Synthesis, Characterization and Biological Evaluation of Some Novel Nitrogen Based Heterocyclic Compounds

A

Dissertation submitted to

Gujarat University, Ahmedabad

for the degree of

Doctor of Philosophy
in
CHEMISTRY

By

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Under the supervision of
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July 2017

Declaration

I, hereby, declare that my Thesis entitled "***Synthesis, Characterization and Biological Evaluation of Some Novel Nitrogen Based Heterocyclic Compounds"*** submitted for the degree of Doctor of Philosophy is record of research work carried out by me during period from… under guidance of Dr. H. R. Dabhi and has not substantially the same as the one which has already been submitted for a degree or diploma of this or any other university or examining body in India or in any other country.

Falguni G. Bhabhor

Date: July 2017

Place: Dahod

Certificate

This is to certify that ***Falguniben Gorsinhbhai Bhabhor***, a candidate for the award of the degree of doctor of philosophy of Gujarat University has worked under my guidance for the period required by university. The work embodied in this thesis is not submitted previously to this or any other university for Ph.D. or any other degree or diploma.

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Acknowledgement

*First and foremost I would like to thank **God**. You have given me the power to believe in myself and pursue my dreams. I could never have done this without the faith in you, the Almighty.*

Research has always been an ongoing process-a journey and not a destination. So has been mine-full of astonishments and amusements. No research is ever the outcome of single individual's talent or efforts. This work is no exception. It provides me pleasure to convey my gratitude to all those who have directly or indirectly contributed to make this work a success. As one flower makes no garland, the present work would not have taken shape without wholehearted encouragement, goodwill and cooperation of a number of people and institutions.

At this juncture, I seize this opportunity to express my deep gratitude to all of them.

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My very special thanks to my parents and family whom I owe everything I am today, my Lt. Grandmother ***Mithuben*** *for always believing in me, for her continuous love. My father* ***Gorsinhbhai Bhabhor,*** *mother* ***Manjulaben Bhabhor,*** *my brother* ***Hardik Bhabhor*** *who showed me the true worth of hard work who raised me with a passion of science and supported me in all my pursuits and because of their hunger desire and dedication towards education I have been successful in achieving my goals and accomplishing their dream and my aspirations.*

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For any errors or inadequacies that may remain in this work, of course, the responsibility is entirely my own.

Falguni G. Bhabhor

List of abbreviations

Nuclear magnetic resonance	NMR
Degree centigrade	°C
Hours	hrs
Per	/
molar	M
That is	i.e
Per centimeter	Cm^{-1}
Mol per Litter	Mol lit^{-1}

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CHAPTER-1

General Introduction

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GENERAL INTRODUCTION

Two hundred years ago, the chemical science was an undivided field, around 1990; a division into inorganic, organic and physical chemistry became necessary. The increases of factual material enforced a progressive segmentation into sub disciplines. A map shows countries and regious neatly separated, similarly, the uninformed observer may regard chemistry as a side by side of numerous disciplines and specialties. The comparison is fallacious, however, because broad overlap is thwarting clear divisions.

Heterocycles form by for the largest of classical division of organic chemistry and are of immerse importance biologically active agrochemicals are heterocyclic while countless addictives and modifiers use in industrial applications ranging from cosmetic, reprography, information storage, and plastic are heterocyclic nature.

Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material science and so on is very well known. Between them, sulfur and nitrogen containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis.

Heterocyclic chemistry is one of the most interesting, applied branches of organic chemistry and of utmost practical and theoretical importance. As a result, a great deal of research carried out in chemistry is devoted to heterocyclic chemistry. It is vast and expanding area of chemistry because of obvious application of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture,

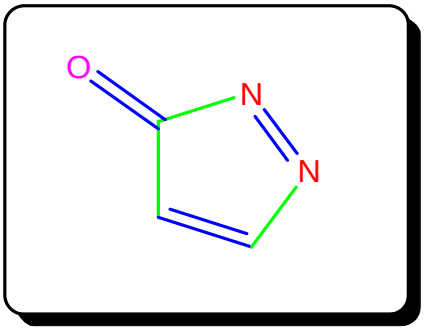
plastic, polymer and other fields. Heterocyclic compounds are widely distributed in nature.

By virtue of their therapeutic properties, they could be employed in the treatment of infectious diseases. Many heterocyclic compounds synthesized in laboratories have been successfully used as clinical agents.

The title of the thesis suggested that the present work is connected with various chalcone and schiff bases of pyrazplone and its derivatives. The present chapter deals with the structural variability and recent applications of pyrazolone, chalcone and schiff bases.

1.1 PYRAZOLONE: Introduction

Pyrazolones are defined as oxo derivatives of five-membered heterocycles containing two adjacent nitrogen atoms. They contain two double bonds within the nucleus, imparting an aromatic character to these molecules. [1] Pyrazolone, a five-membered-ring lactam, is a derivative of pyrazole that has an additional keto (=O) group. It has a molecular formula of $C_3H_2N_2O$.



The chemistry of pyrazolone was started by Knorr in 1883 and reported the first pyrazolone derivative. [2] Antipyrine was the first pyrazolone derivative for clinical use and was synthesized in 1883. [3] It was used as the first agent to reduce fever and also for arthritis.

Most pyrazolones are colorless to yellow solids with melting points of over 100 ^{0}C decreases in the presence of substituents at *N*-1.

Simple low molecular weight pyrazolones are soluble in hot water and the higher mol wt materials are soluble in most organic solvents. Hydrogen bonding has strong influence on the predominant tautomeric form. Pyrazolones possess both basic and acidic character.

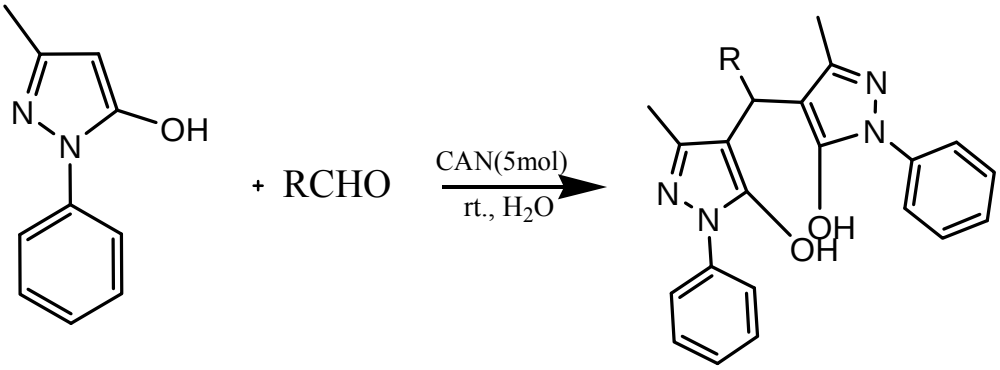
The weakly acidic character generally predominates, so they can be titrated with strong bases.

However, some pyrazolones can also be titrated with perchloric acid in glacial acetic acid.

Most pyrazolones are readily soluble in aqueous alkali.

1.1.1 Synthetic Aspects

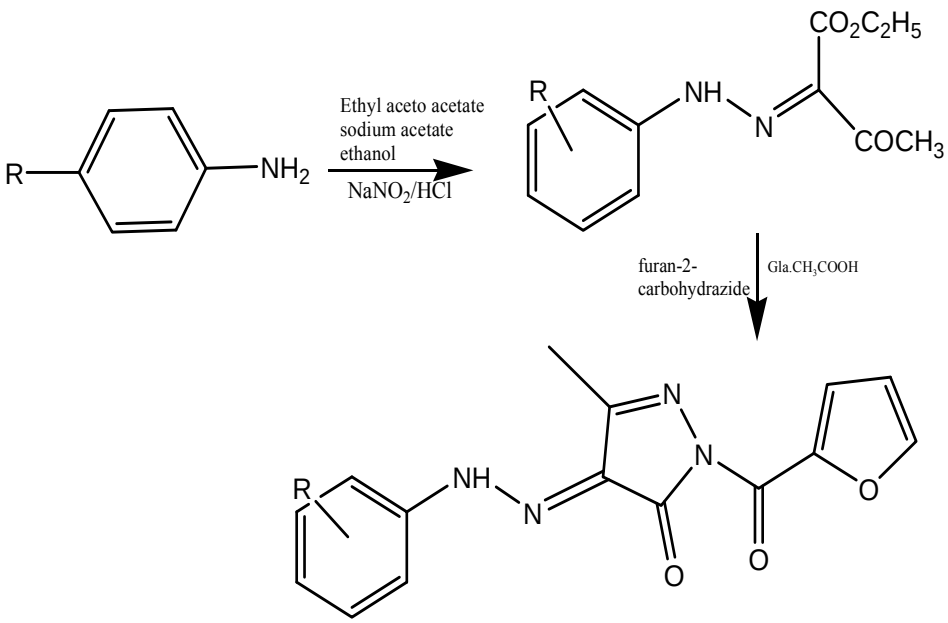
Sujatha *et.al.*.[4] synthesized 4,4'-(arylmethylene) bis (1*H*-pyrazol-5-ole) 3 has been accomplished by tandem Knoevenagel– Michael reaction using CERIC AMMONIUM NITRATE (CAN) as catalyst.



Liu *et.al.* [5] have been reported a novel Photochromic Pyrazolones based on photochromism by employing phosphor $Sr_2P_2O_7$.

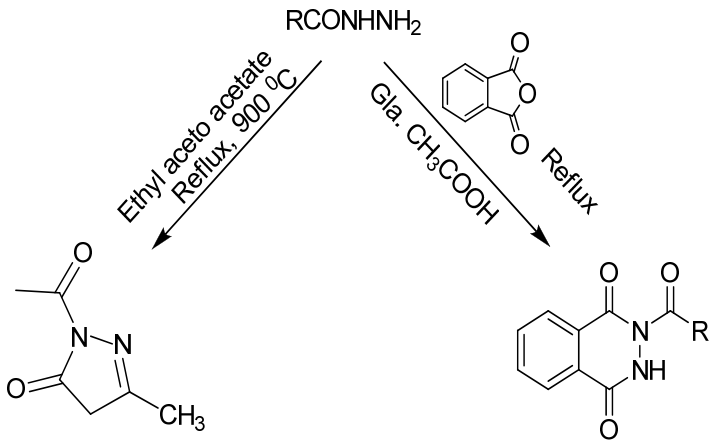
Baciu-Atudosie *et.al.*.[6] have been reported a simple one-pot approach for the synthesis of new 5-substituted-2-[2-(2-substituted-10*H*-phenothiazin- 10-yl)-2-oxoethyl]-2,4-dihydro-3*H*-pyrazol-3-one containing a phenothiazine unit by reaction of *N*-chloroacetyl compound , ethyl acetoacetate with hydrazine hydrate.

Shah *et.al.*. [7] synthesized 1-(furan-2-carbonyl)-3-methyl-4-(2- phenyl hydrazono)-1*H*-pyrazol-5(4*H*)-one by Mannich reaction.



Mosaddegh *et.al.*.[8] have been reported the synthesis of 4,4'-(arylmethylene)bis(3-methyl-1- phenyl-1H-pyrazol-5-ol) was performed effectively by the reaction of aryl aldehydes and 1-phenyl-3-methyl-5-pyrazolone in the presence of a catalytic amount of Ce(SO4)2.4H2O as reusable and environmentally friendly catalyst in water/ethanol solution. The method has the advantages of high yields, short reaction time, simple work-up and reusability of catalyst.

Ahmad *et.al.*.[9] have been reported two novel series of 1-long chain alkanoyl/alkenoyl/hydroxyalkenoyl-3-methyl-1H-pyrazol-5(4H)-ones and 2-long chain alkenoyl/hydroxyalkenoyl-3H-phthalazin-1,4-diones. It is achieved by the cyclization reaction between ethylacetoacetate and hydrazides.



Kadam *et.al.*.[10] synthesized a novel synthesis of 3-amino-4-(4*I*-substituted benzylidene)-1*H*-pyrazol-5(4*H*)-one derivatives and 3-amino-4-(4I-substitued benzylidene)-4, 5-dihydro-5-oxopyrazole-1-carbothioamide derivatives by the reaction of substituted benzaldehyde/heteroaldehyde, ethylcyano acetate and thiosemicarbazide was heated in presence of PEG-400.

Mehta *et.al.*. [11] have been reported the synthesis of diphenylic bispyrazole and diphenylic bispyrazolone compounds.

Sivakumar *et.al.*. [12] have been synthesized an efficient synthesis of some Mannich base of 5-mehyl-2-[(2- oxo-2*H*-chromen-3-yl) carbonyl]-2,4- dihydro-3*H*-pyrazol-3-one have been described by using multicomponant with microwave techniques.

Tu *et. al.* [13] have been reported C-tethered bispyrazol-5-ols via multicomponent domino reactions of acetylenedicarboxylates, phenyl hydrazine and aromatic aldehydes under microwave irradiation.

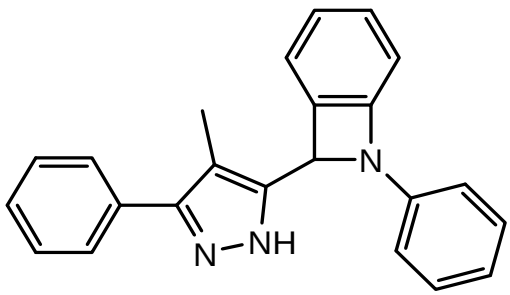
1.1.2 Pharmacological activity

Pyrazolone derivatives are an important class of heterocyclic compounds that occur in many drugs and synthetic products [14,15] These compounds exhibit

remarkable analgesic[16], antitubercular[17], antifungal, antibacterial [18], anti-inflammatory[19], antioxidant and antitumor activities[20]. Due to their easier preparation and rich biological activity, pyrazolone framework plays an essential role and represents an interesting template for combinatorial and medicinal chemistry. Pyrazolones are pharmacophores of numerous compounds that display activities such as analgesic and antipyretic (propylphenazone, phenazone, metamizole etc.) [21], anti-cancer (TELIN) [22], anti-ischemic (edaravone) [23], and anti-anxiolytic [24]. Pyrazolones are gaining importance especially in drug discovery programs towards cerebral ischaemia [25] and cardiovascular diseases [26,27]. Due to its diverse pharmacological properties, the chemistry of pyrazolones is gaining attention, and there have been numerous novel methodologies reported recently [28].

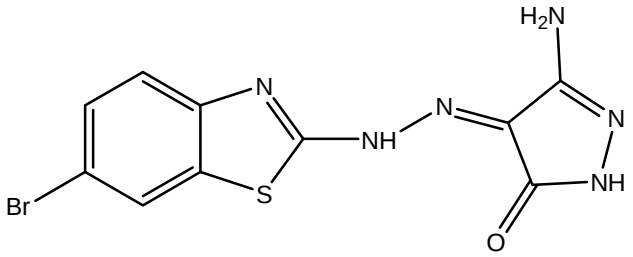
Devnath H.P. *et.al.* [29] reported some pyrazolone derivatives from ciprofloxacin and were evaluated for their cytotoxic ssactivity and it was found that these compounds had shown potential cytotoxic activity against brine shrimp nauplii than ciprofloxacin**.**

Sunitha S. *et.al.* [30] synthesized a series of N-phenyl [(methylphenyl-5-pyrazolyl)methylidene]aniline Compounds and screened for their *in vitro* antimicrobial activity against various gram +ve and gram –ve bacteria .



8-(4-Methyl-5-phenyl-2*H*-pyrazol-3-yl)-7-phenyl-7-aza-bicyclo[4.2.0]octa-1(6),2,4-triene

Kumar Siva *et.al.* [31] synthesized a series of 5-amino-4-[2-(6-bromo-1,3-benzothiazol-2-yl)hydrazinylidene]-2,4-dihydro-3H-pyrazol-3-one derivatives and were screened for their cytotoxic activity.

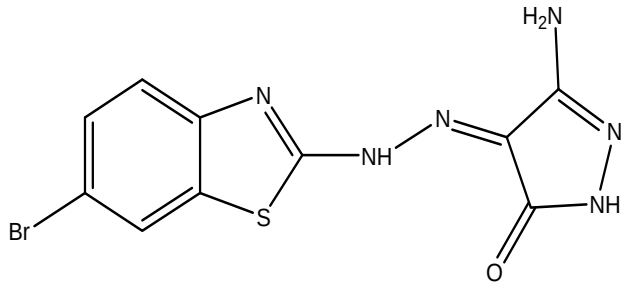


5-Amino-4-[(6-bromo-benzothiazol-2-yl)-hydrazono]-2,4-dihydro-pyrazol-3-one

Parmar N. *et.al.* [32] synthesized some novel 5-pyrazolone based schiff bases by the condensation of 4-acylpyrazolone with different aromatic diamines and it was observed that all of the compounds showed significant antioxidant activity.

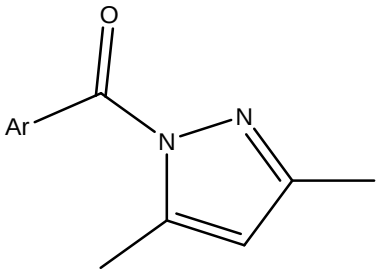
Isloor A. M. *et. al.* [33] reported (4Z)-2-(2,4-dinitrophenyl)-4-[(6-methoxy naphthalene-2-yl)methylidene]-5-methyl-2,4-dihydro-3H-pyrazol-3-one and (4Z)-4-[(6-methoxynaphthalen-2-yl)methylidene]-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one and evaluated for their antimicrobial activity.

Kumar Siva *et.al.* [34] have synthesized 5-amino-4-[2-(6-bromo-1,3-benzothiazol-2-yl)hydrazinylidene]-2,4-dihydro-3H–pyrazol-3-one derivatives and were screened for their antioxidant activity.



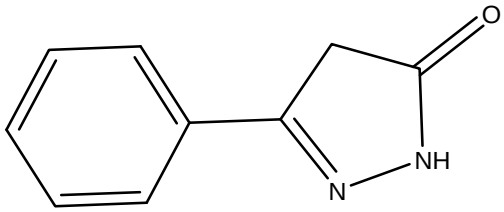
5-Amino-4-[(6-bromo-benzothiazol-2-yl)-hydrazono]-2,4-dihydro-pyrazol-3-one

Amir M. *et.al.* [35] synthesized 3 methyl pyrazol-5-one derivatives diclofenac, ibuprofen, flurbiprofen and it was found that the most of the compounds were screened for their analgesic activity. These compounds had shown potent analgesic activity.



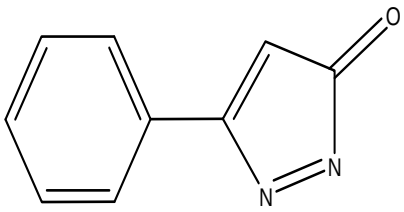
Ar= DIclofenac, Ibuprofen, Flurbiprofen
3-methyl pyrazole-5-one derivatives

Mohmoud M. *et.al.* [36] synthesized various pyrazolone derivatives which had shown fungicidalactivity

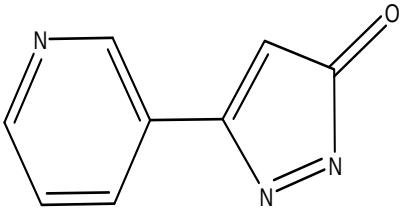


5-Phenyl-2,4-dihydro-pyrazol-3-one

Kuçukguze G. *et.al.* [37*]* synthesized a series of 3-phenyl or pyridyl-5-pyrazolone derivatives which was useful in improving cardiac contractibility.



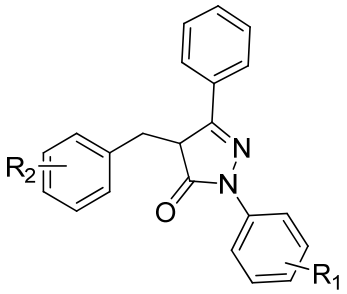
5-Phenyl-pyrazol-3-one



5-Pyridin-3-yl-pyrazol-3-one

Liang P.H. *et.al.* [38] synthesized series of pyrazolone compounds and evaluated by in vitro protease assay using fluorogenic substrate peptide. It was observed

that several compounds showed potent inhibition against the 3C-Like protease and one of the inhibitors was also active against 3Cprotease.

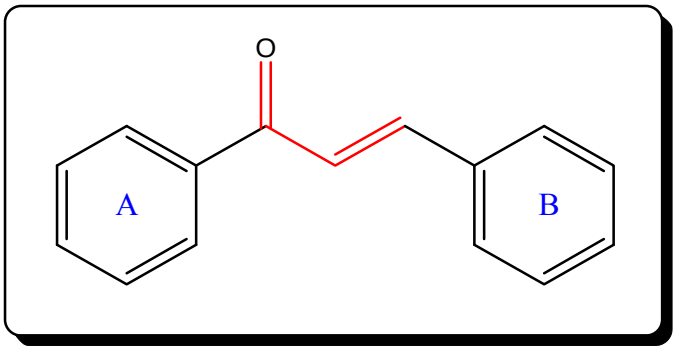


Pyrazolone derivative

1.2 Chalcone: Introduction

Plants from the natural world are linked with the treatment of different human ailments. This is due to the presence of different classes of chemical constituents. Flavonoids are one such class of natural constituents responsible for the activity of plants. Chalcone is a generic term given to compounds bearing the 1, 3-diphenyl-2-propen-1-one framework and belong to the flavonoid family [39-41]. Chemically they are open-chain flavonoids in which the two aromatic rings are joined by a three carbon α,β-unsaturated carbonyl system. The name "Chalcones" was given by Kostanecki and Tambor[42]. These compounds are also known as benzalacetophenone or benzylideneacetophenone. Chalcones are -unsaturated ketone containing the reactive ketoethylenic group –CO-CH=CH-. These are coloured compounds because of the presence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes.

1.2.1 General structure

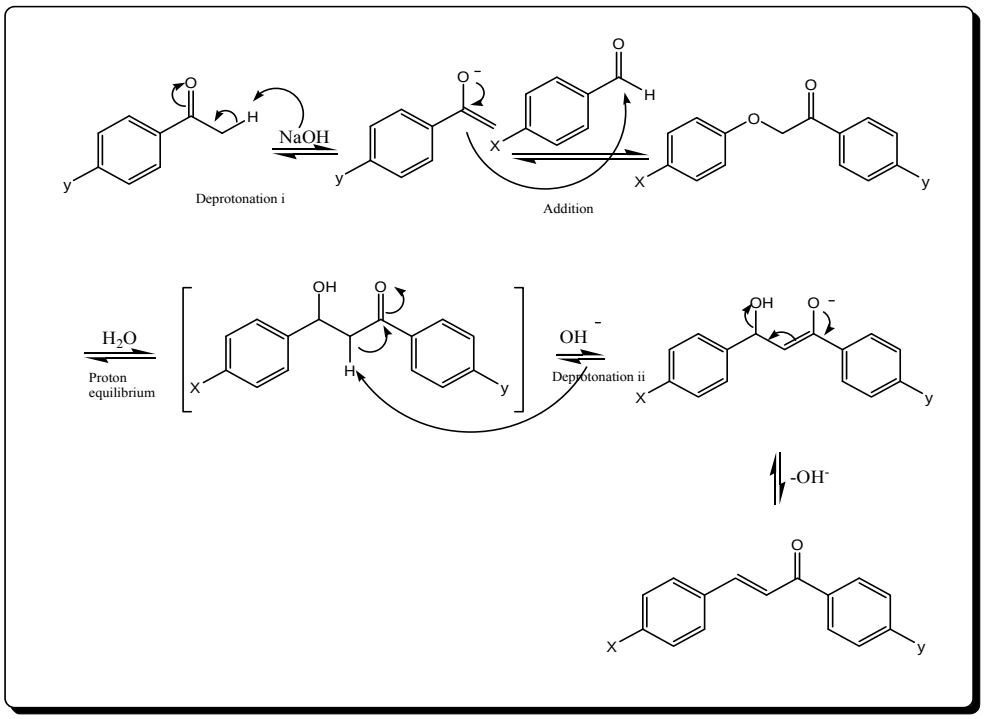


All the chalcones give pink coloration with concentrated sulphuric acid in Wilson's test5 and when a phenolic hydroxyl group is present, they give violet coloration with alcoholic ferric chloride solution.

Chalcones on heating with traces of iodine in dimethyl sulphoxide (DMSO) for two hours give the corresponding flavones. Chalcones were converted into the corresponding flavonols by their oxidation using hydrogen peroxide in methanolic sodium hydroxide solution and these flavonols showed a characteristic greenish yellow fluorescence in ethanolic solution as well as with concentrated sulphuric acid.

1.2.2 Mechanism of chalcone derivatives:

The mechanism of chalcone formation via aldol condensation has four main steps that are deprotonation I, addition, proton equilibrium and dehydration, where dehydration process can be divided into two step, deprotonation II and elimination.

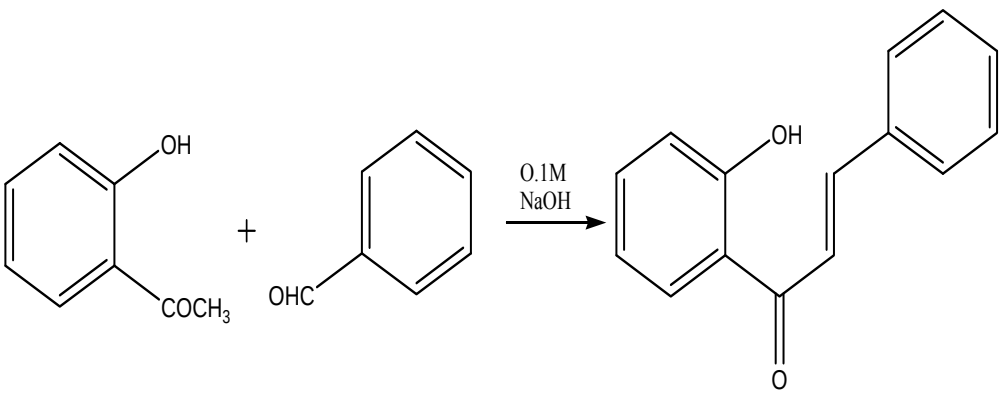


Chalcone formation mechanism via aldol condensation

1.2.3 Synthetic Aspects

Medicinal chemists are working on chalcones and their heterocyclic derivatives. A literature survey was done on the synthesis of the said compounds, where the researchers reported different synthetic pathways. Chalcones can be obtained by the acid or base catalyzed aldol condensation of acetophenones with aromatic aldehydes [43-45]. These reports are presented below:

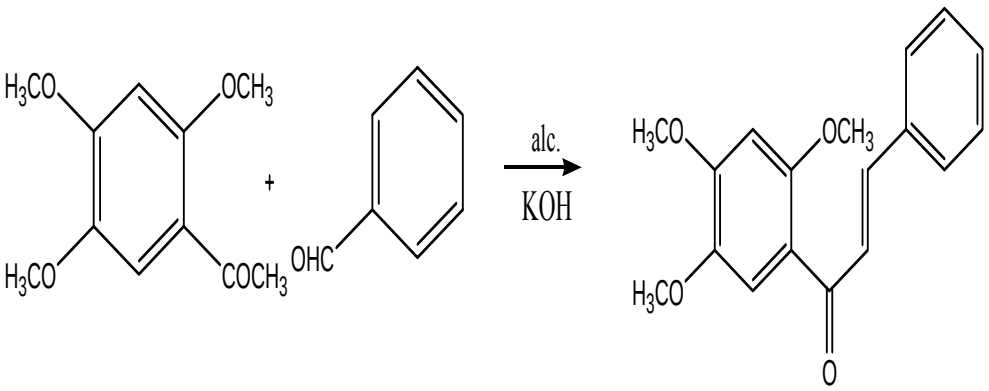
2'-hydroxyacetophenone react with benzaldehyde in the presence of 0.1M NaOH to give the chalcone [46].



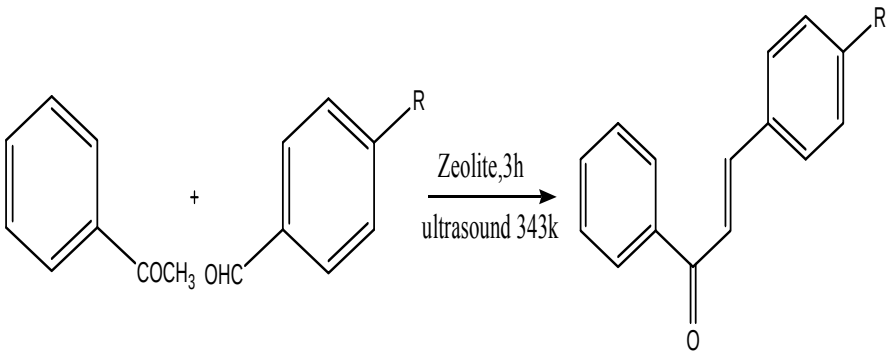
Liquid phase Claisen–Schmidt condensation between 2'-hydroxyaceto- phenone and benzaldehyde was carried out over a zinc oxide supported metal oxide catalyst under solvent free conditions to form 2'-hydroxychalcone [47].

Hans RH *et. al.* synthesized acetylenic chalcones from commercially available hydroxyacetophenone or benzaldehyde and commercially available vanillin or acetovanillone by O-alkylation followed by Claisen-Schmidt condensation [48]

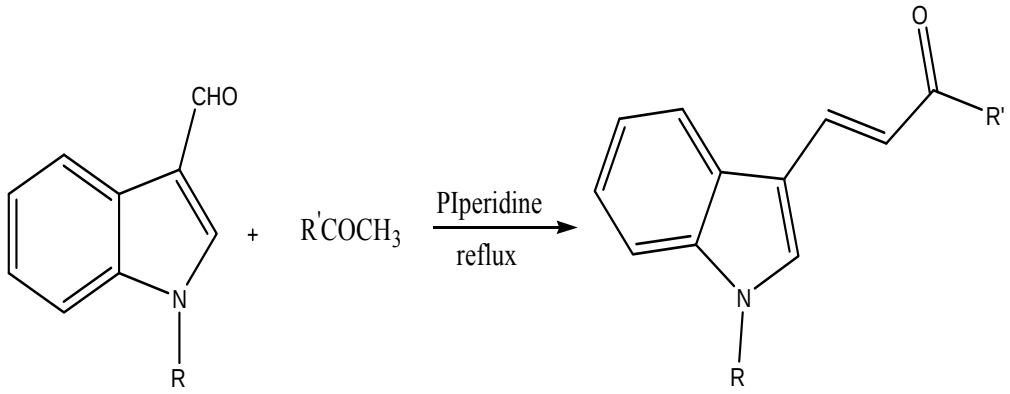
2',4',5'-trimethoxyacetophenone, when condensed with equimolar proportions of aromatic aldehydes in the presence of 30 % alcoholic alkali at room temperature yield chalcones[49]



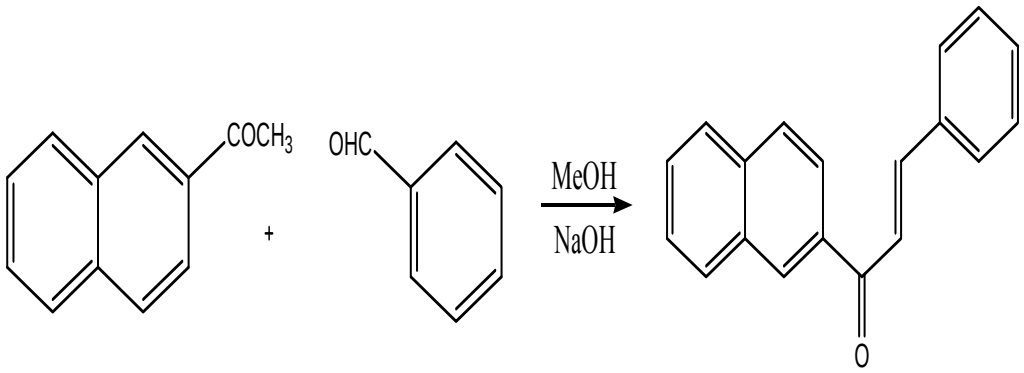
Claisen-Schmidt condensation between benzaldehyde and acetophenone by sonochemical and thermally activated reactions over zeolite as catalyst under solvent free conditions give chalcone [50]



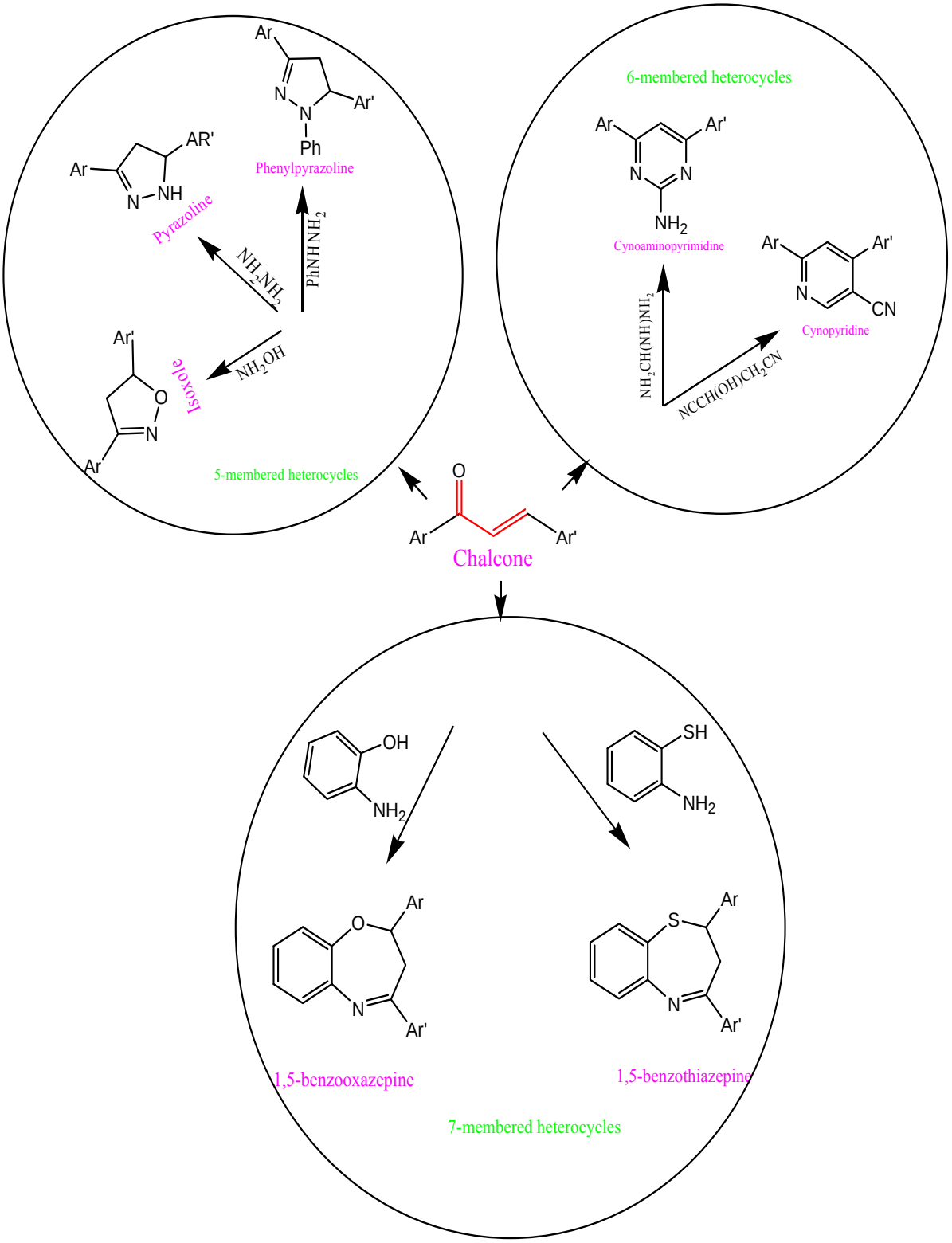
Kumar D *et.al.* synthesized indolyl chalcones by reacting indol-3-carboxaldehyde andappropriate acetophenone in presence of piperidine under reflux [51]



Condensation of 2-naphthylmethyl ketones with substituted arylaldehydes in the presence of NaOH under methanol as solvent gave the corresponding chalcones [52]

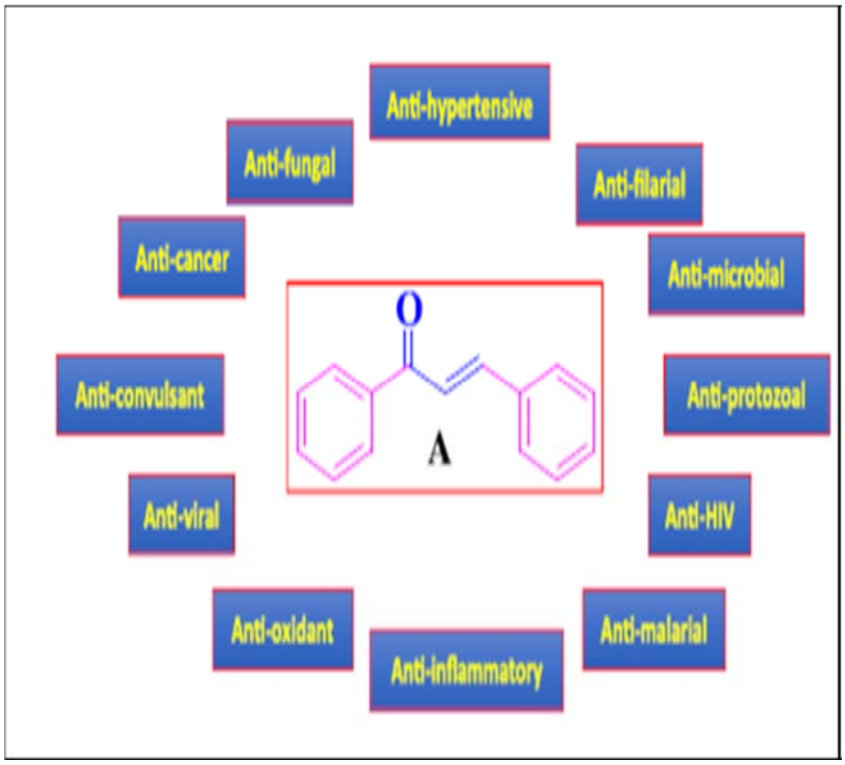


1.2.4 Synthetic potential of chalcone derivatives for the synthesis of heterocyclic analogues:



1.2.5 Therapeutic Potential of Chalcones

Chalcone is unique template that is associated with several biological activities and is also well known for synthesizing various heterocyclic compounds [53]. They are secondary metabolites of terrestrial plants, precursors for the biosynthesis of flavonoids. The introduction of a halogen into the benzenoid part of these α, β-unsaturated ketones enhances their biological activity [54].

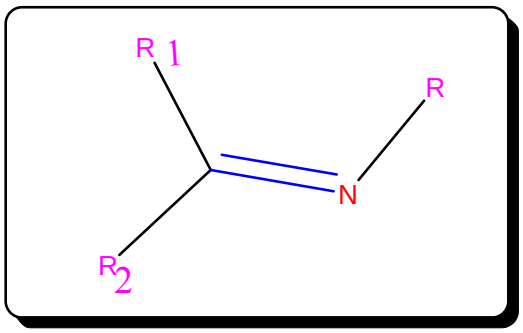


The privileged scaffold chalcone remained a fascination among researchers in the 21st Century due to its simple chemistry, ease of synthesis, diversity of substituents, wide range of biological activities such as anti-diabetic[55], anti-neoplastic[56], antihypertensive[57], anti-retroviral[58], anti-inflammatory [59], anti-parasital[60], anti-histaminic[61], anti-malarial[62], antioxidant[63],anti-fungal[64],anti-obesity[65],antiplatelet[66],anti-tubercular[67], immunosuppressant[68], anti-arrhythmic[69], hypnotic[70], anti-gout[71],

anxiolytic[72], anti-spasmodic[73], anti-nociceptive[74], hypolipidemic[75], anti-filarial[76], anti-angiogenic[77], anti-protozoal[78], anti-bacterial[79], antisteroidal [80], anti-cancer [81] and catalytic agent[82].

1.3 Schiff bases: Introduction

Schiff bases, named after Hugo Schiff and the first preparation of imines were reported in the 19th century [83]. Since then a variety of methods for the synthesis of imines have been described. The classical method involves azeotropic distillation of any primary amine with an aldehyde or a ketone under specific conditions. They can be used as reactive intermediates for the synthesis of many natural products. The general structure of these bases is given below [84]. Where R, R1 and R2 are H, alkyl, cyclohexyl, aryl or heterocyclic readicals, which may be variously substituted. This condensation reaction, along with the chemical and physical properties of Schiff bases have been reviewed [85-87]. Schiff bases are also known anils, imines or azo methines.



Various studies have been shown that the >C=N group has considerable biological importance. This can be substantiated by the fact that the possibility of having a lone pair of electrons in either a π or SP^2 hybridized orbital on trigonally hybridized nitrogen in the >C=N group; which is of fundamental chemical and

biological importance, and together with the variablility of angles of hybridization it makes possible the formation of nitrogen containing molecules with all the delicate differences in physicochemical properties necessary to produce the various phenomena of life.

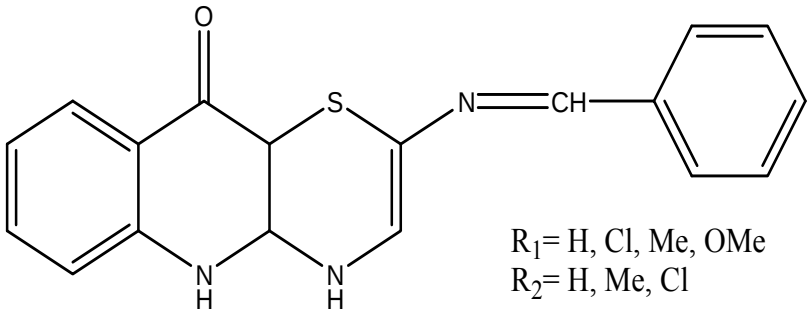
1.3.1 Chemistry and Biological Importance of Schiff bases

Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of Schiff bases by acid anhydrides, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylating agent to the carbon-nitrogen double bond. Reactions of this type have been put to good use in natural product synthesis.

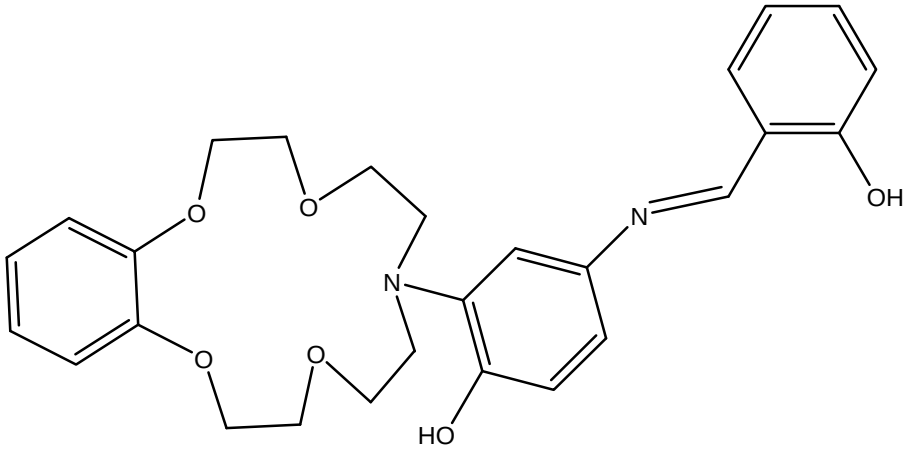
Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base. Stereochemical investigation carried out with the aid of molecular model showed that Schiff base formed between methylglyoxal and the amino group of the lysine side chains of proteins can bent back in such a way towards the N atom of peptide groups that a charge transfer can occur between these groups and oxygen atoms of the Schiff bases. In this respect pyridoxal Schiff bases derived from pyridoxal and amino acids have been prepared and studied from the biological point of view. Transition metal complexes of such ligands are important enzyme models. The rapid development of these ligands resulted in an enhance research activity in the field of coordination chemistry leading to very interesting conclusions.

Lots of researchers studied the synthesis, characterization and structure activity relationship (SAR) of Schiff bases. Schiff bases, derived mostly from variety of heterocyclic rings, were reported to possess a broad spectrum of pharmacological activities with a wide variety of biological properties, development of a new chemotherapeutic Schiff bases is now attracting the attention of medicinal chemist [88]. They are known to exhibit a variety of potent activities. The pharmacologically useful activities include antibacterial [89-92], antioxidant [93-97], anti-inflammatory, anticancer [98-99], anti-hypertensive, anti-fungal, antipyretic, antimicrobial, anti-HIV, cytotoxic activity, hypnotic and herbicidal activities [100]. Metal complexes of Schiff bases have been reported and these are used as chelating ligands in the coordination chemistry of transition metals as radiopharmaceuticals for cancer targeting and agrochemicals [101].

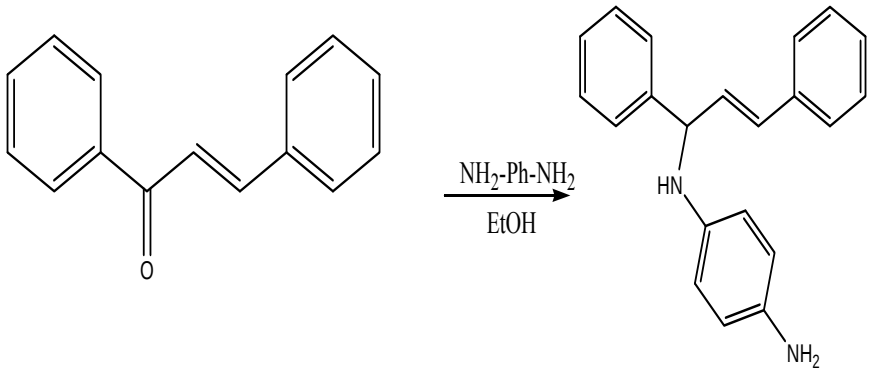
Dabholkar *et. al.*, [102] reported the Schiff bases containing 4, 10-Dihydro-5,7-substituted-9-oxoquinolino-[2,3, e]-2-amino-1,3,4- thiadiazine by microwave irradiation.



Xingyao *et. al.*, [103] synthesized salicyaldimine Schiff bases with benzo-10-aza-15-crown-5-pendant.



Schiff bases derived from newly synthesized chalcones were tested certain microbes for antimicrobial activity by kedar *et. al.* [104]



M. M. Kamel *et. al.* [105], recently reported that a series of sulfapyridine-polyhydroxyalkylidene (or arylidene)-imino derivatives (Schiff's bases) were prepared by condensation of 4-Amino-N-pyridin-2-ylbenzenesulfonamide with different monosaccharides or with aromatic aldehydes.

Kundariya *et. al.*[106] presented a series of novel antimicrobial Schiff bases of 1H-Pyrazole [3, 4-*b*] pyridine-3-amine.

Aly *et. al.* [107] reported some novel 3-aryl-4(3H)- quinazolinones-2-carboxaldehydes and their corresponding Schiff's bases and thiosemicarbazone derivatives.

1.4 AIMS & OBJECTIVES

Aims and objectives of the present investigation are:

(a) To generate several Chalcone, Schiff bases, pyrazole, Benzothiazepine, Azetidinone and 1,3,4 thiadiazole derivative bearing pyrazolone moiety.

(b) To characterize these products for their structural assignment using Spectroscopic techniques like IR, ^{1}H NMR and Mass spectroscopy.

(c) To screen these new derivatives for their antimicrobial activity using different Strains of bacteria and fungi and to compare antimicrobial activity with different known drugs at different concentrations for their MIC values.

In view of these facts, the research work presented in thesis is as follows:

Chapter-2 of thesis comprises three sections. Section -1 Cover the details about techniques and methods used to characterize the compounds,Section-2 deals with the synthesis and characterization of chalcone based on acetyl pyrazolone derivatives and Section -3 deals with the synthesis and characterization of schiff bases based on acetyl pyrazolone derivatives.

Chapter-3 consist of the synthesis and characterization of pyrazole derivatives derived by the reaction of chalcone and hydrazine hydrazide.

Chapter-4 deals with the synthesis and characterization of 1, 5 Benzothiazepine derivatives derived by the reaction of Pyrazolone chalcones and 2- amino thiophenol.

Chapter-5 of this thesis deals with the synthesis and characterization of azetidinone derivatives from schiff bases.

Chapter-6 contains synthesis and characterization of 1, 3, 4 thiadiazole derivatives.

Chapter -7 point out the Biological activity of all compounds (from chapter 2-6)**.**

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CHAPTER-2

Introduction to general characterization techniques and studies on pyrazolone based Chalcones and Schiff bases

Table of Contents

SECTION-A

SECTION-B

SECTION-C

Introduction to general characterization techniques and Studies on pyrazolone bases Chalcones and Schiff Bases.

This present chapter epitomizes three sections.

- Section-A epitomizes characterization techniques used to characterize the produced compounds (shown in following Chapters).
- Section B materializes the synthesis and characterization of various chalcones of pyrazolone derivative.
- Section C comprises the synthesis and characterization of Schiff Bases of pyrazolone derivative.

SECTION-A

Techniques used for Characterization of Compounds

2.1 Elemental Analysis

The majority of organic compounds are composed of small number of elements. The most important ones are: Carbon, hydrogen, oxygen, nitrogen, sulphur, chlorine etc.

Elementary quantitative organic analysis is used to determine the content of carbon, hydrogen, nitrogen and other elements in the molecule of an organic compound.

2.2 Introduction of spectroscopy

Spectroscopy is the most imperative and promising tool for the structural investigation of chemically relevant systems. Spectroscopy deals with the interaction of electromagnetic radiation with matter and it can be used to extract very useful information like structural and other physico-chemical properties of molecules. Electromagnetic radiations are produced by the oscillations of electric and magnetic dipoles residing in the atom. The most important consequence of

electromagnetic interaction is that energy is absorbed or emitted by the matter in discrete amounts called quanta. Spectroscopic methods are generally used to measure the energy difference between various molecular energy levels and to determine the atomic and molecular structures.

The different types of spectroscopic techniques and quantum chemical methods can provide the valuable information about the molecular structure. Electronic spectra are due to transitions between the electronic energy levels in the visible or UV region. It gives information regarding molecular orbitals and bonding. Vibrational transitions occur in infrared region of electromagnetic spectrum and provide the information about the functional groups and bonds of organic compounds. Radiofrequencies offers the transitions in nuclear spins and it gives the information about the chemical environment of hydrogen atoms, the number of hydrogen and carbon atoms of organic compounds.

The use of spectroscopy for probing the structure of simple and even complex molecules has been of inestimable value in the field of structural study of organic, inorganic and organo metallic compounds, biological molecules, polymers and minerals [1-12].

2.3 Infrared Spectroscopy

Infrared spectroscopy is widely used for the identification of organic compounds. Infrared spectroscopy is generally concerned with absorption of infrared radiation incident on the sample. Due to IR radiation absorption, the molecule vibrates and gives rise to closely packed absorption bands. The IR technique when coupled with intensity measurements may be used for qualitative and quantitative analysis.

Currently, this technique has become more popular when compared to other physical techniques (X-ray diffraction, electron spin resonance, etc.,) in the elucidation of the structure of unknown compounds.

2.3.1 Infrared activity

A normal mode of vibration to be infrared active, there must be a change in dipole moment during the course of vibration. During the vibration of a molecule, a continual fluctuation of the dipole moment sets up an alternating electric field, which can interact with the electric vector associated with radiation. The molecule absorbs the infrared radiation by changing its amplitude of vibration and electrical dipole moment as a result of its vibrational or rotational motion.

2.3.2 Selection rule for IR spectra

According to quantum mechanics, the selection rule for the infrared spectrum is determined by the integral

$$[\mu]\nu'\nu'' = \int \psi\nu'^{*}(Qa)\mu\psi\nu''\,(Qa)dQa$$

Here μ is the dipole moment in the electronic ground state. ψ is the vibrational eigen function, ν′ and ν″ are the vibrational quantum numbers of the states before and after transition respectively and Qa is the normal coordinate whose activity is to be determined. The dipole moment can be resolved into three components in the x, y, z directions, as

$$[\mu x]\nu'\nu'' = \int \psi\nu'(Qa)\mu x\psi\nu''\,(Qa)dQa$$

$$[\mu y]\nu'\nu'' = \int \psi\nu'(Qa)\mu y\psi\nu''\,(Qa)dQa$$

$$[\mu z]\nu'\nu'' = \int \psi\nu'(Qa)\mu z\psi\nu''\,(Qa)dQa$$

For the vibrations to be infrared active, atleast one of the components of the derivatives of the dipole moment with respect to the normal coordinate taken at

the equilibrium position, should be non-zero. If all the integrals are zero, the vibration is infrared inactive [13, 14].

Infrared spectroscopy is usually divided into three regions.

- Near infrared (overtone region) – between 12500- 4000cm^{-1}
- Middle infrared (fundamental vibrational region) - between 4000cm^{-1}-667cm^{-1}
- Far infrared (pure rotational region) - between 667cm^{-1} -50cm^{-1}

2.4 Predicted IR

The present thesis epitomizes study of following heterocyclic products:

- Pyrazolone
- Chalcones
- Schiff bases
- Pyrazole
- Benzothiazepine
- Azetidinone
- Thiadiazole

Pyrazolone:

Pyrazolones are hetero compounds. It has five membered ring containing two bonded nitrogen atoms and carbonyl group in their structure. Pyrazolone also named pyrazol-5-one having empirical formula $C_3H_4N_2O$. The bond at about 3400cm^{-1} can easily assign to N-H asymmetric and symmetric stretching vibrations. The corresponding C-H asymmetric and symmetric stretching occurs at respective position. However, the frequencies at about 1000 and 802cm^{-1} are C-

H bending vibration in plane and out of plane of the ring respectively. The frequencies attributed CO stretching at 1750cm-^{1}.

Chalcones:

The α, β-unsaturated carbonyl group, characteristic of a chalcone usually appear as a prominent band in between 1625-1650 cm^{-1}in its IR spectrum[15,16]. The region at which other absorption bands appear depends on the type of aromatic / heteroaromatic rings as well as the substituents present on these rings.

Schiff Bases:

The bands ranges at values (1600- 1620) s cm^{-1}, (1680-1725) m or w cm^{-1}, (3120-3180) vs cm^{-1}, (3280- 3520) w or vw cm^{-1}, (3400-3650) w cm^{-1} and (3560-3600) s or w cm^{-1}.They are assigned to aromaticity, the carbonyl group of tautomerised Schiff base.

Pyrazole:

The characteristic band at 1628-1650 cm^{-1} for C=N stretching are generally found in the pyrazole ring.

Benzothiazepine

The Characteristic sharp band in the region 3070-3362 cm^{-1} for OH stretching of phenolic ring, band at 1510-1611 cm^{-1} for C=N stretching and band at 662-756 for C-S stretching.

Azetidinone:

The carbonyl stretching frequency in acyclic amide usually has value of about 1665cm^{-1} is shifted for azetidinone in the range of 1755-1735cm^{-1} in monocyclic

lactams. This implies that the carbonyl group in β-lactam behaves like an ester carbonyl.

Thiadiazole:

The characteristic band at 662-756cm^{-1} for C-S-C stretching and near 1050 cm^{-1} N=N str. are generally found in Thiadiazole ring.

2.5 ^{1}H- NMR Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is supplementary technique to IR spectroscopy to get detailed information about the structure of organic compounds. Most widely studied nucleus is proton and then the technique is called PMR spectroscopy.

IR spectra give information about the functional group while NMR spectra provide information about the exact nature of proton and its environment. Thus this technique is more useful in the elucidation of an organic compound. IR spectra of isomers may appear same but their NMR spectra will markedly differ.

The phenomenon of nuclear magnetic resonance was first reported independently in 1964 by two groups of physicists: Block, Hansen and Packard at Stanford University detected a signal from the protons from water, and Purcell, Torrey and Pound at Harvard University observed a signal from the protons in paraffin wax. Block and Purcell were jointly awarded the Noble Prize for physics in 1952 for this discovery. Since that time, the advances in NMR techniques leading to wide spread applications in various branches of science resulted in the Noble Prize in chemistry in 1991.

The applications of NMR in clinical, solid state and biophysical sciences are really marvelous. The proton magnetic resonance (PMR) spectroscopy is the most important technique used for the characterization of organic compounds. It gives information about the different kinds of protons in the molecule. In other words it tells one about different kinds of environments of the hydrogen atoms in the molecule.

PMR also gives information about the number of protons of each type and the ratio of different types of protons in the molecule. It is well known that all nuclei carry a positive charge. In some nuclei this charge 'spins' on the nuclear axis, and this circulation of nuclear charge generates a magnetic dipole along the axis. Thus, the nucleus behaves like a tiny bar magnet. The angular momentum of the spinning charge is described in terms of nuclear magnetic moment (μ). The spinning nucleus of a hydrogen atom (1Hor proton) is the simplest and is commonly encountered in organic compounds. The hydrogen nucleus has a magnetic moment, $\mu = 1/2$.Hence, in an applied external magnetic field, its magnetic moment may have two possible orientations. The orientations in which the magnetic moment is aligned with the applied magnetic field is more stable (lower energy).The energy required for flipping the proton from its lower energy alignment to the higher energy alignment depends upon the difference in energy (ΔE) between the two states and is equal to $h\upsilon$ ($\Delta E = h\upsilon$). In principle, the substance could be placed in a magnetic field of constant strength, and then the spectrum can be obtained in the same way as an infrared or an ultraviolet spectrum by passing radiation of steadily changing frequency through the substance and observing the frequency at which radiation is absorbed. In practice,

however, it has been found to be more convenient to keep the radiation frequency constant and vary the strength of the magnetic field. At some value of the field strength the energy required to flip the proton matches the energy of the radiation, absorption occurs and a signal is obtained. Such a spectrum is called a nuclear magnetic resonance (NMR) spectrum.

Two types of NMR spectrometers are commonly encountered. They are

: a) Continuous wave (CW) NMR spectrometer.

b) Fourier transform (FT) NMR spectrometer.

The CW-NMR spectrometer detects the resonance frequencies of nuclei in a sample placed in a magnetic field by sweeping the frequency of RF radiation through a given range and directly recording the intensity of absorption as a function of frequency. The spectrum is usually recorded and plotted simultaneously with recorder synchronized to the frequency of the RF source.

In FT-NMR spectroscopy, the sample is subjected to a high power short duration pulse of RF radiation contains a broad band of frequencies and causes all the spin-active nuclei to resonate all at once at their Larmor frequencies. Immediately following the pulse, the sample radiates a signal called free induction decay (FID), which is modulated by all the frequencies of the nuclei return to equilibrium (intensity as a function of time) is recorded, digitized and stored as an array of numbers in a computer. Fourier transformation of the data affords a conventional (intensity as a function of frequency) representation of the spectrum. The first step in running NMR spectrum is the complete dissociation of a requisite

amount of the sample in the appropriate volume of a suitable NMR solvent. Commonly used solvents are: CCl_4, deuteron chloroform, deuteron DMSO, deuteron methanol, deuteron water, deuteron benzene, trifluroacetic acid.

TMS is generally employed as internal standard for measuring the position of ^{1}H, ^{13}C, and ^{29}Si in the NMR spectrum because it gives a signal sharp peak, is chemically inert miscible with a large range of solvents, being a highly volatile, can easily be removed if the sample has to be recovered, dose not involve in intramolecular association with the sample.

2.5.1 Interpretation of the PMR Spectra

It is not possible to prescribe a set of rules which is applicable on all occasions. The amount of additional information available will most probably determine the amount of information it is necessary to obtain from the PMR spectrum. However, the following general procedure will form a useful initial approach to the interpretation of most spectra.

- By making table of the chemical shifts of all the groups of absorptions in the spectrum. In some cases it will not be possible to decide whether a particular group of absorptions arises from separate sets of nuclei, or from a part of one complex multiplet. In such cases it is probably best initially to include them under one group and to note the spread of chemical shift values.
- By measuring and recording the heights of the integration steps corresponding to each group of absorptions. With overlapping groups of protons it may not be possible to measure these exactly, in which case a

range should be noted. Work out possible proton ratios for the range of heights measured, by dividing by the lowest height and multiplying as appropriate to give internal values.

- By noting any obvious splitting of the absorptions in the table (e.g.,doublet, triplet, etc.). For spectra which Chapter-III: SPECTRAL STUDIES NMR Spectroscopy 208 appears to show first-order splitting, the coupling constants of each multiplets should be determined by measuring the separation between adjacent peaks in the multiplet. Any other recognizable patterns which are not first should be noted.
- By noting any additional information such as the effect of shaking with D2O, use of shift reagent, etc.
- By considering both the relative intensities and the multiplicities of the absorptions attempt to determine which groups of protons are coupled together. The magnitude of the coupling constant may give indication of the nature of the proton involved.
- By relating the information obtained other information available on the compound under.

2.6 Mass spectrometry

A mass spectrometer can be used to determine the molecular mass, molecular formula and information regarding the structure of an organic molecule. In order to study the characteristics of individual molecules, a mass spectrometer converts them to ions so that they can be accelerated and separated by external electric and magnetic fields. The three essential components of a mass spectrometer [1a-c] and their associated functions are:

- The Ion Source: Here the compound to be analyzed is ionized, usually to cations by loss of an electron or by protonation.
- The Mass Analyzer: Here the ions are sorted and separated according to their mass to charge ratios.
- The Ion Detector: The separated ions are then detected, tallied and the results are displayed on a chart.

2.7 General remarks for the Experimental Techniques

- Melting points of all the compounds were measured by capillary method. All the mp's were uncorrected.
- The yield of all compounds reported are of crystallized. All the solvents used were distilled and dried. The purity of the compounds was checked by TLC. Column chromatography was performed on silica gel (60-120mesh).
- C, H, N and S contents of all the compounds were recorded on Thermofinigen 1101flash elemental analyzer.
- IR spectra were recorded in KBR pellets on Nicolet 760D spectrophotometer.
- ^{1}H-NMR spectra were recorded on bruker NMR spectrophotometer.
- MS of selected one sample of each series has been carried out on MSD Trap 01046 instrument using CH_3CN solvent.

SECTION-B

2.8 Experimental

The various chalcones of pyrazolone have been prepared as intermediate of post heterocyclized products. The synthesis and characterization of all the chalcones of pyrazolone are summarized in this section.

2.8.1 Materials

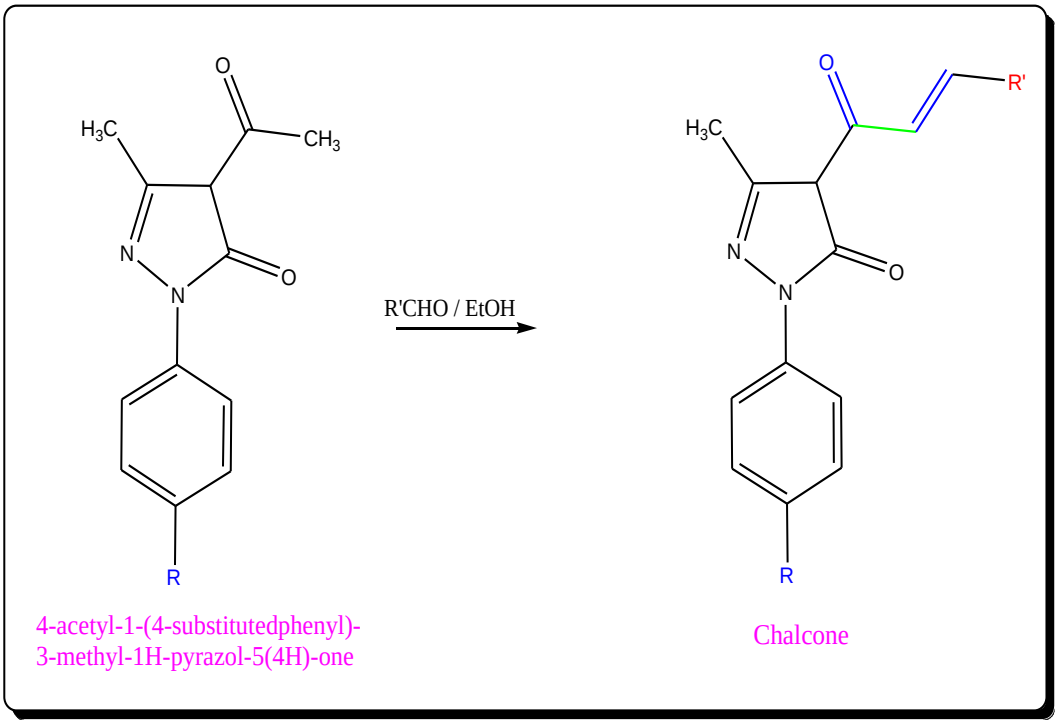
Acetyl pyrazolone i.e 4-acetyl-1-(4-methylphenyl)-3-methyl-1H-pyrazol-5(4H)-one and 4-acetyl-1-(4-chlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one were prepared by reported method. The various benzaldehyde derivatives were obtained from local market. All other chemical were analytical grade.

2.8.2 Synthesis of chalcones of 4-acetyl-1-(4-substitutedphenyl)-3-methyl-1H-pyrazol-5(4H)-one (2a-h) and (3a-h)

A mixture of 4-acetyl-1-(4-methylphenyl)-3-methyl-1H-pyrazol-5(4H)-one (0.01mol) and substituted aldehydes (0.01mol) in EtOH as solvent were mix in RBF. A solution of 40% KOH (5ml) was added and the resulting mixture stirred for 24hrs at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was poured into ice water and then neutralized with HCl. The solid was obtained by filtration, dried and purified by recrystalization from ethanol. The resultant chalcones are designated as 2a-h.

The various chalcones 3a-h have been prepared in similar manner.

