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Research Article

COMPARATIVE DOCKING STUDY OF M1 PROTEIN (INFLUENZA VIRUS) TO CHECK DRUG EFFICACY

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ABSTRACT

The aim of the study was to analyze and model the 3D structure of influenza virus M1 protein and predicting the most effective drug by targeting the protein. The protein was downloaded from RCSB PDB Databank. Initially it was attached to water molecules. The water molecules were removed from the Protein by using Swiss PDB Viewer. The Structural Assessment of the protein was done using Exome Horizon Software. The Ligands (Amantadine, Rimantadine, Oseltamivir and Zanamivir) were drawn using MolDraw Tool of the Exome Horizon followed by the different information of the Ligands were analyzed. The Protein was finally docked with these four ligands. From the docking study it was observed that the drug rimantadine had the least binding energy and considered as the most effective drug against M1 protein of influenza virus. All work were done using commercial Software Exome Horizon available at Bioinformatics Centre (BIF), Centre for Studies in Biotechnology, Dibrugarh University.

Keywords: Exome Horizon, Molecular Docking, M1 Protein, Drug Efficacy.

INTRODUCTION

Viruses are small infectious agents consisting essentially of nucleic acid (either DNA or RNA) enclosed in a protein coat or capsid [1]. The matrix (M1) protein of influenza A virus is a multifunctional protein that plays essential structural and functional roles in the virus life cycle [2]. It drives virus budding and is the major protein component of the virion [3], where it forms an intermediate layer between the viral envelope and integral membrane proteins and the genomic ribonucleoproteins (RNPs) [4]. The binding is not specific to any RNA sequence, and is performed via a peptide sequence rich in basic amino acids as a result It shows multiple regulatory functions, by the interaction with the components of the host cell [5]. The mechanisms regulated include a role in the export of the viral ribonucleoproteins from the host cell nucleus, inhibition of viral transcription, and a role in the virus assembly and budding [5]. The protein has phosphorylation acivity in the host cell [6-7]. The M1 protein has the capacity of forming a layer under the patches of host cell membrane which are very rich with the viral hemagglutinin, neuraminidase and M2 transmembrane proteins [8], and facilitates budding of the mature viruses [2]. The M1 protein has the capacity of forming a layer under the patches of host cell membrane which are very rich with the viral hemagglutinin, neuraminidase and M2 transmembrane proteins [8], and facilitates budding of the mature viruses [2]. Antiviral drugs include M2 inhibitors, which are ion channel blockers (Amantadine and Rimantadine), and the Neuraminidase inhibitors (Oseltamivir and Zanamivir) [9]. Rimantadine is an M2 ion channel inhibitor which specifically inhibits the replication of influenza A viruses by interfering with the uncoating process of the virus [10-11]. M2 inhibitors block the ion channel formed by the M2 protein that spans the viral membrane [12-13]. The influenza virus enters its host cell by receptor-mediated endocytosis. Thereafter, acidification of the endocytotic vesicles is required for the dissociation of the M1 protein from the ribonucleoprotein complexes. After that the ribonucleoprotein particles imported into the nucleus via the nuclear pores. The hydrogen ions needed for acidification pass through the M2 channel which was blocked by rimantadine [13]. So, our work mainly focused the interaction of M1 Protein with the ligands (Amantadine, Rimantadine, Oseltamivir and Zanamivir) try to find the best inhibitor.

MATERIALS AND METHODS

Retrieval of 3D Structure

The 3D structure of the protein was downloaded from RCSB (Research Collaboratory for Structural Bioinformatics), Protein Databank (PDB, http://www.pdb.org). The PDB ID of the selected protein was found to be 1EA3. The Water molecules and ligands attached to the protein were removed by using Swiss PDB Viewer. The Protein was having 157 no. of groups, 2458 no. of atoms and 2479 no. of bonds.

Structural Assessment of the Protein

The protein was sent for structural assessment to Exome Horizon. The Ramchandran Plot, Ramachandran plots for all residue types, Chi1-Chi2 plots, Main-chain parameters, Side-chain parameters, Residue properties, Main-chain bond length, Main-chain bond angles, RMS distances from planarity and distorted geometry were analyzed for input_atom_only [14].

