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PYRROLE ANALOGS AS MYCOBACTERIUM ENOYL ACYL CARRIER PROTEIN REDUCTASE (InhA) INHIBIOTRS: A KEY TARGET FOR ANTITUBERCULAR DRUG DISCOVERY

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Abstract:

Background: Enoyl acyl carrier protein reductase (InhA) is a critical enzyme in fatty acid synthesis, namely mycolic acid biosynthesis. It is a member of the NADH-dependent acyl carrier protein reductase family. The current literature focuses on several pyrrole analogs or enzyme inhibitors that decrease mycolic acid production, namely cell wall formation, by inhibiting the enzyme InhA. Pyrrole analogs were found to be the most effective compounds against InhA, with high bioavailability and MIC. The main objective of the present work to carry out extensive review on Pyrrole containing drugs in the market and thorough information, analysis, structure-activity relationships, and relevant insights on several Pyrrole analogs as InhA inhibitors.

Main body: Comprehensive information on its Pyrrole containing drugs in the market , and relevant insights on several Pyrrole analogs as InhA inhibitors has been gathered and provided in this review article from a variety of web sources, including indexing sites like Web of Science, Scopus, PubMed, and Research Gate. Numerous articles from databases and indexed journals have been gathered and methodically examined.

Conclusion: The present review investigation is very much helpful for researchers and readers to collectively have valuable information on Pyrrole containing drugs in the market , and relevant insights on several Pyrrole analogs as InhA inhibitors. Innovative anti-TB pharmaceutical formulations that reduce drug resistance and shorten treatment duration are in high demand due to the rise of widespread and multi-drug resistant tuberculosis. In order to cure tuberculosis, new anti-TB drugs can now be developed by specifically targeting InhA.

Keyword: Enoyl acyl carrier protein reductase (InhA), Heterocyclic compounds, Multi-drug resistant TB, Pyrrole analogs, antitubercular agents.

Introduction

Heterocyclic chemistry is a significant area of organic chemistry. The molecules that fall under this division have attracted a lot of attention due to their applications in biology and technology, as well as the advancement of civilization. The physiologically active heterocyclic compounds can be obtained from natural sources as well as laboratories [1-9]. Heterocyclic analogs can be made by changing one or more of the ring's carbon atoms to any other group[7,8,10-12]. A variety of pharmacological and bioactive chemical compounds are heterocyclic. Researchers in organic synthetic chemistry have concentrated on nitrogen and sulfur-carrying heterocycles. Heterocyclic compounds exhibit greater polarity and solubility in water due to the substitution of one carbon atom with nitrogen, sulfur, or oxygen [13-16]. Typical medical uses for synthetic heterocyclic compounds include antitumor, antiviral, anticonvulsant, antihistamine, hypnotic, antiseptic, and antineoplastic properties The majority of synthetic heterocyclic molecules are used as therapeutic agents in a variety of diseases[17,18].

Pyrrole is a five membered aromatic ring with the formula C_4H_5N. It is a colourless, volatile liquid that swiftly darkens when exposed to air. F.F. Runge discovered it in coal tar in 1834. It was first isolated in 1857 from bone pyrolysate. Its name is derived from the Greek word pyrroles (fiery), which refers to the red colour that it imparts to wood when soaked with hydrochloric acid. Pyrrole and its derivatives are among the most important nitrogen-containing heterocyclic compounds found in numerous natural products, including bile pigments, heme, cytochromes, vitamin B12, and alkaloids[19].Pyrrole compounds are reported active as antibacterial[20], antioxidant [21], anti-inflammatory[22], antitubercular [23] and antitumor[24].

Tuberculosis (TB) is a highly dangerous infectious disease caused by the bacterial pathogen *Mycobacterium tuberculosis*(Mtb)[25]. The lungs are a vital organ that is affected by tuberculosis; it may also affect the other parts of the body as well.. It is uncommon in high-income countries, but it is still a problem. Low and middle-income people face a public health crisis. Among global health hazards, tuberculosis (TB) remained the second highest cause of mortality from a single infectious disease. In 2012 alone, nearly 1.3 million fatalities are due to TB and over 95% of them are occurred in low- and middle-income countries[26]. According to the latest World Health Organization (WHO) report, 8.6 million new TB cases were recorded and among them three million people were co-infected with both HIV and *Mycobacterium tuberculosis*[26,27]. The individuals infected with TB relied greatly on cocktail of 6-8 drugs such as isonicotinic acid hydrazide (INH), rifampicin (RIF), ethambutol (EMB), streptomycin (STR), ethionamide, *p*-aminosalicylic acid (PAS), pyrazinamide(PZA), fluoroquinolones, etc. for prolonged period up to 24 Months [28].However, most of these drugs have different drawbacks such host toxicity, ineffectiveness against MDR-TB etc[29]. Hence the requirement for novel and effective chemotherapeutic agents to reduce the treatment period and side effects to combat this disease is much higher than ever before[30].

Enoyl ACP reductase (ENR) is an enzyme that synthesises mycolic acids (MAs), which are important structural components of the mycobacterial cell wall. M. tuberculosis-ENR, an InhA-based anti-TB therapeutic target, has received extensive validation. However, the entire genome sequence of tuberculosis bacteria has helped to uncover numerous critical pharmacological targets that may be useful in preventative and therapeutic approaches[31,32]. Mycobacteria have both FAS-I and FAS-II systems, with FAS-I producing fatty acyl chains up to 16 carbons and FAS-II producing long chains up to 56 carbons that are precursors of MAs, implying that the FAS-II system uses FAS-I system products as primers to extend fatty acyl chain lengths even further[33]. The protein encoded by the InhA gene, known as InhA, has a similar amino acid sequence to the two previously characterised enoyl-ACP reductases, FabI from Escherichia coli and ENR1 from Brassica napus[34,35]. Further investigation indicated that InhA catalyses the NADH-dependent reduction of trans double bonds between the sites C2 and C3 of fatty acyl substrates. Furthermore, InhA prefers fatty acyl substrates of C16 or larger, which is consistent with its membership in the mycobacterial FAS-II system[36]. The gene InhA is derived from isoniazid (INH), a first-line antibiotic used to treat tuberculosis for over 50 years and known to block mycolic acid production. InhA is inhibited by the active adduct of INH (INH-NAD), which is covalently formed between NAD+ and the reactive acyl radical of INH produced by the activation of catalase-peroxidase (KatG)[37].