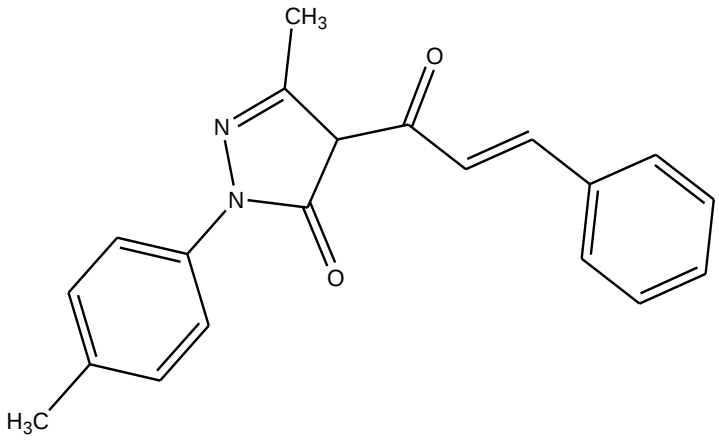
The formation of chalcone is presented in scheme 2.1



Where R = $-CH_3$ & -Cl

Where R'= a. phenyl
b. 4- hydroxy phenyl
c. 4- Nitro phenyl
d. 4- methoxy phenyl
e. 2- methyl phenyl
f. 4-chloro phenyl
g. 4- bromo phenyl
h. 4-methyl phenyl

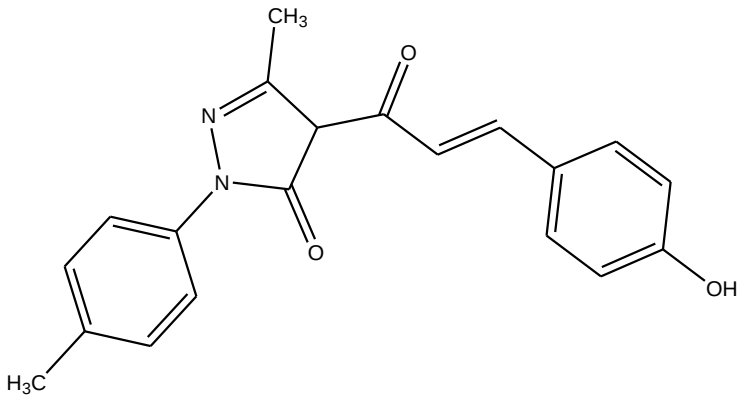
Compound -2a



5-Methyl-4-(3-phenyl-acryloyl)-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{18}N_2O_2$ Molecular weight : 318 gm/mol Melting point: 141-143 ^{0}C (uncorrected) Yield: 82%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 75.45 5.70 8.80 **Found** 75.50 5.72 8.79
IR features around Cm^{-1} 2893Aromatic C-H stretching 1669 C=O 1663,1593 α,β- unsaturated ketones 1605 C=N 1537 C=C	**^{1}H-NMR spectral features (δ-ppm)** 7.10-8.0 (9H,m, Ar-H) 6.88, 7.61 (2H,d, CH=CH) 3.2 (1H,s,Pyrazolone) 1.92 (3H,s,CH_3) 2.4 (3H,s,CH_3)

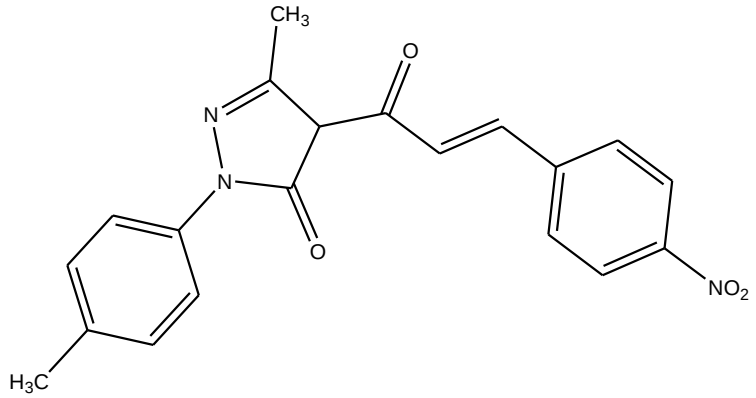
Compound -2b



4-[3-(4-Hydroxy-phenyl)-acryloyl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{18}N_2O_3$ Molecular weight : 334 gm/mol Melting point: 150-152 ^{0}C (uncorrected) Yield: 78%	**Elemental analysis** **%C** **% H** **% N** **Calculate** 71.84 5.43 8.38 **Found** 71.8 5.4 8.3
IR features around Cm^{-1} 3337 -OH(phenolic) 2896 Aromatic C-H stretching 1662 C=O 1658,1590 α,β- unsaturated ketones 1606 C=N 1542 C=C Ar	**^{1}H-NMR spectral features (δ-ppm)** 7.0-7.60 (8H,m, Ar-H) 6.91, 7.64 (2H,d, CH=CH) 3.40 (1H,s,Pyrazolone) 1.94 (3H,s,CH_3) 2.35 (3H,s,CH_3) 4.20 (1H,singlet,OH)

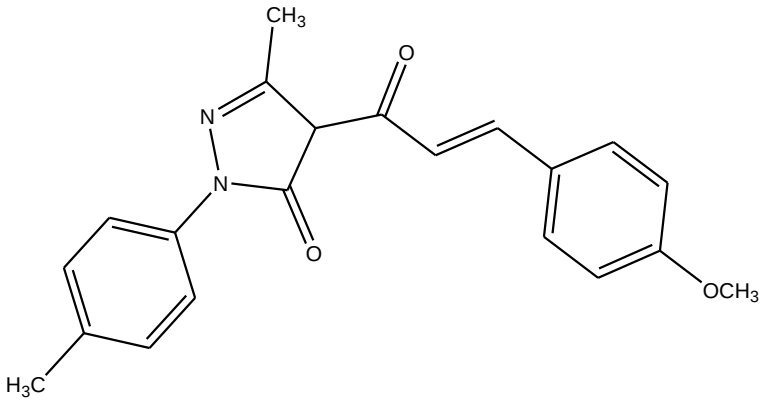
Compound -2c



5-Methyl-4-[3-(4-nitro-phenyl)-acryloyl]-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{17}N_3O_4$ Molecular weight : 363 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 77%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 66.11 4.72 11.56 **Found** 66.1 4.7 11.5
IR features around Cm^{-1} 2904 Aromatic C-H stretching 1674 C=O 1659,1596 α,β- unsaturated ketones 1609 C=N 1548 C=C conjugate	**^{1}H-NMR spectral features (δ-ppm)** 6.98-7.64 (8H,m, Ar-H) 6.94, 7.64 (2H,d, CH=CH) 3.35 (1H,s,Pyrazolone) 1.94 (3H,s,CH_3) 2.37 (3H,s,CH_3)

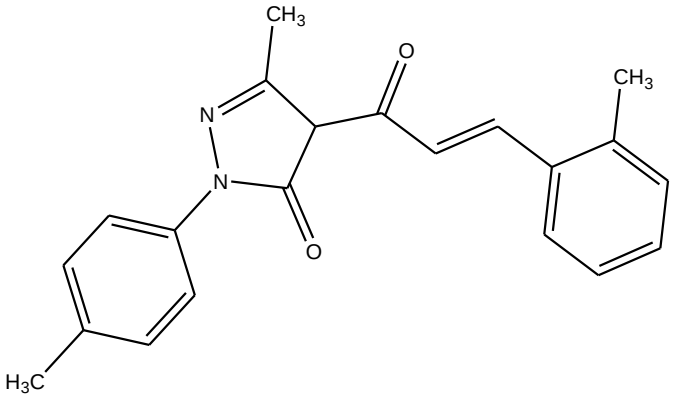
Compound-2d



4-[3-(4-Methoxy-phenyl)-acryloyl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{21}H_{20}N_2O_3$ Molecular weight : 348 gm/mol Melting point: 234-236 ^{0}C (uncorrected) Yield: 74%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 72.40 5.79 8.04 **Found** 72.3 5.7 8.0
IR features around Cm^{-1} 2900 Aromatic C-H stretching 1671C=O 1657,1591 α,β- unsaturated ketones 1609C=N 1542 C=C Ar 2830 -OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.1-7.60 (8H,m, Ar-H) 6.94, 7.64 (2H,d, CH=CH) 3.38 (1H,s,Pyrazolone) 1.94 (3H,s,CH_3) 2.38 (3H,s,CH_3) 3.68 (3H,s, 0CH_3)

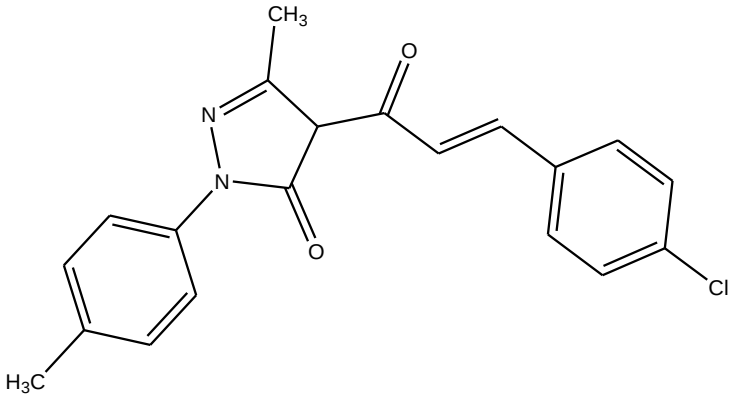
Compound -2e



5-Methyl-2-*p*-tolyl-4-(3-*o*-tolyl-acryloyl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{21}H_{20}N_2O_2$ Molecular weight : 332 gm/mol Melting point: 136-137 ^{0}C (uncorrected) Yield: 80%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 75.88 6.11 8.43 **Found** 75.8 6.0 8.4
IR features around Cm^{-1} 2897 Aromatic C-H stretching 1732 C=O 1664,1595 α,β- unsaturated ketones 1602 C=N 1542 C=C Ar	**^{1}H-NMR spectral features (δ-ppm)** 7.1-7.65 (8H,m, Ar-H) 6.91, 7.64 (2H,d, CH=CH) 3.46 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 2.36 (6H,s,CH_3)

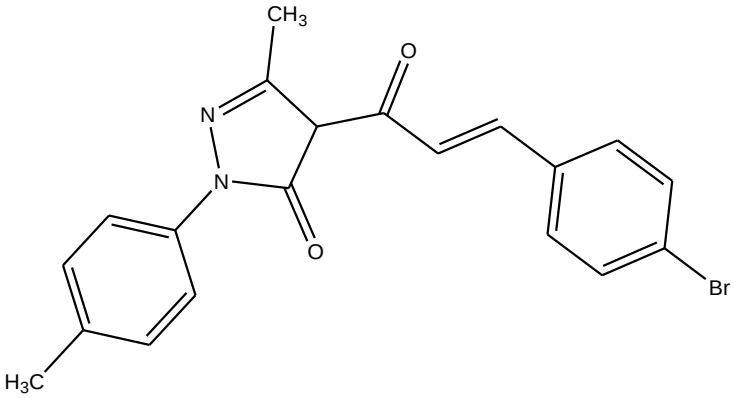
Compound -2f



4-[3-(4-Chloro-phenyl)-acryloyl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{17}ClN_2O_2$ Molecular weight : 352 gm/mol Melting point: 201-203 ^{0}C (uncorrected) Yield: 79%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 68.09 4.86 7.94 **Found** 68.0 4.8 7.9
IR features around Cm^{-1} 2907 Aromatic C-H stretching 1674 C=O 1660,1589 α,β- unsaturated ketones 1608 C=N 1540 C=C conjugate 1053 -C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.23-7.67 (8H,m, Ar-H) 6.92, 7.60 (2H,d, CH=CH) 3.38 (1H,s,Pyrazolone) 1.92 (3H,s,CH_3) 2.38 (3H,s,CH_3)

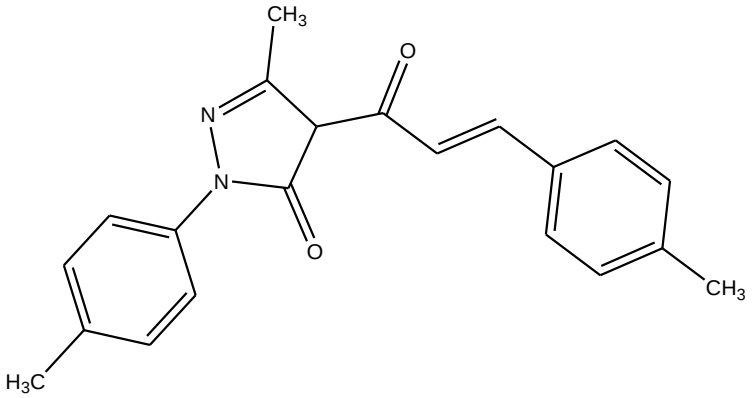
Compound -2g



4-[3-(4-Bromo-phenyl)-acryloyl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

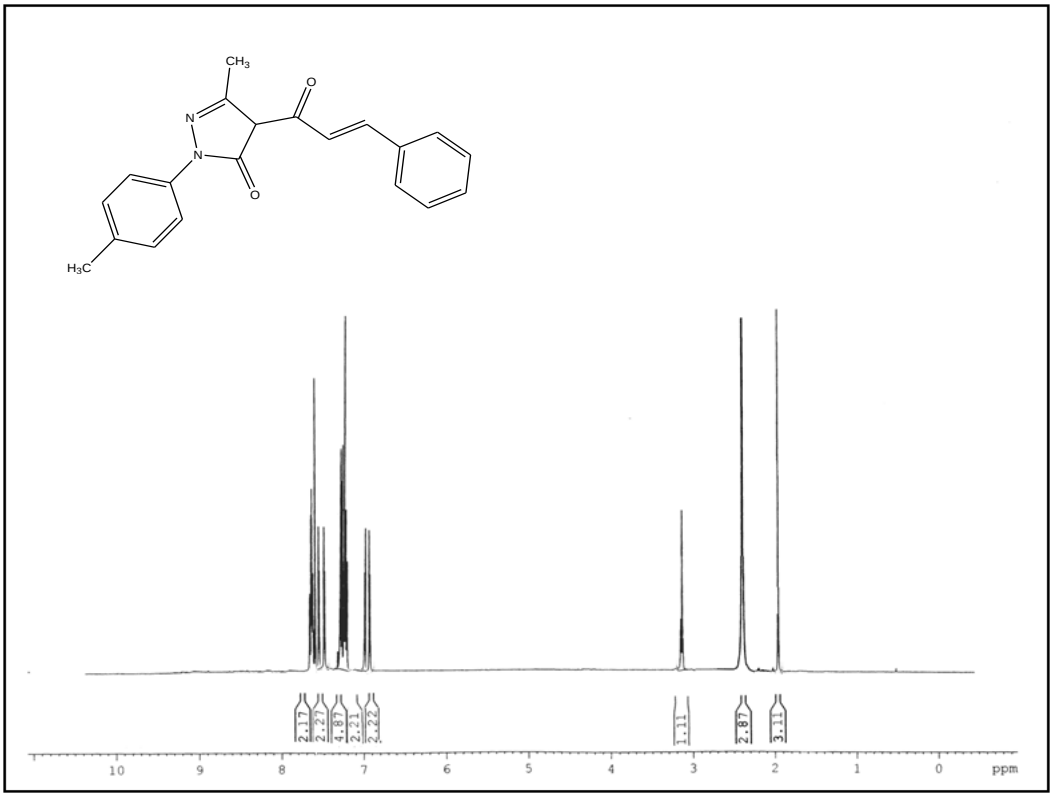
Molecular formula : $C_{20}H_{17}BrN_2O_2$ Molecular weight : 397 gm/mol Melting point: 141-143 ^{0}C (uncorrected) Yield: 82%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 75.45 5.70 8.80 **Found** 75.50 5.72 8.79
IR features around Cm^{-1} 2897 Aromatic C-H stretching 1672 C=O 1662,1588 α,β- unsaturated ketones 1604 C=N 1539 C=C Ar 1055 -C-Br	**^{1}H-NMR spectral features (δ-ppm)** 7.23-7.67 (8H,m, Ar-H) 6.94, 7.64 (2H,d, CH=CH) 3.42 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 2.35 (3H,s,CH_3)

Compound -2h

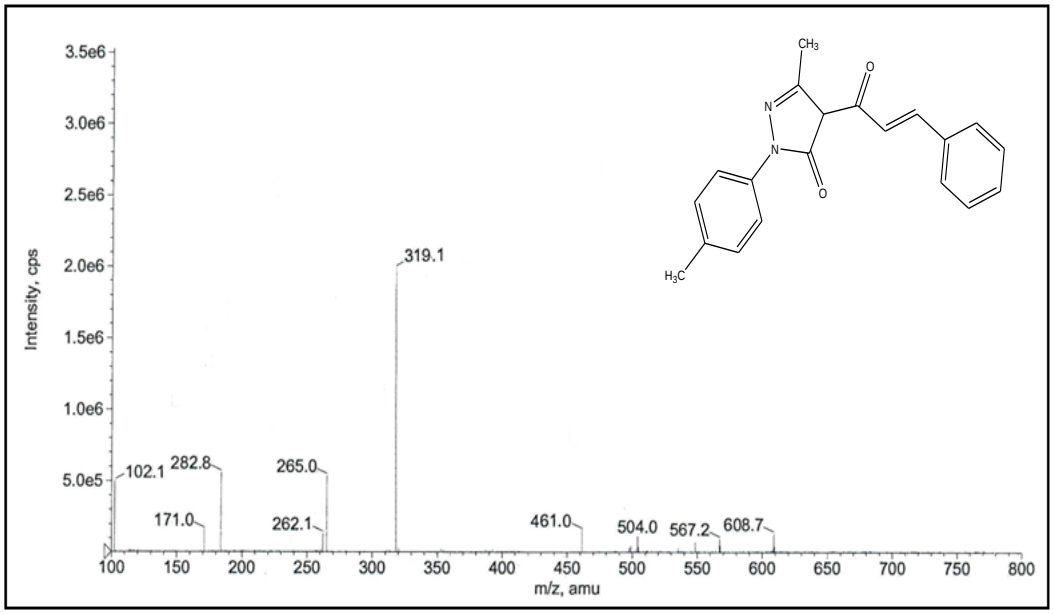


5-Methyl-2-*p*-tolyl-4-(3-*p*-tolyl-acryloyl)-2,4-dihydro-pyrazol-3-one

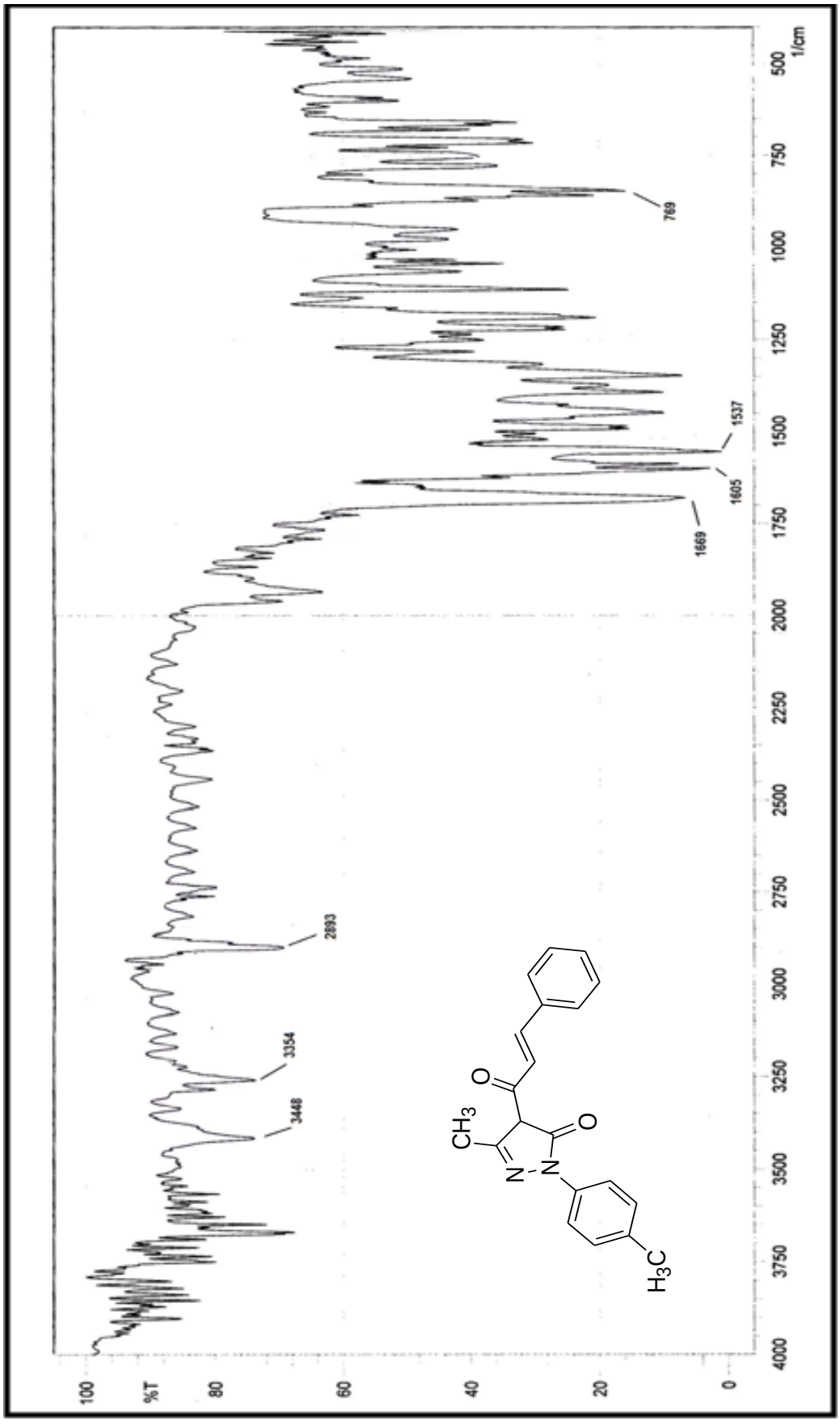
Molecular formula : $C_{21}H_{20}N_2O_2$ Molecular weight : 332 gm/mol Melting point: 195-196 ^{0}C (uncorrected) Yield: 75%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 75.88 6.06 8.43 **Found** 75.8 6.4 8.4
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1370 -CH_3 1676 C=O 1664,1590 α,β- unsaturated ketones 1605 C=N 1534 C=C conjugate	**^{1}H-NMR spectral features (δ-ppm)** 7.1-7.67 (9H,m, Ar-H) 6.94, 7.64 (2H,d, CH=CH) 3.42 (1H,s,Pyrazolone) 1.95 (3H,s,CH_3) 2.37 (6H,s,CH_3)



NMR Spectrum of Compound 2a

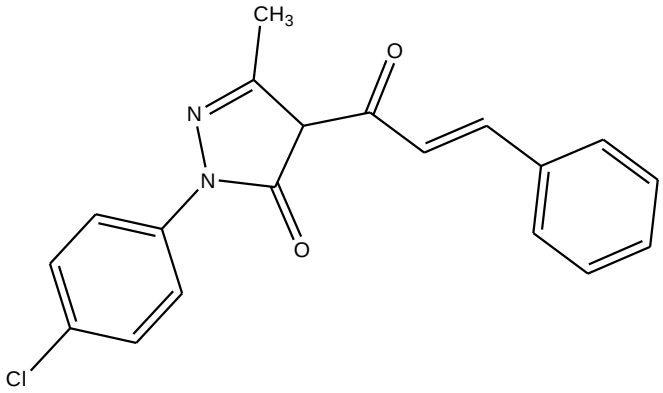


Mass Spectrum of Compound 2a



IR Spactrum of Compound 2a

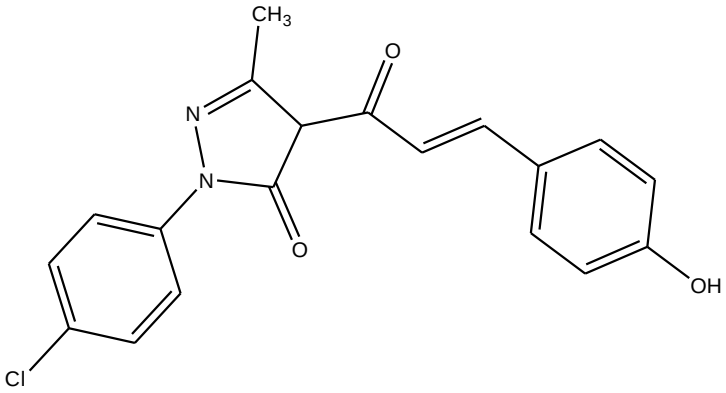
Compound -3a



2-(4-Chloro-phenyl)-5-methyl-4-(3-phenyl-acryloyl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{15}ClN_2O_2$ Molecular weight : 339 gm/mol Melting point: 195-196 ^{0}C (uncorrected) Yield: 75%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 67.36 4.46 8.27 **Found** 67.3 4.4 8.2
IR features around Cm^{-1} 2889 Aromatic C-H stretching 1675 C=O 1661,1588 α,β- unsaturated ketones 1602 C=N 1540 C=C Ar 1086 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.35-7.80 (9H,m, Ar-H) 6.94, 7.64 (2H,d, CH=CH) 3.38 (1H,s,Pyrazolone) 1.93 (3H,s,CH_3)

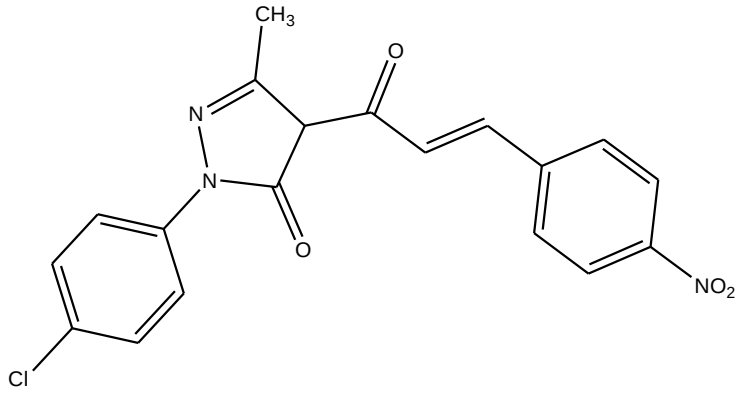
Compound -3b



2-(4-Chloro-phenyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{15}ClN_2O_3$ Molecular weight : 355 gm/mol Melting point: 186-188 ^{0}C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 64.32 4.26 7.90 **Found** 67.2 4.2 7.9
IR features around Cm^{-1} 3452 -OH 2887 Aromatic C-H stretching 1670 C=O 1663,1593 α,β- unsaturated ketones 1601 C=N 1530 C=C Ar 1085 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.10-8.0 (8H,m, Ar-H) 6.88, 7.6 (2H,d, CH=CH) 3.2 (1H,s,Pyrazolone) 1.92 (3H,s,CH_3) 5.56 (1H,singlet OH)

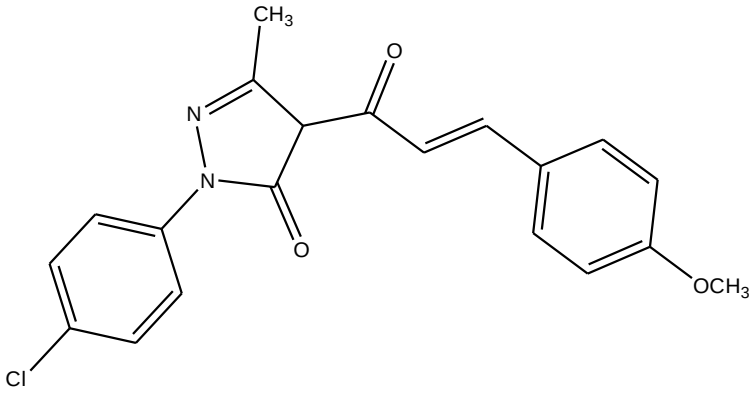
Compound -3c



2-(4-Chloro-phenyl)-5-methyl-4-[3-(4-nitro-phenyl)-acryloyl]-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{14}ClN_3O_4$ Molecular weight : 383 gm/mol Melting point: 176-177 ^{0}C (uncorrected) Yield: 70%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 59.46 3.68 10.95 **Found** 59.3 3.6 10.9
IR features around Cm^{-1} 2885 Aromatic C-H stretching 1665 C=O 1660,1595 α,β- unsaturated ketones 1607 C=N 1534 C=C Ar 1090 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.05-7.80 (9H,m, Ar-H) 6.91, 7.64 (2H,d, CH=CH) 3.34 (1H,s,Pyrazolone) 1.90 (3H,s,CH_3)

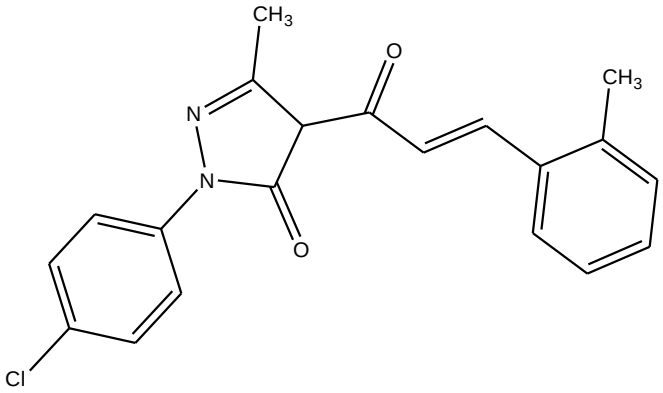
Compound -3d



2-(4-Chloro-phenyl)-4-[3-(4-methoxy-phenyl)-acryloyl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{17}ClN_2O_3$ Molecular weight : 369 gm/mol Melting point: 246-250 ^{0}C (uncorrected) Yield: 73%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.13 4.65 7.60 **Found** 65.1 4.6 7.5
IR features around Cm^{-1} 2887 Aromatic C-H stretching 1670 C=O 1663,1593 α,β- unsaturated ketones 1601 C=N 1530 C=C Ar 1081 C-Cl 2848 -OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.1-7.80 (9H,m, Ar-H) 6.91, 7.62 (2H,d, CH=CH) 3.34 (1H,s,Pyrazolone) 1.90 (3H,s,CH_3) 3.64 (1H,s,OCH_3)

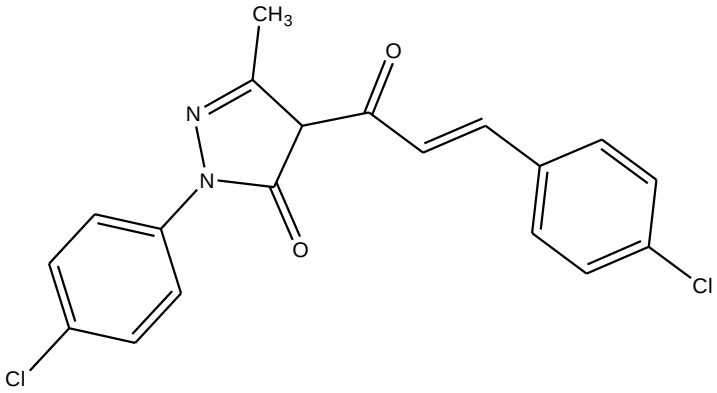
Compound -3e



2-(4-Chloro-phenyl)-5-methyl-4-(3-*o*-tolyl-acryloyl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{17}ClN_2O_2$ Molecular weight : 353 gm/mol Melting point: 160-162 ^{0}C (uncorrected) Yield: 78%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 68.09 4.86 7.94 **Found** 68.0 4.8 7.9
IR features around Cm^{-1} 2889 Aromatic C-H stretching 1667 C=O 1660,1592 α,β- unsaturated ketones 1602 C=N 1537 C=C Ar 1083 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.05-7.80 (8H,m, Ar-H) 6.94, 7.64 (2H,d, CH=CH) 3.29 (1H,s,Pyrazolone) 1.92 (3H,s,CH_3) 2.42 (3H,s,3H)

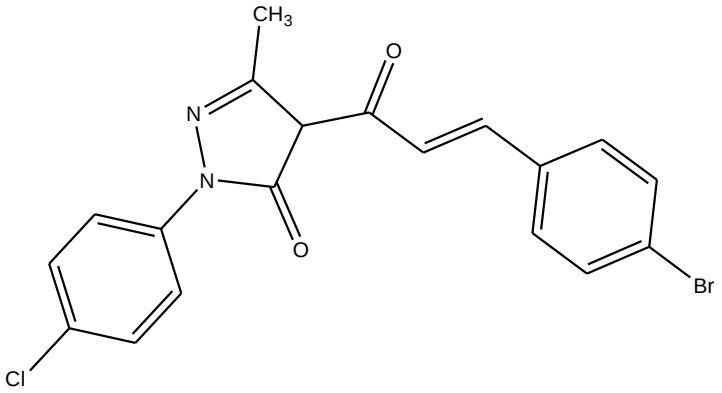
Compound -3f



2-(4-Chloro-phenyl)-4-[3-(4-chloro-phenyl)-acryloyl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{14}Cl_2N_2O_2$ Molecular weight : 373 gm/mol Melting point: 215-216 ^{0}C (uncorrected) Yield: 68%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 61.14 3.78 7.51 **Found** 61.1 3.7 7.4
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1665 C=O 1666,1592 α,β- unsaturated ketones 1609 C=N 1532 C=C Ar 1081 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.35-7.80 (9H,m, Ar-H) 6.94, 7.62 (2H,d, CH=CH) 3.28 (1H,s,Pyrazolone) 1.93 (3H,s,CH_3)

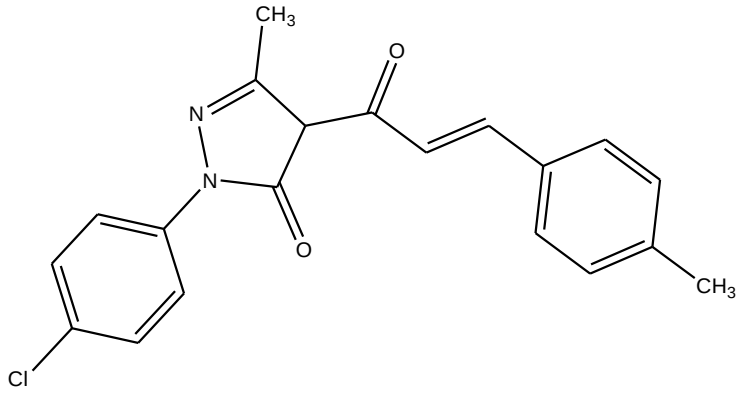
Compound -3g



4-[3-(4-Bromo-phenyl)-acryloyl]-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

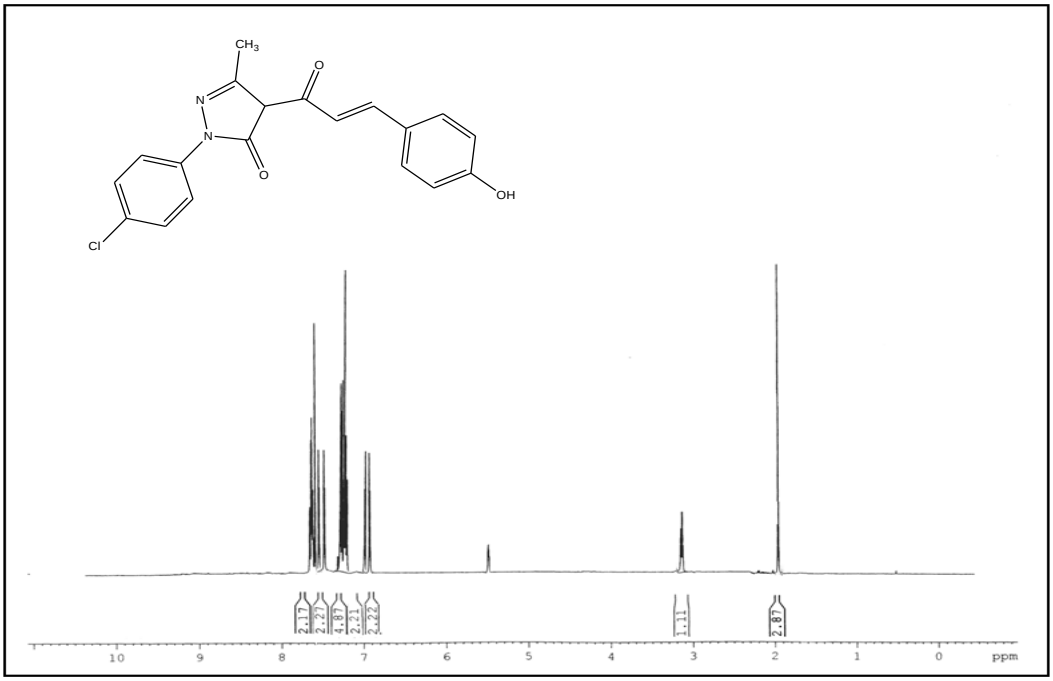
Molecular formula : $C_{19}H_{14}BrClN_2O_2$ Molecular weight : 415 gm/mol Melting point: 221-224 ^{0}C (uncorrected) Yield: 65%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 56.64 3.38 6.71 **Found** 54.5 3.3 6.6
IR features around Cm^{-1} 2885 Aromatic C-H stretching 1665 C=O 1660,1595 α,β- unsaturated ketones 1607 C=N 1534 C=C Ar 1080 C-Cl 1053 C-Br	**^{1}H-NMR spectral features (δ-ppm)** 7.35-7.80 (9H,m, Ar-H) 6.93, 7.62 (2H,d, CH=CH) 3.22 (1H,s,Pyrazolone) 1.95 (3H,s,CH_3)

Compound -3h

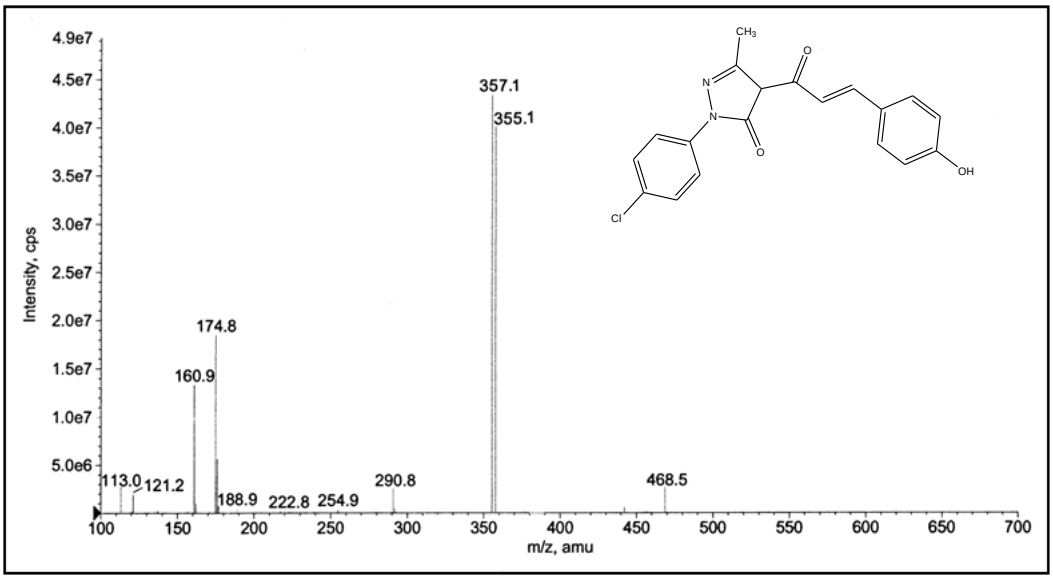


2-(4-Chloro-phenyl)-5-methyl-4-(3-*p*-tolyl-acryloyl)-2,4-dihydro-pyrazol-3-one

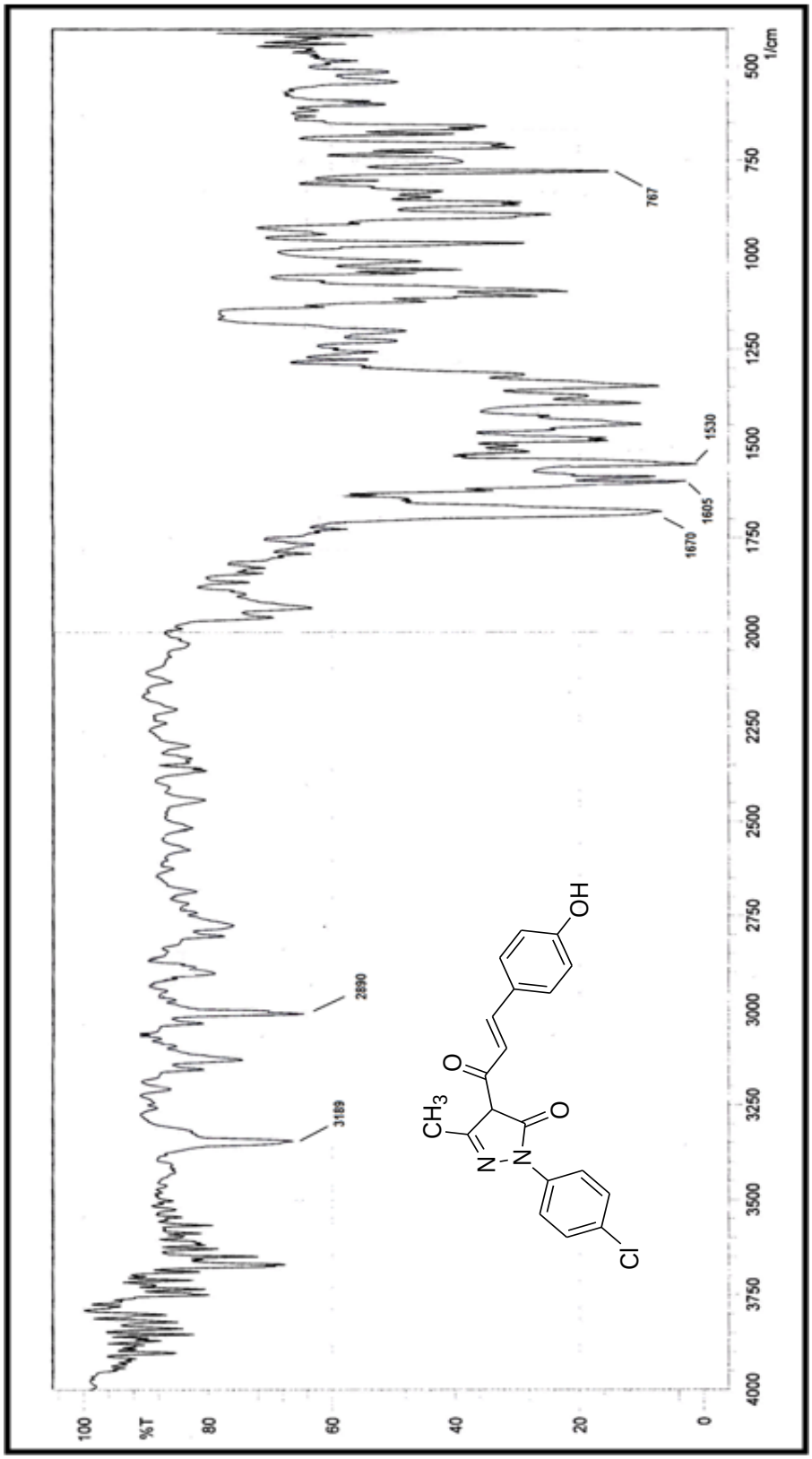
Molecular formula : $C_{20}H_{17}ClN_2O_2$ Molecular weight : 353 gm/mol Melting point:212-214 ^{0}C (uncorrected) Yield: 62%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 68.09 4.86 7.94 **Found** 68.0 4.8 7.9
IR features around Cm^{-1} 2892 Aromatic C-H stretching 1669 C=O 1662,1595 α,β- unsaturated ketones 1604 C=N 1538 C=C Ar 1084 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.35-7.80 (9H,m, Ar-H) 6.94, 7.64 (2H,d, CH=CH) 3.38 (1H,s,Pyrazolone) 1.93 (3H,s,CH_3) 2.30 (3H,s,CH_3)



NMR Spectrum of compound 3b



Mass Spectrum of Compound 3b



IR Spactrum of Compound 3b

SECTION-C

2.9 Experimental

The various Schiff bases of pyrazolone have been prepared as intermediate of post heterocyclized products. The synthesis and characterization of all the Schiff bases of pyrazolone are summarized in this section.

2.9.1 Materials

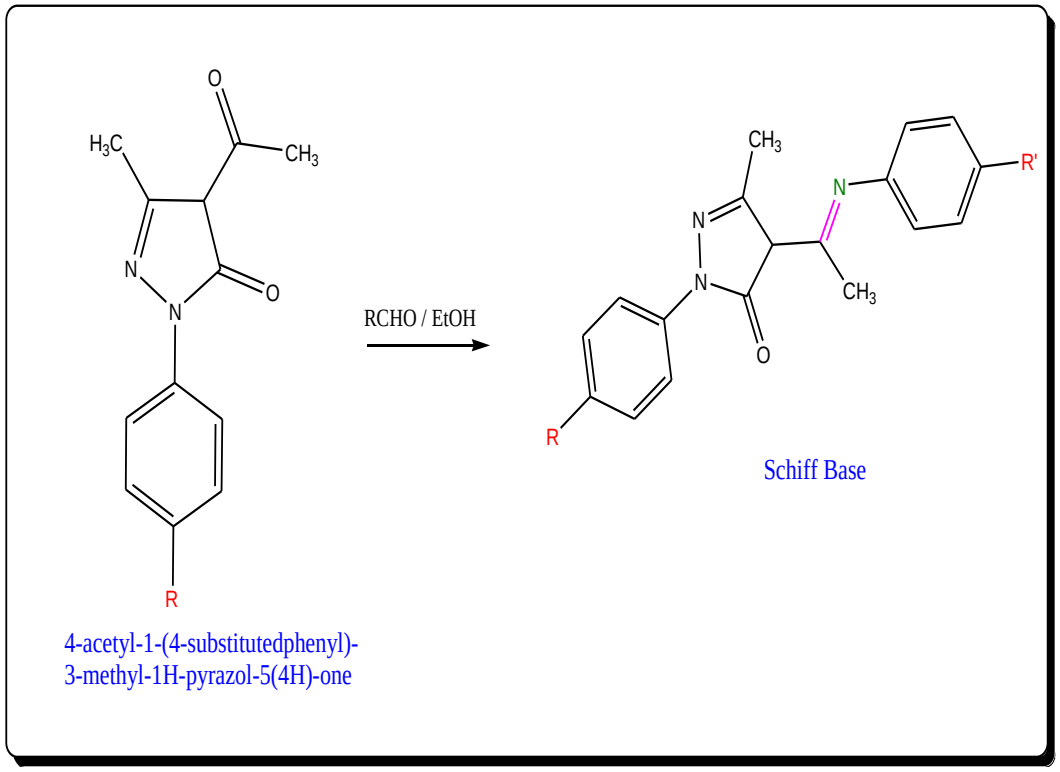
Acetyl pyrazolone i.e 4-acetyl-1-(4-methylphenyl)-3-methyl-1H-pyrazol-5(4H)-one and 4-acetyl-1-(4-chlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one were prepared by reported method. The various aniline derivatives were obtained from local market. All other chemical were analytical grade.

2.9.2 Synthesis of Schiff bases of 4-acetyl-1-(4-substitutedphenyl)-3-methyl-1H-pyrazol-5(4H)-one (4a-h), (5a-h), (6a-f) and (7a-f)

4-acetyl-1-(4-substitutedphenyl)-3-methyl-1H-pyrazol-5(4H)-one (0.01mol) is treated with substituted amine(0.01 mol) in ethanol and reflux for 3- 5 hrs. Then mixture is cooled. Solid yellow product filtered and washed with methanol or ethanol. The resultant schiff bases are designated as 4a-h & 5a-h

The various schiff bases 6a-h & 7a-h have been prepared in similar manner.

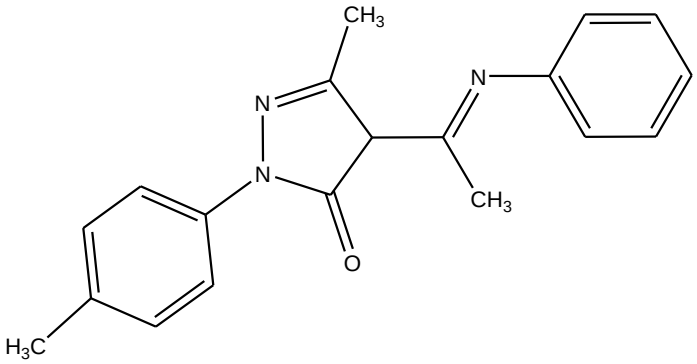
Formation of Schiff base is presented in scheme 2.2



Where R = $-CH_3$ & -Cl

Where R'= a. phenyl
b. 4- chloro phenyl
c. 3- chlorophenyl
d. 4- methyl phenyl
e. 4-nitro phenyl
f. isoniazide
g. 4- methoxy phenyl
h.nicotinic acid

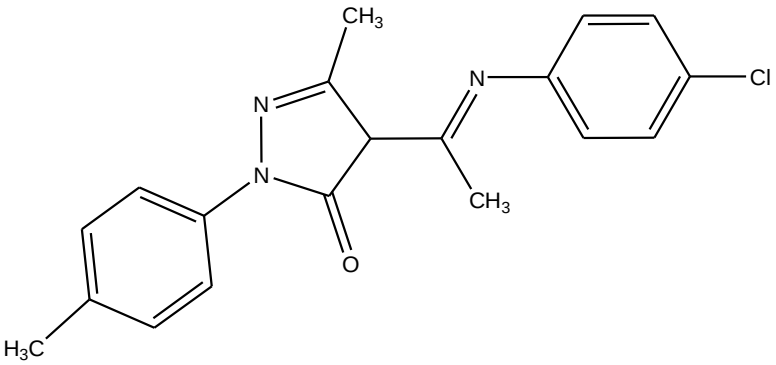
Compound -4a



5-Methyl-4-(1-phenylimino-ethyl)-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{19}N_3O$ Molecular weight : 305 gm/mol Melting point:212-214 ^{0}C (uncorrected) Yield: 82%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 74.73 6.27 13.76 **Found** 74.7 6.3 13.78
IR features around Cm^{-1} 2893 Aromatic C-H stretching 1669 C=O 1605 C=N 1182 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.1-8.0 (9H,m, Ar-H) 2.4 (1H,s,Pyrazolone) 1.92 (6H,s,2CH_3) 2.30 (3H,s,CH_3)

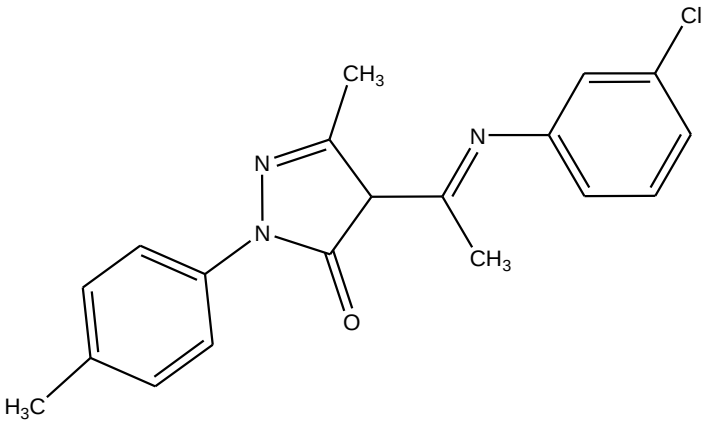
Compound -4b



4-[1-(4-Chloro-phenylimino)-ethyl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{18}ClN_3O$ Molecular weight : 339 gm/mol Melting point:197-198 ^{0}C (uncorrected) Yield: 79%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 67.15 5.34 12.37 **Found** 67.16 5.35 12.33
IR features around Cm^{-1} 2889 Aromatic C-H stretching 1672 C=O 1609 C=N 1186 C-N str. 763 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.35-7.80 (8H,m, Ar-H) 2.46 (1H,s,Pyrazolone) 1.94 (6H,s,2CH_3) 2.32 (3H,s,CH_3)

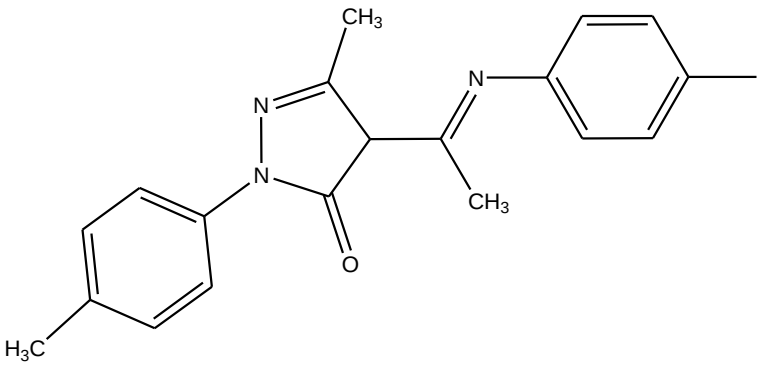
Compound -4c



4-[1-(3-Chloro-phenylimino)-ethyl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{18}ClN_3O$ Molecular weight : 339 gm/mol Melting point:201-203 ^{0}C (uncorrected) Yield: 77%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 67.15 5.34 12.37 **Found** 67.16 5.37 12.36
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1666 C=O 1598 C=N 1180 C-N str. 766 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.37-7.82 (8H,m, Ar-H) 2.48 (1H,s,Pyrazolone) 1.94 (6H,s,2CH_3) 2.30 (3H,s,CH_3)

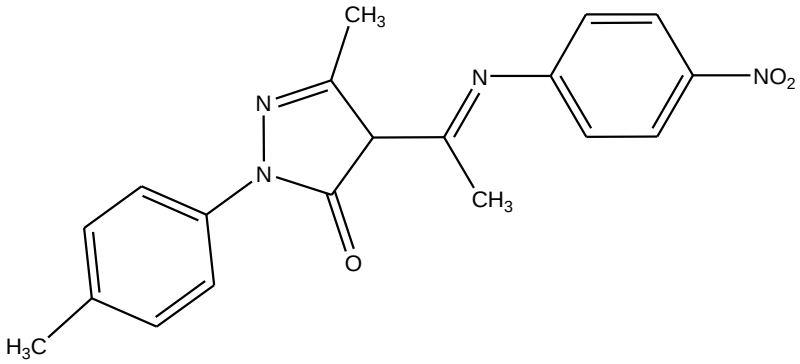
Compound -4d



5-Methyl-2-*p*-tolyl-4-(1-*p*-tolylimino-ethyl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{21}N_3O$ Molecular weight : 319 gm/mol Melting point:181-182 ^{0}C (uncorrected) Yield: 74%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 75.21 6.63 13.16 **Found** 75.2 6.65 13.13
IR features around Cm^{-1} 2886 Aromatic C-H stretching 1373 CH_3 1671 C=O 1602 C=N 1183 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.35-7.80 (8H,m, Ar-H) 2.48 (1H,s,Pyrazolone) 1.95 (6H,s,2CH_3) 2.37 (6H,s,2CH_3)

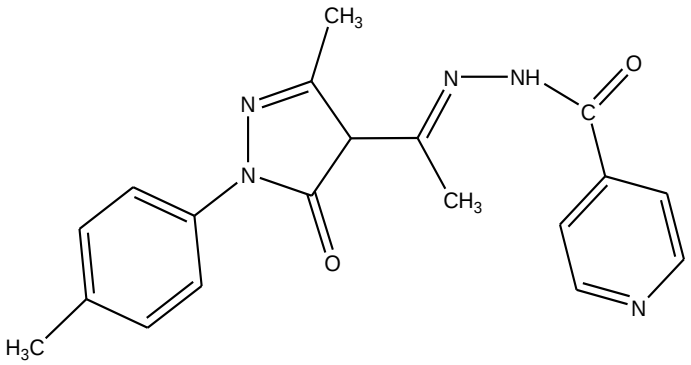
Compound -4e



5-Methyl-4-[1-(4-nitro-phenylimino)-ethyl]-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{18}N_4O_3$ Molecular weight : 350 gm/mol Melting point:186-187 ^{0}C (uncorrected) Yield: 78%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.13 5.18 15.99 **Found** 65.1 5.19 16.02
IR features around Cm^{-1} 2889 Aromatic C-H stretching 1673 C=O 1605 C=N 1181 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.23-7.78 (8H,m, Ar-H) 2.46 (1H,s,Pyrazolone) 1.94 (6H,s,2CH_3) 2.32 (3H,s,CH_3)

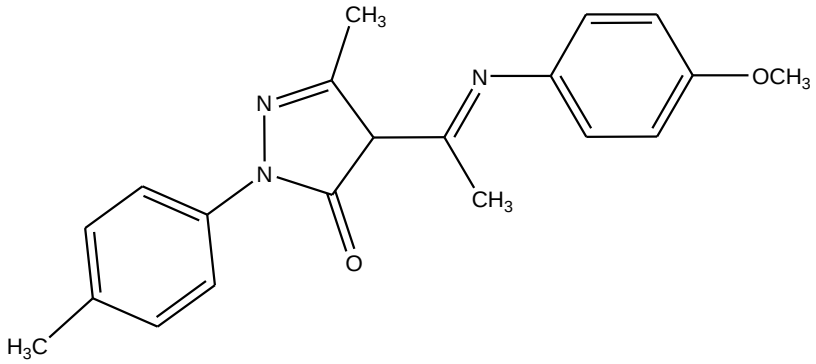
Compound -4f



Isonicotinic acid [1-(3-methyl-5-oxo-1-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-4-yl)-ethylidene]-hydrazide

Molecular formula : $C_{19}H_{19}N_5O_2$ Molecular weight : 349gm/mol Melting point:212-214 ^{0}C (uncorrected) Yield: 79%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.32 5.48 20.04 **Found** 65.3 5.5 20.02
IR features around Cm^{-1} 2895 Aromatic C-H stretching 1673 C=O 1609 C=N 1179 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.10-7.80 (8H,m, Ar-H) 2.47 (1H,s,Pyrazolone) 1.92 (6H,s,2CH_3) 2.36 (3H,s,CH_3) 6.92 (1H,s,NH)

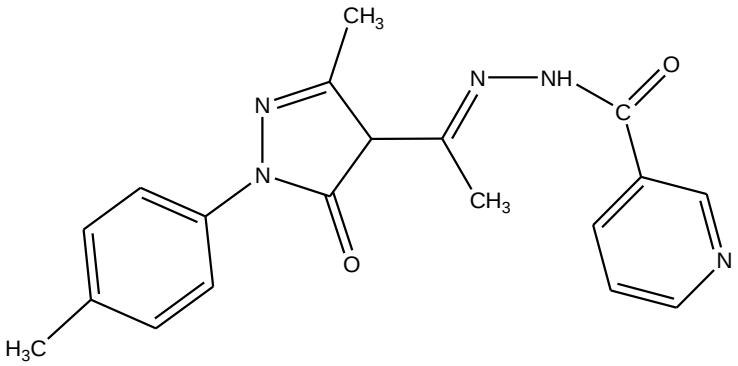
Compound -4g



4-[1-(4-Methoxy-phenylimino)-ethyl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

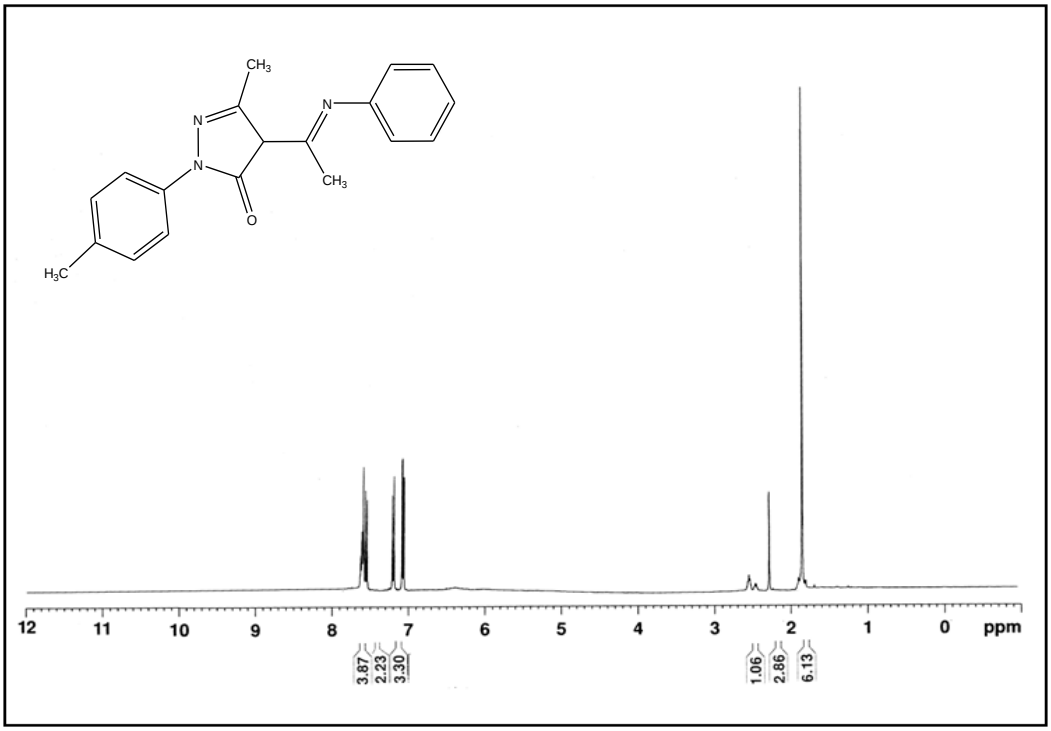
Molecular formula : $C_{20}H_{21}N_3O_2$ Molecular weight : 335 gm/mol Melting point:179-181 ^{0}C (uncorrected) Yield: 74%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 71.62 6.31 12.53 **Found** 71.60 6.32 12.5
IR features around Cm^{-1} 2888 Aromatic C-H stretching 1669 C=O 1605 C=N 1184 C-N str. OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.23-8.12 (8H,m, Ar-H) 2.43 (1H,s,Pyrazolone) 1.91 (6H,s,2CH_3) 2.34 (3H,s,CH_3) 3.73 (3H,s,OCH_3)

Compound -4h

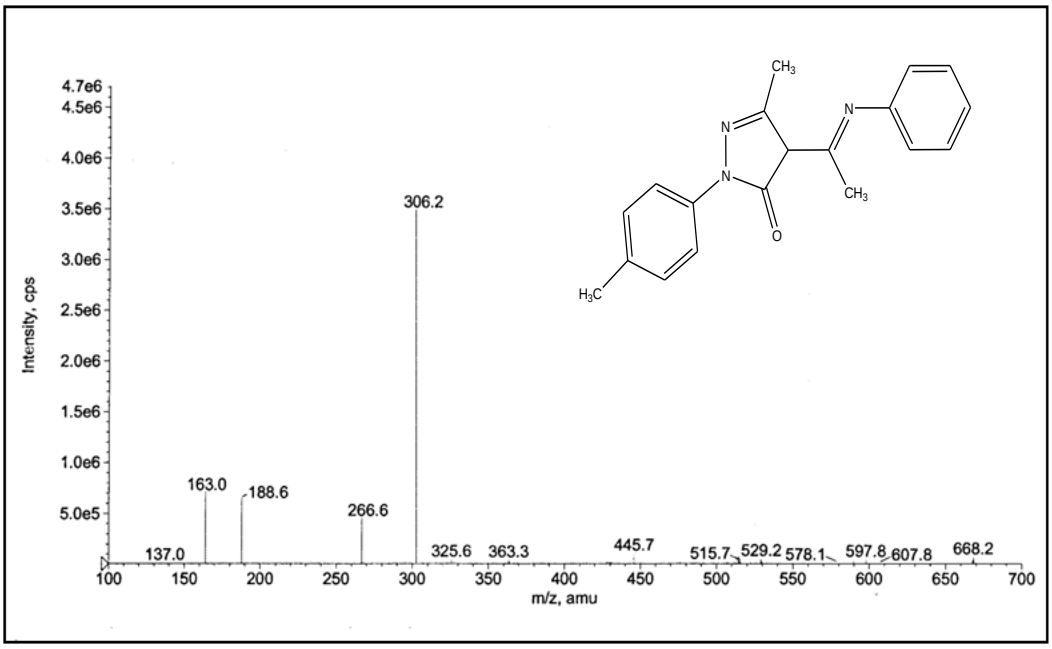


Nicotinic acid [1-(3-methyl-5-oxo-1-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-4-yl)-ethylidene]-hydrazide

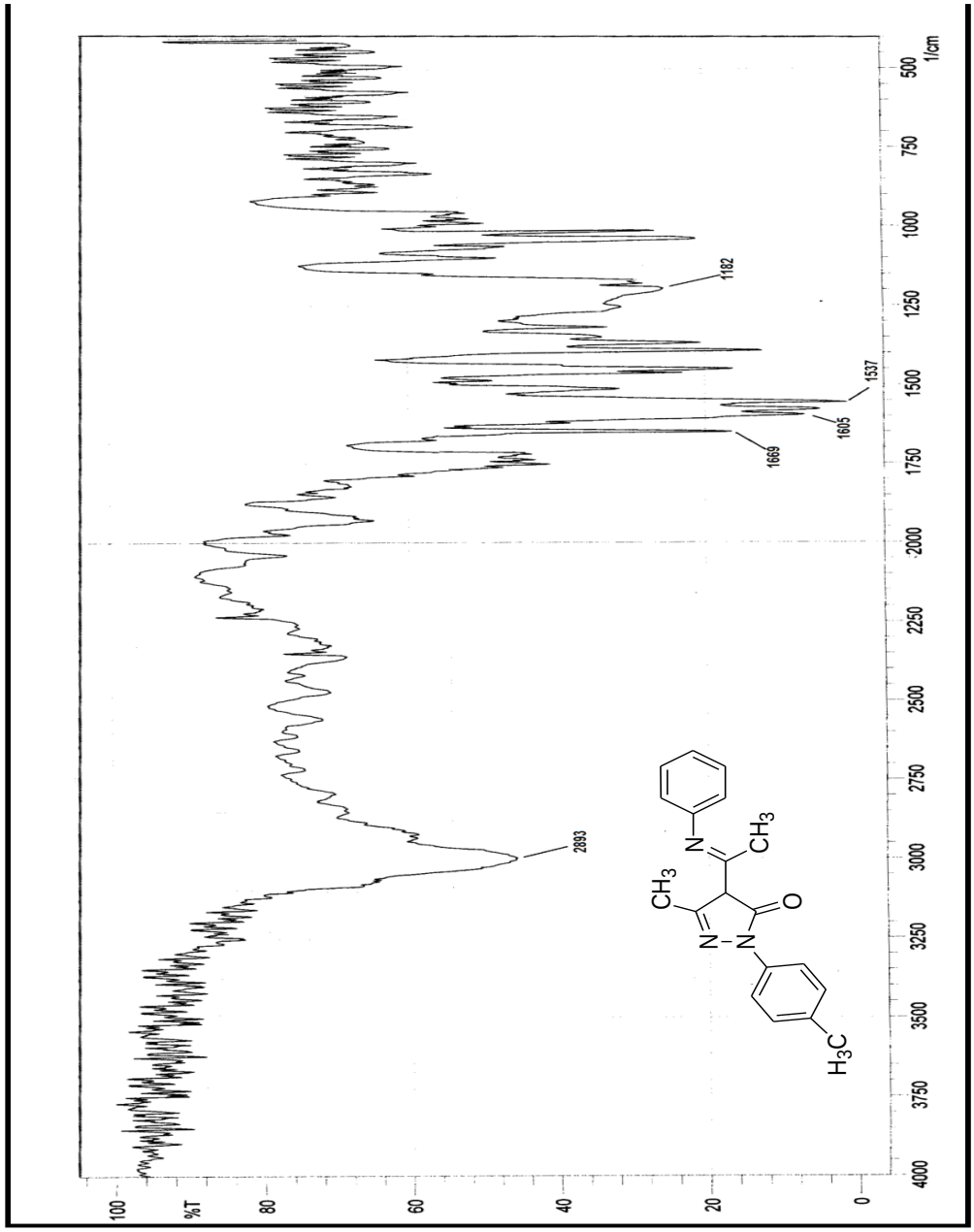
Molecular formula : $C_{19}H_{19}N_5O_2$ Molecular weight : 349gm/mol Melting point:208-210 ^{0}C (uncorrected) Yield: 77%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.32 5.48 20.04 **Found** 65.31 5.5 20.02
IR features around Cm^{-1} 2893 Aromatic C-H stretching 1670 C=O 1602 C=N 1182 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.10-7.88 (8H,m, Ar-H) 2.44 (1H,s,Pyrazolone) 1.95 (6H,s,2CH_3) 2.38 (3H,s,CH_3) 6.96 (1H,s,NH)



NMR Spectrum of Compound 4a

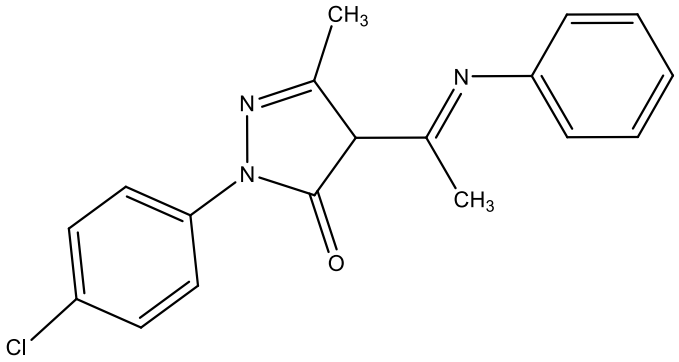


Mass Spectrum of compound 4a



IR Spactrum of Compound 4a

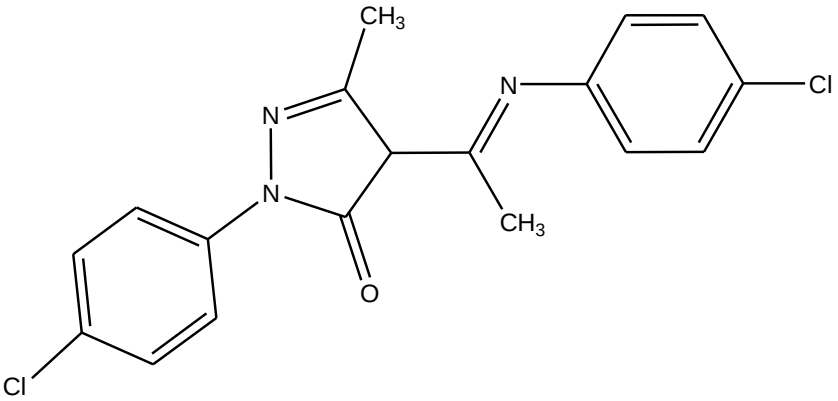
Compound -5a



2-(4-Chloro-phenyl)-5-methyl-4-(1-phenylimino-ethyl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{18}H_{16}ClN_3O$ Molecular weight : 325 gm/mol Melting point:171-172 ^{0}C (uncorrected) Yield: 73%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 66.36 4.95 12.90 **Found** 66.38 4.96 12.89
IR features around Cm^{-1} 2893 Aromatic C-H stretching 1669 C=O 1605 C=N 1182 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.35-8.23 (9H,m, Ar-H) 2.42 (1H,s,Pyrazolone) 1.94 (6H,s,2CH_3)

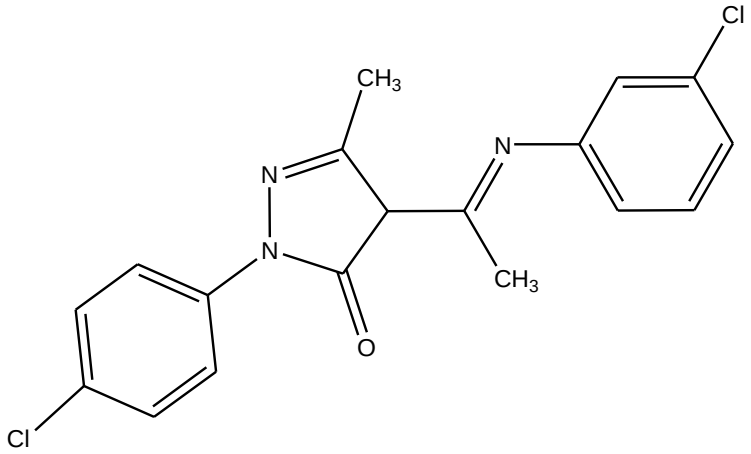
Compound -5b



2-(4-Chloro-phenyl)-4-[1-(4-chloro-phenylimino)-ethyl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{18}H_{15}Cl_2N_3O$ Molecular weight : 359 gm/mol Melting point:196-198 ^{0}C (uncorrected) Yield: 72%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 60.01 4.20 19.68 **Found** 60.02 4.19 19.7
IR features around Cm^{-1} 2897 Aromatic C-H stretching 1676 C=O 1609 C=N 1185 C-N str 767. C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.42-8.18 (8H,m, Ar-H) 2.46 (1H,s,Pyrazolone) 1.92 (6H,s,2CH_3)

