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Original Article

MOLECULAR DOCKING AND ADMET STUDIES OF BENZOTRIAZOLE DERIVATIVES TETHERED WITH ISONIAZID FOR ANTIFUNGAL ACTIVITY

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ABSTRACT

Objective: The incidence of fungal infections is increasing at an alarming rate, presenting an enoromous challenge to health care professionals. This increase is directly related to the growing population of the immunocompromised individuals, resulting from changes in the medical practice such as the use of intensive chemotherapy and immunosuppressive drugs. The ability of many fungi to form biofilms is one of the reasons for the antifungal resistance caused and hence there is an urgent need in the synthesis of new and safer anti-microbial agnets. Benzotriazole is an organic heterocyclic compound with 2 nitrogen atoms in the ring having wide range of biological properties like anti-tubercular, anticancer and anti-microbial etc. isoniazid is the first line drug used to treat tuberculosis. Tethering benzotriazole with isoniazid has shown development of newer compounds that may exhibit better activity on inhibiting the fungal growth and replication and hence has shown a positive effect on the anti-fungal activity.

Methods: Affinity between the protein and ligand was found out using rigid docking technique.3D structure of the fungal protein was downloaded from protein data base. The selected ligand molecules are generated using Chem Draw. ADMET studies for the molecules are determined using SWISS-ADMET website. Rigid docking is employed to find the binding affinities between ligand and protein.

Results: 4 derivatives of benzotriazole tethered with isoniazid were selected and docking studies were carried out for these compounds with the antifungal protein,14 alfa-demethylase with PDB I. D; 5V5Z,using molecular docking tool PyRx and docking scores were-8.3,-7.6,-9.2,-7.4 respectively when compared with the standard compound Fluconazole (-8.0). ADMET studies of the 4 compounds have shown zero violation to lipinski's rule.

Conclusion: In summary, benzotriazole derivatives tethered with isoniazid exhibits promising results based on *in silico* studies. ADMET studies showed that the compounds drug likeness parameters are according to lipinski's rule of five.

Keywords: Autodock vina 1.5.6, Pymol, BIOVIA Discovery Studio2021, Swiss ADME

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INTRODUCTION

Benzotriazole, a bicyclic heterocyclic system consisting of three nitrogen atoms and fused benzene ring, shows wide range of biological and pharmacological activities. Benzotriazole can be synthesized using benzene-1,2-diamine and carboxylic acid. Benzotriazole posses wide spectrum of biological activities like including antibacterial, antifungal, antiviral, anti-inflammatory anthelmintic activity etc [1]. The incidence of fungal infections is increasing at an alarming rate, presenting an enormous challenge to health care professionals. This increase is directly related to the growing population of the immunocompromised individuals, resulting from changes in the medical practice such as the use of intensive chemotherapy and immunosuppressive drugs [2]. HIV and other diseases which cause immunosuppression have also contributed to this problem. The ability of many fungi to form biofilms is one of the reasons for the antifungal resistance caused and hence there is an urgent need in the synthesis of new and safer anti-microbial agents [3].

Superficial and subcutaneous fungal infections affect the skin, keratinous tissues and mucous membranes. Included in this class are some of the most frequently occurring skin diseases, affecting millions of people worldwide. Although rarely life threatening, they can have debilitating effects on a person's quality of life and may in some circumstances spread to other individuals or become invasive. Most superficial and subcutaneous fungal infections are easily diagnosed and readily amenable to treatment [4]. The antibiotic resistance is a major problem associated with the treatment of numerous bacterial infections. The machine learning techniques in the computational chemistry made the drug discovery process easy by reducing the for screening the molecules for their action that is by their ADMET studies and docking methodology. Antifungal action of benzotriazole derivatives tethered with isoniazid against anti-fungal protein 14-alfa-demethylase (5V5Z) is being carried out by using the machine learning techniques like molecular docking and ADMET studies [5].

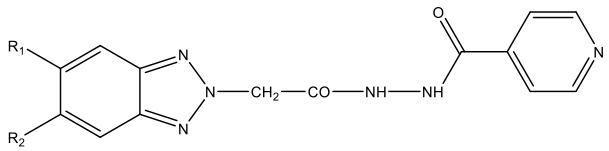

Fig. 1: Chemical structure of derivatives of benzotriazole tethered with isoniazid

Docking studies has been done based on rigid docking using PyRx software. Target proteins were downloaded from protein data bank in PDB format and protein preparation was carried out using Swiss-pdb viewer and BIOVIA Discovery studio 2021 where the removal of

amino acid residues were being carried out [6]. Prior to docking, energy minimization of the ligand molecules, conversion of ligand and proteins into PDBQT format was done.3D interaction between the protein and ligand was carried out using Pymol software and 2D structures were generated by discovery studio 2021. SWISS ADME website was employed in ADMET studies by converting the structures into SMILES formatand the selected compounds has shown zero violation for Lipinski's rule [7].

Molecular docking and ADMET studies of benzotriazole derivatives with isoniazid was carried out and the binding affinity was found to be more for chloro derivative against 14-alfa-demethylase protein [8] (PDB ID; 5V5Z) with a docking score of-9.2. ie a relatively good docking score when compared with the commercially available anti-fungal compound ie; Fluconazole (-8.0). ADMET properties of the compounds when carried out has indicated zero violation from Lipinski rule.

Molecular docking of different derivatives of benzotriazole derivatives tethered with isoniazid against anti-fungal protein 14-alfa-demethylase was carried out. and the binding scores of the ligands with target protein is shown in the following table II.

