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Original Article

REVOLUTIONIZING ANTIMICROBIAL DRUG DISCOVERY: COMPUTATIONAL DESIGN AND ADMET STUDIES OF EMERGING POTENT ANTI-MICROBIAL AGENTS

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ABSTRACT

Objective: This study focuses on designing potential antimicrobial agents, evaluating their binding affinity against target proteins, and assessing their Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties using computational methods.

Methods: This study employed six target proteins from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) and utilized Biovia Discovery Studio 2021 for their preparation. Marvin Sketch is used to draw the ten potential candidates and subjected to molecular docking using Python Prescription (PyRx) software. The Biovia Discovery Studio 2021 was used to visualize the docking outcomes, and ADMET properties were determined using Swiss ADME software.

Results: Docking experiments conducted on ten derivatives against six protein targets, specifically Sortase-A, Clumping factor A, Undecaprenyl diphosphate synthase, Dehydrosqualene synthase, Tyrosyl tRNA synthetase, and Dihydrofolate reductase. Out of the ten derivatives, compounds 1, 2, 3, 5, and 7 demonstrated a significant binding affinity for one or two target proteins. Notably, compound 8 exhibited exceptional docking scores against five of the six protein targets, establishing itself as the most potent ligand among the compounds tested. These results highlight the paramount significance of compound 8 for subsequent investigation. Furthermore, comprehensive documentation of the physicochemical properties of the potent derivatives was carried out.

Conclusion: The findings indicate that the examined compounds have the potential to effectively inhibit various microbial protein targets. *In silico* ADMET studies suggest that these compounds possess desirable drug-like properties. Therefore, these compounds hold promise as lead molecules for further research, potentially leading to the development of novel antimicrobial drugs.

Keywords: Antimicrobial, Benzimidazole quinoline derivatives, Molecular docking, PyRx, Swiss-ADME, Discovery studio 2021, ADMET, Staphylococcus aureus, Drug discovery

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INTRODUCTION

The extensive use of antimicrobial drugs in various domains, such as human medicine, veterinary practises, and agriculture, has led to the emergence of microbial resistance as a significant issue. Microbes develop resistance through various mechanisms, including impeding drug access to their targets, genetic mutations affecting antibacterial targets, and direct modification of drugs [1]. The growing prevalence of microbial resistance to current antimicrobial treatments and its impact on global healthcare highlight the ongoing need for research and advancements in the field of anti-infective drugs [2, 3]. Consequently, there is a compelling need to continue exploring and developing novel antimicrobial medications [4]. The escalating global problem of antimicrobial resistance has necessitated the application of machine learning techniques and artificial intelligence in the field of computational chemistry. These advancements contribute to the design of new antimicrobial agents, aiding in the fight against antimicrobial resistance [5-7].

The field of computational chemistry has revolutionised the process of drug design by enabling the rapid screening of molecules based on their binding affinity and facilitating Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) studies. *In silico* methods have significantly expedited these tasks, contributing to a more efficient and streamlined drug discovery process [8].

Benzimidazole, a highly valuable and extensively studied chemical scaffold in medicinal chemistry, serves as a crucial pharmacophore due to its diverse range of activities across various therapeutic areas [9]. It has demonstrated efficacy as an antidiabetic, antiulcer, anti-inflammatory, anticancer, antiviral, and antimicrobial agent [10]. Numerous studies have underscored the antimicrobial potential of benzimidazole derivatives against various microorganisms [11-14]. The structural versatility of benzimidazole allows for modifications, leading to the creation of a wide array of derivatives with distinct properties. These modifications can exert a profound impact on the physicochemical properties, target specificity, and pharmacokinetic profiles of the compounds, ultimately enhancing their antimicrobial activity [15].

Similarly, the quinoline nucleus also serves as a crucial pharmacophore and is found in numerous antifungal agents. Quinoline derivatives exhibit a diverse range of pharmacological activities, including antimalarial, anticancer, antibacterial, and antifungal properties [16].

