[S5-4] [11/28/2005(Mon) 15:30-16:00/ Guhmoongo Hall A]

Design, Synthesis and Biological Study of Novel Psorospermin/Quinobenzoxazine Hybrid Compounds

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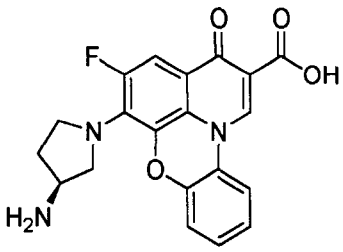
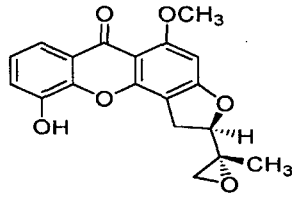
Topoisomerase II, an enzyme that catalyze changes in the topology of DNA, plays several key roles in DNA metabolism and chromosome structure, and it is the primary cytotoxic target for a number of clinically important DNA intercalating agents such as doxorubicin. It seems likely that if these intercalating Topoisomerase II poisons are structurally modified to also be DNA alkylating agents, they will have increased dwell time on the Topoisomerase II-DNA complex and increased potency and selectivity for cancer cells. On the basis of insights into the mechanisms of action of psorospermin and the quinobnzoxazine A-62176 and molecular modeling studies of these compounds with duplex DNA, we have designed and synthesized a series of novel hybrid DNA-interactive compounds that alkylate DNA most efficiently at sequences directed by Topoisomerase II



A-62176



Psorospermin

These hybrid compounds showed enhanced DNA alkylating activity in the presence of Topoisomerase II, exhibited more potent than both parents compounds.