Facile Synthesis of Isoquinoline Natural Alkaloids for the Development of Topoisomerase I Inhibitors

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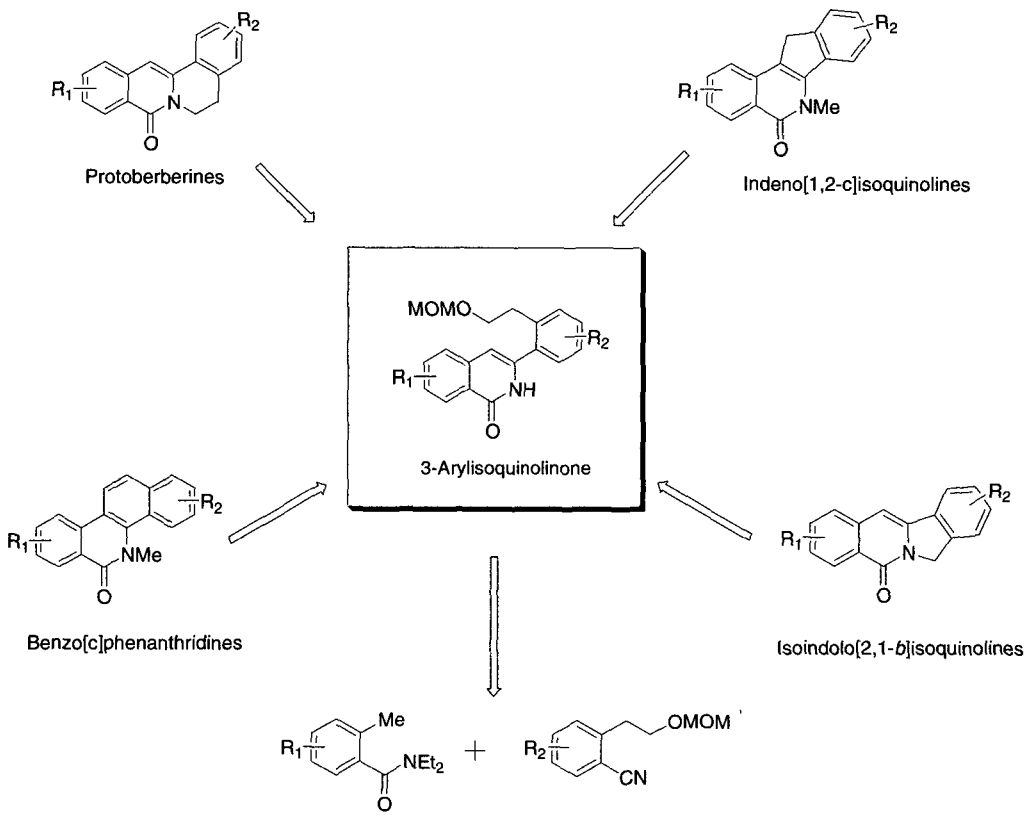
Eukaryotic DNA topoisomerase I (top 1) is an essential enzyme that act to relax supercoiled DNA during the transcription and replication and mitosis.[1] Intracellular levels of top I are elevated in a number of human solid tumors, relative to the respective normal tissues, suggesting that controlling the top I level is important to treat cancer. Topoisomerase poisons show their antitumor activities by stabilizing the cleavable ternary complex consisting of top I enzyme, DNA, and drug.[2] Thus, top I represents a promising target for the development of new cancer chemotherapeutic agents against a number of solid human tumors. Camptothecin is a representative top I targeting compound and its derivatives, topothcan and irinotecan have been developed as clinically using agents. Several non-camptothecin top I inhibitors have also been reported in recent years.[3] These include benzo[*c*]phenanthridines,[4] protoberberines,[5] indenoisoquinolines,[6] saintopin[7] indolocarbazoles,[8] and benzophenazines.[9] We recently reported the synthesis and biological evaluation of 3-arylisoquinolines with the 3D QSAR study.[10] Most of these compounds were shown to be highly cytotoxic in several kinds of human tumor cells. For further investigation of isoquinolinamines on the cytotoxicites with topoisomerase I inhibition activity, systematic synthesis was performed to get interesting compounds. Based on the X-ray structure of topo I and topotecan, a docking study was also carried out. Retrosynthesis of natural isoquinoline alkaloids indicates that the coupling of benzonitrile with *o*-toluamide might afford 3-arylisoquinolinone that would be a key intermediate for the synthesis of isoquinoline alkaloids. Protoberberine or benzo[*c*]phenanthridine alkaloids could be synthesized through the ring closure of the two carbon chains, either on position 2, or 4, of the 3-arylisoquinolinone as shown in scheme 1. Recently, we accomplished the total synthesis of benzo[*c*]phenanthridine alkaloids, protoberberines, indeno[1,2-*c*]isoquinolines and isoindolo[2,1-*b*]isoquinolines using lithiated toluamide-benzonitriles cycloaddition.[11]

Scheme 1. Synthetic pathway for isoquinolines using lithiated toluamide-benzonitrile cycloaddition



Docking study was carried out using Sybyl 6.7 (Tripos, Inc.) on a Silicon Graphics Indigo 2 workstation. Construction of protein-ligand was based on X-ray structure of ternary top I-DNA–topotecan complex (PDB entry 1K4T). Ligand was manually docked into the active site of topotecan binding region. The ethylenediamine group of compound 7d was considered to have strong hydrogen bonding with carboxyl group of Asp 533 (2.221•), phosphoester group of Guanine 12 (1.490 •) and amide carbonyl moiety of Gln 633 (2.739 •) as shown in Figure 3. On the other hand, primary amines did not have good interaction to this binding site due to the lacks of the length of chain to reach the protein functional group.

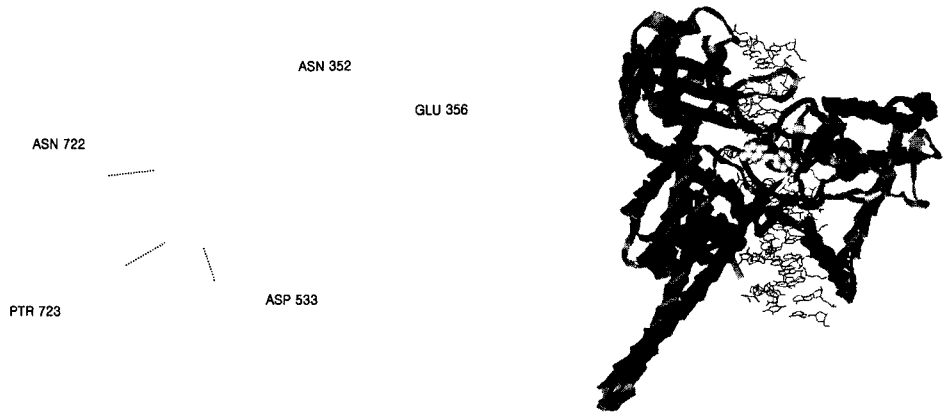


Figure 1. Docking model of 7d with topoisomerase I-DNA complex

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