Hence, the current study highlights the importance of designing and conducting molecular docking investigations on newly developed compounds that incorporate both benzimidazole and quinoline rings, with the goal of assessing their antimicrobial potential. Furthermore, the study aims to evaluate the ADMET properties of these promising compounds using the SwissADME software. By combining the structural features of benzimidazole and quinoline, it is anticipated that the resulting compounds will exhibit enhanced therapeutic potential and versatility, making them potential candidates for further development as antimicrobial agents.

MATERIALS AND METHODS

Selection of target proteins

For this investigation, six protein targets from Staphylococcus aureus were chosen, including Sortase-A (PDB ID: 1T2P), Clumping Factor A (PDB ID: 1N67), Undecaprenyl diphosphate synthase (PDB ID: 4H8E), Dehydrosqualene synthase (PDB ID: 2ZCO), Tyrosyl tRNA synthetase (PDB ID: 1JIJ), and Dihydrofolate reductase (PDB ID: 3FYV) [17]. The X-Ray Diffraction structures of these proteins were

obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank in PDB format [18].

Preparation of protein

The protein structures were prepared using the Biovia Discovery Studio 2021 Client. This involved removing water molecules, unwanted residues, and other inhibitors present in the proteins. Repeated chains were also eliminated. After preparation, the proteins were saved in PDB format [19].

Preparation of ligands

Ten derivatives were sketched using Marvin Sketch [20] and saved in SDF format. Furthermore, a standard drug, Penicillin G [21], was chosen for comparison. The structure of the standard drug was obtained from the PubChem Compound Database and saved in a three-dimensional (3D) conformer as an SDF file [22].

Assigning a grid box

In PyRx software, the protein structures were imported and assigned Kollmann and Gasteiger charges. Subsequently, the protein structures were converted to the PDBQT file format. The ligands were also loaded into the software, subjected to energy minimization, and converted to the PDBQT file format. To define the binding site, a grid box was positioned within the protein structure [23].

Molecular docking study and Visualization of docking poses

Molecular docking was performed using AutoDock Vina in the PyRx software. All ligands were subjected to docking, resulting in the generation of nine poses accompanied by their respective docking scores. Among the ligands docked, the one with the highest score for each of the six proteins, as compared to the standard drug, was selected. The docking interactions of these selected ligands were then visualized in a two-dimensional (2D) conformation using Biovia Discovery Studio 2021.

Pharmacokinetic studies using swiss ADME

To assess the ADMET parameters of the potent molecules, the Swiss ADME software was utilized. The smile notations of the molecules were provided, and the software generated the corresponding ADMET properties [24].

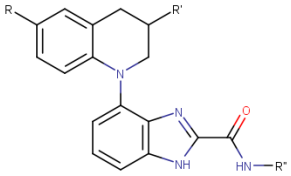

Fig. 1: Structure of benzimidazole derivative

RESULTS AND DISCUSSION

Ligand design

A series of benzimidazole-quinoline derivatives were designed, featuring a 1, 3-benzimidazole-2-carboxamide core with a 3, 6-disubstituted quinolin-1-yl group attached (fig. 1). The incorporation of the benzimidazole-2-carboxamide scaffold serves as a structural foundation with established antimicrobial activity. Additionally, the introduction of the 3, 6-disubstituted quinolin-1-yl group introduces further structural variations and the potential for antimicrobial activity. The specific characteristics of the substituents present on the quinoline ring greatly influence the antimicrobial properties of the compounds, including their potency and the range of microorganisms they can target [25]. The substitutions occurring at the nitrogen atom of the 1, 3-benzodiazole-2-carboxamide moiety, as well as the substitution at the carbon atoms of the quinoline ring, play crucial roles in modifying the physicochemical properties of the compounds [26]. These modifications encompass factors such as lipophilicity [27], hydrogen bonding capacity [28], and overall molecular interactions with microbial targets [29]. Consequently, these alterations can impact the compounds' ability to penetrate microbial cell membranes, interact with target enzymes or receptors, and disrupt vital microbial processes, ultimately resulting in antimicrobial activity [30, 31]. A total of ten derivatives based on the designed scaffold were sketched using Marvin Sketch, and their structures are depicted in fig. 2 and fig. 3.