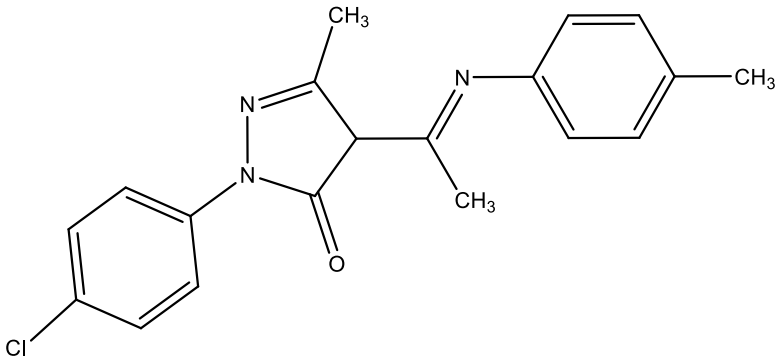
Compound -5c



2-(4-Chloro-phenyl)-4-[1-(3-chloro-phenylimino)-ethyl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{18}H_{15}Cl_2N_3O$ Molecular weight : 359 gm/mol Melting point:199-201 ^{0}C (uncorrected) Yield: 75%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 60.01 4.20 19.68 **Found** 60.02 4.22 19.7
IR features around Cm^{-1} 2895 Aromatic C-H stretching 1676 C=O 1609 C=N 1186 C-N str 764. C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.46-8.10 (9H,m, Ar-H) 2.46 (1H,s,Pyrazolone) 1.92 (6H,s,2CH_3)

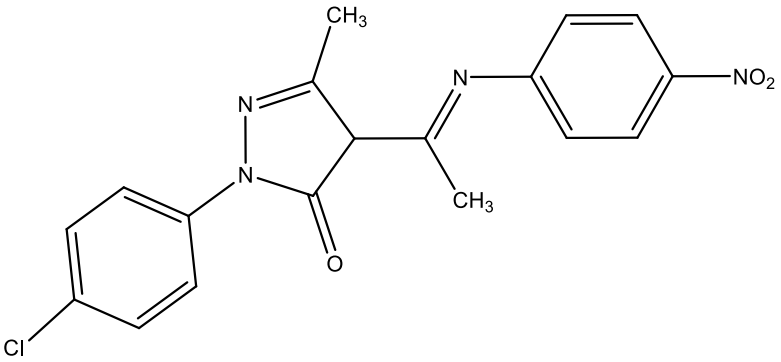
Compound -5d



2-(4-Chloro-phenyl)-5-methyl-4-(1-*p*-tolylimino-ethyl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{18}ClN_3O$ Molecular weight : 339 gm/mol Melting point:177-179 ^{0}C (uncorrected) Yield: 69%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 67.15 5.34 12.37 **Found** 67.16 5.3 12.35
IR features around Cm^{-1} 2892 Aromatic C-H stretching 1376 CH_3 1669 C=O 1605 C=N 1182 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.51-8.16 (9H,m, Ar-H) 2.48 (1H,s,Pyrazolone) 1.94 (6H,s,2CH_3) 2.38 (3H,s,CH_3)

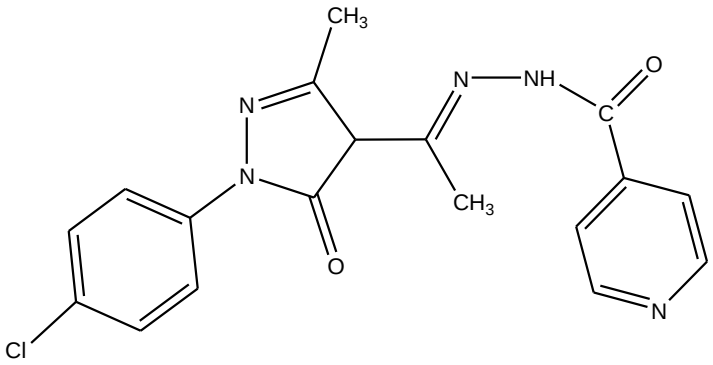
Compound -5e



2-(4-Chloro-phenyl)-5-methyl-4-[1-(4-nitro-phenylimino)-ethyl]-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{18}H_{15}ClN_4O_3$ Molecular weight : 370 gm/mol Melting point:186-187 ^{0}C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 58.31 4.08 9.56 **Found** 58.3 5.01 9.57
IR features around Cm^{-1} 2888 Aromatic C-H stretching 1673 C=O 1607 C=N 1179 C-N str. NO_2	**^{1}H-NMR spectral features (δ-ppm)** 7.53-8.1 (8H,m, Ar-H) 2.43 (1H,s,Pyrazolone) 1.96 (6H,s,2CH_3)

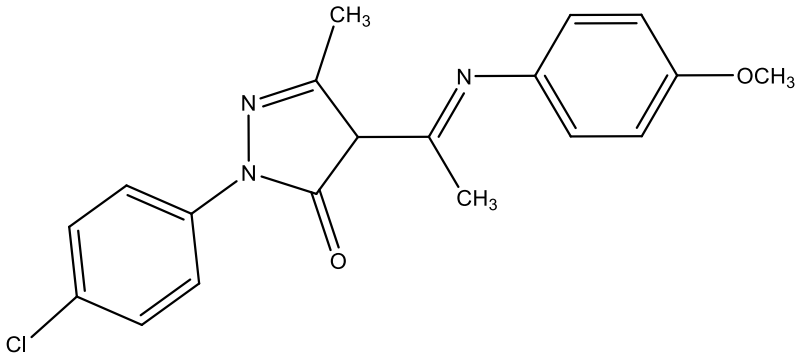
Compound -5f



Isonicotinic acid {1-[1-(4-chloro-phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl]-ethylidene}-hydrazide

Molecular formula : $C_{18}H_{16}ClN_5O_2$ Molecular weight : 369 gm/mol Melting point:183-1184 ^{0}C (uncorrected) Yield: 79%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 58.46 4.36 18.94 **Found** 58.48 4.35 18.95
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1671 C=O 1602 C=N 1177 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.10-8.5 (9H,m, Ar-H) 2.4 (1H,s,Pyrazolone) 1.92 (6H,s,2CH_3) 7.0 (1H,s,NH)

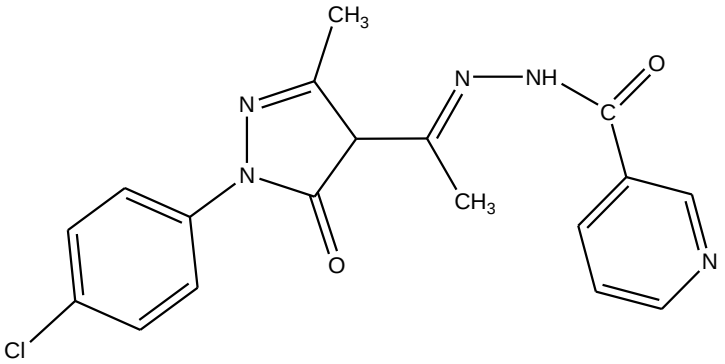
Compound -5g



2-(4-Chloro-phenyl)-4-[1-(4-methoxy-phenylimino)-ethyl]-5-methyl-2,4-dihydro-pyrazol-3-one

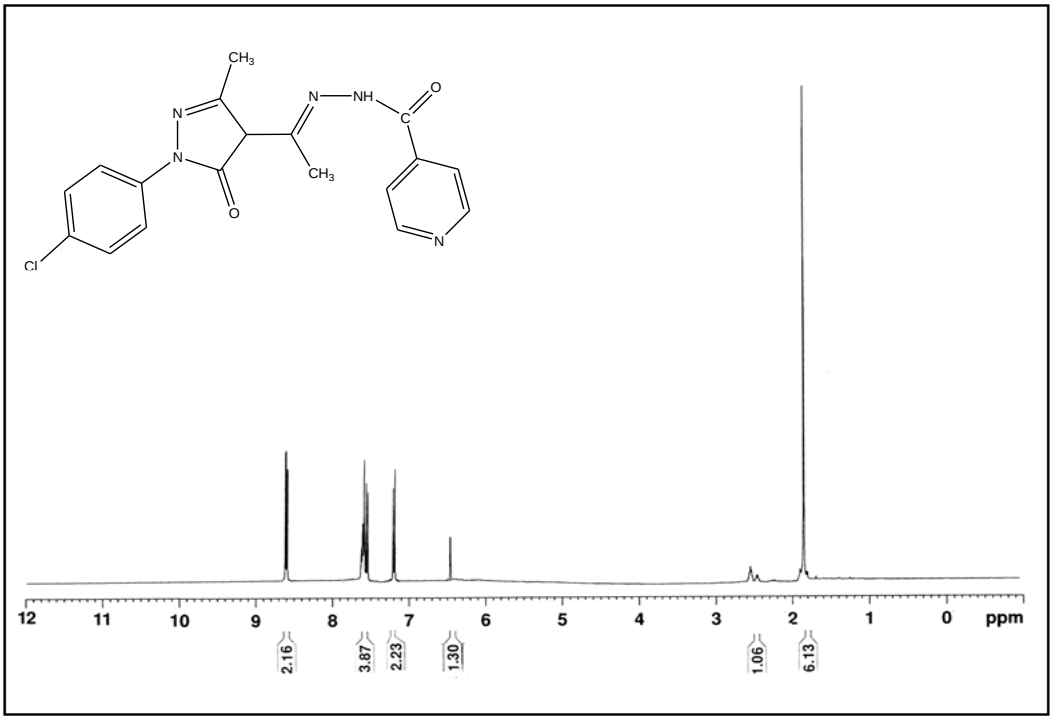
Molecular formula : $C_{19}H_{18}N_3O_2$ Molecular weight : 355 gm/mol Melting point:210-211 ^{0}C (uncorrected) Yield: 82%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 64.13 5.10 11.81 **Found** 64.1 5.09 11.82
IR features around Cm^{-1} 2893 Aromatic C-H stretching 1667 C=O 1599 C=N 1181 C-N str. OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.55-8.2 (8H,m, Ar-H) 2.46 (1H,s,Pyrazolone) 1.94 (6H,s,2CH_3) 3.76 (3H,s,OCH_3)

Compound -5h

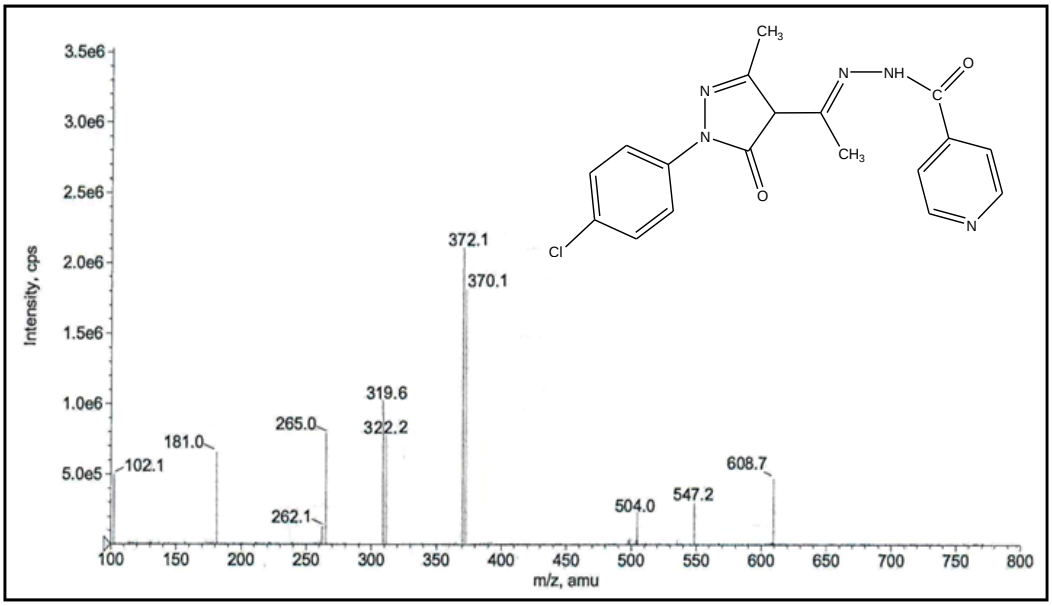


Nicotinic acid {1-[1-(4-chloro-phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl]-ethylidene}-hydrazide

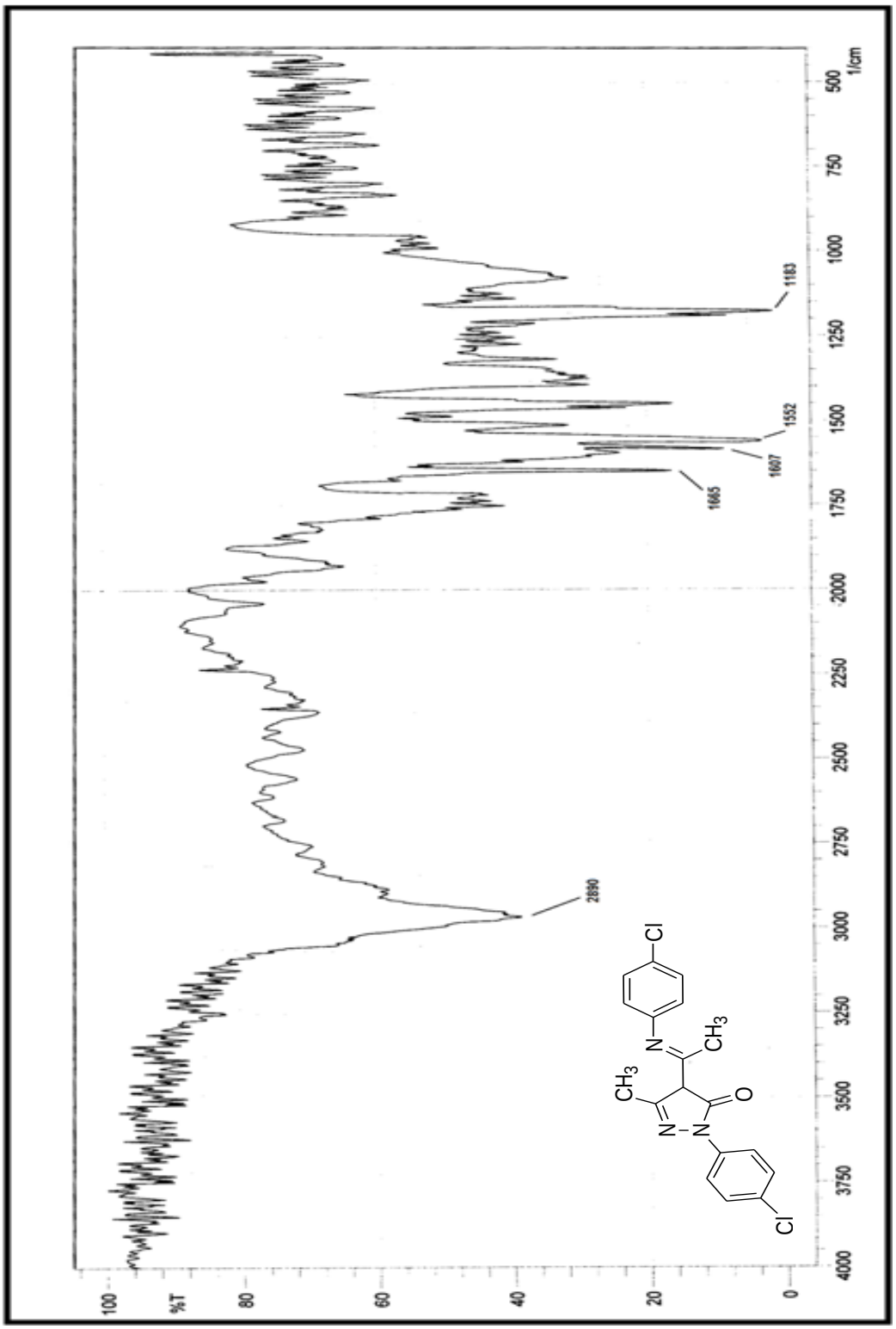
Molecular formula : $C_{18}H_{16}ClN_5O_2$ Molecular weight : 369 gm/mol Melting point:180-182 ^{0}C (uncorrected) Yield: 77%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 58.46 4.36 18.94 **Found** 58.48 4.37 18.95
IR features around Cm^{-1} 2887 Aromatic C-H stretching 1668 C=O 1598 C=N 1177 C-N str.	**^{1}H-NMR spectral features (δ-ppm)** 7.15-8.3 (9H,m, Ar-H) 2.43 (1H,s,Pyrazolone) 1.95 (6H,s,2CH_3) 7.12 (1H,s,NH)



NMR Spectrum of Compound 5e

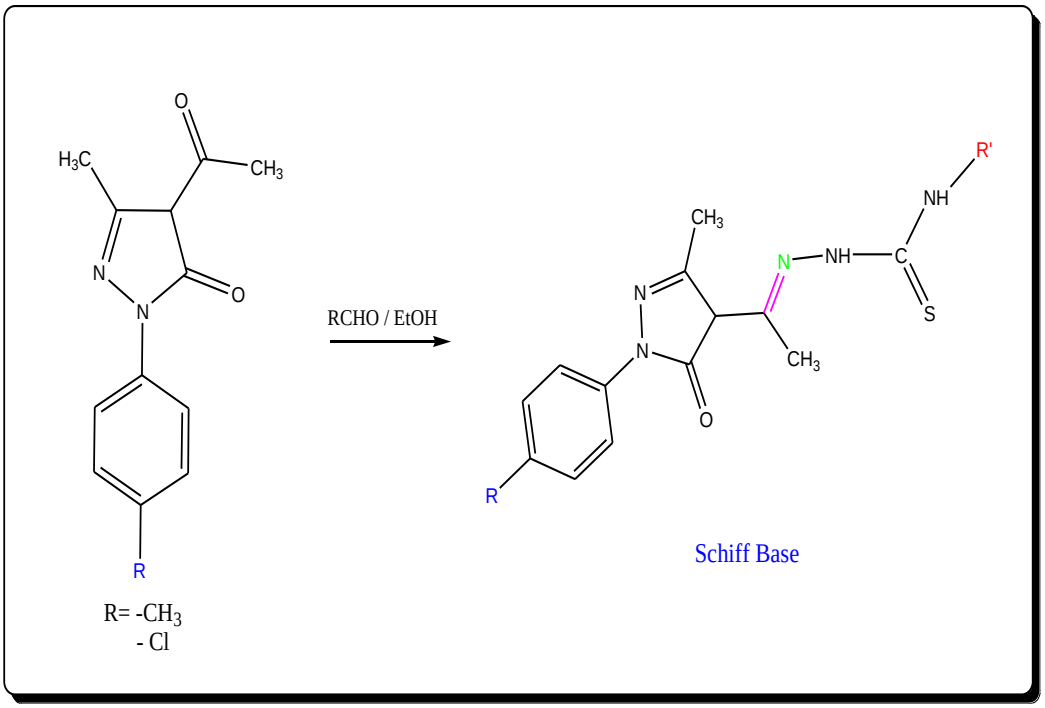


Mass Spactrum of Compound 5e



IR spectrum of Compound 5b

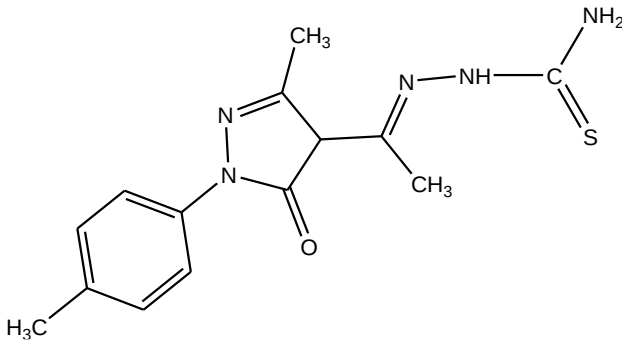
The formation of Schiff base is presented in scheme 2.2



Where R = $-CH_3$ & -Cl

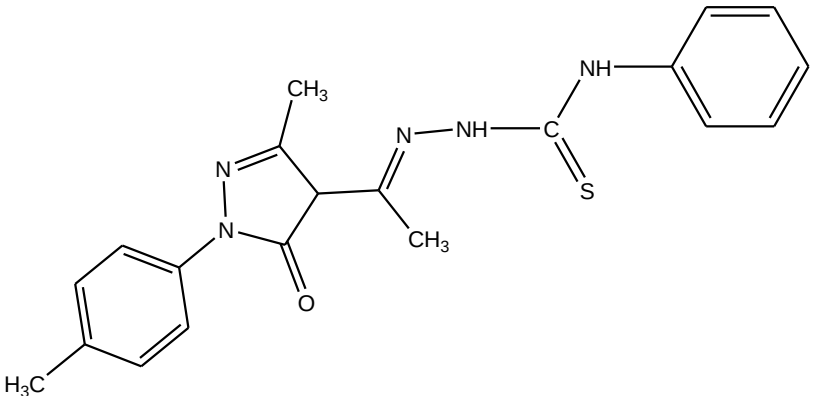
Where R'= a. thiosemicarbazide
b. Phenyl
c.4-Cl Phenyl
d. 2-methyl Phenyl
e. 4-OCH_3 Phenyl
f. 4-Nitro Phenyl

Compound -6a



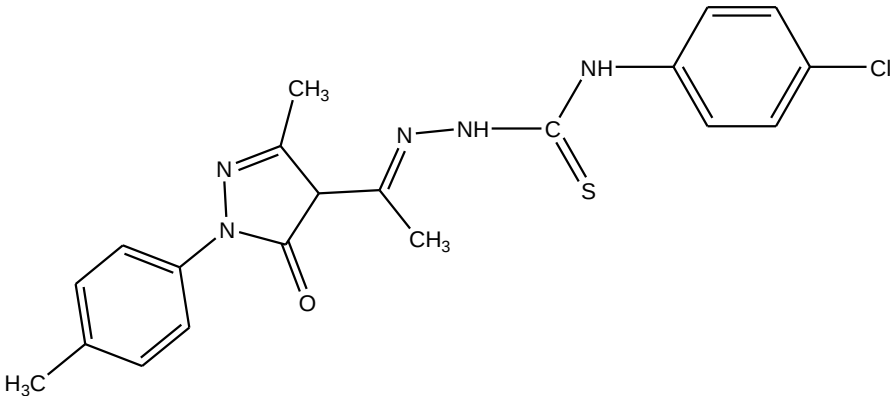
Molecular formula : $C_{14}H_{17}N_5OS$ Molecular weight : 303 gm/mol Melting point:169-170 ^{0}C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 52.42 5.65 23.08 **Found** 52.41 5.67 23.07
IR features around Cm^{-1} 2893 Aromatic C-H stretching 3448 NH_2 1669 C=O 1605 C=N 1087 C=S	**^{1}H-NMR spectral features (δ-ppm)** 7.10-8.0 (4H,m, Ar-H) 2.4 (1H,s,Pyrazolone) 7.0 (1H,s,NH) 8.56 (2H,s,NH_2) 1.92 (6H,s,2CH_3) 2.31 (3H,s,CH_3)

Compound -6b



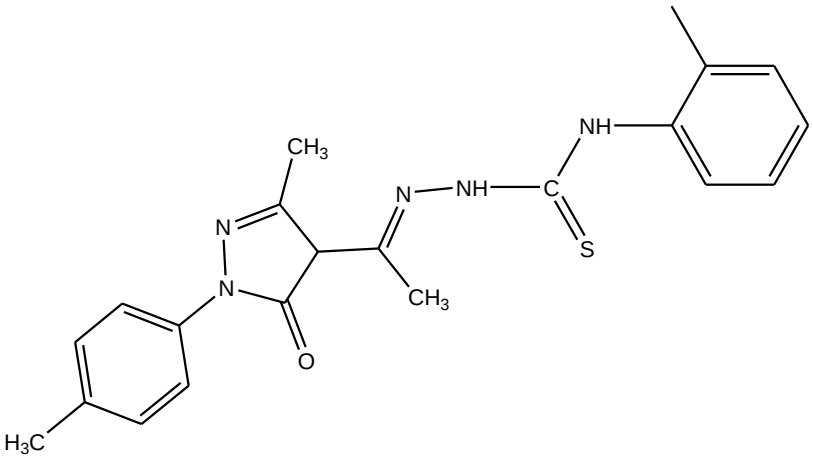
Molecular formula : $C_{20}H_{21}N_5OS$ Molecular weight : 379 gm/mol Melting point:167-168 ^{0}C (uncorrected) Yield: 76%	**Elemental analysis** **%C % H % N** **Calculated** 63.30 5.58 18.46 **Found** 63.32 5.6 18.44
IR features around Cm^{-1} 2890 Aromatic C-H stretching 3190 NH 1673 C=O 1599 C=N 1085 C=S	**^{1}H-NMR spectral features (δ-ppm)** 7.23-7.9 (9H,m, Ar-H) 2.42 (1H,s,Pyrazolone) 6.95 (1H,s,NH) 4.07 (1H,s,NH) 1.92 (6H,s,2CH_3) 2.31 (3H,s,CH_3)

Compound -6c



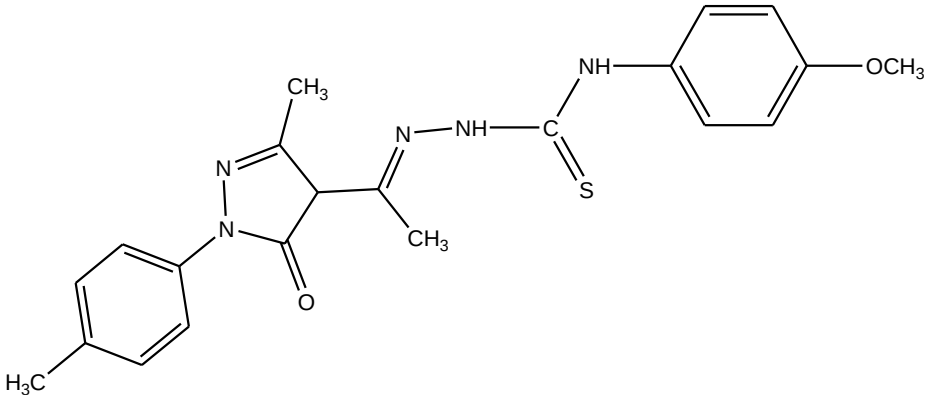
Molecular formula : $C_{20}H_{20}ClN_5OS$ Molecular weight : 413 gm/mol Melting point:172-174 ^0C (uncorrected) Yield: 76%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 58.03 4.87 16.62 **Found** 58.01 4.90 16.6
IR features around Cm^{-1} 2885 Aromatic C-H stretching 3183 NH 1677 C=O 1595 C=N 1082 C=S 759 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.56-8.05 (8H,m, Ar-H) 2.46 (1H,s,Pyrazolone) 6.98 (1H,s,NH) 4.1 (1H,s,NH) 1.95 (6H,s,$2CH_3$) 2.36 (3H,s,CH_3)

Compound -6d



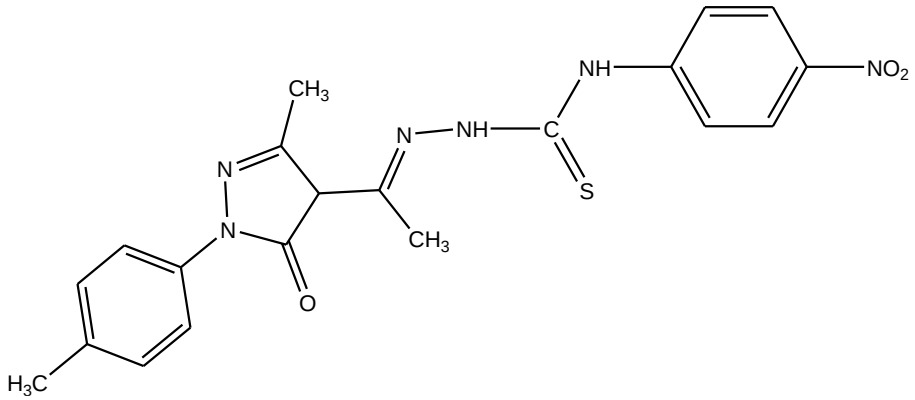
Molecular formula : $C_{21}H_{23}N_5OS$ Molecular weight : 393gm/mol Melting point:176-177 ^{0}C (uncorrected) Yield: 73%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 64.10 5.89 17.80 **Found** 64.09 5.88 17.82
IR features around Cm^{-1} 2894 Aromatic C-H stretching 3190 NH 1371 -CH_3 1673 C=O 1597 C=N 1085 C=S	**^{1}H-NMR spectral features (δ-ppm)** 7.23-7.9 (8H,m, Ar-H) 2.42 (1H,s,Pyrazolone) 6.95 (1H,s,NH) 3.98 (1H,s,NH) 1.92 (6H,s,2CH_3) 2.31 (6H,s,2CH_3)

Compound -6e

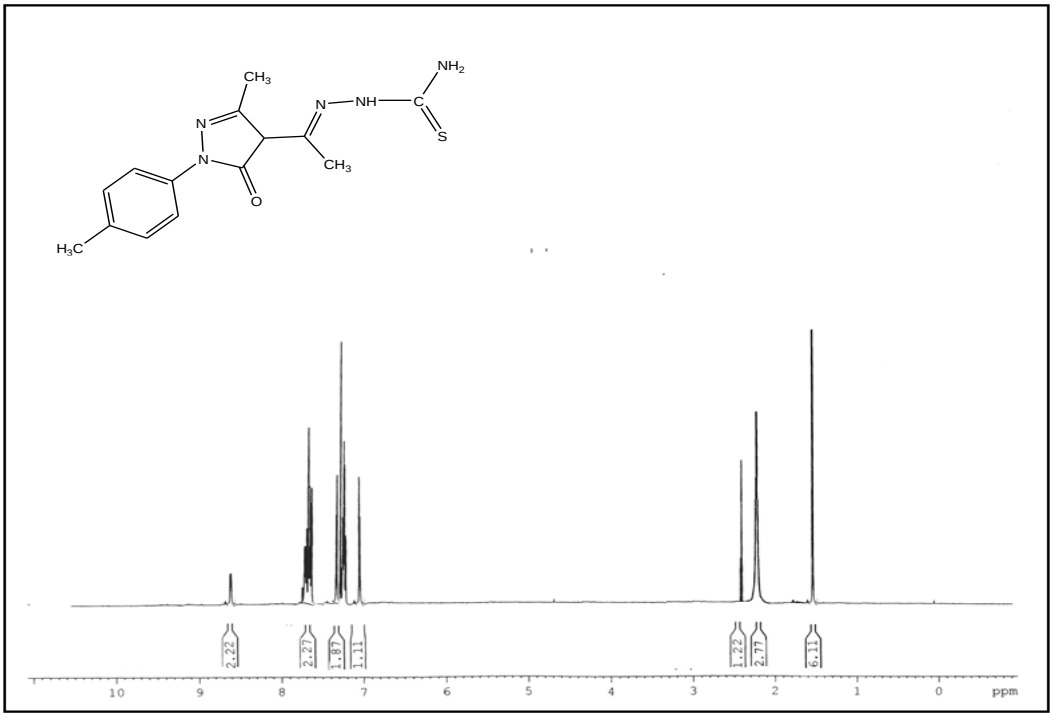


Molecular formula : $C_{21}H_{23}N_5O_2S$ Molecular weight : 409 gm/mol Melting point:164-166 ^{0}C (uncorrected) Yield: 68%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 61.59 5.66 17.10 **Found** 61.6 5.67 17.09
IR features around Cm^{-1} 2890 Aromatic C-H stretching 3187 NH 1670 C=O 1602 C=N 1089 C=S OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.1-8.07 (8H,m, Ar-H) 2.47 (1H,s,Pyrazolone) 6.92 (1H,s,NH) 4.02 (1H,s,NH) 1.96 (6H,s,2CH_3) 2.34 (3H,s,CH_3) 3.79 (OCH_3)

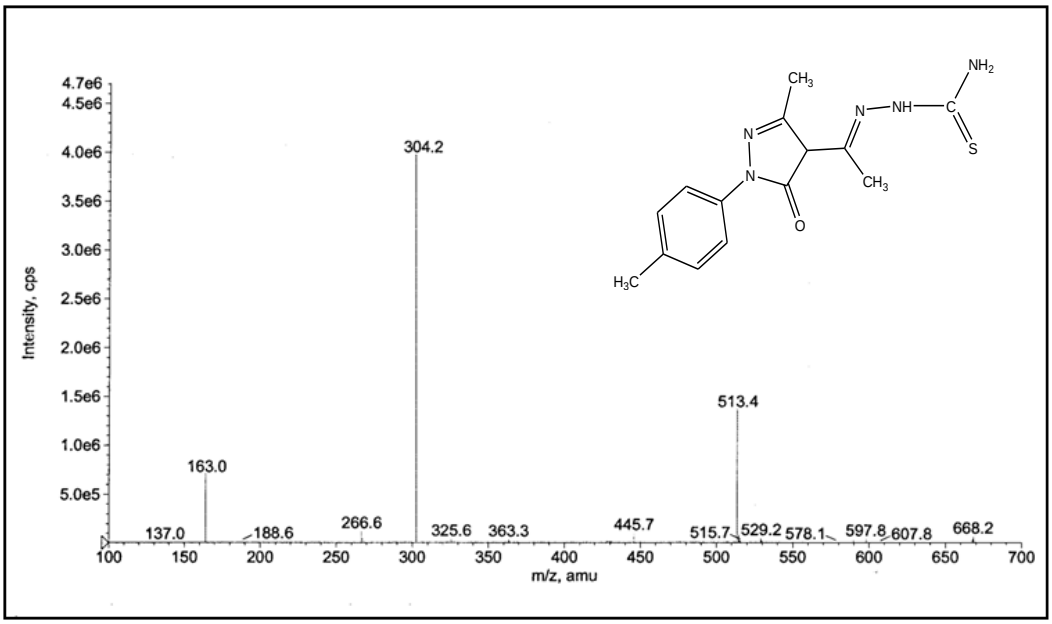
Compound -6f



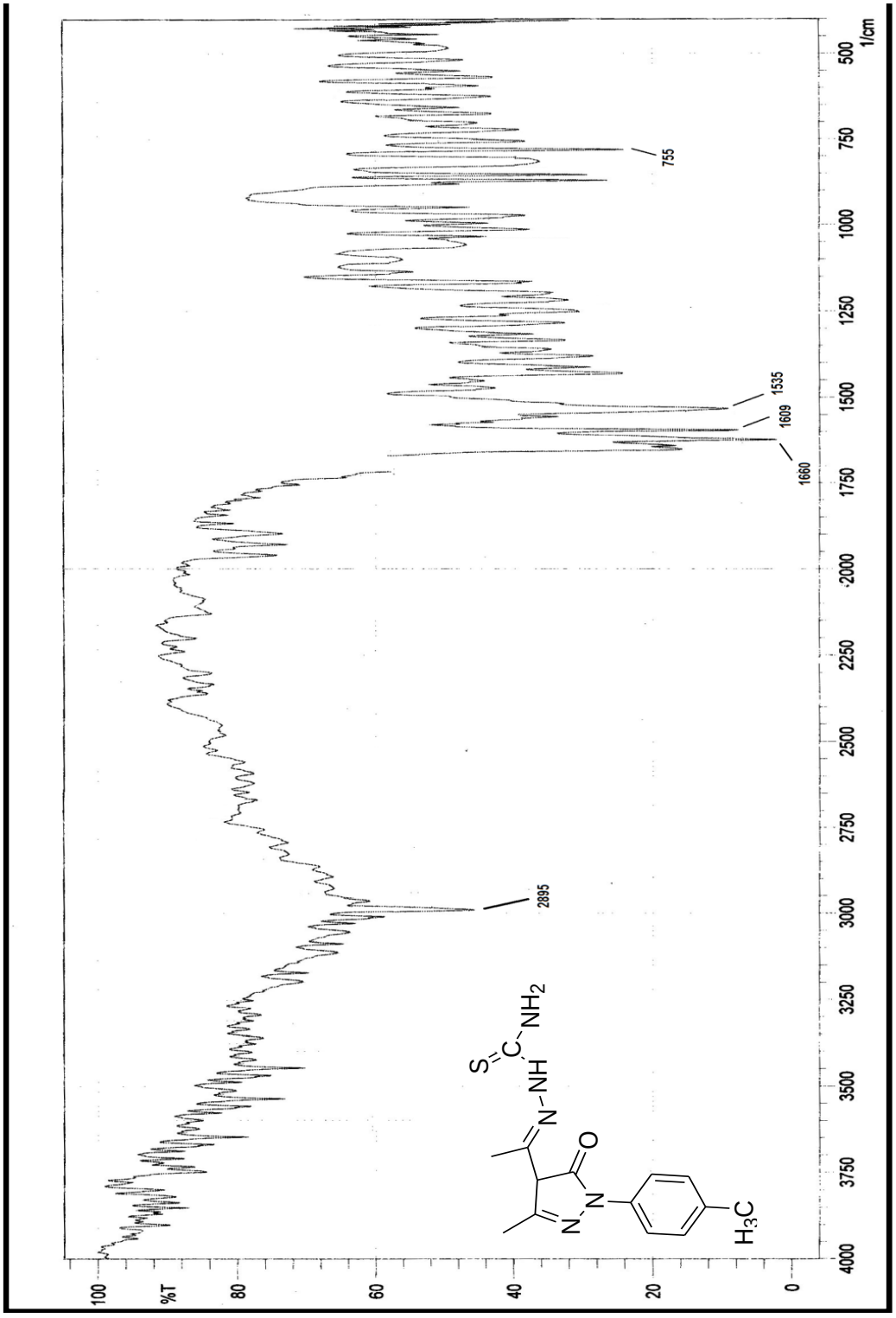
Molecular formula : $C_{20}H_{20}N_6O_3S$ Molecular weight : 424gm/mol Melting point:179-180 ^{0}C (uncorrected) Yield: 76%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 56.59 4.75 19.80 **Found** 56.58 4.77 19.79
IR features around Cm^{-1} 2890 Aromatic C-H stretching 3193 NH 1671 C=O 1599 C=N 1087 C=S NO_2	**^{1}H-NMR spectral features (δ-ppm)** 7.23-7.9 (8H,m, Ar-H) 2.48 (1H,s,Pyrazolone) 6.93 (1H,s,NH) 3.98 (1H,s,NH) 1.91 (6H,s,2CH_3) 2.38 (3H,s,CH_3)



NMR Spectrum of Compound 6a

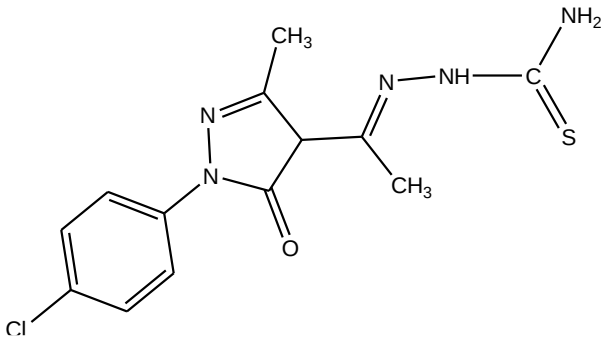


Mass Spactrum of Compound of 6a



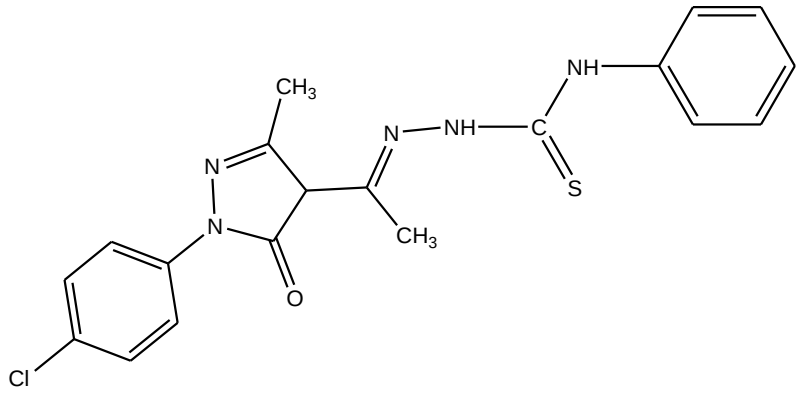
IR Spactrum of Compound 6a

Compound -7a



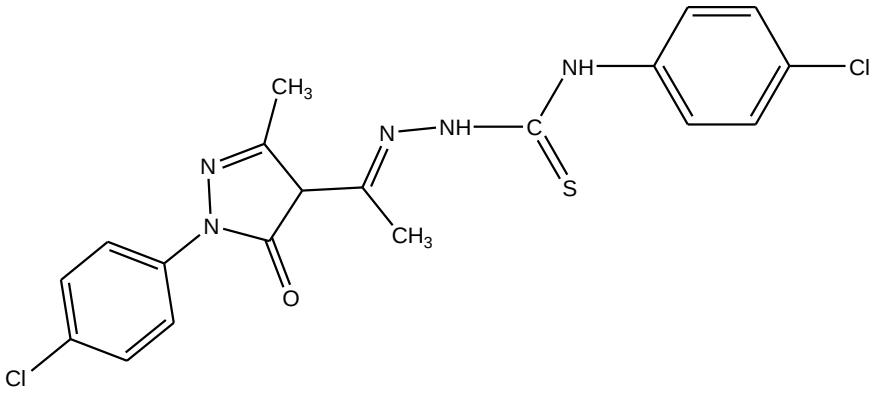
Molecular formula : $C_{13}H_{14}ClN_5OS$ Molecular weight : 323 gm/mol Melting point:161-163 ^{0}C (uncorrected) Yield: 69%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 48.22 4.36 21.63 **Found** 48.2 4.37 21.62
IR features around Cm^{-1} 2890 Aromatic C-H stretching 3452 NH_2 1667 C=O 1596 C=N 1082 C=S	**^{1}H-NMR spectral features (δ-ppm)** 7.23-7.9 (8H,m, Ar-H) 3.97 (1H,s,Pyrazolone) 6.9 (1H,s,NH) 1.93 (6H,s,2CH_3) 8.54 (1H,s,NH_2)

ompound -7b



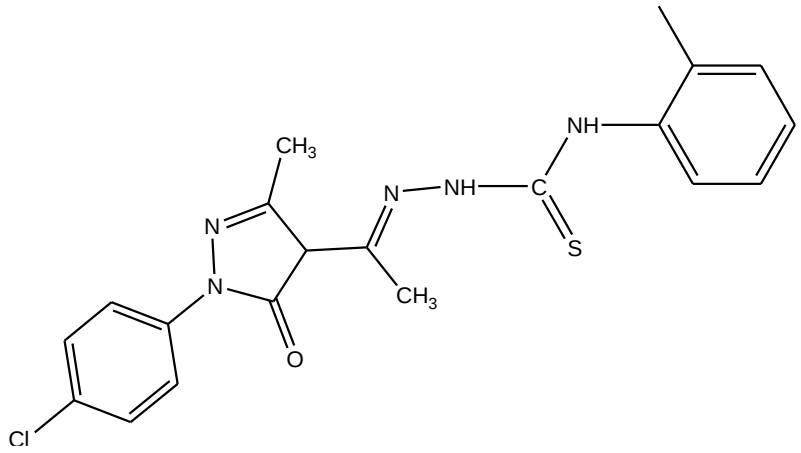
Molecular formula : $C_{19}H_{18}ClN_5OS$ Molecular weight : 399 gm/mol Melting point:165-166 ^0C (uncorrected) Yield: 73%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 57.07 4.54 17.51 **Found** 57.02 4.55 17.5
IR features around Cm^{-1} 2890 Aromatic C-H stretching 3189 NH 1670 C=O 1605 C=N 1085 C=S 756 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.10-8.0 (9H,m, Ar-H) 2.4 (1H,s,Pyrazolone) 7.0 (1H,s,NH) 3.98 (1H,s,NH) 1.92 (6H,s,2CH_3)

Compound -7c



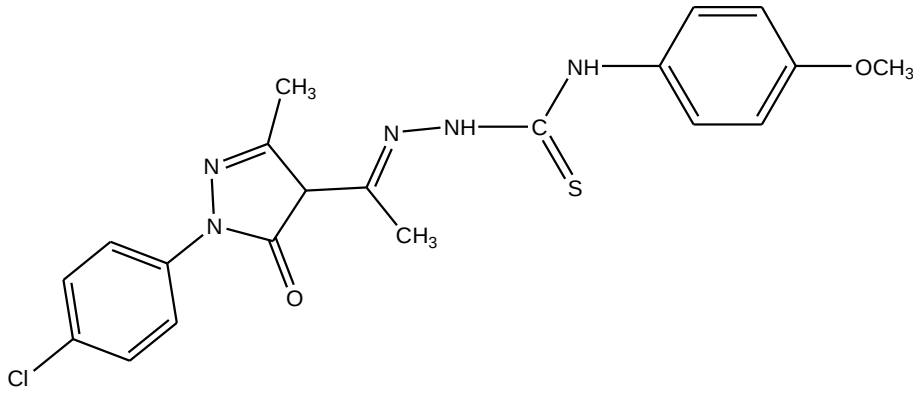
Molecular formula : $C_{19}H_{17}Cl_2N_5OS$ Molecular weight : 369 gm/mol Melting point:180-182 ^0C (uncorrected) Yield: 77%	**Elemental analysis** **%C % H % N** **Calculated** 52.54 3.95 16.12 **Found** 52.5 4.01 16.11
IR features around Cm^{-1} 2888 Aromatic C-H stretching 3190 NH 1673 C=O 1603 C=N 1084 C=S 761 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.18-7.96 (8H,m, Ar-H) 2.43 (1H,s,Pyrazolone) 6.99 (1H,s,NH) 3.96 (1H,s,NH) 1.95 (6H,s,$2CH_3$)

Compound -7d



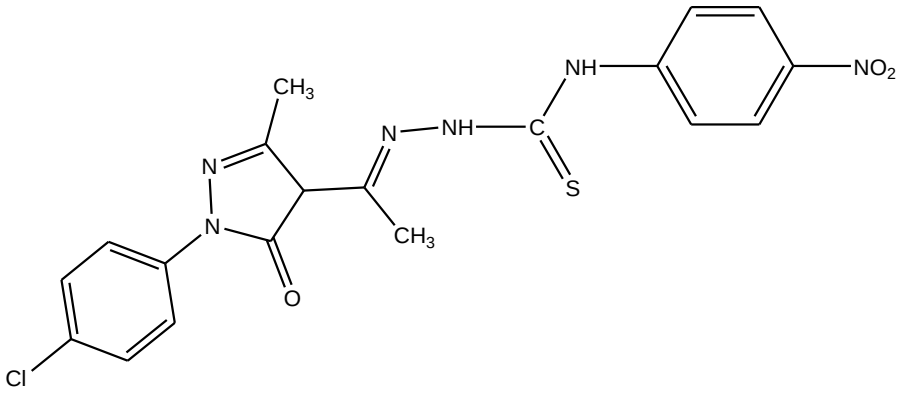
Molecular formula : $C_{20}H_{20}ClN_5OS$ Molecular weight : 413 gm/mol Melting point:176-177 ^0C (uncorrected) Yield: 72%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 58.03 4.87 16.92 **Found** 58.01 4.9 17.02
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1071 CH_3 3184 NH 1668 C=O 1597 C=N 1080 C=S	**^{1}H-NMR spectral features (δ-ppm)** 7.28-7.98 (8H,m, Ar-H) 2.46 (1H,s,Pyrazolone) 7.02 (1H,s,NH) 3.98 (1H,s,NH) 1.95 (6H,s,$2CH_3$) 2.31 (3H,s,CH_3)

Compound -7e

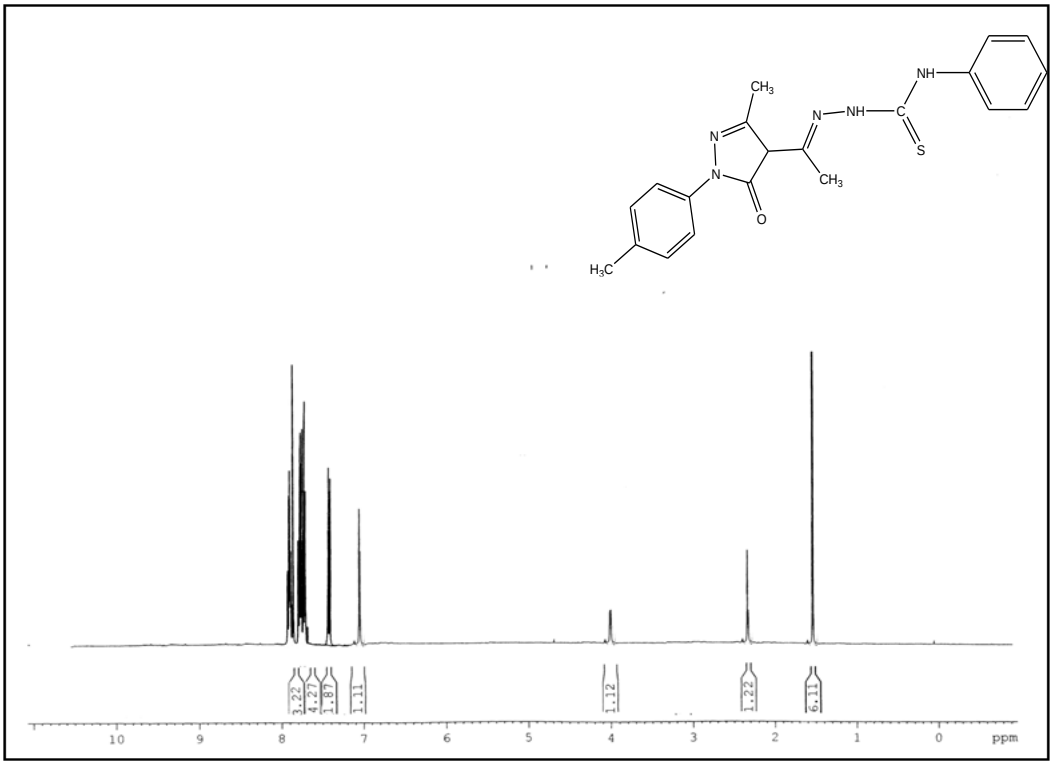


Molecular formula : $C_{20}H_{20}ClN_5O_2S$ Molecular weight : 429 gm/mol Melting point:182-183 ^0C (uncorrected) Yield: 70%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 55.87 4.69 16.29 **Found** 55.89 4.68 16.31
IR features around Cm^{-1} 2887 Aromatic C-H stretching 3193 NH 1674 C=O 1609 C=N 1082 C=S OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.18-7.96 (8H,m, Ar-H) 2.48 (1H,s,Pyrazolone) 6.96 (1H,s,NH) 4.01 (1H,s,NH) 1.97 (6H,s,$2CH_3$) 3.78 (OCH_3)

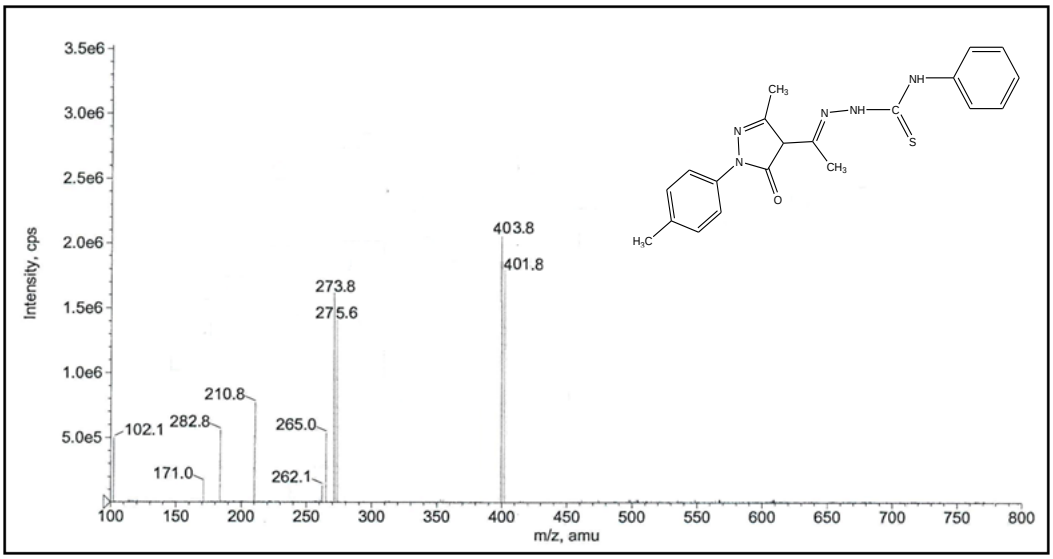
Compound -7f



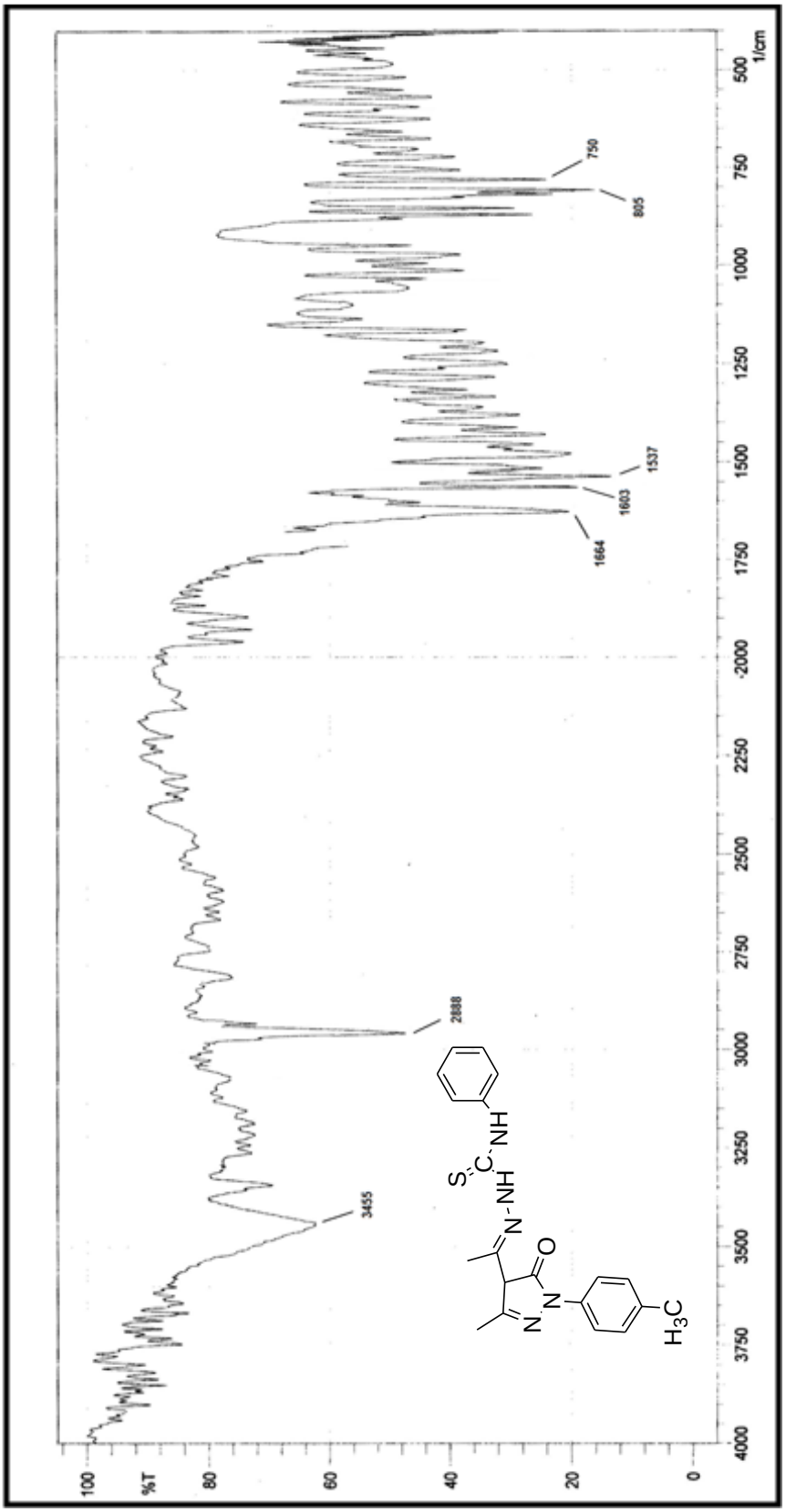
Molecular formula : $C_{19}H_{17}ClN_6O_3S$ Molecular weight : 444 gm/mol Melting point:183-185 ^0C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 51.29 3.85 18.89 **Found** 51.30 3.87 18.9
IR features around Cm^{-1} 2890 Aromatic C-H stretching 3188 NH 1669 C=O 1602 C=N 1087 C=S NO_2	**^{1}H-NMR spectral features (δ-ppm)** 7.35-7.80 (8H,m, Ar-H) 2.44 (1H,s,Pyrazolone) 6.98 (1H,s,NH) 3.96 (1H,s,NH) 1.95 (6H,s,2CH_3)



NMR Spactrum of compound 7b



Mass Spactrum of Compound 7b



IR Spactrum of Compound 7b

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CHAPTER-3

Synthesis and Characterization of Pyrazole derivatives from Chalcone

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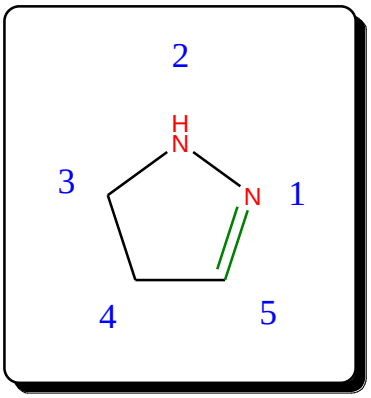
SECTION-A

SECTION-B

SECTION-A

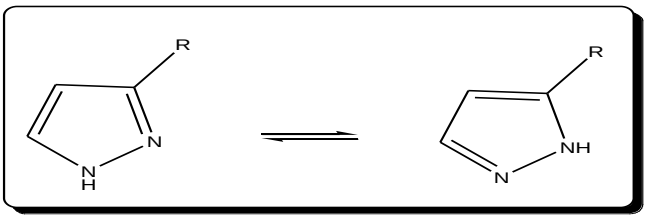
The term Pyrazole was given by Ludwig Knorr in 1883. Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclic diazole series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions, and to the unsubstiuted parent compound. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons [1, 2].



Pyrazole is feebly basic and forms salts with inorganic acids. The imino hydrogen may be replaced by an acyl group. Pyrazole is very resistant to oxidation and reduction, but may be hydrogenated catalytically, first to pyrazoline and then to pyrazolidine. Both of these compounds are stronger bases than pyrazole.

3.1 Annular tautomerism

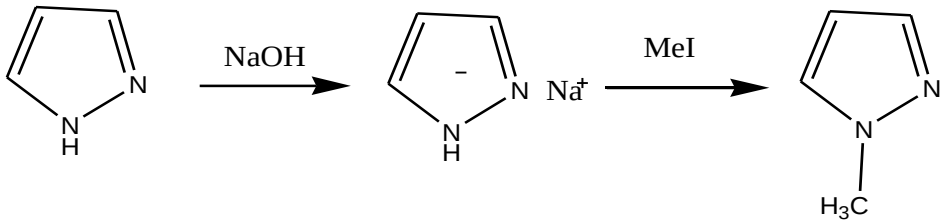
Unsubstiuted Pyrazoles in the 1, 2- position undergoes tautomerism.



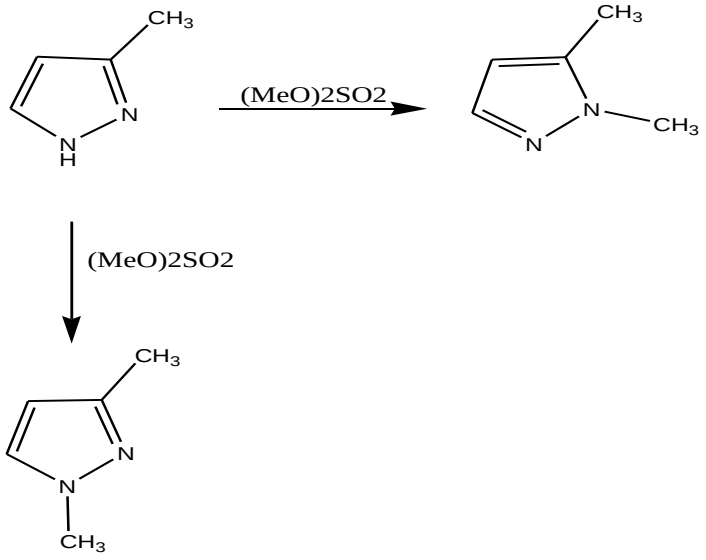
In solution, equilibrium is attained so rapidly that the existence of tautomers can only be demonstrated by means of ^{13}C and ^{15}N NMR spectroscopy. Other than for R = CH_3, the equilibrium lies to the left i.e. the 3-substituted isomer predominates.

3.2Reactions with electrophilic reagents

The procedure for methylation of pyrazole is via the sodium salt which reacts with iodomethane or dimethyl sulfate,



Benzylation, acetylation, benzoylation, methylsulfonation, methoxy-carbonylation and trimethylsilylation of pyrazole are affected by analogous methods. Mixtures of 1,3- and 1,5- disubstituted pyrazoles are formed from 3- and 5- substituted pyrazoles because of the ambient nature of the pyrazolyl anion.



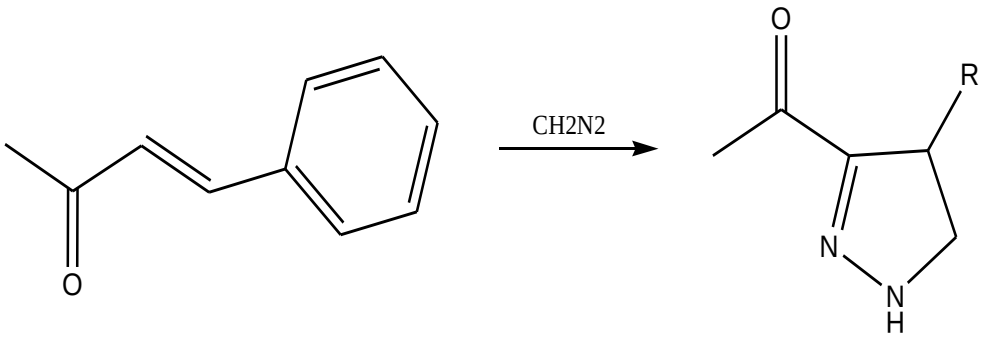
3.3 Reactions with neucleophilic reagents

Pyrazoles either do not react with nucleophiles, or react with them only very slowly. For instance, pyrazoles unsubstiuted in the 3 -position undergo ring opening on heating with alkali hydroxides. Nucleophilic substitution of a halogen in halopyrazoles is also difficult.

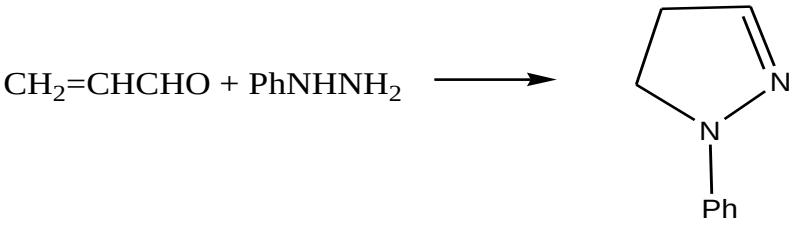
Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocyclic rings in medicinal chemistry. A systematic investigation of this class of heterocyclic lead revealed that pyrazole containing pharmacoactive agents play important role in medicinal chemistry**.** The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead.

3.4 SYNTHETIC ASPECTS

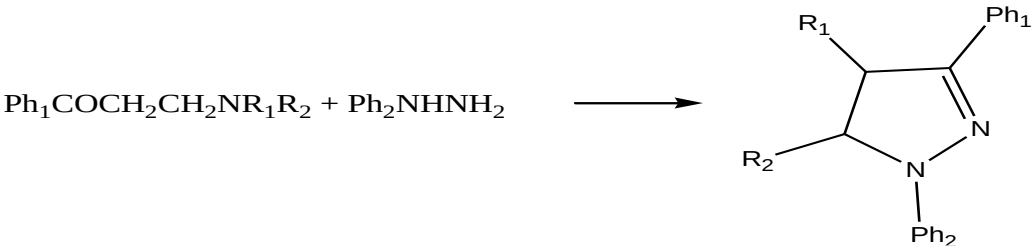
The first example of the synthesis of pyrazoline from the reaction of α, β-unsaturated ketone and diazomethane and was published by azzarello in 1906.[3]



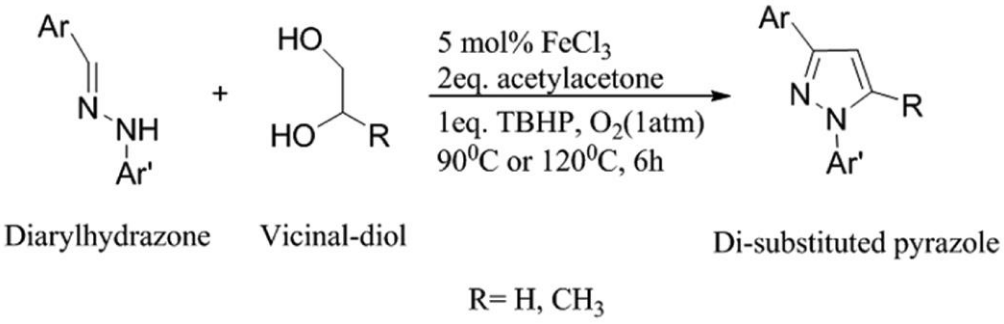
The reaction of hydrazine with α, β- unsaturated carbonyl compounds.



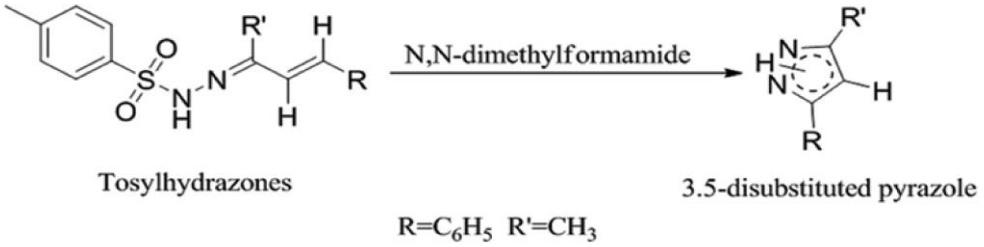
Mannich base on reaction with phenyl hydrazine and aqueous ethanolic NaOH at reflux temperature yield substituted 2- pyrazolines. [4]



Synthesis of 1, 3-substituted pyrazoles an iron-catalyzed route for the regioselective synthesis of 1,3- and 1,3,5-substituted pyrazoles from the reaction of diary hydrazones and vicinal diols.[5]



Synthesis of 3,5-substituted-1H-pyrazole a novel approach to the synthesis of pyrazole derivatives from tosylhydrazones of α, β-unsaturated carbonyl compounds possessing a β-hydrogen is proposed, exploiting microwave activation coupled with solvent free reaction conditions.[6]

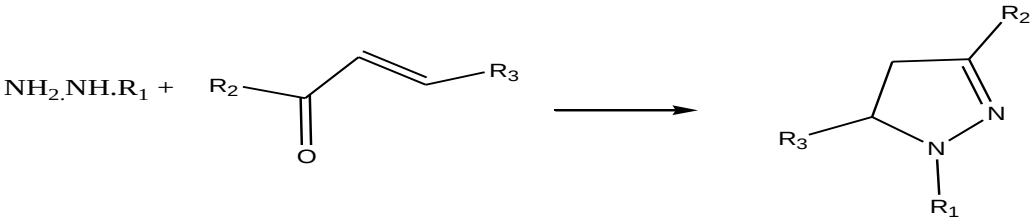


Tosylhydrazones

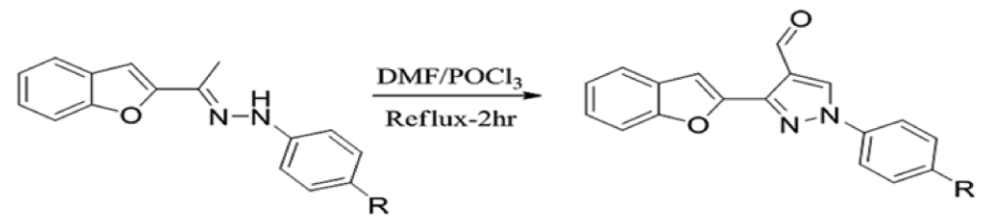
3.5-disubstituted pyrazole

R=C_6H_5 R'=CH_3

The reaction of chalcone with hydrazine is probably the most popular procedure for the synthesis of 2- pyrazoline. The most commonly used method is the reaction of hydrazine and the chalcone in acetic acid solution to prepare 2- pyrazoline in high yield [7-9]. Synthesis of 2- pyrazoline can also be achieved under alkaline conditions by using pyridine as catalyst in ethanolic solution [10]. In the same cases two reactants were refluxed in alcoholic solution without a catalyst to provide 2-pyrazolines [11,12].



Synthesis of 3-benzofuran-2-yl-1-p-tolyl-1H-pyrazole the 2-acyl benzofuro-hydrazones subjected to Vilsmeier– Haack reaction that is reaction with N,N-dimethylformamide (DMF)/POCl3 at an appropriate molar ratio, which underwent smooth cyclization followed by formylation afforded 3-(1-benzofuran-2-yl)-1-(4-fluorophenyl)-1Hpyrazole- 4-carbaldehyde [13].



