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Ligand based virtual screening for identifying potent inhibitors against viral neuraminidase: An in silico approach

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Abstract

Various inhibitors have been developed for neuraminidase but resistance against these drugs in many viral strains makes it an advantageous and interesting task to discover compounds which can be more promising in preventing viral infection through neuraminidase. Virtual screening methods have been proved as an efficient in silico approach for drug discovery processes. In the present study, we used ligand based virtual screening process for identifying potent inhibitors against viral neuraminidase enzyme. The approach utilized in this study has been successful in identifying 15 compounds which may be potential inhibitors of neuraminidase. These compounds were screened via three screening platforms (MVD, PyRx, and FRED) by setting oseltamivir as reference compound, which is an FDA approved drug against influenza virus. These compounds were then filtered by their in silico ADME/T (Absorption, Distribution, Metabolism, Excretion, and Toxicity) values and only 12 of them were found to have comparatively better results. The results of the present study are reported herein so that researchers, who are having required laboratory facilities for synthesizing drugs, can utilize findings of this study for developing new drugs against influenza with better efficacy.

Keywords: Neuraminidase (NA); Haemagglutinin (HA); Neuraminidase inhibitors (NAIs); Molecular docking; ZINC database; Virtual screening (VS); Molegro Virtual Docker (MVD); PyRx; FRED

Abbreviations: VS, virtual screening; HTS, high throughput screening; RC, reference compound; NA, neuraminidase; HA, haemagglutinin; ADME/T, Absorption, Distribution, Metabolism, Excretion, and Toxicity; RMSD, root mean square deviation; APOD, abbreviated profile of drugs; LE1 (ligand efficiency 1), MolDock Score divided by heavy atoms count; LE3 (ligand efficiency 3), Rerank Score divided by heavy atoms count; HA, hydrogen bond acceptor; HD, hydrogen bond donor; MW, molecular weight; LP, lipophilicity; PSA, polar solvent accessibility.

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1. Introduction

Some of the reported worst epidemics in the history of humans have been caused by influenza viruses. Influenza viruses contain two major glycoproteins attached on their surface: haemagglutinin (HA) and neuraminidase (NA). Haemagglutinin helps virus in the attachment and penetration of host cells via sialic acid binding sites [1,2] and neuraminidase enzymatically cleaves bonding between haemagglutinin and sialic acid from cell surface glycoconjugates and thus facilitates the release of progeny virions from infected cells, spreads the new virus particles, and prevents the aggregation of progeny

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virions [3,4]. According to different antigenic properties of haemagglutinin and neuraminidase molecules, influenza type A viruses can be classified into 16 subtypes by haemagglutinin (H1–H16) and 9 subtypes by neuraminidase (N1–N9) [5]. Numerous combinations of haemagglutinin and neuraminidase subtypes have been found in influenza type A viruses on avian species, i.e. bird flu. Among them, H5N1 has received extensive attention in recent years since it has caused a considerable number of human lives worldwide [6].

In theory, both haemagglutinin and neuraminidase can be considered as therapeutic targets for preventing the replication and spread of influenza viruses in host cells. Although the crystal structure of haemagglutinin was already resolved in early 1980s [7], no tightly binding compounds have been discovered for it. As for neuraminidase, many inhibitors with high potencies have been developed. For example, zanamivir and oseltamivir (Tamiflu) are two successful drugs currently in use [8,9]. Nevertheless, resistance against these drugs has subsequently been developed by influenza viruses, still making the development of new classes of neuraminidase inhibitors a significant and urgent task [10,11]. Neuraminidase was chosen as a suitable drug target because NA plays a major role in influenza virus propagation, and the amino acid residues of the active site interacting directly with the substrate or surrounding the central active site of the enzyme are strictly conserved [12].

Virtual screening (VS) is considered as computational approach of high throughput screening (HTS) and refers to the in silico evaluation of properties of different molecular scaffolds including binding affinity, interaction energy, etc. Different applications of machine learning to virtual screening have been presented in the literature including both ligand-based similarity searching and structure-based docking. The main purpose of such applications is to prioritize databases of molecules as active against a particular protein target. Some case studies presented in the same perspective suggest that VS has already played a significant role in the discovery of some compounds that are now in the clinical trial or even in the market [13–18].

2. Materials and methods

2.1. Selection and preparation of target/receptor protein for docking

Target neuraminidase protein (PDB ID: 2HU0) was obtained from the Protein Data Bank (PDB) which is a repository for the 3-D structural data of large biologi-

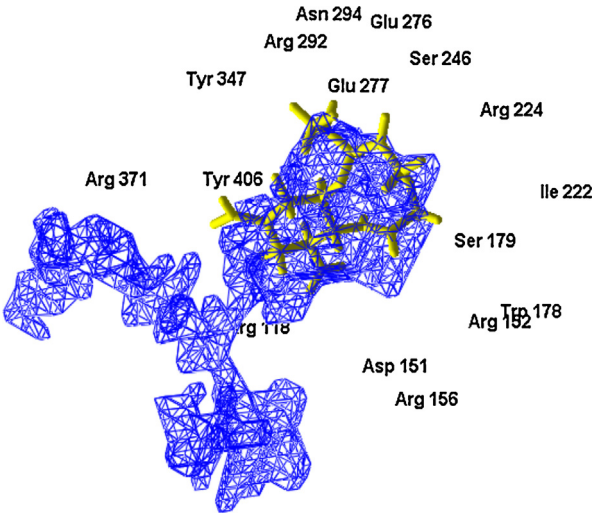

Fig. 1. Active site of NA predicted by MVD (active site residues: Arg118, Asp151, Arg152, Arg156, Trp178, Ser179, Ile222, Arg224, Ser246, Glu276, Glu277, Arg292, Asn294, Arg371, Tyr347, Tyr406).

cal molecules [19]. This protein was selected as target because the observation of the open conformation for the 150-loop in the group-1 structures suggests that, for these enzymes, this conformation of the loop is intrinsically lower in energy than the closed conformation. Group-1 neuraminidases (N1 and N8) initially bind to oseltamivir in this open conformation but eventually adopt the closed conformation. It thus seems that oseltamivir binding to group-1 neuraminidases favors the higher energy or closed conformation of the 150-loop that it probably accesses via a relatively slow conformational change. It should therefore be possible to design new inhibitors for group-1 neuraminidases that are selective for the

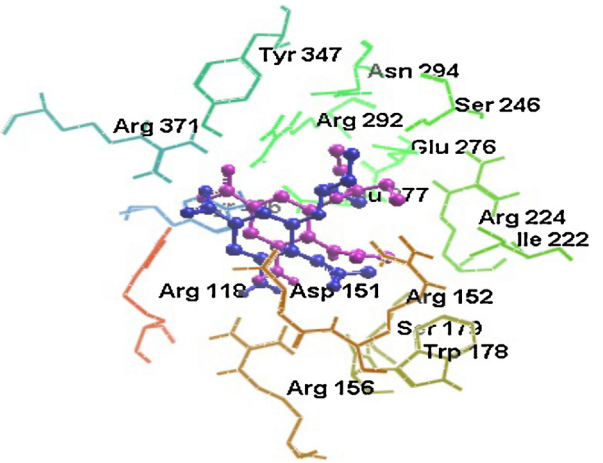

Fig. 2. Superimposed image of highest ranking docked conformer (blue) and co-crystallized neuraminidase with oseltamivir (2HU0) (purple).