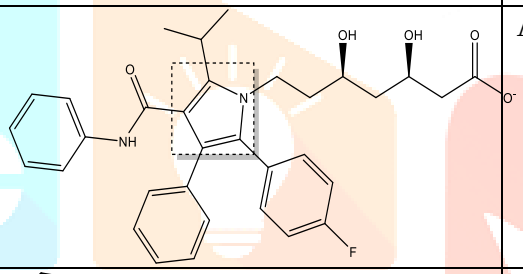
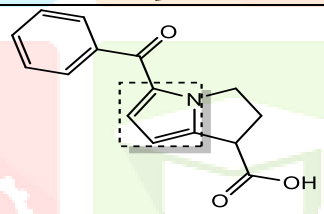
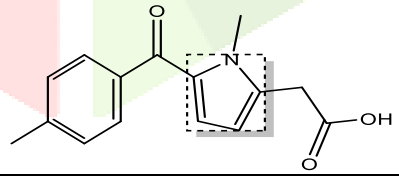
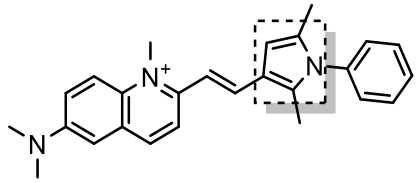
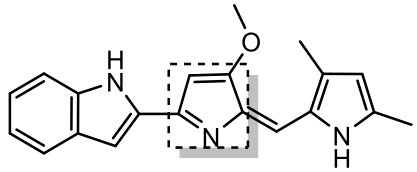
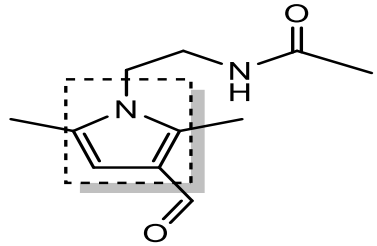
Many researchers have been scientifically worked on various chemical and biological investigations of pyrrole analogsand they have published research papers in various journals and in scientific databases. Literature search revealed that, till date, no reports have been published on its Mycobacterium enoyl acyl carrier protein reductase (InhA)inhibiotrs as a key target for antitubercular drug discoveryHence, there is solid need to have collective information aboutenoyl acyl carrier protein reductase (InhA) inhibitors which will be helpful to other researchers and readers. With respect to this need, we have made an attempt to carry out the present review work.

Main text

1]Methodology for data collection

In the present review article, extensive data on its Pyrrole containing drugs in the market , and relevant insights on several Pyrrole analogs as InhA inhibitors has been gathered and provided in this review article from a variety of web sources, including indexing sites like Web of Science, Scopus, PubMed, and Research Gate. Numerous articles from databases and indexed journals have been gathered and methodically examined.

2]Pyrrole containing drugs in the market:

Sr. no	Drug name	Drug structure	Drug use	Refs
1.	Atorvastatin		Antilipidemic	38
2.	Ketorolac		NSAID	39
3.	Tolmetin		NSAID	40
4.	Pyrvinium		Anthelmintic	38
5.	Obatoclax		Anticancer	41
6.	Aloracetam		Antialzheimer	42

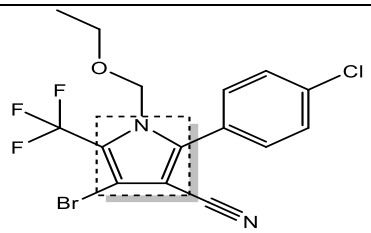
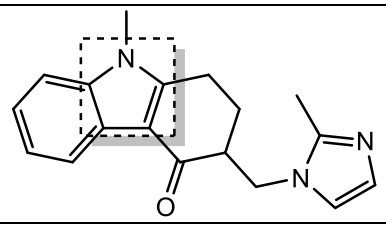
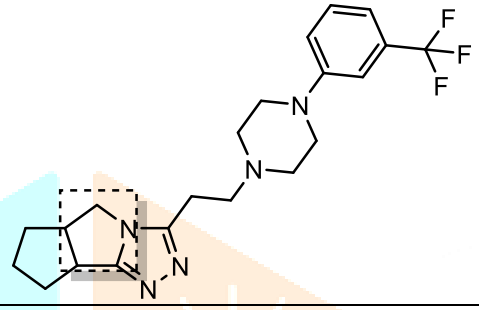
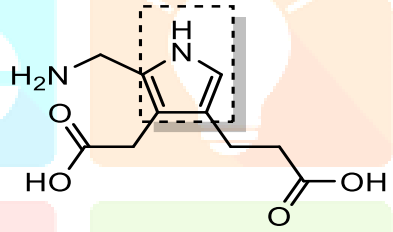
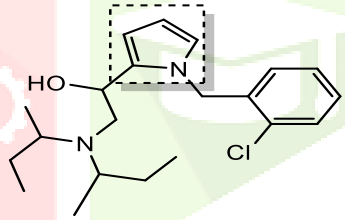
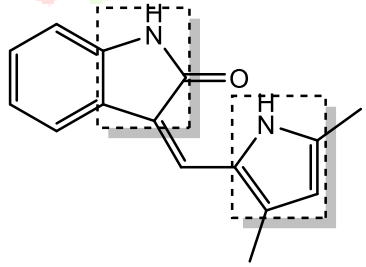
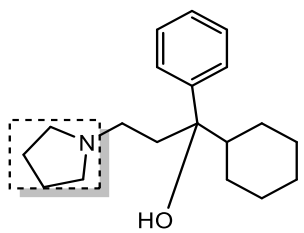
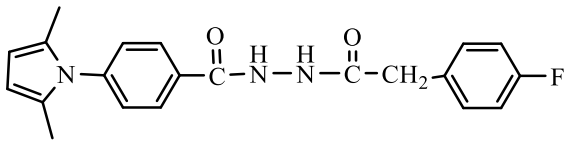
7.	Chlorfenapyr		Insecticidal	38
8.	Ondansetron		Antiemetic	39
9.	Nargenicin		Anticancer	43
10.	Porphobilinogen		Porphyrin metabolism	44
11.	Viminol		Opioid analgesic	45
12.	Semaxanib		Anticancer	46
13.	Procyclidine		Antiparkinsonian	42

Fig 1.Pyrrole containing drugs in the market with different biological activity.

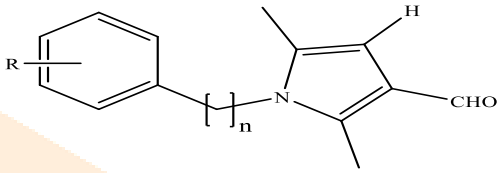
3.Pyrrole analogs as Mycobacterium enoyl acyl carrier protein reductase (InhA) inhibiotrs:

3.1 Pyrrolyl benzohydrazide: Joshi et al.[47] synthesized a novel series of 4-(2,5-dimethyl-1H-pyrrol-1-yl)-N' -(2-(substituted)acetyl) benzohydrazides derivatives and tested them for anti-tuberculosis efficacy.Compound 1 was found to be most potent of all the compounds tested with a MIC value of 0.8µg/mL and % Inhibition of InhA was found 88%.



