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PYRAZOLE DERIVATIVES AS AN ENOYL ACYL CARRIER PROTEIN REDUCTASE (INHA) INHIBITORS WITH PROMISING ANTITUBERCULAR ACTIVITY

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ABSTRACT

Tuberculosis is an infectious disease caused by bacillus Mycobacterium tuberculosis (MTB). New drugs with different mechanisms of action against tuberculosis must be discovered and developed in response to the rising prevalence of multidrug-resistant MTB. Several pyrazole derivatives have been synthesized and tested for anti-tubercular activity in past years. Enoyl acyl carrier protein reductase (InhA), is a clinically proven target for tuberculosis treatment. This review outlines the effectiveness of pyrazole derivatives as an InhA inhibitors and their antitubercular potential.

KEYWORDS: Tuberculosis, Pyrazole, Enoyl Acyl Carrier Protein Reductase (InhA), Antitubercular Activity.

INTRODUCTION

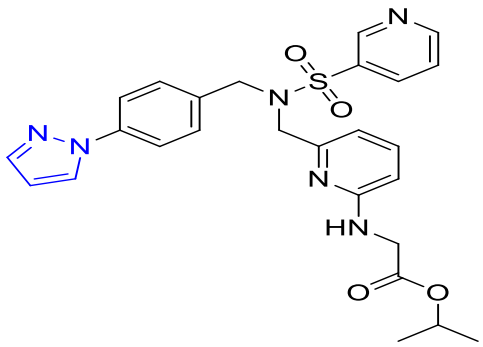
Tuberculosis (TB) disease is usually preventable and curable disease. However, in 2022, tuberculosis accounted for nearly twice as many fatalities globally as HIV/AIDS and was the second most common infectious agent-related cause of death worldwide, after corona virus disease (COVID-19). Each year, more than 10 million people fall ill with tuberculosis. According to the WHO 2023 report, 4,10,000 cases of multidrug-resistant or rifampicin-resistant tuberculosis worldwide.[1] Furthermore, a growing number of MTB strains are becoming resistant to one or more of the widely used anti-TB drugs, which complicates treatment and contributing to the rise in drug-resistant and latent TB infections.

The emergence of MDR and XDR MTB infections accelerated efforts to find new anti-TB drugs with their mechanism of action.[2,3]

The highly intricate and impermeable cell membrane of mycobacteria poses a serious obstacle to the delivery of TB medications. Mycolic acids are a significant and essential element of the mycobacterial cell membrane. They are α-branched, β-hydroxylated fatty acids with chain lengths from 60 to 90 carbon atoms. Enoyl acyl carrier protein reductase (InhA), is an important enzyme involved in the biosynthesis of mycolic acid.[4]

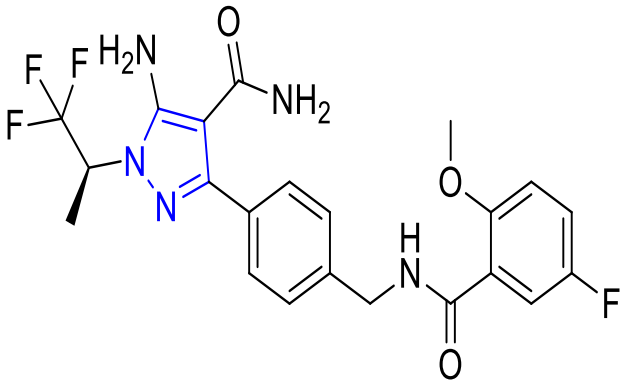
It belongs to the family of short dehydrogenase/reductases, or tyrosine-dependent oxidoreductase, and more specifically to NADH-dependent enoyl ACP reductase. It facilitates the reduction of trans double bonds, which are connected to an intermediate carbonyl group that is covalently attached to an acyl carrier protein in the FAS-II pathway.[5-7] Isoniazid is a prodrug; to produce the active acyl radical form, it must activate the catalase-peroxidase (KatG). Nicotinamide adenine dinucleotide (NAD^+) and this radical are then covalently bonded, resulting in an active INH-NAD adduct that is a strong InhA inhibitor.[8] Due to the mutation of KatG, the high potency of Isoniazid against InhA has been lost. Consequently, a lot of scientists worked to find new inhibitors that could block InhA directly without requiring the KatG activation step. The inhibitors that can act in this way are called direct inhibitors of InhA. One of the primary first-line drugs for M. tuberculosis is isoniazid (INH), which Inhibit the enzyme Enoyl ACP reductase, i.e. InhA an enzyme involved in the biosynthesis of the cell wall of mycobacteria.[9-11] Numerous biological activities have been discovered for the pyrazole skeleton, which is one of the most significant scaffolds in pharmacologically active substances.[12-14]

FDA approved pyrazole containing drugs in 2022 and 2023.[15,16]



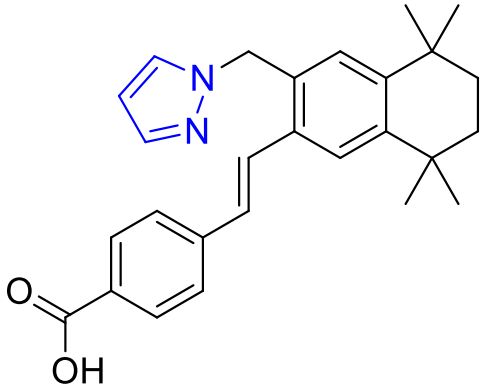
Omidenepag Isopropyl

(Glaucoma)



Pirtobrutinib

(Anticancer)



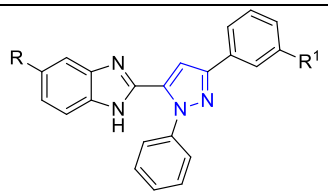
Palovarotene

(Heterotopic ossification and Fibrodysplasia ossificans progressiva)

Fig. 1: Novel drugs approved by FDA.

Pyrazole as InhA inhibitors and antitubercular activity: Because of its wide range of biological activity, pyrazole scaffold offers tremendous potential for medicinal chemistry and is of interest to researchers.[17-18] It has been discovered that pyrazole heterocycle have interesting antitubercular activity. Taking this into account, Prafulla and his co-worker synthesized a series of fused benzimidazole with pyrazole derivatives and assessed using the Alamar-Blue assay for In vitro anti-TB activity against the M. tuberculosis H37Rv strain. Three compounds of this series had interesting activity. Compounds **1a, 1b, 1c** and **1d** were found to be the most potent MIC=6.25 µg/mL (Table 1) and their activity is similar to the reference drug Streptomycin (MIC=6.25 µg/ mL).[19]

Table 1: In vitro antitubercular activity of fused benzimidazole with pyrazole derivatives.

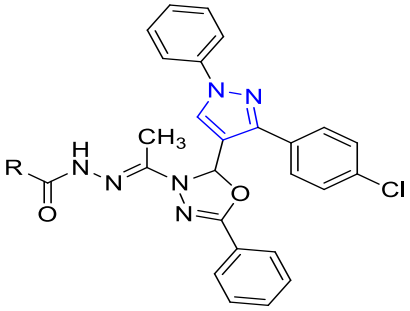


1

Comp.	R	R^1	MIC in µg/mL
1a	$-NO_2$	-H	6.25
1b	$-NO_2$	$-OCH_3$	12.5
1c	$-CH_3$	-H	6.25
1d	$-OCH_3$	$-OCH_3$	6.25
Streptomycin			6.25

The Nisheeth et al[20] focused on antitubercular activity, microwave-assisted synthesis, and docking studies of hybrid pyrazole and oxadiazole compounds in 2021.They synthesized N-(1-(2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-phenyl-1,3,4-oxadiazol-3 (2H) yl) ethylidene) substituted hydrazides **2a-t**(Table 2). They evaluated synthesized compounds against two strains: M. tuberculosis H37Ra and M. bovis BCG. Compounds **2e**, **2h**, **2k**, **2p** and **2s** were the most effective against M. tuberculosis H37Ra.Compounds **2f**, **2g** and **2s** showed significant activity against M. bovis BCG.

