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REVIEW

A Retrospective Study of Synthesis, Structure-Activity Relationship and Antimicrobial Activity of 4-Formyl Pyrazole Containing Isoniazid Moiety

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ABSTRACT

4-Formyl pyrazole is nitrogen containing heterocyclic aromatic molecule containing isoniazid moiety. The molecule is formed by fusion of two heterocyclic ring *i.e.* pyrazole and isoniazid. The current paper covers a vast range of methods for synthesis of 4-formyl pyrazole containing isoniazid moiety and its derivatives using variety of catalyst, solvent medium and microwave irridation with a goal of achieving a high yield and rapid separation of products. This work describes 4-formyl pyrazole and isoniazid antimicrobial activity as well as their structural-activity relationship. It also includes the mechanism of action of pyrazole and isoniazid and includes the list of current patents linked to various pharmacological activities in previous past years.

KEYWORDS

4-Formyl pyrazole, Isoniazid, Pharmacological activity, Heterocyclic, Mechanism of action, Pyrazole.

INTRODUCTION

From a long period, the study of heterocyclic compounds seem to be a fascinating area of research [1]. Due to the presence of their functional subunit heterocyclic compounds are found in the nature and play an essential part in metabolism [2]. In recent decades, the synthesis of various pyrazole derivatives and analysis of their chemical and biological activity has become more significant for biochemical, medical and agricultural purposes [3].

For last 20 years, pyrazole being as a heterocyclic compound grab much more consideration because it is relatively easy to obtain and appear to have a extensive variety of medicinal properties [4]. In 1883, the word pyrazole is firstly introduced by the scientist Ludwig Knorr [5]. Pyrazole is a potent scaffolds containing two nitrogen atom in its five membered ring structure [6]. They are the most investigated chemical compound in the azoles family. Over a year, many of fabrication techniques and substituted derivatives have been published [7]. Especially, they are defined as antibacterial [8], anticancer [9], inhibitor of protein glycation, antifungal [10], antidepressant [11], anti-inflammatory [12], antituberculosis [13], as well as antiviral [14]. Increases in the drug resistance, as an outcome of bacterial infection have become a major public health issue [15,16].

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Every year, many people become infected because of bacterial infection [17].

So there is vital need to designing a novel structure which is impactful and less harmful [18]. Many alkyl pyrazoles have antibacterial, antifungal and bacteriostatic properties [19]. 1*H*-pyrazole-4-carboxylate has strong antibacterial and antifungal properties [19,20]. Treating hydrazones and semicarbazones of ketones with Vilsmier reagent yield pyrazole derivatives [21,22]. Literature shows that treating the substituted acetophenone and isoniazid in the presence of Vilsmier reagent by conventional method to form 4-formyl pyrazole derivatives, which shows good antimicrobial activity [23].

Isoniazid is a first-line antituberculosis medication that kills *M. tuberculosis* bacteria [24]. Isoniazid is commonly recommended antibiotic for TB therapy. Isoniazid is a prodrug that is activated by the enzyme KatG. (Mycobacterial catalase-oxidase) [25,26]. Its derivatives are more active than its proform and have good antimicrobial affect [27,28]. Due to the biological usage, the hydrazide-hydrazones derivatives of isoniazid are more noticed [29] and debate the structural activity relationship (SAR) of antimicrobial activity [30]. Isoniazid is firstly synthesized in 1912 for the treatment of TB without knowing its large importance [31]. When isoniazid used in combination with other drugs like refampin and pyrazinamide it still use as main front line TB drug in worldwide [32].

Isoniazid

The pyridine ring is a basic structure or is required for the drug's antimycobacterial effectiveness [33]. Mainly many substitution on isoniazid occur at N-2 position if any bulkier groups attach at this position will lead to sometime increase in the activity or decrease in the activity (Fig. 1) [34].

For antimycobacterial action, there must be a free hydroxyl group at the *para*-position; any substitution at that location reduces the moiety's activity. When NH proton is substituted with acyl group lead to increase in the activity, which further increases the lipophilicity of the molecule, so the microbial membrane can easily penetrates [35]. Isoniazid derivatives are more active against Gram-negative, such as *E. coli*, than Gram-positive organisms, such as *B. subtilis* and *S. aureus*. This agreement may be seen in the Sbardella *et al.* [36]. According to Guven *et al.* [37], the presence of a substitution at the *ortho* position improves the antifungal and antibacterial properties of an antimicrobial molecule. At *ortho* position, OH group is attached and NH group is replaced by benzoyl moiety it increases the lipophilicity of the molecule and the molecule is find to be more active.

Pyrazole

Substitution at R_5 position of pyrazole ring tends to increases the binding of the molecule to cannabinoid receptor. If the presence of any group like nitro, iodo or amino at *p*-position of substituted phenyl ring attach to the 5 position of pyrazole ring increase the binding affinity [38]. Kumar *et al.* [39] showed that the presence of electron donating group like -OCH_3 on the other substituted ring and presence of fluro, chloro on the C_5 substituted benzene ring of pyrazole increases the activity on the other hand like –CN decreases the activity because it donate electron density. Furthermore, an *in vitro* study by Kumar *et al.* [40] reported that the presence of electronegative group on the benzene ring increases the antimicrobial activity and the presence of electron donating group attach to the substituted ring increase the antifungal activity.

If the nitro group attach to the *para* position of R_1 substitution shows good antimicrobial activity. In the same if nitro is group attach to other substitutent on pyrazole ring like at R_2, R_3 does not reveal any antimicrobial effect [41]. If the pyrazole structure is aromatized it shows antibacterial as well

