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Molecular modeling of the binding of coumarin derivatives to human topoisomerase II

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The aim of this study was to identify ligands which can bind the target protein topoisomerase II. Topoisomerase II plays a central role in both the cure and initiation of human cancer, and therefore molecules that can bind to topoisomerase are potential drugs for treatment of cancer. All ligand molecules were modeled using Gauss View 3.0 software and optimization was carried out using Gaussian 03 software at HF/3-21G level of theory. Frequency calculations were carried out for each optimized ligand structure, and structures were prepared for docking. Since coumarins have anti-cancer activity, seven molecular structures derived from coumarin (Table 1) were used as ligands. All ligands in this study are coumarin derivatives synthesized by our collaborator, Prof. S B Jayashree of Manipal University, India. The receptor file, human topoisomerase II beta in complex with DNA and etoposide, PDB ID: 3QX3, was acquired from the protein data bank, and it was prepared for docking. Due to computational limitations, the monomer of the protein was used as the receptor. Each prepared ligand molecule and the receptor were used for 'rigid docking' using UCSF DOCK6. Ligand 7, 4-(2,4-Dinitro-phenoxymethyl)-7-hydroxy-chromen-2-one has the lowest grid score (-9.011 kJ mol^{-1}), and can be a potential drug for cancer treatment. Ligands 5 and 6 also may be therapeutic agents since their grid scores are closer to -9.011 kJ mol^{-1}. Further studies are needed to confirm the stability of receptor-ligand complexes in solvent environments, and molecular dynamics simulation studies are already underway in our laboratory.

Table 1- Grid Score Values

Ligand		X	X'	X''	Grid Score (kJ mol^{-1})
1		H	H	H	-7.120
2		H	H	Cl	-7.913
3		Cl	H	Cl	-8.023
4		H	Cl	H	-7.495
5		H	H	NO_2	-8.434
6		H	H	OCH_3	-8.559
7		NO_2	H	NO_2	-9.011

Keywords: Coumarins, molecular modeling, potential drugs, rigid docking, topoisomerase II

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