Compound 1

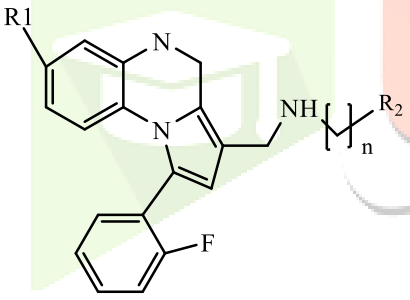
3.2 Pyrrole carbaldehyde: Joshi et.al [48] synthesized a novel series ofpyrrolecarbaldehyde derivatives and tested them for anti-tuberculosis efficacy. Compound 2a was found to be most potent of all the compounds tested with a MIC value of 3.12µg/mL.It showed H-bonding interactions similar to that of triclosan with enoyl-ACP enzyme and with a better docking score (C score 8.81), , while the compound 2b showed additional interaction with MET98.H amino acid residue.



2a R =3 NO_2,
2b R =2 NO_2

Compound 2

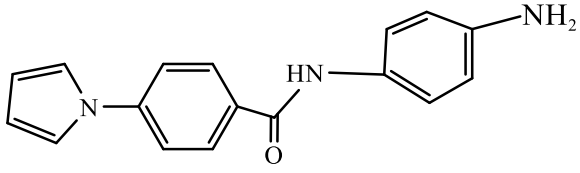
3.3 Pyrrolo[1,2-a] quinoxaline : Youfu Luo et.al [49] synthesized a new series ofPyrrolo[1,2-a] quinoxaline tested for anti-tuberculosis efficacy.Compound 3a was found to be most potent of all the compounds tested with a MIC value of 5µg/mL. as a representative may possess better oral bioavailability and indicated high permeability by the parallel artificial membrane permeation assay of the blood-brain barrier (PAMPA-BBB). Compound 3b were demonstrated to bind well with a classic anti-TB drug target InhA and % Inhibition of InhA was found 64.86%.



3a: R_1=Cl,R_2=3,4-O-CH_3-Phenyl
3b: R_1=Cl,R_2=4-Br-phenyl

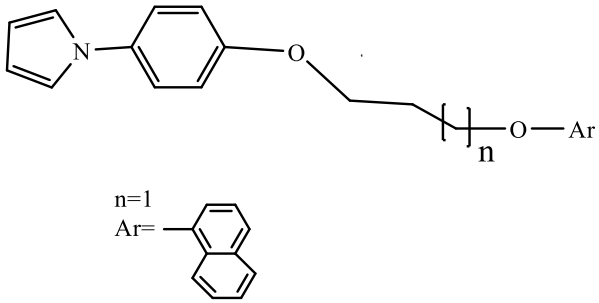
Compound 3

3.4 (1H-pyrrol-1-yl) benzamide: Joshi et.al [50] synthesized a novel series ofpyrrolyl benzamide derivatives were developed using molecular hybridization technique to create novel lead antimycobacterial molecules used to fight against Mycobacterium tuberculosis .The newly synthesized molecules have inhibited InhA, the enoyl-ACP reductase enzyme from the mycobacterial type II fatty acid biosynthetic pathway. Of these, compound 4 showed H-bonding interactions with Tyr158 and co-factor NAD+ that binds the active site of InhA. All the molecules were screened for in vitro antitubercular activity against M. tuberculosis H37Rv, as well as some representative molecules as the inhibitors of InhA. Most of all compounds exhibited good anti-TB activities (MIC = 1.6 µg/mL), but only few representative molecules showed the moderate InhA enzyme inhibition activity.



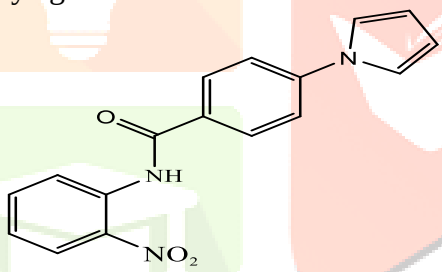
Compound 4

3.5 Pyrrolyl phenoxy: Joshi et.al[51] synthesized a novel series of pyrrolyl phenoxy derivatives bearing alkoxy linker were synthesized and evaluated for anti-tubercular activity (anti-TB) against Mycobacterium tuberculosis**.** Molecular modeling, pharmacophore constructed using GALAHAD to produce an effective alignment of data set and evaluated by Pareto ranking. The pharmacophore features were filtered by Surflex-dock study using enoyl ACP reductase from M. tuberculosis. Compound 5 showed the H-bond with NAD+, whereas compound 5 showed H bonds with Tyr158, Thr196, Met199 and NAD+ that fitted well into the binding pocket of target InhA. The alkoxy linker bridge and acceptor groups with benzene ring were advantageous for anti-TB activity.



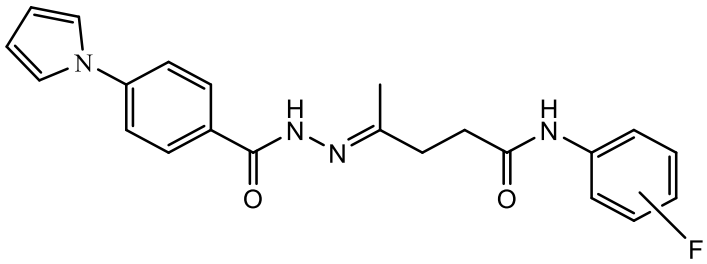
Compound 5

3.6 Pyrrolyl benzamide: Joshi et.al [52] synthesized a novel series ofpyrrolyl benzamide derivatives . The new chemical entities were screened to target enoyl-ACP reductase enzyme. Compound 6 exhibited H-bonding interactions with Tyr158, Thr196 and co-factor NAD+ that binds the active site of InhA. All the pyrrolyl benzamide compounds were evaluated as inhibitors of M. tuberculosis H37Rv as well as inhibitors of InhA. Among them, few representative compounds were tested for mammalian cell toxicity on the human lung cancer cell-line (A549) and MV cell line that presented no cytotoxicity. Five of these compounds exhibited a good activity against InhA.



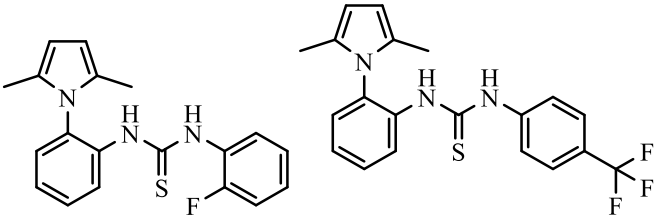
Compound 6

3.7 Pyrrolyl hydrazones : Joshi et.al [53] synthesized a novel series of pyrrolyl hydrazones .Compound 7 exhibited more than 60% binding with the enzyme even at 5 µM (exhibited good IC50 upto 2.4 µM). Most of the active molecules have a very less cytotoxicity against the human lung cancer cell-line A549. The docking and 3D-QSAR studies have been carried out to provide some insights into the mechanism of action for this class of compounds.



