Exploration of β-Oxodithioesters Toward Facile Access to Heterocycles & Synthesis of 2-Oxypyrrole and Fused Pyrazolo-pyridine involving MCRs Strategy

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DOCTOR OF PHILOSOPHY

by

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Dedicated to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled “*Exploration of β-Oxodithioesters Toward Facile Access to Heterocycles & Synthesis of 2-Oxypyrrole and Fused Pyrazolo-pyridine involving MCRs Strategy”* 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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Professor of Chemistry

CERTIFICATE

This is to certify that Mr. Arindam Ghosh has been working in my research group since 27th December 2010 as a regular Institute Research Fellow registered for Ph. D. programme. I am forwarding his thesis entitled "*Exploration of β-Oxodithioesters Toward Facile Access to Heterocycles & Synthesis of 2-Oxypyrrole and Fused Pyrazolo-pyridine involving MCRs Strategy*" 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. Arindam Ghosh has completed his Ph. D. Thesis work from December, 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 "*Exploration of β-Oxodithioesters Toward Facile Access to Heterocycles & Synthesis of 2-Oxypyrrole and Fused Pyrazolo-pyridine involving MCRs Strategy*" 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.

IIT Guwahati
January 28, 2016

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

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Arindam Ghosh

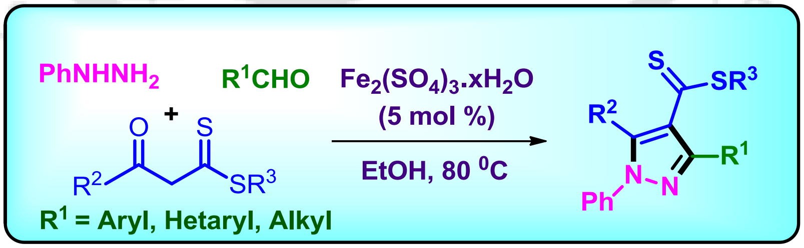
SUMMARY OF THE THESIS

The content of the thesis entitled "**Exploration of *β*-Oxodithioesters Toward Facile Access to Heterocycles & Synthesis of 2-Oxypyrrole and Fused Pyrazolo-pyridine Involving MCRs Strategy**" has been divided into two parts as **Part A** and **Part B**. **Part A** of the thesis comprises four chapters such as Chapter 1, Chapter 2, Chapter 3 and Chapter 4. Likewise, **Part B** of the dissertation contains three chapters namely Chapter 1, Chapter 2 and Chapter 3. Chapter 1 of each part of the dissertation demonstrates a brief review of the work on the relevant topics and the other chapters of thesis elaborate successful results and discussion along with experimental section.

Part A

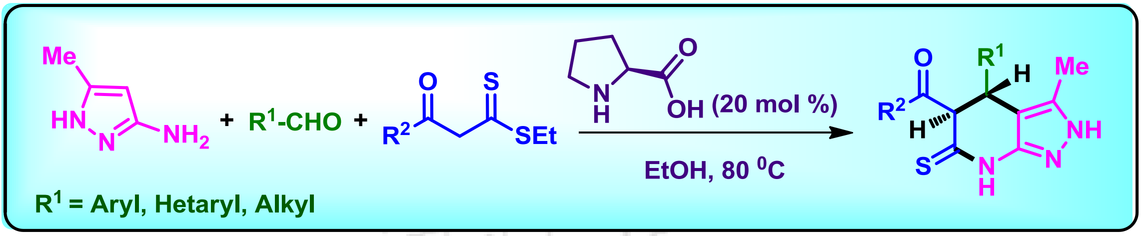
Chapter 1 describes a brief literature survey for the preparation and functionalization of *β*-oxodithioesters. In addition, brief review on exploration of *β*-oxodithioesters for the synthesis of various heterocycles is also highlighted in this chapter.

Chapter 2 demonstrates an efficient method for the synthesis of substituted-1*H*-pyrazole-4-carbodithioates by employing one-pot three-component reaction of phenyl hydrazine, aldehyde and alkyl-3-oxo-3-arylpropanedithioate in presence of 5 mol % ferric sulfate [$Fe_2(SO_4)_3 \cdot xH_2O$] at 80 ^{0}C. Mechanistic investigations as well as variability of all the components in this transformation are addressed in this section. Mild reaction conditions, good yields and shorter reaction time are some of the salient features of the present protocol.

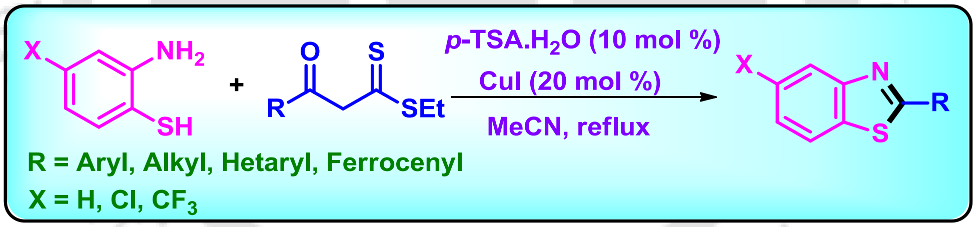


Chapter 3 illustrates a simple and efficient L-proline catalyzed synthesis of tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivatives through sequential one-pot three-component reaction of 3-amino-5-methyl-pyrazole, aldehydes, and ethyl-3-oxo-3-arylpropanedithioate in ethanol under reflux condition. The advantages of the present protocol are: simple reaction procedure, shorter reaction time, good to excellent yields, exclusion of chromatographic

separation, efficiency of producing three new bonds (one C-C and two C-N) and two stereocenter in a single reaction.



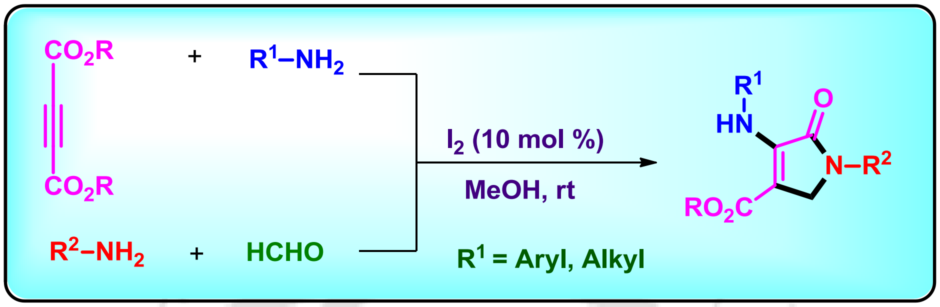
Chapter 4 describes the synthesis and mechanistic aspects of 2-substituted benzo[*d*]thiazole derivatives. An efficient and straightforward one-pot condensation reaction of 2-aminothiophenols and *β*-oxodithioesters is developed for the synthesis of 2-substituted benzo[*d*]thiazole derivatives in presence of combined catalyst *p*-TSA.H_2O-CuI in acetonitrile under reflux condition. In addition, these 2-substituted benzothiazoles can be further utilized as expedient synthons in *ortho*-selective C-H functionalization reactions. Simple experimental procedures, good to excellent yields, mild reaction conditions and applicable on a broad range of substrates are few of the salient features of the presented protocol.



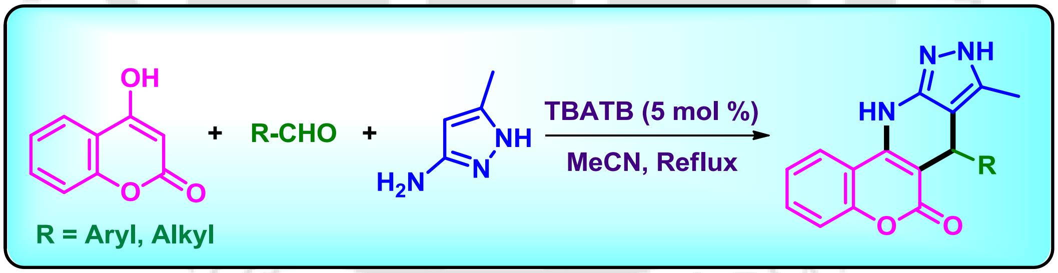
Part B

Chapter 1 highlights a brief literature survey on the multicomponent reactions and its importance in organic synthesis. Additionally, a brief literature survey of methods for the preparation of 2-oxypyrrole and fused pyrazole-pyridine derivatives and its importance as well as synthetic utility are presented in this chapter.

Chapter 2 demonstrates a simple and efficient molecular iodine catalysed synthesis of multi-functionalized dihydro-2-oxypyrrole from dialkylacetylene dicarboxylate, amines and formaldehyde through one-pot four-component domino reaction in methanol at room temperature. The reaction conditions are simple and transformation is widely applicable on a broad range of substrates. The products are easily isolable in good to excellent yields without aqueous work-up, column chromatographic separation and involvement of expensive catalyst.



Chapter 3 elaborates the synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-e] pyridin-6(7*H*)-ones through one-pot three-component reaction of 4-hydroxycoumarin, aldehydes and 3-amino-5-methyl-pyrazole in acetonitrile using 5 mol % TBATB as catalyst under reflux condition. The product formation undergoes through tandem Knoevenagel-Michael reaction followed by concomitant cyclization. Simple reaction procedure, short reaction time, good yields, avoidance of aqueous work-up and column chromatographic separation are some of the salient features of the present protocol.



On the whole, this thesis illustrates some new and efficient synthetic methodologies for the preparation of pyrazoles, pyrazolo-pyridines, benzothiazoles and dihydro-2-oxypyrroles. Because of the advantages of these methodologies over the existing ones, it is believed that these methodologies might be applicable on a target oriented synthesis and some of the synthesized compounds may exhibits pharmacological activity, which might be useful in near future.

CONTENTS

Part A

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam during the period from 27st December, 2010 to 28th January, 2016 as a Ph.D. student under the supervision of Prof. Abu T. Khan and Prof. Bhisma. K. Patel.

The analytical samples were routinely dried *in vacuo* at 50 °C for 8 hours. In TLC experiments, silica gel G (SRL) or silica gels 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 Buechi R-114V instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Varian 400 spectrometer and Bruker DRX 600 MHz NMR Spectrometer TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^1H NMR Spectra are reported in the order: multiplicity, no of protons and coupling constant (J value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet) and dd (doublet of doublet). HRMS 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 Mo$K\alpha$ radiation (λ = 0.71073 Å) at 298 K.

ABBREVIATIONS

Ac	acetyl
BDMS	bromodimethylsulfonium bromide
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	Ammonium cerium (IV) nitrate
CCDC	cambridge crystallographic data centre
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAD	dimethyl acetylene dicarboxylate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EWG	electron withdrowing groups
IR	infrared
MCR	multicomponent reaction
M.p.	melting point
MS	molecular sieves
MW	microwave
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid program
Ph	phenyl
PMB	*p*-methoxy benzyl
ppm	parts per million
Pr	propyl
p-TSA	*p*-toluenesulfonic acid
rt	room temperature
TBATB	*n*-tetrabutylammonium tribromide

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
XRD	x-ray diffraction

1.1 Introduction

One of the most exciting challenges for organic chemists is the development of new and improved methods with high atom economy, and is of great impact in modern synthetic chemistry. There is an increasing demand for selective, efficient and environmentally friendly chemical processes in academic as well as in industry. The efficacy of a target synthesis directly depends on the effectiveness of all the methodologies involved.

The processes that involve the construction and cleavage of multiple chemical bonds represent this target. Due to increasing economic and ecological pressure, another major challenge is to provide maximum structural diversity and complexity with a minimum number of synthetic steps.

The synthesis of highly functionalized bioactive heterocycles from an advanced starting material using one-pot reactions has gained considerable interest. The chemistry of *β*-oxodithioesters has gained attention of synthetic chemists owing to their varied intrinsic chemical properties and is exploited in various functional group transformations and a wide range of applications in organic synthesis and industry. For instance, *β*-oxodithioesters synthons are streamline as parallel to the forefront of 1,3-dicarbonyl chemistry. In a few decades, these synthons are extensively utilized in the synthesis of various heterocycles where the sulfur moiety is present in the precursor. The chemical synthesis and application of *β*-ketoesters have been known for many decades and are explored in reviews and in several books.[1] *β*-ketoesters act as building block for the facile access of several different heterocycles. Recently, *β*-oxodithioesters is also attracting attention as a key intermediate for the potentially rapid access of various important bioactive frameworks such as chromene-2-thione, dihydropyrimidone, furan, indole, isoxazole, pyrrazole, pyrrole, quinoline, thiophene, thiopyran and many more.[2] In addition, *β*-oxodithioesters also acts as ligand for complex formation with metals as well as an analytical reagent due to their accessible enolic form.[3] The electronic configuration of the sulfur atom in *β*-oxodithioesters possess a vacant d-orbital, which access distinctive feature from *β*-ketoesters in terms of synthetic tactics and its versatile organic transformations.

For the past two decades the emphasis on and applications of *β*-oxodithioesters has achieved immense development in theoretical and synthetic chemistry due to its significant scaffold generation. The reactivity and applications of *β*-oxodithioesters framework is mainly due to its two electrophilic and three nucleophilic centres, making it a very useful and versatile synthons in synthetic organic chemistry. Although *β*-oxodithioesters have differential reactivity and numerous applications in organic synthesis, only a little has been done so far.

1.2 Reactive sites of *β*-oxodithioesters

The reactant profile of the *β*-oxodithioester can be attributed to the three nucleophilic and two electrophilic centres (Figure 1). Two nucleophilic centres present on the carbonyl and thiocarbonyl groups are oxygen and sulfur moiety. The third one is present on the carbon atom, bounded by the carbonyl and the thiocarbonyl group. The two electrophilic centers are present on two different carbon atoms bearing carbonyl and thiocarbonyl groups. Owing to these reacting sites, it reacts with different dielectrophilic reagents depending on the molecular structure and nature of the dielectrophile and the reaction conditions. And hence these *β*-oxodithioesters are extensively utilized as synthons in the synthesis of various heterocycles where the sulfur moiety is present in the precursor.

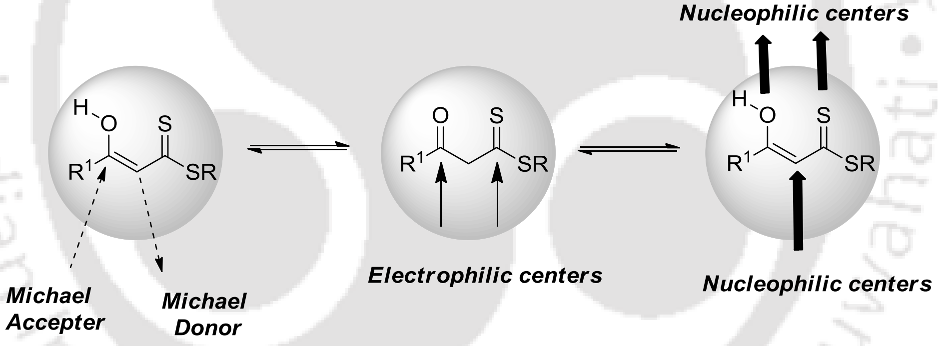
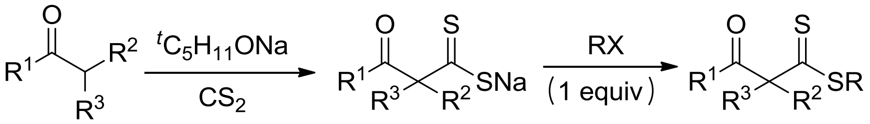


Figure 1. Reactive sites of *β*-oxodithioesters

1.3 Synthesis of *β*-oxodithioesters

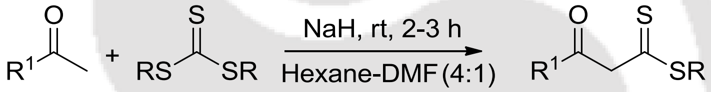
Study on *β*-oxodithioesters was pioneered by Beer and co-workers in 1968. A new dynamic field was opened up in synthetic organic chemistry and assumed as a parallel to the forefront of 1,3-dicarbonyl synthons.[4] Thuillier *et al.*[5] first reported the synthesis of *β*-oxodithioester from the reaction of an active methylene compound and carbon disulfide (CS_2). The process involved the reaction of an enolizable ketone with a strong base sodium *tert*-pentoxide to generate the enolate anion which further reacts with CS_2 to give the sodium salt of dithiocarboxylic acid, subsequently alkylated to produce the corresponding *β*-oxodithioester (Scheme 1). Other active methylene compounds such as acetyl acetone, benzoyl acetone, diethyl malonate, dibenzoyl methane, methyl cyanoacetate and malononitrile also reacted similarly to provide the corresponding functionalized *β*-oxodithioester.



R = Me, Et, Bn
R^1 = Me, Et, *n*-Pr, ^{i}Pr, Bn
R^2 = H, Me
R^3 = H, Me, Et, *n*-Pr, ^{i}Pr, *n*-Bu, C_6H_5

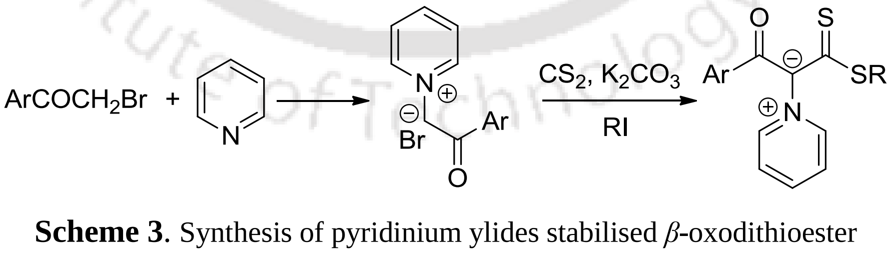
Scheme 1. Synthesis of *β*-oxodithioesters from active methylene compound

From literature survey, numerous structure of *β*-oxodithioesters was achieved through various reaction, and also a general method was described by Junjappa and co-workers.[6] The method described active methylene ketones reacted with dialkyl trithiocarbonate in the presence of NaH in DMF-hexane (1:4) mixture at room temperature (Scheme 2).



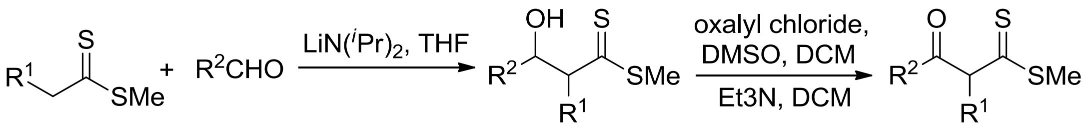
Scheme 2. Synthesis of *β*-oxodithioester from dialkyl trithiocarbonate

Builla, Gálvez, Cuadro, Florencio and Blanco[7] devised an improved procedure for the synthesis of pyridine group substituted *β*-oxodithioester. Pyridinium ylides stabilized, *β*-oxodithioester can be easily prepared by two-step procedures (Scheme 3). First step is the reaction between 2-haloketone and pyridine to furnish 2-oxo-2-arylethyl pyridinium salt that reacts with CS_2 and alkyl iodide in presence of a base like K_2CO_3 to produce *α*-substituted pyridinium salt of *β*-oxodithioester.



Scheme 3. Synthesis of pyridinium ylides stabilised *β*-oxodithioester

Beslin and Houtteville synthesized *β*-oxodithioesters from dithioester through regioselective condensation of dithioester and aldehyde via oxidation of the intermediate *β*-hydroxydithioester (Scheme 4).[8]

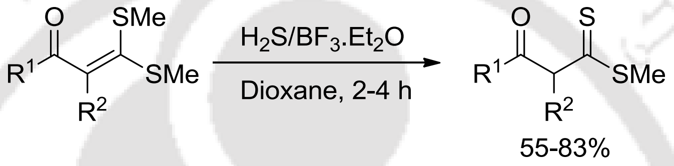


R^1 = Me, Et, Allyl, $(CH_2)_4Me$, $CH_2C_6H_5$, $CH_2SC_6H_5$, C_6H_5

R^2 = Et, *n*-Pr, $CH_2C_6H_5$

Scheme 4. Synthesis of *β*-oxodithioesters from dithioester

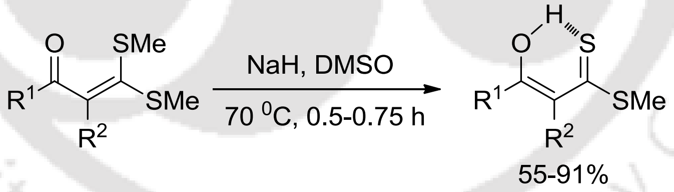
Asokan *et al.*[9] have also accomplished a suitable approach to synthesize *β*-oxodithioesters from *α*-oxoketene-S,S-dithioacetals through sulfo-hydrolysis of the *α*-oxoketene-S,S-dithioacetals on treatment with hydrogen sulfide catalyzed by boron trifluoride etherate under refluxing condition in presence of dioxane solvent (Scheme 5).



R^1 = CH_3, C_6H_5, $4ClC_6H_4$, $4BrC_6H_4$, $4CH_3C_6H_4$, $4CH_3OC_6H_4$, 2-Napthyl, 2-Thienyl

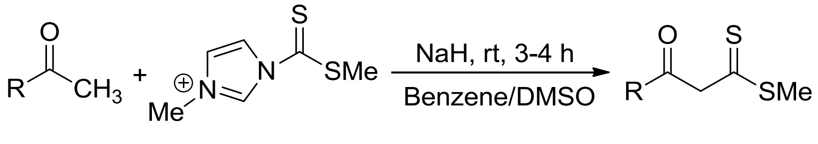
Scheme 5. Sulfo-hydrolysis of *α*-oxoketene-S,S-dithioacetals

Asokan and co-workers have also synthesized *β*-oxodithioester from base induced S-demethylation reaction of *α*-Oxoketene-S,S-dithioacetals with sodium salt of dimethyl sulfoxide (Scheme 6).[10]



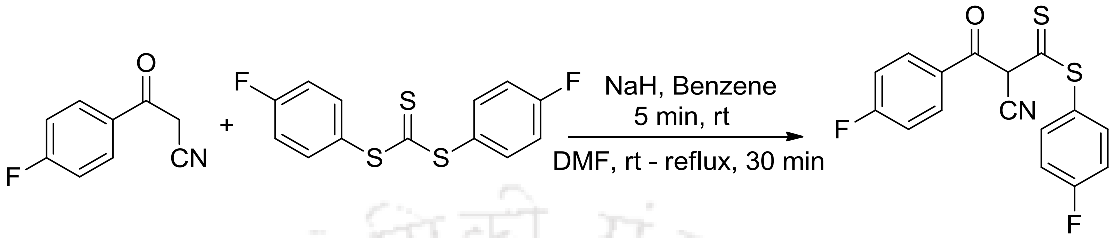
Scheme 6. Synthesis of *β*-oxodithioester from *α*-oxoketene-S,S-dithioacetals

Junjappa *et al.*[11] have also utilized 3-methylimidazolium-1-carbodithioic carbodithioic acid methyl ester instead of dimethyl trithiocarbonate along with active methylene compounds for the facile access of *β*-oxodithioesters (Scheme 7).



Scheme 7. Synthesis of *β*-oxodithioester

Smith *et al.* demonstrated the synthesis of *α*-cyano- *β*-oxodithioester and used it for the preparation of thiophene substituted aminopyrimidine compounds, polo-like kinase 1 inhibitors and was exploit it for the treatment of cancer (Scheme 8).[12]

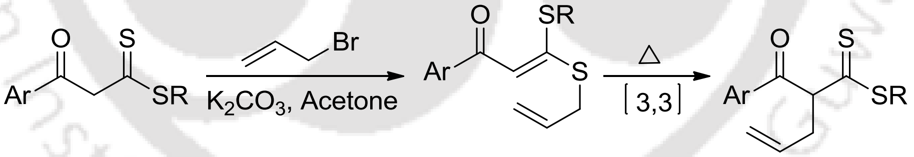


Scheme 8. Synthesis of *β*-oxodithioester from diaryl trithiocarbonate

1.4 Functionalization of *β*-oxodithioesters

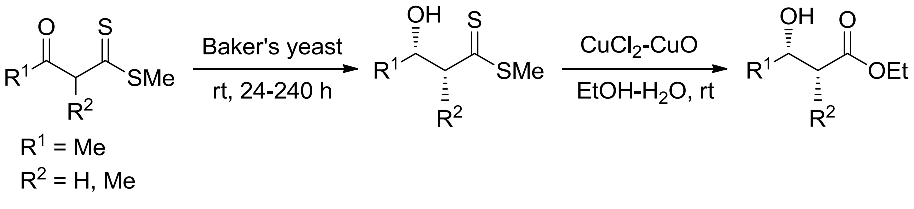
With significant scaffold generation from both theoretical and synthetic points of view, several research groups have accomplished functionalization of *β*-oxodithioester for different purposes. In this section only the functionalization part is outlined. Junjappa *et al.* have demonstrated the synthesis and utilization of structurally similar *α*-allyl-*β*-oxodithioester.

They synthesized *α*-allylation product via a two-step procedure. In the first step *β*-oxodithioester reacted with allyl bromide in the presence of K_2CO_3 in acetone to provide S-alkylated product of *β*-oxodithioester, which on heating underwent a [3+3] thio-Claisen rearrangement to produce *α*-allylation product (Scheme 9).[13]



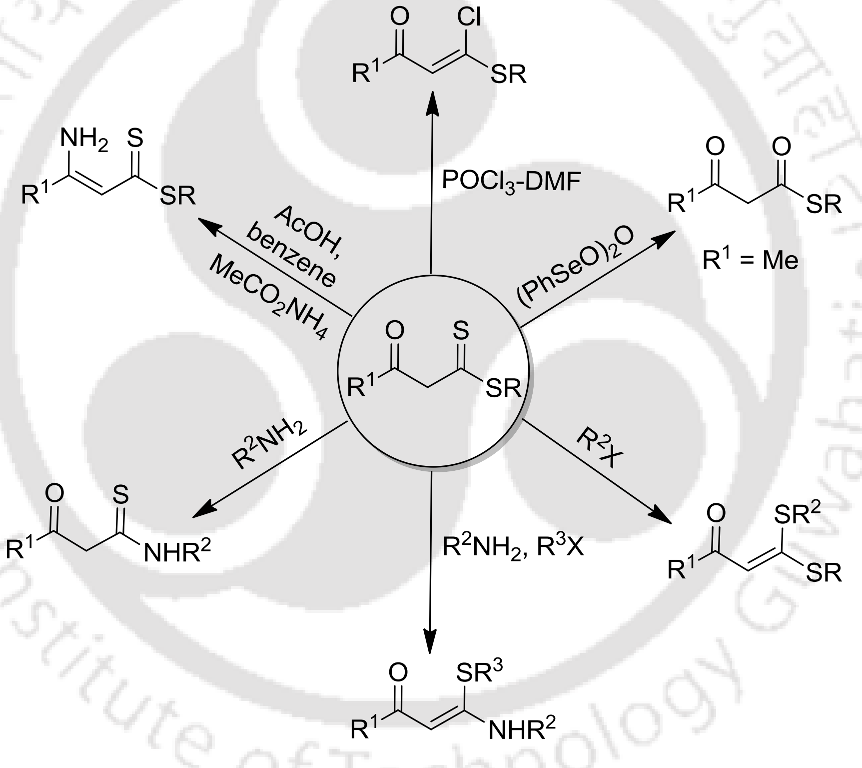
Scheme 9. Synthesis of α-allyl-*β*-oxodithioester

Itoh and co-workers[14] have reported asymmetric reduction of the keto group of *β*-oxodithioester by employing baker’s yeast as catalyst where threo-isomer was obtained as the exclusive product, which on treatment with copper chloride-copper oxide catalyst in presence of ethanol-water mixture as a solvent leads to the formation of *β*-hydroxyester with high optical purity (Scheme 10).



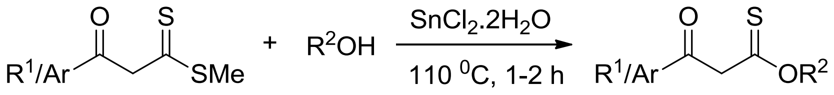
Scheme 10. Synthesis of *β*-hydroxyester from *β*-oxodithioester

Different but familiar and valuable building blocks like *α*-oxoketene-S,S-acetals, *α*-oxoketene-N,S-acetals and *β*-oxothioamides can be easily made from *β*-oxodithioester, also may act as synthons for various organic transformation. *α*-Allylation products of substituted 1,3-diketone compounds are well known as valuable intermediates in organic synthesis (Scheme 11). Vigante *et al.* first synthesized *β*-aminodithiocrotonate by the reaction of *β*-oxodithioester with ammonium acetate in presence of acetic acid.[15] Labiad and villemin[16] have reported the selective conversion of the thiocarbonyl group to carbonyl group using benzeneseleninic anhydride (Scheme 11). Asokan *et al.* described the reaction of *β*-oxodithioester with Vielsmayer–Haack reagent prepared from $POCl_3$-DMF to furnish chlorinated product (Scheme 11).[17]



Scheme 11. Synthesis of different synthons from *β*-oxodithioester

Devi *et al.* have reported the *trans*-esterification reaction of *β*-oxodithioesters catalyzed by stannous chloride under solvent-free condition with different primary, secondary and tertiary alcohols, where the rate of the esterification reaction proceeds with order of primary > secondary > tertiary (Scheme 12).[18]



Ar = C_6H_5, $4ClC_6H_4$, $4MeC_6H_4$, $4MeOC_6H_4$, 2-Thienyl

R^1 = Me

R^2 = ^{i}Pr, *n*-Bu, ^{t}Bu, $CH_2C_6H_5$

Scheme 12. *Trans*-esterification reaction of *β*-oxodithioesters

1.5 Synthesis of heterocycles using *β*-oxodithioesters

Heterocycles are important class of compound and more than half of organic compounds are heterocycles. They have widespread applications in pharmaceuticals and agrochemicals as well as materials sciences. Many natural drugs such as atropine, emetine, papaverine, quinine, reserpine and theophylline are heterocycles. Synthetic drugs such as barbiturates, chlorpromazine, methotrexate, isoniazid and many more are also heterocycles. Moreover for developed nations, synthesis of heterocyles is much more valuable due to their biological and industrial importance.

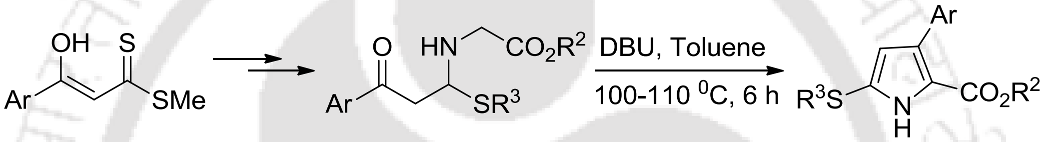
Various methods have been developed for the synthesis of heterocycles having diverse physical, chemical and biological properties from readily available as well as structurally modified starting material. Starting material containing both electrophilic and nucleophilic centers have great potential in developing new reaction pathways for the rapid access of different heterocycles. *β*-Oxodithioesters is one of them; a thio-analogue of the normal *β*-ketoester contains two electrophilic and three nucleophilic centers.

1.5.1. Synthesis of heterocycles having one heteroatom

Heterocycles having one heteroatom are important class of organic molecules are integral part of natural products and have immense potentiality in pharmaceuticals. Numerous synthetic strategies have been developed to synthesize these molecules over the years. Nitrogen, oxygen and sulfur are found to be the most commonly present heteroatom, however heterocycles containing other polyvalent elements such as arsenic, boron, phosphorous, selenium and silicon are also well-known in recent years. But straightforward annulation reactions onto the heterocyclic framework from acyclic precursors is still challenging. Few exciting examples for the synthesis of heterocycles employing *β*-oxodithioesters have been recent reported by several research groups will be presented in this chapter.

Pyrrole and its derivatives are the important structural motifs found in various natural and unnatural products. Functionalized pyrroles rings are present in a variety of alkaloids having wide biological activities.[19] Common naturally occurring molecules containing pyrrole subunit include bile pigments like bilirubin and biliverdin, chlorophyll, chlorins, porphyrins of heme, vitamin B12 and many more. As per literature survey various methods are available for pyrrole synthesis like Hantzsch synthesis, Knorr synthesis, Pall-Knorr synthesis and all the processes involve the reaction of dicarbonyl compounds and an amine.

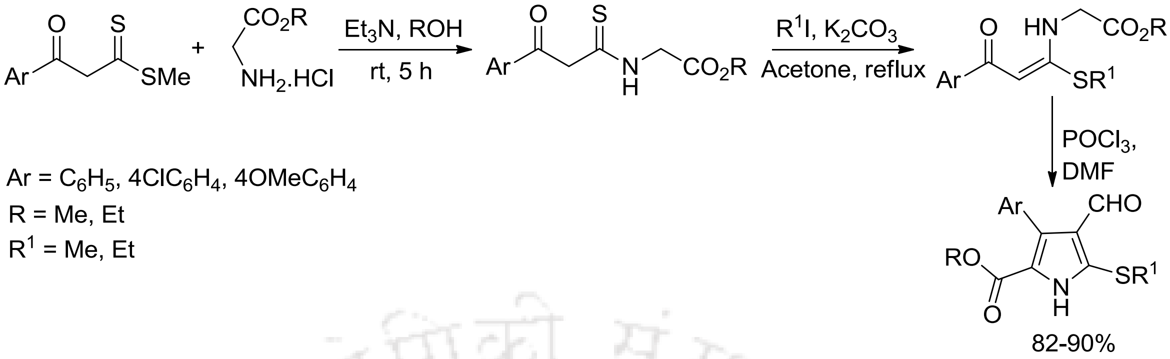
Asokan and Mathew[20] have reported the synthesis of trisubutituted pyrrole derivative from the intermediate N,S-acetal derived from *β*-oxodithioesters with the reaction of non-nucleophilic base DBU in refluxing toluene (Scheme 13).



Ar = $4ClC_6H_4$, R^2 = Me, R^3 = Et (34%)
Ar = C_6H_5, R^2 = Et, R^3 = Et (45%)
Ar = $4ClC_6H_4$, R^2 = Et, R^3 = Me (32%)
Ar = $4BrC_6H_4$, R^2 = Et, R^3 = Et (28%)
Ar = C_6H_5,, R^2 = Et, R^3 = Et (24%)

Scheme 13. Synthesis of trisubstituted pyrrole derivatives

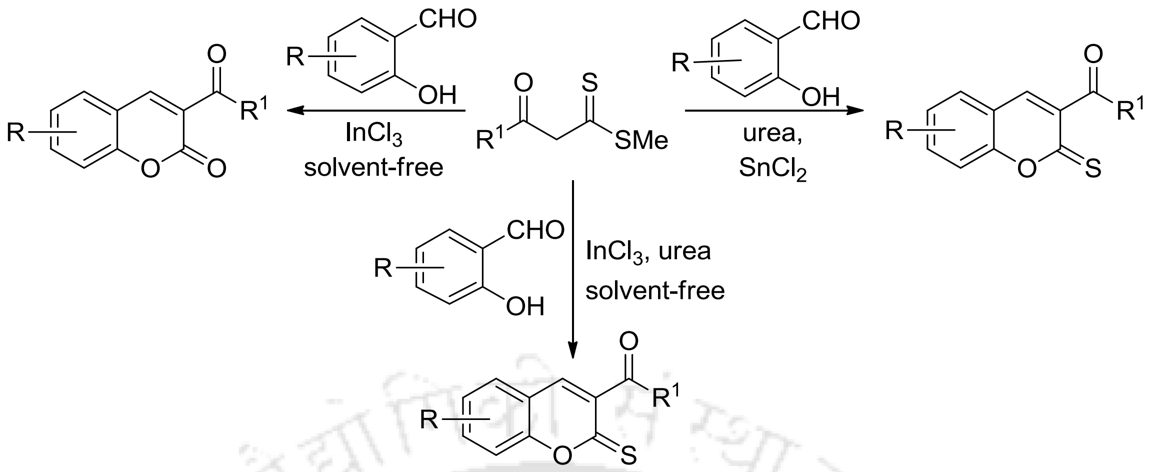
Asokan *et al.* have also discussed a simple and straightforward method for the synthesis of tetrasubstituted pyrrole derivatives from *β*-oxodithioesters.[21] The method follows a three step procedure where in the first step ethyl glycinate reacts with *β*-oxodithioesters to provide the corresponding thioamide in presence of Et_3N under refluxing condition. Subsequent treatment with K_2CO_3 and alkyl iodide in acetone undergoes facile alkylation to produce *α*-oxoketene-N,S-acetal. Finally the intermediate undergoes intramolecular cyclization in presence of Vilsmeier-Haack reagent derived from $POCl_3$/DMF to afford highly substituted pyrroles in excellent yields (Scheme 14).



Scheme 14. Synthesis of tertasubstituted pyrrole derivatives

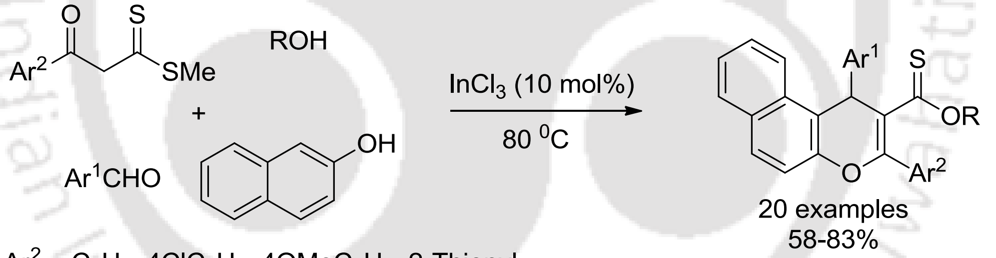
Coumarins are oxygen-containing heterocycles widely distributed in nature. Their derivatives are found in many natural products and considered as privileged structures in pharmaceutical as well as agrochemical industries. Some of the coumarin derivatives possess a wide range of biomedical application such as anti-tumor, anti-coagulant, anti-microbial and anti-inflammatory activities.[22] Moreover, coumarin derivatives are extensively used as chemosensors due to their excellent chromogenic and fluorogenic dye formation. Singh and Devi[23a] synthesized substituted 2H-chromene-2-thione from *β*-oxodithioesters and salicylaldehyde derivatives employing urea and stannous chloride as a catalyst. It was observed that in presence of urea the yield of the reaction increased and in its absence a moderate yields was obtained. The role of urea in these transformations is not very clear. Probably, urea is expected to be a promoter in the reaction.

Later on, Singh *et al.* also described $InCl_3$ catalyzed and solvent free synthesis of substituted chromene-2-thione derivatives.[23b] The interesting features of the protocol is the product formation directly depends on the promoter urea i.e., exclusively, chromene-2-thione derivatives formation occurs in presence of urea but in the absence of urea, coumarin derivatives are the major product (Scheme 15).



Scheme 15. Synthesis of coumarin derivatives

Samai, Nandi and Singh[24] have described a four component reaction of β-oxodithioester, aromatic aldehyde, β-naphthol and primary alcohols for the formation of 4H-benzo[*f*]chromenes in the presence of $InCl_3$ catalyst. The product formation proceeds via a domino Knoevenagel condensation followed by Michael addition, intra-molecular cyclization and *trans*-esterification (Scheme 16).



$Ar^2 = C_6H_5$, $4ClC_6H_4$, $4OMeC_6H_4$, 2-Thienyl

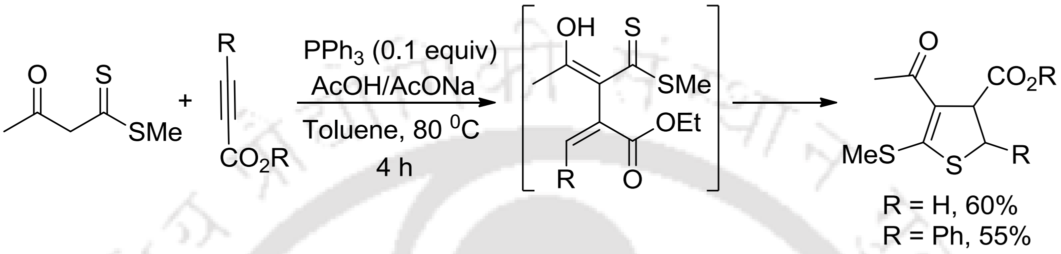
$Ar^1 = C_6H_5$, $2ClC_6H_4$, $3ClC_6H_4$, $4FC_6H_4$, $4NO_2C_6H_4$, $4MeC_6H_4$, $4MeOC_6H_4$, $4OHC_6H_4$

R= Me, Et, ^{i}Pr, *n*-Bu

Scheme 16. Synthesis of 4H-benzo[*f*]chromenes

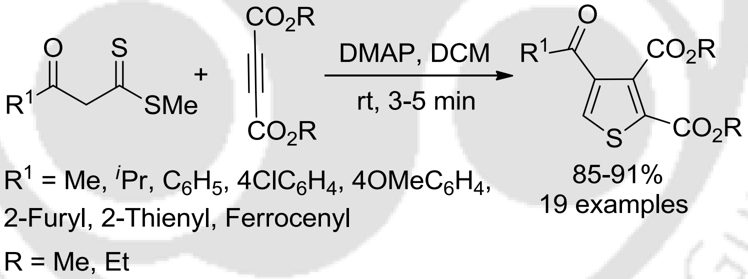
Thiophene derivatives are widely distributed in nature and have emerged as an important class of five-member heterocycles.[25] Some of the thiophene derivatives are top-selling marketed drugs such as articaine, clopidogrel, plavix, patrine, raloxifene, spiriva and zileuton. Because of their specific electronic properties, thiophene derivatives also possess some industrial applications in design and synthesis of several organic materials such as field effect transistors, liquid crystals, molecular wires, organic light-emitting diodes, organic semiconductors and organic solar cells.

Hanedanian and co-workers[26] demonstrated a convenient and efficient synthesis of dihydrothiophene from *β*-oxodithioester and substituted ethylpropiolate in presence of Et_3N, acetic acid/sodium acetate in toluene at 80 ^{0}C (Scheme 17). It was expected that the reaction undergoes via the *α*-carbon addition to generate an adduct driven by PPh_3, followed by cyclization of the resulting adduct to generate dihydrothiophene in reasonable yields.



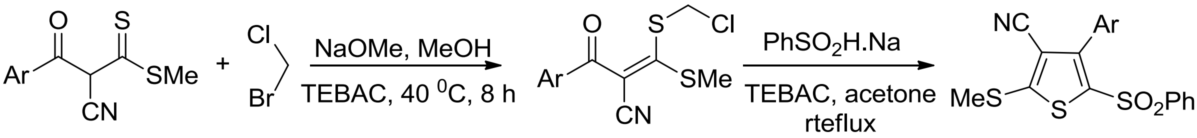
Scheme 17. Synthesis of dihydrothiophene

Singh *et al.* have described an efficient synthetic protocol for the synthesis of substituted thiophene derivatives using *β*-oxodithioester and dialkyl acetylenedicarboxylate. The reaction proceeded with 1-2 (C-S) and 3-4 (C-C) bond connections catalyzed by DMAP in DCM solvent (Scheme 18).[27]



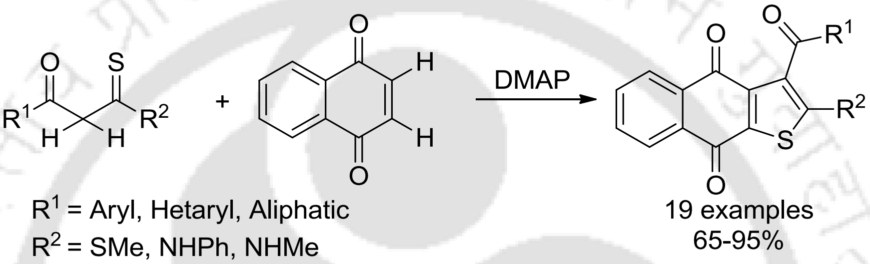
Scheme 18. Synthesis of trisubstituted thiophenes

Forgber and co-workers[28] reported the synthesis of a highly functionalized thiophene ring from *α*-cyanosubstituted-*β*-oxodithioester and bromochloroethane. The reaction proceeded via chloromethylation of *β*-oxodithioester with bromochloroethane in the presence of sodium methoxide in methanol and TEBAC provided the *α*-oxoketene dithioacetal that underwent substitution reaction followed by condensation after treatment with phenyl sulfinic acid in presence of acetone under refluxing condition and provided the highly functionalized thiophene ring (Scheme 19).



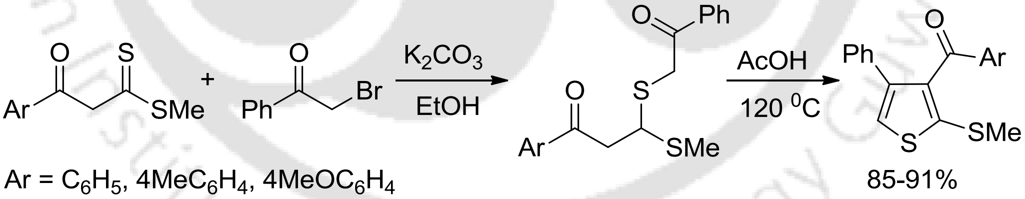
Scheme 19. Synthesis of thiophenes

Singh *et al.* have reported the synthesis of naphtho[2,3-*b*]thiophenes *via* [3+2] oxidative heteroannulation reaction of *α*-enolicdithioesters and *β*-oxothioamides with 1,4-naphthoquinone under solvent-free reaction condition at room temperature (Scheme 20).[29]



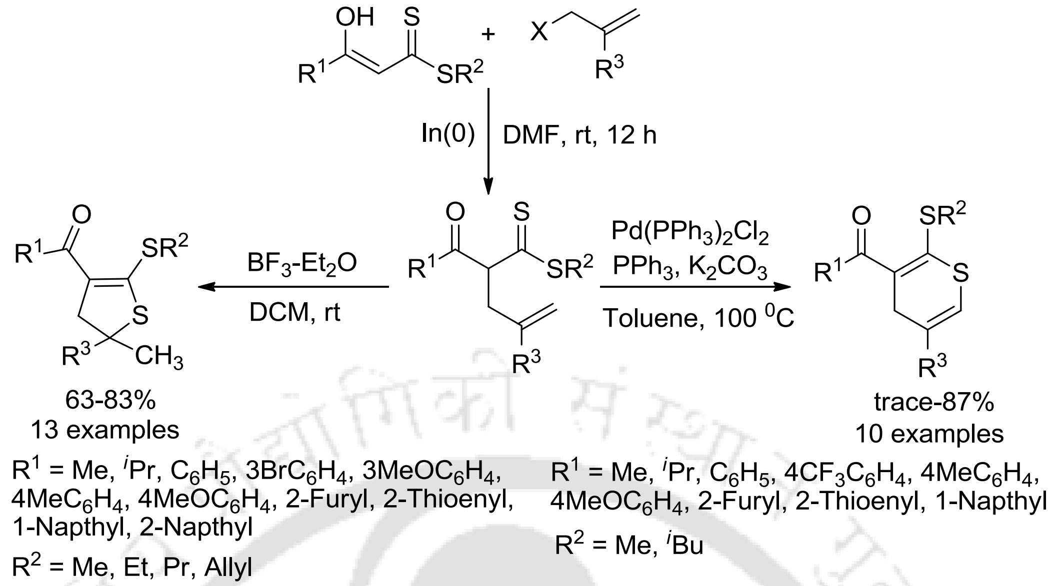
Scheme 20. Synthesis of naphtho[2,3-*b*]thiophenes

Asokan and co-workers[30] described the preparation of thiophenes via the alkylation of *β*-oxodithioester with *α*-haloketones using K_2CO_3 in acetone solvent to afford *α*-oxoketene-S,S-dithioacetal as an intermediate, which after treatment with acetic acid under refluxing condition produced the desired thiophene molecules (Scheme 21).



Scheme 21. Synthesis of substituted thiophenes

Singh *et al.* have developed an efficient and convergent route for the synthesis of 4H-thiopyran and 4,5-dihydrothiophene frameworks *via* regioselective intramolecular C-S fusion of *α*-allyl-*β*-oxodithioesters using two different catalytic systems. In presence of Palladium catalyst, the C_δ-H bond of the allyl group activates and undergoes intra-molecular C_δ-S coupling to provide six-membered thiopyran skeletons exclusively. Alternatively, in presence of BF_3-Et_2O catalyst, the allylic double bond of the same substrate has been activated through C_γ-S cyclization leading to the formation of five-membered dihydrothiophene skeletons (Scheme 22).[31]



63-83%
13 examples

trace-87%
10 examples

R^1 = Me, ^{i}Pr, C_6H_5, $3BrC_6H_4$, $3MeOC_6H_4$, $4MeC_6H_4$, $4MeOC_6H_4$, 2-Furyl, 2-Thioenyl, 1-Napthyl, 2-Napthyl

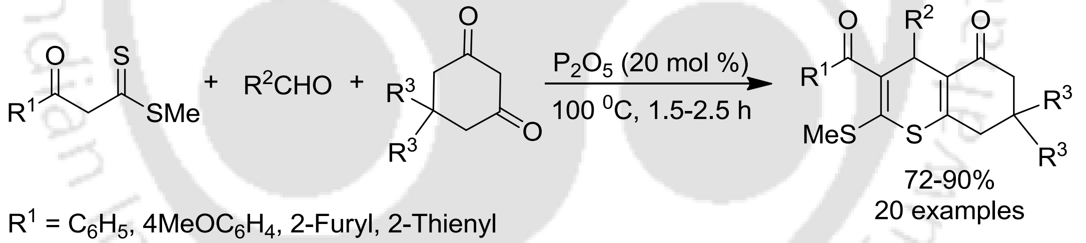
R^2 = Me, Et, Pr, Allyl

R^1 = Me, ^{i}Pr, C_6H_5, $4CF_3C_6H_4$, $4MeC_6H_4$, $4MeOC_6H_4$, 2-Furyl, 2-Thioenyl, 1-Napthyl

R^2 = Me, ^{i}Bu

Scheme 22. Synthesis of thiophene and thiopyran frameworks

A facile and straightforward P_2O_5 catalyzed regioselective synthesis of 4-aryl-3-aroyl-2-methylsulfanyl-4,6,7,8-tetrahydrothiochromen-5-ones was described by Singh *et al.* under solvent-free conditions from *β*-oxodithioesters, aldehydes and cyclic 1,3-diketones (Scheme 23).[32]



72-90%
20 examples

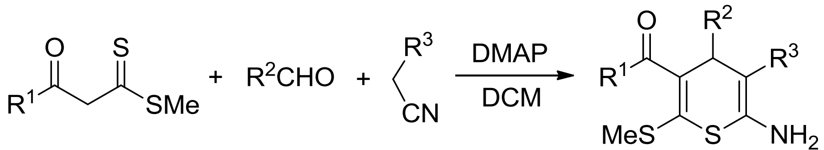
R^1 = C_6H_5, $4MeOC_6H_4$, 2-Furyl, 2-Thienyl

R^2 = C_6H_5, $2ClC_6H_4$, $2,4Cl_2C_6H_3$, $4FC_6H_4$, $4ClC_6H_4$, $3NO_2C_6H_4$, $4NO_2C_6H_4$, $4CF_3C_6H_4$, $2MeOC_6H_4$, $4MeC_6H_4$, $3OHC_6H_4$, $4Cl,3FC_6H_3$

R^3 = H, Me

Scheme 23. Synthesis of thiopyran derivatives

They have also demonstrated a convenient and regioselective heteroannulation reaction for the synthesis of previously unreported highly substituted 2-amino-4-(aryl/alkyl)-5-(aroyl/heteroaroyl)-3-(cyano/carboalkoxy)-6-methylthio-4H-thiopyran derivatives through one-pot three-component condensation of *β*-oxodithioesters, aldehydes, and malononitrile/ethyl or methyl cyanoacetate catalysed by DMAP in presence of DCM solvent as well as under solvent-free conditions (Scheme 24).[33]



R^1 = $C_6H_5C_6H_4$, $4ClC_6H_4$, $4MeC_6H_4$, $4MeOC_6H_4$, 2-Furyl, 2-Thienyl, 1-Napthyl

R^2 = $Me(CH_2)_6$, Cyclohexane, C_6H_5, $2ClC_6H_4$, $3ClC_6H_4$, $4ClC_6H_4$, $4BrC_6H_4$, $4FC_6H_4$, $2NO_2C_6H_4$, $3NO_2C_6H_4$, $4NO_2C_6H_4$, $4MeC_6H_4$, $4MeOC_6H_4$, $3OHC_6H_4$, 2-Furyl, 2-Thienyl

R^3 = CN, CO_2Me, CO_2Et

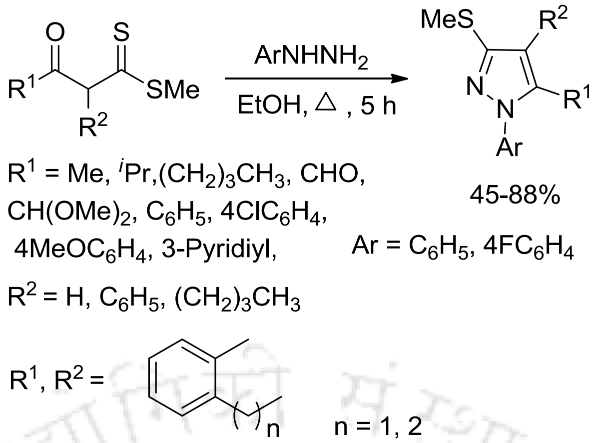
Scheme 24. Synthesis of substituted dihydrothiopyran

1.5.2. Synthesis of heterocycles having more than one heteroatom

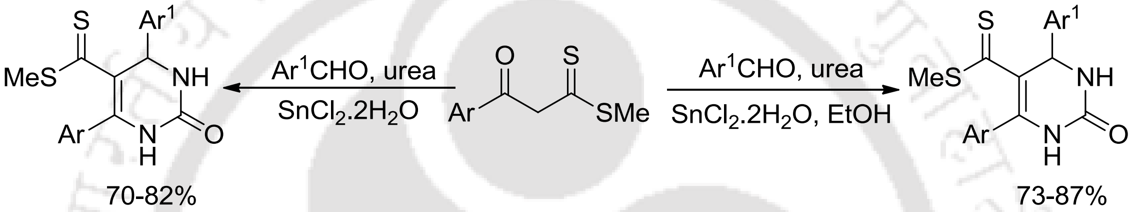
Pyrazole and its derivatives are a special class of hererocyclic compounds, and occupy an important position in medicinal and pesticide chemistry. They possess a wide range of biological activities such as anti-inflammatory inhibitor, analgesic, anti-tumour, HIV-1 reverse transcriptase inhibitor, fungicides and histone deacetyse inhibitors and tubulin polymerization inhibitor.[34]

A highly efficient and regioselective synthesis of 1-aryl-3-(methylthio)-4,5-substituted/annulated pyrazoles was described by Junjappa *et al.*. The reaction proceeds via cyclocondensation reaction of arylhydrazines with *β*-oxodithioesters (Scheme 25).[35]

Singh and Devi[36a] exploited *β*-oxodithioesters as an alternative of 1,3-dicarbonyl compounds in a multicomponent reaction and utilized it in the Biginelli reaction. They have synthesized a wide variety of dihydropyrimidinones by employing the Biginelli reaction of *β*-oxodithioester, aromatic aldehydes and the urea at 100 ^{0}C in the presence of $SnCl_2.2H_2O$ catalyst under solvent-free conditions. The reactions took almost 3-4 h to complete and gave the corresponding dihydropyrimidinones derivatives in 70-82% yield. Further Singh *et al.* reported the same reaction by employing recyclable silica supported sulfuric acid as a catalyst and afforded comparatively better yield (Scheme 26). [36b]



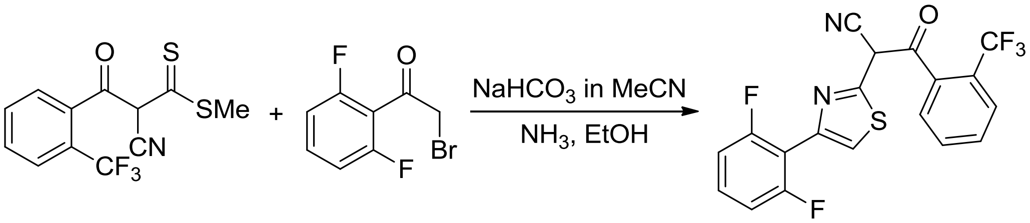
Scheme 25. Synthesis of substituted pyrazoles



Scheme 26. Synthesis of dihydropyrimidinones

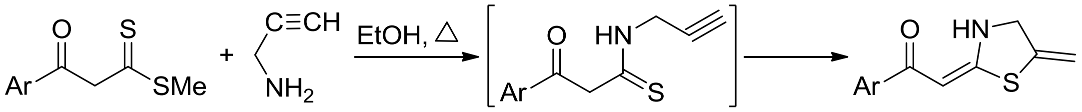
Thiazoles are also an important class of organic molecules because of their potent and significant biological and pharmaceutical applications. They exhibit several biomedical activities such as anti-bacterial, anti-hypertensive, anti-tumor, anti-ulcer, anti-parasitics, cytotoxic, enzyme inhibition and immunosuppressive.[37] Due to their potent and significant biological and pharmaceutical importance, synthesis of these compounds are of considerable interest to the organic chemists.

Yagihara and Suzuki synthesized 2-substituted thiazole derivatives from the reaction of *α*-cyano-*β*-oxodithioesters and 2',6'-difluoro-2-bromoacetophenone in the presence of sodium bicarbonate base in acetonitrile followed by treated with ammonia in ethanol (Scheme 27).[38]



Scheme 27. Synthesis of thiazole derivatives

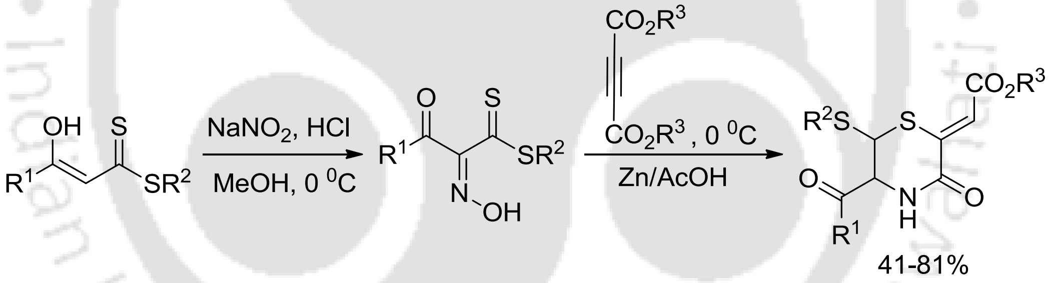
Junjappa *et al.* reported another procedure for the synthesis of thiazoline ring with exocyclic double bond. The reaction proceeds through nucleophilic substitution of SMe group by propargylamine, followed by the intramolecular nucleophilic attack of the thiocarbonyl sulfur on the triple bond of the *β*-oxo-N-propargylthioamide to achieve thiazoline derivatives (Scheme 28).[39]



Ar = C_6H_5, 92%
Ar = $4MeOC_6H_4$, 95%

Scheme 28. Synthesis of thiazoline derivatives

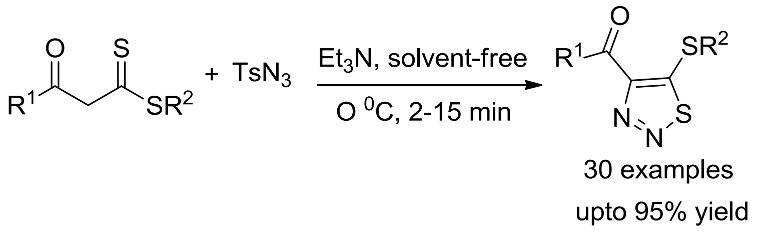
Singh *et al.* devised a simple and straightforward method for the synthesis of 1,4-thiazin-3-ones from *α*-hydroxyimino-*β*-oxodithioesters and dialkyl acetylenedicarboxylates.[40] *α*-hydroxyimino-*β*-oxodithioesters has been obtained by nitrosation of *α*-enolicdithioesters, when further treated with dialkyl acetylenedicarboxylates resulted in a diverse 1,4-thiazin-3-ones via domino reduction/annulation reaction under mild reaction conditions (Scheme 29).



R^1 = Me, C_6H_5, $4CF_3C_6H_4$, $4MeC_6H_4$, $4MeOC_6H_4$, 2-Furyl, 2-Thienyl, 2-Napthyl
R^2 = Me, Allyl, 2-Methylpropene, $CH_2C_6H_5$
R^3 = Me, Et

Scheme 29. Synthesis of 1,4-thiazin-3-one derivatives

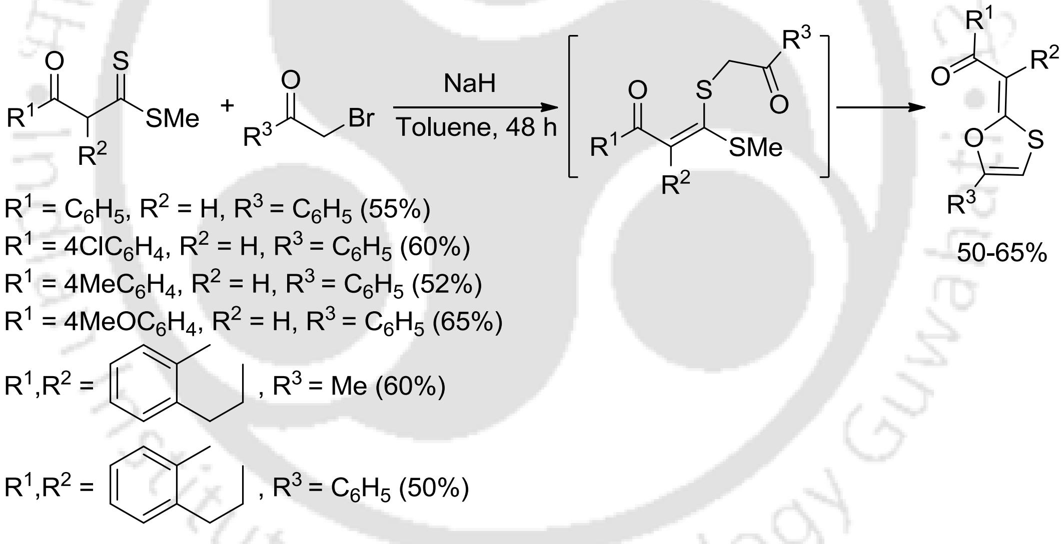
A facile and convenient route for the synthesis of regioselective 4-aroyl/hetaroyl/alkanoyl-5-alkyl/allyl/benzylsulfanyl-1,2,3-thiadiazoles was described by Singh *et al.*.[41] The process consists of one-pot two-component [3+2] cycloaddition of *α*-enolic dithioesters with tosyl azide through nucleophilic attack of *α*-carbon of *β*-oxodithioesters with sp-hybridized electrophilic nitrogen of tosylazide, forming C-N bond to produce an intermediate, which underwent intramolecular cyclization via sulfur to furnish the desired regioselective product 1,2,3-thiadiazole (Scheme 30).



R^1 = Alkyl, Aryl, Hetaryl
R^2 = Me, Et, *n*-Pr, *n*-Bu, *n*-Pentyl, Allyl, Benzyl

Scheme 30. Synthesis of 1,2,3-thiadiazoles

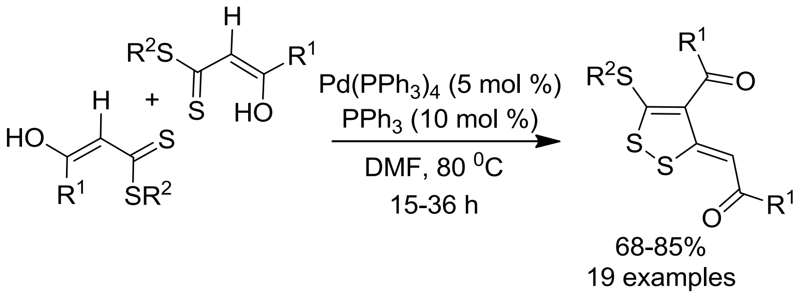
Anabha *et al.* described the reaction of *β*-oxodithioesters with *α*-haloketones such as phenacylbromide or bromoacetone for the facile access of substituted 2-ylidene-1,3-oxathiols in good yield (Scheme 31).[42] Initially, *β*-oxodithioesters reacted with haloketone to generate the intermediate ketene dithioacetal which further underwent base induced intramolecular nucleophilic addition of the enolate anion to the ketene dithioacetal moiety to accomplish substituted 1,3-oxathiols.



$R^1 = C_6H_5$, $R^2 = H$, $R^3 = C_6H_5$ (55%)
$R^1 = 4ClC_6H_4$, $R^2 = H$, $R^3 = C_6H_5$ (60%)
$R^1 = 4MeC_6H_4$, $R^2 = H$, $R^3 = C_6H_5$ (52%)
$R^1 = 4MeOC_6H_4$, $R^2 = H$, $R^3 = C_6H_5$ (65%)
R^1,R^2 = , R^3 = Me (60%)
R^1,R^2 = , $R^3 = C_6H_5$ (50%)

Scheme 31. Synthesis of substituted 1,3-oxathiols

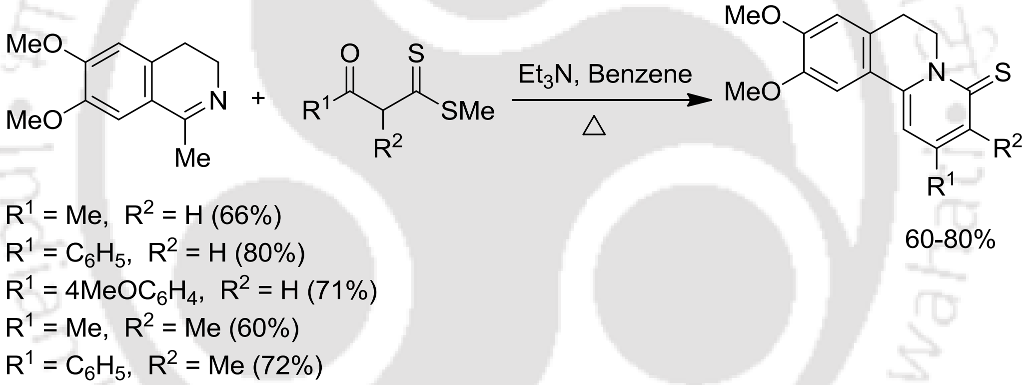
Singh and co-workers[43] accomplished a facile and straightforward reaction for the preparation of 3,4,5-trisubstituted 1,2-dithioles through one-pot self-coupling of *α*-enolic dithioesters by employing $Pd(PPh_3)_4$ as a catalyst, triphenylphosphine as a base and DMF as a solvent. The product formation consists of the activation and cleavage of S-H and C-S bonds followed by the concomitant formation of S-S and C-C bonds to achieve the 3,4,5-trisubstituted 1,2-dithioles (Scheme 32).



Scheme 32. Synthesis of 3,4,5-trisubstituted 1,2-dithioles

1.5.3. Synthesis of polycyclic heterocycles

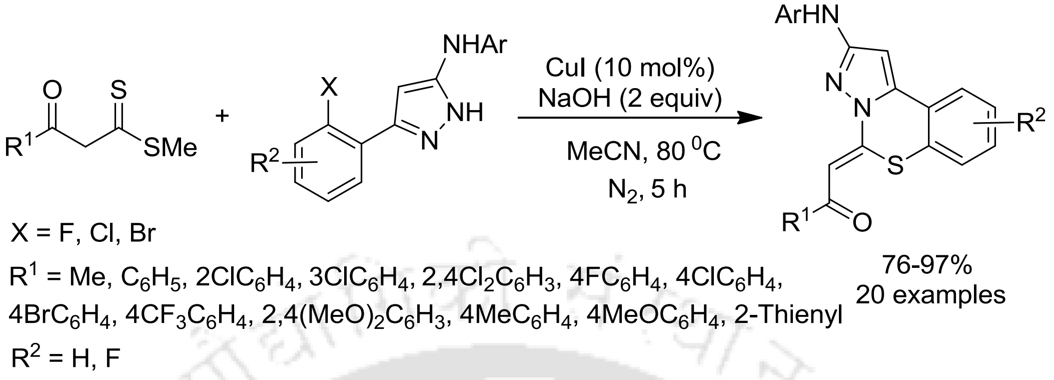
Junjappa *et al.* has been reported an efficient straightforward route for the synthesis of 2,3-substituted and annulated benzo[*a*]quinolizine-4-thiones.[44] The methodology consists of ring annulations of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline with a variety of readily accessible acyclic and cyclic *β*-oxodithioesters in the presence of Et_3N in refluxing benzene (Scheme 33).



