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DEVELOPMENT OF COMPUTATIONAL MODEL FOR EBOLA VIRUS USING PYRROLIDINONECOMPOUND

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Abstract-Ebola virus disease (EVD),also known as Ebola haemorrhagic fever frequently causes death in humans. This is an most deadliest disease which is found in both human and non-human primates with mortality rates up to 90%.The high mortality rate is due to lack of vaccines and antivirals. In the recent years some drugs or vaccine for the Ebola virus had been developed. But still there is no proper treatment found.Here viral protein(antigen) which affects the collagen protein in the human body, which is one of the main structural protein found in skin and other connective tissue is taken.The study mainly focusescomputational models of nine co-crystal structures of pyrrolidinone inhibitors which bound to the viral protein 35 (VP35) to understand the affinity of pyrrolidinone inhibitors on the viral protein 35 (VP35) protein.There is very less information regarding the finding of Ebola virus inhibitor,which may be due to the lack of details on Ebola drug target ,binding siteand mechanism of action of the virus. Computational methods are used to study the interaction of drug and inhibitor of Ebola virus. These computational models which may provide better understanding about the molecular features are responsible for the activity against Ebola virus.This work mainly focuses on the Ebola virus inhibitor and drug which will help for the further studies.
Keywords- Ebola,Collagen,Pyrrolidinone,Inhibitor.

1. INTRODUCTION

Ebola virus disease is also known as Ebola haemorrhagic fever or Ebola.The Ebola disease was found on 1976 in Africa[1].It is a viral fever caused by Ebola virus.There are five types of Ebola virus are i.eZarieebola virus ,sudanEbola virus,Tai forest Ebola virus,Bundibugyo Ebola virus and Reston. The disease was first found in a village which is near the river called Ebola,from this the disease got its name as Ebola.The virus belongs to the family Filoviridae of the order Mononegavirales.The virus is only 0.2 micron in its length which requires the electron microscope for its study. Like many other viruses, Ebola virus contains a negative-sense, and single-stranded RNA which encodes seven different proteins[2]. Those includes the nucleoprotein (NP), virion proteins (VP24, VP30, VP35, andVP40), polymerase protein (L), the transmembrane glycoprotein (GP) and a soluble glycoprotein[3].The disease is spread through animal to human or human to human by the direct contact through the damaged skin of patient or mucous membranes with blood,secretions,organs or other body fluids of infected people and materials like when people share the clothes or sexual contact. It is also transmitted through air or water.In Africa it spreads as a result of close contact of humans with infected bat or chimpanzees [4].The virus attacks every part of the body except bones and skeletal muscles.Symptoms starts within two days and includes fever,sore throat,muscular pain, head ache, vomiting,diarrhea and rash found on body along with this liver and kidney stop its working slowly. During this time the infected person bleeds both externally and internally which leads to death.For the entry of the Ebola virus into the human body the virus requires the npc1 receptor.Niemann-Pick disease, type C1 (NPC1) is a membrane protein that mediates intracellular cholesterol trafficking in mammals. In humans it is encoded by the *NPC1* gene.The virus enter is pacified through virus protein glycoprotein(GP),which attaches the viral particles to cell surface[5]. Figure 1 shows Ebola virus and in Figure 2 how this disease is transmitted is depicted through a figure.

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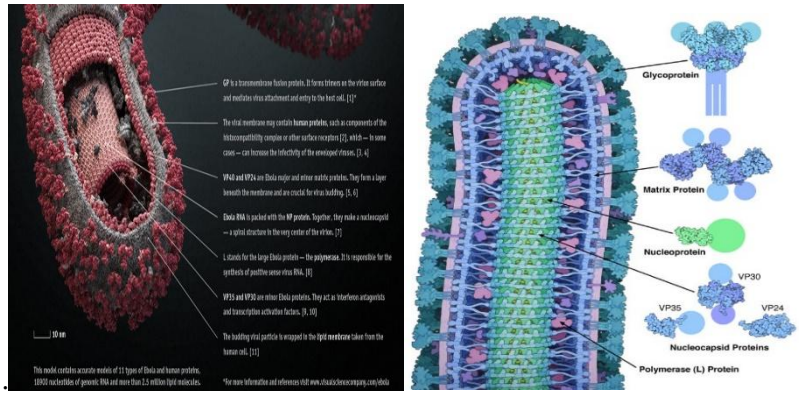