Table 2: In vitro antitubercular activity of pyrazole and oxadiazole hybrids.



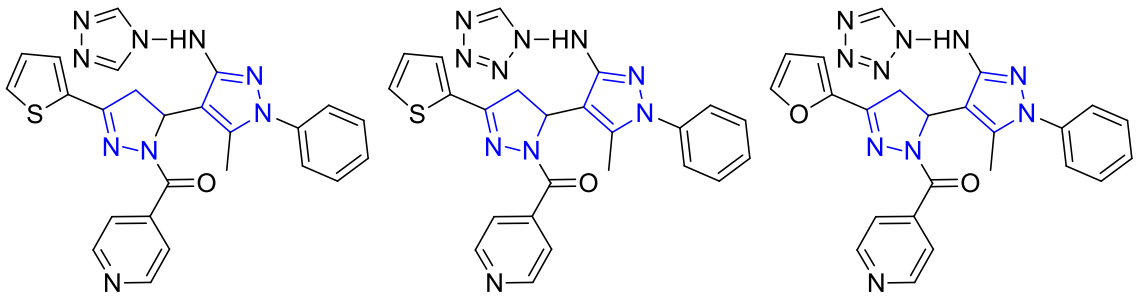
2

Sr. No.	R	Antitubercular activity against M. tuberculosis H37Ra MIC µg/mL	Antitubercular activity against M. bovis BCG MIC µg/mL
2a	$-C_6H_5$	>30	>30
2b	$-2-OH-C_6H_4$	>30	12.34
2c	$-3-OH-C_6H_4$	>30	>30
2d	$-4-OH-C_6H_4$	>30	5.37
2e	$4-NO_2-C_6H_4$	0.92	15.1
2f	$-3-CH_3-C_6H_4$	>30	2.71
2g	$-4-CH_3-C_6H_4$	>30	2.19
2h	$-4-OCH_3-C_6H_4$	19.42	2.88
2i	$-3-Cl-C_6H_4$	>30	>30

2j	-4-Cl-C_6H_4	>30	>30
2k	-CH_2-C_6H_5	1.31	5.48
2l	-CH_2NHCO-C_6H_5	>30	>30
2m	-CH_2-O-C_6H_4-2-CH_3	>30	>30
2n	CH_2-O-C_6H_4-3-CH_3	>30	>30
2o	-CH_2-O-C_6H_4-4-CH_3	>30	>30
2p	-CH_2-O-C_6H_4-2-NO_2	2.56	>30
2q	-H_2-O-C_6H_4-3-NO_2	>30	>30
2r	CH_2-O-C_6H_4-4-NO_2	>30	>30
2s	CH_2-O-C_6H_4-2-Cl	24.43	0.79
2t	CH_2-O-C_6H_4-4-Cl	>30	>30
Rifampicin		0.041	0.015
Isoniazid		0.051	0.033

Compounds with electron-donating functional groups exhibited antitubercular action against M. bovis BCG, while compounds with electron-withdrawing functional groups had excellent MICs against M. tuberculosis H37Ra.

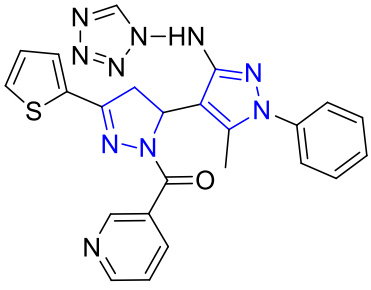
In 2023, Mayursinh Zala et al reported the anti-tubercular activity of pyrazolyl pyrazoline clubbed triazole and tetrazole hybrids **(3a-3p)**. The derivatives of pyrazolyl pyrazoline might fit into InhA's active site well and generate significant bonded and nonbonded interactions.[21] All of the synthesized compounds were tested against M .tuberculosis H37Rv, wherein compounds **3i**, **3k**, **3l**, **3o** and **3p** (Fig.2) were found to be most effective.



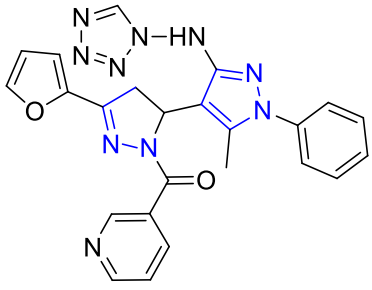
3i
MIC 62.5 µg/mL

3k
MIC 12.5 µg/mL

3l
MIC 25µg/mL



3o
MIC 12.5 µg/mL

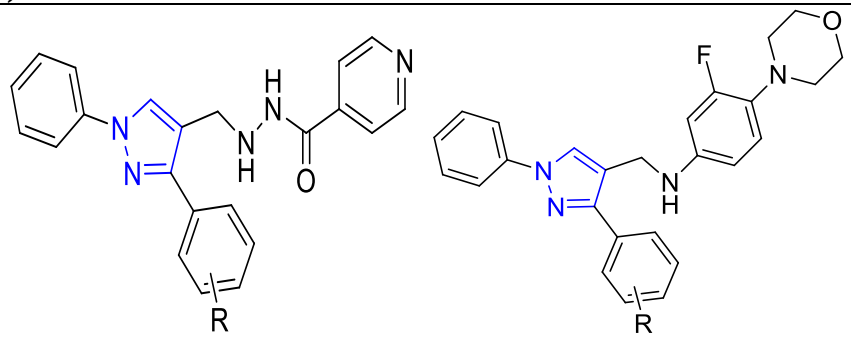


3p
MIC 25 µg/mL

Fig. 2: The structure of pyrazolylpyrazoline-clubbed triazole and tetrazole hybrids.

Sameer[22] found that the hybrid of 1,3,diphenyl pyrazole, coupled with antitubercular drugs, could be a potential lead (**4a-4f** and **5a-5f)** for antitubercular activity. Using the Microplate alamar blue assay, the antitubercular activity of compounds against mycobacterium TB was evaluated. The results reveal that compounds **4c**, **4d**, **5c** and **5d** showed significant antitubercular potential with MIC <20µM(Table 3). The research on cytotoxicity demonstrated that active compounds(**4c**, **4d**, **5c** and **5d**) are non-toxic to HeLa cancer cell lines with a selectivity index >10. The compounds (**4c**, **4d**, **5c** and **5d**) containing electron-withdrawing groups in the para position, including fluoro and bromo, were found to be the most potent anti-tubercular agents. The most effective compounds exhibited potent antitubercular action along with a comparatively low degree of cytotoxicity.

Table 3: In vitro antitubercular activity, cytotoxicity and selectivity index of compounds 4(a-f) and 5(a-f).

