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Short Communication

Investigation of anti-microbial activity of imidazol [2, 1-B][1,3,4] thiadiazole by using molecular docking and ADMET studies

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ABSTRACT

This report consists of molecular docking based on series of imidazol [2,1-b] [1–3] thiadiazole-benzimidazole derivative. Molecular docking is software which gives information about molecular modeling in which molecule fits into target binding sites and predict structure of intermolecular complex. These molecules were investigated by protein ligand binding score, protein ligand interaction and ADME studies. All the target molecules were analyzed against *Staphylococcus aureus* which is a gram positive bacteria found on skin and upper respiratory tract. The protein molecule selected for the analysis was PDB code 4LAE protein ligand. Basically it is a oxidoreductase inhibitor and its structure is based on 7(benzimidazole-1-yl)-2, 4-diaminoquinazolines. Out of all twenty nine compounds five compounds (5B,5G,5H,5N and 5Q) were estimated as most potent molecules as antibacterial agent.

1. Introduction

Imidazo[2,1-b] [1–4] Thiadiazole 1 is a bridgehead nitrogen atom heterocyclic. This compound was discovered in the early 1950s which is composed of four heteroatom and two condensed heterocycles with different -conjugations. This heterocycle is an isoster of biologically significant imidazo [1–4] thiazole, in which the thiazole ring's 3-CH group is replaced by a 3-N atom. The majority of the synthesised compounds have been reported to have a wide range of biological activities as well as the ability to block certain enzymes. Antibacterial, antifungal, leishmanicidal, herbicidal, antitubercular, anticancer, anthelmintic, anticonvulsant, analgesic, antiinflammatory, antipyretic, local anaesthetic, cardiotonic, and diuretic are among the biological activities. Staphylococcus aureus is a common cause of skin infections, respiratory infections, sinusitis and food poisoning. It is also responsible for life threatening diseases. Each year up to 50,000 deaths each year in USA are linked with S. aureus infection. In this report reveals the information of some new molecules of benzimidazole derivative is reported active against S. aureus**.** Molecular docking is a kind of bioinformatic modelling which includes the interplay of two or more molecules to present the solid adduct. Depending upon binding residences of ligand and target, it predicts the 3-dimensional structure of any complex drug molecule. Molecular docking generates distinct possible adduct structures which can be ranked and grouped together by the use of scoring feature inside the software program.

Conducting DMPK (Drug Metabolism and Pharmacokinetics) research, also known as ADMET (Absorption, Distribution, Metabolism, Elimination, and Toxicity) investigations, is an important part of drug discovery and development. These studies aid in determining a medicaments feasibility by explaining terms like absorption, distribution, metabolism and elimination and toxicity.

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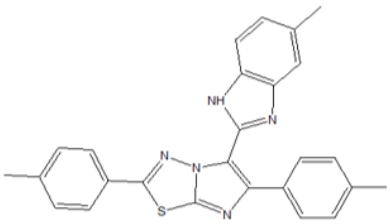
2. Material and Methods

2.1. Designing of compounds

29 derivatives of imidazol[2,1-b][1–3]Thiadiazole has been designed by substitution of different groups at R1,R2 and R3 positions.

2.2. Drawing of 2D and 3D structure of compounds and energy minimization

Two dimensional structures of all the 29 compounds were drawn by using software chem Draw ultra 8.0. Prepared 2D structures were converted into 3D structure by using chem. 3D ultra 8.0. Then 3D structures were optimized by performing energy minimization via molecular mechanics amd re-optimized by using molecular orbital package (MOPAC) until the RMS value became 0.0001Kcal/mol.



S. No	Product	R1	R2	R3
1	5B	4-CH_3, C_6H_4	OCH_3	NO_2
2	5G	2-Cl, C_6H_4	OCH_3	NO_2
3	5H	C_6H_4	OCH_3	NO_2
4	5N	4-F, C_6H_4	OCH_3	NO_2
5	5Q	4-CH_3, C_6H_4	Cl	NO_2

Fig. 1: Common structure of imidazole derivative and its substitution

2.3. Docking procedure

Three dimensional (3D) structure of PDBCode: 4LAE protein ligand was downloaded for from protein data bank. 3D structure of 4LAE protein ligand and designed compounds were imported in the work area space of molegro virtual docker (ver 6.0) and the required bonds, hybridization bond order hydrogen atom and charges were subjected. Surface created and the active site analyzed. Water molecule is removed because it is not consider during docking process. The binding active sites were analyzed through automated process. Grid resolution, probe size were adjusted. After that docking calculation started, Mol Dock score and rerank score of designed compounds were noted.[5]

3. ADMET Studies

Absorption, distribution, metabolism, elimination and toxicity studies were performed on top five compounds 5B, 5G, 5H, 5N and 5Q and the data generated by using computational ADMET software and result was recorded.[6–12]

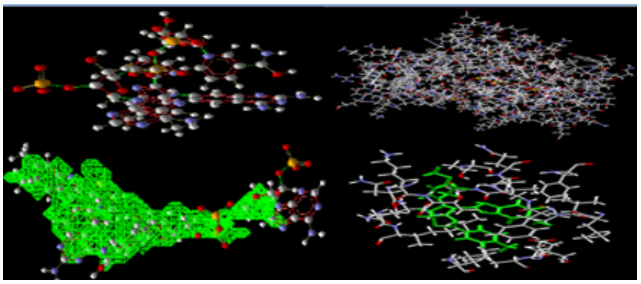


Fig. 2: Protein and molecular structure.

