A Docking Study of Newly Found Natural Neuraminidase Inhibitor: Erystagallin A

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Abstract

It's a threat for the public health that H1N1 (Influenza virus A) causes disease and transmits among humans. WHO (world health organization) declared that the infections caused by the new strain had reached pandemic proportions. The approved neuraminidase inhibitors (Zanamivir and Oseltamivir) and related investigative drug (BCX-1812) are potent, specific inhibitors of influenza A and B viruses. These drugs are highly effective to prevent influenza A and B infections. Early therapeutic use reduces illness duration and respiratory complications. Recently, we found one of the potent inhibitor of erystagallin A (IC$_{50}$ of 2.04 µM) for neuraminidase target, this inhibitor shows most similar structure to its natural substrate, sialic acid. Therefore, we chose 1l7f to get the receptor structure for docking study among many crystal structures. A docking study has been performed in Surflex-Dock module in SYBYL 8.1. In the present study, we attempt to compare the docking studies of pterocarpin and erystagallin A with neuraminidase receptor structure. In the previous report, the methoxy group of pterocarpin had H-bonding with Arg residues. The present docking results for erystagallin A showed the backbone of hydroxyl group shows significant H-bonding interactions with Arg152 and Arg292. The results showed that erystagallin A interacts more favorably with distinctive binding site rather than original active site. Therefore, we tried to reveal plausible binding mode and important amino acid for this inhibitor using docking and site id search calculations of Sybyl. The results obtained from this work may be utilized to design novel inhibitors for neuraminidase.

Keywords: H1N1, Erystagallin A, Pterocarpin, Docking.

1. Introduction

Neuraminidase is a surface glycoprotein that catalyses the cleavage of an á-ketosidic linkage that exists between a terminal sialic acid, N-acetyl neuraminic acid and an adjacent sugar residue[1]. All neuraminidase structures are very similar even though the sequence identity is only about 30%. It is a tetramer with a molecular mass of about 240 kDa[2]. The active site of neuraminidase, however, is invariant for all strains of influenza virus, and inhibition of the neuraminidase enzymatic activity stops virus infection. It seems that the active site, a deep pocket on the neuraminidase surface, is an ideal target for drug design[3]. Pterocarpins are stress induced low molecular weight antibiotics, protecting plants against fungal infections and pest[4].

Because of their biological activity, Pterocarpins are widely used in traditional medicine as antifungal, antibacterial and anti-inflammatory agents. The main structural feature of Pterocarpans is the presence of fused chromophores and the common backbone of prenyl chain and hydroxy/methoxy groups[5]. Recently, Nguyen et al has reported that erystagallin A is one the potent inhibitor for bacterial neuraminidase. Their studies suggested that an addition of prenyl group, hydroxy and/or methoxy substituent’s were responsible for increase in activity for neuraminidase A and B[6]. The main aim of this present work is to understand about the binding mode and identification of important binding amino acid residues for this particular inhibitor, therefore, we tried computational techniques to obtain possible binding mode for erystagallin A.

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2. Computational Procedure

The choice of receptor structure is very important because neuraminidase is known to exhibit small but significant induced fit effects on ligand binding. Therefore the receptor selection is crucial. In the present work we have chosen a structure (PDB code: 1l7f) among many crystal structures as the receptor structure for docking studies, since the ligand in the neuraminidase seemed to be the most similar structurally to its natural substrate, sialic acid. After careful choice of receptor, the X-ray crystal structure of neuraminidase was retrieved from the RCSB protein data bank. The two pterocarpans were prepared by geometry optimization and partial charge assignments after sketching in Sybyl environments. The ligand, metals and all water molecules were removed from this structure. The hydrogen atoms and Kollman charges were added by using Sybyl 8.1. Rigid docking has been performed by using SurflexDock. SurflexDock uses its own scoring function which is a sort of empirical scoring function. The docking algorithm uses the idealized active site called a protomol. A protomol is a computational representation of the intended binding site to which putative ligands are aligned. The purpose of the protomol is to direct the initial placement of the ligand during the docking process. The protomol was generated based on the ligand inside the active site. Protomol were visualized with Sybyl 8.1 to ensure proper coverage of the desired target area. All parameters were employed with default setting. The docking results shows distinct binding site with favorable interaction other than original active site, so, we used site ID module from sybyl to search the potential binding site in a protein using a grid-based flood filled salvation techniques.

3. Results and Discussion

Figure 2 shows the most active pterocarpin has been docked within neuraminidase (PDB code: 1l7f). In the previous report there were two docked poses. In one docked pose, pterocarpin had H-bonding interactions...
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The present study indicates that terminal methoxy groups interacts another Arg groups (Arg152). Arg292 again interacts with pterocarpin, not through terminal methoxy but through ethereal oxygen on the central five-membered ring. Even though Arg292 interacts in both cases, there is not much overlap between the spaces occupied by

Fig. 3. Docking of erystagallin A with neuraminidase.

Fig. 4. Superimposition of pterocarpin (cyan) and erystagallin A (orange).
pterocarpin. Another highly active compound erystagallin A was docked to neuraminidase (Figure 3). Interestingly, the result shows that methoxy group of erystagallin A was recognized in Arg152 which is consistent with the result of pterocarpin. As shown in Figure 4, the two molecules occupy almost the same space inside the active site. It is interesting to note that they all have H-boding interactions with arginine residues. There is a clear need of further study to identify the exact binding site. Therefore, we used site ID search to find out important amino acid residue for this natural neuraminidase inhibitor. The docking studies revealed the potential binding modes and important binding amino acids for these natural compounds. The information was obtained from the docking study were correlated well with the site ID results, it shows the region surrounding the erystagallin A is probably another active site like an allosteric site. Our results suggested that this interacting amino acid in the active site gives an important clue for designing new therapeutic ligands.

4. Conclusion

We found that erystagallin A seems to have a distinctive binding site. Like the previous results with pterocarpin, it interacts with neuraminidase through Arg residues. Arg152 seemed to involve in pterocarpan analogue recognition. The docking studies revealed the potential binding modes and important binding amino acids for these natural compounds. The information was obtained from the docking study were correlated well with the site ID results, it shows the region surrounding the erystagallin A is probably another active site like an allosteric site. Our results suggested that this interacting amino acid in the active site gives an important clue for designing new therapeutic ligands.

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