2-Acyl benzofurohydrazone

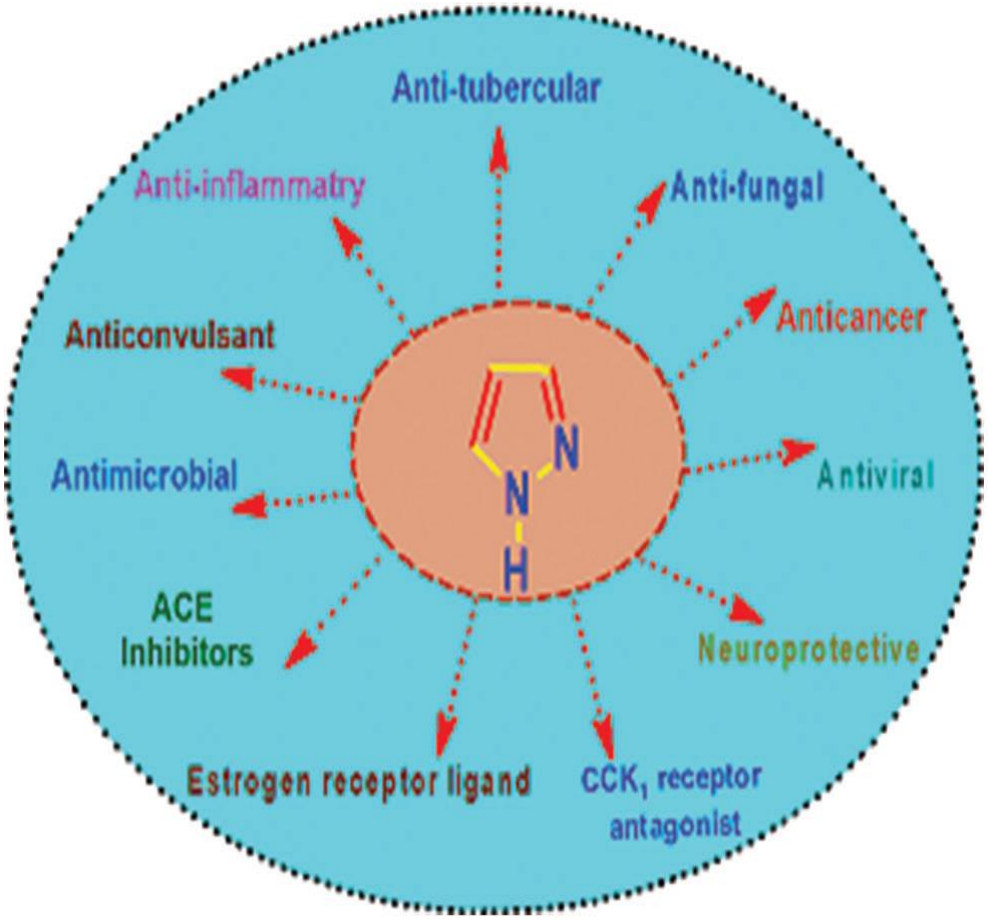
3-Benzofuran-2-yl-1-p-tolyl-1H-pyrazole.

R=H, CH_3, OCH_3

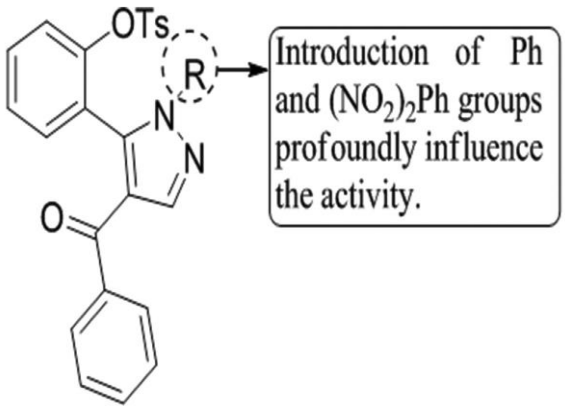
Synthesis of 1,3,5-trisubstituted-1H-pyrazole the reaction of the easily accessible 1, 3-bisaryl-monothio-1,3-diketone or 3-(methylthio)-1,3-bisaryl-2-propenones with arylhydrazines gives 1-aryl-3,5-bisarylpyrazoles with complementary regioselectivity at position 3 and 5[14].

3.5 Pharmacological activity

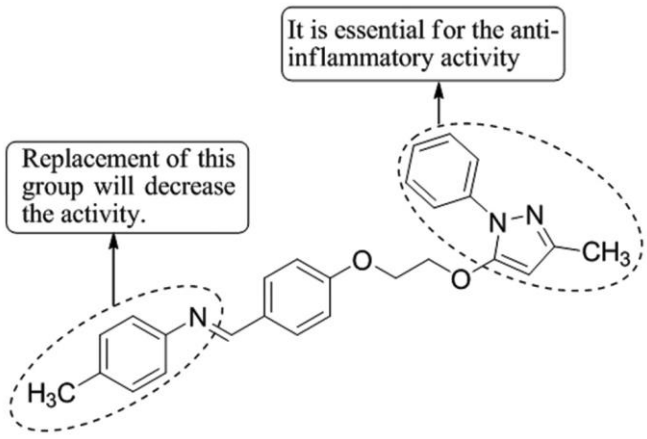
For a very long time, the usefulness and great therapeutic value of pyrazole nucleus have been recognized and widest range of activities of this nucleus evaluated. However, as the first synthetic organic compound having pyrazoline-5-one nucleus, to find use as an important drug.



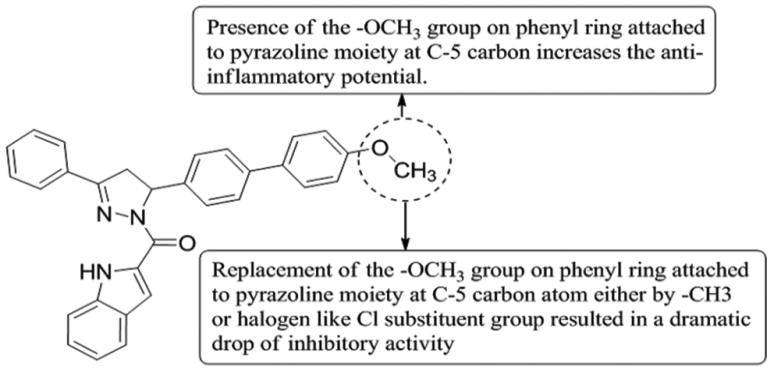
Kendre et al.,[15] have synthesized a new series of pyrazole derivatives by the multi-component cyclo-condensation reaction of 1-phenyl-3-(2-(tosyloxy)phenyl)propane-1,3-dione, DMF dimethyl acetal, and hydrazine by MW technique in aqueous media and tested for their anti-inflammatory activity using indomethacin as standard drug.



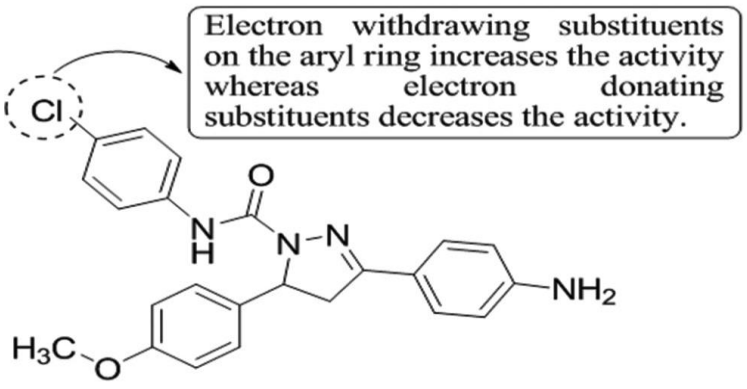
Tewari et al. [16] have synthesized a novel series of pyrazole derivatives and evaluated for their anti-inflammatory activity.



Sharath et al.,[17] have synthesized substituted indole based Scaffolds having a pyrazole ring and evaluate for their anti-inflammatory activity and antioxidant.

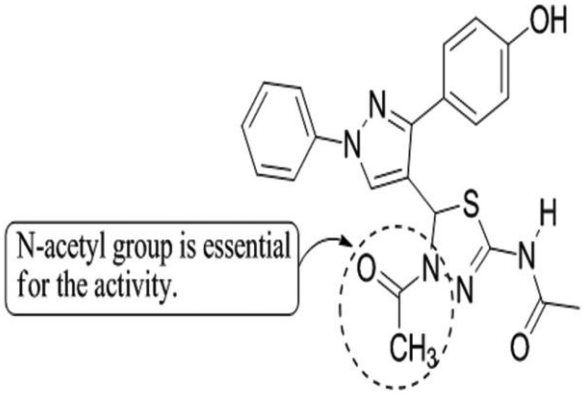


Ahsan and Saini,[18] have designed and synthesized a series of thiocetazone based pyrazoline analogs by the condensation of 4-aminoacetophenone and p-anisidine in methanolic sodium hydroxide solution followed by the cyclization of intermediate chalcone with appropriate semicarbazide/thiosemicarbazide in glacial acetic acid. All the synthesized compounds evaluated for Mycobacterium tuberculosis (MTB H37Rv) with minimum inhibitoryconcentration (MIC) of 7.41 mM .



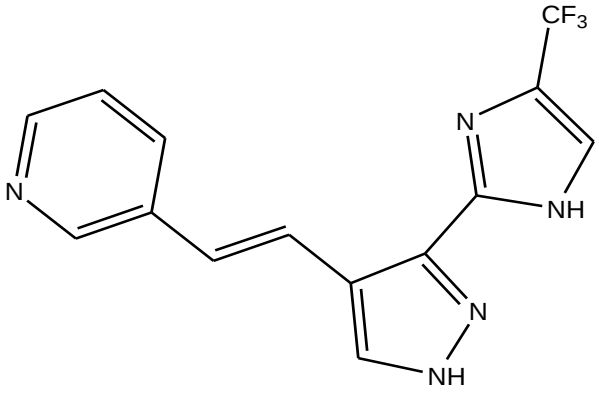
Pathak et al.,[19] have synthesized various substituted 4,6-diarylpyrimidin-2-amine (4), 4,6-diaryl-2-(heteroaryl) pyrimidine and 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl) ethanone and evaluated them for their in vitro anti-tubercular activity against MTB H37Rv strain.

Alegaon et al.,[20] have synthesized 22 1,3,4-trisubstituted pyrazole derivatives and screened for the anti-inflammatory activity by carrageenan-induced paw edema method.

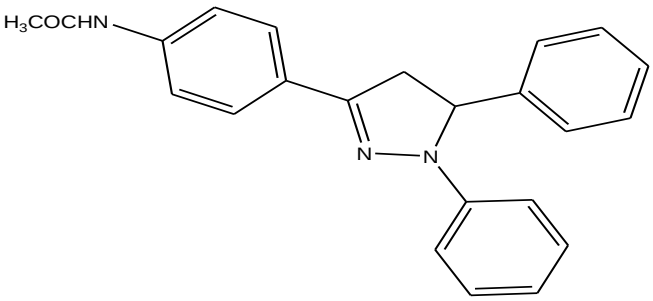


Palaska et al [21] synthesized ten new 3, 5-Diphenyl-2- pyrazoline derivatives and evaluated their antidepressant activities by the 'Porsolt Behavioural Despair Test' on Swiss-Webster mice.

Macro Bonesi *et al*[22]synthesized a series of pyrazole derivatives and screened their potential activity as Angiotensin-I-converting enzymes inhibitory activity by performing assay.

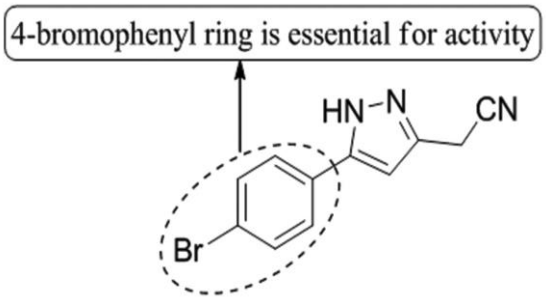


Singh et al [23] synthesized several 3-(3-Acetoamino) phenyl- 1, 5-substituted phenyl-2-pyrazolines and screened for their anticonvulsant activity.

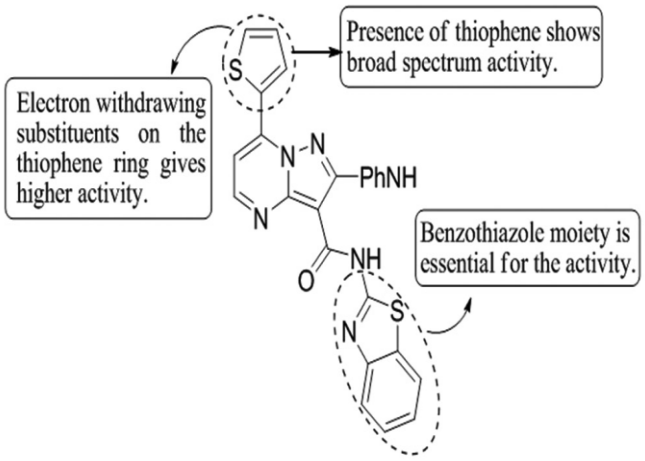


Sivakumar *et al*.[24] synthesized some novel 1,3,5-triphenyl-2-pyrazolines and evaluated their antimicrobial activity.

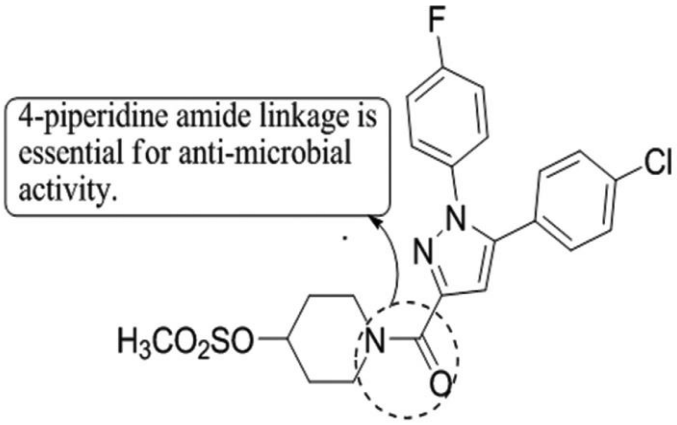
Maurya et al.,[25] have synthesized various substituted pyrazole, and 2,6-diarylpyridine derivatives in and evaluated them for their in vitro anti-tubercular activity against MTB H37Rv strain.



Bondock et al.,[26] have synthesized a series of fused pyrazolepyrimidine derivatives and screened for anti-fungal activity with MICs (6.25 μ/ml) against Aspergillus fumigatus and Fusarium oxysporum comparable with chloroamphenicol.

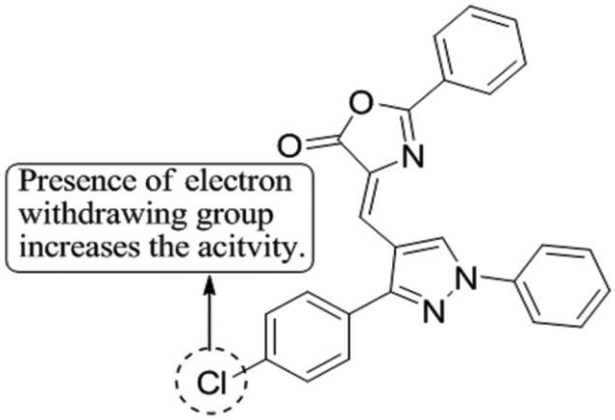


Ahsan et al.,[27] has synthesized a series of 3a,4-dihydro-3H indeno [1,2-c]pyrazole-2-carboxamide/carbothioamide analogs and evaluated them for anti-tubercular activity.

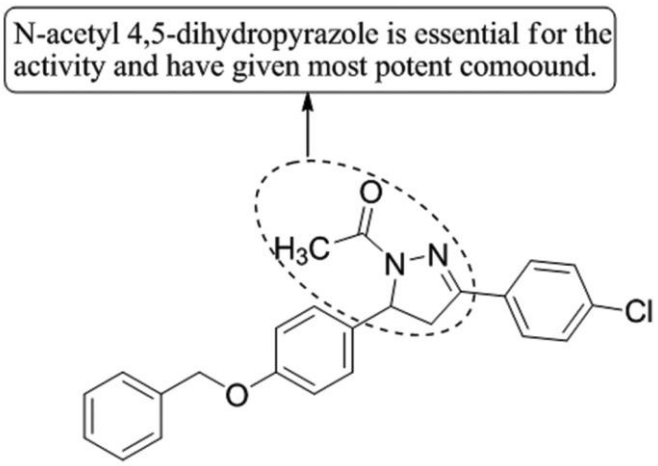


Ragavan et al.,[28] have synthesized a group of novel 1,5-diaryl pyrazole by altering the active part (amide linkage) and tested for anti-bacterial activity.

Argade et al.,[29] have reported the synthesis of pyrazole containing 2,4-disubstituted oxazol-5-one as a new class of anti-microbial compounds.

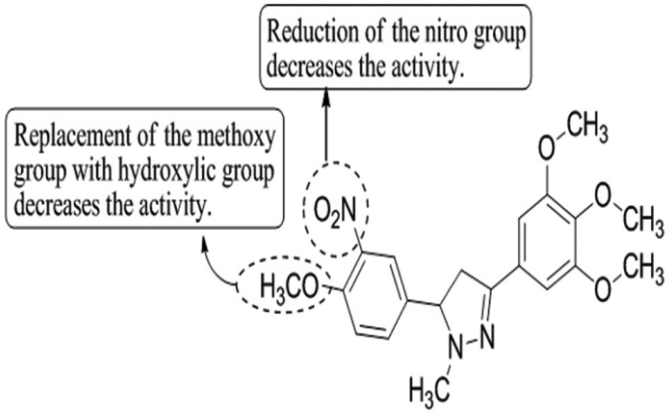


el-Sabbagh et al.,[30] have synthesized 4, 5-disubstituted pyrazole derivatives. The derivative containing R=Cl group showed the potent antiviral activity against a broad panel of viruses in different cell culture (HEL cell cultures).

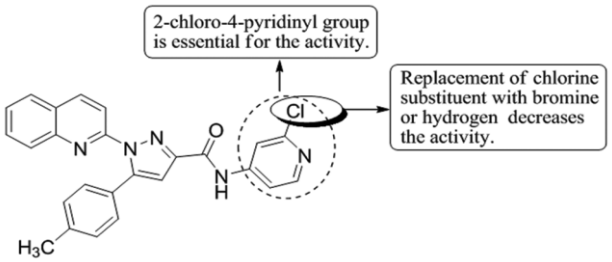


Rashad et al.,[31] have synthesized substituted pyrazole derivatives.These derivatives showed promising antiviral activity against hepatitis.

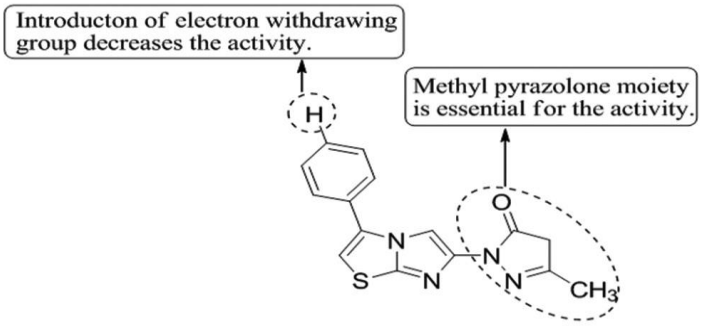
Bonesi et al.,[32] have synthesized a series of pyrazole derivatives and investigated their potential activity as ACE by performing the assay.



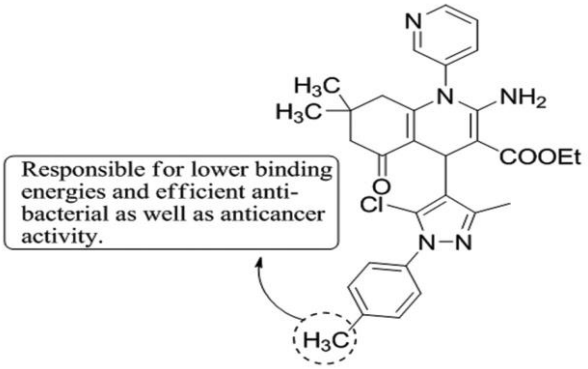
Cankara Pirol et al.,[33] have synthesized a series of novel amide derivatives of 5-(p-tolyl)-1-(quinolin-2-yl)pyrazole-3-carboxylic acid and determined their anti-proliferative activities against three human cancer cell lines (Huh7, human liver; MCF7, breast and HCT116, colon carcinoma cell lines).



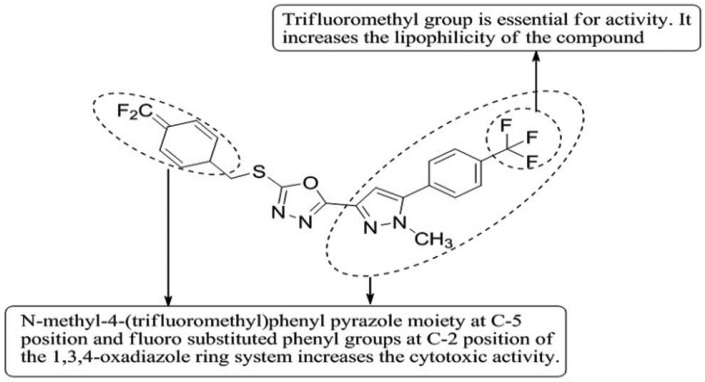
Ali et al.,[34] have synthesized a series of imidazo[2,1-b] thiazoles having pyrazole moieties through the reaction of 6-hydrazinylimidazo[2,1-b]thiazoles with different dicarbonyl compounds. The compounds were screened at the National Cancer Institute, USA for anticancer activity and 5a showed promising results.



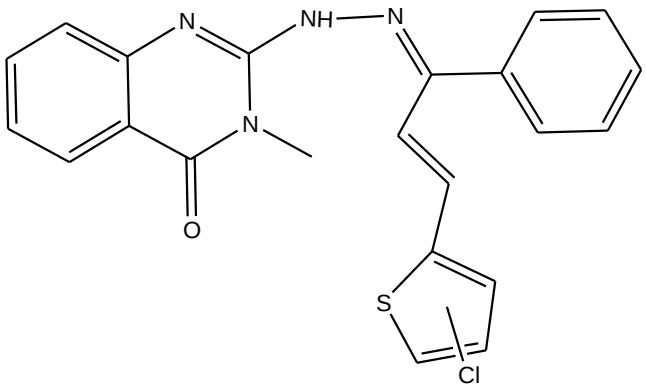
Sangani et al.,[35] have synthesized a series of pyrazole quinolonepyridine hybrids based on molecular hybridization technique and synthesized by a base-catalyzed cyclocondensation reaction through one-pot multicomponent reaction. All compounds were tested for in vitro anti-bacterial and anticancer activities of which 7k showed promising results.



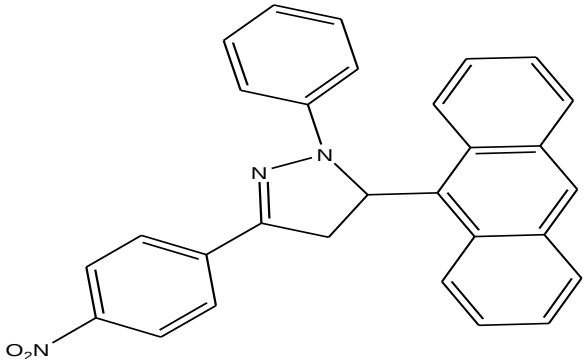
Puthiyapurayil et al.,[36] have designed and synthesized a novelcombinatorial library of S-substituted-1,3,4-oxadiazole bearing N-methyl-4-(trifluoromethyl) phenyl pyrazole moiety and then evaluated for in-vitro cytotoxic activity by 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide assay.



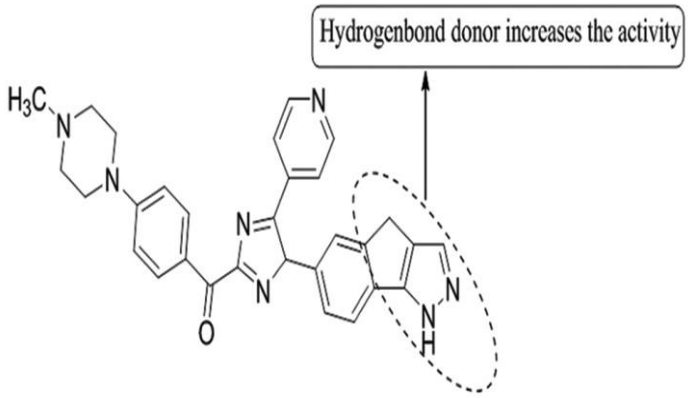
Kelekci et al [37] synthesized a new series of pyrazoline derivatives and tested it for antidepressant, anxiogenic and MAO-A and -B inhibitory activities by *in vivo* and *in vitro* tests respectively.



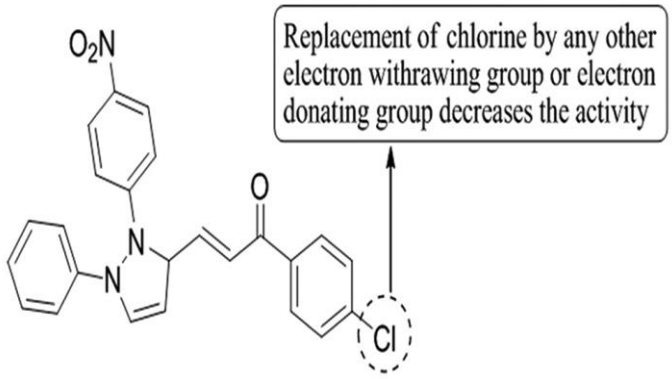
Wang et al [38] synthesized 5-(9-Anthryl)-3-(4-nitrophenyl)-1- phenyl-2-pyrazoline (ANPP) and screened its photoluminescence property.



Niculescu-Duvaz et al.[39] have synthesized a series of analogs leading to the discovery of 6-{2-[4-(4 methyl piperazin-1-yl)-phenyl]-5-pyridin-4-yl-3H-imidazol-4-yl}-2,4-dihydro-indeno [1,2-c] pyrazole and carried out bioassay inhibition of purified mutant BRAF activity in vitro.



Insuasty et al.[40] have synthesized novel (E)-1-aryl- 3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-ones(pyrazolicchalcones), among them some compound showed potent activity against leukemia (K-562 and SR), renal cancer (UO-31), and non-small cell lung cancer (HOP-92) cell lines.



Kapadiya et. al [41] synthesized nitrogen and oxygen based pyrazole Derivatives and screened for their anti- tubercular and antimicrobial activity.

M Pandya et. al[42] synthesized halogenated pyrazole derivatives and evaluated for microbial activity.

SECTION-B

3.6 EXPERIMENTAL

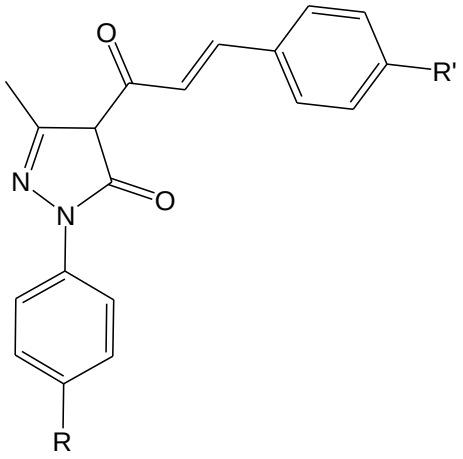
Various chalcones of acyl pyrazolone derivatives were mentioned in chapter 2, further on heterocyclization with hydrazine hydrate yields the biologically active pyrazoles.These pyrazole derivatives were characterized on the basis of elemental analysis, IR, ^{1}H- NMR and Mass fragmentation data. The reaction scheme is shown in scheme 5.1.

3.6.1 Material

The chalcone have been chosen for the synthesis of pyrazole derivatives, their synthesis has already described in Chapter 2. Other chemicals and solvent used were purified and LR grade.

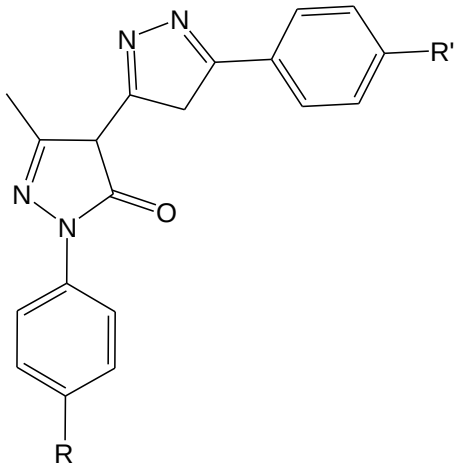
3.6.2 General procedure for synthesis of Pyrazoline derivatives (8a-h) and (9a-h)

A mixture of Substituted Chalcones (5mmoles) and hydrazine hydrate (5mmoles) was dissolved in Pyridine (10ml) and refluxed for 2-3 hrs. Completion of reaction is observed by TLC.The reaction mixture was poured into dil. HCl and stirred; the solid thus obtained was filtered off and washed with water .The resulting solid was allowed to air dry and recrystallized from ethanol. The yield, melting points and other characterization data of these compounds are given as below.



Chalcone 2(a-h) and 3(a-h)
R = - CH_3 and - clr

NH.NH2 in py.
Reflux 2h



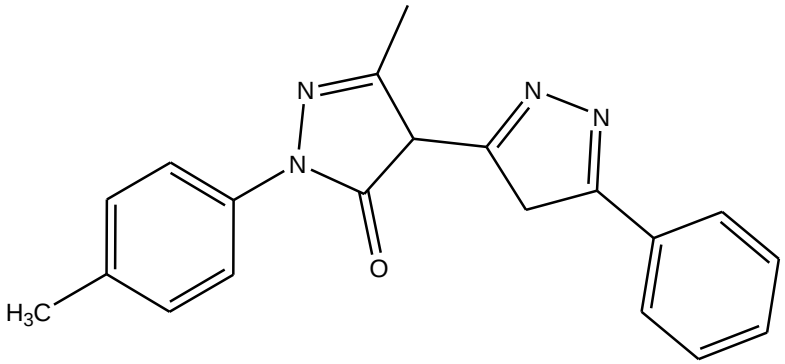
Pyrazolone derivatives 8 (a-h)

Scheme -3.1

Where R = $-CH_3$ & -Cl

Where R'= a. phenyl
b. 4- hydroxy phenyl
c. 4- Nitro phenyl
d. 4- methoxy phenyl
e. 2- methyl phenyl
f. 4-chloro phenyl
g. 4- bromo phenyl
h. 4-methyl phenyl

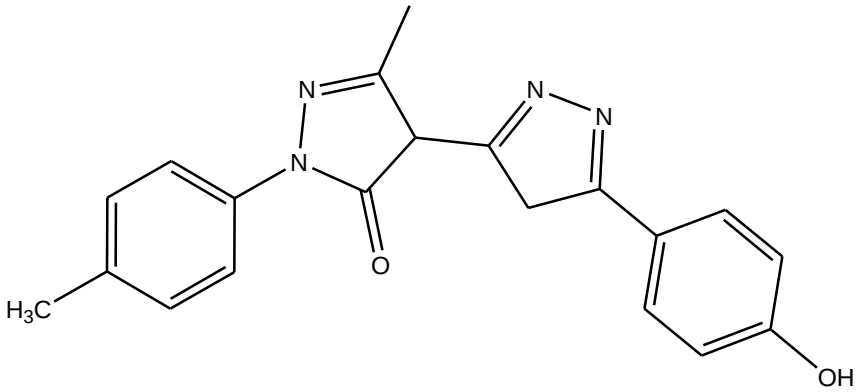
Physical data of compounds 8a



5-Phenyl-2'-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{20}H_{18}N_4O$ Molecular weight : 330 gm/mol Melting point: 163-165 ^{0}C (uncorrected) Yield: 82%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 72.71 5.49 16.96 **Found** 72.7 5.51 16.93
IR features around Cm^{-1} 2895 Aromatic C-H stretching 1362 -CH_3 1660 C=O 1609 C=N	**^{1}H-NMR spectral features (δ-ppm)** 7.23-8.51 (9H,m, Ar-H) 1.52 (2H,s,CH_2 Pyrazole) 2.46 (1H,s,CH,Pyrazolone) 1.96 (3H,s,CH_3) 2.36 (3H,s,CH_3)

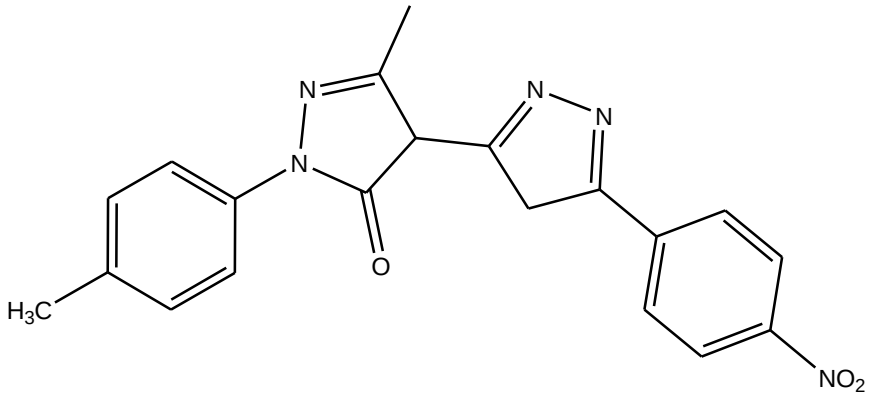
Physical data of compounds 8b



5-(4-Hydroxy-phenyl)-5'-methyl-2'-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{20}H_{18}N_4O_2$ Molecular weight : 346 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 78%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 69.35 5.24 16.17 **Found** 69.4 5.22 16.19
IR features around Cm^{-1} 2897 Aromatic C-H stretching 1370 -CH_3 1665 C=O 1611 C=N 3345 -OH	**^{1}H-NMR spectral features (δ-ppm)** 7.48-8.51 (9H,m, Ar-H) 1.55 (2H,s,CH_2 Pyrazole) 2.42 (1H,s,CH,Pyrazolone) 1.94 (3H,s,CH_3) 2.37 (3H,s,CH_3) 4.22 (1H,s,OH)

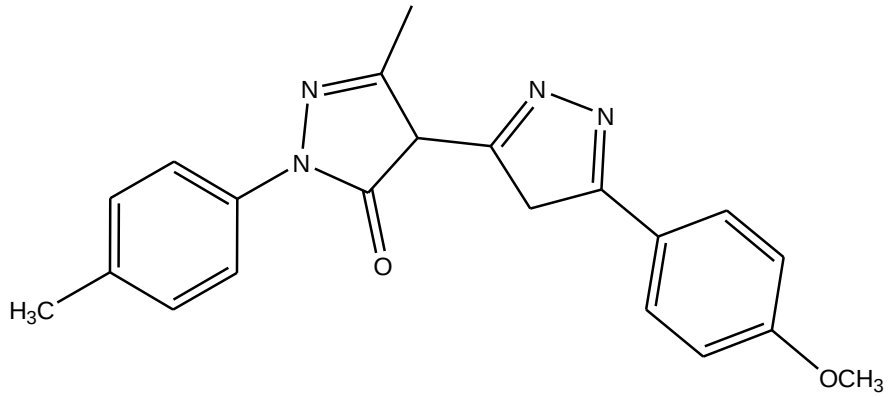
Physical data of compounds 8c



5'-Methyl-5-(4-nitro-phenyl)-2'-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{20}H_{17}N_5O_3$ Molecular weight : 375 gm/mol Melting point: 165-167 ^{0}C (uncorrected) Yield: 77%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 63.99 4.56 18.66 **Found** 64.1 4.55 18.6
IR features around Cm^{-1} 2897 Aromatic C-H stretching 1373 -CH_3 1670 C=O 1606 C=N	**^{1}H-NMR spectral features (δ-ppm)** 7.84-8.53 (8H,m, Ar-H) 1.53 (2H,d,CH_2 Pyrazole) 2.47 (1H,s,CH,Pyrazolone) 1.89 (3H,s,CH_3) 2.31 (3H,s,CH_3)

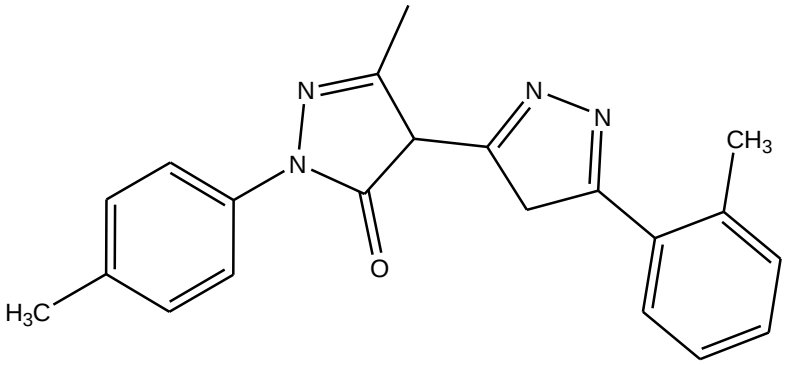
Physical data of compounds 8d



5-(4-Methoxy-phenyl)-5'-methyl-2'-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{21}H_{20}N_4O_2$ Molecular weight : 360 gm/mol Melting point: 165-167 ^{0}C (uncorrected) Yield: 73%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 69.98 5.59 15.55 **Found** 69.95 5.6 15.5
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1368 -CH_3 1664 C=O 1609 C=N 2338 -OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.23-8.51 (8H,m, Ar-H) 1.57 (2H,s,CH_2 Pyrazole) 2.39 (1H,s,CH,Pyrazolone) 1.92 (3H,s,CH_3) 2.39 (3H,s,CH_3) 3.68 (3H,s ,OCH_3)

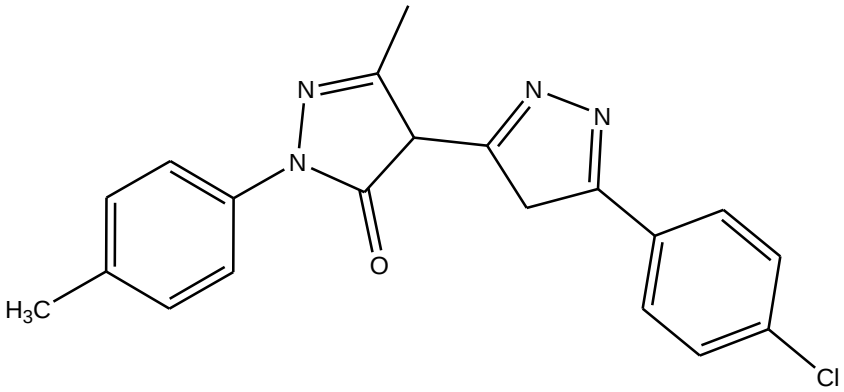
Physical data of compounds 8e



5'-Methyl-5-*o*-tolyl-2'-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{21}H_{20}N_4O$ Molecular weight : 344 gm/mol Melting point: 165-167 ^{0}C (uncorrected) Yield: 80%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 73.23 5.85 16.27 **Found** 73.2 5.52 16.3
IR features around Cm^{-1} 2904 Aromatic C-H stretching 1371-CH_3 1669 C=O 1602 C=N	**^{1}H-NMR spectral features (δ-ppm)** 6.75-8.48 (9H,m, Ar-H) 1.50 (2H,d,CH_2 Pyrazole) 2.37 (1H,s,CH,Pyrazolone) 1.97 (3H,s,CH_3) 2.38 (6H,s,2CH_3)

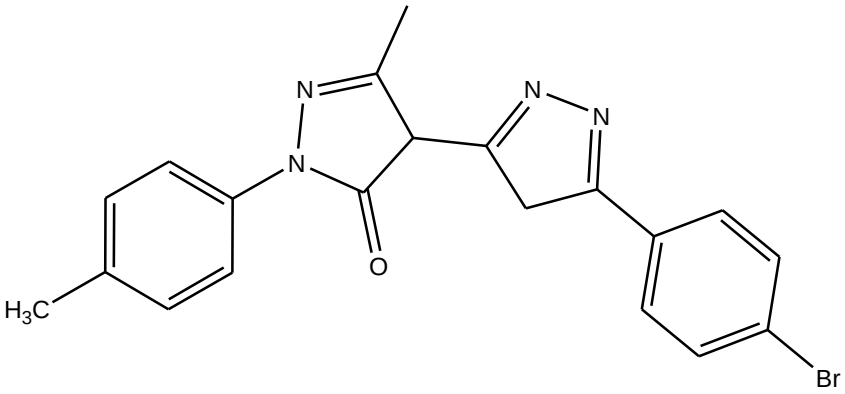
Physical data of compounds 8f



5-(4-Chloro-phenyl)-5'-methyl-2'-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{20}H_{17}ClN_4O$ Molecular weight : 364 gm/mol Melting point: 165-167 ^{0}C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.84 4.70 9.72 **Found** 64.1 4.55 18.6
IR features around Cm^{-1} 2899 Aromatic C-H stretching 1368 -CH_3 1668 C=O 1605 C=N 755 -C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.0-8.5 (8H,m, Ar-H) 1.52 (2H,s,CH_2 Pyrazole) 2.4 (1H,s,CH,Pyrazolone) 1.92 (3H,s,CH_3) 2.30 (3H,s,CH_3)

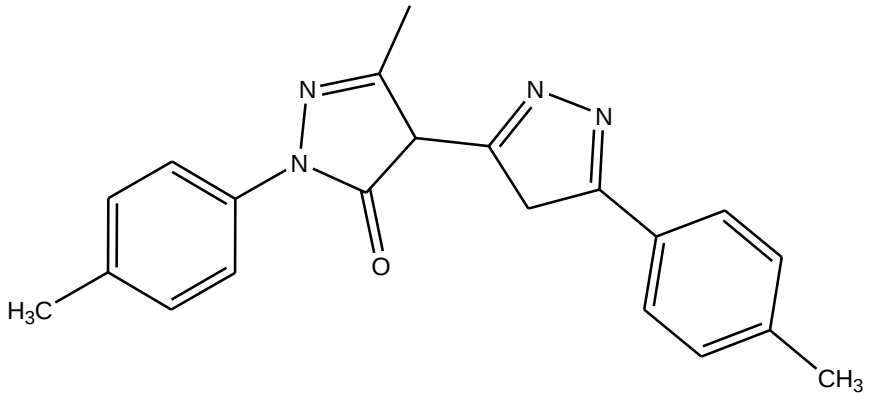
Physical data of compounds 8g



5-(4-Bromo-phenyl)-5'-methyl-2'-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

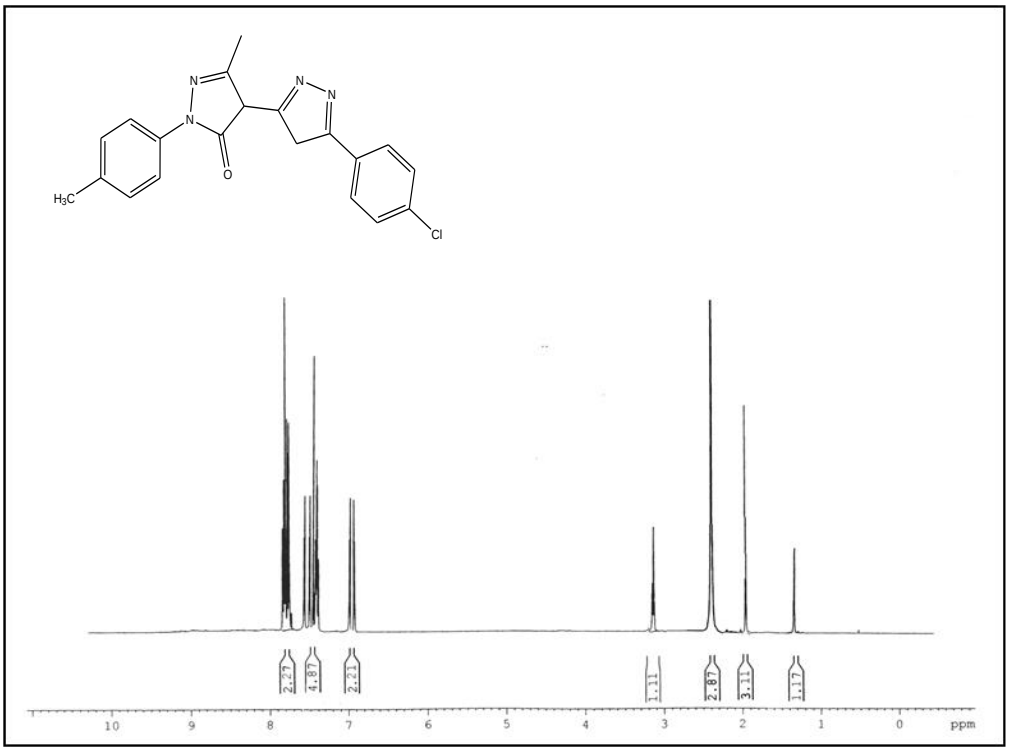
Molecular formula : $C_{20}H_{17}BrN_4O$ Molecular weight : 408 gm/mol Melting point: 165-167 ^{0}C (uncorrected) Yield: 67%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 58.59 4.19 13.69 **Found** 58.57 4.22 13.7
IR features around Cm^{-1} 2903 Aromatic C-H stretching 1367 -CH_3 1670 C=O 1604 C=N 1084 -C-Br	**^{1}H-NMR spectral features (δ-ppm)** 7.88-8.53 (9H,m, Ar-H) 1.58 (2H,s,CH_2 Pyrazole) 2.49 (1H,s,CH,Pyrazolone) 1.86 (3H,s,CH_3) 2.32 (3H,s,CH_3)

Physical data of compounds 8h

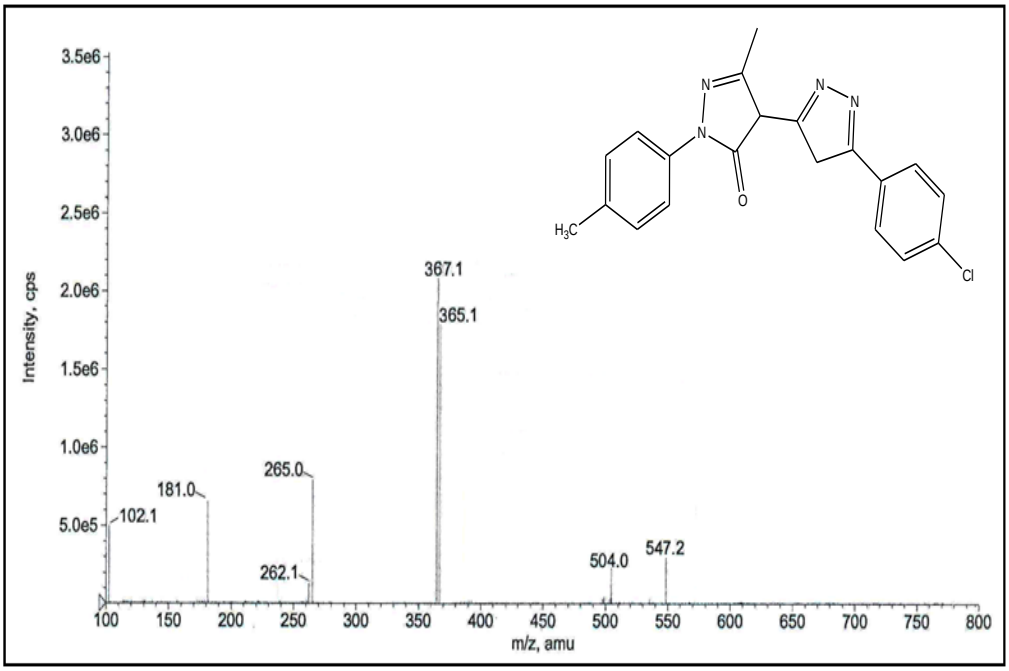


5'-Methyl-5,2'-di-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

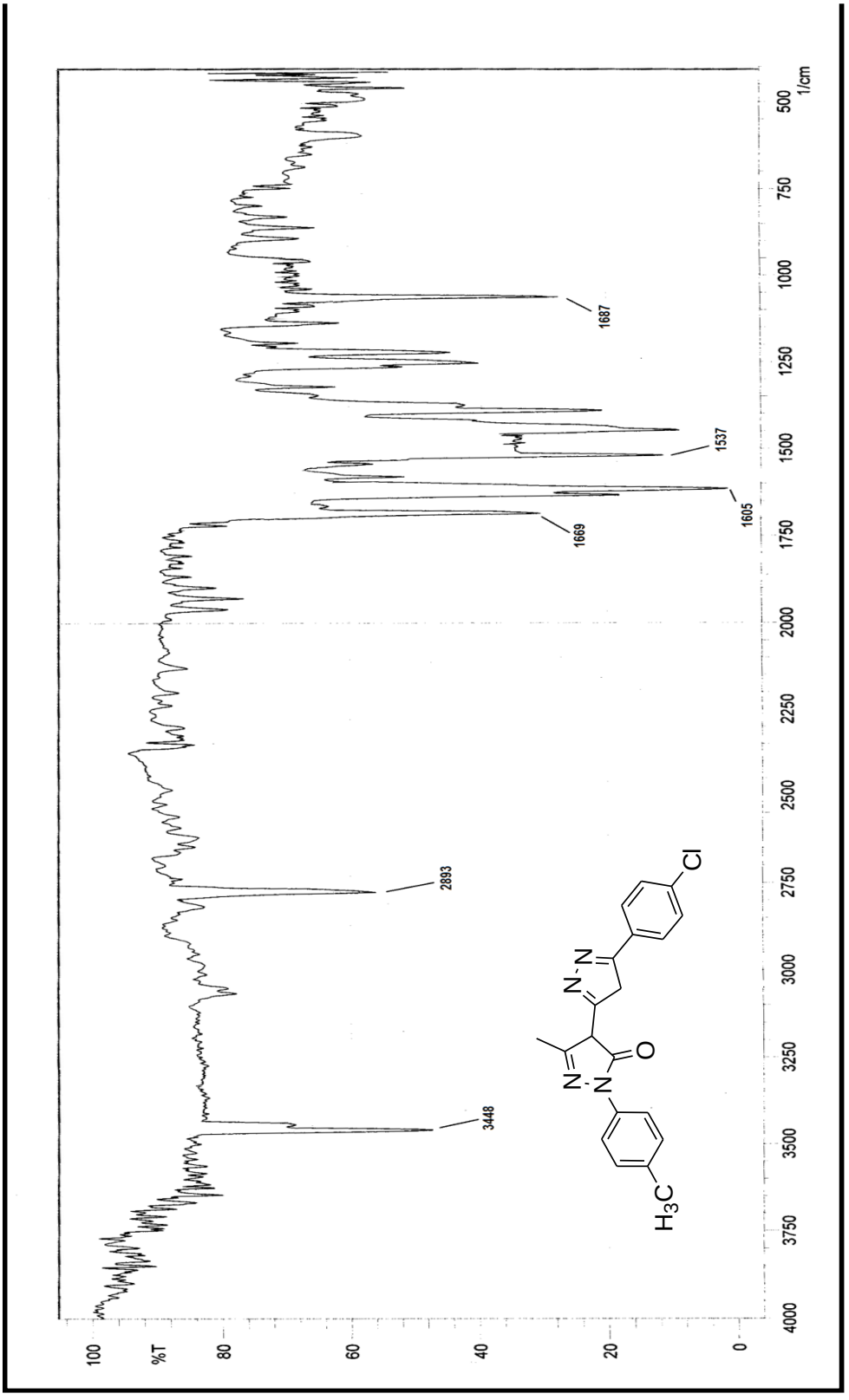
Molecular formula : $C_{20}H_{17}N_4O$ Molecular weight : 344gm/mol Melting point: 165-167 ^{0}C (uncorrected) Yield: 76%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 73.23 5.85 16.27 **Found** 73.26 5.8 16.3
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1370 -CH_3 1661 C=O 1609 C=N	**^{1}H-NMR spectral features (δ-ppm)** 7.84-8.47 (9H,m, Ar-H) 1.48 (2H,s,CH_2 Pyrazole) 2.41 (1H,s,CH,Pyrazolone) 1.89 (3H,s,CH_3) 2.34 (6H,s,2CH_3)



NMR Spactrum of Compound 8f

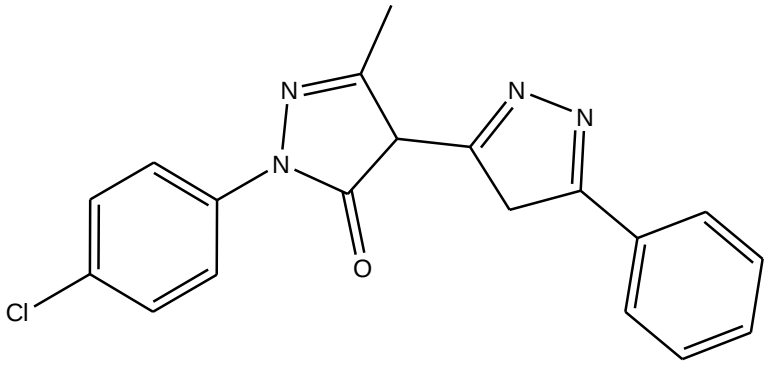


Mass Spactrum of Compound 8f



IR Spactrum of Compound 8f

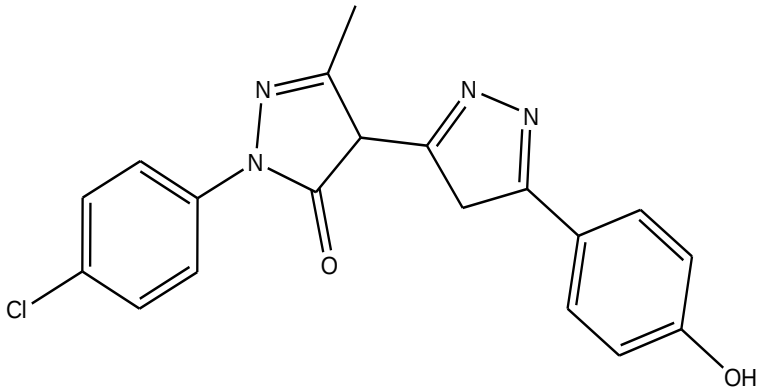
Physical data of compounds 9a



2'-(4-Chloro-phenyl)-5'-methyl-5-phenyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{19}H_{15}ClN_4O$ Molecular weight : 350 gm/mol Melting point: 163-165 ^{0}C (uncorrected) Yield: 77%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.05 4.31 15.97 **Found** 65.0 4.33 16.01
IR features around Cm^{-1} 2887 Aromatic C-H stretching 1667 C=O 1598 C=N 759 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.84-8.5 (9H,m, Ar-H) 1.49 (2H,d,CH_2 Pyrazole) 2.46 (1H,s,CH,Pyrazolone) 1.89 (3H,s,CH_3)

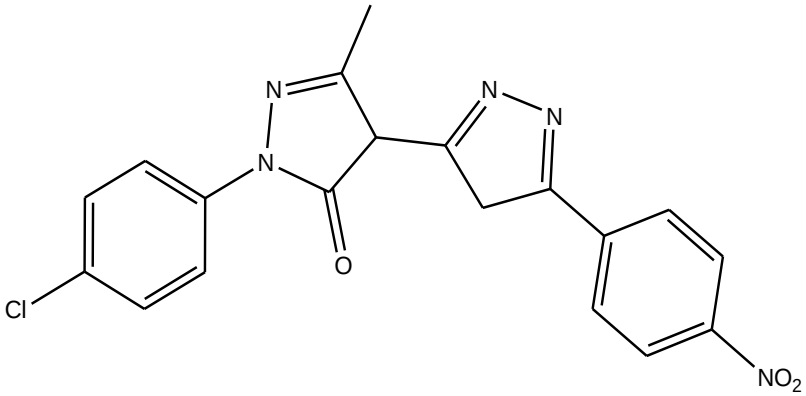
Physical data of compounds 9b



2'-(4-Chloro-phenyl)-5-(4-hydroxy-phenyl)-5'-methyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{19}H_{15}ClN_4O_2$ Molecular weight : 366 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 75%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 62.21 4.12 15.27 **Found** 62.2 4.09 15.29
IR features around Cm^{-1} 2888 Aromatic C-H stretching 1664 C=O 1603 C=N 3455 -OH 750 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.57-8.23 (8H,m, Ar-H) 1.47 (2H,s,CH_2 Pyrazole) 2.36 (1H,s,CH,Pyrazolone) 1.86 (3H,s,CH_3)

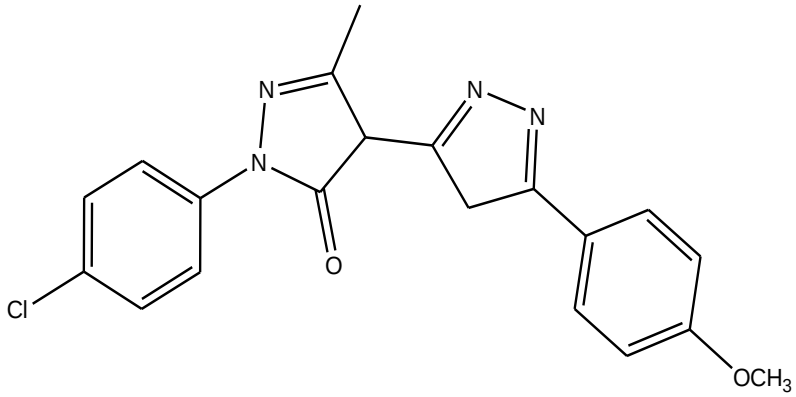
Physical data of compounds 9c



2'-(4-Chloro-phenyl)-5'-methyl-5-(4-nitro-phenyl)-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{19}H_{15}ClN_5O_3$ Molecular weight : 395 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 80%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 57.66 3.57 17.69 **Found** 57.6 3.59 17.7
IR features around Cm^{-1} 2893 Aromatic C-H stretching 1667 C=O 1606 C=N 752 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.84-8.5 (8H,m, Ar-H) 1.46 (2H,s,CH_2 Pyrazole) 2.46 (1H,s,CH,Pyrazolone) 1.89 (3H,s,CH_3)

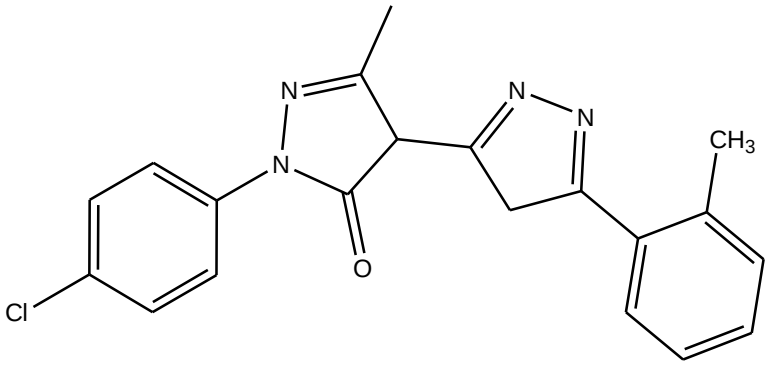
Physical data of compounds 9d



2'-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-5'-methyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{20}H_{17}ClN_4O_2$ Molecular weight : 380 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 78%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 63.07 4.50 14.71 **Found** 63.09 4.47 14.7
IR features around Cm^{-1} 2885 Aromatic C-H stretching 1669 C=O 1605 C=N 2334 -OCH_3 756 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.84-8.5 (9H,m, Ar-H) 1.49 (2H,s,CH_2 Pyrazole) 2.42 (1H,s,CH,Pyrazolone) 1.87 (3H,s,CH_3) 3.65 (3H,s,OCH_3)

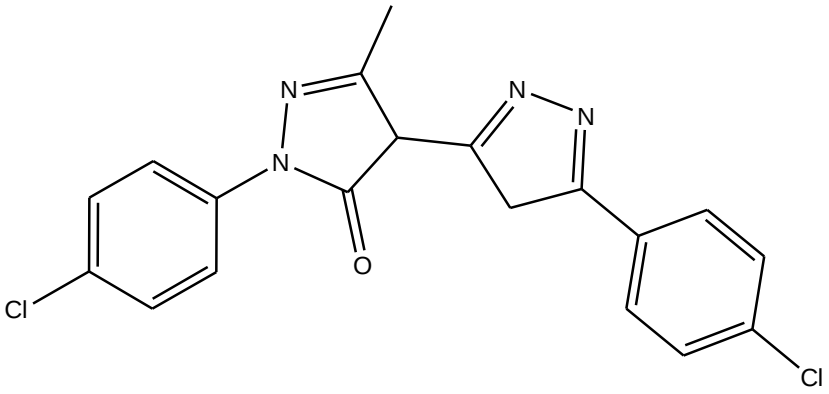
Physical data of compounds 9e



2'-(4-Chloro-phenyl)-5'-methyl-5-*o*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{20}H_{17}ClN_4O$ Molecular weight : 364 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 74%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.84 4.70 15.36 **Found** 65.88 4.68 15.4
IR features around Cm^{-1} 2992 Aromatic C-H stretching 1376 -CH_3 1671 C=O 1602 C=N 757 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.67-8.47 (8H,m, Ar-H) 1.43 (2H,s,CH_2 Pyrazole) 2.38 (1H,s,CH,Pyrazolone) 1.95 (3H,s,CH_3) 2.35 (3H,s,CH_3)

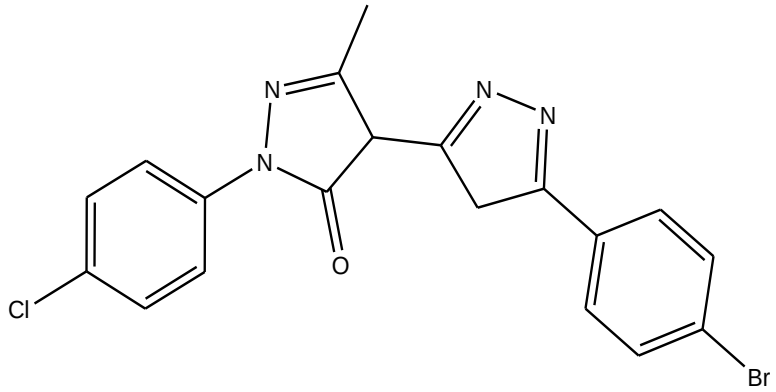
Physical data of compounds 9f



5,2'-Bis-(4-chloro-phenyl)-5'-methyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

Molecular formula : $C_{19}H_{14}Cl_2N_4O$ Molecular weight : 384 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 64%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 59.24 3.66 14.54 **Found** 65.88 4.68 15.4
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1663 C=O 1604 C=N 765 -C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.2-8.42 (8H,m, Ar-H) 1.53 (2H,s, CH) 2.42 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3)

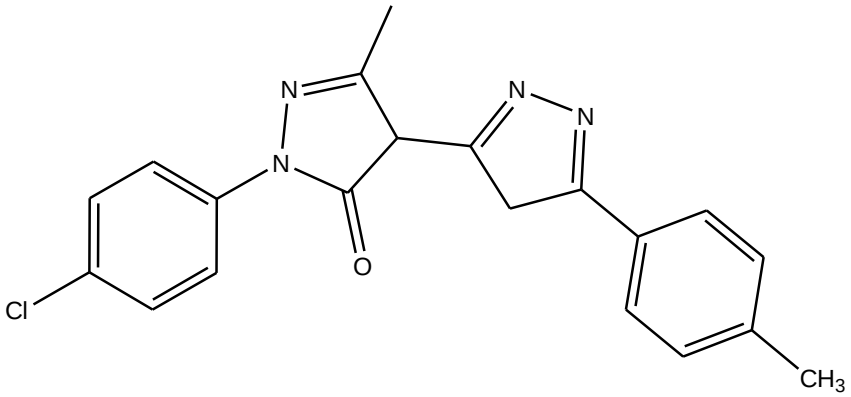
Physical data of compounds 9g



5-(4-Bromo-phenyl)-2'-(4-chloro-phenyl)-5'-methyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

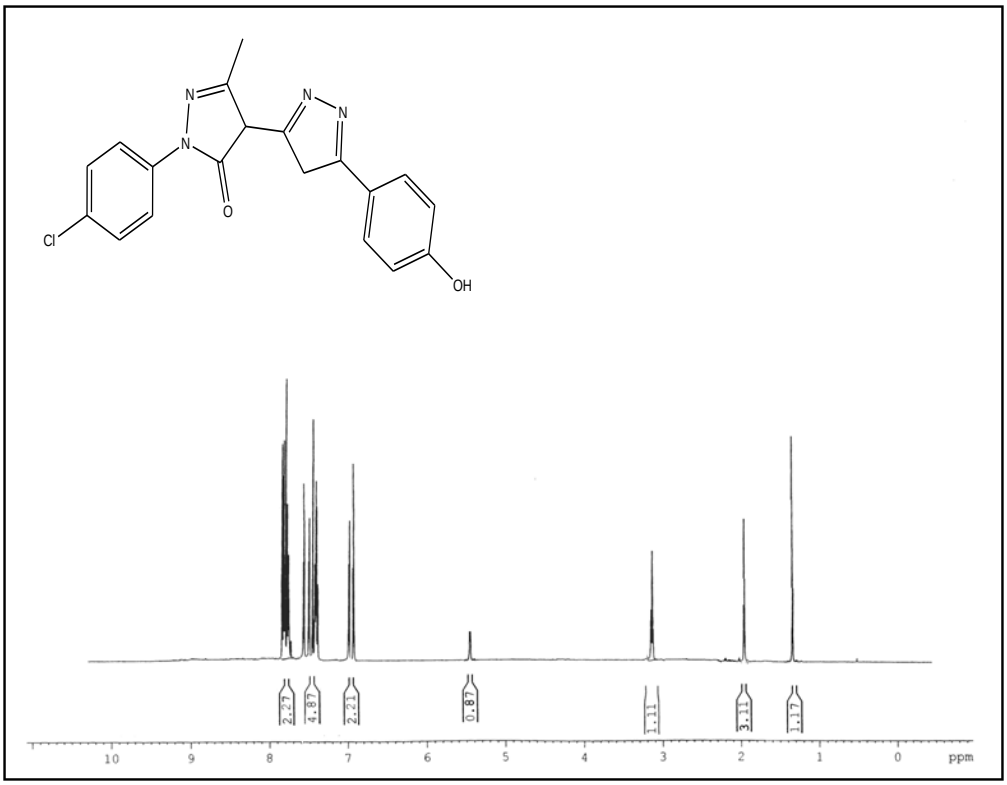
Molecular formula : $C_{19}H_{14}BrClN_4O$ Molecular weight : 429 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 68%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 53.11 3.28 13.04 **Found** 53.09 3.3 13.09
IR features around Cm^{-1} 2901 Aromatic C-H stretching 1660 C=O 1605 C=N 1081 -C-Br 759 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.98-8.16 (8H,m, Ar-H) 1.47 (2H,s, CH) 2.47 (1H,s,Pyrazolone) 1.95 (3H,s,CH_3)

Physical data of compounds 9h

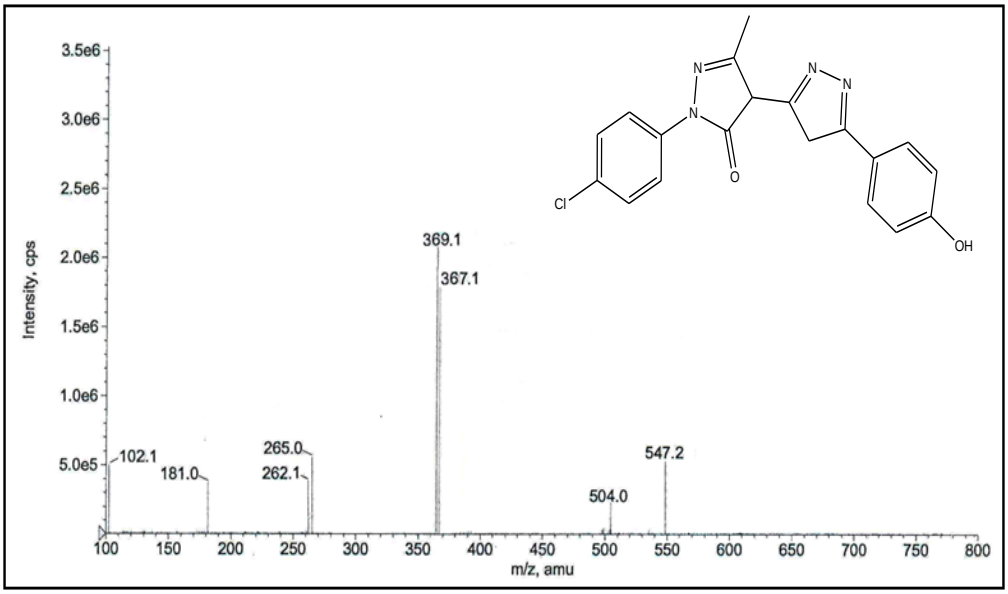


2'-(4-Chloro-phenyl)-5'-methyl-5-*p*-tolyl-2',4'-dihydro-4*H*-[3,4']bipyrazolyl-3'-one

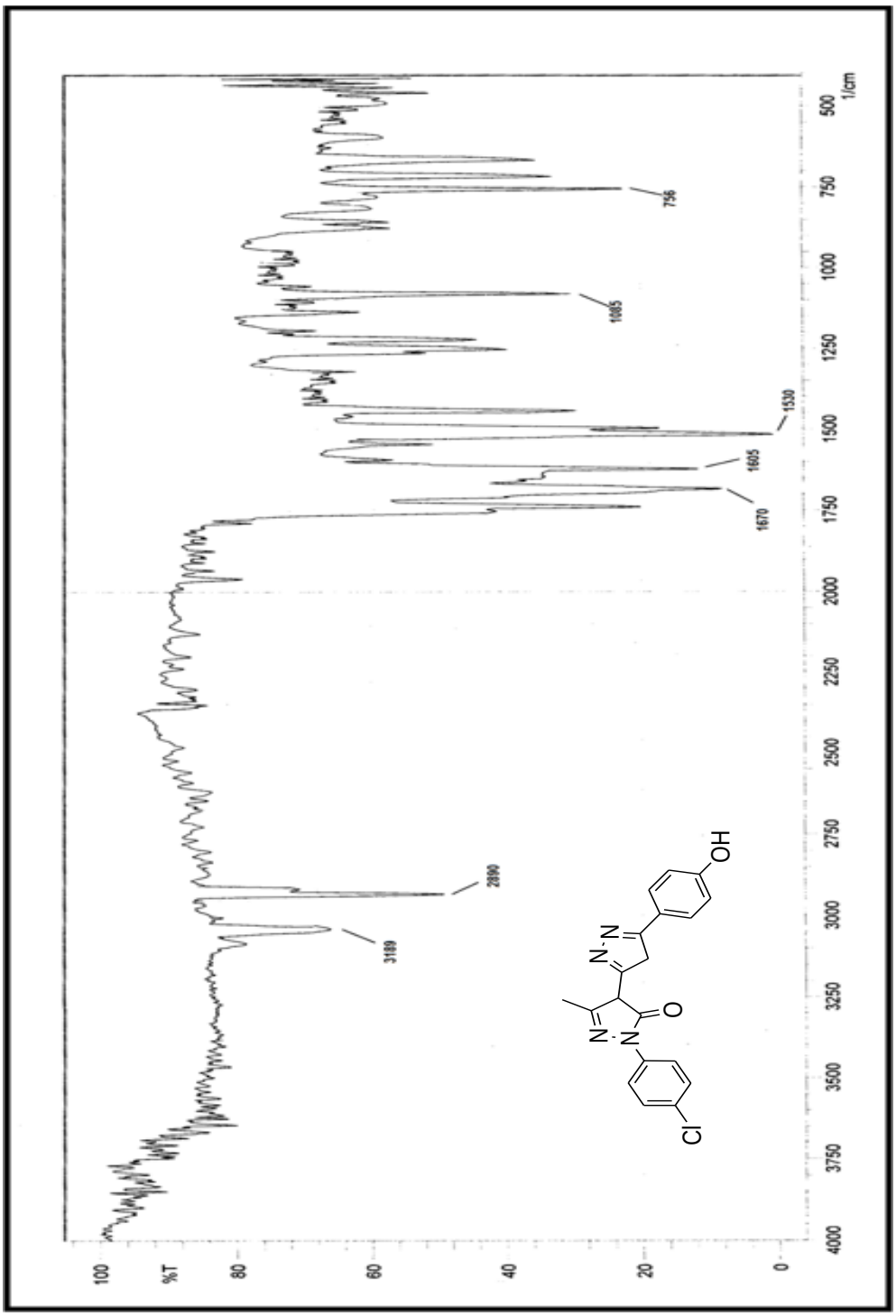
Molecular formula : $C_{20}H_{17}ClN_4O$ Molecular weight : 364 gm/mol Melting point: 156-158 ^{0}C (uncorrected) Yield: 81%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.84 4.70 15.36 **Found** 65.51 4.73 45.3
IR features around Cm^{-1} 3051 Aromatic C-H stretching 2950,1370 -CH_3 1725 C=O 1620 C=N 761 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.82-8.49 (8H,m, Ar-H) 1.49 (2H,s, CH) 2.44 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 2.37 (3H,s,CH_3)



NMR Spactrum of Compound 9b



Mass Spactrum of Compound 9b



IR Spactrum of Compound 9b

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CHAPTER-4

Synthesis and Characterization of Benzothiazepine derivatives from Chalcone

Table of Contents

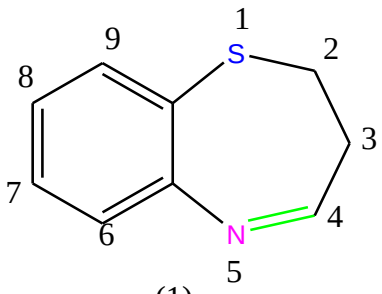
SECTION-A

SECTION-B

SECTION-A

4.1 General Introduction

The 1,5-benzothiazepines are important nitrogen- and sulfur-containing seven-membered heterocyclic compounds in drug research since they possess diverse bioactivities. 1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine and one of the three possible benzo-condensed derivatives, viz. 1,4, 4,1and 1,5-benzothiazepines.



