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Original Article

MOLECULAR DOCKING AND COMPUTATIONAL PHARMACOKINETIC STUDY OF SOME NOVEL COUMARIN–BENZOTHIAZOLE SCHIFF'S BASE FOR ANTIMICROBIAL ACTIVITY

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ABSTRACT

Objective: The present study discusses molecular docking of some novel coumarin–benzothiazole Schiff bases and the prediction of pharmacokinetic properties of potent molecules by the computational method.

Methods: Five protein targets were selected for the study and their structures were taken from RCSB Protein Data Bank in PDB format. Preparation of proteins was done using Discovery Studio 2021 Client. A total of twenty derivatives were drawn using ChemDraw 20.0 and saved in Mol format. Molecular docking was performed using PyRx software. Docking results were visualized by Discovery Studio 2021 Client. The pharmacokinetic properties of the best compounds were determined using the pkCSM tool.

Results: All twenty derivatives were docked against the five proteins, namely DNA Ligase (PDB ID: 3PN1), Topoisomerase (PDB ID: 3TTZ), Sterol demethylase (PDB ID: 5FSA), Enoyl-acyl-carrier protein (PDB ID: 1BVR) and Glutamate racemase (PDB ID: 5HJ7). The compound JJB18 has shown the best binding score against DNA ligase (-10.7 kcal/mol), Glutamate racemase (-8.4 kcal/mol), and Enoyl-acyl-carrier protein (-10.8 kcal/mol). Further, compound JJB19 has shown the best score for fungal sterol demethylase (-10.6 kcal/mol) and compound JJB20 towards topoisomerase (-9.4 kcal/mol) than the standard drugs. The physicochemical properties of potent derivatives were also reported.

Conclusion: Molecular Docking study indicates that coumarin–benzothiazole Schiff bases may be effective inhibitors for the different microbial proteins. Additionally, *in silico* ADMET studies predicts drug-like features. Hence, these compounds may be considered lead molecules and further investigation of their analogues may help in the development of novel drugs for the treatment of microbial diseases.

Keywords: Coumarin, Benzothiazole, Discovery studio, PyRx, DNA ligase, Topoisomerase, Sterol demethylase, Glutamate racemase, Enoyl-Acyl-carrier protein, Molecular docking, Antimicrobial activity

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INTRODUCTION

Antimicrobial resistance has become a global threat due to the development of internal mechanisms in microbes like bacteria, fungi, protozoans, etc., against the current antibiotics. Many synthetic therapeutic drugs like penicillin, cephalosporins, azole antifungals, isoniazid, rifampicin, etc. were designed and developed for the treatment of infections. However, the overuse and misuse of these drugs have triggered the insusceptibility of microbes. Among the categories of antimicrobial resistance, bacterial, fungal and tuberculosis resistance has been growing rapidly. As per the WHO report, these three types of resistance account for millions of deaths every year [1]. Examples include Klebsiella pneumoniae resistance towards carbapenems, fluoroquinolones, staphylococcus aureus resistance towards penicillin, aminoglycosides, M. tuberculosis resistance towards isoniazid, and rifampicin causing multidrug and extensive drug resistance, azole resistance in some aspergillus, dermatophytes, trichophyton species, etc. This enormous global problem enforces the pursuit of the discovery and development of novel antimicrobials for combating resistance [2].

Coumarin is a fused benzo-pyranone molecule naturally plant-derived and is a major structural moiety present in flavonoids. It accounts for substantial pharmacological activity in different therapeutic classes of antimicrobials, antioxidant, anti-inflammatory, anticancer, antipsychotics, anticonvulsants, etc. [3]. Benzothiazole compounds contain benzene rings fused with thiazole and account for a majority of anti-infective agents. They also act as potential anticancer, anti-inflammatory, anthelmintics, antiamoebics, etc. [4]. Schiff bases are also considered an important class of nitrogen-containing compounds bearing an imine linkage in their structure and exhibit potential biological activity as anti-infectives, anticancer, anti-inflammatory, etc. [5].