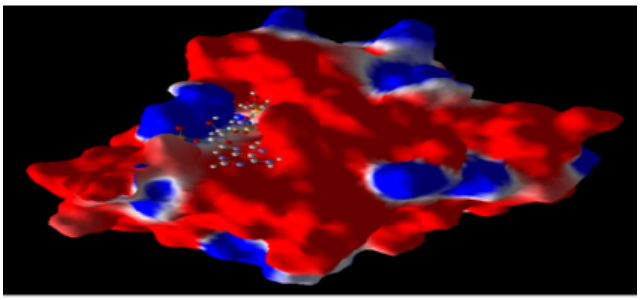


Fig. 3: Cavity detection.

4. Result and Discussion

29 compounds of imidazole derivatives were designed on the basis of literature review and docking was performed against *Staphylococcus aureus* and co crystallized with PDB code 4LAE protein ligand. The co crystallized ligand of PDB 4LAE protein ligand was also validated. The mole dock score, Rerank score and the amino acid interactions are reported in the Table 1. And the amino acid intractions of maximum compound were matched with interaction of 4LAE protein ligand PDB.[13]

The prediction of ADMET properties is critical in the drug design process because these features are responsible for around 60% of all medication failures in clinical trials. Whereas in the past, ADME techniques were used at the conclusion of the drug development process, today ADME is used from the beginning of the process to eliminate compounds with poor ADME features from the drug development pipeline, resulting in significant research and development cost savings. The ADMET studies performed in this research article show the good ADME properties of drug and hence, these molecules can further proceed in relation to discover the new molecule of imidazole derivative against microbial activity. The result of ADMET studies of top five molecules of imidazole derivative are metioned in Table 2.

Among all the 29 compounds of imidazole derivatives, five compounds (5B, 5G, 5H, 5N and 5Q) showed highest binding affinity on the basis of mole dock score. And good

Table 1: Molecular docking results of five most active compounds.

Name	Ligand	MolDock Score	Rerank Score	Hbond
[00] Unknown 1-1	Unknown 1-1	-203.623	-155.38	-2.39631
[00] Unknown 1-6	Unknown 1-6	-199.59	-154.053	-1.04589
[00] Unknown 1-7	Unknown 1-7	-193.59	-151.805	-1.00938
[00] Unknown 1-13	Unknown 1-13	-189.784	-148.136	-1.21446
[00] Unknown 1-16	Unknown 1-16	-187.767	-105.438	-1.26163
[00] 1 VM-202[X}	1VM-202[X]	-164.481	-115.795	-8.26014

Table 2: ADMET results of five most active compounds.

D	5B	5G	5H	5N	5Q
BBB	0.075371	0.131596	0.0784861	0.0729208	0.332617
Buffer solubillitymg L	8.48558	3.93941	12.0501	22.5624	5.35538
Caco2	13.5296	147996	10.1905	10.4004	27.9027
CYP-2C19-inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
CYP-2C9-inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
CYP-3A4-inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
CYP-3A4-substrate	Weakly	Weakly	Weakly	Weakly	Weakly
HIA	95.12479	95.35868	9511191	95.112	95.65509
MDCK	0.0443935*	0.459089*	0.467651	0.0440318*	0.0502164*
Pgp inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
Plasma Proteen Binding	97-.5373	93.95624	97.86767	95.72839	92.27109
Pure water solution mg L	0.00127453	0.000844191	0.00437652	0.00205459	0.000267375
Skin Permeabillity	-2.84945	-2.84945	-2.99576	-3.0358	-2.78736
SklogD value	6.31467	6.48898	5.8283	5.96534	7.02987
SklogP value	6.31467	6.48898	5.8283	5.82834	7.02987
Sklogs buffer	-475483	-5.10608	-4.58971	-4.33368	-4.95868
Sklogs pure	-8.57816	-8.77507	-8.02957	-8.37434	-9.26035

ADMET value on the basis of computation ADMET tool. Hence, this five molecules were estimated as most potent molecules as antibacterial agent.

5. Summary and Conclusion

In conclusion it is estimated through molecular docking that compounds which are having nitro group substitution at R3 position show good anti-bacterial properties then other aginst S. aureus. Out of twenty nine compound Good pharmacokinetic properties of 5b, 5g, 5h, 5n and 5q were investigated through ADME studies. The ADMET studies performed in this research article show the good ADME properties of drug and hence, these molecules can further proceed in relation to discover the new molecule of imidazole derivative against microbial activity.

6. Source of Funding

None.

7. Conflict of Interest

None.

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