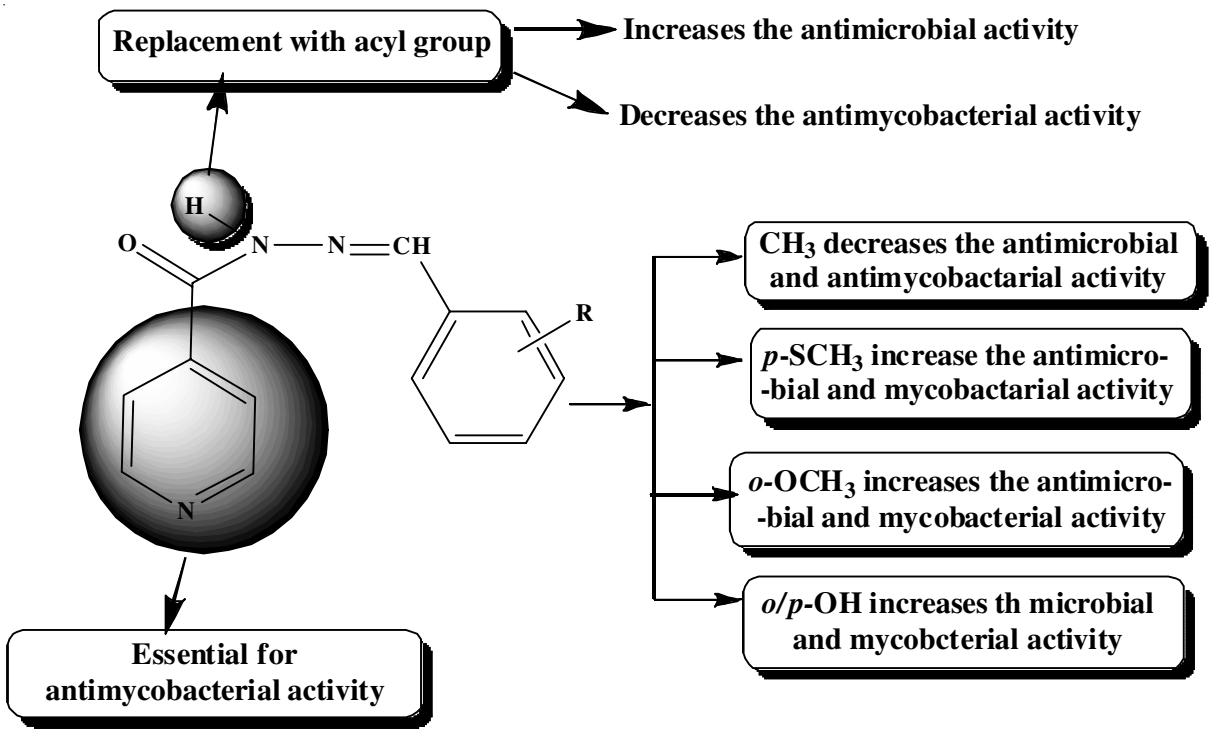


Fig. 1. The structural-activity relationship of isoniazid

as antifungal activity. Presence of any substitution further on the C4 substituted phenyl ring of pyrazole alters the antimicrobial activity. Substitution at *para* position increases the activity.

Presence of *para*-cholorobenzyl moiety at C4 position of pyrazole ring is important for the antimycobacterial activity. Different substitution are allowed at position N_1, N_2 and C_3 of pyrazole ring to enhance the antimycobacterial activity [42]. Synthesis of pyrazole 3-carboxamide showed that in the derivatives, the chiral unit must be present for antimicrobial activity as the chiral unit interact with bioactive molecule easily. The presence of bulkier group on the (R) amino alcohol of pyrazole -3-carboxamide derivatives enhances the antimicrobial activity.

Various synthesis of 4-formyl pyrazole containing isoniazid moiety: Derivatives of 4-formyl pyrazole using isoniazid are base on the biological activity. Various researchers synthesized the pyrazole derivatives based on microwave irradiation and conventional method to yield good quantity and quality of derivatives, which posses some biological activity and have the active moiety that reach to the active site of the disease that are caused by microbes. The details of several marketed drugs bearing 4-formyl pyrazole moiety are given in Table-1 [43-46].

Pyrazole derivatives are synthesized by using isonicotinohydrazide under microwave irradiation. Isoniazid and ethyl-2-cyanoacetate were condensed under solvent free mixture in microwave irradiation resulted in 3-amino-1-isonicotinoyl-1*H*-pyrazole-5-[4*H*]-one which further react with various substitutes of benzaldehyde to form **1** (**Scheme-I**). The final products were evaluated for antimicrobial activity and good antifungal and antibacterial effect [47].

2-[3-nitrophenyl-1-(pyridine-4-ylcarbonyl)-1*H*-pyrazole-4yl]-3-substituted-1 and 3-thiazolidin-4-one is synthesized by three steps reaction. In the first step, isonicotinic acid hydrazide react with substituted acetophenone yield N-[1-(4-nitrophenyl)-ethylidene] isonicotinic hydrazide. In second step, the resulted product was treated with Vilsmeyer-Hack reagents to give 1-isonicotinoyl-3-(4-nitrophenyl)-1*H*-pyrazole-4-carbaldehyde, which on further behaviour towards aromatic amine in the appearance of toluene produced the final product (**Scheme-II**) and all the compounds show antimicrobial activities [48].

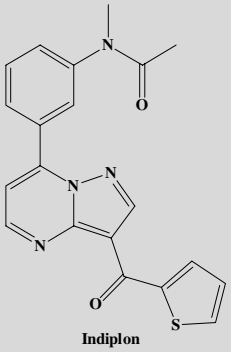
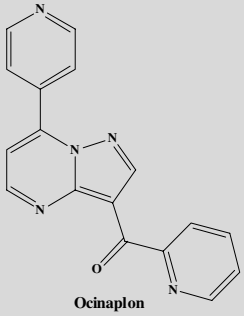
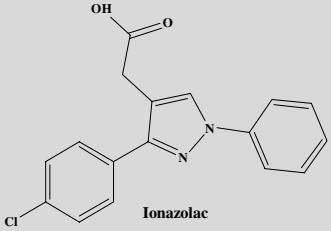
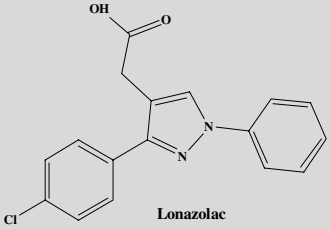
Under microwave irradiation, Vilsmier-Hack reagents are used to make a new sequence of pyrazole-4-carbaldehyde derivatives. In two-step reaction, first isoniazid reacts with substituted acetophenone in ethanol under microwave. Secondly, the synthesized product reacts with Vilsmier-Hack reagent to form 1-isonicotinoyl-3-[4-nitrophenyl]-1*H*-pyrazole-4-carbaldehyde (**Scheme-III**) [49].

