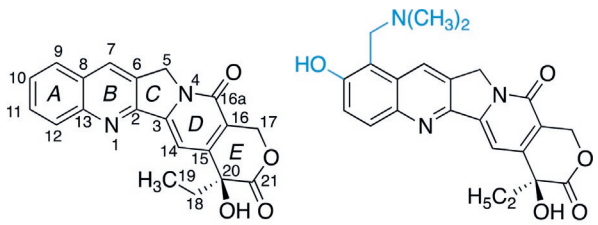
target validated the inhibition of this enzyme as a goal for cancer chemotherapy and prompted the search for water-soluble, more active, less toxic analogs.[66,67] Structure–activity relationship studies showed that substituents at ring A and at the C-7 position of ring B were allowed, whereas the ring E lactone was essential for activity. Because these Top1-targeted drugs are S-phase specific, they achieve optimal inhibitory activity when the tumor is continuously exposed to the drugs for long periods of time and are adequate for tumors with a high proportion of proliferating cells but unsuitable for those tumors that have high numbers of noncycling cells in the G_1 phase, such as prostate and kidney cancer.

The main problem associated with CPT is its very poor water solubility, which hampers its formulation. Two CPT analogs that solve this problem by the introduction of basic substituents that allow the preparation of salts, namely topotecan and irinotecan (CPT-11), were introduced into clinical trials in the 1980s and gained regulatory agency approval for the treatment of various cancers in the 1990s. Topotecan (Hycampin®) is used for the treatment of fluoropyrimidine-refractory ovarian and small cell lung cancers,[68] although hematological toxicity is a common side effect due to the destruction of bone marrow progenitors.



Camptothecin Topotecan

Irinotecan (Camptosar®), which received accelerated approval by the U.S. Food and Drug Administration (FDA) in 1996 and full approval in 1998, is a prodrug that needs to be hydrolyzed by a carboxylesterase[69] to its active metabolite SN-38 (Figure 7.15). It is used in colorectal cancer, showing synergism with cisplatin.[70] Several studies have underscored the importance of pharmacogenetic considerations in its clinical application[71] because there is a considerable degree of polymorphism in the main enzyme involved in its hepatic metabolism, namely uridinediphosphate glucuronosyl transferase 1A1 (UGT1A1).[72] Simmitecan is a closely related prodrug, whose active form is known as chimmitecan, and is being studied in phase I for the treatment of advanced solid tumors.[73]

One of the main limitations of all CPT derivatives is their spontaneous and rapid inactivation (within minutes) by opening of the lactam function in the E ring. This reaction is reversible and both species are present at physiological pH, but the carboxylic form binds readily to serum albumin, thereby shifting the lactone–carboxylate equilibrium toward the inactive species (Figure 7.16).[74] Any factor hampering the binding to albumin favors activity; for instance, the higher potency of topotecan and irinotecan with regard to CPT has been attributed to interference of their substituents with binding to albumin.[75] Furthermore, a higher E ring stability leads to lower bladder toxicity, one of the main problems associated with the use of CPT derivatives. The reason is that the relatively low pH of urine prompts the cyclization of the secreted carboxylate form, leading to the local formation of high amounts of the cytotoxic lactone species.[76]