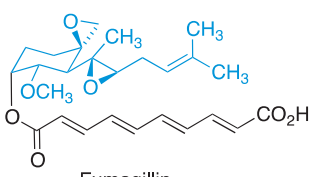
6.3 FUMAGILLIN ANALOGS

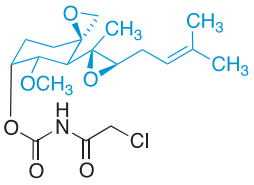
Among several natural products with activity as angiogenesis inhibitors,[102] one of the best studied is fumagillin, a mycotoxin isolated from *Aspergillus fumigatus* that is one of the most potent angiostatic agents widely employed as an antifungal in honeybees infected with *Nosema apis*. Fumagillin is a covalent inhibitor of methionine aminopeptidase-2 (MetAp2),[103] a cytosolic metalloenzyme and one of two methionine aminopeptidases responsible for protein stability and post-translational modifications that catalyze the hydrolytic removal of N-terminal methionine residues from nascent proteins. Current data support the hypothesis that MetAp2 may play a central role in endothelial cell proliferation and tumorigenesis, although the mechanism by which inhibition of MetAp2 function inhibits angiogenesis has not been clearly defined.[104] Fumagillin also inhibits the expression of the transcription factor ETS1, one member of the E26 transformation-specific transciption factors, which regulates the expression of VEGFs.[105]

Among the studied fumagillin analogs, the covalent binding inhibitor TNP-470 progressed to clinical trials, showing significant antitumor activity in cervical, breast, and lung cancers. However, its dose-limiting neurotoxicity and short half-life prevented its incorporation into further clinical studies.[106] In order to prevent their access to the central nervous system through the blood–brain barrier conjugate prodrugs have been developed.[107] These conjugates are accumulated selectively in tumor vessels because of the enhanced permeability and retention effect (see Chapter 13, Section 4).[108] Caplostatin is a water-soluble conjugate of TNP-470 in which this active compound is bonded to *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer through a Gly-Phe-Leu-Gly linker. In the oral formulation of TNP-470 known as lodamin, this drug was conjugated to monomethoxy polyethylene glycol–polylactic acid to form an amphiphilic molecule that forms micelles in aqueous solution. These nanopolymeric micelles can be absorbed by the intestine and selectively accumulate in tumors (see Chapter 13, Section 7.2).[109]

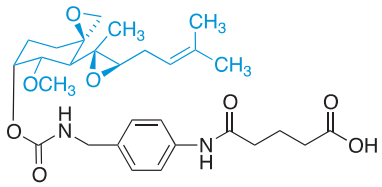
XMT-1107 is a conjugate of the fumagillol derivative XMT-1191 with Fleximer®, a biodegradable, hydrophilic polymer that does not cross the blood-brain barrier. This conjugate has entered clinical trials for advanced solid tumors.



Fumagillin



TNP-470



XMT-1191

These compounds bind covalently to their target by alkylating the His-231 residue through its ring epoxide (Figure 11.25).[110]