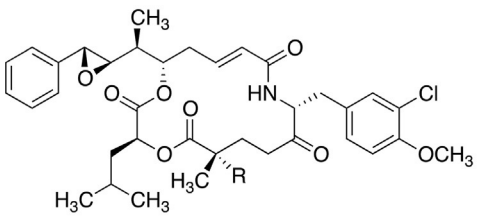
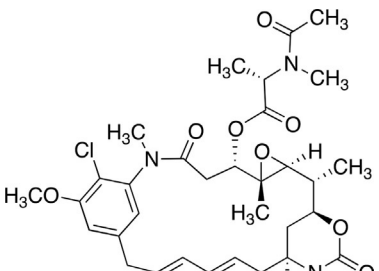
Cryptophycin-1 is a depsipeptide isolated from the cyanobacterium *Nostoc* species that was initially described as an antifungal agent[29] and was later shown to have antimitotic and cytotoxic activity. Subsequently, many cryptophycins have been isolated and prepared by synthesis, the most important one being cryptophicin 52 (LY-3555703), which entered clinical trials for the treatment of solid tumors.[30] The cryptophycins are among the most potent antimitotic agents described, and their binding is very strong and poorly reversible, making them relatively exempt from efflux by the Pgp-170-mediated multidrug resistance (MDR) mechanism.[31] The somewhat related natural product maytansine 1 is another inhibitor of tubulin polymerization, approximately 1000-fold more potent than vincristine. Although its toxicity led to abandoning clinical trials, it was approved by the FDA in 2013 as the conjugate trastuzumab emtansine or ado-trastuzumab emtansine (Kadcyla®) (see Chapter 13, Section 4.6).



Cryptopyicin 1 R = H
Cryptopyicin 52 R = CH_3
(LY-355703)



Maytansine 1

The spongistatins[32] are macrocyclic lactones containing six pyran rings, four of which are incorporated into two spiroketal moieties, which were isolated from sponges of the *Hytrios* genus. The spongistatins elicit extraordinarily potent (10^{-11} M) cytotoxic responses, especially in solid tumors, and they are being examined in phase I clinical trials.[33] Spongistatin 1 is a noncompetitive inhibitor of the binding of [^{3}H]vinblastine and [^{3}H]dolastatin to tubulin, in contrast to competitive patterns obtained with vincristine versus [^{3}H]vinblastine and with a stereoisomer of dolastatin 10 versus [^{3}H]dolastatin 10. Because dolastatin 10 is itself a noncompetitive inhibitor of *Vinca* alkaloid binding to tubulin, this implies the existence of at least three distinct binding sites in the *Vinca* domain.[34] Molecular modeling studies of the binding of the spongistatins led to the discovery of a hydrophobic pocket containing an unusual cluster of 10 aromatic amino acids, which allowed the rational design of the SPIKET compounds, containing a single spiroketal system. SPIKET-P inhibited the division of human breast cancer cells at low-nanomolar concentrations.[35]