In Silico Identification of Potential Inhibitors of ADP-Ribose Phosphatase of SARS-CoV-2 nsP3 by Combining E-Pharmacophore- and Receptor-Based Virtual Screening of Database

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SUPPORTING INFORMATION

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1. METHODS AND MATERIALS

1.1. Dataset collection

The X-ray crystal structure of viral protein (PDB ID: 6W02, Resolution: 1.5 Å) was retrieved from RCSB protein databank. The database MolPort (https://www.molport.com) which contains commercially available natural products and natural product derivatives has been utilized for virtual screening (VS) and identification of potential SARS-CoV-2 nsP3 inhibitors. The database was prepared by using Ligprep module of Schrodinger.[1] All in silico works were performed using Windows 10, OS architecture 64-bit, Core (TM) 2 Due CPU machine.

Figure S1. Crystal structure of ADP-ribose phosphatase of nsP3 (Fig. A) and crystal structure of co-ligand inserted into active site of nsP3 of SARS-CoV-2 (Fig. B).

1.2. Protein preparation and receptor-grid generation

The X-ray crystal structure of ADP-ribose phosphatase of nsP3 of SARS-CoV-2 (PDB ID: 6W02) was prepared using ‘Protein Preparation Wizard’ workflow in Maestro 12.2.[2] During protein preparation, the protein structure bond order was assigned by using chemical compound database (CCD), adding hydrogens, by creating zero bond order with metals, filling missing side chains and loops using prime, and finally removed water beyond 5.00 Å. The energy of
the protein-coligand complex was minimized until the RMSD between the energetically optimized structure and the starting structure reached to 0.30 Å, using the OPLS3 force field. The receptor grid box of 15Å cube was generated by selecting the co-ligand within the active site.

1.3. Validation of docking

The co-crystallized ligand of 6W02 (N3) was split from receptor-coligand complex and the co-ligand again was subjected to Extra Precision (XP) Glide docking with the corresponding receptor grid of 6W02 to calculate the Root Mean Square Deviation (RMSD). Then, RMSD was calculated by superimposing the docked co-ligand on its originally bound X-ray crystallographic conformation.

1.4. E-pharmacophore model generation

The E-pharmacophore method is based on mapping of the energy terms of the Glide XP score function onto atom centers.[3] This approach generates the energetically optimized structure-based E-pharmacophores. The prepared protein-coligand complex is used for building of E-pharmacophoric hypothesis. Phase[4] provides a standard set of six pharmacophore features namely hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic group (H), negatively ionisable (N), positively ionisable region (P), and aromatic ring (R). The possible pharmacophore sites of co-ligand (A1, A12, N22, N21, R23, D20, A10) are automatically generated from the protein-ligand (N3) complex and superimposed on its co-ligand.

1.5. E-Pharmacophore based virtual screening (VS) of database

The E-pharmacophore[5,6] technique has utilized the XP Glide’s scoring function to precisely characterize protein-ligand interactions, resulting in enhanced database screening enrichments. The E-pharmacophore based virtual screening was conducted for screening of MolPort database containing 113687 numbers of natural product or natural product derivatives.

1.6. Structure based VS of database
The hits resulted after E-pharmacophore based VS, are subjected to structure based Virtual Screening (VS) using Glide. In the VS workflow, the hits are filtered through QikProp, followed by Lipinski’s rule of five and removal of reactive functionalities. After filtration, the resultant hits were subjected to structure based virtual screening in order to identify molecules having more binding affinity towards 6W02. The Glide module contains a rational VS workflow from HTVS to SP to XP. In each stage, lesser number of molecules is forwarded to the next level with higher binding accuracy.

1.7. ADME study

The ADME (Absorption, Distribution, Metabolism, and Excretion) prediction programme established by Prof. William L. Jorgensen used QikProp to predict the drug likeness properties of drug candidates. ADME properties of the hits were predicted by using QikProp to find out the drug-likeness of the hits. At the first step of structure based virtual screening, the E-pharmacophores based hits (6025 hits) has been filtered through QikProp to predict the drug likeness of the molecules. The QikProp properties of the molecules are comparable with 95% of known drugs.

2. References

[1] Schrödinger Release 2020-4: LigPrep, Schrödinger, LLC, New York, NY, 2020.
[2] Schrödinger Release 2020-4: Maestro, Schrödinger, LLC, New York, NY, 2020.
[3] K. Loving, N. K. Salam, W. Sherman, J. Comput. Aided Mol. Des. 2009, 23, 541–554.
[4] Phase, Schrödinger, LLC, New York, NY, 2020.
[5] S. L. Dixon, A. M. Smondyrev, E. H. Knoll, S. N. Rao, D. E. Shaw, R. A. Friesner. J. Comput. Aided Mol. Des. 2006, 20, 647-671.
[6] S. L. Dixon, A. M. Smondyrev, S. N. Rao, Chem. Biol. Drug Des. 2006, 67, 370-372.