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Exploring the mechanism of Zanamivir as Anti-AIV agent by Molecular Docking and receptor based electrostatic analysis

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ABSTRACT

Neuraminidase inhibitor has been an attractive target for the development of novel anti-influenza drugs. In present work we have carried out docking analysis of Zanamivir with Human Neuraminidase (H1N1) to understand the structural features responsible for their potent anti-Anti-Aiv activity. The analysis reveals that the majority of interactions of Zanamivir are hydrophobic, polar and steric in nature. Zanamivir forms hydrogen bond with the amino acid residues Asp(a)151, Arg(a)118, Arg(a) 371, Arg(a) 292,Glu(a)277, Glu(a)276, Arg(a) 152,Trp(a) 178,Glu(a)227(Figure 4(b)). The present docking analysis reveals that three water molecules directly affect the interaction of Zanamivir with neuraminidase. Field analysis divulge that acetamido group at c-3 position of pyran nucleus is serve as strong electronegative centre (charges -9.88 and -10.18) and act as electron acceptor in Zanamivir neuraminidase H-bond interaction. This can be useful to get alert about the particular part of the field is required for binding.

Keywords: Anti-influenza, docking, Field analysis, Neuraminidase, Zanamivir,

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INTRODUCTION

Influenza is a long-standing health problem causing significant mortality in annual epidemics by infection of the human respiratory system. The worldwide spread of H5N1 avian flu and the recent outbreak of the new type H1N1 human flu have raised public concerns of the global influenza pandemics. Neuraminidase (NA), a glycoprotein expressed on the influenza virus

surface, is essential for virus replication and infectivity by breaking the linkage between the progeny virus from the surface sialo-receptor of host cells. Thus, inhibition of NA by the structure-based strategy has been applied in discovery of anti-influenza drugs1.Currently few drugs are available for AIV treatment. The licensed existing drugs are the zanamivir[2] (1) and oseltamivir phosphate[3] (2) (Fig. 1) as specific neuraminidase (NA) inhibitors.

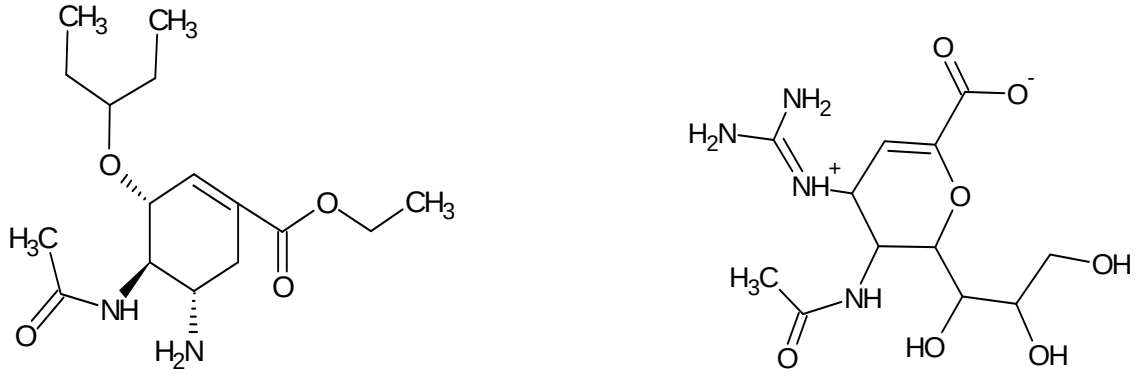


Figure1: The structures of Oseltamivir (1) and Zanamivir (2).

