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Design and *In silico* Study of Amides Containing Heterocyclic Nitrogen as Potent Antituberculosis Agent

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Abstract
Tuberculosis (TB) remains a serious infectious disease caused by *Mycobacterium tuberculosis*, representing a global health concern, especially owing to the increasing incidence of resistancy, including multidrug-resistant tuberculosis (MDR-TB). Among the potential therapeutic targets for new antituberculosis agents is enoyl-acyl carrier protein (ACP) reductase (InhA), an essential enzyme in the biosynthetic pathway responsible for the formation of vital components of the *M. tuberculosis* cell wall. This study aims to modify the compound *N*-(4-fluorobenzyl)pyrazine-2-carboxamide **(1)** by replacing the pyrazine group with *N*-(4-fluorobenzyl)-1H-pyrrole-2-carboxamide **(4)** and *N*-(4-fluorobenzyl)-1H-indole-2-carboxamide **(5)**, and to evaluate their antituberculosis activity *in silico*, which has not been reported previously. Molecular docking was performed against the InhA receptor (PDB ID: 4TZK) using AutoDock 4.2.6 software. Method validation was performed using a gridbox with dimensions 30 × 24 × 16 and a grid center at coordinates 10,119; 32,370; 60,728; yielding an RMSD value of 1,16 Å. The docking results indicated that the three modified compounds provided lower binding energies than the control drugs, with compound **5** showing the lowest energy (-8.48 Kcal/mol), followed by compound **4** (-7.44 Kcal/mol) and compound **1** (-7.09 Kcal/mol). Pharmacokinetic predictions indicate that all three compounds comply with Lipinski's Rule of Five and Veber's filter, with high gastrointestinal absorption. The study results suggest that modified compound **5** has the strongest potential as an antituberculosis drug candidate and warrants further evaluation *in vitro* and *in vivo*.

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INTRODUCTION

Tuberculosis (TB), infected by *Mycobacterium tuberculosis* disease, is becoming a major worldwide health challenge, with more than 10 million new cases reported each year, including over 400.000 cases involving drug-resistant strains (WHO, 2023). Multidrug-resistant tuberculosis (MDR-TB) is one of the most prevalent resistance cases, specifically a strain of *M. tuberculosis* that is unresponsive to first-line antituberculosis drugs (Wotale *et al.*, 2024). According to data presented by the World Health Organization (WHO), in 2023 there were 175.923 patients diagnosed with MDR-TB, accounting for 44% of all drug-resistant cases. Drug resistance to *M. tuberculosis* is one of the biggest obstacles in the treatment of this disease. The increase in resistance cases necessitates the development of antituberculosis drugs with minimal resistance and greater efficacy.

Isoniazid and pyrazinamide are two of the most critical first-line antituberculosis drugs in the treatment of TB disease. Both drugs contain substituted amide groups on heterocycles. Heterocyclic structures have been evaluated for their antimicrobial and antimycobacterial activity. Among all types of heterocyclic structures, heterocyclic nitrogen or *N*-heterocyclic

structures show promising antituberculosis activity (Olaru *et al*., 2017). One of the *N*-heterocyclic structures extensively evaluated for antituberculosis activity is the pyrazine ring. Previous research by Wati *et al.* (2020) synthesized a new heteroaromatic amide from the modification of the pyrazine-2-carboxamide group that was substituted with 4-fluorobenzyl, namely *N*-(4-fluorobenzyl)pyrazine-2-carboxamide **(1)**, which exhibited inhibitory activity against *M. tuberculosis* with an MIC <6,25 µg/mL. In addition to the pyrazine ring, *N*-heterocyclic structures with antimycobacterial activity evaluated for their inhibitory activity against *M. tuberculosis* include pyrrole and indole (Atukuri *et al*., 2021; Mahnashi *et al*., 2024). The pyrrole-2-carboxamide analog compound, *N*-(adamantane-2-yl)-4-(2,4-dichlorophenyl)-1H-pyrrole-2-carboxamide **(2)**, was reported by Zhao *et al*. (2022), was successfully synthesized and exhibited high inhibitory activity against *M. tuberculosis* with an MIC of 0,06 µg/mL. Another study by Franz *et al.* (2017), which synthesized an indole-2-carboxamide analog, namely *N*-cyclooctylindole-2-carboxamide **(3)**, displaying antituberculosis activity with MIC of 0,39 µg/mL.

