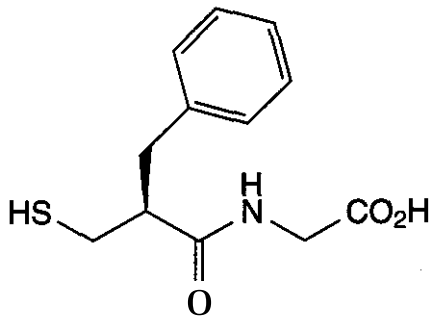
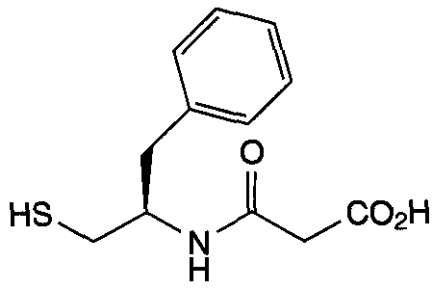


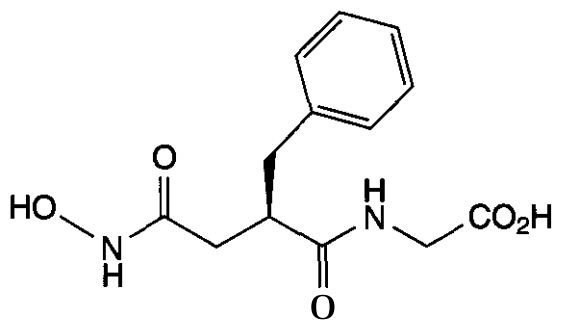
Thiorphan

(48)



Retrothiorphan

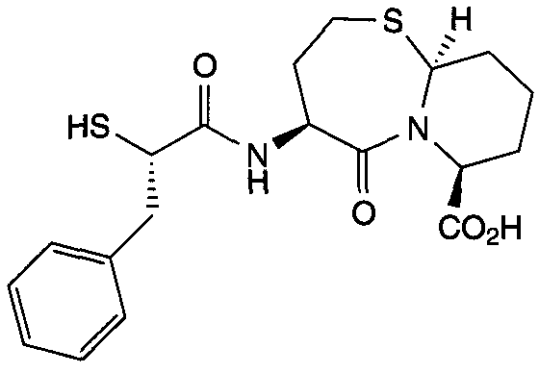
(49)



Kelatorphan

(50)

Figure 15.23. Examples of TSA as NEP inhibitors.

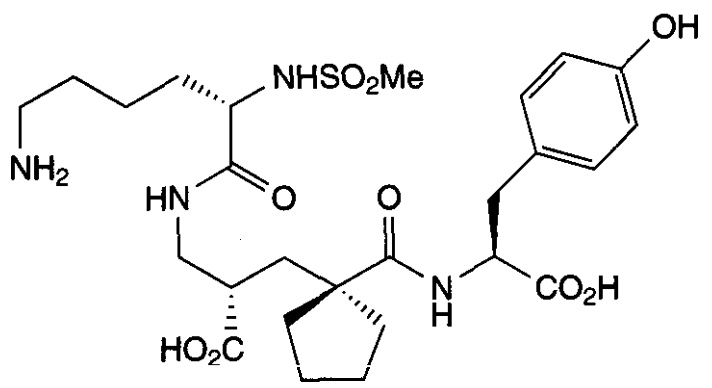


Omapatrilat

ACE $IC_{50} = 6$ nM

NEP $IC_{50} = 9$ nM

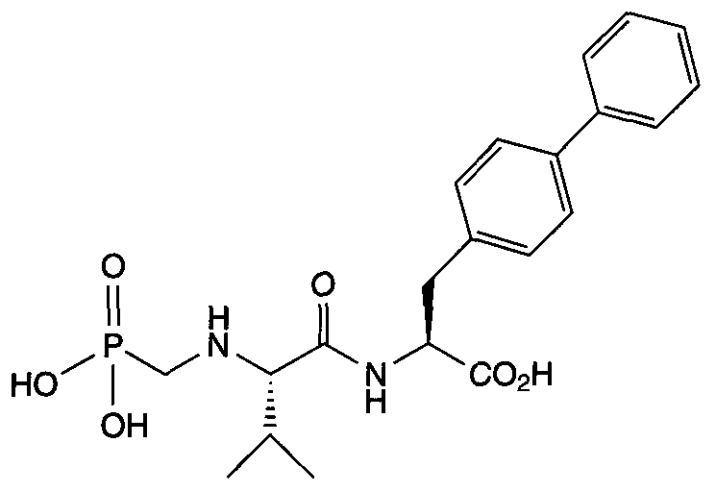
(51)



Sampatrilat

ACE $IC_{50} = 7$ nM

NEP $IC_{50} = 20$ nM



ACE $IC_{50} = 25$ nM

NEP $IC_{50} = 3$ nM

Figure 15.24. Examples of TSA as dual ACE/NEP inhibitors.

sive response (106, 107). Several dual inhibitors are in phase III clinical trial for treating hypertension (Fig. 15.24). Omapatrilat (51, BMS-189921) is the furthest along as of late 2001 (105).

Matrix metalloproteases (MMP) are also inhibited by hydroxamic acids and/or thiols. Over 25 variants of these enzymes are known, and some are involved in diseases ranging from inflammation to metastatic cancer (108). MMPs contain a zinc ion in the active site and function through the metallopeptidases catalytic mechanism already discussed. However, subtle differences between enzymes enable selective inhibitors to be developed (109). Fig. 15.25 lists some of the reported MMP inhibitors that use carboxylic acid (**52–53**), a hydroxamic acid (**54–55**), or thiol groups (56)as metal chelators.

Other reported zinc binding chelators used in matrix metalloproteinase inhibitors are summarized in Fig. 15.26. For instance, one of the oxygens in the phosphonamide (57) binds strongly to the zinc ion, whereas the other one coordinates weakly with the metal (110). More recently, "suicide substrate" MMP inhibitors have appeared (58)(Fig. 15.26) (111). The se-