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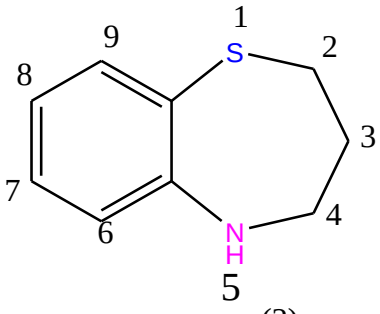
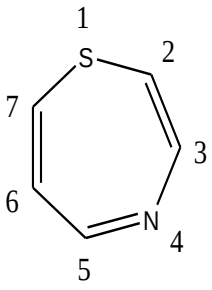


(2)

General structures of !,5 - benzothiazepine



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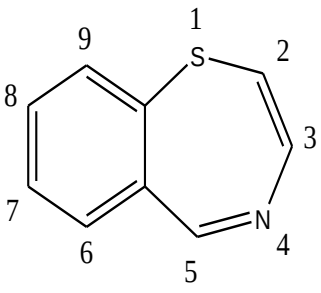

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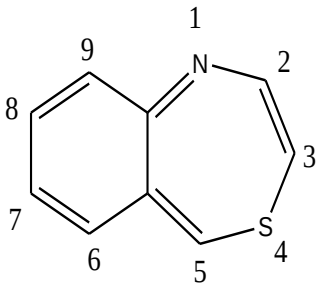


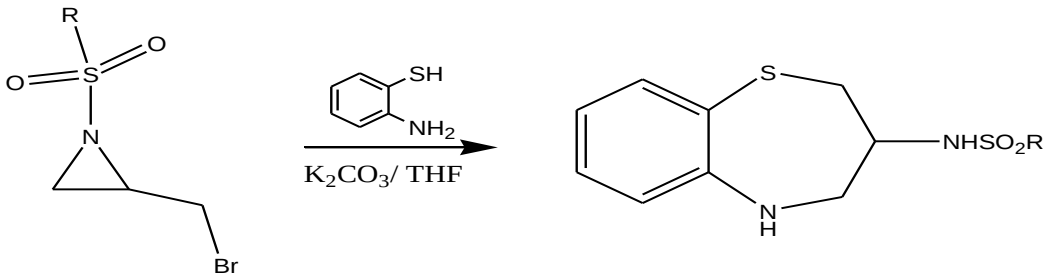
(5)

The 1, 5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets. The first molecule of 1, 5-benzothiazepine used clinically was diltiazem, followed by clentiazem, for their cardiovascular action. Some of the 1, 5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim, clothiapine and quetiapine. Therefore, the 1, 5-benzothiazepines are useful compounds in the drug research which has stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations.

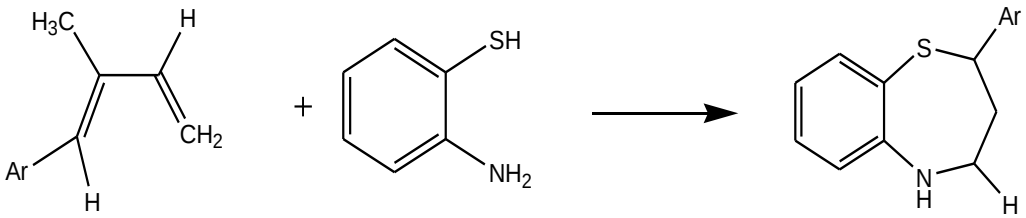
The common strategy for the construction of the 1, 5-benzothiazepine moiety is the reaction of 1, 3-diarylprop-2-enones with o-aminothiophenol. The various reported methodologies involve the use of inorganic solid supports such as alumina, silica gel and clay under microwave irradiation, acetic acid or trifluoroacetic acid, hydrochloric acid, piperidine.

4.2 Synthetic Aspects

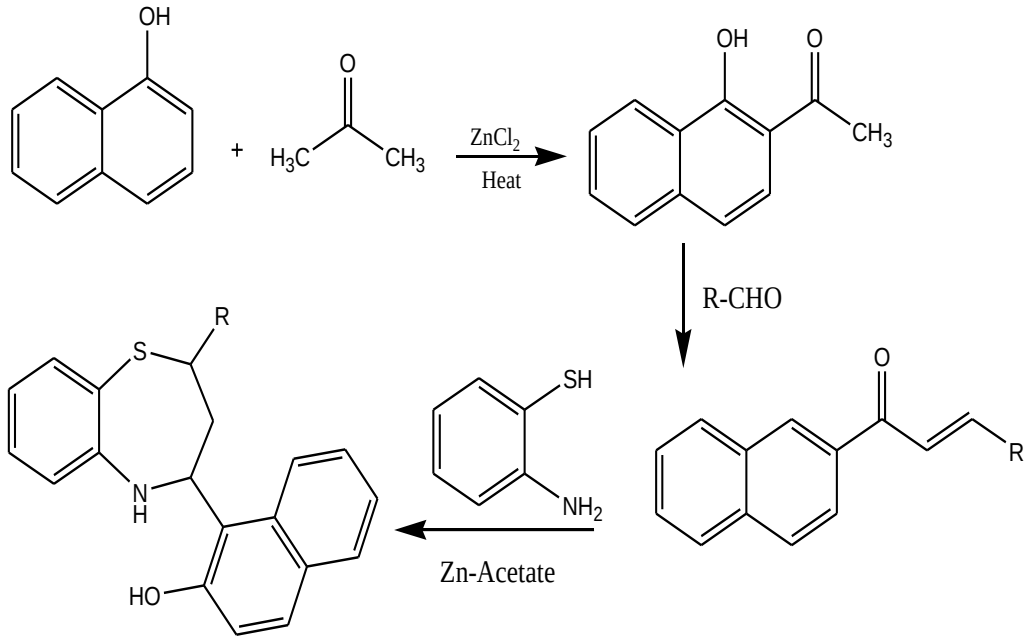
Michinori*et al* [1] had been reported the synthesis of 3-sulfonamido-2, 3, 4, 5-tetrahydro-1,5- benzothiazepines Treatment of 2 (bromomethyl) aziridines with 1.2 equiv of 2-aminothiophenol in THF in the presence of potassium carbonate.



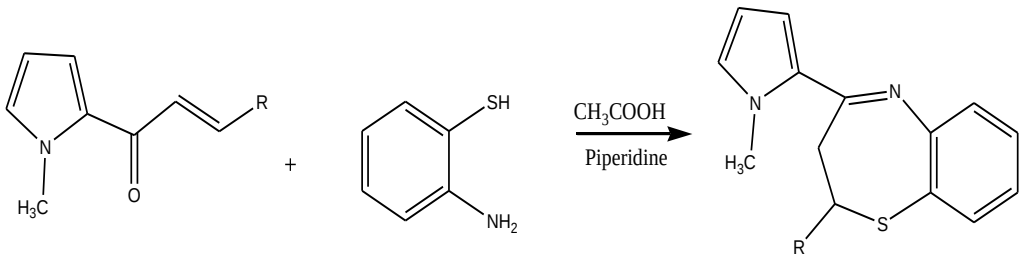
Prakash *et al* [2] had been reported 1,5-benzothiazepines from reaction of chalcone with o-aminothiophenol.



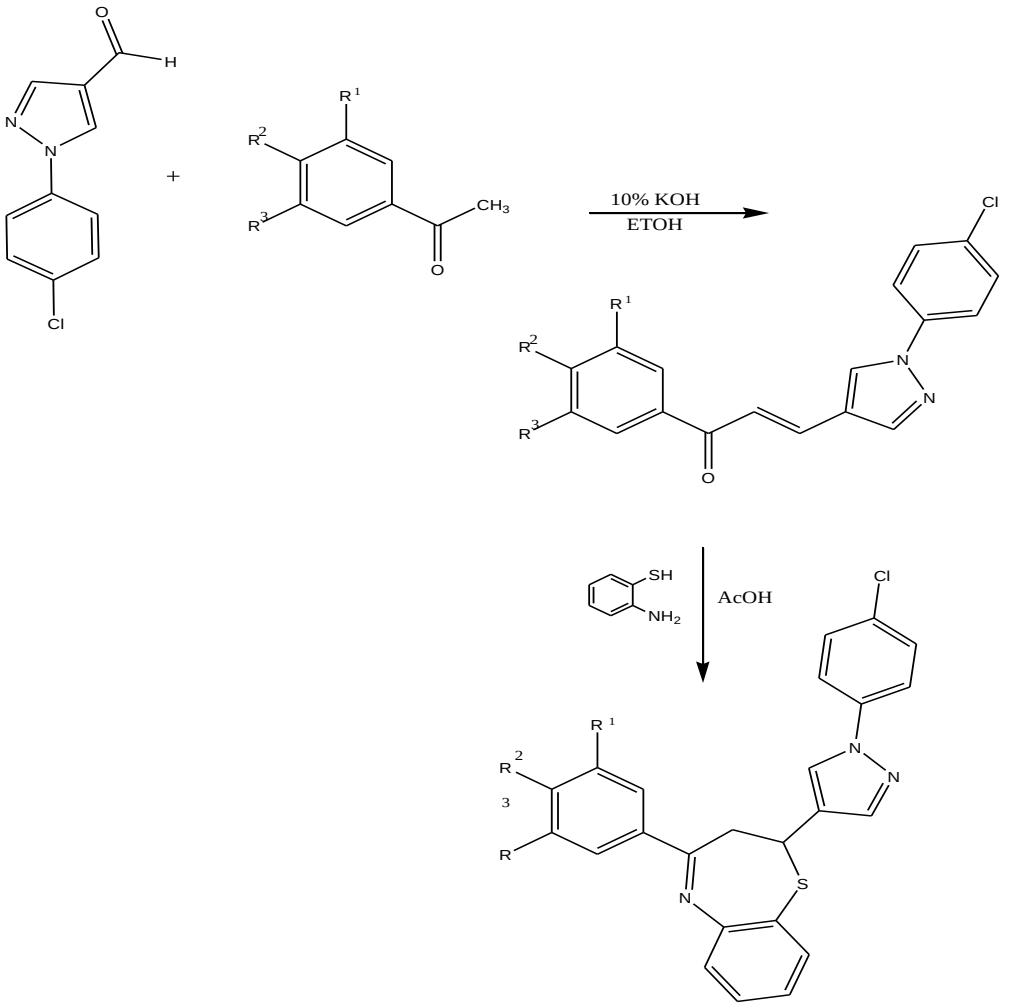
Vyawahare*et al* [3] had been reported 2, 3-dihydro-2-substituted-4-(naphthalene-2-ol)-yl-1,5-benzothiazepines from 1,3-substituted-prop-2-en-1-one. Cyclocondensation of with 2-aminothiophenol in presence of ecofriendly catalyst zinc acetate in the solvent free condition under microwave irradiation.



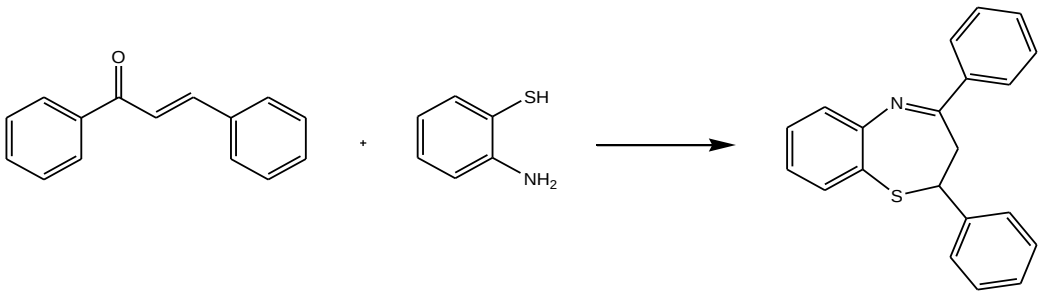
Ahmad *et al*[4] synthesised 1, 5-benzothiazepines from chalcones obtained from 2- acetyl-1-methylpyrrole.



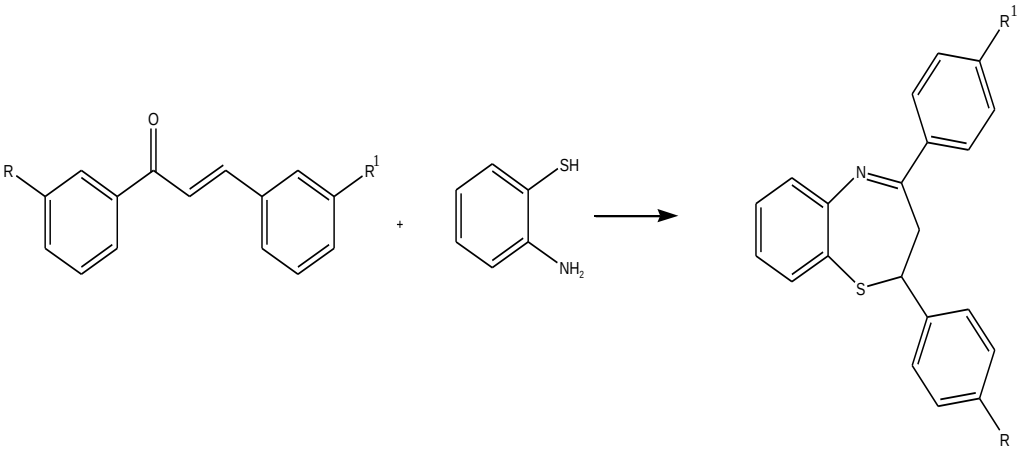
Mhaske*et al* [5] synthesized Novel 1, 5-benzothiazepine reaction of 1-(4-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde, *o*-hydroxyacetophenones and chalcone



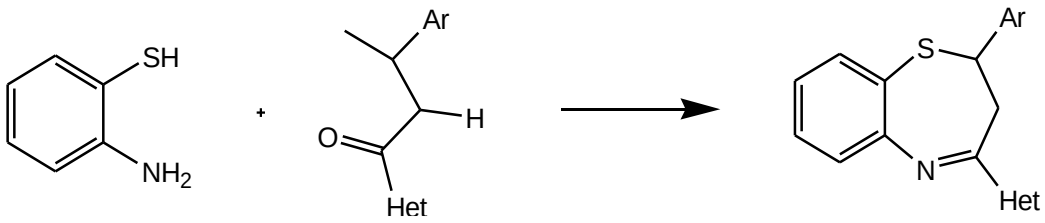
Arya *et al* [6] reported substituted 1,5-benzothiazepines from chalcones with o-aminothiophenol



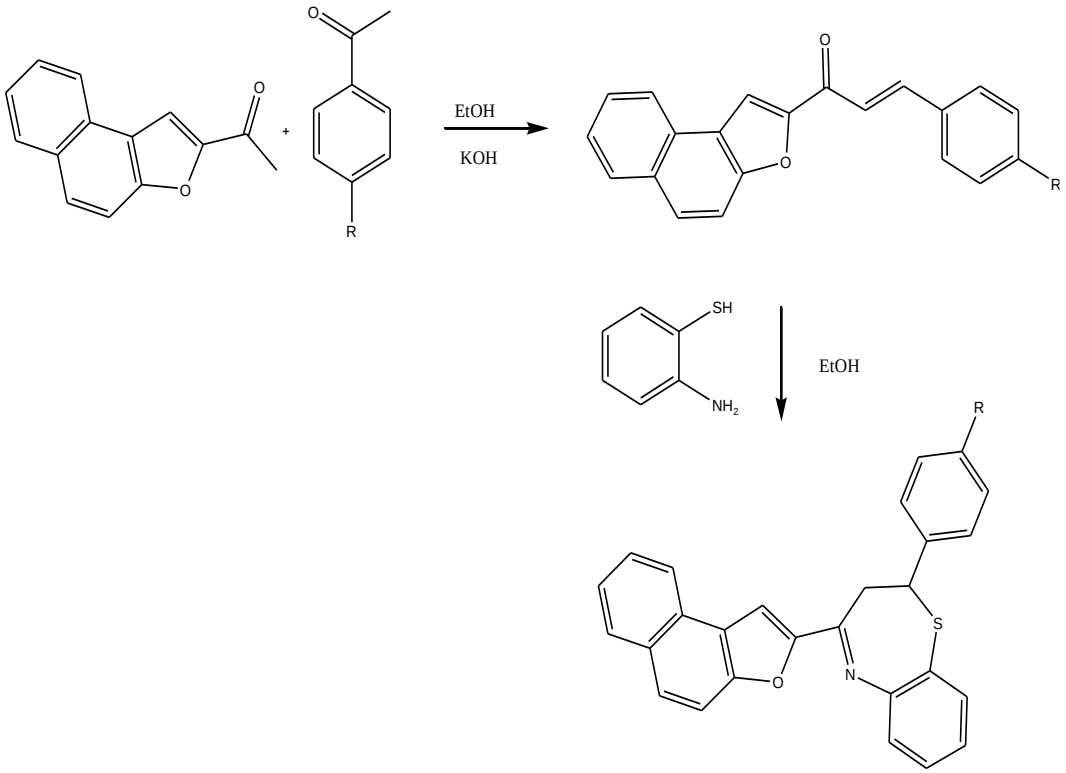
.Dandia*et al*[7] had been reported 1,5-benzothiazepines from o-aminothiophenol and chalcones under gallium triflate catalysis.



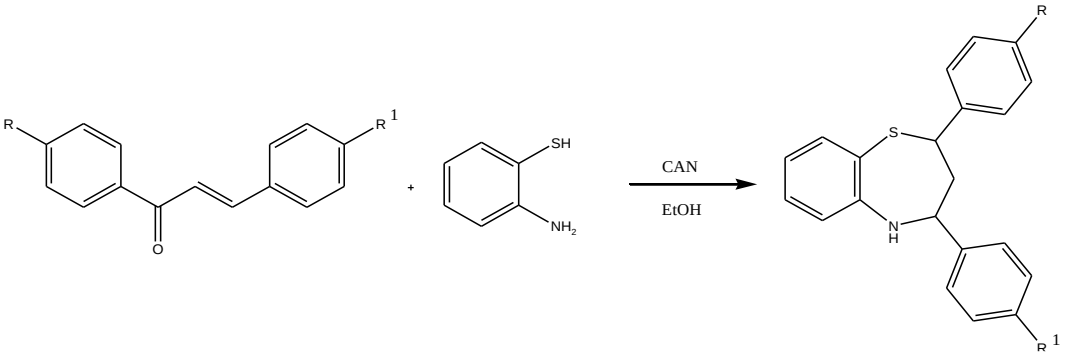
Ahmad *et al* [8] established 1,5-benzothiazepines reaction of o-aminothiophenol with α,β-unsaturated ketones or chalcones.



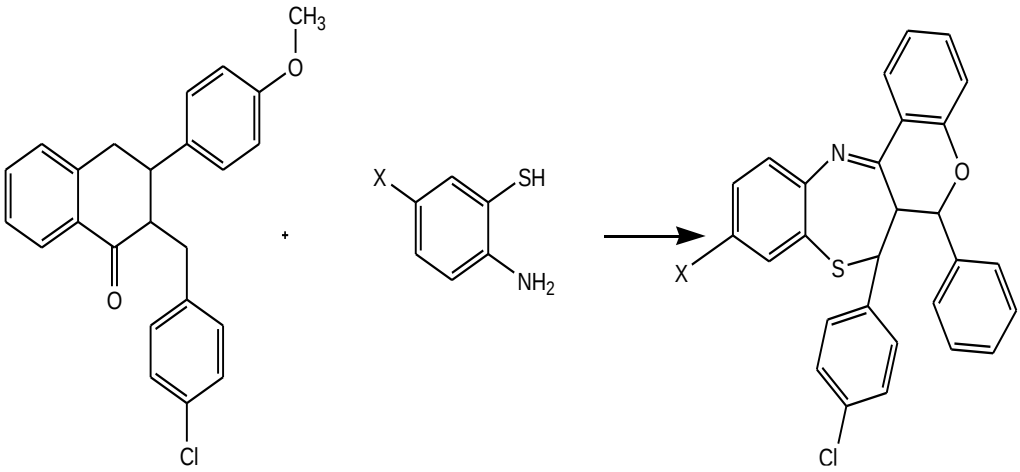
Gaikwad *et al* [9] reported novel 2, 3-diydro -4-(naphtho [2, 1-b] furan -2yl)-2- substitued [1,5] benzothiazepines mixture of 1-(naphtho [2,1-b] furan-2-yl)-3-penyl prop-2-en-1-one and o-amino thiophenol.



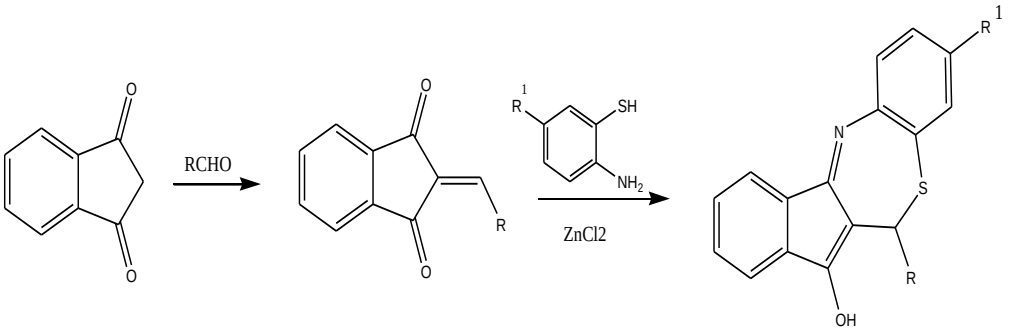
Chate *et al* [10] established Synthesis of 1,5-Benzothiazepines Using from chalcones and o-aminothiophenol using Ceric Ammonium Nitrate as a catalysts under ultrasonic irradiation.



Jain *et al* [11] reported 10-fluoro- 6a, 7-dihydro-6H-7-(3-chlorophenyl)- 6-(4-methoxyphenyl)-[1]benzopyrano[3,4-c][1,5]-benzothiazepine 3-(3-chlorobenzylidine)flavanone and 5-substituted-2-aminothiophenols in dry toluene containing trifluoroacetic acid as catalyst.



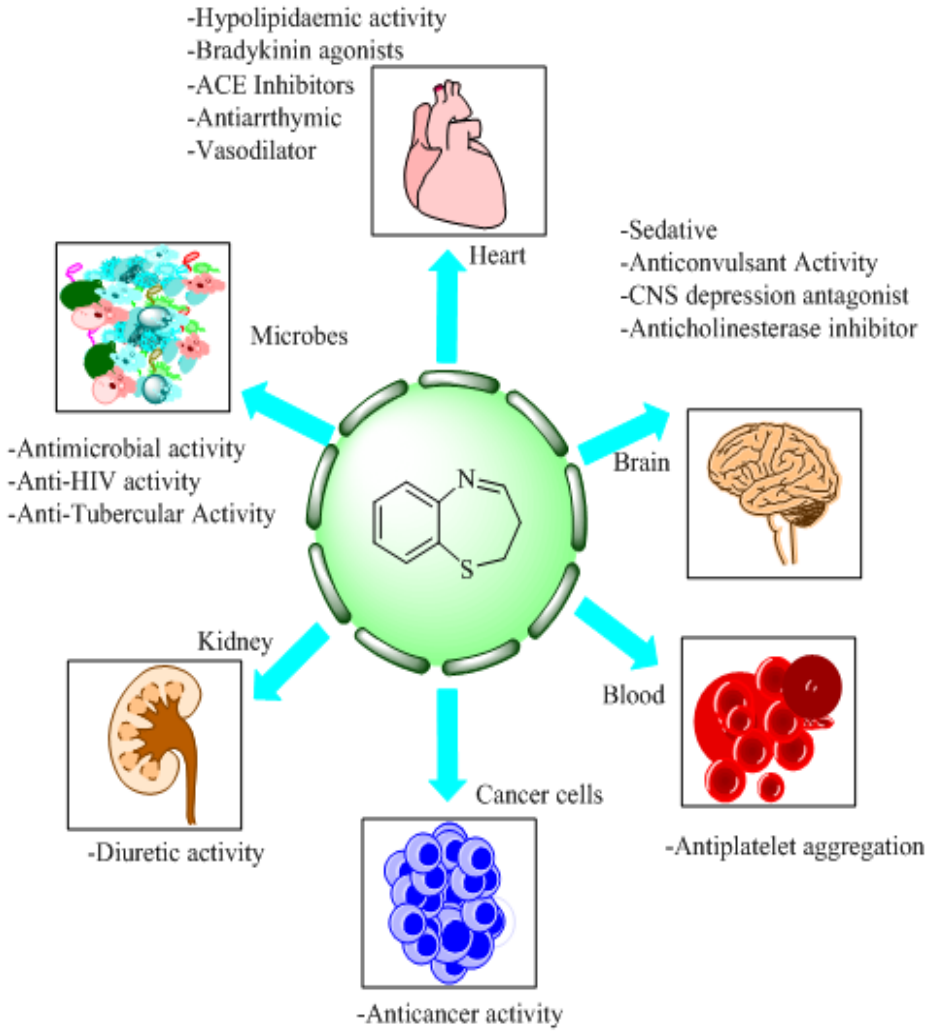
Carolyn *et al* [12] reported tetracyclic benzothiazepines(BTZs) from 1,3-indandione, 1 mmol of aldehyde, 0.2 mmol of the catalyst L-Proline, and then MeOH (2 ml). Intermediate, 2- arylidene-1,3-indandione, was used in the next step with 2-aminothiophenol and anhydrous ZnCl2 in anhydrous THF. The reaction mixture was heated in a microwave reactor at 100^0C for 1 hr.



The preparation of 1,5-benzothiazepin-4(5H)-ones occurs by the reaction of 2-aminothiophenol and propiolic acid with subsequent cyclisation of the addition product in the presence of dicyclohexylcarbodimide

4.3 Pharmacological aspects

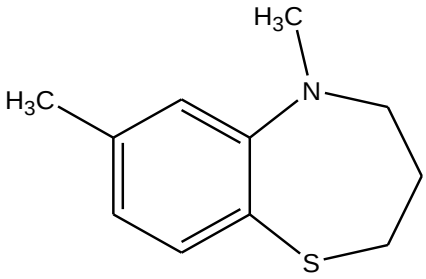
The 1,5-benzothiazepine nucleus, a biologically accepted pharmacophore in medicinal compounds, has versatile heterocyclic nucleus possessing wide spectrum of biological activities.



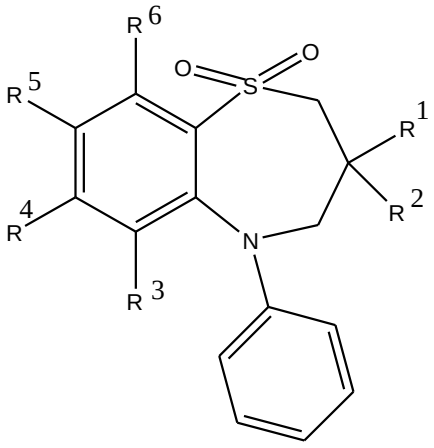
The importance of the l,5-benzothiazepine nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents.70 A number of biological activities have been associated with it, such as Derivatives of 1,5-benzothiazepines are of particularinterest for lead discovery because they have been found active against different families of targets, as compound bearing this structural unit

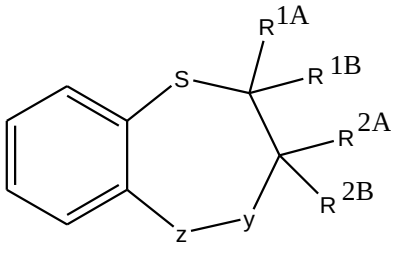
possess a broad spectrum of biological activities such as antifeedent [13], antihypertensive [14], antimicrobial [15], coronary vasodilatory [16], antidepressant [17], antiarrythmic [18], calcium channel blocker [19], CNS β-stimulant [20], antifungal [21], anticancer [22], anti-HIV [23], antimalerial [24].

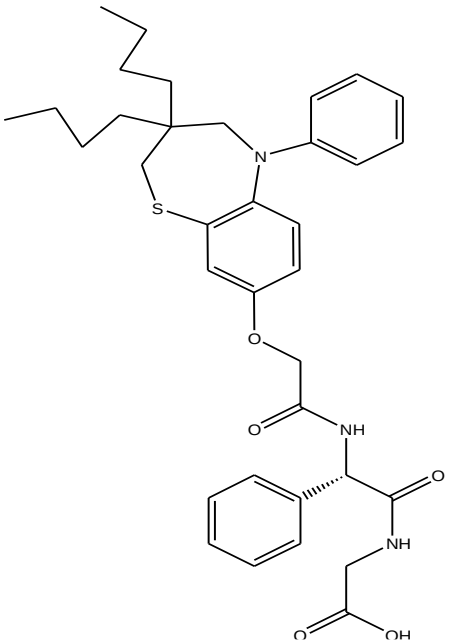
Donahue et al. [25]reported synthesis of conjugates of quetiapine hapten. Smith et al. [26] reported compoundinhibit store-overload induced calcium release (SOICR) through the RyR_2 channel and showed antiarrhythmic effect.



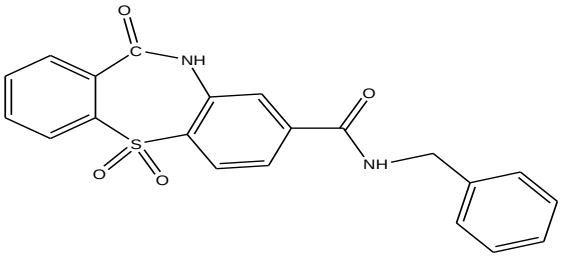
Starke et al.[27] studied 1,5-benzothiazepine derivatives and reported that compound possess ileal bile acid transport inhibitory activity and was found to decrease the risk of hyperlipidemia. Whereas 1,5 -benzothiazepine derivative is useful as Hypocholesterolemic Agents and reported with inhibitory activity against type-1 and type-2 diabites.



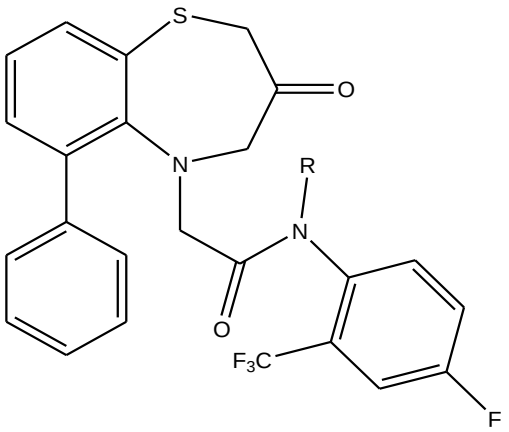




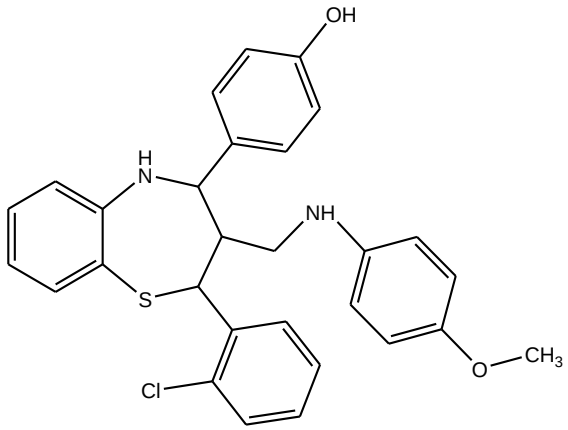
Guo et al. [28]reported compound useful as pregenomic RNA encapsidation inhibitors of Hepatitis B virus for treatment of Hepatitis B Virus infection and related conditions



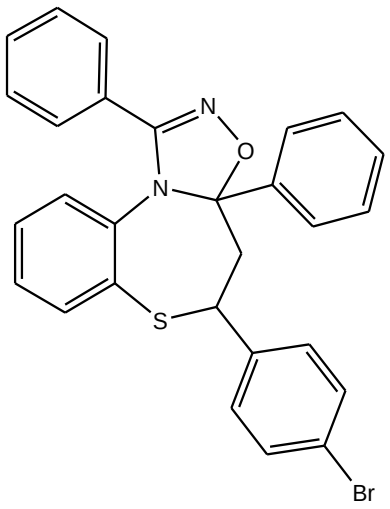
Tabata and coworkers reported[29] an acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors.



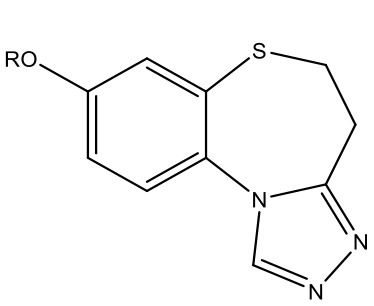
Garg et al. [30] reported anticonvulsant activity of a new series of 4-(4'-Hydroxyphenyl)-2-(3-substituted phenyl)-3-(4-substituted phenyl amino methylene)-2,3-dihydro-1,5-benzothiazepine .

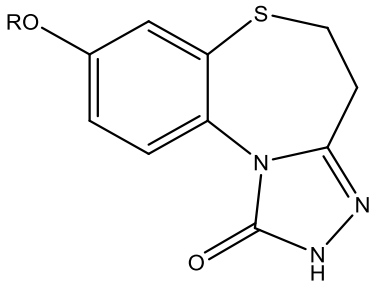


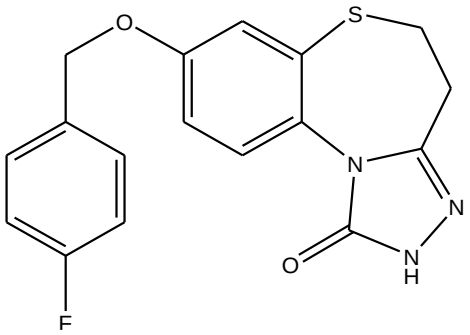
Sarro et al.[31] synthesize 5H-[1,2,4]Oxadiazolo[5,4-d][1,5]benzothiazepines and found that the 5-(4-bromophenyl)-1,3-diphenyl derivative had potent anticonvulsant activity.



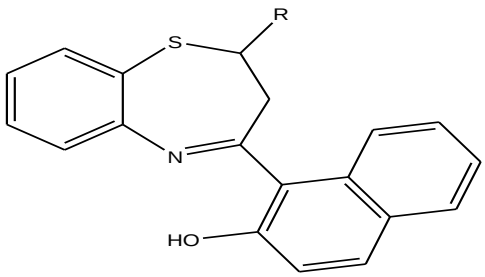
Deng et al. [32] reported two series of 8-alkoxy-4,5-dihydrobenzo[b]-[1,2,4]triazolo[4,3-d][1,4]thiazepine derivatives and evaluated for their anticonvulsant activity.



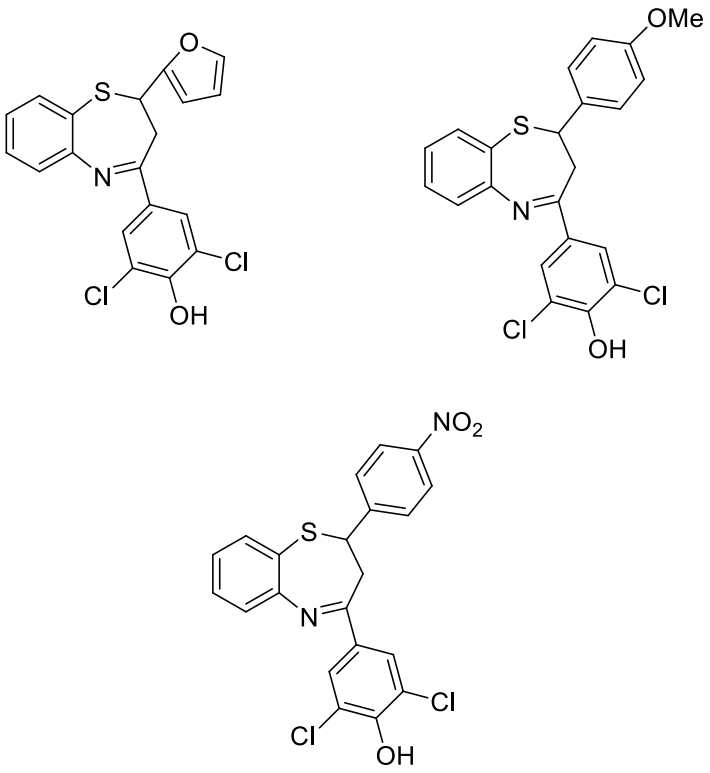




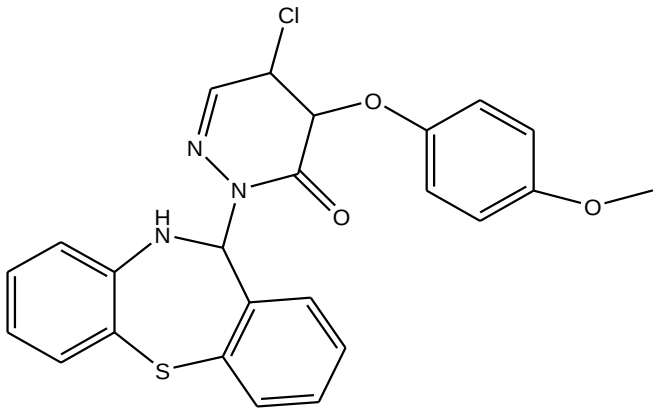
Vyawahare et al. [33] performed solvent free green synthesis of 2,3-dihydro-2-substituted-4-(naphthalen-2'-ol)-yl-1,5-benzothiazepin. These compounds exhibited excellent results against CNS depressant activity.



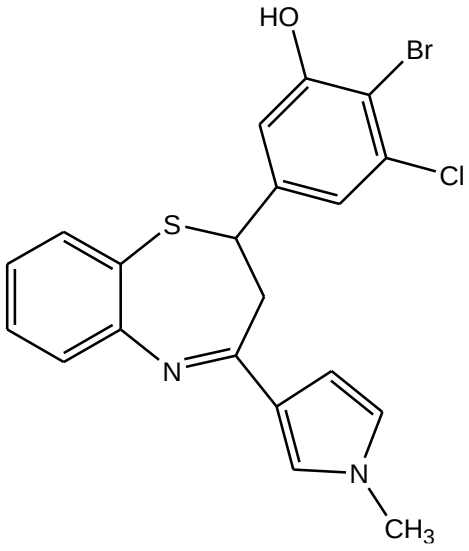
Nikalje et al. [34] reported of 2, 4-substituted 2, 3-dihydro-1,5-benzothiazepine derivatives as benzodiazepines bioisosters and study of CNS depressant activity of these compounds using sleep deprivation method revealed that compounds excellent lead.



Guerrero et al.,[35] synthesized the feeding behavior of mice by acting on neuropeptides.



Yenupuri et al.[36] a series of 2,3-dihydro-2-(susbtituted)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepines demonstrated their in vitro cytotoxic activity using Brine shrimp lethality assay. Compound showed significant cytotoxic activity.


HO
Br
Cl
S
N
N
CH3

SECTION-B

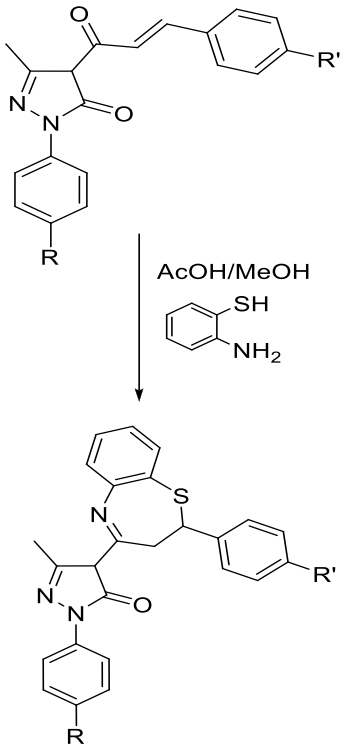
4.4 Material and Method

The same chemicals, solvents, procedures and instruments that were mentioned in chapter-3 were also used here. 2-Aminothiophenol is obtained from the local supplier and the chalcones used as described in chapter-2.

4.4.1 General procedure for the preparation of Benzothiazepine derivatives

To a solution of Chalcone (0.002mol) in 10ml of pyridine, 0.002mol of O-aminothiophenol was added. The reaction mixture was refluxed by heating for 6hrs, and the progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solution was cooled and transferred into crushed ice. The solid product was filtered and recrystallized from ethanol.

4.5 Reaction scheme

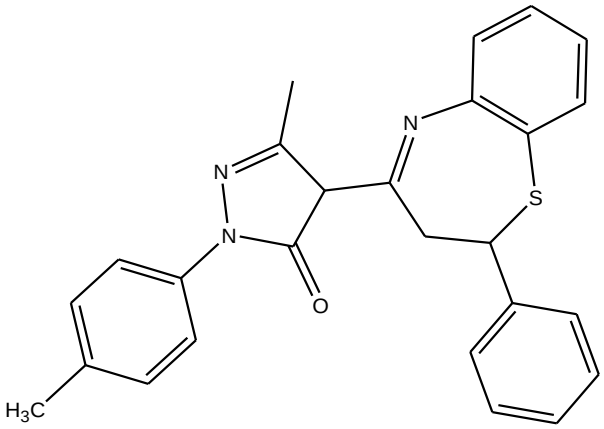


Reaction scheme 4.1

Where R = -CH_3 & -Cl

Where R'= a. phenyl
b. 4- hydroxy phenyl
c. 4- Nitro phenyl
d. 4- methoxy phenyl
e. 2- methyl phenyl
f. 4-chloro phenyl
g. 4- bromo phenyl
h. 4-methyl phenyl

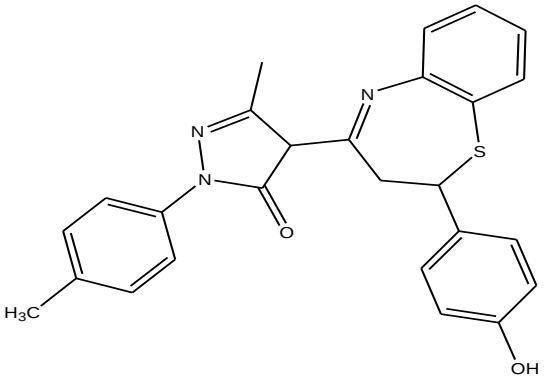
Physical data of compounds 10a



5-Methyl-4-(2-phenyl-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{26}H_{23}N_3OS$ Molecular weight : 425 gm/mol Melting point: 163-165 ^{0}C (uncorrected) Yield: 72%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 73.38 5.45 9.87 **Found** 73.4 5.48 9.9
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1668 C=O 1605 C=N 1539 C=C 762 C-S-C	**^{1}H-NMR spectral features (δ-ppm)** 7.19-8.11 (13H,m, Ar-H) 1.76 (2H,s,CH_2) 2.46 (1H,s,Pyrazolone) 3.62 (1H,s,CH) 1.92 (3H,s,CH_3) 2.38 (3H,s,CH_3)

Physical data of compounds 10b

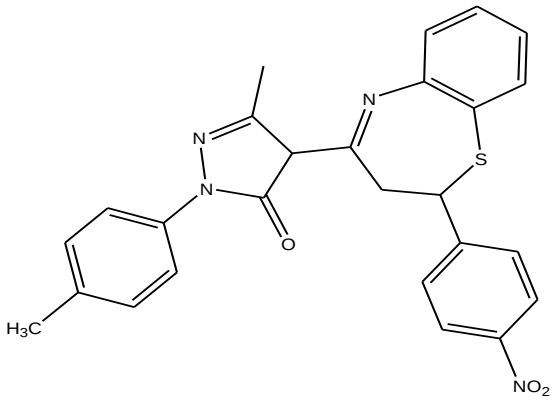


4-[2-(4-Hydroxy-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{26}H_{23}N_3O_2S$	**Elemental analysis**
Molecular weight : 442 gm/mol	**%C** **% H** **% N**
Melting point: 165-166 ^{0}C	**Calculated** 70.72 5.25 9.52
(uncorrected)	**Found** 70.75 5.26 9.55
Yield: 78%	

IR features around Cm^{-1}		**^{1}H-NMR spectral features (δ-ppm)**	
2887	Aromatic C-H stretching	7.23-8.11	(12H,m, Ar-H)
1676	C=O	1.79	(2H,s,CH_2)
1609	C=N	2.43	(1H,s,Pyrazolone)
1542	C=C	3.68	(1H,s,CH)
765	C-S-C	1.96	(3H,s,CH_3)
3450	OH	2.36	(3H,s,CH_3)
		4.32	OH

Physical data of compounds 10c

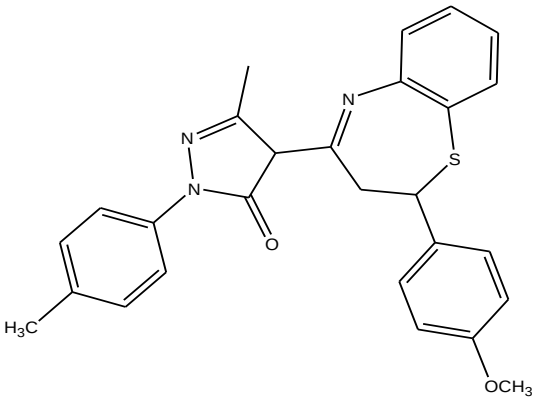


5-Methyl-4-[2-(4-nitro-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{26}H_{22}N_4O_3S$	**Elemental analysis**			
Molecular weight : 471 gm/mol		**%C**	**% H**	**% N**
Melting point: 165-167 ^{0}C	**Calculated**	66.37	4.71	11.91
(uncorrected)	**Found**	66.4	4.70	12.0
Yield: 73%				

IR features around Cm^{-1}		**^{1}H-NMR spectral features (δ-ppm)**	
2887	Aromatic C-H stretching	7.06-8.1	(12H,m, Ar-H)
1671	C=O	1.73	(2H,s,CH_2)
1600	C=N	2.42	(1H,s,Pyrazolone)
1543	C=C	3.62	(1H,s,CH)
769	C-S-C	1.92	(3H,s,CH_3)
		2.38	(3H,s,CH_3)

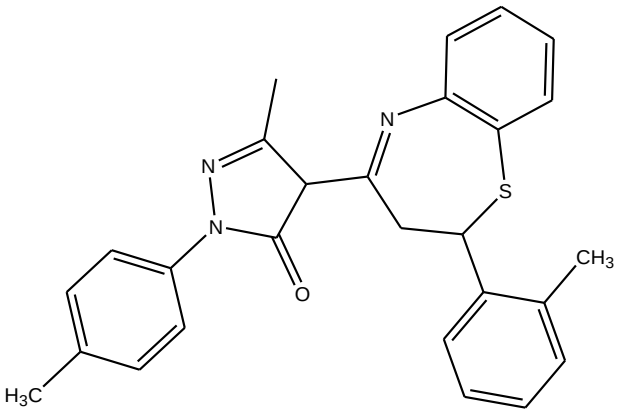
Physical data of compounds 10d



4-[2-(4-Methoxy-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{27}H_{25}N_3O_2S$ Molecular weight : 455 gm/mol Melting point: 170-171 ^{0}C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 71.18 5.53 9.22 **Found** 71.08 5.51 9.23
IR features around Cm^{-1} 2906 Aromatic C-H stretching 1674 C=O 1607 C=N 1541 C=C 772 C-S-C 2348 OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.3-8.16 (12H,m, Ar-H) 1.79 (2H,s,CH_2) 2.4 (1H,s,Pyrazolone) 3.72 (1H,s,CH) 1.98 (3H,s,CH_3) 2.33 (3H,s,CH_3) 3.62 (3H.s,OCH_3)

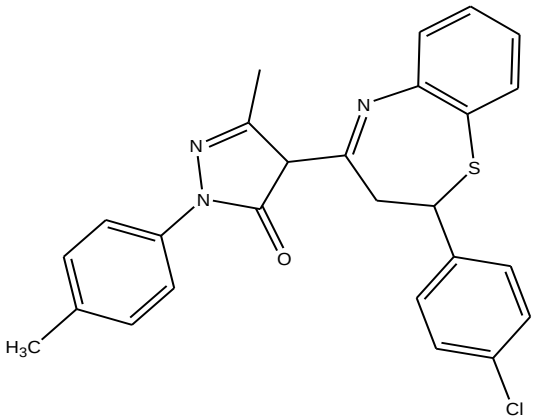
Physical data of compounds 10e



5-Methyl-2-*p*-tolyl-4-(2-*o*-tolyl-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{27}H_{25}N_3OS$ Molecular weight : 439 gm/mol Melting point: 162-163 ^{0}C (uncorrected) Yield: 68%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 73.77 5.73 9.56 **Found** 73.70 5.76 9.60
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1075 CH_3 1668 C=O 1605 C=N 1539 C=C 762 C-S-C	**^{1}H-NMR spectral features (δ-ppm)** 7.19-8.11 (12H,m, Ar-H) 1.72 (2H,s,CH_2) 2.43 (1H,s,Pyrazolone) 3.58 (1H,s,CH) 1.92 (3H,s,CH_3) 2.36 (6H,s,CH_3)

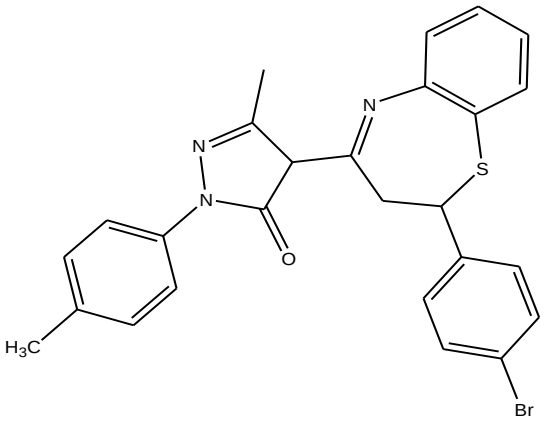
Physical data of compounds 10f



4-[2-(4-Chloro-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{26}H_{22}ClN_3OS$ Molecular weight : 460 gm/mol Melting point: 175-176 ^{0}C (uncorrected) Yield: 72%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 67.89 4.82 9.13 **Found** 67.90 4.81 9.09
IR features around Cm^{-1} 2900 Aromatic C-H stretching 1670 C=O 1605 C=N 1541 C=C 764 C-S-C 756 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.13-8.11 (13H,m, Ar-H) 1.79 (2H,s,CH_2) 2.49 (1H,s,Pyrazolone) 3.62 (1H,s,CH) 1.92 (3H,s,CH_3) 2.39 (3H,s,CH_3)

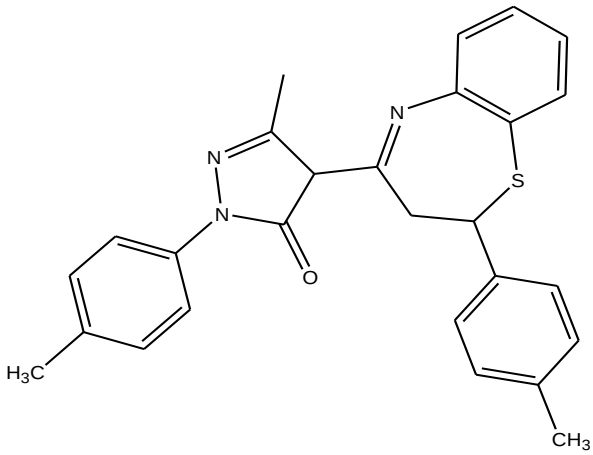
Physical data of compounds 10g



4-[2-(4-Bromo-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

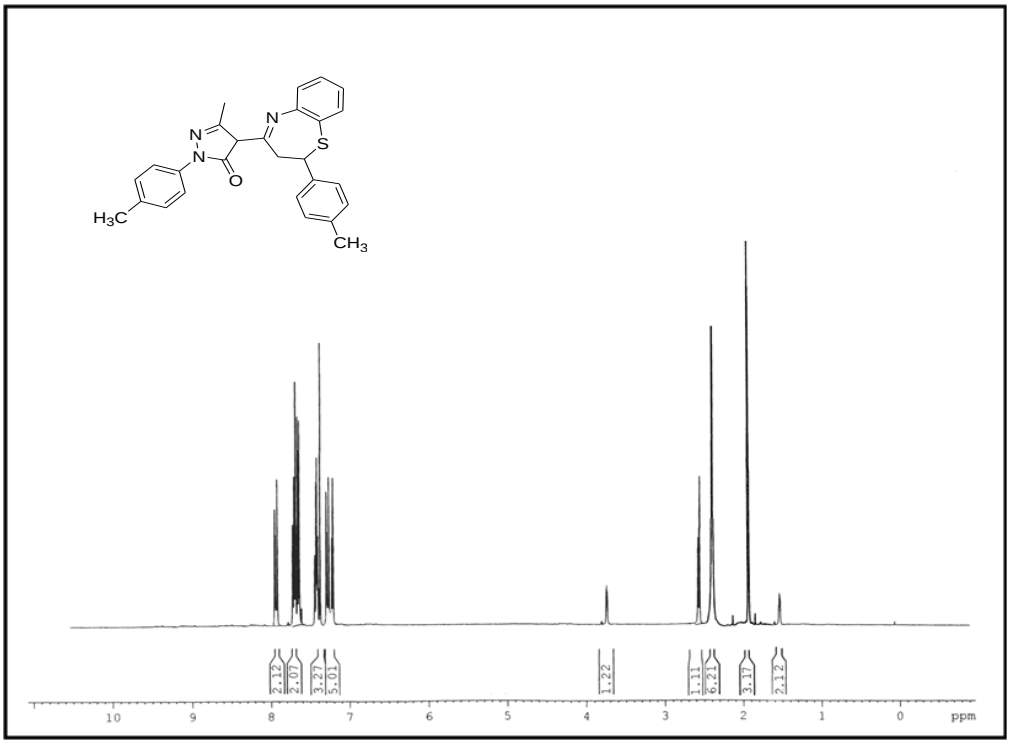
Molecular formula : $C_{26}H_{22}BrN_3OS$ Molecular weight : 504 gm/mol Melting point: 159-160^{0}C (uncorrected) Yield: 75%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 61.91 4.40 8.33 **Found** 62.01 4.42 8.34
IR features around Cm^{-1} 2899 Aromatic C-H stretching 1673 C=O 1600 C=N 1535 C=C 768 C-S-C 1092 C-Br	**^{1}H-NMR spectral features (δ-ppm)** 7.16-8.20 (12H,m, Ar-H) 1.79 (2H,s,CH_2) 2.46 (1H,s,Pyrazolone) 3.7 (1H,s,CH) 1.96 (3H,s,CH_3) 2.36 (3H,s,CH_3)

Physical data of compounds 10h

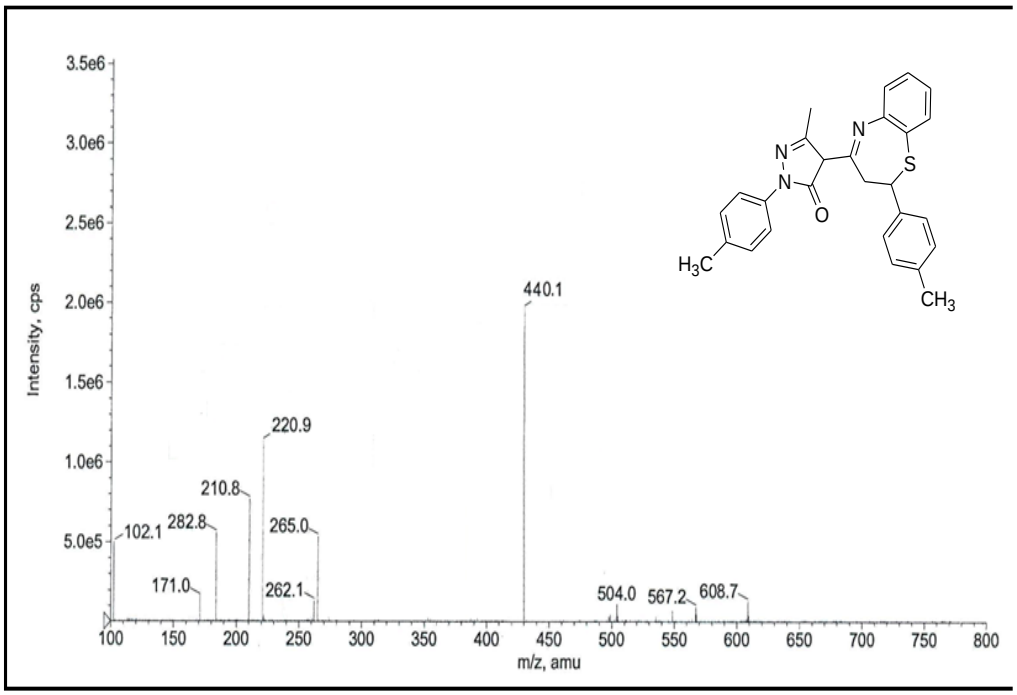


5-Methyl-2-*p*-tolyl-4-(2-*p*-tolyl-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)-2,4-dihydro-pyrazol-3-one

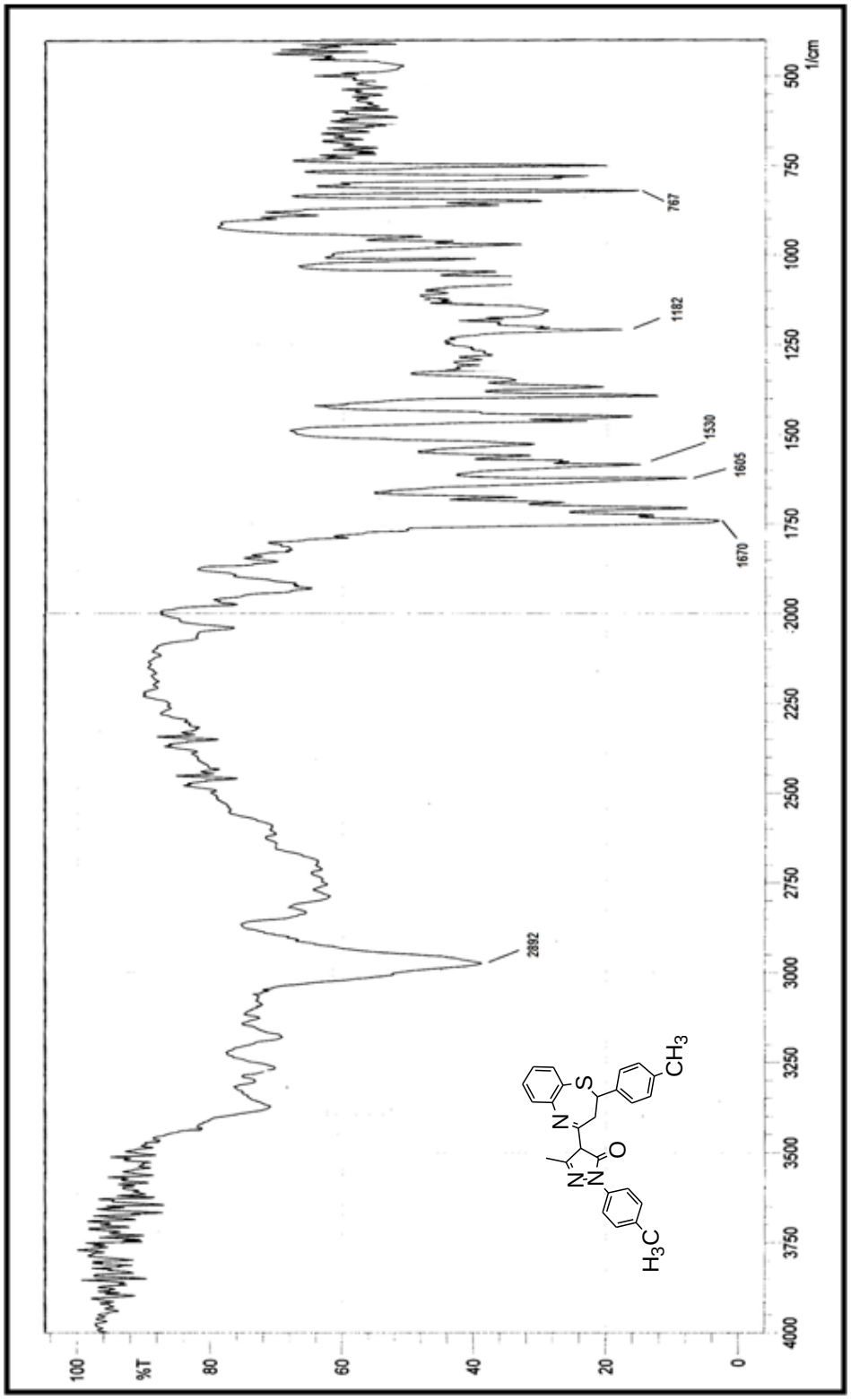
Molecular formula : $C_{27}H_{25}N_3OS$ Molecular weight : 439 gm/mol Melting point: 171-173 ^{0}C (uncorrected) Yield: 77%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 73.77 5.73 9.56 **Found** 73.78 5.71 16.93
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1077 CH_3 1668 C=O 1605 C=N 1540 C=C 760 C-S-C	**^{1}H-NMR spectral features (δ-ppm)** 7.0-8.09 (12H,m, Ar-H) 1.73 (2H,s,CH_2) 2.4 (1H,s,Pyrazolone) 3.7 (1H,s,CH) 1.93 (3H,s,CH_3) 2.33 (6H,s,CH_3)



NMR Spactrum of Compound 10e

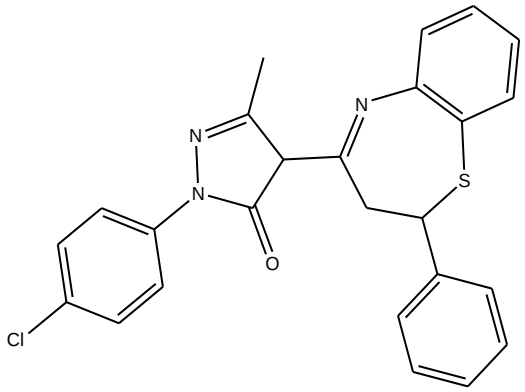


Mass Spactrum of Compound 10e



IR Spactrum of Compound 10e

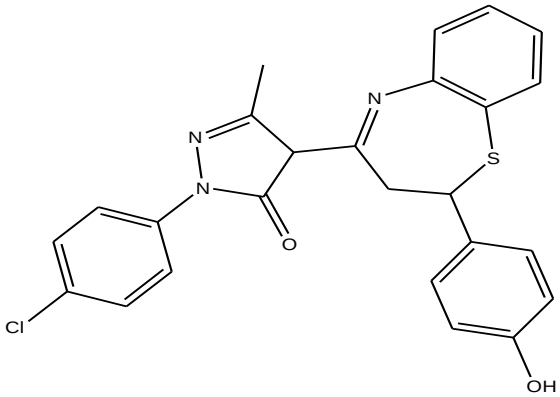
Physical data of compounds 11a



2-(4-Chloro-phenyl)-5-methyl-4-(2-phenyl-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{25}H20\,ClN_3OS$ Molecular weight : 330 gm/mol Melting point: 165-166 ^0C (uncorrected) Yield: 82%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 72.71 5.49 16.96 **Found** 72.7 5.51 16.93
IR features around Cm^{-1} 2902 Aromatic C-H stretching 1673 C=O 1608 C=N 1543 C=C 766 C-S-C 751 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.0-8.11 (13H,m, Ar-H) 1.76 (2H,s,CH_2) 2.37 (1H,s,Pyrazolone) 3.76 (1H,s,CH) 1.96 (3H,s,CH_3) 2.32 (3H,s,CH_3)

Physical data of compounds 11b

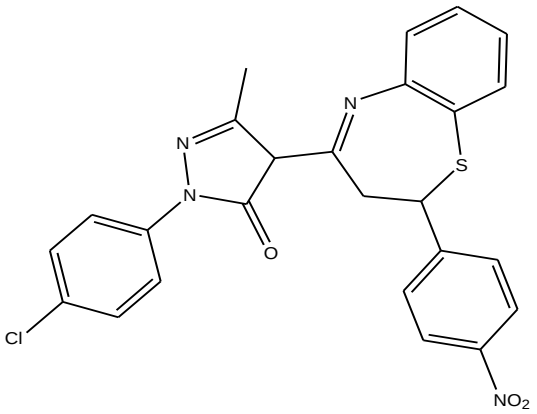


2-(4-Chloro-phenyl)-4-[2-(4-hydroxy-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{25}H_{20}ClN_3O_2S$	**Elemental analysis**
Molecular weight : 461 gm/mol	**%C** **% H** **% N**
Melting point: 163-165 ^{0}C	**Calculated** 65.00 4.36 9.10
(uncorrected)	**Found** 65.02 4.37 9.09
Yield: 65%	

