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Screening of Antiviral Therapeutic Ligands against Lassa Virus I Protein by using Autodock

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Abstract

Old world Arena virus (Lassa virus) is belongs to the family *Arenaviridae*, causes Lassa fever and Lassa hemorrhagic fever. In the present study the L protein of Lassa virus is targeted for the screening of antiviral therapeutic ligands. This Lassa virus L protein plays an important role in viral mRNA synthesis. In this study the structure of Lassa virus L protein was retrieved from the RCSB Protein Databank. The unliganded protein structure was docked with several antiviral ligands, and best five selected and analyzed. It was observed that five of screened compounds have the maximum potential against the protein. The analysis was performed on the basis of scoring and binding ability and one of them indicated minimum energy score with high number of interactions with active site residues and the simulation study revealed that this selected ligand could efficiently bind to the Lassa virus L protein. These findings conclude that this selected ligand could be a promising inhibitor of Lassa virus L protein.

Key-Words: Lassa virus, Docking and *Arenaviride*

Introduction

Lassa fever is a hemorrhagic fever caused by Lassa virus (LV), an old-world Arenavirus[1]LASV was first isolated in 1969 from a missionary nurse who worked in a clinic in a small town, Lassa, in northeastern Nigeria[2]. Lassa virus is a segmented negative-strand RNA virus of the family *Arenaviridae*. It belongs to the Old World complex of the arenaviruses, which also includes the prototype virus of the family, lymphocytic choriomeningitis virus (LCMV). Lassa virus is endemic in large areas of West Africa, where its natural reservoir host, the rodent *Mastomys natalensis*[3, 4], is prevalent. Arenaviruses have pleomorphic virions from 40 to more than 200 nm in diameter that consists of nucleocapsid surrounded by a lipid envelope[5]. On electron micrographs the interior of virions shows a characteristic granular appearance due to incorporation of host cell ribosomes in virus particles during assembly[6]. This, yet unexplained, phenomenon was the basis for the family name (arenosus = sandy)[6]. The genome of arenaviruses consists of two single-stranded RNA segments, small (S) and large (L)[6]. Both genomic segments have an ambisense gene organization and encode two genes in opposite orientation[6].

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The L RNA (~7 kb) encodes the viral RNA-dependent RNA polymerase (L) and the small RING finger zinc-binding protein (Z)[6]. The S RNA (~3.4 kb) encodes the glycoprotein precursor protein (GPC) and the nucleoprotein (NP)[6]. GPC is posttranslationally cleaved to yield two envelope glycoproteins GP1 and GP2 and the stable signal peptide (SSP)[6]. The enzymatic machinery for RNA synthesis in arenaviruses is contained within a single L polymerase protein[6]. This 250-450 kDa protein utilizes viral RNA templates that consist of genomic RNA encapsidated by the viral nucleocapsid protein NP and comprises viral ribonucloprotein (RNP)[5]. L polymerase of arenaviruses contains the SDD motif characteristic of all RNA-dependent RNA polymerases (RdRp)[6]. Upon infection, once the virus RNP is delivered into the cytoplasm of the host cell, the L polymerase associated with the viral RNP initiates transcription from the genome promoter[7]. In the present study the antiviral ligands are screened against the L protein of Lassa virus to identify a putative inhibitor for Lassa virus L protein.

Material and Methods

Retrieval of protein structure

The protein structures of Lassa virus L protein was retrieved from RCSB Protein Data Bank[8] in Brookhaven's PDB format and protein cleaning (removal of ligand and water molecules) was done by using Autodock 4.2.1 and UCSF Chimera[9].

Binding site prediction

Binding sites, active sites, surface structural pockets (accessible), interior cavities (inaccessible), shape (alpha complex and triangulation), area and volume (solvent and molecular accessible surface) of each pocket and cavities of proteins were found by using CASTp[10].

Compounds selection & preparation

The pdb files of antiviral therapeutic ligands were retrieved from the drug bank[11].

Molecular docking

Virtual screening of the Ligand-Protein interaction for their binding affinity was carried out using AutoDock 4.2.1[12] and the results that include the understanding of the association that involves H-bonding and hydrophobic interactions were analyzed using LIGPLOT1.4.5[13], a program to generate schematic diagrams of protein ligand interactions.

The search for the best ways is to fit ligand molecules into structure, using Autodock 4.2.1 resulted in docking files that contained detailed records of docking. The obtained log files were read in ADT (Auto Dock Tool) to analyze the results of docking. The similarity of docked structures was measured by computing the root mean square deviation (RMSD) between the coordinates of the atoms and creating clusters of the conformations based on the RMSD values[14]. The lowest binding energy conformation in all clusters was considered as the most favorable docking pose[14]. Binding energies that are reported represent the sum of the total intermolecular energy, total internal energy and tensional free energy minus the energy of the unbound System[14]. The top three ligands were selected based on the energy score after virtual screening.

