RESEARCH PAPER

Bioactive Pyrrole Analogs Targeting InhA: An In Silico Study for the Creation of New Antitubercular Agents

T. M. Inamdar[1*, 2*], S. D. Joshi[2*], A. V. Zagade[3], S. A. Zargad[4], I. M. Madawali[5], R. A. Rajeghorpade[6], Savitha. N[7], S. M. Patel[1] and A. M.Thaikar[1]

[1]*Department of Pharmaceutical Chemistry, Rani Chennamma College of Pharmacy, Belagavi, Karnataka, India-590010*
[2]*Novel Drug Design and Discovery Laboratory, Department of Pharmaceutical Chemistry, SET's College of Pharmacy, Sangolli Rayanna Nagar, Dharwad, Karnataka, India-580002.*
[3]*Department of Pharmaceutical Chemistry, Anekant Education Society's College of Pharmacy, Baramati, Maharashtra, India-413102*
[4]*Department of Pharmaceutics, Anekant Education Society's College of Pharmacy, Baramati, Maharashtra, India-413102*
[5]*Department of Pharmaceutical Chemistry, Maratha Mandal's College of Pharmacy, Belagavi, Karnataka, India-590010*
[6]*Department of Pharmaceutical Quality Assurance, Pioneer Pharmacy College, Vadodara, Gujarat, India-390019*
[7]*Department of Pharmaceutical Chemistry, Gautham College of Pharmacy, Bengaluru, Karnataka, India-560032*
Corresponding author: *tabsmulani08@gmail.com, shrinivasdj@rediffmail.com*

Received: 14th June, 2026; Revised: 20th July 2026; Accepted: 20th August, 2026; Available Online: 05th September 2026

ABSTRACT

The enoyl-acyl carrier protein reductase (InhA) of *Mycobacterium tuberculosis* is an essential enzyme involved in fatty acid elongation and mycolic acid biosynthesis, making it an important molecular target for developing novel antitubercular agents. The present study employed an *in silico* drug-design approach to investigate pyrrole-based compounds as potential inhibitors of InhA (PDB ID: 6R9W). Molecular docking was performed using AutoDock Tools 1.5.6, and ligand–protein interactions were analysed using BIOVIA Discovery Studio 2021. The ten selected compounds exhibited binding energies ranging from -6.7 to -9.8 kcal/mol. Among them, Compound 3, *N'-(2-amino-3-phenylpropanoyl)-4-(1H-pyrrol-1-yl) benzohydrazide*, demonstrated the most favourable docking score of −9.8 kcal/mol, suggesting a potentially favourable interaction with the InhA binding site. These findings highlight the potential of pyrrole-based scaffolds for further investigation in antitubercular drug discovery. However, experimental validation is required to confirm their inhibitory activity against InhA and their antitubercular efficacy.

Keywords: *Mycobacterium tuberculosis, pyrrole analogs, InhA, molecular docking, binding energy, antitubercular agents.*

How to cite this article: Inamdar TM, Joshi SD, Zagade AV, Zargad SA, Madawali IM, Rajeghorpade RA, Savitha N, Patel SM, Thaikar AM., Bioactive Pyrrole Analogs Targeting InhA: An In Silico Study for the Creation of New Antitubercular Agents. Int J Drug Deliv Technol. 2026;16(8): 124-129; DOI: 10.25258/ijddt.16.8.10
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

Tuberculosis (TB), a chronic contagious illness that mostly affects the lungs and is spread by inhaling infectious aerosols from infected people.[1-4] An projected 10.8 million persons Worldwidecontracted tuberculosis (TB) in 2023, and 1.25 million of those cases resulted in death, according to the WHO Global Tuberculosis Report 2024.Treatment is made more difficult by the emergence of rifampicin and multidrug resistant TB, which also draws attention to the shortcomings of current treatments.

