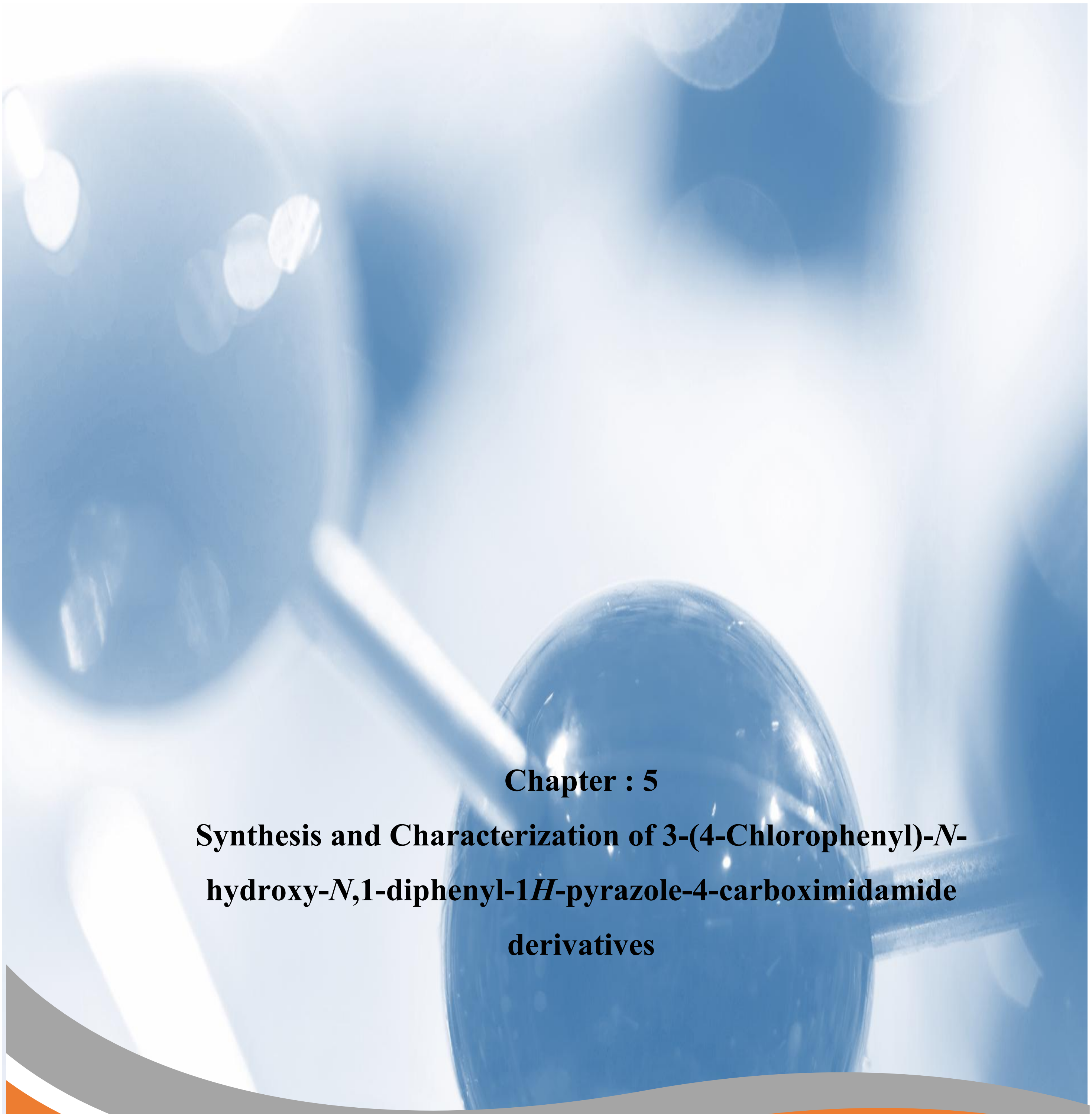


# Chapter : 5

# Synthesis and Characterization of 3-(4-Chlorophenyl)-*N*-hydroxy-*N*,1-diphenyl-1*H*-pyrazole-4-carboximidamide derivatives

# 5. Study on Pyrazole:

## 5.1 Introduction:

Pyrazole is a remarkable and extensively studied five-membered aromatic heterocycle with a distinctive ring structure comprising two adjacent nitrogen atoms. This class of compounds has been a subject of significant scientific interest and exploration, given its versatile properties and wide-ranging applications in diverse fields, including chemistry, biology, agrochemicals, and pharmaceuticals.[321]

The pyrazole ring system consists of four carbon atoms and one nitrogen atom, forming a planar structure with a conjugated π-electron system. Its unique molecular arrangement contributes to its distinct chemical and physical properties. The synthesis and study of pyrazole derivatives have been central to the development of various applications owing to their reactivity and stability.[322] One of the notable features of pyrazoles is their aromaticity, which arises from the resonance stabilization of the nitrogen lone pair electrons with the π-electron system of the ring. This aromatic character imparts special reactivity and stability to pyrazoles, making them key building blocks for the construction of more complex structures in organic chemistry.[323]

In the realm of organic synthesis, pyrazoles have become essential precursors and intermediates. The synthesis of pyrazoles involves diverse methods, including cyclization reactions, condensations, and multi-step procedures. These methods enable the preparation of a wide array of pyrazole derivatives with varying substituents, offering a rich palette for the design and creation of novel compounds.[324]

Pyrazoles have found widespread applications in medicinal chemistry and drug discovery. Many pharmaceutical compounds with pyrazole moieties have exhibited promising bioactivities, leading to the development of therapeutic agents targeting various diseases. The pharmacological activities of pyrazole-containing compounds include anti-inflammatory [325] [326] , anticonvulsant [327] , antiangiogenic [328] , antipyretic[329], antitumor[330], antitubercular[331], [332], antimicrobial[333], [334], antiviral, and antifungal properties. [335] One notable example is the class of non-steroidal anti-inflammatory drugs (NSAIDs), which often feature a pyrazole ring in their structures. These drugs are widely used to alleviate pain, reduce inflammation, and treat various conditions, showcasing the therapeutic significance of pyrazole-containing compounds in the field of medicine. [336] In the agrochemical industry, pyrazoles also play a pivotal role. Pesticides and herbicides containing pyrazole moieties have been developed for crop protection, offering effective solutions for pest, and weed control. The unique properties of pyrazoles contribute to the design of agrochemicals that are environmentally friendly and exhibit enhanced selectivity.[337]

The biological activities of pyrazole derivatives extend beyond medicinal and agricultural applications. They have been explored for their potential as antioxidants, enzyme inhibitors, and ligands in coordination chemistry. The ability of pyrazoles to interact with metal ions has led to the development of novel coordination complexes with diverse properties and applications in catalysis and materials science.[338]

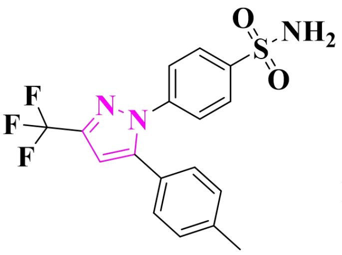
The study of pyrazoles has been facilitated by advancements in analytical techniques, including spectroscopy, chromatography, and crystallography. These techniques provide valuable insights into the structural elucidation, reactivity, and behavior of pyrazole-containing compounds, further advancing our understanding of their properties and applications.[339]

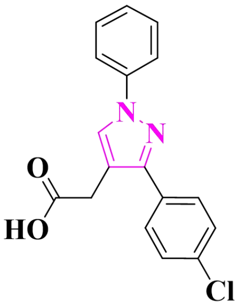
In conclusion, pyrazole stands as a fascinating and multifaceted class of compounds with a rich history of exploration and utilization. Its unique structure, aromatic character, and versatile reactivity have positioned pyrazoles at the forefront of research in various scientific disciplines. As ongoing studies continue to uncover new facets of pyrazole chemistry, it is evident that this class of heterocycles will continue to contribute significantly to advancements in chemistry, biology, medicine, agriculture, and materials science.

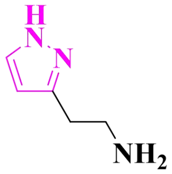
In recent times, pyrazole systems have garnered increased interest as biomolecules, owing to their noteworthy pharmacological properties. This heterocycle is discernible in numerous established drugs spanning various categories, each exhibiting diverse therapeutic activities.[20-26]

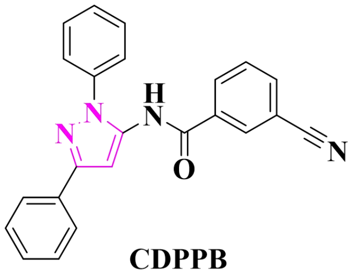
- **Medications incorporating the pyrazole nucleus are currently available in the market:**

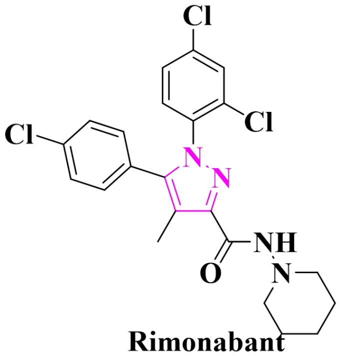
- Celecoxib as Anti-inflammatory [347]
- Lonazolac as Anti-inflammatory agent[348]
- Betazole as $H_2$-receptor agonist [349]
- CDPPB as Anti-psychotic[350]
- Rimonadant as Anti-Obesity[351]
- Difenamizole as Analgesic[352]
- Fipronil as Insecticide [353]
- Fezolamine as Anti-depressant[354]

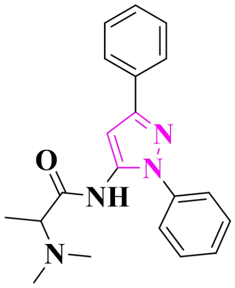

**celecoxib**

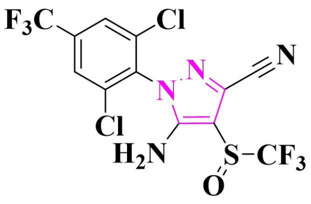

**Lonazolac**


**Betazole**


**CDPPB**


**Rimonabant**


**Difenamizole**


**Fipronil**

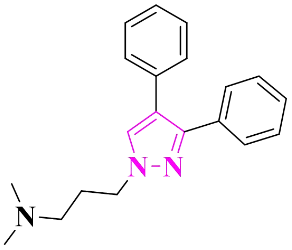
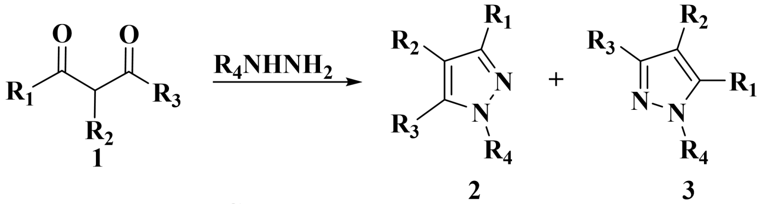

**Fezolamine**

Fig.5.1: Pyrazole nucleus are currently available in the market

## 5.1 Common Procedures for pyrazole Synthesis:

The predominant approach for synthesizing substituted pyrazoles involves a cyclocondensation reaction wherein an apt hydrazine, functioning as a bidentate nucleophile, reacts with a carbon unit such as a 1,3-dicarbonyl compound, its derivatives, or an α, β-unsaturated ketone.[355]

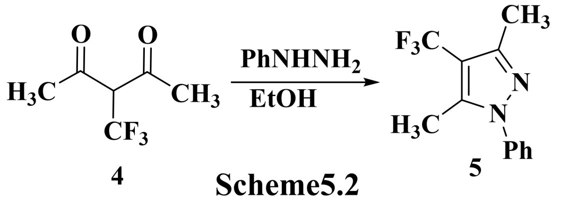
The cyclocondensation reaction between 1,3-dicarbonyl compounds and hydrazine derivatives represents a straightforward and expeditious method for the synthesis of polysubstituted pyrazoles. In 1883, Knorr [356] conducted the initial synthesis of substituted pyrazoles by reacting β-diketone **1** with hydrazine derivatives, resulting in the formation of two regioisomers, namely **2** and **3**.**(Scheme5.1)**



$R_1=R_2=R_3=R_4=H,CH_3$

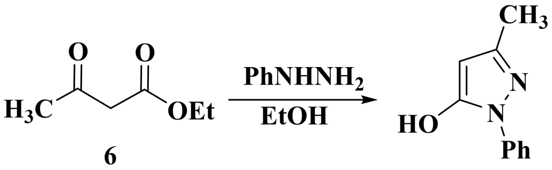
**Scheme5.1**

Ohtsuka et al., [357] Investigations were conducted on the condensation reaction between phenylhydrazine and 2-(trifluoromethyl)-1,3-diketone **4** in ethanol, resulting in the synthesis of 1,3,4,5-substituted pyrazole **5** with a favorable yield of 60-63%. **(Scheme5.2)**



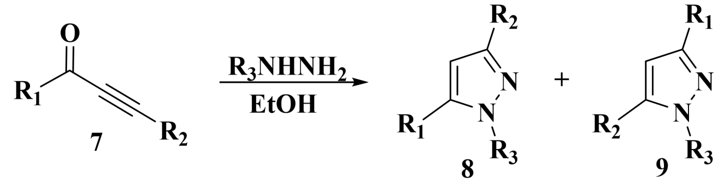
**Scheme5.2**

Girish et al.,[358] reported the synthesis of 1,3,5-substituted pyrazole derivatives were achieved by condensing phenylhydrazine with ethyl acetoacetate **6** in the presence of a catalytic amount of nano-ZnO, resulting in good yields. This technique offers notable advantages, including a rapid response time and a straightforward work-up procedure. **(Scheme5.3)**



**Scheme5.3**

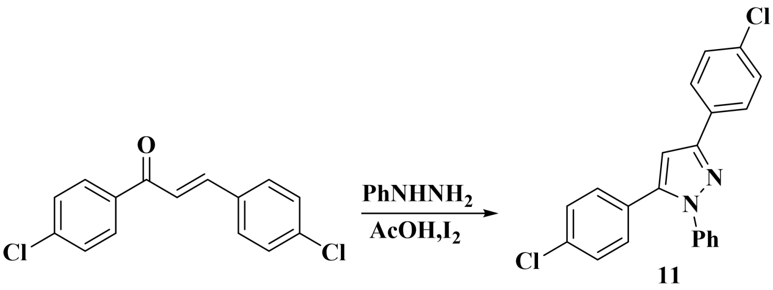
Moureu et al., [359] reported the cyclocondensation reaction between hydrazine derivatives and acetylenic ketones **7**, a well-acknowledged process for over a century, leads to the formation of pyrazoles. Nevertheless, this reaction typically results in the production of a mixture comprising two regioisomers **8** and **9**. **(Scheme5.4)**



**$R_1$=$R_2$=H,$CH_3$;$R_3$=ph**

**Scheme5.4**

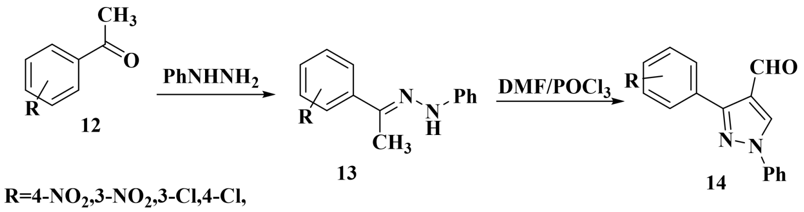
Ponnala et al.,[360] reported method for synthesizing 1,3,5-trisubstituted pyrazoles **11** involves the reaction of α, β-ethylenic ketones **10** with phenylhydrazine in acetic acid, facilitated by a catalytic amount of iodine. **(Scheme5.5)**



**10** **Scheme5.5**

Pyrazole compounds containing an aldehydic functional group, such as 1*H*-pyrazole-4-carbaldehyde and its derivatives, are highly valued as intermediates in the production of drugs. The pyrazole derivatives discussed in this thesis are produced from 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde. Below, we present the biological and synthetic properties of 1*H*-pyrazole-4-carbaldehydes.