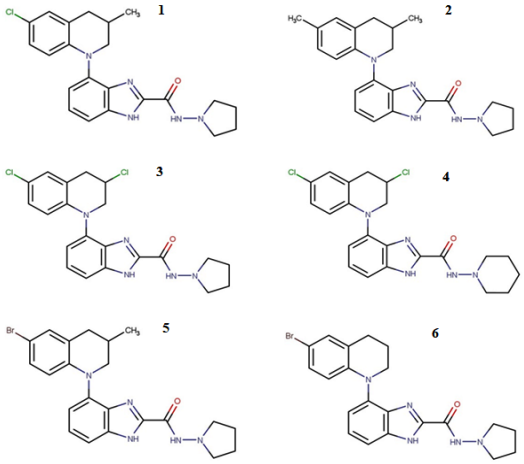

Fig. 2: Structures of the newly designed ligands

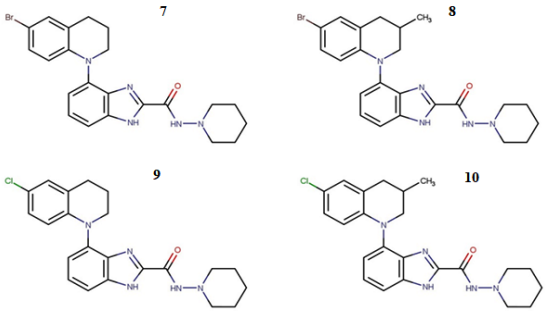

Fig. 3: Structures of the newly designed ligands (Contd.)

A docking study was conducted to examine the molecular interactions and binding affinity of the test and standard compounds with microbial proteins. The study assessed parameters such as the binding energies of the molecules, the number of hydrogen bonds formed, and the root mean square deviation (RMSD) values. Notably, the RMSD values were determined to be zero, indicating a high degree of structural similarity and favourable binding conformation. All ten derivatives were subjected to docking against the selected target proteins. Sortase A showed the most favourable binding scores, with compounds 2, 3, and 5, all yielding a value of-9 kcal/mol. Clumping Factor A, on the other hand, exhibited the highest binding scores with compounds 5 and 8, both at-10.3 kcal/mol. Notably, Compound 8 displayed impressive binding scores against multiple targets, including Dehydrosqualene synthase (-9.7 kcal/mol), Tyrosyl tRNA synthetase (-10.4 kcal/mol), Dihydrofolate reductase (-10.8 kcal/mol), and Undecaprenyl diphosphate synthase (-8.6 kcal/mol). Compound 1 showed the best binding score against Tyrosyl tRNA synthetase (-10.4 kcal/mol), while Compound 7 exhibited the highest binding score against Dihydrofolate reductase (-10.8 kcal/mol). Comparing these findings to the standard drug Penicillin G, it is evident that the tested compounds yield superior results.

According to the findings, compound 8 exhibited the highest docking scores among the ten derivatives against five out of the six target proteins. Notably, it displayed the most favourable binding scores against Dehydrosqualene synthase, Tyrosyl tRNA synthetase,

Dihydrofolate reductase, Undecaprenyl diphosphate synthase, and Clumping factor A. These results strongly suggest that compound 8 possesses significant potential as a potent inhibitor for these specific target proteins.

Table 1 provides the docking scores for all the ligands, indicating their binding affinity to the target protein. Additionally, in fig. 4 to fig. 14, the two-dimensional (2D) interactions of potent ligands with the corresponding protein are illustrated.

