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Molecular screening of some antiviral compounds against four viral diseases H1N1, Chikungunya, Ebola and Dengue

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Abstract-
In last few years H1N1, Chikungunya, Ebola and Dengue epidemic was lethal which was found to be affecting multiple countries including India and till date there is no reported common drug which can be used against these viral diseases. That's why we have designed this study. For this purpose we have selected these four viruses which are responsible for H1N1, Chikungunya, Ebola and Dengue so that we have prepared the 3D structure of their conserved region and then targeted these with the different ligands taken from the pubchem available selected antiviral compounds. This study was performed with the help of homology modeling& molecular docking followed by the multiple sequence alignment of different target sequence to find out a drug to cure H1N1, Chikungunya, Ebola and Dengue with a common medicine.
Keywords: Epidimic, H1N1, Alignment, Conserved.

Introduction

Some human diseases are apparently caused by the body response to virus infection. Viruses cause many diseases of economically important animals and plants, some of them are transmitted by carriers such as insects. Some viruses which infect human like measles, mumps, smallpox, yellow fever, rabies, poliomyelitis, influenza, and the common cold [1]. This Insilco study and molecular modelling are the best computational techniques to identify 3D structure of unknown proteins. There are so many structural proteins of viruses which cause infection in their host but still their structures yet to be identified.

Swine Flu [H1N1]

Influenza A virus causes influenza in birds and some mammals, and is the only species of influenza virus A. Influenza virus is a genus of the Orthomyxoviridae family of viruses. Strains of all subtypes of influenza a virus have been isolated from wild birds, although disease is uncommon. Some isolates of influenza A virus cause severe disease both in domestic poultry and, rarely, in humans [2]. The annually updated, trivalent influenza vaccine consists of hemagglutinin (HA) surface glycoprotein components from influenza H3N2, H1N1, and B influenza viruses [3].

Chikungunya

The chikungunya virus (CHIKV) is an arthropod-borne virus transmitted by *Aedes* mosquitoes that is mostly responsible for acute and chronic articular manifestations [4].Chikungunya is an acute viral disease characterized by fever and painful arthralgia. Chikungunya virus (CHIKV) is a mosquito-transmitted alphavirus belonging to the togaviridae family, first isolated in Tanzania in 1952.The main vectors are mosquitoes from the *Aedes*species[5]. Currently there are no vaccines or antivirals for the prevention or treatment of CHIKV infections. Treatment is symptomatic with analgesics, antipyretics and non-steroidal anti-inflammatory agents. Passive immunization with human IgGderived from CHIKV infected patients has been shown to be protective in mice against CHIKV challenge [6].

Ebola

Ebola virus belongs to filoviridae family. Recently, Ebola outbreak has appeared drastically in West Africa. The 2014 Ebola epidemic was lethal was found to be affecting multiple countries in West Africa. Till date there is no reported host for Ebola infection but it is most likely spread through bats. Still, mankind is struggling to combat this pandemic infection. There is no reported drug in Ebola virus. Therefore are no reported inhibitors for the same [7].

Dengue:

Dengue virus belongs to family *Flaviviridae*, having four serotypes that spread by the bite of infected *Aedes*mosquitoes [8].Dengue is a systemic viral infection transmitted among human by Aedes mosquitoes which was first referred as "water poison" associated with Chinese medical. Dengue viruses (DV) belong to family *Flaviviridae*and there are four serotypes of the virus referred to as DV-1, DV-2, DV-3 and DV-4 [9].

Material and Methodology

Protein and Ligand Preparation-four target protein of H1N1 influenza (Id-A4GC7), chikungunya (Id-Q5WQY5), ebola(Id-Q0518) and Dengue (Id-V5KXU3) were from uniprot database (http://www.uniprot.org/). To identify conserve domain among four target protein these four protein sequence were reverse translated to RNA with the help of EMBOSS server (http://www.ebi.ac.duk/tools/st/) to identify the conserve domains among them. As result we found 1680 nucleotide of Influenenza A virus protein's RNA, 3720 nucleotide of Chickguniya virus protein's RNA, 960 nucleotide of Ebola virus protein's RNA and 10170 nucleotide of Dengue virus protein's RNA were found. Because it was difficult to get the conserved regions from the viral target sequence directly. Library of antiviral compound (ligands) were collected from Pubchem database**.** These ligands are drug like ligands.