IR features around Cm^{-1}		**^{1}H-NMR spectral features (δ-ppm)**	
2895	Aromatic C-H stretching	7.21-8.0	(12H,m, Ar-H)
1678	C=O	1.71	(2H,s,CH_2)
1602	C=N	2.43	(1H,s,Pyrazolone)
1546	C=C	3.66	(1H,s,CH)
763	C-S-C	1.92	(3H,s,CH_3)
743	C-Cl	2.30	(3H,s,CH_3)
3450	OH	4.48	(1H,s,OH)

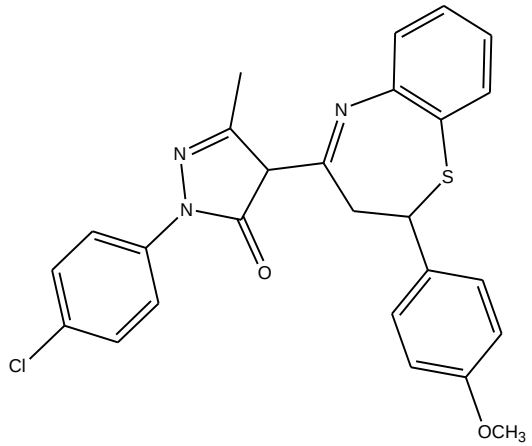
Physical data of compounds 11c



2-(4-Chloro-phenyl)-5-methyl-4-[2-(4-nitro-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{25}H_{19}ClN_4O_3S$ Molecular weight : 490 gm/mol Melting point: 177-178 ^{0}C (uncorrected) Yield: 69%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 61.16 3.90 11.41 **Found** 61.06 3.91 11.40
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1672 C=O 1605 C=N 1537 C=C 760 C-S-C 748 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.00-8.09 (13H,m, Ar-H) 1.73 (2H,s,CH_2) 2.4 (1H,s,Pyrazolone) 3.7 (1H,s,CH) 1.93 (3H,s,CH_3) 2.38 (3H,s,CH_3)

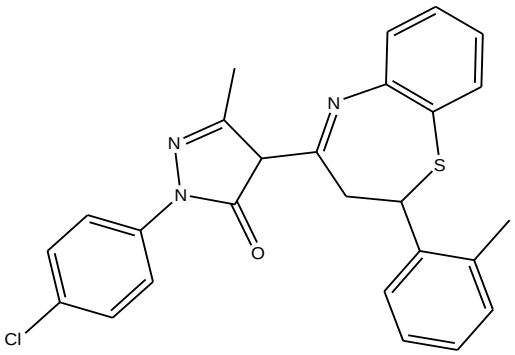
Physical data of compounds 11d



2-(4-Chloro-phenyl)-4-[2-(4-methoxy-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{26}H_{22}ClN_3O_2S$ Molecular weight : 475 gm/mol Melting point: 168-169 ^{0}C (uncorrected) Yield: 65%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.61 4.66 8.83 **Found** 65.63 4.67 8.81
IR features around Cm^{-1} 2892 Aromatic C-H stretching 1668 C=O 1599 C=N 1534 C=C 759 C-S-C 746 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.11-8.09 (12H,m, Ar-H) 1.79 (2H,s,CH_2) 2.44 (1H,s,Pyrazolone) 3.70 (1H,s,CH) 1.96 (3H,s,CH_3) 2.35 (3H,s,CH_3) 3.66 (1H,s,OCH_3)

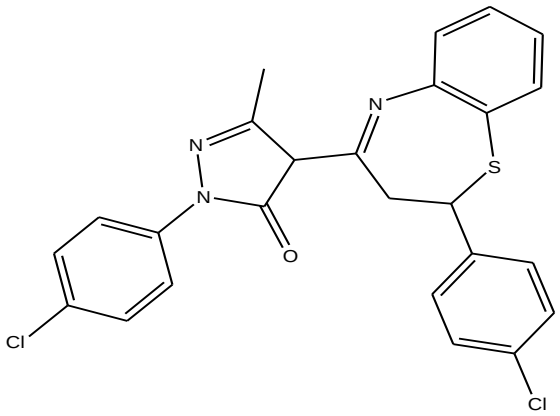
Physical data of compounds 11e



2-(4-Chloro-phenyl)-5-methyl-4-(2-*o*-tolyl-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{26}H_{22}ClN_3OS$ Molecular weight : 459 gm/mol Melting point: 181-182 ^{0}C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 67.89 4.82 9.13 **Found** 67.91 4.83 9.11
IR features around Cm^{-1} 2897 Aromatic C-H stretching 1670 C=O 1603 C=N 1538 C=C 761 C-S-C 750 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.06-8.09 (12H,m, Ar-H) 1.77 (2H,s,CH_2) 2.41 (1H,s,Pyrazolone) 3.68 (1H,s,CH) 1.93 (3H,s,CH_3) 2.30 (6H,s,CH_3)

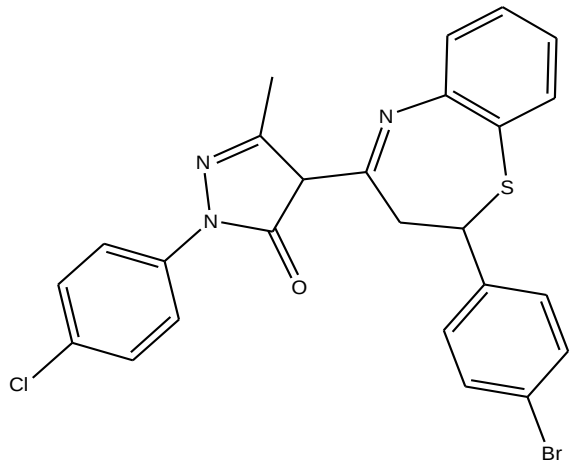
Physical data of compounds 11f



2-(4-Chloro-phenyl)-4-[2-(4-chloro-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{25}H_{19}Cl_2N_3OS$ Molecular weight :480 gm/mol Melting point: 169-170 ^{0}C (uncorrected) Yield: 72%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 62.50 3.99 8.75 **Found** 62.51 4.02 8.76
IR features around Cm^{-1} 2900 Aromatic C-H stretching 1670 C=O 1605 C=N 1541 C=C 764 C-S-C 756 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.13-8.09 (13H,m, Ar-H) 1.70 (2H,s,CH_2) 2.44 (1H,s,Pyrazolone) 3.73 (1H,s,CH) 1.95 (3H,s,CH_3) 2.38 (3H,s,CH_3)

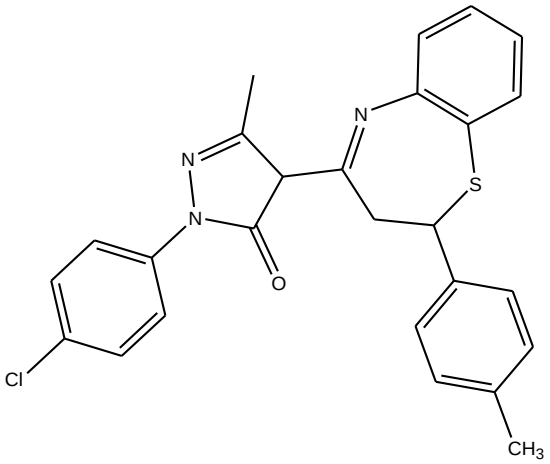
Physical data of compounds 11g



4-[2-(4-Bromo-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

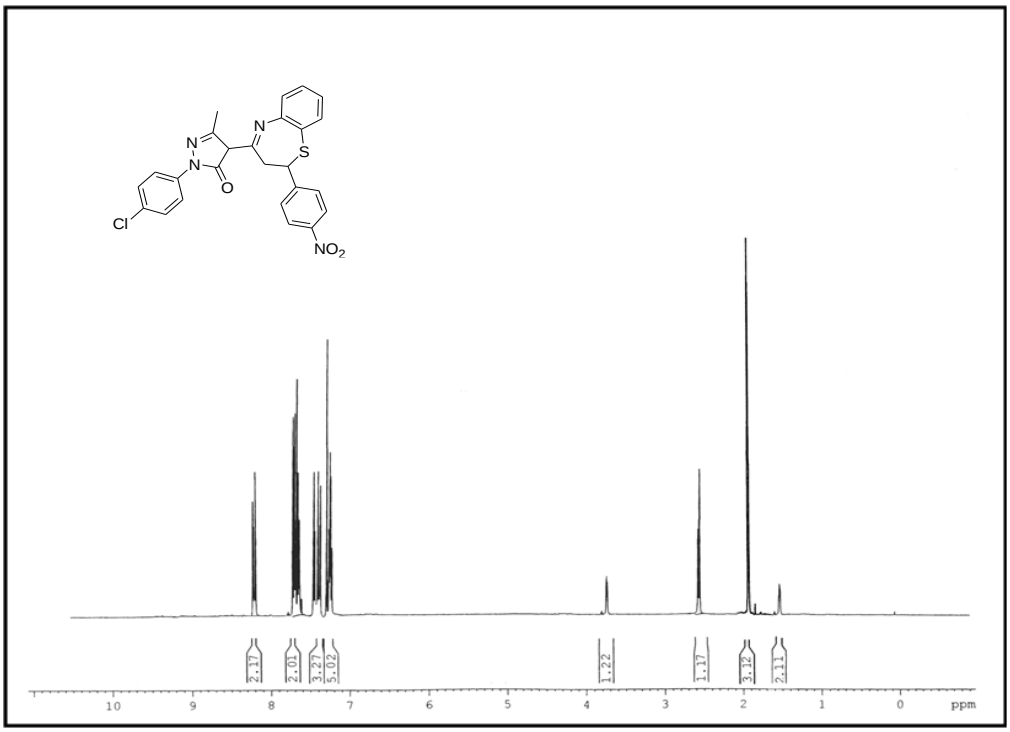
Molecular formula : $C_{25}H_{19}ClBrN_3OS$ Molecular weight : 524 gm/mol Melting point: 159-160 ^{0}C (uncorrected) Yield: 70%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 57.21 3.65 8.01 **Found** 57.23 3.63 8.05
IR features around Cm^{-1} 2904 Aromatic C-H stretching 1676 C=O 1605 C=N 1543 C=C 760 C-S-C 747 C-Cl 1089 C-Br	**^{1}H-NMR spectral features (δ-ppm)** 7.29-8.19 (13H,m, Ar-H) 1.76 (2H,s,CH_2) 2.46 (1H,s,Pyrazolone) 3.71 (1H,s,CH) 1.97 (3H,s,CH_3) 2.32 (3H,s,CH_3)

Physical data of compounds 11h

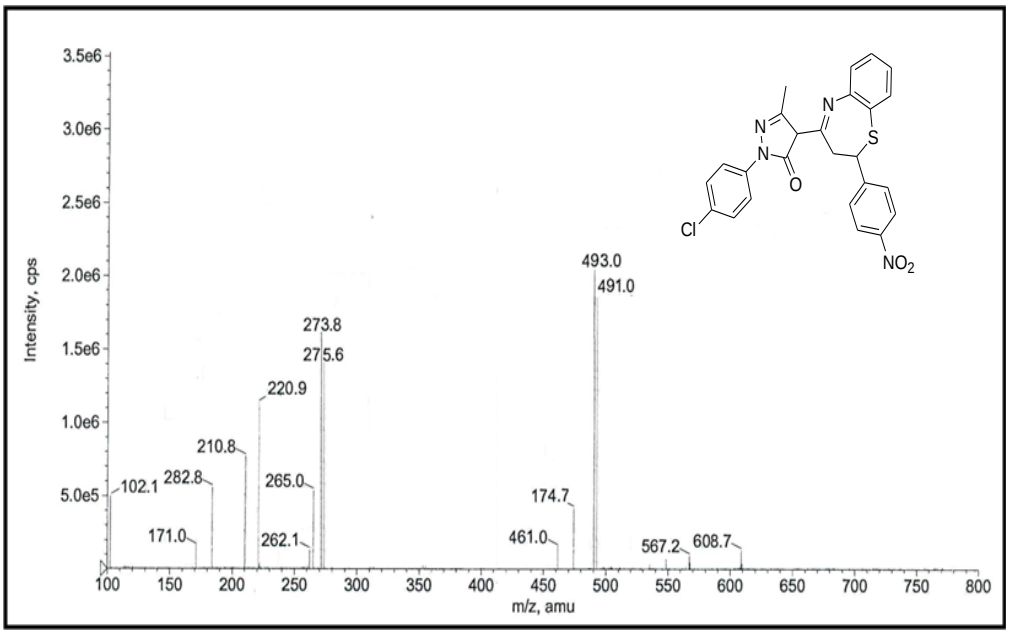


2-(4-Chloro-phenyl)-5-methyl-4-(2-*p*-tolyl-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)-2,4-dihydro-pyrazol-3-one

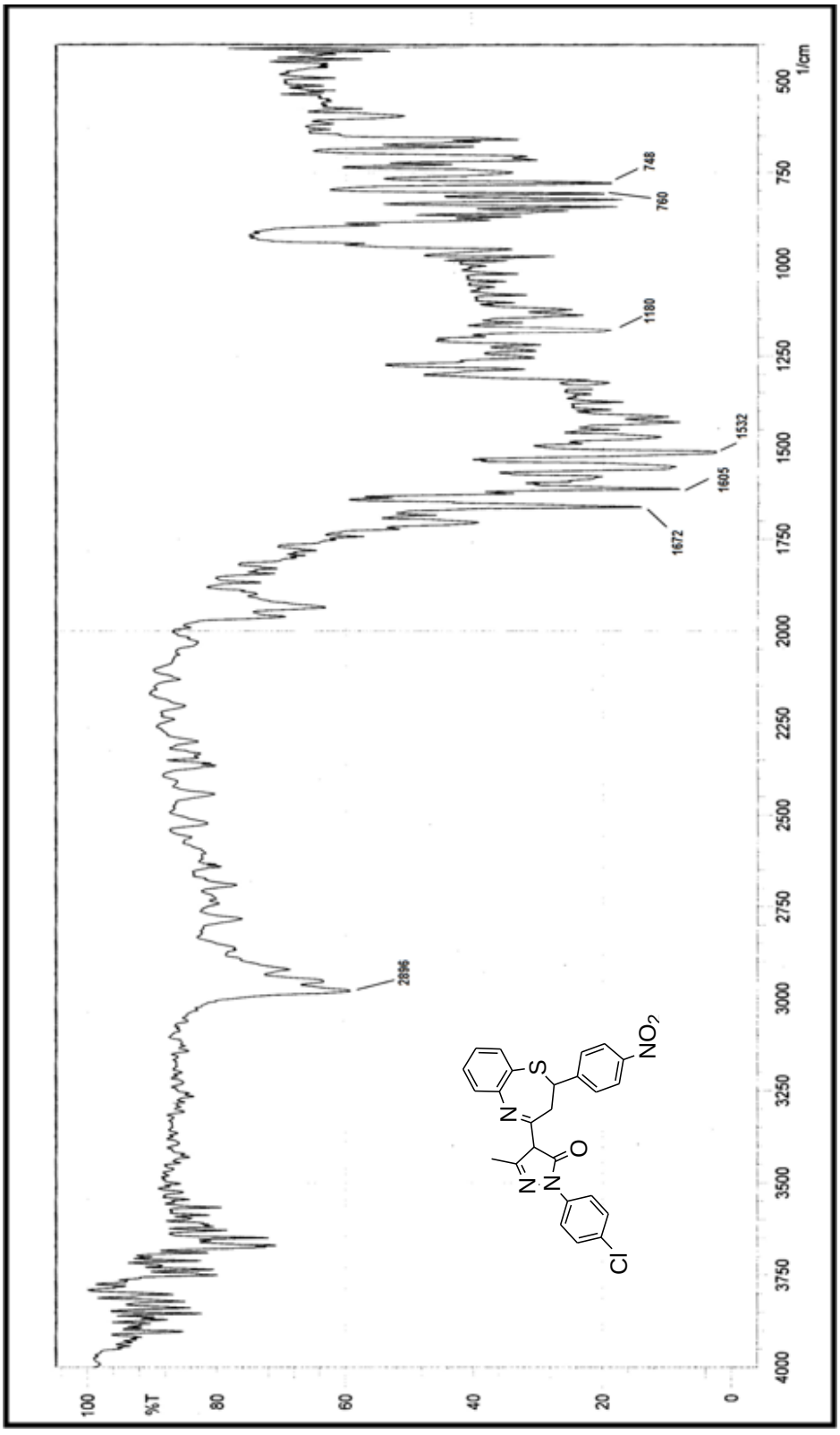
Molecular formula : $C_{26}H_{22}ClN_3OS$ Molecular weight : 459 gm/mol Melting point: 160-161 ^{0}C (uncorrected) Yield: 67%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 67.89 4.82 9.13 **Found** 67.88 4.83 9.11
IR features around Cm^{-1} 2894 Aromatic C-H stretching 1668 C=O 1602 C=N 1536 C=C 763 C-S-C 748 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.00-8.09 (13H,m, Ar-H) 1.73 (2H,s,CH_2) 2.43 (1H,s,Pyrazolone) 3.72 (1H,s,CH) 1.93 (3H,s,CH_3) 2.33 (6H,s,CH_3)



NMR Spactrum of Compound 11c



Mass Spactrum of Compound 11c



IR Spactrum of Compound 11c

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CHAPTER-5

Synthesis and Characterization of Azetidinone derivatives from Schiff Base

Table of Contents

SECTION-A

SECTION-B

SECTION-A

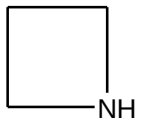
5.1 General Introduction

The β-lactams are 4-membered cyclic amides derived from 3-aminopropanoic acids. Though the first member synthesized by Staudinger in 1907[1], the β-lactams as a class acquired importance since the discovery of penicillin which contains β-lactam unit as an essential structural feature of its molecule, this interest continued unabated because of the therapeutic importance of β-lactam antibiotics and recent finding of new naturally occurring β-lactams. As a result of vigorous research, a vast literature has been accumulated over the years, and the chemistry of azetidinones continues to be blossoming field.

Recent years have seen a resurgence of interest in the development of stereo and enatioselective methodologies. The utility of azetidinones as synthons for various biologically active compounds, as well as their recognition as cholesterol absorption inhibitors and enzyme inhibitors has given impetus to these studies.

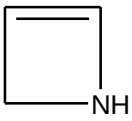
In the late 1990s, several groups reported novel methodologies for the synthesis of azetidinones of potential biological activities by applying known methods. β-Lactum antibiotics are the most commonly used antibiotics. The 2-carbonyl derivatives of azetidine (four-membered heterocyclic ring with nitrogen as heteroatom) are designated as 2- Azetidinone or, more commonly. Azetidin (I), azetin (II), 2-azetin (III) and azete (IV) are the nitrogen analogues of cyclobutane, cyclobutene and cyclobutadiene respectively as shown in Fig. 1. Azetidins are well studied, in particular their derivatives the azetidin -2-ones (β-lactams) have received considerable attention mainly because of the antibacterial properties of

penicillin and cephalosporins. The chemistry of both 1-and 2-azetidins has been developed only since the mid-1960 and these systems have not yet been comprehensively reviewed.



(I)

(II)



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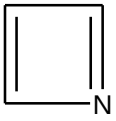

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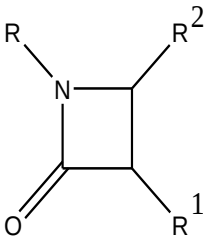
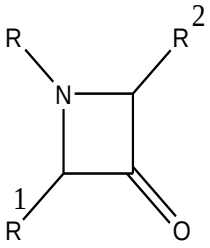
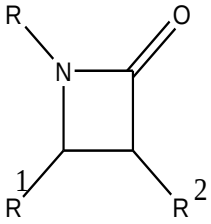


Azetidin-2-one



Azetidin-3-one



Azetidin-4-one

Fig.1

5.1.1Structure:

Azetidin-2-one [2] is a hydrolytically sensitive. It is colourless solid having melting point 73-74 ^{0}C as shown in Fig. 2. Other simple 2-Azetidines are usually low melting solids or oils.

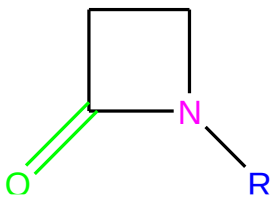
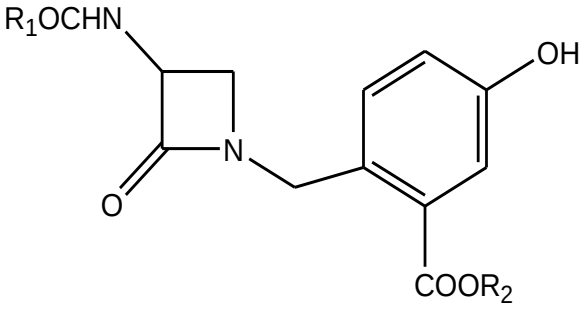


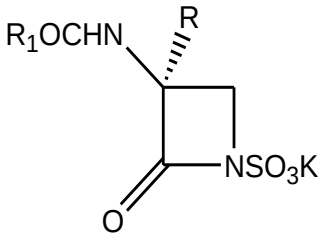
Fig.2

5.1.2 Reactivity:

Azetidin-2-ones are the most extensively studied derivatives of azetidin-2-one, largely as a result of the discovery of the antibacterial properties of penicillin, cephalosporin and cephamycin. Recently, there has been considerable interest in other fused β-lactams, such as clavulanic acid, thienamycin and the related clavulanic acid derivative and the penems. Nonfused β-lactam containing natural products include the nocardicins**(2)** and the monobactams **(3)** as well as the more complex pachystermines A and B wild firetoxin.



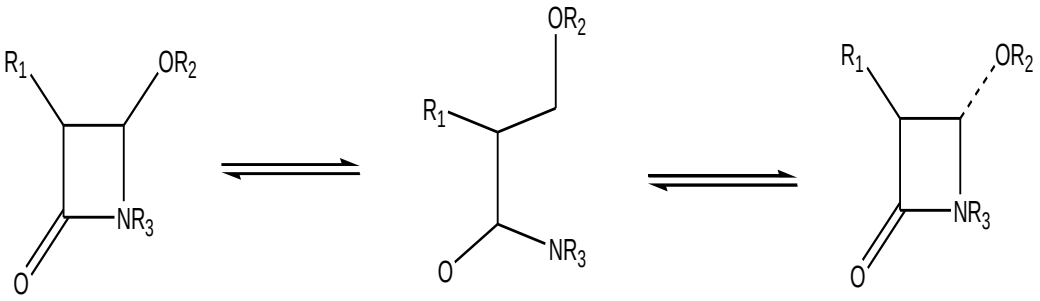
(2)



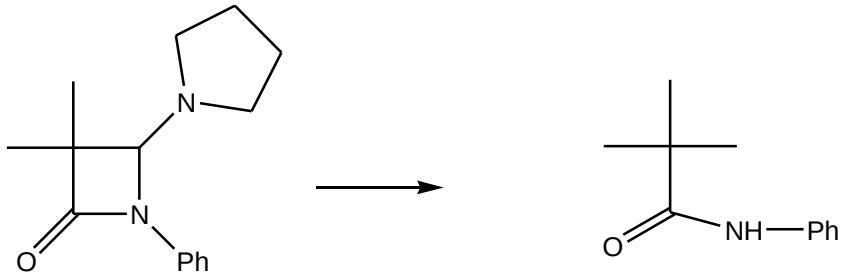
(3)

Incorporation of an amide linkage into a four membered ring results in angle strain and some degree of inhibition of amide resonance, rendering β-lactams more susceptible than normal amides to nucleophilic attack at the carbony1 group. Not surprisingly, β-lactams undergo N(1)-C(2) cleavage on treatment with a variety of nucleophiles and this ability of a β-lactam to act as an acylating agent is generally considered to be, at least in part, responsible for the antibacterial properties of penicillins and cephalosporins. These strained bicyclic β-lactams inhibit bacterial cell wall biosynthesis, apparently by acylatingtranspeptidases.

Polymerization of β-lactams, involving cleavage of the amide bond can be induced by treatment with strongly basic catalysts or by acylating agents. Introduction of a heteroatom substituent at C-4 tends to destabilize the β-lactams, promoting N (1)-C (4) bond cleavage. This ability is illustrated by the facile epimerization of the 4- alkoxyazetidinones**(4)** and **(5),** and the acid catalyzed ring opening of **(6)** as shown in below.



(4) (5)

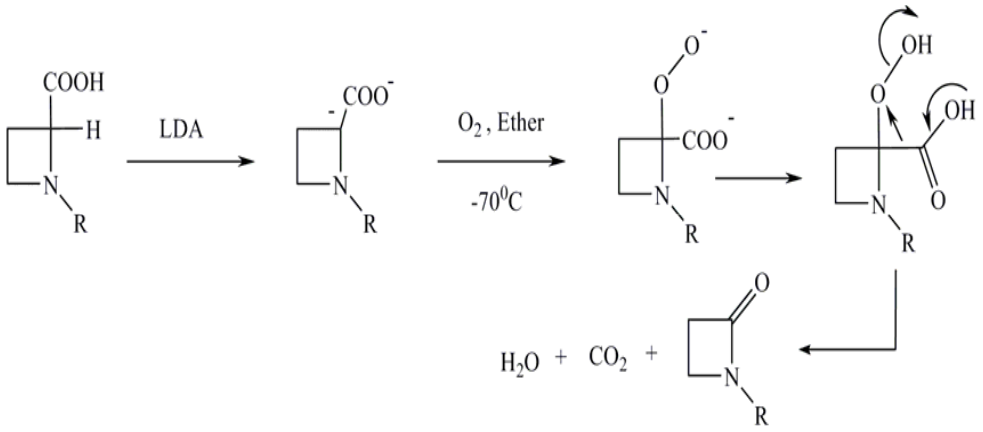


(6)

5.2 Syntheticaspects

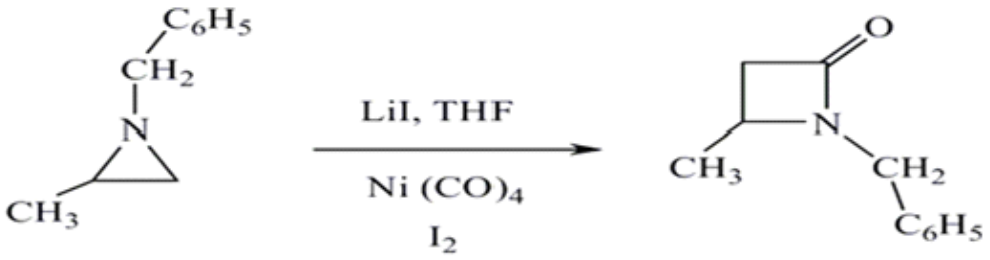
5.2.1 From substituted Azetidines

N-substituted azetidine-2-carboxylic acid can be converted intoazetidinones by the following sequence involving a dicarbanion intermediate [3]. The azetidine carboxylic acid is treated with lithium diisopropylamide and resultant dicarbanion is decarboxylatedoxidatively.



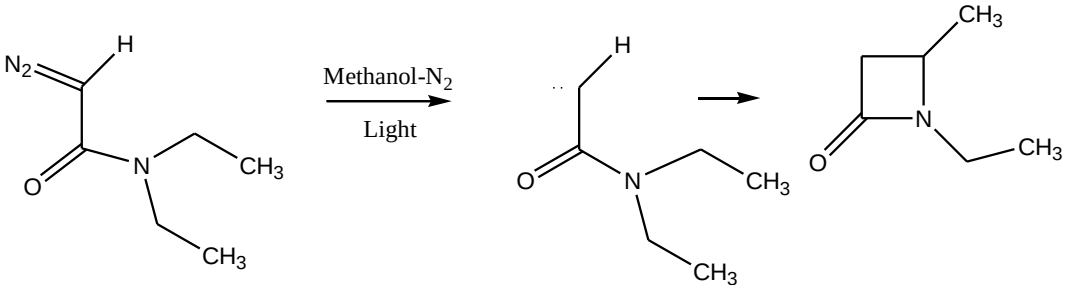
5.2.2 From Azeridines

Because of readily availability of Aziridines a one-pot synthesis has been developed for the preparation of Azetidinones [4]. The reaction involves treatment of an aziridine derivatives with lithiumiodide followed by treating the reaction mixture with nickel tetracarbonyl and finally addition of solid iodine.



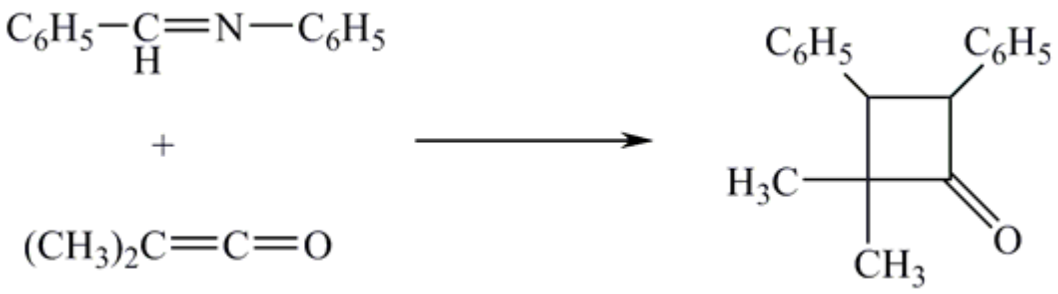
5.2.3 Insertion of Carbenes

Generation and intramolecular insertion of carbenes in a C-C bond in appropriate substrates results in azetidinone formation N,N-Diethyldiazoacetamide for instance on photolysis yields 1-Ehtyl-4-methyl-2-azetidinone in a yield of 57% [5]



5.2.4 Reaction of ketenes with imines

The direct combination of ketene itself or substituted ketenes with anils or other imines has been the most commonly employed method of synthesis. For example, the reaction of dimethylketene with benzylideneanilinegoes to completion at room temperature in a few hours, and the β-lactam can be easily isolated as a stable crystalline compound.[6]



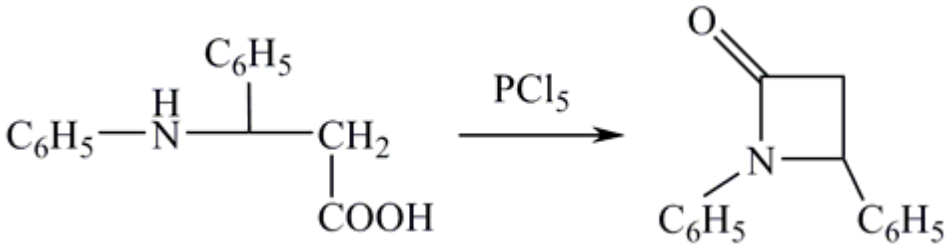
5.2.5 Reactions of ketenes with aromatic nitroso compounds

Nitroso compounds, such as nitrosobenzene and pnitrosodimethylaniline, react with ketenes. Apparently, a fourmembered ring may form which is, however, very

unstable and splits to give the Schiff base and carbon dioxide. The Schiff base can then react with another molecule of diphenylketene to give the β-lactam [7].

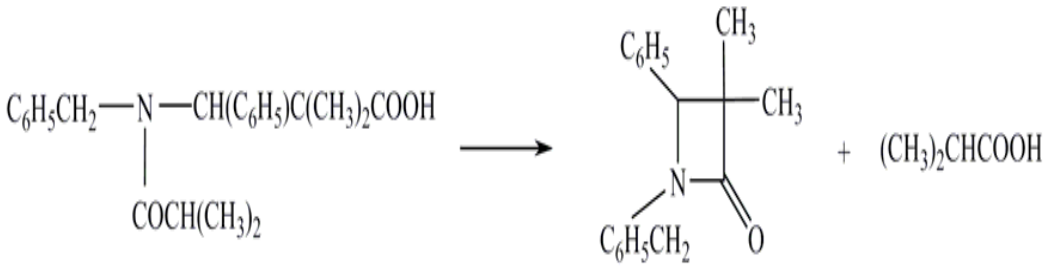
5.2.6 Cyclization of β–amino acids

A commonly employed is the cyclization of free amino acids using acyl chloride, phosphorous trichloride or thionyl chloride as illustrated below. No cyclization of the amino acid takes place on heating; rather it splits into an amine and acid.[8]



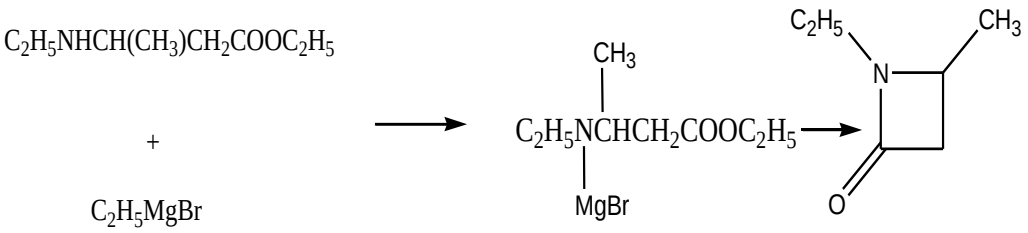
5.2.7 Cyclization of β–acylamino acids.

When certain β-acylamino acids are heated at their melting points, ring closure is affected with the loss of the carboxylic acid which was originally present as the acyl group in the β-acylaminoacids [9]



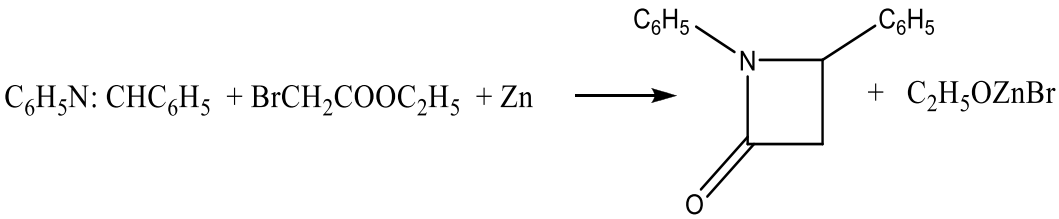
5.2.8 Cyclization of β–acylamino esters with organometallic compounds

Ring closure between β-acylamino esters and Grignard reagent is generally used to produce a β-lactam.



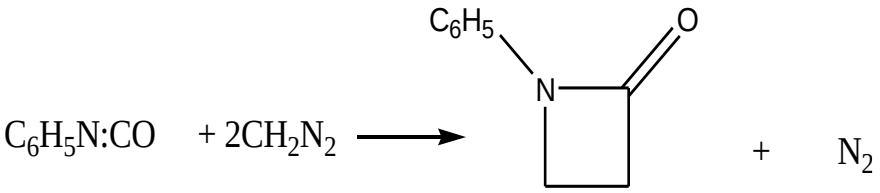
5.2.9 Reaction of anils with halogenated esters

Gilman and Speeter [10] demonstrated that benzylideneaniline reacts with either ethyl bromoacetate or ethyl bromopropionate in the presence of zinc to give the corresponding β-lactam

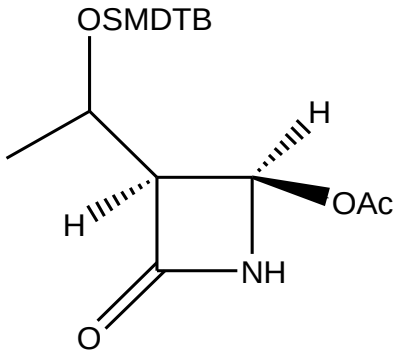


5.2.10 Reaction of an isocyanate with diazomethane

1-Phenylazetidinone has been prepared in 20% yield by the reaction of phenyl isocyanate with two molecules of diazomethane [11]

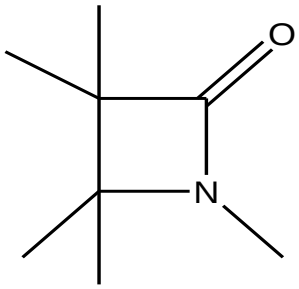


Gerard van Koten *et. al.*[12] have synthesized a new and efficient route to 3-amino-2-azetidinone via zinc enolates of N, N-disubstituted glycine esters.



5.3 Pharmacological activity

The four membered 2-Azetidinone ring (appears to be smallest cyclic system that is of accommodating the amide function as a consistent which is also known as β–lactam ring.



Due to the effectiveness and lack of toxicity, 2-azetidinone compounds are amongst the most successful and widely used antibiotics in history. However, the emergence of multi-drug resistant bacterial strains such as *Staphylococcus aureus* is threatening the effectiveness of 2- azetidinone antibiotics. [13] The common resistance mechanism in Gram "-"ve bacteria is the cellular expression of β-lactamases (or penicillinase), which hydrolyze the 2-azetidinone ring and thus inactivate antibiotics.[14-17]

Besides their importance as the key structural component of 2-azetidinone antibiotics, they have been attracting considerable interest in organic synthesis as versatile synthetic intermediates and chiral synthons [18-21]. In addition, the 2-

azetidinone scaffold has found new pharmaceutical applications other than its use as antibiotics, such as LHRH (luteinizing hormone-releasing hormone) antagonists, [22] cholesterol absorption inhibitors [23] and anticancer agents. [24-27] The ring strain of the 2-azetidinone skeleton facilitates ring-opening reactions [28,29] and this unique property has been exploited for the synthesis of a variety of medicinally active compounds. For the last couple of decades, a large number of 2-azetidinone based synthetic methods collectively termed as "2-azetidinone synthon method" has been developed.

Most of the researches up to early 90's have been focused on synthesis and study of antibacterial property of 2-azetidinones. In recent decades, renewed interest has been focused on the synthesis and modification of 2-azetidinone ring to obtain compounds with diverse pharmacological activities.

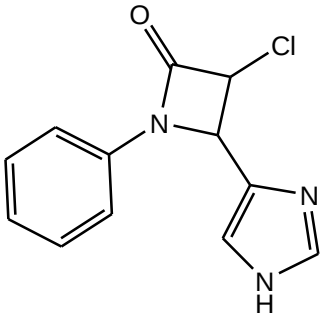
Bausare*et. al.*[30] reported the synthesis of novel azetidin-2-one derivatives containing aryl sulfonate moiety in good to moderate yield, few of them showed good anti-inflammatory activity.

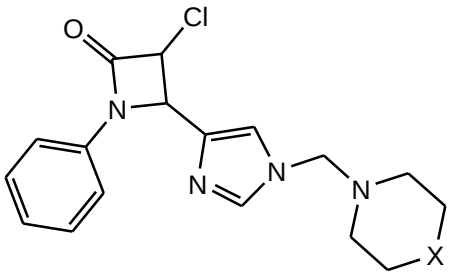
Pathak *et. al.*[31] reported such 3-(4-chlorophenyl)-4-substitutedpyrazole-azetidinone derivatives and evaluated as good to excellent antimicrobial and anti-tubercular activity.

Recently, Patel *et. al.* [32]synthesized a new series of 3-chloro-4-{4-[2-{5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-pyrazol-1-yl}-2 oxoethoxy]pheny-l}-1-(substituted-phenyl)azetidin-2-one derivatives and subjected to evaluate their antimicrobial activity.

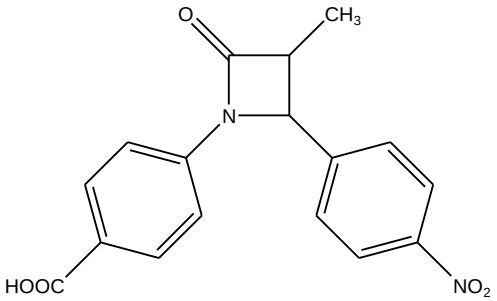
Kumar and co-workers[33] have synthesized bioactive azetidinones and thiazolidinones of 3- methyl-1-phenyl-1H-pyarazol-5-ol and screened them for biological activities against bacterial strains

Recently Esther and co-workers[34] reported Synthesis and antimicrobial susceptibility of derivatives of 3-chloro-4-(1H-imidazol-4-yl)-1-(4-substituted phenyl) azetidin-2-one and 3-chloro-4-(1-(morpholinomethyl)-1H-imidazol-4-yl)-1-phenylazetidin-2-one.

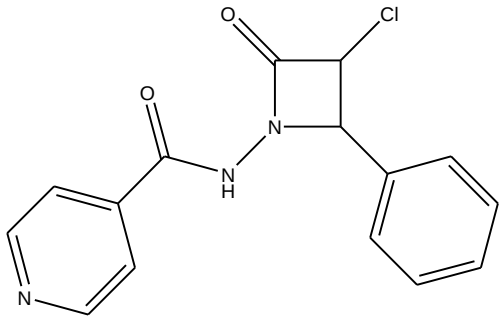




Sugumaran*et. al.*[35]have synthesized 2-azetidinone and 4 thiazolidinone derivatives exhibiting promising antimicrobial activity against a set of micro-organisms.



Nikalje*et. al.*[36]reported a novel N-(3-chloro-2-oxo-4-substituted azetidin-1-yl) isonicotinamide derivatives as antimycobacterial agents.



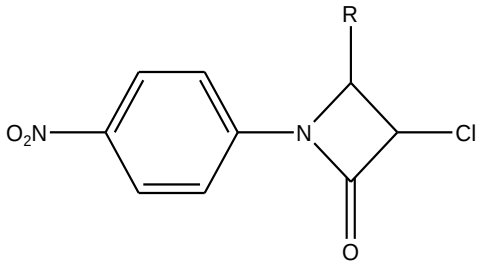
A series of 3-chloro-1-(aryl)-4-(2-(2-chloro-6-methylquinolin-3-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-4-ethyl-azetidin-2-ones, have been synthesized and were screened for their antibacterial activity by Dodiya*et. al.*[37].

Mashelkar*et. al.*[38]reported 1, 3, 4-substituted-(4-(1-oxo-1H-isochromen-3-yl)-1-aryl-3-phenyl azetidin-2-ones)-2-azetidinones.

Stereoselective synthesis of racemic and optically active novel β-lactams using Staudinger cycloaddition reaction with imines and ketenes and identification of a few β-lactams demonstrating anticancer activity has been achieved by Banik [39].

Desai *et. al.*[40]have synthesized azitidinone derivatives 7-(4-(4-(2-benzoyl-hydrazinyl)-6-(2-chloro-3-oxo-4-substitutedbenzaldehyde-azetidin-1-yl- amino)-1,3,5-triazin-2-yl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-di-hydro quinoline-3-carboxylic acid and evaluated for antimicrobial activity.

Sarangi *et. al.*[41] reported new derivatives of 3-chloro-1-(4-nitrophenyl)-4-phenylazetidin-2-one and their antimicrobial activity against both strains of Gram "+"ve and Gram "-"ve strains.



Recently, a series of coumarin based azetidine-2-one (3-Chloro-1-[4-(2-oxo-2H-chromen-4-ylamino)-phenyl}-4-phenyl-azetidin-2-one derivatives have been successfully synthesized by Joshi [42] and were tested for their *in-vitro* antimicrobial activity.

Recently, synthesis and characterization of some new derivatives of 2-azetidinones have been reported by Prabhakar[43].

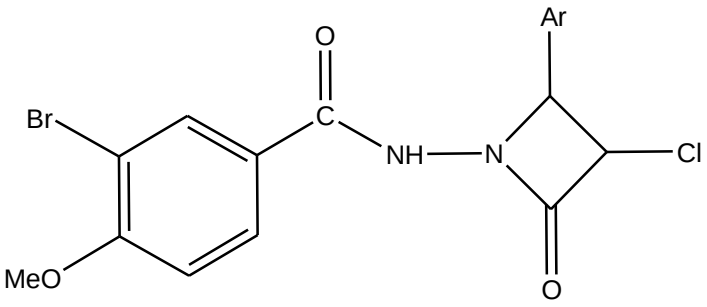
Some new 2-azetidinone derivatives displaying moderate to good antimicrobial activity possessing benzimidazole nucleus were synthesized and screened by Joshi [44].

1-(substituted-phenyl)-spiro[5-bromoindole-3,4-3-chloroazetidin]-2,2-1H-dione has been reported by Al-Majidi*et. al.*[45].

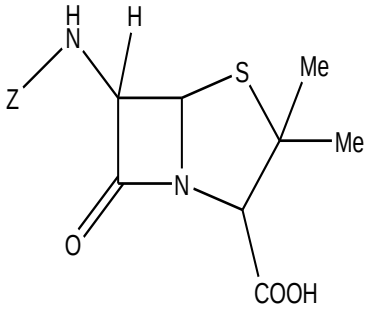
A series of cyanovinylpyrrole containing aroylhydrazones, derived from ethyl 2-cyano-3-(5-formyl-1H-pyrrol-2-yl)-acrylate [46].

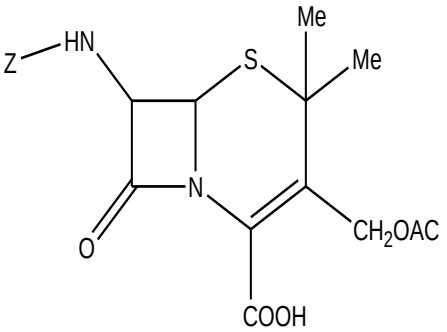
Priyadarshini *et. al.*[47] have prepared azetidinones and carried out their anti-microbial activity.

Freedy *et. al.*[48]reported certain substituted azetidinones and evaluated them for antimicrobial activity.



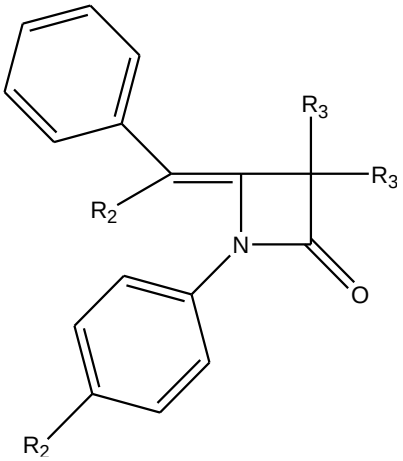
John [49] obtained certain useful azetidinonederavitives and reportedtheir bacteriostatic activity against both types of organisms.



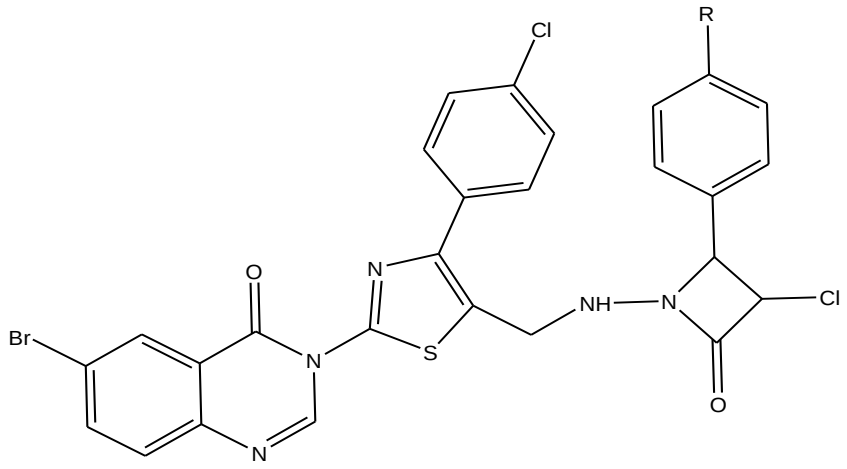


Z= monoacyl

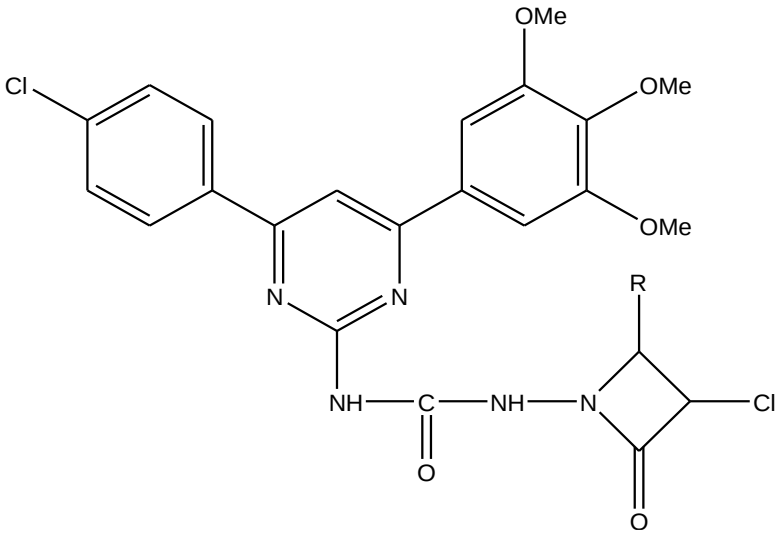
Vildan Adar GÜNER *et. al.*[50] have synthesized 4-substituted- styryl-2-azetidinones and biologically evaluated for antimicrobial activity.



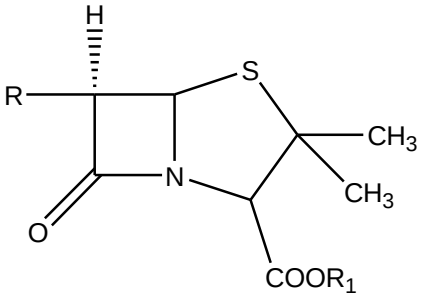
Ashok Kumar *et. al.* [51] have synthesized substituted azetidinone/thiazolidinone as anti-inflammatory agent.

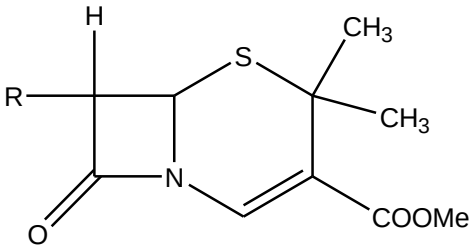


Chikhalia KH *et. al.* [52] have obtained pyrimidine based thiazolidinones and azetidinones as antimicrobial and antitubercular agents.



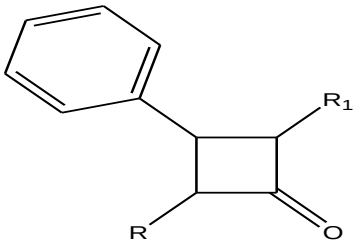
Myer[53] reported following azetidin-2-ones and noted their antibacterial action.





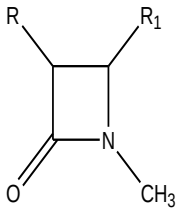
R= H, Ph-CH2, t-Butyl, - OMe
R1= - OH

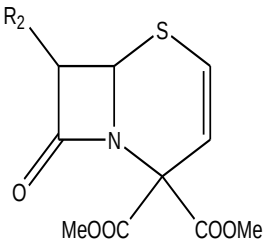
Spasov *et. al.*[54] have reported synthesis and bactericidal property of different 2-azetidinones.

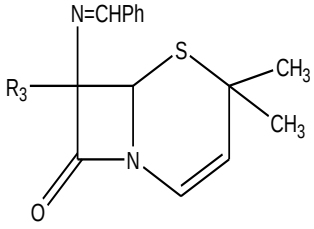


R= Ph, P- CH3C8H4
R1= H or Ph

Kolaus *et. al.*[55]prepared several 2 azetidinones which were proved to be bactericidal agents.





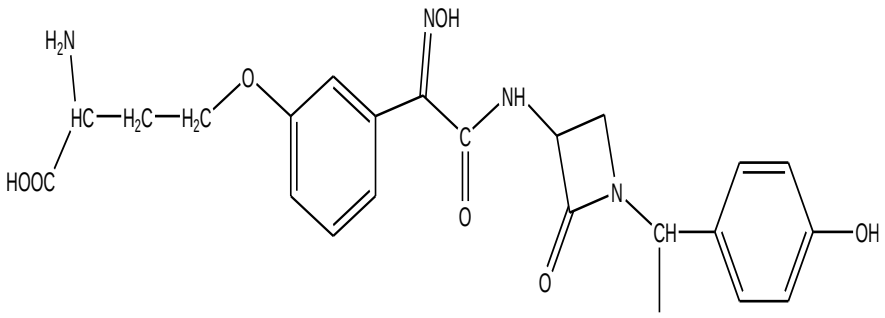


R= N3
R1= CH3 or C2H5
R2= H or COOCH3
R3= Ch2-Ph, CH3, CH2C6H4OCH3

Bose carried out synthesis and anti-microbial property of 2-azetidinones.

Takashi *et. al.*[56] synthesized approx 545 deravitives and proved to beactive against bacillus subtillis, E coli and S. *aureus*. They also prepared 2-Azetidinones and carried out their antibacterial evaluation.

Hassan *et. al.*[57] prepared 2-Azetidinones and observed that these are active antibacterial agents.



Osman *et. al.*[58] prepared several 2-Azetidinones and evaluated their antibacterial property.

Desai *et. al.*[59] prepared 2-Azetidinones derived from thiadiazole and screened from antibacterial property.

Diumo *et. al.*[60] prepared certain 2-Azetidinones and shown their antibacterial property (invitro) few deravitives shown marked antabactarial property.

Bhat *et. al.*[61]prepared group of 2-azetidinones and evaluated them for antifungal antituberclar and antibacterial properties.

Udupi *et. al.*[62] prepared certain 2-Azetidinones and evaluated them for antibacterial and anti-inflammatory property.

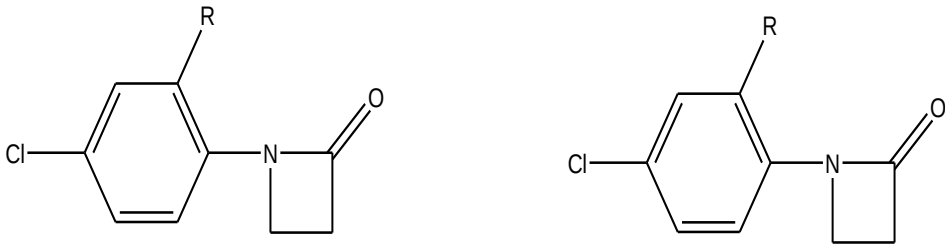
Levinine *et. al.*[63] synthesized certain 2-Azetidinones and carried out their antiviral activity.

Takayanagi *et. al.*[64] synthesized 2-azetidinones derivatives and carried out the screening of cytotoxic activity.

Piffer *et. al.*[65] prepared large number of 2-Azetidinones and evaluated them for anti-inflammatory property.

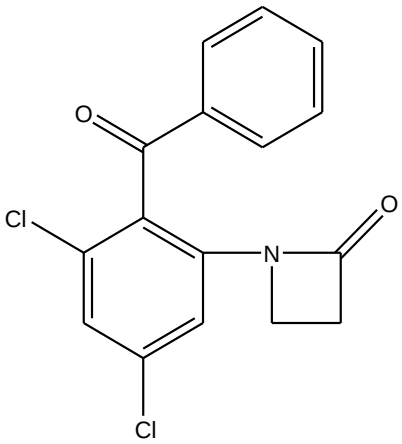
Tandon *et. al.*[66]prepared certain 2-Azetidinones and screened them from different biological profiles.

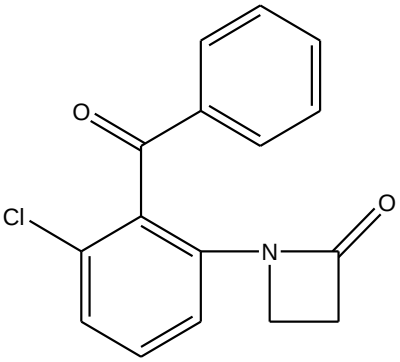
Peter *et. al.*[67]prepared several 2-Azetidinones and evaluated their anticonvulsant property.

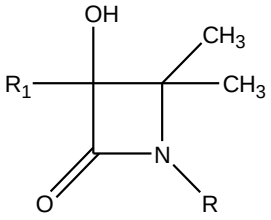


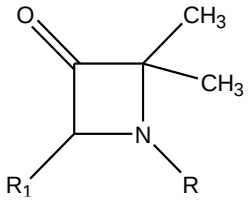
R= benzoyl

Several 2-Azetidinones and 3-Azetidinones have been prepared and screened against hypotensicproperty [68-70].

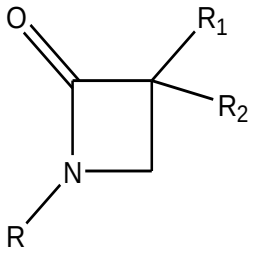




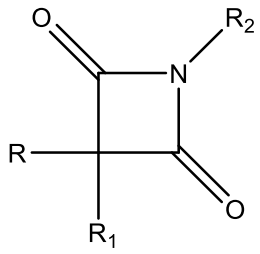




Maffi[71] synthesized several 2-azetidinones and reported their hypnotic,sedative and anticonvulsant activity.



Testa *et. al.*[72-73]prepared certain disubstituted 2-azetidinones and reported thier sedative property.



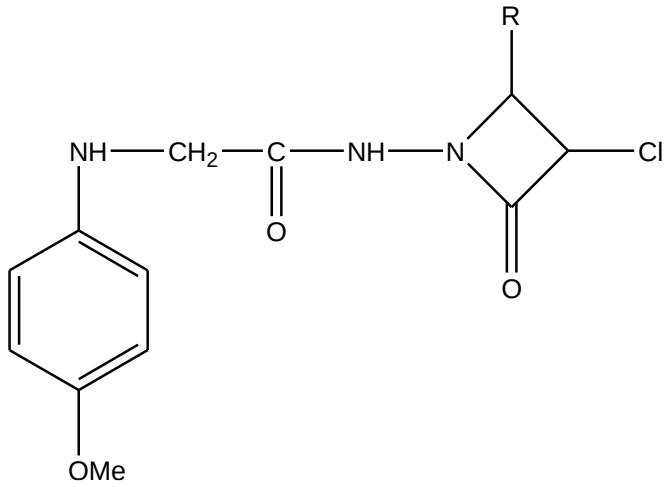
R= H
R1= Cyclohexyl
R2= H

Parekh *et. al.*[74]reportedsynthes of certain 2-azetidinones bearing Benzimidazole moiety and carried out their antimycobacterial activity.

Udupi *et. al.*[75] synthesized certain 2-azetidinones from naproxen and carried out their antimycobacterial and antimicrobial studies.

Pai *et. al.*[76]carried out their work on the preparation and pharmacological property of 2-azetidinones. The synthesize compounds were evaluated for antimicrobial and antifungal property. The derivatives shown to possess significant antibacterial property and not active as fungal agents.

Bhat *et. al.*[77]carried out preparation and study on their antibacterial property of some azetidinone derivatives with the p-anisidine moiety.



SECTION-B

5.4 Experimental

The 4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3H-pyrazole-3-one was prepared by reported method.

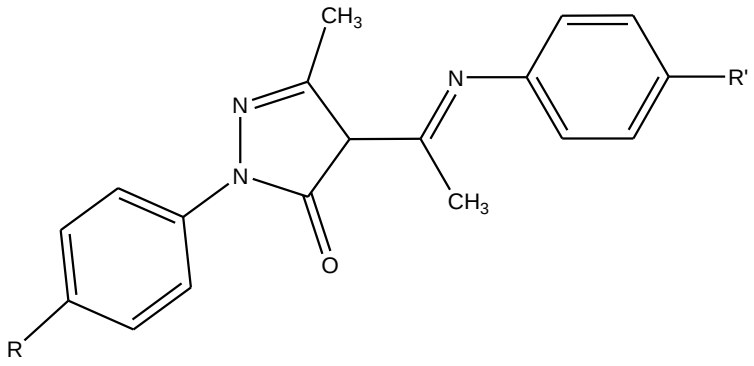
5.4.1. General procedure for synthesis of Schiff Base (12a-h) and (13a-h)

4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3H-pyrazole-3-one (0.01mol) is treated with substituted amine in ethanol reflux for 3- 5 hrs and the progress of the reaction was monitored by TLC. After completion of the reaction the mixture is cooled. Solid yellow product filtered and washed with methanol or ethanol.

5.4.2. Synthesis of 2- azetidinone derivatives

Schiff base (0.01mol) in DMF on treatment with base triethylamine (0.01mol) and acylated with chloroacetyl chloride (0.01mol) as cyclic agent. The reaction mixture was stirred for 10-15 hrs. The product was isolated and recrystallized from ethanol.