Finding novel, secure, and potent antitubercular medications is therefore essential.In order to find viable antitubercular medication development, the current study candidates for additional of pyrrole based compounds that target the InhA enzyme of Mycobacterium tuberculosis.[5]To address this ongoing public health issue, novel chemotherapeutic drugs that are safer, more effective, and use multiple routes must be developed soon.[6]

For Mycobacterium TB to survive and preserve the integrity of its cell wall, mycolic acid production is necessary. Mycolic acid synthesis depends on InhA, a NADH-dependent enoyl acyl carrier protein (ACP) reductase that is part of the fatty acid synthase II (FAS-II) pathway. It is a therapeutic target that has been validated for the optimization of antitubercular therapeutics. Even if isoniazid inhibit InhA after KatG activation, the creation of new InhA inhibitors may offer ways to get around the current drawbacks of traditional antitubercular treatment.[7-8]

Pyrrole is present in many physiologically active substances, a major heterocyclic scaffold associated with a range of pharmacological effects, including analgesic,

**Author for Correspondence: tabsmulani08@gmail.com*

antibacterial, antitubercular, and anticancer characteristics.[9-10] These properties have prompted the optimization of new compounds based on pyrrole that may have several therapeutic applications. The undertaken study focuses on the design and Computational docking assessment of pyrrole based compounds incorporating a pyrrolyl benzohydrazide scaffold in order to identify potential inhibitors of InhA, an Key enzyme responsible for mycolic acid biosynthesis. The structural features of well known drugs like triclosan, isoniazid, and BM212 justify the investigation of novel antitubercular potential. This study employs a structure based in silico drug discovery approach to evaluate ligand protein interactions and identify intriguing pyrrole derivatives for further investigation.

EXPERIMENTAL

Molecular docking simulations was carried out using the AutoDock Tool version 1.5.6. The Biovia Studio 2021was used to investigate ligand-protein interactions.[11]

Selection and preparation of target protein

The protein data repository (https://www.rcsb) provided the enoyl acyl carrier protein (ACP) reductase (InhA), PDB ID: 6R9W, with a resolution of 1.75 for docking.Biovia Discovery Studio software version 2021was used to prepare the protein for molecular docking. First, all non-essential components were removed, including heteroatoms such as co-crystallized ligands and water molecules. After that, hydrogen atoms were incorporated to polar groups to improve the protein structure, and gasteiger charges were calculated to take electrostatic characteristics into consideration.[11]

Selection of ligand molecules

ChemSketch (*Fig.-1*) was employed to create ligands, and Open Babel was utilized to convert molecular File formats.[11] ArgusLab was appiled to minimize energy. The drug-likeness was evaluated Using Lipinski's rule of five and predicted ADME features using SwissADME.[12,13]