Compound 7

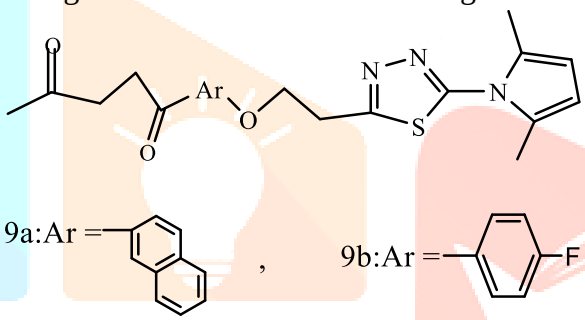
3.8 Pyrrolyl pyrazoline, isoxazole and phenyl thiourea : Joshi et.al[54] synthesized a novel series of pyrrolyl derivatives bearing pyrazoline, isoxazole and phenyl thiourea moieties. Docking analysis of the crystal structure of ENR performed using Surflex-Dock in Sybyl-X 2.0 software indicates the occupation of substituted pyrrolyl derivatives into hydrophobic pocket of InhA enzyme. Compounds 8a and 8b exhibited the highest antitubercular activity almost close to isoniazid (0.4 µg/mL) with a MIC value of 0.8 µg/mL. The compounds were further test moieties for mammalian cell toxicity using human lung cancer cell-line (A549) and were nontoxic. Some compounds exhibited inhibition activities against InhA.



Compound 8a Compound 8b

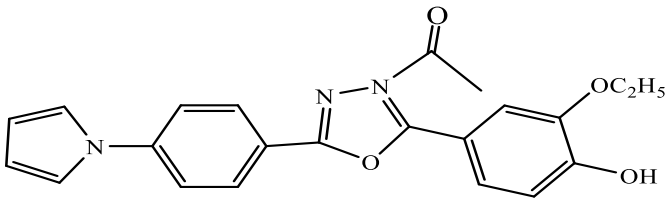
Compound 8

3.9 Pyrroyl-1,3,4-thiadiazole: Joshi et.al [55] synthesized a novel series of pyrroyl-1,3,4-thiadiazole moieties. Compounds 9a and 9b displayed significant activities 3.125 and 6.25 µg/mL respectively against M. tuberculosis H37Rv strain. Three-dimensional quantitative structure–activity relationships (3D-QSAR) were established for pyrrolyl substituted aryloxy-1,3,4-thiadiazole series of InhA inhibitors using the comparative molecular field analysis (CoMFA). Docking analysis of the crystal structure of ENR performed by using Surflex-Dock in Sybyl-X 2.0 software indicates the occupation of pyrrolyl substituted aryloxy 1,3,4-thiadiazole into hydrophobic pocket of InhA enzyme. Based on docking and database alignment rules, two computational models were established to compare their statistical results. The analysis of 3D contour plots allowed us to investigate the effect of different substituent groups at different positions of the common scaffold. In vitro testing of ligands using biological assays substantiated the efficacy of ligands that were screened through in silico methods.



Compound 9

3.10 Pyrrolyl –oxadiazoles and pyrrolyl –pyridazines: Joshi et.al[56] synthesized a novel series of a series of 4-(4-pyrrol-1-yl/2,5-dimethyl-4-pyrrol-1-yl) benzoic acid hydrazide analogs, some derived oxadiazoles and azines have been synthesized in good yields and structures of these compounds were established by IR, 1 H NMR, 13C NMR, mass spectral and elemental analysis.Compound 10a displayed promising anti-tubercular activity. some compounds were also assessed for their cytotoxic activity (IC50) against mammalian Vero cell lines and A549 (lung adenocarcinoma) cell lines using the MTT assay method. The results revealed that these compounds exhibit anti-tubercular activity at non-cytotoxic concentrations. The docking of inhibitors into InhA using Sybyl-X 2.0 software revealed the vital interactions and binding conformation of the inhibitors.

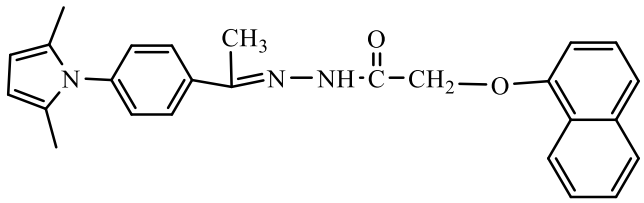


Compound 10a

Compound 10

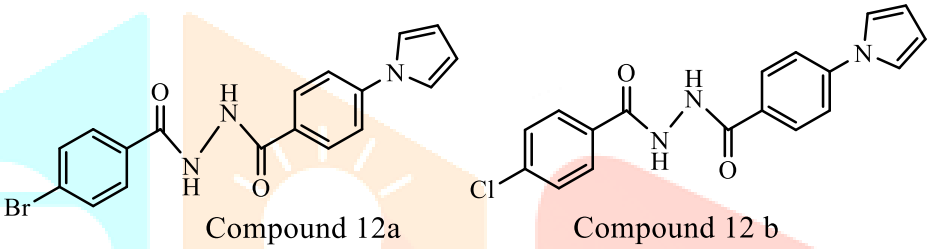
3.11 Pyrrole hydrazine derivatives: Joshi et.al [57] synthesized a novel series of pyrrole hydrazine derivatives. Highly active compound 11 (MIC 0.2 mg/mL) showed hydrogen bonding interactions with Tyr158 and NAD+ in the same manner as those of ligands PT70 and triclosan. The CoMFA and CoMSIA models generated with database alignment were the best in terms of overall statistics. The predictive ability of the CoMFA and CoMSIA models was determined using a test set of 13 compounds, which gave predictive correlation coefficients (rpred2) of 0.896 and 0.930, respective. pyrrole hydrazine derivatives have been synthesized and screened which target the essential enoyl-ACP reductase. The

binding mode of the compounds at the active site of enoyl-ACP reductase was explored using surflex-docking method. The binding model suggests one or two hydrogen bonding interactions between pyrrole hydrazones and InhA enzyme.



Compound 11

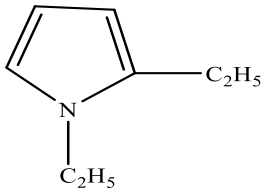
3.12. Pyrrolyl benzohydrazides:Joshi et.al[58] synthesized a novel series of 19 pyrrolyl benzohydrazides were synthesized and screened to target enoyl-ACP reductase enzyme, which is one of the important enzymes involved in type II fatty acid biosynthetic pathway of M. tuberculosis. Pharmacophores were constructed using GALAHAD to generate alignment of data sets and calculated by Pareto ranking. The pharmacophore features were then filtered by Surflex-dock study using enoyl ACP reductase from M. tuberculosis. Compounds 12a and 12b showed H bonding interactions with Tyr158, Thr196 and co-factor NAD+ that fitted well within the binding pocket of InhA. All the synthesized compounds were screened for preliminary antibacterial activities against Gram-positive S. aureus and Gram-negative E. coli and M. tuberculosis H37Rv to evaluate their antitubercular activity.