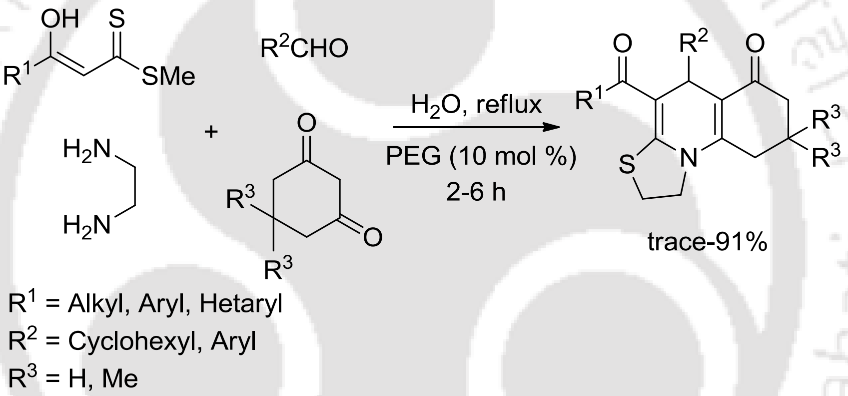
Scheme 33. Synthesis of benzo[*a*]quinolizine-4-thiones

Wen, Yuan and Li developed an efficient CuI catalysed synthetic protocol for the chemoselective synthesis of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives from *β*-oxodithioesters with 3-(2-bromoaryl)-1H-pyrazoles in the presence of NaOH in CH_3CN at 80 °C under N_2 atmospheric condition. The reaction proceeds through tandem Ullmann coupling reactions *i.e.* C-S bond formation, in which 3-(2-bromoaryl)-1H-pyrazoles plays dual roles as both a substrate and a ligand (Scheme 34).[45]

Singh *et al.* recently demonstrated a highly convergent and eco-friendly route for the synthesis of highly functionalized thiazoloquinoline scaffolds through one-pot four-component cascade reaction by employing *α*-enolic dithioesters, cysteamine, aldehydes and cyclic 1,3-diketones in water-PEG-400. The new convenient and sequential protocol produces two rings through the formation of N,S-acetal, followed by Knoevenagel reaction, aza-ene reaction, imine-enamine/keto-enol tautomerization and N-cyclization (Scheme 35).[46]



Scheme 34. Synthesis of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine

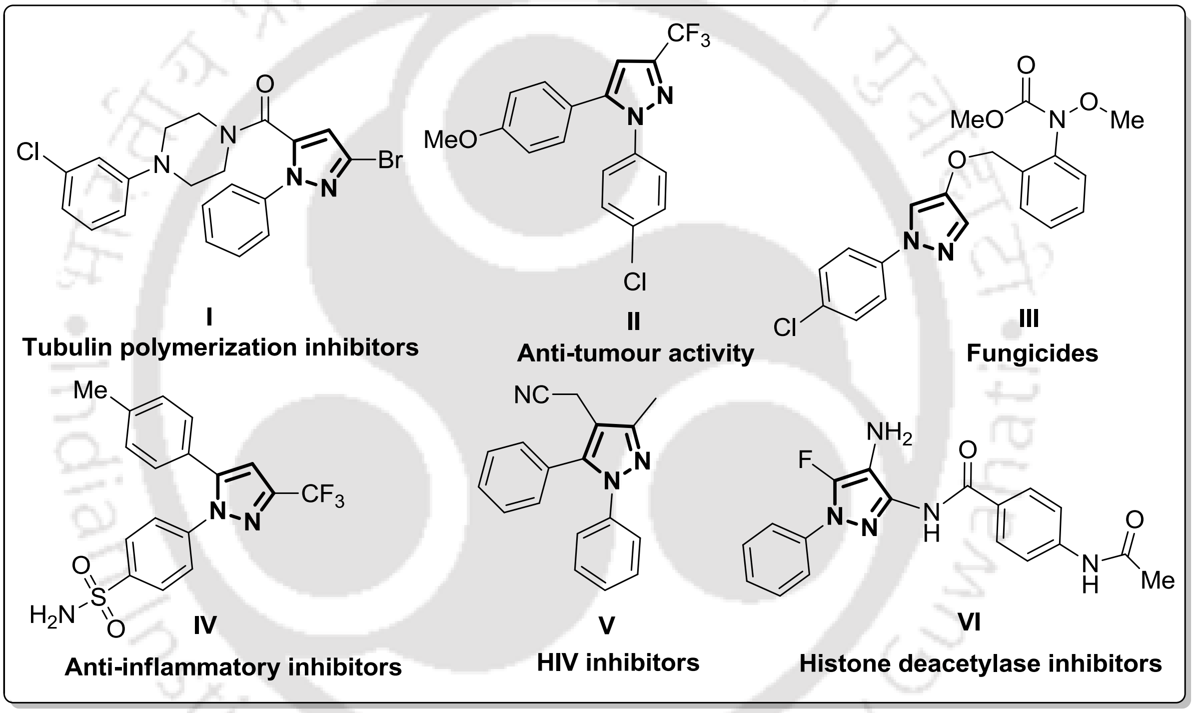


Scheme 35. Synthesis of thiazoloquinoline

It is to stress the well-established ubiquitous importance of *β*-oxodithioesters as a key substrate for domino/cascade reactions in the field of organic chemistry and the consequent interest manifested in this area. Because domino reactions proceed through comparatively milder reaction conditions and tolerate a wide variety of functional groups, protection-deprotection steps are often avoided and the resulting intermediate undergoes a variety of transformations to produce highly substituted heterocycles. It is a well-known fact that various well-established methodologies were successfully applied to *β*-oxodithioesters by laboratories worldwide to synthesize them in environment-friendly approaches. Often many methodologies employed in this context occasionally require reaction conditions that are not tolerated by the reagents involved and new strategies or conceptually novel ideas are needed to be developed to increase the potential of *β*-oxodithioesters.

2.1. Pyrazoles and its importance

Nitrogen-containing heterocycles are found in many complex natural products and many of them are marketed as drugs.[47] Among them, various pyrazole derivatives also possess a wide range of pharmacological activities such as tubulin polymerization inhibitor,[48] anti-tumour,[49] fungicides, anti-inflammatory inhibitor,[49] HIV-1 reverse transcriptase inhibitor,[50] analgesic,[51] and histone deacetylase inhibitors[52] (Figure 2). Pyrazole derivatives also can act as ligands[53] in complex formation with metals as well as analytical reagent.[54] As a matter of fact, the synthesis of these compounds may be useful to study biological activity in near future.



I Tubulin polymerization inhibitors

II Anti-tumour activity

III Fungicides

IV Anti-inflammatory inhibitors

V HIV inhibitors

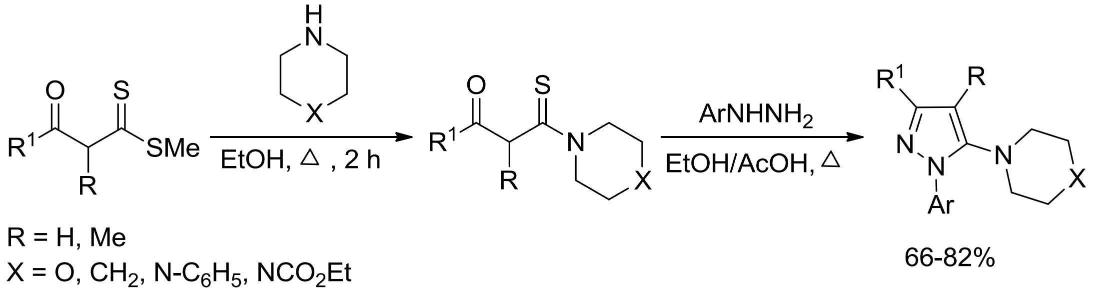
VI Histone deacetylase inhibitors

Figure 2. Some of the biologically active compound containing pyrazole structural unit

2.2. General approaches for the construction of substituted pyrazoles

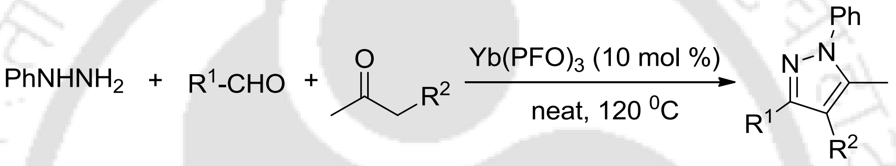
Over the years, various methods have been developed for the synthesis of pyrazole derivatives with different substituent pattern. Some approaches to devise these pyrazole derivatives are: annulations, ring-closing metathesis, condensation reaction and various multicomponent reactions.

Singh *et al.* developed an efficient and highly regioselective protocol for the synthesis of 5-amino substituted pyrazoles[55] via a one-pot and three-component cyclocondensation of β-oxodithioester, amine, and hydrazine in refluxing with EtOH in the presence of a catalytic amount of AcOH (Scheme 36).



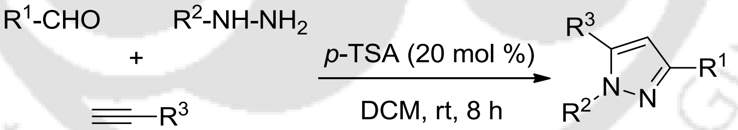
Scheme 36. Synthesis of 5-amino substituted pyrazoles

Qian *et al.* described a convenient one-pot synthesis of fully substituted pyrazoles[56] via three-component condensations of phenylhydrazine, aldehydes and 1,3-dicarbonyl compounds using ytterbium perfluorooctanoate [Yb(PFO)$_3$] as catalyst under solvent-free reaction condition (Scheme 37).



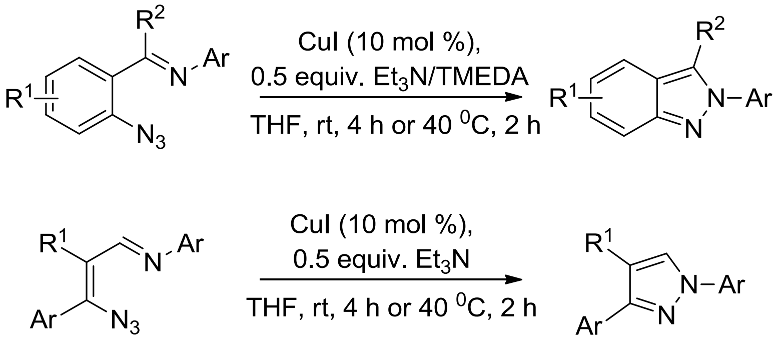
Scheme 37. Synthesis of fully substituted pyrazoles

Wang *et al.* reported a convenient one-pot synthesis of 1,3,5-trisubstituted pyrazoles[57] derivatives from aldehydes, hydrazines and alkynes via Mannich-type-cyclization-oxidation tandem process using *p*-toluenesulfonic acid monohydrate (PTSA) as a multifunctional catalyst (Scheme 38).



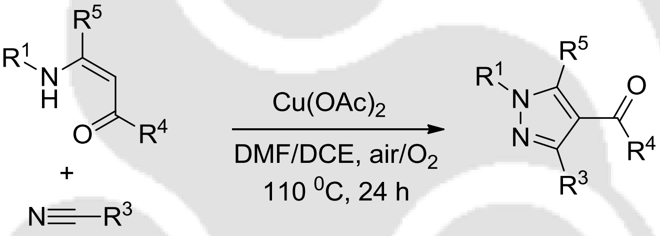
Scheme 38. Synthesis of 1,3,5-trisubstituted pyrazoles derivatives

Rao *et al.*[58] developed an efficient copper-catalyzed intramolecular amination reaction for the synthesis of a wide variety of multi-substituted 2*H*-indazole and 1*H*-pyrazole derivatives from easily accessible starting materials under mild conditions. The utility of this methodology was further extended for the synthesis of a ligand that was found highly selective for estrogen receptor *β* (Scheme 39).



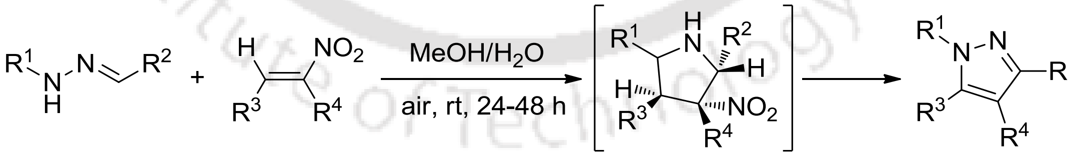
Scheme 39. Synthesis of multi-substituted 2*H*-indazole and 1*H*-pyrazole derivatives

Recently Glorius *et al.* reported an efficient Cu-catalyzed synthesis of tetrasubstituted pyrazoles[59] from readily available enamines and nitriles employing molecular oxygen as the sole stoichiometric oxidant. The construction of tetrasubstituted pyrazole ring was achieved by reaction of readily available enamines and nitriles via C-C and N-N bond formation (Scheme 40).



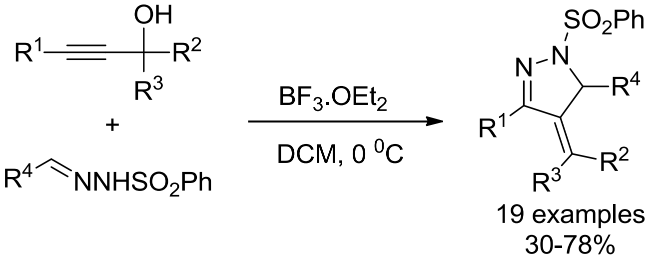
Scheme 40. Synthesis of tetrasubstituted pyrazole derivatives

Deng *et al.* demonstrated a novel regioselective synthesis of substituted pyrazoles from N-monosubstituted hydrazones and nitroolefins under mild reaction conditions in moderate to excellent yields. The product was obtained via a nitropyrazolidine intermediate in a one-pot manner (Scheme 41).[60]



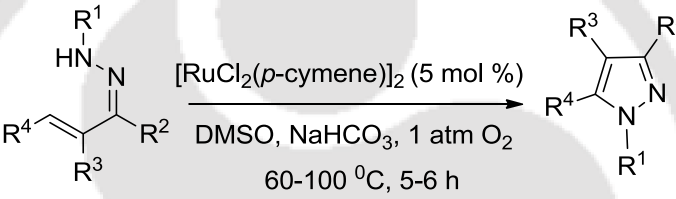
Scheme 41. Synthesis of substituted pyrazole derivatives

Wang *et al.* described an efficient and straightforward tandem reaction for the synthesis of 4-methylene-1-(phenylsulfonyl)-4,5-dihydro-1H-pyrazole derivatives[61] through one-pot condensation reaction of propargyl alcohol and N-sulfonylhydrazone catalyzed by BF_3-OEt_2 in presence of DCM (Scheme 42).



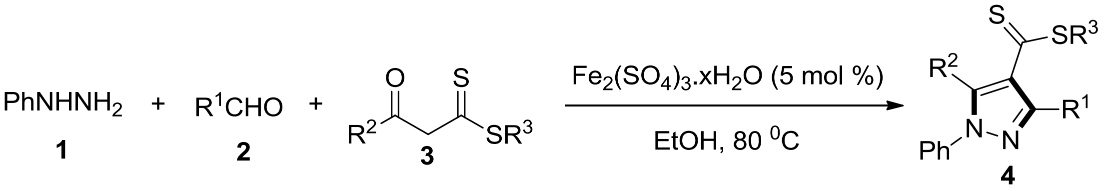
Scheme 42. Synthesis of dihydro-1H-pyrazole derivatives

Rao *et al.* developed an unprecedented ruthenium(II)-catalyzed intramolecular oxidative C-N coupling strategy for the facile access of a variety of synthetically challenging tri and tetrasubstituted pyrazole derivatives employing dioxygen gas as the oxidant. The reaction demonstrated excellent reactivity, functional group tolerance, and high yields (Scheme 43).[62]



Scheme 43. Synthesis of tri and tetrasubstituted pyrazole derivatives

From the literature survey, it was evident that the pyrazole derivatives are present in various bio-active molecules and exhibits diverse range of pharmacological activities. Even though, several methods have been reported for the synthesis of substituted pyrazoles over the year but few of these are associated with certain drawbacks such as unsatisfactory yields, high temperatures, longer reaction times and the use of stoichiometric and/or relatively expensive catalysts. Development of new methodologies using cheaper catalyst related to the synthesis of pyrazole derivatives seems a challenging task. In this chapter we report a one-pot and three-component reaction of phenyl hydrazine, aldehyde and alkyl-3-oxo-3-arylpropanedithioate for the synthesis of trisubstituted-1*H*-pyrazole-4-carbodithioate derivatives using cheaper $Fe_2(SO_4)_3 \cdot xH_2O$ as a catalyst (Scheme 44).

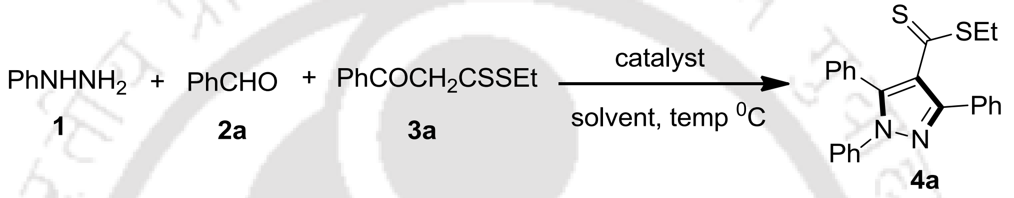


Scheme 44. Synthesis of trisubstituted-1*H*-pyrazole-4-carbodi-thioates

2.3. Results and discussion

Ferric sulfate is found to be a cheap and readily available and used for various organic transformations such as synthesis of acylals from aldehydes,[63a] tetrahydropyranylation of alcohols,[63b] Ferrier rearrangement and per-*o*-acetylation of sugars.[64] From our previous experience for the synthesis of tetrahydroquinoline derivatives using Povarov reaction.[65] For the present study, the reaction was performed with phenyl hydrazine (**1**), benzaldehyde (**2a**), ethyl 3-oxo-3-phenylpropanedithioate (**3a**) as the model substrates to find out the suitable reaction condition (Table 1).

Table 1. Optimization of the reaction conditions



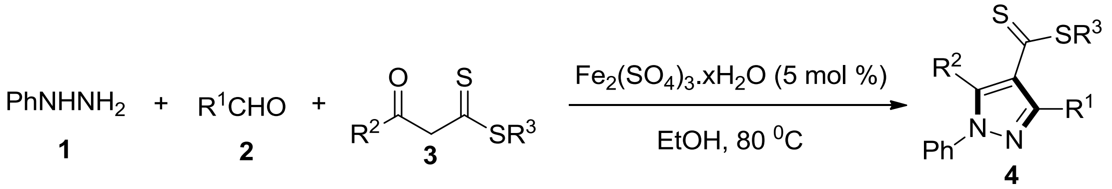
Entry	Catalyst	Mol %	Temp (^{0}c)	Solvent	Time (h)	Yield (%)[b]
1	-	-	rt	EtOH	24	NR
2	BDMS	10	rt	EtOH	24	NR
3	CAN	10	80	EtOH	8	NR
4	$Fe_2(SO_4)_3\cdot xH_2O$	5	60	MeOH	10	52
5	$Fe_2(SO_4)_3\cdot xH_2O$	5	80	MeOH	6	62
6	**$Fe_2(SO_4)_3\cdot xH_2O$**	**5**	**80**	**EtOH**	**3**	**68**
7	$Fe_2(SO_4)_3\cdot xH_2O$	5	80	CH_3CN	8	58
8	$Fe_2(SO_4)_3\cdot xH_2O$	5	80	DMF	8	54
9	$Fe_2(SO_4)_3\cdot xH_2O$	10	80	EtOH	5	61
10	$Fe_2(SO_4)_3\cdot xH_2O$	10	80	MeOH	8	55
11	$Co(OTf)_2$	10	80	EtOH	8	30
12	$In(OTf)_3$	10	80	EtOH	8	28
13	$ZnCl_2$	10	80	EtOH	8	20
14	L-Proline	10	80	EtOH	8	10
15	$FeCl_3$	10	80	EtOH	8	35

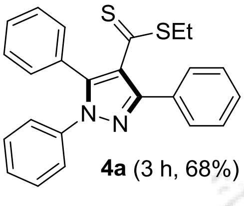
[a]The reactions were performed in 1 mmol scale using phenyl hydrazine (**1**), benzaldehyde (**2a**) and ethyl 3-oxo-3-phenylpropane dithioate (**3a**). [b]Isolated yield.

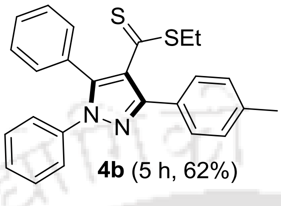
We noticed 5 mol % ferric sulfate in ethanol at 80 ^{0}C gave the best yield (Table 1, entry 6). It is to mention that the reaction did not take place in presence of other catalysts such as bromodimethylsulfonium bromide (BDMS) or ceric ammonium nitrate (CAN). Also excess loading of the catalyst, ferric sulfate decreased the yield (Table 1, entry 9). The other catalysts such as $Co(OTf)_2$, $In(OTf)_3$, $ZnCl_2$, L-Proline, $FeCl_3$ in ethanol were also scrutinized, which provided lower yields and required longer reaction time. Various solvents were also examined with 5 mol % ferric sulfate under identical reaction conditions and ethanol was found the best suited solvent.

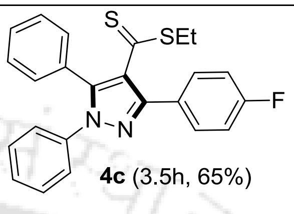
After optimization of the reaction condition, a reaction was carried out with phenyl hydrazine (**1**), 4-methylbenzaldehyde (**2b**) and ethyl 3-oxo-3-phenylpropane-dithioate (**3a**) in presence of 5 mol % $Fe_2(SO_4)_3{\cdot}xH_2O$ and the desired product ethyl 1,5-diphenyl-3-(*p*-tolyl)-1*H*-pyrazole-4-carbodithioate **(4b)** was afforded in 62 % yield. Likewise, various aromatic aldehydes (**2c-e**) having various halogen substituent at the *para* position in the aromatic ring and thiophene-2-aldehyde (**2f**) were examined with phenyl hydrazine (**1**) and ethyl 3-oxo-3-phenylpropanedithioate (**3a**) in the presence of same amount of catalyst and the desired products **4c-f** were obtained in 65-70% yield (Table 2, entries 3-6). Encouraged by these successful results, we further scrutinized the reactions with various aliphatic aldehydes such as formaldehyde (**2g**), *n*-butylaldehyde (**2h**), cyclohexyl aldehyde (**2i**) with phenyl hydrazine (**1**) and ethyl 3-oxo-3-phenylpropanedithioate (**3a**) in presence of 5 mol % $Fe_2(SO_4)_3{\cdot}xH_2O$ in the optimized reaction condition and the desired products **4g-i** were isolated in good yields (Table 2, entries 7-9). For generalizing the reaction procedure, we have further examined the reactions with different methyl 3-oxo-3-phenylpropane-dithioate (**3b**) with phenyl hydrazine (**1**) and benzaldehyde (**2a**) and 4-chlorobenzaldehyde (**2d**) and the products **4j** and **4k** were obtained in 65 % and 70 % yields respectively. We have also verified the reactions ethyl 3-(4-chlorophenyl)-3-oxo-propanedithioate (**3c**) with 4-methoxybenzaldehyde (**2j**), acetaldehyde (**2k**), n-propylaldehyde (**2l**), 3-methylbutyraldehyde (**2m**) and phenyl hydrazine (**1**) in presence of 5 mol % amount of the catalyst under optimized reaction conditions and the desired products **4l-o** from moderate to good yields (Table 2, entries 12-15). Similarly, ethyl 3-(4-methoxyphenyl)-3-oxopropanedithioate (**3d**) also provided the trisubstituted-1*H*-pyrazole-4-carbodithioates **4p** and **4q** on treatment with phenyl hydrazine (**1**) and *n*-butylaldehyde (**2h**), cyclohexyl aldehyde (**2i**), respectively.

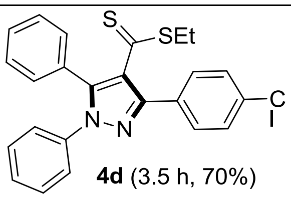
Table 2. $Fe_2(SO_4)_3{\cdot}xH_2O$ catalyzed synthesis of trisubstituted-1*H*-pyrazole-4-carbodithioates (**4**)

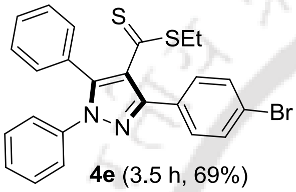


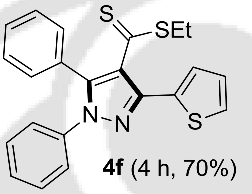

4a (3 h, 68%)

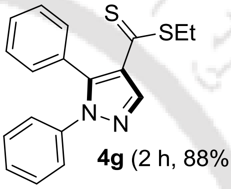

4b (5 h, 62%)

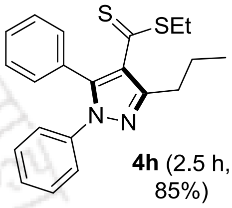

4c (3.5h, 65%)

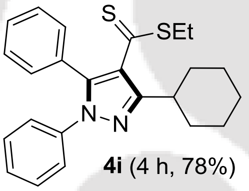

4d (3.5 h, 70%)

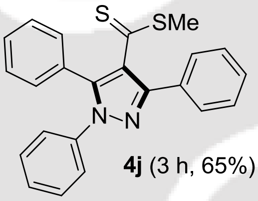

4e (3.5 h, 69%)

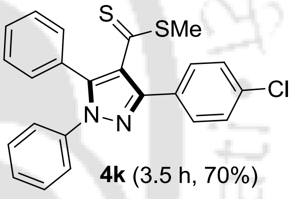

4f (4 h, 70%)

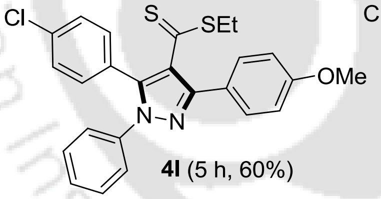

4g (2 h, 88%)

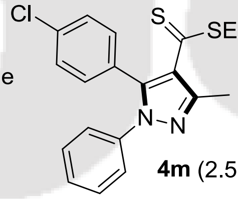

4h (2.5 h, 85%)

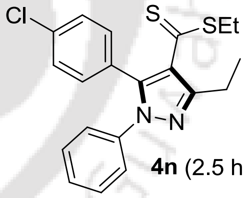

4i (4 h, 78%)

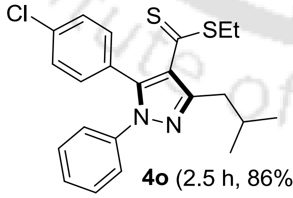

4j (3 h, 65%)

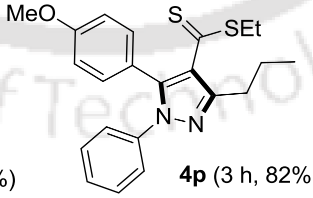

4k (3.5 h, 70%)

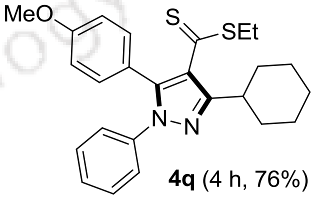

4l (5 h, 60%)


4m (2.5 h, 86%)


4n (2.5 h, 82%)


4o (2.5 h, 86%)

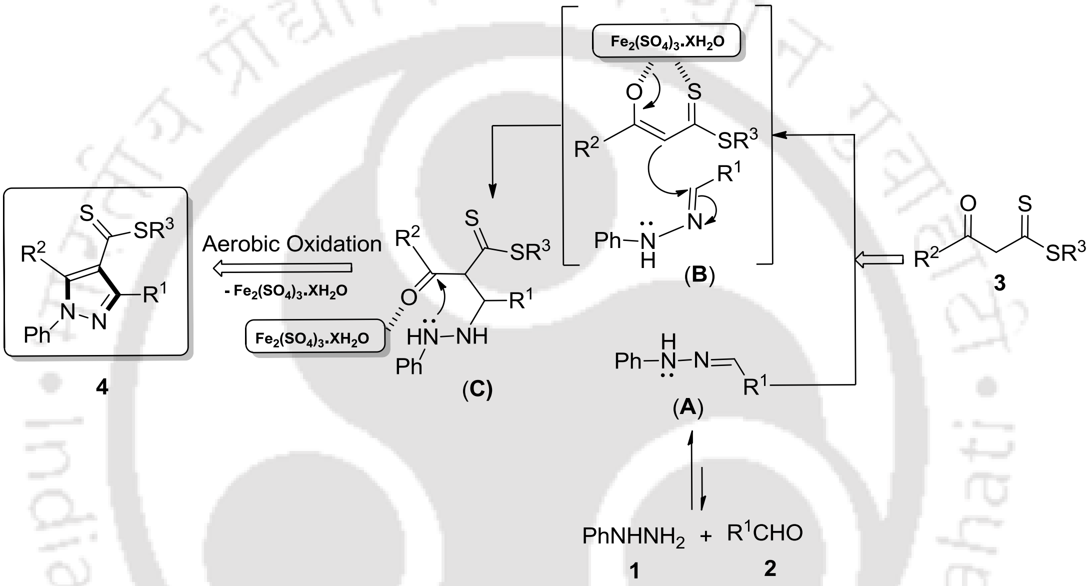

4p (3 h, 82%)


4q (4 h, 76%)

[a]All the reactions were carried out using phenyl hydrazine (**1**), aldehyde (**2**), alkyl-3-oxo-3-arylpropanedithioate(**3**) using 1 mmol of each reactant and $Fe_2(SO_4)_3{\cdot}xH_2O$ (5 mol %) in EtOH at 80 ^{0}C. [b]Isolated yield.

Unfortunately, the reaction was failure when 4-nitrobenzaldehye was treated with phenyl hydrazine (**1**) and ethyl 3-oxo-3-phenylpropanedithioate (**3a**) under identical reaction conditions. From the above successful results, it is noteworthy to mention that aliphatic aldehydes provided better yield and also required shorter reaction time as compared to the aromatic aldehyde, which may have negative inductive effect of the phenyl ring.

The formation of the product can be explained as: Initially phenyl hydrazine (**1**) reacts with aldehyde **2** to form phenylhydrazone **A**. The alkyl-3-oxo-3-arylpropanedithioate **3** may coordinate with $Fe_2(SO_4)_3 \cdot xH_2O$ and stabilize the enol followed by Mannich type reaction with phenylhydrazone **A** to give the species **C**. The intermediate **C** undergoes cyclization followed by aerobic oxidation to provide the desired product of trisubstituted-1*H*-pyrazole-4-carbodithioate **4** (Scheme 45).



Scheme 45. Plausible mechanism for the formation of trisubstituted-1*H*-pyrazole-4-carbodithioate **4**.

The present protocol worked with various alkyl-3-oxo-3-arylpropanedithioate as well as different aliphatic and aromatic aldehydes. All the isolated products were fully characterized by IR, ^1H NMR, ^{13}C NMR and elemental analyses. In addition, the structure of the presentated compounds were further confirmed through single-crystal X-ray crystallographic data which revealed that **4k** crystallized as monoclinic space group $P2_1/c$. The crystal structure shows that **4k** formed dimer via unprecedented weak supramolecular chlorine sulfur intermolecular interaction (Cl···S = 3.525 Å, <C-Cl···S = 171°) (Figure 2). The Cl···S interaction forms C-Cl···S-C at a dihedral angle of 39°. Here one of the two sulfur atoms of a molecule participates in Cl···S bonding interaction with chlorine atom of other molecule and vice-versa. Thus there is no extension of the dimensionality of the structure. In the last few years, halogen bonding interactions have afforded a great deal of interest among the family of pharmaceutical, optical and

functional materials.[66]It also can play important role in the biological systems.[67] Of these, studies of halogen-sulfur interactions seem to be less known in the literature.

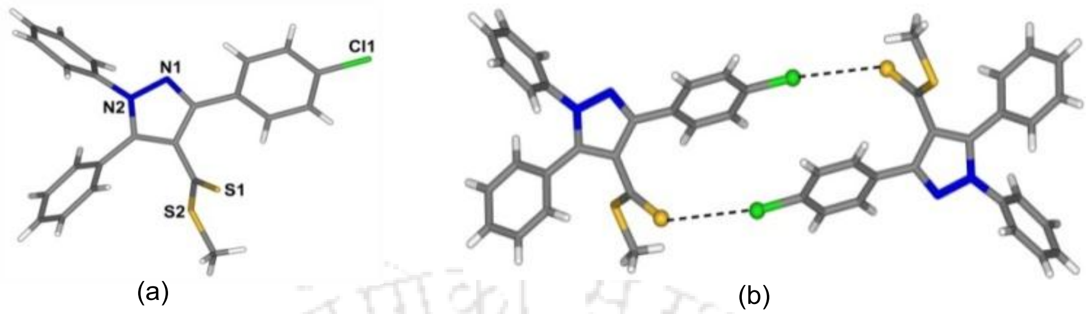


Figure 3. (a) Crystal structure of **4k** (CCDC 894780) (b) Intermolecular chlorine sulfur interaction in **4k**

Among them, I···S has attracted special interest due to their potential applications in the systematic study to understand the principle and method associated with co-crystal synthesis of anti-thyroid drug.[68] However in the halogen-sulfur interactions for the design of supramolecular synthons, Cl···S has been largely unexplored. Here we report elusive weak supramolecular Cl···S interaction in the dimer of **4k**. This chlorine-sulfur interaction can be used as a tool for the co-crystal synthesis in supramolecular chemistry.

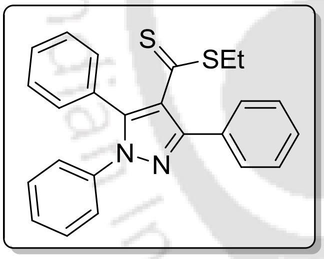
In conclusion, we have developed a newer synthetic protocol for the synthesis of trisubstituted-1*H*-pyrazole-4-carbodithioate by sequential multicomponent reaction of one-pot condensation reaction of aldehyde, phenyl hydrazine and alkyl-3-oxo-3-arylpropanedithioate using inexpensive ferric sulfate as the catalyst. Some of the important aspects of this present protocol are simplicity, easy to handle, good yields, shorter reaction time and substrate scope compatibility. The biological studies on the synthesized trisubstituted-1*H*-pyrazole-4-carbodithioate derivative are under process that will be reported in due course of time. In particular, weak intermolecular Cl···S interactions have been illustrated in the dimeric unit of **4k**. This result is expected to make significant impact among the researchers working in the area of supramolecular chemistry and crystal engineering, especially for the design and synthesis of co-crystals.

2.4. Experimental Section

General procedure for the synthesis of trisubstituted-1H-pyrazole-4-carbodithioate:

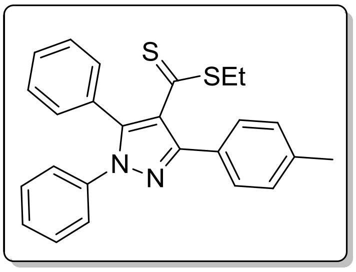
In 25 ml round bottomed flask, a mixture of phenyl hydrazine (1 mmol), aldehyde (1 mmol) was taken in 5 mL of ethanol and stirred at room temperature. After 15 minutes of stirring, alkyl-3-oxo-3-arylpropanedithioate (1 mmol) was added and the solution turns yellow in colour. Then the catalyst, $Fe_2(SO_4)_3{\cdot}xH_2O$ (5 mol %) was added on the reaction mixture at 80 ^{0}C on a pre-heated oil-bath and the solution turned into green colour slowly. Later on the reaction mixture was changed into orange colour when the reaction was over, which was further ascertained by checking TLC. Ethanol was removed under reduced pressure and the crude residue was extracted in dichloromethane (20 mL x 3). The organic extract was washed with water dried over anhydrous sodium sulfate. Finally, the solvent was removed and the crude residue was passed through a silica gel column chromatography to obtain the pure product of trisubstituted-1*H*-pyrazole-4-carbodithioate **4**. All the products were obtained by eluting with a mixture of hexane and ethyl acetate (99:1).

*Ethyl 1,3,5-triphenyl-1H-pyrazole-4-carbodithioate (**4a**)*:



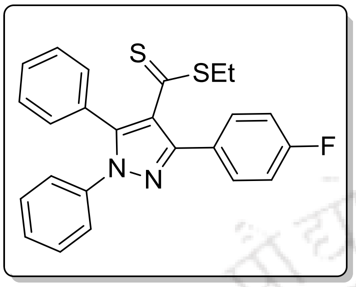
Red semi-solid: (0.272 g, 68%); R_f = 0.64 (Hexane: ethyl acetate 11:1); IR (KBr): 1072, 1595, 2924 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.2 Hz, 3H), 3.20 (q, J = 7.2 Hz, 2H), 7.25-7.32 (m, 10H), 7.37 (d, J = 8.0 Hz, 3H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.02, 31.46, 125.51, 127.88, 128.46, 128.56, 129.01, 129.15, 130.28, 132.21, 139.46, 140.85, 149.10, 223.17; Anal. Calcd for $C_{24}H_{20}N_2S_2$: C, 71.96; H, 5.03; N, 6.99. Found: C, 71.83; H, 4.89; N, 6.85.

*Ethyl 1,5-diphenyl-3-(p-tolyl)-1H-pyrazole-4-carbodithioate (**4b**)*:



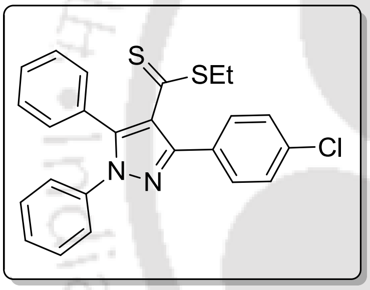
Red semi-solid: (0.257 g, 62%); R_f = 0.64 (Hexane: ethyl acetate 11:1); IR (KBr): 1070, 1596, 2922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J = 7.2 Hz, 3H), 2.37 (s, 3H), 3.20 (q, J = 7.2 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.24-7.31 (m, 10H), 7.61 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.05, 21.56, 31.46, 109.10, 118.27, 125.51, 127.83, 128.41, 128.46, 129.00, 129.21, 130.30, 138.19, 139.52, 149.11, 223.45; Anal. Calcd for $C_{25}H_{22}N_2S_2$:C, 72.43; H, 5.35; N, 6.76. Found: C, 72.36; H, 5.26; N, 6. 64.

*Ethyl 3-(4-fluorophenyl)-1,5-diphenyl-1H-pyrazole-4-carbodithioate (**4c**)*:



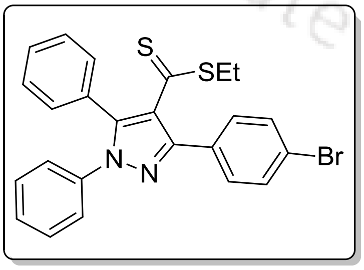
Red semi-solid: (0.272 g, 65%); R_f = 0.76 (Hexane: ethyl acetate 11:1); IR (KBr): 1068, 1596, 2921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.21 (t, *J* = 7.2 Hz, 3H), 3.21 (q, *J* = 7.2 Hz, 2H), 7.07 (t, *J* = 8.8 Hz, 2H), 7.23-7.35 (m, 10H), 7.67-7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.05, 31.52, 102.08, 115.39, 115.60, 125.51, 128.00, 128.52, 129.08, 130.29, 139.40, 140.94, 148.22, 223.05; Anal. Calcd for $C_{24}H_{19}FN_2S_2$: C, 68.87; H, 4.58*; N,* 6.69. Found: C, 68.76; H, 4.49; N, 6.61.

*Ethyl 3-(4-chlorophenyl)-1,5-diphenyl-1H-pyrazole-4-carbodithioate (**4d**)*:



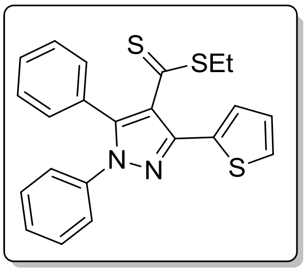
Red semi-solid: Yield (0.304 g, 70%*).* R_f = 0.73 (Hexane: ethyl acetate 11:1); IR (KBr): 1072, 1596, 2926 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.21 (t, *J* = 7.2 Hz, 3H), 3.20 (q, *J* = 7.2 Hz, 2H), 7.25-7.32 (m, 10H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 12.01, 31.52, 125.47, 128.02, 128.33, 128.51, 128.70, 129.06, 129.80, 130.24, 130.75, 134.37, 139.34, 140.98, 147.91, 222.91; Anal. Calcd for $C_{24}H_{19}ClN_2S_2$: C, 66.27; H, 4.40; N, 6.44. Found: C, 66.16; H, 4.31; N, 6.34.

*Ethyl 3-(4-bromophenyl)-1,5-diphenyl-1H-pyrazole-4-carbodithioate (**4e**)*:



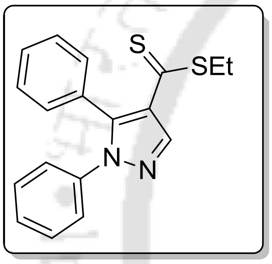
Red semi-solid: (0.331 g, 69%); R_f = 0.72 (Hexane: ethyl acetate 11:1); IR (KBr): 1069, 1596, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.13 (t, *J* = 7.2 Hz, 3H), 3.13 (q, *J* = 7.2 Hz, 2H), 7.23-7.17 (m, 10H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.02, 31.54, 109.94, 122.67, 125.48, 128.03, 128.52, 129.08, 130.10, 130.27, 131.24, 131.65, 139.36, 141.02, 147.94, 222.91; Anal. Calcd for $C_{24}H_{19}BrN_2S_2$: C, 60.12; H, 3.99*;* N, 5.84. Found: C, 60.06; H, 3.88; N, 5. 74.

*Ethyl 1,5-diphenyl-3-(thiophen-2-yl)-1H-pyrazole-4-carbodithioate (**4f**)*:



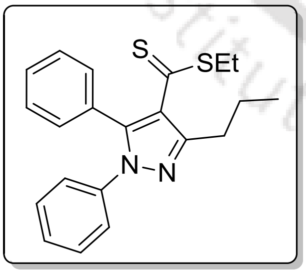
Red semi-solid: (0.284 g, 70%); R_f = 0.70 (Hexane: ethyl acetate 11:1); IR (KBr): 1068, 1595, 2922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3H), 2.78 (q, J = 7.2 Hz, 2H), 6.76 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.2 Hz, 4H), 7.49 (t, J = 7.2 Hz, 3H), 7.65 (d, J = 7.6 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.59, 32.13, 102.09, 108.23, 125.50, 125.90, 127.73, 128.15, 128.29, 128.86, 129.08, 133.05, 136.82, 139.90, 152.20, 220.63; Anal. Calcd for $C_{22}H_{18}N_2S_3$: C, 64.99; H, 4.46; N, 6.89. Found: C, 64.85; H, 4.32; N, 6.75.

*Ethyl 1,5-diphenyl-1H-pyrazole-4-carbodithioate (**4g**)*:



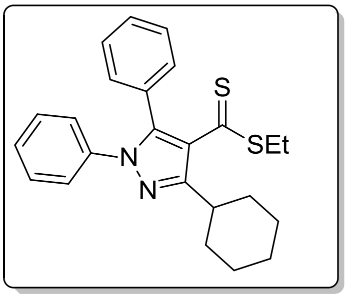
white solid: (0.262 g, 88%); m.p. 110-112 °C; R_f = 0.66 (Hexane: ethyl acetate 11:1); IR (KBr): 1065, 1591, 2921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H), 3.22 (q, J = 7.2 Hz, 2H), 7.187-7.18 (m, 1H), 7.20-7.19 (m, 1H), 7.24 (t, J = 2 Hz, 3H), 7.26-7.28 (m, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.35 (d, J = 7.2 Hz, 2H), 8.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.56, 30.49, 125.45, 128.06, 128.57, 128.91, 129.37, 129.59, 130.56, 130.85, 139.25, 140.45, 141.25, 217.38; Anal. Calcd for $C_{18}H_{16}N_2S_2$: C, 66.63; H, 4.97; N, 8.63. Found: C, 66.53; H, 4.89; N, 8.55.

*Ethyl 1,5-diphenyl-3-propyl-1H-pyrazole-4-carbodithioate (**4h**)*:



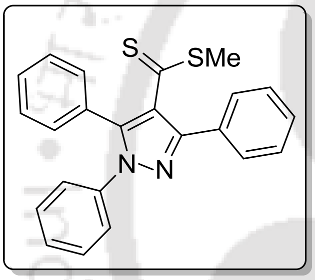
Red semi-solid: (0.311 g, 85%); R_f = 0.76 (Hexane: ethyl acetate 11:1); IR (KBr): 1061, 1593, 2961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.6 Hz, 3H), 1.77 (sextet, J = 7.6 Hz, 2H), 2.87 (t, J = 7.6 Hz, 2H), 3.20 (q, J = 7.6 Hz, 2H), 7.19-7.21 (m, 4H), 7.24-7.26 (m, 2H), 7.27-7.28 (m, 2H), 7.29-7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.21, 14.37, 22.80, 29.80, 31.12, 125.40, 127.56, 128.37, 128.60, 128.79, 128.87, 129.58, 130.28, 139.46, 140.08, 151.63, 222.26; Anal. Calcd for $C_{21}H_{22}N_2S_2$: C, 68.81; H, 6.05; N, 7.64. Found: C, 68.73; H, 5.92; N, 7.55.

*Ethyl 3-cyclohexyl-1,5-diphenyl-1H-pyrazole-4-carbodithioate (**4i**)*:



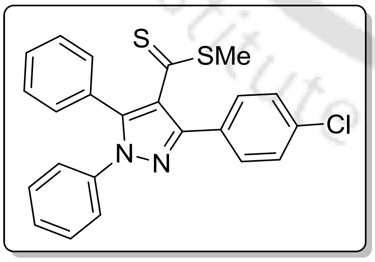
Red solid: (0.317 g, 78%); m.p. 104-105 °C; R_f = 0.82 (Hexane: ethyl acetate 11:1); IR (KBr): 1060, 1593, 2926 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J = 7.2 Hz, 3H), 1.29-1.36 (m, 4H), 1.69 (t, J = 7.2 Hz, 2H), 1.80-1.83 (m, 2H), 2.05 (d, J = 8.4 Hz, 2H), 3.10 (t, J = 12 Hz, 1H), 3.21 (q, J = 7.2 Hz, 2H), 7.18-7.17 (m, 1H), 7.19-7.20 (m, 1H), 7.21-7.22 (m, 1H), 7.23-7.26 (m, 6H), 7.28-7.29 (m ,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.16, 26.22, 26.75, 31.20, 32.83, 36.11, 125.42, 127.40, 128.28, 128.38, 128.65, 128.82, 129.66, 130.20, 139.60, 155.72, 222.73; Anal. Calcd for $C_{24}H_{26}N_2S_2$: C, 70.89; H, 6.45; N, 6.89. Found: C, 70.75; H, 6.34; N, 6.77.

*Methyl 1,3,5-triphenyl-1H-pyrazole-4-carbodithioate (**4j**)*:



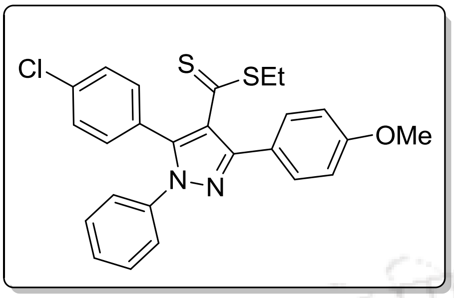
Red solid: (0.209 g, 65%); m.p. 123-124 °C; R_f = 0.60 (Hexane: ethyl acetate 11:1); IR (KBr): 1057, 1596, 2922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.18-7.23 (m, 4H), 7.24-7.33 (m, 9H), 7.35-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.65, 101.98, 125.42, 127.70, 127.86, 128.50, 128.92, 128.98, 129.64, 130.25, 130.38, 139.34, 140.48, 1487.94, 222.14; Anal. Calcd for $C_{23}H_{18}N_2S_2$: C, 71.47; H, 4.69; N, 7.25. Found: C, 71.35; H, 4.54; N, 7.17.

*Methyl 3-(4-chlorophenyl)-1,5-diphenyl-1H-pyrazole-4-carbodithioate (**4k**)*:



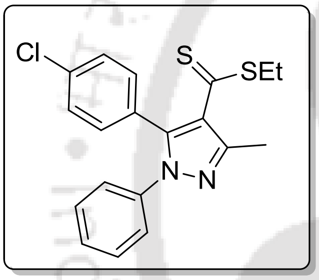
Red solid: (0.294 g, 70%); m.p. 187-189 °C; R_f = 0.70 (Hexane: ethyl acetate 11:1); IR (KBr): 1069, 1597, 2921 cm^{-1}.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.25-7.33 (m, 9H), 7.35 (d, J = 7.2 Hz, 3H), 7.64 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.11, 125.47, 128.03, 128.24, 128.55, 128.74, 128.96, 129.05, 129.16, 129.79, 130.27, 130.80, 134.38, 139.33, 141.07, 148.01, 223.59; Anal. Calcd for $C_{23}H_{17}ClN_2S_2$: C, 65.62; H, 4.07; N, 6.65. Found: C, 65.55; H, 3.95; N, 6.56.

*Ethyl 5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-4-carbodithioate (**4l**)*:



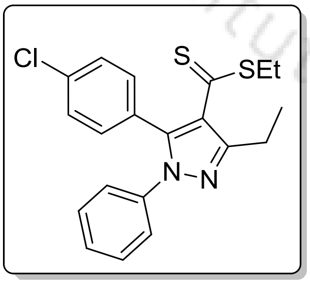
Red semi-solid: (0.279 g, 60%); R$_f$ = 0.54 (Hexane: ethyl acetate 11:1); IR (KBr): 1078, 1605, 2924 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): *δ* 1.23 (t, *J* = 7.2 Hz, 3H), 3.22 (q, *J* =7.2 Hz, 2H), 3.82 (s, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 3H), 7.25-7.34 (m, 6H), 7.64 (d, *J* = 8.8 HZ, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 12.06, 31.56, 55.49, 102.56, 113.98, 125.56, 128.06, 128.31, 128.85, 129.19, 129.79, 131.59, 139.31, 139.57, 148.90, 159.96, 223.31; Anal. Calcd for $C_{25}H_{21}ClN_2OS_2$: C, 64.57; H, 4.55; N, 6.02. Found: C, 64.46; H, 4.49; N, 5.91.

*Ethyl 5-(4-chlorophenyl)-3-methyl-1-phenyl-1H-pyrazole-4-carbodithioate (**4m**):*



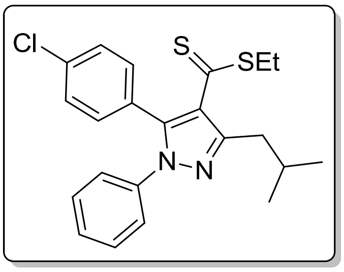
Red semi-solid: (0.321 g, 86%); R$_f$ = 0.67 (Hexane: ethyl acetate 11:1); IR (KBr): 1061, 1596, 2924 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): *δ* 1.25 (t, *J* = 7.6 Hz, 3H), 2.48 (s, 3H), 3.22 (q, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.17-7.20 (m, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 12.28, 13.30, 31.17, 101.99, 125.47, 127.94, 128.12, 128.85, 129.10, 129.30, 131.00, 131.63, 135.14, 136.94, 139.19, 147.85, 221.27; Anal. Calcd for $C_{19}H_{17}ClN_2S_2$: C, 61.19; H, 4.59; N, 7.51. Found: C, 61.10; H, 4.50; N, 7.42.

*Ethyl 5-(4-chlorophenyl)-3-ethyl-1-phenyl-1H-pyrazole-4-carbodithioate (**4n**)*:



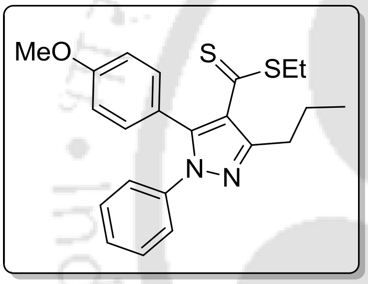
Red semi-solid: (0.317g, 82%); R$_f$ = 0.73 (Hexane: ethyl acetate 11:1); IR (KBr): 1062, 1591, 2970 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): *δ* 1.26 (t, *J* = 7.6 Hz, 3H), 1.32 (t, *J* = 7.6 Hz, 3H), 2.92 (q, *J* = 7.6 Hz, 2H), 3.23 (q, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 6.8 Hz, 2H), 7.24-7.30 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 12.12, 13.64, 20.47, 31.07, 125.30, 127.67, 127.95, 128.63, 128.91, 131.43, 134.86, 138.77, 139.09, 152.69, 221.56; Anal. Calcd for $C_{20}H_{19}ClN_2S_2$: C, 62.08; H, 4.95; N, 7.24. Found: C, 62.00; H, 4.85; N, 7.16.

*Ethyl 5-(4-chlorophenyl)-3-isobutyl-1-phenyl-1H-pyrazole-4-carbodithioate (**4o**)*:



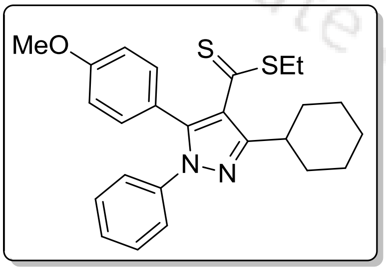
Red solid: (0.324 g, 86%); m.p. 94-95 °C. R_f = 0.78 (Hexane: ethyl acetate 11:1); IR (KBr): 1059, 1599, 2957 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.97 (s, 3H), 0.98 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H), 2.02-2.12 (m, 1H), 2.79 (d, *J* = 7.2 Hz, 2H), 3.21 (q, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.18-7.20 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.26-7.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.11, 22.69, 28.46, 31.01, 35.59, 125.26, 127.63, 127.92, 128.57, 128.87, 129.25, 131.42, 134.80, 138.56, 139.07, 150.61, 221.83; Anal. Calcd for $C_{22}H_{23}ClN_2S_2$: C, 63.67; H, 5.59; N, 6.75. Found: C, 63.55; H, 5.45; N, 6.66.

*Ethyl 5-(4-methoxyphenyl)-1-phenyl-3-propyl-1H-pyrazole-4-carbodithioate (**4p**)*:



Red semi-solid: (0.325 g, 82%);. R_f = 0.64 (Hexane: ethyl acetate 11:1); IR (KBr): 1027, 1604, 2958 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.00 (t, *J* = 7.6 Hz, 3H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.76 (sextet, *J* = 7.6 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 3.21 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.21-7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.27, 14.36, 14.4, 22.81, 29.18, 31.10, 55.29, 113.86, 121.68, 125.42, 127.47, 128.68, 128.89, 131.58, 139.58, 139.97, 151.60, 159.94, 222.53; Anal. Calcd for $C_{22}H_{24}N_2OS_2$: C, 66.63; H, 6.10; N, 7.06. Found: C, 66.52; H, 6.01; N, 6. 97.

*Ethyl 3-cyclohexyl-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-4-carbodithioate (**4q**):*



Red solid: (0.332 g, 76%); m.p. 107-109 °C; R_f = 0.68 (Hexane: ethyl acetate 11:1); IR (KBr): 1030, 1607, 2925 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.23 (t, *J* = 7.2 Hz, 3H), 1.27-1.42 (m, 3H), 1.62-1.71 (m, 3H), 1.81 (d, *J* = 11.6 Hz, 2H), 2.04 (d, *J* = 12 Hz, 2H), 3.11-3.05 (m, 1H), 3.21 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 6.77 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.20-7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.28, 26.29, 26.83, 31.28, 32.89, 36.21, 55.29, 102.03, 113.86, 121.88, 125.54, 127.38, 128.23, 128.89, 131.58, 139.81, 155.75, 159.91, 223.17; Anal. Calcd for $C_{25}H_{28}N_2OS_2$: C, 68.77; H, 6.46; N, 6.42. Found: C, 68.70; H, 6.35; N, 6.34.

XRD for Compound **4k**

Crystallographic data for **4k**: Monoclinic space group $P2_1/c$, a = 12.2000(4), b = 9.7024(3), c = 18.1853(6) Å, β = 106.092(2)°, V = 2068.24(12) Å^3, Z = 4, ρ_{calcd}= 1.352 g.cm^{-3}, μ = 0.398 mm^{-1} , T = 298(2) K, R1 = 0.0494 , wR2 = 0.1460, GOF = 0.993 for $I>2\sigma(I)$, Mo$_{k\alpha}$-Ray (λ = 71,073 pm). Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 894780. 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).

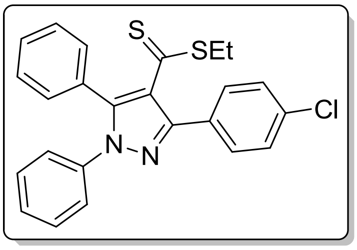
Table 3. Crystal data and structure refinement for **4k**, for atomic coordinates and equivalent isotopic displacement parameters and bond angles, please check the CIF

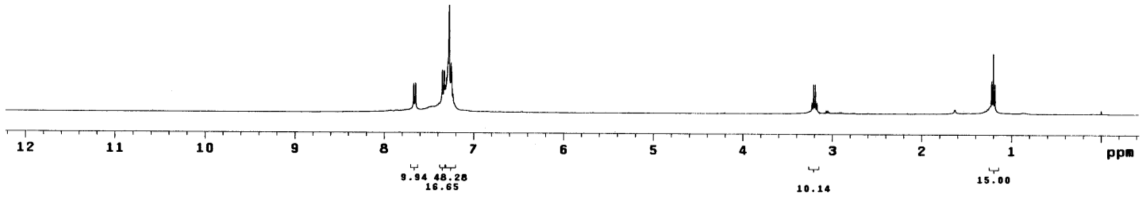
Parameters	**Compound**
Formula	$C_{20}H_{22}ClN_3S_2$
CCDC number	894780
Formula weight	403.98
T (K)	298(2)
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	$P2_1/c$
a (Å)	12.2000(4)
b (Å)	9.7024(3)
c (Å)	18.1853(6)
α (^{0})	90.00
β (^{0})	106.092(2)
γ (^{0})	90.00
V (Å)^3	2068.24(12)
Z	4
D_{calcd} (g m^{-3})	1.297
μ (mm^{-1})	0.395
F (0 0 0)	848

Reflection collected	30375
Unique reflections	3371
Goodness-of-fit (GOF)[a] on F^2	0.993
R [I > 2σ(I)]	[b]$R_1 = 0.0494$, [c]$wR_2 = 0.1460$
R indices (all data)	[b]$R_1 = 0.0786$, [c]$wR_2 = 0.1651$

^{1}H **NMR (400 MHz, CDCl$_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate* (***4d***)*:*

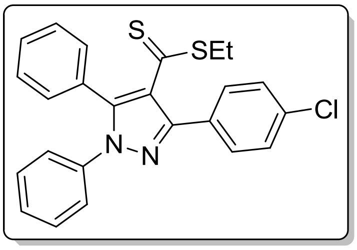
```
AG_PY_Cl

expl  s2pul

      SAMPLE                SPECIAL
date   Mar 19 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             100   hs                nn
ct             100        PROCESSING
   TRANSMITTER       lb              0.10
tn              H1   fn             65536
sfrq       399.853          DISPLAY
tof          362.8   sp            -171.8
tpwr            57   wp            5063.0
pw           9.850   rfl            801.5
    DECOUPLER        rfp                0
dn             C13   rp             111.0
dof              0   lp             -85.3
dm             nnn           PLOT
dmm              c   wc               250
dpwr            50   sc                 0
dmf          15900   vs                27
                     th                20
                     nm   cdc   ph
```

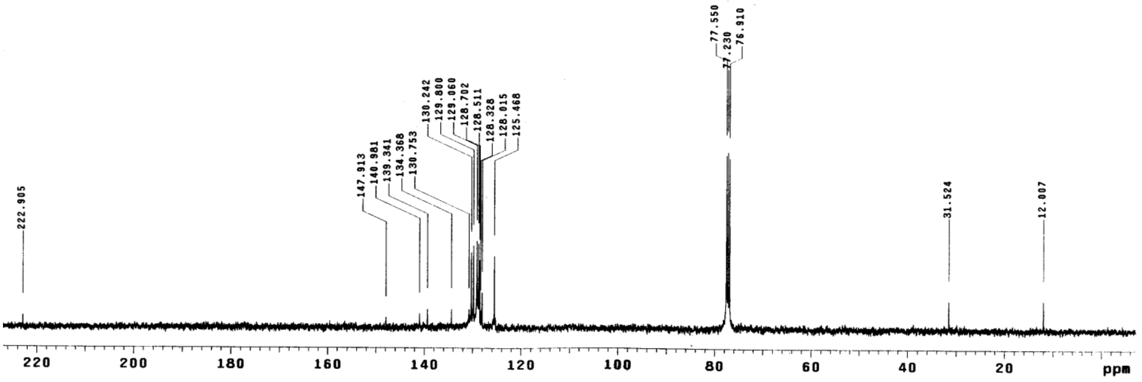




^{13}C **NMR (100 MHz, CDCl$_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate* (***4d***)*:*

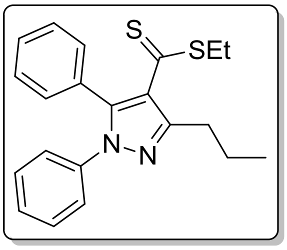
```
AG_PY_Cl_13C

expl  s2pul

      SAMPLE                SPECIAL
date   Mar 18 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              10   in                 n
d1           1.000   dp                 y
nt            3000   hs                nn
ct            3000        PROCESSING
   TRANSMITTER       lb              2.00
tn             C13   fn             65536
sfrq       100.554          DISPLAY
tof         1536.3   sp            -718.9
tpwr            61   wp           23639.6
pw           9.300   rfl           9275.9
    DECOUPLER        rfp           7764.9
dn              H1   rp             -72.4
dof              0   lp            -308.4
dm             yyy           PLOT
dmm              w   wc               250
dpwr            42   sc                 0
dmf           8900   vs                42
                     th                 2
                     nm   no   ph
```

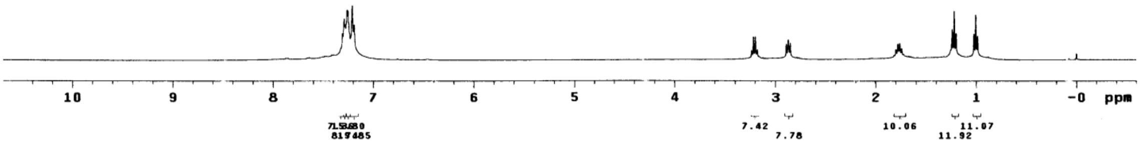




^{1}H **NMR (400 MHz, CDCl$_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate (**4h**):*

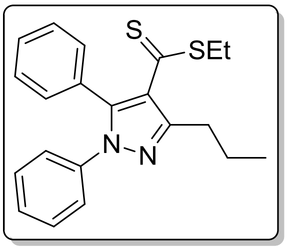
```
AG_PY_N_BU

exp1  s2pul

       SAMPLE                  SPECIAL
date    Jun 22 2012   temp        not used
solvent        CDCl3  gain        not used
file /export/home/~   spin        not used
ciftemp/AG_PY_N_BU    hst            0.008
    ACQUISITION       pw90          19.700
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            -242.0
tof            362.8  wp            4517.3
tpwr              57  rfl            796.0
pw             9.850  rfp                0
     DECOUPLER        rp             123.4
dn               C13  lp             -98.6
dof                0            PLOT
dm               nnn  wc               250
dmm                c  sc                 0
dpwr              50  vs                14
dmf            15900  th                19
                      nm  cdc  ph
```

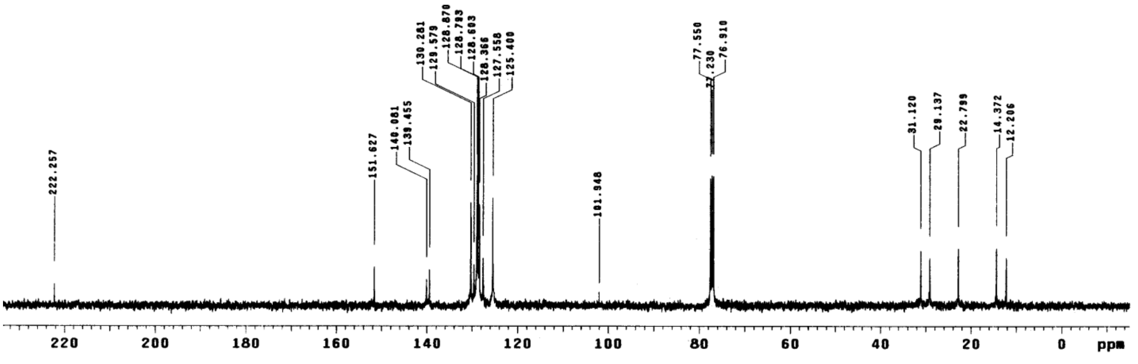




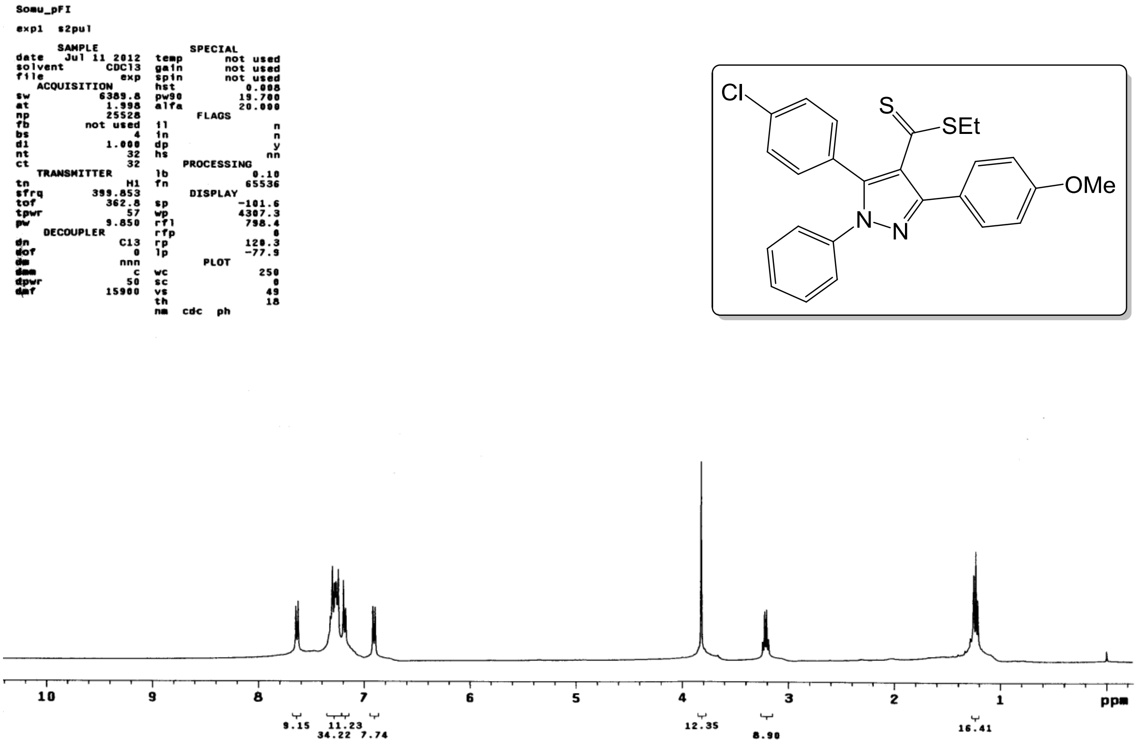
^{13}C **NMR (100 MHz, CDCl$_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate (**4h**):*

```
AG_PY_N_BU_13C

exp1  s2pul

       SAMPLE                  SPECIAL
date    Jun 22 2012   temp        not used
solvent        CDCl3  gain        not used
file /export/home/~   spin        not used
ciftemp/AG_PY_N_BU~   hst            0.008
                _13C  pw90          18.600
   ACQUISITION        alfa          20.000
sw           25125.6           FLAGS
at             1.199  il                 n
np             60270  in                 n
fb             13800  dp                 y
bs                 4  hs                nn
d1             1.000         PROCESSING
nt              7000  lb              2.00
ct              1600  fn             65536
    TRANSMITTER              DISPLAY
tn               C13  sp           -1517.2
sfrq         100.554  wp           25125.6
tof           1536.3  rfl           9282.1
tpwr              61  rfp           7764.9
pw             9.300  rp             -64.3
     DECOUPLER        lp            -338.7
dn                H1            PLOT
dof                0  wc               250
dm               yyy  sc                 0
dmm                w  vs                30
dpwr              42  th                 3
dmf             8900  nm  no  ph
```



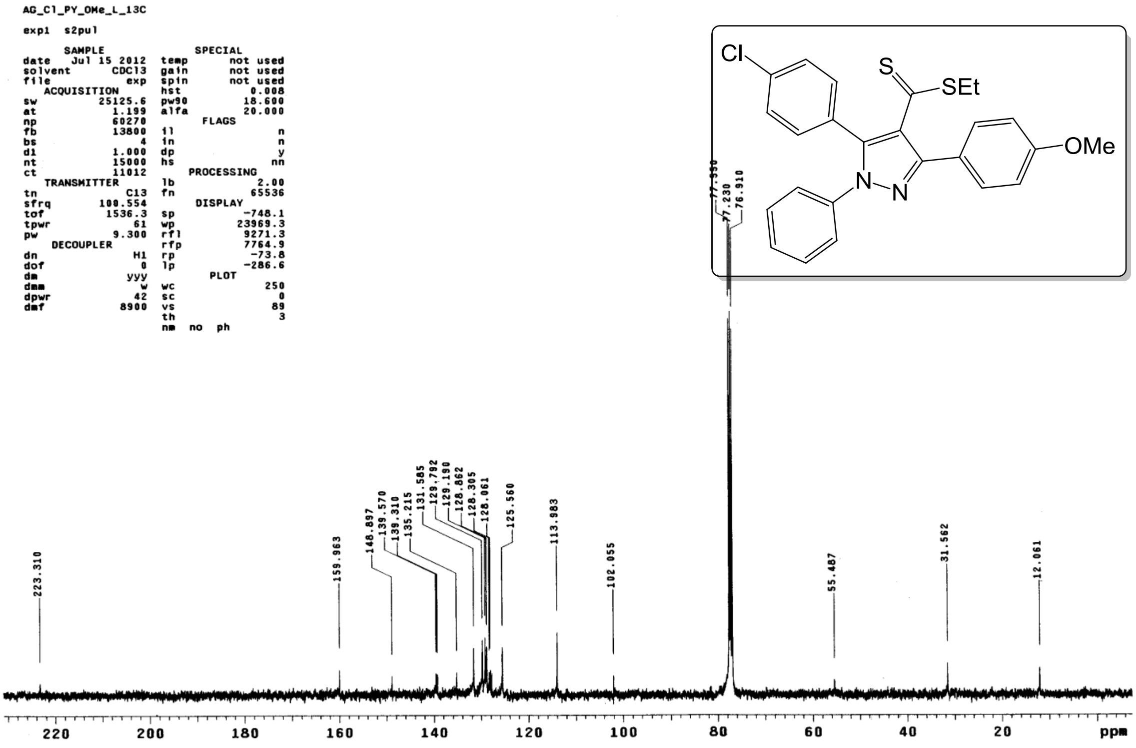


^{1}H **NMR (400 MHz, CDCl$_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate (**4l**):*



```
Somu_pFI

expl  s2pul

      SAMPLE                  SPECIAL
date   Jul 11 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            -101.6
tpwr            57   wp            4307.3
pw           9.850   rfl            798.4
    DECOUPLER        rfp                0
dn             C13   rp             120.3
dof              0   lp             -77.9
dm             nnn            PLOT
dmm              c   wc               250
dpwr            50   sc                 0
dmf          15900   vs                49
                     th                18
                     nm  cdc  ph
```

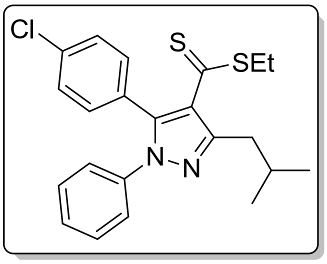
^{13}C **NMR (100 MHz, CDCl$_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate (**4l**):*

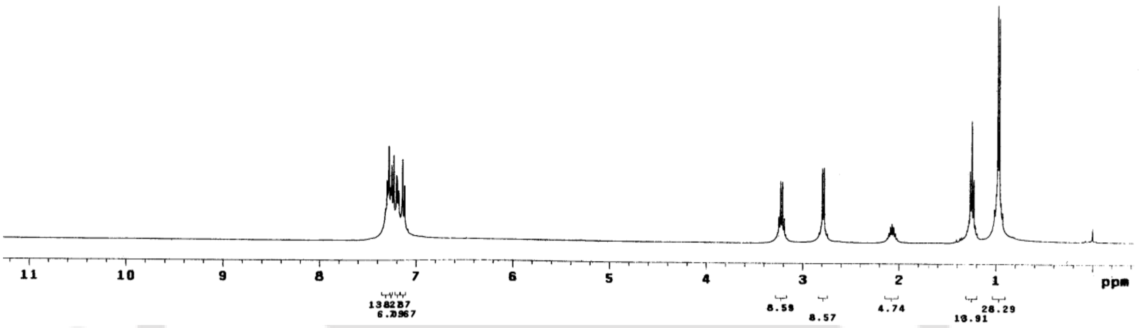


```
AG_Cl_PY_OMe_L_13C

expl  s2pul

      SAMPLE                  SPECIAL
date   Jul 15 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           15000   hs                nn
ct           11012        PROCESSING
   TRANSMITTER       lb              2.00
tn             C13   fn             65536
sfrq       100.554          DISPLAY
tof         1536.3   sp            -748.1
tpwr            61   wp           23969.3
pw           9.300   rfl           9271.3
    DECOUPLER        rfp           7764.9
dn              H1   rp             -73.8
dof              0   lp            -286.6
dm             yyy            PLOT
dmm              w   wc               250
dpwr            42   sc                 0
dmf           8900   vs                89
                     th                 3
                     nm  no  ph
```

