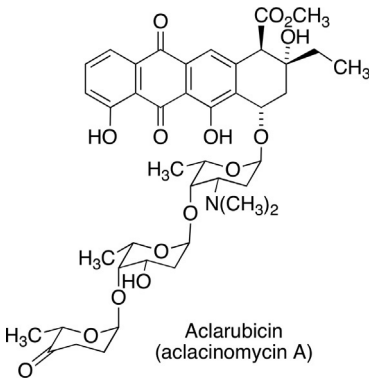
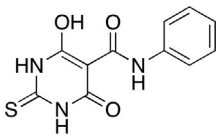


Aclarubicin
(aclacinomycin A)

7.1.2 Merbarone

Merbarone is a derivative of thiobarbituric acid that was discovered during the course of a study of a large number of barbituric acid analogs by the NCI. This compound has been shown to inhibit the induction of DNA–Top2 cleavable complexes and has been tested clinically against a large number of tumors,[168] although it showed nephrotoxicity and poor anticancer activity.



Merbarone

7.1.3 Bis(dioxopiperazines)

These drugs[169] were introduced as chelating agents because they behave as prodrugs to EDTA amides, being useful cardioprotectors when associated with anthracyclines. Subsequently, it was shown that they also inhibit Top2 at a point upstream from the formation of the cleavable DNA–enzyme complex by stabilizing the closed-clamp form of Top2 as a post-passage complex.[170] This is achieved after interaction with the enzyme N-terminal domain by inhibiting its ATPase activity. The use of dexrazoxane hydrochloride (Totec®, Savene®) as cardioprotector against the cardiotoxic side effects of anthracyclines has been restricted because of its association with secondary malignancies.[171] This cardiomyocyte protection has been traditionally associated with the iron chelating activity displayed by the dexrazoxan hydrolysis product, as discussed in Chapter 4, but recent studies suggest that Top2 inhibition may have a role in this effect.[172] Sobuzoxane (MST-16, Perazolin®) has obtained approval in Japan for treatment of leukemia and lymphoma.