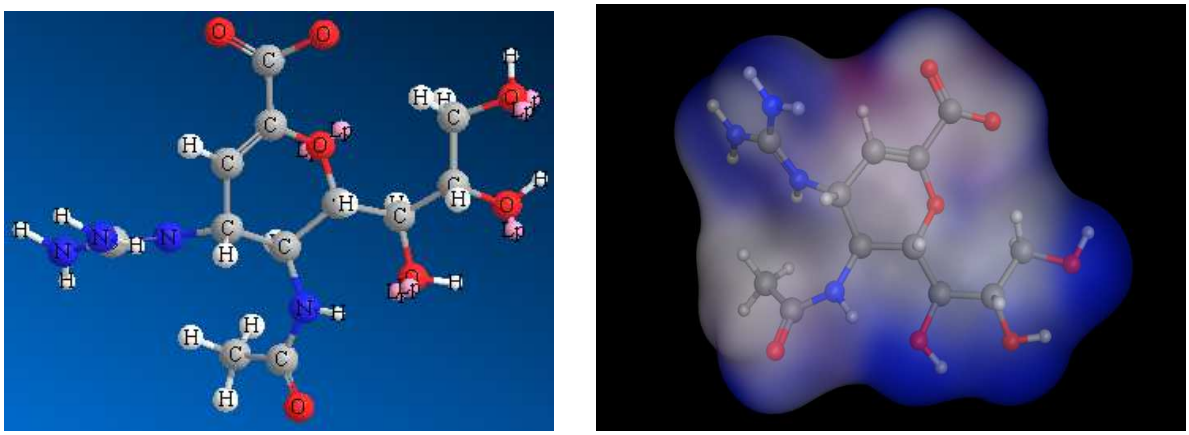
Sixteen subtypes have currently been defined for the hemagglutinin protein (H1-H16) and nine for the neuraminidase protein (N1-N9).[4] The hemagglutinin antigen binds to the sialic acid receptor on the cell surface, which mediates the virus entry. The neuraminidase cleaves the specific linkage of the sialic acid receptor, resulting in the release of the newly formed virions from the infected cells. Additionally, the neuraminidase may function to facilitate the early process of influenza virus infection of lung epithelial cells.[5] Hence, neuraminidase inhibitor has been an attractive target for the development of novel anti-influenza drugs.

Modern drug designing techniques like QSAR, Molecular Docking etc. are widely used to understand the structural features responsible for pharmacological activities of compounds[6]. The in depth understanding can be utilized to enhance the pharmacological properties of organic compounds. In this article we are reporting docking analysis of Zanamivir with H1N1 receptor. The objectives of this work are: (1) to understand structural features responsible for Anti-AIV activity of Zanamivir. (2) to identify the types of interactions involved between Zanamivir with receptor site of H1N1 receptor. (3) to analyze hydrophobic, electronic and steric characteristics of Zanamivir and (4) to explain the role of water in drug receptor interaction.

MATERIALS AND METHODS

Modeling studies:

Molecular modeling study and conformational alignment studies of the Zanamivir were performed in order to rationalize the obtained biological results (Fig. 1). The complete molecular docking studies were performed using human H1N1 crystal structure (PDB ID: 3b7e).



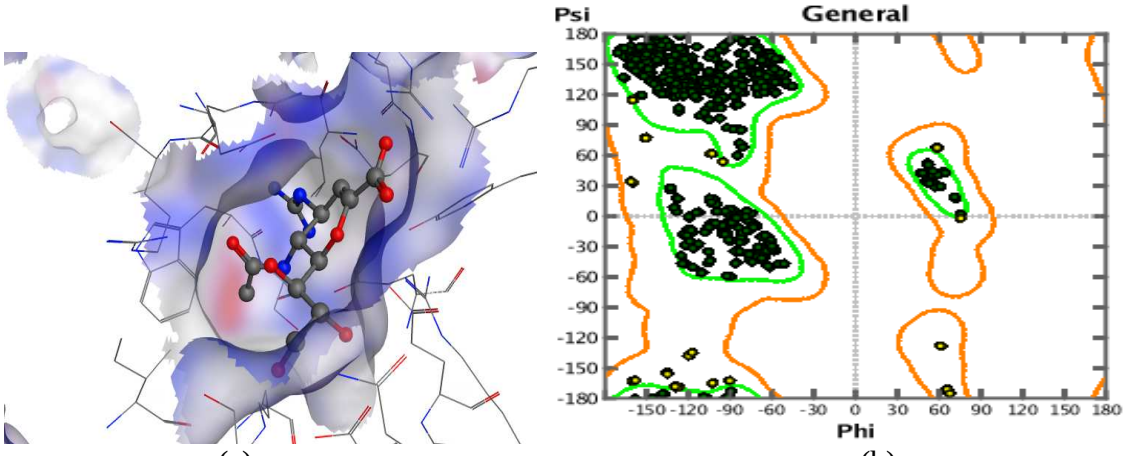
(a) **(b)**

Figure 1. (a) Energy minimized 3D conformation and (b) Molecular surface areas of Zanamivir red= mild polar, blue= H-bonding and white = hydrophobic region.

