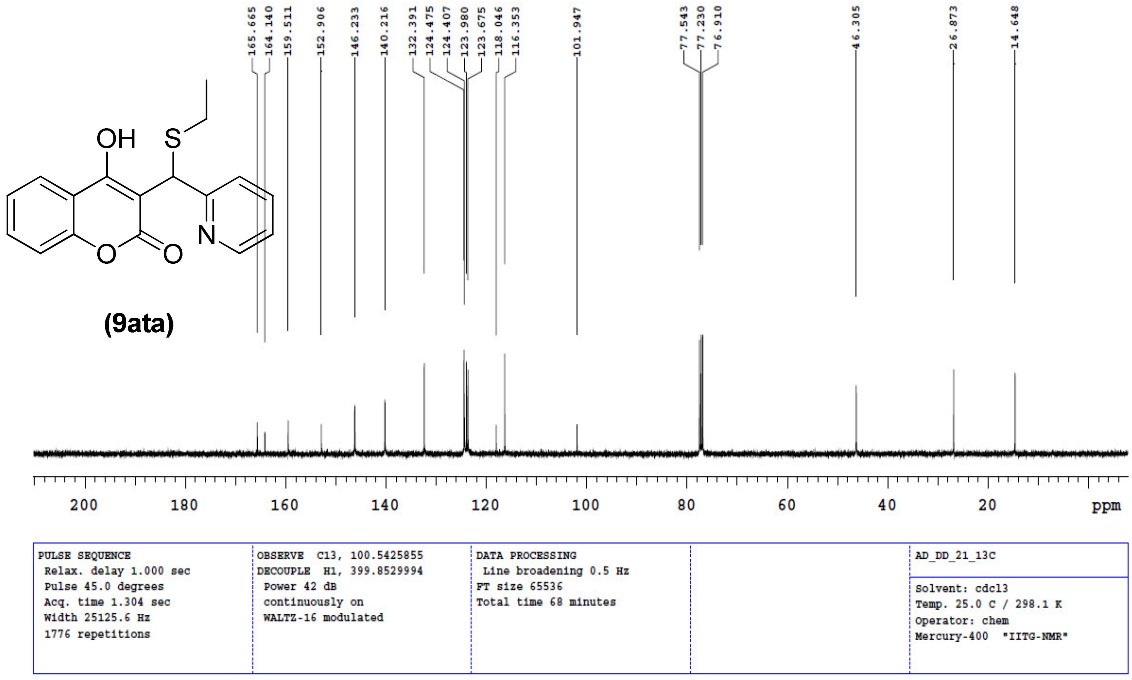

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DECOUPLE  H1, 399.8529994
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 continuously on
 WALTZ-16 modulated

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Figure 3.16

3.3 References

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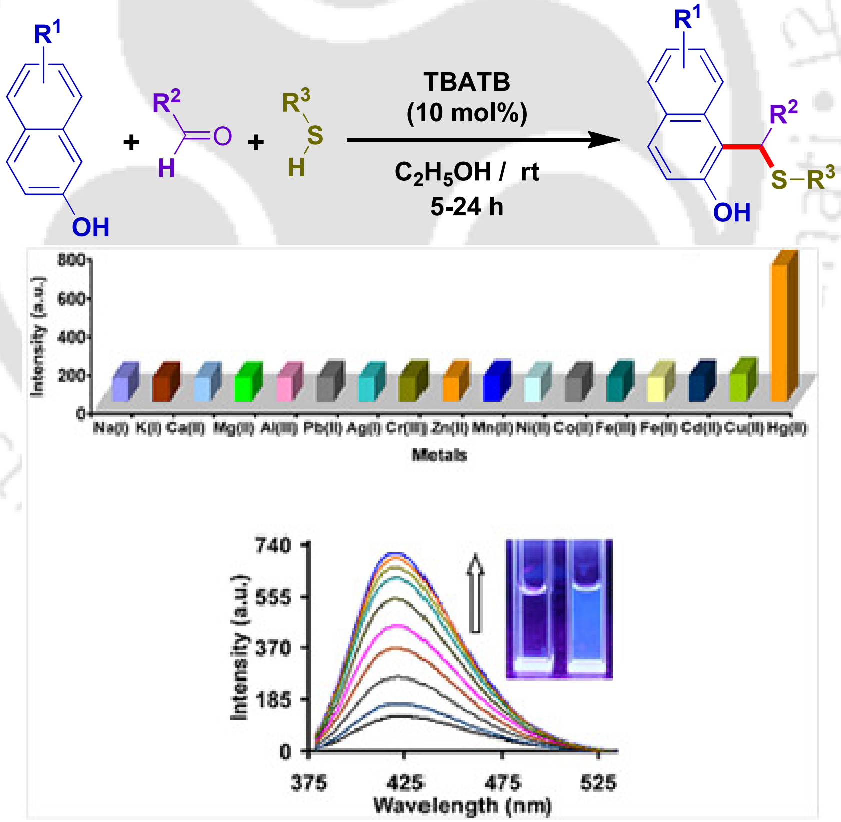
Chapter 4

Synthesis of unsymmetrical sulfides catalyzed by *n*-tetrabutylammonium tribromide: A selective fluorescence probe for mercury ion

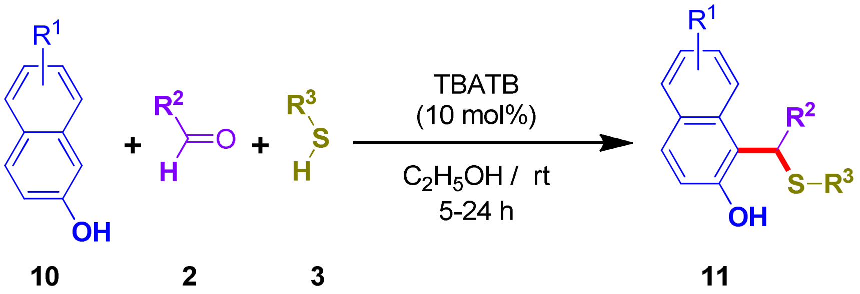


CHAPTER 4: Results and Discussion

4.1 Results and Discussion

In this chapter we would like to address the successful results for the usefulness and trapping of *o*-naphthoquinone methide intermediate, which is generated *in situ* from 2-naphthol and aromatic aldehyde. This *in situ* generated *o*-naphthoquinone methide intermediate is a useful Michael acceptor, which reacts with sulfur containing nucleophile, for the synthesis of 1-[(alkylthio)(phenyl) methyl]-naphthalene-2-ol. Interestingly, one of the synthesized unsymmetrical sulfide (**11aaa**) was used as selective fluorescence probe for mercury (II) ion.

Highly reactive intermediates *i.e ortho*-Quinone methides (*o*-QMs), have been explored for the synthesis of complex natural products.[1] These short lived species play the role of cytotoxins which are responsible for the effect of some antitumor drugs, antibiotics[2] and DNA alkylators.[3] Katritzky and his co-worker reported[4] the generation of 2-naphthoquinone-1-methide intermediate from 1-[α-(benzotriazol-1-yl)alkyl]-2-naphthols and its synthetic application for [4+2] hetero-Diels-Alder cycloaddition with electron rich dienophiles. Recently, Popik and his co-worker demonstrated their pioneering work for the development of bioorthogonal ‘click’ reactions for light-induced hetero-Diels-Alder reaction[5] and patterned surface derivatization[6] involving *in situ* generated 2-naphthoquinone-3-methide intermediate. Because of their high reactivity, they usually undergo instantaneously either [4+2] hetero-Diels-Alder reaction with electron rich dienophiles to form chroman derivatives with a high regio- and chemoselective[7] manner or they may undergo 1,4-Michael addition reaction with a suitable nucleophile.[8] Moreover, they may undergo new type [4+4] complementary ambiphile pairing reaction.[9] It has been observed that 2-naphthoquinone-1-methide intermediate can be generated very easily from 2- naphthol and aromatic aldehydes under appropriate reaction conditions, which can be trapped with various nucleophiles.[10] Recently, we have reported that the same reactive intermediate can be trapped for the synthesis of sulfides[11] using BDMS. We conceived that organic ammonium tribromide may be further explored for thia-Michael reaction, not explored earlier. A few years ago, Chaudhuri et al. demonstrated[12] an environmentally benign synthesis of *n*-tetrabutylammonium tribromide (TBATB) and we have proven that it can be used as a very good brominating reagent[13] or as a catalyst[14] for various organic transformations. In this chapter, we would like to report TBATB catalyzed synthesis of unsymmetrical sulfides by trapping *in situ* generated 2-naphthoquinone-1-methides with thiols and its usefulness for Hg (II) ion sensing (Scheme 4.1).



R^1 = H (10a)

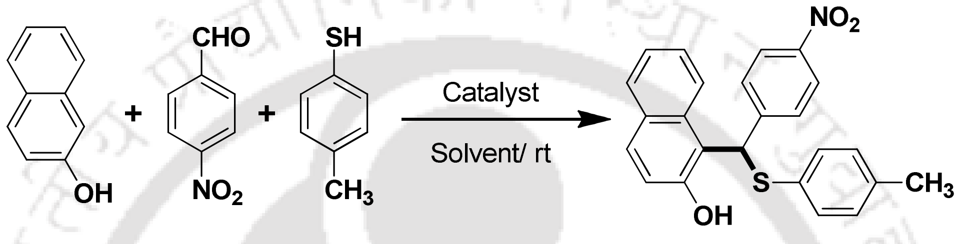
R^2 = Ph (2a), 4-MeOPh (2b), 4-ClPh (2e), 4-OHPh (2g), 4-NO_2Ph (2h), 2-Naphthyl (2l), 2-NO_2Ph (2m), 2-ClPh (2o), 3-ClPh (2y*), 3-BrPh (2z), 3-OHPh (2z*)

R^3 = Et (3a), Pr (3b), Ph (3d), 4-MePh (3e), 2-Naphthyl (3h), 4-MeOPh (3i), $HOCH_2CH_2$ (3m)

Scheme 4.1. One-pot three-component reaction for the synthesis of unsymmetrical sulfides

For the present study, the catalyst was prepared by following the literature procedure.[12] In order to find out suitable reaction conditions, 2-naphthol (**10a**), 4-nitrobenzaldehyde (**2h**) and 4-methylthiophenol (**3e**) were chosen as the model substrates. A mixture of compounds of **10a**, **2h** and **3e** in 3 mL of ethanol was stirred in presence of 5 mol% TBATB at room temperature. The product 1- [(*p*-tolylthio)(4-nitrophenyl)methyl] naphthalen-2-ol (**11ahe**) was obtained in 57% yield along with dithioacetal derived from aldehyde. The structure of compound (**11ahe)** was determined by recording IR, ^{1}H NMR, ^{13}C NMR spectra and by elemental analysis. The ^{1}H NMR spectrum of compound (**11ahe)** showed the signals at δ 2.22 (s, 3H), 6.60 (s, 1H), 6.98 (d, J = 7.60 Hz, 2H), 7.15 (d, J = 8.8 Hz, 1H), 7.25-7.35 (m, 4H), 7.66 (d, J = 8.4 Hz, 3H), 7.72 (t, J = 8.4 Hz, 2H), 8.10 (d, J = 8.8 Hz, 2H), 9.46 (s, 1H, OH) and ^{13}C NMR signals at δ 21.1, 50.2, 116.1, 119.2, 122.7, 123.5, 123.8 (3C), 127.1, 129.1, 129.3 (2C), 129.7, 130.1 (2C), 130.7, 131.7 (2C), 132.5, 138.2, 147.0, 147.5, 153.1 respectively. The appearance of peaks at δ 6.60 for methine proton and 9.46 for OH group in the ^{1}H NMR spectrum and ^{13}C NMR signals at δ 50.2 are the characteristics of desired product (**11ahe**). Furthermore, similar reactions were performed in presence of 10% and 15% TBATB under identical reaction conditions and the product **11ahe** was obtained in 82% and 80% yield, respectively. For choosing, the suitability of other solvent, identical reaction was performed in dichloromethane (DCM) and acetonitrile (CH_3CN), respectively and product (**11ahe)** was obtained in relatively lower yield (Table 4.1, entries 5 and 6). Ethanol was found to be the most appropriate solvent for this reaction. To examine the efficacy with other catalysts, same reactions were screened in presence of iodine and *p*-toluenesulfonic acid (*p*-TsOH), which provided moderate yields as mentioned in Table 4.1. It was noted that the combination of 2-naphthol, aldehyde, thiol and TBATB in the ratio of 1:1:1.2:0.1 respectively gave the best result. Interestingly, no product was formed in the absence of catalyst, giving clear indication that TBATB plays a significant role for the formation of the product.

Table 4.1. Optimization for reaction conditions[a]



10a **2h** **3e** **11ahe**

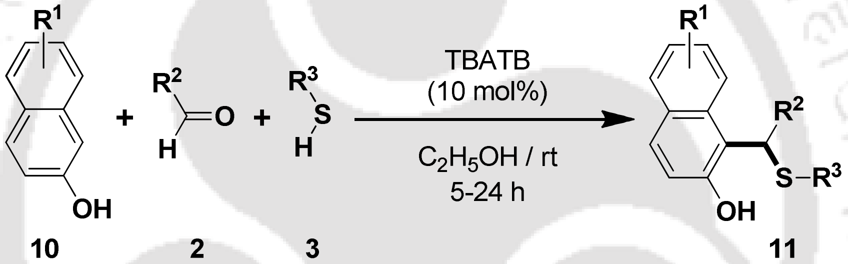
Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	No catalyst (0)	Ethanol	24	0
2	TBATB (5)	Ethanol	24	57
3	**TBATB (10)**	**Ethanol**	**24**	**82**
4	TBATB (15)	Ethanol	24	80
5	TBATB (10)	DCM	24	67
6	TBATB (10)	CH_3CN	24	70
7	I_2 (10)	Ethanol	24	51
8	*p*-TsOH (10)	Ethanol	24	62

[a]All the reactions were carried out using 2-naphthol (1 mmol), 4-nitrobenzaldehyde (1 mmol) and 4-methylthiophenol (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

After optimizing reaction conditions, the similar kind of reactions were carried out with various aromatic aldehydes having substituents such as Cl, Br, OMe, OH and NO_2 at the different positions in the aromatic ring with different thiols in presence of TBATB at room temperature under identical reaction conditions and the successful results are summarized in Table 4.2. The desired unsymmetrical sulfides **11aaa-11ama** were obtained in fairly good to high yields except in few cases such as entries 7, 12, 21 and 22. It was noted that the aromatic aldehydes containing electron withdrawing groups reacted faster as compared to electron donating groups and provided good yields. Interestingly, the reaction of 2-naphthol, 4-

nitrobenzaldehyde and thiophenol afforded the desired product in 70% yield (Table 4.2, entry 16) whereas it gave poor yield in case of 2-naphthol, 4-chlorobenzaldehyde and thiophenol (Table 4.2, entry 12), which may be due to poor nucleophilicity of thiophenol. It has been observed that 2-naphthol, 2- nitrobenzaldehyde and ethanethiol provided only 20% yield (Table 4.2, entry 22) under similar reaction conditions, which may be due to steric hindrance of nitro group at the *ortho*-position. Unfortunately, no product was obtained under identical condition when 2-chlorobenzaldehyde was used. All these products were characterized by recording melting point, IR, ^{1}H NMR, ^{13}C NMR spectra and by elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compounds **11ay*e, 11aba, 11aee** and **11ala** are given in the Experimental Section (Figure 4.5, 4.6, 4.7 and 4.8).

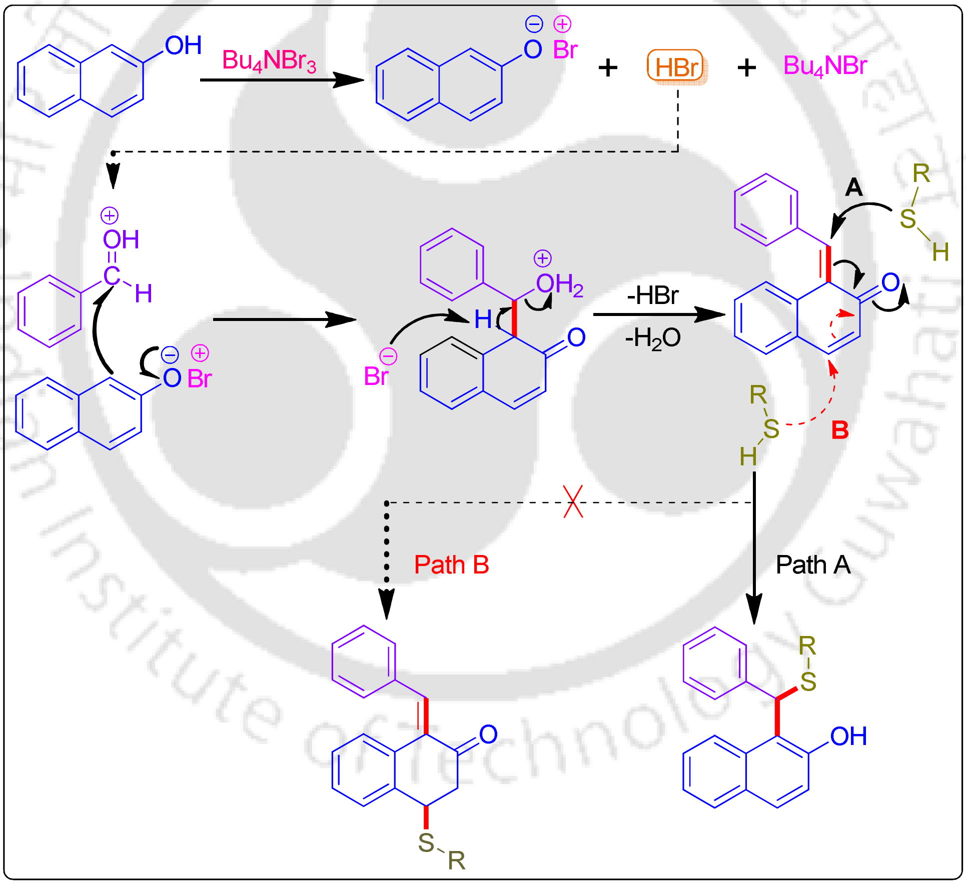
Table 4.2. Synthesis of sulfide through three component reaction[a]



Entry	2-Naphthol	Aldehyde (2)	Thiol (3)	Product (11)	Yield (%)[b]
1	**10a**	**2a**	**3a**	**11aaa**	75
2	**10a**	**2a**	**3e**	**11aae**	74
3	**10a**	**2a**	**3m**	**11aam**	65
4	**10a**	**2y***	**3b**	**11ay*b**	75
5	**10a**	**2y***	**3e**	**11ay*e**	71
6	**10a**	**2z**	**3a**	**11aza**	76
7	**10a**	**2z***	**3e**	**11az*e**	31
8	**10a**	**2b**	**3a**	**11aba**	63
9	**10a**	**2b**	**3i**	**11abi**	56
10	**10a**	**2e**	**3a**	**11aea**	80
11	**10a**	**2e**	**3b**	**11aeb**	79
12	**10a**	**2e**	**3d**	**11aed**	32
13	**10a**	**2e**	**3e**	**11aee**	74
14	**10a**	**2e**	**3i**	**11aei**	73

15	**10a**	**2e**	**3m**	**11aem**	69
16	**10a**	**2h**	**3d**	**11ahd**	70
17	**10a**	**2h**	**3e**	**11ahe**	82
18	**10a**	**2h**	**3i**	**11ahi**	71
19	**10a**	**2h**	**3h**	**11ahh**	72
20	**10a**	**2l**	**3a**	**11ala**	75
21	**10a**	**2g**	**3a**	**11aga**	50
22	**10a**	**2m**	**3a**	**11ama**	20
23	**10a**	**2o**	**3a**	**11aoa**	00

[a]All the reactions were performed using 2-naphthol (1 mmol), aldehyde (1 mmol) and thiol (1.2 mmol). [b]Isolated yield.



Scheme 4.2. Plausible Mechanism for the formation of unsymmetrical sulfides.

The formation of the 1-[(alkylthio)(phenyl)methyl] naphthalene-2-ol can be explained as follows: It is proposed that TBATB reacts with 2- naphthol to generate HBr in the reaction medium, which actually catalyzes the reaction (Scheme 4.2). The reaction of 2-naphthol with aromatic aldehydes in the presence of HBr give 2-naphthoquinone-1- methide intermediates.

These *in situ* generated intermediates can react with thiols by two possible pathways either path A or path B. Since the pathway A is more favourable, due to restoration of aromaticity in 2-naphthol moiety in contrast to pathway B, to form the desired products.

Next, we have studied the synthesized unsymmetrical sulfide (**11aaa**) for the selective detection of mercury (Hg^{2+}) ion in aqueous solution. The thiophilic nature of Hg^{2+} ion is well known and has been utilized by several research groups in the selective detection of Hg^{2+} ion over other metal ions.[15] Also, mercury ions are considered as a major source of carcinogen and due to their presence in contaminated natural water is harmful for humans.[16] Therefore, design and synthesis of new chemical tools for the detection of natural and anthropogenic environmental contaminants, such as toxic mercury salts, is a topic of recent concern among scientific community. Consequently, the high sensitivity and selectivity for the detection of toxic contaminants is a fundamental goal for organic and analytical chemists all over the world.[17] In our mercury detection experiment, the aqueous solubility of the ligand (**11aaa**) was achieved at a basic pH of 9.5 due to the deprotonation of phenolic –OH moeity and at this particular pH, fluorescence enhancement of the ligand was found to be quite prominent in the presence of mercury (II) salts. Therefore, pH 9.5 condition was maintained in all the titration experiments reported in this work. To examine the selectivity of ligand towards metal ions, we performed the fluorescence titration of (**11aaa**) (13 μM) in 25 mM PBS buffer solution at a pH 9.5.

According to the Figure 4.1(a), compound **11aaa** was weakly fluorescent upon excitation at 360 nm and no fluorescence enhancement was observed in the presence of various other alkali as well as transition metal ions such as Na^{+}, K^{+}, Ca^{2+}, Mg^{2+}, Al^{3+}, Pb^{2+}, Ag^{+}, Cr^{3+}, Zn^{2+}, Mn^{2+}, Ni^{2+}, Co^{2+}, Fe^{3+}, Fe^{2+}, Cd^{2+}, Cu^{2+} even at 20 μM concentration. However, in presence of increasing concentration of Hg^{2+} ions, an emission band centered at 420 nm with fluorescence intensity enhancement appeared and this fluorescence intensity enhancement leveled off at 13 μM concentration of Hg^{2+} ion, till 1:1 ratio was reached [Figure 4.1(b)]. However, 50% fluorescence intensity enhancement was observed at a very less concentration 4.6 μM of Hg^{2+} ion. We also examined the selectivity of ligand (**11aaa**) for Hg^{2+} ion in a competitive environment of other metal ions in the same concentration as maintained for Hg^{2+} in the solution. The blue emission color of ligand-Hg^{2+} complex was visualized under UV light as shown in Figure 4.1(b) inset.

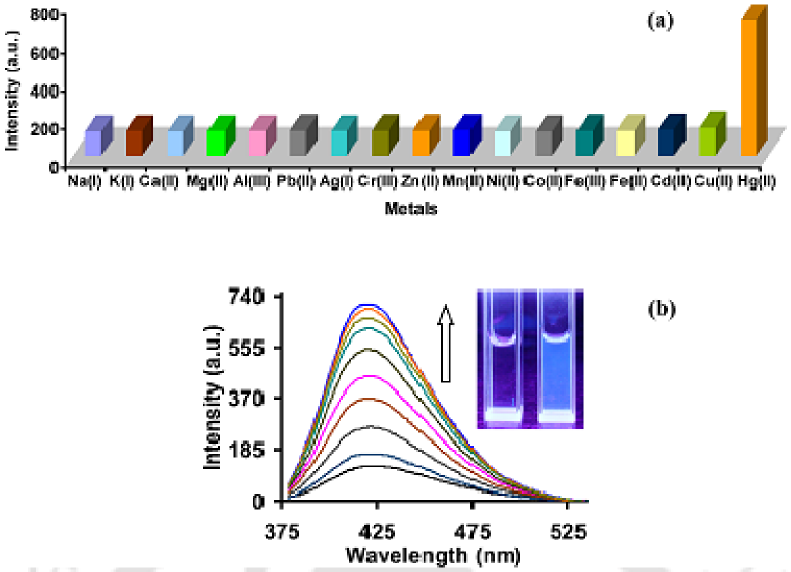


Figure 4.1. (a) Only Hg^{2+} interaction with compound revealed fluorescence enhancement property of the ligand (**11aaa**) in 1:1 of (**11aaa**) and Hg^{2+} but other metals were found to be inactive even in 1:1.5 ratio. (b) PL enhancement of Comp. (**11aaa**) (13 µM) by the interaction of Hg^{2+} (13 µM) in basic pH aqueous solution and on adding Hg^{2+} into the compound aqueous solution, blue fluorescence was observed.

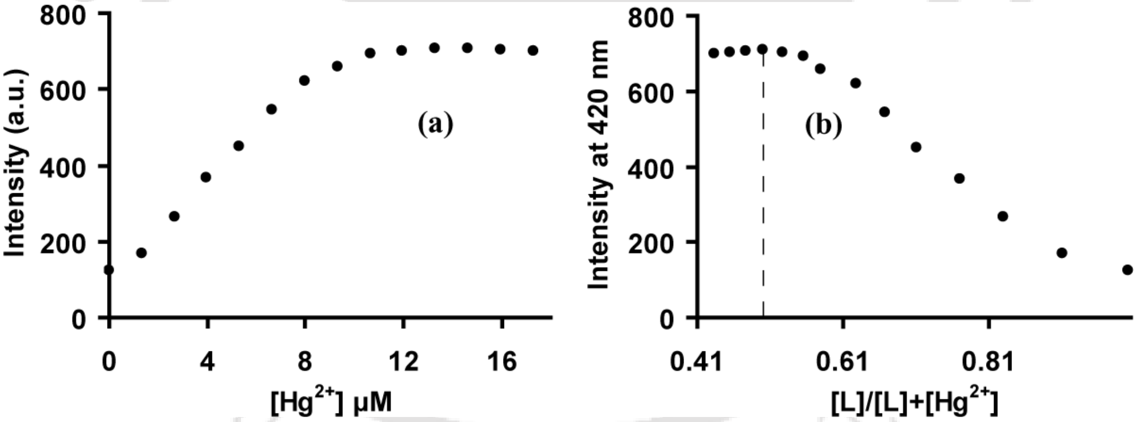


Figure 4.2. (a) Fluorescence intensity as function of Hg^{2+} concentration. (b) Job plot for the interaction between ligand and $[Hg^{2+}]$ in aqueous medium showing 1:1 stoichiometry.

The high affinity of Hg^{2+} ion for soft sulfur donor is well known. Therefore fluorescence enhancement of ligand in the presence of Hg^{2+} ion may be due to the disruption of ICT from soft sulfur and also it may be due to ceasing of non-radiative channels through complex formation, as the complex is rigid with respect to the free ligand. Hence flexible modes responsible for non-radiative processes are inactive in the complex. As a result, in the absence of metal, we observed very weak fluorescence of the ligand. The fluorescence intensity enhancement pattern was plotted against the Hg^{2+} concentration (Figure 4.2(a)) and the obtained 1:1 stoichiometry from the fluorescence titration of ligand (**11aaa**) with Hg^{2+} was also confirmed by Job's plot (Figure 4.2(b)).

Further UV/Vis titration of ligand (**11aaa**) in the presence of Hg^{2+} ion was performed in 25 mM PBS buffer (pH 9.5) solution (Figure 4.3). Absorption spectra of ligand (**11aaa**) in the presence of Hg^{2+} ion exhibit an absorption band centered at 358 nm that progressively shifts towards lower wavelength with increase in absorption intensity. This clearly indicates the formation of ligand–Hg^{2+} complex band centered at 348 nm with the same concentration ratio as we observed in fluorescence spectra. However, absorption spectra of ligand (**11aaa**) was found to be unaffected with other metal ions used in the present experiment, providing evidence of selectivity of ligand (**11aaa**) towards Hg^{2+} ion over all other metal ions reported here.

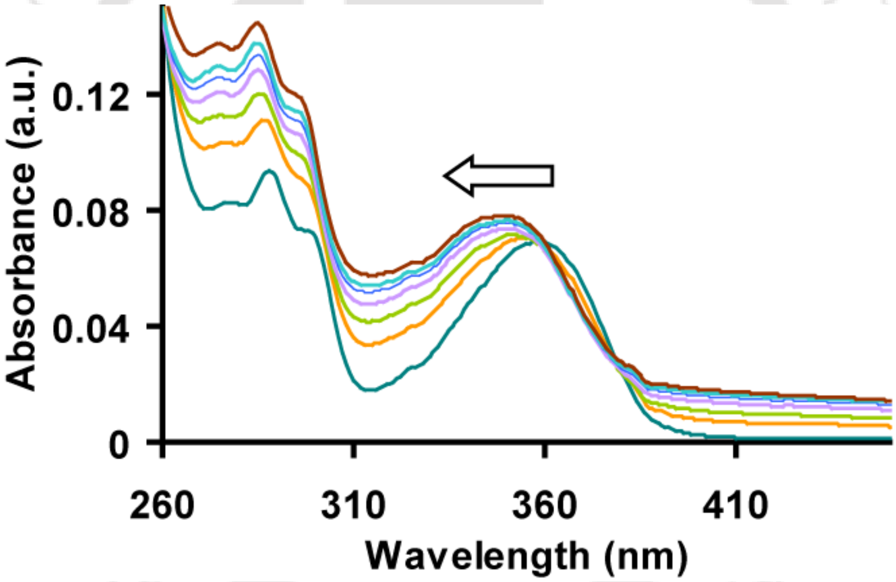


Figure 4.3. Absorption spectra of ligand (**11aaa**) (13 μM) on addition of Hg^{2+} (13 μM) in 25 mM PBS buffer solution.

The sensitivity of ligand (**11aaa**) towards Hg^{2+} was calculated on the basis of linear relationship between maximum emission intensity at 420 nm and the concentration of Hg^{2+} ion. The intensity at 420 nm increased linearly with 0 to 29×10^{-8} M concentration of Hg^{2+} as shown in Figure 4.4.

Detection limit was calculated using the equation 3σ/K, where σ is the standard deviation and K is the slope of the plot. The detection limit calculated for the ligand was found to be 21 nM. This value is much below the values prescribed by EPA. Since this ligand (**11aaa**) is easy to synthesize, soluble in aqueous medium and capable of performing detection of mercury ions in aqueous medium at high pH selectively, the utility of this compound as a turn-on fluorescence sensor are of practical importance.

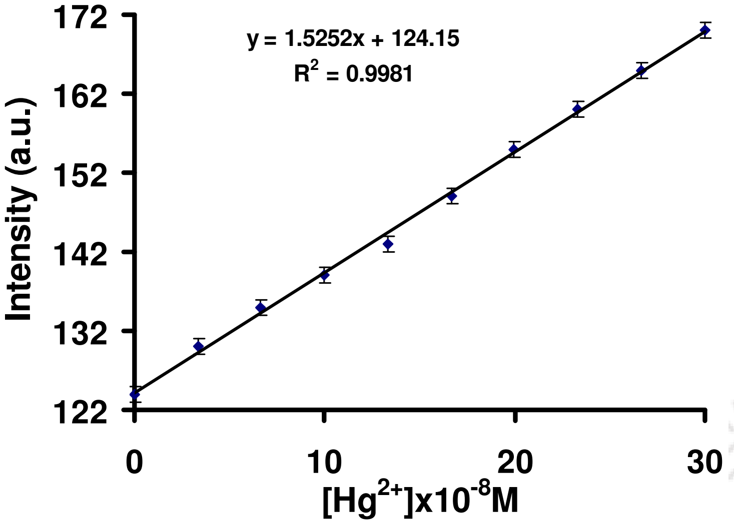
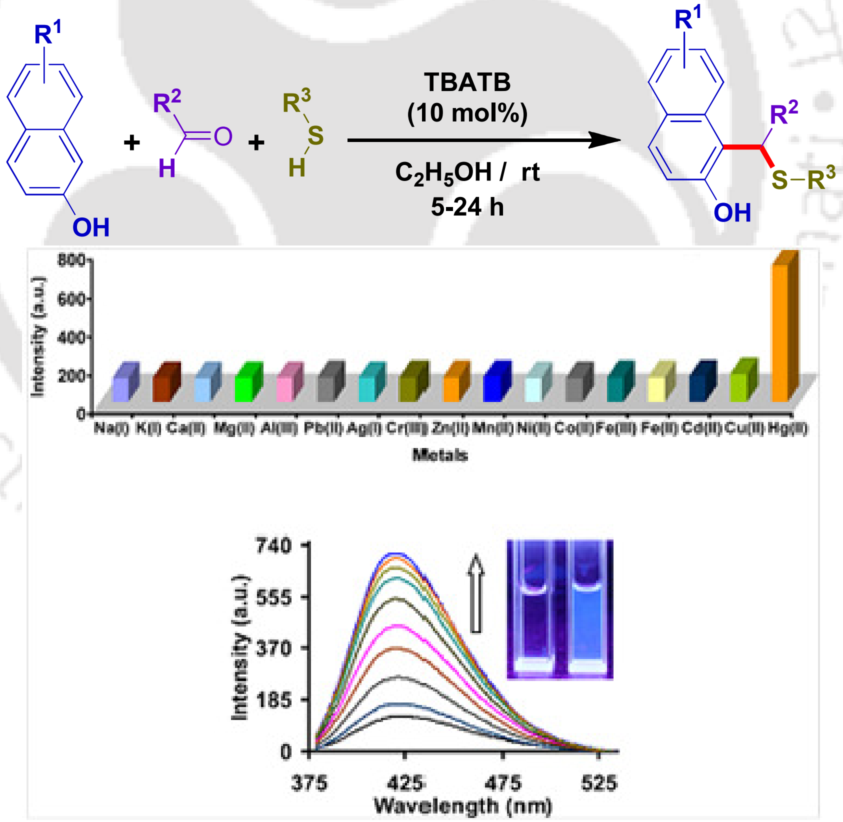


Figure 4.4. A linear relationship between maximum emission intensity at 420 nm and the concentration of Hg^{2+} ion.

In conclusion, we have revealed that environmentally benign reagent terabutyl-ammonium tribromide (TBATB) for the synthesis of unsymmetrical sulfides by trapping 2-naphthoquinone-1-methide intermediates and its usefulness for detecting mercury ions. The main advantages of the present protocol are mild reaction conditions, high efficiency, clean, economically viable, and tolerance to a wide range of substrates. In addition, the synthesized unsymmetrical sulfides are useful material for selective detection of mercury (II) ion.

Chapter 4

Synthesis of unsymmetrical sulfides catalyzed by *n*-tetrabutylammonium tribromide: A selective fluorescence probe for mercury ion



4.2 Experimental Section

Materials and Methods

All the reagents and solvents were purchased from Aldrich Chemicals (India), Merck (India) or Ranbaxy (India) and were used as received. Milli-Q water was used in all the experiments. The solutions of metal ions from NaCl, KCl, $CaCl_2.2H_2O$, $MgCl_2$, $AlCl_3.6H_2O$, $Pb(NO_3)_2$, $AgNO_3$, $CrCl_3.6H_2O$, $Zn(ClO_4)_2.6H_2O$, $Mn(ClO_4)_2.H_2O$, $NiCl_2.6H_2O$, $Co(ClO_4)_2.6H_2O$, $Fe(ClO_4)_3.H_2O$, $Fe(ClO_4)_2.H_2O$, $Cd(ClO_4)_2.H_2O$, $Cu(ClO_4)_2.6H_2O$, $HgCl_2$ were prepared in 25 mM PBS solution. Deionized water was used for the preparation of PBS solution.

General UV-vis and fluorescence spectra measurements

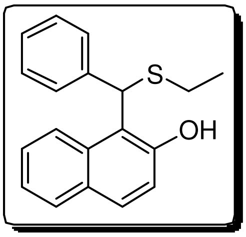
An aqueous solution of ligand (**11aa**) (13 μM in 25 mM PBS solution) was placed in the quartz cell and the UV-vis as well as fluorescence spectra were recorded for increasing portions of metal salts up to 13 μM. The experiments were performed at room temperature and changes monitored and recorded carefully.

General procedure for synthesis of compounds (11)

The catalyst, TBATB (0.048 g, 0.1 mmol) was added to a stirred solution of 2-naphthol (0.144 g, 1 mmol) and aromatic aldehyde (1 mmol) in 3 mL of ethanol at room temperature. After 10 mins of stirring, thiol (1.2 mmol) was added to the above reaction mixture slowly. After completion of the reaction as indicated by TLC, ethanol was removed in a rotary evaporator and the crude residue was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with water followed by brine solution. The organic extract was dried over anhydrous sodium sulfate and the solvent was removed in a rotary evaporator. The crude residue was purified by passing through a silica gel column. The compounds **11aem** and **11aam** were eluted with hexane/ethyl acetate (70:30) and rest of them were eluted with hexane/ethyl acetate (98:2) respectively.

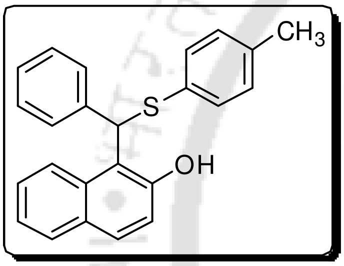
Spectral data of Compounds:

1-((Ethylthio)(phenyl)methyl)naphthalen-2-ol (11aaa):



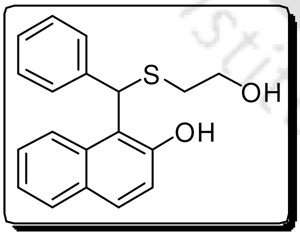
Nature: Pale yellow semi-solid; **IR** (KBr): 3452, 3102, 2963, 1619, 1599, 1491, 1449, 1404, 1257, 1222, 1148, 809, 699 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.6 Hz, 3H), 2.45-2.58 (m, 2H), 6.32 (s, 1H), 7.22 (d, *J* = 9.2 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.39-7.42 (m, 3H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 9.04 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 26.7, 46.2, 113.7, 120.2, 121.8, 123.3, 127.1, 127.7, 128.3 (2C), 128.9 (2C), 129.2, 129.5, 130.4, 133.3, 138.7, 155.2. **Anal. Calcd** for $C_{19}H_{18}OS$ (294.41): C, 77.51; H, 6.16. Found: C, 77.41; H, 6.02.

1-((p-tolylthio)(phenyl)methyl)naphthalen-2-ol (11aae):



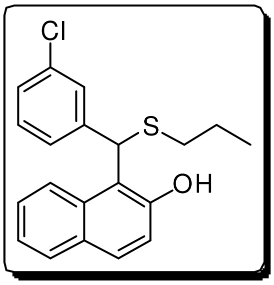
Nature: Pale yellow semi-solid; **IR** (KBr): 3457, 2923, 1622, 1252, 1220, 808, 698 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 6.55 (s, 1H), 6.92 (d, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.22-7.36 (m, 7H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 1H), 8.49 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 51.5, 115.1, 120.1, 122.2, 123.3, 127.0, 127.9, 128.6 (2C), 129.0 (3C), 129.5, 130.0 (3C), 130.4, 131.8 (2C), 133.1, 138.2, 138.5, 154.5. **Anal. Calcd** for $C_{24}H_{20}OS$ (356.48): C, 80.86; H, 5.65. Found: C, 80.68; H, 5.57.