^{1}H **NMR (400 MHz, CDCl$_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate (**4o**):*

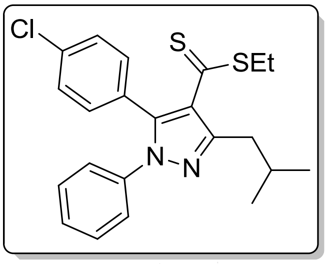
```
AG_C1_PY_ISO

exp1  s2pul

      SAMPLE                  SPECIAL
date   Jun 27 2012   temp        not used
solvent      CDC13   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            -173.6
tpwr            57   wp            4735.5
pw           9.850   rfl            794.8
    DECOUPLER        rfp                0
dn             C13   rp             107.0
dof              0   lp             -84.4
dm             nnn            PLOT
dmm              c   wc               250
dpwr            50   sc                 0
dmf          15900   vs                59
                     th                20
                     nm   cdc   ph
```

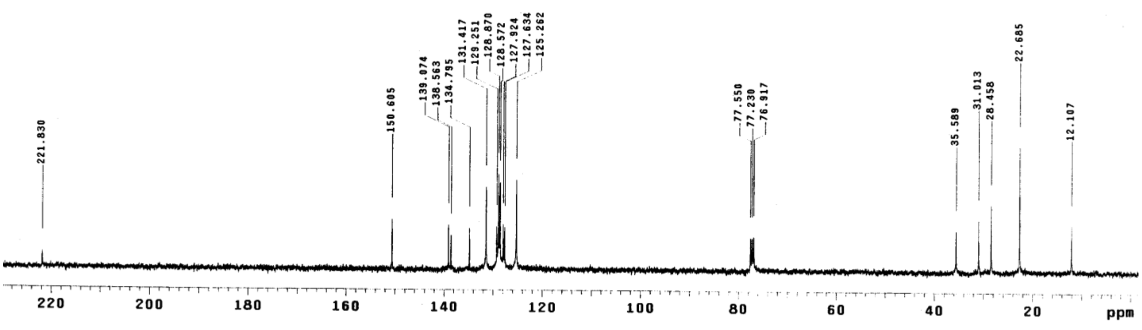




^{13}C **NMR (100 MHz, CDCl$_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate (**4o**):*

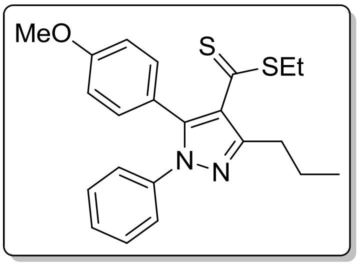
```
AG_C1_PY_ISO_13C

exp1  s2pul

      SAMPLE                  SPECIAL
date   Jun 27 2012   temp        not used
solvent      CDC13   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            5000   hs                nn
ct             816        PROCESSING
   TRANSMITTER       lb              2.00
tn             C13   fn             65536
sfrq       100.554          DISPLAY
tof         1536.3   sp            -184.5
tpwr            61   wp           23331.3
pw           9.300   rfl           9296.6
    DECOUPLER        rfp           7764.9
dn              H1   rp             -74.7
dof              0   lp            -323.1
dm             yyy            PLOT
dmm              w   wc               250
dpwr            42   sc                 0
dmf           8900   vs                29
                     th                 3
                     nm   no   ph
```

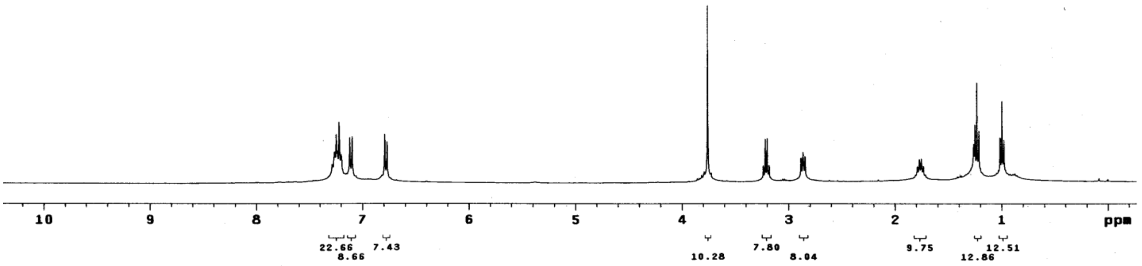




^{1}H **NMR (400 MHz, $CDCl_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate* (***4p***):

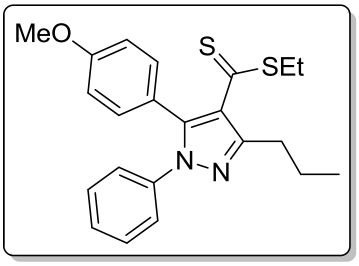
```
AG_OMe_PY_Bu

exp1  s2pul

        SAMPLE              SPECIAL
date    Jul 12 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            -107.8
tpwr             57   wp            4265.4
pw            9.850   rfl            796.2
    DECOUPLER         rfp                0
dn              C13   rp             100.1
dof               0   lp             -84.0
dm              nnn            PLOT
dmm               c   wc               250
dpwr             50   sc                 0
dmf           15900   vs                44
                      th                20
                      nm  cdc  ph
```

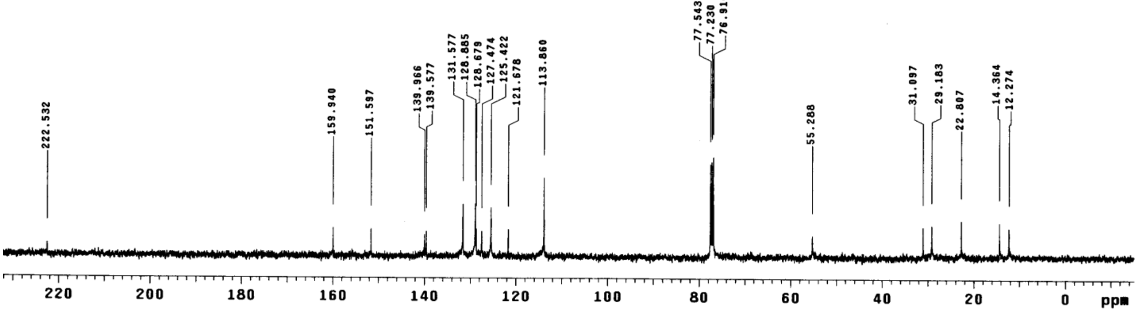




^{13}C **NMR (100 MHz, $CDCl_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate (**4p**):*

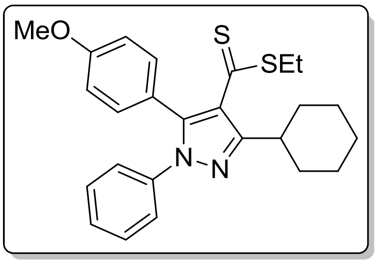
```
AG_OMe_PY_BU_13C

exp1  s2pul

        SAMPLE              SPECIAL
date    Jul 12 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             5000   hs                nn
ct             1256        PROCESSING
   TRANSMITTER        lb              2.00
tn              C13   fn             65536
sfrq        100.554          DISPLAY
tof          1536.3   sp           -1515.6
tpwr             61   wp           25125.6
pw            9.300   rfl           9280.5
    DECOUPLER         rfp           7764.9
dn               H1   rp             -95.0
dof               0   lp            -271.4
dm              yyy            PLOT
dmm               w   wc               250
dpwr             42   sc                 0
dmf            8900   vs                22
                      th                 2
                      nm  no  ph
```

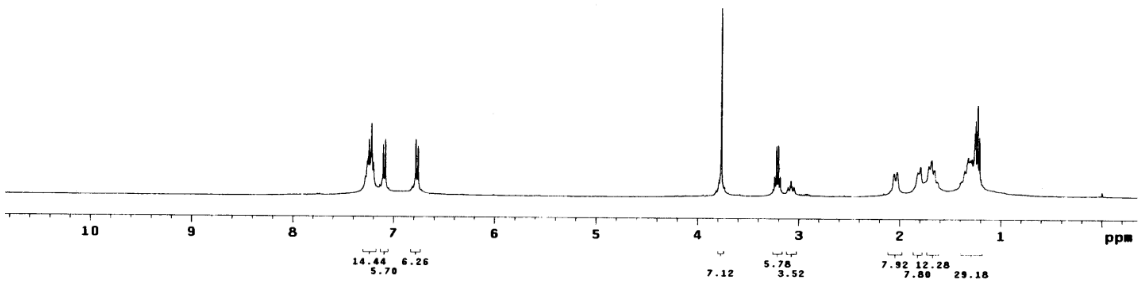




^{1}H **NMR (400 MHz, $CDCl_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate* (***4q***):

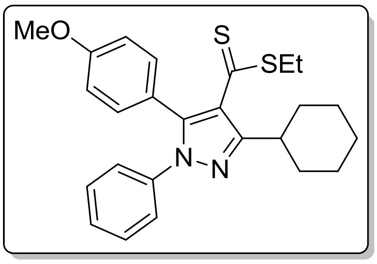
```
AG_OMe_PY_L_CY

expl  s2pul

      SAMPLE                 SPECIAL
date   Jul 20 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            -143.1
tpwr             57  wp            4525.7
pw            9.850  rfl            798.0
    DECOUPLER        rfp                0
dn              C13  rp             103.0
dof               0  lp             -94.3
dm              nnn            PLOT
dmm               c  wc               250
dpwr             50  sc                 0
dmf           15900  vs                46
                     th                 7
                     nm  cdc  ph
```

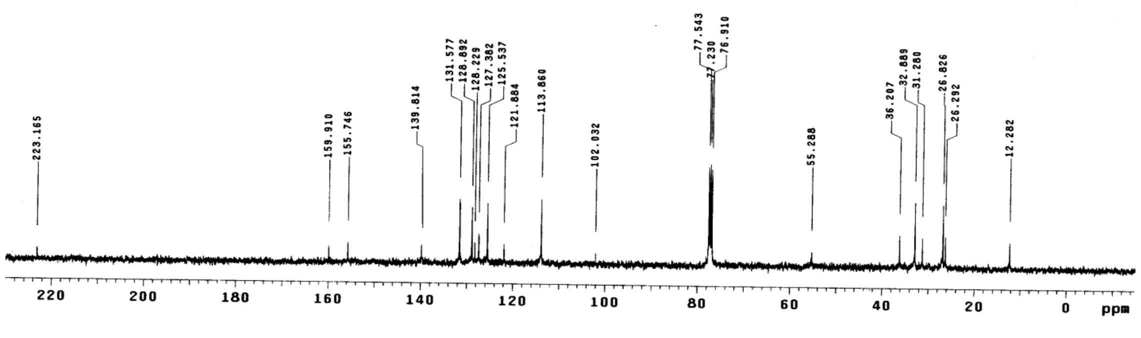




^{13}C **NMR (100 MHz, $CDCl_3$):** *trisubstituted-1H-pyrazole-4-carbodithioate (**4q**):*

```
AG_OMe_PY_CY_L_13C

expl  s2pul

      SAMPLE                 SPECIAL
date   Jul 19 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             5000  hs                nn
ct             3240        PROCESSING
   TRANSMITTER       lb              2.00
tn              C13  fn             65536
sfrq        100.554          DISPLAY
tof          1536.3  sp           -1509.5
tpwr             61  wp           25125.6
pw            9.300  rfl           9274.4
    DECOUPLER        rfp           7764.9
dn               H1  rp             -58.3
dof               0  lp            -363.5
dm              yyy            PLOT
dmm               w  wc               250
dpwr             42  sc                 0
dmf            8900  vs                24
                     th                 2
                     nm  no  ph
```





3.1. Pyrazolo[3,4-*b*]pyridine and its importance

Nitrogen-containing heterocyclic is one of the most versatile areas for synthetic and pharmaceutical chemists. Especially, functionalized pyrazole and their fused derivatives exhibit importance pharmacological activities such as anti-inflammatory, anti-tumor, analgesic and fungicides. For example, substituted pyrazolo[3,4-*b*]pyridine derivative (**VII**) BAY 41-2272[69] relaxes isolated human ureter in a standardized *ex vivo* model. Pyrazolo[3,4-*b*]pyridine derivatives (**VIII**, **IX**, **X** and **XI**) also possess a wide range of pharmacological activities such as anti-proliferative,[70] anti-microbial,[71] tumor growth inhibitors[72] and anxiolytic drug (Figure 4). Pyrazolo[3,4-*b*]pyridine acts as ligand for complex formation with transitional metal and acts as potential anti-cancer agent.[73] Therefore, the synthesis of pyrazolo[3,4-*b*]pyridine derivatives are considered useful for their biological activity in near future.

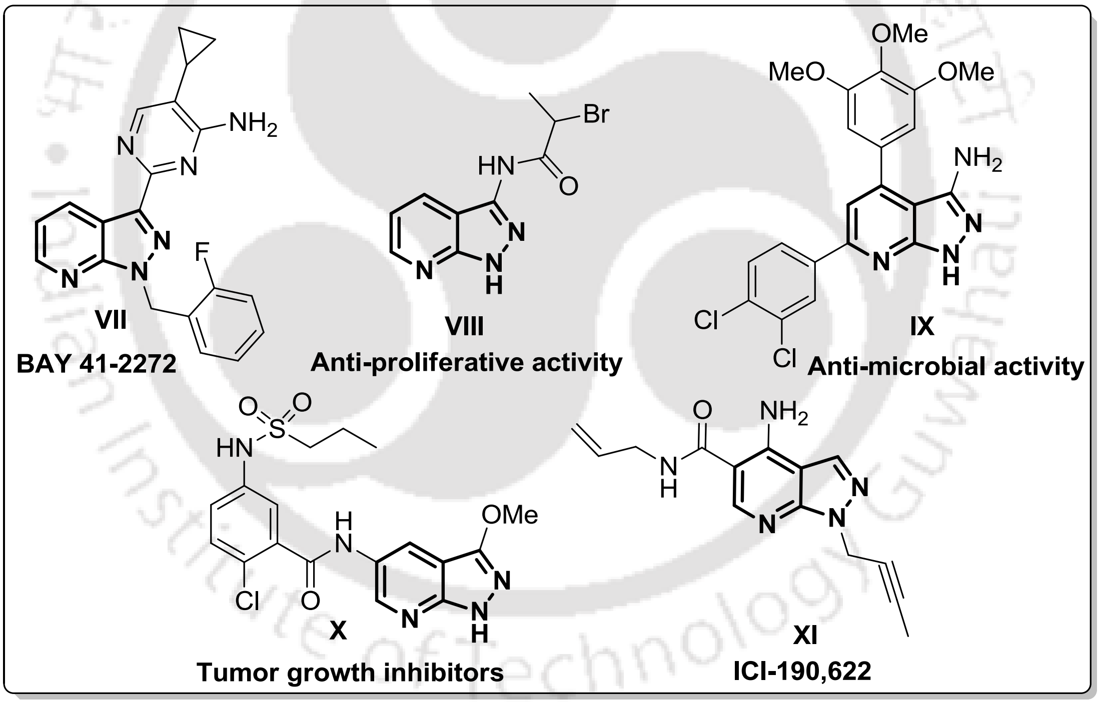
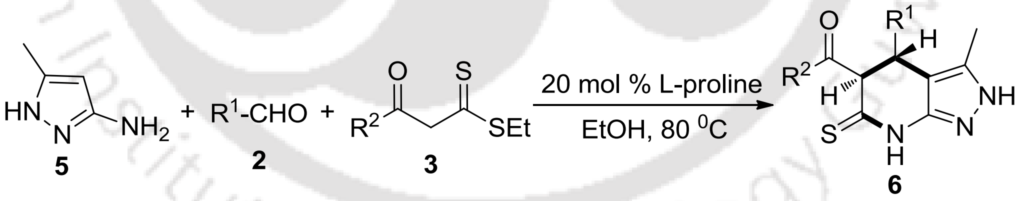


Figure 4. Biologically active compound containing pyrazolo-pyridine structural unit

3.2. Results and Discussion

The synthesis of pyrazolo[3,4-*b*]pyridines was first reported by Hoehn three decades ago.[74] Since then several methods have been developed for the synthesis of pyrazolo[3,4-*b*]pyridines, but all these methods have been suffered from several drawbacks such as lower yield, longer reaction time, use of hazardous organic solvents, toxic and expensive catalysts, harsh reaction conditions and costly purification process. Recently, various synthetic strategies were utilized to achieve pyrazolo-pyridines core frameworks and will be separately discussed in Chapter 1 of Part B.

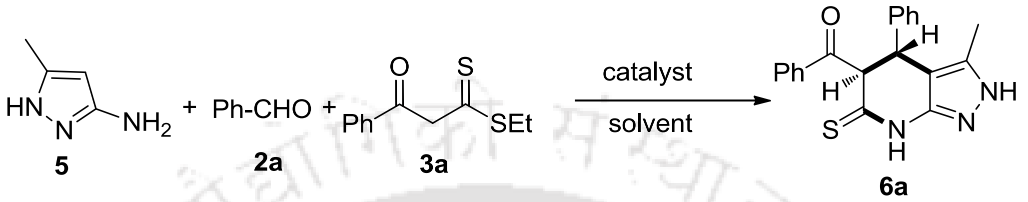
According to our previous study[75] as well as by others with L-proline (an abundant, readily available and inexpensive catalyst) can act either as an acid or a base or both simultaneously, as a nucleophile and has tendency to form enamine/iminium intermediates when reacted with carbonyl/*α, β*-unsaturated carbonyl compounds.[76] It has been also exploited in aldol,[77] asymmetric reactions,[78] Mannich,[79] Michael,[80] Biginelli,[81] Diels-Alder/Knoevenagel[82] as well as in a diverse range of multicomponent reactions. So we conceived L-proline can also utilized as an efficient catalyst for one-pot diastereoselective synthesis of tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivatives from 3-amino-5-methyl-pyrazole, aldehydes and ethyl-3-oxo-3-arylpropanedithioate involving MCR strategy. Herein, we would like to report the diastereoselective synthesis of densely functionalized tetrahydro-2H-pyrazolo[3,4-*b*]pyridine (Scheme 46).



Scheme 46. Synthesis of tetrahydro-2H-pyrazolo[3,4-*b*]pyridines

For our present study, we started with reactions of 3-amino-5-methyl-pyrazole (**5**), benzaldehyde (**2a**) and ethyl-3-oxo-3-phenylpropanedithioate (**3a**) as model substrates in ethanol at room temperature and also in refluxing condition for 24 h without any catalyst and no product formations were observed. The same reaction in presence of L-proline catalyst at room temperature in ethanol also did not produce any desired product. However, when the reaction mixture was refluxed in presence of 10 mol % L-proline in ethanol at 80 ^{0}C, provided the desired product in 60% yield (Table 4, entry 4). Remarkably, when the same reaction mixture was refluxed in presence of 20 mol % L-proline in ethanol at 80 ^{0}C, it afforded product **6a** in 72% yield (Table 4, entry 5), which was characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra as well as elemental analyses.

Table 4. Optimization of reaction conditions for the synthesis of tetrahydro-2H-pyrazolo[3,4-*b*]pyridines[a]



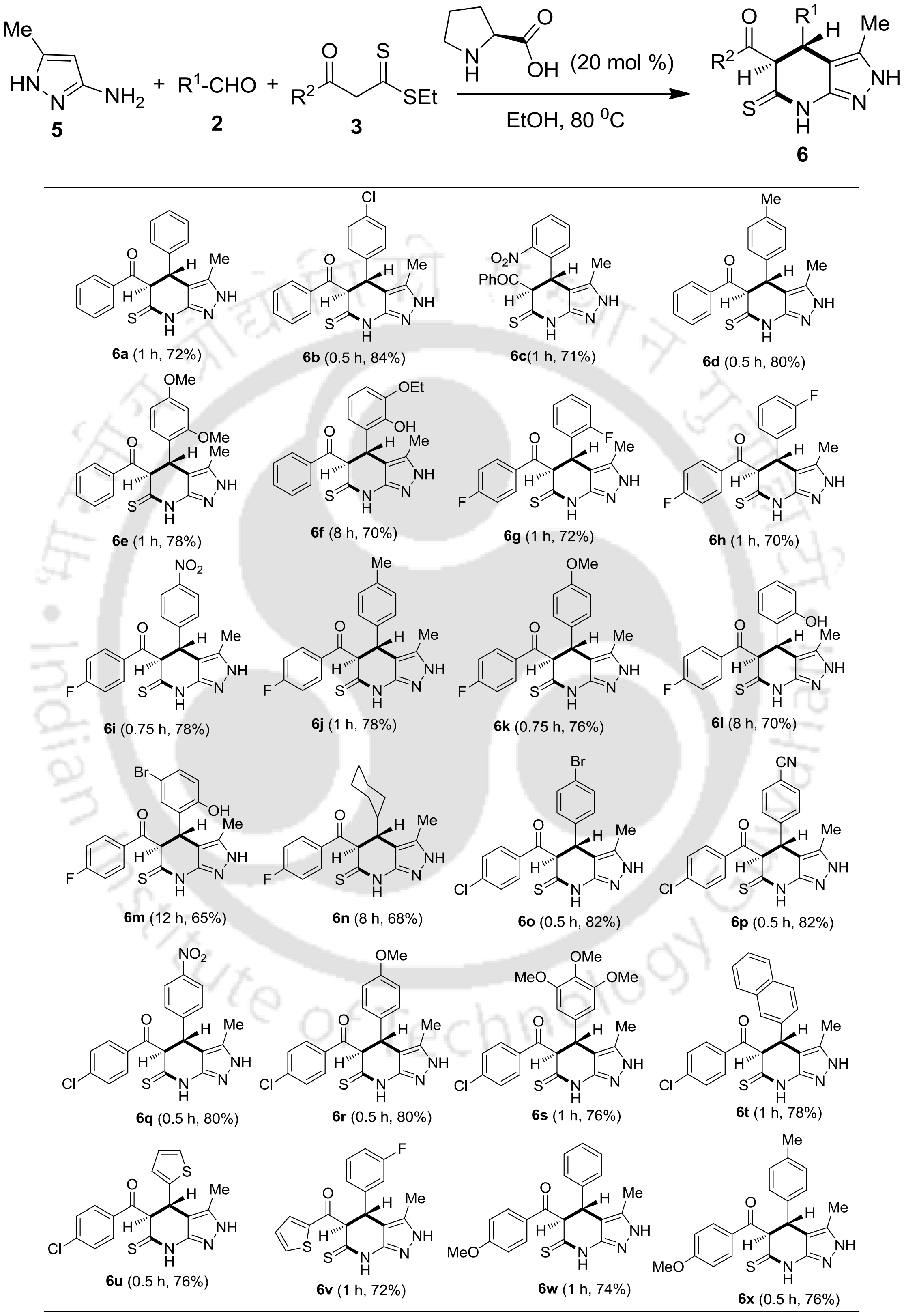
Entry	Catalyst	Mol %	Temp (^{0}C)	Solvent	Time (h)	Yield (%)[b]
1	-	-	rt	EtOH	24	NR
2	-	-	80	EtOH	24	NR
3	L-proline	10	rt	EtOH	24	NR
4	L-proline	10	80	EtOH	8	60
5	**L-proline**	**20**	**80**	**EtOH**	**1**	**72**
6	L-proline	30	80	EtOH	8	65
7	L-proline	20	65	MeOH	8	50
8	L-proline	20	80	MeCN	8	65
9	L-proline	20	150	DMF	8	48
10	L-proline	20	80	*t*-BuOH	12	60
11	*p*-TSA	20	80	EtOH	12	20
12	AcOH	20	80	EtOH	12	24
13	Et_3N	20	80	EtOH	12	40
14	Piperidine	20	80	EtOH	24	35
15	CAN	20	80	EtOH	12	NR
16	$In(OTf)_3$	20	80	EtOH	24	NR

[a]The reactions were performed in 1 mmol scale using 3-amino-5-methyl pyrazole (**5**), benzaldehyde (**2a**) and ethyl 3-oxo-3-phenylpropanedithioate (**3a**). [b]Isolated yield.

It was also noted that the yield did not improve significantly in presence of 30 mol % L-proline (Table 4, entry 6). Later on, in a quest to improve the product yield, the reaction was carried out with different solvents e.g. MeOH, MeCN, DMF and *t*-BuOH (Table 4, entries 7-10). Likewise, other catalysts such as *p*-TSA, AcOH, Et_3N, and piperidine in ethanol were also scrutinized to verify the efficacy of the catalysts in terms of yield and reaction time (Table 4, entries 11-14). It is noteworthy to mention that the reaction did not take place in presence of other catalysts such as ceric ammonium nitrate (CAN) and $In(OTf)_3$. From these observations, it is found that 20 mol % L-proline in ethanol under reflux condition is the most suitable reaction condition for this above transformation (Table 4).

After optimization of reaction conditions, a reaction was carried out with 3-amino-5-methyl-pyrazole (**5**), 4-chlorobenzaldehyde (**2d**) and ethyl-3-oxo-3-phenylpropanedithioate (**3a**) in presence of 20 mol % L-proline under identical reaction conditions. The product (4-(4-chlorophenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(phenyl)methanone (**6b**) was afforded in 84 % yield. Various aromatic aldehydes having different electron-withdrawing and electron-donating substituents at different position in the aromatic ring were examined with 3-amino-5-methyl-pyrazole (**5**) and ethyl-3-oxo-3-phenylpropanedithioate (**3a**) under the optimized reaction condition and the desired products **6c-f** were obtained in 70-80% yield (Table 5). We also verified the reactions of ethyl-3-(4-fluorophenyl)-3-oxopropanedithioate (**3b**) with various aromatic aldehydes with different substituents such as F, NO_2, Me, MeO, OH, Br in the aromatic ring and the desired products **6g-m** were obtained in moderate to good yield (Table 5). For generalizing the reaction procedure, we further examined the reactions between 3-amino-5-methyl-pyrazole (**5**), ethyl-3-(4-chlorophenyl)-3-oxopropanedithioate (**3c**) with aliphatic aldehydes such as cyclohexyl aldehydes (**2i**), aromatic aldehydes, poly-aromatic aldehydes (**2n**) and hetero-aromatic aldehydes (**2f**) in the presence of same amount of catalyst and the desired products **6n-u** were obtained in moderate to excellent yield (Table 5). Encouraged by these successful results, we also scrutinized the reactions of 3-amino-5-methyl-pyrazole (**5**), 3-fluorobenzaldehyde (**2o**) and ethyl-3-oxo-3-(thiophen-2-yl)propanedithioate (**3d**) in a similar manner and (4-(3-fluorophenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (**6v**) was obtained in 72% yield (Table 5). Similarly, reaction between 3-amino-5-methyl-pyrazole (**5**), different aromatic aldehydes (**2a** and **2b**) and ethyl-3-(4-methoxyphenyl)-3-oxopropanedithioate (**3e**) under similar reaction condition resulted in the desired products in good yields (Table 5). Unfortunately, the

Table 5. Diastereoselective synthesis of various tetrahydro-2H-pyrazolo[3,4-*b*]pyridines



[a]The reactions were performed in 1 mmol scale using 3-amino-5-methyl pyrazole (**5**), benzaldehyde (**2**) and ethyl 3-oxo-3-phenylpropanedithioate (**3**) in EtOH at 80 ^{0}C. [b]Isolated yield.

reaction between 3-amino-5-methyl-pyrazole (**5**), aliphatic aldehydes such as butyraldehyde (**2h**) and isovaleraldehyde (**2m**) and ethyl-3-oxo-3-arylpropanedithioate afforded an inseparable mixture of compounds under optimized reaction condition.

In domino process, two C-C bonds, one C-N bond and one six-membered ring were formed with the concomitant cyclization. Importantly, this three-component reaction for tetrahydro-2H-pyrazolo[3,4-*b*]pyridine **6** generated two chiral centers, but only one stereoisomer was observed through ^{1}H NMR, ^{13}C NMR and X-ray diffraction analysis of **6n** revealed that the products **6** adopted *trans* configuration (Figure 5).

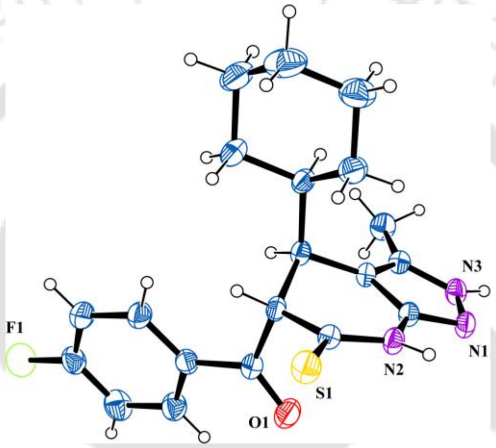
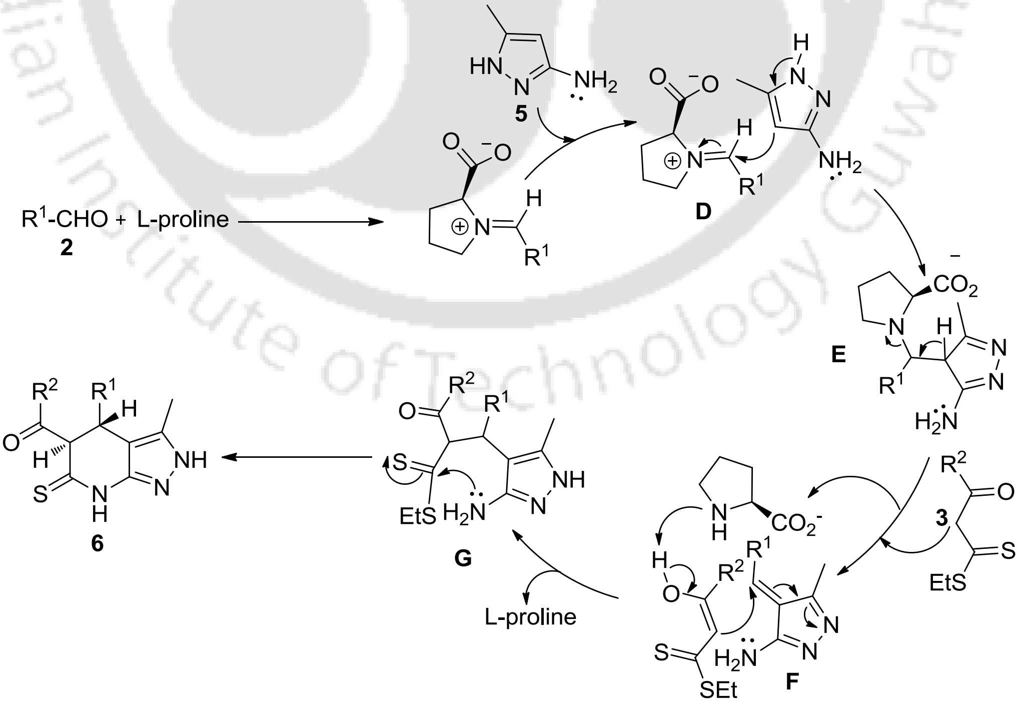


Figure 5. ORTEP structure of compound **6n** (CCDC No. 1038414)



Scheme 47. Plausible mechanism for the formation tetrahydro-2H-pyrazolo[3,4-*b*]pyridine

A plausible mechanism for the formation of the tetrahydro-2H-pyrazolo[3,4-*b*]pyridine **6** is depicted (Scheme 47). Initially aldehyde reacts with L-proline to give an iminium species **D**. Then 3-amino-5-methyl-pyrazole **5** and the iminium species **D** reacts *via* Mannich type reaction to generate intermediate **F**, through intermediate **E**. Subsequently, the addition reaction of the ethyl-3-oxo-3arylpropanedithioate **3** to intermediate **F** furnishes the intermediate **G**, which undergoes concomitant cyclization via intramolecular nucleophilic reaction to provide the desired product of tetrahydro-2H-pyrazolo[3,4-*b*]pyridine **6** (Scheme 47).

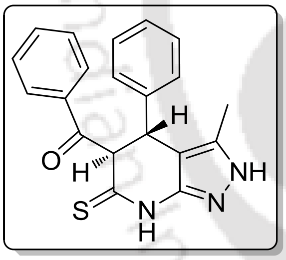
In conclusion, we have developed a new synthetic protocol for the diastereoselective synthesis of tetrahydro-2H-pyrazolo[3,4-*b*]pyridine by three-component reaction of 3-amino-5-methyl-pyrazole, aldehyde, and ethyl-3-oxo-3-arylpropanedithioate using L-proline as a catalyst which is both facile and efficient. Some of the important aspects of this present protocol are simpler experimental procedure, easy to handle, good to excellent yields, shorter reaction times and substrate scope compatibility.

3.3. Experimental Section

General procedure for the synthesis of tetrahydro-2H-pyrazolo[3,4-b]pyridine:

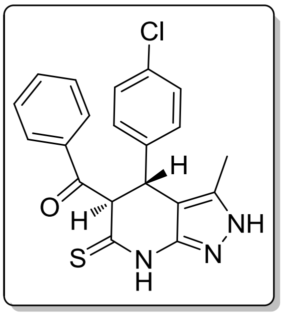
In 25 mL two-necked round-bottomed flask fitted with a reflux condenser, a mixture of 3-amino-5-methyl-pyrazole (0.097 g, 1.0 mmol), the corresponding aldehyde (1.0 mmol), and L-proline (0.023 g, 0.20 mmol) was taken in 3 mL of ethanol and stirred at 80 ^{0}C in a pre-heated oil-bath for 15 minutes. Then, ethyl-3-oxo-3-arylpropanedithioate (1.0 mmol) was added into it and the reaction mixture was refluxed at 80 ^{0}C with constant stirring for the stipulated period of time. The progress of the reaction was monitored by TLC. The reaction mixture was then cooled and the crude residue was extracted in dichloromethane (20 mL x 3). The organic extract was washed with water and dried over anhydrous sodium sulfate. Then, the solvent was concentrated and hexane was added into it. The solid product came out slowly which was filtered through Buchner funnel and it was washed with 1 mL of ethanol. Finally it was dried under reduced pressure.

*((4R,5R)-3-methyl-4-phenyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(phenyl)methanone (**6a**)*:



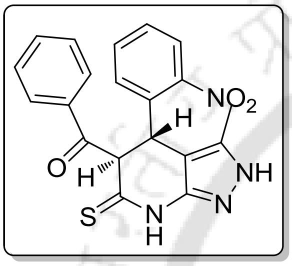
White solid: (0.250 g, 72%); m.p. 286-288 °C; IR (KBr): 1068, 1112, 1286, 1673, 2962, 3337 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 1.71 (s, 3H), 4.35 (d, *J* = 6.0 Hz, 1H), 5.34 (d, *J* = 6.0 Hz, 1H), 7.18-7.22 (m, 3H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 2H), 12.16 (s, 1H), 12.94 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$-DMSO-d$_6$): δ 8.91, 38.71, 63.59, 100.95, 126.49, 127.91, 128.04, 128.18, 132.57, 135.22, 135.66, 141.16, 147.06, 194.09, 194.58; Anal Calcd. for $C_{20}H_{17}N_3OS$ (347.4335): requires C, 69.14; H, 4.93; N, 12.09%. Found C, 69.05; H, 4.80; N, 12.00%. HRMS (ESI) calcd. for $C_{20}H_{17}N_3OS$ (M + H+) 348.1171 found 348.1170.

*((4R,5R)-4-(4-chlorophenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(phenyl)methanone (**6b**)*:



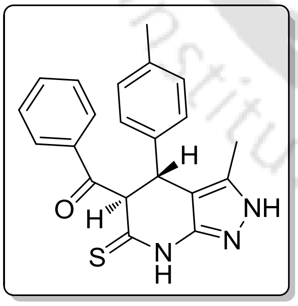
White solid: (0.321 g, 84%); m.p. 232-234 °C; IR (KBr): 1068, 1107, 1258, 1672, 2961, 3340 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$-DMSO-d$_6$): δ 1.70 (s, 3H), 4.16 (d, *J* = 5.2 Hz, 1H), 5.04 (d, *J* = 5.2 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.77 (d, J = 7.6 Hz), 11.48 (s, 1H), 12.18 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$-DMSO-d_6): δ 9.34, 38.49, 63.70, 100.99, 128.40, 128.62, 132.46, 133.00, 135.49, 136.33, 139.96, 147.30, 194.25, 194.73; Anal Calcd. for $C_{20}H_{16}ClN_3OS$ (381.8785): requires C, 62.90; H, 4.22; N, 11.00%. Found C, 62.75; H, 4.12; N, 10.91%. HRMS (ESI) calcd. for $C_{20}H_{16}ClN_3OS$ (M + H+) 382.0781 found 382.0777.

*((4R,5R)-3-methyl-4-(2-nitrophenyl)-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(phenyl)methanone (**6c**)*:



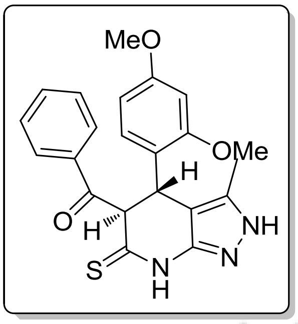
Brown solid: (0.279 g, 71%); m.p. 280-282 °C; IR (KBr): 1000, 1115, 1248, 1353, 1527, 1661, 2924, 3329 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.61 (s, 3H), 4.83 (d, J = 9.2 Hz, 1H), 5.58 (d, J = 9.2 Hz, 1H), 7.41-7.44 (m, 3H), 7.54-7.61 (m, 3H), 7.83 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H), 12.29 (s, 1H), 13.00 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 9.04, 33.33, 60.97, 101.97, 124.10, 128.47, 128.54, 128.69, 129.58, 133.13, 133.28, 134.57, 135.52, 137.05, 147.73, 149.63, 194.74, 196.02; Anal Calcd. for $C_{20}H_{16}N_4O_3S$ (392.4310): requires C, 61.21; H, 4.11; N, 14.28%. Found C, 61.12; H, 4.01; N, 14.14%. HRMS (ESI) calcd. for $C_{20}H_{16}N_4O_3S$ (M + H+) 393.1021 found 393.1020.

*((4R,5R)-3-methyl-6-thioxo-4-(p-tolyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(phenyl)methanone (**6d**)*:



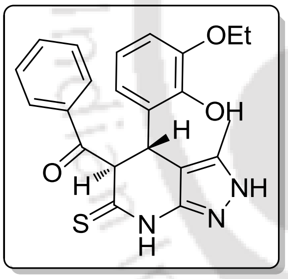
White solid: (0.289 g, 80%); m.p. 245-247 °C; IR (KBr): 1066, 1106, 1257, 1663, 2924, 3346 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.69 (s, 3H), 2.20 (s, 3H), 4.30 (d, J = 5.4 Hz, 1H), 5.31 (d, J = 6.0 Hz, 1H), 7.07 (dd, J_1 = 8.4 Hz, J_2 = 13.2, 4H), 7.49 (t, J = 7.2, 2H), 7.59 (t, J = 7.2, 1H), 7.91 (d, J = 7.8 Hz, 2H), 12.15 (s, 1H), 12.94 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$-DMSO-d_6): δ 9.64, 20.86, 39.02, 64.31, 102.00, 126.92, 128.65, 128.78, 129.54, 133.23, 135.65, 136.80, 138.63, 147.56, 195.08, 195.18; Anal Calcd. for $C_{21}H_{19}N_3OS$ (361.4601): requires C, 69.78; H, 5.30; N, 11.63%. Found C, 69.62; H, 5.21; N, 11.54%. HRMS (ESI) calcd. for $C_{21}H_{19}N_3OS$ (M + H+) 362.1327 found 362.1324.

*((4S,5R)-4-(2,4-dimethoxyphenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(phenyl)methanone (**6e**)*:



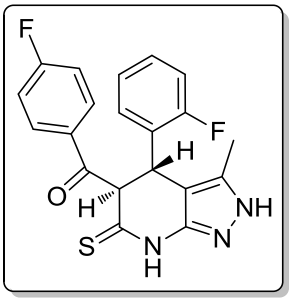
White solid: (0.318 g, 78%); m.p. 235-37 °C; IR (KBr): 1028, 1105, 1206, 1299, 1669, 2953, 3348 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 1.79 (s, 3H), 3.72 (s, 3H), 3.81 (s, 3H), 4.39 (d, J = 3.0 Hz, 1H), 5.20 (d, J = 3.0 Hz, 1H), 6.41 (dd, J_1 = 2.4 Hz, J_2 = 8.4, 1H), 6.57-6.60 (m, 2H), 7.60 (t, J = 7.8 Hz, 2H), 7.69 (t, J = 7.8 Hz, 1H), 8.01 (d, J = 7.2, 2H), 12.15 (s, 1H), 12.87 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.01, 32.03, 55.16, 55.27, 63.75, 98.67, 100.76, 104.79, 121.56, 128.22, 128.74, 128.88, 133.59, 135.33, 148.59, 156.92, 159.69, 194.67, 195.03; Anal Calcd. for $C_{22}H_{21}N_3O_3S$ (407.4854): requires C, 64.85; H, 5.19; N, 10.31%. Found C, 64.72; H, 5.11; N, 10.19%. HRMS (ESI) calcd. for $C_{22}H_{21}N_3O_3S$ (M + H+) 408.1382 found 408.1378.

*((4S,5R)-4-(3-ethoxy-2-hydroxyphenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(phenyl)methanone (**6f**)*:



White solid: (0.285 g, 70%); m.p. 258-260 °C; IR (KBr): 1068, 1112, 1275, 1657, 2923, 3357 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 1.36-1.39 (m, 3H), 1.80 (s, 3H), 4.03-4.06 (m, 2H), 4.56 (d, J = 2.4 Hz, 1H), 5.30 (d, J = 3.0 Hz, 1H), 6.24 (d, J = 7.2 Hz, 1H), 6.63 (t, J = 8.4 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 8.12 (d, J = 7.2, 2H), 8.89 (s, 1H), 12.14 (s, 1H), 12.85 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 8.96, 14.68, 32.27, 63.17, 64.02, 101.18, 111.41, 119.02, 119.32, 128.11, 128.85, 133.51, 135.27, 135.33, 143.20, 146.59, 148.46, 194.78, 194.90; Anal Calcd. for $C_{22}H_{21}N_3O_3S$ (407.4854): requires C, 64.85; H, 5.19; N, 10.31%. Found C, 67.72; H, 5.10; N, 10.21%. HRMS (ESI) calcd. for $C_{22}H_{21}N_3O_3S$ (M + H+) 408.1382 found 408.1368.

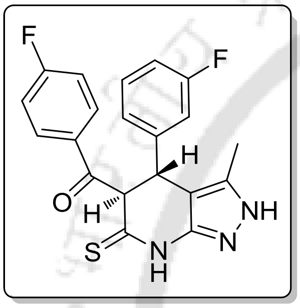
*(4-fluorophenyl)((4S,5R)-4-(2-fluorophenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6g**)*:



White solid: (0.276 g, 72%); m.p. 288-290 °C; IR (KBr): 1067, 1110, 1159, 1227, 1667, 2919, 3363 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.69 (s, 3H), 4.63 (d, J = 6.8 Hz, 1H), 5.38 (d, J = 6.4 Hz, 1H), 7.09-7.12 (m, 1H), 7.15-7.16 (m, 1H), 7.18-7.21

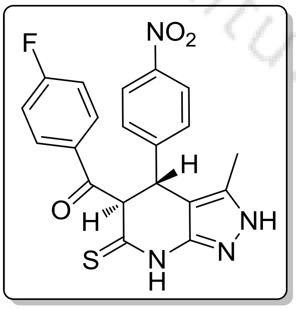
(m, 1H), 7.25-7.28 (m, 1H), 7.34 (t, *J* = 8.4 Hz, 2H), 8.04 (dd, J_1 = 6.0 Hz, J_2 = 8.4, 2H), 12.25 (s, 1H), 13.01 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 8.89, 31.60, 61.75, 100.76, 115.51, 115.66, 115.76, 115.90, 124.82, 127.75, 127.84, 129.03, 129.20, 129.25, 131.61, 131.67, 132.81, 135.45, 147.78, 158.84, 160.46, 164.24, 165.91, 193.81, 194.47; Anal Calcd. for $C_{20}H_{15}F_2N_3OS$ (383.4144): requires C, 62.65; H, 3.94; N, 10.96%. Found C, 62.49; H, 3.88; N, 10.90%. HRMS (ESI) calcd. for $C_{20}H_{15}F_2N_3OS$ (M + H+) 384.0982 found 384.0981.

*(4-fluorophenyl)((4R,5R)-4-(3-fluorophenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6h**)*:



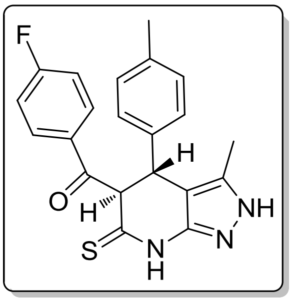
White solid: (0.268 g, 70%); m.p. 264-266 °C; IR (KBr): 1067, 1104, 1158, 1230, 1274, 1670, 2967, 3387 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.69 (s, 3H), 4.46 (d, *J* = 7.2 Hz, 1H), 5.43 (d, *J* = 7.6 Hz, 1H), 7.00-7.05 (m, 1H), 7.08-7.12 (m, 2H), 7.13-7.35 (m, 3H), 8.03 (dd, J_1 = 5.6 Hz, J_2 = 8.0, 2H), 12.22 (s, 1H), 12.98 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.19, 38.30, 62.36, 101.96, 113.82, 113.96, 114.24, 114.38, 115.70, 115.85, 123.76, 130.59, 130.64, 131.62, 131.69, 133.13, 135.60, 144.33, 147.34, 161.34, 162.96, 164.16, 165.83, 194.04, 194.76; Anal Calcd. for $C_{20}H_{15}F_2N_3OS$ (383.4144): requires C, 62.65; H, 3.94; N, 10.96%. Found C, 62.52; H, 3.86; N, 10.88%. HRMS (ESI) calcd. for $C_{20}H_{15}F_2N_3OS$ (M + H+) 384.0982 found 384.0983.

*(4-fluorophenyl)((4R,5R)-3-methyl-4-(4-nitrophenyl)-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6i**)*:



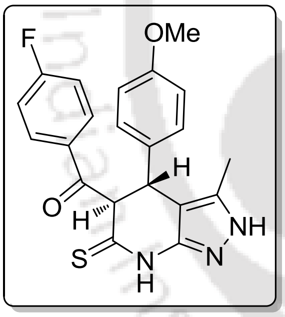
White solid: (0.320 g, 78%); m.p. 278-280 °C; IR (KBr): 1069, 1153, 1257, 1346, 1524, 1677, 2921, 3361 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 1.68 (s, 3H), 4.59 (d, *J* = 7.2 Hz, 1H), 5.41 (d, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 8.01 (dd, J_1 = 5.4 Hz, J_2 = 8.4, 2H), 12.24 (s, 1H), 13.00 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.40, 38.43, 62.20, 101.48, 115.92, 116.06, 124.01, 129.15, 131.86, 131.91, 133.09, 135.98, 146.66, 147.55, 149.40, 164.38, 166.05, 193.94, 194.43; Anal Calcd. for $C_{20}H_{15}FN_4O_3S$ (410.4215): requires C, 58.53; H, 3.68; N, 13.65%. Found C, 58.40; H, 3.61; N, 13.55%. HRMS (ESI) calcd. for $C_{20}H_{15}FN_4O_3S$ (M + H+) 411.0927 found 411.0900.

*(4-fluorophenyl)((4R,5R)-3-methyl-6-thioxo-4-(p-tolyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6j**)*:



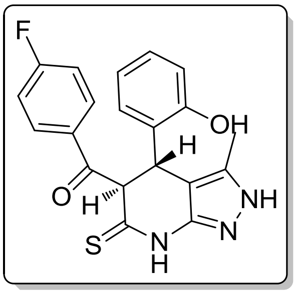
White solid: (0.296 g, 78%); m.p. 284-286 °C; IR (KBr): 1067, 1103, 1258, 1664, 2922, 3354 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.67 (s, 3H), 2.22 (s, 3H), 4.33 (d, J = 6.8 Hz, 1H), 5.33 (d, J = 6.8 Hz, 1H), 7.09 (dd, J_1 = 7.6 Hz, J_2 = 13.6, 4H), 7.32 (t, J = 8.4 Hz, 2H), 8. 01 (t, J = 6.8 Hz, 2H), 12.15 (s, 1H), 12.93 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.20, 20.53, 38.26, 63.05, 102.37, 115.74, 115.88, 127.31, 129.23, 131.56, 131.62, 133.03, 135.51, 136.08, 138.56, 147.40, 164.13, 165.80, 194.04, 194.87; Anal Calcd. for $C_{21}H_{18}FN_3OS$ (379.4505): requires C, 66.47; H, 4.78; N, 11.07%. Found C, 66.30; H, 4.63; N, 11.02%. HRMS (ESI) calcd. for $C_{21}H_{18}FN_3OS$ (M + H+) 380.1233 found 380.1234.

*(4-fluorophenyl)((4R,5R)-4-(4-methoxyphenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6k**)*:



White solid: (0.301 g, 76%); m.p. 276-278 °C; IR (KBr): 1067, 1103, 1152, 1254, 1665, 2924, 3354 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.67 (s, 3H), 3.68 (s, 3H), 4.33 (d, J = 7.2 Hz, 1H), 5.34 (d, J = 7.2 Hz, 1H), 6.83 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 8.01 (dd, J_1 = 5.6 Hz, J_2 = 8.0, 2H), 12.15 (s, 1H), 12.93 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.21, 37.91, 54.93, 63.08, 102.66, 113.99, 115.71, 115.85, 128.54, 131.54, 131.61, 133.16, 133.34, 135.47, 147.36, 158.10, 164.10, 165.77, 194.19, 195.02; Anal Calcd. for $C_{21}H_{18}FN_3O_2S$ (395.4499): requires C, 63.78; H, 4.59; N, 10.63%. Found C, 63.65; H, 4.50; N, 10.52%. HRMS (ESI) calcd. for $C_{21}H_{18}FN_3O_2S$ (M + H+) 396.1182 found 396.1185.

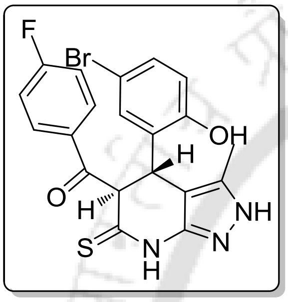
*(4-fluorophenyl)((4S,5R)-4-(2-hydroxyphenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6l**):*



White solid: (0.267 g, 70%); m.p. 290-292 °C; IR (KBr): 1064, 1159, 1232, 1667, 2924, 3305 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.79 (s, 3H), 4.51 (d, J = 7.2 Hz, 1H), 5.31 (d, J = 7.6 Hz, 1H), 6.62-6.69 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 7.04

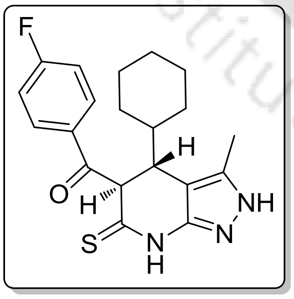
(t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 8.18 (dd, J_1 = 5.6 Hz, J_2 = 8.0, 2H), 9.99 (s, 1H), 12.16 (s, 1H), 12.89 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 8.93, 32.43, 62.67, 101.03, 115.32, 115.68, 115.83, 119.16, 127.34, 127.76, 127.99, 131.78, 131.84, 132.23, 135.28, 148.38, 154.20, 164.30, 165.97, 193.72, 194.62; Anal Calcd. for $C_{20}H_{16}FN_3O_2S$ (381.4233): requires C, 62.98; H, 4.23; N, 11.02%. Found C, 62.79; H, 4.15; N, 11.00%. HRMS (ESI) calcd. for $C_{20}H_{16}FN_3O_2S$ (M + H+) 382.1026 found 382.1023.

*((4S,5R)-4-(5-bromo-2-hydroxyphenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(4-fluorophenyl)methanone (**6m**)*:



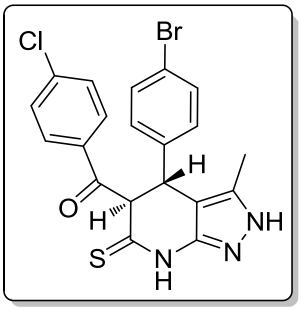
Yellow solid: (0.299 g, 65%); m.p. 310-312 °C; IR (KBr): 1067, 1106, 1159, 1231, 1672, 2965, 3308 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 1.83 (s, 3H), 4.50 (d, *J* = 2.4 Hz, 1H), 5.31 (d, *J* = 2.4 Hz, 1H), 6.72 (m, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, J_1 = 2.4 Hz, J_2 = 9.0, 1H), 7.36 (t, *J* = 9.0 Hz, 2H), 8.16 (dd, J_1 = 6.0 Hz, J_2 = 9.0, 2H), 10.36 (s, 1H), 12.20 (s, 1H), 12.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 8.95, 32.25, 62.47, 100.39, 110.20, 115.73, 115.87, 117.54, 130.07, 130.72, 131.81, 131.87, 132.12, 135.68, 148.31, 153.75, 193.49, 194.35; Anal Calcd. for $C_{20}H_{15}BrFN_3O_2S$ (460.3194): requires C, 52.18; H, 3.28; N, 9.13%. Found C, 52.06; H, 3.19; N, 9.05%. HRMS (ESI) calcd. for $C_{20}H_{15}BrFN_3O_2S$ (M + H+) 460.0131 found 460.0133.

*((4S,5R)-4-cyclohexyl-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(4-fluorophenyl)methanone (**6n**)*:



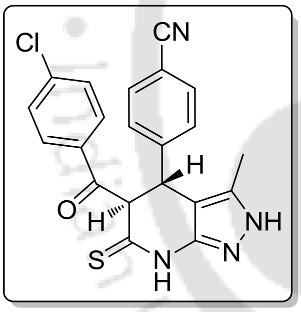
White solid: (0.253 g, 68%); m.p. 288-290 °C; IR (KBr): 1025, 1108, 1231, 1681, 2923, 3442 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 0.88-0.94 (m, 1H), 0.97-1.07 (m, 2H), 1.18-1.22 (m, 2H), 1.56-1.76 (m, 6H), 1.99 (s, 3H), 2.73 (s, 1H), 5.18 (s, 1H), 7.40 (t, *J* = 7.2 Hz, 2H), 8.03 (s, 2H), 12.08 (s, 1H), 12.79 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.66, 25.66, 25.84, 28.59, 29.82, 38.96, 44.05, 61.85, 99.70, 116.09, 116.24, 131.18, 131.45, 131.52, 135.87, 148.10, 164.32, 166.00, 193.43, 195.31; Anal Calcd. for $C_{20}H_{22}FN_3OS$ (371.4716): requires C, 64.67; H, 5.97; N, 11.31%. Found C, 64.56; H, 5.89; N, 11.25%. HRMS (ESI) calcd. for $C_{20}H_{22}FN_3OS$ (M + H+) 372.1546 found 372.1545.

*((4R,5R)-4-(4-bromophenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(4-chlorophenyl)methanone (**6o**)*:



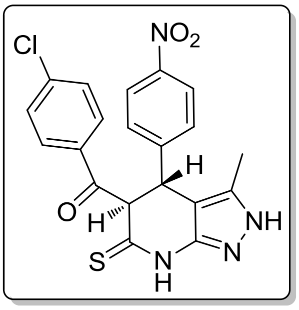
Yellow solid: (0.378 g, 82%); m.p. 290-292 °C; IR (KBr): 1068, 1098, 1255, 1672, 2923, 3350 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 1.68 (s, 3H), 4.23 (d, J = 7.2 Hz, 1H), 5.37 (d, J = 7.2 Hz, 1H), 7.20-7.21 (m, 2H), 7.46-7.48 (m, 2H), 7.55-7.56 (m, 2H), 7.94-7.95 (m, 2H), 12.20 (s, 1H), 12.96 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.27, 38.01, 62.44, 101.93, 120.12, 128.86, 129.86, 130.49, 131.52, 135.12, 135.58, 138.25, 140.77, 147.34, 194.43, 194.57; Anal Calcd. for $C_{20}H_{15}BrClN_3OS$ (460.7746): requires C, 52.13; H, 3.28; N, 9.12%. Found C, 52.05; H, 3.17; N, 9.07%. HRMS (ESI) calcd. for $C_{20}H_{15}BrClN_3OS$ (M + H+) 459.9886 found 459.9873.

*4-((4R,5R)-5-(4-chlorobenzoyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-4-yl)benzonitrile (**6p**)*:



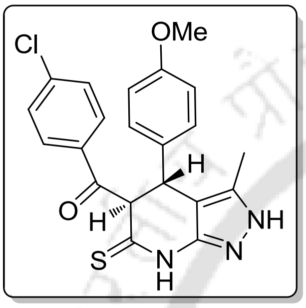
White solid: (0.334 g, 82%); m.p. 250-252 °C; IR (KBr): 1067, 1103, 1255, 1679, 2226, 2923, 3354 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.66 (s, 3H), 4.55 (d, J = 7.2 Hz, 1H), 5.44 (d, J = 6.8 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 12.23 (s, 1H), 13.00 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.26, 38.52, 62.03, 101.51, 109.95, 118.55, 128.78, 128.87, 130.54, 132.64, 135.05, 135.72, 138.35, 147.08, 147.37, 194.29, 194.37; Anal Calcd. for $C_{21}H_{15}ClN_4OS$ (406.8880): requires C, 61.99; H, 3.72; N, 13.77%. Found C, 61.85; H, 3.57; N, 13.67%. HRMS (ESI) calcd. for $C_{21}H_{15}ClN_4OS$ (M + H+) 407.0733 found 407.0722.

*(4-chlorophenyl)((4R,5R)-3-methyl-4-(4-nitrophenyl)-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6q**)*:



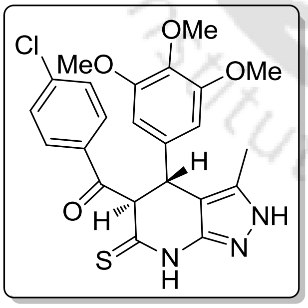
Brown solid: (0.342 g, 80%); m.p. 246-248 °C; IR (KBr): 1068, 1101, 1254, 1345, 1521, 1677, 2922, 3364 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.67 (s, 3H), 4.64 (d, J = 7.2 Hz, 1H), 5.47 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 8.0 Hz, 4H), 7.97 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 12.27 (s, 1H), 13.05 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): *δ* 9.34, 38.32, 62.02, 101.45, 123.88, 128.91, 129.11, 130.60, 135.09, 135.82, 138.39, 146.55, 147.41, 149.21, 194.27; Anal Calcd. for $C_{20}H_{15}ClN_4O_3S$ (426.8761): requires C, 56.27; H, 3.54; N, 13.12%. Found C, 56.17; H, 3.47; N, 13.04%. HRMS (ESI) calcd. for $C_{20}H_{15}ClN_4O_3S$ (M + H+) 427.0632 found 427.0609.

*(4-chlorophenyl)((4R,5R)-4-(4-methoxyphenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6r**)*:



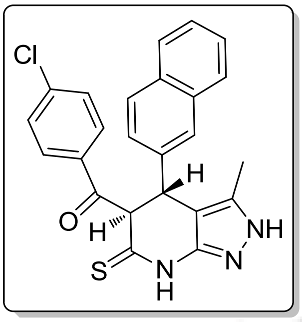
White solid: (0.330 g, 80%); m.p. 280-282 °C; IR (KBr): 1066, 1101, 1173, 1255, 1667, 2955, 3361 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): *δ* 1.67 (s, 3H), 3,68 (s, 3H), 4.34 (d, *J* = 7.2 Hz, 1H), 5.32 (d, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 12.15 (s, 1H), 12.92 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): *δ* 9.26, 37.95, 54.94, 63.02, 102.73, 114.00, 128.64, 128.87, 130.46, 133.17, 135.25, 135.54, 138.18, 147.38, 158.13, 194.72, 195.02; Anal Calcd. for $C_{21}H_{18}ClN_3O_2S$ (411.9045): requires C, 61.23; H, 4.40; N, 10.20%. Found C, 61.09; H, 4.27; N, 10.14%. HRMS (ESI) calcd. for $C_{21}H_{18}ClN_3O_2S$ (M + H+) 412.0887 found 412.0887.

*(4-chlorophenyl)((4R,5R)-3-methyl-6-thioxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6s**)*:



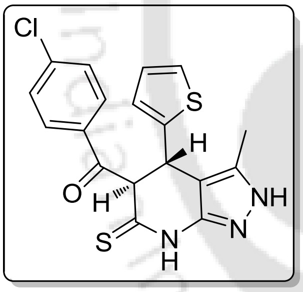
White solid: (0.359 g, 76%); m.p. 296-298 °C; IR (KBr): 1003, 1106, 1235, 1264, 1669, 2962, 3358 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): *δ* 1.75 (s, 3H), 3,57 (s, 3H), 3,67 (s, 6H), 4.33 (d, *J* = 7.6 Hz, 1H), 5.45 (d, *J* = 7.6 Hz, 1H), 6.57 (s, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 12.15 (s, 1H), 12.94 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): *δ* 9.33, 39.08, 55.88, 59.93, 62.30, 102.55, 105.03, 128.80, 130.51, 135.33, 135.62, 136.36, 136.86, 138.20, 147.23, 152.87, 194.93, 195.42; Anal Calcd. for $C_{23}H_{22}ClN_3O_4S$ (471.9565): requires C, 58.53; H, 4.70; N, 8.90%. Found C, 58.40; H, 4.57; N, 8.83%. HRMS (ESI) calcd. for $C_{23}H_{22}ClN_3O_4S$ (M + H+) 472.1098 found 472.1098.

*(4-chlorophenyl)((4R,5R)-3-methyl-4-(naphthalen-2-yl)-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6t**)*:



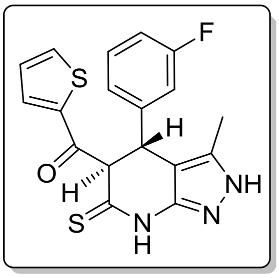
White solid: (0.337 g, 78%); m.p. 254-256 °C; IR (KBr): 1067, 1106, 1284, 1668, 2962, 3356 cm^{-1}.; ^1H NMR (400 MHz, DMSO-d_6): δ 1.58 (s, 3H), 4.57 (d, J = 7.6 Hz, 1H), 5.50 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 3H), 7.50 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.81 (d, J = 8.8 Hz, 3H), 7.93 (d, J = 7.6 Hz, 2H), 12.21 (s, 1H), 13.00 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 9.29, 38.97, 62.57, 102.24, 126.33, 127.51, 127.64, 128.53, 128.89, 130.51, 132.08, 132.86, 135.27, 135.80, 138.24, 138.70, 147.49, 194.72, 194.93; Anal Calcd. for $C_{24}H_{18}ClN_3OS$ (431.9372): requires C, 66.74; H, 4.20; N, 9.73%. Found C, 66.61; H, 4.12; N, 9.64%. HRMS (ESI) calcd. for $C_{24}H_{18}ClN_3OS$ (M + H+) 432.0937 found 432.0935.

*(4-chlorophenyl)((4S,5R)-3-methyl-4-(thiophen-2-yl)-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6u**)*:



White solid: (0.295 g, 76%); m.p. 280-282 °C; IR (KBr): 1062, 1105, 1263, 1662, 2961, 3362 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 1.86 (s, 3H), 4.71 (d, J = 4.8 Hz, 1H), 5.41 (d, J = 4.8 Hz, 1H), 6.92-6.93 (m, 1H), 7.02 (s, 1H), 7.34 (d, J = 4.2 Hz, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 12.21 (s, 1H), 12.96 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 9.14, 33.79, 63.98, 102.30, 124.96, 125.01, 127.02, 128.99, 130.55, 134.57, 135.83, 138.47, 145.23, 147.07, 193.87, 193.98; Anal Calcd. for $C_{18}H_{14}ClN_3OS_2$ (387.9063): requires C, 55.73; H, 3.64; N, 10.83%. Found C, 55.60; H, 3.53; N, 10.72%. HRMS (ESI) calcd. for $C_{18}H_{14}ClN_3OS_2$ (M + H+) 388.0345 found 388.0344.

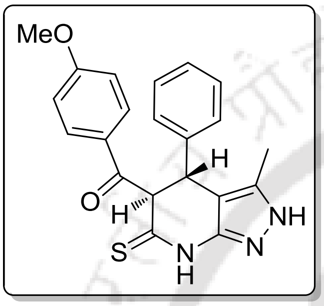
*((4R,5R)-4-(3-fluorophenyl)-3-methyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)(thiophen-2-yl)methanone (**6v**)*:



White solid: (0.267 g, 72%); m.p. 290-292 °C; IR (KBr): 1058, 1109, 1230, 1283, 1643, 2959, 3350, 3375 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.72 (s, 3H), 4.46 (d, J = 6.4 Hz, 1H), 5.25 (d, J = 6.4 Hz, 1H), 7.02-7.09 (m, 3H), 7.22 (s, 1H), 7.32-7.36 (m, 1H), 8.00-8.04 (m, 2H), 12.22 (s, 1H), 12.98 (s, 1H); ^{13}C

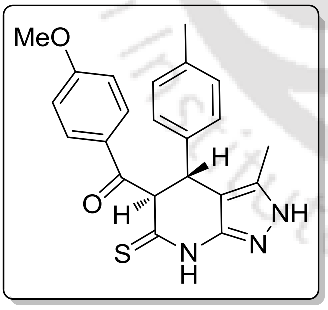
NMR (150 MHz, DMSO-d$_6$): δ 9.21, 38.64, 64.09, 101.89, 113.87, 114.01, 114.19, 114.34, 123.72, 128.98, 130.70, 134.39, 135.65, 135.88, 143.54, 144.51, 147.41, 161.37, 162.99, 188.07, 194.18; Anal Calcd. for $C_{18}H_{14}FN_3OS_2$ (371.4517): requires C, 58.20; H, 3.80; N, 11.31%. Found C, 58.11; H, 3.71; N, 11.22%. HRMS (ESI) calcd. for $C_{18}H_{14}FN_3OS_2$ (M + H+) 372.0641 found 372.0643.

*(4-methoxyphenyl)((4R,5R)-3-methyl-4-phenyl-6-thioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6w**)*:



White solid: (0.280 g, 74%); m.p. 262-264 °C.; IR (KBr): 1066, 1107, 1166, 1270, 1649, 2961, 3347 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.74 (s, 3H), 3.83 (s, 3H), 4.31 (d, J = 2.8 Hz, 1H), 5.29 (d, J = 3.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H), 7.22 (s, 3H), 7.29 (s, 2H), 7.92 (d, J = 8.0 Hz, 2H), 12.18 (s, 1H), 12.94 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.16, 38.74, 55.55, 63.19, 102.06, 114.13, 126.98, 127.18, 128.58, 128.74, 130.59, 130.99, 135.57, 142.22, 147.48, 163.30, 193.42, 194.99; Anal Calcd. for $C_{21}H_{19}N_3O_2S$ (377.4595): requires C, 66.82; H, 5.07; N, 11.13%. Found C, 66.67; H, 5.00; N, 11.07%. HRMS (ESI) calcd. for $C_{21}H_{19}N_3O_2S$ (M + H+) 378.1276 found 378.1278.

*(4-methoxyphenyl)((4R,5R)-3-methyl-6-thioxo-4-(p-tolyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-b]pyridin-5-yl)methanone (**6x**)*:



White solid: (0.298 g, 76%); m.p. 272-274 °C; IR (KBr): 1063, 1104, 1161, 1266, 1655, 2959, 3328 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$-DMSO-d$_6$): δ 1.76 (s, 3H), 2.18 (s, 3H), 3.77 (s, 3H), 4.12 (d, J = 4.0 Hz, 1H), 5.10 (d, J = 3.6 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.95 (q, J = 8.0 Hz, 4H), 7.82 (d, J = 8.4 Hz, 2H), 11.28 (s, 1H), 11.92 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$-DMSO-d$_6$): δ 8.84, 20.19, 38.39, 54.81, 63.50, 101.21, 113.31, 126.18, 127.63, 128.81, 130.40, 135.71, 135.88, 138.48, 146.90, 162.95, 192.90, 194.46; Anal Calcd. for $C_{22}H_{21}N_3O_2S$ (391.4860): requires C, 67.50; H, 5.41; N, 10.73%. Found C, 67.39; H, 5.33; N, 10.59%. HRMS (ESI) calcd. for $C_{22}H_{21}N_3O_2S$ (M + H+) 392.1433 found 392.1437.

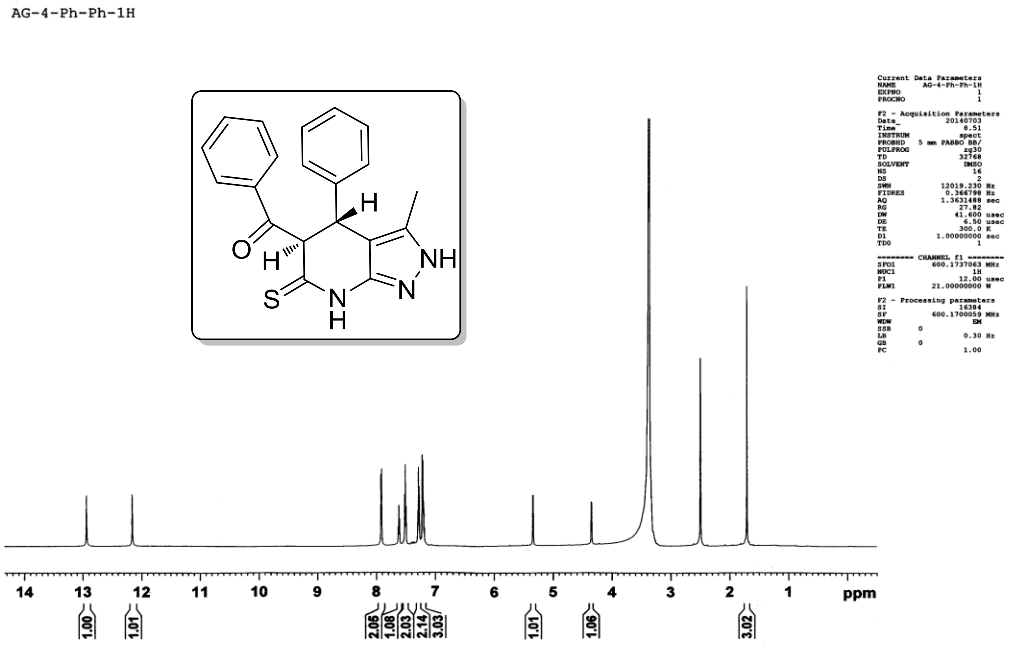
XRD for Compound **6n**

Complete crystallographic data of **6n** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1038414. 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).

