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Structures of the Human Topoisomerase I-DNA Covalent Complex Bound to Three Classes of Anticancer Agents. B. Staker, M. Feese, M. Cushman, Y. Pommier, D. Zembower, L. Stewart, A. Burgin, Structural Biology, deCODE Genetics, 7869 NE Day Rd. W., Bainbridge Island, WA 98110 USA.

Human topoisomerase I (topo I) is a 765 amino acid type Ib topoisomerase. Topoisomerases regulate the topological state of DNA, assisting in transcription, replication and recombination. All topoisomerases act via a mechanism where a conserved tyrosine residues links covalently to a phosphodiester of the DNA backbone. The covalent topo I DNA intermediate is a well-known target for a variety of anti-cancer compounds. We report three X-ray crystal structures of human topo I covalently bound to a 22mer dsDNA substrate in ternary complex with one of three structurally diverse classes of anti-cancer compounds; indolocarbazole, indenoisoquinoline or camptothecin. A comparative analysis reveals that these structurally diverse compounds bind to the ternary complex using similar strategies that optimize the intercalation binding site of the covalent protein-DNA complex. Some general principles of topo I poison binding are identified. All compounds intercalate the -1 and +1 base pairs and form hydrophobic base stacking interactions with the upstream and downstream bases. A common element of all poisons visualized is the presence of a free electron pair near Arg364 of topo I. Co-crystals of the ternary complexes of indolocarbazole and camptothecin diffracted to 3.0 Å in space group $P2_1$ with unit cell dimensions of a=57, b=115, c=74 and b=93. Indenoisoquinoline ternary complex crystals diffracted to 3.0 Å in space group C2 with unit cell dimensions of a=261, b=75, c=57, and b=97. Data were collected at BNL beamline X25 and APS beamline 32.