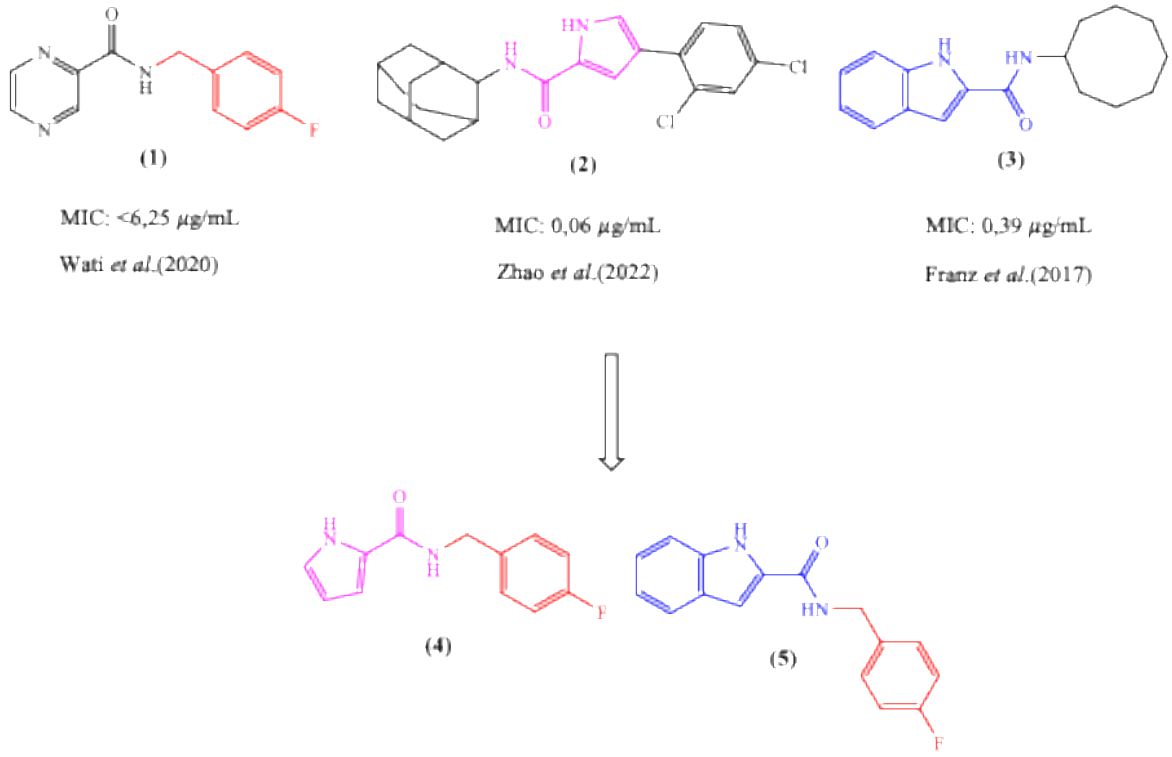


Figure 1. Modification of heteroaromatic amide compounds

In recent years, compound modifications have been carried out with the aim of developing compounds with better antituberculosis potential (Wati *et al*., 2020; Zulqurnain *et al*., 2023). The modifications were based on findings that the compounds evaluated had good antituberculosis activity. Previous studies have shown that the 4-fluorobenzyl group substituted on the nitrogen heterocyclic amide, pyrazine-2-carboxamide, exhibits satisfactory antituberculosis activity. Additionally, other heterocyclic amides, such as pyrrole-2-carboxamide and indole-2-carboxamide, have been reported to possess high antituberculosis activity. Based on these findings, in this study, the compound was modified by replacing the pyrazine-2-carboxamide group in *N*-(4-fluorobenzyl)pyrazine-2-carboxamide **(1)** with other heterocyclic compounds, namely pyrrole-2-carboxamide and indole-2-carboxamide, to form new analog compounds *N*-(4-fluorobenzyl)-1*H*-pyrrole-2-carboxamide **(4)** and *N*-(4-fluorobenzyl)-1*H*-indole-2-carboxamide **(5)**, as shown in Figure 1. This study aims to evaluate the antituberculosis activity of these new modified compounds through a bioinformatics approach, or *in silico* studies, including molecular docking and pharmacokinetic properties. To

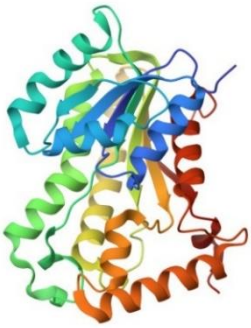
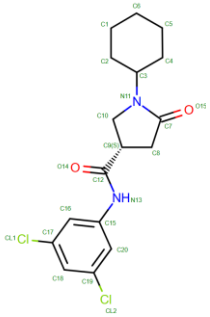
the best of our knowledges, evaluation of designed molecules **(4**, **5)** as antituberculosis agent have not been explored and reported.

METHOD

Receptor Preparations

The molecular docking study employed the enoyl-acyl carrier protein (ACP) reductase (InhA) receptor from Mycobacterium tuberculosis, complexed with the reference ligand (3S)-1-cyclohexyl-N-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide (641), retrieved from the Protein Data Bank (PDB ID: 4TZK). Receptor preparation and optimization were carried out using AutoDockTools 1.5.6 by removing all non-essential residues, including water molecules, and subsequently adding polar hydrogens and Kollman charges. Next, the reference ligand (641) was separated from the receptor in (*.pdb) format and prepared in (*.pdbqt) format (Zulqurnain *et al*., 2024).