Multiple sequence alignment -MSA of four viral protein M-RNA sequences were done to find out the conserved

regions among them, and then conserved region has been translated to its amino acid sequence.

Modelling –The 3 Dimensional structures of proteins were modelled using online server Phyre2. Qualities of generated models were evaluated by Errat 2.0 plot analysis.

Docking Studies and Interaction studies: -All the ligands, (antiviral compound) docked with H1N1 Influenza,Chikungunya, Ebola and Dengue protein in the Software MVD using a genetic algorithm. It predicts Catalyst generated ligand conformations in the protein active site. Standard default parameter settings were used to evaluate the protein- ligand compounds) ligands were collected

under ADMET studies. We have used OSIRIS PROPERTY EXPLORER (10) to check whether they are obeying all the ADMET properties or not. On the basis of bonded and Interactions. We find interactions from MVD in terms of good scoring function and search space. We find active sites from MVD and cross checked with pocket-finder. These nine antiviral from pubchem which act

non-bonded interactions, ADMET properties scoring functions, we can propose a common drug like ligand for these four diseases.

OSRIS PROPERTIES EXPLORER (10) was used to know the mutagenesis, carcinogenesis, reproductively & Toxicity.

Results and Discussion

To propose best ligand as a common druglike to protect/cure these four diseases we have selected these nine ligands which follow the Lipinski rule of five.

inhibitor was done on the basis of non-bonded interaction, ADMET property and scoring functions.

ADMET stands for Absorption, Distribution, metabolism, Excretion and Toxicity, if a ligand follows ADMET properties then its likeness to become a drug molecule increases. Pharmacokinetics & Pharmacodynamics come

Visualization of Docked Complex: -The docked complexes were visualized in MVD showing how the ligand interacts with the proteins.

Best Ligand Selection & ADMET analysis: -Selection of best druglike ligand as a potent

S. No	Ligand Pubchem ID	IUPAC NAME
1	CID_37510	4-acetamidobenzoic acid;9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-3H-purin-6-one;1-(dimethylamino)propan-2-ol
2	CID_3043	9-[5-(hydroxymethyl)oxolan-2-yl]-3H-purin-6-one
3	CID_5726	1-[4-azido-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione
4	CID_20039	[(2S,5R)-5-(6-aminopurin-9-yl)oxolan-2-yl]methanol
5	CID_24066	Zalcitabine
6	CID_35370	1-[(2R,4S,5S)-4-azido-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione
7	CID_50599	9-[(2R,5S)-5-(hydroxymethyl)oxolan-2-yl]-3H-purin-6-one
8	CID_451515	1-[(2R,4R,5S)-4-azido-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione
9	CID_544007	3,5-dichloro-4-cyclohexylsulfanyl-2,6-dimethylpyridine

Table 2– shows the interaction among ligand and proteins. Molecular docking result

S.No	Ligand	H1N1 influenza(A4GCJ7)			Chikunguniya(Q5WQY5)		
		Moledock score	RMSD	Interaction	Moledock score	RMSD	Interaction
1	CID_37510	-86.29	0.14	6	-93.42	0.11	4
2	CID_3043	-88.02	0.14	4	-80.39	0.73	3
3	CID_5726	-97.49	0.2	7	-75.9	0.41	3
4	CID_20039	-97.65	0.13	4	-88.5	0.17	4
5	CID_24066	-70.74	0.3	4	-67.2	0.15	1
6	CID_35370	-82.41	0.03	7	-75.4	0.52	4
7	CID_50599	-84.66	0.19	5	-75.74	0.67	5
8	CID_451515	-80.62	0.98	5	-77.33	0.58	2
9	CID_544007	-81.85	0.22	7	-87.9	0.12	3

