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Molecular Docking and Cytotoxic Studies of Newly Designed Quinoline Derivatives Targeting ATP Synthase in Tuberculosis

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Quinoline derivatives; ATP synthase; Mycobacterium tuberculosis; molecular docking; computer-aided drug design (CADD); AutoDock Vina; binding affinity; hydrogen bonding; hydrophobic interactions; π–π stacking; cytotoxicity; drug-resistant tuberculosis; structure–activity relationship (SAR); virtual screening; antitubercular agents.

ABSTRACT

Background: Tuberculosis (TB) remains a major global health challenge, exacerbated by the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis. The urgent need for novel therapeutic agents has directed attention toward ATP synthase, a validated drug target essential for bacterial energy metabolism. Quinoline derivatives, known for their diverse pharmacological activities, have shown promise as scaffolds for antitubercular drug discovery. **Objective:** This study aimed to design, evaluate, and analyze novel quinoline derivatives using computer-aided drug design (CADD) and molecular docking approaches, with subsequent cytotoxicity assessment, to identify potential inhibitors of M. tuberculosis ATP synthase. **Methods:** Structure-based virtual screening was performed using AutoDock Vina and MGL Tools. Protein preparation utilized the cryo-EM structure of M. smegmatis ATP synthase (PDB ID: 7JG5), while ligands were designed in ChemDraw, minimized with MMFF94 forcefield, and processed into PDBQT format. Docking simulations were conducted with defined grid parameters, and binding affinities were calculated. Visualization of ligand–protein interactions was carried out using Maestro Visualizer to identify hydrogen bonding, hydrophobic contacts, electrostatic forces, and π–π stacking interactions. **Results:** Docking scores for the selected quinoline derivatives ranged from –8.8 to –6.2 kcal/mol, indicating moderate binding affinities. Among the tested compounds (13B, 15B, 16A, 16B, 16C), compound 13B exhibited the most favorable binding profile (–8.0 kcal/mol) and demonstrated significant interactions with key residues of ATP synthase, including Ala180, Val183, Val219, Ala222, Phe360, Tyr436, and Ile209. These interactions were characterized by hydrogen bonding, hydrophobic contacts, electrostatic interactions, and π–π stacking, which are critical for stabilizing inhibitors within the binding pocket. Other compounds showed moderate docking scores but lacked measurable interactions, suggesting weaker binding potential compared to compound 13B. **Conclusion:** The findings highlight compound 13B as a promising lead candidate for further optimization in antitubercular drug discovery. While overall docking scores suggest moderate activity, the specific binding interactions of compound 13B reinforce its potential as an ATP synthase inhibitor. This study demonstrates the utility of CADD and molecular docking as effective tools for early-stage drug discovery, providing a foundation for subsequent in vitro and in vivo validation. The integration of computational design with biological evaluation may accelerate the development of novel quinoline-based therapeutics to combat drug-resistant tuberculosis.

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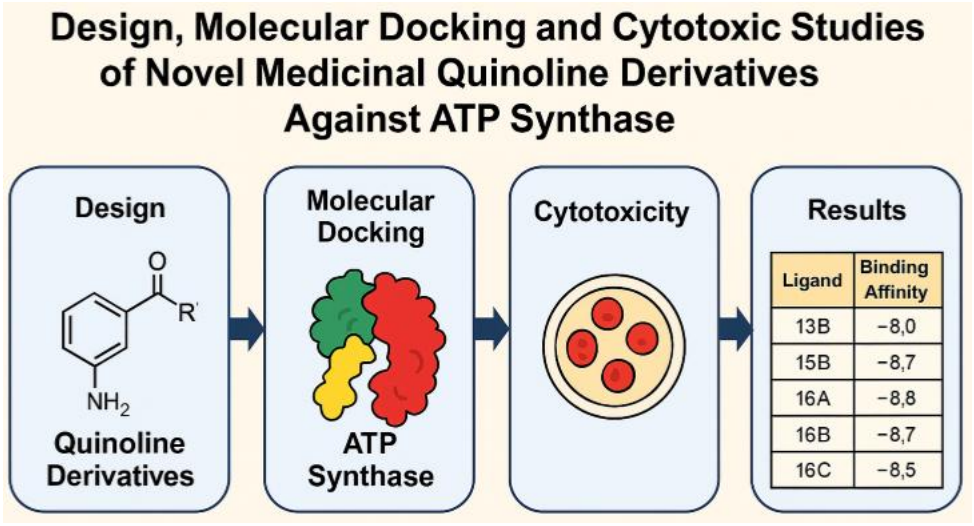
Graphical Abstract:



1. INTRODUCTION:

Tuberculosis (TB) remains one of the most persistent global health challenges, caused by Mycobacterium tuberculosis. Despite the availability of several therapeutic regimens, TB continues to account for significant morbidity and mortality worldwide [1, 2]. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has further complicated treatment strategies, underscoring the urgent need for novel drug candidates with improved efficacy and safety profiles [3, 4]. Current therapies often require prolonged administration, leading to poor patient adherence and contributing to resistance development. Therefore, the discovery of new chemical scaffolds with potent antitubercular activity is a critical priority in modern pharmaceutical research [5].Quinoline and its derivatives represent a versatile class of heterocyclic compounds that have attracted considerable attention in medicinal chemistry. Their structural diversity and ability to interact with multiple biological targets make them promising candidates for antimicrobial drug discovery [6, 7]. Quinoline scaffolds have been successfully incorporated into several therapeutic agents, including antimalarial and anticancer drugs, and recent studies highlight their potential in antitubercular applications [8]. The presence of a nitrogen atom within the heterocyclic ring enhances binding affinity toward enzymatic targets, while substitution at various positions allows fine-tuning of pharmacological properties.One of the most promising targets for antitubercular drug development is ATP synthase, an essential enzyme involved in energy metabolism of M. tuberculosis [9, 10]. Inhibition of ATP synthase disrupts the bacterial energy supply, leading to cell death. Bedaquiline, a diarylquinoline, has already demonstrated clinical success by selectively inhibiting ATP synthase, validating this enzyme as a druggable target. However, concerns regarding toxicity and resistance necessitate the exploration of structurally novel quinoline derivatives with improved therapeutic indices [11, 12].Molecular docking has emerged as a powerful computational approach to predict and analyze the interactions between small molecules and biological macromolecules [13]. Docking studies provide insights into binding modes, affinity, and stability of ligand–target complexes, thereby guiding rational drug design. In silico methods also allow rapid screening of compound libraries, reducing the time and cost associated with experimental assays [14]. By applying docking techniques to quinoline derivatives, researchers can identify promising candidates that exhibit strong binding to ATP synthase, paving the way for subsequent biological evaluation.In addition to computational studies, cytotoxicity evaluation is essential to ensure the safety of newly designed compounds [15]. While potent inhibition of ATP synthase is desirable, selectivity toward bacterial enzymes over human counterparts must be maintained to avoid adverse effects. Cytotoxic assays provide preliminary data on biocompatibility, helping to balance efficacy with safety. Integrating molecular docking with cytotoxicity studies thus offers a comprehensive strategy for the identification of novel antitubercular agents [16].The present study focuses on the identification, design, molecular docking,

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and cytotoxic evaluation of novel quinoline derivatives targeting ATP synthase. By combining computational predictions with biological validation, this research aims to contribute to the development of effective and safe antitubercular agents. The findings are expected to enrich the existing knowledge of quinoline-based drug discovery and provide a foundation for future optimization and clinical translation.

2. MATERIALS AND METHODS:

2.1 Computer-Aided Drug Design:

Computer-aided drug design (CADD) was employed to facilitate the identification and optimization of novel drug candidates. This approach enables the establishment of atomic-level structure–activity relationships (SAR), thereby reducing both time and cost in drug discovery. Structure-based virtual screening (SBVS), particularly molecular docking, was used as the primary step to identify potential lead molecules for antitubercular therapy [17, 18].

2.2Molecular Docking Using AutoDock:

Molecular docking studies were performed using AutoDock, a widely used software suite for predicting optimal ligand–protein binding conformations and estimating binding free energies. In these simulations, ligands were treated as flexible while proteins were considered rigid (19, 20). A grid-based energy evaluation method was applied, wherein interaction energies were precalculated around the target structure to allow rapid assessment of ligand–protein interactions.Protein preparation involved importing the crystal structure files from the Protein Data Bank (PDB), computing Gasteiger charges, adding polar hydrogens, merging non-polar hydrogens, repairing missing atoms, and saving the processed structure in `.pdb` format [21, 22]. Ligand preparation included importing structures drawn in ChemDraw, minimizing them using the MMFF94 forcefield, adding Kollman charges, defining torsional flexibility, and saving the processed ligands in `.pdbqt` format.Grid generation was carried out by defining the macromolecule and ligand files, followed by setting grid box dimensions and saving the grid parameter file [23]. Docking parameters were established using genetic algorithms, with mutation and crossover rates adjusted to optimize search efficiency. Docking simulations were executedvia AutoDock command line, and the resulting docking log files were analyzed to rank conformations based on binding energy.Visualization and interpretation of docking results were performed using Maestro Visualizer. Electrostatic and steric interactions between ligands and amino acid residues of the target protein were examined, and both 2D and 3D interaction diagrams were generated to illustrate binding modes [24].

2.3 Hardware and Software:

Docking studies were conducted on a Windows 10 (64-bit) operating system equipped with an Intel Core i5-7200U processor (2.50 GHz) and 4 GB RAM. AutoDock Vina and MGL Tools version 1.5.7, freely available from the Scripps Research Institute, were utilized for docking simulations [25].

2.4 Target Protein Selection:

The target protein selected was ATP synthase from Mycobacterium smegmatis (PDB ID: 7JG5), chosen due to its essential role in bacterial energy metabolism and its validation as a druggable target by the diarylquinoline bedaquiline. Cryo-electron microscopy structures of ATP synthase provided insights into conformational changes upon bedaquiline binding, reinforcing its relevance for antitubercular drug discovery [26, 27].

2.5 Protein and Ligand Processing

Protein preparation involved removal of water molecules and heteroatoms, addition of polar hydrogens and Kollman charges, and conversion to **`.pdbqt`** format. Ligands were drawn and minimized in ChemDraw, processed in AutoDock Tools by merging non-polar hydrogens, adding Gasteiger charges, and defining torsions, before being saved in **`.pdbqt`** format [28].

2.6 Docking and Grid Parameters:

Docking grids were centered on the ligand binding site with the following parameters: exhaustiveness = 8; center coordinates x = 160.019, y = 137.61, z = 200.22; grid size x = 25, y = 25, z = 25 [29].

2.7 Visualization and Analysis of the Results:

Docking conformations were analyzed, and the best poses were selected based on binding energy (Table 1). Interaction diagrams were generated to depict ligand–protein binding [30, 31].

Table 1: Docking Scores

Ligand	Binding Affinity (kcal/mol)
16A	-8.8
15B	-8.7
16B	-8.7
16C	-8.5
13B	-8.0

3. RESULTS AND DISCUSSION:

3.1 Docking:

Molecular docking simulations were performed using the prepared compounds against the ATP synthase enzyme of Mycobacterium tuberculosis (PDB ID: 7JG5). The selected ligands included compounds 13B, 15B, 16A, 16B, and 16C. The docking scores obtained ranged between –8.8 and –6.2 kcal/mol, indicating moderate binding affinities

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across the tested molecules (Table 2).

Among the evaluated ligands, compound 13B demonstrated the most favorable binding energy (–8.0 kcal/mol) and exhibited significant interactions within the active site of ATP synthase. The docking analysis revealed that the major stabilizing forces for compound 13B included hydrogen bonding, hydrophobic contacts, electrostatic interactions, π–π stacking, and π–cation stacking. These interactions are critical for maintaining ligand stability within the binding pocket of the receptor (Table 3).

In contrast, compounds 15B (–8.7 kcal/mol), 16A (–8.8 kcal/mol), 16B (–8.7 kcal/mol), and 16C (–8.5 kcal/mol) showed moderate docking scores but lacked measurable or specific interactions with the enzyme, suggesting weaker binding compared to compound 13B. Isoniazid, used as a reference drug, also displayed moderate affinity.

Residue-level analysis indicated that compound 13B interacted with key amino acids of ATP synthase, including Ala180, Val183, Val219, Ala222, Phe360, Tyr436, and Ile209 (Table 4). These interactions highlight the potential of compound 13B as a promising lead candidate for further optimization and development in antitubercular drug discovery.