Table 1: Molecular docking scores of ligands with different target proteins of Staphylococcus aureus

Ligands	Sortase a (1T2P)	Clumping factor a (1N67)	Undecaprenyl diphosphate synthase (4H8E)	Dehydrosqualene synthase (2ZCO)	Tyrosyl tRNA synthetase (1JIJ)	Dihydrofolate reductase (3FYV)
1	-8.7	-9.3	-8.3	-8.9	-9.3	-10.8
2	-9	-9.9	-8	-9.2	-9	-10.2
3	-9	-9.6	-8.3	-9	-8.4	-9.9
4	-8.9	-9.7	-7.9	-9.5	-8.7	-10.7
5	-9	-10.3	-8.2	-8.5	-8.4	-10.4
6	-8.1	-10	-7.6	-8.9	-9.8	-9.8
7	-8.1	-10.2	-8.5	-9.1	-10.4	-10
8	-8.3	-10.3	-8.6	-9.7	-10.4	-10.8
9	-8.4	-10.1	-8.5	-9	-10.3	-10
10	-8.2	-10.2	-8.4	-8.7	-8.6	-10.7
Penicillin G	-6.8	-6.8	-6.9	-7.5	-7.4	-9.3

2D representation of the interactions between ligands and target proteins

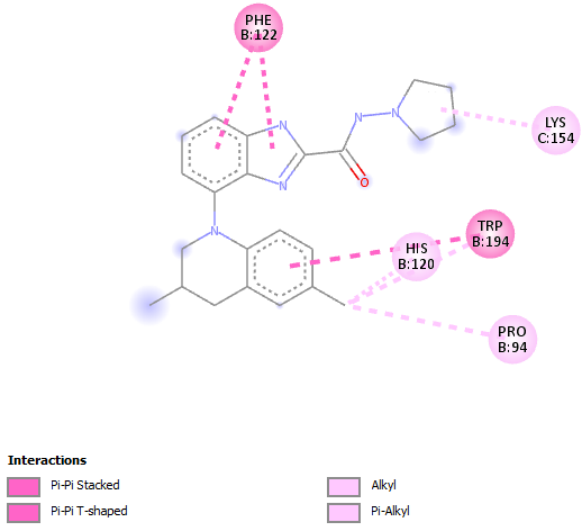

Fig. 4: Interactions of compound 2 with sortase-A

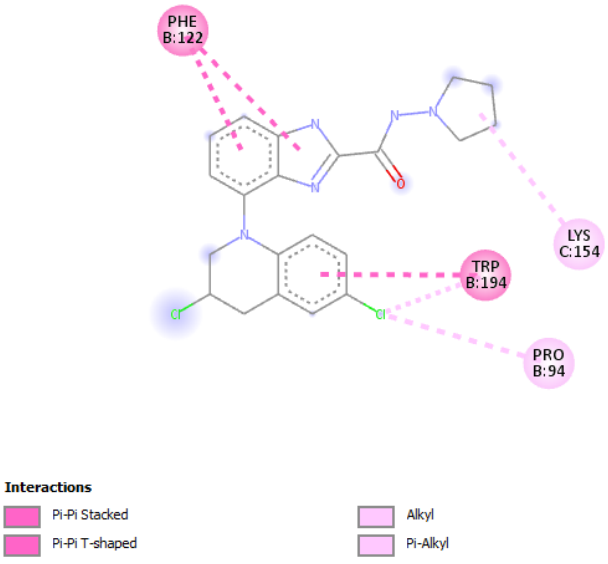

Fig. 5: Interactions of compound 3 with sortase-A

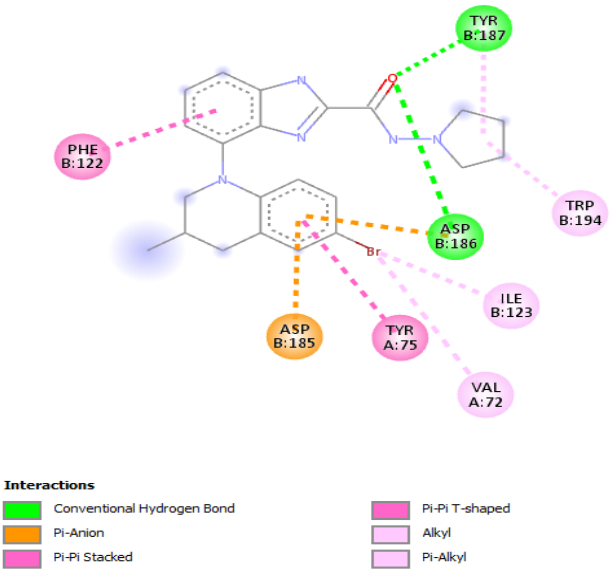

Fig. 6: Interactions of compound 5 with sortase-a

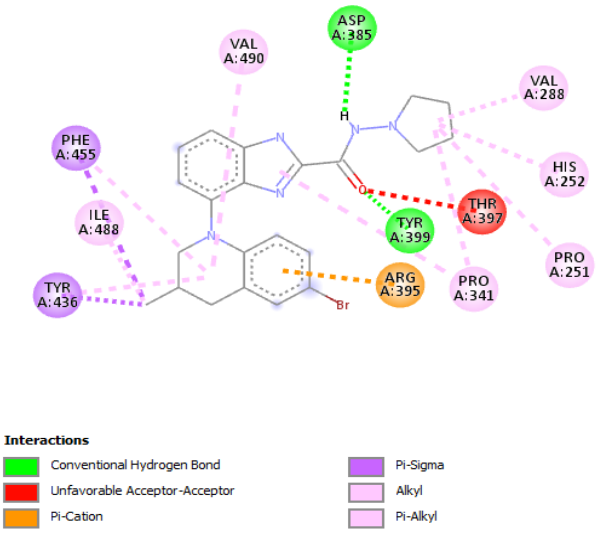

Fig. 7: Interactions of compound 5 with clumping factor-a (ClfA)

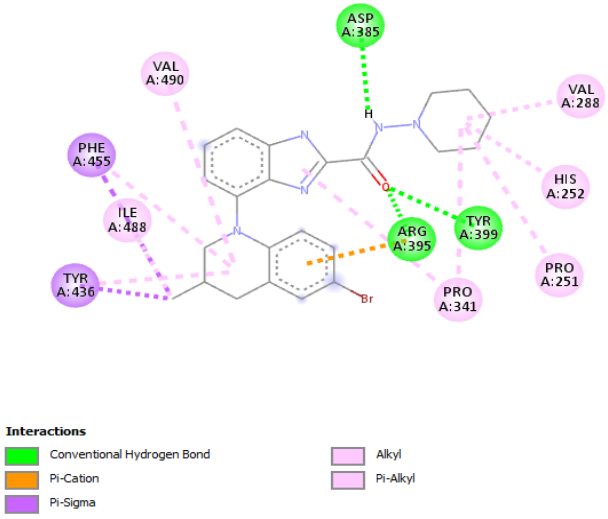

Fig. 8: Interactions of compound 8 with clumping factor-A (ClfA)

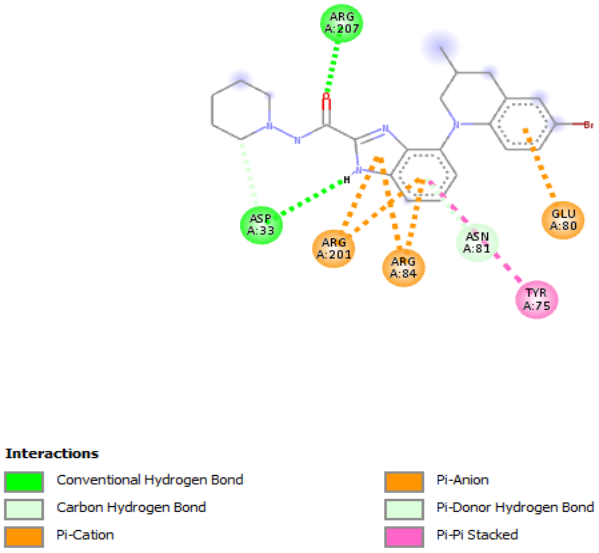

Fig. 9: Interactions of compound 8 with undecaprenyl diphosphate synthase (UPPS)