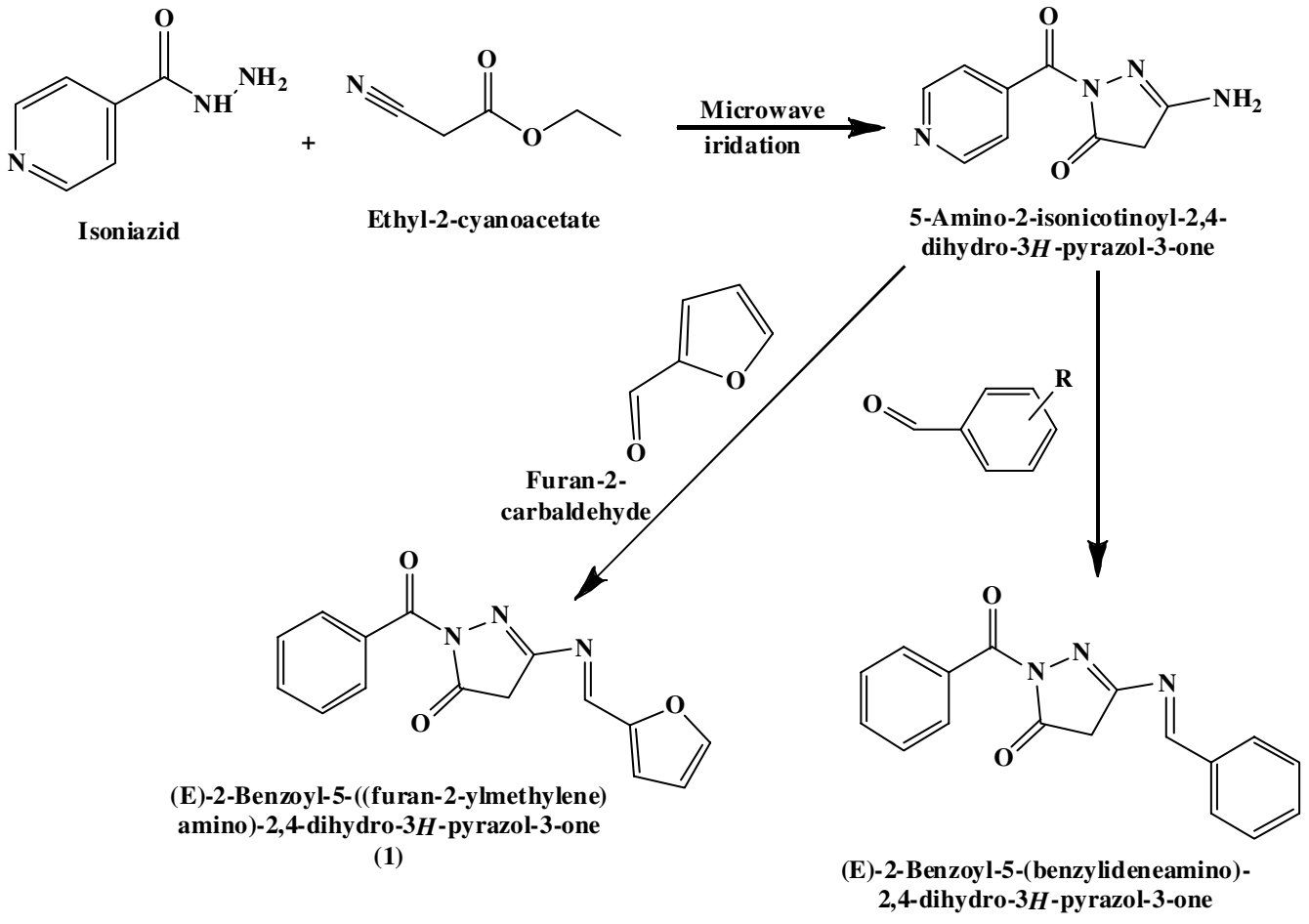
In **Scheme-IV**, the first step involves the formation of hydrazones occur, the hydrazones were synthesized by reacting with pyrazole aldehyde derivative and the prepared hydrazones derivatives further react with $POCl_3$/DMF to give pyrazole aldehyde then the synthesis of bipyrazole derivative occur. The synthesis of bipyrazole derivative occurs under microwave irradiation using isoniazid. As microwave method is more effective than conventional method and less time consuming [50].

Szymanska and Kiec-Kononowicz [51] reported that in the primary assay for antimycobaterial activity against *M. tuberculosis* H_{37}RV several 5-(chlorobenzylidene)-2-isoniazido and 5-(chlorobenzylidene)-2-amino substituted imidazoline-4-one derivatives are synthesized (**Scheme-V**). The synthesized compounds inhibit the 90% of *Mycobacterium tuberculosis* growth. The *in vitro* antimicrobial activity of compound 5-(3-chlorobenzylidene)-2-(isonicotinoylhydrazino)imidazoline-4-one was compared and tested with refampin resulting value lies in between MIC = 0.8 µg/mL, SI > 78.

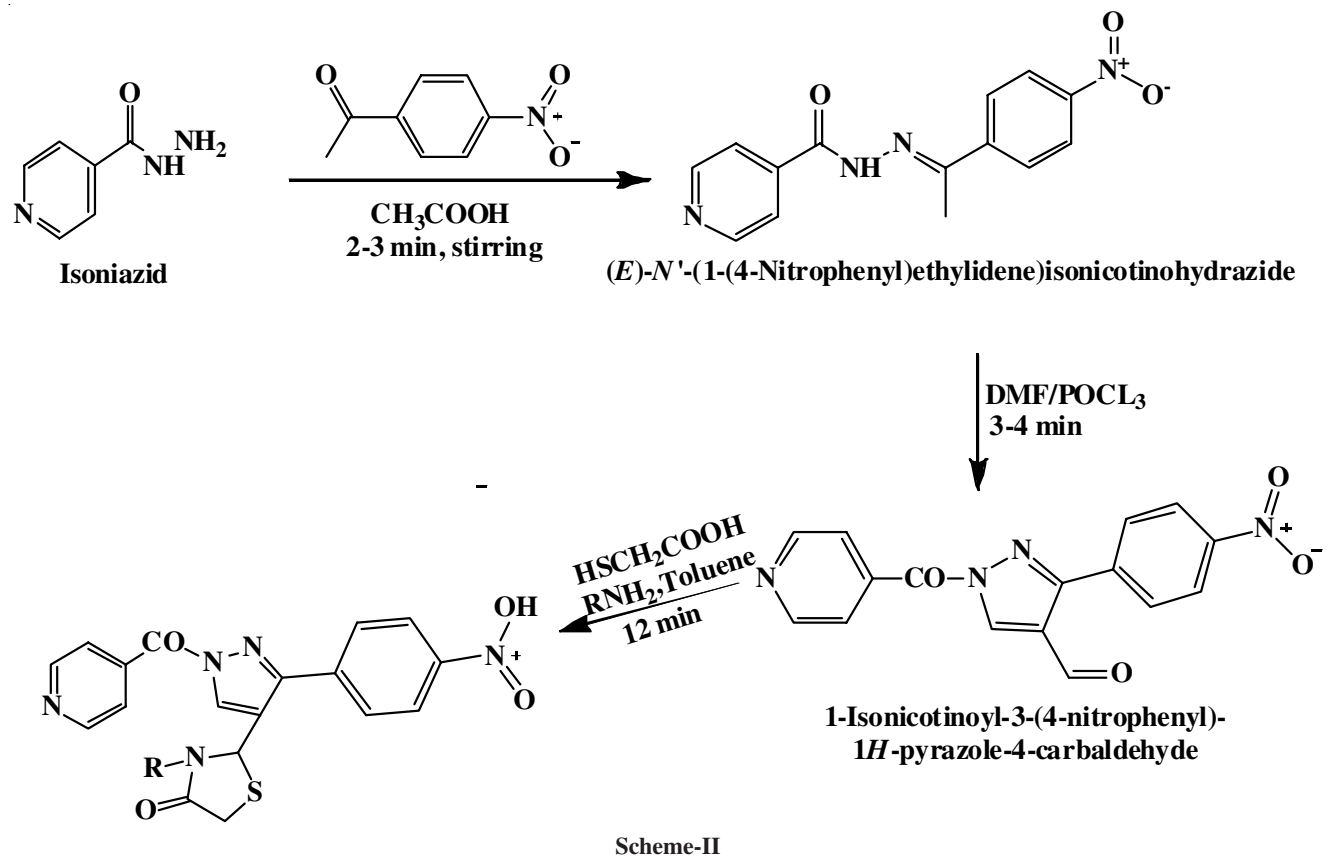
Nayak *et al.* [52] synthesized a new series of isonicotinohydrazide based pyrazole derivatives (**Scheme-VI**). All new derivatives were screened for *in vitro* antimycobacterial activity

