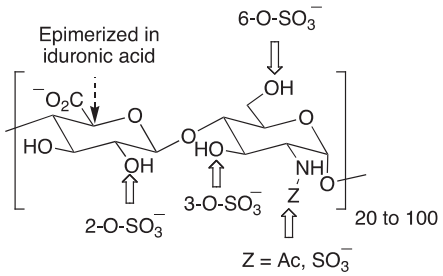
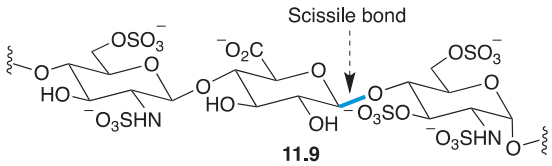
3 HEPARANASE INHIBITORS

Heparanase is an endo-β-D-glucuronidase that degrades polymeric heparan sulfate (HS), a polysaccharide formed by alternating, repetitive units of D-glucosamine and D-glucuronic acid/L-iduronic acid. HS proteoglycans are important components of the endothelial cell layer and are formed by a protein core covalently bound to HS side chains. Its cleavage affects the integrity and functional state of tissues and is involved in the response to changes in the extracellular microenvironment.



Heparanase is preferentially expressed in human tumors, in which it confers a highly invasive phenotype by releasing angiogenic factors. It recognizes sequences as small as a trisaccharide provided they are highly sulfated, as is the case with structure **11.9** (Figure 11.20a).[55] Its catalytic mechanism involves two acidic residues, a proton donor at Glu-225 and a nucleophile at Glu-343 (Figure 11.20b).[56]



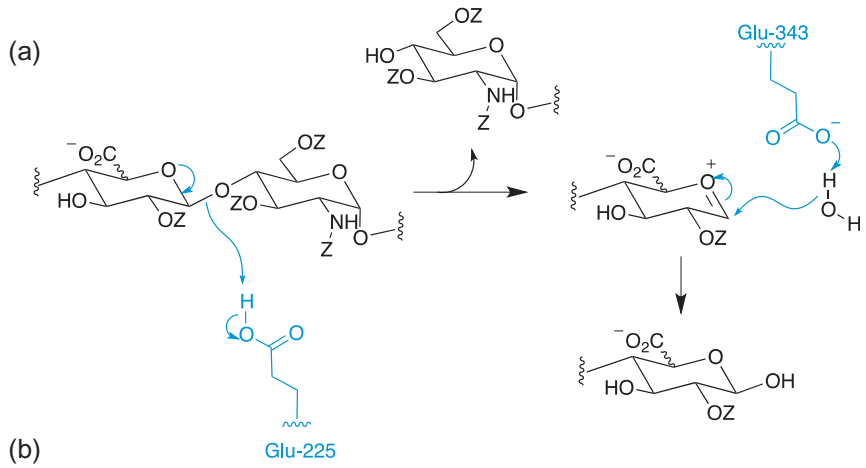


FIGURE 11.20

(a) Recognition sequence of heparan sulfate. (b) Mechanism of the reaction catalyzed by heparanase.