Anticancer Drug Development

The past decade has witnessed an immense increase in the development and clinical use of novel and more potent anticancer agents. A large proportion of these drugs function by way of their ability to interact with DNA and more specifically by modulating the activities of the nuclear enzymes topoisomerase I and II. These enzymes involved in generating the necessary topological and conformational changes in DNA are critical to many cellular processes such as replication and transcription.

![Routes of topoisomerase II-drug-DNA complex formation.](image)

The three possible routes for cleavage complex formation are shown. Route 1 involves drug binding to DNA, followed by the enzyme binding to the drug-DNA complex. Route 2 consists of enzyme binding to DNA, followed by the drug binding to the enzyme-DNA complex. Route 3 involves binding of drug to enzyme, followed by binding of the drug-enzyme complex to the DNA. Brackets are used to denote the transient nature of the cleavage complex.

Topoisomerases have been classified into type I and II depending on their ability to produce transient protein mediated single strand or double strand breaks. Inhibitors that interfere with the breaking and rejoining reactions of these enzymes by trapping an abortive enzyme-DNA cleavable complex have been termed topoisomerase poisons. Such inhibition of mammalian topoisomerases has been recognized as an effective approach for developing cancer chemotherapeutic agents. Recently, the characterization of the physical structure of these enzymes and the availability of high resolution crystal structures of the enzyme with DNA have increased the interest in rational drug design aimed at the development and synthesis of novel therapeutic agents. Several clinically used chemotherapeutic drugs are now known to be inhibitors of topoisomerase-I or II. *Camptothecin* and its derivatives *topotecan* and *irinotecan* are examples of clinically used topoisomerase I poisons. *Doxorubicin*, *m-AMSA* and *etoposide* are a few examples of clinically used topoisomerase II poisons.

Our group is looking at compounds of both natural and synthetic origin as potential source for developing topoisomerase I and II poisons. For the past quarter of a century, global marine sources have provided a vast array of new medicinally valuable natural products with anticancer activities. These natural products exist as secondary metabolites in marine invertebrates such as sponges, bryazoa, tunicates and ascidians. The isolation of C-nucleosides from the Caribbean sponge, Cryptotheca crypta, provided the basis for the synthesis of *cytarabine*, the first marine derived anticancer agent to be developed for clinical use. We are working on developing cancer drugs based on a class of marine alkaloids that has shown topoisomerase II inhibition and in vitro & in vivo anticancer activity.
We have also identified a class of synthetic heterocyclic compounds that are potent inhibitors of the enzyme topoisomerase I. Saturated transfer difference (STD) - NMR methods are being applied towards examining the interactions of the lead compound with the enzyme. This will provide a clear advantage in rational drug design, allowing the determination of binding epitope of the ligand with the enzyme.