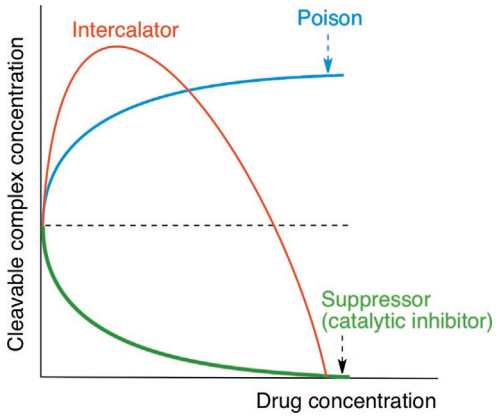

FIGURE 7.14

Modes of topoisomerase inhibition.

Because the level and time course of expression of these enzymes vary in different cell types, and the development of resistance to one type of inhibitor is often accompanied by a concomitant rise in the level of the other enzyme, there is increasing interest in drugs that can act as dual Top1/2 poisons.[61,62]

5 SPECIFIC TOPOISOMERASE I INHIBITORS

Compounds that inhibit TopI[63] can be divided into two categories:

1. Topoisomerase I suppressors, which are those compounds that inhibit the enzyme but do not stabilize the intermediate DNA–Top1 covalent complex.
2. Topoisomerase I poisons, which act after DNA cleavage by inhibiting religation. This can be achieved through three different mechanisms involving (1) binding of the enzyme to the previously formed drug–DNA binary complex, (2) recognition of the enzyme–DNA binary complex by the drug, or (3) interaction of DNA with the drug–enzyme complex.[64]

It is interesting to note that although Top1 seems not to be essential for cell survival because other topoisomerases can (at least temporarily) play its role, its inhibition nevertheless leads to cell death. This means that the cause of apoptosis is not the suppression of the catalytic activity but, rather, the series of molecular events that take place upon trapping of the DNA–Top1 complex, and these are not known in full detail.[65]

5.1 CAMPTOTHECINS

Camptothecin (CPT) is an alkaloid that was isolated in 1966 from the bark of the Chinese tree *Camptoteca acuminata* as a potent anticancer drug, although its therapeutic development was initially limited by its poor solubility and unacceptable toxicity. Identification of Top1 as its sole