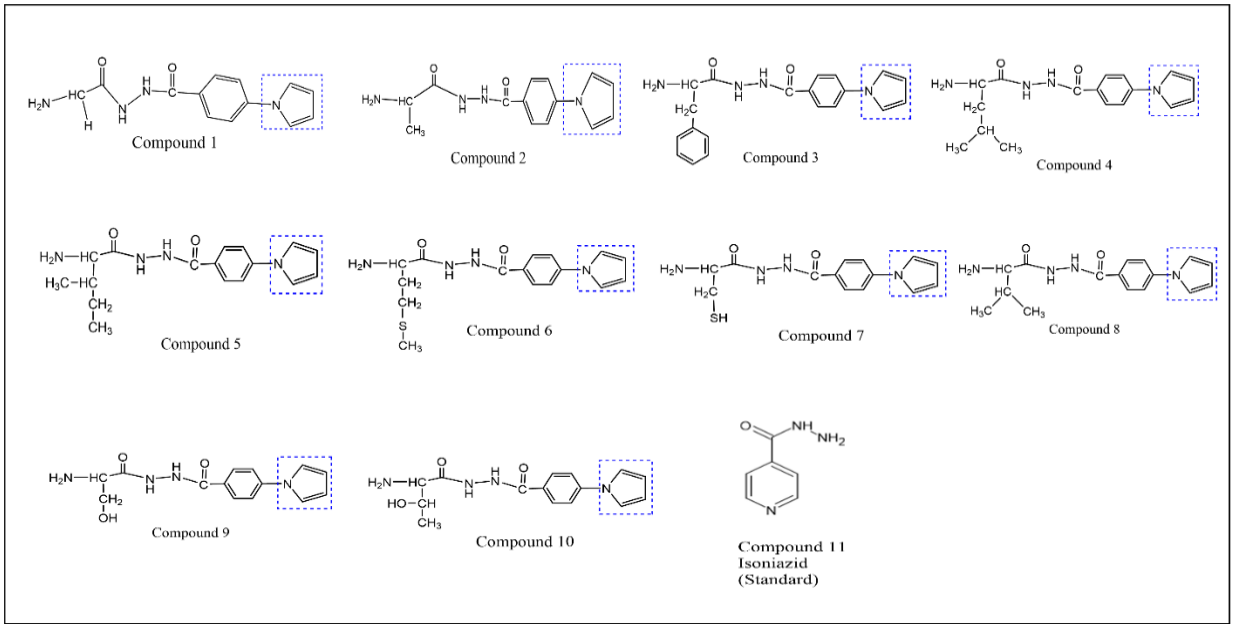


Fig.-1: 2D structure of chosen compound along with standard compound Isoniazid

Computational Docking Studies

The computational docking evaluation was performed using AutoDock Tool version 1.5.6. Bioactive substances (ligands) were chosen once the completed protein structure was uploaded as a macromolecule. Prior to formatting it for Auto Dock ligands (pdbqt), the program first decreased the ligand energy. After the grid box was used to cover the entire protein structure, blind docking was eventually started to find the bioactive compounds that best fit the energy value.

Each simulation was ran roughly ten times to produce ten docked conformations. As a result, it was shown that configurations with lowerenergy had the strongest binding conformations.

Finally, Biovia Discovery Studio examined the optimal lig and protein docked combination.[14, 15] The parameters chosen for the online servers and softwares utilized in the computational studies are depicted in Table 1.

Table-1: Parameter selected for different software.

Sr.no	Software/Server	Parameters	Description
1)	ChemDraw /ChemSketch	Ligand file	Pyrrole analogs (2D and 3D)
2)	Auto Dock Tool 1.5.6	A) Ligand file	Pyrrole analogs in sdf file.
		B) Receptor file	*InhA inhibitor (PDB ID: 6R9W) as Pdb file and mtDHFR inhibitor (PDB*

			ID:1DF7) as Pdb file
3)	Swiss ADME	Input file	Sdf
		Properties to calculate	ADME
4)	ProTox-II web server	Input file	Sdf (ligand)
5)	Biovia Discovery Studio Visualizer 2021	Input file	Pdf
		Protein representation	3D
		Ligand representation	3D
6)	Open Babel 3.1.1	Ligand input file	Sdf
		Ligand output file	pdb

ADMET Studies

Molecular ADME features were estimated using the Swiss ADME online program, and potential toxicological profile s were assessed using the ProTox-II web server.[16-21]

RESULTS AND DISCUSSION

By catalysing the NADH-dependent reduction of enoyl-acyl carrier protein reductase in Mycobacterium tuberculosis (InhA; PDB ID: 6R9W), which was resolved at 1.75 Å, is an important target for the development of antitubercular drugs. Molecular weight, rotatable bonds, hydrogen bond donors, and acceptors were all evaluated in the in silico drug likeness assessment of the chosen active compounds. Every molecule met Lipinski's Rule of Five, demonstrating advantageous drug like characteristics are depicted in Table 2.

Table-2: Lipinski rule-related information of selected compounds studied along with standard compound

Sr. No	Compound no.	Mol wt (g/mol)	LogP o/w	LogS	H donors	H acceptors	No. of rotatable bonds	Lipinski violation
1	Compound 1	258.28	1.60	-7.73	3	3	6	0
2	Compound 2	272.30	1.39	-7.54	3	3	6	0
3	Compound 3	348.40	2.65	-6.87	3	3	8	0
4	Compound 4	314.38	2.59	-6.85	3	3	8	0
5	Compound 5	314.38	2.83	-6.85	3	3	8	0
6	Compound 6	332.42	2.36	-7.45	3	3	9	0
7	Compound 7	304.37	2.26	-7.79	3	3	7	0
8	Compound 8	300.36	3.19	-7.02	3	3	7	0
9	Compound 9	288.30	1.73	-8.38	4	4	7	0
10	Compound10	302.33	1.71	-8.16	3	3	7	0
11	Compound11 (Std)	137.14	0.03	-7.63	2	3	2	1 violation MW <160

The enzyme or protein interactions with the designated ligand library were examined, predicted, and understood using docking studies, which also helped to analyse the potential binding. Biovia Discovery Studio, was used to dock pyrrole derivatives with receptors (6R9W) using the Autodock Tool.1.5.6, and Table 3 shows the binding energy and interaction residues that were found.Fig.2-4 shows the 3D and 2D diagrams with protein 6R9W for the chosen compounds with the highest docking energy as compound 3, compound 5, and reference compound.

