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COMPARATIVE DOCKING STUDY OF M1 PROTEIN OF INFLUENZA VIRUS BY RIMANTADINE AND ITS DERIVATIVES TO EVALUATE DRUG EFFICACY

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Abstract

The goal of this examination is to explore the 3D structure of M1 Protein of influenza virus to check the best medication by focusing on protein. Structure of Protein was downloaded from Protein Databank. Water molecules were attached to that protein structure, were removed by using Discovery studio 4.1 and by using Autodock software. Autodock was used to perform assessment of structure. Ligand Rimantadine was drawn from PubChem Database and made more ligands by modification in Rimantadine by using Discovery studio 4.1 and PDBQT files of ligands made by using Autodock software. Protein was docked with rimantadine and four modified rimantadine ligands. From the Molecular Docking showed that the modified rimantadine drugs had greater binding energy than the rimantadine drug that's why modified rimantadine was considered as the more effective against influenza virus. Autodock and Autodock vina softwares were used to perform molecular docking.

Keywords: M1 Protein, Autodock vina, Molecular Docking, Rimantadine, Discovery studio 4.1, Autodock

Introduction

Viruses are infectious agents consist on nucleic acid which may be DNA or RNA enrapped in a protein capsid or coat. M1 protein is a bifunctional protein which that participates essentially in the functional and structural parts of virus's life cycle. [1] Structural proteins play important role in attaching envelop of virus with the inner DNA or RNA. These perform a critical part in arrangement of virus and relate with the RNP complex in addition to membrane of virus. They are present in many enveloped viruses. Example is the M1 protein of influenza virus which presenting similarity to glycoproteins placed in the host cell membrane on one side and attraction for the RNP complex molecules on other side which makes structure at the membrane of a complex made of the viral ribonucleoprotein at the inner side indirectly related to the viral glycoproteins projecting from the membrane. It causes virus budding, which the main protein component. It makes a middle of the road layer between the viral envelope and vital film proteins and the genomic ribonucleoproteins (RNPs). The coupling is not exact to any RNA grouping that is the reason it is done by a peptide arrangement which is rich in fundamental amino acids and at last thus it shows multiple regulatory functions on account of the relations with the parts of the host cell. [2,3] The components synchronized have work in fare of the viral ribonucleoproteins from host cell core and hindrance of viral transcription and furthermore participates in its arrangement and growing. The protein has appeared to experience phosphorylation activity in the viral cell. The M1 protein makes layer under the patches of host cell film which are exceptionally rich with the viral hemagglutinin, neuraminidase and M2 transmembrane proteins and also facilitates budding of mature viruses. [1,4] M2 protein is proton specific ion channel protein and fundamental in the capsule of influenza A virus. [5] The channel is the homotetramer where the units are helices balanced out by two disulfide bonds and activated by low pH. M2 Protein is encoded on seventh RNA fragment together with the M1 protein. Proton conductance by the M2 protein in influenza A is essential for viral reproduction. [6] Antiviral drug comprises M2 inhibitors that are ion channel inhibitors, that medication is Rimantadine. Rimantidine is an M2 ion channel blocker which is accepted to repress the replication of influenza A viruses by meddling with the decoating procedure of the virus simply like stopping the decoating virus protective envelops which are capsids. [7] M2 inhibitors obstruct the ion channel made by the M2 protein which stretches the membrane of virus. [8] Influenza virus goes into its own cell from receptor-mediated endocytosis by acid activation membrane fusion in endosome then viral ribonucleoprotein particles transferred to the cytosol and separated from the protein M1 and then ribonucleoprotein particles transferred to the nucleus by its pores. Hydrogen ions required for acidification that goes via M2 channel that were obstructed by rimantadine. [9] This study centered the association of M1 Protein with the ligand Rimantadine and modified forms of Rimantadine in order to locate better inhibitor.

Materials and Methods

Software Required

1) Discovery studio 4.1
2) PyMOL
3) Autodock
4) Autodock vina
5) MedChem

Protein structure

We needed 3D structure of the M1 protein. We used RCSB Protein Databank to download it. IEA3 was the PDB I.D. for M1 protein. Discovery studio 4.1 and Autodock were used to remove water molecules. M1 Protein has 2458 numbers of atoms, 157 numbers of groups and 2479 numbers of bonds.

Ligand Preparation

The ligand was drawn from Pubchem Database which has CID: 5017. Ligand was Rimantadine and then made more ligands by the addition of different elements in the structure of Rimantadine by using Discovery studio 4.1.