TABLE-1
SOME MARKETED DRUG CONTAINING 4-FORMYL PYRAZOLE MOIETY

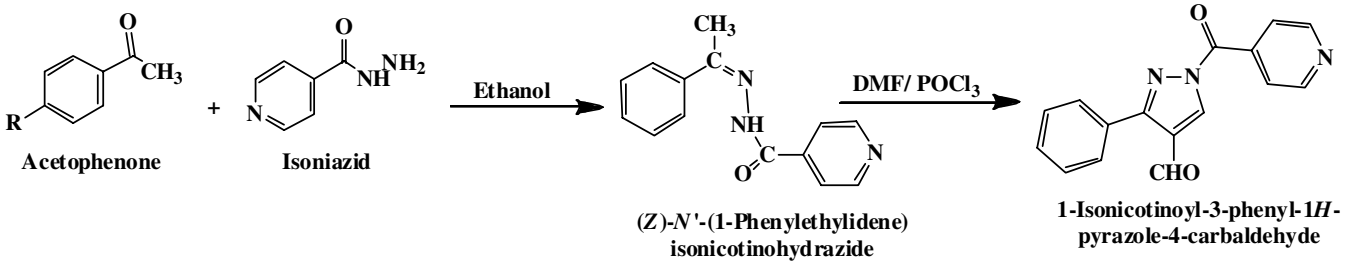
Structures	Marketed drug bearing 4-formyl pyrazole moiety	Structures	Marketed drug bearing 4-formyl pyrazole moiety
 Indiplon	Indiplon is a hypnotic sedative use in sleep disorder [43].	 Ocinaplon	Ocinaplon is a drug that is used to alleviate anxiety [45].
 Ionazolac	Ionazolac is non-steroidal anti-inflammatory drug [44].	 Lonazolac	Lonzolac is mostly addicted drug among the NSAID category. It is Used in the treatment of rheumatic diseases [46].



