Computer Design of Novel Alkylating-agents as Anti-Cancer Drugs

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Alkylating agents are a class of chemotherapy drugs that bind to DNA and prevent proper DNA replication. They have chemical groups that can form permanent covalent bonds with nucleophilic substances in the DNA. Alkylating agents are used as part of chemotherapy in different types of cancers. There are three known mechanisms for the interaction of an alkylating agent with DNA. In one of the mechanisms an alkylating agent attaches alkyl groups to DNA bases. This alteration results in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases. [1]

In this study we employed molecular dynamics (MD) and docking simulations, to design new alkylating agents as anti-cancer drug candidates. 24 known alkylating agents were chosen to check their interactions with DNA structure, in order to select suitable lead compounds for further rational drug design. These compounds were drawn using HyperChem Professional 7.0 and the generated structures were subjected to geometry optimization by HF calculations using Guassian 03 and 3-21G basis set. Three DNA structures with PDB ID's (4HC9, 4AWL and 3US0) taken from protein data bank were served as receptors. Using Gromacs 4.0.5 simulation package, three separate MD simulations were done on DNA structures at 310K to bring them to the semi physiological environment. The DNA structures were modeled using the AmberGS forcefield. Cubic simulation boxes contained DNA, water molecules and necessary counter-ions. All DNA structures carry negative charges due to presence of phosphorylated backbones. Zinc cations were employed to neutralize the simulation systems due to their significant impact on DNA replication, transcription and repair. Equilibration was confirmed via analysis of RMSD plots and gyration radiuses.

In the next step, selected drugs were docked into DNA structures employing the MolegroVirtual Docker. [2] 18 docking iterations were performed for each drug-DNA pair and the resulting free energies of binding (ΔG) were averaged to get a single value. Comparison of these values led to the selection of three alkylating agent drugs (Uramustine, Melphalan and Chlorambucil), having stronger interactions with DNA, as lead compounds. Some functional groups were added to the lead compounds at different situations to obtain new compounds which were docked then to DNA structures after energy minimization. Finally based on docking results and ADME properties some compounds were selected as new alkylating agent anti-cancer drugs.

References

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2. R. Thomsen and M. H. Christensen: J. Med. Chem. (2006) 49, 3315-3321