Figure 1:Ebola virus

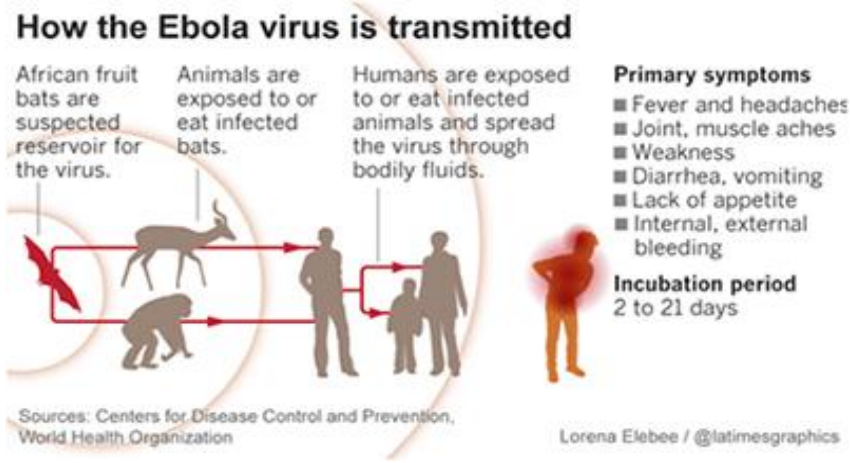

Figure 2:Ebola virus transmission.

2. METHODOLGY

A common feature pharmacophore for FDA-approved drugs inhibiting the Ebola virus.This paper shows the experimental results of how drug compounds are active against Ebola virus disease.They have discussed about the role of pyrrolidinone against Ebola virus disease. Experimental results has shown that the nine co-crystal structure of pyrrolidinonehas bound to the vp35 protein. The pyrrolidinones bind to an alpha helix which is proposed as important for viral function[6].

PDB ID 4IBI was used for docking by using the hex software. Receptor-ligand for the VP35 protein were generated from crystal structures of 4IBB, from the protein data bank PDB.Here computational methods was carried out for understanding the binding properties of viral protein vp35 and pyrrolidinone molecule.

Docking process was carried out using the software Hexv8.0[7]. Here we have done 5 successful models,of which the best one was choosen for the further studies.The receptor and ligand was clustered by the energy, where the correlation was skin plus shape. Once docking process was done,pymol software was used for the visualization.

PyMOL is an open-source tool to visualize molecules available from (www.pymol.org) [8]. Theprocess of validation of the model was done through choosing the best by analysing the interaction of protein and drug molecule.

3.RESULT

The binding site of the pyrrolidine which binds to the alpha helix of viral protein vp35 which gives the different parameter has been shown in the below table.

Table 1- Different paramaters for binding site of the pyrrolidine

	Cluste	Solution	Models	H-bonds	Bumps	RMS	Etotal	Eshape	Eforce	Eair
Model 1	1	1	0:0	-1	-1	-2.00	-88.17	-88.17	0.00	0.00

3.1 Admet Property--

SwissADME a free web tool was used to calculate the Pharmacokinetics, drug-likeness, Medical Chemistry of pyrrolidinonemolecule[10].

