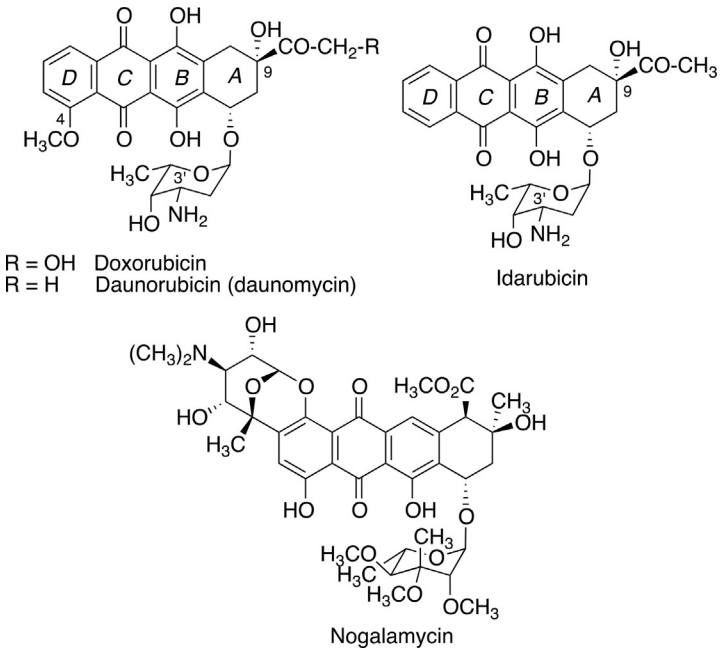

Anthracyclines are typical intercalating agents, and their tetracyclic A–D chromophore is oriented with its long axis perpendicular to the long axis of adjacent base pairs at the intercalation site. The daunorubicin–DNA complex is stabilized by the stacking interactions of rings B and C and by hydrogen bonding involving the hydroxyl group at C-9 of ring A, which acts as a donor to N-3 of guanine and as an acceptor from the amino group of the same guanine. Ring D protrudes into the major groove, and the amino sugar moiety lies in the minor groove and also takes part in hydrogen bonding with DNA (Figure 7.22).

As other antitumor intercalating agents, anthracyclines are Top2 poisons because of the formation of a stable drug–DNA–Top2 ternary complex and the consequent inhibition of replication and transcription. The sugar unit is crucial for the stabilization of this complex, and suppression of the C-4 methoxy and C-3′ amino groups increases Top2 inhibition.[141] In the case of nogalamycin, the presence of two sugar residues at both ends of the chromophore leads to a special way of interacting with DNA called threading intercalation,[142] in which one of the sugar units is located at the minor groove and the other at the major groove (Figure 7.23). The structure of the nogalamycin–DNA complex has been studied by X-ray diffraction.[143]

Mitoxantrone (Novantrone®) is a simplified analog of the anthracyclines that has a complex mechanism of action, including the generation of a stable drug–DNA–Top2 ternary complex. It has been approved for leukemias and advanced hormone refractory prostate cancer and is the only Top2 poison that has been approved for a noncancer indication, multiple sclerosis.[144] Isosteric substitution of one or more carbons of the benzene rings by nitrogen atoms has been employed as a strategy for the design of mitoxantrone analogs with geometries similar to those of the parent compounds but with increased affinity for DNA due to the presence of sites suitable for hydrogen bonding or ionic interactions. This increased affinity allows the suppression of the phenolic hydroxyls of mitoxantrone, which are responsible