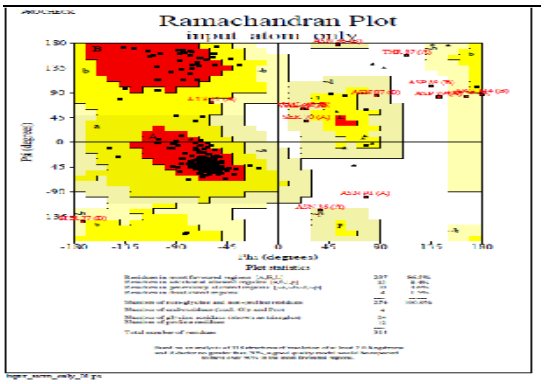
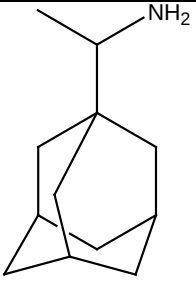
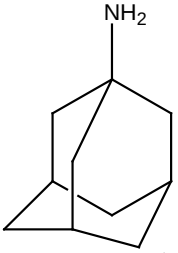
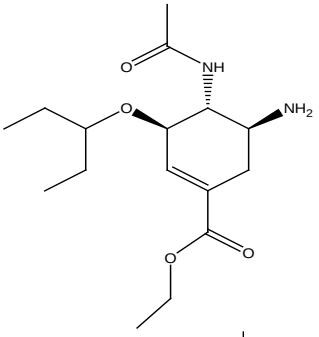
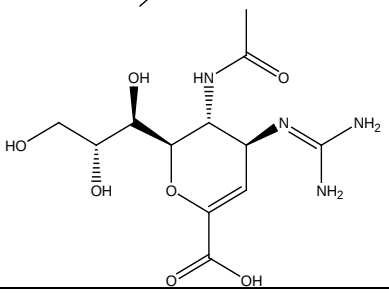


Fig. 1: Ramchandran Plot the refined M1 Protein

Ligand Preparation

The ligands were drawn using Moldraw tool of Exome™ Horizon in 2D and were converted into 3D before submission of docking [15].

Table 1: Name of the Ligands

S. No.	Name of the Ligand	IUPAC Name	Molecular Formula	2D structure
1	Rimantadine	1-Adamantan-1-yl-ethylamine	$C_{12}H_{21}N$	
2	Amantadine	Adamantan-1-ylamine	$C_{10}H_{17}N$	
3	Oseltamivir	4-Acetyleamino-5-amino-3- (1-ethyl-propoxy)-cyclohex-1-encarbocylic acid ethyl ester	$C_{16}H_{22}N_2O_4$	
4	Zanamivir	5-Acetylamino-4-guanidino-6-(1,2,3-trihydroxy-propyl)-5, 6-dihydro-4*H*-pyran-2-carboxylic acid	$C_{12}H_{20}N_4O_7$	

Protein-Ligand Docking Studies

Protein-ligand docking is used to check the structure, position and orientation of a protein when it interacts with small molecules like ligands. Protein-ligand docking aims to predict and rank the structures arising from the association between a given ligand and a target protein of known 3D structure. Protein-Ligand Docking module is further divided into different parts for user convenience like Receptor Preparation, Ligand Preparation, Binding Site Analysis, Dock and Analysis.

Binding Site Analysis

Binding Site analysis is a fast detection program for 'the identification and visualization of possible binding sites and 'the distribution of surrounding residues in the active sites'. The centre of active site was chosen as grid map values for preparation of the grids. The spacing of grid was set to 1.00 ^{0}A and the no. of grid point were taken as 60 x 60 x 60 ^{0}A and protein-ligand docking was performed using Lamarckian genetic algorithm using default parameter [16].

Table 2: Active sites of the Protein

S. No.	Name of Active Site	Residues in Active site	Centre of active site
1	H1	IIPSTIASQLIFHE	21.981, 26.337, 39.706
2	H2	PLNALGNMGAVTTE	13.218, 17.524, 34.706
3	H3	QRLDVKNTDLVL	28.640, 22.302, 15.641
4	H4	DLKEWTRPIAGKN	31.542, 16.497, 29.300

