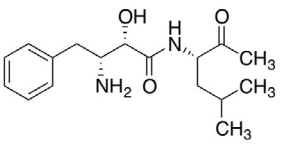
2.3 INHIBITORS OF AMINOPEPTIDASES

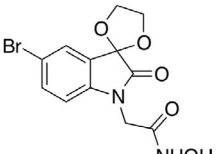
Aminopeptidases are proteolytic enzymes that hydrolyze the peptide bond involving the N-termini of peptide substrates, thereby releasing a single amino acid residue. Although they are anticancer targets, their development lags far behind that of MMP inhibitors.

Aminopeptidase N (APN, CD13) is a Zn^{2+}-dependent membrane-bound ectopeptidase that degrades preferentially proteins and peptides with an N-terminal neutral amino acid. The active sites of APN and MMP-2 are similar, and both enzymes contain two hydrophobic cavities (the S1 and S1′ pockets) around the catalytic zinc ion, although APN possesses another binding site rich in electropositive amino acid residues that provide H-bonding interactions. APN has been associated with the growth of different human cancers as a cell-surface marker for malignant myeloid cells, and it is also regarded as a good target for cancer therapy.[43] The key angiogenesis regulator VEGF induces APN expression at an early stage of tumor growth,[44] and high levels of APN are associated with the progression of several tumors, including breast, ovarian, and prostate cancer.

Although to date no inhibitors of these proteolytic enzymes (APNIs) are available as clinical agents, some compounds have shown considerable interest. For instance, ubenimex (Bestatin®), a peptidomimetic obtained from *Streptomyces olivoreticuli*, is an inhibitor of APN that entered clinical trials for acute myeloid leukemia, CML, lymphomas, and stage I squamous cell lung carcinoma.[45] Compound **11.8**, which was discovered in a virtual screening of a specifically filtered commercial database, exhibited good antiproliferative activities against a broad spectrum of human cancer cell lines.[46]



Ubenimex



11.8

Tosedostat (CHR-2797) is an ester prodrug that liberates by hydrolysis the poorly membrane-permeable active metabolite CHR-79888, a hydroxamic acid derivative that acts as an inhibitor of the M1 family of aminopeptidases (Figure 11.17). It has given encouraging clinical responses in patients with acute leukemia and several other blood-related cancers, and it is also under clinical study for solid tumors.[47]

The tosedostat active metabolite acts by a unique mechanism of action involving amino acid depletion in cancer cells by disruption of the cycle summarized in Figure 11.18, in which the action of aminopeptidases is essential to recycle the peptide fragments derived from the action of proteasome on proteins. This amino acid deprivation disrupts the turnover of cell cycle intermediates and prevents cancer cell survival or proliferation.

2.4 INHIBITORS OF CATHEPSINS

Other proteases that increase the metastatic potential of cancer cells are the cathepsins, which are cysteinyl and aspartyl proteases normally present inside the lysosomes as inactive pro-enzymes. When released at the extracellular space and activated, they facilitate cell migration and invasiveness. They are also transported into the cell nucleus, where they enhance the expression of genes involved in the