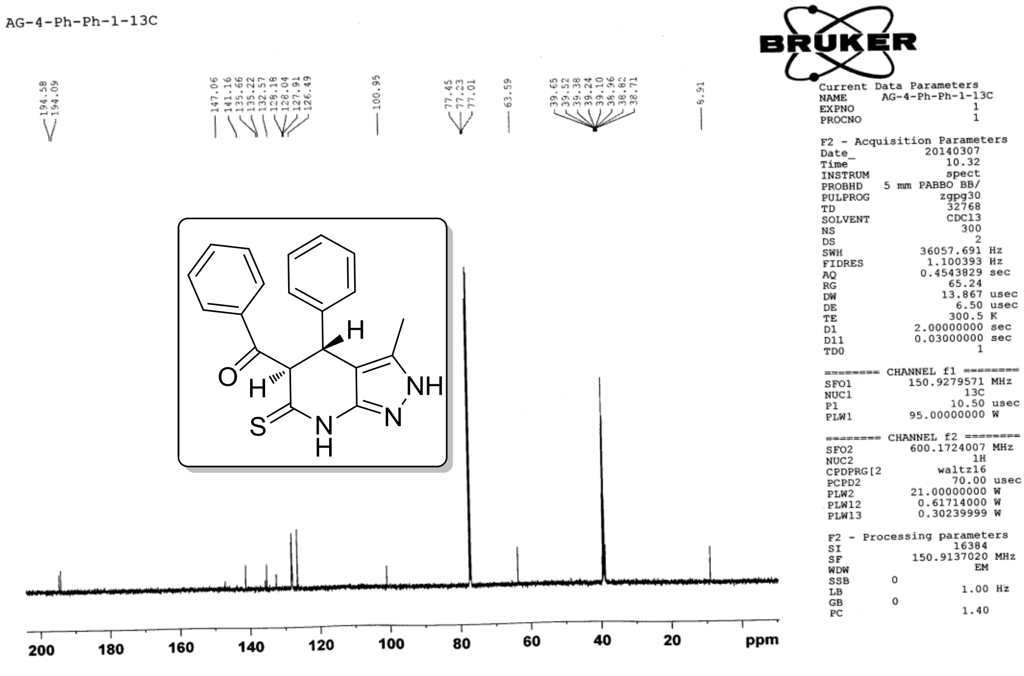
Table 6. Crystal data and structure refinement for **6n**, for atomic coordinates and equivalent isotopic displacement parameters and bond angles, please check the CIF

Parameters	**Compound**
Formula	$C_{20} H_{22} F N_3 O S, C_2 H_6 O S$
CCDC number	1038414
Formula weight	449.59
T (K)	296(2)
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	P -1
a (Å)	8.7666(5)
b (Å)	10.8920(5)
c (Å)	13.0745(7)
α (^{0})	107.241(3)
β (^{0})	102.575(3)
γ (^{0})	92.165(3)
V $(Å)^3$	1156.70(10)
Z	2
D_{calcd} (g m^{-3})	1.291
μ (mm^{-1})	0.261
F (0 0 0)	476
Reflection collected	14055
Unique reflections	2956
Goodness-of-fit (GOF)^a on F^2	1.186
R [I > 2σ(I)]	$^bR_1 = 0.0496$, $^cwR_2 = 0.1467$
R indices (all data)	$^bR_1 = 0.0690$, $^cwR_2 = 0.1793$

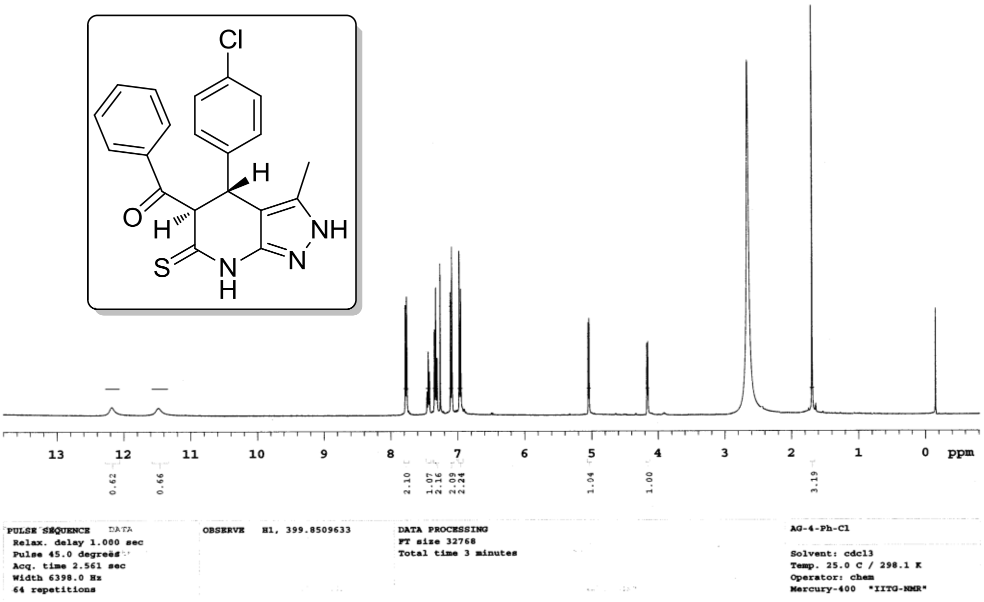
^{1}H **NMR (600 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative (***6a***):



^{13}C **NMR (150 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative ***(6a)***:

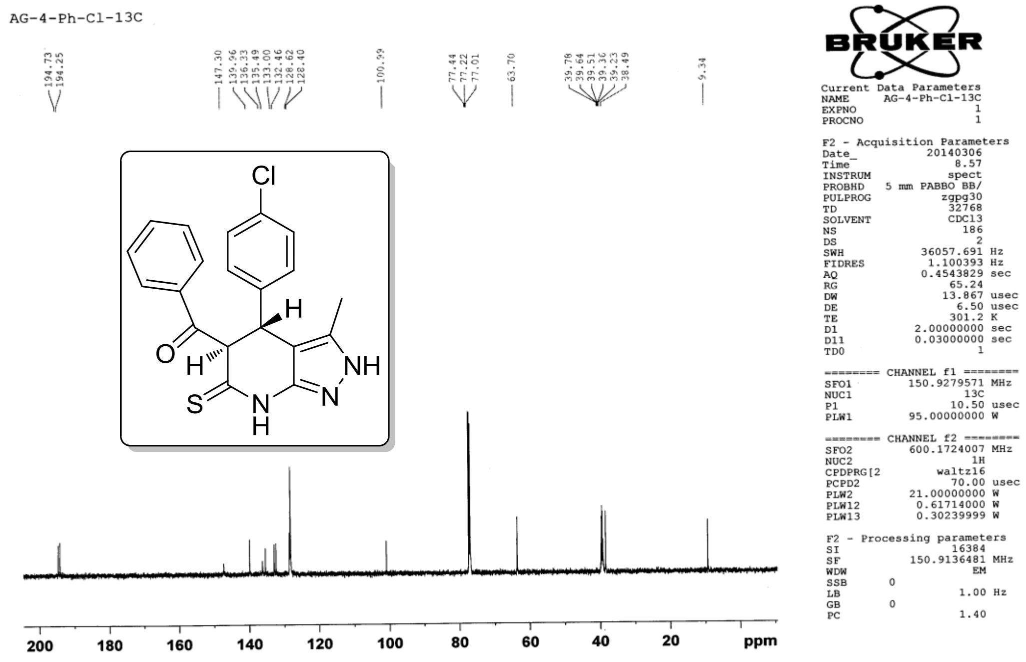


^{1}H **NMR (400 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative (***6b***):



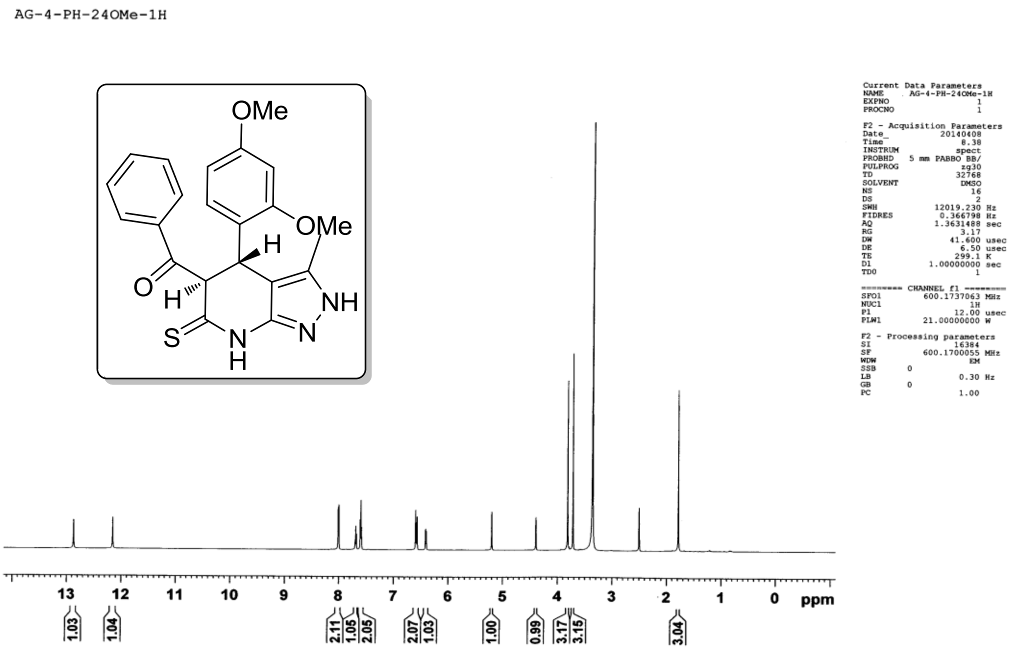
```
PULSE SEQUENCE                  OBSERVE   H1, 399.8509633    DATA PROCESSING            AG-4-Ph-Cl
 Relax. delay 1.000 sec                                       FT size 32768
 Pulse 45.0 degrees                                           Total time 3 minutes      Solvent: cdcl3
 Acq. time 2.561 sec                                                                    Temp. 25.0 C / 298.1 K
 Width 6398.0 Hz                                                                        Operator: chem
 64 repetitions                                                                         Mercury-400  "IITG-NMR"
```

^{13}C **NMR (150 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative ***(6b)***:

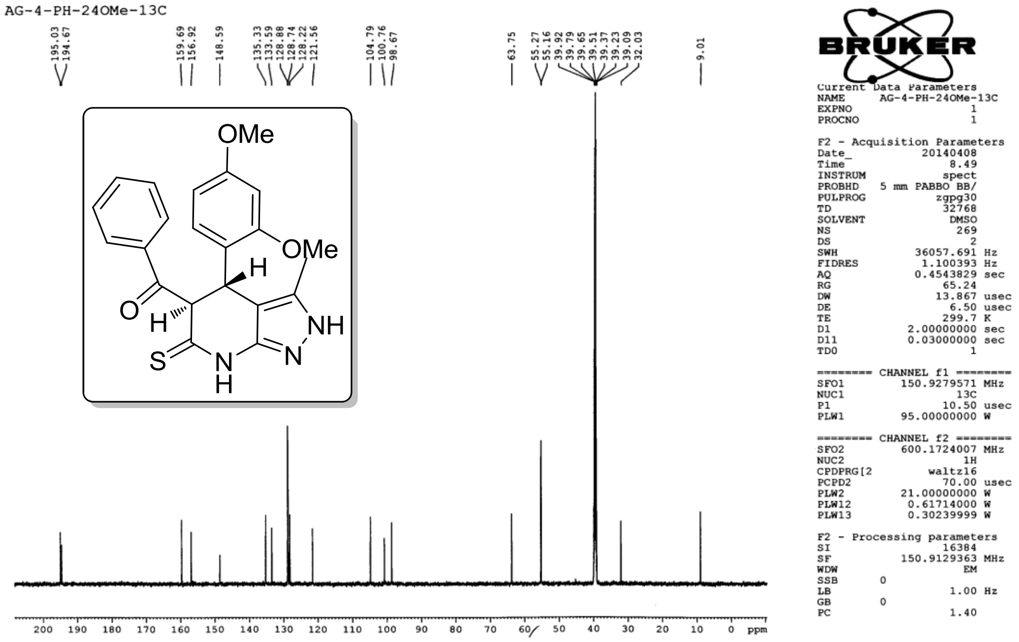


```
Current Data Parameters
NAME       AG-4-Ph-Cl-13C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20140306
Time                 8.57
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   186
DS                     2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                 65.24
DW                13.867 usec
DE                  6.50 usec
TE                 301.2 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                 10.50 usec
PLW1         95.00000000 W

======== CHANNEL f2 ========
SFO2         600.1724007 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              70.00 usec
PLW2         21.00000000 W
PLW12         0.61714000 W
PLW13         0.30239999 W

F2 - Processing parameters
SI                 16384
SF           150.9136481 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

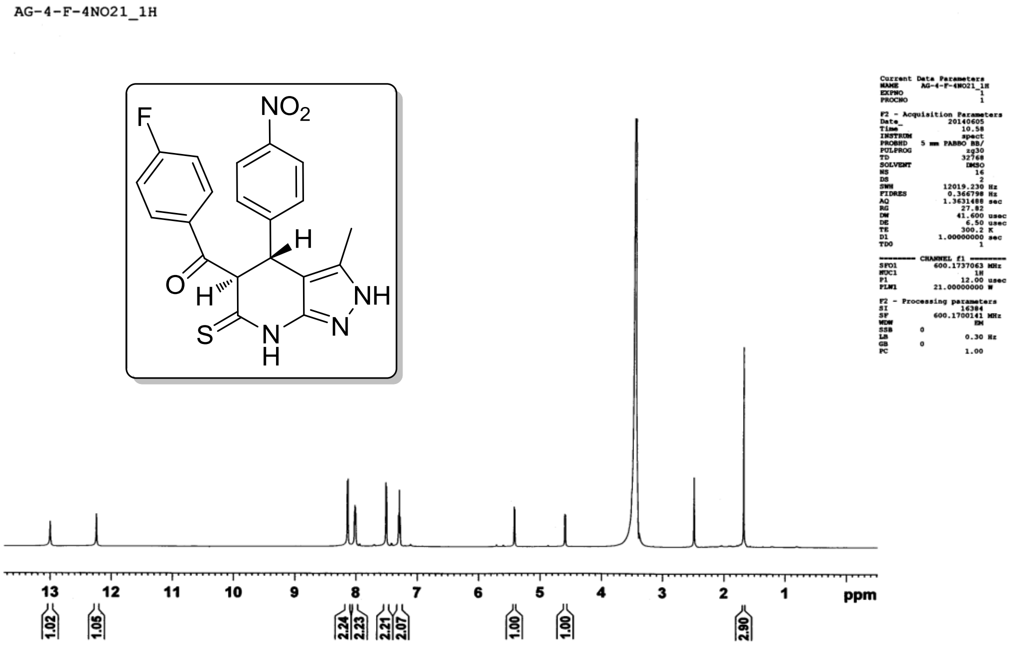
^{1}H **NMR (600 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative (***6e***):



^{13}C **NMR (150 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative ***(6e)***:

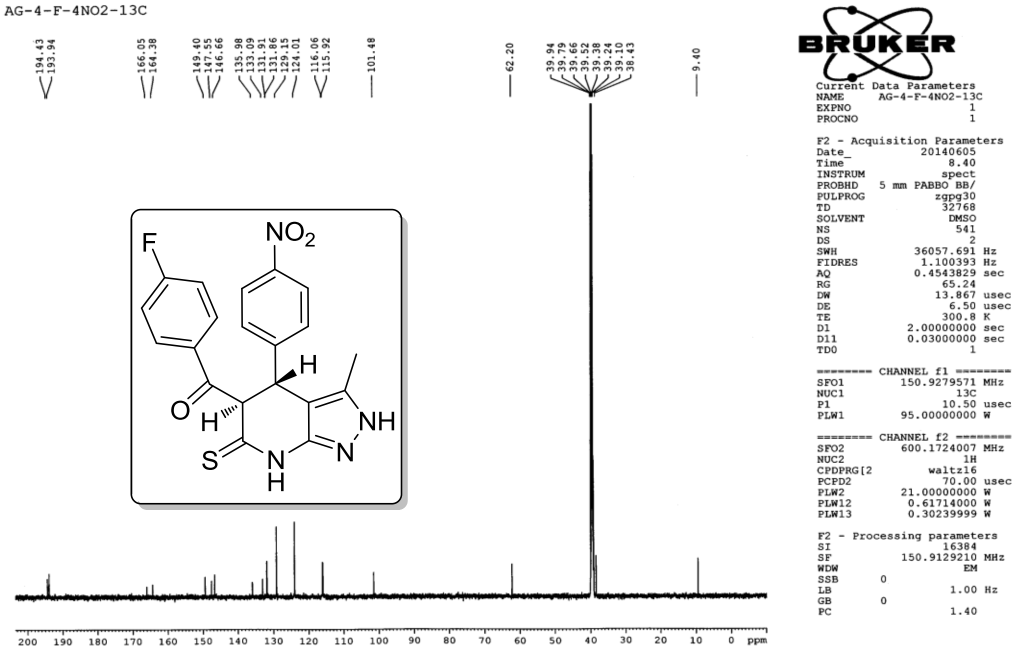


^{1}H **NMR (600 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative (***6i***):



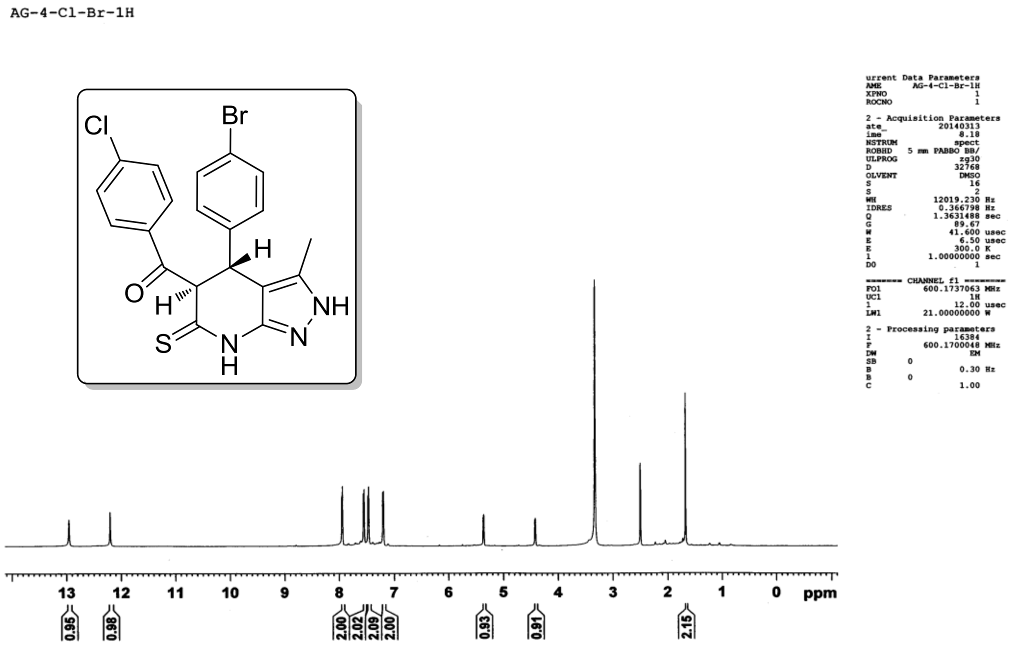
```
Current Data Parameters
NAME      AG-4-F-4NO21_1H
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20140605
Time                10.58
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG              zg30
TD                  32768
SOLVENT              DMSO
NS                     16
DS                      2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                  27.82
DW                 41.600 usec
DE                   6.50 usec
TE                  300.2 K
D1            1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1        600.1737063 MHz
NUC1                   1H
P1                  12.00 usec
PLW1         21.00000000 W

F2 - Processing parameters
SI                  16384
SF          600.1700141 MHz
WDW                    EM
SSB      0
LB                   0.30 Hz
GB       0
PC                   1.00
```

^{13}C **NMR (150 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative ***(6i)***:



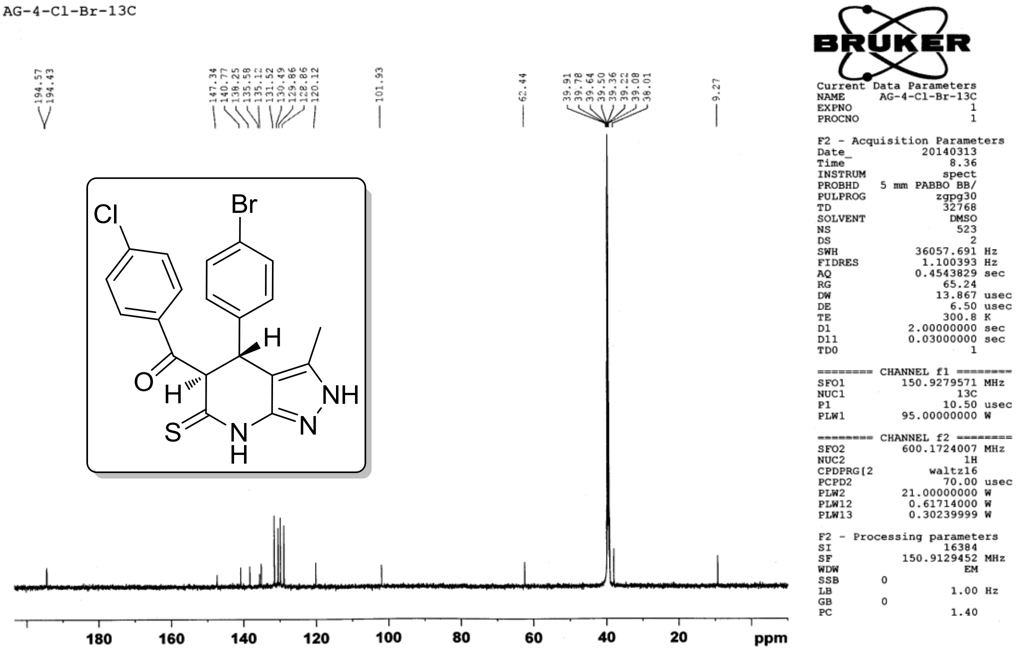
```
Current Data Parameters
NAME      AG-4-F-4NO2-13C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20140605
Time                 8.40
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                  32768
SOLVENT              DMSO
NS                    541
DS                      2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                  65.24
DW                 13.867 usec
DE                   6.50 usec
TE                  300.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1        150.9279571 MHz
NUC1                  13C
P1                  10.50 usec
PLW1         95.00000000 W

======== CHANNEL f2 ========
SFO2        600.1724007 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2               70.00 usec
PLW2         21.00000000 W
PLW12         0.61714000 W
PLW13         0.30239999 W

F2 - Processing parameters
SI                  16384
SF          150.9129210 MHz
WDW                    EM
SSB      0
LB                   1.00 Hz
GB       0
PC                   1.40
```

^{1}H **NMR (600 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative (***6o***):



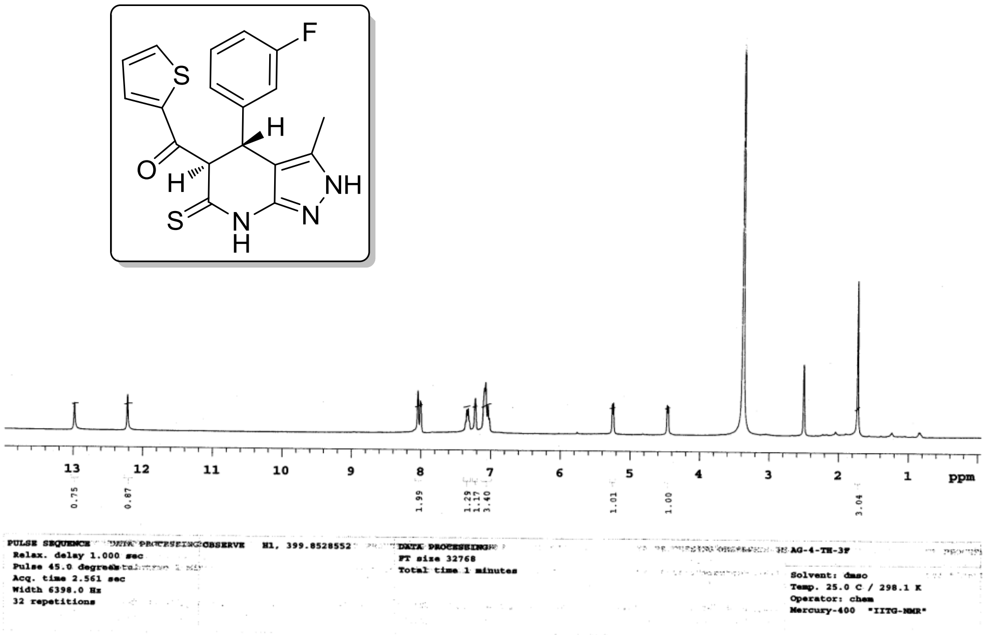
```
urrent Data Parameters
AME      AG-4-Cl-Br-1H
XPNO                 1
ROCNO                1

2 - Acquisition Parameters
ate_          20140313
ime               8.18
NSTRUM           spect
ROBHD   5 mm PABBO BB/
ULPROG            zg30
D                32768
OLVENT            DMSO
S                   16
S                    2
WH          12019.230 Hz
IDRES        0.366798 Hz
Q           1.3631488 sec
G                89.67
W              41.600 usec
E                6.50 usec
E               300.0 K
1          1.00000000 sec
D0                   1

======= CHANNEL f1 ========
FO1        600.1737063 MHz
UC1                 1H
1                12.00 usec
LW1        21.00000000 W

2 - Processing parameters
I                16384
F          600.1700048 MHz
DW                  EM
SB       0
B                 0.30 Hz
B        0
C                 1.00
```

^{13}C **NMR (150 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative ***(6o)***:



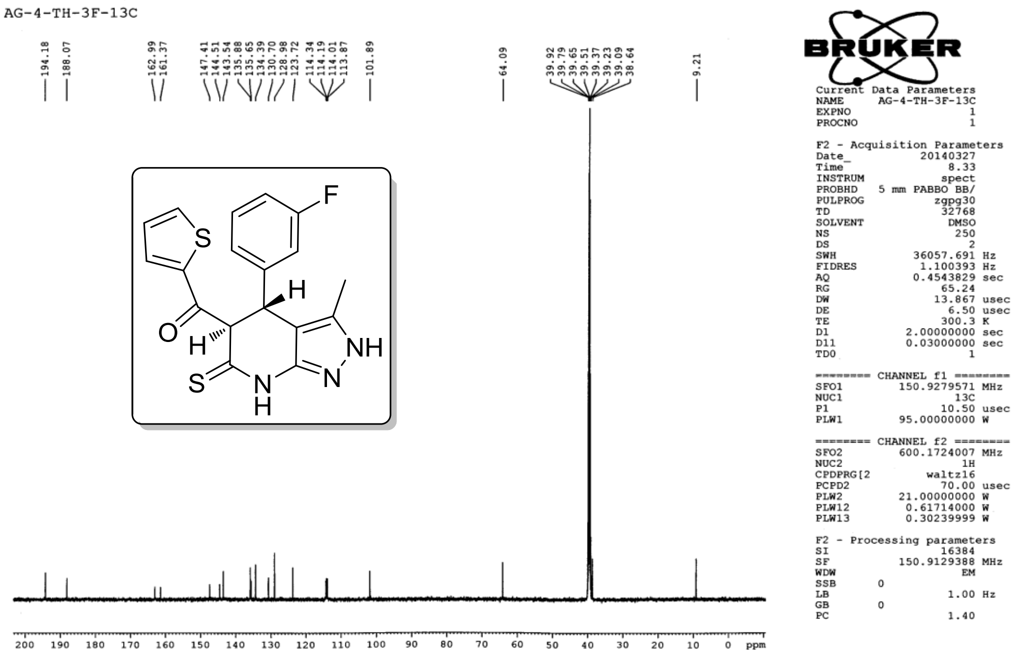
```
Current Data Parameters
NAME      AG-4-Cl-Br-13C
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140313
Time                8.36
INSTRUM            spect
PROBHD    5 mm PABBO BB/
PULPROG           zgpg30
TD                 32768
SOLVENT             DMSO
NS                   523
DS                     2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                 65.24
DW                13.867 usec
DE                  6.50 usec
TE                 300.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                 10.50 usec
PLW1         95.00000000 W

======== CHANNEL f2 ========
SFO2         600.1724007 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              70.00 usec
PLW2         21.00000000 W
PLW12         0.61714000 W
PLW13         0.30239999 W

F2 - Processing parameters
SI                 16384
SF           150.9129452 MHz
WDW                   EM
SSB         0
LB                  1.00 Hz
GB          0
PC                  1.40
```

^{1}H **NMR (400 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative (***6v***):



```
PULSE SEQUENCE          OBSERVE    H1, 399.8528552      DATA PROCESSING                 AG-4-TH-3F
 Relax. delay 1.000 sec                                 FT size 32768
 Pulse 45.0 degrees                                     Total time 1 minutes            Solvent: dmso
 Acq. time 2.561 sec                                                                    Temp. 25.0 C / 298.1 K
 Width 6398.0 Hz                                                                        Operator: chem
 32 repetitions                                                                         Mercury-400  "IITG-NMR"
```

^{13}C **NMR (150 MHz, DMSO-d$_6$):** tetrahydro-2H-pyrazolo[3,4-*b*]pyridine derivative ***(6v)***:



```
Current Data Parameters
NAME       AG-4-TH-3F-13C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20140327
Time                 8.33
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 32768
SOLVENT             DMSO
NS                   250
DS                     2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                 65.24
DW                13.867 usec
DE                  6.50 usec
TE                 300.3 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                 10.50 usec
PLW1         95.00000000 W

======== CHANNEL f2 ========
SFO2         600.1724007 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              70.00 usec
PLW2         21.00000000 W
PLW12         0.61714000 W
PLW13         0.30239999 W

F2 - Processing parameters
SI                 16384
SF           150.9129388 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

4.1. Benzothiazoles and its importance

Benzazoles such as benzothiazoles, benzoxazoles and benzimidazoles are eminent class of organic molecules. They are integral part of natural products and have promising prospects in pharmaceutical and agrochemical industries. In particular functionalized 2-substituted benzothiazoles is a privileged bicyclic ring system, present in a variety of alkaloids having wide biological activities and have applications in advanced material science for the preparation of liquid crystals,[83] nonlinear optics (NLO)[84] and organic light-emitting diodes (OLED).[85] Luciferin, a benzothiazoles derivative (**XII**) has been found responsible for the characteristic yellow light emission from fireflies. Zopolrestat (**XIII**)[86] is an anti-diabetic agent; erythrazole B (**XIV**)[87] showed excellent anti-lung cancer activity; riluzole (**XV**) is a well-known drug used for amyotrophic lateral sclerosis and Schiff bases (**XVI**) are used for the treatment of Alzheimer's disease[88] (Figure 6). In addition the chemistry of benzothiazoles derivatives has attracted attention for the facile access of bioactive lead molecules. These molecules exhibit a wide range of pharmacological activities such as anti-microbial,[89] anti-convulsant,[90] anti-tubercular,[91] anti-viral[92] and anti-inflammatory[93]. Also benzothiazoles derivatives find several interesting applications in chemo-sensing,[94] cosmetics,[95] dyes[96] and rubber industries.

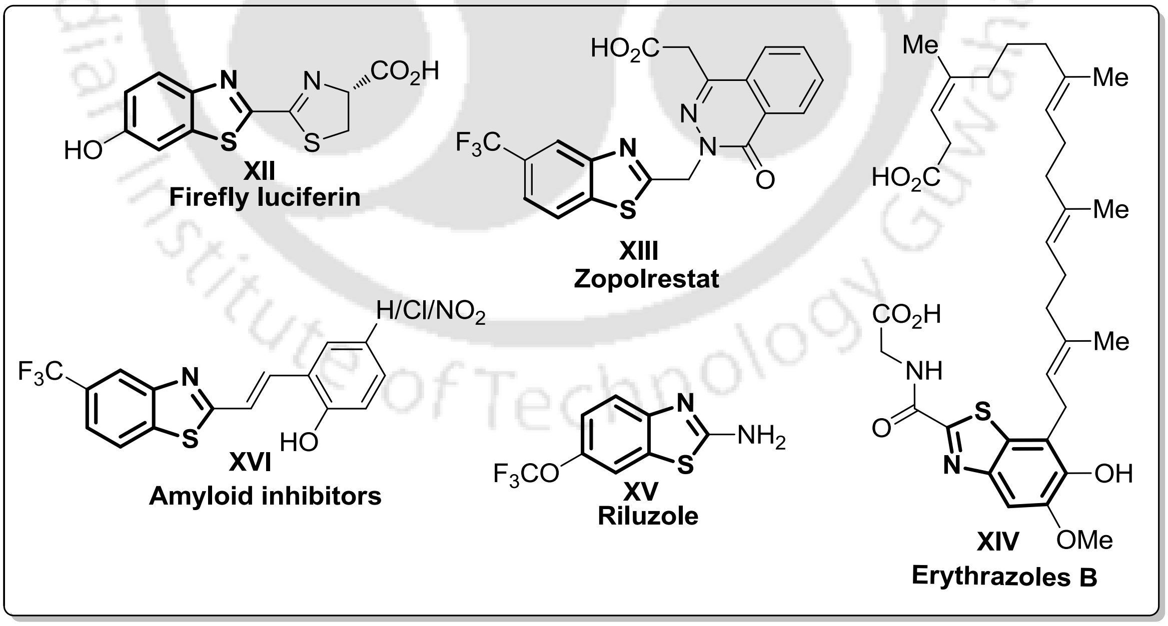
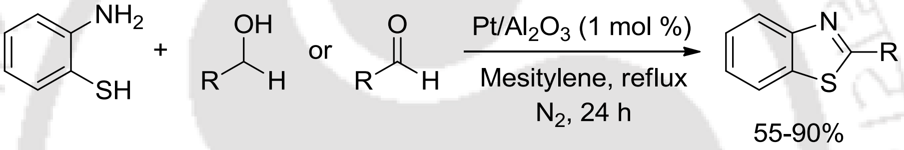


Figure 6. Biologically active compounds having benzo[*d*]thiazole unit

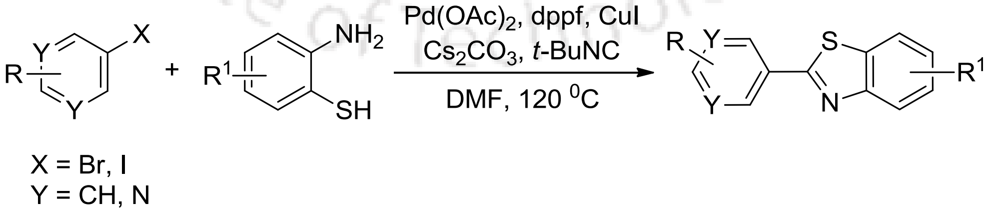
4.2. General approaches for the construction of benzothiazoles

The design and development of a new methodology for synthesizing the above mentioned class of compounds has attracted considerable attention in recent times. Literature study revealed that two conventional methods have been evolved for the synthesis of benzothiazole framework. One method consists of the condensation reaction of various 2-aminothiophenol derivatives with aldehydes, acids, amines, alcohols, nitriles, ketones, β-diketones or β-ketoesters under either oxidative reaction conditions or high temperature and microwave radiation conditions and the other methods consist of transition-metal-catalyzed intramolecular cyclization of thiobenzanilides under refluxing reaction condition. Recently, Shimizu *et al.* reported Pt/Al_2O_3 catalyzed dehydrogenative synthesis of 2-substituted benzothiazoles from alcohols or aldehydes under acceptor-free and additive-free conditions (Scheme 48).[97]



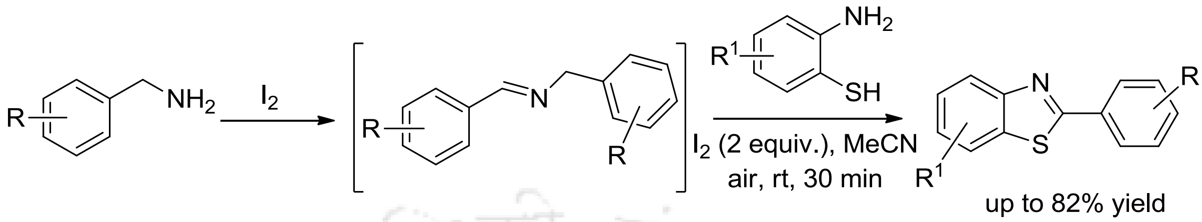
Scheme 48. Synthesis of 2-substituted benzo[*d*]thiazole derivatives

Lang *et al.* developed a convenient one-pot palladium-catalyzed cascade process for the preparation of benzothiazole derivatives[98] by the reaction of 2-aminothiophenol derivatives, aryl halides and *tert*-butyl isocyanide in presence of dppf (1,1'-bis(diphenylphosphino)ferrocene) as ligand in DMF under heating condition. The addition of copper co-catalyst allowed efficient preparation of these compounds *via in situ* formation of the unsubstituted benzothiazole followed by copper-catalyzed C-H activation before this fragment joins the regular palladium catalytic cycle (Scheme 49).



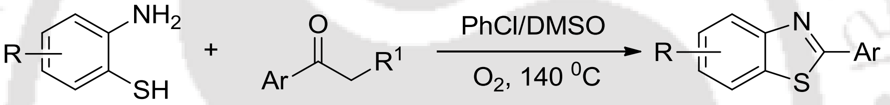
Scheme 49. Synthesis of benzo[*d*]thiazoles from isocyanides

Narender *et al.*[99] demonstrated a molecular iodine promoted divergent synthesis of benzothiazoles through a one-pot condensation reaction of 2-aminothiophenols and benzylamines. This transformation presumably proceeds *via* an oxidative dimerization of benzylamine in the presence of iodine to produce the imine with the loss of ammonia, followed by the transimination with 2-aminothiophenol and subsequent cycloaddition and further oxidation of the intermediate in a sequence (Scheme 50).



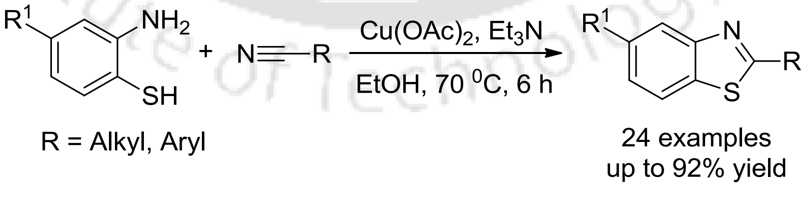
Scheme 50. Synthesis of benzo[*d*]thiazoles from benzylamines

Deng *et al.* described the synthesis of 2-aryl benzothiazole from aryl ketones and 2-aminobenzenethiols under metal and I_2 free conditions. Various 2-aryl benzothiazoles were selectively obtained in good yields using molecular oxygen as oxidant. DMSO played an important role in this transformation (Scheme 51).[100]



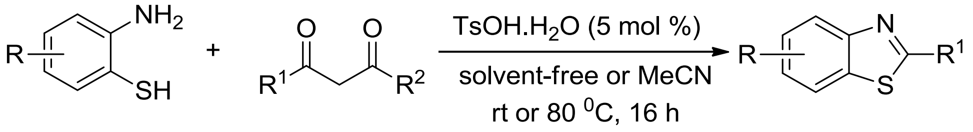
Scheme 51. Synthesis of benzo[*d*]thiazoles from ketones

Jiang *et al.* developed an efficient and convenient method for the formation of 2-substituted benzothiazole derivatives via a copper-catalyzed condensation of 2-aminobenzenethiols with nitriles. The reaction proceeded through copper prompted sulfilimine formation and followed by intramolecular cyclization. The developed strategy is applicable to a wide range of nitriles containing different functional groups furnishing excellent yields of the corresponding products (Scheme 52).[101]



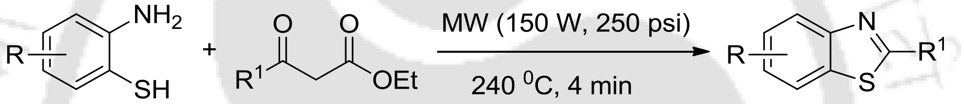
Scheme 52. Synthesis of benzo[*d*]thiazoles from nitriles

Bao *et al.* reported Brønsted acid catalyzed cyclization reactions of 2-amino thiophenols with *β*-diketones to afford 2-substituted benzothiazole derivatives under oxidant, metal, and radiation-free conditions. Various 2-substituted benzothiazoles were obtained in satisfactory to excellent yields (Scheme 53).[102]



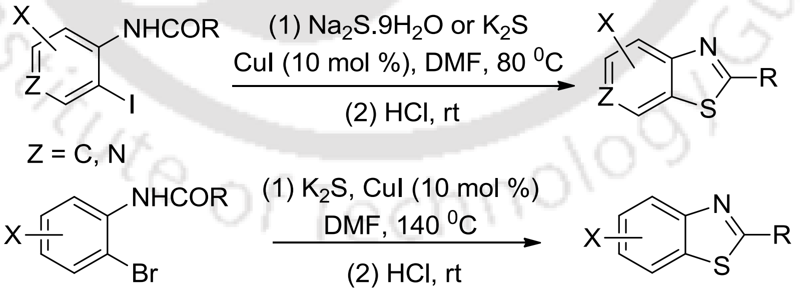
Scheme 53. Synthesis of benzo[*d*]thiazoles from *β*-diketones

Biehl *et al.*[103] described the synthesis of 2-substituted benzothiazoles from 2-aminothiophenol and aromatic or aliphatic *β*-ketoesters under solvent-free microwave heating conditions with excellent yields (Scheme 54). The formation of 2-substituted benzothiazoles is believed to be the nucleophilic addition of the thiol group to the keto group of the *β*-ketoester with subsequent elimination of ethyl acetate from the resulting adduct and the adduct then undergoes an intramolecular addition of the *o*-amino group to the carbonyl group to generate another adduct from which water is eliminated to afford the 2-substituted benzothiazoles.



Scheme 54. Synthesis of benzo[*d*]thiazoles from *β*-ketoesters

Ma *et al.* developed a novel and efficient synthesis of 2-substituted benzothiazoles by using copper-catalyzed coupling reactions of 2-haloanilides with nucleophiles. The product formation occurs via CuI catalyzed direct coupling of metal sulfides with aryl halides, followed by subsequent intramolecular condensation (Scheme 55).[104]

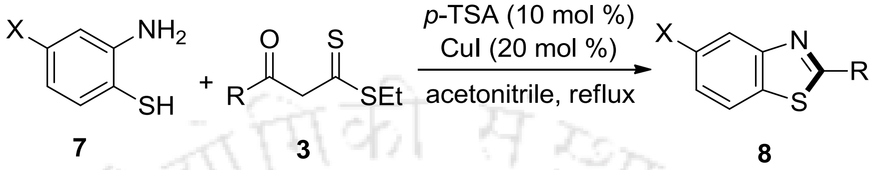


Scheme 55. Synthesis of benzo[*d*]thiazoles from 2-haloanilides

Although the reported methods are effective and represent the synthetic requirements toward a facile access of benzothiazole framework, harsh reaction conditions like high temperature reaction conditions or microwave radiation, photo-catalytic reaction conditions, expensive catalyst or excess amount of an additive, use of toxic organic solvents and strong oxidizing reagents are their drawbacks.

4.3. Results and Disscussion

In this chapter we report a simple, efficient and straightforward one-pot condensation reaction of 2-aminothiophenol and *β*-oxodithioesters for the synthesis of 2-substituted benzo[*d*]thiazole derivatives by using *p*-toluenesulfonic acid and CuI as a combined catalyst (Scheme 56).

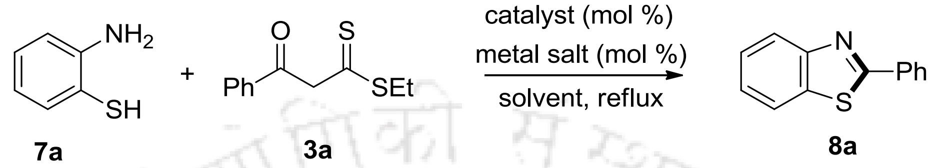


Scheme 56. Synthesis of 2-substituted benzo[*d*]thiazoles

According to our previous studies as well as by others, *p*-toluenesulfonic acid (*p*-TSA) is found abundant, readily available and is an inexpensive Brønsted acid catalyst.[105] It has been exploited for various organic transformations such as carbonylation of formaldehyde,[106] regiospecific nitration of phenols,[107] synthesis of 4(3H)-quinazolinones[108] and chromeno[3,4-*b*]quinoline involving MCRs strategy. Recently *β*-oxodithioesters have attracted much attention as a key intermediate for potentially rapid access of various important bioactive frameworks such as chromene-2-thione, dihydropyrimidone, furan, indole, isoxazole, pyrrazole, pyrrole, quinoline, thiophene, thiopyran and many more.[109] We conceived that *p*-TSA.H_2O can be utilized as an efficient catalyst for one-pot synthesis of 2-substituted benzo[*d*]thiazole derivatives from different 2-aminothiophenols and *β*-oxodithioesters.

Optimization studies were performed with 2-aminothiophenol (0.5 mmol, **7a**) and ethyl-3-oxo-3-phenylpropanedithioate (0.5 mmol**, 3a**) as a model substrate and treated with *p*-toluenesulfonic acid monohydrate (*p*-TSA.H_2O) (10 mol %) in acetonitrile was stirred under refluxing condition for 24 h. The reaction provided desired product 2-phenylbenzo[*d*]thiazole (**8a**) in an isolated yield of 30%. In similar reaction condition in presence of 20 mol % *p*-TSA.H_2O under reflux in acetonitrile produced only 32% product. However when the reaction mixture was refluxed in presence of 10 mol % *p*-TSA.H_2O and 10 mol % CuI in acetonitrile at 80 ^{0}C provided the desired product 75% yield (Table 7, entry 3). Remarkably, when the same reaction mixture was refluxed in presence of combined catalyst (10 mol % *p*-TSA.H_2O and 20 mol % CuI) in acetonitrile at 80 ^{0}C for 16 h, it afforded product **8a** in 85% yield (Table 7, entry 4) as characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra as well as elemental analysis. It was also noted that the yield did not improve significantly in presence of 10 mol % *p*-TSA.H_2O and 30 mol % CuI (Table 7, entry 5). It is noteworthy to mention that the reaction did not take place in absence of acid catalyst (Table 7, entry 6).

Table 7. Optimization of the reaction conditions for the synthesis of 2-phenylbenzo[*d*]thiazoles (**3a**)



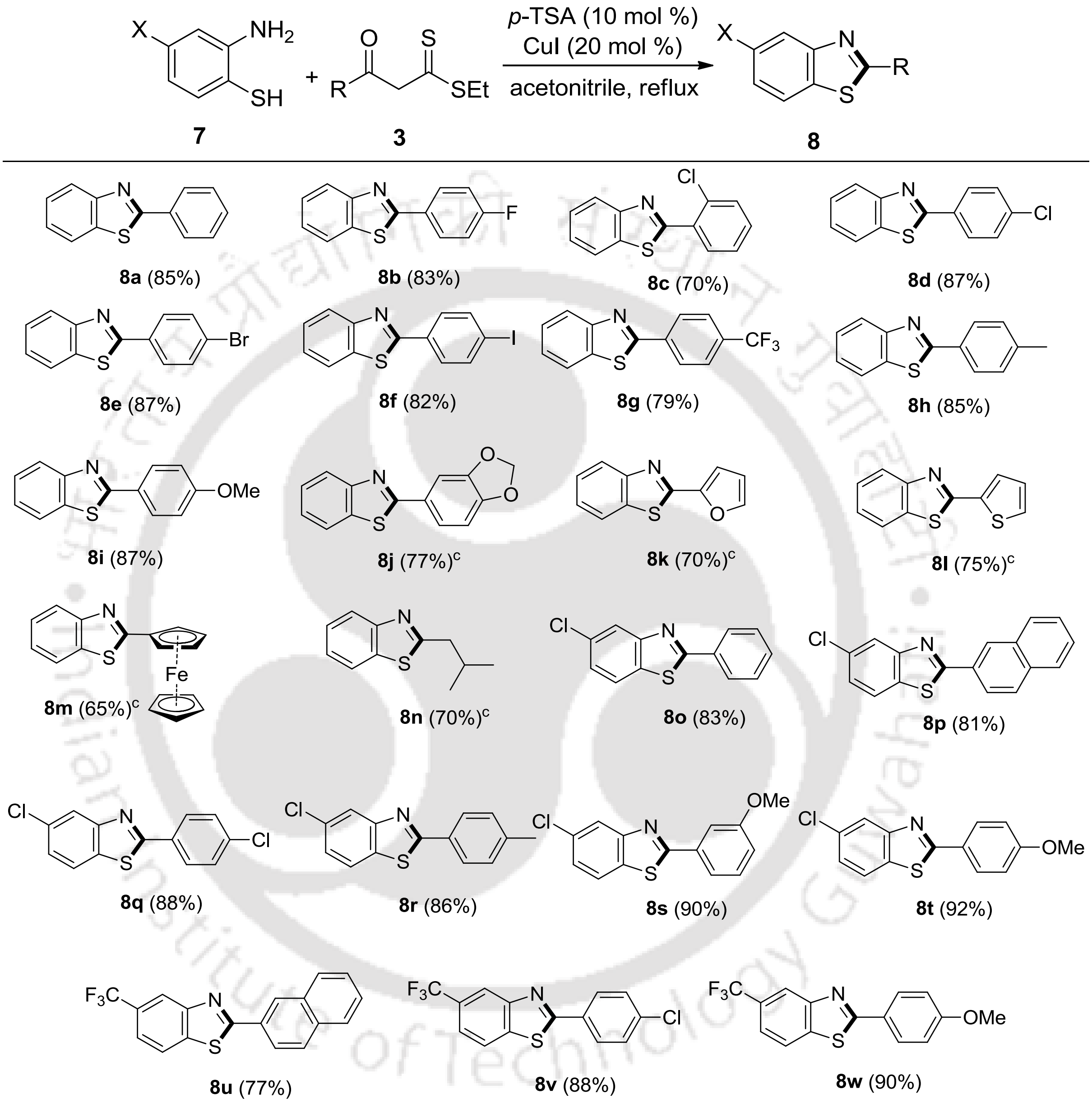
entry	Catalyst (mol %)	Co-Catalyst (mol %)	solvent	Time (h)	yield^b (%)^b
1	*p*-TSA (10)	-	CH_3CN	24	30
2	*p*-TSA (20)	-	CH_3CN	24	32
3	*p*-TSA (10)	CuI (10)	CH_3CN	16	75
4	***p*-TSA (10)**	**CuI (20)**	**CH_3CN**	**16**	**85**
5	*p*-TSA (10)	CuI (30)	CH_3CN	16	84
6	-	CuI (20)	CH_3CN	24	NR
7	*p*-TSA (10)	CuBr (20)	CH_3CN	16	75
8	*p*-TSA (10)	$Cu(OAc)_2$ (20)	CH_3CN	16	30
9	*p*-TSA (10)	$FeCl_3.6H_2O$ (20)	CH_3CN	16	40
10	*p*-TSA (10)	$Fe(NO_3)_3.9H_2O$ (20)	CH_3CN	16	55
11	CH_3COOH	CuI (20)	CH_3CN	16	10
12	PhCOOH	CuI (20)	CH_3CN	16	15
13	TfOH	CuI (20)	CH_3CN	16	10
14	*p*-TSA (10)	CuI (20)	DCE	24	70
15	*p*-TSA (10)	CuI (20)	toluene	24	80
16	*p*-TSA (10)	CuI (20)	THF	24	35

[a] All the reactions were carried out using 2-aminothiophenol (**7a,** 0.5 mmol), ethyl-3-oxo-3-phenylpropanedithioate (**3a,** 0.5 mmol), catalyst, metal salt, and solvent (2ml) under reflux condition. [b] Isolated yield.

Using other metal salts such as CuBr, $Cu(OAc)_2$, $FeCl_3.6H_2O$ and $Fe(NO_3)_3.9H_2O$ gave inferior results compared to using CuI (Table 7, entries 7-10). The acid catalyst *p*-TSA.H_2O was superior over the other acid catalysts screened, such as acetic acid (CH_3CO_2H), benzoic acid ($C_6H_5CO_2H$) and triflic acid (TfOH) (Table 7, entries 11-13). In a quest to improve the product yield, the reaction was carried out with other solvents. Toluene gave a yield of 80% compared to other solvents such as DCE and THF (Table 7, entries 14-16). From these observations, it can be concluded that 10 mol % *p*-TSA.H_2O and 20 mol % CuI in acetonitrile under reflux condition is the most suitable reaction condition (Table 7).

On the basis of above optimized reaction condition, the scope and generality of this methodology was further investigated with 2-aminothiophenol (**7a**) and a variety of β-oxodithioesters. A wide array of β-oxodithioesters (**3**) bearing R as aryl groups (containing both electron-donating and electron-withdrawing substituents), extended aromatic, heteroaromatic and alkyl groups could be involved affording the desired products in good to excellent yields (Table 8). Interestingly, β-oxodithioesters (**3**) bearing R as halogen substituted aromatic ring such as fluoro, chloro, bromo and iodo at *para* position also gave the corresponding benzo[*d*]thiazole in good to excellent yield. However, chloro substituted at *ortho* position afforded comparatively lower yield (**8c**, 70%). Importantly, other electron-withdrawing and electron-donating substituents like CF_3, Me, OMe also proceeded smoothly (**8g-i**). Likewise various β-oxodithioesters (**3**) bearing R as heteroaromatic and alkyl such as furyl, thioenyl, ferrocenyl and isobutyl groups were also examined with 2-aminothiophenol (**7**) in a similar manner in the presence of same amount of catalyst and the desired products (**8k-n**) were obtained in 65-75% yield (Table 8). For generalizing the reaction procedure, we further examined the reactions by using different *para* substituted 2-aminothiophenol such as 2-amino-4-chlorothiophenol (**7b**) and 2-amino-4-(trifluoromethyl)thiophenol (**7c**) with various β-oxodithioesters. The reaction was performed between 2-amino-4-chlorothiophenol (**7b**) and different β-oxodithioesters bearing R as aromatic and poly-aromatic under the optimized reaction condition and the desired products were obtained in excellent yields (Table 8, **8o-t**). Encouraged by these successful results, we also scrutinized the reactions of 2-amino-4-(trifluoromethyl)thiophenol (**7c**), with different β-oxodithioesters bearing R as poly-aromatic (napthyl) and aromatic (4-Cl and 4-OMe) in the presence of same amount of catalyst and the desired products were obtained in good to excellent yields (Table 8, **8u**-**w**).

Table 8. Synthesis of various 2-substituted benzo[*d*]thiazoles



8a (85%) **8b** (83%) **8c** (70%) **8d** (87%)

8e (87%) **8f** (82%) **8g** (79%) **8h** (85%)

8i (87%) **8j** (77%)[c] **8k** (70%)[c] **8l** (75%)[c]

8m (65%)[c] **8n** (70%)[c] **8o** (83%) **8p** (81%)

8q (88%) **8r** (86%) **8s** (90%) **8t** (92%)

8u (77%) **8v** (88%) **8w** (90%)

[a]All the reactions were carried out using 2-aminothiophenol (**7a,** 0.5 mmol), ethyl-3-oxo-3-phenylpropanedithioate (**3a,** 0.5 mmol), *p*-TSA.H_2O (10 mol %, 0.0095 g), and CuI (20 mol %, 0.0190 g) and solvent (2ml) under reflux condition for 16h. [b]Isolated yield. [c]The reactions were carried out in 0.25 mmol scale using 2-aminothiophenol and *β*-oxodithioester (1: 1) under reflux condition for 16h.

All the products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR, HRMS and elemental analyses. In addition the structure of **8u** was also confirmed by X-ray crystallographic data (Figure 7).

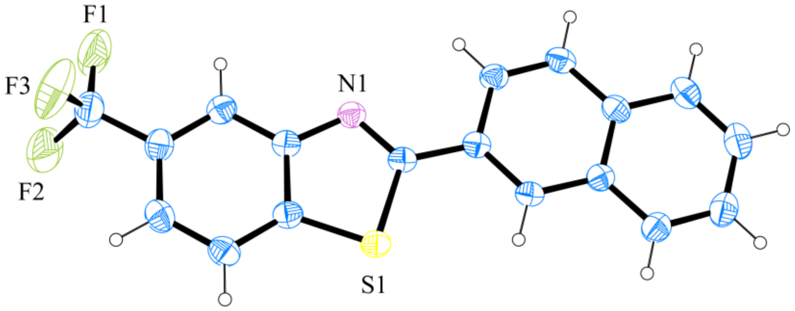
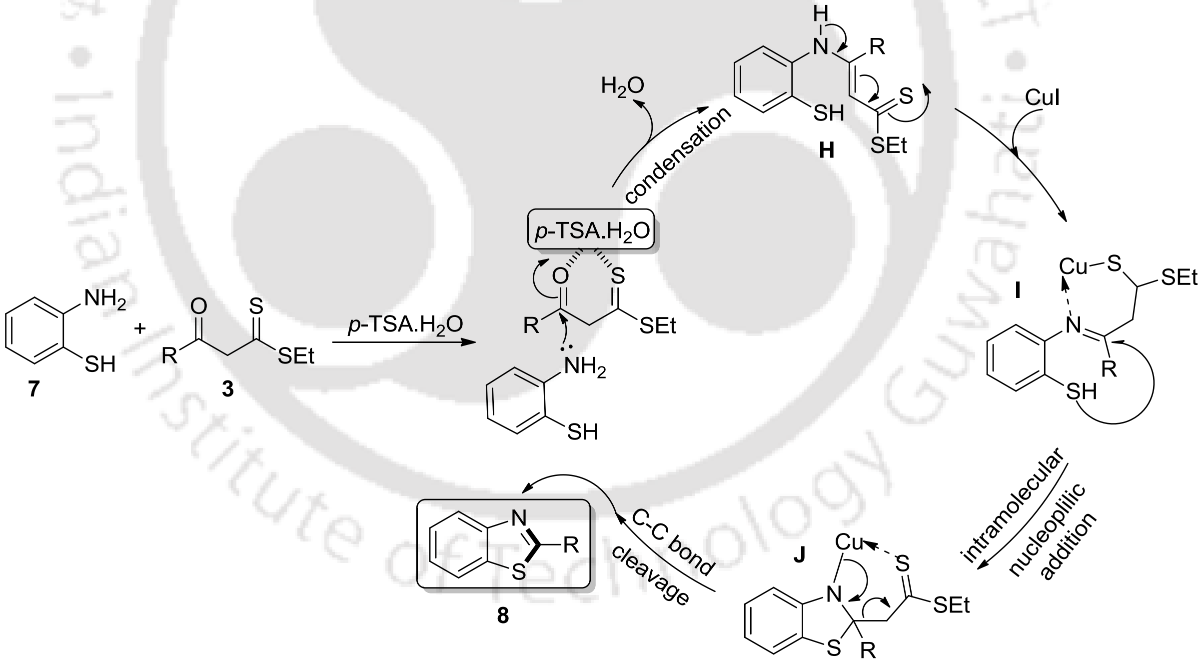


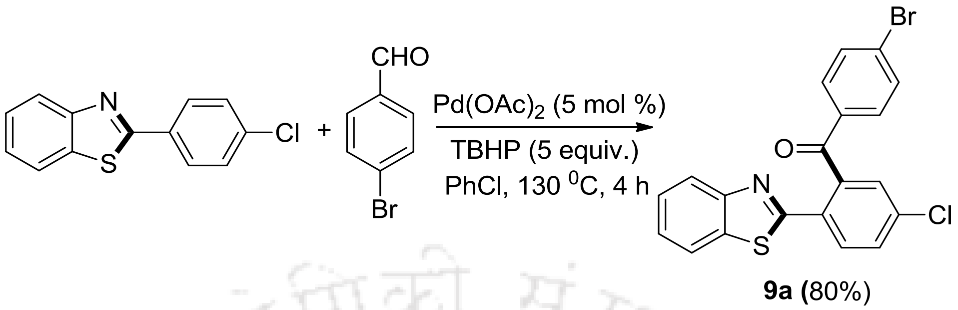
Figure 7. ORTEP structure of compound **8u** (CCDC No. 1442548)

Based on literature reports,[110] a plausible mechanism for the formation of the 2-substituted benzo[*d*]thiazole **8** is depicted (Scheme 57). Initially 2-aminothiophenol condensed with *β*-oxodithioesters to generate mono enaminodithioester intermediate **H** in presence of *p*-TSA.H_2O, which may coordinate with CuI to give an iminium intermediate **I**. The intermediate **I** undergoes intramolecular nucleophilic addition to furnish the adduct **J**. Finally, adduct **J** undergoes C-C bond cleavage to provide the desired product 2-substituted benzothiazoles **8**.



Scheme 57. Plausible mechanism for the formation benzo[*d*]thiazole

It is noteworthy to mention that the 2-substituted benzothiazoles can be further utilized as expedient synthons in *ortho*-selective C-H functionalization reactions (Scheme 58).[111] The reaction was performed with 2-(4-chlorophenyl)benzo[*d*]thiazole (0.25 mmol) and 4-bromobenzaldehyde (0.30 mmol) in presence of Pd(OAc)$_2$ as a catalyst and TBHP (*tert*-butyl hydroperoxide) as an oxidant in chlorobenzene solvent under reflux condition and the desired product (2-(benzo[*d*]thiazol-2-yl)-5-chlorophenyl)(4-bromophenyl)methanone was obtained in 80% yield.



Scheme 58. Application of 9d in *ortho*-aroylation reaction

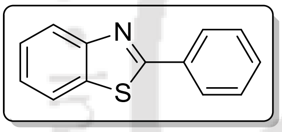
In conclusion, we have developed an efficient and straightforward synthetic protocol for the facile access of 2-substituted benzothiazoles through one-pot condensation reaction of 2-aminothiophenol and β-oxodithioesters using combined catalyst *p*-TSA.H_2O and CuI. Some of the important aspects of this present protocol are simple experimental procedure, easy to handle, good to excellent yields and substrate scope compatibility.

4.4. Experimental Section

General procedure for the synthesis of 2-phenylbenzo[*d*]thiazole:

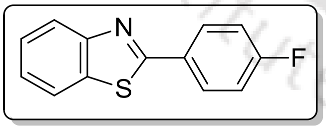
Into an oven dried 25 mL round-bottomed flask fitted with a reflux condenser, a mixture of 2-aminothiophenol (**7a**) (0.063 g, 0.5 mmol), ethyl 3-oxo-3phenylpropanedithioate (**3a**) (0.112 g, 0.5 mmol), *p*-TSA.H_2O (0.0095 g, 10 mol %) and CuI (0.0190 g, 20 mol %) was taken in 2 mL of acetonitrile and stirred at 80^0 C in a pre-heated oil-bath for the stipulated period of time. The progress of the reaction was monitored TLC. The reaction mixture was then cooled and the water was added into it. The crude residue was extracted with ethyl acetate (10 mL x 3) and the combined organic layers were washed with a saturated $NaHCO_3$ solution. The organic extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was further purified by silica gel column chromatography (hexane/ethyl acetate, 10:0.5) to yield pure 2-phenylbenzo[*d*]thiazole (**8a**, 0.090 g, 85%) as white solid.

*2-phenylbenzo[d]thiazole (**8a**)*:



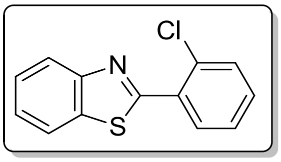
White solid (0.090 g, 85%); mp: 117-118 °C; IR (KBr): 1070, 1224, 1312, 1433, 1477, 1632, 2924 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.39 (t, *J* = 7.2 Hz, 1H), 7.49-7.52 (m, 4H), 7.90 (d, *J* = 7.8 Hz, 1H), 8.10-8.13 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 121.82, 123.37, 125.44, 126.58, 127.79, 129.23, 131.25, 133.65, 135.13, 154.10, 168.35; Anal. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63. Found: C, 73.81; H, 4.19; N, 6.49. HRMS (ESI): Calcd. For $C_{13}H_9NS$ (MH+) 212.0534; Found 212.0534.

*2-(4-fluorophenyl)benzo[d]thiazole (**8b**)*:



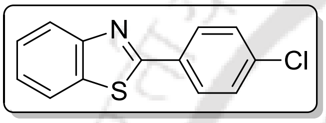
White solid (0.095 g, 83%); mp: 100-101 °C; IR (KBr): 1096, 1228, 1404, 1481, 1636, 2926 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.4 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 8.06-8.10 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ, 116.30, 116.45, 121.83, 123.42, 125.47, 126.64, 129.72, 129.77, 130.21, 135.28, 154.33, 163.85, 165.52, 166.96; Anal. Calcd for $C_{13}H_8FNS$: C, 68.10; H, 3.52; N, 6.11. Found: C, 68.01; H, 3.39; N, 6.02. HRMS (ESI): Calcd. For $C_{13}H_8FNS$ (MH+) 230.0440; Found 230.0448.

*2-(2-chlorophenyl)benzo[d]thiazole (**8c**)*:



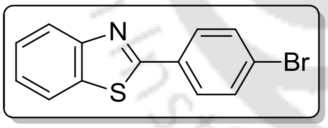
White solid (0.086 g, 70%); mp: 80-81 °C; IR (KBr): 1038, 1061, 1262, 1271, 1432, 1638, 2924 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): *δ* 7.43-7.47 (m, 3H), 7.54-7.56 (m, 2H), 7.97 (d, *J* = 7.8 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.26 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 121.66, 123.63, 125.82, 126.66, 127.43, 131.09, 131.54, 132.08, 132.28, 133.00, 136.24, 152.33, 164.88; Anal. Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70. Found: C, 63.41; H, 3.19; N, 5.62. HRMS (ESI): Calcd. For $C_{13}H_8ClNS$ (MH+) 246.0144; Found 246.0148.

*2-(4-chlorophenyl)benzo[d]thiazole (**8d**)*:



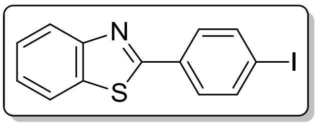
White solid (0.107 g, 87%); mp: 114-116 °C; IR (KBr): 1087, 1249, 1398, 1431, 1472, 1641, 2925 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): *δ* 7.38 (t, *J* = 7.8 Hz, 1H), 7.44-7.45 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 8.00 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 121.81, 123.47, 125.58, 126.64, 128.86, 129.43, 132.27, 135.23, 137.19, 154.23, 166.77; Anal. Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70. Found: C, 63.43; H, 3.16; N, 5.64. HRMS (ESI): Calcd. For $C_{13}H_8ClNS$ (MH+) 246.0144; Found 246.0146.

*2-(4-bromophenyl)benzo[d]thiazole (**8e**)*:



White solid (0.126 g, 87%); mp: 134-135 °C; IR (KBr): 1012, 1068, 1226, 1476, 1632, 2924 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): *δ* 7.40 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 121.85, 123.44, 125.69, 126.75, 129.11, 132.43, 132.55, 135.09, 154.01, 166.95; Anal. Calcd for $C_{13}H_8BrNS$: C, 53.81; H, 2.78; N, 4.83. Found: C, 53.63; H, 2.65; N, 4.68. HRMS (ESI): Calcd. For $C_{13}H_8BrNS$ (MH+) 289.9639 and 291.9619; Found 289.9639 and 291.9630.

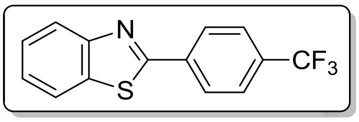
*2-(4-iodophenyl)benzo[d]thiazole (**8f**)*:



White solid (0.138 g, 82%); mp: 155-156 °C; IR (KBr): 1056, 1250, 1313, 1385, 1468, 1636, 2924 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): *δ* 7.41 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.81- 7.85 (m, 4H), 7.90 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H) ; ^{13}C

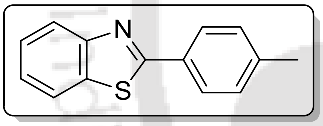
NMR (150 MHz, $CDCl_3$): δ 97.90, 121.89, 123.44, 125.78, 126.82, 129.18, 133.03, 135.00, 138.43, 153.86, 167.23; Anal. Calcd for $C_{13}H_8INS$: C, 44.46; H, 2.18; N, 4.32. Found: C, 44.32; H, 2.09; N, 4.25. HRMS (ESI): Calcd. For $C_{13}H_8INS$ (MH+) 337.9500; Found 337.9500.

*2-(4-(trifluoromethyl)phenyl)benzo[d]thiazole (**8g**)*:



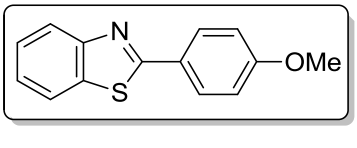
White solid (0.110 g, 79%); mp: 161-162 °C; IR (KBr): 1067, 1119, 1248, 1323, 1400, 1625, 2938 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (t, J = 7.8 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 2H), 7.91 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 121.31, 121.94, 123.11, 123.80, 124.92, 126.02, 126.21, 126.72, 126.88, 127.97, 132.36, 132.58, 132.80, 133.02, 135.35, 136.86, 154.10, 166.29; Anal. Calcd for $C_{14}H_8F_3NS$: C, 60.21; H, 2.89; N, 5.02. Found: C, 60.11; H, 2.72; N, 5.09. HRMS (ESI): Calcd. For $C_{14}H_8F_3NS$ (MH+) 280.0408; Found 280.0408.

*2-(p-tolyl)benzo[d]thiazole (**8h**)*:



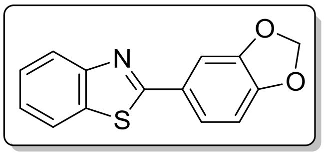
White solid (0.096 g, 85%); mp: 82-83 °C; IR (KBr): 1071, 1116, 1226, 1250, 1432, 1481, 1607, 2924 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.31 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.75, 121.80, 123.01, 125.44, 126.68, 127.83, 130.00, 130.54, 134.66, 142.06, 153.45, 168.77; Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22. Found: C, 74.51; H, 4.80; N, 6.29. HRMS (ESI): Calcd. For $C_{14}H_{11}NS$ (MH+) 226.0690; Found 226.0696.

*2-(4-methoxyphenyl)benzo[d]thiazole (**8i**)*:



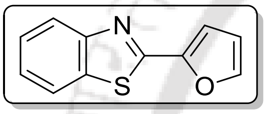
White solid (0.105 g, 87%); mp: 130-132 °C; IR (KBr): 1085, 1172, 1261, 1398, 1637, 2940 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.01 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.70, 114.64, 121.74, 122.97, 125.10, 126.51, 129.42, 134.91, 154.11, 162.26, 168.22; Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.56; H, 4.48; N, 5.89. HRMS (ESI): Calcd. For $C_{14}H_{11}NOS$ (MH+) 242.0640; Found 242.0640.