Table 1. Receptor and Reference Ligand

PDB ID	Method	Resolution	Structure	Reference Ligand
4TZK	X-Ray Diffraction	1,62 Å		 (641)

Method Validation

Method validation was performed by combining the reference ligand 641 and receptor 4TZK in a grid. The center and size (dimensions) of the gridbox used for docking were determined. Then, it was saved in the format (*.gpf). The reference ligand 641 and receptor 4TZK structures were combined in docking. The Lamarckian genetic algorithm was set with GA run 100 and formed in the format (*.dpf). Docking between the reference ligand 641 and the 4TZK receptor was performed using AutoDock 4.2.6 software (Harini *et al*., 2021). Then, the RMSD (root mean square deviation) value of the overlapping reference ligand 641 with the active site of the 4TZK receptor was evaluated. An acceptable RMSD value is less than 2 Å (Zulqurnain *et al*., 2025).

Molecular Docking and Visualization

Molecular docking was performed by drawing the 2D structures of three new modified compounds, namely *N*-(4-fluorobenzyl)pyrazine-2-carboxamide **(1)**, *N*-(4-fluorobenzyl)-1H-pyrrole-2-carboxamide **(4)**, *N*-(4-fluorobenzyl)-1H-indole-2-carboxamide **(5)**, using MarvinSketch version 24.1.3. MMFF94 (Merck Molecular Force Field) from MarvinSketch was utilized to minimize the energy of ligands (Gentile *et al*., 2020). Docking simulations were performed using AutoDock 4.2.6 software. The active site of the InhA receptor (4TZK) was determined by grid center and grid box size consistent with the validated method. The Lamarckian genetic algorithm was employed to find the most likely ligand binding pose with 100 genetic algorithm runs (Harini *et al*., 2021). From the docking results, the ligand

conformation with the lowest binding energy was opted in a file in the format (*.dlg). The selected conformation was then combined with the 4TZK receptor and formatted in the (*.pdb) format. It was subsequently analyzed and visualized using BioVia Discovery Studio Visualizer, copyright © 2024 (Mohapatra *et al*., 2021).