Molecular Docking

Ligand was drawn from Pubchem Database which I selected and saved as SDF file. Ligand opened in a Discovery studio 4.1. Ligand was Rimantadine and then made more ligands by the addition of different elements in the structure of Rimantadine. Structure of Rimantadine modified with Cl at the position of H32, other structure of Rimantadine modified with CH_3 at the position of H30, other structure of Rimantadine modified with OH at the position of H30, then other structure of Rimantadine modified with CH_2OH at the position of H32 and all modifications done by using Discovery studio 4.1 and then all ligands saved as PDB files. Protein was downloaded from Protein Databank as PDB file. Water molecules connected with the M1 Protein were detached by using Discovery studio 4.1 and saved as PDB file. Then modified ligands opened in Autodock software and saved as PDBQT file. Then, M1 Protein opened in Autodock software and made a grid box with number of points in x-dimension 38, y-dimension 44, z-dimension 46 and central grid box values x-center 19.944, y-center 20.111, z-center 30.139 and then saved as PDBQT file. PDBQT file of ligand and M1 Protein opened in vina folder of Autodock vina software and put command to proceed the docking and in the end got result of docking. By using PyMOL, we checked the attachment of ligands with M1 protein in figures.

Results

We downloaded the 3D structure of Rimantadine from PubChem Database. Then we modified the rimantadine structure. When rimantadine modified with Cl at the position of H32 and proceed docking with M1 Protein then the affinity of modified ligand is -5.8 kcal/mol which is equal to the affinity of rimantadine which is also -5.8 kcal/mol. When Rimantadine modified with OH at the position of H30 and proceed docking with M1 Protein then affinity of modified ligand is -6.0 kcal/mol , when rimantadine modified with CH_3 at the position of H30 and proceed docking with M1 Protein then affinity of modified ligand is -5.9 kcal/mol , when rimantadine modified with CH_2OH at the position of H32 and proceed docking with M1 protein then affinity of modified rimantadine ligand is -5.9 kcal/mol and these affinities are greater than rimantadine affinity which is -5.8 kcal/mol. So, modified ligands rimantadine act as best inhibitors against M1 Protein of influenza virus as compare to the rimantadine.

CONCLUSION

The results of this study show that the modified rimantadine has more activity against M1 protein of influenza virus than that of rimantadine. So, it is concluded that modified rimantadine ligands are the best drugs to bind and inhibit the active sites of M1 Protein.

References

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Modification

Table 1: Ligand preparation by modifications in Rimantadine

Ligand Name	Position	Modification
Ligand 1	H30	OH
Ligand 2	H30	CH_3
Ligand 3	H32	Cl
Ligand 4	H32	CH_2OH

Docking Energies

Table 2: Docking energies of different ligands with substrate protein (Pockets 1-9)

Modes	1	2	3	4	5	6	7	8	9
Rimantadine	-5.8	-5.8	-5.7	-5.7	-5.6	-5.5	-5.5	-5.4	-5.4
Ligand 1	-6.0	-5.9	-5.9	-5.5	-5.4	-5.4	-5.4	-5.4	-5.4
Ligand 2	-5.9	-5.9	-5.5	-5.5	-5.4	-5.3	-5.2	-5.2	-5.2
Ligand 3	-5.8	-5.8	-5.7	-5.7	-5.7	-5.4	-5.3	-5.3	-5.2
Ligand 4	-5.9	-5.9	-5.7	-5.6	-5.5	-5.5	-5.4	-5.3	-5.2

ADMET Properties

Table 3: ADMET Properties of Ligands

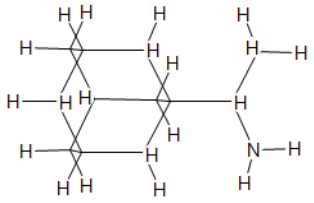
Structure Name	MlogP	S+logP	S+logD	RuleOf5	Rule of 5_Code	MWt	M_NO	T_PSA	HBDH
Rimantadine	3.075	3.083	0.820	0.000	-	179.307	1.000	26.020	2.000
Ligand 1	2.194	1.861	0.428	0.000	-	195.307	2.000	46.250	3.000
Ligand 2	3.347	3.604	1.607	0.000	-	193.334	1.000	26.020	2.000
Ligand 3	3.347	3.418	2.330	0.000	-	213.752	1.000	26.020	2.000
Ligand 4	2.466	2.277	0.608	0.000	-	209.334	2.000	46.250	3.000