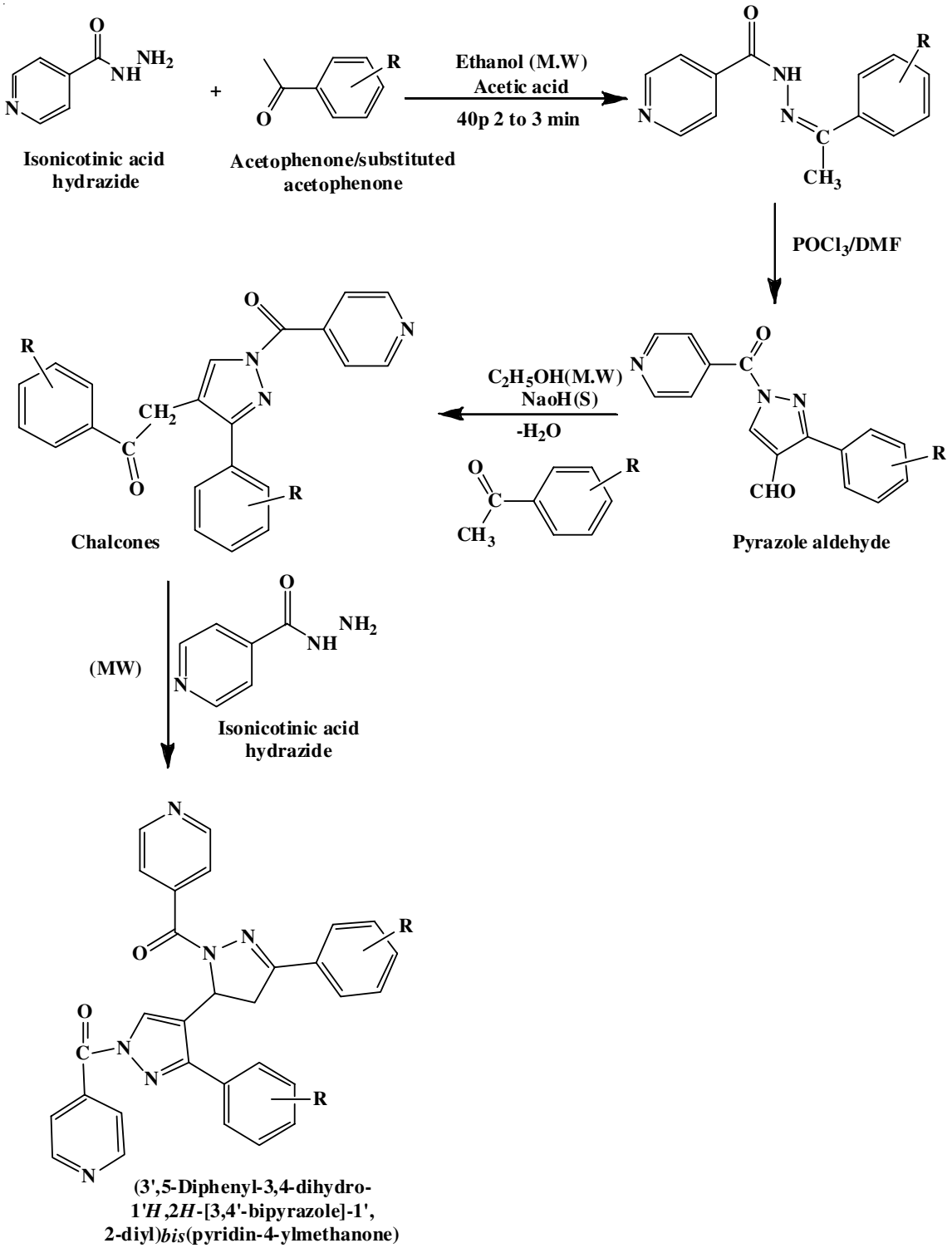
Scheme-I



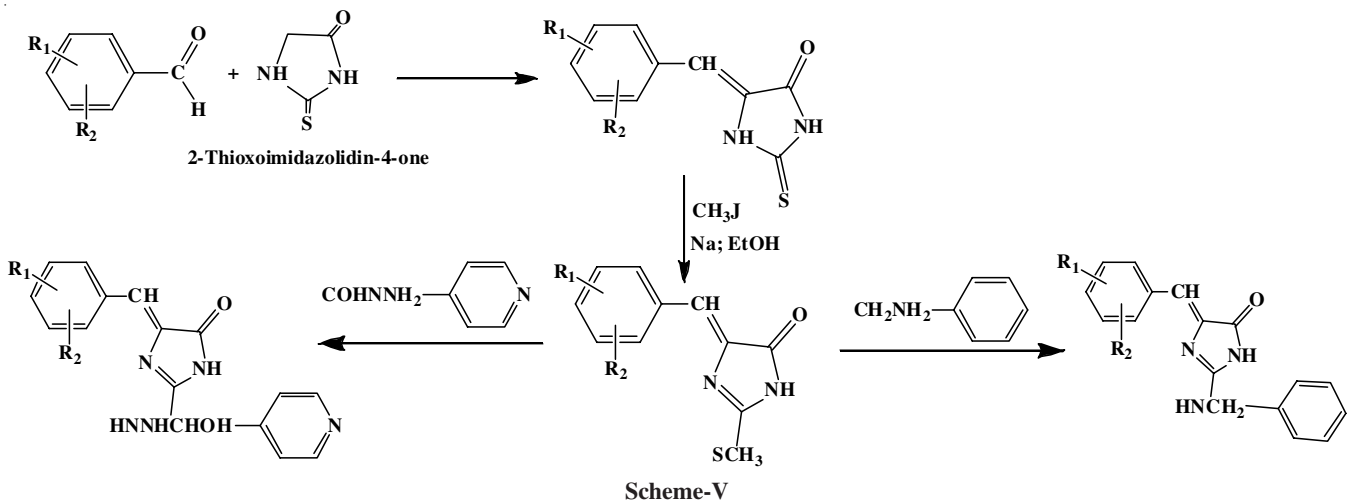
Scheme-II



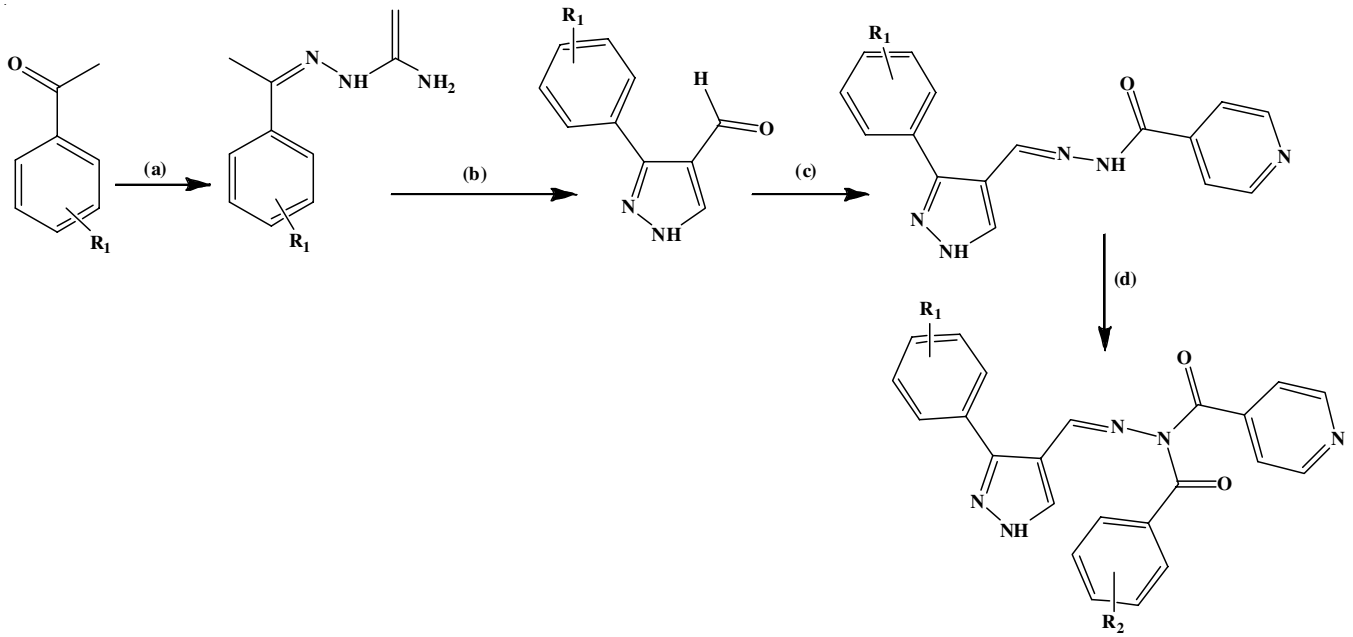
Scheme-III



Scheme-IV



Scheme-V



Scheme-VI: Synthetic route of target compounds (**5a-r**). Reagents and conditions: (a) semicarbazide hydrochloride, sodium acetate, ethanol, 80 °C, 8 h; (b) $POCl_3$, DMF, 80 °C, 2 h; (c) isonicotinohydrazide, ethanol, cat. sulfuric acid, 80 °C, 4 h; (d) aromatic acid derivative, EDC, HOBt, DMAP, dichloromethane, room temperature, 16 h

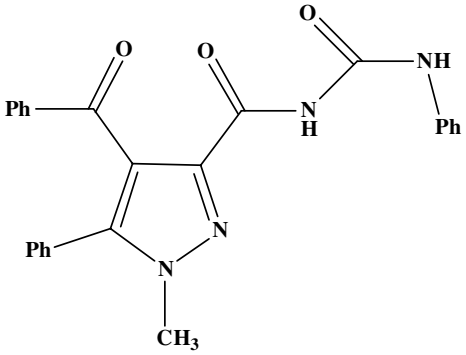
against *Mycobacterium tuberculosis* $H_{37}Rv$ (MTB) strain. Four compounds emerged as promising antitubercular agents with the structure and antitubercular activity relationship was further supported by *in silico* molecular docking study of the active compounds against enoyl acyl carrier protein reductase (InhA) enzyme of *M. tuberculosis*.