Pharmacokinetis Properties Predict

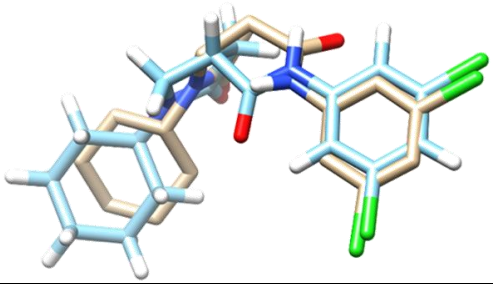
Physicochemical profile predictions were performed using the SwissADME website (http://www.swissadme.ch/) (Daina *et al.*, 2017). Physicochemical profile predictions are based on Lipinski's 5 rules and the Veber filter (K *et al.*, 2021; Kralj *et al.*, 2023; Zulqurnain *et al.*, 2024). ADME and toxicity predictions, including AMES parameters (mutagenicity), hepatotoxicity, and LD50, were performed using the pkCSM website (https://biosig.lab.uq.edu.au/pkcsm/) (Pires *et al.*, 2015).

RESULTS AND DISCUSSION

Molecular Docking Analysis

Molecular docking is an initial analysis to predict which compounds can or cannot be used as drugs to treat a disease. Molecular docking studies of modified compounds **1**, **4**, and **5** were conducted by targeting the inhibition of the enoyl acyl carrier protein (ACP) reductase (InhA) receptor from *M. tuberculosis* (PDB ID: 4TZK). The crystal structure of enoyl-acyl carrier protein (ACP) reductase (InhA) was analyzed in complex with the ligand **(641)**, while retaining the NAD cofactor. Validation was conducted using a grid box sized 30 × 24 × 16 with its center positioned at coordinates 10,119; 32,370; and 60,728. The resulting root mean square deviation (RMSD) was 1,16 Å. An RMSD value < 2 Å indicates that the protocol or method used can form ligand-receptor interactions close to the original form, making it suitable for further molecular docking processes (Zulqurnain *et al.*, 2023).

Table 2. Result of redocking reference ligand for validation method



Gridbox			RMSD (Å)	Grid Spacing	Grid Center		
X	Y	Z			X	Y	Z
32	26	22	1,16	0,375	10,119	32,370	60,728

Enoyl acyl carrier protein (ACP) reductase (InhA) from *M. tuberculosis* is an important part of the FAS-II (fatty acid synthase-II) pathway, particularly in the biosynthesis of mycolic acid. Due to mycolic acid being an essential component of the mycobacteria cell wall, this pathway is crucial to mycobacteria's survival (Khalifa *et al.*, 2023). Inhibition of InhA can disrupt the integrity of the *M. tuberculosis* cell wall, making it a promising target for new anti-tuberculosis drugs. InhA is a tyrosine and NADH dependent oxidoreductase enzyme (Prasad *et al.*, 2021). It is known that isoniazid is a tuberculosis drug that inhibits InhA by binding to the NADH cofactor at the active site of InhA (Manjunatha *et al.*, 2015). The molecular docking study of modified compounds against the InhA receptor aims to evaluate the activity of the compounds as new anti-tuberculosis agents in efforts to address resistance to isoniazid and pyrazinamide.

