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Designing of New Benzotriazole Analogs using Molecular Docking Studies against Receptor 1EA1.Pdb & 1IYL.Pdb for Treatment of Fungal Infection

Mohammad Rizwan Khan[1], Love Kumar Soni[2], R.K. Nema[1], Neelam Balekar[3]

[1]Lakshmi Narain College of Pharamcy (RCP), Indore MP India 453331

[2]School of Pharmacy, DAVV, Indore MP India 452012

[3]IPS Academy College of Pharmacy, Rajendra Nagar, Indore MP India 452012

ABSTRACT

Infectious diseases raise consciousness of our global liability and the aptitude of mankind to prepare medicinally significant molecules during the past century has lead to decrease in the mortality rate from numerous infectious diseases. Benzotriazole derivatives have showed activities like antibacterial, antifungal, antiviral, antiprotozoal and anthelmentic action. These investigations propose the option of emerging a lead compound of benzotriazole having a potential antifungal activity. Molecular docking simulation based virtual screening with ligand library having benzotriazole derivatives have been performed to identify possible lead molecules to inhibit 1EA1.pdb & 1IYL.pdb receptor for treatment of fungal infection. Further the docked conformation of ligand should be perfectly overlayed with the crystal structure of the downloaded protein. This testing is completed successful and the docked confirmation of the fluconazole is perfectly superimposed with reference structure of fluconazole used by the Autodock docking algorithm.

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INTRODUCTION:

Infectious disease are of major concern now a days as the infectious diseases are responsible for more than 9.5 million deaths people around the world. Infectious diseases are also destructive to the health of adults, causing disability, a diminished quality of life, decreased productivity or death. Co-infection is also a matter of great concern as people infected with one infectious disease become more susceptible to other diseases. Examples include: HIV/AIDS co-infection with tuberculosis or malaria. Treatment of these infections with rapid development of resistance in organisms has added fuel to worsened situation.

Recent study showed that several benzotriazole and 1,2,4-triazole derivatives represented an interesting class of heterocycle and became the most rapidly expanding group of antifungal compounds with the advantage of low toxicity, high oral bioavailability and broad spectrum activity. Moreover, a variety of benzotriazoles have been reported to inhibit the growth of some microorganisms and some benzotriazole derivatives show anti-inflammatory properties. Benzotriazole moiety has distinct property on biological system as antifungal, antibacterial, diuretics etc. Benzotriazole, benzimidazole and Imidazole moiety and to screen their diverse activity like antifungal, anti-inflammatory and antimicrobial activity. Tuberculosis is also the top most cause for the death of HIV-infected individuals, as immune compromised HIV-infected individuals are highly prone to get infected with *Mycobacterium tuberculosis* bacteria [1]. Multi drug-resistant tuberculosis (MDR-TB) plus resistance to a fluoroquinolone and at least one second-line injectable agent, such as amikacin, kanamycin and/or capreomycin, is called extensively drug-resistant TB (XDR-TB) [2-3].

MATERIALS AND METHODS:

The compounds were designed on the basis of virtual screening and quantitative structure activity relationship studies.[4] The designed benzotriazole compounds was validated by molecular docking simulations using Molegro as docking tool on various receptor model like 1EA1.pdb and 1IYL.pdb obtained from Brookhaven Protein Data Bank (http://www.rcsb.org/pdb).

Molecular docking simulations of designed compounds

All the calculations were carried out by using *Molegro* as docking tool. The visualization and other programs necessary for docking studies were performed out by means of *Pymol*, *Chimera*, *DS visualizer*, *MMP Plus*.

Docking of MTCYP51 complex

Docking studies was performed with crystal structure (1EA1 & 1IYL) of protein consisting of receptor associated with bound ligand for antifungal activity of the designed compounds.

Crystal structure of 1EA1 & 1IYL.pdb

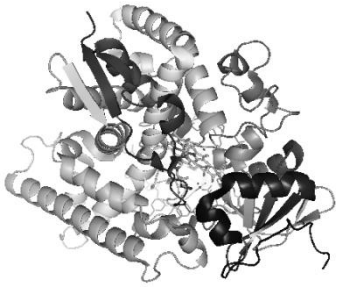

Figure 1: Crystal structure of 1EA1.pdb

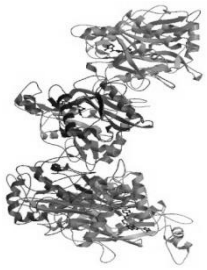

Figure 2: Crystal structure of 1IYL.pdb

Processing of Protein

Receptor Preparation**:** The X-ray crystal structures of (1EA1.pdb & pdb id: 1IYL) was obtained from Brookhaven Protein Data Bank (http://www.rcsb.org/pdb). Chain A of 1IYL.pdb was selected for docking by parsing the protein structure in *Chimera* (UCSF, CA, USA).

Ligand: The ligand is separated from the receptors1EA1.pdb & 1IYL.pdb by the means of Chimera software than it was saved as pdb file and then this ligand was docked into receptors using the Molegro program.

Grid Box: The regions of interest used by AUTODOCK were defined by considering grid area by

making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimension (Figure 5).

The crystal structures of the protein consisting of receptor associated with bound ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (1EA1.pdb & pdb id: 1IYL) registered in the Protein data bank was used (**Figure 1 & 2**).