Pharmacological activity of isoniazid and pyrazole: Pyrazole and isoniazid posses various biological activities such as pyrazole possess antimicrobial [53,54], antifungal [55], antitubercular [56,57], anti-inflammatory [58], anticonvulsant [59], anticancer [60], antiviral [61], antidiabetics [62], antibacterial [63,64] angiotensin converting enzyme (ACE) inhibitor, neuroprotective [65] and isoniazid posses antitubercular [25], antimicrobial [66], antibacterial and antifungal [67] activities. Among all these activities our main focus is on the antimicrobial activity of pyrazole and isoniazid to synthesized a potent 4-formyl pyrazole derivative containing isoniazid moiety that posses good antimicrobial effect.

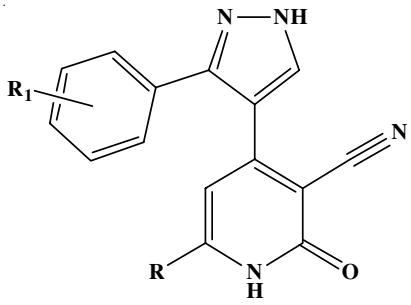
Antimicrobial activity of 4-formyl pyrzole: Akbas *et al.* [68] synthesized that when methyl hydrazine reacted with furandione give a sequence of 1*H*-pyrazole-3-carboxylic acid derivatives which give virtuous the antibacterial activity. In opposition to Gram-negative bacteria *E. coli* and *P. putida* and Gram-positive bacteria *S. aureus* and *B. cereus*. It is concluded that compound **8** shows efficacy against Gram-positive and Gram-negative bacteria.

Isloor *et al.* [69] reported that 4,6-disubsituted-3-cyano-2-pyrodone derivatives after reacting with 3-substituted-1*H*-pyrazole-4-carbaldehyde by Vilsmier-Hack reaction. Synthesized derivative **9** showed good antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

A series of 1*H*-pyrazol-3-carboxylate coupled with germicide using Vilsmier-Hack reagent were evaluated and synthesized for antibacterial activity by. Compound **10** remarkably most potent to hamper the growth of germs ranged from



4-Benzoyl-1-methyl-5-phenyl-*N*-(phenylcarbamoyl)-1*H*-pyrazole-3-carboxamide (8)



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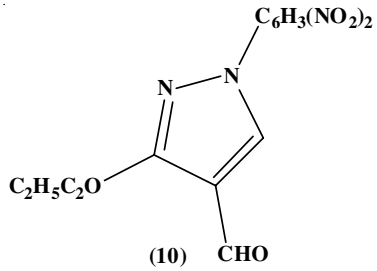
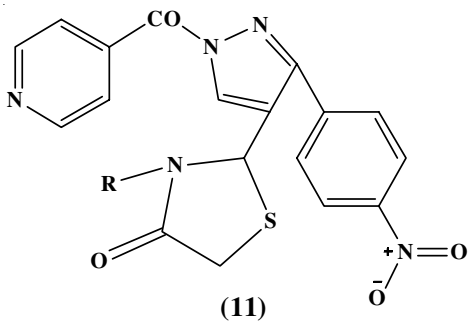


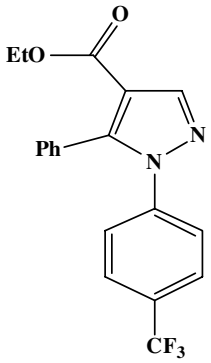
(10)

25.6% to 97.9% [70]. A series of 2-[3-nitrophenyl-1-pyridin-4-yicarbonyl]-1*H*-pyrazol-4yl-3-subsitituted-1,3-thiazolidin-9-one were synthesized and assessed for the antibacterial and antifungal against four antibacterial and two antifungal pathogen. Compound **11** shows the moderate antibacterial and antifungal activity [48].



(11)

Chandrakantha *et al.* [71] reported the synthesis and antimicrobial activity of ethyl 1-(*N*-substituted)-5-phenyl-1*H*-pyrazole-4-carboxylate derivatives. For microbes like *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*, the antibacterial activity of pyrazole derivative were evaluated. Compounds **12**, **13**, **14** and **15** conveyed the marvelous antibacterial activities in opposition to all the tested bacterial strains and standard drug cefrioxane.



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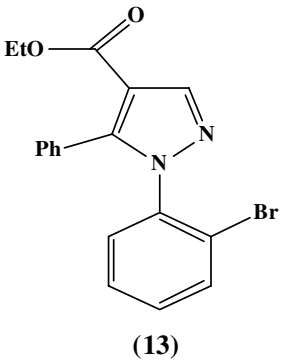

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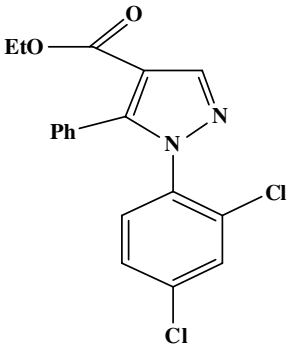

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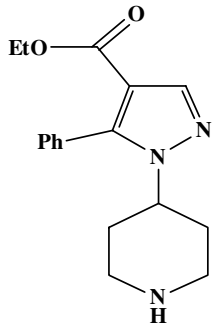
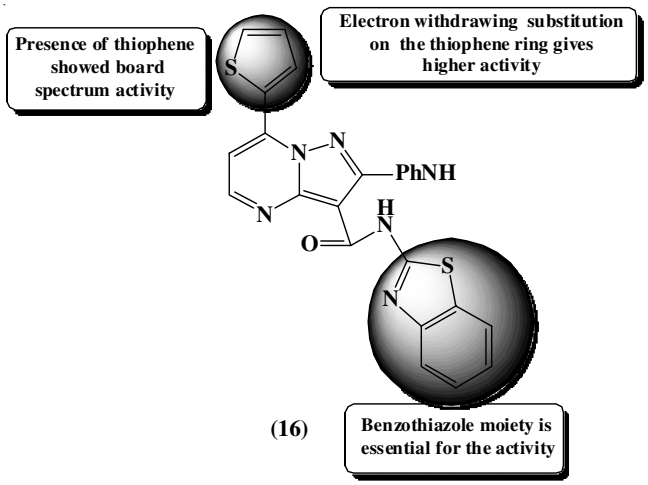


(15)

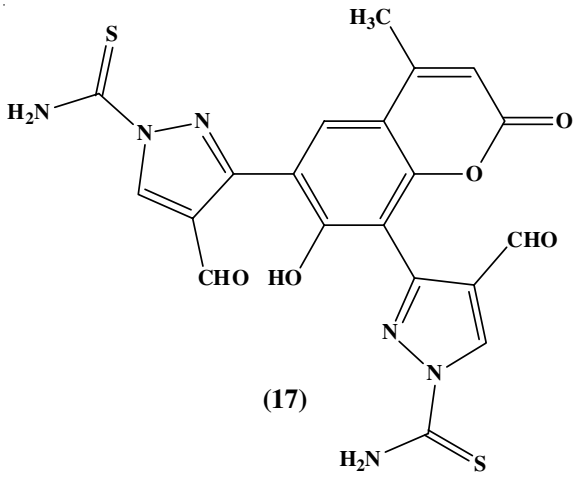
A sequence of fused pyrazole-pyrimidine derivatives was synthesized by Bondock *et al.* [72]. The synthesized compounds are screened for antibacterial and antifungal activity. In this, compound **16** exhibited the most potent *in vitro* antifungal activity with MIC value 6.25 µg/mL against the *Aspergillus fumigates* and *Fusarium oxyporum* when compared with the standard drug, chloramphenicol.