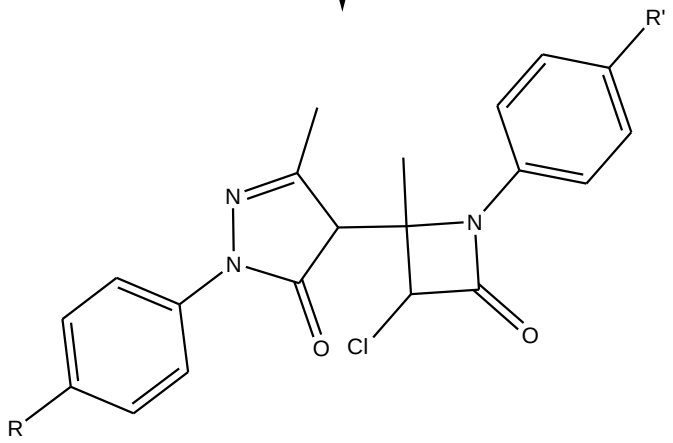
5.4.3. Reaction scheme



Schiff Base

DMF
7-8hrs

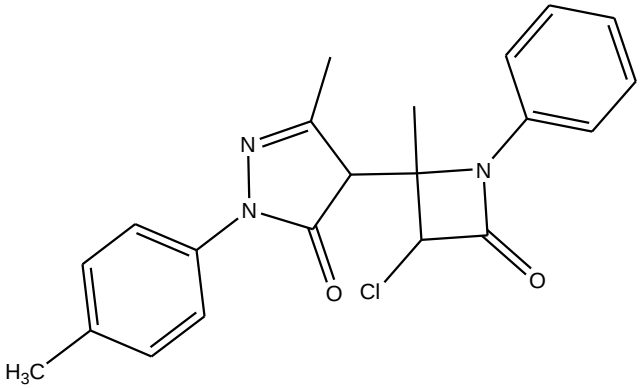
$ClCH_2COCl$
$N(C_2H_5)_3$



Where R = $-CH_3$ & -Cl

Where R'= a. phenyl
b. 4- chloro phenyl
c. 3- chlorophenyl
d. 4- methyl phenyl
e. 4-nitro phenyl
f. isoniazide
g. 4- methoxy phenyl
h.nicotinic acid

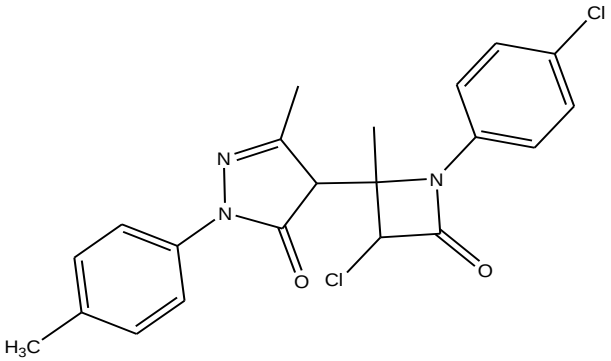
Physical data of compounds 12a



4-(3-Chloro-2-methyl-4-oxo-1-phenyl-azetidin-2-yl)-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{20}ClN_3O_2$ Molecular weight : 381gm/mol Melting point: 141-143 ^{0}C (uncorrected) Yield: 65%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 66.05 5.28 11.0 **Found** 66.03 5.30 11.04
IR features around Cm^{-1} 2893 Aromatic C-H stretching 1669 C=O 1605 C=N 1537 C=C Ar. 759 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 6.98-7.63 (8H,m, Ar-H) 3.1 (1H,s,Pyrazolone) 5.04 (1H,s,CH) 1.96 (3H,s,CH_3) 2.34 (3H,s,CH_3) 1.56 (3H,s,CH_3)

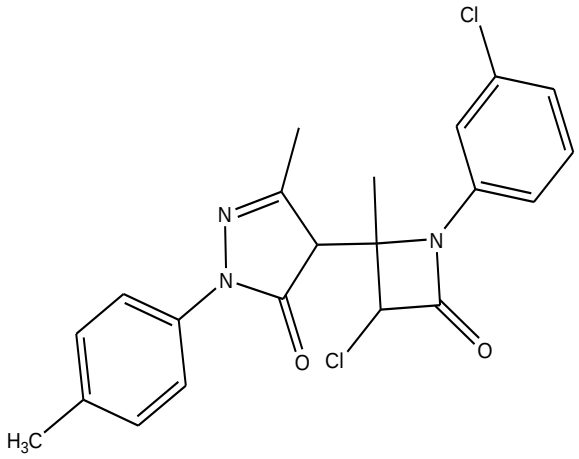
Physical data of compounds 12b



4-[3-Chloro-1-(4-chloro-phenyl)-2-methyl-4-oxo-azetidin-2-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{19}Cl_2N_3O_2$ Molecular weight : 416 gm/mol Melting point: 156-157 ^{0}C (uncorrected) Yield: 68%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 60.59 4.60 10.09 **Found** 60.57 4.65 10.1
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1665 C=O 1602 C=N 1542 C=C Ar. 762 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.0-8.09 (8H,m, Ar-H) 3.0 (1H,s,Pyrazolone) 5.04 (1H,s,CH) 1.93 (3H,s,CH_3) 2.33 (3H,s,CH_3) 1.53 (3H,s,CH_3)

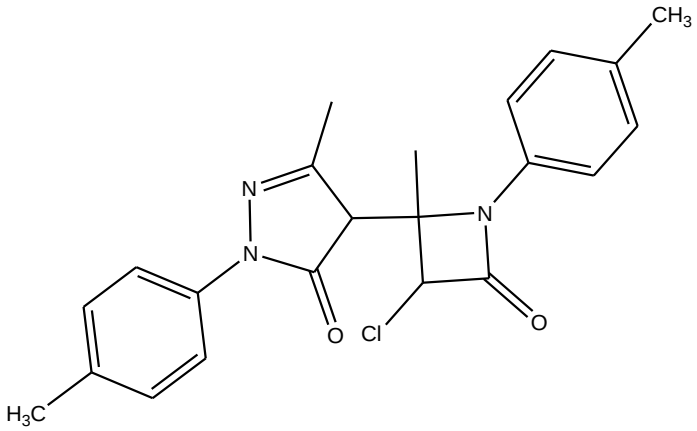
Physical data of compounds 12c



4-[3-Chloro-1-(3-chloro-phenyl)-2-methyl-4-oxo-azetidin-2-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{19}Cl_2N_3O_2$ Molecular weight : 318 gm/mol Melting point: 147-148 ^{0}C (uncorrected) Yield: 67%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 60.59 4.60 10.09 **Found** 60.6 4.61 10.07
IR features around Cm^{-1} 2899 Aromatic C-H stretching 1668 C=O 1609 C=N 1540 C=C Ar. 763 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.0-8.09 (8H,m, Ar-H) 3.1 (1H,s,Pyrazolone) 5.06 (1H,s,CH) 1.93 (3H,s,CH_3) 2.34 (3H,s,CH_3) 1.52 (3H,s,CH_3)

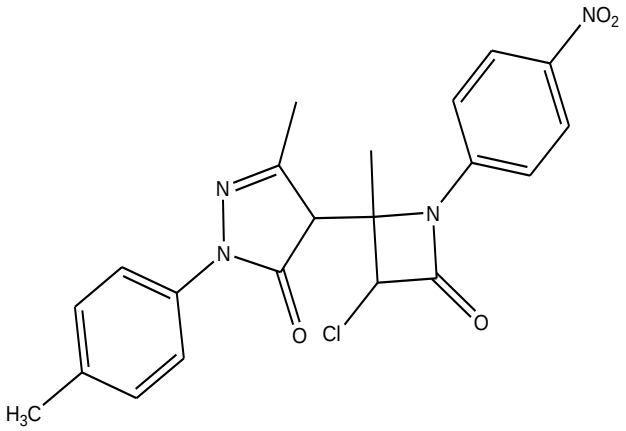
Physical data of compounds 12d



4-(3-Chloro-2-methyl-4-oxo-1-*p*-tolyl-azetidin-2-yl)-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{22}H_{22}ClN_3O_2$ Molecular weight : 395gm/mol Melting point: 154-155 ^{0}C (uncorrected) Yield: 70%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 66.75 5.60 10.61 **Found** 66.8 5.59 10.62
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1370 -CH_3 1662 C=O 1610 C=N 1535 C=C conjugate 757 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 6.99-7.86 (8H,m, Ar-H) 3.04 (1H,s,Pyrazolone) 5.02 (1H,s,CH) 1.96 (3H,s,CH_3) 2.33 (6H,s,2CH_3) 1.52 (3H,s,CH_3)

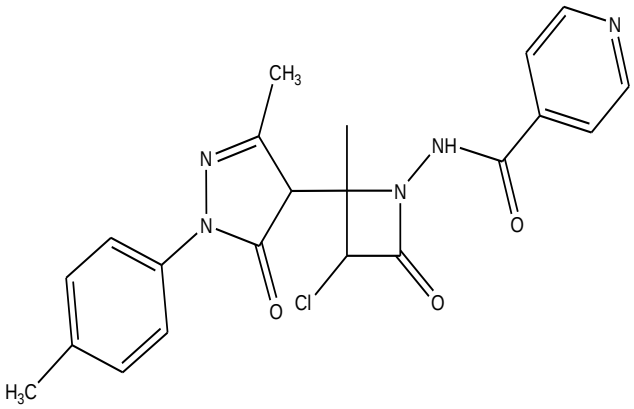
Physical data of compounds 12e



4-[3-Chloro-2-methyl-1-(4-nitro-phenyl)-4-oxo-azetidin-2-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{21}H_{19}ClN_4O_4$ Molecular weight : 426 gm/mol Melting point: 148-149 ^{0}C (uncorrected) Yield: 64%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 59.09 4.49 13.13 **Found** 59.11 4.48 13.1
IR features around Cm^{-1} 2902 Aromatic C-H stretching 1670 C=O 1608 C=N 1534 C=C Ar. 756 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.0-8.85 (8H,m, Ar-H) 3.2 (1H,s,Pyrazolone) 5.12 (1H,s,CH) 1.96 (3H,s,CH_3) 2.35 (3H,s,CH_3) 1.55 (3H,s,CH_3)

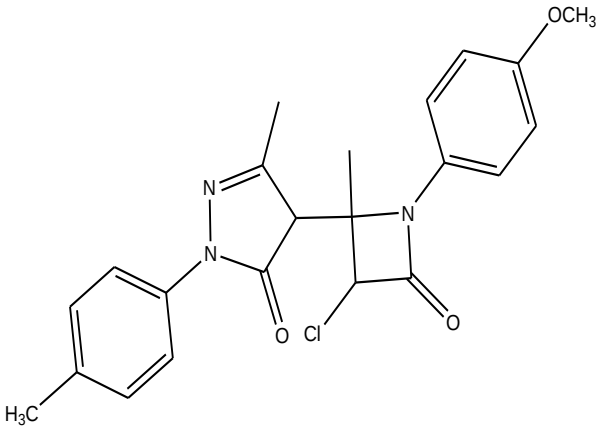
Physical data of compounds 12f



N-[3-Chloro-2-methyl-2-(3-methyl-5-oxo-1-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-4-yl)-4-oxo-azetidin-1-yl]-isonicotinamide

Molecular formula : $C_{21}H_{20}ClN_5O_3$ Molecular weight : 425 gm/mol Melting point: 155-156 ^{0}C (uncorrected) Yield: 70%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 59.23 4.73 16.44 **Found** 59.2 4.71 16.46
IR features around Cm^{-1} 2901 Aromatic C-H stretching 3190 NH 1670 C=O 1609 C=N 1543 C=C Ar. 753 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.2-7.9 (8H,m, Ar-H) 3.1 (1H,s,Pyrazolone) 5.1 (1H,s,CH) 1.95 (3H,s,CH_3) 2.37 (3H,s,CH_3) 1.47 (3H,s,CH_3)

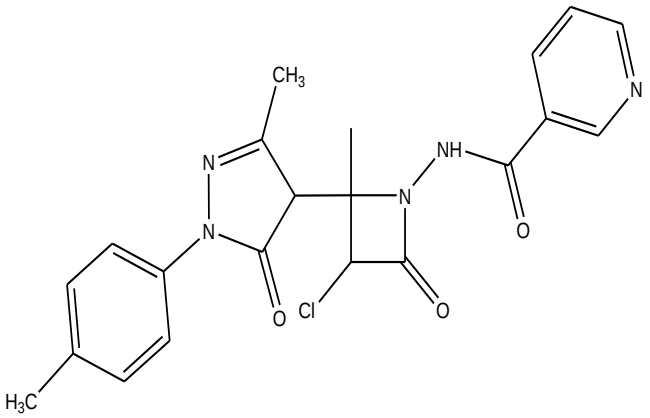
Physical data of compounds 12g



4-[3-Chloro-1-(4-methoxy-phenyl)-2-methyl-4-oxo-azetidin-2-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

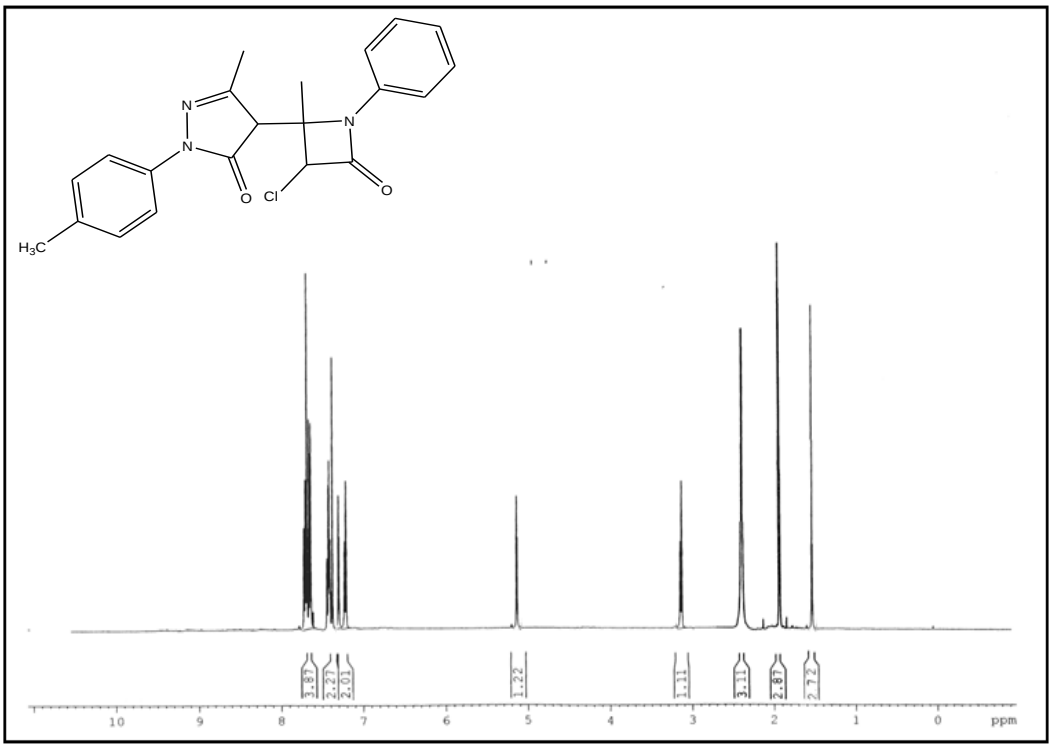
Molecular formula : $C_{22}H_{22}ClN_3O_3$ Molecular weight : 411gm/mol Melting point: 165-166 ^{0}C (uncorrected) Yield: 63%	**Elemental analysis** **%C % H % N** **Calculated** 64.15 5.38 10.20 **Found** 64.1 5.40 10.21
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1667 C=O 1605 C=N 1538 C=C Ar. 759 C-Cl 2340 OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 6.89-8.65 (8H,m, Ar-H) 3.0 (1H,s,Pyrazolone) 5.04 (1H,s,CH) 1.98 (3H,s,CH_3) 2.31 (3H,s,CH_3) 1.38 (3H,s,CH_3) 3.79 (3H,s,OCH_3)

Physical data of compounds 12h

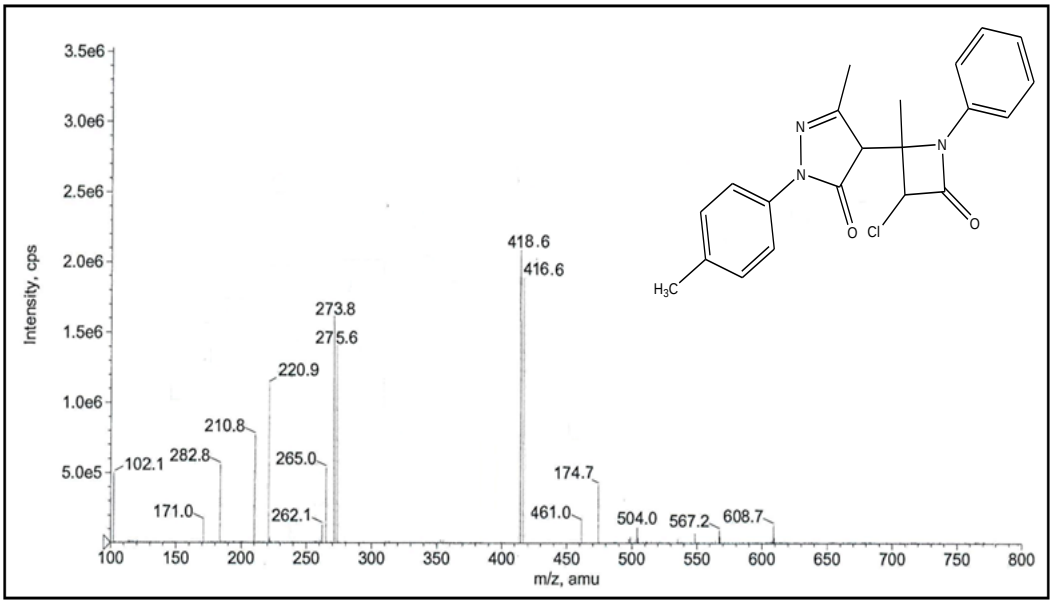


N-[3-Chloro-2-methyl-2-(3-methyl-5-oxo-1-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-4-yl)-4-oxo-azetidin-1-yl]-nicotinamide

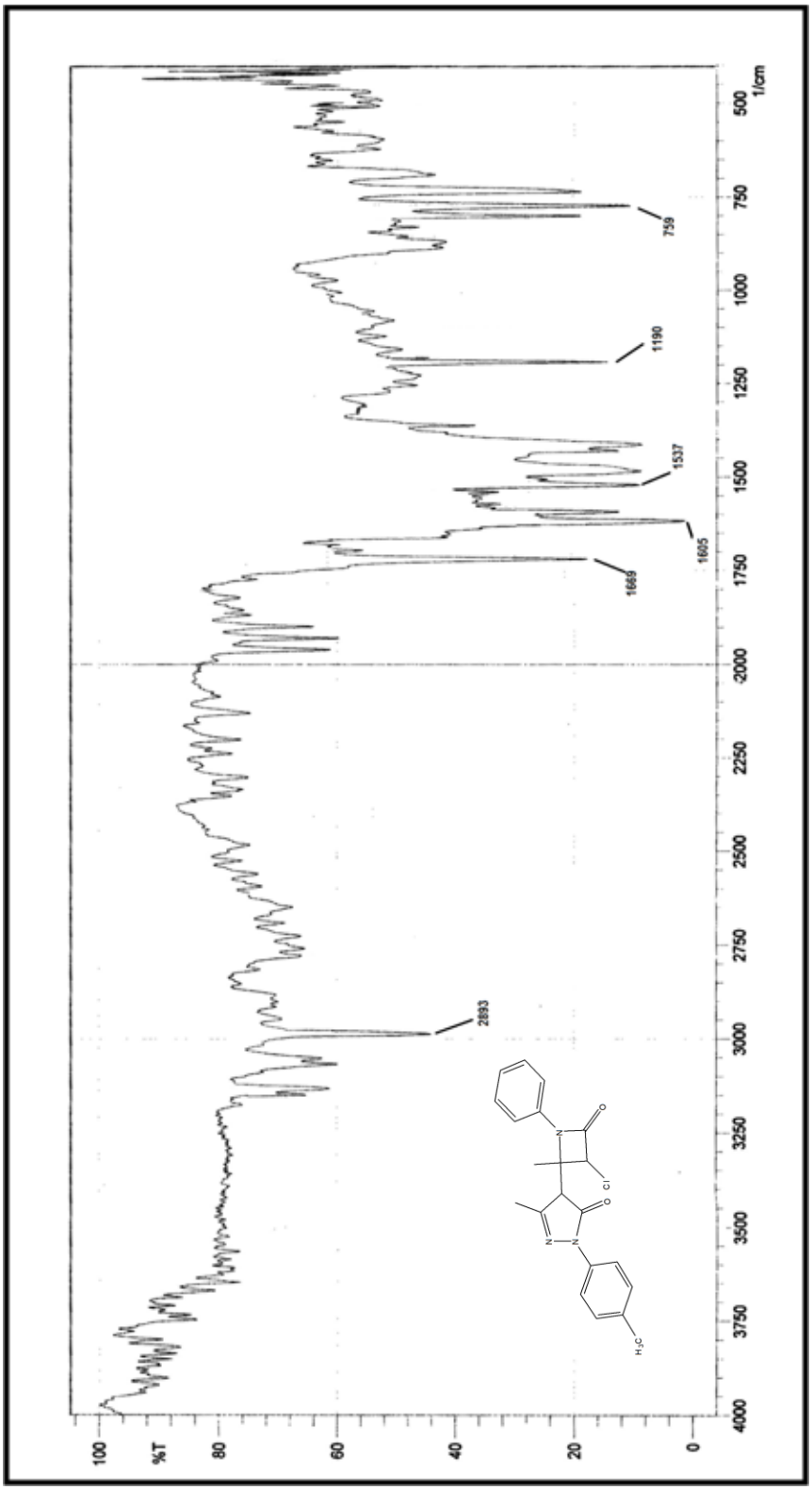
Molecular formula : $C_{19}H_{19}N_3O$ Molecular weight : 305gm/mol Melting point: 178-180 ^{0}C (uncorrected) Yield: 80%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 74.73 6.27 13.76 **Found** 74.70 6.26 13.8
IR features around Cm^{-1} 2904 Aromatic C-H stretching 3190 NH 1671 C=O 1609 C=N 1546 C=C Ar. 750 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.2-8.0 (8H,m, Ar-H) 3.06 (1H,s,Pyrazolone) 5.0 (1H,s,CH) 1.97 (3H,s,CH_3) 2.35 (3H,s,CH_3) 1.49 (3H,s,CH_3)



NMR Spactrum of Compound 12a

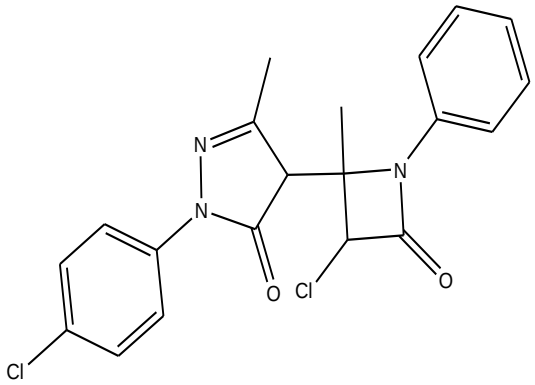


Mass Spactrum of Compound 12a



IR Spactrum of Compound 12a

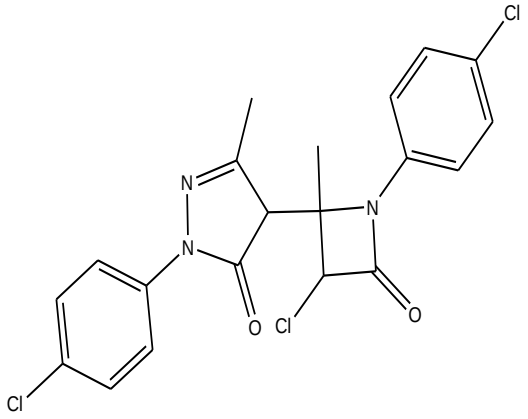
Physical data of compounds 13a



4-(3-Chloro-2-methyl-4-oxo-1-phenyl-azetidin-2-yl)-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{17}Cl_2N_3O_2$ Molecular weight : 402 gm/mol Melting point: 171-173 ^{0}C (uncorrected) Yield: 69%	**Elemental analysis** **%C % H % N** **Calculated** 59.71 4.26 10.45 **Found** 59.7 4.28 10.44
IR features around Cm^{-1} 2900 Aromatic C-H stretching 1665 C=O 1600 C=N 1538 C=C Ar. 750 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.0-8.09 (9H,m, Ar-H) 5.1 (1H,s,CH) 3.0 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 1.53 (3H,s,CH_3)

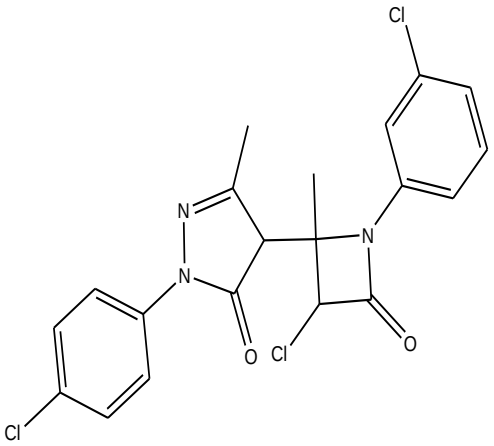
Physical data of compounds 13b



4-[3-Chloro-1-(4-chloro-phenyl)-2-methyl-4-oxo-azetidin-2-yl]-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{16}Cl_3N_3O_2$ Molecular weight : 436 gm/mol Melting point: 168-169 ^{0}C (uncorrected) Yield: 69%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 55.0 3.69 9.62 **Found** 55.08 3.71 9.60
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1666 C=O 1604 C=N 1535 C=C Ar. 753 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.23-8.1 (9H,m, Ar-H) 5.1 (1H,s,CH) 3.1 (1H,s,Pyrazolone) 1.95 (3H,s,CH_3) 1.48 (3H,s,CH_3)

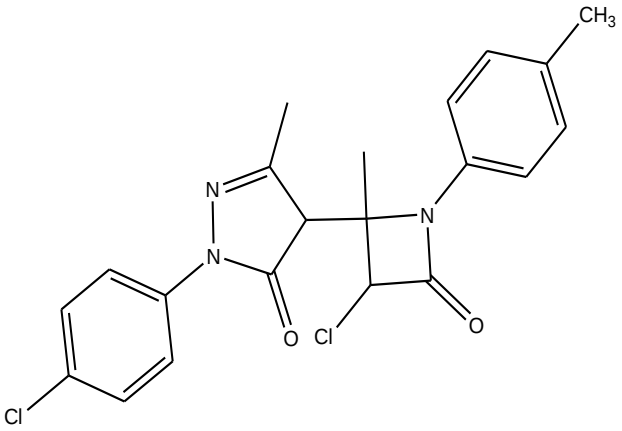
Physical data of compounds 13c



4-[3-Chloro-1-(3-chloro-phenyl)-2-methyl-4-oxo-azetidin-2-yl]-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{16}Cl_3N_3O_2$ Molecular weight : 436 gm/mol Melting point: 141-143 ^{0}C (uncorrected) Yield: 66%	**Elemental analysis** **%C % H % N** **Calculated** 55.0 3.69 9.62 **Found** 55.07 3.70 9.60
IR features around Cm^{-1} 2899 Aromatic C-H stretching 1670 C=O 1607 C=N 1539 C=C Ar. 763 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.23-8.1 (9H,m, Ar-H) 5.1 (1H,s,CH) 3.13 (1H,s,Pyrazolone) 1.95 (3H,s,CH_3) 1.48 (3H,s,CH_3)

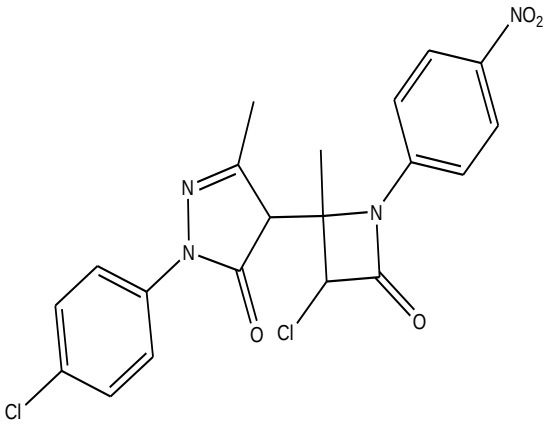
Physical data of compounds 13d



4-(3-Chloro-2-methyl-4-oxo-1-*p*-tolyl-azetidin-2-yl)-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{21}H_{19}Cl_2N_3O_2$ Molecular weight : 425 gm/mol Melting point: 151-153 ^{0}C (uncorrected) Yield: 67%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 60.59 4.60 10.09 **Found** 60.02 4.59 10.07
IR features around Cm^{-1} 2893 Aromatic C-H stretching 1379 CH_3 1668 C=O 1603 C=N 1542 C=C Ar. 765 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.23-7.8 (8H,m, Ar-H) 4.89 (1H,s,CH) 3.11 (1H,s,Pyrazolone) 1.98 (3H,s,CH_3) 2.34 (3H,s,CH_3) 1.47 (3H,s,CH_3)

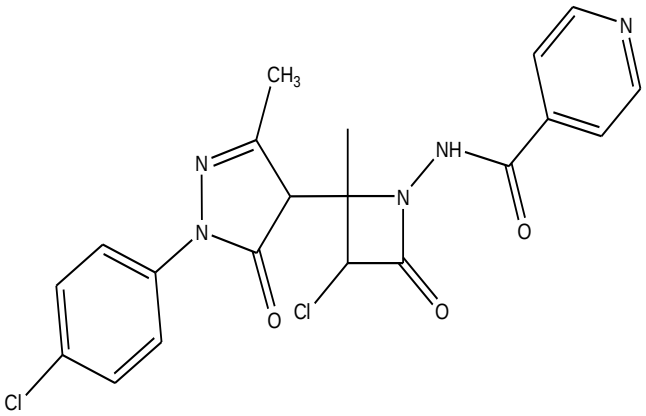
Physical data of compounds 13e



4-[3-Chloro-2-methyl-1-(4-nitro-phenyl)-4-oxo-azetidin-2-yl]-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{16}Cl_2N_4O$ Molecular weight : 425 gm/mol Melting point: 141-143 ^{0}C (uncorrected) Yield: 64%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 53.71 3.61 12.53 **Found** 53.70 3.64 12.51
IR features around Cm^{-1} 2885 Aromatic C-H stretching 1669 C=O 1605 C=N 1537 C=C Ar. 759 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.43-8.2 (8H,m, Ar-H) 5.23 (1H,s,CH) 3.12 (1H,s,Pyrazolone) 1.97 (3H,s,CH_3) 1.53 (3H,s,CH_3)

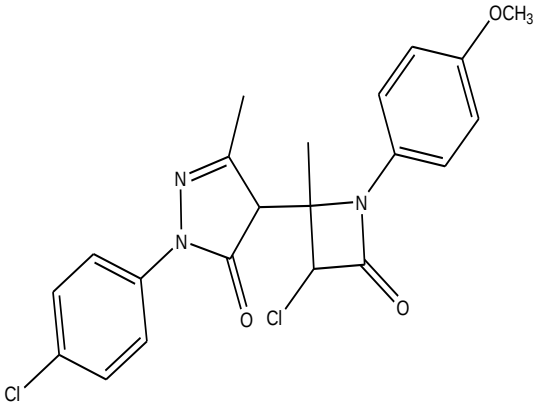
Physical data of compounds 13f



N-{3-Chloro-2-[1-(4-chloro-phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl]-2-methyl-4-oxo-azetidin-1-yl}-isonicotinamide

Molecular formula : $C_{21}H_{17}Cl_2N_5O_3$ Molecular weight : 446 gm/mol Melting point: 165-166 ^{0}C (uncorrected) Yield: 68%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 53.83 3.84 15.69 **Found** 53.84 3.81 15.71
IR features around Cm^{-1} 2909 Aromatic C-H stretching 3194 NH 1673 C=O 1603 C=N 1542 C=C Ar. 756 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.53-8.1 (9H,m, Ar-H) 5.4 (1H,s,CH) 3.02 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 1.51 (3H,s,CH_3)

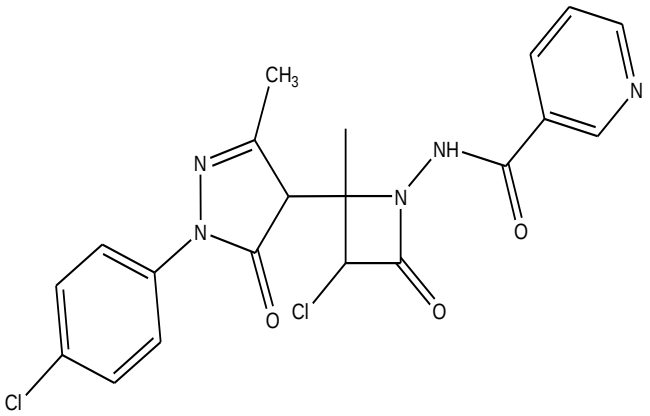
Physical data of compounds 13g



4-[3-Chloro-1-(4-methoxy-phenyl)-2-methyl-4-oxo-azetidin-2-yl]-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

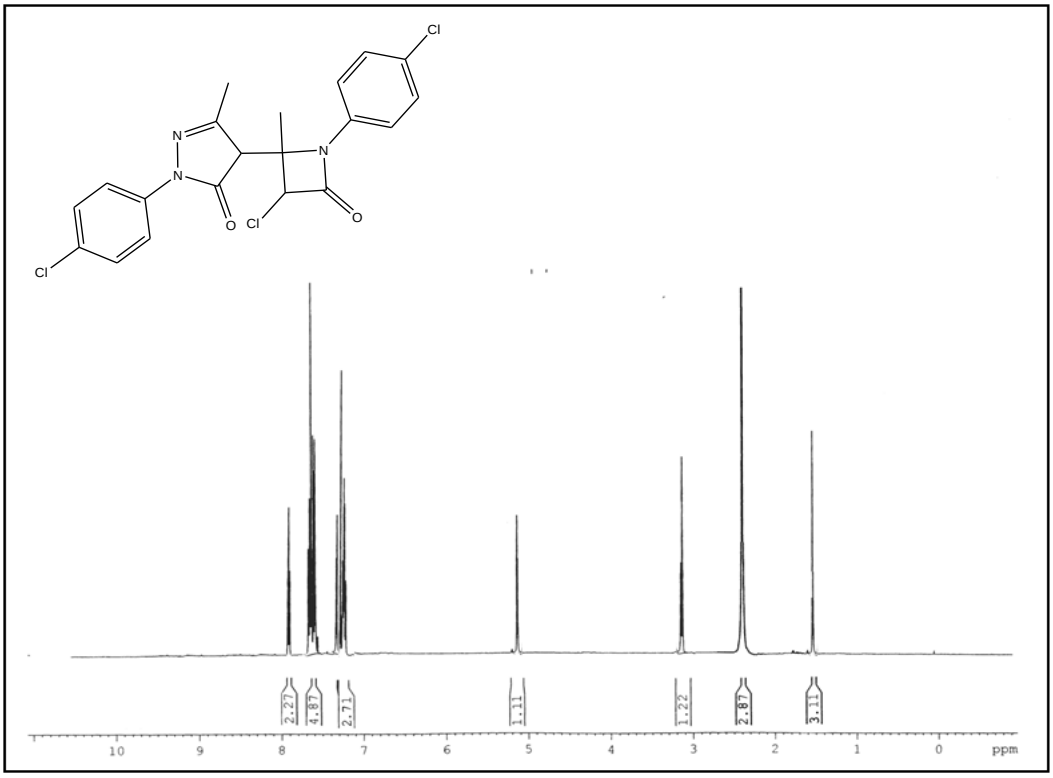
Molecular formula : $C_{21}H_{19}Cl_2N_3O_3$ Molecular weight : 432 gm/mol Melting point: 171-172 ^{0}C (uncorrected) Yield: 62%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 58.34 4.43 9.72 **Found** 58.32 4.45 9.70
IR features around Cm^{-1} 2887 Aromatic C-H stretching 1674 C=O 1602 C=N 1534 C=C Ar. 760 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 6.8-7.79 (9H,m, Ar-H) 5.3 (1H,s,CH) 3.09 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 1.49 (3H,s,CH_3) 3.92 (3H,s,OCH_3)

Physical data of compounds 13h

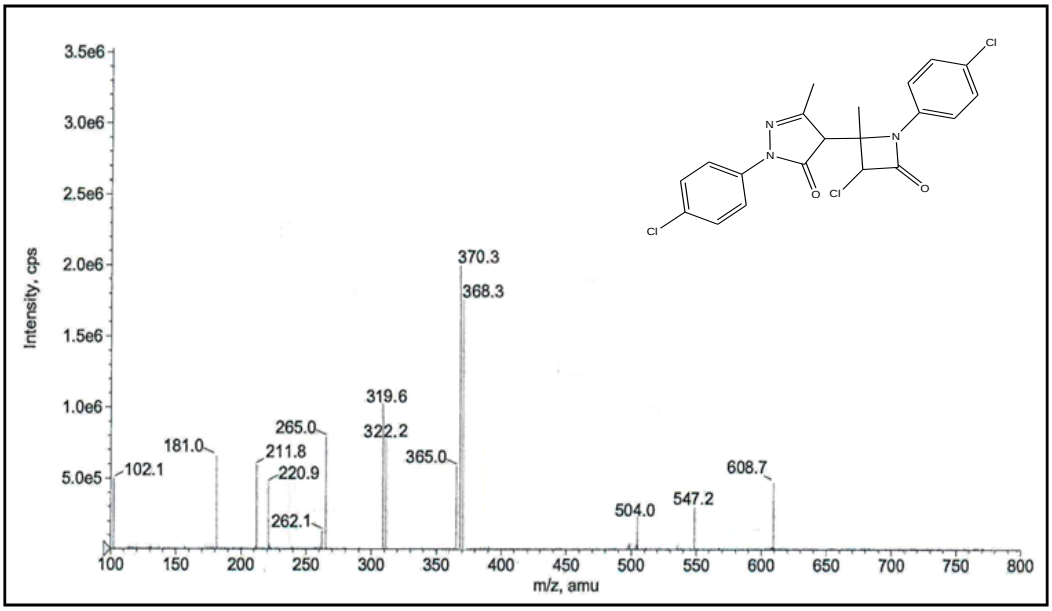


N-{3-Chloro-2-[1-(4-chloro-phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl]-2-methyl-4-oxo-azetidin-1-yl}-nicotinamide

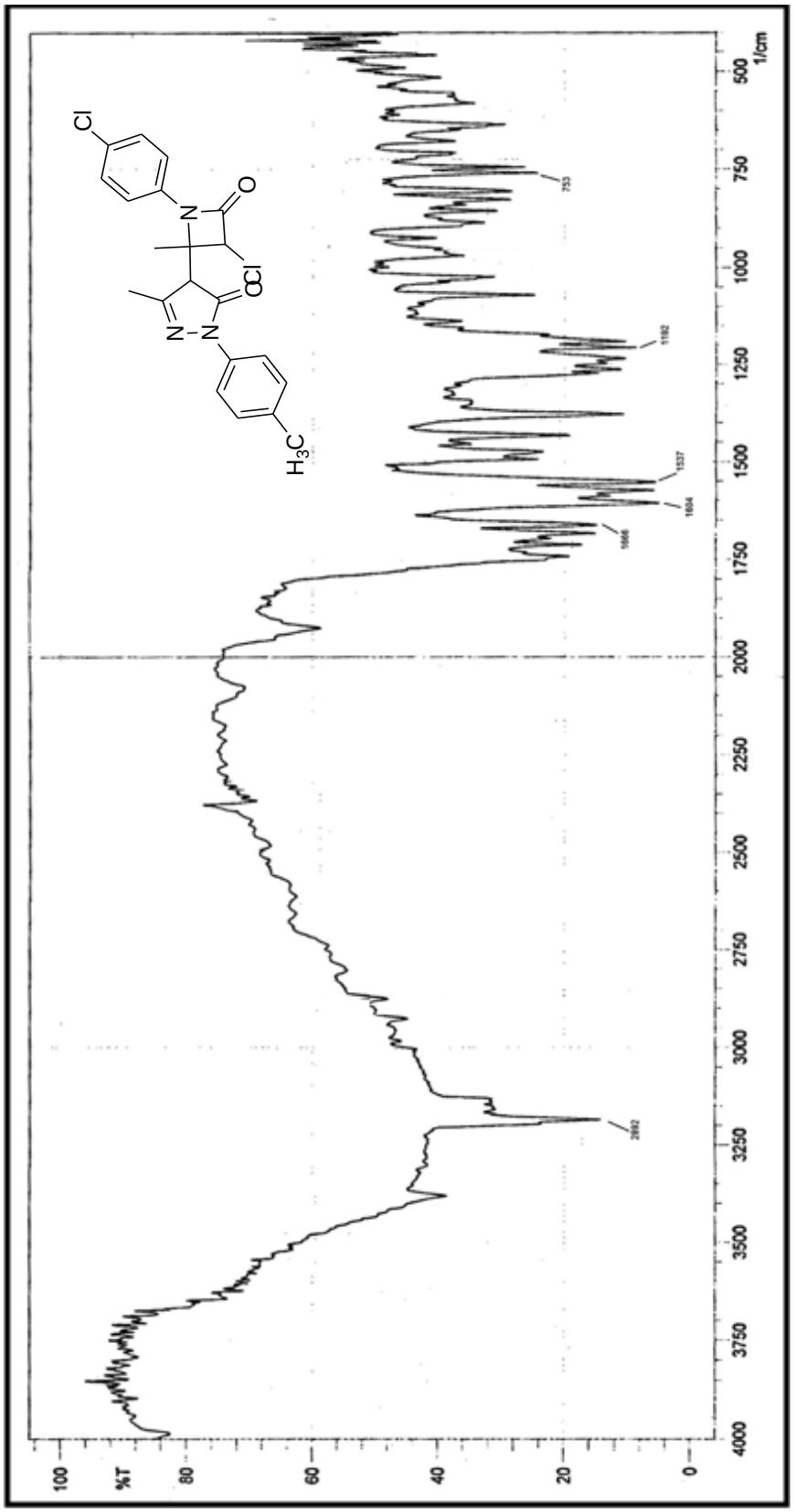
Molecular formula : $C_{21}H_{17}Cl_2N_5O_3$ Molecular weight : 446 gm/mol Melting point: 141-143 ^{0}C (uncorrected) Yield: 70%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 53.83 3.84 15.69 **Found** 53.85 3.81 15.7
IR features around Cm^{-1} 2902 Aromatic C-H stretching 3191 NH 1672 C=O 1606 C=N 1542 C=C Ar. 753 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.53-8.1 (8H,m, Ar-H) 5.4 (1H,s,CH) 3.09 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 1.51 (3H,s,CH_3)



NMR Spactrum of Compound 13b



Mass Spactrum of compound 13b



IR Spactrum of Compound 13b

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CHAPTER-6

Synthesis and Characterization of Thiadiazole derivatives from Schiff Base

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SECTION-A

SECTION-B

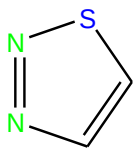
SECTION-A

6.1 Introduction

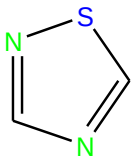
The biological activity of compounds mainly depends on their molecular structure. Heterocyclic moieties can be found in a large number of compounds which display large number of biological activity. Thiadiazole is a versatile moiety that exhibits a wide variety of activity due to the presence of N=C-S moiety in the ring. They have become an important class of heterocycles of great interest of researches because of their broad types of biological activity. Many drugs containing 1,3,4-thiadiazole nucleus like acetazolamide, butazolamide, sulfamethazole(3) are available in market. In addition other analogues have found to be used as dye, pesticides, lubricants and conducting polymers [1].

6.1.1 Chemistry

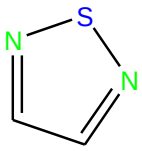
Thiadiazole is an important five membered heterocyclic ring containing two nitrogen atoms and a sulphur atom as hetero atoms with the general formula of C2H2N2S. They occur in four isomeric forms namely 1, 2, 3-thiadiazole, 1,2,4thiadiazole, 1,2,5- thiadiazole, 1,3,4- thiadiazole. Among them 1, 3, 4 thiadiazole ring exhibits more versatile activities.



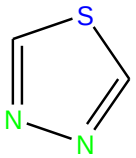
[1,2,3]Thiadiazole



[1,2,4]Thiadiazole



[1,2,5]Thiadiazole



[1,3,4]Thiadiazole

The ring system is less aromatic than benzene, thiophene, and pyridine. The aromatic character is measured by π electron delocalization which decreases in the order 1, 2, 5 thiadiazole>thiophene>thiazole>1, 3, 4- Thiadiazole [2]. The

electron withdrawing nature of the nitrogen atoms ensures that electrophilic attack at carbon is very rare and nucleophilic substitution reactions are common. Electrophilic attack at the sulphur atom has been observed. 1, 3, 4 – thiadiazoles are weak base due to the inductive effects of extra hetero atoms and are readily alkylated and acylated at N3 [1]. The ring is relatively stable in aqueous acid solutions but the ring gets cleaved in aqueous basic solutions. 1, 3, 4-thiadiazole core skeletons are subjected to various substitution reactions with alkyl halides, acid chlorides, and sulfonyl chlorides to afford various drug like 2-amino-substituted 1, 3, 4- thiadiazole derivatives [3]. When substituents are introduced into 2' or 5' position of this ring, the ring is highly reactive and forms different derivatives of thiadiazole easily.

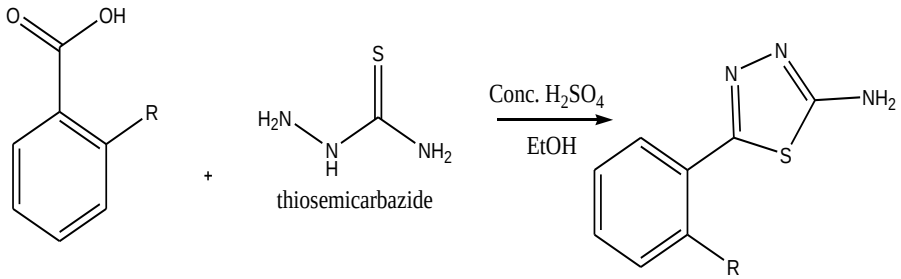
The reactivity of ring nitrogen atom arises from electrophilic reactions depending on tautomeric equilibrium of thione-thiol or amine-imine. In thione or imine form deprotonation of ring N-H can take place and ring nitrogen atom becomes vulnerable to alkylation or acylation or transformation to 1,3,4 –thiadiazolium salt. The reactions are conducted with electrophiles such as alkyl halides, trimethylsilylmethyltrifluoromethanesulfonate, formaldehyde [4] etc.

6.2 Pharmacological activity

Remarkable progress has been made in the development of thiadiazole derivatives in the recent years and the most recent studies have revealed that of thiadiazole derivatives has a wide spectrum of pharmacological properties like antimicrobial [5] antitubercular[6,7] anticonvulsants[8] antidepressant and anxiolitic[9] anti-inflammatory[10,11] analgesic[12] 1,3,4-Thiadiazoles

are thus a group of heterocycles whose derivatives are important in industry, medicine and agriculture [13-15].

Mahendrasinh M Raj [16] et al reported thiadiazole derivatives by the reaction between benzoic acid 2-hydroxy benzoic acid with thiosemicarbazide using conc. H_2SO_4 as oxidising agent. The synthesized compounds screened for their antibacterial and antifungal activities by paper disc diffusion technique. All the synthesized compounds showed moderate activity against bacteria and fungi.



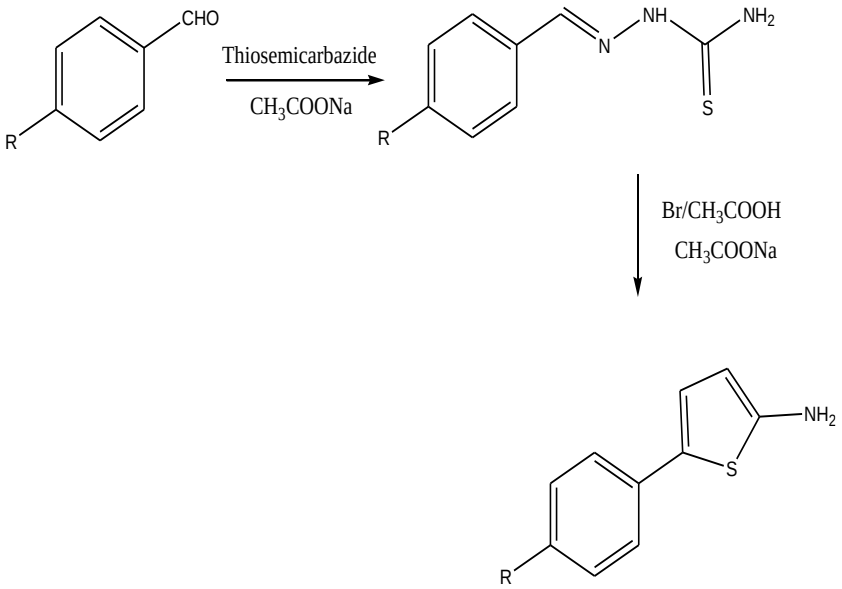
R= H & CH_3

Suddasatwa Banerjee [17] et al synthesized thiadiazole derivatives with new amino group by refluxing furan-2-carboxylic acid with thiosemicarbazide

Doaa E. Abdel Rahman [18] et al synthesized substituted imidazo [2,1-b]-1, 3,4–thiadiazoles, substituted 1,3,4-thiadiazolo[3,2-a] pyrimidines and substituted thioureas. Most of the tested compounds exhibited potent cytotoxicity. Docking studies were performed to explore the possible binding modes of these compounds with the binding site of fibroblast stromelysin-1 enzyme, which is involved in several pathological conditions including cancer.

Prasanna A Datar [19] et al designed thiadiazole compounds as antidiabetic agent using docking studies.Molecular docking revealed that synthesized derivatives and target proteins were actively involved in binding and had significant correlation with biological activity.

Alokpandey [20] et al synthesized Schiff bases of 2-amino-5-aryl-1,3,4-thiadiazole derivatives with different aromatic aldehyde. 1, 3, 4 – thiadiazole derivatives were prepared by the reaction of thiosemicarbazide, sodium acetate and aromatic aldehyde. All the synthesized compounds exhibited analgesic, anti-inflammatory, antibacterial and anti-tubercular activities act various minimum inhibitory concentration levels.



Abhay Kumar Verma [21] et al synthesized N-phenyl thiosemicarbazide from aromatic amine by refluxing with CS2 and hydrazine hydrate in ethanol and from phenyl isothiocyanate by reacting with hydrazine hydrate in ethanol. The synthesized thiosemicarbazides where condensed with aromatic carboxylic acid in presence of conc. H_2SO_4 to form thiadiazole analogues. The compounds were screened for anti-inflammatory activity.

ArunNaskar [22] et al synthesized 2-amino-5- aryl -1,3,4- thiadiazoles by oxidative cyclization of thiosemicarbazones using $FeCl_3$ catalyst .

SECTION-B

6.3 EXPERIMENTAL

Various schiff Bases of pyrazolone derivatives were mentioned in chapter 2, further on cyclization with $FeCl_3$ these Thiadiazole derivatives were characterized by IR, 1H-NMR and Mass fragmentation data.

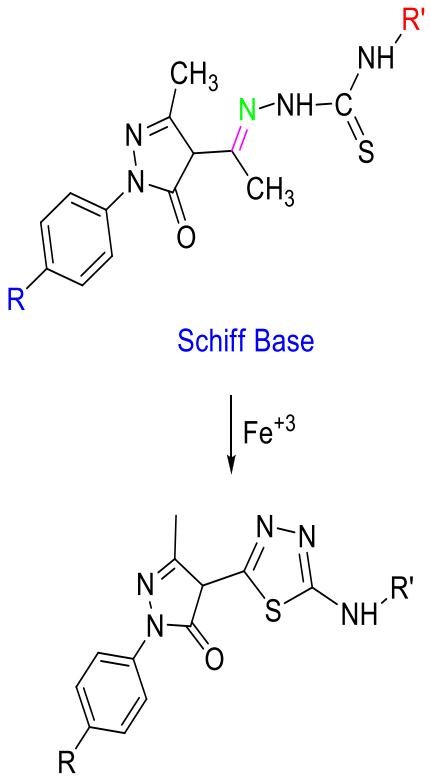
6.3.1 Material

The schiff bases have been chosen for the synthesis of above said compounds. Their synthesis has already been described in **Chapter- 2**. Other chemicals and solvents used were purified and of LR grade.

6.3.2 General procedure for synthesis of Thiadiazole

Schiff bases (0.015 mol) was suspended in 300 mL warm water. To this ferric chloride (0.045 mol) in 100 mL water was added quantitatively, slowly with constant stirring. The contents were heated at 80–90. The solution was filtered hot, and then 100 mL citrate buffer containing citric acid (0.033 mol) and sodium citrate (0.015 mol) were added. The resulting mixture was neutralized with aq. Ammonia (10%) at pH 7.

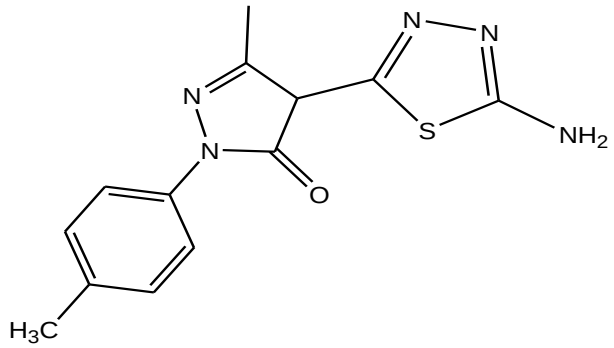
Reaction scheme-6.1



Where R = $-CH_3$ & -Cl

Where R'= a. thiosemicarbazide
b. Phenyl
c.4-Cl Phenyl
d. 2-methyl Phenyl
e. 4-OCH_3 Phenyl
f. 4-Nitro Phenyl

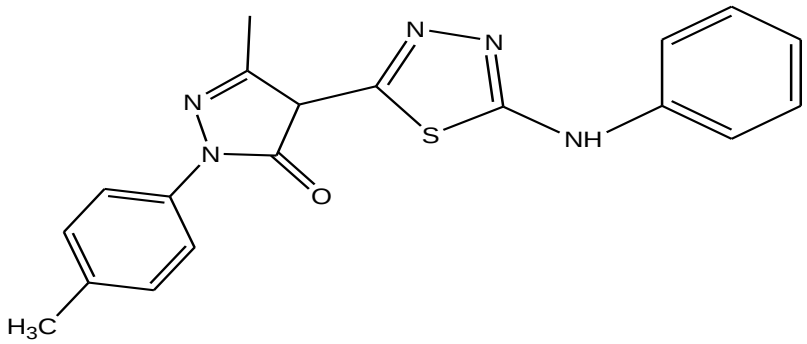
Physical data of compounds 14a



4-(5-Amino-[1,3,4]thiadiazol-2-yl)-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{13}H_{13}N_5OS$ Molecular weight : 287 gm/mol Melting point: 178-179 ^{0}C (uncorrected) Yield: 73%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 54.34 4.56 24.37 **Found** 54.3 4.6 24.36
IR features around Cm^{-1} 2893 Aromatic C-H stretching 3448,3355 (asy & sym str. NH_2) 1669 C=O 1605 C=N 769 C-S-C str.	**^{1}H-NMR spectral features (δ-ppm)** 7.15-8.09 (4H,m, Ar-H) 3.7 (2H,s, -NH_2) 3.82 (1H,s,Pyrazolone) 1.94 (3H,s,CH_3) 2.3 (3H,s,CH_3)

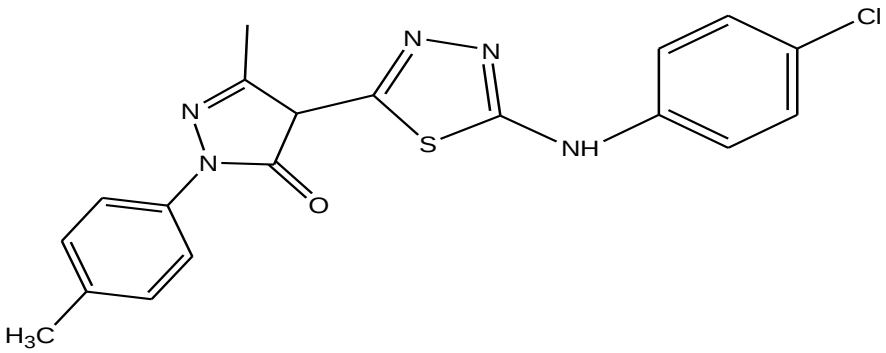
Physical data of compounds 14b



5-Methyl-4-(5-phenylamino-[1,3,4]thiadiazol-2-yl)-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{17}N_5OS$ Molecular weight : 363 gm/mol Melting point: 186-189 ^{0}C (uncorrected) Yield: 70%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 62.79 4.71 19.27 **Found** 62.8 4.73 19.3
IR features around Cm^{-1} 2896 Aromatic C-H stretching 1674 C=O 1608 C=N 763 C-S-C str.	**^{1}H-NMR spectral features (δ-ppm)** 7.23-8.09 (9H,m, Ar-H) 4.2 (1H,s,-NH) 3.88 (1H,s,Pyrazolone) 1.94 (3H,s,CH_3) 2.34 (3H,s,CH_3)

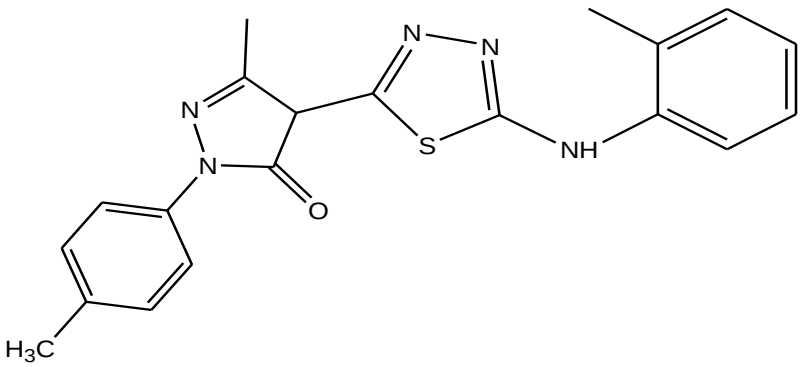
Physical data of compounds 14c



4-[5-(4-Chloro-phenylamino)-[1,3,4]thiadiazol-2-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{16}ClN_5OS$ Molecular weight : 397gm/mol Melting point: 182-184 ^{0}C (uncorrected) Yield: 69%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 63.64 5.07 18.55 **Found** 63.61 5.09 18.53
IR features around Cm^{-1} 2890 Aromatic C-H stretching 1670 C=O 1598 C=N 767 C-S-C str. 756 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 7.1-7.80 (8H,m, Ar-H) 3.98 (1H,s, NH) 3.85 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 2.38 (3H,s,CH_3)

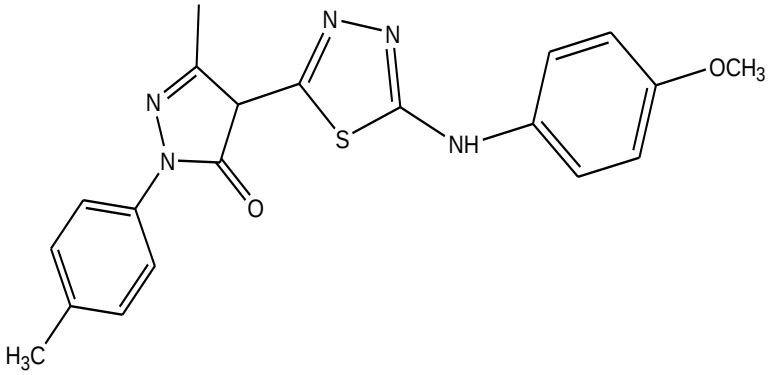
Physical data of compounds 14d



5-Methyl-2-*p*-tolyl-4-(5-*o*-tolylamino-[1,3,4]thiadiazol-2-yl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{20}H_{19}N_5OS$ Molecular weight :377 gm/mol Melting point: 163-165 ^{0}C (uncorrected) Yield: 75%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 65.50 4.63 16.08 **Found** 65.51 4.62 16.1
IR features around Cm^{-1} 2901 Aromatic C-H stretching 1676 C=O 1602 C=N 756 C-S-C str. 1370 -CH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.1-7.80 (8H,m, Ar-H) 4.0 (1H,s, NH) 3.92 (1H,s,Pyrazolone) 1.95 (3H,s,CH_3) 2.34 (3H,s,CH_3)

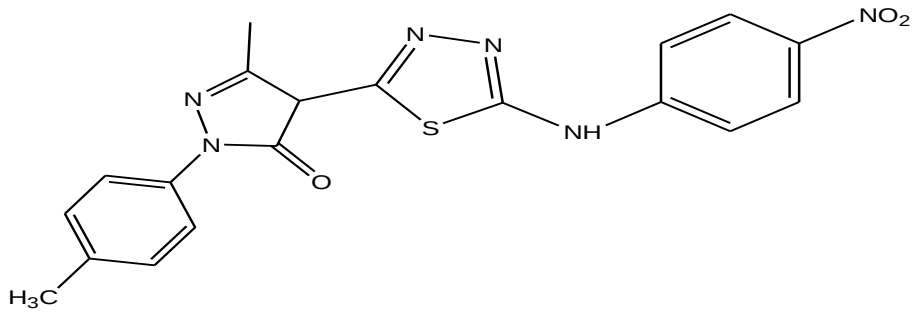
Physical data of compounds 14e



4-[5-(4-Methoxy-phenylamino)-[1,3,4]thiadiazol-2-yl]-5-methyl-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

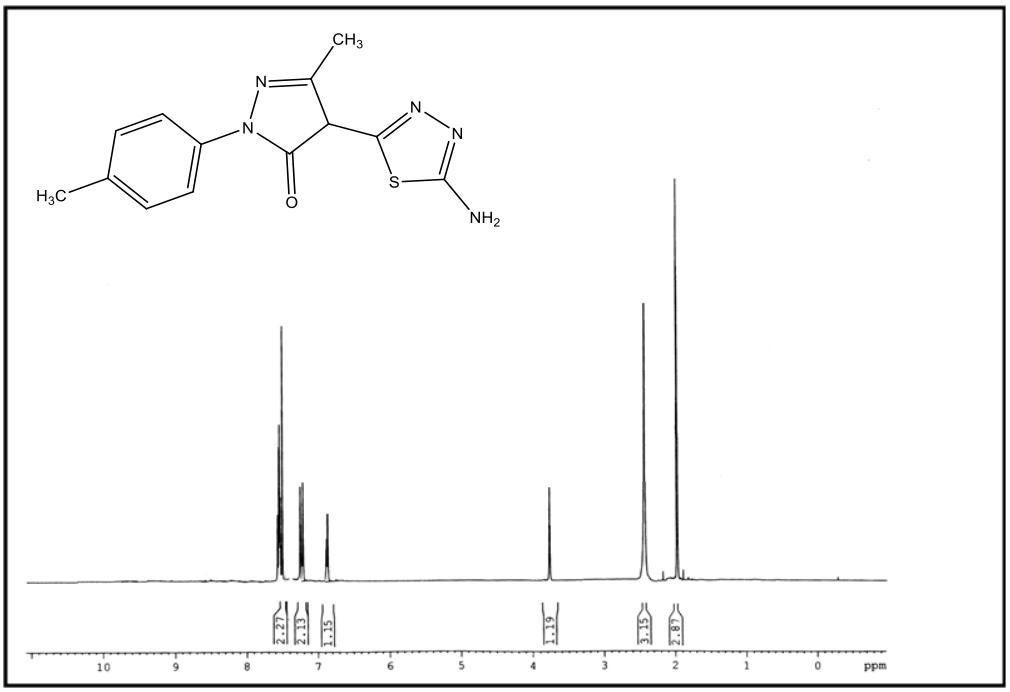
Molecular formula : $C_{20}H_{19}N_5O_2S$ Molecular weight : 393gm/mol Melting point: 163-165 ^{0}C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 61.05 4.87 17.80 **Found** 61.06 4.88 17.82
IR features around Cm^{-1} 2898 Aromatic C-H stretching 1670 C=O 1599 C=N 759 C-S-C str. 2828 OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.1-8.11 (8H,m, Ar-H) 3.94 (1H,s,NH) 3.84 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 2.35 (3H,s,CH_3) 3.69 (3H,s,OCH_3)

Physical data of compounds 14f

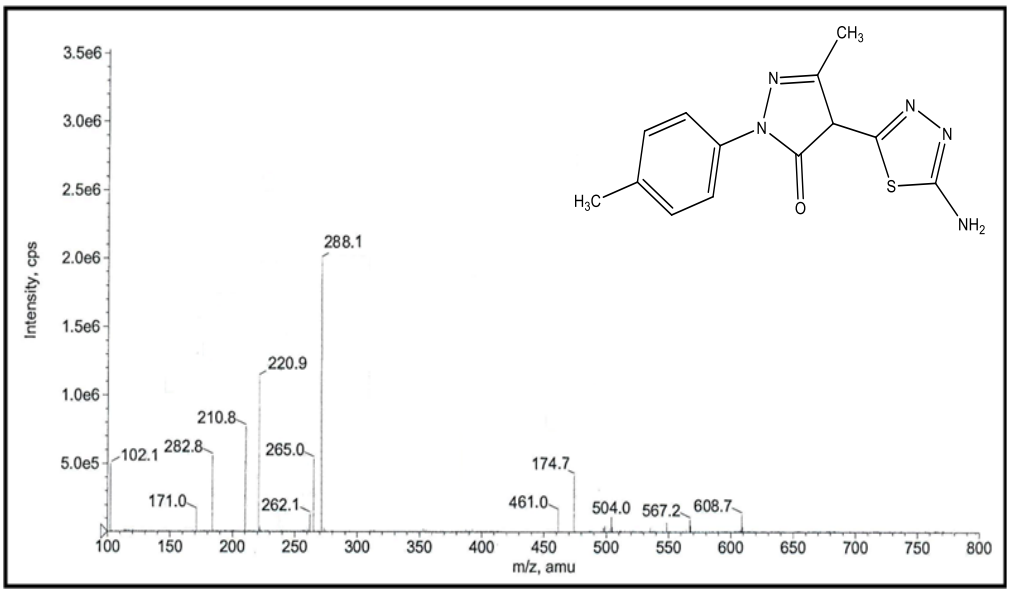


5-Methyl-4-[5-(4-nitro-phenylamino)-[1,3,4]thiadiazol-2-yl]-2-*p*-tolyl-2,4-dihydro-pyrazol-3-one

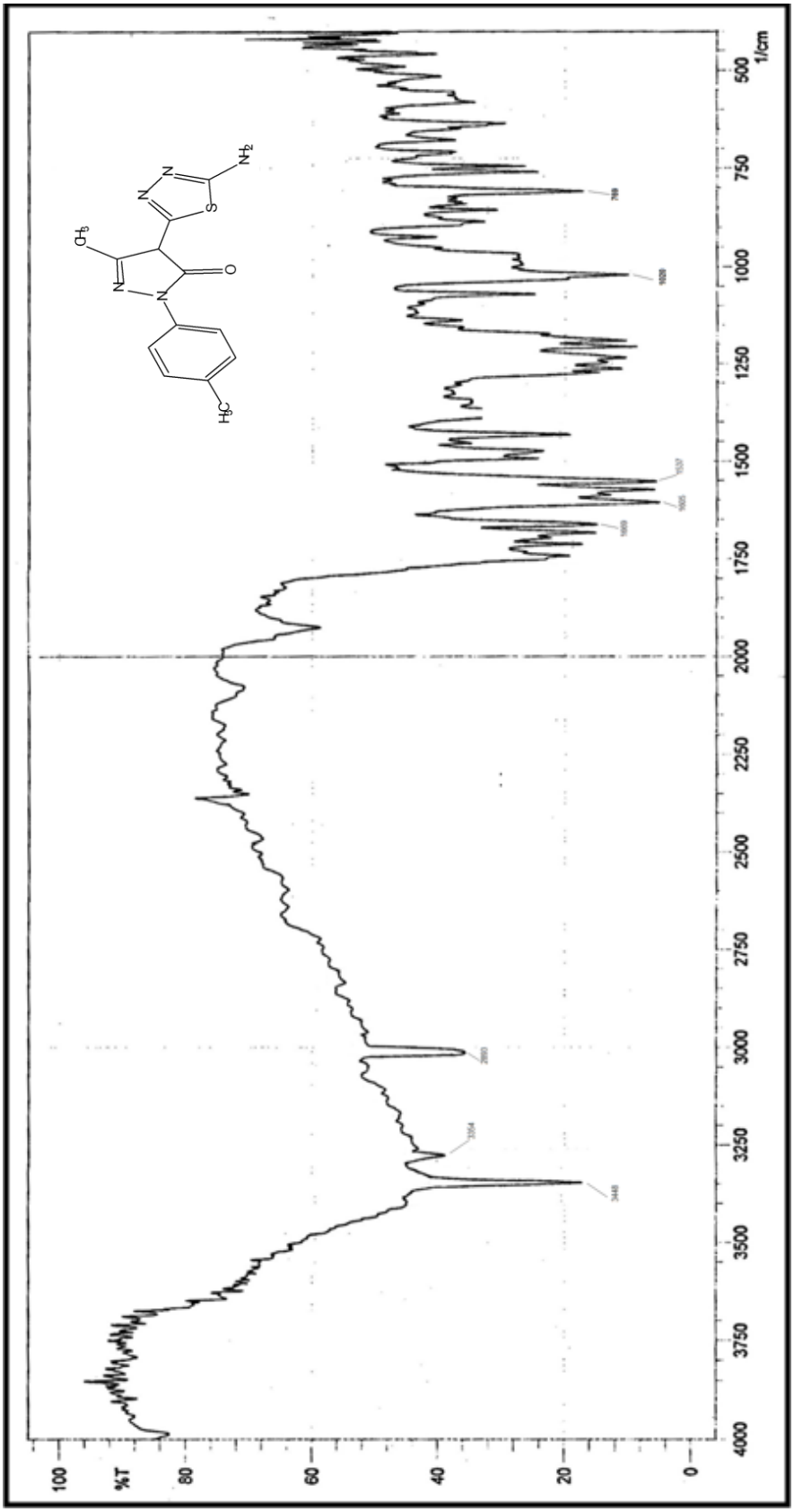
Molecular formula : $C_{19}H_{16}N_6O_3S$ Molecular weight : 408 gm/mol Melting point: 163-165 ^{0}C (uncorrected) Yield: 72%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 55.87 3.95 20.58 **Found** 55.9 3.9 20.56
IR features around Cm^{-1} 2902 Aromatic C-H stretching 1676 C=O 1608 C=N 756 C-S-C str.	**^{1}H-NMR spectral features (δ-ppm)** 7.2-8.11 (8H,m, Ar-H) 3.91 (1H,s,NH) 3.83 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 2.38 (3H,s,CH_3)



NMR Spactrum of Compound 14a

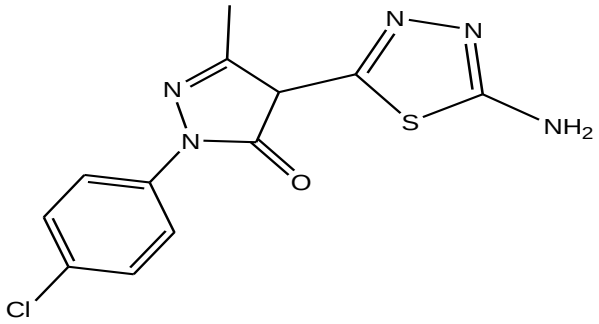


Mass Spactrum of Compound 14a



IR Spactrum of Compound 14a

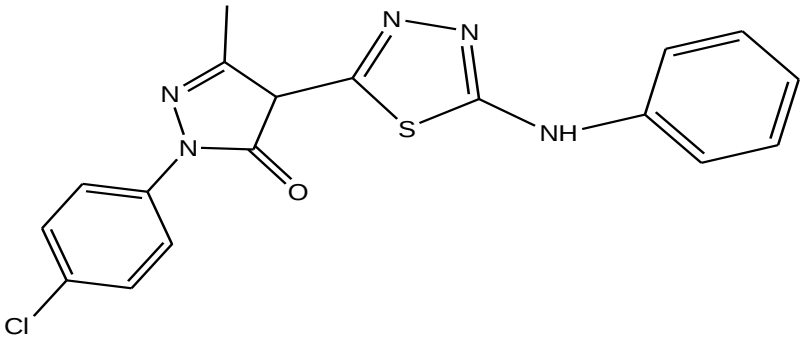
Physical data of compounds 15a



4-(5-Amino-[1,3,4]thiadiazol-2-yl)-2-(4-chloro-phenyl)-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{12}H_{10}ClN_5OS$ Molecular weight : 307 gm/mol Melting point: 163-164 ^{0}C (uncorrected) Yield: 71%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 46.83 3.28 22.76 **Found** 46.8 3.3 22.74
IR features around Cm^{-1} 2891 Aromatic C-H stretching 3446,3352 (asy & sym str. NH_2) 1667 C=O 1602 C=N 764 C-S-C str.	**^{1}H-NMR spectral features (δ-ppm)** 6.82-8.1 (4H,m, Ar-H) 3.9 (2H,s, -NH_2) 3.72 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3)

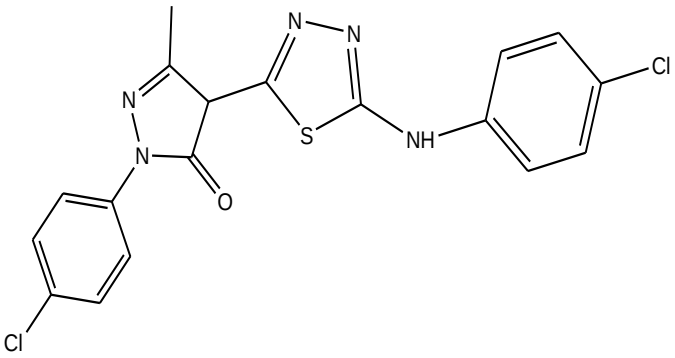
Physical data of compounds 15b



2-(4-Chloro-phenyl)-5-methyl-4-(5-phenylamino-[1,3,4]thiadiazol-2-yl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{18}H_{14}ClN_5OS$ Molecular weight : 383 gm/mol Melting point: 166-167 ^{0}C (uncorrected) Yield: 68%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 56.32 3.68 18.24 **Found** 56.3 3.7 18.26
IR features around Cm^{-1} 2890 Aromatic C-H stretching 3189 -NH 1670 C=O 1605 C=N 767 C-S-C str.	**^{1}H-NMR spectral features (δ-ppm)** 6.80-8.0 (9H,m, Ar-H) 4.0 (1H,s,-NH) 3.7 (1H,s,Pyrazolone) 1.94 (3H,s,CH_3)

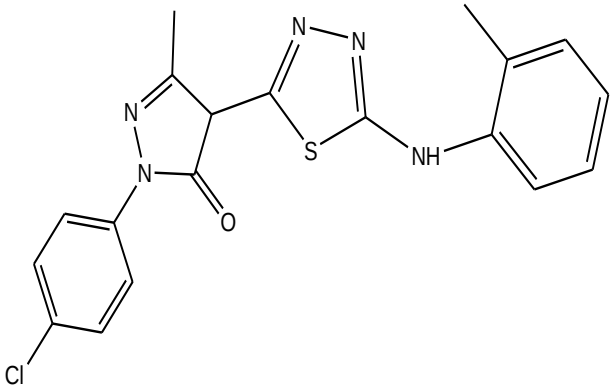
Physical data of compounds 15c



2-(4-Chloro-phenyl)-4-[5-(4-chloro-phenylamino)-[1,3,4]thiadiazol-2-yl]-5-methyl-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{18}H_{13}Cl_2N_5OS$ Molecular weight : 417 gm/mol Melting point: 173-174 ^{0}C (uncorrected) Yield: 65%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 51.68 3.13 16.74 **Found** 51.7 3.1 16.76
IR features around Cm^{-1} 2896 Aromatic C-H stretching 3187 -NH 1676 C=O 1602 C=N 769 C-S-C str. 756 C-Cl	**^{1}H-NMR spectral features (δ-ppm)** 6.9-7.92 (8H,m, Ar-H) 3.98 (1H,s, NH) 3.71 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3)

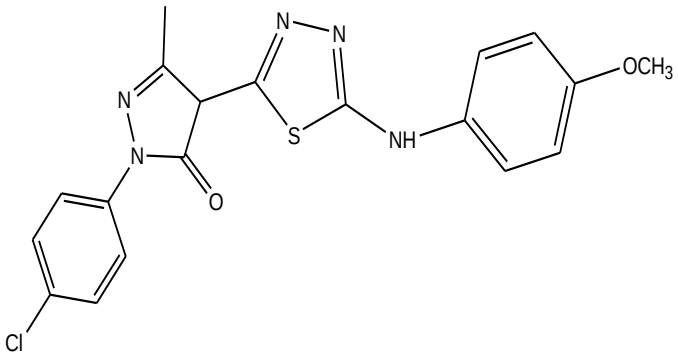
Physical data of compounds 15d



2-(4-Chloro-phenyl)-5-methyl-4-(5-*o*-tolylamino-[1,3,4]thiadiazol-2-yl)-2,4-dihydro-pyrazol-3-one

Molecular formula : $C_{19}H_{16}ClN_5OS$ Molecular weight : 397 gm/mol Melting point: 164-165 ^{0}C (uncorrected) Yield: 68%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 57.35 4.05 17.60 **Found** 57.36 4.07 17.62
IR features around Cm^{-1} 2892 Aromatic C-H stretching 3190 -NH 1667 C=O 1607 C=N 763 C-S-C str.	**^{1}H-NMR spectral features (δ-ppm)** 7.1-7.85 (8H,m, Ar-H) 4.0 (1H,s, NH) 3.79 (1H,s,Pyrazolone) 1.95 (3H,s,CH_3)

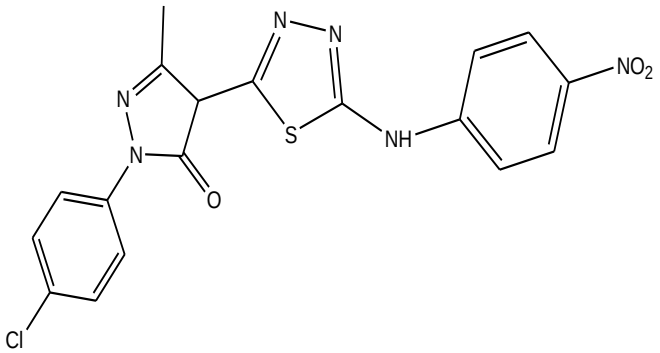
Physical data of compounds 15e



2-(4-Chloro-phenyl)-4-[5-(4-methoxy-phenylamino)-[1,3,4]thiadiazol-2-yl]-5-methyl-2,4-dihydro-pyrazol-3-one