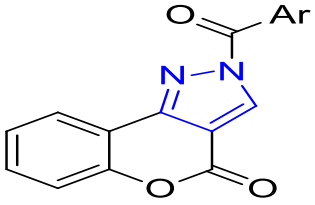


4 **5**

Sr. No.	R	Anti-TB MIC (µM)	Cytotoxicity HeLa GI50 (µM)	Selectivity Index
4a	H	134.70	-	-
4b	4-Cl	61.70	-	-
4c	4-F	16.06	256.96	>16
4d	4-Br	13.91	222.67	>16
4e	4-NO_2	60.07	-	-
4f	4-OCH_3	31.15	-	-
5a	H	116.22	-	-
5b	4-Cl	26.92	-	-
5c	4-F	13.94	223.11	>16
5d	4-Br	12.30	201.80	>16
5e	4-NO_2	26.30	-	-
5f	4-NO_2	108.64	-	-
Isoniazid		0.87	NA	NA
Ciprofloxacin		9.41	NA	NA
Rifampicin		0.70	NA	NA
paclitaxal			0.004	NA

Angelova[23] reported 2-aroyl-[1] benzopyrano [4,3-c]pyrazol-4 (1H)-one derivatives (**6a-6f**). In vitro tests were performed to determine the antimycobacterial activity against the reference strain of Mycobacterium TB H37Rv and the cytotoxicity against the human embryonic kidney cell line HEK-293. The result shows that all drugs had minimum inhibitory concentrations (MIC) that ranged from 0.28 to 1.69 µM, which were similar to isoniazid (Table 4).

Table 4: Antimycobacterial activity and In vitro cytotoxicity.

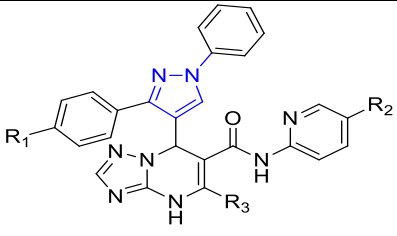


6

Compd.	Ar	MIC (µM)	IC50 (µM)	SI
6a	2-furyl	0.72	>200.00	>282
6b	p-methoxyphenyl	0.62	>200.00	>645
6c	p-(N,N- imethylamino)phenyl	0.59	>200.00	>408
6d	o,p-dihydroxy phenyl	0.62	>200.00	>308
6e	p-hydroxyphenyl	0.32	>200.00	>625
6f	2-methyl-3-furyl	1.69	>200.00	>119
EMB. 2HCl		1.46		
INH		0.79		

Jaimin D. Bhatt and his coworkers synthesized a series of new pyrazole-based triazole-pyrimidine hybrids and checked their anti-tubercular activity against the M. tuberculosis H37Rv strain (Table 5). The In vitro study of the hybrids yielded five potent entities (**7a-7e**) owing to their potency in micromolar range moreover not causing any cytotoxicity to Vero cells.[24]

Table 5: In-vitro anti-tuberculosis activity and cytotoxicity of triazole-pyrimidine hybrids.



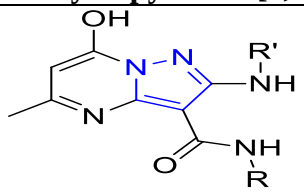
7

Compd.	R_1	R_2	R_3	MIC µg/mL	% Inhibition (at 6.25 µg /mL
7a	H	Br	Me	3.13 ±0.313	95
7b	NO_2	Br	Me	1.56 ± 0.083	96

7c	Cl	Br	Me	0.78 ±0.039	98
7d	F	H	Me	0.78 ±0.039	99
7e	F	Br	Me	0.39 ± 0.019	99
Rifampicin				0.5	99
Ethambutol				3.125	99

Palmi and her cowerker[25] performed study of structure-based drug designing leads and developed novel, clinically active molecules. They synthesized twenty-six novel pyrazolo[1,5-a]pyrimidine analogues (**8a-8z**) and using the alamar blue assay technique, all of the synthesized compounds were assessed for their in vitro anti-tubercular activity against the H37Rv strain (Table 6). Synthesized compounds exhibit potential antitubercular activities. Amongst all the tested compounds **8p, 8g, 8n** and **8h** showed promising anti-tubercular activity. These potent substances were also assessed for cytotoxic study, MDR-TB, and XDR-TB. MIC values of 3.12µg/mL, compounds **8g** and **8n** have an activity that is similar to that of standard drug ciprofloxacin and pyrazinamide. MIC of 6.25 mg/mL was observed in **8h**, which is similar to the streptomycin.

Table 6: Anti-mycobacterial activity of pyrazolo [1, 5-a] pyrimidine.

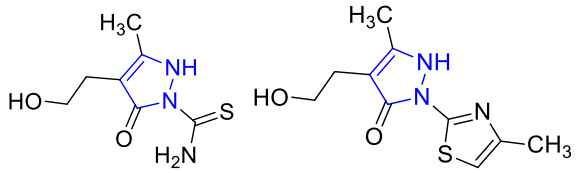


8

Compd.	R	R’	MIC(µg/mL)	Cytotoxicity IC50 (µg/mL)
8a	4-OCH_3	4-OCH_3	12.5	ND
8b	4-OCH_3	4-Cl	12.5	ND
8c	4-OCH_3	2,3-di-CH_3	50	ND
8d	4-OCH_3	-NH	50	ND
8e	4-OCH_3	Morpholine	25	ND
8f	4-CH_3	-NH	50	ND
8g	4-CH_3	4-Cl	3.12	20.99
8h	-NH_2	3,4-di-Cl	6.25	29.02
8i	4-Ethoxyniline	2,4-di-CH_3	50	ND
8j	4-Cl	2,4-di-CH_3	50	ND
8k	2,4-di-CH_3	4-OCH_3	50	ND
8l	2,3-di-CH_3	3,4-di-Cl	50	ND
8m	4-F	2,4-di-CH_3	50	ND
8n	2-OCH_3	3-CH_3	3.12	21.26
8o	-NH_2	4-Cl	50	ND
8p	4-F	3,4-di-F	0.8	13.57
8q	4-Ethoxy aniline	-NH	50	ND
8r	2,3-di-Cl	N-Et piperazine	50	ND

8s	3,4-di-Cl	Pyrrolidine	25	ND
8t	NH	-NH	50	ND
8u	-NH	4-CH_3	100	ND
8v	-NH	4-Cl	50	ND
8w	3-Cl 4-F	4-CH_3	12.5	ND
8x	3-Cl 4-F	4-OCH_3	25	ND
8y	3-Cl	4-F	12.5	ND
8z	3-Cl	2,3-di-CH_3	50	ND
Pyrazinamide			3.12	
Ciprofloxacin			3.12	
Streptomycin			6.25	

In 2017, The Bachar Rebat Moulkrere et al evaluated pyrazole derivatives as antitubercular agents with InhA inhibition properties.[9] They synthesized pyrazole derivatives from 2-acetylbutyrolactone and checked their antitubercular activity against M. tuberculosis H37Rv strain. Among them, compounds **9** and **10** were the most potent with MICs 2.5 µg/mL and 5 µg/mL (Fig.3).



9 **10**

MIC- 2.5 µg/mL **MIC- 5 µg/mL**

Fig. 3: Pyrazole derivatives as antitubercular agents with InhA inhibition properties.

