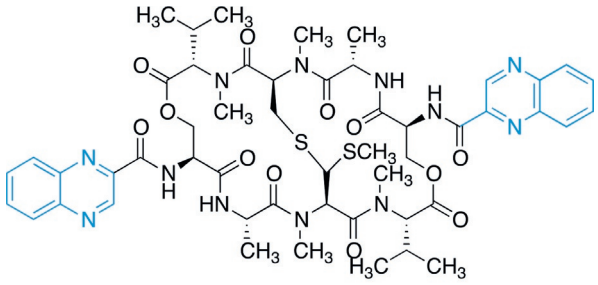
Echinomycin is an antitumor antibiotic isolated from *Streptomyces echinatus* that consists of two quinoxaline chromophores attached to a cyclic octadepsipeptide ring, with a thioacetal cross-bridge. Because of its potent antitumor activity, this compound advanced to several phase II clinical studies,[45,46] although it was eventually withdrawn from further clinical trials because it showed a high toxicity without any marked therapeutic benefit. Recently, echinomycin has been characterized as a very potent inhibitor of the binding of hypoxia-inducible factor 1 (HIF-1) to DNA. This is an interesting feature because HIF-1 is a transcription factor that controls genes involved in processes important for tumor progression and metastasis, including angiogenesis, migration, and invasion.[47]



Echinomycin

Several studies have proven that both echinomycin quinoxaline rings bis intercalate into DNA, with CG selectivity, while the inner part of the depsipeptide establishes hydrogen bonds with the DNA bases of the minor groove region of the two base pairs between the chromophores (Figure 7.8).[48] A calorimetric study proved that the binding reaction is entropically driven, showing that the complex is predominantly stabilized by hydrophobic interactions, although direct molecular recognition between echinomycin and DNA, mediated by hydrogen bonding and van der Waals contacts, also plays an important role in stabilizing the complex.[49]

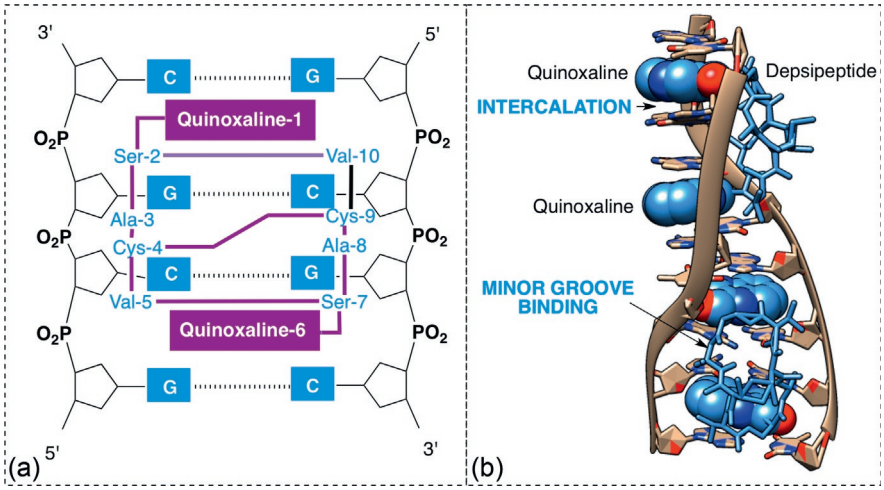


FIGURE 7.8

Interaction of echinomycin with a DNA fragment. The three-dimensional structure of the echinomycin-d (ACGTACGT) duplex was generated from Protein Data Bank reference 3G03[50] and displayed with Chimera 1.8.1.