*2-(benzo[d][1,3]dioxol-5-yl)benzo[d]thiazole (**8j**)*:



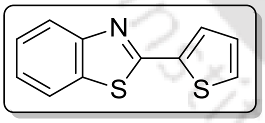
Yellow solid (0.049 g, 77%); mp: 124-126 °C; IR (KBr): 1033, 1102, 1233, 1440, 1472, 1627, 1734, 2923 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ 6.07 (s, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.66 (m, 2H), 7.87 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 102.06, 107.88, 108.98, 121.76, 122.84, 123.16, 125.50, 126.82, 127.38, 134.40, 134.40, 148.69, 150.73, 153.05, 168.22; Anal. Calcd for $C_{14}H_9NO_2S$: C, 65.87; H, 3.55; N, 5.49. Found: C, 65.76; H, 3.46; N, 5.44. HRMS (ESI): Calcd. For $C_{14}H_9NO_2S$ (MH+) 256.0432; Found 256.0434.

*2-(furan-2-yl)benzo[d]thiazole (**8k**)*:



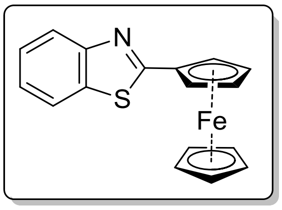
White solid (0.035 g, 70%); mp: 100-102 °C; IR (KBr): 1012, 1069, 1245, 1286, 1434, 1504, 1728, 2925 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ 6.61 (m, 1H), 7.27 (d, J = 2.4 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 1.2 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 112.19, 112.87, 121.82, 123.20, 125.55, 126.85, 134.26, 145.14, 148.73, 153.44, 157.89; Anal. Calcd for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.59; H, 3.42; N, 6.88. HRMS (ESI): Calcd. For $C_{11}H_7NOS$ (MH+) 202.0327; Found 202.0329.

*2-(thiophen-2-yl)benzo[d]thiazole (**8l**)*:



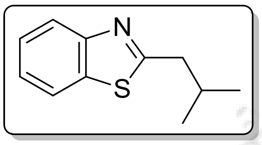
White solid (0.041 g, 75%); mp: 94-96 °C; IR (KBr): 1046, 1249, 1394, 1476, 1615, 2925 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.16 (t, J = 3.6 Hz, 1H) 7.16 (t, J = 3.6 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.53 (d, J = 4.8 Hz, 1H), 7.74 (d, J = 3.0 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 121.71, 123.04, 125.62, 126.84, 128.42, 129.32, 129.90, 134.57, 137.05, 153.25, 161.81; Anal. Calcd for $C_{11}H_7NS_2$: C, 60.80; H, 3.25; N, 6.45. Found: C, 60.67; H, 3.14; N, 6.58. HRMS (ESI): Calcd. For $C_{11}H_7NS_2$ (MH+) 218.0098; Found 218.0099.

*ferrocenyl-benzo[d]thiazole (**8m**)*:



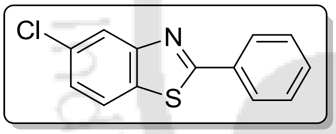
Red semi-solid (0.052 g, 65%); IR (KBr): 1051, 1073, 1128, 1176, 1228, 1261, 1333, 1427, 1465, 1521, 1614, 2926 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$OD): δ 4.15 (s, 5H), 4.58 (s, 2H), 4.60 (s, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD): δ 69.11, 70.83, 71.61, 77.27, 122.08, 121.70, 125.24, 126.88, 134.85, 153.78, 171.88; Anal. Calcd for $C_{17}H_{14}FeNS$: C, 63.77; H, 4.41; N, 4.37. Found: C, 63.65; H, 4.32; N, 4.48. HRMS (ESI): Calcd. For $C_{17}H_{14}FeNS$ (MH+) 320.0196; Found 320.0195.

*2-isobutylbenzo[d]thiazole (**8n**)*:



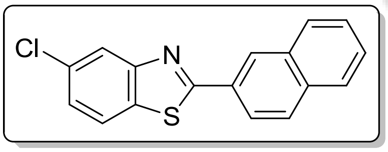
Yellow semi-solid (0.033 g, 70%); IR (KBr): 1083, 1261, 1385, 1401, 1401, 1639, 2925 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 1.07-1.078 (m, 6H), 2.31 (m, 1H), 3.16 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.75 (t, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.61, 30.31, 42.48, 121.91, 122.01, 126.12, 127.30, 131.06, 133.67, 149.56, 174.08; Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.00; H, 6.69; N, 7.45. HRMS (ESI): Calcd. For $C_{11}H_{13}NS$ (MH+) 192.0847; Found 192.0847.

*5-chloro-2-phenylbenzo[d]thiazole (**8o**)*:



White solid (0.102 g, 83%); mp: 139-140 °C; IR (KBr): 1067, 1260, 1431, 1475, 1610, 2924 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.36 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.49-7.51 (m, 3H), 7.80 (d, *J* = 8.4 Hz, 1H), 8.06-8.08 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 122.51, 123.22, 125.88, 127.83, 129.31, 131.58, 132.56, 133.42, 133.48, 155.12, 170.17; Anal. Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70. Found: C, 63.43; H, 3.17; N, 5.59. HRMS (ESI): Calcd. For $C_{13}H_8ClNS$ (MH+) 246.0144; Found 246.0146.

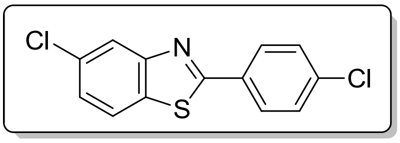
*5-chloro-2-(naphthalen-2-yl)benzo[d]thiazole (**8p**)*:



White solid (0.120 g, 81%); mp: 154-155 °C; IR (KBr): 1051, 1114, 1229, 1331, 1461, 1498, 1612, 2924 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.37 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.54-7.58 (m, 2H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.87-7.89 (m, 1H), 7.94-7.97 (m, 2H), 8.09 (d, *J* = 1.8 Hz, 1H), 8.17 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 8.54 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 122.53, 123.20, 124.50, 125.94, 127.21, 127.93, 128.06, 128.12, 129.11, 129.15, 130.73, 132.65, 133.33, 133.52, 134.99, 155.17, 170.22; Anal. Calcd for $C_{17}H_{10}ClNS$: C, 69.03; H, 3.28; N, 4.74.

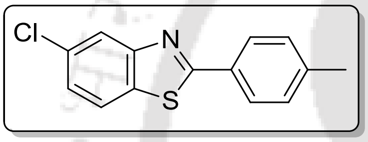
Found: C, 68.93; H, 3.16; N, 4.68. HRMS (ESI): Calcd. For $C_{17}H_{10}ClNS$ (MH+) 296.0301; Found 296.0313.

*5-chloro-2-(4-chlorophenyl)benzo[d]thiazole (**8q**)*:



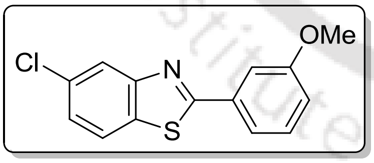
White solid (0.123 g, 88%); mp: 152-153 °C; IR (KBr): 1056, 1104, 1259, 1337, 1401, 1478, 1592, 1613, 2924 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.35-7.37 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 8.03 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 122.54, 123.30, 126.10, 128.95, 129.57, 131.93, 132.72, 133.49, 133.49, 133.49, 137.67, 155.10, 168.68; Anal. Calcd for $C_{13}H_7Cl_2NS$: C, 55.73; H, 2.52; N, 5.00. Found: C, 55.59; H, 2.44; N, 5.08. HRMS (ESI): Calcd. For $C_{13}H_7Cl_2NS$ (MH+) 279.9755; Found 279.9769.

*5-chloro-2-(p-tolyl)benzo[d]thiazole (**8r**)*:



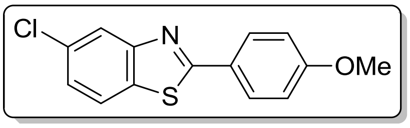
White solid (0.112 g, 86%); mp: 130-131 °C; IR (KBr): 1064, 1264, 1431, 1522, 1638, 2921 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 2.43 (s, 3H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.33-7.35 (m, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 8.03 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.77, 122.46, 123.05, 125.69, 127.79, 130.02, 130.75, 130.75, 132.50, 133.36, 142.18, 155.12, 170.36; Anal. Calcd for $C_{14}H_{10}ClNS$: C, 64.73; H, 3.88; N, 5.39. Found: C, 64.62; H, 3.76; N, 5.30. HRMS (ESI): Calcd. For $C_{14}H_{10}ClNS$ (MH+) 260.0301; Found 260.0301.

*5-chloro-2-(3-methoxyphenyl)benzo[d]thiazole (**8s**)*:



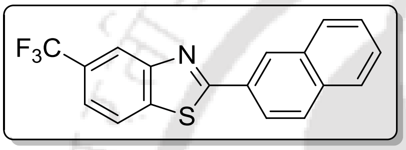
White solid (0.124 g, 90%); mp: 112-114 °C; IR (KBr): 1047, 1275, 1299, 1435, 1498, 1608, 2924 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 3.90 (s, 3H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.63 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.66, 112.24, 117.81, 120.39, 122.42, 123.12, 125.82, 130.24, 132.46, 133.42, 134.55, 154.92, 160.20, 169.94; Anal. Calcd for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66; N, 5.08. Found: C, 60.89; H, 3.55; N, 5.03. HRMS (ESI): Calcd. For $C_{14}H_{10}ClNOS$ (MH+) 276.0250; Found 276.0256.

*5-chloro-2-(4-methoxyphenyl)benzo[d]thiazole (**8t**)*:



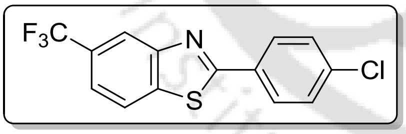
White solid (0.127 g, 92%); mp: 145-146 °C; IR (KBr): 1073, 1172, 1258, 1434, 1480, 1604, 1641, 2963 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.00-7.01 (m, 2H), 7.33 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 8.01-8.03 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.73, 114.70, 122.40, 122.82, 125.48, 126.18, 129.49, 132.48, 133.24, 155.15, 162.52, 169.99; Anal. Calcd for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66; N, 5.08. Found: C, 60.87; H, 3.57; N, 5.14. HRMS (ESI): Calcd. For $C_{14}H_{10}ClNOS$ (MH+) 276.0250; Found 276.0259.

*2-(naphthalen-2-yl)-5-(trifluoromethyl)benzo[d]thiazole (**8u**)*:



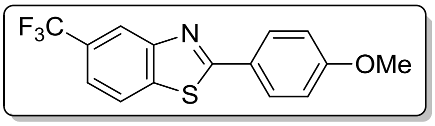
White solid (0.127 g, 77%); mp: 189-190 °C; IR (KBr): 1019, 1099, 1231, 1418, 1452, 1577, 2962 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48-7.51 (m, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.87-7.90 (m, 2H), 7.96 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.26 (s, 1H), 8.47 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 119.99, 121.32, 122.26, 123.14, 123.99, 124.94, 126.93, 127.70, 127.78, 128.56, 128.67, 128.84, 130.10, 132.84, 134.60, 138.38, 153.55, 170.00; Anal. Calcd for $C_{18}H_{10}F_3NS$: C, 65.64; H, 3.06; N, 4.25. Found: C, 65.53; H, 3.00; N, 4.17. HRMS (ESI): Calcd. For $C_{18}H_{10}F_3NS$ (MH+) 330.0564; Found 330.0566.

*2-(4-chlorophenyl)-5-(trifluoromethyl)benzo[d]thiazole (**8v**)*:



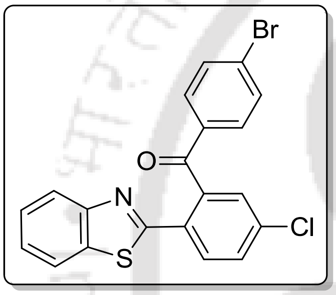
White solid (0.138 g, 88%); mp: 132-134 °C; IR (KBr): 1016, 1124, 1274, 1432, 1496, 1599, 2924 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.97-8.01 (m, 3H), 8.30 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 120.64, 120.67, 120.69, 121.65, 121.65, 121.91, 121.93, 122.46, 123.45, 125.26, 127.06, 129.02, 129.29, 129.50, 129.64, 129.72, 131.69, 137.95, 138.62, 153.85, 168.85; Anal. Calcd for $C_{14}H_7ClF_3NS$: C, 53.60; H, 2.25; N, 4.46. Found: C, 53.51; H, 2.17; N, 4.55. HRMS (ESI): Calcd. For $C_{14}H_7ClF_3NS$ (MH+) 314.0018; Found 314.0018.

*2-(4-methoxyphenyl)-5-(trifluoromethyl)benzo[d]thiazole (**8w**)*:



White solid (0.139 g, 90%); mp: 125-126 °C; IR (KBr): 1069, 1092, 1260, 1400, 1429, 1473, 1585, 2920 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ 3.88 (s, 3H), 7.00 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 8.28 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 55.71, 114.75, 120.05, 120.07, 120.10, 121.33, 121.76, 122.29, 123.56, 125.36, 125.93, 127.17, 128.79, 129.01, 129.23, 129.45, 129.56, 138.44, 153.93, 162.67, 170.15; Anal. Calcd for $C_{15}H_{10}F_3NOS$: C, 58.25; H, 3.26; N, 4.53. Found: C, 58.16; H, 3.18; N, 4.59. HRMS (ESI): Calcd. For $C_{15}H_{10}F_3NOS$ (MH+) 310.0513; Found 310.0515.

*(2-(benzo[d]thiazol-2-yl)-5-chlorophenyl)(4-bromophenyl)methanone (**9a**)*:



Yellow semi-solid (0.086 g, 80%); IR (KBr): 1067, 1096, 1166, 1257, 1371, 1371, 1457, 1585, 1677, 1734, 2840, 2924 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.33 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 1.8 Hz, 1H), 7.59-7.63 (m, 3H), 7.74 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 121.71, 123.66, 125.94, 126.65, 126.65, 128.34, 128.97, 130.51, 130.62, 130.75, 130.97, 131.93, 135.29, 136.36, 137.05, 140.67, 153.55, 163.92, 195.10; Anal. Calcd for $C_{20}H_{11}BrClNOS$: C, 56.03; H, 2.59; N, 3.27. Found: C, 56.09; H, 2.41; N, 3.16. HRMS (ESI): Calcd. For $C_{20}H_{11}BrClNOS$ (MH+) 427.9512 and 429.9491; Found 427.9515 and 429.9493.

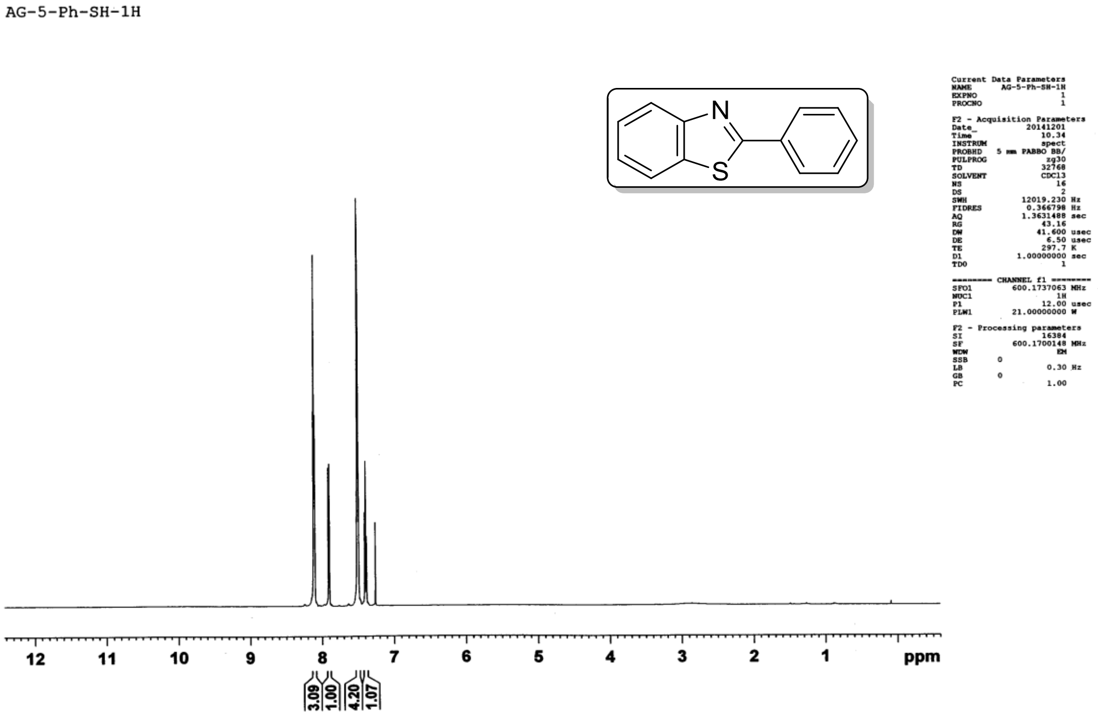
XRD for Compound **8u**

Complete crystallographic data of **8u** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1442548. 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 9. Crystal data and structure refinement for **8u**, for atomic coordinates and equivalent isotopic displacement parameters and bond angles, please check the CIF

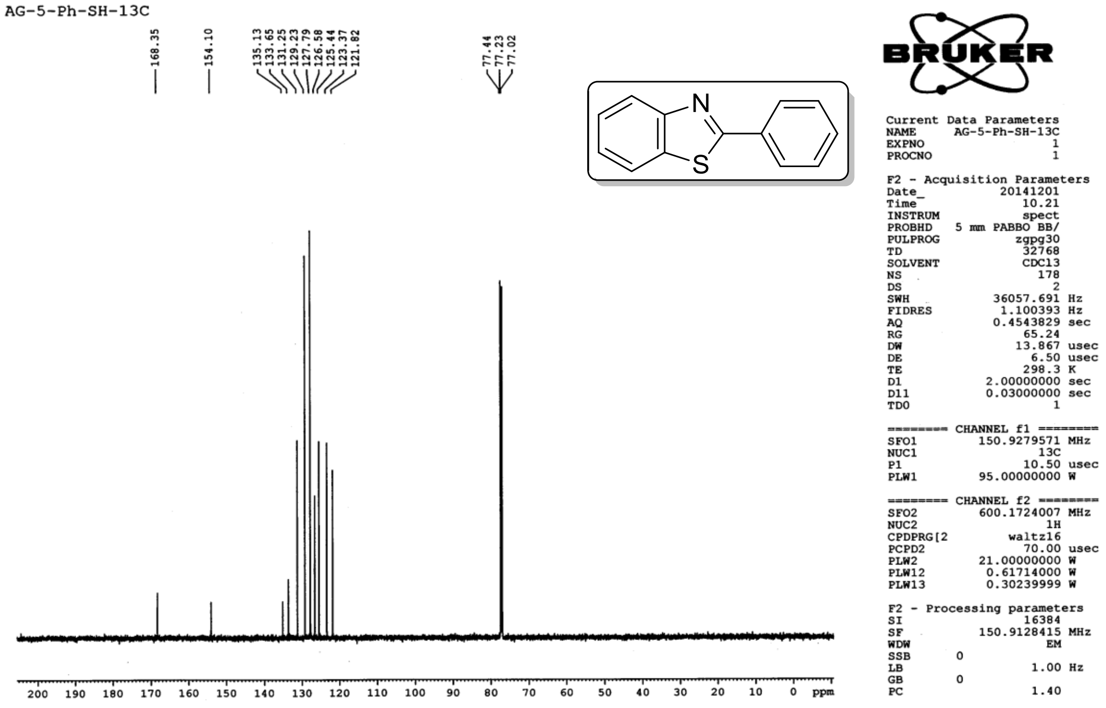
Parameters	**Compound**
Formula	$C_{18} H_{10} F_3 N S$
CCDC number	1442548
Formula weight	329.33
T (K)	296 (2)
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	P -1
a (Å)	17.7801(5)
b (Å)	5.8536(2)
c (Å)	15.5875(5)
A (^{0})	90.00
B (^{0})	115.737(2)
γ (^{0})	90.00
V (Å)^3	1461.37(8)
Z	4
D_{calcd} (g m^{-3})	1.497
μ (mm^{-1})	0.252
F (0 0 0)	672
Reflection collected	25971
Unique reflections	2664
Goodness-of-fit (GOF)^a on F^2	1.108
R [I > 2σ(I)]	$^bR_1 = 0.0460$, $^cwR_2 = 0.1505$
R indices (all data)	$^bR_1 = 0.0620$, $^cwR_2 = 0.1640$

^{1}H **NMR (600 MHz, CDCl$_3$):** 2-substituted benzo[*d*]thiazole (***8a***):



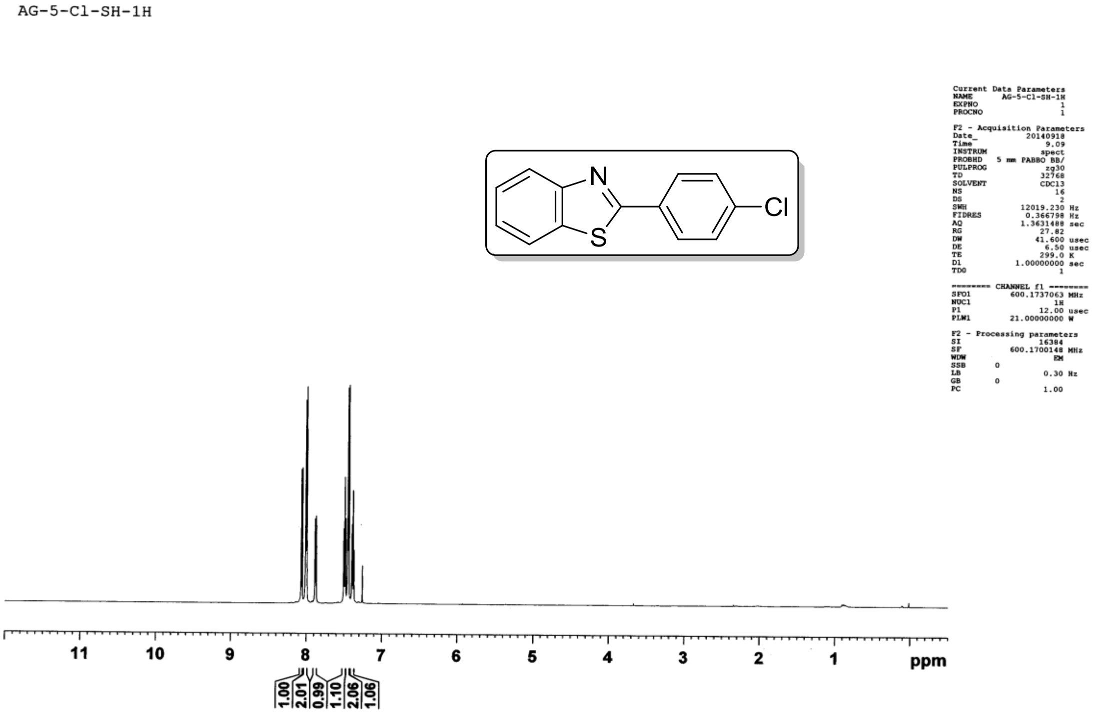
```
Current Data Parameters
NAME       AG-5-Ph-SH-1H
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141201
Time               10.34
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                 43.16
DW                41.600 usec
DE                  6.50 usec
TE                 297.7 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1737063 MHz
NUC1                  1H
P1                 12.00 usec
PLW1         21.00000000 W

F2 - Processing parameters
SI                 16384
SF           600.1700148 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

^{13}C **NMR (150 MHz, CDCl$_3$):** 2-substituted benzo[*d*]thiazole *(**8a**):*



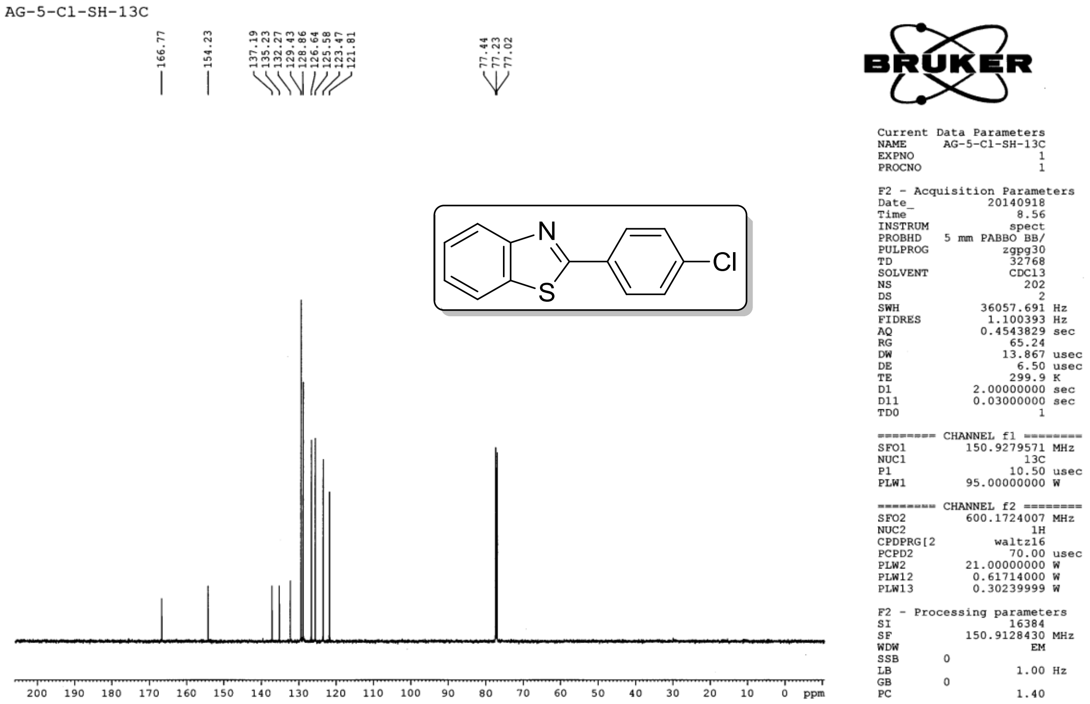
```
Current Data Parameters
NAME       AG-5-Ph-SH-13C
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141201
Time               10.21
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   178
DS                     2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                 65.24
DW                13.867 usec
DE                  6.50 usec
TE                 298.3 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                 10.50 usec
PLW1         95.00000000 W

======== CHANNEL f2 ========
SFO2         600.1724007 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              70.00 usec
PLW2         21.00000000 W
PLW12         0.61714000 W
PLW13         0.30239999 W

F2 - Processing parameters
SI                 16384
SF           150.9128415 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

^{1}H **NMR (600 MHz, CDCl₃):** 2-substituted benzo[*d*]thiazole (***8d***):



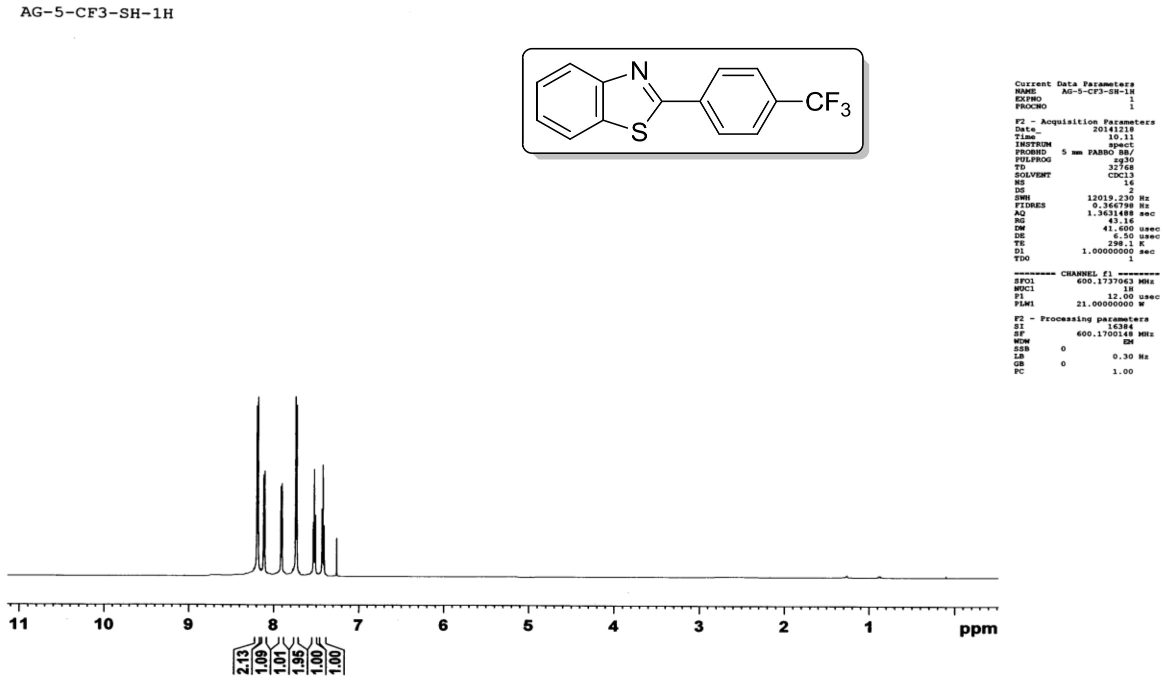
```
Current Data Parameters
NAME       AG-5-Cl-SH-1H
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140918
Time                9.09
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                 27.82
DW                41.600 usec
DE                  6.50 usec
TE                 299.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1737063 MHz
NUC1                  1H
P1                 12.00 usec
PLW1         21.00000000 W

F2 - Processing parameters
SI                 16384
SF           600.1700148 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

^{13}C **NMR (150 MHz, CDCl₃):** 2-substituted benzo[*d*]thiazole ***(8d):***



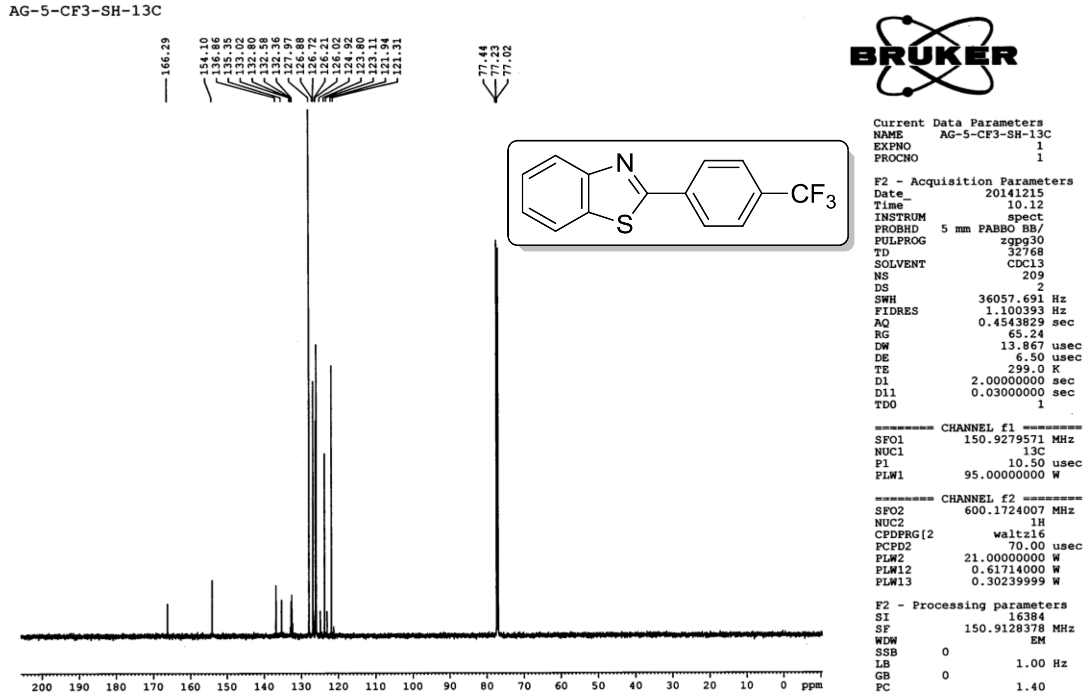
```
Current Data Parameters
NAME        AG-5-Cl-SH-13C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140918
Time                  8.56
INSTRUM              spect
PROBHD     5 mm PABBO BB/
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     202
DS                       2
SWH              36057.691 Hz
FIDRES            1.100393 Hz
AQ               0.4543829 sec
RG                   65.24
DW                  13.867 usec
DE                    6.50 usec
TE                   299.9 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           150.9279571 MHz
NUC1                   13C
P1                   10.50 usec
PLW1           95.00000000 W

======== CHANNEL f2 ========
SFO2           600.1724007 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                70.00 usec
PLW2           21.00000000 W
PLW12           0.61714000 W
PLW13           0.30239999 W

F2 - Processing parameters
SI                   16384
SF             150.9128430 MHz
WDW                     EM
SSB      0
LB                    1.00 Hz
GB       0
PC                    1.40
```

^{1}H **NMR (600 MHz, $CDCl_3$):** 2-substituted benzo[*d*]thiazole (***8g***):



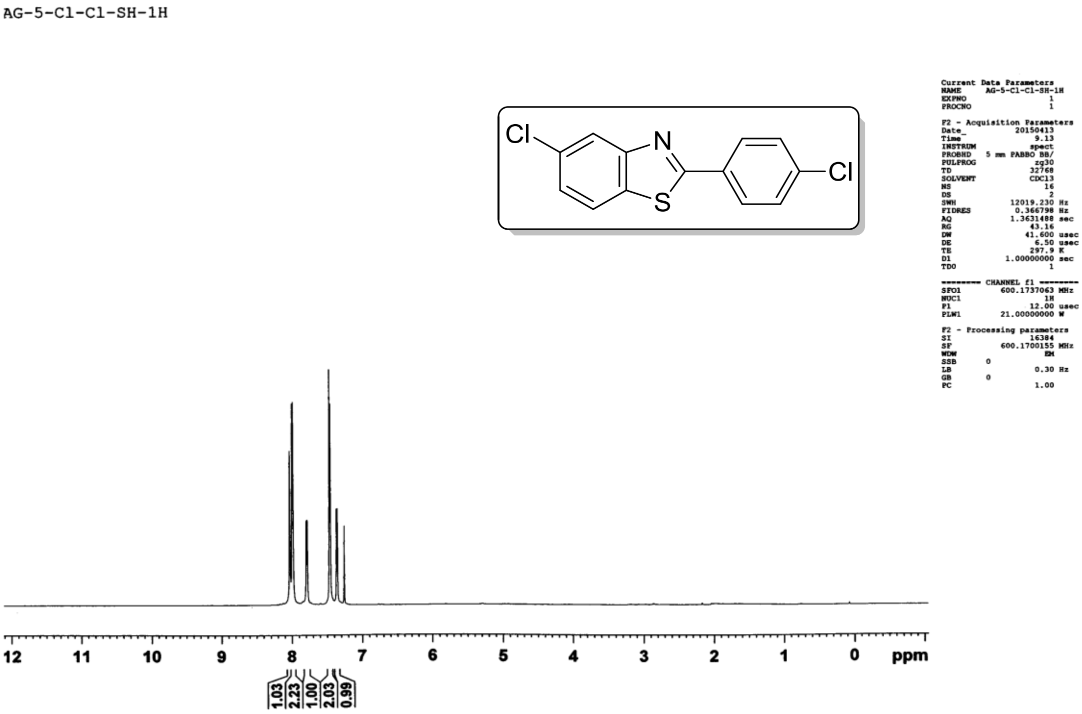
```
Current Data Parameters
NAME      AG-5-CF3-SH-1H
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141218
Time               10.11
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                 43.16
DW                41.600 usec
DE                  6.50 usec
TE                 298.1 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1737063 MHz
NUC1                  1H
P1                 12.00 usec
PLW1         21.00000000 W

F2 - Processing parameters
SI                 16384
SF           600.1700148 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

^{13}C **NMR (150 MHz, $CDCl_3$):** 2-substituted benzo[*d*]thiazole ***(8g):***



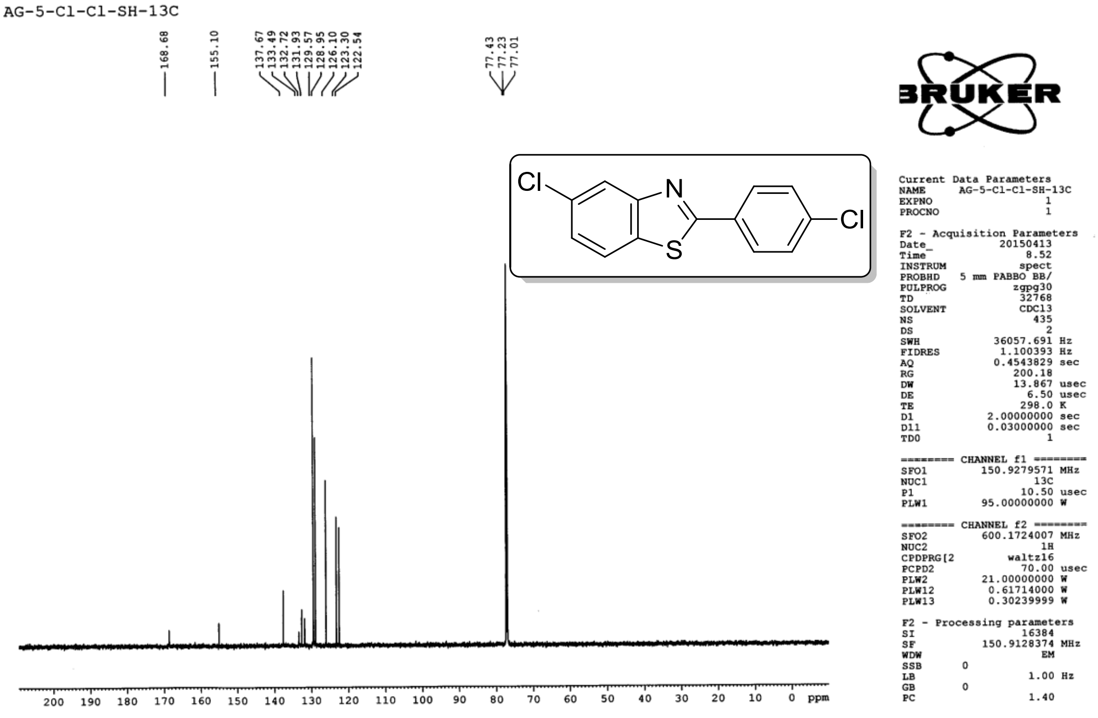
```
Current Data Parameters
NAME       AG-5-CF3-SH-13C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20141215
Time                 10.12
INSTRUM              spect
PROBHD     5 mm PABBO BB/
PULPROG             zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     209
DS                       2
SWH              36057.691 Hz
FIDRES            1.100393 Hz
AQ               0.4543829 sec
RG                   65.24
DW                  13.867 usec
DE                    6.50 usec
TE                   299.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           150.9279571 MHz
NUC1                   13C
P1                   10.50 usec
PLW1           95.00000000 W

======== CHANNEL f2 ========
SFO2           600.1724007 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                70.00 usec
PLW2           21.00000000 W
PLW12           0.61714000 W
PLW13           0.30239999 W

F2 - Processing parameters
SI                   16384
SF             150.9128378 MHz
WDW                     EM
SSB      0
LB                    1.00 Hz
GB       0
PC                    1.40
```

^{1}H **NMR (600 MHz, CDCl$_3$):** 2-substituted benzo[*d*]thiazole (***8q***):



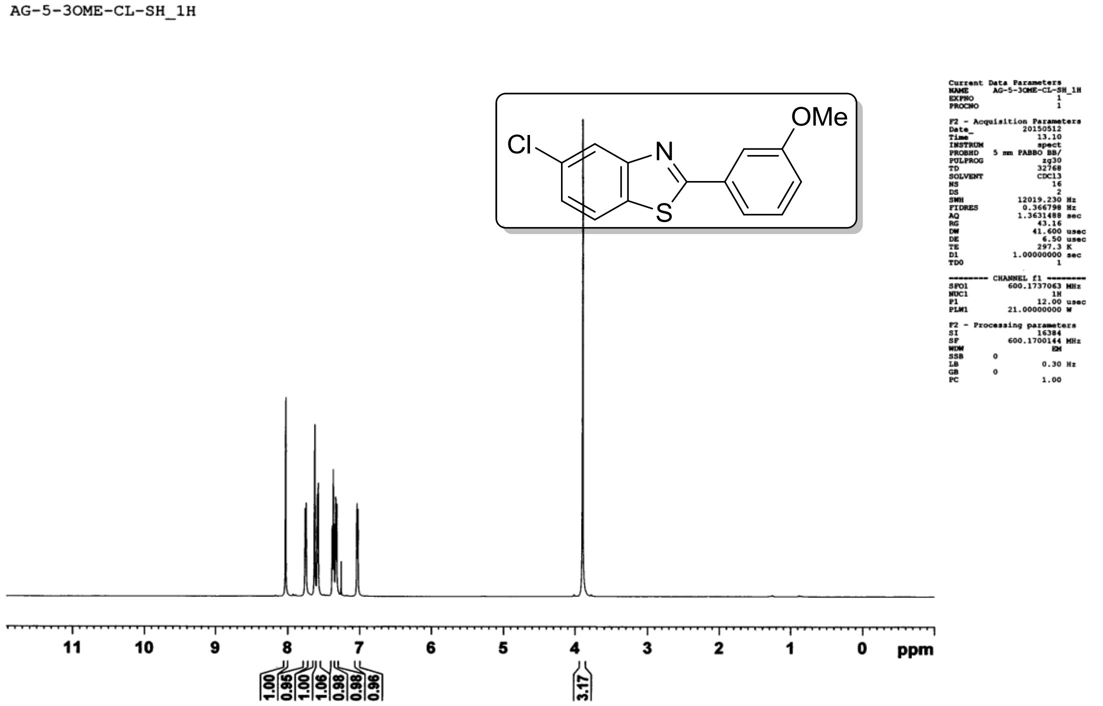
```
Current Data Parameters
NAME      AG-5-Cl-Cl-SH-1H
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20150413
Time                  9.13
INSTRUM              spect
PROBHD   5 mm PABBO BB/
PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              12019.230 Hz
FIDRES            0.366798 Hz
AQ               1.3631488 sec
RG                   43.16
DW                  41.600 usec
DE                    6.50 usec
TE                   297.9 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           600.1737063 MHz
NUC1                    1H
P1                   12.00 usec
PLW1           21.00000000 W

F2 - Processing parameters
SI                   16384
SF             600.1700155 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.00
```

^{13}C NMR (150 MHz, CDCl$_3$): **2-substituted benzo[*d*]thiazole *(8q):***



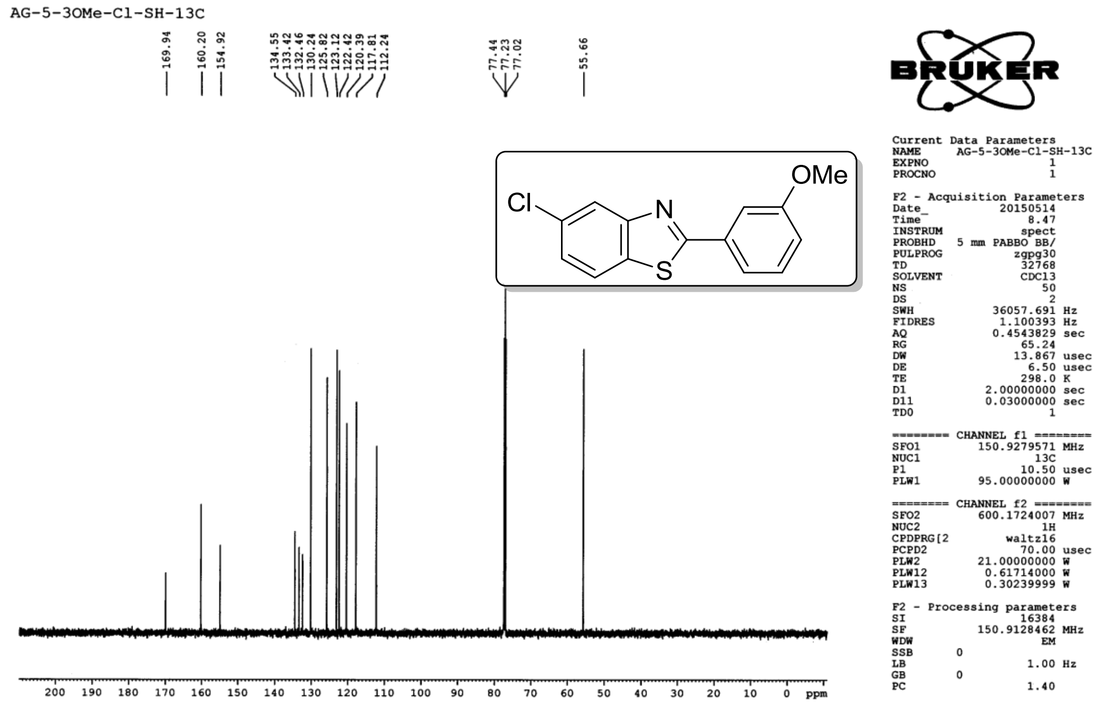
```
Current Data Parameters
NAME      AG-5-Cl-Cl-SH-13C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20150413
Time                  8.52
INSTRUM              spect
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     435
DS                       2
SWH              36057.691 Hz
FIDRES            1.100393 Hz
AQ               0.4543829 sec
RG                  200.18
DW                  13.867 usec
DE                    6.50 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           150.9279571 MHz
NUC1                   13C
P1                   10.50 usec
PLW1           95.00000000 W

======== CHANNEL f2 ========
SFO2           600.1724007 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                70.00 usec
PLW2           21.00000000 W
PLW12           0.61714000 W
PLW13           0.30239999 W

F2 - Processing parameters
SI                   16384
SF             150.9128374 MHz
WDW                     EM
SSB      0
LB                    1.00 Hz
GB       0
PC                    1.40
```

^{1}H **NMR (600 MHz, CDCl$_3$):** 2-substituted benzo[*d*]thiazole (***8s***):



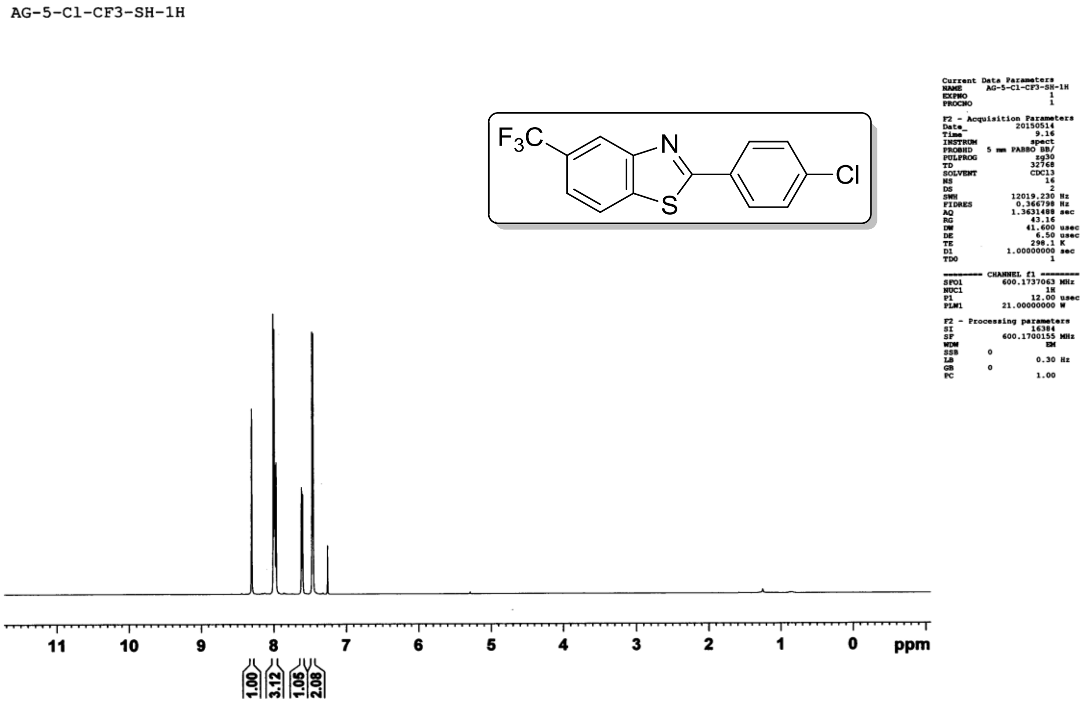
```
Current Data Parameters
NAME     AG-5-3OME-CL-SH_1H
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150512
Time                  13.10
INSTRUM               spect
PROBHD   5 mm PABBO BB/
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               12019.230 Hz
FIDRES             0.366798 Hz
AQ                1.3631488 sec
RG                    43.16
DW                   41.600 usec
DE                     6.50 usec
TE                    297.3 K
D1               1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1            600.1737063 MHz
NUC1                     1H
P1                    12.00 usec
PLW1            21.00000000 W

F2 - Processing parameters
SI                    16384
SF              600.1700144 MHz
WDW                      EM
SSB      0
LB                     0.30 Hz
GB       0
PC                     1.00
```

^{13}C **NMR (150 MHz, CDCl$_3$):** 2-substituted benzo[*d*]thiazole ***(8s)****:*



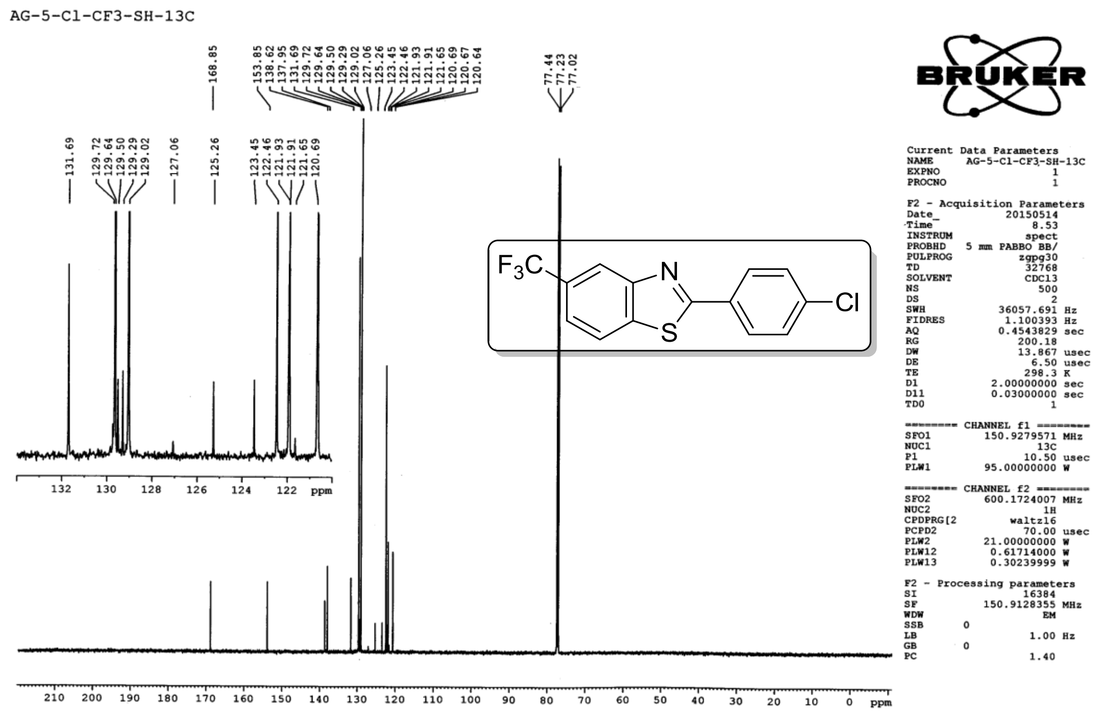
```
Current Data Parameters
NAME      AG-5-3OMe-Cl-SH-13C
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150514
Time                   8.47
INSTRUM               spect
PROBHD   5 mm PABBO BB/
PULPROG             zgpg30
TD                    32768
SOLVENT               CDCl3
NS                       50
DS                        2
SWH               36057.691 Hz
FIDRES             1.100393 Hz
AQ                0.4543829 sec
RG                    65.24
DW                   13.867 usec
DE                     6.50 usec
TE                    298.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1            150.9279571 MHz
NUC1                    13C
P1                    10.50 usec
PLW1            95.00000000 W

======== CHANNEL f2 ========
SFO2            600.1724007 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 70.00 usec
PLW2            21.00000000 W
PLW12            0.61714000 W
PLW13            0.30239999 W

F2 - Processing parameters
SI                    16384
SF              150.9128462 MHz
WDW                      EM
SSB      0
LB                     1.00 Hz
GB       0
PC                     1.40
```

^{1}H **NMR (600 MHz, $CDCl_3$):** 2-substituted benzo[*d*]thiazole (***8v***):



```
Current Data Parameters
NAME      AG-5-Cl-CF3-SH-1H
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150514
Time                   9.16
INSTRUM               spect
PROBHD     5 mm PABBO BB/
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        2
SWH              12019.230 Hz
FIDRES            0.366798 Hz
AQ               1.3631488 sec
RG                    43.16
DW                  41.600 usec
DE                    6.50 usec
TE                   298.1 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1           600.1737063 MHz
NUC1                     1H
P1                    12.00 usec
PLW1            21.00000000 W

F2 - Processing parameters
SI                    16384
SF              600.1700155 MHz
WDW                      EM
SSB        0
LB                     0.30 Hz
GB         0
PC                     1.00
```

^{13}C **NMR (150 MHz, $CDCl_3$):** 2-substituted benzo[*d*]thiazole ***(8v):***



```
Current Data Parameters
NAME      AG-5-Cl-CF3-SH-13C
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20150514
Time                   8.53
INSTRUM               spect
PROBHD     5 mm PABBO BB/
PULPROG              zgpg30
TD                    32768
SOLVENT               CDCl3
NS                      500
DS                        2
SWH              36057.691 Hz
FIDRES            1.100393 Hz
AQ               0.4543829 sec
RG                   200.18
DW                  13.867 usec
DE                    6.50 usec
TE                   298.3 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1           150.9279571 MHz
NUC1                    13C
P1                    10.50 usec
PLW1            95.00000000 W

======== CHANNEL f2 ========
SFO2           600.1724007 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 70.00 usec
PLW2            21.00000000 W
PLW12            0.61714000 W
PLW13            0.30239999 W

F2 - Processing parameters
SI                    16384
SF              150.9128355 MHz
WDW                      EM
SSB        0
LB                     1.00 Hz
GB         0
PC                     1.40
```

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1.1 Introduction

Nitrogen containing heterocycles are predominant class of organic molecules. They are integral part of natural products and often are bioactive precursors.[1] Synthesis of nitrogen containing heterocycles have become target in drug discovery and developments, advanced materials, and synthesis of bulk intermediates in chemical industry. Large libraries of nitrogen containing heterocycles lend a rapid access to novel complex molecules. Numerous synthetic strategies have been developed to synthesize these precursors and the foremost interesting route to synthesis these molecules may be achieved through multicomponent reactions. Conventional organic synthesis proceeds with individual bond formation in a sequence and each step involves isolation, purification of intermediates and often alteration of reaction condition for the next synthetic step. An ideal synthesis targets molecule that is prepared from readily available starting materials in a simple, safe, environmentally-acceptable, and resource-effective operation that proceeds quickly yet provides quantitative yield (Figure 1).[2]

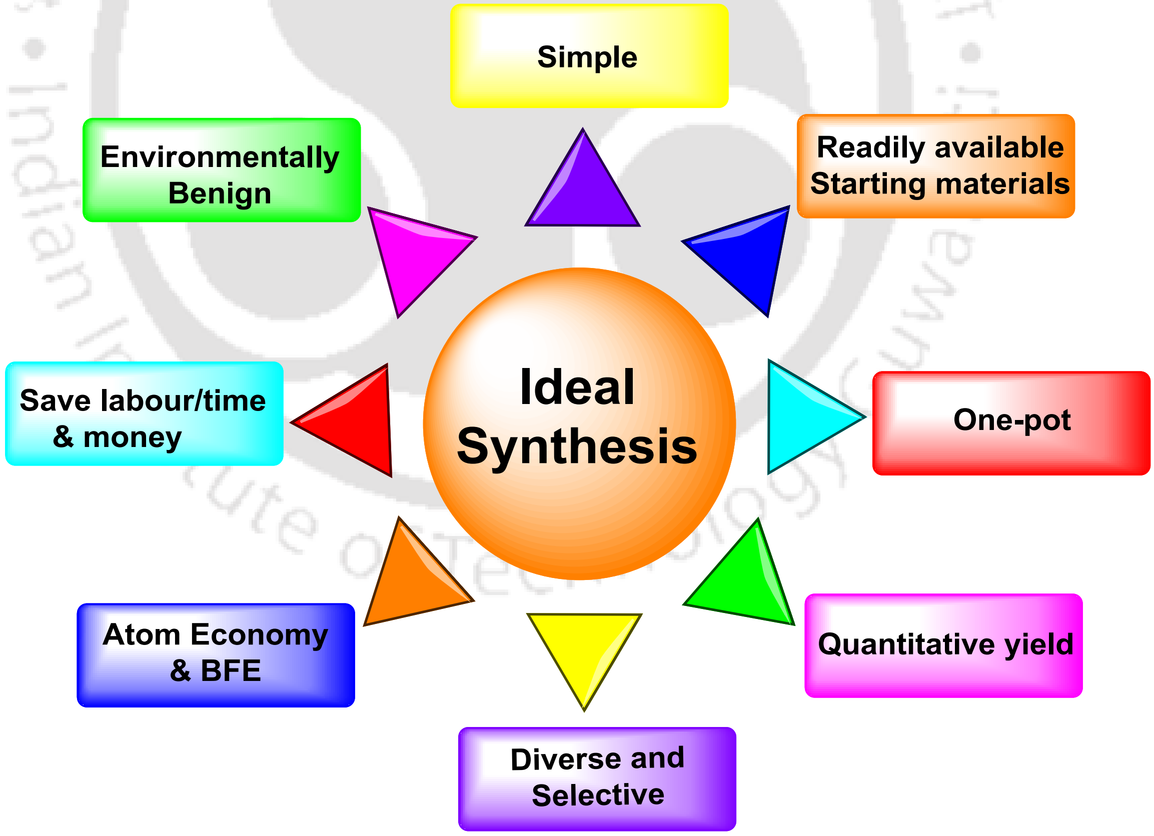


Figure 1. The ideal chemical synthesis

Over the past decade, many research groups have aimed for this concept of "ideal synthesis" of complex molecules by operating multi-step process in a single operation strategy and without isolating intermediates. Such reactions commonly known as tandem reactions allows environmentally and economically favorable synthesis of a wide range of organic molecules. A paramount subclass of tandem sequential reactions is the multi-component reactions or MCRs.

1.2 Multicomponent reactions (MCRs)

Multicomponent reactions (MCRs) are chemical transformations in which three or more reactants are combined in a way that the final product retains significant portions of all starting material. Albeit the term MCR compatible with 'one-pot', 'domino', 'cascade' and 'tandem' processes, a somewhat specific definition is necessary for direct comparison. Performing consecutive reactions in a vessel can be an efficient way to achieve molecular diversity. The definition of multicomponent reaction as given by Ugi and his co-workers a few years ago as:

"Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product."

Dömling, A.; Ugi, I. *Angew. Chem. Intl. Ed.* **2000**, *39*, 3168-3210.

The definition can also be represented schematically (Figure 2). Multicomponent reactions have inherent convergence and high productivity in combination with their exploratory power arising from their conciseness makes them very powerful tool for the synthesis of drug-like compounds, which are the essential part of the research performed in pharmaceutical and agrochemical industries. They have significant advantages over conventional reactions in several aspects. Some features of MCRs are (a) simple experimental procedure and mild reaction conditions; (b) superior atom-economy and bond forming efficiency (BFE); (c) use of environmentally benign solvents; (d) avoidance of protection-deprotection steps; (e) cost and time effectiveness with good yields; and (f) a platform for the rapid generation of small-molecule libraries from readily available starting materials.

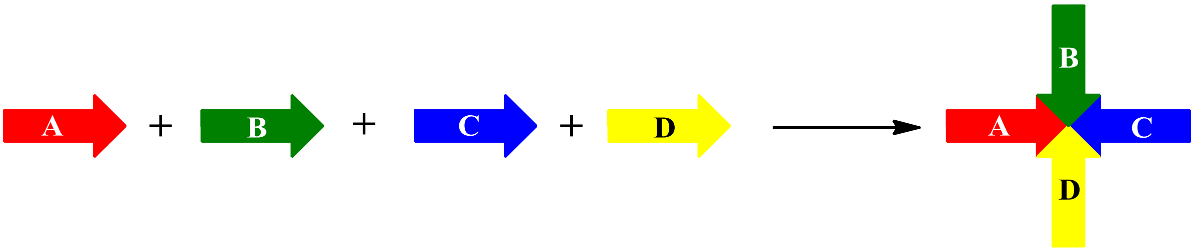


Figure 2.

MCRs have become a very attractive and powerful strategy in modern organic synthesis for facile access to large libraries of complex organic molecules, especially heterocyclic molecules in a shorter time with diverse substitute pattern. As compared to multistep synthesis, MCRs as mentioned above, have several advantages such as operational simplicity, flexibility, convergence and pot, atom, step, and cost economy (PASCE) (Figure 3).

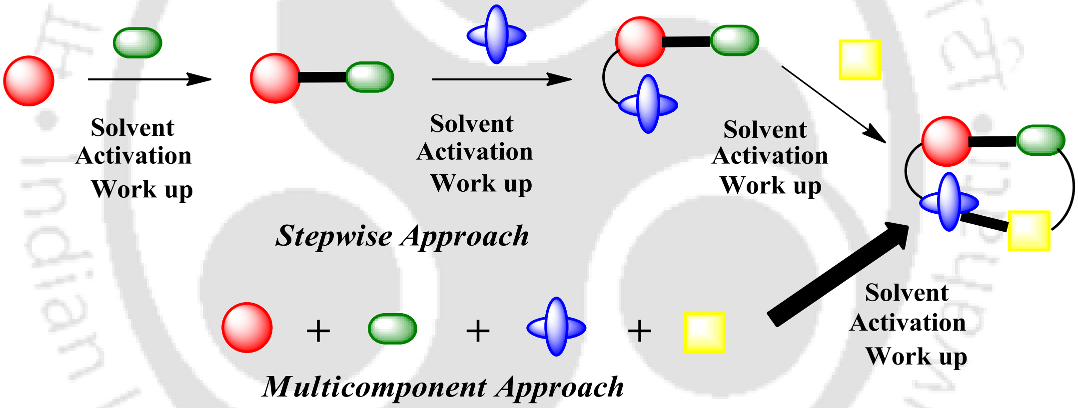


Figure 3. Comparison of stepwise and multicomponent approach

MCRs enable the convenient assembly of complex molecules and also furnish structurally diverse libraries of small organic molecules, which might be used as the most important potential drug candidates for future generation. MCRs play a significant role in lead identification and optimization processes in drug discovery programmes. With a small set of readily available starting materials, very large libraries of organic compounds can be constructed in a short span of time which can be used as pharmaceuticals in near future.[3] MCRs have become a rapidly developing area of research field in the context of drug discovery and organic scaffold generation.

1.3. Classification of MCRs

MCRs are often classified by the number of molecules and functional groups participating (Figure 4). Example:

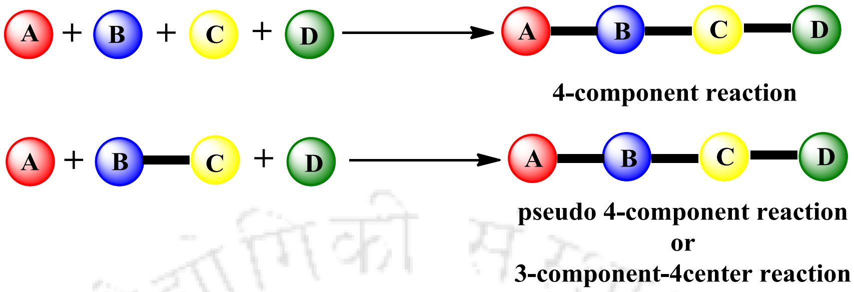


Figure 4.

The classifications of multicomponent reactions was further meticulously described for better understanding by Orru and his co-workers in their recent review.[4] MCRs can be further subdivided based on their rational design strategies as: (a) Single reactant replacement (SRR), (b) Modular reaction sequences (MRS), (c) Conditions-based divergence (CBD) and (d) Combination of MCRs (MCR^2). Beyond four components, there is still a scope to expand the MCRs by unifying two or more MCRs,[5] two different approaches have been successfully utilized (Figure 5).

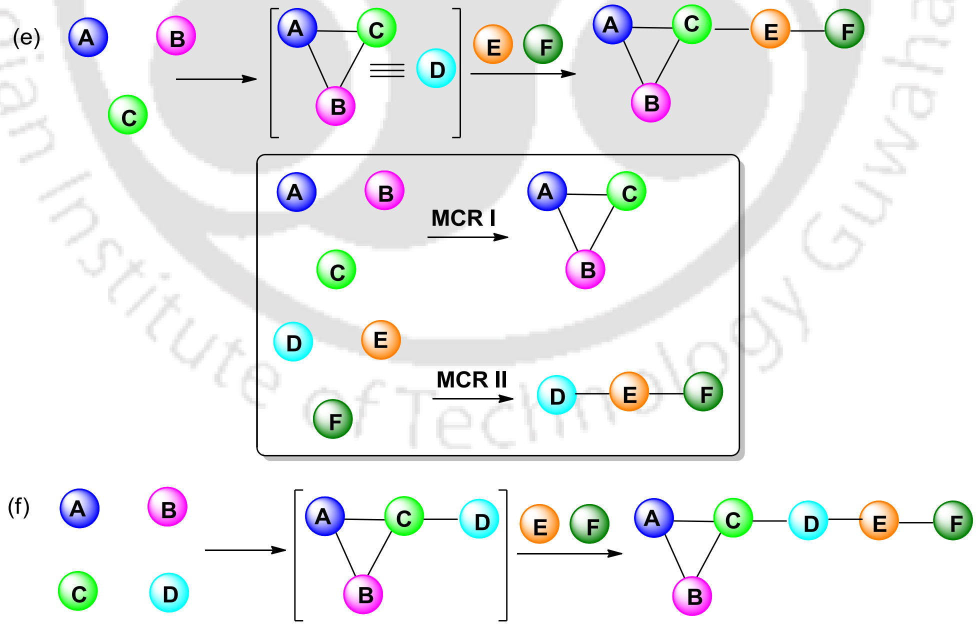
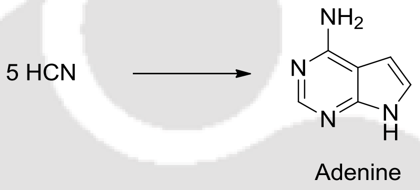


Figure 5. (e) Intermediate generation for a successive MCR. (f) Combination of MCRs with orthogonal functionalities

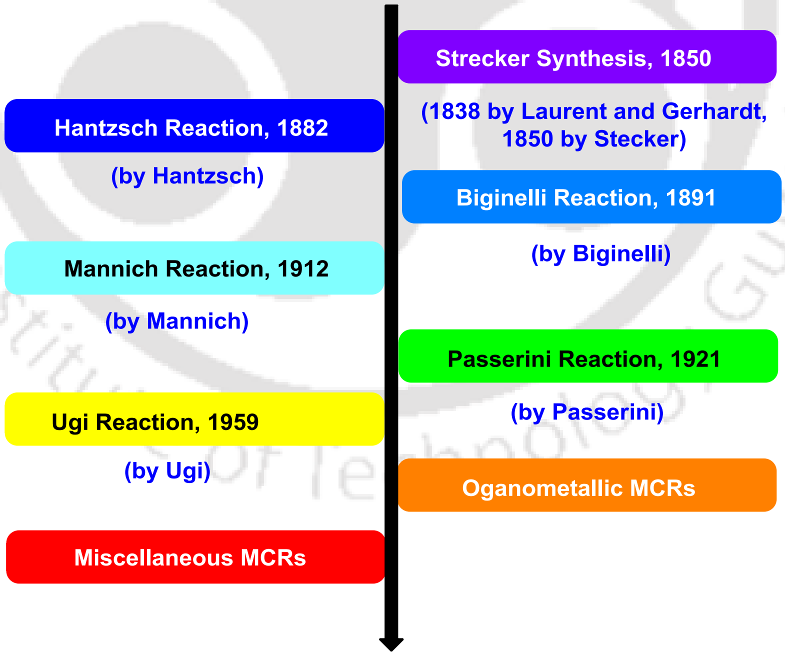
The first type MCR (Fig. 4e) generates intermediate compound D and is the starting material in the subsequent MCR, results in a product consisting of 5 different starting materials. The second type of MCR, also called combined MCR (Fig. 4f), exploits a starting material furnishes two different reactive groups, permitting two orthogonal MCR reactions to occur simultaneously. These reactions can be executed either as a one-pot process, keeping the reaction conditions constant during the entire reaction (*i.e.* ‘‘true’’ MCR), or as a sequential process by which the reaction conditions of the first MCR are modified according to the demands of the subsequent MCR (*i.e.* tandem MCR).

1.4 Developments and Synthetic Application of MCRs

Nature also plays a significant role in evolution of MCRs and has made remarkable contribution to the synthesis by employing similar strategy. For example, adenine (**1**), one of the major constituents of DNA and RNA, was prebiotically synthesized by oligomerization of HCN in presence of NH_4OH at pH 9.2 (Scheme 1).[6]



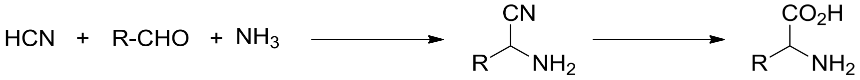
Scheme 1. Prebiotic synthesis of adenine



The Brief History of MCRs

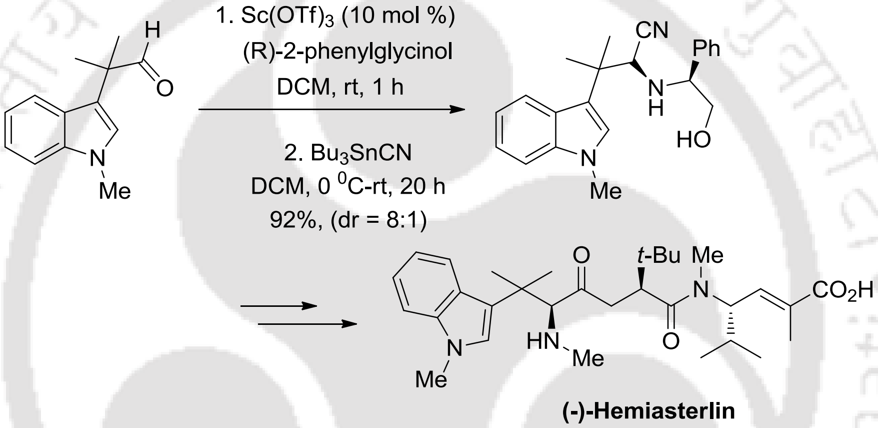
Figure 6.

In 1850, Adolph Strecker first reported the synthesis of α-amino nitrile derivatives by the condensation of aldehyde/ketone, hydrogen cyanide and amine or its equivalent, which is a major break-through in the development of multicomponent reaction.[7]



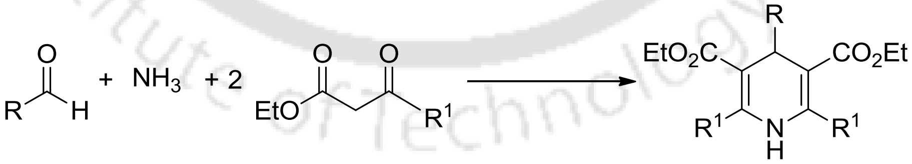
Scheme 2.