Hence, the present study focuses on molecular docking studies of novel coumarin–benzothiazole Schiff's base derivatives for antimicrobial activities and determination of the ADMET properties of potent molecules by the pkCSM tool.

MATERIALS AND METHODS

Selection of target protein and ligand

In this study, five protein targets were selected, namely DNA ligase (PDB ID: 3PN1), Topoisomerase (PDB ID: 3TTZ), 14-α Sterol demethylase (PDB ID: 3PN1), Glutamate racemase (PDB ID: 5HJ7) and Enoyl-acyl-carrier protein (PDB ID: 1BVR) and their X-Ray Diffraction structures were taken from RCSB Protein Data Bank in PDB format [6].

Preparation of protein

The proteins were prepared using Discovery Studio 2021 Client. In this, water molecules, unwanted residues and other inhibitors (ligands) already present in protein were removed. The repeated chains were also eliminated. The binding site was defined based on the inhibitor present and Its dimensions were noted. The protein was then saved in PDB file format [7].

Preparation of ligands

The structures of twenty derivatives were drawn using ChemDraw 20.0 and saved in SDF file format. All the ligands were then converted to PDB file format using Discovery Studio 2021 Client. Five standard drugs, namely Ciprofloxacin, Moxifloxacin, Ketoconazole, Fluconazole, and Isoniazid were selected for comparison of docking scores and their structures were taken from Pubchem and saved in 3D conformer as SDF format [8].

Assigning a grid box to define the binding site

The structure of the protein was loaded in PyRx software, where the Kollmann and Gasteiger charges were assigned. The proteins were then converted to PDBQT file format. Then the ligands were loaded into PyRx, energy minimized, and converted to PDBQT file format.

Then protein and the ligands were selected for docking and a grid box appeared in the protein structure. The position of the grid box was adjusted based on the dimensions noted for the binding site. The grid size was 25 x 25 x 25 for both proteins [9].

Molecular docking study

Molecular docking was performed using Vina in PyRx software after assigning grid dimensions [10]. The process was allowed to run and all the ligands were docked, each giving nine poses with corresponding docking scores.

Visualization of docking poses

The ligand which gave the best score compared to standard drugs against the two proteins was chosen and its docking interactions were visualized in 2D conformation using Discovery Studio 2021 Client [11].

Table 1: Molecular docking studies-selected target proteins

S. No.	Target proteins	PDB ID	Activity
1.	DNA Ligase	3PN1	Antibacterial activity
2.	Topoisomerase	3TTZ	Antibacterial activity
3.	14-α Sterol Demethylase	5FSA	Antifungal activity
4.	Glutamate Racemase	5HJ7	Antitubercular activity
5.	Enoyl-acyl-carrier protein	1BVR	Antitubercular activity

Pharmacokinetic studies using pkCSM

The ADMET parameters were determined for potent molecules using the pkCSM online tool in which the smile notations of the molecules are given and ADMET properties are generated [12].

RESULTS AND DISCUSSION

Scaffold design

The scaffold was designed by conjugating benzothiazole derivatives with coumarin through imine linkage. The structure of the scaffold is given in fig. 1. A total of twenty derivatives of the designed scaffold were prepared using ChemDraw 20.0 and their structures are given in fig. 2 and 3.