Table 3. Result of molecular docking analysis

Compounds	Binding Energy (Kcal/mol)	Inhibition Constant (μM)
(1)	-7,09	6,31
(4)	-7,44	2,83
(5)	-8,48	0,39
Isoniazid (control drug)	-4,75	330,25
Pirazinamida (control drug)	-4,38	676,20

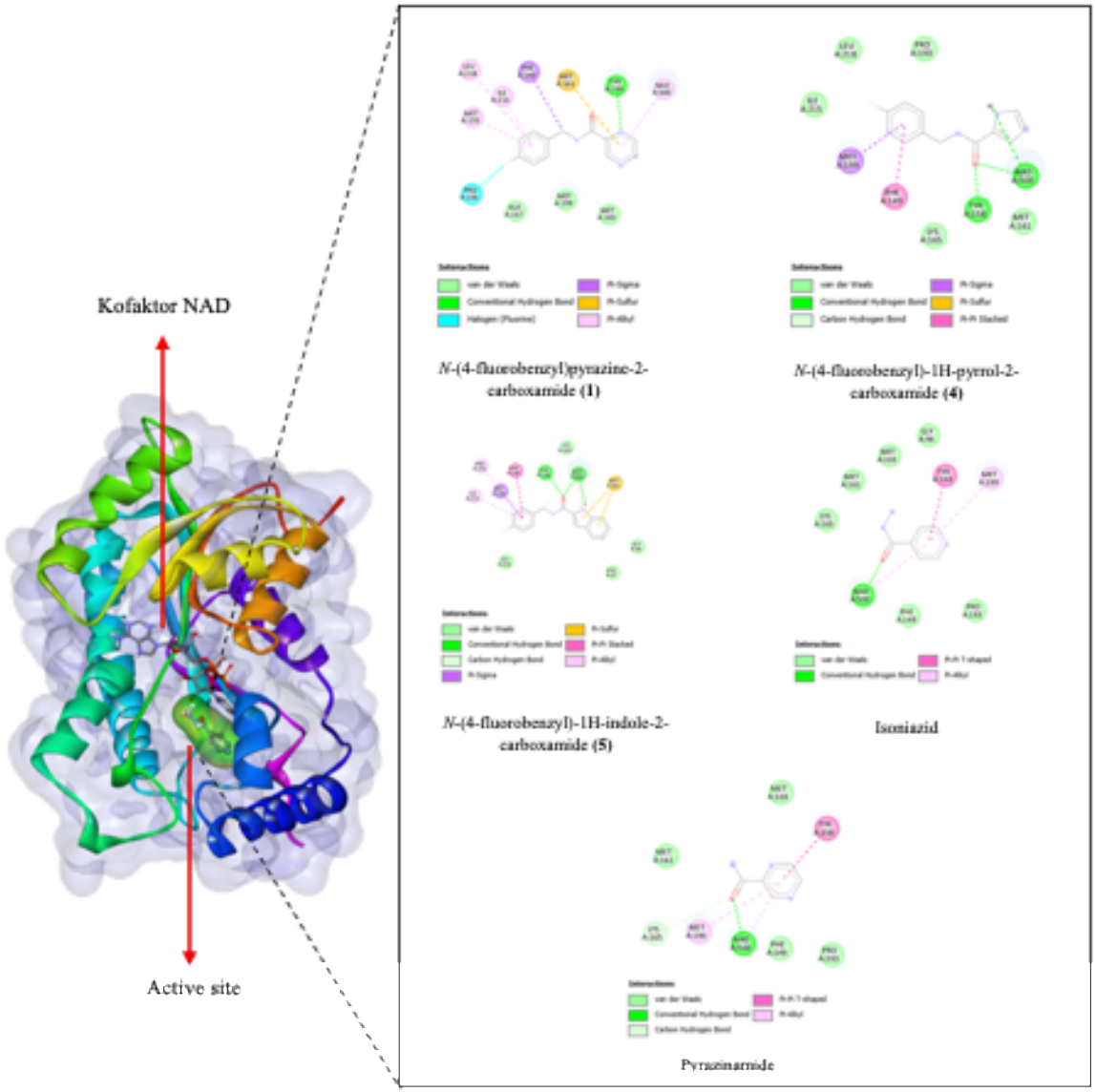


Figure 2. Visualization 2D of three modified compound and control drug with InhA *M. tuberculosis*