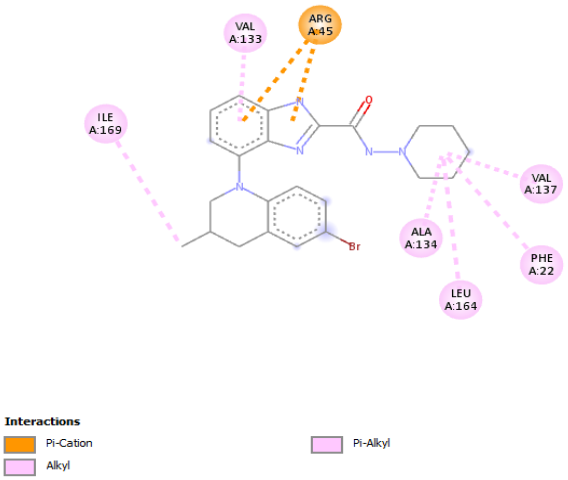

Fig. 10: Interactions of compound 8 with dehydrosqualene synthase (CrtM)

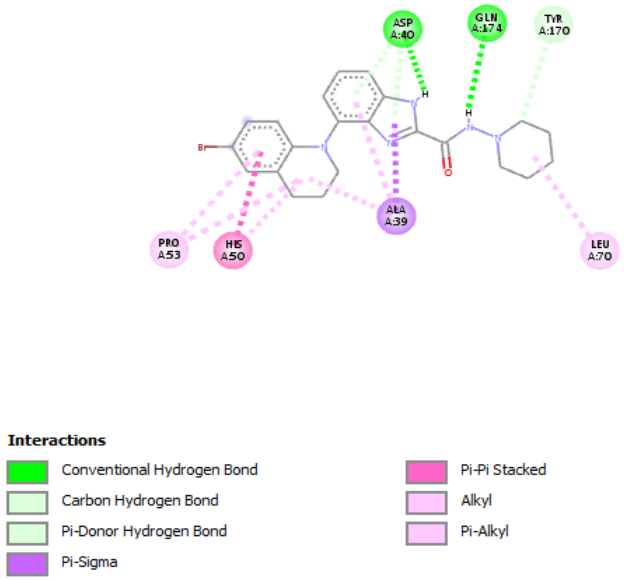

Fig. 11: Interactions of compound 7 with tyrosyl tRNA synthetase (TyrRS)

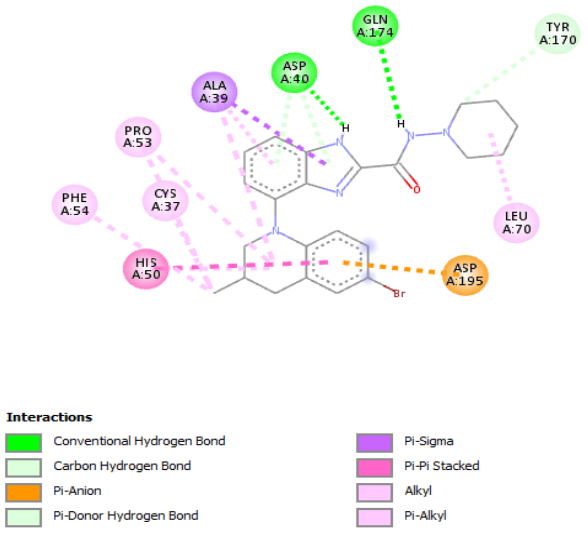

Fig. 12: Interactions of compound 8 with tyrosyl tRNA synthetase (TyrRS)