Compound 12a Compound 12 b

Compound 12

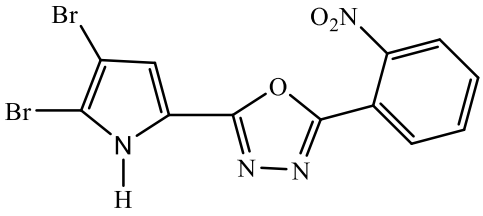
3.13. Carbazole tethered pyrrole derivatives: Md. Perwez Alam Ansari[59] focus in the tubercular drug research is on the development of agents inhibiting the enzyme targets involved in potential role in the life cycle of the pathogen. In the present research work the docking studies was performed on the human pathogenic bacterial enzyme InhA from its parent domain Mycobacterium Tuberculosis. In this present study, the flexible and extra precision docking simulation were performed on twenty new carbazole tethered pyrrole derivative against InhA by using Glide v5.6. All the derivatives were considered and docked as well as bound to ligand binding domain EAcCPR. All the compounds show good Glide score as compared to isoniazid as standard drug. Compound 13 showing highest glide score (-9.518). The result obtain were valuable for synthesis and thereafter biological screening of promising hits and it could be useful for development of new anti- tubercular agents.



Compound 13

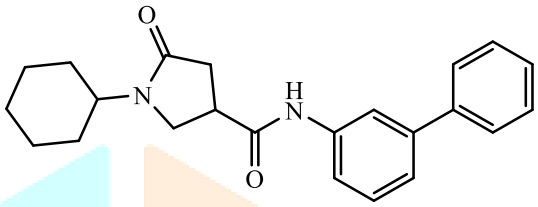
3.14 Oxadiazole-Ligated Pyrrole: Asgaonkar et.al[60] was developed a quantitative structure-activity relationship model on a series of compounds containing oxadiazole-ligated pyrrole pharmacophore to identify key structural fragments required for anti-tubercular activity. 2D- and 3D-QSAR results shed light on the electronic, steric, hydrophobic, and topological nature of the substitution pattern around the selected pyrrole-ligated oxadiazole pharmacophore. The 2D-QSAR study indicated the requirement of T_O_O_5 and the sds CHE index which positively contributed to the biological activity. 3D-QSAR gave information about the nature of the substituents like the electron-withdrawing group at the 4th and 5th position of pyrrole, the less steric group at meta, para, and ortho position on the benzene ring, the electron withdrawing group at the 4th position of benzene, and finally the more hydrophobic group at para position of the benzene ring is required for good antimycobacterial activity. The designed compounds were subjected to Lipinski's filter, which gave information about the pharmacokinetic behavior. The designed compounds also showed a good binding interaction with the enoyl-ACP (CoA) reductase enzyme.

compound showed two hydrogen bonds as compared to the standard (isoniazid) which showed three hydrogen bonds.



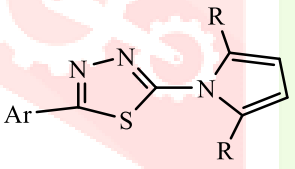
Compound 14

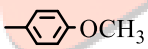
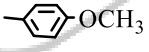
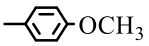
3.15 Pyrrolidine-3-carboxamide: Babu joseph et.al[61] was done a molecular docking one aspect of a novel new approach to researching the binding of tiny molecules to receptor proteins.Compound15 ,CHEMBL441373 [1-cyclohexyl-5-oxo-N-(3-phenyl) pyrrolidine-3-carboxamide]become located to possess maximum appropriate docking energy (-11.1Kcal/mol), and it has become suitable as candidate molecules of cell wall protein inhibitor (4U0J).



Compound 15

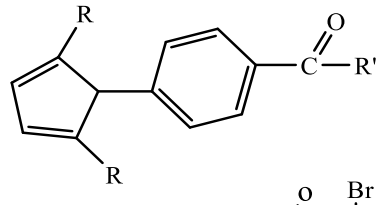
3.16 Pyrrolyl thiadiazoles: Joshi et.al[62] synthesized a novel series of Pyrrolyl thiadiazole compounds exhibited moderate activity against M. tuberculosis. Compounds 16a, 16b, and 16d inhibited growth of M. tuberculosis very effectively at a MIC value of 12.5 µg/mL .Most of the molecules could effectively bind to the substrate binding site of ENR. The key H-bonding interactions with Tyr158, Met98, and cofactor NAD+ , as well as hydrophobic amino acid residues, stabilized the ligand–receptor complex to conclude that molecules are efficiently bound at the active site of ENR and, hence, can be better ENR inhibitors. The predicted in silico Surflex-Dock values obtained through docking studies have pointed the most promising inhibitors.

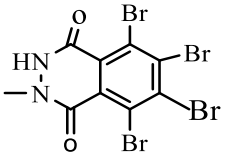


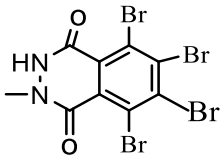
	R	Ar
16a	H	
16b	CH_3	
16c	CH_3	

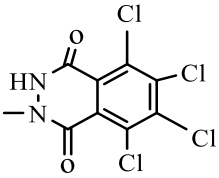
Compound 16

3.17 Pyrrolyl benzohydrazide: Joshi et.al[63] synthesized a novel pyrrolyl benzohydrazide derivatives. For most of the potent compounds (17a, 17band 17c), the IC50 values were determined using the 4-parameter curve-fitting software XLFit (IDBS) considering at least five to six points. The binding mode of compounds at the active site of enoyl-ACP reductase was explored using the surflex-docking method. The model suggests one or two H-bonding interactions between the compounds and the InhA enzyme. Some compounds exhibited good activities against InhA in addition to promising activities against M. tuberculosis.



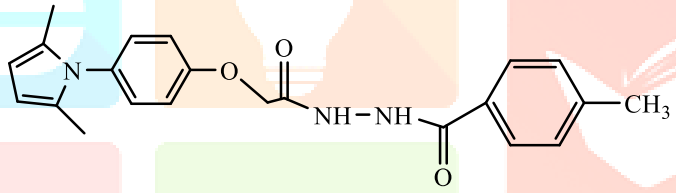
17a : R=H,R'= 

17b : R= CH_3,R'= 

17c:R=CH_3,R'= 

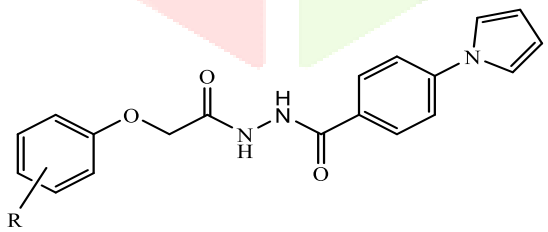
Compound 17

3.18Dimethyl-pyrrolyl-acetohydrazide derivatives: Joshi et.al[64] synthesized a novel series of dimethyl-pyrrolyl-acetohydrazide derivatives .The pyrrolyl acetohydrazides exhibited one or two H-bonding connections with InhA enzyme. Compound 18 was found to be a most potent with MIC 0.4 µg/mL and % Inhibition of InhA was found 70% at 50 µM and showed H-bonding connections with Tyr158 and NAD+ in a similar mode to that of ligand pyrrolidine carboxamide.