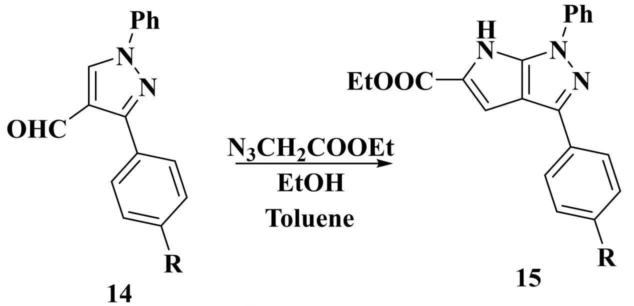
Shapranova et al., [361] reported the Vilsmeier-Haack reaction was used to yield 3-substituted-1-phenyl-1*H*-pyrazole-4-carbaldehydes **14** by reacting suitable phenylhydrazones **13** with aryl methyl ketone **12** and phenylhydrazine. **(Scheme5.6)**



R=4-NO$_2$,3-NO$_2$,3-Cl,4-Cl,
3,4-CH$_3$,4-CH$_3$,3-CH$_3$

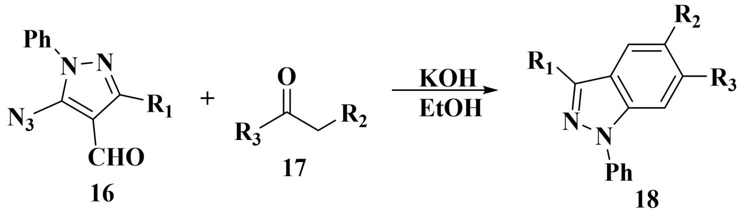
**Scheme5.6**

Aly et al., [362] reported synthesis initiated Heating 3-aryl-1-phenyl-1*H*-pyrazol-4-carbaldehydes **14** with ethyl azidoacetate in ethanol and then heating in toluene at reflux resulted in pyrrolo[2,3-c]pyrazole derivatives **15**. **(Scheme5.7)**



**Scheme5.7**

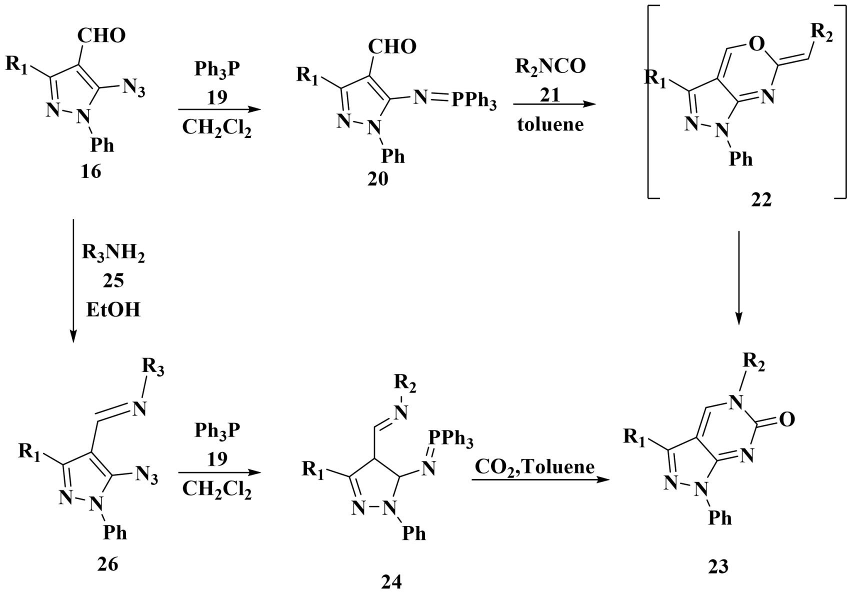
Zheng et al., [363] reported one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes **16** with arylethanone, acetone, acetylacetone, or benzoylacetone **17** in an ethanolic KOH solution yielded the corresponding pyrazolo[3,4-*b*]pyridine derivatives **18**. formation of **18** can be described by the diazo-transfer process, that utilizes 5-azidopyrazole-4-carboxaldehyde **16** and ketones, and the Friedlander reaction, which combines 5-amino-1-phenylpyrazole-4-carboxaldehyde as well as ketones. **(Scheme5.8)**



R$_1$=CH$_3$,C$_6$H$_5$;R$_2$=H,COCH$_3$;
R$_3$=C$_6$H$_5$,4-CH$_3$C$_6$H$_5$,4-OCH$_3$C$_6$H$_5$,CH$_3$

**Scheme5.8**

Molina et al., [364] reported the treatment of 5-azido-3-substituted-1-phenyl-1*H*-pyrazole-4-carbaldehyde **16** with aromatic amines **25** in ethanol resulted in 1-(5-azido-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*-arylmethanimines **26**. To create iminophosphoranes **20** and **24**, 5-azidopyrazoles **16** and **26** were combined with triphenylphosphine **19** in a conventional Staudinger reaction. The reaction Iminophosphorane **20** was combined with isocyanates **21** to create pyrazolo[3,4-d]pyrimidines **23**. The **20** to **19** conversion starts with an aza-Wittig reaction between 5-((triphenylphosphaneylidene)amino)-1*H*-pyrazole-4-carbaldehyde **20** and isocyanate **21**, resulting in a carbodiimide. This carbodiimide then undergoes electrocyclic ring closure, resulting in an unstable 3-substituted-*N*,1-diphenylpyrazolo[3,4-*d*][1,3]oxazin-6-imine **22**. In a typical Dimroth rearrangement, the latter molecule undergoes ring-opening and closure **23**. **(Scheme5.9)**

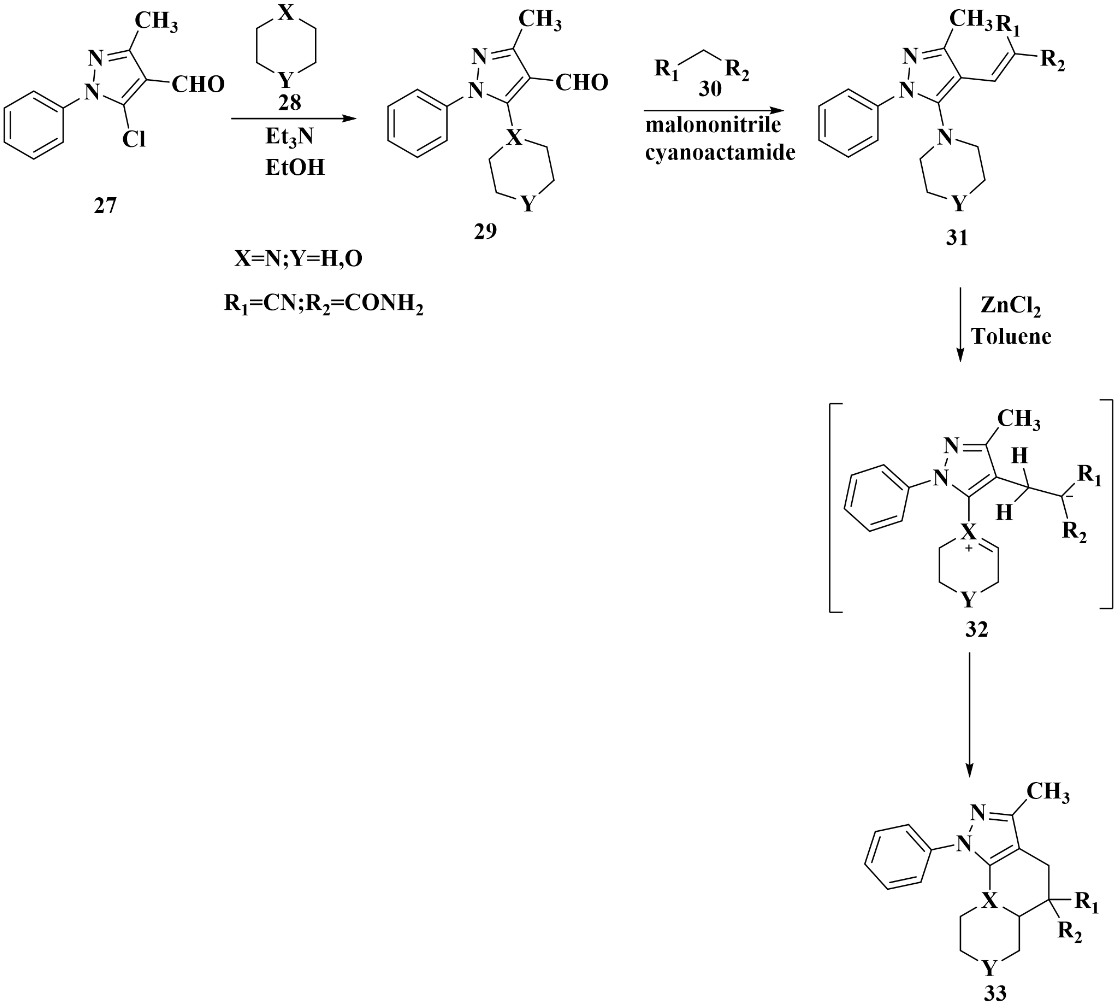


**$R_1$=$CH_3$;$R_2$=$C_6H_5$,4-$CH_3$-$C_6H_4$;**
**$R_3$=$C_2H_5$,$CH_2$=CH-$CH_2$,3-Cl-$C_6H_4$,**
**4-Cl-$C_6H_4$,4-$OCH_3$-$C_6H_4$**

**Scheme5.9**

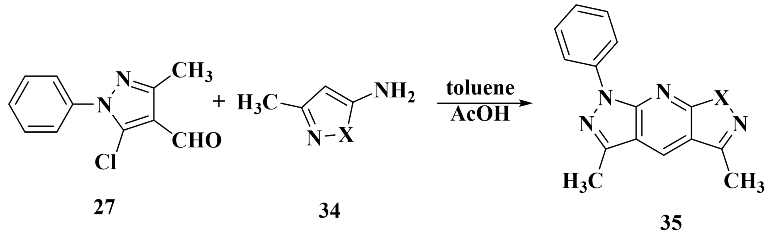
Prajapati et al., [365] reported the 5-chloro atom in 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde **27** is easily replaced by nucleophiles. As a result, when coupled with cyclic secondary amines **28** such as pyrrolidine, piperidine, and morpholine, it smoothly converts into the 5-tert-amino derivatives **29**. Subsequently, these compounds were employed in Knoevenagel condensation reactions with malononitrile to yield the corresponding pyrazolin-5-ylmethylenemalonodinitriles.

These materials subsequently underwent cyclization in the presence of anhydrous zinc chloride, resulting in the formation of the their respective pyrazolinoquinolizines and 1,4-oxazinopyrazolines **33**. **(Scheme5.10)**



**Scheme5.10**

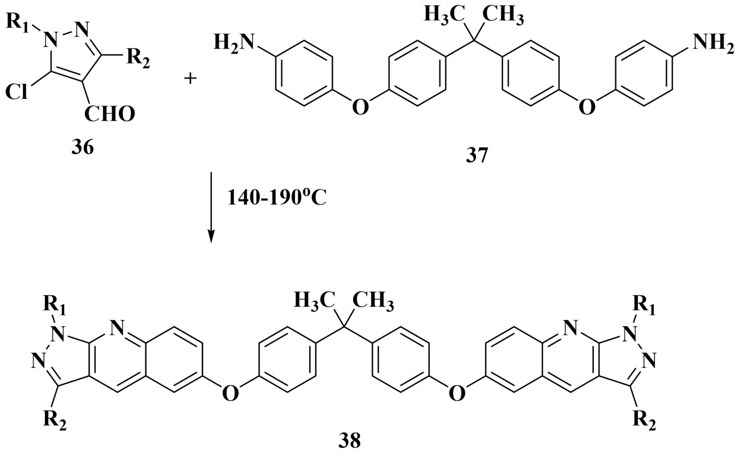
Abramov et al., [366] study documented that a condensation reaction involving 5-amino-1,2-azoles and 5-chloropyrazole-4-carbaldehydes resulted in the formation of dipyrazolo[3,4-*b*:4',3'-e]pyridines, isoxazolo[5,4-*b*]pyrazolo[4,3-e]pyridine, and isothiazolo[5,4-*b*]pyrazolo[4,3-e]pyridine. compounds when the reaction was carried out at reflux temperature in toluene. **(Scheme5.11)**



X=NC$_6$H$_5$,O,S,NCH$_3$

**Scheme5.11**

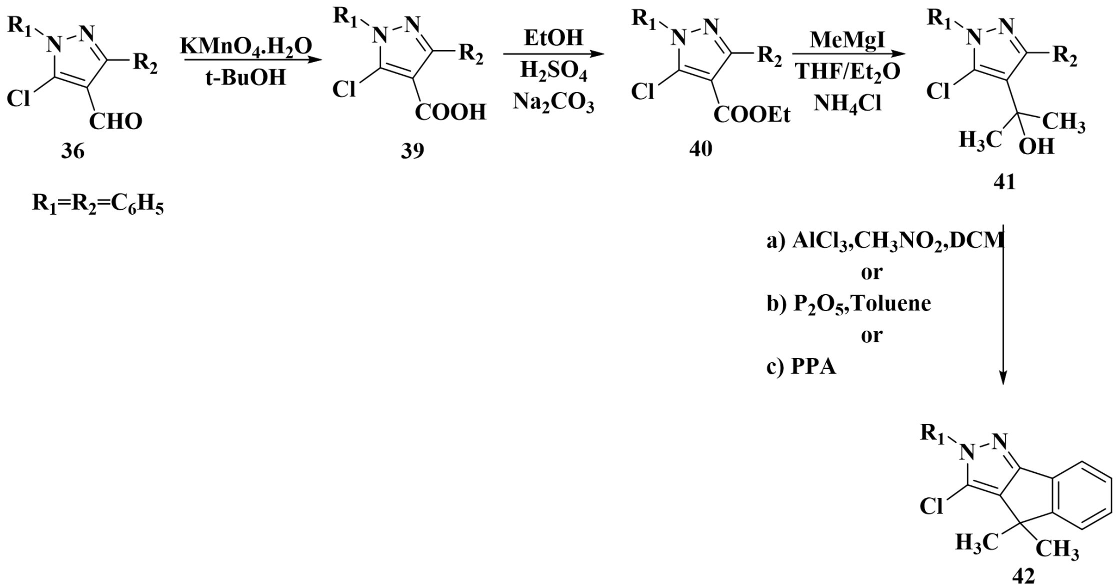
Gondek et al., [367] reported compound 6,6'-((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(1,3-disubstituted-1*H*-pyrazolo[3,4-*b*]quinoline) **38** were produced by heating 4,4'-((propane-2,2-diylbis(4,1-phenylene))bis(oxy))dianiline **37** and disubstituted-5-chloropyrazole-4-carbaldehydes **36** simultaneously at 140–190 °C for a duration of 1 hour. **(Scheme5.12)**



R$_1$=C$_6$H$_5$,CH$_3$;R$_2$=C$_6$H$_5$,CH$_3$

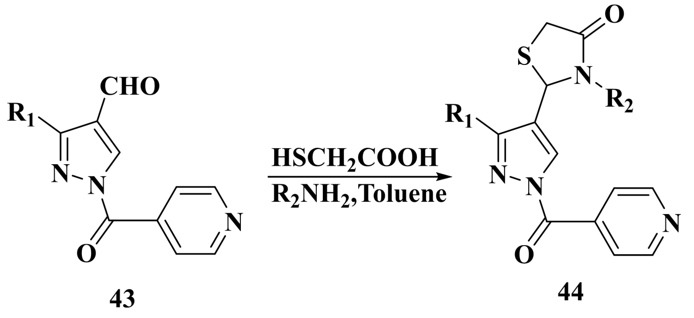
**Scheme5.12**

Abd El-Aal et al., [368] documented a series by using KMnO4 to oxidize the 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **36**, 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid **39** was formed. Alkanols **41** were produced by Grignard reagent on reacting ethyl-5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxylate **40**, which was obtained by heating **39** in 100% ethanol at reflux and concentrated sulfuric acid. The ring closure of Friedel–Crafts type was used to cyclize the 2-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)propan-2-ol **41**, resulting in the 3-chloro-2,4-dihydro-4,4-dimethyl-2-phenylindeno[1,2-c]pyrazole **42**. **(Scheme5.13)**



**Scheme5.13**

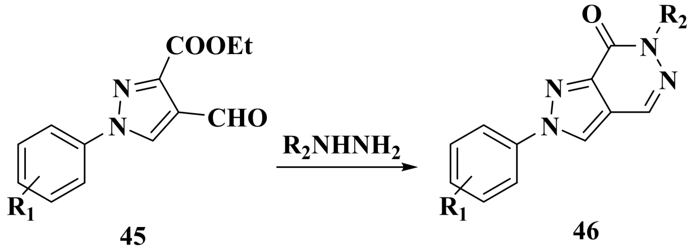
Visagaperumal et al.,[369] reported synthesis initiated by reacting 1-isonicotinoyl-3-substitutedphenyl-1*H*-pyrazole-4-carbaldehyde **43** with 2-mercaptoacetic acid and various substituted aromatic amines in toluene, derivatives of 2-(1-isonicotinoyl-3-phenyl-1*H*-pyrazol-4-yl)-3-phenylthiazolidin-4-one **44** have been produced. **44** have demonstrated antitubercular action in addition to mild to moderate antibacterial and antifungal properties. **(Scheme5.14)**



$R_1$=4-$NO_2C_6H_4$;$R_2$=$C_6H_5$,4-$NO_2C_6H_4$,
4-$ClC_6H_4$,4-$FC_6H_4$,3-$NO_2C_6H_4$,4-$BrC_6H_4$

**Scheme5.14**

Nikitenko and Mattichuk et al.,[368-369] reported treatment of ethyl 1-aryl-4-formyl-1*H*-pyrazole-3-carboxylates **45** derivatives with hydrazine and methylhydrazine resulted in the generation of their respective 2,6-dihydro-7*H* pyrazolo[3,4-*d*]pyridazin-7-ones **46**. **(Scheme5.15)**

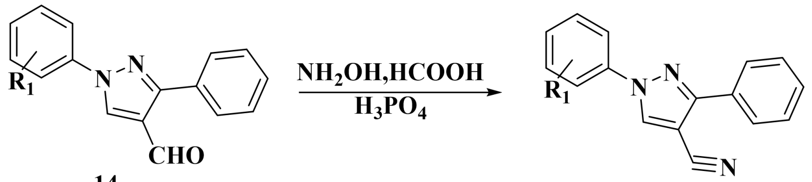


**45** **46**

**$R_1$=H,4F,2-Cl,3-Cl,4-Cl,3,4-$CH_3$,**
**4-$OCH_3$,3-$CF_3$,$R_2$=H,$CH_3$**

**Scheme5.15**

Choudhare et al., [372] Combining derivatives of pyrazole-4-carbaldehyde **14** with formic acid and hydroxylamine hydrochloride in the presence of orthophosphoric acid yields derivatives of 1,3-diphenyl-1*H*-pyrazole-4-carbonitrile **47**. **(Scheme5.16)**

