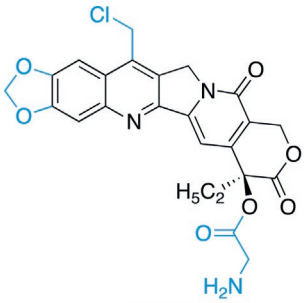
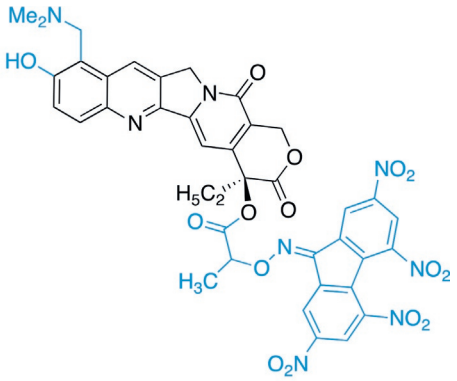
ester of a CPT derivative that has undergone promising preclinical studies.[98] TLC388 (Lipotecan®) was designed as a multitarget drug because it contains a molecule of topotecan and another of a tetranitrofluorene oxime, with the two active fragments linked by a molecule of lactic acid. The E ring modification stabilizes the lactone moiety, and the presence of the nitro substituents makes the compound a strong radio- and chemosensitizer. This compound demonstrated significant effectiveness in phase I and II clinical trials on patients with hepatocellular carcinoma, and in 2010 it was granted orphan drug designation for this indication by both the EMA and the FDA. In 2013, it was included in the "Green Path" program by the Chinese State Food and Drug Administration (SFDA).



CMMD-Gly



TLC388 (Lipotecan)

The mode of action of CPT and other Top1 inhibitors is very different compared to that of other enzyme inhibitors. They do not bind to DNA or to Top1 by themselves because they require the presence of both Top1 and DNA associated in a cleavable complex. This observation led to the hypothesis that CPT binds at the interface of both Top1 and DNA in a ternary complex. This hypothesis, which was confirmed by the determination of the crystal structure of a ternary Top1 cleavable complex with topotecan,[99] converted these drugs into the paradigm for interfacial inhibitors, which differ from orthosteric and allosteric inhibitors in that they bind at the interface of two or more macromolecules (Figure 7.17). This mode of drug–target interaction is uncommon, but it has also been observed for other anticancer drugs that can only bind to certain points ("hot spots") of the interfaces formed between two biological macromolecules, including Top2 inhibitors (adriamycin, etoposide, and dexrazoxane) and tubulin binders (paclitaxel, vinblastine, and colchicine). The following are the main characteristics of interfacial inhibitors:[100]

1. Their target is a biological system formed by two macromolecules (proteins or nucleic acids).
2. They couple to the interface generated upon binding of these macromolecules to each other. The precise binding site is generated by the movements of the macromolecules upon, for instance, cleavage of DNA or bending of the microtubule filament.
3. Drugs normally bind reversibly by hydrogen bonding, π-stacking, or metal chelation. Drug binding to these "hot spots" tends to be highly enantiospecific.

The very deep penetration of CPT into its site leads to a thermodynamically favorable increase in entropy upon binding due to the liberation of a large number of molecules of hydration water, as shown in Figure 7.18.[101]