(16)

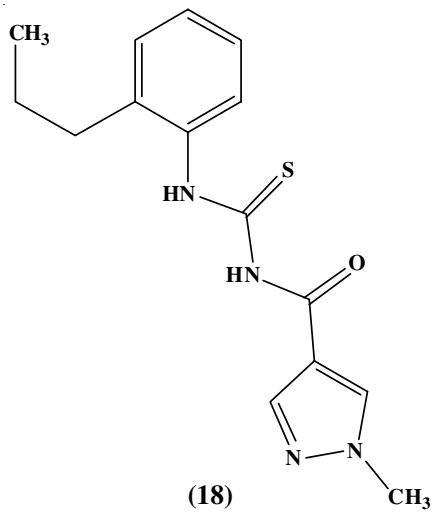
Nagamallu *et al.* [73] reported a sequence of novel 2*H*-1-benzopyran-2-one pyrazole hybrid *via* Vilsmier-Hack formylation synthesis. Among all the synthesized compound **17** shows good antimicrobial activity against disparate bacterial and fungal strain with MIC value 12.5-50 µg/mL.

Sun and Zhou [74] synthesized the derivatives of *N*-(1-methyl-1*H*-pyrazole-4-carbonyl)thiourea by the addition of various anilines substitutes. The entire synthesized compounds



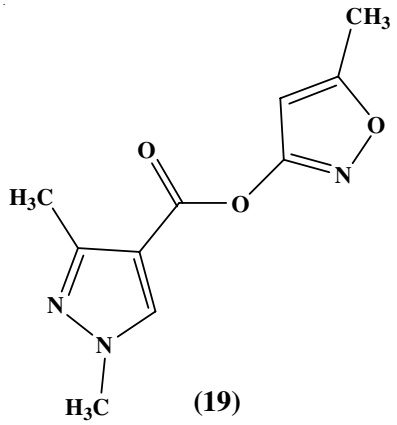
(17)

were estimated for their antimicrobial activity against infectious bacteria. Compound **18** was determined for the antimicrobial activity which found to be the most efficient against microbial agent.



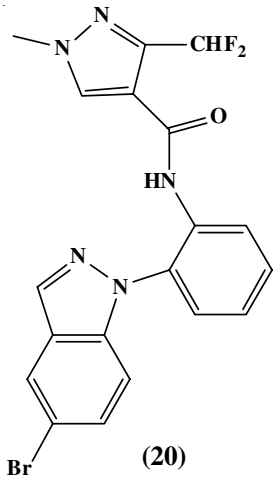
(18)

A study by Sun and Zhou [74] developed and synthesized a number of pyrazole carboxamide and isooxazole pyrazole carboxylate derivatives by using mycelium growth inhibition process. Compounds were also evaluated *in vitro* against four type of phytopathogenic fungus. Amid all the isooxazole pyrazole carboxylate **19** showed strong antifungal activity against *R. solani* with an EC_{50} value 0.37 µg/mL.



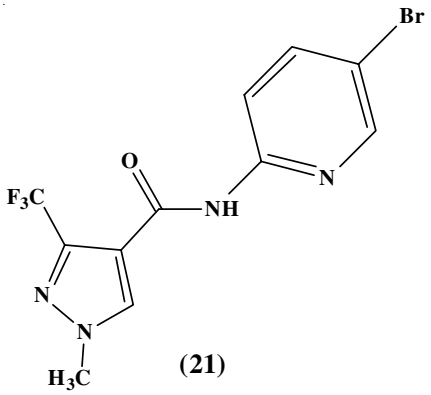
(19)

Du *et al.* [75] reported that an *in vitro* mycelia growth inhibition assay was used to monitor the activities of a variety of novel 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid amide against seven phytopathogenic fungi. Compound **20** displays better antifungal activity than bascalid in opposition to seven phytopathogenic fungi.



(20)

Wu *et al.* [76] synthesized the derivatives of *N*-(substituted pyridinyl)-1-methyl(phenyl)-3-trifluoromethyl-1*H*-pyrazole-4-carboxamide. The synthesized structure was tested for three phytopathogenic fungi name as *Gibberella zea*, *Fusarium oxysperum* and *Cytopora mandshurica.* Amid all the derivatives, the structure of **21** disposed more than 50% diffidence activity in opposition to *G. zea* at 100 µg/mL. A new sequence of pyrazole derivatives were tested for antimicrobial activity by Kendre *et al.* [77]. Despite of all the synthesized compounds **22** and **23** show excellent antibacterial and antifungal activity.



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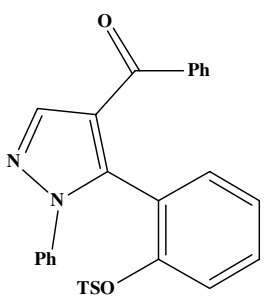

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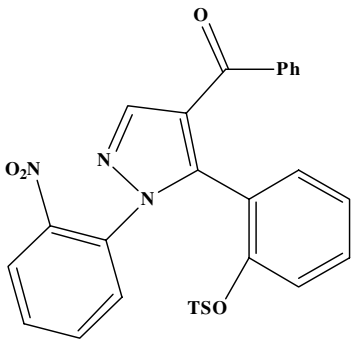
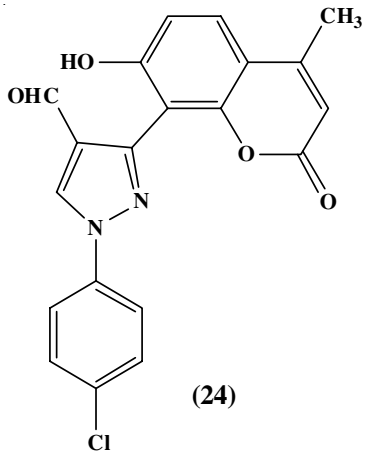


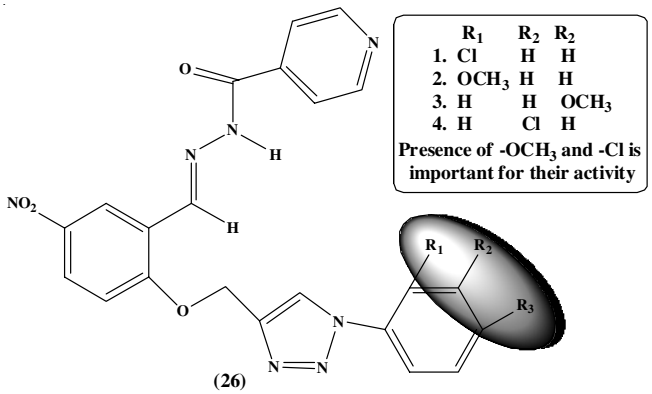
(23)

A series of coumarin modified formyl pyrazole derivatives were synthesized by Renuka *et al.* [78] and *in vitro* screened for antimicrobial and antifungal activity. Among all, the synthesized derivative **24** shows good the antimicrobial and antifungal activity with MIC value 15-6 µg/mL in opposition to tested strain.



