Technical Sessions : A - 32

A computational study on the inhibition of MCL-1 anti-apoptotic protein to activate apoptosis in cancer cells *via* commercially available natural product derivatives

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Bcl-2, BCL-XL and MCL-1 (Myeloid cell leukemia-1) are important anti-apoptotic proteins. The objective of this research was to identify commercially available natural product derivatives to inhibit MCL-1. Ligands were obtained from the ZINC12 database which provides 30793 chemically modified, commercially available natural product derivatives. Compound S63845, which binds with high affinity to the BH3 binding groove of MCL-1 was the reference.

Initial docking was carried out using GOLD Suite v5.3 with Hermes v1.7.0. Crystal structures for MCL-1, Bcl-2 and Bcl-XL were obtained through RCSB PDB server. The single ZINC database SDF file was split into 20 SDF files for the ease of docking using MayaChemTools with Perl scripts from Strawberry Perl. Protein was prepared for docking by removing attached ligands and water molecules, and by adding hydrogen atoms. The binding pocket was defined by a predefined list of residues. CHEMPLP[85] scoring function was selected for docking. S63845 was optimized to obtain the equilibrium geometry with Spartan'14 v1.1.0 applying Hartree-Fock 3-21G force field, and used for molecular docking with both GOLD Suite v5.3 and AutoDock Vina. 75 ligands were selected from initial docking and optimized using RESP ESP charge Derive Server (R.E.D. Server). Default Project.config and System.config files were used for the optimization with Gaussian 2016 (B01) version, and docked with Bcl-2 and Bcl-XL to determine specificity to MCL-1. Drug-like properties, absorption, distribution, metabolism, and excretion, of ligands and reference compound were analyzed with SwissADME server and DruLito software. Molecular dynamics simulations were carried out using Amber 16 suite. The system was solvated by TIP3P cubic boxes and water box size was 8 x 8 x 8Å. Neutralization was done using tleap by adding required charges. A salt concentration of 0.10 M was maintained. System minimization was executed using sander module while heating, and equilibration and production were carried out using pmemd.cuda module. Molecular dynamics were performed on Nvidia GTX 1080 graphics processor. The system was minimized for 10000 steps with a 500 kcal/mol$Å^2$ force constant restraint, and then minimized for another 4000 steps without any force constant limitation. Heating was under NVT conditions from 0K to 300K with a weak force constraint of 10 kcal/mol $Å^2$. With pmemd module, the system was equilibrated under NPT (number of molecules, pressure, and temperature) conditions for 1 ns, and equilibrated until time vs. RMSD curve showed a stable horizontal gradient. Production step was performed under NVT conditions with SHAKE algorithm applying hydrogen constraint. Blind docking was performed, and search space of 100×100×100 Å box was defined. Three MCL-1 specific ligands were identified; N-[[(2R,3S,4R)-4-(dibenzylamino)-3-hydroxy-tetrahydrofuran-2-yl] methyl]-3,3-dimethyl-butanamide (ZINC77263702), 7-benzyl-1-[[4-[(7-benzyl-3-methyl-2,6-dioxo-purin-1-) methyl] phenyl] methyl]-3-methyl-purine-2,6-dione (ZINC33354648) and N-[[(2R,3S,4R)-4-(dibenzylamino)-3-hydroxy-tetrahydrofuran-2-yl] methyl]benzamide (ZINC77263752).

These ligands have demonstrated the potential to be used as selective inhibitors for MCL-1, and exhibit far better drug-like and ADME properties compared to the reference compound.

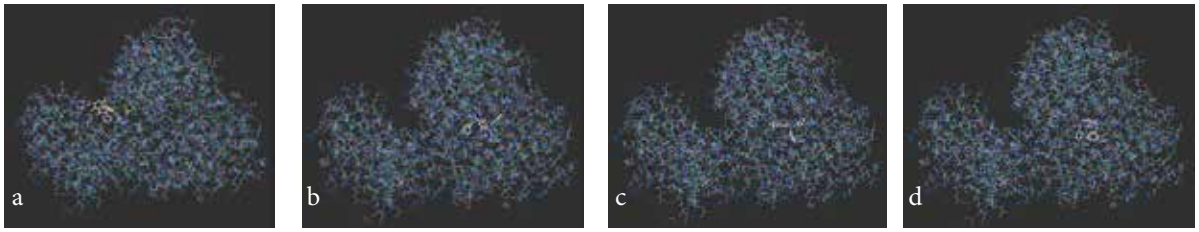

Figure 1. Blind docked positions of ligands with MCL-1; S63845 (a), ZINC77263702 (b), ZINC77263752 (c) and ZINC33354648 (d)