Table-3: Docking-related information of synthesized compounds on PBD ID: 6R9W studied along with standard compound Isoniazid

Comp.no.	Interacting residue	No. of H bond	Interaction energy (Kcal/mol)
Compound 1	Ser20,Gly14,Gly96,Ile21,Ala191	3(Ser20,Gly14,Gly96)	-6.7
Compound 2	Ala157,Met155,Ala154,Phe108,Val163	2(Ala157,Met155)	-6.7
Compound 3	**Ser94,Gly14,Gly96,Ile21,Ala191,Val65,Phe41,Ile95**	**4(Ser94,Gly14,Gly96,Ile21)**	**-9.8**
Compound 4	Ala191,Phe149,Tyr158,Ala157,Pro156,Met155,Leu218	0	-7.4
Compound 5	**Gly14,Ser94,Gly96,Phe41,Ile95,Ile21,Ala191**	**3(Gly14,Ser94,Gly96)**	**-8.0**
Compound 6	Ser20,Gly14,Gly96,Val65,Ile95,Ile122,Phe41,Ile21, Ala191	3(Ser20,Gly14,Gly96)	-7.1
Compound 7	Ala22,Ile21,Gly14,Gly96,Ile95,Ala191	4(Ala22,Ile21,Gly14,Gly96)	-7.0
Compound 8	Gly14, Gly96,Ile21,Ile95, Ala191	3(Gly14, Gly96,Ile21)	-7.6

Compound 9	Asn159,Phe108,Asn106,Pro107,Ala154,Val163	3(Asn159,Phe108,Asn106)	-6.9
Compound 10	Gly14, Gly96, Ile21,Ala191	2(Gly14, Gly96)	-7.2
Compound 11 Std (Isoniazid)	Leu63, Thr39, Gly14, Val65, Phe41, Ile95, Ile122	3(Thr39,Leu63 ,Gly14)	-9.9