Drug Scoring Table

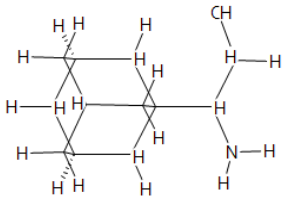
Table 4: Scoring Table of Protein with Ligands

Ligand Name	Ligand Rejection	RMSD	Rank	Score
Rimantadine	0	None	1	-60
Ligand 1	0	None	1	-76
Ligand 2	0	None	1	-70
Ligand 3	0	None	1	-68
Ligand 4	0	None	1	-70

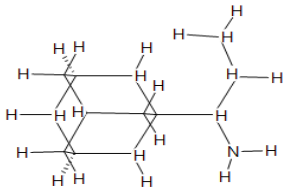
Structures from MedChem



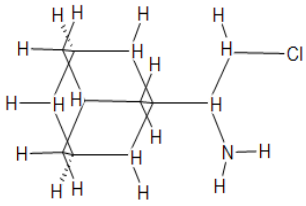
Rimantadine



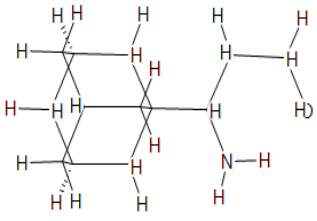
Ligand 1



Ligand 2



Ligand 3



Ligsand 4

Interaction between substrate and ligand

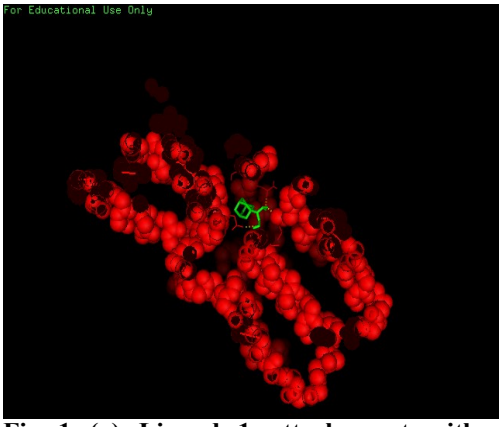


Fig 1 (a) Ligand 1 attachement with protein

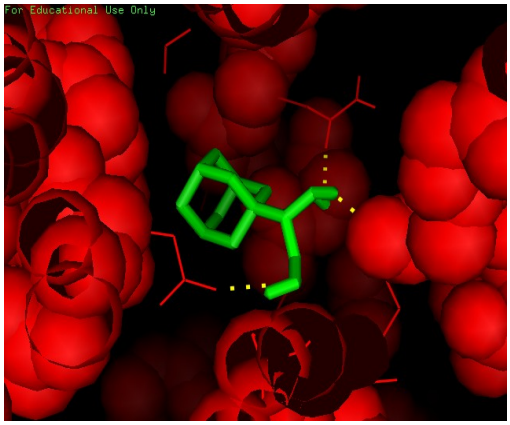