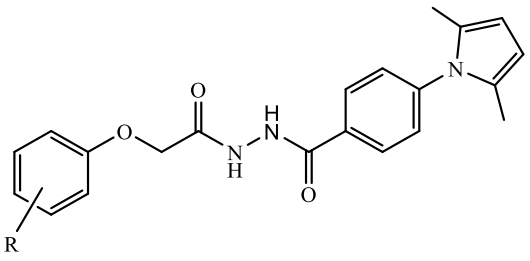


Compound 18

3.19Pyrrolyl-benzohydrazide derivatives: Joshi et.al[65] synthesized a novel series pyrrolyl-benzohydrazide derivatives.In vitro assays indicated that the compounds 19 a to 19 g have significant enzyme inhibitory action against both the ENR-enzyme and DHFR enzyme enzymes. All the compounds had moderate to good potency against tuberculosis, as shown by MICs ranging from 1.6 to 12.5 µg/ml.



19 a : R = OH
19 b : R = 2,4-di CH_3
19 c : R =3,5-di OH
19 d : R=3,5-di CH_3



19 e : R = H
19 f : R = 2,4-di CH_3
19 g : R =3CH_3

Compound 19

Conclusion

Innovative anti-TB pharmaceutical formulations that reduce drug resistance and shorten treatment duration are in high demand due to the rise of widespread and multi-drug resistant tuberculosis. Fatty acid production involves the mycolic acid pathway, of which InhA is an essential component. It has been discovered to be a unique target for every species of Mycobacterium since it is blocked by a variety of scaffolds. In order to cure tuberculosis, new anti-TB drugs can now be developed by specifically targeting InhA. Several scaffolds have been shown to exhibit anti-TB and anti-InhA properties in vitro. Using screening techniques like fragment-based screening, encoded library technology, and high throughput

screening, a number of InhA inhibitors have been discovered. Scaffolds used for InhA action include pyrrolyl benzohydrazide pyrroles, pyrrolyl acetamides, pyrrolyl thiadiazoles, pyrrolyl triazole, and pyrrolyl acetohydrazides, as well as its derivatives that were found to be active against Mtb .The notion that a direct inhibitor of InhA is a viable substitute for acquiring new compounds to be used in drug combinations in upcoming therapies is supported by emerging data. Multi-drug combinations will be used to treat tuberculosis (TB) in the foreseable future.

Disclaimer (artificial intelligence)

The authors declare that there is no generative AI technologies such as ChatGPT, COPILOT, etc and text to image generators have been used during writing this manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Abbreviations

TB: Tuberculosis, Mtb:*Mycobacterium tuberculosis,* ENR: Enoyl ACP reductase, MAs: mycolic acids.

Summary

This review provides valuable insights into marketed pyrrole-containing drugs and pyrrole analogs as InhA inhibitors. With the growing challenge of drug-resistant tuberculosis, there is an urgent need for innovative anti-TB formulations that reduce resistance and treatment duration. Targeting InhA offers a promising strategy for the development of new anti-TB drugs.

References

1. Prandi C, Occhiato EG From synthetic control to natural products: A focus on N-heterocycles. Pest Manag Sci. 2019: 75(9):2385-2402.
2. Heda LC, Sharma R, Pareek C, Chaudhari PB.Synthesis and antimicrobial activity of some derivatives of 5-substituted indole dihydropyrimidines, E J Chem .2009; 6:770-74.
3. Hassan R, Mohi-Ud-Din R, Dar MO, Shah AJ, Mir PA, Shaikh M, *et al.* Bioactive heterocyclic compounds as potential therapeutics in the treatment of gliomas: A review. Anticancer. Agents Med. Chem. 2022 ; 22(3):551-565.
4. Mir RH, Mohi-ud-din R, Wani TU, Dar MO, Shah AJ, Lone B, *et al.* Indole: a privileged heterocyclic moiety in the management of cancer. Curr Org Chem. 2021; 25 (6): 724-736.
5. Mir RH, Sawhney G, Verma R, Ahmad B, Kumar P, Ranjana S, *et al*. Origanumvulgare L.: in vitro assessment of cytotoxicity, molecular docking studies, antioxidant and anti-inflammatory activity in LPS stimulated RAW 264.7 cells. Med Chem. 2021;17 (9):983-93.
6. Mohi-Ud-Din R, Mir RH, Mir PA, Farooq S, Raza SN, Raja WY, *et al.* Ethnomedicinaluses, phytochemistry and pharmacological aspects of the genus berberislinn: A comprehensive review. Chem High Throughput Screen. 2021 ;24(5):624-44.
7. Mohi-Ud-Din R, Mir RH, Wani TU, Shah AJ, Banday N, Pottoo FHBerberine in the treatment of neurodegenerative diseases and nanotechnology enabled targeted delivery. Comb Chem High Throughput Screen .2022; 25(4):616-33.
8. Comb. Chem. High Throughput Screen., Ahmad G, Hassan R, Dhiman N, Ali A.Assessment of anti-inflammatory activity of 3-acetylmyricadiol in LPS Stimulated raw 264.7 macrophages. Comb. Chem. High Throughput Screen . 2022; 25(1):204-10.
9. Mohi-Ud-Din R, Mir RH, Wani TU, Shah AJ, Mohi-Ud-Din I, Dar MA *et al*. Novel drug delivery system for curcumin: Implementation to improve therapeutic efficacy against neurological disorders.Comb Chem High Throughput Screen .2022;25(4):607-15.
10. Fatahala SS, Mohamed MS, Sabry JY, Mansour YE.Synthesis strategies and medicinal value of

pyrrole and its fused heterocyclic compounds. Med Chem. 2022;18(10):1013-43.