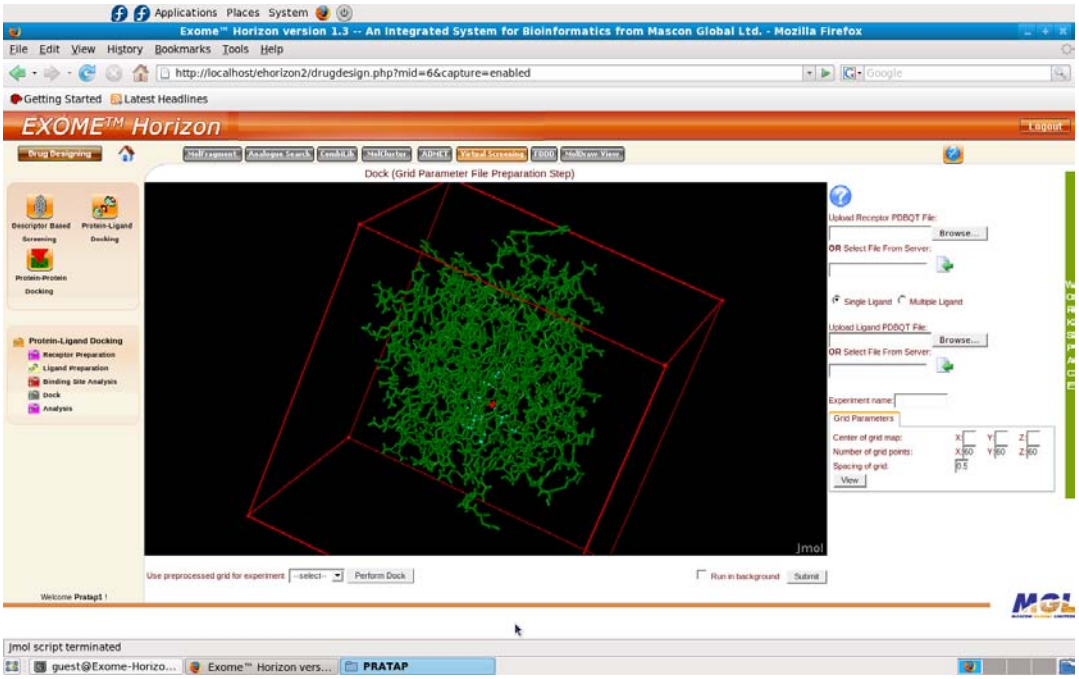


Fig. 2: Grid Preparation of M1 Protein (Bioinformatics Centre, Centre for Studies in Biotechnlogy, Dibrugarh University)