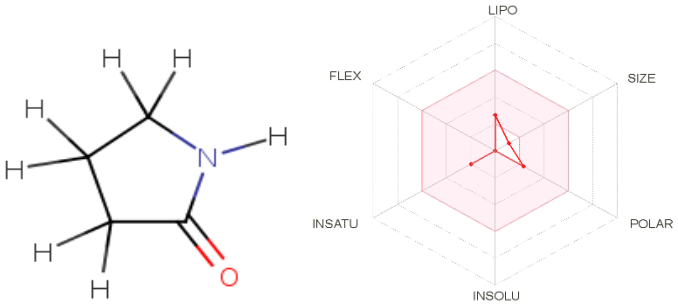

Fig 3.The pink area represents the optimal range for each properties (lipophilicity: XLOGP3 between −0.7 and +5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 $Å^2$, solubility: log *S* not higher than 6, saturation: fraction of carbons in the sp3hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. In this example, the compound is predicted not orally bioavailable, because too flexible and too polar.

Table2-The physiochemical property of the pyrrolidinone molecule

Formula	C4H7NO
Molecular weight	85.10 g/mol
Num. heavy atoms	6
Num. arom. heavy atoms	0
Fraction Csp3	0..75
Num. rotatable bonds	0
Num. H-bond acceptors	1
Num. H-bond donors	1
Molar Refractivity	26.14
TPSA	29.10 Å²

Table 3-Liphophilicity

Log Po/w (iLOGP)	Log Po/w (XLOGP3)	Log Po/w (WLOGP)	Log Po/w (MLOGP)	Log Po/w (SILICOS-IT)	Consensus Log Po/w
1.06	-0.85	-0.48	-0.31	1.11	0.10

Table 3 shows (Partition coefficient between n-octanol and water, iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT are five different freely available predictive models to calculate Lipophilicity).

Table 4-Water Solubility

Log S (ESOL)		Log S (Ali)		Log S (SILICOS-IT)	
Solubility	1.25e+02mg/ml;1.47e+00 mol/l	Solubility	4.46e+02 mg/ml ; 5.24e+00 mol/l	Solubility	1.29e+01 mg/ml ; 1.51e-01 mol/l
Class	Highly soluble	Class	Highly soluble	Class	Soluble

Table 4shows three different model (ESOL, Ali et al,SILICOS-IT) used to predict the water solubility of pyrrolidinone.

Table 5-Pharmacokinetics

GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
Low	No	no	No	No	No	No	No	-7.42 cm/s

Table 5shows the pyrrolidinonePharmacokinetics calculation of molecule which shows that the GI absorption is low and there is no Blood-Brain Barrier permeability. Pyrrolidinone being a substrate to P-Glycoprotein shows poor absorption and bioavailability. Log Kp (skin permeation value) -7.42 shows that skin permeation is very low which show that administration through skin also fails in delivering the drug. The molecule also acts as a non-substrate to 5 isoforms of cytochrome P450 (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) which is crucial for the elimination of drug from the body. The overall result obtained signifies that the oral drug administration is not of much use, which leaves the intravenous administration of pyrrolidinonethe better option.

Table 6-Druglikeness

Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
Yes; 0 violation	No; 4 violations: MW<160, WLOGP<-0.4, MR<40, #atoms<20	yes	yes	No; 2 violations: MW<200, #C<5	0.55

Table 6 shows pyrrolidinone The fact that follow all Five Lipinski rule is a favourable chance for the use of the molecule as a drug.

Table 7-Medicinal Chemistry

PAINS	Brenk	Leadlikeness	Synthetic accessibility
0 alert	0 alert	No; 1 violation: MW<250	1.00

Table 7shows PAINS, Brenk which are the two pattern recognition methods allowed for the identification of potentially problematic fragments.

4. CONCLUSION

As mentioned pyrrlidoine is the drug which is bound to the alpha helix of the viral protein vp35. In this paper, we are suggesting that VP35 may be the target based on the overlap of receptor-based pharmacophores and docking into the crystal structure. FDA has already approved drugs that could target this protein-protein interaction. For docking processes we have used the commercially available software. Computational methods are much easier compared to the wet lab experimental methods. We suggest this computational method for the other infectious disease which does not have proper treatment like other virus related to the Ebola.

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