Experimental Protocol:

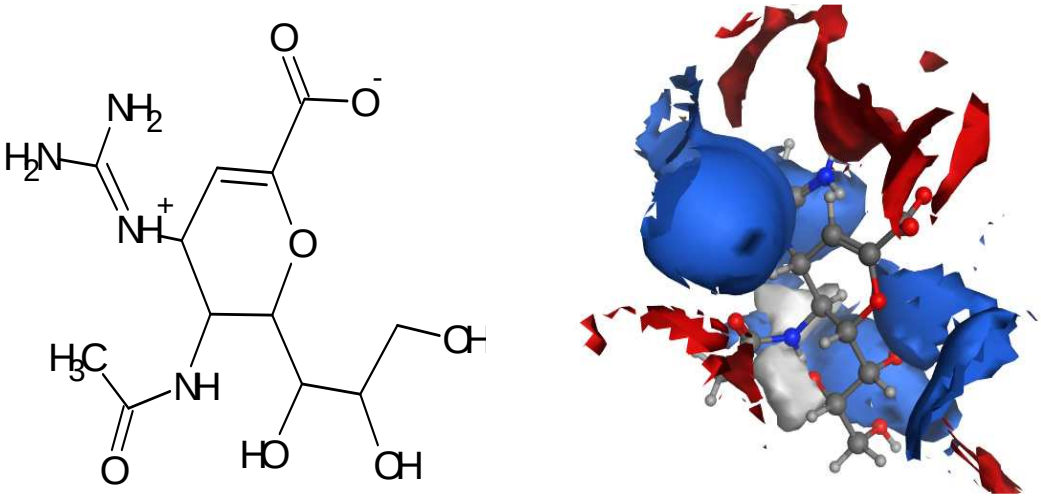
Computer-assisted simulated docking experiments were carried out in human MAO-A crystal structure (PDB ID: 3b7e). Docking simulation study of Zanamivir using Autodock 4.2 with the following protocol.

(1) Enzyme structure was checked for missing atoms, bonds and contacts. Ramchandran plot was plotted to check the health of protein. (2) Hydrogen atoms were added to enzyme structure. Bound ligands were manually deleted from the enzyme. (3) The ligand molecules were constructed using ACD Chem Sketch 12.0 freeware and optimized structure was used for docking. (4) The active site was generated and ligands were docked within the Human H1N1 active site. (5) The lowest energy conformation was selected and subjected to an energy minimization.



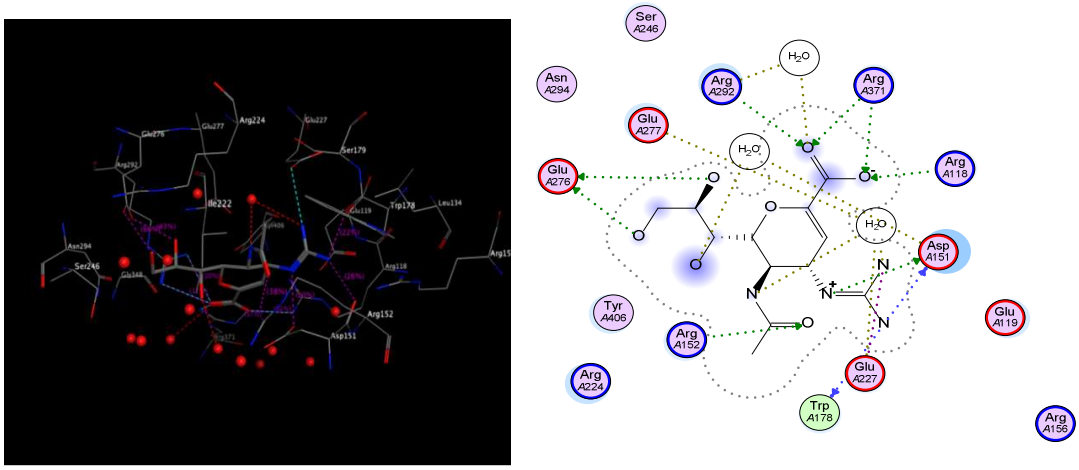
(a) (b)

Figure 2: (a) Docking pose of Zanamivir in the active site of human H1N1 receptor.(b) Ramchandran Plot for pdb 3b7e after energy and residue optimization.



(2*R*,3*R*,4*S*)-3-acetamido-4-guanidino-2-((1*R*,2*R*)-1,2,3-trihydroxypropyl)-3,4-dihydro-2*H*-pyran-6-carboxylic acid

Figure 3: (a) Structure of Zanamivir (b) Receptor based Electrostatics regions in the active site of human *H1N1 receptor. Blue = donor, Red = acceptor and white = hydrophobic regions.*



(a) (b)

Figure.4: (a) Showing % H-bond interaction between Zanamivir and human H1N1 receptor .
(b) Showing various amino acid residue bind to human H1N1 receptor through hydrogen bonding.

Before molecular docking, the 3D structure of ligand was optimized. The pdb 3b7e was subjected to energy and residue optimization. The health of protein was ascertain by plotting Ramchandran plot (Fig. 2).