1-((2-hydroxyethylthio)(phenyl)methyl)naphthalen-2-ol (11aam):



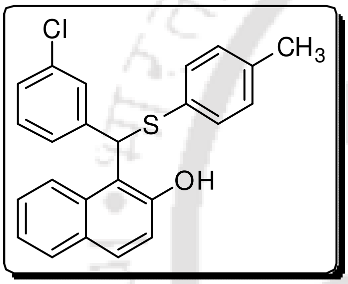
Nature: Pale yellow semi-solid; **IR** (KBr): 3458, 3434, 2926, 1633, 698 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.37 (s, 1H, OH), 2.58-2.70 (m, 2H), 3.61-3.71 (m, 2H), 6.40 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.22-7.29 (m, 3H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 8.55 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 34.9, 45.6, 61.2, 115.4, 119.4, 123.0, 123.3, 126.8, 127.4, 128.1 (2C), 128.7 (2C), 129.0, 129.6, 130.3, 132.8, 139.1, 153.9. **Anal. Calcd** for $C_{19}H_{18}O_2S$ (310.41): C, 73.52; H, 5.84. Found: C, 73.31; H, 5.73.

1-((3-chlorophenyl)(propylthio)methyl)naphthalen-2-ol (11ay*b):



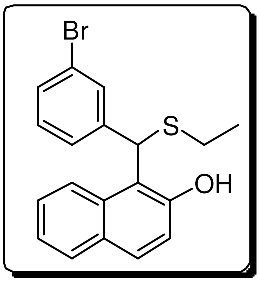
Nature: Pale yellow semi-solid; **IR** (KBr): 3197, 2961, 2346, 1621, 1600, 1401, 1252, 1223, 1146, 816, 744 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.55-1.63 (m, 2H), 2.39-2.46 (m, 1H), 2.51-2.57 (m, 1H), 6.22 (s, 1H), 7.18-7.20 (m, 2H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.25-7.28 (m, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.41-7.45 (m, 2H), 7.80 (d, *J* = 8.8 Hz, 3H), 8.97 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.5, 22.4, 34.8, 46.1, 113.0, 120.4, 121.6, 123.5, 126.6, 127.3, 128.1, 128.6, 129.3, 129.5, 130.2, 130.8, 133.3, 134.7, 141.0, 155.3. **Anal. Calcd** for $C_{20}H_{19}OSCl$ (342.88): C, 70.06; H, 5.59. Found: C, 69.91; H, 5.51.

1-((p-tolylthio)(3-chlorophenyl)methyl)naphthalen-2-ol (11ay*e):



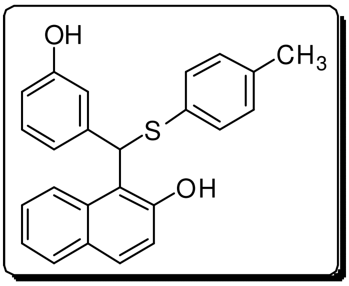
Nature: Pale yellow semi-solid; **IR** (KBr): 3413, 3247, 3054, 1620, 1591, 1492, 1468, 1401, 1250, 1220, 1143, 810, 743 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.14 (s, 3H), 6.48 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.16-7.18 (m, 2H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.33 (dt, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 2H), 7.51 (s, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 8.24 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 50.7, 115.1, 119.7, 122.2, 123.4, 126.6, 127.1, 128.0, 128.6, 129.0, 129.5, 130.0 (3C), 130.1, 130.5, 131.8 (2C), 132.8, 134.7, 138.3, 141.0, 153.9. **Anal. Calcd** for $C_{24}H_{19}OSCl$ (390.93): C, 73.74; H, 4.90. Found: C, 73.53; H, 4.78.

1-((3-bromophenyl)(ethylthio)methyl)naphthalen-2-ol (11aza):



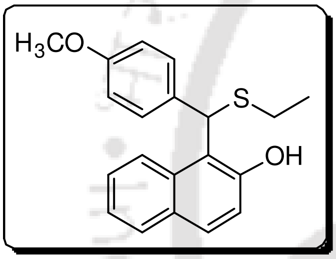
Nature: Pale yellow semi-solid; **IR** (KBr): 3417, 3199, 2926, 1621, 1596, 1469, 1401, 1252, 1223, 1145, 816, 744 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 7.6 Hz, 3H), 2.35-2.52 (m, 2H), 6.18 (s, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 9.2 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.24-7.27 (m, 2H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 1H), 8.82 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 26.9, 45.7, 112.9, 120.3, 121.6, 123.0, 123.5, 127.0, 127.4, 129.3, 129.5, 130.5, 130.8, 131.0, 131.5, 133.2, 141.1, 155.3. **Anal. Calcd** for $C_{19}H_{17}OSBr$ (373.31): C, 61.13; H, 4.59. Found: C, 61.01; H, 4.50.

1-((p-tolylthio)(3-hydroxyphenyl)methyl)naphthalen-2-ol (11az*e):



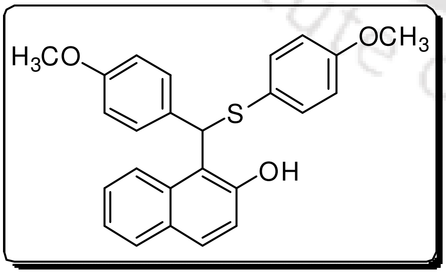
Nature: Pale yellow semi-solid; **IR** (KBr): 3436, 2925, 1622, 1599, 1450, 1252, 1144, 814, 745 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.14 (s, 3H), 6.48 (s, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.93 (s, 1H), 7.07-7.16 (m, 3H), 7.21-7.25 (m, 3H), 7.31 (dt, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 7.62 (dd, J_1 = 3.2 Hz, J_2 = 9.2 Hz, 1H), 7.67 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.2, 51.2, 115.1, 115.5, 119.9, 120.8, 122.3, 123.3, 127.0, 129.0, 129.5, 130.0 (4C), 130.3, 130.4, 131.6 (2C), 133.0, 138.1, 140.4, 154.1, 156.3. **Anal. Calcd** for $C_{24}H_{20}O_2S$ (372.48): C, 77.39; H, 5.41. Found: C, 77.21; H, 5.32.

1-((ethylthio)(4-methoxyphenyl)methyl)naphthalen-2-ol (11aba):



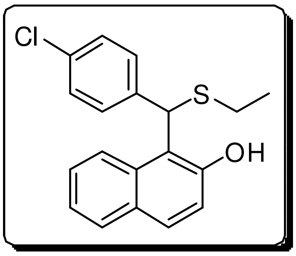
Nature: Pale yellow semi-solid; **IR** (KBr): 3138, 2966, 1620, 1600, 1509, 1405, 1247, 1225, 1175, 1027, 833, 747 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.22 (t, *J* = 7.6 Hz, 3H), 2.45-2.57 (m, 2H), 3.70 (s, 3H), 6.30 (s, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.43 (t, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 9.2 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 1H), 9.15 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.4, 26.7, 45.8, 55.4, 113.7, 114.3 (2C), 120.3, 121.8, 123.3, 127.2, 129.2, 129.4, 129.5 (2C), 130.4, 130.5, 133.3, 155.3, 159.1. **Anal. Calcd** for $C_{20}H_{20}O_2S$ (324.44): C, 74.04; H, 6.21. Found: C, 73.90; H, 6.08.

1-((4-methoxyphenylthio)(4-methoxyphenyl)methyl) naphthalen-2-ol (11abi):



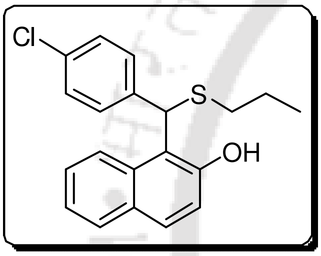
Nature: Pale yellow semi-solid; **IR** (KBr): 3414, 2956, 1591, 1508, 1493, 1286, 1248, 1174, 1031, 827, 746 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.63 (s, 3H), 3.74 (s, 3H), 6.44 (s, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 9.2 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 9.6 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 8.71 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 52.1, 55.3, 55.4, 114.3 (3C), 114.7 (2C), 115.2, 120.1, 122.1, 123.2, 123.8, 126.8, 128.9, 129.4, 129.7 (2C), 130.2, 133.1, 134.5 (2C), 154.4, 159.2, 159.9. **Anal. Calcd** for $C_{25}H_{22}O_3S$ (402.51): C, 74.60; H, 5.51. Found: C, 74.43; H, 5.44.

1-((4-chlorophenyl)(ethylthio)methyl)naphthalen-2-ol (11aea):



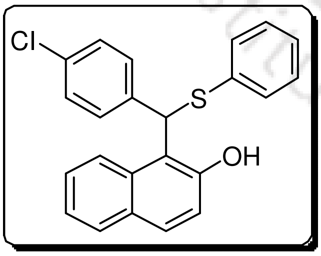
Nature: Pale yellow semi-solid; **IR** (KBr): 3167, 2927, 1621, 1600, 1488, 1402, 1256, 1224, 1146, 1086, 830, 744 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.22 (t, J = 7.6 Hz, 3H), 2.44-2.60 (m, 2H), 6.27 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.42 (t, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 7.6 Hz, 1H), 8.94 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.3, 26.8, 45.5, 113.2, 120.3, 121.6, 123.5, 127.3, 129.1 (2C), 129.3, 129.5, 129.8 (2C), 130.7, 131.2, 133.6, 137.2, 155.3. **Anal. Calcd** for $C_{19}H_{17}OSCl$ (328.86): C, 69.39; H, 5.21. Found: C, 69.28; H, 5.12.

1-((4-chlorophenyl)(propylthio)methyl)naphthalen-2-ol (11aeb):



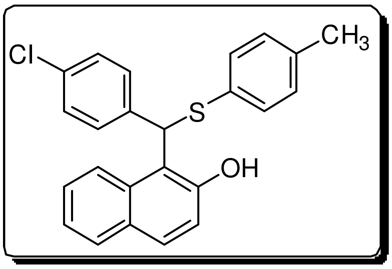
Nature: Pale yellow solid; mp 88-91 °C; **IR** (KBr): 3447, 2963, 1619, 1596, 1487, 1401, 1256, 1219, 1088, 830, 755 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.78 (t, J = 7.6 Hz, 3H), 1.45 (sext, J = 7.6 Hz, 2H), 2.25-2.32 (m, 1H), 2.37-2.44 (m, 1H), 6.12 (s, 1H), 7.10-7.12 (m, 3H), 7.18 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 8.88 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 13.5, 22.4, 34.7, 45.9, 113.4, 120.3, 121.6, 123.4, 127.3, 129.1 (2C), 129.3, 129.5, 129.8 (2C), 130.7, 133.2, 133.6, 137.4, 155.2. **Anal. Calcd** for $C_{20}H_{19}ClOS$ (342.88): C, 70.06; H, 5.59. Found: C, 69.95; H, 5.48.

1-((4-chlorophenyl)(phenylthio)methyl)naphthalen-2-ol (11aed):



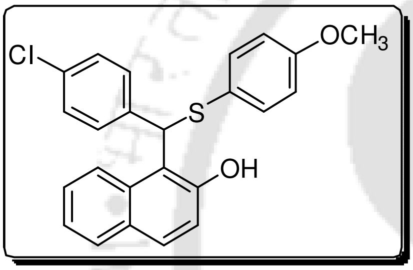
Nature: Pale yellow semi-solid; **IR** (KBr): 3442, 2917, 1623, 1599, 1487, 1250, 1218, 1089, 1012, 823, 741 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 6.49 (s, 1H), 7.05-7.08 (m, 3H), 7.20 (d, J = 7.6 Hz, 2H), 7.22 (t, J = 8.4 Hz, 1H), 7.26-7.31 (m, 4H), 7.36 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 50.0, 115.2, 119.9, 122.2, 123.5, 127.2, 128.0, 129.2 (3C), 129.3 (2C), 129.6, 129.9 (3C), 130.6, 131.2 (2C), 132.8, 133.7, 137.2, 154.0. **Anal. Calcd** for $C_{23}H_{17}ClOS$ (376.90): C, 73.29; H, 4.55. Found: C, 73.09; H, 4.46.

1-((p-tolylthio)(4-chlorophenyl)methyl)naphthalen-2-ol (11aee):



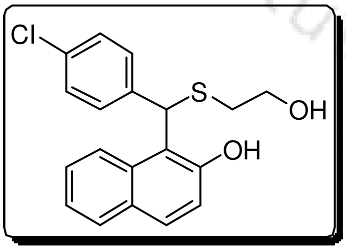
Nature: Pale yellow semi-solid; **IR** (KBr): 3436, 2922, 1622, 1488, 1401, 1252, 1222, 1145, 1090, 808, 743 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.18 (s, 3H), 6.49 (s, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.24-7.28 (m, 5H), 7.35 (dt, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 3H), 8.29 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.1, 50.6, 115.3, 119.7, 122.2, 123.4, 127.0, 129.0 (3C), 129.5, 129.9 (3C), 130.0 (2C), 130.5, 131.7 (2C), 132.8, 133.5, 137.3, 138.1, 153.9. **Anal. Calcd** for $C_{24}H_{19}OSCl$ (390.93): C, 73.74; H, 4.90. Found: C, 73.53; H, 4.81.

1-((4-methoxyphenylthio)(4-chlorophenyl)methyl)naphthalen-2-ol (11aei):



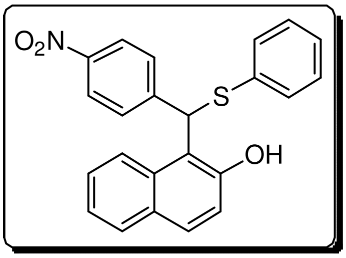
Nature: Pale yellow semi-solid; **IR** (KBr): 3453, 1631, 1492, 1248, 1174, 1089, 823, 746 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.66 (s, 3H), 6.41 (s, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 9.2 Hz, 1H), 7.22-7.27 (m, 3H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 8.38 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 52.0, 55.4, 114.8 (3C), 120.0, 122.0, 123.4, 127.0, 129.0 (2C), 129.1 (2C), 129.5, 130.0 (2C), 130.6, 133.0, 133.7, 134.8 (2C), 137.1, 154.3, 160.2. **Anal. Calcd** for $C_{24}H_{19}ClO_2S$ (406.92): C, 70.84; H, 4.71. Found: C, 70.72; H, 4.62.

1-((2-hydroxyethylthio)(4-chlorophenyl)methyl)naphthalen-2-ol (11aem):



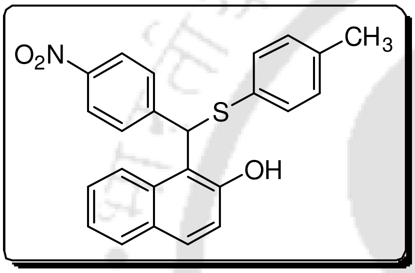
Nature: Pale yellow semi-solid; **IR** (KBr): 3447, 1626, 1514, 1487, 1285, 1253, 1061, 811, 749 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.82 (brs, 1H, OH), 2.66-2.77 (m, 2H), 3.75 (s, 2H), 6.39 (s, 1H), 7.20-7.27 (m, 2H), 7.31-7.36 (m, 4H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 3H), 8.41 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 35.3, 45.5, 61.5, 114.4, 119.8, 122.4, 123.6, 127.2, 129.0 (3C), 129.2, 129.7 (2C), 130.8, 133.0, 133.6, 137.4, 154.4. **Anal. Calcd** for $C_{19}H_{17}O_2SCl$ (344.86): C, 66.17; H, 4.97. Found: C, 66.08; H, 4.88.

1-((4-Nitrophenyl)(phenylthio)methyl)naphthalen-2-ol (11ahd):



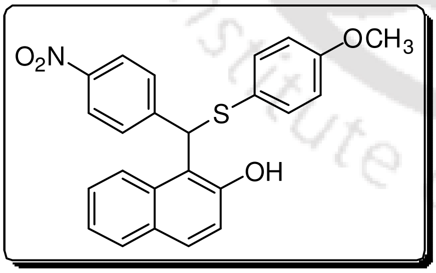
Nature: Pale yellow semi-solid; **IR** (KBr): 3444, 2928, 1624, 1594, 1515, 1344, 1252, 1109, 955, 827, 743 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 6.67 (s, 1H), 7.12 (s, 1H), 7.16 (t, *J* = 6.4 Hz, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.35–7.41 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.74 (t, *J* = 8.8 Hz, 3H), 8.10 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 49.4, 116.4, 119.0, 122.8, 123.6, 123.9 (3C), 127.1, 127.8, 129.1, 129.3 (4C), 129.7, 130.7, 131.1, 132.4, 134.4, 147.0, 147.5, 152.8. **Anal. Calcd** for C$_{23}$H$_{17}$NO$_3$S (387.45): C, 71.30; H, 4.42; N, 3.62. Found: C, 71.19; H, 4.33; N, 3.51.

1-((p-tolylthio)(4-nitrophenyl)methyl)naphthalen-2-ol (11ahe):



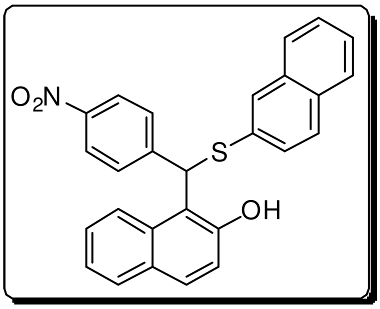
Nature: Pale yellow semi-solid; **IR** (KBr): 3445, 2917, 1632, 1515, 1345, 1264, 1110, 808, 745 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.22 (s, 3H), 6.60 (s, 1H), 6.98 (d, *J* = 7.60 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.25-7.35 (m, 4H), 7.66 (d, *J* = 8.4 Hz, 3H), 7.72 (t, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 2H), 9.46 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.1, 50.2, 116.1, 119.2, 122.7, 123.5, 123.8 (3C), 127.1, 129.1, 129.3 (2C), 129.7, 130.1 (2C), 130.7, 131.7 (2C), 132.5, 138.2, 147.0, 147.5, 153.1. **Anal. Calcd** for C$_{24}$H$_{19}$NO$_3$S (401.48): C, 71.80; H, 4.77. Found: C, 71.61; H, 4.68.

1-((4-methoxyphenylthio)(4-nitrophenyl)methyl) naphthalen-2-ol (11ahi):



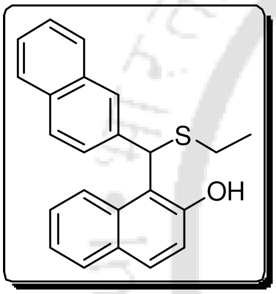
Nature: Pale yellow semi-solid; **IR** (KBr): 3438, 2924, 2851, 1635, 1517, 1347, 1248, 1023, 823, 746 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.47 (s, 3H), 6.38 (s, 1H), 6.51 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.54-7.57 (m, 3H), 7.91 (d, *J* = 8.4 Hz, 2H), 8.24 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 51.4, 55.3, 114.9 (2C), 115.8, 119.3, 122.3, 122.6, 123.6, 123.9 (2C), 127.1, 129.1, 129.3 (2C), 129.7, 130.7, 132.6, 134.8 (2C), 147.0, 147.2, 153.3, 160.1. **Anal. Calcd** for C$_{24}$H$_{19}$NO$_4$S (417.48): C, 69.05; H, 4.59; N, 3.36. Found: C, 68.90; H, 4.48; N, 3.22.

1-((naphthalen-2-ylthio)(4-nitrophenyl)methyl)naphthalen-2-ol (11ahh):



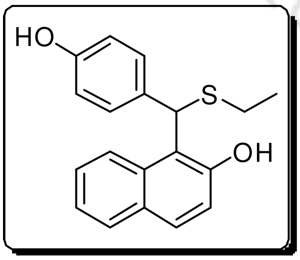
Nature: Pale yellow semi-solid; **IR** (KBr): 3445, 2928, 1621, 1591, 1514, 1343, 1251, 1108, 1059, 809, 743 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 6.78 (s, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.35-7.47 (m, 4H), 7.59-7.77 (m, 8H), 7.8 (s, 1H), 8.12 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 49.1, 116.7, 118.8, 123.1, 123.6, 123.7 (3C), 126.4, 126.7, 127.1, 127.4, 127.7, 128.0, 128.9, 129.2 (2C), 129.7, 129.8, 130.7, 132.1, 132.3, 132.4, 133.6, 146.8, 147.7, 152.6. **Anal. Calcd** for $C_{27}H_{19}NO_3S$ (437.51): C, 74.12; H, 4.38; N, 3.20. Found: C, 74.01; H, 4.27; N, 3.09.

1-((ethylthio)(naphthalen-2-yl)methyl)naphthalen-2-ol (11ala):



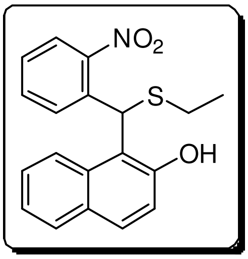
Nature: Pale yellow semi-solid; **IR** (KBr): 3406, 3175, 2961, 1618, 1599, 1401, 1253, 1223, 1143, 958, 817, 745 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.25 (t, *J* = 7.6 Hz, 3H), 2.49-2.65 (m, 2H), 6.47 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.30 (dt, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.38-7.43 (m, 3H), 7.60 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 7.69-7.72 (m, 1H), 7.75-7.82 (m, 5H), 7.90 (d, *J* = 8.4 Hz, 1H), 9.10 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.4, 26.9, 46.6, 113.5, 120.3, 121.9, 123.4, 126.29, 126.32, 126.5, 127.1, 127.2, 127.7, 128.2, 128.7, 129.2, 129.5, 130.6, 132.9, 133.4, 133.5, 136.0, 155.4. **Anal. Calcd** for $C_{23}H_{20}OS$ (344.47): C, 80.19; H, 5.85. Found: C, 80.06; H, 5.76.

1-((ethylthio)(4-hydroxyphenyl)methyl)naphthalen-2-ol (11aga):



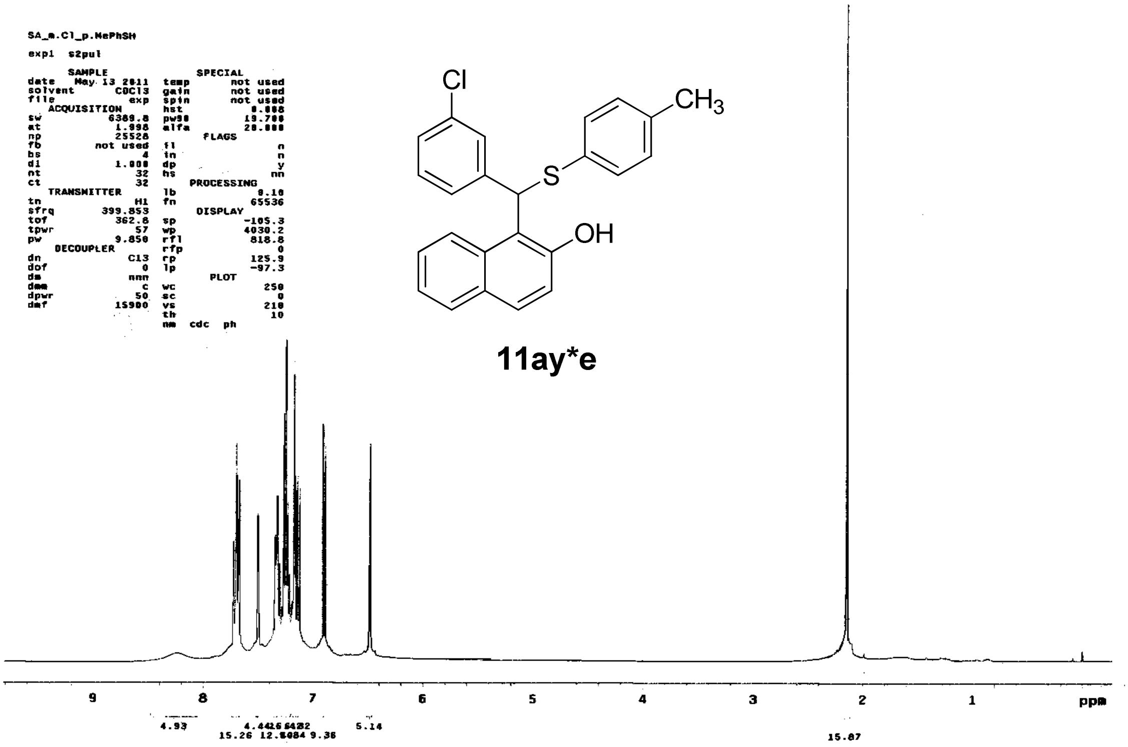
Nature: Yellow semi-solid; **IR** (KBr): 3398, 2961, 2962, 1619, 1596, 1509, 1438, 1252, 1223, 1172, 1146, 818, 743 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.19 (t, *J* = 7.6 Hz, 3H), 2.39-2.54 (m, 2H), 5.39 (s, 1H, OH), 6.26 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 2H), 7.19-7.25 (m, 3H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 9.22 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.3, 26.7, 45.8, 114.0, 115.9 (2C), 120.2, 121.8, 123.4, 127.2, 129.2, 129.5, 129.7 (2C), 130.4 (2C), 133.3, 154.9, 155.3. **Anal. Calcd** for $C_{19}H_{18}O_2S$ (310.14): requires C, 73.52; H, 5.84. Found: C, 73.42; H, 5.78.

1-((ethylthio)(2-nitrophenyl)methyl)naphthalen-2-ol (11ama):



Nature: Pale yellow semi-solid; **IR** (KBr): 3433, 1528, 1353 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.25 (s, J = 7.6 Hz, 3H), 2.56-2.64 (m, 2H), 7.23 (s, 1H), 7.25 (d, J = 9.2 Hz, 1H), 7.28 (dd, J_1 = 3.6 Hz, J_2 = 5.6 Hz, 1H), 7.34 (t, J = 6.8 Hz, 1H), 7.38 (dd, J_1 = 3.6 Hz, J_2 = 6.4 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.95 (dd, J_1 = 3.6 Hz, J_2 = 5.6 Hz, 1H), 9.55 (s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 13.9, 27.7, 41.4, 111.4, 120.5, 121.9, 123.7, 125.7, 127.8, 129.0, 129.2, 129.6, 130.6, 131.2, 133.0, 133.5, 133.6, 149.1, 156.5. **Anal. Calcd** for $C_{19}H_{17}NO_3S$ (339.41): C, 67.24; H, 5.05, N, 4.13. Found: C, 67.12; H, 4.95, N, 4.04.

^{1}H NMR (400 MHz, CDCl$_3$): *1-((p-tolylthio)(3-chlorophenyl)methyl)naphthalen-2-ol* (**11ay*e**)



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SA_m.Cl_p.MePhSH

exp1  s2pul

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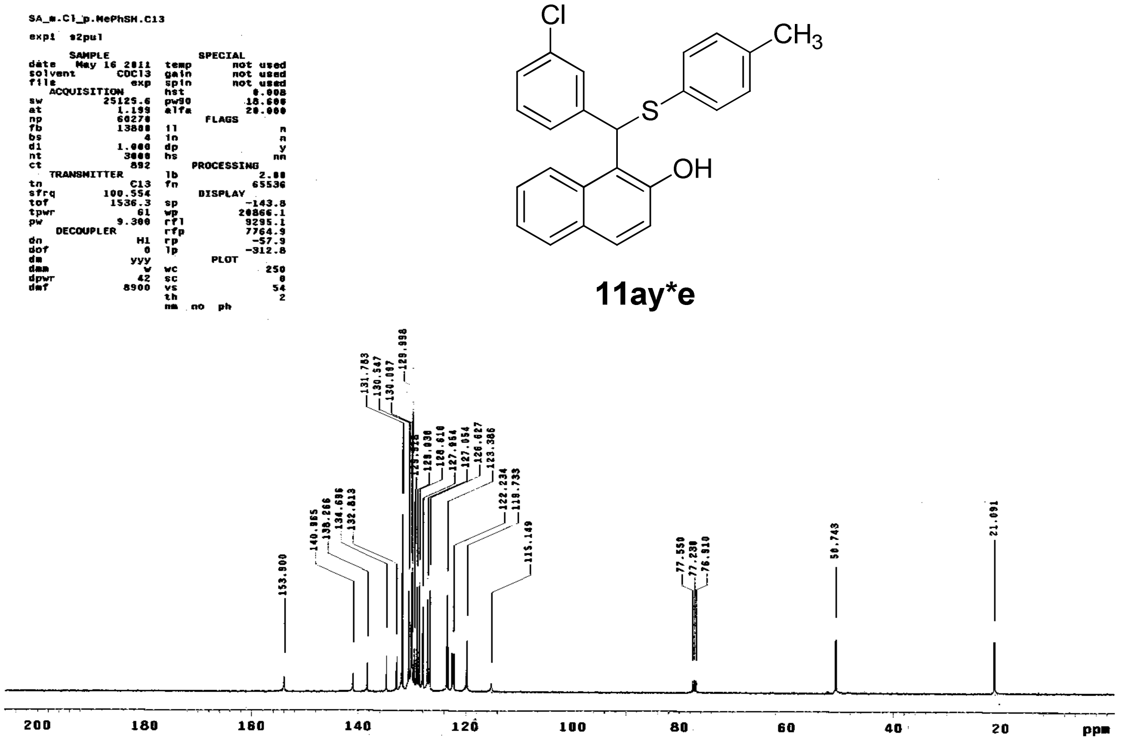
solvent      CDCl3   gain       not used
file           exp   spin       not used
   ACQUISITION       hst           0.008
sw          6389.8   pw90         19.700
at           1.998   alfa         20.000
np           25528          FLAGS
fb        not used   il                n
bs               4   in                n
di           1.000   dp                y
nt              32   hs               nn
ct              32        PROCESSING
   TRANSMITTER       lb             0.10
tn              H1   fn            65536
sfrq       399.853          DISPLAY
tof          362.8   sp           -105.3
tpwr            57   wp           4030.2
pw           9.850   rfl           818.8
    DECOUPLER        rfp               0
dn             C13   rp            125.9
dof              0   lp            -97.3
dm             nnn            PLOT
dmm              c   wc              250
dpwr            50   sc                0
dmf          15900   vs              210
                     th               10
                     nm  cdc  ph
```

11ay*e

^{13}C NMR (100 MHz, CDCl$_3$): *1-((p-tolylthio)(3-chlorophenyl)methyl)naphthalen-2-ol* (**11ay*e**)



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SA_m.Cl_p.MePhSH.C13

exp1  s2pul

      SAMPLE                 SPECIAL
date   May 16 2011   temp       not used
solvent      CDCl3   gain       not used
file           exp   spin       not used
   ACQUISITION       hst           0.008
sw         25125.6   pw90         18.600
at           1.199   alfa         20.000
np           60270          FLAGS
fb           13800   il                n
bs               4   in                n
d1           1.000   dp                y
nt            3000   hs               nn
ct             892        PROCESSING
   TRANSMITTER       lb             2.00
tn             C13   fn            65536
sfrq       100.554          DISPLAY
tof         1536.3   sp           -143.8
tpwr            61   wp          20866.1
pw           9.300   rfl          9295.1
    DECOUPLER        rfp          7764.9
dn              H1   rp            -57.9
dof              0   lp           -312.8
dm             yyy            PLOT
dmm              w   wc              250
dpwr            42   sc                0
dmf           8900   vs               54
                     th                2
                     nm  no  ph
```

11ay*e

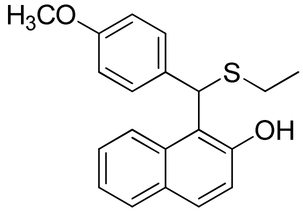
Figure 4.5

***^{1}H NMR (400 MHz, $CDCl_3$):** 1-((ethylthio)(4-methoxyphenyl)methyl)naphthalen-2-ol* (**11aba**)

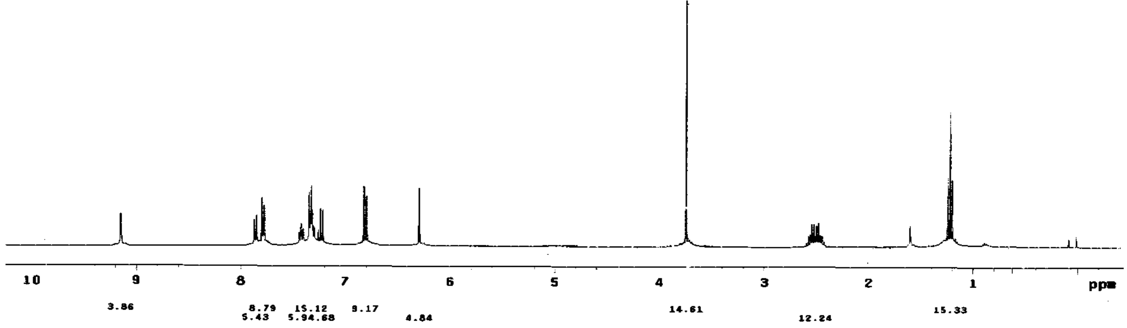
```
AD_30

exp1  s2pul

      SAMPLE                    SPECIAL
date   May  7 2011   temp         not used
solvent       CDCl3   gain         not used
file            exp   spin         not used
   ACQUISITION        hst             0.008
sw           6389.8   pw90           19.700
at            1.998   alfa           20.000
np            25528             FLAGS
fb         not used   il                  n
bs                4   in                  n
d1            1.000   dp                  y
nt               32   hs                 nn
ct               32          PROCESSING
   TRANSMITTER        lb               0.10
tn               H1   fn              65536
sfrq        399.853             DISPLAY
tof           362.8   sp             -106.1
tpwr             57   wp             4273.8
pw            9.850   rfl            3698.7
    DECOUPLER         rfp            2902.9
dn              C13   rp              113.0
dof               0   lp              -85.3
dm              nnn               PLOT
dmm               c   wc                250
dpwr             50   sc                  0
dmf           15900   vs                 72
                      th                 20
                      nm   cdc   ph
```



11aba

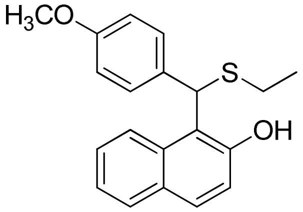


***^{13}C NMR (100 MHz, $CDCl_3$):** 1-((ethylthio)(4-methoxyphenyl)methyl)naphthalen-2-ol* (**11aba**)

```
AD_30.C13

exp1  s2pul

      SAMPLE                    SPECIAL
date   May  7 2011   temp         not used
solvent       CDCl3   gain         not used
file            exp   spin         not used
   ACQUISITION        hst             0.008
sw          25125.6   pw90           18.600
at            1.199   alfa           20.000
np            60270             FLAGS
fb            13800   il                  n
bs                4   in                  n
d1            1.000   dp                  y
nt             3000   hs                 nn
ct              180          PROCESSING
   TRANSMITTER        lb               2.00
tn              C13   fn              65536
sfrq        100.554             DISPLAY
tof          1536.3   sp             -294.1
tpwr             61   wp            20998.0
pw            9.300   rfl            9280.5
    DECOUPLER         rfp            7764.9
dn               H1   rp              -39.0
dof               0   lp             -350.7
dm              yyy               PLOT
dmm               w   wc                250
dpwr             42   sc                  0
dmf            8900   vs                 33
                      th                  2
                      nm   no   ph
```



11aba

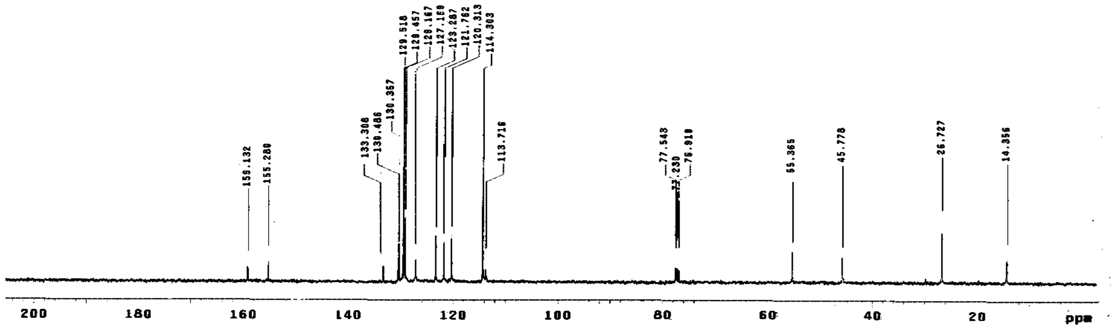
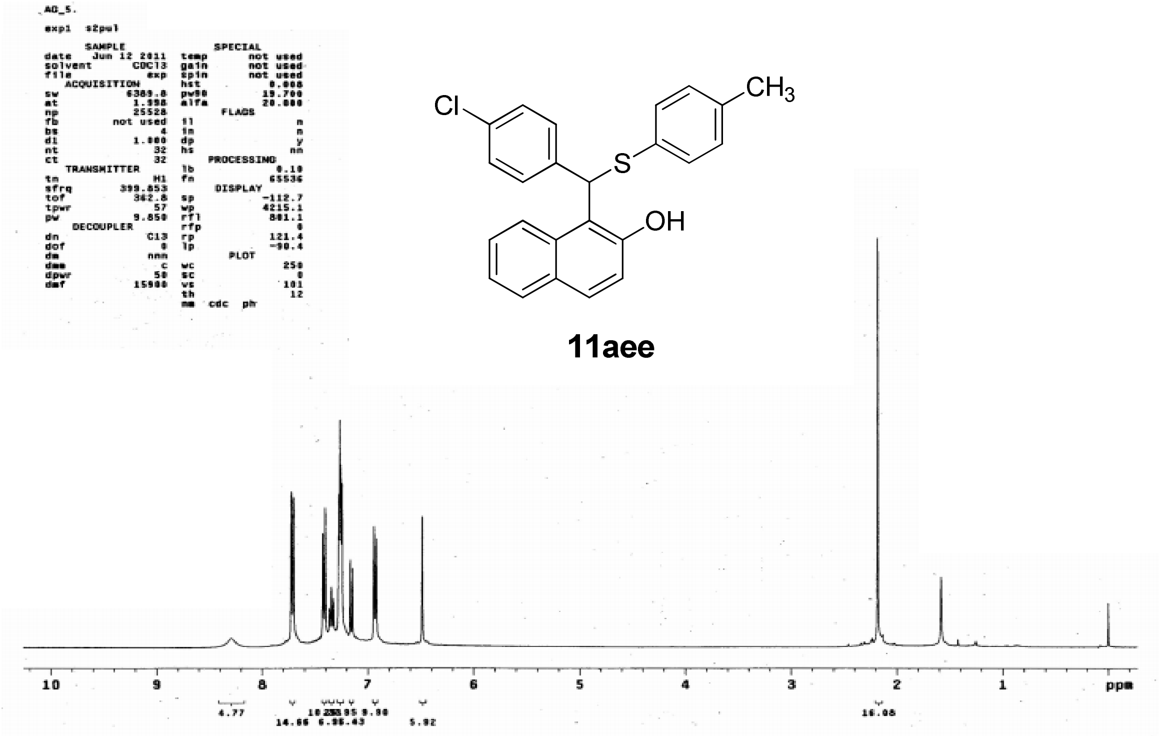