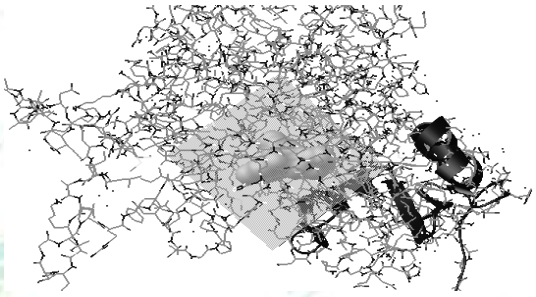

Figure 3: Grid box covering all active sites in receptor

Validation of Docking Process

Internal validation

To ensure that the ligand orientations and positions obtained from the docking studies represent valid and reasonable potential binding modes of the inhibitors, the docking methods and parameters used were validated by redocking the crystallized DCKA and overlaying the docked and crystallized DCKA chemical structures and calculating the rms value.

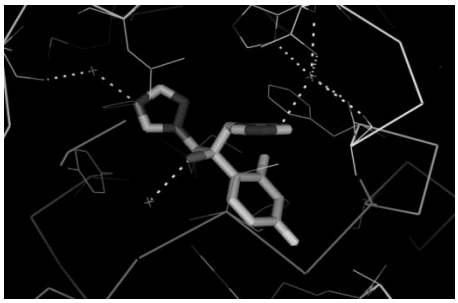

Figure 4: 1EA1- ligand interaction rcsb data base

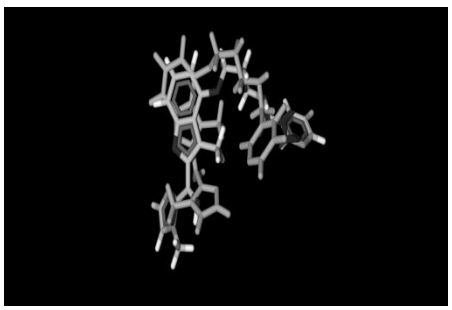

Figure 5: 1IYL.pdb- ligand interaction rcsb data base.

The internal method validation is performed to obtain the orientation of the ligand and fluconazole molecule. Further the designed molecules were validated by taking the overlay of the three molecules i.e. the ligand, fluconazole internal reference and the designed molecule to obtain orientation and position of the site of attachment to give maximum effect.

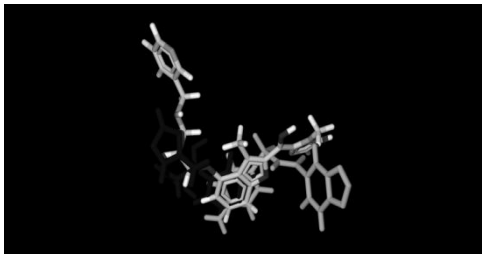

Figure 6: 1IYL.pdb- ligand, fluconazole & designed interaction rcsb data base.

RESULT & DISCUSSION:

Docking Studies

To strengthen the designing of the compounds further the docking studies were performed of the designed compounds. For the docking studies the protein molecule selected for inhibition was 1EA1.pdb and 1IYL.pdb was into consideration. The docking studies were performed using Molgro Virtual Docker (MVD) software. All the compounds as well as fluconazole were docked into the active site of 14a-demethylase which was obtained from Protein Data Bank using molegro virtual docker. Docking score showed that these compounds docked to the active site of the enzyme comparable to fluconazole. All new azole compounds plus fluconazole were characterized by a docking mode in the active site of the cytochrome P450 14a-sterol demethylase.

Table 1: Docking studies of designed compounds.

Comp. No.	Benztriazole Analogs	1EA1.pdb		1IYL.pdb	
		MolDock Score	Rerank Score	MolDock Score	Rerank Score
MRK2	N-(4-chloro-2-nitrophenyl)-1H-benzo[d][1,2,3]triazole-5-carboxamide	-124.826	-102.933	-127.367	-104.427
MRK3	N-(2,4-dinitrophenyl)-1H-benzo[d][1,2,3]triazole-5-carboxamide	-132.387	-100.089	-130.291	-108.232
MRK7	N-(4-aminophenylsulfonyl)-1H-benzo[d][1,2,3]triazole-5-carboxamide	-115.437	-94.3645	-126.319	-107.959
MRK8	N-(2,6-dimethylphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxamide	-119.713	-100.962	-119.246	-99.8017
MRK9	N-(4-nitrophenyl)-1H-benzo[d][1,2,3]triazole-5-carboxamide	-118.428	-96.2889	-122.037	-102.098
MRK11	N-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-chloro-4-nitrobenzenamine	-119.276	-97.7265	-121.333	-102.304
MRK12	N-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-4-chloro-2-nitrobenzenamine	-123.532	-97.9336	-126.359	-102.057
MRK13	N-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2,4-dinitrobenzenamine	-119.554	-96.4469	-130.782	-106.987
MRK19	N-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-4-nitrobenzenamine	-118.188	-95.8836	-130.981	-103.662

CONCLUSION:

There is some correlation between antifungal activity and docking energy. Thus for the compounds MRK02, MRK03, MRK07, MRK09, MRK11, MRK12 and MRK19 show potent growth inhibition and have good docking energy. All of these compounds are found to be active but docking studies shows that compound 3 and 19 are the most active compounds with better biological activity.

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