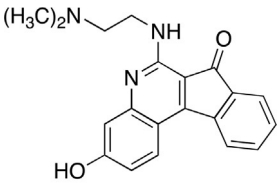
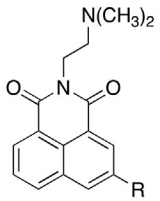


TAS-103

In addition to being an intercalating agent, TAS-103 is also considered a dual Top1–2 inhibitor, although other studies have indicated that cellular susceptibility to TAS-103 is not correlated with Top2 expression. A search for other proteins able to bind this drug showed that it is recognized by the signal recognition particle, a universally conserved ribonucleoprotein that directs the traffic of proteins within the cell and allows their secretion.[30]

2.4 NAPHTHALIMIDES AND RELATED COMPOUNDS

Naphthalimide derivatives bearing an aminoalkyl side chain, such as mitonafide[31] and amonafide,[32] have shown interesting cytotoxic activity[33] that is due to intercalation and Top2 inhibition.[34] Both compounds have been extensively tested in clinical trials, but although they have been used as leads in the design of bis intercalators (see later), they have not been employed in therapeutics.



R = NO_2 Mitonafide
R = NH_2 Amonafide

2.5 CHARTREUSIN, ELSAMICIN A, AND RELATED COMPOUNDS

Chartreusin and elsamicin A are structurally related antitumor antibiotics that were isolated from *Streptomyces chartreusis* and from an unidentified actimomycete strain, respectively. Both compounds bind to GC-rich tracts in DNA, with a clear preference for B-DNA over Z-DNA conformation. They also inhibit RNA synthesis and cause single-strand scission of DNA through formation of free radicals (see Chapter 4, Section 6). Elsamicin A binding to the P1 and P2 promoter regions of the *c-Myc* oncogene, which is mutated in many types of cancer, inhibits the binding of the transcription factor specificity protein 1 (Sp1), thus inhibiting transcription.[35]

Chartreusin suffers from unfavorable pharmacokinetic properties (slow oral absorption and biliar excretion), which prevented its clinical development. Among semisynthetic chartreusin analogs with