Figure 4.6

***^{1}H NMR (400 MHz, CDCl$_3$)**: 1-((p-tolylthio)(4-chlorophenyl)methyl)naphthalen-2-ol* **(11aee)**

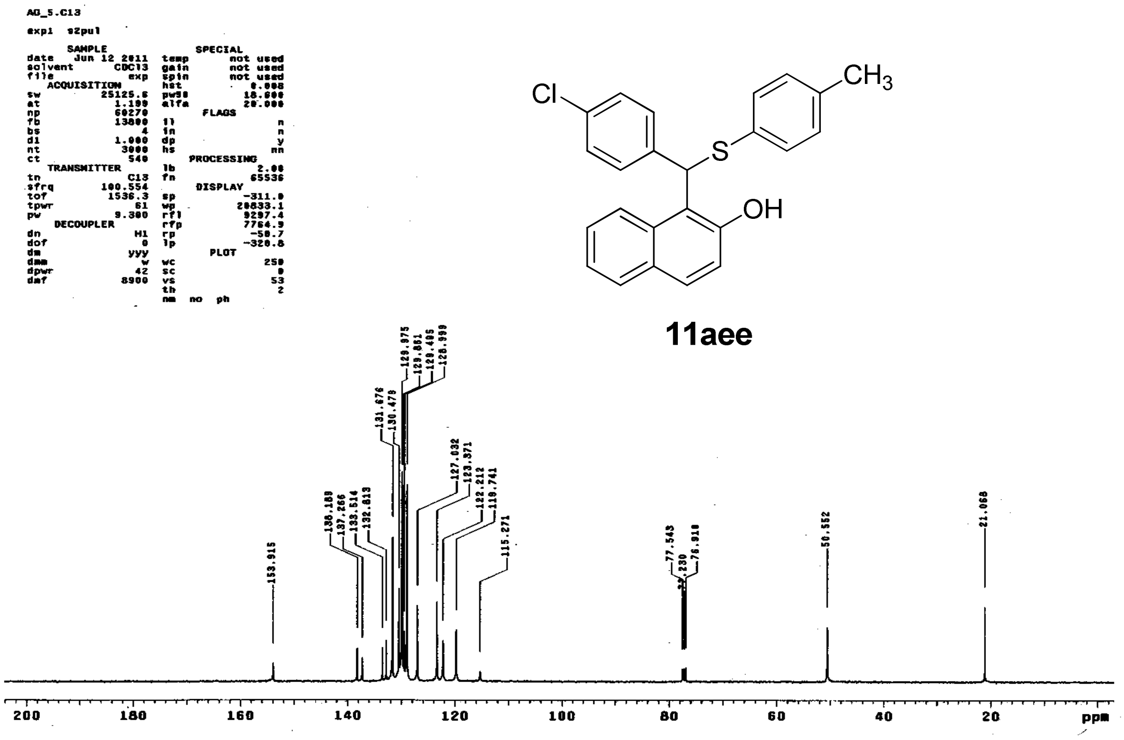


```
AG_5.

exp1  s2pul

       SAMPLE                  SPECIAL
date    Jun 12 2011   temp        not used
solvent        CDCl3   gain        not used
file             exp   spin        not used
    ACQUISITION        hst            0.008
sw            6389.8   pw90          15.700
at             1.998   alfa          20.000
np             25528          FLAGS
fb          not used   il                 n
bs                 4   in                 n
d1             1.000   dp                 y
nt                32   hs                nn
ct                32        PROCESSING
    TRANSMITTER        lb              0.10
tn                H1   fn             65536
sfrq         399.853         DISPLAY
tof            362.8   sp            -112.7
tpwr              57   wp            4215.1
pw             9.850   rfl            801.1
     DECOUPLER         rfp                0
dn               C13   rp             121.4
dof                0   lp             -90.4
dm               nnn          PLOT
dmm                c   wc               250
dpwr              50   sc                 0
dmf            15900   vs               101
                       th                12
                       nm  cdc  ph
```

***^{13}C NMR (100 MHz, CDCl$_3$)**: 1-((p-tolylthio)(4-chlorophenyl)methyl)naphthalen-2-ol* **(11aee)**



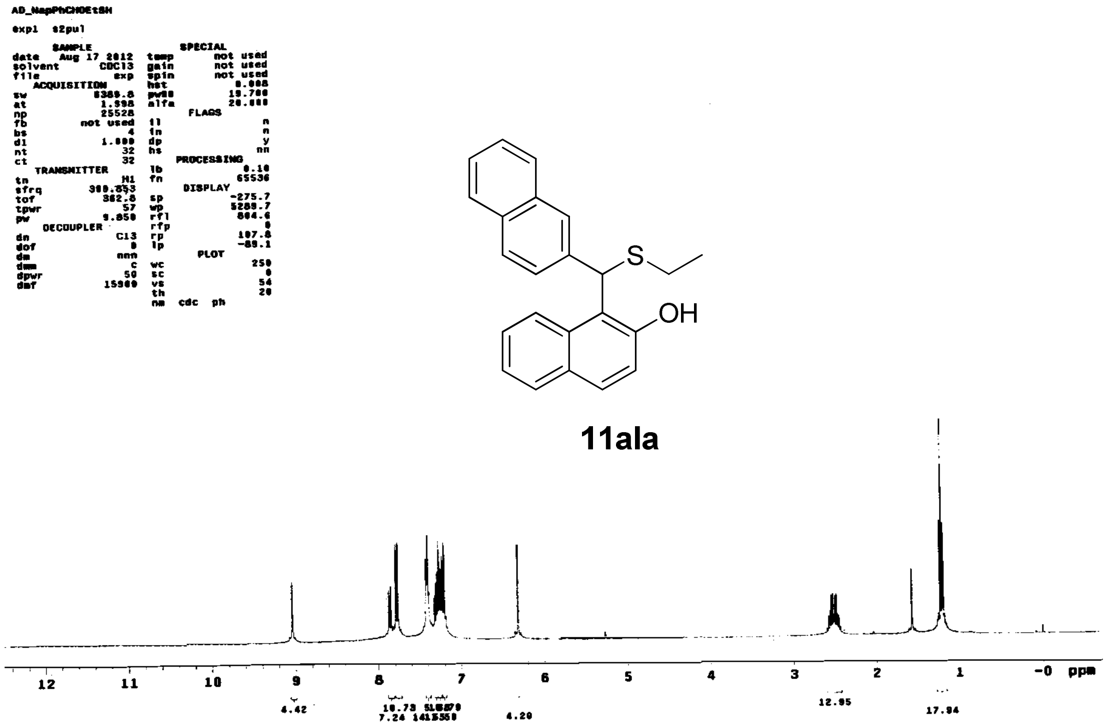
```
AG_5.C13

exp1  s2pul

       SAMPLE                  SPECIAL
date    Jun 12 2011   temp        not used
solvent        CDCl3   gain        not used
file             exp   spin        not used
    ACQUISITION        hst            0.008
sw           25125.6   pw90          18.600
at             1.199   alfa          20.000
np             60270          FLAGS
fb             13800   il                 n
bs                 4   in                 n
d1             1.000   dp                 y
nt              3000   hs                nn
ct               540        PROCESSING
    TRANSMITTER        lb              2.00
tn               C13   fn             65536
sfrq         100.554         DISPLAY
tof           1536.3   sp            -311.0
tpwr              61   wp           20833.1
pw             9.300   rfl           9297.4
     DECOUPLER         rfp           7764.9
dn                H1   rp             -58.7
dof                0   lp            -320.8
dm               yyy          PLOT
dmm                w   wc               250
dpwr              42   sc                 0
dmf             8900   vs                53
                       th                 2
                       nm  no  ph
```

Figure 4.7

^{1}H NMR (400 MHz, CDCl$_3$): 1-((p-tolylthio)(4-chlorophenyl)methyl)naphthalen-2-ol (**11ala**)



^{13}C NMR (100 MHz, CDCl$_3$): 1-((p-tolylthio)(4-chlorophenyl)methyl)naphthalen-2-ol (**11ala**)

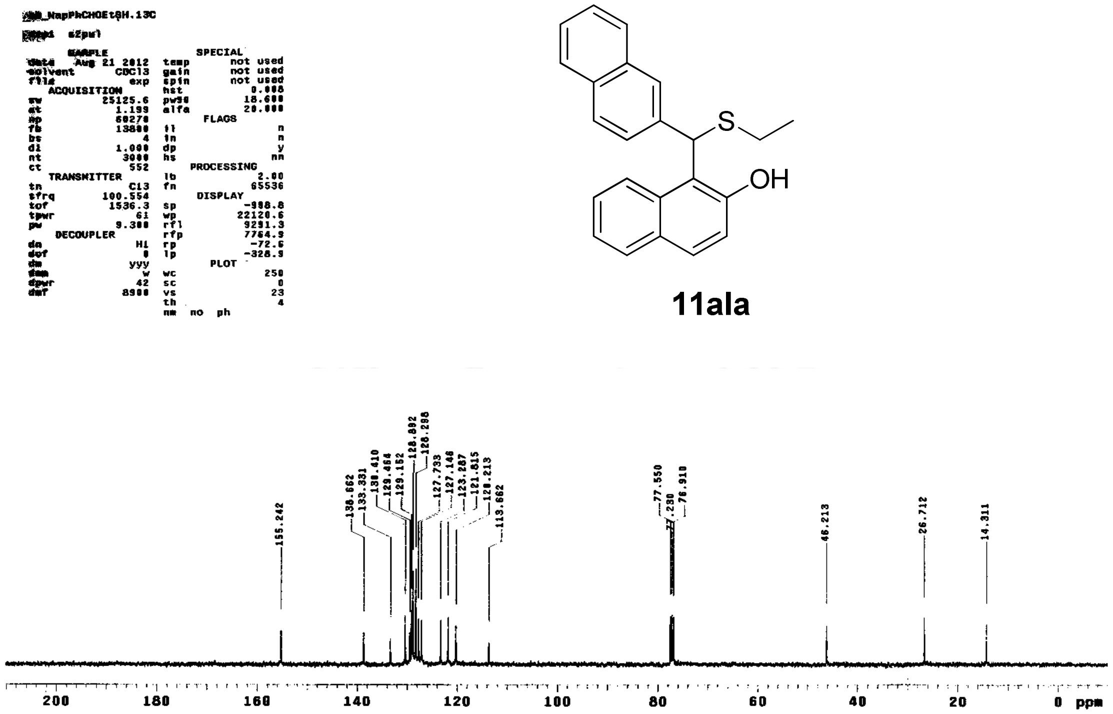


Figure 4.8

4.3 References

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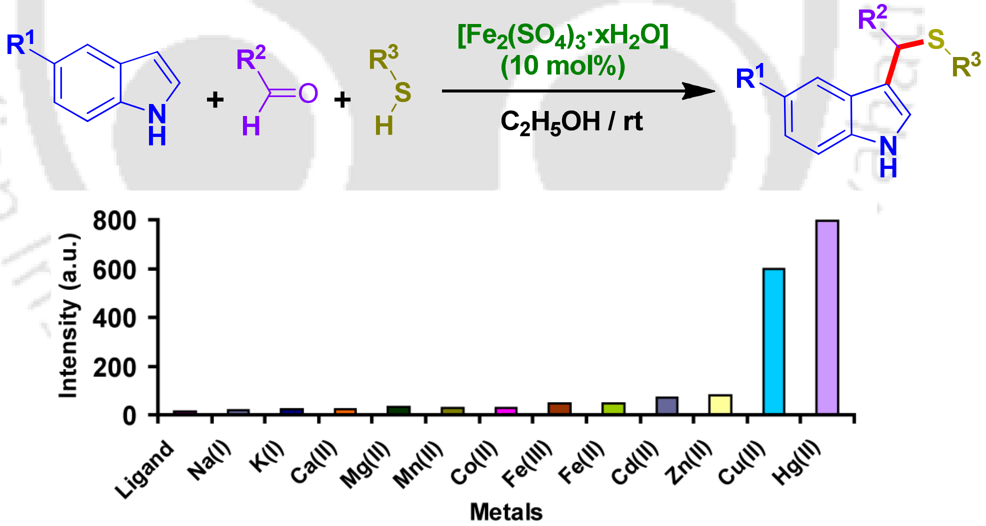
Chapter 5

Hydrated ferric sulfate catalyzed synthesis of 3-[(alkyl/arylthio) (aryl)methyl]-1H-indole derivatives through one-pot reaction: As a selective chemosensor for Hg^{2+} and Cu^{2+}



CHAPTER 5: Results and Discussion

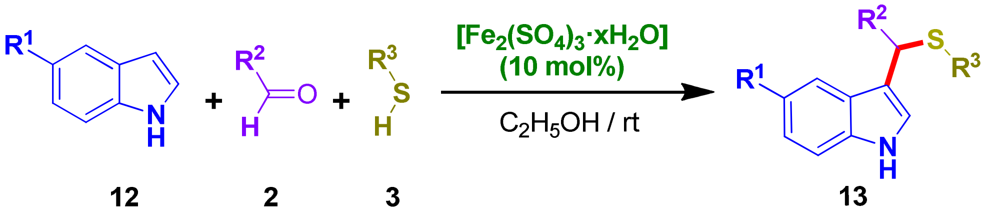
5.1 Results and Discussion

Indoles and 3-substituted indole derivatives exhibit interesting biological properties and are found as such in nature.[1] Recently various research groups have paid considerable attention to synthesize these compounds due to their wide range of biological activities such as antioxidant, antibacterial, anti-insecticidal and anticancer activity.[2] Numerous synthetic methods have been developed for the synthesis using either indole or 3-indolecarboxaldehyde. By employing powerful carbon-carbon bond forming reactions, the synthesis of 3-substituted indole derivatives were achieved using Mannich reaction,[3] Friedel–Crafts alkylation reactions of indoles,[4] conjugate addition of indoles to unsaturated carbonyl compounds and the reaction of two equivalents of indoles with carbonyl groups in the presence of a protic acid[5] or Lewis acid.[6] Interestingly, 3-substituted indole derivatives containing sulfur atom were to be explored. As a matter of fact, the synthesis of these compounds containing sulfur atom is highly desirable because they might exhibit interesting pharmacological activities.[7]

In this chapter, we report one-pot synthesis of of 3-[(alkyl/arylthio)(aryl)methyl]-1H-indole derivatives from indoles, aromatic aldehydes and thiols at room temperature using hydrated ferric sulfate as a Lewis acid catalyst.

Moreover, one of the derivatives **(13aad)** demonstrated chemosensor activity towards environmental and clinically important metal ions *viz.* Hg^{2+} and Cu^{2+}, *via* fluorescence intensity enhancement. Normally, Hg^{2+} and Cu^{2+} cause fluorescence quenching *via* spin-orbit coupling enhancement or energy or electron transfer mechanism respectively. The fluorescence enhancement in the presence of interfering metal ions makes the method superior over others. Also, the detection of Hg^{2+} and Cu^{2+} ions is a subject of an increasing societal demand and is responsible for neurodegenerative disorders.

In recent years, hydrated ferric sulfate [$Fe_2(SO_4)_3{\cdot}xH_2O$] has received considerable attention as a mild, inexpensive and reusable Lewis acid catalyst for various organic transformations *viz.* tetrahydropyranylation of alcohols,[8] preparation of acylals from aldehydes,[9] 2,3-unsaturated glycosides *via* Ferrier rearrangement,[10] per-*O*-acetylation of sugars,[11] synthesis of tetrahydroquinoline derivatives[12] and 1*H*-pyrazole-4-carbodithioate.[13] We conceived that hydrated ferric sulfate can be exploited further for the synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indole (Scheme 5.1).



R^1 = H (12a), Br (12b)

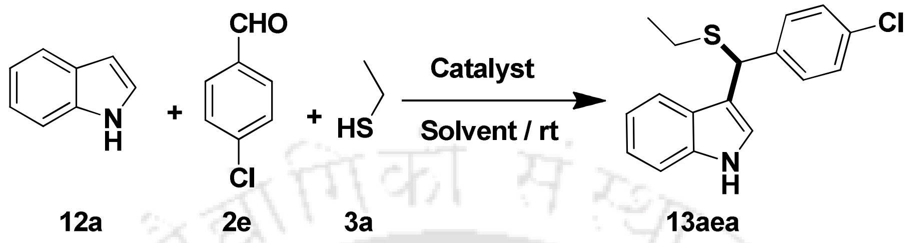
R^2 = Ph (2a), 4-MeOPh (2b), 4-MePh (2c), 4-ClPh (2e), 4-BrPh (2f),
4-NO_2Ph (2h), 4-CNPh (2i), 3-NO_2Ph (2j), 2-Naphthyl (2l),
2-NO_2Ph (2m), 2-ClPh (2o), 4-FPh (2v)

R^3 = Et (3a), Pr (3b), PhCH_2 (3c), Ph (3d), 4-MePh (3e),
4-MeOPh (3i), $HOCH_2CH_2$ (3m), 4-NO_2Ph (3n)

Scheme 5.1. Synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indoles

Initially, we investigated the reaction of *p*-chlorobenzaldehyde, indole and ethanethiol in 3 mL of ethanol in the absence of catalyst at room temperature. The product (**13aea**) was isolated only in 12% yield after 12 h of stirring (Table 5.1, entry 1) was fully characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and by elemental analysis. The signals appears in the ^{1}H NMR spectrum at δ 1.23 (t, J = 7.6 Hz, 3H), 2.44 (q, J = 7.2 Hz, 2H), 5.40 (s, 1H), 7.05 (s, 1H), 7.07 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H, NH). The signals at δ 5.40 for methine proton and 7.29 for NH group clearly indicate the formation of the desired product. Similarly, the various peaks obtained in the ^{13}C NMR spectrum are at δ 14.6, 26.3, 45.3, 111.5, 116.4, 119.7, 119.8, 122.6, 123.3, 126.3, 128.7 (2C), 129.8 (2C), 132.7, 136.7, 140.8 and the characteristic peak at δ 45.3 resulting only due to the formation of product. After getting the desired product, we tried to optimize the reaction condition using 5, 10 and 15 mol% hydrated ferric sulfate in ethanol (3 mL) at room temperature, the required product (**13aea**) was obtained in 42%, 73% and 74% of yields respectively (Table 5.1, entries 2-4). It was noted that the yield of the product (**13aea**) did not improve significantly by further increasing the amount of catalyst. Various reactions were also scrutinized with the same combination of the substrates in presence of other Lewis acid catalysts such as anhydrous ferric chloride, hydrated ferrous chloride, ceric ammonium nitrate (CAN), nickel chloride hexahydrate ($NiCl_2.6H_2O$) and vanadyl acetylacetonate ($VO(acac)_2$) and the product (**13aea**) in 70%, 68%, 16%, 63% and 58% yield, respectively were obtained (Table 5.1, entries 5-9). The same reactions were also performed in different solvents such as dichlorometh-ane (CH_2Cl_2), acetonitrile (CH_3CN), water (H_2O), tertrahydrofuran (THF), 1,4-dioxane, dimethylformamide (DMF) and 1,2-dichloroethane ($C_2H_4Cl_2$) (Table 5.1, entry 9-16). From these observations, it was concluded that the best result was obtained using 10 mol% catalyst in ethanol in terms of yield and reaction time.

Table 5.1. Optimization for reaction conditions[a]

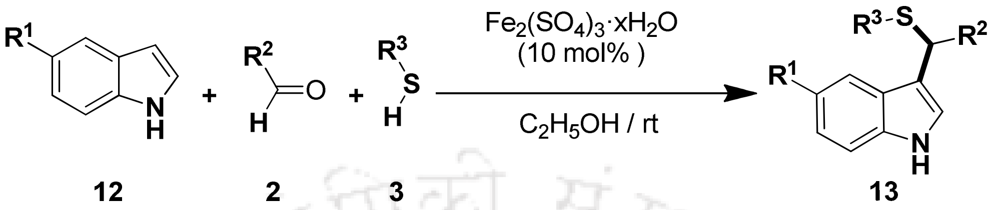


Entry	Catalyst (mol %)	Solvent	Time/h	Yield (%)[b]
1	No catalyst (0)	Ethanol	12	12
2	$Fe_2(SO_4)_3.H_2O$ (5)	Ethanol	6.0	42
3	**$Fe_2(SO_4)_3.H_2O$ (10)**	**Ethanol**	**4.0**	**73**
4	$Fe_2(SO_4)_3.H_2O$ (15)	Ethanol	4.0	74
5	$FeCl_3$ (10)	Ethanol	5.0	70
6	$FeCl_2.xH_2O$ (10)	Ethanol	5.0	68
7	CAN (10)	Ethanol	5.0	16
8	$NiCl_2.6H_2O$ (10)	Ethanol	5.0	63
9	$VO(acac)_2$ (10)	Ethanol	5.0	58
10	$Fe_2(SO_4)_3.H_2O$ (10)	CH_2Cl_2	4.0	66
11	$Fe_2(SO_4)_3.H_2O$ (10)	CH_3CN	4.0	68
12	$Fe_2(SO_4)_3.H_2O$ (10)	H_2O	5.0	27
13	$Fe_2(SO_4)_3.H_2O$ (10)	THF	5.0	67
14	$Fe_2(SO_4)_3.H_2O$ (10)	Dioxane	5.0	25
15	$Fe_2(SO_4)_3.H_2O$ (10)	DMF	5.0	30
16	$Fe_2(SO_4)_3.H_2O$ (10)	$C_2H_4Cl_2$	5.0	65

[a]All the reactions were carried out using indole (1 mmol), *p*-chlorobenzaldehyde (1 mmol) and ethanethiol (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

After optimizing the reaction conditions, indole, benzaldehyde and ethanethiol were reacted to afford the desired product **13aaa** in 70% yield. In order to find the scope of the reaction, a wide variety of aromatic aldehydes were treated with indole and ethanethiol under identical reaction conditions and the desired products **13afa-13aja** were obtained from moderate to good yields (Table 5.2, entries 3-8) depending upon the type and position of substitution on the aromatic ring. It was observed that aromatic aldehydes containing electron-withdrawing groups in the ring provided better yield as compared to the aldehydes having electron-donating substituent. Similarly, *ortho*-substituted aromatic aldehydes also provide lower yield due to steric hindrance. We have also examined the reactions with different aliphatic thiols namely propanethiol, benzylthiol and 2-mercaptoethanol with indole and various aromatic aldehydes under similar reaction conditions and we have isolated the desired products **13aab-13aam** from moderate to good yields (Table 5.2, entries 9-13). Encouraged by these successful results, the scope of the protocol was studied using various aromatic thiols. Then the reaction was carried out with indole, benzaldehyde and thiophenol under identical reaction conditions, which gave only 24% desired product (**13aad**) along with *bis*-(indolyl) methane derivative 30% (Table 5.2, entry 14). The formation of low yield of the expected product might be due to less nucleophilicity of thiophenol. However, when the reactions were executed with indole, benzaldehyde with *p*-methylthiophenol or *p*-methoxythiophenol, it afforded the desired products (**13aae** and **13aai**) in 64% and 67% yield, respectively (Table 5.2, entries 15 & 16). From these observations, it is clear that substituted thiophenols containing electron-rich substituent in the ring provided much better yields as compared to thiophenol. It is worthwhile to mention that the protocol also provided the desired product (**13aan**) *albeit* in low yield with aromatic thiol containing electron-withdrawing group (Table 5.2, entry 17). Subsequently, we have examined the reaction with indole, different aromatic aldehydes containing electron-rich as well as electron-withdrawing substituent in the ring and electron-rich thiophenols and the corresponding desired products **13afe-13avi** were obtained from moderate to good yields. It was observed that aromatic aldehydes having electron-withdrawing substituents provided better yield as compared to the aromatic aldehydes having electron-donating substituent (Table 5.2, entries 18-23). Interestingly, *para*-nitrobenzaldehyde also provided the desired product (**13ahn**) in 40% yield on reaction with indole and *p*-nitrothiophenol under the experimental conditions. Likewise, the desired product (**13ale**) was obtained from indole, 2-naphthylaldehyde and 4-methylthiophenol under identical conditions. Apart from indole, the reaction was performed by using 5-bromoindole, *p*-chlorobenzaldehyde and ethanethiol under the experimental reaction condition the desired product (**13bea**) was obtained in 69% yield (Table 5.2, entry 26). However, when a reaction was carried out with indole, cyclohexanecarboxaldehyde and *p*-methylthiophenol in 3 mL of ethanol using the same amount of catalyst under identical reaction condition, the corresponding *bis*-(indolyl) methane derivative in 40% yield was isolated instead of the desired product.

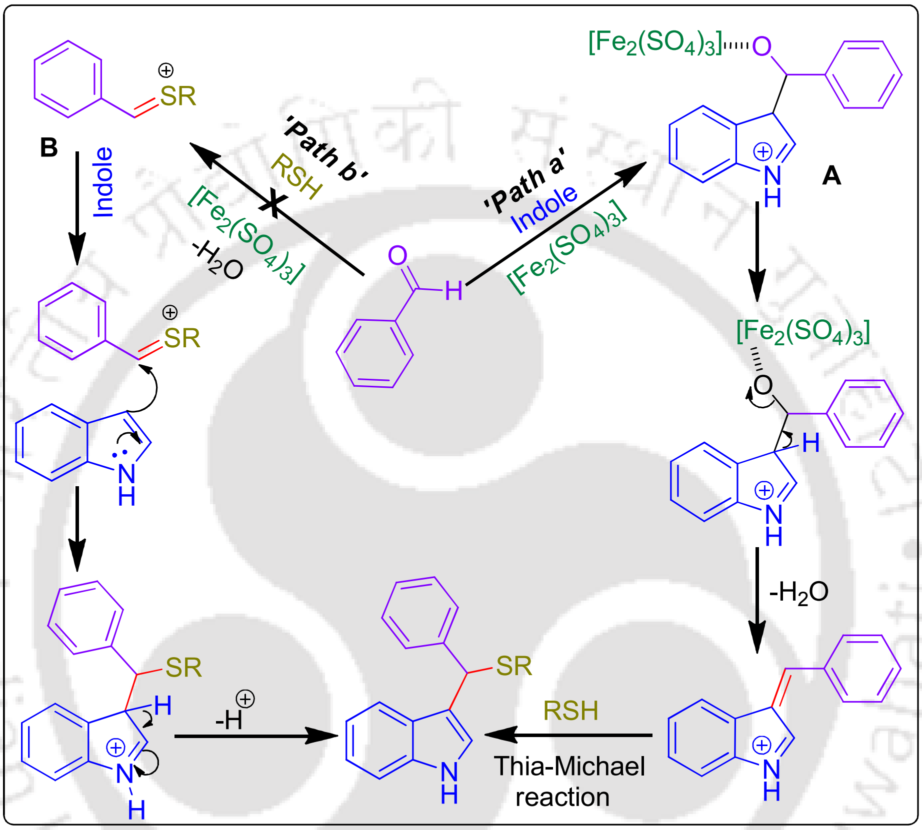
Table 5.2. $Fe_2(SO_4)_3.xH_2O$ catalyzed synthesis of substituted 3-thiolalkyl/arylated indoles[a]



Entry	Indole (12)	Aldehyde (2)	Thiol (3)	Product[a]	Yield (%)[b]
1	**12a**	**2a**	**3a**	**13aaa**	70
2	**12a**	**2e**	**3a**	**13aea**	73
3	**12a**	**2f**	**3a**	**13afa**	72
4	**12a**	**2b**	**3a**	**13aba**	53
5	**12a**	**2h**	**3a**	**13aha**	74
6	**12a**	**2o**	**3a**	**13aoa**	25
7	**12a**	**2m**	**3a**	**13ama**	30
8	**12a**	**2j**	**3a**	**13aja**	75
9	**12a**	**2a**	**3b**	**13aab**	69
10	**12a**	**2e**	**3b**	**13aeb**	71
11	**12a**	**2c**	**3b**	**13acb**	51
12	**12a**	**2a**	**3c**	**13aac**	61
13	**12a**	**2a**	**3m**	**13aam**	62
14	**12a**	**2a**	**3d**	**13aad**	24
15	**12a**	**2a**	**3e**	**13aae**	64
16	**12a**	**2a**	**3i**	**13aai**	67
17	**12a**	**2a**	**3n**	**13aan**	20
18	**12a**	**2f**	**3e**	**13afe**	68
19	**12a**	**2c**	**3e**	**13ace**	49
20	**12a**	**2b**	**3e**	**13abe**	46
21	**12a**	**2h**	**3i**	**13ahi**	71
22	**12a**	**2i**	**3e**	**13aie**	70
23	**12a**	**2v**	**3i**	**13avi**	66

24	**12a**	**2h**	**3n**	**13ahn**	40
25	**12a**	**2l**	**3e**	**13ale**	68
26	**12b**	**2e**	**3a**	**13bea**	69

[a]All the reactions were performed using **12** (1 mmol), aldehyde (1 mmol) and thiol (1.2 mmol). [b]Isolated yield.



Scheme 5.2. Plausible mechanism for the formation of the product **13.**

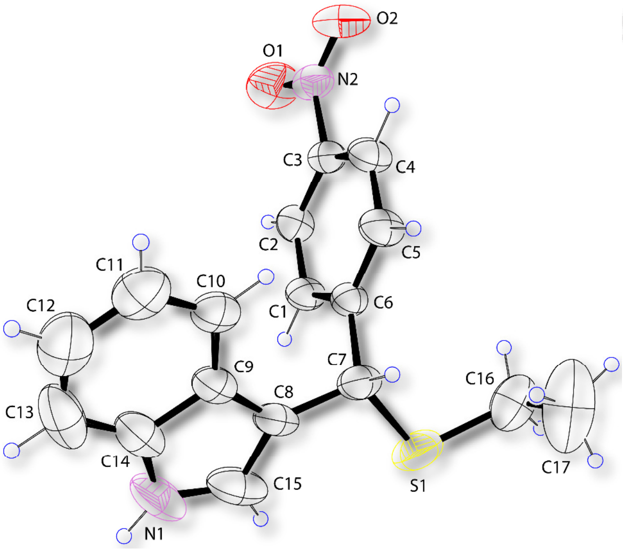
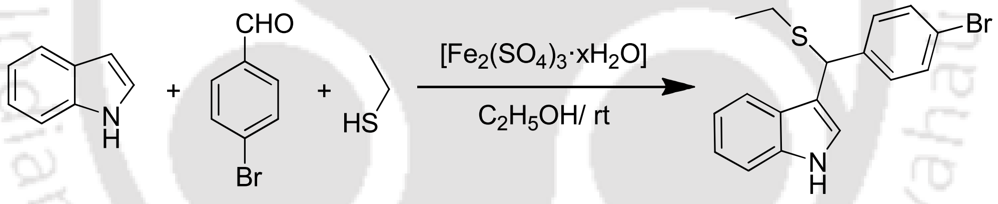


Figure 5.1. X-ray structure of compound **13aha.**

The formation of the products can be rationalized by two possible mechanistic pathways (Scheme 5.2). In *pathway a,* an aromatic aldehyde reacts with indole to give intermediate iminium ion **A**, which reacts with thiol immediately to furnish the final product **13**. Alternatively, a thiol may react with an aromatic aldehyde to provide a reactive sulfonium ion intermediate **B**, which may react with indole to afford the final product **13** in (*pathway b*). However, we believe that the '*pathway a*' is more favorable as we have obtained the desired product **13aan** even with a less nucleophilic aromatic thiol such as *p*-nitrothiophenol. Hydrated ferric sulphate, [$Fe_2(SO_4)_3 \cdot xH_2O$] acts as a Lewis acid in the present transformation.

All the isolated products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and by elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compounds **13aba, 13aja, 13aad, 13aie** and **13bea** are given in the Experimental Section (Figure 5.6, 5.7, 5.8, 5.9 and 5.10). Moreover, the structure of **13aha** was further confirmed by single XRD crystallographic data (Figure 5.1).

Table 5.3. Results of the study on the recovery and reusability of [$Fe_2(SO_4)_3 \bullet xH_2O$][a]



12a **2f** **3a** **13afa**

Round	Catalyst recovered/mg	Reaction time (h)	Yield (%)[b]
1	126	4.0	72
2	121	4.0	70
3	117	4.0	67
4	113	4.0	61
5	106	4.0	55

[a] All the reactions were performed with 3 mmol scale of the reactants using 9 mL of ethanol at room temperature. [b] Isolated yield.

The catalyst [$Fe_2(SO_4)_3 \cdot xH_2O$] was recovered conveniently from the reaction mixture at the end of the reaction after each cycle. After completion of the reaction, the ethanol was removed in a rotatory evaporator and the crude residue was dissolved in 10 mL of dichloromethane. On adding dichloromethane, the catalyst was separated out and it was filtered off through a Büchner funnel. The reusability of the recovered catalyst was examined for another four successive cycles with a similar set of reactions (Table 5.3). Due to the loss of the catalyst in each cycle, the yield decreased relatively.

Next, we have studied the chemosensor activities by synthesized ligand **(13aad)** towards metal ions *viz.* Hg^{2+} and Cu^{2+}, *via* fluorescence intensity enhancement. Heavy and transition metal ions recognition is of great concern for environmental or biological applications.[14] Mercury ions are highly toxic, and in contaminated natural water, it is considered as a major source of human exposure.[15] Once the mercury finds the way inside the human body as organic or inorganic form, results in kidney dysfunction, damaging liver, brain and central nervous system, enormous cognitive and motion disorders and Minamata disease.[16] Also copper has been considered to have both beneficial[17] as well as toxic effects.[18] Copper is most abundant trace element in human physiology and other biological systems.[19] However in excess it is a significant metal pollutant and in deficiency causes neurological disorders (Menkes disease, Wilson disease and Alzheimer's disease) and mis-metalate other metal binding sites.[20] Also free copper has potential ability to generate reactive oxygen species by catalysing the Fenton type reactions, that can break down the DNA.[21] The prescribed value of Maximum Contaminant Level (MCL) for Hg^{2+} and Cu^{2+} by U.S. Environmental Protection Agency's in drinking water are 10 nM and 1.3 milligrams per litre. Therefore, rapid and facile Hg^{2+} and Cu^{2+} detection with suitable and sensitive fluorescent probes is the subject of an increasing societal demand.[22] Also most of the sensor probes for mercury and copper ions that have been developed, show a turn off response.[23] However, a sensitive and selective synthetic receptor with a turn on response remains a challenging task. Generally, to design such type of probes, internal charge transfer (ICT) is disrupted from donor, by blocking the photo induced electron transfer (PET), within the molecule. As a result due to chelation enhanced fluorescence (CHEF), a fluorescent species is obtained.[24] Since the indole based chromophores are reported to be sensitive towards changes in the local perturbation and environment,[25] these changes in the form of signals can be well utilized to establish a chemosensor for a particular analyte. In continuation of our research for the development of chemosensors aimed at metal ions detection,[26] the synthesized 3-(phenyl(phenylthio)methyl)-1H-indole (**13aad**)[27] (Table 5.2), which was exploited as a dual chemosensor for Hg^{2+} and Cu^{2+} metal ions in CH_3CN/H_2O (9:1) media.

In early reports, indole based chemosensors[28] have been utilized in the detection of anions by utilizing indole NH bond.[29] However introduction of electron donating groups into an indole based skeleton could decrease the affinity towards anions[30] and indole based skeleton may be utilized for the selective detection of positively charged species such as metal ions. Chemosensor activities of designed ligand **(13aad)** (33 μM) towards various metals ions were checked in CH_3CN/H_2O (9:1) with an excitation wavelength at 280 nm. According to the Figure 5.2(a) fluorescence spectra of ligand **(13aad)** with an excitation wavelength at 280 nm, was almost unaffected and no fluorescence intensity enhancement was observed in the presence of various alkali as well as transition metal ions such as Na^+, K^+, Ca^{2+}, Mg^{2+}, Mn^{2+}, Co^{2+}, Fe^{3+}, Fe^{2+}, Cd^{2+}, Zn^{2+}, even at 50 μM concentration. However, fluorescence intensity enhancement of ligand **(13aad)** with an emission band centered at 338 nm (Figure 5.2b and 5.2c) was observed in the presence of increasing concentration of Hg^{2+} and Cu^{2+} ions and these fluorescence intensities enhancement were levelled off at 16 μM and 37 μM concentration of Hg^{2+} and Cu^{2+} ions, respectively.

It was observed that 16 μM concentration of Hg^{2+} was able to enhance the fluorescence of ligand **(13aad)** by 57 fold, whereas 37 μM of Cu^{2+} was able to enhance the original fluorescence intensity of ligand **(13aad)** by 43 fold. Therefore, Hg^{2+} was found to be more efficient than Cu^{2+} towards fluorescence intensity enhancement of ligand **(13aad)**. Furthermore, to examine whether designed ligand **(13aad)** was able to detect Hg^{2+} and Cu^{2+} in a competitive environment of other metal ions, two separate solutions of metal ions, one with Hg^{2+} and other with Cu^{2+} ion were prepared. When these two solutions were added separately into the solution of ligand **(13aad)** (33 μM), it was observed that the fluorescence intensity enhancement was similar to the earlier observation. Therefore, it was concluded that the designed ligand **(13aad)** was able to detect Hg^{2+} and Cu^{2+} ions even in a competitive environment of other metal ions.

The better response of mercury towards fluorescence enhancement may be due to the high affinity of Hg^{2+} ion for soft sulfur donor. Moreover fluorescence enhancement may be attributed to ceasing of non-radiative channels through complex formation, as the complex is rigid with respect to the free ligand **(13aad)**. Therefore flexible modes may be responsible for non-radiative processes. Further binding ratios between ligand **(13aad)** and metals were confirmed by Job's plot (Figure 5.3a and 5.3c). Stoichiometry obtained between ligand **(13aad)** and mercury was 2:1 whereas between ligand **(13aad)** and copper was found 1:1.

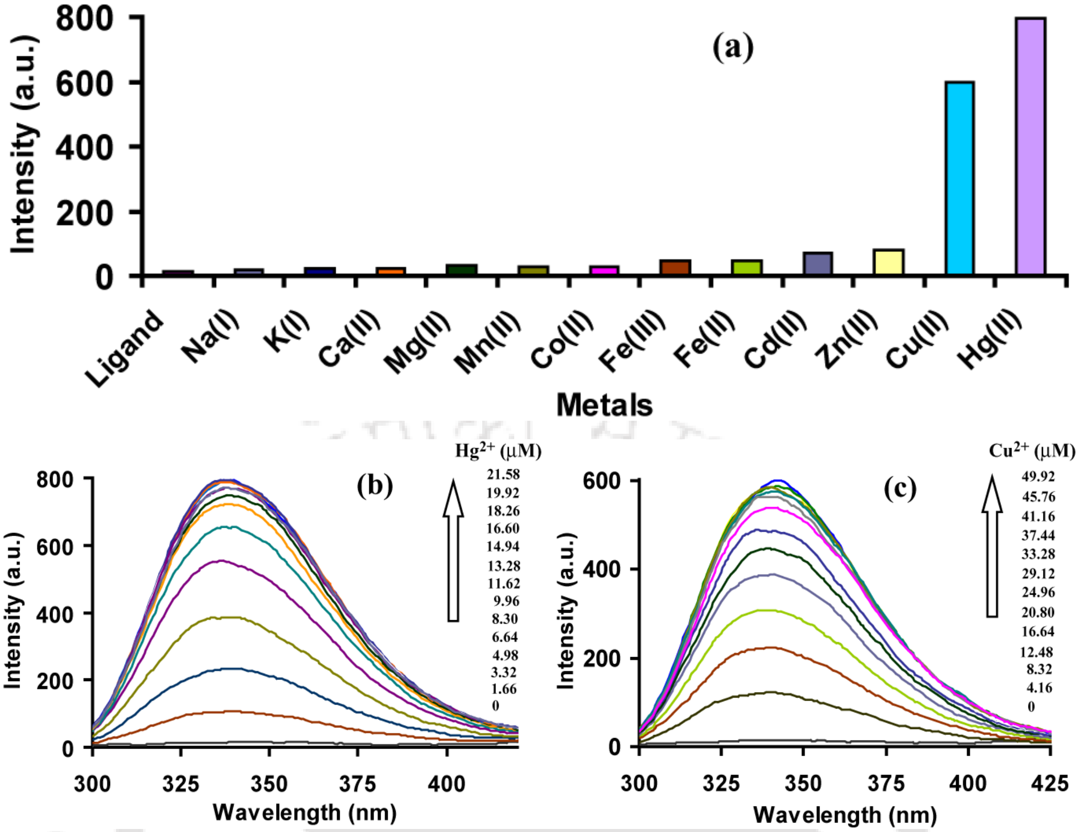


Figure 5.2. (a) Changes in the fluorescence intensity of ligand **(13aad)** (33 μM) in presence of various metals upto 50 μM concentration. (b) Fluorescence intensity enhancement of ligand **(13aad)** (33 μM) in presence of increasing concentration of Hg^{2+} ion. (c) Fluorescence intensity enhancement of ligand **(13aad)** in presence of increasing concentration of Cu^{2+} ion in CH_3CN/H_2O (9:1) solution.

Therefore, mercury may be quite efficient towards ceasing the non-radiative channels through complex formation, than copper. Also binding constants values 0.07 and 0.05 M^{-1}, for Hg^{2+} and Cu^{2+} obtained by Benesi-Hildebrand curve (Figure 5.3b and 5.3d), were found in good agreement, as stated above in Job's plot, that mercury is quite more efficient than copper towards complex formation with ligand **(13aad)**.

