[PC1-44] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

The activity - binding affinity relationship of topoisomerase I inhibitors by flexible docking with FlexiDock

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Human Topoisomerase I (topo I) helps the control of DNA supercoiling in cells by assisting breaking and religation of DNA strand. It is essential for cellular metabolism and survival, hence, a good target for a novel class of anticancer drugs. As topo I inhibitor binds to the DNA-topo I complex, the religation of DNA strand is suppressed which results in the death of the target cell. Seven compounds of 1H-Imidazo[4,5-g]phthalazine-4,9-dione derivatives with IC_{50} in the range of 0.001 and 6.27 μM in 5 different cancer cells and four compounds of 7-chloro-6-quinazoline-5,8-dione derivatives with positive and negative topo I inhibition activities were studied. Computer docking with FlexiDock was carried out to illustrate the binding modes between these compound and DNA-topo I binary complex of the DNA-topo I-topothecan ternary complex structure determined by crystallography. The results show that, in phthalazine derivatives, 3 compounds form one or two H-bonds each with Arg364, an important active site residue and 2 compounds form a H-bond each with P-Tyr723 with a water molecule as a bridge. One compound forms H-bond with Thr718. In quinazoline derivatives, 2 compounds with highly positive activity intercalated properly between DNA helices while the two negative compounds did not. The binding modes obtained demonstrated the overall correlation between the activity and the binding affinity, presenting the possible use of the modeling system for the prediction of the activity and design of novel drugs.

[PC1-45] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Codonoposide 1_C is a potent inducer of apoptosisin Human Leukemia cell line, HL-60.

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Codonopside 1c is an active natural compound isolated from the roots of Codonopsis lanceolata (Campanulaceae), a Korean medicinal herb. In the present study, we investigated the in vitro effect of Codonopside 1c on the proliferation and induction of apoptosis in HL-60 human promyelocytic cells. When HL-60 cells were treated with Codonopside 1c, evidence of apoptotic features, including DNA fragmentation, formation of DNA ladder in agarose gel elecrophoresis and increse of annexin V binding, were obtained. Our investigation of apoptosis in HL-60 cells showed an intracellular events that included (1) activation of caspase-3, caspase-8 and caspase-9; (2) decrease of bid and bax protein in cytosol; (3) decrease of XIAP, inhibitor of apoptotic protein; and (4) induction the release of Smac into cytosol. Broad caspase inhibitor (z-VAD-fmk), caspase 9 inhibitor (Ac-LEHD-fmk) ,caspase 8 inhibitor (Ac-IETD-fmk) and caspase-3 inhibitor (Z-DEVD-fmk) almost completely suppressed the DNA fragmentation. The induction of apoptosis by Codonopside 1c may provide a pivotal mechanism for its chemotherapeutic action.

[PC1-46] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Antioxidant enzyme acitivity of flavonol quercetin in the presence of different anticxidants.

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It has been known that quercetin is one of bioflavonid compounds and has anti-tumor effect by suppressing tumor growth in vitro and in vivo, including multiple biological effects by antioxidant and effective anti-inflammatory agent. The present study investigated whether quercetin can enhance antioxidant enzyme activity (glutathione proxidase: GPX, superoxide dismutase: SOD, catalase: CAT) and regulate the intracellular reactive oxygen intermediate levels on the B16F10 murine melanoma cells in the presensece of vitamin E, L-ascorbic acid