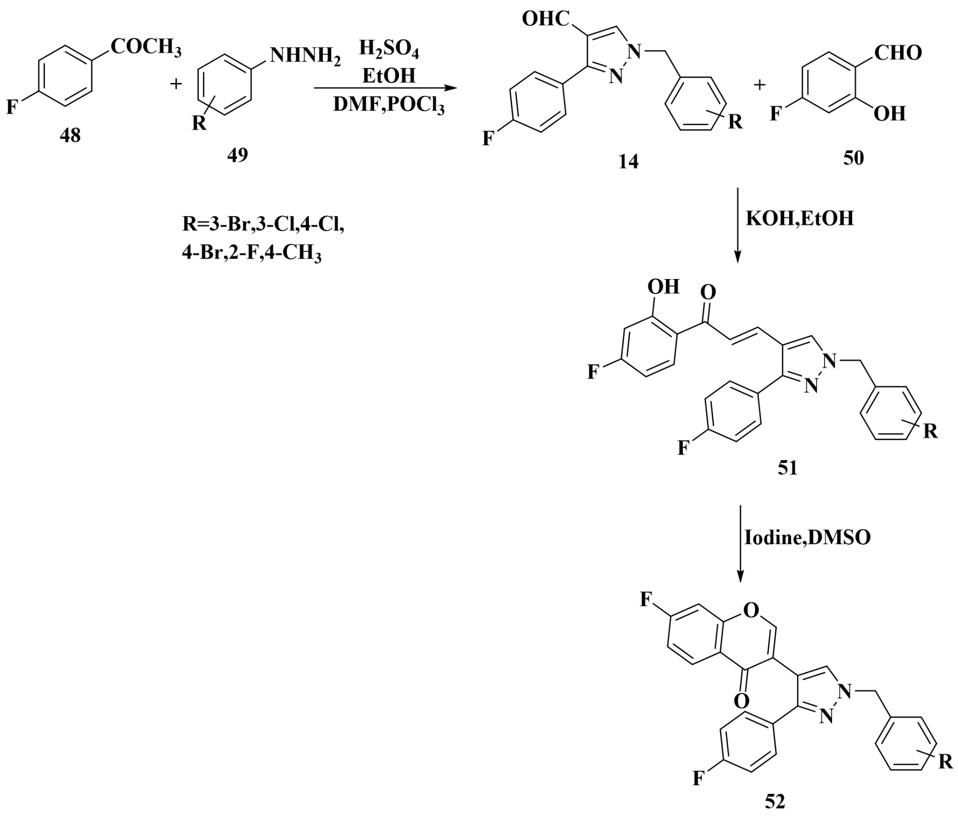


**14** **47**

**$R_1$=H,4-$CH_3$,4-F,**
**4-Br,4-Cl,3-Br,3-Cl**

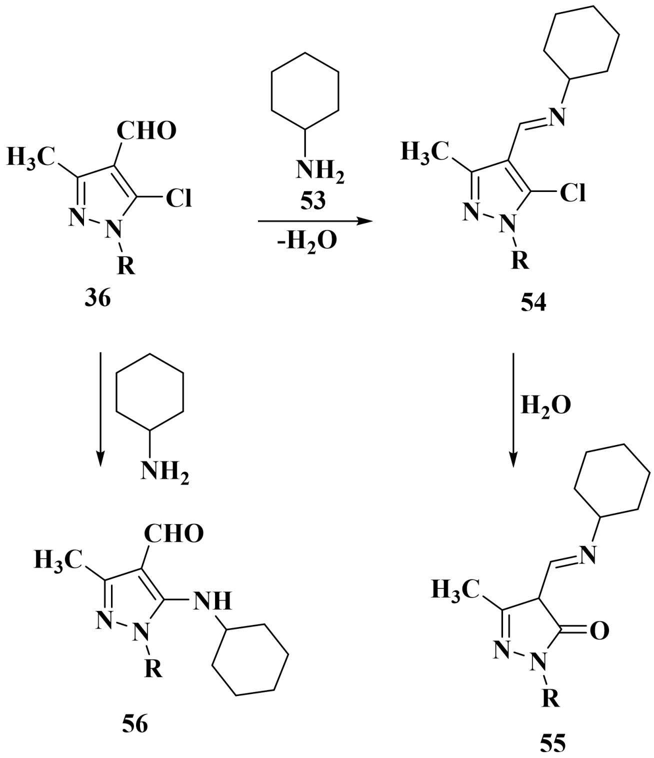
**Scheme5.16**

Hon et al., [373] reported synthesis initiated with 1-Benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **14** were synthesized through the Vilsmeier-Haack reaction employing the appropriate 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazines, derived from 4-fluoroacetophenone **48** and substituted 2-benzylhydrazines **49**. The synthesis of 3-(1-Benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **51** was accomplished by reacting 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **14** with 1-(4-fluoro-2-hydroxyphenyl)ethanone **50** in 10% aqueous KOH. Furthermore, the formation of 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-17-fluoro-4*H*-chromen-4-ones **52** was achieved by subjecting 3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **51** to a reaction with dimethyl sulfoxide (DMSO) and $I_2$. **(Scheme5.17)**



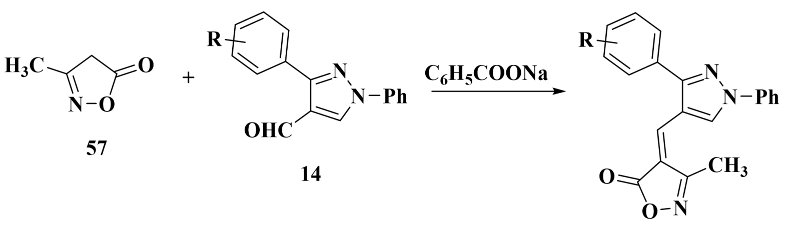
**Scheme5.17**

Orrego Hernandez et al., [374] reported synthesis starting from material cyclohexylamine **53** reacts with 5-chloro-3-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carbaldehyde **36**, nucleophilic substitution occurs, yielding 5-cyclohexylamino-3-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carbaldehyde **56**. Conversely, when reacting with 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **36**, the product obtained is 4-[(cyclohexylamino)methylidene]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **55**, formed through condensation followed by hydrolysis. **(Scheme5.18)**



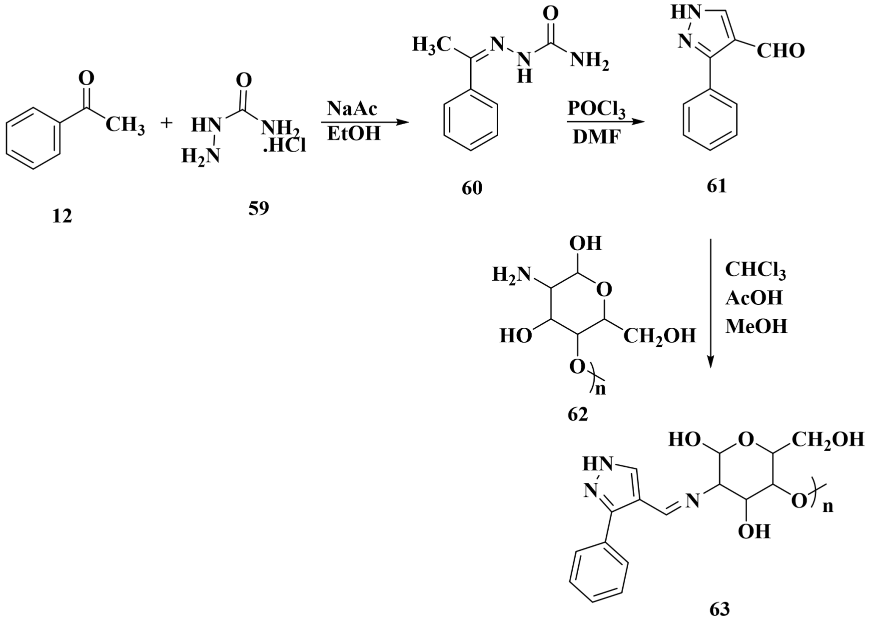
**Scheme5.18**

Wazalwar et al.,[375] documented the synthesis pathway leading to substituted 4-((1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)methylene)isoxazol-5(4*H*)-one derivatives **58**, involves two key steps. Initially, ethyl acetoacetate undergoes a reaction with hydroxylamine hydrochloride, yielding an oxime which subsequently eliminates an ethanol molecule to form cyclic compound **57**. In an aqueous environment, compound **57** exists predominantly in its enolic form. In the second step, deprotonation of the alcoholic OH group in **57** occurs, generating an alkoxide ion which then forms a carbanion. This carbanion undergoes Knoevenagel condensation with substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **14**, resulting in the formation of **58**. These synthesized compounds exhibit antibacterial activity against S. aureus, and some demonstrate antifungal activity against C. albicans. **(Scheme5.19)**



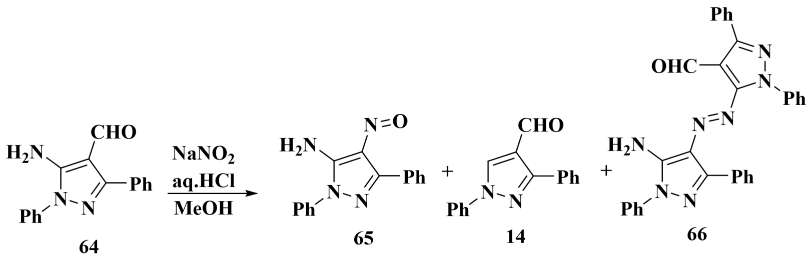
**Scheme5.19** **58**

Balakrishna Prabhu et al., [376] reported the synthesis of the chitosan derivative **63** involved a three-step process. Initially, 3-phenyl-1*H*-pyrazole-4-carbaldehyde **61** was synthesized by refluxing ethanol, acetophenone **43**, semicarbazidehydrochloride **59**, and sodium acetate at 78°C for 4 hours, resulting in the formation of semicarbazone **60**. In the subsequent step, semicarbazone **60** was reacted with dimethylformamide and phosphorous oxychloride to get 3-phenyl-1*H*-pyrazole-4-carbaldehyde **61**. To this mixture 3-phenyl-1*H*-pyrazole-4-carbaldehyde **61,** acetic acid, chitosan powder **62**, and methanol were added and agitated for 16 hours to obtain the chitosan derivative **63**. **(Scheme5.20)**



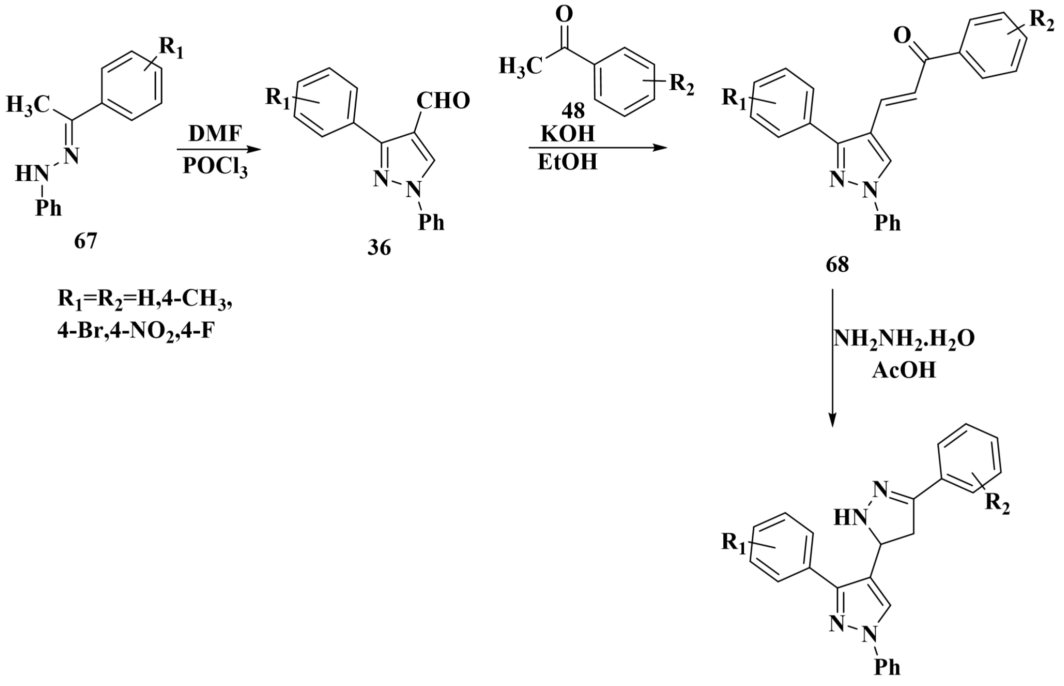
**Scheme5.20**

Hsiao et al., [377] reported the reactant utilized was 5-Amino-1*H*-pyrazole-4-carbaldehyde **64**, which underwent reaction with $NaNO_2$ in a Methanol solution in the presence of various equivalent concentration of HCl. This reaction predominantly yielded 5-amino-4-nitrosopyrazole **65** as the major product, accompanied by a small amount of pyrazole-4-carbaldehyde **14** or diazenylpyrazole **66** as trace byproducts. In a diluted acidic solution (≤ 2 N HCl in Methanol solution), 5-amino-4-nitrosopyrazoles **65** were predominantly produced via a series of redox, formylation, and nitration reactions of $NaNO_2$. Interestingly, under more concentrated acidic conditions (6N HCl in Methanol solution), pyrazole-4-carbaldehyde **14** emerged as the primary product. **(Scheme5.21)**



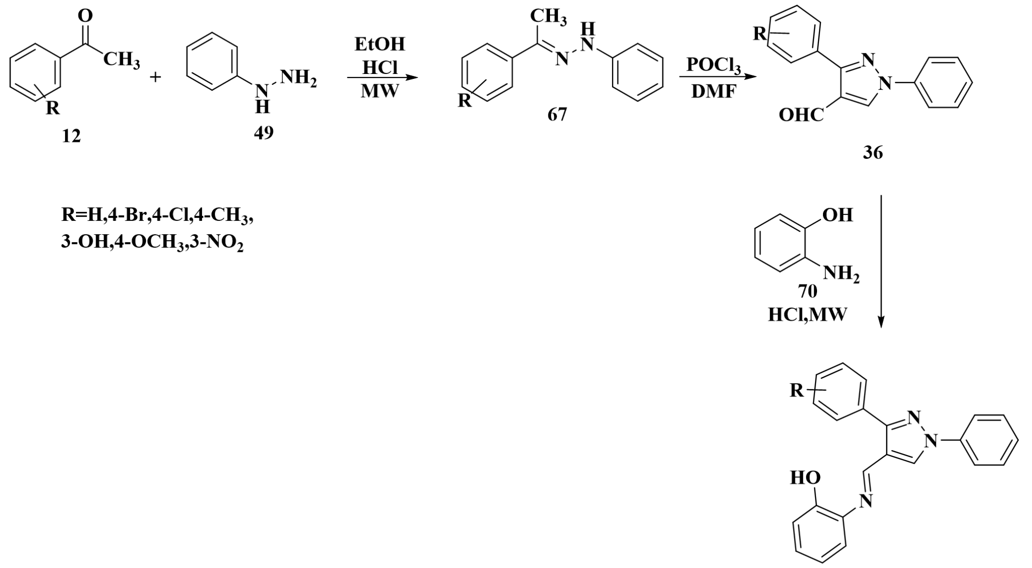
Scheme5.21

Ramadan et al., [378] reported Chalcone derivatives were synthesized via Claisen-Schmidt condensation, involving the reaction of aliphatic or aromatic ketones with aromatic aldehydes in the presence of a base, resulting in the formation of 1-phenyl-2-(1-phenylethylidene)hydrazine **67**. Subsequently, 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **36** were efficiently prepared through Vilsmeier-Haack reaction of 1-phenyl-2-(1-phenylethylidene)hydrazine **67** with $POCl_3$ in dimethylformamide. These aldehydes were then treated with substituted acetophenones in the presence of potassium hydroxide, yielding chalcone derivatives **68**. By conducting a solvent-free reaction of chalcone derivatives **68** with hydrazine hydrate in the presence of a catalytic amount of glacial acetic acid at room temperature, 3-aryl-4-(3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-1-phenyl-1*H*-pyrazoles **69** were obtained. The synthesized compounds were assessed for their antimicrobial activity in vitro against E. coli, S. aureus, and Candida albicans. **(Scheme5.22)**



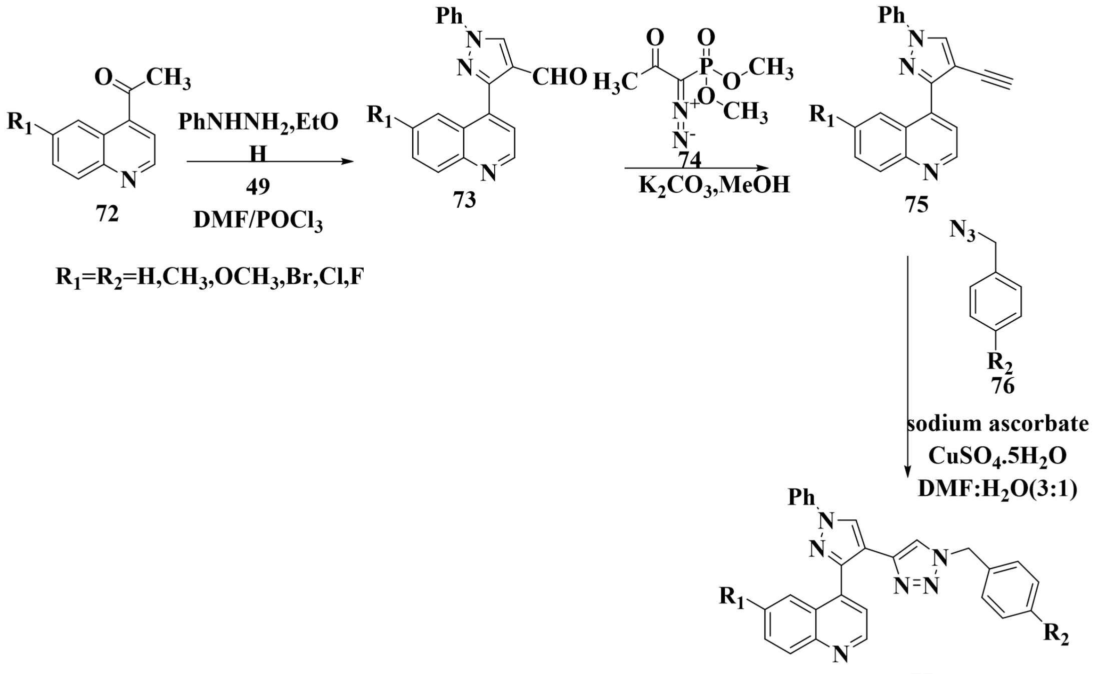
**Scheme5.22**

Wazalwar et al., [379] reported synthesis initiated with Phenyl hydrazones **67** were obtained by reacting substituted acetophenone **12** with phenyl hydrazine **49** in presence of ethanol, hydrochloric acid underwent microwave condition. Substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **36** was synthesized via the well-established Vilsmeier-Haack reaction($POCl_3$+DMF). Then Pyrazole-containing Schiff bases **71** were synthesized by combining the corresponding substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **36** with 2-aminophenol **70** under microwave condition. Compound **71** exhibited anticancer activity comparable to the well-known anticancer agent doxorubicin. **(Scheme5.23)**