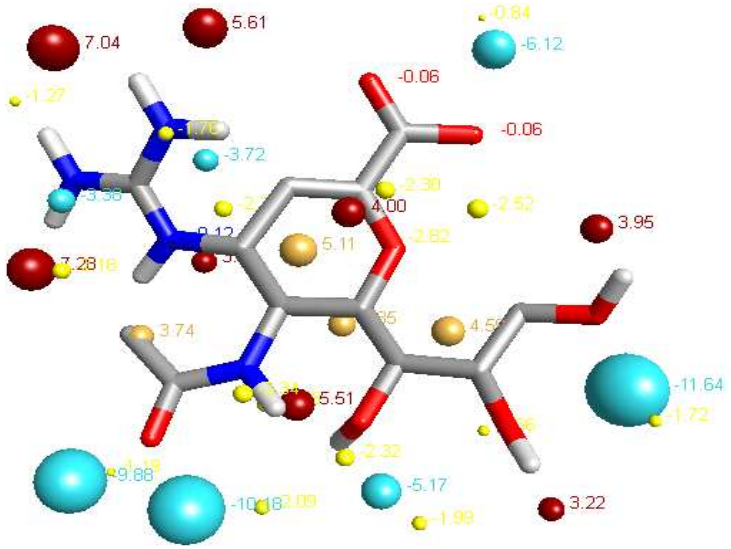


Figure: 5 showing important field points with respective charges in Zanamivir.
Blue*: Negative field points,* ***Red****: Positive field points,* ***Yellow****: van der Waals surface field points (steric),* ***Gold/Orange****: Hydrophobic field points*

RESULT AND DISCUSSION

Molecular docking of ligands with target proteins are routinely and extensively used to reduced cost and time of drug discovery. Docking of Zanamivir into the active site of human H1N1 receptor reveals some interesting facts like Zanamivir intereact with H1N1 receptor through hydrogen bonding ,hydrophobic as well as steric interactions. When Zanamivir dock into the active site of the receptors where it forms hydrogen bond with the amino acid residues Asp(a)151, Arg(a)118, Arg(a) 371, Arg(a) 292,Glu(a)277, Glu(a)276, Arg(a) 152,Trp(a) 178,Glu(a)227(Figure 4(b)). Amino acids like Asp(a)151, Glu(a)277, Arg(a) 292, Glu(a)227 are involved in Zanamivir neuraminidase interaction through water which support the hypothesis of involvement of water and its crucial role in drug receptor interactions (Figure 4(b)).The present docking analysis reveals that three water molecules directly affect the interaction of drug with neuraminidase. Strong drug receptor interaction depends upon % of Hydrogen bonding. The amino acid Arg (a) 371(55-57%), Arg (a) 118 (52%) and Arg (a) (66%) Clarified the above fact and interacted strongly with human neuraminidase through hydrogen bonding. (Figure 4 (a)). To disclose better insight into the Zanamivir neuraminidase interaction, we have carried out field analysis of Zanamivir in order to get better idea about field point and alignment with charges necessary to interact with the neuraminidase (Figure 5). This can be useful to get alert about the particular part of the field is required for binding. Field analysis reveals that acetamido group at c-3 position of pyran nucleus is serve as strong electronegative centre (charges -9.88 and -10.18) and act as electron acceptor in Zanamivir neuraminidase H-bond interaction . Further 1, 2, 3-trihydroxypropyl group at c-2 position serve as strong electronegative centre and played important role in interaction.

Stereospecificity has long been known as being very important for biologically active compounds to exhibit their activity. In particular, it has been believed to play significant roles in the interactions with their targets in vivo as postulated in the classical lock and key theory of

enzymatic reactions as well as in the receptor theory of drugs. Herein Zanamivir interacts with neuraminidase by van der Waal's interaction (Figure 5).

In order to get useful results that may be valuable in future drug designing we carried out receptor based electrostatic analysis also (Figure 3(b)). Acetamido group at c-3 position of pyran nucleus showing strong electronegative field as well as hydrophobic region which reveals that presence of acetamido group is favourable and enhances both electrostatic as well as hydrophobic interaction with neuraminidase.1, 2, 3- trihydroxypropyl group at c-2 position of pyran nucleus showing strong electropositive region indicating presence of electron donor is favourable for Anti-Aiv activity. Guanidine functionality at c-4 position showed characteristic electropositive region which indicate that presence of electron donar enhances the activity. Further carboxylic group at c-6 position showed strong electronegative field which indicate that electron acceptor group is favorable and enhances the drug receptor interaction.

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