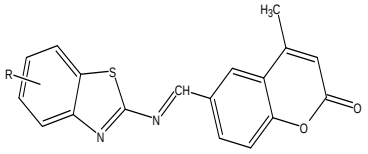

Fig. 1: Coumarin-benzothiazole schiff base

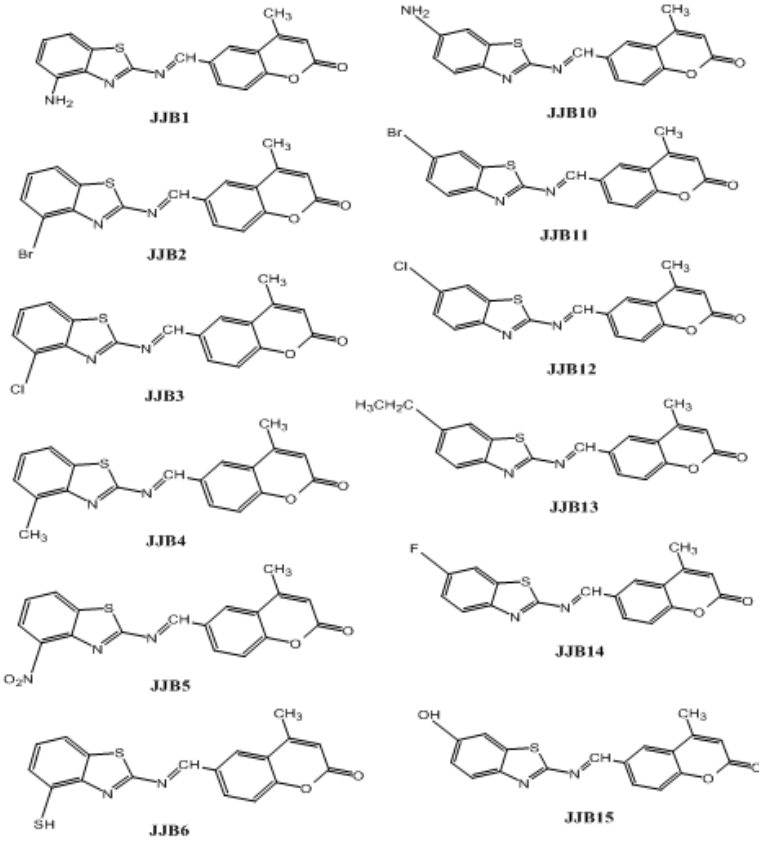

Fig. 2: Structure of ligands

To study the molecular basis of interaction and affinity of binding of test and standard to microbial proteins, all the ligands were docked against the selected target proteins. Among the twenty derivatives, compound JJB18 has shown the best binding score of-10.7,-8.4, and-10.8 kcal/mol against DNA ligase, Glutamate racemase, and Enoyl-acyl-carrier protein, respectively. Further, compound JJB19 has

shown the best score of-10.6 kcal/mol for fungal sterol demethylase and compound JJB20 has shown a better binding affinity towards topoisomerase with-9.4 kcal/mol than the standard drugs. Hence, the derivatives designed in the present study showed better docking scores and potential interaction with the selected target proteins as compared to the ones discussed in other studies [3, 4, 7, 9]. The docking scores of all the ligands are given in table 2 and 2D interactions of potent ligands with the corresponding protein are shown in fig. 4-8. The interaction energy includes van der Waals energy, electrostatic energy, as well as intermolecular hydrogen bonding were calculated for each minimized complex. The residues thus predicted are energetically important for ligand binding inside the binding site via hydrophobic, hydrogen bond interactions in almost all complexes.