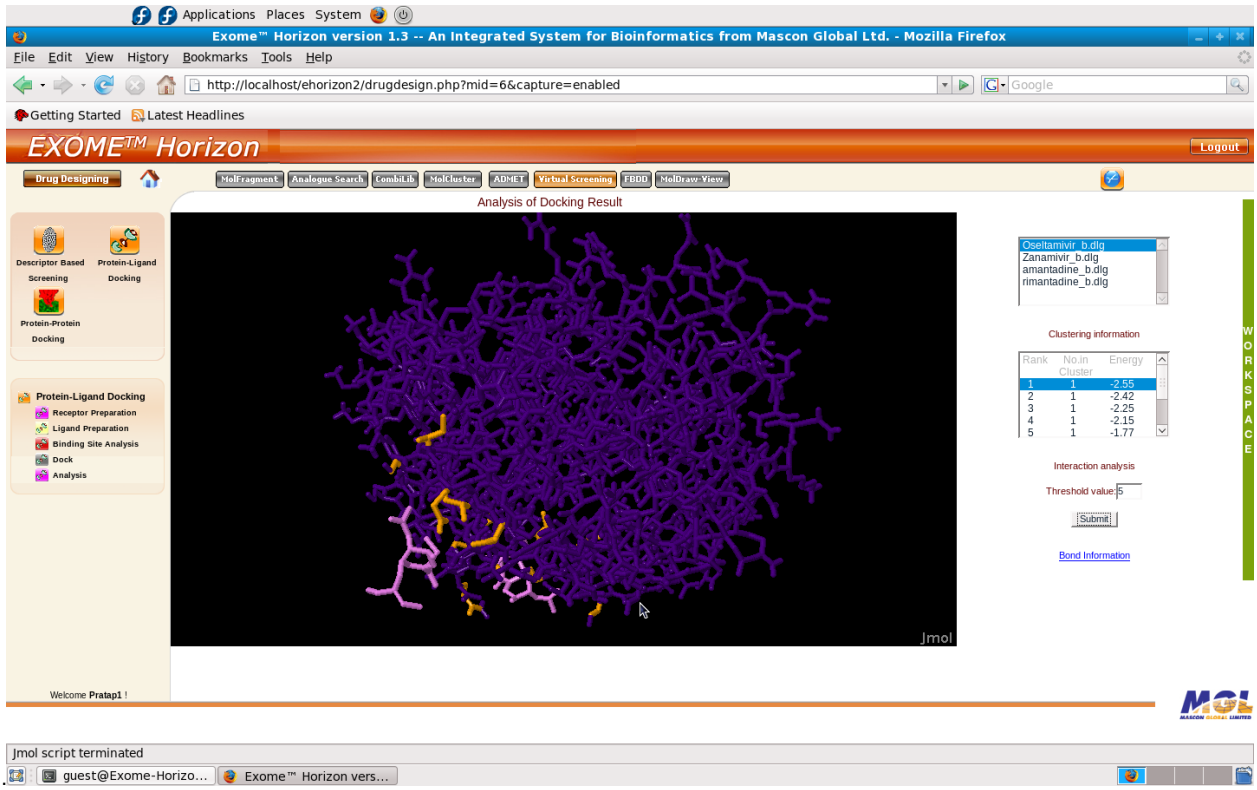


Fig. 3: Docking of M1 Protein with multiple ligands (Rimantadine, Amantadine, Oseltamivir, Zanamivir) in Exome Horizon at Bioinformatics Centre, Centre for Studies in Biotechnology, Dibrugarh University

RESULT AND DISCUSSION

The key result in a docking log file (DLG) are the docked structure or conformation found at the end of each run, the energies of these docked structures and their similarities to each other. The DLG file provides docked conformations, orientations and the binding energies. The similarity of docked structures is measured by computing the root-mean-square deviation (RMSD) between the coordinates of selected molecular conformation with the molecular conformation having lowest interaction energy which is ranked on top.

Clusters are created based on the comparison of conformations using RMSD values. The docking results consist of the PDBQT of the

transformed 3D Cartesian coordinates of the ligand atoms as docked to the receptor molecule [14]. The binding energy of the selected ligands were plotted in the graph and from the graph the binding energy of all the active sites were observed among which the best ligand which shows better activity in all the active site was found to be Rimantadine (Fig:4).

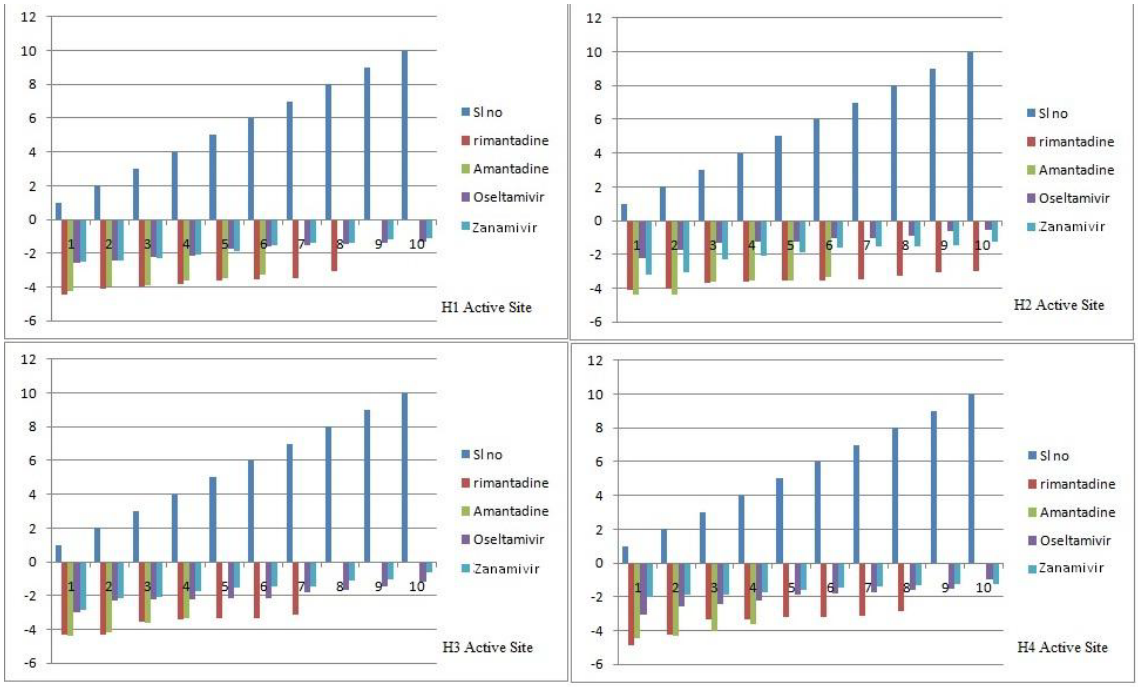


Fig. 4: Rimantadine shows best activity in three active sites (H1, H3 and H4) and Amantadine shows best activity in only one active Site (H2). The energy was measured in Kcal/mole.

CONCLUSION

From the result analysis it was observed that rimantadine shows best activity in three binding site where as amantadine shows best activity in one active site. From these results it was found that rimantadine is the best drug to block the active sites of the M1 Protein.

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