Tables 2: Structure and Binding Energy of docking compounds

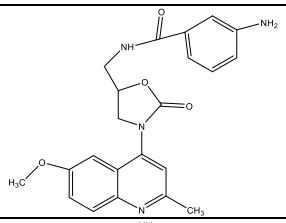
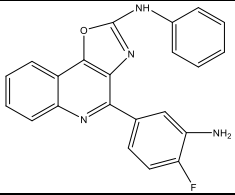
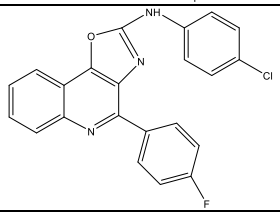
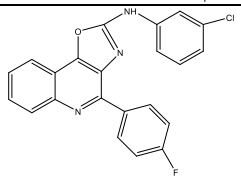
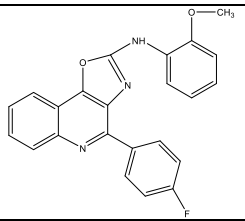
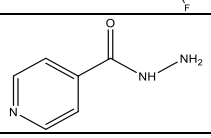
Compound	Binding Affinity	Chemical Structure
13b 3-amino-N-[[3-(6-methoxy-2-methylquinolin-4-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl]benzamide	-8	
15b 4-(3-amino-4-fluorophenyl)-N-phenyl-[1,3]oxazolo[4,5-c]quinolin-2-amine	-8.7	
16a N-(4-chlorophenyl)-4-(4-fluorophenyl)-[1,3]oxazolo[4,5-c]quinolin-2-amine	-8.8	
16b N-(3-chlorophenyl)-4-(4-fluorophenyl)-[1,3]oxazolo[4,5-c]quinolin-2-amine	-8.7	
6c 4-(4-fluorophenyl)-N-(2-methoxyphenyl)-[1,3]oxazolo[4,5-c]quinolin-2-amine	-8.5	
Isoniazid (INH) pyridine-4-carbohydrazide	-4.6	

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Table 3: 2D and 3D snapshots showing the hydrophilicity interaction with the (PDB=4JG5) receptors

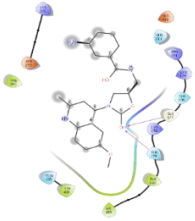
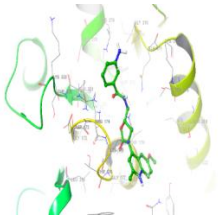
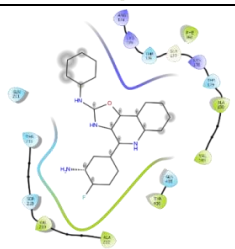
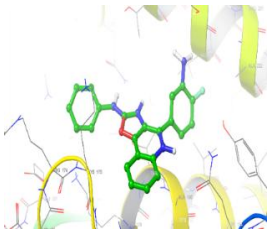
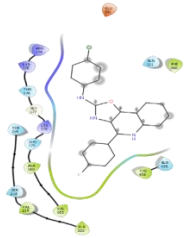
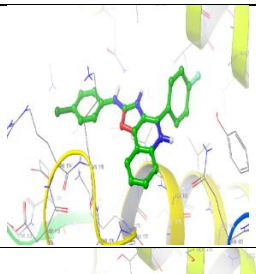
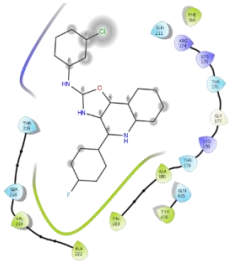
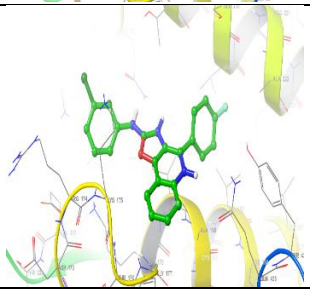
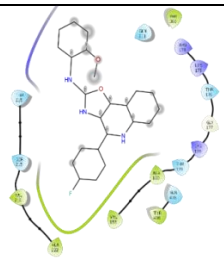
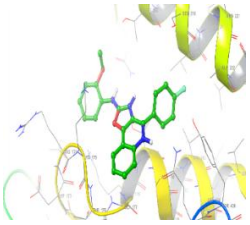
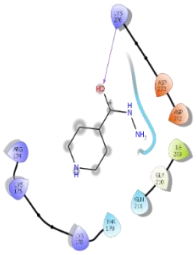
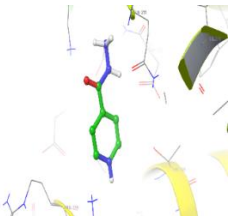
Compound Name	2D Structure	3D Structure
13b		
15b		
16a		
16b		
16c		
Isoniazid (INH)		