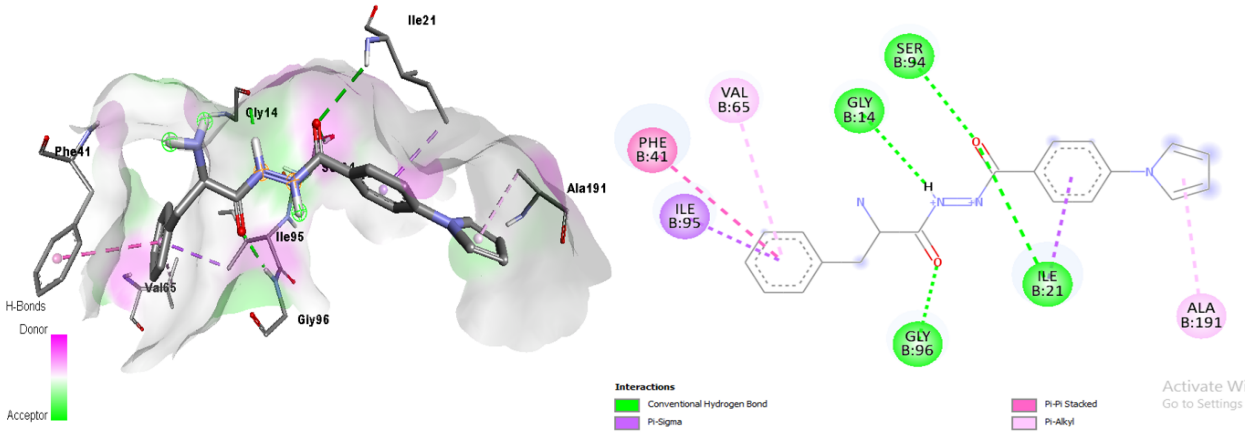


Fig.-2: 3D and 2D diagram of compound 3 interaction with 6R9W

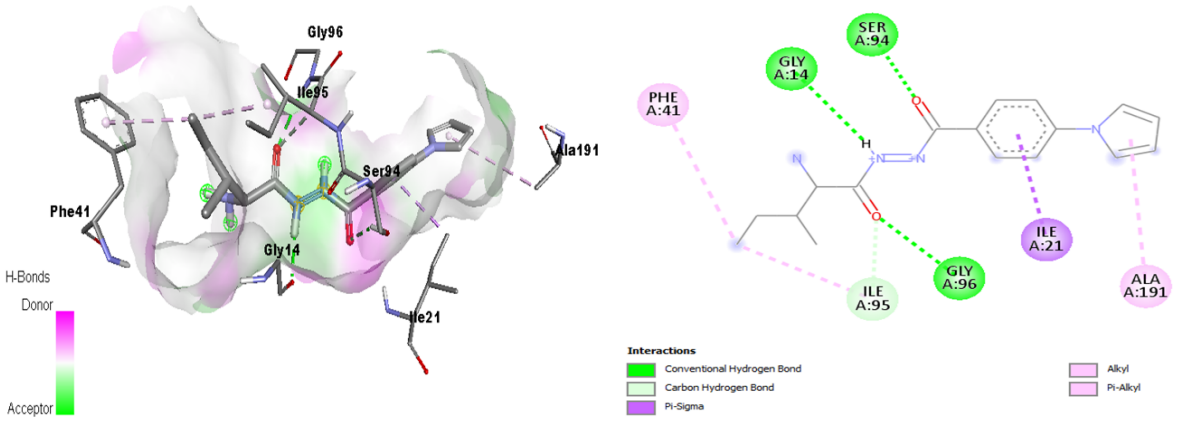


Fig.-3: 3D and 2D diagram of compound 5 interaction with 6R9W

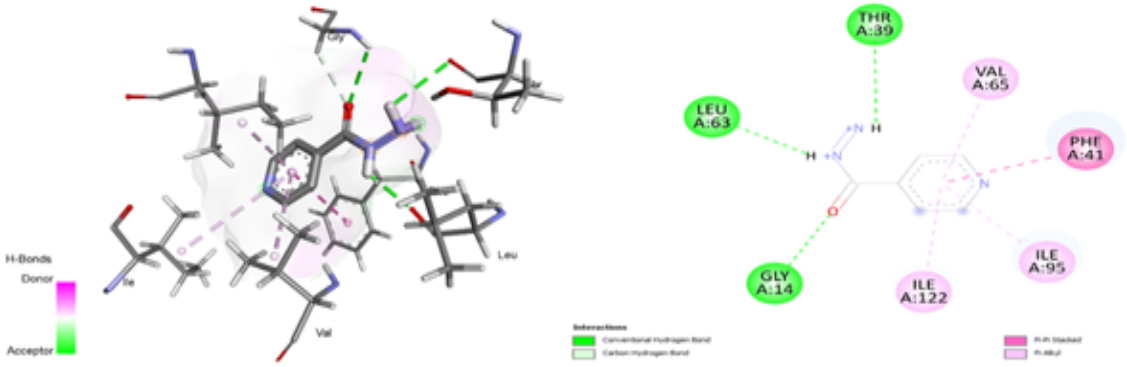


Fig.- 4: 3D and 2D diagram of compound 11 (Isoniazid) interaction with 6R9W

Young children and individuals with weakened immune systems are especially susceptible.to the airborne infectious illness tuberculosis (TB). Macrophages can harbor Mycobacterium tuberculosis, which can lie latent for years. The necessity to create new substances with strong antitubercular action is highlighted by the rise of drug resistant strains. As a result, leading to the development potent antimycobacterial drugs continues to be a top priority in TB research.[22]The aim of this of this research was to produce compounds that could bind to the 6R9W protein in order to potentially treat Mycobacterium tuberculosis in the future.

The ten bioactive molecules under exploration possessed predicted binding energies ranging from -6.7 to -9.8 Kcal/moL.Compound 3, also known as N'-(2-amino-3-phenylpropanoyl)-4- (1H-pyrrol-1-yl)benzohydrazide, has the lowest binding energy(-9.8Kcal/mol) with 6R9W (Fig.-2, Table 3).