Sr.No	Ligand	Ebola (Q05128)				Dengue(V5KXU3)	
		Moledockscore	RMSD	Interaction	Moledockscore	RMSD	Interaction
1	CID_37510	-129.7	0.12	9	40.34	0.04	4
2	CID_3043	-110.7	0.8	3	-67.64	0.071	2
3	CID_5726	-113.5	0.49	6	-57.32	0.02	1
4	CID_20039	-111.05	0.17	5	-66.94	0.59	1
5	CID_24066	-92.46	0.93	6	-49.47	0.059	1
6	CID_35370	-102.6	0.2	6	-55.12	0.031	1
7	CID_50599	-115.74	0.14	5	-67.6	0.13	2
8	CID_451515	-110.8	0.16	3	-49.8	0.1	1
9	CID_544007	-101.7	0.09	6	-57.9	0.16	1

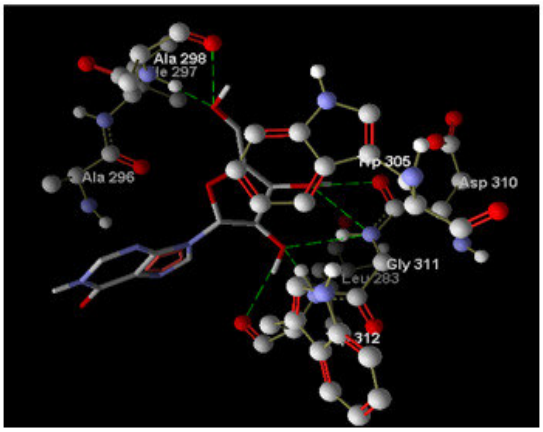
On the basis of moldock score, RMSD and interaction study we have selected only three ligand for further study. The table 3 shows the favorable interaction among ligand and protein. The Isoprinosine show the best interaction results with all target protein which is also clearly understand by the Hydrogen bond interaction and docking view of isoprinosine with target proteins.

Table 3- Ligands which show best docking results with target proteins

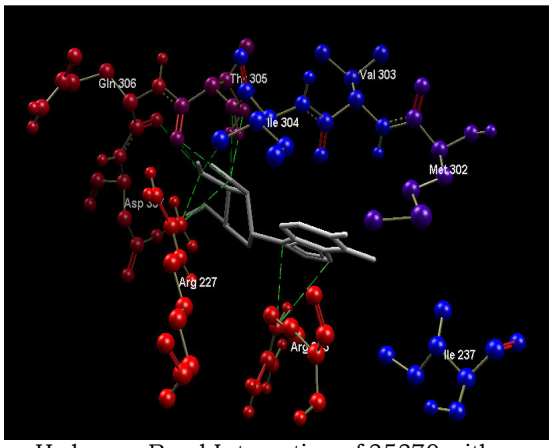
Protein Target S. No.	A4GCJ7 (Hemagglutinin) Ligand		Q5WQY5 (Structural polyprotein) Ligand		Q05128 (Matrix protein VP40) Ligand		V5KXU3 (Genome polyprotein) Ligand	
1	35370	Zidovudine	37510	**Isoprinosine**	544007	3,5-dichloro-4-cyclohexylsulfanyl-2,6-dimethylpyridine	5726	3'-Azido-3'-deoxythymidine
2	20039	2',3'-Dideoxyadenosine	544007	3,5-dichloro-4-cyclohexylsulfanyl-2,6-dimethylpyridine	37510	**Isoprinosine**	35370	Zidovudine
3	37510	**Isoprinosine**	24066	Zalcitabine	20039	2',3'-Dideoxyadenosine	37510	**Isoprinosine**

Table 4 – This Ligand was checked in ADMET (OSIRIS PROPERTY EXPLORE) study and found that it follows ADMET property very well.

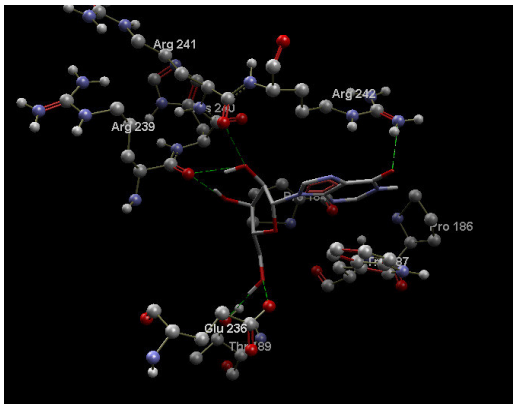
Ligand	clogP	Solubility	DrugLikeness	Drugscore	Mol Weight
37510 Isoprinosine	**-2.3815**	**-1.969**	**1.076**	**0.82**	**268.228**