In addition to PL titration, UV/Vis titration of ligand **(13aad)** in the presence of Hg^{2+} and Cu^{2+} ions were also performed in CH_3CN/H_2O (9:1) solvent (Figure 5.4a and 5.4b). For ligand **(13aad)** three absorption bands centered at 220 nm, 278 nm and 288 nm were observed. On addition of increasing concentration of Hg^{2+} ion (0 to 50 μM) into the ligand **(13aad)** (33 μM), absorption intensities at 220 nm, 278 nm and 288 nm gradually increased without any shift in absorption position. Whereas, in the presence of increasing concentration of Cu^{2+} ion (0 to 50 μM), ligand **(13aad)** absorption intensity at 278 and 288 nm were gradually decreased and the absorption intensity at 220 nm increased.

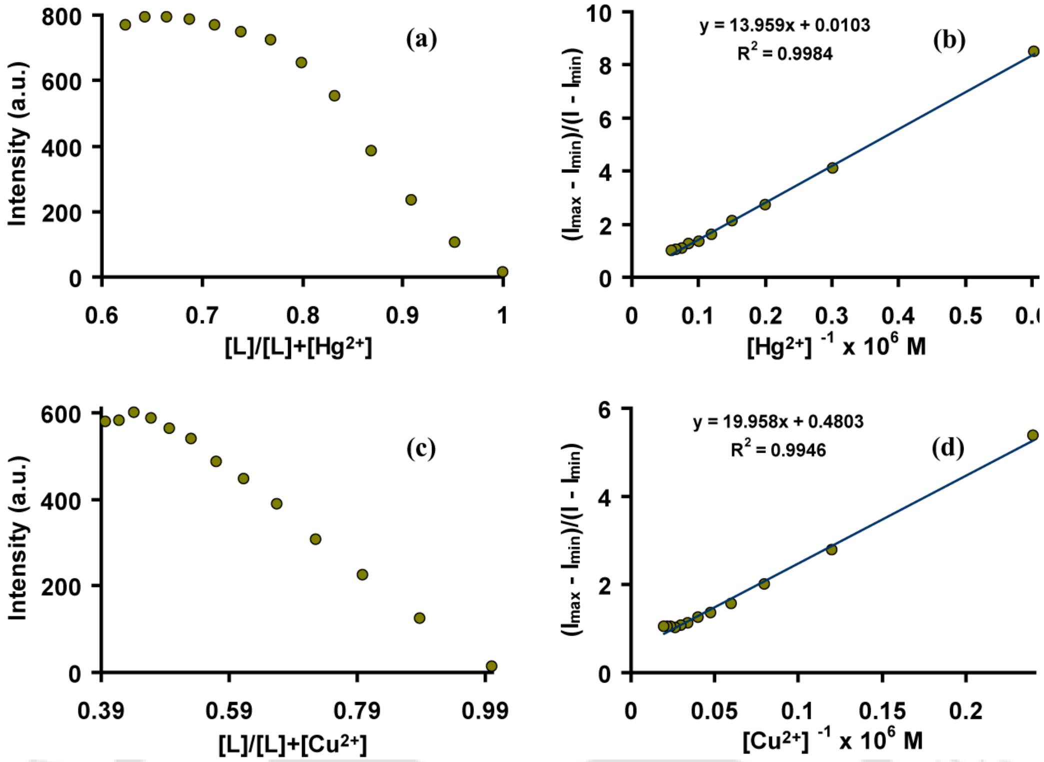


Figure 5.3. (a) Job's plot depicting the binding ratio between ligand **(13aad)** and Hg^{2+} ion. (b) Benesi-Hildebrand curve for the evaluation of binding constant of ligand **(13aad)** with Hg^{2+} ion. (c) Job's plot depicting the binding ratio between ligand **(13aad)** and Cu^{2+} ion. (d) Benesi-Hildebrand curve for the evaluation of binding constant of ligand **(13aad)** with Cu^{2+} ion.

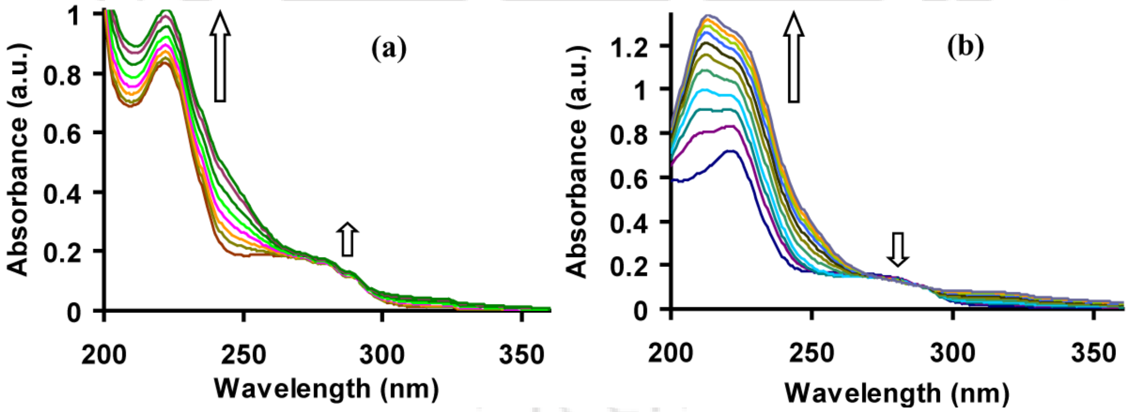


Figure 5.4. Changes in absorption spectra of ligand **(13aad)** (33 μM) on addition of (a) Hg^{2+} (0-50 μM) and (b) Cu^{2+} (0-50 μM) in CH_3CN/H_2O (9:1) solution.

Further to evaluate the limit of detection (LOD) of metals by our designed ligand **(13aad)**, a linear relationship between maximum emission intensity at 338 nm and the concentration of metal ions was obtained (Figure 5.5a and 5.5b). We observed that fluorescence intensity centered at 338 nm increased linearly with increasing concentrations of Hg^{2+} from 0 to 8.3×10^{-6} M (Figure 5.5a) and Cu^{2+} from 0 to 20.8×10^{-6} M (Figure 5.5b).

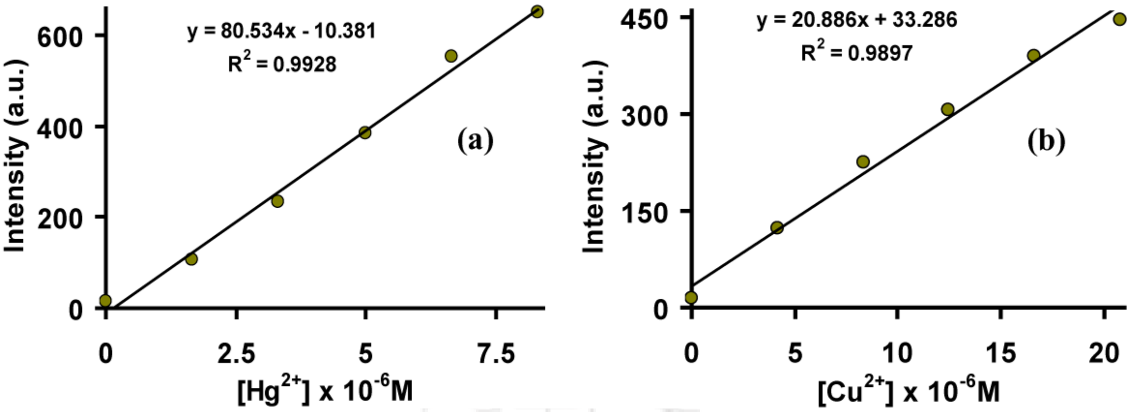


Figure 5.5. A linear relationship between maximum emission intensity at 338 nm and the concentrations of (a) Hg^{2+} ion (0 to 8.3 × 10^{-6} M) and (b) Cu^{2+} ion (20.8 × 10^{-6} M).

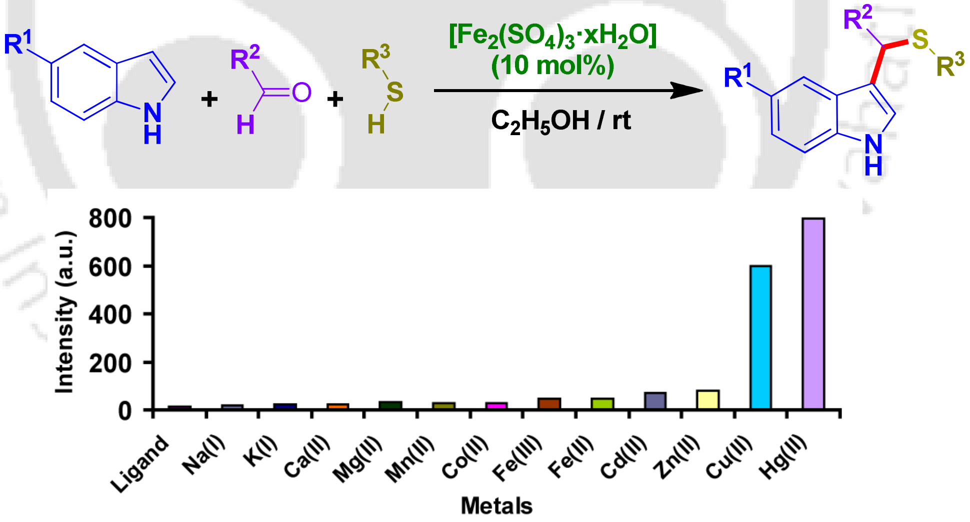
LOD was calculated using the equation 3σ/K, where σ is the standard deviation and K is the slope of the plot. The calculated limit of detection for Hg^{2+} and Cu^{2+} were found to be 30 nM and 108 nM, respectively. LOD value obtained for Hg^{2+} is close to the prescribed MCL value, given by U.S. Environmental Protection Agency's (EPA) in drinking water. The LOD of Cu^{2+} is much below the MCL values prescribed by EPA, thus demonstrating the efficiency of our designed ligand **(13aad)** towards the chemosensor activity.

In summary, the synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indole derivatives from indoles, aromatic aldehydes and various aliphatic/aromatic thiols was achieved using a catalytic amount of hydrated ferric sulfate at room temperature. This reaction strategy involves use of a cheap and non-toxic hydrated ferric sulfate as the catalyst.

One of the derivatives was employed as "turn-on" flourometric probe for dual detection of Hg^{2+} and Cu^{2+} ions, that has environmental and clinical importance in our daily life, with high detection limits of 30 nM (Hg^{2+}) and 108 nM (Cu^{2+}), respectively. From the Job's plot, stoichiometry was attained as 2:1 for ligand **(13aad)**:Hg^{2+} and 1:1 for ligand **(13aad)**:Cu^{2+}. Using Benesi-Hildebrand equation, the binding constants values were also calculated for Hg^{2+} (0.07 M^{-1}) and Cu^{2+} (0.05 M^{-1}) and found in good agreement that mercury is quite more efficient than copper towards complex formation with ligand **(13aad)**.

Chapter 5

Hydrated ferric sulfate catalyzed synthesis of 3-[(alkyl/arylthio) (aryl)methyl]-1H-indole derivatives through one-pot reaction: As a selective chemosensor for Hg^{2+} and Cu^{2+}



CHAPTER 5: *Experimental Section*

5.2 Experimental Section

Materials and Methods

All the reagents and solvents were purchased from Aldrich Chemicals (India), Merck (India) or Ranbaxy (India) and were used as received. Milli-Q water was used in all the experiments. The solutions of metal ions from NaCl, KCl, $CaCl_2.2H_2O$, $MgCl_2$, $Zn(ClO_4)_2.6H_2O$, $Mn(ClO_4)_2.H_2O$, $Co(ClO_4)_2.6H_2O$, $Fe(ClO_4)_3.H_2O$, $Fe(ClO_4)_2.H_2O$, $Cd(ClO_4)_2.H_2O$, $CuCl_2$, $HgCl_2$ were prepared in deionized water.

General UV-vis and fluorescence spectra measurements

CH_3CN/H_2O (9:1) solution of ligand (33 μM solution) was placed in the quartz cell and the UV-vis as well as fluorescence spectra were recorded for increasing portions of metal salts up to 50 μM. The experiments were performed at room temperature and changes monitored and recorded carefully.

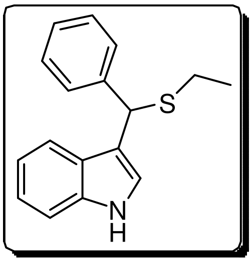
General procedure for synthesis of compounds (13)

Hydrated ferric sulfate (0.042 g, 0.1 mmol) was added to a stirred mixture of indole (1 mmol) and aldehyde (1 mmol) in 3 mL of ethanol at room temperature. Subsequently, thiol (1.2 mmol) was added into it and stirring was further continued. After completion of the reaction as monitored by TLC, ethanol was removed in rotary evaporator and the crude residue was extracted with dichloromethane (2 × 15 mL). The organic layer was washed with water followed by brine solution. The organic extract was dried over anhydrous sodium sulfate and it was concentrated in a rotary evaporator. Finally, the crude residue was passed through a silica gel column to obtain the desired pure product. All the desired products were eluted with ethyl acetate: hexane (1:9) mixture during column chromatography except the compound **13aam** and **13ahn** were eluted with 1:1 mixture of the same solvent system.

For recovery of the catalyst, the reaction was carried out in 3 mmol scale in ethanol. After completion of reaction, ethanol was removed and dichloromethane (9 mL) was added into it. Then the catalyst comes out, and it was filtered and dried for next cycle reaction.

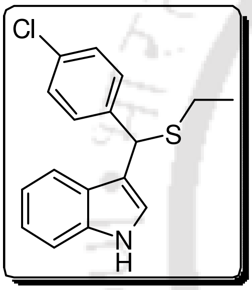
Spectral data of Compounds:

3-((Ethylthio)(phenyl)methyl)-1H-indole (13aaa):



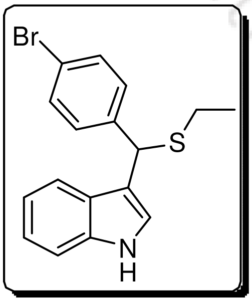
Nature: Dark pink semi-solid; $R_f = 0.40$; **IR** (KBr): 3396 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.6 Hz, 3H), 2.35-2.38 (m, 2H), 5.35 (s, 1H), 6.95 (s, 1H), 6.98 (t, *J* = 6.8 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 26.3, 45.9, 111.4, 116.9, 119.7, 119.9, 122.4, 123.3, 126.5, 127.1, 128.5 (2C), 128.6 (2C), 136.7, 142.2. **Anal. Calcd** for $C_{17}H_{17}NS$ (267.39): C, 76.36; H, 6.41; N, 5.24. Found: C, 76.23; H, 6.34; N, 5.15.

3-((p-Chlorophenyl)(ethylthio)methyl)-1H-indole (13aea):



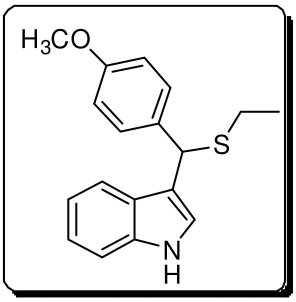
Nature: Red oily liquid; $R_f = 0.40$; **IR** (KBr): 3412 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.6 Hz, 3H), 2.44 (q, *J* = 7.2 Hz, 2H), 5.40 (s, 1H), 7.05 (s, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.97 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 26.3, 45.3, 111.5, 116.4, 119.7, 119.8, 122.6, 123.3, 126.3, 128.7 (2C), 129.8 (2C), 132.7, 136.7, 140.8. **Anal. Calcd** for $C_{17}H_{16}ClNS$ (301.83): C, 67.65; H, 5.34, N, 4.64. Found: C, 67.53; H, 5.26; N, 4.57.

3-((p-Bromophenyl)(ethylthio)methyl)-1H-indole (13afa):



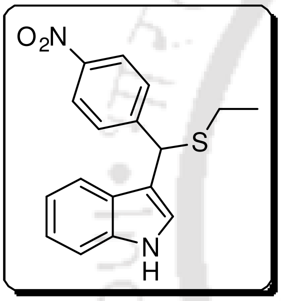
Nature: Red oily liquid; $R_f = 0.60$; **IR** (KBr): 3413 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.6 Hz, 3H), 2.41 (q, *J* = 7.2 Hz, 2H), 5.36 (s, 1H), 6.93 (s, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 26.2, 45.3, 111.5, 116.2, 119.7, 119.8, 120.8, 122.5, 123.3, 126.2, 130.2 (2C), 131.6 (2C), 136.6, 141.2. **Anal. Calcd** for $C_{17}H_{16}BrNS$ (346.28): C, 58.96; H, 4.66; N, 4.04. Found: C, 58.81; H, 4.57; N, 3.96.

3-((Ethylthio)(p-methoxyphenyl)methyl)-1H-indole (13aba):



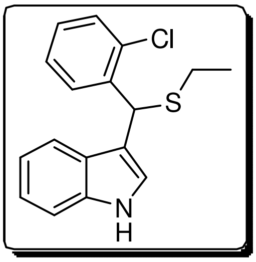
Nature: Dark red oily liquid; $R_f = 0.40$; **IR** (KBr): 3416 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.6 Hz, 3H), 2.38-2.44 (m, 2H), 3.70 (s, 3H), 5.39 (s, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.94 (s, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.90 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 26.1, 45.2, 55.3, 111.4, 113.9 (2C), 116.9, 119.5, 119.8, 122.2, 123.3, 126.4, 129.4 (2C), 134.2, 136.6, 158.5. **Anal. Calcd** for $C_{18}H_{19}NOS$ (297.41): C, 72.69; H, 6.44; N, 4.71. Found: C, 72.57; H, 6.36; N, 4.65.

3-((Ethylthio)(p-nitrophenyl)methyl)-1H-indole (13aha):



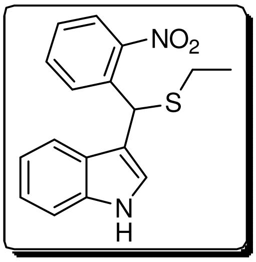
Nature: Yellow solid; mp 128 °C; $R_f = 0.37$; **IR** (KBr): 3395 (-NH), 1508 (-NO_2), 1340 (-NO_2) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.6 Hz, 3H), 2.48 (q, *J* = 7.6 Hz, 2H), 5.49 (s, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H), 8.17 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 26.5, 45.5, 111.6, 115.4, 119.5, 120.1, 122.8, 123.5, 123.9 (2C), 126.2, 129.3 (2C), 136.8, 147.0, 150.0. **Anal. Calcd** for $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.36; H, 5.16; N, 8.97. Found: C, 65.24; H, 5.08, N, 8.90.

3-((o-Chlorophenyl)(ethylthio)methyl)-1H-indole (13aoa):



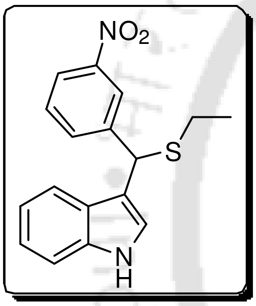
Nature: Reddish oily liquid; $R_f = 0.33$; **IR** (KBr): 3412 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.6 Hz, 3H), 2.42 (q, *J* = 7.2 Hz, 2H), 5.91 (s, 1H), 6.97 (s, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 7.03 (dd, *J* = 1.2 Hz, J = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 1.2 Hz, J = 7.6 Hz, 1H), 7.54-7.57 (m, 2H), 7.82 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.7, 26.4, 41.6, 111.4, 115.9, 119.5, 119.7, 122.4, 123.6, 126.4, 127.2, 128.2, 129.4, 130.3, 133.4, 136.5, 139.7. **Anal. Calcd** for $C_{17}H_{16}ClNS$ (301.83): C, 67.65; H, 5.34, N, 4.64. Found: C, 67.52; H, 5.26, N, 4.57.

3-((Ethylthio)(o-nitrophenyl)methyl)-1H-indole (13ama):



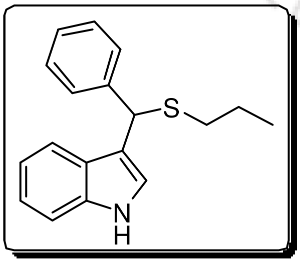
Nature: Yellowish oily liquid; $R_f = 0.33$; **IR** (KBr): 3420 (-NH), 1524 (-NO$_2$), 1353 (-NO$_2$) cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.23 (t, J = 7.6 Hz, 3H), 2.51 (q, J = 7.2 Hz, 2H), 6.25 (s, 1H), 7.07 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 7.17 (t, J = 6.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H, NH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.5, 26.9, 40.0, 111.5, 115.2, 119.6, 119.9, 122.6, 124.0, 124.3, 126.3, 127.9, 131.0, 132.9, 136.7, 136.8, 149.3. **Anal. Calcd** for $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.36; H, 5.16; N, 8.97. Found: C, 65.25; H, 5.08; N, 8.89.

3-((Ethylthio)(m-nitrophenyl)methyl)-1H-indole (13aja):



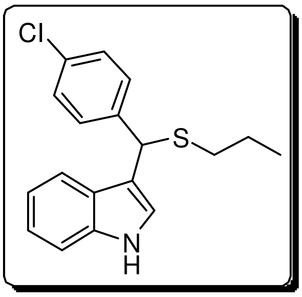
Nature: Yellowish oily liquid; $R_f = 0.46$; **IR** (KBr): 3420 (-NH), 1526 (-NO$_2$), 1350 (-NO$_2$) cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.27 (t, J = 7.2 Hz, 3H), 2.50 (q, J = 7.2 Hz, 2H), 5.53 (s, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H, NH), 8.39 (t, J = 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.4, 26.4, 45.3, 111.6, 115.2, 119.3, 119.8, 122.1, 122.6, 123.2, 123.5, 126.0, 129.4, 134.6, 136.7, 144.7, 148.3. **Anal. Calcd** for $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.36; H, 5.16; N, 8.97. Found: C, 65.22; H, 5.07, N, 8.83.

3-(Phenyl(propylthio)methyl)-1H-indole (13aab):



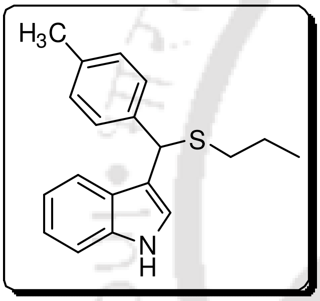
Nature: Light red oily liquid; $R_f = 0.40$; **IR** (KBr): 3415 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.94 (t, J = 7.6 Hz, 3H), 1.55-1.62 (m, 2H), 2.38-2.44 (m, 2H), 5.40 (s, 1H), 7.04 (s, 1H), 7.07 (d, J = 7.2 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 3H), 7.49 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H, NH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 13.8, 22.8, 34.4, 46.2, 111.4, 117.0, 119.7, 119.8, 122.4, 123.4, 126.5, 127.1, 128.5 (2C), 128.6 (2C), 136.7, 142.3. **Anal. Calcd** for $C_{18}H_{19}NS$ (281.42): C, 76.82; H, 6.81; N, 4.98. Found: C, 76.70; H, 6.73, 4.88.

3-((p-Chlorophenyl)(propylthio)methyl)-1H-indole (13aeb):



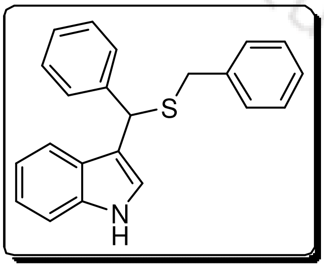
Nature: Dark pink semi-solid; $R_f = 0.50$; **IR** (KBr): 3433 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$/DMSO): δ 0.87 (t, *J* = 7.6 Hz, 3H), 1.47-1.57 (m, 2H), 2.38-2.44 (m, 2H), 5.30 (s, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 9.42 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7, 22.8, 34.4, 45.6, 111.5, 116.6, 119.7, 119.8, 122.6, 123.3, 126.4, 128.7 (2C), 129.9 (2C), 132.7, 136.7, 140.9. **Anal. Calcd** for $C_{18}H_{18}ClNS$ (315.86): C, 68.45; H, 5.74, N, 4.43. Found: C, 68.36; H, 5.65, N, 4.35.

3-((Propylthio)(p-tolyl)methyl)-1H-indole (13acb):



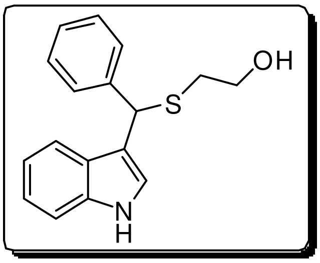
Nature: Dark red semi-solid; $R_f = 0.33$; **IR** (KBr): 3389 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.55-1.63 (m, 2H), 2.30 (s, 3H), 2.37-2.43 (m, 2H), 5.38 (s, 1H), 7.03-7.08 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.8, 21.3, 22.8, 34.4, 45.9, 111.4, 117.2, 119.6, 119.9, 122.3, 123.3, 126.6, 128.4 (2C), 129.3 (2C), 136.7 (2C), 139.2. **Anal. Calcd** for $C_{19}H_{21}NS$ (295.44): C, 77.24; H, 7.16, N, 4.74. Found: C, 77.18; H, 7.04; N, 4.68.

3-((Benzylthio)(phenyl)methyl)-1H-indole (13aac):



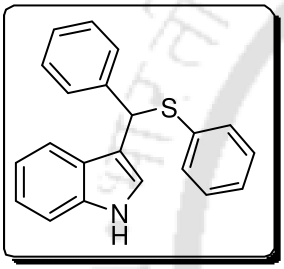
Nature: Dark red semi-solid; $R_f = 0.40$; **IR** (KBr): 3408 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.57 (d, *J* = 13.2 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 5.23 (s, 1H), 6.94 (d, *J* = 1.6 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 8.0 Hz, 2H), 7.22-7.34 (m, 7H), 7.48 (d, *J* = 8.8 Hz, 2H),), 7.53 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 36.7, 45.5, 111.4, 116.5, 119.7, 119.8, 122.4, 123.6, 126.4, 127.1, 127.2, 128.5 (2C), 128.6 (2C), 128.7 (2C), 129.2 (2C), 136.6, 138.5, 141.7. **Anal. Calcd** for $C_{22}H_{19}NS$ (329.46): C, 80.20; H, 5.81; N, 4.25. Found: C, 80.08; H, 5. 74; N, 4.13.

2-(((1H-indol-3-yl)(phenyl)methyl)thio)ethanol (13aam):



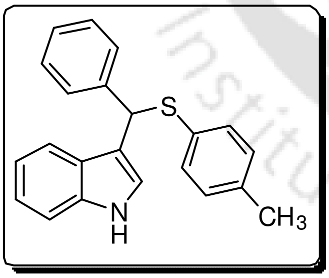
Nature: Dark red oily liquid; $R_f = 0.73$; **IR** (KBr): 3410 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.35 (s, 1H, OH), 2.52 (t, *J* = 6.0 Hz, 2H), 3.50-3.54 (m, 2H), 5.35 (s, 1H), 6.92 (s, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 7.11-7.21 (m, 4H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 8.06 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 35.2, 46.1, 60.7, 111.5, 116.0, 119.7 (2C), 122.4, 123.6, 126.2, 127.3, 128.4 (2C), 128.6 (2C), 136.7, 141.7. **Anal. Calcd** for $C_{17}H_{17}NOS$ (283.39): C, 72.05; H, 6.05; N, 4.94. Found: C, 71.94; H, 5.98; N, 4.87.

3-(Phenyl(phenylthio)methyl)-1H-indole (13aad):



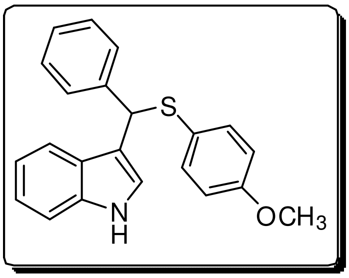
Nature: Dark red semi-solid; $R_f = 0.40$; **IR** (KBr): 3414 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.68 (s, 1H), 6.84 (s, 1H), 6.94-7.08 (m, 6H), 7.10 (s, 1H), 7.15 (t, *J* = 8.4 Hz, 4H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 49.9, 111.5, 116.3, 119.8 (2C), 122.5, 124.1, 126.4, 126.5, 127.3, 128.5 (2C), 128.6 (2C), 128.9 (2C), 130.5 (2C), 136.7, 136.8, 141.4. **Anal. Calcd** for $C_{21}H_{17}NS$ (315.43): C, 79.96; H,5.43; N, 4.44. Found: C, 79.82; H, 5.37; N, 4.35.

3-(Phenyl(p-tolylthio)methyl)-1H-indole (13aae):



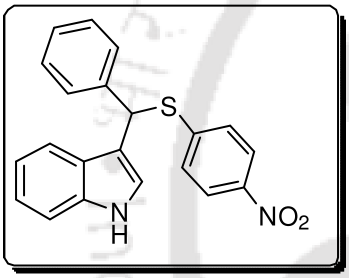
Nature: Dark red semi-solid; $R_f = 0.37$; **IR** (KBr): 3396 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.15 (s, 3H), 5.63 (s, 1H), 6.89 (t, *J* = 8.0 Hz, 2H), 6.92 (s, 1H), 6.98 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 3H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 50.6, 111.5, 116.3, 119.7, 119.8, 122.4, 124.0, 126.3, 127.2, 128.4 (2C), 128.5 (2C), 129.6 (2C), 131.3 (2C), 132.9, 136.6, 136.7, 141.7. **Anal. Calcd** for $C_{22}H_{19}NS$ (329.46): C, 80.20; H, 5.81; N, 4.25. Found: C, 80.09; H, 5.72; N, 4.18.

3-(((p-Methoxyphenyl)thio)(phenyl)methyl)-1H-indole (13aai):



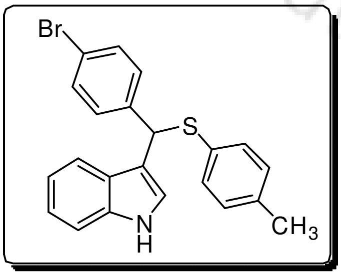
Nature: Dark red oily liquid; $R_f = 0.37$; **IR** (KBr): 3415 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.58 (s, 3H), 5.50 (s, 1H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 2H), 7.08-7.16 (m, 5H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.83 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 51.9, 55.4, 111.4, 114.4 (2C), 116.4, 119.7, 120.0, 122.4, 123.8, 126.5, 126.6, 127.2, 128.4 (2C), 128.6 (2C), 134.7 (2C), 136.7, 141.9, 159.3. **Anal. Calcd** for $C_{22}H_{19}NOS$ (345.46): C, 76.49; H, 5.54; N, 4.05. Found: C, 76.36; H, 5.48; N, 3.97.

3-(((4-nitrophenyl)thio)(phenyl)methyl)-1H-indole (13aan):



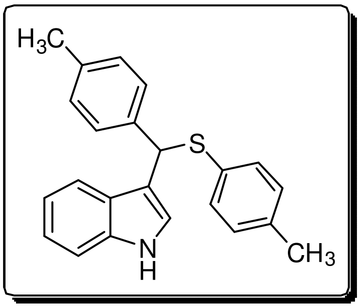
Nature: Yellowish oily liquid; $R_f = 0.33$; **IR** (KBr): 3421 (-NH), 1511 (-NO_2), 1337 (-NO_2) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.02 (s, 1H), 7.06 (s, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.21-7.40 (m, 7H), 7.54 (d, *J* = 6.9 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 2H), 8.18 (s, 1H, NH); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 48.0, 111.5, 114.8, 119.2, 120.0, 122.7, 123.8 (2C), 124.2, 125.9, 126.9 (2C), 127.8, 128.2 (2C), 128.8 (2C), 136.6, 139.5, 144.9, 147.7. **Anal. Calcd** for $C_{21}H_{16}N_2O_2S$ (360.43): C, 69.98; H, 4.47; N, 7.77. Found: C, 69.78; H, 4.39; N, 7.62.

3-((p-Bromophenyl)(p-tolylthio)methyl)-1H-indole (13afe):



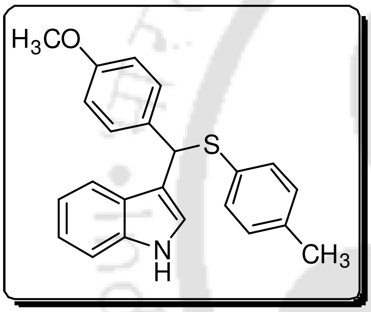
Nature: Dark red oily liquid; $R_f = 0.40$; **IR** (KBr): 3434 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 5.58 (s, 1H), 6.92 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 1.6 Hz, 1H), 7.02 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 50.2, 111.5, 116.1, 119.8, 119.9, 121.1, 122.7, 123.9, 126.3, 129.8 (2C), 130.3 (2C), 131.6 (2C), 131.8 (2C), 132.4, 136.8, 137.2, 140.9. **Anal. Calcd** for $C_{22}H_{18}BrNS$ (408.35): C, 64.71; H, 4.44; N, 3.43. Found: C, 64.60; H, 4.35; N, 3.37.

3-(p-Tolyl(p-tolylthio)methyl)-1H-indole (13ace):



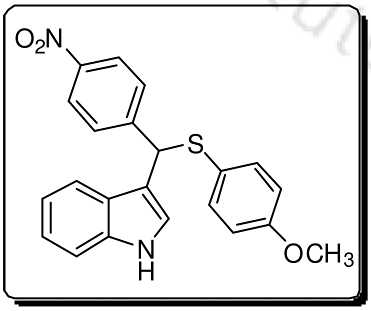
Nature: Dark red oily liquid; $R_f = 0.40$; **IR** (KBr): 3445 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.25 (s, 3H), 5.65 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.97-7.06 (m, 4H), 7.08-7.15 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.92 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 50.2, 111.4, 116.8, 119.8, 119.9, 122.4, 124.0, 126.5, 128.4 (2C), 129.3 (2C), 129.6 (2C), 131.1 (2C), 133.3, 136.6, 136.7, 136.8, 138.7. **Anal. Calcd** for $C_{23}H_{21}NS$ (343.48): C, 80.42; H, 6.16; N, 4.08. Found: C, 80.40; H, 6.09; N, 4.01.

3-((p-Methoxyphenyl)(p-tolylthio)methyl)-1H-indole (13abe):



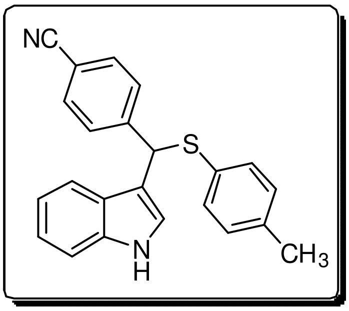
Nature: Dark red oily liquid; $R_f = 0.46$; **IR** (KBr): 3429 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.65 (s, 3H), 5.60 (s, 1H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 7.6 Hz, 2H), 6.93 (s, 1H), 6.95-7.00 (m, 1H), 7.05-7.10 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 49.9, 55.4, 111.4, 113.9 (2C), 116.8, 119.7, 119.9, 122.4, 124.0, 126.4, 129.6 (3C), 130.0, 131.2 (2C), 133.1, 133.8, 136.6, 136.8, 158.7. **Anal. Calcd** for $C_{23}H_{21}NOS$ (359.48): C, 76.85; H, 5.89; N, 3.90. Found: C, 76.73; H, 5.80; N, 3.82.

3-(((4-methoxyphenyl)thio)(4-nitrophenyl)methyl)-1H-indole (13ahi):



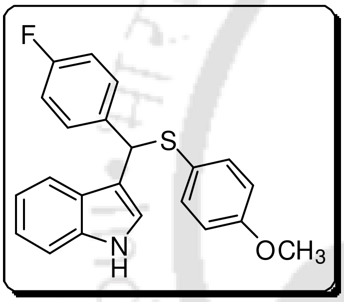
Nature: Red oily liquid; $R_f = 0.26$; **IR** (KBr): 3419 (-NH), 1517 (-NO_2), 1345 (-NO_2) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 5.62 (s, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 7.18-7.22 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 8.13 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 51.5, 55.4, 111.6, 114.6 (2C), 114.8, 119.5, 120.0, 122.7, 123.6 (2C), 123.7, 125.0, 126.1, 129.3 (2C), 135.5 (2C), 136.7, 146.8, 149.7, 159.9. **Anal. Calcd** for $C_{22}H_{18}N_2O_3S$ (390.45): C, 67.67; H, 4.65; N, 7.17. Found: C, 67.55; H, 4.58; N, 7.09.

4-((1H-indol-3-yl)(p-tolylthio)methyl)benzonitrile (13aie):



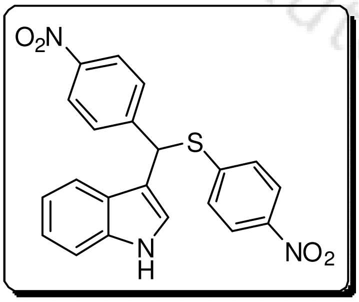
Nature: Red oily liquid; R_f = 0.36; **IR** (KBr): 3406 (-NH), 2226 (-CN) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 5.68 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 7.02 (s, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.46 (s, 4H), 7.54 (d, *J* = 8.0 Hz, 1H), 8.17 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 50.6, 110.4, 111.7, 114.7, 119.0, 119.4, 119.8, 122.5, 123.8, 125.9, 129.1 (2C), 129.7 (2C), 131.4, 132.1 (4C), 136.6, 137.5, 147.4. **Anal. Calcd** for $C_{23}H_{18}N_2S$ (354.46): C, 77.93; H, 5.12; N, 7.90. Found: C, 77.82; H, 5.03; N, 7.81.

3-((p-Fluorophenyl)((p-methoxyphenyl)thio)methyl)-1H-indole (13avi):



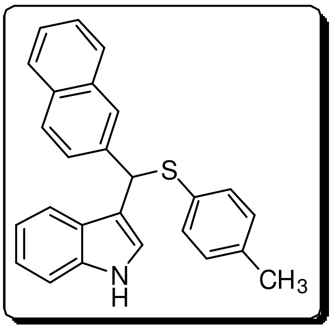
Nature: Dark red oily liquid; R_f = 0.30; **IR** (KBr): 3431 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.63 (s, 3H), 5.49 (s, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 6.84 (t, *J* = 8.8 Hz, 2H), 6.94 (s, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.19-7.26 (m, 3H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 51.3, 55.4, 111.5, 114.5 (3C), 115.1, 115.3, 116.4, 119.8, 119.9, 122.6, 123.7, 126.3, 126.4, 130.1, 130.2, 135.0 (3C), 136.8, 159.6. **Anal. Calcd** for $C_{22}H_{18}FNOS$ (363.45): C, 72.70; H, 4.99; N, 3.85. Found: C, 72.68; H, 4.87; N, 3.77.

3-((4-nitrophenyl)((4-nitrophenyl)thio)methyl)-1H-indole (13ahn):



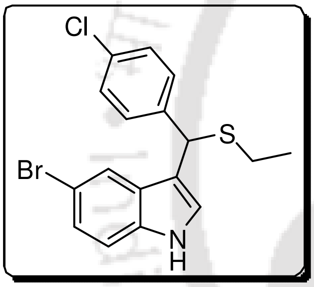
Nature: Yellow solid; mp 183 °C; R_f = 0.15; **IR** (KBr): 3474 (-NH), 1518 (-NO_2), 1334 (-NO_2) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.07 (s, 1H), 6.09 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 8.24 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3/CD_2Cl_2$): δ 47.9, 111.8, 113.6, 119.1, 120.5, 123.2, 124.1 (2C), 124.2 (2C), 124.4, 125.7, 127.9 (2C), 129.4 (2C), 136.9, 145.7, 146.1, 147.3, 147.5. **Anal. Calcd** for $C_{21}H_{15}N_3O_4S$ (405.43): C, 62.21; H, 3.73; N, 10.36. Found: C, 62.08; H, 3.65; N, 10.28.