According to the molecular docking results, it was found that the third modified compound binds to the InhA receptor of *M. tuberculosis* with a lower binding energy than isoniazid (-4,75 Kcal/mol) and pyrazinamide (-4,38 Kcal/mol). Compound **5** has a lower binding energy compared to the other two compounds, at -8,48 Kcal/mol. This is followed by compounds **4** and **1**, with binding energies of -7,44 and -7,09 Kcal/mol, respectively. Binding energy refers to the Gibbs free energy that arises when an interaction or complex formation occurs between a ligand and a receptor. A more negative or lower binding energy indicates higher complex stability and more optimal inhibitory activity (Millan-Casarrubias *et al.*, 2025). This indicates

that the three compounds are predicted to have more effective inhibitory activity against the InhA receptor of *M. tuberculosis* compared to isoniazid and pyrazinamide. Compound **5** has the highest inhibitory activity, followed by compounds **4** and **1**.

The position and type of interactions formed between ligands and receptors are evaluated through visualization, as shown in Figure 2. The complex forms various interactions, such as hydrogen bonds, hydrophobic interactions, and van der Waals, which influence the bond energy value (Arwansyah *et al.*, 2014). Compounds **4** and **5** were observed to form three and four hydrogen bonds, respectively, while compound **1** could only form one hydrogen bond. This type of bond significantly affects the stability of the complex, meaning that the more hydrogen bonds formed, the more stable the ligand-receptor complex (Yu *et al.*, 2024). This is evidenced by the binding energy of compounds **4** and **5** to the receptor being more negative or smaller compared to compound **1**. Additionally, compound **5** was observed to form more hydrophobic and van der Waals interactions compared to compounds **1** and **4**, making compound **5** the most stable complex. Hydrophobic and van der Waals interactions play a role in enhancing the stability of the ligand-receptor complex (Gholam, 2022).

Table 4. Type of interactions

Compounds	Type of Interactions		
	Hydrogend Bond	**Hydrophobic Interaction**	**Van der Waals**
(1)	**Tyr 158**	**NAD 500**, **Met 161**, **Phe 149**, Ile 215, **Leu 218**, Met 155, Pro 156	Ala 157, **Met 199**, **Met 103**
(4)	**Tyr 158**, **NAD 500**	**Phe 149**, **Met 199**	**Met 161**, **Lys 165**, Ile 215,Leu 218, **Pro 193**
(5)	**Tyr 158**, **NAD 500**	**Met 161**, **NAD 500**, **Phe 149**, **Met 199**, **Pro 193**, Ile 215	Leu 218, Phe 97, **Gly 96**, **Lys 165**
Isoniazid (control drug)	**NAD 500**	**Tyr 158**, **NAD 500**, **Met 199**	**Phe 149**, **Pro 193**, **Lys 165**, **Met 161**, **Gly 96**
Pirazinamida (control drug)	**NAD 500**, **Lys 165**	**Tyr 158**, **NAD 500**, **Met 199**	**Met 103**, **Met 161**, **Phe 149**, **Pro 193**

Based on the visualization results, it can be evaluated that the three modified compounds have similar residue interactions with the commercial OAT positive control. These similar residue interactions validate that the three modified compounds have the same inhibitory activity potential as the control drug (Shifeng *et al.*, 2022; Sururi *et al.*, 2023). The drug control shows interactions with residues Tyr 158, Met 199, Met 103, Met 161, Phe 149, Pro 193, Lys 165, Gly 96, and the NAD 500 cofactor. Previous research by Wahan *et al*., (2024) reported that the InhA receptor has an active binding site consisting of a hydrophobic pocket containing residues including Tyr 158, Phe 149, Met 199, Trp 222, Leu 218, Met 161, and Pro 193. Compounds **4** and **5** form hydrogen bonds with the Tyr 158 residue and the NAD 500 cofactor, while compound **1** only forms a hydrogen bond with NAD 500.