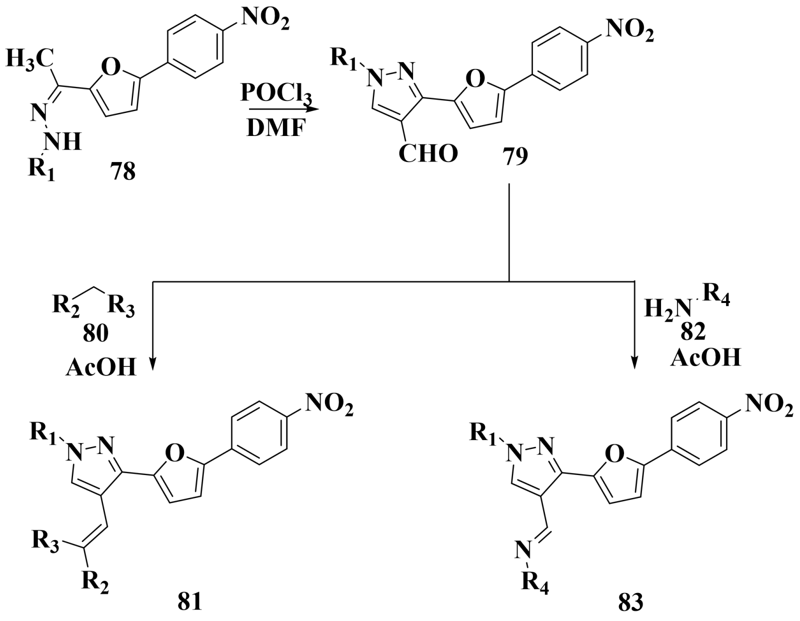
**Scheme5.23**

Thakare et al., [380] reported the condensation of 1-(quinolin-4-yl)ethanone **72** with phenyl hydrazine **49**, followed by formylation using DMF and $POCl_3$, produced 1-phenyl-3-(quinolin-4-yl)-1*H*-pyrazole-4-carbaldehyde **73**. This aldehyde **73** was then reacted with dimethyl(1-diazo-2-oxopropyl)phosphonate **74**, known as the Bestmann–Ohira reagent, in methanol to yield 4-(4-ethynyl-1-phenyl-1*H*-pyrazol-3-yl)quinoline **75**. The resulting quinoline-pyrazolyl alkyne **75** underwent a click reaction with substituted benzyl azide **76** in a DMF:$H_2O$ (3:1) mixture, forming 4-(4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)quinoline **77**. Many of the synthesized compounds exhibited significant antibacterial activity and were particularly effective against Mycobacterium tuberculosis H37Ra strains. **(Scheme5.24)**



**Scheme5.24**

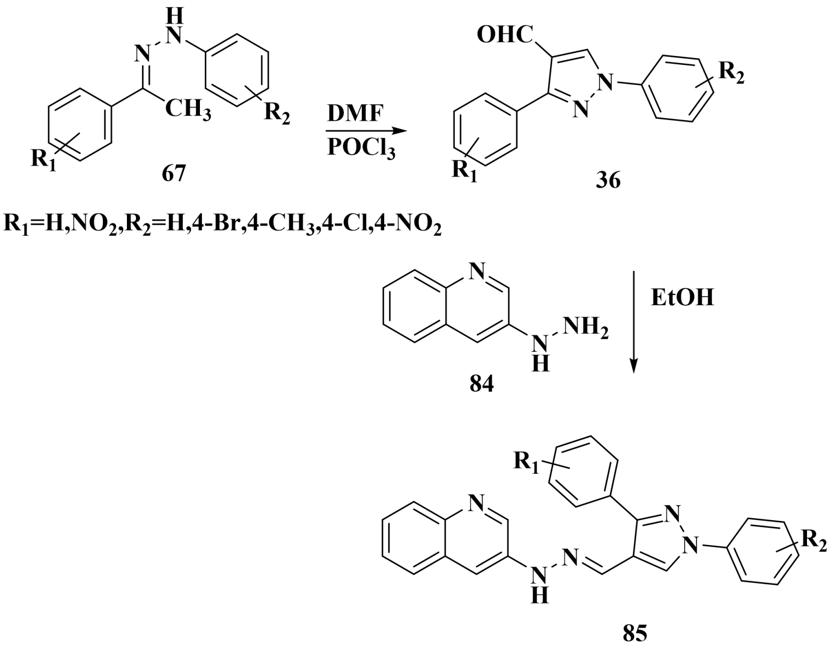
Barus et al., [381] reported synthesis on 1-(1-(5-(4-Nitrophenyl)furan-2-yl)ethylidene)-2-phenylhydrazine **78** was transformed into 3-(5-(4-nitrophenyl)furan-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **79** through formylation using DMF and POCl3. This aldehyde **79** was then reacted with an equimolar amount of the corresponding methylene active compounds **80** (such as malononitrile, ethyl cyanoacetate, cyanoacetamide, and thiooxoimidazolidin-2-one) in acetic acid, resulting in 4-alkenyl-functionalized 3-[5-(4-nitrophenyl)furan-2-yl]-1*H*-pyrazoles **81**. Similarly, an equimolar amount of nitrogen-containing nucleophiles **82** (including semicarbazone, thiosemicarbazone, and oxime) reacted with aldehyde **79** in acetic acid to produce 4-imino-functionalized 3-[5-(4-nitrophenyl)furan-2-yl]-1*H*-pyrazoles **83**. Compounds **81** and **83** demonstrated good antimicrobial activity against S. aureus, E. coli, and C. albicans bacteria. **(Scheme5.25)**



**$R_1$=H,Ph;$R_{2,3}$= malononitrile, ethyl cyanoacetate, cyanoacetamide, thiooxoimidazolidin-2-one; $R_4$=semicarbazone, thiosemicarbazone ,oxime**

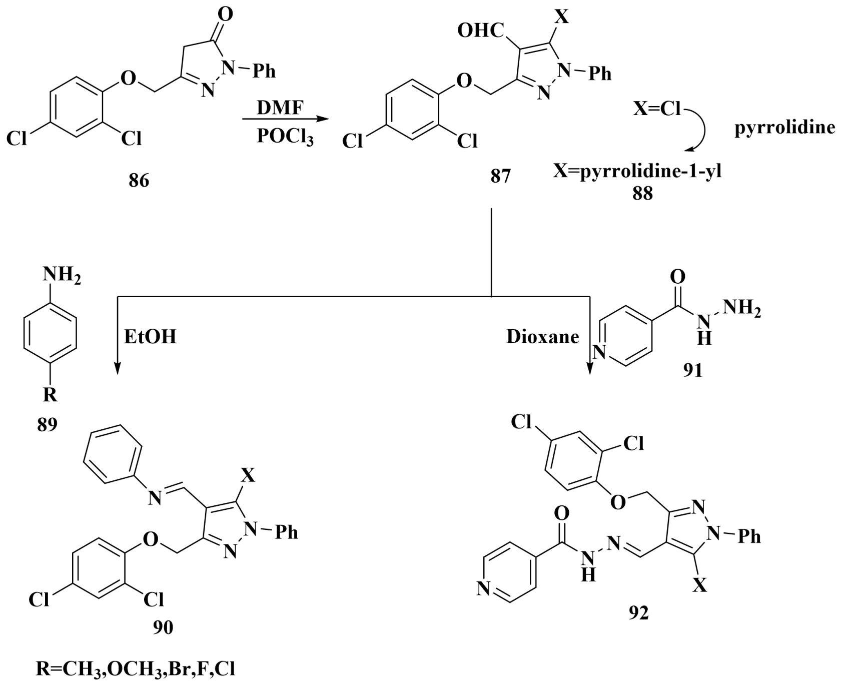
**Scheme5.25**

Saini et al., [382] reported the combination of substituted acetophenone and substituted phenyl hydrazine in the presence of glacial acetic acid led to the formation of acetophenone phenyl hydrazine **67**. The intermediate 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **36** was synthesized using the Vilsmeier-Haack reaction with phosphorus oxychloride and DMF. This intermediate **36** was then condensed with 3-hydrazinyl quinoline **84** in ethanol to produce derivatives of 1-((1,3-diphenyl-1*H*-pyrazole-4-yl)methylene)-2-(quinoline-3-yl)hydrazine **85**. These derivatives 85 exhibited significant anthelmintic activity, surpassing the standard drug Albendazole. **(Scheme5.26)**



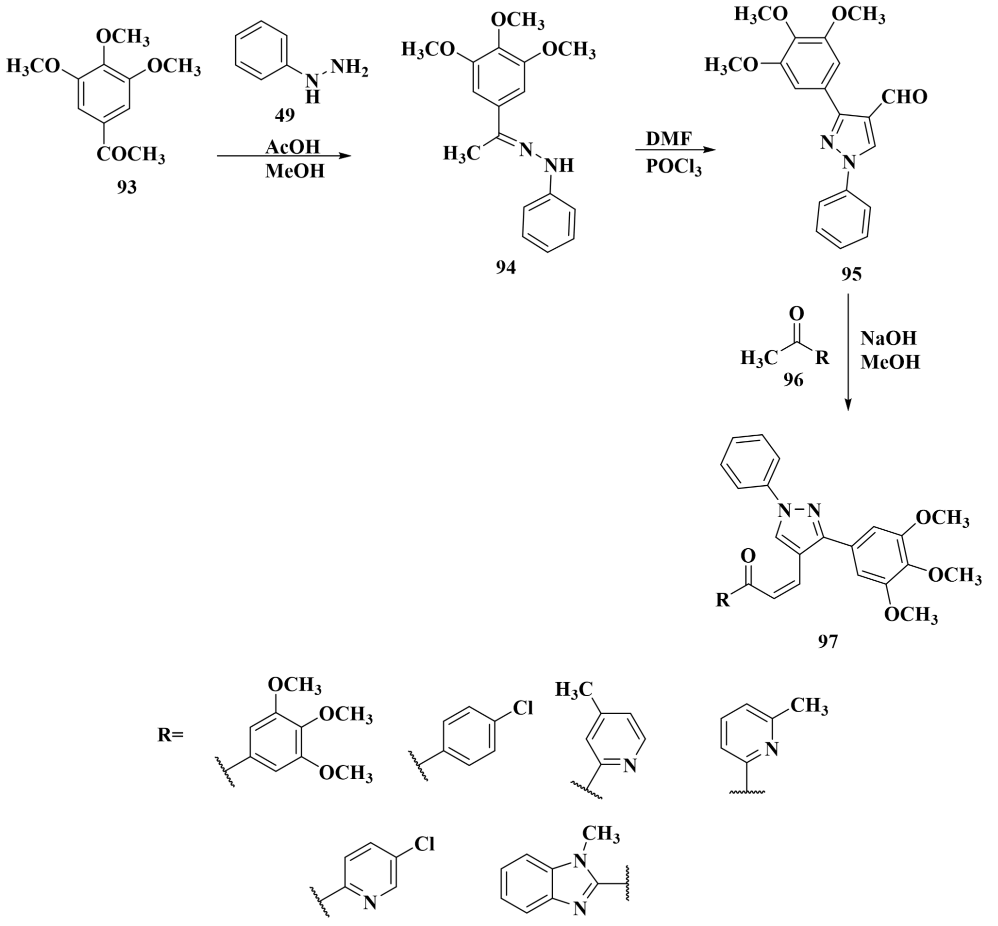
**Scheme5.26**

Shehry et al.,[383] reported synthesis stating from 5-((2,4-Dichlorophenoxy)methyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **86** underwent a Vilsmeier–Haack chloroformylation, resulting in the formation of 5-chloro-3-((2,4-dichlorophenoxy)methyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **87**. This compound 87 was then subjected to a nucleophilic substitution reaction with pyrrolidine in DMSO, yielding 3-((2,4-dichlorophenoxy)methyl)-1-phenyl-5-(pyrrolidin-1-yl)-1*H*-pyrazole-4-carbaldehyde **88**. Subsequent reaction of **88** with selected amines **89** in ethanol produced Schiff bases 1-(3-((2,4-dichlorophenoxy)methyl)-1-phenyl-5-(pyrrolidin-1-yl)-1*H*-pyrazol-4-yl)-*N*-phenylmethanimine derivatives **90** in high yield. Additionally, reacting **88** with isonicotinic hydrazide **91** in dioxane led to the formation of *N*'-((3-((2,4-dichlorophenoxy)methyl)-1-phenyl-5-(pyrrolidin-1-yl)-1*H*-pyrazol-4-yl)methylene)isonicotinohydrazide derivative **92**. This derivatives of **90** and **92** demonstrated antitumor activity, which was evaluated using the SRB assay on four cell lines: lung carcinoma (A549), human hepatocellular carcinoma (HepG2), colon carcinoma (HCT116), and mammary gland breast cancer (MCF-7) cell lines. **(Scheme5.27)**



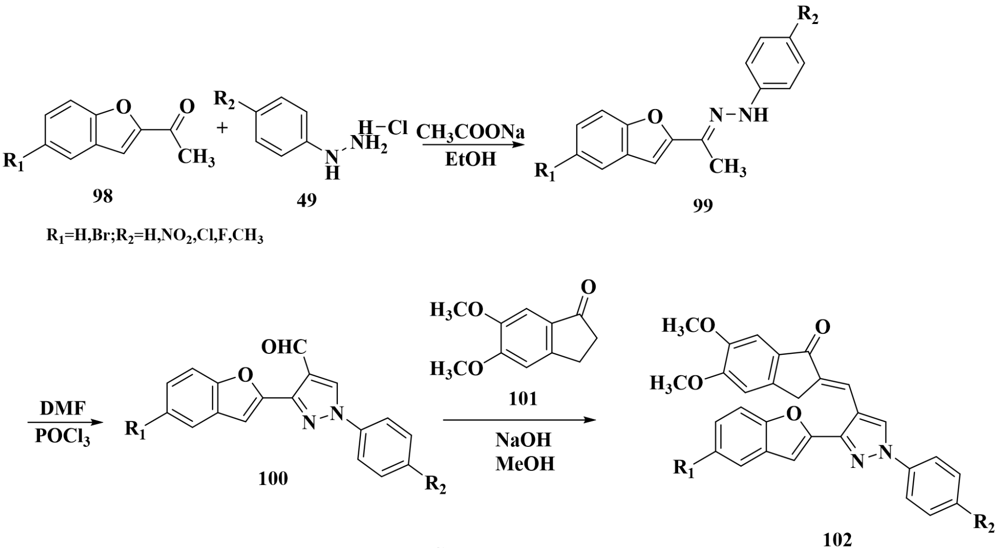
**Scheme5.27**

Krishna Prasad et al., [384] reported synthesis on 3,4,5-Trimethoxyacetophenone **93** was reacted with phenyl hydrazine **49** in the presence of acetic acid and methanol, producing 1-phenyl-2-(1-(3,4,5-trimethoxyphenyl)ethylidene)hydrazine **94**. This compound **94** was then treated with the Vilsmeier–Haack reagent (DMF and $POCl_3$), resulting in the formation of 1-phenyl-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole carboxaldehyde **95**. Subsequently, compound **95** underwent a Claisen–Schmidt reaction with various aryl and heteroaryl-substituted acetophenones **96** in the presence of alcoholic alkali, yielding 3-(1-phenyl-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-4-yl)-1-substitutedprop-2-en-1-one derivatives **97**. These derivatives **97** exhibited antibacterial activity against E. coli, P. aeruginosa, S. aureus, and B. subtilis, and demonstrated in vitro cytotoxic potential against the human lung carcinoma (A549) cell line using the MTT assay. **(Scheme5.28)**



**Scheme5.28**

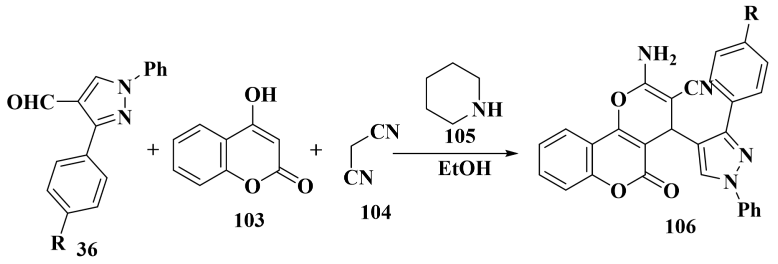
R et al., [383] reported a reaction mixture of 6-substituted 3-acetyl coumarin **98** and substituted phenyl hydrazine hydrochloride **49** was stirred in dry ethanol with sodium acetate at room temperature, forming 6-substituted-3-{1-[2-(4-substituted)hydrazinylidene]ethyl}-2*H*-chromen-2-one **99**. This intermediate **99** was then subjected to Vilsmeier formylation, producing 3-(6-substituted-2-oxo-2*H*-chromen-3-yl)-1-(4-substituted)-1*H*-pyrazole-4-carbaldehyde derivatives **100**. These derivatives **100** were further reacted with 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one **101** in presence of sodium methoxide solution under reflux conditions, yielding 2-((3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2,3-dihydro-5,6-dimethoxyinden-1-one derivatives **102**. Derivatives of **100** and **102** were found to exhibit both analgesic and anti-inflammatory activities. **(Scheme5.29)**



**Scheme5.29**

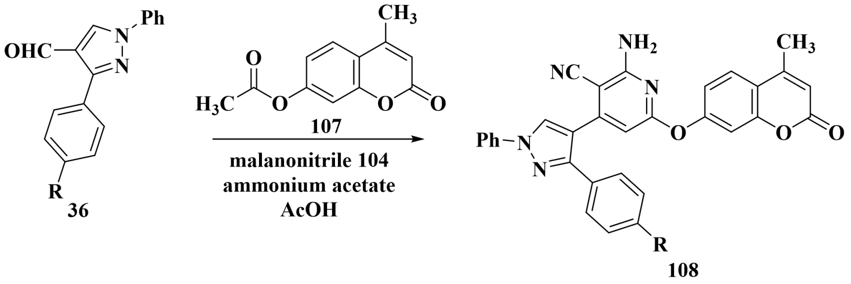
Thakor et al.,[386] reported Substituted pyrazole aldehyde **36** and 4-hydroxycoumarin **103** were refluxed in ethanol for 4-5 hours using piperidine **105** as a base catalyst. This synthesis involved a Knoevenagel condensation between substituted pyrazole-4-carbaldehyde **36** and malononitrile **104**, resulting in the loss of water molecules, followed by a Michael addition to produce 2-amino-4-(3-(4-substituted)-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-4*H*,5*H*-pyrano[3,2-c]chromene-3-carbonitrile derivatives **106**.**(Scheme5.30)**

Additionally, synthesized 7-acetyloxy-4-methylcoumarin **107** was coupled with substituted pyrazole aldehyde **36** in the presence of malononitrile and ammonium acetate in acetic acid, yielding 2-amino-4-(3-(4-substituted)-1-phenyl-1*H*-pyrazol-4-yl)-6-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)nicotinonitrile **108**.**(Scheme5.31)** Both compounds **106** and **108** were evaluated for their in vitro cytotoxicity against the NCI-H522 lung cancer cell line.



R=OH,F,Cl,NO$_2$,NH$_2$

Scheme5.30



Scheme5.31

Pyrazole derivatives are among the most active five-membered nitrogen-containing heterocycles. This study highlights the significant role of pyrazole-4-carbaldehydes as precursors in the synthesis of pyrazole-fused heterocyclic systems over the decades. Various synthetic methods for preparing pyrazole-4-carbaldehydes were reviewed, demonstrating their versatility as precursors for creating diverse pyrazole-substituted heterocyclic hybrid molecules.