Table 1: Derivatives of benzotriazoles tethered with isoniazid

Compounds	R1	R2
BVSA1a	H	H
BVSA1b	NO2	H
BVSA1c	Cl	H
BVSA1d	F	H

Table 2: Molecular docking scores of benzotriazole derivatives with anti-fungal protein 14-alfa-demethylase

Compounds	Docking scores with 14-alfa-demethylase(5V5Z)
BVSA1a	-8.3
BVSA1b	-7.6
BVSA1c	-9.2
BVSA1d	-7.4
Standard (Fluconazole)	-8.0

2D interactions of benzotriazole derivatives tethered with isoniazid against 14-alfa-demethylase

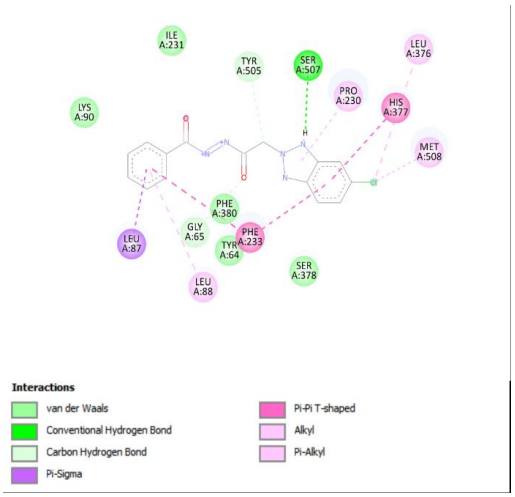

Fig. 2: Interaction of BVSA1c with 5V5Z

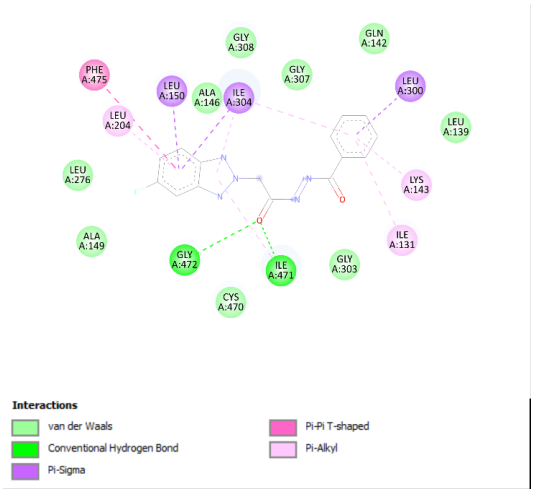

Fig. 3: Interaction of BVSA1d with 5V5Z

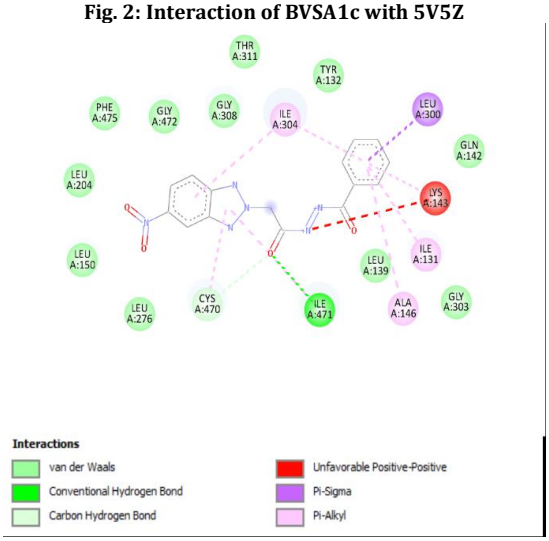

Fig. 4: Interaction of BVSA1b with 5V5Z

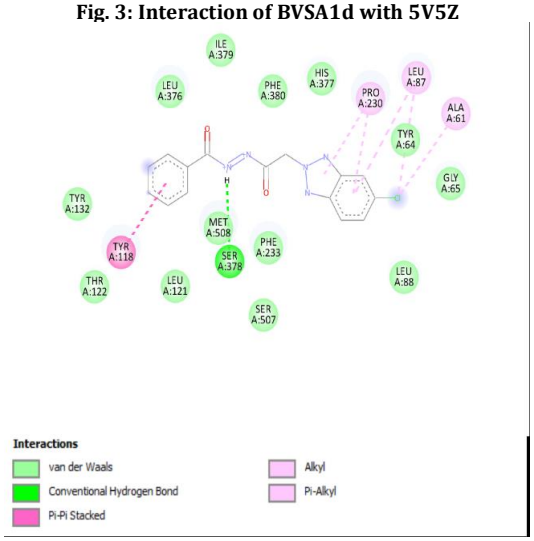

Fig. 4: Interaction of BVSA1a with 5V5Z

ADMET studies were carried out using Swiss ADME website. According to Lipinskis rule of five an orally active compound should have less than two violations, and the parameters are shown in the following table III

Table 3: ADMET studies of benzotriazole derivatives tethered with Isoniazid

Compounds	Molecular weight	Hydrogen bond acceptor	Hydrogen bond donor	Molar refractivity
BVSA1a	295.30	4	2	79.12
BVSA1b	340.29	6	2	87.94
BVSA1c	329.74	4	2	84.13
BVSA1d	313.29	2	2	79.07
Drug likeliness	<500	<10	<5	40-130

In conclusion, Molecular docking studies for benzotriazole derivatives tethered with isoniazid was carried out against 14-alfa-demethylase (PDB ID: 5V5Z) and chloro derivative of benzotriazole exhibited good binding affinity with a docking score of-9.2,which is higher than the commercially available anti-fungal drug Fluconazole (-8.0). ADMET properties have shown zero violation from Lipinski rule of five. Hence the chloro derivative can be considered as a potential molecule for antifungal activity.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

We hereby declare that there is no conflict of interest.

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