Molecular Docking study

Experimental

Preparation of the collected compounds

67 collected compounds were constructed into a 3D model using the builder interface of the MOE program. After checking their structures and the formal charges on atoms by 2D depiction, the following steps were conducted:

- The target compounds were subjected to a conformational search.
- All conformers were subjected to energy minimization, all the minimizations were performed with MOE until an RMSD gradient of 0.05 kcal·mol^{-1}Å^{-1} with MMFF94x force field and the partial charges were automatically calculated.
- The obtained database was then saved as Molecular Data Base (MDB) file to be used in the docking calculations.

Preparation of the target protein

The X-ray crystallographic structure of COVID-19 main protease in apo form (PDB ID: 6M03) was downloaded from the protein data bank in pdb format (http://www.rcsb.org/). The enzyme was prepared for docking study by:

- Removal unnecessary water molecules which are not involved in the binding.
- *Protonate 3D* protocol in MOE with default options.
- The main protease central binding site was defined for docking study through the key amino acids reported before.

Docking of the collected compounds to the main protease binding site

Docking of the target compounds database was done using MOE software. The following methodology was generally applied:

- The enzyme file was loaded and the Dock tool was initiated. The program specifications were adjusted to:

- Selection of the essential amino acid residues as the main docking site.
- Triangle matcher as the placement methodology to be used.
- London dG as Scoring methodology to be used and was adjusted to its default values.

- The MDB file of the ligands to be docked was uploaded and dock calculations were run automatically. The attained poses were studied and the poses showed best ligand-enzyme interactions were chosen.