Selection of the small molecules

The small molecules for the present study are retrieved from InterBioScreen database[1] . A total of 200 small molecules were considered for that were further filtered based on the Lipinski’s rule of 5. Accordingly, the compounds that demonstrates a molecular weight ≤500, hydrogen bonds donors ≤ 5, hydrogen bond acceptors ≤ 10 and logP ≤ 5 [2]. This rule foretells the oral bioavailability of a given compound [3]. The resultant compounds were upgraded to binding affinity studies to delineate on the binding mode and key residue interactions

Selection of the target

#### The target for the current investigation is the X-ray structure of cyclin dependent kinase 2 (CDK2) cocrystallized with inhibitor diaminopyrimidine PDB ID: 2FVD (hereinafter referred to as ref) displaying a resolution of 1.85 Å. The protein structure was prepared by dislodging the water molecules. The missing residues were filled in the Discovery Studio Visualizer (hereinafter referred to as DS) by enabling Tools → Macromolecules → Build and Edit Protein. The structure was then refined using the GalaxyWEB server [4]. For the molecular docking, the binding site was selected for all the atoms around the cocrystallised ligand that span around 9 Å with X, Y and Z coordinates as 1.156700 Å, 28.449967 Å and 8.538567 Å, respectively. Accordingly, the key residues are marked for residues Ile10, Val18, Ala31, Lys33, Val64, Phe80, Glu81, Phe82, Leu83, His84, Gln85, Asp86, Lys89, Gln131, Asn132, Leu134, Ala144, and Asp145, respectively. The correspondingly prepared target and the ligands were escalated to binding affinity studies employing PyRx.

Binding affinity studies

The molecular docking studies were conducted employing PyRx that permits the screening of small molecules. The python programming language is employed to build PyRx[5] and works utilizing AutoDock Vina, AutoDock and Open Babel[6]. Before initiating the molecular docking, the ref was redocked into the binding pocket. The result showed that the redocked pose was bound in a similar manner as that of the ref (Supplementary Figure), implying that the parameters chosen for the molecular docking were reproducible. Subsequently, the prepared target and the ligands were upgraded to molecular docking studies.

**Results**

**Binding affinity**

The binding affinity studies have revealed two compounds that have demonstrated lower binding affinity than that of the ref. These compounds have additionally interacted with the key residues thereby adhering at the binding pocket of the target. The binding poses were correspondingly manually clustered and visualized for key residue interactions. The best poses that have fulfilled the above criteria were subjected to molecular dynamics simulations to comprehend on the behavior of the ligand at the binding pocket of the ligand.

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