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Table 4: Docking interactions of selected compounds with ATP synthase (PDB=4JG5)

S.no	Compound	Binding affinity	Hydrophobic interaction	Hydrogen bond
1.	**13b**	-8	ALA180, VAL183, PHE360,TYR436	GLY177, THR179
2.	**15b**	-8.7	ALA180, VAL183, VAL219, ALA222, PHE360, TYR436	--
3.	**16a**	-8.8	ALA180, VAL183, VAL219, ALA222, PHE360, TYR436	--
4.	**16b**	-8.7	ALA180, VAL183, VAL219, ALA222, PHE360, TYR436	--
5.	**16c**	-8.5	ALA180, VAL183, VAL219, ALA222, PHE360, TYR436	--
6.	**Isoniazid (INH)**	-4.6	ILE209	LYS276

3.2 Toxicity Radar

Toxicity radar of novel compounds refers to the process of evaluating and predicting the potential toxicity of newly developed chemical compounds. The goal is to identify and assess any adverse effects that these compounds may have on human health or the environment before they are widely used or released into various applications. By using computational methods for toxicity radar, the time and resources required for experimental testing are significantly reduced, contributing to more efficient and informed decision-making in compound screening and selection. The ProTox-II data showed that the tested compounds (**13b, 15b, 16a, 16b, 16c and Isoniazid**) were predicted to have oral LD50 values ranging from 420 to 1000mg/kg in a rat model. Through screening the toxicity radar results, we found that compound 13b, 15b, 16a, 16b had a higher predictable LD50, which agrees with the results obtained from the molecular docking and the biological activities (Table 5; Figure 1).

Table 5: The predicted toxicity for compounds 13b, 15b, 16a, 16b, 16c using Pro Tox-II

	13b	**15b**	**16a**	**16b**	**16c**
Predicted LD50 (mg/kg)	1000mg/kg	1000mg/kg	1000mg/kg	1000mg/kg	740mg/kg
Predicted toxicity class	4	4	4	4	4
Average Similarity (%)	59.97%	45.33%	45.89%	45.17%	45.29%
Prediction Accuracy (%)	67.38%	54.26%	54.26%	54.26%	54.26%

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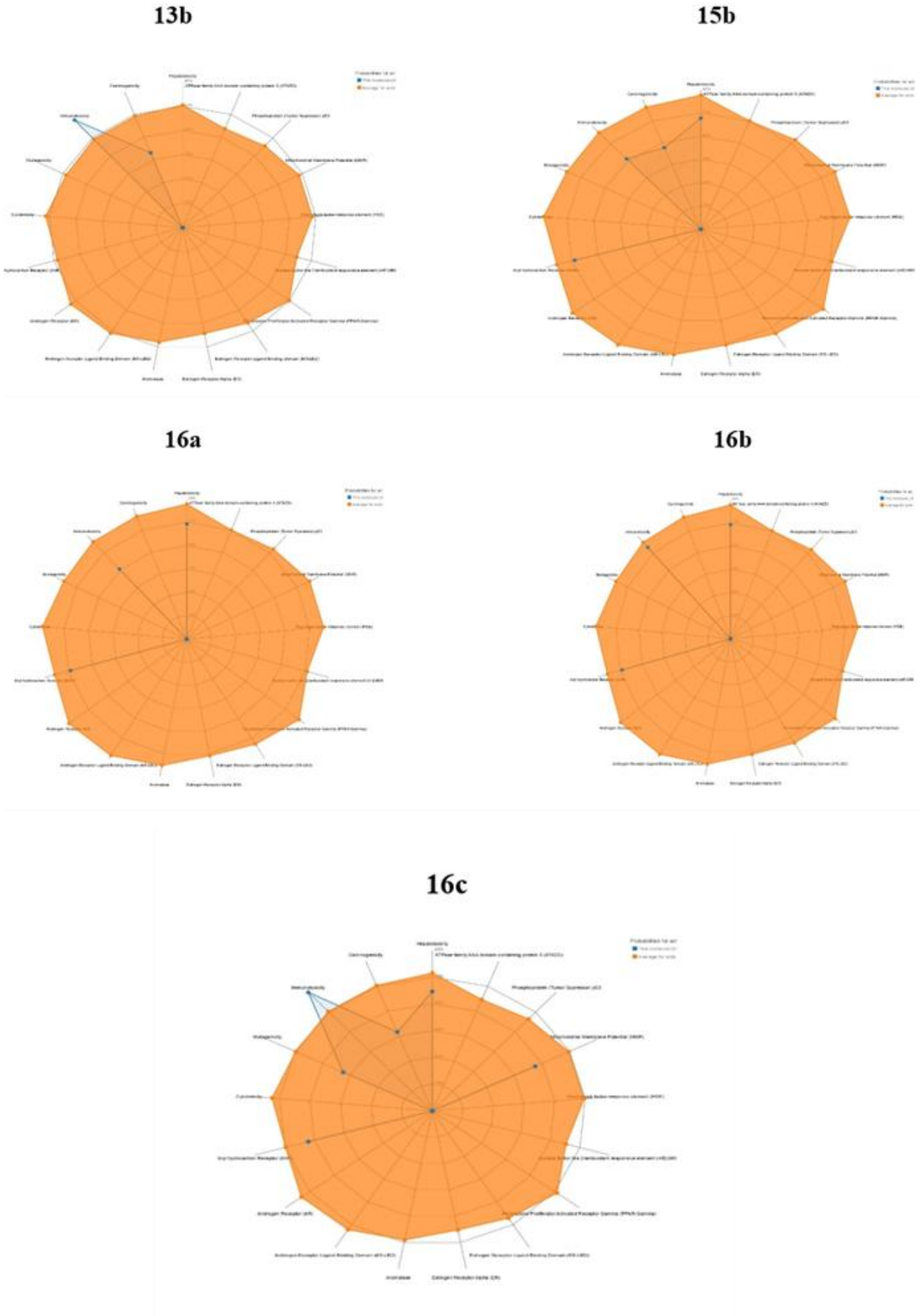