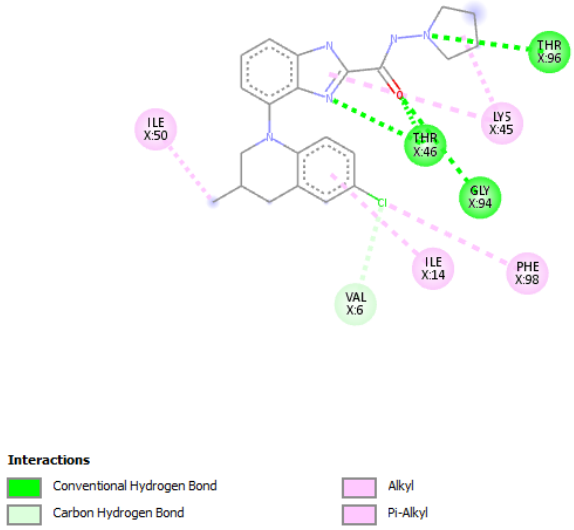

Fig. 13: Interactions of compound 1 with dihydrofolate reductase (DHFR)

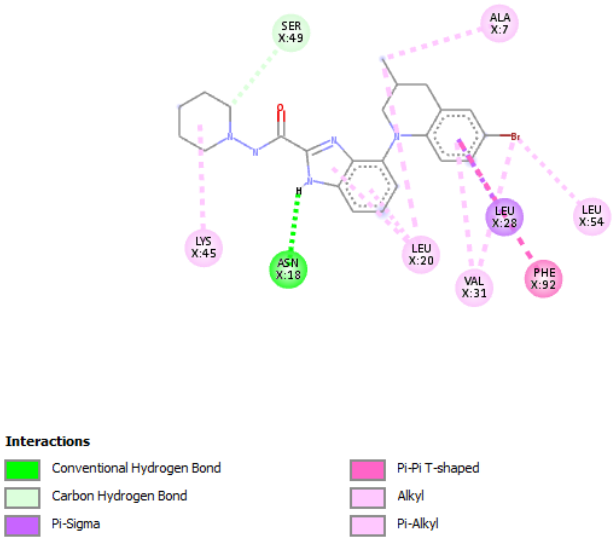

Fig. 14: Interactions of compound 8 with dihydrofolate reductase (DHFR)

The physicochemical properties of the potent molecules were assessed using the SwissADME software, and the corresponding findings are displayed in table 2. The results reveal that the selected potent molecules conform to Lipinski's Rule of Five without any violations, indicating their drug-like characteristics. Given these encouraging outcomes, it is highly recommended to proceed with additional investigations aimed at optimizing the lead compounds.

Table 2: Physicochemical properties of potent molecules

Physicochemical properties	1	2	3	5	7	8
Molecular weight	409.91	389.49	430.33	454.36	454.36	468.39
No. of Rotatable Bonds	4	4	4	4	4	4
Hydrogen Bond Donor	2	2	2	2	2	2
Hydrogen Bond Acceptor	3	3	3	3	3	3
Log P	3.75	3.48	3.75	3.86	3.59	4.06
Molar Refractivity	123.06	123.02	123.05	125.75	125.75	130.56
Central Nervous System (CNS) Permeability	Yes	Yes	Yes	Yes	Yes	Yes
Blood Brain Barrier (BBB) Permeation	Yes	Yes	Yes	Yes	Yes	Yes

CONCLUSION

The molecular docking study suggests that the benzimidazole-quinoline derivatives (Compounds 1, 2, 3, 5, 7, and 8) have the potential to act as effective inhibitors of the selected microbial target proteins. Compound 8, in particular, yielded high docking scores against five out of six target proteins. Moreover, *in silico* ADMET studies indicate that these compounds possess drug-like characteristics. Therefore, these compounds can be considered lead molecules for further research that may aid in developing novel drugs to combat microbial diseases.

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AUTHORS CONTRIBUTIONS

This study was conducted by the sole author, who contributed to all aspects of the research and manuscript preparation.

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Nil

CONFLICTS OF INTERESTS

The author has no conflicts of interest to declare that are relevant to the content of this article.

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