## 5.2 Result and Discussion:

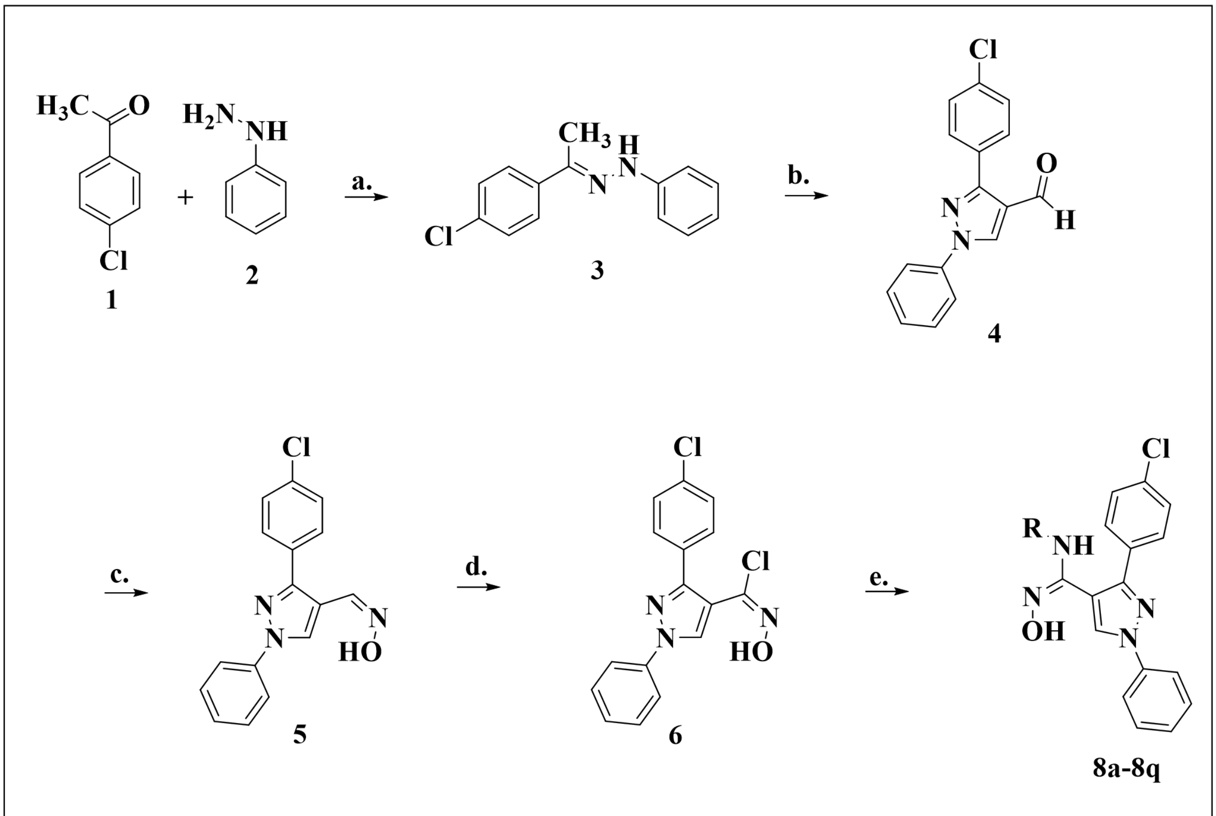
The synthesis of 1-(1-(4-chlorophenyl)ethylidene)-2-phenylhydrazine (3) commenced through the condensation reaction between 4-chloroacetophenone (1) and phenylhydrazine (2) in the presence of ethanol as the solvent and glacial acetic acid as the catalyst. The resulting product (3) was then subjected to a reaction with the Vilsmeier-Hack reagent mixture, leading to the formation of 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4). Subsequent treatment of compound (4) with hydroxylamine and sodium carbonate yielded 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime (5). Further modification of (5) was achieved by reacting it with *N*-chlorosuccinimide and utilizing DMF as the solvent, resulting in the formation of 3-(4-chlorophenyl)-*N*-hydroxy-1-phenyl-1*H*-pyrazole-4-carbimidoylchloride (6). By employing equimolar amounts of (6) and various derivatives of aniline (7), and utilizing potassium carbonate in a THF and $H_2O$ solvent mixture, a series of novel compounds, namely 3-(4-chlorophenyl)-*N*,-hydroxy-*N*,1-diphenyl-1*H*-pyrazole-4-carboximidamide (8a-8q) were successfully synthesized.

Compounds was characterized through $^1$H NMR spectroscopy employing DMSO-$d^6$ as the solvent and TMS (tetramethylsilane) as the internal standard reference. The proton signals attributed to the Phenyl and chlorophenyl ring protons: Typically appear in the range of 7.0-8.0 ppm. Pyrazole ring proton: The proton on the pyrazole ring typically appears around 7.88 ppm as a singlet or doublet depending on coupling. The OH proton typically appears as a broad singlet and can be exchangeable, usually found around 7-8 ppm depending on hydrogen bonding interactions. The NH proton of the carboximidamide group can appear around 10-12 ppm as a broad singlet due to hydrogen bonding.

Further structural confirmation was obtained through $^{13}$C NMR spectroscopy, with DMSO-$d^6$ as the solvent and TMS as the internal standard reference. The $^{13}$C NMR spectrum revealed the Aromatic carbons (Phenyl and Chlorophenyl) at120-140 ppm, and Pyrazole ring carbons at 100-120 ppm.

Additionally, mass spectrometry further supported the characterization, yielding an observed mass of 403.3. To ensure the authenticity of the synthesized compounds, their structures were confirmed through spectral analyses, including IR, Mass Spectroscopy, $^1$H NMR, and $^{13}$C NMR. The isolated products were further purified through recrystallization from methanol.

## 5.3 Reaction Scheme:



**a) EtOH, gla.acetic acid; b) DMF,$POCl_3$; c) $NH_2OH.HCl$, $Na_2CO_3$, MeOH; d) NCS, DMF; e) $RNH_2$(7a-7q), $NaHCO_3$, THF:$H_2O$**

## 5.4 Physical Characteristics:

**Table 5.1: physical characteristics of synthesized compound**

| Entry | Compound code | R | Molecular weight | Molecular formula | M.P. in $^{O}$C | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 8a | 4-$CH_3$ | 402.88 | $C_{23}H_{19}OClN_4$ | 191-193 | 81 |
| 2 | 8b | 4-Cl | 423.30 | $C_{22}H_{16}OCl_2N_4$ | 198-200 | 79 |
| 3 | 8c | 4-$OCH_3$ | 418.88 | $C_{23}H_{19}O_2ClN_4$ | 194-196 | 80 |
| 4 | 8d | 4-F | 406.85 | $C_{22}H_{16}OClFN_4$ | 180-182 | 85 |
| 5 | 8e | H | 388.86 | $C_{22}H_{17}OClN_4$ | 190-192 | 85 |
| 6 | 8f | 4-Br | 467.75 | $C_{22}H_{16}OBrClN_4$ | 199-201 | 79 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | 8g | 3-Cl | 423.30 | $C_{22}H_{16}OCl_2N_4$ | 182-184 | 71 |
| 8 | 8h | 2-$CH_3$ | 402.88 | $C_{23}H_{19}OClN_4$ | 192-194 | 67 |
| 9 | 8i | 2-$OCH_3$ | 418.88 | $C_{23}H_{19}O_2ClN_4$ | 190-192 | 61 |
| 10 | 8j | 3-$CH_3$ | 402.88 | $C_{23}H_{19}OClN_4$ | 189-191 | 61 |
| 11 | 8k | 2,4-$CH_3$ | 416.91 | $C_{24}H_{21}OClN_4$ | 194-196 | 68 |
| 12 | 8l | 3,4-Cl | 457.74 | $C_{22}H_{15}OCl_3N_4$ | 185-187 | 51 |
| 13 | 8m | 3-Cl,4-F | 441.29 | $C_{22}H_{15}OCl_2FN_4$ | 183-185 | 54 |
| 14 | 8n | 2,4,5-Cl | 492.18 | $C_{22}H_{14}OCl_4N_4$ | 188-190 | 57 |
| 15 | 8o | 2,4-F | 424.84 | $C_{22}H_{15}OClF_2N_4$ | 194-196 | 59 |
| 16 | 8p | 2,6-$CH_3$ | 416.91 | $C_{24}H_{21}OClN_4$ | 186-188 | 58 |
| 17 | 8q | 2-$CH_2CH_3$,6-$CH_3$ | 430.94 | $C_{25}H_{23}OClN_4$ | 193-195 | 59 |

All compounds are crystalline yellow solid.

## 5.5 Conclusion:

In this study, we have successfully synthesized and characterized 3-(4-chlorophenyl)-*N*-hydroxy-*N*,1-diphenyl-1*H*-pyrazole-4-carboximidamide derivatives. The synthetic pathway employed was efficient and provided high yields of the target compound. The condensation reaction between 4-chlorophenylhydrazine, diphenylamine, and hydroxylamine hydrochloride proceeded smoothly, demonstrating the reliability and effectiveness of the methodology. Comprehensive spectral analysis, including $^{1}H$ NMR, $^{13}C$ NMR, and mass spectrometry, confirmed the structural integrity and composition of the synthesized compound. The presence of the characteristic imidazole ring and carboximidamide group was verified, ensuring the successful formation of the desired structure. The synthesized compound exhibits structural features that are of interest in medicinal chemistry, particularly due to the potential for biological activity arising from the pyrazole and hydroxamic acid motifs. The introduction of the 4-chlorophenyl and diphenyl groups enhances the structural diversity and possibly the pharmacological profile of the compound.

Overall, the successful synthesis and detailed characterization of 3-(4-chlorophenyl)-*N*-hydroxy-*N*,1-diphenyl-1*H*-pyrazole-4-carboximidamide highlight its potential as a valuable candidate for further studies in drug discovery. Future research efforts should focus on evaluating its biological activities and exploring its potential therapeutic applications, aiming to harness its full potential in medicinal chemistry.

## 5.6 Experimental Section:

### 5.6.1 Materials and Methods:

Commercial-grade solvents and reagents were employed without additional purification. The melting points of various substances were assessed using open capillary tubes in a melting point apparatus. To verify the compounds' purity, thin-layer chromatography (TLC) was conducted on silica F254-coated aluminium plates (Merck) as an adsorbent, with UV light and an iodine chamber serving as visualizing agents. Solvents were removed using a rotary evaporator. The Shimadzu Model FTIR-435 recorded IR spectra (KBr in $cm^{-1}$). For $^1H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz), a Bruker Advance spectrometer was utilized in DMSO-$d^6$ as a solvent. The NMR spectrum was recorded with TMS (tetramethylsilane) as the internal reference standard, and chemical shift values were expressed in parts per million (ppm). Mass spectra were obtained using a mass spectrometer.

### 5.6.2 General Procedures:

**General procedure for 1-(1-(4-chlorophenyl)ethylidene)-2-phenylhydrazine (3):**

The compounds were synthesized through a condensation reaction involving derivatives of acetophenone and the respective hydrazine in ethanol, employing a procedure previously documented for analogous systems. 4-chloroacetophenone **(1)** (10 mmol) was introduced into a solution of phenylhydrazine **(2)** (10 mmol) in 20 mL of ethanol and few drop of glacial acetic acid at a reflux temperature of 60°C for 1-2 hr. the reaction mixture was cooled to room temperature, poured into ice cold water. Subsequently, yellow solid precipitated, and it was collected through filtration. The isolated product underwent recrystallization from hot ethanol.[387] Yield: 90%.

### General procedure for 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4):

A solution containing 1-(1-(4-chlorophenyl)ethylidene)-2-phenylhydrazine **(3)** (10 mmol) was combined with a Vilsmeier-Hack reagent mixture, prepared from 0.59 ml of DMF and 3.13 ml of $POCl_3$ at $0^oC$ to -5°C, added in small aliquots while maintaining a reaction temperature of 60–65°C for 3-4hr. The progress of the reaction was monitored using thin-layer chromatography (TLC). Once deemed complete, the reaction mixture was gradually quenched by pouring it into crushed ice with continuous stirring and subsequently neutralized with solid $NaHCO_3$. The resulting precipitate was filtered, dried, and subjected to purification through recrystallization from methanol.[388]yield:86%.

### General procedure for 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime (5):

3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **(4)** (10 mmol) dissolved in 20 ml of methanol was subjected to a reaction with $NH_2OH\cdot HCl$(10 mmol), and the resulting mixture was stirred at room temperature. $Na_2CO_3$(10 mmol) was incrementally added over 5 minutes, and stirring was maintained for an additional 30 minutes. Upon completion, the reaction mixture was slowly poured into ice-cold water. The solid product was collected via filtration, washed with water and n-hexane, and then allowed to dry in the refrigerator overnight.[389] Yield: 88%.

### General procedure for 3-(4-chlorophenyl)-*N*-hydroxy-1-phenyl-1*H*-pyrazole-4-carbimidoylchloride (6):

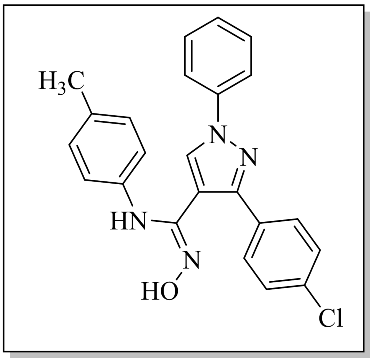
3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime **(5)** (10 mmol) was dissolved in 5 ml of DMF, and the reaction mixture was stirred at 0°C for 10 minutes. *N*-chlorosuccinimide (NCS) (10 mmol) was slowly added in portions. The reaction mixture was then stirred at room temperature overnight. After completion, the reaction mixture was gradually poured into ice-cold water. The resulting solid product was collected through filtration, washed with water, and allowed to dry in the refrigerator overnight.[390] Yield: 89%

### General procedure for novel 3-(4-chlorophenyl)-*N'*-hydroxy-*N*,1-diphenyl-1*H*-pyrazole-4-carboximidamide (8a-8q):

3-(4-chlorophenyl)-*N*-hydroxy-1-phenyl-1*H*-pyrazole-4-carbimidoyl chloride (**6**, 1 gm, 0.003 mol, 1 eq) was placed in a mixture of THF and $H_2O$, and derivatives of aniline (**7**, 0.35 gm, 0.003 mol, 1.2 eq) were incorporated into the solution. Anhydrous $NaHCO_3$(0.40 gm, 0.003 mol, 1.5 eq) was then added. agitated the reaction mixture. for 5-10 minutes at ambient temperature and subsequently refluxed for 4-6 hr at 60°C. TLC tracked the reaction's progress at room temperature until it was finished. Upon completion, Ice-cold water was gradually added to the reaction mixture. The solid product that was produced has been collected through filtration, cleaned with water and left to air dry in the refrigerator overnight. producing goods that are inside the spectrum of 54-85%.

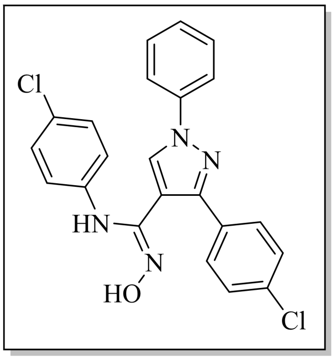
## 5.6.3 Spectral Characterization:

### 3-(4-chlorophenyl)-*N'*-hydroxy-1-phenyl-*N*-(p-tolyl)-1*H*-pyrazole-4-carboximidamide (8a):



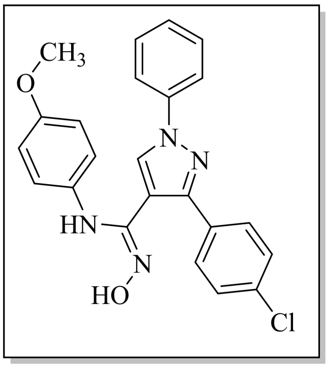
Yellow crystal; Yield: 81%; M.P.: 191-193°C; FTIR($\nu_{max}$,$cm^{-1}$): 3155, 3055, 2924, 1790, 1597, 1504, 1458; $^1H$ NMR (400 MHz, DMSO-$d^6$) δ 2.07 (s, 3H), 6.54 (d, 2H), 6.75 (d, 2H), 7.34 (t, 1H), 7.43 – 7.39 (m, 2H), 7.50 (dt, 2H), 7.62 – 7.58 (m, 2H), 7.91 (d, 2H), 8.28 (s, 1H), 8.73 (s, 1H), 10.25 (s, 1H); MS (*m/z*) 403.3 ($M^+$); Anal. Calcd. For $C_{23}H_{19}ClN_4O$ : C, 68.57; H, 4.75; N, 13.91;found: C, 68.51; H, 4.70; N, 13.90.

**3-bis(4-chlorophenyl)-*N*'-hydroxy-1-phenyl-1*H*-pyrazole-4-carboximidamide(8b):**



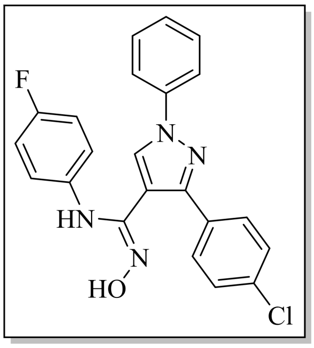
Yellow crystal; Yield: 79%; M.P.: 198-200°C; FTIR( KBr $\nu_{max}$,cm$^{-1}$): 3649, 3155, 3055, 2870, 1790, 1589, 1504; $^1$H NMR (400 MHz, DMSO-*d*$^6$) δ $^1$H NMR (400 MHz, DMSO) δ 7.44 (d, *J* = 9.4 Hz, 4H), 7.55 (s, 2H), 7.73 (s, 1H), 7.90 (s, 1H), 8.00 (s, 3H), 8.05 (s, 2H), 9.37 (s, 1H), 9.95 (s, 1H), 11.82 (s, 1H); $^{13}$C NMR (101 MHz, DMSO-*d*$^6$) δ 40.60, 119.90, 128.63, 129.79, 130.29; MS (*m/z*) 423.3 (M$^+$); Anal. Calcd. For $C_{22}H_{16}Cl_2N_4O$ : C, 62.42; H, 3.81; N, 13.24 ;found: C, 62.41; H, 3.79; N, 13.21.

