Angiotensin converting enzyme (ACE)

ACE is a zinc-containing dipeptidyl carboxypeptidase, which converts angiotensin I to angiotensin II.

Angiotensin II is an octapeptide that contracts blood vessels and increases salt and water reabsorption in the kidney (mainly by stimulating the release of aldosterone), resulting in the increase of blood pressure.

Inhibitors of ACE, like captopril, enalaprilat and lisinopril are important antihypertensive drugs.

Captopril, enalaprilat and lisinopril are antihypertensive drugs used to lower high blood pressure in hypertensive individuals. Their mechanism of action is inhibition of angiotensin converting enzyme (ACE).

Chemistry of captopril

Captopril was developed (by Ondetti and Cushman at Squibb), using rational design, based on (1) the analogy of its target ACE to carboxypeptidase A, a much studied enzyme, and (2) the structure of its inhibitor, benzylsuccinate.
Carboxypeptidase A (CPA)
A proteolytic enzyme with a catalytic zinc at the active site
Selectively cleaves at a C-terminal aromatic residue, e.g., phenylalanine

Based on the potent CPA inhibitory activity of benzylsuccinic acid, succinyl-proline was designed as an inhibitor of ACE - it had modest activity (K_i 0.3 mM) The CH_3-group (Ala side-chain) was attached that improved the K_i (0.02 mM). The COOH-group was replaced by an SH-group for stronger binding to the active site Zn leading to captopril with a superior K_i-value of 2 x 10^-8 M (0.00002 mM) and potent in vivo activity. Enalaprilat (K_i-value of 1.2 x 10^-8 M ) was subsequently developed to replace the oxidizable SH-group with a COOH. In addition, an NH- and a phenylethyl-group were inserted to compensate for the loss of the strong Zn-S bond

Complex of captopril with angiotensin converting enzyme

Captopril bound to the active site of ACE
- The thiol (SH) group of captopril makes direct interaction with Zn^{2+}
- The carbonyl group forms strong hydrogen bonding with two histidines, His 513 and His 353
- One oxygen of proline carboxylate group is H-bonded to Tyr 520, Gln 281 and Lys 511
Side effects of captopril lead to the design of enalaprilat. The carboxylate group introduced to replace the SH-group binds to Zn²⁺ as well as to Glu 384 and Tyr 523. The carboxyl group attached to proline forms strong H-bonds with two histidines, His 513 and His 353, similarly to captopril. One oxygen of the proline carboxylate group is H-bonded to Tyr 520, Gln 281 and Lys 511, similarly to captopril. The carbonyl oxygen of Ala 354 forms a H-bond to the new NH-group. The phenylethyl side-chain introduced occupies a hydrophobic pocket lined by Phe 512 and Val 518.

In lisinopril the alanine of enalaprilat is replaced by lysine. The positively charged side-chain of lysine binds to Glu 162 as well as to Asp 377 via a bridging water molecule (green).