The interaction of the compound with the Tyr 158 and NAD 500 residues is one of the key interactions in the inhibition of InhA, as reported by Angelova *et al*. (2022). The pyrrole group (compound **4**) and indole group (compound **5**), which contain −NH and O atoms in the C=O group of compounds **4** and **5**, provide donors and acceptors for hydrogen bonding. The presence of the 4-fluorobenzyl group in the three modified compounds provides π electrons that can form hydrophobic interactions through attractive forces with the π electron cloud, sigma (σ) bonds, alkyl groups, and sulfur from residues Phe 149, Met 199, Met 155, Ile 215, Leu 218, and Pro 193. These hydrophobic interactions enable the compounds to strengthen their interaction with InhA.

Based on the interactions observed, it can be evaluated that the three modified compounds have the potential to inhibit InhA of *M. tuberculosis* by binding to the NAD cofactor in accordance with the inhibition mechanism of InhA inhibitors (Manjunatha *et al.*, 2015). These results are supported by previous research by Angelova *et al*. (2022), where the interactions of compounds 1, 4, and 5 in the active site binding domain of InhA M. tuberculosis, specifically with NAD 500 and Tyr 158, support the hypothesis that the three compounds act as antituberculosis agents through the mechanism of InhA receptor inhibition. The way the three modified compounds form more stable binding, as indicated by more negative binding energy values, suggests that the three compounds can be used to overcome the resistance mechanisms of isoniazid and pyrazinamide. Further investigations can be planned with *in vitro* and *in vivo* tests of the compounds' inhibitory effects on M. tuberculosis.

Pharmacokinetis Properties Predict

The pharmacokinetic propoerties, including absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the three modified compounds were evaluated using an *in silico* approach. Physicochemical parameters were focused on analyzing the druglikeness of the modified compounds based on Lipinski's Rule of Five and Veber's filter. These parameters are related to the bioavailability of the compound in the body through oral activity. Lipinski's Rule of Five require that a drug candidate have effective oral activity if it has a molecular weight (MW) <500 g/mol, hydrogen bond acceptors (HBA) <10, hydrogen bond donors (HBD) <5, Log P < 5, and a molar refractive index between 40–130 (K *et al.*, 2021). The Veber filter includes two rules for drug candidate compounds with high bioavailability if they have a topological polar surface area (TPSA) <140 $Å^2$ and rotatable bonds <10 (Kralj *et al.*, 2023). The results show that the three modified compounds have molecular weights of 231,23; 218.23; and 268,29 g/mol, respectively, and fall within the required range. Log P is a measure of a compound’s lipophilicity, or its ability to penetrate biological membranes (Wu *et al.*, 2024).

The three modified compounds have LogP values ranging from 0,75 to 2,75, which fall within the optimal range for penetrating biological membranes. TPSA is used as an indicator of a compound's absorption potential (Maximo Da Silva *et al.*, 2015). The three modified compounds exhibit good absorption with TPSA values ranging from 44,89 to 54,88 $Å^2$. The results indicate that the three modified compounds meet the parameters required by Lipinski's Rule of Five and the Veber filter. Thus, the three modified compounds have the potential to serve as orally administered drugs with high bioavailability.

Table 4. Physicochemical properties of three modified compounds

Compounds	Physicochemical Parameters						
	MW (g/mol)	**TPSA ($Å^2$)**	**HBA**	**HBD**	**MLogP**	***Rotatable Bonds***	**MR**
(1)	231,23	54,88	4	1	0,75	4	59,47
(4)	218,23	44,89	2	2	1,64	4	58,23
(5)	268,29	44,89	2	2	2,75	4	75,74

ADMET analysis was performed to evaluate gastrointestinal absorption, BBB permeability, P-gp substrate, cytochrome P450 (CYP) isoenzymes, total clearance, mutagenicity (AMES), hepatotoxicity, and LD50. The three modified compounds demonstrated high gastrointestinal absorption, as indicated by Caco-2 permeability values (oral drug absorption in intestinal mucosa) ranging from 1,296 to 1,329, and intestinal absorption percentages of 91–95%. High gastrointestinal absorption increases bioavailability, thereby optimizing therapeutic effects (Joseph *et al.*, 2019). Compounds **1** and **2** are not permeable to the BBB, while compound **5** has BBB-permeable properties. The blood-brain barrier (BBB) is a semipermeable endothelial cell barrier that regulates the movement of molecules and protects the central nervous system (Daneman & Prat, 2015).