**3-(4-chlorophenyl)-*N*'-hydroxy-*N*-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboximidamide(8c):**



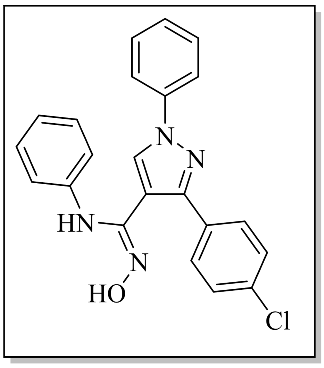
Yellow crystal; Yield: 80%; M.P.: 194-196°C; FTIR( KBr $\nu_{max}$,cm$^{-1}$): 3155, 3055, 2839, 1790, 1597, 1504; $^1$H NMR (400 MHz, DMSO) δ $^1$H NMR (400 MHz, DMSO) δ 3.58 (d, *J* = 12.0 Hz, 3H), 6.55 (d, *J* = 10.3 Hz, 2H), 7.38 – 7.43 (m, 3H), 7.44 (d, *J* = 9.0 Hz, 3H), 7.51 (s, 2H), 7.53 (d, *J* = 7.7 Hz, 4H), 8.16 (d, *J* = 12.0 Hz, 1H), 9.16 (d, *J* = 8.6 Hz, 1H), 11.84 (s, 1H); $^{13}$C NMR (101 MHz, DMSO-*d*$^6$) δ 40.60, 119.58, 129.08, 129.38, 130.25, 130.83; MS (*m/z*) 419.3 (M$^+$); Anal. Calcd. For $C_{23}H_{19}ClN_4O_2$ : C, 65.95; H, 4.57; N, 13.38; found: C, 65.94; H, 4.54; N, 13.35.

### 3-(4-chlorophenyl)-*N*-(4-fluorophenyl)-*N*'-hydroxy-1-phenyl-1*H*-pyrazole-4-carboximidamide(8d):



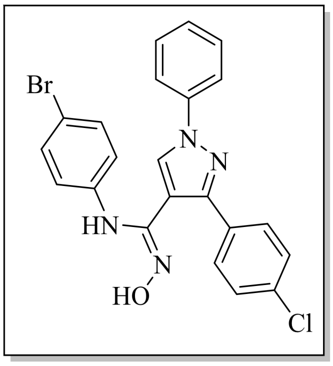
Yellow crystal, Yield: 85%, M.P.: 180-182°C; Anal. Calcd. For $C_{22}H_{16}ClFN_4O$ : C, 64.95; H, 3.96; N, 13.77; found: C, 64.91; H, 3.95; N, 13.78.

### 3-(4-chlorophenyl)-*N*'-hydroxy-*N*,1-diphenyl-1*H*-pyrazole-4-carboximidamide(8e):



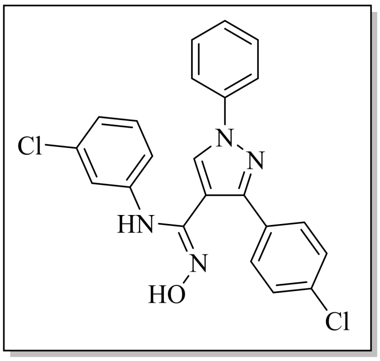
Yellow crystal, Yield: 85%, M.P.: 190-192°C; FTIR(KBr $\nu_{max}$,cm$^{-1}$): 3410, 3155, 3063, 2924, 1782, 1589, 1512; $^1$H NMR (400 MHz, DMSO-*d*$^6$) δ 7.46 (s, 4H), 7.98 (s, 5H), 7.99 (s, 4H), 9.45 (s, 1H), 9.98 (s, 1H), 11.79 (s, 1H); MS (*m/z*) 385.3 (M$^+$); Anal. Calcd. For $C_{22}H_{17}ClN_4O$ : C, 67.95; H, 4.41; N, 14.41; found: C, 67.94; H, 4.40; N, 14.40.

### *N*-(4-bromophenyl)-3-(4-chlorophenyl)-*N*'-hydroxy-1-phenyl-1*H*-pyrazole-4-carboximidamide(8f):



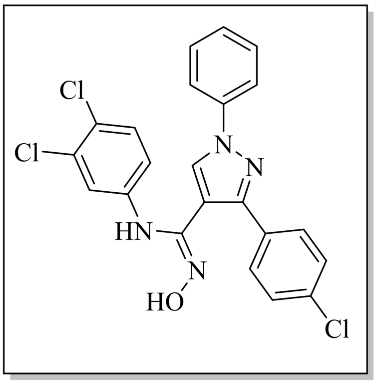
Yellow crystal, Yield: 79%, M.P.: 199-201°C; FTIR(KBr $\nu_{max}$,cm$^{-1}$): 3356, 3155, 3036, 2962, 1790, 1589, 1504. Anal. Calcd. For $C_{22}H_{16}BrClN_4O$ : C, 56.49; H, 3.45; N, 11.98; found: C, 56.47; H, 3.44; N, 11.97.

**_N_-(3-chlorophenyl)-3-(4-chlorophenyl)-_N_'-hydroxy-1-phenyl-1_H_-pyrazole-4-carboximidamide (8g):**



Yellow crystal, Yield: 71%, M.P.: 182-184°C; $^{13}$C NMR (101 MHz, DMSO-*d*$^6$) δ 40.67, 119.90, 128.63, 129.79, 130.30; Anal. Calcd. For $C_{22}H_{16}Cl_2N_4O$: C, 62.42; H, 3.81; N, 13.24; found: C, 62.42; H, 3.81; N, 13.24.

**3-(4-chlorophenyl)-_N_-(3,4-dichlorophenyl)-_N_'-hydroxy-1-phenyl-1_H_-pyrazole-4-carboximidamide (8l):**



Yellow crystal, Yield: 51%, M.P.: 185-187°C; MS (*m/z*) 453.8 ($M^+$); Anal. Calcd. For : $C_{22}H_{15}Cl_3N_4O$: C, 57.73; H, 3.30; N, 12.24; found: C, 57.72; H, 3.28; N, 12.22.