11. Mir RH, Shah AJ, Sabreen S, Wani TU, Masoodi MH, Akkol EK, *et al.* Plant-derived natural compounds for the treatment of amyotrophic lateral sclerosis: an update. Cur Neuropharmacol. 2022; 20(1):179.
12. Hassan Mir R, Godavari G, Siddiqui NA, Ahmad B, Mothana RA, Ullah R, *et al.* Design, synthesis, molecular modelling, and biological evaluation of oleanolic acid-arylidene derivatives as potential anti-inflammatory agents. Drug Des Devel Ther. 2021:385-97.
13. Hosseinzadeh Z, Ramazani A, Razzaghi-Asl N.Anti-cancer nitrogen-containing heterocyclic compounds. Curr Org Chemis. 2018;22(23):2256-79.
14. Shah AJ, Mir RH, Pottoo FH, Masoodi MH, Bhat ZA. Depression: an insight into heterocyclic and cyclic hydrocarbon compounds inspired from natural sources. Curr. Neuropharmacol. 2021;19 (11):2020.
15. Mir RH, Shah AJ, Mohi-Ud-Din R, Pottoo FH, Dar M, Jachak SM, Masoodi MH. Natural Anti-inflammatory compounds as Drug candidates in Alzheimer's disease.Curr Med Chem. 2021; 28(23):4799-825.
16. Mir RH, Masoodi MH. Anti-inflammatory plant polyphenolics and cellular action mechanisms. Curr Bioac. Compd. 2020;16(6):809-17.
17. Liu RS.Synthesis of oxygen heterocycles via alkynyltungsten compounds. Pure Appl Chem. 2001; 73(2):265-269.
18. JeelanBasha N, Basavarajaiah SM, Shyamsunder K. Therapeutic potential of pyrrole and pyrrolidine analogs: an update .Mol Divers. 2022;26(5):2915-37.
19. Gholap SS .Pyrrole: An emerging scaffold for construction of valuable therapeutic agents.Eur J Med Chem. 2016; 1(10):13-31.
20. Inamdar TM, Joshi SD, Avunoori S. *In Silico* Approach to Identify Potent Bioactive Pyrrole Analogs as Inhibitors against the Enoyl-acyl Carrier Protein (ACP) Reductase Enzyme of *Mycobacterium tuberculosis* . RGUHS J Pharm Sci .2025;15(3):25-31.
21. Inamdar TM, Joshi SD, Chaubey A ,Salunkhe H, Mujawar M, Yadav N. *In Silico* Approach to Identify Potent Bioactive Pyrrole Analogs as Inhibitors against the *Mycobacterium tuberculosis* Dihydrofolate Reductase Enzyme .Adv. Res. 2026;27(1):305-14.
22. Inamdar TM, Joshi SD. Synthesis, Molecular Docking Research On Dual Enoyl Acp Reductase And *Mt*DHFR Enzyme Inhibitors, And Biological Assessment of Several Novel 4-(1H-Pyrrol-1yl)Benzohydrazide Derivatives As Antimycobacterial Agents. Rasayan J Chem.2026;19(2):701-710.
23. Joshi SD, Kulkarni VH, Kumar SP, Basha J.Synthesis, antitubercular and antibacterial activities of novel N'-(substituted)-2-(2,5-dimethyl-1h-pyrrol-1-yl) phenyl) benzamide derivatives. Indo Am J Pharm Res. 2019; 8(1):1846-51.
24. Kuznietsova H, Dziubenko N, Byelinska I, Hurmach V, Bychko A, LynchakO,et al. Pyrrole derivatives as potential anti-cancer therapeutics: synthesis, mechanisms of action, safety. J Drug Target. 2020 ;28(5):547-63.
25. Rothschild BM, Martin LD, Lev G, Bercovier H, Bar-Gal GK, Greenblatt C, *et al. Mycobacterium tuberculosis* complex DNA from an extinct bison dated 17,000 years before the present. Clin Infect Dis. 2001;33(3):305-11.
26. Tollefson D, Bloss E, Fanning A, Redd JT, Barker K, McCray E. Burden of tuberculosis in indigenous peoples globally: a systematic review. Int J Tuberc Lung Dis. 2013,17(9):1139-50.
27. Vladimirova S, Bijev A. Synthesis of new derivatives of pyrrole tuberculostatics providing structural diversity. 2015 ; Pharmacia 62(1):3-8.
28. Stephanie F, Saragih M, Tambunan US.Recent progress and challenges for drug- resistant tuberculosis treatment. Pharmaceutics. 2021;13(5):592.
29. Surineni G, Yogeeswari P, Sriram D, Kantevari S. Design and synthesis of novel carbazole tethered pyrrole derivatives as potent inhibitors of *Mycobacterium tuberculosis*.Bioorg Med Chem Lett. 2010 ; 25(3):485-91.
30. Zumla AI, Gillespie SH, Hoelscher M, Philips PP, Cole ST, Abubakar I, *et al.* New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. Lancet Infect Dis. 2014;14(4):327-40.
31. Cole S, Brosch R, Parkhill J, Garnier T, Churcher C, Harris D, *et al.*Deciphering the biology of

Mycobacterium tuberculosis from the complete genome sequence. Nature. 1998;396(6707):190.
32. De Souza MV, Ferreira MD, Pinheiro AC, Saraiva MF, Almeida MV, Valle MS. Synthesis and biological aspects of mycolic acids: an important target against Mycobacterium tuberculosis. Sci World J .2008; 8:720-51.
33. Marrakchi H, Laneelle MA, Daffe M.Mycolic acids: structures, biosynthesis, and beyond. Chem Biol .2014;21(1):67-85.
34. Lone MY, Athar M, Gupta VK, Jha PC .Identification of Mycobacterium tuberculosis enoyl-acyl carrier protein reductase inhibitors: A combined in-silico and in-vitro analysis. J Mol Graph Model. 2017;76:172-80.
35. Marrakchi H, Laneelle G, Quémard A.InhA, a target of the antituberculous drug isoniazid, is involved in a mycobacterial fatty acid elongation system, FAS-II. Microbiology. 2000;146(2):289-96.
36. Kim SJ, Ha BH, Kim KH, Hong SK, Shin KJ, Suh SW, Kim EE. Dimeric and tetrameric forms of enoyl-acyl carrier protein reductase from Bacillus cereus.Biochem Biophys Res Commun. 2010 ;400(4):517-22.
37. Veyron-Churlet R, Zanella-Cléon I, Cohen-Gonsaud M, Molle V, Kremer L .Phosphorylation of the Mycobacterium tuberculosis β-ketoacyl-acyl carrier protein reductase MabA regulates mycolic acid biosynthesis. J Biol Chem. 2010 ; 5(17):12714-25.
38. Ahmad S, Alam O, Naim MJ, Shaquiquzzaman M, Alam MM, Iqbal M, *et al*.Pyrrole: An insight into recent pharmacological advances with structure activity relationship. Eur J Med Chem. 2018;157:527-61.
39. Petri GL, Spano V, Spatola R, Holl R, Raimondi MV, Barraja P, *et al*.. Bioactive pyrrole-based compounds with target selectivity. Eur J Med Chem. 2020; 208:112783.
40. Konovalova IS, Kovalenko SM, Kravchenko DV, Chuev VP .Crystal structure of the non-steroidal anti-inflammatory drug (NSAID) tolmetinsodium.ActaCrystallogr. E Crystallogr Commun . 2021; 77(2):134-7.
41. Or CH, Huang CW, Chang CC, Lai YC, Chen YJ . Obatoclax, a Pan-BCL-2 inhibitor, downregulates survivin to induce apoptosis in human colorectal carcinoma cells via suppressing WNT/β-catenin signaling. Int J Mol Sci. 2020; 21(5):1773.
42. Fischer F, Matthisson M, Herrling P (2004) List of drugs in development for neurodegenerative diseases. Neurodegener Dis. 2004;1(1):50.
43. Kim SH, Yoo JC, Kim TS .Nargenicin enhances 1, 25-dihydroxyvitamin D3-and all-trans retinoic acid-induced leukemia cell differentiation via PKCβI/MAPK pathways.Biochem Pharmacol. 2009;77(11):1694-701.
44. Aarsand AK, Petersen PH, Sandberg S.Estimation and application of biological variation of urinary δ-aminolevulinic acid and porphobilinogen in healthy individuals and in patients with acute intermittent porphyria. Clin Chem. 2006; 52(4):650-6.
45. Baptista,Hon DT, Smith M, Singleton S, Antonides LH, NicDaeid N, McKenzie C, *et al*.Activation of μ opioid receptors by MT45 (1cyclohexyl4(1, 2diphenylethyl) piperazine) and its fluorinated derivatives. Br J Pharmacol. 2020; 177(15):3436-48.
46. Lockhart AC, Cropp GF, Berlin JD, Donnelly E, Schumaker RD, Schaaf L,*et.al*. Phase I/pilot study of SU5416 (semaxinib) in combination with irinotecan/bolus 5-FU/LV (IFL) in patients with metastatic colorectal cancer. Am J Clin Onco .2006; 29(2):109-15.
47. Mahnashi MH, Koganole P, Ashgar SS, Shaikh IA, Joshi SD, Alqahtani AS. Synthesis, Molecular Docking Study, and Biological Evaluation of New 4-(2, 5-Dimethyl-1 H-pyrrol-1-yl)-N'-(2-(substituted) acetyl) benzohydrazides as Dual Enoyl ACP Reductase and DHFR Enzyme Inhibitors. Antibiotics. 2023;12(4):763.
48. Joshi SD, Kumar D, More UA, Yang KS, Aminabhavi TM. Design and development of pyrrole carbaldehyde: an effective pharmacophore for enoyl-ACP reductase. Med Chem Res. 2016; 25:672-89.
49. Wang T, Tang Y, Yang Y, An Q, Sang Z, Yang T.*et.al*. Liu P, Zhang T, Deng Y, Luo Y,*et al*. Discovery of novel anti-tuberculosis agents with pyrrolo [1,2-a] quinoxaline-based scaffold.Bioorg Med Chem Lett. 2018; 28(11):2084-90.
50. Joshi SD, Kumar SP, Patil S, Vijayakumar M, Kulkarni VH, Nadagouda MN,*et al*. Chemical synthesis, molecular modeling and pharmacophore mapping of new pyrrole derivatives as inhibitors of InhA enzyme and Mycobacterium tuberculosis growth. Med Chem Res. 2019;

