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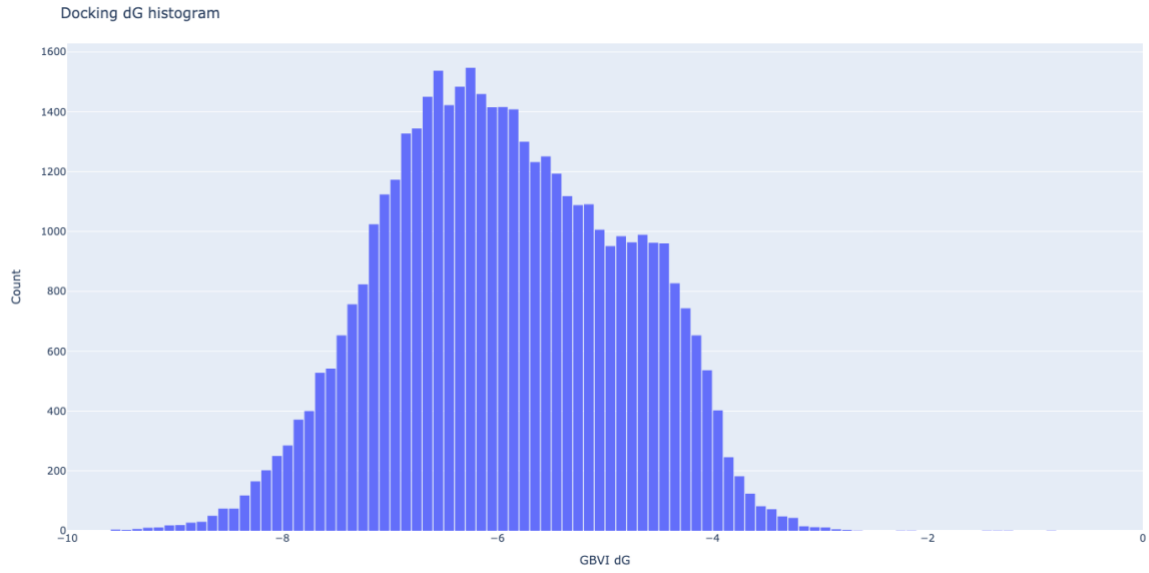
DrugBank Screening for 3CL inhibitors

The molecular docking of all 3D structures available in DrugBank database (8773 compounds) to 3CL protease binding pocket was conducted with MOE 2019.01 software in AMBER10/EHT forcefield and scored with GBVI/WSA dG function which estimates the free energy of binding (ΔG). Ligands conformational search by bond rotations was applied. After docking five best poses of each molecule were retained.



Histogram of docking values. 54 poses were scored below -9 kcal/mol, 1062 poses were scored below -8 kcal/mol and 7569 below -7 kcal/mol.

Among best-scored 50 poses four HIV-1 protease inhibitors were found. One of them (**indinavir**) is approved by the FDA, while the others (**BEA403**, **BEA425** and **BEA568**) are in experimental phase. Those compounds were directed to further analysis. Structures were parametrized for CHARMM36 forcefield and directed to molecular dynamics simulation with NAMD2.13 software. Human body temperature, standard pressure, full-atom TIP3 solvent model, NaCl in 0.05 M concentration and periodic boundaries conditions were applied. After careful system thermalization and equilibration, 5 ns MD were run. For free binding energy estimation MMGBSA calculations were run.

Free energy of binding to 3CL protease in MD simulation

Compound	**Mean ± SEM**
BEA403	-24.92 ± 0.22
BEA425	-30.40 ± 0.10
BEA568	-25.57 ± 0.14
indinavir	-19.98 ± 0.11

Systems stability was investigated with RMSD and internal energy evaluation. The system acquired stability after 0.5-1 ns.
All ligands remained bound to the catalytical cleft, however their orientation and conformation has notably changed at the beginning of simulation. This suggest that docking experiment has placed them in too narrow energy minima, however the MD results show that those compounds present potential for stable interaction with 3CL binding pocket.

MMGBSA Free energy of binding during 5 ns molecular dynamics simulation.