ADMET properties

ADMET properties of ligands were retrieved from the drug bank[11].

Results and Discussion

Table-1 represents the average seasonal concentrations of air pollutants in the ambient air of sampling site have been computed from the basic data. Result indicated higher **Retrieval of protein structure**

Table 1: Showing details of Lassa virus L protein

Pdb ID	Length (aa)	Resolution
4MIW	178	1.72

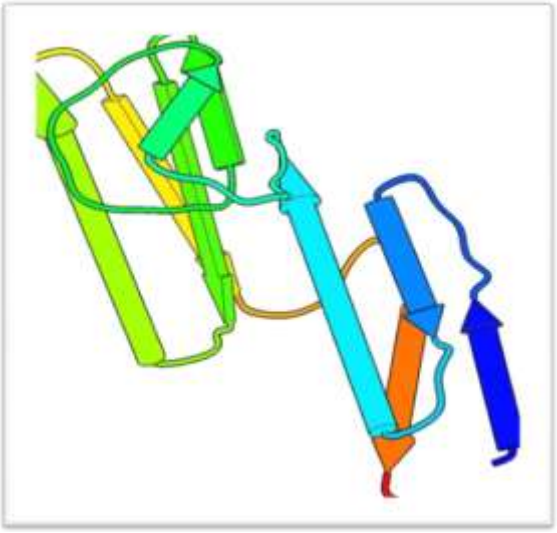

Fig 1: shows the structure of Lassa virus L protein (Pipes and Plank)

Binding site prediction

Binding pockets were calculated by CastP[10] server and selected according to maximum pocket area and pocket volume[15] (Table 2). This pocket contains ARG21, LYS44, LEU48, GLU51, HIS62, ASN63, SER64, ASP66, VAL87, PRO88, and ASP89.

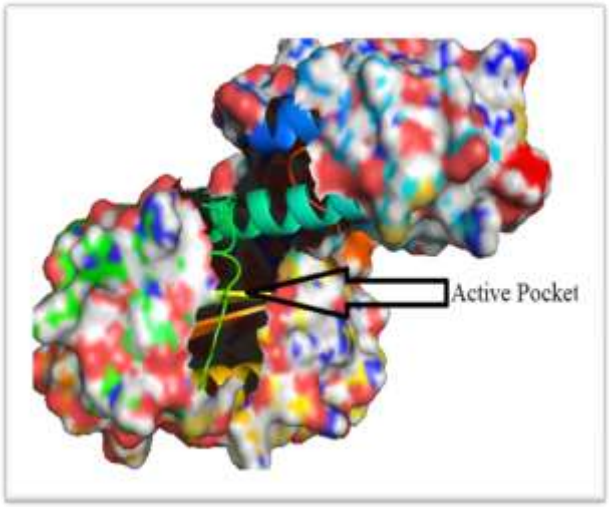

Fig 2: Shows the active pocket of Lassa virus L protein

Molecular docking

From the inspection of ligand molecules, it was found that the RMSD value of the selected five ligands were Zero and the five ligands which showed best value are given in Table 2.

Table 2: shows binding energy and other parameters of ligands.

SN	Ligand	Binding energy	Inhibition constant	H- bonds
1	Abcavir	-4.68 kcal/mol	373.90 uM	4
2	Adefovir Dipivoxil	-2.38 kcal/mol	18.08 mM	2
3	Alpha-Linolenic Acid	-1.71 kcal/mol	55.83 mM	1
4	Capreomycin	-3.14 kcal/mol	5.01 mM	5
5	Cinoxacin	-3.24 kcal/mol	4.22 mM	1