Nagabhushana Nayak and co-workers developed promising antitubercular leads.[26] They designed and synthesized a series of isonicotinohydrazide-based pyrazole derivatives. Compounds **11a**, **11b** and (**12a-12r**) were synthesized and evaluated against M. tuberculosis H37Rv (MTB) strain using the Microplate alamar blue assay (MABA). Isoniazid, ethambutol, and pyrazinamide were used as the standard drugs. All compounds displayed significant inhibition activity (Fig.4). Among these, compound **11b** showed a significant activity MIC- 1.6 µg/mL whereas compound **11a** with a 4-chloro substitution displayed a moderate activity. **12j, 12k** MIC **(**1.6µg/mL) and **12l (**0.8µg/mL) are the most potent molecules which are comparable with the MIC value of standard drug Isoniazid, whereas the inhibition activity of compounds **11b,12j, and 12k** is significantly higher than that of standard drug, ethambutol.

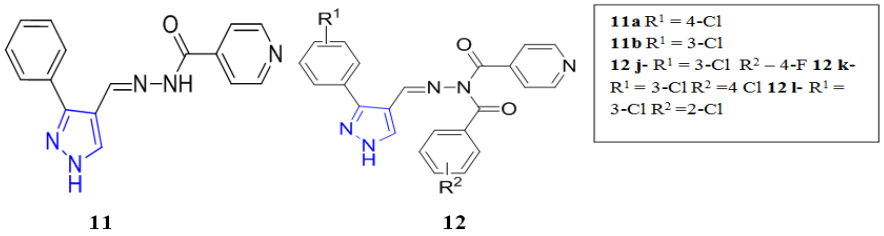
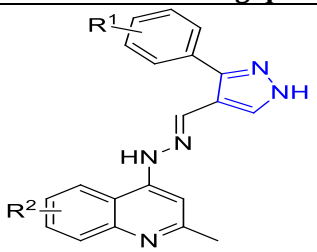


Fig. 4: The structure of isonicotinohydrazide based pyrazole derivatives.

In 2016, Nagabhushana Nayak[27] designed and synthesized 21 fluorine-containing quinoline-pyrazole hybrid derivatives and evaluated them for their antitubercular activity against M. tuberculosis. Among them Four derivatives(**13b**, **13c**, **13j** and **13o**) displayed significant antitubercular activity (Table 7).

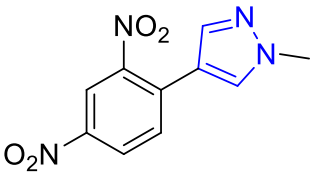
Table 7: Antitubercular activity of fluorine-containing quinoline-pyrazole hybrid derivatives.



13

Compd.	R^1	R^2	MIC(µg/mL)	Cytotoxicity IC50 (µg/mL)
13a	4-F	8-CF_3	25	ND
13b	4-Cl	8-CF_3	12.5	121.67
13c	3-Cl	8-CF_3	12.5	240.00
13d	4-Br	8-CF_3	25	ND
13e	4-OCH_3	8-CF_3	25	ND
13f	4-CH_3	8-CF_3	25	ND
13g	H	8-CF_3	50	ND
13h	4-F	6-F	50	ND
13i	4-Cl	6-F	25	ND
13j	3-Cl	6-F	12.5	238.33
13k	4-Br	6-F	50	ND
13l	4-OCH_3	6-F	25	ND
13m	4-CH_3	6-F	25	ND
13n	H	6-F	25	21.26
13o	4-F	6-OCH_3	12.5	>1000
13p	4-Cl	6-OCH_3	50	ND
13q	3-Cl	6-OCH_3	50	ND
13r	4-Br	6-OCH_3	50	ND
13s	4-OCH_3	6-OCH_3	50	ND
13t	4-CH_3	6-OCH_3	50	ND
13u	H	6-OCH_3	25	ND
Isoniazid Ethambutol			0.1 3.13	
Pyrazinamide			50	

Pan et al performed SAR studies of InhA inhibitors. They described pyrazole scaffolds as InhA inhibitors.[28] Among the derivatives, the dinitrophenyl analogue **14** (Fig.5) provided better anti-tubercular activity giving an IC50 of 2.4 µM and a MIC value of 2.5µM against M. tuberculosis H37Rv.



14

Fig. 5: The structure of dinitrophenyl pyrazole scaffolds.

A series of pyrazole-substituted benzimidazole derivatives was identified by Vijay et al in 2022. They performed in silico studies and docking studies against M. tuberculosis InhA bound with ETH-NAD adduct. As per the results of the binding interactions, binding energies, and ADMET predictions, the most active compounds were synthesized, containing para halo phenyl substitutions in the pyrazole nucleus associated with benzimidazole. Further, the synthesized compounds were evaluated for anti-tubercular activity using the Microplate alamar blue assay method. They synthesized 10 compounds and checked the antitubercular activity of two compounds **(15a & 15b)** amongst all synthesized compounds (Fig.6). Compound **15a** had a MIC value of 50 µg/ml, while compound **15b** had a value of 25 µg/ml. Compound **15b** has greater sensitivity in relation to bacterial strains. H37Rv M. tuberculosis. **15a** with chloro-substituted phenyl ring on the pyrazole showed moderate anti-tubercular activity.[29]

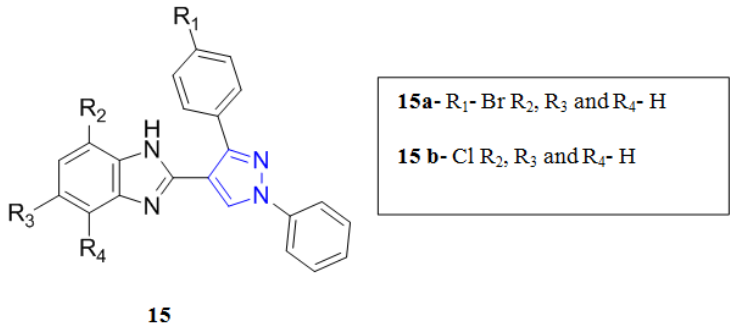


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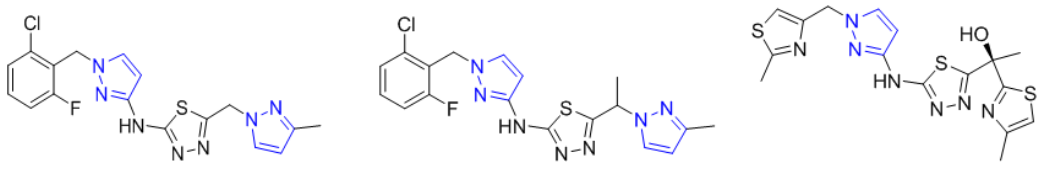
Fig. 6: The structure of pyrazole substituted benzimidazole derivatives.

María Martínez-Hoyos and his coworkers[30] presented a series of InhA direct inhibitors thiadiazole and pyrazole hybrid which are active against multidrug (MDR) and extensively

(XDR) drug-resistant clinical isolates. GlaxoSmithKline (GSK), and the TB Alliance has carried out a screening against InhA using the GSK compound (**16a, 16b**, **16c**) having MIC - 0.2µM, <1 µM and 1 µM respectively (Fig.7). Cytotoxic activity was found to be >100 and >199.5 µM.

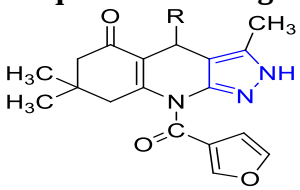


16a **16b** **16c**

Fig. 7: The structures of thiadiazole and pyrazole hybrid series.

N. R. Babu[31] synthesized ten pyrazole-quinoline analogues against the rising bacterial resistance**.** Molecular docking studies were performed for all the synthesized compounds against a specific protein, Enoyl acyl carrier protein reductase (InhA). Six derivatives **(17a-f)** were found to be more active at concentrations of 1.6g/mL and were found to be more active than pyrazinamide (Table 8).