Later on, Vedejs and his co-workers[8] described the utility of asymmetric Strecker reaction for the construction of key intermediate amino nitrile, which was ultimately converted into the enantioselective total synthesis of (-)-Hemiasterlin, a marine tripeptide having cytotoxic and antimitotic activity (Scheme 3).



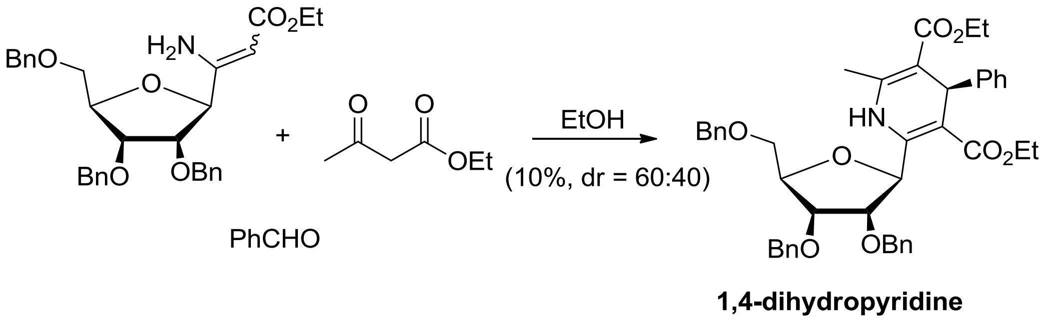
Scheme 3. Synthesis of Hemiasterlin

Further progress of multicomponent reaction can be assigned to the work of Arthur Rudolf Hantzsch in 1882. He synthesized symmetrically substituted dihydropyridines from aldehydes, NH_3 and two equivalents of *β*-ketoesters (Scheme 4).[9]



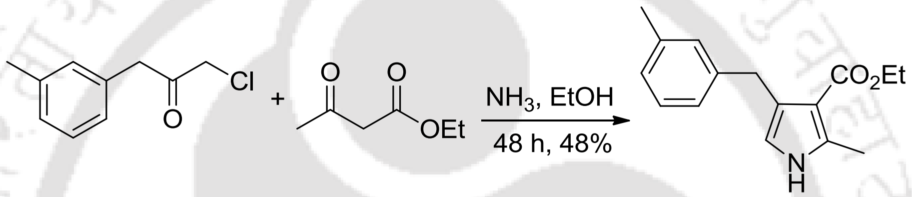
Scheme 4. Synthesis of dihydropyridines

A. Dondoni *et al.* further exploited the above-mentioned approach for the synthesis of asymmetric 1,4-dihydropyridine from enamine, aldehyde and 1,3-dicarbonyl compound (Scheme 5).[10]



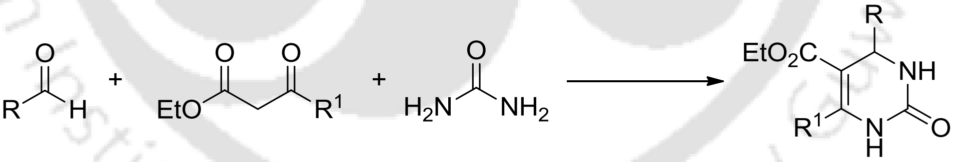
Scheme 5. Synthesis of asymmetric 1,4-dihydropyridine derivatives

Additionally, the synthesis of substituted pyrroles derivatives was also reported by Hantzsch involving MCRs strategy through the reaction of primary amines, *β*-ketoesters and *α*-halogenated-*β*-ketoesters (Scheme 6).[11]



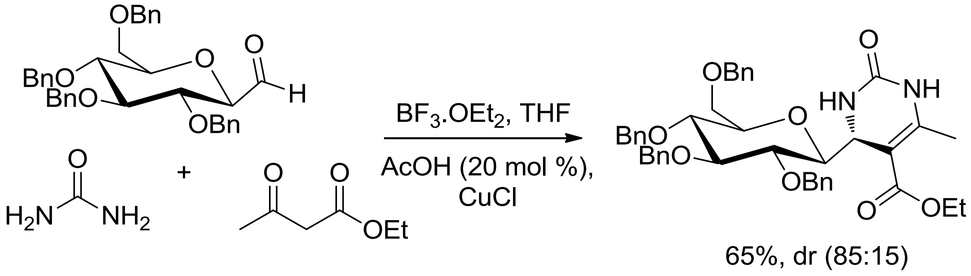
Scheme 6. Synthesis of substituted pyrroles derivatives

In 1893 Pietro Biginelli reported the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones by one-pot three-component reaction of an aromatic aldehydes, *β*-ketoesters and urea in presence of acid catalyst, which is one of the most popular and useful multicomponent reactions (Scheme 7).[12]



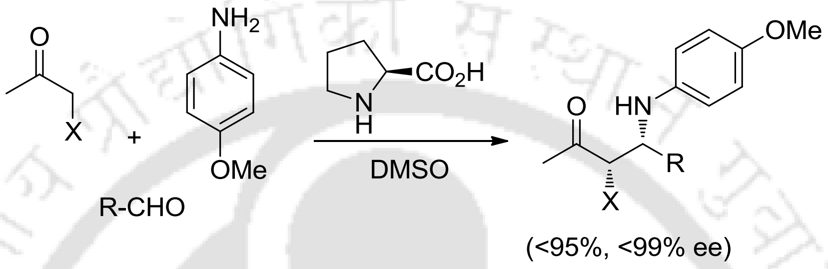
Scheme 7. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives

Aparicio *et al.* reported the synthesis of stereoselective sugar substituted dihydropyrimidine derivatives from a sugar aldehyde, urea and ethyl acetoacetate by modifying Biginelli reaction (Scheme 8).[13]



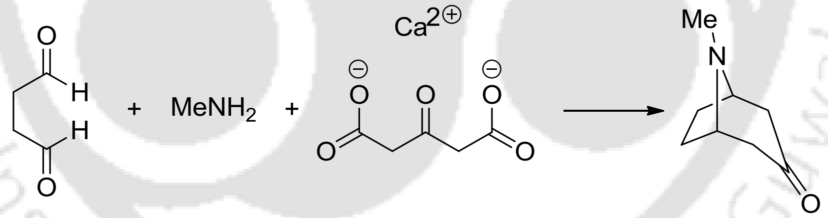
Scheme 8.

Mannich reaction was first reported in 1912, and consists of the condensation reaction of an active methylene compound, a non-enolizable aldehyde or ketone and a primary or a secondary amine to accomplish *β*-amino carbonyl derivatives.[14] Its immense synthetic utility has been further utilized for the synthesis of numerous pharmaceuticals and natural products. Recently, List *et al.* utilized Mannich reaction in L-proline-catalyzed highly enantioselective three-component reactions (Scheme 9).[15]



Scheme 9.

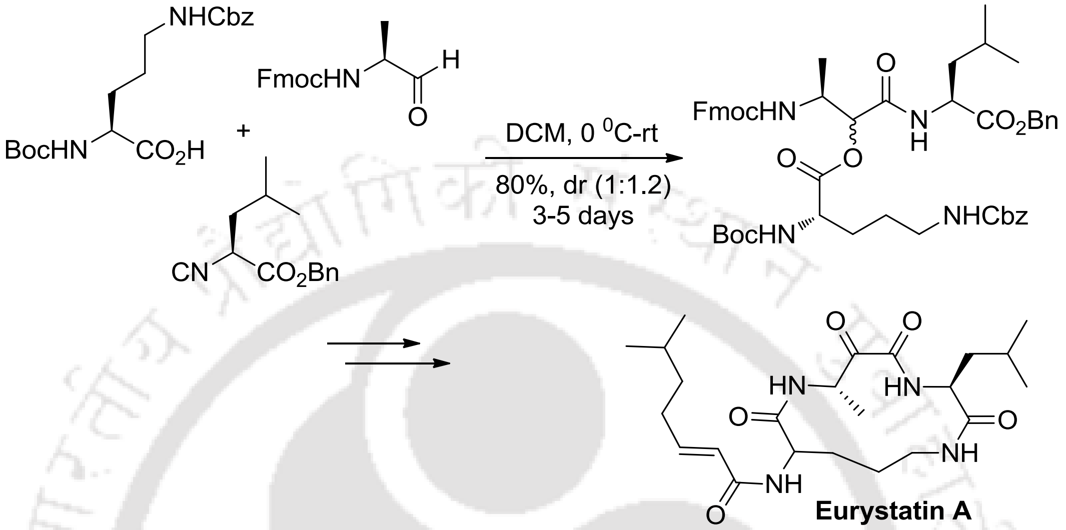
In 1917, the important application of MCRs in natural product synthesis was first described by Robinson through his tremendous work for the synthesis of alkaloid tropinone from succinic dialdehyde, methylamine and calcium salt of acetonedicarboxylic acid (Scheme 10).[16]



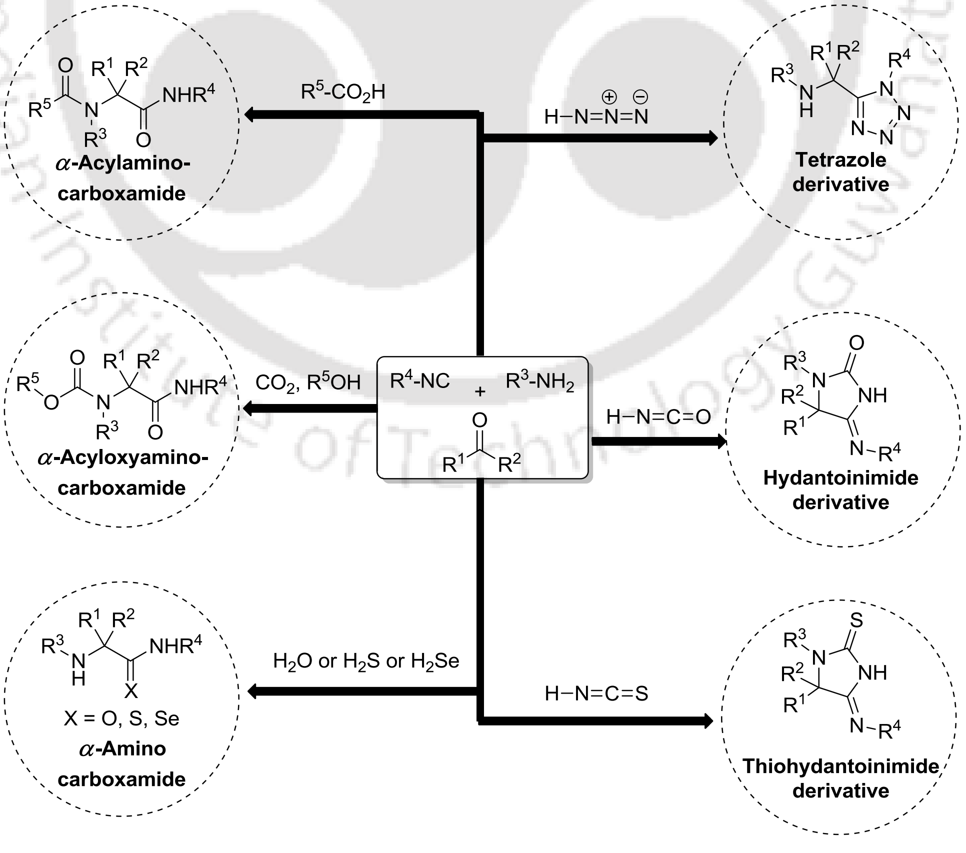
Scheme 10. Synthesis of alkaloid tropinone

Mario Passerini in 1921 first discovered an isocyanides based MCR involving one-pot condensation reaction of Carboxylic acids, carbonyl compounds and isocyanides to accomplish *α*-acyloxy carboxamides.[17] Later on, Owens *et al.* utilized it for the synthesis of Eurystatin A, which is a 13-membered macrocyclic product (Scheme 11).[18]

In 1959, one of the most significant multicomponent reactions was discovered by Ugi *et al.* Synthesis of *α*-acylamino amides was achieved through a four-component condensation reaction of aldehydes, primary amines, carboxylic acids and isocyanides. This transformation is popularly known as Ugi's four-component reaction (Ugi-4CR).[19] By employing different nucleophiles such as carboxylic acid, hydrazoic acid, cyanates, thiocyanates, carbonic acid, monoester, water, hydrogen sulfide and hydrogen selenide as one of the key substrate, Ugi and his co-workers have shown the versatility of multicomponent reaction for synthesizing a large number of new scaffolds through Ugi reaction. Thus, Ugi reaction also found a prevalent application in combitorial chemistry (Scheme 12).[20]

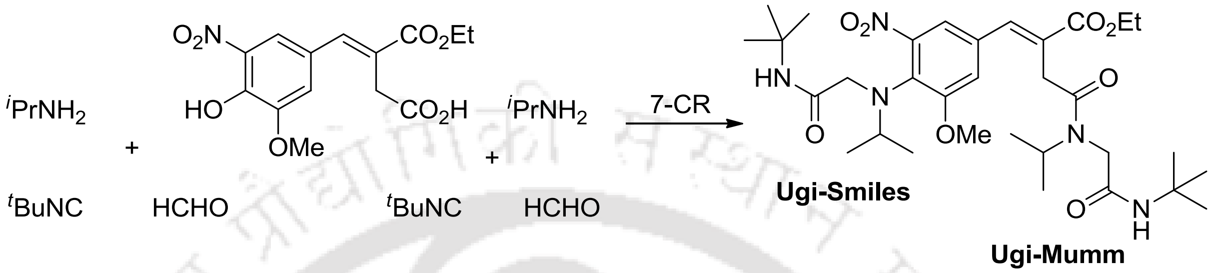


Scheme 11. Synthesis of Eurystatin A



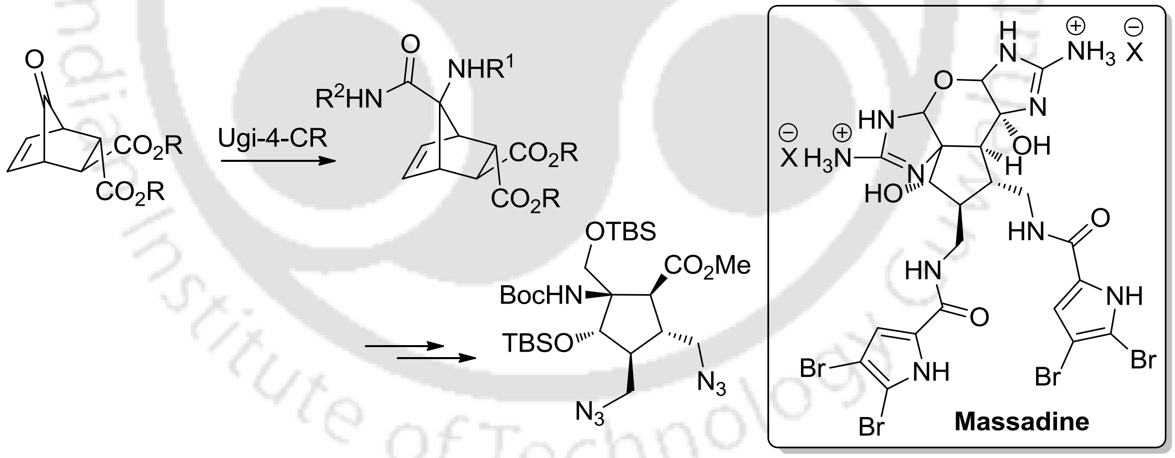
Scheme 12.

Brauch *et al.*[21] demonstrated a sequential seven-component reaction for the synthesis of highly diverse peptide and glycopeptides like compounds from acid, formaldehyde, *iso*-propyl amine and *tert*-butyl isonitrile involving chemoselective Ugi-Mumm and Ugi-Smiles reaction. The Ugi-Mumm and Ugi-Smiles products were afforded in 55% yield with the yield of each bond-forming steps exceeded 90% (Scheme 13).



Scheme 13.

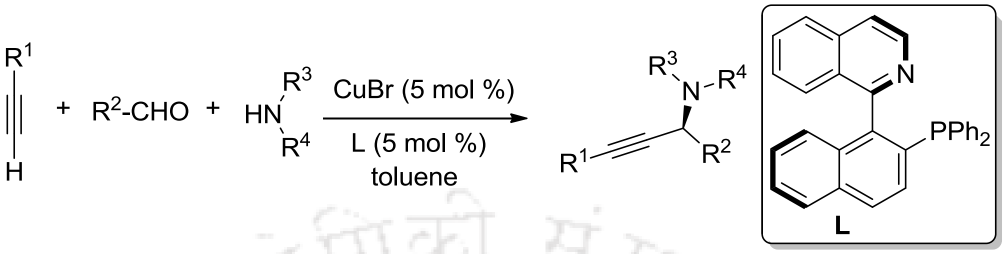
The synthetic approach of Ugi reaction was further utilized for the synthesis of various natural products and biologically active compounds. Recently, Chinigo *et al.* utilized Ugi-4-CR for the synthesis of a key intermediate of the natural product Massadine (Scheme 14).[22]



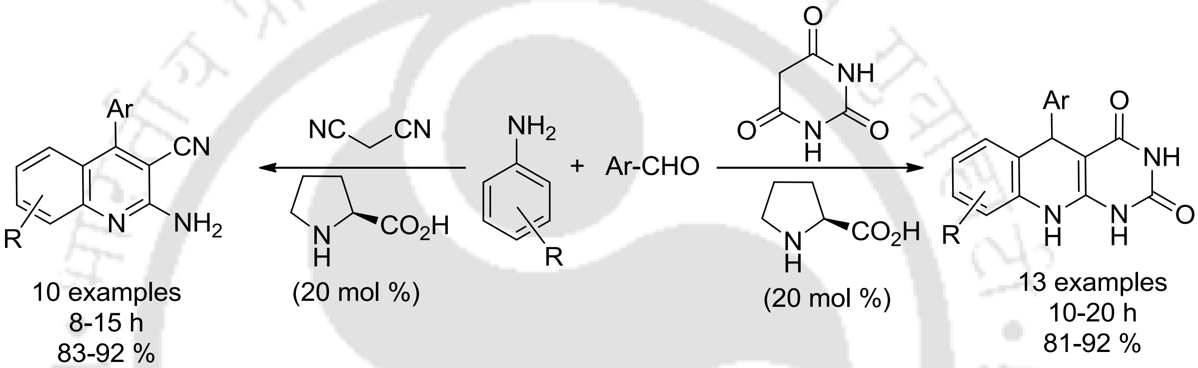
Scheme 14.

Knochel *et al.* developed a new three-component organometallic asymmetric MCRs for the synthesis of 1,2 addition product from terminal alkyne, aldehyde and secondary amine in presence of CuBr catalyst (Scheme 15).[23]

Khalafi-Nezhad *et al.* accomplished a green and efficient L-proline catalysed three-component reaction for the preparation of 5-aryl-pyrimido[4,5-*b*]quinoline-dione derivatives from anilines, aldehydes and barbituric acids in aqueous medium and under similar reaction condition. 2-amino-4-arylquinoline-3-carbonitrile derivatives were also obtained by replacing the barbituric acid with malononitrile in the designed protocol (Scheme 16).[24]

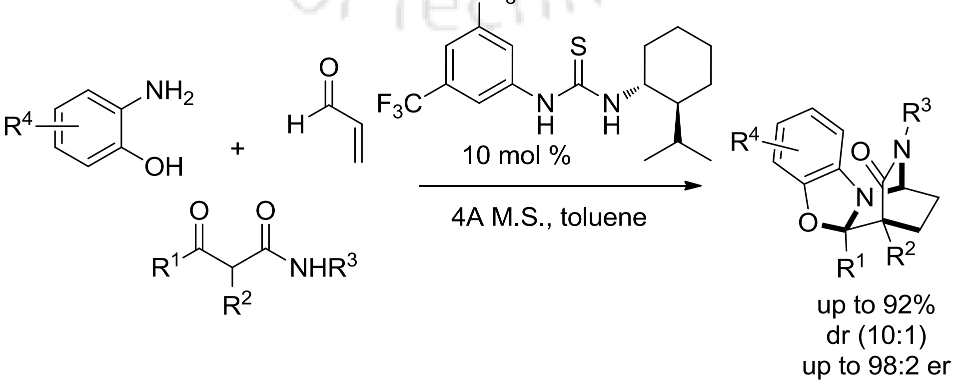


Scheme 15.



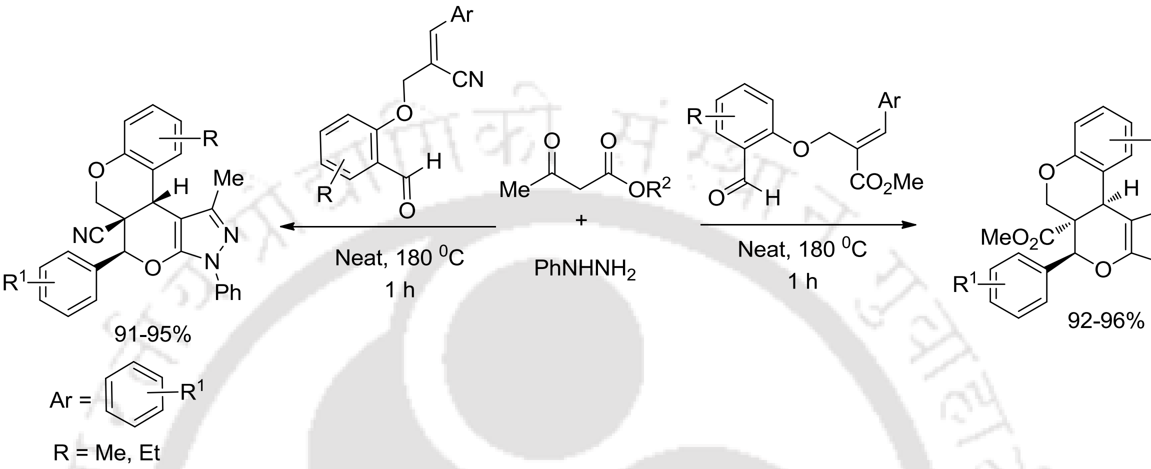
Scheme 16.

Rodriguez and co-workers[25] described enantioenriched synthesis of diazabicyclo[2.2.2]octanone (2,6-DABCO) derivatives from the reaction of *β*-ketoamides, acrolein and aminophenols catalyzed by an organocatalyst, bifunctional thiourea-tertiary amine. The chemoselective reaction sequence introduced five new bonds and three stereocenters, two of which were adjacent tetrasubstituted centers with excellent yields and high levels of stereoselectivity (Scheme 17).



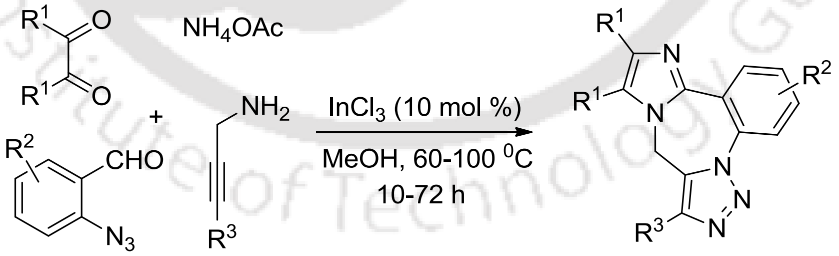
Scheme 17. Synthesis of diazabicyclo[2.2.2]octanone (2,6-DABCO) derivatives

Bakthadoss *et al.* reported an efficient catalyst and solvent free synthesis of chromeno-pyran-pyrazole derivatives employing multicomponent cascade reaction strategy.[26] This novel reaction generated two N–C, two C–C and one O–C bonds through a domino process for the construction of three new rings and three contiguous stereogenic centers with high stereoselectivity (Scheme 18).



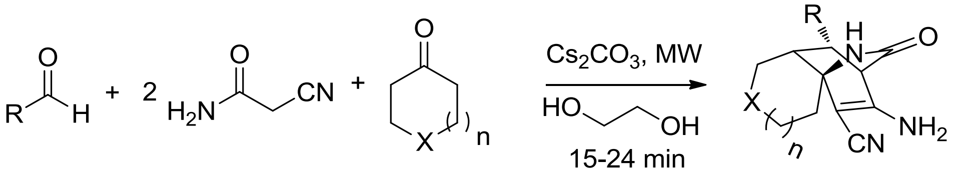
Scheme 18. Synthesis of chromeno-pyran-pyrazole derivatives

Kurth *et al.* described a simple, one-pot multicomponent reaction for the synthesis of 9H-benzo[*f*]imidazo[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepine derivatives from diketones, *ortho*-azidobenzaldehydes, propargylic amines, and ammonium acetate. This process includes tandem $InCl_3$-catalyzed cyclocondensation and intramolecular azide-alkyne 1,3-dipolar cycloaddition reactions (Scheme 19).[27]



Scheme 19. Synthesis of diazepine derivatives

Jiang and co-workers[28] accomplished a four-component domino reaction for the synthesis of tricyclo[6.2.2.0^{1,6}]dodecane derivatives from aldehydes, cyclic ketones, and cyano-acetamide in presence of K_2CO_3 base in ethylene glycol under microwave heating. The reaction proceeded at fast rates and was accomplished within 15-24 minutes (Scheme 20).



Scheme 20. Synthesis of tricyclo[6.2.2.0^{1,6}]dodecane derivatives

From literature survey it is obvious that development of MCRs has become a challenging area for the synthesis of diverse compounds for screening libraries and the recent increase in the discovery of new reactions. The concept of MCRs has allowed reaching high molecular complexity with eminent levels of selectivity with simple experimental procedures, as well as advantages of savings in energy, solvent, time and costs. Therefore, we were inspired to work on this encouraging field of research. In this part of my thesis work, focused at the synthesis of N-heterocycles such as 2-oxypyrrole and fused pyrazolo-pyridine derivatives are focused. I would also like to address their importance as well as some recently developed synthetic strategies as represented below.

1.5. 2-Oxypyrroles and its importance

Pyrrole and its derivatives such as dihydro-2-oxypyrroles and pyrrolidines are the important structural motifs that are found in natural and unnatural products.[29] Especially, functionalized dihydro-2-oxypyrroles rings are present in a variety of alkaloids having wide biological activities and are used as optoelectronic materials.[30] For example, dihydro-2-oxypyrroles derivative (**I**) has been used as PI-091,[31] a novel platelet aggregation inhibitor; imrecoxib (**II**) selective cyclooxygenase-II (COX-II) inhibitors;[32] thiomarinol A 4 (**III**), a potent antibiotic; bilirubin (**IV**), yellowish pigment found in bile also contains 2-oxypyrrole core units which exhibit an immense bioactive applications; compound (**V**), acts as vascular endothelial growth factor receptor (VEGF-R) inhibitor[33] (Figure 7). They also act as cardiac cyclic AMP phosphodiesterase inhibitors[34] and potent protein kinase C (PKC) inhibitor.[35] In addition, their herbicidal,[36] pesticidal,[37] and anti-tumor[38] activities as well as useful intermediates increasingly necessitate new research.

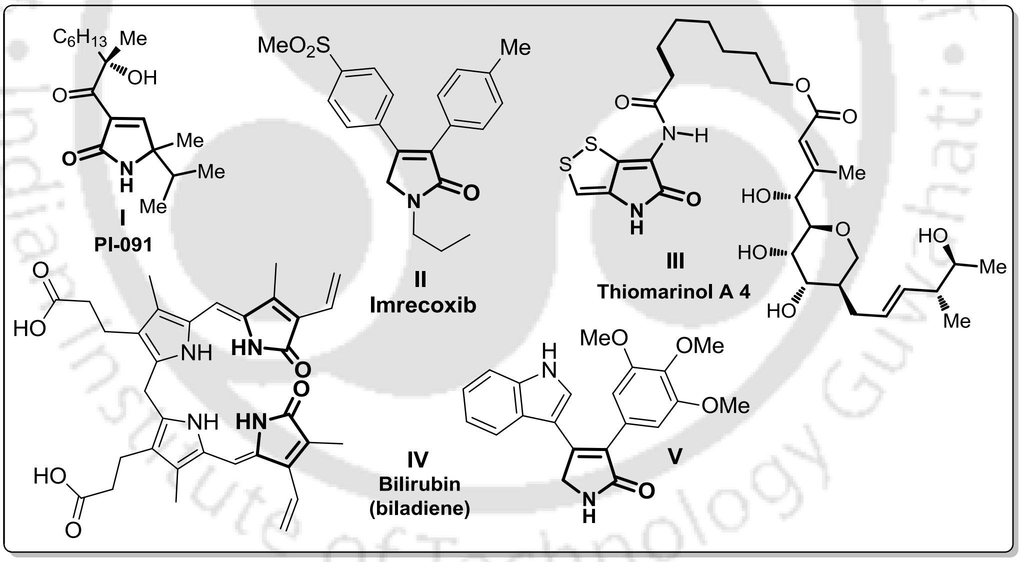
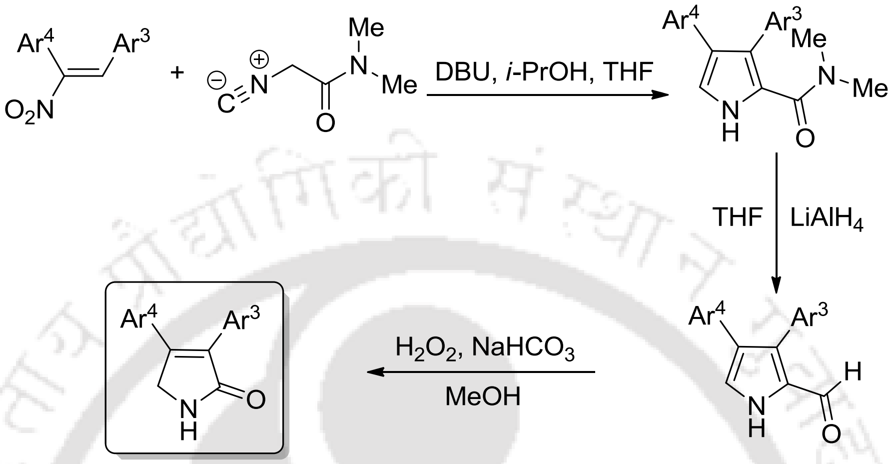


Figure 7. Biologically active compounds having 2-oxypyrrole unit

1.6. General Approaches for the Construction of 2-Oxypyrroles

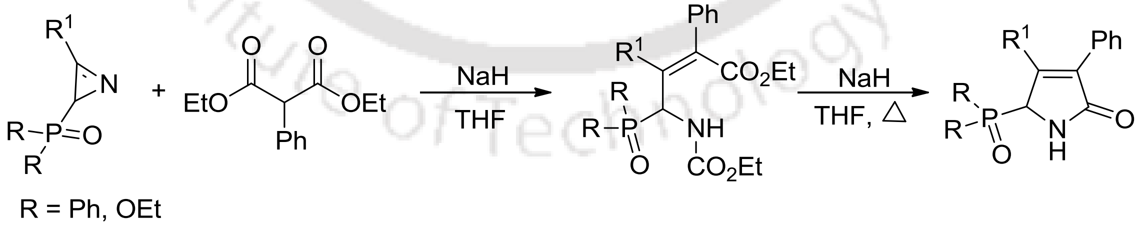
The classical Hantzsch pyrrole synthesis is one of the simplest and most efficient methods for the synthesis of biologically important and pharmacologically useful pyrrole derivatives from *β*-ketoesters, ammonia or primary amines and *α*-haloketones. Over the years various reaction strategies were developed for the synthesis of pyrrole derivatives with different substitution pattern. Recently, Pelkey *et al.* developed a regiocontrolled method for the synthesis of unsymmetrical 3,4-diaryl-3- pyrrolin-2-ones from 1,2-diaryl-

1-nitroethenes and 2-isocyano-N,N-dimethylacetamide in a three steps procedure. A Barton Zard pyrrole cyclo-condensation reaction between 1,2-diaryl-1-nitroethenes and 2-isocyano-N,N-dimethylacetamide gave the corresponding pyrrole Weinreb amides, which were then converted into the desired 3-pyrrolin-2-ones in two steps (Scheme 21).[39]



Scheme 21. Synthesis of 3,4-diaryl-3- pyrrolin-2-ones

Palacios *et al.*[40] described a simple and efficient synthesis of 1,5-dihydro-3-pyrrolin-2-ones containing a phosphine oxide or a corresponding phosphonate from substituted 2H-azirinylphosphine oxide and diethyl 2-phenylmalonate in presence of sodium hydride in THF under heating condition. Initially, azirines and the enolate derived from diethyl 2-phenylmalonate reacts to give vinylogous α-aminoalkylphosphine oxides or corresponding phosphonate, which underwent the ring closure reaction in the presence of base to afford 1,5-dihydro-3-pyrrolin-2-ones containing a phosphine oxide or a phosphonate (Scheme 22).

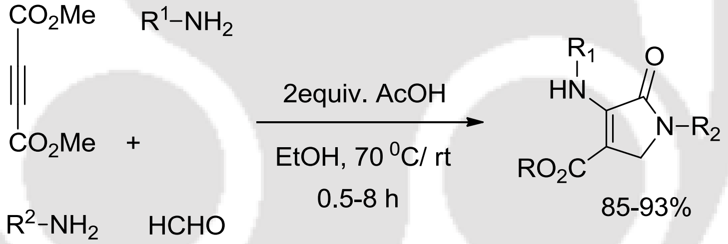


Scheme 22. Synthesis of 1,5-dihydro-3-pyrrolin-2-ones

Ryabukhin and co-workers[41] developed a convenient method for the synthesis of 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones through a three-component condensation of active methylene compounds, aldehydes and amines. It was reported that the use of acetic acid as the reaction medium was suitable for the considerably reactive substrates with no additional functionalities and the substrates with low reactivity and those possessing carboxylic groups or additional basic centers required the use of DMF as the solvent and chlorotrimethylsilane as the reaction promoter (Scheme 23).

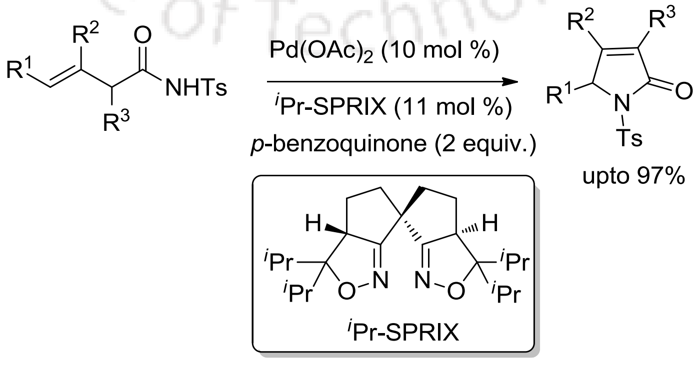
Scheme 23. Synthesis of 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones

Jiang *et al.* reported the one-pot multicomponent reactions (MCRs) of DMAD, amines and formaldehydes at room temperature or at 70 °C to afford tetrasubstituted polyfunctional dihydropyrroles (Scheme 24).[42] The reaction proceeds through a domino hydroamination/nucleophilic addition/amidation-cyclization process and leads to the formation of tetrasubstituted polyfunctional dihydropyrroles. The primary biological screening in vitro against HIV-1 were also tested for few compounds and they exhibited significant activity with IC_{50} in micromolar range (38-58 μM).



Scheme 24. Synthesis of polyfunctional dihydropyrroles

Sasai *et al.*[43] demonstrated a novel Pd-bis(isoxazoline) catalysed 5-endo-trig-type cyclization approach to access substituted 3-pyrrolin-2-ones using *β,γ*-unsaturated alkenamides in *p*-benzoquinone (Scheme 25).



Scheme 25. Synthesis of 3-pyrrolin-2-ones

1.7. Importance of Pyrazolo-pyridine

Among various nitrogen containing heterocyclic compounds, pyrazoles[44] and their fused derivatives[45] exhibit important pharmacological activities such as anti-inflammatory, anti-pyretic, analgesic, anti-arthritic and hypnotic. The chemistry of pyrazolo-pyridine derivatives has captivated much attention in view of their importance as leads in the pharmaceutical industry and their prevalence as core structures of numerous biologically active compounds. For example, functionalized dihydrochromeno[4,3-*b*]pyrazolo-pyridine derivative (**VI**) has been used as a fluorescence dye.[46] Similarly, pyrazolo[3,4-*b*]pyridine derivatives (**VII**) and (**VIII**) are potential inhibitors of protein kinases[47] and are used in the treatment of proliferative diseases such as cancer and inflammation.[48] Compound (**IX**) acts as CHK-1 inhibitor;[49] pyrazolo-pyridine derivative (**X**) used as selective PKCθ inhibitor[50] and cartazolite (**XI**) has been exploited as anxiolytic drug (Figure 8).[51]

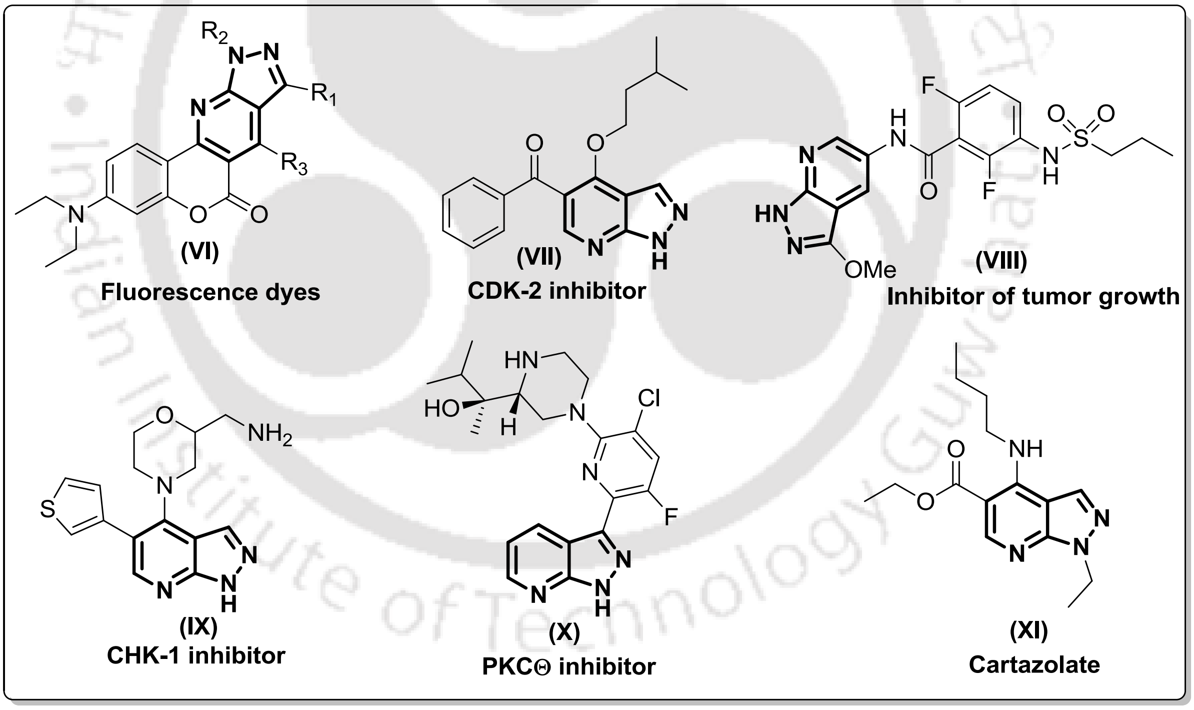
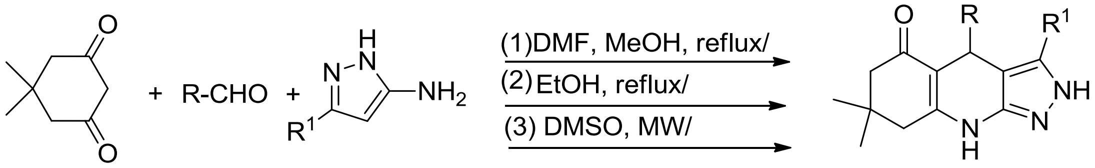


Figure 8. Heterocyclic compounds containing pyrazolo-pyridine skeleton

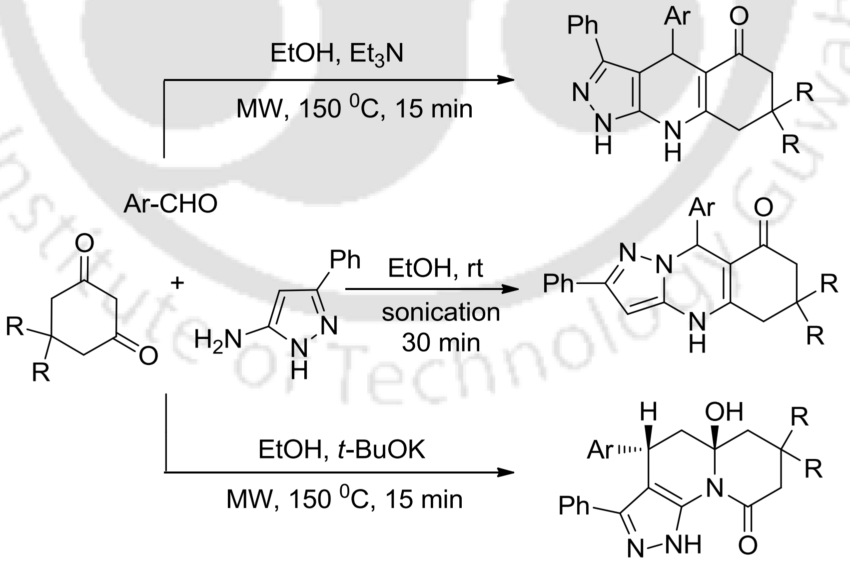
1.8. General Approaches for the Construction of fused pyrazolo-pyridine

Quiroga and his co-workers[52] reported the synthesis of 4,7,8,9-tetrahydro-2H-pyrazolo[3,4-*b*]-quinolin-5(6*H*)-ones using aldehydes, dimedone, 3-amino-pyrazole derivative by involving MCR strategy under different reaction conditions. Later on, other research groups demonstrated structurally similar compounds applying a combination of aldehydes, dimedone, and 3-aminopyrazole under different reaction conditions such as refluxing condition or microwave heating condition (Scheme 26) .[53]



Scheme 26. Synthesis of 4,7,8,9-tetrahydro-2H-pyrazolo[3,4-*b*]-quinolin-5(6*H*)-ones

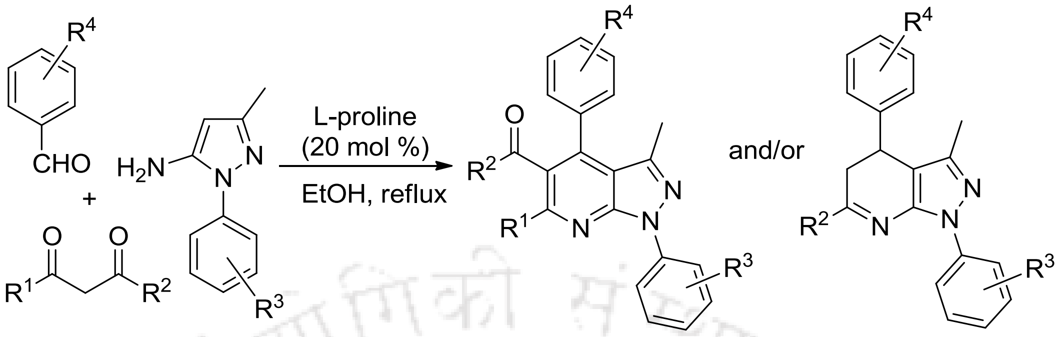
Recently, Chebanov *et al.*[54] described a regio and chemoselective multicomponent strategy for the synthesis of 1,4,6,7,8,9-hexahydro-1*H*pyrazolo[3,4-*b*]quinolin-5-ones, 5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8-ones and 5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones from 5-amino-3-phenylpyrazole, cyclic 1,3-dicarbonyl compounds and aromatic aldehydes. In presence of ethanol under reflux conditions, the three-component reaction provided mixtures of pyrazoloquinolinones and pyrazoloquinazolinones. The condensation can be evolved toward the formation pyrazoloquinolinones by performing the reaction at 150 °C in the presence of the base, Et_3N and applying sealed vessel microwave or conventional heating. On the other hand, applying sonication at room temperature under neutral conditions promotes the formation of the isomeric pyrazoloquinazolinones (Scheme 27).



Scheme 27.

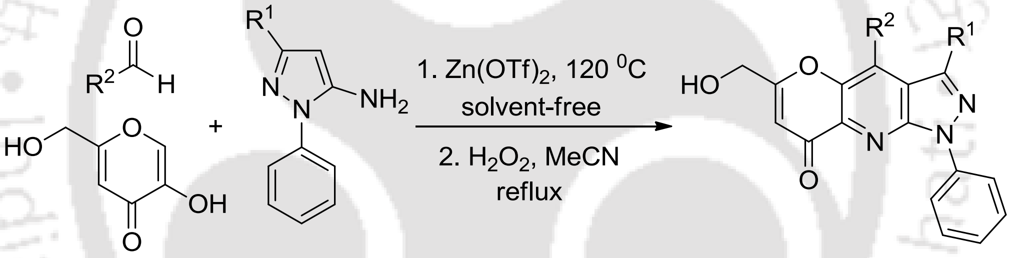
Perumal *et al.* reported a L-proline catalysed synthesis of novel 3-methyl-1-aryl-1H-pyrazolo[3,4-*b*]pyridines from the reaction of 3-methyl-1-aryl-1H-pyrazol-5-amines, 1,3-

dicarbonyl compounds and aromatic aldehydes in ethanol involving MCRs strategy (Scheme 28).[51]



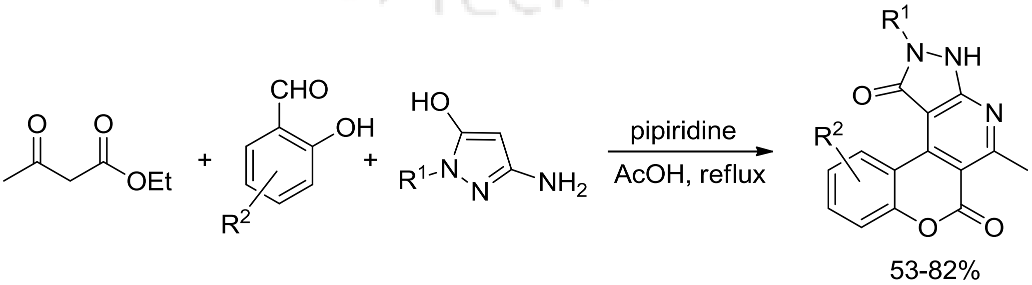
Scheme 28. Synthesis of 3-methyl-1-aryl-1H-pyrazolo[3,4-*b*]pyridines

Recently, Safaei *et al.* reported the synthesis of dihydropyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones employing kojic acid, aldehydes and 1H-pyrazol-5-amines on treatment with catalytic amount Zn(OTf)$_2$ followed by H_2O_2-mediated oxidation (Scheme 29).[55]



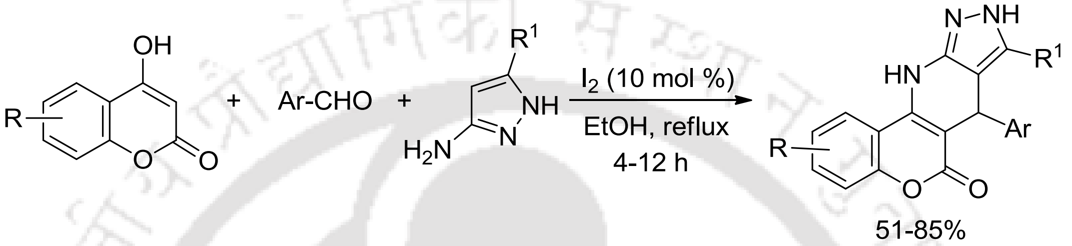
Scheme 29. Synthesis of dihydropyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones

A few years ago, the synthesis of anti-bacterial compounds[56] such as 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones was accomplished by Magedov *et al.* from 3-amino-pyrazol-5-ones, substituted salicylaldehydes and ethyl acetoacetate under reflux condition employing piperidine and acetic acid sequentially (Scheme 30).



Scheme 30. Synthesis of 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones

Recently, Choudhury and his co-workers demonstrated iodine catalysed synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones[57] in a one-pot manner from aromatic aldehydes, 4-hydroxycoumarin derivatives and 3-aminopyrazoles under reflux condition. Though the method reported by Choudhury *et al.* is quite useful, but it has few disadvantages: longer reaction time, poor yields, and failure to synthesise the desired dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones using aliphatic aldehyde (Scheme 31).

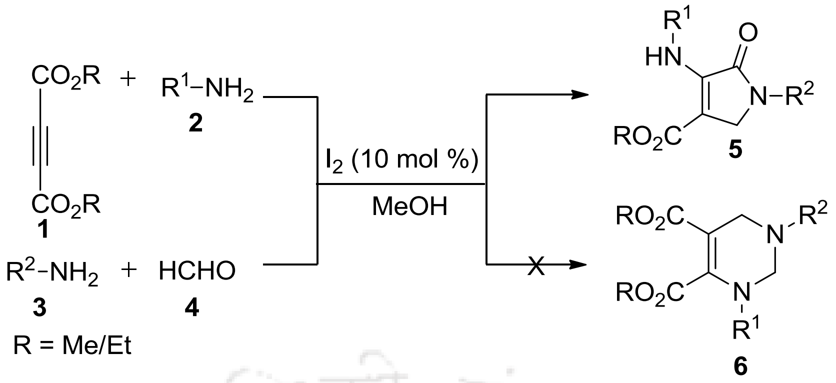


Scheme 31. Synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones

From the literature survey it is obvious that the 2-oxypyrrole and fused pyrazolo-pyridine derivatives are present in several important natural products, drugs and displays a widerange of biological as well as pharmaceutical activities. Therefore the synthesis of pyrazolo-pyridine derivatives is highly desirable for their immense pharmocological potential. Even though various methods have been described for the construction of 2-oxypyrrole and fused pyrazolo-pyridine derivatives over the years but some of these methods are associated with certain limitations. There still remains a scope to develop a simpler and newer methodology for the synthesis of such molecules. In an endeavour to strike our goal, we have developed newer methodologies employing Lewis acid (I_2) and *n*-tetrabutylammonium tribromide (TBATB) as catalysts which will be discussed in subsequent chapters 2 and 3 of Part B.

2.1. Results and Discussion

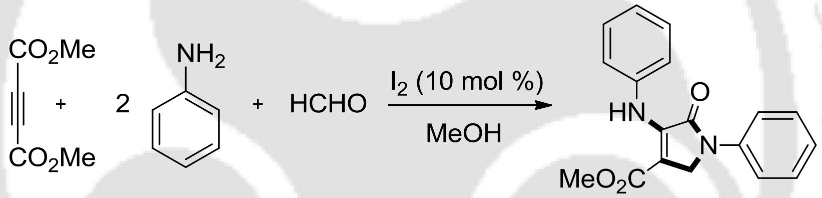
MCRs have emerged as versatile synthetic tool in organic synthesis due to their advantages over the conventional multi-step synthesis. In addition they are eco-friendly, with superior atom-economy, less time consuming, cheaper purification processes and protection-deprotection steps are often avoided and it is discussed in Chapter 1 of Part B. Its importance, synthetic applicability and some recent strategies for the synthesis of dihydro-2-oxypyrrole were discussed in the earlier chapter. In continuation of our endeavour to develop applicability of new reagents in organic synthesis, we sought to investigate the catalytic activity of molecular iodine as a Lewis acid catalyst for the development of new synthetic methodology in multicomponent reactions leading to formation of dihydro-2-oxypyrrole derivatives. Because of their biological and pharmaceutical importance, we conceived a new methodology for the synthesis of dihydro-2-oxypyrrole derivatives using MCRs would be relevant. Considering the importance of dihydro-2-oxypyrrole derivatives, a significant attention has been paid to the synthesis of these compounds over the years. These methods are associated with certain limitations such as drastic reaction conditions, longer reaction times, expensive and excess amount of catalyst used and costly column chromatographic purification. Therefore, there remains a scope to develop a synthetic methodology using an efficient catalyst, which might work under milder reaction conditions. According to our previous experience with molecular iodine[58] as well as by other groups,[59] it has been found to be a useful Lewis acid for various organic transformations due to its non-toxic, non-metallic, ready availability and environmentally benign nature. The same catalyst has also been exploited for a diverse range of multicomponent reactions[60] as well as the synthesis of various heterocycles.[61] Molecular iodine could be further utilized for the synthesis of highly substituted dihydro-2-oxypyrrole derivatives from dimethyl acetylenedicarboxylate (DMAD), amines and formaldehyde involving MCRs. In this chapter, we have demonstrated the synthesis and mechanistic aspects of densely functionalized dihydro-2-oxypyrrole derivatives involving MCRs strategies (Scheme 32).



Scheme 32. Synthesis of substituted dihydro-2-oxypyrroles

Initially, the reaction of dimethyl acetylenedicarboxylate (1 mmol), aniline (2.1 mmol) and formaldehyde (1.2 mmol) was carried out in presence of 10 mol % of iodine in methanol at room temperature and product **5a** in 82% yield was reported as characterized by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.

Table 1. Optimization of reaction conditions[a]



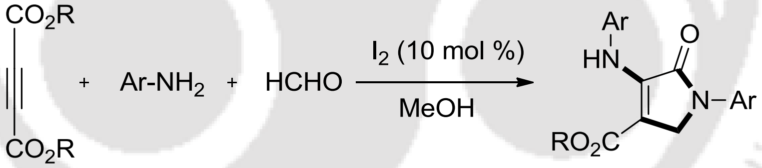
Entry	Catalyst	Catalyst (mol %)	Solvent	Time/h	Yield (%)[b]
1	No catalyst	0	MeOH	24	trace
2	Iodine	5	MeOH	2	60
3	**Iodine**	**10**	**MeOH**	**1**	**82**
4	Iodine	15	MeOH	1	80
5	$NiCl_2$	10	MeOH	8	52
6	$ZnCl_2$	10	MeOH	8	45
7	BDMS	10	MeOH	8	50
8	Iodine	10	EtOH	8	76
9	Iodine	10	MeCN	8	60
10	Iodine	10	DCM	8	42
11	Iodine	10	THF	8	40

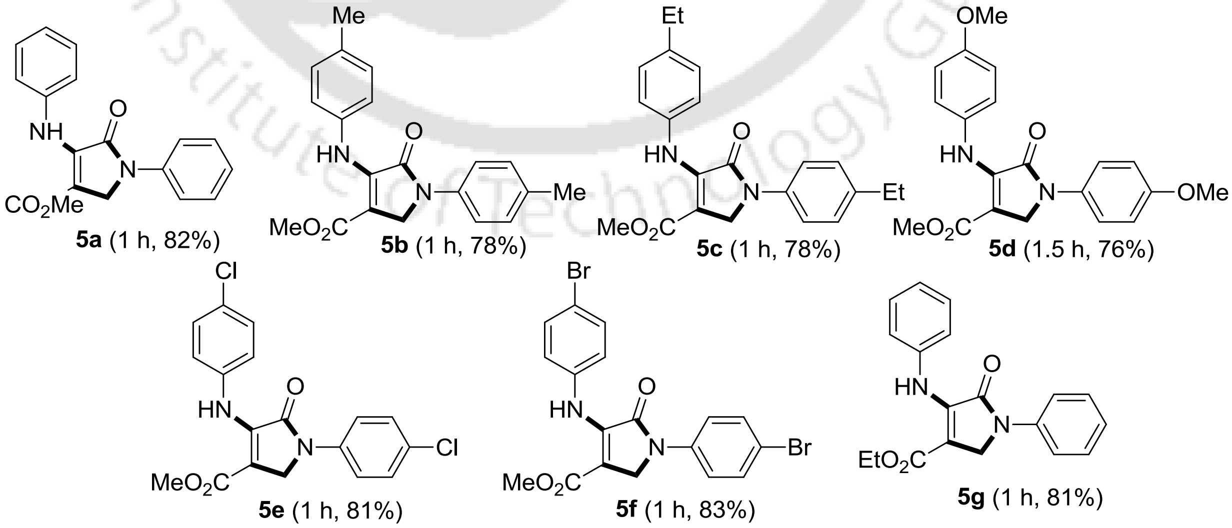
[a]The reaction were carried out in the same scale and identical conditions. [b]Isolated yields.

Other catalysts were also examined for the same reaction such as $NiCl_2$, $ZnCl_2$ and BDMS (Entries 5-7, Table 1) to verify the efficacy of the other catalysts in terms of yield and reaction time. Likewise, different solvents were also scrutinized e.g. EtOH, MeCN, DCM and THF (Entries 8-11, Table 1) to examine the aptness of the solvent. From these observations, we may conclude that 10 mol % iodine in methanol or ethanol is found to be the most suitable reaction conditions for this transformation (Table 1).

After optimization of the reaction conditions, the reaction mixture of DMAD (1 mmol), 4-methylaniline (2.1 mmol) and formaldehyde (1.2 mmol) was treated with 10 mol % iodine at room temperatures and the desired product **5b** (Table 2) was obtained in 78% yield. A variety of anilines with substitutents Et, OMe, Cl and Br at *para* position were examined with DMAD and formaldehyde under identical conditions and the corresponding dihydro-2-oxypyrrole derivatives (**5c-f,** Table 2**)** were obtained in good yields (Table 2). To examine the effect of alkyl group in acetylenedicarboxylate, we have performed the reaction of diethyl acetylenedicarboxylate with aniline and formaldehyde in the presence of the same catalyst under identical reaction conditions and it afforded **5g** (Table 2) in yield 81%.

Table 2. Synthesis of various dihydro-2-oxypyrroles using anilines





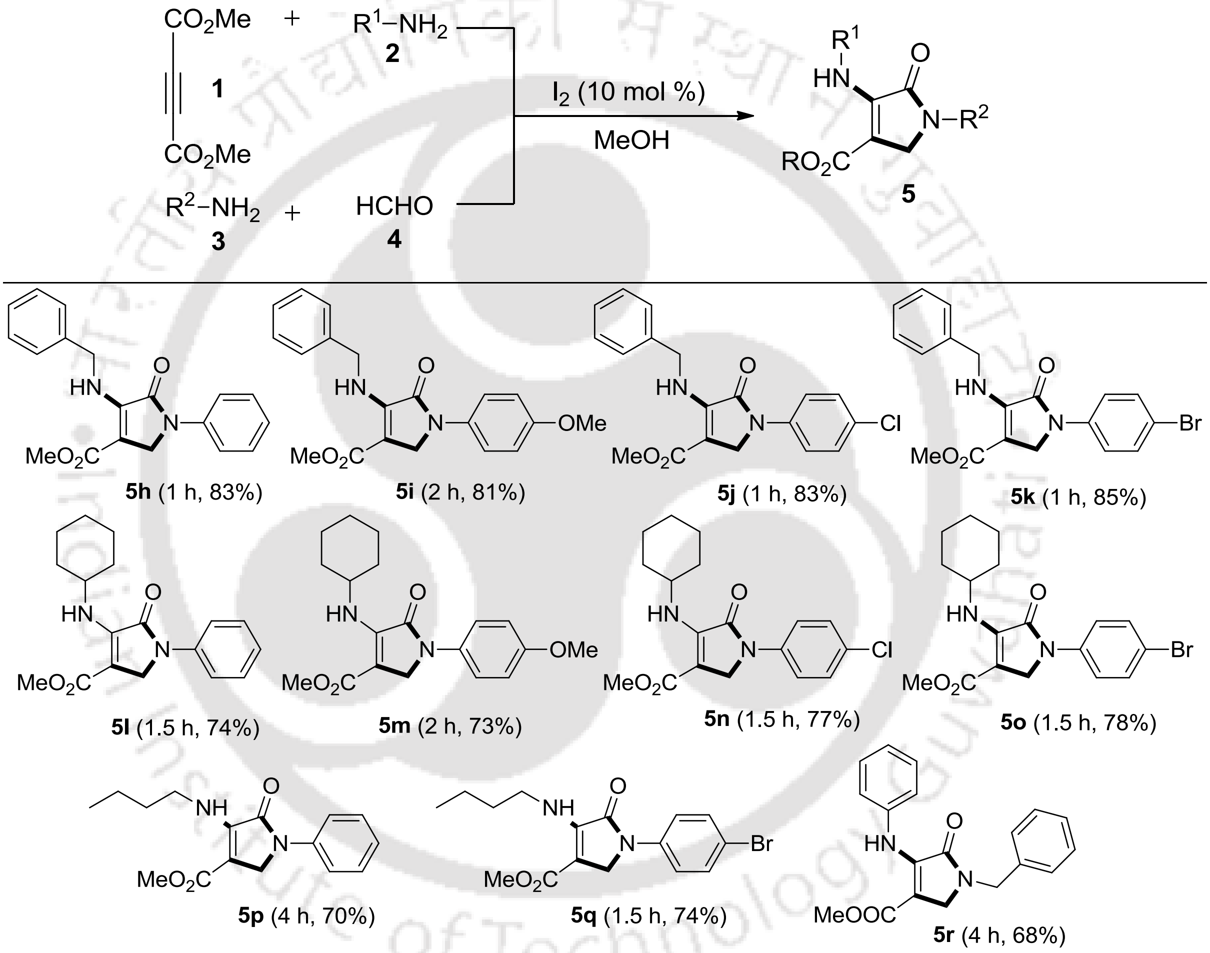
5a (1 h, 82%) **5b** (1 h, 78%) **5c** (1 h, 78%) **5d** (1.5 h, 76%)

5e (1 h, 81%) **5f** (1 h, 83%) **5g** (1 h, 81%)

[a]All the reactions were carried out with DMAD/amine/formaldehyde (1 mmol:2.1 mmol:1.2 mmol). [b]Isolated yields.

Next, we explored the methods using two different amines for the synthesis of different substituted dihydro-2-oxypyrroles. The mixture of DMAD (1 mmol) and benzylamine (1 mmol) was stirred for 10-15 min at room temperature and then aniline (1 mmol), formaldehyde (1.2 mmol) and 10 mol % iodine were added sequentially in the reaction mixture. The product **5h** was isolated in 83% yield and was characterized by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.

Table 3. Synthesis of dihydro-2-oxypyrroles using two different amines



5h (1 h, 83%) **5i** (2 h, 81%) **5j** (1 h, 83%) **5k** (1 h, 85%)

5l (1.5 h, 74%) **5m** (2 h, 73%) **5n** (1.5 h, 77%) **5o** (1.5 h, 78%)

5p (4 h, 70%) **5q** (1.5 h, 74%) **5r** (4 h, 68%)

[a]All the reactions were carried out with DMAD/ aliphatic amine/aromatic amine /formal- dehyde (1.0 mmol :1.0 mmol: 1.0 mmol: 1.2 mmol). [b]Isolated yields.

Encouraged by the results, the reactions of various other amine combinations were also investigated in a similar manner and small libraries of compounds **5h-r** were accomplished (Table 3). All the products were fully characterized by IR, ^{1}H and ^{13}C NMR and elemental analysis. As a matter of fact, the desirable substituted dihydro-2-oxypyrrole derivatives can also be obtained by changing the sequence of addition of amine with dimethyl acetylenedicarboxylate due to the formation of selective hydroamination product (Table 3). Moreover, the structure of **5o** was confirmed by X-ray crystallography (Figure 9).

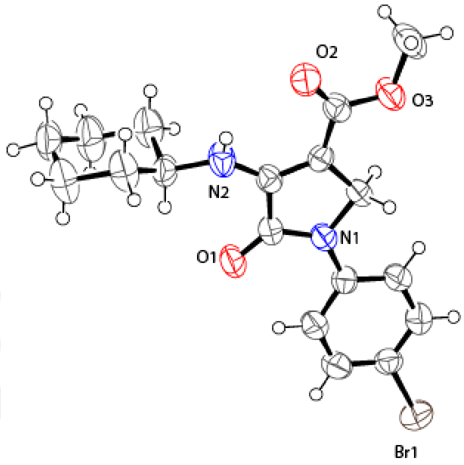
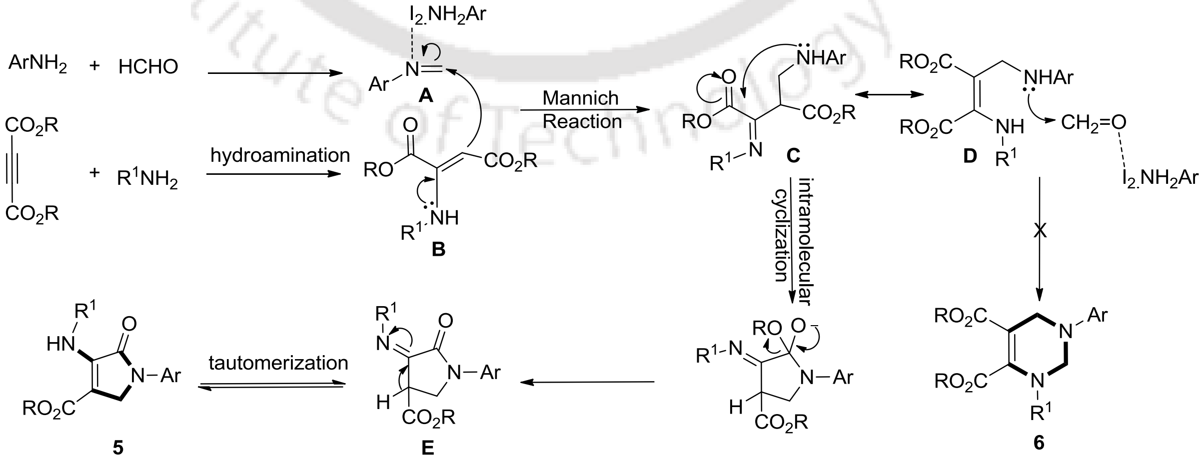


Figure 9. X-ray crystal structure of compound **5o** (CCDC No. 856176)

A plausible mechanism for the formation of dihydro-2-oxypyrrole was proposed. Initially the amine reacts with formaldehyde and DMAD to form the imine **A** and hydroamination intermediate **B** respectively. The intermediate **B** undergoes Mannich type reaction with activated imine **A** in the presence of molecular iodine leading to the formation of intermediate **C**. The intermediate **C** can also exist other possible resonating structure **D**. The intermediate **C** undergoes concomitant cyclization *via* intramolecular nucleophilic reaction giving adducts **E,** which finally tautomerizes to the desired dihydro-2-oxypyrrole derivatives **5** (Scheme 33). Similarly, the intermediate D may also react with another molecule of formaldehyde to give pyrimidine derivatives **6**, which is reported by us in the presence of silica supported perchloric acid.



Scheme 33. Plausible mechanism for the formation dihydro-2-oxypyrroles

We did not observe the formation of compound **6** because molecular iodine acts as Lewis acid.

In conclusion, we have demonstrated a mild and efficient iodine catalyzed synthesis of functionalized dihydro-2-oxypyrroles using one-pot four-component reactions of DMAD, amines and formaldehyde. However, we have not obtained pyrimidine under the optimized experimental conditions. The significant advantages of present protocol are simple experimental procedure, non-toxic by-product, high atom-economy, good yields and used of eco-friendly, cost-effective catalyst. The new heterocyclic entities containing *β*-amino acid skeleton might exhibit interesting pharmacological activities.

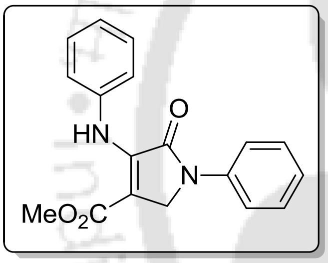
2.2. Experimental Section

*General procedure for dihydro-2-oxopyrroles (**5a**)*:

Into a 25 mL of round-bottomed flask was taken DMAD (0.142 g, 1.0 mmol) in methanol (3 mL). Then, aniline (0.093 g, 1 mmol) was added into it. The reaction mixture was stirred for 10 min. After that aniline (0.093 g, 1 mmol), formaldehyde (1.5 mmol) and iodine (10 mol %) were added successively. Then the reaction mixture was kept for stirring at room temperature until the reaction was complete, which was monitored by TLC. The solid precipitate appeared at the end of the reaction, which was filtered through a Büchner funnel. The product was washed with 1 mL of ethanol to remove unreacted starting materials. The pure product was obtained after recrystallization from ethanol.

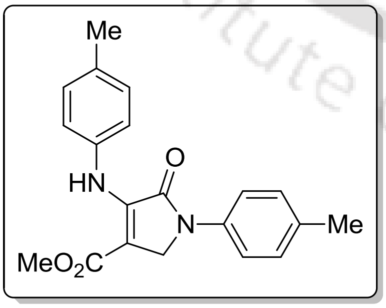
Spectral data of dihydro-2-oxypyrroles:

*Methyl 2,5-dihydro-5-oxo-1-phenyl-4-(phenylamino)-1H-pyrrole-3-carboxylate **(5a)***:



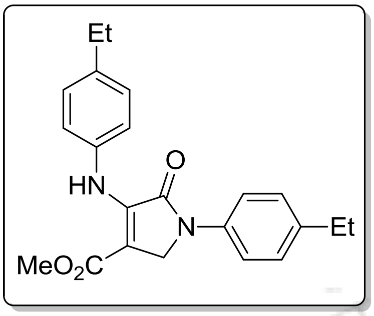
White solid: m.p. 155-156 °C; IR (KBr): 1646, 1646, 3269 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.73 (s, 3H), 4.54 (s, 2H), 7.14 (d, *J* =8.4 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 8.4Hz, 2H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 48.36, 51.39, 103.03, 119.30, 122.86, 124.71, 125.16, 128.43, 129.24, 138.78, 142.98, 163.91, 164.85; Anal Calcd. $C_{18}H_{16}N_2O_3$ (308.33): requires C, 70.12; H, 5.23; N, 9.09%. Found C, 70.10; H, 5.20; N, 9.01%.

*Methyl 4-(p-tolylamino)-2,5-dihydro-5-oxo-1-p-tolyl-1H-pyrrole-3-carboxylate **(5b)***:



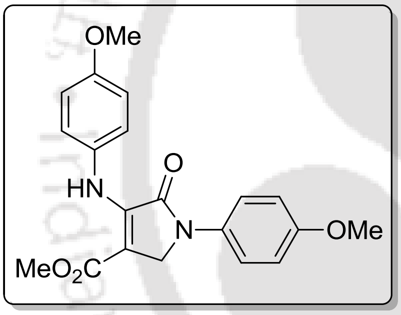
White solid: m.p. 177-178 °C; IR (KBr): 1642, 1701, 3331 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.32 (s, 6H), 3.72 (s, 3H), 4.47 (s, 2H), 7.01 (d, *J* = 8.4, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.8, 2H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 20.90, 21.03, 48.25, 51.28, 101.86, 119.17, 123.10, 128.95, 129.64, 134.41, 134.71, 136.05, 136.33, 143.51, 163.59, 164.94; Anal Calcd. $C_{20}H_{20}N_2O_3$ (336.38): requires C, 71.41; H, 5.99; N, 8.33%. Found C, 71.31; H, 5.87; N, 8.34%.