### 5.6.4 Representative Spectra:

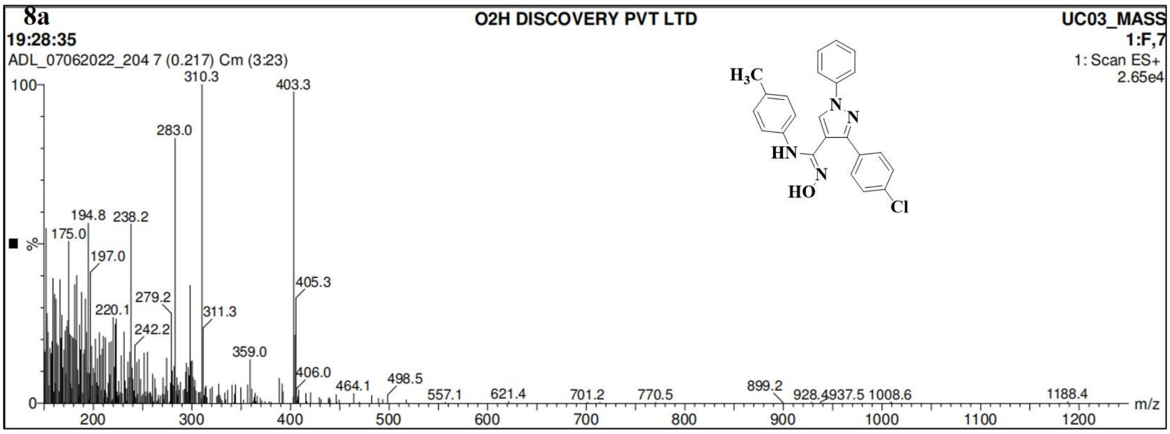


**Fig.5.2:** Representative mass spectrum of compound 8a

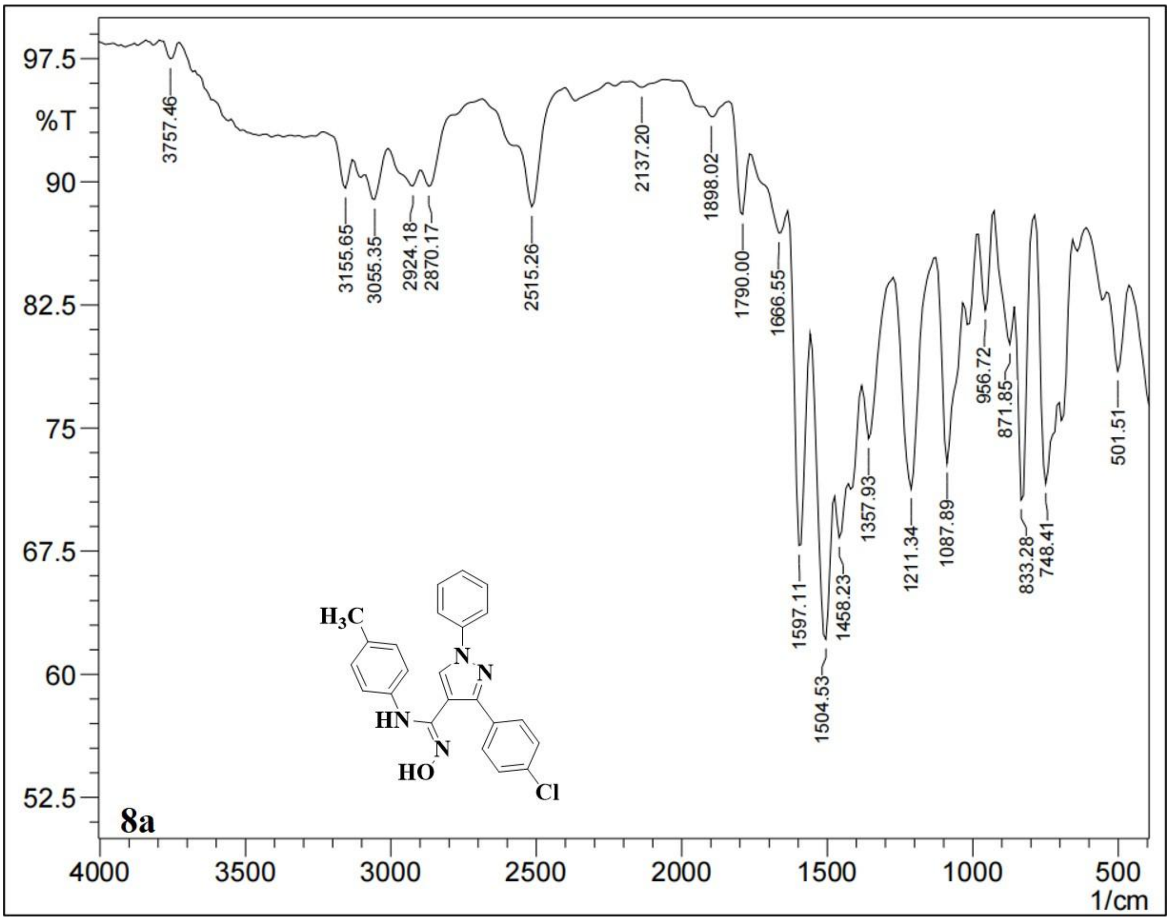


**Fig.5.3:** Representative IR spectrum of compound 8a

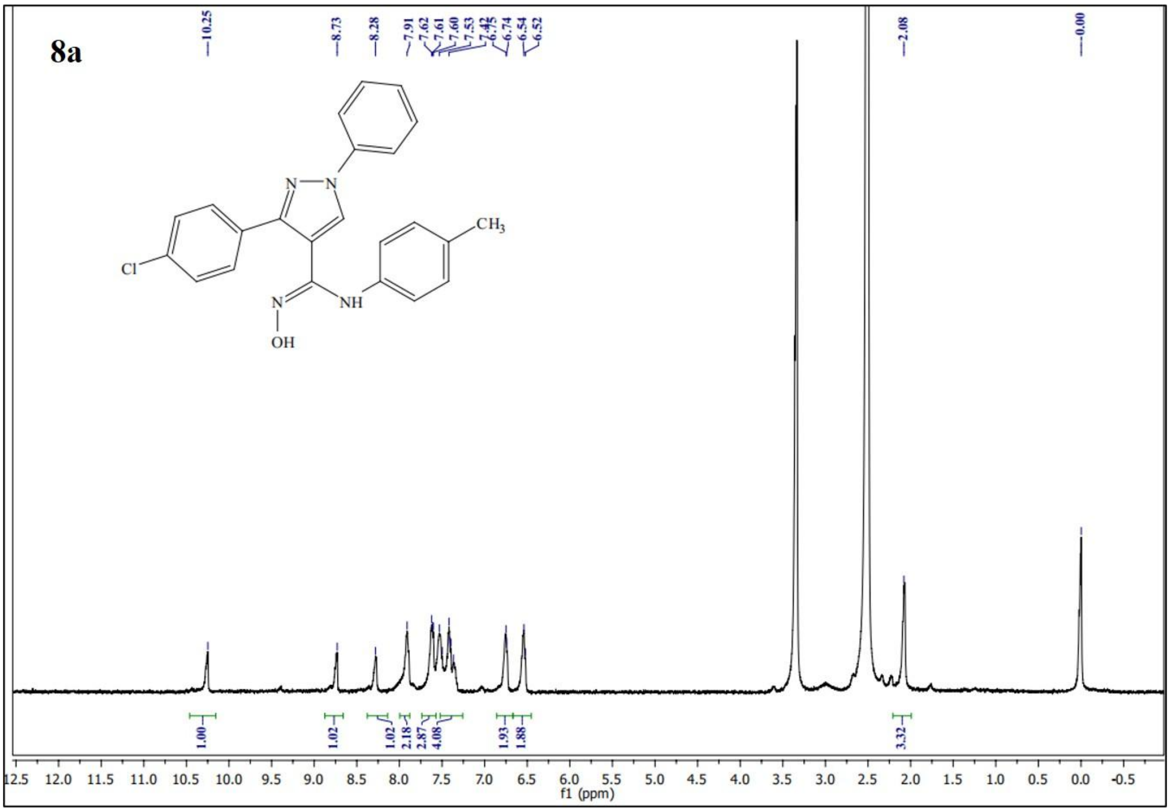


**Fig.5.4:** Representative $^1$H NMR spectrum of compound 8a

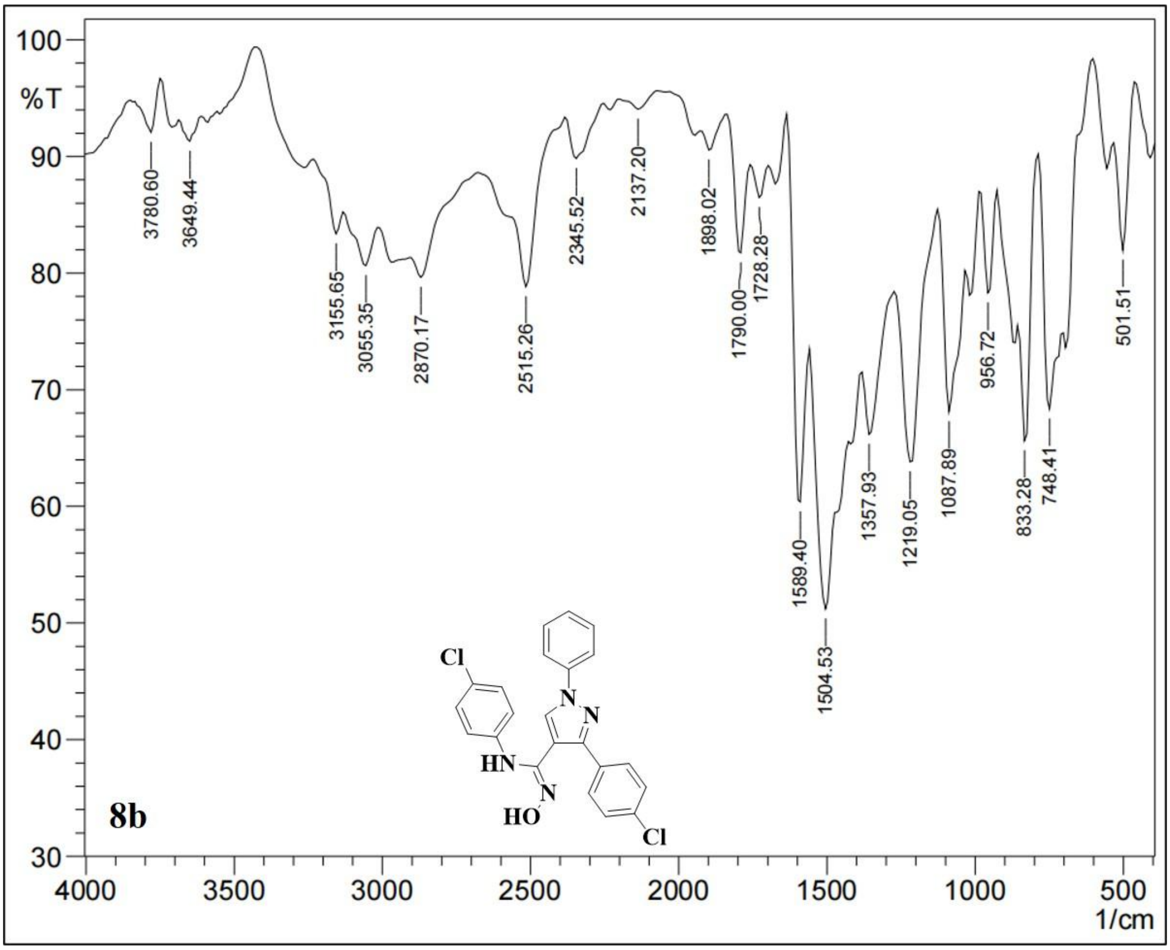


**Fig.5.5:** Representative IR spectrum of compound 8b

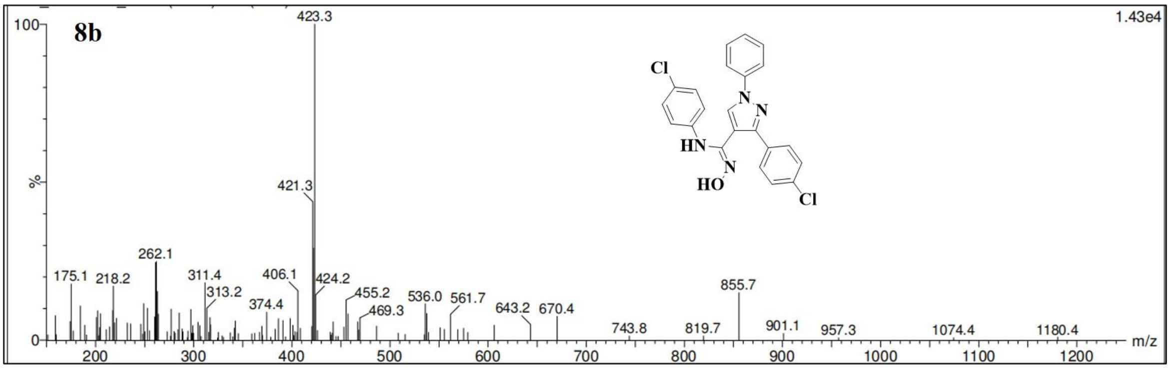


**Fig.5.6:** Representative mass spectrum of compound 8b

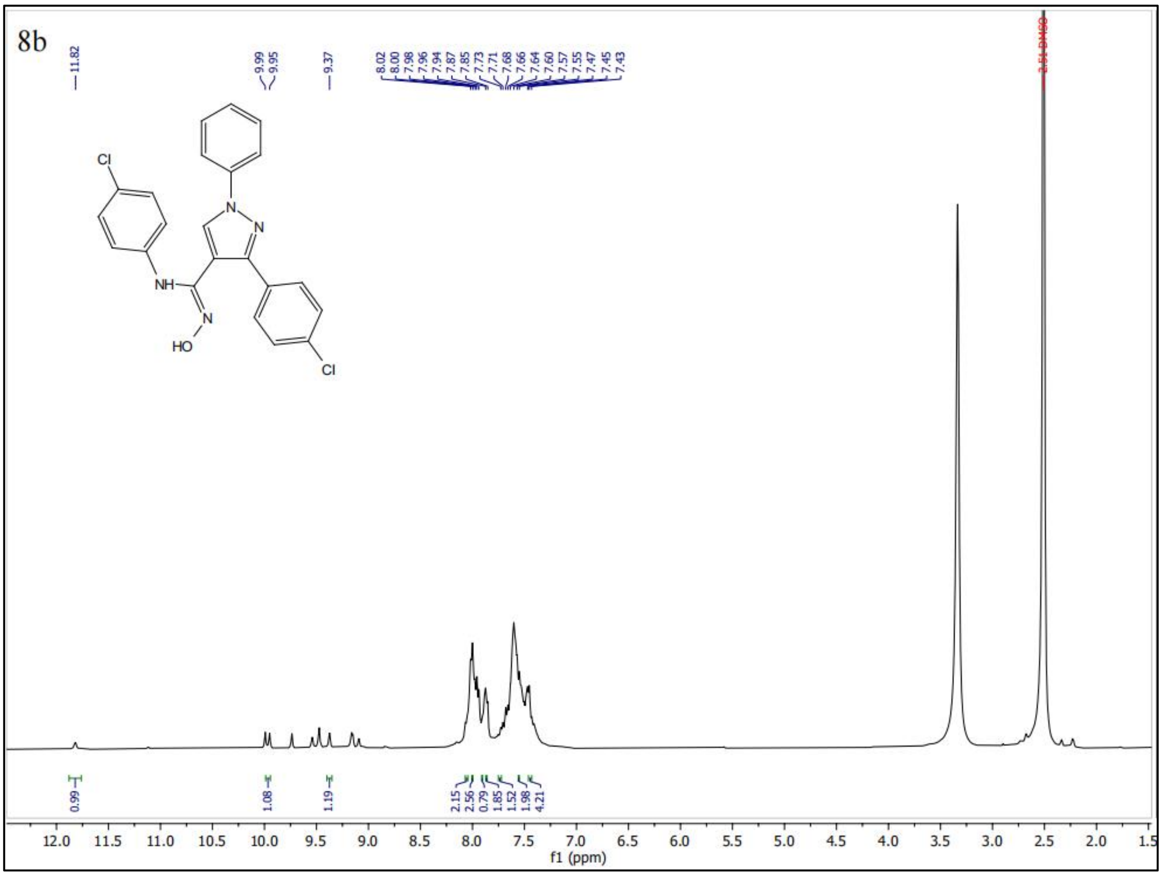
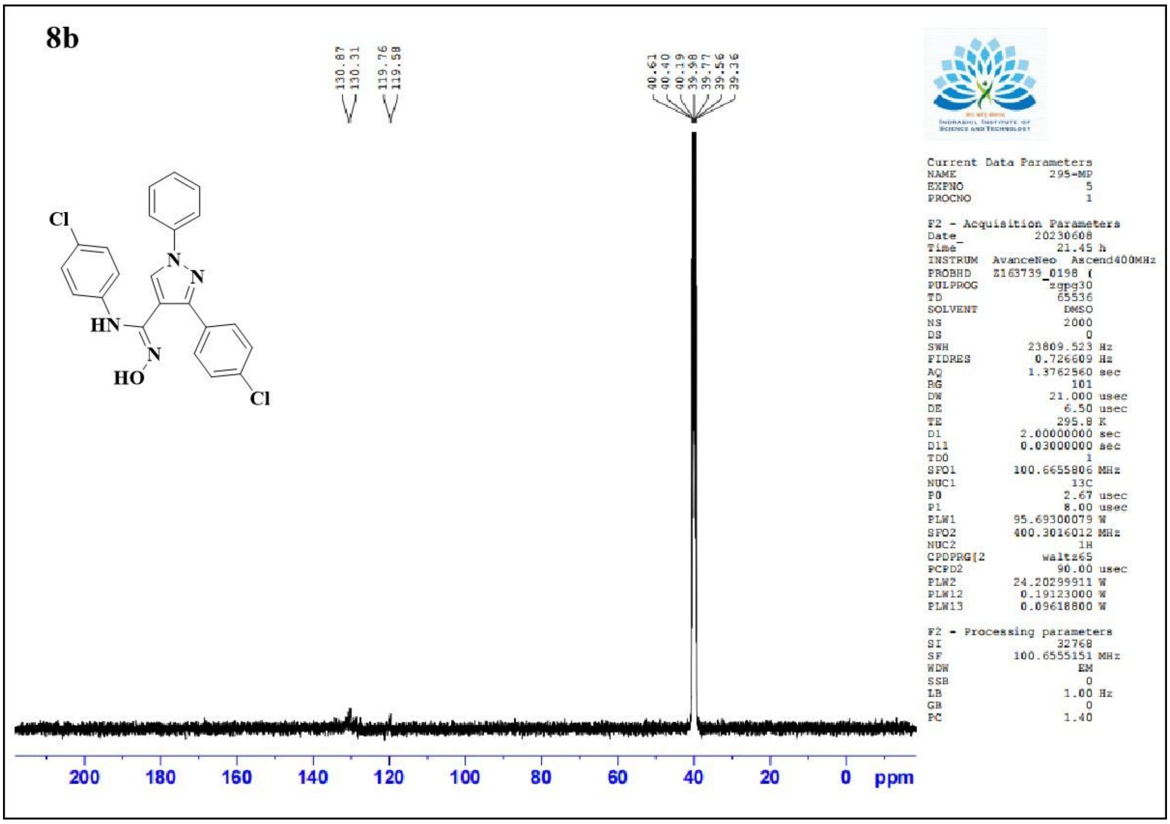


**Fig.5.7:** Representative $^{1}$H NMR spectrum of compound 8b



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TD                 65536
SOLVENT             DMSO
NS                  2000
DS                     0
SWH            23809.523 Hz
FIDRES          0.726609 Hz
AQ             1.3762560 sec
RG                   101
DW                21.000 usec
DE                  6.50 usec
TE                 295.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1         100.6655806 MHz
NUC1                 13C
P0                  2.67 usec
P1                  8.00 usec
PLW1         95.69300079 W
SFO2         400.3016012 MHz
NUC2                  1H
CPDPRG[2         waltz65
PCPD2              90.00 usec
PLW2         24.20299911 W
PLW12         0.19123000 W
PLW13         0.09618800 W

F2 - Processing parameters
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**Fig.5.8:** Representative $^{13}$C NMR spectrum of compound 8b

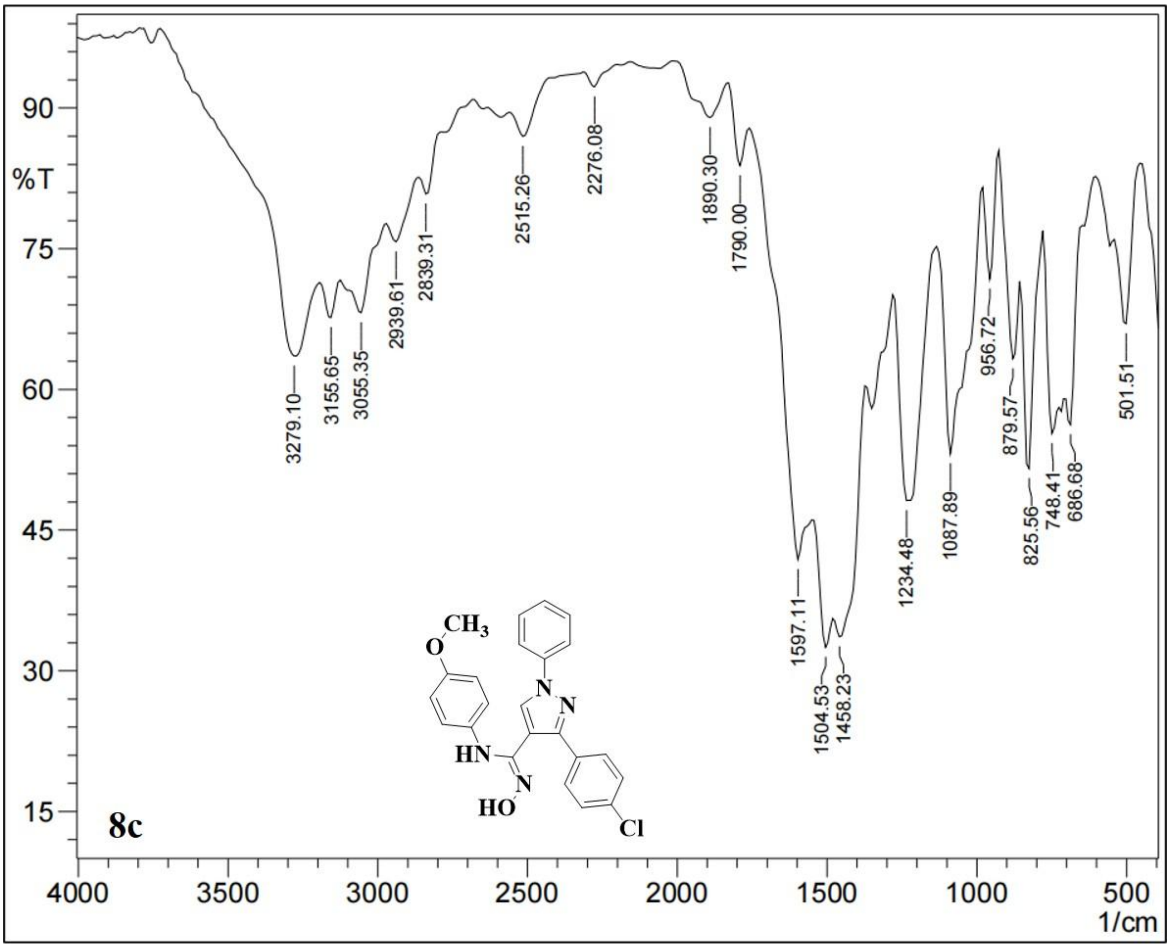


**Fig.5.9:** Representative IR spectrum of compound 8c

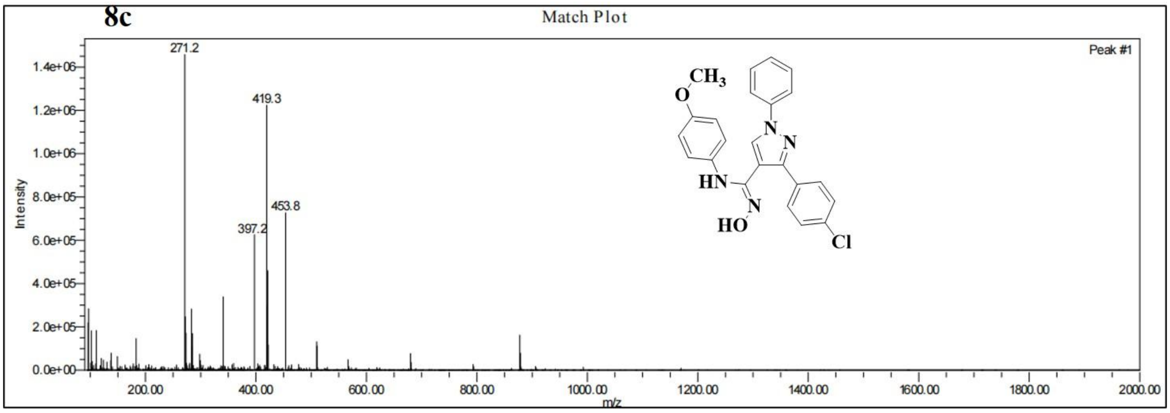


**Fig.5.10:** Representative mass spectrum of compound 8c

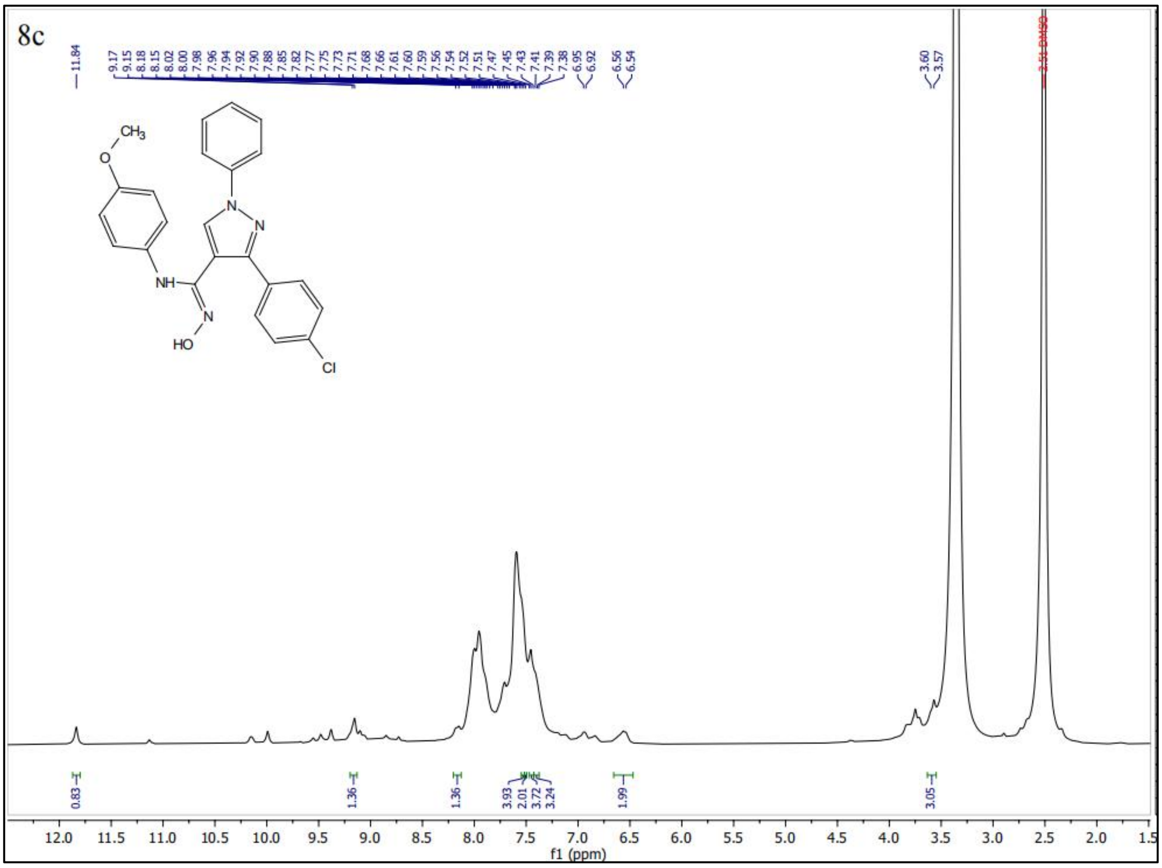
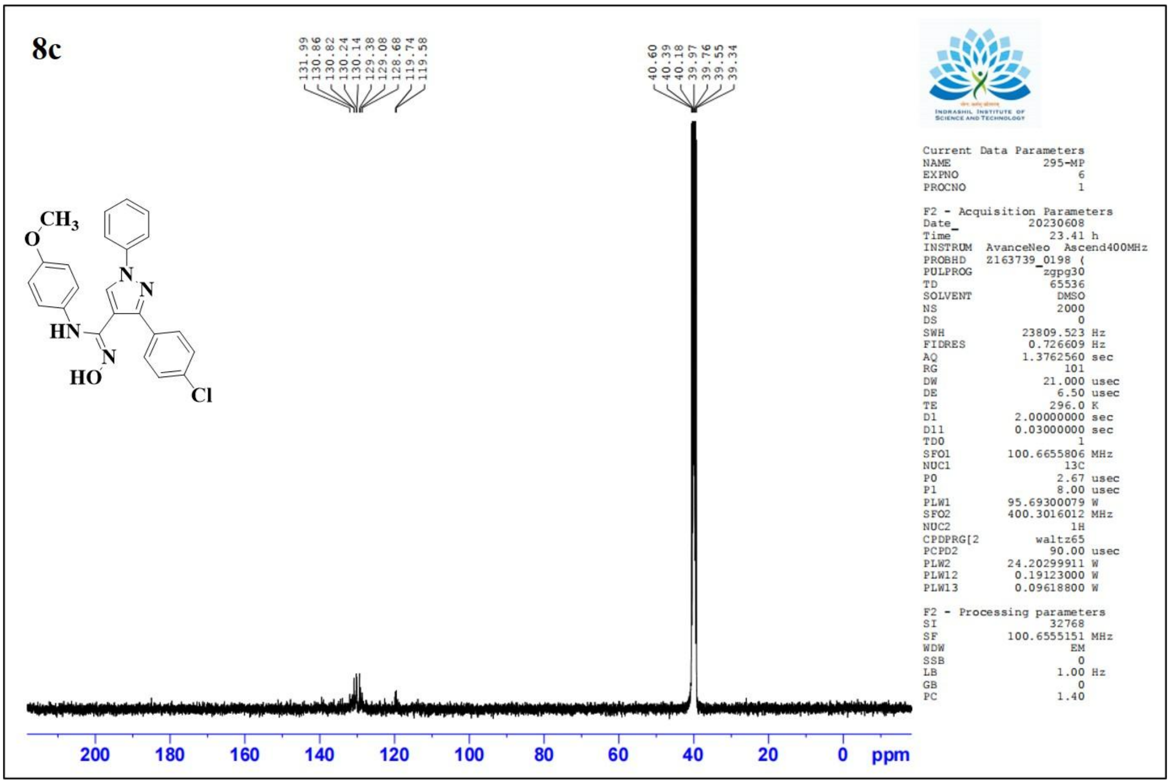