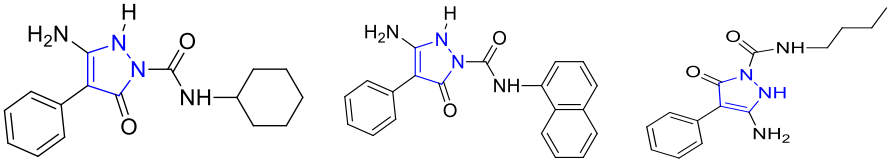
Table 8: pyrazolo-quinoline analogues.



17

Compound Code	R
17a	4-CH_3 C_6H_4
17b	C_6H_5
17c	3-F C_6H_4
17ds	4-OCH_3 C_6H_4
17e	3-Cl C_6H_4
17f	3,4-di $OCH_3C_6H_4$

Swatko-Ossor Marta et al developed N-substituted 3-amino-4-phenyl-5-oxo-pyrazolinecarboxamide derivatives **(18a, 18b and 18c)** and their antitubercular potential against different mycobacterial strains was estimated (Fig.8). Compound **18a, 18b** and **18c** exhibited very promising antimycobacterial activity MIC 32µg/mL, 16µg/mL and 32 µg/mL respectively.[32]

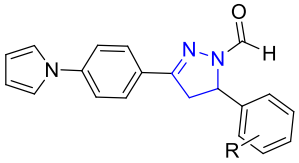


18a **18b** **18c**

Fig. 8: The structure of N-substituted 3-amino-4-phenyl-5-oxo-pyrazoline carboxamide derivatives.

Sheshagiri and other researcher[33] developed pyrrolyl pyrazoline carbaldehydes enoyl-ACP reductase inhibitors **(19a-19o)**. They examined the interactions between the compounds bound to the active site of the M. tuberculosis enzyme enoyl ACP reductase, which is crucial to the biosynthesis of FAS-II in M. tuberculosis**.** All compounds showed moderate to good activity but compound **19i** demonstrated potent activity with a MIC value of 3.125 µg/mL with no cytotoxicity towards the human lung cancer cell line (A549) (Table 9).

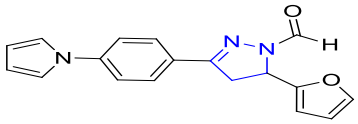
Table 9: Antitubercular activity and cytotoxicity of Pyrrolyl Pyrazoline Carbaldehydes as Enoyl-ACP Reductase Inhibitors derivatives.



19

Compd.	R	MIC(µg/mL)s	Cytotoxicity IC50 (µg/mL)
19a	-H	100	ND
19b	4-Cl	12.5	75.64
19c	2,3-diCl	12.5	ND
19d	2,4-diCl	25	ND
19e	2,6-diCl	25	ND
19f	4-CH_3	25	ND
19g	4-OCH_3	6.25	ND
19h	3-OCH_3	6.25	76.54
19i	2,4-diOCH_3	3.125	73.32
19j	3,4-diOCH_3	12.5	70.36
19k	4-F	12.5	ND
19l	4-$CH(CH_3)_2$	100	71.07
19m	3-Br	12.5	76.03
19n	3-Phenoxy	12.5	72.87
Pyrazinamide		3.125	
Streptomycin		6.25	

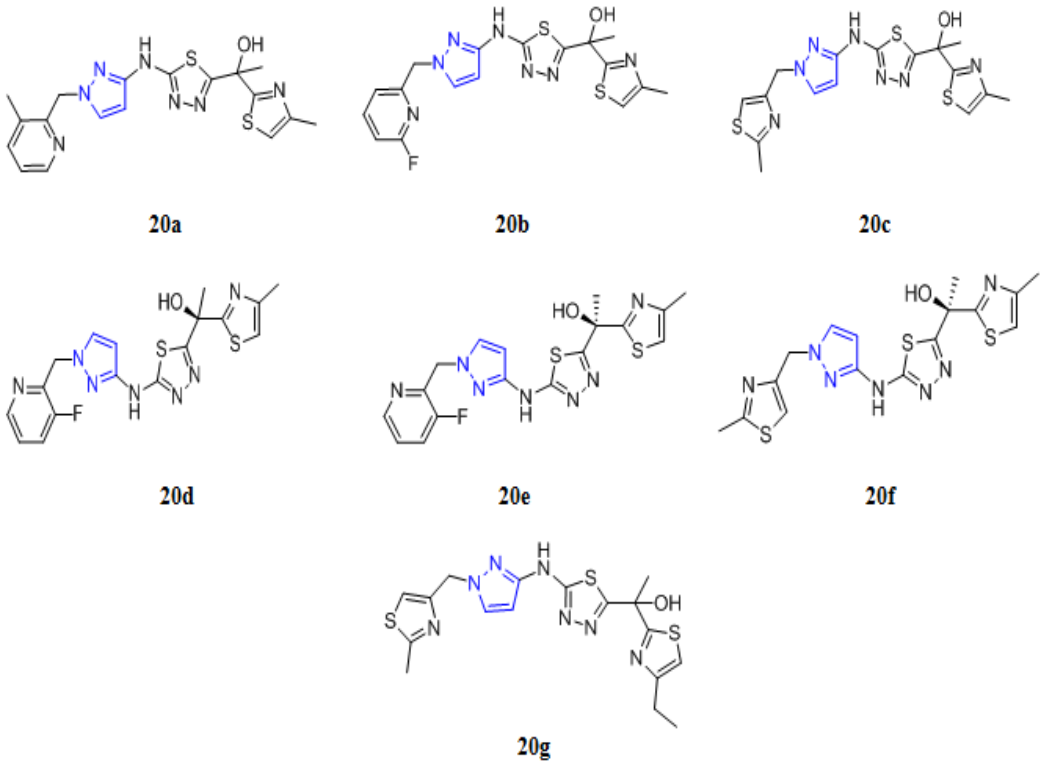
Further,3-(4-(1H-pyrrol-1-yl)phenyl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde (**19o**) has been synthesized by that in silico studies and identified as potent InhA inhibitors. (MIC- 50 µg/mL (Fig.9).



19o

Fig. 9: The structure of 3-(4-(1H-pyrrol-1-yl) phenyl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde.

In 2011, Glaxo Group Ltd. synthesized and evaluated a series of pyrazole derivatives as InhA inhibitors.[34] All the compounds showed good inhibitory activity against the M. tuberculosis H37Rv strain. Among the synthesized compounds some compounds (**20a- 20g**) MIC value was 1 µM or less (Fig.10).



20a **20b** **20c**

20d **20e** **20f**

20g

Fig. 10: The structures of Pyrazole derivatives synthesized by Glaxo group.

Zhi Xu and his colleagues[35] reported pyrazole-containing derivatives as inhA inhibitors. Thiazole-thiadiazole-pyrazole hybrid **21** demonstrated strong enzyme inhibition (IC50-0.003µM) and was a direct, reversible inhibitor of InhA. Pyrazole clubbed triazolo [1, 5-a] pyrimidine hybrid derivatives are active against MTB H37Rv and exhibited significant

growth inhibitory activity at a concentration of 6.25 µg/mL. In particular, the most active compound **22** (MIC- 0.39 µg/mL) was found to be not toxic against VERO cells (IC50-20µg/mL). Further, they reported a series of novel N-benzyl-4-((heteroaryl) methyl)-benzamides class of direct InhA inhibitors. Compound **23** displayed potent activity against MTB (MIC90: 6->125 µM). Derivatives of benzofuran pyrazole (MIC90: 0.05->31 µM) showed significant in vitro activity against MTB H37Rv and **24a** showed significant activity with MIC90 of 0.05 µM. Compound **24b** has potent anti-tubercular activity (MIC90- 0.5 µM), strong InhA inhibition (IC50- 0.004 µM), and a favourable pharmacokinetic profile (Fig.11).