*Methyl 4-(4-ethylphenylamino)-1-(4-ethylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate **(5c)***:



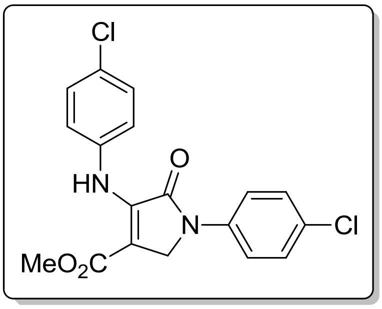
White solid: m.p. 178-179 °C; IR (KBr): 1650, 1675, 3284 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.21-1.25 (m, 6H), 2.64 (q, *J* = 7.6 Hz, 4H), 3.73 (s, 3H), 4.51 (s, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7. 21 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 8.03 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 15.72, 15.78, 28.44, 28.49, 48.40, 51.44, 102.05, 119.50, 123.19, 127.88, 128.62, 136.24, 136.52, 140.92, 141.35, 163.71, 165.15; Anal Calcd. $C_{22}H_{24}N_2O_3$ (364.44): requires C, 72.50; H, 6.64; N, 7.69%. Found C, 72.41; H, 6.60; N, 7.58%.

*Methyl 4-(4-methoxyphenylamino)-2,5-dihydro-1-(4-methoxyphenyl)-5-oxo-1H-pyrrole-3-carboxylate **(5d)***:



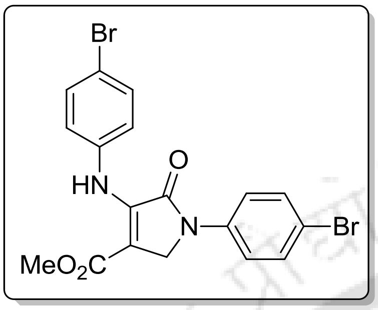
Brown solid: m.p. 176-177 °C; IR (KBr): 1646, 1675, 3286 cm^{-1}; ^{1}H NMR (400MHz, CDCl$_3$): δ 3.74 (s, 3H), 3.80 (s, 6H), 4.47 (s, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 13.2 Hz, 2H), 7.09 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 48.55, 51.42, 55.56, 55.61, 100.93, 113.69, 114.35, 121.20, 125.19, 131.61, 132.05, 144.17, 157.03, 157.22, 163.50, 165.25; Anal Calcd. $C_{20}H_{20}N_2O_5$ (368.38): requires C, 65.21; H, 5.47; N, 7.60%, Found C, 65.10; H, 5.41; N,7.50%.

*Methyl 1-(4-chlorophenyl)-4-(4-chlorophenylamino)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate **(5e)***:



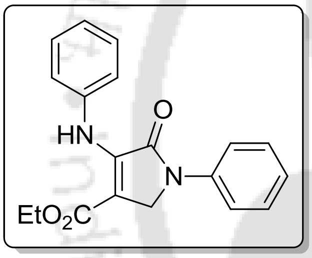
White solid: m.p. 173-174 °C; IR (KBr): 1651, 1677, 3288 cm^{-1}; ^{1}H NMR (400MHz, CDCl$_3$): δ 3.78 (s, 3H), 4.51 (s, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 48.26, 51.77, 103.74, 120.44, 124.39, 128.43, 129.43, 130.34, 130.53, 137.07, 137.31, 143.17, 163.68, 164.96; Anal Calcd. $C_{18}H_{14}Cl_2N_2O_3$ (376.04): requires C, 57.31; H, 3.74; N, 7.48%. Found C, 57.23; H, 3.68; N, 7.40%.

*Methyl 1-(4-bromophenyl)-4-(4-bromophenylamino)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate **(5f)***:



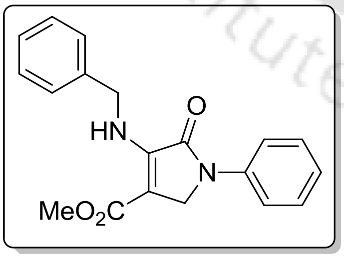
Yellow solid: m.p. 179-180 °C; IR (KBr): 1641, 1674, 3432 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 3.78 (s, 3H), 4.50 (s, 2H), 7.01 (d, *J* = 8 HZ, 2H), 7.42 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.17, 51.78, 103.95, 117.96, 118.21, 120.85, 124.61, 131.58, 132.34, 137.57, 137.78, 142.99, 163.64, 164.89; Anal Calcd. $C_{18}H_{14}Br_2N_2O_3$ (466.12): requires C, 46.38; H, 3.03; N, 6.01%. Found C, 46.30; H, 3.10; N, 5.89%.

*Ethyl 2,5-dihydro-5-oxo-1-phenyl-4-(phenylamino)-1H-pyrrole-3-carboxylate **(5g)***:



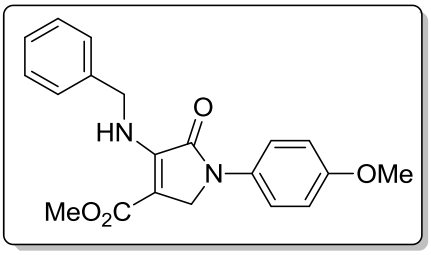
White solid: m.p. 139-140 °C; IR (KBr): 1642, 1701, 3317 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.2 Hz, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.53 (s, 2H), 7.12 (d, *J* = 8.0 Hz, 3H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.23, 48.45, 60.41, 103.66, 119.29, 122.58, 124.52, 125.12, 128.43, 129.21, 138.79, 138.98, 142.53, 164.10, 164.55; Anal Calcd. $C_{19}H_{18}N_2O_3$ (322.36): requires C, 70.59; H, 5.63; N, 8.69%. Found C, 70.50; H, 5.54; N, 8.58%**.**

*Methyl 4-(benzylamino)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate **(5h)***:



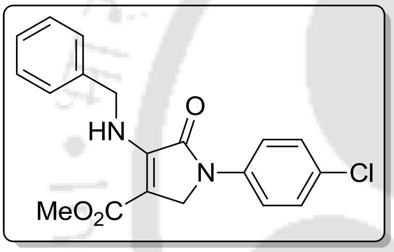
White solid: m.p. 139-140 °C; IR (KBr): 1641, 1703, 3310 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 4.43 (s, 2H), 5.12 (d, *J* = 6.4 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 4.4 Hz, 1H), 7.35 (d, *J* = 4.4 Hz, 3H), 7.40 (t, *J* = 8.0 Hz, 3H), 7.75 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.73, 48.10, 51.22, 97.51, 119.55, 125.22, 127.47, 127.63, 128.25, 129.25, 138.82, 139.56, 164.59, 165.61; Anal Calcd. $C_{19}H_{18}N_2O_3$ (322.36): requires C, 70.79; H, 5.63; N, 8.69%. Found C, 70.68; H, 5.49; N, 8.60%.

Methyl 4-(benzylamino)-2,5-dihydro-1-(4-methoxyphenyl)-5-oxo-1H-pyrrole-3-carboxylate ***(5i)***:



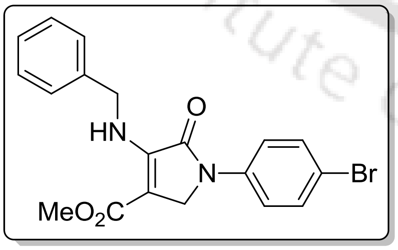
Brown solid: m.p. 129-130 °C; IR (KBr): 1646, 1703, 3306 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.77 (s, 3H), 3.82 (s, 3H), 4.39 (s, 2H), 5.12 (d, *J* = 6.4 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 7.34 (d, *J* = 4.4 Hz, 5H), 7.63 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 46.67, 48.49, 51.11, 55.55, 97.21, 114.39, 121.43, 127.45, 127.64, 128.79, 132.00, 139.61, 157.12, 164.27, 165.67; Anal Calcd. $C_{20}H_{20}N_2O_4$ (352.38): requires C, 68.17; H, 5.72; N, 7.95%. Found C, 68.07; H, 5.66; N, 7.86%.

Methyl 4-(benzylamino)-1-(4-chlorophenyl)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***(5j)***:



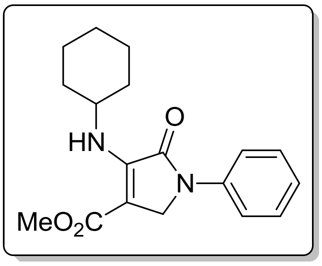
White solid: m.p. 147-148 °C; IR (KBr): 1643, 1701, 3308 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.78 (s, 3H), 4.40 (s, 2H), 5.10 (d, *J* = 6.8 Hz, 2H), 7.26 (s, 2H), 7.34 (s, 2H), 7.35 (d, *J* = 2.0 Hz, 2H), 7.37 (s, 2H), 7.72 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 46.86, 48.05, 51.27, 97.52, 120.46, 127.53, 127.60, 128.84, 129.26, 130.27, 137.46, 139.47, 164.57, 165.58; Anal Calcd. $C_{19}H_{17}ClN_2O_3$ (356.80): requires C, 63.96; H, 4.80; N, 7.85%. Found C, 63.87; H, 4.71; N, 7.77%.

Methyl 4-(benzylamino)-1-(4-bromophenyl)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***(5k)***:



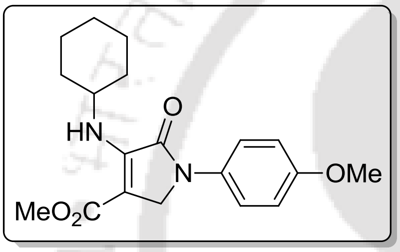
Yellow solid: m.p. 120-121 °C; IR (KBr): 1642, 1701, 3307 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.78 (s, 3H), 4.39 (s, 2H), 5.10 (d, *J* = 6.8 Hz, 2H), 7.28 (t, *J* = 4.4 Hz, 1H), 7.34 (d, *J* =4.4 Hz, 4H), 7.50 (d, *J* = 9.2 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 46.68, 47.89, 51.25, 97.43, 117.90, 120.63, 127.55, 128.80, 132.15, 137.15, 139.43, 164.53, 165.58; Anal Calcd. $C_{19}H_{17}BrN_2O_3$ (400.04): requires C, 56.87; H, 4.27; N, 6.98%. Found C, 56.78; H, 4.20; N, 6.90%.

Methyl 4-(cyclohexylamino)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate ***(5l)***:



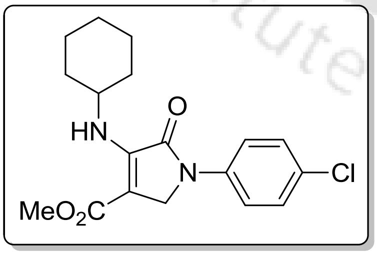
White solid: m.p. 96-97 °C; IR (KBr): 1633, 1703, 3320 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18-1.27 (m, 3H), 1.37-1.44 (m, 2H), 1.61-1.64 (m, 2H), 1.72-1.76 (m, 2H), 2.01-2.03 (m, 2H), 3.79 (s, 3H), 4.41 (s, 2H), 4.60 (s, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.75 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.73, 25.58, 34.79, 48.05, 50.92, 95.80, 119.44, 125.01, 129.10, 138.85, 164.40, 165.65; Anal Calcd. $C_{18}H_{22}N_2O_3$ (314.38): requires C, 68.77; H, 7.05; N, 8.91%. Found C, 68.66; H, 6.98; N, 8.81%.

Methyl 4-(cyclohexylamino)-1-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***(5m)***:



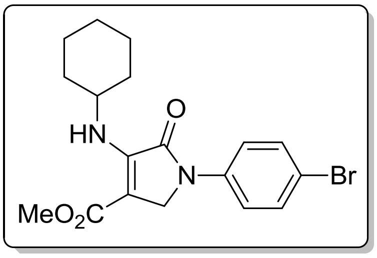
Brown solid: m.p. 128-129 °C; IR (KBr): 1630, 1684, 3313 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17-1.26 (m, 4H), 1.36-1.46 (m, 3H), 1.72-1.77 (m, 2H), 1.99-2.02 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 4.37 (s, 2H), 4.61 (s, 1H), 6.92 (d, J = 9.2 Hz, 2H), 7.63 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.78, 25.61, 34.86, 48.51, 50.96, 55.49, 55.54, 95.59, 113.65, 114.30, 121.40, 124.55, 132.07, 157.04, 164.11, 165.67; Anal Calcd. $C_{19}H_{24}N_2O_4$ (344.17): requires C, 66.26; H, 7.02; N, 8.13%. Found C, 66.16; H, 6.94; N, 7.92%.

Methyl 1-(4-chlorophenyl)-4-(cyclohexylamino)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***(5n)***:



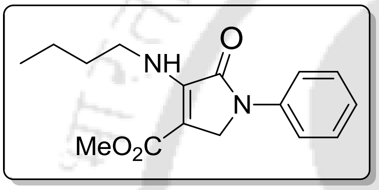
White solid: m.p. 124-125 °C; IR (KBr): 1637, 1695, 3302 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21-1.23 (m, 4H), 1.40-1.43 (m, 3H), 1.73-1.76 (m, 2H), 2.00-2.02 (m, 2H), 3.79 (s, 3H), 4.38 (s, 2H), 4.59 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.68, 25.51, 34.74, 47.76, 50.93, 95.77, 120.15, 129.02, 129.93, 137.40, 164.28, 165.62; Anal Calcd. $C_{18}H_{21}ClN_2O_3$ (348.82): requires C, 61.98; H, 6.07; N, 8.03%. Found C, 61.89; H, 6.00; N, 7.92%.

Methyl 1-(4-bromophenyl)-4-(cyclohexylamino)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***(5o)***:



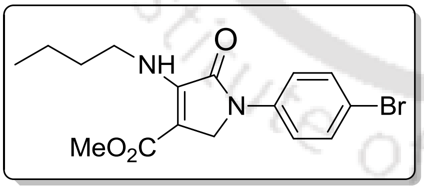
Yellow solid: m.p. 123-124 °C; IR (KBr): 1631, 1700, 3309 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.15-1.27 (m, 3H), 1.37-1.46 (m, 3H), 1.61-1.68 (m, 1H), 1.73-1.77 (m, 2H), 1.99-2.02 (m, 2H), 3.79 (s, 3H), 4.37 (s, 2H), 4.57 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.8Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 24.81, 25.62, 34.89, 47.95, 51.14, 95.92, 117.89, 120.73, 132.17, 138.02, 164.51, 165.62; Anal Calcd. $C_{18}H_{21}BrN_2O_3$ (392.07): requires C, 54.97; H, 5.38; N, 7.12%. Found C, 54.88; H, 5.28; N, 7.03%.

Methyl 4-(butylamino)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate ***(5p)***:



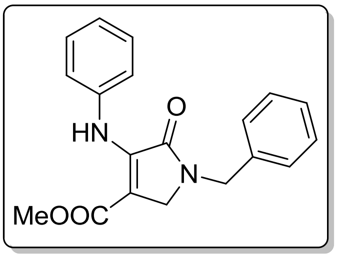
White solid: m.p. 60-61 °C; IR (KBr): 1635, 1700, 3347 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.39 (sextet, *J* = 7.2 Hz, 2H), 1.57 (quintet, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.85 (t, *J* = 7.2 Hz, 2H), 4.39 (s, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.97, 19.97, 33.53, 42.91, 48.18, 51.06, 96.04, 119.54, 125.16, 129.25, 138.94, 164.67, 165.74; Anal Calcd. $C_{16}H_{20}N_2O_3$ (288.34): requires C, 66.65; H, 6.99; N, 9.72%. Found C, 66.56; H, 6.90; N, 9.62%.

Methyl 1-(4-bromophenyl)-4-(butylamino)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***(5q)***:



Yellow solid: m.p. 108-109 °C; IR (KBr): 1639, 1701, 3357 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.38 (sextet, *J* = 7.2 Hz, 2H), 1.56 (quintet, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.82 (t, *J* = 7.2, 2H), 4.34 (s, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.73, 19.72, 33.19, 42.68, 47.51, 50.83, 95.76, 117.34, 119.99, 131.75, 137.75, 164.18, 165.20; Anal Calcd. $C_{16}H_{19}BrN_2O_3$ (366.24): requires C, 52.33; H, 5.21; N, 7.63%. Found C, 52.24; H, 5.10; N, 7.53%.

Methyl 1-benzyl-2,5-dihydro-5-oxo-4-(phenylamino)-1H-pyrrole-3-carboxylate ***(5r)***:



White solid: m.p. 140-141°C; IR (KBr): 1639, 1692, 3301 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.70 (s, 3H), 3.96 (s, 2H), 4.65 (s, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.26-7.36 (m, 8H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 46.95, 47.27, 104.46, 123.89, 127.99, 128.35, 128.38, 128.93, 129.63, 136.28, 137.23, 143.31, 164.67, 165.02; Anal Calcd. $C_{19}H_{18}N_2O_3$ (322.36): requires C, 70.79; H, 5.63; N, 8.69 %. Found C, 70.81; H, 5.57; N, 8.64%.

XRD for Compound **5o**

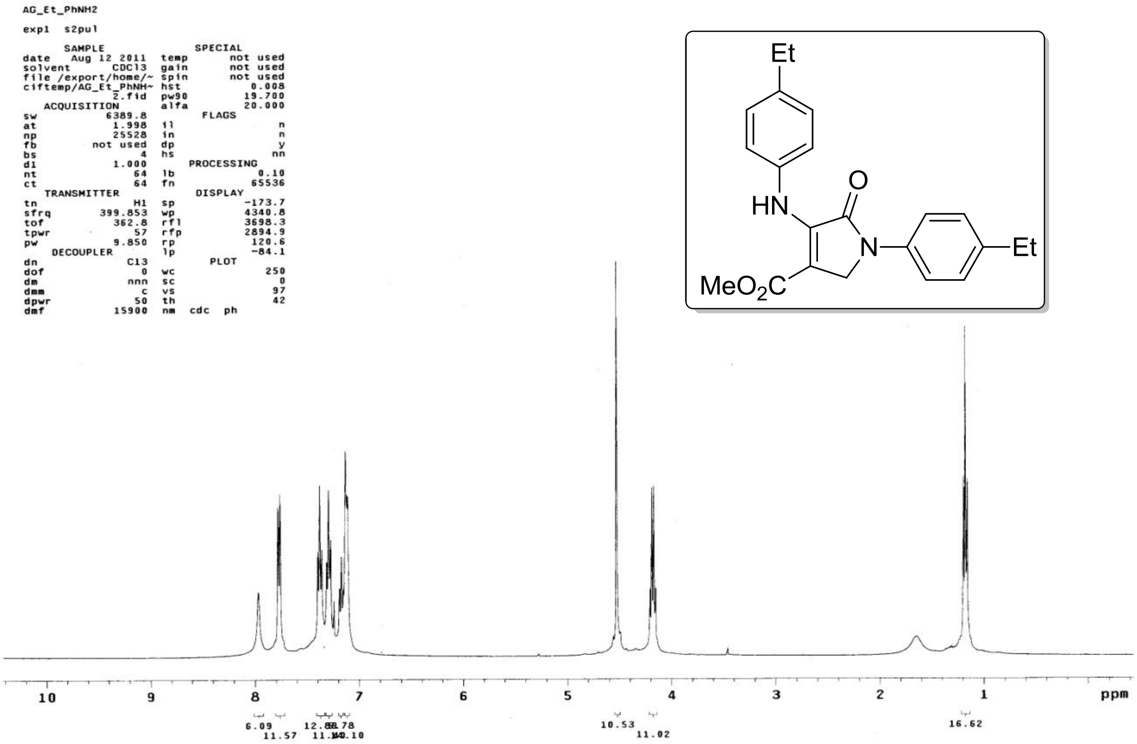
Complete crystallographic data of **5o** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 856176. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 4. Crystal data and structure refinement for **5o**, for atomic coordinates and equivalent isotopic displacement parameters and bond angles, please check the CIF

Parameters	**Compound**
Formula	$C_{12} H_{13} Br N_2 O_3$
CCDC number	856176
Formula weight	313.15
T (K)	296(2)
Wavelength (Å)	0.71073
Crystal system	orthorhombic
Space group	P -1
a (Å)	18.8684(12)
b (Å)	9.6269(6)
c (Å)	19.5155(11)
α (^{0})	90.00
β (^{0})	90.00
γ (^{0})	90.00
V (Å)^3	3544.9(4)
Z	11

D_{calcd} (g m^{-3})	1.614
μ (mm^{-1})	3.191
F (0 0 0)	1738
Reflection collected	27211
Unique reflections	1778
Goodness-of-fit (GOF)[a] on F^2	0.868
R [I > 2σ(I)]	[b]R_1 = 0.0481, [c]wR_2 = 0.1282
R indices (all data)	[b]R_1 = 0.1583, [c]wR_2 = 0.1775

^{1}H NMR (400 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5c**):*



```
AG_Et_PhNH2

exp1  s2pul

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date    Aug 12 2011  temp      not used
solvent       CDCl3  gain      not used
file /export/home/~  spin      not used
ciftemp/AG_Et_PhNH~  hst          0.008
              2.fid  pw90        19.700
    ACQUISITION      alfa        20.000
sw           6389.8          FLAGS
at            1.998  il               n
np            25528  in               n
fb         not used  dp               y
bs                4  hs              nn
d1            1.000        PROCESSING
nt               64  lb            0.10
ct               64  fn           65536
    TRANSMITTER             DISPLAY
tn               H1  sp          -173.7
sfrq        399.853  wp          4340.8
tof           362.8  rfl         3698.3
tpwr             57  rfp         2894.9
pw            9.850  rp           120.6
     DECOUPLER       lp           -84.1
dn              C13           PLOT
dof               0  wc             250
dm              nnn  sc               0
dmm               c  vs              97
dpwr             50  th              42
dmf           15900  nm   cdc   ph
```
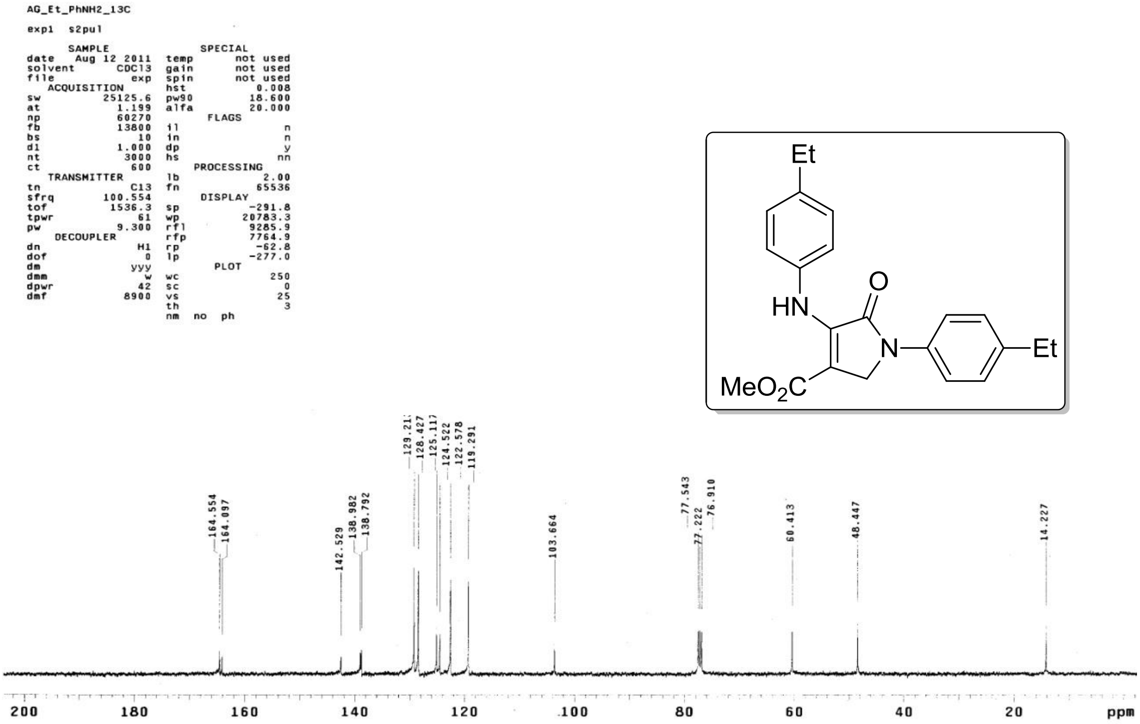

^{13}C NMR (100 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5c**):*



```
AG_Et_PhNH2_13C

exp1  s2pul

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date    Aug 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               10  in               n
d1            1.000  dp               y
nt             3000  hs              nn
ct              600        PROCESSING
    TRANSMITTER      lb            2.00
tn              C13  fn           65536
sfrq        100.554         DISPLAY
tof          1536.3  sp          -291.8
tpwr             61  wp         20783.3
pw            9.300  rfl         9285.9
     DECOUPLER       rfp         7764.9
dn               H1  rp           -62.8
dof               0  lp          -277.0
dm              yyy           PLOT
dmm               w  wc             250
dpwr             42  sc               0
dmf            8900  vs              25
                     th               3
                     nm   no   ph
```
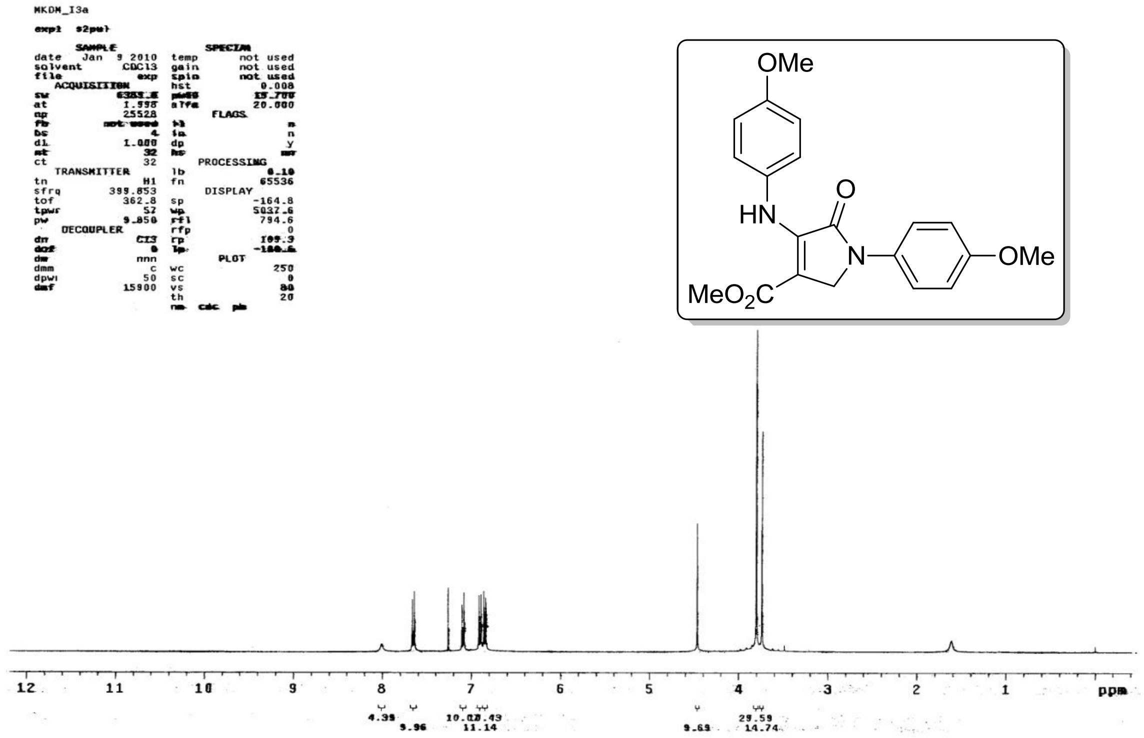
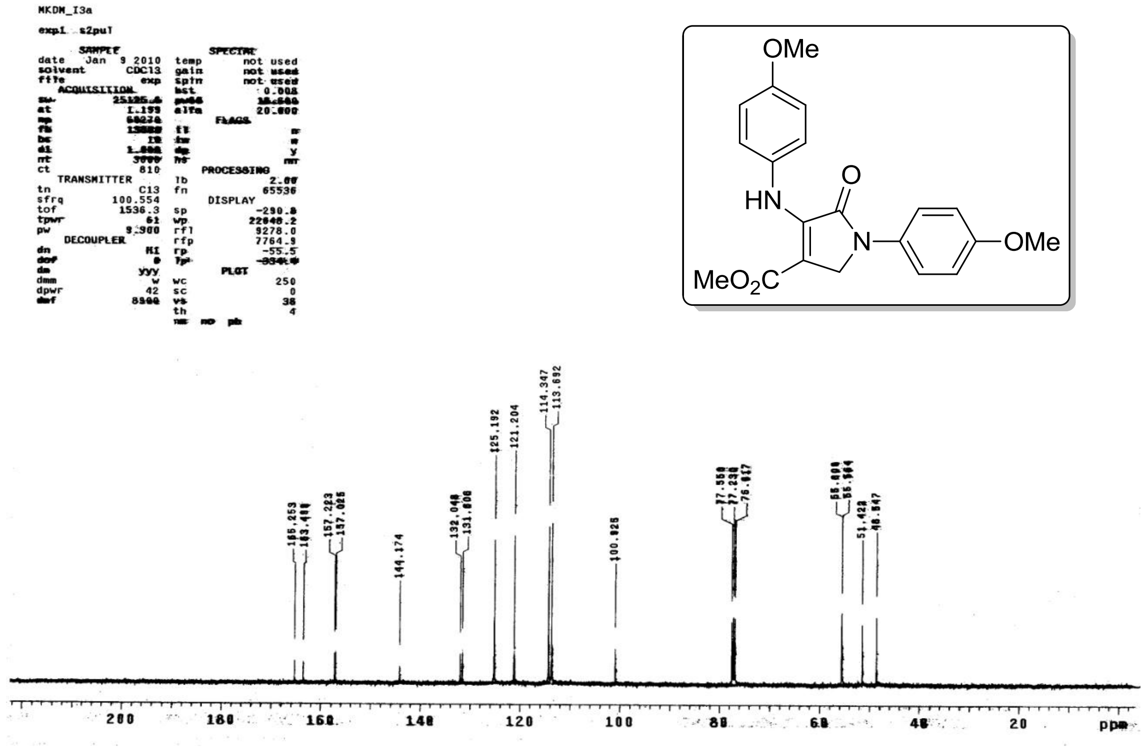
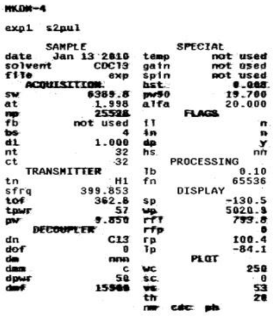

^{1}H NMR (400 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5d**):*



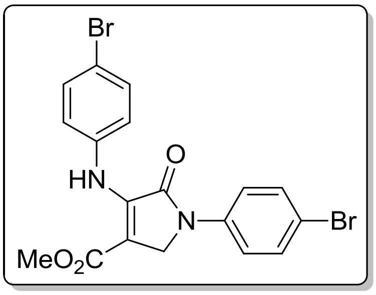
^{13}C NMR (100 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5d**):*

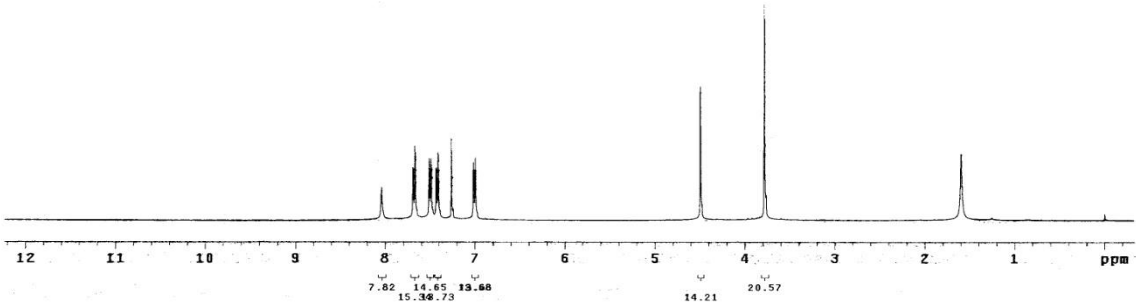


^{1}H NMR (400 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5f**):*

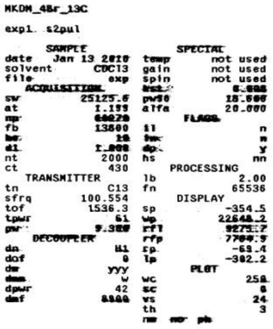


```
MKDM-4

exp1  s2pul

        SAMPLE                 SPECIAL
date    Jan 13 2010    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            -130.5
tpwr             57    wp            5020.9
pw            9.850    rfl            793.8
      DECOUPLER        rfp                0
dn              C13    rp             100.4
dof               0    lp             -84.1
dm              nnn            PLOT
dmm               c    wc               250
dpwr             50    sc                 0
dmf           15900    vs                53
                       th                20
                       nm  cdc  ph
```

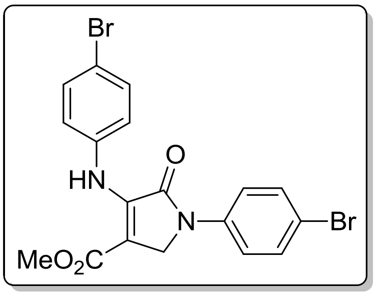


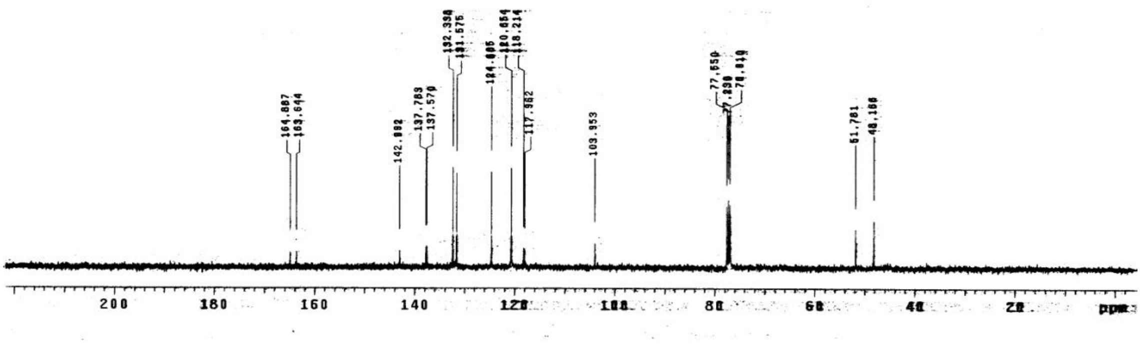


^{13}C NMR (100 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5f**):*

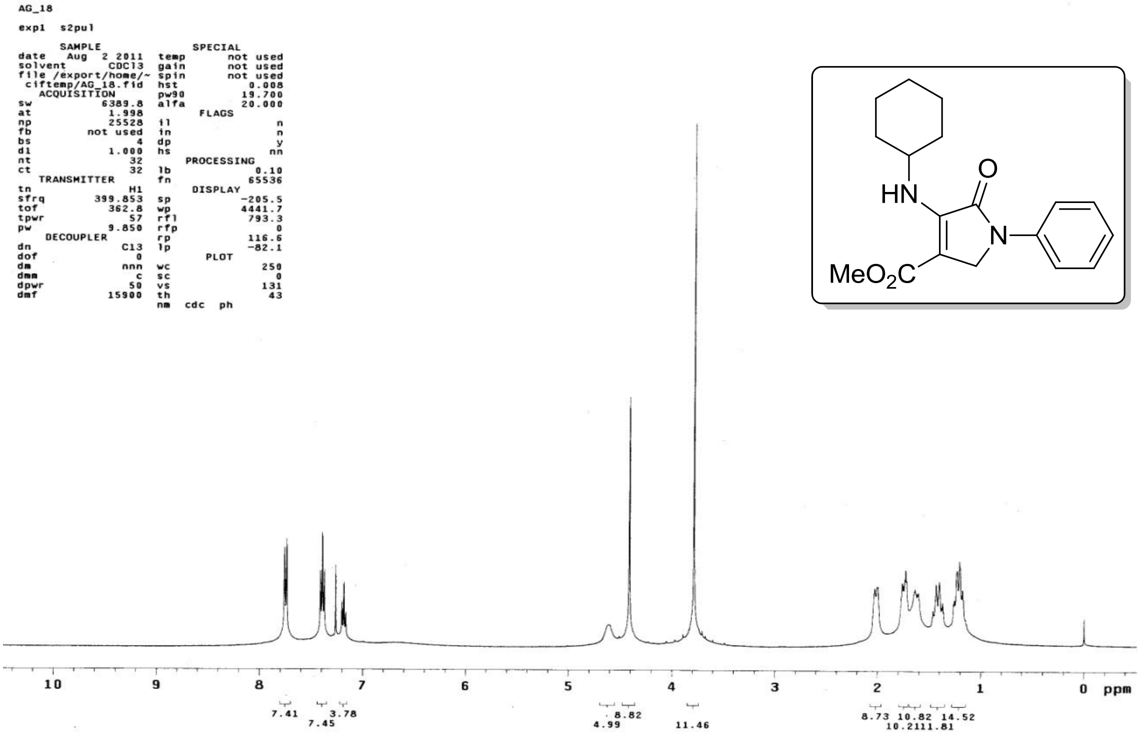


```
MKDM_4Br_13C

exp1  s2pul

        SAMPLE                 SPECIAL
date    Jan 13 2010    temp        not used
solvent       CDCl3    gain        not used
file            exp    spin        not used
     ACQUISITION       hst            0.008
sw          25125.6    pw90          18.600
at            1.193    alfa          20.000
np            60270           FLAGS
fb            13800    il                 n
bs               16    in                 n
d1            1.000    dp                 y
nt             2000    hs                nn
ct              430        PROCESSING
     TRANSMITTER       lb              2.00
tn              C13    fn             65536
sfrq        100.554           DISPLAY
tof          1536.3    sp            -354.5
tpwr             61    wp           22648.2
pw            9.300    rfl           9275.7
      DECOUPLER        rfp           7704.9
dn               H1    rp             -63.4
dof               0    lp            -302.2
dm              yyy            PLOT
dmm               w    wc               250
dpwr             42    sc                 0
dmf            8900    vs                24
                       th                 3
                       nm  no  ph
```





^{1}H NMR (400 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5l**):*


```
AG_18

exp1  s2pul

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date   Aug  2 2011  temp      not used
solvent      CDCl3  gain      not used
file /export/home/~ spin      not used
 ciftemp/AG_18.fid  hst          0.008
   ACQUISITION      pw90        19.700
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          -205.5
tof          362.8  wp          4441.7
tpwr            57  rfl          793.3
pw           9.850  rfp              0
    DECOUPLER       rp           116.6
dn             C13  lp           -82.1
dof              0            PLOT
dm             nnn  wc             250
dmm              c  sc               0
dpwr            50  vs             131
dmf          15900  th              43
                    nm   cdc   ph
```
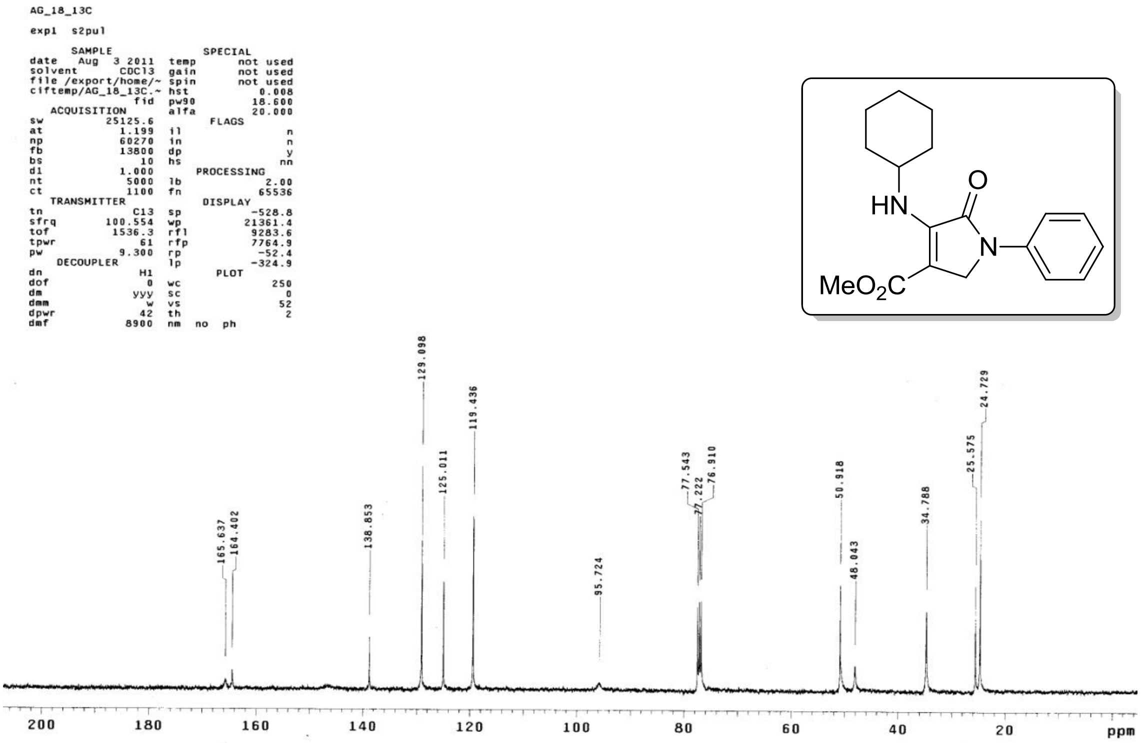
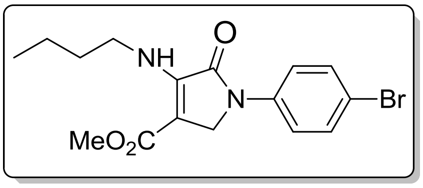
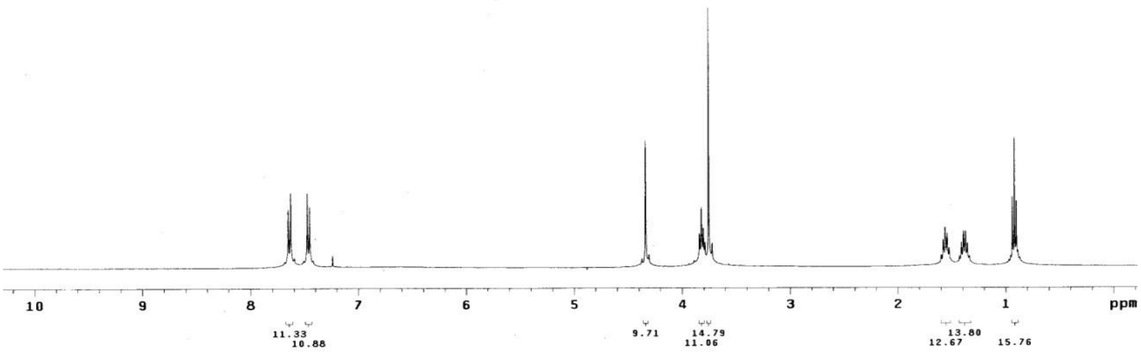

^{13}C NMR (100 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5l**):*


```
AG_18_13C

exp1  s2pul

      SAMPLE              SPECIAL
date   Aug  3 2011  temp      not used
solvent      CDCl3  gain      not used
file /export/home/~ spin      not used
ciftemp/AG_18_13C.~ hst          0.008
               fid  pw90        18.600
   ACQUISITION      alfa        20.000
sw         25125.6           FLAGS
at           1.199  il               n
np           60270  in               n
fb           13800  dp               y
bs              10  hs              nn
d1           1.000         PROCESSING
nt            5000  lb            2.00
ct            1100  fn           65536
   TRANSMITTER              DISPLAY
tn             C13  sp          -528.8
sfrq       100.554  wp         21361.4
tof         1536.3  rfl         9283.6
tpwr            61  rfp         7764.9
pw           9.300  rp           -52.4
    DECOUPLER       lp          -324.9
dn              H1            PLOT
dof              0  wc             250
dm             yyy  sc               0
dmm              w  vs              52
dpwr            42  th               2
dmf           8900  nm   no   ph
```

^{1}H NMR (400 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5q**):*

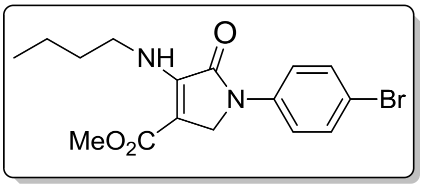
```
AG_22N

exp1  s2pul

       SAMPLE               SPECIAL
date   Aug  7 2011   temp       not used
solvent       CDC13  gain       not used
file /export/home/~  spin       not used
ciftemp/AG_22N.fid   hst           0.008
   ACQUISITION       pw90         19.700
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               64        PROCESSING
ct               64  lb             0.10
  TRANSMITTER        fn            65536
tn               H1         DISPLAY
sfrq        399.853  sp           -106.4
tof           362.8  wp           4223.4
tpwr             57  rfl          3698.1
pw            9.850  rfp          2894.9
    DECOUPLER        rp            117.8
dn              C13  lp            -84.0
dof               0           PLOT
dm              nnn  wc              250
dmm               c  sc                0
dpwr             50  vs               64
dmf           15900  th               11
                     nm  cdc  ph
```

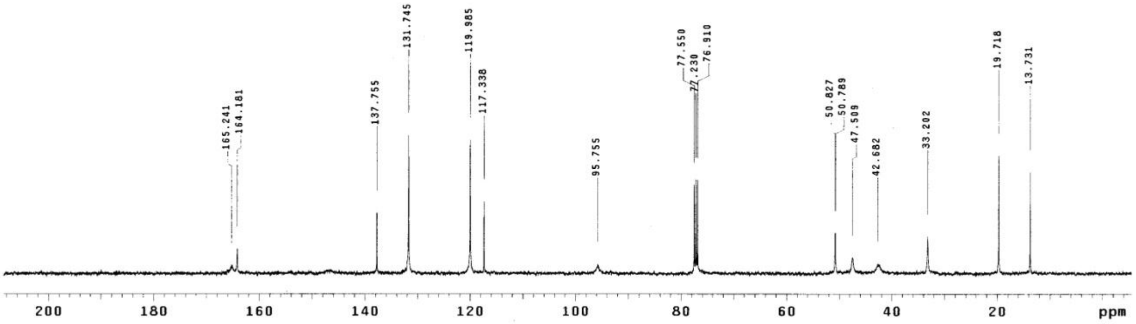




^{13}C **NMR (100 MHz, CDCl$_3$):** *dihydro-2-oxypyrrole derivative (**5q**):*

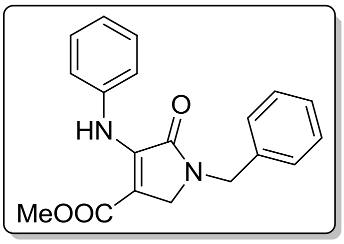
```
AG_22_13C

exp1  s2pul

       SAMPLE               SPECIAL
date   Aug  6 2011   temp       not used
solvent       CDC13  gain       not used
file /export/home/~  spin       not used
ciftemp/AG_22_13C.~  hst           0.008
                fid  pw90         18.600
   ACQUISITION       alfa         20.000
sw          25125.6          FLAGS
at            1.199  il                n
np            60270  in                n
fb            13800  dp                y
bs               10  hs               nn
d1            1.000        PROCESSING
nt             5000  lb             2.00
ct              670  fn            65536
   TRANSMITTER              DISPLAY
tn              C13  sp           -548.7
sfrq        100.554  wp          21508.6
tof          1536.3  rfl          9296.6
tpwr             61  rfp          7764.9
pw            9.300  rp            -48.7
    DECOUPLER        lp           -328.4
dn               H1           PLOT
dof               0  wc              250
dm              yyy  sc                0
dmm               w  vs               32
dpwr             42  th                1
dmf            8900  nm  no  ph
```

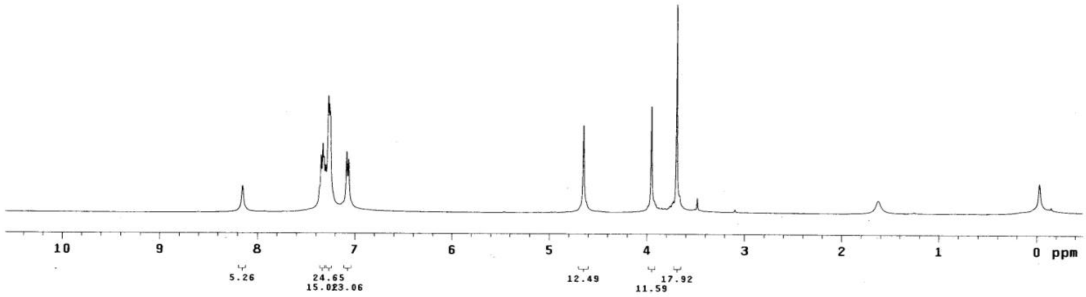




^{1}H NMR (400 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5r**):*

```
AG_Last

expl  s2pul

       SAMPLE              SPECIAL
date   Nov 17 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              64  hs                nn
ct              64       PROCESSING
   TRANSMITTER      lb              0.10
tn              H1  fn             65536
sfrq       399.853         DISPLAY
tof          362.8  sp            -190.3
tpwr            57  wp            4424.9
pw           9.850  rfl            794.8
    DECOUPLER       rfp                0
dn             C13  rp             107.0
dof              0  lp             -88.7
dm             nnn          PLOT
dmm              c  wc               250
dpwr            50  sc                 0
dmf          15900  vs               120
                    th                20
                    nm  cdc  ph
```





^{13}C NMR (100 MHz, CDCl$_3$): *dihydro-2-oxypyrrole derivative (**5r**):*

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AG_Last_13C

expl  s2pul

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file           exp  spin        not used
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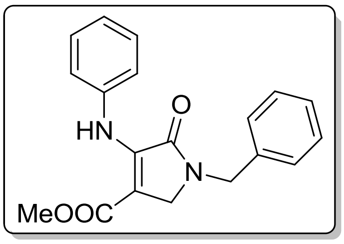
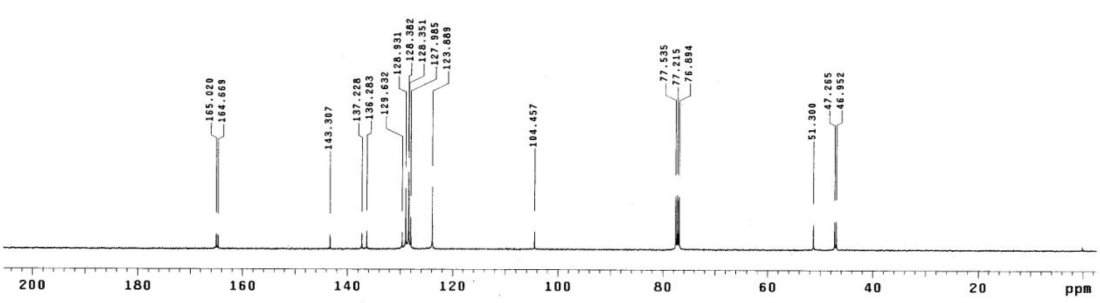
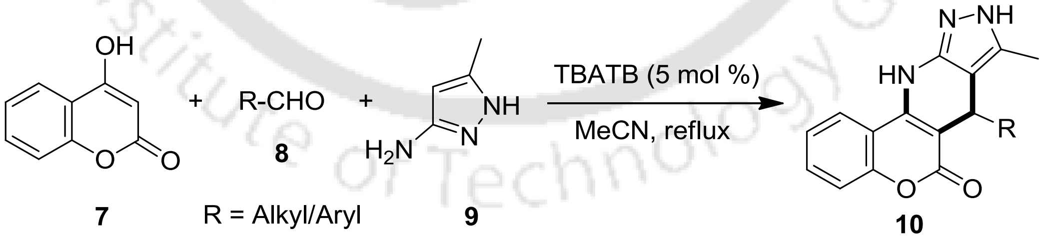




3.1. Results and Discussion

The importance and synthetic strategies of fused pyrazolo-pryidine derivatives were discussed in Chapter 1 of Part B. In this chapter, we would like to present *n*-tetrabutylammonium tribromide (TBATB) catalyzed synthesis of densely functionalized dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones from aldehydes, 4-hydroxycoumarin and 3-amino-5-methyl-pyrazoles using MCRs strategy. A few years ago, Chaudhuri *et al.* reported environmentally benign synthesis of *n*-tetrabutylammonium tribromide (TBATB), a useful brominating reagent for various organic substrates.[62] Because of its unique catalytic activity, stability and ease of handling, it has been exploited for various organic transformations: cleavage of dithioacetals[63a] and *tert*-butyldimethylsilyl (TBDMS) ethers;[63b] chemoselective acetalization of carbonyl compounds;[63c] interconversion of carbonyl compounds into oxathioacetals and vice-versa;[63d] *o*-isopropylidenation of sugars;[63e] bromodeboronation of organotrifluoroborates[64a] and synthesis of naturally occurring aurones flavones from 2'-acetoxychalcone derivatives.[64b] The catalytic activity of TBATB has also been exploited for a diverse range of multicomponent reactions[65a] for the synthesis of various heterocycles.[65b,c]

We conceived that it can be further utilized for one-pot synthesis of the substituted dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one derivatives from 4-hydroxy coumarin, aldehydes and 3-amino-5-methyl-pyrazole involving MCRs strategy (Scheme 34).

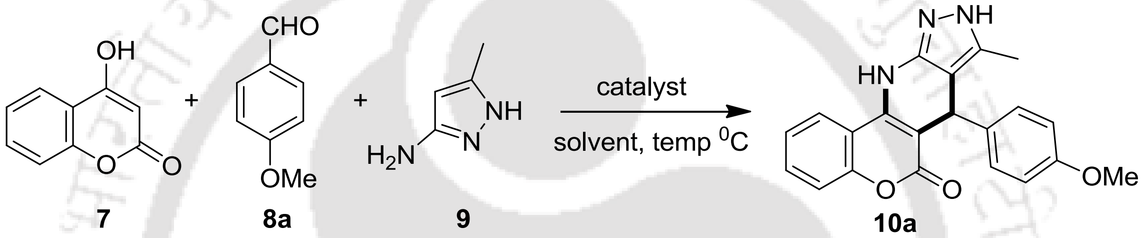


Scheme 34. Synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones

A mixture of 4-hydroxycoumarin (1 mmol), 4-methoxybenzaldehyde (1 mmol) and 3-amino-5-methyl-pyrazole (1 mmol) in acetonitrile was stirred at room temperature for 24 hours without any catalyst and no product formation was observed. However on refluxing in acetonitrile and ethanol provided the desired product in 45% and 42% yield, respectively (Entry 2 and 3, Table 4). Remarkably, when the same reaction mixture was refluxed in presence of 5 mol % of TBATB, it afforded product **10a** in 84% yield (Entry

4, Table 4) as characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra as well as elemental analysis. It was also noted that the yield did not improve significantly in presence of 10 mol % TBATB (Entry 5, Table 4). Different solvents MeOH, EtOH, and DMF (Entries 6-8, Table 4) were scrutinized to find out a suitable solvent for the above transformation. Likewise, various catalysts were also examined for the same reaction such as 33% HBr in AcOH, BDMS and NBS (Entries 9-11, Table 4) to verify the efficacy of the catalysts in terms of yield and reaction time. From these observations, it is found that 5 mol % TBATB in acetonitrile under reflux condition was the most suitable reaction condition for this transformation (Table 4).

Table 5. Optimization of the reaction conditions



Entry	Catalyst	Mol %	Temp (^{0}C)	Solvent	Time (h)	Yield (%)^b
1	-	-	rt	MeCN	24	-
2	-	-	80	MeCN	6.0	45
3	-	-	80	EtOH	6.0	42
4	**TBATB**	**5**	**80**	**MeCN**	**0.5**	**85**
5	TBATB	10	80	MeCN	4.0	76
6	TBATB	5	65	MeOH	4.0	68
7	TBATB	5	80	EtOH	4.0	65
8	TBATB	5	150	DMF	6.0	35
9	HBr	5	80	MeCN	8.0	72
10	BDMS	5	80	MeCN	6.0	74
11	$NiCl_2$	5	80	MeCN	6.0	50
12	$ZnCl_2$	5	80	MeCN	6.0	52
13	$FeCl_3$	5	80	MeCN	6.0	50
14	NH_4Cl	5	80	MeCN	6.0	60

[a]The reaction was performed using (1mmol) 4-hydroxycoumarin (1mmol), 4-methoxybenzaldehyde (1mmol), 3-amino-5-methyl pyrazole(1mmol). [b]Isolated yield.

Having optimized the reaction conditions, the reaction mixture of 4-hydroxycoumarin (1 mmol), benzaldehyde (1 mmol) and 3-amino-5-methyl-pyrazole (1 mmol) was refluxed in presence of 5 mol % TBATB and the desired product **10b (**Table 5**)** was obtained in 78% yield. A wide variety of aromatic aldehydes having electron-withdrawing substituents such as F, Cl, Br, CN and NO_2 at the different position on the aromatic ring were examined with 4-hydroxycoumarin and 3-amino-5-methyl-pyrazole under identical conditions and the corresponding dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one derivatives (**10c-l)** were isolated in moderate to good yields (Table 5). The reaction was also carried out with various aldehydes having electron-donating substituents such as Me, OMe and OH group at the different positions on aromatic ring and the corresponding dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one derivatives (**10m-q)** were isolated in good yields (Table 5). Subsequently, heteroaromatic aldehyde such as thiophene-2-aldehyde was also examined with 4-hydroxycoumarin (**7**) and 3-amino-5-methyl-pyrazole (**9**) under identical reaction condition and the desired product **10r** was isolated in 78% yield (Table 5). Next, our protocol was further verified with various aliphatic aldehydes namely cyclohexylcarboxaldehyde, butyraldehyde and isovaleraldehyde and the desired products **10s-t** were obtained in 30-40% yield (Table 6).

All the products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR, HRMS and elemental analyses. In addition, the structure of **10o** was also confirmed by X-ray crystallographic data (Figure 10).

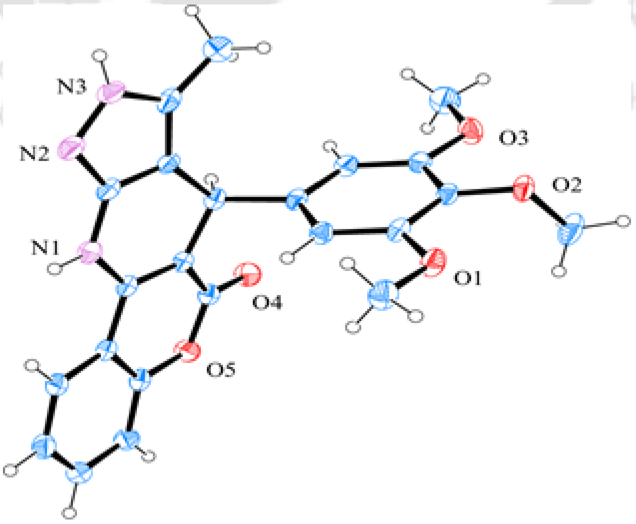
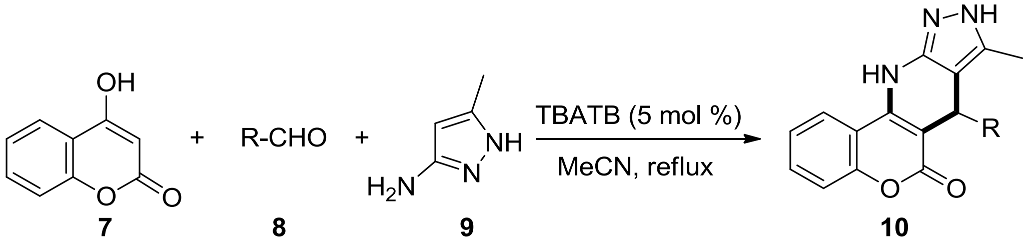
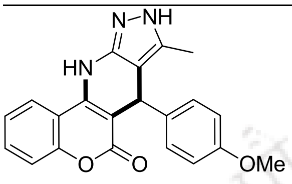
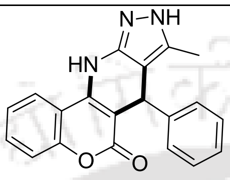


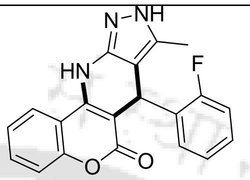
Figure 10. ORTEP structure of compound **10o** (CCDC No. 958056)

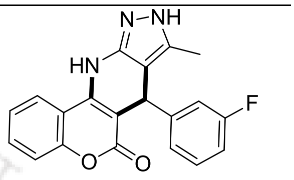
Table 6. Synthesis of various dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones

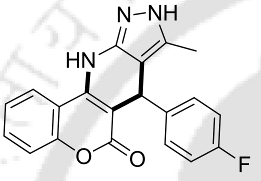


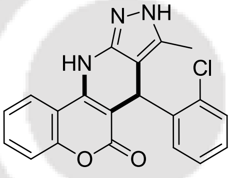

10a (0.5 h, 84%)

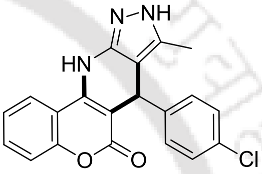

10b (0.25 h, 78%)[c]

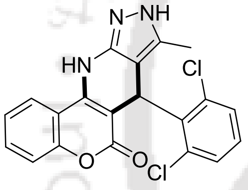

10c (2 h, 64%)

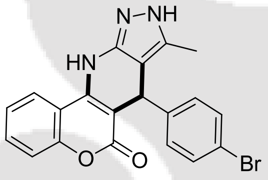

10d (2 h, 70%)

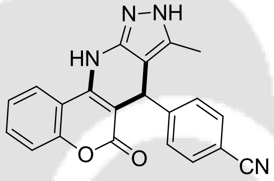

10e (1 h, 74%)

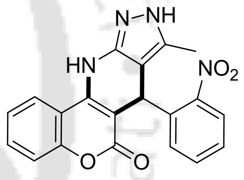

10f (1 h, 70%)

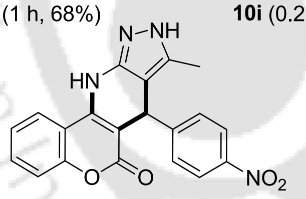

10g (0.25 h, 76%)

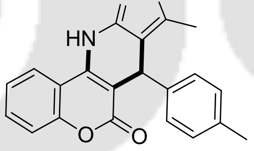

10h (1 h, 68%)

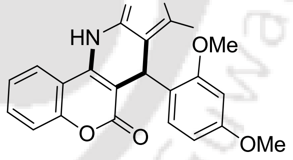

10i (0.25 h, 74%)

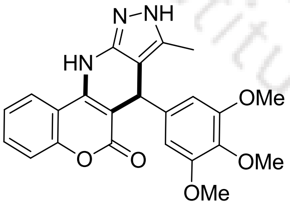

10j (0.25 h, 72%)

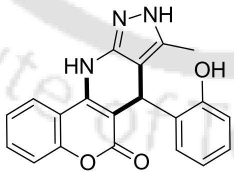

10k (1 h, 70%)

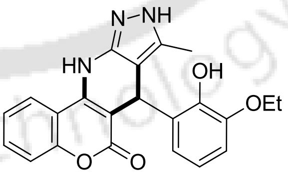

10l (0.5 h, 72%)

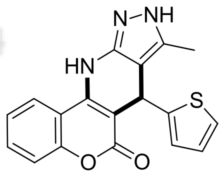

10m (0.5 h, 80%)

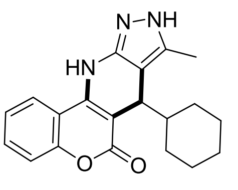

10n (0.5 h, 72%)

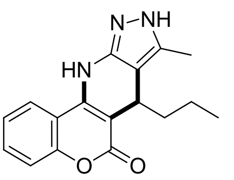

10o (0.75 h, 78%)

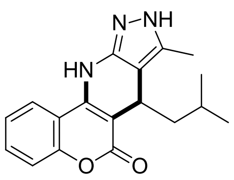

10p (0.5 h, 76%)


10q (0.5 h, 74%)


160r (1 h, 78%)

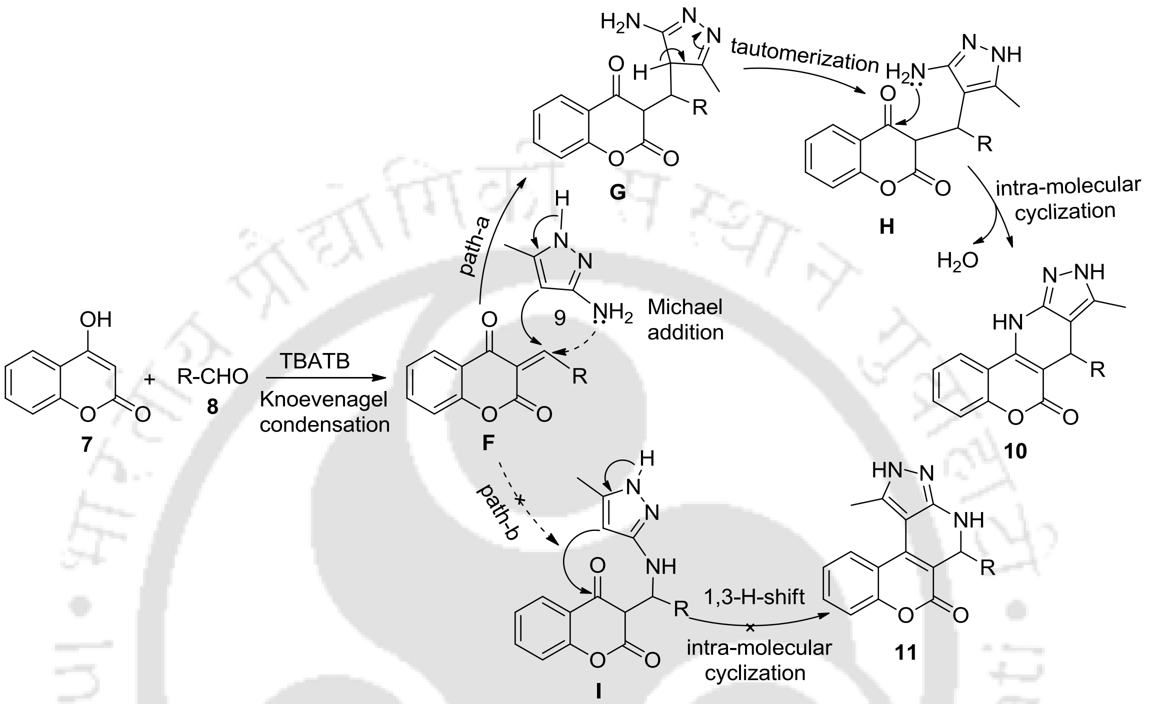

10s (9 h, 40%)


10t (3 h, 30%)[c]


10u (2.5 h, 35%)

[a]All the reactions were carried out in 1 mmol scale using 4-hydroxycoumarin, aldehyde and 3-amino-5-methyl pyrazole (1:1:1).[b] Isolated yield. [c]Yield after recrystallization.

A plausible mechanism for the formation of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one may be explained as: we believe that 4-hydroxycoumarin reacts with aldehyde to give a Knoevenagel intermediate **A**. There can be two possible mechanistic pathways (Scheme 35).



Scheme 35. Plausible mechanism for the formation dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one

In '*path a*', the intermediate **F** reacts with 3-amino-5-methyl-pyrazole (**9**) through Michael addition reaction to afford intermediate **G,** which undergoes concomitant tautomerization (**H**) followed by intra-molecular cyclization to give desired dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one derivatives **10** (Scheme 35). Alternatively, in *'path b'*, 3-amino-5-methyl-pyrazole (**9**) may also react with the intermediate **F** via 1,4 addition reaction to generate intermediate **I**, which undergoes concomitant intra-molecular cyclization and tautomerization to afford the product **11**. However, we did not observe the formation of product **11** as it is going through preferably attack by C-nucleophile site of 3-amino-5-methyl-pyrazole.

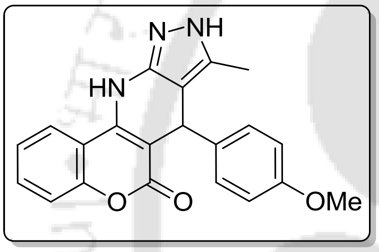
In conclusion, we have demonstrated a mild and efficient TBATB catalyzed synthesis of functionalized dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones using one-pot three-component reaction of 4-hydroxycoumarin, aldehydes and 3-amino-5-methyl-pyrazole. The advantage of the present protocol is simple experimental procedure, shorter reaction time, avoidance of tedious work-up, superior atom-economy and good yields. Moreover, the aliphatic aldehydes gave the desired dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones, which was unsuccessful in the earlier reported methods.

3.2. Experimental Section

General procedure for dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one ***(10)***:

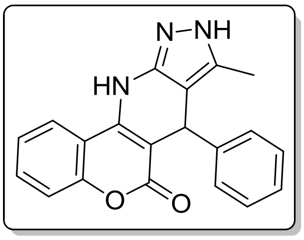
Into an oven dried 25 mL two necked round bottomed flask fitted with a reflux condenser was taken a mixture of 4-hydroxycoumarin (0.162 g, 1.0 mmol), the corresponding aldehyde (1.0 mmol), 3-amino-5-methyl-pyrazole (0.097 g, 1.0 mmol) and TBATB (0.024 g, 0.05 mmol) in 3 mL of acetonitrile. Then, the reaction mixture was refluxed in a pre-heated oil-bath with constant stirring and the progress of the reaction was monitored by TLC. The solid precipitate appeared at the end of the reaction. The precipitate was just filtered through a Büchner funnel and it was washed with 1 mL of acetonitrile. Finally it was dried under reduced pressure.

7-(4-methoxyphenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (***10a***):



White solid: (0.301 g, 84%); m.p. 256-258 °C; IR (KBr): 1612, 1670, 3076, 3254 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.96 (s, 3H), 3.65 (s, 3H), 5.08 (s, 1H), 6.77 (d, *J* = 6.4 Hz, 2H), 7.11 (d, *J* = 6.4 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.57 (s, 1H), 8.36 (d, *J* =6.8 Hz, 1H), 10.48 (s, 1H), 12.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.39, 35.85, 54.90, 97.42, 102.83, 113.37, 114.11, 116.59, 123.09, 123.70, 128.41, 131.49, 135.08, 139.38, 144.40, 145.84, 152.09, 157.38, 160.78; Anal Calcd. $C_{21}H_{17}N_3O_3$ (359.378): requires C, 70.18; H, 4.77; N, 11.69 %. Found C, 70.07; H, 4.69; N, 11.58 %. HRMS (ESI) calcd for $C_{21}H_{17}N_3O_3$ (M + H+) 360.1343, found 360.1342.