3-(Naphthalen-2-yl(p-tolylthio)methyl)-1H-indole (13ale):



Nature: Dark pink solid; mp 145 °C; R_f = 0.48; **IR** (KBr): 3434 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.11 (s, 3H), 5.77 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 1.6 Hz, 1H), 6.96 (t, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.29-7.33 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.59-7.62 (m, 1H), 7.64-7.68 (m, 2H), 7.73 (s, 1H), 7.77 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 51.0, 111.5, 116.5, 119.8, 119.9, 122.5, 124.1, 126.0, 126.2, 126.5, 127.0, 127.1, 127.8, 128.2, 128.3, 129.7 (2C), 131.5 (2C), 132.8, 132.9, 133.5, 136.8, 136.9, 139.1. **Anal. Calcd** for $C_{26}H_{21}NS$ (379.52): C, 82.28; H, 5.58; N, 3.69. Found: C, 82.15; H, 5.51; N, 3.61.

5-bromo-3-((4-chlorophenyl)(ethylthio)methyl)-1H-indole (13bea):



Nature: Light yellow oily liquid; R_f = 0.40; **IR** (KBr): 3431 (-NH) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.6 Hz, 3H), 2.44-2.50 (m, 2H), 5.37 (s, 1H), 7.10 (s, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.78 (s, 1H), 8.13 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 26.4, 45.0, 112.9, 113.2, 116.4, 122.4, 124.5, 125.6, 128.1, 128.9 (2C), 129.8 (2C), 133.0, 135.4, 140.3. **Anal. Calcd** for $C_{17}H_{15}BrClNS$ (380.73): C, 53.63; H, 3.97, N, 3.68. Found: C, 53.48; H, 3.85; N, 3.56.

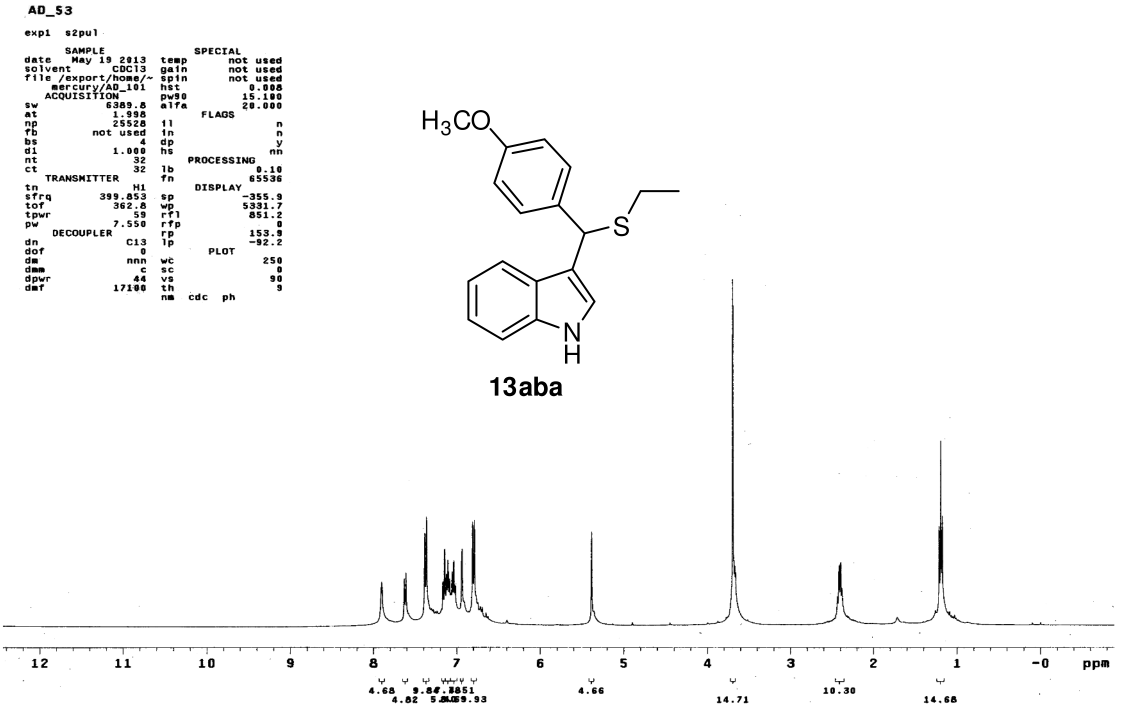
Crystallographic description:

Complete crystallographic data of **13aha** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 930601. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 5.4. Crystal data and structures refinement for the compound **13aha** for atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check the CIF.

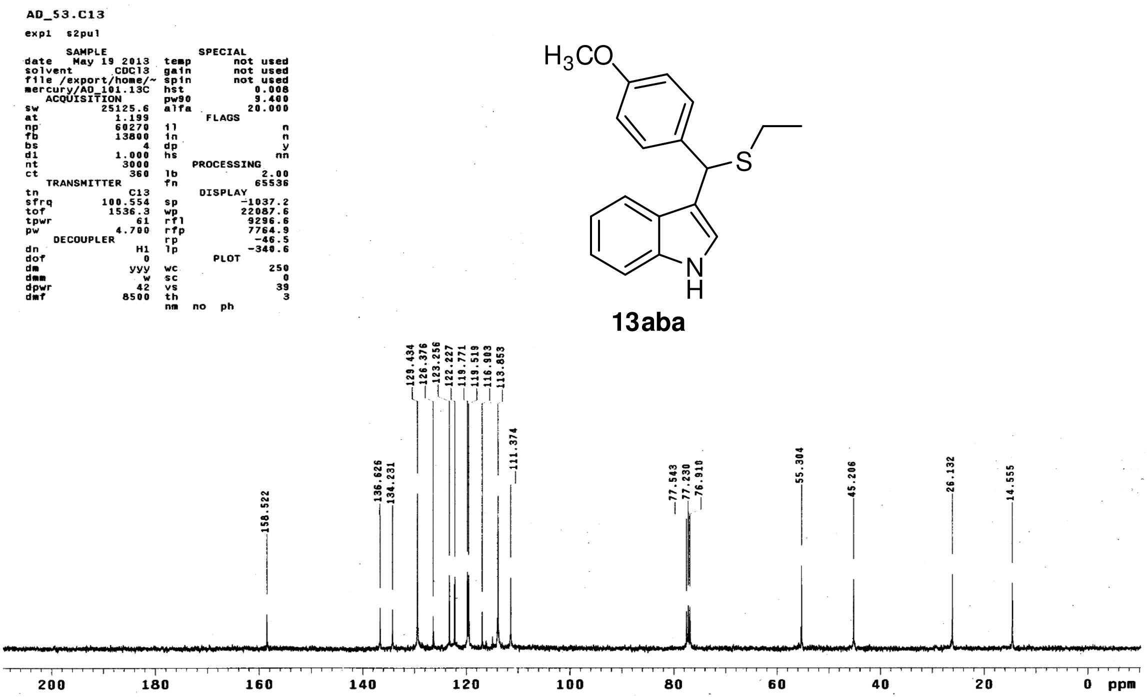
Parameters	**Compound 13aha**
Empirical Formula	$C_{17} H_{16} N_2 O_2 S$
Formula weight	312.39
Temperature	0 K
Wavelength	0.71070 (Å)
Crystal system	Monoclinic
Space group	C 1 2/c 1
Radiation type	Mo K\a
Radiation source	'SuperNova (Mo) X-ray Source'
Unit cell dimensions	a = 16.315 (2) (Å), $\alpha = 90°$
	b = 10.4846 (7) (Å), $\beta = 118.484(18)°$
	c = 21.538 (3) (Å), $\gamma = 90°$
Unit cell volume	3238.3 (9) $Å^3$
Z	8
Density	1.281 g/cm^3
F(0 0 0)	1313.5
Index ranges	$-20 \leq h \leq 20$, $-12 \leq k \leq 14$, $-28 \leq l \leq 24$
Reflections collected	7030
Independent reflections	3686 [R(int) = 0.0274]
Theta range for data collection	2.90 to 28.78°
Completeness to theta	28.78° 97.71 %
Number of parameters	199
Number of restraints	0
Goodness-of-fit (GOF)^a on F^2	1.147
Refinement method	Full-matrix least-squares on F^2
CCDC number	930601

^{1}H NMR (400 MHz, CDCl$_3$): *3-((Ethylthio)(p-methoxyphenyl)methyl)-1H-indole* (**13aba**)



```
AD_53

exp1  s2pul

       SAMPLE              SPECIAL
date   May 19 2013   temp       not used
solvent        CDCl3  gain       not used
file /export/home/~  spin       not used
    mercury/AD_101   hst           0.008
   ACQUISITION       pw90         15.100
sw          6389.8   alfa         20.000
at           1.998          FLAGS
np           25528   il                n
fb        not used   in                n
bs               4   dp                y
d1           1.000   hs               nn
nt              32       PROCESSING
ct              32   lb             0.10
   TRANSMITTER       fn            65536
tn              H1          DISPLAY
sfrq       399.853   sp           -355.9
tof          362.8   wp           5331.7
tpwr            59   rfl           851.2
pw           7.550   rfp               0
    DECOUPLER        rp            153.9
dn             C13   lp            -92.2
dof              0           PLOT
dm             nnn   wc              250
dmm              c   sc                0
dpwr            44   vs               90
dmf          17100   th                9
                     nm   cdc   ph
```

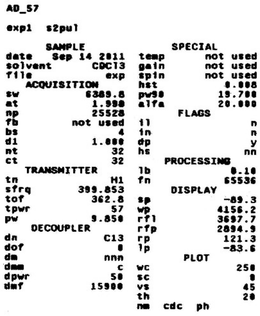
^{13}C NMR (100 MHz, CDCl$_3$): *3-((Ethylthio)(p-methoxyphenyl)methyl)-1H-indole* (**13aba**)



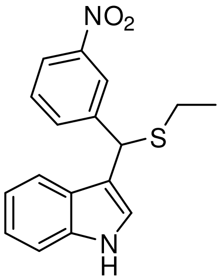
```
AD_53.C13

exp1  s2pul

       SAMPLE              SPECIAL
date   May 19 2013   temp       not used
solvent        CDCl3  gain       not used
file /export/home/~  spin       not used
mercury/AD_101.13C   hst           0.008
   ACQUISITION       pw90          9.400
sw         25125.6   alfa         20.000
at           1.199          FLAGS
np           60270   il                n
fb           13800   in                n
bs               4   dp                y
d1           1.000   hs               nn
nt            3000       PROCESSING
ct             360   lb             2.00
   TRANSMITTER       fn            65536
tn             C13          DISPLAY
sfrq       100.554   sp          -1037.2
tof         1536.3   wp          22087.6
tpwr            61   rfl          9296.6
pw           4.700   rfp          7764.9
    DECOUPLER        rp            -46.5
dn              H1   lp           -340.6
dof              0           PLOT
dm             yyy   wc              250
dmm              w   sc                0
dpwr            42   vs               39
dmf           8500   th                3
                     nm   no   ph
```

Figure 5.6

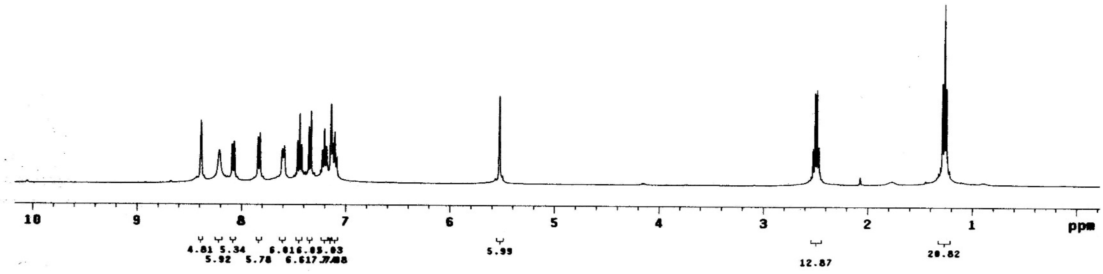
^{1}*H NMR (400 MHz, CDCl$_3$): 3-((Ethylthio)(m-nitrophenyl)methyl)-1H-indole* (**13aja**)



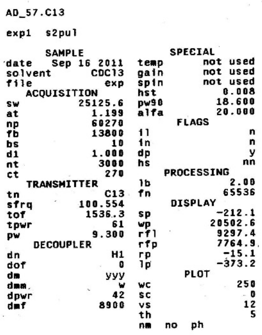
```
AD_57

exp1  s2pul

      SAMPLE                SPECIAL
date   Sep 14 2011   temp        not used
solvent      CDCl3   gain        not used
file           exp   spin        not used
   ACQUISITION       hst            0.008
sw          6389.8   pw90          19.700
at           1.998   alfa          20.000
np           25528           FLAGS
fb        not used   il                 n
bs               4   in                 n
d1           1.000   dp                 y
nt              32   hs                nn
ct              32         PROCESSING
   TRANSMITTER       lb              0.10
tn              H1   fn             65536
sfrq       399.853           DISPLAY
tof          362.8   sp             -89.3
tpwr            57   wp            4156.2
pw           9.850   rfl           3697.7
    DECOUPLER        rfp           2894.9
dn             C13   rp             121.3
dof              0   lp             -83.6
dm             nnn            PLOT
dmm              c   wc               250
dpwr            50   sc                 0
dmf          15900   vs                45
                     th                20
                     nm   cdc   ph
```



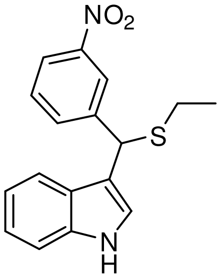
13aja



^{13}*C NMR (100 MHz, CDCl$_3$): 3-((Ethylthio)(m-nitrophenyl)methyl)-1H-indole* (**13aja**)



```
AD_57.C13

exp1  s2pul

      SAMPLE                SPECIAL
date   Sep 16 2011   temp        not used
solvent      CDCl3   gain        not used
file           exp   spin        not used
   ACQUISITION       hst            0.008
sw         25125.6   pw90          18.600
at           1.199   alfa          20.000
np           60270           FLAGS
fb           13800   il                 n
bs              10   in                 n
d1           1.000   dp                 y
nt            3000   hs                nn
ct             270         PROCESSING
   TRANSMITTER       lb              2.00
tn             C13   fn             65536
sfrq       100.554           DISPLAY
tof         1536.3   sp            -212.1
tpwr            61   wp           20502.6
pw           9.300   rfl           9297.4
    DECOUPLER        rfp           7764.9
dn              H1   rp             -15.1
dof              0   lp            -373.2
dm             yyy            PLOT
dmm              w   wc               250
dpwr            42   sc                 0
dmf           8900   vs                12
                     th                 5
                     nm   no   ph
```



13aja

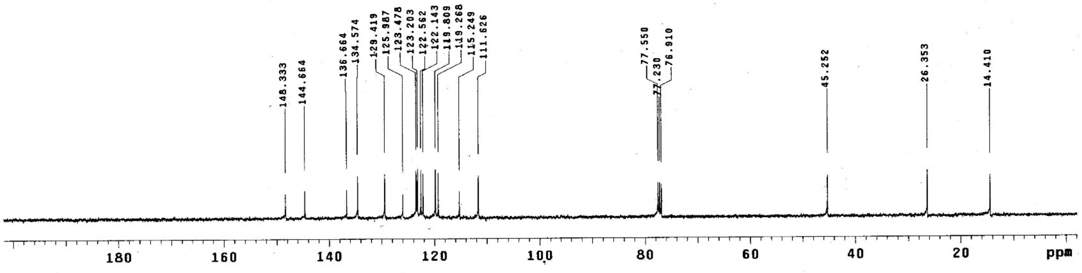
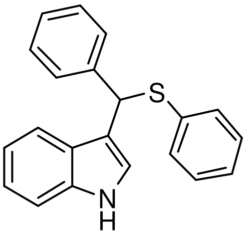


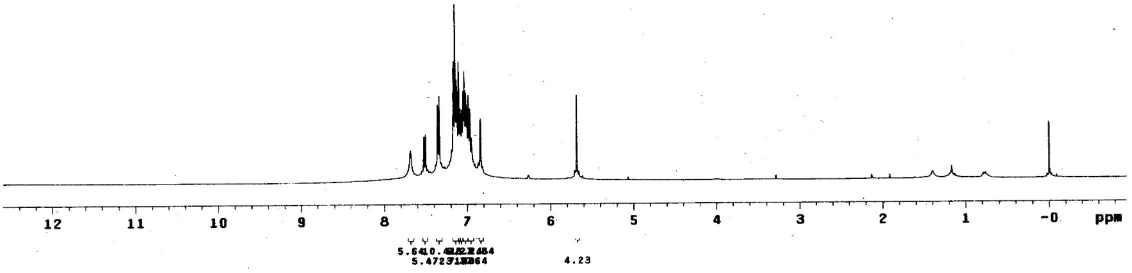
Figure 5.7

^{1}H NMR (400 MHz, CDCl$_3$): 3-(Phenyl(phenylthio)methyl)-1H-indole (**13aad**)

```
AD_50

exp1  s2pul

      SAMPLE                      SPECIAL
date   Oct 16 2012   temp           not used
solvent        CDCl3   gain           not used
file             exp   spin           not used
   ACQUISITION        hst               0.008
sw            6389.8   pw90             19.700
at             1.998   alfa             20.000
np             25528             FLAGS
fb          not used   il                   n
bs                 4   in                   n
d1             1.000   dp                   y
nt                32   hs                  nn
ct                32           PROCESSING
   TRANSMITTER         lb                0.10
tn                H1   fn               65536
sfrq         399.853            DISPLAY
tof            362.8   sp              -378.9
tpwr              57   wp              5415.7
pw             9.850   rfl              882.6
    DECOUPLER          rfp                  0
dn               C13   rp                96.0
dof                0   lp               -78.0
dm               nnn               PLOT
dmm                c   wc                 250
dpwr              50   sc                   0
dmf            15900   vs                  42
                       th                  20
                       nm   cdc   ph
```

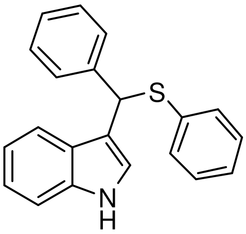


13aad



^{13}C NMR (100 MHz, CDCl$_3$): 3-(Phenyl(phenylthio)methyl)-1H-indole (**13aad**)

```
AD_50.13C

exp1  s2pul

      SAMPLE                      SPECIAL
date   Oct 16 2012   temp           not used
solvent        CDCl3   gain           not used
file             exp   spin           not used
   ACQUISITION        hst               0.008
sw           25125.6   pw90             18.600
at             1.199   alfa             20.000
np             60270             FLAGS
fb             13800   il                   n
bs                 4   in                   n
d1             1.000   dp                   y
nt              3000   hs                  nn
ct              1180           PROCESSING
   TRANSMITTER         lb                2.00
tn               C13   fn               65536
sfrq         100.554            DISPLAY
tof           1536.3   sp              -994.2
tpwr              61   wp             21625.2
pw             9.300   rfl             9286.7
    DECOUPLER          rfp             7764.9
dn                H1   rp               -40.7
dof                0   lp              -373.8
dm               yyy               PLOT
dmm                w   wc                 250
dpwr              42   sc                   0
dmf             8900   vs                  33
                       th                   4
                       nm   no   ph
```



13aad

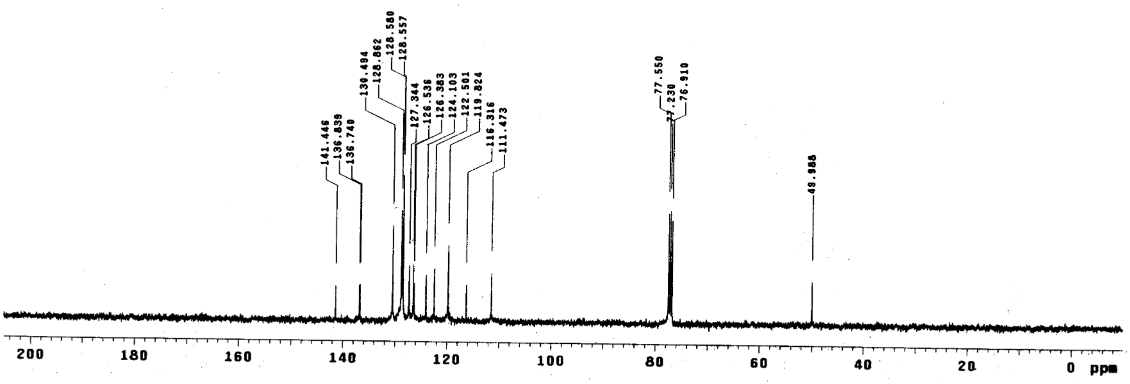
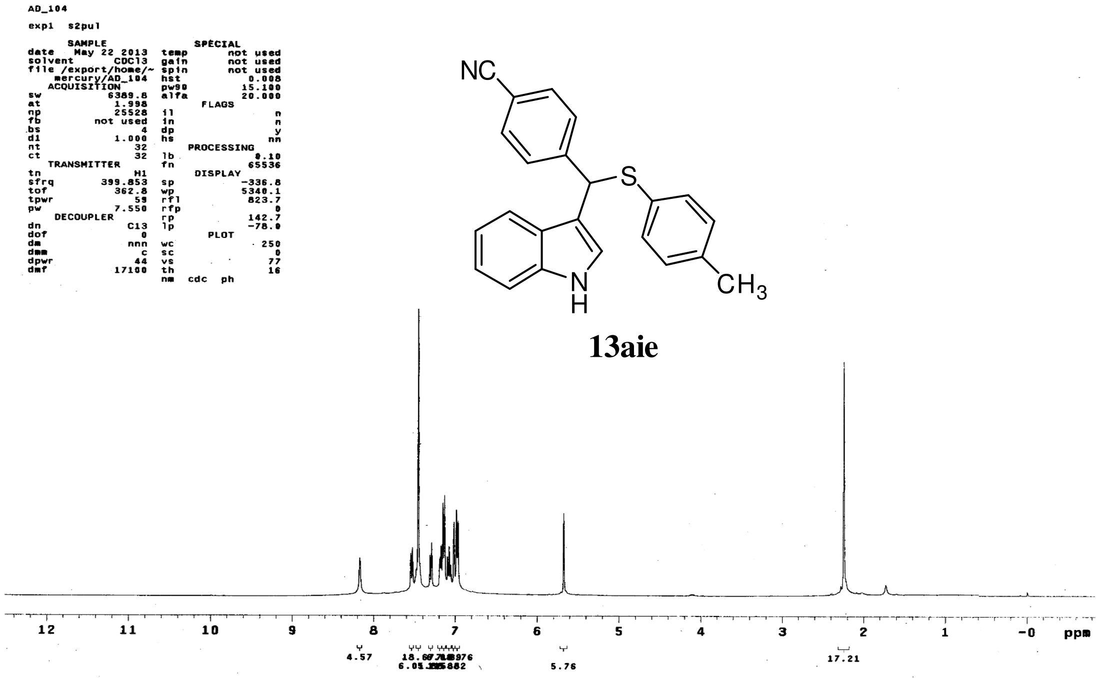


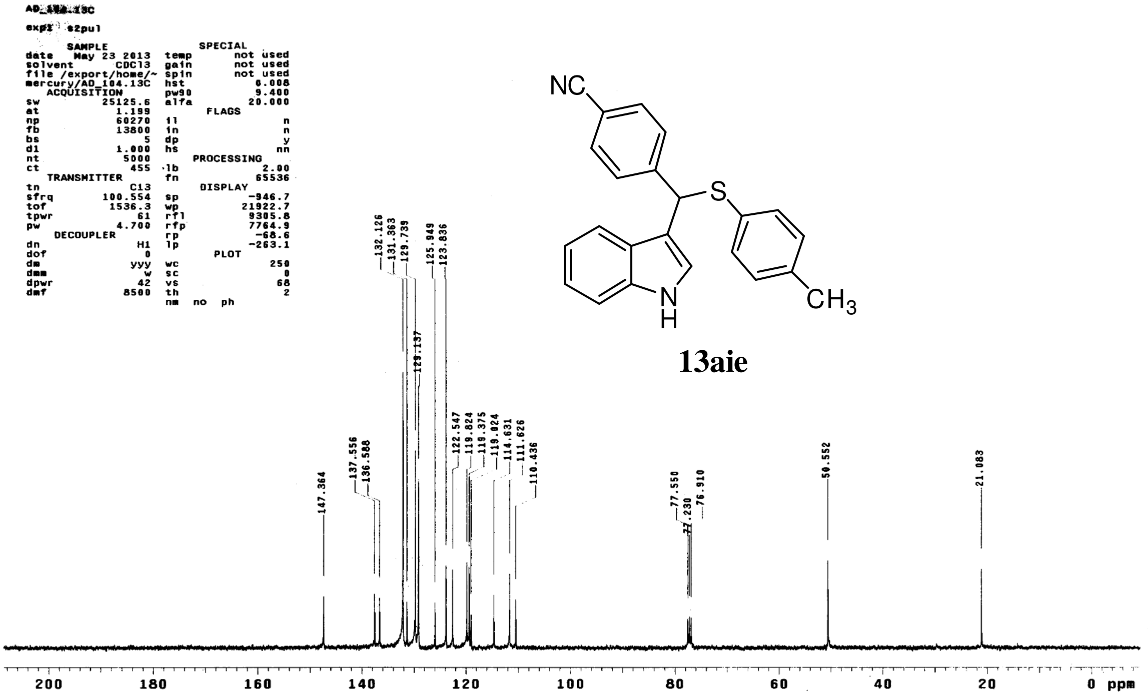
Figure 5.8

^{1}***H NMR (400 MHz, CDCl$_3$)**: 4-((1H-indol-3-yl)(p-tolylthio)methyl)benzonitrile* (**13aie**)



```
AD_104

exp1  s2pul

     SAMPLE                     SPECIAL
date   May 22 2013  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
   mercury/AD_104   hst           0.008
   ACQUISITION      pw90         15.100
sw          6389.8  alfa         20.000
at           1.998            FLAGS
np           25528  il                n
fb        not used  in                n
bs               4  dp                y
d1           1.000  hs               nn
nt              32         PROCESSING
ct              32  lb             0.10
   TRANSMITTER      fn            65536
tn              H1          DISPLAY
sfrq       399.853  sp           -336.8
tof          362.8  wp           5340.1
tpwr            59  rfl           823.7
pw           7.550  rfp               0
    DECOUPLER       rp            142.7
dn             C13  lp            -78.0
dof              0            PLOT
dm             nnn  wc              250
dmm              c  sc                0
dpwr            44  vs               77
dmf          17100  th               16
                    nm   cdc   ph
```

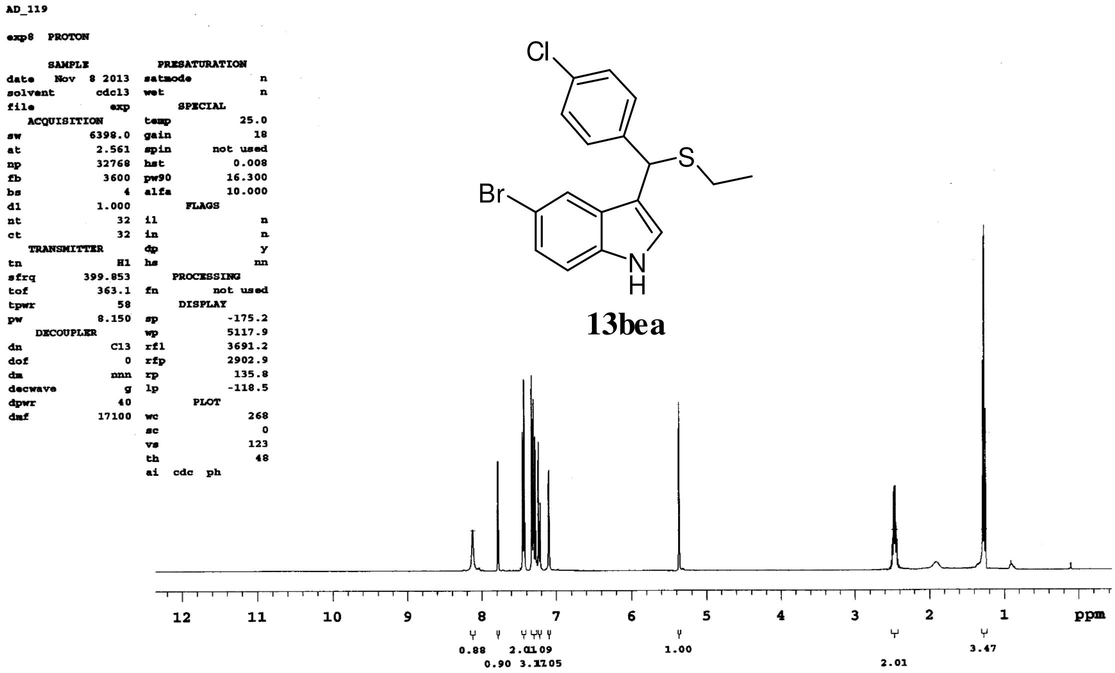
^{13}***C NMR (100 MHz, CDCl$_3$)**: 4-((1H-indol-3-yl)(p-tolylthio)methyl)benzonitrile* (**13aie**)



```
AD_[illegible].13C

exp1  s2pul

     SAMPLE                     SPECIAL
date   May 23 2013  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
mercury/AD_104.13C  hst           0.008
   ACQUISITION      pw90          9.400
sw         25125.6  alfa         20.000
at           1.199            FLAGS
np           60270  il                n
fb           13800  in                n
bs               5  dp                y
d1           1.000  hs               nn
nt            5000         PROCESSING
ct             455  lb             2.00
   TRANSMITTER      fn            65536
tn             C13          DISPLAY
sfrq       100.554  sp           -946.7
tof         1536.3  wp          21922.7
tpwr            61  rfl          9305.8
pw           4.700  rfp          7764.9
    DECOUPLER       rp            -68.6
dn              H1  lp           -263.1
dof              0            PLOT
dm             yyy  wc              250
dmm              w  sc                0
dpwr            42  vs               68
dmf           8500  th                2
                    nm   no   ph
```

Figure 5.9

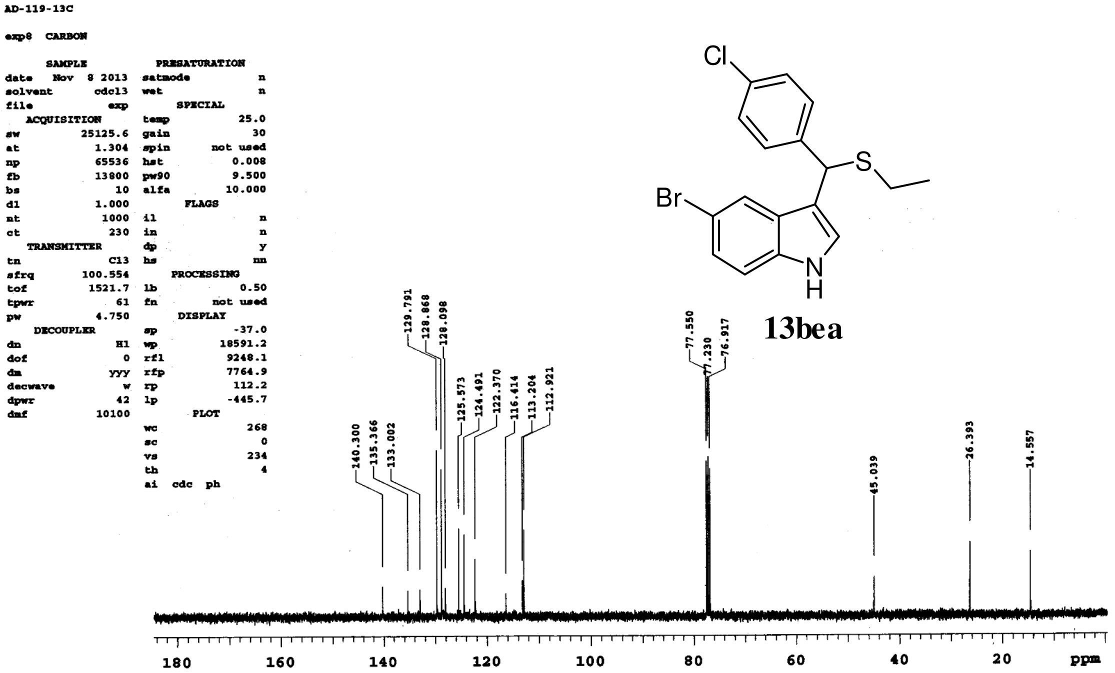
***^{1}H NMR (400 MHz, CDCl$_3$)**: 5-bromo-3-((4-chlorophenyl)(ethylthio)methyl)-1H-indole* (**13bea**)



```
AD_119

exp8   PROTON

      SAMPLE              PRESATURATION
date    Nov  8 2013     satmode            n
solvent       cdcl3     wet                n
file            exp           SPECIAL
   ACQUISITION          temp            25.0
sw           6398.0     gain              18
at            2.561     spin        not used
np            32768     hst            0.008
fb             3600     pw90          16.300
bs                4     alfa          10.000
d1            1.000           FLAGS
nt               32     il                 n
ct               32     in                 n
   TRANSMITTER          dp                 y
tn               H1     hs                nn
sfrq        399.853         PROCESSING
tof           363.1     fn          not used
tpwr             58           DISPLAY
pw            8.150     sp            -175.2
     DECOUPLER          wp            5117.9
dn              C13     rfl           3691.2
dof               0     rfp           2902.9
dm              nnn     rp             135.8
decwave           g     lp            -118.5
dpwr             40            PLOT
dmf           17100     wc               268
                        sc                 0
                        vs               123
                        th                48
                        ai   cdc   ph
```

13bea

***^{13}C NMR (100 MHz, CDCl$_3$)**: 5-bromo-3-((4-chlorophenyl)(ethylthio)methyl)-1H-indole* (**13bea**)



```
AD-119-13C

exp8   CARBON

      SAMPLE              PRESATURATION
date    Nov  8 2013     satmode            n
solvent       cdcl3     wet                n
file            exp           SPECIAL
   ACQUISITION          temp            25.0
sw          25125.6     gain              30
at            1.304     spin        not used
np            65536     hst            0.008
fb            13800     pw90           9.500
bs               10     alfa          10.000
d1            1.000           FLAGS
nt             1000     il                 n
ct              230     in                 n
   TRANSMITTER          dp                 y
tn              C13     hs                nn
sfrq        100.554         PROCESSING
tof          1521.7     lb              0.50
tpwr             61     fn          not used
pw            4.750           DISPLAY
     DECOUPLER          sp             -37.0
dn               H1     wp           18591.2
dof               0     rfl           9248.1
dm              yyy     rfp           7764.9
decwave           w     rp             112.2
dpwr             42     lp            -445.7
dmf           10100            PLOT
                        wc               268
                        sc                 0
                        vs               234
                        th                 4
                        ai   cdc   ph
```

13bea

Figure 5.10

5.3 References

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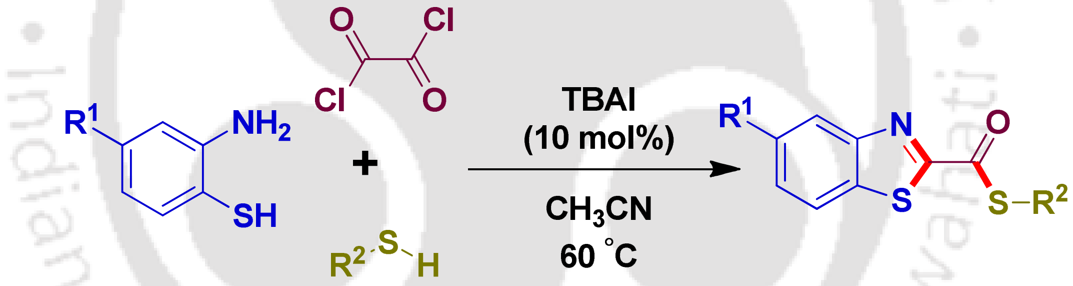
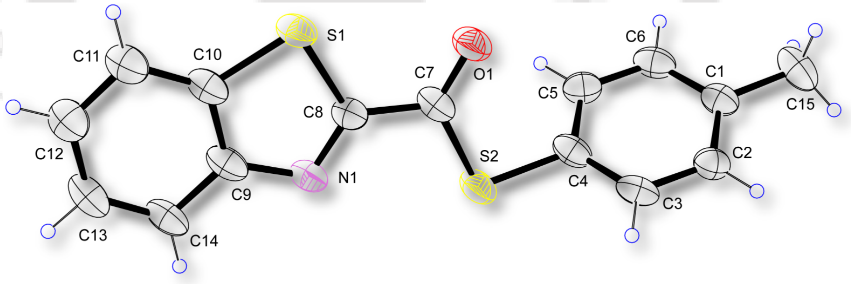
Chapter 6

One-pot synthesis and evaluation of antileishmanial activities of functionalized *S*-alkyl/aryl benzothiazole-2-carbothioate scaffold





CHAPTER 6: Results and Discussion

6.1 Results and Discussion

Giorgio et al. carried out structure activity relationships (SARs) of position 2 substitution-bearing 6-nitro- and 6-amino- benzothiazoles and their corresponding anthranilic acid derivatives against *Leishmania infantum* and *Trichomonas vaginalis*. They also reported that the benzothiazole group on a parent 'amino-9-(10H)-acridinone' ring improved antileishmanial abilities and the presence of a 6-amino-benzothiazole group on second position at amino chain was essential for specific antiamastigote properties. Fazal et al, studied antileishmanial activities of the benzothiazole derivatives containing electron donating group, enhances the activity, compared to the electron withdrawing group completely makes the compounds inactive.[1]

The antileshmanial activity of sulfones derivatives has been discussed in the chapter 2. In continuation of our efforts to find a new class of antileshmanial agents, a series of unreported benzothiazole-thioester derivatives were employed for evaluation of antileishmanial activities. Substituted benzothiazoles are important class of heterocycles widely distributed in nature and exhibits a wide range of biological activities.[2] These scaffolds are used as functional materials in ratiometric fluorescent pH indicators, sensors and bioluminogenic probe, and as agrochemicals. Various marine and terrestrial natural products namely Erythrazoles A and B, isolated from mangrove sediments, are useful intermediates for dyes and are versatile ligands for catalytic reactions.[3] It is well known that amalgamation of benzothiazoles with other functionalities opens doors to design novel drug like molecules. Some of substituted benzothiazoles used as drugs and also exhibit pharmacological properties such as riluzole (an anticonvulsant drug), zopolrestat (to treat endotoxin-related inflammatory diseases namely sepsis, asthma, and uveitis), 5F203 and PMX 610 (exhibit antitumor properties). They are also used as imaging agents for Aβ plaques in cerebral amyloid angiopathy, radioactive β-amyloid imagining agents, γ-aminobutyric acid (GABA-A) inhibitors, inhibitors of fatty acid oxidation, aldose reductase inhibitors (ARIs), falcipain inhibitors, microsomal triglyceride transfer protein inhibitors (MTP), and fatty acid amide hydrolase (FAAH) inhibitors (Figure 6.1).[4]

A metal-free protocols is highly desirable, particularly in the pharmaceutical synthesis. Metal-catalysed synthesis of benzothiazole derivatives involves numerous limitations, use of expensive metal catalysts, tedious work up procedures, and metallic toxic wastes as offshoots. Other protocols mainly includes cyclization of different aromatic thiourea linkages, condensation of various *ortho*-haloanilides or their analogues with different thiocyanate and isothiocyanate, condensation of 2-aminothiophenols and carbon-disulfide/sodium sulfide/acids/acid chlorides/aldehydes/ esters/nitriles/ketones/thio-esters under mild conditions.[5] Introducing an acyl group at the 2-position of benzothiazoles has been synthetically challenging.[6] However, the synthesis of S-alkyl/aryl benzothiazole-2-carbothioate have not been reported.