Figure 1: Toxicity radar for compounds 13b, 15b, 16a, 16b, 16c

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3.3 Swiss ADME Studies

Computational ADME prediction serves as an efficient screening tool, helping researchers prioritize compounds for further development and reducing the cost and time associated with experimental testing. A potent antagonistic interaction of inhibitors with a receptor protein or enzyme cannot guarantee the ability of an inhibitors to act as a drug; therefore, ADME assessment is essential in drug development. Inhibitors having low ADME properties and high toxicity effects on biological systems are often the dominant reasons for the failure of most medicines in the experimental phase. Figure 2 shows the output of the ADME studies and the drug-likeness properties; it was observed that the 13b, 15b and 16c molecules display zero violations of Lipinski's rule. The drug-likeness parameters are related to aqueous solubility and intestinal permeability, determining the first step of oral bioavailability. The results also indicated good pharmacokinetic properties, in which compounds 13b, 15b and 16c have high gastrointestinal absorption.

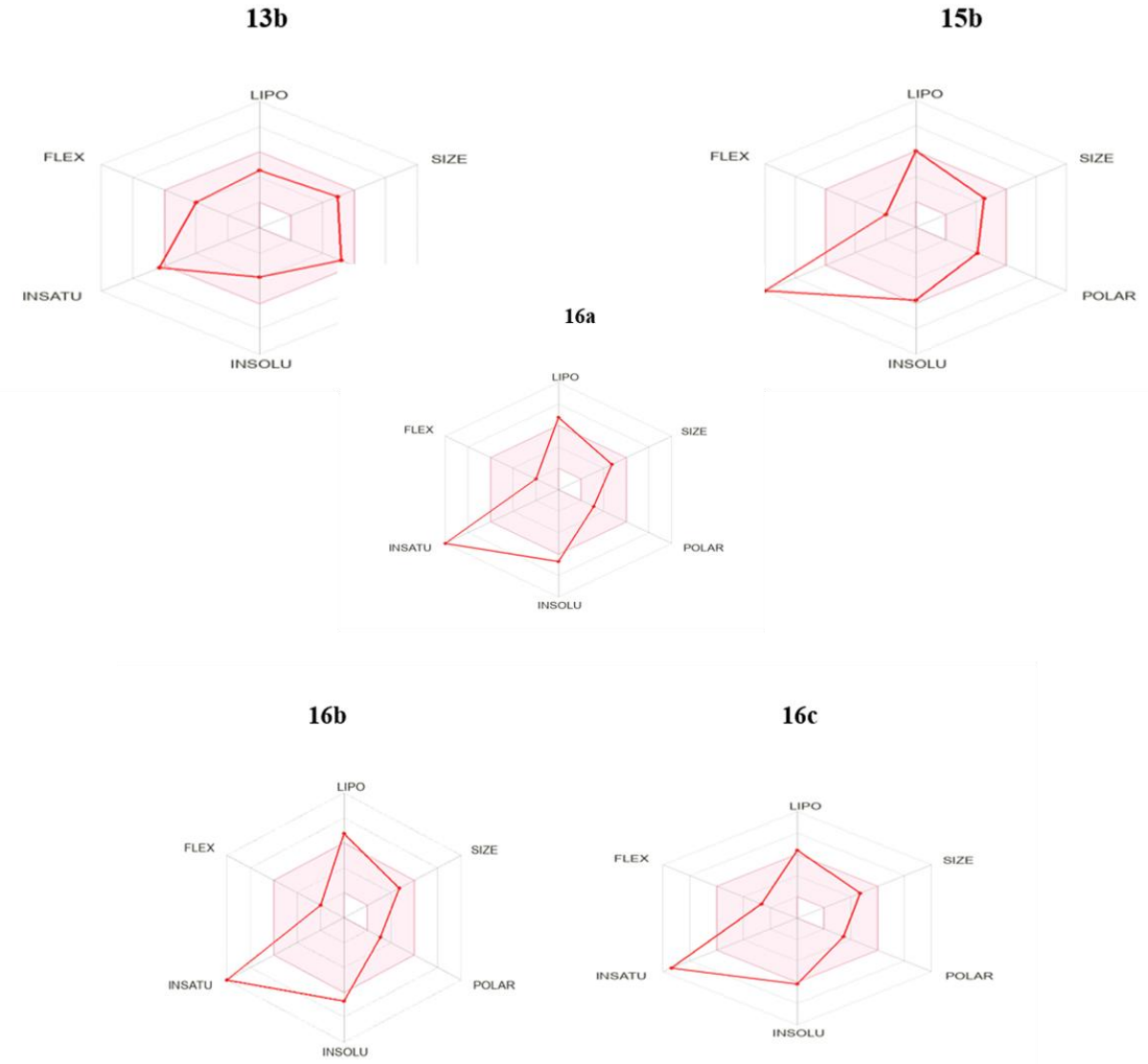

Figure 2: Toxicity profiles of the evaluated compounds using the Swiss ADME server.

4. CONCLUSION

Quinoline derivatives offer exciting prospects as anti-TB agents due to their diverse chemical structures and multi-targeted mechanisms of action. In vitro and in vivo studies have demonstrated their potent anti-mycobacterial activity, making them attractive candidates for further development. The optimization of quinoline derivatives, guided by SAR studies, holds promise for enhancing their potency, selectivity, and pharmacokinetic properties. Further research and clinical studies are warranted to evaluate the safety, efficacy.