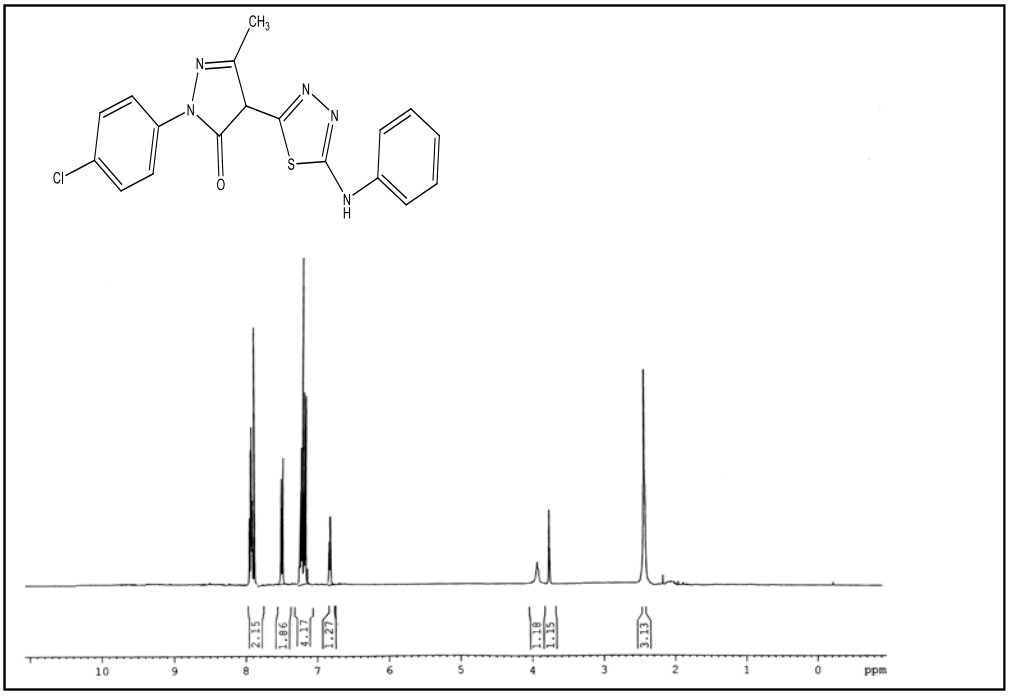
Molecular formula : $C_{19}H_{16}ClN_5O_2S$ Molecular weight : 413 gm/mol Melting point: 163-165 ^{0}C (uncorrected) Yield: 65%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 55.14 3.90 16.92 **Found** 55.16 3.92 16.90
IR features around Cm^{-1} 2894 Aromatic C-H stretching 3194 -NH 1677 C=O 1609 C=N 768 C-S-C str. 2838 OCH_3	**^{1}H-NMR spectral features (δ-ppm)** 7.1-8.11 (8H,m, Ar-H) 3.94 (1H,s,NH) 3.69 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3) 3.69 (3H,s,OCH_3)

Physical data of compounds 15f

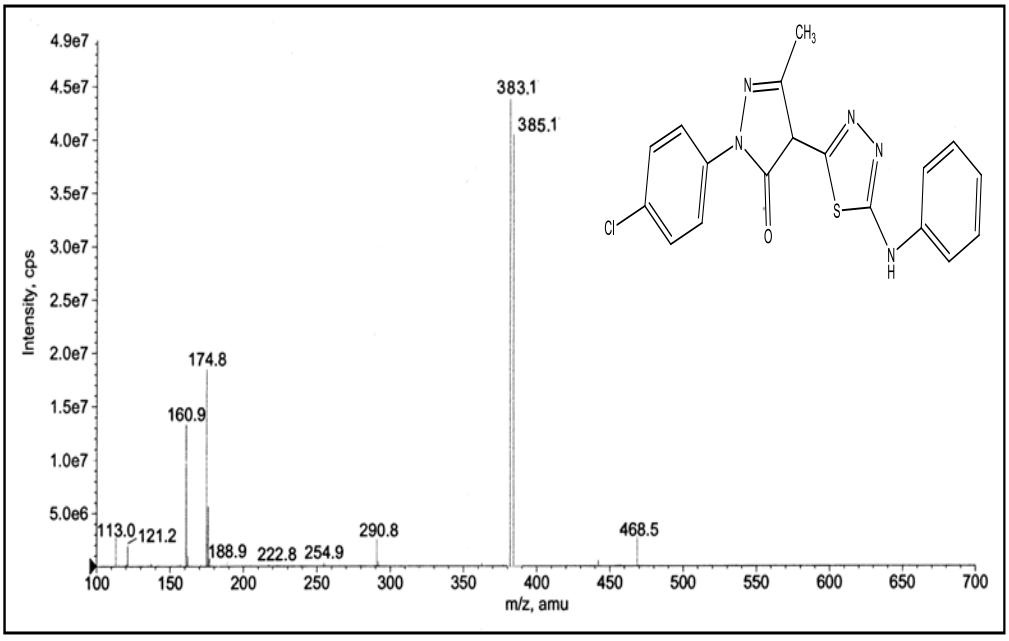


2-(4-Chloro-phenyl)-5-methyl-4-[5-(4-nitro-phenylamino)-[1,3,4]thiadiazol-2-yl]-2,4-dihydro-pyrazol-3-one

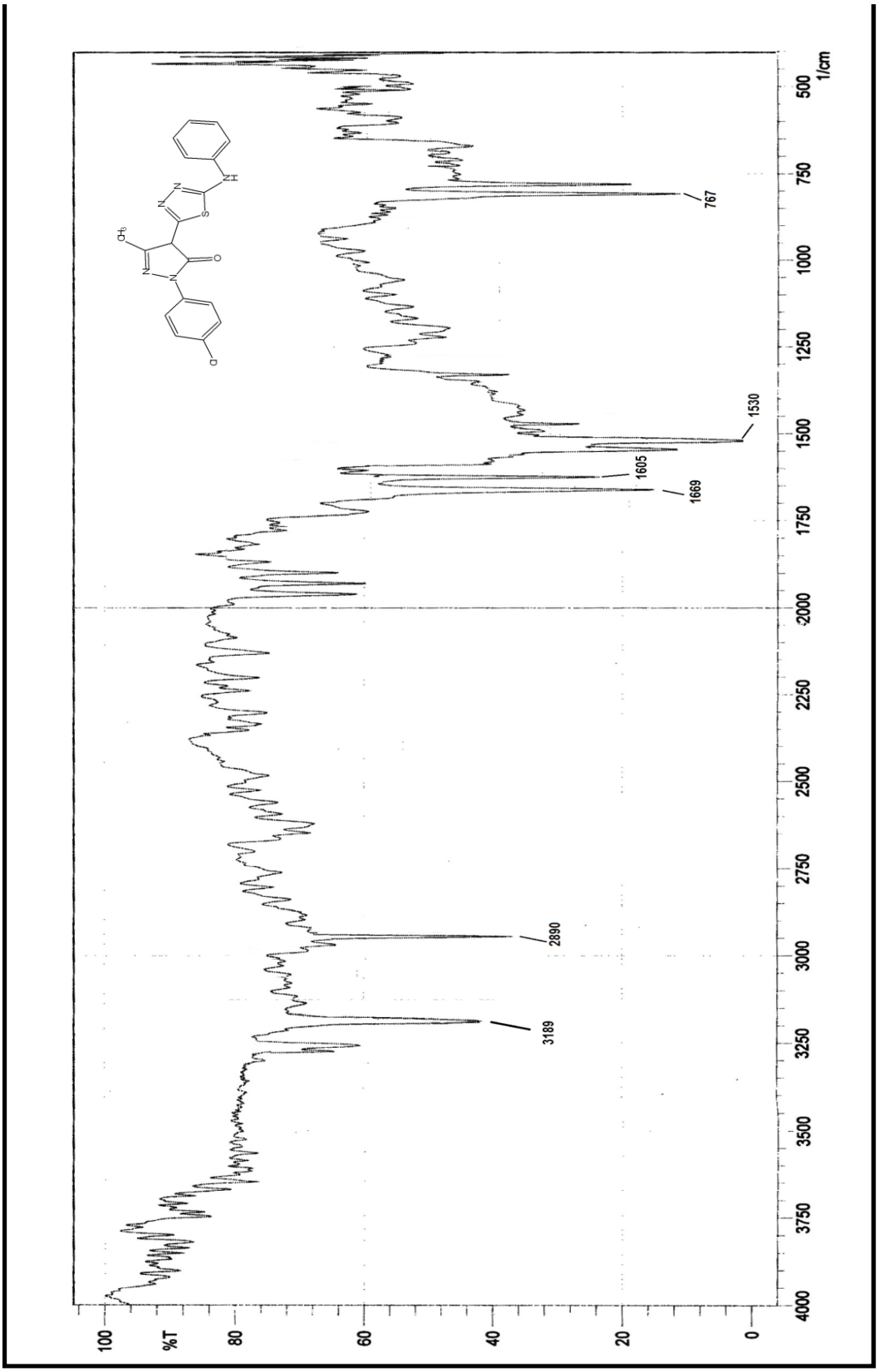
Molecular formula : $C_{18}H_{13}ClN_6O_3S$ Molecular weight : 428 gm/mol Melting point: 163-165 ^{0}C (uncorrected) Yield: 66%	**Elemental analysis** **%C** **% H** **% N** **Calculated** 50.41 3.06 19.60 **Found** 50.42 3.04 19.62
IR features around Cm^{-1} 2888 Aromatic C-H stretching 3190 -NH 1669 C=O 1605 C=N 767 C-S-C str.	**^{1}H-NMR spectral features (δ-ppm)** 7.2-8.1 (8H,m, Ar-H) 3.91 (1H,s,NH) 3.43 (1H,s,Pyrazolone) 1.96 (3H,s,CH_3)



NMR Spactrum of Compound 15b



Mass Spactrum of Compound 15b



IR Spactrum of Compound 15b

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CHAPTER-7

Anti-Microbial activity

Table of Contents

7.1. ANTIBACTERIAL ACTIVITY

7.1.1. Introduction

The science dealing with the study of the prevention and treatment of diseases caused by micro-organisms is known as medical microbiology. Its sub-disciplines are virology (study of viruses), bacteriology (study of bacteria), mycology (study of fungi), phycology (study of algae) and protozoology (study of protozoa). For the treatment of diseases inhibitory chemicals employed to kill micro-organisms or prevent their growth, are called antimicrobial agents. These are classified according to their application and spectrum of activity, as germicides that kill micro-organisms, whereas micro-biostatic agents inhibit the growth of pathogens and enable the leucocytes and other defense mechanism of the host to cope up with static invaders. The germicides may exhibit selective toxicity depending on their spectrum of activity. They may act as viricides (killing viruses), bacteriocides (killing bacteria), algicides (killing algae) or fungicides (killing fungi).

The beginning of modern chemotherapy has largely been due to the efforts of Dr. Paul Ehrlich (1910), who used salvarsan, as arsenic derivative effective against syphilis. Paul Ehrlich used the term chemotherapy for curing the infectious disease without injury to the host's tissue, known as chemotherapeutic agents such as antibacterial, antiprotosoal, antiviral, antineoplastic, antitubercular and antifungal agents. Later on, Domagk (1953) prepared an important chemotherapeutic agent sulfanilamide.

7.1.2. Classification of Antibacterial Agents

I. Antibiotics and chemically synthesized chemotherapeutic agents.

II. Non-antibiotic chemotherapeutic agents (Disinfectants, antiseptics and preservatives)

III. Immunological products.

(I) Antibiotics

They are produced by micro-organisms or they might be fully or partly prepared by chemical synthesis. They inhibit the growth of micro-organisms in minimal concentrations. Antibiotics may be of microbial origin or purely synthetic or semisynthetic. They can be classified by manner of biosynthesis or chemical structure.

Synthetic antimicrobial agents include sulfonamides, diamino pyrimidine derivatives, antitubercular compounds, nitrofuran compounds, 4-quinoline antibacterials, imidazole derivatives, flucytosine etc.

(II) Non-antibiotics

The second category of antibacterial agents includes non-antibiotic chemo-therapeutic agents which are as follows:

1) Acids and their derivatives

Some organic acids such as sorbic, benzoic, lactic and propionic acids are used for preserving food and pharmaceuticals. Salicyclic acid has strong antiseptic and germicidal properties as it is a carboxylated phenol. The presence of –COOH group appears to enhance the antiseptic property and to decrease the destructive effect. Benzoic acid is used externally as an antiseptic and is employed in lotion and ointment. Benzoic acid and salicylic acid are used to control fungi that cause disease such as athlete's foot. Benzoic acid and sodium benzoate are used as antifungal preservatives. Mandolic acid possesses good bacteriostatic and bactericidal properties.

2) Alcohols and related compounds

They are bactericidal and fungicidal, but are not effective against endospores and some viruses. Various alcohols and their derivatives have been used as antiseptics e.g. ethanol and propanol. The antibacterial value of straight chain alcohols increases with an increase in the molecular weight and beyond C8-the activity begins to fall off. The isomeric alcohol shows a drop in activity from primary, secondary to tertiary. Ethanol has extremely numerous uses in pharmacy.

3) Chlorination and compound containing chlorine

Chlorination is extensively used to disinfect drinking water, swimming pools and for the treatment of effluent from industries. Robert Koch in 1981 first referred to the bactericidal properties of hypochlorites. N-chloro compounds are represented by amides, imides and amidines wherein one or more hydrogen atoms are replaced by chlorine.

4) Iodine containing compounds

Iodine containing compounds are widely used as antiseptic, fungicide and amoebicide. Iodophores are used as disinfectants and antiseptics. The soaps used for surgical scrubs often contain iodophores.

5) Heavy metals

Heavy metals such as silver, copper, mercury and zinc have antimicrobial properties and are used in disinfectant and antiseptic formulations. Mercurochrome and merthiolate are applied to skin after minor wounds. Zinc is used in antifungal antiseptics. Copper sulfate is used as algicides.

6) Oxidising agents

Their value as antiseptics depends on the liberation of oxygen and all are organic compounds.

7) Dyes

Organic dyes have been extensively used as antibacterial agents. Their medical significance was first recognized by Churchman [2] in 1912. He reported inhibitory effect of Crystal violet on Gram-positive organism. The acridines exert bactericidal and bacteriostatic action against both Gram-positive and Gram-negative organisms.

8) 8-Hydroxyquinolines

8-Hydroxyquinoline or oxine is unique among the isomeric hydroxyl-quinolines, for it alone exhibits antimicrobial activity. This attributes to its ability to chelate metals [3], which the other isomers do not exhibit.

9) Surface active agents

Soaps and detergents are used to remove microbes mechanically from the skin surface. Anionic detergents remove microbes mechanically; cationic detergents have antimicrobial activities and can be used as disinfectants and antiseptics.

(III) Immunological products

Certain immunological products such as vaccines and monoclonal antibodies are used to control the diseases as a prophylactic measure.

7.1.3. Mode of Action

Antimicrobial drugs interfere chemically with the synthesis of function of vital components of micro organisms. The cellular structure and functions of eukaryotic cells of the human body. These differences provide us with selective toxicity of chemotherapeutic agents against bacteria.

Antimicrobial drugs may either kill microorganisms outright or simply prevent their growth. There are various ways in which these agents exhibit their antimicrobial activity [4]. They may inhibit

1. Cell-wall synthesis
2. Protein synthesis
3. Nucleic acid synthesis
4. Enzymatic activity
5. Folate metabolism or
6. Damage cytoplasmic membrane

7.2. Bacteriostatic Dyes

Stearn and Stearn[5] attributed the bacteriostatic activity to triphenylmethane dyes. Fischer and Munzo[6] have found the relationship between their structure and effectiveness of such dyes.

A number of drugs are metal-binding agents. The chelates are the active form of drugs. The site of action within the cell or on the cell surface has not been established. The site of action of oxine and its analogs has been suggested inside the bacterial cell [7] or on cell surface [8].

Detoxification of antibacterial

P-Aminobenzoic acid is a growth factor for certain micro-organisms and competitively inhibits the bacteriostatic action of sulfonamides. The metabolites identified in man are p-amino-benzoylglucoronide; p-aminohippuric acid, p-acetylaminobenzoic acid. 8-Hydroxyquinoline (oxine) and 4-hydroxyquinoline are excerted as sulfate esters or glucorinides.

Bacteria

The bacteria are microscopic organisms with relatively simple and primitive forms of prokaryotic type. Danish Physician Christian Grams, discovered the differential staining technique known as Gram staining, which differentiates the bacteria into two groups “Gram positive” and “Gram negative”, Gram positive bacteria retain the crystal violet and resist decolorization with acetone or alcohol and hence appear deep violet in colour; while Gram negative bacteria, which loose the crystal violet, are counter-stained by saffranin and hence appear red in colour.

These two groups of bacteria are recently classified into four different categories as follows:

The world of bacteria I: "Ordinary" Gram negative bacteria.

The world of bacteria II: "Ordinary" Gram positive bacteria.

The world of bacteria III: "Bacteria" with unusual properties.

The world of bacteria IV: Gram positive filamantous bacteria of complex morphology.

1. *Staphylococcus aureus*: Family (micrococcaceae)

In 1878, Koch observed micrococcus like organisms in pus; Pasteur (1880) cultivated these cocci in liquid media. They are Gram-positive cocci, ovoid or spheroidal, non-motile, arranged in group of clusters; they grow on nutrient agar and produce colonies, which are golden yellow, white or lemon yellow in colour; pathogenic strains produce, coagulated and ferment glucose lactose, mannitol with production of acid, liquefy gelation and produce pus in the lesion.

Genus: *Staphylococcus*

The word *staphylococcus* is derived from the Greek language (Gr. Staphylo =bunch of grapes; Gr. Coccus = a grain or berry), while the species name is derived from Latin language (L. aureus = golden). Staphylococcus is differentiated from micrococcus and another genus of the same family by its ability to utilize glucose, mannitol and pyruvate anaerobically. Cells of staphylococci, which are slightly smaller than those of Micrococci, are found on the skin or mucus membrane of the animal body.

Species: *Staphylococcus aureus*

Basic habital of *St. aureus* is the anterior naves, though it is also a normal flora of human skin, and of the respiratory and gastrointestinal tracts. The individual cells are 0.8 to 0.9 μ in diameter. They are oval or spherical, non-

motile, non-capsulated, non-sporulating strains with ordinary aniline dyes and are Gram-positive, typically arranged in groups or irregular clusters like branches of groups in pus seen single or in pairs.

They easily grow on nutrient agar; the optimum temperature for the growth is 35 ºC.

They are notorious as they cause suppurative (pyogenic or pus forming) conditions, mostitis of women and cows, boils and food poisioning. ***St. aureus*** grows rapidly and produce circular (1-2 mm) endive edge, convex, soft, glistening colonies having a golden yellow pigment. St. aureus can tolerate moderately high concentration of NaCl, hence they can be selectively isolated on the nutrient medium containing 7.5 % sodium chloride. It is also able to ferment mannitol to organic acid. St. aureus also produce the coagulase which is able to clot citrated plasma. It also produces the enzymes catalase, hyaluronidase as well as other virulent factors like hemolysins, leucocidins, enterotoxins and exofoliatin.

2. STREPTOCOCCUS PYOGENES

Genus: *Streptococcus*

The term *Streptococcus* was first introduced by Bilroth [1874] and the term *Streptococcus Pyogenes* was used by Rosenbach [1884]. These are spherical or ovoid cells; divide in one axis and form chains; nonmotile and nonsporing. The growth is absence of native proteins in the medium; they produce characteristic haemolytic changes in media containing blood; produce acid only by fermentation of carbohydrates; often fail t liquefy gelatin; some strains produce exotoxin and extracellular products; a few of them are Anaerobic.

Species: *Streptococcus Pyogenes*

Streptococcus Pyogenes is pathogenic to human and found in sore throat, follicular tonsillitis, septicemia, acute or malignant ulcerative endocarditis etc. These are spherical Cocci 0.5 to 0.75 micro in diameter, arranged in moderately long chains of round Cocci and easily differentiated from Enterococci that from short chains of 2 to 4 spheres.

Streptococcus Pyogenes is recently isolated from throat or other lesions; they show either mucoid or matt colonies. On keeping in the laboratory, they undergo varation to a glossy type. Streptococci are susceptible to destructive agents, and to penicillin and sulphomamides.

3. *Escherichia coli*: Enterobacteriaceae

They are Gram-negative rods, motile with peritrichate flagella or non-motile. They do not form spores. All are sometimes (i.e. from rarely to, invariably) found in intestinal treatment of man or lower animals.

Genus: *Escherichia*

This genus comprises Escherichia coli and several variants.

Species: *Escherichia coli*

Escherichia in 1885 discovered *Escherichia coli* which is a commensal of the human intestine and is found in the sewage, water or soil contaminated by faecal matters. These are Gram- negative rods, 2 to 4 μ, commonly seen in coccobacillary form, which do not form any spore and have 4 to 8 paritrichate flagella, are sluggishly motile, are facultative anaerobes and grow in laboratory media. *E. coli* are generally non-pathogenic and are incriminated as pathogens, because in certain instance some strains have been found to produce

septicemia, inflammation of liver and gall bladder, appendix and other infections and this species is a recognized pathogen in the veterinary field.

4. *Pseudomonas aeruginosa*

Genus: *Pseudomonas*

Pseudomonas is a Greek word (Gr. Pseudo = false, Gr. Monas = a unit) while the word *aeruginosa* is of Latin origin (L. aeruginosa = full of copper rust i.e. green).

Species: *Pseudomonas aeruginosa*

P.aeruginosa is Gram-negative short rod with variable length (1.5-3.0 x 0.5 μm). They are motile by means of one or two polar flagella. Organisms are non-sporulating and non-capsulated, however, few strains possess slime layer up of polysaccharide. Primary habitat of *P.aeruginosa* is human and animal gastro- intestinal tract, water, sewage, soil and vegetation. It is physiologically versatile and flourishes as a saprophyte in warm moist situations in the human environment, including sinks, drains, respirators, humidifiers, etc. *P.aeruginosa* produces several virulence factors, including exotoxin A., proteases, a leukocidin, and phospholipase *C. pseudomonas* is an opportunistic pathogen which is able to cause infections when the natural resistance of the body is low. They are mostly related with hospital infections and post burn infections. They also cause infections of middle ear, eyes and urinary tracts. It is also associated with diarrhoea, pneumonia and osteomyelitis. Due to drug resistant nature of *P. aeruginosa* it causes infection in patients receiving long term antibiotic therapy for wounds, burns and cystic fibrosis and other illness. Approximately 25% of burn victims develop infection which frequently leads to fatal septicemia.

7.3. Evaluation Techniques

The following conditions must be met for the screening of antimicrobial activity:

There should be intimate contact between the test organisms and substance to be evaluated.

Required conditions should be provided for the growth of microorganisms.

Conditions should be same through the study.

Aseptic / sterile environment should be maintained.

Various methods have been used from time to time by several workers to evaluate the antimicrobial activity. The evaluation can be done by the following methods:

1. Turbidometric method.
2. Agar streak dilution method.
3. Serial dilution method.
4. Agar diffusion method.

Following Techniques are used as agar diffusion method:

1. Agar Cup method.
2. Agar Ditch method.
3. Paper Disc method.

We have used the **Agar cup Method** to evaluate the antibacterial activity. It is one of the non automated in vitro bacterial susceptibility tests. This classic method yields a zone of inhibition in mm result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms. It is carried out in Petri plates.

7.4. Experimental

7.4.1. Materials And Methods

The bacteriostatic property of the compounds was tested by disc diffusion method as described by Bauer kirby's method.

[A] Preparation of Mueller-Hinton agar

- Beef Infusion : 300g
- Acid hydrolysate of casein : 17.5g
- Starch : 1.5g
- Agar : 17g
- Dis. Water : 1lit

The above constituents were weighed and dissolved in water. The mixture was warmed on water bath till agar dissolved. This was then sterilized in an autoclave at 15 lbs pressure and 121 ^{o}C for fifteen minutes. The sterilized medium (20 ml) was poured in sterilized Petri dishes under aseptic condition, allowing them to solidify on a plane table.

[B] Preparation of Antibacterial Solution

Compound was taken at concentration of 100 µg/ml for testing antibacterial activity. The compound diffused into the medium produced a concentration gradient. After the incubation period, the zones of inhibition were measured in mm. The tabulated results represent the actual readings control.

[C] Test culture

Escherichia coli	Gram Negative
Pseudomonas aeruginosa	Gram Nagative
Staphylococcus aureus	Gram Positive
Streptococcus Pyogenes	Gram Positive

Candida albicans	Fungus
Aspergillus Niger	Fungus

[D] Inoculum's preparation

The inoculum was standardized at $1*10^6$ CFU/ml comparing with turbidity standard (0.5 MacFarland tube).

[E] Swabs preparation

A supply of cotton wool swabs on wooden applicator sticks was prepared. They were sterilized in tins, culture tubes, or on paper, either in the autoclave or by dry heat.

[F] Experimental procedure

The plates were inoculated by dipping a sterile swab into inoculums. Excess inoculum was removed by pressing and rotating the swab firmly against the side of the tube, above the level of the liquid.

- The swab was streaked all over the surface of the medium three times, rotating the plate through an angle of 60 ºC after each application. Finally the swab was passed round the edge of the agar surface. The inoculation was dried for a few minutes, at room temperature, with the lid closed.
- Ditch the bore in plate. Add compounds solution in bore.
- The plates were placed in an incubator at 37 ºC within 30 minutes of preparation for bacteria and 22 ºC for fungal.
- After 48 hrs incubation for bacteria and 7-days for fungal, the diameter of zone (including the diameter disc) was measured and recorded in mm. The measurements were taken with a ruler, from the bottom of the plate, without opening the lid.

Antibacterial activity of Standard drugs

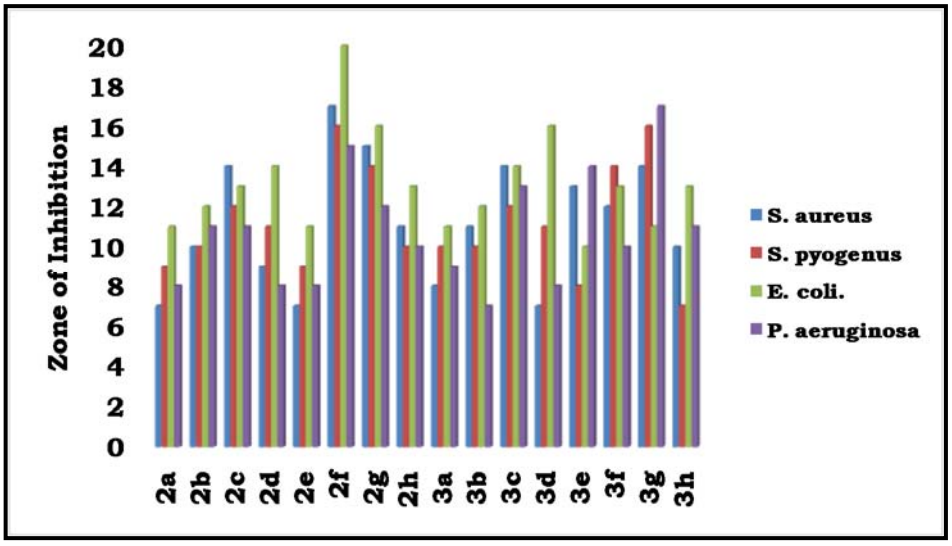
Standard	Zone of inhibition(in mm)			
	Gram Positive		Gram Negative	
	S. aureus	S. pyogenes	E. coli	P. aeruginosa
Chloroamphinocol	20	20	23	19
Ampicilin	22	21	28	26

Antifungal activity of Standard drugs

Standard	Zone of Inhibition(in mm)	
	C. albicans	A. niger
Greseofulvin	27	29

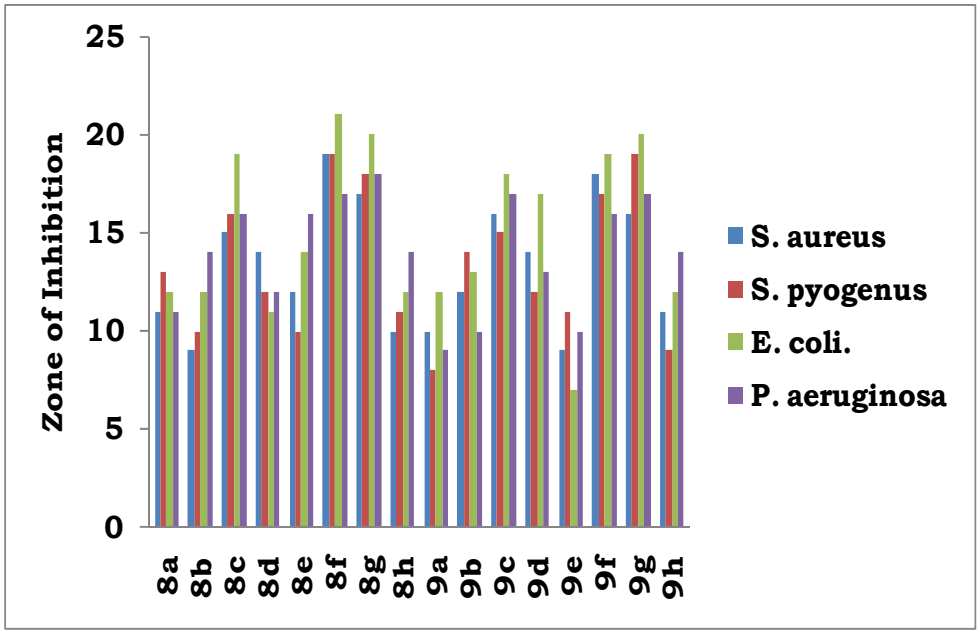
Antibacterial activity of pyrazolone chalcones

Compound	Zone of Inhibition			
	Gram Positive		Gram Negative	
	S. aureus	S. pyogenus	E. coli	P. aeruginosa
2a	07	09	11	08
2b	10	10	12	11
2c	14	12	13	11
2d	09	11	14	08
2e	07	09	11	08
2f	17	16	20	15
2g	15	14	16	12
2h	11	10	13	10
3a	08	10	11	09
3b	11	10	12	07
3c	14	12	14	13
3d	07	11	16	08
3e	13	08	10	14
3f	12	14	13	10
3g	14	16	11	17
3h	10	07	13	11



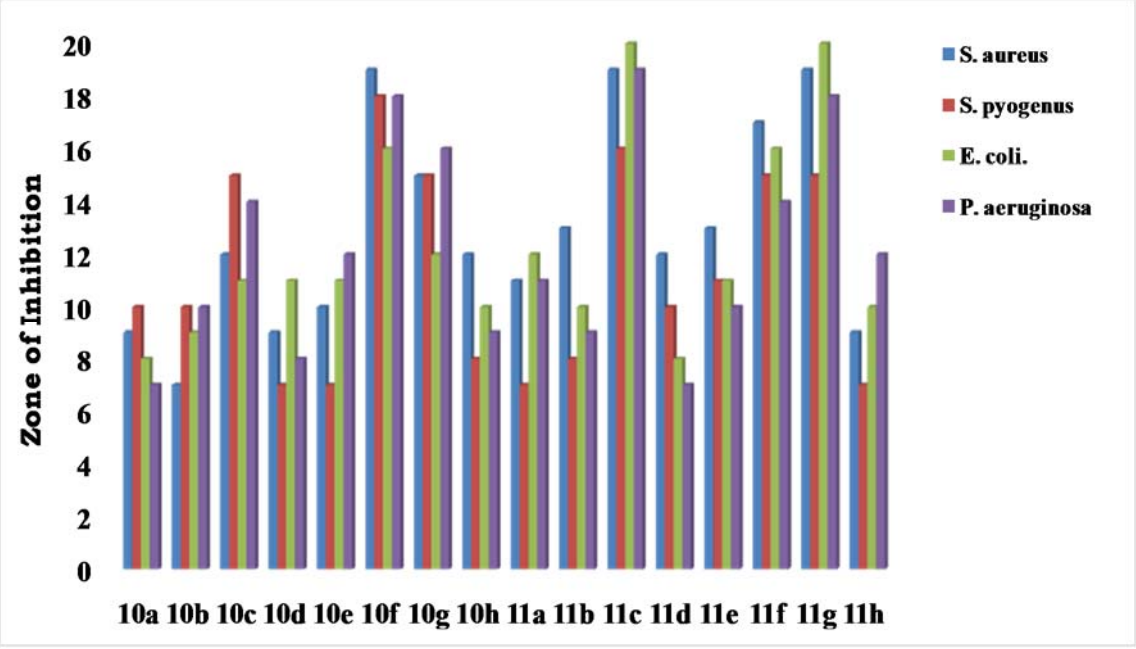
Antibacterial activity of pyrazole derivatie

Compound	Zone of Inhibition			
	Gram Positive		Gram Negative	
8a	11	13	12	11
8b	09	10	12	14
8c	15	16	19	16
8d	14	12	11	12
8e	12	10	14	16
8f	19	19	21	17
8g	17	18	20	18
8h	10	11	12	14
9a	10	08	12	09
9b	12	14	13	10
9c	16	15	18	17
9d	14	12	17	13
9e	09	11	07	10
9f	18	17	19	16
9g	16	19	20	17
9h	11	09	12	14



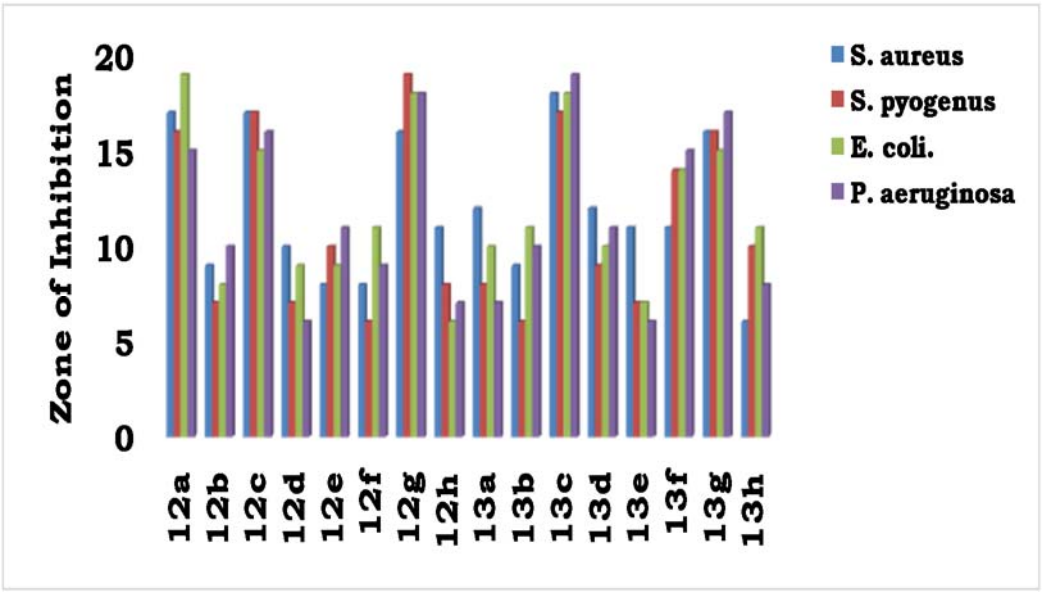
Antibacterial activity of 1,5 Benzothiazepine derivatives

Compound	Minimum Inhibition Concentration			
	Gram Positive		Gram Negative	
10a	O9	10	08	07
10b	07	10	09	10
10c	12	15	11	14
10d	09	07	11	08
10e	10	07	11	12
10f	19	18	16	18
10g	15	15	12	16
10h	12	08	10	09
11a	11	07	12	11
11b	13	08	10	09
11c	19	16	20	19
11d	12	10	08	07
11e	13	11	11	10
11f	17	15	16	14
11g	19	15	20	18
11h	09	07	10	12



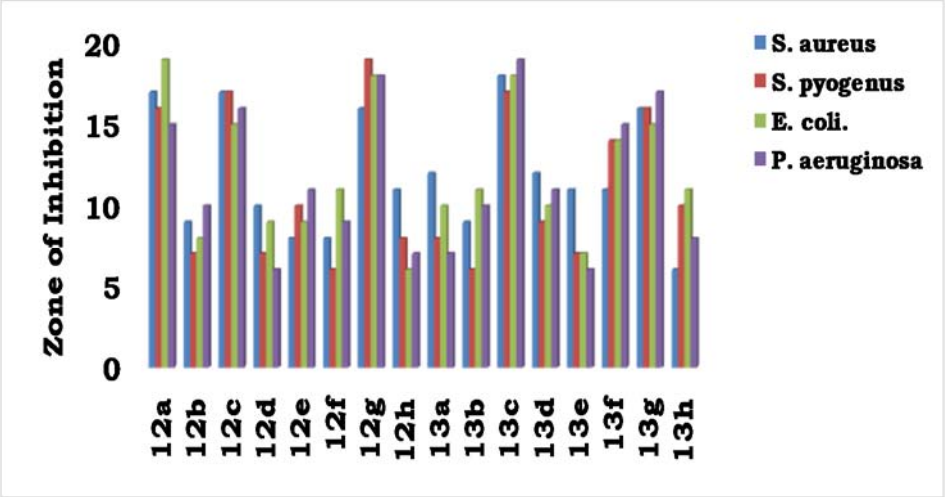
Antibacterial activity of Azetidinone derivatives

Compound	Minimum Inhibition Concentration			
	Gram Positive		Gram Negative	
12a	17	16	19	15
12b	09	07	08	10
12c	17	17	15	16
12d	10	07	09	06
12e	08	10	09	11
12f	08	06	11	09
12g	16	19	18	18
12h	11	08	06	07
13a	12	08	10	07
13b	09	06	11	10
13c	18	17	18	19
13d	12	09	10	11
13e	11	07	07	06
13f	11	14	14	15
13g	16	16	15	17
13h	06	10	11	08



Antibacterial activity of Thiadiazole derivatives

Compound	Zone of Inhibition			
	Gram Positive		Gram Negative	
14a	20	19	19	17
14b	09	06	10	08
14c	08	05	07	06
14d	18	16	17	17
14e	10	08	11	11
14f	09	10	10	12
15a	17	16	19	15
15b	06	05	09	10
15c	09	07	07	06
15d	16	19	18	16
15e	10	08	09	10
15f	11	12	12	09



7.5. ANTIFUNGAL ACTIVITY

7.5.1. Introducton

There are perhaps over 10,000 species of fungi, but less than 100 cause diseases in human.[9] Fungi may cause benign, but unsightly infections of the skin, nail or hair, relatively trivial infection of mucous membranes (thrush) or systemic infection causing progressive often fatal disease.

7.5.2. Classification of Medically Important Fungi [10]

1. True yeasts (e.g. Cryptococcus neoformans)
2. Yeast like fungi that produce a pseudomycelium (e.g. Candida albicans)
3. Filamentous fungi that produce a true mycelium (e.g. Aspergillus fumigatus)
4. Dimorphic fungi that grow as yeast or filamentous fungi depending on the cultural conditions (e.g. Histoplasma capsulatum)

CANDIDA ALBICANS

Genus: C andida

Candida species reproduce by yeast like budding cells but they also show formation of pseudomycellum. These pseudomycellum are chains of elongated cells formed from buds and the buds elongated without breaking of the mothercell. They are very fragile and separate easily. Mycelia also form by the elongation of the germ tube produced by a mother cell.

Species: C andida albicans

Candida albicans may remain as a commensal of the mucous membrane with or without causing any pathologic changes to the deeper tissues of the same fungus may cause pathological lesion of the skin. Such a

fungus under favorable conditions can cause superficial, intermediate of deep mycoses depending on the condition of the host.

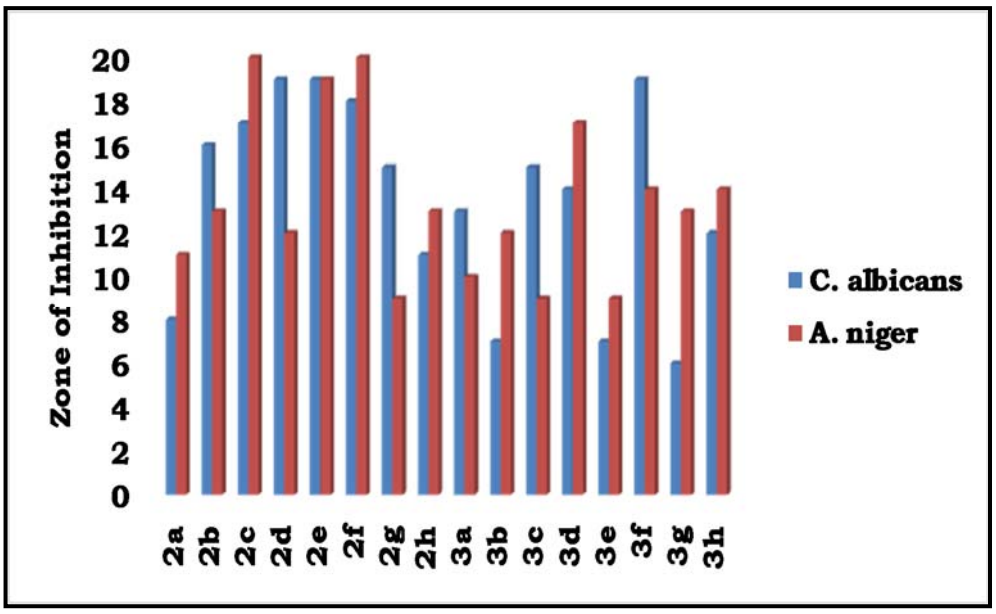
ASPERGILLUS NIGER

Genus: A spergillus

The Aspergilli are widespread in nature, being found on fruits, vegetables and other substrates, which may provide nutriment. Some species are involved in food spoilage. They are important economically because they are used in a number of industrial fermentations, including the production of citric acid gluconic acid. Aspergilli grow in high concentrations of sugar and salt, indicating that they can extract water required for their growth from relatively dry substances.

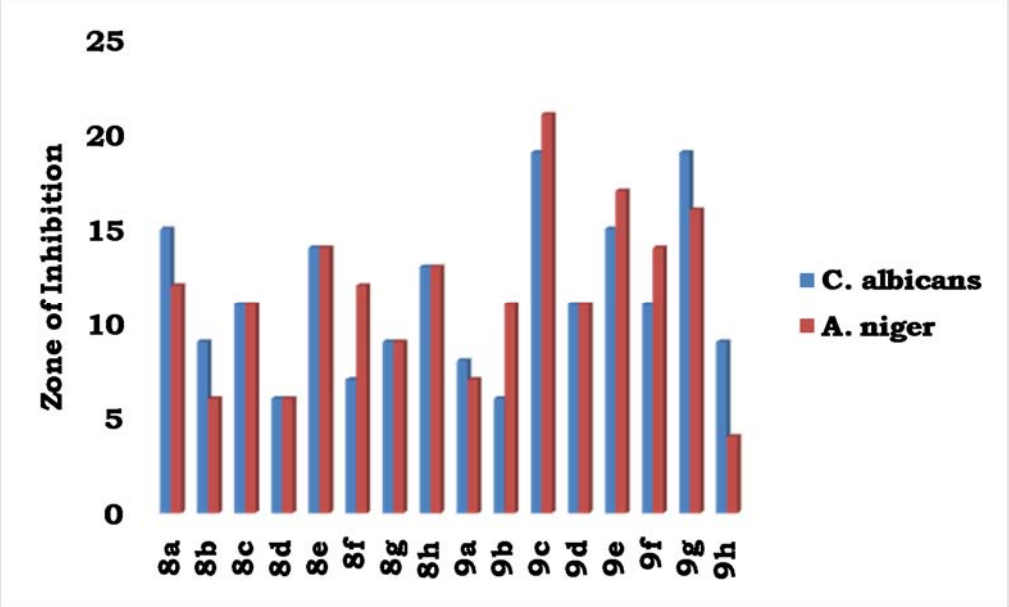
Antifungal activity of Pyrazolone Chalcone (2a-2h & 3a-3h)

Compound	Zone of Inhibition(in mm)	
	C. albicans	A. niger
2a	08	11
2b	16	13
2c	17	20
2d	19	12
2e	19	19
2f	18	20
2g	15	09
2h	11	13
3a	13	10
3b	07	12
3c	15	09
3d	14	17
3e	07	09
3f	19	14
3g	06	13
3h	12	14



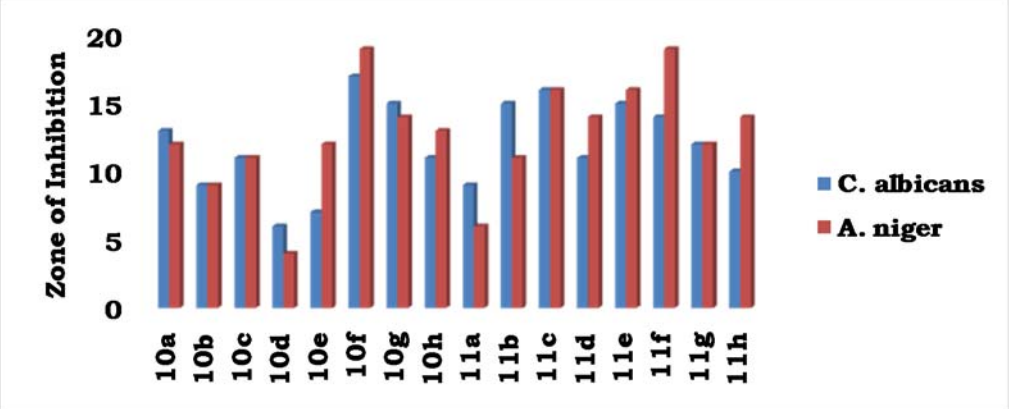
Antifungal activity of Pyrazole derivatives.

Compound	Zone of Inhibition(in mm)	
	C. albicans	A. niger
8a	15	12
8b	09	06
8c	11	11
8d	06	06
8e	14	14
8f	07	12
8g	09	09
8h	13	13
9a	08	07
9b	06	11
9c	19	21
9d	11	11
9e	15	17
9f	11	14
9g	19	16
9h	09	04



Antifungal activity of 1, 5 Benzothiazepine derivatives

Compound	Zone of Inhibition(in mm)	
	C. albicans	A. niger
10a	13	12
10b	09	09
10c	11	11
10d	06	04
10e	07	12
10f	17	19
10g	15	14
10h	11	13
11a	09	06
11b	15	11
11c	16	16
11d	11	14
11e	15	16
11f	14	19
11g	12	12
11h	10	14

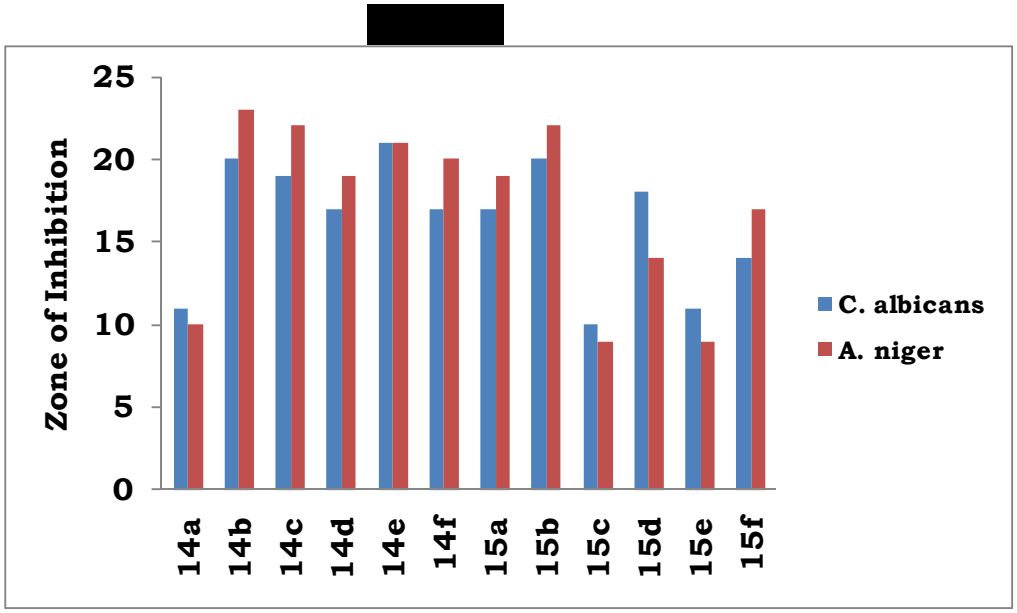


Antifungal activity of Azetidinone derivatives

Compound	Zone of Inhibition(in mm)	
	C. albicans	A. niger
12a	08	07
12b	17	21
12c	17	20
12d	19	19
12e	19	20
12f	11	13
12g	20	22
12h	13	10
13a	17	18
13b	18	14
13c	12	10
13d	06	09
13e	15	14
13f	11	16
13g	19	13
13h	14	11

Antifungal activity of Thiadiazole derivatives

Compound	Zone of Inhibition(in mm)	
	C. albicans	A. niger
14a	11	10
14b	20	23
14c	19	22
14d	17	19
14e	21	21
14f	17	20
15a	17	19
15b	20	22
15c	10	09
15d	18	14
15e	11	09
15f	14	17



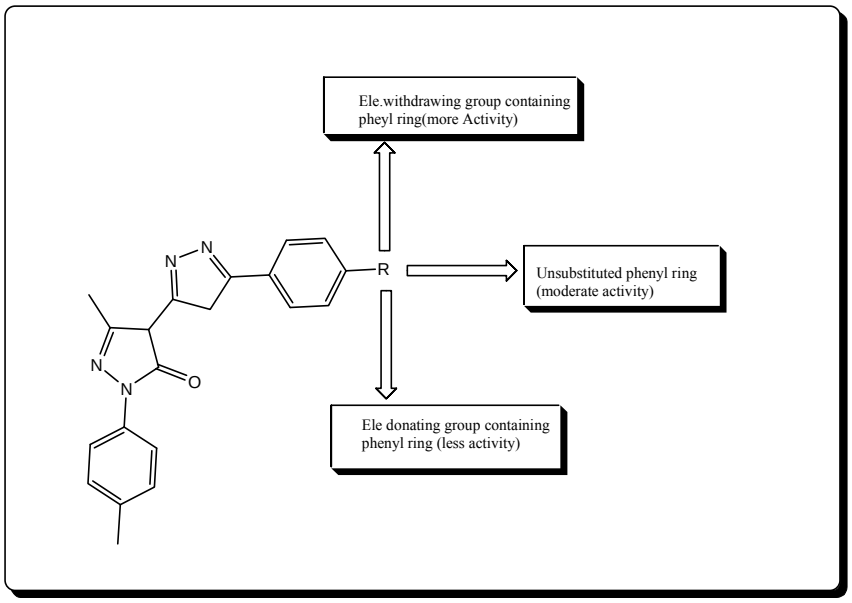
7.6. Result and Discussion

Comparison of Antimicrobial activity of produced compounds with that of standard antimicrobial drugs reveals that the produce chalcones and its derivatives shows moderate to good activity against all four strains.

Antibacterial activity

Among pyrazolone Chalcone compounds **2c, 2f, 2g, 3g, 3c** showed good antibacterial activity.

Among pyrazole derivatives compounds **4c, 4f, 4g, 5c, 5h, 5g** showed potent antimicrobial activity compared to standard drug which might be due to the presence of electron withdrawing substitution like chloro, bromo and nitro groups on phenyl ring attached at C-5 of the pyrazole nucleus. Compounds possessing electron donating substituent like methoxy, methyl and hydroxyl group demonstrate less in vitro antimicrobial activity. SAR studies reveal that compounds possessing an electron- withdrawing group displayed better activity than the compound containing ele. donating groups, whereas the unsubstiuted derivative displayed moderate activity.



Among Benzothiazepine derivatives **6f, 7c, 7f, 7g** showed good antibacterial activity. When the results of antibacterial activity of the chalcones compared with those of the 1,5- benzothiazepines, it is evident that the chalcones were more potent than the 1,5- benzothiazepines in most of the cases indicating the cyclization into 1,5-benzothiazepines reduced the activity. However, among the 1,5-benzothiazepines showing the activity against compounds with electron withdrawing groups enhanced the activity, a similar observation seen in the case of chalcones. The results also indicated the contribution of α,β-unsaturated carbonyl group present in chalcones in enhancing the activity.

Among Azetidinone derivatives compounds **8a, 8c, 8g, 9c, 9g** showed good antibacterial activity.

Among Thiadiazole derivatives compounds **10a, 10d, 11a, 11d** showed good antibacterial activity.

Antifungal activity

From the above results, it is evident that most of the compounds showed moderate to good activity.

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Summary

Chemistry of heterocyclic compounds continues to be as an important field related to medicinal chemistry. Finding useful therapy to any disease is most important and integral part of the history of the main kind. The normal procedure to prepare novel class of agents is to explore the representative moiety which may be a known synthetic or the natural medicinal agents. The present work is planned to correlate reactivity of several class of organic and heteroaryl compounds interns of their structure and pharmacological profiles. This helps to establish new modern synthetic drugs for a diverse biological applications as an attempt to overcome resistance to organisms the following class of compounds were synthesized.

- Pyrazole derivatives from Chalcones
- 1,5 –Benzothiazepine derivatives from Chalcone
- Azetidinone derivatives from schiff bases
- Thiadiazole derivatives from schiff bases

The anti bacterial and antifungal activities carried out for synthesized compounds.

- **Pyrazole derivatives from Chalcones**

Chalcone and its derivatives like pyrazoles have attracted particular interest due to the use of such ring system as the core structure in many drug molecules covering wide range of pharmaceutical and medicinal applications. The prevalence of pyrazole derivatives in pharmacologically effective drug molecules has increased the necessarily for needful ways to make them as an important lead moiety in heterocyclic chemistry. Several pyrazoline analogues are known to have

biological properties which necessitated the research work in this field. The present work provided an insight view to pyrazole synthesis and their biological activities. The chalcones required for the preparation of pyrazolines were obtained from Acetyl pyrazolones and substituted aromatic aldehydes. The chalcones reacted with hydrazine hydrate to get required pyrazole derivatives. The pyrazole derivatives were established on the basis of their elemental analysis and spectral studies like IR, ^{1}H NMR and Mass.

The above compounds were screened for their antibacterial and antifungal activity. The bacterial screening of the compounds revealed that the majority of the compounds posses moderate to good activity and week to moderate antifungal activity.

- **Benzothiazepine derivatives from Chalcones**

Benzothiazepines are seven member heterocyclic compounds now a day they have received considerable attention and claimed various therapeutic activities and hence, they utilized in drug research. Chalcones reacted with 2- aminothio phenol to get required derivatives. The Benzothiazepine derivatives were characterized by elemental analysis, IR, ^{1}H NMR and Mass.

The above compounds screened for their antimicrobial activity. The majority of compounds were posses moderate to good activity.

- **Azetidinone derivatives from schiff bases**

The β-lactum antibiotics are extensively used for bacterial infections. In addition a large number of antibiotics contain 2-azetidinone moiety such as penicillin, cephalo sporins and carbepenams, which are associated with a variety of therapeutic activities. Hence 2- azetidinones were prepared following the general

procedure. The Schiff Bases on reaction with aryl chloride furnished the azetidinone derivatives. 2-azetidinone derivatives were established on the basis of IR, ^{1}HNMR, and mass spectral studies. The spectral data were in full agreement with the expected structure of the compounds synthesized. All the compounds of 2-azetidinone series were screened for antibacterial and antifungal activities by the known standard procedures. The compounds exhibited significant to moderate antimicrobial activity.

- **Thiadiazole derivatives**

Schiff bases cyclization with Fe^{+3} produced Thiadiazole compounds. All the Thiadiazole compounds were established on the basis of elemental analysis and their spectral analysis like IR, ^{1}H NMR and mass. All the compounds screened for antimicrobial activity. The compounds show moderate to good activity.

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Synthesis characterization and antimicrobial studies of Fe (III) complexes of thiaosemicarbazide

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ABSTRACT

Some Schiff base derived from 4 -thiosemicarbazone -3-methyl–1-[4-nitrophenyl]-2-pyrazoline -5-one with benzoyl chloride, acetyl chloride, propionyl chloride, p-toluyl chloride. The structures of new compounds were established on the basis of elemental IR and ^{13}C-NMR data, the compounds were evaluated for their antibacterial activities.

Keywords: Thiosemicarbezide, TGA, Antimicrobial activity, Spectral studies

INTRODUCTION

In the Synthetic chemistry, Thiosemicarbazide (TSC) is interesting molecule due to various organic revolutions in which they can take part. The chemistry of thiosemicarbazone complexes of the transition metal ions has been receiving potential attention because of the straight functional mobility of these complexes on the bio system [1]. The anti-proliferative properties of thiosemicarbazones have been attributed to their ability to chelate metal ions because of the presence of an NNS (Nitrogen–Nitrogen–Sulfur) tridentate set of donor atoms that bind not only iron, but also copper, nickel, zinc [2-5]. Most of the derivatives of the thiosemicarbazone and their metal complexes are well known for their wide range of biologically activities that include cytotoxic, anti-bacterial, anti-fungal, anti-tumor, anti-malarial and anti-leukemic [6-11]. We are reporting synthesis, characterization, TGA and Anti-microbial properties of thisemicarbezone adduct of Fe (III) derived from B_tMNPO, AtMNPO, P_tMNPO, and TtMNPO.

MATERIALS AND METHODS

Experimental

All the chemicals used in the present study were of A. R. grade. Melting points were taken in open glass capillaries. The ligands were analyzed for Carbon, Hydrogen, Nitrogen and Sulfur were estimated on a Perkin Elmer, Series II, 2400 C H N S analyzer (CSIR, Bhavnagar, India). The infrared spectra of the ligands were recorded on a FT-IR in KBr pellets (Gujarat Laboratory, Ahmedabad, India). The ^{13}C-NMR spectra in DMSO of all ligands were recorded on a Bruker DRX - 200 FT - NMR spectrophotometer.

Synthesis of ligands

The following procedure has been used in the preparation of all ligands B_tMNPO, A_tMNPO, P_tMNPO, and TtMNPO.

The Acylthiosemicarbazones were prepared by refluxing 1: 1 mole of 4 – Acyl - 3 - methyl - 1 – [4′ - nitrophenyl] - 2 - pyrazolin - 5 - one and thiosemicarbazide hydrochloride in ethanol for two hours on water bath. The resulting mixture was allowed to stand overnight. The solid product thus obtained was collected by filtration, washed with water and air dried. The acylthiosemicarbazones were then recrystallized in ethanol.

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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF PYRAZOLINE DERIVATIVES DERIVED FROM CHALCONE

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ABSTRACT

A Chalcone was prepared by the reaction of 4-acetyl-5-methyl-2-(4-methylphenyl)-2, 4-dihydro-3H-pyrazole-3-one with different substituted aldehydes. Treatment of this Chalcone with hydrazine hydrate afforded the corresponding pyrazoline in good yields. All the new compounds have been characterized by IR, ^{1}H-NMR, GC-MS and element analysis. The antibacterial activity of these compounds was determined with the reference of standard drug.

KEYWORDS: Chalcone, Pyrazoline, Antibacterial activity.

INTRODUCTION

Heterocyclic nitrogenous compounds and their fused analogs represent in important class of heterocyclic compounds. They exist in numerous natural products and display a wide range of biological and pharmaceutical activities. α, β-Unsaturated ketones are biogenetic precursors of flavonoids in higher plants. Also known chemically as Chalcone, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three carbon chain.[1] They display a wide range of pharmacological properties, including cytotoxity towards cancer cell lines[2,3], antimitotic[4], antimutagenic[5] and antitumor-promoting activities; antibacterial[6], antiviral[7], anti-inflammatory[8], antiulcerative[9] and hepatoprotectiv activities.[10] They are also useful in materials science fields such as non-linear optics (NLO)[11], optical limiting[12], electrochemical sensing[13], Langmuir films and photo initiated polymerization.[14] Various Chalcone derivatives are notable materials for their second harmonic generation (SHG)[15] They are well known intermediates for synthesizing various heterocyclic compounds. Cyclization of Chalcone, leading to thiazines,

SYNTHESIS, CHARACTERIZATION OF SOME NEW CHALCONE ANALOGUES CONTAINING CYCLOHEXENONE DERIVATIVES

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SUBJECT:
KEYWORDS: Chalcone, Cyclohexenone, Antibacterial activity, Spectral studies

ABSTRACT

Base catalysed condensation of ketone 1 with different aldehydes give chalcones (E)-4-(3-(4-chlorophenyl) acryloyl)-5-methyl-2-(p-tolyl)-1H-pyarazol-3(2H)-one [3a-e]. These chalcones on cyclization with ethyl acetoacetate in presence of base give [5a-e] respectively.The product 5a-e were fully characterized by using spectral techniques like IR, ^{1}H NMR,All these compounds were screened for anti-fungal, anti-bacterial and activity. Cyclohexene derivatives, in general, showed better anti-fungal and anti-bacterial activity than parent chalcones.

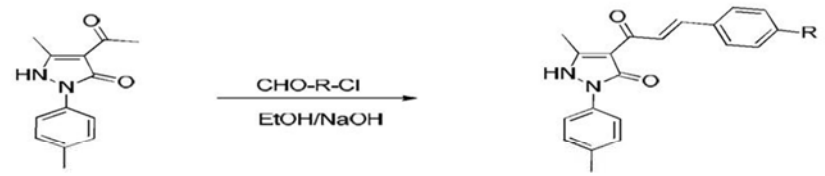
INTRODUCTION

1,3-Diaryl-2-propen-1-ones, commonly known as chalcones are prominent secondary metabolites and precursors of flavonoids and is flavonoids in plants, these compounds are usually prepared by base or acid catalyzed aldol condensation between aromatic aldehydes andketones under the homogeneous condition. . They serve as starting material for the synthesis of a variety of heterocyclic compounds that are of physiological significance. Because of their different functionalities, these compounds confer biological activities, such as synthons for the production of fiveandsix-member ring systems [1,2] for example Pyrazoles[3],Pyrazolines[4], isoxazolines[5], aurones[6], pyrimidine [7],falvanones[8] and di-aryl cyclohexenones[9]. The biological activities of chalcones are equally wide ranging. In fact, not many structural templates can claim association with sucha diverse range of pharmacological activities, among which antimicrobial [10], anti-leishmanial[11], anti-malarial [12], antifungal [13], anti-viral [14], anti-inflammatory [15], cytotoxicity [16], anti-tumor [17], nematicidal[18] and anti-oxidant [19] are widely cited.

In the presence of basic catalysts Chalcones and their hetero-analogs is the ability to act as activated unsaturated systems in conjugated addition reactions of carbanions.[20-21]. this type of reaction more commonly used for preparation of 3, 5-diaryl-6-carbethoxycyclohexenones via addition of ethyl acetoacetate[22]

The cyclohexenones are efficient synthons in building of spiranic compounds or intermediates in the synthesis of fused heterocycles, such as benzoselenadiazoles and benzothiadiazoles, benzopyrazoles,benzisoxazoles, carbazole, indazole derivatives and etc. [23-28]

Scheme-1



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Research Article

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Synthesis, characterization and biocedal activities of pyrazole compounds derived from chalcone

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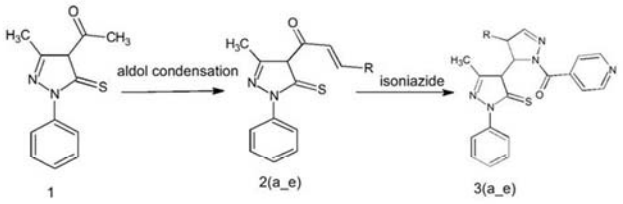
ABSTRACT

The 1- (3-Methyl-1-Phenyl-5-thioxo-4,5-dihydro-1H-Pyrazole-4-yl)-Ethanone condensation with various substituted aldehydes was yielding various Chalcone. Further this Chalcone conversed into pyrazole by condensation with various synthesized Chalcone with isoniazide. In the present research article a new series of pyrazole derivatives have been synthesized. The structure of newly synthesized compounds is characterized on the basis of IR, ^{1} H NMR, Mass spectroscopes and elemental analysis. The newly synthesized compounds were studied for biocedal activity.

Key words: Synthesis, Chalcone, isoniazide, pyrazole, spectral studies and biocedal activity

INTRODUCTION

The discovery and development of antimicrobial agent are among the most significant and successful achievements of modern science and technology for the control of plants and human pathogenic microbes. Pyrazoline are well known important nitrogen containing five member heterocyclic compounds. They process a broad spectrum of biological activities viz antibacterial, antifungal, antitumor, antidepressant, anticonvulsant, insecticidal and antiiocieptive. pyrazoline is used extensively as useful synthon in organic synthesis. The chemistry of Chalcone has generated intensive scientific interest due to their biological and industrial application. Chalcone are exhibiting various biological activities, such as antioxidant, anti-inflammatory, anti malarial, anticancer and antitileshamanial. In addition, Chalcone are very important compounds as a Michael acceptor in organic synthesis. In continuation of our earlier research work, the facile synthesis of pyrazole derivatives from Chalcone and isoniazide in the presence of pyridine is described in scheme 1.The synthesized compounds were evaluated for its antifungal and antibacterial activity.



where (a) Ph (b) 2 - $CH_3C_6H_4$ (c) 2 - OHC_6H_4 (d) 4 - OHC_6H_4
(e) 4 - $OCH_3C_6H_4$ (f) 4 - $CH_3C_6H_4$ (g) 4 - ClC_6H_4 (h) 4 - BrC_6H_4

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Synthesis and characterization of biologically potent chalcone bearing 1,3,4-oxadiazole linkage

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ABSTRACT

In this article, we have described to design and synthesized a series of substituted chalcone based 1,3,4-oxadiazole derivatives. Titled compounds (E)-S-(-5-phenyl-1,3,4-oxadiazol-2-yl) 2-(4-(3-(5-methyl-3oxo-2(p-tolyl)-2,3-dihydro-1H-pyrazol-4-yl)-3-oxoprop-1-en-1-yl)phenoxy) etanethioate (**III$_{1-6}$**) were synthesized using of derivatives of S-(-5-phenyl-1,3,4 oxadiazole-2-yl)2-chloroethaethioate (**I$_{1-6}$**) were reacted with (E)-4-(3-(4-hydroxyphenyl)acryloyl)-5-methyl-2(*p*-tolyl)-1H-pyrazol-3(2H)-one (**II**) in presence of K_2CO_3 in DMF as a solvent. The synthesized compounds were evaluated for their antimicrobial activity. The newly synthesized compounds were characterized by analytical and spectral (IR, ^{1}H NMR, and LC-MS) Methods.

1. INTRODUCTION

The versatility of chalcone and its wide range of applicability in medicinal chemistry have attracted scientists all over the globe to concentrate their research around it. They consist of open-chain flavonoids in which the two aromatic rings are joined by a three carbon chain [1]. Chalcones are natural biocides [2] and well known as intermediates for synthesizing of various heterocycles which have impressive array of biological activities; antibacterial [3], antiviral [4], anti-inflammatory [5],antiulcerative [6],antimalarial [7], anticancer [8].In addition, benzofuran derivatives are nowadays an important class of organic compounds that occur in a great number of natural products [9].

The small nitrogen and oxygen containing molecules have been under investigation since long because of their important medicinal properties. 1,3,4-oxadiazole is commonly utilized pharmacophore has been subjected to extensive study in the recent years due to their metabolic profile and ability to engage in hydrogen bonding with receptor site. 1,3,4-Oxadiazoles are an important class of heterocyclic compounds with a wide range of biological activities such as antiviral [10], antimicrobial [11], antineoplastic [12], fungicidal [13], anticancer [14,15], inhibition of tyrosinase [16], They are also useful intermediates in organic synthesis [17] and widely employed as electron transporting and hole-blocking materials.

In the present communication, we report here a series of hybrid heterocyclic scaffolds by clubbing chalcone with 1,3,4-oxadiazole [18], In this present study. The structures of the various synthesized compounds were assigned on the basis of infrared (IR), proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) spectral data, and elemental analysis.

Conference

Presented a paper entitled Synthesis, Spectral characterization and Antimicrobial activity of Fe(III) and Cr (III) complexes of 4- carboxaldehyde 2,4-dinitrophenyl hydrazone-3-methyl-pyrazole-5-one at UGC sponsored National conference on "**latest Developments in Basic and Applied Sciences**" Organized by M. B. Patel science college, Ananad on Saturday , 10th January 2015

Attended a National seminar on "Confluence **of Superamolecular Chemistry & Nanoscience**'' Organized by Department of Chemistry School of Science, Gujarat uni, Ahemedabad, on 27th & 28th March.

Presented a paper entitled Synthesis and Characterization of some new chalcone analogues containing cyclohexanone derivatives in National conference on " **Recent Research Trends in All Subjects**" held on 17th Aug at Junagadh.

Attended an International conference on "**Recent Trends in Applied Sciences: Building the Institutional and Industrial Avenues**" at A.N.Patel Post graduate institute Anand on 10th-12th December 2015.

Presented a paper at UGC sponsored National seminar on " **Spectrocopy and Stereo Chemistry**" organized by J & J science College , Nadiad on 19th December.

Participated in short-term training programme on "**Instrumental methods of Chemical Analysis"** during July 25-29, 2016.