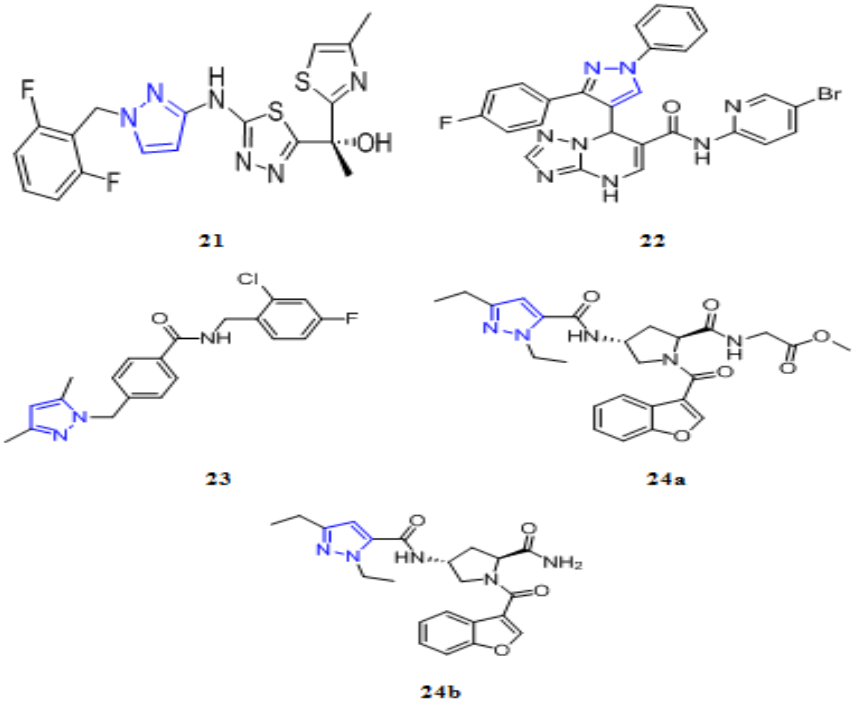


Fig. 11: The structures of pyrazole nucleus clubbed with other heterocycles.

Vekariya and co-worker[36] designed and synthesized a series of Morpholine-Pyrimidine-Pyrazole Hybrids. They synthesized 27 compounds, all the compounds showed good anti-tubercular activity but **25a**, **25b**, **25c** and **25d** showed significant inhibition activity with a MIC of 6.25 µg/mL, and the other two compounds i. e. **25e** and **25f** displayed good activity with a MIC of 12.5 mg/mL due to the presence of a halo group on the phenyl ring. The remaining compound showed MIC values between 25 and 250µg/mL. (Fig. 12)

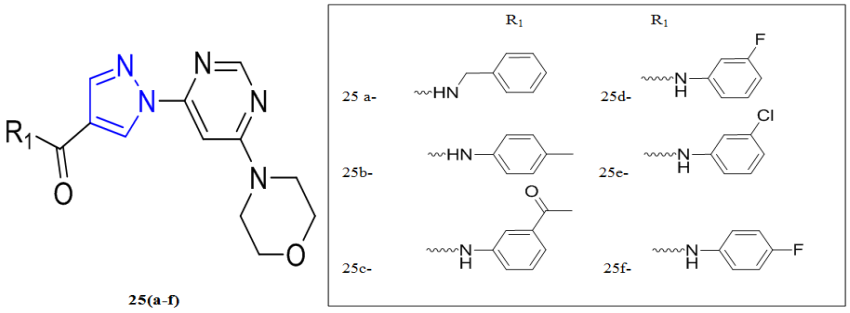
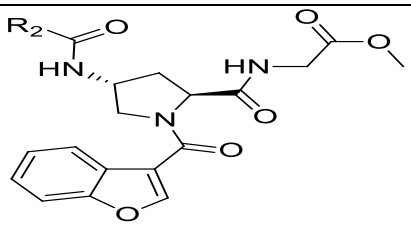


Fig. 12: The structures of pyrazole- pyrimidine-morpholine hybrid.

Encinas and his friends discovered a potent lead and selective class of bactericidal direct inhibitors **26a-h, 27a-f** of M. tuberculosis InhA.[37] They designed, synthesized, and evaluated various substituted pyrazole derivatives and checked their anti TB activity by H37Rv and InhA enzyme assay (Table 10 & 11).

Table 10: Antitubercular activity of Pyrazole derivatives as enoyl-ACP reductase inhibitors (InhA).



26

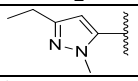
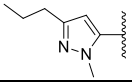
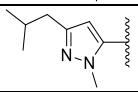
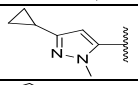
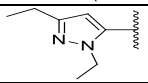
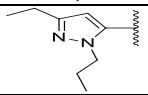
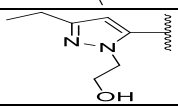
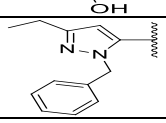
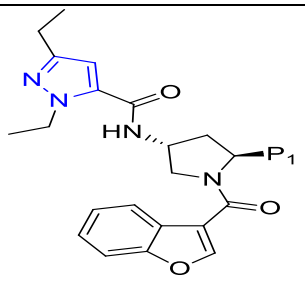
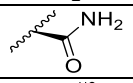
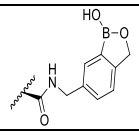
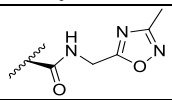
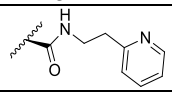
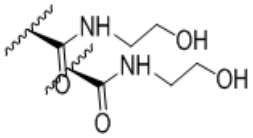
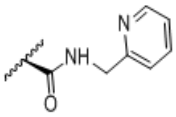
Compd.	R_2	InhA IC_{50} [µM]	MtbH37Rv MIC_{90}[µM]
26a		0.005	0.5
26b		0.022	0.5
26c		>1	>31
26d		0.015	1
26e		0.003	0.05
26f		0.001	1
26g		>1	>31
26h		>1	>31

Table 11: Antitubercular activity of Diethylpyrazole derivatives as Enoyl-ACP Reductase Inhibitors (InhA).