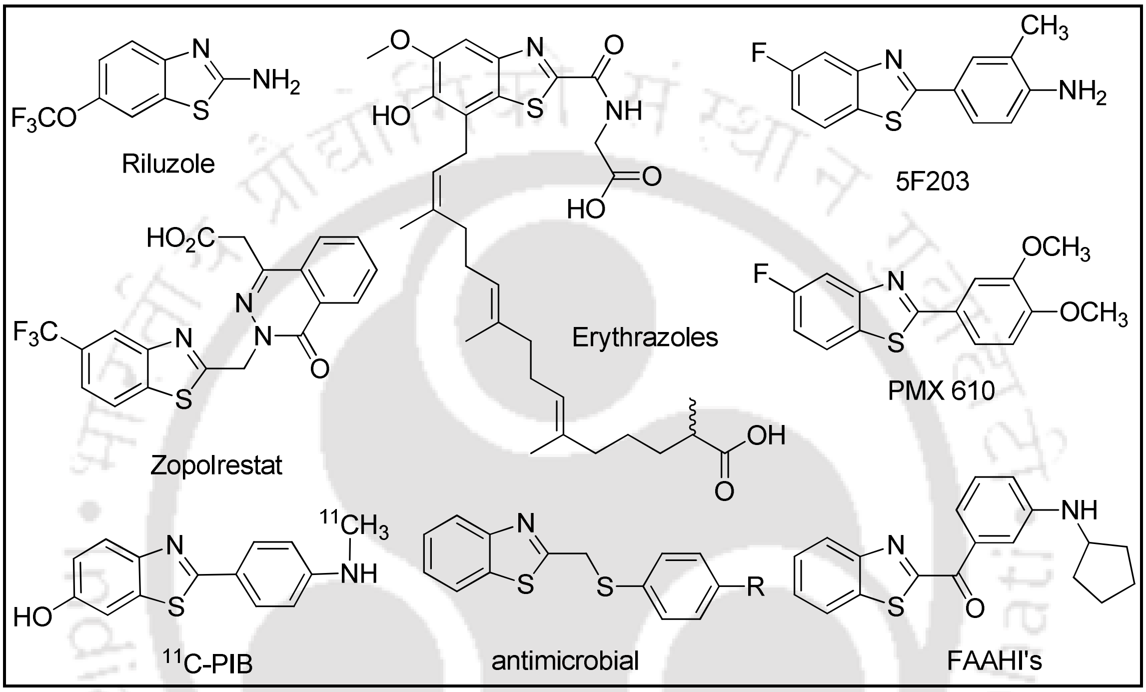
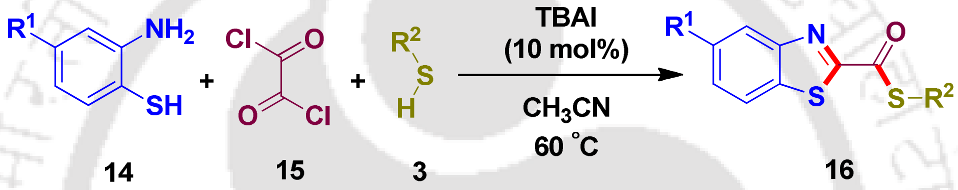


Figure 6.1. Structures of bioactive 2-substituted benzothiazoles.

Thioester moiety is another useful and versatile functional group in organic transformations because of its less resonance stabilization, owing to high reactivity in its ground state. They are the key intermediates used for β-lactam synthesis, carbocyclization, peptide coupling, in natural product synthesis, acyl transfer reactions, functional group transformations, carbon-carbon bond formation, in biosynthetic reactions and in certain instances, as protecting groups.[7]

The synthesis of thioesters by direct reaction of the corresponding thiols with a suitable acid chloride[8a] or acid anhydride[8b] are most well-known methods. They have also been synthesized by transthioesterification of active carboxylic acid derivatives, esters,[8c] N-acylbenzotriazoles,[8d] with thiols, in the presence of varied reaction conditions and catalysts.[8e] Recently, *tert*-butyl protected thiols have been utilized for the preparation of thioesters.[8f] More recently the N–S acyl shift, mediated by attaching a thiol auxiliary residue to the peptide backbone, has been applied to peptide thioester syntheses.[8g] They have also been accessed from thiols and carbon monoxide by carbonylation of organic substrates catalysed by transition metals such as Pt[8h] or Pd.[8i] The Dess–Martin periodinane (DMP)-mediated reaction of thiols and aldehydes[8j] and coupling of aldehyde with disulfide or thiol *via* free radical mechanism are the another methods for the synthesis of thioesters.[9]

In this chapter we would like to report an unprecedented synthesis of S-alkyl/aryl benzothiazole-2-carbothioate using one-pot three-component reaction between thiols, oxalyl chloride and 2-aminothiophenol using *n*-tetrabutylammonium iodide (TBAI) in acetonitrile (Scheme 6.1) and the activity of S-alkyl/aryl benzothiazole-2-carbothioate against promastigotes of *L. donovani* was evaluated.



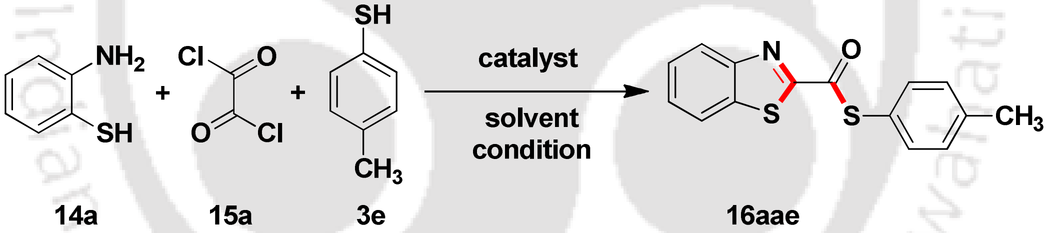
R^1 = H (14a), Cl (14b), CF_3 (14c)

R^2 = Et (3a), Pr (3b), $PhCH_2$ (3c), Ph (3d), 4-MePh (3e), 4-ClPh (3f), 4-BrPh (3g), 2-Naphthyl (3h), 4-MeOPh (3i), 2-$ClPhCH_2$ (3j), 2-ClPh (3k), 2-BrPh (3l), 4-NO_2Ph (3n), 4-OHPh (3o), 4-FPh (3p), 3-MeOPh (3q), 3-ClPh (3r), 2-MePh (3s), dodecyl (3t)

Scheme 6.1. Synthesis of S-alkyl/aryl benzothiazole-2-carbothioate.

We started by examining the reaction of 2-methylthiophenol and oxalyl chloride with 2-aminothiophenol in acetonitrile at room temperature in the absence of catalyst and no desired product was obtained (Table 6.1, entry 1). When the reaction mixture was subjected to heating at 60 °C and the desired product was isolated in 15% yield (Table 6.1, entry 2). The structure of compound (**16aae**) was determined by recording IR, ^{1}H NMR, ^{13}C NMR spectra, HRMS and by elemental analysis. The ^{1}H NMR spectrum of compound (**16aae**) showed the signals at δ 2.42 (S, 3H), 7.30 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H) and ^{13}C NMR signals at δ 21.6, 122.5, 122.9, 125.6, 127.4, 127.9, 130.5 (2C), 135.0 (2C), 136.9, 140.5, 153.1, 164.0, 185.6 respectively. The appearance of peaks at δ 164.0 and 185.6 in the ^{13}C NMR spectrum corresponds to C=N and C=O respectively, and their sharp peaks at 1659 cm^{-1} and 1482 cm^{-1}, in IR spectrum are the characteristic for desired product (**16aae**). In order to increase the efficiency of the reaction, the same reaction was examined using 10 mol% *n*-tetrabutylammonium iodide (TBAI) and the desired product was obtained in 75% yield. No significant increase in yield was noted when the reaction was carried out with 20 mol% catalyst (Table 6.1, entry 4). Further, the yield of the desired product dropped to 40% (Table 6.1, entry 5) when the reaction was carried out with 5 mol% catalyst. A lower yield was observed when the reaction temperatures exceeded 70 °C. Various other salts of iodine such as sodium iodide, potassium iodide and molecular iodine, as well as other quaternary ammonium salts namely *n*-tetrabutylammonium chloride (TBACl) and *n*-tetrabutylammonium bromide (TBABr) were examined under similar reaction conditions. TBAI was found to give the best yields (Table 6.1, entries 6-10). The choice of solvent was also examined by carrying out the reaction in 1,2-dichloroethane, ethanol, methanol, dichloromethane and tetrahydrofuran. 1,2-dichloroethane furnished the desired product in comparable yield as with acetonitrile, while other solvents were found ineffective (Table 6.1, entries 11-15).

Table 6.1. Optimization for reaction conditions[a]



Entry	Catalyst (mol %)	Solvent	Time/h	Yield (%)[b]
1	No catalyst	CH_3CN	12	0
2	No catalyst	CH_3CN	12	15[c]
3	**TBAI (10)**	**CH_3CN**	**4.0**	**75**
4	TBAI (20)	CH_3CN	4.0	77
5	TBAI (5)	CH_3CN	4.0	40
6	NaI (10)	CH_3CN	4.0	24
7	KI (10)	CH_3CN	4.0	28
8	I_2 (10)	CH_3CN	4.0	20
9	TBACl (10)	CH_3CN	4.0	30
10	TBABr (10)	CH_3CN	4.0	40
11	TBAI (10)	DCE	4.5	72

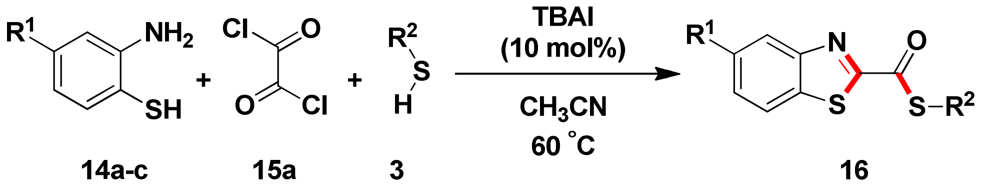
12	TBAI (10)	C_2H_5OH	6.0	≤10
13	TBAI (10)	CH_3OH	6.0	<10
14	TBAI (10)	DCM	6.0	<20
15	TBAI (10)	THF	6.0	≤15

[a] All the reactions were carried out in 1 mmol scale. [b] Isolated yield. [c] The reaction was carried out at 60 °C

After optimization of reaction conditions, the substrate scope was explored using various substituted thiols and *para*-substituted 2-aminothiophenols. At first, 2-aminothiophenol (**14a**) was treated with a set of aromatic thiols bearing both electron-donating and electron-withdrawing substituents and the corresponding products were obtained in good yields. The substrates with 4-methyl (**3e**) and 4-methoxy (**3i**) substituents underwent reactions to give S-aryl benzothiazole-2-carbothioates **16aae** and **16aai** (Table 6.2) respectively in high yields. The substrates with 4-chloro (**3f**), 4-bromo (**3g**), 4-hydroxyl (**3o**), and 4-fluoro (**3p**) groups, underwent condensation to afford S-aryl benzothiazole-2-carbothioates **16aaf**, **16aag, 16aao** and **16aap** respectively (65–76% yields, Table 6.2). Moreover the reaction of *para* substituted thiophenol with 4-nitro group (**3n**) did not provide any desired product under the optimized condition. Substrates **3q** and **3r** with 3-methoxy and 3-chloro substituents furnished the products **16aaq** and **16aar** (78% and 72% yields, Table 6.2). It was observed that aromatic thiols with electron-donating groups served as efficient reacting partners. Presence of an electron-withdrawing group however gave slightly lower yields.

Likewise, the steric factor due to *ortho*-substituted thiophenols have less impact on the present protocol as evident from the substrates with 2-methyl (**3s**), 2-chloro (**3k**) and 2-bromo (**3l**) correspondingly provided **16aas**, **16aak,** and **16aal** in good yields. In addition, thiophenol (**3d**) and 2-naphthalenethiol (**3h**) also reacted with 2-aminothiophenol to obtain the products **16aad** and **16aah** (68% and 70% yields respectively, Table 6.2). It was found that benzylthiol (**3c**) and 2-chlorobenzylthiol (**3j**) reacted to give corresponding S-alkylbenzothiazole-2-carbothioates **16aac** and **16aao** respectively (Table 6.2) on condensation with 2-aminothiophenol (**14a**). Aliphatic thiols such as ethanethiol (**3a**), propanethiol (**3b**) and dodecanethiol (**3t**) also underwent reaction to give the corresponding S-alkyl benzothiazole-2-carbothioates **16aaa**, **16aab** and **16aat** (Table 6.2), in good yields.

Table 6.2. Reaction of 2-aminobenzenethiol with various thiols[a]



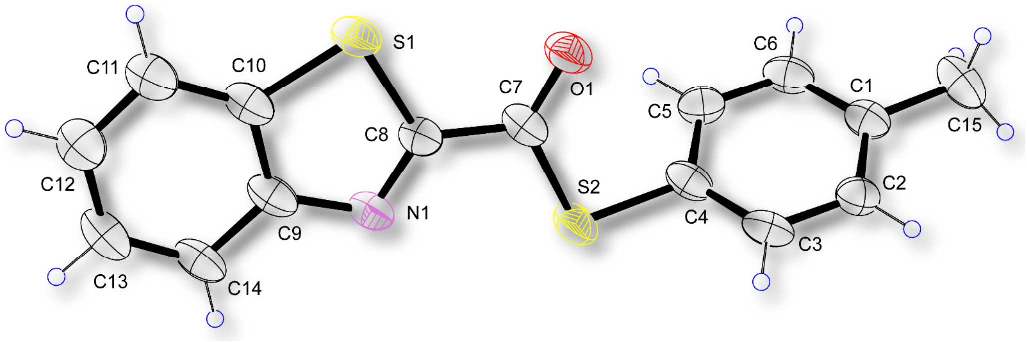
Entry	2-Aminobenzenethiol (14)	Oxalyl chloride (15)	Thiol (3)	Product[a] (16)	Yield (%)[b]
1	**14a**	**15a**	**3e**	**16aae**	78
2	**14a**	**15a**	**3i**	**16aai**	80
3	**14a**	**15a**	**3f**	**16aaf**	74
4	**14a**	**15a**	**3g**	**16aag**	76
5	**14a**	**15a**	**3o**	**16aao**	70
6	**14a**	**15a**	**3p**	**16aap**	65
7	**14a**	**15a**	**3q**	**16aaq**	78
8	**14a**	**15a**	**3r**	**16aar**	72
9	**14a**	**15a**	**3s**	**16aas**	72
10	**14a**	**15a**	**3k**	**16aak**	70
11	**14a**	**15a**	**3l**	**16aal**	73
12	**14a**	**15a**	**3d**	**16aad**	68
13	**14a**	**15a**	**3h**	**16aah**	70
14	**14a**	**15a**	**3c**	**16aac**	71
15	**14a**	**15a**	**3j**	**16aaj**	73
16	**14a**	**15a**	**3a**	**16aaa**	70
17	**14a**	**15a**	**3b**	**16aab**	68
18	**14a**	**15a**	**3t**	**16aat**	66
19	**14b**	**15a**	**3d**	**16bad**	71
20	**14b**	**15a**	**3e**	**16bae**	77
21	**14b**	**15a**	**3f**	**16baf**	73
22	**14b**	**15a**	**3g**	**16bag**	75
23	**14c**	**15a**	**3e**	**16cae**	60
24	**14c**	**15a**	**3i**	**16cai**	62
25	**14c**	**15a**	**3k**	**16cak**	56

26	**14c**	**15a**	**3l**	**16cal**	58

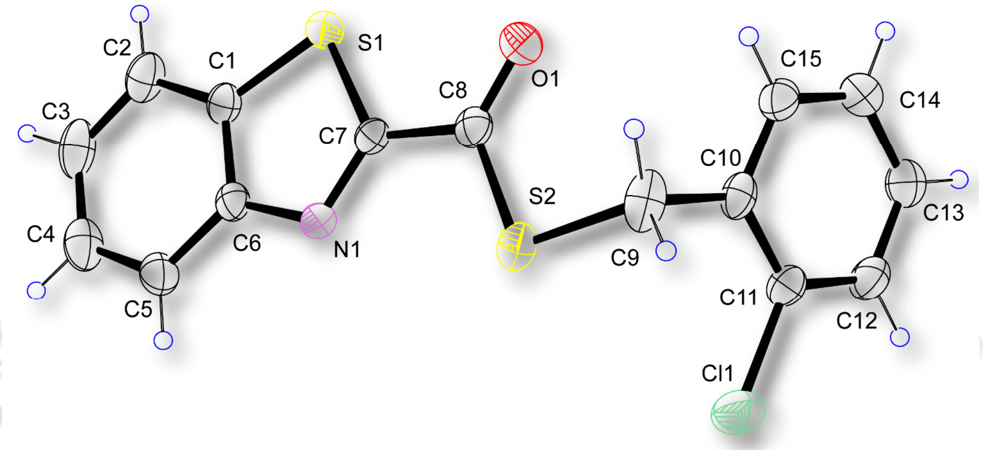
[a]Conditions: **14** (1 mmol), **15a** (1 mmol), **3** (1 mmol), CH_3CN (3.0 mL), 60 °C, 4 h.
[b]Isolated yield.

To explore the scope of the reaction, the presence of chloro group at 4-position of the 2-aminothiophenol did not interfere with the formation of the product *i.e.*, when 2-amino-4-chlorobenzenethiol was used instead of 2-aminobenzenethiol, the yield was found similar. However the presence of trifluoromethyl at 4-position of the 2-aminothiophenol decreases the rate of reaction and eventually the product formation. In addition, the remaining factors for the synthesis of **16bad** to **16cal** (Table 6.2) were identical as discussed above *i.e.,* the reactions of 2-amino-4-chlorobenzenethiol (**14b**) with thiophenol (**3d**) produced **16bad** in 71% yield, while substrates bearing substituted aryl rings with 4-methyl (**3e**), 4-chloro (**3f**), and 4-bromo (**3g**) functionalities produced the corresponding S-alkylbenzothiazole-2-carbothioates **16bae-g** in 73–77% yields. Similarly the reactions of 2-amino-4-trifluoromethylbenz-enethiol (**14c**) with thiophenol having 4-methyl (**3e**), 4-methoxy (**3i**), 2-chloro (**3k**), and 2-bromo (**3l**) substituents in the aryl ring underwent reaction to furnish **16cae-16cal** in 56-62% yields. As can be seen from the above results, maximum yields were observed when both the substrates possess electron-donating groups. Replacement in any of the substrates either with an electron neutral or electron-withdrawing substituent reduced the yields. A further drop in the yields was noticed when electron-withdrawing groups were present on both the reacting substrates.

All the isolated products were confirmed on the basis of their analytical data (^{1}H NMR, ^{13}C NMR, IR, HRMS and by elemental analysis). All the isolated products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, HMRS and by elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compounds **16aai, 16aaj, 16aab, 16bae and 16cae** are given in the Experimental Section (Figure 6.6, 6.7, 6.8, 6.9 and 6.10). Additionally, the target compounds **16aae** and **16aaj** were further determined by X-ray crystallographic analysis (Figure 6.2).



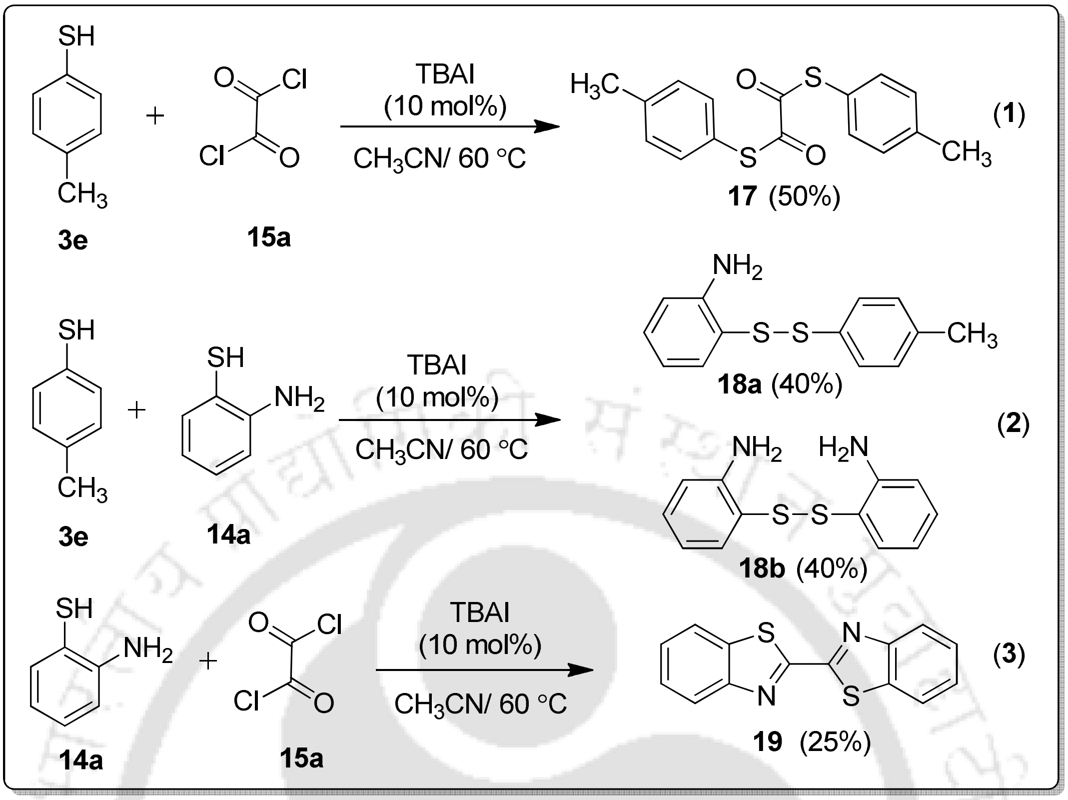
(16aae).



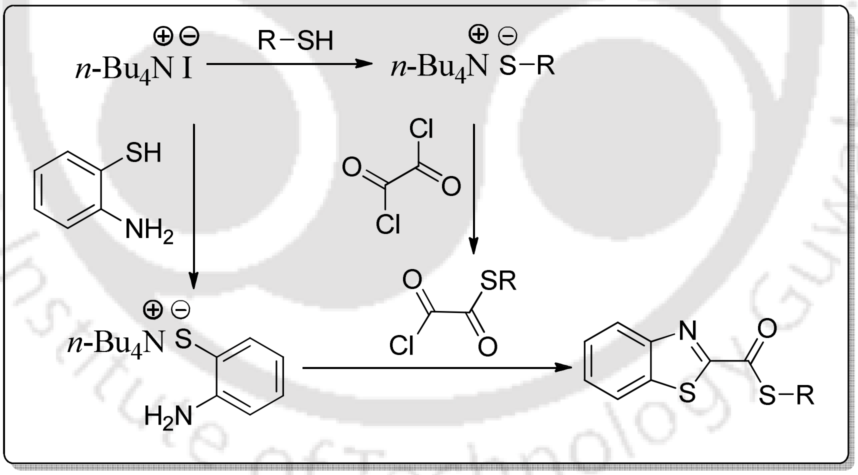
(16aaj)

Figure 6.2. X-ray crystal structures of compounds **16aae** and **16aaj.**

To understand the reaction mechanism, three sets of reaction were carried out using permutation and combination of three substrates as shown in Scheme 6.2. It was observed that 4-methylthiophenol (**3e**) reacts with oxalyl chloride (**15a**) under the experimental conditions to give the expected product **17** in 50% yield by nucleophilic substitution reaction along with some unreacted starting material (Scheme 6.2, Eq. 1). Similarly, 4-methylthiophenol (**3e**) was reacted with 2-aminothiophenol (**14a**) under identical reaction conditions, the expected products **18a** and **18b** were obtained in equal ratio (Scheme 6.2, Eq. 2). Likewise, treatment of 2-aminothiophenol (**14a**) with oxalyl chloride (**15a**) furnished **19,** but in lower yield and major starting materials were recovered (Scheme 6.2, Eq. 3). On the basis of these results, it can be speculated that present protocol suppresses the formation of these above by-product during the course of reaction, thereby generating the desired product in major yields.



Scheme 6.2. Crossover experiments.



Scheme 6.3. Proposed Reaction Mechanism.

The formation of the S-alkyl benzothiazole-2-carbothioate products can be proposed as: TBAI reacts with thiol (**3**) to generate thiolate anion in the reaction medium. Subsequently, the anion attacks on one side of oxalyl chloride (**15a**) to form thioester moiety intermediate. Finally, 2-aminobenzenethiol (**14a**) in the presence of TBAI can undergo condensation with the *in situ* generated thioester intermediate to form the desired products (Scheme 6.3).

The antileishmanial activity and mammalian cell toxicity of the 16 S-alkyl/aryl benzothiazole-2-carbothioate derivatives were investigated. The IC_{50} and IC_{90} values were calculated for each compound (Table 6.3). The results showed all the compounds possessed moderate to potent activity against the promastigote forms of *L. donovani.* However, toxicity incurred on mammalian cell line RAW264 by few of them could limit their use as antileishmanial agents. For instance, four compounds namely **16aae**, **16bad**, **16aas**, and **16aai** displayed toxicity towards the mammalian macrophage cells with IC_{50} values of 275.63 μM, 276.70 μM, 334.22 μM, and 490.67 μM respectively.

Table 6.3. Leishmanicidal activity of compounds against *L. donovani* promastigotes

	Activity		**Cytotoxicity**	
	L. donovani promastigotes		**Macrophages**	
Compounds	**(IC_{50} μM)**	**(IC_{90} μM)**	**(IC_{50} μM)**	**(IC_{90} μM)**
16aae	223.914	403.045	275.63	496.11
16aai	271.00	487.80	490.67	883.21
16aao	232.01	417.63	6756.75	12162.16
16aap	193.12	347.62	789.88	1421.80
16aaq	232.55	418.60	1612.90	2903.22
16aar	229.35	412.84	769.23	1384.61
16aas	223.01	401.42	334.22	601.60
16aak	240.15	432.27	3205.12	5769.23
16aad	219.10	394.39	580.72	1045.29
16aah	269.68	485.43	2824.85	5084.74
16aac	397.140	714.85	1623.37	2922.07
16bad	187.33	337.20	276.70	498.06
16cae	201.45	362.61	2487.56	4477.61
16cai	203.50	366.30	777.60	1399.68
16cak	200.24	360.43	6578.94	11842.11
16cal	211.95	381.51	2325.58	4186.04

These values against macrophages are near to IC_{90} values against promastigotes. Therefore, the efficacy of these compounds could be limited due to their toxicity. The compounds **16aap**, **16cai**, **16aad**, **16aar**, **16aao**, **16aaq**, **16aak**, **16aah**, and **16aac** with IC_{50} values of 193.12 μM, 203.50 μM, 219.10 μM, 229.35 μM, 232.01 μM, 232.55 μM, 240.15 μM, 269.68

µM, and 397.140 µM, respectively against promastigotes forms could be potent antileishmanial agents as their toxic effect towards macrophage is negligible at the doses used against the parasite (as depicted by their IC_{50} values). Herein, the compounds **16cak**, **16cae,** and **16cal** are found to be most effective against promastigotes with IC_{50} values of 200.24 µM, 201.45 µM, and 211.95 µM, respectively. These three compounds (whose IC_{50} values against macrophage are quite high) represent promising lead compounds for antileishmanial therapy. The percent cell viability of *L. donovani* and peritoneal macrophages with increase in concentration of these three compounds from 0.00 to 500 µM were also evaluated as shown in Figure 6.3 and Figure 6.4, respectively.

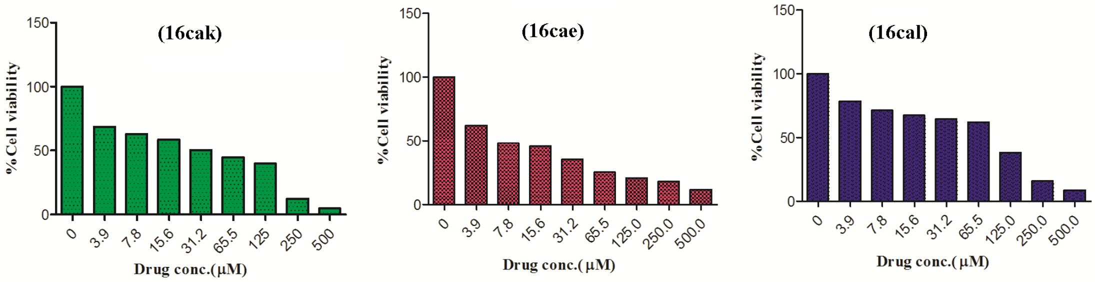


Figure 6.3: Leishmanicidal effect of **16cak**, **16cae** and **16cal** on promastigotes of *L. donovani*. *L. donovani* promastigotes were treated for 24 h with increasing concentrations of three different compounds **16cak**, **16cae** and **16cal** and then cell viability was assessed using alarm blue reagent (as described in material and methods).

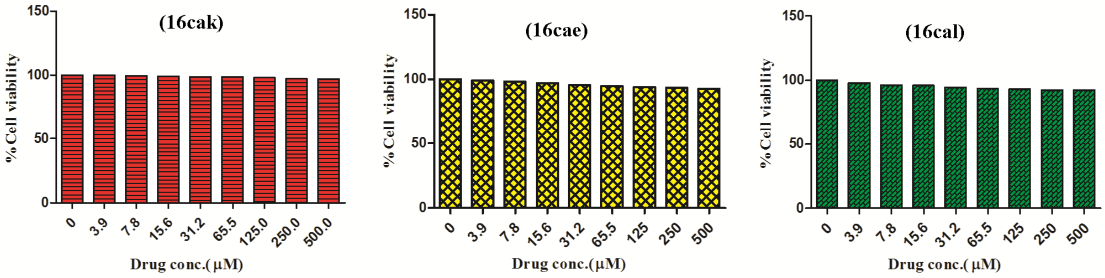
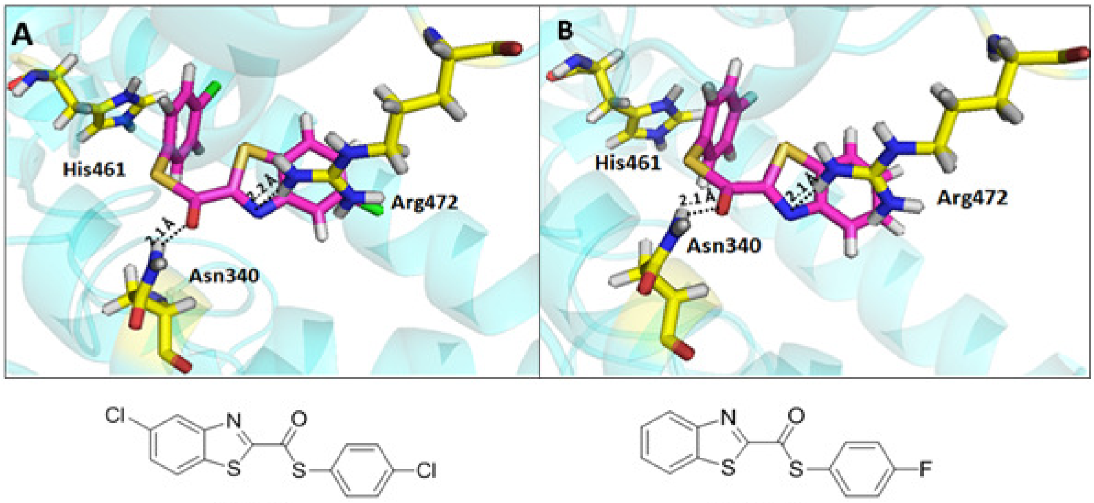


Figure 6.4: Toxic effect of **16cak**, **16cae** and **16cal** on murine peritoneal macrophages. Peritoneal macrophages were treated for 24 h with increasing concentrations of these three compounds **16cak**, **16cae** and **16cal** and cell viability was assessed.

The molecular docking of benzothiazole-2-carbothioate derivatives against Trypanothione Reductase (TryR) showed that most of the compounds are showing hydrogen bonds with Asn 340 and Arg 472. Interestingly, some of these derivatives show hydrophobic interaction with His-461 (protonated histidine) which is a part of catalytic triad (Cys-52-His-461-Cys-57). The His-461 forms a π-cation interaction with the aryl group of these derivatives whereas, the Arg 472 is showing π-cation interaction with the benzothiazole nucleus which may help in stabilizing the ligand in the cavity.

The two representative examples revealing the mode of interactions are shown in Figure 6.5.



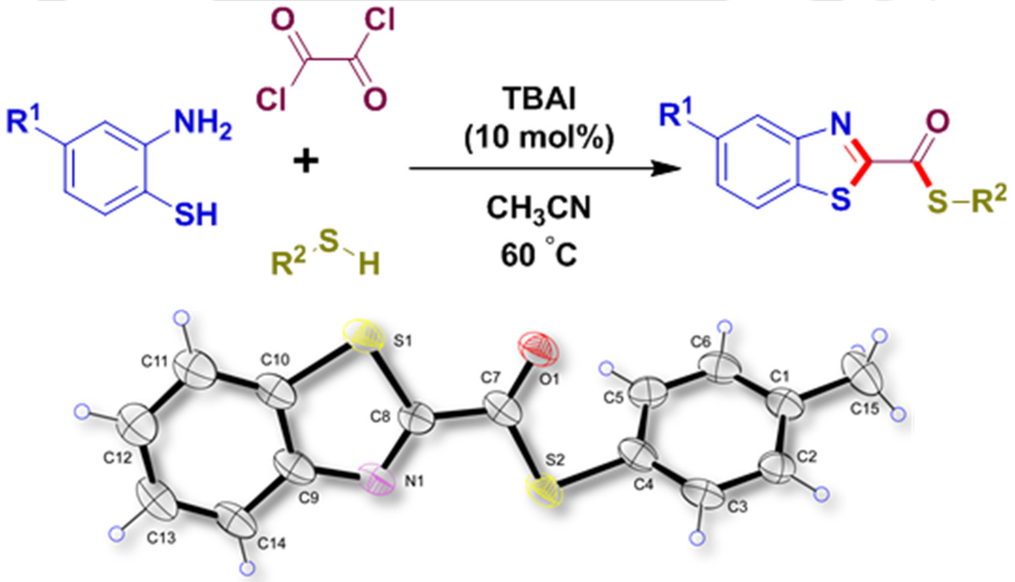
(16baf) **(16aap)**

Fig 6.5. Binding model of ligands at the interface of homodimer. Ligands are shown in stick models (magenta colour). Hydrogen bonding interactions are shown as black dashes and residues involved in hydrogen bonding or hydrophobic interactions (π-cation) are represented in stick models. (A) Represent the binding mode of **16baf** and (B) Represent the binding mode of **16aap**.

In conclusion, a one pot three-component condensation with a variety of thiols and 2-aminothiophenols with oxalyl chloride in acetonitrile through multicomponent reaction (MCR) strategy, in a mild reaction conditions, with high efficiency, tolerance to a wide range of substrates and easy synthesis of S-alkyl/aryl benzothiazole-2-carbothioate derivatives was developed. The *n*-tetrabutylammonium iodide (TBAI) was found to be particularly suitable and of importance for the success of this transformation. The protocol involves the formation of three new bonds *i.e.* two C–S and one C=N in a highly efficient, atom economical and without addition of oxidizing or reducing agents or coupling catalysts. *In vitro* analysis indicated compounds **16cak**, **16cae** and **16cal** to be most active among the others. Docking studies also revealed a possible mode of binding of in the binding pocket of TryR. Benzothiazole-2-carbothioate derivatives can be expected as promising lead molecules for the advancement of novel drug against leishmania.

Chapter 6

One-pot synthesis and evaluation of antileishmanial activities of functionalized S-alkyl/aryl benzothiazole-2-carbothioate scaffold



6.2 Experimental Section

Cell Culture and Parasite. *L. donovani* strain AG83 (MHOM/IN/1983/AG83), originally isolated from an Indian kala-azar patient was maintained by serial passage in hamsters. *L. donovani* amastigotes periodically recovered from the spleens of infected hamsters were transformed into promastigotes through amastigote culture in M199 supplemented with 10% FCS, 2 mM glutamine, penicillin G (100 U/ml), streptomycin sulfate (100 µg/ml) at 22°C. Promastigotes were used at the log phase of growth, approximately 2 to 3 days after subculture. Parasites were kept in culture by weekly passaging.

In vitro antipromastigote activity. Antiparasitic activity of compounds against *L. donovani* (AG83) promastigotes was determined by a quantitative colorimetric assay using Alamar blue reagent (Life Technologies). When cells are alive they maintain a reducing environment within their cytosol. Resazurin/AlamarBlueH (7-Hydroxy-3H-phenoxazin-3- one 10-oxide), the active ingredient of AlamarBlue reagent, is a non-toxic, cell permeable compound that is blue in color and virtually non-fluorescent. Upon entering cells, resazurin is reduced to resorufin, a compound that is red in colour and highly fluorescent. Viable cells continuously convert resazurin to resorufin, increasing the overall fluorescence and colour of the media surrounding cells. Assays were performed in sterile 96-well plates using 100 µl of log-phase promastigotes adjusted to 2×10^6 cells/ml. These cells were incubated in the absence (control) and presence of 3.9 µM, 7.8 µM, 15.6 µM, 31.2 µM, 65.5 µM, 125.0 µM, 250.0 µM, and 500.0 µM of compounds and the equivalent volume of the solvent (DMSO) for 24 h. After completion of treatment, 10 µl of the resazurin dye (0.01%) was added, and plates were incubated for a further 4 h at 37 °C. After incubation cells were analyzed in a microplate reader (SpectraMax spectrofluorometer, Molecular Devices) at a wavelength of 570 nm, using 600 nm as a reference wavelength (normalized to the 600 nm value). Absorbance in the absence of any compound, or solvent was set as the 100% control. Cell viability was evaluated based on a comparison with untreated control cells and the inhibitory concentration of the compounds or the solvents that are necessary to reduce the growth of promastigotes by 50% (IC_{50} values) and 90% (IC_{90} values) was calculated.

Culture of RAW264 macrophage cell line and its cytotoxicity measurement.

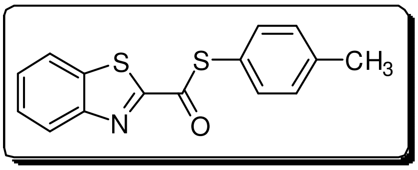
The murine macrophage-like cell line, RAW 264.7 was cultured in RPMI medium containing 10 percent FBS in tissue culture flasks (Falcon, Becton Dickinson). For the experiment, cells were detached in medium using cell scraper. The cells were counted and plated overnight ($5x10^4$ cells /well) in a 96 well culture plate. The cytotoxic effect of compounds on RAW cells was than evaluated in the absence and presence 3.9 µM, 7.8 µM, 15.6 µM, 31.2 µM, 65.5 µM, 125.0 µM, 250.0 µM and 500.0 µM of compounds and the equivalent volume of the solvent (DMSO) for 24 h. After completion of treatment, 10 µl AlamarBlue reagent was employed to determine cytotoxicity as described above. The cell viability was evaluated based on a comparison with untreated control cells and the concentration of the compounds or the solvents that are necessary to reduce the viability of macrophages by 50% (IC_{50} values) and 90% (IC_{90} values) was calculated.

Molecular Docking Study. There is no crystal structure yet available for trypanothione reductase of *L. donovani* and thus conducted our molecular docking studies (by using Glide 5.8 module in maestro 9.3.) with trypanothione reductase from *L. infantum* as there is 98% similarity between the trypanothione reductase of *L. donovani* and *L. infantum*. The molecular docking study was carried out using X-ray crystal structures of trypanothione reductase from *L. infantum* (PDB code: 2jk6, 2.95 Å).

General procedure for synthesis of compounds (16). To a stirred reaction mixture of thiol (**3**) (1.0 mmol), oxalyl chloride (**15**) (1.0 mmol) and catalyst TBAI (0.10 mmol) in acetonitrile (2 mL) at room temperature was added dropwise a solution of 2-aminobenzenethiol (**14a**) or 2-amino-4-chlorobenzenethiol (**14b**) (1.0 mmol) in acetonitrile (2 mL), in case of 2-amino-4-(trifluoromethyl)benzenethiol hydrochloride (**14c**) the solution is being neutralised with potassium bicarbonate for 10 min before addition, and subjected to heating at 60 °C till reaction completion. After the completion of reaction (as indicated by TLC), the solvent was evaporated under reduced pressure and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the crude product, which was purified by by column chromatography on silica gel (60-120 mesh) to give the pure product (hexane:ethyl acetate).