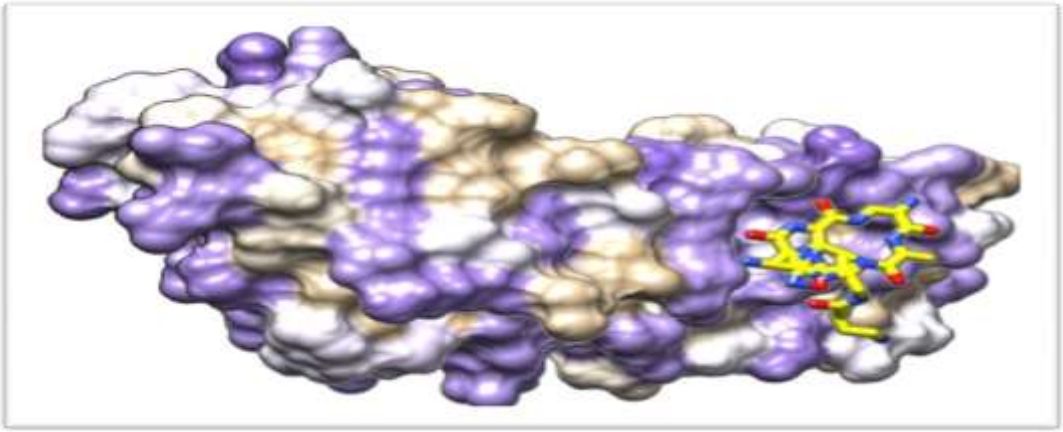

Fig 3: shows Ligand Capreomycin in the cavity of protein

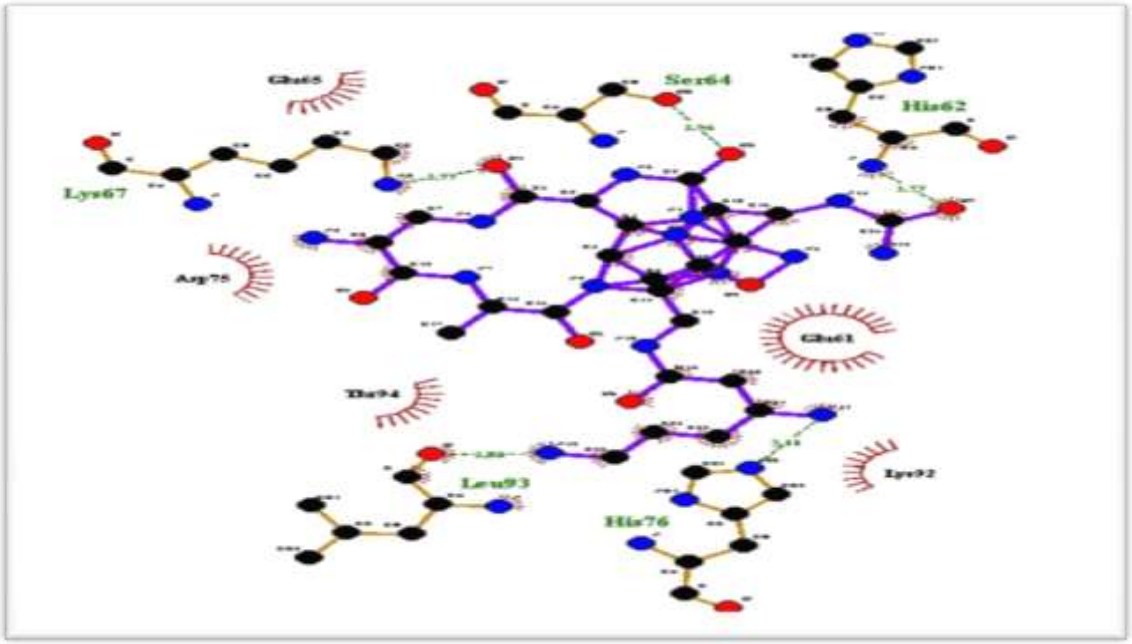

Fig 4: Ligplot image of protein ligand complex shows hydrogen bonds at Lys67, Ser64, His62, His76 and Leu93 between protein and ligand Capreomycin

Table 4: ADMET of ligand Capreomycin from Drug Bank

Property	Value	Probability
Human Intestinal Absorption	+	0.6871
Blood Brain Barrier	-	0.9287
Caco-2 permeable	-	0.6762
P-glycoprotein substrate	Substrate	0.8642
P-glycoprotein inhibitor I	Non-inhibitor	0.742
P-glycoprotein inhibitor II	Non-inhibitor	0.9864
Renal organic cation transporter	Non-inhibitor	0.7924
CYP450 2C9 substrate	Non-substrate	0.6651
CYP450 2D6 substrate	Non-substrate	0.8065
CYP450 3A4 substrate	Non-substrate	0.5716
CYP450 1A2 substrate	Non-inhibitor	0.9053
CYP450 2C9 substrate	Non-inhibitor	0.8828
CYP450 2D6 substrate	Non-inhibitor	0.9196
CYP450 2C19 substrate	Non-inhibitor	0.881
CYP450 3A4 substrate	Non-inhibitor	0.9435
CYP450 inhibitory promiscuity	Low CYP Inhibitory Promiscuity	0.9907
Ames test	Non AMES toxic	0.6035
Carcinogenicity	Non-carcinogens	0.894
Biodegradation	Not ready biodegradable	0.991
Rat acute toxicity	2.5199 LD50, mol/kg	Not applicable

Conclusion

Molecular docking is a key tool in structural molecular biology and computer assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode (s) of a ligand with a protein of known three dimensional structures[15, 16]. Screening studies of these ligands obtained from Drug bank[11] database are docked against L protein of Lassa virus using Autodock 4.2.1 resulted in 5 ligands mentioned in table 2 obtained as best compounds. The present study concludes that the Capreomycin was found to be most active against L protein of Lassa virus.

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