27

Compd.	P_1	InhA IC_{50} [µM]	MtbH37Rv MIC_{90}[µM]
27a		0.004	0.50
27b		0.002	0.20
27c		0.004	0.50
27d		0.004	0.50
27e		0.003	1.00
27f		0.002	0.7

Shankar and his group synthesized and evaluated a series of 1, 3, 4-trisubstituted pyrazole derivatives. Among them, compounds **28a**, **28b**, **28c**, **28d**, **28e** and **28f** showed the most significant anti-mycobacterial activity with MIC 0.78 to 1.56 µg/mL as compared to the standard drug Isoniazid (MIC=1.56µg/mL), Pyrazinamide (MIC- 50µg/mL) and Ciprofloxacin (MIC-12.5 µg/mL). Further, MTT assay was used to assess the active compounds cytotoxic potential against a normal HDF cell line (Fig.13). These compounds had a favorable drug-likeness score of 0.6, 0.19, 0.3, 0.46, 0.05, and 0.12 respectively, and a good selective index profile (>200). 1, 3, 4-trisubstituted pyrazole analogues have been found through molecular docking studies to engage favourably with the active site of the MTB NADH-dependent enoyl acyl carrier protein reductase.[38]

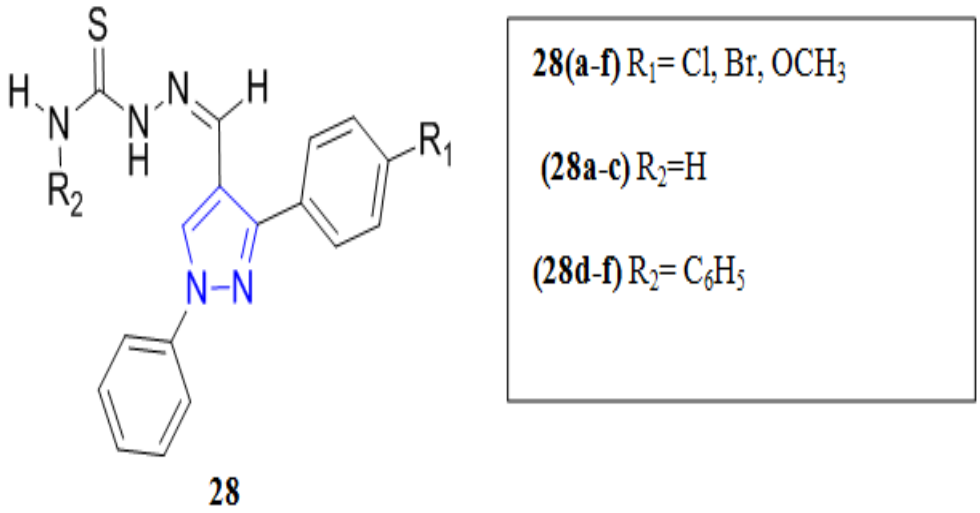
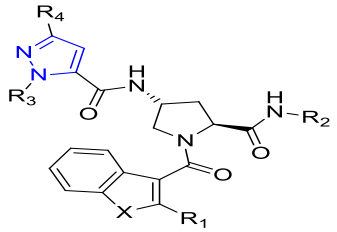


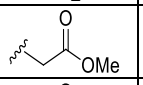
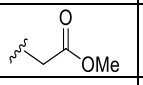
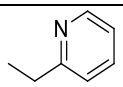
Fig. 13: The structures of 1, 3, 4-trisubstituted pyrazole derivatives.

Pharit Kamsria and his group designed Benzofuran pyrrolidine pyrazole derivatives (**29a-d**) as highly potent anti-tuberculer agents.[39] Based on CoMFA and CoMSIA studies they investigated the structural requirement needed for good activity against InhA and M. tuberculosis. Additionally, key binding interactions of benzofuran pyrrolidin pyrazole in InhA were evaluated using MD simulations (Table 12).

Table 12: Designed chemical structures and activities against InhA and M. tuberculosis of benzofuran pyrrolidine pyrazole derivatives.



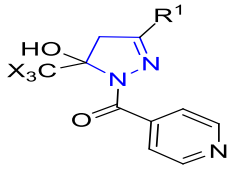
29

Compd.	X	R_1	R_2	R_3	R_4	IC_{50}(µM)	MIC_{90}(µM)
29a	O	H		Me	Et	0.005	0.50
29b	O	H		Et	Et	0.003	0.05
29c	O	H	H	Et	Et	0.004	0.50
29d	O	H		Et	Et	0.002	0.70

Pedro and his friends synthesized series of 3-substituted 5-hydroxy-5-trifluoro [chloro] methyl-1H-1-isonicotinoy l-4,5-dihydropyrazoles by the cyclocondensation reaction of 4-methoxy-1,1,1-trifluoro [chloro]-4-(substituted)-alk-3-en-2-ones and isoniazid (INH). Amongst the synthesized compounds, Nine pyrazole derivatives were evaluated against four

INH-resistant clinical isolates and INH susceptible M. tuberculosis.[40] Five pyrazole derivatives (**30a**, **30b**, **30c**, **30d** and **30f**) showed good activity against M. tuberculosis H37Rv with MICs ranging from 0.77 µM and 18.66 µM (Table 13).

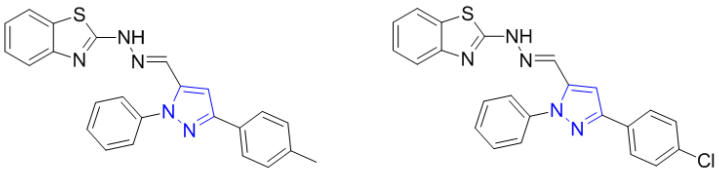
Table 13: In vitro antimycobacterial activity of pyrazole derivatives.



30

Compd.	R^1	X	MIC_{90}(µM)
30a	H	F	0.77
30b	Me	F	5.71
30c	Ph	F	18.66
30d	4-MePh	F	2.23
30e	2-thienyl	F	>293.26
30f	2-furyl	F	9.6
30g	4-MePh	Cl	>251.89
30h	2-thienyl	Cl	>257.07
30i	2-furyl	Cl	268.09
Isoniazid			1.45

Mahesh Bhat[41] and his friends synthesized two novel series of pyrazole-conjugated benzothiazole derivatives and checked their anti-TB activity using alamar blue assay. All compounds showed good activity. Amongst synthesized compounds two compounds **31a** and **31b** exhibited MIC value of 1.6 µg/mL compared with the reference drug Pyrazinamide and Ciprofloxacin MIC- 3.125 µg/Ml (Fig.14).



31a **31b**

Fig. 14: The structure of the pyrazole-conjugated benzothiazole derivatives.

In 2018, Mahesh and co-workers[42] designed and synthesized Novel 1,4-dihydropyrano [2,3-c] pyrazole derivatives. The binding affinity of the compounds with enoyl-ACP reductase was determined by a molecular docking study. All synthesized compounds have been subjected to In vitro antibacterial, anti-tuberculosis, and cytotoxicity studies. Biological study

revealed that the synthesized compound **32a, 32b,** and **32c** are showing good anti-tuberculer activity at 25µg/mL (Fig.15).

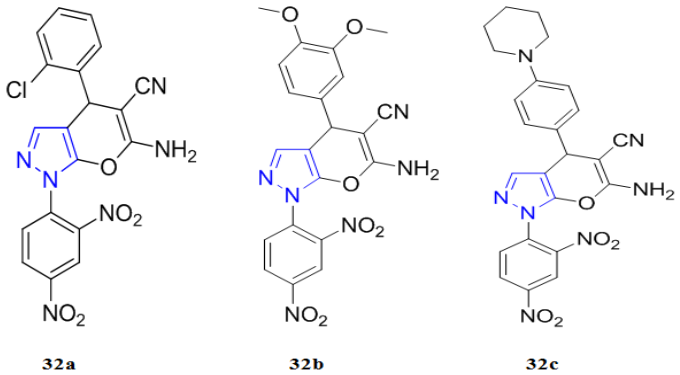


Fig. 15: The structures of 1,4-dihydropyrano [2,3-c]pyrazole derivatives.

A novel class of direct NADH-Dependent 2-trans enoyl–acyl carrier protein reductase (InhA) inhibitors synthesized by Ana Guardia and his colleagues.[43] Some of the compounds among synthesized compounds showed significant anti-tubercular activity against the $H_{37}RV$ strain. Compounds **33a** and **33b** showed good anti TB activity having MIC 10 µM and 31µM (Fig.16).