28:1838-63.
51. More UA, Joshi SD, Aminabhavi TM, Kulkarni VH, Badiger AM, Lherbet C, *et al.* Discovery of target based novel pyrrolyl phenoxy derivatives as antimycobacterial agents: An in silico approach. Eur J Med Chem. 2015; 94:317-39.
52. Joshi SD, Dixit SR, Basha J, Kulkarni VH, Aminabhavi TM, Nadagouda MN, *et al.* Pharmacophore mapping, molecular docking, chemical synthesis of some novel pyrrolyl benzamide derivatives and evaluation of their inhibitory activity against enoyl-ACP reductase (InhA) and Mycobacterium tuberculosis. Bioorg Chem. 2018 ; 81:440-53.
53. Joshi SD, Kumar D, Dixit SR, Tigadi N, More UA, Lherbet C, *et.al.* Synthesis, characterization and antitubercular activities of novel pyrrolyl hydrazones and their Cu-complexes. Eur J Med Chem. 2016; 121:21-39.
54. Joshi SD, Dixit SR, Kirankumar MN, Aminabhavi TM, Raju KV, Narayan R, *et al* .Synthesis, antimycobacterial screening and ligand-based molecular docking studies on novel pyrrole derivatives bearing pyrazoline, isoxazole and phenyl thiourea moieties. Eur J Med Chem. 2016; 107:133-52.
55. Joshi SD, More UA, Koli D, Kulkarni MS, Nadagouda MN, Aminabhavi TM ,*et al.* Synthesis, evaluation and in silico molecular modeling of pyrroyl-1, 3, 4-thiadiazole inhibitors of InhA. Bioorg Chem. 2015; 59:151-67.
56. Joshi SD, More UA, Pansuriya K, Aminabhavi TM, Gadad AK.Synthesis and molecular modeling studies of novel pyrrole analogs as antimycobacterial agents. J Saudi Chem Soc. 2017; 21(1):42-57.
57. More UA, Joshi SD, Aminabhavi TM, Gadad AK, Nadagouda MN, Kulkarni VH,*et.al.*(2014) Design, synthesis, molecular docking and 3D-QSAR studies of potent inhibitors of enoyl-acyl carrier protein reductase as potential antimycobacterial agents. European journal of medicinal chemistry. Eur J Med Chem. 2014; 71:199-218.
58. Joshi SD, Dixit SR, Kulkarni VH, Lherbet C, Nadagouda MN, Aminabhavi TM, *et al*. Synthesis, biological evaluation and in silico molecular modeling of pyrrolyl benzohydrazide derivatives as enoyl ACP reductase inhibitors. Eur J Med Chem .2017;126:286-97.
59. Ansari MP.Molecular docking studies of novel Carbazole tethered pyrrole derivatives as potent inhibitors of Mycobacterium tuberculosis.Int J Innov. 2017;6(9):187-9.
60. Asgaonkar KD, Mote GD, Chitre TS .QSAR and molecular docking studies of oxadiazole-ligated pyrrole derivatives as enoyl-ACP (CoA) reductase inhibitors. Sci pharm. 2014;82(1):71-86.
61. Sarkar D, Maiti AK, Alenazy R, Joseph B.In silico Approach to Identify Potent Bioactive Compounds as Inhibitors against the Enoyl-acyl Carrier Protein (acp) Reductase Enzyme of Mycobacterium tuberculosis. Biointerface Res Appl Chem .2022;12:7023-39.
62. Joshi SD, More UA, Sorathiya S, Koli D, Aminabhavi TM. Pyrrolyl thiadiazoles as Mycobacterium tuberculosis inhibitors and their in silico analyses. Research and Reports in Medicinal Chemistry. 2015;5 :1-20.
63. Joshi SD, More UA, Dixit SR, Balmi SV, Kulkarni BG, Ullagaddi G, *et al.* Chemical synthesis and in silico molecular modeling of novel pyrrolyl benzohydrazide derivatives: Their biological evaluation against enoyl ACP reductase (InhA) and Mycobacterium tuberculosis. Bioorg Chem. 2017; 75:181-200.
64. Kumar SP, Shaikh IA, Mahnashi MH, Alshahrani MA, Dixit SR, Joshi SD, *et al* Design, synthesis and computational approach to study novel pyrrole scaffolds as active inhibitors of enoyl ACP reductase (InhA) and Mycobacterium tuberculosis antagonists.Indian Chem Soc J 2022;99(11):100674.
65. MahnashiMH, Avunoori S, Gopi S, Shaikh IA, Saif A, Joshi SD. Synthesis, molecular docking study and biological evaluation of new pyrrole scaffolds as potential antitubercular agents for dual targeting of enoyl ACP reductase and dihydrofolatereductase. Plos one 2024; 19(5):0303173.