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Molecular docking study and structure-based design of novel camptothecin analogues used as topoisomerase I inhibitor

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This paper involves the molecular docking study on the inhibition of Human topoisomerase I (top1) which is the molecular target of a diverse set of anti-cancer compounds by Glycinate, camptothecin and its analogs. Their reaction mechanisms involving their interaction to a transient top1-DNA covalent complex, in order to inhibit the resealing of a single-strand nick created by the enzyme to relieve superhelical tension in duplex DNA, were confirmed using Quantum computational techniques in ICM-Pro Molsoft program. Our research findings on this reaction inquiry of the human top1-DNA complex bound with camptothecin analogs were helpful in improving the activities of top1 poisons through a structure based computational drug design. our results indicate that the Pi-Pi interactions of the camptothecin drugs with DNA as a result of its planner nature and the presence of some fragments on the lactone E-ring were directly responsible for its stable ternary complex with topo 1. The molecular docking result of our study shows Morpholinodoxorubicin (-32.835 kcal/mol), 9-Amino-20-RS-Camptothecin (-28.792 kcal) and Camptothecin Lysinate HCl (-28.224 kcal) best inhibit topo 1 when compared with other NSC compounds within our data set. These compounds were further utilized in designing new potent antitumor compounds by attaching potent fragments to the lactone ring of the compounds. Most of these compounds were reported to be more active than the parent structure, some of which includes CLD-12, CLD-7, CD-9 with a binding affinity of -40.307kcal/mol, -36.743kcal/mol and -36.072kcal/mol respectively. At the end of our study, we were able to optimize potent novel compounds that can be used to inhibit topoisomerase 1 enzyme.

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