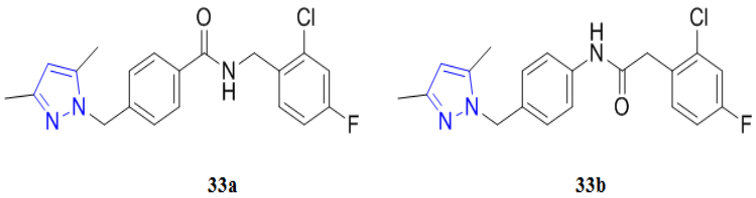
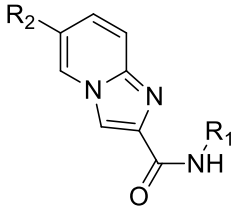


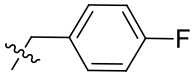
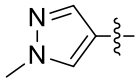
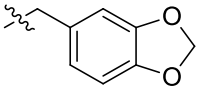
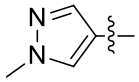
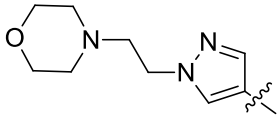
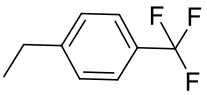
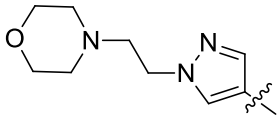
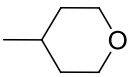
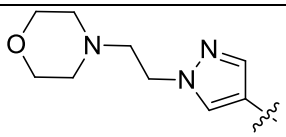
Fig. 16: Pyrazole derivatives active against enoyl acyl carrier protein reductase (InhA).

Gilish Jose and his friends[44] developed new anti-tubercular agents, imidazo [1,2-a] pyridine-2-carboxamide derivatives (**34a-34e**). Compounds were evaluated against M. tuberculosis H37Rv and their cytotoxicity against the HEK-293T cell line. Amongst the tested compounds **34a**, **34b**, **34c**, **34d** and **34e** emerged as good anti-tubercular agents with low cytotoxicity (Table 14).

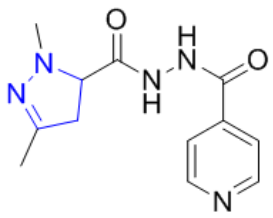
Table 14: Anti-mycobacterial activity and cytotoxicity of compounds.



34

Compound no.	R_1	R_2	MIC (µg/mL)	Cytotoxicity at 50 µg/mL
34a			25	36.12
34b			6.25	25.56
34c			25	29.12
34d			12.5	22.16
34e			6.25	30.06
Isoniazid			0.36	
Rifampicin			0.02	

Mardianingrum and his friends performed a docking and molecular dynamic study of N ’-(1, 3-dimethyl-1 h- pyrazole-5-carbonyl) isonicotino hydrazide **35** (Fig.17) as an anti-tuberculosis drug candidate. Based on docking and molecular dynamic study found its interaction with M. tuberculosis enoyl-Acyl carrier protein reductase (InhA). Molecular docking shows that compound **35** has the best interaction.[45]

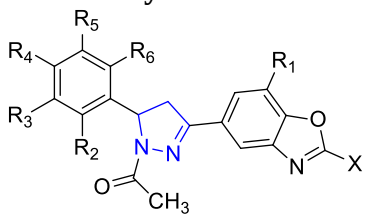


35

Fig. 17: The structure of N ’-(1, 3-dimethyl-1 h- pyrazole-5-carbonyl) isonicotino hydrazide.

Rana and co-workers discovered new antitubercular agents based on a pharmacophore study. Researchers combined two well-known pharmacophores pyrazoline and benzoxazole nucleus to designed and synthesized a series of substituted pyrazoline-based benzoxazole derivatives (**36a-36i**). In vitro antitubercular evaluation showed that the majority of the target compounds showed significant activity (MIC-1.25–25µlg/mL) against M. tuberculosis H37Rv, multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) strains. where few compounds were found to be superior to isoniazid against MDR-TB (MIC = 3.25 µg/mL) and XDR-TB(MIC = 12.5 µg/mL)(Table 15).These active compounds cytotoxicity test in VERO cell lines showed an excellent selectivity index.[46]

Table 15: In vitro antitubercular activities and cytotoxicities of target compounds.

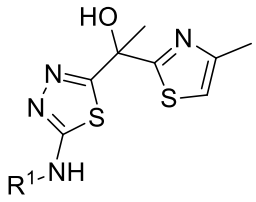


36

Comp no.	X	R_1	R_2	R_3	R_4	R_5	R_6	$H_{37}RV$	MDR-TB	XDR-TB	Cytotoxicity IC50 (µg/mL)
36a	-SH	-H	-H	-Cl	-H	-H	-H	3.25	12.5	12.5	>62.5
36b	-SH	-H	-H	-H	-OCH3	-H	-H	6.25	6.25	50	ND
36c	-SH	-H	-H	-H	-Cl	-H	-H	3.25	25	50	32.5
36d	-SH	-OCH3	-H	-Cl	-H	-H	-H	25	6.25	25	ND
36e	-SH	OCH_3	-H	-H	-Cl	-H	-H	3.25	25	50	>62.5
36f	-SH	$-OCH_3$	-H	-Br	-H	-H	-H	1.25	50	50	>62.5
36g	-SH	$-OCH_3$	-H	-H	-Br	-H	-H	3.25	25	12.5	32.5
36h	$-NH_2$	-H	-H	$-OCH_3$	$-OCH_3$	-H	-H	6.25	6.25	25	ND
36i	$-NH_2$	-H	-H	-H	-Cl	-H	-H	6.25	3.25	>100	ND

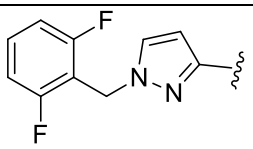
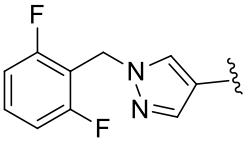
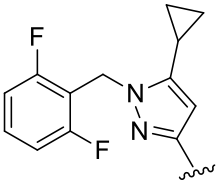
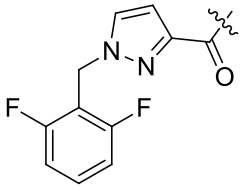
Shirude and co-workers[47] designed, synthesized, and evaluated novel inhibitors targeting InhA in M. tuberculosis. Compounds **37a**, **37b**, **37c,** and **37d** showed good inhibition against InhA and Mtb strains (Table 16).

Table 16: Potent Inhibitors of InhA.



37

Comp. no.	R^1	InhA (IC_{50}) µM	Mtb (MIC) µM

37a		0.004	0.5
37b		0.234	7.5
37c		0.97	>12.7
37d		34	>100

CONCLUSION

In this review, we have compiled the information that is currently accessible on pyrazole scaffold as enoyl acyl carrier protein reductase (InhA) inhibitors and their antitubercular activity. Pyrazole moiety has been successfully coupled with another promising heterocycles. The substances examined in this article are enoy lacyl carrier protein reductase (InhA) inhibitors and their antitubercular activity.

Nevertheless, new research supports to the idea that a direct inhibitor of InhA is a practical way to produce novel compounds for use in anti-tubercular medications. It is our aim that this review would encourage researchers to focus on InhA and develop novel methodologies for drug discovery.

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