(24)

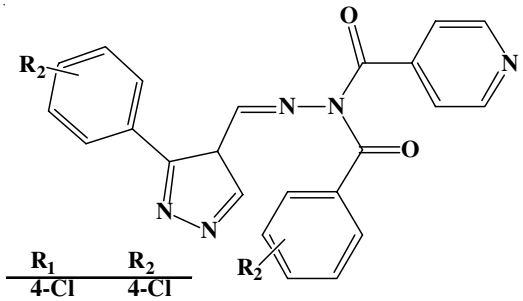
Antimicrobial activity: Patil *et al.* [79] reported a new sequence of isoniazid emended triazole derivatives. The synthesized structures are reported for the *in vitro* antitubercular and antimicrobial activities. Among all the structure only five structure have shown the antimicrobial activity against Gram-positive and Gram-negative pathogens. Nayak *et al.* [52] aimed to design and synthesized a sequence of isoniazid based pyrazole derivatives. All the new synthesized structures were broadcasted for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}R$ strain. Among all, the synthesized derivatives **1**, **2** and **3** showed a good antibacterial activity against the tested bacterial strain.



	R_1	R_2	R_2
1.	Cl	H	H
2.	OCH_3	H	H
3.	H	H	OCH_3
4.	H	Cl	H

Presence of -OCH_3 and -Cl is important for their activity

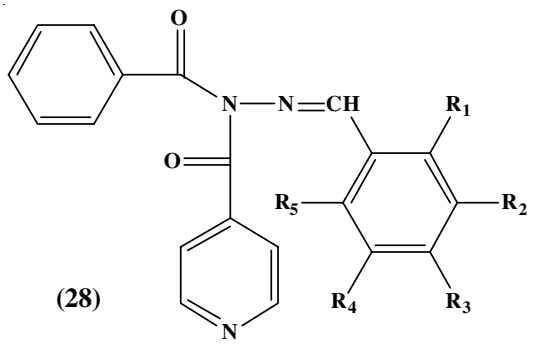
(26)



R_1	R_2
4-Cl	4-Cl
3-Cl	4-Cl
4-Cl	-H

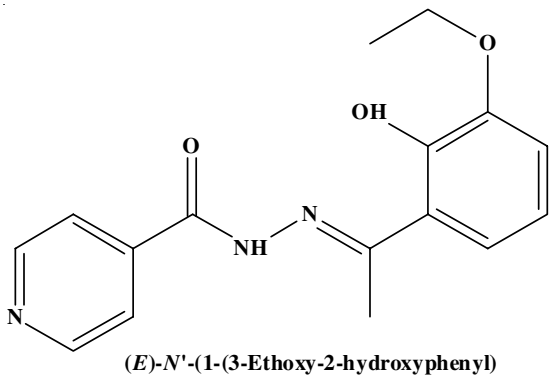
(27)

Judge *et al.* [80] synthesized and tested antimicrobial and antimycobacterial activity of isonicotinic hydrazide derivatives. The synthesized compounds were tested for *Staphylococcus faureus*, *Bacillus subtilis* and *Escherichia coli.* Amid all, the compounds containing OH, SCH_3 and OCH_3 group have good antimicrobial activity against the tested strain. Pahlavani *et al.* [81] synthesized a compound that contains isoniazid. The new synthesized compound was tested for antimicrobial and anti-tubercular activity. The antibacterial activity is tested against *S. aureus, E. coli* out of both the bacteria synthesis compound showed the best result against *S. aureus*.



(28)

R_1	R_2	R_3	R_4	R_5
OCH_3	H	H	H	OCH_3
H	H	SCH_3	H	H
H	OCH_3	OH	H	H

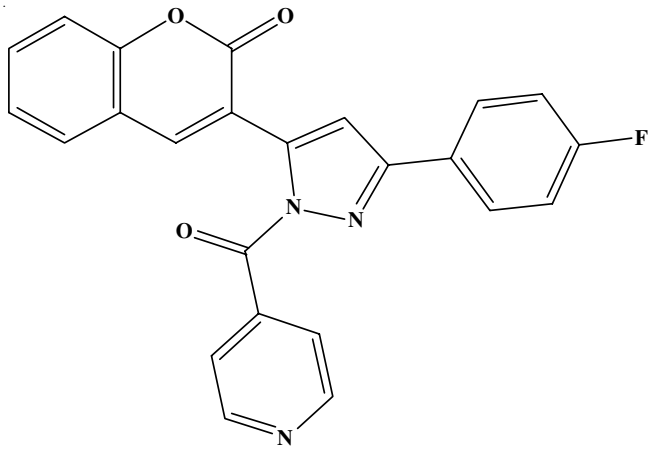


(*E*)-*N*'-(1-(3-Ethoxy-2-hydroxyphenyl) ethylidene)isonicotinohydrazide

The main object for this report is to assess the anti-mycobacterial activity of many derivatives obtained from the isoniazid pharmacophores along with coumarin scaffold. In this study, isoniazid has been transformed into a pyrazole core, which further comprises a coumarin ring system. The anti-mycobacterial activity of synthesized compound were reported against *Mycobacterium tuberculosis* $H_{37}Rv$ and MIC value ranging from 0.625 to 2.50 µg/mL. Out of all synthesized compound, 3-[3-(4-fluorophenyl)-1-isonicotinoyl-1*H*-pyrazole-5-yl]-2*H*-chromen-2-one (**27**) shows the most active MIC of 0.625 µg/mL [1].

Conclusion

In this study, a literature on 4-formyl pyrazole, isoniazid and their fusion chemistry is conducted. Moreover, in the context of synthetic methods to pharmacological activities of 4-formyl pyrazole and isoniazid, references gathered were



3-[3-(4-Fluorophenyl)-1-isonicotinoyl-1*H*-pyrazol-5-yl]-2*H*-chromen-2-one

regarded to review and summarized their significant antimicrobial activity for systematic exploration of the compound in synthesis and their functioning.

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