Fig 1(b) Ligand 1 attachement withy protein

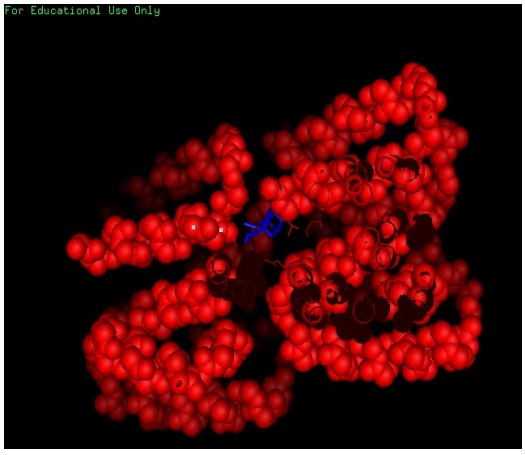


Fig 2(a): Ligand 2 attached with Protein

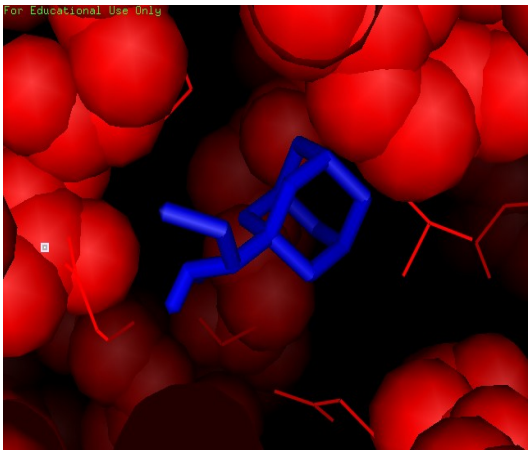


Fig 2(b): Ligand 2 attached with Protein

Fig 3(a): Ligand 3 attached with Protein

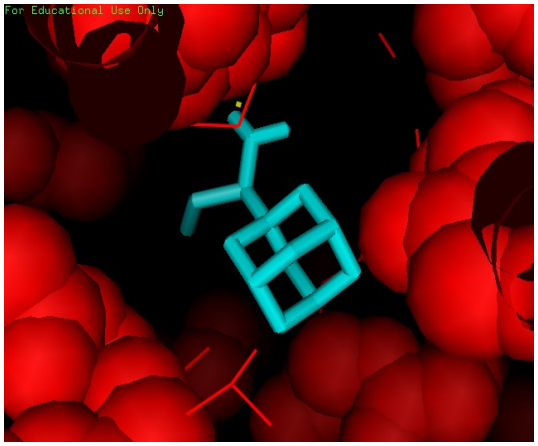


Fig 3(b): Ligand 3 attached with Protein

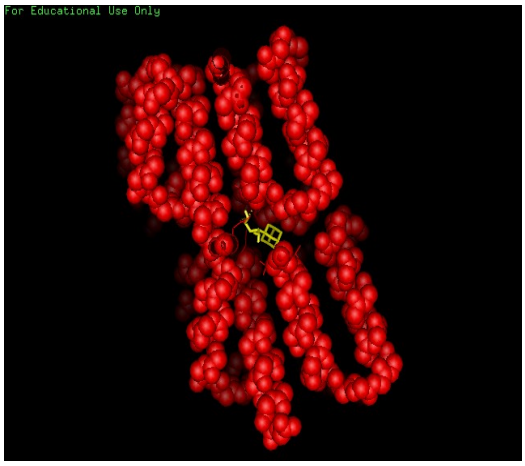


Fig 4(a): Ligand 4 attached with Protein

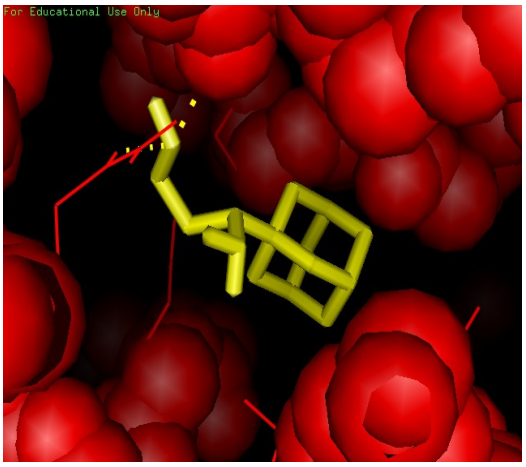


Fig 4(b): Ligand 4 attached with Protein

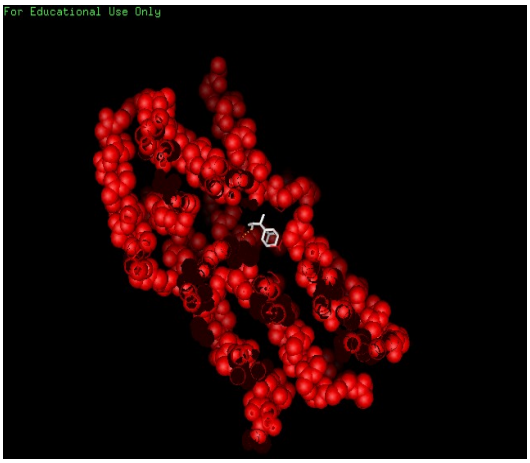


Fig 5(a): Rimantadine attached with Protein

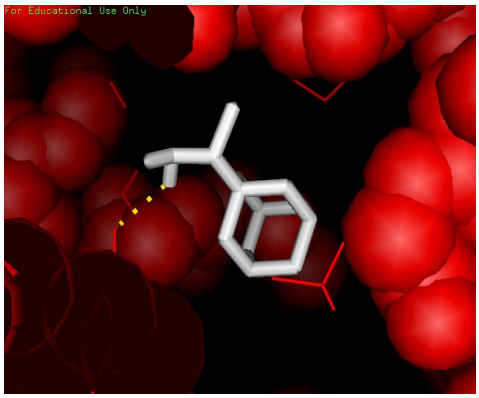


Fig 5(b): Rimantadine attached with Protein