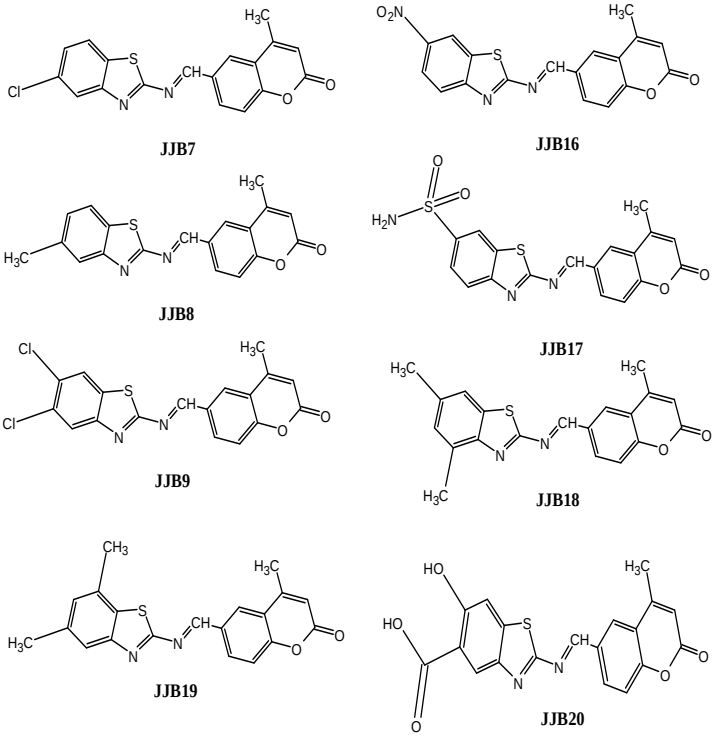

Fig. 3: Structure of ligands

Table 2: Docking scores of ligands against selected target proteins

S. No.	Ligands	Docking scores				
		DNA ligase (3PN1)	Topoisomerase (3TTZ)	Sterol demethylase (5FSA)	Glutamate racemase (5HJ7)	Enoyl-acyl-carrier protein (1BVR)
1.	JJB1	-10.0	-8.5	-10.0	-7.6	-9.9
2.	JJB2	-10.2	-8.7	-9.9	-7.7	-10.2
3.	JJB3	-10.1	-8.7	-9.9	-7.6	-10.2
4.	JJB4	-10.2	-8.7	-10.0	-7.8	-10.5
5.	JJB5	-10.5	-9.2	-10.3	-8.2	-10.4
6.	JJB6	-9.9	-8.4	-9.6	-7.5	-9.8
7.	JJB7	-10.1	-8.6	-10.1	-7.6	-9.8
8.	JJB8	-10.3	-8.6	-10.1	-8.0	-10.2
9.	JJB9	-10.4	-8.7	-10.1	-8.0	-9.7
10.	JJB10	-9.9	-8.6	-9.6	-7.4	-9.6
11.	JJB11	-10.2	-8.7	-10.1	-7.9	-9.6
12.	JJB12	-10.3	-8.8	-10.0	-7.9	-9.8
13.	JJB13	-10.4	-8.5	-10.3	-7.9	-9.5
14.	JJB14	-10.2	-8.8	-10.0	-7.6	-10.2
15.	JJB15	-10.3	-8.6	-9.7	-7.4	-9.8
16.	JJB16	-10.4	-8.8	-10.1	-7.1	-9.3
17.	JJB17	-10.4	-8.8	-10.2	-7.1	-9.6
18.	JJB18	-10.7	-9.0	-10.5	-8.4	-10.8
19.	JJB19	-10.6	-8.7	-10.6	-7.9	-10.4
20.	JJB20	-10.3	-9.4	-10.1	-7.3	-9.3
21.	Ciprofloxacin	-8.9	-7.6	-	-	-
22.	Moxifloxacin	-9.9	-7.1	-	-	-
23.	Ketoconazole	-	-	-10.2	-	-
24.	Fluconazole	-	-	-7.3	-	-
25.	Isoniazid	-	-	-	-5.1	-6.2