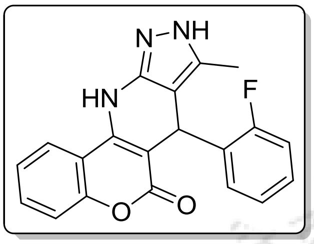
8-methyl-7-phenyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (***10b***):



White solid: (0.257 g, 78%); m.p. 304-306 °C; IR (KBr): 1614, 1669, 3082, 3173 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.95 (s, 3H), 5.12 (s, 1H), 7.18-7.23 (m, 3H), 7.31-7.39 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.58-7.64 (m, 1H), 7.93-7.95 (m, 1H), 8.35 (d, *J* = 6.8 Hz, 1H), 10.50 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.48, 36.85, 97.15, 102.68, 114.10, 116.72, 123.86, 125.97, 127.49, 128.13, 128.65, 129.35, 131.70, 132.96, 135.31, 144.82, 145.82, 147.16, 152.18, 160.89; Anal Calcd. $C_{20}H_{15}N_3O_2$ (329.352): requires C, 72.94; H, 4.59; N, 12.76 %.

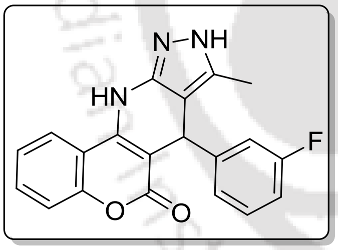
Found C, 72.80; H, 4.50; N, 12.66 %. HRMS (ESI) calcd for $C_{20}H_{15}N_3O_2$ (M + H+) 330.1237, found 330.1236.

7-(2-fluorophenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (***10c***):



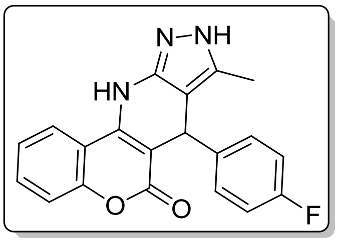
White solid: (0.222 g, 64%); m.p. 326-328 °C; IR (KBr): 1614, 1669, 2913, 3074, 3203 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.95 (s, 3H), 5.41 (s, 1H), 7.01-7.09 (m, 2H), 7.13-7.21 (m, 2H), 7.32 (d, *J* = 8.0 Hz ,1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 10.56 (s, 1H), 12.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.10, 30.50, 95.68, 101.54, 113.99, 114.94, 115.16, 116.70, 123.18, 123.79, 124.41, 127.89, 130.04, 131.68, 133.55, 133.68, 135.28, 145.37, 145.85, 152.21, 158.02, 160.70; Anal Calcd. $C_{20}H_{14}FN_3O_2$ (347.3425): requires C, 69.16; H, 4.06; N, 12.10 %. Found C, 69.05; H, 3.91; N, 11.98 %. HRMS (ESI) calcd for $C_{20}H_{14}FN_3O_2$ (M + H+) 348.1143, found 348.1144.

7-(3-fluorophenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (***10d***):



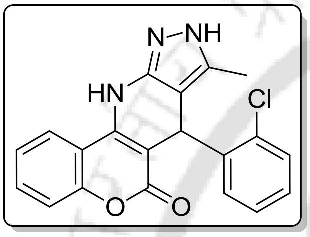
White solid: (0.243 g, 70%); m.p. 329-330 °C; IR (KBr) 1615, 1673, 3076, 3284 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ1.98 (s, 3H), 5.20 (s, 1H), 6.92 (t, *J* = 8.4Hz, 1H), 7.02-7.06 (m, 2H), 7.22-7.27 (m, 1H), 7.30-7.36 (m, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 10.57 (s, 1H), 12.11 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.45, 36.69, 96.52, 102.05, 112.58, 112.79, 114.03, 114.29, 116.67, 123.23, 123.60, 123.77, 129.90, 129.98, 131.67, 135.45, 144.96, 145.78, 149.96, 152.18, 160.86, 163.27; Anal Calcd. $C_{20}H_{14}FN_3O_2$ (347.3425): requires C, 69.16; H, 4.06; N, 12.10 %. Found C, 69.09; H, 4.00; N, 11.95 %. HRMS (ESI) calcd for $C_{20}H_{14}FN_3O_2$ (M + H+) 348.1143, found 348.1148.

7-(4-fluorophenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (***10e***):



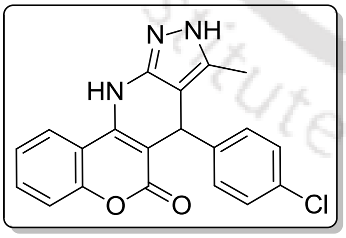
White solid: (0.257 g, 74%); m.p. 360-362 °C; IR (KBr): 1612, 1665, 2915, 3072, 3199 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.95 (s, 3H), 5.16 (s, 1H), 7.02 (t, *J* = 8.4 Hz , 2H), 7.24 (t, *J* = 6.0 Hz , 2H), 7.29 (d, *J* = 8.4 Hz , 1H), 7.34-7.36 (m, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 8.37 (d, *J* = 7.6 Hz, 1H), 10.53 (s, 1H), 12.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.40, 36.14, 97.00, 102.47, 114.07, 114.59, 114.80, 116.66, 123.19, 123.77, 129.23, 129.31, 131.62, 135.32, 143.32, 144.73, 145.81, 152.17, 159.31, 160.85; Anal Calcd. $C_{20}H_{14}FN_3O_2$ (347.3425): requires C, 69.16; H, 4.06; N, 12.10 %. Found C, 69.07; H, 4.01; N, 11.97 %. HRMS (ESI) calcd for $C_{20}H_{14}FN_3O_2$ (M + H+) 348.1143, found 348.1146.

7-(2-chlorophenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (***10f***):



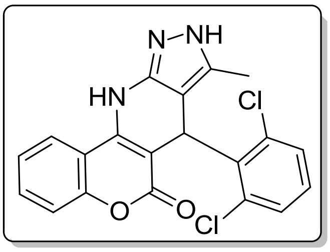
White solid: (0.263 g, 70%); m.p. 336-337 °C; IR (KBr): 1610, 1707, 3074, 3207 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.94 (s, 3H), 5.58 (s, 1H), 7.09-7.20 (m, 3H), 7.29-7.37 (m, 3H), 7.56 (t, *J* = 7.6 Hz, 1H), 8.38 (d, *J* = 7.6 Hz, 1H), 10.55 (s, 1H), 12.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.56, 34.37, 96.42, 101.74, 113.95, 116.66, 123.21, 123.77, 127.42, 127.56, 128.96, 130.74, 131.45, 131.67, 135.46, 144.27, 145.32, 145.87, 152.24, 160.62; Anal Calcd. $C_{20}H_{14}ClN_3O_2$ (363.797): requires C, 66.03; H, 3.88; N, 11.55 %. Found C, 65.90; H, 3.79; N, 11.47 %. HRMS (ESI) calcd for $C_{20}H_{14}ClN_3O_2$ (M + H+) 364.0847, found 364.0848.

7-(4-chlorophenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (***10g***):



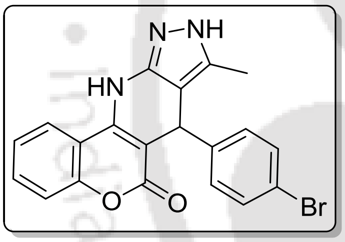
White solid: (0.284 g, 76%); m.p. 342-344 °C; IR (KBr): 1614, 1700, 2920, 3082, 3206 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.95 (s, 3H), 5.15 (s, 1H), 7.21-7.28 (m, 4H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 10.54 (s, 1H), 12.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.42, 36.29, 96.64, 102.12, 113.98, 116.72, 123.19, 123.85, 128.04, 129.36, 130.40, 131.77, 135.40, 144.87, 145.73, 146.04, 152.15, 160.81; Anal Calcd. $C_{20}H_{14}ClN_3O_2$ (363.797): requires C, 66.03; H, 3.88; N, 11.55 %. Found C, 65.92; H, 3.78; N, 11.45 %. HRMS (ESI) calcd for $C_{20}H_{14}ClN_3O_2$ (M + H+) 364.0847, found 364.0849.

*7-(2,6-dichlorophenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10h**)*:



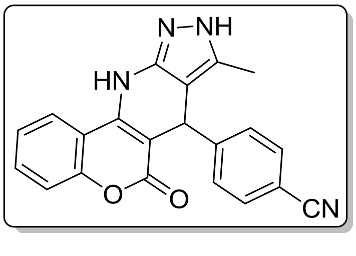
White solid: (0.271 g, 68%); m.p. 348-350 °C; IR (KBr): 1613, 1675, 2923, 3216, 3422 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.84 (s, 3H), 6.06 (s, 1H), 7.18-7.20 (m, 1H), 7.22-7.26 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 10.59 (s, 1H), 12.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.24, 34.03, 93.80, 98.96, 113.66, 116.70, 123.16, 123.84, 128.07, 128.51, 130.32, 131.82, 134.76, 135.30, 138.41, 146.41, 152.24, 160.33; Anal Calcd. $C_{20}H_{13}Cl_2N_3O_2$ (398.242): requires C, 60.32; H, 3.29; N, 10.55 %. Found C, 60.21; H, 3.20; N, 10.42 %. HRMS (ESI) calcd for $C_{20}H_{13}Cl_2N_3O_2$ (M + H+) 398.0458, found 398.0459.

*7-(4-bromophenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10i**)*:



Brown solid: (0.302 g, 74%); m.p. 309-310 °C; IR (KBr): 1611, 1667, 2910, 3068, 3192 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.95 (s, 3H), 5.13 (s, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.32-7.34 (m, 1H), 7.37-7.41 (m, 3H), 7.58-7.60 (m, 1H), 8.35 (d, *J* = 6.8 Hz, 1H), 10.53 (s, 1H), 12.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.48, 36.40, 96.63, 102.07, 114.00, 116.75, 118.94, 123.21, 123.90, 129.80, 130.99, 131.81, 135.48, 144.92, 145.70, 146.48, 152.18, 160.85; Anal Calcd. $C_{20}H_{14}BrN_3O_2$ (408.248): requires C, 58.84; H, 3.46; N, 10.29 %. Found C, 58.72; H, 3.38; N, 10.20 %. HRMS (ESI) calcd. for $C_{20}H_{14}BrN_3O_2$ (M + H+) 408.0342, 410.0342 found 408.0341, 410.0351.

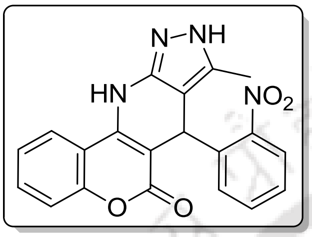
*4-(8-methyl-6-oxo-6,7,9,11-tetrahydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-7-yl)benzonitrile (**10j**)*:



White solid: (0.255 g, 72%); m.p. 375-376 °C; IR (KBr): 1613, 1665, 2229, 2916, 3072, 3202 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.93 (s, 3H), 5.24 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 8.36 (d, *J* = 8.0 Hz, 1H), 10.60 (s, 1H), 12.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ

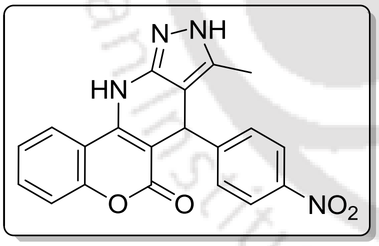
9.49, 37.21, 96.07, 101.59, 108.79, 113.96, 116.83, 119.08, 123.31, 123.99, 128.68, 131.97, 132.29, 135.74, 145.29, 145.73, 152.25, 152.49, 160.93; Anal Calcd. $C_{21}H_{14}N_4O_2$ (354.361): requires C, 71.18; H, 3.98; N, 15.81 %. Found C, 71.08; H, 3.87; N, 15.73 %. HRMS (ESI) calcd for $C_{21}H_{14}N_4O_2$ (M + H+) 355.1190, found 355.1188.

*8-methyl-7-(2-nitrophenyl)-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10k**)*:



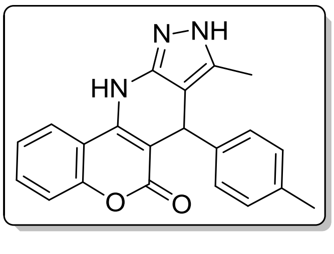
Yellow solid: (0.262 g, 70%); m.p. 327-328 °C; IR (KBr): 1359, 1527, 1616, 1664, 3419 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.99 (s, 3H), 5.80 (s, 1H), 7.25-7.38 (m, 4H), 7.52 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H), 10.67 (s, 1H), 12.21 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.46, 31.35, 96.97, 101.02, 113.81, 116.75, 122.98, 123.28, 123.90, 127.10, 131.64, 133.22, 135.88, 140.93, 144.56, 146.29, 148.52, 152.09, 160.86; Anal Calcd. $C_{20}H_{14}N_4O_4$ (374.349): requires C, 64.17; H, 3.77; N, 14.97 %. Found C, 64.10; H, 3.69; N, 14.86 %. HRMS (ESI) calcd for $C_{20}H_{14}N_4O_4$ (M + H+) 375.1088, found 375.1093.

*8-methyl-7-(4-nitrophenyl)-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10l**)*:



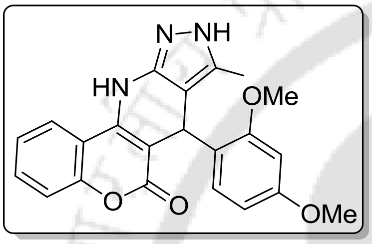
Yellow solid: (0.270 g, 72%); m.p. 365-367 °C; IR (KBr): 1346, 1510, 1615, 1666, 2910, 3074, 3200 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94 (s, 3H), 5.32 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 2H), 8.39 (d, J =8.0 Hz, 1H), 10.65 (s, 1H), 12.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.41, 36.98, 95.90, 101.32, 113.88, 116.72, 123.25, 123.47, 123.84, 128.77, 131.84, 135.70, 145.21, 145.71, 152.20, 154.42, 160.78; Anal Calcd. $C_{20}H_{14}N_4O_4$ (374.349): requires C, 64.17; H, 3.77; N, 14.97%. Found C, 64.06; H, 3.65; N, 14.88 %. HRMS (ESI) calcd for $C_{20}H_{14}N_4O_4$ (M + H+) 375.1088, found 375.1083.

*8-methyl-7-(p-tolyl)-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10m**)*:



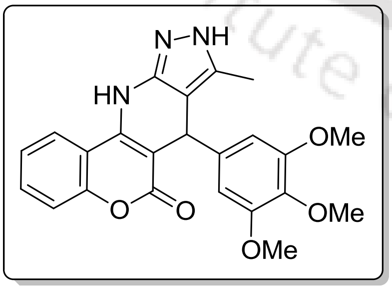
White solid: (0.274 g, 80%); m.p. 276-278 °C; IR (KBr): 1615, 1670, 2915, 3451 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.95 (s, 3H), 2.19 (s, 3H), 5.07 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 10.47 (s, 1H), 12.01 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.47, 20.62, 36.37, 97.29, 102.76, 114.11, 116.68, 123.13, 123.81, 127.35, 128.66, 131.62, 134.85, 144.25, 144.64, 152.14, 160.84; Anal Calcd. $C_{21}H_{17}N_3O_2$ (343.379): requires C, 73.45; H, 4.99; N, 12.24 %. Found C, 73.32; H, 4.90; N, 12.12 %. HRMS (ESI) calcd for $C_{21}H_{17}N_3O_2$ (M + H+) 344.1394, found 344.1395.

*7-(2,4-dimethoxyphenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10n**)*:



White solid: (0.280 g, 72%); m.p. 306-307 °C; IR (KBr): 1613, 1665, 3070, 3259 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.98 (s, 3H), 3.66 (s, 3H), 3.77 (s, 3H), 5.42 (s, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 6.49 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.31-7.38 (m, 2H), 7.56 (t, *J* = 8.0 Hz, 1H),8.38 (d, *J* = 8.0 Hz, 1H), 10.40 (s, 1H), 11.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.32, 29.65, 55.01, 55.58, 97.02, 98.34, 103.02, 105.03, 122.99, 123.66, 128.22, 128.99, 131.35, 134.76, 145.21, 146.05, 152.14, 156.55, 158.60, 160.59; Anal Calcd. $C_{22}H_{19}N_3O_4$ (389.404): requires C, 67.86; H, 4.92; N, 10.79 %. Found C, 67.70; H, 4.81; N, 10.70 %. HRMS (ESI) calcd for $C_{22}H_{19}N_3O_4$ (M + H+) 390.1448, found 390.1447.

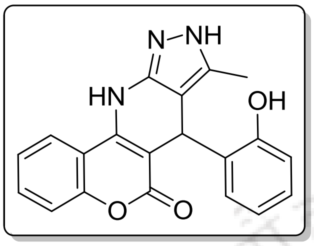
*8-methyl-7-(3,4,5-trimethoxyphenyl)-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10o**)*:



White solid: (0.326 g, 78%); m.p. 310-311 °C; IR (KBr): 1611, 1667, 2936, 3275, 3337 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 2.05 (s, 3H), 3.59 (s, 3H), 3.65 (s, 6H), 5.14 (s, 1H), 6.50 (s, 2H), 7.32-7.37 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 10.47 (s, 1H), 12.05 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.67, 37.07, 55.82, 59.92, 96.77, 102.40, 104.79, 114.08, 116.69, 123.17, 123.76, 131.61, 135.33, 135.87, 143.01, 144.89, 145.87, 152.17, 152.60, 160.94; Anal Calcd. $C_{23}H_{21}N_3O_5$ (419.430): requires C, 65.86; H, 5.05; N, 10.02 %. Found C, 65.72;

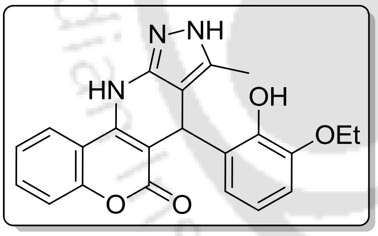
H, 4.90; N, 9.92 %. HRMS (ESI) calcd for $C_{23}H_{21}N_3O_5$ (M + H+) 420.1554, found 420.1554.

*7-(2-hydroxyphenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10p**)*:



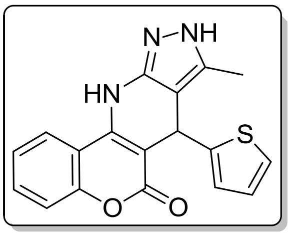
White solid: (0.262 g, 76%); m.p. 328-330 °C.; IR (KBr): 1613, 1671, 2905, 3076, 3209, 3447 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.00 (s, 3H), 5.44 (s, 1H), 6.60 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.88-6.92 (m, 2H), 7.32 (d, *J* =8.0 Hz, 1H), 7.36 (t, *J* =7.6 Hz, 1H), 7.59 (t, *J* =8.0 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 9.34 (s, 1H), 10.38 (s, 1H), 11.90 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.41, 30.26, 97.08, 103.00, 114.17, 115.30, 116.66, 119.13, 123.03, 123.77, 126.71, 128.93, 131.51, 133.73, 135.06, 145.33, 146.10, 152.13, 153.59, 160.86; Anal Calcd. $C_{20}H_{15}N_3O_3$ (345.351): requires C, 69.56; H, 4.38; N, 12.17 %. Found C, 69.42; H, 4.27; N, 12.10 %. HRMS (ESI) calcd for $C_{20}H_{15}N_3O_3$ (M + H+) 346.1186, found 346.1184.

*7-(3-ethoxy-2-hydroxyphenyl)-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10q**)*:



White solid: (0.288 g, 74%); m.p. 306-307 °C; IR (KBr): 1614, 1674, 3091, 3265, 3456 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.33 (t, *J* = 6.8 Hz, 3H), 2.00 (s, 3H), 3.95-3.99 (m, 2H), 5.48 (s, 1H), 6.49-6.57 (m, 2H), 6.66 (d, *J* = 7.6 Hz, 1H), 7.31-7.38 (m, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 8.33-8.36 (m, 2H), 10.38 (s, 1H), 11.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.47, 14.79, 30.25, 64.00, 97.09, 102.89, 110.13, 114.19, 116.67, 118.75, 120.78, 123.08, 123.79, 131.54, 133.94, 135.14, 142.87, 145.26, 146.10, 146.41, 152.14, 160.88; Anal Calcd. $C_{22}H_{19}N_3O_4$ (389.404): requires C, 67.86; H, 4.92; N, 10.79 %. Found C, 67.70; H, 4.85; N, 10.69 %. HRMS (ESI) calcd for $C_{22}H_{19}N_3O_4$ (M + H+) 390.1448, found 390.1453.

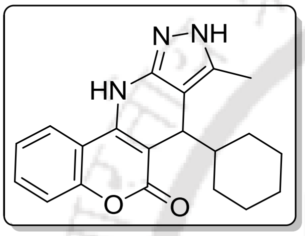
*8-methyl-7-(thiophen-2-yl)-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10r**)*:



White solid: (0.262 g, 78%); m.p. 344-345 °C; IR (KBr): 1613, 1666, 2907, 3071, 3192 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6):

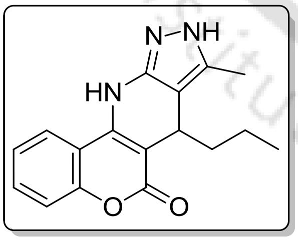
δ 2.09 (s, 3H), 5.51 (s, 1H), 6.84-6.88 (m, 2H), 7.20 (d, *J* = 4.8 Hz, 1H), 7.33-7.37 (m, 2H), 7.59 (t, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 2H), 10.58 (s, 1H), 12.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 9.47, 31.34, 96.66, 102.09, 114.01, 116.75, 123.16, 123.38, 123.83, 123.89, 126.52, 131.83, 135.55, 144.38, 145.78, 151.40, 152.05, 160.96; Anal Calcd. $C_{18}H_{13}N_3O_2S$ (335.380): requires C, 64.46; H, 3.91; N, 12.53%. Found C, 64.33; H, 3.84; N, 12.45 %. HRMS (ESI) calcd for $C_{18}H_{13}N_3O_2S$ (M + H+) 336.0801, found 336.0800.

7-cyclohexyl-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one ***(10s)***:



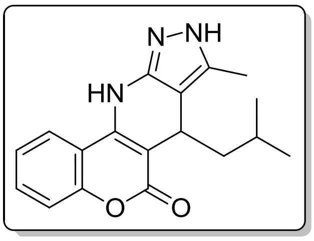
White solid: (0.134 g, 40%); m.p. 286-288 °C; IR (KBr): 1611, 1663, 2923, 3071, 3199 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 0.60-0.68 (m, 1H), 0.89-1.14 (m, 4H), 1.36-1.39 (m, 1H), 1.51-1.65 (m, 5H), 2.21 (s, 3H), 3.95 (s, 1H), 7.31-7.35 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 10.23 (s, 1H), 12.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 10.49, 25.87, 26.00, 26.23, 27.19, 30.66, 35.82, 45.07, 96.08, 99.75, 114.03, 116.63, 122.74, 123.70, 131.39, 134.61, 146.27, 148.12, 151.94, 161.23; Anal Calcd. $C_{20}H_{21}N_3O_2$ (335.400): requires C, 71.62; H, 6.31; N, 12.53 %. Found C, 71.51; H, 6.22; N, 12.44 %. HRMS (ESI) calcd for $C_{20}H_{21}N_3O_2$ (M + H+) 336.1707, found 336.1706.

8-methyl-7-propyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one ***(10t)***:



White solid: (0.89 g, 30%); m.p. 246-248 °C; IR (KBr): 1611, 1666, 2924, 3232, 3301 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 0.77 (t, *J* = 6.0 Hz, 3H), 1.02-1.09 (m, 2H), 1.67-1.71 (m, 2H), 2.20 (s, 3H), 4.10-4.12 (m, 1H), 7.30-7.34 (m, 2H), 7.82 (d, *J* = 6.6 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 10.21 (s, 1H), 11.98 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.68, 14.08, 17.88, 30.00, 37.97, 101.32, 113.97, 116.58, 119.86, 122.75, 123.18, 129.87, 132.69, 145.58, 146.15, 151.96, 161.01; Anal Calcd. $C_{17}H_{17}N_3O_2$ (295.3358): requires C, 69.14; H, 5.80; N, 14.23 %. Found C, 69.00; H, 5.65; N, 14.14 %. HRMS (ESI) calcd for $C_{17}H_{17}N_3O_2$ (M + H+) 296.1399, found 296.1416.

7-isobutyl-8-methyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one ***(10u)***:



White solid: (0.108 g, 35%); m.p. 272-274 °C; IR (KBr): 1612, 1662, 2922, 3069, 3199 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d$_6$): δ 0.76 (s, 3H), 0.84 (d, *J* = 6.0 Hz , 3H), 1.34-1.36 (m, 1H), 1.51-1.54 (m, 2H), 2.20 (s, 3H), 4.08-4.10 (m, 1H), 7.32-7.35 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 10.24 (s, 1H), 11.99 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$): δ 9.87, 22.39, 23.93, 24.09, 28.67, 45.99, 97.44, 102.06, 114.06, 116.58, 122.74, 123.66, 131.38, 134.50, 145.36, 146.89, 151.94, 161.04; Anal Calcd. $C_{18}H_{19}N_3O_2$ (309.3624): requires C, 69.88; H, 6.19; N, 13.58 %. Found C, 69.77; H, 6.05; N, 13.44 %. HRMS (ESI) calcd for $C_{18}H_{19}N_3O_2$ (M + H+) 310.1555, found 310.1556.

XRD for Compound **10o**

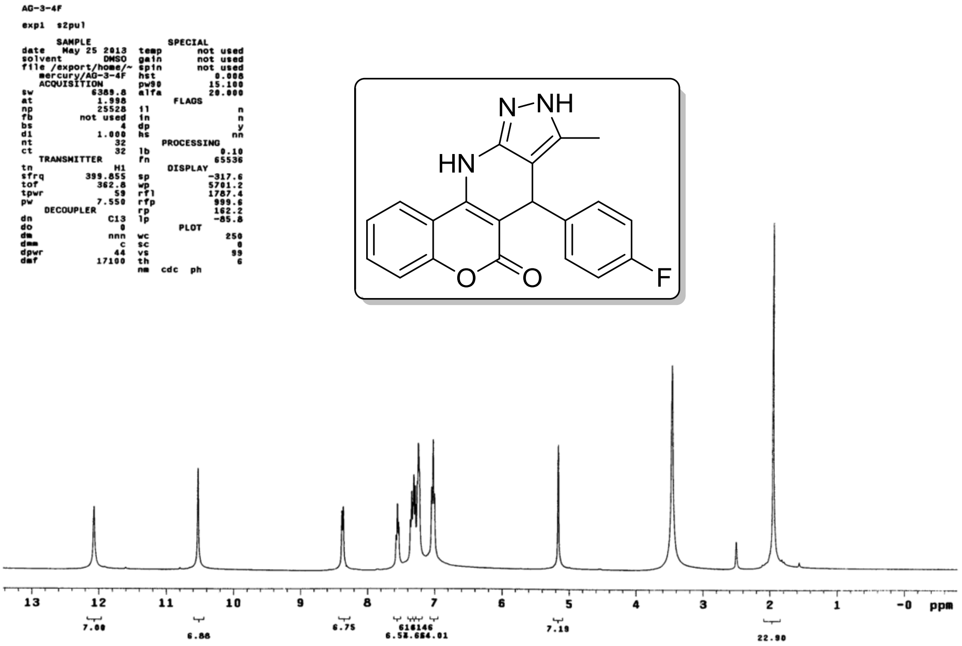
Complete crystallographic data of **10o** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 958056. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 7. Crystal data and structure refinement for **10o**, for atomic coordinates and equivalent isotopic displacement parameters and bond angles, please check the CIF

Parameters	**Compound**
Formula	$C_{23} H_{21} N_3 O_5$, $H_2 O$
CCDC number	958056
Formula weight	437.44
T (K)	296(2)
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	P -1
a (Å)	8.5797(4)
b (Å)	10.1030(4)
c (Å)	12.5931(5)

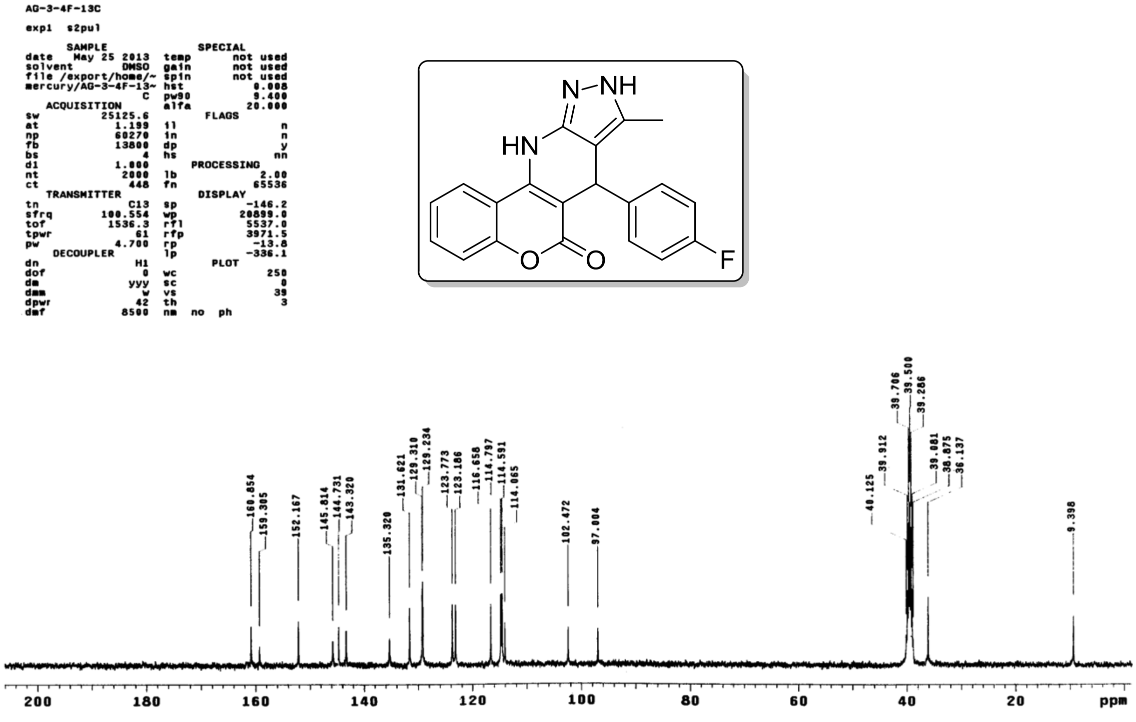
α (^{0})	81.982(2)
β (^{0})	75.433(2)
γ (^{0})	83.983(2)
V (Å)^3	1043.39(8)
Z	2
D_{calcd} (g m^{-3})	1.392
μ (mm^{-1})	0.102
F (0 0 0)	460
Reflection collected	12494
Unique reflections	2747
Goodness-of-fit (GOF)^a on F^2	1.090
R [I > 2σ(I)]	$^bR_1 = 0.0668$, $^cwR_2 = 0.1895$
R indices (all data)	$^bR_1 = 0.0865$, $^cwR_2 = 0.2288$

^{1}H **NMR (400 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* (***10e***):



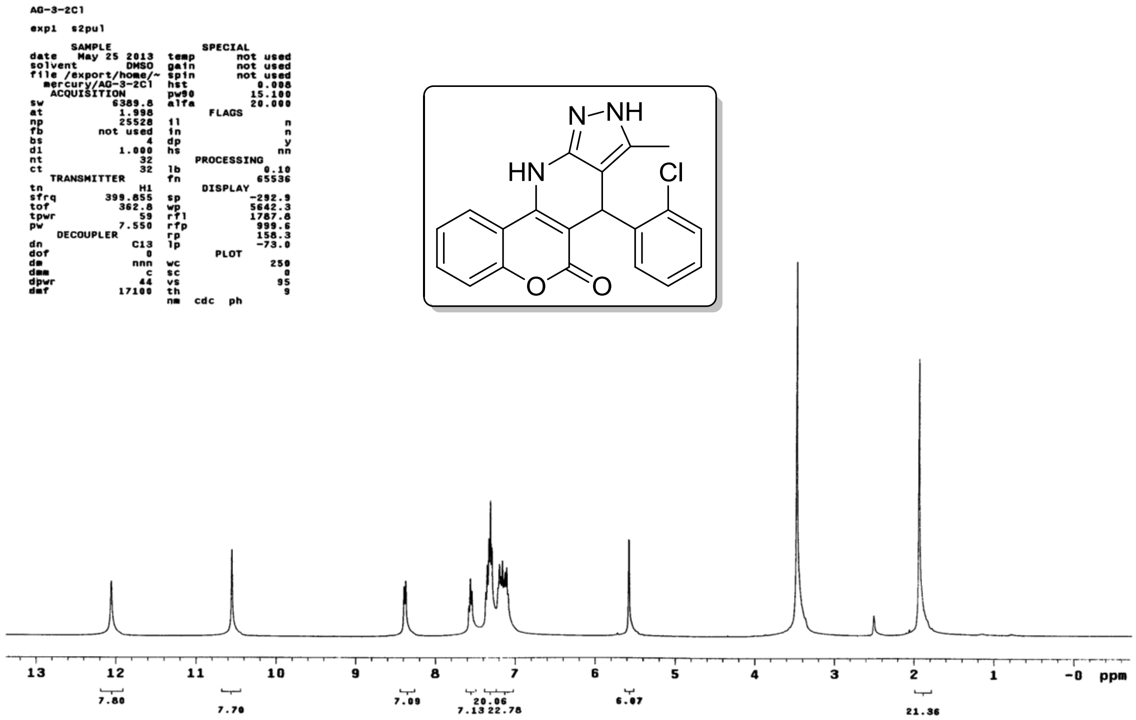
```
AG-3-4F

expl  s2pul

      SAMPLE                SPECIAL
date   May 25 2013  temp        not used
solvent       DMSO  gain        not used
file /export/home/~ spin        not used
   mercury/AG-3-4F  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       399.855  sp            -317.6
tof          362.8  wp            5701.2
tpwr            59  rfl           1787.4
pw           7.550  rfp            999.6
    DECOUPLER       rp             162.2
dn             C13  lp             -85.8
do               0           PLOT
dm             nnn  wc               250
dmm              c  sc                 0
dpwr            44  vs                99
dmf          17100  th                 6
                    nm   cdc   ph
```

^{13}C **NMR (100 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10e**)*:



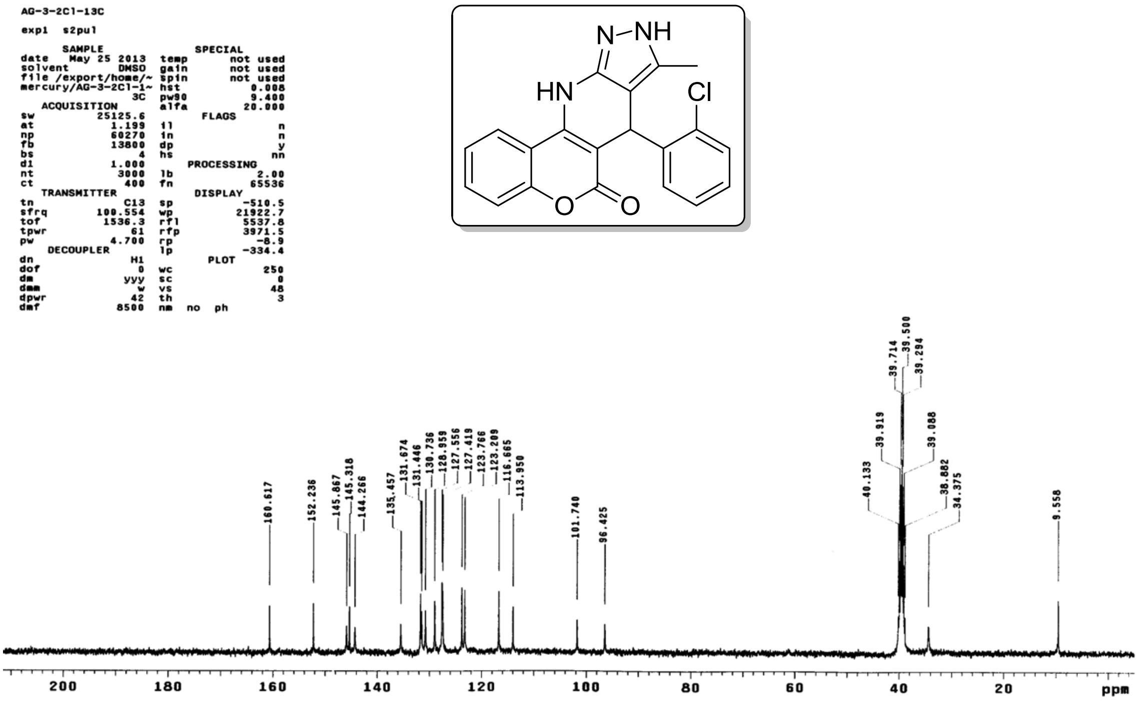
```
AG-3-4F-13C

expl  s2pul

      SAMPLE                SPECIAL
date   May 25 2013  temp        not used
solvent       DMSO  gain        not used
file /export/home/~ spin        not used
mercury/AG-3-4F-13~ hst            0.008
                 C  pw90           9.400
   ACQUISITION      alfa          20.000
sw         25125.6          FLAGS
at           1.199  il                 n
np           60270  in                 n
fb           13800  dp                 y
bs               4  hs                nn
d1           1.000        PROCESSING
nt            2000  lb              2.00
ct             448  fn             65536
   TRANSMITTER              DISPLAY
tn             C13  sp            -146.2
sfrq       100.554  wp           20899.0
tof         1536.3  rfl           5537.0
tpwr            61  rfp           3971.5
pw           4.700  rp             -13.8
    DECOUPLER       lp            -336.1
dn              H1           PLOT
dof              0  wc               250
dm             yyy  sc                 0
dmm              w  vs                39
dpwr            42  th                 3
dmf           8500  nm   no   ph
```

^{1}H **NMR (400 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* (***10f***):



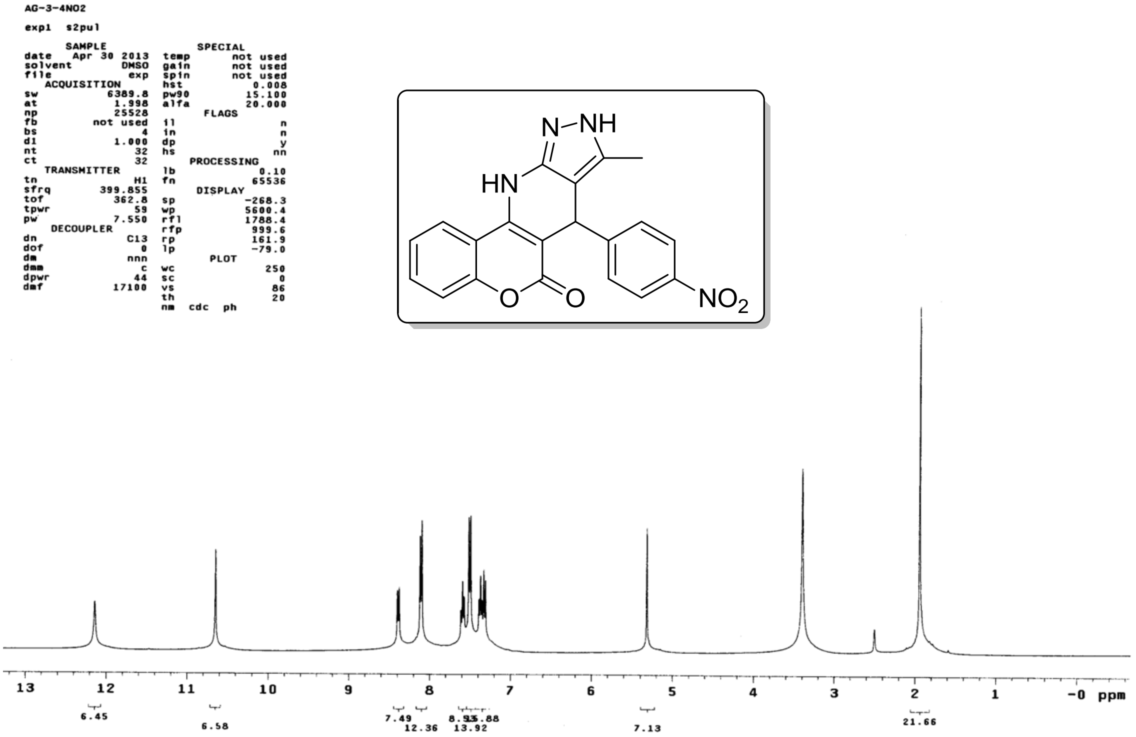
```
AG-3-2C1

expl   s2pul

         SAMPLE                     SPECIAL
date    May 25 2013   temp        not used
solvent        DMSO   gain        not used
file /export/home/~   spin        not used
  mercury/AG-3-2C1    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        399.855   sp            -292.9
tof           362.8   wp            5642.3
tpwr             59   rfl           1787.8
pw            7.550   rfp            999.6
     DECOUPLER        rp             158.3
dn              C13   lp             -73.0
dof               0             PLOT
dm              nnn   wc               250
dmm               c   sc                 0
dpwr             44   vs                95
dmf           17100   th                 9
                      nm   cdc   ph
```

^{13}C **NMR (100 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* ***(10f***):



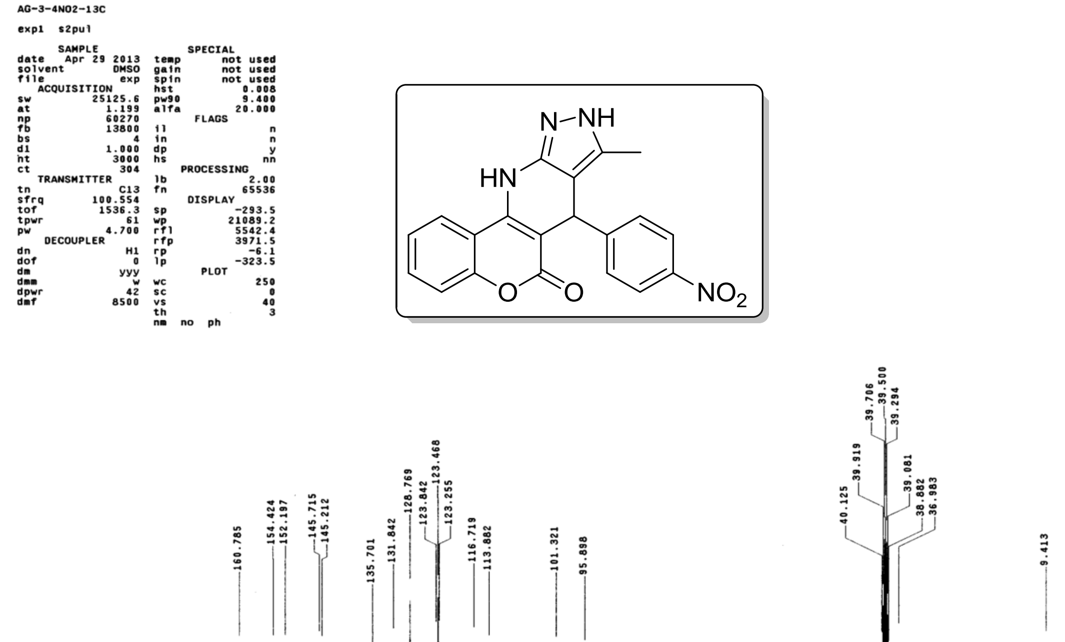
```
AG-3-2C1-13C

expl   s2pul

         SAMPLE                     SPECIAL
date    May 25 2013   temp        not used
solvent        DMSO   gain        not used
file /export/home/~   spin        not used
mercury/AG-3-2C1-1~   hst            0.008
                 3C   pw90           9.400
    ACQUISITION       alfa          20.000
sw          25125.6            FLAGS
at            1.199   il                 n
np            60270   in                 n
fb            13800   dp                 y
bs                4   hs                nn
d1            1.000         PROCESSING
nt             3000   lb              2.00
ct              400   fn             65536
    TRANSMITTER               DISPLAY
tn              C13   sp            -510.5
sfrq        100.554   wp           21922.7
tof          1536.3   rfl           5537.8
tpwr             61   rfp           3971.5
pw            4.700   rp              -8.9
     DECOUPLER        lp            -334.4
dn               H1             PLOT
dof               0   wc               250
dm              yyy   sc                 0
dmm               w   vs                48
dpwr             42   th                 3
dmf            8500   nm   no   ph
```

^{1}H **NMR (400 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* (***10l***):



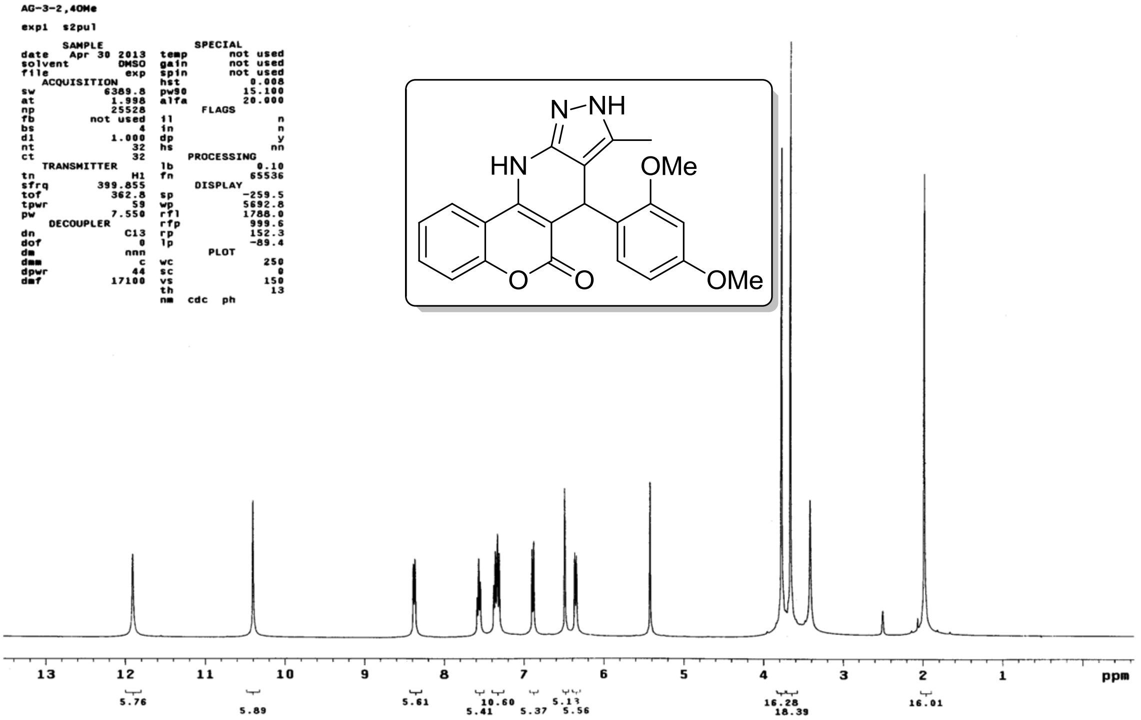
```
AG-3-4NO2

exp1  s2pul

      SAMPLE                  SPECIAL
date    Apr 30 2013   temp         not used
solvent        DMSO   gain         not used
file            exp   spin         not used
    ACQUISITION       hst             0.008
sw           6389.8   pw90           15.100
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        399.855          DISPLAY
tof           362.8   sp             -268.3
tpwr             59   wp             5600.4
pw            7.550   rfl            1788.4
     DECOUPLER        rfp             999.6
dn              C13   rp              161.9
dof               0   lp              -79.0
dm              nnn             PLOT
dmm               c   wc                250
dpwr             44   sc                  0
dmf           17100   vs                 86
                      th                 20
                      nm   cdc   ph
```

^{13}C **NMR (100 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* (***10l***):



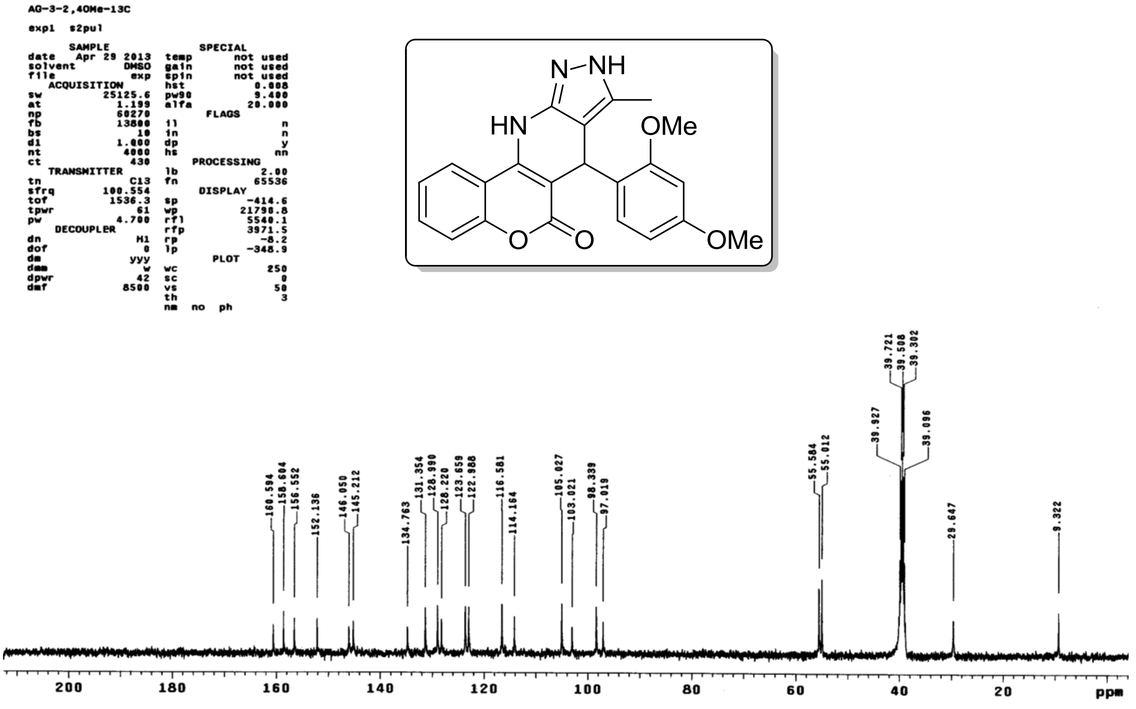
```
AG-3-4NO2-13C

exp1  s2pul

      SAMPLE                  SPECIAL
date    Apr 29 2013   temp         not used
solvent        DMSO   gain         not used
file            exp   spin         not used
    ACQUISITION       hst             0.008
sw          25125.6   pw90            9.400
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              304         PROCESSING
    TRANSMITTER       lb               2.00
tn              C13   fn              65536
sfrq        100.554          DISPLAY
tof          1536.3   sp             -293.5
tpwr             61   wp            21089.2
pw            4.700   rfl            5542.4
     DECOUPLER        rfp            3971.5
dn               H1   rp               -6.1
dof               0   lp             -323.5
dm              yyy             PLOT
dmm               w   wc                250
dpwr             42   sc                  0
dmf            8500   vs                 40
                      th                  3
                      nm   no   ph
```

^{1}H **NMR (400 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* (***10n***):



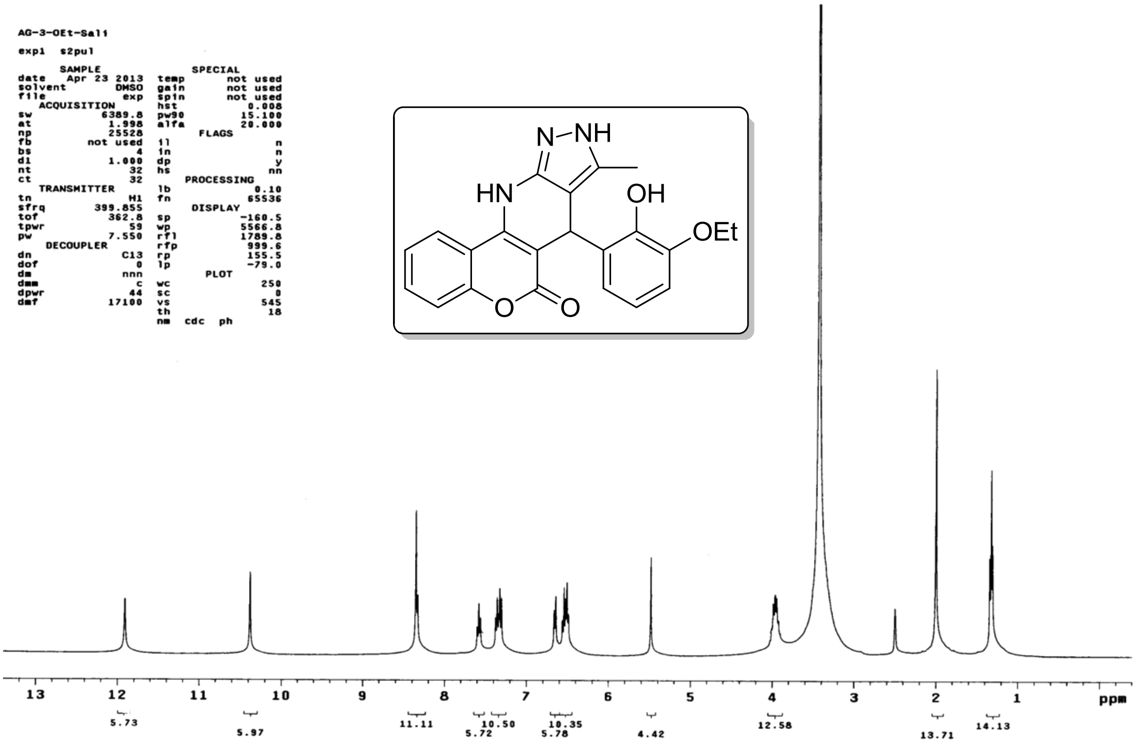
```
AG-3-2,4OMe

exp1  s2pul

      SAMPLE                  SPECIAL
date   Apr 30 2013   temp         not used
solvent       DMSO   gain         not used
file           exp   spin         not used
   ACQUISITION       hst             0.008
sw          6389.8   pw90           15.100
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       399.855         DISPLAY
tof          362.8   sp             -259.5
tpwr            59   wp             5692.8
pw           7.550   rfl            1788.0
    DECOUPLER        rfp             999.6
dn             C13   rp              152.3
dof              0   lp              -89.4
dm             nnn           PLOT
dmm              c   wc                250
dpwr            44   sc                  0
dmf          17100   vs                150
                     th                 13
                     nm   cdc   ph
```

^{13}C **NMR (100 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10n**)*:

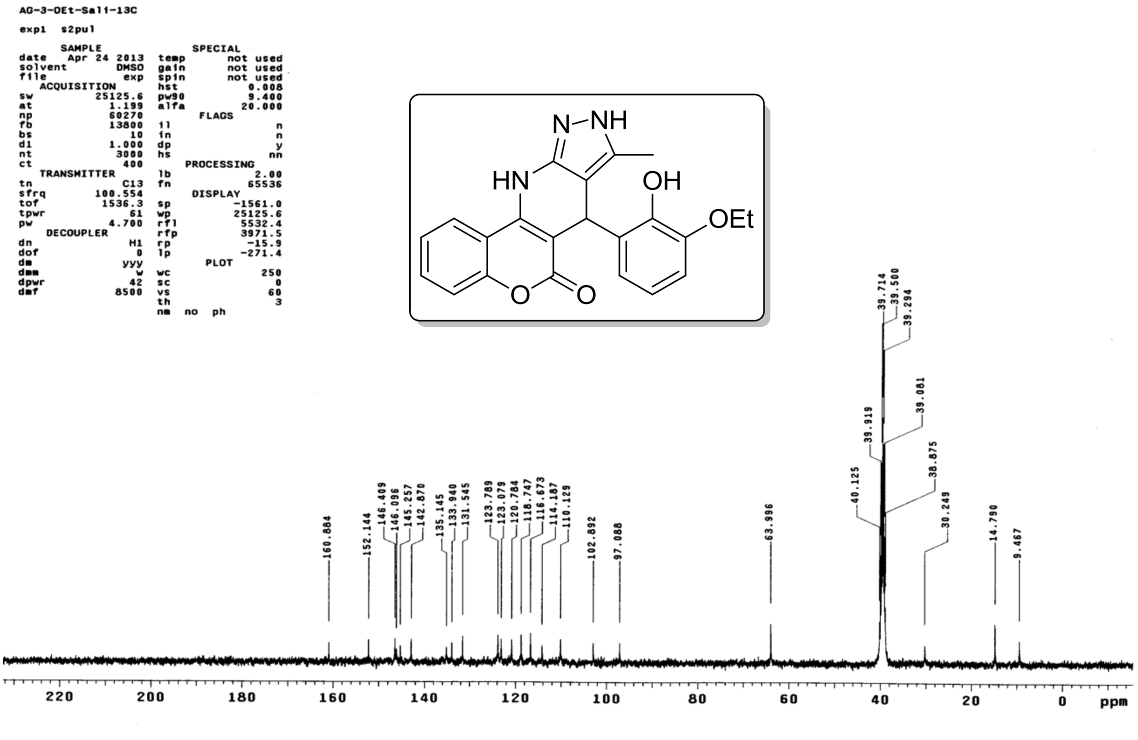


```
AG-3-2,4OMe-13C

exp1  s2pul

      SAMPLE                  SPECIAL
date   Apr 29 2013   temp         not used
solvent       DMSO   gain         not used
file           exp   spin         not used
   ACQUISITION       hst             0.008
sw         25125.6   pw90            9.400
at           1.199   alfa           20.000
np           60270          FLAGS
fb           13800   il                  n
bs              10   in                  n
d1           1.000   dp                  y
nt            4000   hs                 nn
ct             430        PROCESSING
   TRANSMITTER       lb               2.00
tn             C13   fn              65536
sfrq       100.554         DISPLAY
tof         1536.3   sp             -414.6
tpwr            61   wp            21790.8
pw           4.700   rfl            5540.1
    DECOUPLER        rfp            3971.5
dn              H1   rp               -8.2
dof              0   lp             -348.9
dm             yyy           PLOT
dmm              w   wc                250
dpwr            42   sc                  0
dmf           8500   vs                 50
                     th                  3
                     nm   no   ph
```

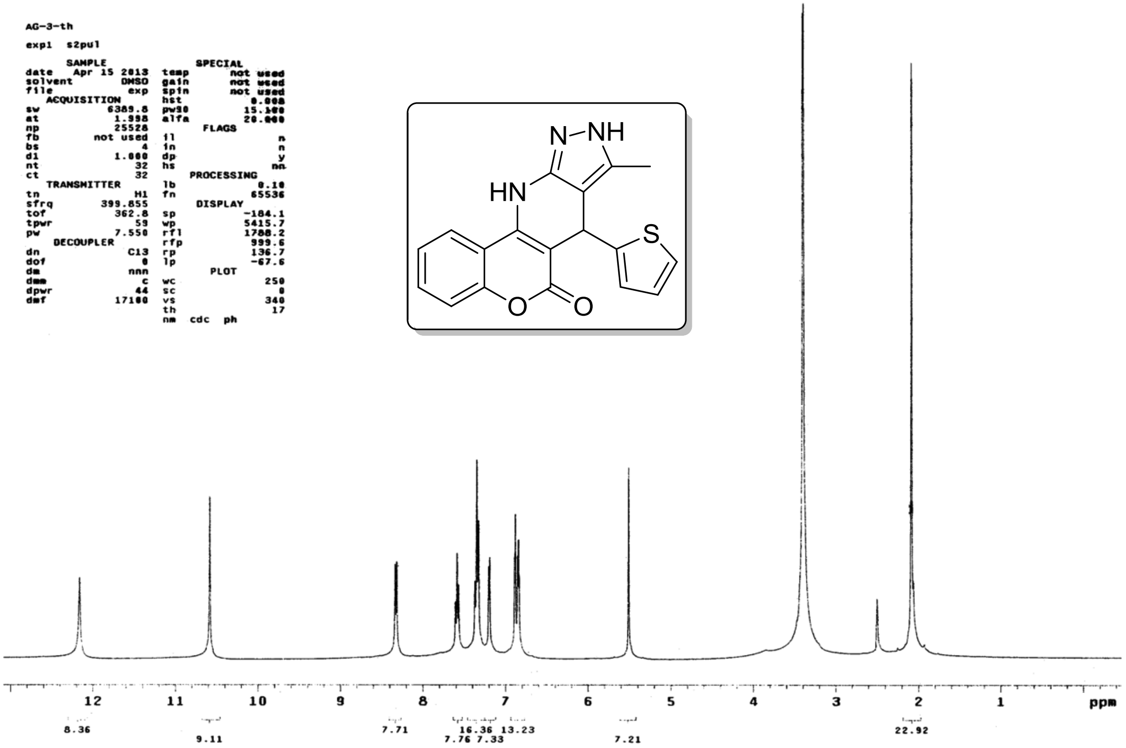
^{1}H **NMR (400 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* (***10q***):



^{13}C **NMR (100 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* (***10q***):

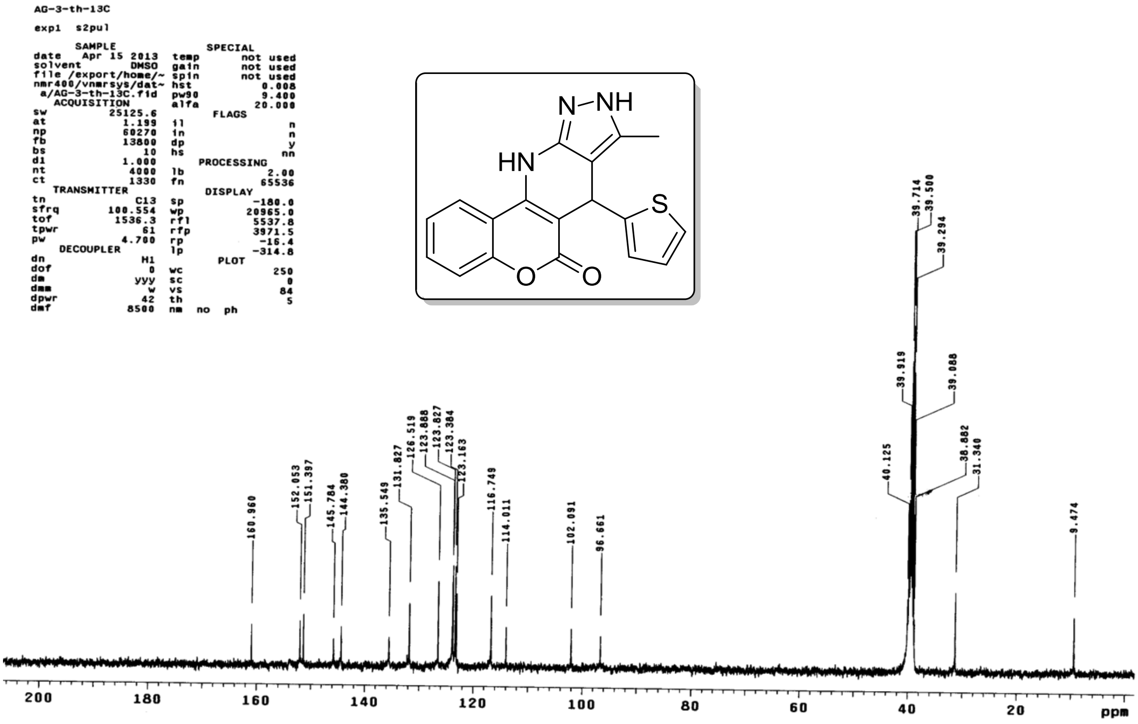


^{1}H **NMR (400 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one* (***10r***):



```
AG-3-th

exp1  s2pul

       SAMPLE                  SPECIAL
date   Apr 15 2013   temp        not used
solvent        DMSO  gain        not used
file            exp  spin        not used
   ACQUISITION       hst            0.008
sw           6389.8  pw90          15.100
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        399.855        DISPLAY
tof           362.8  sp            -184.1
tpwr             59  wp            5415.7
pw            7.550  rfl           1788.2
    DECOUPLER        rfp            999.6
dn              C13  rp             136.7
dof               0  lp             -67.6
dm              nnn          PLOT
dmm               c  wc               250
dpwr             44  sc                 0
dmf           17100  vs               340
                     th                17
                     nm   cdc   ph
```

^{13}C **NMR (100 MHz, DMSO-d$_6$):** *dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-6(7H)-one (**10r**)*:



```
AG-3-th-13C

exp1  s2pul

       SAMPLE                  SPECIAL
date   Apr 15 2013   temp        not used
solvent        DMSO  gain        not used
file /export/home/~  spin        not used
nmr400/vnmrsys/dat~  hst            0.008
 a/AG-3-th-13C.fid   pw90           9.400
   ACQUISITION       alfa          20.000
sw          25125.6         FLAGS
at            1.199  il                 n
np            60270  in                 n
fb            13800  dp                 y
bs               10  hs                nn
d1            1.000       PROCESSING
nt             4000  lb              2.00
ct             1330  fn             65536
   TRANSMITTER             DISPLAY
tn              C13  sp            -180.0
sfrq        100.554  wp           20965.0
tof          1536.3  rfl           5537.8
tpwr             61  rfp           3971.5
pw            4.700  rp             -16.4
    DECOUPLER        lp            -314.8
dn               H1          PLOT
dof               0  wc               250
dm              yyy  sc                 0
dmm               w  vs                84
dpwr             42  th                 5
dmf            8500  nm   no   ph
```

References

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Conclusion and Future Perspective

In summary, we have successfully achieved the synthesis of nitrogen containing heterocycles such as trisubstituted-1*H*-pyrazole-4-carbodithioates, tetrahydro-2H-pyrazolo[3,4-*b*]pyridines and 2-substituted benzo[*d*]thiazole derivatives starting from *β*-oxodithioester as an initial synthons, which are the new additions in the area of synthetic organic chemistry. We have developed cost effective methods for the synthesis of various dihydro-2-oxypyrroles and dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7H)-one derivatives by involving multi-component reactions strategy, which can be visualized easily in the figure below. Moreover, we have also demonstrated the usefulness of *β*-oxodithioesters as well as multi-component reactions strategy for the synthesis of various nitrogen, oxygen and sulfur containing heterocycles.

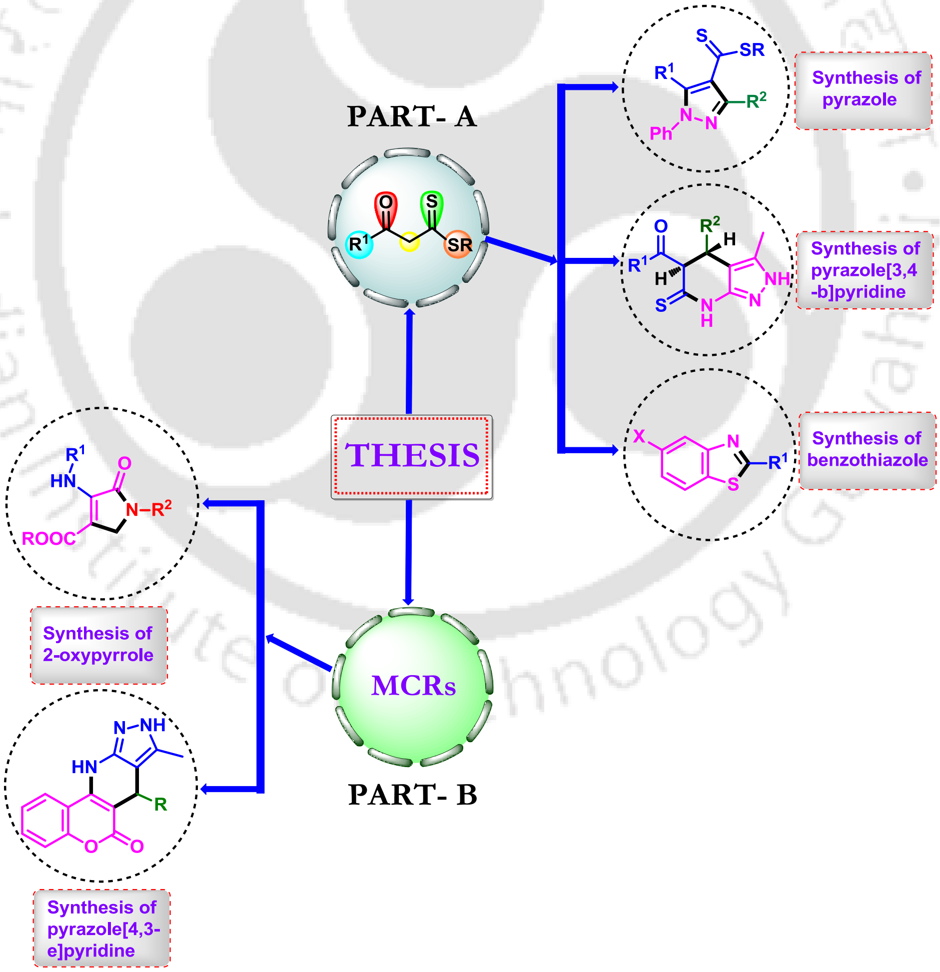

Figure. 1

In future, we believed that these multi-component based methodologies would be applicable in target-oriented synthesis as well as valuable additions in the modern synthetic organic synthesis. Further, trisubstituted-1*H*-pyrazole-4-carbodithioates, 2-substituted benzo[*d*]thiazole derivatives and dihydro-2-oxypyrroles may be utilized as effective synthons in *ortho*-selective C-H functionalization reactions. Also, we believe that further functionalization of the N-heterocyclic compounds prepared by these methodologies might be useful classes of compounds for further study for biological activities.

LIST OF AUTHOR’S PUBLICATIONS AND COMMUNICATIONS

1. One-pot four-component domino reaction for the synthesis of substituted Dihydro-2- oxypyrroles catalyzed by molecular iodine; Abu T. Khan, **Arindam Ghosh** and Md. Musawwer Khan *Tetrahedron Lett.* **2012**, *53,* 2622-2626.

2. Synthesis of trisubstituted 1*H*-pyrazole-4-carbodithioate using one-pot three-component reaction catalyzed by ferric sulfate $[Fe_2(SO_4)_3\cdot xH_2O]$; Abu T. Khan, **Arindam Ghosh**, Sidick Basha R and Mohammad Hedayetullah Mir *Asian J. Org. Chem.* **2013**, *2*, 126-129.

3. Synthesis of Unsymmetrical Sulfides Catalyzed by *n*-Tetrabutyl-ammonium tribromide: A Selective Fluorescence Probe for Mercury ion; Ajaz A. Dar, Shahzad Ali, **Arindam Ghosh**, Abu T. Khan, Atul K. Dwivedi and Parameswar K. Iyer *Sensors and Actuators B* **2014**, *193,* 509-514.

4. Synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-e]pyridin-6(7H)-ones involving one-pot three-component tandem Knoevenagel-Michael reaction catalyzed by *n*-tetrabutyl ammonium tribromide (TBATB) **Arindam Ghosh** and Abu T. Khan *Tetrahedron Lett.* **2014**, *55*, 2006-2009.

5. Expedient L-proline catalyzed diastereoselective synthesis of substituted tetrahydro-2H-pyrazolo[3,4-*b*]pyridine in one pot three component reaction; **Arindam Ghosh**, Sidick Basha R and Abu T. Khan (Communicated).

6. Brønsted acid-metal salt combined catalyzed synthesis of benzothiazoles from 2-aminothiophenols and β-oxodithioesters; **Arindam Ghosh** and Abu T. Khan (Communicated).