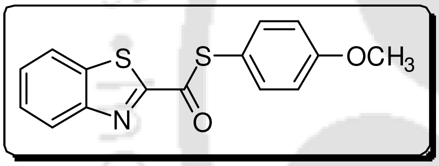
Spectral data of Compounds:

S-p-tolyl benzo[d]thiazole-2-carbothioate (16aae):



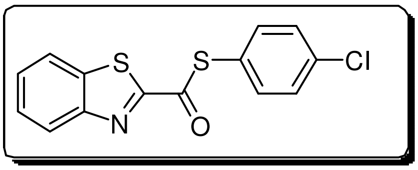
Nature: White solid; R_f = 0.73; mp 137-139 °C; **IR** (KBr): 3055, 1919, 1810, 1690, 1659, 1616, 1593, 1548, 1482, 1455, 1421, 1399, 1376, 1318, 1281, 1240, 1203, 1180, 1157, 1127, 1104, 1063, 1038, 1018, 947, 880, 868, 853, 806, 758, 731, 700, 673, 636, 617, 540, 480 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.42 (S, 3H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 122.5, 122.9, 125.6, 127.4, 127.9, 130.5 (2C), 135.0 (2C), 136.9, 140.5, 153.1, 164.0, 185.6. **HRMS** (ESI): calcd for $C_{15}H_{11}NOS_2$ $[M + H]^+$: 286.0355; Found: 286.0374. **Anal. Calcd** for $C_{15}H_{11}NOS_2$ (285.38): C, 63.13; H, 3.89; N, 4.91. Found: C, 63.01; H, 3.80; N, 4.80.

S-(4-methoxyphenyl) benzo[d]thiazole-2-carbothioate (16aai):



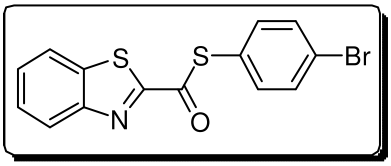
Nature: White solid; R_f = 0.53; mp 150-152 °C; **IR** (KBr): 2959, 2837, 2048, 1965, 1929, 1893, 1801, 1692, 1673, 1612, 1592, 1573, 1550, 1497, 1480, 1455, 1439, 1419, 1408, 1316, 1294, 1253, 1203, 1185, 1174, 1123, 1109, 1061, 1033, 964, 948, 879, 859, 835, 808, 763, 731, 701, 674, 641, 619, 579, 545, 499 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.5, 115.2 (2C), 116.8, 122.4, 125.5, 127.3, 127.8, 136.5 (2C), 136.8, 153.0, 161.2, 163.9, 185.9. **HRMS** (ESI): calcd for $C_{15}H_{11}NO_2S_2$ $[M + H]^+$: 302.0304; Found: 302.0306. **Anal. Calcd** for $C_{15}H_{11}NO_2S_2$ (301.38): C, 59.78; H, 3.68; N, 4.65. Found: C, 59.64; H, 3.57; N, 4.56.

S-(4-chlorophenyl) benzo[d]thiazole-2-carbothioate (16aaf):



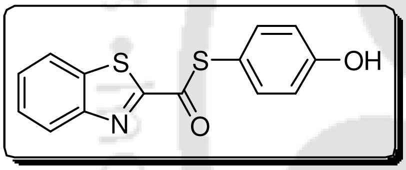
Nature: White solid; R_f = 0.71; mp 161-163 °C; **IR** (KBr): 3422, 3088, 2925, 2853, 1959, 1909, 1793, 1690, 1670, 1612, 1573, 1552, 1487, 1475, 1457, 1419, 1389, 1318, 1267, 1203, 1164, 1125, 1090, 1012, 941, 878, 861, 815, 758, 747, 726, 703, 669, 619, 529, 484 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 (dd, J_1 = 7.6 Hz & J_2 = 8.4 Hz, 4H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 122.6, 125.1, 125.7, 127.6, 128.1, 129.9 (2C), 136.3 (2C), 136.7, 137.0, 153.1, 163.5, 184.8. **HRMS** (ESI): calcd for $C_{14}H_8ClNOS_2$ [M + H]$^+$: 305.9809; Found: 305.9810. **Anal. Calcd** for $C_{14}H_8ClNOS_2$ (305.80): C, 54.99; H, 2.64; N, 4.58. Found: C, 54.85; H, 2.55; N, 4.48.

S-(4-bromophenyl) benzo[d]thiazole-2-carbothioate (16aag):



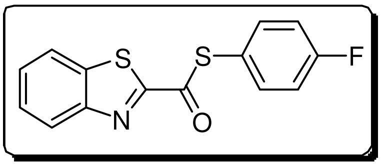
Nature: White solid; R_f = 0.68; mp 191-193 °C; **IR** (KBr): 3085, 2923, 2853, 1912, 1671, 1567, 1551, 1486, 1472, 1454, 1419, 1384, 1317, 1202, 1162, 1090, 1066, 1009, 885, 877, 844, 815, 758, 726, 703, 670, 619, 548, 477 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 3H), 7.80 (d, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 122.6, 125.0, 125.7 (2C), 127.6, 128.1, 132.8 (2C), 136.5 (2C), 137.0, 153.1, 163.5, 184.7. **HRMS** (ESI): calcd for $C_{14}H_8BrNOS_2$ [M + H]$^+$: 351.9282; Found: 351.9291. **Anal. Calcd** for $C_{14}H_8BrNOS_2$ (350.25): C, 48.01; H, 2.30; N, 4.00. Found: C, 47.85; H, 2.18; N, 3.90.

S-(4-hydroxyphenyl) benzo[d]thiazole-2-carbothioate (16aao):



Nature: White solid; R_f = 0.14; mp 191-192 °C; **IR** (KBr): 3452, 3059, 2923, 2848, 1650, 1624, 1597, 1581, 1550, 1497, 1480, 1455, 1429, 1417, 1337, 1317, 1269, 1201, 1168, 1098, 1062, 1010, 949, 880, 830, 816, 761, 731, 700, 671, 637, 624, 564, 509 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.34 (s, 1H, OH), 6.81 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$/DMSO): δ 114.5, 116.7 (2C), 122.2, 125.1, 127.1, 127.6, 136.3 (2C), 136.4, 152.7, 159.2, 163.6, 185.9. **HRMS** (ESI): calcd for $C_{14}H_9NO_2S_2$ [M + H]$^+$: 288.0147; Found: 288.0149. **Anal. Calcd** for $C_{14}H_9NO_2S_2$ (287.36): C, 58.52; H, 3.16; N, 4.87. Found: C, 58.37; H, 3.05; N, 4.79.

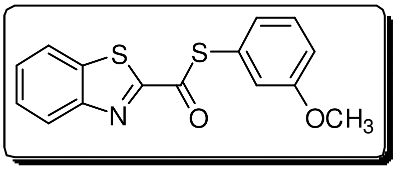
S-(4-fluorophenyl) benzo[d]thiazole-2-carbothioate (16aap):



Nature: White solid; R_f = 0.64; mp 139-141 °C; **IR** (KBr): 3428, 3093, 3058, 1891, 1664, 1588, 1553, 1488, 1456, 1397, 1317, 1293, 1223, 1205, 1160, 1124, 1088, 1064, 1012, 941, 879, 860, 820, 758, 726, 696, 670, 635, 619, 542, 499 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.8 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 3H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 116.8, 117.0, 121.8, 121.8, 122.5, 125.7, 127.5, 128.1, 136.9, 137.1, 137.2, 153.1, 162.8, 163.5, 165.3, 185.3. **HRMS** (ESI): calcd for $C_{14}H_8FNOS_2$ [M + H]$^+$: 290.0104;

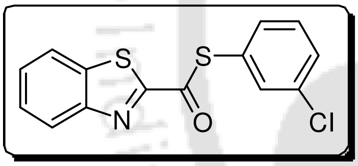
Found: 290.0106. **Anal. Calcd** for $C_{14}H_8FNOS_2$ (289.35): C, 58.11; H, 2.79; N, 4.84. Found: C, 57.97; H, 2.68; N, 4.75.

S-(3-methoxyphenyl) benzo[d]thiazole-2-carbothioate (16aaq):



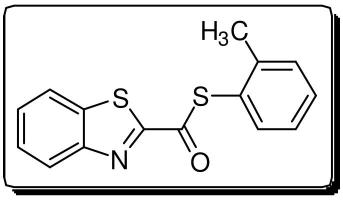
Nature: White solid; $R_f = 0.50$; mp 108-110 °C; **IR** (KBr): 3056, 3001, 2943, 2839, 1922, 1861, 1801, 1692, 1665, 1615, 1590, 1550, 1481, 1463, 1454, 1439, 1421, 1346, 1318, 1276, 1255, 1201, 1185, 1160, 1127, 1106, 1072, 1063, 1028, 991, 947, 896, 881, 872, 863, 809, 786, 758, 731, 705, 687, 675, 625, 558 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 7.03 (d, $J = 8.0$ Hz, 1H), 7.13 (s, 1H), 7.17 (d, $J = 7.6$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.56 (t, $J = 7.2$ Hz, 1H), 7.62 (t, $J = 7.6$ Hz, 1H), 8.00 (d, $J = 7.6$ Hz, 1H), 8.26 (d, $J = 8.0$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.6, 116.4, 120.0, 122.5, 125.6, 127.2, 127.4, 127.5, 128.0, 130.3, 136.9, 153.1, 160.2, 163.9, 185.1. **HRMS** (ESI): calcd for $C_{15}H_{11}NO_2S_2$ $[M + H]^+$: 302.0304; Found: 302.0313. **Anal. Calcd** for $C_{15}H_{11}NO_2S_2$ (301.38): C, 59.78; H, 3.68; N, 4.65. Found: C, 59.64; H, 3.58; N, 4.56.

S-(3-chlorophenyl) benzo[d]thiazole-2-carbothioate (16aar):



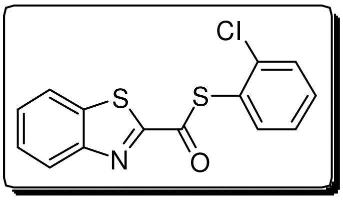
Nature: White solid; $R_f = 0.64$; mp 132-133 °C; **IR** (KBr): 3422, 3055, 2961, 1798, 1669, 1612, 1575, 1566, 1488, 1457, 1399, 1316, 1261, 1207, 1162, 1082, 1070, 1024, 995, 947, 881, 844, 820, 820, 776, 757, 726, 703, 678, 661, 623 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.48 (m, 3H), 7.57 (t, $J = 8.0$ Hz, 2H), 7.63 (t, $J = 7.6$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 8.27 (d, $J = 8.4$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 122.6, 125.7, 127.6, 128.2, 128.3, 130.4, 130.6, 133.2, 134.8, 135.2, 137.0, 153.0, 163.4, 184.6. **HRMS** (ESI): calcd for $C_{14}H_8ClNOS_2$ $[M + H]^+$: 305.9809; Found: 305.9827. **Anal. Calcd** for $C_{14}H_8ClNOS_2$ (305.80): C, 54.99; H, 2.64; N, 4.58. Found: C, 54.84; H, 2.54; N, 4.49.

S-o-tolyl benzo[d]thiazole-2-carbothioate (16aas):



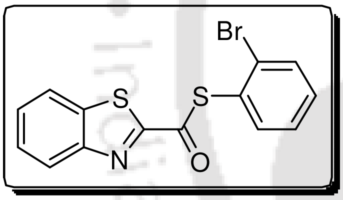
Nature: White solid; $R_f = 0.62$; mp 65-67 °C; **IR** (KBr): 3053, 2925, 1918, 1798, 1697, 1662, 1627, 1589, 1550, 1482, 1456, 1419, 1318, 1281, 1209, 1125, 1060, 1037, 1013, 945, 879, 857, 814, 804, 755, 730, 703, 675, 669, 619, 551 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.29 (t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 7.2$ Hz, 2H), 7.56 (t, $J = 8.0$ Hz, 2H), 7.62 (t, $J = 7.2$ Hz, 1H), 8.00 (d, $J = 7.6$ Hz, 1H), 8.28 (d, $J = 8.0$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0, 122.5, 125.6, 125.9, 127.0, 127.4, 127.9, 130.8, 131.1, 136.3, 136.9, 142.9, 153.1, 164.0, 184.6. **HRMS** (ESI): calcd for $C_{15}H_{11}NOS_2$ $[M + H]^+$: 286.0355; Found: 286.0369. **Anal. Calcd** for $C_{15}H_{11}NOS_2$ (285.38): C, 63.13; H, 3.89; N, 4.91. Found: C, 62.97; H, 3.77; N, 4.81.

S-(2-chlorophenyl) benzo[d]thiazole-2-carbothioate (16aak):



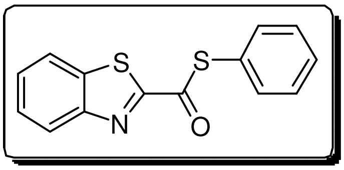
Nature: White solid; R_f = 0.64; mp 144-149 °C; **IR** (KBr): 2924, 2850, 1957, 1921, 1692, 1673, 1612, 1573, 1551, 1485, 1450, 1433, 1419, 1382, 1319, 1249, 1208, 1115, 1064, 1034, 982, 950, 879, 852, 809, 759, 750, 725, 700, 670, 657, 617, 545, 469 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.54-7.62 (m, 3H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 122.6, 125.7, 126.2, 127.5, 127.7, 128.1, 130.7, 131.9, 137.0, 137.6, 139.5, 153.1, 163.4, 183.5. **HRMS** (ESI): calcd for $C_{14}H_8ClNOS_2$ $[M + H]^+$: 305.9809; Found: 305.9829. **Anal. Calcd** for $C_{14}H_8ClNOS_2$ (305.80): C, 54.99; H, 2.64; N, 4.58. Found: C, 54.83; H, 2.52; N, 4.47.

S-(2-bromophenyl) benzo[d]thiazole-2-carbothioate (16aal):



Nature: White solid; R_f = 0.63; mp 167-169 °C; **IR** (KBr): 2926, 2856, 1740, 1691, 1672, 1610, 1485, 1457, 1447, 1429, 1415, 1384, 1319, 1258, 1208, 1109, 1064, 1018, 923, 879, 851, 808, 759, 749, 726, 697, 669, 646, 616 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 122.6, 125.8, 127.6, 128.1, 128.4, 128.5, 130.2, 131.9, 134.0, 137.0, 137.6, 153.1, 163.4, 183.6. **HRMS** (ESI): calcd for $C_{14}H_8BrNOS_2$ $[M + H]^+$: 351.9282; Found 351.9285. **Anal. Calcd** for $C_{14}H_8BrNOS_2$ (350.25): C, 48.01; H, 2.30; N, 4.00. Found: C, 47.86; H, 2.19; N, 3.92.

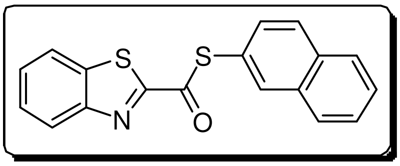
S-phenyl benzo[d]thiazole-2-carbothioate (16aad):



Nature: White solid; R_f = 0.69; mp 121-123 °C; **IR** (KBr): 3057, 2959, 2870, 1951, 1925, 1882, 1807, 1687, 1663, 1615, 1551, 1482, 1477, 1457, 1439, 1420, 1320, 1201, 1154, 1129, 1062, 1025, 948, 878, 808, 761, 749, 730, 723, 704, 686, 673, 620, 543, 457 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (s, 3H), 7.53-7.63 (m, 4H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 122.4, 125.5, 126.4, 127.4, 127.9, 129.5 (2C), 130.1, 134.9 (2C), 136.8, 153.0, 163.7, 185.1. **HRMS** (ESI):

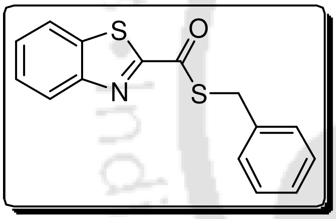
calcd for $C_{14}H_9NOS_2$ [M + H]$^+$: 272.0198; Found: 272.0208. **Anal. Calcd** for $C_{14}H_9NOS_2$ (271.36): C, 61.97; H, 3.34; N, 5.16. Found: C, 61.82; H, 3.23; N, 5.08.

S-naphthalen-2-yl benzo[d]thiazole-2-carbothioate (16aah):



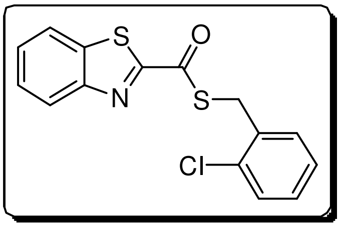
Nature: White solid; R_f = 0.66; mp 127-129 °C; **IR** (KBr): 3050, 2963, 1687, 1659, 1591, 1574, 1551, 1495, 1456, 1346, 1316, 1291, 1250, 1201, 1177, 1095, 1064, 1028, 943, 877, 860, 815, 758, 744, 728, 701, 671, 641, 544, 477 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.57 (t, *J* = 8.4 Hz, 3H), 7.63 (t, *J* = 8.4 Hz, 2H), 7.89 (t, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 8.29 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 122.6, 123.9, 125.7, 126.9, 127.5, 127.6, 128.0, 128.1 (2C), 128.3, 129.3, 131.1, 133.8, 135.2, 137.0, 153.2, 163.9, 185.5. **HRMS** (ESI): calcd for $C_{18}H_{11}NOS_2$ [M + H]$^+$: 322.0355; Found: 322.0354. **Anal. Calcd** for $C_{18}H_{11}NOS_2$ (321.42): C, 67.26; H, 3.45; N, 4.36. Found: C, 67.11; H, 3.34; N, 4.28.

S-benzyl benzo[d]thiazole-2-carbothioate (16aac):



Nature: White solid; R_f = 0.68; mp 102-104 °C; **IR** (KBr): 3418, 3059, 3031, 2924, 2856, 1946, 1656, 1631, 1551, 1496, 1482, 1454, 1420, 1384, 1318, 1210, 1070, 1020, 943, 884, 855, 820, 758, 729, 697, 675, 617, 561, 474 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 4.37 (s, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 33.7, 122.5, 125.6, 127.4, 127.7, 127.9, 128.9 (3C), 129.3 (2C), 136.8, 153.1, 164.1, 186.3. **HRMS** (ESI): calcd for $C_{15}H_{11}NOS_2$ [M + H]$^+$: 286.0355; Found: 286.0354. **Anal. Calcd** for $C_{15}H_{11}NOS_2$ (285.38): C, 63.13; H, 3.89; N, 4.91. Found: C, 62.98; H, 3.78; N, 4.82.

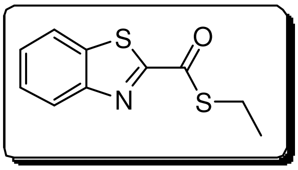
S-2-chlorobenzyl benzo[d]thiazole-2-carbothioate (16aaj):



Nature: White solid; R_f = 0.62; mp 131-132 °C; **IR** (KBr): 3447, 3056, 2925, 1656, 1634, 1552, 1491, 1471, 1439, 1420, 1404, 1316, 1279, 1246, 1209, 1160, 1123, 1068, 1050, 1035, 948, 889, 872, 856, 822, 762, 739, 729, 704, 688, 670, 584, 455 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 4.48 (s, 2H), 7.22 (t, *J* = 4.4 Hz, 2H), 7.38 (t, *J* = 4.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 31.5, 122.4, 125.5, 127.2, 127.3, 127.8, 129.2, 129.8, 131.5, 134.5, 134.7, 136.6, 153.0, 163.8, 186.1. **HRMS**

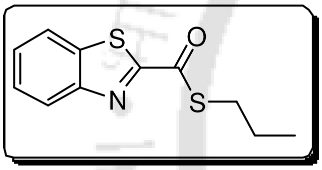
(ESI): calcd for $C_{15}H_{10}ClNOS_2$ $[M + H]^+$: 319.9965; Found: 319.9981. **Anal. Calcd** for $C_{15}H_{10}ClNOS_2$ (319.83): C, 56.33; H, 3.15; N, 4.38. Found: C, 56.17; H, 3.03; N, 4.27.

S-ethyl benzo[d]thiazole-2-carbothioate (16aaa):



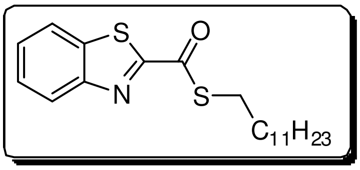
Nature: White solid; $R_f = 0.76$; mp 91-93 °C; **IR** (KBr): 3050, 2967, 2933, 1948, 1912, 1708, 1657, 1636, 1551, 1484, 1455, 1422, 1410, 1373, 1317, 1270, 1211, 1165, 1125, 1059, 1011, 969, 883, 863, 850, 824, 766, 731, 705, 682, 617 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.40 (t, $J = 7.6$ Hz, 3H), 3.14 (q, $J = 8.0$ Hz, 2H), 7.52 (t, $J = 7.6$ Hz, 1H), 7.58 (t, $J = 8.0$ Hz, 1H), 7.97 (d, $J = 8.4$ Hz, 1H), 8.21 (d, $J = 8.4$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 23.8, 122.5, 125.6, 127.3, 127.8, 136.7, 153.2, 164.6, 187.0. **HRMS** (ESI): calcd for $C_{10}H_9NOS_2$ $[M + H]^+$: 224.0198; Found: 224.0203. **Anal. Calcd** for $C_{10}H_9NOS_2$ (223.31): C, 53.78; H, 4.06; N, 6.27. Found: C, 53.65; H, 3.96; N, 6.17.

S-propyl benzo[d]thiazole-2-carbothioate (16aab):



Nature: Semi-solid; $R_f = 0.76$; **IR** (KBr): 3062, 2963, 2930, 2871, 1701, 1660, 1636, 1554, 1487, 1457, 1422, 1378, 1339, 1317, 1292, 1241, 1206, 1162, 1125, 1092, 1066, 1012, 941, 881, 854, 821, 760, 729, 703, 677, 617, 577 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05 (t, $J = 7.6$ Hz, 3H), 1.74 (sext, $J_1 = 7.2$ Hz & $J_2 = 7.6$ Hz, 2H), 3.11 (t, $J = 7.6$ Hz, 2H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.56 (t, $J = 8.4$ Hz, 1H), 7.96 (d, $J = 7.6$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6, 22.8, 31.2, 122.5, 125.5, 127.3, 127.7, 136.7, 153.1, 164.6, 186.9. **HRMS** (ESI): calcd for $C_{11}H_{11}NOS_2$ $[M + H]^+$: 238.0355; Found: 238.0355. **Anal. Calcd** for $C_{11}H_{11}NOS_2$ (237.34): C, 55.67; H, 4.67; N, 5.90. Found: C, 55.53; H, 4.56; N, 5.80.

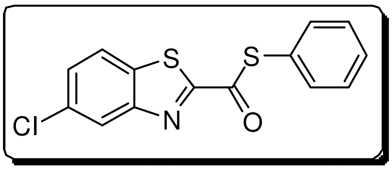
S-dodecyl benzo[d]thiazole-2-carbothioate (16aat):



Nature: Gummy liquid; $R_f = 0.84$; **IR** (KBr): 3449, 2952, 2915, 2850, 1659, 1633, 1486, 1471, 1383, 1317, 1209, 1069, 881, 855, 824, 757, 723, 678 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, $J = 7.6$ Hz, 3H), 1.23 (s, 16H), 1.45 (t, $J = 7.6$ Hz, 2H), 1.69-1.74 (m, 2H), 3.14 (t, $J = 7.2$ Hz, 2H), 7.52 (t, $J = 8.4$ Hz, 1H), 7.58 (t, $J = 8.0$ Hz, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 8.22 (d, $J = 8.0$ Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.9, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8 (2C), 29.9, 32.1, 122.5, 125.6, 127.3, 127.8, 136.7, 153.2, 164.7, 187.0. **HRMS** (ESI): calcd for $C_{20}H_{29}NOS_2$ $[M + H]^+$:

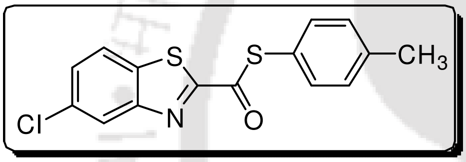
364.1763; Found: 364.1762. **Anal. Calcd** for $C_{20}H_{29}NOS_2$ (363.58): C, 66.07; H, 8.04; N, 3.85. Found: C, 65.91; H, 7.92; N, 3.77.

S-phenyl 5-chlorobenzo[d]thiazole-2-carbothioate (16bad):



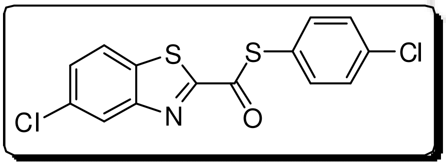
Nature: White solid; $R_f = 0.69$; mp 148-150 °C; **IR** (KBr): 3419, 3058, 2924, 2852, 1902, 1749, 1680, 1642, 1585, 1570, 1538, 1487, 1477, 1438, 1308, 1204, 1176, 1092, 1068, 1060, 1023, 920, 866, 828, 808, 775, 756, 745, 735, 718, 687, 668, 648, 604 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.57 (m, 6H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.23 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 123.3, 125.1, 126.2, 128.6, 129.7 (2C), 130.3, 133.7, 134.6, 135.0 (2C), 153.8, 165.7, 185.1. **HRMS** (ESI): calcd for $C_{14}H_8ClNOS_2$ $[M + H]^+$: 305.9809; Found: 305.9813. **Anal. Calcd** for $C_{14}H_8ClNOS_2$ (305.80): C, 54.99; H, 2.64; N, 4.58. Found: C, 54.84; H, 2.53; N, 4.48.

S-p-tolyl 5-chlorobenzo[d]thiazole-2-carbothioate (16bae):



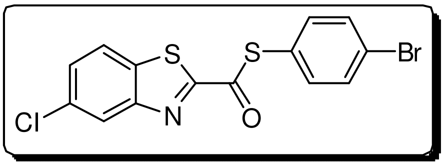
Nature: White solid; $R_f = 0.65$; mp 169-171 °C; **IR** (KBr): 3420, 2923, 2854, 1743, 1681, 1640, 1568, 1541, 1485, 1434, 1404, 1310, 1203, 1182, 1091, 1068, 919, 867, 834, 806, 718, 669, 603, 544, 478 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.25 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 122.7, 123.3, 125.2, 128.6, 130.5 (2C), 133.6, 134.9 (2C), 135.1, 140.7, 153.9, 165.8, 185.5. **HRMS** (ESI): calcd for $C_{15}H_{10}ClNOS_2$ $[M + H]^+$: 319.9965; Found: 319.9969. **Anal. Calcd** for $C_{15}H_{10}ClNOS_2$ (319.83): C, 56.33; H, 3.15; N, 4.38. Found: C, 56.19; H, 3.05; N, 4.29.

S-(4-chlorophenyl) 5-chlorobenzo[d]thiazole-2-carbothioate (16baf):



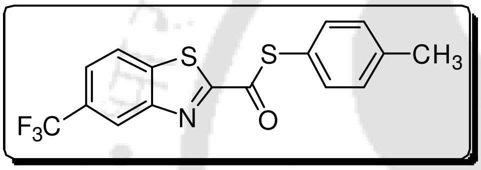
Nature: White solid; $R_f = 0.75$; mp 166-168 °C; **IR** (KBr): 3430, 3088, 2924, 2853, 1892, 1697, 1682, 1640, 1588, 1573, 1541, 1489, 1477, 1432, 1389, 1310, 1201, 1179, 1093, 1071, 1013, 919, 871, 833, 815, 798, 736, 718, 669, 648, 602, 532, 483 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45-7.50 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 8.24 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 123.3, 124.8, 125.2, 128.7, 129.9 (2C), 133.8, 135.1, 136.2 (2C), 136.8, 153.8, 165.2, 184.6. **HRMS** (ESI): calcd for $C_{14}H_7Cl_2NOS_2$ $[M + H]^+$: 339.9419; Found: 339.9415. **Anal. Calcd** for $C_{14}H_7Cl_2NOS_2$ (340.25): C, 49.42; H, 2.07; N, 4.12. Found: C, 49.28; H, 1.98; N, 4.05.

S-(4-bromophenyl) 5-chlorobenzo[d]thiazole-2-carbothioate (16bag):



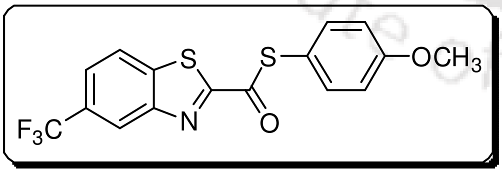
Nature: White solid; R_f = 0.73; mp 185-187 °C; **IR** (KBr): 3447, 3082, 2924, 2852, 1894, 1677, 1634, 1589, 1540, 1488, 1470, 1431, 1382, 1310, 1204, 1086, 1067, 1006, 916, 875, 836, 809, 729, 718, 669, 647, 603, 547, 480 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 1H), 8.23 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 123.3, 125.1, 125.2, 125.4, 128.8, 132.9 (2C), 133.8, 135.1, 136.4 (2C), 153.8, 165.2, 184.5. **HRMS** (ESI): calcd for $C_{14}H_7BrClNOS_2$ [M + H]$^+$: 385.8891; Found: 385.8893. **Anal. Calcd** for $C_{14}H_7BrClNOS_2$ (384.70): C, 43.71; H, 1.83; N, 3.64. Found: C, 43.58; H, 1.73; N, 3.55.

S-p-tolyl 5-(trifluoromethyl)benzo[d]thiazole-2-carbothioate (16cae):



Nature: White solid; R_f = 0.84; mp 153-155 °C; **IR** (KBr): 3428, 3047, 2924, 2856, 1918, 1732, 1678, 1645, 1490, 1463, 1332, 1318, 1254, 1224, 1203, 1176, 1146, 1132, 1071, 1051, 1021, 924, 895, 828, 807, 725, 667, 643 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.55 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 122.5, 122.7, 122.8, 122.9, 123.0, 123.4, 124.1, 125.4, 130.1, 130.4, 130.6 (3C), 134.9 (3C), 140.0, 140.8, 152.6, 166.2, 185.5. **HRMS** (ESI): calcd for $C_{16}H_{10}F_3NOS_2$ [M + H]$^+$: 354.0229; Found: 354.0224. **Anal. Calcd** for $C_{16}H_{10}F_3NOS_2$ (353.38): C, 54.38; H, 2.85; N, 3.96. Found: C, 54.22; H, 2.73; N, 3.87.

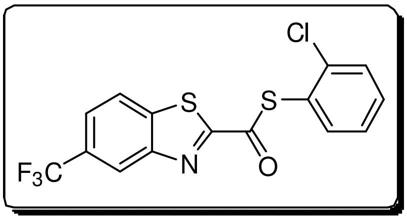
S-(4-methoxyphenyl) 5-(trifluoromethyl)benzo[d]thiazole-2-carbothioate (16cai):



Nature: White solid; R_f = 0.64; mp 139-141 °C; **IR** (KBr): 3299, 3064, 2922, 2850, 2548, 2048, 1897, 1677, 1643, 1593, 1574, 1531, 1488, 1463, 1445, 1409, 1335, 1321, 1293, 1254, 1207, 1190, 1174, 1146, 1125, 1069, 1050, 1028, 925, 889, 833, 820, 800, 759, 728, 707, 666 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 7.02 (d, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 8.54 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.6, 114.8, 115.4 (2C), 116.4, 122.7, 122.8, 122.9, 123.4, 124.0, 124.1, 125.4, 130.0, 130.3, 132.8, 136.6 (2C), 140.0, 152.6, 161.4, 166.2, 185.9. **HRMS** (ESI): calcd for $C_{16}H_{10}F_3NO_2S_2$

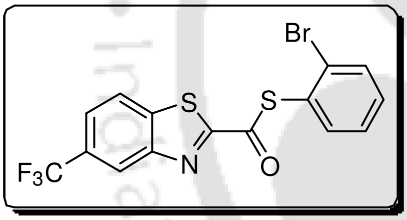
[M + H]$^+$: 370.0178; Found: 370.0178. **Anal. Calcd** for $C_{16}H_{10}F_3NO_2S_2$ (369.38): C, 52.03; H, 2.73; N, 3.79. Found: C, 51.88; H, 2.62; N, 3.69.

S-(2-chlorophenyl) 5-(trifluoromethyl)benzo[d]thiazole-2-carbothioate (16cak):



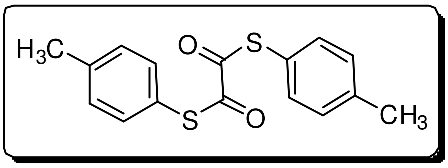
Nature: White solid; $R_f = 0.75$; mp 113-115 °C; **IR** (KBr): 3433, 3075, 2924, 2853, 1979, 1934, 1909, 1687, 1635, 1612, 1574, 1488, 1453, 1435, 1421, 1331, 1259, 1224, 1205, 1179, 1150, 1135, 1070, 1054, 1034, 923, 895, 865, 821, 756, 738, 723, 702, 666, 658, 638 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 8.56 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 122.94, 122.99, 123.0, 123.1, 123.5, 124.2, 124.3, 125.8, 127.8, 130.2, 130.4, 130.8, 132.1, 137.5, 139.4, 140.1, 152.6, 165.6, 183.4. **HRMS** (ESI): calcd for $C_{15}H_7ClF_3NOS_2$ [M + H]$^+$: 373.9682; Found: 373.9681. **Anal. Calcd** for $C_{15}H_7ClF_3NOS_2$ (373.80): C, 48.20; H, 1.89; N, 3.75. Found: C, 48.03; H, 1.77; N, 3.65.

S-(2-bromophenyl) 5-(trifluoromethyl)benzo[d]thiazole-2-carbothioate (16cal):



Nature: White solid; $R_f = 0.74$; mp 117-119 °C; **IR** (KBr): 3445, 3078, 2924, 2853, 1973, 1934, 1907, 1688, 1634, 1614, 1575, 1561, 1488, 1460, 1450, 1432, 1417, 1332, 1258, 1224, 1205, 1179, 1151, 1135, 1070, 1054, 1018, 923, 894, 821, 754, 730, 716, 707, 698, 665, 638 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.78 (dd, J_1 = 7.6 Hz & J_2 = 8.8 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 1H), 8.56 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 122.6, 122.91, 122.95, 122.99, 123.0, 123.5, 124.2, 124.3, 125.3, 128.0, 128.4, 130.0, 130.1, 130.4, 132.1, 134.1, 137.5, 140.1, 152.5, 165.6, 183.4. **HRMS** (ESI): calcd for $C_{15}H_7BrF_3NOS_2$ [M + H]$^+$: 417.9177; Found: 417.9174. **Anal. Calcd** for $C_{15}H_7BrF_3NOS_2$ (418.25): C, 43.07; H, 1.69; N, 3.35. Found: C, 42.92; H, 1.58; N, 3.26.

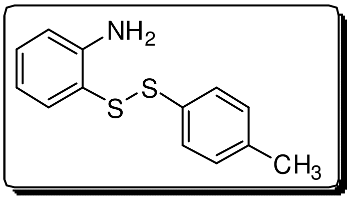
S,CS-di-p-tolyl ethanebis(thioate) (17):



Nature: White solid; mp 177-179 °C. **IR** (KBr): 3447, 2959, 2922, 2853, 1908, 1684, 1637, 1595, 1489, 1398, 1302, 1261, 1210, 1182, 1114, 1093, 1040, 1016, 809, 781, 698, 668, 627 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.41 (s, 6H), 7.28 (d, *J* = 7.8 Hz, 4H), 7.34 (d, *J* = 7.8 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.6, 122.1, 130.6, 134.5, 140.8, 187.6. **HRMS** (ESI): calcd for $C_{16}H_{14}O_2S_2$ [M +

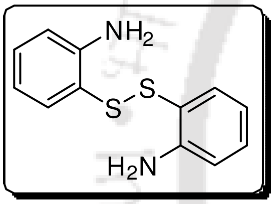
H]$^+$: 341.0067; Found: 341.0056. **Anal. Calcd** for $C_{16}H_{14}O_2S_2$ (302.41): C, 63.55; H, 4.67. Found: C, 63.49; H, 4.55.

2-(p-tolyldisulfanyl)aniline (18a):



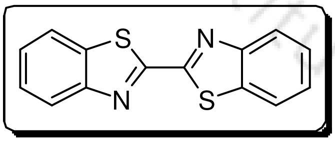
Nature: Gummy solid; **IR** (KBr): 3470, 3373, 3064, 3017, 2919, 2853, 1690, 1608, 1506, 1488, 1476, 1446, 1397, 1307, 1251, 1209, 1179, 1158, 1139, 1115, 1078, 1017, 936, 806, 748, 620 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.38 (s, 2H, NH_2), 6.65 (t, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.27-7.29 (m, 1H), 7.43-7.44 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 21.3, 115.8, 118.7, 119.6, 129.9 (2C), 131.3 (3C), 133.9, 135.6, 138.5, 147.8. **HRMS** (ESI): calcd for $C_{13}H_{13}NS_2$ [M + H]$^+$: 248.0562; Found: 248.0550. **Anal. Calcd** for $C_{13}H_{13}NS_2$ (247.38): C, 63.12; H, 5.30; N, 5.66. Found: C, 62.97; H, 5.19; N, 5.57.

2,2'-disulfanediyldianiline (18b):



Nature: White solid; mp 94-96 °C. **IR** (KBr): 3380, 3297, 3064, 1624, 1584, 1473, 1446, 1302, 1247, 1156, 1093, 1046, 1024, 963, 863, 848, 754, 696, 668 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.24 (s, 4H), 6.60 (t, *J* = 7.8 Hz, 2H), 6.72 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 115.4, 115.5, 118.4, 118.6, 131.8 (3C), 137.0 (3C), 148.6, 148.8. **HRMS** (ESI): calcd for $C_{12}H_{12}N_2S_2$ [M + H]$^+$: 249.0515; Found: 249.0504. **Anal. Calcd** for $C_{12}H_{12}N_2S_2$ (248.37): C, 58.03; H, 4.87; N, 11.28. Found: C, 57.89; H, 4.75; N, 11.18.

2,2'-bibenzo[d]thiazole (19):



Nature: White solid; R_f = 0.35; mp 239-240 °C. **IR** (KBr): 3056, 1691, 1660, 1596, 1550, 1484, 1457, 1423, 1402, 1378, 1320, 1205, 1182, 1159, 1128, 1105, 1065, 1019, 948, 881, 869, 855, 805 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.49 (t, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 7.8 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 122.3 (2C), 124.3 (2C), 126.9 (2C), 127.1 (2C), 136.0 (2C), 153.8 (2C), 161.8 (2C). **HRMS** (ESI): calcd for $C_{14}H_8N_2S_2$ [M + H]$^+$: 269.0202; Found: 269.0198. **Anal. Calcd** for $C_{14}H_8N_2S_2$ (268.36): C, 62.66; H, 3.00; N, 10.44. Found: C, 62.51; H, 2.89; N, 10.35.

