

W0357

Topoisomerase I Poisoning by Camptothecins: Homocamptothecin AG260 Binds in the E-ring Open Carboxylate Form. Michael D. Feese, Bart Staker, Alex Burgin, Kathryn Hjerrild, Lance Stewart, deCODE biostructures, Bainbridge Island, WA 98110.

Since the isolation of the anticancer agent camptothecin (CPT) in 1966 a great deal of attention has been focused on its reactive α -hydroxylactone ring. The α -hydroxylactone is in reversible, pH dependent equilibrium with its corresponding carboxylate. Structure-activity studies established this functional group to be an essential and stereo-selective pharmacophore. Since the first clinic trials with CPT in the early 1970s it has been widely held that the carboxylate form of CPT is inactive.

The sole target of CPT has been established to be DNA Topoisomerase I. CPTs stabilize the transient covalent Topo I – DNA intermediate, forming a ternary complex called the cleavable complex. Collision of replication forks or elongation complexes with cleavable complexes results in double strand DNA breaks, leading to apoptosis. This discovery rekindled interest in development of CPT and its analogues as anticancer agents. Among the most promising CPT analogues are the homocamptothecins (hCPTs) in which the 6-membered α -hydroxylactone is replaced by a 7-membered β -hydroxylactone. hCPTs show anticancer activity and inhibition of Topo I that is enhanced with respect to camptothecin.

We report the 3.0 Å crystal structure of the hCPT AG260 bound to the cleavable complex. The β -hydroxylactone is clearly in the ring-opened carboxylate form. Our analysis suggests that the carboxylate of CPTs is required to stabilize the cleavable complex and is essential for their anticancer properties.