Compound 5 IUPAC designation *N′*-(2-amino-3-methylpentanoyl)-4-(1H-pyrrol-1-yl) benzohydrazide, was shown to be an appropriate ligand to bind with the lowest energy (-8.0 Kcal/mol) with 6R9W as depicted in Fig.-3, Table 3. Isoniazid was utilized as a therapy during the global *Mycobacterium TB* outbreak (Fig. 4 and Table 3). The 6R9W protein was used to estimate the mechanism and binding energy of this drug (isoniazid binding energy: -9.9 Kcal/mol). Most of all selected compounds exhibited favourable binding affinities toward the InhA enzyme (PDB ID: 6R9W), and several of them displayed higher binding affinities than isoniazid. These findings support the possibility that pyrrole derivatives could be competent candidate for further study as InhA inhibitors. Due to extensive chemical screening, conventional drug discovery is costly and time consuming. Computer aided drug design, or CADD, is a cost-effective way to find and rank potential therapeutic candidates. The proposed pyrrole derivatives favourable docking scores indicate that they may interact with the InhA active site, which calls for more experimental confirmation.[22]

ADMET Studies

ProTox-II was used to predict toxicities, and the in silico Swiss ADME online software was used to assess molecular ADME features. The expected ADMET research results represent that all of these compounds have drug- like properties. The suggested compounds may be considered strong lead molecules with high membrane permeability and oral bioavailability as the results showed that they all have acceptable pharmacokinetic and physicochemical characteristics.

CONCLUSION

The docking of molecules is part of a ground breaking new way to researching how tiny chemicals attach to receptor proteins.The antituberculosis efficacy of pyrrole scaffoldings InhA, as NADH dependent enoyl acyl carrier protein (ACP) reductase inhibitor, PDB ID: 6R9W has been investigated in innovative therapeutics. Compound 3's IUPAC name is N'-(2-amino-3-phenylpropanoyl)-4-(1H-pyrrol-1-yl) benzohydrazide was shown to have the highest acceptable docking energy (-9.8 Kcal/mol), making it a promising chemical as a InhA inhibitor. It should be further researched in vitro.

ACKNOWLEDGMENTS

The authors acknowledge Dr. A. Madarkhandi, Dr. S. G. Vasantharaju, Dr. U. B. Bolmal, and Dr. A.D.Taranali, teaching and non-teaching staff of Rani Chennamma College of Pharmacy in Belagavi, Karnataka, India. We are grateful to Dr. H. V. Dambal, Dr. V.G. Jamakandi, and Dr. V. H. Kulkarni from S. E. T's College of Pharmacy in Dharwad, Karnataka, India. The authors are grateful for the University's cooperation and support.

CONFLICT OF INTERESTS

The writers claim that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The current project is associated with SDG-
3: Good health and well-being, which seeks to eradicate tuberculosis epidemics by 2040.Each author made a substa ntial contribution to this work, took part in its
review and editing, and gave the final draft their approval f or publication.

REFERENCES

1. Natarajan A, Beena PM, Devnikar AV, Mali S. A systemic review on tuberculosis. Indian J Tuberc 2020;67(3):295–311. https://doi.org/10.101 /j.ijtb.2020.02.005
2. Addo J, Pearce D, Metcalf M, Lundquist C, Thomas G, Barros-Aguirre D, Koh GCKW, Strange M. Living with tuberculosis: a qualitative study of patients' experiences with disease and treatment. BMC Public Health 2022;22:1717. https://doi.org/10.1186/s12889-022-14115-7
3. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: A systematic review of qualitative research. PLoS Med 2007;4(7):e238. https://doi.org/10.1371/journal.pmed.0040238
4. Goletti D, Al-Abri S, Migliori GB, Arlehamn CL, Haldar P, Sundling C, et al. World Tuberculosis Day 2024 theme "Yes! We can end TB" can be made a reality through concerted global efforts that advance detection, diagnosis, and treatment of tuberculosis infection and disease. Int J Infect Dis 2024;141:106993. https://doi.org/10.1016/j.ijid.2024.106993
5. World Health Organization (WHO), Global Tuberculosis Report 2024, Geneva, Switzerland: World Health Organization, 2024, https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024
6. Mahnashi MH, Ramachandraiah PKS, Al Awadh AA, Almazni IA, Asiri YI, Shaikh IA, et al. Design, synthesis and in silico molecular modelling studies of 2-hydrazineyl-2-oxoethyl-4-(1H-pyrrol-1-yl) benzoate derivatives: a potent dual DHFR and ENR-reductase inhibitors with antitubercular, antibacterial and cytotoxic potential. PLoS One 2025;20(5):e0323702. https://doi.org/10.1371/journal.pone.0323702
7. Inamdar TM, Joshi SD, Zargad S, Patil K, Yadav N. In Silico Investigation of Pyrrole-Based Compounds Targeting InhA for the Development of Novel Antitubercular Agents. High Technol Lett