Crystallographic description:

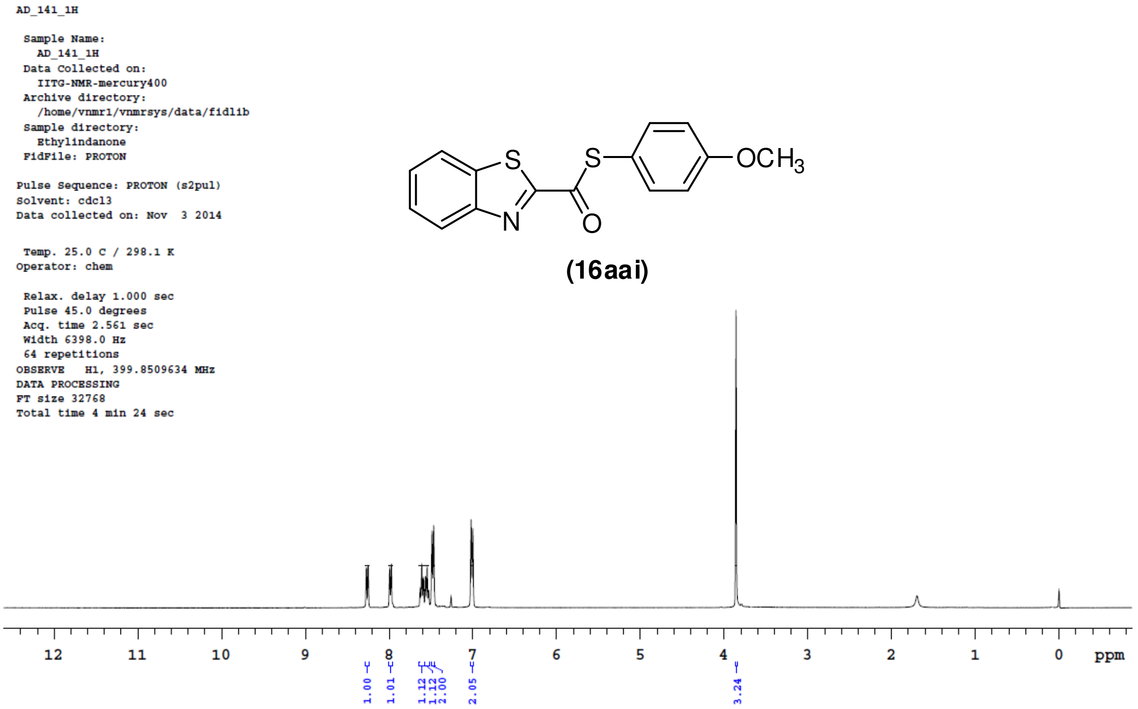
Complete crystallographic data of **16aae** and **16aaj** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1430385 and 1430384 respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 6.4. Crystal data and structures refinement for **16aae** and **16aaj**. For atomic coordinates, equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**16aae**	**16aaj**
Empirical Formula	$C_{15}H_{11}NOS_2$	$C_{15}H_{10}ClNOS_2$
Formula weight	285.37	319.81
Temperature	296 K	293 K
Wavelength	0.71073 (Å)	0.71073 (Å)
Crystal system	Triclinic	Triclinic
Space group	*P*-1	*P*-1
Radiation source	'fine-focus sealed tube'	'fine-focus sealed tube'
Unit cell dimensions	a = 5.6221(11) (Å), α = 87.223(8)°	a = 8.1250(7) (Å), α = 90.930(8)°
	b = 9.6836(17) (Å), β = 88.919(9)°	b = 8.2239(9) (Å), β = 96.487(7)°
	c = 12.619(2) (Å), γ = 85.132(9)°	c = 10.6956(8) (Å), γ = 93.239(8)°
Unit cell volume	683.7(2) Å^3	708.77(11) Å^3
Z	2	2
Density	1.386 g/cm^3	1.499 g/cm^3
Reflections collected	4468	4749
Independent reflections	2428 [R(int) = 0.0289]	2495 [R(int) = 0.0231]
Final R_1 values ($I > 2\sigma(I)$)	0.0796	0.0407
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1883	0.0964
Final R_1 values (all data)	0.1511	0.0597
Final $wR(F2)$ values (all data)	0.2469	0.1152
Absorption coefficient, μ/mm	0.379	0.557
Radiation type	Mo K\a	Mo K\a

Goodness-of-fit (GOF) on F^2	1.148	1.077
$F(0\ 0\ 0)$	296.0	328.0
Theta range for data collection	1.62 to 25.25°	2.99 to 25.00°
Index ranges	$-5 \le h \le 5$, $-11 \le k \le 10$, $-15 \le l \le 15$	$-9 \le h \le 9$, $-6 \le k \le 9$, - $12 \le l \le 12$
Completeness to theta	25.25° 98.1 %	25.00° 99.9 %
Number of parameters	173	181
Number of restraints	0	0
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
CCDC number	1430385	1430384

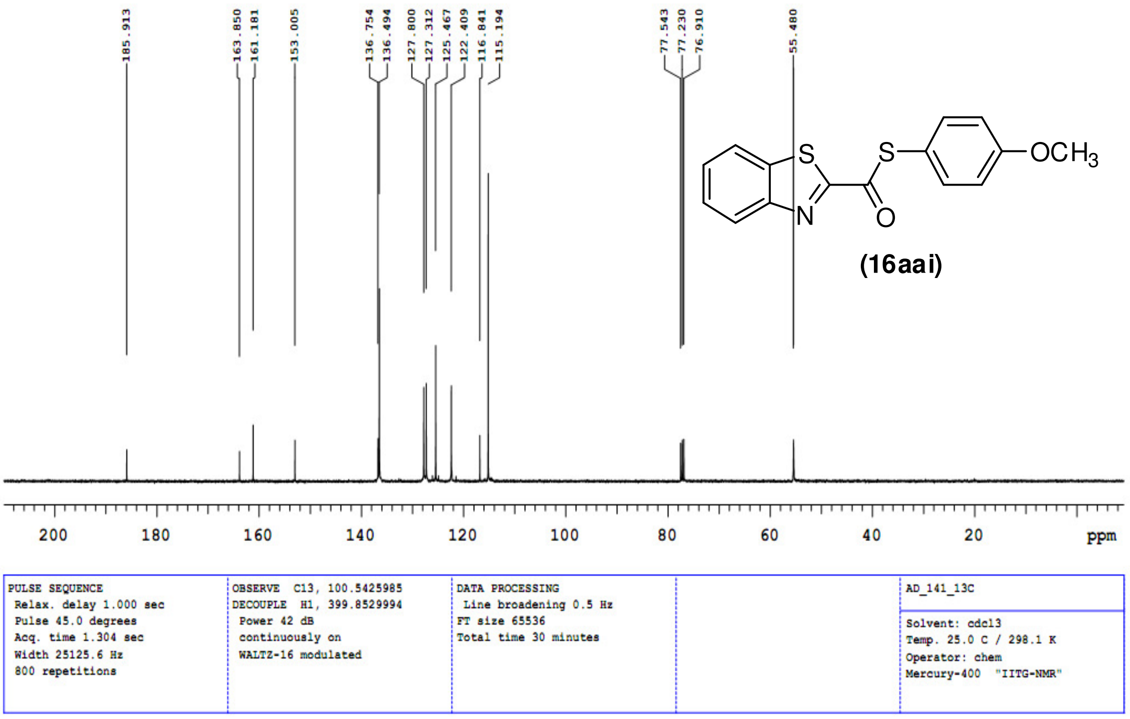
***^{1}H NMR (400 MHz, CDCl$_3$):** S-(4-methoxyphenyl) benzo[d]thiazole-2-carbothioate* (**16aai**)



```
AD_141_1H

 Sample Name:
   AD_141_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /home/vnmr1/vnmrsys/data/fidlib
 Sample directory:
   Ethylindanone
 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov  3 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```

(16aai)

***^{13}C NMR (100 MHz, CDCl$_3$):** S-(4-methoxyphenyl) benzo[d]thiazole-2-carbothioate* (**16aai**)

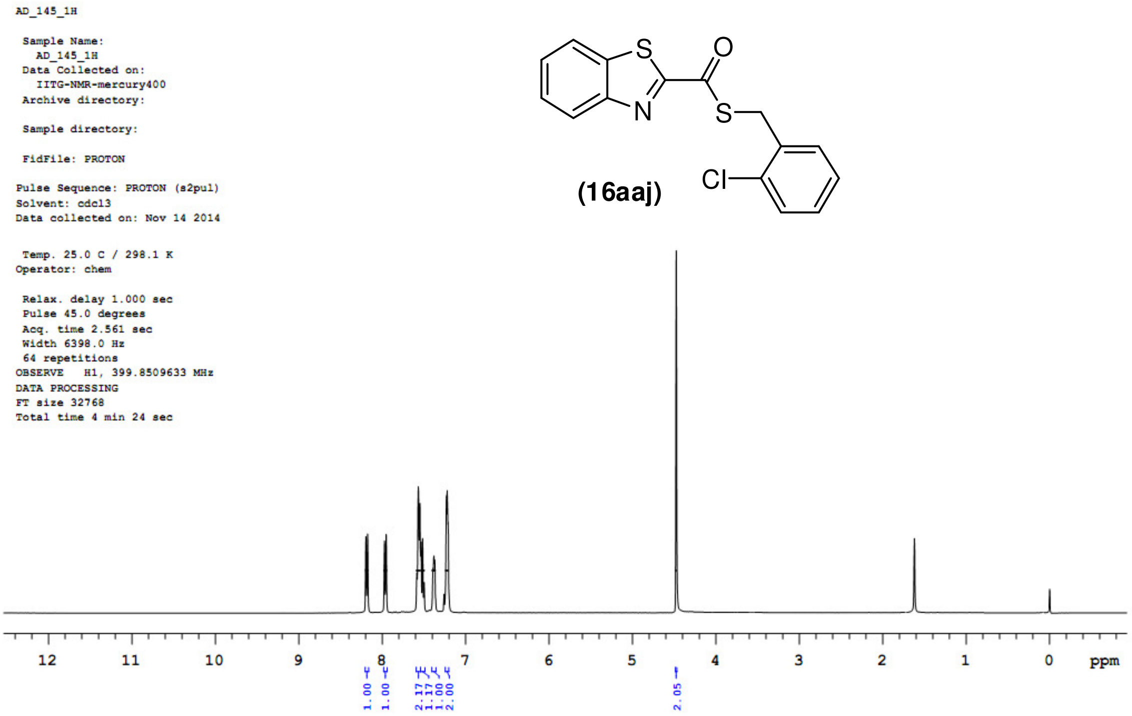


(16aai)

```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 800 repetitions

OBSERVE  C13, 100.5425985
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 30 minutes

AD_141_13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

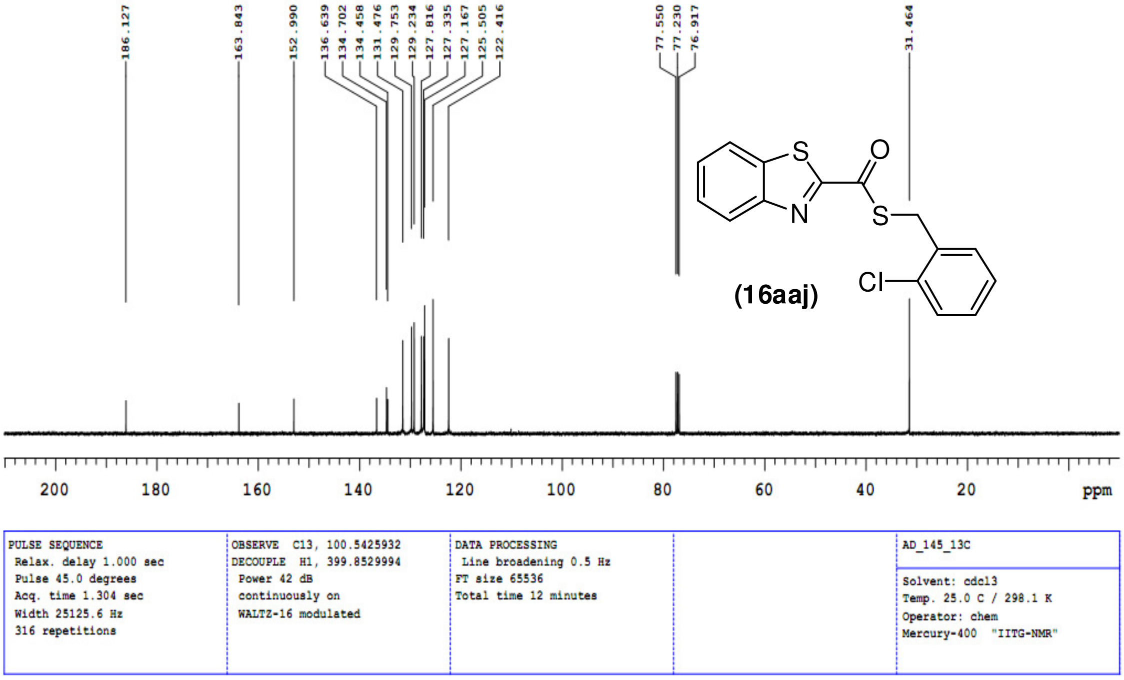
Fig 6.6

^{1}H NMR (400 MHz, $CDCl_3$): S-2-chlorobenzyl benzo[d]thiazole-2-carbothioate **(16aaj)**



```
AD_145_1H

 Sample Name:
   AD_145_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:

 Sample directory:

 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 14 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509633 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```

^{13}C NMR (100 MHz, $CDCl_3$): S-2-chlorobenzyl benzo[d]thiazole-2-carbothioate **(16aaj)**



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 316 repetitions
```

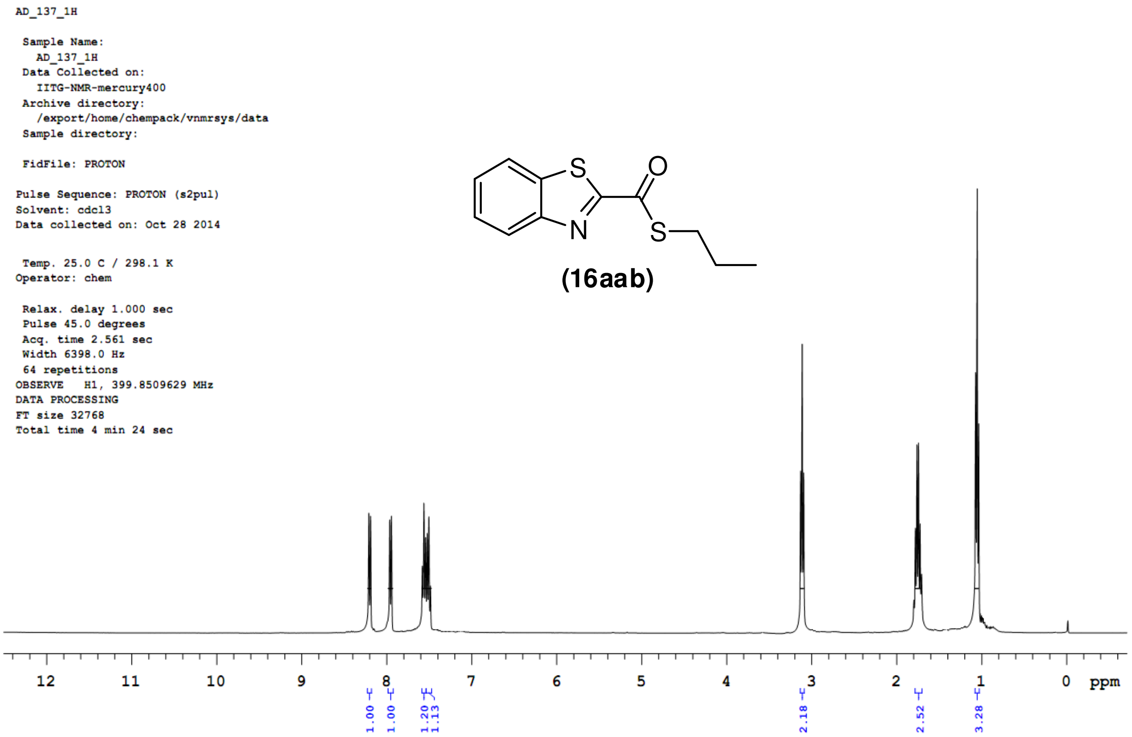
```
OBSERVE  C13, 100.5425932
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated
```

```
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 12 minutes
```

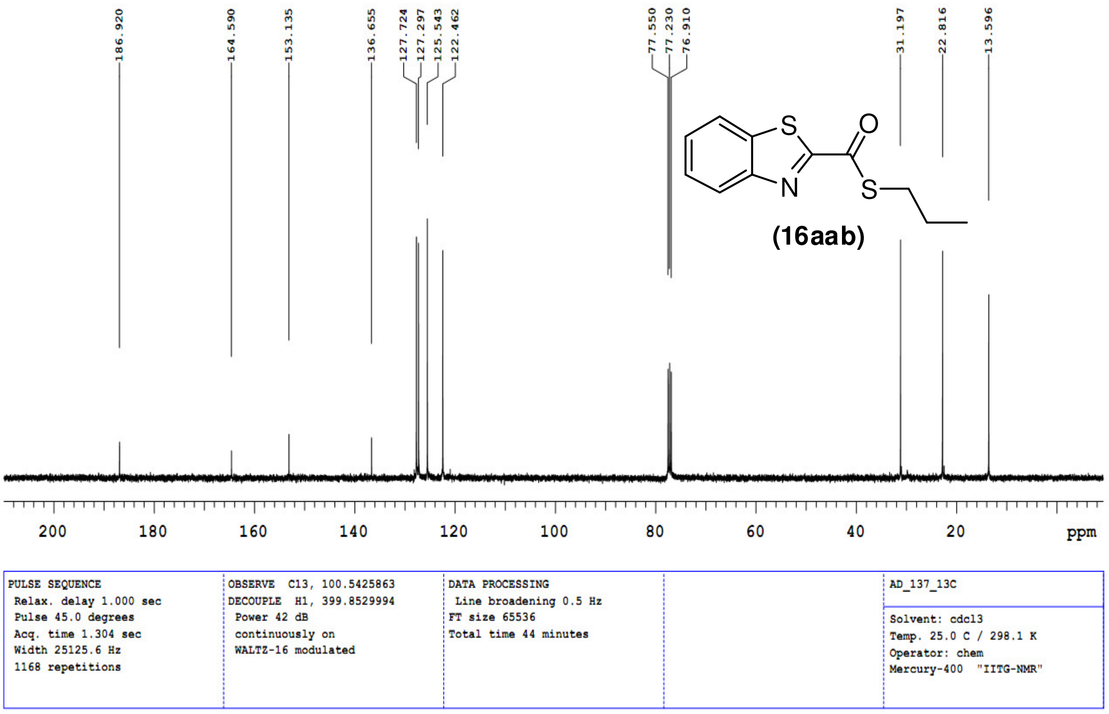
```
AD_145_13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

Fig 6.7

^{1}H NMR (400 MHz, CDCl$_3$): *S-propyl benzo[d]thiazole-2-carbothioate* (16aab)


```
AD_137_1H

 Sample Name:
   AD_137_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 28 2014

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509629 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```

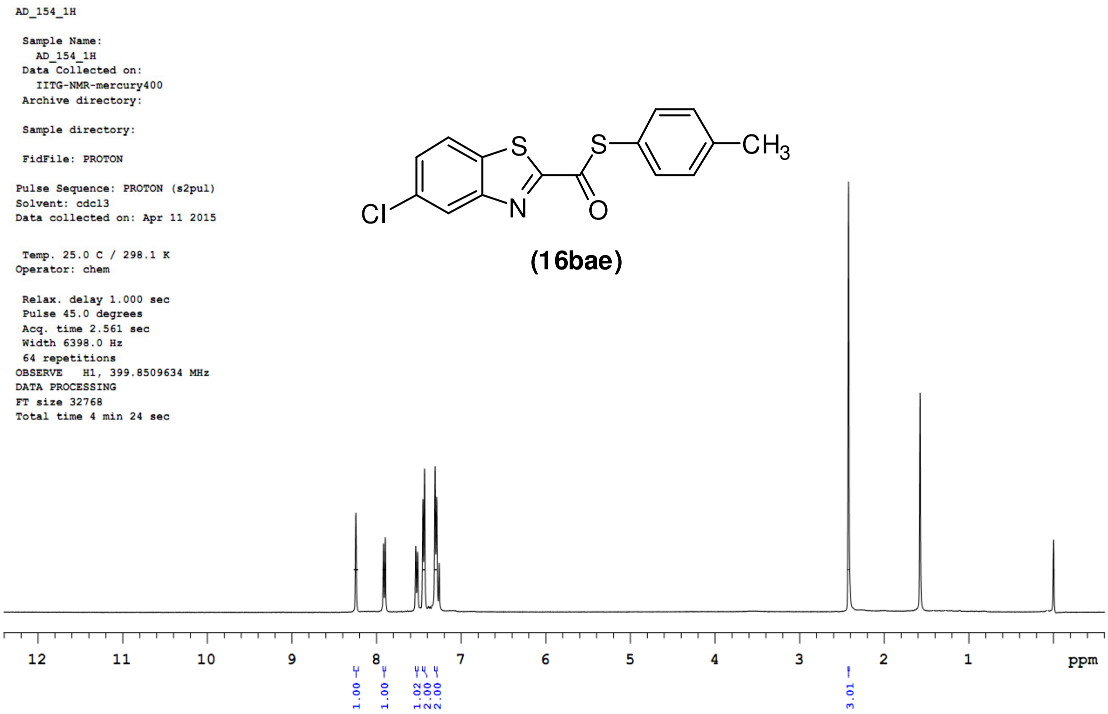
^{13}C NMR (100 MHz, CDCl$_3$): *S-propyl benzo[d]thiazole-2-carbothioate* (16aab)



```
PULSE SEQUENCE        OBSERVE  C13, 100.5425863   DATA PROCESSING              AD_137_13C
 Relax. delay 1.000 sec  DECOUPLE  H1, 399.8529994  Line broadening 0.5 Hz
 Pulse 45.0 degrees      Power 42 dB               FT size 65536               Solvent: cdcl3
 Acq. time 1.304 sec     continuously on           Total time 44 minutes       Temp. 25.0 C / 298.1 K
 Width 25125.6 Hz        WALTZ-16 modulated                                    Operator: chem
 1168 repetitions                                                              Mercury-400  "IITG-NMR"
```

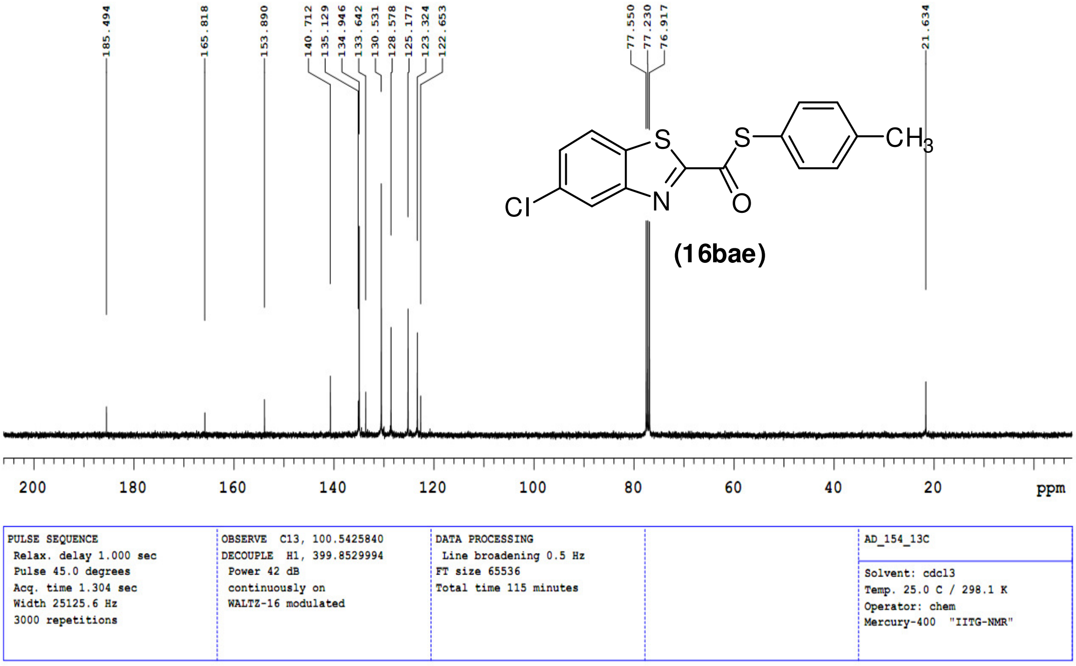
Fig 6.8

^{1}H NMR (400 MHz, CDCl$_3$): *S-p-tolyl 5-chlorobenzo[d]thiazole-2-carbothioate* **(16bae)**



```
AD_154_1H

 Sample Name:
   AD_154_1H
 Data Collected on:
   IITG-NMR-mercury400
 Archive directory:

 Sample directory:

 FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 11 2015

 Temp. 25.0 C / 298.1 K
Operator: chem

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 64 repetitions
OBSERVE   H1, 399.8509634 MHz
DATA PROCESSING
FT size 32768
Total time 4 min 24 sec
```

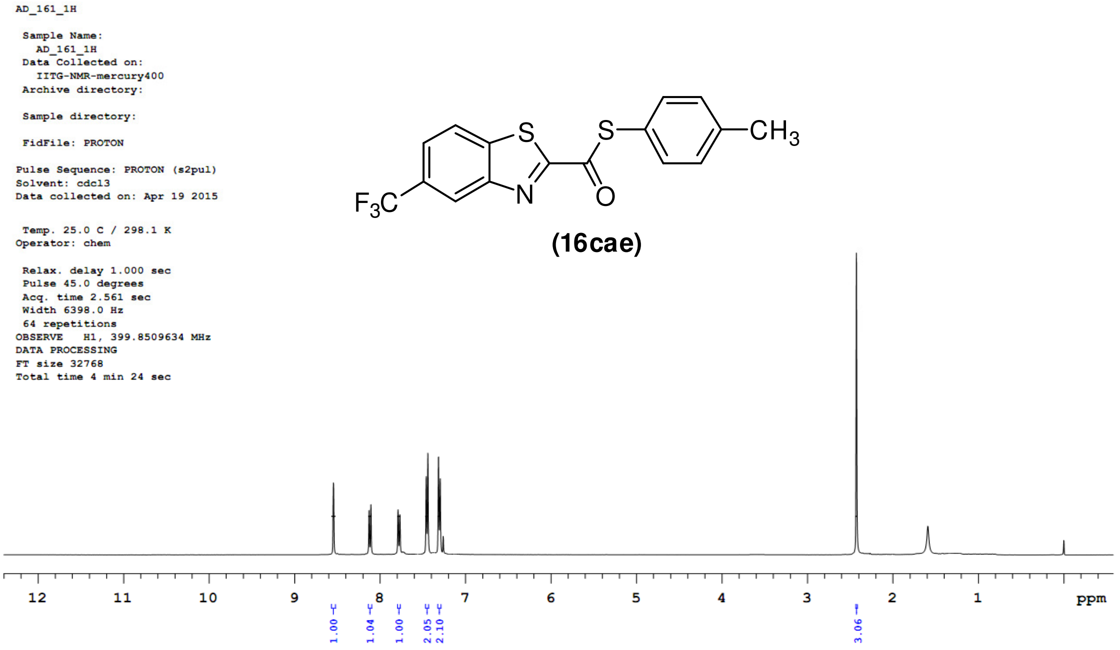
^{13}C NMR (100 MHz, CDCl$_3$): *S-p-tolyl 5-chlorobenzo[d]thiazole-2-carbothioate* **(16bae)**



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 3000 repetitions

OBSERVE  C13, 100.5425840
DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 115 minutes

AD_154_13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

Fig 6.9

^{1}H NMR (400 MHz, CDCl$_3$): *S-p-tolyl 5-(trifluoromethyl)benzo[d]thiazole-2-carbothioate* **(16cae)**



^{13}C NMR (100 MHz, CDCl$_3$): *S-p-tolyl 5-(trifluoromethyl)benzo[d]thiazole-2-carbothioate* **(16cae)**

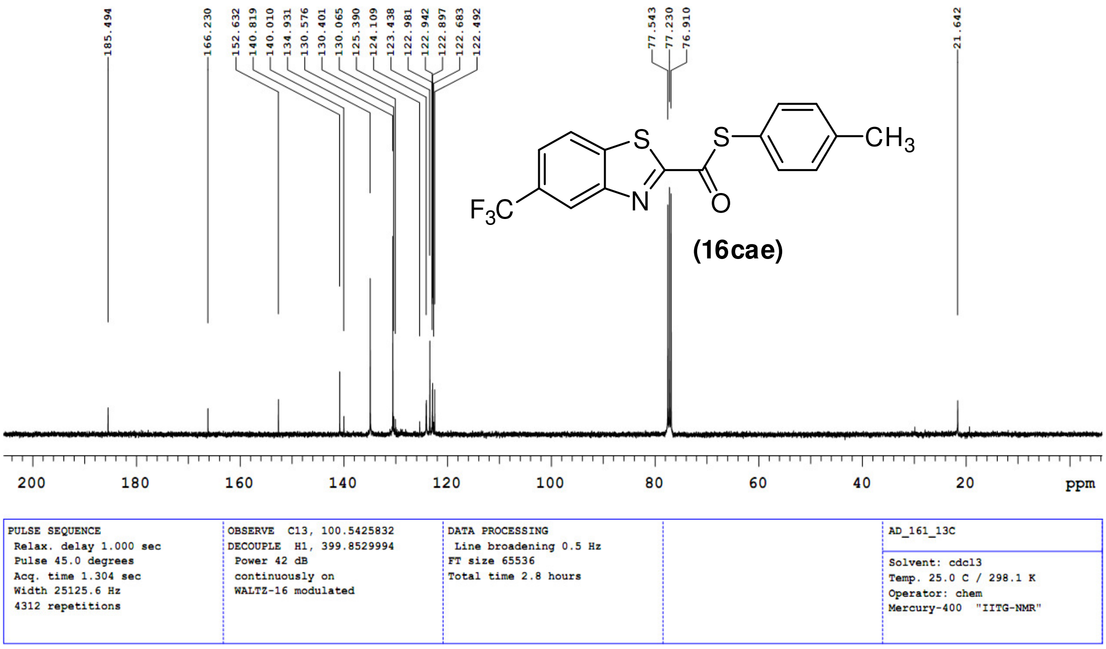


Fig 6.10

6.3 References

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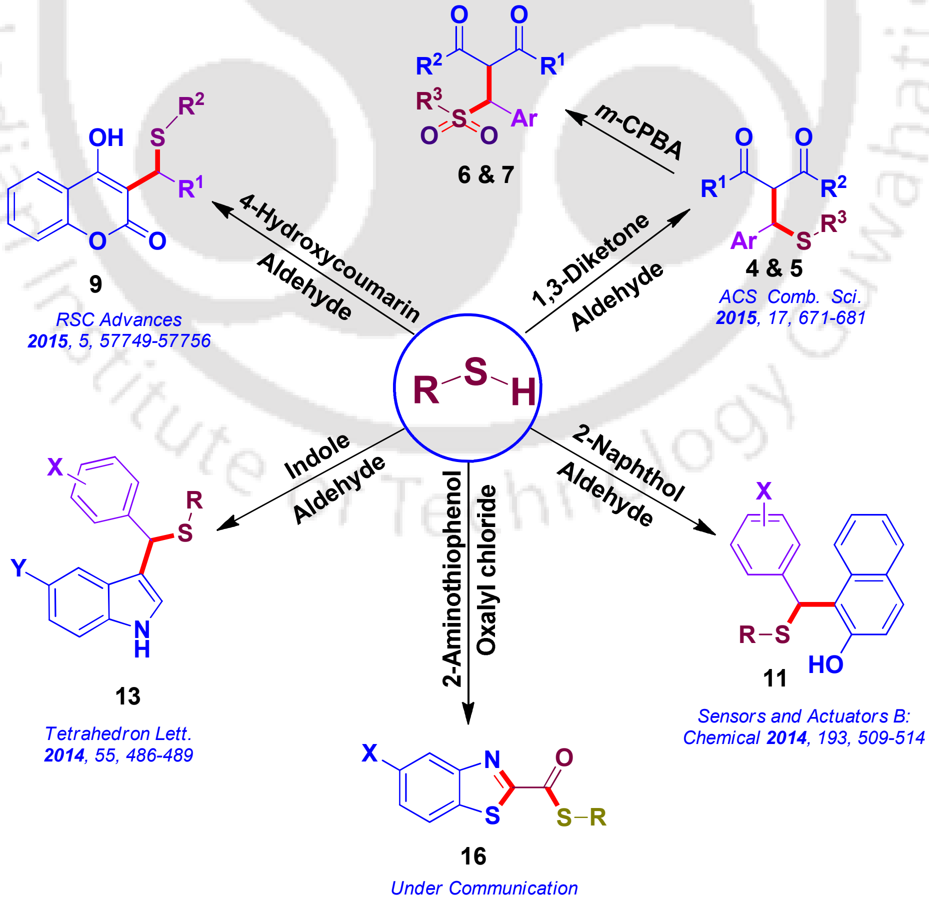
Conclusion and Future Perspective

In conclusion, the thesis described the synthesis of sulfur containing organic compounds such as highly substituted unsymmetrical sulfides starting from 1,3-dicarbonyl compounds using multicomponent reactions (MCRs) and their oxidation in to corresponding sulfones to find out effective antileishmanial agents. The synthesis of 4-hydroxy-3-thiomethylcoumarin derivatives, 1-[(alkylthio)(phenyl)-methyl] naphthalene-2-ol derivatives and 3-[(alkyl/arylthio)(aryl)-methyl]-1H-indole derivatives were reported by employing 4-hydroxycoumarin, 2-naphthol and indole using MCRs, respectively.

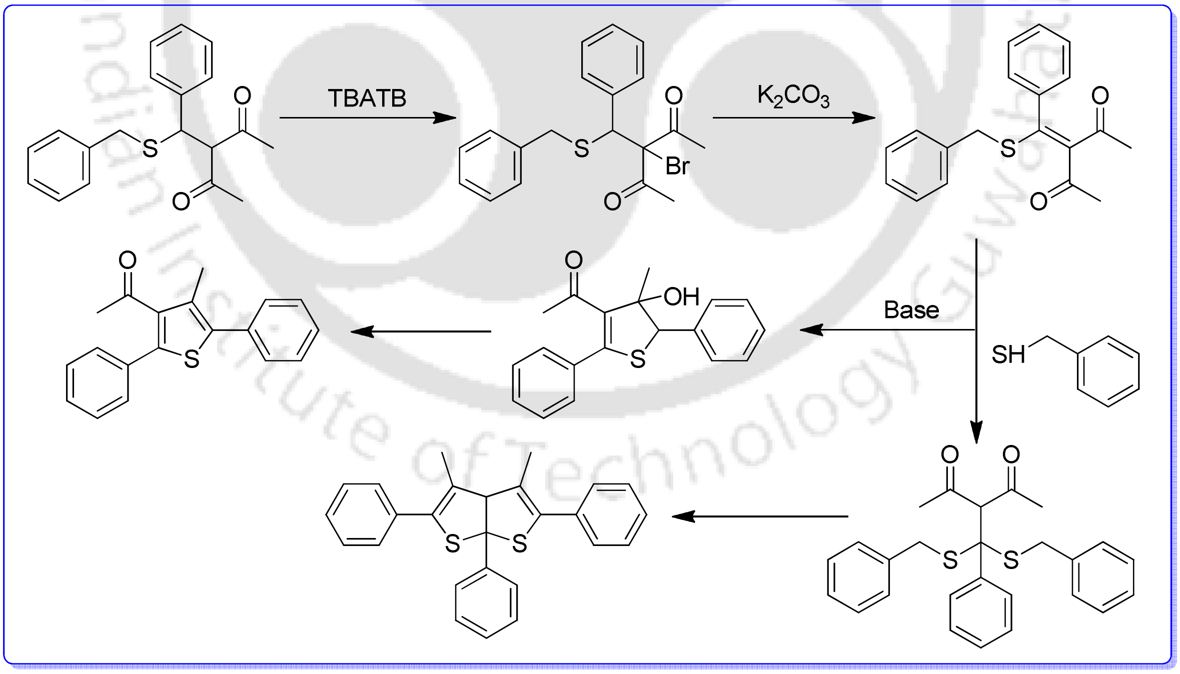
In addition, their derivatives were found to possess photo-physical properties that were utilized for the detection of transition metal ion for the detection and discrimination of Co^{2+} and Ni^{2+} ions by 3-((ethylthio)(pyridin-2-yl)methyl)-4-hydroxy-2H-chromen-2-one, detection of Hg^{2+} ions by 1-((ethylthio)(phenyl)methyl)naphthalen-2-ol and selective chemosensing activity for Hg^{2+} and Cu^{2+} by 3-(phenyl(phenylthio)methyl)-1H-indole. Moreover, the synthesis of functionalized S-alkyl/aryl benzothiazole-2-carbothioate was carried out and its derivatives were used for evaluation of antileishmanial activities.



Figure

We have shown the utility of thiols for the synthesis of important sulfur containing organic compounds based on multicomponent reactions (Figure).

In future, we would like to explore these synthesized sulfur based organic compounds for other transformations like Pummerer-type reactions, Truce-Smiles rearrangement, desulfitative reaction and as synthetic equivalents or synthons for formation of other new starting materials or complex molecules. Subsequently in future, the investigation will be carried out for the newly synthesized agents, further study on lead optimization through *in vitro* and *in vivo* model of visceral leishmaniasis could allow development of new anitleishmanial drug. Furthermore, due to their photophysical properties the synthesized compounds will be explored for practical utility. Additionally, our research group has already started utilization of these sulfur based organic compounds for the synthesis of unsymmetrical ethers, naphtho[2,1-b]furan and dihydronaphtho[2,1-b]furan derivatives. Moreover, we will try to achieve the synthesis of highly substituted heterocyclic moieties from these sulfide derivatives as shown in Scheme below.



Scheme

LIST OF AUTHOR'S PUBLICATIONS AND COMMUNICATIONS

1. *'New three-component reaction: Synthesis of 1-[(alkylthio)(phenyl)methyl]-naphthalene-2-ol catalyzed by bromodimethylsulfonium bromide (BDMS)'* Abu T. Khan,* Shahzad Ali, **Ajaz A. Dar** and Mohan Lal *Tetrahedron Lett.,* **2011,** *52,* 5157–5160.
2. *Hydrated ferric sulfate catalyzed synthesis of 3-[(alkyl/ arylthio)(aryl)methyl]-1H-indole derivatives through one-pot reaction* **Ajaz A. Dar**, Shahzad Ali, Abu T. Khan* *Tetrahedron Lett.,* **2014**, *55*, 486–489.
3. *Synthesis of Unsymmetrical Sulfides Catalyzed by n-Tetrabutylammonium tribromide: A Selective Fluorescence Probe for Mercury ion* **Ajaz A. Dar**, Shahzad Ali, Arindam Ghosh, Abu T. Khan,* Atul K. Dwivedi, Parameswar K. Iyer *Sensors & Actuators: B. Chemical* **2014**, *193*, 509–514.
4. *One-pot synthesis of functionalized 4-hydroxy-3-thiomethylcoumarins: detection and discrimination of Co^{2+} and Ni^{2+} ions* **Ajaz A. Dar**, Sameer Hussain, Debasish Dutta, Parameswar K. Iyer and Abu T. Khan* *RSC Adv.,* **2015**, *5*, 57749–57756.
5. *Synthesis of Unsymmetrical Sulfides and Their Oxidation to Sulfones to Discover Potent Antileishmanial Agents* **Ajaz A. Dar**, Nagasuresh Enjamuri, Md. Shadab, Nahid Ali and Abu T. Khan* *ACS Comb. Sci.* **2015**, *17,* 671–681.
6. *A direct approach for the expedient synthesis of Unsymmetrical Ethers through Bromodimethylsulfonium bromide (BDMS) mediated C-S bond cleavage of naphthalene-2-ol sulfides* Kobirul Islam, R. Sidick Basha, **Ajaz A. Dar**, Deb K. Das and Abu T. Khan* *RSC Adv.,* **2015**, *5*, 79759–79764.
7. *One-pot Synthesis and Evaluation of Antileishmanial Activities of Functionalized S-alkyl/aryl benzothiazole-2-carbothioate scaffold* **Ajaz A. Dar**, Md. Shadab, Nahid Ali and Abu T. Khan* (Communicated).
8. *Indole derived "turn-on" fluorometric probe for dual detection of Hg^{2+} and Cu^{2+} ions at nanomolar level* **Ajaz A. Dar**, Atul K. Dwivedi, Parameswar K. Iyer and Abu T. Khan* (will be communicated).