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The present study employed computer-aided drug design and molecular docking approaches to evaluate novel quinoline derivatives as potential inhibitors of Mycobacterium tuberculosis ATP synthase. Docking simulations revealed that all tested compounds exhibited moderate binding affinities, with scores ranging from –8.8 to –6.2 kcal/mol. Among them, compound 13B demonstrated the most promising profile, showing significant interactions with key amino acid residues such as Ala180, Val183, Val219, Ala222, Phe360, Tyr436, and Ile209. These interactions, including hydrogen bonding, hydrophobic contacts, electrostatic forces, and π–π stacking, are critical for stabilizing ligands within the enzyme's binding pocket.Although the overall docking scores suggest moderate activity, the specific binding behavior of compound 13B highlights its potential as a lead candidate for further optimization. The comparative analysis with other derivatives and the reference drug isoniazid underscores the importance of structural modifications in enhancing antitubercular activity.This study reinforces the utility of molecular docking as a primary screening tool in drug discovery, enabling rapid identification of promising scaffolds prior to experimental validation.

On Conclusion, the findings provide a foundation for subsequent in vitro and in vivo studies aimed at improving the efficacy and selectivity of quinoline-based inhibitors. Ultimately, the integration of computational design with biological evaluation may accelerate the development of novel antitubercular agents targeting ATP synthase, addressing the urgent need for effective therapies against drug-resistant tuberculosis.

5.CONFLICT OF INTEREST:

None.

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