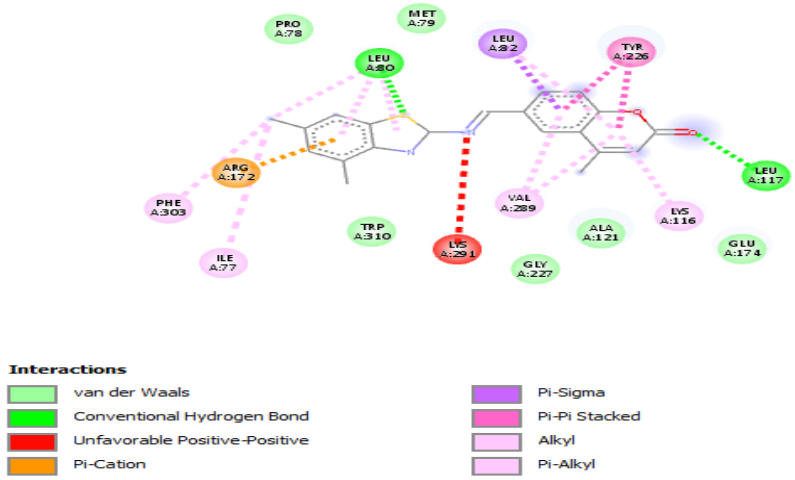

Fig. 4: 2D interaction of compound JJB18 with DNA ligase

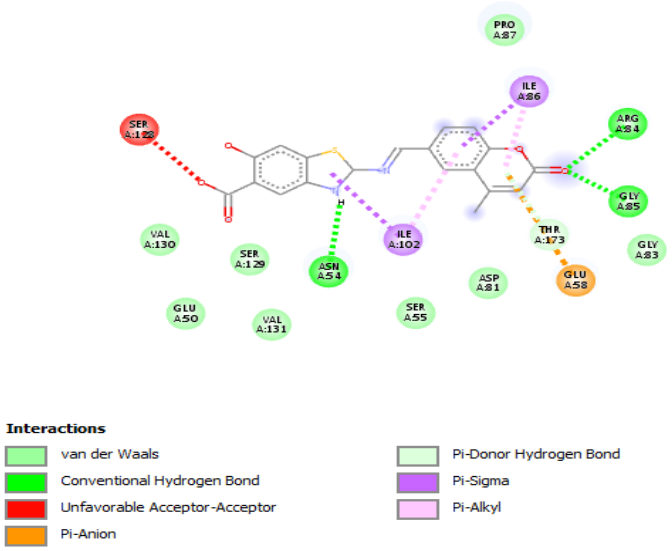

Fig. 5: 2D interaction of compound JJB20 with topoisomerase

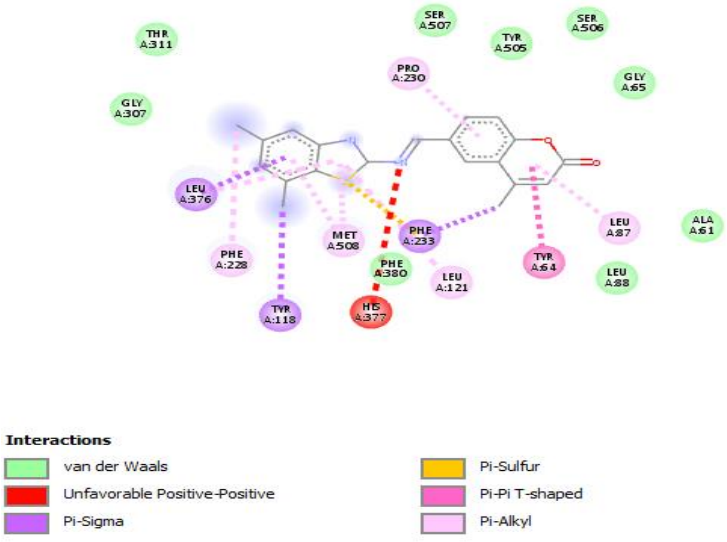

Fig. 6: 2D interaction of compound JJB19 with sterol demethylase

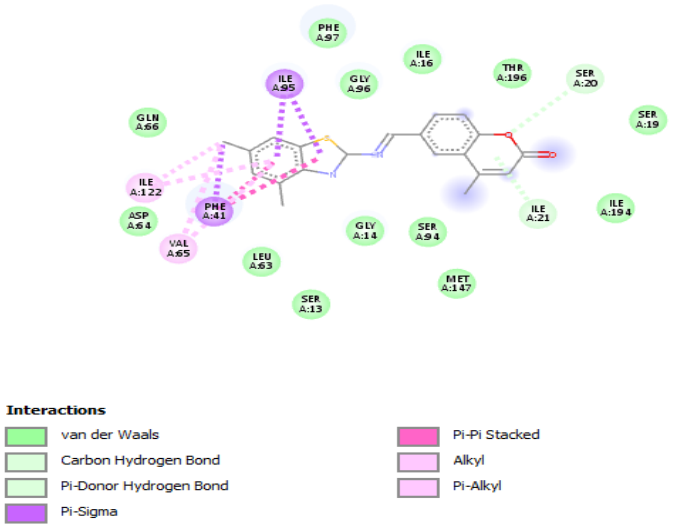

Fig. 7: 2D interaction of compound JJB18 with Enoyl-acyl-carrier protein

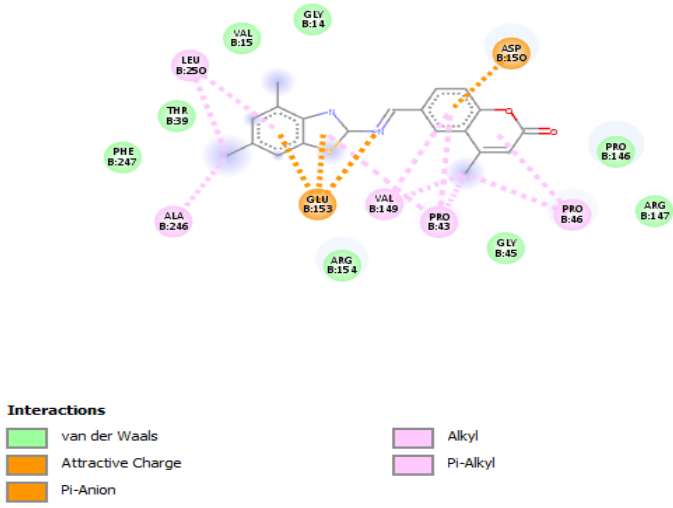

Fig. 8: 2D interaction of compound JJB18 with glutamate racemase

The physicochemical properties of potent molecules were determined by the pkCSM tool, and the results are summarized in table 3. Based on the results, it is found that the selected potent molecules exhibit good physicochemical characteristics with higher logP values resulting in greater CNS permeation as compared to the compounds discussed in other articles [4, 7]. They are also in compliance with the Lipinski Rule of Five, indicating that the compounds possess "Drug-like" features. Further, these compounds could be studied for lead optimization.

Table 3: Physicochemical properties of potent molecules

S. No.	Physicochemical properties	Compounds		
		JJB18	JJB19	JJB20
1.	Molecular Formula	$C_{20}H_{16}N_2O_2S$	$C_{20}H_{16}N_2O_2S$	$C_{19}H_{12}N_2O_5S$
2.	Molecular Weight	348.42	348.42	380.38
3.	No. of Rotatable bonds	2	2	3
4.	No. of H–Acceptors	5	5	7
5.	No. of H–Donors	0	0	2
6.	Log P	5.07	5.07	3.86
7.	Surface area	148.033	148.033	155.481
8.	Molar Refractivity	104.26	104.26	103.31

CONCLUSION

Molecular Docking study indicates that coumarin-benzothiazole Schiff's bases may be effective inhibitors of the selected microbial proteins. Additionally, *in silico* ADMET studies predicts drug-like features. Hence, these compounds may be considered lead molecules and further investigation of their analogues may help in the development of novel drugs for the treatment of microbial diseases.

DATA AVAILABILITY

Not applicable

FUNDING

Nil

AUTHORS CONTRIBUTIONS

The study protocol was designed by Judy Jays and coordinated the overall project. Molecular docking studies were done by Burhanuddin Madriwala and ADMET studies were performed by G. Chaitanya Sai.

CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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