2026;32(10):212–227
https://doi.org/10.37896/HTL32.10/122110

8. 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):305–314. https://doi.org/10.9734/air/2026/v27i11591
9. Hassan GB, Raj AG, Aruchamy B, Nanjan P, Drago C, Ramani P. Pyrrole: A Decisive Scaffold for the Development of Therapeutic Agents and Structure-Activity Relationship. ChemMedChem 2024;19(1):e202300447. https://doi.org/10.1002/cmdc.202300447
10. Chetty S, Armstrong T, Sharma Kharkwal S, Drewe WC, De Matteis CI, Evangelopoulos D, et al. New InhA Inhibitors Based on Expanded Triclosan and Di-Triclosan Analogues to Develop a New Treatment for Tuberculosis. Pharmaceuticals 2021;14(4):361. https://doi.org/10.3390/ph14040361
11. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. J Cheminform 2011;3:33. https://doi.org/10.1186/ 1758-2946-3-33, PMID 21982300
12. Lafitte D, Lamour V, Tsvetkov PO, Makarov AA, Klich M, Deprez P, et al. DNA gyrase interaction with coumarin-based inhibitors: the role of the hydroxybenzoate isopentenyl moiety and the 5′-methyl group of the noviose. Biochemistry 2002;41(23):7217–7223. https://doi.org/10.1021/bi0159837
13. Parmar GR, Shah AP, Sailor GU, Seth AK. In Silico Discovery of Novel Phytoconstituents of Amyris pinnata as a Mitotic Spindle Kinase Inhibitor. Curr Drug Res Rev 2020;12(2):175–182. https://doi.org/10.2174/2589977512666200220122211
14. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem 2009;30(16):2785–2791. https://doi.org/10.1002/jcc.21256
15. Adasme MF, Linnemann KL, Bolz SN, Kaiser F, Salentin S, Haupt VJ, et al. PLIP 2021: Expanding the Scope of the Protein–Ligand Interaction Profiler to DNA and RNA. Nucleic Acids Res 2021;49(W1):W530–W534. https://doi.org/10.1093/nar/gkab294
16. Joshi SD, Vagdevi HM, Vaidya VP, Gadaginamath GS. Synthesis of new 4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems: A novel class of potential antibacterial and antitubercular agents. Eur J Med Chem 2008;43(9):1989–1996. https://doi.org/10.1016/j.ejmech.2007.11.016
17. Pratama MRF, Poerwono H, Siswodiharjo S. ADMET properties of novel 5-O-benzoylpinostrobin derivatives. J Basic Clin Physiol Pharmacol 2019;30(6):20190251. https://doi.org/10.1515/jbcpp-2019-0251
18. Joshi SD, Kumar SRP, 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(11):1838–1863. https://doi.org/10.1007/s00044-019-02418-1
19. Savajjera CR, Shastri LA, Kumar SKP, Dalbanjan NP, Joshi SD. Synthesis, antimicrobial activity, and molecular docking studies of triazole-tethered piperazine pharmacophores. Russ J Org Chem 2024;60(10):1968–1973. https://doi.org/10.1134/S1070428024100129
20. Zawadzka K, Felczak A, Głowacka IE, Piotrowska DG, Lisowska K. Evaluation of the antimicrobial potential and toxicity of a newly synthesised 4-(4-(benzylamino)butoxy)-9H-carbazole. Int J Mol Sci 2021;22(23):12796 https://doi.org/10.3390/ijms222C.312796
21. Salve PS, Parchure P, Araujo L, Kavalapure RS, Jalalpure SS, Sriram D, et al. Design and synthesis of new 3-((7-chloroquinolin-4-yl)amino)thiazolidin-4-one analogs as Mycobacterium tuberculosis DNA gyrase inhibitors. Future J Pharm Sci 2021;7:10. https://doi.org/10.1186/s43094-020-00162-7
22. Inamdar TM, Joshi SD. Synthesis, molecular docking research on dual enoyl ACP reductase and MtDHFR enzyme inhibitors, and biological assessment of several novel 4-(1H-pyrrol-1-yl)benzohydrazide derivatives as antimycobacterial agents. Rasayan J Chem 2026;19(2):701–710 https://doi.org/10.9734/air/2026/v27i11591