If compound **5** is permeable to the BBB, it has the potential to cause adverse effects on the central nervous system. Therefore, further analysis is needed to evaluate the interaction of compound **5** with the central nervous system. Compounds **4** and **5** have the potential to be P-gp substrates, causing these compounds to be easily pumped out of the cell (Sururi *et al.*, 2024). P-gp is an efflux pump that transports substances out of cells in the opposite direction of their concentration gradient (Ahmed Juvale *et al.*, 2022). However, this mechanism can be inhibited by P-gp inhibitors found in food, preventing the compounds from being pumped out of cells (Yu *et al.*, 2017). Compounds **1** and **4** selectively inhibit the CYP1A2 isoenzyme, while compound **5** selectively inhibits the CYP1A2, CYP2C19, and CYP3A4 isoenzymes. This selective inhibition indicates that the compounds do not pose a risk of side effects or toxicity to other CYP isoenzymes (Zulqurnain *et al.*, 2025). Compounds that function as CYP inhibitors have the potential to accumulate other drugs to toxic levels and produce side effects (Gilani & Cassagnol, 2023). Compound **1** is predicted to have no mutagenic potential but may have hepatotoxic properties. Compounds **4** and **5** are predicted to have mutagenic potential but no hepatotoxic potential.

Table 5. ADMET profile of three modified compounds

Parameters	**Compounds**		
	***N*-(4-fluorobenzyl)pyrazine-2-carboxamide (1)**	***N*-(4-fluorobenzyl)-1H-pyrrole-2-carboxamide (4)**	***N*-(4-fluorobenzyl)-1H-indole-2-carboxamide (5)**
Caco-2 Perm.	1,329	1,296	1,315
HI absorption (%)	95,112	92,858	91,083
BBB perm.	-0,165	0,286	0,423
P-gp Substrat	No	Yes	Yes
CYP3A4 inhibitor	No	No	Yes
CYP1A2 inhibitor	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	Yes
CYP2D6 inhibitor	No	No	No
CYP2C9 inhibitor	No	No	No
Total clearence	0,551	0,288	0,280
AMES toxicity	No	Yes	Yes
Hepatoxicity	Yes	No	No
LD_{50} (mol/kg)	2,266	2,454	2,252

CONCLUSION

This research resulted in new antituberculosis candidates to treat drug-resistant TB cases. Modification of the compound *N*-(4-fluorobenzyl)pyrazine-2-carboxamide **(1)** produced two new derivatives, namely *N*-(4-fluorobenzyl)-1H-pyrrole-2-carboxamide **(4)** and *N*-(4-fluorobenzyl)-1H-indole-2-carboxamide **(5)**, with strong potential as inhibitors of the InhA receptor of M. tuberculosis. The compound *N*-(4-fluorobenzyl)-1H-indole-2-carboxamide **(5)** exhibits the lowest binding energy and forms the most stable interactions with the active site residues and NAD cofactor of the InhA receptor. These results indicate the strongest antituberculosis activity *in silico*, followed by the compounds *N*-(4-fluorobenzyl)-1H-pyrrole-2-carboxamide **(4)** and *N*-(4-fluorobenzyl)pyrazine-2-carboxamide **(1)**. All three modified compounds meet Lipinski's Rule of Five and Veber's filter criteria. The ADMET profiles of the three modified compounds show high gastrointestinal absorption. Compound **5** has the strongest potential as an antituberculosis drug candidate that requires further evaluation *in vitro* and *in vivo*.

RECOMMENDATIONS

For the next study, synthesis route of carboxamides are explored and carried out. *In vitro* study of the compounds can be conducted, as well.

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