**Fig.5.11:** Representative $^{1}$H NMR spectrum of compound 8c



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PULPROG            zgpg30
TD                  65536
SOLVENT              DMSO
NS                   2000
DS                      0
SWH             23809.523 Hz
FIDRES           0.726609 Hz
AQ              1.3762560 sec
RG                    101
DW                 21.000 usec
DE                   6.50 usec
TE                  296.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6655806 MHz
NUC1                  13C
P0                   2.67 usec
P1                   8.00 usec
PLW1          95.69300079 W
SFO2          400.3016012 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2          24.20299911 W
PLW12          0.19123000 W
PLW13          0.09618800 W

F2 - Processing parameters
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LB                   1.00 Hz
GB                      0
PC                   1.40
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**Fig.5.12:** Representative $^{13}$C NMR spectrum of compound 8c

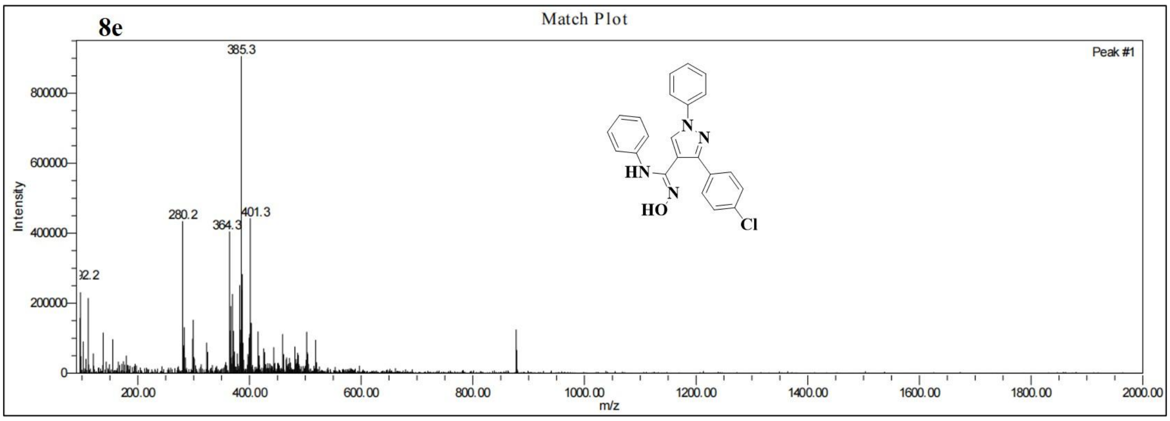


**Fig.5.13:** Representative mass spectrum of compound 8e

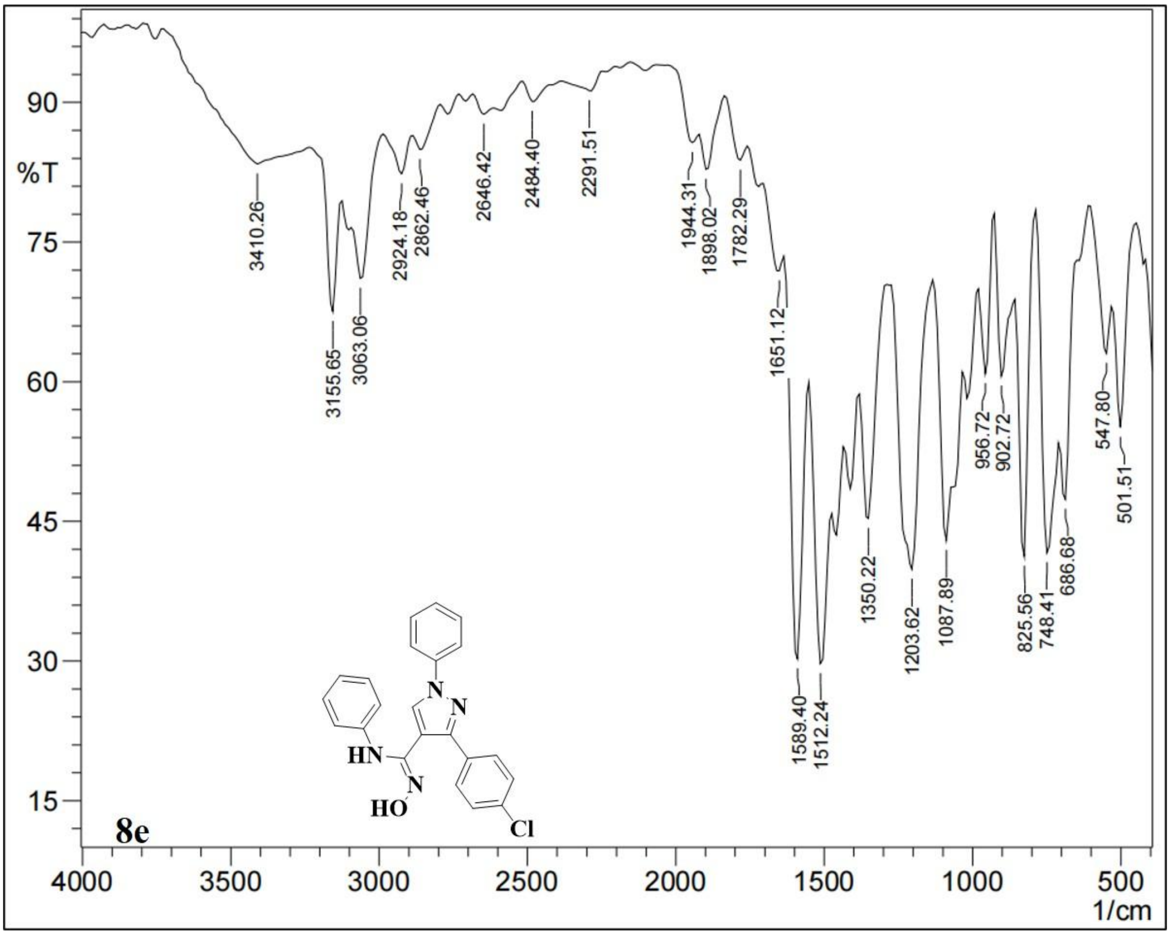


**Fig.5.14:** Representative IR spectrum of compound 8e

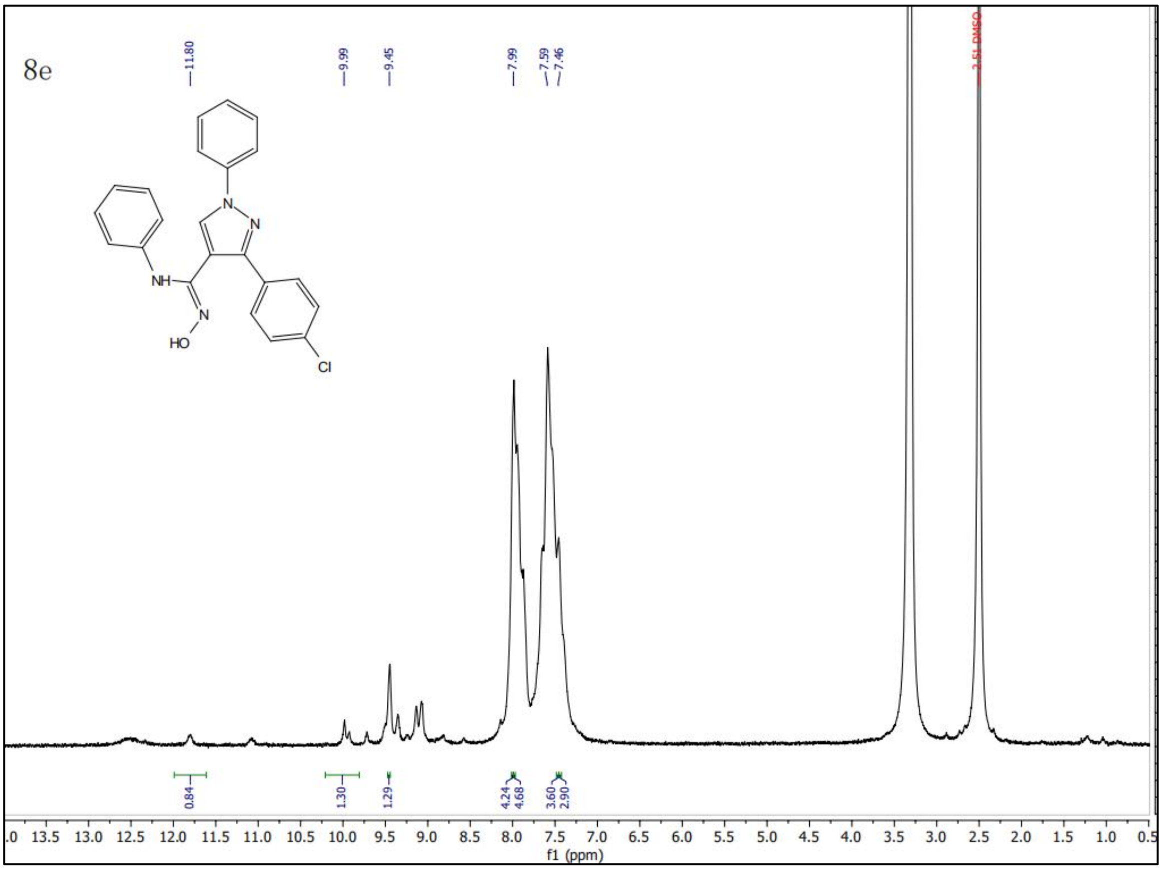


**Fig.5.15:** Representative $^1$H NMR spectrum of compound 8es

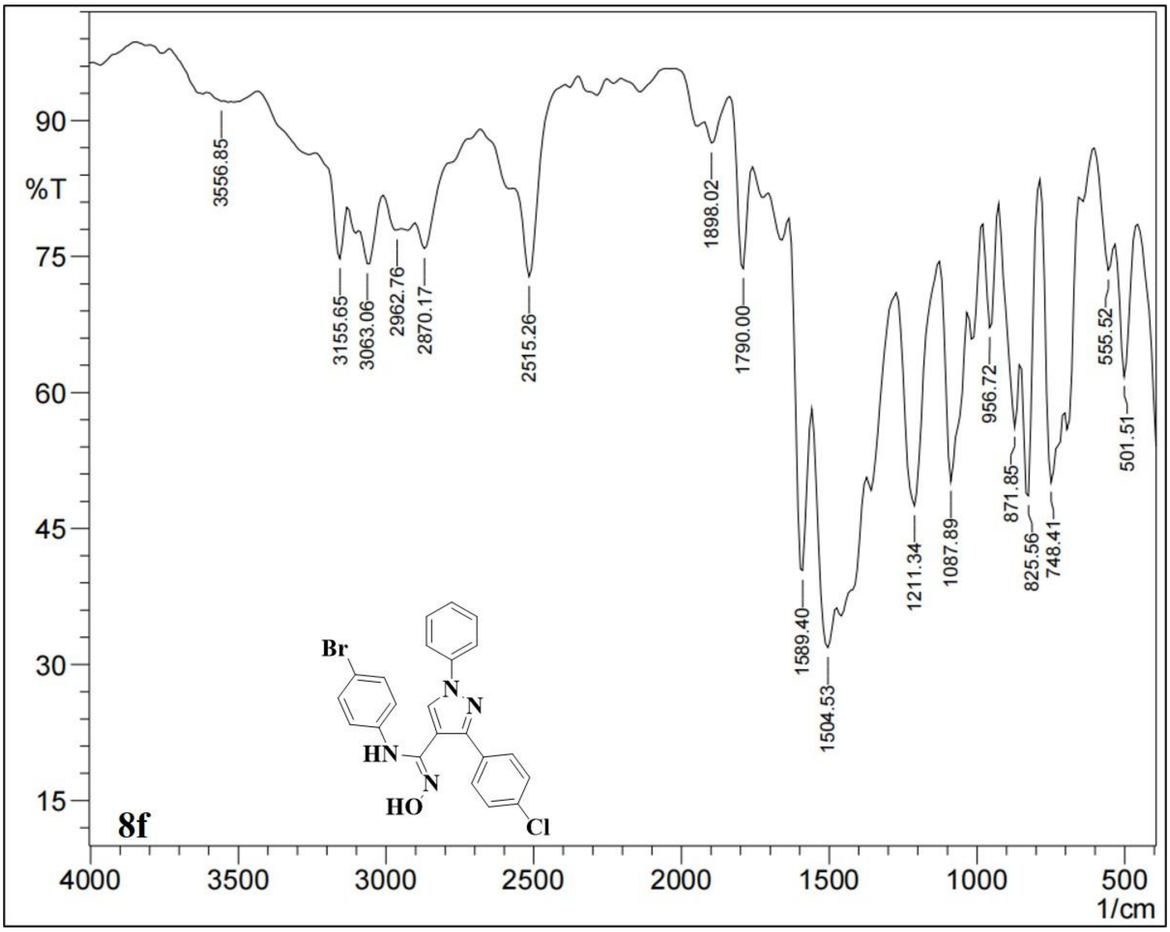
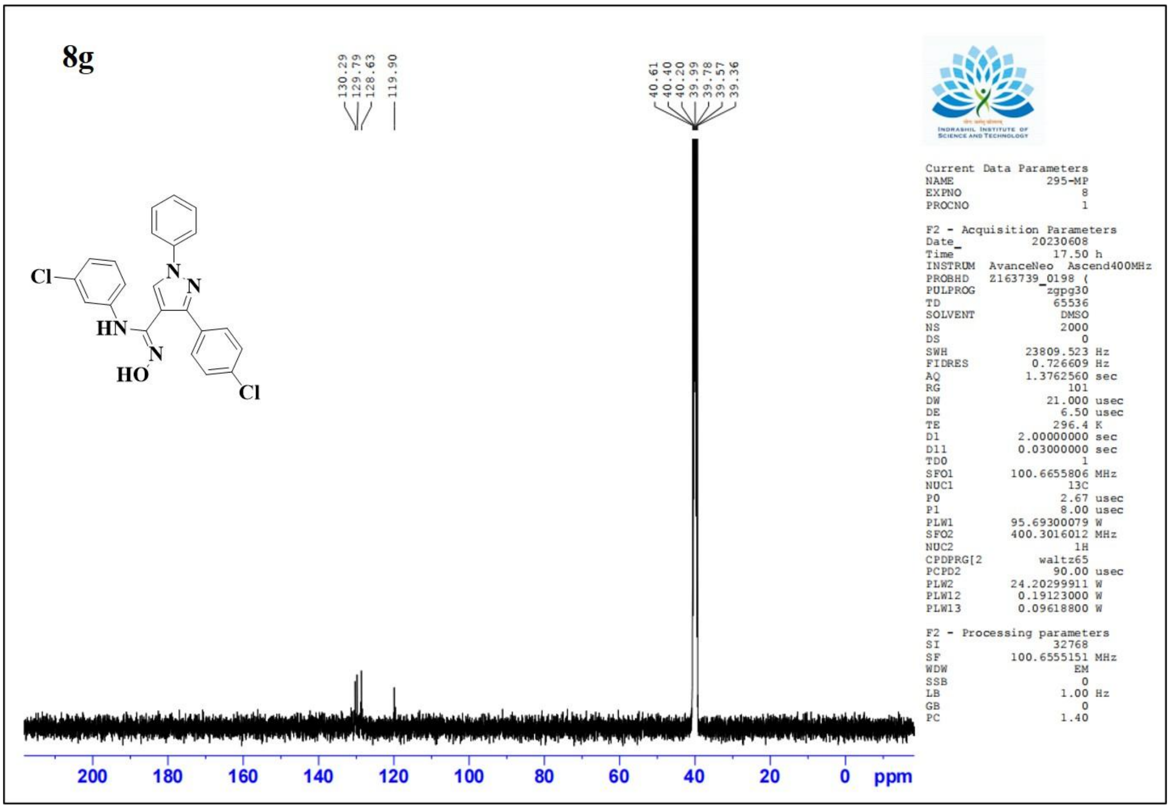


**Fig.5.16:** Representative IR spectrum of compound 8f



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SOLVENT             DMSO
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FIDRES          0.726609 Hz
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TE                 296.4 K
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TD0                    1
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NUC1                 13C
P0                  2.67 usec
P1                  8.00 usec
PLW1         95.69300079 W
SFO2         400.3016012 MHz
NUC2                  1H
CPDPRG[2         waltz65
PCPD2              90.00 usec
PLW2         24.20299911 W
PLW12         0.19123000 W
PLW13         0.09618800 W

F2 - Processing parameters
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WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
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**Fig.5.17:** Representative $^{13}$C NMR spectrum of compound 8g

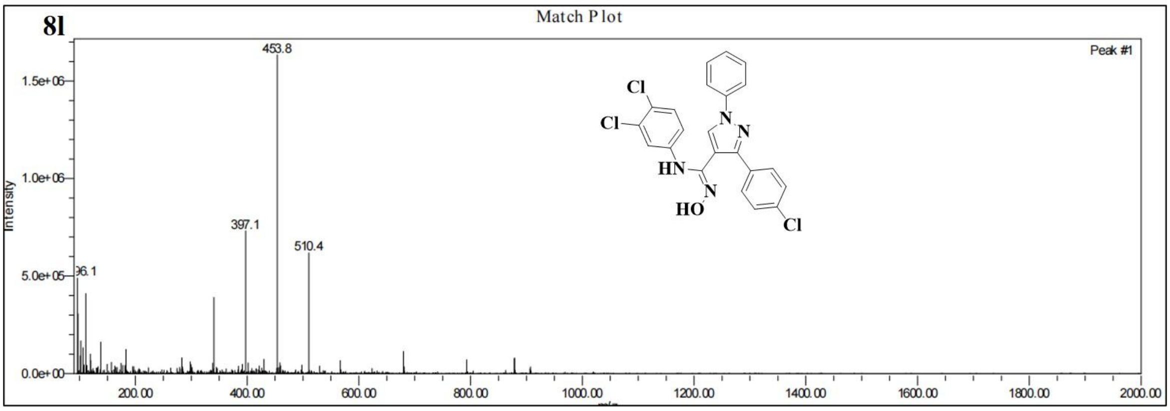

**Fig.5.18:** Representative mass spectrum of compound 8l