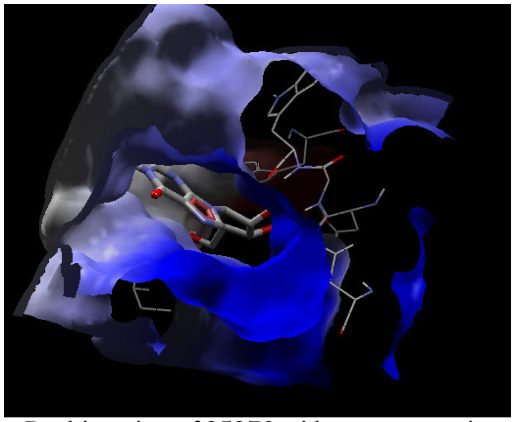
Hydrogen Bond Interaction of 35370 with target protein A4GCJ7



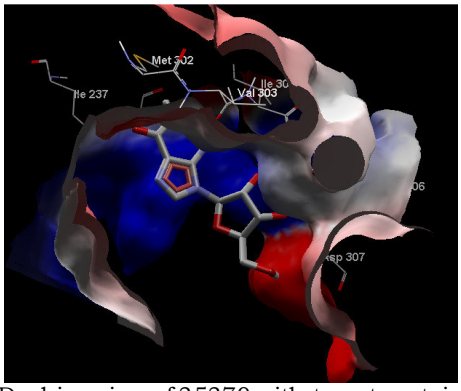
Hydrogen Bond Interaction of 35370 with target protein V5KXU3



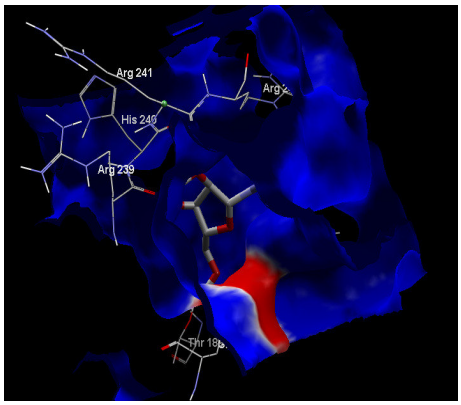
Hydrogen Bond Interaction of 35370 with target protein Q5WQY5



Docking view of 35370 with target protein A4GCJ7 interaction



Docking view of 35370 with target protein Q5WQY5 interaction



Docking view of 35370 with target protein Q05128 interaction

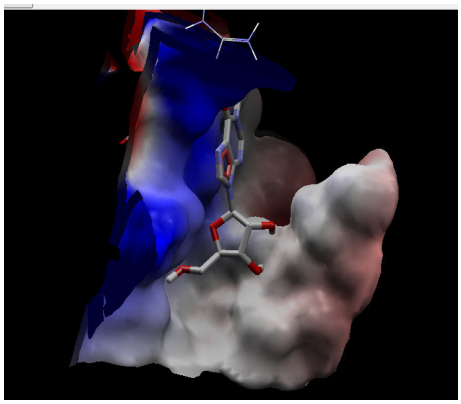

Docking view of 35370 with target protein V5KXU3 interaction

Figure : Molecular dock score and hydrogen bond interaction of ligands with four different target proteins

As this proposed ligand showing optimum Lipinski properties for selection of chemical compound as drug. Isoprinosine is a bioactive compound showing good interaction and following ADMET property, so on the basis of above result it can be used as a common potent and active inhibitor against these four viral diseases.

Conclusion

Drug discovery process is a very important and crucial for the selection of chemical entity which has potential to act like drug against specific target. As per our interaction studies of antiviral compounds with H1N1 influenza(A4GCJ7), Chikunguniya(Q5WQY5), Ebola (Q05128), Dengue(V5KXU3), only three ligands of different target proteins were found to be stable on the basis of moledock score and also found promising in protein-ligands interactions.

On the basis of our study CID_37510 is quit promising at all ADMET properties so we may conclude that CID_37510 is best drug like ligand and can be used as a common drug against all these four diseases.

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