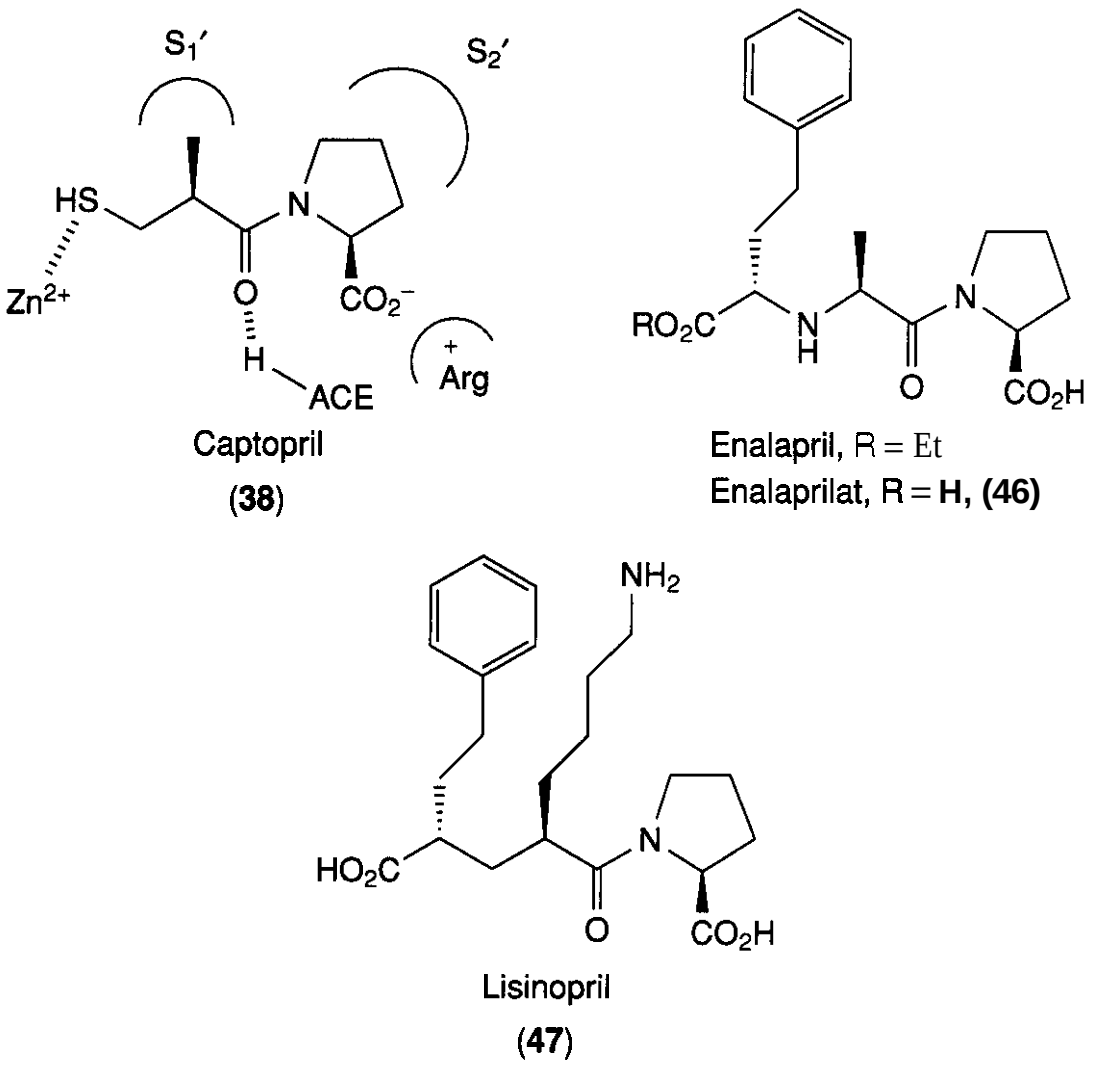

Captopril
(**38**)

Enalapril, R = Et
Enalaprilat, R = **H, (46)**

Lisinopril
(**47**)

Figure 15.22. Examples of TSA as ACE inhibitors.

6.2 TSA in Metallo Peptidase Inhibitors

The discovery of the angiotensin converting enzyme inhibitors in the middle 1970s constitutes one of the major advances in the rational design of drugs, the consequences of which are still being realized. The discovery of these metallo peptidase inhibitors was carried out by Ondetti et al. as part of a long-term study to develop antihypertensive drugs (80); in 1999 they received the Lasker Prize in Clinical Medicine for their work.

Angiotensin converting enzyme (ACE) is a carboxy zinc metallo dipeptidase that cleaves His-Leu from the C-terminus of angiotensin-I. Ondetti et al. reasoned that the product of normal reaction, the carboxyl group, could bind to the active site zinc ion, and that the carboxyl group of a collected-product inhibitor also could bind weakly. To improve the interaction between inhibitor and enzyme zinc ion, they replaced the carboxyl group with a sulfhydryl group, which binds zinc about 1000 times more tightly. This led to captopril (Capoten) **(38)** (Fig. 15.22) (80). Later developments by other companies led to many ACE inhibitors. Some are illustrated by enalaprilat (**46**) and lisinopril (47) (Fig. 15.22) (101, 102).

Most metallopeptidase inhibitors append a zinc chelating functionality to a peptide or peptidomimetic that is recognized by the S1′–S3′ subsites in the target enzyme. Successful clinical candidates invariably contain groups that replace the initial di- and tri-peptide moieties to achieve selectivity and orally activity. For example, neutral endopeptidase (NEP), another endopeptidase involved in degrading the larger opioid peptides dynorphan and/or endorphan, is inhibited by thiorphan (48) (103) and a variety of NEP inhibitors: retrothiorphan (49) (104) and kelatorphan (50) (Fig. 15.23) (105). The hydroxamic acid moiety is used in many inhibitors of metallopeptidases.

Inhibition of NEP also prevents the degradation of atrial natriuretic factor (ANF), a natural hypotensive peptide. Dual inhibitors of NEP and ACE have been designed successfully because both enzymes share significant structural homology, particularly in their active sites. Simultaneous inhibition of both peptidases produces a more powerful hypoten-